Trastuzumab Combined with Pyrotinib and Capecitabine as Postoperative Adjuvant Therapy in Non-Pathological Complete Response HER2-Positive Early Breast Cancer Following Neoadjuvant Therapy: A Multicenter Phase II Study

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Background

- HER2-positive early breast cancer patients achieving a pathological complete response (pCR) during neoadjuvant therapy demonstrate a more favorable prognosis.
- The KATHERINE study indicated that for HER2-positive early breast cancer patients who did not achieve pCR (the presence of residual tumor lesions) after neoadjuvant therapy, the administration of TDM-1 during postoperative adjuvant therapy significantly reduces the risk of disease recurrence compared to trastuzumab.
- This study aims to evaluate the efficacy and safety of trastuzumab in combination with pyrotinib and capecitabine in HER2-positive early breast cancer patients who did not achieve pCR following neoadjuvant therapy.

Methods

- This single-arm, open-label, multicenter study (ClinicalTrials.gov identifier NCT05292742) enrolled patients with HER2-positive early breast cancer who did not achieve pCR (defined as residual invasive tumor >1 cm or lymph node metastasis) following neoadjuvant therapy.

Key eligibility criteria	Treatment
•HER2-positive (IHC 3+ and/or FISH positive), confirmed by central laboratory •Histologically confirmed invasive breast cancer •Known hormone receptor status •ECOG performance status of 0–1 •Left ventricular ejection fraction ≥55% •Did not achieve a pathological complete response (pCR) and have residual tumor (primary invasive breast lesion >1 cm or axillary lymph node metastasis) after at least six cycles of trastuzumab-based neoadjuvant therapy.	• Pyrotinib: 400 mg daily for one year (primary prophylaxis with loperamide was administered to mitigate pyrotinib-induced diarrhea). • Trastuzumab: Initial loading dose of 8 mg/kg followed by 6 mg/kg every three weeks for a total of one year (including both neoadjuvant and adjuvant settings). • Capecitabine: 1000 mg/m² twice daily for six 3-week cycles, with continuation at the investigator's discretion beyond six cycles.

Endpoints

•**Primary:** 3-year invasive disease-free survival (iDFS) rate

•**Secondary:** Distant disease-free survival (DDFS), overall survival (OS), and safety

Results

- From July 2021 to November 2023, a total of 102 patients were enrolled, all of whom did not achieve pCR following neoadjuvant therapy.
- The median age was 52 years (range: 27-71 years). At initial diagnosis, most patients had T2 tumors (57.8%), with the majority exhibiting lymph node involvement (85.3%) and hormone receptor positivity (67.6%).Regarding prior neoadjuvant therapy, most patients (92.2%) had received a trastuzumab plus pertuzumab–based regimen, most commonly TCbHP (docetaxel, carboplatin, trastuzumab, and pertuzumab; 71.6%). Following neoadjuvant treatment, most tumors were downstaged, with 57.8% of patients categorized as T1 and 33.3% achieving N0 lymph node status. However, 4.9% of patients remained in the N3 category (Table 1).

Table 1. Baseline characteristics

Variables	All (N=102)
Age (years), median (range)	52 (27-71)
T stage at initial diagnosis, n (%)	
T0	1 (1.0%)
T1	11 (10.8%)
T2	59 (57.8%)
T3	23 (22.5%)
T4	5 (4.9%)
Unknown	3 (2.9%)
Lymph node status at initial diagnosis, n (%)	
Positive	87 (85.3%)
Negative	11 (10.8%)
Unknown	4 (3.9%)
Hormone receptor status, n (%)	
Positive	69 (67.6%)
Negative	33 (32.4%)
Prior neoadjuvant regimens, n (%)	
Trastuzumab alone	8 (7.8%)
TCbH	5 (4.9%)
EC-TH	2 (2.0%)
Other	1 (1.0%)
Trastuzumab + pertuzumab	94 (92.2%)
TCbHP	73 (71.6%)
THP	10 (9.8%)
EC-THP	11 (10.8%)

- As of the data cutoff on June 30, 2025, the median follow-up was 25 months. The 2-year iDFS rate was 91.3% (95% CI, 83.3-95.6) (Figures 1) , and the 2-year DDFS rate was 96.8% (95% CI, 90.5-99.0) (Figure 2); Data for 3-year iDFS were not yet mature.
- As for safety, 22 patients (21.6%) experienced grade ≥3 adverse events, with the most common being diarrhea (14.7%), white blood cell count decreased (2.0%), and hand-foot syndrome (1.0%) (Table 2). Adverse events led to the treatment interruption of any agent in 66 patients (64.7%), discontinuation of any agent in 8 patients (7.8%), and dose reduction of any agent in 37 patients (36.3%).

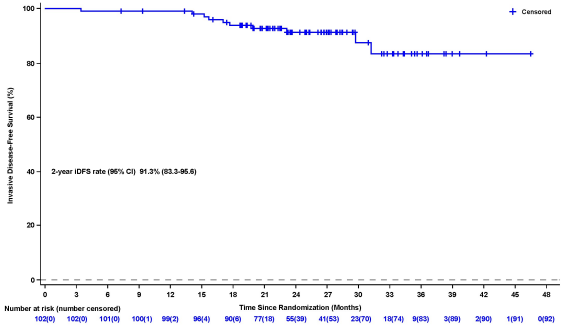


Figure 1. Kaplan-Meier curves for iDFS

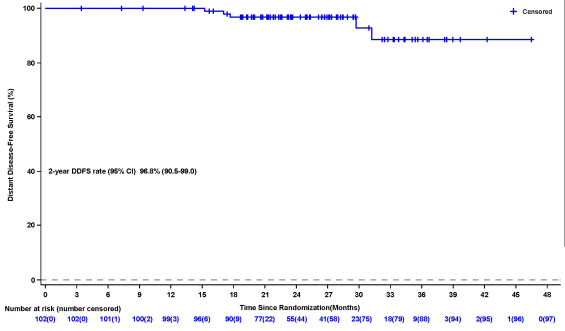


Figure 2. Kaplan-Meier curves for DDFS

Table 2. Treatment-related adverse event (TRAE) occurring in at least 10% of the patients

Events, n (%)	Grade 1-2	Grade ≥3
Diarrhea	84 (82.4%)	15 (14.7%)
Decreased appetite	63 (61.8%)	0
Vomiting	53 (52.0%)	0
Nausea	50 (49.0%)	0
Hand-foot syndrome	49 (48.0%)	1 (1.0%)
Fatigue	30 (29.4%)	0
Rash	26 (25.5%)	0
Oral mucositis	19 (18.6%)	0
Insomnia	17 (16.7%)	0
Epigastric pain	17 (16.7%)	0
Pyrexia	16 (15.7%)	0
Weight loss	15 (14.7%)	0
Constipation	14 (13.7%)	0
White blood cell count decreased	13 (12.7%)	2(2.0%)
Bone pain	12 (11.8%)	0
Abdominal distension	11 (10.8%)	0

Conclusions

For patients with HER2-positive early breast cancer who did not achieve pCR following neoadjuvant therapy, the combination of pyrotinib, trastuzumab and capecitabine as postoperative adjuvant therapy appears to improve prognosis. The overall safety profile of the regimen was acceptable, with no new safety signals identified. Primary prophylaxis with loperamide effectively reduced the incidence of grade ≥3 diarrhea during adjuvant therapy with pyrotinib.

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