Pyrotinib in Patients with HER2-Amplified Advanced Non–Small Cell Lung Cancer: A Prospective, Multicenter, Single-Arm Trial

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ABSTRACT

Purpose: In this study, we aimed to evaluate the efficacy and safety of pyrotinib, a pan-HER inhibitor, in patients with *HER2*-amplified non–small cell lung cancer (NSCLC).

Patients and Methods: In this prospective, multicenter, single-arm trial (ChiCTR1800020262), patients with advanced NSCLC with *HER2* amplification, as determined by next-generation sequencing, were enrolled and administered pyrotinib orally at 400 mg per day. The primary endpoint was 6-month progression-free survival (PFS) rate. Other endpoints included objective response rate (ORR), disease control rate (DCR), PFS, overall survival (OS), and safety.

Results: The enrolled cohort included 27 patients with *HER2* amplification. The 6-month PFS rate was 51.9% [95% confidence interval (CI), 34.0–69.3]. The median PFS (mPFS) was 6.3 months (95% CI, 3.0–9.6 months), and median OS was 12.5 months (95% CI, 8.2–16.8 months). Pyrotinib elicited a confirmed ORR of 22.2% (95% CI, 10.6%−40.8%). Patients administered pyrotinib as first-line treatment achieved an mPFS of 12.4 months. Moreover, 30.8% of the patients who had progressed on EGFR tyrosine kinase inhibitor (TKI) responded to pyrotinib. Patients with brain metastases had an ORR of 40%. Treatment-related adverse events (TRAE) occurred in all patients (grade 3, 22.2%), but no grade 4 or higher TRAEs were documented. Diarrhea was the most frequent TRAE (all, 92.6%; grade 3, 7.4%). Loss of *HER2* amplification was detected upon disease progression.

Conclusions: Pyrotinib provided antitumor efficacy with a manageable safety profile in *HER2*-amplified patients with NSCLC.

Introduction

In the past decades, systemic treatment targeting driver gene mutations has radically transformed the clinical care of patients with non–small cell lung cancer (NSCLC). However, there are currently no targeted agents approved for patients with HER2-positive NSCLC. HER2-positivity, which commonly refers to HER2 overexpression and/or *HER2* amplification, occurs in 2% to 15% of patients with NSCLC (1–5). Although HER2-targeting drugs have improved clinical outcomes compared with chemotherapy alone in malignancies such as breast and gastric cancers, an array of anti-HER2 agents show limited clinical efficacy in patients with HER2-positive NSCLC (6–9). Dacomtinib, a pan-HER tyrosine kinase inhibitor (TKI), is ineffective in patients with *HER2*-amplified advanced lung cancer ($N = 4$; ref. 10). In a retrospective study, afatinib, another HER family inhibitor, elicited a response in four of 12 metastatic NSCLC with *HER2* amplification, yielding a median progression-free survival (mPFS) of 3.3 months (11). In two basket studies, pertuzumab plus trastuzumab and ado-trastuzumab emtansine (T-DM1) monotherapy produced objective response rates (ORR) of only 13% and 6.7%, respectively, among patients with advanced NSCLC with *HER2* amplification and/or HER2 overexpression (12, 13). Chemotherapy, the current standard of care for HER2-positive NSCLC, typically elicits an mPFS of 5 to 6 months in the first-line setting and is associated with intolerable toxicities, significantly limiting its clinical utility (14–16). Therefore, there is an unmet need to explore effective targeted therapies for this subset of patients.

Pyrotinib, an irreversible pan-HER TKI inhibiting HER1/EGFR, HER2, and HER4, attracts increasing attention as a potential treatment for HER2-positive solid tumors. It was initially approved in China for treating patients with advanced or metastatic HER2-positive breast cancer (17). Beyond breast cancer, there exists evidence showing robust antitumor activities of pyrotinib in patients with HER2-positive advanced gastric cancer (18). In NSCLC, pyrotinib was found to exert promising efficacy in *HER2*-mutated patients according to two phase II trials; however, little is known about its effects on NSCLC with *HER2* amplification or HER2 overexpression (19, 20). In a retrospective basket study, 4 of 9 patients with *HER2*-amplified/HER2-overexpressed lung

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Translational Relevance

Pyrotinib, a pan-HER inhibitor, has shown antitumor activity in patients with *HER2*-amplified and/or HER2-overexpressed advanced breast cancer and *HER2*-mutated non–small cell lung cancer (NSCLC), but little is known about its effects in *HER2*-amplified and/or HER2-overexpressed NSCLC. Chemotherapy, the current standard of care for *HER2*-amplifid NSCLC, typically elicits a median progression-free survival (mPFS) of 5 to 6 months in the first-line setting and is associated with intolerable toxicities, significantly limiting its clinical utility. In this prospective study, we reported that pyrotinib exhibited promising efficacy and acceptable safety in 27 patients with advanced *HER2*-amplified NSCLC. Patients who had prior exposure to EGFR tyrosine kinase inhibitor (EGFR-TKI) therapy and brain metastases can benefit from pyrotinib as well. In addition, we utilized circulating tumor DNA (ctDNA) to monitor disease progression, and found a loss of *HER2* amplification was detected from 4 patients upon disease progression, indicating their potential roles in the resistance to pyrotinib.

cancer responded to pyrotinib, suggesting the potential of pyrotinib in treating this subset of patients (21).

In this study, we aimed to evaluate in a prospective manner the efficacy and safety of pyrotinib in patients with *HER2*-amplified NSCLC. In addition, we also explored the potential utility of genomic profiles obtained from circulating tumor DNA (ctDNA) to monitor disease progression.

Patients and Methods

Patients

Between January 4, 2019 and April 15, 2020, patients were prospectively recruited in nine centers. Patients who met the following criteria were eligible: age ≥18 years; histocytologically confirmed unresectable stage III B or IV NSCLC; at least one radiographically measurable lesion; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 to 2; *HER2* amplification as determined by next-generation sequencing (NGS).

Patients with previous surgery, chemotherapy, radiotherapy, or any other targeted therapy for NSCLC within 4 weeks before the initiation of the study treatment were also excluded. This study was registered in the Chinese Clinical Trial Registry (ChiCTR1800020262) and approved by each institution's ethic committee in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Each patient provided written informed consent before the initiation of any study-related treatment.

Study design and treatment

Pyrotinib was administered orally within 0.5 hours after breakfast at a dose of 400 mg/day. Treatment was discontinued when progressive disease (PD) or intolerable adverse events occurred, or at patient's request. The dose of pyrotinib was reduced to 320 mg daily in case of intolerable toxicities. Depending on sample availability, biopsy tissue or peripheral blood was collected from each patient at baseline and subjected to NGS.

Outcomes

The primary endpoint was PFS rate at 6 months, defined as no progression or death due to any cause within the first 6 months after initiation of pyrotinib. Secondary endpoints were ORR [rate of patients with confirmed partial response (PR) or complete response (CR) at two consecutive evaluations at least 4 weeks apart per RECIST version 1.1], PFS (time between the start of the study treatment and PD or any-cause death), overall survival [OS (time between the start of the study treatment and any-cause death)], duration of response (time between the first objective response and PD or any-cause death), disease control rate [DCR, the sum of stable disease (SD), PR, and CR, lasting ≥ 6 weeks before PD}, and safety. Patients were monitored for adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (22). Radiologic assessments were conducted every 6 weeks in the first year, and every 9 weeks thereafter. Upon PD, patients were followed up every 3 months until death. The associations of baseline clinicophysiologic characteristics with ORR, PFS, OS, and DCR were also examined.

NGS

NGS-based molecular profiling was performed using baseline tissue or blood samples to identify genetic aberrations, including but not limited to alterations in the driver genes (*EGFR*, *ALK*, *ROS1*, *MET*, *BRAF*, *RET*, *HER2*, *KRAS*, *NTRK1*, *NTRK2*, and *NTRK3*) recommended by the National Comprehensive Cancer Network (NCCN) for NSCLC. The gene list of 150-gene and 23-gene panels are attached in Supplementary Tables S1 and S2. Under patients' consents, blood samples were also collected from some patients upon disease progression and assessed using NGS. Sample preparation, sequencing, and data analysis were performed as previously described by 3D Medicines, Inc., a clinical laboratory accredited by the College of American Pathologists (CAP) and certified by the Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory (Supplementary Methods; refs. 23, 24). BIC-seq2 was used for detecting copy-number variants (CNV), and *HER2* amplification was defined as $\log_2$ ratio > 0.7 and gene copy number (GCN) ≥ 6 (23, 25).

Statistical analysis

A total of 24 patients would provide 80% power to detect a 6-month PFS rate of 50% at a 0.5% α level under the null hypothesis that the 6-month PFS rate of chemotherapy is 20% (26). With the consideration of a dropout rate of 10%, a total of 27 patients would need to be enrolled. The SPSS statistical package (version 20.0) and GraphPad prism (version 7) were applied for performing statistical analyses. Kaplan–Meier curves showing PFS and OS were assessed by the log-rank test. The Fisher exact test was performed to analyze ORR and DCR between different groups. Cox regression was conducted for calculating HR and 95% confidence intervals (CI). Two-tailed $P < 0.05$ was considered statistically significant.

Data availability statement

The data generated in this study are available within the article and its Supplementary Data files.

Ethics approval and consent to participate

This study was registered in the Chinese Clinical Trial Registry (ChiCTR1800020262) and approved by each institution's ethic committee in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Informed consent was obtained from all individual participants included in the study.

Results

Patient characteristics

From January 4, 2019 to April 15, 2020, a total of 33 patients with NSCLC were enrolled, among whom 6 were excluded, for no *HER2* amplification ($n = 3$), an ECOG PS score of 3 ($n = 1$), no radiographically measurable lesion ($n = 1$), and informed consent withdrawal before treatment ($n = 1$). Twenty-seven patients received pyrotinib treatment and were included in efficacy and safety analyses (Supplementary Fig. S1). As of January 11, 2021, 4 patients remained on study treatment, and 23 discontinued pyrotinib treatment after disease progression. The median follow-up duration was 12.5 months (range, 2.8–17.7 months).

The median age of the patients was 61 years. The majority of them were nonsmokers (63.0%; **Table 1**). All patients had stage IV disease, and adenocarcinoma (92.6%) was the predominant pathologic subtype. Approximately 85.0% of the patients had PS scores of 0 to 1, and brain metastases were observed in 18.5% of the patients. The detected molecular alterations at baseline in all patients are listed in Supplementary Table S3. Mutations in the driver genes *EGFR*, *ALK*, *MET*, and *KRAS* were detected, and concurrent driver mutations were found in twelve cases (44.4%). Seventeen (63.0%) patients had at least one line of prior chemotherapy, while 13 (48.1%) and one cases were previously treated with EGFR-TKI and an ALK inhibitor, respectively. Most patients received pyrotinib as secondary line or higher therapy (first-line, 22.2%; second-line or higher, 77.8%).

Efficacy

As of January 11, 2021, the median duration of drug exposure was 6.3 months. The 6-month PFS rate was 51.9% (95% CI, 34.0–69.3; **Fig. 1**). The 12-month PFS and OS rates were 13.3% and 54.1%, respectively. As of data cutoff, 85.2% (23/27) of the patients experienced PFS events, and the mPFS was 6.3 months (95% CI, 3.0–9.6 months). A total of 17 patients (63.0%) died, showing a median OS (mOS) of 12.5 months (95% CI, 8.2–16.8 months). The confirmed ORR based on investigator's assessment was 22.2% (95% CI, 10.6–40.8; **Fig. 2**; **Table 2**). The DCR was 81.5% (95% CI, 63.3–91.8). The median duration of response was 7.2 months (95% CI, 5.2–8.4 months; **Fig. 3**).

After stratification based upon baseline characteristics (Supplementary Table S4), patients with adenocarcinoma had significantly prolonged OS (12.8 vs. 4.9 months; HR = 0.10; 95% CI, 0.02–0.54; $P < 0.001$) compared with squamous carcinoma cases. Patients with a PS score of 2 trended to have numerically inferior mPFS (3.3 vs. 7.2 months; HR = 2.73; 95% CI, 0.84–8.92; $P = 0.081$) and mOS (9.2 vs. 13.2 months; HR = 2.95; 95% CI, 0.92–9.43; $P = 0.056$) than those with PS scores of 0 to 1. Smoking history, gender, or brain metastases were not correlated with ORR, PFS, or OS (Supplementary Fig. S2; Supplementary Table S4). Of note, patients with brain metastases had an ORR of 40%. Among the 5 patients with brain metastases, 2 achieved PR, of whom 1 had an intracranial response and another had extracranial response with stable intracranial lesions.

With regard to subgroups defined by the line of treatment, patients treated in the second-line or higher had reduced PFS (4.7 vs. 12.4 months; HR = 3.89; 95% CI, 1.12–13.60; $P = 0.023$) than the first-line group, whereas no significant difference in OS was observed between these two groups. Among the 13 patients previously exposed to EGFR-TKI, 4 achieved PR, 7 had SD, and 2 experienced PD, achieving an ORR of 30.8%, an mPFS of 7.2 months, and an mOS of 12.8 months. In addition, ORR was 50% in 4 patients who had previously received afatinib, and the ORR was 28.6% in 7 who received TKIs without a reported activity against HER2. Patients who had previously received anticancer chemotherapy exhibited numerically worse ORR (17.6% vs. 30.0%; $P = 0.638$), DCR (70.6% vs. 100.0%;

Table 1. Patient characteristics.

Characteristics	
Age, years	
Median (range)	61 (39–78)
<60	13 (48.1)
≥60	14 (51.9)
Sex, *n* (%)	
Male	18 (66.7)
Female	9 (33.3)
Smoking status, *n* (%)	
Former	10 (37.0)
Never	17 (63.0)
ECOG PS, *n* (%)	
0	4 (14.8)
1	19 (70.4)
2	4 (14.8)
Histology, *n* (%)	
Adenocarcinoma	25 (92.6)
Squamous carcinoma	2 (7.4)
Stage, *n* (%)	
IV	27 (100)
Brain metastases, *n* (%)	
No	22 (81.5)
Yes	5 (18.5)
Pyrotinib treatment line, *n* (%)	
1	6 (22.2)
2	6 (22.2)
≥3	15 (55.6)
Prior chemotherapy, *n* (%)	
Yes	17 (63.0)
No	10 (37.0)
Prior EGFR-TKI, *n* (%)	
Yes	13 (48.1)
Icotinib	5 (18.5)
Afatinib	4 (14.8)
Gefitinib	1 (3.7)
Gefitinib, afatinib[a]	1 (3.7)
Gefitinib, osimertinib[a]	1 (3.7)
Icotinib, osimertinib, afatinib[a]	1 (3.7)
No	14 (51.9)
Driver mutation status[b], *n* (%)	
Positive	12 (44.4)
Negative	15 (55.6)
HER2 mutation status, *n* (%)	
Positive	9 (33.3)
Negative	18 (66.7)
EGFR mutation status, *n* (%)	
Positive	10 (37.0)
Negative	17 (63.0)
ALK fusion status, *n* (%)	
Positive	1 (3.7)
Negative	26 (96.3)
TP53 mutation status, *n* (%)	
Positive	20 (74.1)
Negative	7 (25.9)

[a]Sequential therapy.
[b]Driver mutation: pathogenic mutation in driver genes, including EGFR, ALK, ROS1, MET, BRAF, RET, HER2, KRAS, NTRK1, NTRK2, and NTRK3.

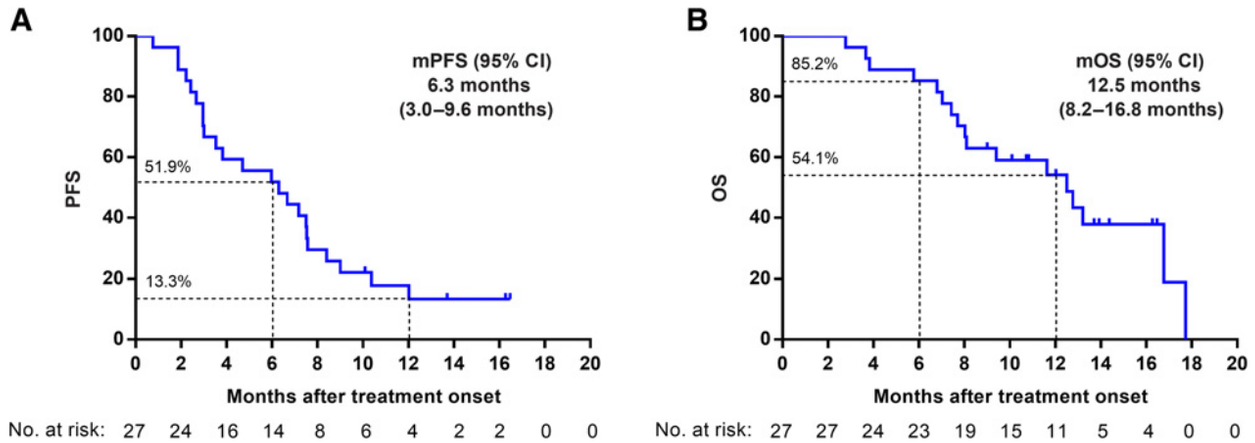

Figure 1.
Kaplan–Meier survival curves of PFS (**A**) and OS (**B**) in pyrotinib-treated patients with NSCLC with *HER2* amplification.

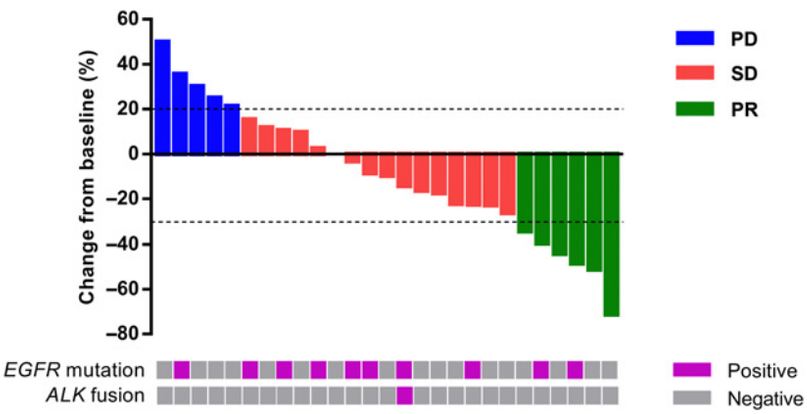

Figure 2.
Waterfall plot of maximum percentage change from baseline in target lesions.

$P = 0.124$), and PFS (4.7 vs. 7.8 months; $P = 0.083$) compared with those not previously treated with chemotherapy. Patients with concurrent driver mutations tended to have numerically inferior ORR than their wild-type (WT) counterparts. Mutations in *HER2*, *EGFR*, or *TP53* were not associated with ORR, PFS, or OS (Supplementary Table S4; Supplementary Fig. S2).

Table 2. Clinical response to pyrotinib in patients with NSCLC with *HER2* amplification.

Variable	
Best response, *n* (%)	
PR	6 (22.2)
SD	16 (59.3)
PD	5 (18.5)
ORR, % (95% CI)	22.2 (10.6–40.8)
DCR, % (95% CI)	81.5 (63.3–91.8)
PFS	
Events, *n* (%)	23 (85.2)
Median, months (95% CI)	6.3 (3.0–9.6)
OS	
Events, *n* (%)	17 (63.0)
Median, months (95% CI)	12.5 (8.2–16.8)

Safety

Treatment-related toxicities were observed in all patients (**Table 3**). The most common treatment-related adverse event (TRAE) was diarrhea (92.6%), followed by anemia (48.1%), nausea (37.0%), fatigue (37.0%), vomiting (33.3%), and cough (33.3%). Grade 3 TRAEs occurred in 6 patients (22.2%), including two diarrhea (7.4%), two vomiting (7.4%), one alanine aminotransferase (ALT) increase (3.7%), and one rash (3.7%) cases. No grade 4 or higher TRAEs were reported. Three patients had a dose reduction due to intolerable toxicities, and no patients discontinued the study treatment as a result of TRAEs.

The feasibility of utilizing ctDNA to monitor disease progression

Among the 23 patients with PD in the enrolled cohort, 7 patients had somatic mutation profiling done both at baseline and upon PD (Supplementary Table S5). A loss of *HER2* amplification was detected from 4 patients upon PD, consistent with a previous study which pointed out a potential role for loss of *HER2* CNV in resistance to anti-HER2 TKI (27). In addition, appearance of *EGFR* amplification was identified from another patient at disease progression. One patient had a loss of *EGFR* T790M and a concurrent loss of *EGFR* amplification.

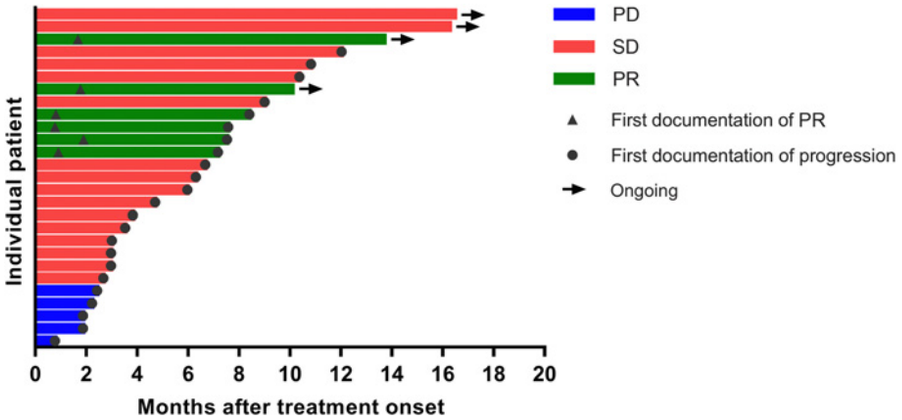

Figure 3.
Swimming plot showing the duration of pyrotinib treatment.

Discussion

In this prospective trial conducted in 27 patients with *HER2*-amplified NSCLC, the 6-month PFS rate achieved by pyrotinib was 51.9%, with an ORR of 22.2%, an mPFS of 6.3 months, and an mOS of 12.5 months. TRAEs were reported in all patients (grade 3, 22.2%), but no grade 4 or higher TRAEs were observed. Moreover, 30.8% of cases who had progressed on EGFR-TKI were also able to respond to pyrotinib. Patients with brain metastases had an ORR of 40%.

The clinical outcomes of HER2-positive patients remain dismal, since the current standard-of-care, chemotherapy, is associated with an mPFS of only 5 to 6 months in the first-line setting (15). Additionally, drug-associated toxicities render chemotherapy intolerable for a vast number of patients (16). In the present study, the mPFS achieved by pyrotinib was 12.4 months in the first-line, indicating that pyrotinib may be a better option than chemotherapy for first-line treatment, which need to be validated in randomized controlled trials. With regard to safety, the incidence of grade 3 or 4 TRAEs resulting from chemotherapy was 30% to 60% according to previous reports (28, 29), whereas pyrotinib led to grade 3 TRAEs in approximately 20% of individuals without causing any grade 4 or higher TRAEs in this study. This finding was also supported by previous studies where pyrotinib resulted in around 20% TRAEs, suggesting that pyrotinib may be safer than chemotherapy (19, 20).

Table 3. TRAEs.

	Pyrotinib (n = 27), n (%)			
Adverse event	**All grades[a]**	**Grade 1**	**Grade 2**	**Grade 3**
Any	27 (100)	26 (96.3)	17 (63.0)	6 (22.2)
Occurring in ≥10% of patients				
Diarrhea	25 (92.6)	14 (51.9)	9 (33.3)	2 (7.4)
Anemia	13 (48.1)	11 (40.7)	2 (7.4)	
Nausea	10 (37.0)	7 (25.9)	3 (11.1)	
Fatigue	10 (37.0)	8 (29.6)	2 (7.4)	
Vomiting	9 (33.3)	6 (22.2)	1 (3.7)	2 (7.4)
Cough	9 (33.3)	9 (33.3)		
Dizziness	8 (29.6)	8 (29.6)		
Hand–foot syndrome	8 (29.6)	7 (25.9)	1 (3.7)	
AST increased	8 (29.6)	6 (22.2)	2 (7.4)	
Decreased appetite	7 (25.9)	6 (22.2)	1 (3.7)	
Blood creatinine increased	6 (22.2)	5 (18.5)	1 (3.7)	
WBC decreased	6 (22.2)	3 (11.1)	3 (11.1)	
Hypokalemia	5 (18.5)	5 (18.5)		
Hyponatremia	4 (14.8)	4 (14.8)		
Weight decreased	4 (14.8)	4 (14.8)		
Headache	4 (14.8)	3 (11.1)	1 (3.7)	
Thrombocytopenia	4 (14.8)	4 (14.8)		
ALT increased	4 (14.8)	3 (11.1)		1 (3.7)
Constipation	3 (11.1)	3 (11.1)		
Blood bilirubin increased	3 (11.1)	3 (11.1)		
Hypochloremia	3 (11.1)	3 (11.1)		
Rash	3 (11.1)	2 (7.4)		1 (3.7)
Hoarseness	3 (11.1)	3 (11.1)		

Abbreviations: AST, aspartate aminotransferase; WBC, white blood cell.
[a]No grade 4 or higher adverse events occurred.

In recent years, much effort has been devoted to developing targeted therapies to improve clinical outcomes of patients with HER2-positive NSCLC. Anti-HER2 agents, such as dacomitinib, pertuzumab plus trastuzumab, and T-DM1, have shown limited clinical efficacy in this subset of patients, with ORRs of 0%, 13%, and 6.7%, respectively, whereas pyrotinib administration exhibited an improved ORR of 22.2% as seen in this study (7, 10, 12). In a retrospective basket study of pyrotinib effects in HER2-postive solid tumors, the ORR for lung cancer was 44% (4/9), which is higher than that observed in this study, but the mPFS (6.3 vs. 2.5 months) and mOS (12.5 vs. 9.9 months) determined above were longer than their values (21). This could be explained by the fact that the latter study included patients with HER2 overexpression and/or *HER2* amplification as determined by IHC and/or FISH, while this study included *HER2*-amplified patients as determined by NGS. Depending on the testing methods, HER2-postivity may represent biologically different subtypes of NSCLC, and may have different sensitivities to anti-HER2 therapies (30, 31). Recently, several studies demonstrated that T-DM1 and trastuzumab deruxtecan (T-DXd) had a promising activity in HER2-overexpressing or *HER2*-amplified lung cancers, with an ORR of around 50% (32, 33). DESTINY-Lung01 study assessed the clinical activity of T-DXd in a cohort including 49 patients with HER2-overexpressing NSCLC, and presented similar efficacy (ORR = 24.5%, mPFS = 5.4 months, mOS = 11.3 months) with our study (ORR = 22.2%, mPFS = 6.3 months, mOS = 12.5 months; ref. 34).

In our study, we observed progression within 6 months after pyrotinib treatment. Previous studies investigating T-DM1/T-DXd in *HER2*-amplified lung cancers also revealed a considerable proportion of patients who progressed on T-DM1 within 6 months (32, 33). To vanquish resistance and prolong the responding duration, Bob T. Li and his colleagues attempted to combine T-DM1 with irreversible pan-HER inhibitors, including afatinib and neratinib, and results showed

that the combinational treatment improved efficacy (32). Most serendipitously, they found that a patient with breast cancer with *HER2* amplification can still benefit from neratinib plus T-DM1 at disease progression on T-DM1. For pyrotinib is an irreversible pan-HER inhibitor, it is rational to speculate that to conquer resistance or a lack of response to pyrotinib and T-DM1/T-DXd, a combination of pyrotinib and T-DM1 or T-DXd may be a potential option in treating NSCLC with *HER2* amplification.

One of the intriguing results with respect to prespecified analyses of survival was that patients previously treated with EGFR-TKIs had an ORR of 30.8% and an mPFS of 7.2 months. After receiving EGFR-TKI as first-line treatment, most patients with NSCLC eventually experience progression due to drug resistance, with mPFS of 11.2 to 18.9 months (35–38). *HER2* amplification occurred in approximately 12% of tumors that acquired resistance to EGFR-TKI versus 1% of untreated lung adenocarcinomas (39, 40). The above data suggested that pyrotinib could also potentially benefit *HER2*-amplified patients progressing on EGFR-TKI. T-DM1 also exhibited potential in this setting as previously reported: 2 of 6 patients who harbored both *HER* amplification and *EGFR* mutation responded to T-DM1 at disease progression upon EGFR-TKI (32). As for treatment settings, numerically better ORR and PFS were observed in patients administered pyrotinib in the first-line compared with the second-line or higher, suggesting the antitumor activities of pyrotinib are better early on during the course of the disease. Numerically improved ORR and PFS were also observed in chemotherapy-naive individuals compared with chemotherapy-treated patients, implying better outcomes elicited by pyrotinib in chemotherapy-naive patients than their chemotherapy-treated counterparts. Another result worth note was that 18.5% of the patients with *HER2*-amplified NSCLC had brain metastases, which was not revealed in previous studies (12, 13). This subset of patients was also included in the present study and benefited from pyrotinib, showing an ORR of 40%.

In addition, whether baseline-cooccurred driver mutations affect pyrotinib efficacy was also explored. Previous studies demonstrated the sensitivity of *HER2*-mutated tumors to pyrotinib in patients with NSCLC (19, 20). In the above subgroup analysis, patients harboring *HER2* mutations had similar ORR, mPFS, and mOS compared with those without *HER2* mutations, suggesting that concurrent *HER2* mutations do not affect the clinical efficacy of pyrotinib in patients with *HER2*-amplified NSCLC. Consistently, a recent study reported that T-DM1 unleashed similar antitumor activity in *HER2*-amplified tumors versus those with concurrent amplification and mutation in *HER2* (32).

This study was limited by the small sample size due to the low prevalence of *HER2* amplification in NSCLC. Since there was no control arm, the comparison between pyrotinib and other therapies was not feasible. Another limitation of the present study is that we did not perform FISH, the commonly recommended method for identifying *HER2* amplification, to validate the status of *HER2* amplification. Therefore, FISH should be conducted in future studies to obtain more solid results. In addition, since the majority of patients in this study had high levels of *HER2* amplification, we did not further analyze pyrotinib's effects among patients with different levels of *HER2* amplification.

In conclusion, this is the first prospective study demonstrating the promising efficacy and acceptable safety of pyrotinib in patients with *HER2*-amplified NSCLC. These data warrant further larger randomized clinical trials for confirmation.

Authors' Disclosures

S.-Q. Chen reports other support from 3D Medicines Inc. outside the submitted work. T. Bei reports other support from 3D Medicines Inc. outside the submitted work. No disclosures were reported by the other authors.

Authors' Contributions

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