Clinical Application of CDK4/6 Inhibitors in Breast Cancer: Current Evidence, Resistance, and Future Directions

Yunfeng Wang*

Scientific Research Department, School of Medicine, the Sixth Affiliated Hospital of South China University of Technology (Nanhai District People's Hospital of Foshan), Foshan, 528200

Email: 202421058373@mail.scut.edu.cn

Abstract

Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors have transformed the management of hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2−) breast cancer by converting endocrine therapy into a more durable strategy of combined estrogen-receptor and cell-cycle suppression. Palbociclib, ribociclib, and abemaciclib are established treatments in advanced disease, while dalpiciclib has generated phase III evidence in predominantly Chinese populations. The clinical scope of the class has expanded from first- and later-line metastatic treatment to adjuvant therapy for selected patients with early-stage disease. Abemaciclib has produced sustained invasive disease-free survival and a statistically significant overall-survival benefit in node-positive, high-risk early breast cancer, whereas ribociclib has reduced recurrence across a broader stage II–III population. By contrast, adjuvant palbociclib trials were negative, demonstrating that efficacy in advanced disease cannot automatically be extrapolated as a class effect in the curative setting. More recent data have extended CDK4/6 inhibition to maintenance therapy for HR+/HER2+ advanced breast cancer and have refined strategies after prior CDK4/6 exposure through estrogen-receptor degraders and PI3K/AKT/mTOR-pathway inhibition. Nevertheless, intrinsic and acquired resistance involving RB1 loss, cyclin E–CDK2 activation, growth-factor signaling, and estrogen-receptor evolution remains a major limitation. Treatment selection therefore requires integration of disease tempo, previous endocrine exposure, molecular findings, comorbidity, toxicity susceptibility, access, and patient preference. This review summarizes the biological basis, pivotal clinical evidence, resistance mechanisms, safety management, and emerging precision approaches for CDK4/6 inhibitors in breast cancer. It emphasizes that the future value of these agents will depend less on indiscriminate expansion and more on their use in the appropriate patient, at the appropriate time, and within a biologically coherent treatment sequence.

Key words

Breast cancer, CDK4/6 inhibitors, Endocrine therapy, Drug resistance, Adjuvant therapy, Precision oncology

1. Introduction

Breast cancer is the most frequently diagnosed malignant tumor in women worldwide and comprises several biologically distinct diseases. Approximately two thirds of breast cancers express the estrogen receptor and/or progesterone receptor without overexpression or amplification of human epidermal growth factor receptor 2, and are therefore categorized as hormone receptor-positive, HER2-negative (HR+/HER2−) disease. This

subtype often follows a comparatively indolent course, but its apparent biological restraint should not be confused with low clinical risk. Recurrences may occur many years after primary treatment, and metastatic tumors commonly acquire resistance through continued estrogen-receptor signaling, activation of alternative survival pathways, and reprogramming of the cell-cycle machinery. Endocrine monotherapy can achieve meaningful control, yet adaptive restoration of proliferation frequently limits the depth and duration of response.

The development of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors directly addressed this connection between estrogen-receptor signaling and cell-cycle progression. By preventing retinoblastoma protein phosphorylation and restricting the transition from the G1 to the S phase, these agents delay tumor growth while generally preserving quality of life and postponing the need for cytotoxic chemotherapy. Palbociclib, ribociclib, and abemaciclib have established CDK4/6 inhibition as a treatment backbone for HR+/HER2− advanced breast cancer, and the China-developed agent dalpiciclib has confirmed the therapeutic principle in large phase III studies. Long-term follow-up has also clarified that individual agents do not produce identical outcomes in every disease setting, particularly when progression-free survival, overall survival, treatment duration, and toxicity are considered together.

The clinical role of CDK4/6 inhibitors is now broader and more complex than their initial use in metastatic HR+/HER2− disease. Abemaciclib and ribociclib have entered adjuvant treatment for selected patients with early breast cancer, whereas palbociclib failed to improve outcomes in two major adjuvant trials. The PATINA study established a maintenance strategy incorporating palbociclib for HR+/HER2+ advanced disease after induction therapy. Meanwhile, studies conducted after progression on a previous CDK4/6 inhibitor have produced heterogeneous results, and biomarker-directed combinations with oral estrogen-receptor degraders or PI3K-pathway inhibitors are reshaping treatment sequencing. This review critically summarizes the biological rationale, clinical evidence, resistance mechanisms, toxicity management, and future development of CDK4/6 inhibitors in breast cancer, with emphasis on the distinction between proven indications and promising but still investigational strategies.

2. Biological Rationale and Pharmacologic Characteristics

CDK4 and CDK6 are serine/threonine kinases that translate extracellular mitogenic signals into cell-cycle progression. Growth-factor and hormone-receptor signaling increases the abundance and activity of D-type cyclins, which bind to CDK4/6 and promote phosphorylation of the retinoblastoma protein (RB). Hypophosphorylated RB restrains E2F transcription factors; its progressive phosphorylation releases E2F and activates genes required for DNA synthesis, thereby enabling the G1/S transition. The cyclin D–CDK4/6–RB–E2F axis is therefore a central checkpoint between proliferative signaling and genome duplication. Selective CDK4/6 inhibition maintains RB in a growth-suppressive state and causes predominantly reversible G1 arrest in tumors that retain functional RB[1–2].

The pathway is particularly relevant to hormone receptor-positive breast cancer. Estrogen-receptor transcription promotes CCND1 expression and supports formation of active cyclin D–CDK4/6 complexes, while cell-cycle signaling can in turn reinforce estrogen-receptor function. Endocrine therapy reduces estrogen-dependent growth but may leave residual or adaptively restored CDK4/6 activity, whereas a CDK4/6 inhibitor blocks a major downstream convergence point. This complementary biology explains why combined therapy is substantially more effective than endocrine monotherapy for most patients with advanced HR+/HER2− disease. The requirement for an intact RB checkpoint also explains why RB1 loss, although uncommon before treatment, can confer strong resistance when it emerges under selective pressure.

CDK4/6 inhibition may exert effects beyond short-term cell-cycle arrest. Prolonged exposure can induce senescence-like states, alter tumor metabolism and DNA-damage responses, and influence chromatin organization. Preclinical studies also suggest enhanced antigen presentation, suppression of regulatory T-cell proliferation, and changes in inflammatory signaling within the tumor microenvironment. These observations provide a rationale for combinations with immune, DNA-damage, and pathway-directed therapies. However, most noncanonical effects have not yet yielded validated biomarkers for routine drug selection, and potentially increased inflammatory toxicity remains a concern in some experimental combinations. Clinical decisions should therefore continue to rest primarily on disease subtype and prospective outcome data rather than on unconfirmed mechanistic extrapolation.

Palbociclib, ribociclib, and abemaciclib share the same core targets but differ in kinase selectivity, pharmacokinetics, dosing schedule, and adverse-event profile. Palbociclib and ribociclib are usually administered for 21 consecutive days followed by 7 days off treatment in a 28-day cycle. Their principal dose-limiting toxicity is neutropenia, which generally reflects reversible cell-cycle arrest of marrow precursors rather than irreversible precursor-cell destruction. Abemaciclib

has relatively greater activity against CDK4 and can be given continuously twice daily; diarrhea, fatigue, venous thromboembolism, and hepatic abnormalities are comparatively prominent. Ribociclib can prolong the corrected QT interval and therefore requires electrocardiographic, electrolyte, and drug-interaction assessment. Dalpiciclib is also given intermittently and is associated mainly with neutropenia and leukopenia.

These pharmacologic differences prevent the class from being treated as completely interchangeable. Ribociclib has shown a notably consistent overall-survival benefit across several metastatic phase III trials, whereas palbociclib did not achieve a statistically significant overall-survival improvement in PALOMA-2 despite a large progression-free survival gain. Abemaciclib combines metastatic activity with positive adjuvant evidence, but its gastrointestinal and thromboembolic toxicities may be problematic in susceptible patients. Practical selection should integrate the strength of survival data, treatment setting, previous endocrine exposure, disease burden, organ function, electrocardiographic risk, baseline bowel function, concomitant medication, monitoring feasibility, access, and patient preference. Cross-trial numerical comparisons cannot substitute for direct randomized comparisons, because trial populations, endocrine partners, follow-up, and subsequent therapies differ substantially.

3. Treatment of HR+/HER2− Advanced Breast Cancer

For patients with HR+/HER2− unresectable locally advanced or metastatic breast cancer who do not have a visceral crisis, a CDK4/6 inhibitor combined with endocrine therapy is the preferred initial systemic approach in most contemporary treatment algorithms. Visceral metastasis alone does not define visceral crisis. The clinically relevant distinction is whether organ function is rapidly deteriorating and an immediate, high-probability cytoreductive response is required. In the absence of such failure, CDK4/6-based endocrine therapy can produce high response rates, durable disease control, delayed chemotherapy, and maintained quality of life even in patients with liver or lung metastases.

PALOMA-2 established palbociclib plus letrozole as an effective initial treatment in postmenopausal patients. Median progression-free survival was substantially longer with the combination than with letrozole alone, although the final overall-survival analysis did not cross the prespecified threshold for statistical significance[3–4]. PALOMA-3 extended the evidence to endocrine-resistant disease: palbociclib plus fulvestrant improved progression-free survival after previous endocrine therapy and produced a clinically relevant, although statistically nondefinitive, overall-survival trend in long-term follow-up[5]. These results established the value of palbociclib in both endocrine-sensitive and endocrine-resistant settings, while illustrating that a robust progression-free survival effect does not inevitably translate into a statistically significant overall-survival result. Subsequent therapy, crossover, treatment exposure, population heterogeneity, and statistical power all influence the survival endpoint.

The MONALEESA program provides particularly consistent survival evidence for ribociclib. In MONALEESA-2, ribociclib plus letrozole extended median overall survival from 51.4 to 63.9 months in postmenopausal patients receiving first-line treatment[6]. MONALEESA-3 demonstrated an overall-survival benefit when ribociclib was combined with fulvestrant in first- or second-line treatment[7]. MONALEESA-7 confirmed improved survival in premenopausal or perimenopausal patients treated with ovarian suppression and endocrine therapy[8]. The reproducibility of benefit across menopausal status and endocrine partners is an important reason to favor ribociclib when its monitoring requirements and cardiac, hepatic, and interaction risks are acceptable. Nevertheless, the MONALEESA trials enrolled different populations and should not be compared numerically as if they constituted a head-to-head evaluation against other CDK4/6 inhibitors.

Abemaciclib has also generated evidence across endocrine-resistant and initial metastatic treatment. In MONARCH 2, abemaciclib plus fulvestrant improved both progression-free and overall survival after progression during prior endocrine therapy; extended follow-up reported a median overall survival of approximately 45.8 months versus 37.3 months with fulvestrant alone[9]. In MONARCH 3, abemaciclib plus a nonsteroidal aromatase inhibitor produced a major progression-free survival benefit and prolonged median overall survival by approximately 15 months, although the final statistical test did not reach the prespecified boundary[10]. Continuous dosing and substantial response activity make abemaciclib attractive when rapid but endocrine-based tumor reduction is desired. Its modest penetration into the central nervous system is biologically interesting, but intracranial response rates in dedicated studies have been limited; the presence of brain metastases alone does not establish abemaciclib as an absolute preferred agent.

Dalpiciclib has broadened the evidence base for Asian populations. In DAWNA-1, dalpiciclib plus fulvestrant increased median progression-free survival from 7.2 to 15.7 months after progression on previous endocrine therapy[11]. DAWNA-2 evaluated patients without previous systemic treatment for advanced

disease and reported median progression-free survival of 30.6 months with dalpiciclib plus letrozole or anastrozole versus 18.2 months with the endocrine partner alone[12]. Neutropenia and leukopenia were the most frequent high-grade toxicities. These trials confirm that dual suppression of estrogen-receptor signaling and cell-cycle progression is effective in Chinese patients, but mature overall-survival data, direct comparisons among drugs, and longer real-world safety observation remain important unmet needs.

The endocrine partner should be chosen according to previous treatment and the pattern of endocrine sensitivity. A nonsteroidal aromatase inhibitor is appropriate for many patients with de novo metastatic disease, recurrence after a prolonged treatment-free interval, or no evidence of aromatase-inhibitor resistance. Fulvestrant or an appropriate oral estrogen-receptor-directed agent may be preferred when relapse occurs during adjuvant aromatase-inhibitor therapy or shortly after its completion. Premenopausal and perimenopausal women require ovarian-function suppression when an aromatase inhibitor or fulvestrant is used. Men may also require a gonadotropin-releasing hormone agonist depending on the endocrine partner. Older adults can derive similar relative benefit, but marrow reserve, frailty, nutrition, polypharmacy, cognition, transportation, and adherence deserve explicit assessment; chronological age alone should neither exclude combined therapy nor obscure a high vulnerability to treatment burden.

Whether every patient must receive a CDK4/6 inhibitor in the first metastatic line has been debated. The SONIA trial compared immediate use of a CDK4/6 inhibitor with an aromatase inhibitor followed by fulvestrant at progression against deferred use with fulvestrant in the second line. The primary endpoint of progression-free survival after two lines was not significantly different, whereas immediate use increased total CDK4/6 exposure and high-grade adverse events[13]. Most participants received palbociclib, so the findings should not be interpreted as negating the overall-survival evidence for ribociclib or abemaciclib, nor should they be generalized to patients with high burden, short disease-free interval, or aggressive biology. A reasonable clinical interpretation is that combined treatment remains preferred for most suitable patients, while carefully selected individuals with exceptionally indolent disease, substantial comorbidity, restricted access, or a strong preference to minimize treatment intensity may discuss endocrine monotherapy and deferred CDK4/6 inhibition.

Clinical benefit must be evaluated beyond radiographic progression. The ability to delay chemotherapy, preserve daily function, control symptoms, and maintain an acceptable treatment routine is central to the value of CDK4/6-based therapy. At the same time, prolonged oral treatment can impose cumulative laboratory visits, medication costs, fatigue, gastrointestinal symptoms, restrictions from drug interactions, and anxiety around monitoring. Shared decision-making should therefore include absolute expected benefit, the evidentiary strength of each drug in the relevant setting, the practical monitoring schedule, and the likely effect of toxicity on work and family responsibilities. Dose modification is an integral component of treatment and should not be viewed as therapeutic failure.

4. Application in Early Breast Cancer

The adjuvant setting differs fundamentally from metastatic disease because most patients have no radiographically detectable tumor and many are already cured by surgery, radiotherapy, chemotherapy when indicated, and endocrine therapy. An effective adjuvant CDK4/6 strategy must eradicate or suppress microscopic residual disease sufficiently to improve long-term outcomes after the inhibitor has been discontinued. The tolerance for toxicity and cost is correspondingly lower, and absolute recurrence risk is more important than relative risk reduction. Trial results have demonstrated a strong dependence on the selected agent, treatment duration, and enrolled risk population.

The monarchE trial enrolled patients with HR+/HER2−, node-positive early breast cancer and high clinicopathologic risk, adding two years of abemaciclib to standard endocrine therapy. High-risk eligibility was defined principally by at least four positive axillary lymph nodes, or one to three positive nodes accompanied by grade 3 disease or a primary tumor of at least 5 cm. With a median follow-up of 76.2 months, abemaciclib reduced the risk of death by 15.8%; estimated seven-year overall survival was 86.8% with abemaciclib and 85.0% with endocrine therapy alone. Seven-year invasive disease-free survival was 77.4% versus 70.9%, indicating a carryover benefit after completion of the two-year course[14]. Abemaciclib is therefore the adjuvant CDK4/6 inhibitor with mature, statistically positive overall-survival evidence in this high-risk population. The absolute survival difference remains modest, however, and must be weighed against baseline recurrence risk, two years of treatment, diarrhea, fatigue, thromboembolic risk, and monitoring.

NATALEE evaluated three years of ribociclib at a reduced dose of 400 mg, given for 21 days of each 28-day cycle, together with a nonsteroidal aromatase inhibitor. The trial included stage II and III HR+/HER2−

early breast cancer and therefore covered a broader population than monarchE, including selected patients with high-risk node-negative disease. Five-year follow-up showed invasive disease-free survival of approximately 85.5% with ribociclib versus 81.0% with endocrine therapy alone, corresponding to a hazard ratio of approximately 0.72; overall survival favored ribociclib but had not yet reached a definitive statistical conclusion at that analysis[15–16]. The broader eligibility range increases the number of potentially treatable patients, but a three-year course, electrocardiographic and laboratory surveillance, treatment discontinuation, and cumulative cost must be incorporated into individualized decisions.

The positive results of monarchE and NATALEE contrast with the adjuvant palbociclib experience. PALLAS tested two years of palbociclib with endocrine therapy in stage II–III disease and did not improve invasive disease-free survival[17]. PENELOPE-B enrolled patients with residual high-risk disease after neoadjuvant chemotherapy and tested one year of palbociclib, again without long-term benefit[18]. Differences in drug pharmacology, schedule, exposure, discontinuation, duration, population risk, and the biology of microscopic residual disease have been proposed, but no single explanation is sufficient. These findings show that metastatic efficacy cannot be directly extrapolated as an adjuvant class effect. Palbociclib should not be used routinely as adjuvant therapy solely because it is active in advanced disease.

No head-to-head trial establishes abemaciclib or ribociclib as universally superior when a patient is eligible for both. Abemaciclib offers a shorter two-year course and mature overall-survival evidence in a node-positive, high-risk population; ribociclib has demonstrated recurrence reduction across a broader stage II–III population, including selected node-negative disease, but requires three years of treatment and has different monitoring requirements. Selection should consider the exact recurrence-risk features, lymph-node status, endocrine partner, gastrointestinal vulnerability, thromboembolic history, QT-prolongation risk, liver function, concomitant medication, and regional regulatory indication. In lower-risk early disease, standard endocrine therapy remains the foundation, and a small absolute benefit may not justify additional toxicity and burden.

Neoadjuvant studies have consistently shown that combining a CDK4/6 inhibitor with endocrine therapy can rapidly suppress Ki-67 and increase the proportion of tumors achieving complete cell-cycle arrest. This pharmacodynamic effect confirms potent antiproliferative activity, but pathologic complete response has not improved in proportion to the reduction in Ki-67, and definitive long-term event data are limited. HR+/HER2− tumors have a lower pathologic complete response rate and a weaker relationship between pathologic complete response and survival than triple-negative or HER2-positive disease. Short-term biomarker suppression should therefore not be equated with curative benefit. Neoadjuvant CDK4/6 inhibition remains primarily a clinical-trial strategy or an individualized research-oriented option for selected patients unsuitable for chemotherapy, rather than a replacement for standard risk-adapted neoadjuvant care.

5. Expansion to Other Subtypes and Treatment Settings

The biological boundary of CDK4/6 inhibition is extending beyond HER2-negative disease. HR+/HER2+ breast cancers can be driven simultaneously by estrogen-receptor, HER2, and cyclin D–CDK4/6 signaling, and reciprocal pathway activation may allow escape from dual HER2 and endocrine blockade. In PATINA, patients with HR+/HER2+ locally advanced or metastatic breast cancer who had not progressed after induction chemotherapy with trastuzumab, with or without pertuzumab, were assigned to maintenance anti-HER2 and endocrine therapy with or without palbociclib. Adding palbociclib reduced the risk of progression or death by approximately 24%, while overall-survival data remained immature[19]. In June 2026, the United States Food and Drug Administration approved palbociclib with trastuzumab, with or without pertuzumab, and endocrine therapy for this defined maintenance setting[27].

The PATINA result should be interpreted according to its treatment sequence. It supports palbociclib after successful induction in patients without progression, not indiscriminate addition of a CDK4/6 inhibitor to every HER2-positive regimen. It does not replace established HER2-directed induction therapy in patients requiring prompt tumor control, nor does it define treatment for HER2-positive, hormone receptor-negative disease. The study nevertheless validates simultaneous control of HER2, estrogen-receptor, and cell-cycle signaling and creates a clinically important chemotherapy-sparing maintenance option for appropriately selected patients.

In triple-negative breast cancer, potential sensitivity has been proposed for RB-intact tumors, androgen receptor-positive disease, and the luminal androgen receptor molecular subtype. Combinations with androgen-receptor blockade, PI3K-pathway inhibition, immunotherapy, or selected cytotoxic agents are biologically plausible. However, triple-negative breast cancer is highly heterogeneous, and frequent RB loss, cyclin E–CDK2 activation, and rapid proliferation can produce intrinsic resistance. No CDK4/6 inhibitor

currently has an established routine indication in this subtype. Use should remain restricted to biomarker-informed clinical trials rather than extrapolated from the success observed in HR+/HER2− disease.

Other investigational settings include central nervous system disease, oligometastatic treatment, and combinations with radiotherapy. Abemaciclib reaches measurable concentrations in the central nervous system, but clinical intracranial response has been modest and local therapy remains central for symptomatic or threatening brain metastases. Concurrent administration with radiotherapy may enhance cell-cycle arrest and radiosensitivity but can also increase marrow, gastrointestinal, skin, or pulmonary toxicity depending on the irradiated field. Because prospective safety evidence is limited, temporary interruption and multidisciplinary planning are often appropriate. These applications illustrate the difference between pharmacologic plausibility and a clinically validated indication.

6. Resistance and Therapeutic Strategies After Progression

Intrinsic and acquired resistance limits the durability of CDK4/6 inhibition. RB1 loss or functional inactivation removes the principal downstream substrate and permits proliferation independent of CDK4/6-mediated RB phosphorylation. Upregulation or amplification of CCNE1, activation of cyclin E–CDK2, amplification of CDK6 or AURKA, loss of FAT1, and activation of Hippo–YAP/TAZ signaling can restore the G1/S transition. Resistance may also arise through FGFR1, HER2, RAS–MAPK, or PI3K–AKT–mTOR signaling, which preserves proliferative and survival outputs despite CDK4/6 blockade. ESR1 mutations primarily confer resistance to aromatase inhibition, but they weaken the endocrine component of a combination and can thereby contribute indirectly to clinical progression[2,20].

Resistance is rarely governed by a single static alteration. Different metastatic lesions may harbor distinct clones, and treatment pressure changes their relative abundance over time. A tissue biopsy samples one site at one moment, whereas circulating tumor DNA (ctDNA) can capture a broader but still incomplete representation of tumor evolution. At progression, molecular testing is most useful when it identifies an actionable mechanism—such as ESR1, PIK3CA, AKT1, PTEN, BRCA1/2, or PALB2 alteration—or a phenotypic shift in HER2 expression that changes the next therapeutic option. It is less useful when interpreted as a binary test of whether all future CDK4/6 inhibition will or will not work.

Continuation of the same CDK4/6 inhibitor after progression is not supported as a universal strategy. In PACE, continuing palbociclib with fulvestrant after progression on a previous CDK4/6 inhibitor and aromatase inhibitor did not improve progression-free survival compared with fulvestrant alone[21]. By contrast, the phase II MAINTAIN trial changed the endocrine partner and used ribociclib, producing a progression-free survival improvement, while the phase III postMONARCH trial found that abemaciclib plus fulvestrant reduced progression risk after prior CDK4/6 therapy, although the absolute median progression-free survival difference was limited[22–23]. These heterogeneous results suggest that switching the inhibitor and endocrine partner can benefit a subset, but efficacy depends on previous drug, duration of response, endocrine sensitivity, and resistance mechanism.

Oral selective estrogen-receptor degraders are changing post-CDK4/6 sequencing. In EMBER-3, imlunestrant plus abemaciclib significantly prolonged progression-free survival compared with imlunestrant alone in a population in which most patients had previously received a CDK4/6 inhibitor; an updated analysis reported median progression-free survival of approximately 10.9 and 5.5 months, respectively[24]. Imlunestrant monotherapy is also relevant for ESR1-mutated disease. The combination supports renewed CDK4/6 blockade when paired with more effective estrogen-receptor degradation in selected patients, but it should not be interpreted as proof that resistance to every member of the class can be reversed merely by changing the endocrine partner.

Targeted inhibition of PI3K/AKT/mTOR signaling is another central strategy. INAVO120 enrolled patients with PIK3CA-mutated HR+/HER2− advanced disease that recurred during or within 12 months after completion of adjuvant endocrine therapy and who had not received systemic therapy for advanced disease. Inavolisib, palbociclib, and fulvestrant significantly improved progression-free survival compared with placebo, palbociclib, and fulvestrant[25]. This regimen demonstrates the value of simultaneously suppressing mutant PI3K signaling, estrogen-receptor activity, and CDK4/6 at the point of early endocrine-resistant metastatic relapse. Molecular selection is mandatory, and hyperglycemia, stomatitis, diarrhea, rash, and marrow suppression require active prevention and monitoring.

VIKTORIA-1 evaluated the pan-PI3K/mTOR inhibitor gedatolisib after progression on endocrine therapy in metastatic disease. In patients without a detected PIK3CA mutation, gedatolisib plus fulvestrant and palbociclib achieved a median progression-free survival of 9.3 months compared with 2.0 months for

fulvestrant alone; gedatolisib plus fulvestrant without palbociclib also outperformed the control. The U.S. Food and Drug Administration approved gedatolisib with fulvestrant, with or without palbociclib, in July 2026 for the specified HR+/HER2− locally advanced or metastatic setting[28]. The result shows that coordinated pathway inhibition can overcome resistance in selected tumors, but it does not establish that every patient should continue CDK4/6 inhibition after progression. The incremental contribution of palbociclib, previous exposure patterns, overall survival, toxicity, and access must all be considered.

Serial ctDNA monitoring offers a potential means of intervening before radiographic progression. SERENA-6 screened patients receiving first-line aromatase inhibition plus a CDK4/6 inhibitor and, when an ESR1 mutation emerged in ctDNA without radiographic progression, randomized them to switch the aromatase inhibitor to camizestrant or continue it while maintaining the same CDK4/6 inhibitor. Early switching significantly improved progression-free survival from randomization, with a hazard ratio of approximately 0.44[26]. However, the trial did not directly compare the complete strategies of mutation-triggered switching versus treatment change at radiographic progression followed by an effective ESR1-directed therapy. Overall survival, patient-reported outcomes, testing logistics, false-negative results, and the cardiac safety of some combinations remain relevant uncertainties. Molecular progression is therefore an important research concept but should not automatically mandate treatment change without regulatory and guideline support.

Choice after progression should be driven by clinical urgency and tumor biology. A patient with slow, asymptomatic progression after prolonged benefit may reasonably receive a new endocrine partner with a targeted agent selected by molecular testing, whereas rapidly progressive visceral disease, functional organ compromise, or broad endocrine resistance may require an antibody–drug conjugate or chemotherapy. Germline BRCA1/2 or PALB2 alterations may support PARP inhibition in appropriate settings; low HER2 expression can affect antibody–drug conjugate eligibility; and PIK3CA, AKT1, PTEN, or ESR1 alterations can direct pathway-specific treatment. The goal is not to preserve CDK4/6 inhibition at all costs, but to construct a sequence that remains biologically active while preserving future options.

7. Biomarkers, Safety, and Treatment Individualization

No routinely available biomarker reliably predicts superior response to one CDK4/6 inhibitor among otherwise eligible HR+/HER2− tumors. Hormone-receptor and HER2 status remain the basic selection criteria. Functional RB is mechanistically important, but pretreatment RB1 loss is relatively uncommon, assays are not standardized, and routine exclusion based on RB testing has not been established. High Ki-67, CCND1 amplification, p16 loss, PIK3CA mutation, or ESR1 mutation cannot alone select or exclude a CDK4/6 inhibitor. Ki-67 is primarily prognostic and reflects proliferation; it is no longer a mandatory condition for the adjuvant abemaciclib indication. Molecular testing becomes especially valuable after progression because it can identify a target for the next line rather than because it gives a simple answer about continued class sensitivity.

Hematologic toxicity is most prominent with palbociclib, ribociclib, and dalpiciclib. Neutropenia often appears early, but febrile neutropenia is uncommon. Management usually consists of complete blood count monitoring, temporary interruption, and dose reduction rather than routine prophylactic granulocyte colony-stimulating factor. The cyclic schedule permits marrow recovery, and dose reduction has generally not eliminated treatment benefit in clinical and real-world analyses. Persistent anemia or thrombocytopenia, recurrent infection, or unexpectedly prolonged cytopenia should prompt evaluation for other causes, including marrow involvement, nutritional deficiency, concomitant medication, or an underlying hematologic disorder.

Abemaciclib-associated diarrhea typically begins during the first treatment weeks and can become clinically consequential if education and early intervention are inadequate. Patients should receive antidiarrheal medication instructions before treatment and should begin hydration, dietary modification, and loperamide promptly when symptoms occur. Temporary interruption and stepwise dose reduction are appropriate for persistent or severe events. Fatigue, reduced appetite, and nausea can compound dehydration and functional decline, particularly in older adults. Venous thromboembolism is uncommon but more frequent than with endocrine therapy alone; risk history, new limb swelling, chest pain, or dyspnea requires timely assessment. Liver enzymes should be monitored, especially during early cycles.

Ribociclib requires attention to corrected QT interval, electrolytes, liver function, and interacting medication. Baseline and early-treatment electrocardiography should be performed according to the prescribing information, and hypokalemia, hypomagnesemia, or hypocalcemia should be corrected. Concomitant drugs that substantially prolong QT or increase ribociclib exposure should be avoided when possible. All major CDK4/6 inhibitors are metabolized predominantly through CYP3A; strong CYP3A

inhibitors can raise exposure and toxicity, while strong inducers can reduce efficacy. Medication reconciliation should include anti-infectives, antiepileptics, cardiovascular agents, herbal products, supplements, and grapefruit-containing foods.

All CDK4/6 inhibitors have been associated with uncommon but potentially severe interstitial lung disease or pneumonitis. New cough, dyspnea, fever, or hypoxemia requires prompt interruption and diagnostic evaluation for infection, tumor progression, pulmonary embolism, cardiac disease, and drug-induced lung injury. Severe cases require permanent discontinuation and appropriate treatment. Abemaciclib can inhibit renal tubular creatinine transport, increasing serum creatinine without a true reduction in glomerular filtration. Cystatin C or another renal assessment may help when clinical findings are discordant. These examples underscore that laboratory abnormalities should be interpreted mechanistically rather than managed solely by numerical thresholds.

Individualization is especially important in early breast cancer, where the patient may already be cured. The discussion should express benefit in absolute terms and relate it to the individual's recurrence risk rather than presenting only a hazard ratio. In metastatic disease, the balance includes tumor response, symptom control, treatment-free time from chemotherapy, quality of life, convenience, monitoring, and the ability to transition to later therapies. Clinical trials generally show maintenance of global quality of life, but maintenance does not mean absence of burden. Diarrhea, fatigue, neutropenia, frequent visits, out-of-pocket cost, and work disruption can materially change a patient's evaluation of benefit.

Adherence deserves the same attention as drug selection. Oral therapy shifts daily responsibility to the patient and can conceal missed doses, unsupervised treatment interruptions, or use of interacting nonprescription products. Written dosing calendars, early nurse or pharmacist contact, rapid access for toxicity questions, and proactive dose adjustment can sustain exposure more effectively than insisting on the nominal starting dose. In both early and advanced disease, an evidence-based lower dose that a patient can continue is generally preferable to repeated severe toxicity followed by permanent discontinuation.

8. Future Perspectives

Future research is moving from broad expansion of CDK4/6 use toward more precise definition of who benefits, when treatment should begin, and what should follow progression. In early breast cancer, longer overall-survival follow-up and high-quality real-world studies are needed to determine the net benefit of two or three years of therapy across different absolute-risk groups. Integrated models combining clinicopathologic features, genomic information, and ctDNA detection of molecular residual disease may eventually refine escalation and de-escalation. Such models must be prospectively validated, because an analytically detectable signal does not by itself prove that earlier intervention improves survival.

In advanced disease, trials should evaluate complete treatment strategies rather than only endpoints measured from a biomarker-defined switching time. More selective CDK4 inhibitors may preserve efficacy while reducing CDK6-related marrow toxicity, and agents that inhibit CDK2 may address cyclin E-mediated escape. Combinations targeting RB-bypass mechanisms, estrogen-receptor degradation, PI3K/AKT/mTOR signaling, and growth-factor pathways are likely to be increasingly biomarker defined. The optimal sequence with antibody–drug conjugates is also unresolved. Concurrent immune combinations remain mechanistically attractive but require caution because hepatotoxicity, pulmonary toxicity, and the responsive population have not been adequately defined.

Patient-centered implementation will be as important as drug development. Broader use in the curative setting magnifies disparities in genomic testing, electrocardiographic and laboratory monitoring, medication access, and supportive care. Trials should report treatment discontinuation, dose intensity, financial toxicity, work impact, and patient-reported function in addition to conventional efficacy endpoints. Comparative-effectiveness research may clarify whether the biologically most intensive regimen is also the most sustainable option for a given patient and health system.

9. Conclusion

CDK4/6 inhibitors have changed the treatment paradigm of breast cancer. In HR+/HER2− advanced disease, combination with endocrine therapy remains the foundation for most patients without visceral crisis. Ribociclib, abemaciclib, palbociclib, and dalpiciclib all improve disease control in defined populations, although the strength of overall-survival evidence and the toxicity profile differ. In high-risk early breast cancer, abemaciclib and ribociclib have established positive adjuvant strategies through monarchE and NATALEE, with mature overall-survival benefit currently demonstrated for abemaciclib, whereas adjuvant palbociclib has not improved outcomes. In HR+/HER2+ advanced disease, PATINA has created a new maintenance application after induction therapy.

Progression on a CDK4/6 inhibitor should prompt reassessment rather than automatic continuation. Switching the inhibitor, strengthening estrogen-receptor degradation, or adding PI3K/AKT/mTOR-pathway inhibition can benefit selected patients, but the choice must reflect prior exposure, disease tempo, actionable alterations, toxicity, and the quality of prospective evidence. As long-term follow-up, liquid biopsy, and new pathway-directed therapies mature, the clinical value of CDK4/6 inhibition will increasingly depend on using the appropriate agent for the appropriate patient at the appropriate point in the treatment sequence.

References

[1] Sherr CJ, Roberts JM. CDK inhibitors: positive and negative regulators of G1-phase progression. Genes & Development. 1999;13(12):1501-1512.

[2] Goel S, Bergholz JS, Zhao JJ. Targeting CDK4 and CDK6 in cancer. Nature Reviews Cancer. 2022;22(6):356-372.

[3] Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. New England Journal of Medicine. 2016;375(20):1925-1936.

[4] Slamon DJ, Neven P, Chia S, et al. Overall survival with palbociclib plus letrozole in advanced breast cancer. Journal of Clinical Oncology. 2024;42(9):994-1000.

[5] Cristofanilli M, Rugo HS, Im SA, et al. Overall survival with palbociclib and fulvestrant in women with HR+/HER2− advanced breast cancer: updated exploratory analyses of PALOMA-3. Clinical Cancer Research. 2022;28(16):3433-3442.

[6] Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall survival with ribociclib plus letrozole in advanced breast cancer. New England Journal of Medicine. 2022;386(10):942-950.

[7] Slamon DJ, Neven P, Chia S, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. New England Journal of Medicine. 2020;382(6):514-524.

[8] Lu YS, Im SA, Colleoni M, et al. Updated overall survival of ribociclib plus endocrine therapy versus endocrine therapy alone in pre- and perimenopausal patients with HR+/HER2− advanced breast cancer in MONALEESA-7. Clinical Cancer Research. 2022;28(5):851-859.

[9] Neven P, Rugo HS, Tolaney SM, et al. Final overall survival results from MONARCH 2. JCO Oncology Advances. 2025. doi:10.1200/OA-25-00052.

[10] Goetz MP, Toi M, Campone M, et al. Abemaciclib plus a nonsteroidal aromatase inhibitor as initial therapy for HR+/HER2− advanced breast cancer: final overall survival results of MONARCH 3. Annals of Oncology. 2024;35(8):718-727.

[11] Xu B, Zhang Q, Zhang P, et al. Dalpiciclib or placebo plus fulvestrant in HR+/HER2− advanced breast cancer: a randomized phase 3 trial. Nature Medicine. 2021;27(11):1904-1909.

[12] Zhang P, Zhang Q, Tong Z, et al. Dalpiciclib plus letrozole or anastrozole versus placebo plus letrozole or anastrozole in HR+/HER2− advanced breast cancer (DAWNA-2). Lancet Oncology. 2023;24(6):646-657.

[13] Sonke GS, Hart LL, Campone M, et al. Early versus deferred use of CDK4/6 inhibitors in advanced breast cancer: the phase 3 SONIA trial. Nature. 2024;636:474-480.

[14] Johnston S, Martin M, O'Shaughnessy J, et al. Overall survival with abemaciclib in early breast cancer. Annals of Oncology. 2026;37(2):155-165.

[15] Slamon D, Lipatov O, Nowecki Z, et al. Ribociclib plus endocrine therapy in early breast cancer. New England Journal of Medicine. 2024;390(12):1080-1091.

[16] Crown J, Stroyakovskii D, Yardley DA, et al. Adjuvant ribociclib plus nonsteroidal aromatase inhibitor therapy in patients with HR+/HER2− early breast cancer: 5-year follow-up of NATALEE efficacy outcomes and updated overall survival. ESMO Open. 2025. doi:10.1016/j.esmoop.2025.105858.

[17] Gnant M, Dueck AC, Frayer-Smith K, et al. Adjuvant palbociclib for early breast cancer: the PALLAS trial results. Journal of Clinical Oncology. 2022;40(3):282-293.

[18] Loibl S, Marmé F, Martin M, et al. Palbociclib for residual high-risk invasive HR-positive and HER2-negative early breast cancer: the PENELOPE-B trial. Journal of Clinical Oncology. 2021;39(14):1518-1530.

[19] Metzger O, et al. Palbociclib for hormone-receptor-positive, HER2-positive advanced breast cancer. New England Journal of Medicine. 2026. doi:10.1056/NEJMoa2511218.

[20] Wander SA, Cohen O, Gong X, et al. The genomic landscape of intrinsic and acquired resistance to cyclin-dependent kinase 4/6 inhibitors in patients with HR+/HER2− metastatic breast cancer. Cancer Discovery. 2020;10(8):1174-1193.

[21] Mayer EL, Ren Y, Wagle N, et al. Fulvestrant, palbociclib, and avelumab after progression on cyclin-dependent kinase 4/6 inhibitor therapy in HR+/HER2− metastatic breast cancer: the PACE trial. Journal of Clinical Oncology. 2024;42(17):2050-2060.

[22] Kalinsky K, Accetta R, Burenson A, et al. Randomized phase II trial of endocrine therapy with or without ribociclib after progression on CDK4/6 inhibition in HR+/HER2− metastatic breast cancer: MAINTAIN trial. Journal of Clinical Oncology. 2023;41(24):4004-4013.

[23] Kalinsky K, Bardia A, Layman RM, et al. Abemaciclib plus fulvestrant in advanced breast cancer after progression on CDK4/6 inhibition: results from the phase III postMONARCH trial. Journal of Clinical Oncology. 2025;43(1):23-34.

[24] Jhaveri KL, Wander SA, et al. Imlunestrant with or without abemaciclib in advanced breast cancer. New England Journal of Medicine. 2025;392:1189-1202.

[25] André F, Ciruelos EM, Juric D, et al. Inavolisib-based therapy in PIK3CA-mutated advanced breast cancer. New England Journal of Medicine. 2024;391:1584-1596.

[26] Bidard FC, Kalinsky K, et al. First-line camizestrant for emerging ESR1-mutated advanced breast cancer. New England Journal of Medicine. 2025;393:1718-1730.

[27] U.S. Food and Drug Administration. FDA approves palbociclib with trastuzumab, with or without pertuzumab, and endocrine therapy for maintenance treatment of HR-positive, HER2-positive advanced breast cancer. Published June 24, 2026.

[28] U.S. Food and Drug Administration. FDA approves gedatolisib with fulvestrant, with or without palbociclib, for

HR-positive, HER2-negative locally advanced or metastatic breast cancer. Published July 14, 2026.