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Use of CDK4/6 Inhibitors in the First-Line Treatment of HR+/HER2− Metastatic Breast Cancer: A Real-Life Experience in Morocco

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Abstract

Introduction: Luminal/HER2− negative breast cancer represents approximately 70% of all breast cancers. Historically, endocrine therapy was the standard first-line treatment. Over the past two decades, major therapeutic advances, particularly the introduction of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors in combination with endocrine therapy, have significantly improved progression-free survival (PFS) and overall survival (OS) in this population. **Material and Methods:** We conducted a retrospective cohort study at the Department of Medical Oncology, Hassan II University Hospital, including 60 patients with HR+/HER2− metastatic breast cancer, either *de novo* or recurrent, who were treatment-naïve in the metastatic setting. All patients received a CDK4/6 inhibitor (palbociclib or ribociclib) in combination with endocrine therapy between January 2020 and June 2025. Clinical, histopathological, and therapeutic data were collected, and treatment response was assessed according to RECIST 1.1 criteria. **Results:** The median age was 53.3 years (range: 27 - 92), with 53% postmenopausal. A family history of cancer was reported in 8.3% of patients. Most patients had good performance status (WHO 0 - 1: 85%). The most common metastatic sites were bone (76.7%) and lymph nodes (58.3%). Palbociclib was used in 47% of patients, and ribociclib in 53%. Mean PFS was 33.0 months (95% CI: 22.2 - 43.7), while median OS was not reached at the time of analysis. Patients with hormone-sensitive disease or secondary resistance had significantly longer PFS than those with primary resistance (33.6 vs 3.5 months; $p < 0.001$). The main toxicities were hematologic, with grade 3 and 4 neutropenia occurring in 21.7% and 6.7% of patients, respectively. **Conclusion:** CDK4/6 inhibitors combined with endocrine therapy are effective and well-tolerated in the first-line management of HR+/HER2− met-

astatic breast cancer in a real-world Moroccan cohort, supporting their role as the current standard of care.

Keywords

HR+/HER2− Breast Cancer, CDK4/6 Inhibitors, First-Line Therapy, Real-World Study, Morocco

1. Introduction

Breast cancer is the most common malignancy among women in Morocco, representing 39.1% of all female cancers [1]. Globally, it is the second most frequent cancer across both sexes, with approximately 2.3 million new cases in 2022 (11.6% of all cancers) [2]. Despite considerable progress in early diagnosis and treatment, a substantial proportion of patients progress to advanced-stage disease. According to the literature, 20% - 30% of early-stage breast cancers eventually develop metastatic disease [3].

Breast cancer is a heterogeneous disease, characterized by clinical, pathological, and biological diversity [4]. Heterogeneity is mainly defined by estrogen receptor (ER) and progesterone receptor (PR) expression, HER2 amplification, and Ki-67 proliferation index. Among molecular subtypes, hormone receptor-positive (HR+) and HER2− negative tumors account for 70% - 80% of cases [5].

For many years, endocrine therapy alone was the standard first-line treatment in this population [6]. However, over the past two decades, major advances, particularly the introduction of CDK4/6 inhibitors in combination with endocrine therapy, have transformed management and improved clinical outcomes [7]-[9].

Real-world data on the use of CDK4/6 inhibitors remain limited, particularly in low- and middle-income countries. Therefore, we conducted a retrospective, single-center study at Hassan II University Hospital in Fez, Morocco, including 60 patients with HR+/HER2− metastatic breast cancer who received a CDK4/6 inhibitor combined with endocrine therapy as first-line treatment between 2020 and 2025.

The primary endpoint was progression-free survival (PFS), defined as the time from initiation of CDK4/6 inhibitor therapy to documented radiological or clinical progression according to RECIST 1.1 criteria. Secondary endpoints included overall survival (OS), objective response rate (ORR), clinical benefit rate (CBR, defined as partial response or stable disease ≥24 weeks), and safety profile.

2. Materials and Methods

2.1. Study Design

This retrospective study included patients treated with CDK4/6 inhibitors for HR+/HER2− metastatic breast cancer in first-line therapy at Hassan II University Hospital between January 2020 and June 2025.

2.2. Study Population

A total of 60 patients with metastatic HR+/HER2− breast cancer were included. The main inclusion criteria were: histologically confirmed invasive breast cancer, luminal molecular profile (A or B)/HER2 negative, treatment with a first-line combination of a CDK4/6 inhibitor plus endocrine therapy at the Medical Oncology Department of CHU Hassan II in Fez, with available clinical and radiological follow-up data.

Overall, 150 medical records of patients with metastatic HR+/HER2− breast cancer were reviewed. Among them, 90 were excluded due to incomplete data or having received CDK inhibitors outside the first-line setting. Therefore, 60 patients were ultimately included in the study.

2.3. Data Collection

Data were retrospectively extracted from electronic medical records (Hosix.net), including clinical, radiological, histopathological, and therapeutic information. Treatment response and disease progression were evaluated using standard imaging according to RECIST 1.1.

2.4. Statistical Analysis

Descriptive statistical analyses of clinical, histological, and immunohistochemical characteristics, as well as patient outcomes, were performed.

The primary endpoint was to evaluate treatment efficacy, assessed by progression-free survival (PFS), defined as the time from the initiation of CDK4/6 inhibitor therapy to clinically and radiologically confirmed disease progression, according to the RECIST 1.1 criteria, based on imaging performed regularly, usually every 3 months, following the practice of our department.

Secondary endpoints included overall survival (OS), objective response rate (ORR), clinical benefit rate—defined as partial response or stable disease lasting more than 24 weeks—and treatment-related toxicity. Patients who were alive at the time of the last follow-up or at the administrative cutoff date (June 30, 2025) were censored at that date.

All statistical analyses were performed using SPSS software (IBM Corp., Armonk, NY, USA). A two-sided p-value < 0.05 was considered statistically significant.

2.5. Ethical Considerations

The study was approved by the Ethics Committee of Hassan II University Hospital in Fez. All patients were managed in accordance with the principles of the Declaration of Helsinki, with strict respect for data confidentiality.

3. Results

3.1. Patient Characteristics

A total of 60 patients were included between January 2020 and June 2025, with 4 patients diagnosed between 2019-2021, 23 patients between 2022-2023, and 33 patients between 2024-2025. The median age was 53.57 years (range: 27 - 92), with

43.33% of patients older than 55 years and 56.67% younger. The majority of the cohort were postmenopausal (53%) (Table 1).

Clinically, the most common presentation was self-palpation of a breast nodule. Other presenting symptoms included back pain in 5% of patients and mastodynia in 10% (Figure 1).

Microscopically, invasive ductal carcinoma predominated (91.7%, n = 55), while invasive lobular carcinoma accounted for 8.3% (n = 5). At initial diagnosis, 51.7% of tumors were classified as cT4, and 46.7% of patients had at least one positive lymph node. According to the modified Scarff-Bloom-Richardson (SBR) grading system by Elston and Ellis, grade II tumors were the most frequent (76.7%) (Table 2).

Regarding metastatic disease, 40 patients (66.7%) were diagnosed *de novo* at the metastatic stage, whereas 20 patients (33.3%) developed metastatic relapse after initial curative-intent treatment.

The most frequent metastatic sites were bone (76.7%, n = 46), followed by lymph nodes (58.3%, n = 35), pleuropulmonary sites (40%, n = 24), and liver (30%, n = 18). Notably, 46.66% of patients had more than two metastatic sites.

Molecular analysis showed high estrogen receptor (ER) expression (>80%) in 76.66% of patients, while progesterone receptor (PR) expression >80% was observed in 30% of patients. Regarding HER2 status, all patients were HER2− negative, with 60% (n = 36) classified as HER2 ultra-low (Table 3).

Table 1. Demographic and clinical characteristics of the patients included in the study, including age, menopausal status, parity, family history of cancer and performance status according to the WHO classification (N = 60).

Features	Number of patients N = 60	Frequency%
Age in Years		
≥55 years	26	43.33
<55 years	34	56.67
Menopausal Status		
Menopausal	32	53
Premenopausal	28	47
Parity		
Nulliparous	18	30
Pauciparous	16	26.66
Multiparous	26	43.33
Family history of cancer		
Breast	4	2.4
Ovarian	1	0.6
Performance OMS		
0 - 1	51	85
≥2	9	16

Table 2. Histopathological characteristics of the tumors (N = 60), cT: clinical tumor stage; N: lymph node status; SBR: Scarff-Bloom-Richardson histological grade.

Features	Number of patients N = 60	Frequency%
Histopathological type		
Invasive ductal Carcinome	55	91.7
Invasive lobular carcinoma	5	8.3
Tumor size		
cT1	4	6.7
cT2	16	26.7
cT3	9	15
cT4 (abcd)	31	51.7
Lymph node status		
N0	21	35
N1	28	46.7
N2	8	13.3
N3	3	5
SBR Grade		
I	3	5
II	46	76.7
III	11	18.3

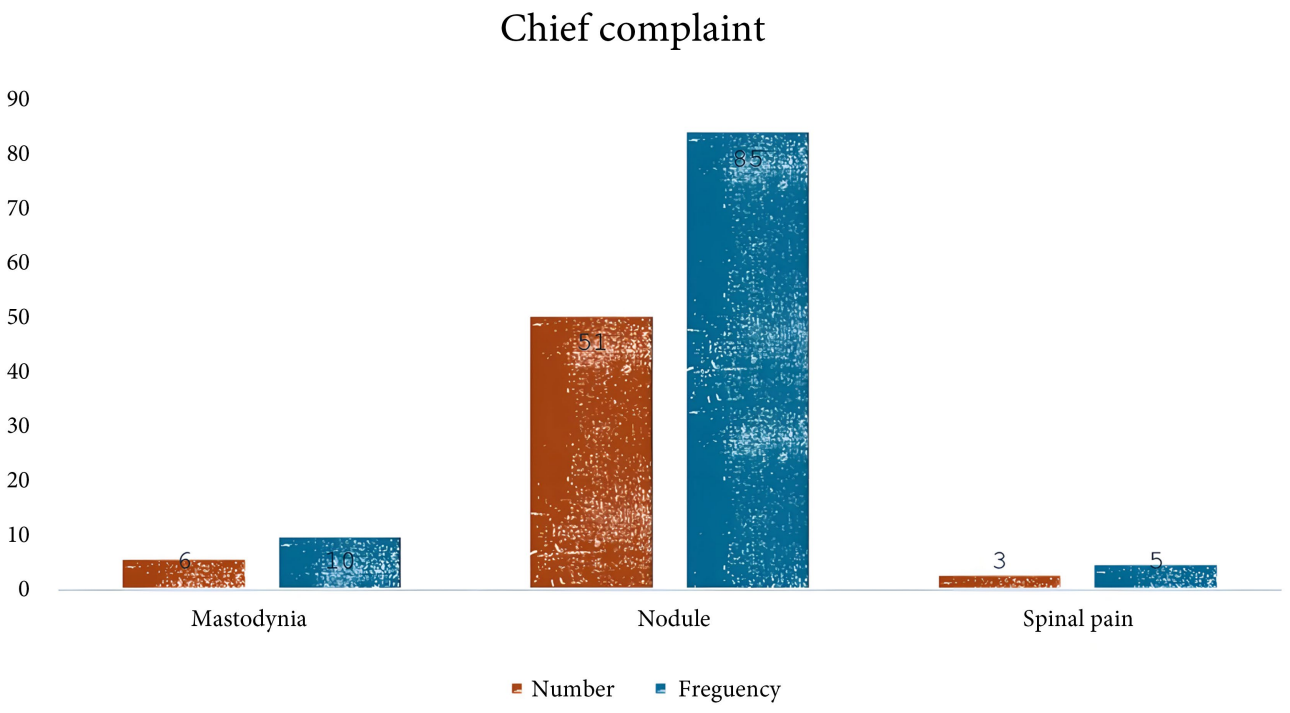

Figure 1. Distribution of patients according to the main presenting symptoms.

Table 3. Clinical characteristics of the patients, including type of metastatic presentation (*de novo* or recurrent), relapse interval, sites of metastasis, and previous treatments received.

Features	Number of patients N = 60	Frequency%
Clinical presentation		
De novo metastatic	40	66.7
Recurrent metastatic	20	33.3
Relapse interval		
≥12 months	59	98.3
<12 months	1	1.7
Sites of metastasis		
Pleuro-pulmonary	24	40
Hépatique	18	30
Cérébro-méningée	2	3.3
Peritoneal	1	1.7
Osseuses	46	76.7
Ganglionnaires	35	58.3
Autres	4	6.7
Previous treatments receveid		
Chirurgical	14	23.4
Neoadjuvant chemotherapy	9	15
Adjuvant chemotherapy	9	15
Adjuvant hormonetherapy	20	33.33
Radiotherapy	13	21.66

3.2. Treatment Management

In our series, 33.3% of patients (n = 20) had previously received curative-intent treatment. Among them, 23.4% underwent radical surgery, including Patey mastectomy in 21.7% and other procedures in 1.7% of cases. Adjuvant and neoadjuvant chemotherapy was administered to 30% of patients, and all patients received adjuvant endocrine therapy.

In the metastatic setting, CDK4/6 inhibitors were administered as first-line therapy in all patients. Ribociclib was used in 53% of cases, whereas palbociclib was administered to 47% of patients.

Regarding treatment response, 36.66% of patients achieved an objective response, including 8.33% (n = 5) with complete response and 28.33% (n = 17) with partial response. Disease stabilization was observed in 45% (n = 27) of patients, while 18.33% (n = 11) experienced tumor progression (Table 4).

The main toxicities were primarily hematologic, dominated by neutropenia. Grade 3 and grade 4 neutropenia occurred in 21.7% and 6.7% of patients, respectively. Non-hematologic toxicities were mainly represented by hepatic cytolysis,

with grade 3 and 4 observed in 4% and 3% of patients, respectively.

Table 4. Treatment characteristics of patients receiving CDK4/6 inhibitors, including line of therapy, type of CDK4/6 inhibitor used, associated hormone therapy, treatment response, and survival status of the time of analysis.

Features	Number of patients N = 60	Frequency%
CDK4/6 inhibitor Used		
Palbociclib	32	53
Ribociclib	28	47
Hormone therapy		
Anti-Aromatase	56	93.3
Fulvestrant	4	6.6
Reponse to treatment		
Full response	5	8.33
Partial response	17	28.33
Stable disease	27	45
Progressive disease	11	18.33
Status at the time of analysis		
Alive	56	93.3
Deceased	4	6.7

3.3. Survival

After a median follow-up of 8.8 months, the median progression-free survival (PFS) was not reached at the time of analysis. The mean PFS was 33.01 months (95% CI: 22 - 44). The median overall survival (OS) was not reached due to an insufficient number of events, with a mean OS of 46.25 months (95% CI: 31.06 - 61.42) observed during follow-up.

Furthermore, stratification of PFS according to the presence of primary resistance revealed a significant reduction in PFS among patients with primary resistance (3.51 vs. 33.6 months, $p < 0.001$).

4. Discussion

Our retrospective, single-center study represents one of the first large-scale evaluations focusing specifically on the use of CDK4/6 inhibitors in the first-line management of HR+/HER2− metastatic breast cancer in our setting. It provides real-world clinical data on the efficacy and tolerability of these treatments in the Moroccan population.

In our cohort, the combination of CDK4/6 inhibitors (palbociclib and ribociclib) with endocrine therapy demonstrated notable efficacy, with an objective response rate of 36.7%, including 8.3% complete responses and 28.3% partial responses. Furthermore, 45% of patients achieved disease stabilization, defined as

stable disease lasting at least 24 weeks, reflecting a high rate of tumor control consistent with published literature.

In the MONALEESA-2 trial, which evaluated the combination of letrozole and ribociclib, the authors reported 3.1% complete responses, 49.6% partial responses, 37.1% stable disease, and 5.1% progression. Although some quantitative differences were observed, particularly in partial responses, the overall response profiles remain comparable, confirming the clinical efficacy of this combination [10].

Regarding progression-free survival (PFS), the median was not reached in our series due to an insufficient number of events, with a mean PFS of 33 months (95% CI: 22.3 - 43.7). These results are not directly comparable to pivotal trials, mainly due to the retrospective nature of our study and the relatively short follow-up duration.

In the PALOMA-2 study, the addition of palbociclib to letrozole in the first-line setting significantly improved median PFS (24.8 months versus 14.5 months in the control arm; HR = 0.58; 95% CI: 0.46 - 0.72; $p < 0.001$). Similarly, the MONALEESA-2 trial demonstrated a significant benefit for ribociclib, with an 18-month PFS rate of 63% versus 42.2% in the control arm (HR = 0.56; 95% CI: 0.43 - 0.72; $p < 0.001$), reflecting a substantial reduction in the risk of progression [10] [11].

Our results are consistent with those reported in some real-world studies, in which median PFS and overall survival (OS) under first-line ribociclib were not reached due to an insufficient number of events [12]. These observed differences between randomized clinical trials and some observational studies highlight the challenges of translating pivotal trial results into daily clinical practice, where patients often present with more complex clinical characteristics and greater heterogeneity.

Analysis of the impact of hormonal sensitivity on treatment efficacy showed a significant reduction in PFS among patients with primary resistance. However, in pivotal trials, including STEPP analyses, the benefit of CDK4/6 inhibitors was maintained regardless of the treatment-free interval in patients who had received adjuvant endocrine therapy [13]. These differences may be explained by the heterogeneity of our population and the characteristics inherent to real-world studies.

Regarding overall survival, after a median follow-up of 8.8 months, 6.7% of patients (n = 4) had died. Median OS was not reached, with a mean estimated OS of 46.2 months (95% CI: 31.1 - 61.4).

In our cohort, the toxicity profile was dominated by hematologic adverse events, particularly neutropenia. Grade 3 and 4 neutropenia were observed in 21.7% and 6.7% of patients, respectively, consistent with the results reported in the pivotal PALOMA and MONALEESA trials [10] [11]. Although frequent, this toxicity is mainly laboratory-based, reversible, and rarely associated with complications, which explains the absence of severe infections or treatment-related deaths in our cohort.

However, our findings should be interpreted in light of several limitations, in-

cluding the small sample size, the absence of a comparator group to evaluate the relative benefit of CDK4/6 inhibitors versus endocrine therapy alone, and a follow-up duration insufficient for a comprehensive analysis of long-term survival outcomes.

Nevertheless, our study provides original data in the North African context, highlighting the value and impact of combining CDK4/6 inhibitors with endocrine therapy in the real-world management of HR+/HER2− metastatic breast cancer. These results underscore the need for prospective, multicenter studies to better characterize prognostic and predictive factors in this population.

Conflicts of Interest

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

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