Cyclin-Dependent Kinase 4/6 Inhibitors in Postmenopausal Hormone Receptor–Positive Metastatic Breast Cancer: Efficacy, Safety, and Clinical Integration

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Abstract

Background: Hormone receptor–positive, human epidermal growth factor receptor 2–negative (HR+/HER2−) metastatic breast cancer (MBC) represents the most prevalent subtype of advanced breast cancer in postmenopausal women. Endocrine therapy has historically been the cornerstone of treatment; however, the development of primary and acquired endocrine resistance has limited long-term disease control. Dysregulation of the cyclin D–cyclin-dependent kinase (CDK) 4/6–retinoblastoma pathway is a key driver of tumor proliferation and endocrine resistance in HR+ breast cancer. The introduction of CDK4/6 inhibitors has therefore marked a paradigm shift in the management of metastatic disease, offering substantial improvements in clinical outcomes when combined with endocrine therapy.

Aim: This review aims to comprehensively evaluate the efficacy, safety, and clinical integration of CDK4/6 inhibitors—palbociclib, ribociclib, and abemaciclib—in the treatment of postmenopausal women with HR+/HER2− metastatic breast cancer. We summarize evidence from pivotal randomized clinical trials and real-world studies, discuss differences in toxicity profiles, and highlight practical considerations for patient selection, sequencing strategies, and management of adverse events.

Conclusion: Across multiple phase III trials, the combination of CDK4/6 inhibitors with endocrine therapy has consistently demonstrated significant improvements in progression-free survival and, in several studies, overall survival compared with endocrine therapy alone. These benefits are observed in both endocrine-sensitive and endocrine-resistant disease, establishing CDK4/6 inhibition as the standard of care in the first-line and subsequent treatment settings for postmenopausal HR+/HER2− MBC. Although the three approved agents exhibit comparable efficacy, they differ in safety profiles, particularly with respect to hematologic, gastrointestinal, hepatic, and cardiac toxicities, necessitating individualized treatment decisions. Ongoing research into predictive biomarkers, mechanisms of resistance, and optimal sequencing after CDK4/6 inhibitor progression will further refine clinical integration. Overall, CDK4/6 inhibitors represent a cornerstone of metastatic breast cancer therapy, enabling durable disease control with a favorable balance between efficacy and tolerability..

Keywords: *Cyclin-Dependent Kinase 4/6 Inhibitors, Metastatic Breast Cancer*

Introduction

Breast cancer is the most commonly diagnosed malignancy among women worldwide and remains a leading cause of cancer-related mortality, with postmenopausal women representing the largest affected population. Hormone receptor–positive, human epidermal growth factor receptor 2–negative (HR+/HER2−) breast cancer accounts for approximately two-thirds of all breast cancer cases and dominates the metastatic disease landscape. Despite advances in early detection and adjuvant therapies, a significant proportion of patients present with de novo metastatic disease or eventually develop distant relapse, underscoring the persistent global burden of metastatic breast cancer [1].

In the metastatic setting, breast cancer is considered incurable, and treatment strategies aim to prolong survival, delay disease progression, preserve quality of life, and minimize treatment-related toxicity. Endocrine therapy has long served as the foundation of treatment for HR+/HER2− metastatic breast cancer in postmenopausal women due to its favorable tolerability profile and demonstrated survival advantage compared with chemotherapy in endocrine-sensitive disease. Aromatase inhibitors, selective estrogen receptor modulators, and selective estrogen receptor degraders remain essential therapeutic options across multiple lines of treatment [2].

However, resistance to endocrine therapy represents a major clinical challenge, with approximately 40–50% of patients developing intrinsic or acquired resistance during the course of metastatic disease. Molecular mechanisms underlying endocrine resistance are multifactorial and include alterations in estrogen receptor signaling, activation of compensatory growth factor pathways, and deregulation of cell-cycle control, ultimately leading to disease progression and limited durability of endocrine monotherapy [3].

Dysregulation of the cyclin D–cyclin-dependent kinase (CDK) 4/6–retinoblastoma (Rb) pathway has been identified as a critical driver of tumor proliferation and endocrine resistance in HR+ breast cancer. CDK4 and CDK6 facilitate phosphorylation of the Rb protein, resulting in release of E2F transcription factors and progression from the G1 to S phase of the cell cycle. Aberrant activation of this pathway through cyclin D1 amplification or loss of endogenous CDK inhibitors is a common molecular feature of HR+ breast cancer, providing a strong biological rationale for therapeutic CDK4/6 inhibition [4].

Preclinical studies demonstrated a synergistic interaction between endocrine therapy and CDK4/6 inhibition, with combined treatment inducing sustained cell-cycle arrest and overcoming endocrine resistance more effectively than either approach alone. These findings provided the translational foundation for the rapid clinical development of selective CDK4/6 inhibitors and their evaluation in combination with endocrine therapy for HR+/HER2− metastatic breast cancer [5].

Over the past decade, three orally available CDK4/6 inhibitors—palbociclib, ribociclib, and abemaciclib—have transformed the therapeutic landscape of HR+/HER2− metastatic breast cancer. Large randomized phase III trials from the PALOMA, MONALEESA, and MONARCH programs consistently demonstrated significant improvements in progression-free survival when CDK4/6 inhibitors were added to endocrine therapy, with several studies also showing overall survival benefit. These results firmly established CDK4/6 inhibition as the standard of care in the first-line and subsequent treatment settings [6].

Despite their comparable efficacy, CDK4/6 inhibitors differ in pharmacokinetic properties, dosing schedules, and toxicity profiles, which has important implications for individualized treatment selection. Hematologic toxicity predominates with palbociclib and ribociclib, whereas abemaciclib is more commonly associated with gastrointestinal adverse events; ribociclib additionally carries risks of hepatotoxicity and QT interval prolongation. As patients experience prolonged survival and extended treatment durations, optimal management of adverse events and sequencing strategies following

CDK4/6 inhibitor progression have become increasingly important clinical considerations [7].

Aim of the Review: The aim of this review is to critically evaluate the efficacy, safety, and clinical integration of CDK4/6 inhibitors in postmenopausal women with HR+/HER2− metastatic breast cancer. By synthesizing evidence from pivotal clinical trials, real-world studies, and contemporary clinical guidelines, this review seeks to inform optimal patient selection, toxicity management, and therapeutic sequencing, while highlighting current gaps in knowledge and future research directions [6].

Mechanism of Action of CDK4/6 Inhibitors in Hormone Receptor–Positive Breast Cancer

Cell-cycle progression is a tightly regulated biological process that ensures controlled cellular proliferation in normal tissues. Transition from the G1 to the S phase of the cell cycle is primarily governed by the cyclin D–cyclin-dependent kinase (CDK) 4/6 complex, which integrates mitogenic, hormonal, and growth factor–mediated signals. In hormone receptor–positive (HR+) breast cancer, estrogen receptor (ER) signaling directly induces cyclin D1 expression, thereby promoting CDK4/6 activation and cell-cycle progression. This close interaction between ER signaling and cell-cycle machinery provides a strong biological rationale for combining endocrine therapy with CDK4/6 inhibition in metastatic breast cancer management [8].

Upon activation, CDK4 and CDK6 phosphorylate the retinoblastoma (Rb) tumor suppressor protein, a critical regulator of the G1–S checkpoint. Phosphorylation of Rb results in the release of E2F transcription factors, which activate downstream genes required for DNA replication and cell-cycle entry into the S phase. In HR+ breast cancer, frequent molecular alterations such as cyclin D1 amplification, loss of endogenous CDK inhibitors (e.g., p16), and persistent estrogen-driven signaling lead to continuous Rb phosphorylation and uncontrolled cellular proliferation [9].

CDK4/6 inhibitors exert their antitumor effect by selectively inhibiting CDK4 and CDK6 activity, thereby preventing Rb phosphorylation and maintaining Rb in its active, hypophosphorylated state. This results in sustained sequestration of E2F transcription factors and induction of G1 cell-cycle arrest. Importantly, this mechanism requires functional Rb protein, which is preserved in the vast majority of HR+ breast cancers, explaining the particular sensitivity of this subtype to CDK4/6 inhibition [10].

Preclinical models have demonstrated that CDK4/6 inhibition not only suppresses tumor cell proliferation but also enhances sensitivity to endocrine therapy. Estrogen deprivation or ER blockade reduces cyclin D1 expression, while concurrent CDK4/6 inhibition further enforces cell-cycle arrest, producing a synergistic antitumor effect. This dual targeting strategy effectively delays or overcomes endocrine resistance, which is a major limitation of endocrine monotherapy in metastatic disease [11].

Beyond direct cell-cycle inhibition, CDK4/6 inhibitors have been shown to exert additional biological effects that may contribute to their clinical efficacy. These include modulation of tumor immune microenvironment, enhancement of antitumor immunity through increased antigen presentation, and suppression of DNA damage repair pathways. Such pleiotropic effects may partially explain the durable clinical benefit observed with CDK4/6 inhibitors in combination with endocrine therapy [12].

Despite sharing a common mechanism of action, palbociclib, ribociclib, and abemaciclib differ in their selectivity for CDK4 versus CDK6, pharmacokinetic properties, and off-target effects. Abemaciclib demonstrates greater selectivity for CDK4 and continuous dosing capability, whereas palbociclib and ribociclib require intermittent dosing due to hematologic toxicity. These pharmacologic differences translate into distinct toxicity profiles and have important implications for individualized patient management [13].

Clinical Trial Evidence: PALOMA Studies (Palbociclib)

Palbociclib was the first cyclin-dependent kinase 4/6 (CDK4/6) inhibitor to demonstrate clinical efficacy in hormone receptor–positive, human epidermal growth factor receptor 2–negative (HR+/HER2−) metastatic breast cancer and to receive regulatory approval. Its clinical development program, known as the PALOMA trials, was designed to evaluate palbociclib in combination with endocrine therapy across different disease settings, including endocrine-sensitive and endocrine-resistant metastatic breast cancer. These trials established the foundation for CDK4/6 inhibition as a standard therapeutic strategy in

postmenopausal women with HR+/HER2− metastatic disease [14].

The randomized phase II PALOMA-1/TRIO-18 trial evaluated palbociclib in combination with letrozole versus letrozole alone as first-line therapy in postmenopausal women with previously untreated HR+/HER2− metastatic breast cancer. The addition of palbociclib resulted in a significant improvement in median progression-free survival (PFS), increasing from 10.2 months in the letrozole-alone arm to 20.2 months in the combination arm. This study provided the first clinical proof-of-concept that CDK4/6 inhibition could substantially enhance the efficacy of endocrine therapy in metastatic breast cancer [15].

These findings were subsequently confirmed in the phase III PALOMA-2 trial, which enrolled a larger population of postmenopausal women with treatment-naïve HR+/HER2− metastatic breast cancer. In this pivotal study, palbociclib combined with letrozole significantly prolonged median PFS compared with letrozole plus placebo (24.8 vs. 14.5 months), corresponding to a 42% reduction in the risk of disease progression. Importantly, the PFS benefit was consistent across predefined subgroups, including patients with visceral metastases, older age, and varying disease burden [16].

The role of palbociclib in endocrine-resistant disease was evaluated in the phase III PALOMA-3 trial, which investigated palbociclib in combination with fulvestrant in patients whose disease had progressed during or after prior endocrine therapy. Palbociclib plus fulvestrant significantly improved median PFS compared with fulvestrant alone (11.2 vs. 4.6 months), demonstrating robust efficacy in both pretreated postmenopausal and premenopausal women receiving ovarian suppression. This trial firmly established the benefit of CDK4/6 inhibition beyond the first-line setting [17].

Updated analyses of the PALOMA-3 trial provided important insights into overall survival (OS). Although the primary OS endpoint was not met with statistical significance, a numerically longer median OS was observed in the palbociclib–fulvestrant arm compared with placebo–fulvestrant (34.9 vs. 28.0 months). Subgroup analyses suggested greater survival benefit in patients with endocrine-sensitive disease, absence of prior chemotherapy for metastatic disease, and nonvisceral metastases, highlighting the importance of patient selection [18].

Across the PALOMA trials, palbociclib demonstrated a predictable and manageable safety profile. Neutropenia was the most frequently reported adverse event, reflecting on-target inhibition of CDK4/6 in hematopoietic progenitor cells. Importantly, palbociclib-associated neutropenia was predominantly uncomplicated, rapidly reversible with dose interruptions or reductions, and associated with a low incidence of febrile neutropenia. These safety characteristics supported long-term treatment continuity in most patients [19].

Real-world studies have largely confirmed the efficacy and tolerability observed in the PALOMA clinical trials, demonstrating consistent PFS benefits and manageable toxicity in routine clinical practice. Observational cohorts have also suggested that palbociclib retains activity in older patients and those with comorbidities, populations often underrepresented in randomized trials. These findings reinforce the generalizability of PALOMA trial results to real-world postmenopausal metastatic breast cancer populations [20].

Clinical Trial Evidence: MONALEESA Studies (Ribociclib)

Ribociclib is a selective cyclin-dependent kinase 4/6 (CDK4/6) inhibitor that has demonstrated robust clinical efficacy in hormone receptor–positive, human epidermal growth factor receptor 2–negative (HR+/HER2−) metastatic breast cancer across multiple disease settings. The MONALEESA clinical trial program was specifically designed to evaluate ribociclib in combination with endocrine therapy in both endocrine-sensitive and endocrine-resistant disease, as well as across menopausal subgroups. Collectively, these trials have provided some of the strongest overall survival data supporting CDK4/6 inhibition in metastatic breast cancer [21].

The phase III MONALEESA-2 trial investigated ribociclib in combination with letrozole versus letrozole alone as first-line therapy in postmenopausal women with HR+/HER2− metastatic breast cancer. Ribociclib significantly improved progression-free survival, with a median PFS of 25.3 months compared with 16.0 months in the placebo arm. Extended follow-up revealed a substantial overall survival benefit,

with a median OS of 63.9 months in the ribociclib arm versus 51.4 months in the placebo arm, representing one of the longest survival outcomes reported in this patient population [22].

The efficacy of ribociclib in combination with fulvestrant was evaluated in the phase III MONALEESA-3 trial, which enrolled postmenopausal women with HR+/HER2− metastatic breast cancer in both first-line and second-line settings. Ribociclib plus fulvestrant significantly prolonged progression-free survival compared with fulvestrant alone, with median PFS improving from 12.8 to 20.5 months in the overall population. Importantly, a significant overall survival benefit was also observed, confirming ribociclib's effectiveness beyond aromatase inhibitor–based therapy [23].

The MONALEESA-7 trial uniquely focused on premenopausal and perimenopausal women receiving ovarian function suppression, thereby expanding the applicability of ribociclib across menopausal statuses. Patients treated with ribociclib plus endocrine therapy demonstrated a median PFS of 23.8 months compared with 13.0 months in the placebo group. Long-term follow-up showed a meaningful overall survival advantage, with a median OS of 58.7 months in the ribociclib arm versus 48.0 months in the control arm, highlighting the broad efficacy of ribociclib across age groups [24].

Across all MONALEESA trials, ribociclib demonstrated consistent efficacy across key clinical subgroups, including patients with visceral metastases, de novo metastatic disease, and endocrine-resistant tumors. Tumor response rates were significantly higher in ribociclib-containing regimens, contributing to rapid disease control and symptomatic improvement. These findings support the use of ribociclib as a preferred first-line treatment option for HR+/HER2− metastatic breast cancer when overall survival benefit is a primary therapeutic goal [25].

The safety profile of ribociclib is characterized primarily by hematologic toxicity, particularly neutropenia, which is typically reversible and manageable with dose modifications. Unique safety considerations include hepatotoxicity and QT interval prolongation, necessitating routine monitoring of liver function tests and electrocardiograms during treatment. Despite these risks, treatment discontinuation rates due to adverse events were low, and the majority of patients were able to maintain long-term therapy with appropriate monitoring and dose adjustments [26].

Clinical Trial Evidence: MONARCH Studies (Abemaciclib)

Abemaciclib is a potent and selective cyclin-dependent kinase 4/6 (CDK4/6) inhibitor with distinct pharmacologic properties compared with palbociclib and ribociclib, including greater selectivity for CDK4 and the ability to be administered on a continuous dosing schedule. The MONARCH clinical trial program was designed to evaluate abemaciclib both as monotherapy and in combination with endocrine therapy in hormone receptor–positive, human epidermal growth factor receptor 2–negative (HR+/HER2−) metastatic breast cancer, particularly in patients with prior endocrine resistance [27].

The phase II MONARCH-1 trial was the first study to demonstrate single-agent activity of a CDK4/6 inhibitor in heavily pretreated patients with HR+/HER2− metastatic breast cancer. This study enrolled patients who had progressed on prior endocrine therapy and received one or two lines of chemotherapy in the metastatic setting. Abemaciclib monotherapy achieved an objective response rate of 19.7% and a clinical benefit rate of 42.4%, with a median progression-free survival of 6.0 months and overall survival of 17.7 months, confirming intrinsic antitumor activity independent of endocrine therapy [28].

The randomized phase III MONARCH-2 trial evaluated abemaciclib in combination with fulvestrant versus fulvestrant alone in patients with HR+/HER2− metastatic breast cancer who had progressed on prior endocrine therapy. The addition of abemaciclib significantly improved median progression-free survival from 9.3 months to 16.4 months and was also associated with a statistically significant overall survival benefit. With extended follow-up, median overall survival reached 46.7 months in the abemaciclib–fulvestrant arm compared with 37.3 months in the control arm, firmly establishing the role of abemaciclib in endocrine-resistant disease [29].

The efficacy of abemaciclib in the first-line setting was evaluated in the phase III MONARCH-3 trial, which enrolled postmenopausal women with HR+/HER2− metastatic breast cancer who had not received prior systemic therapy for advanced disease. Patients treated with abemaciclib in combination with a

nonsteroidal aromatase inhibitor demonstrated a significant improvement in progression-free survival compared with endocrine therapy alone, with a median PFS of 28.2 months versus 14.8 months. These results confirmed the benefit of abemaciclib as an initial treatment option in endocrine-sensitive metastatic breast cancer [30].

Across the MONARCH trials, abemaciclib demonstrated a safety profile distinct from other CDK4/6 inhibitors. Gastrointestinal toxicity, particularly diarrhea, was the most common adverse event and typically occurred early in treatment but was manageable with dose adjustments and antidiarrheal therapy. In contrast to palbociclib and ribociclib, rates of severe neutropenia were lower, allowing continuous dosing without prolonged treatment interruptions. These characteristics make abemaciclib a valuable option for patients in whom hematologic toxicity is a concern [31].

Real-world evidence has supported the efficacy and tolerability of abemaciclib observed in clinical trials, including in elderly patients and those with visceral disease or prior exposure to multiple lines of therapy. Observational studies suggest that appropriate toxicity management enables sustained treatment exposure and clinical benefit. Together, data from the MONARCH program position abemaciclib as a key component of endocrine-based therapy for HR+/HER2− metastatic breast cancer across multiple lines of treatment [32].

Comparative Efficacy of CDK4/6 Inhibitors in Postmenopausal Metastatic Breast Cancer

Direct head-to-head randomized clinical trials comparing palbociclib, ribociclib, and abemaciclib are currently lacking; therefore, comparative efficacy assessments rely on indirect comparisons across pivotal phase III trials and large meta-analyses. Despite differences in trial design, patient populations, endocrine partners, and follow-up durations, all three CDK4/6 inhibitors have consistently demonstrated substantial improvements in progression-free survival when combined with endocrine therapy compared with endocrine therapy alone. This consistency across independent trial programs supports a class effect of CDK4/6 inhibition in hormone receptor–positive, HER2-negative metastatic breast cancer [33].

Meta-analyses pooling data from randomized phase II and III trials have confirmed that CDK4/6 inhibitors significantly reduce the risk of disease progression and death compared with endocrine therapy alone. A comprehensive meta-analysis including PALOMA, MONALEESA, and MONARCH trials demonstrated a relative reduction in the risk of progression of approximately 45–55% across agents, with overall survival benefits emerging particularly for ribociclib and abemaciclib. These findings suggest comparable efficacy in disease control, while highlighting potential differences in survival outcomes across agents [34].

Overall survival benefit represents an increasingly important endpoint in metastatic breast cancer. Ribociclib has demonstrated statistically significant overall survival improvement across multiple phase III trials, including MONALEESA-2, MONALEESA-3, and MONALEESA-7, in both first-line and subsequent treatment settings. Abemaciclib has also shown a clear overall survival benefit in the MONARCH-2 trial in endocrine-resistant disease, whereas palbociclib has shown numerically favorable but not statistically significant overall survival results. These differences should be interpreted cautiously, as they may reflect variations in trial design, crossover rates, and subsequent therapies rather than true differences in drug efficacy [35].

Subgroup analyses across CDK4/6 inhibitor trials have shown consistent efficacy regardless of disease burden, presence of visceral metastases, age, or prior endocrine sensitivity. Patients with bone-only disease, visceral involvement, or de novo metastatic presentation all derive meaningful benefit from CDK4/6 inhibition. Importantly, patients with endocrine-resistant disease also experience significant prolongation of progression-free survival, supporting the use of CDK4/6 inhibitors beyond the first-line setting in postmenopausal women [36].

Real-world evidence has further contributed to understanding comparative effectiveness among CDK4/6 inhibitors. Observational studies and registry-based analyses generally confirm similar progression-free survival outcomes across agents in routine clinical practice. Treatment selection in real-world settings is often driven by patient comorbidities, toxicity profiles, drug–drug interactions, and physician experience rather than perceived differences in efficacy. These findings reinforce the concept that all three CDK4/6

inhibitors represent effective options when appropriately integrated into endocrine-based treatment strategies [37].

Taken together, available evidence supports the conclusion that palbociclib, ribociclib, and abemaciclib offer broadly comparable efficacy in controlling hormone receptor–positive metastatic breast cancer, with survival advantages increasingly documented for ribociclib and abemaciclib. In the absence of direct comparative trials, treatment choice should be individualized based on patient characteristics, toxicity profiles, monitoring requirements, and clinical context rather than assumptions of superior antitumor efficacy [38].

Safety and Tolerability of CDK4/6 Inhibitors

The integration of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors into the treatment of hormone receptor–positive, HER2-negative metastatic breast cancer has been facilitated by their overall favorable safety profile compared with cytotoxic chemotherapy. Across pivotal randomized trials, CDK4/6 inhibitors combined with endocrine therapy were associated with predictable and manageable adverse events, allowing prolonged treatment exposure and preservation of quality of life. Most toxicities are mechanism-based, reversible, and manageable with dose modifications and supportive care, making these agents suitable for long-term administration in postmenopausal patients [39].

Hematologic toxicity represents the most common adverse effect associated with CDK4/6 inhibitors, particularly palbociclib and ribociclib. Neutropenia occurs frequently but differs biologically from chemotherapy-induced neutropenia, as it reflects reversible cell-cycle arrest of bone marrow progenitors rather than cytotoxic damage. Febrile neutropenia is rare, occurring in less than 2% of patients, and routine growth factor support is generally unnecessary. Dose interruptions and reductions effectively manage neutropenia without compromising treatment efficacy [40].

Abemaciclib demonstrates a distinct toxicity profile, with gastrointestinal adverse events being more prominent than hematologic toxicity. Diarrhea is the most frequently reported adverse event, often occurring early in treatment and typically manageable with prompt initiation of antidiarrheal agents, dietary modifications, and dose adjustments. Although diarrhea can impact quality of life if not proactively managed, treatment discontinuation due to gastrointestinal toxicity remains uncommon in clinical trials and real-world practice [41].

Hepatotoxicity is an important safety consideration, particularly with ribociclib. Elevations in alanine aminotransferase and aspartate aminotransferase have been reported across trials, necessitating routine liver function monitoring during treatment. Most hepatic adverse events are asymptomatic, reversible, and manageable with dose interruption or reduction. Permanent discontinuation due to hepatotoxicity is infrequent when appropriate monitoring guidelines are followed [42].

Ribociclib is also associated with a risk of QT interval prolongation, which distinguishes it from other CDK4/6 inhibitors. Electrocardiographic monitoring is therefore recommended at baseline and during early treatment cycles, particularly in patients with preexisting cardiac conditions or those receiving concomitant QT-prolonging medications. With appropriate patient selection and monitoring, clinically significant cardiac events remain rare, and treatment can be safely continued in most cases [43].

Nonhematologic adverse events common to all CDK4/6 inhibitors include fatigue, nausea, stomatitis, alopecia, and decreased appetite, most of which are mild to moderate in severity. These symptoms are generally cumulative rather than acute and can often be alleviated through supportive care measures. Importantly, patient-reported outcomes from randomized trials consistently demonstrate maintenance or improvement in quality of life with CDK4/6 inhibitor–based therapy compared with endocrine therapy alone [44].

Long-term safety data and real-world evidence have reinforced the tolerability observed in clinical trials, including in elderly patients and those with comorbidities. Dose reductions are common in routine practice but do not appear to compromise clinical efficacy. These findings underscore the importance of individualized toxicity management strategies to optimize treatment adherence and maximize therapeutic benefit in postmenopausal metastatic breast cancer patients [45].

Clinical Integration and Treatment Sequencing of CDK4/6 Inhibitors

Endocrine-based therapy combined with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors is now established as the standard-of-care for postmenopausal women with hormone receptor–positive, HER2-negative metastatic breast cancer in the absence of visceral crisis. Multiple international guidelines recommend CDK4/6 inhibitors as preferred first-line therapy due to consistent improvements in progression-free survival and overall survival compared with endocrine therapy alone. This paradigm shift has significantly reduced the upfront use of chemotherapy, allowing effective disease control with improved tolerability and quality of life [46].

In the first-line setting, treatment selection is influenced by prior exposure to endocrine therapy in the adjuvant setting and the endocrine sensitivity of the disease. For patients who relapse more than 12 months after completing adjuvant aromatase inhibitor therapy or who present with de novo metastatic disease, a CDK4/6 inhibitor combined with an aromatase inhibitor is the preferred approach. In contrast, patients who experience early relapse during or shortly after adjuvant endocrine therapy are more appropriately treated with a CDK4/6 inhibitor in combination with fulvestrant, reflecting underlying endocrine resistance [47].

Patient-specific factors play a critical role in selecting among available CDK4/6 inhibitors. Palbociclib and ribociclib are often favored in patients without significant baseline gastrointestinal comorbidity, whereas abemaciclib may be preferred in individuals with prior hematologic vulnerability or those requiring continuous dosing. Ribociclib requires additional caution in patients with preexisting cardiac disease or those receiving QT-prolonging medications, highlighting the importance of individualized treatment planning [48].

The optimal management strategy following disease progression on a CDK4/6 inhibitor remains an area of active investigation. Current evidence does not support routine continuation of the same CDK4/6 inhibitor beyond progression; however, switching endocrine partners or introducing targeted agents based on tumor molecular profiling is recommended. Options include alpelisib for PIK3CA-mutated tumors, everolimus-based combinations, or chemotherapy in cases of endocrine resistance or high disease burden [49].

Rechallenge with a CDK4/6 inhibitor after a treatment-free interval or with a different endocrine backbone is an emerging concept supported by limited prospective and retrospective data. While not yet considered standard practice, select patients with prolonged initial response and indolent disease biology may derive benefit from CDK4/6 inhibitor rechallenge, particularly within clinical trials or carefully selected real-world scenarios [50].

Integration of molecular testing into treatment sequencing has become increasingly important in guiding post-CDK4/6 inhibitor therapy. Assessment of somatic PIK3CA mutations, ESR1 mutations, and germline BRCA1/2 status can inform the selection of subsequent targeted therapies and help delay the initiation of chemotherapy. As understanding of resistance mechanisms evolves, biomarker-driven sequencing strategies are expected to further personalize treatment for postmenopausal metastatic breast cancer patients [51].

Overall, successful clinical integration of CDK4/6 inhibitors requires a multidisciplinary, patient-centered approach that considers disease biology, prior treatments, toxicity profiles, comorbidities, and patient preferences. When appropriately selected and managed, CDK4/6 inhibitor–based regimens enable durable disease control, improved survival outcomes, and meaningful preservation of quality of life in postmenopausal women with metastatic breast cancer [52].

Resistance Mechanisms and Predictive Biomarkers for CDK4/6 Inhibitor Therapy

Despite the substantial clinical benefits achieved with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, disease progression eventually occurs in most patients with hormone receptor–positive, HER2-negative metastatic breast cancer. Resistance may be present at baseline (primary resistance) or develop after an initial response (acquired resistance). Understanding the biological mechanisms underlying resistance is essential for optimizing treatment sequencing and for developing strategies to prolong therapeutic benefit in postmenopausal patients [53].

Alterations in the retinoblastoma (RB1) gene represent one of the most well-characterized mechanisms of resistance to CDK4/6 inhibition. Since the antitumor activity of CDK4/6 inhibitors depends on the presence of functional Rb protein, loss of RB1 function through mutation or deletion renders tumor cells insensitive to CDK4/6 blockade. Although RB1 loss is uncommon in treatment-naïve HR+ breast cancer, it has been identified in tumor biopsies obtained after progression on CDK4/6 inhibitors, suggesting a role in acquired resistance [54].

Activation of alternative cell-cycle pathways is another key resistance mechanism. Upregulation of cyclin E1 and activation of cyclin-dependent kinase 2 (CDK2) can bypass CDK4/6 inhibition and restore cell-cycle progression despite continued therapy. Amplification of CCNE1 and increased CDK2 activity have been associated with reduced sensitivity to CDK4/6 inhibitors in preclinical models and clinical samples, highlighting the complexity of cell-cycle regulation in resistant tumors [55].

Aberrant activation of the phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR signaling pathway has also been implicated in resistance to CDK4/6 inhibitor–based therapy. Mutations in PIK3CA or loss of PTEN can promote cell survival and proliferation independent of cell-cycle arrest, thereby attenuating the antitumor effects of CDK4/6 inhibition. These findings provide a strong rationale for combining CDK4/6 inhibitors with PI3K or mTOR pathway inhibitors and support molecular profiling at progression [56].

Estrogen receptor (ESR1) mutations represent an additional mechanism of resistance, particularly in patients previously treated with aromatase inhibitors. ESR1 mutations lead to ligand-independent activation of the estrogen receptor, reducing the effectiveness of endocrine therapy partners and indirectly diminishing the benefit of CDK4/6 inhibition. Detection of ESR1 mutations through circulating tumor DNA analysis has emerged as a promising approach for guiding subsequent endocrine-based treatment strategies [57].

The search for reliable predictive biomarkers to guide selection of CDK4/6 inhibitors remains an unmet clinical need. To date, no validated biomarker—including Ki-67, cyclin D1 amplification, or p16 loss—has consistently predicted benefit from CDK4/6 inhibition. Consequently, CDK4/6 inhibitors are currently prescribed broadly to eligible patients based on clinical criteria rather than molecular stratification, underscoring the importance of continued translational research in this area [58].

Liquid biopsy techniques, particularly circulating tumor DNA analysis, are increasingly being explored to monitor treatment response and detect emerging resistance mechanisms in real time. Dynamic changes in genomic alterations such as RB1, ESR1, and PIK3CA mutations during therapy may enable earlier identification of resistance and inform timely treatment adaptation. Integration of such approaches into routine clinical practice has the potential to significantly refine personalized treatment strategies in metastatic breast cancer [59].

In summary, resistance to CDK4/6 inhibitors is multifactorial and involves complex interactions between cell-cycle regulation, endocrine signaling, and oncogenic survival pathways. Ongoing efforts to elucidate resistance mechanisms and identify predictive biomarkers will be critical for optimizing therapeutic sequencing, developing rational combination strategies, and improving long-term outcomes for postmenopausal women with HR+/HER2− metastatic breast cancer [60].

Conclusion

Cyclin-dependent kinase 4/6 inhibitors have reshaped the management of postmenopausal hormone receptor–positive, HER2-negative metastatic breast cancer and are now firmly established as a cornerstone of endocrine-based systemic therapy. Their integration with endocrine treatment has resulted in substantial and durable improvements in progression-free survival, and in many clinical settings, overall survival,

while preserving quality of life and delaying the need for cytotoxic chemotherapy. The consistent benefit observed across diverse patient subgroups underscores the robustness of CDK4/6 inhibition as a class effect in this disease.

Despite these significant advances, metastatic breast cancer remains an incurable condition, and therapeutic resistance to CDK4/6 inhibitors ultimately develops in most patients. Increasing insight into resistance mechanisms, including alterations in cell-cycle control, estrogen receptor signaling, and oncogenic survival pathways, has highlighted the biological complexity of treatment failure and the need for rational therapeutic sequencing. The absence of validated predictive biomarkers continues to necessitate broad clinical use of CDK4/6 inhibitors based on clinicopathologic criteria rather than molecular selection.

Future progress in this field will depend on refining patient selection, optimizing treatment sequencing after disease progression, and integrating emerging targeted and endocrine therapies. Advances in molecular profiling, circulating tumor DNA analysis, and real-world data are expected to further personalize treatment strategies and improve long-term disease control. Through continued clinical and translational research, CDK4/6 inhibitor–based therapy will remain central to improving outcomes and quality of life for postmenopausal women with hormone receptor–positive metastatic breast cancer.

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