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ORIGINAL RESEARCH

Efficacy, Safety, and Prognostic Factors of Dalpiciclib Combined with Endocrine Therapy After Progression on CDK4/6 Inhibitors in Patients with HR+/HER2- Advanced Breast Cancer: A Retrospective Study

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Background: While the combination of cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) and endocrine therapy (ET) has established efficacy as first-line treatment for HR+/HER2- advanced breast cancer (ABC), resistance remains a critical clinical challenge. Dalpiciclib, a novel Chinese-developed CDK4/6i, has shown promising results in first-line therapy, yet data on its efficacy following progression on prior CDK4/6i is limited.

Methods: This retrospective, multicenter study enrolled 58 patients with HR+/HER2− ABC who experienced disease progression after prior CDK4/6i therapy and received dalpiciclib combined with ET between July 2022 and October 2024. The primary endpoint was progression-free survival (PFS); secondary endpoints included objective response rate (ORR), disease control rate (DCR), and safety. Subgroup analyses were performed based on baseline clinical characteristics and prior treatment histories.

Results: The median PFS was 6.3 months (95% CI: 5.2–11.0). The ORR and DCR were 8.6% and 32.8%, respectively. Patients with liver metastases exhibited significantly shorter PFS compared to those without (4.2 vs 8.0 months, p=0.027; HR=2.19, 95% CI: 1.08–4.43). Sequential use of dalpiciclib following progression on prior CDK4/6i progression was associated with longer PFS (8.0 vs 5.2 months, p=0.013; HR=0.42, 95% CI: 0.21–0.86). Patients with secondary endocrine resistance also experienced significantly longer PFS than those with primary resistance (7.2 vs 4.0 months, p=0.002; HR=3.28, 95% CI: 1.52–7.08). The most common grade ≥3 adverse events were neutropenia (22.4%) and leukopenia (17.2%). No patients discontinued treatment due to adverse events.

Conclusion: Dalpiciclib combined with endocrine therapy demonstrates clinical efficacy and a manageable safety profile as a cross-line treatment for HR+/HER2- ABC patients who progressed on prior CDK4/6i. Subgroups including those without liver metastases, with secondary endocrine resistance, and receiving sequential CDK4/6i therapy appear to derive greater benefit. These findings support dalpiciclib as a viable cross-line therapeutic option, warranting further prospective validation.

Keywords: dalpiciclib, CDK4/6 inhibitor, HR+/HER2- breast cancer, endocrine resistance, cross-line therapy

Introduction

Breast cancer is one of the most common malignancies among women. According to data from the World Health Organization's International Agency for Research on Cancer, 2.296 million new breast cancer cases and 666,000 deaths were reported worldwide in 2022, ranking it as the second most prevalent malignancy worldwide after lung cancer.[1,2] Hormone receptor (HR)+/human epidermal growth factor receptor 2 (HER2)- breast cancer represents the most common subtype, accounting for approximately

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70% of all cases.[3] Although patients with early-stage HR+/HER2- breast cancer generally have favorable outcomes with endocrine therapy, survival remains poor in the advanced setting, highlighting the need for more effective treatment strategies.

In recent years, Cyclin-Dependent Kinase 4/6 Inhibitors (CDK4/6i) have emerged as a novel targeted therapeutic agent, significantly transforming the therapeutic landscape for HR+/HER2- advanced breast cancer (ABC).[4] CDKs are critical in cell division, with CDK4 and CDK6 controlling the G1 to S phase transition. CDK4/6 inhibitors can effectively block cell proliferation signals, thereby inhibiting the growth of tumor cells.[5] Clinical trials (MONALEESA-2, PALOMA-2, MONARCH-3, and DAWNA-2) examining CDK4/6 inhibitor combined with aromatase inhibitors (AIs) in postmenopausal women with HR+/HER2- ABC in the first-line setting have shown that this combination reduces the risk of disease progression by nearly 50% compared to AI monotherapy.[6–9] Due to their remarkable efficacy demonstrated in multiple trials, the combination of CDK4/6 inhibitor with endocrine therapy (ET) has emerged as the first-line standard treatment for HR +/HER2- advanced breast cancer.[10] However, the widespread use of CDK4/6 inhibitors has been accompanied by emerging drug resistance. A real-world study indicated that about 12.5% of patients treated with CDK4/6 inhibitor experienced rapid disease progression within six months.[11] Resistance mechanisms include altered cell cycle regulation, activation of alternative signaling pathways, and changes in the tumor microenvironment.[12] Hence, the identification of effective post-progression therapies for CDK4/6i-treated patients remains an unmet clinical need. Currently, treatment after CDK4/6 inhibitors progression is usually selected according to prior treatment history, molecular alterations, and tumor burden. Targeted therapies such as PI3K/AKT inhibitors, oral SERDs, PARP inhibitors, or T-DXd may be considered in selected patients with actionable biomarkers, but many patients still lack a clearly defined treatment option.[13] If there is no specific target identified, CDK4/6 inhibitors can be considered for cross-line therapy with excellent tolerability and safety profile. Additionally, chemotherapy-based regimens may be chosen for patients with a high tumor burden.[14,15]

In China, four CDK4/6 inhibitors are currently approved: ribociclib, palbociclib, abemaciclib, and dalpiciclib—the latter being the first CDK4/6 inhibitor developed independently in China. The Phase III DAWNA-2 trial demonstrated dalpiciclib combined with letrozole or anastrozole as first-line treatment for HR+/HER2- advanced breast cancer achieved a median progression-free survival (PFS) of 33.4 months, with favorable efficacy and safety profiles.[9] However, evidence regarding dalpiciclib as a cross-line treatment after progression on prior CDK4/6 inhibitor remains limited. Therefore, we conducted this multicenter retrospective study to evaluate the efficacy and safety of dalpiciclib combined with ET in HR+/HER2- advanced breast cancer patients who progressed on previous CDK4/6 inhibitor treatment, and to explore potential prognostic factors.

Materials and Methods

Study Design

This two-center, retrospective study enrolled patients with HR+/HER2- advanced breast cancer who had progressed after treatment with CDK4/6 inhibitors at the Cancer Hospital of the Chinese Academy of Medical Sciences and Peking Union Medical College Hospital between July 2022 and October 2024. The inclusion criteria were as follows: 1) Female patients aged ≥18 years. 2) Histologically or cytologically confirmed HR+/HER2- tumor pathology, where HR+ was defined as immunohistochemistry (IHC) showing ≥1% of tumor cells expressing estrogen receptor (ER) or progesterone receptor (PR), and HER2- was defined as HER2 IHC 0/1+ or HER2 IHC 2+ with negative in-situ hybridization (ISH). 3) Patients with advanced breast cancer, defined as de novo stage IV or recurrent metastatic breast cancer, verified by clinical or imaging criteria. For patients initially diagnosed at early stages, only those who developed confirmed distant metastasis were included. 4) Received dalpiciclib cross-line therapy (continued dalpiciclib treatment after progression on a previous CDK4/6 inhibitor, allowing for discontinuous treatment with dalpiciclib and the previous CDK4/6 inhibitor) until disease progression, unacceptable toxicity, or patient death. 5) Availability of complete clinical data, including previous medications and durations, reasons for medication changes, and tumor progression status. 6) Minimum 3-month follow-up after starting dalpiciclib treatment. A total of 158 patients were initially screened for eligibility. Among them, 100 patients were excluded according to the predefined exclusion criteria, including 87 patients treated only with dalpiciclib without prior CDK4/6 inhibitor therapy, nine patients who switched to dalpiciclib not for disease progression (due to intolerance or adverse reactions to prior CDK4/6 inhibitor), three patients with HER2-positive disease, and one patient with a history of another solid tumor (Figure 1). Ultimately, a total of 58 patients were included in the

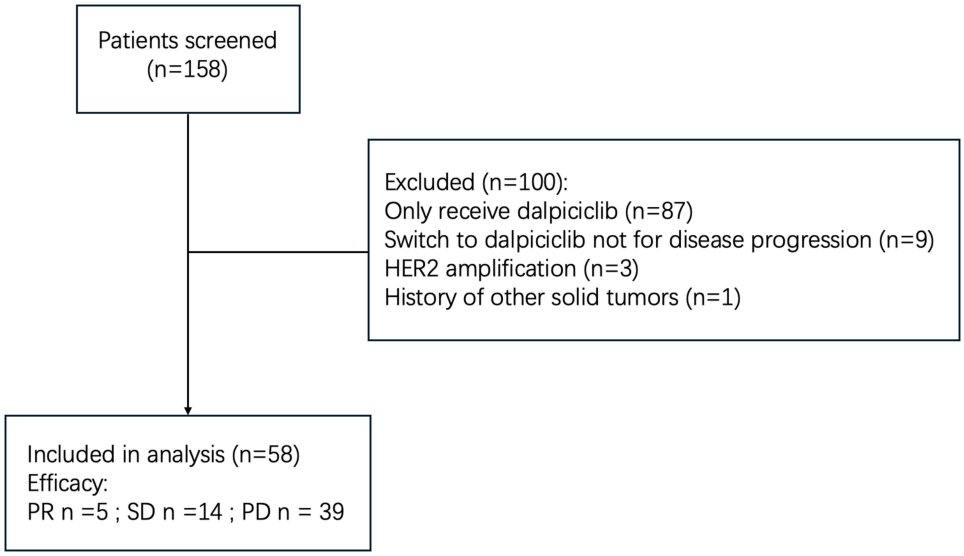

Figure 1 Study schematic.

analysis, and their clinical data were collected. The collected information included age, ECOG score, pathological features, tumor stage, previous treatments and duration, metastasis sites, adverse events, etc (Table 1). Dalpiciclib, the study drug, was administered at 150mg daily on a 21-day on/7-day off schedule in 28-day cycles. Dose adjustments were made by physicians based on patients' adverse reactions and individual circumstances. All CDK4/6 inhibitors were given in 28-day cycles until disease progression or intolerable toxicity. In our study, primary endocrine resistance and secondary endocrine resistance were defined according to the ABC6 guidelines.[16] Primary endocrine resistance is defined as relapse while on the first two years of adjuvant ET, or PD within first six months of first line ET-based therapy for ABC, while on ET (regardless of CDK4/6 inhibitors use). Secondary endocrine resistance is defined as other clinical situations. Sequential CDK4/6 inhibitor use was defined as

Table 1 Baseline Characteristics of HR+/HER2− Advanced Breast Cancer Patients Treated with Cross-Line Dalpiciclib Therapy

Characteristic	Patients (n=58)
Age, years, median (range)	59 (34–79)
ECOG performance status, No. (%)	
0–1	46 (79.3)
≥2	12 (20.7)
Stage, No. (%)	
I	5 (8.6)
II	15 (25.9)
III	8 (13.8)
De novo IV stage	9 (15.5)
NA	21 (36.2)
HER2 expression, No. (%)	
IHC 0	17 (29.3)
IHC 1+	12 (20.7)
IHC 2+ and FISH-	17 (29.3)
NA	12 (20.7)
Endocrine resistance status, No. (%)	
Primary endocrine resistance	13 (22.4)
Secondary endocrine resistance	45 (77.6)

(*Continued*)

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Table 1 (Continued).

Characteristic	Patients (n=58)
Metastatic sites, No. (%)	
Liver	23 (39.7)
Lung	27 (46.6)
Bone	45 (77.6)
Brain	4 (6.9)
Lymph node	45 (77.6)
Visceral metastases, No. (%)	
Yes	37 (63.8)
No	21 (36.2)
Number of metastatic lesions, No. (%)	
1 lesion	7 (12.1)
2 lesions	21 (36.2)
≥3 lesions	30 (51.7)
Previous treatment for advanced disease, No. (%)	
Previous chemotherapy	29 (50)
Previous CDK4/6i therapy	
Abemaciclib	37 (63.8)
Palbociclib	32 (55.2)
Ribociclib	1 (1.7)
Clinical trial	1 (1.7)
Prior CDK4/6i treatment, No. (%)	
1 line	44 (75.9)
≥2 lines	14 (24.1)
Prior CDK4/6i efficacy duration ≥ 6 months, No. (%)	
Yes	47 (81)
No	11 (19)
Prior CDK4/6i efficacy duration ≥ 12 months, No. (%)	
Yes	34 (58.6)
No	24 (41.4)
Sequential treatment of dalpiciclib, No. (%)	
Yes	38 (65.5)
No	20 (34.5)
Prior treatment lines in total, No. (%)	
1 line	22 (37.9)
2–3 lines	24 (41.4)
≥4 lines	12 (20.7)
Prior chemotherapy treatment lines, No. (%)	
0	31 (53.4)
1 line	17 (29.3)
>1 line	10 (17.2)
Prior endocrine treatment lines, No. (%)	
1 line	26 (44.8)
>1 line	32 (55.2)

Abbreviations: ECOG, eastern cooperative oncology group; NA, not available; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization.

a direct switch to dalpiciclib after prior CDK4/6 inhibitor treatment, without any intervening systemic therapy or change to other anti-tumor drugs. Patients who received other therapies between the prior CDK4/6 inhibitor and dalpiciclib were classified as non-sequential.

Endpoints

The primary endpoint of this study was progression-free survival (PFS), while the secondary endpoints included overall response rate (ORR), disease control rate (DCR), and toxicity. In this study, PFS was defined as the duration from the initiation of dalpiciclib treatment to the occurrence of tumor progression or death from any cause. Patients without progression or death at the data cutoff were censored at the date of last follow-up. ORR refers to the proportion of patients who achieved a complete response (CR) or partial response (PR) in tumor size reduction according to RECIST 1.1 criteria. DCR included patients with complete response (CR), partial response (PR), or stable disease (SD) as assessed by RECIST 1.1 criteria. The severity of adverse events (AEs) was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0).

Statistical Analysis

Descriptive statistical methods were used to analyze the baseline characteristics of patients. To simplify the model, continuous variables such as age were converted into categorical variables, which were described using frequencies and percentages. The median PFS (mPFS) was calculated using Kaplan–Meier plots with the log-rank test and Cox proportional hazards model. The effects of the variables were expressed as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). A level of $p < 0.05$ was considered significant. All statistical analyses in this study were conducted using SPSS and R software. No formal sample size calculation or multiple-testing correction was performed because of the retrospective and exploratory nature of this study. Therefore, subgroup analyses should be interpreted as exploratory.

Results

Patient Characteristics

The study ultimately enrolled 58 patients with HR+/HER2- advanced breast cancer from the Cancer Hospital of the Chinese Academy of Medical Sciences and Peking Union Medical College Hospital between July 2022 and October 2024. The median follow-up time was 11.5 months. The median age of the patients was 59 years (range 34–79 years). Detailed information is shown in Table 1. Five patients (8.6%) were initially diagnosed as stage I, 15 patients (25.9%) as stage II, eight patients (13.8%) as stage III, nine patients (15.5%) as *de novo* IV stage, and the stage of 21 patients (36.2%) was unknown. Although five patients were initially diagnosed at stage I, all developed distant metastases and met the inclusion criteria as recurrent metastatic breast cancer cases. 46 patients (79.3%) had an ECOG PS 0–1. Based on HER2 expression status, 17 patients (29.3%) were IHC 0, 12 patients (20.7%) were IHC 1+, another 17 patients (29.3%) were IHC2+/FISH-, and the status of 12 patients (20.7%) was unknown. The missing data for initial stage and HER2 expression were mainly due to the retrospective nature of the study, as some patients were referred from outside institutions and their original diagnostic records or complete pathology reports were unavailable in the medical charts. According to the ABC6 criteria, 13 patients (22.4%) had primary endocrine resistance, and 45 patients (77.6%) had secondary endocrine resistance. Twenty-three patients (39.7%) had liver metastases, 27 (46.6%) had lung metastases, 45 (77.6%) had bone metastases, four (6.9%) had brain metastases, 45 (77.6%) had lymph node metastases, and 37 (63.8%) had visceral metastases.

In the prior dalpiciclib treatment, 29 patients (50%) had received chemotherapy, 37 patients (63.8%) received previous CDK4/6 inhibitor treatment with abemaciclib, 32 (55.2%) received palbociclib, one (1.7%) received ribociclib, and one patient had participated in a CDK4/6 inhibitor clinical trial. Forty-four patients (75.9%) had received one CDK4/6 inhibitor before dalpiciclib, while 14 patients (24.1%) had received ≥2 CDK4/6 inhibitors. Regarding the efficacy of prior CDK4/6 inhibitor, 47 patients (81%) had a response duration of ≥6 months, and 34 patients (58.6%) had a response duration of ≥12 months. Dalpiciclib was sequentially administered after prior CDK4/6 inhibitors progression in 38 patients (65.5%). Before receiving dalpiciclib, most patients had undergone multiple lines of treatment for advanced disease. There were 22 patients (37.9%) received 1 line of prior treatment, 24 (41.4%) received 2–3 lines, and 12 patients (20.7%) received ≥ 4 lines (the cross-line dalpiciclib treatment was not included).

Efficacy

As of December 2024, among 58 patients, none achieved CR, 5 patients achieved PR, 14 patients achieved SD, and 39 patients experienced disease progression. The ORR was 8.6% (5/58), and the DCR was 32.8% (19/58). The mPFS for all patients included in the analysis was 6.3 (95% CI: 5.2–11) months (Figure 2A).

We subsequently stratified patients based on their baseline characteristics and conducted subgroup analyses. Notably, patients with liver metastasis had a significantly shorter mPFS than those without (4.2 vs 8 months, p=0.027; HR=2.19, 95% CI: 1.08–4.43; Figure 2B). Among patients with lung, bone, brain, and visceral metastases, the mPFS was shorter than those without such metastases, but the differences were not statistically significant (lung: 6.3 vs 7 months, p=0.934; bone: 6.3 vs NA months, p=0.638; brain: 5.25 vs 6.3 months, p=0.178; viscera: 5.5 vs NA months, p=0.081; Figure 2C–F). Simultaneously, patients with more metastatic sites had a shorter mPFS (6 vs 7 vs NA months, p=0.263; Figure 3A).

Regarding prior treatment, patients who received multiple lines of frontline endocrine therapy had a significantly shorter mPFS (5.3 vs NA months, p<0.001; Figure 3B). Patients who received more than one line of chemotherapy also had a meaningfully shorter mPFS compared to those who received only one line or no chemotherapy (4 vs 6.3 vs 11 months, p=0.007; Figure 3C). Furthermore, patients with diverse total treatment lines prior to crossline dalpiciclib therapy demonstrated a notably distinct mPFS duration. The patients who received 1 prior treatment line had a longer mPFS than those patients who received 2–3 and ≥ 4 lines (NA vs 6 vs 4 months, p<0.001; Figure 3D). Patients previously treated with two or more CDK4/6 inhibitors demonstrated a significantly shorter mPFS compared to those who received only one (5.2 vs 7.4 months, p=0.013; Figure 3E). Additionally, patients who received dalpiciclib sequentially after previous CDK4/6 inhibitors progression had a longer mPFS (8 vs 5.2 months, p=0.013; HR=0.42, 95% CI: 0.21–0.86; Figure 3F).

For patients with a prior CDK4/6 inhibitor response duration of ≥6 months, the mPFS was numerically longer than that in patients with a duration of <6 months, however, the difference was not statistically significant (6.5 vs 4 months,

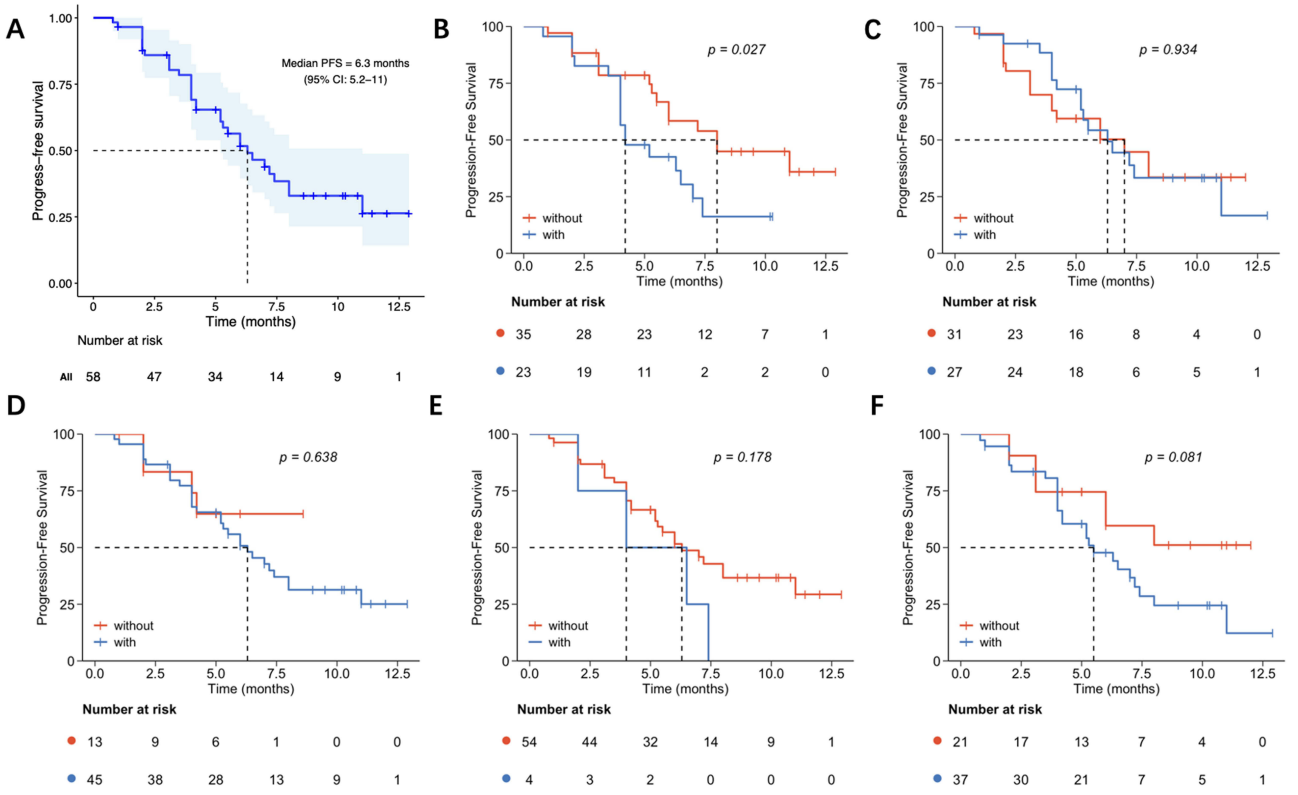

Figure 2 Kaplan–Meier plot for PFS in all patients and subgroups. (**A**) Kaplan–Meier plot for PFS in all patients who received cross-line dalpiciclib treatment. (**B**) Kaplan–Meier plot for liver metastases-associated PFS. (**C**) Kaplan–Meier plot for lung metastases-associated PFS. (**D**) Kaplan–Meier plot for bone metastases-associated PFS. (**E**) Kaplan–Meier plot for brain metastases-associated PFS. (**F**) Kaplan–Meier plot for visceral metastases-associated PFS. NA indicates that the median PFS was not reached by the data cutoff.

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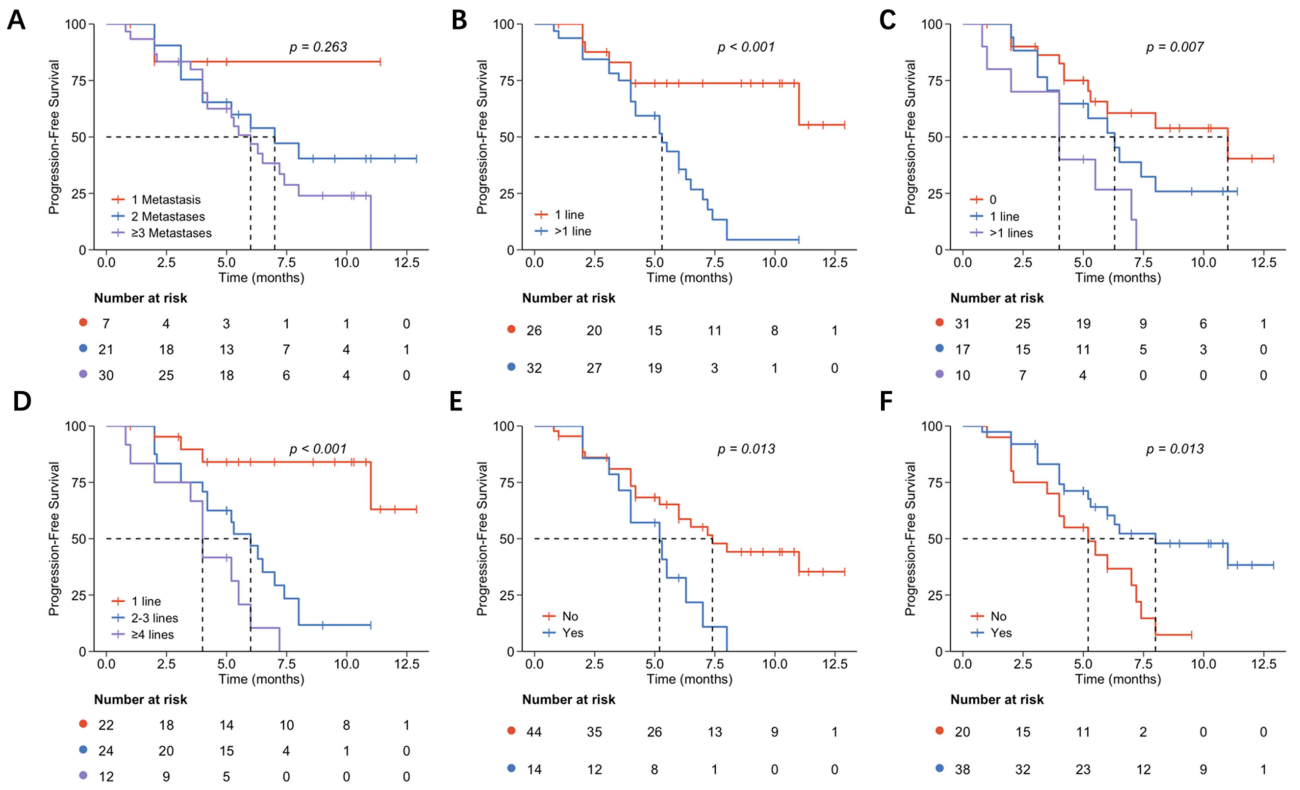

Figure 3 Kaplan–Meier plot for PFS in subgroups. (**A**) Kaplan–Meier plot for PFS in patients with different metastatic sites. (**B**) Kaplan–Meier plot for PFS in patients with different lines of prior endocrine therapy. (**C**) Kaplan–Meier plot for PFS in patients with different lines of prior chemotherapy. (**D**) Kaplan–Meier plot for PFS in patients with different lines of prior total therapy. (**E**) Kaplan–Meier plot for PFS stratified by whether patients received ≥2 lines of frontline CDK4/6 inhibitors. (**F**) Kaplan–Meier plot for PFS stratified by whether patients received sequential dalpiciclib therapy after previous CDK4/6 inhibitors. NA indicates that the median PFS was not reached by the data cutoff.

p=0.14; Figure 4A). Similarly, no statistically significant difference in mPFS was observed between patients with a prior CDK4/6 inhibitor efficacy duration of ≥12 months and those with a duration of <12 months (7.4 vs 6 months, *p*=0.381; Figure 4B). The mPFS of dalpiciclib was 6 months for patients who received abemaciclib as prior CDK4/6 inhibitor treatment and 5.5 months for those who received palbociclib.

According to patients' sensitivity to endocrine therapy, those with primary endocrine resistance had a significantly shorter mPFS compared to those with secondary endocrine resistance (4 vs 7.2 months, *p*=0.002; HR=3.28, 95% CI: 1.52–7.08; Figure 4C).

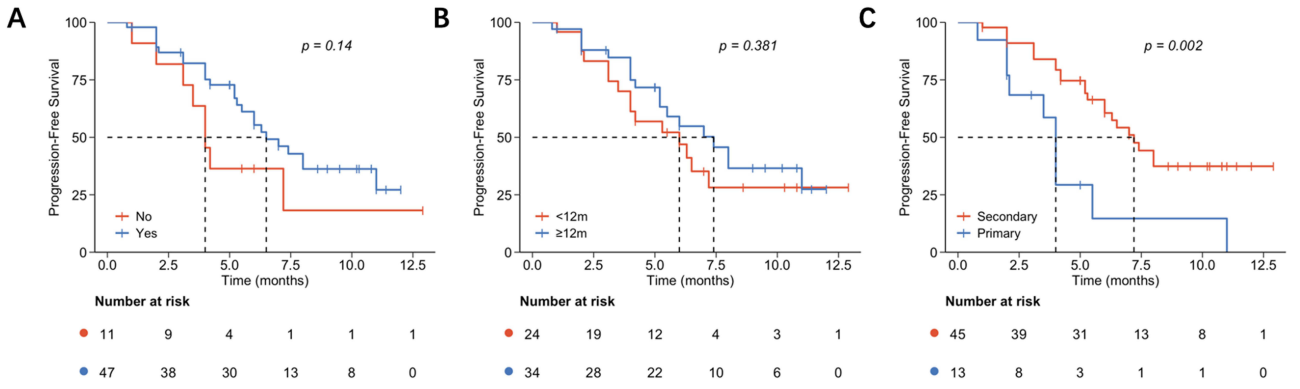

Figure 4 Kaplan–Meier plot for PFS in subgroups. (**A**) Kaplan–Meier plot for PFS stratified by whether the efficacy of prior CDK4/6 inhibitors was ≥ 6 months. (**B**) Kaplan–Meier plot for PFS stratified by whether the efficacy of prior CDK4/6 inhibitors was ≥ 12 months. (**C**) Kaplan–Meier plot for PFS in patients with different endocrine resistance status.

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We further analyzed patients by HER2 expression. Among 46 patients with known HER2 IHC status, 29 were HER2-low (IHC 1+ or 2+/FISH-) and 17 were HER2-zero (IHC 0). The median PFS was 8 months for HER2-low and 4 months for HER2-zero patients (p=0.24).

Safety

All adverse events (AEs) observed in patients receiving cross-line dalpiciclib treatment are presented in Table 2. The primary AEs associated with this therapy were hematological toxicities, with the most common ≥ grade 3 adverse events being neutropenia (22.4%), leukopenia (17.2%), and thrombocytopenia (3.4%). The overall incidence of neutropenia was 72.4%, leukopenia was 69.0%, and anemia was 34.5%. Non-hematological toxicities were less severe, with AST/ALT elevations (15.5%/20.7%), creatinine elevations (20.7%), nausea (8.6%), and rash (6.9%) being more common, although the incidence of ≥ grade 3 was below 2% for all these events. No patients discontinued dalpiciclib treatment due to adverse reactions. Only two (3.4%) patients required a dose reduction of dalpiciclib - one for rash intolerance and another for hematologic toxicity. In our real-world practice, only one patient experienced grade 4 leukopenia, which prompted dose reduction of dalpiciclib. For other adverse events, treatment dose adjustment was determined by the treating physician according to the patient's individual clinical status and tolerability. No severe AEs were observed, indicating that cross-line dalpiciclib therapy exhibits a favorable safety profile with manageable hematological toxicities.

Discussion

The combination of CDK4/6 inhibitors and endocrine therapy has become the standard first-line treatment for patients with HR+/HER2- advanced breast cancer. While CDK4/6 inhibitors have significantly improved patient outcomes, they have also introduced new clinical challenges, primarily due to treatment resistance and disease progression in many patients. Currently, no standardized treatment exists for patients who progress on prior CDK4/6 inhibitors, making cross-line therapy with these agents a focal point of research. However, studies on cross-line use of CDK4/6 inhibitors have not reached consistent conclusions. Notably, only ribociclib (MAINTAIN study) and abemaciclib (postMONARCH study) have demonstrated significant efficacy in cross-line treatment, providing evidence-based support for the cross-line application of CDK4/6 inhibitors. The Phase II MAINTAIN trial demonstrated that ribociclib combined with endocrine therapy (ET) significantly prolonged progression-free survival (PFS) by nearly 2.5 months compared to ET alone in patients who progressed on palbociclib or other CDK4/6 inhibitors (5.29 vs 2.76 months, HR=0.57, 95% CI: 0.39–0.85).[17] The phase III postMONARCH study confirmed the efficacy of abemaciclib as a cross-line treatment, showing that the combination of fulvestrant and abemaciclib extended PFS compared to fulvestrant monotherapy (6.0 vs 5.3 months, HR=0.73, 95% CI: 0.57~0.95).[18] Additionally, multiple retrospective studies and meta-analysis have supported the clinical benefits and favorable

Table 2 Adverse Events of All Grades

AE	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3/4 n (%)
Anemia	6 (10.3)	13 (22.4)	1 (1.7)	0 (0)	20 (34.5)	1 (1.7)
Leukopenia	5 (8.6)	25 (43.1)	9 (15.5)	1 (1.7)	40 (69.0)	10 (17.2)
Neutropenia	5 (8.6)	24 (41.4)	13 (22.4)	0 (0)	42 (72.4)	13 (22.4)
Thrombocytopenia	2 (3.4)	4 (6.9)	2 (3.4)	0 (0)	8 (13.8)	2 (3.4)
AST elevation	4 (6.9)	5 (8.6)	0 (0)	0 (0)	9 (15.5)	0 (0)
ALT elevation	5 (8.6)	7 (12.1)	0 (0)	0 (0)	12 (20.7)	0 (0)
TBIL elevation	1 (1.7)	2 (3.4)	0 (0)	0 (0)	3 (5.2)	0 (0)
Creatinine elevation	11 (19.0)	1 (1.7)	0 (0)	0 (0)	12 (20.7)	0 (0)
Fatigue	2 (3.4)	0 (0)	0 (0)	0 (0)	2 (3.4)	0 (0)
Nausea	3 (5.2)	2 (3.4)	0 (0)	0 (0)	5 (8.6)	0 (0)
Diarrhea	2 (3.4)	0 (0)	0 (0)	0 (0)	2 (3.4)	0 (0)
Rash	1 (1.7)	2 (3.4)	1 (1.7)	0 (0)	4 (6.9)	1 (1.7)

Abbreviations: AE, Adverse Event; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; TBIL, Total Bilirubin.

safety profile of cross-line treatment with CDK4/6 inhibitors.[19–21] However, not all cross-line CDK4/6 inhibitors have shown significant efficacy. The phase II PACE trial revealed that the combination of fulvestrant and palbociclib did not improve PFS compared to fulvestrant monotherapy (4.6 vs 4.8 months, HR=1.11, 95% CI: 0.74~1.66).[22] Likewise, the PALMIRA study showed no significant improvement in PFS with continued use of palbociclib combined with second-line endocrine therapy after progression on palbociclib-based treatment (4.2 vs 3.6 months, HR=0.84, 95% CI: 0.66–1.07).[23] These findings suggest that switching only the endocrine therapy drug while continuing palbociclib after disease progression may not be effective. To facilitate cross-study interpretation, we added Table 3 comparing the baseline characteristics and efficacy outcomes of the current cross-line CDK4/6 inhibitor trials, including MAINTAIN, PACE, PALMIRA, and postMONARCH. Therefore, the 2024 CSCO guidelines recommend switching to another CDK4/6 inhibitor combined with ET as a 2A-level recommendation for post-CDK4/6i progression.[24] At the same time, the Chinese-developed CDK4/6 inhibitor dalpiciclib demonstrated a significant PFS advantage in the DAWNA-2 study, potentially offering a new option for cross-line therapy.

Therefore, this study investigated the efficacy, safety, and prognostic factors of dalpiciclib combined with endocrine therapy in HR+/HER2- advanced breast cancer patients who progressed on prior CDK4/6 inhibitors. The results showed that this treatment strategy still provided good clinical benefits for patients with advanced disease who had undergone multiple lines of therapy, with a mPFS of 6.3 months, slightly longer than reported in previous large-scale clinical studies. However, a smaller real-world study involving 30 patients revealed a mPFS of 11.8 months with continued CDK4/6 inhibitor use after initial progression, surpassing our study's results.[25] Notably, this population had fewer prior lines of treatment and a lower percentage of visceral metastases, which could explain the longer PFS observed. Although the improvement in survival duration was not significant, dalpiciclib demonstrated a manageable safety profile compared to other optional regimens, particularly chemotherapy and antibody-drug conjugates (ADC) drugs, thus enhancing its acceptability among patients.

Regarding prognostic factors, patients with liver metastasis had a significantly shorter mPFS and nearly doubled the progression risk compared to those without, consistent with a German multicenter retrospective study.[26] This suggests that liver metastasis was associated with shorter PFS for cross-line CDK4/6 inhibitors treatment. A retrospective study by Qi Zhao et al confirmed that patients with liver metastasis had a shorter mPFS (11.4 vs 6.1 months).[21] Clinical trials, such as MONARCH 2 and 3, also demonstrated significantly shorter PFS in patients with liver metastasis treated with abemaciclib.[8,27] These findings indicate that liver metastasis is a significant negative prognostic factor for CDK4/6 inhibitor treatment, even in cross-line therapy. Although liver metastasis is a type of visceral metastasis, in our study, there was no significant correlation between the absence of visceral metastasis and PFS benefit, with a p-value of 0.08. Furthermore, our research on the number of metastatic sites showed that a higher number of metastatic sites corresponded to a shorter mPFS, albeit not statistically significant. We predict that a greater metastatic burden may contribute to a poorer prognosis. Given the limited sample size of our study, further investigation with a larger patient population is necessary. Importantly, this finding should not be interpreted to mean that patients with liver metastases are unsuitable for

Table 3 Key Characteristics and Efficacy Outcomes of Representative Cross-Line CDK4/6i Trials

Study	PALMIRA	MAINTAIN	PACE	postMONARCH
Investigational CDK4/6i	Palbociclib	Ribociclib	Palbociclib	Abemaciclib
Study phase	II	II	II	III
Sample size	198	119	220	368
Treatment regimen	Palbociclib + ET vs ET alone	Ribociclib + switched ET vs placebo + switched ET	Palbociclib + fulvestrant ± PD-L1 inhibitor vs fulvestrant alone	Abemaciclib + fulvestrant vs placebo + fulvestrant
Prior treatment lines	1L	1–4L	1–2L	–
Prior CDK4/6 inhibitor exposure	198 (100%) palbociclib	103 (86.5%) palbociclib; 14 (11.7%) ribociclib; 2 (1.7%) abemaciclib	200 (90.9%) palbociclib; 10 (4.5%) ribociclib; 9 (4.1%) abemaciclib	217 (59%) palbociclib; 122 (33.2%) ribociclib; 28 (7.6%) abemaciclib
Median PFS	4.2 vs 3.6 months; HR=0.84 (95% CI: 0.66–1.07)	5.29 vs 2.76 months; HR=0.57 (95% CI: 0.39–0.85)	4.6 vs 4.8 months; HR=1.11 (95% CI: 0.79–1.55)	6.0 vs 5.3 months; HR=0.73 (95% CI: 0.57–0.95)
Study outcome	Negative	Positive	Negative	Positive

Abbreviation: ET, endocrine therapy.

cross-line dalpiciclib treatment. Rather, it indicates that these patients had poorer outcomes than those without liver metastases in our cohort. Because this was a single-arm study without a control group, we could not determine whether dalpiciclib was preferable to chemotherapy or other treatment options in this subgroup.

As we did not limit the number of previous CDK4/6 inhibitor therapy lines for enrolled patients, over half had undergone multiple treatment regimens prior to dalpiciclib. Our subgroup analysis focused on factors such as the number and duration of prior lines of therapy, whether they were consecutive, and the types of medications used (chemotherapy or endocrine therapy). Since the number of prior therapy lines represents the full extent of treatment before initiating dalpiciclib, it effectively reflects the treatment line at which dalpiciclib was introduced. Regarding the impact of treatment lines, Müller et al and Edman Kessler et al demonstrated in their real-world studies that the number of previous treatment lines is an independent predictor of CDK4/6 inhibitor efficacy.[26,28] This aligns with our findings, the observed association between fewer prior lines and improved PFS suggests that earlier use of dalpiciclib may lead to better clinical outcomes. We speculate that the possible reason for the above phenomenon is that patients who have received more lines of therapy have developed resistance to multiple treatments, thus exhibiting a poorer response to therapy. Furthermore, we found that patients who had previously used a greater variety of CDK4/6 inhibitor therapies were at increased risk of disease progression during cross-line treatment than those who had only used one type. This suggests that patients who have repeatedly used CDK4/6 inhibitor in the past may develop drug resistance, indicating a need to switch to alternative therapies targeting different pathways to achieve better survival durations. Furthermore, we noticed significant variations in the efficacy of prior CDK4/6 inhibitor therapy among different patients. Therefore, we grouped patients based on the duration of prior CDK4/6 inhibitor therapy response, using 6 and 12 months as cut-offs. Our analysis revealed that patients who experienced longer durations of response to prior CDK4/6 inhibitor therapy showed better responses to subsequent dalpiciclib treatment, resulting in longer PFS, although the difference was not statistically significant. However, a retrospective study by Qi Zhao et al reported contrary findings. In their study, a subgroup of patients who responded to prior CDK4/6 inhibitor therapy for more than 6 months had a higher number of prior treatment lines, which may have influenced the ultimate conclusion.[21] Future research could explore these observations further by expanding the sample size and conducting matched prospective studies.

A study by Wander et al demonstrated that sequential CDK4/6 inhibitor therapy (abemaciclib after prior CDK4/6 inhibitor progression) significantly prolonged median progression-free survival compared to the non-sequential group (8.4 vs 3.9 months), reducing the risk of disease progression by 58%.[20] This suggests that continuous targeted inhibition of the cell cycle may delay disease progression. Similarly, in our research, the sequential administration of dalpiciclib and frontline CDK4/6 inhibitor therapy led to an extended mPFS, offering a PFS advantage of 2.8 months, aligning with the results observed in Wander's study and supporting the clinical benefit of cross-line CDK4/6 inhibitor use.

Endocrine resistance plays a pivotal role in HR+/HER2− ABC, as approximately half of HR+ patients develop endocrine resistance during treatment. Therefore, based on the ABC6 criteria, we divided the patients into two subgroups: primary endocrine resistance and secondary endocrine resistance. Our results reveal that patients with primary endocrine resistance had shorter PFS than those with secondary resistance. The elevated progression risk in the primary resistance group may reflect its intrinsic estrogen-independent characteristics, such as baseline PIK3CA mutations or dysregulated cell cycle control, suggesting that ER-independent targeted strategies should be explored for this population.[29]

Notably, while HER2-low breast cancer has gained research attention, our analysis found no significant outcome differences between HER2-low (IHC 1+ or 2+/FISH-) and HER2-zero (IHC 0) patients. This result may be confounded by sample size limitations, warranting validation in larger cohorts to clarify HER2 expression's role in cross-line CDK4/6 inhibitor efficacy.

In terms of safety, the cross-line therapy involving dalpiciclib in our study exhibited manageable safety profiles. Hematologic toxicity was the primary concern, whereas non-hematologic effects were mild. Grade ≥3 events primarily included neutropenia (22.4%) and leukopenia (17.2%), with all-grade neutropenia affecting 72.4% of patients—none required treatment discontinuation. Non-hematologic toxicities, such as elevated AST/ALT (15.5%/20.7%), were predominantly of grade 1–2, with grade 3 or higher events infrequently reported. Dalpiciclib, through classical isostere replacement in its molecular structure, introduces a piperidine moiety, eliminating the risk of glutathione capture and reducing the risk of liver injury.[30] This is supported by DAWNA-2 data, where first-line dalpiciclib showed below 2% grade ≥3 AST/ALT elevations,

indicating lower hepatotoxicity than other CDK4/6 inhibitors.[9] It is noteworthy that no patients in our study discontinued treatment due to adverse events, suggesting that dalpiciclib maintains favorable tolerability in cross-line therapy. This safety profile is consistent with other CDK4/6 inhibitors, though dalpiciclib's relatively lower hepatotoxicity and milder gastrointestinal reactions may represent potential advantages, supporting its continued use in cross-line therapy.

Our study has several limitations. First, the retrospective design and relatively small sample size may introduce selection bias. Second, the inclusion of heavily pretreated patients, with varying prior therapy lines, could confound efficacy assessments. Third, this was a single-arm study without a control group, which limited direct comparison with other treatment strategies and reduced the interpretability of the findings. In addition, patients in the non-sequential group may have had different baseline clinical characteristics or more urgent clinical needs, which could have introduced selection bias in the comparison between sequential and non-sequential treatment. In addition, because endocrine therapy partners could be changed during cross-line treatment, it is difficult in this single-arm observational study to distinguish whether the observed PFS benefit was attributable to dalpiciclib itself, the change in endocrine therapy, or the combined effect of both. Furthermore, given the limited sample size and the number of potentially relevant prognostic variables, we did not perform a multivariable Cox regression analysis because the model might have been unstable and prone to overfitting. Therefore, the prognostic analyses in this study should be considered exploratory. It is important to note that all patients included in our study were Chinese, as dalpiciclib is currently only approved and available in China. Therefore, caution should be exercised when extrapolating these findings to other populations. This study is further limited by its retrospective, single-country design and lack of an external validation set.

However, because of unfiltered enrollment, our real-world retrospective study provides a comprehensive overview of dalpiciclib as a cross-line treatment for Chinese patients with HR+/HER2- advanced breast cancer after progression on CDK4/6 inhibitors. The prognostic factors identified in this study, including liver metastasis, endocrine resistance type, number of prior treatment lines, and whether dalpiciclib was used sequentially, may provide guidance for clinical decision-making. For patients with adverse prognostic factors, such as liver metastasis or extensive prior treatment, closer monitoring and timely treatment adjustments are recommended. The predictive value of identified prognostic factors requires further validation in independent cohorts, ideally through multicenter, international prospective studies to assess generalizability across diverse populations. Moreover, future large-scale, prospective randomized controlled trials incorporating molecular biomarker analyses are warranted to validate these findings and refine patient selection strategies.

Conclusions

In summary, our study demonstrates that for patients with HR+/HER2- advanced breast cancer who have progressed after prior CDK4/6 inhibitor treatment, the combination of dalpiciclib with endocrine therapy as a cross-line treatment regimen can provide clinical benefits with an overall favorable safety profile. Longer progression-free survival was observed in patients without liver metastasis, those with secondary endocrine resistance, and those receiving sequential CDK4/6 inhibitor therapy; however, these subgroup findings should be interpreted as exploratory. Hematologic adverse events are the primary toxicities, but they can be effectively managed through dose adjustments. These findings support dalpiciclib as a viable therapeutic option for post-CDK4/6i resistance settings, characterized by favorable tolerability and safety. Future research should prioritize large-scale prospective randomized controlled trials to validate these results and identify predictive biomarkers, which may guide the development of precision treatment strategies for this patient population.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author Qiao Li upon reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the Independent Ethics Committee of the National Cancer Center/Cancer Hospital Chinese Academy of Medical Sciences and Peking Union Medical College (25/021-4967) and was conducted in accordance with the principles of the Declaration of Helsinki. Since this study was retrospective and all data were analyzed anonymously, the requirement for informed consent was waived.

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Disclosure

The authors report no conflicts of interest in this work.

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