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Neoadjuvant Osimertinib for Resectable *EGFR*-Mutated Non–Small Cell Lung Cancer

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ABSTRACT

PURPOSE Adjuvant osimertinib is the standard of care for patients with resected epidermal growth factor receptor (*EGFR*)–mutated non–small cell lung cancer (NSCLC). Neoadjuvant treatment could improve surgical and long-term outcomes.

METHODS In this randomized, controlled, phase III study, patients with resectable, *EGFR*-mutated, stage II-IIIB NSCLC were randomly assigned (1:1:1) to receive neoadjuvant osimertinib (80 mg orally once daily for ≥9 weeks) plus platinum-based chemotherapy (once every 3 weeks for three cycles), osimertinib monotherapy (for ≥9 weeks), or placebo plus platinum-based chemotherapy (control), followed by surgical resection. Adjuvant osimertinib was offered to eligible patients after completion of surgery. The primary end point was major pathologic response (MPR) by blinded central pathology review. Event-free survival (EFS) was a secondary end point.

RESULTS Overall, 358 patients were randomly assigned to receive osimertinib plus chemotherapy (121 patients), osimertinib monotherapy (117 patients), or placebo plus chemotherapy (120 patients). Osimertinib plus chemotherapy (MPR rate 26%) and osimertinib monotherapy (25%) demonstrated statistically significant improvement in the MPR rate versus placebo plus chemotherapy (2%), with corresponding odds ratios of 19.82 (95.002% CI, 4.60 to 85.33; $P < .0001$) and 19.28 (99.9% CI, 1.71 to 217.39; $P < .0001$), respectively. With 15% data maturity, the EFS rates at 12 months were 93%, 95%, and 83% with osimertinib plus chemotherapy, osimertinib monotherapy, and placebo plus chemotherapy, respectively. In the neoadjuvant period, grade ≥3 adverse events of any cause occurred in 36%, 13%, and 33% of patients with osimertinib plus chemotherapy, osimertinib monotherapy, and placebo plus chemotherapy, respectively. No new safety concerns were identified.

CONCLUSION Neoadjuvant osimertinib with or without chemotherapy demonstrated statistically significant improvement in the MPR rate over chemotherapy alone in patients with resectable, *EGFR*-mutated, stage II-IIIB NSCLC.

ACCOMPANYING CONTENT

Editorial, p. 2847

Listen to the podcast by Dr Thomas Stinchcombe and Dr Ece Cali at https://ascopubs.org/do/jco-asco-annual-meeting-neoadjuvant-osimertinib-resectable-egfr-mutated-nsclc

Appendix

Data Sharing Statement

Data Supplement

Protocol

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INTRODUCTION

Approximately 30% of patients with non–small cell lung cancer (NSCLC) present with early-stage disease that is potentially resectable.[1,2] Epidermal growth factor receptor (*EGFR*) mutations are common oncogenic drivers in NSCLC.[3]

Osimertinib is a third-generation, irreversible, oral EGFR tyrosine kinase inhibitor (EGFR-TKI) that potently and selectively inhibits both EGFR-TKI sensitizing and *EGFR p.Thr790Met* resistance mutations.[4] On the basis of the statistically significant improvements in disease-free survival (DFS) and overall survival (OS) observed in the phase III ADAURA trial, adjuvant osimertinib has become the standard of care for patients with resected, *EGFR*-mutated NSCLC.[5-9]

The resectable NSCLC treatment landscape continues to evolve, and neoadjuvant therapy may offer additional benefit by reducing the likelihood of progressive disease (PD) before surgery and improving surgical and long-term treatment outcomes.[10] Neoadjuvant or adjuvant chemotherapy are options for patients with resectable NSCLC,[5,11,12] but are

CONTEXT

Key Objective

Does neoadjuvant osimertinib, given with or without chemotherapy, improve surgical and long-term treatment outcomes versus chemotherapy alone in resectable, epidermal growth factor receptor (*EGFR*)–mutated, stage II-IIIB non–small cell lung cancer (NSCLC)?

Knowledge Generated

Major pathologic response rates were significantly higher for osimertinib given with (26%) and without (25%) chemotherapy versus placebo plus chemotherapy (2%); fewer patients did not undergo surgery owing to disease progression with the osimertinib-containing regimens (both 1%) versus placebo plus chemotherapy (6%), and early event-free survival (EFS) data favored the osimertinib-containing regimens. Over 90% of patients completed surgery with both osimertinib-containing regimens, and safety findings were consistent with the known profiles of osimertinib and chemotherapy.

Relevance *(T.E. Stinchcombe)*

For patients with *EGFR* mutant NSCLC and stage III disease pre-operative osimertinib alone or with chemotherapy may become options if a clinically relevant difference in EFS is observed with longer follow-up.*

*Relevance section written by *JCO* Associate Editor Thomas E. Stinchcombe, MD.

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associated with similarly modest improvement in 5-year survival (approximately 5%) versus surgery alone.[13-15] Evidence regarding the efficacy of neoadjuvant chemotherapy in *EGFR*-mutated NSCLC is limited; however, pathologic response outcomes are poor, with between 0% and 4% of tumors demonstrating major pathologic response (MPR).[16,17]

Recently, pivotal phase III studies have demonstrated improved pathologic and clinical outcomes with the addition of neoadjuvant or perioperative immunotherapy to chemotherapy,[18-22] establishing a role for chemoimmunotherapy regimens in the resectable NSCLC setting. Most of these studies excluded patients with *EGFR*-mutated disease, and the few that included such patients did not demonstrate clear evidence of benefit with immunotherapy in the *EGFR*-mutant subgroup.[16,18,19,22] Thus, the role of neoadjuvant therapy in *EGFR*-mutated NSCLC is yet to be defined.

NeoADAURA (ClinicalTrials.gov identifier: NCT04351555) is a global, phase III, randomized, controlled, three-arm study evaluating pathologic and clinical outcomes with neoadjuvant osimertinib, with or without chemotherapy, versus chemotherapy alone for the treatment of resectable, *EGFR*-mutated, stage II-IIIB NSCLC. We report the results for the primary study end point.

METHODS

Trial Population

Eligible patients were aged 18 years and older and had a WHO performance status of 0 or 1, with histologically or cytologically documented nonsquamous NSCLC considered to be completely resectable by a multidisciplinary team (stage II-IIIB per the American Joint Committee on Cancer staging manual, eighth edition[23]). They also had sensitizing *EGFR* mutations (exon 19 deletions [Ex19del] or exon 21 p.Leu858Arg [L858R] point mutations), confirmed by sponsor preapproved local or central tissue testing. Details regarding the procedures for disease staging (including invasive confirmation of N2 disease) and *EGFR* mutation testing are provided in the Data Supplement (online only). Complete eligibility criteria are available in the protocol.

Trial Design and Treatment

The trial design is shown in the Data Supplement (Fig S1). Patients were randomly assigned 1:1:1 to oral osimertinib 80 mg once daily for ≥9 weeks plus platinum-based chemotherapy (once every 3 weeks; three cycles); oral osimertinib 80 mg once daily for ≥9 weeks as monotherapy; or oral placebo once daily for ≥9 weeks plus platinum-based chemotherapy (once every 3 weeks; three cycles). Chemotherapy was intravenous pemetrexed (500 mg/m^2) plus investigators' choice of carboplatin (AUC, 5) or cisplatin (75 mg/m^2) administered according to local practice and prescribing information. Osimertinib and placebo were administered in a double-blinded fashion in the chemotherapy combination groups, and osimertinib monotherapy was administered in an open-label, sponsor-blinded fashion. Random assignment was stratified by disease stage (II *v* III), race (Chinese *v* other Asian *v* non-Asian), and *EGFR* mutation type (Ex19del *v* L858R).

Eligibility for surgery was assessed after neoadjuvant treatment. Surgery was scheduled to take place within

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12 weeks after the start of neoadjuvant treatment, with an additional week allowed subject to the sponsor's approval. All patients who underwent surgery, or who did not complete surgery for any reason other than PD, entered the event-free survival (EFS) follow-up period and remained in follow-up until an EFS event occurred. Patients who did not undergo or complete surgery owing to PD entered the survival follow-up period. Patients received optimal care in the EFS follow-up period, as defined by the investigator or multidisciplinary team; for eligible patients who completed surgery, this could include sponsor-supplied adjuvant osimertinib. Postoperative radiotherapy and chemotherapy were permitted before starting adjuvant osimertinib. Written informed consent was provided by all patients, and an independent data and safety monitoring committee monitored efficacy and safety. The protocol and all amendments were approved by the relevant ethics committees or institutional review boards. The trial was performed in accordance with the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, International Council for Harmonisation Good Clinical Practice Guidelines, and all applicable laws and regulations.

End Points and Assessments

The primary end point was MPR. Secondary end points included EFS, pathologic complete response (pCR), and nodal downstaging at surgery. Safety was also assessed. A complete summary of trial end points is available in the protocol.

Pathologic response to neoadjuvant therapy was assessed by blinded central pathology review using recommendations from the International Association for the Study of Lung Cancer.[24] Patients with ≤10% residual viable tumor in the lung primary tumor at the time of resection were considered to have had an MPR. Patients also had to have a no evidence of tumor at surgical margin (R0) result to be classified as responders. Patients who were not evaluable per blinded central pathology review, including those who did not undergo or complete surgery, were classified as not having an MPR response. Information regarding the assessment of secondary end points and safety is provided in the Data Supplement.

Statistical Analysis

The planned sample size was approximately 351 patients, providing approximately 90% power to detect an improvement of 20% in the MPR rate for the osimertinib plus chemotherapy and osimertinib monotherapy groups compared with the placebo plus chemotherapy group (control) at a two-sided 5% significance level, assuming an MPR rate of 20% with placebo plus chemotherapy.

A final analysis of MPR was planned to occur after the last patient had the opportunity to complete surgery and central MPR assessment. The interim analysis of EFS was timed to coincide with the final analysis of MPR. A multiple testing procedure was applied to control the overall type I error at the 5% (two-sided) level at the interim and final analyses for the primary end point of MPR and secondary end point of EFS (Data Supplement, Fig S2). Additional details are provided in the Data Supplement.

Efficacy data were analyzed and summarized on the basis of all randomly assigned patients (the full analysis set) and safety data on the basis of all randomly assigned patients who received ≥1 dose of any study treatment (the safety analysis set). For the primary analyses, the binary variable of MPR was analyzed using a stratified Cochran-Mantel-Haenszel test; pCR and nodal downstaging were analyzed using the same method. EFS, a time-to-event variable, was analyzed using a stratified log-rank test. The data cutoff date for this analysis was October 15, 2024.

RESULTS

Patients and Treatment

Between January 11, 2021, and December 26, 2023, 358 patients from 25 countries were randomly assigned to receive neoadjuvant treatment with osimertinib plus chemotherapy (121 patients), osimertinib monotherapy (117 patients), or placebo plus chemotherapy (120 patients; Fig 1). The characteristics of the study population were generally representative of an international population with resectable, *EGFR*-mutated NSCLC (Table 1; Data Supplement, Table S1).

Baseline characteristics of the patients are presented in Table 1. The median age was 65 years. Most of the patients were female (66%), had a performance status of 0 (81%), and had never smoked (71%). Half of the patients had stage III disease, and over one third had N2 disease. Baseline characteristics were balanced between the treatment groups, although there was a higher proportion of female patients and never smokers in the placebo plus chemotherapy group versus the osimertinib plus chemotherapy and osimertinib monotherapy groups.

Two patients randomly assigned to osimertinib plus chemotherapy did not receive any neoadjuvant treatment (Data Supplement, Table S2). Most of the patients completed all neoadjuvant study treatments in the osimertinib plus chemotherapy (90%), osimertinib monotherapy (98%), and placebo plus chemotherapy (93%) groups. Overall, 91% and 93% of patients completed all three cycles of neoadjuvant chemotherapy in the osimertinib plus chemotherapy and placebo plus chemotherapy groups, respectively. Exposure to neoadjuvant osimertinib or placebo was similar across the groups (Data Supplement, Table S3); nearly all patients received osimertinib or placebo for ≥9 weeks in the osimertinib plus chemotherapy (94%), osimertinib monotherapy (97%), and placebo plus chemotherapy (96%) groups. Most of the patients received sponsor-supplied adjuvant osimertinib after surgery, including 82%, 86%, and 80% of patients in the osimertinib plus chemotherapy, osimertinib monotherapy, and placebo plus chemotherapy groups, respectively. At the data cutoff, 95%, 93%, and 92% of patients remained on

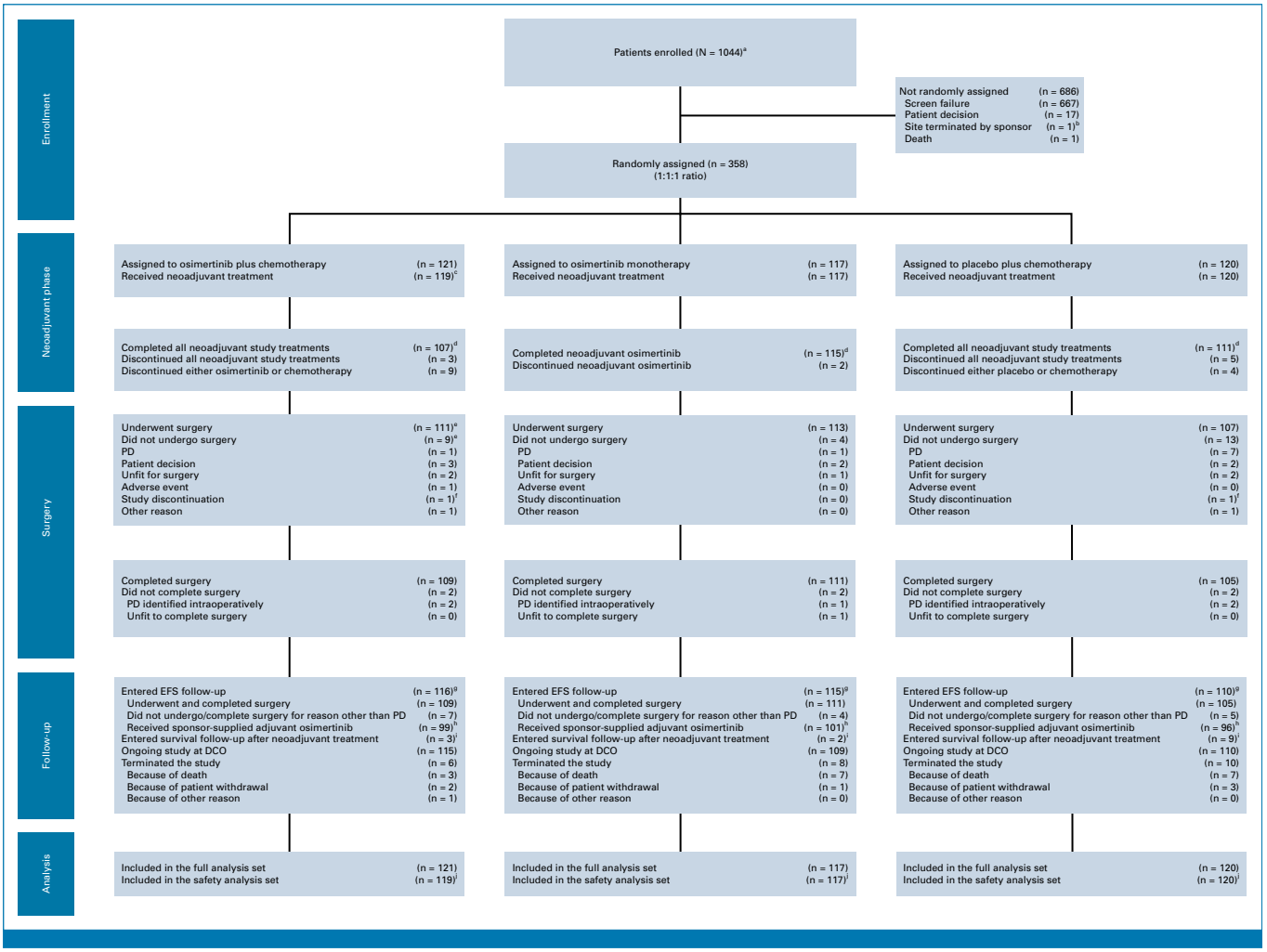

FIG 1. CONSORT diagram. [a]Written informed consent received. [b]One patient who was not randomly assigned because of screen failure was incorrectly categorized as site terminated in error. [c]Two patients allocated to osimertinib plus chemotherapy did not receive any neoadjuvant study treatment: 1 patient withdrew consent before dosing and 1 patient was withdrawn by the investigator. [d]Includes patients who completed both osimertinib/placebo and chemotherapy for the osimertinib plus chemotherapy and placebo plus chemotherapy groups and patients who completed osimertinib for osimertinib monotherapy group; a patient is considered to have completed chemotherapy if they had completed all the required chemotherapy study drugs. [e]Surgery status was missing for 1 patient allocated to osimertinib plus chemotherapy. [f]One patient in the osimertinib plus chemotherapy group and 1 patient in the placebo plus chemotherapy group did not undergo surgery because of study discontinuation. These patients did not enter the EFS follow-up period. [g]Limited to patients who underwent and completed surgery and patients who did not have surgery/complete surgery for reasons other than PD; patients who did not undergo surgery owing to PD entered the survival follow-up period. [h]In addition to patients who received sponsor-supplied adjuvant osimertinib, five patients received adjuvant osimertinib from commercial supply, including two patients in the osimertinib plus chemotherapy group, 1 patient in the osimertinib monotherapy group, and two patients in the placebo plus chemotherapy group. [i]Includes patients who did not undergo surgery because of PD or patients whose planned surgery was not completed because of PD. [j]The safety analysis set includes all randomly assigned patients who received at least 1 dose of any neoadjuvant study treatment. DCO, data cutoff; EFS, event-free survival; PD, progressive disease.

study in the osimertinib plus chemotherapy, osimertinib monotherapy, and placebo plus chemotherapy groups, respectively. Most of the patients remained on treatment with sponsor-supplied adjuvant osimertinib (79%, 82%, and 77% of patients in each group, respectively).

Surgery

After neoadjuvant treatment, most of the patients underwent curative-intent surgery in the osimertinib plus chemotherapy (92%), osimertinib monotherapy (97%), and placebo plus chemotherapy (89%) groups (Data Supplement, Table S4). Overall, 6% of patients did not undergo surgery because of PD with placebo plus chemotherapy, compared with 1% of patients for both osimertinib-containing regimens. Surgery was completed in nearly all patients who underwent surgery (98% in each group); 2%, 1%, and 2% of patients started but did not complete surgery owing to PD with osimertinib plus chemotherapy, osimertinib monotherapy, and placebo plus chemotherapy,

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TABLE 1. Demographic and Clinical Characteristics of Patients at Baseline

Characteristic	Osimertinib + Chemotherapy (n = 121)	Osimertinib Monotherapy (n = 117)	Placebo + Chemotherapy (n = 120)
Age, years, median (range)	63 (31-82)	66 (42-83)	65 (36-86)
Sex, No. (%)			
Male	49 (40)	41 (35)	30 (25)
Female	72 (60)	76 (65)	90 (75)
Smoking status, No. (%)			
Current/former	39 (32)	40 (34)	26 (22)
Never	82 (68)	77 (66)	94 (78)
Race, No. (%)[a]			
Chinese[b]	29 (24)	27 (23)	31 (26)
Other Asian	59 (49)	59 (50)	59 (49)
Non-Asian	33 (27)	31 (26)	30 (25)
WHO performance status score, No. (%)			
0	97 (80)	93 (79)	100 (83)
1	24 (20)	24 (21)	20 (17)
AJCC disease stage, No. (%)[c]			
II	59 (49)	59 (50)	61 (51)
III	62 (51)	58 (50)	59 (49)
TNM classification, primary tumor, No. (%)			
T1	20 (17)	22 (19)	15 (13)
T2	57 (47)	55 (47)	56 (47)
T3	35 (29)	28 (24)	38 (32)
T4	9 (7)	12 (10)	11 (9)
TNM classification, regional lymph nodes, No. (%)			
N0	31 (26)	31 (26)	35 (29)
N1	42 (35)	44 (38)	44 (37)
N2	47 (39)	41 (35)	41 (34)
N3	1 (1)	1 (1)	0
Baseline tumor size, cm, mean (SD)	4.2 (1.4)	4.0 (1.5)	4.3 (1.6)
EGFR mutation type at study entry, No. (%)[d]			
Exon 19 deletion	60 (50)	60 (51)	61 (51)
L858R mutation	61 (50)	57 (49)	59 (49)

NOTE. Baseline demographics and clinical characteristics are summarized on the basis of the full analysis set.
Abbreviations: AJCC, American Joint Committee on Cancer; EGFR, epidermal growth factor receptor; L858R, exon 21 p.Leu858Arg; M, metastasis; N, lymph node; SD, standard deviation; T, tumor.
[a]Investigators reported race by interactive voice response.
[b]Defined as Chinese patients living in mainland China.
[c]Disease stages are classified according to the AJCC staging manual (eighth edition) and summarized on the basis of data collected by interactive voice response.
[d]*EGFR* mutational status at study entry was determined by local or central tissue testing and summarized on the basis of data collected by interactive voice/web response system. Patients may have had other *EGFR* mutations in addition to exon 19 deletions and L858R mutations.

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respectively. Overall, 91%, 95%, and 93% of patients who underwent surgery had an R0 resection with osimertinib plus chemotherapy, osimertinib monotherapy, and placebo plus chemotherapy, respectively. Further details of surgery are provided in the Data Supplement (Table S5). Across all treatment groups, the median time from the last neoadjuvant dose of osimertinib or placebo to surgery was 3 days and the median time from surgery to the first dose of sponsor-supplied adjuvant osimertinib was 35 days. Among patients who completed surgery, 91% in each treatment group had started sponsor-supplied adjuvant osimertinib at the time of data cutoff.

Pathologic Response and Nodal Downstaging

In the primary analysis, a significantly higher proportion of patients had an MPR with osimertinib plus chemotherapy (26%; 95% CI, 18 to 34) and osimertinib monotherapy (25%;

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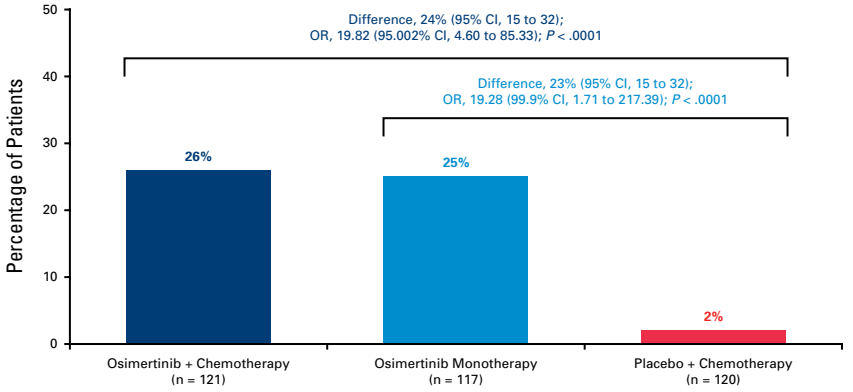
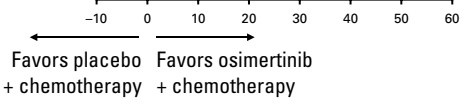
A MPR (Full Analysis Set)



B Subgroup Analysis of MPR (Osimertinib + Chemotherapy *v* Placebo + Chemotherapy)

Subgroup		n	MPR, % Osimertinib + Chemotherapy (n = 121)	MPR, % Placebo + Chemotherapy (n = 120)	Difference in MPR, % (95% CI)
All patients		241	26	2	24 (15 to 32)
Age at random assignment	<65 years	121	26	0	25 (14 to 36)
	≥65 years	120	25	3	21 (8 to 33)
Sex	Male	79	27	3	18 (5 to 32)
	Female	162	25	1	24 (13 to 34)
WHO PS	0	197	25	2	23 (14 to 33)
	1	44	29	0	NA Not calculated
Race	Chinese	60	34	0	34 (16 to 51)
	Other Asian	118	17	2	15 (5 to 25)
	Non-Asian	63	33	3	30 (13 to 47)
Smoking	Yes	65	28	0	28 (12 to 43)
	No	176	24	2	22 (12 to 32)
***EGFR* mutation type**	Ex19del	121	30	2	28 (16 to 40)
	L858R	120	21	2	19 (8 to 30)
Disease stage (AJCC 8th ed.)	Stage II	120	22	3	18 (7 to 30)
	Stage III	121	29	0	29 (17 to 40)
Central plasma ctDNA EGFR	Positive	67	36	0	37 (21 to 53)
	Negative	164	20	2	17 (7 to 26)
	Unknown	10	50	0	NA Not calculated



C Subgroup Analysis of MPR (Osimertinib Monotherapy *v* Placebo + Chemotherapy)

Subgroup		n	MPR, % Osimertinib Monotherapy (n = 117)	MPR, % Placebo + Chemotherapy (n = 120)	Difference in MPR, % (95% CI)
All patients		237	25	2	23 (15 to 32)
Age at random assignment	<65 years	110	31	0	30 (17 to 43)
	≥65 years	127	20	3	18 (7 to 29)
Sex	Male	71	29	3	30 (13 to 47)
	Female	166	22	1	21 (11 to 31)
WHO PS	0	193	27	2	26 (16 to 35)
	1	44	17	0	NA Not calculated
Race	Chinese	58	41	0	41 (23 to 60)
	Other Asian	118	20	2	18 (8 to 29)
	Non-Asian	61	19	3	NA Not calculated
Smoking	Yes	66	23	0	NA Not calculated
	No	171	26	2	24 (14 to 35)
***EGFR* mutation type**	Ex19del	121	30	2	28 (16 to 40)
	L858R	116	19	2	18 (7 to 29)
Disease stage (AJCC 8th ed.)	Stage II	120	27	3	25 (12 to 37)
	Stage III	117	22	0	22 (12 to 33)
Central plasma ctDNA EGFR	Positive	62	29	0	28 (11 to 44)
	Negative	156	26	2	23 (13 to 34)
	Unknown	19	0	0	NA Not calculated

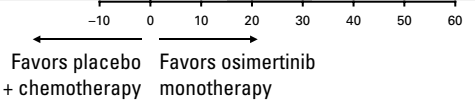


FIG 2. MPR, assessed by blinded central pathology review. Pathologic response is summarized on the basis of the full analysis set and was assessed using recommendations from the International Association for the Study of Lung Cancer (2020). Patients with ≤10% residual viable tumor cells in the lung primary tumor at the time of resection were considered to have had an MPR. Patients also had to have a R0 margin result to be classified as having an MPR. Patients who were not evaluable per blinded central pathology review were classified as not having an MPR. Panel (A) shows MPR results for the full analysis set. Panels (B and C) show forest plots of MPR in prespecified subgroups for the comparison of osimertinib plus chemotherapy versus placebo plus chemotherapy and osimertinib monotherapy versus placebo plus chemotherapy, respectively. The data points show the difference in MPR rates with 95% CIs as analyzed using the Cochran–Mantel–Haenszel (continued on following page)

FIG 2. (Continued). test stratified by disease stage (II *v* III), race (Chinese *v* other Asian *v* non-Asian) and *EGFR* mutation type (Ex19del *v* L858R). The size of the data points is proportional to the number of patients in each subgroup. The horizontal bars represent the 95% CIs and the shading indicates the the difference in MPR rates and 95% CIs for the full analysis set (all randomized patients). Differences in the proportion of patients with MPR between treatment groups was not calculated for subgroups with <10 patients who had an MPR (across the osimertinib plus chemotherapy and placebo plus chemotherapy groups or across osimertinib monotherapy and placebo plus chemotherapy groups). Disease stage was defined according to the AJCC Cancer Staging Manual (eight edition). AJCC, American Joint Committee on Cancer; ctDNA, circulating tumor DNA; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; L858R, exon 21 p.Leu858Arg; MPR, major pathologic response; NA, not applicable; OR, odds ratio; PS, performance status; R0, no evidence of tumor at surgical margin.

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95% CI, 17 to 34) versus placebo plus chemotherapy (2%; 95% CI, 0 to 6), with corresponding odds ratios (ORs) of 19.82 (95.002% CI, 4.60 to 85.33; $P < .0001$) and 19.28 (99.9% CI, 1.71 to 217.39; $P < .0001$), respectively (Fig 2A). MPR results were similar among prespecified subgroups with sufficient responders for analysis (Figs 2B and 2C). Depth of pathologic response in the primary tumor was greater overall in the osimertinib plus chemotherapy and osimertinib monotherapy groups than the placebo plus chemotherapy group (Fig 3). The proportion of patients with a pCR was 4% (95% CI, 1 to 9) with osimertinib plus chemotherapy, 9% (95% CI, 4 to 15) with osimertinib monotherapy, and 0% (95% CI, 0 to 3) with placebo plus chemotherapy.

Among patients with baseline N2 disease and an assessment at the time of surgery, the proportion downstaged at surgery (to N0 or N1) was 53% (95% CI, 38 to 68; n = 47) with osimertinib plus chemotherapy, 53% (95% CI, 36 to 69; n = 38) with osimertinib monotherapy, and 21% (95% CI, 9 to 38; n = 34) with placebo plus chemotherapy. The corresponding ORs comparing osimertinib plus chemotherapy and osimertinib monotherapy with placebo plus chemotherapy were 4.77 (95% CI, 1.62 to 14.00) and 4.18 (95% CI, 1.44 to 12.14), respectively.

Interim Analysis of EFS

At the time of data cutoff, with 15% data maturity, the median duration of follow-up for EFS in all patients was 14.3 (range, <0.1 to 41.9), 18.3 (range, 2.1-41.9), and 14.3 (range, 1.7-41.8) months for the osimertinib plus chemotherapy, osimertinib monotherapy, and placebo plus chemotherapy groups, respectively. The hazard ratio (HR) for EFS comparing osimertinib plus chemotherapy with placebo plus chemotherapy was 0.50 (99.8% CI, 0.17 to 1.41; $P = .04$; Fig 4); this difference did not reach statistical significance per the prespecified two-sided significance level of 0.002. The HR for EFS comparing osimertinib monotherapy with placebo plus chemotherapy was 0.73 (95% CI, 0.40 to 1.35); no formal statistical comparison was performed because of the lack of statistical significance of the prior comparison. Overall, 93%, 95%, and 83% of patients in the osimertinib plus chemotherapy, osimertinib monotherapy, and placebo plus chemotherapy groups, respectively, had not experienced an EFS event at 12 months after random assignment. The relationship between MPR and EFS across the three treatment groups was assessed in an exploratory analysis: A single EFS event was observed in patients who had an MPR (1/62 patients [2%]) and the remaining 52 EFS events were reported in patients who did not have an MPR (52/296 patients [18%]).

Safety and Surgical Complications

During the neoadjuvant phase, adverse events (AEs) of any cause occurred in 89%-93% of patients across the three treatment groups (Data Supplement, Table S6). Most AEs were low grade and nonserious. The proportion of patients with grade ≥3 and serious AEs was similar with osimertinib plus chemotherapy (36% and 20%, respectively) and placebo plus chemotherapy (33% and 20%, respectively). Meanwhile, grade ≥3 and serious AEs occurred in 13% and 11% of patients, respectively, with osimertinib monotherapy. The proportion of patients who had AEs leading to discontinuation of osimertinib or placebo was 2%-3% across the three groups. AEs leading to discontinuation of chemotherapy were reported in 8% of patients with osimertinib and 5% of patients with placebo. No fatal AEs were reported. The most common AEs in each group are presented in Table 2.

Regarding AEs of special interest, the proportion of patients with hematologic toxicities (as a grouped term) was highest with osimertinib plus chemotherapy (52%), followed by placebo plus chemotherapy (40%) and osimertinib monotherapy (11%; Data Supplement, Table S7). Cardiac effects (as a grouped term) were reported in 1%-3% of patients across the three groups (all patients had decreased ejection fraction). Wound complications and interstitial lung disease or pneumonitis (both as grouped terms) were each reported in ≤2% of patients with the osimertinib-containing regimens.

One patient in the osimertinib plus chemotherapy group did not undergo surgery because of grade 3 thromboembolism (assessed by the investigator as causally related to chemotherapy). Among patients who underwent surgery, 10%, 5%, and 7% had serious AEs causally related to surgery with osimertinib plus chemotherapy, osimertinib monotherapy, and placebo plus chemotherapy, respectively. Wound infection and pneumothorax were the most common serious AEs causally related to surgery with osimertinib plus chemotherapy (both reported in two patients); meanwhile,

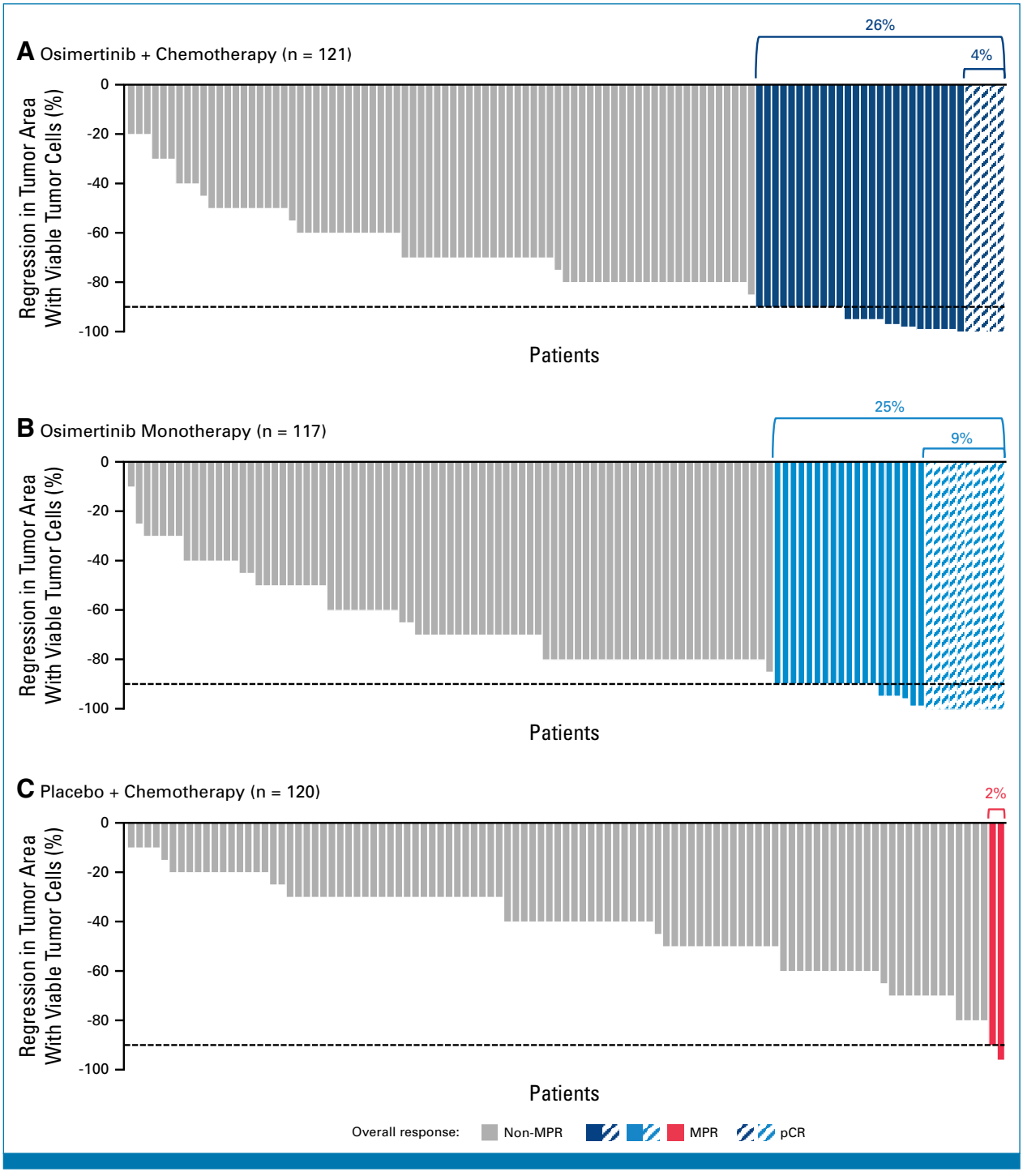

FIG 3. Depth of pathologic response, assessed by blinded central pathology review. Depth of pathologic regression in the primary tumor is summarized on the basis of patients who were evaluable per blinded central pathology review (n = 109 in the osimertinib plus chemotherapy group; n = 110 in the osimertinib monotherapy group; and n = 105 in the placebo plus chemotherapy group) and assessed using recommendations from the International Association for the Study of Lung Cancer (2020). The reported MPR and pCR rates are based on the full analysis set with patients who were not evaluable per blinded central pathology review classified as not having an MPR or pCR. The waterfall plots show the percentage of regression in tumor area with viable cells (percentage of residual viable tumor minus 100%) for each evaluable patient in the osimertinib plus chemotherapy group (panel A), osimertinib monotherapy group (panel B), and placebo plus chemotherapy group (panel C). Gray indicates patients classified as not having an MPR, solid and hashed indicates patients with MPR, and hashed indicates patients with pCR. Patients had to have an R0 result to be classified as responders. MPR was defined as ≤10% residual viable tumor cells in the lung primary tumor at resection (dotted line at −90% denotes the MPR cut-off). pCR was defined as no residual viable tumor in surgical specimens including primary tumors and lymph nodes. MPR, major pathologic response; pCR, pathologic complete response; R0, no evidence of tumor at surgical margin.

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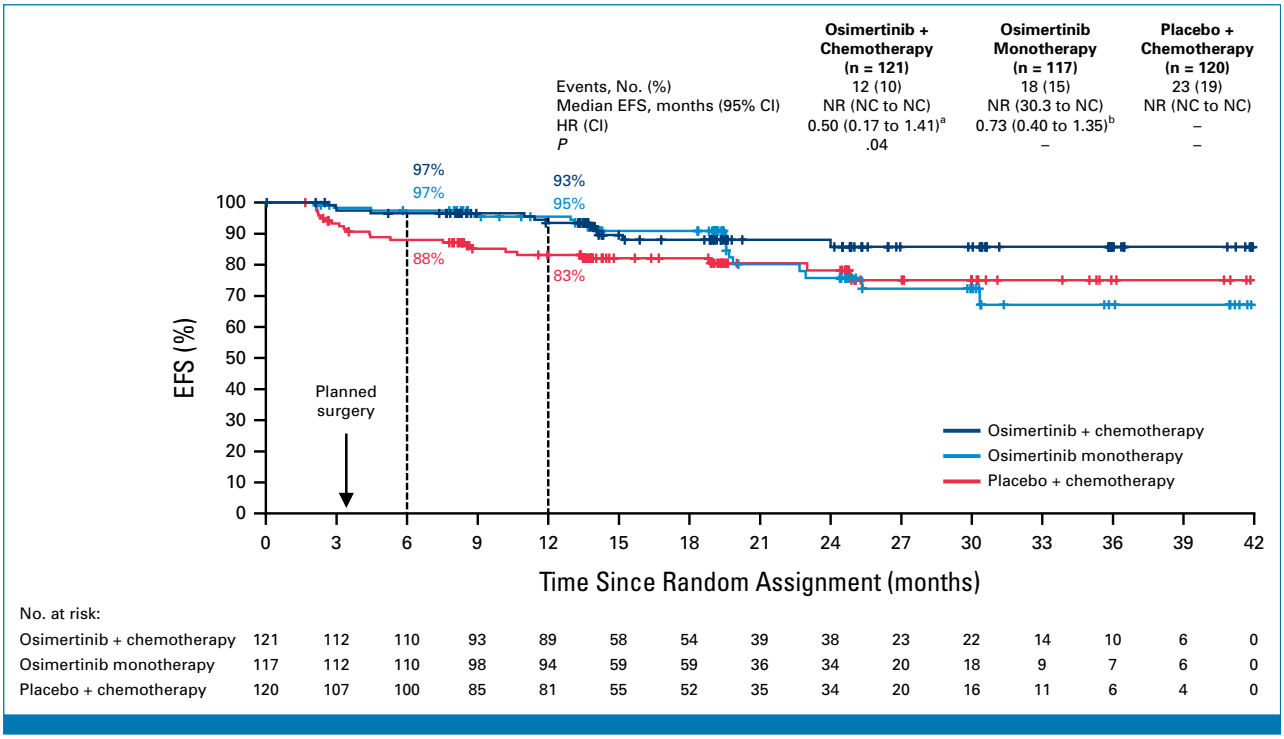

FIG 4. EFS, according to investigator assessment. The figure shows Kaplan-Meier estimates of EFS among patients in the full analysis set. EFS was measured from the time of random assignment. Tick marks indicate censored data, and the vertical lines indicate landmark analyses of EFS at 6 and 12 months after random assignment. An event was defined as the first of the following: documented PD that precluded surgery or prevented completion of definitive surgery; disease recurrence or a new lesion, local or distant, after surgery (a new primary malignancy, confirmed by pathology if clinically feasible, was not considered to be an EFS event); for patients who did not undergo surgery for reasons other than PD, documented PD after the neoadjuvant period; discovery upon attempting surgery that the surgery could not be completed because of PD; or death due to any cause. In the interim analysis of EFS, the median duration of follow-up for EFS in censored patients was 15.9 (range, <0.1 to 41.9), 18.3 (range, 2.2-41.9), and 18.8 (range, 1.7-41.8) months for the osimertinib plus chemotherapy, osimertinib monotherapy, and placebo plus chemotherapy groups, respectively. [a]A 99.8% CI for the HR is presented for the comparison of osimertinib plus chemotherapy versus placebo plus chemotherapy; as a statistically significant improvement was not reached for this comparison (a $P < .002$ was required to declare statistical significance), the treatment difference in EFS between the osimertinib monotherapy group and placebo plus chemotherapy group was not formally tested in accordance with the multiple testing procedure. [b]A 95% CI for the HR is presented for the comparison of osimertinib monotherapy versus placebo plus chemotherapy. EFS, event-free survival; HR, hazard ratio; NC, not calculable; NR, not reached; PD, progressive disease.

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pulmonary embolism was the most common event with osimertinib monotherapy (reported in two patients) and pneumonia was the most common event with placebo plus chemotherapy (reported in two patients). No patients died within 30 days after surgery. One patient in the osimertinib monotherapy group died within 90 days after surgery (PD and non–treatment-emergent sepsis were the causes of death).

DISCUSSION

In patients with resectable, *EGFR*-mutated, stage II-IIIB NSCLC, neoadjuvant osimertinib with or without chemotherapy was associated with statistically significant improvement in the proportion of patients who had an MPR versus placebo plus chemotherapy. In addition, over half of patients with baseline N2 disease were downstaged at surgery with the osimertinib-containing regimens compared with 21% of patients with placebo plus chemotherapy. Together, these pathologic findings demonstrate the robust antitumor efficacy of neoadjuvant osimertinib. Previous studies have demonstrated strong correlation of MPR and nodal response with survival outcomes, supporting their role as surrogate end points.[25-28] Rates of MPR and nodal downstaging with placebo plus chemotherapy were low, indicating that neoadjuvant chemotherapy alone is an inadequate standard of care for *EGFR*-mutated NSCLC.

Neoadjuvant osimertinib, with or without chemotherapy, did not have a detrimental impact on the feasibility or outcomes of surgery, and no patients died within 30 days after surgery. Over 90% of patients underwent surgery with both osimertinib-containing regimens, with similar rates reported in recent single-arm studies of neoadjuvant osimertinib[29,30]; acknowledging the limitations of cross-trial comparisons, this is higher than the rates observed with

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TABLE 2. Most Common AEs of Any Cause, Neoadjuvant Period

	Osimertinib + Chemotherapy (n = 119), No. of Patients (%)			Osimertinib Monotherapy (n = 117), No. of Patients (%)			Placebo + Chemotherapy (n = 120), No. of Patients (%)		
Event[a]	Any Grade	Maximum Grade 2	Maximum Grade ≥3	Any Grade	Maximum Grade 2	Maximum Grade ≥3	Any Grade	Maximum Grade 2	Maximum Grade ≥3
Any	110 (92)	49 (41)	43 (36)	104 (89)	52 (44)	15 (13)	111 (93)	52 (43)	40 (33)
Nausea	33 (28)	7 (6)	1 (1)	8 (7)	0	0	30 (25)	13 (11)	3 (3)
Constipation	32 (27)	7 (6)	1 (1)	17 (15)	6 (5)	0	41 (34)	10 (8)	0
Neutrophil count decreased	30 (25)	14 (12)	13 (11)	2 (2)	0	0	22 (18)	12 (10)	7 (6)
Diarrhea	29 (24)	7 (6)	1 (1)	31 (26)	5 (4)	3 (3)	12 (10)	3 (3)	0
Rash	28 (24)	5 (4)	1 (1)	15 (13)	3 (3)	0	9 (8)	7 (6)	0
Decreased appetite	25 (21)	5 (4)	1 (1)	7 (6)	1 (1)	0	22 (18)	6 (5)	0
Platelet count decreased	23 (19)	8 (7)	10 (8)	5 (4)	4 (3)	0	3 (3)	1 (1)	0
Anemia	22 (18)	17 (14)	1 (1)	6 (5)	0	1 (1)	23 (19)	9 (8)	6 (5)
Stomatitis	22 (18)	4 (3)	0	10 (9)	3 (3)	1 (1)	12 (10)	1 (1)	0
WBC count decreased	15 (13)	9 (8)	1 (1)	1 (1)	1 (1)	0	8 (7)	4 (3)	1 (1)
Cough	13 (11)	6 (5)	0	16 (14)	7 (6)	0	19 (16)	7 (6)	0
Vomiting	13 (11)	3 (3)	1 (1)	1 (1)	0	0	15 (13)	10 (8)	0
Pyrexia	13 (11)	4 (3)	0	3 (3)	0	0	5 (4)	1 (1)	0
Fatigue	11 (9)	1 (1)	0	5 (4)	1 (1)	0	18 (15)	7 (6)	1 (1)
Paronychia	8 (7)	2 (2)	0	14 (12)	3 (3)	0	1 (1)	0	0
Procedural pain	6 (5)	3 (3)	0	11 (9)	7 (6)	0	14 (12)	7 (6)	0
Dermatitis acneiform	5 (4)	1 (1)	0	15 (13)	3 (3)	0	3 (3)	0	0

NOTE. Safety data are summarized on the basis of the safety analysis set. The neoadjuvant analysis period is the time from the first dose to the minimum of the date of the last dose in the neoadjuvant period plus 28 days, the next treatment start date minus 1, the date of withdrawal of consent, or the date of death.

Abbreviation: AE, adverse event.

[a]Included are AEs reported at any grade in ≥10% of patients in any treatment group; the AE preferred terms are listed in a descending order of frequency for the osimertinib plus chemotherapy group.

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neoadjuvant chemotherapy and chemoimmunotherapy in recent phase III studies of patients with resectable NSCLC (range, 73%-83%).[18-21] Rates of R0 resection, a strong prognostic indicator of improved survival outcomes,[31] were also above 90% with both osimertinib-containing regimens.

With 15% maturity, EFS outcomes favored the osimertinib-containing regimens versus placebo plus chemotherapy, although the findings were not statistically significant as per the prespecified statistical significance level. Early separation of the Kaplan-Meier curves for the osimertinib-containing regimens versus placebo plus chemotherapy ahead of the anticipated timing of planned surgery could be attributed, at least partially, to the lower frequency of PD precluding definitive surgery observed with these regimens. The proportion of patients who did not undergo surgery owing to PD with the osimertinib-containing regimens (1% for both) was also low compared with corresponding findings with neoadjuvant chemotherapy and chemoimmunotherapy in recent phase III studies of patients with resectable NSCLC (range, 2%-15%).[18-21] While NeoADAURA was designed to evaluate outcomes with neoadjuvant osimertinib, adjuvant osimertinib had already demonstrated robust and statistically significant improvements in survival outcomes in the phase III ADAURA study.[8] Consequently, adjuvant osimertinib was offered to all eligible patients who completed surgery in NeoADAURA and over 90% of patients who completed surgery had started adjuvant osimertinib by the time of data cutoff in all three treatment groups. This essentially makes NeoADAURA a perioperative study, where patients were randomly assigned to one of three different neoadjuvant treatments before surgery but were all given the opportunity to benefit from adjuvant osimertinib after completing surgery. Considering the robust DFS benefit associated with adjuvant osimertinib,[8] the high uptake of this treatment is expected to affect treatment outcomes at the protocol-specified final analysis of EFS. Nevertheless, the low frequency of PD precluding definitive surgery and favorable pathologic outcomes observed with the osimertinib-containing regimens compared with placebo plus chemotherapy, along with high rates of surgery and R0 resection, highlight the utility of neoadjuvant osimertinib as part of a broader perioperative treatment strategy. Osimertinib-containing regimens could enable a greater number of patients to proceed through neoadjuvant treatment and on to surgery with favorable outcomes than chemotherapy alone.

The safety profile of the osimertinib regimens was consistent with the known profile of osimertinib used alone and in combination with chemotherapy.[8,32-34] As expected, hematologic toxicities were more common with the chemotherapy-containing regimens than osimertinib monotherapy. Reassuringly, the overall incidence of high-grade AEs, serious AEs, and serious AEs causally related to surgery with chemotherapy was similar regardless of osimertinib use. As expected, osimertinib monotherapy was associated with a lower incidence of high-grade and serious AEs compared with the chemotherapy-containing regimens.

Single-arm studies have previously demonstrated favorable tumor responses, high rates of surgery, and a feasible safety profile with neoadjuvant osimertinib,[29,30,35] as well as first-generation and second-generation EGFR-TKIs.[36] For example, 24% of patients had an MPR with neoadjuvant osimertinib in the phase II NORA study, and all 25 patients enrolled in the study underwent surgery and had R0 resection.[30] NeoADAURA provides the first randomized, phase III data supporting the benefit of this approach in *EGFR*-mutated NSCLC, demonstrating that a high proportion of patients are able to undergo surgery and that the proportion of patients who achieve an MPR is significantly improved when neoadjuvant osimertinib is used alone or with chemotherapy. To our knowledge, NeoADAURA is the first randomized, phase III study to demonstrate the benefit of any targeted therapy in the neoadjuvant NSCLC setting, raising questions regarding the possible use of other targeted therapies to provide more tailored options for neoadjuvant treatment. Ongoing analyses from NeoADAURA, including analyses exploring the relationship of minimal residual disease with efficacy end points, may provide insight into predictive biomarkers for improved outcomes with neoadjuvant osimertinib.

A limitation of NeoADAURA is the use of MPR as the primary end point. Although OS is the traditional gold-standard end point in oncology trials, substitutive surrogate end points are considered in early-stage disease settings, or biomarker-selected populations, owing to the need for large sample sizes and protracted study durations.[26] As the population targeted for recruitment in NeoADAURA is small, conducting a large enough study to allow sufficient power for assessment of traditional end points was not feasible. MPR was selected as the primary end point to allow for a small study size and earlier assessment of treatment effect. pCR was a secondary end point as the proportion of patients with a pCR was expected to be too low to allow a sufficiently powered analysis.[17] MPR strongly correlates with improved survival outcomes in studies of neoadjuvant therapy,[25,27,28] including studies of EGFR-TKIs.[29,37,38] In a recent report from a single-arm phase II trial of neoadjuvant gefitinib, MPR was associated with significantly prolonged DFS and OS.[38] NeoADAURA builds on this body of evidence, with all but one EFS event across all three treatment groups being reported in patients who did not have an MPR.

Findings from NeoADAURA demonstrate statistically significant improvement in the proportion of patients who had an MPR with neoadjuvant osimertinib, with or without chemotherapy, compared with chemotherapy alone. Neoadjuvant osimertinib with or without chemotherapy should be considered when planning treatment for patients with resectable, *EGFR*-mutated, stage II-IIIB NSCLC.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/JCO-25-00883. Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://www.astrazenecaclinicaltrials.com/our-transparency-commitments/. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. The AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Neoadjuvant Osimertinib for Resectable *EGFR*-Mutated Non–Small Cell Lung Cancer

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