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Original Research

Real-World Efficacy and Prognostic Factors of CDK4/6 Inhibitors Combined With Aromatase Inhibitors in Postmenopausal Patients With Hormone Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer: A Retrospective Study

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Abstract

Background: In postmenopausal patients with hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2-) advanced breast cancer (ABC), the combination of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors and aromatase inhibitors (AIs) is used to overcome endocrine resistance. However, real-world evidence regarding the efficacy of dalpiciclib, a CDK4/6 inhibitor, remains limited. This study evaluated the real-world efficacy and safety of dalpiciclib combined with letrozole compared with letrozole monotherapy and explored factors associated with progression-free survival (PFS). **Methods:** This retrospective cohort study consecutively enrolled 172 postmenopausal patients with HR+/HER2- ABC who received first-line endocrine therapy and completed follow-up between January 2022 and December 2025. Participants were allocated to a combination therapy group (dalpiciclib + letrozole; n = 88) or a monotherapy group (letrozole; n = 84). PFS was the primary endpoint, and secondary endpoints included objective response rate (ORR), clinical benefit rate (CBR), and safety. **Results:** At 24-month follow-up, the combination therapy group demonstrated a significantly longer median PFS (20 months vs. 12 months) and a higher 24-month PFS rate (48.86% vs. 30.95%) compared to the monotherapy group (hazard ratio (HR) = 0.453; 95% confidence interval (CI): 0.304–0.676; $p < 0.001$). The combination group also demonstrated a significantly higher ORR (71.59% vs. 44.05%) and CBR (86.36% vs. 70.24%) (both $p < 0.05$). Multivariable logistic regression identified visceral metastasis, Luminal B subtype, Ki-67 >20%, and progesterone receptor (PgR) negativity as independent prognostic factors for PFS (all $p < 0.001$). Safety analysis revealed that neutropenia and leukopenia were the most frequent grade 3–4 adverse events in the combination group. Overall, the regimen exhibited a manageable safety profile. **Conclusions:** In postmenopausal patients with HR+/HER2- ABC, real-world evidence indicates that dalpiciclib in combination with AIs is associated with significantly improved first-line efficacy outcomes compared with AI monotherapy, with a manageable safety profile. Furthermore, visceral metastasis, the Luminal B subtype, elevated Ki-67 index, and PgR negativity were identified as independent factors associated with poorer prognosis. Causal inference is limited by the retrospective, non-randomized study design.

Keywords: dalpiciclib; CDK4/6 inhibitors; aromatase inhibitors; breast cancer; real-world study

1. Introduction

Breast cancer remains a great challenge worldwide, as approximately 2.3 million women were diagnosed with the disease in 2022, accounting for the highest number of new cases, whereas around 670,000 deaths were attributed to the condition [1]. Breast cancer remains a heterogeneous group of diseases, characterized by diverse morphology, biology, clinical features, and response to treatment. The hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2-) breast cancer is the most common molecular subtype, representing approximately 74% of all cases [2]. This cancer's growth and proliferation mainly depend on the sustained estrogen pathway activation [3]. Therefore, endocrine therapy serves as the cornerstone of treatment. The core strategy for the management of HR+/HER2- breast cancer, particularly in advanced or metastatic stages, involves blocking or interfering with the binding of estrogen to its receptors to inhibit downstream pro-proliferative signaling pathways [4]. For postmenopausal patients, aromatase inhibitors (AIs) such as letrozole, anastrozole, and exemestane effectively lower systemic estrogen. They work by blocking the peripheral conversion of androgens to estrogens, thereby suppressing tumor growth [5].

However, long-term observation in clinical practice has revealed the inherent limitations of endocrine monotherapy, specifically the development of endocrine resistance [6]. This resistance is classified as either primary or acquired. Regardless of the form, the emergence of en-

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docrine resistance signifies that tumor cells have developed escape mechanisms to bypass their dependence on the estrogen signaling pathway, leading to disease progression and ultimately becoming the primary reason for treatment failure [7,8]. In-depth investigation into the resistance mechanisms has uncovered a complex underlying molecular network, including mutations in the estrogen receptor 1 (*ESR1*) gene, the activation of bypass signaling pathways, and the dysregulation of the cyclin-dependent kinase (CDK) pathway [9]. Among these, the aberrant activation of the cell cycle regulatory pathway is considered a key mechanism that leads to endocrine resistance and drives continuous tumor cell proliferation [10,11].

Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors, which target cell cycle progression, have emerged as pivotal therapeutic agents for HR+/HER2- breast cancer [12]. These drugs function by blocking the interaction between CDK4/6 and Cyclin D, being responsible for maintaining the retinoblastoma protein (Rb) in a hypophosphorylated state. This, in turn, prevents E2 promoter-binding factor (E2F)-mediated gene transcription and subsequent S-Phase entry by stabilizing the Rb-E2F complex [13]. This molecular-level inhibition induces cell cycle arrest at the G1/S transition, thereby suppressing tumor proliferation and improving patient progression-free survival (PFS). Currently, the food and drug administration (FDA)-approved CDK4/6 inhibitors for advanced breast cancer (ABC) include palbociclib, ribociclib, and abemaciclib [14]. Dalpiciclib, the first domestically developed CDK4/6 inhibitor for the treatment of HR+/HER2- breast cancer in China, received its approval from the National Medical Products Administration (NMPA) in December 2021. In June 2023, the NMPA granted further approval for its use in combination with AIs as a first-line endocrine therapy for HR+/HER2- ABC [15].

Although the therapeutic regimen of CDK4/6 inhibitors combined with AIs has demonstrated significant efficacy in clinical trials, the applicability of the efficacy and safety data from these trials to real-world settings requires further validation [16]. As a recently launched CDK4/6 inhibitor developed in China, dalpiciclib still has limited real-world evidence regarding its efficacy and safety. While existing research has predominantly focused on the clinical trial level [17], no clear conclusions have been established regarding the efficacy differences between dalpiciclib plus an AI versus AI monotherapy in a real-world context; furthermore, key factors influencing patient prognosis remain unidentified. Concurrently, the prognosis of HR+/HER2- ABC patients is influenced by multiple factors. Identifying these prognostic factors is of great significance for optimizing treatment selection, developing individualized therapeutic strategies, and improving patient outcomes.

It was therefore the aim of the present study to compare first-line dalpiciclib plus an AI with AI monotherapy in postmenopausal Chinese patients with HR+/HER2- ABC. This study not only focuses on objective survival data such as PFS, objective response rate (ORR) and clinical benefit rate (CBR), but also systematically evaluates and compares the safety profiles of the two regimens, particularly the hematological toxicities of concern associated with combination therapy. Furthermore, this study will investigate a range of clinicopathological factors that may influence patient prognosis, attempting to identify key variables that can independently predict PFS through this analysis. We anticipate that the results of this study will provide valuable clinical evidence for positioning dalpiciclib in real-world practice, validating and supporting its status as a preferred first-line treatment strategy for postmenopausal HR+/HER2- ABC patients while offering new insights for optimizing patient selection and achieving personalized precision medicine.

2. Materials and Methods

2.1 Study Design and Population

This retrospective cohort study consecutively enrolled 172 postmenopausal patients with HR+/HER2- ABC who received first-line endocrine therapy and completed follow-up between January 2022 and December 2025. Patients were stratified into two groups according to their first-line treatment regimen: the combination therapy group (receiving dalpiciclib plus letrozole) and the monotherapy group (receiving letrozole only). The choice of treatment was non-randomized and was based on patient preference, financial status, underlying comorbidities, and the physician's comprehensive assessment. A detailed study flowchart is provided in Fig. 1.

2.2 Inclusion Criteria

This retrospective study involves participants who fulfill the following inclusion criteria: (1) diagnosed with HR+/HER2- ABC; (2) confirmed postmenopausal status; (3) all patients received the treatment regimen in the first-line setting. Prior (neo) adjuvant endocrine therapy was permissible, provided that the interval from the end of the last (neo) adjuvant endocrine therapy to recurrence in the advanced setting was >12 months; (4) Eastern Cooperative Oncology Group performance status (ECOG) score of 0–2; (5) presence of evaluable baseline tumor lesions, with complete records of treatment, follow-up, and radiological assessments.

2.3 Exclusion Criteria

Exclusion criteria were as follows: (1) prior use of any CDK4/6 inhibitor; (2) concurrent use of other anti-tumor therapies during the study treatment; (3) presence of other active malignancies.

2.4 Sample Size Calculation

As this was an exploratory, real-world, retrospective study, the sample size was not determined by an a priori

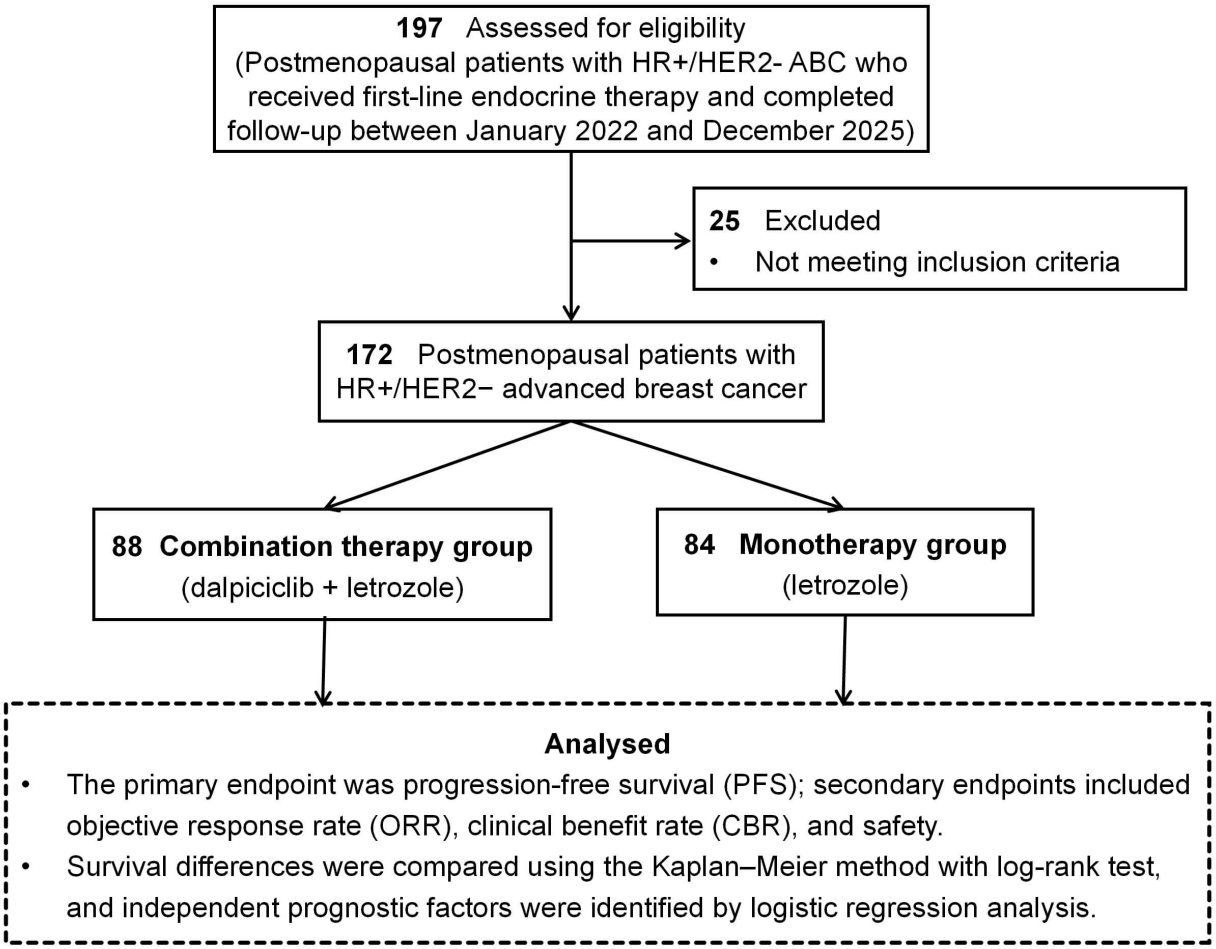


Fig. 1. Flowchart outlines the study design and population selection criteria. HR+, hormone receptor–positive; HER2-, human epidermal growth factor receptor 2–negative.

calculation based on hypothesis testing. To obtain comprehensive real-world data, we aimed to include all eligible patients throughout the study period. A post-hoc analysis was subsequently evaluated the statistical power of the study. Based on the observed median PFS difference between the combination and monotherapy groups (20.0 months vs. 12.0 months) and a hazard ratio (HR) of 0.453, the power was calculated using a log-rank test. With a two-sided alpha level set at 0.05, the final enrolled sample of 172 patients yielded a statistical power of approximately 90% to detect the observed HR. This indicates that the sample size within this study was adequate to detect a clinically meaningful survival difference between the two groups with a high probability.

2.5 Treatment Regimens

Combination therapy group: Patients received oral dalpiciclib at a dose of 150 mg once daily for 3 consecutive weeks, followed by a 1-week off period, constituting a 28-day cycle. Concurrently, they received continuous oral letrozole at 2.5 mg daily.

Monotherapy group: patients received continuous oral letrozole at 2.5 mg daily.

During the treatment period, dose modifications (interruption or reduction) and/or symptomatic supportive care for adverse events caused by dalpiciclib were permitted in accordance with the manufacturer's prescribing information and clinical practice guidelines.

2.6 Clinical Outcome Measures

Disease progression was assessed at monthly intervals as per response evaluation criteria in solid tumors (RECIST) version 1.1.

2.6.1 Primary Efficacy Endpoint

PFS: defined as the time from initiation of first-line therapy for advanced disease to the first documented radiological progression or death from any cause.

2.6.2 Secondary Efficacy Endpoints

(1) ORR: the proportion of patients achieving a complete response (CR) or partial response (PR).

(2) CBR: the proportion of patients achieving a CR, PR, or confirmed stable disease lasting ≥24 weeks.

2.6.3 Safety Endpoints

All adverse events (AEs) during treatment were collected from medical records, nursing notes, and laboratory reports. Severity was graded (1–5) in accordance with the national cancer institute common terminology criteria for adverse events (NCI-CTCAE) version 5.0. Key endpoints included the incidence of all-grade and grade 3–4 AEs.

Hematological toxicities: incidence and severity of neutropenia, leukopenia, anemia, and thrombocytopenia.

Non-hematological toxicities: such as abnormal liver function, nausea, vomiting, fatigue, and arthralgia.

2.7 Statistical Data Analysis

Statistical data analysis was performed using SPSS software version 26.0 (IBM, Armonk, New York, USA). Continuous variables were presented as mean ± standard deviation (SD) compared by *t*-test or median interquartile range (IQR) compared by Mann-Whitney U test, on the basis of distribution. Categorical variables were shown as n (%) and compared using χ^2 tests. PFS was analyzed with Kaplan-Meier curves (log-rank test) and reported as HR with 95% confidence interval (CI). Prognostic factors for PFS were identified via logistic regression. $p < 0.05$ was considered significant.

3. Results

3.1 Baseline Characteristics

As depicted in Table 1, there were no statistically significant differences ($p > 0.05$) were found regarding baseline clinicopathological characteristics including age, body mass index (BMI), cause of menopause, visceral metastasis, bone metastasis, number of metastatic organs, ECOG performance status score, molecular subtype at initial diagnosis (Luminal A/B), Ki-67 expression level, PgR expression status or prior history of endocrine therapy and chemotherapy.

3.2 Comparison of Patient PFS

As shown in Tables 2,3 and Fig. 2, at a follow-up of 24 months, the combination therapy group demonstrated a mean PFS of 19.557 months (95% CI: 18.544–20.570) and a median PFS of 20 months. In comparison, the monotherapy group achieved a mean PFS of 14.143 months (95% CI: 12.664–15.622) and a median PFS of 12 months.

The combination therapy group showed a significantly higher 24-month PFS rate than the monotherapy group (48.86% vs. 30.95%; Log-rank $\chi^2 = 18.661$, $p < 0.001$). The HR analysis for disease progression further revealed that patients receiving combination therapy exhibited a 54.7% reduction in the risk of disease progression or death compared to the monotherapy group (HR = 0.453, 95% CI: 0.304–0.676). This clearly revealed the significant superiority of the combination therapy regimen in prolonging progression-free survival.

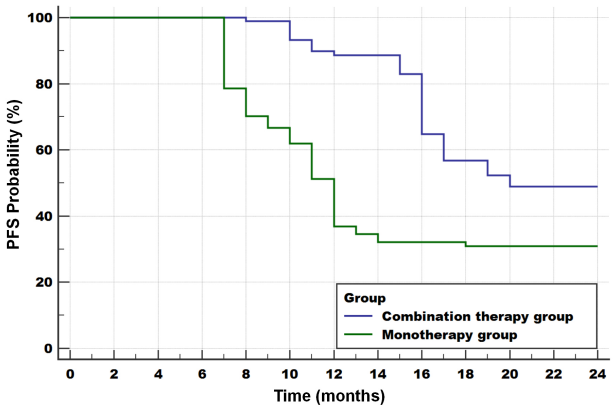


Fig. 2. Kaplan-Meier curves of PFS in patients receiving combination therapy versus monotherapy.

3.3 Comparison of ORR and CBR

As illustrated in Table 4, the ORR for the combination therapy group was 71.59%, significantly higher than the 44.05% for the monotherapy group ($\chi^2 = 13.396$, $p < 0.001$). Similarly, the CBR for the combination therapy group, at 86.36%, was also significantly higher than the 70.24% observed in the monotherapy group ($\chi^2 = 6.619$, $p = 0.010$). Results suggested that the combination therapy not only yields higher response rates but also enables more patients to achieve long-term, stable disease control.

3.4 Univariate Analysis of Factors Associated With Disease Progression

Patients were stratified into two cohorts based on the occurrence of disease progression within 24 months: a poor prognosis group (those with disease progression, n = 103) and a good prognosis group (those without progression, n = 69). Table 5 presents a univariate analysis of the association between baseline characteristics and patient prognosis.

The results demonstrated that visceral metastasis, Luminal B subtype, Ki-67 >20%, and PgR negativity were all significantly more prevalent in the poor prognosis group compared to good prognosis group ($p < 0.05$). In contrast, factors including age, BMI, bone metastasis, number of metastatic organs, ECOG score, and prior treatment history showed no statistically significant difference ($p > 0.05$). These findings provide an initial identification of key prognostic factors that may influence patient survival outcomes.

3.5 Logistic Regression Analysis

A logistic regression analysis was performed to investigate factors associated with disease progression at 24 months, with the results presented in Table 6. The analysis demonstrated that visceral metastasis (OR = 4.160, 95%

Table 1. Comparison of baseline patient data between combined therapy and monotherapy.

Variables	Combination therapy group (n = 88)	Monotherapy group (n = 84)	t/χ^2	p
Age (years), mean ± SD	55.73 ± 5.25	56.13 ± 6.04	−0.468	0.640
BMI (kg/m^2), mean ± SD	25.01 ± 3.21	25.34 ± 3.02	−0.695	0.488
Causes of menopause, n (%)			0.661	0.719
Natural menopause	67 (76.14)	61 (72.62)		
Surgical reasons	12 (13.64)	11 (13.10)		
Drug-related reasons	9 (10.23)	12 (14.29)		
Visceral metastasis, n (%)	50 (56.82)	45 (53.57)	0.183	0.669
Bone metastasis, n (%)	48 (54.55)	42 (50.00)	0.356	0.551
Number of metastatic organs, n (%)			0.851	0.356
<2	42 (47.73)	46 (54.76)		
≥2	46 (52.27)	38 (45.24)		
ECOG, n (%)			0.307	0.579
0	22 (25.00)	18 (21.43)		
≥1	66 (75.00)	66 (78.57)		
Initial diagnosis classification, n (%)			0.037	0.847
Luminal A	39 (44.32)	36 (42.86)		
Luminal B	49 (55.68)	48 (57.14)		
Ki-67 status, n (%)			0.490	0.484
≤20%	36 (40.91)	30 (35.71)		
>20%	52 (59.09)	54 (64.29)		
PgR status, n (%)			0.354	0.552
Positive	31 (35.23)	26 (30.95)		
Negative	57 (64.77)	58 (69.05)		
Previous endocrine therapy, n (%)			0.136	0.713
Yes	37 (42.05)	33 (39.29)		
No	51 (57.95)	51 (60.71)		
Previous chemotherapy, n (%)			0.507	0.477
Yes	35 (39.77)	29 (34.52)		
No	53 (60.23)	55 (65.48)		

Note: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group performance status; SD, standard deviation; PgR, progesterone receptor.

Table 2. Comparison of PFS between combination therapy group and monotherapy group.

PFS	n (%)	Mean (95% CI)	Median (95% CI)	HR (95% CI)	Log–rank χ^2	p
Combination therapy group	43 (48.86)	19.557 (18.544–20.570)	20.000 (17.000–20.000)	0.453 (0.304–0.676)	18.661	<0.001
Monotherapy group	26 (30.95)	14.143 (12.664–15.622)	12.000 (11.000–13.000)			

Note: PFS, progression-free survival; CI, confidence interval; HR, hazard ratio.

Table 3. Number of patients at risk in the combined therapy group and monotherapy group at follow-up time points.

Time (months)	0	2	4	6	8	10	12	14	16	18	20	22
Combined therapy group	88	88	88	88	87	82	78	78	57	50	43	43
Monotherapy group	84	84	84	84	59	52	31	27	27	26	26	26

CI: 2.177–7.951), initial diagnosis of the Luminal B subtype (OR = 6.434, 95% CI: 3.275–12.638), Ki-67 expression >20% (OR = 5.120, 95% CI: 2.633–9.958), and progesterone receptor (PgR) negative status (OR = 3.017, 95% CI: 1.564–5.821) were all independent poor prognostic factors for PFS ($p < 0.001$).

3.6 Incidence of Adverse Reactions

A detailed record and comparison of the AEs and their severity grades that occurred during the treatment period in both the combination and monotherapy groups are shown in Table 7A and Table 7B, respectively.

In the combination therapy group (Table 7A), the safety data showed that AEs were predominantly hematological in nature. These findings are consistent with the

Table 4. ORR and CBR comparison, n (%).

Group	n	ORR	CBR
Combination therapy group	88	63 (71.59%)	76 (86.36%)
Monotherapy group	84	37 (44.05%)	59 (70.24%)
χ^2		13.396	6.619
p		<0.001	0.010

Note: ORR, objective response rate; CBR, clinical benefit rate.

mechanism of action of CDK4/6 inhibitors. Among these, neutropenia was the most prominent AE, with a very high overall incidence; the combined rate of grade 3–4 neutropenia reached 85.22%. Leukopenia was also common, with a grade 3 incidence of over 65%. In contrast, while the incidence of anemia and thrombocytopenia was notable, the vast majority of these events were mild to moderate (grade 1–2). With respect to non-hematological toxicities, the most frequent occurrences included elevated liver enzymes, urinary tract infections, nausea, and fatigue. However, the incidence of severe (grade 3 or higher) events was extremely low, indicating good overall tolerability.

In the monotherapy group (Table 7B), the types and incidences of AEs were markedly different. The incidence of hematological toxicities was generally low, and virtually no severe (grade 3 or higher) events were observed. Non-hematological toxicities primarily included elevated liver enzymes, arthralgia, and hyperuricemia, with incidences that were not significantly different from those in the combination therapy group.

Compared to monotherapy, the addition of dalpiciclib significantly increased the risk of hematological toxicities, especially neutropenia. However, the pattern of these toxicities was predictable and manageable through clinical intervention. Regarding non-hematological toxicities, the combination regimen did not exhibit any unexpected or uncontrollable adverse reactions.

4. Discussion

For HR+/HER2- ABC, endocrine therapy remains the standard treatment, however, its clinical efficacy is often limited by the development of resistance [18]. By regulating key nodes of the cell cycle, CDK4/6 inhibitors provide a crucial therapeutic strategy for overcoming or delaying endocrine resistance [19]. This real-world study evaluated the efficacy and safety of first-line dalpiciclib combined with AI in postmenopausal HR+/HER2- ABC patients. The results clearly demonstrate that, compared with AI monotherapy, the combination regimen provides patients with a statistically significant PFS benefit and improves tumor response rates. This conclusion not only provides compact, regional evidence for the value of dalpiciclib in routine clinical practice but also offers new insights into the key clinicopathological features that influence the prognosis of this patient population.

The findings of this study are consistent with the core conclusions of a series of landmark Phase III clinical trials, such as the PALOMA-2 study for palbociclib [20], the MONALEESA-2 study for ribociclib [21], and the MONARCH-3 study for abemaciclib [22]. Together, these trials established the combination of a CDK4/6 inhibitor and AI as the global first-line standard of care for HR+/HER2- ABC. The data from our study are particularly significant as they validate that dalpiciclib the fourth CDK4/6 inhibitor to be marketed- can replicate its superior efficacy in a complex, real-world medical setting, beyond the data from its pivotal DAWNA-2 registrational clinical trial [23]. The clinical utilization of a real-world study lies in its addition of a more heterogeneous patient population, which may have a wider range of comorbidities and performance status scores than traditional clinical trials. Therefore, the significant prolongation of PFS and the notable improvements in ORR and CBR observed in our study serve as a vigorous supplement to, and real-world confirmation of, the conclusions of the DAWNA-2 study. This demonstrates a successful translation from clinical trial to clinical practice, indicating that the efficacy of the dalpiciclib combination regimen possesses good generalizability and stability in a broader Chinese patient population.

This study conducted an in-depth investigation into the independent prognostic factors affecting patient PFS. Logistic regression analysis revealed that treatment regimen, Ki-67 expression status, PgR status, molecular subtype at initial diagnosis, and visceral metastasis were independent predictors of PFS. Among these, a Ki-67 index >20%, PgR-negative status, the Luminal B subtype, and the presence of visceral metastasis were significantly associated with shorter PFS. Collectively, these factors reflect higher biological aggressiveness and greater proliferative activity of the tumor.

Visceral metastasis, particularly involving the liver and lungs, typically signifies a higher tumor burden and more aggressive disease biology. Consequently, it has been confirmed as a poor prognostic factor in numerous studies [24]. Luminal B breast cancer is characterized by higher proliferative activity and relatively lower sensitivity to endocrine therapy, which explains its association with a poorer prognosis [25,26]. Jones et al. [27] found that cell cycle and proliferation related genes, such as *TOP2A*, *CCNB1*, and *CDC20*, were significantly upregulated in Luminal B breast cancer, further supporting its high proliferative nature. As a direct marker of cell proliferation, high expression of Ki-67 intuitively reflects the rapid division of tumor cells and is a recognized indicator of poor prognosis [28,29]. Notably, PgR-negative status also demonstrated independent prognostic value. This suggests that even within estrogen receptor (ER) positive tumors, the integrity of the PgR pathway may be crucial for maintaining sensitivity to endocrine therapy. The absence of PgR may imply a certain dysfunction in the ER signaling path-

Table 5. Univariate analysis of factors associated with disease progression.

Variables	Poor prognosis group (n = 103)	Good prognosis group (n = 69)	t/χ^2	p
Age (years), mean ± SD	55.65 ± 5.41	56.33 ± 5.98	−0.777	0.438
BMI (kg/m^2), mean ± SD	25.40 ± 3.17	24.84 ± 3.01	1.163	0.247
Causes of menopause, n (%)			2.977	0.226
Natural menopause	80 (77.67)	48 (69.57)		
Surgical reasons	10 (9.71)	13 (18.84)		
Drug-related reasons	13 (12.62)	8 (11.59)		
Visceral metastasis, n (%)	71 (68.93)	24 (34.78)	19.488	<0.001
Bone metastasis, n (%)	59 (57.28)	31 (44.93)	2.528	0.112
Number of metastatic organs, n (%)			0.705	0.401
<2	50 (48.54)	38 (55.07)		
≥2	53 (51.46)	31 (44.93)		
ECOG, n (%)			2.220	0.136
0	28 (27.18)	12 (17.39)		
≥1	75 (72.82)	57 (82.61)		
Initial diagnosis classification, n (%)			31.579	<0.001
Luminal A	27 (26.21)	48 (69.57)		
Luminal B	76 (73.79)	21 (30.43)		
Ki-67 status, n (%)			24.661	<0.001
≤20%	24 (23.30)	42 (60.87)		
>20%	79 (76.70)	27 (39.13)		
ER status, n (%)				
Positive	103	69	-	-
Negative	0	0		
PgR status, n (%)			11.217	0.001
Positive	24 (23.30)	33 (47.83)		
Negative	79 (76.70)	36 (52.17)		
Previous endocrine therapy, n (%)			0.854	0.355
Yes	39 (37.86)	31 (44.93)		
No	64 (62.14)	38 (55.07)		
Previous chemotherapy, n (%)			1.146	0.284
Yes	35 (33.98)	29 (42.03)		
No	68 (66.02)	40 (57.97)		

ER, estrogen receptor; PgR, progesterone receptor.

Table 6. Logistic regression analysis of independent prognostic factors for PFS.

Variables	β	S.E	Z	p	OR (95% CI)
Visceral metastasis	1.426	0.330	4.313	<0.001	4.160 (2.177–7.951)
Initial diagnosis classification (Luminal B)	1.862	0.344	5.404	<0.001	6.434 (3.275–12.638)
Ki-67 status (>20%)	1.633	0.339	4.813	<0.001	5.120 (2.633–9.958)
PgR status (negative)	1.104	0.335	3.294	<0.001	3.017 (1.564–5.821)

way or the presence of bypass activation, thereby leading to a poorer prognosis [30,31]. The identification of these factors enables clinicians to recognize high-risk patients at the outset of treatment, allowing for closer monitoring and management. For patients presenting with these features, the risk of disease progression remains relatively high despite an intensified combination regimen, potentially necessitating closer follow-up or the exploration of further combination treatment strategies in the future.

The safety evaluation revealed a significantly higher incidence of hematological toxicities, particularly neutropenia and leukopenia, in the combination therapy group compared to monotherapy. Notably, grade 3–4 neutropenia affected 85.22% of the combination group, which is consistent with the known myelosuppressive properties of the CDK4/6 inhibitor class of drugs [32,33]. This incidence is comparable to that reported in the pivotal DAWNA-2 trial (86.0%) [23] and higher than in the PALOMA-2 trial (66.4%) [20]. This discrepancy may be attributed to several factors inherent to real-world practice: more heterogeneous patient populations with varying comorbidities, differences in monitoring frequency and laboratory assess-

Table 7A. Adverse reaction incidence during the combination therapy [n, (%)].

Adverse events	Combination therapy group (n = 88)			
	Grade 1–2	Grade 3	Grade 4	Grade 5
Hematological toxicities				
Anemia	53 (60.23)	6 (6.82)	0 (0.00)	0 (0.00)
Thrombocytopenia	43 (48.86)	3 (3.41)	1 (1.14)	0 (0.00)
Leukopenia	28 (31.82)	58 (65.91)	1 (1.14)	0 (0.00)
Neutropenia	11 (12.50)	57 (64.77)	18 (20.45)	0 (0.00)
Lymphopenia	9 (10.23)	3 (3.41)	1 (1.14)	0 (0.00)
Non-hematological toxicities				
Aspartate aminotransferase increased	26 (29.55)	2 (2.27)	0 (0.00)	0 (0.00)
Alanine aminotransferase increased	24 (27.27)	1 (1.14)	0 (0.00)	0 (0.00)
Urinary tract infection	20 (22.73)	0 (0.00)	0 (0.00)	0 (0.00)
Nausea	16 (18.18)	0 (0.00)	0 (0.00)	0 (0.00)
Arthralgia	14 (15.91)	0 (0.00)	0 (0.00)	0 (0.00)
Asthenia	12 (13.64)	1 (1.14)	0 (0.00)	0 (0.00)
Hyperuricaemia	12 (13.64)	0 (0.00)	0 (0.00)	0 (0.00)
Hypokalaemia	11 (12.50)	1 (1.14)	0 (0.00)	0 (0.00)
Blood creatinine increased	11 (12.50)	0 (0.00)	0 (0.00)	0 (0.00)
Vomiting	10 (11.36)	0 (0.00)	0 (0.00)	0 (0.00)
Hypophosphataemia	10 (11.36)	0 (0.00)	0 (0.00)	0 (0.00)
Upper respiratory tract infection	10 (11.36)	0 (0.00)	0 (0.00)	0 (0.00)
Blood alkaline phosphatase increased	5 (5.68)	0 (0.00)	0 (0.00)	0 (0.00)

Table 7B. Adverse reaction incidence during monotherapy group [n, (%)].

Adverse events	Monotherapy group (n = 84)			
	Grade 1–2	Grade 3	Grade 4	Grade 5
Hematological toxicities				
Anemia	7 (8.33)	1 (1.19)	0 (0.00)	0 (0.00)
Thrombocytopenia	7 (8.33)	0 (0.00)	1 (1.19)	0 (0.00)
Leukopenia	11 (13.10)	0 (0.00)	0 (0.00)	0 (0.00)
Neutropenia	11 (13.10)	0 (0.00)	0 (0.00)	0 (0.00)
Lymphopenia	1 (1.19)	0 (0.00)	0 (0.00)	0 (0.00)
Non-hematological toxicities				
Aspartate aminotransferase increased	31 (36.90)	1 (1.19)	0 (0.00)	0 (0.00)
Alanine aminotransferase increased	28 (33.33)	1 (1.19)	0 (0.00)	0 (0.00)
Urinary tract infection	18 (21.43)	2 (2.38)	0 (0.00)	0 (0.00)
Nausea	6 (7.14)	0 (0.00)	0 (0.00)	0 (0.00)
Arthralgia	13 (15.48)	0 (0.00)	0 (0.00)	0 (0.00)
Asthenia	8 (9.52)	0 (0.00)	0 (0.00)	0 (0.00)
Hyperuricaemia	13 (15.48)	0 (0.00)	0 (0.00)	0 (0.00)
Hypokalaemia	6 (7.14)	0 (0.00)	0 (0.00)	0 (0.00)
Blood creatinine increased	3 (3.57)	0 (0.00)	0 (0.00)	0 (0.00)
Vomiting	4 (4.76)	0 (0.00)	0 (0.00)	0 (0.00)
Hypophosphataemia	3 (3.57)	0 (0.00)	0 (0.00)	0 (0.00)
Upper respiratory tract infection	8 (9.52)	0 (0.00)	0 (0.00)	0 (0.00)
Blood alkaline phosphatase increased	7 (8.33)	0 (0.00)	0 (0.00)	0 (0.00)

ment schedules, and variations in dose modification patterns. In our cohort, dose reductions due to hematologic toxicity occurred in 34.1% (30/88) of patients, and granulocyte colony-stimulating factor (G-CSF) support was administered in 28.4% (25/88) of cases. Despite the higher incidence of grade 3–4 neutropenia, the vast majority of these events were clinically manageable through standardized monitoring, dose modifications, or symptomatic supportive care, with no treatment-related deaths reported. However, the vast majority of these hematological toxicities were

clinically manageable through dose modifications or symptomatic supportive care, with no treatment-related deaths reported. Non-hematological toxicities, such as abnormal liver function, gastrointestinal reactions, and fatigue, were also of similarly low severity in both groups. This safety profile aligns with data from clinical trials of dalpiciclib and other CDK4/6 inhibitors, indicating that in real-world clinical practice, the hematological toxicities of the combination therapy are predictable and manageable with standardized monitoring and timely intervention [34,35,36]. Although the monotherapy group exhibited mild hematological toxicity, its efficacy in disease control was found to be relatively limited; therefore, clinical decision-making requires an individualized trade-off between therapeutic benefit and risk of toxicity.

This study highlights key considerations for optimizing treatment in clinical practice. For postmenopausal HR+/HER2- ABC patients, especially those with high-risk features like visceral metastasis, a high Ki-67 index, Luminal B subtype, or PgR negativity, a first-line regimen combining a CDK4/6 inhibitor with AIs should be considered the preferred strategy to maximally delay disease progression and improve treatment response. It is important to note that while the real-world safety data support the feasibility of this combination therapy in a broad population, it necessitates the establishment of standardized protocols for toxicity monitoring and management, especially for the prevention and treatment of neutropenia. The independent prognostic factors identified in this study provide valuable clinical utility by aiding in pre-treatment risk stratification. In the future, these findings may enable more refined research into treatment selection based on these factors, such as exploring whether high-risk populations require combination with other targeted agents or earlier intervention with chemotherapy. As a CDK4/6 inhibitor indigenous to China, dalpiciclib demonstrated an efficacy and safety profile in this study similar to that of other internationally available drugs in its class. This provides an important therapeutic option for Chinese patients and supports its active use in the indicated patient population.

5. Study Limitations

First, treatment allocation was based on patient preference, financial considerations, and physician assessment rather than randomization, introducing potential selection bias. While baseline characteristics were comparable between groups, unmeasured confounders may influence outcomes. Second, we used logistic regression to analyze factors associated with disease progression at 24 months rather than Cox proportional hazards modeling for time-to-event data. This approach examines binary progression status rather than time to progression, which may limit comparability with randomized trials. Consequently, our findings demonstrate associations rather than causal relationships. The observed superiority of combination therapy may reflect unmeasured patient characteristics or treatment selection factors rather than true treatment effects. These results should be interpreted as hypothesis-generating real-world evidence complementary to randomized controlled trials such as DAWNA-2 [23], rather than definitive evidence of causality. The prognostic analysis pooled both treatment arms with treatment group as a covariate. Due to limited sample size, we were unable to validate prognostic factors separately within each treatment arm or formally test treatment-by-covariate interactions. Therefore, the identified prognostic factors should be interpreted as reflecting overall prognostic value rather than treatment-specific predictive effects. Future studies with larger cohorts should examine whether these factors differentially predict outcomes by treatment received.

6. Conclusions

This real-world study confirms that among postmenopausal HR+/HER2- ABC patients, first-line treatment with dalpiciclib plus letrozole significantly prolongs PFS and improves both ORR and CBR compared to letrozole monotherapy, while maintaining a manageable safety profile. Furthermore, Ki-67 status, PgR status, molecular subtype at initial diagnosis, and presence of visceral metastasis were identified as independent factors affecting prognosis. These results provide strong evidence for the application of dalpiciclib in real-world clinical practice, supporting its role as an important first-line treatment option for this patient population and offering a basis for individualized treatment decisions and prognostic assessment.

Availability of Data and Materials

The data supporting the findings of this study can be obtained from the corresponding author, upon request.

Author Contributions

YL was the principal designer of the study and was responsible for drafting the initial manuscript. KL was responsible for data organization and management. BL contributed to study design and conceptualization, supervised the research, critically revised the manuscript, provided final approval of the submitted version, assumes full responsibility for the integrity of the data and the accuracy of the data analysis, and serves as the primary contact for all editorial and reader correspondence. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by Yiyang Central Hospital Ethics Committee. (NO. 2025-28). The study was conducted in accordance with the Declaration of Helsinki. The

study design solely involved the analysis of pre-existing clinical data, did not interfere with patient treatment decisions, maintained the confidentiality of the patients, and posed minimal risk to patients. Therefore, a waiver of written informed consent was granted by the IRB. Patient data were fully anonymized to ensure privacy protection.

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Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/CEOG50016.

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