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Neoadjuvant Osimertinib for the Treatment of Stage I-IIIA Epidermal Growth Factor Receptor–Mutated Non–Small Cell Lung Cancer: A Phase II Multicenter Study

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ABSTRACT

PURPOSE To assess the safety and efficacy of the third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor osimertinib as neoadjuvant therapy in patients with surgically resectable stage I-IIIA *EGFR*-mutated non–small cell lung cancer (NSCLC).

PATIENTS AND METHODS This was a multi-institutional phase II trial of neoadjuvant osimertinib for patients with surgically resectable stage I-IIIA (American Joint Committee on Cancer [AJCC] V7) *EGFR*-mutated (L858R or exon 19 deletion) NSCLC (ClinicalTrials.gov identifier: NCT03433469). Patients received osimertinib 80 mg orally once daily for up to two 28-day cycles before surgical resection. The primary end point was major pathological response (MPR) rate. Secondary safety and efficacy end points were also assessed. Exploratory end points included pretreatment and post-treatment tumor mutation profiling.

RESULTS A total of 27 patients were enrolled and treated with neoadjuvant osimertinib for a median 56 days before surgical resection. Twenty-four (89%) patients underwent subsequent surgery; three (11%) patients were converted to definitive chemoradiotherapy. The MPR rate was 14.8% (95% CI, 4.2 to 33.7). No pathological complete responses were observed. The ORR was 52%, and the median DFS was 40.9 months. One treatment-related serious adverse event (AE) occurred (3.7%). No patients were unable to undergo surgical resection or had surgery delayed because of an AE. The most common co-occurring tumor genomic alterations were in *TP53* (42%) and *RBM10* (21%).

CONCLUSION Treatment with neoadjuvant osimertinib in surgically resectable (stage IA-IIIA, AJCC V7) *EGFR*-mutated NSCLC did not meet its primary end point for MPR rate. However, neoadjuvant osimertinib did not lead to unanticipated AEs, surgical delays, nor result in a significant unresectability rate.

ACCOMPANYING CONTENT

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Data Sharing Statement

Protocol

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INTRODUCTION

The epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) osimertinib is the current standard first-line therapy for patients with metastatic non–small cell lung cancer (NSCLC) harboring an *EGFR* exon 21 p.L858R mutation or exon 19 deletion on the basis of the FLAURA trial showing superiority of osimertinib compared with earlier generation EGFR TKIs both in terms of progression-free survival (PFS) and overall survival (OS).[1,2] More recently, the ADUARA trial demonstrated that adjuvant treatment with osimertinib for up to 3 years after surgical resection improved both disease-free survival (DFS) and OS for patients with stage IB-IIIA EGFR-mutated (p.L858R or exon 19 deletion) NSCLC when compared with placebo.[3] Whether treatment with osimertinib before surgery (neoadjuvant) in patients with early-stage, surgically resectable *EGFR*-mutated NSCLC is safe or effective is unknown.

The potential benefits of neoadjuvant therapy for the treatment of NSCLC are (1) early exposure to systemic therapy to treat micrometastatic disease and (2) potential for shorter duration of treatment compared with adjuvant therapy.[4] Potential risks of neoadjuvant therapy include (1)

CONTEXT

Key Objective

To determine the major pathological response (MPR) rate of neoadjuvant osimertinib for stage IA-IIIA epidermal growth factor receptor-mutated non–small cell lung cancer.

Knowledge Generated

Treatment with neoadjuvant osimertinib resulted in an MPR rate of approximately 15%, which did not meet the primary end point of the study. Neoadjuvant osimertinib did not result in unexpected delays in surgery or significant toxicity in the perioperative setting. The unresectability rate after neoadjuvant osimertinib was 11%.

Relevance (*T.E. Stinchcombe*)

The pathological response data indicate single agent osimertinib has insufficient activity as preoperative therapy. Trials of combination therapy are ongoing.*

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

treatment-related adverse events (AEs) that delay surgery or lead to surgical ineligibility and (2) tumor progression during the neoadjuvant treatment window leading to tumor unresectability. Neoadjuvant platinum-based chemotherapy given before surgical resection for patients with resectable NSCLC had been an acceptable alternative to adjuvant chemotherapy.[5] Recent trials have shown that the addition of anti-PD1/PDL1 immune checkpoint inhibitors (ICIs) to neoadjuvant chemotherapy improves pathological complete response (pCR) and major pathological response (MPR) rates and event-free survival (EFS) compared with chemotherapy alone.[6,7] However, multiple studies have shown lack of benefit to ICIs for the treatment of *EGFR*mt NSCLC,[8-10] and exposure to an ICI may increase the risk of serious immune-related adverse events (iRAEs) on subsequent treatment with osimertinib.[11] Therefore, neoadjuvant platinum-based chemotherapy remains the only standard option for the treatment of EGFRmt NSCLC before surgery. Given the benefit of EGFR TKI therapy compared with chemotherapy in the metastatic setting,[12,13] neoadjuvant EGFR TKIs including erlotinib and osimertinib are being evaluated[14,15]. While these studies suggest activity of neoadjuvant EGFR TKI therapy, the relevance of ORR as the primary end point in these neoadjuvant trials is unclear,[4] as is the generalizability of these findings to the US population of patients with *EGFR*mt NSCLC.

PATIENTS AND METHODS

Study Design

This was a phase II, single-arm, open-label, multicenter study at three National Cancer Institute–designated Cancer Centers in the United States to evaluate the safety and efficacy of osimertinib administered orally daily to patients with stage I-IIIA (American Joint Committee on Cancer [AJCC] V7), *EGFR*mt (L858R or exon 19 deletion) NSCLC who were planning to undergo surgical resection of their cancer. *EGFR* mutations were identified by local Clinical Laboratory Improvement Amendments–approved molecular testing on tumor biopsies as described in Appendix 1 (online only). All eligible patients were assigned to receive osimertinib 80 mg orally once daily for up to two 28-day cycles before undergoing surgical resection of their lung cancer. Dose reduction to osimertinib 40 mg orally once daily was allowed at the discretion of the treating investigator. Patients were eligible to receive a second cycle of osimertinib treatment if they did not experience a ≥grade 3 AE during cycle 1 of treatment and if imaging after cycle 1 of treatment did not show progressive disease (PD) by RECIST 1.1 criteria. Surgical resection was required to occur within 14 days after the completion of cycle 2. Patients were instructed to continue osimertinib treatment up until 3-7 days before surgery. Adjuvant therapy was administered when indicated per National Comprehensive Cancer Network guidelines[16] at the discretion of the treating physician in discussion with the patient. Adjuvant osimertinib was not US Food and Drug Administration–approved until patient 14 enrolled on the study and was not a requirement of the study. The study was approved by the research ethics institutional review boards at each study site and was conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent.

Participants

Detailed inclusion and exclusion criteria are included in Appendix 1. Major inclusion criteria included age ≥18 years, histopathologic diagnosis of NSCLC on a tissue biopsy performed within 90 days of enrollment, documented *EGFR* mutation as described above, staging positron emission tomography-computed tomography (PET-CT), and brain magnetic resonance imaging (MRI) within the last 60 days showing stage IA-IIIA (AJCC v7) NSCLC (mediastinal staging

by endobronchial ultrasound or mediastinoscopy allowed but not required), primary tumor ≥1 cm in its longest diameter on CT scan, and documentation that the patient is a candidate for surgical resection of their lung cancer by an American Board of Thoracic Surgery certified surgeon. Major exclusion criteria included history of interstitial lung disease (ILD), prior treatment with EGFR-targeted therapy, and active second malignancy.

Outcomes

The primary end point was MPR rate defined as ≤10% viable tumor present histologically in the resected tumor specimen after neoadjuvant treatment.[17] Details of preplanned secondary and exploratory endpoints and post hoc analyses are described in Appendix 1.

Assessments

Surgical resectability assessment was performed by multidisciplinary tumor board review, which included a board-certified thoracic surgeon, radiologist, radiation oncologist, pathologist, and medical oncologist. Pretreatment research biopsies of the primary tumor were performed within 30 days before C1D1 when considered within acceptable safety risk by the treating investigator in consultation with the biopsy performing radiologist. CT scans of the chest, abdomen, and pelvis and transthoracic echocardiograms and electrocardiograms were performed within 30 days before C1D1 and were repeated at cycle 1 day 28 (C1D28) and cycle 2 day 28 (C2D28) ±3 days. Laboratory tests were performed as detailed in Appendix 1. MPR, pCR, and percent pathological regression were determined by central review according to IASLC guidelines.[17] Other pathological response assessments were performed by local pathologist. RECIST 1.1 response was determined by investigator assessment. Disease-free survival (DFS) was defined as the numbers of days from surgical resection to documented radiographic recurrence or death due to any cause. EFS was defined as the numbers of days from first dose of study drug to documented radiographic progression/recurrence, decision to forgo surgery, or death due to any cause.

Statistical Methods

The study sample size of 27 patients was selected to provide at least 85% power to detect a 30% increase in the observed proportion of treated patients achieving the primary MPR outcome compared with a null value of 20% as significant at the 5% level, using the exact binomial test. MPR was assessed in all patients who received at least one dose of osimertinib. Those who received one dose and became ineligible for surgery were deemed not to have achieved an MPR. Analyses for efficacy and safety outcomes were based on the intention-to-treat (ITT) population that included all patients who received at least one dose of osimertinib. An interim safety analysis was performed after enrollment of nine patients. Conversion to unresectable status in two or more of the first nine patients was set as the threshold for early study discontinuation. Additional details regarding statistical methods are included in Appendix 1.

RESULTS

Patients

Fifty-four patients were screened for eligibility at three National Cancer Institute–designated Comprehensive Cancer Centers in the United States between July 1, 2018, and October 4, 2022 (Fig 1). Twenty-seven patients were found to be ineligible for the reasons indicated (Fig 1). Twenty-seven eligible patients were enrolled in the study and received at least one cycle of neoadjuvant osimertinib therapy and were evaluable as the ITT population. Eight patients received one cycle and 19 patients received two cycles of neoadjuvant osimertinib. Demographics and clinical characteristics of enrolled/treated patients are listed in Table 1. The majority of patients were female (81.5%), never smoked (63%), and were predominantly White (55.6%) or Asian (40.7%). All pretreatment biopsies (n = 27) were adenocarcinomas with *EGFR* p.L858R mutations identified in 59.3% (n = 16) of cases and *EGFR* exon 19 deletions in 40.7% (n = 11). Eight patients (29.6%) had stage IA or IB disease, 19 patients (70.4%) had stage IIA-IIIA disease. Twenty-four patients underwent surgical resection, one patient (3.7%) was unable to undergo surgical resection because of disease progression, two patients (7.4%) elected not to have surgery because of requirement of pneumonectomy. Eight patients (33.3%) received adjuvant platinum (cisplatin or carboplatin) + pemetrexed chemotherapy. Six patients (25%) received adjuvant osimertinib (3 of whom also received adjuvant chemotherapy). Two patients (8.3%) received postoperative radiation therapy (PORT). The median DFS follow-up was 17.5 months. Nine patients (37.5%) who underwent surgical resection have experienced disease recurrence. Fifteen patients (62.5%) remain disease-free in follow-up. Three patients (11.1%) who enrolled in the study have died, with a median survival follow-up of 25.8 months.

Efficacy

The primary end point of the study was MPR rate in patients who received at least one dose of neoadjuvant osimertinib (ITT population). The ITT MPR rate was 14.8% (95% CI, 4.2 to 33.7), which did not meet the primary end point of 50% that the study was powered to detect. The MPR was 16.7% (95% CI, 4.7 to 37.4) in patients who underwent surgical resection (Fig 2). Secondary and exploratory pathological end points are presented in Table 2. The rate of conversion to inoperable status was 11.1% (95% CI, 2.4 to 29.2). The pathological complete response rate (pCR) was 0% (95% CI, 0.0 to 12.8), the rate of <50% viable tumor was 54.2% (95% CI, 32.8 to 74.4), the rate of positive surgical margins was 4.2% (95% CI, 0.11 to 21.1), the rate of pathological upstaging was 16.7% (95% CI, 4.7 to 37.4), and the rate of LVI was 16.7% (95% CI, 4.7 to 37.4).

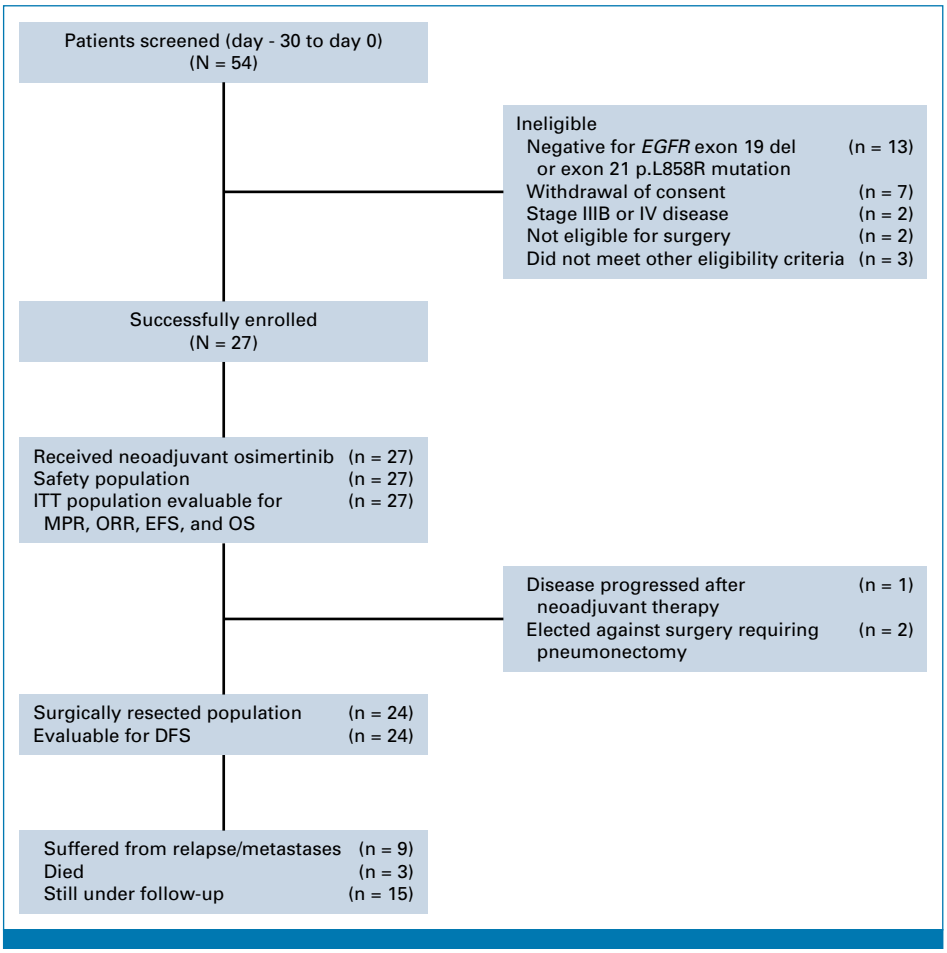

FIG 1. CONSORT diagram. DFS, disease-free survival; EFS, event-free survival; ITT, intention-to-treat; MPR, major pathological response; ORR, objective response rate; OS, overall survival.

Radiographic secondary efficacy end points included radiographic ORR: 51.9% (95% CI, 31.9 to 71.3) and median depth of response: −32% (IQR, −12 to −40) with one patient experiencing disease progression (Appendix Fig A1). The median DFS in the resected population was 40.9 months (95% CI, 26.0 to not reached [NR]; Fig 3A), and the median OS has not been reached (Fig 3B). Five-year DFS and OS data are immature.

Safety

The most common treatment-emergent AEs were consistent with the known toxicity of osimertinib (Table 3). The rate of treatment-related grade 3 or 4 AEs was 11.1% (Table 3). Eight patients (29.6%) experienced a dose hold and three patients (11.1%) a dose reduction. Two patients (7.4%) discontinued therapy because of an AE. Patient 29 discontinued treatment after two cycles during the presurgical window because of grade 2 stomatitis. Patient 44 discontinued treatment after one cycle because of grade 2 neutropenia. No patients experienced a delay in surgery or became ineligible for surgery because of an AE. No significant intraoperative complications were reported. During the postoperative monitoring period, which including the day of surgery until 6 weeks after surgery, the most common AEs were atrial fibrillation (25%), dyspnea (20.8%), and chest pain (16.7%; Appendix Table A1). One patient experienced a grade 3 pulmonary embolism with grade 3 dyspnea that was deemed to be a serious AE. All AEs occurring in at least 5% of patients are reported in Appendix Table A2.

Tumor Genomic Analysis

Clinically validated targeted next-generation DNA sequencing (NGS) of 479 cancer-related genes by UCSF500[18] or 324 cancer-related genes by Foundation One CDx were evaluable from 15 of 27 pretreatment biopsies (Appendix Fig A3A), and UCSF500 was evaluable from 17 of 24 post-treatment resected tumors (Appendix Fig A3B). Ten patients had both pretreatment and post-treatment tumors that were evaluable by UCSF500 (Appendix Fig A3C). In total, 19 of 24 patients who underwent surgical resection had NGS data evaluable from either a pretreatment or post-treatment tumor (Fig 2). The most common pretreatment and post-treatment co-occurring alterations were in *TP53* (47% and 35%, respectively) and *RBM10* (20% and 18%, respectively;

Table 1. Patient Clinical Characteristics and Demographics (intention-to-treat population)

Characteristic	N = 27
Sex, No. (%)	
Female	22 (81.5)
Male	5 (18.5)
Race or ethnicity, No. (%)	
White	15 (55.6)
Asian	11 (40.7)
Hispanic	1 (3.7)
Age, years, median (range)	68 (39-85)
Smoking status, No. (%)	
Never	17 (63.0)
Former	10 (37.0)
Current	0 (0)
ECOG performance status, No. (%)	
0	11 (40.7)
1	16 (59.3)
Preoperative staging, No. (%)	
EBUS	11 (40.7)
PET/CT	16 (59.3)
T stage (AJCC V7), No. (%)	
1	8 (29.6)
2	8 (29.6)
3	9 (33.3)
4	2 (7.4)
N stage (AJCC V7), No. (%)	
0	17 (63.0)
1	3 (11.1)
2	6 (22.2)
X	1 (3.7)
Overall clinical stage (AJCC V7), No. (%)	
IA	5 (18.5)
IB	3 (11.1)
IIA	3 (11.1)
IIB	7 (25.9)
IIIA	9 (33.3)
Pretreatment histology, No. (%)	
Adenocarcinoma	27 (100)
Nonadenocarcinoma	0 (0)
EGFR-activating mutation, No. (%)	
Exon 19 deletion	11 (40.7)
Exon 21 p.L858R	16 (59.3)

Abbreviations: AJCC; American Joint Committee on Cancer; CT, computed tomography; EBUS, endobronchial ultrasound; ECOG, Eastern cooperative oncology group; *EGFR*, epidermal growth factor receptor; PET, positron emission tomography; T, tumor; N, node; X, could not be evaluated.

Appendix Fig A3). *TP53*, *MDM2*, and *RBM10* mutations were detectable in both paired pretreatment and post-osimertinib tumors (Appendix Fig A3C).

Exploratory Studies

There were no significant difference in DFS (Appendix Fig A2A) or OS (Appendix Fig A2B) between patients whose tumors demonstrated an MPR after osimertinib treatment compared with those who did not achieve an MPR, although the small number of patients who achieved an MPR make the significance of these findings difficult to interpret. Patients whose tumors showed pathological regression of >50% after neoadjuvant osimertinib treatment showed improvements in DFS (Appendix Fig A2C) and OS (Appendix Fig A2C). When comparing hazard ratios estimated with and without adjusting for receipt of adjuvant therapy, no clear differences were observed (see Appendix 1 for details).

The median event-free survival (EFS) in the ITT population was 34.7 months (95% CI, 27.0 to NR; Appendix Fig A3A), with median OS not reached (Appendix Fig A3B). Differences in EFS or OS were not observed based on MPR status (Appendix Figs A3A and A3D); however, patients whose tumor showed pathological regression of >50% showed improvements in EFS and OS in the ITT population (Appendix Figs A3E and A3F). No patient or tumor characteristics correlated with MPR rate (Appendix Table A3), although the limited number of patients who achieved an MPR makes this difficult to interpret. The presence of co-occurring *RBM10* mutations correlated with lack of pathological regression >50% (Appendix Table A4). Co-occurring *TP53* mutations correlated with worse DFS and OS (Appendix Table A5).

DISCUSSION

We found that the MPR rate after 1-2 cycles of osimertinib treatment in 27 patients with surgically resectable stage IA-IIIA EGFRmt NSCLC was 14.8% in an ITT analysis. This did not meet the primary end point of an MPR rate of 50% that the study was powered to detect. This was a negative study. Overall, the MPR rate to neoadjuvant osimertinib was lower than expected. The reasons for this are likely due to multiple factors. Differences in MPR or pathological response were not observed on the basis of tumor stage, nodal status, *EGFR* mutation subtype, or number of cycles of therapy. While we cannot rule out that extending osimertinib treatment beyond two cycles may have improved the MPR rate, or that a larger trial may show a higher MPR rate, these data suggest that tumor intrinsic biological factors may be driving the relatively low pathological response to osimertinib treatment.

We investigated the possible impact of co-occurring tumor genomic mutations in limiting the pathological response to neoadjuvant osimertinib treatment. We found that the most frequently co-occurring tumor genomic mutations were in *TP53* and *RBM10*. Co-occurring *TP53* mutations were associated with decreased DFS and OS, consistent with the known deleterious effects of co-occurring *TP53* mutations in metastatic *EGFR*mt NSCLC.[20] In patients whose tumors harbored a concurrent *RBM10* mutation, no MPR or pathological

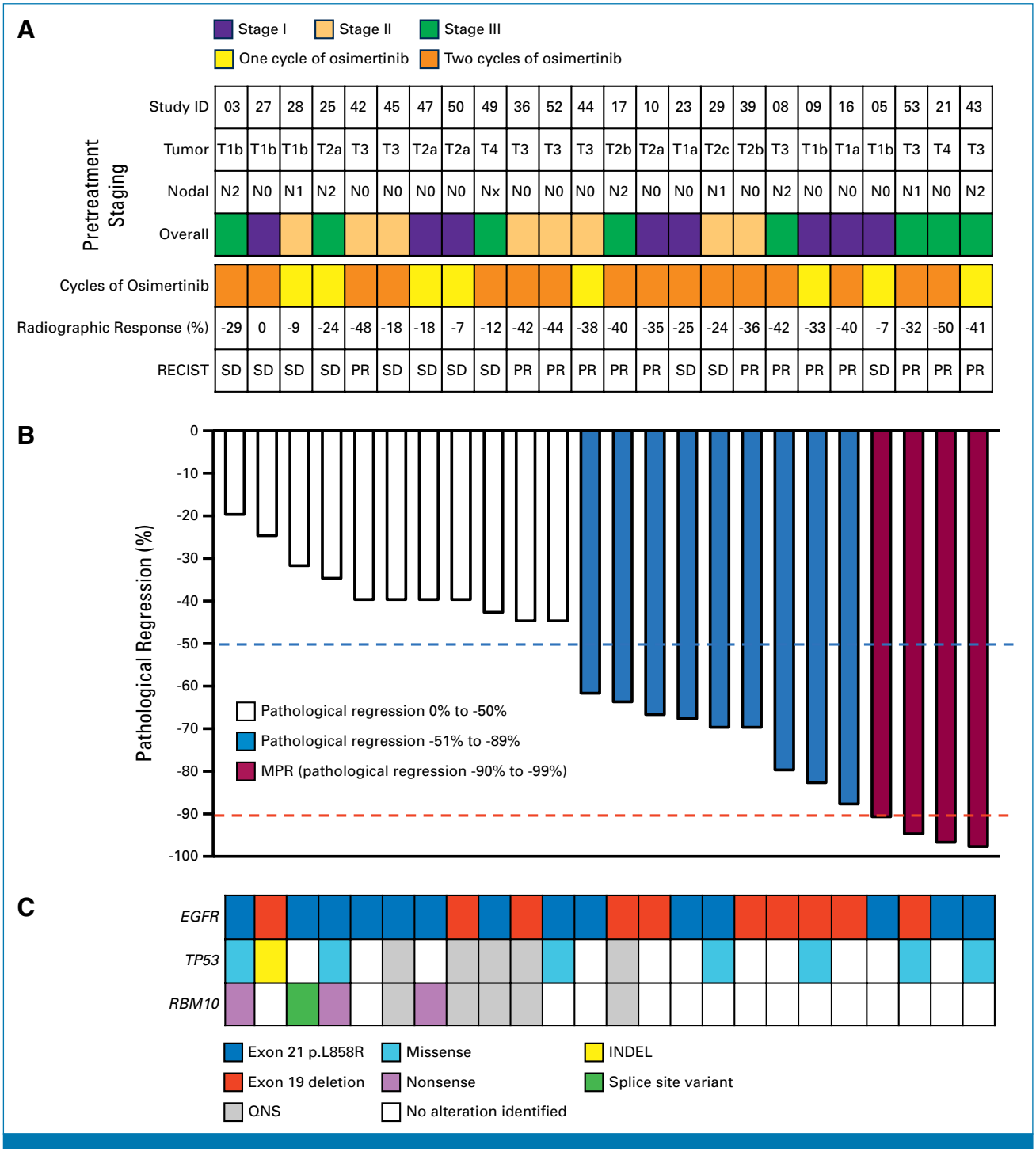

FIG 2. Radiographic and pathologic response to treatment in patients who underwent surgical resection. (A) Patient stage (AJCC v7) before osimertinib treatment is indicated, as are the number of cycles of osimertinib received before surgery. Depth of best radiographic response and RECIST response (unconfirmed) are indicated. (B) Waterfall plot showing % pathological regression after osimertinib treatment. Tumors that achieved a MPR or pathological regression > 50% are indicated. (C) Pretreatment *EGFR* mutation subtypes are indicated by blue and red boxes. Detection and classification of *TP53* or *RBM10* mutations in either the pretreatment biopsy or resected tumor specimen by next-generation DNA sequencing is indicated. AJCC, American Joint Committee on Cancer; *EGFR*, epidermal growth factor receptor; INDEL, insertion or deletion; MPR, major pathological response; PR, partial response; SD, stable disease; QNS, quantity not sufficient for next-generation sequencing.

Table 2. Postoperative Pathological Evaluation

Variable	No. (%)
Surgery	24 (88.9)
R0	23 (85.2)
R1	1 (3.7)
Not resected	3 (11.1)
Pathological response in resected tumors	
pCR (0% viable tumor)	0 (0)
MPR (≤10% viable tumor)	4 (16.7)
11%-49% viable tumor	9 (37.5)
<50% viable tumor	13 (54.2)
≥50% residual viable tumor	11 (45.8)
Pathological upstaging	4 (16.7)
Tumor upstaging	3 (12.5)
T1 to ypT2	2 (40)
T2 to ypT3	1 (25)
Lymph node upstaging	2 (8.3)
N0 to ypN1	1 (6.7)
N1 to ypN2	1 (33.3)
Pathological downstaging	13 (54.2)
Tumor downstaging	12 (50)
T4 to ≤ ypT3	2 (100)
T3 to ≤ ypT2	7 (87.5)
T2 to ypT1	2 (28.5)
T1b to ypT1a	1 (20)
Lymph node downstaging	4 (44.4)
N2 to ypN0	2 (22.2)
N2 to ypN1	1 (11.1)
N1 to ypN0	1 (11.1)
Type of resection	
Sublobectomy	1 (4.2)
Lobectomy	19 (79.1)
Bilobectomy	3 (12.5)
Pneumonectomy	1 (4.2)
Postoperative histologic classification	
Adenocarcinoma, acinar predominant	13 (54.2)
Adenocarcinoma, lepidic predominant	6 (25)
Adenocarcinoma, papillary predominant	1 (4.2)
Adenocarcinoma, poorly differentiated	1 (4.2)
Adenocarcinoma, NOS	2 (8.3)
Pleomorphic Carcinoma	1 (4.2)
VPI	6 (25)
LVI	4 (16.7)

Abbreviations: LVI, lymphovascular invasion; MPR, major pathological response; N, node; NOS, not otherwise specified; R0, microscopically negative tumor resection margin; R1, microscopically positive tumor resection margin; T, tumor; VPI, visceral pleural invasion; yp, post-treatment pathologic stage.

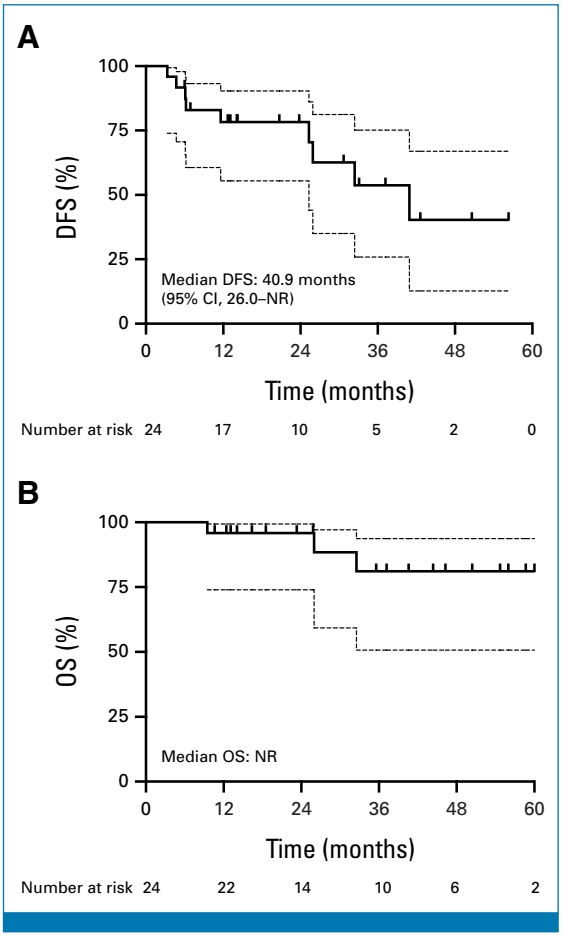

FIG 3. Postresection (A) DFS, n = 24 and (B) OS, n = 24. Kaplan-Meier curves with 95% CIs of DFS and OS for all patients who underwent surgical resection. (A) Median DFS with 95% CI indicated. (B) Median OS NR. DFS, disease-free survival; NR, not reached; OS, overall survival.

regression >50% were observed. We previously showed that *RBM10* loss-of-function (LOF) mutations result in decreased responsiveness to EGFR TKI treatment in preclinical models of EGFRmt NSCLC through upregulation of Bcl-xL.[23] While co-occurring *RBM10* LOF mutations may account for a portion of the poor pathological responses to osimertinib, they were identified in only 15% of the patients treated with neoadjuvant osimertinib in this trial, suggesting that other mechanisms likely also contribute to lack of pathological response.

We previously assessed transcriptional changes within tumor cells at residual disease (RD) after EGFR TKI treatment, which included a subset of samples obtained from patients enrolled in this neoadjuvant osimertinib clinical trial.[24] This analysis showed that at RD, tumor cells exhibit increased WNT/β-catenin activity.[24] We have also found evidence of upregulation of YAP and its downstream effectors at the RD state after osimertinib treatment.[25] Previous work has also identified upregulation of the NF-κB transcription factor RELA and subsequent transcriptional upregulation of *IL6* as a driver of EGFR TKI persistence,[26] while other studies have identified activation of the TPX2-

Table 3. Treatment-Emergent AEs

AE (incidence >5% or grade 3-4)	Grade 1-4, No. (%)	Grade 3-4, No. (%)	SAE, No. (%)
All	27 (100)	3 (11.1)	2 (7.4)
Diarrhea	14 (52.0)	0	0
Rash	11 (40.7)	0	0
Fatigue	8 (29.6)	0	0
Nausea	5 (18.5)	0	0
Dry skin	5 (18.5)	0	0
Cough	4 (14.8)	0	0
Dry mouth	4 (14.8)	0	0
Neutropenia	4 (14.8)	0	0
Stomatitis	4 (14.8)	1 (3.7)	0
Leukopenia	3 (11.1)	0	0
Thrombocytopenia	3 (11.1)	0	0
Abdominal pain	2 (7.4)	0	0
ALT elevation	2 (7.4)	0	0
AST elevation	2 (7.4)	0	0
Dry eyes	2 (7.4)	0	0
Dyspnea	2 (7.5)	0	0
Paronychia	2 (7.4)	0	0
Pruritis	2 (7.4)	0	0
Weakness	2 (7.4)	0	0
Pulmonary embolism	1 (3.7)	1 (3.7)	1 (3.7)
Atrial fibrillation	1 (3.7)	1 (3.7)	1 (3.7)

Abbreviations: AE, adverse event; SAE, serious adverse event.

Aurora Kinase A axis in the EGFR-TKI drug-tolerant persister state.[27] The tumor microenvironment (TME) may also play an important role in tumor cell survival in response to osimertinib treatment.[24] Ultimately, multiple tumor intrinsic mechanisms are likely involved in allowing *EGFR*mt tumor cells to survive osimertinib treatment, limiting major pathological response rate.

The results of this trial do not match the high MPR and pCR rates for neoadjuvant chemotherapy plus ICI observed in *EGFR*wt NSCLCs.[6,7] This suggests that activation of an immune response against NSCLC is able to achieve a higher degree of cytotoxic activity than TKI treatment is and that finding ways to induce an anticancer immune response in *EGFR*mt NSCLC may ultimately be critical to improving long-term DFS and OS.

While this trial did not meet its primary efficacy end point, a larger study will be needed to fully evaluate neoadjuvant osimertinib in early-stage *EGFR*mt NSCLC. Importantly, there were no safety concerns that arose from this study that would preclude further investigation of neoadjuvant osimertinib. Potential clinical benefit from neoadjuvant osimertinib was observed in a subset of patients that may warrant further investigation. Approximately 50% of patients achieved >50% pathological regression within their resected tumors after neoadjuvant osimertinib treatment which correlated with improved DFS, EFS, and OS compared with those who did not achieve >50% pathological regression. However, we cannot rule out that the receipt of adjuvant therapy in a subset of patients may have influenced survival outcomes. Ultimately, combination therapies may be needed to identify the optimal neoadjuvant treatment strategy for *EGFR*mt NSCLC. The FLAURA2 trial showed that adding platinum doublet chemotherapy to osimertinib led to significantly longer median PFS than osimertinib monotherapy as first-line treatment for patients with metastatic *EGFR*mt NSCLC (25.5 *v* 16.7 months, HR, 0.62, $P < .001$).[28] Whether the addition of platinum doublet chemotherapy to osimertinib in the neoadjuvant setting will improve MPR for patients with surgically resectable EGFRmt NSCLC is being tested in the phase III NeoADAURA trial.[29]

In conclusion, neoadjuvant osimertinib treatment did not meet its primary end point for MPR rate and did not demonstrate a significant improvement in MPR over what would be expected by chemotherapy alone. The major limitations of this trial include the small samples size, the lack of a chemotherapy control arm, and insufficient pretreatment and post-treatment tumor tissue available for comprehensive biomarker analyses. Future studies will aim to address these limitations.

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Neoadjuvant Osimertinib for the Treatment of Stage I-IIIA Epidermal Growth Factor Receptor–Mutated Non–Small Cell Lung Cancer: A Phase II Multicenter Study

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APPENDIX 1.

Details of Epidermal Growth Factor Receptor Testing

Epidermal growth factor receptor (*EGFR*) mutations were identified by one of the following assays performed in a Clinical Laboratory Improvement Amendments (CLIA)–approved laboratory: (1) next-generation sequencing, UCSF500,18 San Francisco, CA; Foundation CDX, Cambridge, MA; or Archer VariantPlex, Coralville, IA), (2) Pyrosequencing (ARUP Laboratories, Salt Lake City, UT), (3) qPCR (Biocartis Idylla, Jersey City, NJ or Cobas EGFR Mutation Test v2, Roche Diagnostics, Santa Clara, CA), or (4) Sanger Sequencing (Neogenomics, Fort Myers, FL).

Details of Eligibility

Patients were consented and screened for all inclusion and exclusion criteria. The screening period to determine eligibility after patients signed consent was 30 days. All patients determined to be ineligible were identified within 30 days before their planned study-drug treatment start date. If patients were found to be eligible, they proceeded with their planned treatment start date, and no additional consent was required. If patients were found to be ineligible, they were withdrawn from the study and did not receive a dose of study drug.

Inclusion Criteria

Inclusion criteria included (1) male and female patients ≥18 years; (2) histologically or cytologically confirmed NSCLC, performed on a biopsy that occurred within the last 90 days; (3) documented activating EGFR mutation (exon 19 deletion, T790M, or L858R) on tumor samples by CLIA-approved test; (4) positron emission tomography-computed tomography (PET-CT) within the last 60 days showing radiographic stage I-IIIa lung cancer (mediastinal staging biopsy is allowed but not required); (5) brain MRI (or CT if contraindication to MRI) within the last 60 days showing no evidence of metastatic disease; (6) documentation that the patient is a candidate for surgical resection of their lung cancer by an American Board of Thoracic Surgery–certified surgeon; (7) the patient must have a tumor size ≥1 cm in its longest diameter; (8) Eastern Cooperative Oncology Group performance status of 0-1; (9) any unresolved toxicities from prior therapy greater than Common Terminology Criteria for Adverse Events grade 1 at the time of starting study treatment, with the exception of alopecia and grade 2 prior platinum therapy–related neuropathy is allowed; (10) adequate organ function defined by AST and ALT ≤2.5 × upper limit of normal (ULN), bilirubin ≤1.5× ULN, (patients with documented Gilbert syndrome and conjugated bilirubin within the normal range were allowed into the study), potassium, magnesium, and calcium within normal range, leukocytes >3,000/mcL, hemoglobin ≥9 g/dL, with no blood transfusions in the 28 days before study entry, absolute neutrophil count >1,500/mcL, platelets >100,000/mcL, creatinine ≤1.5 × ULN OR creatinine clearance >50 mL/min/1.73 m^2 for patients with creatinine levels ≤1.5 × upper limit above institutional normal; (11) ability to swallow oral medications; (12) women of childbearing potential must have a negative serum pregnancy test within 3 days before the first dose of study treatment and agree to use highly effective contraception, during the study and for 90 days following the last dose of osimertinib; (13) men with a female partner of childbearing potential must have either had a prior vasectomy agree to use effective contraception as described in the full protocol for at least 14 days before administration of the first dose of study treatment, during the study, and for 120 days after the last dose of osimertinib. Men also cannot donate sperm within this time period.

Exclusion Criteria

Exclusion criteria included (1) leptomeningeal carcinomatosis or other CNS metastases; (2) stage IIIB or distant metastases (including malignant pleural effusion) identified on PET-CT scan or biopsy (PET abnormalities that were negative for malignancy on biopsy were considered on a case by case basis); (3) medical history of interstitial lung disease (ILD), drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD; (4) patients who are known to be serologically positive for HIV; (5) active second malignancy (patients with a history of malignancy that was completely treated, with no evidence of that cancer at the time of enrollment were permitted to enroll in the trial provided all chemotherapy for prior malignancy was completed >12 months prior and/or bone marrow transplant >2 years prior); (6) patients who are currently receiving treatment with contraindicated QTc prolonging medications or potent CYP3A4 inducers; (7) any of the following cardiac abnormalities or history: mean resting corrected QT interval (QTc) >470 ms, obtained from 3 ECGs, using the screening clinic ECG machine derived QTc value, any clinically important abnormalities in rhythm, conduction or morphology of resting ECG for example, complete left bundle branch block, third-degree heart block and second-degree heart block, any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, electrolyte abnormalities (including: serum/plasma potassium <lower limit of normal (LLN); serum/plasma magnesium <LLN; serum/plasma calcium <LLN), congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death at age younger than 40 years in first-degree relatives or any concomitant medication known to prolong the QT interval; (8) prior treatment with osimertinib or other drugs that target *EGFR*-mutant NSCLC (including erlotinib, afatinib, gefitinib, rocelitinib); (9) treatment with concurrent anticancer therapy including chemotherapy, radiation, hormonal treatment (except corticosteroids and megesterol acetate, or immunotherapy) ≤14 days before treatment with osimertinib; (10) any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardize compliance with the protocol, or known active infection including chronic active hepatitis B virus (HBV), hepatitis C virus, and HIV. Patients with chronic HBV with negative HBV viral load on appropriate antiviral therapy were permitted, if able to continue appropriate antiviral therapy throughout treatment period; (11) active tuberculosis; (12) signs or symptoms of infection within 2 weeks before first day of study; (13) therapeutic oral or IV antibiotics within 2 weeks before first day of study treatment; (14) class II-IV heart failure as defined by the New York Heart Association functional classification system. Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction <50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate, to be eligible. Patients who have experienced untreated and/or uncontrolled cardiovascular conditions and/or have symptomatic cardiac dysfunction (unstable angina, congestive heart failure, myocardial infarction within the previous 3 months; coronary angioplasty or stenting or bypass grafting within the past 6 months; cardiac ventricular arrhythmias requiring medication; any history of second- or third-degree atrioventricular conduction defects); (15) females who are pregnant or breastfeeding; (16) presence of active GI disease (including GI bleeding or ulceration) or other condition that could affect GI absorption (eg, malabsorption syndrome, history of biliary tract disease), including refractory nausea or vomiting, or chronic GI disease which may affect absorption or tolerance to oral medications; (17) history of hypersensitivity to active or inactive excipients of osimertinib or drugs with a similar chemical structure or class to osimertinib; (18) involvement in the planning and/or conduct of the study (applies to both investigator staff and/or staff at the study site); (19) participation in another clinical study with an investigational product during the past 3 months or within five half-lives of the compound, whichever is longer; (20) uncontrolled medical, psychological, familial, sociological, or geographical conditions that interfere with the patient's safety, ability to provide informed consent, or ability to comply with the protocol.

Details of Patient Assessments

CBCs and blood chemistry tests to assess electrolytes, kidney, and liver function were performed within 30 days prior to C1D1 and were repeated at cycle 1, day 15 (C1D15), cycle 1, day 28 (C1D28), cycle 2 day 15 (C2D15), and cycle 2, day 28 (C2D28) ± 3 days. Plasma was collected for circulating tumor DNA analysis on C1D1, C1D28, day of surgery before resection, and at the end of treatment visit 30 days after d15 postoperative visit ± 3 days. Radiographic assessments occurred every 3 months for the first year after surgery and then every 6 months until up to 5 years postsurgery, disease recurrence, withdrawal of consent, or death.

Details of Secondary and Exploratory Outcomes and Post hoc Analyses:

Preplanned secondary end points included (1) median and 5-year disease-free survival (DFS) in patients who underwent surgical resection, (2) median and 5-year overall survival (OS) in patients who underwent surgical resection, (3) radiographic objective response rate (ORR), (4) radiographic depth of response (DpR), (5) complete pathological response rate (pCR), (6) treatment emergent adverse events (AEs) defined by NCI-CTC version 4.03, (7) rate of conversion to inoperable status because of treatment-related toxicity or progressive disease, (8) rate of surgical or perioperative complications. Preplanned exploratory end points included (1) rate of pathological upstaging, (2) rates of positive surgical margins, (3) rates of lymphovascular invasion (LVI), and (4) differences in genomic alterations between pretreatment biopsies and resected tumors.

Post hoc surgical and pathological analyses included (1) rate of pathological response, defined as <50% residual viable tumor (2) type of resection, (3) rate of tumor downstaging, (4) rate of lymph node downstaging, (5) postoperative histologic classification, and (6) rate of visceral pleural invasion (VPI). Post hoc analysis was also performed to determine the correlation between MPR, pathological regression,

DFS, and OS with (1) *EGFR* mutation subtype, (2) *TP53* mutation status, (3) *RBM10* mutation status, (4) tumor stage, (5) nodal status, (6) sex, (7) race, (8) age, (9) best RECIST response, and (10) number of cycles of therapy.

Post hoc survival analyses included (1) median event-free survival (EFS) in intention-to-treat (ITT) population, (2) median OS in ITT population, (3) comparison of DFS between patients who underwent a surgical resection and achieved an MPR and those who did not, (4) comparison of DFS between patients who underwent a surgical resection and achieved pathological regression of >50% and those who did not, (5) comparison of EFS in ITT population between patients who achieved an MPR and those who did not, (6) comparison of EFS in ITT population between patients who achieved pathological regression of >50% and those who did not, (7) comparison of OS between patients who underwent surgical resection and achieved an MPR and those who did not, (8) comparison of OS between patients who underwent surgical resection and achieved pathological regression of >50% and those who did not, (9) comparison of OS in ITT population who achieved an MPR and those who did not, and (10) comparison of OS between OS in ITT population who achieved pathological regression of >50% those and who did not.

Details of Statistical Methods

Secondary end points: Median and DFS and OS were summarized using Kaplan-Meier estimates with 95% CIs. End points expressed as binary indicators (pCR, ORR, rate of conversion to nonsurgical treatment) were summarized as proportions with exact binomial 95% CIs. DpR was expressed as a median with interquartile range. Treatment emergent AEs and rate of surgical or perioperative complications were summarized as percentages. Preplanned exploratory end points expressed as binary indicators (rate of pathological upstaging, rates of positive surgical margins, rates of LVI) were summarized as proportions with exact binomial 95% CIs. Differences in genomic alterations between pretreatment biopsies and resected tumors were summarized as percentages. Demographic and baseline characteristics were summarized using frequencies and percentages. Post hoc event time outcomes including DFS, EFS, and OS outcomes were summarized using Kaplan-Meier estimates, overall, for the ITT and resected populations, and in subgroups based on MPR and pathological regression status. Between-group differences were evaluated using hazard ratios for Cox proportional hazards models and with log-rank tests. To address possible mediation of the effects of pathological regression rates on DFS and OS outcomes by subsequent receipt of adjuvant chemotherapy or osimertinib, we added binary indicators of these adjuvants to separate Cox models comparing survival in groups of patients differing by regression rates (>50% and ≤50%). Because of the limited sample size and number of events, no formal statistical evaluation of this is possible. Additional exploratory analyses of the association between pathological regression proportions (DFS and OFS rates) and groups defined by selected demographic, tumor, and treatment variables used Fisher exact (log-rank) tests. Post hoc surgical and pathological analyses included (1) type of resection, (2) rate of pathological regression >50%, (3) rate of tumor stage downstaging, (4) rate of lymph node downstaging, (5) postoperative histologic classification, and (5) rate of VPI and were summarized as proportions.

TABLE A1. Postoperative AEs

Postoperative AEs (incidence >5% or SAE)	Grade 1-4, No. (%)	Grade 3-4, No. (%)	SAE, No. (%)
All	15 (62.5)	1 (4.2%)	1 (4.2)
Atrial fibrillation	6 (25)	0	0
Dyspnea	5 (20.8)	1 (4.2)	1 (4.2)
Cough	5 (20.8)	0	0
Chest pain	4 (16.7)	0	0
Constipation	3 (12.5)	0	0
Hoarseness	2 (8.3)	0	0
Nausea	2 (8.3)	0	0
Pulmonary edema	2 (8.3)	0	0
Pneumonia	2 (8.3)	0	0
Pneumothorax	2 (8.3)	0	0
Pulmonary embolism	1 (4.2)	1 (4.2)	1 (4.2)

Abbreviations: AE, adverse event; SAE, serious adverse event.

TABLE A2. AEs

AE (incidence >5%)	Grade 1-4, No. (%)	Grade 3-4, No. (%)	SAE, No. (%)
Rash	17 (63.0)	0	0
Diarrhea	14 (52.0)	0	0
Fatigue	10 (37.0)	0	0
Dyspnea	9 (33.3)	1 (3.7)	1 (3.7)
Cough	8 (29.6)	0	0
Nausea	8 (29.6)	0	0
Atrial fibrillation	7 (25.9)	1 (3.7)	1 (3.7)
Dry skin	6 (22.2)	0	0
Dry mouth	5 (18.5)	0	0
Constipation	5 (18.5)	0	0
Chest pain	4 (14.8)	0	0
Neutropenia	4 (14.8)	0	0
Stomatitis	4 (14.8)	1 (3.7)	0
Thrombocytopenia	4 (14.8)	0	0
Blurred vision	3 (11.1)	0	0
Abdominal pain	3 (11.1)	0	0
Leukopenia	3 (11.1)	0	0
Pruritis	3 (11.1)	0	0
Weakness	3 (11.1)	0	0
Headache	2 (7.4)	0	0
Lightheadedness	2 (7.4)	0	0
ALT elevation	2 (7.4)	0	0
AST elevation	2 (7.4)	0	0
Abdominal pain	2 (7.4)	0	0
Dizziness	2 (7.4)	0	0
Dry eyes	2 (7.4)	0	0
Fever	2 (7.4)	0	0
Hoarseness	2 (7.4)	0	0
Hyponatremia	2 (7.4)	2 (7.4)	0
Nail dystrophy	2 (7.4)	0	0
Neuropathy	2 (7.4)	0	0
Paronychia	2 (7.4)	0	0
Pneumonia	2 (7.4)	0	0
Pneumothorax	2 (7.4)	0	0
Pulmonary edema	2 (7.4)	0	0
Pulmonary embolism	2 (7.4)	2 (7.4)	1 (3.7)

Abbreviations: AE, adverse event; SAE, serious adverse event.

TABLE A3. Exploratory Analysis of MPR in Resected Tumors

Factor	No MPR, No. (%)	MPR, No. (%)	*P*[a]	Relative Risk (95% CI)
EGFR L858R	11 (78.5)	3 (21.4)	.615	0.87 (0.62 to 1.23)
EGFR exon19 Del	9 (90)	1 (10)		
TP53 mutated	6 (75)	2 (25)	1.00	0.92 (0.56 to 1.49)
TP53 wt	9 (81.8)	2 (18.2)		
RBM10 mutated	4 (100)	0 (0)	.530	1.36 (1.01 to 1.85)
RBM10 wt	11 (73.3)	4 (26.7)		
Stage I	7 (87.5)	1 (12.5)	1.00	1.08 (0.76 to 1.53)
Stage II/III	13 (81.2)	3 (18.8)		
N0	13 (86.6)	2 (13.3)	.615	1.11 (0.75 to 1.67)
N1/N2	7 (77.8)	2 (22.2)		
Male	4 (100)	0 (0)	1.00	1.25 (1.00 to 1.56)
Female	16 (80)	4 (20)		
Asian	9 (90)	1 (10)	.615	1.15 (0.81 to 1.61)
Non-Asian	11 (78.6)	3 (21.4)		
Age < 68	10 (76.9)	3 (23.1)	.596	0.85 (0.60 to 1.20)
Age > 68	10 (90.9)	1 (9.9)		
RECIST PR	10 (76.9)	3 (23.1)	.596	0.85 (0.60 to 1.20)
RECIST SD/PD	10 (90.9)	1 (9.9)		
One cycle	6 (75)	2 (25)	.578	0.86 (0.55 to 1.33)
Two cycles	14 (87.5)	2 (12.5)		

Abbreviations: Del, deletion; MPR, major pathological response; N, node; PD, progressive disease; PR, partial response; SD, stable disease.
[a]*P* value determined by two-sided Fisher exact test.

TABLE A4. Exploratory Analysis of Pathological Regression in Resected Tumors

Factor	Pathological Regression ≤50%	Pathological Regression >50%	Fisher Exact *P* Value[a]	Relative Risk (95% CI)
EGFR L858R	8 (57.1)	6 (42.9)	.240	1.90 (0.67 to 5.44)
EGFR Exon19 Del	3 (30)	7 (70)		
TP53 mutated	4 (50)	4 (50)	.377	1.83 (0.56 to 6.01)
TP53 wt	3 (27.3)	8 (72.7)		
RBM10 mutated	4 (100)	0 (0)	**.009**	*5.00 (1.82 to 13.76)*
RBM10 wt	3 (20)	12 (80)		
Stage I	3 (37.5)	5 (62.5)	.679	0.75 (0.27 to 2.08)
Stage II/III	8 (50)	8 (50)		
N0	7 (46.7)	8 (53.3)	1.00	1.05 (0.42 to 2.61)
N1/N2	4 (44.4)	5 (57.1)		
Male	2 (50)	2 (50)	1.00	1.11 (0.37 to 3.32)
Female	9 (45)	11 (55)		
Asian	4 (40)	6 (60)	.697	0.80 (0.32 to 2.01)
Non-Asian	7 (50)	7 (50)		
Age <68	5 (38.5)	8 (61.5)	.682	0.71 (0.29 to 1.69)
Age >68	6 (54.5)	5 (45.5)		
RECIST PR	3 (23.1)	10 (76.9)	.038	0.32 (0.11 to 0.91)
RECIST SD/PD	8 (72.7)	3 (27.3)		
One cycle	4 (50)	4 (50)	1.00	1.14 (0.47 to 2.78)
Two cycles	7 (43.8)	9 (56.2)		

NOTE. Bold entries indicate statistically significant *P* values.
Abbreviations: Del, deletion; N, node; PD, progressive disease; PR, partial response; SD, stable disease.
[a]*P* value determined by two-sided Fisher exact test.

TABLE A5. Exploratory Analysis of DFS and OS

Factor	DFS (median)	DFS: HR (95% CI)	DFS: Log-Rank *P* Value	OS: HR (95% CI)	OS: Log-Rank *P* Value
EGFR L858R	NR	1.54 (0.39 to 6.04)	.53	2.66 (0.27 to 25.82)	.38
EGFR exon19 Del	40.9				
TP53 mutated	25.3	5.25 (1.01 to 27.28)	**.03**	—	**.01**
TP53 wt	NR				
RBM10 mutated	25.3	2.50 (0.42 to 15.00)	.30	1.16 (0.12 to 11.25)	.90
RBM10 wt	NR				
Stage I	40.9	1.14 (0.30 to 4.33)	.84	0.56 (0.06 to 5.49)	.61
Stage II/III	NR				
N0	40.9	0.69 (0.18 to 2.61)	.58	0.72 (0.10 to 5.19)	.74
N1/N2	25.9				
Male	NR	0.68 (0.08 to 5.48)	.71	1.58 (0.16 to 15.21)	.69
Female	40.9				
Asian	40.9	1.18 (0.31 to 4.44)	.81	—	.10
Non-Asian	NR				
Age <68	25.9	2.73 (0.56 to 13.34)	.20	0.70 (0.09 to 5.16)	.73
Age >68	40.9				
RECIST PR	40.9	0.41 (0.10 to 1.73)	.21	0.33 (0.03 to 3.14)	.31
RECIST SD/PD	25.3				
One cycle	40.9	1.31 (0.32 to 5.35)	.71	0.74 (0.08 to 7.10)	.79
Two cycles	NR				

NOTE. Bold entries indicate statistically significant *P* values.
Abbreviations: Del, deletion; DFS, disease-free survival; N, node; NR, not reached; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.

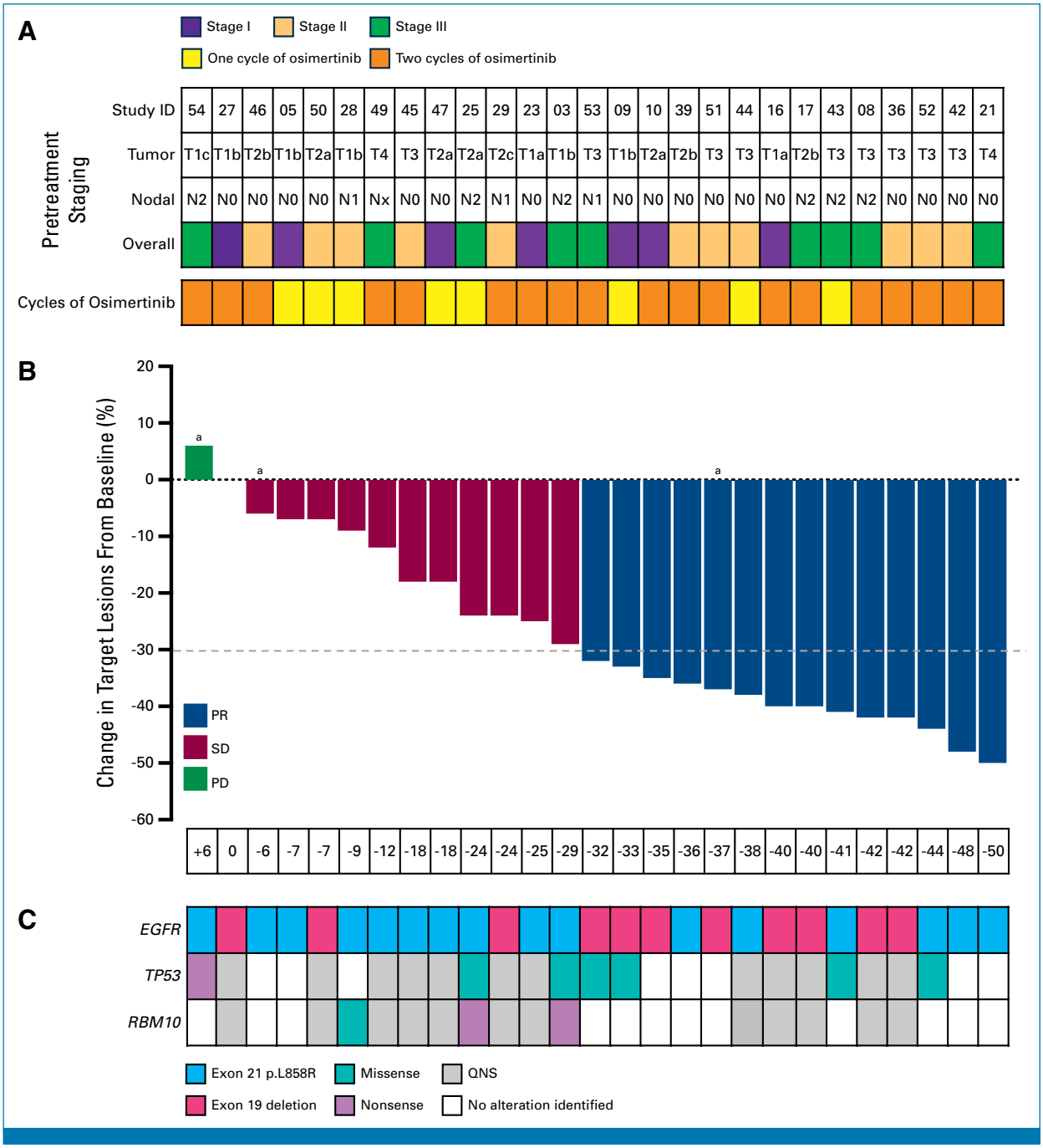

FIG A1. Radiographic response to treatment in ITT population. (A) Patient stage (AJCC v7) before osimertinib treatment is indicated, as are the number of cycles of osimertinib received before surgery. (B) Waterfall plot of unconfirmed best RECIST 1.1 radiographic response after osimertinib treatment is shown. PR, SD, and PD are indicated. (C) Pretreatment *EGFR* mutation subtype indicated by blue and red boxes. Detection and classification of *TP53* or *RBM10* mutations in pretreatment biopsy is indicated. [a]Denotes patients who did not undergo lung cancer surgical resection. AJCC, American Joint Committee on Cancer; ITT, intention-to-treat; PD, progressive disease; PR, partial response; QNS, quantity not sufficient for next-generation sequencing; SD, stable disease.

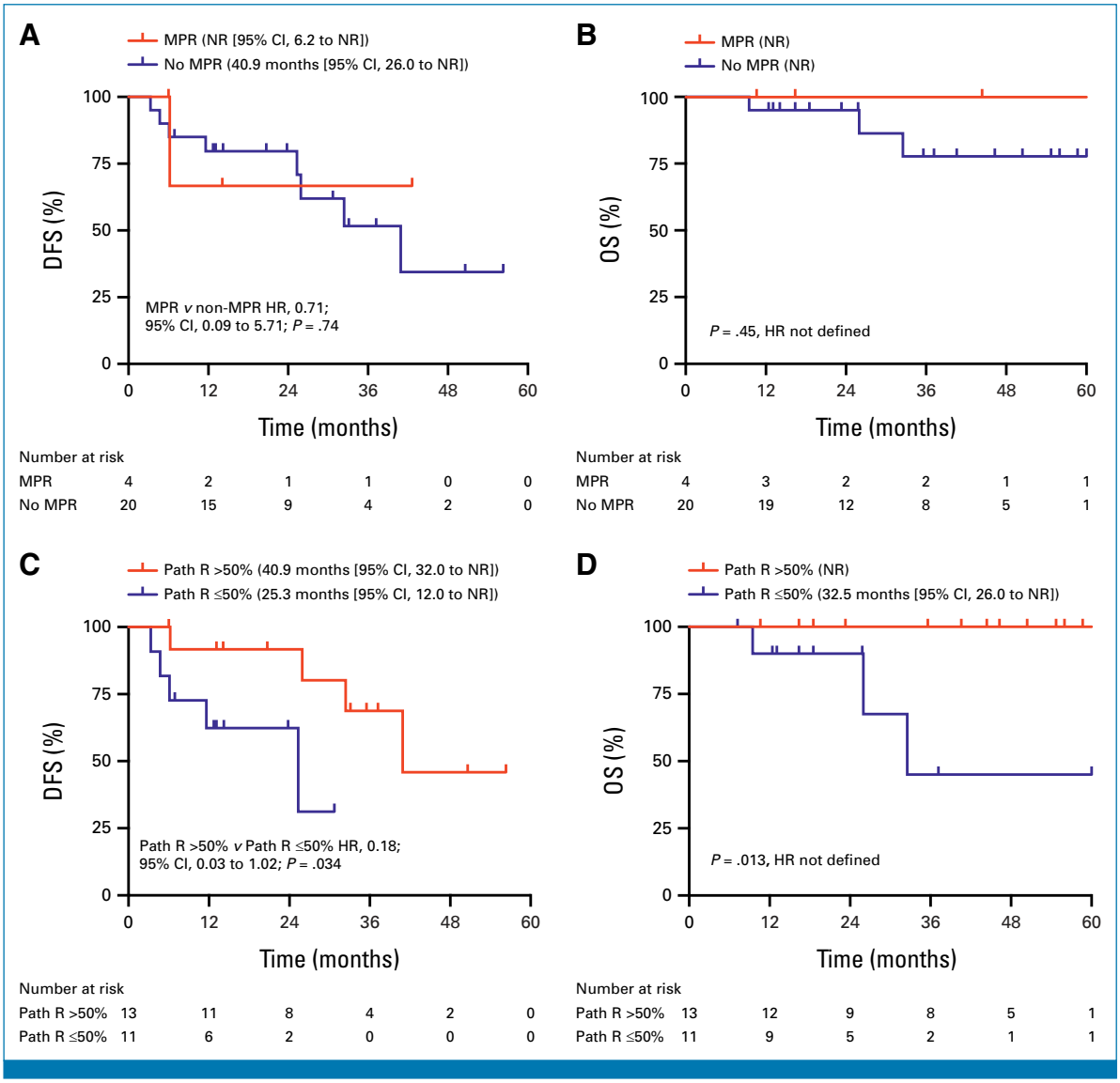

FIG A2. Postresection DFS and OS for patients who underwent surgical rection. (A) Kaplan-Meier curves comparing DFS for patients whose tumors showed an MPR (red) compared with those whose tumors did not show an MPR (blue). Median DFS indicated. (B) Kaplan-Meier curves comparing OS for patients whose tumors showed an MPR (red) compared with those whose tumors did not show an MPR (blue). (C) Kaplan-Meier comparison of DFS for patients whose tumors showed a pathological regression (Path R) of >50% (red) compared with those whose tumors did not show pathological regression >50% (blue). Median DFS with 95% CI are indicated. (D) Kaplan-Meier comparison of OS for patients whose tumors showed a pathological regression (Path R) of >50% (red) compared with those whose tumors did not show pathological regression >50% (blue). Median OS with 95% CI are indicated. DFS, disease-free survival; HR, hazard ratio; MPR, major pathological response; NR, not reached; OS, overall survival.

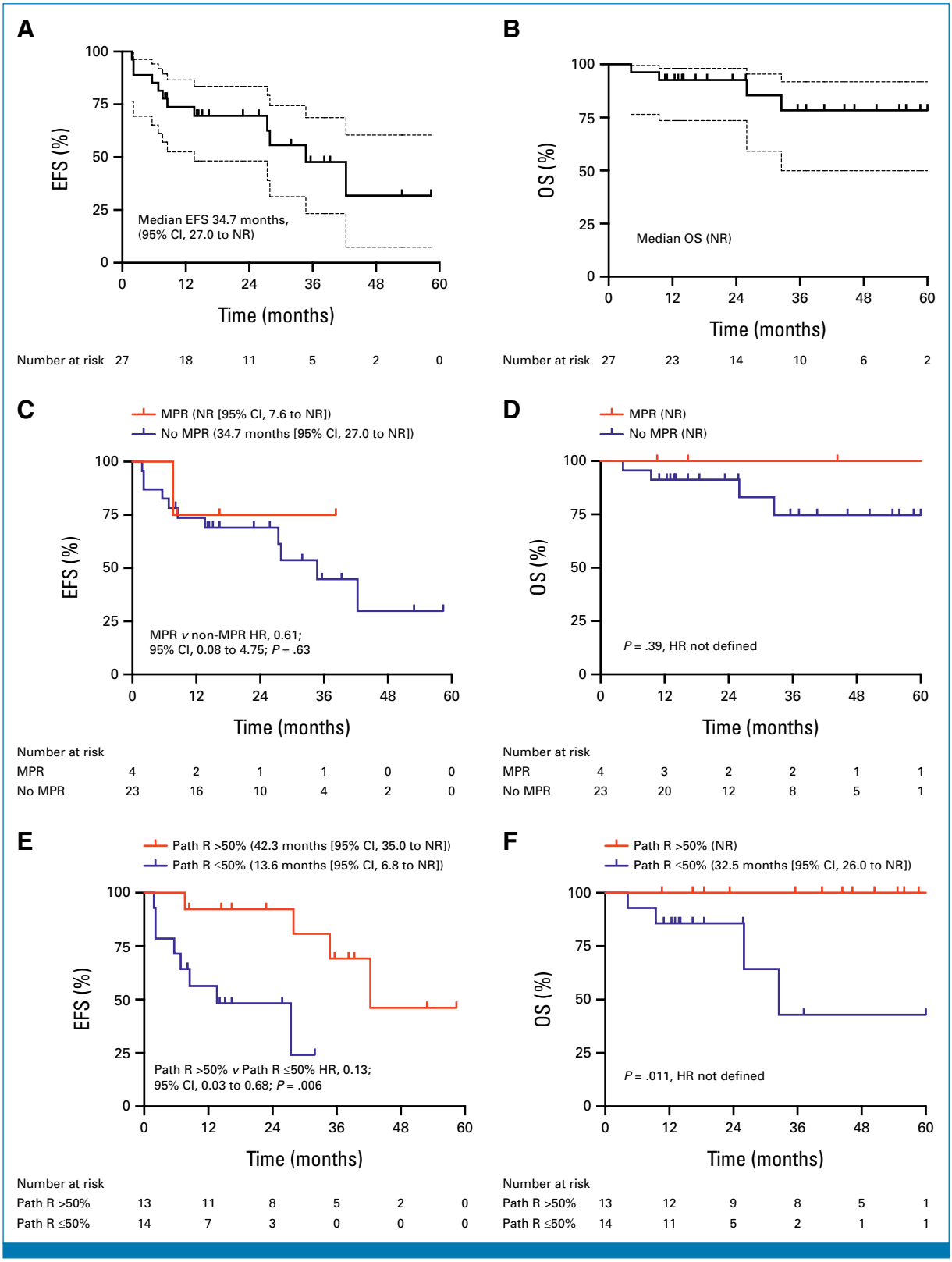

FIG A3. EFS and OS for ITT population (n = 27). (A and B) Kaplan-Meier curves with 95% CIs of EFS and OS for all ITT patients. (A) Median EFS with 95% CI indicated. (B) Median OS NR. (C) Kaplan-Meier curves comparing EFS for ITT patients whose tumors showed an MPR (red) compared with those whose tumors did not show an MPR (blue). Median EFS indicated. (D) Kaplan-Meier curves comparing OS for ITT patients whose tumors showed an MPR (red) compared with those whose tumors did not show an MPR (blue). (E) Kaplan-Meier comparison of EFS for ITT patients whose tumors showed a pathological regression (Path R) of >50% (red) compared with those whose tumors did not show pathological regression >50% (blue). Median EFS with 95% CI are indicated. (F) Kaplan-Meier comparison of OS for ITT patients whose tumors showed a pathological regression (continued on following page)

FIG A3. (Continued). (Path R) of >50% (red) compared with those whose tumors did not show pathological regression >50% (blue). Median OS with 95% CI are indicated. EFS, event-free survival; HR, hazard ratio; ITT, intention-to-treat; MPR, major pathological response; NR, not reached; OS, overall survival.

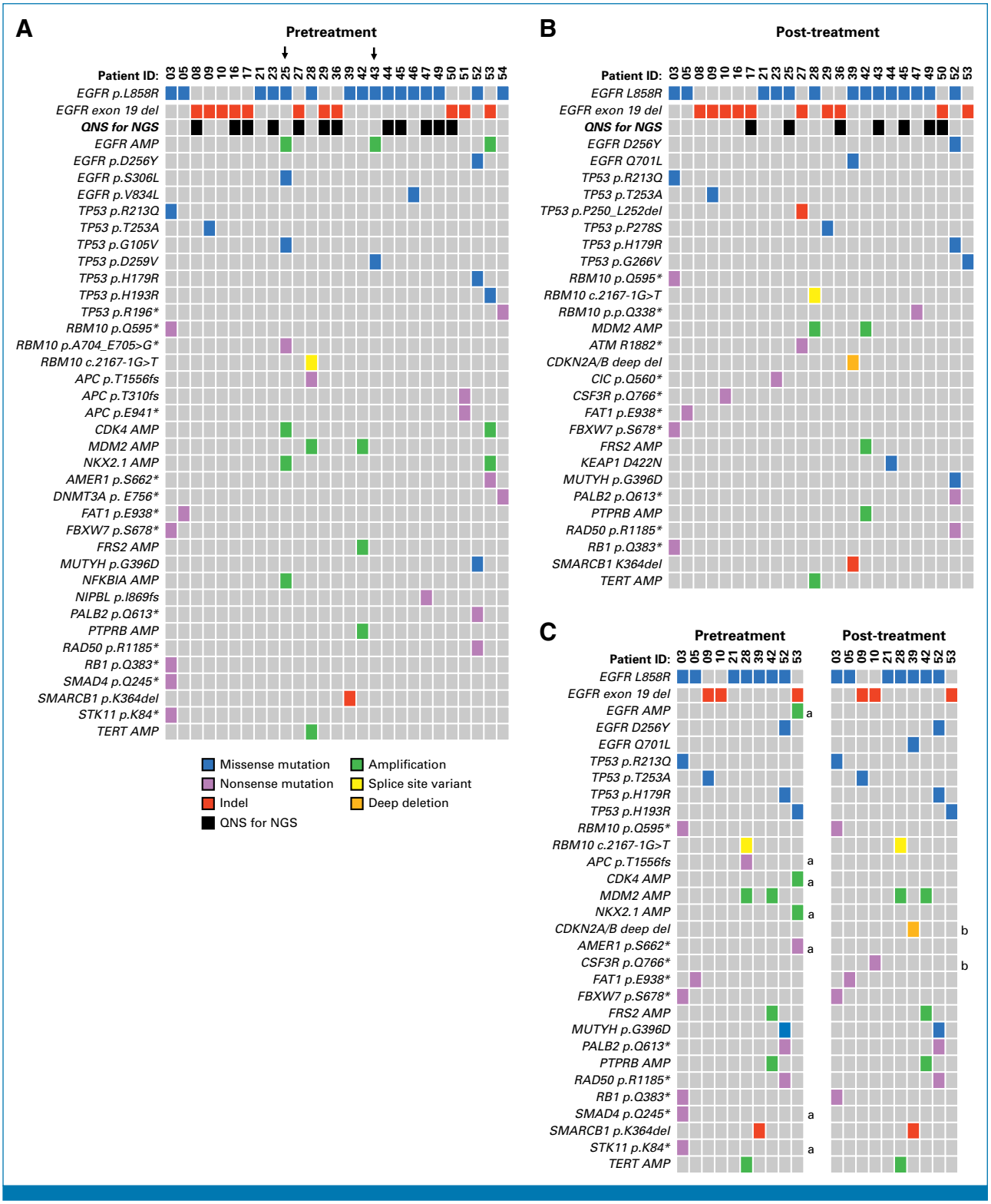

FIG A4. Oncoprint showing co-occurring tumor genomic alterations identified by clinical NGS performed on (A) pretreatment biopsies or (B) post-treatment resected tumors. Two pretreatment tumors (arrows) were analyzed by Foundation One CDx, all other samples were analyzed by UCSF500. Alterations identified through these assays and included in the clinical sequencing reports are indicated. (C) UCSF500 analysis of paired pretreatment and post-osimertinib tumors. [a]Denotes alterations that were detectable in pretreatment but not post-treatment samples. [b]Denotes alterations that were only detectable in post-treatment samples. NGS, next-generation DNA sequencing; QNS, quantity not sufficient for next-generation sequencing.