


Retrospective Analysis of Pyrotinib-Based Therapy for Metastatic Breast Cancer: Promising Efficacy in Combination with Trastuzumab

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Purpose: To evaluate the efficacy and safety of a pyrotinib-based therapy for human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC) in the real world.

Methods: Clinical data of 218 patients with HER2-positive MBC who received a pyrotinib-based therapy from January 2020 to March 2023 at the First Affiliated Hospital of Zhengzhou University were retrospectively analyzed.

Results: Finally, 195 patients were included in the efficacy cohort. The median progression-free survival (PFS) in the total population is 12.4 months (95% CI, 9.8–15.0 months). More than half of the patients in the efficacy cohort received pyrotinib mono-targeted therapy (103 cases, 52.8%). Among the remaining patients, 74 (37.9%) patients chose a combined trastuzumab-targeted therapy and 17 (8.7%) chose to combine inetetamab. Median PFS in the pyrotinib group vs pyrotinib plus trastuzumab group was 10.5 months vs 20.1 months ($P < 0.001$). The median PFS of primary trastuzumab resistance population reached to 20.1 months in pyrotinib plus trastuzumab group. Double-targets' advantage was also observed in the brain metastases subgroup (17.9 months vs 10.0 months, $P = 0.386$). The patients who received pyrotinib plus inetetamab as second and higher-line treatment reached a median PFS of 7.9 months (95% CI, 4.0–11.8 months). Forty-one (19.8%) of 207 patients included in the safety cohort experienced grade 3 or higher diarrhea, the most common adverse event in safety analysis, and no adverse event-related deaths.

Conclusion: The combination of pyrotinib and trastuzumab demonstrated promising efficacy in the treatment of HER2-positive metastatic breast cancer, including those who had primary resistance to trastuzumab and brain metastases. Pyrotinib plus trastuzumab is expected to be a potent option in the first-line. Additionally, the concurrent administration of pyrotinib and inetetamab could be an alternative to consider in the second and higher-line treatment for metastatic breast cancer. The adverse reactions of pyrotinib were tolerable in general.

Keywords: pyrotinib, HER2, metastatic breast cancer, trastuzumab, inetetamab

Introduction

According to Global Cancer Statistics 2020,¹ breast cancer has surpassed lung cancer, becoming the most prevalent cancer among women worldwide. It is known to us that compared with other pathologic subtypes of breast cancer, overexpression of HER2 increases the invasiveness of cancer and the possibility of metastases, especially brain metastases (BM),² thus the prognosis of HER2-positive breast cancer tends to be poorer.³ The advent of HER2-targeted drugs brought dramatic improvements in the prognosis of patients with HER2-positive breast cancer.

Trastuzumab was the first drug for targeted treatment of HER2-positive breast cancer approved by FDA (Food and Drug Administration). With the release of results of the CLEOPATRA study,⁴ the classic dual-targets, trastuzumab and pertuzumab, consolidated their status in the treatment of HER2-positive metastatic breast cancer (MBC). However, it is hard to guarantee consistent benefits from trastuzumab for patients because of primary or secondary resistance to trastuzumab.⁵ Meanwhile, as a large molecule, trastuzumab's efficacy in brain metastases (BM) is limited by the

blood–brain barrier. As a result, research for new HER2-targeted drugs has become increasingly urgent and positive in recent years.

Tyrosine kinase inhibitors (TKIs), antibody-drug conjugates (ADCs), and inetinamab have all shown potential in some previous research. Pyrotinib, a novel oral TKI independently developed in China, covalently binds to the ATP-binding site of the intracellular kinase region of HER1, HER2 and HER4 of the HER family, prevents the formation of HER family homo-/heterodimers, inhibits self-phosphorylation, and blocks downstream activation of the PI3K/AKT/mTOR and MEK/MAPK signaling pathways, thus inhibits tumor cell growth.⁶ A pooled analysis⁷ based on three clinical studies of pyrotinib + capecitabine for HER2-positive treatment showed that pyrotinib + capecitabine significantly improved median Progression-Free-Survival (PFS) (22.0 months vs 6.9 months) and median OS (59.9 months vs 31.2 months) when comparing to previous TKI, lapatinib + capecitabine in HER2-positive MBC patients. Mechanistically, pyrotinib may have the potential to exert a stronger anti-cancer ability compared to trastuzumab, which binds to the extracellular domain IV of HER2 only. A meta-analysis⁸ has proved that a pyrotinib-containing regimen did show considerable tumor response, disease control, and survival with manageable adverse effects in any lines of the treatment of MBC. In addition, some studies^{9,10} have found that the combination of TKI with trastuzumab can simultaneously act on HER2 intracellular and extracellular and show promising efficacy in patients with HER2-positive MBC, even with BM. In the PHILA study,¹¹ the dual-target combination of pyrotinib + trastuzumab demonstrated a strong ability to improve survival outcomes with a median PFS of 24.3 months.

Inetinamab, an innovative HER2 monoclonal antibody independently developed in China, which was approved by the National Medical Products Administration (NMPA) in 2020, has shown stronger antibody-dependent cell-mediated cytotoxicity (ADCC) than trastuzumab in vitro studies.¹² The efficacy of pyrotinib plus inetinamab, called *Chinese dual-targets*, still lacks real-world data to validate.

In this study, we retrospectively analyzed the efficacy and safety of a pyrotinib-based therapy for the treatment of HER2-positive MBC in the real world. The results uncovered the promising efficacy of pyrotinib plus trastuzumab in HER2-positive MBC, particularly in patients who received this dual-targets regimen as the first-line treatment. And the strength also manifests in patients with trastuzumab resistance or BM. The new dual-targets regimen of pyrotinib plus inetinamab may improve survival outcomes in the second and higher-line treatment of MBC.

Materials and Methods

Study Design

Clinical data were collected from patients with HER2-positive MBC who received a pyrotinib-based treatment regimen from January 2020 to March 2023 at the First Affiliated Hospital of Zhengzhou University. Inclusion criteria: (1) female breast cancer patients with pathologic immunohistochemistry-confirmed primary or metastatic lesion of Her2- 3+ or Her2- 2+ with in situ hybridization (ISH) +; (2) patients with complete medical records after receiving pyrotinib; Exclusion criteria: (1) having previously received pyrotinib at an earlier baseline; (2) patients who discontinued pyrotinib-based therapy due to adverse events in no more than two cycles of treatment. The study was reviewed and approved by the Ethics Committee of The First Affiliated Hospital of Zhengzhou University (2023-KY-0814-001), written informed consent for participation was not required for this retrospective study following the national legislation and the institutional requirements.

Treatment and Dose Modification

The recommended dosage of pyrotinib was 400 mg orally once a day, every 21 days is a cycle, the starting dose and dose adjustments during treatment were determined by the clinician based on the patient's physical condition and tolerance of adverse effects.

Efficacy and Safety Assessments

Based on the response evaluation criteria in solid tumors 1.1 (RECIST 1.1), patients' clinical records and examination data were reviewed. Adverse events (AEs) were assessed according to the National Cancer Institute Common

Terminology Criteria for Adverse Events (CTCAE 5.0). AEs were collected based on patients' feedback and biochemical test results.

The primary endpoint was progression-free survival (PFS), which is defined as the time interval between the date of initiating pyrotinib and the occurrence of disease progression (PD) or death from any cause, whichever came first. The efficacy of patients who had measured lesions was evaluated according to RECIST 1.1, comprising complete response (CR), partial response (PR), disease stabilization (SD), disease progression (PD), and not evaluable (NE). Secondary endpoints included objective response rate (ORR), the percentage of patients achieving CR or PR lasting no less than 4 weeks; clinical benefit rate (CBR), the percentage of patients with CR or PR or SD confirmed for at least 24 weeks; disease control rate (DCR), the percentage of patients with CR or PR or SD confirmed for at least 4 weeks; exploration of predictors for PFS; and safety.

Statistical Analysis

IBM SPSS Statistics software (version 26.0, Armonk, NY, USA: IBM Corp) was used to analyze all data. Descriptive analyses were used to demonstrate clinical characteristics. The Kaplan–Meier method was used to estimate PFS and 95% confidence intervals (CIs) for the total population and each subgroup. The predictors for PFS were determined by Cox univariate and multivariate models. All tests were two-sided and a $P < 0.05$ was considered to be statistically significant.

Results

Patient Characteristics

Totally 218 patients with HER2-positive metastatic breast cancer provided by a pyrotinib-based regimen were reviewed. And 195 patients (median age, 52 years; range, 26–78 years) were finally enrolled in the efficacy cohort for analysis according to inclusion and exclusion criteria (Figure 1). The clinical characteristics of the patients are shown in Table 1. Hormone receptor (HR)-negative in this study was defined as estrogen receptor (ER)-negative and progesterone receptor (PR)-negative ($< 1\%$ positive cells). The HR-positive was defined as ER-positive and (or) PR-positive ($\geq 1\%$ positive cells). To demonstrate the real-world setting of pyrotinib, we did not exclude the patients with an ECOG (Eastern Cooperative Oncology Group) score of 3/4 in the study design. However, there was only one patient with an ECOG 3 had been recruited in the data collection stage, and this patient was excluded from the efficacy analysis for the discontinuation of the pyrotinib in no more than 2 cycles of treatment. And no patients with an ECOG of 4 were included in our study. As

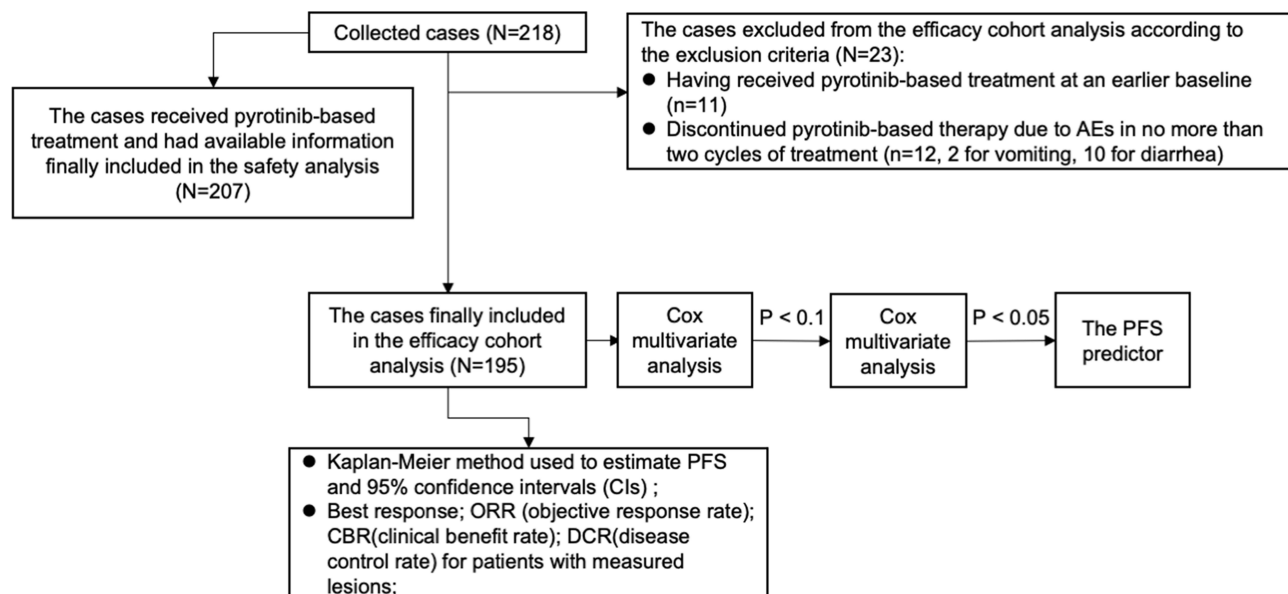


Figure 1 Flow diagram of the analysis.

Table I Baseline Characteristics of 195 Patients

| Combined Regimens | No. (N = 195) | % |
|------------------------------------|------------------|---------|
| Age | | |
| Median (range) | 52 | (26–78) |
| <60 | 154 | 79.0 |
| ≥60 | 41 | 21.0 |
| Menstrual status | | |
| Pre-menopausal | 91 | 46.7 |
| Post-menopausal | 104 | 53.3 |
| ECOG | | |
| 0–1 | 156 | 80.0 |
| 2 | 39 | 20.0 |
| HR | | |
| Negative | 91 | 46.7 |
| Positive | 104 | 53.3 |
| HER2 | | |
| 2+ and ISH + | 33 | 16.9 |
| 3+ | 162 | 83.1 |
| Ki-67 | | |
| <20% | 8 | 4.1 |
| ≥20% | 187 | 95.9 |
| Timing of distant metastases | | |
| Synchronously with primary lesion | 46 | 23.6 |
| Metachronously with primary lesion | 149 | 76.4 |
| Previous anti-HER2 treatment | | |
| Yes | 154 | 79.0 |
| Trastuzumab | 152 | 77.9 |
| Pertuzumab | 35 | 17.9 |
| Lapatinib | 9 | 4.6 |
| Inetetamab | 6 | 3.1 |
| TDM-I | 2 | 1.0 |
| Neratinib | 1 | 0.5 |
| No | 41 | 21.0 |

(Continued)

Table 1 (Continued).

| Combined Regimens | No. (N = 195) | % |
|---|------------------|------|
| Primary resistance to trastuzumab | | |
| No | 135 | 69.2 |
| Yes | 60 | 30.8 |
| Metastatic sites | | |
| Lymph nodes | 93 | 47.7 |
| Lung | 80 | 41.0 |
| Liver | 74 | 37.9 |
| Bone | 83 | 42.6 |
| Brain | 47 | 24.1 |
| Line of pyrotinib in metastatic setting | | |
| 1 | 77 | 39.5 |
| 2 | 68 | 34.9 |
| ≥3 | 50 | 25.6 |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; ISH, in situ hybridization; TDM-1, ado-trastuzumab emtansine.

a result, there were 156 patients (80.0%) with an ECOG 0–1 and 39 patients (20.0%) with an ECOG 2 were finally enrolled in the efficacy analysis. The metastases in our study were defined as discovered upon the initial diagnosis of cancer-synchronous metastases (SM) or during follow-up after treatment of the localized disease-metachronous metastases (MM). Of the 152 patients (77.9%) who had received trastuzumab-targeted therapy before, 60 patients (30.8%) in this study demonstrated primary trastuzumab resistance. Primary trastuzumab resistance was defined as the same as the PICTURE trial,¹³ progression during (neo)adjuvant trastuzumab or within 12 months of completing (neo)adjuvant trastuzumab, or progression within 6 months after initiation of first-line trastuzumab for advanced disease.

Treatment Administration

The treatment regimens, pyrotinib-dose adjustments, and pyrotinib therapy status at the end of follow-up for 195 patients are shown in Table 2. A total of 103 cases (52.8%) were treated with pyrotinib single-target regimen, 74 (37.9%) were provided with trastuzumab combined, 17 (8.7%) were conducted based on dual-targets with pyrotinib and inेतetamab, and only 1 patient (0.5%) was treated with TDM-1. The most common concomitant chemotherapeutic agent was capecitabine (96, 49.2%), followed by paclitaxel (35, 17.9%), Eribulin (13, 6.7%), vinorelbine (7, 3.6%), and other agents (10, 5.1%). Four patients (2.1%) discontinued pyrotinib due to intolerance of adverse effects, and two (1.0%) discontinued for inaccessibility. Of the 10 death cases, 9 patients died from the progression of breast cancer metastases, and only one patient died from COVID-19 (Corona Virus Disease 2019).

Efficacy

Total Population

The follow-up ended on September 30, 2023, and the median follow-up time was 21.7 months (95% CI, 18.1–25.3 months). The median PFS was 12.4 months (95% CI, 9.8–15.0 months) in the total population of 195 patients (Figure 2A). The efficacy results for patients with measured lesions are shown in Table 3. In the best response assessment, only one patient confirmed CR, 65 reached PR, 83 reached SD, and 13 reached PD, with an ORR of 39.3%, a DCR of 88.7%, and a CBR of 66.1%.

Table 2 Treatment Administration

| Line of Pyrotinib in Metastatic Setting (First-Line /Second and Higher-Line) | | Combined Anti-HER2 Regimens with Pyrotinib | | | | Total, n(%) |
|--|----------------|--|-------------|------------|--------|-------------------|
| | | None | Trastuzumab | Inetetamab | TDM-1 | |
| Combined regimens | None | 4/11 | 8/9 | 0/1 | 0/1 | 12(6.2)/22(11.3) |
| | Capecitabine | 20/51 | 7/11 | 4/3 | 0/0 | 31(15.9)/65(33.3) |
| | Vinorelbine | 0/5 | 2/0 | 0/0 | 0/0 | 2(1.0)/5(2.6) |
| | Paclitaxel | 1/3 | 21/6 | 2/2 | 0/0 | 24(12.3)/11(5.6) |
| | Eribulin | 0/2 | 4/2 | 2/3 | 0/0 | 6(3.1)/7(3.6) |
| | Other | 0/6 | 2/2 | 0/0 | 0/0 | 2(1.0)/8(4.1) |
| Total of first-line, n(%) | | 25(12.8) | 44(22.6) | 8(4.1) | 0 | 77(39.5) |
| Total of second- and higher-line, n(%) | | 78(40.0) | 30(15.4) | 9(4.6) | 1(0.5) | 118(60.5) |
| Total, n(%) | | 103(52.8) | 74(37.9) | 17(8.7) | 1(0.5) | 195(100) |
| Pyrotinib dosage and adjustment | | | | | | |
| Starting dosage (mg/d) | 80 | 0 | 0 | 1 | 0 | 1(0.5) |
| | 240 | 1 | 0 | 0 | 0 | 1(0.5) |
| | 320 | 5 | 3 | 0 | 0 | 8(4.1) |
| | 400 | 97 | 71 | 16 | | 185(94.9) |
| Total, n(%) | | 103(52.8) | 74(37.9) | 17(8.7) | 1(0.5) | 161(100) |
| Dose reduction (mg/d) | 400→320→240 | 0 | 0 | 1 | 0 | 1(0.5) |
| | 400→320 | 11 | 2 | 0 | 0 | 13(6.7) |
| | 320→240 | 1 | 2 | 0 | 0 | 3(1.5) |
| Total, n(%) | | 12(6.1) | 4 (2.1) | 1 (0.5) | 0 | 17(8.7) |
| Dose escalation (mg/d) | 320→400 | 3 | 1 | 0 | 0 | 4(2.1) |
| | 240→320 | 2 | 0 | 0 | 0 | 2(1.0) |
| | 80→160→240→320 | 0 | 0 | 1 | 0 | 1(0.5) |
| Total, n(%) | | 5(2.6) | 1(0.5) | 1 (0.5) | 0 | 7(3.6) |
| Interruption of treatment | | 10 | 7 | 0 | 0 | 17(8.7) |
| Pyrotinib therapy status at the end of follow-up | | | | | | |
| Discontinued, n(%) | | 81(41.5) | 51(26.2) | 11(5.6) | 1(0.5) | 144(73.8) |
| Discontinued for adverse effects in the third or later cycle of treatment | | 2 | 2 | 0 | 0 | 4(2.1) |
| Discontinued for inaccessibility of pyrotinib | | 0 | 0 | 2 | 0 | 2(1.0) |
| Discontinued as planned | | 10 | 18 | 2 | 1 | 31(15.9) |
| Death | | 8 | 2 | 0 | 0 | 10(5.1) |
| Transferred to the regimen without pyrotinib after PD | | 61 | 29 | 7 | 0 | 97(49.7) |
| Ongoing, n(%) | | 18(9.2) | 22(11.3) | 6(3.1) | 0 | 46(23.6) |

(Continued)

Table 2 (Continued).

| Line of Pyrotinib in Metastatic Setting (First-Line /Second and Higher-Line) | Combined Anti-HER2 Regimens with Pyrotinib | | | | Total, n(%) |
|--|--|-------------|------------|-------|-------------|
| | None | Trastuzumab | Inetetamab | TDM-1 | |
| Had not achieve PD | 14 | 15 | 6 | 0 | 35(17.9) |
| Received regimen containing pyrotinib after PD | 4 | 7 | 0 | 0 | 11(5.6) |
| Unknown, n(%) | 4(2.1) | 1(0.5) | 0 | 0 | 5(2.6) |

Abbreviations: HER2, human epidermal growth factor receptor 2; TDM-1, ado-trastuzumab emtansine; PD, progressive disease.

Median PFS was 16.7 months versus 10.5 months for those who received pyrotinib-based regimen as a first-, second- and higher-line regimen, respectively ($P=0.106$) (Figure 2B).

In the Cox univariate and multivariate analysis (Table 4), the combination of trastuzumab exhibited the ability to reduce a 53.6% of risk PD or death (Hazard ratio, HazR=0.464, 95% CI: 0.310–0.693, $P<0.001$).

Pyrotinib versus Pyrotinib + Trastuzumab

The results of the median PFS analysis of the pyrotinib single-target group versus the pyrotinib plus trastuzumab dual-targets group for the characterized populations are displayed in Figure 3. The median PFS in the two subgroups were 10.5 months (95% CI, 9.3–11.7 months) versus 20.1 months (95% CI, 12.6–27.6 months) ($P<0.001$) (Figure 4A). The trastuzumab-combined subgroup also showed marginally better ORR (43.9% vs 37.9%), DCR (92.4% vs 85.1%), and CBR (68.2% vs 66.7%) than the pyrotinib-alone group.

No significant differences were observed between patients who did not exhibit primary trastuzumab resistance and those who did, either in the pyrotinib single-target subgroup ($P=0.853$) or dual-targets subgroup ($P=0.736$).

Pyrotinib + Inetetamab

A total of 17 patients who received targeted therapy with pyrotinib and inetetamab had a median PFS of 9.3 months (95% CI, 7.6–11.0 months) (Figure 4B), the median PFS of patients who received pyrotinib and inetetamab as first-line vs second and higher-line treatment is 14.5 months (95% CI: not evaluable) vs 7.9 months (95% CI: 4.0–11.8 months) ($P = 0.015$). The ORR, CBR, and DCR of the subgroup are 28.6%, 50.0%, and 92.9%, respectively.

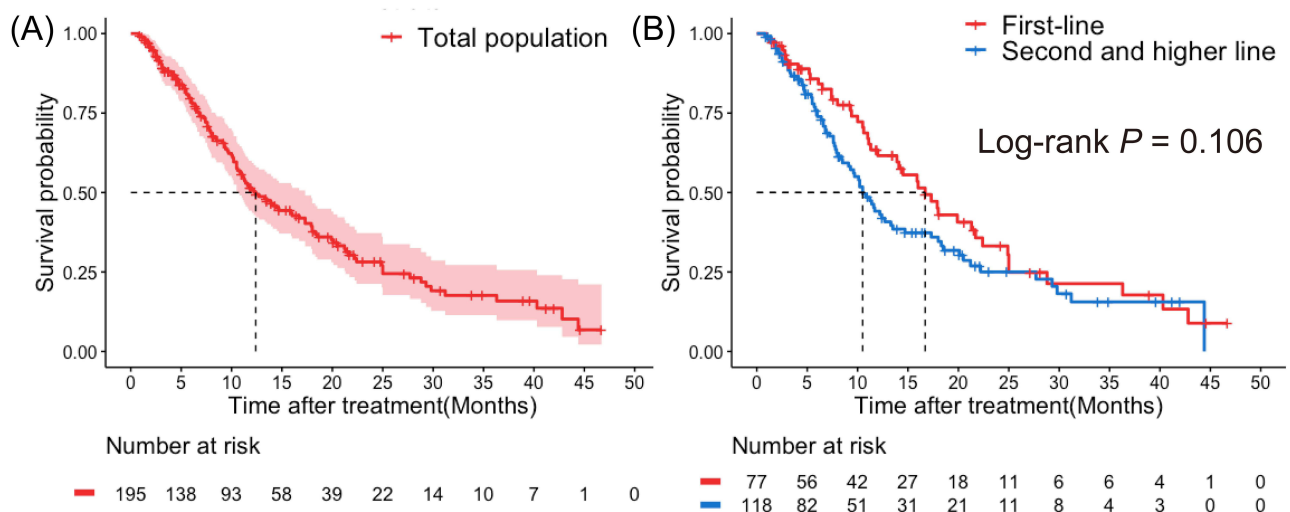


Figure 2 Kaplan–Meier curves of progression-free survival (PFS) in total population (A) and lines of pyrotinib in metastatic setting (1 vs ≥2) (B).

Table 3 Efficacy for Total Population and Subgroups with Measured Lesions

| Best Response in Patients with Measured Lesions | Total (N=168) | Pyro (n1=87) | Pyro+H (n2=66) | Pyro+I (n3=14) | Pyro+TDM-I (n4=1) | BM-NS/NR (nb=12) |
|---|---------------|--------------|----------------|----------------|-------------------|------------------|
| CR | 1 | 1 | 0 | 0 | 0 | 1 |
| PR | 65 | 32 | 29 | 4 | 0 | 5 |
| SD | 83 | 41 | 32 | 9 | 1 | 2 |
| PD | 13 | 8 | 4 | 1 | 0 | 2 |
| NE | 6 | 5 | 1 | 0 | 0 | 2 |
| ORR/CNS-ORR (n, %) | 66(39.3) | 33(37.9) | 29(43.9) | 4(28.6) | 0 | 6(50.0) |
| DCR/CNS-DCR (n, %) | 149(88.7) | 74(85.1) | 61(92.4) | 13(92.9) | 1(100) | 8(66.7) |
| CBR/CNS-CBR (n, %) | 111(66.1) | 58(66.7) | 45(68.2) | 7(50.0) | 1(100) | 7(58.3) |

Note: BM-NS/NR subgroup only includes the patients without local treatment.

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; CNS, central nervous system; ORR, objective response rate; DCR, disease control rate; CBR, clinical benefit rate; Pyro, pyrotinib; H, trastuzumab; I, inetanab; TDM-I, ado-trastuzumab emtansine; BM, brain metastases.

Table 4 The Predictor of PFS

| Characteristics | | Univariable Cox | Multivariable Cox | |
|---|-----------------------------|-----------------|-------------------|---------|
| | | P-value | HazR (95% CI) | P-value |
| Age | <60 vs ≥60 | 0.955 | | |
| Menstrual status | Pre- vs Post- | 0.146 | | |
| HR status | Negative vs Positive | 0.941 | | |
| HER2 | 3+ vs 2+ and ISH+ | 0.538 | | |
| Ki-67 | <20% vs ≥20% | 0.286 | | |
| Forms of distant metastases | Synchronous vs Metachronous | 0.523 | | |
| Previous anti-HER2 treatment | No vs Yes | 0.078 | | 0.966 |
| Primary resistance to trastuzumab | No vs Yes | 0.965 | | |
| Metastatic sites | | | | |
| Lung | No vs Yes | 0.896 | | |
| Liver | No vs Yes | 0.055 | | 0.077 |
| Bone | No vs Yes | 0.748 | | |
| Brain | No vs Yes | 0.118 | | |
| Lymph nodes | No vs Yes | 0.189 | | |
| Line of pyrotinib in metastatic setting | 1 vs ≥2 | 0.108 | | |

(Continued)

Table 4 (Continued).

| Characteristics | | Univariable Cox | Multivariable Cox | |
|--|-----------------------|------------------|---------------------|------------------|
| | | P-value | HazR (95% CI) | P-value |
| Combined anti-HER2 regimens with pyrotinib | | 0.002 | | 0.002 |
| None | | | | |
| Trastuzumab | None vs + Trastuzumab | <0.001 | 0.464 (0.310–0.693) | <0.001 |
| Inetetamab | None vs + Inetetamab | 0.867 | 1.069 (0.488–2.343) | 0.867 |
| TDM-1 | None vs + TDM-1 | 0.973 | / | 0.973 |
| Combined chemotherapeutics | | 0.932 | | |
| None | | | | |
| Capecitabine | None vs Capecitabine | 0.605 | | |
| Vinorelbine | None vs Vinorelbine | 0.663 | | |
| Paclitaxel | None vs Paclitaxel | 0.613 | | |
| Eribulin | None vs Eribulin | 0.878 | | |
| Other | None vs Other | 0.704 | | |

Note: The statistically significant results are bolded.

Abbreviations: HazR, hazard ratio; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; ISH, in situ hybridization; TDM-1, ado-trastuzumab emtansine.

Brain Metastases

In this study, 47 patients (24.1%) were diagnosed with BM at baseline. The characteristics of BM population were shown in [Table S1](#). 87.2% of patients (41 cases) in BM subgroup had received trastuzumab before. The most common site of brain metastasis is cerebrum (39 cases, 83.0%). The overall median PFS reached 10.0 months (95% CI, 7.6–12.4 months) ([Figure 5A](#)) and was similar to the median CNS-PFS result (10.5 months, 95% CI: 7.4–13.6 months) ([Figure 5B](#)).

The combined treatments were shown in [Table S2](#). The median CNS-PFS of pyrotinib-alone group and dual-targets-pyrotinib plus trastuzumab group was 10.5 months vs 18.3 months ($P=0.282$) ([Figure 5C](#)). Capecitabine (28 cases, 59.6%) still ranked first among combined chemotherapeutics. The patients who received chemotherapeutics combined received a median CNS-PFS of 11.2 months ([Figure 5D](#)). The capecitabine combined subgroup reached a median CNS-PFS of 10.5 months ([Figure 5E](#)). Although the survival outcomes in the above combined chemotherapy groups were numerically superior to the outcomes in the non-chemotherapy combined group, this advantage was not statistically observed. In the BM subgroup, 11 patients (23.4%) had undergone surgery (S) for brain lesions. Twelve patients (25.5%) and two patients (4.3%) had received SRS/SRT (stereotactic radiosurgery/stereotactic radiotherapy) and WBRT (whole-brain radiation therapy), respectively. In addition to this, one patient had received brain radiotherapy (R) at another hospital, but the type of radiotherapy was not recorded. Totally, the median CNS-PFS of 26 patients who had received local treatment (S/R) simultaneously versus the rest of patients (NS/NR) was 17.9 months vs 7.2 months ($P=0.010$) ([Figure 5F](#)).

Patients with measurable brain metastases lesions and without local treatment (12 cases) had a CNS-ORR of 50.0%, a CNS-DCR of 66.7%, and a CNS-CBR of 58.3%.

Safety

Two hundred and seven patients who received a pyrotinib-based therapy and had available data were included in the drug safety analysis ([Table 5](#)). The main toxic side effect associated with pyrotinib was diarrhea, 41 patients (19.8%) occurred grade 3 and higher diarrhea. Due to intolerable diarrhea, 12 patients (5.8%) eventually discontinued pyrotinib, of which

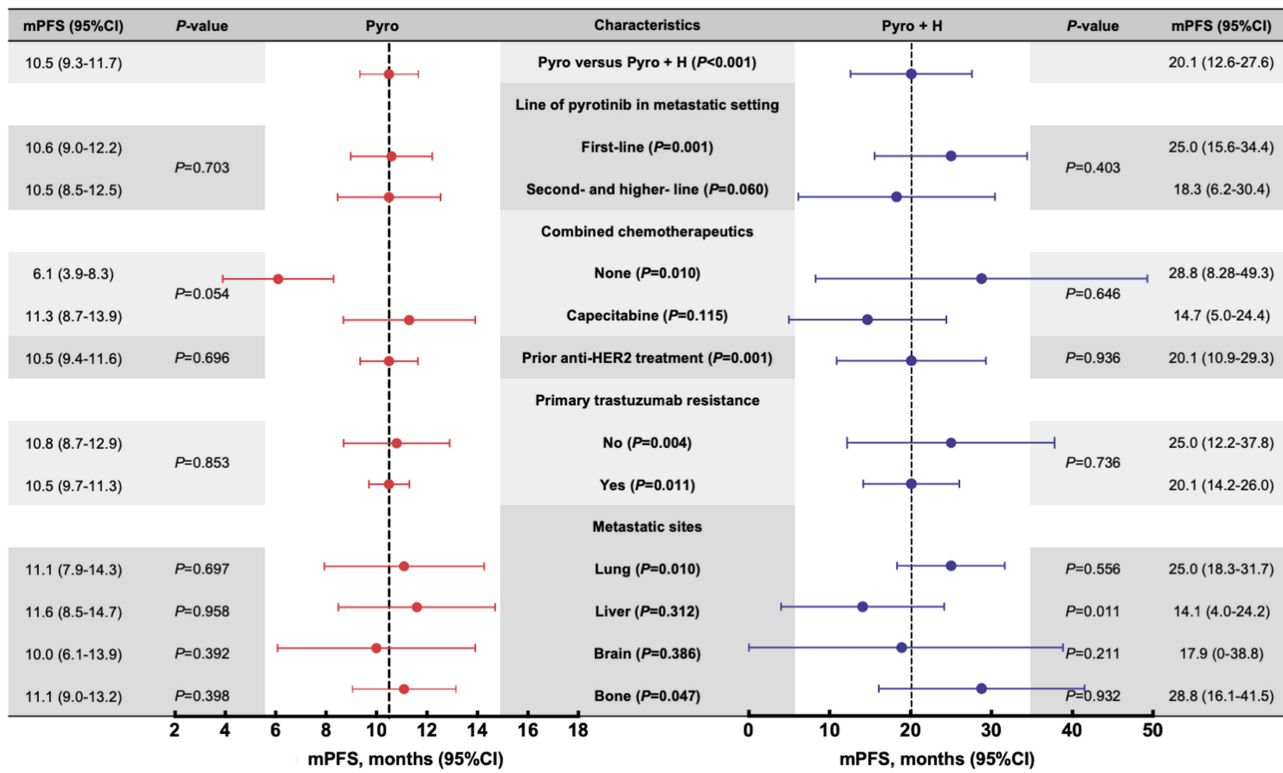


Figure 3 Forest plot for survival outcomes of characterized patients in single-target pyrotinib subgroup and dual-targets pyrotinib plus trastuzumab subgroup. **Abbreviations:** Pyro, pyrotinib; H, trastuzumab; mPFS, median progression-free survival; CI, confidence interval.

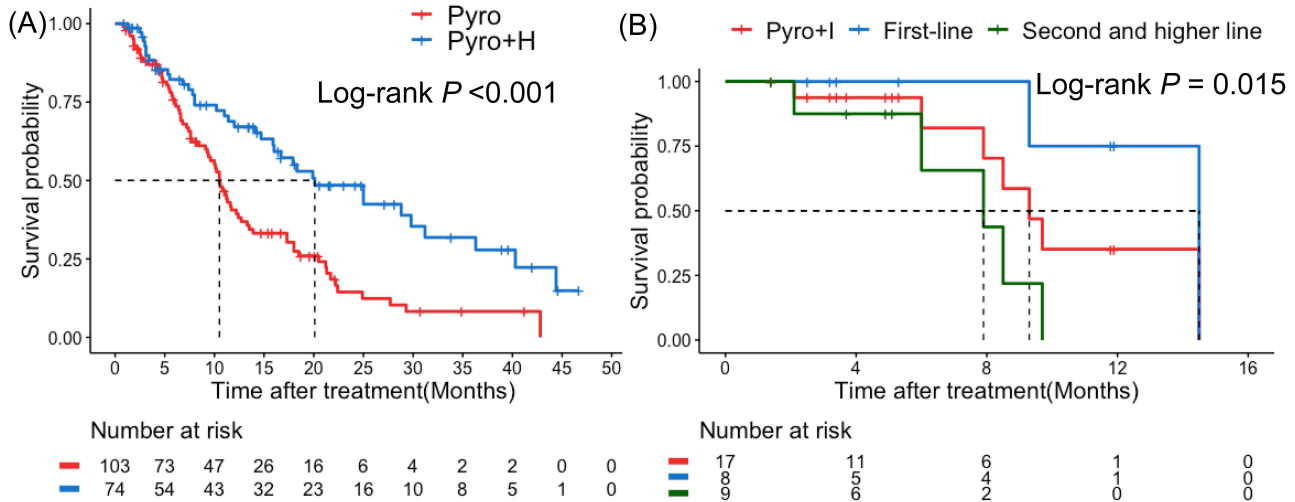


Figure 4 Kaplan–Meier curves of progression-free survival (PFS) of subgroup single-target: Pyro vs subgroup dual-targets: Pyro+H (A); subgroup dual-targets: Pyro+I and lines of Pyro+I in metastatic setting (1 vs ≥2) (B). **Abbreviations:** Pyro, pyrotinib; H, trastuzumab; I, inetetamab.

10 occurred in no more than 2 cycles of treatment. One patient (0.5%) each discontinued pyrotinib for hand-foot syndrome and cough. The next relevant toxicities that occurred at grade 3 and above were nausea and vomiting (18 patients, 8.7%), neutropenia (13, 6.3%), hypokalemia (11, 5.3%), leukopenia (10, 4.8%), hand-foot syndrome (9, 4.3%), anemia (8, 3.9%), thrombocytopenia (5, 2.4%), and Alanine aminotransferase/Aspartate aminotransferase (ALT/AST) increased (3, 1.4%). No adverse events-related deaths were found in this study.

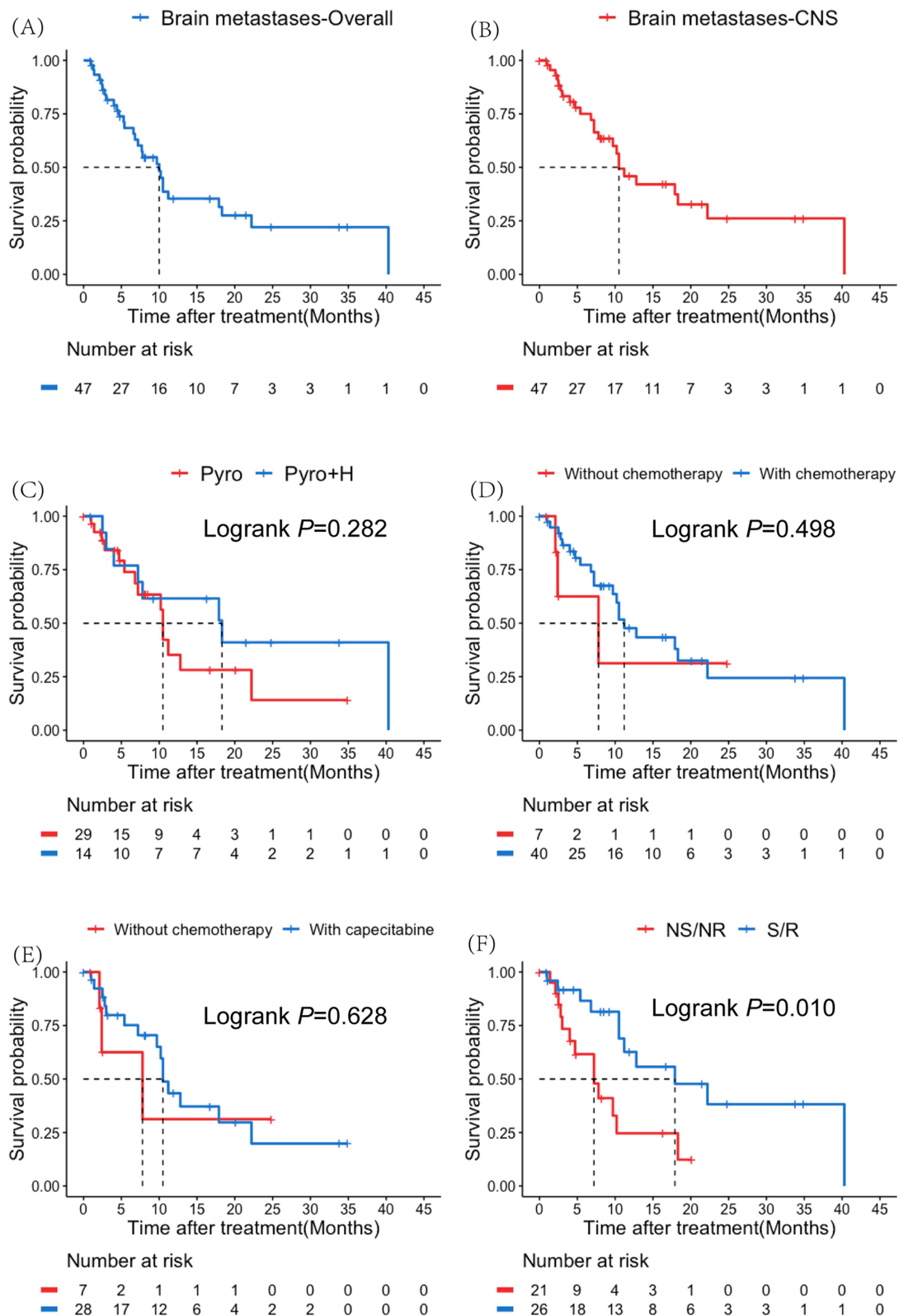


Figure 5 Kaplan–Meier curves of overall progression-free survival (PFS) in subgroup brain metastases (A); CNS-PFS in subgroup brain metastases (B); CNS-PFS of subgroup single-target: Pyro vs subgroup dual-targets: Pyro+H in subgroup brain metastases (C); CNS-PFS of subgroup chemotherapy combined vs no chemotherapy combined (D); CNS-PFS of subgroup capecitabine combined vs no chemotherapy combined (E); CNS-PFS of patients with or without local treatment in subgroup brain metastases (F). **Abbreviations:** CNS, central nervous system; Pyro, pyrotinib; H, trastuzumab; S, surgery; R, radiotherapy.

Table 5 Adverse Events (AEs) of 207 Patients

| AEs | All Grades, n(%) | ≥Grade 3, n(%) |
|----------------------|------------------|----------------|
| Diarrhea | 194 (93.7) | 41 (19.8) |
| Nausea and Vomit | 137 (66.2) | 18 (8.7) |
| Hand-foot syndrome | 114 (55.1) | 9 (4.3) |
| Leucopenia | 95 (45.9) | 10 (4.8) |
| Neutropenia | 78 (37.7) | 13 (6.3) |
| Anemia | 61 (29.5) | 8 (3.9) |
| ALT/AST increased | 50 (24.2) | 3 (1.4) |
| Hypokalemia | 44 (21.3) | 11 (5.3) |
| Thrombocytopenia | 19 (9.2) | 5 (2.4) |
| Peripheral neuritis | 30 (14.5) | 0 |
| Oral mucositis | 7 (3.4) | 0 |
| Fatigue | 7 (3.4) | 0 |
| Cough | 5 (2.4) | 0 |
| Pigmentation of skin | 2 (1.0) | 0 |
| Rash | 1 (0.5) | 0 |
| Epistaxis | 1 (0.5) | 0 |

Abbreviations: AEs: adverse events; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase.

Discussion

Patients with HER2-positive breast cancer have a higher risk of recurrence and distant metastases, resulting in a poorer prognosis.³ The publication of the results of the PHILA trial¹¹ has further emphasized the role of pyrotinib in the front-line treatment of metastatic HER2-positive breast cancer. For HER2-positive patients who were failed in trastuzumab treatment or developed brain metastases in the clinic, TKIs have undoubtedly inspired many patients. The efficacy of pyrotinib has been verified in many previous studies,^{11,13,14} but there is still an urgent need for more meaningful agents and combinations to improve the patients' prognosis who were diagnosed with MBC. This study further complemented the data on the real-world treatment patterns of pyrotinib.

The median PFS of patients received pyrotinib as first-line vs second-line and higher regimens in this study was 16.7 months vs 10.5 months ($P=0.106$), suggesting that the difference between the lines of pyrotinib treatment may not be significant. In the PHOEBE study,¹⁴ pyrotinib plus capecitabine showed a 61% reduction in the risk of PD compared to the control group of lapatinib and capecitabine (HazR=0.39, 95% CI: 0.27–0.56) in the second-line setting for HER2-positive MBC. Based on the results of the PHOEBE study, Xu et al conducted the PHILA¹¹ study on the feasibility of pyrotinib in the first-line setting for MBC. It turns out that the patients without any therapy for breast cancer before achieved a median PFS of up to 21.9 months after receiving pyrotinib + trastuzumab + docetaxel. The regimen also helps to decrease the risk of PD compared to the control group – trastuzumab + docetaxel (HazR=0.45, 95% CI: 0.26–0.54). The inspiring results promoted the appliance of pyrotinib in early-line therapy for MBC. The above studies indicated that pyrotinib showed considerable efficacy in the treatment of HER2-positive MBC at different baselines, but the application of pyrotinib in earlier lines of therapy may produce a better prognostic benefit.

Previous studies have demonstrated that TKI plus trastuzumab exhibit dual HER2-blocking antitumor activity and good tolerability.^{10,15} Xu et al also clarified in the PHILA study¹¹ that pyrotinib plus trastuzumab and docetaxel

significantly prolonged the PFS in patients with HER2-positive MBC compared to single-target regime trastuzumab and docetaxel (median PFS: 24.3 months vs 10.4 months, $P < 0.001$). In our study, the median PFS of pyrotinib single target group vs pyrotinib + trastuzumab group (10.5 months vs 25.0 months, $P < 0.001$) further confirmed the above finding. Additionally, our study and PHILA trial both revealed that the combination of pyrotinib and trastuzumab can reduce the risk of PD or death with a hazard ratio (HazR) of 46.4% and 41%, respectively. What is the most striking is the median PFS (25.0 months, 95% CI: 15.6–34.4 months) of patients who received pyrotinib plus trastuzumab as the first-line treatment for MBC is even superior to that of 18.5 months in CLEOPATRA study.¹⁶ Despite possible bias in our study, the advantages are undeniable. In the future, a rigorous head-to-head study between the two regimens should be implemented to verify whether the combination of pyrotinib and trastuzumab could replace the traditional dual-targets in the first-line treatment. In the PICTURE trial,¹³ researchers observed the efficacy of pyrotinib and capecitabine in 100 locally metastatic and metastatic patients with primary trastuzumab resistance with a median PFS of 11.8 months (95% CI, 8.4–15.1 months), which was higher than the results of resistance population in our pyrotinib single-targets subgroup (10.5 months, 95% CI: 9.7–11.3 months) to an acceptable extent because of the inclusion of locally metastatic patients. As some basic studies^{17,18} suggested before, trastuzumab-resistant patients are expected to overcome or even reverse the resistance with TKI. Also, a prior study¹⁹ indicated that patients with progressive disease after trastuzumab treatment may still benefit from trastuzumab treatment. In our study, the patients treated with pyrotinib + trastuzumab in the resistance subgroup truly received an enjoyable result of a median PFS of 20.1 months (95% CI: 14.2–26.0 months), which was much better than that of the above single-targeted, suggesting that in the patients who have been treated with trastuzumab or even exhibited primary trastuzumab resistance, the dual-targeted regimen of pyrotinib + trastuzumab still possibly achieve a promising effect. All of the above suggest that, in the clinical practice, the option of dual targets pyrotinib plus trastuzumab would better improve the survival outcome of patients, especially in the first-line treatment of MBC and even those who had primary trastuzumab resistance. Other than trastuzumab resistance, there are also some endocrine resistant breast cancer patients exist in clinic. One of the key mechanisms of endocrine resistance is relative to the upregulation of HER2,^{20,21} which is believed to promote downstream activation of PI3K/AKT pathways, and ultimately enhancing tumor cell proliferation and endocrine resistance. Meanwhile, some studies noted that trastuzumab resistance is relative to the crosstalk between HER2 and ER α .^{22,23} Consequently, treatment strategies targeting either pathway are associated with upregulation of the other one, ultimately resulting in resistance to therapy. Therefore, HER2 targeted therapy combined with endocrine therapy may help to overcome either endocrine or HER2 resistance for HR +/HER2+ patients with endocrine resistance. Combined with the efficacy of pyrotinib in the trastuzumab-resistant population in this study, perhaps pyrotinib could be preferred as a HER2-targeted therapy in these populations.

The EMILIA trial²⁴ and DESTINY-Breast03 trial²⁵ promoted TDM-1 (trastuzumab emtansine) and T-DXd (trastuzumab deruxtecan) to be the standard second-line treatment options for HER2-positive MBC, but given the cost–benefit ratios and drug accessibility in China, only a small proportion of patients could get access to the above standard therapies. With the increase in the variety of targeted drugs, more treatment patterns are being explored in the later-line treatment of MBC. Inetetamab is a type of HER2-targeted recombinant human monoclonal antibody with an engineered Fc segment that optimizes the ADCC effect developed in China. The preliminary results from 57 patients in an ongoing single-arm multicenter Phase II study (median PFS = 7.3 months)²⁶ implied that inetetamab plus pyrotinib demonstrating synergistic potentiated antitumor effects in the second and higher line treatment of MBC. This is similar to the PFS results (7.9 months, 95% CI: 4.0–11.8 months) of the second or higher-line population in the inetetamab subgroup of our study. Although the PFS results of the Chinese dual-targets in current studies^{26,27} were not more advantageous than TDM-1 in the EMILIA trial (9.6 months),²⁴ it still has the potential to be an option for the second- and higher-line treatment of MBC when considering the cost for Chinese patients. Further expansion of the population in pyrotinib plus inetetamab studies is needed to obtain more convincing results.

As a member of TKIs, pyrotinib still shows good efficacy in brain metastases as other members, such as lapatinib²⁸ and tucatinib.⁹ The median overall-PFS (10.0 months, 95% CI: 7.6–12.4 months) and the median CNS-PFS (10.5 months, 95% CI: 7.4–13.6 months) of the BM subgroup in this study were both similar to the PFS result of PERMEATE trial²⁹ (10.8 months, 95% CI: 7.6–13.9 months), a study exploring the efficacy of pyrotinib plus capecitabine in the treatment of BM. Although no statistical difference was observed, an advantage of dual-target therapy, pyrotinib and trastuzumab, in the median PFS could get our attention in the BM population compared to the

pyrotinib monotherapy subgroup (17.9 months vs 10.0 months, $P=0.386$). This also completes the discussion on the superiority of the dual-targets mentioned above. A previous study³⁰ noticed that the concentration of lapatinib in brain metastases is only 10%–20% of that in peripheral metastases, suggesting that even small-molecule TKIs are still difficult to cross the blood–brain barrier in a great number. Therefore, local radiotherapy or neurosurgery is still the preferred treatment for BM in clinical practice. Of the 47 patients with BM in this study, the median PFS in the S/R (Surgery/Radiotherapy) subgroup (17.9 months) was significantly longer than that in the NS/NR (No Surgery and No Radiotherapy) subgroup (5.3 months) ($P=0.002$), implying that the combination of pyrotinib and local treatment truly have the chances to improve survival outcomes in patients with BM. In recent years, researchers in PERMEATE trial²⁹ have found that under the close follow-up, pyrotinib may have the ability to postpone local radiotherapy in patients with controllable local symptoms of BM. This finding undoubtedly shocked the previous standard of preferring localized treatment for patients with BM. However, it should be clarified that although cerebral contrast-enhanced magnetic resonance imaging (MRI) is primarily used for screening for BM in the clinic, guidelines for standardizing examination intervals are still lacking. This results in patients presenting with more severe and complex conditions when diagnosed with BM in the clinic. Therefore, when selecting and arranging treatments for patients with BM, we need to consider their symptoms, imaging results, and cost-effectiveness. In previous studies,^{29,31} capecitabine was used most often in combination with pyrotinib. In our study, the combination of capecitabine was numerically superior to the median PFS results in patients without chemotherapy, but this advantage did not demonstrate statistically. We considered that this might be related to the number of people included in the BM subgroup was still relatively small. Further expansion of the cohort is needed to get more convincing results. To be mentioned, there are also 2 patients with meningeal metastasis included in our analysis and one of them had not reach the endpoint at the end of follow-up. The survival of patients with leptomeningeal metastasis remains poor. However, due to the low incidence of meningeal metastases, there is a lack of research on HER2-targeted drugs for meningeal metastases. With prolonged survival, the incidence of meningeal metastases will undoubtedly increase in the future. We would like to see a future study exploring the efficacy of HER2-targeted drugs for meningeal metastases.

Among the adverse events observed in this study, diarrhea was the most common, which is consistent with previous pyrotinib-related studies.^{11,13,14} Twelve patients discontinued for intolerable diarrhea, ten of them occurred in the first two cycles of treatment. A previous study³² showed that diarrhea most often occurs within the first week of the first cycle of pyrotinib application, with a mean onset of 2.86 days, resulting in the alteration of the drug and failure to get benefits from pyrotinib treatment. Coadministration of loperamide and pyrotinib is now mostly recommended to prevent diarrhea in patients who suffered interruption to pyrotinib treatment caused by grade ≥ 3 diarrhea when recommencing pyrotinib. Nevertheless, there is no standard scheme for primary prevention of diarrhea. Effective and standardized prophylactic treatment of pyrotinib-associated diarrhea should be investigated to improve patient compliance and treatment efficacy in the future.

There are also some limitations in this study. First, this is a single-center retrospective study, so some recall bias and confounding bias are inevitable. Second, the scale of the pyrotinib plus inestetamab subgroup needs to be enlarged to get a more convincing result. Finally, further analysis of third-line and later treatment populations could be considered.

Conclusions

In summary, pyrotinib combined with trastuzumab shows great promise in the treatment of HER2-positive metastatic breast cancer especially in the first-line treatment and even those who developed brain metastases. Moreover, patients who were treated with trastuzumab and exhibited primary trastuzumab resistance also could benefit from the combination. The *Chinese dual-targets*, pyrotinib plus inestetamab may provide another choice in the second and higher-line treatment for metastatic breast cancer. And the adverse effects of pyrotinib are generally well tolerated.

Data Confidentiality Statement

The data of patients included in our study was anonymized and properly protected, including encrypted storage of patient information, strict control of access, and timely destruction of unnecessary information.

Data Sharing Statement

The data of this study could be obtained from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and the 1964 Helsinki Declaration and its later amendments. The ethics approval was obtained from Ethics Committee of The First Affiliated Hospital of Zhengzhou University (2023-KY-0814-001). According to the national legislation and the institutional requirements, written informed consent was waived in this retrospective study.

Author Contributions

All authors contributed to the study's conception and design. Data analysis was performed by QG, YW, and MZ. The first draft of the manuscript was written by QG and all authors contributed to revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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-a Can J Clin.* 2021;71(3):209–249. doi:10.3322/caac.21660
2. Pestalozzi BC, Zahrieh D, Price KN, et al. Identifying breast cancer patients at risk for Central Nervous System (CNS) metastases in trials of the International Breast Cancer Study Group (IBCSG). *Ann Oncol.* 2006;17(6):935–944. doi:10.1093/annonc/mdl064
3. Slamon DJ, Clark GM, Wong SG, et al. Human Breast Cancer: Correlation of Relapse and Survival with Amplification of the HER-2/ neu Oncogene. *Science.* 1987;235(4785):177–182. doi:10.1126/science.3798106
4. Swain SM, Miles D, Kim SB, et al. 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
5. Nahta R, Yu DH, Hung MC, Hortobagyi GN, Esteva FJ. Mechanisms of disease: understanding resistance to HER2-targeted therapy in human breast cancer. *Nature Clin Pract Oncol.* 2006;3(5):269–280. doi:10.1038/npcnc0509
6. Xuhong JC, Qi XW, Zhang Y, Jiang J. Mechanism, safety and efficacy of three tyrosine kinase inhibitors lapatinib, neratinib and pyrotinib in HER2-positive breast cancer. *Am J Canc Res.* 2019;9(10):2103–2119.
7. Guan XW, Ma F, Li Q, et al. Pyrotinib plus capecitabine could significantly improve overall survival in HER2-positive metastatic breast cancer. *Sig Trans Target Therap.* 2023;8(1). doi:10.1038/s41392-023-01322-w
8. Hu W, Yang J, Zhang Z, Xu D, Li N. Pyrotinib for HER2-positive metastatic breast cancer: a systematic review and meta-analysis. *Transl Canc Res.* 2023;12(2):247–256. doi:10.21037/tcr-22-1746
9. Lin NU, Borges V, Anders C, et al. 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–+. doi:10.1200/jco.20.00775
10. Blackwell KL, Burstein HJ, Storniolo AM, et al. 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
11. Ma F, Yan M, Li W, et al. Pyrotinib versus placebo in combination with trastuzumab and docetaxel as first line treatment in patients with HER2 positive metastatic breast cancer (PHILA): randomised, double blind, multicentre, phase 3 trial. *BMJ.* 2023;383. doi:10.1136/bmj-2023-076065
12. Wang X, Liu P, Fenghua LU, Tan Q. Evaluation of Critical Quality Attributes of an Anti-HER2 Humanized Monoclonal Antibody Drug. *Chin Pharm J.* 2015;50(12):1054–1061.
13. Cao J, Teng Y, Li HP, et al. Pyrotinib plus capecitabine for trastuzumab-resistant, HER2-positive advanced breast cancer (PICTURE): a single-arm, multicenter Phase 2 trial. *BMC Med.* 2023;21(1). doi:10.1186/s12916-023-02999-0
14. Xu BH, 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
15. Blackwell KL, Zaman K, Qin SK, et al. Neratinib in combination with Trastuzumab for the treatment of patients with advanced HER2-positive Breast Cancer: A Phase I/II Study. *Clinic Breast Canc.* 2019;19(2):97–+. doi:10.1016/j.clbc.2018.12.011

16. Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer. *N Engl J Med.* 2012;366(2):109–119. doi:10.1056/NEJMoa1113216
17. Oshima Y, Tanaka H, Murakami H, et al. Lapatinib sensitivities of two novel trastuzumab-resistant HER2 gene-amplified gastric cancer cell lines. *Gastric Cancer.* 2014;17(3):450–462. doi:10.1007/s10120-013-0290-6
18. Scaltriti M, Rojo F, Ocaña A, et al. Expression of p95HER2, a truncated form of the HER2 receptor, and response to anti-HER2 therapies in breast cancer. *J Nation Canc Inst.* 2007;99(8):628–638. doi:10.1093/jnci/djk134
19. Extra JM, Antoine EC, Vincent-Salomon A, et al. Efficacy of Trastuzumab in Routine Clinical Practice and After Progression for Metastatic Breast Cancer Patients: the Observational Hermine Study. *Oncologist.* 2010;15(8):799–809. doi:10.1634/theoncologist.2009-0029
20. Dong C, Wu J, Chen Y, Nie J, Chen C. Activation of PI3K/AKT/mTOR pathway causes drug resistance in Breast Cancer. *Front Pharm.* 2021;12:628690. doi:10.3389/fphar.2021.628690
21. Willman M, Willman J, Lucke-Wold B. Endocrine resistant breast cancer: brain metastasis. *Explor Target Antitumor Ther.* 2022;3(2):240–251. doi:10.37349/etat.2022.00081
22. Giuliano M, Trivedi MV, Schiff R. Bidirectional crosstalk between the estrogen receptor and human epidermal growth factor receptor 2 signaling pathways in Breast Cancer: Molecular basis and clinical implications. *Breast Care.* 2013;8(4):256–262. doi:10.1159/000354253
23. Kwon YS, Nam KS, Kim S. Tamoxifen overcomes the trastuzumab-resistance of SK-BR-3 tumorspheres by targeting crosstalk between cytoplasmic estrogen receptor α and the EGFR/HER2 signaling pathway. *Biochem Pharm.* 2021;190:114635. doi:10.1016/j.bcp.2021.114635
24. Verma S, Miles D, Gianni L, et al. Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer. *N Engl J Med.* 2012;367(19):1783–1791. doi:10.1056/NEJMoa1209124
25. Cortés J, Kim SB, Chung WP, et al. Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. *N Engl J Med.* 2022;386(12):1143–1154. doi:10.1056/NEJMoa2115022
26. Zhao J, Cai Y, Ding L, et al. Inetetamab combined with pyrotinib and Chemotherapy in Pretreated Patients with HER2-positive metastatic breast cancer, a single arm, multicenter phase II clinical trial. *Cancer Res.* 2023;83(5): 5
27. Cai S, Chen H, Chen X, Zhang J. Clinical efficacy observation of multi-line therapy of inetetamab combined with pyrotinib(China double target) in patients with Her2 positive breast cancer. *J Chong Medl Univ.* 2022;47(12):1479–1484.
28. Bachelot T, Romieu G, Camponé M, et al. 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
29. Yan M, Ouyang Q, Sun T, et al. Pyrotinib plus capecitabine for patients with HER2-positive metastatic breast cancer and brain metastases: 3-year follow-up results from the phase 2 PERMEATE trial. *J Clin Oncol.* 2023;41(16):1048. doi:10.1200/JCO.2023.41.16_suppl.1048
30. Taskar KS, Rudraraju V, Mittapalli RK, et al. Lapatinib distribution in HER2 overexpressing experimental brain metastases of Breast Cancer. *Pharm Res.* 2012;29(3):770–781. doi:10.1007/s11095-011-0601-8
31. Jiang ZF, Yan M, Hu XC, et al. Pyrotinib combined with capecitabine in women with HER2+metastatic breast cancer previously treated with trastuzumab and taxanes: a randomized Phase III study. *J Clin Oncol.* 2019;37(15):1001. doi:10.1200/JCO.2019.37.15_suppl.1001
32. Fang C, Wen J, Kang M, et al. Incidence and management of pyrotinib-associated diarrhea in HER2-positive advanced breast cancer patients. *Annals Palliative Med.* 2022;11(1):210–216. doi:10.21037/apm-21-3978

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