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REVIEW ARTICLE

Cyclin-dependent kinase 4/6 inhibitor resistance mechanisms and strategies for subsequent treatment in breast cancer: A comprehensive review

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Abstract

Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors have transformed the therapeutic landscape for hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer, demonstrating significant efficacy in both early and advanced stages of the disease. Combined with endocrine therapy, these inhibitors have dramatically improved survival outcomes. However, resistance to CDK4/6 inhibitors inevitably develops, posing a significant challenge in clinical management. Resistance to CDK4/6 inhibitors can develop through inherent and acquired fashions, and their mechanisms are explored in this comprehensive review. Inherent resistance arises from pre-existing genetic or signaling pathway alterations that diminish cancer cell sensitivity to CDK4/6 inhibitors. Acquired resistance, on the other hand, develops over time through mechanisms, such as the activation of alternative signaling pathways or changes in the tumor microenvironment. The review also examines potential biomarkers for predicting resistance, especially circulating tumor DNA markers, and discusses strategies to overcome resistance. These include combination therapies targeting multiple pathways simultaneously, sequential approaches to delay the onset of resistance, and the development of next-generation CDK4/6 inhibitors with improved efficacy and reduced resistance potential. Understanding resistance mechanisms and developing effective countermeasures are crucial for optimizing patient outcomes and extending the clinical benefits of CDK4/6 inhibitors in cancer therapy. Leveraging these insights will enable clinicians to personalize treatment strategies, ultimately enhancing the long-term effectiveness of CDK4/6 inhibitors in managing breast cancer.

Keywords: CDK4/6 inhibitors; Endocrine resistance; Breast cancer; Drug resistance mechanisms; Treatment strategies

1. Introduction

Breast cancer is the most prevalent malignant tumor in women, constituting approximately 11.6% of all cancer diagnoses worldwide. In 2022, nearly 2.5 million new breast cancer cases were recorded globally, representing roughly a quarter of all cancer cases.[1] It is categorized into three subtypes depending on the presence of estrogen receptor (ER), progesterone receptor, and human epidermal growth factor receptor 2 (HER2): hormone receptor (HR)-positive, HER2-positive, and triple-negative. Among these, HR-positive breast cancer accounts for approximately 60% to 70% of all cases. Although HR-positive breast cancer is generally associated with a better prognosis compared to other subtypes, patients with this subtype still experience two distinct peaks of recurrence – one occurring within the first 1 – 3 years and another even after 10 years – underscoring the urgent need for novel therapeutic strategies to improve long-term patient outcomes.[2,3]

Building on the foundation of endocrine therapy, cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors have emerged as powerful targeted therapies, particularly for HR-positive breast cancer. CDK4 and CDK6 are crucial regulators of the G1-to-S phase transition in the cell cycle, a process essential for cellular proliferation.[4] These kinases form complexes with D-type cyclins, particularly cyclin D1, which phosphorylate and inactivate the retinoblastoma (RB) tumor suppressor protein. This phosphorylation releases E2F transcription factors, enabling the transcription of genes required for DNA synthesis and cell cycle progression.[5] By blocking CDK4/6 activity, these drugs prevent the phosphorylation of RB, thereby inhibiting cell cycle progression and tumor growth.

The combination of CDK4/6 inhibitors with endocrine therapy has significantly benefited both early-stage and advanced HR-positive/HER2-negative breast cancer, transforming the treatment paradigm. Clinical trials such as NATALEE and MONARCH E have expanded treatment options for patients with early HR-positive/HER2-negative breast cancer, demonstrating the potential of CDK4/6 inhibitors to reduce recurrence risk and improve overall survival (OS).[6,7] Furthermore, advanced clinical trials, such as PALOMA-2,[8] MONALEESA-7[9] and -3,[10] and MONARCH-3[11] have shown that this combination therapy significantly improves progression-free survival (PFS) for patients with metastatic HR-positive/HER2-negative breast cancer.

However, resistance to CDK4/6 inhibitor therapy remains a significant clinical challenge, resulting in disease progression in some early-stage patients and nearly all advanced-stage patients. Understanding the underlying mechanisms of resistance is crucial for improving patient outcomes, developing novel therapies, and optimizing treatment sequencing.[5,12-14] This review aims to provide a comprehensive summary of current resistance mechanisms to CDK4/6 inhibitors and explore potential approaches to overcome such resistance.

2. The operational mechanism and clinical application of CDK4/6 inhibitors

As illustrated in Figure 1, CDK4/6 kinases are pivotal in governing cell cycle progression, especially during the transition from the G1 phase to the S phase. They form complexes with cyclin D1 proteins, which then phosphorylate the RB protein, which is a key tumor suppressor.[15] Phosphorylation of RB disrupts its interaction with E2F transcription factors, thereby releasing E2F to activate the transcription of genes essential for DNA replication and cell cycle progression.[15] In HR-positive/HER2-negative breast cancer, CDK4/6 inhibitors are used in conjunction with anti-estrogen therapies, including aromatase inhibitors (AIs), fulvestrant, and tamoxifen, to achieve a synergistic effect.[16] This combination has become the standard of care for advanced HR-positive/HER2-negative breast cancer.[17] Currently, four selective CDK4/6 inhibitors have been approved, including palbociclib, ribociclib, dalpiciclib, and abemaciclib.[5,18] These agents specifically target CDK4/6 kinase and exhibit comparable inhibitory effects on both kinases. Palbociclib, dalpiciclib, and ribociclib share structural similarities and display similar kinase inhibitory activities. These drugs are typically administered on a three-week-on, one-week-off schedule to mitigate myelosuppression, their primary dose-limiting toxicity.[5,18] In contrast, abemaciclib exhibits a distinct inhibitory profile, with higher selectivity for CDK4 compared to CDK6, consistent with its reported high potency against CDK4.[5] In addition, abemaciclib inhibits multiple other kinases, including CDK1, CDK2, CDK5, CDK9, and albeit at lower potencies.[16] The predominant toxicities of abemaciclib are diarrhea and fatigue.[5] A comparative summary of the mechanisms and side effect profiles of these four CDK4/6 inhibitors is shown in Table 1.

3. Mechanisms of resistance to CDK4/6 inhibitors

Resistance to CDK4/6 inhibitors can be broadly categorized into two types: intrinsic and acquired, each driven by distinct mechanisms that contribute to treatment failure, particularly in HR-positive/HER2-negative breast cancer. Intrinsic resistance arises from pre-existing genetic or molecular alterations that render tumor cells inherently unresponsive to CDK4/6 inhibition. In contrast, acquired resistance develops over time as adaptive changes in tumor

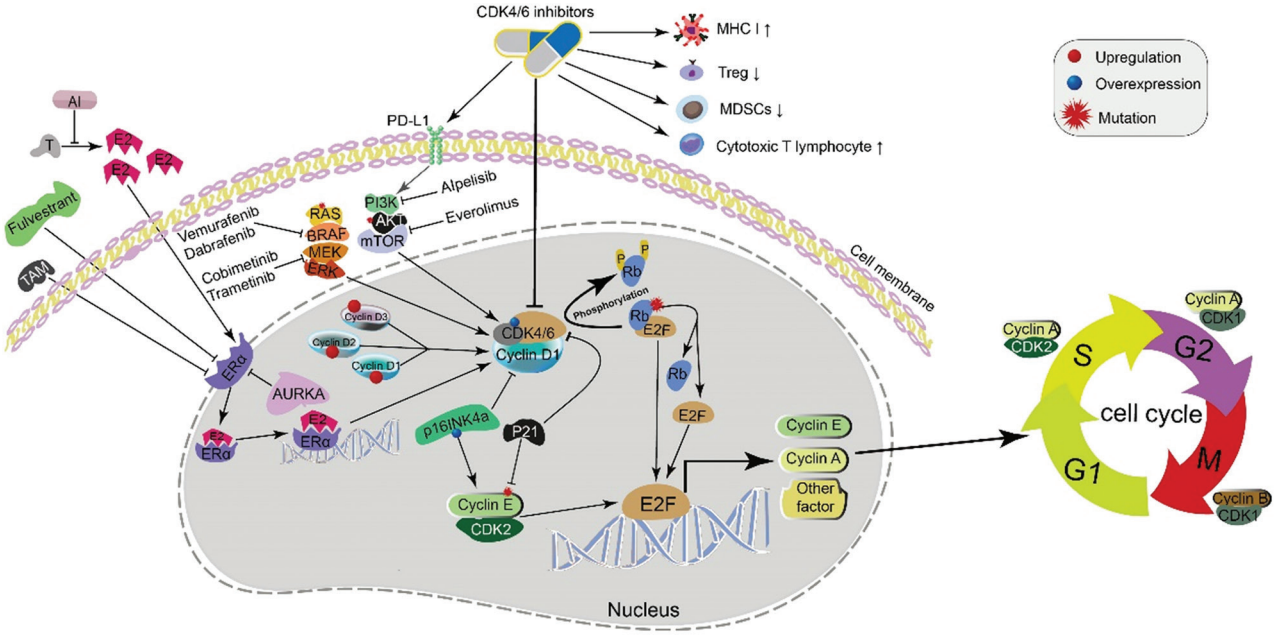


Figure 1. Schematic diagram illustrating the mechanisms of action and resistance of CDK4/6 inhibitors in combination with endocrine therapy. Abbreviations: CDK4/6: Cyclin-dependent kinase 4 and 6; MHC1: Major histocompatibility complex class 1; MDSCs: Myeloid-derived suppressor cells; Treg: Regulatory T cell; TAM: Tamoxifen; T: Testosterone; AI: Aromatase inhibitors; E2: Estradiol; PD-L1: Programmed death-ligand 1; ERα: Estrogen receptor alpha; E2F: E2F transcription factor; Rb: Retinoblastoma; AURKA: Aurora kinase A; RAS: Rat sarcoma; BRAF: B-Raf protooncogene; MEK: Mitogen-activated protein kinase kinase; ERK: Extracellular signal-regulated kinase; mTOR: Mammalian target of rapamycin.

biology occur during treatment. Understanding these resistance mechanisms is crucial for devising effective strategies to overcome them and improve patient outcomes.

3.1. Intrinsic resistance mechanisms

Intrinsic resistance refers to the inherent ability of some tumors to resist CDK4/6 inhibitors from the outset. One of the most significant mechanisms involves the loss or mutation of the RB protein, a critical cell cycle regulator.[17] Tumors lacking functional RB bypass CDK4/6 inhibition, allowing uninterrupted cell cycle progression.[12,19] In addition, overexpression of CDK4 or CDK6 can independently drive cell cycle progression by promoting RB phosphorylation, thereby enabling tumor cells to evade the inhibitory effects of CDK4/6 inhibitors.[19,20] Similarly, the upregulation of cyclins, particularly cyclin D1, D2, or D3, contributes to resistance by forming hyperactive complexes with CDK4/6 that are less susceptible to inhibition.[20] In some tumors, especially ER-positive breast cancer, non-canonical activation of CDK2 facilitates S-phase entry despite CDK4/6 inhibition. This mechanism allows cancer cells to sustain proliferation even in the presence of inhibitors.[12,21] Furthermore, paradoxical resistance can arise from the overexpression of p16INK4a proteins. Although p16INK4a typically inhibits CDK4/6 activity, its overexpression disrupts normal cell cycle regulation and activates alternative pathways that support tumor growth.[20,21] A detailed schematic representation of these pathways is demonstrated in Figure 1.

3.2. Acquired resistance mechanisms

Acquired resistance to CDK4/6 inhibitors typically develops after an initial period of therapeutic sensitivity, primarily due to genetic and epigenetic alterations within the tumor. Common mutations in genes such as the RB protein, protein kinase B (AKT), rat sarcoma, aurora kinase A (AURKA), and cyclin E have been identified as key drivers of resistance. These mutations activate alternative signaling pathways that bypass CDK4/6 activity, thereby diminishing the efficacy of treatment.[22] As illustrated in Figure 1, tumors can engage compensatory pathways such as phosphoinositide 3-kinase (PI3K)/AKT or mitogen-activated protein kinase (MAPK) signaling, to sustain cell survival and proliferation despite CDK4/6 inhibition. This adaptive rewiring of signaling networks undermines the long-term effectiveness of CDK4/6 inhibitors.[12,22] In addition, changes in ER status, including loss or downregulation, have been associated with reduced responsiveness to combined endocrine therapy and CDK4/6 inhibition.[22] Epigenetic modifications further contribute to acquired resistance by altering gene expression profiles, enabling tumors to adapt their growth

Table 1. Comparison of the mechanisms of four CDK4/6 inhibitors

CDK4/6 inhibitor	Primary target	Mechanism type	IC50 values	Binding affinity	Additional targets	Cellular effect	Dosing schedule	Main Side effects	References
Palbociclib	CDK4/6	ATP-competitive	Similar potency for CDK4 and CDK6	Similar affinity for CDK4/cyclin D3 and CDK6/cyclin D1	Highly specific for CDK4/6	Cytostasis only	21 days on/ 7 days off	Neutropenia	5,16,50,51
Ribociclib	CDK4/6	ATP-competitive	CDK4: 10 nM CDK6: 39 nM	5-fold greater affinity for CDK4/ cyclin D3	Highly specific for CDK4/6	Cytostasis only	21 days on/ 7 days off	Neutropenia, QTc prolongation	5,16,46,50,51
Abemaciclib	CDK4/6	ATP-competitive	CDK4: 2 nM, CDK6: 10 nM	9-fold greater affinity for CDK4/ cyclin D3; 14 times more potent against CDK4 than CDK6	Also inhibits CDK1, CDK2, CDK5, CDK9, and other kinases	Both cytostasis and cytotoxicity	Continuous dosing	Diarrhea, fatigue	5,16,50-52
Dalpiciclib	CDK4/6	ATP-competitive	CDK4: 12.4 nM, CDK6: 9.9 nM	Shows selectivity toward CDK4 and CDK6	Specific for CDK4/6	Induces G1 arrest and cellular senescence	21 days on/ 7 days off	Neutropenia, leukopenia	18,53-55

Abbreviations: ATP: Adenosine triphosphate; CDK: Cyclin-dependent kinase; CDK4/6: Cyclin-dependent kinase 4 and 6; QTc: Corrected QT interval.

and survival strategies in response to ongoing therapy. These modifications may include DNA methylation, histone acetylation, or chromatin remodeling, which collectively promote tumor plasticity and resistance.[21,22]

3.3. Immune-mediated resistance mechanisms

Recent research has identified immune-mediated mechanisms as a significant contributor to acquired resistance against CDK4/6 inhibitors. These inhibitors have been shown to reprogram transcriptional activity in both tumor and immune cells, enhancing tumor immunogenicity and fostering an immune-enriched tumor microenvironment.[23] However, tumors can counteract these effects by upregulating immune checkpoint proteins, such as programmed cell death-ligand 1, and disrupting antigen presentation mediated by the major histocompatibility complex (MHC). These adaptations enable immune evasion and establish immunosuppressive conditions within the tumor microenvironment.[24,25] This resistance is further exacerbated by a decrease in regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), which play a pivotal role in maintaining anti-tumor immunity (Figure 1).[26] Paradoxically, while CDK4/6 inhibitors reduce Tregs and MDSCs, the resulting immune dysregulation can promote tumor adaptation. Tumors may also undergo phenotypic changes as a form of adaptive resistance, allowing them to evade immune surveillance even after an initial response to CDK4/6 inhibitor therapy.[23,25]

4. Novel biomarkers for predicting resistance

Circulating tumor DNA (ctDNA) analysis has emerged as a highly promising method for tracking treatment responses and identifying resistance mechanisms to CDK4/6 inhibitors. Sequential ctDNA assessments demonstrate high sensitivity (75%) and specificity (92%) in detecting disease progression, often identifying an increase in tumor DNA approximately three months before radiological evidence of progression.[27] This non-invasive approach is particularly valuable for monitoring treatment responses in challenging scenarios, such as bone metastases or small-sized target lesions, where traditional imaging modalities may have limitations.[27,28]

Compared to conventional serum tumor markers, such as carcinoembryonic antigen or cancer antigen 15-3, ctDNA analysis offers superior sensitivity for monitoring tumor response to CDK4/6 inhibitors.[27] Moreover, ctDNA has proven effective in detecting acquired genetic alterations associated with resistance to these inhibitors. For example, loss of function in the *RB* gene is strongly

associated with resistance, with *RB* mutations detected through ctDNA linked to poorer PFS in patients treated with palbociclib and fulvestrant.[27-29] Similarly, mutations in the Kirsten rat sarcoma viral oncogene homolog gene, detectable through ctDNA, are significantly associated with resistance to palbociclib, leading to earlier tumor relapse and reduced efficacy.[28] In addition, upregulation of *c-myc* has been observed in palbociclib-resistant cell lines, with clinical data showing that 5 – 9% of patients receiving abemaciclib developed new *MYC* genetic alterations during treatment.[29,30]

Longitudinal ctDNA analysis has identified other acquired mutations linked to resistance, including phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) and tumor protein p53 (*TP53*) alterations.[31] Impressively, rising levels of *PIK3CA*-mutated ctDNA were detected 4 – 17 months before imaging evidence of progression. Moreover, genomic complexity metrics such as blood tumor mutational burden derived from ctDNA have been shown to predict early progression during combined endocrine therapy and CDK4/6 inhibition.[32] The ctDNA marker is detailed in the schematic diagram Figure 2.

5. Strategies to overcome resistance

Combining CDK4/6 inhibitors with endocrine therapy is now the standard of care for advanced HR-positive/HER2-negative breast cancer, significantly improving PFS and OS compared to endocrine therapy alone.[4,8-11] The MONALEESA-2 trial exemplifies this, demonstrating prolonged PFS and improved OS when ribociclib was added to letrozole in patients with advanced HR-positive/HER2-negative breast cancer.[4]

To address resistance, combining CDK4/6 inhibitors with inhibitors of the PI3K/AKT/mechanistic target of the rapamycin (mTOR) pathway has emerged as a promising strategy, as this pathway is frequently activated in resistant tumors.[15] mTOR inhibitors, such as everolimus have shown potential in restoring sensitivity to endocrine therapy when co-administered with AIs.[33] Similarly, PI3K inhibitors, such as alpelisib, combined with fulvestrant, have demonstrated prolonged PFS in patients with PIK3CA-mutated advanced luminal breast cancer.[33]

Vemurafenib is a selective BRAF inhibitor that targets the B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) V600E mutation, effectively suppressing tumor growth by inhibiting the MAPK/extracellular signal-regulated kinase (ERK) signaling pathway, which is hyperactivated in BRAF-mutant cancers. However, resistance to vemurafenib often arises due to reactivation of the MAPK pathway through mechanisms such as cyclin D1 upregulation or alternative signaling pathways. Studies indicate that combining CDK4/6 inhibitors with vemurafenib can overcome resistance by targeting cyclin D1–CDK4/6 signaling, inducing cell cycle arrest, and delaying tumor progression.[34] Dabrafenib, another selective BRAF

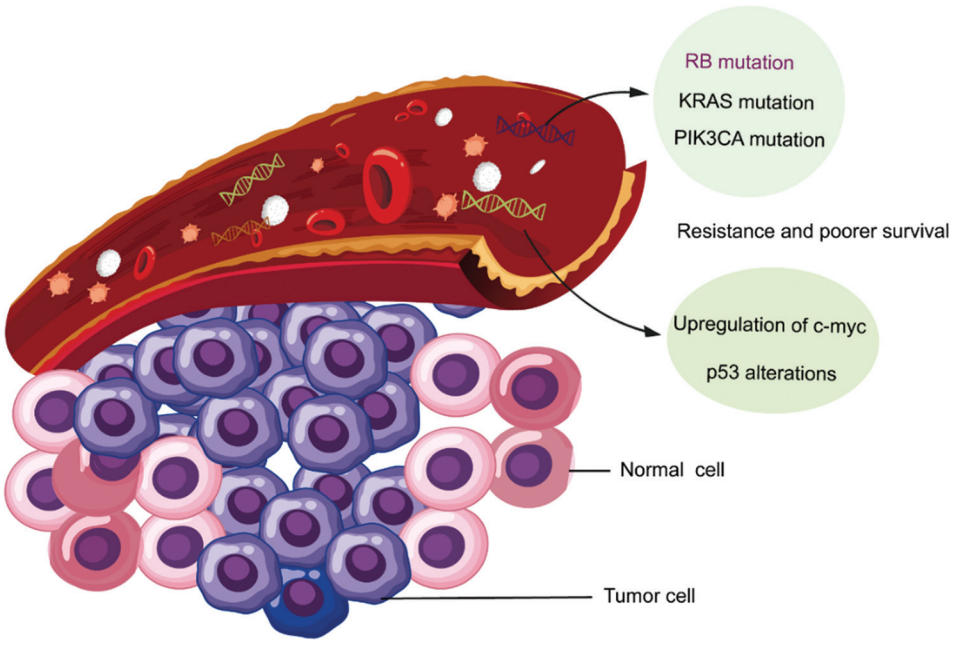


Figure 2. Detection of circulating tumor DNA as a predictive marker for resistance to CDK4/6 inhibitors.
Abbreviations: RB: Retinoblastoma; PIK3CA: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

inhibitor, blocks MAPK pathway activation by inhibiting mutated BRAF kinase activity (e.g., V600E and V600K mutations). Resistance mechanisms include upregulation of CDK4 and cyclin D1, which bypass CDK4/6 inhibition and reactivate cell cycle progression.[35] Pre-clinical models have demonstrated that combining dabrafenib with CDK4/6 inhibitors significantly reduces tumor growth by simultaneously targeting the MAPK and cell cycle pathways.[36] This dual inhibition prevents compensatory activation of cyclin D1–CDK4 signaling, which is a key driver of dabrafenib resistance.

Cobimetinib is a selective MEK1/2 inhibitor that blocks downstream ERK activation in the MAPK pathway. Resistance to cobimetinib often involves reactivation of ERK further downstream or activation of parallel pathways, such as PI3K/AKT. Pre-clinical studies suggest that combining cobimetinib with CDK4/6 inhibitors enhances anti-tumor efficacy by simultaneously targeting both MAPK and cell cycle pathways.[37] This combination is particularly effective in tumors with cyclin D1 amplification or p16INK4a loss. Trametinib is an allosteric MEK1/2 inhibitor that prevents phosphorylation and activation of ERK, effectively blocking MAPK signaling. Resistance mechanisms include reactivation of the MAPK pathway or compensatory activation of alternative survival pathways, such as PI3K/AKT/mTOR. The combination of trametinib with CDK4/6 inhibitors has demonstrated synergistic effects in pre-clinical models by inhibiting both MAPK and cell cycle pathways.[37,38] This dual inhibition restores sensitivity to trametinib-resistant cells by suppressing proliferation and inducing apoptosis.

An emerging approach involves combining CDK4/6 inhibitors with immunotherapy to enhance anti-tumor immunity. This combination increases T-cell infiltration and activation within the tumor microenvironment. Clinical trials are currently underway to assess the efficacy of this combination across various cancer types.[28]

Sequential therapeutic approaches systematically administer various treatments to optimize therapeutic efficacy and delay resistance. For example, the sequential application of CDK4/6 inhibitors and endocrine therapy may mitigate or postpone resistance development.[39] Novel CDK inhibitors are under development to address the limitations of existing CDK4/6 inhibitors by offering enhanced selectivity and potency. These inhibitors aim to demonstrate efficacy against tumors that have developed resistance.[14] In addition, dual inhibitors targeting multiple CDKs and other cell cycle regulatory kinases are being investigated as potential strategies to overcome resistance.[40]

A pivotal strategy involves identifying and targeting alternative pathways that sustain cell proliferation in resistant tumors. Inhibition of cyclin E-CDK2 signaling has demonstrated potential in overcoming resistance to CDK4/6 inhibitors in certain cases.[15] Other promising targets implicated in resistance include components of the MAPK pathway, AURKA, and cyclin E.[15,28] These strategies aim to prolong the effectiveness of CDK4/6 inhibitors and improve patient outcomes in resistant tumors. Continued research and clinical trials are expected to refine these methodologies and may reveal additional strategies to counteract resistance.

6. Treatment options following CDK4/6 inhibitor resistance

The selection of subsequent treatments after resistance to CDK4/6 inhibitors poses a significant challenge. Several strategies are being explored to optimize outcomes for patients with HR-positive/HER2-negative breast cancer. One common approach involves switching endocrine agents, such as transitioning from an AI to fulvestrant, or vice versa, which may provide clinical benefits in some cases.[39,41] In addition, the combination of exemestane and everolimus has shown efficacy in patients who progressed on CDK4/6 inhibitors, with median PFS ranging from 4.2 to 5.8 months across various studies.[42]

For targeted therapies, PI3K inhibitors, such as alpelisib combined with fulvestrant, have demonstrated a median PFS of 5.6 – 8.0 months in patients with *PIK3CA* mutations following CDK4/6 inhibitor treatment.[42,43] Similarly, AKT inhibitors, such as capivasertib plus fulvestrant have shown a median PFS of 5.5 months in AKT-altered tumors following CDK4/6 inhibitor treatment.[43] Emerging evidence also supports continuing the same CDK4/6 inhibitor while switching the endocrine partner in select cases.[42,44] Limited data suggest potential benefits in switching to a different CDK4/6 inhibitor, such as abemaciclib, after progression on palbociclib or ribociclib.[42]

Innovative therapies are under investigation for resistant breast cancer. Antibody-drug conjugates and poly ADP-ribose polymerase inhibitors have shown promise in clinical trials.[45,46] Chemotherapy remains an option for patients with a visceral crisis or rapid disease progression, although it is generally less favored due to its toxicity profiles.[42,47] Recent studies indicate that trastuzumab deruxtecan is a viable alternative for HR-positive, HER2-low, or HER2-ultra-low metastatic breast cancer patients who have received one or more lines of endocrine therapy. This agent has achieved a median PFS of 13.2 months, approximately five months longer than chemotherapy.[48]

The optimal sequencing of treatments after CDK4/6 inhibitor resistance continues to evolve. Treatment selection should be personalized based on prior therapies,

mutation status, and individual patient factors. Ongoing clinical trials are evaluating novel agents and combinations to further improve outcomes for patients with CDK4/6 inhibitor-resistant breast cancer.[45,46]

7. Future directions in research and clinical practice

Ongoing clinical trials are focused on developing novel strategies to overcome resistance to CDK4/6 inhibitors. These include combination therapies pairing CDK4/6 inhibitors with immune checkpoint inhibitors across various cancer types, leveraging the immunomodulatory effects of CDK4/6 inhibitors to enhance anti-tumor immunity.[23] As shown in Figure 1, CDK4/6 inhibitors increase MHC class I expression, reduce Tregs, and promote cytotoxic T lymphocyte activation, creating a tumor microenvironment conducive to immunotherapy.

In addition, researchers are exploring innovative dosing regimens, such as intermittent dosing or lead-in periods, to optimize efficacy while minimizing toxicity.[23] Expanding the scope of CDK4/6 inhibitors beyond advanced HR-positive/HER2-negative breast cancer is another area of interest. Trials are assessing their efficacy in diverse breast cancer subtypes and clinical scenarios, including early-stage disease and tumors with unique molecular profiles.[4]

In terms of resistance detection, emerging technologies like ctDNA analysis are being utilized for their non-invasive nature in detecting genetic alterations associated with resistance. ctDNA has proven effective in identifying *RB* mutations, *MYC* amplifications, and cyclin E overexpression – key markers of resistance to CDK4/6 inhibitors – often months before radiological progression.[27,30] This ability of early detection allows for more informed treatment decisions and personalized therapeutic strategies.[49] Genomic profiling is also being employed to uncover novel genetic alterations linked to resistance, including loss-of-function mutations in FAT atypical cadherin 1, which may contribute to bypassing CDK4/6 inhibition.[49]

Personalized medicine approaches are at the forefront of current research, with biomarker-driven treatment selection playing a pivotal role. Reliable biomarkers such as RB status or cyclin E protein expression levels are being investigated to predict response to CDK4/6 inhibitors.[12,49] Adaptive treatment strategies are also under investigation, which involve modifying therapy based on early molecular or clinical indicators of response or resistance. For example, switching to alternative therapies or adding targeted agents like PI3K/AKT/mTOR inhibitors may counter specific resistance mechanisms in tumors with pathway activation.[12,13] Furthermore, personalized combination therapies targeting multiple pathways are being developed based on individual tumor molecular profiles. For instance, combining CDK4/6 inhibitors with PI3K/AKT/mTOR pathway inhibitors has shown promise in overcoming resistance by addressing compensatory signaling pathways frequently activated in resistant tumors.

8. Conclusion

CDK4/6 inhibitors have revolutionized the treatment landscape for HR-positive/HER2-negative breast cancer, significantly improving PFS and OS. However, resistance to these therapies remains a critical clinical challenge. Ongoing research into resistance mechanisms, the development of predictive biomarkers to guide treatment, and novel therapeutic strategies offer hope for enhancing treatment efficacy and extending benefits to a broader range of patients.

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Conflict of interest

The authors declare they have no competing interests.

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