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Personalized Medicine and Cyclin-Dependent Kinase 4/6 (CDK4/6) Inhibitors in Breast Cancer Treatment

Molecular profiling, genetic testing, endocrine resistance, and CDK4/6 inhibitors

Individualized treatment approaches for breast cancer (BC)[1,2,3,4]

In 2020, 2.3 million new cases of BC were reported, with 685,000 deaths recorded globally

Individualized treatment in BC refers to the use of anticancer therapeutics for a subset of patients whose cancer displays specific molecular or cellular features

Molecular profiling and genomic testing are widely utilized to guide personalized treatments

Personalized treatment approaches can stratify an individual's risk of relapse from BC based on clinical and biological factors and help in choosing appropriate anticancer therapeutics

Molecular profiling[1,5,6]

Molecular profiling is the assessment of genomic content and/or proteins within a cancer tissue

Following molecular profiling, bioinformatics tools are utilized to assess the correlations between gene/protein alterations to guide treatment decisions

Molecular profiling techniques

- Immunohistochemistry (IHC)
- *In situ* hybridization (ISH)
  - Chromogenic ISH (CISH)
  - Fluorescence ISH (FISH)
- Sanger sequencing
- Polymerase chain reaction
- Pyrosequencing
- Next-generation sequencing
- Fragment analysis

Important IHC biomarkers

- Estrogen receptor (ER)
- Progesterone receptor (PR)
- Human epidermal growth factor receptor 2 (HER2)
- Proliferation markers such as Ki-67

BC can be classified into four major molecular subtypes and their IHC-surrogates

- Luminal A (ER-positive [ER+] and/or PR-positive [PR+], HER2 negative [HER2−])
- Luminal B (ER+ and/or PR+, HER2 positive [HER2+])
- Triple-negative or basal-like (ER−, PR−, HER2−)
- HER2-enriched (ER−, PR−, and HER2+)

The use of biomarkers, including breast cancer subtypes, can help in determining the prognosis and aid treatment decision-making

Gene assays[7]

- Gene assay refers to the analysis of multiple genes simultaneously to generate clinical scores that provide prognostic (recurrence/survival) or predictive (treatment response) information
- Multigene assays such as Oncotype DX, EndoPredict, MammaPrint, and Prosigna are widely used in the prognostic assessment of HER2+ and HER2− BC
- These assays can identify a low- to intermediate-risk group that might not benefit from adjuvant chemotherapy
- Only Oncotype and MammaPrint have a level of evidence 1A

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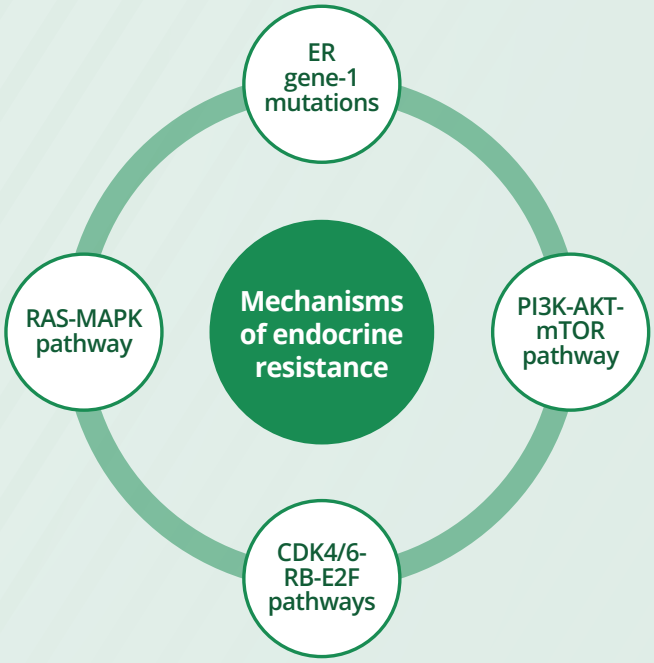
Endocrine resistance[8,9,10]

Endocrine resistance is a major challenge in treating patients with ER+ BC

Approximately 20 to 40% of tumors submitted to endocrine therapy in the adjuvant setting subsequently develop endocrine resistance and virtually all ER+ tumors develop endocrine resistance in the metastatic setting

Mechanisms of endocrine resistance

- Expression of ER in BC tumors may be lost or modified, leading to the emergence of resistance
- ER gene-1 mutations can cause acquired resistance to endocrine therapy
- Pathways involved in the development of resistance to endocrine therapy include:
  - Phosphoinositide 3 kinase (PI3K)/AKT/mammalian (or mechanistic) target of rapamycin (mTOR) pathway
  - RAS/mitogen-activated protein kinase (MAPK)
  - Cyclin-dependent kinase (CDK)
  - Retinoblastoma protein (RP)
  - Early region 2 (E2F) binding factor



HER2 overexpression/amplification is also a biomarker of endocrine resistance

Treatment options to overcome resistance mechanisms include:

- Selective ER modulators
- Complete ER antagonists
- Selective ER degraders
- Proteolysis-targeting chimera
- Selective ER covalent antagonists
- Combination strategies, such as endocrine therapy + CDK4/6 inhibitors and ER + PIK3CA inhibitors

Patient factors that influence BC treatment decisions[11,12]

Patient characteristics that can affect treatment decision-making

- Biological age
- Sex
- Comorbidities
- Performance status
- Menopausal status
- COVID-19 and other infectious diseases

Pathological, clinical, and molecular characteristics of BC need to be considered to tailor the treatment strategy for each patient

CDK4/6 inhibitors[13,14,15,16,17,18]

Resistance to conventional therapies is a major challenge in BC

CDK4 and CDK6 are key enzymes that regulate cell division

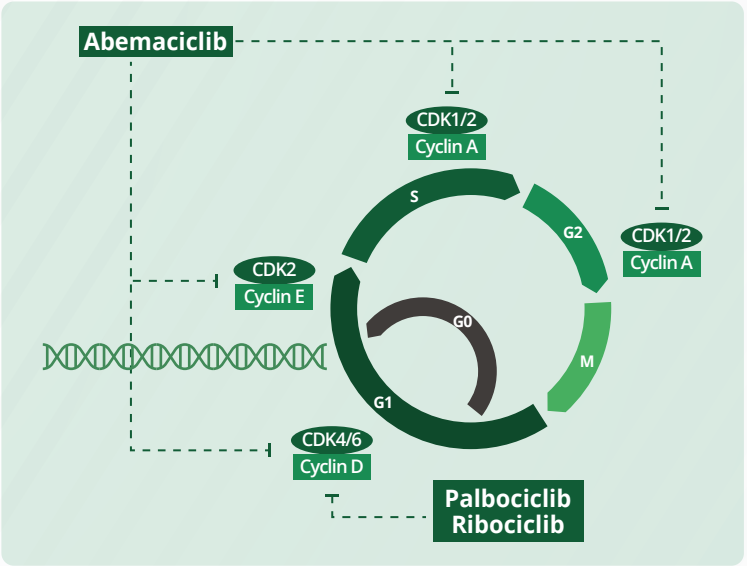
Targeting the cell cycle to inhibit the uncontrolled growth of cancer cells is a viable and promising strategy for BC treatment

At present, three CDK4/6 inhibitors are approved for the treatment of HR+ advanced BC

- Palbociclib
- Ribociclib
- Abemaciclib

Mechanism of action of CDK4/6 inhibitors

- CDK4 and CDK6 bind to D-type cyclins to form cyclin-CDK complexes which regulate the cell cycle
- CDK4/6 inhibitors limit the kinase activity of the cyclin-CDK complex and arrest the progression of the cell cycle in the G1 phase



Pharmacokinetics and pharmacodynamics

	Half-life	Cell cycle arrest	Primary site of metabolism	Targets	Dosing
Palbociclib	29 (+/−5) hours	G1 phase	Liver	CDK4 and CDK6	125 mg; once daily for 21 days followed by 7 days off
Ribociclib	32 hours	G1 phase	Liver	CDK4 and CDK6	600 mg; once daily for 21 days followed by 7 days off
Abemaciclib	18.3 hours	G1, G2 phase	Liver	CDK1, CDK2, CDK4, CDK5, CDK6, CDK9, CDK14, and CDKs16–18	150 mg; twice a day continuously

Positioning of CDK4/6 inhibitors in BC treatment paradigm[14,19,20]

HR+/HER2− BC has a high sensitivity to CDK4/6 inhibition

CDK4/6 inhibitors combined with either an aromatase inhibitor (AI) or fulvestrant are recommended as first-line treatment for the majority of patients with HR+/HER2− advanced BC

It is also possible to give endocrine therapy combined with a CDK4/6 inhibitor as second-line therapy for patients with HR+/HER2− advanced BC

The use of CDK4/6 inhibitors has been shown to significantly improve the survival of patients with HR+/HER2− advanced BC and to improve invasive-disease-free survival of patients with HR+/HER2− early BC

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Clinical trials of CDK4/6 inhibitors for early-stage BC (EBC)[21,22]

PALLAS trial
Phase III, randomized open-label clinical trial

- **Study participants**: patients with stage II–III EBC (N = 5,761)
- **Treatment**: palbociclib 125 mg daily; 3 weeks on/1 week off for 2 years
- **Primary endpoint**: invasive disease-free survival (iDFS)
  - CDK 4/6 group: 84.2% ◦ Control: 84.5% [HR = 0.96; p = 0.65; median follow-up = 31 months]

monarchE trial
Phase III, randomized open-label clinical trial

- **Study participants**: patients with HR+, HER2– high-risk, and EBC (N = 5,637)
- **Treatment**: abemaciclib 150 mg twice daily for 2 years
- **Primary endpoint**: iDFS
  - CDK 4/6 group: 92.3% ◦ Control: 89.3% [HR = 0.75; p = 0.003; median follow-up = 19 months]

NATALEE trial
Phase III, randomized open-label clinical trial

- **Study participants**: patients with stage II–III EBC (N = 4,000 estimated)
- **Treatment**: nonsteroidal AI (NSAI) plus ribociclib at 400 mg daily, 3 weeks on/1 week off for 3 years
- **Primary endpoint**: iDFS
  - Ribociclib plus NSAI: 90.4% ◦ NSAI alone: 87.1% [HR = 0.75; p = 0.003; median follow-up = 27.7 months]

PENELOPE-B trial
Phase III, randomized placebo-controlled clinical trial

- **Study participants**: patients with high risk after neoadjuvant chemotherapy (N = 1,250)
- **Treatment**: palbociclib 125 mg daily; 3 weeks on/1 week off for 1 year
- **Primary endpoint**: iDFS
  - CDK 4/6 group: 81.2% ◦ Control: 77.7% [HR = 0.93; p = 0.525; median follow-up = 42.8 months]

*HR: hazard ratio

Clinical trials of CDK4/6 inhibitors for metastatic BC (MBC)[13]

Trial	MONARCH-2	MONARCH-3	PALOMA-2	MONALEESA-2
Phase	III	III	III	III
N	669	493	666	668
Treatments	Fulvestrant + abemaciclib vs. placebo	NSAI + abemaciclib vs. placebo	Letrozole + palbociclib vs. placebo	Letrozole + ribociclib vs. placebo
Primary endpoint	PFS 16.4 vs 9.3 months (HR = 0.553, 95% CI: 0.449–0.681)	PFS 28.18 vs 14.76 months (HR = 0.540, 95% CI: 0.418–0.698)	PFS 24.8 vs 14.5 months (HR = 0.58, 95% CI: 0.46–0.72)	PFS 25.3 vs 16.0 months (HR = 0.568, 95% CI: 0.457–0.704)

PFS: progression-free survival

Approval for clinical use[13,14,23]

- The United States Food and Drug Administration (FDA) has approved palbociclib, abemaciclib, and ribociclib for HR +/HER2– advanced BC
- European Medicines Agency (EMA) has approved palbociclib, ribociclib, and abemaciclib for the treatment of HR+ and HER2− MBC
- Ribociclib and abemaciclib are now approved for EBC by both FDA and EMA

Efficacy and safety across the class of CDK4/6 inhibitors[24]

A recent network meta-analysis comparing the efficacy and safety of different combinations of CDK4/6 inhibitors revealed that abemaciclib plus fulvestrant or ribociclib plus AI were promising for the treatment of HR+/HER2− MBC with superior efficacy and safety

Key messages

- Clinical, pathological, and biological factors, including relevant biomarkers, are vital for optimizing BC treatments with targeted anticancer therapies
- A combination of CDK4/6 inhibitors and endocrine therapy is recommended as the first-line therapy for the majority of patients with HR+/HER2− MBC

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