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Efficacy and Safety of Cyclin-Dependent Kinase 4/6 Inhibitor in Patients with Advanced Breast Cancer: A Real-World Experience

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Abstract | **Original Research Article**

***Background*:** CDK4/6 inhibitors (CDK4/6i) combined with endocrine therapy (ET) represent the standard of care for HR+/HER2- metastatic breast cancer (MBC). Real-world evidence (RWE) is essential to evaluate their effectiveness and safety in routine practice. This study describes the initial experience with CDK4/6i within the Medical Oncology Department of the Moulay Ismail Military Hospital in Meknes, Morocco. ***Methods*:** A retrospective observational cohort study was conducted on 30 patients with HR+/HER2- MBC, followed between January 2020 and December 2024, and treated with palbociclib (n=13) or ribociclib (n=17) in combination with ET. Clinicopathological, therapeutic, early response, safety (graded according to CTCAE v5.0), dose reduction, and temporary interruption data were collected and descriptively analyzed. ***Results*:** The mean patient age was 56.5 years; 36.7% (n=11) were premenopausal. Disease was de novo metastatic in 76.7% of patients, and 86.7% had ≥3 metastatic sites. CDK4/6i were predominantly used in the first line (83.3%), with a slight predominance of ribociclib (56.7%) over palbociclib (43.3%), mainly combined with letrozole (80%). The mean number of cycles received per patient was 9.53. Safety management required frequent adjustments: dose reductions occurred in 76.9% (10/13) of patients on palbociclib and 52.9% (9/17) on ribociclib. Temporary treatment interruptions were necessary for 76.9% (10/13) of patients on palbociclib and 52.9% (9/17) on ribociclib. Median progression-free survival (PFS), estimated using the Kaplan-Meier method, was 64 weeks. The most frequent adverse events (AEs) were hematological, notably Grade 3-4 neutropenia (Palbociclib 53.8%, Ribociclib 47.1%) and febrile neutropenia (Palbociclib 7.7%, Ribociclib 5.9%). Anemia and thrombocytopenia were common but mostly Grade 1-2. Fatigue (mainly Grade 1-2) was also common. Specific AEs noted with ribociclib included Grade 1-2 QT interval prolongation (11.8%), Grade 1-2 deep vein thrombosis (5.9%), and Grade 3-4 liver function test elevation (11.8%). ***Conclusion*:** In this real-world Moroccan cohort, the use of CDK4/6i aligns with therapeutic standards, often in patients with extensive disease. The detailed safety profile, including AE grading, confirms the high frequency of toxicities, particularly hematological ones (G3-4 neutropenia affecting about half of the patients), necessitating very frequent therapeutic adjustments (dose reductions and temporary interruptions in 50-75% of patients). Preliminary efficacy appears encouraging but requires confirmation with longer follow-up. The small sample size limits the scope of the conclusions. Larger prospective or retrospective studies are needed to validate these observations in this setting.

Keywords: Metastatic Breast Cancer, HR-positive, HER2-negative, CDK4/6 Inhibitors, Real-World Data.

1. INTRODUCTION

Breast cancer remains the most common neoplasm and the leading cause of cancer mortality among women worldwide [1, 2]. The subtype expressing hormone receptors (HR+) and negative for human epidermal growth factor receptor 2 (HER2-) represents the majority of cases, approximately 70% [3]. Endocrine therapy (ET) has long been the cornerstone of systemic treatment for HR+/HER2- advanced breast cancer (ABC) [4]. However, primary or acquired resistance to ET is a major limitation, inevitably leading to disease progression in most patients [5].

Understanding resistance mechanisms has highlighted the crucial role of the dysregulation of the Cyclin D-Cyclin-dependent kinase 4/6 (CDK4/6)-Retinoblastoma protein (Rb) pathway in cell proliferation and endocrine resistance [6, 7]. This led to the development of selective CDK4/6 inhibitors (CDK4/6i): palbociclib, ribociclib, and abemaciclib. Phase III randomized controlled trials (RCTs) (such as PALOMA-2, MONALEESA-2, MONARCH 3 in the first line; PALOMA-3, MONALEESA-3, MONARCH 2 in subsequent lines) have robustly demonstrated that adding a CDK4/6i to ET significantly improves

progression-free survival (PFS) compared to ET alone [8-10]. Furthermore, several of these trials have shown an overall survival (OS) benefit for ribociclib and abemaciclib [10, 11], thus establishing the CDK4/6i + ET combination as the first-line standard of care for the majority of patients with HR+/HER2- ABC [12].

Despite these advances, questions remain. RCT populations are selected, and confirming the efficacy and safety of these agents in routine clinical practice ("real-world" setting) is essential, particularly in diverse populations or those with specific clinical characteristics [13-16]. Furthermore, the lack of head-to-head trials comparing the different CDK4/6i raises the question of whether clinically relevant differences in efficacy or safety exist that could guide therapeutic choice [14-19]. Analysis of real-world data (RWD) is therefore crucial to refine our understanding and optimize the use of CDK4/6i.

The objective of this study is to describe the initial experience of the Medical Oncology Department at the Moulay Ismail Military Hospital in Meknes (Morocco) with the use of palbociclib and ribociclib in the treatment of HR+/HER2- MBC, focusing on patient characteristics, treatment patterns, and the safety of these treatments.

2. PATIENTS AND METHODS

- **2.1. Study Design and Population**

This was a single-center, retrospective, observational cohort study conducted within the Medical Oncology Department of the Moulay Ismail Military Hospital in Meknes. The analysis included 30 consecutive patients followed between January 2020 and December 2024, presenting with hormone receptor-positive (HR+) and HER2-negative (HER2-) metastatic breast cancer, and treated with CDK4/6 inhibitors (palbociclib n=13 or ribociclib n=17). Abemaciclib was not used in this cohort during the study period. HR+/HER2- status was confirmed by local immunohistochemical analysis.

- **2.2. Data Collection**

Data were retrospectively extracted from patient medical records. Collected variables included: demographic data (age at diagnosis, menopausal status, contraception), relevant history (family history of breast cancer), tumor characteristics (histological type, HR status [ER/PR], Ki-67 proliferation index, number and sites of metastases, presence of visceral crisis, de novo vs. recurrent metastatic disease), details of CDK4/6 inhibitor treatment (type of inhibitor, line of treatment, ET partner, number of cycles administered), therapeutic modifications (frequency and reasons for dose reductions, frequency and reasons for temporary treatment interruptions), tumor response assessments (per investigator assessment at cycles 3, 6, etc.), and observed adverse events (AEs) (type and maximum grade reached per patient, classified according to the Common Terminology Criteria for Adverse Events - CTCAE version 5.0). Progression-free survival (PFS) data were collected up to the data cut-off date. Overall survival (OS) data were not available or sufficiently mature for analysis.

- **2.3. Endpoints and Definitions**

The primary objective of the study was to describe the clinicopathological characteristics of the population, the treatment patterns used, and the detailed safety profile of CDK4/6i (including the frequency and severity of AEs by type and CTCAE grade, as well as the frequency of dose reductions and temporary interruptions). Secondary objectives included describing tumor response and estimating progression-free survival (PFS). PFS was defined as the time from the date of initiation of CDK4/6i treatment to the date of disease progression (documented clinically or radiologically) or the date of death (from any cause), whichever occurred first. Patients alive without documented progression at the date of the last assessment were censored at that date. PFS estimation was performed using the Kaplan-Meier method.

- **2.4. Statistical Analysis**

The statistical analysis is descriptive. Categorical variables are presented as counts (n) and percentages (%). Continuous variables are presented as mean ± standard deviation (SD) or median and range (minimum-maximum). The mean number of treatment cycles was calculated. The frequencies of AEs (by type, CTCAE grade, and drug) as well as the frequencies of dose reductions and temporary interruptions were calculated. Analyses were performed using Microsoft Excel 2019.

3. RESULTS

- **3.1. Patient Characteristics (Table 1)**

Thirty patients meeting the inclusion criteria were analyzed. The mean age at the start of CDK4/6i treatment was 56.5 years (range: 32-90 years). Eleven patients (36.7%) were premenopausal at treatment initiation. The predominant histological type was infiltrating carcinoma NOS (Not Otherwise Specified) (96.7%, n=29), with one case of adenocarcinoma. All tumors were ER-positive, and 90% (n=27) were also PR-positive. The Ki-67 index was ≥15% in 86.7% (n=26) of patients for whom it was available. The disease was metastatic from the outset (de novo) in a large majority of patients (76.7%, n=23). Tumor burden appeared high, with 86.7% (n=26) of patients presenting with at least three metastatic sites. The most frequent metastatic locations were bone (76.7%), lung (43.3%), and liver (23.3%). Visceral crisis, defined by clinical criteria, was present in 13.3% (n=4) of patients at initiation.

Table 1: Patient Characteristics (N=30)

Characteristic	Number (n)	Percentage (%)
Âge		
Mean age (years)	56,53	-
Range (years)	32 - 90	-
Menopausal Status		
Postmenopausal	19	63,33%
Premenopausal	11	36,67%
Histological Type		
Infiltrating carcinoma NOS	29	96,67%
Adenocarcinoma	1	3,33%
Hormone Receptor Status		
RE Positive	30	100%
RP Positive	27	90,00%
RP Négative	3	10,00%
Ki-67 Index		
< 15%	4	13,33%
≥ 15%	20	66,67%
15-25%	6	20%
Initial Metastatic Status		
De novo metastatic	23	76,67%
After prior treatment	7	23,33%
Number of Metastatic Sites		
< 3	4	13,33%
≥ 3	26	86,67%
Metastatic Sites		
Bone	23	76,67%
Lung	13	43,33%
Liver	7	23,33%
Brain	2	6,67%
Skin	2	6,67%
Adrenals	1	3,33%
Muscle	1	3,33%
Mediastinal node	1	3,33%
Parotid	1	3,33%
Visceral Crisis at Initiation		
Yes	4	13,33%
No	26	86,67%

- **3.2. Treatment Patterns and Dose Modifications (Table 2)**

CDK4/6i were administered in the first-line metastatic setting for 83.3% (n=25) of patients, second-line for 13.3% (n=4), and fourth-line for one patient (3.3%). Ribociclib was slightly more prescribed (56.7%, n=17) than palbociclib (43.3%, n=13). The most frequent endocrine therapy partner was letrozole (80%, n=24), followed by fulvestrant (16.7%, n=5) and then anastrozole (3.33%, n=1). The total number of CDK4/6i cycles administered in the cohort was 286, corresponding to a mean of 9.53 cycles per patient. Safety management required frequent dose adjustments:

- Dose Reductions: At least one dose reduction was necessary for 76.9% (10/13) of patients treated with palbociclib and 52.9% (9/17) of patients treated with ribociclib.
- Temporary Interruptions: At least one temporary treatment interruption (cycle delay or intra-cycle pause) was documented in 76.9% of patients on palbociclib and 52.9% on ribociclib. These interruptions were mainly related to managing toxicities, particularly hematological ones.

Table 2: Therapeutic Regimens and Dose Modifications of CDK4/6 Inhibitors (N=30)

Characteristics	Number (n)	Percentage (%)
Line of CDK4/6i Treatment		
1st line	25	83,33%
2nd line	4	13,33%
4th line	1	3,33%
Type of CDK4/6i Used		
Ribociclib	17	56,67%
Palbociclib	13	43,33%
Abemaciclib	0	0%
Associated Endocrine Therapy		
Letrozole	24	80,00%
Fulvestrant	5	16,67%
Anastrozole	1	3,33%
CDK4/6i Cycles Received		
Total number of cycles	286	-
Mean number per patient	9,53	-
Dose Reductions		
Palbociclib (n=13 patients)	10	76,92%
Ribociclib (n=17 patients)	9	52,94%
Temporary Interruptions		
Palbociclib (n=13 patients)	-	76,9%
Ribociclib (n=17 patients)	-	52,9%

- **3.3. Efficacy (Figure 1)**

A preliminary PFS analysis was performed; 10 PFS events (progressions or deaths) had been observed, and 20 patients were censored. The median progression-free survival (median PFS) estimated by the Kaplan-Meier method for the entire cohort was 64 weeks (Figure 1). Tumor response assessment at cycle 3 (C3) was available for all patients: 6.7% (n=2) had a partial response (regression), 80% (n=24) had stable disease, and 13.3% (n=4) had disease progression.

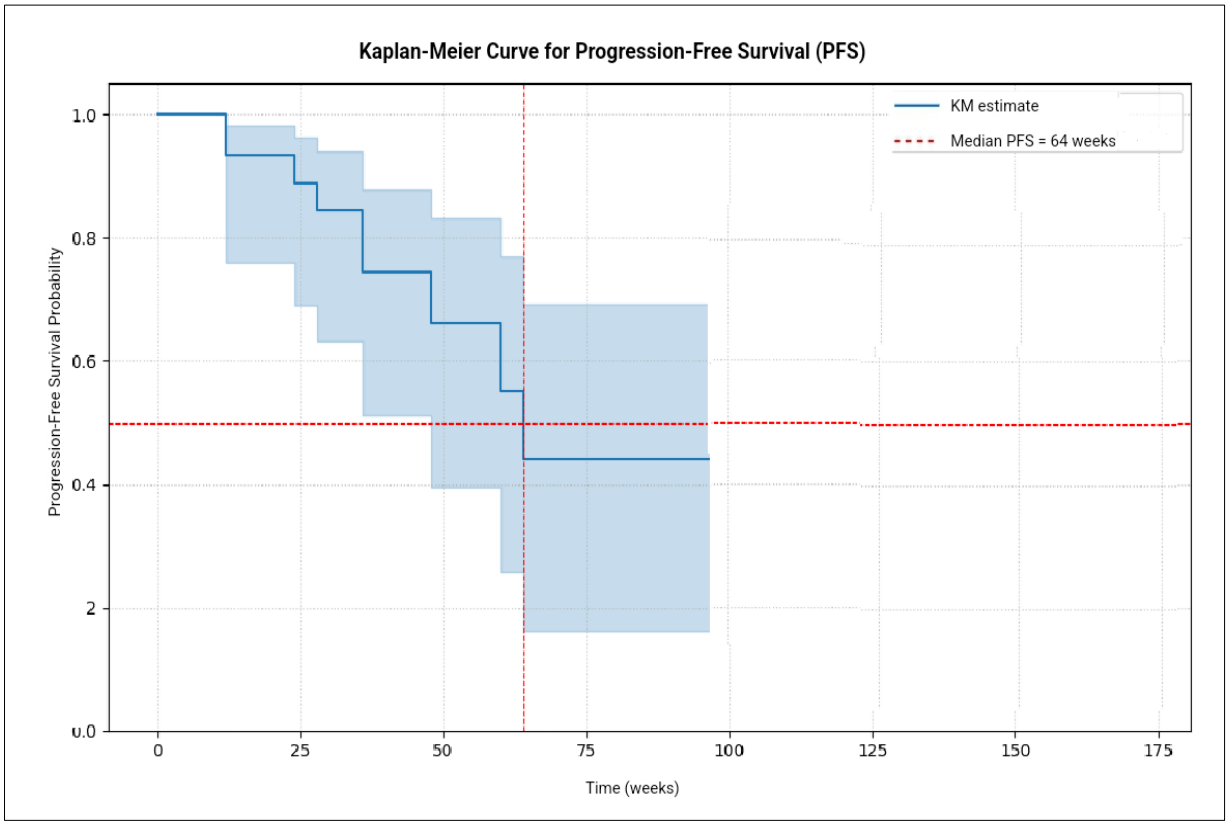

Figure 1: Kaplan-Meier Curve for Progression-Free Survival estimated at 64 weeks.

- **3.4. Safety (Table 3)**

The detailed safety profile, based on the highest CTCAE v5.0 grade reached per patient for each type of AE, is presented in Table 3.

- **Hematological Toxicities:** Neutropenia was the most frequent and severe AE. Grade 3-4 neutropenia occurred in 53.8% of patients on palbociclib and 47.1% on ribociclib. Febrile neutropenia was observed in 1 patient on palbociclib (7.7%) and 1 patient on ribociclib (5.9%). Grade 3-4 leukopenia affected 30.8% of patients on palbociclib and 41.2% on ribociclib. Anemia was frequent but predominantly Grade 1-2 (Palbociclib: 76.9% G1-2; Ribociclib: 41.2% G1-2), with no Grade 3-4 cases reported. Thrombocytopenia was also frequent and mainly Grade 1-2 (Palbociclib: 61.5% G1-2; Ribociclib: 23.5% G1-2); Grade 3-4 cases occurred in 1 patient on palbociclib (7.7%) and 2 patients on ribociclib (11.8%).

- **Non-Hematological Toxicities:** Fatigue was very common, mainly Grade 1-2 (Palbociclib: 53.8%; Ribociclib: 70.6%), with rare Grade 3-4 cases (Palbociclib: 7.7%; Ribociclib: 5.9%). Nausea (Palbociclib: 53.8%; Ribociclib: 35.3%) and vomiting (Palbociclib: 30.8%; Ribociclib: 0%) were reported, exclusively Grade 1-2. Gastrointestinal disorders also included diarrhea (G1-2: Palbociclib 30.8%, Ribociclib 11.8%), abdominal pain (G1-2: Palbociclib 15.4%, Ribociclib 17.6%), and constipation (G1-2: Palbociclib 23.1%, Ribociclib 17.6%), with no severe grade cases. Alopecia (Grade 1-2) was observed in 23.1% of patients on palbociclib and 23.5% on ribociclib.
  - Adverse Events of Special Interest:
    - With ribociclib, Grade 1-2 QT interval prolongation was detected in 2 patients (11.8%), with no cases of Grade ≥3. Grade 1-2 deep vein thrombosis (DVT) occurred in 1 patient (5.9%). Grade 3-4 elevation of liver function tests (transaminases or bilirubin) was noted in 2 patients (11.8%), compared to 1 patient (7.7%) on palbociclib.
    - Grade 3-4 elevated creatinine was observed in 1 patient on palbociclib (7.7%) and 1 patient on ribociclib (5.9%).
    - No cases of interstitial lung disease were reported. Dry skin (Grade 1-2) was noted in 2 patients on palbociclib (15.4%). Hypokalemia was not reported as a clinically significant AE.

Table 3: Safety Profile - Adverse Events (AEs) by Maximum CTCAE v5.0 Grade per Patient

Adverse Event (AE)	Palbociclib (n=13)		Ribociclib (n=17)	
	Grade 1-2 n (%)	Grade 3-4 n (%)	Grade 1-2 n (%)	Grade 3-4 n (%)
HEMATOLOGICAL TOXICITIES				
Neutropenia |	12 (92,3%)	7 (53,8%)	16 (94,1%)	8 (47,1%)
Febrile Neutropenia	0 (0%)	1 (7,7%)	0 (0%)	1 (5,9%)
Leucopenia	-	4 (30,8%)	-	7 (41,2%)
Anemia	10 (76,9%)	0 (0%)	7 (41,2%)	0 (0%)
Thrombocytopenia	8 (61,5%)	1 (7,7%)	4 (23,5%)	2 (11,8%)
NON-HEMATOLOGICAL TOXICITIES				
Fatigue	7 (53,8%)	1 (7,7%)	12 (70,6%)	1 (5,9%)
Nausea	7 (53,8%)	0 (0%)	6 (35,3%)	0 (0%)
Vomiting	4 (30,8%)	0 (0%)	0 (0%)	0 (0%)
Diarrhea	4 (30,8%)	0 (0%)	2 (11,8%)	0 (0%)
abdominal pain	2 (15,4%)	0 (0%)	3 (17,6%)	0 (0%)
Constipation	3 (23,1%)	0 (0%)	3 (17,6%)	0 (0%)
Alopecia	3 (23,1%)	0 (0%)	4 (23,5%)	0 (0%)
AEs OF SPECIAL INTEREST				
QT Interval Prolongation	0 (0%)	0 (0%)	2 (11,8%)	0 (0%)
Elevated Liver Function Tests	2 (15,4%)	1 (7,7%)	3 (17,6%)	2 (11,8%)
Elevated Creatinine	3 (23,1%)	1 (7,7%)	2 (11,8%)	1 (5,9%)
Deep Vein Thrombosis	0 (0%)	0 (0%)	1 (5,9%)	0 (0%)
Interstitial Lung Disease	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dry Skin	2 (15,4%)	0 (0%)	0 (0%)	0 (0%)
Hypokalemia	0 (0%)	0 (0%)	0 (0%)	0 (0%)

4. DISCUSSION

The introduction of CDK4/6 inhibitors combined with endocrine therapy has transformed the management of HR+/HER2- metastatic breast cancer, with established benefits in PFS and OS in clinical trials [8-14]. Our study sheds light on the use of these agents in routine clinical practice in a Moroccan center, confirming their integration as the standard of care in the first line.

The characteristics of our cohort reveal a population with a notable proportion of premenopausal patients (37%) and often high tumor burden (77% de novo, 87% ≥3 metastatic sites), which may differ from the more selected populations of RCTs. These factors could influence the observed efficacy outcomes. The estimated median PFS of 64 weeks (~15 months) in our series, although encouraging, appears lower than the medians often exceeding 24 months reported in pivotal first-line trials [8, 9]. This potential difference must be interpreted with great caution due to the small size of our sample (N=30), the low number of PFS events (n=10) limiting the precision of the Kaplan-Meier estimate, and the potentially more aggressive disease characteristics in our cohort (87% ≥3 metastatic sites). Longer follow-up and larger sample sizes are necessary to assess efficacy more robustly in this context.

The main contribution of our study lies in the detailed safety analysis, thanks to the collection of CTCAE grades. The general AE profile is consistent with published data [13-19]. Grade 3-4 neutropenia is confirmed as the major dose-limiting toxicity, affecting approximately half of the patients (Palbociclib 54%, Ribociclib 47%), rates similar to those in RCTs. The observed rate of febrile neutropenia (6-8%) seems slightly higher than the <2% typically reported in pivotal trials, a point that might warrant special attention in real-world practice, potentially related to patient characteristics or management practices.

The need for active and individualized safety management is clearly highlighted by the very high rates of therapeutic adjustments. Dose reductions (Palbociclib 77%, Ribociclib 53%) and temporary interruptions (Palbociclib 77%, Ribociclib 53%) proved necessary in a majority of patients. These figures, higher than those sometimes reported in other RWE studies [13-15], underscore that dose adaptation is an essential component of management to allow patients to continue long-term treatment. It is important to note that studies suggest these adjustments, when properly conducted, do not appear to compromise the overall efficacy of the treatment [15].

The graded analysis also allows for refining the comparison of safety profiles between the two agents in our series:

- Severe hematological toxicity (G3-4) is predominant for both, with similar rates of G3-4 neutropenia.
- Ribociclib-specific AEs (G3-4 hepatotoxicity (12%), G1-2 QT prolongation (12%), G1-2 DVT (6%)) are found at frequencies consistent with the literature, emphasizing the importance of specific monitoring (liver function tests, ECG).
- Other toxicities (fatigue, GI disorders, alopecia) are frequent but predominantly low-grade for both molecules.

These observations fit within the framework of the distinct safety profiles described in network meta-analyses (NMAs) and systematic reviews [17-19], which can guide individualized therapeutic choice based on comorbidities and patient preferences.

5. CONCLUSION

CDK4/6 inhibitors associated with endocrine therapy represent the standard of care for patients with HR+/HER2- metastatic breast cancer. Our initial real-world experience at the Moulay Ismail Military Hospital in Meknes confirms the feasibility of this approach and its application consistent with international recommendations, including in patients with aggressive disease features (de novo, multi-metastatic) or those who are sometimes elderly. The detailed safety analysis highlights the high frequency of toxicities, particularly hematological ones. This toxicity requires active and individualized management. The small cohort size mandates great caution in interpreting and generalizing these results. Prospective or multicenter retrospective studies, including larger numbers of patients with extended follow-up, are essential to better characterize the efficacy and safety of CDK4/6i in the Moroccan population.

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