A Multicenter Phase II Clinical Trial of Pyrotinib Combined with Dalpiciclib and Letrozole in the Treatment of ER-positive and HER2-positive Advanced Breast Cancer

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Background

Estrogen receptor-positive and HER2-positive breast cancer accounts for approximately 10-15% of breast cancers. Standard metastatic regimens combining trastuzumab-based HER2-targeted therapy with chemotherapy show limited efficacy in this subtype. In SYSUCC-002 trial, trastuzumab plus endocrine therapy was not inferior to trastuzumab plus chemotherapy therapy in first-line HER2+HR+ metastatic breast cancer, suggesting the possibility of omission of chemotherapy[1]. The CDK4/6 pathway may be involved in HER2-targeted therapy resistance due to the HER2-ER signaling cross-talk and thus CDK4/6 inhibitor may become a strategy for patients with HER2+ER+ breast cancer[2]. Pyrotinib, an irreversible pan-HER tyrosine kinase inhibitor, shows synergistic activity with CDK4/6 blockade in preclinical models[3]. Building on this rationale, we evaluated a novel, chemotherapy-free regimen of pyrotinib, dalpiciclib, and letrozole in patients with HER2+ER+ metastatic breast cancer.

Introduction

Based on the rationale for chemotherapy de-escalation in HER2+/HR+ metastatic breast cancer and evidence of cross-talk between HER2 and ER signaling pathways, we designed a phase II trial to evaluate a novel, all-oral, chemotherapy-free triplet. This study investigates the combination of pyrotinib (a pan-HER inhibitor), dalpiciclib (a CDK4/6 inhibitor), and letrozole, aiming to provide a synergistic and better-tolerated therapeutic option for this patient population. The following schema outlines the trial design.Primary endpoint: Objective Response Rate (ORR)；Secondary endpoints: Progression-Free Survival (PFS); Overall Survival (OS); Clinical Benefit Rate (CBR); Duration of Response (DoR); incidence of Adverse Events (AEs) and Serious Adverse Events (SAEs). We hypothesized ORR of 55% in this trial, using Simon's optimal two-stage design, at the significance level of type I error rate at 0.05 and power of 0.8, a total of 22 patients was accrued in stage I. If there were more than 9 responses among these evaluable 22 patients, the study would enter stage II. The registration number of this trial was NCT07014410.

Methods and Materials

Eligible patients had ER+HER2+ metastatic breast cancer, defined as ER≥1%, and HER2 positivity (immunohistochemistry 3+ or in situ hybridization positive). Patients should previously receive at most one systemic treatment containing trastuzumab for metastatic breast cancer. Patients with stable brain metastases and no clinical symptoms could be enrolled. Eligible patients received pyrotinib (320 mg orally once daily, every 4 weeks), dalpiciclib (125 mg orally once daily on days 1-21 of a 4-week cycle), and letrozole (2.5 mg orally once daily, every 4 weeks) until disease progression or intolerable toxicity. Pre/peri-menopausal patients received GnRH agonist. Radiographic evaluation was conducted every two cycles. The primary endpoint was objective response rate (ORR).

Table1. Study Design

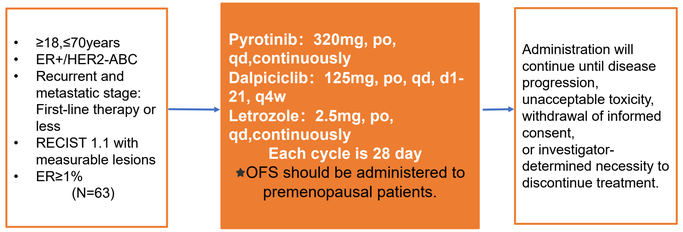


Table 2. Baseline demographic and Tumor Characteristics

Baseline demographic and Tumor Characteristics N=19		n (%)
Median age (range), years		55(34-71)
Menopausal status	Postmenopausal	10 (52.6%)
	Pre/perimenopause	9 (47.4%)
Disease status	Metastatic,de novo	5 (26.3%)
	Metastatic recurrent	14 (73.7%)
Previous anti-HER2 therapy	Trastuzumab-treated	14 (73.7%)
	Trastuzumab-naive	5 (26.3%)
HER2 status，n（%）	IHC3+	14 (73.7%)
	2+&Fish+	5 (26.3%)
HR status，n（%）	ER≥50%	14 (73.7%)
	ER＜50%	5 (26.3%)
Ki-67 Expression(%)	ki67≥30%	13 (68.4%)
	ki67＜30%	6 (21.6%)
Distant metastasis	Visceral metastasis Bone metastasis Thorax metastasis	16(84.2%) 2(10.5%) 1(5.3%)

Results

Between February 2023 and Sptember 2025, 19 patients were enrolled. The median age was 55 years (range, 34-71). Ki67 expression at baseline included 12 patients (68.4%) with ≥30%. Of these 19 patients, 14 (73.7%) previously received trastuzumab, whereas 5 patients (26.3%) did not receive this treatment. Approximately 84.2% of the patients exhibited multiple organ metastases, indicating a significant tumor burden.As of September 25, 2025, 16 of 19 patients had evaluable radiographic data. In these evaluable 16 patients, 11 patients achieved confirmed responses (2 complete response, 11 partial responses), yielding an ORR of 81.25% (95% confidence interval [CI], 53.9%, 96.0%). Despite inadequate patients in stage I, outstanding efficacy result indicated the study could enter stage II. The most common grade 3 adverse events were white blood cell count decreased (84.2%) and neutropenia (47.4%). One instance of a Grade 4 adverse reaction was reported, presenting as thrombocytopenia,and there were no deaths.

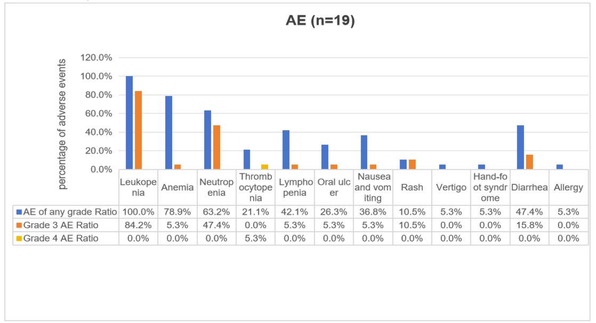
Table3. Tumor Response

Best Overall Response	N（ORR rate）
Complete response（CR）	2(12.50%)
Partial response(PR)	11(68.75%)
Stable disease(SD)	3(18.75%)
Progressive disease(PD)	0(0%)

Table4. Safety Profile

Safety Profile N=19			
Any TEAES	AE of any grade	Grade 3 AE	Grade 4 AE
Leukopenia	19	16	0
Anemia	15	1	0
Neutropenia	12	9	0
Thrombocytopenia	4	0	1
Lymphopenia	8	1	0
Diarrhea	9	3	0
Oral ulcer	5	1	0
Nausea and vomiting	7	1	0
Rash	2	2	0
Vertigo	1	0	0
Hand-foot syndrome	1	0	0
Allergy	1	0	0

Table5. Safety and tolerance



Discussion

This phase II study demonstrates that the chemotherapy-free triplet of pyrotinib, dalpiciclib, and letrozole exhibits promising efficacy and manageable toxicity in patients with HER2+/ER+ metastatic breast cancer. The observed objective response rate of 81.25% surpasses both the prespecified threshold of 55% and the historical reference of 37.2% reported in the trastuzumab-plus-endocrine therapy arm of the SYSUCC-002 trial[1]. These results reinforce the mechanistic rationale for simultaneously targeting HER2, ER, and CDK4/6 to exploit pathway cross-talk and overcome resistance.Although based on interim data from the first stage of a Simon's two-stage design, the marked antitumor activity supports further investigation of this strategy. The predefined criterion for continuation has been met, warranting progression into the second stage of the trial. Additional follow-up and expanded enrollment will be essential to verify the response durability, evaluate progression-free survival, and determine the potential of this regimen as a new therapeutic option in this population.

Conclusions

This chemotherapy-free, triplet targeted regimen demonstrated promising antitumor activity with a manageable safety profile in patients with HER2-positive, ER-positive metastatic breast cancer in the first- or second-line setting.No new safety signal was identified, and all AEs were manageable.

Having met the pre-specified efficacy threshold in the first stage of Simon's two-stage design, the study has successfully proceeded to the planned phase II expansion to further evaluate the efficacy of this strategy.

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