Gefitinib as neoadjuvant therapy for resectable stage II-IIIA non–small cell lung cancer: A phase II study

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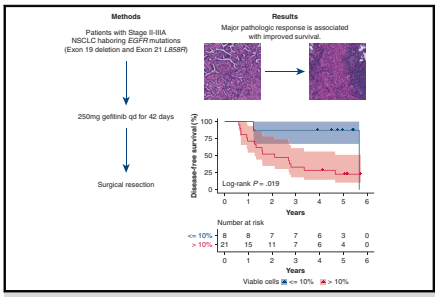
ABSTRACT

Introduction: Currently, limited data on tyrosine kinase inhibitors as neoadjuvant therapy exist. This prospective study aimed to investigate the efficacy and safety of preoperative gefitinib in patients with stage II-IIIA operable non–small cell lung cancer (NSCLC).

Methods: This was a single-arm, phase II trial performed in the Shanghai Cancer Center. Between August 2013 and October 2015, patients with operable stage II-IIIA NSCLC with epidermal growth factor receptor (*EGFR*) exon 19 deletion or exon 21 L858R mutation were enrolled. Patients were treated with preoperative gefitinib (250 mg once daily for 42 days), followed by surgical resection. The primary endpoint was objective response rate (ORR); secondary endpoints were the rate of major pathologic response (MPR), disease-free survival (DFS), overall survival, and adverse events (AEs). ORR was defined as the proportion of patients achieving complete response or partial response radiologically. MPR was defined as no more than 10% viable tumor.

Results: Of the 35 eligible patients, 33 were considered as intention-to-treat population. ORR, the primary endpoint, was 54.5% (95% confidence interval [CI], 37.7-70.7), and the rate of MPR was 24.2% (95% CI, 11.9-40.4). Median DFS was 33.5 months (95% CI, 19.7-47.3); median overall survival was not reached. Skin toxicity (24/35,68.6%) and gastrointestinal symptoms (17/35,48.6%) were the most common AEs; no patients reported grade 3 or 4 AEs. After surgery, 4 patients experienced chylothorax (4/33,12.1%). Patients with MPR had a prolonged survival compared with those without (DFS, $P = .019$).

Conclusions: Neoadjuvant therapy with gefitinib in patients with stage II-IIIA NSCLC is safe and may be a viable treatment for patients whose tumors have *EGFR* mutations. Patients with MPR were associated with improved survival. (J Thorac Cardiovasc Surg 2021;161:434-42)



Major pathologic response was associated with improved disease-free survival.

CENTRAL MESSAGE

Gefitinib as neoadjuvant therapy for stage II-IIIA NSCLC with *EGFR* mutations is acceptable in terms of drug toxicity and surgical complication. Major pathologic response indicates improved survival.

PERSPECTIVE

Neoadjuvant therapy with gefitinib was safe and feasible for patients harboring *EGFR* mutation in clinical practice. Patients with major pathologic response were associated with improved survival. Future clinical trials of neoadjuvant therapy may consider taking pathological evaluation as a surrogate endpoint.

See Commentaries on pages 443, 444, and 446.

Primary lung cancer is the most common malignancy worldwide, and cancer of the lung and bronchus is the leading cause of cancer death.[1-3] Surgical resection is the optimal treatment for early-stage non–small cell lung cancer (NSCLC). However, the 5-year overall survival (OS) rate after stage II-IIIA lung cancer resection is estimated to be between 65% and 41%.[4] Deaths are often caused by distant metastases.[5] NSCLC may exhibit undetectable micrometastases. The current clinical guidelines recommend adjuvant cisplatin treatment for patients with stage II-IIIA NSCLC after complete resection to reduce possibility of possible micrometastases.[6] Adjuvant treatments improve 5-year OS by 4% to 8%. The use of neoadjuvant chemotherapy in patients with NSCLC has also conferred a similar benefit.[7]

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Abbreviations and Acronyms

AE = adverse event
CI = confidence interval
CR = complete response
CT = computed tomography
DFS = disease-free survival
EGFR = epidermal growth factor receptor
FEV1 = forced expiratory volume in 1 second
IQR = interquartile range
ITT = intention-to-treat
MPR = major pathologic response
NSCLC = non–small-cell lung cancer
ORR = objective response rate
OS = overall survival
PR = partial response
RECIST = Response Evaluation Criteria in Solid Tumors
SD = stable disease
TKI = tyrosine kinase inhibitor

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The development of targeted therapy has enhanced lung cancer treatment. Epidermal growth factor receptor (*EGFR*) mutations are frequently found in patients of east Asian descent with NSCLC and are present in approximately one half of all patients. In particular, exon 19 deletions and L858R mutations are the most common, identified in 22.1% and 20.9% of patients with advanced NSCLC, respectively.[8] Patients with these mutations respond better to *EGFR*-tyrosine kinase inhibitors (TKIs) than those without the mutations. Adjuvant gefitinib in patients with resectable, *EGFR*-mutant NSCLC was explored in the ADJUVANT study. ADJUVANT demonstrated a significant improvement in disease-free survival (DFS) when patients were treated with gefitinib (28.7 months; 95% confidence interval [CI], 24.9-32.5) compared with vinorelbine and cisplatin (18.0 months; 95% CI, 13.6-22.3), with a hazard ratio of 0.60 (95% CI, 0.42-0.87; $P = .0054$).[9] Other studies have explored the safety and efficacy of *EGFR*-TKI in a neoadjuvant setting, but few studies have analyzed its impact on prognosis.

This phase II trial examines the efficacy of neoadjuvant gefitinib in patients with clinically diagnosed stage II-IIIA NSCLC with *EGFR*-TKI-sensitive mutations. Our report presents the results of prognosis, pathologic responses, and toxicity.

METHODS

Study Design

This was a single-arm, phase II study conducted at the Shanghai Cancer Center, Fudan University, approved by the local independent ethics committee (research no. FUSCC1301). The study was registered with ClinicalTrials.gov (NCT01833572).

Patient Enrollment

Patients with stage II-IIIA NSCLC (based on seventh edition of lung cancer TNM staging system) with a pathologic diagnosis of *EGFR* exon 19 deletion or exon 21 L858R mutation, older than the age of 18 years, fit for surgery, with an Eastern Cooperative Oncology Group performance status of 0 or 1, were recruited for this study. Patients were required to have a life expectancy >12 weeks, absolute neutrophil count >2.0 * 10^9/L, platelet count >100 * 10^9/L, hemoglobin >9 g/dL, and with normal liver and kidney function. Patients who were pregnant or breastfeeding, those

TABLE 1. Baseline characteristics of patients who received neoadjuvant gefitinib

Variable	No. of patients (%)
Sex	
Male	11 (31.4)
Female	24 (68.6)
Age, y, median (IQR)	57 (52-63)
BMI	
≤24	19 (54.3)
>24	16 (45.7)
Smoking status	
Ever	10 (28.6)
Never	25 (71.4)
Family malignant history	
Yes	10 (28.6)
No	25 (71.4)
FEV1%, median (IQR)*	90 (80-103)
DLCO%, median (IQR)*	92 (77-105)
Blood loss, mL, median (IQR)*	100 (100-200)
Operation time, h, median (IQR)*	1.8 (1.5-2)
Hospital stay, d, median (IQR)*	12 (11-16)
Duration from clinic to surgery, d, median (IQR)	61 (56-69)
cTNM stage	
IIA	6 (17.1)
IIB	2 (5.7)
IIIA	27 (77.1)
EGFR mutation	
Exon 19 deletion	24 (68.6)
L858R	11 (31.4)
Operative procedure*	
Lobectomy	31 (93.9)
Bi-lobectomy	2 (6.1)
Resected LN count*	
Mean ± SD	22.6 ± 9.5
Median (IQR)	21 (15-28)

IQR, Interquartile range; *BMI*, body mass index; *FEV1*, forced expiratory volume in 1 second; *DLCO*, diffusing capacity for carbon monoxide; *cTNM*, clinical tumor/node/metastasis staging; *EGFR*, epidermal growth factor receptor; *LN*, lymph node; *SD*, standard deviation. *Data were available in 33 patients.

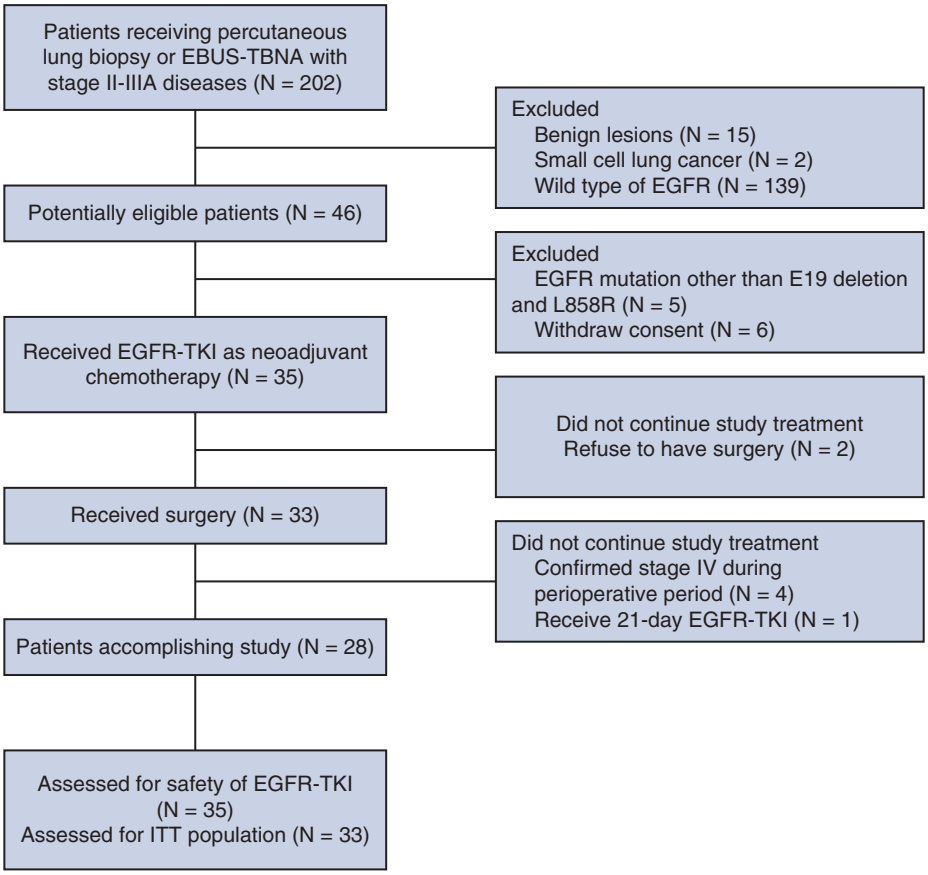


FIGURE 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the study design. *EBUS-TBNA*, endobronchial ultrasound-guided transbronchial needle aspiration; *EGFR*, epidermal growth factor receptor; *TKI*, tyrosine kinase inhibitor; *ITT*, intention-to-treat.

with interstitial lung disease or pulmonary fibrosis, impaired lung function (forced expiratory volume in 1 second <40% predicted value, or arterial blood gas partial pressure of oxygen <60 mm Hg), those who had used drugs directly acting on the *EGFR* pathway (including but not limited to erlotinib, gefitinib, cetuximab, or trastuzumab), or other lung cancer chemotherapy or systematic antitumor therapy, and patients with *EGFR*-T790M mutations were ineligible for this study.

Treatment Schedule

Preoperative treatment comprised 250 mg of oral gefitinib daily for 42 days before surgery. Surgical resection was scheduled after the treatment and involved resection of the tumor, preferably by lobectomy, and systematic lymph node dissection. Postoperative treatment was not specified in the research protocol and was prescribed at the discretion of the treating physician. Normally, platinum doublet chemotherapy was routinely recommended as adjuvant therapy for patients with stage II-IIIA NSCLC.

Assessment of Response

Computed tomography (CT) scans were performed to assess treatment response. All CT scans were reviewed by the same radiologists (S.W. and Q.L.), and radiologic tumor response was assessed by Response Evaluation Criteria in Solid Tumors (RECIST) measurement criteria (version 1.1) after 21 and 42 days of treatment.[10] The responses were classified as progressive disease (no less than 20% increased in size or the appearance of new lesions radiologically), stable disease (SD, less than 30% decreased and less than 20% increased in size radiologically), partial response (PR, no less than 30% decreased in size radiologically), and complete response (CR, no resident lesion radiologically).

Outcomes

The primary endpoint of this study was objective response rate (ORR), defined as the proportion of patients achieving CR or PR according to RECIST version 1.1.[10] Secondary endpoints were the rate of major pathologic response (MPR), DFS, OS, and adverse events (AEs). MPR was defined as the percentage of patients with major pathologic response, which was defined as no more than 10% viable tumor.[11,12]

Identification of EGFR Mutations

RNA was extracted from lung tumor needle biopsies, and total RNA was reverse transcribed into cDNA. Exons 19 to 21 of *EGFR* were amplified by polymerase chain reaction using exon-specific primers (forward primer: 5′-TGAAGGCTGTCCAACGAATG-3′ and reverse primer: 5′-AGGCGTTCTCCTTTCTCCAG-3′), and amplified products were analyzed by direct dideoxynucleotide sequencing.

Follow-up

Follow-up was conducted by personal visit or telephone. Physical examination, CT scans of the chest, ultrasonography of abdominal/cervical/supraclavicular regions, magnetic resonance imaging, or CT scans of the brain were performed every 4 months for the first 3 years after surgery, every 6 months for 3 to 5 years, and annually from then on; bone scans were performed annually. The cut-off date was November 2019, and follow-up was conducted until death. OS was considered to be the length of time between

TABLE 2. Adverse events and surgery-related complications reported in the study

Type of event	No. of patients			
	Grade 1/2		Grade 3/4	
	n	%	n	%
Adverse event (N = 35)	30	82.9	0	0
Skin toxicity	24	68.6	0	0
Gastrointestinal symptoms	17	48.6	0	0
Elevated ALT	7	20.0	0	0
Elevated AST	3	8.6	0	0
Expectoration	3	8.6	0	0
Liver disease	2	5.7	0	0
Cough	2	5.7	0	0
Chest discomfort	1	2.9	0	0
Loss of appetite	1	2.9	0	0
Muscle discomfort	1	2.9	0	0
Paronychia	1	2.9	0	0
Dizziness	1	2.9	0	0
Anemia	1	2.9	0	0
Hematuria	1	2.9	0	0
Increased urobilinogen	1	2.9	0	0
Surgery-related complication (N = 33)				
Chylothorax	4	12.1		

ALT, Alanine aminotransferase; *AST*, aspartate aminotransferase.

the day of surgery and the day of death or last follow-up. DFS was defined as the length of time from the day of surgery to the day of first recurrence or last follow-up. When calculating DFS, patients who died from other causes were considered censored with no event. Locoregional recurrence was defined as the recurrence in the primary site, ipsilateral hilar ipsilateral mediastinal lymph nodes or supraclavicular lymph nodes, while distant recurrence was defined as recurrence in other sites.

Statistical Analysis

Data were analyzed by using SPSS software (version 25.0; IBM Corp, Armonk, NY). Log-rank test was conducted to compare the differences between subgroups, and the Kaplan–Meier method was used to analyze DFS and OS. All tests were 2-tailed.

RESULTS

Patient Baseline Characteristics

Between August 2013 and October 2015, there were 202 potentially enrolled patients receiving percutaneous lung biopsy or endobronchial ultrasound-guided transbronchial needle aspiration with stage II-IIIA diseases. There were 167 excluded patients (15 patients with benign lesions, 2 patients with small cell lung cancer, 139 patients with wild type of *EGFR*, 5 patients with *EGFR* mutation other than E19 deletion and L858R, and 6 patients withdrawing consent). As a result, 35 patients who met the study criteria received preoperative gefitinib. Median age at diagnosis was 57 years (range, 31-76 years), and 11 (11/35; 31.4%) patients were male. Clinical and histologic baseline characteristics are detailed in Table 1. Two patients refused surgery and 1 underwent surgery after 21 days of gefitinib treatment. Six patients (6/35, 17.1%) had stage IIA disease at baseline, 2 (2/35, 5.7%) had stage IIB, and 27 (27/35, 77.1%) had stage IIIA. In the end, 28 patients received 42 days of gefitinib followed by resection surgery, and 33 patients were enrolled as the intention-to-treat (ITT) population (Figure 1). *EGFR* exon 19 deletions were found in the tumors of 24 patients receiving surgery (24/35, 68.6%), and exon 21 L858R mutations were found in 11 patients (11/35, 31.4%). Of 35 enrolled patients, 31 patients (31/35, 88.6%) underwent percutaneous lung biopsy, whereas the rest (4/35, 11.4%) underwent endobronchial ultrasound-guided transbronchial needle aspiration. Eight patients (8/25, 32%) had comorbidities (hypertension, diabetes, and coronary heart disease). Among 33 patients undergoing surgery, the median percentages of both forced expiratory volume in 1 second (FEV1) was 90% (interquartile range [IQR], 80-103), while that of diffusing capacity for carbon monoxide was 92% (IQR, 77-105). All patients underwent open thoracotomy, and no patients died within 90 days after surgery. The median blood loss was 100 mL (IQR, 100-200), and operative time was 1.8 hours (IQR, 1.5-2). All enrolled patients underwent systematic lymph node dissections. The median days of hospital stay and duration from first clinic visit to surgery were 12 (IQR, 11-16) and 61 (IQR, 56-69) days, respectively.

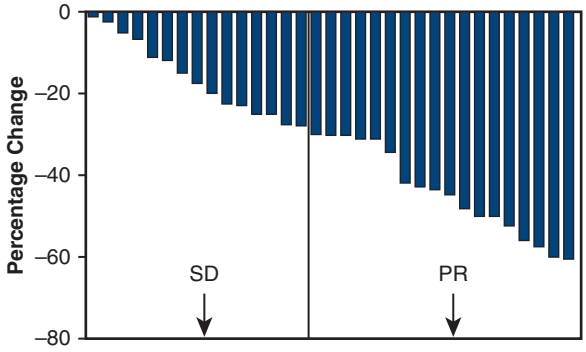


FIGURE 2. Waterfall plot of tumor size reduction and best response by patient after neoadjuvant gefitinib treatment. Each *bar* represents best response of each patient. *SD*, Stable disease; *PR*, partial response.

Treatment Toxicity and Feasibility

No unexpected toxicities were observed in the patient cohort (Table 2). Of the patients receiving neoadjuvant gefitinib, 30 of the 35 (85.7%) patients reported a total of 66 AEs. Skin toxicity (24/35, 68.6%) and gastrointestinal symptoms (17/35, 48.6%) were the most common ADEs, but were usually mild. There was no grade 3 or 4 ADE, and no reinterventions were necessary.

For surgery-related complications, 4 patients experienced chylothorax (4/33, 12.1%). No postoperative deaths occurred due to surgical procedures. All patients were discharged after receiving noninvasive procedures and recovering from surgery-related complications.

Primary Endpoint

In ITT analyses, the primary outcome, ORR, in this study was 54.5% (95% CI, 37.7-70.7). There were no patients with

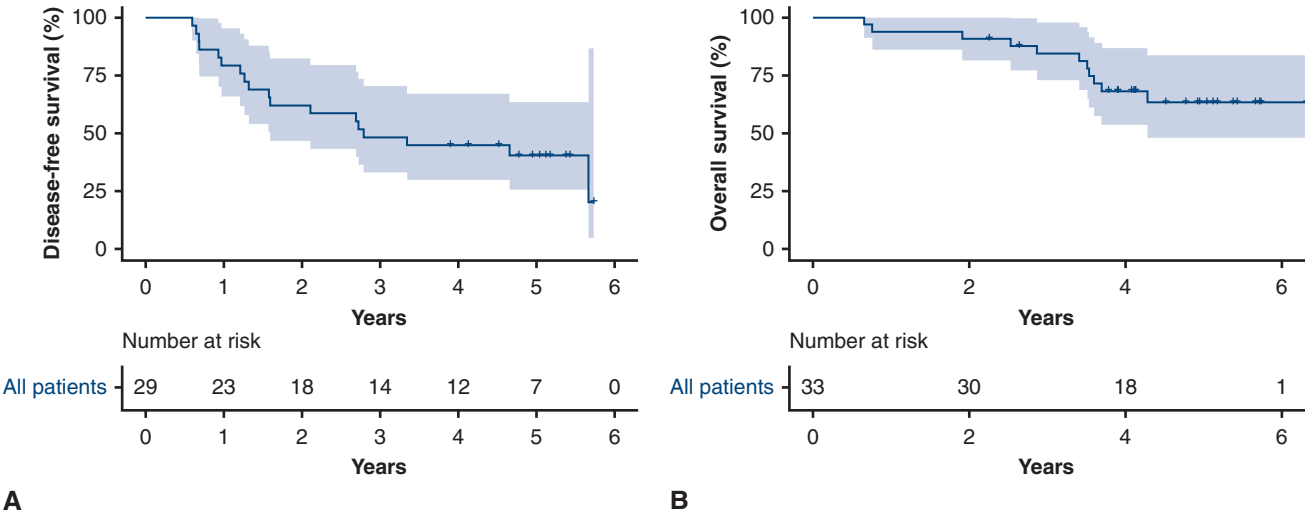


FIGURE 3. Kaplan–Meier curves of disease-free survival (A) and overall survival (B) of all enrolled patients (intention-to-treat population).

CR radiologically (0/33, 0%) and 4 patients with CR pathologically (4/33, 12.1%). Complete resection was achieved in 29 patients. PR was observed in 18 patients (18/33, 54.5%), and SD was observed in 15 patients (15/33, 45.5%). Response rates for each patient are shown in Figure 2.

Secondary Endpoints

As for secondary endpoints, the rate of MPR was 24.2% (95% CI, 11.9-40.4). Median follow-up time was 5.0 years. Secondary endpoints for the study also included DFS and OS (Figure 3). There were 4 patients later found to be stage IV (the metastatic sites were present at initial images and confirmed by follow-up), and DFS was not available for them. At data cut-off (November 2019), 11 (11/29, 37.9%) patients were disease free. Median DFS was 33.5 months (95% CI, 19.7-47.3). 22 of the 33 (22/33, 66.7%) patients were alive, and median OS was not reached. There was no patient died from other causes except lung cancer. All patients received adjuvant platinum doublet chemotherapy and/or radiotherapy. Pemetrexed plus cisplatin for 4 cycles were used as the adjuvant chemotherapy, and adjuvant radiotherapies were conducted by 50-62 Gy/25-28 Fx. Recurrence occurred in 18 of the 29 (62.1%) patients. Moreover, distant recurrences (14/18, 77.8%), 6 of which occurred in the brain, were more common than locoregional (4/18, 22.2%) recurrences (Table E1).

Survival Analyses

As detailed in Table 3, in the ITT population, survival analyses based on DFS showed tumors with MPR and lower ypTNM were related to improved DFS (viable tumor, $P = .015$; ypTNM, $P < .001$; Table 3 and Figure 4, *A*). Similarly, survival analyses based on OS showed high FEV1% were associated with prolonged survival (FEV1%, $P = .025$; Table E2), whereas patients with MPR had no significant difference of OS compared with those without ($P = .134$; Figure 4, *B*).

In addition, patients with SD achieved better DFS and OS than those with PR (DFS, $P = .015$; OS, $P = .131$). We also compared the percentage of viable cells stratified by radiologic response. Among patients with SD, there were 26.6% with MPR, whereas there were only 22.2% of PR patients with MPR (Figure E1). To compare the neoadjuvant role of gefitinib and platinum doublet chemotherapy, we selected 69 patients who received preoperative platinum doublet chemotherapy and surgery in our institution from 2007 to 2016. Survival difference in DFS or OS was not observed between neoadjuvant gefitinib and platinum doublet patients (DFS, $P = .21$; OS, $P = .15$, Figure E2).

DISCUSSION

EGFR-TKIs has been used as first-line therapies in advanced *EGFR*-mutant NSCLC, but there were few studies investigating the use of neoadjuvant *EGFR*-TKIs. The results of this study demonstrated that the use of neoadjuvant gefitinib could be considered for patients with NSCLC harboring *EGFR* mutations and was well tolerated. The primary endpoint of the study was the ORR, which was 54.5% (95% CI, 37.7-70.7). A recent study by Xiong and colleagues[13] investigated the use of neoadjuvant erlotinib in a similar patient group to our study and found an ORR of 42.1%, whereas EMERGING-CTONG 1103 reported an ORR of 54.1% for neoadjuvant erlotinib.[14] The ORR of our study was consistent with previous studies. However, ORR of neoadjuvant *EGFR*-TKIs seems lower than that of first-line *EGFR*-TKIs in patients with advanced *EGFR*-mutant NSCLC. One possible reason is the limited time of drug use. In and our studies and the study of Zhong and colleagues,[14] the duration of neoadjuvant *EGFR*-TKIs therapy was 42 days, and patients in the study of Xiong and

TABLE 3. Log-rank analyses for disease-free survival (intention-to-treat population)*

Variable	No. of patients	2-y DFS (%)	Median DFS, mo (95% CI)	*P* value
Sex				.243
Female	20	75.0	40.2 (0-80.5)	
Male	9	33.3	18.9 (9.9-27.9)	
Smoking				.363
Ever	8	37.5	15.8 (9.7-21.9)	
Never	21	71.4	40.2 (9.8-70.5)	
BMI				.209
≤24	14	71.4	68.0 (NR)	
>24	15	53.3	25.3 (8.4-42.2)	
Comorbidities				.891
Yes	7	71.4	32.3 (14.3-50.3)	
No	22	59.1	40.2 (0-90.5)	
FEV1%				.076
<95	16	43.8	18.9 (12.5-25.3)	
≥95%	13	84.6	NR	
DLCO				.601
<95	17	58.8	32.7 (13.3-52.0)	
≥95%	12	66.7	55.9 (34.6-77.1)	
Objective response				**.015**
PR	15	46.7	19.1 (0-39.9)	
SD	14	78.6	NR	
Viable tumor				**.019**
≥10%	21	52.4	25.3 (5.3-45.3)	
<10%	8	87.5	68.0 (0-NR)	
EGFR mutation type				.921
Exon 19 deletion	19	63.2	33.5 (1.3-65.7)	
L858R	10	60.0	25.3 (0-63.0)	
cTNM				.546
II	7	71.4	40.2 (20.0-60.4)	
IIIA	22	59.1	32.7 (0-70.8)	
ypTNM				**<.001**
0/I/II	14	85.7	NR	
IIIA	15	40.0	15.8 (10.0-21.6)	

DFS, Disease-free survival; *CI*, confidence interval; *BMI*, body mass index; *NR*, not reached; *FEV1*, forced expiratory volume in 1 second; *DLCO*, diffusing capacity for carbon monoxide; *PR*, partial response; *SD*, stable disease; *EGFR*, epidermal growth factor receptor; *cTNM*, clinical tumor/node/metastasis staging; *ypTNM*, pathologic TNM after neoadjuvant therapy. The *P* values in bold indicated statistical significance ($P < .05$). *In total, 29 patients of intention-to-treat population were analyzed for DFS. Four patients were later found to be stage IV, and DFS was not available for them.

colleagues[13] received preoperative *EGFR*-TKIs for 56 days. It might be not enough for tumors to decrease radiologically, because the necrotic tissues after targeted therapy still need a relatively long period to be absorbed even if tumors respond to the therapy. Another reason is the different malignancy of tumors in patient with different stages of NSCLC. For patients with advanced NSCLC, the biological behavior of tumors is more malignant than those of early-stage NSCLC, making tumors more sensitive to the drug. It leads to the greater ORR in patients with advanced NSCLC.

The studies of Xiong and colleagues and Zhong and colleagues mainly focused on patients with locally advanced *EGFR*-mutant NSCLC (IIIA-N2),[13,14] whereas patients were enrolled with stage II or IIIA in our study, including some patients whose disease remained local (stage II and stage IIIA excluding N2). We investigated the role of neoadjuvant gefitinib, whereas other studies focused on erlotinib. Therefore, to our knowledge, this is the first time the use of neoadjuvant gefitinib in patients with NSCLC has been investigated. The study suggests that neoadjuvant *EGFR*-TKI may have a role in eliciting a better response than traditional neoadjuvant regimens across different stages of disease. However, it is necessary to expand the sample size of this trial to further validate this observation and to ascertain the specific tumor characteristics that may confer this improved response.

As for the debate on adjuvant versus neoadjuvant therapy of EGFR-TKIs in lung cancer, there is still no consensus. There are some differences between current adjuvant[9,15,16] and neoadjuvant[13,14] EGFR-TKI therapy in patient selection and treatment schedule. However, for most neoadjuvant EGFR-TKIs clinical trials, the enrolled patients had stage IIIA-N2 NSCLC with EGFR mutation. For most adjuvant EGFR-TKIs clinical trials, the enrolled patients had early-stage diseases without detecting EGFR mutation. In addition, patients of some neoadjuvant EGFR-TKIs clinical trials such as EMERGING-CTONG 1103[14] also received gefitinib after surgery. Therefore, the comparison between adjuvant and neoadjuvant EGFR-TKI therapy could not be conducted based on current studies. Future clinical trials on adjuvant versus neoadjuvant EGFR-TKI therapy should be designed.

In our study, we found radiologic evaluation may not be as correlative as a pathologic one. Previous studies indicated radiologic methods were significant for evaluate the efficacy of drugs. In many studies,[17,18] patients with PR or CR achieved longer survival times than those with SD or progressive disease. However, the use of tumor shrinkage (as determined by CT) as the evaluation criteria after neoadjuvant treatment may cause false-negative responses.[12,19,20] As a matter of fact, the duration of drug exposure is essential to evaluate tumor response. Our analyses showed similar proportion of tumors achieving MPR in patients with SD or PR (SD, the rate of MPR: 26.6%; PR, the rate of MPR: 22.2%). The inconsistency between radiologic and pathologic response might result from the slow transition of apoptotic and necrotic cells, requiring several months. Evaluations in our study were performed at 21 and 42 days after neoadjuvant treatment, which may not have been sufficient for an effect to be observed. Lesions with SD radiologically and MPR simultaneously were likely to be consist of inflammatory cells, and patients with such lesions tended to have improved survival. Therefore, we believe radiologic response according to RECIST measurement criteria may not be a

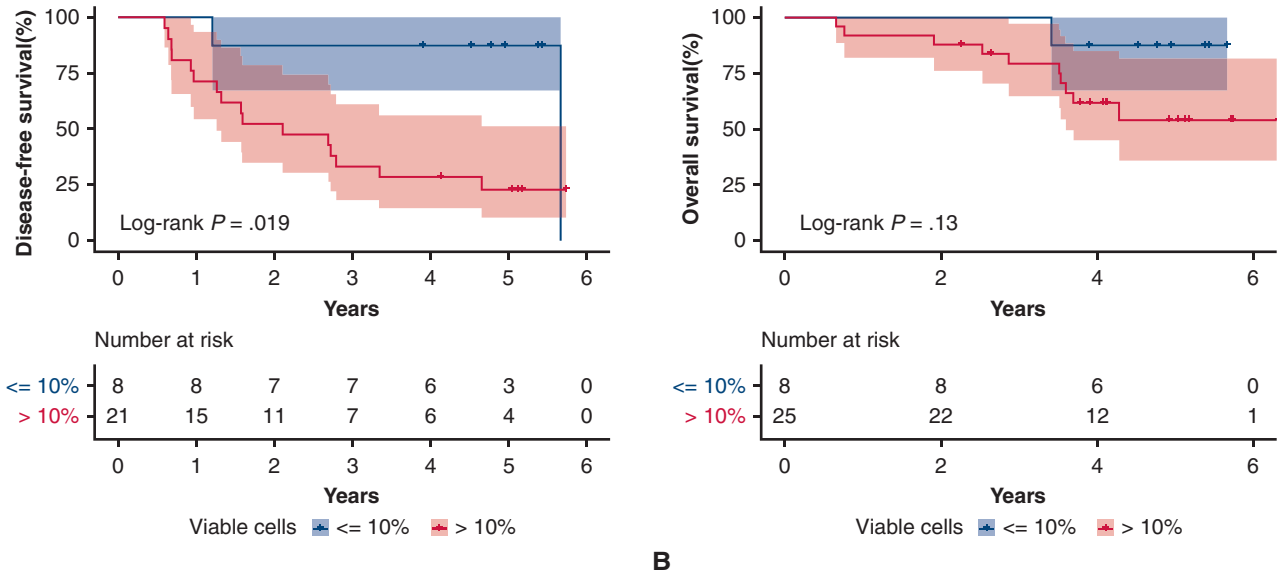


FIGURE 4. Kaplan–Meier curves of disease-free survival (A) and overall survival (B) stratified by viable cells pathologically (intention-to-treat population).

reliable variable of evaluation for neoadjuvant clinical trials, especially for trials with short period of drug exposure.

Furthermore, in our study, patients achieving MPR have better survival than those not (DFS, $P = .019$; OS, $P = .134$), implicating MPR is an essential endpoint for neoadjuvant trials. The study of William and colleagues[20] also showed MPR was associated with overall survival (hazard ratio, 2.39, $P = .05$). In the study of Chaft and colleagues,[21] of

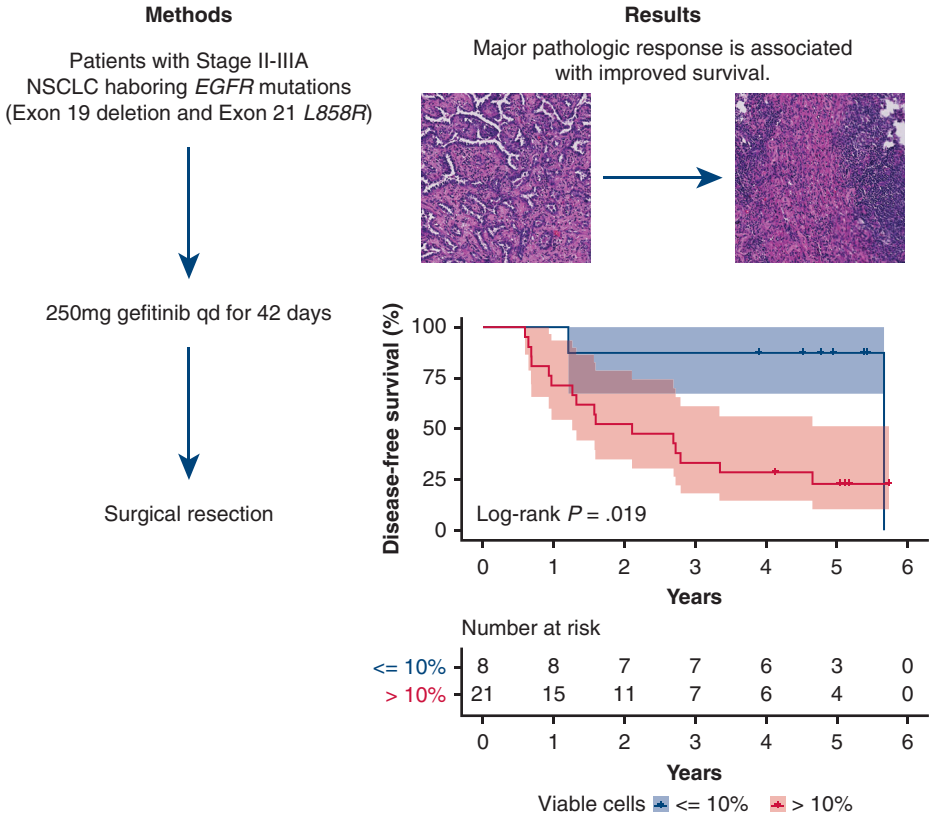
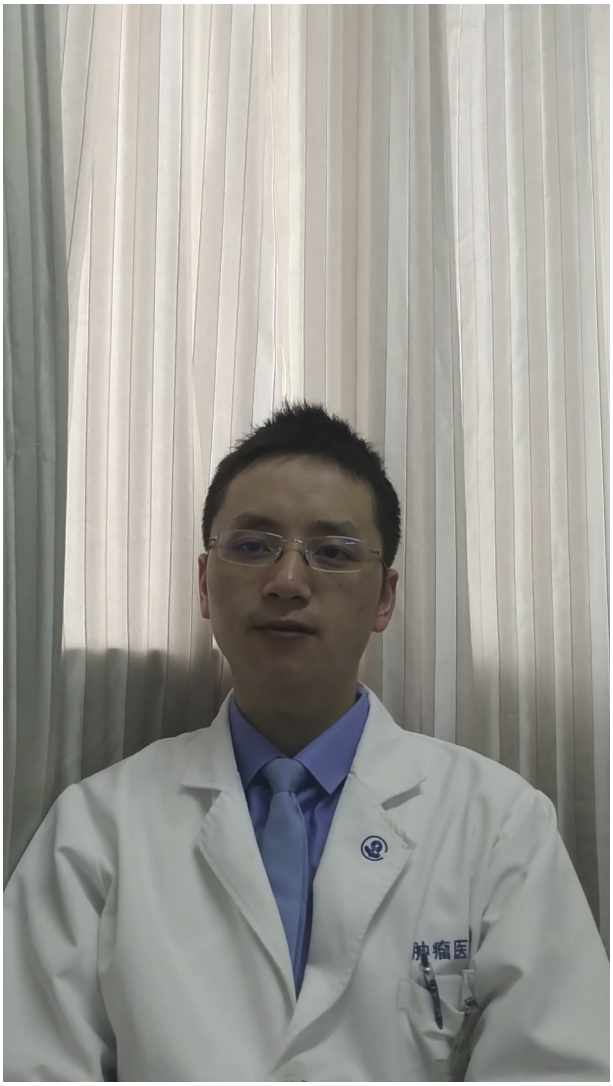


FIGURE 5. Methods, results, and implications of this study. This phase II trial demonstrated that neoadjuvant gefitinib was feasible in patients with clinically diagnosed stage II-IIIA NSCLC with EGFR-TKI–sensitive mutations. Pathologic evaluations might be a better predictor of survival than radiological assessments. *NSCLC*, Non–small cell lung cancer; *EGFR*, epidermal growth factor receptor.



VIDEO 1. A brief introduction of the study. Video available at: https://www.jtcvs.org/article/S0022-5223(20)30625-5/fulltext.

50 patients with stage IB-IIIA NSCLCs receiving neoadjuvant platinum doublet chemotherapy and bevacizumab, 22% patients achieved MPR. As for neoadjuvant PD-1, there were 45.0% patients with MPR in the study of Forde and colleagues.[22] Compared with EMERGING-CTONG 1103 (MPR, 9.7%), the rate of MPR in our study was much higher (MPR, 24.2%). The difference may result from limited patient numbers and distinct drugs of 2 studies. Moreover, Hellmann and colleagues[12] thought MPR could serve as a surrogate endpoint for neoadjuvant chemotherapy in resectable NSCLC. Since most of traditional clinical trials of neoadjuvant chemotherapy consider patients' survival as their primary endpoint, it takes a long time to publish the data, leading to slow progress in resectable NSCLC. In our study, patients with MPR had significantly better DFS ($P = .019$) and no significant difference on OS ($P = .134$), compared with those without MPR. The reason for this finding might be that some patients received treatment with EGFR-TKIs at recurrence, which did not decrease DFS but may have impacted the OS. Among of 28 patients completing the study, 7 patients received treatment with EGFR-TKIs after recurrence (5 patients were without MPR). Our results demonstrated the rate of MPR was correlated with improved survival, adding to the evidence that the rate of MPR could serve as a surrogate endpoint for neoadjuvant trials. Moreover, there are few studies investigating prognostic effect of MPR, and future neoadjuvant trials should focus on the association between MPR and improved survival.

Of the 35 patients receiving gefitinib, 30 (85.7%) reported a total of 66 AEs. All the reported AEs were grade 1 or 2, with skin and gastrointestinal events being the most common. This study is in line with published studies, which report rash and diarrhea to be commonly observed AEs associated with gefitinib.[23,24] A class-effect toxicity of *EGFR*-TKI is pneumonitis, although its incidence is relatively low. In a meta-analysis of 136 cohorts around the world, 1.12% of patients treated with *EGFR*-TKI reported pneumonitis, and 2.11% when looking at the 33 cohorts which only included patients with *EGFR* mutations.[25] None of the patients in our study had pneumonitis. Toxicity is not a limiting factor for using neoadjuvant gefitinib for the treatment of resectable, stage II-IIIA NSCLC with *EGFR* mutations. Gene sequencing of tumors before commencing treatment with *EGFR*-TKI should therefore be considered to derive the maximum benefit of targeted treatments. In addition, the complications of surgery were also acceptable in our study. Therefore, neoadjuvant *EGFR*-TKIs in patients harboring *EGFR* mutation were safe and feasible in clinical practice. Since osimertinib has been become the first- line agent in advanced *EGFR*-mutant NSCLC,[26] clinical trials regarding to neoadjuvant osimertinib may need further investigations.

There were several limitations in this study. First, this was a single-arm study, so it is not possible to determine any relative survival benefits resulting from neoadjuvant gefitinib treatment. Even though we compared it with our historical data, the comparison seemed to be of low-level evidence. Second, the sample size in this study was small, leading to inadequate power to determine DFS or OS benefit. Third, this study was performed at only one center. Multicenter studies with external validation are required in the future. Finally, postoperative treatment was determined by the treating physician and was not included in the trial protocol, which may have impacted patient outcomes. As such, it is difficult to attribute survival effects solely to neoadjuvant gefitinib treatment. Given the positive results from adjuvant *EGFR*-TKI studies, including the use *EGFR*-TKI in retreatment after relapse or recurrence, inclusion of gefitinib as adjuvant treatment following surgery may lead to further survival benefits.[27-29]

CONCLUSIONS

Gefitinib as neoadjuvant therapy for stage II-IIIA NSCLC with *EGFR*-TKI-sensitive mutations has an acceptable toxicity profile and is feasible in clinical practice. Pathologic evaluations might be a better predictor of survival than radiologic assessments (Figure 5). Although the sample size in this study is relatively small, the effects of neoadjuvant gefitinib on OS and DFS are promising. The use of gefitinib in a preoperative setting warrants further validation in a larger population. A brief introduction to this study is shown in Video 1.

Conflict of Interest Statement

AstraZeneca provided gefitinib to enrolled patients as neoadjuvant therapy free of charge. Drs Zhang and Chen received speaker fees from AstraZeneca. All other authors have nothing to disclose with regard to commercial support.

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Key Words: non–small cell lung carcinoma, neoadjuvant therapy, gefitinib, epidermal growth factor receptor

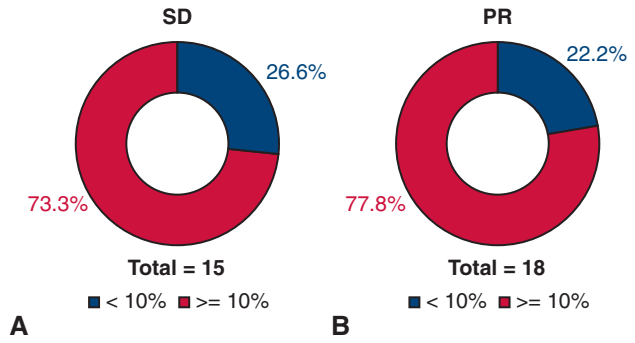

FIGURE E1. Percentage of patients with no more than 10% and more than 10% viable cells stratified by SD (A) and PR (B) (intention-to-treat population). *SD*, Stable disease; *PR*, partial response.

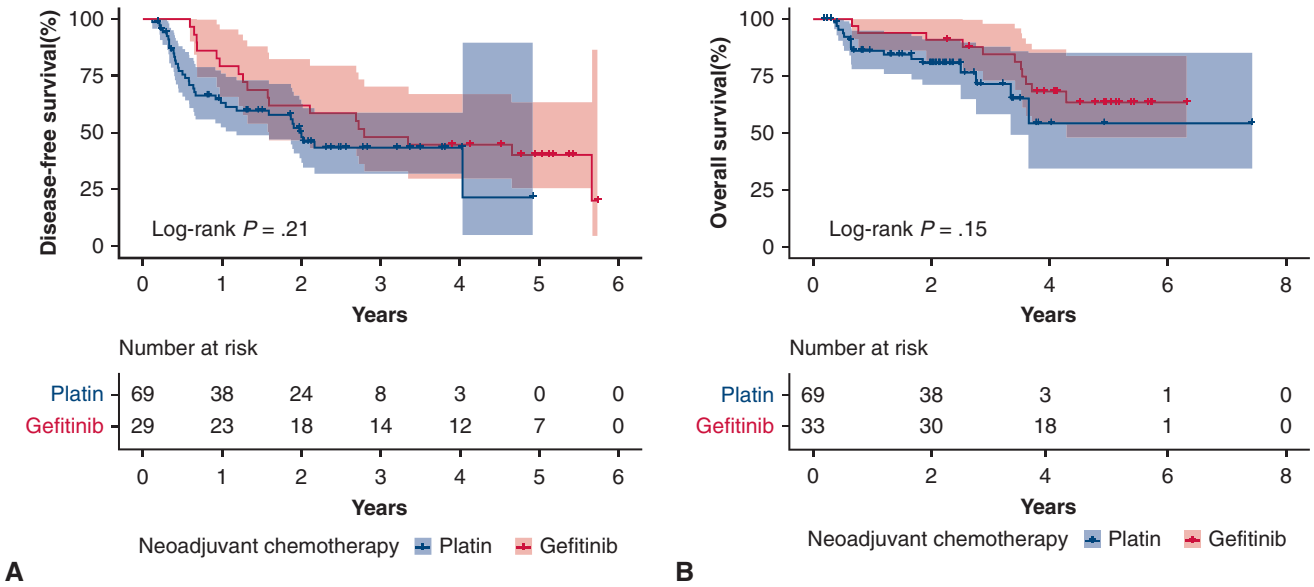

FIGURE E2. Kaplan–Meier curves of disease-free survival (A) and overall survival (B) between patients with neoadjuvant gefitinib and platinum doublet therapy.

TABLE E1. Disease recurrence after EGFR-TKI as neoadjuvant chemotherapy

Recurrent patterns	Number (%)
Locoregional recurrence (n = 4)	
Ipsilateral lung	1 (25.0)
Ipsilateral mediastinal LN	2 (50.0)
Ipsilateral cervical LN	1 (25.0)
Distant recurrence (n = 14)	
Brain	6 (42.9)
Bone	5 (35.7)
Contralateral lung	4 (28.5)
Liver	1 (7.1)

EGFR, Epidermal growth factor receptor; *TKI*, tyrosine kinase inhibitor.

TABLE E2. Log-rank analyses for overall survival (intention-to-treat population)

Variable	No. of patients	2-y OS (%)	Median OS, mo (95% CI)	*P* value
Sex				.180
Female	23	95.7	NR	
Male	10	80.0	44.4 (NR)	
Smoking				.083
Ever	9	77.8	44.4 (34.3-54.4)	
Never	24	95.8	NR	
BMI				.080
≤24	17	88.2	NR	
>24	16	93.8	51.4 (NR)	
Objective response				.131
PR	18	88.9	51.4 (NR)	
SD	15	93.3	NR	
Co-morbidities				.897
Yes	8	100.0	NR	
No	25	88.0	NR	
FEV1%				**.025**
<95	19	84.2	44.4 (NR)	
≥95%	14	100.0	NR	
DLCO				.731
<95	20	90.0	NR	
≥95%	13	92.3	NR	
Viable tumor				.134
>10%	25	88.0	NR	
≤10%	8	100.0	NR	
EGFR mutation type				.868
Exon 19 deletion	22	86.4	NR	
L858R	11	100.0	NR	
cTNM				.203
II	7	85.7	43.2 (41.2-45.2)	
IIIA	26	92.3	NR	
ypTNM				.416
0/I/II	14	92.9	NR	
III/IV	19	89.5	NR	

OS, Overall survival; *CI*, confidence interval; *NR*, not reached; *BMI*, body mass index; *PR*, partial response; *SD*, stable disease; *FEV1*, forced expiratory volume in 1 second; *DLCO*, diffusing capacity for carbon monoxide; *EGFR*, epidermal growth factor receptor; *cTNM*, clinical tumor/node/metastasis staging; *ypTNM*, pathologic TNM after neoadjuvant therapy. The *P* values in bold indicated statistical significance ($P < .05$).