PS2-13-08 Neoadjuvant Dalpiciclib Plus Letrozole Versus Standard Chemotherapy in High-Risk HR+/HER2–Negative Breast Cancer (DARLING-02): A Randomized Phase II Trial

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Introduction

- Patients with hormone receptor-positive (HR+), HER2-negative (HER2–) breast cancer respond poorly to neoadjuvant chemotherapy.
- DARLING 01 (NCT05512780) was the first prospective study of neoadjuvant dalpiciclib in patients with HR+/HER2– breast cancer, which is a multicenter, single-arm exploratory trial. The study found the promising tumor response to neoadjuvant dalpiciclib plus letrozole in postmenopausal patients with HR+/HER2– breast cancer, with a manageable safety profile [1].
- The present DARLING 02 study (NCT06107673) aimed to explore the efficacy and safety of neoadjuvant dalpiciclib plus letrozole compared with standard chemotherapy in patients with high-risk HR+/HER2–early breast cancer.

Methods

- DARLING-02 was a multicenter, randomized, phase II non-inferiority trial.
- The study design is shown in Figure 1.
- Patients were randomized 1:1 to receive 24-week treatment. The experimental arm received dalpiciclib 150 mg orally once daily (3 weeks on, 1 week off) plus letrozole 2.5 mg orally once daily. The control arm received epirubicin 100 mg/m² plus cyclophosphamide 500 mg/m² intravenously on day 1 every 3 weeks for 4 cycles, followed by docetaxel 100 mg/m² intravenously on day 1 every 3 weeks for 4 cycles.
- The primary endpoint was objective response rate (ORR), assessed by investigator according to the Response Evaluation Criteria In Solid Tumors version 1.1. Secondary endpoints included total pathological complete response (tpCR; ypT0/is ypN0) rate; preoperative endocrine prognostic index (PEPI) score, and safety.

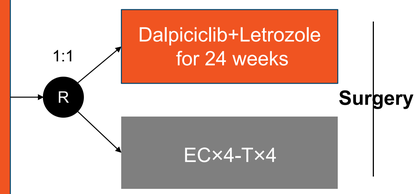
Results

- Between August 2023 and April 2025, 170 patients were screened; 139 met the eligibility criteria and were randomized to the dalpiciclib–letrozole (n=71) or chemotherapy (n=68) group. Baseline characteristics are shown in Table 1.
- The ORR was 69.0% (49/71) with dalpiciclib–letrozole and 70.5% (48/68) with chemotherapy (Table 2).
- The tpCR rate was 5.6% (4/71) and 1.5% (1/68; Figure 2), respectively.
- More patients with chemotherapy (74.6%) had PEPI score ≥4 than those with dalpiciclib–letrozole (53.3%; Table 3).
- Grade ≥3 adverse events were predominantly hematological toxicities and occurred less frequently with dalpiciclib–letrozole than with chemotherapy (decreased neutrophil count: 77.5% vs 77.9%; Table 4).

Conclusions

- These findings support dalpiciclib plus letrozole as a promising neoadjuvant option for patients with high-risk HR+/HER2–early breast cancer and warrant confirmation in phase III trials.

Eligibility criteria:
- Aged ≥18 years;
- HER2− breast cancer;
- ER level ≥50%;
- T1c-2N1-2 or T3-4N0-2 stage;
- Ki67 ≤**30%**;
- ECOG PS 0-1



Primary endpoint:
- ORR

Secondary endpoints:
- tpCR
- PEPI score
- Safety

Figure 1. Clinical Trial Design

Table 1. Baseline characteristics

Characteristics	Dalpiciclib+Letrozole (n=71)	EC × 4-T × 4 (n=68)
Age (years), median (range)	53 (32-75)	51 (33-72)
AJCC stage, n (%)		
IIA-IIB	53 (74.6%)	52 (76.5%)
IIIA-IIIC	18 (25.4%)	16 (23.5%)
Menopausal status, n (%)		
Pre-menopausal	28 (39.4%)	32 (47.1%)
Peri-menopausal	5 (7.0%)	6 (8.8%)
Post-menopausal	38 (53.5%)	29 (42.6%)
Clinical T stage, n (%)		
T1	8 (11.3%)	4 (5.9%)
T2	43 (60.6%)	47 (69.1%)
T3	9 (12.7%)	8 (11.8%)
T4	11 (15.4%)	9 (13.2%)
Lymph node involvement, n (%)		
N0	7 (9.9%)	7 (10.3%)
N1	56 (78.9%)	58 (85.3%)
N2	7 (9.9%)	3 (4.4%)
N3	1 (1.4%)	0
HR status, n (%)		
ER-positive and PR-positive	64 (90.1%)	67 (98.5%)
ER-positive and PR-negative	7 (9.9%)	1 (1.5%)
Ki-67 level (%), median (range)	15 (5-30)	20 (5-30)

Table 2. Radiographic response before surgery

Response, n (%)	Dalpiciclib+ Letrozole (n=71)	EC × 4-T × 4 (n=68)
Complete response	1 (1.4%)	0
Partial response	48 (67.6%)	48 (70.6%)
Stable disease	22 (31.0%)	20 (29.4)
Progressive disease	0	0
Objective response	49 (69.0%)	48 (70.5)

Table 3. PEPI score

Score, n (%)	Dalpiciclib+ Letrozole (n=60)	EC × 4-T × 4 (n=59)
0	2 (3.3%)	2 (3.4%)
1-3	26 (43.3%)	13 (22.0%)
≥4	32 (53.3%)	44 (74.6%)

Figure2. Total pathological complete response (tpCR) rate

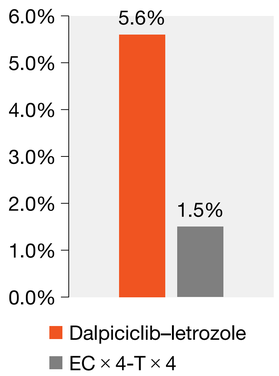


Table 4. Adverse events

Event, n (%)	Dalpiciclib+ Letrozole (n=71)		EC × 4-T × 4 (n=68)	
	Grade 1-2	Grade ≥3	Grade 1-2	Grade ≥3
Hematologic toxicities				
Neutrophil count decreased	16 (22.5%)	55 (77.5%)	10 (14.7%)	53 (77.9%)
Anemia	34 (47.9%)	0	49 (72.1%)	0
Platelet count decreased	20 (28.2%)	0	26 (38.2%)	0
Non-hematologic toxicities				
Fatigue	41 (57.7%)	0	49 (72.1%)	0
Pain	2 (2.8%)	0	52 (76.5%)	0
Anorexia	5 (7.0%)	0	36 (52.9%)	0
Alopecia	4 (5.6%)	0	63 (92.6%)	0
Nausea	3 (4.2%)	0	52 (76.5%)	0

*At the investigator's discretion, some patients in the control group routinely received injections of long-acting leukocyte-boosting drugs for primary prophylaxis.

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Reference:
[1] Zhang et al. Clinical efficacy and therapy response prediction of neoadjuvant dalpiciclib plus letrozole in postmenopausal patients with HR+/HER2- stage II-III breast cancer (DARLING 01): a single-arm, open-label, exploratory study. Breast Cancer Research. (2025) 27:21.

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