Original Article

Treatment Outcomes in Hormone Receptor-positive, HER2-negative Metastatic Breast Cancer Patients with and without Progression after Completion of Reimbursed Cyclin-dependent Kinase 4/6 Inhibitors in Taiwan: A Single-institution Experience

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Abstract

Background: Combining cyclin-dependent kinase 4/6 inhibitors (CDK4/6is) with endocrine therapy is the standard first-line treatment for metastatic hormone receptor (HR)-positive, HER2-negative breast cancer. In Taiwan, it is estimated that nearly half of the patients completing 2 years of CDK4/6i treatment reimbursed by the National Health Insurance (NHI) program remain free of disease progression. Continuing CDK4/6i treatment beyond the reimbursement period imposes a financial burden on patients and makes it challenging for clinicians to determine optimal subsequent therapies, especially in resource-limited settings. This real-world, retrospective study aimed to evaluate the outcomes of HR-positive, HER2-negative metastatic breast cancer (MBC) patients who completed 19 months of CDK4/6i therapy, particularly those without disease progression. **Materials and Methods:** A total of 106 patients diagnosed with HR-positive, HER2-negative MBC and treated with CDK4/6is between September 1, 2015, and November 28, 2022, were enrolled for chart review and monitored until death or December 31, 2024. The exclusion criteria were loss to follow-up or unclear medication information ($n = 7$), concurrent treatment for a second cancer ($n = 6$), enrollment in clinical trials ($n = 3$), switching treatment between two CDK4/6is ($n = 1$), and HER2-positive disease after pathology revision ($n = 1$). Survival analysis was performed using the Kaplan–Meier method and compared using the log-rank test. Multivariate analysis was used to test the associations between clinical factors and survival using Cox proportional hazard models. All statistical tests were two-sided, and statistical significance was defined as $P < 0.05$. **Results:** Eighty-nine patients were eligible for evaluation, with a median follow-up time of 33.1 months. Fifty-three patients used CDK4/6is as first-line (1 L) therapy, and 35 used CDK4/6is as second or later lines (≥2 L). The median progression-free survival (PFS) was 22.1 months for the 1 L CDK4/6i users and 7.9 months for the ≥2 L CDK4/6i users. The median overall survival (OS) was

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72.8 months for the 1 L CDK4/6i users and 28.8 months for the ≥2 L CDK4/6i users. The differences in both PFS and OS were statistically significant (log-rank test, *P* = 0.008 and 0.003, respectively). Among the 26 patients who received CDK4/6is for more than 19 months, we compared the "Lack of NHI reimbursement (NHIr)" group with the "Progression disease (PD) after 19 mo" group (patients who progressed after 19 months of 1 L CDK4/6i treatment). In the univariable model, the "Lack of NHIr" group was less likely to experience progression on post-CDK4/6i therapy compared to the "PD after 19 mo" group. After further adjustment, CDK4/6i type (ribociclib), proton pump inhibitor use, and post-CDK treatment were independent prognostic factors associated with PFS2 events, whereas NHIr status was not significantly associated with subsequent treatment outcomes. **Conclusion:** In this single-institution retrospective study, PFS and OS in the patients who received CDK4/6i treatment were comparable to those reported in pivotal phase 3 clinical trials, both in first-line and later-line settings. In terms of disease progression on next-line therapy in the patients who used CDK4/6is >19 months, ribociclib showed better PFS2, compared to palbociclib or abemaciclib. Due to the limited sample size, factors such as age, the presence of more than two metastatic sites, and lack of reimbursement were not significantly correlated with poorer outcomes.

Keywords: Cyclin-dependent kinase 4/6 inhibitor, overall survival, progression-free survival, real-world data, Taiwan national health insurance reimbursement

INTRODUCTION

Combining cyclin-dependent kinase 4/6 inhibitors (CDK4/6is) with endocrine therapy (ET) is the standard first-line treatment for metastatic hormone receptor (HR)-positive, HER2-negative breast cancer without visceral crisis, as demonstrated by early phase III clinical trials. In Taiwan, the national health insurance (NHI) program has approved reimbursement for 2 years of ET combined with either palbociclib or ribociclib for this patient subgroup since 2019. Phase III clinical trials (PALOMA-2, MONALEESA-2, MONALEESA-7)[1-3] and subsequent real-world studies (P-REALITY X, PARSIFAL-LONG)[4,5] have reported median progression-free survival (PFS) ranging from 19.3 to 27.9 months with these combination therapies as front-line treatment. Based on these findings, it is estimated that nearly half of the patients completing 2 years of reimbursed CDK4/6i treatment remain free of disease progression.

However, continuing CDK4/6i treatment beyond the reimbursement period imposes a financial burden on patients and makes it challenging for clinicians to determine optimal subsequent therapies, especially in resource-limited settings. This real-world, retrospective study aimed to evaluate the outcomes of HR-positive, HER2-negative metastatic breast cancer (MBC) patients who had received CDK4/6i therapy, regardless of the lineage or duration, and particularly those without progression. We also examined the impact of discontinuing therapy due to financial or reimbursement constraints and proposed potential post-CDK4/6i treatment strategies for these patients.

MATERIALS AND METHODS

Study subjects

We enrolled 106 patients diagnosed with HR-positive, HER2-negative MBC at Mackay Memorial Hospital who received CDK4/6is between September 1, 2015, and November 28, 2022. A chart review was conducted to collect clinical and pathological information, including demographic data, surgical histories, comorbidities, medications, treatment-related toxicities, and imaging results. Eligible patients and medical charts were obtained from the electronic databases of Mackay Memorial Hospital. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Mackay Memorial Hospital (Approval No. 23MMHIS056e; Approval date: March 14, 2023). The patient consent is waived by IRB.

The enrolled patients were monitored until death or December 31, 2024. The exclusion criteria were enrollment in blinded clinical trials (*n* = 3), loss to follow-up or unclear medication information (*n* = 7), revised pathology reports indicating HER2-positive disease by fluorescence *in situ* hybridization (*n* = 1), concurrent active treatment for a second cancer (*n* = 6), and discontinuing CDK4/6i treatment within 3 months due to neutropenia (*n* = 1). All patients provided informed consent for publication of the case.

Statistical analysis

Age was defined as the time from the patients' date of birth to initiating CDK4/6i therapy. In this study, we classified the interval between adjuvant ET and metastasis into three categories: *De novo* MBC, metastatic event within the first 24 months of adjuvant ET, and metastatic event after the first 24 months of adjuvant ET. PFS was defined as the time from starting to stopping CDK4/6i therapy; PFS2 was defined as the time from starting to stopping subsequent therapy following CDK4/6i therapy. Post-CDK4/6i therapy was defined as subsequent therapy following CDK4/6i therapy, regardless of the reason for discontinuing CDK4/6i therapy. Proton pump inhibitor (PPI) use was defined as any use of oral PPI while receiving CDK4/6i therapy, regardless of the duration. Overall survival (OS) was defined as the time from the starting CDK4/6i therapy to cancer-related death.

Categorical variables are presented as counts (percentages) and were compared using the Chi-squared test or Fisher's exact test, as appropriate. Continuous data without normal distribution are presented as median and interquartile range (IQR, 25th–75th percentile) and were analyzed using the Wilcoxon rank–sum test. Kaplan–Meier curves were drawn, and the log-rank test was used for OS. Cox proportional hazard regression with backward selection was used to identify

factors for adjustment related to first-line CDK4/6i treatment and to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for overall mortality in all patients and those with progression on post-CDK4/6i therapy who used first-line CDK4/6i treatment >19 months.

For overall mortality, the candidate factors were age, number of metastasis sites, use of PPIs, hepatitis-B virus (HBV) carriers, primary ET resistance, and CDK4/6i information (type, status, and post-CDK4/6i treatment). A two-sided $P < 0.05$ was regarded as being statistically significant. Overall mortality was the event of interest, and the follow-up time was calculated as the date of starting CDK4/6i therapy to death or last visit.

For progression on post-CDK4/6i therapy, CDK4/6i exposure time was added to the candidate factors. Progression on post-CDK4/6i therapy was the event of interest, and the follow-up time was calculated from the date of stopping CDK4/6i therapy to the date of stopping post-CDK4/6i therapy.

Data management and statistical analyses were conducted using SAS version 9.4 software (SAS Institute, Inc.) (Cary, North Carolina, USA).

RESULTS

In this single-center, retrospective study conducted from September 1, 2015, to December 31, 2024, 89 patients were eligible for evaluation, with a median follow-up time of 33.1 months. Fifty-three patients used CDK4/6is as first-line (1 L) therapy, and 35 used CDK4/6is as second or later lines (≥2 L). The median ages of the 1 L and ≥2 L groups were 60.4 (range 32.1–86.5) years and 55.6 (range 30.3–90.2) years, respectively. In the whole cohort, 40 (45.4%) patients were ≥60 years old. Most of the patients (27 in the 1 L group [50.9%] and 19 in the ≥2 L [54.2%] group) used ribociclib. Regarding the reasons for discontinuing CDK4/6i therapy, most patients (32 in the 1 L [60.3%] group and 29 in the ≥2 L [82.8%] group) stopped the treatment due to disease progression. Eighteen patients in the 1 L group (34%) discontinued CDK4/6i therapy due to the lack of NHI reimbursement (NHIr). Other patient characteristics are detailed in Table 1.
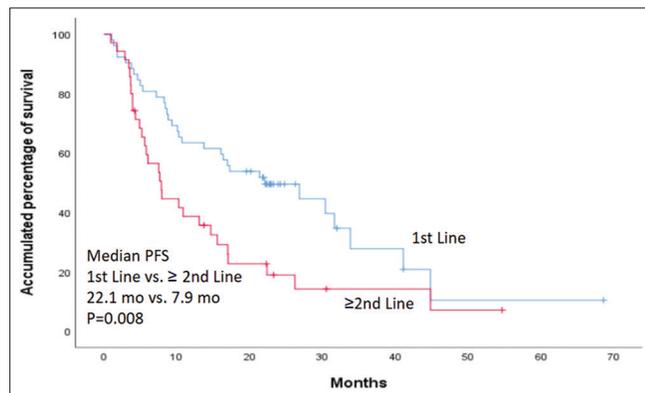

Figure 1: Kaplan Meier survival curve for PFS of 1L & ⩾ 2L CDK4/6i users

Kaplan–Meier curves of PFS and OS are shown in Figures 1 and 2. The median PFS (mPFS) was 22.1 months for the 1 L CDK4/6i users and 7.9 months for the ≥2 L CDK4/6i users. The median OS was 72.8 months for the 1 L CDK4/6i users and 28.8 months for the ≥2 L CDK4/6i users. The differences in both PFS and OS were statistically significant (log-rank test, $P = 0.008$ and 0.003, respectively).

Overall survival analysis

Fifty-two of the 53 patients (one patient who used CDK4/6is <3 months was excluded) who received 1 L CDK4/6i were included in OS analysis [Table 2]. The mean age was 59.8 ± 11.4 years. Most of the patients had metastases at ≥2 sites (73.1%), received PPIs (88.5%), and were HBV noncarriers (69.2%). Three-quarters (75.0%) were ET sensitive. Ribociclib was the most commonly prescribed CDK4/6i (51.9%). Over half (53.8%) of the cohort were treated with CDK4/6is for more than 19 months, with a median duration of 20.8 months (IQR: 8.6–24.1). During a mean follow-up period of 38.2 months, 61.5% of the patients experienced progression on CDK4/6i therapy, 82.0% progressed on post-CDK4/6i therapy, and 34.6% died.

The patients who survived were more likely to have received CDK4/6is for >19 months (73.5% vs. 16.7%, $P < 0.001$), had

Table 1: Patient demographics

	1L (*n*=53), *n* (%)	≥2L (*n*=35), *n* (%)
Age		
Median (range)	60.4 (32.1–86.5)	55.6 (30.3–90.2)
≥60 years	27 (51)	13 (37.1)
CDK4/6i		
Palbociclib	25 (47.2)	7 (20)
Abemaciclib	1 (1.9)	9 (25.7)
Ribociclib	27 (50.9)	19 (54.2)
Interval between adjuvant ET and metastasis		
De novo MBC	11 (20.7)	7 (20)
≥24 months from start of adjuvant ET to metastasis	39 (73.6)	27 (77.1)
<24 months from start of adjuvant ET to metastasis	3 (5.7)	1 (2.9)
Number of metastatic sites		
Single site	15 (28.3)	4 (11.4)
≥ 2 sites	38 (71.7)	31 (88.5)
HBV carrier	11 (20.7)	6 (17.1)
Concurrent PPI use	6 (11.3)	2 (5.7)
CDK4/6i discontinuation	51 (96.2)	34 (97.1)
Reasons for Stopping CDK4/6i treatment		
Toxicities	1 (1.9)	2 (5.7)
Disease progression	32 (60.3)	29 (82.8)
Lack of NHI reimbursement	18 (34.0)	3 (8.5)
CDK4/6i exposure time (average, months)	18.75	12.84

ET: Endocrine therapy, CDK4/6i: Cyclin-dependent kinase 4/6 inhibitors, NHI: National Health Insurance, HBV: Hepatitis-B virus, PPI: Proton pump inhibitor

Table 2: Distribution between patients who died and survivors

Variable	Total (*n*=52)	Survivor (*n*=34)	Died (*n*=18)	*P*
Age	59.8±11.4	58.1±10.3	62.9±13.1	0.158
Metastasis site				0.070
Single site (bone only)	6 (11.5)	4 (11.8)	2 (11.1)	
Single site (except bone)	8 (15.4)	8 (23.5)	0	
≥2 sites	38 (73.1)	22 (64.7)	16 (88.9)	
PPI use				0.405
No	46 (88.5)	31 (91.2)	15 (83.3)	
Yes	6 (11.5)	3 (8.8)	3 (16.7)	
HBV carrier				0.339
Noncarrier	36 (69.2)	25 (73.5)	11 (61.1)	
Carrier	11 (21.2)	5 (14.7)	6 (33.3)	
Unknown	5 (9.6)	4 (11.8)	1 (5.6)	
Primary ET resistance				0.873
ET sensitive	39 (75.0)	26 (76.5)	13 (72.2)	
ET resistance	3 (5.8)	2 (5.9)	1 (5.6)	
De novo MBC	10 (19.2)	6 (17.6)	4 (22.2)	
CDK4/6i information				
CDK4/6i type				0.059
Palbociclib	24 (46.2)	13 (38.2)	11 (61.1)	
Abemaciclib	1 (1.9)	0	1 (5.6)	
Ribociclib	27 (51.9)	21 (61.8)	6 (33.3)	
CDK4/6i using status				**<0.001**
≤19 months	24 (46.2)	9 (26.5)	15 (83.3)	
>19 months	28 (53.8)	25 (73.5)	3 (16.7)	
PD	8	6	2	
Lack of NHIr	18	17	1	
Keep using	2	2	0	
CDK4/6i exposure time (months)	20.8 (8.6–24.1)	22.5 (17.0–26.3)	9.7 (4.1–16.4)	**0.004**
Post-CDK4/6i treatment				**0.007**
Chemotherapy	25 (48.1)	12 (35.3)	13 (72.2)	
Afinitor	8 (15.4)	7 (20.6)	1 (5.6)	
ET only/no further therapy	14 (26.9)	13 (38.2)	1 (5.6)	
Others	5 (9.6)	2 (5.8)	3 (16.7)	
Outcomes				
Progression on CDK4/6i	32 (61.5)	15 (44.1)	17 (94.4)	**<0.001**
Progression on post-CDK4/6i drug	41/50 (82.0)	23/32 (71.9)	18/18 (100.0)	**0.018**
Overall survival time (months)	38.2±17.9	43.6±16.0	27.9±17.2	**0.002**

The continuous data with normal distribution are presented as mean±SD and analyzed using Student's *t*-test. The continuous data without normal distribution are presented as median and IQR (IQR, 25th–75th percentile) and analyzed using the Wilcoxon rank-sum test. Categorical variables are presented as counts (percentages) and compared using the Chi-squared test or Fisher's exact test, as appropriate. Significant results (*P*<0.05) are shown in bold. SD: Standard deviation, CDK4/6i: Cyclin-dependent kinase 4/6 inhibitors, HBV: Hepatitis-B virus, ET: Endocrine therapy, NHI: National Health Insurance, MBC: Metastatic breast cancer, PPI: Proton pump inhibitor

longer median exposure (22.5 vs. 9.7 months, *P* = 0.004), and were less likely to receive post-CDK chemotherapy (35.3% vs. 72.2%, *P* = 0.007). Kaplan–Meier analysis showed a significantly longer OS among the patients treated with CDK4/6is for >19 months [*P* < 0.001, Figure 3].

In multivariable Cox regression analysis [Table 3], a shorter duration of CDK4/6i treatment (≤19 months) was associated with a significantly increased risk of mortality (adjusted HR [aHR]: 6.19, 95% CI: 1.89–20.22, *P* = 0.003). Post-CDK chemotherapy (aHR: 8.59, 95% CI: 1.38–35.45, *P* = 0.043) and PPI use (aHR: 7.01, 95% CI: 1.07–69.15, *P* = 0.019) were also independently associated with higher mortality.

Subgroup analysis: patients treated with cyclin-dependent kinase 4/6 inhibitors for >19 months

Among the 26 patients who received CDK4/6is for ≥19 months (excluding those who continued therapy beyond the study period), we compared the "Lack of NHIr" group (patients who discontinued therapy due to the lack of NHIr, *n* = 18) with the "progression disease (PD) after 19 mo" group (patients who had disease progression after 19 months of 1 L CDK4/6i treatment, *n* = 8). The baseline characteristics of both groups are summarized in Table 4. The "Lack of NHIr" group had a lower incidence of PFS2 events, defined as disease progression on post-CDK4/6i therapy (50.0% vs. 100.0%, *P* = 0.023),
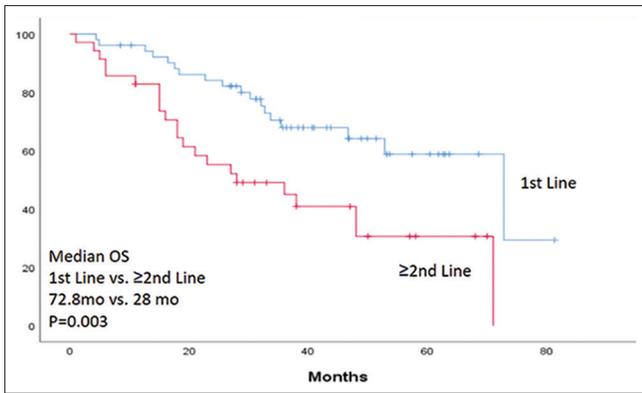
Figure 2: Kaplan–Meier survival curve for OS of 1L and ≥2L CDK4/6i users
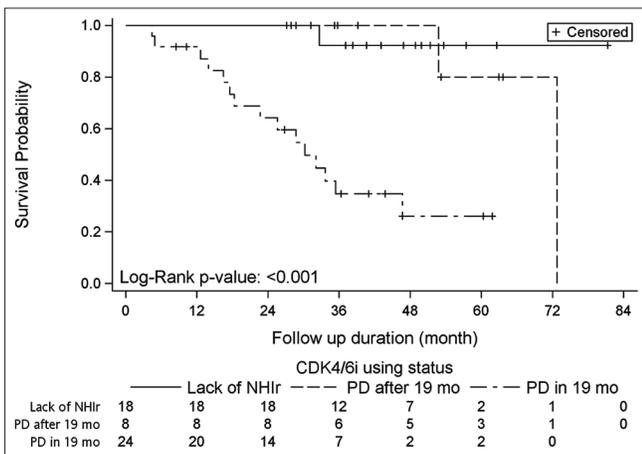

Figure 3: Kaplan–Meier curve for overall survival curve of CDK4/6i using status. NHIr: NHI reimbursement, PD: progressive disease; mo, month. *Keep using CDK only 2 cases, not enrolled in the survival plot
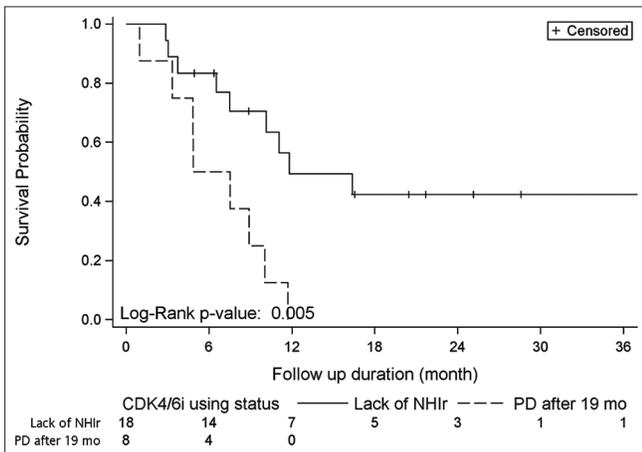

Figure 4: Kaplan–Meier curve for progression on post-CDK4/6i therapy of CDK4/6i using status. NHIr: NHI reimbursement, PD: progressive disease, mo, month

and ribociclib was more frequently prescribed in the "Lack of NHIr" group than in the "PD after 19 mo" group (72.2% vs. 25.0%, $P = 0.043$). Kaplan–Meier analysis demonstrated

a significantly longer PFS2 in the "Lack of NHIr" group than in the "PD after 19 mo" group [$P = 0.005$, Figure 4].

Table 5 presents the results of univariable and multivariable Cox regression analyses (Models 1 and 2). In the univariable model, the "Lack of NHIr" group was less likely to experience progression on post-CDK4/6i therapy compared to the "PD after 19 mo" group. Using backward selection, ribociclib use, PPI use, and post-CDK treatment type were identified as significant covariates in Model 1, which revealed that ribociclib and PPI use, were associated with a significantly lower risk of progression on post-CDK4/6i therapy (aHR = 0.17, 95% CI: 0.05–0.59, $P = 0.005$; aHR = 0.12, 95% CI: 0.01–0.97, $P = 0.047$, respectively). Among the post-CDK treatments, the patients who received Afinitor and other therapies had a markedly higher risk of progression (aHR = 16.05, 95% CI: 2.36–108.95, $P = 0.005$; aHR = 38.03, 95% CI: 2.59–558.91, $P = 0.008$). After adjusting for these variables, the group effect (i.e., "Lack of NHIr" vs. "PD after 19 mo") was no longer statistically significant (Model 2), suggesting that CDK4/6i type, PPI use, and post-CDK treatment were independent prognostic factors associated with PFS2 events, whereas NHIr status (i.e., whether treatment was discontinued due to lack of NHI coverage or disease progression) was not significantly associated with subsequent treatment outcomes.

DISCUSSION

Progression-free survival – comparison between randomized controlled trials and real-world studies

CDK4/6is have gradually become the backbone of treatment for HR-positive MBC over the past decade. As the use of these agents becomes more prevalent, real-world studies play an important role in bridging the gap between clinical practice and randomized controlled trials, as well as providing valuable information for clinical scenarios.

The mPFS of the patients in this study who received 1 L and ≥2 L CDK4/6i therapy was 22.1 and 7.9 months, respectively. The PFS in the 1 L group is generally consistent with that observed in the Paloma-2, Monaleesa-2 and 7, and Monarch-3 phase 3 randomized control trials, which reported mPFS of 27.6, 25.3, 23.8, and 29 months, respectively.[1-3,6] However, compared to real-world data, our results are shorter than in a study conducted in Poland,[7] which reported real-world PFS (rwPFS) of 29.0 months, 32.0 months, and not reached for palbociclib, ribociclib, and abemaciclib, respectively, combined with an aromatase inhibitor. In the P-reality X study, the rwPFS of palbociclib + aromatase inhibitor was 19.3 months,[4] while in the Parsiful-Long study, the rwPFS with the same treatment combination was 33.2 months.[5] On the other hand, the CompLEEment-1 study evaluated ribociclib + letrozole in HR-positive, HER2-negative advanced breast cancer patients, and reported a mPFS of 27.1 months.[8] One single-center study from the UK, focusing on the first-line use of CDK4/6is, also revealed comparable results, with an mPFS of 27.9 months

Table 3: The effect of cyclin-dependent kinase 4/6 inhibitors using status for overall survival (*n*=52)

Variables	Univariate		Multivariable[a]	
	Crude HR (95% CI)	*P*	aHR (95% CI)	*P*
Age	1.03 (0.99–1.08)	0.173		
CDK4/6i type				
Palbociclib/abemaciclib	1			
Ribociclib	0.43 (0.16–1.15)	0.094		
CDK4/6i using status				
>19 months	1		1	
≤19 months	15.78 (3.57–69.85)	<0.001	6.19 (1.89–20.22)	0.003
Metastasis site				
Single site	1			
≥2 sites	3.32 (0.76–14.56)	0.112		
PPI use				
No	1		1	
Yes	1.21 (0.33–4.39)	0.770	7.01 (1.38–35.45)	0.019
HBV carrier				
Noncarrier	1			
Carrier	2.47 (0.88–6.88)	0.085		
Unknown	0.39 (0.05–3.22)	0.386		
Primary ET resistance				
ET resistance	1			
ET sensitive	1.14 (0.15–8.85)	0.898		
De novo MBC	1.20 (0.13–11.10)	0.871		
Post-CDK4/6i treatment				
ET only/no further therapy	1		1	
Afinitor	1.20 (0.07–19.54)	0.896	0.31 (0.02–6.05)	0.437
Chemotherapy	7.61 (0.99–58.50)	0.051	8.59 (1.07–69.15)	0.043
Others	12.54 (1.28–122.33)	0.030	7.50 (0.76–74.03)	0.084

CDK4/6i: Cyclin-dependent kinase 4/6 inhibitors, MBC: Metastatic breast cancer, PPI: Proton pump inhibitor, HBV: Hepatitis-B virus, ET: Endocrine therapy, CI: Confidence interval, HR: Hormone receptor, aHR: Adjusted hazard ratio, [a]: Backward selection method was used to select the related factors for mortality

for palbociclib and 29 months for ribociclib.[9] A multicenter study in Germany reported an mPFS of 23 months in patients receiving first-line CDK4/6i treatment.[10] Another real-world study conducted in Singapore reported a similar mPFS of 28.1 months in those receiving first-line treatment.[11] Taken together, the mPFS for the patients receiving 1 L CDK4/6i treatment in the current study is comparable to mPFS reported in randomized control trials and several real-world studies.

In contrast, the mPFS in the ≥2 L CDK4/6i group in the current study (7.9 months) is shorter than the mPFS reported in the Paloma-3, Monaleesa-3, and Monarch-3 phase 3 randomized control trials, which reported values of 11.2, 14.6, and 16.4 months, respectively.[12-14] This discrepancy may be due to the small sample size and less strict inclusion criteria in our cohort. However, the difference in mPFS between the 1 L and ≥2 L groups was statistically significant (log–rank *P* = 0.008). This is consistent with data from the PRAEGNANT study, which reported significantly lower mPFS in the patients who received CDK4/6is as second-line (8.7 months) or third-line (4.7 months) therapy compared to first-line treatment (24.7 months).[15] This suggests that the most notable benefit of CDK4/6i therapy may be limited to the first-line setting.

Independent predictors of overall survival in the 1 L cyclin-dependent kinase 4/6 inhibitor users

In multivariate Cox regression analysis of OS in the 1 L CDK4/6i users [Table 3], "concurrent PPI use" was a predictor of poorer survival. In a prospective study conducted in 2023 in Turkey, 86 HR-positive and HER-2-negative MBC patients were treated with palbociclib and ribociclib. Concurrent PPI users were compared with non-PPI users, and the result showed that PPIs could affect the solubility of CDK4/6is and their concentration in the plasma because of their pH-dependent bioavailability.[16] The mPFS was 10.9 months in the concurrent PPI use group, while the mPFS in the non-PPI use group was not reached. A meta-analysis of nine studies (2737 patients) found a better PFS in the PPI nonusers (HR 2.09, *P* < 0.001), as well as in the subgroups receiving ribociclib and Palbociclib.[17] In our cohort, the eight patients who used PPIs received either ribociclib or palbociclib, which is consistent with the aforementioned studies. However, some studies have reported opposite results. In a real-world retrospective study of 281 patients using either palbociclib or abemaciclib conducted in 2024, there was no significant difference in mPFS between the groups receiving CDK4/6is with and without PPIs (18 vs. 17 months, respectively [HR 0.83, *P* = 0.2518]).[18] In another

Table 4: 1st Line cyclin-dependent kinase 4/6 inhibitors treatment >19 months by cyclin-dependent kinase 4/6 inhibitors discontinuation reason (*n*=26)

Variables	Total (*n*=26)	Lack of NHIr (*n*=18)	PD after 19 month during 1st line CDK4/6i treatment (*n*=8)	*P*
Age	59.1±10.5	58.5±10.4	60.6±11.4	0.642
Metastasis site				0.186
Single site (bone only)	3 (11.5)	3 (16.7)	0	
Single site (except bone)	4 (15.4)	4 (22.2)	0	
≥2 sites	19 (73.1)	11 (61.1)	8 (100.0)	
PPI use				0.529
No	23 (88.5)	15 (83.3)	8 (100.0)	
Yes	3 (11.5)	3 (16.7)	0	
HBV carrier				0.424
Noncarrier	19 (73.1)	12 (66.7)	7 (87.5)	
Carrier	3 (11.5)	2 (11.1)	1 (12.5)	
Unknown	4 (15.4)	4 (22.2)	0	
Primary ET resistance				>0.999
ET sensitive	21 (80.8)	14 (77.8)	7 (87.5)	
De novo MBC	5 (19.2)	4 (22.2)	1 (12.5)	
CDK4/6i information				
CDK4/6i type				**0.043**
Palbociclib	10 (38.5)	5 (27.8)	5 (62.5)	
Abemaciclib	1 (3.8)	0	1 (12.5)	
Ribociclib	15 (57.7)	13 (72.2)	2 (25.0)	
CDK4/6i exposure time (months)	23.2 (22.1–30.4)	22.8 (22.1–24.2)	31.0 (24.5–37.5)	0.059
Post-CDK4/6i treatment				0.076
Chemotherapy	12 (46.2)	7 (38.9)	5 (62.5)	
Afinitor	5 (19.2)	2 (11.1)	3 (37.5)	
ET only/no further therapy	7 (26.9)	7 (38.9)	0	
Others	2 (7.7)	2 (11.1)	0	
Outcomes				
Progression on post-CDK4/6i drug (PFS2 event)	17 (65.4)	9 (50.0)	8 (100.0)	**0.023**
End of CDK4/6i ~ end of post-CDK drug (PFS2)	8.9 (4.9-16.4)	10.6 (6.4-20.5)	6.2 (4.1-9.5)	0.090

The continuous data with normal distribution are presented as mean±SD and analyzed using Student's *t*-test. The continuous data without normal distribution are presented as median and interquartile range (IQR, 25th–75th percentile) and analyzed using the Wilcoxon rank sum test. The categorical variables are presented as counts (%) and compared by the Chi-squared test or Fisher's exact test, as appropriate. Significant results (*P*<0.05) are shown in bold. NHIr: 3 NHI reimbursement, PD: Progressive disease, SD: Standard deviation, MBC: Metastatic breast cancer, PPI: Proton pump inhibitor, HBV: Hepatitis-B virus, CDK4/6i: Cyclin-dependent kinase 4/6 inhibitors

retrospective study of 205 patients receiving ribociclib or palbociclib, the concurrent use of PPIs did not affect the efficacy of CDK4/6i's.[19] In the present study, the results did not indicate that the number of metastasis sites was a significant survival predictor, although a previous study suggested that patients with multiple metastasis sites had worse OS than those with a single metastasis site.[20] Age is an important prognostic factor in patients with metastatic luminal A breast cancer. In general, younger patients (especially those ≤40 years old) have poor outcomes, including significantly worse relapse-free survival,[21] 5-year disease-free survival, and distant metastasis-free survival.[22] An analysis from the Surveillance, Epidemiology, and End Results database found a U-shaped relationship between age and prognosis of metastatic luminal A breast cancer, with both younger (<40 years) and older (>60 years) patients having worse outcomes compared to middle-aged patients.[23] As with the number of metastasis sites, the age was not significantly correlated with survival

outcomes in the present study. Our study is limited by the relatively small sample size, and larger studies are warranted for more accurate and consistent results.

1 L cyclin-dependent kinase 4/6 inhibitor usage >19 months: patient characteristics and independent predictors of progression-free survival2

The Taiwan NHI system balances the expenses and patient benefits of CDK4/6i treatment, reimbursing 2 years of palbociclib or ribociclib combined with ET for patients with metastatic HR-positive, HER2-negative breast cancer. Nevertheless, there is currently no evidence regarding the prognosis after discontinuing CDK4/6i treatment after 2 years of reimbursement. Among the 1 L CDK4/6i users in our study, the average CDK4/6i exposure was 18.9 months; the shortest exposure time due to reimbursement limits was 19.5 months. Therefore, we set 19 months as the cut-off value for reimbursement in our statistical analysis. As shown in Table 4

Table 5: Survival analysis of 1st Line cyclin-dependent kinase 4/6 inhibitors treatment >19 months for progression on post-cyclin-dependent kinase 4/6 inhibitors therapy (PFS2_event) (*n*=26)

Variables	Univariate		Model 1		Model 2	
	Crude HR (95% CI)	*P*	aHR (95% CI)	*P*	aHR (95% CI)	*P*
Age	1.01 (0.96–1.05)	0.807				
CDK4/6i type						
Palbociclib/abemaciclib	1		1		1	
Ribociclib	0.22 (0.08–0.60)	**0.003**	0.17 (0.05–0.59)	**0.005**	0.22 (0.06–0.87)	**0.030**
CDK4/6i exposure time (month)	1.03 (0.96–1.10)	0.432				
CDK4/6i using status						
PD after 19 months during CDK4/6i treatment	1				1	
Lack of NHIr	0.24 (0.09–0.70)	**0.008**			2.07 (0.39–11.04)	0.396
Metastasis site						
Single site	1					
≥2 sites	1.85 (0.53–6.48)	0.335				
PPI use						
No	1		1		1	
Yes	0.81 (0.18–3.56)	0.781	0.12 (0.01–0.97)	**0.047**	0.17 (0.02–1.62)	0.122
HBV carrier						
Non-carrier	1					
Carrier	1.55 (0.43–5.50)	0.501				
Unknown	0.59 (0.13–2.64)	0.489				
Primary ET resistance						
ET sensitive	1					
De novo MBC	0.80 (0.23–2.79)	0.726				
Post-CDK4/6i Treatment						
ET only/no further therapy	1		1		1	
Afinitor	2.66 (0.59–12.00)	0.202	16.05 (2.36–108.95)	**0.005**	8.42 (0.77–92.40)	0.081
Chemotherapy	1.84 (0.49–6.94)	0.370	2.93 (0.69–12.49)	0.147	1.96 (0.35–11.06)	0.445
Others	8.38 (1.26–55.53)	**0.028**	38.03 (2.59–558.91)	**0.008**	35.35 (2.28–548.73)	**0.011**

Model 1: The related factors were selected using backward selection until all variables with *P*<0.05 in the final model, Model 2: The covariates in model 1 were the adjustments and added CDK4/6i using status in the model. Significant results (*P*<0.05) are shown in bold. NHIr: NHI reimbursement, PD: Progressive disease, HR: Hormone receptor, aHR: Adjusted hazard ratio, CDK4/6i: Cyclin-dependent kinase 4/6 inhibitors

and Figure 4, we found that the patients who discontinued CDK4/6i treatment due to the lack of NHIr had better PFS2 outcomes, compared to those who had disease progression after 19 months during CDK4/6i treatment. However, after further statistical adjustment, reimbursement status no longer affected PFS2, implying that early discontinuation of CDK4/6i treatment at around 19 months without disease progression may be an optional clinical decision if financial burden is a major concern. Nevertheless, whether this finding can be generalized as a standard of practice remains unclear due to the small sample size.

We also found that the patients who received ribociclib as the 1 L CDK4/6i for ≥19 months had better PFS2 outcomes, compared to those who received palbociclib/abemaciclib [Table 5]. A meta-analysis from the European Society for Medical Oncology in 2021 comprised eight studies (MONALEESA-2/3/7, MONARCH-2/3, PALOMA-1/2/3), and five of which reported PFS2 data (MONALEESA-3/7, MONARCH-2/3, PALOMA-2).[24] The results showed no significant difference in PFS2 h (0.64–0.69) between ribociclib, abemaciclib, and palbociclib. A real-world study conducted in Poland found no significant differences in PFS2 between three CDK4/6is in combination with an aromatase inhibitor in both first-and

second-line settings. In contrast, ribociclib + fulvestrant was superior to palbociclib/abemaciclib + fulvestrant in both lines.[7] In our study, the type of ET used with the CDK4/6i was not specified. In addition, the CDK4/6i exposure time in the above two studies is not compatible with ours. Further studies may be needed to explain this finding.

Limitations

There are some limitations to this study. First, the retrospective design makes bias and misinterpretation of medical records inevitable. There may be a subjective determination on initial data collection and statistical coding. Second, the sample size of this cohort was limited, and the 95% CI was relatively wide. Both facts may affect the generalizability of our findings. Finally, the follow-up time in this study was limited. The consequence of early CDK4/6i discontinuation due to the lack of NHIr may have been more evident and definitive if the patients had been followed for a longer period.

CONCLUSION

In this single-institution retrospective study, PFS and OS with CDK4/6i use were comparable to those reported in pivotal

phase 3 clinical trials, both in first-line and later-line settings. In terms of disease progression on next-line therapy in the patients who received CDK4/6i therapy for >19 months, ribociclib showed better PFS2, compared to palbociclib or abemaciclib. Due to the limited sample size, associations between factors such as age, the presence of more than two metastatic sites, and lack of reimbursement with poorer outcomes did not reach statistical significance.

Author contributions

Concept: Yi-Hsuan Hsu, Ying-Wen Su; Design: Yi-Hsuan Hsu, Ying-Wen Su; Definition of intellectual content: Yi-Hsuan Hsu, Ying-Wen Su, Huan-Chao Lin; Literature search: Yi-Hsuan Hsu, Po-Shen Yang, Wen-Ching Ko; Clinical studies: Yi-Hsuan Hsu, Yuan-Ching Chang; Experimental studies: Yi-Hsuan Hsu, Hung-Bun Lam; Data acquisition: Yi-Hsuan Hsu, Fang Lee, Chung-Hsin Tsai; Data analysis: Yi-Hsuan Hsu, Chia-Yen Hung; Statistical analysis: Yi-Hsuan Hsu, Johnson Lin; Manuscript preparation: Yi-Hsuan Hsu, Nei-Wen Su; Manuscript editing: Yi-Hsuan Hsu, Yi-Hao Chiang; Manuscript review: Yi-Hsuan Hsu, Ying-Wen Su. All authors have read and agreed to the final version of the manuscript.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflicts of interest

There are no conflicts of interest.

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