Neoadjuvant Pyrotinib, Trastuzumab, Dalpiciclib, and Exemestane in Triple-Positive Breast Cancer: A Multicenter Phase II Trial

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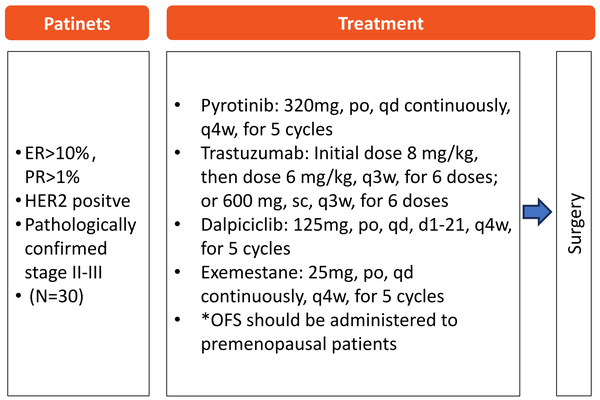
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Abstract

Triple-positive breast cancer (TPBC), defined by concurrent expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), accounts for 10-15% of breast cancers. Standard neoadjuvant regimens combining trastuzumab-based HER2-targeted therapy with chemotherapy show limited efficacy in this subtype. Resistance is attributed to HER receptor heterodimerization, HER2-ER signaling cross-talk, and activation of PI3K/AKT/mTOR pathways. Integrating HER2-targeted therapy with endocrine therapy and cyclin-dependent kinase 4/6 (CDK4/6) inhibitors may help overcome this resistance. The NA-PHER2 study demonstrated the potential benefit of a chemotherapy-free regimen, trastuzumab, pertuzumab, palbociclib, and fulvestrant, in TPBC. Pyrotinib, an irreversible pan-HER tyrosine kinase inhibitor, shows synergistic activity with CDK4/6 blockade in preclinical models. In the phase II MUKDEN 01 trial, pyrotinib combined with dalpiciclib and letrozole showed promise in TPBC, though efficacy remains suboptimal. Building on this rationale, we evaluated a novel, chemotherapy-free neoadjuvant regimen of pyrotinib, trastuzumab, dalpiciclib, and exemestane in patients with stage II-III TPBC.

Figure 1. Study design.



Methods and Materials

Eligible patients had previously untreated stage II-III TPBC, defined as ER >10%, PR >1%, and HER2 positivity (immunohistochemistry 3+ or in situ hybridization positive). Patients received pyrotinib (320 mg orally once daily, every 4 weeks, for 5 cycles), trastuzumab (intravenously: loading dose 8 mg/kg, then 6 mg/kg every 3 weeks for 6 cycles; or subcutaneously: 600 mg every 3 weeks for 6 cycles), dalpiciclib (125 mg orally once daily on days 1-21 of a 4-week cycle, for 5 cycles), and exemestane (25 mg orally once daily, every 4 weeks, for 5 cycles), followed by surgery. The primary endpoint was total pathological complete response (tpCR), defined as ypT0/is ypN0.

Table 1. Baseline characteristics

Characteristic	All (n=33)
Age, years, median (range)	48 (29-75)
Menopausal status, n (%)	
Premenopausal or perimenopausal	26 (78.8%)
Postmenopausal	7 (21.2%)
Clinical TNM stage, n (%)	
IIA	17 (51.5%)
IIB	11 (33.3%)
III	5 (15.2%)
Clinical T stage, n (%)	
T1	1 (3.0%)
T2	27 (81.8%)
T3	5 (15.2%)
Clinical nodal status, n (%)	
N0	16 (48.5%)
N1	14 (42.4%)
N2	2 (6.1%)
N3	1 (3.0%)
Estrogen receptor expression, n (%)	
<50%	6 (18.2%)
≥50%	27 (81.8%)
Ki-67 expression, n (%)	
<30%	8 (24.2%)
≥30%	25 (75.8%)

Results

Between September 2022 and February 2025, 33 patients were enrolled. The median age was 48 years (range, 29-75). Disease stage at baseline included 17 patients (51.5%) with stage IIA, 11 (33.3%) with stage IIB, 4 (12.1%) with stage IIIA, and 1 (3.0%) with stage IIIC. Ki-67 expression at baseline was ≥30% in 25 patients (75.8%). As of June 10, 2025, 30 patients had undergone surgery with available pathological data. The tpCR rate was 23.3% (7 of 30). Residual cancer burden 0-1 was observed in 23 patients (76.7%) and 24 (80.0%) achieved a Miller-Payne grade 4-5 response. Among them, 15 achieved complete response and 15 had partial response, yielding an objective response rate of 100%. Adverse events occurred most frequently during the first two treatment cycles. No grade ≥4 events were reported. The most common grade 3 adverse events was diarrhea (30.3%).

Table 2. Outcomes

Outcome	Patients
Pathologic response, n (%)	
Total pathological complete response	7/30 (23.3%)
Breast pathological complete response	9/30 (30.0%)
Residual cancer burden, n (%)	
0	7 (23.3%)
I	16 (53.3%)
II	4 (13.3%)
III	3 (10.0%)
Miller-Payne grade, n (%)	
Grade 5	9 (30.0%)
Grade 4	15 (50.0%)
Grade 3	2 (6.7%)
Grade 2	4 (13.3%)
Radiologic response (magnetic resonance imaging), n (%)	
Complete response	15 (50.0%)
Partial response	15 (50.0%)

Table 3. Safety profiles

Adverse event, n (%)	Any grade	Grade 3
Diarrhea	29 (87.9%)	10 (30.3%)
Anemia	22 (66.7%)	2 (6.1%)
Neutropenia	19 (57.6%)	7 (22.6%)
Rash	17 (51.5%)	0
Nausea	16 (48.5%)	0
Fatigue	16 (48.5%)	0
Alanine aminotransferase increased	14 (42.4%)	1 (3.0%)
Headache	13 (39.4%)	0
Hypokalemia	12 (36.4%)	1 (3.0%)
Hyperuricemia	12 (36.4%)	0
Vomiting	11 (33.3%)	0
Aspartate aminotransferase increased	9 (27.3%)	0
Oral ulcer	9 (26.3%)	0
Lymphopenia	8 (24.2%)	1 (3.0%)
Hypertriglyceridemia	7 (21.2%)	0
Hyponatremia	6 (18.2%)	0
Gamma-glutamyl transferase increased	5 (15.2%)	0
Hand–foot syndrome	3 (9.1%)	0
Hypercholesterolemia	3 (9.1%)	0
Alkaline phosphatase increased	3 (9.1%)	0
Hypercalcemia	2 (6.1%)	0

Conclusions

This chemotherapy-free, quadruple-targeted neoadjuvant regimen demonstrated promising activity and manageable toxicity in early-stage TPBC. These data support further evaluation of this regimen as a potential alternative to standard chemotherapy-based neoadjuvant approaches in TPBC.

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References

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