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Molecular Mechanisms of Mammary Carcinogenesis: Current Understanding and Prospects for Targeted Therapy

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Abstract

Breast cancer (BC) is the leading oncologic disease among women worldwide: in 2022, approximately 2.3 million new cases and 670,000 deaths were reported. The disease's molecular heterogeneity — the presence of luminal, HER2-amplified, and triple-negative subtypes — underlies the complexity of therapeutic approaches. This review synthesizes current data on oncogenic signaling pathways (PI3K/AKT/mTOR, RAS/MAPK, NOTCH, Wnt/β-catenin), epigenetic disturbances, and mechanisms of drug resistance in BC. Particular emphasis is placed on the evidence base for targeted drugs approved between 2018 and 2025: CDK4/6 inhibitors, PI3K/AKT pathway antagonists, antibody-drug conjugates (T-DXd, sacituzumab govitecan), PARP inhibitors, and immune checkpoint inhibitors. Based on an analysis of 31 high-level evidence sources (PubMed, Scopus, WoS), prospects for personalized oncology and overcoming resistance are discussed. The search for scientific publications was conducted in the following databases: PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. The following search queries in English were used: 'breast cancer molecular mechanisms carcinogenesis», «breast cancer targeted therapy», «HER2 CDK4/6 inhibitors breast cancer», «triple-negative breast cancer immunotherapy PARP inhibitors», «antibody-drug conjugates breast cancer trastuzumab deruxtecan», and 'PI3K/AKT/mTOR breast cancer». The search was conducted without language restrictions, with preference given to publications in English and Russian. Additional searches were conducted using the reference lists of selected articles.

Keywords: Breast cancer, molecular subtypes, carcinogenesis, targeted therapy, CDK4/6 inhibitors, HER2, PI3K/AKT/mTOR, PARP inhibitors, antibody-drug conjugates, immunotherapy, triple-negative cancer.

Introduction

Breast cancer (BC) is the leading malignant neoplasm among women worldwide and remains a leading cause of cancer-related mortality. According to the International Agency for Research on Cancer (IARC), in 2022, approximately 2.3 million new cases of BC were diagnosed globally, and the number of deaths was around 670,000. If current trends continue, the incidence is projected to reach 3.2 million new cases per year by 2050 [29]. This high disease burden drives ongoing interest in the scientific community in studying the molecular basis of oncogenesis and in developing highly selective therapeutic strategies (Fig.1).

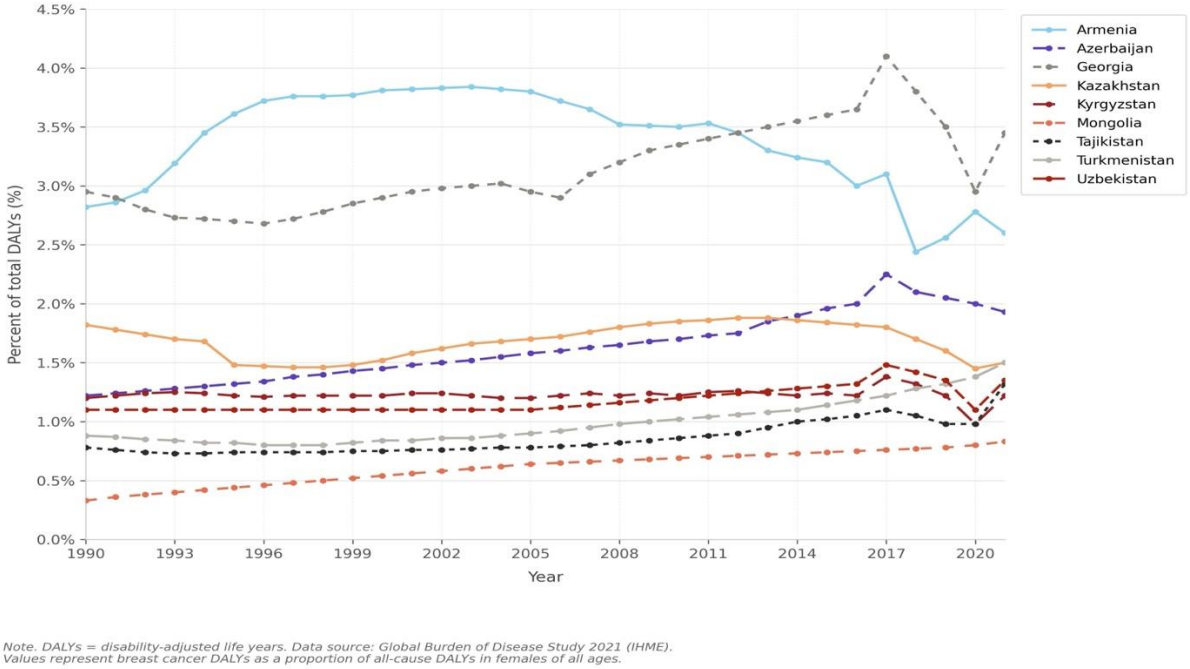

Fig. 1. Trends in the share of DALYs attributable to breast cancer among women in Central Asia and the Caucasus (1990–2023).

The graph shows the dynamics of the proportion of DALYs attributable to breast cancer in women of all ages in Central Asian and Transcaucasian countries over the period 1990–2023. Overall, there are differences between countries in the level and direction of changes. The highest values are observed in Armenia and Georgia, where the indicator has exceeded 3.0% of the total DALYs for many years. In Armenia, after an increase in the 1990s reaching a peak in the early 2000s, there is a gradual decline, particularly noticeable after 2018–2020. In Georgia, on the other hand, following a moderate decrease at the beginning of the period, there has been a steady increase with maximum values in the mid- and late 2010s, followed by some decline and partial recovery by 2023.

In Azerbaijan, a gradual and steady increase in the indicator has been observed from the early 1990s until the late 2010s, after which stabilisation at around 2% has been maintained. In Kazakhstan and Kyrgyzstan, the values remain moderate, with Kazakhstan experiencing a slight decline in recent years following growth in the 2000s and 2010s, while Kyrgyzstan shows fluctuations with a subsequent decline in 2020 and recovery by 2023. In Tajikistan, Turkmenistan, and Uzbekistan, an overall upward trend is also noted, which may indicate an increasing contribution of maternal mortality to the overall disease burden among women in these countries.

Progress in the fields of genomics, transcriptomics, and proteomics over the past two decades has enabled the identification of key driver mutations and oncogenic signalling pathways specific to various molecular subtypes of breast cancer — luminal A and B, HER2-enriched, and triple-negative (TNBC) [3]. Simultaneously, clinical oncology has undergone a revolution: highly affine monoclonal antibodies, antibody-drug conjugates (ADCs), small molecules — CDK4/6 and PI3K/AKT/mTOR inhibitors, PARP inhibitors, as well as immune checkpoint inhibitors — have emerged [1,8]. These advances have fundamentally changed the prognosis for advanced and metastatic breast cancer; however, the problem of primary and acquired resistance to therapy remains unresolved and requires further in-depth study [17,30].

Molecular subtypes and molecular-genetic heterogeneity of breast cancer

The modern classification of breast cancer (BC) is based on the receptor expression profile and the molecular characteristics of the tumour. According to the traditional classification, luminal A (ER+/PR+/HER2−, Ki-67<20%), luminal B (ER+/HER2+/−, high Ki-67), HER2-enriched (ER−/PR−/HER2+), and triple-negative (ER−/PR−/HER2−) subtypes are distinguished [9]. This classification not only has prognostic significance but also key predictive value, as it directly determines the choice of treatment strategy.

According to comparative genomic analysis data (TCGA,

2012), breast cancer can be further stratified based on somatic mutation profiles, copy number variations, and DNA methylation patterns. The most recurrent mutations include: PIK3CA (found in approximately 35–40% of all molecular subtypes), TP53 (around 35%, especially in TNBC), ESR1 (about 30–40% of metastatic HR+ cases, associated with acquired resistance to endocrine therapy), GATA3, CDH1, MAP3K1, BRCA1/2 [1,19].

In 2022, the concept of HER2-low (IHC 1+ or 2+/ISH−) was proposed, which fundamentally changed the treatment paradigm for patients traditionally classified as HER2-negative. The DESTINY-Breast04 study demonstrated a significant advantage of trastuzumab deruxtecan over chemotherapy specifically in this cohort, thereby opening up a new therapeutic niche [28].

PI3K/AKT/mTOR pathway

The phosphatidylinositol 3-kinase pathway is one of the most frequently disrupted in breast cancer. Activating mutations of the PIK3CA gene, which encodes the catalytic subunit p110α of PI3K-α, are detected in 35–40% of cases, predominantly in luminal subtypes [13]. This pathway integrates signals from receptor tyrosine kinases (RTKs), including HER2, IGFR1, FGFR, and regulates key cellular processes: proliferation, survival, metabolism, and angiogenesis through the activation of AKT and mTOR [20].

Mutations in the PTEN gene (a phosphatase that negatively regulates PI3K) are detected in approximately 15–25% of breast cancer patients and also contribute to constitutive pathway activation. The clinical significance of PIK3CA mutations has been confirmed in the SOLAR-1 (alpelisib) and CAPItello-291 (capivasertib) studies: the combination of PI3K/AKT inhibitors with fulvestrant significantly improves progression-free survival in HR+/HER2− patients with confirmed molecular alterations in this pathway.

The signalling pathways that regulate cell proliferation, differentiation, and survival play a key role in the development of breast cancer (BC) and the formation of drug resistance. Among these, the RAS/MAPK, NOTCH, and Wnt/β-catenin cascades are of particular importance, as they are involved in maintaining tumour growth, invasion, and the stem-like properties of tumour cells.

The RAS–RAF–MEK–ERK (MAPK) pathway is one of the central regulators of cellular proliferation and differentiation. Its hyperactivation is considered an important mechanism of secondary resistance to CDK4/6 inhibitors and endocrine therapy in patients with HR+/HER2− breast cancer subtype [21]. In this context, activating mutations in genes of the RAS family are relatively rare in primary breast cancer (approximately 5–10% of cases). More often, increased signalling is associated with activation of receptor tyrosine kinases such as EGFR and HER2, which is especially characteristic of triple-negative breast cancer (TNBC) [15].

The NOTCH signalling pathway, which mediates intercellular interactions, plays an important role in maintaining the stem cell properties of tumour cells. Activation of the NOTCH1 and NOTCH4 receptors is associated with the preservation of the tumour stem cell population, the development of resistance to chemotherapy, and the formation of a more aggressive tumour phenotype. These processes are most pronounced in TNBC and the HER2-positive subtype of breast cancer [9,4].

The Wnt/β-catenin pathway is equally significant, as its dysregulation contributes to tumour progression. Its hyperactivation is associated with the initiation of epithelial-mesenchymal transition (EMT), enhanced invasion, and metastasis. β-catenin functions as a transcriptional co-activator, stimulating the expression of proliferation genes (CCND1, MYC) and EMT markers (Vimentin, SNAIL). Increased activity of this pathway is more frequently observed in triple-negative breast cancer (TNBC) and is linked to the development of drug resistance [2]. The expression of oestrogen receptors (ER-α), encoded by the ESR1 gene, is detected in approximately 70% of breast cancer cases (luminal subtypes). ER-α acts as a ligand-dependent transcription factor, activating genes involved in the cell cycle (CCND1), proliferation, and survival [8]. ESR1 mutations in metastatic HR+ breast cancer after endocrine therapy are found in 30–40% of patients and lead to constitutive receptor activity in the absence of ligand, which is a key mechanism of secondary resistance to aromatase inhibitors [11].

Regulation of the cell cycle and CDK4/6 targets

The cyclin D–CDK4/6–INK4–RB pathway is a central regulator of the cell transition from the G1 phase to the S phase. Normally, cyclin D forms a complex with CDK4 or CDK6, leading to the phosphorylation of the retinoblastoma protein (Rb), the release of transcription factors E2F, and subsequent activation of DNA replication genes [18, 11]. In breast cancer, amplification of the CCND1 gene (cyclin D1), deletion of CDKN2A (p16INK4a), or overexpression of CDK4/6 are often observed, which results in uncontrolled proliferation.

CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib) in combination with endocrine therapy have become the standard first-line treatment for HR+/HER2− metastatic breast cancer. An updated systematic review (82 real-world clinical studies, 2025) showed a median PFS of 23.4–44.0 months, and a median OS of 38.0–58.0 months, depending on the agent used [7].

Epigenetic mechanisms of carcinogenesis

Epigenetic disturbances — DNA methylation, post-translational modifications of histones, and non-coding RNAs — play a key role in the initiation and progression of breast cancer alongside genetic changes [24]. Hypermethylation of CpG islands in the promoter regions of tumour suppressor genes (BRCA1, CDKN2A, E-cadherin) leads to their transcriptional silencing without altering the nucleotide sequence of the DNA.

Remodelling of chromatin through SWI/SNF complexes and disruption of the balance between acetylation/methylation of histones (H3K4me3, H3K27me3, H3K9ac) alters the accessibility of regulatory

genomic elements, which influences the expression of oncogenes and tumour suppressor genes [22]. In particular, the imbalance between H3K9ac and H3K27me3 is significantly associated with increased proliferation of breast cancer cells and metastasis. Promising therapeutic targets in this context include HDAC (histone deacetylase) inhibitors and EZH2 (histone H3K27 methyltransferase) inhibitors, several of which are in active clinical trial phases for breast cancer [8].

DNA repair and PARP inhibitors

BRCA1 and BRCA2 are key genomic 'guardians' that ensure highly accurate repair of double-strand DNA breaks through the homologous recombination (HR) mechanism. Germline mutations in BRCA1/2 are associated with a cumulative risk of developing breast cancer up to 80 years of approximately 50–70% (BRCA1) and 45–85% (BRCA2) [31]. Somatic mutations in BRCA or epigenetic silencing of BRCA1 are characteristic of about 25% of cases (TNBC).

PARP inhibitors (poly ADP-ribose polymerase) exert their cytotoxicity through a synthetic lethality mechanism: in cells with HR deficiency, inhibition of PARP1/2 leads to the accumulation of unrepaired single-strand DNA breaks, their conversion into double-strand breaks, and the death of the tumour cell [8]. Olaparib and talazoparib are approved by the FDA for metastatic and early HER2-negative breast cancer with germline BRCA1/2 mutations. In the OlympiAD study, olaparib significantly outperformed chemotherapy in median PFS (7.0 versus 4.2 months; HR 0.58) with a manageable adverse event profile [14,16].

Antibody–drug conjugates (ADCs)

ADCs are three-component molecules consisting of a monoclonal antibody that specifically binds to a tumour antigen, a cleavable linker, and a cytotoxic 'payload'. The high drug-to-antibody ratio (DAR) and the «bystander effect' phenomenon (transfer of the cytotoxin to neighbouring tumour cells) have established this class as revolutionary in heterogeneous tumours [12].

Trastuzumab deruxtecan (T-DXd) — an ADC with an antibody against HER2 and a topoisomerase I inhibitor as payload (DAR~8) — in the DESTINY-Breast03 study established a new second-line standard for HER2+ metastatic breast cancer, providing a median PFS of 28.8 months compared to 6.8 months for T-DM1 (HR 0.33; p<0.001) [15]. The extension of indications to HER2-low breast cancer in the DESTINY-Breast04 study (PFS 9.9 vs 5.1 months; OS 23.4 vs 16.8 months) marked a fundamentally new therapeutic concept [5].

Sacituzumab govitecan (SG), directed against the TROP-2 antigen with SN-38 as the payload, demonstrated in the ASCENT (TNBC) study a median PFS of 5.6 months compared to 1.7 months (HR 0.41; p<0.0001) and OS of 12.1 months compared to 6.7 months with chemotherapy. In the TROPiCS-02 study (HR+/HER2−), SG increased OS to 14.4 months compared to 11.2 months (HR 0.79; p=0.02) [2].

Immunotherapy for triple-negative breast cancer

TNBC is characterized by the highest immunogenicity among breast cancer subtypes: high levels of PD-L1 expression, significant density of tumor-infiltrating lymphocytes (TILs), and high tumor mutational burden (TMB) [22]. This justifies the use of immune checkpoint inhibitors (ICIs) specifically in TNBC.

The KEYNOTE-522 study established that the addition of pembrolizumab (anti-PD-1) to neoadjuvant chemotherapy in patients with early high-risk TNBC significantly increases the rate of pathological complete response (pCR: 64.8% vs 51.2%; p<0.001) and improves event-free survival (EFS). Based on these results, in 2021, the FDA approved the use of pembrolizumab for early TNBC regardless of PD-L1 status [26].

The combination of PARP inhibitors with ICT represents a strategically justified approach: PARP inhibitors activate immunogenic death of tumour cells through STING-dependent mechanisms, enhancing the anti-tumour immune response [23,26]. The KEYNOTE-162 study (niraparib + pembrolizumab) in TNBC with BRCA mutations showed an ORR of 47% and a median PFS of 8.3 months in the BRCA-mutant patient group [10.31].

Comparative analysis of key studies on molecular mechanisms and targeted therapy of breast cancer

Table 1. Comparative analysis of key studies on molecular mechanisms and targeted therapy of breast cancer

Authors, Year	Study Type	Sample/Cohort Size	Method / Drug	Key Results	Level of Evidence
Samad et al., 2025 [**Error! Reference source not found.**]	Systematic Review	Not Applicable	Molecular analysis of BC signaling pathways, targeted therapy	Described mechanisms of resistance to ET (ESR1 mutations in 30–40% of mBC), the role of PIK3CA, HER2, epigenetics,	Review (Scopus Q1, MedComm)

				and new drug classes (ADCs, ICIs)	
Cetinkaya & Avci, 2022 [**Error! Reference source not found.**]	Literature Review	Not Applicable	PI3K/AKT/mTOR, HER2, CDK4/6, VEGF, PARP inhibitors	Molecular classification of BC as the basis for targeted therapy; role of each pathway in tumor cell proliferation and survival	Review (Scopus, Med Oncol)
Cortés et al., 2022 [**Error! Reference source not found.**]	Randomized Controlled Trial (RCT) Phase III (DESTINY-Breast03)	524 patients	T-DXd vs T-DM1 (HER2+, mBC)	Median PFS: 28.8 vs 6.8 months (HR 0.33); ORR 79.7% vs 34.2%. T-DXd significantly outperforms T-DM1	RCT Phase III (NEJM, Q1)
Modi et al., 2022 [**Error! Reference source not found.**]	RCT Phase III (DESTINY-Breast04)	557 patients	T-DXd vs chemotherapy (HER2-low, mBC)	PFS 9.9 vs 5.1 months; OS 23.4 vs 16.8 months (HR+). First evidence of HER2-targeted therapy efficacy in HER2-low BC	RCT Phase III (NEJM, Q1)
Rugo et al., 2023 [**Error! Reference source not found.**]	RCT Phase III (TROPiCS-02)	543 patients	Sacituzumab govitecan vs chemotherapy (HR+/HER2−, mBC)	Median OS: 14.4 vs 11.2 months (HR 0.79; p=0.02); PFS: 5.5 vs 4.0 months	RCT Phase III (Lancet, Q1)
Lambert et al., 2025 [**Error! Reference source not found.**]	Systematic Review (82 RWE studies)	Multicenter data	CDK4/6i (palbociclib, ribociclib, abemaciclib) + ET, 1st-line HR+/HER2−	Median PFS 23.4–44.0 months; OS 38.0–58.0 months depending on the agent. Ribociclib demonstrates best OS	Systematic Review (Frontiers, Q1)

Han et al., 2025 [**Error! Reference source not found.**]	Review	Not Applicable	PARP inhibitors (olaparib, talazoparib) in TNBC with BRCA1/2 mutations	Synthetic lethality as the primary mechanism; resistance pathways described: BRCA mutation reversion, decreased PARP trapping	Review (Scopus, Int Oncol)

Note: PFS — progression-free survival; OS — overall survival; ORR — objective response rate; HR — hazard ratio; mBC — metastatic breast cancer; HR+ — hormone receptor-positive; HER2− — HER2-negative; ET — endocrine therapy; T-DXd — trastuzumab deruxtecan; ADC — antibody–drug conjugate.

Approved targeted therapy drugs for breast cancer

Table 2. Classes of targeted therapy drugs for breast cancer, their molecular targets, and clinical indications

Drug Class	Drug(s)	Molecular Target	BC Subtype	Key Studies	FDA Approval Year
CDK4/6 Inhibitors	Palbociclib, Ribociclib, Abemaciclib	Cyclin D–CDK4/6–Rb axis	HR+/HER2−, advanced/metastatic	PALOMA-2/3, MONALEESA-2/7, MONARCH-3	2015–2023
PI3K/AKT Inhibitors	Alpelisib, Capivasertib	PI3Kα (PIK3CA mut.), AKT	HR+/HER2−; PIK3CA-mutation	SOLAR-1, CAPItello-291	2019, 2023
Anti-HER2 ADCs	T-DXd (Trastuzumab deruxtecan)	HER2 (IHC 3+, 2+/ISH+, low)	HER2+, HER2-low	DESTINY-Breast03, -Breast04	2019, 2022
Anti-Trop-2 ADCs	Sacituzumab govitecan (SG)	TROP-2	TNBC; HR+/HER2−	ASCENT, TROPiCS-02	2020, 2023
PARP Inhibitors	Olaparib, Talazoparib	PARP1/2 (synthetic lethality with BRCA1/2 mut.)	TNBC and HR+/HER2−; gBRCA1/2 mut.	OlympiAD, EMBRACA, OlympiA	2018, 2022
Immune Checkpoint Inhibitors	Pembrolizumab, Atezolizumab	PD-1 / PD-L1	TNBC (PD-L1+); early-stage TNBC	KEYNOTE-522, IMpassion130	2021 (pembrolizumab)
Anti-HER2 Monoclonal Antibodies	Trastuzumab, Pertuzumab	HER2 ECD (domains IV, II)	HER2+	CLEOPATRA, APHINITY, NeoSphere	1998, 2012
Aromatase Inhibitors	Letrozole, Anastrozole, Exemestane	Aromatase (CYP19A1)	HR+, postmenopausal	ATAC, BIG 1-98	1995–2005

Note: T-DXd — trastuzumab deruxtecan; T-DM1 — trastuzumab emtansine; ADC — antibody–drug conjugate; FDA — U.S. Food and Drug Administration; IHC — immunohistochemistry; ISH — in situ hybridization.

Discussion

Molecular heterogeneity as a key therapeutic issue

The fundamental barrier to the 'cure' of breast cancer remains its molecular and clonal heterogeneity. Intratumoural heterogeneity is caused not only by differences in the mutation profiles of subclones but also by dynamic changes in the tumour's epigenetic landscape under the pressure of therapeutic selection [25]. Single-cell genomics and spatial transcriptomics technologies offer unprecedented opportunities for detailed study of this phenomenon, although their widespread implementation in clinical practice is still limited.

Circulating tumour DNA (ctDNA) in liquid biopsy has become a powerful tool for monitoring minimal residual disease, early detection of resistant mutations (ESR1, RB1, PIK3CA), and adapting therapy in real time. Nevertheless, standardisation of ctDNA detection methods and clinical validation of threshold values remain important challenges.

Mechanisms of resistance to targeted therapy

Resistance to CDK4/6 inhibitors can be primary (around 20% of tumours) or acquired and is mediated by several non-exclusive mechanisms: mutations/deletion of RB1 (loss of the target), amplification of CCND1 and CCNE1/CDK2 (bypassing cell cycle blockade), activation of alternative pathways (PI3K/AKT/mTOR, FGFR1, RAS/MAPK), as well as activating mutations of ESR1, which eliminate dependence on oestrogen stimulation [13]. Combined blockade of multiple pathways simultaneously (CDK4/6i + AKTi, CDK4/6i + PI3Ki) appears to be a promising strategy to overcome resistance.

Resistance to PARP inhibitors in TNBC may develop due to reversion mutations in BRCA that restore HR function, disruption of PARP-DNA complex trapping, activation of replication fork repair mechanisms (RADP1, SMARCAL1), or increased expression of MDR transporters [27]. Rational combinations of PARPi with IKT or ATM inhibitors aim to overcome resistance through the synergy of immunological and genotoxic effects.

Prospects of new therapeutic strategies

Among the most promising directions are: (1) PROTAC (proteolysis-targeting chimeras) — molecules that induce the degradation of the target protein via the ubiquitin-proteasome pathway, including ERα degraders (ARV-471/vepdegestrant) for HR+ breast cancer with ESR1 mutations; (2) bispecific antibodies that simultaneously block two signalling pathways; (3) oral SERDs of the new generation (elacestrant, camizestrant), effective in ESR1-mutant tumours [2, 14]; (4) new ADCs with improved linkers and payloads (dato-DXd, patritumab deruxtecan, lacotuzumab viscintin); (5) cellular immunotherapies (CAR-T, TIL therapy), currently undergoing clinical trials in TNBC.

Conclusion

The molecular heterogeneity of breast cancer, determined by mutation profiles (PIK3CA, ESR1, TP53, BRCA1/2), patterns of epigenetic disturbances, and the immune microenvironment, is a determinant of differences in tumour biology, prognosis, and response to therapy across various molecular subtypes.

The PI3K/AKT/mTOR signalling pathway is the most frequently mutated in breast cancer (~35–40% in PIK3CA); its clinical targetability has been confirmed in the SOLAR-1 and CAPItello-291 studies, which demonstrated a significant improvement in PFS in cohorts with molecularly confirmed pathway alterations.

CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib) have established a new standard of treatment for HR+/HER2− metastatic breast cancer with a median overall survival of up to 58 months in real-world settings and proven benefit in the adjuvant context (monarchE, NATALEE).

The concept of HER2-low and the development of ADC T-DXd have fundamentally changed the therapeutic algorithm, extending the benefits of HER2-targeted therapy to a significantly larger patient population. Sacituzumab govitecan confirmed an OS benefit in TNBC and HR+/HER2−.

Immunotherapy in combination with chemotherapy has become the standard of neoadjuvant treatment for early high-risk TNBC (KEYNOTE-522). Combinations of ICT with PARP inhibitors demonstrate synergy in BRCA-mutant cases.

The main mechanisms of resistance are: ESR1 and RB1 mutations, CCNE1 amplification, activation of alternative signalling pathways, and epigenetic reprogramming of tumour cells; monitoring these through liquid biopsy ensures therapy adaptation to the evolution of the clone.

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