WILEY

Mechanism of Action, Clinical Efficacy, and Biomarker-Driven Decisions for Use of Emerging Therapeutics in Breast Cancer

Strategies for mitigating therapy resistance and improving the patient management

Emerging therapeutics for breast cancer (BC)

BC is broadly categorised[1] into:

- Human epidermal growth factor receptor (HER2)-positive: 15–20%
- HER2-negative, oestrogen receptor (ER), and/or progesterone receptor (PR)-positive: 70%
- Triple negative BC (TNBC): ~15%

Endocrine therapy (ET) targeting the ER signalling pathways is a major component of BC therapeutics

ETs[1]

Mechanisms of action[1]

Selective ER modulators (SERMs)
Block oestrogen production (oral tamoxifen)

Aromatase inhibitors (AIs)
- Competitive inhibitor of oestrogen binding to ER
- Engage co-repressors to inhibit ER transcriptional activity (oral anastrozole, letrozole, and exemestane)

Selective ER degraders
Prevents nuclear translocation of ER, targets for proteasomal degradation

New-generation anti-oestrogen therapies to circumvent therapy resistance[1]

Complete ER antagonists	Recruit co-repressors to block transcriptional activation of ER
Proteolysis targeting chimeric	Bifunctional molecules that bind to ER and the E3 ubiquitin ligase, leading to proteasomal degradation of ER
Selective ER covalent antagonists	Covalently binds to inactivate ER, resulting in inhibition of gene transcription

Key clinical trials[1]

EMERALD

Elacestrant vs. standard of care ET

Median progression-free survival (PFS) in overall population: **2.8 vs. 1.9 months**

12-month PFS in patients with oestrogen receptor 1mutation:

The newer ETs are in early stages of development or clinical evaluation

Visit https://breastcancer.apac.knowledgehub.wiley.com for additional resources

Cyclin-dependent kinase (CDK) 4 and 6 inhibitors

Abemaciclib, ribociclib, and palbociclib[2]

Approved in combination with ET for hormone receptor (HR)-positive/ HER-negative BC[2]

Mechanisms of action[2]

- Inhibitors of cell cycle progression
- Prevents phosphorylation of retinoblastoma (Rb) protein and induces G1-phase arrest in the cell cycle

Key clinical trials

PALOMA-2[2]

Palbociclib + letrozole vs. placebo + letrozole

Median PFS: 38.8 months vs. 28.8 months

MONALEESA-2[2]

Ribociclib + letrozole vs. placebo + letrozole

Median PFS: 25.3 months vs. 16.0 months

MONARCH E[2]

Abemaciclib + ET vs. ET

4-year invasive disease-free survival: 85.8% vs. 79.4%

MONARCH 2

Abemaciclib + fulvestrant (ER antagonist) vs. placebo + fulvestrant

Median PFS: 16.4 months vs. 9.3 months

Manageable adverse events (AEs) like neutropenia, QTc prolongation, and gastrointestinal toxicity noted[3]

Resistance to therapy is often acquired by activation of PI3K signalling

INAVO120 trial[4]

Inavolisib (PI3Ka* inhibitor) + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant
Extended PFS: 15 vs. 7.3 months*

*Phosphoinositide 3-kinase a [PI3Ka]

*In PIK3CA HR-positive, HER-negative locally advanced, or MBC who relapsed within 12 months of adjuvant ET[4]

CAPItello-291 trial[5]

Capivasertib (AKT inhibitor) + fulvestrant vs. placebo + fulvestrant
Median PFS in AKT-altered population*: 7.3 vs. 3.1 months

*In patients who relapsed after AI therapy
Protein Kinase B (AKT)

Antibody drug conjugates (ADC)

Trastuzumab emtansine (T-DM1)[6]

T-DM1 is trastuzumab, the antibody targeting HER2 linked to microtubule inhibitory agent DM1

Mechanisms of action[6]

- Trastuzumab binding to HER2
- Internalisation of ADC increases intracellular levels of DM1
  → mitotic arrest and apoptosis

Key clinical trials

EMILIA study[7]

TDM1 vs. lapatinib plus capecitabine
Median PFS: 9.6 vs. 6.4 months*

*Patients previously treated for locally advanced or MBC with trastuzumab and a taxane

T-deruxtecan (T-DXd)

T-DXd, trastuzumab linked to topoisomerase I inhibitor

Key clinical trials

Destiny Breast-03[8]
T-DM1 vs. T-DXd
PFS: 12 months* (34.1% vs. 75.8%)

DESTINY-Breast-09[9]
TDXd/pertuzumab vs. THP (taxane + trastuzumab + pertuzumab)
Median PFS*: 40.7 vs. 26.9 months

*In HER2-positive MBC

Sacituzumab govitecan

Anti–trophoblast cell surface antigen 2 (Trop-2) antibody coupled to a cytotoxic SN-38 payload

Key clinical trials

ASCENT trial[10]
Median PFS*: 4.8 vs. 1.7 months

*For metastatic TNBC with >2 prior therapies

Visit https://breastcancer.apac.knowledgehub.wiley.com for additional resources

Poly (ADP-ribose) polymerase (PARP) inhibitors[11]

Olaparib and talazoparib

- Approved in metastatic HER2-negative BC with germline breast cancer gene (*BRCA*) mutation (gBRCAm)

Mechanism of action[11]

- Synthetic lethality due to lack of DNA single-strand break repair
- PARP1 trapping causing DNA damage and cell death

Key clinical trials[11]

OlympiAD[12]

Olaparib vs. treatment of physician's choice (TPC)
Median PFS: 2.8 months longer for olaparib
42% lower risk of disease progression

EMBRACA trial[11]

Talazoparib vs. TPC
Median PFS: 3 months longer

PARP inhibitors are well tolerated and AEs are manageable with supportive treatment or dose reduction

Personalised approach to therapy[13]

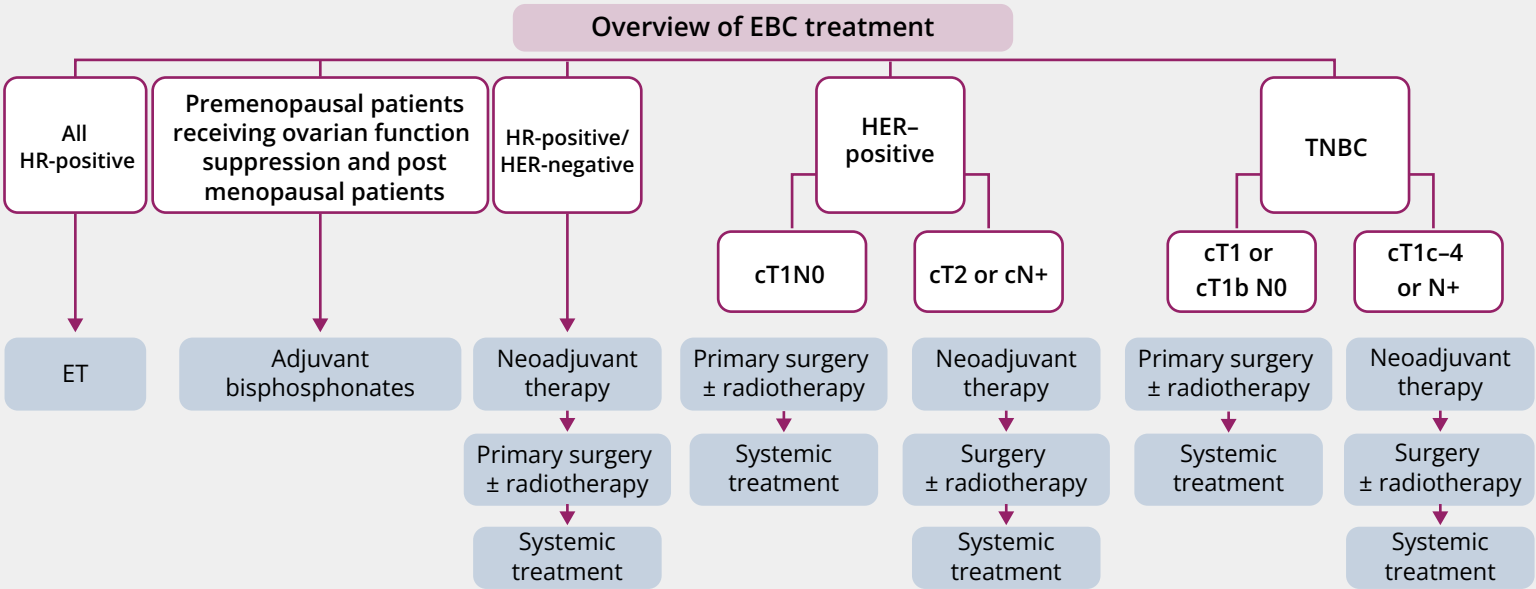
BC is a heterogeneous malignancy requiring diverse treatment approaches

Patient outcomes remain suboptimal due to primary or acquired resistance to therapy

Identification of robust predictive biomarkers to refine patient selection and treatment strategies is essential

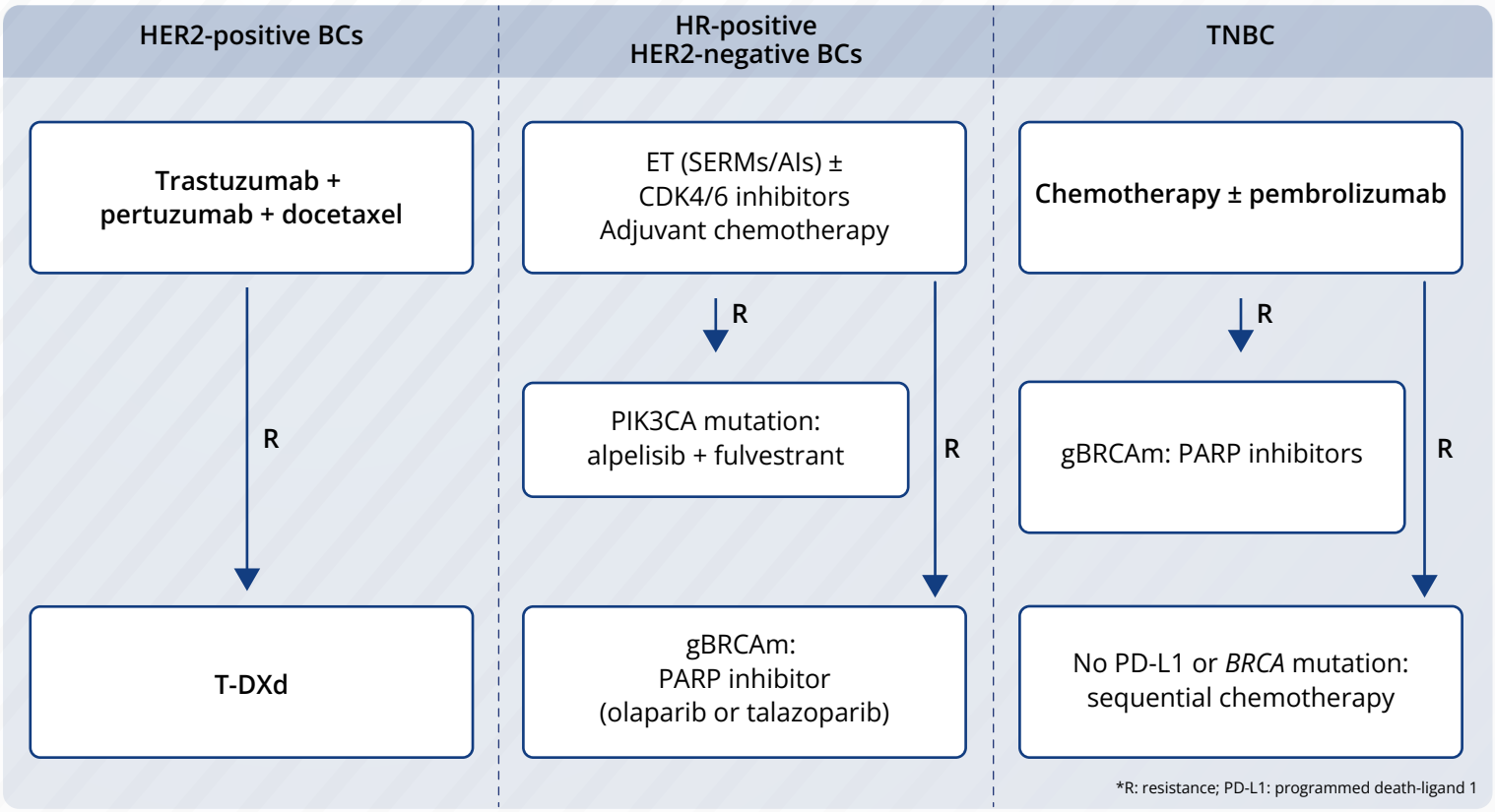
Risk stratification enables personalised early screening and diagnosis, while biomarker profiles help identify patient-centred therapeutic strategies

Biomarker profiles and corresponding therapeutic strategies for early BC (EBC)[15]



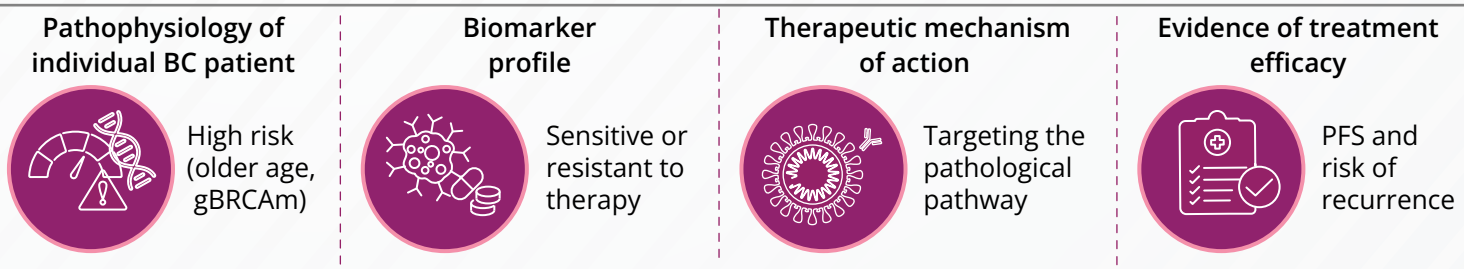
Visit https://breastcancer.apac.knowledgehub.wiley.com for additional resources

Strategies for optimising treatment for metastatic BC based on patient biomarker profiles[13,14,18,19]



*R: resistance; PD-L1: programmed death-ligand 1

Integration of mechanism, evidence from clinical trials, and biomarkers enables optimal, personalised therapy[18]



Key messages

- New-generation therapeutics have emerged to tackle various categories of BC
- Therapy resistance is a key challenge during the treatment of BC
- Integration of clinical trial evidence is essential for the optimal management of BC

References:

1. Patel, R., Klein, P., Tiersten, A., & Sparano, J. A. (2023). An emerging generation of endocrine therapies in breast cancer: a clinical perspective. *Npj Breast Cancer, 9*(1).
2. Gao, T., Sun, Y., Leng, P., Liu, D., Guo, Q., & Li, J. (2025). CDK4/6 inhibitors in breast cancer therapy: mechanisms of drug resistance and strategies for treatment. *Frontiers in Pharmacology, 16.*
3. Onesti, C. E., & Jerusalem, G. (2020). CDK4/6 inhibitors in breast cancer: differences in toxicity profiles and impact on agent choice. A systematic review and meta-analysis. *Expert Review of Anticancer Therapy, 21*(3), 283–298.
4. Turner, N. C., Im, S., Saura, C., Juric, D., Loibl, S., Kalinsky, K., ... & Jhaveri, K. L. (2024). Inavolisib-based therapy in PIK3CA-mutated advanced breast cancer. *New England Journal of Medicine, 391*(17), 1584–1596.
5. Turner, N. C., Oliveira, M., Howell, S. J., Dalenc, F., Cortes, J., Moreno, H. L. G., ... & Rugo, H. S. (2023). Capivasertib in hormone receptor–positive advanced breast cancer. *New England Journal of Medicine, 388*(22), 2058–2070.
6. Barok, M., Joensuu, H., & Isola, J. (2014). Trastuzumab emtansine: mechanisms of action and drug resistance. *Breast Cancer Research, 16*(2).
7. Verma, S., Miles, D., Gianni, L., Krop, I. E., Welslau, M., Baselga, J., ... & Blackwell, K. (2012). Trastuzumab emtansine for HER2-positive advanced breast cancer. *New England Journal of Medicine, 367*(19), 1783–1791.
8. Cortés, J., Kim, S., Chung, W., Im, S., Park, Y. H., Hegg, R., ... & Hurvitz, S. A. (2022). Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. *New England Journal of Medicine, 386*(12), 1143–1154.
9. Schettini, F., Nucera, S., Pascual, T., Martínez-Sáez, O., Sánchez-Bayona, R., Conte, B., ... & Villacampa, G. (2024). Efficacy and safety of antibody-drug conjugates in pretreated HER2-low metastatic breast cancer: a systematic review and network meta-analysis. *Cancer Treatment Reviews, 132*, 102865.
10. Bardia, A., Rugo, H. S., Tolaney, S. M., Loirat, D., Punie, K., Oliveira, M., ... & Hurvitz, S. A. (2024). Final results from the randomized Phase III ASCENT clinical trial in metastatic triple-negative breast cancer and association of outcomes by human epidermal growth factor receptor 2 and trophoblast cell surface antigen 2 expression. *Journal of Clinical Oncology, 42*(15), 1738–1744.
11. Daly, G. R., AlRawashdeh, M. M., McGrath, J., Dowling, G. P., Cox, L., Naidoo, S., ... & Young, L. (2024). PARP inhibitors in breast cancer: a short communication. *Current Oncology Reports, 26*(2), 103–113.
12. Robson, M., Tung, N., Conte, P., Im, S., Senkus, E., Xu, B., ... & Domchek, S. (2019). OlympiAD final overall survival and tolerability results: olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. *Annals of Oncology, 30*(4), 558–566.
13. Wang, B., He, X., Dutta, S., Chen, S., Liang, J., Huang, W., ... & Wang, Y. (2025). New progress and challenges of targeted therapies for breast cancer. *Annals of Palliative Medicine, 14*(4), 345–352.
14. Lopez-Gonzalez, L., Cendra, A. S., Cendra, C. S., Cervantes, E. D. R., Espinosa, J. C., Pekarek, T., ... & Diaz-Pedrero, R. (2024). Exploring biomarkers in breast cancer: hallmarks of diagnosis, treatment, and follow-up in clinical practice. *Medicina, 60*(1), 168.
15. Park, K. H., Loibl, S., Sohn, J., Park, Y. H., Jiang, Z., Tadjoedin, H., ... & Harbeck, N. (2024). Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with early breast cancer. *ESMO open, 9*(5), 102974.
16. Colomer, R., González-Farré, B., Ballesteros, A. I., Peg, V., Bermejo, B., Pérez-Mies, B., ... & Palacios, J. (2024). Biomarkers in breast cancer 2024: an updated consensus statement by the spanish society of medical oncology and the spanish society of pathology. *Clinical & Translational Oncology, 26*(12), 2935–2951.
17. Witkiewicz, A. K., & Knudsen, E. S. (2014). Retinoblastoma tumor suppressor pathway in breast cancer: prognosis, precision medicine, and therapeutic interventions. *Breast Cancer Research, 16*(2).
18. Starzer, A. M., Berghoff, A. S., & Bartsch, R. (2022). Biomarkers and translational research approaches in breast cancer—an update. *Memo - Magazine of European Medical Oncology, 16*(1), 42–46.
19. Im, S. A., Gennari, A., Park, Y. H., Kim, J. H., Jiang, Z. F., Gupta, S., ... & Harbeck, N. (2023). Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, staging and treatment of patients with metastatic breast cancer. *ESMO open, 8*(3), 101541.

Published by WILEY

Visit https://breastcancer.apac.knowledgehub.wiley.com for additional resources

This Knowledge Hub is supported by Eli Lilly, Daiichi Sankyo, Novartis, and Pfizer