

# Optimal Treatment of Hormone Receptor-positive Advanced Breast Cancer Patients With Palbociclib

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**Abstract.** *Background/Aim:* Palbociclib was the first cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor approved worldwide. Currently, CDK4/6 inhibitors are strongly recommended for endocrine therapy in the first or second line with hormone receptor-positive advanced breast cancer. It is expected the use of CDK4/6 inhibitor will further increase. Therefore, the aim was to investigate and better understand the use of palbociclib. *Patients and Methods:* We retrospectively analyzed the data of patients with advanced breast cancer who were treated with palbociclib in three hospitals between 2018 and 2022. Clinical data were obtained from the patients' medical electronic records. *Results:* A total of 143 patients were enrolled. The median age was 66 years (range=33-89), and the majority (90.9%) were postmenopausal patients. In total, median time-to-treatment discontinuation (TTD) (95% confidence interval, CI) was 7 (6-10) months. Median TTD (95% CI) was 13 (7-20) months for the first or second line, and significantly prolonged compared to TTD for the third or later lines with palbociclib ( $p<0.0001$ ). The importance of front-line use was indicated. Multivariate analyses showed that no visceral metastasis or first or second line therapy influenced the longer TTD. Between patients above or below 70 years of age, older age did not negatively affect TTD, though there were significantly more cases of dose reduction or withdrawal in patients over 70 years old. The variation of adverse events (AEs) among hospitals was very large (9.0%, 31.3%, 4.5%). We found that understanding of AE management was

important. *Conclusion:* This study showed that dose reduction or withdrawal of palbociclib had no harmful effects in Japanese patients. Efficacy was also high in older patients. It is important to manage palbociclib administration more safely and appropriately. A combination of dose reduction and withdrawal is key to this therapeutic strategy.

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer deaths worldwide (1); it is the fifth most common in Japan (2). More than two-thirds of breast cancers are hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) (3, 4). Recently, palbociclib, the world's first cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor, was approved as a new treatment for hormone therapy, based on the results of the large-scale clinical trials PALOMA-2 and PALOMA-3 (5-7). Currently, level 1 evidence supports the use of CDK4/6 inhibitors in combination with endocrine therapy for patients with HR+HER2- metastatic breast cancer (MBC) (8, 9). Three CDK4/6 inhibitors (palbociclib, abemaciclib, and ribociclib) have been approved worldwide, and their clinical use is increasing markedly.

Previous trials have reported impressive results for the efficacy of palbociclib (PALOMA-2: median PFS of 24.8 months vs. 14.5 months, hazard ratio=0.576; PALOMA-3: median PFS of 9.2 months vs. 3.8 months, hazard ratio=0.422) (5, 7). Dose reductions, cycle delays and dose discontinuation of palbociclib due to neutropenia have been found to occur more frequently in Japanese patients than in the overall population (10). Therefore, management is important to allow for safer and more optimal administration of palbociclib.

Although it is expected that the number of older patients with breast cancer will continue to increase (1, 11), limited data are available about the tolerability, safety profile and benefit of CDK4/6 inhibitors in older patients (12).

This study aimed to investigate the use of palbociclib and provides insights into side effects and clinical outcomes for

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their long-term use. In addition, we evaluated the usefulness of palbociclib in patients aged 70 years or older.

## Patients and Methods

**Study design and patients.** This retrospective cohort study was conducted in three institutions: Kyoto Prefectural University of Medicine, Kyoto Okamoto Memorial Hospital and Japanese Red Cross Kyoto Daini Hospital. Between January 1, 2018, and September 30, 2022, patients diagnosed with advanced breast cancer and treated with palbociclib for at least 1 month were included. Patients were followed-up between treatment initiation and death or cut-off date. This study was approved by the institutional review board of each hospital. The need for written informed consent was waived because of the retrospective nature of the study. We present the findings following the format recommended by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

**Outcomes.** The primary outcome was time-to-treatment discontinuation (TTD) (13), which was defined as the time from the start of treatment with palbociclib until the time of discontinuation, due to any reason including adverse events. Secondary outcomes were safety of palbociclib and outcomes of older patients.

**Statistical analyses.** Descriptive statistics were used to analyze the demographic and clinical characteristics. We used the Kaplan-Meier method and the log-rank test to assess TTD and OS. We defined significance as  $p < 0.05$ . All statistical analyses were conducted with JMP ver. 14 (SAS Institute Inc., Cary, NC, USA).

## Results

**Patient characteristics.** A total of 143 patients with MBC undergoing administration of palbociclib were included in the analysis. The patients' characteristics are listed in Table I. Only one case (0.7%) was male, and most were female (99.7%). The median age was 66 years (range=33-89), and the majority (90.9%) were postmenopausal breast cancer patients. Only 11.2% had bone metastases alone, and more than half (52.4%) had visceral metastases. Half of the patients were treated in the first and second line with palbociclib (29.4% and 28.6%, respectively), while 24.5% of the patients were treated in the fourth line or later. In 2018 and 2019, 60% of fourth line or later treatment patients received palbociclib due to its immediate use after approval.

**Treatment outcomes.** The median TTD was 7 [95% confidence interval (CI)=6-10] months (Figure 1A). The median TTD of palbociclib in the Japanese real world first line data was 8.7 months (95% CI=8.1-9.0) (13), suggesting that there was no significant difference. Median TTD was 13 (95% CI=7-20) months for the first or second line, and significantly prolonged compared to TTD for the third or later lines with palbociclib ( $p < 0.0001$ ) (Figure 1B). Similar to previous clinical trials, the importance of upfront use was

demonstrated. The results of univariate analysis and multivariate Cox regression analyses for TTD are shown in Table II. In the univariate analysis, the presence of visceral metastases, bone only metastasis and first- or second-line therapy significantly prolonged TTD. Similarly, in multivariate analysis, the presence of visceral metastases and first- or second-line therapy improved TTD.

**Dose adjustment.** We calculated the relative dose intensity (RDI) of palbociclib by dose and dosing schedule (Table III). We measured palbociclib 125mg once daily (QD) on a 28-day cycle; 3 weeks on and 1 week off treatment as 100% of the regular dose. The results showed that 109/143 (76.2%) of the patients had started at the regular dose and schedule of palbociclib, namely RDI of 100%. In contrast, 134/143 (93.7%) of the patients had a dose reduction at the beginning or during treatment for any reason.

**Safety.** At the point of data cutoff, 37/143 (25.9%) remained on treatment. The reasons for palbociclib discontinuation were disease progression in 84 patients (58.7%), adverse event (AE) in 19 patients (13.3%), and death in 3 patients (2.1%). The 13.3% of discontinuations due to AEs had very large variation between three hospitals (9.0%, 31.3%, 4.5%). The most frequent reason for AE discontinuation was neutropenia in 7 patients (4.9%), followed by fatigue in 5 patients (3.5%). These factors also showed variation between hospitals (neutropenia: 4.5%, 9.4%, 4.5%, fatigue: 1.1%, 12.5%, 0%).

**Older patients.** Table IV shows a comparison of patients aged 70 years and older versus those younger than 70 years. Although there were significantly more cases of dose discontinuation in older patients, there was no significant difference in duration of treatment. The fact that the patients were older than 70 years did not have a negative effect. Comparison of TTD showed no difference between the two groups ( $p = 0.5817$ ) (Figure 2A). OS also showed no difference between the two groups ( $p = 0.6000$ ) (Figure 2B). However, it should be noted that the rate of treatment discontinuation due to AEs was predominantly higher in patients aged 70 years or older.

## Discussion

In this study, we examined the use of palbociclib in a retrospective, multicenter collaboration of the Kyoto Prefectural University of Medicine Group, which provides a deep understand of the actual use of CDK4/6 inhibitors in Japan, and also provides insights into side effects and clinical outcomes for their long-term use in HR+, HER2- advanced breast cancer.

Concerning treatment efficacy, the PFS in PALOMA-2 trial, a clinical trial of first line treatment, was 24.8 months (5), and in PALOMA-3, a trial of second line treatment, PFS

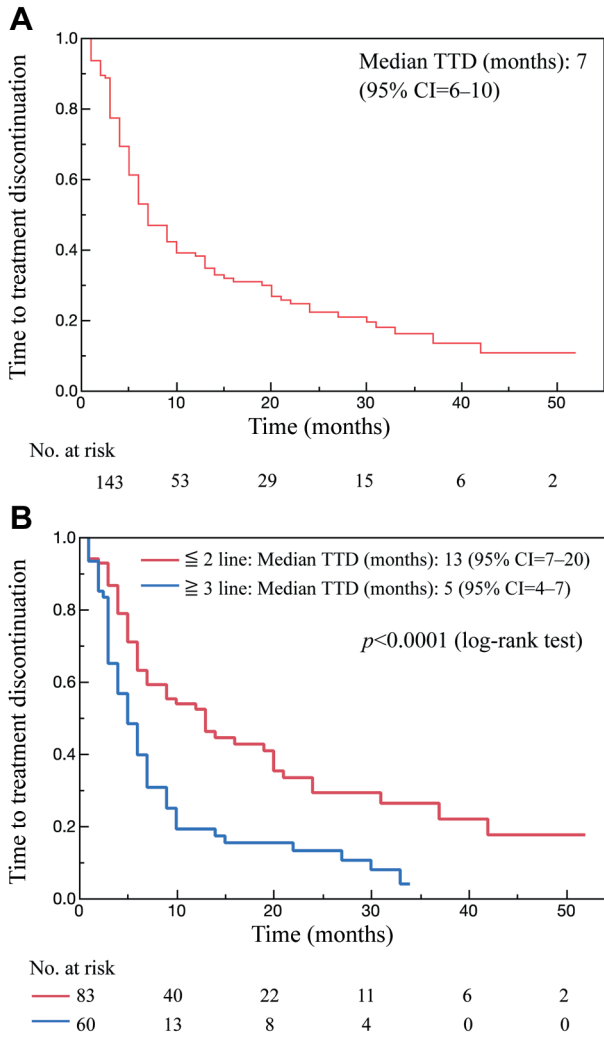


Figure 1. Kaplan-Meier curves of time-to-treatment discontinuation for treatment with palbociclib. (A) All lines of therapy; (B) Compared with first or second line of therapy and third or later lines of therapy.

was 9.2 months (11.2 months in an additional analysis) (6). Moreover, real-world data from the U.S. also showed PFS of first line treatment was 20 months after stabilized inverse probability treatment weighting adjustment (15). However, in real clinical settings, it is difficult to evaluate PFS according to a protocol-defined schedule and assessment, similar to clinical trials. Therefore, we investigated the TTD, which is one of the tools used to evaluate drug response rates in real world studies. As a result, the median PFS in this study was 7 months (95% CI=6-10) (Figure 1A). The median TTD was 13 months (95% CI=7-20) when the number of treatment lines was limited to the first and second line. The results indicate that, as in previous reports (16), it is important to use palbociclib in more up-front treatment. In addition, a retrospective study using the Japanese administrative claims

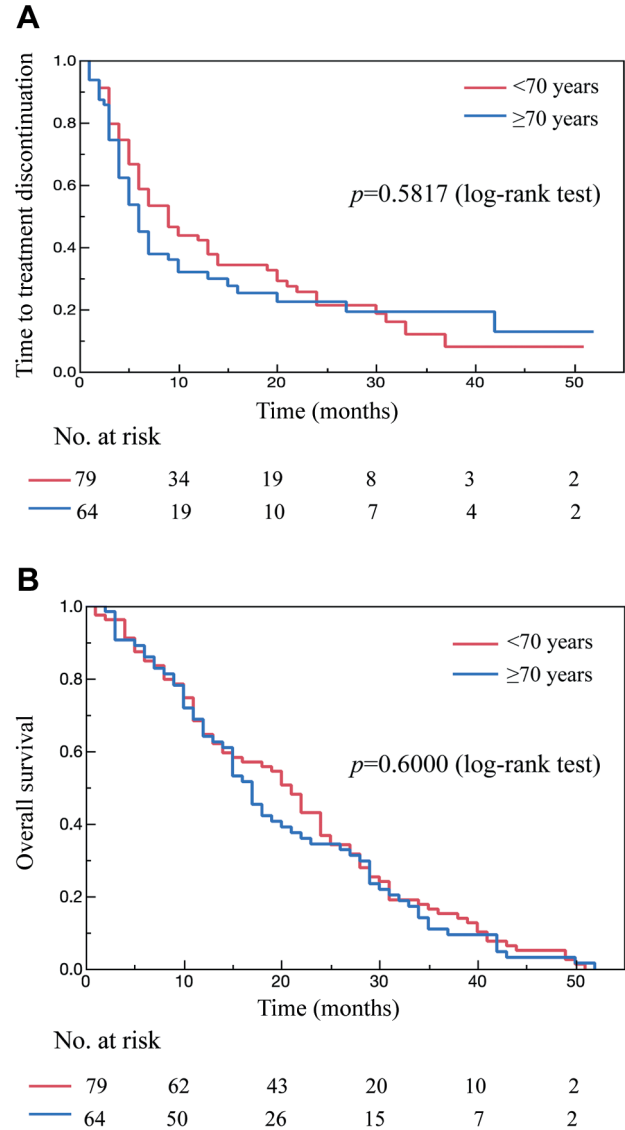


Figure 2. Kaplan-Meier curves of time-to-treatment discontinuation and overall survival between older patients (over 70 years) and younger patients (under 70 years).

database (6442 cases) reported a median TTD of 8.7 months (95% CI=8.1-9.0) for first line treatment with palbociclib (14), which was similar to the present study.

The study found that 19/143 (13.3%) patients discontinued palbociclib due to AEs, with 7/143 (4.9%) due to neutropenia and 5/143 (3.5%) due to fatigue. This is higher than the 2.3% and 0.8% in the long-term safety pooled analysis (17). This is a very large variation between hospitals. The percentage of discontinuations due to AEs at each hospital varied between 9.0%, 31.3%, and 4.5%. Neutropenia varied between 4.5%, 9.4% and 4.5%, while fatigue varied between 1.1%, 12.5% and 0%, respectively. This shows that

Table I. Baseline patient characteristics.

		N=143
Age at Palbociclib treatment, median (range)		66 (33-89)
Menopausal status at Palbociclib treatment, n (%)	Pre/peri-menopausal	12 (8.4)
	Post-menopausal	130 (90.9)
Sex, n (%)	Female	142 (99.3)
	Male	1 (0.7)
Disease stage at initial diagnosis, n (%)	I-III	108 (75.5)
	De novo	33 (23.1)
	Unknown	2 (1.4)
Visceral metastases, n (%) <sup>a</sup>	No	68 (47.6)
	Yes	75 (52.4)
Bone-only metastasis, n (%)	No	127 (88.8)
	Yes	16 (11.2)
Line of therapy, n (%)	First	42 (29.4)
	Second	41 (28.6)
	Third	25 (17.5)
	Forth or later	35 (24.5)
Treatment duration, months, median (range)		6 (1-52)
Status at cut-off date, n (%)	On-going treatment	37 (25.9)
	Discontinued treatment	106 (74.1)
Reasons for treatment discontinuation	Disease progression	86 (81.1)
	Death	1 (1.0)
	Adverse event	19 (17.9)

<sup>a</sup>Refers to lung (including pleura) and/or liver involvement (including peritoneum).

Table II. Univariate and multivariate analyses of potential prognostic factors for time to treatment discontinuation.

Potential prognostic factor	Univariate		Multivariate analyses	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Age at Palbociclib treatment, ≥70	1.110 (0.754-1.632)	0.5973	1.054 (0.710-1.567)	0.7932
Disease stage at initial diagnosis, <i>De novo</i>	1.183 (0.744-1.880)	0.4773	1.170 (0.730-1.876)	0.5135
Visceral metastases	2.005 (1.318-3.048)	0.0011	1.883 (1.172-3.027)	0.0089
Bone-only metastasis	0.418 (0.194-0.900)	0.0258	0.678 (0.292-1.577)	0.3673
Line of therapy, ≤2	0.483 (0.327-0.713)	0.0002	0.460 (0.310-0.685)	0.0001

Table III. Relative dose intensity of palbociclib and dosing schedule.

Palbociclib	125 mg	100 mg	75 mg
28-day cycle 3 weeks on/1 week off	100%	80%	60%
35-day cycle 3 weeks on/2 weeks off	80%	64%	48%
28-day cycle 2 weeks on/2 weeks off	66.6%	53.3%	40%

understanding AE management is very important. Therefore, it is expected that treatment discontinuation due to AEs will be reduced at hospitals with little experience by instructing appropriate management methods from hospitals with extensive experience in using palbociclib.

Aging is a complex process with large individual differences; therefore, a multidimensional approach is needed. In brief, it needs careful consideration to guide the management of older patients and the uptake of novel therapeutic approaches, including CDK4/6 inhibitors.

Table IV. Characteristics of older patients (over 70 years) and younger patients (under 70 years).

	Age <70 (N=79)	Age ≥70 (N=64)	p-Value
Age at Palbociclib treatment, y, median (range)	57 (33-69)	75 (70-89)	
Disease stage at initial diagnosis, n (%)			
I-III	63 (79.8)	45 (70.3)	0.4235
<i>De novo</i>	15 (19.0)	18 (28.1)	
Unknown	1 (1.2)	1 (1.6)	
Visceral metastases, n (%) <sup>a</sup>			
No	34 (43.0)	21 (32.8)	0.2114
Yes	45 (57.0)	43 (67.2)	
Bone-only metastasis, n (%)			
No	70 (88.6)	57 (89.1)	0.9316
Yes	9 (11.4)	7 (10.9)	
Line of therapy, n (%)			
First	24 (30.4)	18 (28.1)	0.3865
Second	19 (24.1)	22 (34.3)	
Third	13 (16.4)	12 (18.8)	
Forth or later	23 (29.1)	12 (18.8)	
Treatment duration, months, median (range)	9 (1-51)	6 (1-52)	0.3861
Status at cut-off date, n (%)			
On-going treatment	19 (24.1)	18 (28.1)	0.4461
Discontinued treatment	60 (75.9)	46 (71.9)	
Reasons for treatment discontinuation			
Disease progression	53 (88.3)	33 (71.7)	0.0389
Death	1 (1.7)	0	
Adverse event	6 (10.0)	13 (28.3)	
Dose reduction, n (%)			
No	19 (24.1)	6 (9.4)	0.0180
Yes	57 (72.2)	57 (89.1)	
Unknown	3 (3.8)	1 (1.6)	
Baseline count neutrophile, median (range)	3,520 (1,060-8,700)	3,830 (1,300-9,130)	0.9290

<sup>a</sup>Refers to lung (including pleura) and/or liver involvement (including peritoneum).

PALOMA-3 did not result in a significantly increased risk of grade 3-4 neutropenia in older patients. However, although there was no statistically significant difference, there was a trend associated with infections and grade 3-4 neutropenia in those aged 70 years and older (18). In fact, in this study, discontinuation due to AEs was significantly more frequent than in patients under 70 years. Therefore, sufficient caution is required. Visceral metastases tended to be more frequent in patients aged 70 and older compared to younger patients. This is speculated to be due to the aggressive use of palbociclib in advanced cases, where chemotherapy would normally be a choice. Even under such conditions, there was no difference in the duration of treatment compared to patients younger than 70 years of age. Therefore, palbociclib is considered to be an effective drug that can be safely used in older patients with caution.

Next, we discuss dose reduction and cessation of palbociclib. Between patients with early dose reduction of palbociclib within 180 days of treatment initiation and patients without, the median duration of treatment was 589.0 days and 427.0 days in PALOMA-2, respectively (5).

Similarly, in PALOMA-3, it was 241.5 and 413.0 days, respectively (6, 7). It has been reported that there is no significant difference in the duration of response even with early dose reduction (10). Regarding cessation of palbociclib, an *in vitro* study examining the mechanism of palbociclib-induced bone marrow suppression showed that recovery of bone marrow suppression was observed within 4 days of cessation of the drug (19). In addition, the neutropenia from palbociclib was recovered rapidly and was non-cumulative, and its anti-proliferative effect on precursor cells was significantly weaker than that of chemotherapy (20). The simulation of the time course of palbociclib administration and neutrophil counts showed that the patient reaches a nadir around day 21 after the start of administration, and then recovers during the first 8 days of the next cycle. It was then found that this pattern was repeated thereafter (20). In other words, even if the patient is not fully recovered on the start date of the next cycle, he/she will recover later, therefore no dose reduction is required. It has also been reported that the CDK4/6 inhibitor resistance phenotype is reversible *in vitro* and *in vivo* by a prolonged drug holiday (21). This indicates

that cancers that have acquired resistance to CDK4/6 inhibitors in primary therapy may recover sensitivity to CDK4/6 inhibitors in secondary therapy by a prolonged drug holiday. Taken together, this suggests that a prolonged drug holiday may be a promising option from the viewpoint of drug resistance. In fact, more patients in the longer TTD group (TTD  $\geq$ 20 months) were able to reduce the dose and prolong a drug holiday in this study (Table III).

Furthermore, in regard to RDI, palbociclib 75 mg QD on a 28-day cycle; 3 weeks on and 1 week off treatment had an RDI of 60%, whereas palbociclib 100 mg QD on a 35-day cycle; 3 weeks on and 2 weeks off treatment had a higher RDI of 64% (Table IV). Therefore, combination of prolonged drug holiday and dose reduction is a very important strategy for long-term palbociclib treatment.

**Study limitations.** It was retrospective in nature, and lacked quality of life assessment. Especially, in elderly patients, we were unable to obtain a comprehensive geriatric assessment (CGA) for performance status (PS), comorbidities, and adverse events of palbociclib, which is an issue for the future. Battis et al. proposed an algorithm to guide the use of CDK4/6 inhibitors based on CGA (12), and this is a helpful guide. In addition, the TTD tended to be shorter than in many previous reports due to a large variation in each hospital. The failure to adjust for TTD, which may have had a significant impact on TTD, should be interpreted with caution.

## Conclusion

In conclusion, scheduled changes due to dose reduction, prolonged drug holiday, or interruption of palbociclib for adverse events do not affect the efficacy of palbociclib in Japanese patients. Therefore, it is important that we use the successful combination of dose reduction and prolonged drug holiday for longer-term use of palbociclib. In addition, closing the knowledge and experience gap would reduce variation among hospitals and enable a more appropriate treatment approach for older patients.

## Conflicts of Interest

Dr. Naoi has received research funding from Sysmex and AstraZeneca; he has received honoraria from AstraZeneca, Pfizer, Eli Lilly, Taiho, MSD, Daiichi Sankyo, Celltrion, Eisai and Chugai, outside the submitted work. All other Authors declare no conflicts of interest.

## Authors' Contributions

Study concept and design: Midori Morita, Yasuto Naoi. Data acquisition: Midori Morita, Asako Ooe, Wataru Ishii, Akira Watanabe, Chise Matsui, Yuka Okuyama, Sae Kitano, Chikage

Kato, Mie Onishi, Koichi Sakaguchi. Quality control of data and algorithms: Midori Morita. Data analysis and interpretation: Midori Morita, Yasuto Naoi. Statistical analysis: Midori Morita. Manuscript preparation and editing: Midori Morita, Yasuto Naoi. All Authors revised and approved the final version of the manuscript.

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