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Original Article

Efficacy and safety of pyrotinib combined with trastuzumab and chemotherapy in patients with HER2-positive locally advanced breast cancer: a multicenter real-world study

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Abstract: Objectives: This multicenter real-world investigation aimed to assess the outcomes resulting from the incorporation of pyrotinib into trastuzumab and chemotherapy regimens for the neoadjuvant treatment of individuals diagnosed with HER2-positive locally advanced breast cancer (LABC). Methods: A multicenter retrospective cohort analysis was carried out, including patients diagnosed with HER2-positive locally advanced breast cancer from nine medical institutions in Hebei Province, China. Participants were enrolled from January 2023 to June 2023 and followed until December 2025. Based on the neoadjuvant therapy received, patients were divided into two groups: trastuzumab plus chemotherapy (n=127) and pyrotinib plus trastuzumab and chemotherapy (n=101). The main assessment criterion focused on the rate of total pathological complete response (tpCR). Among the secondary evaluation metrics were the breast pathological complete response (bpCR) rate, the objective response rate (ORR), progression-free survival (PFS), overall survival (OS), as well as adverse events related to the treatment. Results: A total of 228 patients were analyzed. The pyrotinib group showed significantly higher tpCR rate (46.53% vs. 31.50%, *P*=0.020), bpCR rate (51.49% vs. 35.43%, *P*=0.015), and ORR (88.12% vs. 77.17%, *P*=0.032) compared with the trastuzumab-only group. Time to initial response was shorter (6.24 vs. 7.84 weeks, *P*<0.001), and PFS was prolonged (21.06 vs. 18.68 months, *P*<0.001) in the pyrotinib group. However, higher incidences of diarrhea (72.28% vs. 21.26%, *P*<0.001), rash (28.71% vs. 9.45%, *P*<0.001), and hematological toxicities were observed. Conclusions: In a real-world setting the addition of pyrotinib to trastuzumab and chemotherapy significantly improved pathological and radiographic responses and prolonged PFS, albeit with an increased but manageable toxicity profile.

Keywords: Locally advanced breast cancer, human epidermal growth factor receptor 2-positive, neoadjuvant therapy, total pathological complete response, adverse events

Introduction

Breast cancer constitutes a significant global health challenge, with the subtype defined by the overexpression of the human epidermal growth factor receptor 2 (HER2) accounting for approximately 15% to 30% of all diagnosed instances [1-3]. HER2 amplification and overexpression are well-established drivers of aggressive tumor biology, associated with rapid proliferation and an elevated risk of recurrence and metastasis, which historically resulted in poor

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outcomes [1, 4, 5]. This acknowledgment has positioned HER2 both as a significant factor for prognosis and as a principal target for therapeutic interventions [2].

The advent of therapies targeting HER2, especially the monoclonal antibody trastuzumab, dramatically transformed the therapeutic approach for patients with this subtype [2, 6]. Trastuzumab improves survival by inhibiting downstream signaling and inducing immune-mediated cytotoxicity [6, 7]. The subsequent development of dual blockade strategies, including the combination of pertuzumab with trastuzumab, was designed to improve efficacy and address resistance issues. This approach has become a standard of care in the neoadjuvant treatment for high-risk, locally advanced breast cancer (LABC) [8-10].

Despite these advances, not every patient attains a pathological complete response and the need for more effective combinations persists [11]. In this context, pyrotinib, an oral irreversible pan-HER tyrosine kinase inhibitor (TKI) offers a promising avenue [12, 13]. By covalently binding to the intracellular kinase domains of HER1, HER2 and HER4, pyrotinib inhibits receptor dimerization and downstream signaling, a mechanism distinct from extracellular monoclonal antibody blockade [12, 14].

While clinical trials in metastatic settings have shown potent antitumor activity, real-world evidence validating its effectiveness and safety in the neoadjuvant setting, especially when added to trastuzumab and chemotherapy in routine clinical practice, is crucial [13, 15]. Such studies complement trial data by assessing therapeutic performance in broader, more heterogeneous populations [15-17]. Real-world evidence is therefore crucial to validate the effectiveness and safety of this combination in routine clinical practice, where treatment decisions must account for diverse patient profiles and practical constraints. Such studies can elucidate whether the benefits observed in clinical trials are maintained across varied healthcare settings and patient subgroups, while also identifying patterns of tolerability and management of adverse events in everyday oncology care. This gap in real-world validation forms the essential rationale for the present multicenter investigation.

Methods

Study design and case selection

This retrospective cohort study, carried out among nine medical facilities in Hebei Province, China, spanned from January 2023 to June 2023, with the monitoring of participants continuing until December 2025. The objective of this research was to evaluate the effectiveness and safety of integrating pyrotinib alongside trastuzumab and chemotherapy as a neoadjuvant therapy for patients with HER2-positive early-stage breast cancer (EBC). Eligible patients were identified through electronic medical record (EMR) systems and included if they met the following criteria: (1) female patients with invasive breast cancer confirmed through histological examination; (2) age ≥18 years; (3) newly diagnosed, operable breast cancer with clinical stage IIA-IIIC according to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging system [18]; (4) HER2-positive status was characterized by either an immunohistochemistry (IHC) score of 3+ or an IHC score of 2+ in conjunction with fluorescence in situ hybridization (FISH) verification of HER2 gene amplification. Exclusion criteria comprised: (1) significant dysfunction of the heart, liver, kidneys, or other critical organs; (2) ongoing breast cancer treatments such as chemotherapy, endocrine therapy, radiotherapy, or immunotherapy; (3) participation in other interventional clinical trials; (4) confirmed pregnancy or lactation; and (5) any concomitant disease judged by investigators to significantly affect patient safety or study completion.

Informed consent was not required for this study approved by the Institutional Review Board (IRB) of The Fourth Hospital of Hebei Medical University (Approval No. 2023066), owing to its retrospective nature. This research strictly complied with the principles set forth in the Declaration of Helsinki and adhered to national and institutional guidelines for retrospective studies. To ensure confidentiality and protect patient privacy throughout the research process, all personal identifiers were eliminated from the dataset.

Grouping and treatment methods

All patients in both treatment groups received taxane-based chemotherapy as the cytotoxic

backbone. Specifically, paclitaxel injection (Hainan Chily Pharmaceutical Co., Ltd., National Medicine Permit Number H20063169, 5 mL: 30 mg) was delivered through intravenous infusion at a dosage of 135 mg/m^2 over a duration of 6 hours on the first day of each cycle with each cycle lasting 21 days.

In the Trastuzumab + Chemotherapy group (n=127), patients received intravenous trastuzumab (Hangzhou Bio-Rad Biomedical Pharmaceutical Co., Ltd., National Medicine Permit Number S20233107, 150 mg) in addition to paclitaxel. The trastuzumab dosing followed the standard protocol: an initial loading dose of 8 mg/kg was given, followed by a maintenance dose of 6 mg/kg administered intravenously over more than 90 minutes, once every 3 weeks. The neoadjuvant treatment duration was 18 weeks, corresponding to approximately 6 cycles of therapy.

In the Pyrotinib + Trastuzumab + Chemotherapy group (n=101), patients received the identical regimen of paclitaxel and trastuzumab as described above, supplemented with oral pyrotinib maleate tablets (Jiangsu Hengrui Medicine Co., Ltd., National Medicine Permit Number H20180013, 80 mg). Pyrotinib administered at a dose of 400 mg once daily was taken at the same time every day, 30 minutes following a meal. The treatment with pyrotinib was also continued for 18 weeks concurrently with the chemotherapy and trastuzumab.

Follow-up

Patients were systematically followed up every three months via outpatient visits or telephone interviews for a period of two years, with a cut-off date of December 2025. The first six months after treatment initiation served as the primary observation period for recording treatment-related adverse events. Throughout the entire follow-up period, overall survival (OS) and progression-free survival (PFS) were continuously monitored.

Outcome indicators

Data were meticulously extracted from the EMRs of the participating institutions. The extracted information included patient demographics, baseline clinical and pathological characteristics, detailed treatment records, efficacy outcomes, and safety data.

The primary goal of this research was to ascertain the rate of total pathological complete response (tpCR). This response was defined by the lack of invasive carcinoma cells both in the main breast tumor and in the sampled ipsilateral axillary lymph nodes following the conclusion of neoadjuvant treatment (classified as ypT0/Tis ypN0 according to the AJCC pathologic staging criteria [18]). The tpCR rate was determined by the proportion of individuals who attained a tpCR relative to the total count of patients in each treatment cohort who had undergone surgical procedures and for whom pathological assessment data were accessible [19].

Secondary endpoints included various efficacy and safety metrics. The breast pathological complete response (bpCR) rate was measured defined as the lack of invasive cancer in the primary breast tumor irrespective of the lymph node status (ypT0/Tis). The objective response rate (ORR) was determined through radiographic evaluations (such as ultrasound and MRI) performed during and after neoadjuvant therapy, adhering to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines [20]. ORR was calculated as summing the rates of complete response (CR) and partial response (PR). Tumor response dynamics were analyzed by measuring the changes in tumor size from baseline to post-treatment, the time to initial radiographic response, and the time to best radiographic response. Survival outcomes, including progression-free survival (PFS), defined as the time from treatment initiation to disease progression or death from any cause, were calculated. OS, defined as the time from treatment initiation to death from any cause was also analyzed. The follow-up duration for survival outcomes was documented. Safety was assessed by carefully documenting the occurrence, nature, and intensity of all adverse events (AEs) during the entire treatment duration. The severity of AEs was classified using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [21]. The frequency of each AE was determined for both groups.

Statistical analysis

Statistical analyses were conducted utilizing SPSS software version 25.0; IBM Corp., Armonk, NY, USA and R language version 4.1.2;

R Foundation for Statistical Computing, Vienna, Austria. Given that this was a multicenter retrospective investigation, the sample size was not predetermined but was determined by the count of eligible patients who received the designated neoadjuvant treatments across nine participating institutions from January 2023 to June 2023, and 228 patients were included in the final analysis. To evaluate whether this sample size was adequate for detecting significant differences in the primary endpoint-total pathological complete response [tpCR] rate, a post-hoc power analysis was conducted utilizing G*Power software version 3.1. With observed tpCR rates of 46.53% in the pyrotinib group versus 31.50% in the trastuzumab-only group, and a two-sided alpha level of 0.05, the current sample sizes of 101 and 127 patients per group provided over 80% statistical power, confirming the adequacy of the sample size.

Continuous variables were described using the mean and standard deviation (SD) if the data followed a normal distribution; for data not normally distributed, the median along with the interquartile range (IQR) was provided. These determinations were made based on results from the Shapiro-Wilk test. In the case of categorical variables, they were presented as counts and proportions (n, %). The baseline demographic and clinical characteristics of the two treatment groups were compared utilizing appropriate statistical tests. For continuous variables, an independent samples t-test was used for normally distributed data, while the Mann-Whitney U test (Wilcoxon rank-sum test) was applied for non-normally distributed data. For categorical variables, the Chi-square test or Fisher's exact test was employed, with the latter used when expected cell counts were less than five.

Survival outcomes were estimated using the Kaplan-Meier method with differences between the treatment groups assessed via the log-rank test. To identify factors associated with achieving tpCR, univariate logistic regression was initially conducted for each candidate baseline variable presented in **Table 1**. Variables demonstrating a *P* value of less than 0.10 in univariate analysis were identified as potential predictors and subsequently included in a multivariable logistic regression model. The inclusion of these variables was processed through a backward stepwise selection method which relied on the likelihood ratio criterion for determining their retention in the model.

Regarding missing data, complete case analysis was conducted as less than 2% of data were missing across all baseline variables, and no imputation was applied due to the low proportion of missingness. All statistical tests were two-sided with a *P* value less than 0.05 deemed statistically significant.

Results

Baseline demographic and clinical characteristics of the study cohort

The foundational demographic and clinical features of the participant group were equally split across both treatment arms (**Table 1**). There were no significant statistical discrepancies detected regarding age, body mass index, menopausal state, clinical T stage, clinical N stage, overall clinical stage, hormone receptor status, HER2 status, ECOG performance score, tumor side, histological subtype, Ki-67 index, or previous exposure to anthracycline-based therapy (all $P>0.05$). This suggests that the two cohorts were comparable at baseline thereby minimizing potential confounding factors in subsequent efficacy and safety analyses.

Efficacy outcomes: pathologic complete response and objective response rates

The inclusion of pyrotinib alongside trastuzumab and chemotherapy notably enhanced both pathological and objective response rates. The tpCR rate was 46.53% in the pyrotinib group compared with 31.50% in the trastuzumab-only group ($P=0.020$). Similarly, the breast pathological complete response (bpCR) rate was 51.49% versus 35.43% ($P=0.015$). The objective response rate (ORR) was also higher in the pyrotinib group (88.12% vs. 77.17%, $P=0.032$), with higher rates of complete response (CR) observed (**Table 2**). These findings demonstrate that the pyrotinib-based regimen is associated with superior antitumor activity in the neoadjuvant setting.

Safety profile and adverse events

Table 3 illustrates a significantly greater overall incidence of diarrhea in the pyrotinib-contain-

Table 1. Baseline demographic and clinical characteristics of patients in the two treatment groups

Characteristic	Pyrotinib + Trastuzumab + Chemotherapy (n=101)	Trastuzumab + Chemotherapy (n=127)	t/χ^2	*P* value
Age (years)	51.33 ± 8.59	52.41 ± 9.14	0.910	0.364
BMI (kg/m^2)	23.61 ± 3.28	24.02 ± 3.51	0.901	0.368
Menopausal status, n (%)			0.082	0.775
Premenopausal	56 (55.45)	68 (53.54)		
Postmenopausal	45 (44.55)	59 (46.46)		
Clinical T stage, n (%)			0.116	0.990
T1	12 (11.88)	16 (12.60)		
T2	61 (60.40)	74 (58.27)		
T3	20 (19.80)	26 (20.47)		
T4	8 (7.92)	11 (8.66)		
Clinical N stage, n (%)			0.129	0.988
N0	25 (24.75)	33 (25.98)		
N1	50 (49.50)	60 (47.24)		
N2	18 (17.82)	24 (18.90)		
N3	8 (7.92)	10 (7.87)		
Clinical stage, n (%)			0.040	0.841
II	93 (92.08)	116 (91.34)		
III	8 (7.92)	11 (8.66)		
HR status, n (%)			0.065	0.798
Positive	55 (54.46)	67 (52.76)		
Negative	46 (45.54)	60 (47.24)		
HER2 status, n (%)			0.095	0.758
IHC 3+	75 (74.26)	92 (72.44)		
IHC 2+/FISH+	26 (25.74)	35 (27.56)		
ECOG performance status, n (%)			0.066	0.968
0	70 (69.31)	86 (67.72)		
1	28 (27.72)	37 (29.13)		
2	3 (2.97)	4 (3.15)		
Laterality, n (%)			0.027	0.870
Left	52 (51.49)	64 (50.39)		
Right	49 (48.51)	63 (49.61)		
Histological type, n (%)			0.082	0.960
IDC	88 (87.13)	109 (85.83)		
ILC	8 (7.92)	11 (8.66)		
Other	5 (4.95)	7 (5.51)		
Ki-67 index (%)	42.33 ± 18.24	41.87 ± 17.96	0.189	0.850
Previous anthracycline exposure, n (%)			0.078	0.780
Yes	48 (47.52)	58 (45.67)		
No	53 (52.48)	69 (54.33)		

BMI: Body Mass Index; ECOG: Eastern Cooperative Oncology Group; HR: hormone receptor; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; FISH: fluorescence in situ hybridization; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma.

ing group compared to the trastuzumab-only group (72.28% [73/101] vs. 21.26% [27/127], *P*<0.001). Similarly, increased total frequencies were observed for leukopenia (52.48% [53/101] vs. 35.43% [45/127], *P*=0.010), neutropenia (47.52% [48/101] vs. 31.50%

Table 2. Comparison of pathological complete response rates between the treatment groups [n (%)]

Endpoint	Pyrotinib + Trastuzumab + Chemotherapy (n=101)	Trastuzumab + Chemotherapy (n=127)	χ^2	*P* value
tpCR rate	47 (46.53)	40 (31.50)	5.392	0.020
bpCR rate	52 (51.49)	45 (35.43)	5.930	0.015
ORR	89 (88.12)	98 (77.17)	4.577	0.032
CR	21 (20.79)	18 (14.17)		
PR	68 (67.33)	80 (62.99)		
SD	10 (9.90)	25 (19.69)		
PD	2 (1.98)	4 (3.15)		

tpCR: total pathological complete response; bpCR: breast pathological complete response; ORR: objective response rate; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

Table 3. Incidence and severity of treatment-related adverse events in the two treatment groups [n (%)]

Adverse Event	Pyrotinib + Trastuzumab + Chemotherapy Group (n=101)		Trastuzumab + Chemotherapy Group (n=127)		*P* value
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	
Diarrhea	65 (64.36)	8 (7.92)	25 (19.69)	2 (1.57)	<0.001
Leukopenia	42 (41.58)	11 (10.89)	38 (29.92)	7 (5.51)	0.010
Neutropenia	39 (38.61)	9 (8.91)	35 (27.56)	5 (3.94)	0.014
Nausea	37 (36.63)	1 (0.99)	29 (22.83)	0 (0.00)	0.015
Fatigue	31 (30.69)	2 (1.98)	24 (18.90)	1 (0.79)	0.025
Rash	28 (27.72)	1 (0.99)	12 (9.45)	0 (0.00)	<0.001
ALT elevation	26 (25.74)	3 (2.97)	18 (14.17)	1 (0.79)	0.011
AST elevation	24 (23.76)	2 (1.98)	16 (12.60)	0 (0.00)	0.011
Anemia	22 (21.78)	0 (0.00)	27 (21.26)	1 (0.79)	0.962
Vomiting	21 (20.79)	1 (0.99)	19 (14.96)	0 (0.00)	0.183
Hand-foot syndrome	18 (17.82)	2 (1.98)	14 (11.02)	0 (0.00)	0.065
Thrombocytopenia	15 (14.85)	1 (0.99)	17 (13.39)	0 (0.00)	0.601
Mucositis	14 (13.86)	0 (0.00)	9 (7.09)	0 (0.00)	0.092
Alopecia	98 (97.03)	0 (0.00)	124 (97.64)	0 (0.00)	1.000

ALT: alanine aminotransferase; AST: aspartate aminotransferase.

[40/127], *P*=0.014), nausea (37.62% [38/101] vs. 22.83% [29/127], *P*=0.015), rash (28.71% [29/101] vs. 9.45% [12/127], *P*<0.001), and ALT elevation (28.71% [29/101] vs. 14.96% [19/127], *P*=0.011). However, no significant differences were found for anemia (21.78% [22/101] vs. 22.05% [28/127], *P*=0.962), vomiting (21.78% [22/101] vs. 14.96% [19/127], *P*=0.183), or alopecia (97.03% [98/101] vs. 97.64% [124/127], *P*=1.000) between the groups (**Table 3**). These findings confirm that pyrotinib augments gastrointestinal and dermatological toxicities while maintaining comparable hematological safety to trastuzumab-based therap.

Tumor response dynamics and shrinkage metrics

Tumor response dynamics favored the pyrotinib-based regimen across several metrics. Baseline tumor sizes were similar between the groups (*P*=0.907). After treatment, the residual tumor size was significantly smaller in the pyrotinib group (1.24 ± 0.57 cm) compared to the trastuzumab-only group (1.64 ± 0.75 cm, *P*<0.001). The time to initial radiographic response was also shorter in the pyrotinib group (6.24 ± 2.14 weeks) compared to the trastuzumab-only group (7.84 ± 2.65 weeks, *P*< 0.001). Similarly, the time to achieve the best

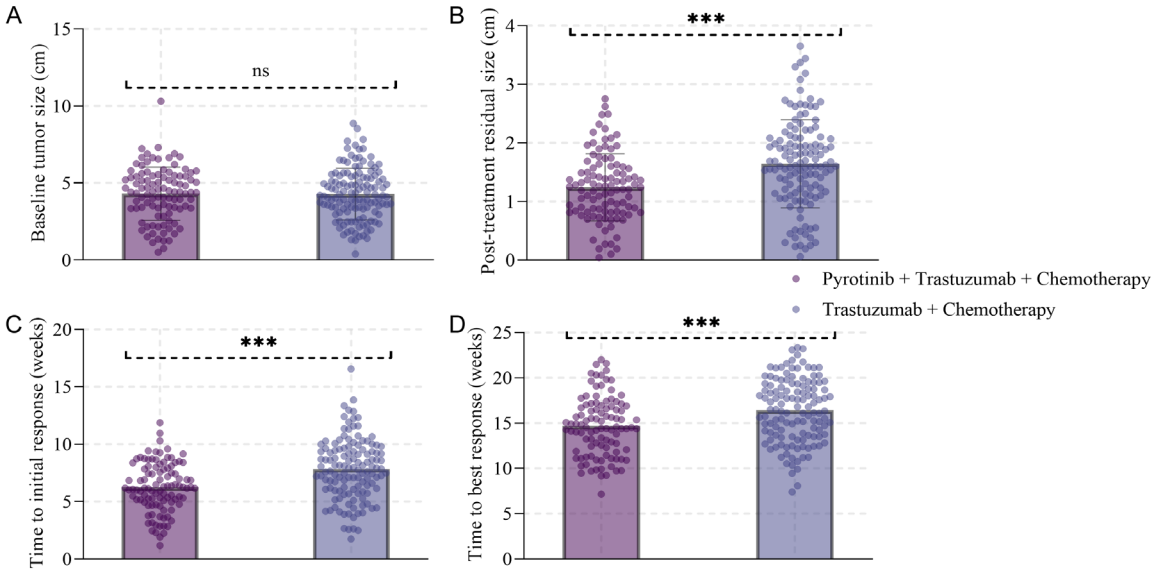

Figure 1. Tumor size changes and response timing in the two treatment groups. A. Baseline tumor size (cm); B. Post-treatment residual size (cm); C. Time to initial response (weeks); D. Time to best response (weeks). ***P<0.001.

response was shorter in the pyrotinib group (14.67 ± 3.28 weeks) than that in the trastuzumab-only group (16.42 ± 3.51 weeks, P< 0.001) (**Figure 1**). These results indicate that pyrotinib accelerates tumor shrinkage and improves depth of response.

Survival outcomes at follow-up

With a median follow-up of approximately two years, survival outcomes were promising in both groups but significantly better in the pyrotinib cohort for progression-free survival (PFS). The PFS was 21.06 ± 4.12 months in the pyrotinib group versus 18.68 ± 3.88 months in the trastuzumab-only group (P<0.001). OS showed a numerical improvement with pyrotinib (23.59 ± 4.63 months vs. 22.49 ± 4.94 months) although the difference did not reach statistical significance (P=0.086, **Figure 2**). These data suggest that pyrotinib contributes to prolonged disease control.

Univariable and multivariable analyses of factors affecting the tpCR rate

Univariate analysis identified HR-negative status, Ki-67 index >30%, and treatment with the pyrotinib-based regimen as significant predictors of achieving tpCR (all P<0.05) (See **Table 4**). In multivariate logistic regression, these three factors remained as independent predictors: HR-negative status (OR=1.900, 95% CI: 1.109-3.279, P=0.020), Ki-67 >30% (OR 1.908, 95% CI [1.099-3.364], P=0.023), and pyrotinib-based treatment (OR1.893, 95% CI [1.104-3.267], P=0.021) (See **Table 5**). This confirms that the pyrotinib regimen significantly enhances the probability of achieving pathological complete response especially in biologically aggressive tumors.

Discussion

This multicenter real-world investigation offers significant evidence supporting the inclusion of pyrotinib, an oral and irreversible pan-HER tyrosine kinase inhibitor, in the neoadjuvant treatment regimen for patients with HER2-positive locally advanced breast cancer. The results indicate that adding pyrotinib to trastuzumab and chemotherapy led to notable improvements in tpCR rates, ORR and PFS compared to treatment with trastuzumab and chemotherapy alone. These efficacy outcomes are consistent with those reported in the phase III PHEDRA trial, which demonstrated a significantly higher tpCR rate with pyrotinib plus trastuzumab and docetaxel versus placebo plus trastuzumab and docetaxel [22]. Moreover, the accelerated time to initial response and deeper tumor shrinkage observed in our pyrotinib-treated cohort align with the potent and rapid antitumor activity previously described in early-

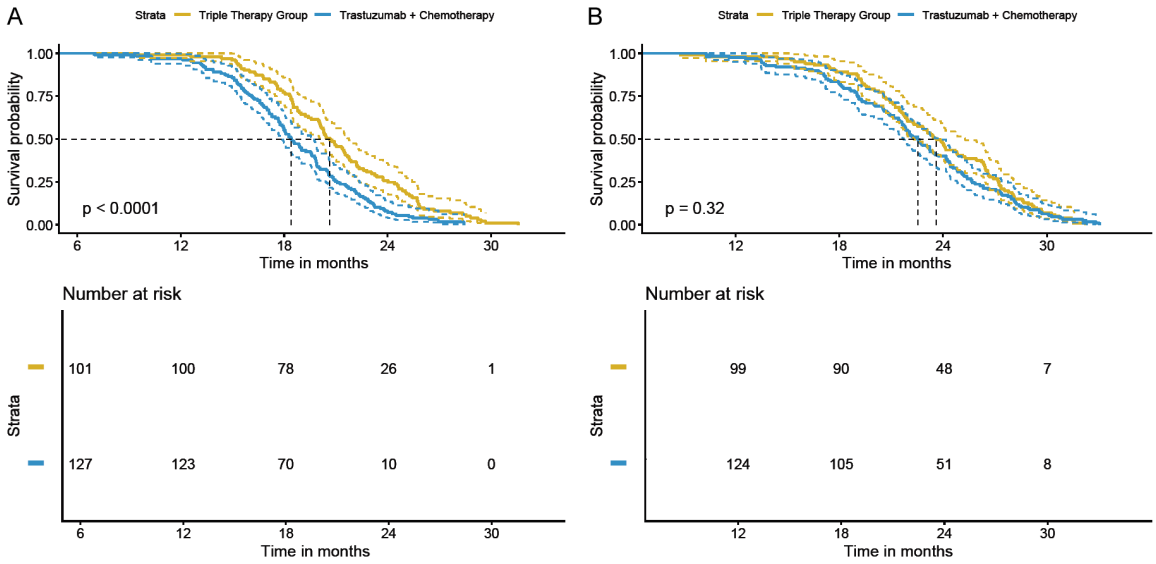

Figure 2. Survival outcomes including progression-free survival, disease-free survival, and overall survival at follow-up. A. PFS (months); B. OS (months). PFS: progression-free survival; OS: overall survival.

phase studies [23]. However, unlike clinical trials, this real-world analysis captures outcomes in a more heterogeneous population across multiple centers, thereby enhancing the generalizability of these findings. Notably, the increased incidence of diarrhea, rash, and liver enzyme elevations observed in the pyrotinib group mirrors the toxicity profile documented in both clinical trial and real-world settings [15, 24], reinforcing the need for proactive monitoring and supportive care. Collectively, our results corroborate and extend existing evidence by demonstrating that the efficacy and safety of pyrotinib-based neoadjuvant therapy are reproducible in routine clinical practice, particularly in patients with high-risk features such as hormone receptor-negative status or high Ki-67 index.

Concerning pathological and objective response rates, the regimen including pyrotinib demonstrated higher rates of both total and breast pathological complete response compared to the combination of trastuzumab and chemotherapy. This finding is consistent with the proposed mechanism of pyrotinib as an oral irreversible pan-HER tyrosine kinase inhibitor [22, 25, 26]. While monoclonal antibodies like trastuzumab primarily target the extracellular domain, pyrotinib acts intracellularly, by covalently binding to the kinase domains of HER1, HER2, and HER4. This action inhibits downstream signaling pathways like PI3K/AKT and MAPK/ERK [27, 28]. This complementary mechanism may lead to more comprehensive blockade of the HER2 signaling network, potentially overcoming some intrinsic or adaptive resistance mechanisms associated with antibody therapy alone [29, 30]. The higher objective response rate, including more complete radiographic responses, further supports enhanced tumor cell kill with the triplet combination. These efficacy trends are consistent with findings from earlier-phase clinical trials. For instance, Yin et al. [19] reported encouraging pathological complete response rates when pyrotinib was utilized alongside trastuzumab and chemotherapy in phase II neoadjuvant setting. This provides a basis for evaluating its effectiveness in wider patient populations.

The analysis of tumor response dynamics revealed that the pyrotinib-based regimen was associated with a more rapid initial radiographic response and a deeper overall tumor reduction, as indicated by smaller residual tumor size post-treatment. This acceleration and augmentation of response may be clinically meaningful, potentially allowing for earlier surgical intervention or identifying responders more quickly [23, 31]. The mechanism may be linked to the potent and immediate inhibition of kinase activity by pyrotinib, which, when combined with the antibody-dependent cellular cy-

Table 4. Univariate analysis of baseline factors influencing total pathologic complete response rate [n (%)]

Characteristic	Total [n (%)]	non-tpCR (n=141)	tpCR (n=87)	*P* value
Age				0.537
<50 years	112 (49.12)	67 (59.82)	45 (40.18)	
≥50 years	116 (50.88)	74 (63.79)	42 (36.21)	
Menopausal status				0.200
Premenopausal	124 (54.39)	72 (58.06)	52 (41.94)	
Postmenopausal	104 (45.61)	69 (66.35)	35 (33.65)	
Clinical T stage				0.785
T1	28 (12.28)	18 (64.29)	10 (35.71)	
T2	135 (59.21)	80 (59.26)	55 (40.74)	
T3	46 (20.18)	31 (67.39)	15 (32.61)	
T4	19 (8.33)	12 (63.16)	7 (36.84)	
Clinical N stage				0.851
N0	58 (25.44)	38 (65.52)	20 (34.48)	
N1	110 (48.25)	65 (59.09)	45 (40.91)	
N2	42 (18.42)	27 (64.29)	15 (35.71)	
N3	18 (7.89)	11 (61.11)	7 (38.89)	
Clinical stage				0.267
II	209 (91.67)	127 (60.77)	82 (39.23)	
III	19 (8.33)	14 (73.68)	5 (26.32)	
HR status				0.019
Positive	122 (53.51)	84 (68.85)	38 (31.15)	
Negative	106 (46.49)	57 (53.77)	49 (46.23)	
HER2 status				0.694
IHC 3+	167 (73.25)	102 (61.08)	65 (38.92)	
IHC 2+/FISH+	61 (26.75)	39 (63.93)	22 (36.07)	
Ki-67 index				0.023
≤30%	95 (41.67)	67 (70.53)	28 (29.47)	
>30%	133 (58.33)	74 (55.64)	59 (44.36)	
Treatment group				0.020
Pyrotinib-based	101 (44.30)	54 (53.47)	47 (46.53)	
Trastuzumab-only	127 (55.70)	87 (68.50)	40 (31.50)	

HR: hormone receptor; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; FISH: fluorescence in situ hybridization; tpCR: total pathological complete response.

Table 5. Multivariate logistic regression analysis of independent predictors for total pathologic complete response

	Coefficient	Std. Error	Wald	*P* value	OR (95% CI)
HR status (Negative vs. Positive)	0.642	0.276	2.326	0.020	1.900 (1.109-3.279)
Ki-67 index (>30% vs. ≤30%)	0.646	0.285	2.268	0.023	1.908 (1.099-3.364)
Treatment group (Pyrotinib-based vs. Trastuzumab-only)	0.638	0.276	2.311	0.021	1.893 (1.104-3.267)

HR: hormone receptor; OR: odds ratio; CI: confidence interval.

totoxicity induced by trastuzumab and the cytotoxic effect of chemotherapy, creates a multipronged attack on tumor cells [32-34].

The survival data, with a follow-up period of around two years, showed that patients receiving pyrotinib experienced an extension in pro-

gression-free survival. This suggests that the improved pathological responses and deeper tumor shrinkage may translate into a delay in disease progression. The numerical increase in overall survival, while not meeting the threshold for statistical difference in this analysis with limited follow-up, points toward a potential long-term benefit that requires further observation. This pattern of early efficacy signals translating into delayed progression has been observed with other intensified HER2-targeted strategies.

However, the enhanced efficacy comes with a modified safety profile. The pyrotinib-containing group experienced a notably higher incidence of certain adverse events, particularly diarrhea, rash, and elevations in liver enzymes, alongside increases in hematological toxicities like leukopenia and neutropenia. Diarrhea and rash are known side effects of tyrosine kinase inhibitors targeting the HER family, often related to the inhibition of EGFR (HER1) [35-37]. The manageable nature of these events in our study, with most being low-grade, is consistent with the safety profile reported in metastatic settings [24, 38]. For example, Miao et al. [15] described similar gastrointestinal and dermatological toxicities with pyrotinib combinations, which were generally controllable with supportive care. The comparable rates of other events like anemia and alopecia suggest that the incremental toxicity is primarily tied to the specific mechanism of pyrotinib rather than a general amplification of chemotherapy-related effects [39-41].

Multivariable analysis identified hormone receptor-negative status, a higher Ki-67 index, and treatment with the pyrotinib-based regimen as independent factors associated with achieving a total pathological complete response. This underscores that the benefit of pyrotinib augmentation is observable even after accounting for known aggressive tumor biology features. It reinforces the role of this combination in tumors with biologically aggressive phenotypes, where achieving a maximal response is critically important.

From a clinical and practical standpoint, these real-world findings have substantial value. They demonstrate that the efficacy signals observed in controlled trial environments can be translated into the routine care of a diverse patient cohort across multiple centers. The manageable, albeit increased, toxicity profile provides oncologists with actionable information for patient counseling, proactive monitoring, and supportive care planning, particularly for diarrhea and skin reactions. This evidence supports the consideration of pyrotinib-based neoadjuvant therapy as a potentially more effective option for patients with HER2-positive locally advanced breast cancer, especially those with high-risk features, within a framework of vigilant toxicity management.

This study has several limitations that need to be recognized. First, the study's retrospective and non-randomized nature inherently carries risks of selection bias and unmeasured confounding variables, despite the baseline characteristics being comparable across the groups. Second, relatively short follow-up period (median approximately two years) limits our capacity to draw conclusive findings about long-term outcomes such as overall survival, and further follow-up is warranted. Third, detailed records on dose modifications, treatment delays, or interruptions due to adverse events were not systematically captured across all participating centers, which may affect the interpretation of the safety profile and tolerability of the pyrotinib-based regimen. Fourth, although the sample size was adequate for detecting the primary endpoint, it may still limit statistical power for subgroup analyses or rare adverse events. Finally, data on specific supportive care interventions (e.g., antidiarrheal or antiemetic medications) were not uniformly documented, precluding a more nuanced understanding of adverse event management in real-world practice. Further prospective, randomized studies with an increased number of participants, prolonged monitoring periods, and uniform recording practices for dosage modifications and supportive treatments are required to validate these results and enhance the efficacy-safety balance of neoadjuvant therapies incorporating pyrotinib. In addition, comparative effectiveness research against other dual HER2 blockade strategies, such as trastuzumab plus pertuzumab, will be valuable for informing clinical decision-making.

In conclusion, this real-world analysis suggests that adding pyrotinib to trastuzumab and chemotherapy as neoadjuvant therapy for HER2-positive locally advanced breast cancer is as-

sociated with improved pathological and radiographic responses, faster tumor shrinkage, and delayed disease progression, though it introduces a characteristic pattern of increased but manageable toxicities. These results contribute to the evolving landscape of HER2-targeted therapy, offering clinicians evidence from routine practice to inform treatment decisions for eligible patients.

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Disclosure of conflict of interest

None.

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