An Exploratory Clinical Trial of CDK4/6 Inhibitor Dalpiciclib Combined with Aromatase Inhibitors as Neoadjuvant Therapy for Stage II-III HR-positive HER2-negative Breast Cancer

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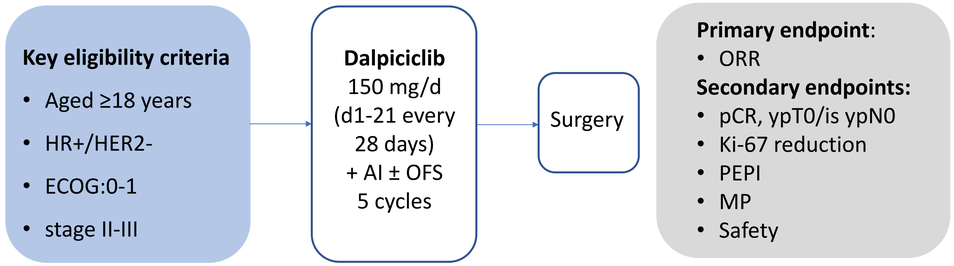
Background

- Hormone receptor positive (HR+) / human epidermal growth factor receptor 2 negative (HER2-) breast cancer accounts for ~60% of all breast cancer cases.
- Neoadjuvant endocrine therapy (NET) offers comparable objective response rate (ORR) and breast-conserving rate to chemotherapy but with lower toxicity.
- Dalpiciclib, a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i), arrests the cell cycle to suppress tumor proliferation.
- This trial evaluates its combination with aromatase inhibitors (AIs) in stage II-III HR+/HER2- breast cancer, seeking an optimized, low-toxicity neoadjuvant strategy.

Methods

- This single-arm, multicenter, open-label phase II trial enrolled 45 treatment-naive women with stage II-III HR+ (estrogen receptor >10%) and HER2- breast cancer.
- Participants receive dalpiciclib 150 mg/d (d1-21 every 28 days) + AIs (letrozole 2.5 mg/d, anastrozole 1 mg/d, or exemestane 25 mg/d); premenopausal women add ovarian suppression (goserelin/leuprolide).
- The primary endpoint was ORR.
- Secondary endpoints encompassed pathological complete response (pCR, ypT0/is ypN0), Ki-67 reduction from baseline, preoperative endocrine prognostic index (PEPI), Miller/Payne (MP), and safety.

Figure 1. Study Design.



Results

- From March 2023 to June 2025, 45 patients were enrolled. Median age was 57 years (28-79). Among the subjects, 48.8% (21/45) were pre/perimenopausal women.
- Most patients had T2 (55.6%), N1 (53.3%), Stage III (53.3%) tumors.

Table 1.Baseline Characteristics of Patients.

Characteristics	Patients(N= 45)
Age	
Median(range),years	57 (28, 79)
≥40, n(%)	41(91.1)
< 40, n(%)	4(8.9)
Menopausal status, n(%)	
Premenopausal	21(46.7)
Postmenopausal	24(53.3)
Tumor size, n(%)	
T1	2(4.4)
T2	25(55.6)
T3	7(15.6)
T4	10(22.2)
UK	1(2.2)
Lymph node status, n (%)	
N0	4(8.9)
N1	24(53.3)
N2	11(24.4)
N3	4(8.9)
Nx	1(2.2)
UK	1(2.2)
Stage at baseline, n (%)	
II	20(44.4)
III	24(53.3)
UK	1(2.2)

- 24 patients completed the neoadjuvant treatment and underwent surgery (8 patients are still receiving treatment, 12 patients withdrew from the study, and 1 patient showed progression).
- ORR was 46.9% (95% CI: 29.6%-64.2%), with 32 patients having completed at least one cycle of treatment and undergone efficacy evaluation, including 3.2% (1/32) complete response (CR) and 45.2% (14/32) partial response (PR).
- No patient achieved pCR.

Table 2. Tumor response.

	Patients(N= 32)
BOR, n(%)	
CR	1(3.1)
PR	14(43.8)
SD	17(53.1)
ORR, % (95% CI)	**46.9 (29.6, 64.2)**

- Ki-67 decreased from a baseline of 20% (IQR: 10%-40%) to 5% (IQR: 3%-26.25%) before surgery, indicating suppressed tumor proliferation; the interquartile range may suggest heterogeneous patient responses.
- The median MP grade was 3 (IQR: 2.75-3), with the majority (70.8%) showing grade 3, indicating moderate pathological response to therapy.
- Median PEPI was 4 (IQR: 3-5), and 33.3% (8/24) patients were classified as medium-risk (1≤PEPI≤3).
- Grade ≥3 adverse event was neutropenia (35.2%), with no treatment-related deaths.

Table 3. Pathological Responses and PEPI.

	Patients(N= 24)
Pathologic Complete Response	0
Miller/Payne grade, n(%)	
1	1(4.2)
2	5(20.8)
3	17(70.8)
4	1(4.2)
PEPI Score, n(%)	
Median (IQR)	4 (3, 5)
0	0
1-3	8(33.3)
≥4	16(66.7)

Conclusion

Dalpiciclib combined with AIs demonstrates promising efficacy and manageable toxicity as neoadjuvant therapy for stage II-III HR+/HER2- breast cancer, offering a new chemotherapy-free option. Future research should focus on biomarker-guided patient selection, long-term outcomes assessment, and comparative trials with other neoadjuvant therapies, aiming to improve the treatment paradigm for HR+/HER2- breast cancer.

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