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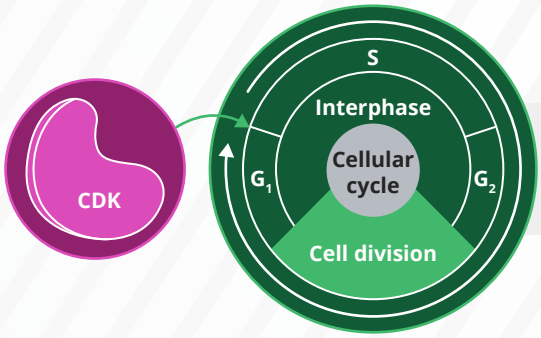
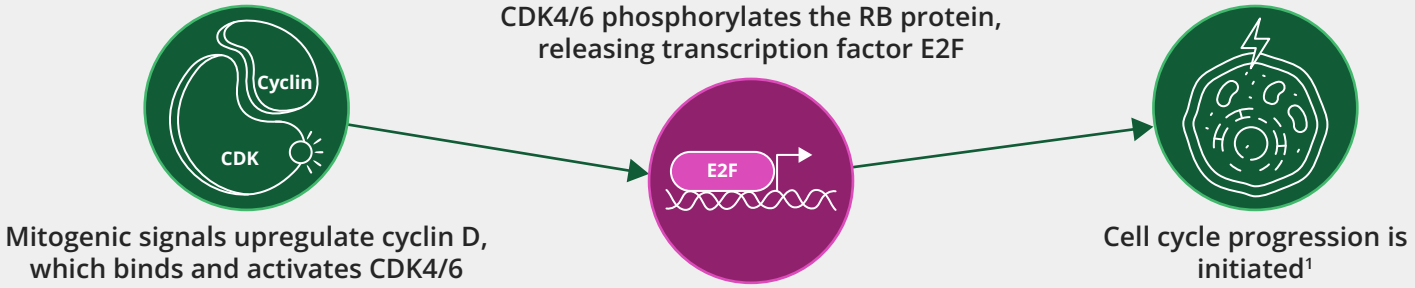
CDK4/6 Inhibitors in Metastatic Breast Cancer

Mechanisms and novel therapeutic combinations for improved efficacies



CDK4 and CDK6 are enzymes essential for cell cycle control[1]



Hyper-activated CDK4/6 activity leads to unconstrained cell growth in the absence of mitogenic signals[1]

HR$^+$ breast cancer is heavily dependent on cyclin D1, a direct transcriptional target of the ER

Acquired resistance to endocrine therapy is associated with the continued dependence of HR$^+$ breast cancer on cyclin D1 and CDK4/6[2]

CDK4/CDK6 inhibitors in breast cancer therapeutics[3]

Three small molecule CDK4/6 inhibitors are clinically approved for the treatment of HR$^+$/HER2$^-$ advanced breast cancer, in combination with ET

They bind to the ATP-binding pocket of CDK4/6, inactivate the cyclin D-CDK4/6 complex, and prevent phosphorylation of RB[3]

	Palbociclib[6]	Ribociclib[8]	Abemaciclib[7]
Orally administered	✓	✓	✓
Selective for CDK4	✓	✓	
High potency in CDK4-dependent cells		✓	✓
Haematological toxicity grades 3 and 4	✓	✓	
Haematological toxicity less frequent			✓

*Abbreviations: CDK: cyclin-dependent kinase; RB: retinoblastoma protein; HR: hormone receptor; ER: estrogen receptor; HER: human epidermal growth factor receptor; ET: endocrine therapy; E2F: elongation factor

Visit https://breastcancer.knowledgehub.wiley.com/pt-br/ for additional resources

CDK4/CDK6 inhibitors: Mechanism of action[2,4]

- Bind to sequester monomeric (inactive) CDK4/6, preventing holoenzyme assembly
- Activate distinct non-CDK4/6 kinase targets

Molecular biomarkers to predict sensitivity or resistance to CDK4/6 inhibition are yet to be identified

Potential markers being evaluated:

- Cyclin D1 amplification
- Loss of functional RB1
- *CCNE1*
- *PIK3CA* mutations
- *ESR1* mutations

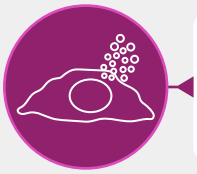
Results from a clinical trial for CDK4/6 inhibitors[4]

- Robust anti-proliferative and clinical activity of CDK4/6 inhibitor monotherapy in HR$^+$ breast cancer
- Synergistic improvement in progression-free and overall survivals when combined with ET
- Overcoming ET resistance
- Showed benefits for both pre- and post-menopausal women

Tumour cell-intrinsic and -extrinsic responses to CDK4/6 inhibition[1]

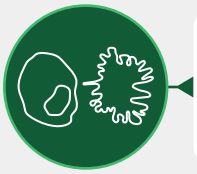
Sustained binding and inhibition of additional E2F functions

- Proliferative arrest
- Blocks DNA damage response
- Chromatin remodelling
- Metabolism, differentiation, and apoptosis



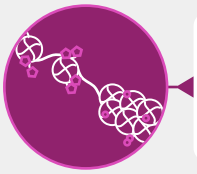
RB-dependent senescence

- Cell cycle withdrawal
- Chromatin remodelling
- Metabolic dysregulation
- Resistance to apoptosis
- SASP



Sustained binding and inhibition of additional E2F functions

- In haematological malignancies:
  - RB-independent metabolic dysregulation
  - Apoptosis
- In solid tumours, such as breast cancer:
  - CDK4/6 monotherapy induces sustained E2F inhibition
  - Proliferative arrest

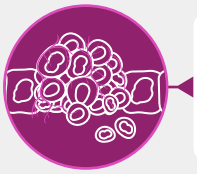


Non-canonical RB functions

- Recruitment of histone modifiers
- Activation of other transcription factors

Non-RB substrates of CDK4/6

- Phosphorylate targets (FOXM1, DNMT1) are important in senescence, apoptosis, and immunogenicity



Impact on tumour microenvironment and clinical response

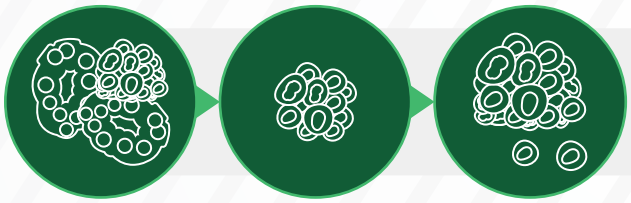
- Promote anti-tumour T lymphocyte effector function; inhibit immunosuppressive Treg cells
- Induce senescence phenotypes in fibroblasts; promote tumour growth
- Cell cycle arrest in endothelial cells

*Abbreviations: *CCNE1*: Cyclin E; DNMT1: DNA methyltransferase 1; *ESR1*: estrogen receptor alpha; FOXM1: forkhead box protein M1; *PIK3CA*: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; SASP: Senescence-associated secretory phenotype; Treg: regulatory T

Patients who initially respond to treatment often develop resistance; many tumours exhibit preexisting, intrinsic resistance to CDK4/6 inhibitors[2]

Identifying the underlying mechanisms of resistance enables the selection of treatment following disease progression[5]

- PI3K-AKT signalling participates in non-canonical activation of cyclin D-CDK2 complex; inhibition of PI3K-AKT pathway overcomes resistance
- Immune checkpoint inhibitors anti-PD1 and anti-CTLA4 show benefits in resistant populations
- Continuing CDK4/6i through progression by substituting ET or CDK4/6i



Future therapeutic approaches following the progression on CDK4/6 inhibitors[2,5]

Progression-free survival (in months) achieved with the indicated therapeutic combinations

MAINTAIN (CDK4/6 inhibitor)[9]

- Ribociclib + Switch ET: 5.29
- Placebo + Switch ET: 2.76

PADA-1 (endocrine therapy)[10]

- Fulvestrant (ET) + palbociclib: 12.8
- Aromatase inhibitor + palbociclib: 5.8

EMERALD (endocrine therapy)[11]

All patients	Patients with *ESR1* mutation
Elacestrant: 34.3	Elacestrant: 40.8
ET (SERD of choice): 20.4	ET (SERD of choice): 19.1

SERENA-2 (oral SERDs)

All patients	*ESR1* mutations detected
Camizestrant: 7.2 → 7.7	Camizestrant: 6.3 → 9.2
Fulvestrant: 3.7	Fulvestrant: 2.2

75 mg / 150 mg

CAPItello-291 (PI3K pathway inhibitor)

All patients	AKT pathway-altered population
Capivasertib + fulvestrant: 7.2	Capivasertib + fulvestrant: 7.3
Placebo + fulvestrant: 3.6	Placebo + fulvestrant: 3.1

DESTINY-Breast04 (antibody-drug conjugate anti-HER2)

- Trastuzumab deruxtecan: 8.8
- TPC: 4.2

TROPiCS-02 (antibody-drug conjugate anti-Trop2)[12]

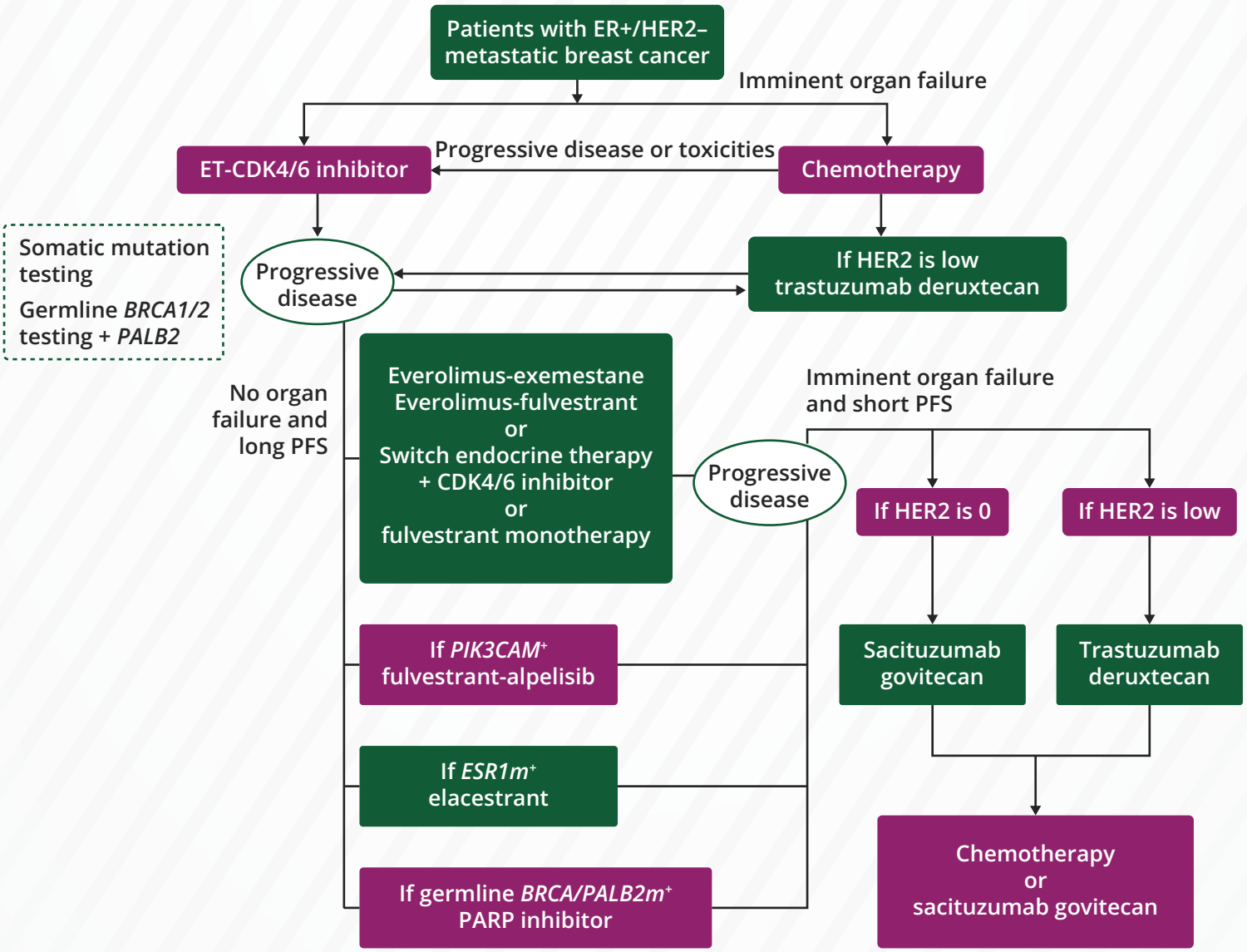
- Sacituzumab govitecan: 5.2
- TPC: 4.0

TROPION-Breast01 (antibody-drug conjugate anti-Trop2)

- Datopotamab deruxtecan: 6.9
- Chemotherapy: 4.9

*Abbreviations: PI3K: phosphatidylinositol 3-kinases; SERD: selective estrogen receptor downregulator; TPC: treatment of physician's choice

European Society of Medical Oncology Clinical Living guidelines for ER+/HER2– breast cancer[13,14]



Key messages

- CDK4/6 inhibitors have dramatically improved clinical outcomes for patients with HR+, HER2–early, and metastatic breast cancer
- Evaluation of novel therapeutic combinations will help identify newer approaches to overcome treatment resistance

References:

1. Goel, S., Bergholz, J. S., & Zhao, J. J. (2022). Targeting CDK4 and CDK6 in cancer. *Nature Reviews Cancer, 22*(6), 356–372.
2. Fassl, A., Geng, Y., & Sicinski, P. (2022). CDK4 and CDK6 kinases: From basic science to cancer therapy. *Science, 375*(6577), eabc1495.
3. Schettini, F., De Santo, I., Rea, C. G., De Placido, P., Formisano, L., Giuliano, M., ... & Del Mastro, L. (2018). CDK 4/6 inhibitors as single agent in advanced solid tumors. *Frontiers in Oncology, 8,* 608.
4. Morrison, L., Loibl, S., & Turner, N. C. (2024). The CDK4/6 inhibitor revolution - a game-changing era for breast cancer treatment. *Nature Reviews Clinical Oncology, 21*(2), 89–105.
5. ernas, S., Tolaney, S. M., Winer, E. P., & Goel, S. (2018). CDK4/6 inhibition in breast cancer: current practice and future directions. *Therapeutic Advances in Medical Oncology, 10,* 175883591878645.
6. Fry, D. W., Harvey, P. J., Keller, P. R., Elliott, W. L., Meade, M., Trachet, E., ... & Toogood, P. L. (2004). Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. *Molecular Cancer Therapeutics, 3*(11), 1427–1438.
7. Kim, S., Loo, A., Chopra, R., Caponigro, G., Huang, A., Vora, S., ... & Brain, C. (2013). Abstract PR02: LEE011: An orally bioavailable, selective small molecule inhibitor of CDK4/6– Reactivating Rb in cancer. *Molecular Cancer Therapeutics, 12*(11_Supplement), PR02–PR02.
8. Gelbert, L. M., Cai, S., Lin, X., Sanchez-Martinez, C., del Prado, M., Lallena, M. J., ... & de Dios, A. (2014). Preclinical characterization of the CDK4/6 inhibitor LY2835219: in-vivo cell cycle-dependent/independent anti-tumor activities alone/in combination with gemcitabine. *Investigational New Drugs, 32*(5), 825–837.
9. Kalinsky, K., Accordino, M. K., Codruta Chiuzan, Mundi, P. S., Sakach, E., Sathe, C., ... & O'Dea, A. (2023). Randomized phase II trial of endocrine therapy with or without ribociclib after progression on cyclin-dependent kinase 4/6 inhibition in hormone receptor–positive, human epidermal growth factor receptor 2–negative metastatic breast cancer: MAINTAIN trial. *The Journal of Clinical Oncology, 41*(24), 4004–4013.
10. Bidard, F. C., Hardy-Bessard, A. C., Dalenc, F., Bachelot, T., Pierga, J. Y., de la Motte Rouge, T., ... & de Gramont, A. (2022). Switch to fulvestrant and palbociclib versus no switch in advanced breast cancer with rising ESR1 mutation during aromatase inhibitor and palbociclib therapy (PADA-1): a randomised, open-label, multicentre, phase 3 trial. *The Lancet Oncology, 23*(11), 1367–1377.
11. Bidard, F. C., Kaklamani, V. G., Neven, P., Streich, G., Montero, A. J., Forget, F., ... & Bardia, A. (2022). Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer: results from the randomized phase III EMERALD trial. *Journal of Clinical Oncology, 40*(28), 3246.
12. Bardia, A., Vahdat, L., Diamond, J., Kalinsky, K., O'Shaughnessy, J., Moroose, R., ... & Mayer, I. (2018). Abstract GS1-07: Sacituzumab govitecan (IMMU-132), an anti-Trop-2-SN-38 antibody-drug conjugate, as ≥3rd-line therapeutic option for patients with relapsed/refractory metastatic triple-negative breast cancer (mTNBC): efficacy results. *Cancer Research, 78*(4_Supplement), GS1-07.
13. Curigliano, G., Castelo-Branco, L., Gennari, A., Harbeck, N., Criscitiello, C., & Trapani, D. (2021). ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Annals of Oncology, 32*(12), 1475–1495.
14. ESMO Metastatic Breast Cancer Living Guidelines. v1.1 May 2023. https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline

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