Efficacy and safety of pyrotinib in combination with albumin-bound paclitaxel for the treatment of HER2-positive advanced breast cancer: A real-world study

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Abstract. The present study aimed to determine the efficacy and safety of pyrotinib in combination with albumin-bound paclitaxel in patients with HER2-positive advanced breast cancer (ABC). A total of 48 patients diagnosed with HER2-positive ABC were included in the present study, and these patients were prescribed a combination of pyrotinib and albumin-bound paclitaxel in routine clinical practice. During a 21-day cycle, the standard dosage of pyrotinib was 400 mg single dose/day, which was administered orally, and 130 mg/m^2/day albumin-bound paclitaxel on days 1, 8 and 15, which was administered by intravenous drip. The primary efficacy endpoint was progression-free survival (PFS) and the secondary efficacy endpoint was overall response rate (ORR), which was defined as the percentage of patients with complete remission or partial remission. Safety indicators were also observed in the present study. The results of the present study demonstrated that the median PFS (mPFS) was 8.1 months for all patients, ranging from 3.3-10.6 months. Patients receiving pyrotinib as second-line therapy exhibited a longer mPFS of 8.5 months compared with those receiving it as third- or higher-line therapy (mPFS, 5.9 months). In 17 patients with brain metastases, mPFS was 7.3 months, ranging from 4.8-10.1 months. The results of the present study also demonstrated that the ORR for the 48 patients was 33.3%. Notably, diarrhea was the most common grade 3-4 adverse event, occurring in 22.9% of patients, followed by neutropenia (6.3%), leukopenia (4.2%) and anemia (4.2%). Collectively, the results of the present study indicated that pyrotinib-based treatment is effective for patients with HER2$^+$ ABC, including those who have previously been treated with trastuzumab. Thus, the combination of pyrotinib with albumin-bound paclitaxel is recommended due to high levels of efficacy, convenience and tolerability.

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Introduction

Breast cancer is the most prevalent malignancy in women worldwide and poses a notable threat to human health (1). Notably, 20-30% of patients with breast cancer exhibit HER2 upregulation in the tumor tissue (2,3). HER2-positive tumors are particularly aggressive, and are associated with a poor prognosis due to reduced overall survival (OS) and progression-free survival (PFS) (4). In addition, the results of a previous study indicated that HER2-positive tumors are more likely to metastasize to internal organs and the central nervous system (CNS) (5). At present, there is no cure for metastatic breast cancer (MBC); thus, treatment options that extend survival, achieve remission and optimize quality of life are required. The majority of anti-HER2-targeted therapies combined with chemotherapy significantly improve the outcomes of patients with HER2-positive breast cancer (6).

The development of anti-HER2 drugs has led to a significant improvement in the survival of patients with HER2-positive advanced breast cancer (ABC). Notably, anti-HER2 drugs, such as trastuzumab, pertuzumab, lapatinib, ado-trastuzumab emtansine, neratinib and trastuzumab deruxtecan, have offered great benefit to this group of patients (6-12). Trastuzumab, also known as Herceptin, was the first targeted anti-HER2 therapeutic drug to be used in clinical practice. Notably, there are two types of trastuzumab resistance: Primary and secondary trastuzumab resistance. Primary trastuzumab resistance refers to progressive disease (PD) development during adjuvant trastuzumab treatment after early breast cancer surgery, or PD development within 1 year of the end of trastuzumab treatment. Secondary trastuzumab resistance refers to PD development 1 year after the end of adjuvant trastuzumab therapy following surgery for early breast cancer, or re-emergence of PD after effective MBC trastuzumab treatment (13). In patients with HER2-positive ABC for whom trastuzumab therapy has failed, the development of alternative targeted agents is required.

In addition to targeting HER1, HER2 and HER4, pyrotinib is an oral, irreversible, pan-erbB tyrosine kinase inhibitor (TKI) (14). During phase I, II and III studies, pyrotinib has been shown to exert notable clinical benefits when combined with capecitabine, and it has been reported to be well-tolerated by patients with HER2+ MBC (15-18). The results of a randomized, open-label, multicenter, phase II clinical trial demonstrated that treatment with pyrotinib and capecitabine resulted in a notable improvement in objective response rate (ORR) and a longer median PFS (mPFS), when compared with lapatinib and capecitabine (15). Furthermore, the results of the phase III, double-blind, multicenter, randomized PHENIX study demonstrated that pyrotinib plus capecitabine significantly prolonged mPFS (11.1 vs. 4.1 months) and improved ORR (68.6 vs. 16.0%) compared with capecitabine monotherapy (19). The results of the phase III PHOEBE trial also revealed that pyrotinib plus capecitabine significantly prolonged mPFS compared with lapatinib plus capecitabine (16). The results of previous studies have demonstrated that treatment with pyrotinib and capecitabine may lead to increased survival rates in patients; however, OS data are lacking. Notably, earlier studies only included patients with HER2-positive MBC without two or more prior systemic therapy regimens (15,20). In August 2018, pyrotinib was approved in China as a second-line targeted therapy for $HER2^+$ MBC. Notably, capecitabine is a commonly used chemotherapy regimen in clinical practice, and numerous patients may receive chemotherapy prior to receiving pyrotinib. In addition, the therapeutic efficacy of pyrotinib in combination with other chemotherapeutic agents is unclear; therefore, the choice of chemotherapeutic agents for clinicians is limited at present.

Nanoparticulate albumin-bound paclitaxel is an albumin-bound paclitaxel nanoparticle formulation suspended in saline (21). This drug exhibits a lower risk of allergy and an improved toxicity compared with solvent-based paclitaxel, and does not require pre-treatment (21). In patients with MBC, PFS has been shown to be significantly longer following treatment with albumin-bound paclitaxel compared with docetaxel (22). In 2005, the United States Food and Drug Administration approved albumin-bound paclitaxel for the treatment of MBC. This medication is specifically intended for patients who have either failed combination chemotherapy or experienced cancer recurrence within 6 months of completing adjuvant chemotherapy (23).

Patients who have not responded to trastuzumab treatment are provided with several treatment options. Patients may choose to receive T-DM1, a small molecule TKI drug combined with chemotherapy, or pertuzumab dual-target therapy combined with trastuzumab. However, in China, T-DM1 is costly and not currently covered by medical insurance reimbursement. Alternatively, Chinese patients with HER2-positive breast cancer for whom trastuzumab treatment has failed may receive pyrotinib in combination with chemotherapy, or pertuzumab dual-target therapy combined with trastuzumab. The present study aimed to explore the efficacy and safety of pyrotinib in combination with albumin-bound paclitaxel for the treatment of HER2-positive breast cancer. The cohort used in the present study included both trastuzumab-sensitive and -resistant patients.

Materials and methods

Patients and dose regimen. Pyrotinib combined with albumin-bound paclitaxel was used to treat patients with HER2-positive ABC admitted to Xingtai People's Hospital (Xingtai, China) between October 2018 and June 2020. All participants provided written informed consent and the present study was approved by the institutional review board.

The inclusion criteria were as follows: i) Patients with MBC with immunohistochemistry (IHC) class 3+ or HER2 gene amplification confirmed using fluorescence *in situ* hybridization. In cases where a re-biopsy of the metastatic site was not possible, HER2 status was determined using the most recent primary tumor specimen; ii) patients with at least one measurable lesion according to the solid tumor efficacy evaluation criteria version 1.1 (RECIST 1.1) (24). The exclusion criteria were as follows: i) Patients who were involved in pyrotinib-related clinical trials; ii) patients who refused to provide written informed consent. In addition, patients who discontinued pyrotinib treatment due to financial reasons were excluded from the efficacy analysis. A total of 48 patients were enrolled in the efficacy cohort.

A combination of chemotherapy and/or anti-HER2-targeting agents was frequently used with pyrotinib in routine clinical practice. Initial dosing, dose adjustment and treatment discontinuation of pyrotinib were determined by the associated physician based on clinical efficacy, AE class, physical performance status and patient preference.

The treatment regimen was as follows: Intravenous administration of albumin-bound paclitaxel (130 mg/m^2) on days 1, 8 and 15, every 21 days for 2-8 cycles, together with oral administration of 400 or 320 mg pyrotinib once daily until disease progression.

Efficacy assessments were performed every 8 weeks and at the end of study treatment. Throughout the study, all patients were monitored for survival and safety assessments were conducted regularly. Assessments included physical examinations, evaluations of Eastern Cooperative Oncology Group performance status (25), vital signs, clinical laboratory assessments and cardiac monitoring. The left ventricular ejection fraction function was monitored at 12-week intervals in all patients. In addition, AEs and serious AEs were documented.

Assessments. Data collection included demographic and baseline information, including age, histological characteristics, treatment history, metastatic site, prior therapies, medical history and any concomitant conditions.

The present study aimed to determine PFS, defined as the length of time from the administration of pyrotinib until disease progression or death from any cause. In addition, the secondary study endpoint was ORR, calculated as the percentage of patients who achieved complete remission (CR) or partial remission (PR).

Oncologic efficacy was assessed using RECIST 1.1, along with physical examination and imaging. A retrospective analysis of medical records and laboratory results was conducted to identify the safety risks associated with pyrotinib treatment. AE grade was assigned according to the Common Terminology Criteria 5.0 for AEs by the National Cancer Institute (26). Trastuzumab resistance was defined as new

Table I. Baseline patient characteristics (n=48).

Characteristic	Value
Median age, years	59
Lines of advanced systemic therapy, n (%)	
≥3	24 (50%)
2	23 (47.9%)
1	1 (2.1%)
Brain metastases, n (%)	
No	31 (64.6%)
Yes	17 (35.4%)
Hormone receptors[a] status, n (%)	
Positive	33 (68.8%)
Negative	15 (31.2%)
Trastuzumab resistance status, n (%)	
Resistance	25 (52.1%)
Sensitive	23 (47.9%)
Visceral metastases, n (%)	
Yes	37 (77.1%)
No	11 (22.9%)
Number of metastatic sites, n (%)	
≥3	18 (37.5%)
≤2	30 (62.5%)

[a]Estrogen receptor and progesterone receptor.

Table II. Treatment administration.

Treatment	Number of patients (%)
Pyrotinib	
Starting dosage	
400 mg/day	46 (95.8)
320 mg/day	2 (4.2)
Dose reduction	
400→320 mg/day	7 (14.6)
400→320→240 mg/day	1 (2.1)
Interruption	5(10.4)
Albumin-bound-paclitaxel	
Dose reduction due to AEs	
Yes	10 (20.8)
No	38 (79.2)
Interruption of albumin-bound-paclitaxel due to AEs	4 (8.3)

AEs, adverse events.

recurrence within 12 months of surgery or diagnosed within 12 months, or disease progression while receiving first-line trastuzumab therapy.

Statistical analysis. In the present study, mPFS was determined using the Kaplan-Meier method and univariate analysis was conducted using the log-rank test. The Cox proportional hazards model was used for multivariate analysis. All statistical analyses were carried out using SPSS (version 25.0; IBM Corp.) and 'ggplot2' package (27) in R version 4.2.2 (http://www.r-project.org). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Clinical characteristics. A total of 48 female patients with HER2$^+$ MBC were admitted with pyrotinib plus albumin-bound paclitaxel at Xingtai People's Hospital between October 2018 and June 2020. Baseline characteristics are presented in Table I. All patients were female. The median age of patients at diagnosis was 59 years (range, 32-74 years). In total, 37.5% of patients exhibited more than three sites of metastases, and the most common sites of metastases included the lung (54.2%) and liver (35.4%). A total of 77.1% of patients experienced visceral metastases and 17 patients (35.4%) experienced brain metastases. Almost all patients were treated with anti-HER2 therapy. Of these, 95.8% of patients were treated with trastuzumab and 35.4% of patients were treated with lapatinib. In addition, 50% of patients received three or more systemic treatments prior to pyrotinib plus albumin-bound paclitaxel treatment.

Dose adjustment. A total of 95.8% of patients started treatment with pyrotinib at the standard dose of 400 mg/day, while 4.2% started treatment with pyrotinib at a dose of 320 mg/day (Table II). Moreover, a total of 8 (16.7%) and 5 (10.4%) patients experienced pyrotinib dose reductions or interruptions. A total of 10 (20.8%) patients experienced a dose reduction of albumin-bound paclitaxel due to AEs and 4 (8.3%) patients experienced interruptions to albumin-bound paclitaxel treatment. No patients permanently discontinued treatment due to AEs.

Efficacy. All patients were included in the PFS analysis with a median follow-up of 8.7 months. The mPFS for 48 patients was 8.1 months (range, 3.3-10.6 months; Fig. 1). Patients who experienced metastases to the brain exhibited a mPFS of 7.3 months (Fig. 2). Notably, there was no significant difference in PFS between patients who experienced metastases to the brain and those who did not (7.3 months vs. 8.3 months; data not shown). In addition, 48 patients were included in the ORR analyses. The results of the present study demonstrated that no patients experienced CR, 16 patients experienced PR and the ORR was 33.3% (Table III).

The results of the univariate analysis demonstrated that age (<60 years vs. ≥60 years), hormone receptor status (positive vs. negative), number of metastatic sites (≤2 vs. >2) and whether lapatinib was previously applied (yes vs. no) were not significantly associated with mPFS (Table IV). By contrast, trastuzumab resistance status (resistant vs. not resistant) and number of treatment lines (2 vs. ≥3) were significantly associated with mPFS (Table IV). mPFS was 6.8 months in patients with prior trastuzumab resistance and 8.4 months in patients with no prior trastuzumab resistance (Fig. 3). Moreover, mPFS was 8.5 months in patients with ≤2 lines of prior therapy and

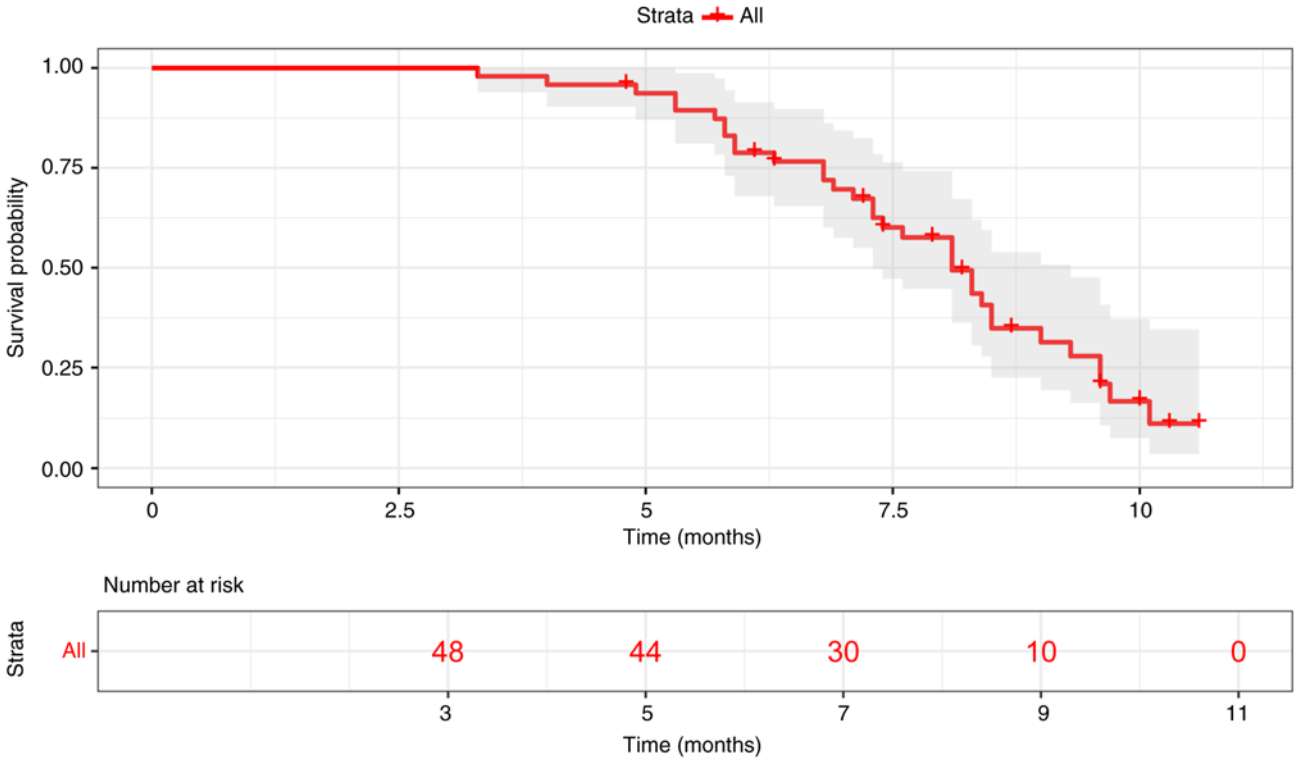

Figure 1. Kaplan-Meier curve demonstrating the progression-free survival of all patients.

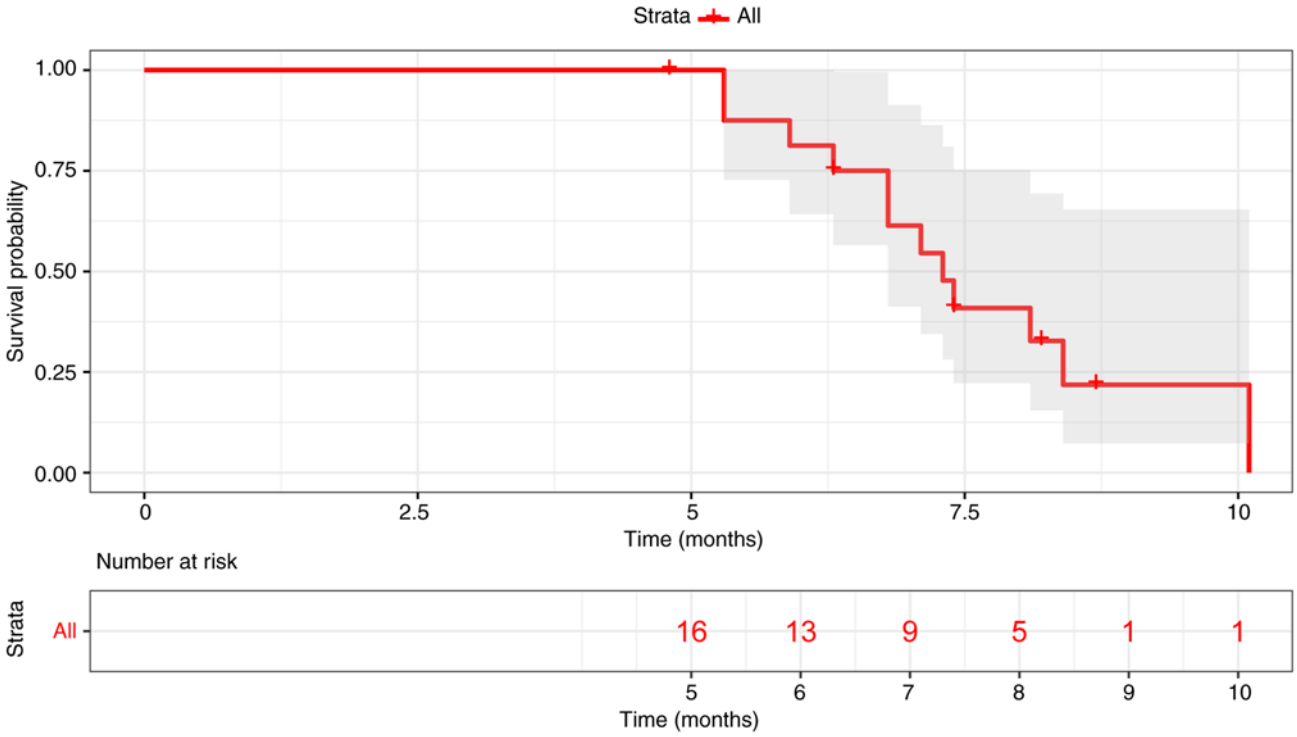

Figure 2. Kaplan-Meier curve showing the progression-free survival of patients with brain metastasis.

6.35 months in patients with ≥3 lines of prior therapy (Fig. 4). However, the results of the multivariate analysis demonstrated that trastuzumab resistance was not an independent predictor of mPFS, and the number of prior treatment lines was an independent predictor of mPFS.

Safety indicators. Using laboratory findings and medical records of patients, AEs were reported in the present study. The results of the present study demonstrated that the most common grade 3-4 AEs included diarrhea (22.9%), neutropenia (6.3%), anemia (4.2%) and leukopenia (4.2%; Table V). Notably,

Table III. ORR in all patients (n=48).

Response	Number of patients (%)
Complete response	0 (0)
Partial response	16 (33.3)
Stable disease	24 (50.0)
Progressive disease	8 (16.7)
ORR	16 (33.3)

ORR, objective response rate.

Table IV. Log-rank and Cox multivariate analysis of factors associated with progression-free survival.

	Log-rank test		Cox multivariate analysis	
Characteristic	HR	P-value	HR	P-value
Hormone receptor status (positive vs. negative)	1.074	0.424		
Trastuzumab resistance status (resistance vs. refractoriness)	2.023	0.034	1.577	0.265
Age group (<60 years vs. ≥60 years)	1.499	0.231		
Number of metastatic sites (≤2 vs. >2)	0.9491	0.878		
Prior exposure to lapatinib (yes vs. no)	1.209	0.588		
Lines of advanced pyrotinib plus albumin-bound paclitaxel systematic therapy (2 vs. ≥3)	0.3381	0.001	0.329	0.009

Table V. Grade 3-4 adverse events in all patients (n=48).

Grade 3-4 adverse events	Number of patients (%)
Diarrhea	11 (22.9)
Neutropenia	3 (6.3)
Leukopenia	2 (4.2)
Anemia	2 (4.2)
Thrombocytopenia	1 (2.1)
Nausea and vomiting	1 (2.1)
Fatigue	1 (2.1)
Weight loss	1 (2.1)

treatment with pyrotinib in combination with albumin-bound paclitaxel did not result in any treatment-related deaths.

Discussion

HER2 upregulation is an independent indicator of poor prognosis (4). Despite notable improvements in the outcomes of patients with HER2-positive breast cancer following treatment with anti-HER2-targeted therapy coupled with chemotherapy, resistance often develops after 12 months (6). In clinical practice, patients with primary HER2-positive MBC and prior treatment with multiple anti-HER2 therapies have demonstrated responses to pyrotinib-based therapies. Various chemotherapy regimens include combinations such as vinorelbine and paclitaxel (28). Pyrotinib is a newly approved anti-HER2 TKI agent in China. The results of the present study indicated that pyrotinib plus albumin-bound paclitaxel resulted in an 8.1-month median PFS and a 33.3% ORR in patients with $HER2^+$ MBC.

The results of a previous study demonstrated that trastuzumab, pertuzumab and capecitabine as a second-line treatment, increased the mPFS to 11.1 months (29). In addition, a combination of lapatinib and capecitabine has been shown to result in a PFS of 8.4 months (9). The results of the present study revealed that the mPFS was 8.5 months in patients with $HER2^+$ MBC following treatment with second-line pyrotinib plus albumin-bound paclitaxel, and was 6.3 months in patients with $HER2^+$ MBC treated with third- or higher-line pyrotinib plus albumin-bound paclitaxel. Thus, pyrotinib in combination with albumin-bound paclitaxel may be used as a first-, second- or higher-line treatment option.

The results of a previous phase III study of pyrotinib plus capecitabine demonstrated that mPFS was 11.1 months and ORR was 68.6% (15). Variations observed between the results obtained in the present study and those of previous studies may be attributed to dissimilarities in population sample sizes and cohorts, as well as differences in the chemotherapeutic drugs used in conjunction with pyrotinib. The cohort used in the present study consisted of patients who had previously received trastuzumab, and 50% of patients previously received three or more systemic therapies. By contrast, previous clinical trials included patients who received a maximum of two treatments, and some patients did not receive anti-HER2 therapy.

The cohort used in the present study included patients with trastuzumab resistance. The general population of patients with HER2-positive MBC typically receive aggressive treatment with a variety of anti-HER2 medications. Therefore, the results of the present study may offer valuable insights for clinicians treating patients with HER2-positive MBC in non-clinical trial settings. In addition, the present study exhibited a short follow-up period of only 8.7 months, and >30% of patients were still undergoing treatment at the time of study conclusion. Notably, a previous phase III study did not include patients who had previously received lapatinib (30), and 50.5% of patients included in the present study received lapatinib prior to the study treatment. The results of the phase III EMILIA trial demonstrated that T-DM1

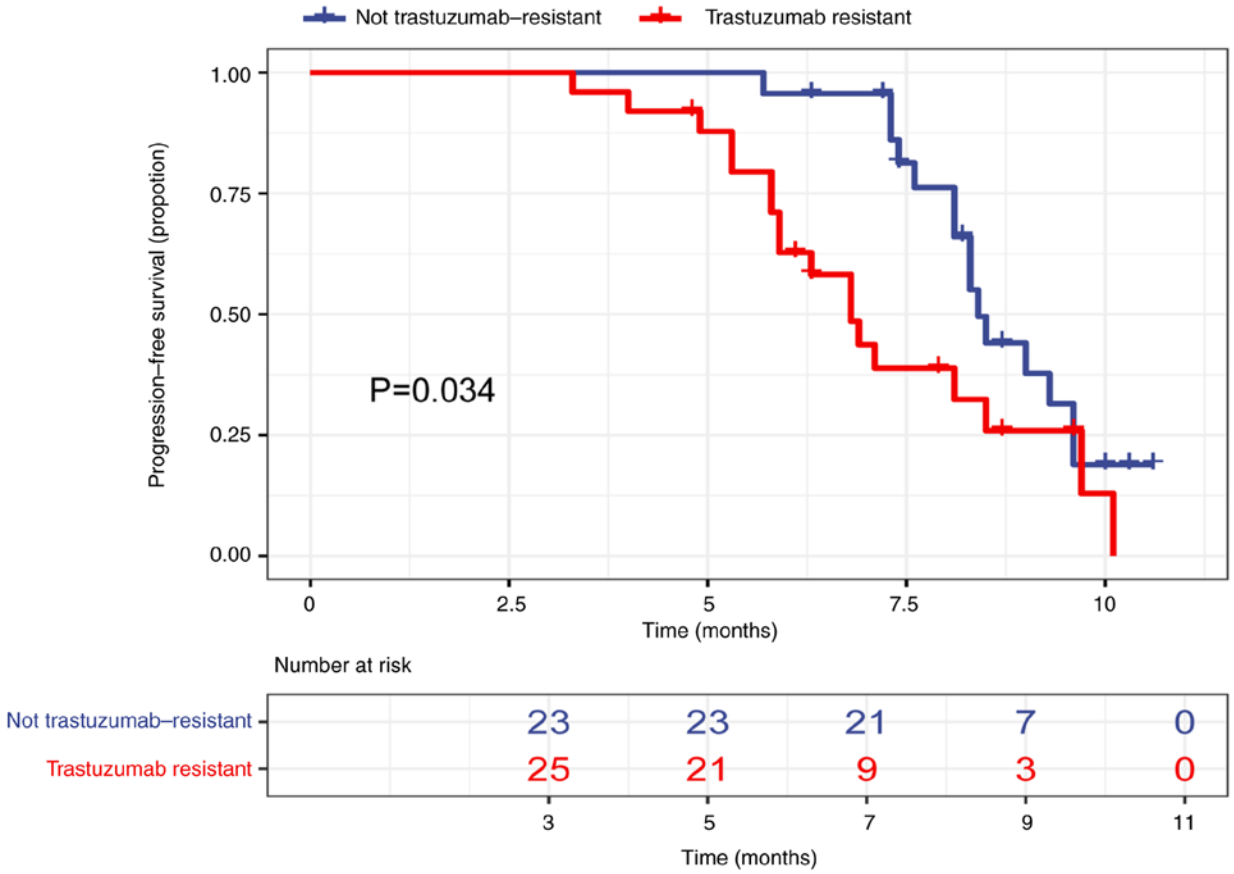

Figure 3. Kaplan-Meier curve showing the progression-free survival of patients with or without trastuzumab resistance.

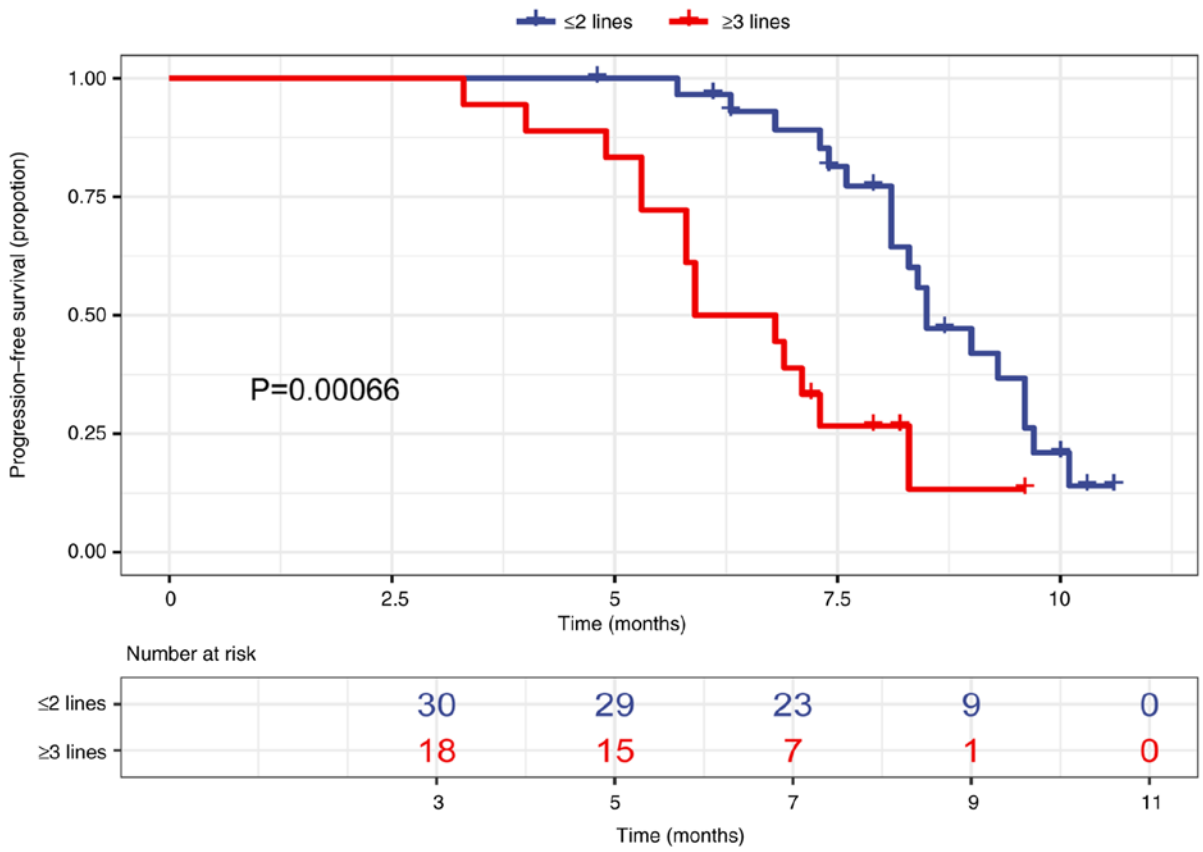

Figure 4. Kaplan-Meier curve showing the progression-free survival of patients receiving pyrotinib plus albumin-bound paclitaxel as their second-or-lower or third-or-higher-line treatment.

enhanced the clinical outcomes in patients with metastatic HER2-positive breast cancer; however, treatment with T-DM1 did not exert an impact on the rate of CNS progression (6). Based on the results of the DESTINY-Breast03 trial, T-DXd, a type of antibody-drug conjugate, also known as DS8201, has been recommended as standard second-line therapy following trastuzumab for patients with advanced HER2-positive breast cancer. The T-DXd group demonstrated a highly clinically meaningful and statistically significant improvement in PFS, compared with patients with HER2-positive MBC treated with T-DM1 (31). Pertuzumab, T-DM1 and/or T-DXd are widely used as first or second-line treatment options in patients with HER2-positive breast cancer worldwide; however, pertuzumab, T-DM1 and T-DXd are not yet included in China's Medicare drug list. Thus, further investigations into the use of pertuzumab, TDM1 and T-DXd are required.

A previous retrospective study evaluated the efficacy and safety of pyrotinib-based treatments in a real-world setting (32). Notably, capecitabine was primarily used as the main component in the combination chemotherapy regimen. The results of a single-center retrospective study demonstrated that the mPFS of patients with HER2-positive MBC treated with pyrotinib was 6.3 months and the ORR was 29.5% (32). Moreover, the results of a further multicenter analysis demonstrated that the mPFS of patients treated with pyrotinib was 8.07 months and the ORR was 40.7% (25). However, the combination therapy was only administered to a small number of patients in both studies. In addition, the results of the present study demonstrated that the mPFS was 8.5 months in patients following second-or-lower-line treatment, which was higher than the 8.1-month mPFS reported in a previous multicenter retrospective study using pyrotinib-based regimens that included vincristine (33). Despite these differences, pyrotinib is considered an effective treatment for $HER2^+$ MBC, particularly as a second-line therapy.

Patients with HER2-positive MBC exhibit an increased risk of developing brain metastases, compared with patients who are HER2-negative (34). However, despite the use of anti-HER2 therapy, survival 34 in patients with brain metastases remain low due to limited treatment options (35). The macromolecular structure of trastuzumab makes it difficult to penetrate the blood-brain barrier; thus, the impact of this treatment on the brain of patients with brain metastases remains to be fully elucidated (36). Patients with cancer that has metastasized to the brain are often treated with anti-HER2 TKIs with a small molecular weight and a high permeability for penetration through the blood-brain barrier (37). A meta-analysis of 12 studies revealed that the combined use of lapatinib and capecitabine resulted in a mPFS of 4 months in patients with $HER2^+$ MBC with brain metastases (38). The results of the TBCRC022 study demonstrated that the mPFS of lapatinib-naïve patients with HER2-positive MBC and brain metastases was 5.5 months following treatment with neratinib plus capecitabine, and 3.1 months in lapatinib-treated patients with HER2-positive MBC and brain metastases (39). The results of the present study demonstrated that the mPFS of 17 patients with brain metastases was 7.3 months. This finding is consistent with the results of the PHENIX study, which demonstrated a mPFS of 6.9 months in a cohort of patients with brain metastases who were treated with pyrotinib plus capecitabine (19).

The results of the present study demonstrated that a combination of pyrotinib and albumin-bound paclitaxel was generally well tolerated, despite diarrhea being the most common grade 3-4 AE, which is in line with the results of previous clinical studies (16,19). Notably, all AEs were effectively managed and did not result in the discontinuation of either pyrotinib or albumin-bound paclitaxel during the study. The results of the present study also demonstrated that the incidence of grade 3 or 4 neutropenia and leukopenia was higher than previous phase III trials, at 6.3 and 4.2%, respectively (16,19). This may be due to the concomitant use of albumin-bound paclitaxel in the present study. Moreover, AEs may have been under reported in the present study due its retrospective nature.

The present study exhibits a number of limitations. Notably, the present study was conducted retrospectively and in an observational manner, which may have resulted in missing data, and potential recall and information bias. Moreover, the follow-up time of the present study was short, leading to inconclusive OS data. However, to the best of our knowledge, the present study is the first to investigate the efficacy of the combined use of pyrotinib and albumin-bound paclitaxel in a real-world setting. The results of the present study provide key insights into the treatment patterns and safety profiles of pyrotinib and albumin-bound paclitaxel in a real-world clinical setting, which may aid in guiding clinicians in decision-making processes.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to restrictions applied by Xingtai People's Hospital but are available from the corresponding author on reasonable request.

Authors' contributions

LY and LZ conceived and designed the study. Material preparation and data collection were performed by PP, FK, SZ and XT. The draft of the manuscript was written by PP and revised by SZ and LY. All authors read and approved the final manuscript. LY and PP confirm the authenticity of all the raw data. Each of the authors has sufficiently participated in the work to take public responsibility for appropriate parts of the content, and agrees to be accountable for all aspects of the work to ensure that questions regarding the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

All procedures performed in the present study involving human participants were in accordance with The Declaration of Helsinki (as revised in 2013). The study was approved by

the Institutional Ethics committee of Xingtai People's Hospital [approval no. 2021(030)]. Written informed consent was obtained from each patient.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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