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Efficacy and Safety of Pyrotinib for Patients with HER2-Positive Advanced Breast Cancer: A Retrospective Multicenter Real-World Study

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Abstract

Background: The incidence of breast cancer ranks first among female malignancies that affect women's health. Human epidermal receptor type 2 (HER-2) positive breast cancer accounts for 20% - 30% of the invasive breast cancer, which is related to the poor prognosis of the tumor. This study aimed to observe the efficacy and safety of pyrotinib in HER2-positive ad-

vanced breast cancer in the real world.

Methods: This multicenter retrospective study was performed on the clinical data of HER2-positive advanced breast cancer patients treated with pyrotinib from March 2019 to April 2022. Progression-free survival (PFS), overall survival (OS), objective response rate (ORR), disease control rate (DCR), clinical benefit rate (CBR) and occurrence of adverse events were observed after treatment, and possible predictors of efficacy were explored.

Results: A total of 91 female patients enrolled, with a median age of 51 years (range, 30-76), a median PFS of 14.3 months (95%CI: 8.8-19.8), and a median OS of 30.0 months (95%CI: 23.8-36.2). Short-term efficacy showed that 4 cases of complete remission (CR), 61 cases of partial remission (PR), 23 cases of stable disease (SD) and 3 cases of progression disease (PD) were identified, and the ORR, DCR and CBR were 71.4%, 96.7% and 74.7%, respectively. The main treatment-related adverse event was diarrhea. Log-rank analysis showed a significant difference in OS between patients with liver metastases and patients with non-liver metastases (15.8 months vs 31.4 months, HR =2.30, P <0.05). The results of the Cox regression model indicated that the number of pyrotinib treatment lines was an independent risk factor affecting PFS and OS of patients (HR_{PFS} =1.81, HR_{OS} =1.91, P <0.05).

Conclusions: Pyrotinib-based regimens were safe and effective in the treatment of HER2-positive advanced breast cancer, and the earlier use was better. Pyrotinib-based therapy might have some advantages in patients without liver metastases.

Keywords: Pyrotinib; Breast Cancer; Human Epidermal Growth Factor Receptor Type 2 (HER2); Chemotherapy

Introduction

Cancer is a major public health problem worldwide. Breast cancer is a common cancer in the world and the number one malignant tumor affecting women's health [1,2]. Over-expression of the epidermal growth factor receptor (EGFR) family, particularly human epidermal receptor type 2 (HER2), is prominently characterized in breast cancer and is significantly associated with poor prognosis [3]. HER2-positive breast cancer is highly aggressive and rapidly progressive, thus, anti-HER2 targeted therapy is the key to the treatment of HER2-positive breast cancer. With the advent of more anti-HER2 targeted therapies, patients with HER2-positive breast cancer have more treatment options and improved outcomes. Pyrotinib is a novel small molecule tyrosine kinase inhibitor (TKI), which is orally administered and well tolerated, exhibiting anti-tumor activity in HER2-positive advanced and metastatic breast cancer [4,5]. However, relatively few studies have focused on the treatment of pyrotinib, and even fewer predictors of the survival of pyrotinib treatment. This study aimed to observe the clinical efficacy and safety of pyrotinib treatment by retrospectively analyzing clinical data in patients with HER2--positive advanced breast cancer treated with a pyrotinib based regimen, furthermore, to explore possible predictors of survival.

Methods

Study Design

This study was a multi-center retrospective analysis. The patients came from four oncology departments in Guizhou province, China. The four centers were: The Affiliated Cancer Hospital of Guizhou Medical University, Guizhou Provincial People's Hospital, Affiliated Hospital of Zunyi Medical University and Hospital of Guizhou Panjiang Coal Power Group Co., LTD. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of The Affiliated Cancer Hospital of Guizhou Medical University (No. SL-202105130). Individual consent for this retrospective analysis was waived.

Data Collection

The data were collected from 91 patients with HER2-positive advanced breast cancer. The patients received pyrotinib-based therapy from March 2019 to April 2022. The main data were from medical records and labora-

tory results, with a few subjective indicators derived from outpatient review and telephone follow-up. Follow-up was until February 2023.

Inclusion Criteria

The inclusion criteria were as follows: (I) aged 18–80 years; (Ⅱ) female with advanced breast cancer; (Ⅲ) Eastern Cooperative Oncology Group (ECOG) performance status 0–2; (Ⅳ) pathologically confirmed HER2-positive (immunohistochemical score of 3+, or 2+ with fluorescence in situ hybridization positive) (6); (V) at least a measurable lesion according to response evaluation criteria in solid tumor (RECIST) version 1.1 (7); (Ⅵ) adequate hematologic, hepatic, and renal functions; (Ⅶ) expected survival time ≥3 months; and (Ⅷ) complete treatment and follow-up data.

Treatment

The basic therapeutic drug was pyrotinib, which was produced by Jiangsu Hengrui Pharmaceuticals Co., LTD. The standard dose of pyrotinib was 400 mg once a day. Depending on the adverse events (AEs), adjustment of pyrotinib and symptomatic treatment were allowed.

Outcomes

To assess tumor response to pyrotinib-based therapy, patients underwent comprehensive imaging at baseline, every six weeks during the therapy, and every three months after the therapy. The investigators assessed the objective responses according to RECIST v1.1.

According to RECIST v1.1, complete response (CR) was defined as the disappearance of all target lesions, partial response (PR) was defined as a reduction of ≥30% in the total long diameter of baseline lesions, progressive disease (PD) was defined as an increase of >20% in the total long diameter of baseline lesions, an increase of 5 mm in the minimum absolute value, or the appearance of new lesions, and stable disease (SD) was defined the sum of the long diameter of the baseline lesions decreased but did not reach PR or increased but did not reach PD [7]. The objective response rate (ORR) was defined as CR + PR, the disease control rate (DCR) was defined as CR + PR + SD, and the clinical benefit rate (CBR) was defined as CR + PR + SD ≥6 months. Overall survival (OS) was defined as the time from the start of treatment to death. Progression-free survival (PFS) was defined as the time from the start of treatment to the first occurrence of PD or death from any cause.

The assessment of AEs was based on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE5.0).

Statistical Analysis

All statistical tests were completed using SPSS 26.0, both were two-sided and considered significant when P <0.05. PFS and OS were estimated using Kaplan-Meier curves. Univariate analysis of clinical variables was performed by Log-rank method and multivariate analysis using Cox regression model. Survival curves were completed by Graphpad Prism 7.0.

Results

Patient Characteristics

From March 11, 2019 to April 19, 2022, a total of 91 patients were enrolled, and their demographic characteristics and baseline characteristics were shown in Table 1. The median age was 51 years (range, 30-76). Patients with liver metastases, brain metastases, bone metastases, and lung metastases accounted for 31.9%, 42.9%, 46.2%, and 44.0%, respectively. Pyrotinib therapy combined with chemotherapy, radiotherapy and targeted drugs accounted for 87.9%, 24.2% and 14.3%, respectively.

In this study, only 5 patients received pyrotinib treatment alone. Of the remaining 86 patients, 36 patients received pyrotinib with capecitabine therapy, and 22 patients received pyrotinib with paclitaxel therapy, and 13 patients received pyrotinib with trastuzumab therapy, and 8 patients received pyrotinib with vinorelbine therapy, and 6 patients received pyrotinib with endocrine therapy, and 1 patients received pyrotinib with gemcitabine therapy.

Table 1: Patients' demographic characteristics and baseline characteristics (n=91)

Characteristic	Patients (n, %)
Age (years), median (range)	51 (30–67)
<60	78 (85.7)
≥60	13 (14.3)
Menopausal status	
Pre-menopausal	36 (39.6)
Post-menopausal	55 (60.4)
Taken adjuvant therapy or neoadjuvant therapy at the initial diagnosis	
Yes	54 (59.3)
No	37 (40.7)
Previously received anti-HER2 therapy	
Yes	79 (86.8)
No	12 (13.2)
Liver metastasis	
Yes	29 (31.9)
No	62 (68.1)
Brain metastasis	
Yes	39 (42.9)
No	52 (57.1)
Bone metastasis	
Yes	42 (46.2)
No	49 (53.8)
Lung metastasis	
Yes	40 (44.0)
No	51 (56.0)
Lines of pyrotinib	
≤2	74 (81.3)
>2	17 (18.7)
Combined chemotherapy	
Yes	80 (87.9)
No	11 (12.1)
Combined local radiotherapy	
Yes	22 (24.2)
No	69 (75.8)

Combined targeted drugs	
Yes	13 (14.3)
No	78 (85.7)

Efficacy

All patients had completed at least four cycles of treatment. The median follow-up period was 25.5 months (95%CI: 19.7-31.3). Survival curves of patients after pyrotinib treatment were shown in Figure 1. The median PFS was 14.3 months (95%CI: 8.8-19.8), and the median OS was 30.0 months (95%CI: 23.8-36.2).

Efficacy assessment of patients after treatment was shown in Figure 2. There were 4 cases of CR (4.4%), 61 cases of PR (67.0%), 23 cases of SD (25.3%) and 3 cases of PD (3.3%), and the ORR, DCR and CBR were 71.4% (65/91), 96.7% (88/91) and 74.7% (68/91), respectively.

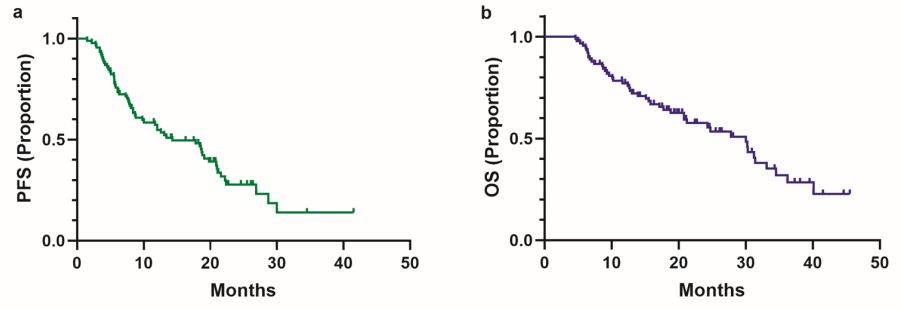

Figure 1: Survival curves of patients after pyrotinib treatment (n=91) (a) PFS; (b) OS. PFS, progression-free survival; OS, overall survival

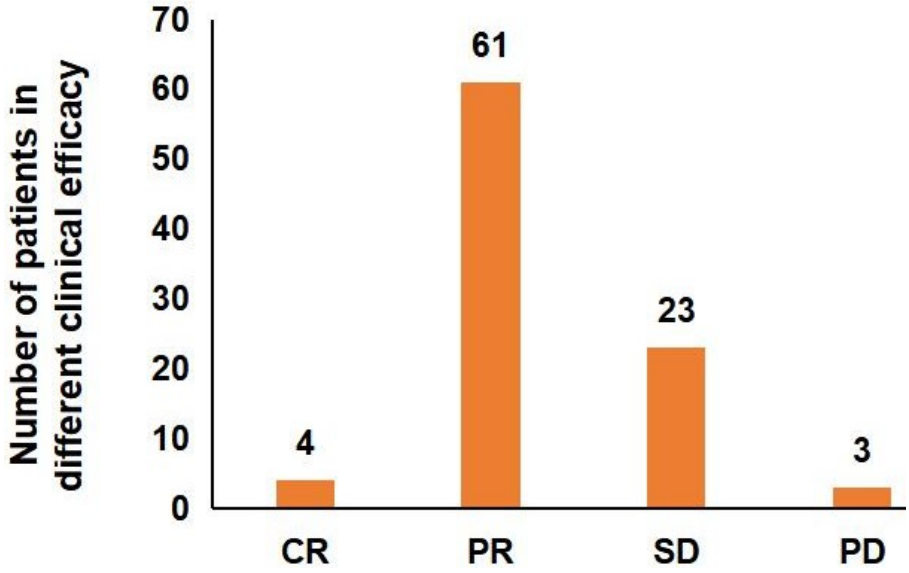

Figure 2: Efficacy assessment of patients after treatment (n=91) CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

Safety

AEs of 91 patients were recorded and the results were shown in Table 2. The most common AEs were diarrhoea (93.4%), leukopenia (47.3%), anemia (46.2%), Nausea (45.1%) and neutropenia (40.7%). AEs of Grade 3 and above were diarrhea (33.0%), leukopenia (13.2%), neutropenia (8.8%), anemia (2.2%) and thrombocytopenia (1.1%).

The occurrence of diarrhea during different cycles of treatment was shown in Figure 3. As the pyrotinib treatment progressed, the number of patients without diarrhea (Normal) gradually increased, and the patients with moderate diarrhea (Grade 2) and severe diarrhea (Grade 3) gradually decreased. Patients with mild diarrhea (Grade 1) first increased and then decreased.

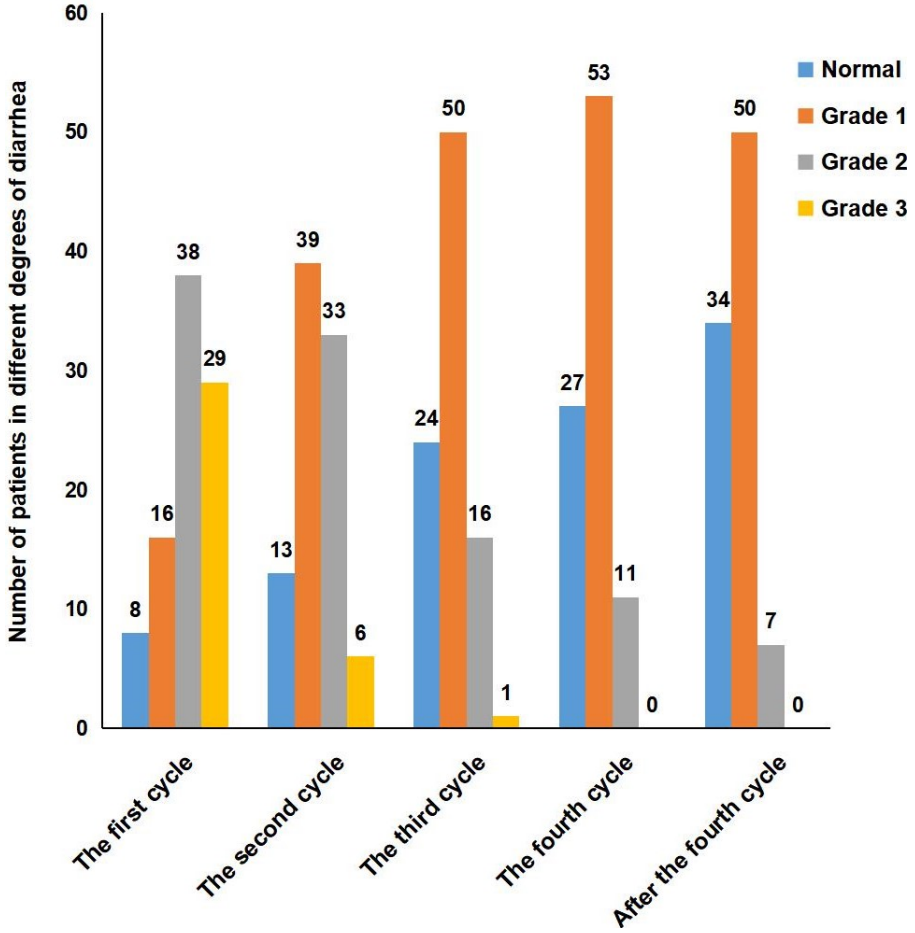

Figure 3: Development of diarrhea in different cycles of treatment (n=91)

Survival-Related Factors

The results of the Cox regression model indicated that the number of pyrotinib treatment lines was an independent risk factor affecting PFS and OS (HR_{PFS} =1.81, HR_{OS} =1.91, P <0.05). Log-rank analysis showed that PFS of patients with pyrotinib treatment lines >2 was significantly shorter than PFS of patients with pyrotinib treatment lines ≤2 (6.1 months vs 19.1 months, HR =3.16, P <0.05), as well as their OS (11.6 months vs 30.3 months, HR =2.34, P <0.05). Log-rank analysis also showed a significant difference in OS between patients with liver metastases and those with non-liver metastases (15.8 months vs 31.4 months, HR =2.30, P <0.05). Survival curves of patients with different factors were shown in Figure 4.

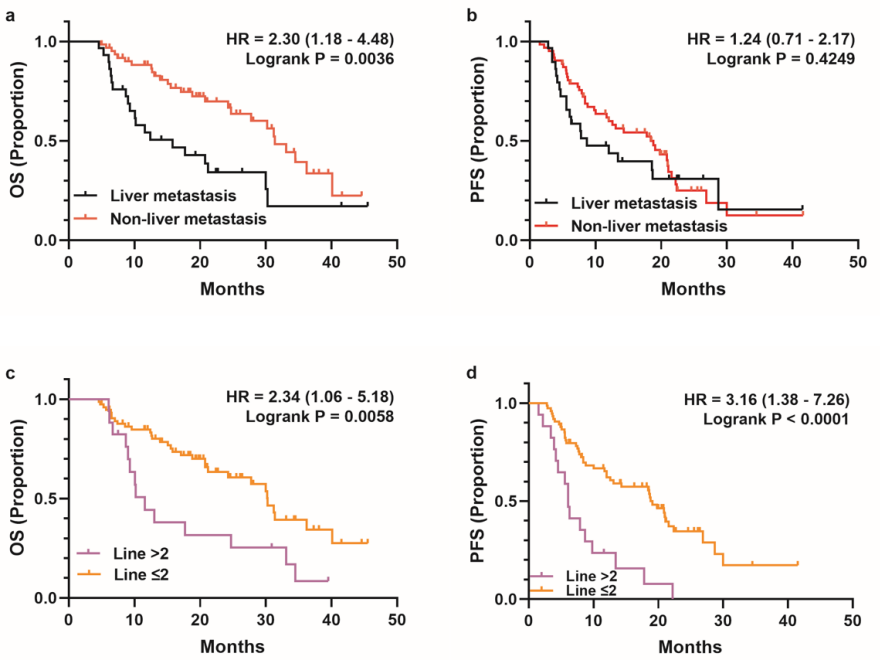

Figure 4: Survival curves of patients with different factors (n=91).

(a) OS with liver metastasis and non-liver metastasis; (b) PFS with liver metastasis and non-liver metastasis; (c) OS with pyrotinib treatment line >2 and pyrotinib treatment line ≤2; (d) PFS with pyrotinib treatment line >2 and pyrotinib treatment line ≤2. PFS, progression-free survival; OS, overall survival; HR, hazard ratio

Discussion

This study aimed to observe the efficacy and safety of pyrotinib in real-world treatment of HER2-positive advanced breast cancer. Through retrospective study analysis, this study found that pyrotinib-based regimen was safe and effective in treating HER2-positive advanced breast cancer, and improved survival may be achieved in patients with non-liver metastases and earlier treatment. This study on a series of patients provided real-world data to complement the results of previous clinical trials and set the stage for further exploration of the treatment paradigm of pyrotinib.

In previous studies, pyrotinib-based regimens had shown promising treatment in HER2-positive advanced breast cancer. In the 2021 Guidelines and Norms for the Diagnosis and Treatment of Breast Cancer of the Chinese Anti-Cancer Association, pyrotinib combined with capecitabine regimen could be used as the first-line treatment for HER2-positive metastatic breast cancer, and it was also the second-line treatment for patients with anti-HER2 progression. In phase Ⅱ PERMEATE clinical study, pyrotinib combined with capecitabine raised ORR to 78.5% in 78 patients with HER2-positive recurrent or metastatic breast cancer and prolonged the median PFS to 18.1 months [4]. In phase Ⅲ PHOEBE study, pyrotinib plus capecitabine for HER2--positive advanced breast cancer patients extended the median PFS of 134 patients to 12.5 months and increased their ORR to 67.2% and CBR to 73.1% [5]. A phase Ⅱ trial showed that 40 HER2-positive metastatic breast cancer patients who received pyrotinib plus trastuzumab and chemotherapy had the median PFS of 7.5 months, ORR of 50.5%, CBR of 75.5%, and DCR of 97.5% [8]. After pyrotinib-based treatment, the 91 patients with advanced breast cancer in this study had an ORR of 71.4%, a DCR of 96.7%, a CBR of 74.7%, and a median PFS of 14.3 months (95%CI: 8.8-19.8), which were similar to the previous results.

In a retrospective study, the median PFS of 62 patients treated with pyrotinib-based therapy as first, second, or later treatment was 15.0, 10.3, and 6.8 months, respectively, suggesting that the number of lines treated with pyrotinib might affect the prognosis of patients [9]. An additional multicenter retrospective study analysis showed that in 141 patients, PFS of patients receiving pyrotinib-based therapy as their >2 lines therapy was numerically lower than ≤2 lines therapy (8.4 months vs 15.1 months), but with no significant difference [10]. In this study, both Log-rank analysis

and Cox regression model showed the correlation of pyrotinib treatment lines between PFS and OS, indicating that the number of pyrotinib treatment lines was an independent risk factor affecting PFS and OS of patients.

A study of 55 patients with HER2-positive metastatic breast cancer failing treatment with trastuzumab and lapatinib revealed that these patients could benefit from subsequent pyrotinib treatment, especially in those who had previously benefited from lapatinib or without liver metastases [11]. In a study of 141 patients with HER2-positive advanced breast cancer, the median PFS in patients without liver metastases had longer PFS than in patients with liver metastases (12.3 months vs 8.7 months) [10]. A study of 40 patients with metastatic breast cancer showed that liver metastases and / or lung metastases were important adverse prognostic factors for PFS treated with pyrotinib [8]. In this study, there was a significant difference between OS in patients with and without liver metastases, suggesting that patients without liver metastases could benefit more from the treatment of pyrotinib compared to patients with liver metastases. However, this study did not find an association between lung metastases and poor prognosis after pyrotinib treatment. Further studies should be needed to confirm that pyrotinib could bring better survival benefits to patients without lung metastases and / or liver metastases of breast cancer.

Approximately 25% - 50% of patients with HER2--positive advanced breast cancer develop brain metastases, and effective treatment options are very few [12-15]. Many studies have confirmed that brain metastases make worse prognosis in patients with breast cancer [16-18]. In a retrospective study of 557 patients with breast cancer brain metastases, brain metastasis was an independent prognosis of shorter OS with a risk ratio of 1.58 (95%CI: 1.04-2.41, P = 0.033) [17]. Pyrotinib is a small molecule drug that can cross the blood-brain barrier, and several retrospective analysis studies had shown excellent efficacy of pyrotinib in patients with breast cancer brain metastases [10,18-21]. But there had been few studies on whether brain metastases could affect the prognosis of pyrotinib treatment. This study included 39 patients with brain metastases and 52 patients without brain metastases. However, Log-rank method analysis and Cox regression model analysis both found no significant difference in PFS and OS between patients with brain metastases and patients without brain metastases, suggesting that patients with and without brain metastases could be treated with pyrotinib.

Furthermore, a study shown that pyrotinib increased the radio-sensitivity of HER2-positive breast cancer cells and increased radiation-induced DNA damage by inhibiting mechanisms such as the induction of HER2 nuclear transport [22], suggesting that pyrotinib in combination with radiotherapy would be promising in patients with advanced HER2-positive breast cancer. This study included 22 patients with local radiotherapy, but there was no significant difference in PFS and OS of patients with or without local radiotherapy. In the previous study, brain metastases patients without concurrent radiotherapy and/ or brain surgery had a lower ORR than those who received local treatment (6.3% vs 66.7%) [23]. There was no significant difference in PFS and OS between the two groups after grouping 39 patients with brain metastases according to whether they received local radiotherapy or not. Whether pyrotinib can enhance the therapeutic effect of radiotherapy for metastatic breast cancer needs more data to support.

The most predominant AE observed in this study was diarrhea, which was consistent with previous studies [24,25]. In addition, common AEs also included leukopenia, anemia, nausea, and neutropenia [26,27]. The safety and tolerance of pyrotinib treatment were generally good.

There were some limitations to our study. First, as a retrospective study, some clinical data were inevitably missed, leading to information bias. Second, the results of this study required more data to support, in order to further develop the potential of pyrotinib-based treatment. Third, whether clinical factors such as liver metastases, brain metastases, lung metastases, and combined radiotherapy had an impact on the prognosis of pyrotinib for patients with HER2-positive advanced breast cancer needed larger and more clinical trials to determine.

In summary, this study had certain value and significance for clinical practice. This study provided preliminary evidence that the number of treatment lines for pyrotinib was an independent risk factor for HER2-positive advanced breast cancer patients' survival, and that liver metas-

tases could reduce the survival of patients treated with pyrotinib. Therefore, pyrotinib treatment regimen could be adjusted by monitoring the progression of breast cancer, which contributed to prolonged patients' survival. In addition, by monitoring AEs, physicians could guide patients and their families for corresponding prevention and treatment.

Conclusions

The results of this study suggested that real-world pyrotinib treatment demonstrated good anti-tumor efficacy and tolerable toxicity for HER2-positive breast cancer patients, and longer survival in earlier treatment. Moreover, the results also showed that pyrotinib-based therapy had some advantages for patients without liver metastases.

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Conflict of Interest

There is no conflict of interest to declare.

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Author contributions

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(III) Provision of study materials or patients: All authors;

(IV) Collection and assembly of data: Yongxia Li, Yong Li, Mingyuan He, Hongxia Wang;

(V) Data analysis and interpretation: Yongxia Li, Li Ran;

(VI) Manuscript writing: Yongxia Li, Li Ran;

(VII) Final approval of manuscript: All authors;

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