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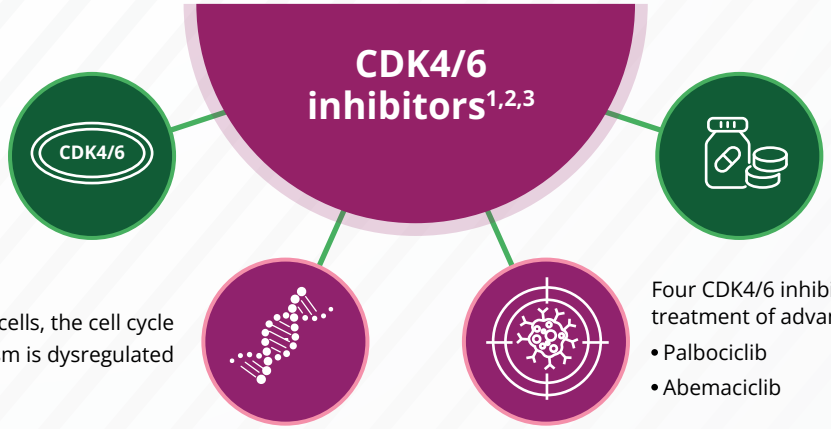
A Comprehensive Overview of Cyclin-Dependent Kinase 4 and 6 (CDK4/6) Inhibitors

Mechanism of action of CDK4/6 inhibitors, their position in cancer treatment algorithm, and management of treatment-related side effects



CDK4/6 are part of a family of serine/threonine kinases that play a key role in the regulation of the cell cycle

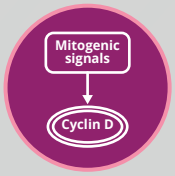
The use of CDK4/6 inhibitors arrests the cell cycle and limits the proliferation of cancer cells

In cancer cells, the cell cycle mechanism is dysregulated

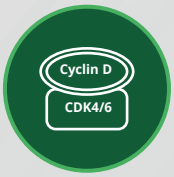
Four CDK4/6 inhibitors are currently available for the treatment of advanced breast cancer

- Palbociclib
- Ribociclib
- Abemaciclib
- Dalpiciclib (China)

Mechanism of action of CDK4/6 inhibitors[1,2]



Mitogenic signals lead to cyclin D synthesis in cells



Binding of cyclin D to CDK4/6 activates the enzymatic activity of both enzymes

Activated CDK4/6 phosphorylates retinoblastoma (Rb) protein, which in turn releases a transcription factor called E2F

E2F is responsible for the transcription of genes needed for DNA synthesis and the progression of the cell cycle entering the S phase

Pharmacokinetics and pharmacodynamics of CDK4/6 inhibitors[4,5]

	Palbociclib	Ribociclib	Abemaciclib	Dalpiciclib
Half-life	29 (+/−5) hours	32 hours	18.3 hours	44.9 hours
Cell cycle arrest	G1 phase	G1 phase	G1, G2 phase	G1 phase
Primary site of metabolism	Hepatic	Hepatic	Hepatic	Hepatic
Targets	CDK4 and CDK6	CDK4 and CDK6	CDK1, CDK2, CDK4, CDK5, CDK6, CDK9, CDK14, CDKs16–18	CDK4 and CDK6
Dosing	125 mg once daily for 21 days, followed by 7 days off	600 mg once daily for 21 days	150 mg twice a day continuously	150 mg once daily for 21 days, followed by 7 days off

(adapted from George *et al.*)

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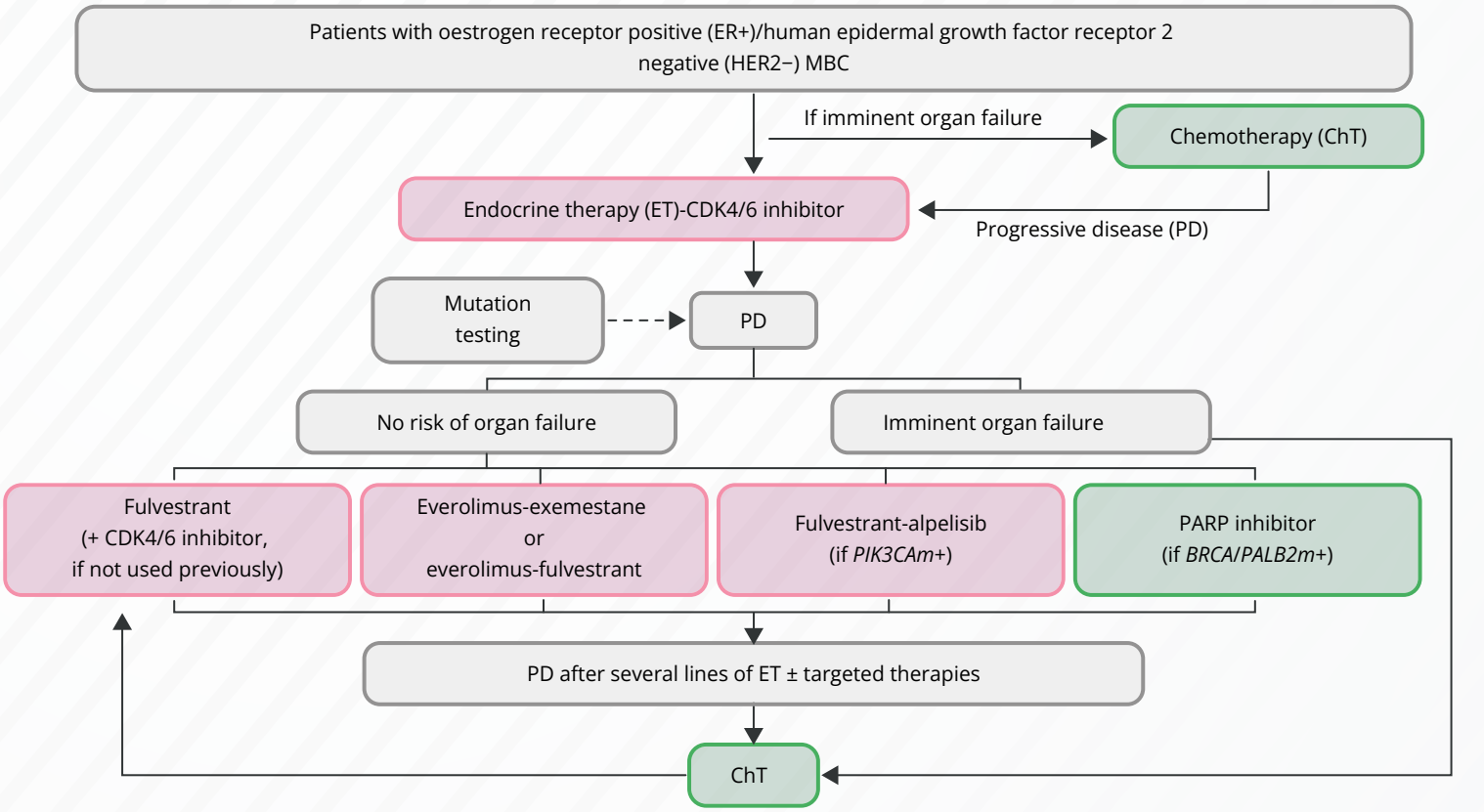
CDK4/6 inhibitors for the treatment of advanced and metastatic breast cancer (MBC)[6]



(adapted from Gennari *et al.*)

BRCA: BReast CAncer susceptibility gene; *PALB2*: partner and localiser of *BRCA2*; *PIK3CA*: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PARP: poly (ADP-ribose) polymerase

Key clinical trials of CDK4/6 inhibitors in early breast cancer (EBC)[7]

	PALLAS trial	NATALEE trial[7,8]	PENELOPE-B trial	monarchE trial
Clinical trial	Phase-III	Phase-III	Phase-III	Phase-III
Study participants	Patients with stage II–III EBC (N = 5,761)	Patients with stage II–III EBC (N = 4,000 estimated)	Patients with HR+, HER2− EBC (N = 1,250)	Patients with hormone receptor–positive (HR+), HER2− high-risk, and EBC (N = 5,637)
Treatment	Palbociclib 125 mg daily	Nonsteroidal aromatase inhibitor (NSAI) + ribociclib 400 mg daily	Palbociclib 125 mg daily	Abemaciclib 150 mg twice daily
Primary end point (iDFS)	• CDK4/6 group: 84.2% • Control: 84.5% Hazard ratio (HR): 0.96; 95% confidence interval (CI): 0.81–1.14; *p* = 0.65	• Ribociclib + NSAI: 90.4% • NSAI alone: 87.1% HR: 0.75; 95% CI: 0.62–0.91; *p* = 0.003	• CDK4/6 group: 81.2% • Control: 77.7% HR: 0.93; 95% CI: 0.74–1.17; *p* = 0.525	• CDK4/6 group: 92.3% • Control: 89.3% HR: 0.713; 95% CI: 0.583–0.871; *p* = 0.0009

Key clinical trials evaluating CDK4/6 inhibitors in MBC[3,9]

	PALOMA-2 (NCT01740427)	MONALEESA-2 (NCT01958021)	MONARCH-3 (NCT02246621)	NCT03481998
Clinical trial	Phase-III	Phase-III	Phase-III	Phase-Ib
Study participants	Postmenopausal women with HR+, HER2− breast cancer (N = 666)	Postmenopausal women with HR+, HER2− breast cancer (N = 668)	Postmenopausal women with HR+, HER2− breast cancer (N = 493)	Women with HR+, HER2− breast cancer (N = 104)
Treatment	Letrozole + palbociclib vs placebo	Letrozole + ribociclib vs placebo	Abemaciclib + NSAI vs placebo	Dalpiciclib (125 or 150 mg) + letrozole/ anastrozole and dalpiciclib (125, 150, or 175 mg) + fulvestrant
Primary endpoint (median PFS)	24.8 vs 14.5 months HR: 0.58, 95% CI: 0.46–0.72	25.3 vs 16.0 months HR: 0.568, 95% CI: 0.457–0.704	28.18 vs 14.76 months HR: 0.540, 95% CI: 0.418–0.698	38.7 vs 24.1 vs 12.0 vs 16.7 vs 12.9 months

iDFS: invasive disease-free survival; PFS: progression-free survival

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Regulatory approval of CDK4/6 inhibitors

Approval from the United States Food and Drug Administration (FDA)[10]

- February 2015: palbociclib received FDA approval
- March 2017: ribociclib received FDA approval
- September 2017: abemaciclib received accelerated approval

Approval from the European Medicines Agency (EMA)[11]

- November 2016: palbociclib received EMA approval
- August 2017: ribociclib received initial EMA approval
- September 2018: abemaciclib received EMA approval

Importance of treatment adherence in clinical settings → Lack of adherence to a prescribed drug regimen → Poor health outcomes

Dose reduction and treatment discontinuation rate of CDK4/6 inhibitors[7]

	PALLAS trial	PENELOPE-B trial	monarchE trial
CDK4/6 inhibitor	Palbociclib 125 mg daily	Palbociclib 125 mg daily	Abemaciclib 150 mg twice daily
Dose reduction (%)	55.2%	47.6%	42.7%
Discontinuation rate (%)	44.9%	20.0%	27.7%

Increased adherence to treatment can directly translate to longer survival times

Factors affecting treatment adherence[12]

Intrapersonal factors

- Lack of information about the efficacy
- Side effects
- Cost
- Difficulty in establishing a routine

Strategies to improve adherence[12]

- Effective communication with the care team
- Support from family and friends
- Experience of other patients with MBC

Coordinated efforts involving healthcare providers, patients with MBC, and specialists are key to improving treatment adherence

Management of side effects[13,14]

- CDK4/6 inhibitors are generally well-tolerated and safe, with a low rate of serious adverse effects
- However, they have diverse toxicity profiles, necessitating their careful consideration during clinical decision-making

Common side effects include:

- Fatigue
- Vomiting
- Nausea
- Diarrhoea

Treatment-related haematological toxicities

- Neutropenia
- Leukopenia

Treatment-specific side effects include:

- Cardiotoxicity
- Respiratory insufficiency
- Renal dysfunction
- Hepatoxicity
- Thromboembolic events

Management of treatment-related side effects[13]

- Haematologic adverse events can be managed with standard supportive care
- Dose reductions or interruptions are effective for resolving treatment-related side effects

CDK4/6 inhibitor[13]	Grade 1 or 2 (ANC 1,000/mm³–<LLN)	Grade 3 (ANC 500–<1,000/mm³)	Grade 3 (ANC 500 –<1, 000/mm³) febrile neutropenia*	Grade 4 (ANC <500/mm³)
Palbociclib	No dose adjustment is required	• Withhold palbociclib on day 1 of the cycle • After recovery to grade ≤2, start the next cycle at the same dose • Consider dose reduction in cases of prolonged (>1 week) recovery or recurring grade 3 neutropenia	• Withhold palbociclib until recovery to grade ≤2 • Resume at the next lower dose	• Withhold palbociclib until recovery to grade ≤2 • Resume at the next lower dose

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CDK4/6 inhibitor[13]	Grade 1 or 2 (ANC 1,000/mm³–<LLN)	Grade 3 (ANC 500–<1,000/mm³)	Grade 3 (ANC 500 –<1, 000/mm³) febrile neutropenia*	Grade 4 (ANC <500/mm³)
Ribociclib	No dose adjustment is required	• Dose interruption until recovery to grade ≤2 • Resume ribociclib at the same dose level • In cases of recurring toxicity (grade 3), dose interruption until recovery, followed by resumption of ribociclib at the next lower dose level	• Dose interruption until recovery of neutropenia to grade ≤2 • Resume ribociclib at the next lower dose level	• Dose interruption until recovery to grade ≤2 • Resume ribociclib at the next lower dose level
Abemaciclib	No dose adjustment is required	• Withhold abemaciclib until recovery to grade ≤2 • Resume abemaciclib at the same dose level	No distinct recommendation in the prescribing information	• Withhold palbociclib until recovery to grade ≤2 • Resume abemaciclib at the next lower dose level

Common side effects with CDK4/6 inhibitor-based treatment[13]

Treatment	Patients	Most common side effects (>30% any grade)	Most common side effects (>20% grade 3/4)
Palbociclib monotherapy (NCT01037790)	Advanced breast cancer (n = 37)	• Leukopenia (100%) • Thrombocytopenia (76%) • Neutropenia (92%) • Lymphopenia (65%) • Anaemia (70%)	• Neutropenia (54%) • Leukopenia (51%) • Lymphopenia (30%)
Ribociclib monotherapy (NCT01237236)	Advanced solid tumours/lymphomas (n = 132)	TEAEs • Neutropenia (46%) • Fatigue (45%) • Leukopenia (43%) • Nausea (42%) • Thrombocytopenia (30%)	• Neutropenia (27%)
Abemaciclib monotherapy, MONARCH-1 (NCT02102490)	HR+, HER2−, advanced breast cancer (n = 132)	TEAEs • Leukopenia (91%) • Diarrhoea (90%) • Anaemia (69%) • Fatigue (65%) • Nausea (64%) • Decreased appetite (46%) • Thrombocytopenia (41%) • Abdominal pain (39%) • Vomiting (35%) • Neutropenia (88%)	• Leukopenia (28%) • Neutropenia (27%) • Diarrhoea (20%)

ANC: absolute neutrophil count; LLN: lower limit of normal; TEAEs: treatment emergent adverse events

Patient education tools to aid the management of side effects and improve adherence[15]

Traditional media tools such as: • Pamphlets • Handouts

Digital tools like:

- **User-friendly mobile health applications**
- **Informative videos (animations with text)**
- **Web-based medical education platform**
  - National Cancer Institute https://www.cancer.gov/about-cancer/treatment/side-effects
  - American Cancer Society https://www.cancer.org/cancer/managing-cancer/side-effects.html

Key messages

- **CDK4/6 inhibitors, including palbociclib, abemaciclib, ribociclib, and dalpiciclib are clinically effective and beneficial for patients with MBC**
- **While CDK4/6 inhibitors are well-tolerated, it is important to monitor and manage side effects with regular clinical assessments**
- **A shared care model involving a multidisciplinary team of medical oncologists, nurse practitioners, and pharmacists can ensure timely treatment using CDK4/6 inhibitors while monitoring for adverse effects**
- **Development of animated patient platforms for educating patients and their caregivers may help improve treatment outcomes and satisfaction**

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