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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

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Abstract

Background Hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) breast cancer is the most common subtype of breast cancer, yet its response to traditional chemotherapy remains limited, posing a challenge in achieving optimal therapeutic outcomes. In this study, we aimed to evaluate the clinical efficacy and safety of dalpiciclib, a novel CDK4/6 inhibitor, combined with letrozole as neoadjuvant therapy (NAT) in postmenopausal patients with HR+/HER2- stage II-III breast cancer. Additionally, we explored potential predictive biomarkers for treatment response using gene analysis.

Methods This single-arm, open-label, exploratory phase II trial involved 35 postmenopausal women with HR+/HER2- breast cancer (ClinicalTrials.gov identifier NCT05512780). Patients received four cycles of dalpiciclib (125 mg/day for 3 weeks, followed by 1 week off) plus continuous letrozole (2.5 mg/day). The primary endpoint was objective response rate (ORR), and secondary endpoints included changes in Ki-67 expression, complete cell cycle arrest (CCCA) rate, residual cancer burden (RCB), and safety profiles. Gene expression profiling and least absolute shrinkage and selection operator (LASSO) regression were conducted to identify biomarkers predictive of response to NAT.

Results Among the 35 enrolled patients, 31 completed the full treatment course. Of the 29 patients with evaluable response data after 4 cycles, 16 achieved partial response (PR), resulting in an ORR of 55.2%. Following two weeks of treatment, the mean Ki-67 expression significantly decreased from a baseline of 17.5–1.8%, and CCCA was observed in 75% of patients. Grade ≥ 3 treatment-emergent adverse events (TEAEs) were mainly decreased neutrophil count

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(45.7%), with a median duration of 3 days. The NAT predictive model, developed using gene expression analysis and clinicopathological factors, achieved an area under the curve (AUC) of 0.928, indicating that TFRC, SCUBE2, and MMP11A could serve as novel predictive biomarkers for response to NAT.

Conclusions Dalpiciclib combined with letrozole demonstrated promising antitumor activity and an acceptable safety profile in postmenopausal patients with HR+/HER2- breast cancer. The identification of TFRC, SCUBE2, and MMP11A as predictive biomarkers provides insights into the potential for personalized neoadjuvant treatment strategies.

Keywords Dalpiciclib, Neoadjuvant endocrine therapy, HR+/HER2- breast cancer, Predictive biomarkers

Background

In 2022, female breast cancer constituted 11.6% of global cancer cases, ranking it as the second most prevalent form of cancer worldwide [1]. Among its various molecular subtypes, the hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) subtype is the most common, accounting for approximately 65–70% of all cases [2]. Neoadjuvant therapy (NAT) is generally recommended for high-risk breast cancer patients, aiming to reduce tumor size and increase the likelihood of breast preservation over mastectomy [3]. While neoadjuvant chemotherapy is widely recognized as a treatment option, its efficacy remains debated due to relatively lower benefits in the HR+/HER2- subtype compared to other breast cancer types [4].

Neoadjuvant endocrine therapy (NET) represents a promising alternative for selected patients with HR+/HER2- breast cancer, particularly those who may not tolerate chemotherapy. NET has been shown to achieve favorable clinical responses with significantly lower toxicity [5]. However, it is important to note that NET is not yet a universally accepted standard of care and is primarily utilized in specific clinical scenarios or research settings. Cyclin-dependent kinases CDK4/6 play a key role in promoting cell cycle progression from G1 to S phase. The inhibition of these kinases prevent cancer cells from advancing to subsequent phases, leading to decreased proliferation of estrogen receptor positive (ER+) tumors and reverse endocrine resistance [6]. Several studies have shown that combining CDK4/6 inhibitors with endocrine therapy in the neoadjuvant setting leads to significantly higher rates of cell cycle arrest and enhances antitumor effects, as indicated by the substantial suppression of Ki-67 expression compared to NET alone [7, 8]. The PALLET study, the largest phase II neoadjuvant trial, further demonstrated that the combination of palbociclib and letrozole improved rates of complete cell cycle arrest (CCCA) in postmenopausal women with HR+/HER2- breast cancer [9].

Dalpiciclib, a novel CDK4/6 inhibitor, has shown significant antitumor activity in preclinical models, with efficacy comparable to that of palbociclib in vivo xenograft studies [10, 11]. The DAWNA-2 trial further confirmed that dalpiciclib combined with letrozole offers superior progression-free survival compared to aromatase inhibitor (AI) alone as a first-line treatment for patients with HR+/HER2- advanced breast cancer [12]. However, no studies have evaluated the use of dalpiciclib in combination with letrozole in the neoadjuvant setting for postmenopausal patients with HR+/HER2- breast cancer.

In this study, we aim to evaluate the efficacy and safety of dalpiciclib combined with letrozole as NAT in postmenopausal women with HR+/HER2- breast cancer, addressing a critical gap in the management of early-stage disease. By exploring this therapeutic combination, the study seeks to provide new insights into personalized treatment strategies for HR+/HER2- breast cancer, with the potential to improve outcomes while reducing the need for more aggressive treatments such as chemotherapy.

Methods

Study design and patients

This openlabel, multicenter, exploratory phase II trial was conducted at nine hospitals in accordance with the Declaration of Helsinki and in compliance with good clinical practice (ClinicalTrials.gov identifier NCT05512780). This study was approved by the institutional ethics committee at each site before enrollment; all patients provided written informed consent. Eligible patients included postmenopausal women with histologically confirmed stage II-III, ER+ (>10% of cells in the tumor expressing ER) and HER2- (0/1+by immunohistochemistry or 2+by immunohistochemistry and fluorescent in-situ hybridisation negative) invasive breast cancer. Other eligibility criteria included: Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0–1, adequate organ function assessed by hematological and blood chemistry analyses. The key exclusion criteria were: bilateral breast cancer, inflammatory breast cancer, or recurrent and metastatic breast cancer. Patients were also excluded if they had prior or concurrent anti-tumor treatment.

Procedures

Patients were treated with four cycles of 4-week NAT. Each cycle consisted of continuous daily letrozole 2.5 mg per day and dalpiciclib 125 mg once daily for 3 weeks, followed by 1 week off. Treatment interruptions or dose reductions were allowed to manage adverse events (AEs) effectively. Dose reductions were permitted for dalpiciclib under dose reduction criteria. Tumor assessments by imaging (computed tomography scan, and/or magnetic resonance imaging) were carried out at baseline (prior to treatment), after cycle 2 and cycle 4, and objective response rate (ORR) was determined accordingly. Tumor biopsies were taken at baseline, after 2 weeks treatment and at surgery. Breast surgery was performed after the last cycle of NAT.

Outcome

The primary efficacy endpoint was ORR, defined as proportion of patients with a clinical complete response (CR) or partial response (PR) from baseline to the end of NAT, according to response evaluation criteria in solid tumors (RECIST 1.1). Secondary objectives assessed the change in Ki-67 expression between baseline and 2 weeks of therapy and post-surgery; CCCA (Ki-67 ≤ 2.7%) post 2 weeks treatment; residual cancer burden (RCB) 0 and I corresponding to pathologic complete response (pCR) and minimum residual cancer that carries the same favorable prognosis as pCR respectively, and safety profiles based on summaries of AE reported in Common Terminology Criteria for Adverse Events (CTCAE version 5.0). Exploratory biomarker analysis of gene expression was also conducted.

Ki-67 detection and quantification

Ki-67 expression was evaluated in the pathology Department of the Fourth Hospital of Hebei Medical University. Formalin-fixed, paraffin-embedded (FFPE) breast tumor samples, obtained from either core biopsies or surgical resections, were stained for Ki-67 at three time points: pre-treatment, two weeks after treatment, and post-surgery. Immunohistochemical staining was performed using a Ki-67 antibody (MIB-1, DAKO, Denmark) according to established Ki-67 interpretation guidelines. Ki-67 expression was quantified as the percentage of positive staining cells within the cancer cell nuclei. CCCA was defined as Ki-67 ≤ 2.7%.

Gene expression analysis

To further elucidate biomarkers associated with the efficacy of NET, the expression of 21 breast cancer-related genes (CCNB1, TFRC, AURKA, GUSB, MKI67, RPLP0, MYBL2, GAPDH, CCNB1, TFRC, AURKA, GUSB, MKI67, RPLP0,BIRC5, ACTB, CD68, BAG1, SCUBE2, GSTM1, BCL2, GRB7, ESR1, ERBB2, PGR, MMP11, CTSV) was assessed in tissue samples using fluorescence quantitative PCR. Gene expression levels were measured both before and after NET administration. The relationship between gene expression changes and treatment response was analyzed to identify potential biomarkers for predicting NET efficacy.

LASSO regression analysis

The Ct values of 21-gene panel result from the baseline tumor biopsy and some independent variables being considered as candidate predictors (age, HER2 status, Ki-67 expression, clinical stage, T stage and node status) were selected to perform the least absolute shrinkage and selection operator (LASSO) regression analysis via the glmnet package in R. The LASSO regression further analyzed the relationship between baseline characteristics, baseline gene expression, and treatment response, with the optimal λ selected via cross-validation to minimize prediction error (λmin). The risk score for each sample was calculated by multiplying the expression value (or status) of each selected variable by its corresponding regression coefficient and then summing the results. The specific formula for calculating the risk score is as follows:

$$\begin{aligned}\text{score} = &-0.0264 - 0.1924 \times \text{Age} - 0.0684 \times \text{HER2.status} \\ &+0.4652 \times \text{Node.State} - 0.4102 \times \text{TFRC} \\ &+0.1622 \times \text{SCUBE2} + 0.3720 \times \text{MMP11}\end{aligned}$$

Receiver operating characteristic (ROC) curve analysis (pROC package in R, version 1.18.5) was further performed to evaluate the efficacy of NAT. The area under the curve (AUC) was calculated to quantify the discriminative ability of the risk score in distinguishing between responders and non-responders.

Statistical analyses

As an exploratory study, a formal sample size calculation was not performed. Statistical analysis was performed using R software (version 4.2.1). Continuous data are presented as mean and standard deviation or mean and 95% confidence intervals (95% CIs). Categorical data are expressed as frequency and percentage. The 95% CIs of ORR, pCR rate, and the proportion of patients with RCB 0 or RCB I was estimated using the Clopper-Pearson method. The difference in the mean percentages of Ki-67 expressing tumor cells between baseline and surgical samples was analyzed by paired t-test. In the biomarker analysis, paired t-tests were used to compare gene expression pre- and post-treatment. Correlations between baseline characteristics and treatment outcomes were analyzed using chi-square tests. Logistic regression was employed to correlate baseline gene expression levels and changes with treatment response.

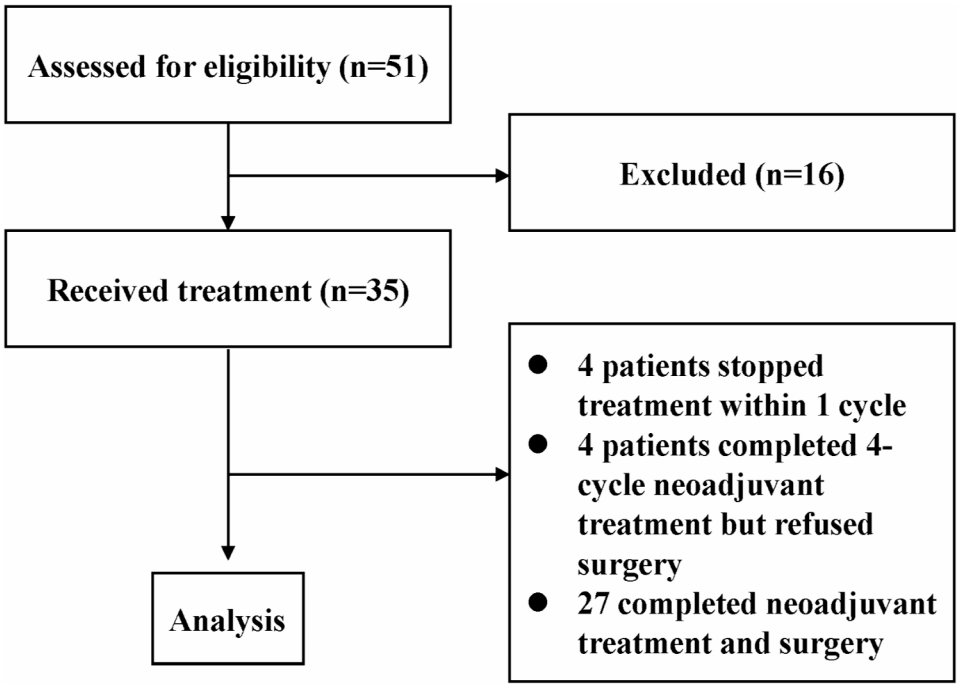

Fig. 1 Patient flowchart

Table 1 Baseline characteristics

Characteristics	Patients ($n=35$)
Age (years), median (range)	66 (52–83)
Clinical stage, n (%)	
IIA	16 (45.7)
IIB	14 (40)
IIIA	2 (5.7)
IIIC	3 (8.6)
ECOG PS, n (%)	
0	34 (97.1)
1	1 (2.9)
T stage, n (%)	
T1	10 (28.6)
T2	23 (65.7)
T3	1 (2.9)
T4	1 (2.9)
N stage, n (%)	
N0	4 (11.4)
N1	24 (68.6)
N2	4 (11.4)
N3	3 (8.6)
Ki-67 expression (%), median (range)	20 (4–40)
Hormone receptor status, n (%)	
ER+; PgR+	30 (85.7)
ER+; PgR-	5 (14.3)
HER2 status, n (%)	
0	7 (20.0)
1+	16 (45.7)
2+	12 (34.3)

ECOG: Eastern Cooperative Oncology Group; PS: Performance Status; ER: oestrogen receptor; PgR: progesterone receptor

Results

Baseline characteristics

From June 2022 to January 2023, 51 postmenopausal women with clinical stage II-III HR+/HER2- breast cancer were assessed for eligibility. Finally, 35 patients received at least one treatment and were enrolled (Fig. 1). Their median age was 66 (range: 52–83) years old, with 85.7% at stage II (45.7% for stage IIA and 40.0% for stage IIB). The majority of patients were T2 (65.7%) and N1 (68.6%) at diagnosis. ER/PgR positivity was observed in 85.7% of the enrolled patients. The median Ki-67 expression level at initial diagnosis was 20% (range: 4-40%). Detailed demographics are shown in Table 1.

Efficacy assessment

During the NAT period, 4 patients discontinued the treatment within the first cycle due to consent withdrawal ($n=3$), unexpected death ($n=1$). The unexpected death resulted from an accidental overdose of sleeping pills caused by a dosage adjustment error. This incident was thoroughly investigated and determined to be unrelated to the study treatment. The remaining 31 patients completed the full 4-cycle treatment, while 4 subsequently refused surgery. Radiologic responses were assessed after 2 and 4 cycles of therapy, with data available for 31 and 29 patients, respectively (Table 2). Following 2 cycles, 11 of 31 patients (35.5%) achieved PR, while 20 patients (64.5%) exhibited stable disease (SD), resulting in an ORR of 35.5%. At the completion of the full treatment course, 16 patients (55.2%) achieved PR and 13 patients (44.8%)

Table 2 Radiologic response before surgery

	2 cycles (*n* = 31)	4 cycles (*n* = 29)
CR, n (%)	0	0
PR, n (%)	11(35.5)	16(55.2)
SD, n (%)	20(64.5)	13(44.8)
PD, n (%)	0	0
ORR (%)	35.5	55.2

CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; ORR: Objective response rate

maintained SD. No patients experienced disease progression during radiographic evaluations after both 2 and 4 cycles, yielding an ORR of 55.2%. Among the 27 patients who underwent definitive surgery, 13 patients achieved RCB II, and 1 patient achieved a pCR (RCB 0).

Ki-67 expression change

Out of the 35 patients at baseline, Ki-67 expression data were available for 28 patients after 2 weeks of NAT and 26 patients following surgery, with the predominant reasons for unavailable results being missing or unevaluable. Expression of Ki-67 was significantly reduced from baseline to both 2 weeks after treatment and surgery. The proportion of Ki-67-positive tumor cells was 17.5% ± 10.1% at baseline versus 1.8% ± 1.3% at week 2 and 5.4% ± 6.1% after surgery (Fig. 2A-B). And the rate of CCCA was 75% (21/28) after 2 weeks of treatment, supporting the effectiveness of this neoadjuvant regimen and the potential mechanism of action in inducing cell cycle arrest.

Safety

Among 35 eligible patients involved in the safety analysis (Table 3), the most frequent treatment-emergent adverse events (TEAEs) were decreased neutrophil count (74.3%), decreased white blood cell count (68.6%), anemia (34.3%); and nonhematologic toxicity included fatigue (31.4%) and rash (28.6%). Grade 3 or 4 occurred most commonly in decreased neutrophil count (45.7%), with a median duration of 3 (range 2–4) days. No cases of febrile neutropenia were observed.

Table 3 Adverse events

Events	Patients (*n* = 35)		
	Any grade, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)
Neutrophil count decreased	26 (74.3)	14 (40.0)	2 (5.7)
White blood cell count decreased	24 (68.6)	3 (8.6)	0 (0.0)
Anemia	12 (34.3)	0 (0.0)	0 (0.0)
Platelet count decreased	9 (25.7)	1 (2.9)	0 (0.0)
Lymphocyte count decreased	8 (22.9)	0 (0.0)	0 (0.0)
Fatigue	11 (31.4)	0 (0.0)	0 (0.0)
Rash	10 (28.6)	0 (0.0)	0 (0.0)
Oral ulcer	5 (14.3)	0 (0.0)	0 (0.0)
Pain (Headache/Toothache/ Neuralgia)	5 (14.3)	0 (0.0)	0 (0.0)
Anorexia	4 (11.4)	0 (0.0)	0 (0.0)
Alopecia	2 (5.7)	0 (0.0)	0 (0.0)

Exploratory biomarker analysis of therapy response

To evaluate the effects of neoadjuvant dalpiciclib and letrozole on gene expression, we conducted an analysis using a 21-gene panel on baseline and post-surgery tumor biopsies from 25 patients. Patients were stratified into responders, defined by a PR, and non-responders, characterized by SD based on radiological assessments. In the responder group, we observed an upward trend in the expression of MYBL2, MK67, and BIRC5 (Supplementary Fig. 1), indicating the potential of these genes as predictive biomarkers for response to NAT. Although these changes were not statistically significant, validation

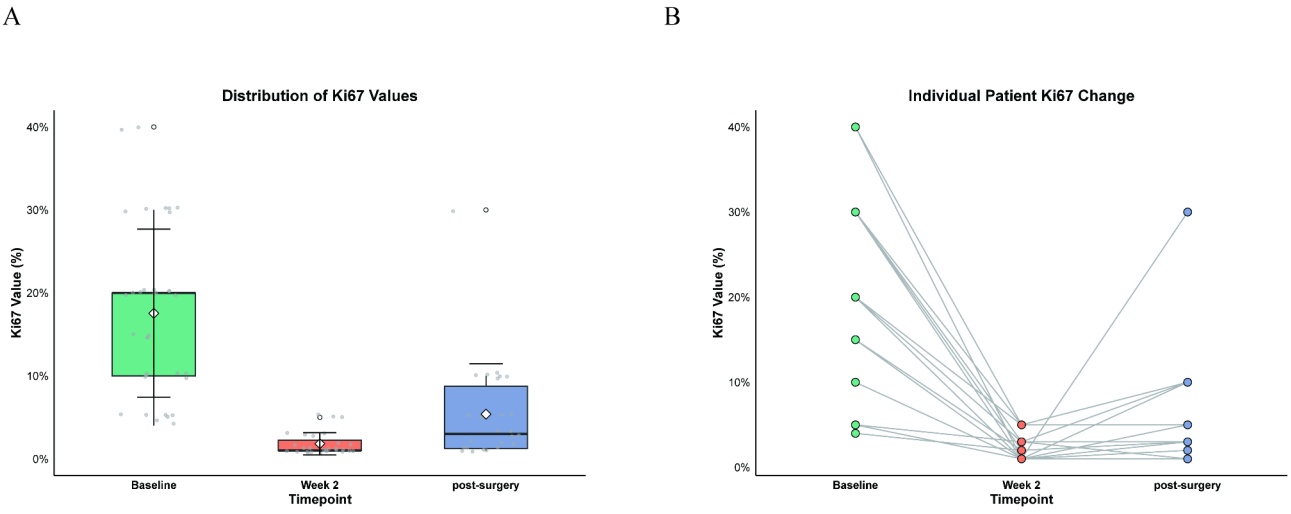

Fig. 2 Ki-67 expression and response. Box plots (**A**) and individual tumors (**B**) of Ki-67 expression of evaluable samples at baseline, 2 weeks posttreatment and post-surgery (Ki-67 value: mean ± standard deviation)

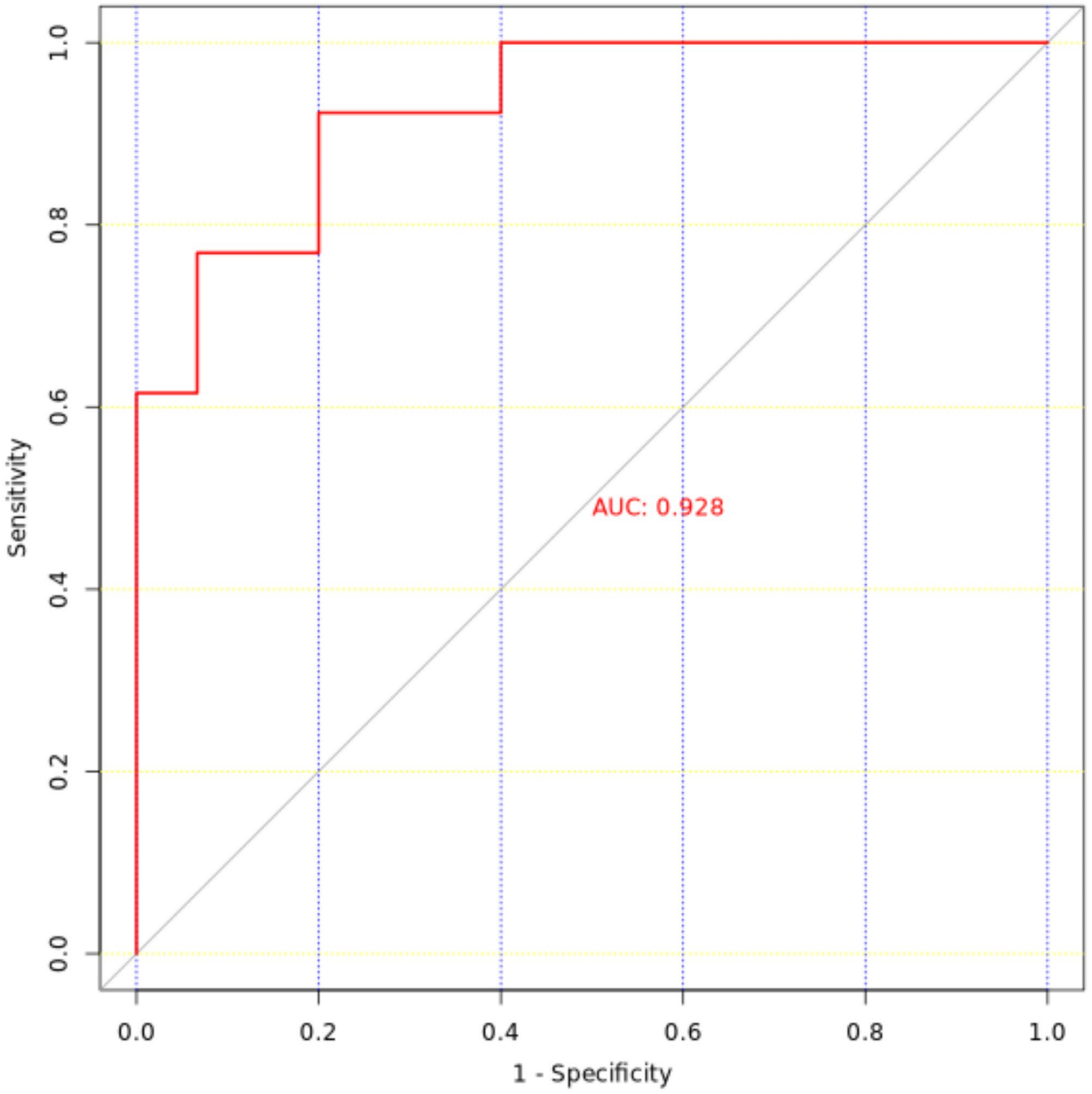

Fig. 3 Prediction model performance. Receiver operating characteristic curve was built with the area under curve of 0.928

in larger patient cohorts is required to substantiate these preliminary findings.

Lasso regression analysis was performed based on baseline gene expression and clinicopathological variables. Three genomic variables (TFRC, SCUBE2, MMP11A) and three clinicopathological factors (age, HER2 status, node status) were selected to construct a predictive model for response to NAT. The model's discrimination ability was assessed using the ROC curve, yielding an AUC of 0.928 (Fig. 3), indicating excellent performance in this dataset. Future investigations should prioritize external validation to confirm the robustness and generalizability of the model.

Discussion

The DARLING 01 trial demonstrated the therapeutic efficacy and safety of neoadjuvant dalpiciclib combined with letrozole in postmenopausal women with HR+/HER2- breast cancer. This combination showed promising anti-tumor activity, with an ORR of 55.2% and an acceptable safety profile. Malignant cell proliferation was significantly reduced, as indicated by Ki-67 after

two weeks of treatment, and a notable CCCA rate (75%) was observed. Additionally, we developed a predictive score system based on a 21-gene panel and constructed a model utilizing clinicopathological characteristics to predict response to NAT.

In line with the strong evidence supporting neoadjuvant AIs, numerous NET trials over the past decade have explored combination therapies for HR+/HER2- breast cancer, particularly with CDK4/6 inhibitors like palbociclib, ribociclib, and abemaciclib. Aligning closely with our results, the neoMONARCH trial showed a favorable benefit-risk profile for abemaciclib plus anastrozole in postmenopausal women with early-stage HR+/HER2 – breast cancer, with an ORR of 54%. Similarly, a recent exploratory trial reported a 51.7% ORR and a CCCA rate of 70% at 16 weeks with dalpiciclib and letrozole in postmenopausal women [13]. A recent meta-analysis further indicated that NET alone generally yields lower ORR rates, positioning AI plus CDK4/6 inhibitors just below chemotherapy in terms of efficacy and safety [14], underscoring their potential in treating HR+/HER2- breast cancer. These findings highlight the potential clinical application of CDK4/6 inhibitors plus AIs in the neoadjuvant setting.

In a selected population of postmenopausal patients with HR+/HER2- breast cancer, NET plus CDK4/6 inhibitor have been proved efficient to improve surgical outcome and better tolerated compared with either chemotherapy or NET alone [15, 16]. The NeoPAL and CORALLEEN trials, which compared palbociclib or ribociclib plus letrozole to conventional chemotherapy, demonstrated lower Ki-67 score, comparable molecular downstaging and better safety profiles [17, 18]. In comparison to AIs alone, the neoMONARCH study showed that 2 weeks of neoadjuvant treatment with abemaciclib, anastrozole, or their combination resulted in greater Ki-67 suppression and CCCA rates in the abemaciclib groups ($p < 0.001$), with Ki-67 reductions of -91% / -93% versus −63% and CCCA rates of 58% / 68% versus 14% [7]. Similarly, the PALLET trial reported greater Ki-67 reduction and higher CCCA rates (90% versus 59%) in patients treated with letrozole and palbociclib compared to letrozole alone [9]. An ongoing phase II study showed that dalpiciclib plus anastrozole or letrozole exhibited biological and clinical activity for ER+/HER2- breast cancer, resulted in an 82.6% CCCA rate at two weeks [19], further validating our results. Our study demonstrated that dalpiciclib plus letrozole led to potent cell-cycle arrest, with CCCA achieved in 75% of patients and a significant reduction in tumor Ki-67 levels (from 17.5 to 1.8%) after 2 weeks, supporting the notion that a cell-cycle inhibitor such as a CDK4/6 inhibitor is important in potent cell-cycle arrest and antitumor activity in HR+/HER2 – breast cancer.

Recent evidence suggests that pCR may not be a reliable indicator of efficacy, particularly in HR+/HER2- breast cancer, where its predictive value is lower [20]. Trials like neoMONARCH, PALLET and NeoPalAna [21] all demonstrated the low pCR rates (4%, 3%, 0% respectively) in postmenopausal women with HR+/HER2- breast cancer, consistent with our findings. The SAFIA phase III trial, which investigated the addition of palbociclib to fulvestrant (the first selective estrogen receptor degrader, SERD) as neoadjuvant therapy, also found no added pathological response benefit compared to fulvestrant alone [22]. Similarly, the FELINE trial suggested potential resistance mechanisms when combining CDK4/6 inhibitors with endocrine therapy [8]. These findings may be attributed to the short duration of treatment. More robust surrogate markers, along with long-term follow-up data on survival outcomes still needed to confirm the prognostic value and benefits of these combination treatments.

In addition to AIs, novel combination strategies involving SERDs and CDK4/6 inhibitors are being actively explored in the neoadjuvant setting for postmenopausal patients with HR+/HER2- early breast cancer. For example, the coopERA trial demonstrated the potential of giredestrant, a potent oral SERD, combined with palbociclib, as a promising approach in this context [23]. The result suggested the potential for CDK4/6 inhibitors combined with SERDs to overcome endocrine resistance and provided tailored treatment options for specific patient populations. As targeted therapies continue to advance, these innovative combinations offer significant opportunities to refine treatment strategies and provide tailored options for selected patient populations.

By establishing a NAT predictive model, we demonstrated its strong ability to predict treatment efficacy, with an AUC of 0.928. This suggests that TFRC, SCUBE2 and MMP11A may serve as novel predictive biomarkers for NAT response in postmenopausal patients with HR+/HER2- stage II-III breast cancer. TFRC has been validated as a stable reference gene for the quantification of biomarkers in breast cancer, highlighting its effectiveness in gene expression studies [24]. MMP11A and SCUBE2 have been identified as prognostic factors in breast cancer. Specifically, MMP11A has been shown to facilitate tumor proliferation by stabilizing Smad2 within the TGF-β signaling pathway [25]. In contrast, overexpression of SCUBE2 has been reported to suppress breast cancer cell proliferation [26], thereby demonstrating the complex and context-dependent roles of these proteins in breast cancer pathology. Recent study confirmed that as a downstream component of ER signaling, SCUBE2 is therefore specifically upregulated in luminal tumors, suggesting its prognostic value in luminal cancer [27]. Thus, the potential prognostic roles of TFRC, SCUBE2 and

MMP11A in patients receiving the NAT still need to be further explored.

The safety profile of dalpiciclib, when combined with letrozole, aligns with other CDK4/6 inhibitors like palbociclib and ribociclib, showing primarily hematological toxicities, particularly neutropenia [28, 29]. This was consistent with findings from the previous DAWNA-1 and DAWNA-2 trials [12, 30]. In this study, 45% of patients experienced grade 3 or 4 decreased neutrophil counts, with a median duration of 3 days (range 2–4). And no cases of febrile neutropenia were reported. Notably, neutropenia caused by CDK4/6 inhibitors differs from chemotherapy-induced neutropenia, as it is rapidly reversible due to its cytostatic effect on neutrophil precursors in the bone marrow. Most hematologic abnormalities are uncomplicated and can be managed with supportive care and dose adjustments [31]. This highlights the controllability of neutropenia risk associated with CDK4/6 inhibitors, even in combination with AIs, with no reports of severe or fatal neutropenia-related events. Nevertheless, vigilant monitoring of patients' blood counts throughout treatment remains essential to promptly identify and mitigate any potential serious AEs.

Some limitations of the current study should be acknowledged. Single-arm design with small sample sizes was inadequate to make definitive conclusions. The predictive performance of our established model requires validation in independent cohorts. Furthermore, the optimal duration of endocrine neoadjuvant therapy remains undefined. Our findings suggest that the ORR of 4-cycle NET may be more effective than 2-cycle NET. Building upon this observation, the DARLING-2 study is currently underway to investigate the efficacy and safety of 6-cycle CDK4/6 inhibitor combined with endocrine neoadjuvant therapy in endocrine-sensitive breast cancer patients.

Conclusions

Dalpiciclib combined with letrozole demonstrated favorable clinical efficacy as a neoadjuvant treatment in postmenopausal patients with HR+/HER2 – breast cancer, with a manageable safety profile. The potential predictive biomarkers of therapeutic efficacy identified in our study provide valuable insights for advancing personalized treatment strategies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13058-025-01976-0.

Supplementary material 1: **Supplementary Fig. 1.** Gene expression analysis. Heatmap of the 21 gene expression profiles pre- and post-treatment in response and non-response patients.

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Author contributions
Lina Zhang analyzed and interpreted the patient data and drafted the manuscript. Yueping Liu did the biomarker analysis. Chao Yang, Jie Ma, Yuntao Li, Ruizhen Luo, Jianjun Han, Xiaochun Wang, Zhisheng Zhang, Li Ma, Haifeng Cai, Xiangshun Kong, Zunyi Wang, Xinping Zhou, Jiajie Shi, Yanshou Zhang, Meiqi Wang, Jiaxing Wang collected the patient data. Cuizhi Geng designed the study and revised the manuscript. All authors read and approved the final manuscript.

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Data availability
Due to intellectual property and confidentiality obligations, individual deidentified participant data that underlie the results reported in this article can be requested 24 months after study completion. Qualified researchers must submit a proposal to the corresponding author at 46300349@hebmu.edu.cn, outlining the reasons for requesting the data. The leading clinical site and sponsor will review the request to ensure compliance with intellectual property and confidentiality obligations and will respond within two weeks. A signed data access agreement with the sponsor is required before any data can be shared. The study protocol is available alongside the published article.

Declarations

Ethics approval and consent to participate
The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the institutional ethics committee at each site and informed consent was taken from all the patients.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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