Scientific Research Publishing

Journal of Cancer Therapy, 2026, 17(2), 83-89
https://www.scirp.org/journal/jct
ISSN Online: 2151-1942
ISSN Print: 2151-1934

Palbociclib in First-Line vs Second-Line Treatment for HR+/HER2– Metastatic Breast Cancer: Real-World Evidence from a Moroccan Cohort

Chaymae Chbihi[1*], Hafssa El Hilali[1], Samia El Hakym[1], Diango Keita[1], Sara Nejjari[1], Lamiae Amaadour[1,2], Karima Oualla[1,2], Zineb Benbrahim[1,2], Samia Arifi[1,2], Nawfel Mellas[1,2]

[1]Department of Medical Oncology, Hassan II University Hospital, Fez, Morocco
[2]Faculty of Medicine, Pharmacy and Dental Medicine of Fez, University of Sidi Mohamed Ben Abdellah, Fez, Morocco
Email: *chaymae.chbihi@gmail.com

How to cite this paper: Chbihi, C., Hilali, H.E., Hakym, S.E., Keita, D., Nejjari, S., Amaadour, L., Oualla, K., Benbrahim, Z., Arifi, S. and Mellas, N. (2026) Palbociclib in First-Line vs Second-Line Treatment for HR+/HER2– Metastatic Breast Cancer: Real-World Evidence from a Moroccan Cohort. *Journal of Cancer Therapy*, **17**, 83-89.
https://doi.org/10.4236/jct.2026.172009

Received: December 17, 2025
Accepted: January 30, 2026
Published: February 2, 2026

Abstract

Introduction: Palbociclib, a CDK4/6 inhibitor, has significantly improved outcomes in patients with HR+/HER2– metastatic breast cancer. While its efficacy has been demonstrated in randomized clinical trials, real-world comparative data between first-line (1L) and second-line (2L) use remain limited. **Materials and Methods:** This single-center retrospective study included 55 patients treated with palbociclib between January 2020 and June 2024. Patients were classified into a first-line group (n = 30; palbociclib plus aromatase inhibitor) and a second-line group (n = 25; palbociclib plus fulvestrant). The primary endpoint was progression-free survival (PFS). **Results:** The mean age was 52.4 years. Median PFS was significantly longer in the first-line group compared with the second-line group (19 vs. 8 months; $p < 0.001$). Overall survival was also superior in the first-line group (36.8 vs. 25.5 months; $p = 0.001$). The objective response rate was higher in first-line treatment (39% vs. 22%; $p = 0.03$). The safety profile was acceptable and consistent with previously published clinical trials and real-world data. **Conclusion:** This real-world study supports the superiority of palbociclib when used in the first-line setting, reinforcing the benefit of early CDK4/6 inhibitor integration in the treatment sequence.

Keywords

Metastatic Breast Cancer, HR+/HER2–, Palbociclib, CDK4/6 Inhibitors, Real-World Study

1. Introduction

Metastatic HR+/HER2-negative breast cancer represents a major therapeutic challenge in oncology [1]. The advent of CDK4/6 inhibitors has revolutionized its management by enhancing the efficacy of endocrine therapy through inhibition of the retinoblastoma (Rb) pathway [2] [3], thereby establishing a new therapeutic standard [4].

Palbociclib, the first agent of this class, has demonstrated significant efficacy in the first-line setting in combination with letrozole (PALOMA-2) and in the second-line setting with fulvestrant (PALOMA-3) [5] [6]. This approval indication raises an important clinical question regarding the optimal timing for CDK4/6 inhibitor initiation.

To date, randomized clinical trials do not allow for a direct comparison between first-line and second-line strategies. Although meta-analyses suggest a potential advantage for first-line use [7], these conclusions rely on indirect comparisons.

Real-world evidence provides a valuable opportunity to address this issue and is increasingly recognized for its complementary role alongside clinical trials [8]. In this context, our retrospective study conducted at the Hassan II University Hospital in Fez aimed to compare the efficacy of palbociclib used in the first-line versus second-line setting in a Moroccan cohort of patients with metastatic HR+/HER2-negative breast cancer.

2. Materials and Methods

2.1. Study Design and Population

We conducted a single-center retrospective study including 55 patients with HR+/HER2-negative metastatic breast cancer treated with palbociclib in either the first-line or second-line setting between January 2020 and June 2024. Eligible patients were aged ≥ 18 years and had histologically confirmed disease.

2.2. Data Collection and Evaluation Criteria

Clinical, pathological, and treatment-related data were collected from medical records. Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 [9]. Adverse events were recorded and graded using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 [10].

2.3. Statistical Analysis

Survival analyses were performed using the Kaplan-Meier method, with comparisons conducted using the log-rank test. Hazard ratios were estimated using Cox proportional hazards regression models. Statistical significance was defined as a two-sided p-value < 0.05. The study was approved by the local ethics committee.

3. Results

3.1. Patient Characteristics

The study included 55 patients with HR+/HER2-negative metastatic breast cancer. The demographic and clinicopathological characteristics of the overall cohort and according to treatment line are summarized in Table 1. The mean age was 52.4 years (range: 32 - 93 years), and most patients (87.3%) had a WHO performance status of 0 - 1 at treatment initiation. Baseline characteristics were largely comparable between the two groups, except for the rate of prior adjuvant endocrine therapy, which was significantly higher in the second-line palbociclib group (80% vs. 50%, p = 0.02). In the second-line cohort, fourteen patients (56%) received endocrine therapy alone as first-line metastatic treatment, whereas 11 patients required chemotherapy due to the presence of visceral crisis, reflecting a more heterogeneous and clinically aggressive population compared with the first-line palbociclib group.

Table 1. Baseline demographic and clinical characteristics of the study population, overall and by treatment line.

	Overall cohort (n = 55)	First-line group (n = 30)	Second-line group (n = 25)	p-value
Mean age (years)	52.4 ± 8.2	51.2 ± 7.8	53.8 ± 8.6	0.24
Menopausal status, n (%)		0.65		
-Premenopausal	24 (43.6%)	14 (46.7%)	10 (40%)	
-Postmenopausal	31 (56.4%)	16 (53.3%)	15 (60%)	
WHO performance status, n (%)		0.42		
-0 - 1	48 (87.3%)	27 (90%)	21 (84%)	
-≥2	7 (12.7%)	3 (10%)	4 (16%)	
Hormone receptor status, n (%)				
-ER+ and PR+	46 (83.6%)	25 (83.3%)	21 (84%)	0.95
-ER+ only	9 (16.4%)	5 (16.7%)	4 (16%)	-
Metastatic sites, n (%)				
-Bone	35 (63.6%)	19 (63.3%)	16 (64%)	0.96
-Liver	18 (32.7%)	9 (30%)	9 (36%)	0.63
-Lung	15 (27.3%)	8 (26.7%)	7 (28%)	0.91
-Brain	5 (9.1%)	2 (6.7%)	3 (12%)	0.49
Number of metastatic sites	2.1 ± 0.9	2.0 ± 0.8	2.2 ± 1.0	0.38
Previous treatment, n (%)				
-Chemotherapy (neoadjuvant/adjuvant)	40 (72.7%)	20 (66.7%)	20 (80%)	0.26
-Adjuvant hormone therapy	35 (63.6%)	15 (50%)	20 (80%)	0.02
-Radiotherapy	32 (58.2%)	17 (56.7%)	15 (60%)	0.80
Previous first-line metastatic treatment				
-Endocrine therapy (AI)	-	-	14 (56%)	-
-Chemotherapy	-	-	11 (44%)	-

3.2. Efficacy Outcomes

After a median follow-up of 38.4 months, the median progression-free survival (PFS) was significantly longer in the first-line group (19 months; 95% CI 17.6 - 22.9) compared to the second-line group (8 months; 95% CI 6.5 - 10.2) with a hazard ratio of 0.48 (95% CI 0.32 - 0.71; $p < 0.001$).

The objective response rate was also higher in the first-line group (39% vs. 22%, $p = 0.03$).

Of note, Overall survival (OS) was calculated from different starting points according to treatment line: from the initiation of first-line metastatic therapy in the first-line palbociclib group, and from the initiation of second-line metastatic therapy in the second-line palbociclib group. The median OS was significantly longer in the first-line group (36.8 months; 95% CI 31 - 40) compared to the second-line group (25.5 months; 95% CI 22 - 30), with a hazard ratio of 0.58 (95% CI 0.42 - 0.79; $p = 0.001$).

3.3. Safety Profile

The safety of palbociclib was evaluated according to treatment line and severity of adverse events. Adverse events were recorded and graded using standard toxicity criteria and are reported as all-grade and grade ≥ 3 events. Hematological toxicities were the most frequently observed adverse events in both cohorts. Dose modifications and treatment discontinuations related to toxicity or death were also analyzed. Safety outcomes according to first-line and second-line palbociclib treatment are summarized in Table 2.

Table 2. Adverse events according to treatment line.

Adverse events	First-line palbociclib all grades n/N (%)	First-line palbociclib grade ≥ 3 n/N (%)	Second-line palbociclib all grades n/N (%)	Second-line palbociclib grade ≥ 3 n/N (%)
Neutropenia	21/30 (70%)	5/30 (16%)	20/25 (80%)	7/25 (28%)
Fatigue	19/30 (63%)	2/30 (6%)	18/25 (72%)	4/25 (16%)
Anemia	5/30 (16%)	1/30 (3%)	2/25 (8%)	0
Nausea	3/30 (10%)	0	2/25(8%)	0
Diarrhea	3/30 (10%)	0	1/25(4%)	0
Dose reduction	15/30 (50%)	-	16/25 (64%)	-
Treatment discontinuation (toxicity or death)	3/30 (10%)	-	4/25 (12%)	-

4. Discussion

This single-center retrospective study provides real-world evidence from a Moroccan cohort highlighting the superior efficacy of palbociclib when used in the first-line compared with the second-line setting in patients with HR+/HER2-neg-

ative metastatic breast cancer.

4.1. Interpretation of Efficacy Results in Context

In our cohort, palbociclib was associated with a significantly longer median progression-free survival (PFS) when administered in the first-line setting compared with the second-line setting (19 vs. 8 months), with a hazard ratio of 0.48 ($p < 0.001$). These findings are consistent with the benefit observed in the pivotal PALOMA trials, while reflecting the inherent differences of real-world populations, which are generally more heterogeneous and less selected than those enrolled in randomized clinical trials [11] [12]. The slightly shorter first-line PFS observed in our study compared with PALOMA-2 (24.8 months) is therefore expected and aligns with previously reported real-world data [13] [14].

The objective response rate (ORR) of 39% in the first-line group, although lower than that reported in PALOMA-2, remains clinically meaningful and reflects the predominantly cytostatic mechanism of action of CDK4/6 inhibitors, in which prolonged disease stabilization contributes substantially to clinical benefit.

A significant difference in overall survival (OS) was observed in favor of first-line palbociclib (36.8 vs. 25.5 months). However, this result must be interpreted with caution. In our study, OS was calculated from different starting points depending on treatment line—namely, from the initiation of first-line metastatic therapy in the first-line palbociclib group and from the initiation of second-line therapy in the second-line group. This methodological approach introduces a lead-time bias that inherently favors the first-line cohort and precludes direct comparison with randomized strategy trials such as SONIA, in which OS was measured from a common baseline [15]. Differences between our findings and the SONIA trial may also be explained by variations in patient characteristics, regional treatment practices, and access to subsequent therapies in real-world settings, where the effectiveness of early disease control may have a greater impact on long-term outcomes [7] [16].

Importantly, patients receiving palbociclib in the second-line setting represented a more heavily pretreated and clinically aggressive population, as a substantial proportion had previously received chemotherapy due to visceral crisis. This heterogeneity likely contributed to the inferior outcomes observed in this group and further supports the rationale for early integration of CDK4/6 inhibitors in the treatment sequence.

4.2. Impact of Prior Endocrine Exposure

Another notable finding was the significantly higher rate of prior adjuvant endocrine therapy in the second-line palbociclib group. This imbalance suggests differences in baseline endocrine sensitivity between the two cohorts and may partially explain the reduced efficacy observed in the second-line setting. Indeed, prior exposure to endocrine therapy has been associated with the development of endocrine resistance in metastatic breast cancer, potentially limiting the subse-

quent effectiveness of CDK4/6 inhibitor-based strategies.

4.3. Safety and Treatment Management

The safety profile of palbociclib observed in our study was consistent with previously published clinical trial and real-world data and was broadly comparable between treatment lines. Hematological toxicities, particularly neutropenia, were the most frequently reported adverse events, while non-hematological toxicities were generally manageable. Although grade ≥ 3 fatigue was more frequently observed in the second-line cohort, this finding likely reflects a more fragile and heavily pretreated patient population rather than a true difference in drug tolerability. Most treatment modifications, including dose reductions and temporary interruptions, allowed continuation of therapy, underscoring the manageable safety profile of palbociclib with appropriate monitoring [7].

4.4. Clinical Implications and Limitations

These results reinforce the clinical relevance of initiating palbociclib early in the metastatic setting to maximize disease control, particularly in resource-limited contexts where access to subsequent treatment lines may be restricted. This study further highlights the complementary role of real-world evidence in informing treatment decisions for patient populations that are often underrepresented in randomized clinical trials.

The main limitations of this study include its retrospective design, modest sample size, and single-center nature. In addition, the heterogeneity of prior treatments and associated endocrine therapies reflects real-world practice but may act as confounding factors. Biomarkers such as Ki-67 and detailed molecular analyses were not systematically assessed and could provide further insights in future studies [15].

5. Conclusion

In conclusion, this real-world analysis from Morocco supports the early use of palbociclib in HR+/HER2-negative metastatic breast cancer, demonstrating a clear advantage in progression-free survival and a favorable overall survival trend when used in the first-line setting. These findings underscore the importance of real-world data in complementing randomized clinical trials and guiding treatment strategies tailored to specific regional and clinical contexts.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Cardoso, F., Paluch-Shimon, S., Senkus, E., Curigliano, G., Aapro, M.S., André, F., *et al.* (2020) 5th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 5). *Annals of Oncology*, **31**, 1623-1649. https://doi.org/10.1016/j.annonc.2020.09.010

[2] Sherr, C.J., Beach, D. and Shapiro, G.I. (2016) Targeting CDK4 and CDK6: From Discovery to Therapy. *Cancer Discovery*, **6**, 353-367. https://doi.org/10.1158/2159-8290.cd-15-0894

[3] Dickson, M.A. (2014) Molecular Pathways: CDK4 Inhibitors for Cancer Therapy. *Clinical Cancer Research*, **20**, 3379-3383. https://doi.org/10.1158/1078-0432.ccr-13-1551

[4] Spring, L.M., Wander, S.A., Andre, F., Moy, B., Turner, N.C. and Bardia, A. (2020) Cyclin-Dependent Kinase 4 and 6 Inhibitors for Hormone Receptor-Positive Breast Cancer: Past, Present, and Future. *The Lancet*, **395**, 817-827. https://doi.org/10.1016/s0140-6736(20)30165-3

[5] Finn, R.S., Martin, M., Rugo, H.S., Jones, S., Im, S., Gelmon, K., *et al.* (2016) Palbociclib and Letrozole in Advanced Breast Cancer. *New England Journal of Medicine*, **375**, 1925-1936. https://doi.org/10.1056/nejmoa1607303

[6] Cristofanilli, M., Turner, N.C., Bondarenko, I., Ro, J., Im, S., Masuda, N., *et al.* (2016) Fulvestrant plus Palbociclib versus Fulvestrant plus Placebo for Treatment of Hormone-Receptor-Positive, HER2-Negative Metastatic Breast Cancer That Progressed on Previous Endocrine Therapy (PALOMA-3): Final Analysis of the Multicentre, Double-Blind, Phase 3 Randomised Controlled Trial. *The Lancet Oncology*, **17**, 425-439. https://doi.org/10.1016/s1470-2045(15)00613-0

[7] Messina, C., Cattrini, C., Buzzatti, G., *et al.* (2018) CDK4/6 Inhibitors in Metastatic Breast Cancer: A Systematic Review and Meta-Analysis. *European Journal of Cancer*, **95**, 33-44.

[8] Sherman, R.E., Anderson, S.A., Dal Pan, G.J., Gray, G.W., Gross, T., Hunter, N.L., *et al.* (2016) Real-World Evidence—What Is It and What Can It Tell Us? *New England Journal of Medicine*, **375**, 2293-2297. https://doi.org/10.1056/nejmsb1609216

[9] Eisenhauer, E.A., Therasse, P., Bogaerts, J., Schwartz, L.H., Sargent, D., Ford, R., *et al.* (2009) New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (Version 1.1). *European Journal of Cancer*, **45**, 228-247. https://doi.org/10.1016/j.ejca.2008.10.026

[10] National Cancer Institute (2017) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. U.S. Department of Health and Human Services.

[11] Rugo, H.S., Finn, R.S., Dieras, V., *et al.* (2019) Palbociclib Plus Endocrine Therapy in Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer: A Systematic Review. *Breast Cancer Research and Treatment*, **176**, 539-546.

[12] Kim, E.S. and Scott, L.J. (2017) Palbociclib: A Review in HR-Positive, HER2-Negative Advanced Breast Cancer. *Drugs*, **77**, 673-684.

[13] DeMichele, A., Clark, A.S., Tan, K.S., *et al.* (2020) CDK4/6 Inhibitor Outcomes in Clinical Practice: A Multicenter Real-World Study. *The Oncologist*, **25**, e1426-e1434.

[14] Messina, C., Cattrini, C., Soldato, D., *et al.* (2021) CDK4/6 Inhibitors in Advanced Hormone Receptor-Positive Breast Cancer: Efficacy and Safety in First-Line versus Later Lines. *ESMO Open*, **6**, Article 100017.

[15] Sonke, G.S., van Ommen-Nijhof, A., *et al.* (2023) First-Line vs Second-Line Use of CDK4/6 Inhibitors in HR+/HER2− Metastatic Breast Cancer (SONIA): A Randomized Phase III Trial. *The Lancet Oncology*, **24**, 74-87.

[16] Garrison, L.P., Neumann, P.J., Erickson, P., Marshall, D. and Mullins, C.D. (2007) Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World Data Task Force Report. *Value in Health*, **10**, 326-335. https://doi.org/10.1111/j.1524-4733.2007.00186.x