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Original Article

Low dose abemaciclib in heavily treated hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer

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Abstract: Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors combined with endocrine therapy are the standard first-line treatment for hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) metastatic breast cancer, yet therapeutic options after progression are limited, particularly in heavily pretreated patients with tolerability concerns. We performed a retrospective real-world analysis of 17 patients with advanced HR+/HER2- breast cancer treated with low-dose abemaciclib at Kaohsiung Chang Gung Memorial Hospital between January 2023 and April 2025, of whom 41.2% had prior CDK4/6 inhibitor exposure and 47.1% had received more than four prior systemic therapy lines. Abemaciclib was administered at 200 mg once daily, with responses assessed by RECIST version 1.1. Partial response and stable disease were each observed in 29.4% of patients, yielding a disease control rate of 58.8%, including activity in patients with brain metastases. Median progression-free survival and overall survival were 10.3 months and 18.8 months, respectively, with numerically better outcomes in CDK4/6 inhibitor-naïve patients. Treatment was well tolerated, with low rates of gastrointestinal toxicity and only one grade 3-4 adverse event, and no treatment interruptions or further dose reductions. These findings suggest that low-dose abemaciclib may retain clinical activity with improved tolerability and represent a feasible option for selected heavily pretreated patients with HR+/HER2- metastatic breast cancer, warranting prospective validation.

Keywords: HR+/HER2- breast cancer, abemaciclib, low-dose, safety

Introduction

Breast cancer is the most frequently diagnosed malignancy among women worldwide and represents the leading cancer by incidence in Taiwan, where it is also the fourth most common cause of cancer-related mortality [1]. Hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) disease is the predominant molecular subtype of breast cancer and is generally associated with a more favorable prognosis than other subtypes [2, 3]. For metastatic status, cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors - palbociclib, ribociclib, and abemaciclib - in combination with endocrine therapy have been considered as the standard first-line treatment. Based on the results of multiple phase III trials, these agents have shown consistent and clinically meaningful improvements in progression-free survival (PFS), with overall survival (OS) benefits, such as palbociclib in PALOMA series [4], ribociclib in MONALEESA series [5-10], and abemaciclib in MONARCH series [11-15].

In HR+ breast cancer, cyclin D-CDK4/6-mediated phosphorylation of the retinoblastoma protein is an important driver of cell-cycle pro-

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gression. Abemaciclib is different pharmacologically from other CDK4/6 inhibitors (palbociclib or ribociclib) by its better selectivity for CDK4 relative to CDK6 and its broader inhibitory activity against additional cyclin-dependent kinases, including CDK1 and CDK2. Its approximately 14-fold higher potency against CDK4 compared with CDK6 is thought to underlie its distinctive toxicity profile, resulting in relatively lower rates of hematologic toxicity but increased gastrointestinal adverse events (AEs). On the other hand, palbociclib and ribociclib are administered on intermittent schedules, but abemaciclib is dosed continuously twice daily, contributed to sustained target inhibition but necessitating ongoing management of chronic toxicities [16-18].

Diarrhea is the most common AE associated with abemaciclib and the severity is related to its dose. In the MONARCH 1 study, abemaciclib was used as monotherapy at a dose of 200 mg twice daily, and diarrhea occurred in 90.2% of patients, including 19.7% with grade 3 events [19]. In MONARCH 2 and MONARCH 3 studies, abemaciclib was combined with endocrine therapy, and the starting dose was reduced to 150 mg twice daily; the incidence of grade 3 diarrhea was down to 13.4% and 9.5%, respectively, although all-grade diarrhea remained frequent [11-15]. This reduction likely reflects both dose modification and improved implementation of early intervention strategies. Other AEs of abemaciclib included upper gastrointestinal symptoms, including nausea, vomiting, and abdominal pain.

In real-world clinical practice, most patients with metastatic HR+/HER2- breast cancer experience multiple lines of treatment, including endocrine therapy, targeted therapy, chemotherapy, and antibody-drug conjugates. Therefore, later-line CDK4/6 inhibition or rechallenge may be given for these patients, although supporting evidence remains limited. MONARCH 1 is focus on abemaciclib monotherapy in heavily pretreated, CDK4/6 inhibitor-naïve patients; the findings showed an objective response rate (ORR) of 19.7%, a disease control rate (DCR) of 67.4%, and a median OS of 22.3 months; nearly half of patients required dose reductions, diarrhea and neutropenia were most common AEs [19]. In the adjuvant setting, several studies revealed that dose-reduced CDK4/6 inhibition may preserve efficacy and improve tolerability. In the NATALEE trial, lower-dose ribociclib (400 mg daily, rather than 600 mg in the metastatic setting) combined with endocrine therapy significantly improved invasive disease-free survival (DFS) with a more favorable safety profile [20, 21]. Similarly, post hoc analyses from MonarchE indicated that dose reduction of abemaciclib in high-risk early-stage breast cancer did not compromise efficacy [22, 23].

To the best of our knowledge, the effectiveness and tolerability of low-dose abemaciclib in heavily pretreated metastatic HR+/HER2- breast cancer is still limited. This study aimed to evaluate the real-world clinical outcomes and safety profile of low-dose abemaciclib in patients with advanced, heavily pretreated HR+/HER2- breast cancer.

Methods

Patient population

This retrospective study included patients with advanced breast cancer who received abemaciclib at Kaohsiung Chang Gung Memorial Hospital between January 2023 and April 2025. Eligible patients met the following criteria: (1) adequate organ function; (2) confirmed HER2-negative status; (3) at least one measurable lesion for evaluation per RECIST; (4) Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; and (5) the use of abemaciclib in combination with hormone therapy (such as aromatase inhibitors or fulvestrant) was permitted; however, concomitant use with other chemotherapeutic agents or targeted therapies was not allowed. Patients with prior or concurrent malignancies were excluded. Seventeen patients met all eligibility criteria.

Treatment response and safety assessments

Abemaciclib was administered orally at a dose of 200 mg once daily and continued until radiologic disease progression or unacceptable toxicity. Patients were evaluated regularly in the outpatient setting with physical examinations, complete blood counts, serum biochemistry, and chest radiography. Baseline staging included chest and abdominal computed tomography, bone scan, and brain imaging when clinically appropriate. Tumor response was as-

Table 1. Baseline characteristics

Variables	Patient number (%)
Age (median)	61 years (range: 40-81)
Sex (female)	17 (100%)
Estrogen receptor	
Positive	14 (94.1%)
Negative	1 (5.9%)
Progesterone receptor	
Positive	12 (70.6%)
Negative	5 (29.4%)
Metastatic sites	
Lung	7 (41.2%)
Liver	7 (41.2%)
Bone	12 (70.6%)
Brain	4 (23.5%)
Others	6 (35.3%)
Treatment lines of Abemaciclib	
≤5	9 (52.9%)
6-10	5 (29.4%)
≥11	3 (17.7%)
Prior palbociclib or ribociclib history	
Yes	7 (41.2%)
No	10 (58.8%)
Prior doxorubicin/epirubicin history	
Yes	5 (29.4%)
No	12 (70.6%)
Prior taxane history	
Yes	11 (64.7%)
No	6 (35.3%)

sessed according to RECIST version 1.1 [24]. All radiologic evaluations were independently reviewed by two radiologists blinded to clinical outcomes. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 [25].

Statistical analysis

Statistical analyses were performed using SPSS software, version 29.0 (IBM Corp., Armonk, NY, USA). PFS was defined as the interval from treatment initiation to disease progression or death from any cause. OS was defined as the interval from treatment initiation to death from any cause or last follow-up. Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. A two-sided *P* value <0.05 was considered statistically significant.

Ethical considerations

The study was approved by the Institutional Review Board of the Chang Gung Medical Foundation (approval number: 202500815B0) and conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived owing to the retrospective study design.

Results

Patient characteristics

Seventeen female patients with advanced breast cancer who received low dose abemaciclib between January 2023 and April 2025 were included. The median age at treatment initiation was 61 years (range, 40-81). All patients had HER2-negative metastatic disease and an ECOG performance status of 0-2. Fourteen patients (94.1%) were estrogen receptor-positive, and twelve (70.6%) were progesterone receptor-positive. The most common metastatic sites were bone (70.6%), liver (41.2%), lung (41.2%), and brain (23.5%). Prior systemic treatments included endocrine therapy and chemotherapy; anthracyclines and taxanes were administered in five (29.4%) and eleven (64.7%) patients, respectively. Seven patients (41.2%) had previously been treated with a CDK4/6 inhibitor. Abemaciclib was initiated as ≤5 prior systemic therapy lines in nine patients (52.9%), as the sixth to tenth line in five patients (29.4%), and as the eleventh line or beyond in three patients (17.7%). Baseline characteristics are summarized in **Table 1**.

Treatment response

According to RECIST version 1.1, partial response (PR) was achieved in five patients (29.4%), stable disease (SD) in five patients

Table 2. Objective response rate of low dose abemaciclib

Treatment response (overall, n=17)	Patient number (%)
Partial response	5 (29.4%)
Stable disease	5 (29.4%)
Progressive disease	7 (41.2%)
Disease control rate	10 (58.8%)
Treatment response (brain metastasis, n=4)	Patient number (%)
Partial response	2 (50%)
Stable disease	0 (0%)
Progressive disease	2 (50%)
Disease control rate	2 (50%)

(29.4%), and progressive disease (PD) in seven patients (41.2%), resulting in a DCR of 58.8%. Among four patients with brain metastases, two achieved PR and two had PD (DCR 50%). Detailed response outcomes are listed in **Table 2**.

Clinical outcomes

Median PFS and OS in the overall cohort were 10.3 months and 18.8 months, respectively (**Figure 1**). Patients without prior exposure to CDK4/6 inhibitors experienced more favorable outcomes, with a median PFS of 11.6 months versus 5.3 months and a median OS of 21.8 months versus 16.3 months compared with those previously treated with CDK4/6 inhibitors (**Figure 2**). A similar trend was observed with respect to prior chemotherapy exposure. Patients naïve to anthracyclines or taxanes demonstrated a numerically longer PFS of 13.8 months versus 5.3 months, with a *p* value of 0.43, whereas median OS was not reached compared with 16.3 months among patients with prior exposure (**Figure 3**). Disease burden showed a distinct relationship with outcomes. The presence of visceral metastases had minimal impact on PFS at 10.5 months versus 10.3 months but was associated with shorter OS at 10.3 months versus 18.8 months (**Figure 4**). Interesting, patients who received abemaciclib after more than five prior systemic treatment lines exhibited superior PFS of 10.5 months versus 5.8 months, with a *p* value of 0.90, and OS of 21.8 months versus 18.8 months, with a *p* value of 0.52, compared to those treated with abemaciclib as less than five prior systemic treatment lines in the disease course (**Figure 5**).

Although there was no statistical significance between subgroup analyses, the difference of PFS and OS across subgroups also suggests potential prognostic factors within this heavily pretreated population.

Safety

The most common AEs were diarrhea (29.4%), nausea (11.8%), fatigue (11.8%), decreased appetite (11.8%), and neutropenia (11.8%). Only one patient (5.9%) experienced grade 3-4 diarrhea and no other grade 3-4 was documented. No patients required treatment interruption or dose reduction due to AEs. Safety outcomes are summarized in **Table 3**.

Discussion

CDK4/6 inhibitors combined with endocrine therapy (ET) represent the standard first-line treatment for HR+/HER2- metastatic breast cancer, based on consistent improvements in PFS and OS with an acceptable safety profile across multiple randomized trials [4, 6, 7, 9, 14, 26, 27]. Compared with chemotherapy, endocrine therapy plus CDK4/6 inhibition provides comparable or superior efficacy with lower toxicity and is therefore preferred, except in patients with rapidly progressive disease or impending organ dysfunction [28, 29]. For patients who relapse or progress after ET plus a CDK4/6 inhibitor, molecular profiling is recommended to guide subsequent treatment selection. This includes assessment of somatic PIK3CA and ESR1 mutations when further endocrine-based therapy is considered, as well as germline BRCA1, BRCA2, and PALB2 mutations when appropriate. However, the optimal sequencing of endocrine-based therapies after CDK4/6 inhibitor progression remains undefined and depends on prior treatment exposure in the early or advanced setting, duration of response to previous endocrine therapy, disease burden, patient preference, and treatment availability. Evidence-supported second-line options include fulvestrant plus alpelisib for PIK3CA-mutated tumors, everolimus-based combinations with exemestane, tamoxifen, or fulvestrant, single-agent endocrine therapy,

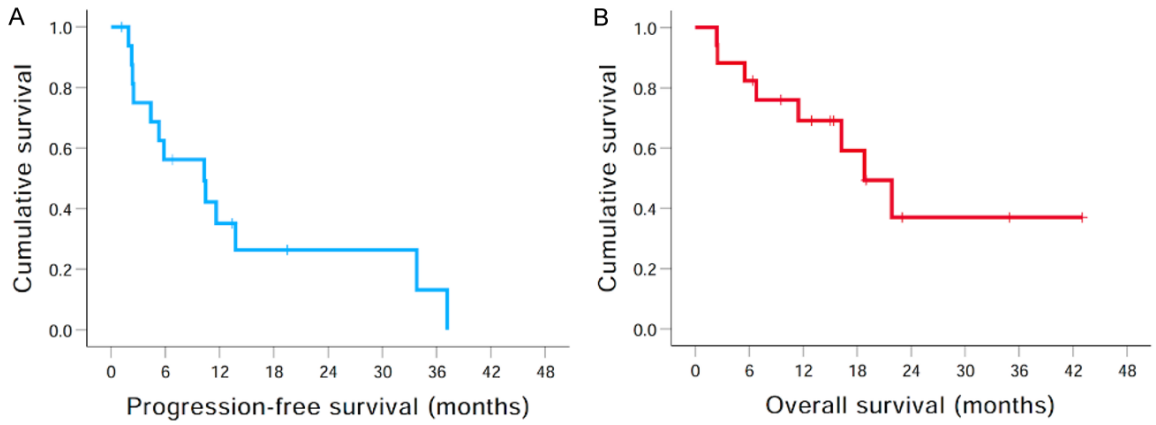

Figure 1. Kaplan-Meier method estimated survival curves for intent-to-treat patients, progression-free survival and overall survival.

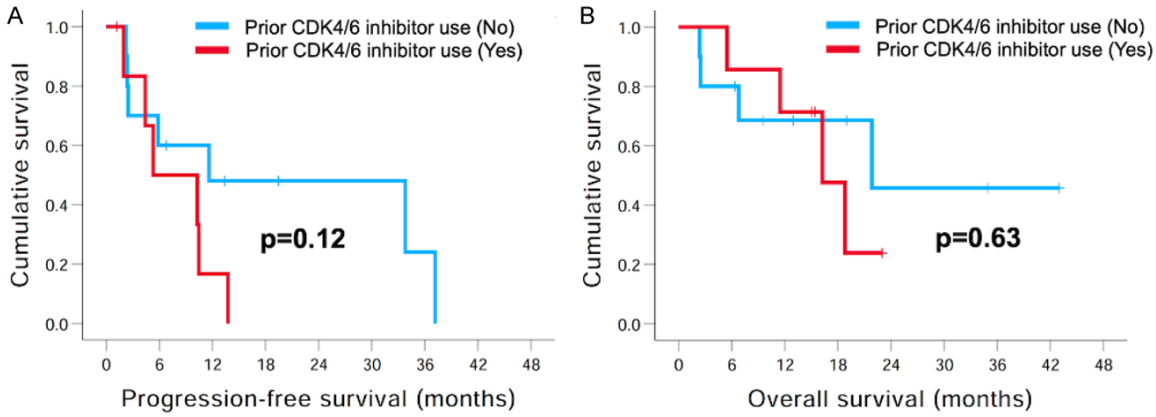

Figure 2. Kaplan-Meier method estimates of survival according to prior CDK4/6 inhibitors exposure.

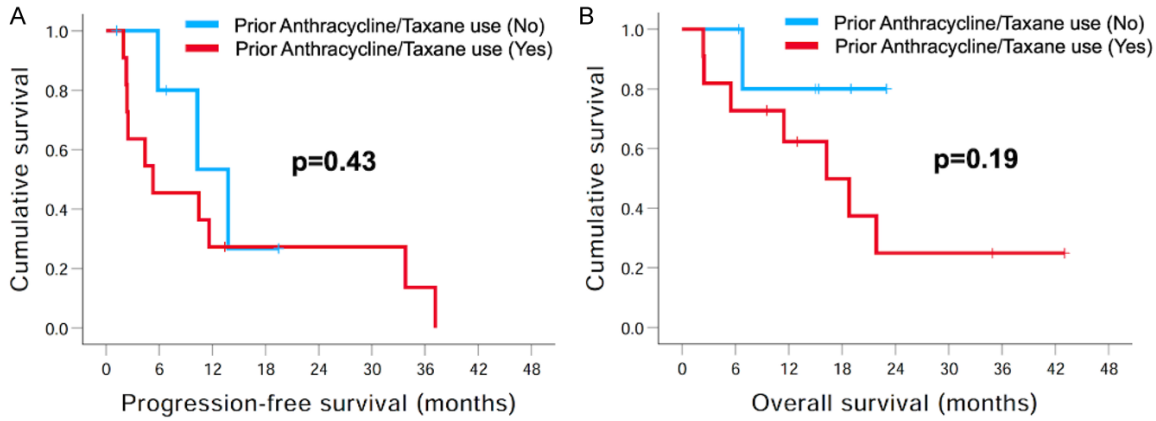

Figure 3. Kaplan-Meier method estimates of survival according to prior anthracyclines or taxanes exposure.

chemotherapy, or poly ADP-ribose polymerase inhibitors for tumors harboring germline BRCA mutations. Data supporting the use of CDK4/6 inhibitors after progression on prior CDK4/6 inhibition are limited, although rechallenge may be feasible following a sufficiently long treatment-free interval. In heavily pretreated patients, treatment tolerability and quality of

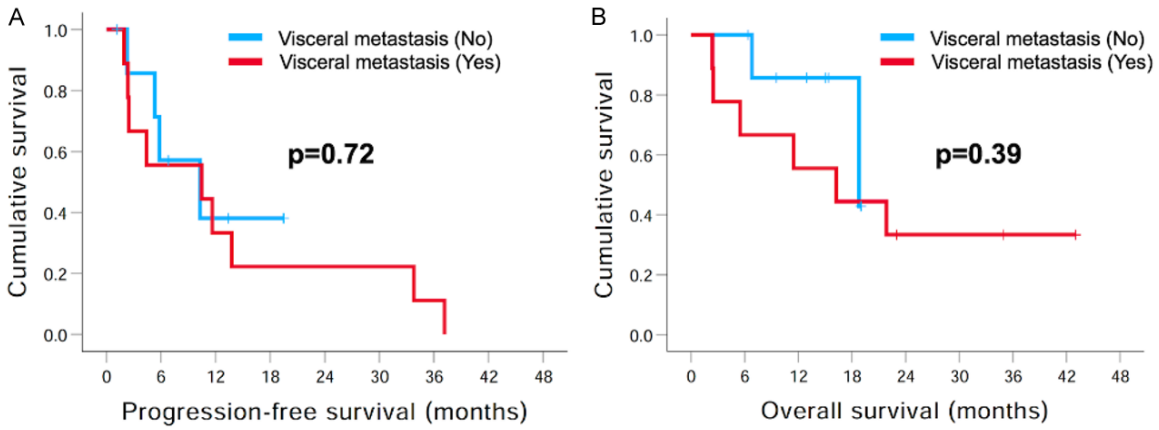

Figure 4. Kaplan-Meier method estimates of survival according to visceral metastasis status.

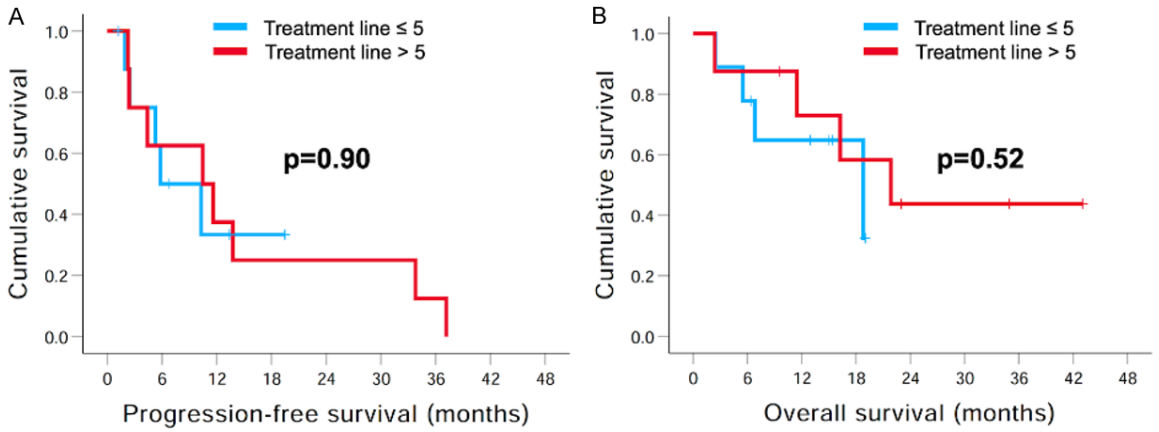

Figure 5. Kaplan-Meier method estimates of survival according to above or below 5 treatment lines.

Table 3. Adverse events

Variables	Any grade	Grade 3/4
Diarrhea	5 (29.4%)	1 (5.9%)
Nausea	2 (11.8%)	0 (0%)
Vomiting	1 (5.9%)	0 (0%)
Fatigue	2 (11.8%)	0 (0%)
Neutropenia	2 (11.8%)	0 (0%)
Anemia	1 (5.9%)	0 (0%)
Thrombocytopenia	1 (5.9%)	0 (0%)
Increased AST/ALT	1 (5.9%)	0 (0%)
Decreased appetite	2 (11.8%)	0 (0%)

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

life become critical considerations. Accordingly, our study evaluated the clinical activity and safety of reduced dose abemaciclib in this population. We observed preserved survival outcomes in patients with prior exposure to CDK4/6 inhibitors and chemotherapy, with numerically greater benefit among those who received abemaciclib after more than five prior lines of systemic therapy. Dose reduction of abemaciclib was generally well tolerated without treatment interruption or further dose reduction and provided maintenance of efficacy with improved tolerability.

In MONARCH 1 trial, abemaciclib was used as monotherapy and administered at 200 mg twice daily in patients with refractory HR+/HER2- metastatic breast cancer. This study excluded patients who had history of prior CDK4/6 inhibitor exposure and only 13.6 percent received more than four prior systemic regimens. MONARCH 1 reported an ORR of 19.7 percent, a median PFS of approximately 6 months, and a median OS of 22.3 months. However, treatment related AEs, particularly diarrhea, was mentioned in nearly 90% of

Table 4. Comparison of clinical outcomes between KCGMH cohort and MONARCH 1 trial

Variables	KCGMH (n=17)	MONARCH 1 (n=132)
Treatment dose	200 mg QD	200 mg BID
Prior CDK4/6 inhibitor	Yes (41.2%)	No
Prior taxane use	64.7%	68.9%
Treatment line ≥4 regimens	47.1%	13.6%
Objective response rate	29.4%	19.7%
Disease control rate	58.8%	67.4%
Progression-free survival	10.3 months	6.0 months
Overall survival	18.8 months	22.3 months
Toxicity (diarrhea, any/grade 3 or 4)	29.4%/5.9%	90.2%/19.7%

KCGMH: Kaohsiung Chang Gung Memorial Hospital; CDK4/6: Cyclin-dependent kinase 4/6.

patients [19]. The biological rationale of dose reduction is supported by the NATALEE and post hoc analyses from MonarchE trials, which demonstrated that reduced dosing of CDK4/6 inhibitors did not compromise efficacy but provided lower incidence of AEs [20-23]. These findings suggest that sustained CDK4/6 inhibition may be achievable at lower doses while improving tolerability. Our current study included a more heavily pretreated population, with 41.2 percent of patients having prior exposure to CDK4/6 inhibitors and 47.1 percent having received more than four prior systemic treatment lines. Despite this, reduced-dose abemaciclib was associated with an ORR of 29.4 percent, a median PFS of 10 months, and a median OS of 18.8 months. Importantly, treatment-related toxicity was markedly lower, with diarrhea reported in 29.4 percent of patients (**Table 4**). Taken together, these findings suggest that dose-reduced abemaciclib may preserve clinical activity and survival benefit while substantially improving tolerability, even in heavily pretreated patients and those with prior CDK4/6 inhibitor exposure.

Prior exposure to CDK4/6 inhibitors may attenuate the efficacy of subsequent CDK4/6 inhibitor rechallenge. In a retrospective cohort study of patients with unresectable stage III or stage IV HR+ breast cancer who had received at least two lines of systemic therapy for advanced disease, including two or more regimens containing a CDK4/6 inhibitor, rechallenge was associated with limited clinical benefit. Among patients who experienced disease progression on initial CDK4/6 inhibitor therapy, rechallenge with either the same or a different CDK4/6 inhibitor resulted in shorter time to treatment failure compared with the initial exposure. Median time to treatment failure declined from 10 months to 4.3 months with the same CDK4/6 inhibitor and from 10 months to 4.7 months with a different CDK4/6 inhibitor, corresponding to hazard ratios of 1.41 and 1.44, respectively. In contrast, patients who discontinued the initial CDK4/6 inhibitor because of toxicity rather than disease progression derived more favorable outcomes from rechallenge, with a median time to treatment failure of 10.1 months compared with 3 months, corresponding to a hazard ratio of 0.40. Shorter time to treatment failure was associated with a higher prevalence of molecular alterations linked to CDK4/6 inhibitor resistance, including TP53 mutations, CDK4 amplification, RB1 loss, and FAT1 loss-of-function alterations [30]. Consistent with these findings, the randomized phase II PACE trial enrolled patients with disease progression on prior endocrine therapy combined with a CDK4/6 inhibitor, predominantly palbociclib, and demonstrated that continuation of palbociclib with fulvestrant did not improve progression-free or overall survival compared with fulvestrant alone [31]. In contrast, the MAINTAIN and postMONARCH trials evaluated patients with disease progression on prior endocrine therapy plus a CDK4/6 inhibitor and reported a progression-free survival benefit with rechallenge using ribociclib or abemaciclib in combination with a switched endocrine therapy backbone [32, 33]. These discrepant results suggest that the efficacy of CDK4/6 inhibitor rechallenge may depend on treatment context, including the choice of CDK4/6 inhibitor and accompanying endocrine partner, and warrant further prospective investigation.

Endocrine therapy combined with a CDK4/6 inhibitor is considered as first-line treatment in patients with HR+/HER2- metastatic breast cancer, except in the presence of imminent organ failure. Upon progression on this regimen, molecular characterization becomes es-

sential to guide subsequent therapy selection. Assessment of somatic PIK3CA and ESR1 mutations and germline BRCA1/2 mutations is recommended to guide targeted endocrine-based therapy selection, including SERDs for ESR1-mutant disease, alpelisib plus fulvestrant for PI3K pathway-altered tumors, PARP inhibitors for germline BRCA1/2 mutation carriers, and mTOR inhibitor-based combinations as an additional option [34-37]. For patients with endocrine-resistant disease in whom targeted therapies have been exhausted or are not applicable because of the absence of actionable molecular alterations, chemotherapy should be considered. Although the optimal chemotherapy sequence in metastatic breast cancer has not been established, taxanes and anthracyclines are typically used earlier, particularly in patients who are treatment-naïve to these agents or who experienced a disease-free interval of at least 12 months after prior exposure [34]. In this study, the median treatment line in our cohort was 6. The rationale for selecting a treatment line cut-off value of 5 is as follows. Our study population consisted of patients with HR+/HER2- breast cancer. In routine clinical practice, most patients in this subgroup are expected to receive multiple lines of standard therapies prior to abemaciclib, including CDK4/6 inhibitors (in Taiwan, only palbociclib and ribociclib are reimbursed) plus aromatase inhibitors, fulvestrant alone or in combination with alpelisib for patients with *PIK3CA* mutations, everolimus plus exemestane, taxane-based chemotherapy, anthracycline-based chemotherapy, and other chemotherapeutic agents (e.g., vinorelbine, capecitabine, trastuzumab deruxtecan). Abemaciclib is therefore typically considered at a later stage, unless specific clinical considerations - such as the desire to avoid alopecia or the presence of brain metastases - necessitate its earlier use. Patients who received abemaciclib after more than five prior lines of therapy demonstrated numerically longer survival. This observation may reflect selection or survivorship bias, as patients able to receive multiple prior therapies are likely to have preserved functional status or more indolent tumor biology. Further investigation is required to clarify the underlying contributors to this finding.

This study has several important limitations. First, its retrospective design and relatively small sample size limit statistical power and constrain the ability to detect or confirm statistically significant differences. Second, the absence of a contemporaneous control group treated with standard-dose abemaciclib precludes direct comparative assessment of efficacy and safety across dosing strategies. Third, treatment selection was influenced in part by economic considerations, as access to standard-dose abemaciclib may be limited by cost in real-world practice. This introduces the potential for socioeconomic bias. Fourth, patients who were able to receive and tolerate later lines of systemic therapy may represent a selected population with more favorable functional status or less aggressive disease biology, introducing potential selection or survivorship bias. Nevertheless, the high financial burden and treatment-limiting AEs associated with standard-dose abemaciclib are common reasons for dose reduction or treatment discontinuation in routine clinical practice in Taiwan. Within this context, the present study represents one of the few real-world analyses evaluating the efficacy and safety of low-dose abemaciclib in advanced breast cancer. Although hypothesis-generating, our findings suggest that dose reduction may mitigate toxicity and economic burden while preserving clinical activity, potentially contributing to improved tolerability and quality of life. Prospective studies are warranted to validate these observations.

Conclusion

Endocrine therapy combined with CDK4/6 inhibition is the standard first-line treatment for HR+/HER2- metastatic breast cancer, yet therapeutic options become limited after progression, particularly in heavily pretreated patients in whom cumulative toxicity and treatment tolerability are critical concerns. In this retrospective real-world study, we evaluated the efficacy and safety of reduced-dose abemaciclib in a heavily pretreated population, including patients with prior CDK4/6 inhibitor exposure, multiple prior systemic therapies, and visceral or central nervous system involvement. The findings of our study showed that low dose abemaciclib demonstrated preserved clinical activity with a markedly lower incidence of gastrointestinal toxicity and provided real-world evidence that low dose abemaciclib may represent a feasible and tolerable treatment

option for selected heavily pretreated HR+/HER2- patients.

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Disclosure of conflict of interest

None.

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