ORIGINAL ARTICLE

Neoadjuvant and Adjuvant Osimertinib in Stage IA to IIIA, *EGFR*-Mutant NSCLC (NORA)

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ABSTRACT

Introduction: Treatment with adjuvant osimertinib for three years is the standard-of-care for resected stage IB to IIIA NSCLC harboring *EGFR* mutations. The role of neoadjuvant osimertinib in the perioperative setting is yet to be elucidated in the NeoADAURA study (NCT04351555).

Methods: This is a single-center, pilot study of patients with clinical stage IA to IIIA NSCLC (American Joint Committee on Cancer eighth edition) harboring an activating *EGFR* mutation (Exon 19 deletion, L858R) (NCT04816838). Patients were treated with two 28-day cycles of neoadjuvant osimertinib followed by surgical resection and three years of adjuvant osimertinib. The primary endpoint was the objective response rate after two cycles of neoadjuvant treatment. Secondary endpoints included the pathologic complete response rate and major pathologic response rate. Exploratory objectives included the correlation of longitudinal circulating tumor DNA testing (Signatera) and response to neoadjuvant osimertinib.

Results: A total of 25 patients were enrolled and treated with neoadjuvant osimertinib, and all patients received surgical resection with R0 resection. The objective response rate was 44% (n = 11) all of which were partial responses. Fourteen patients (56%) reported stable disease after neoadjuvant osimertinib. The major pathologic response and pathologic complete response rates were 24% (n = 6) and 0%, respectively. None of the patients received adjuvant chemotherapy. The median disease-free survival was not reached at a median follow-up of 31 months (range: 13.8–38.6 mo). Six patients (30%) were circulating tumor DNA–positive at baseline and achieved clearance after 1 cycle of neoadjuvant osimertinib. There were no grade 3 adverse events during neoadjuvant treatment.

Conclusions: Two cycles of neoadjuvant osimertinib did not meet its primary endpoint of ORR. Neoadjuvant osimertinib is a feasible approach with a manageable safety profile in resectable *EGFR*-mutant NSCLC.

Keywords: Non-small cell lung cancer; Neoadjuvant; Adjuvant; Osimertinib; Stage IA-IIIA

Introduction

In NSCLC, *EGFR* accounts for 10% to 15% and 30% to 40% of oncogenic driver mutations in Western and Eastern populations, respectively.[1] Osimertinib is a third-generation EGFR tyrosine kinase inhibitor used in

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unresectable stage III NSCLC as consolidative treatment,[2] stage IV metastatic setting,[3] and adjuvant setting in resected NSCLC.[4] Previously, various first-generation EGFR tyrosine kinase inhibitors such as erlotinib in the RADIANT study[5] and gefitinib in CTONG1103[6] and the IMPACT study[7] have failed to show overall survival (OS) benefits as adjuvant treatment. Currently, adjuvant osimertinib for three years remains the standard of care for patients with stage IB to IIIA NSCLC harboring *EGFR*-activating mutations (Exon 19, L858R).[3,4]

Despite the improvement in disease-free survival (DFS) and OS seen with adjuvant osimertinib, some patients experience both loco-regional and distant relapse after the completion of three years of treatment. Although various acquired on-target and off-target resistance mechanisms have been identified in patients treated with osimertinib in metastatic cases, resistance mechanisms in patients who relapsed in the adjuvant setting remain under-reported. It is speculated that, although surgery drastically reduces tumor burden, there may be remaining cancer cells that are tolerant to adjuvant osimertinib. How the cancer cells evade apoptosis despite treatment, especially in the context of early, resectable *EGFR*-mutant NSCLC, remains poorly understood.

As the inclusion of targeted therapies in the perioperative setting is becoming more prominent, there remains an unmet need to understand the clinical relevance of osimertinib resistance mechanisms in the perioperative setting. Osimertinib as a neoadjuvant treatment is currently under investigation in the phase III NeoADAURA study for stage II-IIIB N2 NSCLC (NCT04351555). Recently, a phase II prospective trial assessing the efficacy and safety of osimertinib as perioperative treatment reported a major pathologic response (MPR) rate of 14.8% whereas no pathologic complete responses (pCRs) were observed,[8] indicating that osimertinib as neoadjuvant therapy has its limitations in eliciting pCR. Nevertheless, the intrinsic mechanisms behind lack of tumor regression remain to be elucidated. Moreover, the MPR and pCR rates are lower than those of perioperative immune checkpoint inhibitors with chemotherapy administered to patients without *EGFR* or *ALK* mutations.[9]

Here, we report the clinical efficacy of patients treated with two 28-day cycles of neoadjuvant osimertinib followed by surgical resection and three years of adjuvant osimertinib (NCT04816838).

Materials and Methods

Trial Design and Patients

This was a single center, pilot study conducted at Yonsei Cancer Center. Patients who were histologically or cytologically confirmed to have surgically resectable clinical stage IA to IIIA NSCLC harboring activating *EGFR* mutations (Exon 19 deletion, L858R) were enrolled. For patients with stage III disease, tumor staging with pathological evaluation of mediastinal lymph nodes by endobronchial ultrasound was mandatory. General eligibility criteria included ages 18 years and above, Eastern Cooperative Oncology Group performance status of 0 or 1, adequate bone marrow and organ function, and measurable disease as per Response Evaluation Criteria in Solid Tumor version 1.1 (RECIST v1.1) criteria. Patients with underlying interstitial lung disease, active second malignancy, and uncontrolled systemic disease were excluded. Before enrollment, patients underwent multidisciplinary approach for resectability, and were deemed resectable at the discretion of thoracic surgeon. Tumor staging included contrast-enhanced computed tomography (CT), positron emission tomography scan, and brain magnetic resonance imaging (MRI). Tumor response was assessed with RECIST v1.1 with chest CT after eight weeks of neoadjuvant osimertinib and subsequently every two months after surgery up to one year followed by every three months for four years by medical oncologists. Brain MRI was not mandatory during follow-up. Adverse events (AEs) and clinically significant laboratory abnormalities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.3.

The study was conducted in compliance with the protocol, to which all patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional review board (institutional review board: 4-2020-1335).

Procedures

Patients received neoadjuvant osimertinib 80 mg orally once daily on a 28-day cycle for two cycles. Patients discontinued treatment before the day of surgery or up to three days at the discretion of the investigator. Patients were to receive adjuvant osimertinib 80 mg on a 28-day cycle for three years. Adjuvant chemotherapy was optional and given at the discretion of the investigator.

Objectives and Endpoints

The primary objective was to evaluate the clinical efficacy of two cycles of neoadjuvant osimertinib for patients with early, resectable, *EGFR*-mutant NSCLC on the basis of objective response rate (ORR) using RECIST v1.1 criteria. Secondary objectives included pCR rate, MPR, DFS, event-free survival (EFS), OS, and treatment-related AEs (TRAEs). pCR was defined as the absence of viable tumor (0%),[10] and MPR was defined as 10% or

less of residual viable tumor in the resected tumor specimen,[11] DFS was defined as the time from curative surgery to documented recurrence, progression or death. EFS was defined as time from radiographic relapse, progression, or death. OS was defined as the time from the first day of treatment with neoadjuvant osimertinib to death owing to any cause.

Exploratory objectives were identifying changes in *EGFR* mutations, other hotspot mutations, and variant allele frequencies as detected by the Signatera circulating tumor DNA (ctDNA) assay.

Statistical Analysis

The sample size was calculated on the basis of the previous CTOG 1103 trial with erlotinib[6] with an ORR of 34% in patients treated with neoadjuvant doublet chemotherapy as historical control (P0 = 34%). We used a One Arm Binomial design and hypothesized that the ORR in the osimertinib group would be 65% or higher (P1 = 65%). With a two-sided alpha level of 0.05 and 87% power, a total of 25 patients were enrolled.

Descriptive statistics were used to assess the baseline characteristics of the patients. Safety analyses and efficacy analyses were performed on all patients. The Kaplan-Meier method was used to determine DFS, EFS, and OS. Data was analyzed using Statistical Package for the Social Sciences version 27 (IBM, Chicago, IL; research resource identifiers [RRID]: SCR_002865) and GraphPad Prism 10.0 software (GraphPad Software, Inc., San Diego, CA; RRID: SCR_002798) and were considered significant if the two-sided p value was lower than 0.05. Waterfall plots and bar graphs were created using the ggplot2 package in R (RRID: SCR_014601). In the bar plot showing the difference in clinical features according to *EGFR* mutation, Fisher's exact test was used to determine the significance between groups.

Personalized, Tumor-Informed ctDNA Testing

Assessment of ctDNA was conducted before neoadjuvant osimertinib, at cycle 2 day 1, on the day of surgery (at eight weeks of osimertinib), every two months after surgery until one year of postoperative period, and every three months subsequently for the next two years. Personalized, tumor-informed ctDNA analysis was performed on banked samples using a custom Research Use Only assay (SignateraTM RUO, Natera, Inc.) as previously described.[12] Briefly, whole-exome sequencing (WES) was performed at Yonsei Cancer Center on formalin-fixed, paraffin-embedded tumor tissue and matched normal blood samples from 22 patients and shared with Natera, Inc. Successful Signatera assays were designed for 20 of those 22 patients. A set of up to 16 patient-specific somatic single nucleotide variants (SNVs) from WES results were selected for multiplex polymerase chain reaction. The multiplex polymerase chain reaction primers targeting the personalized SNVs were used to track ctDNA in the corresponding patients' plasma samples. Plasma samples with two or more SNVs detected above a predefined confidence threshold were defined as ctDNA-positive. ctDNA concentration was reported in mean tumor molecules per milliliter of plasma. ctDNA clearance was defined as ctDNA negativity that was succeeded a ctDNA positive timepoint and persisted for subsequent ctDNA timepoints.

Library Preparation and Sequencing for Whole-Exome Sequencing

Genomic DNA of all samples was isolated using the DNeasy Blood & Tissue Kits (Qiagen, Inc., Hilden, Germany; RRID: SCR_008539). The concentration and purity of genomic DNA were assessed by agarose gel electrophoresis and PicoGreen dsDNA assay (Invitrogen, Waltham, MA; RRID: SCR_008410). Exome libraries were generated from tissue samples (preneoadjuvant: 22 samples; postneoadjuvant: 25 samples) and matched normal blood samples using SureSelect version 6 Kit (Agilent Technologies, Santa Clara, CA; RRID: SCR_013575) and sequenced on NovaSeq 6000 (Illumina, CA; RRID: SCR_010233).

Mutation Call Platforms

Sequencing reads were mapped to the human chromosome (hg19). Mutation calling was performed with Illumina Dragen (version 3.10). For somatic mutation calling, matched normal and tumor data were used in WES. Nonsynonymous variants were extracted, and cosmic genes were selected. Somatic mutations were filtered out as those with a mutant allele frequency of less than 0.01 and annotated with Oncotator. Copy number variation was analyzed using CNVkit (etal/cnvkit) with a copy number higher than five as amplification and less than one as deep deletion.

Results

NORA is a single-center, window-of-opportunity study of 25 patients treated with neoadjuvant osimertinib in patients with early, resectable stage IA to IIIA NSCLC harboring activating *EGFR* mutation (Exon 19 deletion, L858R). Patients were enrolled from June 2021 to March 2022 (Supplementary Fig. 1).

Patient Demographics and Baseline Characteristics

The median age was 64 years (range: 59–66) and 17 patients (68%) were female individuals (Table 1). Most of the patients were never smokers (n = 19, 76%).

Table 1. Patient characteristics (N = 25)

Characteristics		Values (% or IQR)
Age (range)		64 (59-66)
Sex	Female	17 (68)
	Male	8 (32)
Smoking status	Never smoker	19 (76)
	Former smoker	6 (24)
	Current smoker	0
Stage	IA	8 (32)
	IB	7 (28)
	IIA	4 (16)
	IIB	4 (16)
	IIIA	2 (8)
ECOG performance status	0	20 (80)
	1	5 (20)
Preoperative Staging	EBUS	11 (44)
	PET	25 (100)
	B MRI	25 (100)
Histology	Adenocarcinoma	25 (100)
EGFR mutation	Ex19del	10 (40)
	L858R	15 (60)
Initial tumor size (total, cm)		3.7 (2.8-4.8)
Initial tumor size (solid, cm)		2.8 (2.4-4.8)
Surgical resection	R0 resection	25 (100)

B MRI, brain magnetic resonance imaging; EBUS, endobronchial ultrasound; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; PET, positron emission tomography.

Patients with stage IA and IB disease comprised 32% (N = 8) and 28% (N = 7) of the cohort, followed by IIA (N = 4, 16%), IIB (N = 4, 16%), and IIIA (N = 2, 8%). All patients underwent positron emission tomography scan and brain MRI, and 11 patients (44%) underwent EBUS for mediastinal staging. All patients had adenocarcinoma histology. EGFR *Ex19del* and *L858R* were present in 40% (N = 10) and 60% of patients (N = 15), respectively.

Clinical Activity of Neoadjuvant Osimertinib

All patients completed two cycles of neoadjuvant osimertinib. The primary endpoint was not met with an observed ORR of 44% (n = 11) with all partial response (PR), and a 56% incidence (N = 14) of stable disease (SD) (Fig. 1). The ORR was not different between the *EGFR* mutations (E19del, L858R) (Supplementary Fig. 2*A*).

All patients underwent R0 resection (Table 1). After neoadjuvant osimertinib, pathologic T-stage and lymph node downstaging were seen in 20 patients (80%) and three patients (12%), respectively (Supplementary Table 1). Although adjuvant chemotherapy was an option for treatment, none of the patients received adjuvant platinum-based chemotherapy. Osimertinib was given before surgery, and resuming with adjuvant osimertinib rather than cytotoxic chemotherapy seemed a better rationale for the investigators. The most common surgical resection was lobectomy (N = 21, 84%) (Supplementary Table 2). Postoperative complications (N = 5, 20%) included prolonged air leak (>5 d) seen in one patient, chyle leakage in three patients, and pneumonia in one patient. Pulmonary thromboembolism (N = 2), and pleural effusion (N = 1) were documented as delayed complications (>30 d). The MPR rate was 24% (n = 6). None of the patients achieved pCR. MPR was not different between the *EGFR* mutations (E19del, L858R) (Supplementary Fig. 2*B*). The proportion of viable tumor, necrosis, and stroma in the tumor bed is seen in Figure 1. Pathologic regression of more than 50% was seen in 17 patients (68%).

At the median follow-up of 31 months (range: 13.8–38.6 mo), the median DFS, EFS, and OS were not reached (Supplementary Fig. 3). There was also no statistically significant difference in DFS in terms of *EGFR* mutations, *TP53* mutations, ORR, MPR, and pathological regression (>50% or <50%). (Supplementary Fig. 4). At the data cutoff date (August 9, 2024), 96% (N = 24) of patients were continuing treatment with adjuvant osimertinib. One patient (YUHS 013) had disease recurrence after treatment withdrawal owing to intolerability during adjuvant treatment and relapse was detected in both lungs (Supplementary Table 3). Rebiopsy was not feasible for this patient owing to the metastatic site being inaccessible for both CT-guided needle-aspiration biopsy and bronchoscopy. The ORR and MPR were not different between the *EGFR* mutations (E19del, L858R) (Supplementary Fig. 3*A* and *B*).

Toxicities

Of the 25 patients, 12 patients (48%) experienced at least one TRAE during treatment with neoadjuvant osimertinib (Table 2). The most common AE were skin rash (N = 5, 20%), anorexia (N = 4, 16%), and pruritus (N = 3, 12%) of grade 1. Most AEs were limited to grade 1. None of the patients had grade 3 AEs during neoadjuvant treatment. There was no dose reduction or discontinuation during neoadjuvant treatment. One patient (4%) had dose interruption owing to coronavirus disease infection. During adjuvant osimertinib, 60% of the patients (N = 15) experienced TRAEs, which were mostly limited to grade 1 and 2, including nail changes (N = 4, 16%) of grade 1 and 2, dry skin of grade 1 (N = 3, 12%), and skin rash of grade 1 (N = 3, 12%). Grade 3 neutropenia (N = 1, 4%), anemia (N = 1, 4%), and increase of creatinine phosphokinase (N = 1, 4%) were observed. None of the patients experience grade 4 or 5 TRAEs during adjuvant treatment. Dose reduction, interruption,

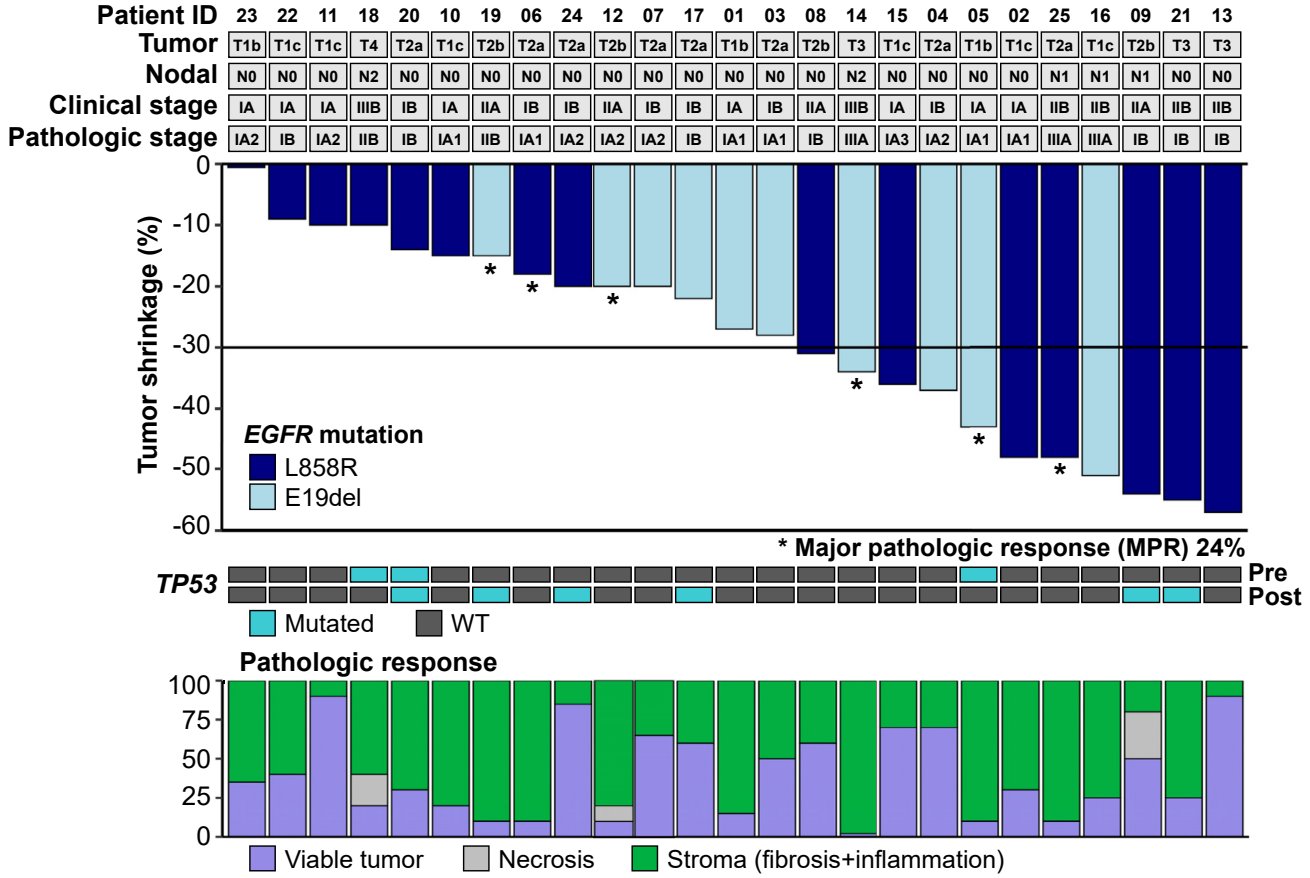

Figure 1. Waterfall plot of patients treated with neoadjuvant osimertinib for eight weeks. The best percentage change in the tumor sum of diameters from baseline (above), *TP53* mutation (top represents pre-osimertinib, below represents post-osimertinib surgical samples), and proportion of viable tumor, necrosis, and stroma in the tumor bed after treatment with neoadjuvant osimertinib (below).

and discontinuation during adjuvant osimertinib were seen in four (16%), eight (32%), and one patient (4%, owing to progression), respectively.

Analysis of ctDNA

Personalized ctDNA assays were designed for 20 patients. Of the five patients, three did not have sufficient tissue for WES. The remaining two patients failed quality control parameters for the Signatera assay design. Six of whom (30%) were ctDNA-positive (N = 2, stage I; N = 2 stage II, N = 2, stage III) before neoadjuvant treatment (Fig. 2). After one cycle of neoadjuvant osimertinib, all patients achieved clearance. Postresection, interim analyses revealed that 18 of the 19 patients who were recurrence-free were ctDNA-negative (95%), demonstrating high concordance between ctDNA results and disease status. There was also no difference in ORR (PR, SD) between patients who were ctDNA positive or negative before treatment with neoadjuvant osimertinib (Supplementary Fig. 2*C*). One patient (YUHS 003) turned ctDNA positive 17.7 months after surgery while on adjuvant osimertinib treatment. Nevertheless, this patient did not show signs of recurrence on the regular CT scans at the time of data cutoff. Another patient (YUHS013) was ctDNA negative while on adjuvant osimertinib, but later went on to relapse 2.6 months after treatment discontinuation. No additional ctDNA time points were available to test after treatment discontinuation and before relapse. Subsequent ctDNA analyses are ongoing for all patients treated with adjuvant osimertinib.

Concurrent Mutations

WES of pre-osimertinib (N = 22) samples revealed that *CRLF2* and *P2RY8* mutations were present in 32% (N = 7) of patients (Fig. 3*A*). In addition, *TP53* and *RBM10* mutations were observed in 14% (N = 3) and 9% (N = 2) of patients, respectively. In the surgically resected, post-osimertinib samples (N = 25), *CRLF2* and *P2RY8* mutations were detected in 36% (N = 7) patients, each, followed by *TP53* (24%, N = 6) and *MUC16* (16%, N = 4) mutations (Fig. 3*B*, Supplementary Fig. 5). *TP53* mutation was enriched in the post-osimertinib samples

Table 2. Treatment-Related Adverse Events to Neoadjuvant and Adjuvant Osimertinib

Neoadjuvant osimertinib (N = 25)	All grade	Grade 1	Grade 2	Grade 3
Skin rash	5 (20)	5 (20)	0	0
Anorexia	4 (16)	4 (16)	0	0
Pruritus	3 (12)	3 (12)	0	0
Constipation	1 (4)	1 (4)	0	0
Diarrhea	1 (4)	0	1 (4)	0
Dyspepsia	1 (4)	1 (4)	0	0
Oral mucositis	1 (4)	1 (4)	0	0
Paronychia	1 (4)	1 (4)	0	0
Adjuvant osimertinib (N = 25)				
Nail changes	4 (16)	3 (12)	1 (4)	0
Dry skin	3 (12)	3 (12)	0	0
Skin rash	3 (12)	3 (12)	0	0
Neutropenia	3 (12)	0	2 (8)	1 (4)
Diarrhea	2 (8)	2 (8)	0	0
Oral mucositis	2 (8)	2 (8)	0	0
Anemia	2 (8)	0	1 (4)	1 (4)
AST increased	1 (4)	1 (4)	0	0
ALT increased	1 (4)	1 (4)	0	0
Constipation	1 (4)	1 (4)	0	0
CPK increased	1 (4)	0	0	1 (4)
Dyspepsia	1 (4)	0	1 (4)	0
General weakness	1 (4)	1 (4)	0	0
Generalized edema	1 (4)	0	1 (4)	0
Itching sense	1 (4)	0	1 (4)	0
Myalgia	1 (4)	1 (4)	0	0
Paronychia	1 (4)	0	1 (4)	0
Scalp rash	1 (4)	0	1 (4)	0
Weight loss	1 (4)	0	1 (4)	0

ALT, alanine transaminase; AST, aspartate transaminase; CPK, creatinine phosphokinase.

with higher proportion in the L858R (N = 4) than in the E19del (N = 2) group.

Discussion

Here, we report the results of a window-of-opportunity trial that investigated the clinical safety and efficacy of neoadjuvant osimertinib followed by surgery and adjuvant osimertinib for resectable, stage IA to IIIA *EGFR*-mutant NSCLC. This study did not meet its primary endpoint for ORR, which was hypothesized to be 65% or higher. Neoadjuvant osimertinib for two 28-day cycles resulted in an ORR of 44%, which was lower than previously reported with an ORR of 71% and 95%, in a phase II trial for resectable stage II to IIIB (NEOS trial),[13] and a phase 2 study of neoadjuvant osimertinib followed by sequential definitive radiation therapy or surgery in stage III, *EGFR*-mutant NSCLC, respectively.[14] The discrepancy of ORR for neoadjuvant osimertinib may be attributed to most patients being enrolled in an earlier stage (stage IA and IB, 32%) and the lack of an adequate sample size to further validate the role of neoadjuvant osimertinib before surgical resection.

Perioperative osimertinib had manageable AEs with no grade 3 AEs experienced during neoadjuvant treatment whereas three cases of grade 3 (neutropenia, anemia, and increase of creatinine phosphokinase) AEs were observed in the adjuvant setting. Only one patient permanently discontinued adjuvant osimertinib owing to intolerability. In contrast to the reported data of diarrhea and rash accounting for 52% and 41% of AEs in a previously reported study,[8] these AEs were less frequently observed in this study.

At the time of data cut-off, only one patient relapsed, and the DFS data remained immature for further analysis in terms of treatment outcome by *EGFR* or *TP53* mutation status. Although pathologic outcomes such as pCR or MPR are debatable as surrogate endpoints for OS, the remaining persistent tumor cells known as drug-tolerant persisters (DTPs) are paramount in understanding why neoadjuvant osimertinib does not result in pCR. This finding is consistent with a previous phase II study which included patients treated with two 28-day cycles of neoadjuvant osimertinib, none of the patients treated with neoadjuvant osimertinib achieved pCR.[8] Similarly, neoadjuvant osimertinib given for six weeks in resectable stage II to IIIB, *EGFR*-mutant NSCLC, resulted in one out of 40 patients (3.6%) achieving pCR in a phase 2b trial.[13] Our pilot study reported similar

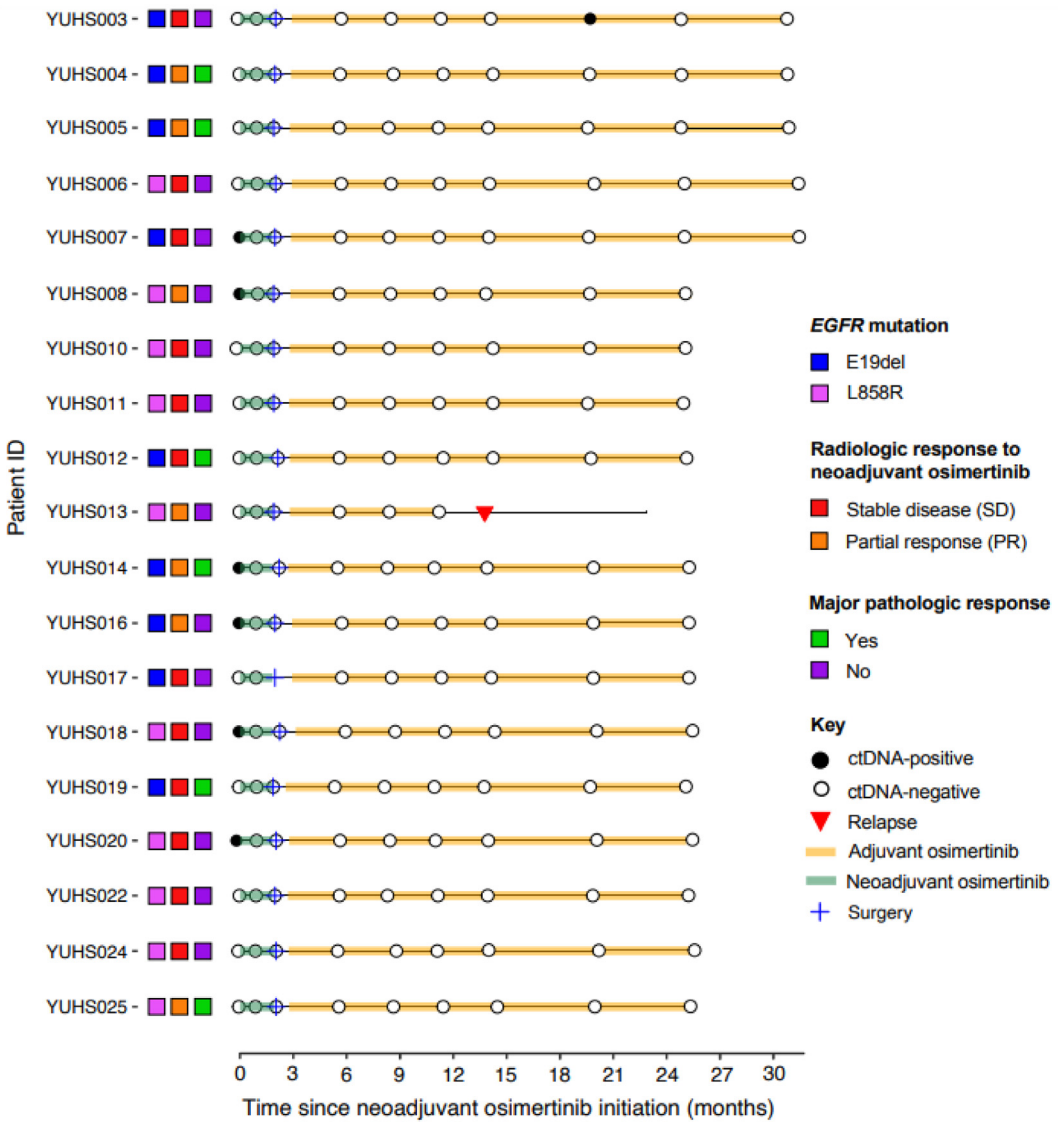

Figure 2. Serial ctDNA analysis of patients treated with neoadjuvant osimertinib and surgery (N = 20). ctDNA, circulating tumor DNA.

treatment responses to targeted therapy with osimertinib. This emphasizes the need to investigate tumor intrinsic mechanisms that interfere with tumor regression in *EGFR*-mutant NSCLC.

We observed that even after eight weeks of osimertinib treatment, tumor cells persisted as there were no patients with pCR for both *EGFR* L858R and E19del. How the cancer cells evade apoptosis despite treatment, especially in the context of early, resectable *EGFR*-mutant NSCLC, remains poorly understood. The biological and immunological basis of the DTP cells has remained limited by inadequate access to patient samples. Preclinical models have shown that high YAP and TEAD pathway activity allows cancer cells to survive in a senescence-like dormant state through epithelial-to-mesenchymal transition.[15] To this end, further in-depth analysis through paired single-cell RNA sequencing is ongoing.[16]

Currently, there are various combination strategies for previously untreated, unresectable *EGFR* mutant NSCLC. The addition of cytotoxic chemotherapy[17] or upfront MET inhibition by amivantamab[18] has shown improved progression-free survival. About 5% to 10% of patients have histologic transformation including squamous cell lung cancer in metastatic NSCLC harboring *EGFR* 19del or L858R mutation.[19] To the best of our knowledge, there are no published reports on histologic transformation after neoadjuvant osimertinib. In our study, none of the surgically resected specimens reported histologic transformation. Although much focus on drug development is on targeted therapy such as antibody-drug conjugates,[20] it is important to

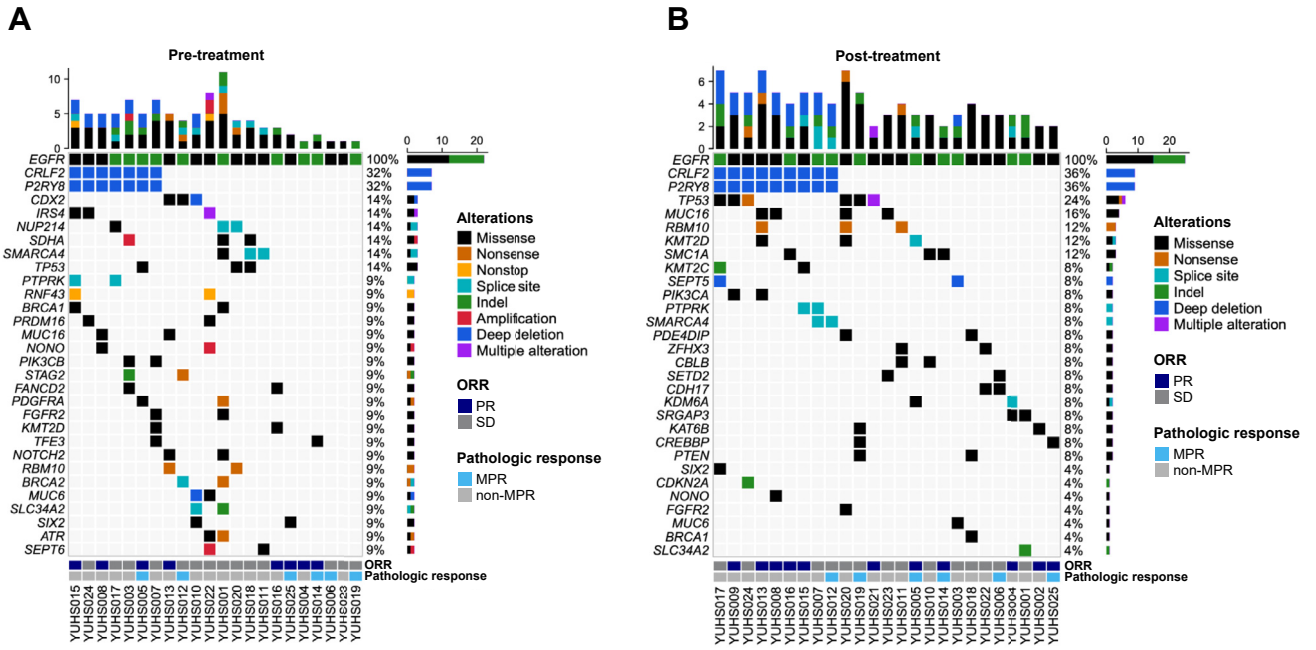

Figure 3. Tumor genomic alterations were identified at *(A)* baseline tumor samples (N = 22) and *(B)* post-osimertinib resected samples (N = 25). MPR, major pathologic response; non-MPR, non-major pathologic response; ORR, objective response rate; PR, partial response; SD, stable disease.

understand the mechanism of DTPs in the future, and to prevent cells from progressing through this pathway. Further investigation is needed to understand the mechanistic role of DTPs in NSCLC.

Conclusion

In summary, the addition of two cycles of neoadjuvant osimertinib is a feasible option in patients with surgically resectable stage IA to IIIA *EGFR*-mutant NSCLC. Although this study did not meet its primary endpoint for ORR, there were no surgical cancellations, and perioperative osimertinib had manageable AEs. Limitations to this study include the small sample size and no in-depth single-cell RNA-sequencing analysis on pre- and post-osimertinib samples to identify potential mechanisms underlying the lack of pathologic response to neoadjuvant osimertinib.

Although pathologic T-stage and N-stage downstaging were seen in 20 (80%) and three patients (12%); none of the patients achieved pCR. This raises the important question of whether we should intensify treatment in those patients who have residual disease after treatment. It remains unknown whether DTP-targeted treatment combinations may be suitable for patients with *EGFR* mutations. This study also highlights the role of neoadjuvant osimertinib in achieving ctDNA clearance after one cycle (28 d). Ongoing ctDNA collection and analysis in the adjuvant setting may help to inform the role of ctDNA monitoring in the prediction of treatment response. Biomarkers integrated with ctDNA may be useful to monitor and track the DTP state and detect subgroups for treatment intensification in the future.

Data Availability Statement

The data generated in this study are available upon request to the corresponding author.

CRediT Authorship Contribution Statement

Jii Bum Lee: Data curation, Formal analysis, Investigation, Visualization, Writing - original draft, Writing - review & editing.

Su Jin Choi: Data curation, Formal analysis, Investigation, Visualization, Writing - original draft, Writing - review & editing.

Hyo Sup Shim: Data curation, Formal analysis, Investigation, Writing - review & editing.

Byung Jo Park: Data curation, Formal analysis, Investigation, Writing - review & editing.

Chang Young Lee: Data curation, Formal analysis, Investigation, Writing - review & editing.

Sumedha Sudhaman: Formal analysis, Investigation, Visualization, Writing - review & editing.

Sharlene Velichko: Methods, Investigation.

Min Hee Hong: Data curation, Formal analysis, Investigation, Writing - review & editing.

Byoung Chul Cho: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Resources, Validation, Writing - review & editing.

Sun Min Lim: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Resources, Validation, Writing - review & editing.

Disclosure

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at [https://doi.org/10.1016/j.jtho.2024.12.023].

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