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CLINICAL TRIAL REPORT

Eribulin plus Pyrotinib in Trastuzumab-Resistant, HER2-Positive Advanced Breast Cancer: A Single-Arm, Multicenter Phase II Trial (EPIC Trial)

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Purpose: This study aimed to assess the efficacy and safety of combining Eribulin with Pyrotinib in patients diagnosed with advanced HER2-positive breast cancer and exhibiting resistance to trastuzumab. This subgroup of patients typically faces a bleak clinical prognosis with limited guidance available for treatment decisions.

Patients and Methods: Patients (N=30) with HER2-positive metastatic breast cancer, ECOG 0–1, and prior trastuzumab/taxane therapy received oral Pyrotinib 400 mg daily and intravenous Eribulin 1.4 mg/m² (days 1/8 of 21-day cycles for 6 cycles), followed by Pyrotinib until progression/intolerable toxicity. The primary endpoint was progression-free survival (PFS).

Results: Between February 2021 and September 2023, 30 patients were enrolled in the study, with a median age of 57 years. All patients had previously received treatment with trastuzumab and taxanes. As of April 14, 2025, the median follow-up duration was 26 months. 18 patients experienced disease progression or death. The median progression-free survival (PFS) was 13.47 months (95% confidence interval [CI], 8.17–16.27), with a 12-month PFS rate of 61.7% (95% CI, 44.2%–86.0%). 12-month overall survival (OS) rate of 75.3% (95% CI 66.2–84.4). The objective response rate was 56.7% (17/30). The disease control rate (DCR) reached 80.0% (24/30), while the clinical benefit rate (CBR) was 73.3% (22/30). The median overall survival was not reached. Any adverse event (AE) of any grade with an incidence of more than 30% was Neutropenia (73.3%), diarrhea (70%), nausea/vomiting (66.7%), Peripheral neuropathy (63.3%), AST/ALT increased (43.3%), Anorexia (33.3%). There were no treatment-related deaths.

Conclusion: The combination of Eribulin and Pyrotinib emerges as a viable treatment option for HER2-positive advanced breast cancer patients who have exhibited resistance to trastuzumab. Despite advancements in anti-HER2 therapies, further research is required to address remaining challenges in this specific clinical scenario.

Keywords: breast cancer, human epidermal growth factor receptor 2, trastuzumab-resistant, pyrotinib, eribulin

Introduction

The human epidermal growth factor receptor 2 (HER2/ERBB2) stands as a molecularly validated therapeutic target in breast oncology, with its gene amplification or protein overexpression occurring in approximately 15–20% of breast carcinomas, correlating with aggressive tumor behavior and distinct clinical outcomes.[1] For metastatic HER2-positive disease, the established first-line therapeutic paradigm combines dual HER2 blockade using the monoclonal antibodies pertuzumab and trastuzumab with taxane-based chemotherapy, achieving median progression-free survival (PFS) exceeding 18 months in clinical trials.[2,3] Despite this advancement, therapeutic resistance manifests in 14–31% of early-stage cases during adjuvant treatment and eventually develops in nearly all metastatic presentations.[3–8] Mechanistically, resistance arises through HER2 extracellular domain structural alterations (eg, p95-HER2 truncations), compensatory signaling via HER3/MET receptors, or constitutive activation of downstream PI3K/AKT/mTOR pathway components

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through PIK3CA mutations or PTEN loss.[4,7] This molecular heterogeneity underscores the imperative for developing next-generation anti-HER2 agents targeting both canonical and alternative resistance pathways.

In the second-line setting, current National Comprehensive Cancer Network (NCCN) guidelines prioritize trastuzumab Deruxtecan (T-DXd), an antibody-drug conjugate linking trastuzumab to topoisomerase I inhibitor deruxtecan (DXd), demonstrating superior efficacy over lapatinib/capecitabine combinations in the EMILIA trial (median PFS 9.6 vs 6.4 months; HR 0.65, p<0.001).[9–11] Historical context reveals that prior to T-DM1's global guideline incorporation, regional variations existed in second-line recommendations. Specifically, certain Asian guidelines previously endorsed trastuzumab rechallenge with chemotherapy (eg, vinorelbine), lapatinib/capecitabine combinations, or dual HER2 inhibition with trastuzumab plus lapatinib,[12–15] strategies now largely superseded by T-DM1 and newer agents.

Pyrotinib, a second-generation irreversible pan-HER tyrosine kinase inhibitor (TKI) targeting EGFR, HER2, and HER4, has emerged as a potent therapeutic option. The landmark phase II trial (NCT02422199) demonstrated pyrotinib 400 mg daily plus capecitabine 1000 mg/m² twice daily significantly outperformed lapatinib/capecitabine in taxane/anthracycline-pretreated patients (N=128), achieving superior objective response rates (78.5% vs 57.1%, p=0.01) and median PFS (18.1 vs 7.0 months; HR 0.36, 95% CI 0.23–0.58).[16,17] In the trastuzumab-resistant subgroup (n=32), the Hazard Ratio (HR) was 0.60 (95% CI 0.29–1.21), which suggests that this population may still benefit from the treatment.[17] These findings were validated in the Phase III PHOEBE trial (NCT03080805), where pyrotinib/capecitabine demonstrated median PFS of 12.5 months versus 6.8 months for lapatinib-based therapy (HR 0.39, p<0.0001) in HER2-positive metastatic breast cancer.[18]

Despite these advances, capecitabine-associated toxicities remain problematic. Pooled analysis reveals grade ≥3 hand-foot syndrome (28%), diarrhea (15%), and neutropenia (24%) with capecitabine-containing regimens,[19] frequently necessitating dose reductions (34% of patients) and impairing quality-of-life metrics (EQ-5D index decrease ≥0.1 in 41% of cases).[20] These limitations have catalyzed investigations into alternative combination partners for HER2-targeted agents.

Eribulin mesylate, a synthetic macrocyclic ketone analog of halichondrin B isolated from the marine sponge Halichondria okadai, exerts unique microtubule-targeting effects distinct from taxanes. Unlike paclitaxel's tubulin stabilization, eribulin preferentially binds microtubule plus-ends, suppressing growth-phase dynamics while permitting shortening, thereby inducing irreversible mitotic arrest.[21] The phase III EMBRACE trial (NCT00388726) randomized 762 heavily pretreated metastatic breast cancer patients (16% HER2-positive) to eribulin versus physician's choice therapy, demonstrating significant overall survival improvement (median 13.1 vs 10.6 months; HR 0.81, 95% CI 0.66–0.99; p=0.041)20. Unlike taxanes that promote microtubule stabilization, eribulin's unique mechanism involves suppression of microtubule growth without affecting shortening phases, potentially circumventing classical taxane resistance pathways. Recent data from the EMERALD trial (ASCO 2024, abstract LBA1001) extended these findings in HER2-positive disease, showing eribulin/trastuzumab/pertuzumab (EHP) achieved non-inferior median PFS versus taxane/HP regimens (14.0 vs 12.9 months; HR 0.95, 95% CI 0.76–1.19), with significantly lower grade ≥3 edema (3.2% vs 11.7%, p=0.02) and peripheral neuropathy (8.1% vs 21.4%, p=0.003).[22,23]

Motivated by these pharmacological synergies and improved tolerability profiles, we conducted this multicenter phase II trial to systematically evaluate the efficacy and safety of eribulin-pyrotinib combination therapy in trastuzumab/taxane-pretreated HER2-positive metastatic breast cancer, aiming to address critical unmet needs in this refractory population.

The initial results of this research have been selected for poster (Abstract #1031) at the 2025 ASCO Annual Meeting.

Material and Methods

Study Design and Participants

This investigator-initiated, multicenter phase II trial enrolled female participants aged 18–70 years with histologically confirmed HER2-positive advanced breast cancer (IHC 3+ and/or FISH amplification ratio ≥2.0) who had documented disease progression following prior taxane chemotherapy and trastuzumab-based therapy. Eligible patients were required to have measurable lesions per RECIST v1.1 criteria, a Karnofsky Performance Status (KPS) ≥70, and adequate organ function defined as: leukocytes >4.0×109/L, absolute neutrophil count >2.0×109/L, platelets >100×109/L, hemoglobin

>90 g/L, serum creatinine 44–133 μmol/L, hepatic transaminases (AST/ALT) ≤1.5×upper limit of normal (ULN), alkaline phosphatase ≤2.5×ULN, total bilirubin ≤ULN, and left ventricular ejection fraction (LVEF) ≥50% by echocardiography. Additional inclusion criteria mandated a life expectancy ≥12 months, negative pregnancy testing for premenopausal women, and written informed consent with protocol compliance. Notably, patients' previous treatments before enrollment may have included Pertuzumab.

Primary trastuzumab resistance was operationalized according to modified ASCO guidelines14 as disease progression during (neo)adjuvant trastuzumab, recurrence within 12 months post-(neo)adjuvant therapy, or progression within 6 months of initiating first-line trastuzumab for metastatic disease, with a mandatory 28-day washout period following last trastuzumab exposure.

Key exclusion criteria encompassed NYHA class II or higher cardiac dysfunction, active systemic infections requiring intravenous antimicrobial therapy, hypersensitivity to eribulin/pyrotinib components, recent anticancer therapy (chemotherapy, radiotherapy, or investigational agents within 30 days prior to enrollment), Pregnancy/lactation or planned conception within 12 months post-treatment and any medical condition deemed to compromise patient safety or trial validity per investigator judgment.

Procedures

Patients received oral pyrotinib at a fixed dose of 400 mg once daily alongside intravenous eribulin mesylate administered at 1.4 mg/m² on days 1 and 8 of each 21-day treatment cycle. This combined regimen was maintained for six consecutive cycles, with pyrotinib therapy continuing beyond this period until protocol-defined discontinuation criteria were met (including disease progression, unacceptable toxicity, or voluntary patient withdrawal).

Dose modifications were protocol-mandated based on adverse event (AE) severity. Pyrotinib dosing followed a predefined de-escalation algorithm: initial reduction from 400 mg to 320 mg, followed by a secondary reduction to 240 mg if toxicity recurred. Dose re-escalation remained prohibited even after AE resolution. Treatment interruptions exceeding 14 cumulative days for pyrotinib necessitated permanent study discontinuation to maintain trial integrity.

Tumor response assessments followed a structured imaging protocol: contrast-enhanced CT/MRI scans were conducted at baseline and repeated every two cycles during the initial six cycles, transitioning to tri-monthly evaluations thereafter. For patients discontinuing treatment prior to progression or death, imaging surveillance continued quarterly until alternative anticancer therapy initiation, confirmed progression, or mortality. Investigators performed all radiological evaluations using RECIST v1.1 criteria with centralized quality control.

Overall survival (OS) tracking occurred through scheduled 12-week follow-ups until study closure, loss to follow-up, or death. Safety monitoring encompassed the entire treatment duration plus a 28-day post-treatment observation window. All AEs were systematically categorized and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE v5.0), with attribution assessment (related/unrelated to study drugs) conducted by an independent safety review committee.

Endpoints

The primary endpoint was progression-free survival (PFS), which was defined as the interval from the initiation of study treatment until either the first documented disease progression according to RECIST v1.1 criteria or death from any cause, whichever occurred first. Secondary endpoints comprised objective response rate (ORR), defined as the proportion of patients achieving a best overall response of either complete response (CR) or partial response (PR) per RECIST v1.1 criteria; duration of response (DoR), defined as the time elapsed from the first documented CR or PR to disease progression as assessed by RECIST v1.1 in patients who had achieved a confirmed objective response; disease control rate (DCR), defined as the proportion of patients whose best overall response was either CR, PR, or stable disease (SD) as assessed by RECIST v1.1 criteria; clinical benefit rate (CBR), defined as the proportion of patients whose best overall response was either CR, PR, or SD maintained ≥6 months as assessed by RECIST v1.1; overall survival (OS), defined as the duration from the initiation of study treatment to death due to any cause; and the evaluation of safety.

Statistical Analysis

We initially planned to enroll 30 patients for the analysis of the primary endpoint. Assuming that survival times followed an exponential distribution, it was calculated that a total of 15 disease progression or death events were required to adequately evaluate the primary endpoint, with a statistical significance level set at 5% and statistical power set at 80%. No modifications were made to the predefined number of events required for the final analysis. The planned duration of patient enrollment was 24 months, and the intended follow-up duration was 32 months.

Efficacy and safety assessments were performed on all patients who received at least one dose of the study medication. Continuous variables were summarized and presented as medians (range), whereas categorical variables were expressed as frequencies (percentages). The 95% confidence intervals (CIs) for objective response rate (ORR) and disease control rate (DCR) were calculated using the Clopper–Pearson method. Comparisons of ORR between patient subgroups were conducted using the chi-square test. Median progression-free survival (PFS) and overall survival (OS) were estimated utilizing the Kaplan–Meier method. Comparisons of PFS among subgroups were performed using the Cox proportional hazards regression model. All statistical analyses were conducted using SAS software, version 9.4, and R software, version 4.0.3. A two-sided P-value of less than 0.05 was considered statistically significant.

Results

Patient Characteristics and Treatment

Between February 2021 and September 2023, a total of 36 patients were screened for eligibility, and 30 patients were enrolled in the study for efficacy and safety analysis (Figure 1). Table 1 summarizes baseline characteristics. It includes details on the median age, the percentage of patients with visceral versus non-visceral metastases, hormone receptor status (ER or PR positivity), and ECOG performance status. The table also provides information on prior treatment history, and the percentage of patients who received capecitabine or Pertuzumab. Notably, only one patient with visceral metastases (86.7% of patients, n=26) had brain metastasis.

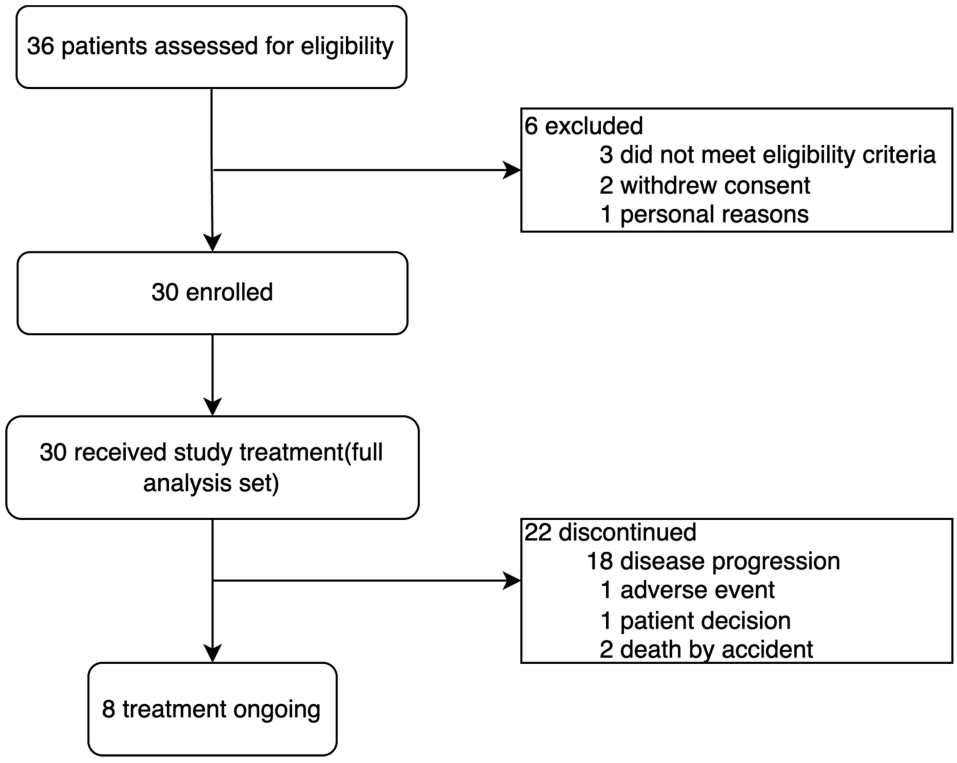

Figure 1 Patient Flowchart.

Table 1 Patient and Disease Characteristic

Age (years), median (range)	57(30–75)
<65, n (%)	22(73.3%)
≥65, n (%)	8(26.7%)
Metastatic sites at screening, n (%)	
Visceral	26(86.7%)
Non-visceral	4(13.3%)
Molecular status, n (%)	
ER or PR positive	21(70.0%)
ER and PR negative	9(30.0%)
HER2 2+	8(26.7%)
HER2 3+	22(73.3%)
ECOG score, n (%)	
0	28(93.3%)
1	2(6.7%)
Previous trasuzumab therapy, n (%)	
For advanced disease	16(53.3%)
As adjuvant or neoadjuvant therapy	12(40.0%)
Both	10(33.3%)
Median duration of trastuzumab for advanced disease, months	10.1
Previous Capecitabine therapy, n (%)	
Yes	9(30.0%)
No	21(70.0%)
Previous chemotherapy, n (%)	
THP	6
TCH	1
TCbHP	2
TXH	7
TXHP	2
ATH	2
AC-THP	3
wTH	7

As of the data cutoff date (April 14, 2025), the median follow-up duration was 26 months. Among the 30 enrolled patients, 8 (26.7%) remained on treatment at the time of analysis, whereas 22 (73.3%) discontinued therapy. The primary reason for discontinuation, observed in 18 patients (60%), was progressive disease (PD) confirmed by RECIST 1.1 criteria. Additionally, treatment was discontinued in one patient (3.3%) due to intolerable toxicity (grade 3 diarrhea with persistent neutropenia). One patient (3.3%) voluntarily withdrew from the study for personal reasons unrelated to treatment efficacy or safety. The remaining two patients discontinued their treatment due to unexpected death. The causes of death were a car accident and a home invasion, respectively.

Efficacy

The regimen achieved a median progression-free survival (PFS) of 13.47 months (95% CI 8.17–16.27) as in Figure 2, with 61.7% of patients (95% CI 44.2–86.0) remaining progression-free at 12 months, reflecting sustained disease control. The responses demonstrated notable durability, with a median duration of response (DoR) of 23.03 months (95% CI 21.7–) and a maximum DoR exceeding 34 months (Figure 3). Objective responses were observed in 56.7% of evaluable patients (17/30), including 2 complete responses (CR) and 15 partial responses (PR) (Figure 4). The disease control rate (DCR) reached 80.0% (24/30), while the clinical benefit rate (CBR) – defined as CR + PR + stable disease maintained ≥6 months – was 73.3% (22/30), underscoring the therapeutic potential of this combination in trastuzumab-refractory disease.

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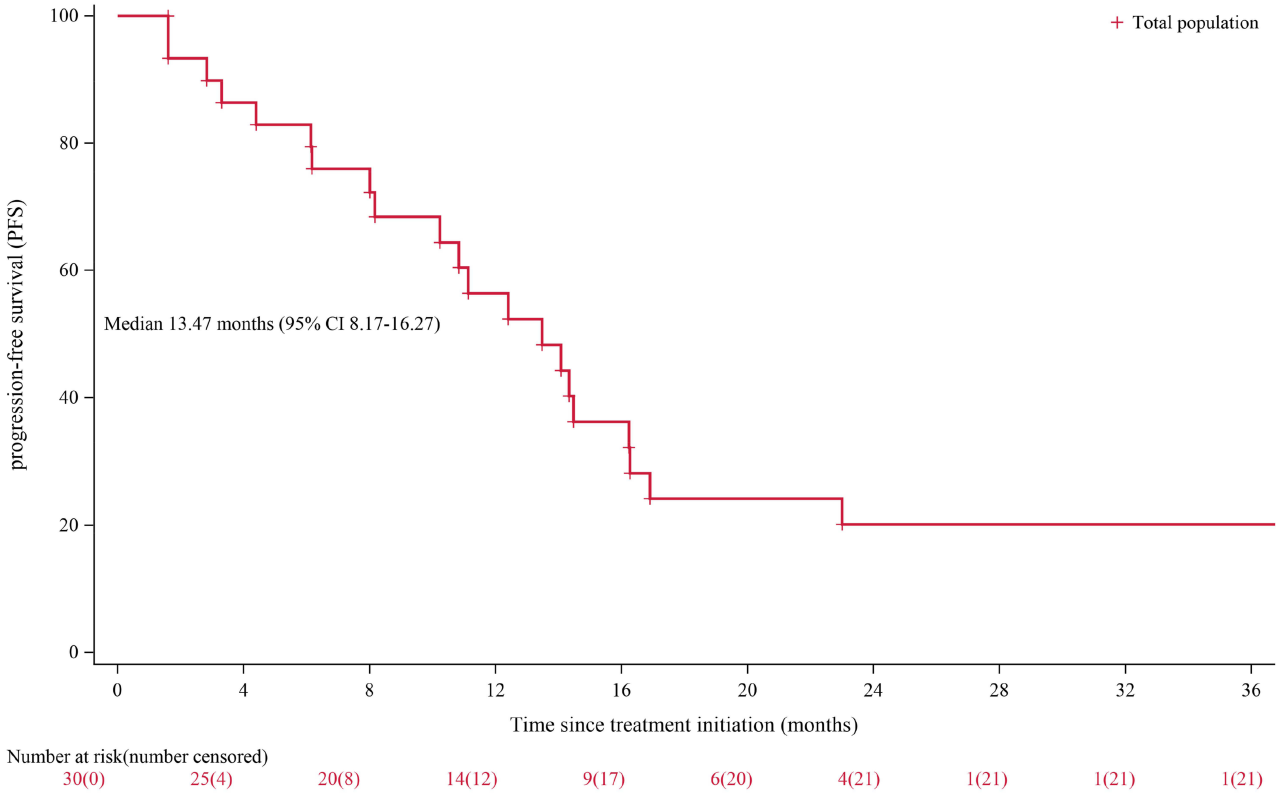

Figure 2 Kaplan–Meier survival curves depicting progression-free survival (PFS) in the intention-to-treat population (N = 30).

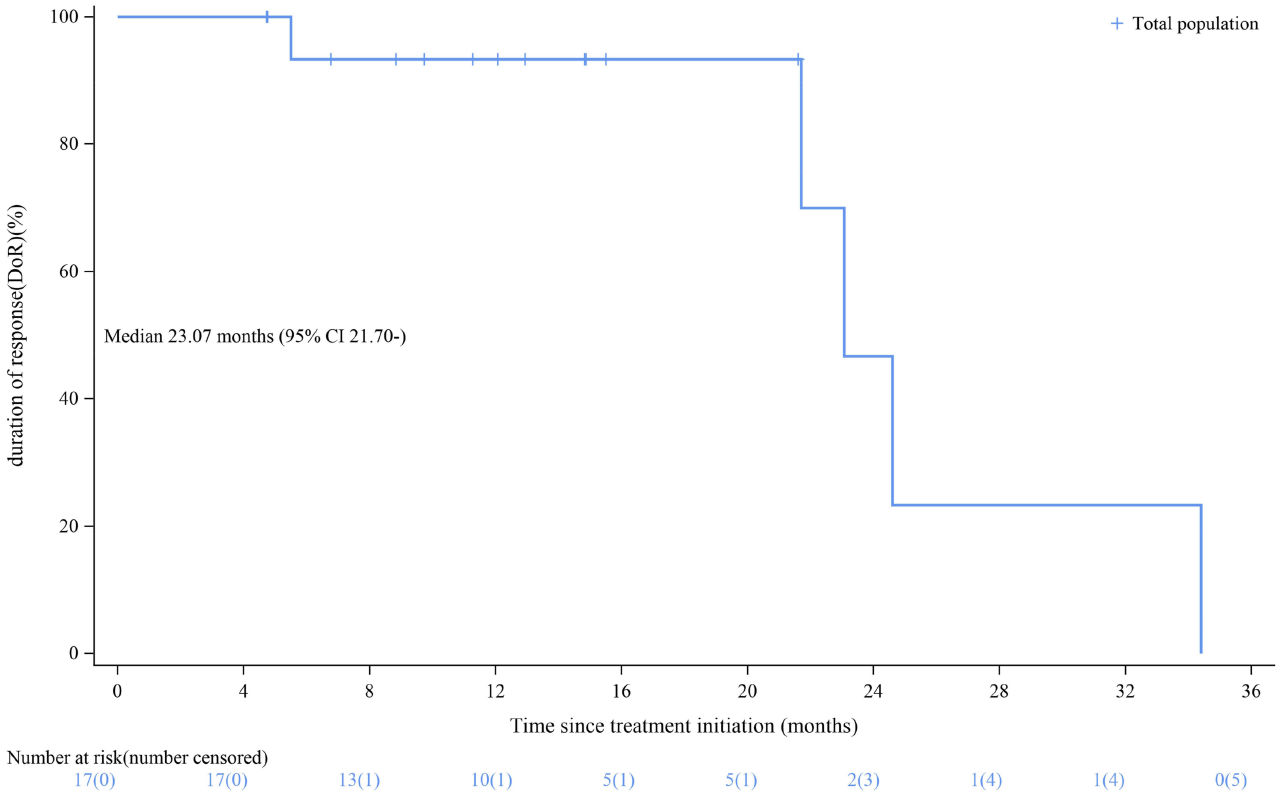

Figure 3 Kaplan–Meier survival curves depicting duration of response (DoR) in the intention-to-treat population (N = 30).

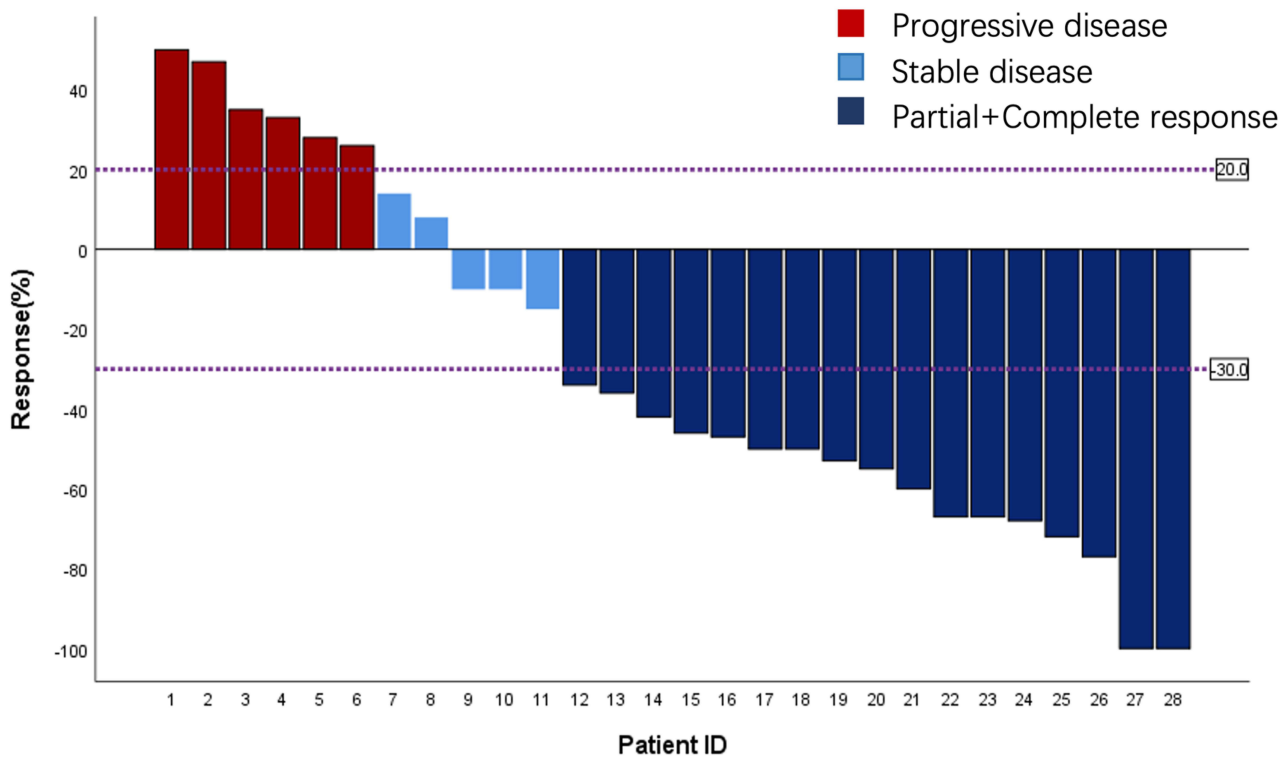

Figure 4 Waterfall plot for best percent change in target lesions from baseline among individual patients (n = 30).

Survival analyses revealed a 12-month overall survival (OS) rate of 75.3% (95% CI 66.2–84.4), with median OS not yet reached at data cutoff. Prespecified subgroup analysis demonstrated consistent treatment effects irrespective of prior capecitabine exposure (P=0.5641 by Chi-Square test; HR 1.02, 95% CI 0.42–2.48), suggesting broad applicability across capecitabine-naïve and capecitabine-pretreated populations (Figure 5).

Safety

The safety profile of the eribulin-pyrotinib combination aligned with established toxicity patterns of both agents, as detailed in Table 2. Treatment-emergent adverse events (TEAEs) occurred in 90.0% of participants (27/30), with grade ≥3 events reported in 33.3% (10/30). Dose modifications due to toxicity included reductions in 23.3% (7/30) and permanent discontinuation in 6.7% (2/30), while one patient (3.3%) withdrew consent due to intolerable symptoms. Notably, no treatment-related mortality was observed, contrasting with historical cytotoxic regimens.

Hematologic toxicity predominated, with all-grade neutropenia occurring in 73.3% (22/30) and grade ≥3 neutropenia in 16.7% (5/30). Gastrointestinal toxicities were frequent but predominantly low-grade: diarrhea affected 70% (21/30; grade ≥3 3.3%) and nausea/vomiting 66.7% (20/30; grade ≥3 6.7%), both manageable through protocol-specified supportive measures.

Non-hematologic toxicities included transient liver function abnormalities (all-grade 63.3%, grade ≥3 6.7%) and cutaneous events (43.3% all-grade), none requiring treatment cessation. This tolerability profile positions the combination favorably against traditional chemotherapy-backboned HER2-targeted regimens, particularly for patients at risk of cumulative neurotoxicity or capecitabine-induced hand-foot syndrome.

Discussion

To our knowledge, this represents the first multicenter phase II trial investigating pyrotinib combined with eribulin in HER2-positive advanced breast cancer patients exhibiting primary trastuzumab resistance. The eribulin-pyrotinib combination exhibited clinically meaningful efficacy in this extensively pretreated HER2-positive advanced breast cancer

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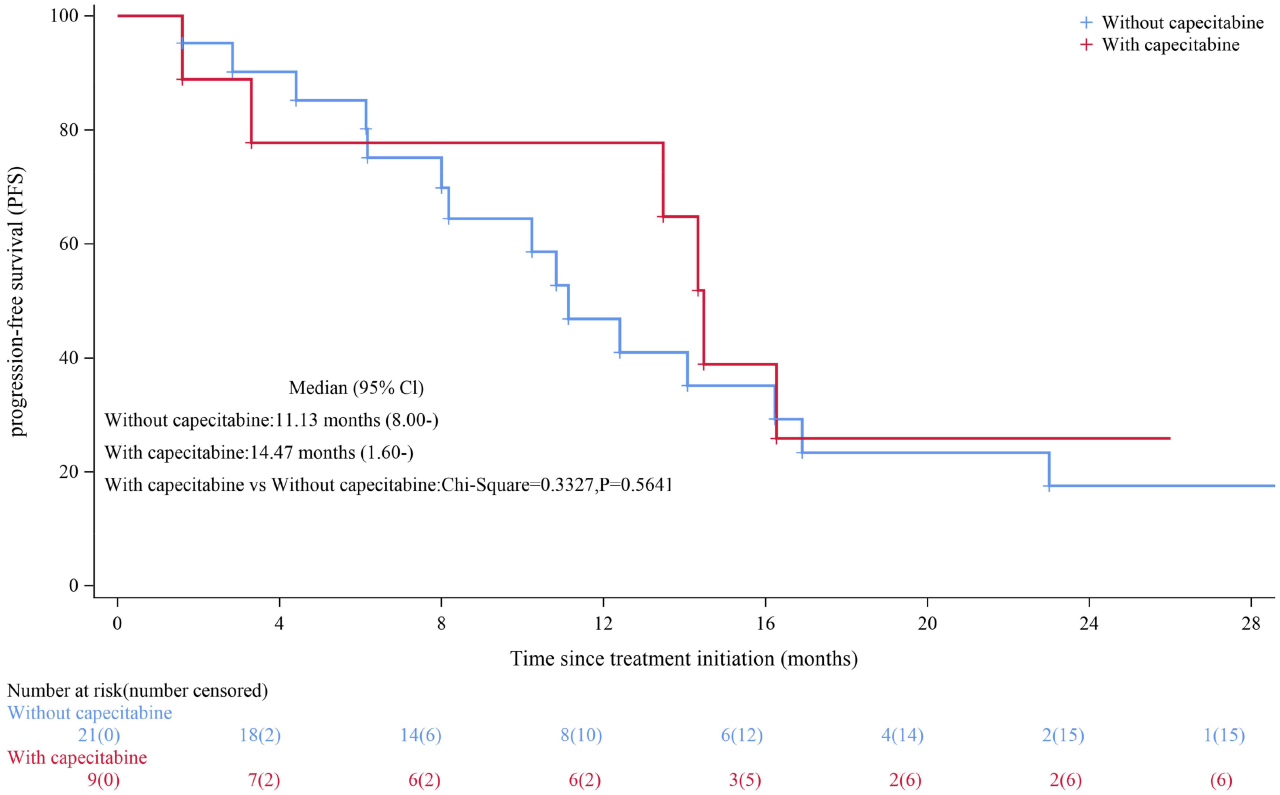

Figure 5 Kaplan–Meier survival curves depicting progression-free survival (PFS) in subgroups stratified by capecitabine use (n = 21 vs n = 9). With capecitabine: previously used capecitabine; Without capecitabine: previously had not used capecitabine.

cohort. Furthermore, the combination demonstrated favorable tolerability without emergent safety signals, maintaining toxicity profiles consistent with individual agent monotherapies.

Notably, patients with primary trastuzumab resistance remain underrepresented in pivotal phase III trials such as EMILIA (NCT00829166) and DESTINY-Breast03 (NCT03529110). Our outcomes compare favorably with contemporary second-line

Table 2 Treatment-Emergent Adverse Events

	Patients (n=30)	
	Grades 1–2	**Grades 3–4**
Any event	27(90.0%)	10(33.3%)
Neutropenia	22(73.3%)	5(16.7%)
Diarrhea	21(70%)	1(3.3%)
Nausea/Vomiting	20(66.7%)	2(6.7%)
Peripheral neuropathy	19(63.3%)	3(10%)
AST/ALT increased	13(43.3%)	4(13.3%)
Anorexia	10(33.3%)	0(0%)
Hypertriglyceridemia	7(23.3%)	0(0%)
Hypokalemia	6(20%)	0(0%)
Anemia	5(16.7%)	1(3.3%)
Blood bilirubin increased	4(13.3%)	0(0%)
Creatinine increased	3(10%)	0(0%)
Fatigue	3(10%)	0(0%)

(*Continued*)

Table 2 (Continued).

	Patients (n=30)	
	Grades 1–2	**Grades 3–4**
Weight loss	3(10%)	0(0%)
Stomatitis	2(6.7%)	0(0%)
Alkaline phosphatase increased	2(6.7%)	0(0%)
Hyperuricemia	2(6.7%)	0(0%)
Hypocalcemia	2(6.7%)	0(0%)
Hyponatremia	2(6.7%)	0(0%)
Hyperglycemia	1(3.3%)	0(0%)
Platelet count decreased	1(3.3%)	0(0%)
Lymphocyte count decreased	1(3.3%)	0(0%)
Hypophosphatemia	1(3.3%)	0(0%)
Hypomagnesemia	1(3.3%)	0(0%)
Cardiac disorders	1(3.3%)	0(0%)
Fever	1(3.3%)	0(0%)
Urinary tract infection	0(0%)	0(0%)
Proteinuria	0(0%)	0(0%)
Thrombosis	0(0%)	0(0%)
ECG QT corrected interval prolonged	0(0%)	0(0%)
Upper respiratory tract infection	0(0%)	0(0%)
Pneumonitis	0(0%)	0(0%)
Rash	0(0%)	0(0%)

Notes: Data are n (%). Grade 1–4 treatment-emergent adverse events are all reported. Each patient was counted once for the highest grade of each event experienced.

benchmarks including T-DM1 (median PFS 9.6 months in EMILIA trial) and trastuzumab deruxtecan (median PFS 28.8 months in DESTINY-Breast03).

The EMILIA trial established trastuzumab emtansine (T-DM1) superiority over lapatinib/capecitabine in taxane-pretreated patients (median PFS 9.6 vs 6.4 months; HR 0.65, 95% CI 0.55–0.77, P <.001; OS 30.9 vs 25.1 months; HR 0.68, P <.001).[9] Subsequent DESTINY-Breast03 demonstrated trastuzumab deruxtecan's (T-DXd) marked superiority over T-DM1 (median PFS 28.8 vs 6.8 months; HR 0.33, P <.0001).[24] Regional evidence from China's PHOEBE trial (NCT03080805) confirmed pyrotinib/capecitabine efficacy versus lapatinib-based therapy (median PFS 12.5 vs 6.8 months; HR 0.39, 95% CI 0.27–0.56).[18] Our regimen's efficacy can be considered alongside data from alternative approaches. For example, afatinib/vinorelbine in LUX-Breast1 had an ORR of 46.1% and a PFS of 5.5 months,[25] while pyrotinib/capecitabine in PICTURE showed a PFS of 11.8 months (95% CI 8.4–15.1),[26] and eribulin/trastuzumab in Italian cohorts had an ORR of 41.7% and a PFS of 5.4 months.[27] Our results demonstrated ORR (56.7%) and PFS (13.47 months), potentially attributable to synergistic microtubule stabilization (eribulin) and pan-HER kinase inhibition (pyrotinib) disrupting compensatory EGFR/HER3 dimerization in resistant clones.

Critical subgroup analysis revealed comparable efficacy regardless of prior capecitabine exposure (P=0.564), with maintained clinical benefit even in capecitabine-refractory patients transitioning to eribulin-based therapy. The safety profile aligned with known toxicity patterns,[18,25–28] featuring predominant hematologic toxicity (grade ≥3 neutropenia 16.7%) and manageable gastrointestinal events (grade ≥3 diarrhea 13.3%). Comparative analysis revealed advantageous safety features versus capecitabine-containing regimens, including lower rates of severe febrile neutropenia (3.3% vs historical 12–18%)18 and grade ≥3 peripheral neuropathy (10.0% vs 22–28%).[19] The regimen demonstrated notable improvement in diarrhea control, with grade ≥3 incidence reduced by 60% compared to the PHOEBE trial's pyrotinib-capecitabine cohort (13.3% vs 33.3%; p=0.02).[18] Protocol-guided prophylactic measures – incorporating pyrotinib dose de-escalation (400→320→240 mg) and preemptive antidiarrheal therapy – achieved superior toxicity management, manifesting as a 60% reduction in grade ≥3 diarrhea compared to PHOEBE trial.

This study has several limitations that warrant careful consideration. The single-arm design inherently introduces potential selection bias, compounded by the modest sample size (N=30) which reflects the challenges of recruiting adequate participants within this rare, treatment-refractory population. Furthermore, the exclusive enrollment of Chinese patients raises questions regarding generalizability across diverse ethnic groups, necessitating validation in multinational cohorts. Methodological constraints include the reliance on investigator-assessed endpoints without independent radiological review, potentially introducing detection bias in response evaluations. Additionally, while the 12-month overall survival rate reached 75.3%, the median overall survival remains undefined due to insufficient follow-up duration, requiring extended observation to fully characterize long-term outcomes. These limitations collectively underscore the preliminary nature of these findings and highlight critical directions for future confirmatory research.

Conclusions

The combination regimen of eribulin and pyrotinib demonstrated a safe and feasible option for second-line treatment in patients with HER2-positive advanced breast cancer. Notably, clinical benefit persists in the capecitabine pretreated population. However, the current evidence is limited to Phase II clinical trial data, necessitating further validation through expanded sample sizes and controlled studies.

Abbreviations

AE, Adverse event; AKT, Protein kinase B; CI, Confidence interval; CR, Complete response; DCR, Disease control rate; EGFR, Epidermal growth factor receptor; HER2, Human epidermal growth factor receptor 2; HER4, Human epidermal growth factor receptor 4; mTOR, Mammalian target of rapamycin; ORR, Objective response rate; OS, Overall survival; PFS, Progression-free survival; PI3K, Phosphatidylinositol 3-kinase; PR, Partial response; RECIST, Response Evaluation Criteria In Solid Tumors; TEAEs, Treatment-emergent adverse events; T-DM1, Trastuzumab emtansine; T-DXd, Trastuzumab deruxtecan; TKI, Tyrosine kinase inhibitor; ULN, Upper limit of normal.

Data Sharing Statement

The data utilized and/or examined in this study can be obtained from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The study was conducted strictly in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. Approval was obtained from the ethics committees of all participating centers including Breast Center of Fourth Hospital of Hebei Medical University; Department of Breast Surgery of Xingtai People's Hospital; Department of Breast Surgery of TangShan People's Hospital; Department of Oncology of Hebei Petrochina Central Hospital. Written informed consent was provided by each patient prior to participation. The clinical trial was registered at chictr.org.cn under the registration number ChiCTR2000038832.

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The abstract of this paper titled, "Eribulin plus yrotinib In trastuzumab-resistant HER2-positive advanced breast cancer: A single-arm, multicenter phase II trial (EPIC trial)" was presented at the 2025 ASCO Annual Meeting as a poster presentation with interim findings. The poster's abstract was published in Journal of Clinical Oncology at https://ascopubs.org/doi/10.1200/JCO.2025.43.16_suppl.1031.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; 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. Slamon DJ, Godolphin W, Jones LA. et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science*. 1989;244 (4905):707–712. doi:10.1126/science.2470152
2. Baselga J, Kim SB, Im SA, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med*. 2012;366(2):109–119. doi:10.1056/NEJMoa1113216
3. 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
4. Perez EA, Romond EH, Suman VJ, et al. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. *J Clin Oncol*. 2011;29(25):3366–3373. doi:10.1200/JCO.2011.35.0868
5. Perez EA, Romond EH, Suman VJ, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. *J Clin Oncol*. 2014;32(33):3744–3752. doi:10.1200/JCO.2014.55.5730
6. Cameron D, Piccart-Gebhart MJ, Gelber RD, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet*. 2017;389(10075):1195–1205. doi:10.1016/S0140-6736(16)32616-2
7. Piccart M, Procter M, Fumagalli D, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer in the APHINITY trial: 6 years' follow-up. *J Clin Oncol*. 2021;39(13):1448–1457. doi:10.1200/JCO.20.01204
8. Perez EA, Barrios C, Eiermann W, et al. Trastuzumab emtansine with or without pertuzumab versus trastuzumab plus taxane for human epidermal growth factor receptor 2-positive, advanced breast cancer: primary results from the phase III MARIANNE study. *J Clin Oncol*. 2017;35 (2):141–148. doi:10.1200/JCO.2016.67.4887
9. 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
10. Diéras V, Miles D, Verma S, et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017;18(6):732–742. doi:10.1016/S1470-2045(17)30312-1
11. Krop IE, Kim SB, Martin AG, et al. Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomised open-label phase 3 trial. *Lancet Oncol*. 2017;18 (6):743–754. doi:10.1016/S1470-2045(17)30313-3
12. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: breast cancer. Version 5.2020. Available from: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed July 15, 2020.
13. Cardoso F, Senkus E, Costa A, et al. 4th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 4). *Ann Oncol*. 2018;29 (8):1634–1657. doi:10.1093/annonc/mdy192
14. Giordano SH, Temin S, Davidson NE. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: ASCO clinical practice guideline update summary. *J Oncol Pract*. 2018;14(8):501–504. doi:10.1200/JOP.18.00290
15. Li J, Jiang Z. CSCO BC guideline: updates for HER2 positive breast cancer in 2020. *Transl Breast Cancer Res*. 2020;1:4. doi:10.21037/tbcr.2020.03.05
16. Ma F, Ouyang Q, Li W, et al. Pyrotinib or lapatinib combined with capecitabine in HER2-positive metastatic breast cancer with prior taxanes, anthracyclines, and/or trastuzumab: a randomized, phase II study. *J Clin Oncol*. 2019;37(29):2610–2619. doi:10.1200/JCO.19.00108
17. Gourd E. Pyrotinib versus lapatinib in HER2-positive breast cancer. *Lancet Oncol*. 2019;20(10):e562. doi:10.1016/S1470-2045(19)30568-6
18. Xu B, Yan M, Ma F, et al. Pyrotinib plus capecitabine versus lapatinib plus capecitabine for the treatment of HER2-positive metastatic breast cancer (PHOEBE): a multicentre, open-label, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2021;22(3):351–360. doi:10.1016/S1470-2045(20)30702-6
19. Smith JA, Wilson L, Azarenko O, et al. Eribulin binds at microtubule ends to a single site on tubulin to suppress dynamic instability. *Biochemistry*. 2010;49(6):1331. doi:10.1021/bi901810u
20. Cortes J, Loesch D, Blum JL, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet*. 2011;377(9769):914–923. doi:10.1016/S0140-6736(11)60070-6
21. Yamashita T, Masuda N, Saji S, et al. Trastuzumab, pertuzumab, and eribulin mesylate versus trastuzumab, pertuzumab, and a taxane as a first-line or second-line treatment for HER2-positive, locally advanced or metastatic breast cancer: study protocol for a randomized controlled, non-inferiority, phase III trial in Japan (JBCRG-M06/EMERALD). *Trials*. 2020;21(1):391. doi:10.1186/s13063-020-04341-y
22. Yamashita T, Saji S, Takano T, et al. Trastuzumab and pertuzumab in combination with eribulin mesylate or a taxane as first-line chemotherapeutic treatment for HER2-positive, locally advanced or metastatic breast cancer: results of a multicenter, randomized, non-inferiority phase 3 trial in Japan (JBCRG-M06/EMERALD). *J Clin Oncol*. 2024;42.

23. Yuan P, Hu X, Sun T, et al. Eribulin mesilate versus vinorelbine in women with locally recurrent or metastatic breast cancer: a randomised clinical trial. *Eur J Cancer*. 2019;112:57–65. doi:10.1016/j.ejca.2019.02.002
24. Hurvitz SA, Hegg R, Chung W-P, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. *Lancet*. 2023;401(10371):105–117. doi:10.1016/S0140-6736(22)02420-5
25. Harbeck N, Huang C-S, Yeh D-C, et al. Afatinib plus vinorelbine versus trastuzumab plus vinorelbine in patients with HER2-overexpressing metastatic breast cancer who had progressed on one previous trastuzumab treatment (LUX-Breast 1): an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2016;17(3):357–366. doi:10.1016/S1470-2045(15)00540-9
26. Lutrino ES, Orlando L, Febbraro A, et al. Eribulin plus trastuzumab in pretreated HER2-positive advanced breast cancer patients: safety and efficacy. *Tumori*. 2020;106(4):301–305. doi:10.1177/0300891619887225
27. Cao J, Teng Y, Li H, 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):300. doi:10.1186/s12916-023-02999-0
28. Sarici F, Altundag K. Efficacy and safety evaluation of eribulin-trastuzumab combination therapy with heavily pretreated HER2-positive metastatic breast cancer. *J BUON*. 2020;25(6):2562–2569.