

ORIGINAL RESEARCH ARTICLE

Comparative efficacy and safety of Zerceptac[®] plus pyrotinib versus Zerceptac[®] plus pertuzumab in combination with chemotherapy as neoadjuvant therapy for HER2-positive breast cancer: A retrospective study

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Abstract

Introduction: HER2-positive breast cancer needs better neoadjuvant options. Pyrotinib (Py) with trastuzumab biosimilar may offer an alternative to dual blockade. Objective: This study analyzed the short-term efficacy and safety of Zerceptac[®], a trastuzumab biosimilar, combined with either Py or pertuzumab and chemotherapy in neoadjuvant therapy for HER2-positive breast cancer. It also compared the efficacy and safety of Zerceptac[®]-pyrotinib-chemotherapy versus Zerceptac[®]-pertuzumab-chemotherapy regimens.

Methods: Clinical data from 62 HER2-positive breast cancer patients who underwent neoadjuvant therapy with Zerceptac[®] combined with Py or pertuzumab and chemotherapy at Anhui Cancer Hospital (February 2021 to December 2023) were retrospectively analyzed. Efficacy and safety were compared among TCbHP (29 cases), TCbHPy (8 cases), THP (9 cases), and TCbH (16 cases) groups. Statistical methods were used to identify factors influencing total pathological complete response (tpCR).

Results: Among the 62 patients, 45 (72.6%) had invasive breast cancer, 11 (17.7%) had invasive carcinomas with intraductal components, five (8.1%) had invasive carcinomas with ductal carcinoma *in situ*, and one (1.6%) had invasive carcinoma with mucinous features. Age and advanced clinical stage were independent risk factors for tpCR ($p < 0.001$). The TCbHPy group showed comparable efficacy to TCbHP ($p = 0.25$). Alopecia (91.9%) was the most common adverse event. Diarrhea incidence was significantly higher in TCbHPy than in TCbHP ($p < 0.001$); however, no grade 4 diarrhea occurred, and triple antidiarrheal therapy reduced its severity to grade 1.

Conclusion: Zerceptac[®] is effective and safe in neoadjuvant therapy for HER2-positive breast cancer. Py (≥ 400 mg) may improve tpCR rates, with diarrhea as the main adverse effect. TCbHPy regimen demonstrated non-inferior efficacy to TCbHP.

Keywords: Zerceptac[®]; Trastuzumab; Pertuzumab; Pyrotinib; HER2-positive breast cancer; Neoadjuvant therapy; Pathological complete response; Adverse events

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1. Introduction

Breast cancer is the most common malignancy among women and ranks first in the incidence rate of female malignant tumors. The incidence and mortality rates of breast cancer have been increasing year by year, posing a serious threat to women's physical and mental health.¹ Human epidermal growth factor receptor 2 (HER2)-positive breast cancer accounts for approximately 20 – 30% of all breast cancer cases. HER2-positive breast cancer is characterized by strong invasiveness and poor prognosis. Over two decades ago, HER2-positive breast cancer had the highest recurrence rate and the worst prognosis among all subtypes. However, the advent of trastuzumab – a humanized monoclonal antibody and the first anti-HER2 targeted drug – in 1998 significantly improved outcomes for patients with this disease. In recent years, an increasing number of new targeted therapies have been approved, further enhancing the survival and prognosis of HER2-positive patients. Present data indicate that the survival rate of patients with early-stage HER2-positive breast cancer receiving chemotherapy and dual antibody therapy exceeds 90%.² Neoadjuvant therapy, an important treatment modality for HER2-positive breast cancer, not only facilitates tumor shrinkage, downstaging, and increased rates of breast-conserving surgery, but also provides pivotal evidence for optimizing subsequent adjuvant treatment strategies.

Trastuzumab is the first-line treatment for HER2-positive breast cancer, but it is relatively expensive, making it difficult for some patients to afford. With the expiration of the Herceptin patent, attention has shifted toward the development of more affordable biosimilars. The European Medicines Agency defines a biosimilar as a biological product that is highly similar to an existing reference product, with no clinically meaningful differences in terms of efficacy and safety.³ Safety mainly refers to the clinical safety of subjects or patients. Therefore, in addition to demonstrating similarity in structure, purity, and biological activity, biosimilars must undergo clinical trials to confirm their efficacy and safety. Biosimilars also occupy a place in clinical applications due to their unique cost advantage. In 2020, the “Expert Consensus on Biosimilars” issued in China pointed out that biosimilars are not the same as generic drugs. The main clinical data requirements for generic drugs are pharmacokinetics and bioequivalence, while biosimilars must also conduct safety and efficacy studies on this basis and support the equivalence of efficacy and safety between biosimilars and reference drugs, allowing them to be used clinically as substitutes for reference drugs.⁴ Zercepac® (HLX02) is a domestically developed trastuzumab biosimilar approved for clinical use

by the National Medical Products Administration in 2020. In a global phase III clinical study, patients with HER2-positive advanced (recurrent or metastatic) breast cancer treated with Zercepac® in combination with docetaxel had an objective response rate (ORR) at week 24 similar to that of the control group receiving trastuzumab plus docetaxel, indicating comparable efficacy. In addition, the safety study results showed no statistically significant difference in the incidence of adverse events between the two drugs.⁵ An American expert panel stated that biosimilars and reference products could be considered equally efficacious for the purpose of inclusion in the American Society of Clinical Oncology clinical practice guidelines, recommending that individual institutions review approved biosimilars with their appropriate drug committees before implementation on their formularies.⁶ Zercepac® has also been approved by the China Food and Drug Administration for the neoadjuvant treatment of breast cancer.

Trastuzumab, a HER2-targeted monoclonal antibody, has been proven to significantly improve the survival outcomes of patients with HER2-positive breast cancer when used in combination with other chemotherapy drugs. However, after more than 20 years of use, many patients have developed resistance, leading to recurrence and metastasis. To address these clinical challenges and improve the prognosis of patients with HER2-positive breast cancer, new HER2-targeted drugs, specifically small molecule tyrosine kinase inhibitors (TKIs), have emerged. Pyrotinib (Py) is an irreversible pan-HER small molecule TKI that acts simultaneously on HER1, HER2, and HER4. Results from the phase III PHEDRA⁷ study confirmed that the Py + trastuzumab + docetaxel regimen significantly increased the pathological complete response (pCR) rate in patients with HER2-positive breast cancer during neoadjuvant treatment. Based on this study, Py was approved in 2022 for the neoadjuvant treatment of HER2-positive breast cancer. However, there are few reports on the efficacy and adverse events of Zercepac® in combination with Py or pertuzumab and chemotherapy in neoadjuvant chemotherapy (NAT) for HER2-positive breast cancer. This study retrospectively analyzed the clinical and pathological data of 62 patients with HER2-positive breast cancer who received Zercepac® in combination with Py or Zercepac® in combination with pertuzumab and chemotherapy as a NAT regimen, and who subsequently underwent surgery. The efficacy and adverse reactions were observed and recorded, and the factors affecting the pCR rate were analyzed, with the aim of providing references for clinical treatment.

2. Materials and methods

2.1. Study population

A retrospective analysis was performed on clinical data from 62 patients with HER2-positive breast cancer who received neoadjuvant therapy (Zercepac® combined with Py or pertuzumab and chemotherapy), followed by surgical resection at the Breast Diagnosis and Treatment Center of Anhui Cancer Hospital between February 2021 and December 2023.

- (i) Inclusion criteria: Only patients with previously untreated HER2-positive breast cancer were included (excluding those who had received radiotherapy or targeted therapy before neoadjuvant treatment);
- (ii) Exclusion criteria: Patients who received fewer than six treatment cycles ($n=3$) or experienced surgical delays exceeding 4 weeks ($n=2$) were excluded;
- (iii) Grouping basis: Treatment regimens were determined by a multidisciplinary team based on guideline recommendations and were not selected by the patients.

2.2. Neoadjuvant treatment regimens and surgical approaches

2.2.1. Neoadjuvant Therapy protocols

Treatment regimens and dosages were administered in accordance with institutional guidelines and the drug manufacturer's specifications. The NAT regimens included:

- (i) TCbHP (29 cases): Docetaxel + carboplatin + trastuzumab (H) + pertuzumab (P)
- (ii) TCbHPy (eight cases): Docetaxel + carboplatin + trastuzumab (H) + Py
- (iii) THP (nine cases): Docetaxel + trastuzumab (H) + pertuzumab (P)
- (iv) TCbH (16 cases): Docetaxel + carboplatin + trastuzumab (H)

All patients received six treatment cycles at 21-day intervals.

2.2.2. Drug administration details

- Docetaxel (Qilu Pharmaceutical, China): 75 mg/m² (all patients).
- Carboplatin (Qilu Pharmaceutical, China): 400 – 500 mg/m² (53 patients).
- Anti-HER2 agents:
- Zercepac® (S20200019, Shanghai Fosun Pharma, China): Initial dose 8 mg/kg, reduced to 6 mg/kg in subsequent cycles (all patients).
- Pertuzumab (S20180029, Shanghai Roche, China): Initial dose 840 mg, adjusted to 420 mg after the loading dose (38 patients).

- Py (Jiangsu Hengrui, China): 400 mg orally once daily (eight patients).

2.2.3. Monitoring and supportive care

- (i) Tumor response was assessed through ultrasound at each cycle, with supplemental breast magnetic resonance imaging conducted at baseline and before surgery.
- (ii) Pretreatment laboratory tests (complete blood count, hepatic/renal function, electrolytes) were mandatory before each treatment cycle. Chemotherapy was administered only if no contraindications were identified.
- (iii) Granulocyte colony-stimulating factor was administered according to the National Comprehensive Cancer Network guidelines for hematologic support.
- (iv) Surgery was performed 14 days after completion of neoadjuvant therapy, followed by 1 year of adjuvant-targeted therapy.
- (v) Left ventricular ejection fraction (LVEF) was measured before initiating Zercepac® (HLX02) treatment and monitored regularly during therapy. Zercepac® (HLX02) treatment was discontinued for at least 4 weeks under the following conditions, with LVEF re-evaluated every 4 weeks:
 - (a) If the absolute value of LVEF decreased by $\geq 16\%$ from baseline. If LVEF returned to the normal range or the decrease was $\leq 15\%$ within 4 – 8 weeks, Zercepac® (HLX02) could be resumed.
 - (b) The use of Zercepac® (HLX02) should be stopped permanently if LVEF continued to decline for more than 8 weeks, or if treatment was interrupted more than 3 times due to cardiotoxicity.
- (vi) During Zercepac® (HLX02) treatment, LVEF was assessed every 3 months and again at the end of the therapy. Following completion of treatment, LVEF was monitored every 6 months for at least 2 years.

2.2.4. Py-specific diarrhea prophylaxis

Patients receiving Py were administered triple antidiarrheal therapy:

- (i) Bifidobacterium: One sachet 3 times daily.
- (ii) Montmorillonite powder: One sachet 3 times daily.
- (iii) Loperamide: Two tablets as needed (maximum six tablets per day).

2.3. Efficacy evaluation

Clinical efficacy was assessed according to Response Evaluation Criteria in Solid Tumors, version 1.1.⁸ Pathological response post-neoadjuvant therapy was evaluated using the Miller–Payne (MP) grading system,⁹ which categorizes tumor regression based on histological examination of surgical specimens.

2.4. Safety assessment

Adverse events were evaluated according to the World Health Organization Toxicity Grading Scale. The following parameters were assessed:

- (i) Laboratory parameters: Complete blood count, hepatic/renal function, and electrolyte profiles.
- (ii) Cardiac monitoring: Electrocardiogram (ECG) and echocardiogram (performed quarterly).
- (iii) Clinical symptoms: Alopecia, nausea/vomiting, diarrhea, abdominal pain, and arthralgia.

Notably, no significant LVEF decline (>10%) or cardiac dysfunction was observed. Cardiac events were defined as:

- (i) ST-T segment abnormalities.
- (ii) Clockwise/counterclockwise rotation on ECG.
- (iii) Premature atrial/ventricular contractions.
- (iv) Sinus arrhythmia.
- (v) Conduction block.
- (vi) Low QRS voltage.
- (vii) Left axis deviation.
- (viii) Left ventricular hypertrophy.

2.5. Statistical analysis

Data were analyzed using SPSS 26.0 (IBM Corp., United States). Categorical variables were compared using the chi-square test or Fisher's exact test. Binary logistic regression was used to identify independent clinicopathological predictors of neoadjuvant therapy efficacy. A two-tailed p -value <0.05 was considered statistically significant.

3. Results

3.1. Baseline clinicopathological characteristics

The study cohort comprised 62 patients with HER2-positive breast cancer, classified into the following histopathological subtypes:

- (i) Invasive ductal carcinoma: 45 cases (72.6%).
- (ii) Invasive carcinoma with intraductal component: 11 cases (17.7%).
- (iii) Invasive carcinoma with ductal carcinoma *in situ*: Five cases (8.1%).
- (iv) Invasive carcinoma with mucinous features: One case (1.6%).

Detailed baseline characteristics are presented in [Table 1](#).

3.2. Predictors of pCR

Univariate logistic regression analysis identified age, tumor-node-metastasis (TNM) stage, and hormone receptor (HR) status as independent predictors of total pCR (tpCR) ([Table 2](#)).

3.3. Multivariate predictors of pCR

Multivariate logistic regression analysis demonstrated that both age and TNM stage independently influenced the likelihood of achieving tpCR:

- (i) Patients aged >50 years had 3.82 times higher odds of achieving tpCR compared to those aged ≤50 years (95% confidence interval [CI]: 1.104 – 13.225, $p=0.034$).
- (ii) Conversely, patients with advanced-stage (cTNM IIb – IIIc) showed a 91.2% reduction in the odds of achieving tpCR compared to those with stage IIa disease (odds ratio [OR] = 0.088, 95% CI: 0.023 – 0.338, $p<0.001$) ([Table 3](#)).

3.4. Univariate predictors of pCR

Univariate analysis based on post-operative pathological assessment identified five significant predictors of tpCR achievement:

- (i) Advanced age (>50 years).
- (ii) Clinical nodal involvement (cN ≥1).
- (iii) Advanced TNM stage (IIb – IIIc).
- (iv) Hormone receptor-negative status.
- (v) Non-use of dual-target therapy.

Detailed comparisons between tpCR and non-tpCR groups are presented in [Table 4](#).

3.5. Adverse events

Treatment-related adverse events occurred in over 40% of patients, with the most frequent being alopecia (91.7%), followed by nausea (48.4%), diarrhea (41.9%), and fatigue (35.5%). Cardiovascular events, though generally mild, included arrhythmias (19.4%), T-wave abnormalities (12.9%), and transient LVEF fluctuations (a >10% change in 6.5% of cases). Notably, no symptomatic heart failure or grade ≥3 cardiac events were observed ([Table 5](#)).

3.6. Comparative analysis of TCbHP versus TCbHPy regimens

3.6.1. Efficacy outcomes

No statistically significant differences were observed between the TCbHP and TCbHPy regimens ([Table 6](#)) in terms of:

- (i) tpCR rate (55.2% versus 37.5%, $p=0.25$).
- (ii) Magnitude of Ki-67 index reduction ($p=0.67$).
- (iii) Miller–Payne pathological regression grading ($p=0.07$).

3.6.2. Safety profile

While both regimens demonstrated comparable toxicity profiles ([Table 6](#)), the incidence of diarrhea differed markedly:

- (i) TCbHPy group: 100% (8/8).
- (ii) TCbHP group: 3.4% (1/29) ($p<0.001$).

Table 1. Baseline characteristics

Variable	Chemotherapy regimen				p
	TCbH	TCbHP	TCbHPy	THP	
BMI (kg/m ² ; mean±standard deviation)	24.96±2.99	23.99±2.89	24.12±2.82	24.41±3.69	0.776
Age (years)					
≤50	5 (31.3)	14 (48.3)	2 (25)	4 (44.4)	0.575
>50	11 (68.8)	15 (51.7)	6 (75)	5 (55.6)	
cT					
1	0 (0)	1 (3.4)	0 (0)	0 (0)	0.773
2	13 (81.3)	22 (75.9)	7 (87.5)	9 (100)	
3	3 (18.8)	6 (20.7)	1 (12.5)	0 (0)	
cN					
0	11 (68.8)	21 (72.4)	3 (37.5)	8 (88.9)	0.072
1	2 (12.5)	7 (24.1)	4 (50)	0 (0)	
2	2 (12.5)	0 (0)	1 (12.5)	1 (11.1)	
3	1 (6.3)	1 (3.4)	0 (0)	0 (0)	
cTNM					
IIa	9 (56.3)	19 (65.5)	3 (37.5)	8 (88.9)	0.231
IIb	4 (25)	8 (27.6)	4 (50)	0 (0)	
IIIa	2 (12.5)	1 (3.4)	1 (12.5)	1 (11.1)	
IIIb	0 (0)	1 (3.4)	0 (0)	0 (0)	
IIIc	1 (6.3)	0 (0)	0 (0)	0 (0)	
Histological grade					
II	13 (81.3)	28 (96.6)	7 (87.5)	7 (87.5)	0.265
III	3 (18.8)	1 (3.4)	1 (12.5)	1 (12.5)	
HR					
Negative	12 (75)	19 (65.5)	6 (75)	3 (33.3)	0.196
Positive	4 (25)	10 (34.5)	2 (25)	6 (66.7)	
Menstrual status					
Pre-menopausal	5 (31.3)	11 (39.3)	2 (25)	4 (44.4)	0.823
Post-menopausal	11 (68.8)	17 (60.7)	6 (75)	5 (55.6)	
BNAT Ki-67					
≤20%	2 (12.5)	3 (10.3)	0 (0)	2 (22.2)	0.609
>20%	14 (87.5)	26 (89.7)	8 (100)	7 (77.8)	

Notes: Data are presented as n (%), unless otherwise specified; Body mass index (BMI) was categorized according to Chinese adult standards¹⁷:

Normal: 18.5 – 23.9 kg/m²; Overweight: 24.0 – 26.9 kg/m²; Obese: ≥27.0 kg/m².

Abbreviations: BNAT: Baseline assessment before neoadjuvant chemotherapy; cN: Clinical lymph node staging (American Joint Committee on Cancer [AJCC] 8th edition); cT: Clinical tumor size staging (AJCC 8th edition); cTNM: Tumor-node-metastasis classification stage; HR: Hormone receptor; Ki-67: Antigen Kiel 67; TCbH: Docetaxel + carboplatin + trastuzumab; TCbHP: Docetaxel + carboplatin + trastuzumab + pertuzumab; TCbHPy: Docetaxel+carboplatin + trastuzumab + pyrotinib; THP: Docetaxel + trastuzumab + pertuzumab.

4. Discussion

Breast cancer has entered the era of precision treatment, with clinical strategies tailored to individual patients based on different molecular subtypes.¹⁰ In the past, HER2-positive breast cancer was associated with the poorest prognosis. However, the advent of the anti-

HER2 targeted drug trastuzumab significantly improved outcomes for patients with this subtype, marking a milestone in its treatment. The neoadjuvant treatment combining trastuzumab (H) and pertuzumab (P) has further transformed the prognosis for HER2-positive breast cancer. The dual-target regimen not only increases the tpCR rate but also improves survival.¹¹ The large-

Table 2. Univariate logistic regression analysis of factors associated with total pathological complete response

Variable	Univariate logistic regression		
	OR	95% CI	p
Age (years)			
≤50	Ref	-	0.022
>50	3.491	1.196 – 10.190	
cT			
1 – 2	Ref	-	0.492
3	0.617	0.156 – 2.447	
cN			
0	Ref	-	0.001
1 – 3	0.100	0.025 – 0.401	
cTNM			
Ia	Ref	-	<0.001
Ib – IIIc	0.094	0.026 – 0.335	
Histological grade			
II	Ref	-	0.128
III	0.179	0.020 – 1.637	
HR			
Negative	Ref	-	0.037
Positive	0.311	0.104 – 0.933	
Menstrual status			
Pre-menstrual	Ref	-	0.093
Post-menstrual	2.516	0.856 – 7.392	
BNAT Ki-67			
≤20%	Ref	-	0.689
>20%	1.383	0.283-6.764	

Abbreviations: BNAT: Baseline assessment before neoadjuvant chemotherapy; CI: Confidence interval; cN: Clinical lymph node staging (American Joint Committee on Cancer [AJCC] 8th edition); cT: Clinical tumor size staging (AJCC 8th edition); cTNM: Tumor-node-metastasis classification stage; HR: Hormone receptor; Ki-67: Antigen Kiel 67; OR: Odds ratio; Ref: Reference.

scale KRISTINE¹² study compared six cycles of TCbHP (docetaxel, carboplatin, trastuzumab, and pertuzumab) with ado-trastuzumab emtansine plus neoadjuvant treatment. The tpCR rate in the TCbHP group was 55.7% (123/221), superior to the 44.4% (99/223) observed in the control group, thus validating both the efficacy and safety of the TCbHP regimen. In our study, the overall tpCR rate among all patients was 50% (31/62). The highest tpCR rate was 55.2% (16/29), observed in the group treated with Zercepac® (a trastuzumab biosimilar) plus pertuzumab in combination with six cycles of docetaxel carboplatin (TCb)

Table 3. Multivariate logistic regression analysis of total pathological complete response predictors

Variable	Multivariate logistic regression		
	Adjusted OR	95% CI	p
Model 1: Full input method N=62			
Age (years)			
≤50	Ref	-	0.999
>50	≈ 0	0 – 0	
cN			
0	Ref	-	0.962
1 – 3	1.067	0.073 – 15.678	
cTNM			
Ia	Ref	-	0.074
Ib – IIIc	0.105	0.009 – 1.247	
HR			
Negative	Ref	-	0.134
Positive	0.373	0.102 – 1.356	
Menstrual status			
Pre-menstrual	Ref	-	0.999
Post-menstrual	≈0	0 – 0	
Model 2: Backward screening method N=62			
Age (years)			
≤50	Ref	-	0.034
>50	3.820	1.104 – 13.225	
cTNM			
Ia	Ref	-	<0.001
Ib – IIIc	0.088	0.023 – 0.338	

Abbreviations: CI: Confidence interval; cN: Clinical lymph node staging (American Joint Committee on Cancer 8th edition); cTNM: Tumor-node-metastasis classification stage; HR: Hormone receptor; Ki-67: Antigen Kiel 67; OR: Odds ratio; Ref: Reference.

chemotherapy, consistent with the aforementioned studies. This suggests that the efficacy of Zercepac® in treating HER2-positive breast cancer is essentially equivalent to that of Herceptin. Previous studies^{5,13} have also confirmed that neoadjuvant treatment combining Zercepac® or Herceptin with pertuzumab and chemotherapy yields comparable efficacy and safety profiles. Moreover, a model-based economic evaluation in China in 2022 showed that Zercepac® is more cost-effective than Herceptin, making it more accessible to patients and aligning with financial constraints in healthcare.¹⁴

In addition to these advantages, Zercepac® offers other benefits. Notably, it does not contain benzyl alcohol as a preservative, while the 440 mg formulation of Herceptin available in China still does. Studies have shown that benzyl alcohol may reduce the efficacy of protein-based drugs and

Table 4. Univariate analysis of clinicopathological factors associated with total pathological complete response (tpCR)

Variable	tpCR (n=31)	Non-tpCR (n=31)	<i>p</i>
BMI (kg/m ² ; mean±standard deviation)	24.31±2.75	24.32±3.24	0.987
Age (years)			
≤50	8 (25.8)	17 (54.8)	0.020
>50	23 (74.2)	14 (45.2)	
cT			
1 – 2	27 (87.1)	25 (80.6)	0.490
3	4 (12.9)	6 (19.4)	
cN			
0	28 (90.3)	15 (48.4)	<0.001
1 – 3	3 (9.7)	16 (51.6)	
cTNM			
IIa	27 (87.1)	12 (38.7)	<0.001
IIb – IIIc	4 (12.9)	19 (61.3)	
Histological grade			
II	29 (96.7)	26 (83.9)	0.195
III	1 (3.3)	5 (16.1)	
HR			
Negative	24 (77.4)	16 (51.6)	0.034
Positive	7 (22.6)	15 (48.4)	
Menstrual status			
Pre-menstrual	8 (25.8)	14 (46.7)	0.090
Post-menstrual	23 (74.2)	16 (53.3)	
BNAT Ki-67			
≤20%	3 (9.7)	4 (12.9)	0.999
>20%	28 (90.3)	27 (87.1)	
Chemotherapy regimen			
TCbH	8 (25.8)	8 (25.8)	0.820
TCbHP	16 (51.6)	13 (41.9)	
TCbHPy	3 (9.7)	5 (16.1)	
THP	4 (12.9)	5 (16.1)	

Note: Data are presented as n (%), unless otherwise specified.

Abbreviations: BMI: Body mass index; BNAT: Baseline assessment before neoadjuvant chemotherapy; cN: Clinical lymph node staging (American Joint Committee on Cancer [AJCC] 8th edition); cT: Clinical tumor size staging (AJCC 8th edition); cTNM: Tumor-node-metastasis classification stage; HR: Hormone receptor; Ki-67: Antigen Kiel 67; TCbH: Docetaxel + carboplatin+trastuzumab; TCbHP: Docetaxel+carboplatin+trastuzumab+pertuzumab; TCbHPy: Docetaxel+carboplatin+trastuzumab+pyrotinib; THP: Docetaxel+trastuzumab+pertuzumab.

pose additional health risks to patients.¹⁵ In August 2022, Fosun Pharma launched a 60 mg formulation of Zerceptac®, while the original trastuzumab and five other biosimilars currently do not offer this dosage. The availability of both 150 mg and 60 mg formulations of Zerceptac® allows for flexible dosing, reduces drug wastage and storage risks, and further lowers costs for patients and health insurance systems.

In summary, given the comparable efficacy and safety of neoadjuvant treatment combining Zerceptac® and

pertuzumab with chemotherapy to that of Herceptin-based regimens, along with Zerceptac®'s cost advantages, this study supports the clinical application of Zerceptac® plus pertuzumab in the neoadjuvant treatment of HER2-positive breast cancer.

Py exerts its anti-tumor effects by targeting the intracellular domains of HER-1, HER-2, and HER-4 in tumor cells.¹⁶ The exploration of combining monoclonal antibodies with small molecule TKIs in the neoadjuvant treatment of HER2-positive breast cancer has been

Table 5. Treatment-related adverse events by regimen

Regimen	TCbH (n=16)	TCbHP (n=29)	TCbHPy (n=8)	THP (n=9)	χ^2	p
Adverse cardiac events (n [%])						
ST-segment changes	3 (18.75%)	1 (3.45%)	1 (12.50%)	0 (0%)	4.30	0.23
Clockwise or counterclockwise rotation	2 (12.50%)	3 (10.34%)	0 (0%)	0 (0%)	2.12	0.55
Premature atrial/ventricular contractions	1 (6.25%)	2 (25.00%)	0 (0%)	2 (22.22%)	8.14	0.04
Sinus arrhythmia ^a	2 (12.50%)	5 (17.24%)	0 (0%)	0 (0%)	3.21	0.36
Conduction block	3 (18.75%)	0 (0%)	0 (0%)	0 (0%)	9.06	0.03
Low QRS voltage	1 (6.25%)	1 (3.45%)	0 (0%)	0 (0%)	1.04	0.79
Left axis deviation	0 (0%)	0 (0%)	1 (12.50%)	1 (11.11%)	5.50	0.14
Left ventricular hypertrophy	2 (12.50%)	1 (3.45%)	0 (0%)	0 (0%)	3.03	0.39
Adverse reactions (n [%])						
Alopecia	15 (93.75%)	25 (86.21%)	8 (100%)	9 (100%)	2.85	0.42
Nausea	5 (31.25%)	17 (58.62%)	3 (37.50%)	5 (55.56%)	3.66	0.30
Diarrhea	0 (0%)	1 (3.45%)	8 (100%)	1 (11.11%)	48.29	< 0.001
Abdominal pain	1 (6.25%)	4 (13.80%)	0 (0%)	0 (0%)	2.85	0.42
Low white blood cell count	1 (6.25%)	5 (17.24%)	2 (25.00%)	0 (0%)	3.49	0.32
Low hemoglobin	5 (31.25%)	2 (6.90%)	0 (0%)	0 (0%)	9.09	0.03
Low platelet count	3 (18.75%)	5 (17.24%)	0 (0%)	0 (0%)	3.49	0.32
Abnormal liver function	3 (18.75%)	9 (31.03%)	1 (12.50%)	1 (11.11%)	2.46	0.48
Arthralgia	2 (12.50%)	3 (10.34%)	0 (0%)	1 (11.11%)	1.04	0.79
Anemia	2 (12.50%)	14 (48.28%)	3 (37.50%)	3 (33.33%)	5.80	0.12

Notes: ^aSinus arrhythmia refers to irregular heart rhythm or tachycardia. Data are presented as n (%). Statistical method: Chi-square test.

Abbreviations: TCbH: Docetaxel + carboplatin + trastuzumab; TCbHP: Docetaxel + carboplatin + trastuzumab + pertuzumab; TCbHPy: Docetaxel + carboplatin + trastuzumab + pyrotinib; THP: Docetaxel + trastuzumab + pertuzumab.

ongoing. As early as 2020, Xuhong *et al.*¹⁷ conducted a phase II clinical trial involving 19 patients, reporting a tpCR rate of 73.7% for Py combined with the EC-TH (epirubicin/cyclophosphamide followed by docetaxel/trastuzumab) regimen in the neoadjuvant treatment of HER2-positive locally advanced breast cancer. The main adverse reactions were diarrhea and leukopenia. Mao *et al.*¹⁸ found that among 97 patients treated with Py-based neoadjuvant therapy, the tpCR rate was 48.5%. The incidence of grade 3 or higher adverse reactions was 35.1%, with diarrhea being the most common, occurring in 63.9% of patients. A real-world study by Fu *et al.*¹⁹ reported a tpCR rate of 44.7% in the trastuzumab + Py group. The lower rate compared to the first prospective cohort study, and its similarity to the retrospective cohort study, may be attributed to dose reductions or treatment discontinuation caused by grade 3 or higher adverse reactions. The study further confirmed that there was a statistically significant difference in tpCR rates based on Py dose reductions and the occurrence of grade 3 or higher adverse reactions in the trastuzumab + Py group. In addition, patient compliance was lower in real-world settings than in strictly controlled clinical studies; some patients reduced or discontinued medication in

response to adverse reactions such as diarrhea, thus affecting treatment efficacy. In a study involving 267 patients with advanced HER2-positive breast cancer, the PHOEBE²⁰ trial confirmed that the median progression-free survival (PFS) was significantly longer in the Py group compared to the lapatinib group (median PFS: 12.5 months versus 6.8 months; hazard ratio [HR] = 0.39, $p < 0.001$). The ORR was also higher in the Py group than in the lapatinib group (67.2% versus 51.5%, $p = 0.016$), with the median duration of the response being 11.1 months versus 7.0 months, respectively. Subgroup analysis revealed that among patients with brain metastases, PFS remained significantly prolonged in the Py group (HR = 0.32). In addition, the Phase II PERMEATE²¹ study, which targeted patients with asymptomatic brain metastases, confirmed that Py could effectively cross the blood-brain barrier, achieving an ORR of 74.6% and improving the prognosis of patients with brain metastases from HER2-positive breast cancer.

In our study, the tpCR rate for the trastuzumab + Py group combined with six cycles of Tcb chemotherapy was 37.5% (3/8), which was lower than the rates reported in the aforementioned prospective and real-world studies.

Table 6. Comparison of efficacy and adverse reactions between TCbHP and TCbHPy regimens

Regimen	TCbHP (n=29)	TCbHPy (n=8)	χ^2	<i>p</i>
Efficacy (n)			4.06	0.25
tpCR	16	3		
bpCR	5	1		
apCR	1	2		
PR	7	2		
Ki-67 variation (n)			0.80	0.67
No reduction	2	0		
Reduction (<15%)	2	1		
Significant reduction (>15%)	25	7		
MP grade (n)			6.91	0.07
Grade 2	2	0		
Grade 3	2	0		
Grade 4	3	4		
Grade 5	22	4		
Cardiac adverse events (n [%])				
ST-segment changes	1 (3.45%)	1 (12.50%)	0.01	0.91
Clockwise or counter-clockwise rotation	3 (10.34%)	0 (0%)	0.05	0.83
Premature atrial or ventricular contractions	0 (0%)	2 (25.00%)	3.55	0.06
Sinus arrhythmia (a)	5 (17.24%)	0 (0%)	0.46	0.50
Conduction block (b)	0 (0%)	0 (0%)	NA	1
Low QRS voltage	1 (3.45%)	0 (0%)	<0.001	1
Left axis deviation	0 (0%)	1 (12.50%)	0.49	0.48
Left ventricular hypertrophy	1 (3.45%)	0 (0%)	<0.001	1
Adverse reactions (n [%])				
Alopecia (hair loss)	25 (86.21%)	8 (100%)	0.22	0.64
Nausea	17 (58.62%)	3 (37.50%)	0.44	0.51
Diarrhea	1 (3.45%)	8 (100%)	26.73	< 0.001
Abdominal pain	4 (13.80%)	0 (0%)	0.22	0.64
Low white blood cell count	5 (17.24%)	2 (25.00%)	<0.001	1
Low hemoglobin	2 (6.90%)	0 (0%)	<0.001	1
Low platelet count	5 (17.24%)	0 (0%)	0.46	0.50
Abnormal liver function	9 (31.03%)	1 (12.50%)	0.35	0.55
Arthralgia (joint pain)	3 (10.34%)	0 (0%)	0.05	0.83
Anemia	14 (48.28%)	3 (37.50%)	0.02	0.89

Abbreviations: apCR: Pathological complete remission of axillary lymph nodes; bpCR: Pathological complete remission of primary breast lesions; MP: Miller-Payne; NA: Not available; PR: Partial pathological response; TCbHP: Docetaxel + carboplatin + trastuzumab + pertuzumab; TCbHPy: Docetaxel + carboplatin + trastuzumab + pyrotinib; tpCR: Total pathological complete response.

This may be due to the small sample size and dose reductions caused by adverse effects. Although the tpCR rate in the trastuzumab + Py group was lower than that in the trastuzumab + pertuzumab group, statistical analyses of partial pathological response, pathological complete remission of primary breast lesions (bpCR), pathological complete remission of axillary lymph nodes (apCR), and

tpCR between the TCbHPy and TCbHP groups showed no significant differences ($p=0.25$). Similarly, MP grading showed no statistically significant difference ($p=0.07$). In terms of adverse reactions, there were no statistically significant differences between the two groups in hair loss, nausea, vomiting, fatigue, diarrhea, loss of appetite, or cardiovascular adverse events (such as pre-mature

ventricular contractions, arrhythmia, sinus tachycardia, sinus bradycardia, sinus arrhythmia, T-wave changes, and changes in cardiac ejection fraction). However, diarrhea showed a statistically significant difference ($p < 0.001$): no cases were reported in the TCbHP group, while all eight patients in the TCbHPy group experienced varying degrees of diarrhea. Furthermore, all eight patients in the TCbHPy group had MP grades above level 4, with a total probability of 75% (6/8) achieving apCR, bpCR, or tpCR. Two out of three tpCR patients were HR-negative. As experience with Py increased, a triple anti-diarrheal method was implemented for first-level prevention: loperamide (two tablets per dose, twice daily, not exceeding eight tablets per day), smectite powder (one packet per dose, 3 times daily), and bifidobacterium (two packets per dose, twice daily). Before introducing this regimen, the incidence of diarrhea in our department included six cases (75%) of Grade 1 and two cases (25%) of Grade 2, with no unexpected Grade 3 events. Following the introduction of triple anti-diarrheal therapy, as of the manuscript submission date, patient compliance in the Py group in our department improved significantly. The median duration of diarrhea was reduced from 7 days to 3 days (interquartile range: 2 – 5), and the patient compliance rate increased to 87.5% (7 out of 8), with an initial dose of 400 mg. The tpCR rate also improved compared to previous statistics. We recognize that the study's small sample size and single-center design may limit the statistical robustness and generalizability of the findings. Nevertheless, we believe the results of this research are of substantial value and can serve as a foundational framework for future large-scale, multicenter investigations.

In real-world clinical practice, the HP dual-target regimen remains the first choice for neoadjuvant treatment for HER2-positive breast cancer. Zercepac® is not inferior to Herceptin in terms of efficacy. With its lack of benzyl alcohol preservatives and cost advantage, Zercepac® can further reduce expenses for both patients and healthcare systems. Moreover, HR and HER2 status are independent factors influencing tpCR rates across all patients. Based on the clinical observations in this study, the trastuzumab + Py regimen, which combines small and large molecules, offers advantages over single-target regimens combined with chemotherapy. It also shows a modest advantage in improving the MP grading of primary tumors compared to regimens based solely on large molecules, especially in HR-negative, HER2-positive patients. The combination of Zercepac® and Py with chemotherapy warrants further investigation. Whether this regimen can benefit improve PFS or even overall survival (OS) remains to be determined through future clinical follow-up and data collection.

5. Conclusion

While the HP dual-target regimen remains the neoadjuvant standard for HER2-positive breast cancer, this study highlights the non-inferiority of Zercepac®'s to originator trastuzumab, along with its preservative-free formulation and cost-efficiency advantages. For HR-negative subgroups, the TCbHPy regimen demonstrates particular promise, achieving high MP regression grades (100% grade ≥ 4) despite modest tpCR rates. The 75% apCR/bpCR composite rate and manageable toxicity profile, with appropriate prophylactic measures, suggest potential clinical utility, although long-term survival outcomes (PFS/OS) require validation in larger cohorts. At present, we are actively collecting and analyzing long-term follow-up data, including PFS and OS. We plan to disclose these results in subsequent research reports. Moving forward, studies should prioritize optimized dosing strategies and biomarker-driven patient selection to maximize the therapeutic index of Py.

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Conflict of interest

The authors declare no conflicts of interest.

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Ethics approval and consent to participate

This retrospective data analysis study, which involved no disclosure of patient identities and complied with ethical standards, is exempt from obtaining informed consent. Data are from Anhui Provincial Cancer Hospital, and its ethical approval is granted by the Ethics Committee of Anhui Provincial Cancer Hospital (Approval Number: 2024-TJK-06).

Consent for publication

The authors verbally informed all participants by telephone during data collection and follow-up regarding the intent to publish study results, and all participants provided verbal consent.

Availability of data

Data are available from the corresponding author upon reasonable request.

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