ORIGINAL ARTICLE

CDK 4/6 Inhibitors in Metastatic Hormone Receptor Positive Breast Cancer: An Outcome-Based Study from a Tertiary Care Center in Pakistan

Warda Saleem[1*], Sidrah Rizwan[1], Syeda Samnita Batool Zaidi[1], Faiza Ahmed[2], Muhammad Saad Salim Naviwala[3], Nawazish Zehra[1], Munira Moosajee[1] and Yasmin A. Rashid[1]

[1]*Aga Khan University Hospital, Karachi, Pakistan*
[2]*Cancer Foundation Hospital, Karachi, Pakistan*
[3]*South City Hospital, Karachi, Pakistan*

ABSTRACT

Background: In the recent era, almost all the hormone receptor (HR) positive, Her2 neu negative metastatic breast cancers are being treated with cyclin dependent kinase (4/6) inhibitors and they include all three agents, Palbociclib, Ribociclib, and Abemaciclib, along with endocrine therapy and this combination has shown to significantly alter the treatment landscape of hormone receptor positive breast cancer in metastatic setting.

Objective: To ascertain the progression-free survival and overall survival among metastatic hormone receptor-positive HER2-negative breast cancer patients receiving CDK 4/6 inhibitors.

Methods: This was a retrospective study carried out at the Department of Oncology, Aga Khan University Hospital, from January 2018 to September 2024. Records of female patients above 18 years of age with histopathological and radiological diagnosis of hormone receptor (HR)-positive, who had received CDK 4/6 inhibitors were reviewed. Those patients who had missing records were omitted from the study.

Results: The bioinformatics analysis identified two ultra-rare protein-truncating heterozygous single-nucleotide variants (SNVs). These included a pathogenic variant in TP53 (p.R342X), associated with hereditary cancer-predisposing syndrome, detected in the father, two probands, and two unaffected sisters, as well as a *de novo* variant (p.S35X) in SDHC in the medulloblastoma proband. Additionally, a new *de novo* deleterious missense variant (p.L167P) in STK11 was identified in the medulloblastoma proband. In the osteosarcoma patient, two missense variants (p.T1777I and p.H1927R) in PLCE1, previously associated with an elevated cancer risk, were also detected.

Conclusion: These results lend credence to using CDK4/6 inhibitors as the gold standard for treating hormone receptor-positive, HER2-negative metastatic breast cancer in Pakistan, while also emphasizing the need for broader access and using local data to inform treatment choices.

Keywords: *Targeted therapy, ribociclib, abemaciclib, palbociclib, Pakistani population, targeted treatment.*

INTRODUCTION

Globally, breast cancer is among the most frequently diagnosed cancers in women [1]. About 2.3 million new cases of breast cancer were recorded globally in 2022, and the most recent GLOBOCAN data estimates that 666,000 people died from the disease [1]. In Pakistan, the occurrence of breast cancer has amplified by over 300% between 1990 and 2019, with mortality rates rising by 200-300% [2]. It is reported that about one in four female cancer-related mortality is attributable to breast cancer in Pakistan [2]. In 2020, the country recorded approximately 25,928 breast cancer cases (14.5% of all cancers) and 13,725 deaths (11.7%) [3].

Breast cancer is a diversified illness with its diverse morphological and histopathological subtypes. Several factors influence its clinical management and prognosis, including age of the patient, tumor type, grade, lymph node involvement, hormone receptor (HR) status, human epidermal growth factor receptor 2 (HER2) expression, and family history [4, 5]. Over the past decade, increased awareness and improved screening programs have led to earlier diagnoses. However, despite advancements in diagnosis and treatment, metastatic disease is still diagnosed in 6% of the patient population that remains incurable. Additionally, among those of early-stage breast cancer, around 20% patients in due course progress to distant metastatic disease [6].

Nearly 70% of all breast cancers are estrogen receptor (ER)-positive, HER2-negative tumors, which also contribute significantly to the death rate from breast cancer [7]. Endocrine therapies like ER modulators (like tamoxifen), steroidal and nonsteroidal aromatase inhibitors (like exemestane, anastrozole, and letrozole), and selective ER degraders (like fulvestrant) are common first- and second-line treatments for ER-positive, HER2-negative metastatic breast cancer [8]. Palbociclib, ribociclib, and abemaciclib are examples of

**Corresponding author: Warda Saleem, Department of Oncology, Aga Khan University Hospital, Karachi, Pakistan,*
Email: drwardasaleem@gmail.com
Received: June 19, 2025; Revised: July 22, 2025; Accepted: August 07, 2025
DOI: https://doi.org/10.37184/lnjcc.2789-0112.6.10

cyclin-dependent kinase (CDK) 4/6 inhibitors that are used in conjunction with endocrine therapy as the standard of care in first- and second-line metastatic situations. Overall survival and progression-free survival (PFS) are greatly augmented by this [9-11].

Cyclin-dependent kinases (CDKs) are vital controlling enzymes, and they control many aspects of the cell cycle, including cell cycle propagation and cell division. The crucial G1-to-S phase transition is controlled by the tumor suppressor retinoblastoma (Rb) protein [12]. By binding to E2F transcription factors and preventing G1/S progression, Rb inhibits early cell division; however, when it is deactivated, the cell cycle can continue [13]. Various growth signals during the G1 phase induce cyclin D to bind with CDK4 or CDK6, leading to Rb phosphorylation, E2F release, and subsequent cell cycle progression [12]. The CDK4/6-Rb axis plays a key role in multiple malignancies, particularly ER-positive breast cancer, where estrogen accelerates G1-to-S phase progression [14]. Estrogen binding to ER-alpha promotes cyclin D1 transcription, CDK4/6 activation, nd Rb phosphorylation, ultimately driving uncontrolled cell proliferation [15]. By selectively inhibiting CDK4/6, the cell cycle is halted in the G1 phase, reducing tumor growth and enhancing treatment response [16].

The therapy of hormone receptor-positive (HR+) metastatic breast cancer has completely altered since the advent of CDK4/6 inhibitors. There have been three agents that are approved in this category, which are highly selective, and reversible CDK4/6 inhibitors for HR+ metastatic breast cancer: Palbociclib, Ribociclib, and Abemaciclib [16]. When these three medications are added to normal endocrine therapy, the median progression-free survival (PFS) is noticeably longer than when endocrine therapy is used alone [17]. A plethora of Phase III trials comprising CDK 4/6 inhibitors show a doubling of the response in terms of progression-free survival [16]. According to a 2020 retrospective study carried out in southern India, women with HR-positive metastatic breast cancer (MBC) who get palbociclib in addition to hormone therapy have a prolonged PFS than those who receive hormone therapy solely [5].

At a tertiary care facility in Karachi, Pakistan, we conducted a retrospective analysis to ascertain the overall survival and progression-free survival of patients with metastatic breast cancer receiving CDK 4/6 inhibitors, as well as to study their side effect profile in this population. So far, to our knowledge, no such studies have been carried out in Pakistan determining the outcomes with CDK 4/6 inhibitors in metastatic breast cancer.

The study's main goal was to ascertain the progression-free survival of patients with metastatic hormone receptor-positive Her 2neu-negative breast cancer who were receiving CDK 4/6 inhibitors. PFS is defined as the amount of time (in months) between the start of CDK 4/6 inhibitor therapy and the date of documented disease progression, either radiologically or clinically. The secondary goal was to find out the overall survival (measured in months from the beginning of CDK 4/6 inhibitor therapy to the date of death from any cause or until the last follow-up) and also to ascertain toxicities among patients with metastatic hormone receptor-positive HER2-negative breast cancer receiving CDK 4/6 inhibitors.

MATERIALS AND METHODS

Our study was a retrospective study that was conducted at the Department of Oncology, Aga Khan University Hospital in Karachi, Pakistan. The study duration spanned from January 2022 to September 2024. We went through the case archives of all female patients above 18 years of age with histo-pathological and radiological diagnosis of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (MBC) who had received CDK 4/6 inhibitors comprising all three agents, Palbociclib, Ribociclib and Abemaciclib on any line of treatment from January 2018 to September 2024 at our institution. Those patients who had missing records were omitted from the study. Patients who received CDK4/6 inhibitors in the adjuvant setting were excluded. Patients with other malignancies diagnosed histologically in addition to breast cancer or treated for any other malignancy diagnosed histologically in the past were also excluded.

The sample comprised all eligible patients meeting the inclusion criteria within the defined period, using a non-probability consecutive sampling technique. No formal sample size calculation was performed as the study included the complete population of interest during the study period.

Data were collected retrospectively through electronic medical records and treatment charts. No direct patient contact or face-to-face interviews were conducted. A structured data collection form was used to extract relevant clinical and demographic information, ensuring consistency across all records reviewed.

The data collection tool was a predesigned form tailored to capture key study variables, including age, ECOG performance status, site of metastasis, tumor grade and subtype, ER/PR/HER2 status, type and line of CDK 4/6 inhibitor used, and treatment-related toxicities. The tool was reviewed for face validity by two senior oncologists.

Statistical analysis was done using SPSS version 20. Descriptive analyses were used to report pathologic and clinical factors. The frequency distributions were used to

report categorical variables, while the median and standard deviation (SD) with 95% confidence intervals were used to summarize continuous variables. (CI). Using a Cox proportional hazards regression model, HR and 95% CI were obtained. Univariable and multivariable Cox regression with 95% CI and a Kaplan-Meier estimator plot were used to assess for distinctions in survival. P-value less than or equal to 0.05 was considered statistically significant.

RESULTS

Our study consisted of 95 females who had received CDK 4/6 inhibitors from January 2018 to September 2024 at our institution. However, 23 patients were excluded due to loss to follow-up, drug unavailability, inaccessibility due to the cost of treatment, and treatment discontinuation due to side effects. Our final analysis thus consisted of 72 females, all of whom have received cell cycle inhibitor therapy. The mean age of the patients was 54 years (range: 30 to 80 years) (SD= 10.9). Most patients had an ECOG performance status of 1 (56.9%), followed by ECOG 2 (29.2%), ECOG 3 (12.5%), and ECOG 4 (1.4%). Regarding menopausal status, 73.6% were postmenopausal and 26.4% were premenopausal. Approximately 37.5% of the patients reported no comorbidities. Among those with comorbid conditions, hypertension (HTN) was most common, reported alone in 15.3% and in combination with diabetes mellitus (DM) in 18.1%. Other comorbidities included DM alone (2.8%), hypothyroidism (4.2%), depression (1.4%), and various other conditions (20.8%). In terms of tumor grade, the majority had grade II disease (43.1%), followed by grade III (26.4%), grade 0 (23.6%) (Grade 0 highlights those cases where grades were not available due to missing data in the patients' charts), and grade I (6.9%). Histologically, invasive ductal carcinoma (IDC) was the predominant subtype (70.8%), followed by invasive lobular carcinoma (ILC) in 13.9%. A small number of patients had IDC with neuroendocrine differentiation (1.4%), while 13.9% had unclassified or unknown subtypes. At the time of diagnosis, 45.8% of patients had *de novo* metastatic disease, whereas 54.2% developed metastasis during follow-up. In terms of metastatic burden, 45.8% had involvement of one site, 29.2% had two sites, 16.7% had three sites, and 8.3% had four sites involved.

Letrozole was the most frequently used hormonal agent in combination with a cell cycle inhibitor (52.1%), followed by Fulvestrant (23.9%), Tamoxifen (9.9%), Exemestane (9.9%), and Anastrozole (4.2%). In terms of treatment line, the majority of patients received the cell cycle inhibitor as first-line therapy (58.3%), while others received it as second-line (33.3%) or in subsequent lines, including third (4.2%), fourth (2.8%), and fifth-line (1.4%) settings.

Treatment-related toxicities were observed in a subset of patients. The most frequent adverse occurrence was cytopenias, reported in 21 patients (2.0%). Gastrointestinal, hepatic, or ascetic fluid toxicities were observed in 9 patients (0.9%) (all GI and hepatic related toxicities were clumped together including those patients that developed ascites secondary to ascetic fluid accumulation due to significant liver toxicity), followed by pleural or pulmonary complications in 5 patients (0.5%), and cardiac toxicities in 3 patients (0.3%). Less frequently reported were electrolyte imbalances (0.2%), cytopenias with gastrointestinal involvement (0.2%), and cytopenias with cardiac complications (0.1%) (**Table 1**).

Table 1: Clinical and demographic variables of the patients.

Variable	Total	Percentages
ECOG Performance		
1	41	56.9
2	21	29.2
3	9	12.5
4	1	1.4
Menopausal Status		
Premenopausal	19	26.4
Postmenopausal	53	73.6
Comorbidities		
None	27	37.5
Hypertension (HTN)	11	15.3
Diabetes Mellitus (DM)	2	2.8
HTN + DM	13	18.1
Hypothyroidism	3	4.2
Depression	1	1.4
Others	15	20.8
Tumour Grade		
NA	17	23.6
I	5	6.9
II	31	43.1
III	19	26.4
Tumour Subtype		
Invasive Ductal Carcinoma (IDC)	51	70.8
Invasive Lobular Carcinoma (ILC)	10	13.9
IDC with Neuroendocrine Differentiation	1	1.4
Not available	10	13.9
Timing of Metastasis		
De novo	33	45.8
Metastatic later	39	54.2
Sites of Metastasis		
1 Site Involved	33	45.8
2 sites involved	21	29.2

3 sites involved	12	16.7
4 sites involved	6	8.3
Hormonal Agent with CDK Inhibitor		
Tamoxifen	7	9.9
Letrozole	37	52.1
Anastrozole	3	4.2
Fulvestrant	17	23.9
Exemestane	7	9.9
Line of Treatment (CDK Inhibitor)		
First Line	42	58.3
Second Line	24	33.3
Third Line	3	4.2
Fourth Line	2	2.8
Fifth Line	1	1.4
Toxicities		
Cytopenias	21	2.0
GI/Hepatic/Ascites	9	0.9
Pleural/Pulmonary	5	0.5
Cardiac	3	0.3
Electrolyte Imbalance	2	0.2
Cytopenias + GI	2	0.2
Cytopenias + Cardiac	1	0.1

Progression Free Survival

The median progression-free survival, which represents the point at which 50% of the patients had encountered the event of interest, was 21.00 months (SE = 4.49, 95% CI: 12.20-29.80) (**Fig. 1**).

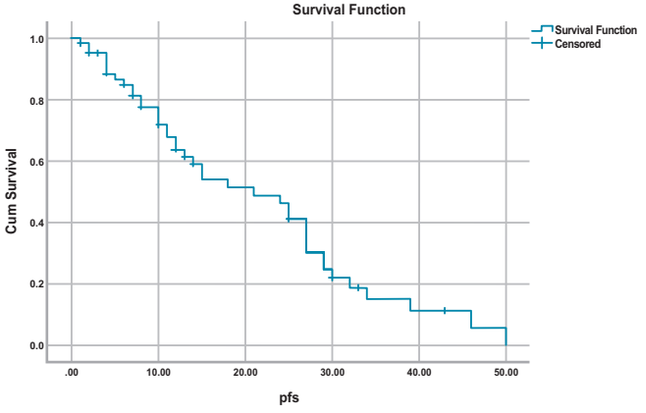

Fig. (1): Kaplan-mere curve for progression free survival of study patients.

Overall Survival

The median overall survival, representing the point at which 50% of the population had experienced the event of interest, was 25.000 months (SE = 12.6, 95% CI: 15.0-64.9) (**Fig. 2**). The relatively narrower confidence interval for the median suggests a more precise estimate of central survival tendency.

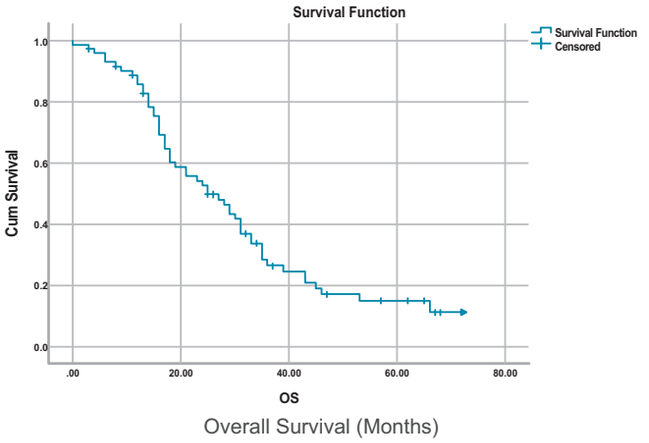

Fig. (2): Kaplan-mere curve for overall survival of study patients.

Univariate Analysis

A univariate Cox proportional hazards regression analysis was used in this study to evaluate the relationship between the outcome of interest and a number of clinical and demographic factors. A significance level of 0.25 was used to determine variables for potential inclusion in the multivariate analysis. Among the variables analyzed, sites of metastasis (p = 0.026, HR = 1.316, 95% CI: 1.034-1.675) showed a statistically significant association with the outcome, indicating that patients with more metastatic sites had a 31.6% % increased risk compared to those without. ECOG performance status (p = 0.107, HR = 1.307, 95% CI: 0.944-1.809), though not statistically significant at the conventional 0.05 level, met the pre-specified inclusion criteria for further analysis (**Table 2**).

Table 2: Univariate analysis.

Variable	p-value	Hazard Ratio (HR)	95% CI (Lower–Upper)
ECOG	0.107	1.307	0.944 – 1.809
Menopausal Status	0.216	0.717	0.424 – 1.214
Comorbidities (if yes, specify)	0.611	1.027	0.926 – 1.139
Grade	0.231	1.152	0.914 – 1.453
Tumor Subtype	0.874	1.026	0.750 – 1.402
Timing of Metastasis	0.071	0.626	0.377 – 1.041
Sites of Metastasis	0.026	1.316	1.034 – 1.675
Line of Treatment, Cell Cycle Inhibitor Used	0.283	1.812	0.554 – 1.188
Cell Cycle Inhibitor Used	0.917	1.024	0.662 – 1581
Hormonal Agent Used in Combination with Cell Cycle Inhibitor	0.299	1.122	0.902 – 1.396
Toxicities	0..536	1.052	0.897 – 1.233

Multivariable Analysis

A multivariable Cox proportional hazards model was employed to calculate the association of clinical and treatment-related variables with progression-free survival (PFS). Among the variables analyzed, the number of metastatic sites (HR = 1.357, 95% CI: 1.029-1.788, p=0.030) was significantly associated with worse PFS, indicating that patients with a higher metastatic burden had an increased risk of disease progression. Additionally, timing of metastasis (HR = 0.548, 95% CI: 0.305-0.986, p=0.045) was determined to be a significant factor, suggesting that patients with *de novo* metastatic disease had better PFS compared to those who developed metastases later during the disease course (**Table 3, Fig. 3**).

Table 3: Multivariate analysis.

Variables	p-value	Hazard Ratio (HR)	95% CI (Lower–Upper)
ECOG	0.910	1.022	0.698 – 1.496
Menopausal Status	0.743	0.871	0.381 – 1.990
Tumor Grade	0.454	1.096	0.862 – 1394
Sites of Metastasis	0.030	1.357	1.029 – 1.788
Timing of Metastasis	0.045	0.548	0.305 – 0.986

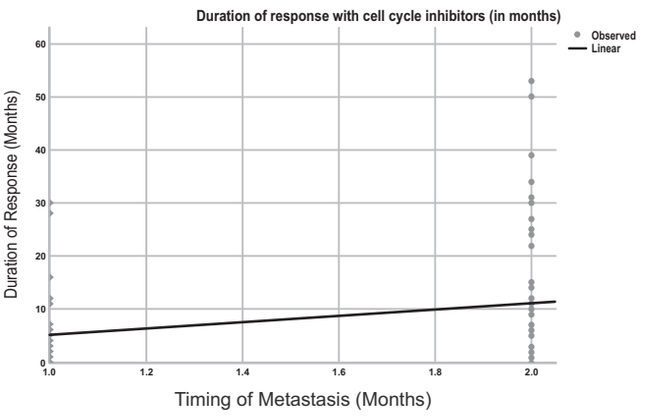

Fig. (3): Multivariate analysis showing the association between timing of metastatic disease and duration of treatment response.

Association & Correlation between Treatment Response Duration and Timing of Metastasis

Association/Correlation: The observed data points indicate that patients with later metastatic timing (coded as 2) tend to have a slightly longer duration of response compared to those with earlier metastasis (coded as 1). However, the regression line suggests a minimal positive association between the timing of metastasis and treatment response duration, implying that later-onset metastasis may be linked to a marginally longer response to cell cycle inhibitors. The clustering of data points at lower response durations suggests that a majority of patients had a short-lived response regardless of metastatic timing, with only a few outliers demonstrating prolonged response.

The association between the time of metastasis and the length of responsiveness to cell cycle inhibitors (measured in months) was assessed using a Pearson correlation analysis. The outcomes demonstrated a weak but statistically significant positive correlation (r = 0.274, p=0.007), indicating that patients with a later timing of metastasis exhibited a slightly prolonged response to cell cycle inhibitors. This suggests that metastatic timing may play a role in influencing treatment duration; however, the strength of the correlation remains modest. Given the statistical significance at the 0.01 level, these findings warrant further investigation to determine whether additional clinical or molecular factors mediate this association (**Table 4, Fig. 4**).

Table 4: Correlation analysis.

Variables	Statistics	Timing of Metastasis	Duration of response with cell cycle inhibitors (in months)
Timing of metastasis	Pearson Correlation	1	0.243***
	Sig. (2-tailed)		0.006
	N	72	72
Duration of response with cell cycle inhibitors (in months)	Pearson Correlation	0.243***	1
	Sig. (2-tailed)	0.006	
	N	72	72
** Correlation is significant at the 0.01 level (2-tailed).			

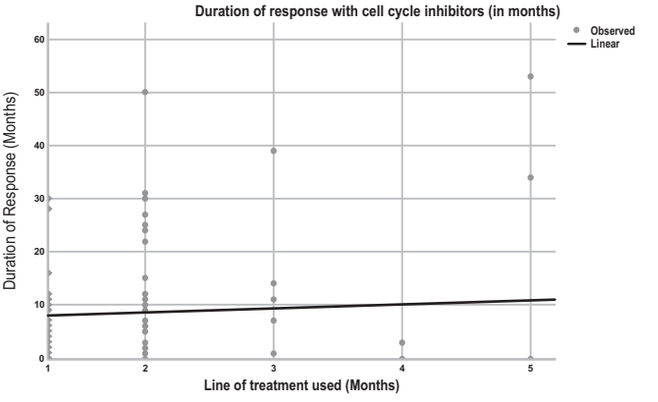

Fig. (4): Association & correlation between treatment response duration and timing of metastasis.

DISCUSSION

Estrogen receptor (ER)-positive, HER2-negative tumors make up the largest proportion of breast cancer cases, nearing 70% and contribute substantially to breast cancer-related mortality as well [7]. Multiple prospective randomized clinical trials over the past decade have demonstrated that agents targeting pathways beyond hormone receptor (HR) interference can enhance the benefits of hormone therapy (HT) alone. Principally, cyclin-dependent kinase (CDK) 4/6 inhibitors have been demonstrated to be successful when combined with HT. When administered in conjunction with HT as first-line or subsequent treatments for metastatic breast cancer (MBC), three such agents, Palbociclib, Ribociclib, and Abemaciclib, have been demonstrated to increase progression-free survival (PFS) [11, 18, 19]. In actual

world practice, oftentimes patients are way more diversified than those who are included in randomized clinical trials. Additionally, this study is directed to present data from the real world, from a low- to middle-income country where the use of generics has been a common practice and patient and service factors play a huge role in impacting the outcomes. No such study has ever been conducted in Pakistan to our knowledge to determine the outcomes of the available drugs in the CDK 4/6 inhibitors realm, and hence, this study holds importance with regard to being the first study determining the outcomes in this genetic pool.

In the randomized, phase III, blinded trial of Ribociclib and Fulvestrant (MONALEESA-3), the median PFS for the Ribociclib arm was considerably higher at 20.5 months (95% CI, 18.5 to 23.5 months) than for the placebo plus Fulvestrant group, that had a PFS of 12.8 months (95% CI, 10.9 to 16.3 months) (hazard ratio, 0.593; 95% CI, 0.480 to 0.732; P <.001) [18]. The median progression-free survival in the Palbociclib-Letrozole group was 24.8 months (95% CI, 22.1 to not estimable) in the PALOMA 2 randomized, phase III, double-blind study, whereas it was 14.5 months (95% CI, 12.9 to 17.1) in the placebo-Letrozole group (hazard ratio for disease progression or death, 0.58; 95% CI, 0.46 to 0.72; P<0.001) [19]. Based on a randomized, phase III, double-blind study of Abemaciclib/placebo (MONARCH 3), which involved 493 postmenopausal women, the Abemaciclib arm's median PFS was considerably longer than the placebo arm's, at 28.18 months. (14.76 months; hazard ratio [95% confidence interval], 0.540 [0.418-0.698]; p = .000002) [11]. Our real-world median PFS of 21.0 months is consistent with the range reported in pivotal trials of CDK4/6 inhibitors (≈ 20-28 months in first-line settings) on patients with HR-positive, HER2-negative metastatic breast cancer.

During the MONALEESA-3 study, 50 deaths (20.7%) occurred in the placebo plus Fulvestrant arm, while 70 deaths (14.5%) occurred in the Ribociclib plus Fulvestrant arm [18]. Overall survival was equal between the arms, according to the MONARCH 3 study, with 32 (9.8%) deaths in the Abemaciclib arm and 17 (10.3%) in the placebo arm (hazard ratio, 0.97) [20]. However, the OS data was immature in both these trials. The PALOMA-2 trial stated that Palbociclib plus Letrozole did not significantly increase OS when compared to placebo plus Letrozole [19]. Palbociclib plus Letrozole exhibited a median OS of 53.9 months (95% CI, 49.8 to 60.8), whilst placebo plus Letrozole had a median OS of 51.2 months (95% CI, 43.7 to 58.9) (hazard ratio [HR], 0.96 [95% CI, 0.78 to 1.18]; stratified one-sided P =.34) [19]. The median overall survival in our study was 25 months, which is significantly lower than the landmark trials. This discrepancy likely reflects the more heavily pre-treated population (many patients in our study received CDK4/6 inhibitors in second or later lines, whereas trials report first-line use) as well as real-world challenges in our setting. Patients in our study had poorer performance status on average and multiple comorbidities; treatment interruptions due to drug cost or availability were common, since only generic versions of the drugs are accessible locally. These factors could contribute to the inferior OS observed and may point us to the fact that better cost and accessibility of these drugs for low- and middle-income countries could benefit these populations.

Neutropenia (59.3%) and leukopenia (21.0%) were the most recurrent grade 3 or 4 adverse events among patients taking Ribociclib; the amount of withdrawal caused by side effects was 7.5% [18]. The PALOMA 2 randomized, phase III, double-blind study. According to this study, the most frequent grade 3 or grade 4 side effect was neutropenia. (66.4%), exhaustion (1.8%), leukopenia (24.8%), and anemia (5.4%) [19]. Our study is also consistent with the same findings, as cytopenias were the most common adverse events in our population. 43 participants (9.7%) in the Palbociclib-Letrozole group had to permanently stop any trial treatment due to adverse events [19]. In the MONARCH 3 trial, the Abemaciclib group had diarrhea, neutropenia, weariness, and nausea as the most reported nuances [20]. Laboratory abnormalities included anemia, reduced white blood cell and neutrophil counts, and elevated serum creatinine [20]. In the Abemaciclib arm, 27.5% of patients encountered serious adverse events, with lung infections contributing to the highest frequency (2.8%) [20]. In our cohort, 55.7% of patients had no reported adverse effects; the most common toxicities were cytopenias (21.6% of patients), followed by gastrointestinal/hepatic (9.3%) and pulmonary complications (5.2%). This pattern mirrors the safety profiles observed in trials: for example, high-grade neutropenia rates of ~60% were seen with ribociclib in MONALEESA-3 and ~66% with Palbociclib in PALOMA-2, and we likewise observed cytopenias as the chief toxicity. No new safety signals emerged in our real-world use, suggesting the tolerability of CDK4/6 inhibitors in our population is comparable to that in controlled trials.

LIMITATIONS

The main drawback of this study is its retrospective design, with the likelihood of obtaining incomplete history since the identification of breast cancer and information for the purpose of this article was collected by reviewing patient files only. We also acknowledge that the sample size is very limited, and this reduces the generalizability, but this represents one of the first efforts to generate real-world data specifically from LMIC in the realm of CDK 4/6 inhibitors. These preliminary findings offer valuable insight into treatment efficacy and tolerability in this specific healthcare context, and we agree that future multi-institutional collaboration would enhance generalizability. In addition, patients were barred because

of loss to follow-up due to missing follow-up data, drug unavailability, inaccessibility due to the cost of treatment, and treatment discontinuation due to side effects. Unfortunately, data regarding local therapies such as surgery or radiation therapy for metastatic disease were not collected in our study and are therefore not available for analysis. One more limitation to our study is that toxicity grading was not included in the original manuscript. As toxicity grade data were not collected in a standardized manner for all patients, we are unable to provide detailed grading information. Future studies should incorporate more robust follow-up mechanisms to minimize data loss. Moreover, data from individuals treated at a single tertiary care center were reviewed. Also, the study included all comers, including much later lines of treatment that have become a significant problem in estimating the true value of overall survival.

CONCLUSION

This study demonstrates that the use of CDK4/6 inhibitors in the Pakistani population with metastatic breast cancer produces outcomes comparable to those observed in major international trials. Patients experienced similar progression-free survival; however, much lower overall survival, which may be attributable to multiple factors, including poor ECOG performance status, multiple co-morbidities at presentation, heavy disease burden, difficulty in accessing medication, cost constraints, and use of non-generic drugs. Similarly, tolerability profiles correlate with already known side effect profiles of CDK 4/6 inhibitors; these results highlight the potency and safety of CDK4/6 inhibitors across diverse genetic and demographic backgrounds. These findings support the incorporation of CDK4/6 inhibitors as the current standard of care for the treatment of hormone receptor-positive, HER2-negative metastatic breast cancer in Pakistan, while also emphasizing the need for broader access and local data to guide treatment decisions.

LIST OF ABBREVIATIONS

HR: Hormone Receptor
HER2: Human Epidermal Growth Factor Receptor 2
ER: Estrogen Receptor
CDK: Cyclin-Dependent Kinase
PFS: Progression-Free Survival
OS: Overall Survival
Rb: Retinoblastoma
MBC: Metastatic Breast Cancer
SD: Standard Deviation
CI: Confidence Intervals
IDC: Invasive Ductal Carcinoma
HR: Hazard Ratio
Eastern Cooperative Oncology Group (ECOG)
HT: Hormone TherapyCDK: Cyclin-Dependent Kinase
PFS: Progression-Free Survival
OS: Overall Survival
Rb: Retinoblastoma
MBC: Metastatic Breast Cancer
SD: Standard Deviation
CI: Confidence Intervals
IDC: Invasive Ductal Carcinoma
HR: Hazard Ratio
Eastern Cooperative Oncology Group (ECOG)
HT: Hormone Therapy

ETHICS APPROVAL

Ethical approval was obtained from the Institutional Ethical Review Board. All procedures performed in studies involving human participants followed the ethical standards of the institution and the Helsinki Declaration.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA

Data is available from the corresponding author upon a reasonable request.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

AUTHORS' CONTRIBUTION

Warda Saleem: Conceptualization, data collection, data analysis, manuscript writing, and project administration, Sidrah Rizwan: Manuscript review, and data collection, Syeda Samnita Batool Zaidi: Literature review and manuscript writing, Faiza Ahmed: Data entry, data verification, and literature support, Muhammad Saad Salim Naviwala: Assistance in data collection and manuscript formatting, Nawazish Zehra: Statistical analysis and data interpretation, Munira Moosajee: Guidance on study design and manuscript editing, Yasmin A. Rashid: Senior supervision, conceptual input, and final manuscript approval. All authors have read and approved the final version of the manuscript.

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