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ORIGINAL RESEARCH

A Retrospective Real-World Study of Pyrotinib in HER-2 Positive Advanced Breast Cancer

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Purpose: To explore the efficacy and safety of pyrotinib in a real-world setting in a population with HER2-positive advanced breast cancer, subgroup analysis was conducted based on different clinicopathological features to further explore the general characteristics of patients, tumor nature, and the effect of various lines of treatment before patients started pyrotinib on the efficacy of pyrotinib in the real-world study.
Methods: The clinical pathological characteristics, drug efficacy and related adverse reactions of HER2-positive MBC patients treated with pyrotinib in six hospitals in Southeast Zhejiang Province from February 2018 to December 2023 were collected and analyzed retrospectively.
Results: A total of 342 patients with HER2-positive MBC were enrolled. The median follow-up time of 42.0 months. The median age of the overall population was 52 years (range from 25–90 year old). Median progression-free survival in the total population was 10.0 months, the median overall survival was 29.0 months. The (objective response rate, ORR) was 40.35% and the (disease control rate, DCR) was 83.92%. The median progression-free survival (PFS) in the total population was 10.0 months, the median overall survival was 29.0 months. And pyrotinib had better mPFS for advanced first-line treatment than for second-third-line and beyond(14.0 months vs.10.0 months vs.6.0 months, P<0.001). Multivariate Cox regression analysis showed that ECOG, HER2 status, brain metastasis, liver metastasis, number of pyrotinib treatment lines, previous lapatinib treatment, combined capecitabine therapy and trastuzumab resistance were independent prognostic factors for PFS. Diarrhea was the most common adverse reaction (ADR) in 205 patients (59.94%), which could be controlled by antidiarrheal drugs.
Conclusion: This multicenter study suggested that the use of pyrotinib for HER2 positive MBC had a relatively good efficacy, especially for those who received first-line pyrotinib treatment and those who were sensitive to previous trastuzumab treatment. Patients with brain metastasis and liver metastases also benefit from pyrotinib treatment, especially for patients treated with brain radiotherapy and/or surgery. ECOG, HER2 status, brain metastasis, liver metastasis, number of pyrotinib treatment lines, previous lapatinib treatment, combined capecitabine therapy and trastuzumab resistance were independent prognostic factors for PFS in HER2 Positive MBC patients treated with pyrotinib. The most common adverse reaction associated with pyrotinib is diarrhea, which can be well controlled through antidiarrheal treatment. Pyrotinib combined with vinorelbine has similar efficacy to pyrotinib combined with capecitabine and has fewer side effects, and can be used as an alternative to capecitabine.

Keywords: pyrotinib, HER2 positive metastatic breast cancer, real-world study, efficacy, safety

Introduction

It is reported that breast cancer has surpassed lung cancer to become the most common malignant tumor in the world.[1] In China, breast cancer ranks first and fourth in incidence and mortality respectively, seriously threatening women's health.[2] According to the expression of (estrogen receptor, ER), (progesterone receptor, PR), (human epidermal growth-factor receptor2, HER2) and Ki-67, breast cancer is mainly divided into Luminal A type, Luminal~type, HER2 positive type and triple negative type, among which HER2 positive type accounts for about 15%~20% of all breast cancers.[3,4] HER2 and EGFR/ErbB1/HER1, ErbB3/HER3, ErbB4/HER4 all belong to membrane receptor tyrosine kinases.[5] HER2 overexpression promotes proliferation, invasion and metastasis of tumor cells by activating MAPK and PI3K/AKT signaling pathways.[6] Therefore, HER2 positive breast cancer was more aggressive, had a higher recurrence and metastasis rate, and had a significantly lower survival rate than HER2 negative patients before the advent of anti-HER2 drugs.[7] In recent years, with the continuous marketing of anti-HER 2-targeted drugs, the prognosis of HER2 positive breast cancer patients has been greatly improved.[8] At present, anti-HER2 drugs used clinically include three categories: monoclonal antibodies represented

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by trastuzumab and pertuzumab; tyrosine kinase inhibitors (TKI) represented by lapatinib, tucatinib and pyrotinib; antibody-drug conjugates represented by ado-trastuzumab emtansine (T-DM1).[9] Double-target combination chemotherapy with trastuzumab (H) and pertuzumab (P) improves 5-year survival in patients with early-stage HER2 positive breast cancer by more than 90%.[10] Based on the results of NeoSphere, TRYPHAENA, and APHINITY, HP dual-target combination chemotherapy has become the standard of care in (new) adjuvant therapy for HER2 positive breast cancer patients.[11–13] The treatment of HER2-positive metastatic breast cancer (MBC) remains a hot topic and difficulty in current research.8-year follow-up of CLEOPATRA study showed that HER2 positive MBC patients treated with THP regimen (pertuzumab + trastuzumab + docetaxel) had significantly improved prognosis and mOS by 16.3 months (57.1 months vs 40.8 months) compared with control group (placebo + trastuzumab + docetaxel).[14] The PUFFIN study based on the Chinese population also yielded results consistent with those of the CLEOPATRA study.[15] Thus, THP regimen has become the first-line treatment regimen for HER2 positive MBC criteria. However, some patients develop trastuzumab resistance due to damage to HER2 binding sites and activation of downstream signal transduction pathways, leading to disease progression.[16] Lapatinib plus capecitabine showed better efficacy than capecitabine alone in patients who progressed on THP regimens, with significantly longer median mPFS (6.2 months vs 4.3 months) and Mos (75 weeks vs 56.4 weeks).[17] In addition, in the EMILIA study, patients treated with T-DM1 after progression on prior trastuzumab had greater benefits in mPFS (9.6 months vs. 6.4 months) and mOS (29.9 months vs. 25.9 months) than those treated with lapatinib plus capecitabine.[18] Therefore, lapatinib plus capecitabine regimen and T-DM1 are both options for second-line treatment of HER2 positive MBC. DESTINY Breast-03 is a multicenter Phase 3 clinical study, the results of which were recently updated, showing that mPFS was significantly longer in the detrastuzumab (trastuzumab deruxtecan, T-DXd) arm than in the T-DM1 arm in patients who had previously failed taxane and trastuzumab therapy,[19] T-DXd may replace T-DM1 as the new standard second-line treatment regimen. In patients with HER2 positive MBC previously treated with more than two anti-HER2 agents, the NALA study showed a greater benefit on mPFS with neratinib plus capecitabine than lapatinib plus capecitabine (8.8 months vs. 6.6 months), and neratinib is a new option for advanced multi-line therapy against HER2.[20] Although the treatment regimen for HER2 positive MBC is continuously optimized and various anti-HER2 drugs are continuously developed and approved, the treatment needs of all patients cannot be met due to problems such as drug resistance and drug accessibility in clinical practice. Therefore, it is imperative to explore new HER2 targeted therapeutic strategies to overcome the clinical dilemma of HER2 positive MBC. Pyrotinib maleate is a novel oral TKI drug independently developed in China. It can irreversibly bind to ATP binding sites in HER1, HER2 and HER4 intracellular segments, inhibit phosphorylation and block activation of RAS/RAF/MEK/MAPK and PI3K/AKT signaling pathways downstream, thereby inhibiting tumor cell growth.[21] The good antitumor activity of pyrotinib has been demonstrated in Phase III randomized controlled clinical trials in HER2 positive MBC patients who have failed prior trastuzumab and/or taxane chemotherapy: PHOEBE analysis showed significant improvements in mPFS (12.5 months vs 6.8 months), ORR (67.2% vs 51.5%),and clinical benefit rate (CBR) (73.1% vs 59.1%) in the pyrotinib + capecitabine arm compared with the lapatinib + capecitabine arm,[22] PHENIX study further confirmed that mPFS and ORR of pyrotinib+capecitabine arm were significantly better than placebo+capecitabine arm.[23] In the 2019–2022 Chinese Society of Clinical Oncology (CSCO) breast cancer diagnosis and treatment guidelines, pyrotinib is recommended for second-line treatment of advanced HER2-positive breast cancer at Class 2A evidence level.[24] However, in clinical studies, strict patient inclusion criteria may not well reflect the efficacy and safety of pyrotinib in a real-world clinical setting.

Although several real-world studies on pyrotinib have been reported,[25,26] there are still shortcomings such as short follow-up time, small sample size, and limited patient subgroup data. Therefore, the purpose of this study is to provide reference for clinical use of pyrotinib by retrospectively analyzing the efficacy and safety of pyrotinib treatment regimens in the real world.

Materials and Methods

Object of Study

The clinical pathological characteristics, drug efficacy and related adverse reactions of HER2 positive MBC patients receiving pyrotinib-based treatment in six hospitals in Southeast Zhejiang Province (the First Affiliated Hospital of

Wenzhou Medical University, the Second Affiliated Hospital of Wenzhou Medical University, Jinhua City Central Hospital, Wenzhou City Central Hospital, Wenzhou People's Hospital and Jinhua City People's Hospital) from February 2018 to December 2023 were collected and analyzed retrospectively.

Inclusion Criteria

(1) Female s≥18 years; (2) breast patients with pathologic immunohistochemistry -confirmed primary or metastatic lesion of Her2-3+ or Her2-2+ with in situ hybridization(ISH)+; (3) including newly diagnosed stage IV and recurrent metastatic advanced breast cancer patients; (4) application of targeted therapy based on pyrotinib; (5) at least one evaluable lesion according to the response evaluation criteria in solid tumor vision,RECIST1.1; (6) complete clinical and pathological data.

The study was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University, number: (KY2023-R078) and all patients signed the informed consent form. Stage of disease at initial diagnosis was determined according to the American Joint Committee on Cancer (AJCC) TNM Staging System, Version 8.[27] Primary trastuzumab resistance refers to progressive disease (PD) within 3 months of first-line trastuzumab treatment in MBC or the first imaging response evaluation, or diagnosis of new recurrent metastasis within 12 months of the end of adjuvant trastuzumab therapy; secondary trastuzumab resistance is defined as PD after ≥ second-line trastuzumab-containing regimens in patients who achieve disease response or stabilization at initial assessment.[28]

Exclusion Criteria

(1) male breast cancer patients; (2) patients previously treated with pyrotinib or participating in pyrotinib-related clinical trials; (3) pregnant or lactating patients; (4) patients with incomplete clinicopathological data or lost to follow-up.

Study Endpoints

Primary Study Endpoint

The primary endpoint of the study was PFS, defined as the time interval from the start of pyrotinib treatment to disease progression, death from any cause, or the cut-off date for follow-up.

Secondary Study Endpoints

Secondary endpoints included overall survival (OS), efficacy of pyrotinib treatment, and safety. OS was defined as the time interval from the start of pyrotinib treatment to death from any cause or to the follow-up cut-off date.

Efficacy evaluation refers to RECIST Version 1.1, and observation indicators include ORR and DCR. ORR is defined as the proportion of patients who achieve a prespecified reduction in lesion volume and maintain the minimum time limit, which is the sum of complete response(CR) and partial response(PR). DCR is defined as the sum of CR+PR and stable disease (SD) as a percentage of evaluable cases.

The safety evaluation refers to the common terminal criteria for adverse events vision 5.0 (CTCAE 5.0)[29] of the National Cancer Institute of the United States, including the evaluation of the incidence and severity of adverse reactions.

Pyrotinib Administration and Follow-Up

The standard administration and dose of pyrotinib is 400mg orally once daily. The actual dose and treatment regimen of pyrotinib monotherapy or combination therapy will be determined by the competent physician according to the patient's clinical manifestation and after obtaining the patient's informed consent. The patients were followed up by telephone and by reviewing the outpatient examination records. The patients were mainly asked about their survival status, the therapeutic effect of pyrotinib, the degree of adverse reactions and their treatment. Patients who failed to be contacted for three times in different periods were treated as lost to follow-up, those who refused to cooperate with follow-up were classified as refusing follow-up, and those who failed to complete follow-up were excluded. The cut-off date of follow-up was November 2024.

Statistical Analysis

The collected data were analyzed using IBM SPSS 26.0 software (version 26.0, Armonk, NY, USA: IBM Corp) and Graph Pad Prism 9.5 softwar e(San Diego, CA, USA). Mean±standard deviation is used to describe the basic characteristics of continuous variable data conforming to normal distribution, and median and interquartile interval are used to describe the basic characteristics of continuous variable data conforming to skewness distribution. Information on categorical variables is expressed in terms of frequency and percentage. The Pearson Chi-square test or Fisher precision test were used to evaluate differences in efficacy of pyrotinib and differences in adverse reactions among treatment regimens. Kaplan-Meier method was used to calculate PFS and draw survival curves. Log rank test was used to compare differences in PFS among subgroups. Cox univariate analysis and Cox proportional hazards regression models were used to determine independent predictors of PFS. P values were two-sided and $P<0.05$ was defined as statistically significant differences.

Result

Baseline Clinical Characteristics of Patients

A total of 342 female patients with HER2-positive MBC were enrolled. Their baseline characteristics are presented in Table 1.

Table 1 Clinical Baseline Characteristics of Patients

Baseline Feature	**Number of Patients n(%)**
Age(years)	
Median age(range)	52(25–90)
<65	307(89.77%)
≥65	35(10.23%)
Menopausal state	
Premenopause	138(40.35%)
Menopause	204(59.65%)
ECOGm ark	
0–1	324(94.74%)
≥2	18(5.26%)
BMI(kg/m^2)	
<18.5	33(9.65%)
18.5–23.9	216(63.16%)
24–27.9	87(25.44%)
≥28	6(1.75%)
Pathological type	
Invasive ductal carcinoma	308(90.06%)
Invasive lobular carcinoma	18(5.26%)
Other types	16(4.68%)

(*Continued*)

Table 1 (Continued).

Baseline Feature	Number of Patients n(%)
Histological grade	
I	52(15.20%)
II	152(44.45%)
III	138(40.35%)
Hormone receptor status	
Positive	163(47.66%)
Negative	179(52.34%)
HER2 status	
2+	76(22.22%)
3+	266(77.78%)
TNM stage at first visit	
I	23(6.73%)
II	155(45.32%)
III	123(35.96%)
IV	41(11.99%)
Number of metastatic sites	
≤2	208(60.82%)
≥2	134(39.18%)
Metastatic site	
Local recurrence	78(22.81%)
Brain	106(30.99%)
Bone	150(43.86%)
Liver	94(27.49%)
Lung	159(46.49%)
Stomach	1(0.29%)
Lymph node	168(49.12%)
Skin	6(1.75%)
Adrenal gland	6(1.75%)
Pleura	47(13.74%)
Spinal cord	6(1.75%)
Pericardial effusion	3(0.88%)
Diaphragmatic muscle	1(0.29%)

(*Continued*)

Table 1 (Continued).

Baseline Feature	Number of Patients n(%)
(new)Adjuvant chemotherapy	
Yes	106(30.99%)
No	236(69.01%)
Adjuvant endocrine therapy	
Yes	145(42.40%)
No	197(57.60%)
Adjuvant radiotherapy	
Yes	119(34.80%)
No	223(65.20%)
Previous trastuzumab treatment	
Yes	336(98.25%)
For(new)adjuvant therapy	99(28.95%)
For metastasis	75(21.93%)
Both	162(47.37%)
NO	6(1.75%)
Trastuzumab resistance	
Yes	275(80.41%)
Primary resistance	135(39.47%)
Secondary resistance	140(40.94%)
No	67(19.59%)
Previous anti-HER2 regimen	
Trastuzumab	336(98.25%)
Pertuzumab	81(23.68%)
Lapatinib	85(24.85%)
T-DM1	17(4.97%)
Disease-free interval(month)	
0	48(14.04%)
≤12	101(29.53%)
≥12	193(56.43%)

Abbreviations: Eastern Cooperative Oncology Group, ECOG; body mass index, BMI; human epidermal growth-factor receptor2, HER2; ado-trastuzumab emtansine, T-DM1.

Pyrotinib Treatment Administration

Most patients received a combination regimen based on pyrotinib. Capecitabine was combined in 171 patients (50.00%), and pyrotinib combined with vinorelbine in 126 patients (36.84%). In addition, 11 patients (2.00%) received pyrotinib monotherapy. Pyrotinib was used in 110 late first-line patients (32.16%), 121 late second-line patients (35.38%), and 111 late third-line patients (32.46%). The initial dose of pyrotinib was 400mg in 312 (91.23%), 320 mg in 125 (7.31%), and 240 mg in 5(1.47%). During pyrotinib treatment, 28 patients (8.19%) stopped taking pirotinib due to adverse reactions, and 7 patients (2.05%) due to other reasons. Besides, a total of 106 (30.99%) patients had brain metastases, among them, 60 cases (17.54%) underwent local radiotherapy and 31 cases (9.06%) underwent surgery (Table 2).

Table 2 Pyrotinib Treatment Regimen for 150 Patients in This Study

Treatment Regimen Containing Pyrotinib	**Number of Patients N (%)**
Combined capecitabine (±endocrine therapy) regimen	171(50.00%)
Pyrotinib+capecitabine	70(20.47%)
Pyrotinib+capecitabine+trastuzumab	60(17.54%)
Pyrotinib+capecitabine+taxanes	9(2.63%)
Pyrotinib+capecitabine+other chemotherapeutics	16(4.68%)
Pyrotinib+capecitabine+trastuzumab+taxanes	5(1.46%)
Pyrotinib+capecitabine+trastuzumab+other chemotherapeutics	11(3.22%)
Combined with vinorelbine (±endocrine therapy) regimen	126(36.84%)
Pyrotinib+vinorelbine	46(16.67%)
Pyrotinib+vinorelbine+trastuzumab	48(12.67%)
Pyrotinib+vinorelbine+taxanes	7(2.00%)
Pyrotinib+vinorelbine+other chemotherapeutics	9(2.67%)
Pyrotinib+vinorelbine+trastuzumab+taxanes	9(2.67%)
Pyrotinib+vinorelbine+trastuzumab+other chemotherapeutics	7(2.00%)
Combination of trastuzumab (±endocrine therapy) regimen	170(46.67%)
Pyrotinib+trastuzumab	10(2.92%)
Pyrotinib+trastuzumab+chemotherapy	110(32.16%)
Pyrotinib+trastuzumab+pertuzumab	50(14.62%)
Pyrotinib monotherapy	11(2.00%)
Pyrotinib+chemotherapy (except capecitabine or vinorelbine)	45(13.16%)
Pyrotinib monotherapy+endocrine therapy	5(1.46%)
Pyrotinib+antiangiogenic agents	4(1.17%)
Number of pyrotinib treatment lines	
First-line	110(32.16%)
Second-line	121(35.38%)
≥Third-line	111(32.46%)

(*Continued*)

Table 2 (Continued).

Treatment Regimen Containing Pyrotinib	Number of Patients N (%)
Pyrotinib starting dose (mg)	
400	312(91.23%)
320	25(7.31%)
240	5(1.47%)
Pyrotinib dose adjustment (mg)	
400→320	16(4.68%)
400→240	11(3.22%)
400→320→400	3(0.88%)
400→320→240	2(0.58%)
Interruption of pyrotinib treatment	
Due to intolerance of adverse reactions	18(5.26%)
Other reasons	7(2.05%)

Note: [a]Other chemotherapeutic drugs include gemcitabine, teggio, platinum and other chemotherapy drugs.

Efficacy of Pyrotinib

The median follow-up time of this study was 39.0 months, and a total of 259 patients experienced disease progression, accounting for 75.73% of the total population. The mPFS of the overall population was 10.0 months (Figure 1), and the mOS was 29.0 months. All 342 patients were evaluable for efficacy, including 25 CR patients, 113 PR patients, 149 SD patients, and 55 PD patients, with ORR of 40.35% and DCR of 83.92% (Table 3).

Subgroup Efficacy Analyses

The efficacy of pyrotinib in patients with brain metastasis was similar to that in patients without brain metastasis, and the difference was not statistically significant (brain metastasis vs no brain metastasis, ORR: 36.79% vs 41.95%, P=0.405; DCR: 80.19% vs 85.59%, P=0.208).

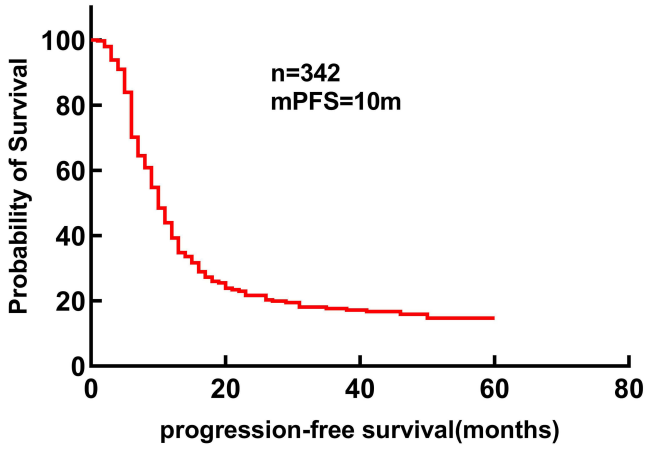

Figure 1 Kaplan-Meier curve of PFS for the total population.

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Table 3 Efficacy of Pyrotinib in 342 Patients

Best Response	Number of Patients
CR	25(7.31%)
PR	113(33.04%)
SD	149(43.57%)
PD	55(16.08%)
ORR	138(40.35%)
DCR	287(83.92%)

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; ORR, objective response rate; DCR, disease control rate.

The efficacy of pyrotinib was similar in patients with and without liver metastasis, and the difference was not statistically significant (liver metastasis vs no liver metastasis, (ORR: 36.17% vs 41.94%, P=0.388; DCR: 80.85% vs 85.08%, P=0.410).

Pyrotinib is more effective in first-line treatment of advanced patients than in second-line, third-line and above treatment (line 1 vs line 2 vs line 3 and above, ORR: 60.00% vs 33.88% vs 27.93%, P<0.001; DCR: 92.73% vs 85.95% vs 72.97%, P<0.001).

There was also no statistical difference in the efficacy of patients receiving pyrotinib plus capecitabine regimen (PX) or pyrotinib plus vinorelbine regimen (PN) (PX regimen vs PN regimen, ORR: 45.61% vs 42.06%, P=0.557; DCR: 91.81% vs 86.51%, P=0.179).

Patients with ≤2 metastatic sites had better efficacy than patients with >2 metastatic sites, and were statistically different (≤2 vs >2, ORR: 46.15% vs 31.34%, P=0.007; DCR: 88.46% vs 76.87%, P=0.006).

Patients who had not previously received lapatinib had significantly better response than patients who had previously received lapatinib (lapatinib untreated vs lapatinib treated, ORR: 43.19% vs 31.76%, P=0.074; DCR: 88.33% vs 70.59%, P<0.001). Patients without prior trastuzumab resistance had better efficacy than patients with prior trastuzumab resistance, and ORR values were statistically different (no resistance vs resistance, ORR: 59.70 vs 35.64%, P<0.001; DCR: 91.04% vs 82.18%, P=0.095) (Table 4).

Table 4 Subgroup Efficacy Analysis

Group	CR (n)	PR (n)	SD (n)	PD (n)	ORR (%)	P	DCR (%)	P
Brain metastases						0.405		0.208
Yes	6	33	46	21	36.79		80.19	
No	19	80	103	34	41.95		85.59	
Liver metastases						0.388		0.410
Yes	5	29	42	18	36.17		80.85	
No	20	84	107	37	41.94		85.08	

(*Continued*)

Table 4 (Continued).

Group	CR (n)	PR (n)	SD (n)	PD (n)	ORR (%)	P	DCR (%)	P
Number of Pyrotinib treatment lines						<0.001		<0.001
Line 1	20	46	36	8	60.00		92.73	
Line 2	4	37	63	17	33.88		85.95	
Line 3	1	30	50	30	27.93		72.97	
Pyrotinib combination regimen						0.557		0.179
Combined capecitabine therapy	14	64	79	14	45.61		91.81	
Combined navelbine therapy	9	44	56	17	42.06		86.51	
Number of metastatic sites						0.007		0.006
≤2	19	77	88	24	46.15		88.46	
≥2	6	36	61	31	31.34		76.87	
Previous lapatinib treatment						0.074		<0.001
Yes	3	24	33	25		31.76		70.59
No	22	89	116	30		43.19		88.33
Trastuzumab resistance profile						<0.001		0.095
Non-resistance	11	29	21	6		59.70		91.04
Resistance	14	84	128	49		35.64		82.18

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; ORR, objective response rate; DCR, disease control rate.

mPFS Results by Subgroup

The mPFS for all patients was 10.0 months, and pyrotinib had better mPFS for advanced first-line treatment than for second-third-line and beyond (14.0 months vs 10.0 months vs 6.0 months, P<0.001) (Figure 2A). The mPFS was longer in patients with ≤2 metastatic sites than >2 metastatic sites (11.0 months vs 7.0 months, P<0.001)(Figure 2B). Patients without liver metastasis had longer mPFS than with liver metastasis (10.0 months vs 9.0 months, P=P<0.001) (Figure 2C). The mPFS for pyrotinib plus capecitabine and vinorelbine was 11.0 months and 10.0 months, respectively, with no statistically significant difference (P=0.275) (Figure 3A). The mPFS was statistically significantly longer in patients treated with pyrotinib plus capecitabine than without combination therapy (11.0 months vs 7.0 months, P=0.004) (Figure 3B). Patients who received lapatinib after prior trastuzumab failure had a statistically significantly worse mPFS than those who did not receive lapatinib (7.0 months vs 11.0 months, P<0.001) (Figure 3C). Patients without liver metastases achieved a longer mPFS than patients with liver metastases (11.0 months vs 7.0 months P<0.001) (Figure 4A). While, the mPFS was numerically better in those who received radiotherapy and or surgery than in those who did not (8.5 months vs 6.0 months, P=0.370) (Figure 4B), and (9.0 months vs 6.0 months, P=0.236) (Figure 4C), but neither was statistically significant. The mPFS was significantly longer in patients without trastuzumab resistance than in patients with primary/secondary trastuzumab resistance (16.0 months vs 9.0 months vs 8.0 months, P<0.001) (Figure 5A). However, there was no significant numerical increase in mPFS for pyrotinib plus trastuzumab compared with no trastuzumab (10.5 months vs 9 months, P=0.278) (Figure 5B).

Univariate Cox Analysis and Multivariate Cox Analysis of PFS

Univariate Cox analysis and multivariate Cox analysis were performed on 342 patients according to the main clinical characteristics to determine the prognostic factors affecting PFS. Univariate Cox analysis showed BMI (P=0.013), ECOG

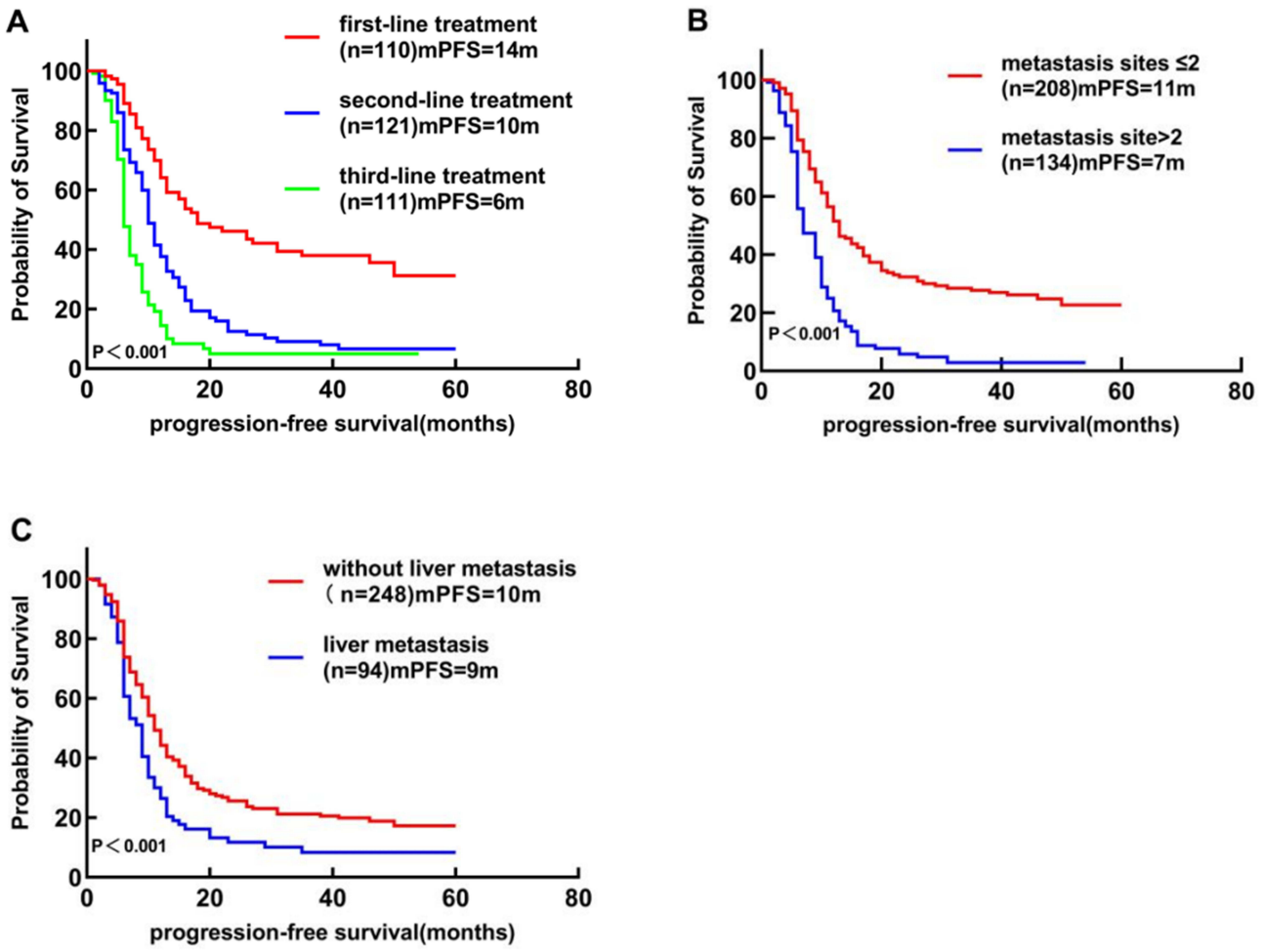

Figure 2 Kaplan–Meier curves of PFS for patients with different characteristics.
Notes: (A) Number of treatment lines. (**B**) Number of metastatic sites. (**C**) Presence or absence of liver metastasis.

score (P<0.001), HER2 status (P=0.004), number of metastatic sites (P<0.001), brain metastasis (P<0.001), liver metastasis (P<0.001), lung metastasis (P<0.001), bone metastasis (P<0.001), number of pyrotinib treatment lines (P<0.001), previous lapatinib treatment (P<0.001), combined with cytarabine therapy (P=0.006) and trastuzumab resistance condition (P<0.001) was significantly associated with PFS. The above statistically significant factors were incorporated into the Cox proportional hazard regression model for multivariate analysis, finally, ECOG, hazard ratio (HR)=0.405, 95% CI 0.236–0.696,P=0.001); HER2 status, (HR)=1.657,95% CI 1.227–2.237,P<0.001); brain metastasis (HR=0.737, 95% CI 0.556–0.977,P=0.034); liver metastasis, (HR=0.740,95% CI 0.554–0.989, P=0.042); number of pyrotinib treatment lines, (line 2 vs line 1, HR=0.488, 95% CI 0.331–0.719; ≥line 3 vs line 1, HR=0.667,95% CI0.481–0.925, P<0.001); previous lapatinib treatment (HR=0.649,95% CI 0.476–0.884, P=0.006); combined capecitabine therapy (HR=1.329, 95% CI 1.026–1.721, P=0.031) and trastuzumab resistance (primary resistance vs non-resistance, HR=0.288, 95% CI 0.178–0.467; secondary resistance vs non-resistance, HR=1.239, 95% CI0.950–1.617, P<0.001) were identified as independent prognostic factors for PFS (Table 5).

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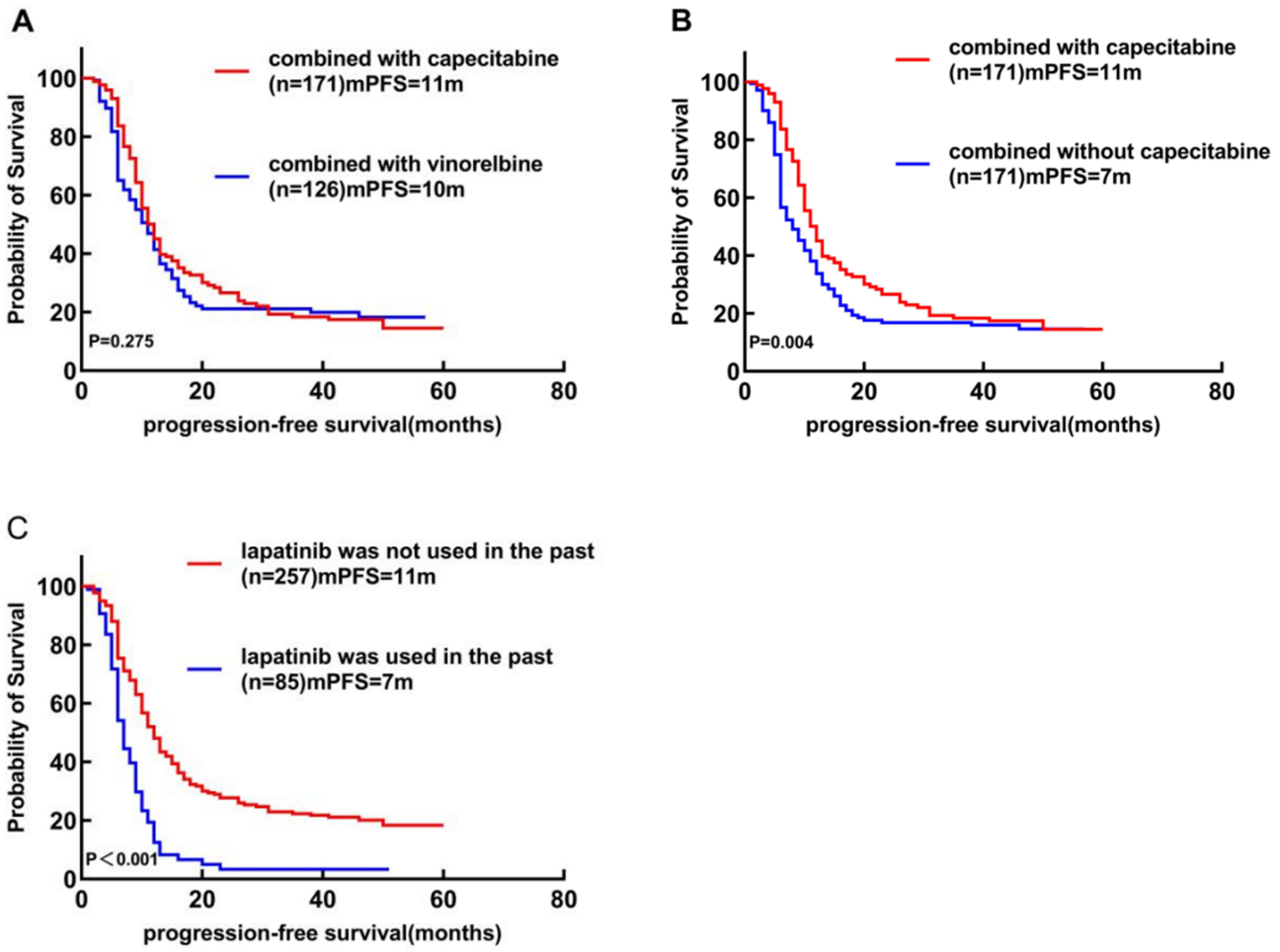

Figure 3 Kaplan–Meier curves of PFS for patients treated with different regimens.
Notes: (**A**) Pyrotinib plus capecitabine or vinorelbine. (**B**) Pyrotinib plus capecitabine or not. (**C**) Prior lapatinib or not.

Pyrotinib-Related Adverse Reactions

All 342 patients were included in the drug safety analysis. Adverse reaction information was collected retrospectively through patient complaints, medical data and clinical laboratory results. The main adverse reactions included diarrhea in 205 cases (59.94%), anemia (40.94%), transaminitis (37.72%), leukopenia (27.49%) and anemia (6.43%). Grade 3 and above adverse reactions occurred in 170 cases (49.71%), including diarrhea in 32 cases (9.36%), leukopenia in 27 cases (7.89%) and anemia in 22 cases (6.43%). No deaths related to pyrotinib treatment were reported,and 18 (5.26%) patients discontinued pyrotinib treatment due to intolerable adverse reactions (Table 6).

Diarrhea occurred in 113 cases (33.04)%and 66 cases (19.30)% in the pyrotinib combined with capecitabine group and the vinorelbine group in the combination regimen respectively; anemia in 69 cases (20.18%) and 48 cases (14.04%); transaminitis in 55 cases (16.08%) and 48 cases (14.04%); leukopenia in 49 cases (14.33%) and 31 cases (9.06%); neutropenia in 45 cases (13.16%) and 26 cases (7.60%); hyperbilirubinemia in 26 cases (7.60%) and 10 cases (2.92%); and hand-foot syndrome in 16 cases (4.68%) and 2 case (0.58%), respectively. The Chi-square test shows the P values of each group as follows: diarrhea(P=0.022), anemia (P=0.720), transaminitis (P=0.324), leukopenia (P=0.508), neutropenia (P=0.274), hyperbilirubinemia (P=0.072) and hand-foot syndrome (P=0.006), which demonstrate that vinorelbine is safer than capecitabine in the combination regimen.

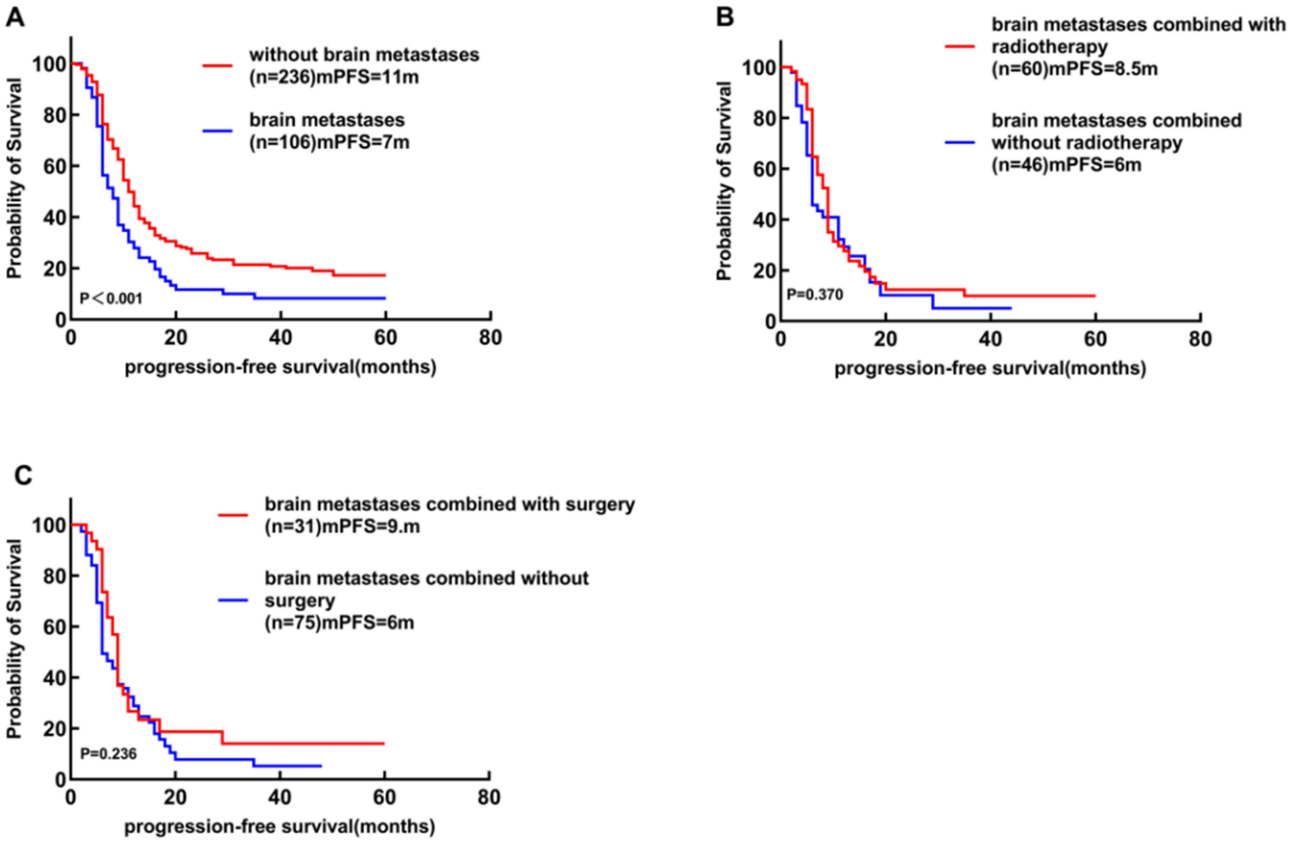

Figure 4 Kaplan-Meier curves for PFS in brain metastasis subgroups.
Notes: (**A**) Brain metastasis or not. (**B**) Radiotherapy or not. (**C**) Surgery or not.

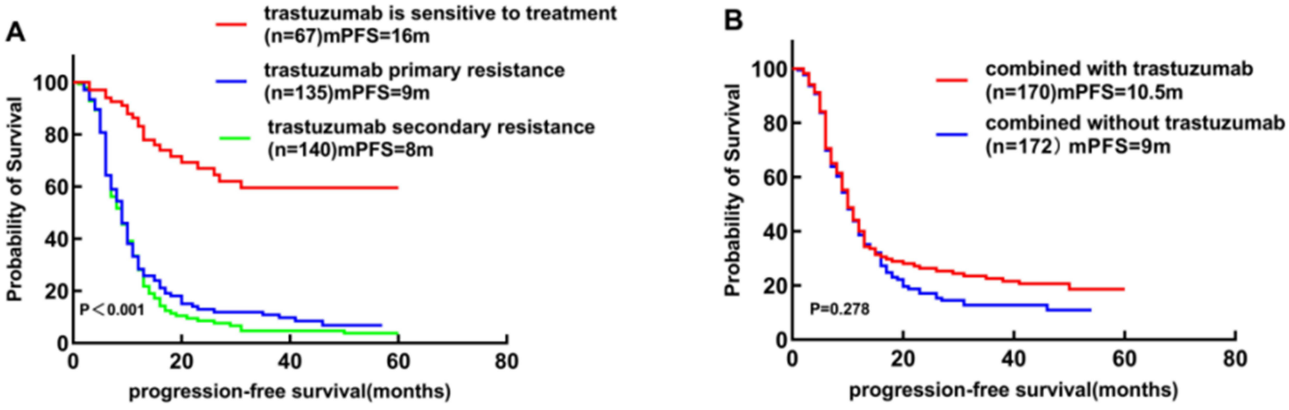

Figure 5 Kaplan-Meier curves of PFS in combined with trastuzumab subgroups.
Notes: (**A**) Different trastuzumab resistance. (**B**) Pyrotinib combined with trastuzumab or not.

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Table 5 Univariate Cox Analysis and Multivariate Cox Analysis Related to PFS

Element	Univariate Cox Analysis		Multivariate Cox Analysis	
	HR (95% CI)	P	HR (95% CI)	P
BMI (kg/m2) 18.5–23.9 vs <18.5 ≥28 vs <18.5 24–27.9 vs <18.5	 1.693(1.171–2.448) 0.924(0.690–1.238) 0.874(0.634–1.204)	 0.013	 1.859(0.633–5.464) 1.659(0.600–4.582) 1.479(0.521–4.194)	 0.564
ECOG (≥2 vs 0–1)	0.451(0.348–0.584)	<0.001	0.405(0.236–0.696)	0.001
HER2 (3+ vs 2+)	1.231(1.070–1.417)	0.004	1.657(1.227–2.237)	<0.001
Number of metastatic sites (2 vs ≤2)	0.655(0.578–0.742)	<0.001	0.740(0.501–1.093)	0.130
Brain metastasis (yes vs no)	0.785(0.689–0.894)	<0.001	0.737(0.556–0.977)	0.034
Liver metastasis (yes vs no)	0.795(0.697–0.908)	<0.001	0.740(0.554–0.989)	0.042
Lung metastasis (yes vs no)	0.739(0.653–0.836)	<0.001	0.870(0.624–1.212)	0.409
Bone metastasis (yes vs no)	0.807(0.714–0.913)	<0.001	0.841(0.620–1.139)	0.262
Number of Pyrotinib treatment lines Line2 vs line1 ≥Line3 vs line1	 0.476(0.392–0.579) 1.070(0.904–1.267)	 <0.001	 0.488(0.331–0.719) 0.667(0.481–0.925)	 0.001
Previous lapatinib treatment (yes vs no)	0.652(0.569–0.748)	<0.001	0.649(0.476–0.884)	0.006
Trastuzumab resistance profile Primary resistance vs non-resistance Secondary resistance vs no resistance	 0.324(0.241–0.435) 1.665(1.370–2.024)	 <0.001	 0.288(0.178–0.467) 1.239(0.950–1.617)	 <0.001
Combined capecitabine therapy (yes vs no)	1.187(1.051–1.342)	0.006	1.329(1.026–1.721)	0.031

Abbreviations: ECOG, Eastern Cooperative Oncology Group; BMI, body mass index; HR, hormone receptor; HER2, human epidermal growth-factor receptor2.

Table 6 Adverse Reactions Related to Pyrotinib

Adverse reaction	Number of patients (n=150)(%)	
	Any Level	≥Grade 3
Not have	42(12.28%)	252(73.68%)
Diarrhea	205(59.94%)	32(9.36%)
Anemia	140(40.94%)	22(6.43%)
Transaminitis	129(37.72%)	21(6.14%)
Leukopenia	94(27.49%)	27(7.89%)
Neutropenia	78(22.81%)	13(3.80%)
γ-glutamyl transpeptidase	64(18.71%)	17(4.97%)
Hyperbilirubinemia	41(11.99%)	8(2.34%)
Creatinine increased	40(11.70%)	3(0.88%)
Thrombocytopenia	36(10.51%)	6(1.75%)

(*Continued*)

Table 6 (Continued).

Adverse reaction	Number of patients (n=150)(%)	
	Any Level	**≥Grade 3**
Anorexia	30(8.77%)	2(0.58%)
Triglycerides increased	28(8.19%)	2(0.58%)
Nausea and vomiting	25(7.31%)	3(0.88%)
Cholesterol increase	25(7.31%)	0
Hand-foot syndrome	20(5.85%)	8(2.34%)
Hyperuricemia	19(5.56%)	2(0.58%)
Lacking in strength	17(4.97%)	1(0.29%)
Stomatitis/conjunctivitis	15(4.39%)	1(0.29%)
Lactate dehydrogenase-elevating	15(4.39%)	1(0.67%)
Sleep disorders	15(4.39%)	0
Eczema	14(4.09%)	1(0.29%)
Swirl	12(3.51%)	0
Palpitation	2(0.58%)	0

Discussion

HER2 positive MBC is highly aggressive and has a short survival, which is the focus and difficulty of breast cancer treatment.[30] The CLEOPATRA study[14] and the EMILIA study[18] laid the foundation for the use of THP regimens and T-DM1 for the first-and second-line standard of care for HER2-positive MBC, respectively; however, prior to the conduct of the present study, the drug penetration of pertuzumab and T-DM1 was limited due to the high price of the drugs. As a new small-molecule TKI drug for oral delivery developed independently by China, pyrotinib has achieved good results in preliminary clinical trials and has been approved for second-line treatment of HER2-positive MBC. There are also a number of small-sample or single-center studies exploring the efficacy of pyrotinib in real-world clinical settings, although the results of real-world studies still differ from clinical trials due to differences in study design. This study was conducted in the population of Southeast Zhejiang, incorporating a sizable sample size and a more complex pyrotinib coadministration scenario, with the aim of complementing the existing real-world and clinical trial data.

After a median follow-up time of 39.0 months, the results of this study showed that in the real world, HER2 positive MBC patients treated with pyrotinib had an mPFS of 10.0 months, an overall ORR of 40.35%, and a DCR of 83.92%. In the PHENIX and PHOEBE studies, the mPFS in the pyrotinib combined with capecitabine groups was 11.1 and 12.5 months, with ORR of 68.6% and 67.2%, and DCR of 91.9% and 88.8%, respectively.[22,23] The mPFS of 11.0 months, ORR of 45.61%, and DCR of 91.81% in the pyrotinib combined with capecitabine group in the present study was lower than in previous clinical trials, possibly due to the fact that 32.46% of patients included in this real-world study received ≥three lines of therapy, and 39.18% of the patients had metastatic sites >2, whereas clinical studies tend to include only ≤2nd line of therapy patients. Several other real-world studies have reported survival results similar to this study. A retrospective study that included 218 patients reported mPFS of 9.3 months with an ORR of 44.0%, with pyrotinib-based therapy used in patients in the first, second,or later line resulting in mPFS of 15.0 months, 10.3 months, and 6.8 months, respectively.[31] A study enrolling 171 patients achieved an mPFS of 12.0 months and an ORR of 45.1% and reported the first mPFS of 5.0 months for pyrotinib cross-line therapy;[32] in another retrospective study that included 141 patients, mPFS was 12.0 months, of which 70 patients were feasibly evaluated for efficacy with an ORR of 38.6%.[33] The

mPFS of pyrotinib used in advanced first-line, second-line, third-line and above patients in this study were 14.0 months, 10.0 months and 6.0 months, respectively. The efficacy analysis showed that pyrotinib used in advanced first-line therapies had the best ORR and DCR, and the difference was statistically significant. It is consistent with the results of previous studies. Multivariate Cox regression analysis also showed that pyrotinib used in first-line therapy had the lowest risk of PFS events (P<0.001) suggesting that the patients benefited more from the early application of pyrotinib. However, there are no head-to-head clinical study results that provide evidence for the use of pyrotinib for the first-line treatment of advanced HER2-positive MBC. Thankfully, preliminary results are available from the Chinese investigator-led PHILA study, a randomized, double-blind, parallel-controlled, multicenter Phase III clinical trial evaluating pyrotinib in combination with trastuzumab and docetaxel versus placebo in combination with trastuzumab and docetaxel for the first-line treatment of HER2 positive MBC. At the European Society for Medical Oncology, ESMO, 2022, researchers reported for the first time that mPFS in the pyrotinib group exceeded 2 years, up to 24.3 months, which was significantly better than the 10.4 months in the control group.[34] The study is expected to set the stage for the future use of pyrotinib for first-line treatment of HER2 positive advanced breast cancer.

Lapatinib and neratinib, like pyrotinib, belong to the TKI family. Lapatinib was approved earlier than pyrotinib for second-line treatment of HER2-positive MBC, but only reversibly inhibits HER1 and HER2 receptors.[35] Phase II clinical trial shows superior efficacy (ORR:78.5%vs.57.1%) and mPFS (18.1 months vs 7.0 months) of pyrotinib over lapatinib.[36] The phase III PHOEBE trial also confirmed significantly prolonged mPFS in the pyrotinib combined with capecitabine group compared to the lapatinib combined with capecitabine group (12.5 months vs 6.8 months).[22] Neratinib, similar to pyrotinib, is an irreversible inhibitor of HER1, HER2, and HER4, and is approved for intensive adjuvant therapy for HER2 positive early-stage breast cancer and third-line therapy for advanced breast cancer.[37] The NALA study showed more benefit in mPFS with neratinib in combination with capecitabine than lapatinib in combination with capecitabine for patients with HER2-positive advanced breast cancer who had been previously treated with 2 or more anti-HER2 agents (8.8 months vs 6.6 months).[20] The use of pyrotinib in advanced third-line and above patients in this study still achieved an mPFS of 6.0 months, suggesting that advanced multiline patients can still benefit from pyrotinib therapy. In the TBCRC022 study exploring neratinib in combination with capecitabine for the treatment of patients with HER2 positive brain metastatic breast cancer, mPFS was 3.1 and 5.5 months in the prior lapatinib-treated and prior lapatinib-untreated groups, respectively.[38] The real-world study by Li et al also reported a significant advantage of pyrotinib in patients untreated with lapatinib (mPFS: lapatinib-untreated group vs lapatinib-treated group: 10.9 months vs 6.9 months).[31] Similarly, in the present study, pyrotinib was used for longer mPFS after progression on prior trastuzumab therapy in the group that had not received lapatinib compared with the group that had received prior lapatinib (11.0 months vs 7.0 months, P<0.001). This effect of efficacy between pyrotinib and lapatinib may be due to potential cross-resistance between the different TKIs.

At present, the combination therapy of large molecule monoclonal antibody and small molecule TKI drug has become a research hotspot. Because they have different HER2 signaling targeting domains, dual anti-HER2 therapies have been shown to enhance anti-tumor activity in many clinical studies. A Phase III clinical trial demonstrated that lapatinib combined with trastuzumab significantly improved outcomes in patients with advanced refractory HER2-positive breast cancer compared to lapatinib alone (mPFS: 3 months vs 2 months, P=0.008; CBR:24.7% vs 12.4%, P=0.01).[39] In the ALTERNATIVE update study, lapatinib combined with trastuzumab and aromatase inhibitors had a significant advantage in mPFS compared to lapatinib combined with aromatase inhibitors (11 months vs 5.6 months, P=0.0063).[32] In this study,170 patients (46.67%) received pyrotinib combined with trastuzumab, and mPFS were better than those without trastuzumab in the regimen (10.5 months vs 9.0 months, P=0.278), indicating a good effect of dual anti-HER2 therapy with small and large molecules.

Capecitabine is currently the most commonly dosed chemotherapeutic agent with pyrotinib. Like pyrotinib, capecitabine is taken orally, which greatly improves medication adherence in patients with advanced disease. The effectiveness of capecitabine in combination with pyrotinib has been demonstrated in the PHENIX[23] study and the PHOEBE[22] study; however, capecitabine, a commonly used chemotherapeutic agent in the clinic, is still used in some patients who have already experienced a failure of capecitabine therapy prior to pyrotinib treatment. Given the synergistic effects of the drugs, chemotherapeutic agents such as vinorelbine and gemcitabine can also be combined with pyrotinib.[40] The real-

world study by Yin et al showed no statistically significant difference in mPFS between those with pyrotinib in combination with capecitabine and those with pyrotinib in combination with vinorelbine (10.2 months vs 12.4 months, P=0.801).[41] Li et al also explored the efficacy of pyrotinib in combination with vinorelbine, showing mPFS of 7.8 months and ORR of 34.3%.[42] The mPFS of those treated with pyrotinib in combination with capecitabine and those treated with vinorelbine in this study were 11.0 and 10.0 months (P=0.0.275), respectively, and the ORR was 45.61% vs 42.06% (P=0.557), neither of which was statistically significant, and the differences were not statistically significant, suggesting that vinorelbine can be used as a reliable alternative to capecitabine.

Brain metastasis have been reported to eventually occur in approximately 25%~50% of patients with HER2-positive MBC.[43] Small molecule TKI drugs are more likely to cross the blood-brain barrier to control brain metastasis due to their small molecular weights.[21] Lapatinib in combination with capecitabine in patients with HER2 positive breast cancer brain metastasis achieves 5.5 months of mPFS in the LANDSCAPE study.[44] The HER2CLIMB study showed that patients with brain metastasis treated with tucatinib also remained CNS progression-free for 9.9 months, while the risk of death was reduced by 42%.[45] The recently published PERMEATE study demonstrated that pyrotinib in combination with capecitabine resulted in mPFS of 11.3 and 5.6 months in patients with brain metastasis not treated with radiotherapy and in patients who progressed after radiotherapy for brain metastasis, with CNS ORRs of 74.6% and 42.1%, respectively.[46] Results of a single-center, small-sample, randomized controlled study showed that in patients with brain metastasis treated with whole-brain radiotherapy, the pyrotinib in combination with capecitabine group significantly increased the overall remission rate (80% vs 40%, P<0.0001) and mPFS (18.5 months vs 6.5 months, P<0.0001) compared to the capecitabine monotherapy group.[47] A total of 106 patients with brain metastasis were included in this study, mPFS reached 7.0 months, ORR was 36.79%, and DCR was 80.19%, which is comparable to the efficacy of other small-molecule TKI agents reported in the literature for HER2-positive brain metastasis, suggesting that pyrotinib is still effective for patients with brain metastasis. In addition, 60 of the 106 patients received cranial radiotherapy and 31 underwent surgery for brain metastasis. The mPFS of those who received cranial radiotherapy was better than those who did not (8.5 months vs 6.0 months, P=0.370), and the mPFS of those who underwent surgery for brain metastasis was also better than those who did not undergo surgical treatment (9.0 months vs 6.0 months, P=0.236), but there was no statistically significant difference between the two groups, which was probably related to the short follow-up time. In patients with HER2 positive breast cancer combined with brain metastasis, a combination of radiotherapy and/or surgery on top of pyrotinib-based therapy may be more favorable.

The most common adverse effect of pyrotinib-based therapy in this study was diarrhea (59.94%), which may be related to irreversible inhibition of HER1 receptors by pyrotinib.[48] Diarrhea was also the main grade 3 and higher adverse reaction, similar to previous findings, but in this paper the incidence was much lower and the severity was mostly grade 1 or 2.[22,23,41,49] This is mainly because before the use of pyrotinib, clinicians usually give patients a detailed account of diarrhea and other adverse effects, and prophylactically apply antidiarrheal drugs such as loperamide and montelukast, and instruct patients to adjust their dietary structure. Anemia, elevated transaminases, and decreases in leukocytes and neutrophils were also common adverse reactions in this study, possibly due to the fact that the majority of patients (86.84%) received a regimen of pyrotinib in combination with a chemotherapeutic agent such as capecitabine, vinorelbine, or paclitaxel. And fewer adverse events occurred in the pyrotinib-combined vincristine group than in the combined capecitabine group, such as: diarrhea in 113 cases (33.04%) vs 66 cases (19.30%), (P=0.022), as studied by Ma et al[50] anemia in 69 cases (20.18%) vs 48 cases (14.04%), (P=0.720); transaminitis in 55 cases (16.08%) vs 48 cases (14.04%), (P=0.324); leukopenia in 49 cases (14.33%) vs 31 cases (9.06%), (P=0.508); neutropenia in 45 cases (13.16%) vs 26 cases (7.60%), (P=0.274); hyperbilirubinemia in 26 cases (7.60%) vs 10 cases (2.92%), (P=0.072); and hand-foot syndrome in 16 cases (4.68%) vs 2 case (0.58%) (P=0.006). Demonstrate that vinorelbine is safer than capecitabine in the combination regimen.

Innovativeness

First, 342 patients were included in this multicenter study, which is a sizable sample size and has more complex history and clinicopathological features, which is more representative of real-world diagnosis and treatment, with less selection bias and more reliable conclusions. Second, this study had a longer median follow-up of 42.0 months. Third, this study

compares the efficacy of different combination regimens of pyrotinib in the real world and the efficacy of patients with brain metastasis receiving pyrotinib in combination with radiotherapy or surgery, which complements the data from previous clinical trials.

Limitations

First, some subgroups, such as the brain metastasis group and the lapatinib-treated group, did not have a sufficiently large number of patients, which may have led to less statistically persuasive conclusions; second, the statistics of adverse events in this study were mainly based on telephone follow-up and outpatient information, and patient subjectivity was unavoidable.

Conclusion

1. This multicenter study suggested that the use of pyrotinib for HER2 positive MBC had a relatively good efficacy, especially for those who received first-line pyrotinib treatment and those who were sensitive to previous trastuzumab treatment.
2. Patients with brain metastasis and liver metastases also benefit from pyrotinib treatment, especially for patients treated with brain radiotherapy and/or surgery.
3. ECOG, HER2 status, brain metastasis, liver metastasis, number of pyrotinib treatment lines, previous lapatinib treatment, combined capecitabine therapy and trastuzumab resistance were independent prognostic factors for PFS in HER2 Positive MBC patients treated with pyrotinib.
4. The most common adverse reaction associated with pyrotinib is diarrhea, which can be well controlled through antidiarrheal treatment.
5. Pyrotinib combined with vinorelbine has similar efficacy to pyrotinib combined with capecitabine and has fewer side effects,andeffects, and can be used as an alternative to capecitabine.

Ethics Approval and Consent to Participate

The study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University, number: (KY2023-R078) and all patients signed the informed consent form.

Disclosure

The authors declare no conflict of interest.

References

1. Sung H. Ferlay J, Siegel RL, et.al. Global cancer statistics 2020:GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.CA Cancer. *J Clin May*. 2021;71(3):209–249. doi:10.3322/caac.21660
2. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229–263. doi:10.3322/caac.21834
3. Giaquinto AN, Sung H, Miller KD, et al. Breast Cancer Statistics,2022.*CA*. *Cancer J Clin Nov*. 2022;72(6):524–541. doi:10.3322/caac.21754
4. Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM, Hortobagyi GN. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. *Oncologist*. 2009;14(4):320–368. doi:10.1634/theoncologist.2008-0230
5. Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. *Nat Rev mol Cell Biol*. 2001;2(2):127–137. doi:10.1038/35052073
6. Prognostic and predictive biomarkers in breast cancer:Past,present and future.*Semin*. *Cancer Biol*. 2018;52(Pt 1):56–73. doi:10.1016/j.semcancer.2017.08.010
7. Krishnamurti U, Silverman JF. HER2 in breast cancer: a review and update. *Adv Anat Pathol*. 2014;21(2):100–107. doi:10.1097/pap.0000000000000015
8. Sun L, Jia X, Wang K, Li M. Unveiling the future of breast cancer therapy: cutting-edge antibody-drug conjugate strategies and clinical outcomes. *Breast*. 2024;78:103830. doi:10.1016/j.breast.2024.103830
9. Systemic therapy for advanced human epidermal growth factor receptor 2-positive breast cancer:ASCO guideline update. *J Clin Oncol*. 2022;40(23):2612–2635. doi:10.1200/jco.22.00519
10. Waks AG, Winer EP. Breast cancer treatment: a review. *JAMA*. 2019;321(3):288–300. doi:10.1001/jama.2018.19323
11. Gianni L, Pienkowski T, Im Y-H. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory,or early-stage HER2-positive breast cancer(NeoSphere):a multicentre, open-label,Phase 2 randomised trial. *Lancet Oncol*. 2016;17(6):791–800. doi:10.1016/s1470-2045(16)00163-7

12. Schneeweiss A, Chia S, Hickish T. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study(TRYPHAENA). *Ann Oncol*. 2013;24(9):2278–2284. doi:10.1093/annonc/mdt182
13. Piccart M, Procter M, Fumagalli D, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer in the aphinity trial:6 years'follow-up. *J Clin Oncol May*. 2021;39(13):1448–1457. doi:10.1200/jco.20.01204
14. Swain SM, Miles D, Kim S-B. Pertuzumab, trastuzumab,and docetaxel for HER2-positive metastatic breast cancer(CLEOPATRA):end-of-study results from a double-blind,randomised, placebo-controlled,phase 3 study. *Lancet Oncol*. 2020;21(4):519–530. doi:10.1016/S1470-2045(19)30863-0
15. Xu B, Li W, Zhang Q. Pertuzumab, trastuzumab,and docetaxel for Chinese patients with previously untreated HER2-positive locally recurrent or metastatic breast cancer(PUFFIN):a Phase III,randomized,double-blind, placebo-controlled study. *Breast Cancer Res Treat*. 2020;182(3):689–697. doi:10.1007/s10549-020-05728-w
16. Trastuzumab: updated mechanisms of action and resistance in breast cancer. *Front Onco*. 2012;2:62. doi:10.3389/fonc.2012.00062
17. Cameron D, Casey M, Oliva C, Newstat B, Imwalle B, Geyer CE. Lapatinib plus capecitabine in women with HER-2-positive advanced breast cancer: final survival analysis of a phase III randomized trial.. *Oncologist*. 2010;15(9):924–934. doi:10.1634/theoncologist.2009-0181
18. Diéras V, Miles D, Verma S. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer(EMILIA):a descriptive analysis of final overall survival results from a randomised,open-label, phase 3 trial. *Lancet Oncol*. 2017;18(6):732–742. doi:10.1016/s1470-2045(17)30312-1
19. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase trial.. *Lancet*. 2023;401(10371):105–117. doi:10.1016/S0140-6736(22)02420-5
20. Saura C, Oliveira M, Feng Y-H. Plus Capecitabine Versus lapatinib plus capecitabine in HER2-positive metastatic breast cancer previously treated with≥2 hER2-directed regimens: phase III NALA Trial.. *J Clin Oncol Sep*. 2020;38(27):3138–3149. doi:10.1200/jco.20.00147
21. Zhu Y, Li L, Zhang G. Metabolic characterization of pyrotinib in humans by ultra-performance liquid chromatography/quadrupole time-of-flight mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2016;1033-1034:117–127. doi:10.1016/j.jchromb.2016.08.009
22. Xu B, Yan M, Ma F, et.al. Pyrotinib plus capecitabine versus lapatinib plus capecitabine for the treatment of HER2-positive metastatic breast cancer(PHOEBE):a multicentre, open-label, randomised, controlled,phase 3 trial. *Lancet Oncol*. 2021;22(3):351–360. doi:10.1016/s1470-2045(20)30702-6
23. Yan M, Bian L, Hu X, et.al. Pyrotinib plus capecitabine for human epidermal factor receptor 2-positive metastatic breast cancer after trastuzumab and taxanes(PHENIX): a randomized, double-blind, placebo-controlled phase 3 study. *Transl Cancer Res*. 1;2020.
24. Jiang Z, Li J, Chen J, et al. Chinese Society of clinical oncology(CSCO)breast cancer guidelines 2022. *Transl Breast Cancer Res*. 2022;3:13. doi:10.21037/tbcr-22-21
25. Viswanathan A, Pathoor NN, Gopal RK, Ganesh PS. Letter to the editor regarding the article"effectiveness and safety of pyrotinib-based therapy in the treatment of HER2-positive breast cancer patients with brain metastases: a multicenter real-world study". *Clin Breast Cancer*. 2024;24(8):e773–e774. doi:10.1016/j.clbc.2024.09.009
26. Wu M, Lei S, Tang Y, et.al. Real-world outcomes of pyrotinib-based therapy for her2-positive breast cancer with brain metastases: a multicentre, retrospective analysis. *Clin Breast Cancer*. 2024. doi:10.1016/j.clbc.2024.11.005
27. National Cancer Institute.AJCC Cancer Staging Manual. 8th edition.definitionsQeios. 2020. Available from: https://www.qeios.com/read/definition/28609. Accessed February 26, 2025.
28. Wong H, Leung R, Kwong A. Integrating molecular mechanisms and clinical evidence in the management of trastuzumab resistant or refractory HER-2^{+}metastatic breast cancer. *Oncologist*. 2011;16(11):1535–1546. doi:10.1634/theoncologist.2011-0165
29. US Department of Health and Human Services Common Terminology Criteria for Adverse Events(CTCAE)(Version 5.0);2017 Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf. Accessed April 11, 2024.
30. Xu L, Xie Y, Gou Q. HER2-targeted therapies for HER2-positive early-stage breast cancer: present and future.. *Front Pharmacol*. 2024;15:1446414. doi:10.3389/fphar.2024.1446414
31. Li C, Bian X, Liu Z. Effectiveness and safety of pyrotinib-based therapy in patients with HER2-positive metastatic breast cancer:A real-world retrospective study. *Cancer Med*. 2021;10(23):8352–8364. doi:10.1002/cam4.4335
32. Zhang X, Li Z, Han L. Efficacy and safety of pyrotinib in human epidermal growth factor receptor 2-positive advanced breast cancer: a multicenter, retrospective,real-world study. *Onco Targets Ther*. 2022;15:1067–1078. doi:10.2147/ott.S379591
33. Zhang L, Wu X, Zhou J. Pyrotinib in the Treatment of women with HER2-positive advanced breast cancer: a multicenter, prospective, real-world study. *Front Oncol*. 2021;11:699323. doi:10.3389/fonc.2021.699323
34. LBA19 Pyrotinib or placebo in combination with trastuzumab and docetaxel for HER2-positive metastatic breast cancer(PHILA):A randomized phase III trial. *Ann Oncol*. 2022.
35. Schlam I, Swain SM. Schlam I,Swain SM.HER2-positive breast cancer and tyrosine kinase inhibitors: the time is now. *NPJ Breast Cancer*. 2021;7(1):56. doi:10.1038/s41523-021-00265-1
36. Ma F, Ouyang Q, Li W. Pyrotinib or lapatinib combined with capecitabine in HER2-positive metastatic breast cancer with prior taxanes, anthracyclines,and/or trastuzumab: a randomized, phase II study. *J Clin Oncol*. 2019;37(29):2610–2619. doi:10.1200/jco.19.00108
37. Chan A, Delaloge S, Holmes FA. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer(ExteNET):a multicentre, randomised, double-blind, placebo-controlled,phase 3 trial. *Lancet Oncol*. 2016;17(3):367–377. doi:10.1016/S1470-2045(15)00551-3
38. Freedman RA, Gelman RS, Anders CK. TBCRC 022:A phase ii trial of neratinib and capecitabine for patients with human epidermal growth factor Receptor 2-positive breast cancer and brain metastases. *J Clin Oncol*. 2019;37(13):1081–1089. doi:10.1200/jco.18.01511
39. Blackwell KL, Burstein HJ, Storniolo AM. Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. *J Clin Oncol*. 2010;28(7):1124–1130. doi:10.1200/jco.2008.21.4437
40. Gómez HL, Neciosup S, Tosello C. A phase II randomized study of lapatinib combined with capecitabine, vinorelbine,or gemcitabine in patients with HER2-Positive metastatic breast cancer with progression after a Taxane(Latin American Cooperative Oncology Group 0801 Study). *Clin Breast Cancer*. 2016;16(1):38–44. doi:10.1016/j.clbc.2015.10.005
41. Yin S, Chi Y, Du Y. Efficacy and safety of pyrotinib-containing regimen in the patients with HER2-positive metastatic breast cancer:A multicenter real-world study. *Cancer Med*. 2023;12(3):2333–2344. doi:10.1002/cam4.5056

42. Li Y, Qiu Y, Li H. Pyrotinib combined with vinorelbine in HER2-positive metastatic breast cancer: a multicenter retrospective study. *Front Oncol*. 2021;11:664429. doi:10.3389/fonc.2021.664429
43. Olson EM, Abdel-Rasoul M, Maly J, Wu CS, Lin NU, Shapiro CL. Incidence and risk of central nervous system metastases as site of first recurrence in patients with HER2-positive breast cancer treated with adjuvant trastuzumab. *Ann Oncol*. 2013;24(6):1526–1533. doi:10.1093/annonc/mdt036
44. Bachelot T, Romieu G, Campone M. Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer(LANDSCAPE):a single-group phase 2 study. *Lancet Oncol*. 2013;14(1):64–71. doi:10.1016/s1470-2045(12)70432-1
45. Lin NU, Borges V, Anders C. Intracranial efficacy and survival with tucatinib plus trastuzumab and capecitabine for previously treated HER2-positive breast cancer with brain metastases in the HER2CLIMB trial. *J Clin Oncol*. 2020;38(23):2610–2619. doi:10.1200/jco.20.00775
46. Yan M, Ouyang Q, Sun T. Pyrotinib plus capecitabine for patients with human epidermal growth factor receptor 2-positive breast cancer and brain metastases(PERMEATE):a multicentre, single-arm, two-cohort,phase 2 trial. *Lancet Oncol*. 2022;23(3):353–361. doi:10.1016/s1470-2045(21)00716-6
47. Tian W, Hao S, Wang L, Chen Y, Li Z, Luo D. Pyrotinib treatment enhances the radiosensitivity in HER2-positive brain metastatic breast cancer patients. *Anticancer Drugs*. 2022;33(1):e622–e627. doi:10.1097/cad.0000000000001199
48. Rugo HS, Di Palma JA, Tripathy D. The characterization, management,and future considerations for ErbB-family TKI-associated diarrhea. *Breast Cancer Res Treat*. 2019;175(1):5–15. doi:10.1007/s10549-018-05102-x
49. Sun Y, Chen B, Li J, et al. Real-world analysis of the efficacy and safety of a novel irreversible HER2 tyrosine kinase inhibitor pyrotinib in patients with HER2-positive metastatic breast cancer. *Cancer Manag Res*. 2021;13:7165–7174. doi:10.2147/cmar.S321428
50. Ma X, Li Y, Li L. Pyrotinib-based treatments in HER2-positive breast cancer patients with brain metastases. *Ann Med*. 2022;54(1):3085–3095. doi:10.1080/07853890.2022.2139411