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The Evolving Landscape Of Breast Cancer Treatment: From Conventional Approaches To Emerging Innovations

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ABSTRACT

Breast cancer remains one of the most prevalent malignancies worldwide, necessitating continuous advancements in treatment strategies to improve patient outcomes. This review explores the current landscape of breast cancer therapies, ranging from conventional approaches such as surgery, radiation therapy, and chemotherapy to emerging targeted and immunotherapeutic modalities. The primary objective of this review is to provide a comprehensive analysis of modern breast cancer treatments, highlighting their mechanisms of action, clinical efficacy, resistance mechanisms, and future directions. Recent advances in targeted therapy, particularly HER2 inhibitors, tyrosine kinase inhibitors (TKIs), CDK4/6 inhibitors, PI3K/AKT/mTOR pathway inhibitors, and PARP inhibitors, have revolutionized breast cancer management, significantly enhancing survival rates. Immunotherapy, including immune checkpoint inhibitors, has shown promise, particularly for triple-negative breast cancer. Despite these advancements, treatment resistance and adverse effects remain significant challenges, necessitating ongoing research into combination strategies, biomarker-driven therapies, and novel therapeutic targets. To ensure a robust and up-to-date synthesis, a structured search strategy was employed across PubMed, Scopus, and Web of Science databases. The search focused on peer-reviewed articles, clinical trials, and meta-analyses published in the last 10 years using keywords such as breast cancer, targeted therapy, immunotherapy, drug resistance, HER2 inhibitors, and precision medicine. Studies were selected based on relevance, clinical significance, and methodological rigor. Future research will focus on overcoming therapeutic resistance, refining combination regimens, and integrating biomarker-driven precision medicine to optimize patient-specific treatment approaches. A multidisciplinary approach, incorporating genomic profiling, immunotherapy, and next-generation targeted therapies, holds the potential to transform breast cancer care and improve long-term survival and quality of life.

Keywords: *Breast cancer, targeted therapy, immunotherapy, drug resistance, precision medicine, HER2 inhibitors, CDK4/6 inhibitors*

1. INTRODUCTION

Breast cancer represents a prevalent invasive cancer at 450,000 deaths globally each year. It is the second greatest cause of cancer-related fatality in women, first being lung cancer. Breast cancers can be classified as invasive or in situ, with in situ cases being more easily treatable. Concern should be expressed for invasive breast cancers, especially invasive ductal carcinoma, which accounts for 80% of all invasive breast cancers [1]. The WHO Global Breast Cancer Initiative (GBCI) aims to prevent 2.5 million breast cancer deaths worldwide between 2020 and 2040 by reducing the global breast cancer mortality rate by 2.5% annually. A 2.5% annual reduction in breast cancer mortality worldwide will prevent 25% of breast cancer deaths by 2030 and 40% of breast cancer deaths among women under the age of 70 by 2040. The three pillars for attaining these objectives are: promoting health for early identification; timely testing; and thorough breast cancer management [2]. Education about public health can help women and their loved ones become more aware of the symptoms and warning signs of breast cancer as well as the need of early identification and treatment. As screening by mammography is currently impracticable in many countries, this may still be accomplished without it [3].

Male breast cancer is an uncommon illness affecting just 0.5–1% of people worldwide. Male morbidity is mostly caused by a low concentration of breast tissue and a different hormonal milieu in milk. Adipose tissue, stromal tissues, milk ducts, and milk storage glands constitute a few of the parts that make up the milk glands [4]. Breast cancer is a complex illness with a range of subgroups that are associated with different clinical results. Breast cancer's aggressive nature, high likelihood of spreading to other parts of the body, occurrence due to multiple factors, and limited diagnostic and predictive options have hindered the advancement of potential treatments. Thus, it is reasonable to view breast cancer as a complicated, multifaceted illness that is caused by both inherited and random causes. Just twenty percent of patients have an increased likelihood of transferring breast cancer due to family history, even though genes influence this tendency [5].

BRCA1, BRCA2, TP53, SKT11, PTEN, CDH1, MSH12, chek2, and palb2 are among the important germ lines that are altered in breast cancer inheritance. Because of their great penetrance, BRCA1 and BRCA2 germ lines are more susceptible. BRCA1 and BRCA2 germ-line abnormalities account for over 40% of hereditary breast cancer cases. The BRCA1, BRCA2, and BRCA1/2 genes contribute to a 36–90% risk of breast cancer, with 72% and 69% of cases attributed to them at the age of 80 [6]. Human epidermal growth factors receptor 2 (HER2-Positive) is a protein that is encoded by extra copies of genes found in the cells of patients with HER2-positive breast cancer [7]. This protein increases the rate at which cancer cells divide, raising the possibility of they will spread. Thus, positive for HER2 carcinoma of the breast is the second leading cause of death after lung cancer[8]. Studies on the etiology of breast cancer demonstrate that the pathogenicity of the disease differs among its subtypes. The most commonly implicated genes in the development of breast cancer are BRCA1 and BRCA2, but other genes, ranked by degree of penetration, include Tp53, ATM, PTEN, LKB 1, HRAS1, NAT1, NAT2, GSTM1, GSTP1, GST1, CYP1A1, CYP1B1, CYP2D6, CYP17, CYP19, ER, AR, AR, COMT, UGT1A1, TNF α, HSP70, HFE, TFR, VDR, APC, APOE, CYP2E1, EDH17B2, HER2, and TβR-I [9].

2. TYPES OF BREAST CANCER

Breast cancer is a highly heterogeneous disease classified based on molecular and histopathological characteristics. The primary classification includes hormone receptor-positive (HR+), HER2-positive, and triple-negative breast cancer (TNBC), each requiring distinct therapeutic approaches. Understanding these subtypes is crucial for optimizing treatment strategies[10].

2.1 Hormone receptor-positive (ER+/PR+) breast cancer

Hormone receptor-positive breast cancer accounts for approximately 70% of all breast cancer cases. These tumors express estrogen receptors (ER) and/or progesterone receptors (PR), making them responsive to hormonal therapies. Treatment approaches are as follows.

Endocrine therapy: Tamoxifen (selective estrogen receptor modulator) and aromatase inhibitors (letrozole, anastrozole, exemestane) inhibit estrogen-driven tumor growth.

CDK4/6 inhibitors: Palbociclib, ribociclib, and abemaciclib block cell cycle progression and are used in combination with endocrine therapy for advanced cases.

PI3K inhibitors: Alpelisib targets PIK3CA-mutated HR+ breast cancer[11].

2.2 HER2-Positive breast cancer

HER2-positive breast cancer constitutes 15–20% of all breast cancer cases and is characterized by overexpression of the human epidermal growth factor receptor 2 (HER2) protein, which promotes aggressive tumor growth. Targeted Therapy Approaches are as follows.

Monoclonal antibodies: Trastuzumab and pertuzumab inhibit HER2 signaling, improving survival rates.

Tyrosine kinase inhibitors (TKIs): Lapatinib, neratinib, and tucatinib block HER2-driven pathways.

Antibody-Drug conjugates (ADCs): Trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan deliver cytotoxic agents to HER2-expressing cancer cells[12].

2.3 Triple-Negative breast cancer (TNBC)

TNBC is highly aggressive, accounting for 10–15% of breast cancer cases, and lacks ER, PR, and HER2 expression. It is associated with a higher risk of recurrence and limited treatment options. Treatment approaches are as follows.

Chemotherapy: Platinum-based regimens (carboplatin, cisplatin) remain the mainstay of treatment.

Immunotherapy: Immune checkpoint inhibitors (pembrolizumab, atezolizumab) have shown efficacy in PD-L1-positive TNBC.

PARP Inhibitors: Olaparib and talazoparib are effective in BRCA1/2-mutated TNBC[13].

2.4 Luminal A vs. Luminal B breast cancer

These subtypes are based on gene expression profiling and influence prognosis and treatment choices.

Luminal A: ER+/PR+, HER2-negative, slow-growing, and highly responsive to endocrine therapy. Best prognosis.

Luminal B: ER+/PR+ but with higher proliferation rates, HER2-positive or negative. Requires chemotherapy + endocrine therapy[14].

3. MECHANISMS OF ACTION

3.1 Inhibitors of HER2 Signaling

Tyrosine autophosphorylation and intrinsic protein tyrosine kinase activity are activated after receptor a dimerization. Angiogenesis, invasion, proliferation, and survival are among the vital cellular processes that are regulated by a series of biochemical and physiological reactions that are set off by these events. There is a vast range of signals because individual receptor complexes can trigger distinct signaling pathways that cause certain physiological reactions[15]. The effect of each receptor's cellular expression and the availability of ligands in each unique cell is thought to be the development of particular dimeric complexes of ErbB receptors and the subsequent stimulation of distinct intracellular signaling pathways[16]. HER-based dimers activate a multitude of signaling pathways, including but not limited to RasRaf-MAPK, PI3K-Akt, PLC-yl, Src, and STATs. The Ras-Raf-MAPK pathway is one of the best-characterized. When Ras is activated, a multistep. MAPK activation is caused by a phosphorylation cascade[17].

Dual specificity kinases activate the MAPKs ERKI and ERK2 by phosphorylating both a tyrosine and a threonine residue. MAPK then controls transcription in cells and has been associated with cell growth, survival, and transformation in lab experiments and, more recently, in research on human tumors. That the PI3K1Akt pathway is another signaling transduction pathway that is triggered by the HER2 network and is crucial for cell survival. One lipid kinase that produces phosphorylated phosphoinositides is called phosphatidylinositol-3 kinase (PI3K)[18]. It is triggered by HER2/HER3 dimers as well as other receptor complexes. Through the pleckstrin homology domain of the proto-oncogene Akt, these phosphorylated lipids attach and attract it to the cell membrane. When they occur, Thr 308 and Ser 473 are phosphorylated, which activates the activity of Akt kinase[19]. According to recent research, it plays a crucial in vivo role in the growth of tumors by promoting cell survival.It's possible that Akt plays a part in controlling cell division. For instance, cyclin Dl increases and enters the cell when Akt phosphorylates and inhibits glycogen synthase kinase cycle. Another crucial regulator of Cyclin drugs, including p21-28 and p27-29, is HER2. Additionally, a number of investigations have demonstrated that Akt phosphorylates p27 and moves it into the cytoplasm, preventing p27 from functioning as a cell cycle brake[20]. A key mechanism in HER2-positive breast cancer involves PI3K mutations leading to uncontrolled cell proliferation. Figure 1 illustrates the HER2-activated PI3K/AKT/mTOR pathway and the inhibitory role of Alpelisib.

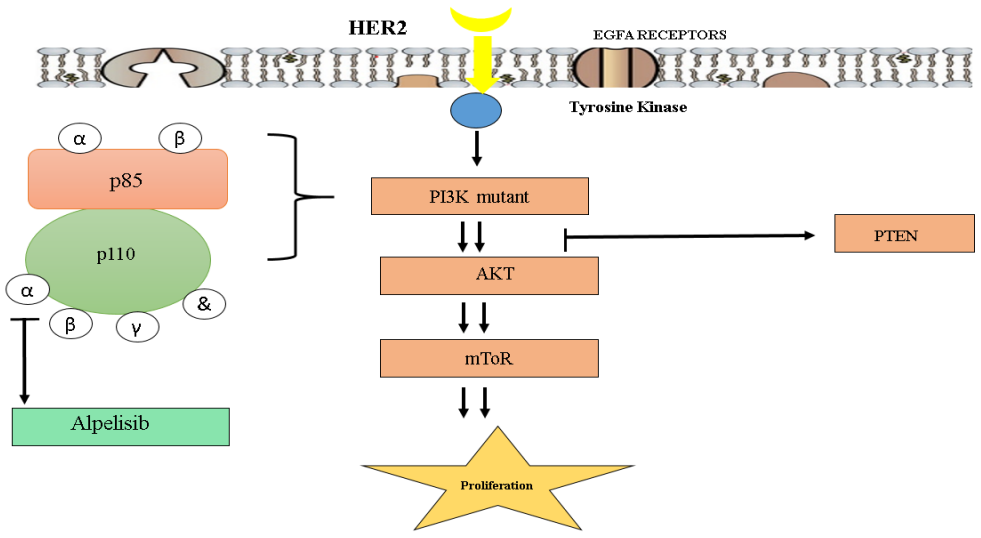


Figure 1. Schematic representation of the HER2/PI3K/AKT/mTOR signaling pathway in HER2-positive breast cancer and the inhibitory effect of Alpelisib on PI3Kα mutations.

3.2 Blocking P13K/ Akt/mTOR pathway

The regulation of cell survival, growth, proliferation, angiogenesis, transcription, translation, and metabolism is significantly influenced by the PI3K/AKT/mTOR signaling pathway as shown in Figure 2. When compared to other significant signaling pathways, the PI3K/AKT/mTOR pathway exhibits abnormalities in the majority of human cancers. It has been reported that

dysregulation of key components of this signaling pathway activates other downstream signaling pathways associated with oncogenesis. Phosphoinositide 3-kinases (PI3Ks) are lipid kinases that function as downstream effectors of G protein-coupled receptors (GPCRs) and receptor tyrosine kinases (RTKs). Phosphatidylinositol (PI) is a unique kind of membrane lipid that may be phosphorylated reversibly to produce phosphoinositides (PIs), such as PI 4-phosphate (PIP) and PI 4,5-bisphosphate (PIP2). Active PI3Ks generate phosphatidylinositol (3,4,5)-trisphosphate [PIP3] by phosphorylating the third carbon of the inositol head of PIP2.[21] Three categories of PI3Ks have been mentioned: class I, II, and III. Class IA and class IB PI3Ks are divisions of class I PI3Ks. Class I PI3Ks are the only sub-class that can only produce PIP3 from PIP2. The RTKs activate class IA PI3Ks, whereas the GPCRs activate class IB PI3Ks. These PI3K sub-classes, along with their associated genetic alterations and mutation frequencies, are summarized in Table 1. An active subunit (p110) plus an adaptor/regulatory subunit (p85) comprise class IA PI3Ks.There are five variations of the p85 regulatory component: p85α, p55α, p50α, p85β, and p55γ. Three distinct genes, PIK3CA, PIK3CB, and PIK3CD, express the three classes of p110 isoforms (p110α, p110β, and p110δ) that have been identified [22–23]. PTK3CA mutations have been regularly seen in a variety of cancer types, including OC. The p110γ catalytic subunit, which employs both the p84 and p101 regulatory subunits, makes up class IB PI3Ks. Three different catalytic isoforms (C2α, C2β, and C2γ) make up class II PI3Ks. No regulatory or adaptor subunits have been found in monomeric class II PI3Ks. They produce PIP2 by using PIP as substrates. Autophagy regulation has been found to be significantly influenced by heterodimeric class III PI3Ks, which are composed of two subunits: a catalytic subunit (Vps34) and an adaptor/regulatory subunit (Vps15).

Table 1. Classification of PI3K and AKT signaling components, their genetic alterations, and frequency of mutations observed in various cancer types.

PI3K signaling pathway component	Groups/subclass	Protein	Gene	Genetic alterations among the sub-classes/sub-groups	Mutation frequencies
PI3K	Class IA Regulatory Catalytic Class IB Regulatory Catalytic Class II Catalytic Catalytic Regulatory Catalytic	 p85α p55α p50α p85β p55γ p110α p110β p110δ p84 p101 p110γ C2α C2β	 PIK3R1 PIK3R2 PIK3R3 PIK3CA PIK3CB PIK3R6 PIK3R5 PIK3CG PIK3C2A PIK3C2B PIK3C2G PIK3R4 PIK3C3	Copy number gains in PIK3CA and PIK3CB mutations in PIK3CAPIK3CA gene amplification PIK3CA activating mutations and Mutationsinthe gene PIK3R1.	**1-** 1.30.5%amplification or somatic mutation in PIK3CA(primary epithelial ovariancancers) . **2-** Mutation in PIK3CAwere prevalent in ovarianclear cell (20%) andendometriosiscarcinoma(20%)compared toserous carcinoma (2.3%) . **3-** 46% PIK3CA mutations in ovarian clear cell carcinoma . **4-** 3% of PIK3CA somatic mutations in high-gradeserous carcinoma . **5-** 3.7% of PIK3CA activating mutations . **6-** 4% of mutations in PIK3R1.

		C2γ Vps15 Vps34			
AKT	AKT1,2 and 3	AKT 1 AKT 2 AKT 3	PKBα PKBβ PKBγ	Mutations in AKT1 amplifications in AKT2 and copy number gainin AKT2 .	1. 2% of point mutations in AKT1 [77]. 2. 13% of amplifications in AKT2 [79]. 3. 18.2% of amplifications in high grade Carcinomas.
PTEN	PTEN	PTEN	-	Loss of PTEN due to homozygous deletions, inactivatin gmutations, LOH or epigenetic modifications .	1. LOH in endometriosis (up to 40%) and serous ovarian carcinoma (up to 28%) . 2. Somatic mutations associated with PTEN (21%) in the majority of grade 1 or stage 1 endometriosis tumors .

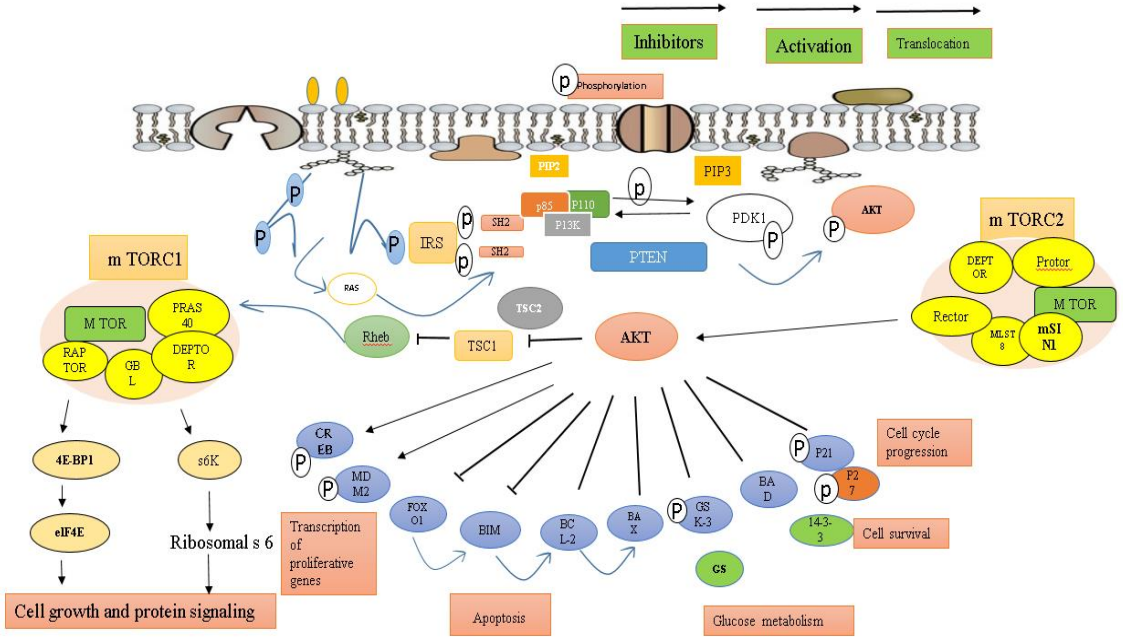


Figure 2.Schematic representation of the PI3K/AKT/mTOR signaling pathway, illustrating key molecular interactions, phosphorylation events, and downstream regulatory mechanisms involved in cell survival, proliferation, and metabolism.

3.3 Cell cycle arrest via CDK4/6 inhibition

Inhibition of CDK4/6 plays a crucial role in inducing G1-phase arrest by preventing the phosphorylation of the retinoblastoma protein (Rb) as shown in figure 3. In order to identify the beginnings of CDK4/6 inhibitor resistance, a number of research are currently being carried out to look into the cell cycle machinery and upstream signaling networks, such as the MAPK and PI3K/Akt/mTOR pathways. Rb is a significant biomarker that CDK4/6 phosphorylates. Extensive exposure to palbociclib or ribociclib has been shown to result in acquired resistance, and research in animal models has shown that loss of Rb1 is connected to de-novo resistance to CDK4/6 inhibitor. Additionally, clinical resistance among people with breast cancer treated with inhibitors of CDK4/6 has been connected to acquired mutations in Rb1 detected in circulating tumor DNA (ctDNA) [24]. Analysis of the HER-2 and HER-3 studies showed that high cyclin E1 (CCNE1) mRNA expression was associated with a less wealthy progression-free survival in patients who had previously received treatment (PALOMA-3 cohort), but not among people who had not received therapy (HER-2)[25]. The role of p16 amplification as a biomarker is yet unknown because the results of biomarker analysis of HER-1, HER-2, and HER-3 showed no appreciable difference in PFS between the p16/CCND1 cohort and the unselected group. The ECLIPS research looks for predictive biomarkers for the treatment of palbociclib with ET using prospective pharmacogenetic research. Since those who had disease progression had much higher levels of TK1, a critical regulator of the S/G2 stage, before treatment than three months later, the data suggest a connection between acquired resistance to CDK4/6i and TIK1 mRNA copies/mL[26].

Gene findings from 348 HR-positive HER2-negative metastatic BC samples were analyzed, and the loss of the format known as F1, a tumor suppressor from the cadherin family that enhances CDK6 expression through the Hippo pathway and may be a predictor of CDK4/6i resistance, was associated with a shorter PFS. Following first-line treatment with letrozole and ribociclib, a phase IIIb trial called Bioitalee is currently examining ct DNA changes and their development. For initial biomarker analysis, samples from 271 of the 287 postmenopausal participants in the research were suitable. The primary findings showed that PIK3CA was the most altered gene (23.15%).In contrast to de novo advanced BC, patients with recurrent disease are more likely to have mutations in KTM2C or changes in genes associated with the "estrogen receptor nuclear function" (ERnf) pathway, such as KTM2C, ESR1, GATA3, and MYC, whereas individuals with more aggressive infection are more likely to have a copy number gain of FGFRs . TP53 mutations, MYC gain, and changes in the She family and CDK4 and CD pathway genes were more common in patients with early disease progression, indicating that these indicators might represent innate resistance to letrozole and ribociclib first-line therapy. The changing patterns of final biomarkers and pharmacogenomics are still being studied [27].

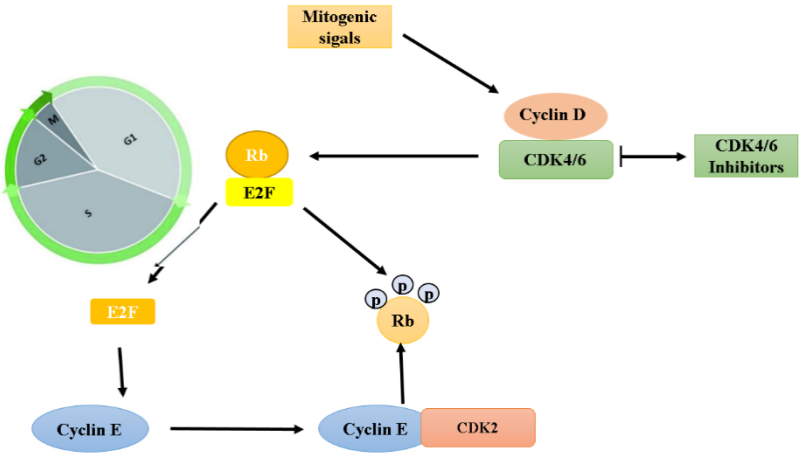


Figure 3. CDK4/6 inhibition-induced cell cycle arrest.

4. SYNTHETIC LETHALITY IN BRCA-DEFICIENT CELL -

4.1 Classic models: A number chromosomal theories have been proposed to explain how PARP inhibition selectively encourages synthetic lethality in cancer cells that do not have HR[28]. First, the SSB repair function of was examined. According to this theory, a decline in PARP function is caused by the accumulation of unrepaired SSBs in the genome due to replication forks and SSBs colliding, which in turn increases the levels of DSBs. cancer cells with HR deficiency repair DSBs at collapsing replication forks using error-prone repair pathways, including as nonhomologous end joining [NHEJ][29]. This leads to the creation of dangerous repair products and the selective cell death caused by PARP inhibition.Thus, the combination of HR loss and SSB repair leads to synthetic lethality in the removal of cancer cells lacking, demonstrating that PARP inhibition damages DNA by trapping on DNA. This shows that in cultures with and without PARP inhibitors entrap PARP1/2 at SSBs, preventing replication forks and increasing DSBs. The fact that deficient cells are particularly susceptible to death by PARP inhibitors due to their failure to accurately and efficiently repair DSBs (Figure 1B) confirms a synthetic lethal relationship between HR loss and PARP entrapment. The resistance of deficient cells with PARP1 mutations to PARP inhibitors indicates that PARP1 is the primary target for ensnaring and killing deficient cells. PARP inhibitors have emerged as a promising class of targeted therapeutics, particularly for cancers with homologous recombination deficiency, such as BRCA-mutated ovarian and breast cancers[30]. Several PARP inhibitors have been developed, differing in their PARP1-trapping potency, molecular targets, and regulatory approval status. Among them, olaparib, rucaparib, niraparib, and talazoparib have received FDA approval for clinical use, while others remain in investigational stages. Table 2 provides a comprehensive overview of FDA-approved and investigational PARP inhibitors, detailing their alternative names, PARP1-trapping ability relative to olaparib, molecular targets, manufacturers, and FDA approval status[31].

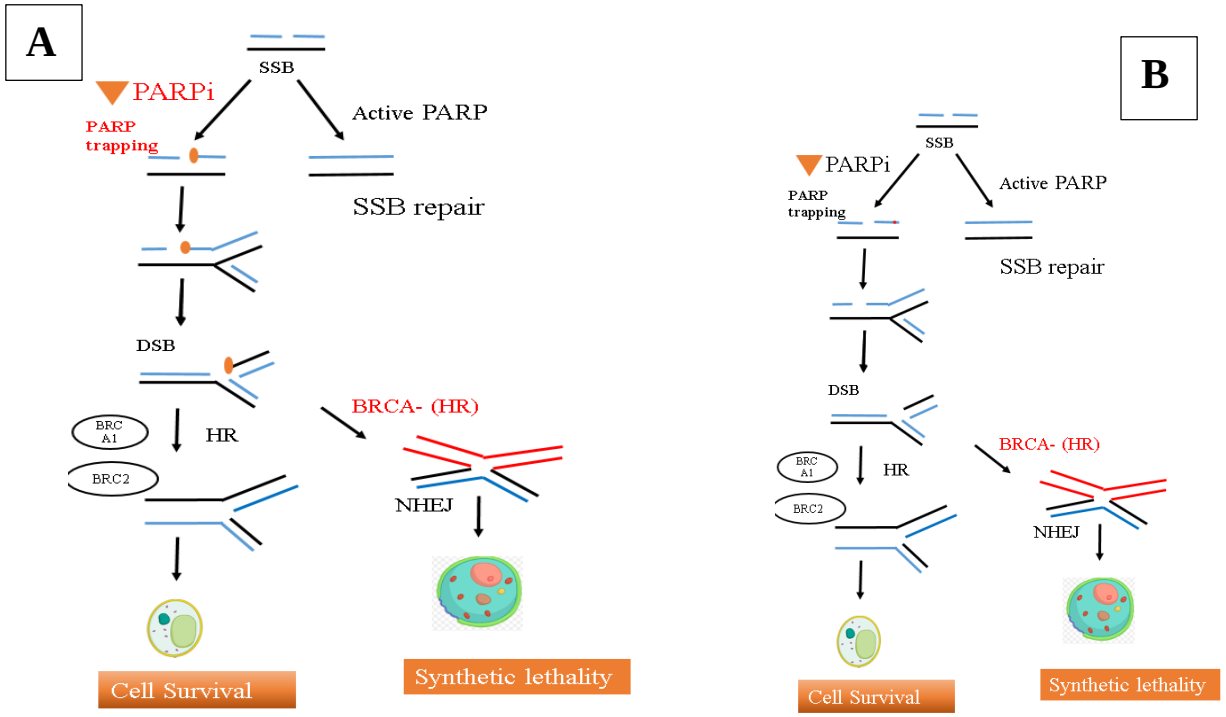
Table 2. FDA-Approved and Investigational PARP Inhibitors with Their Alternative Names, Target Specificity, and PARP1-Trapping Ability.

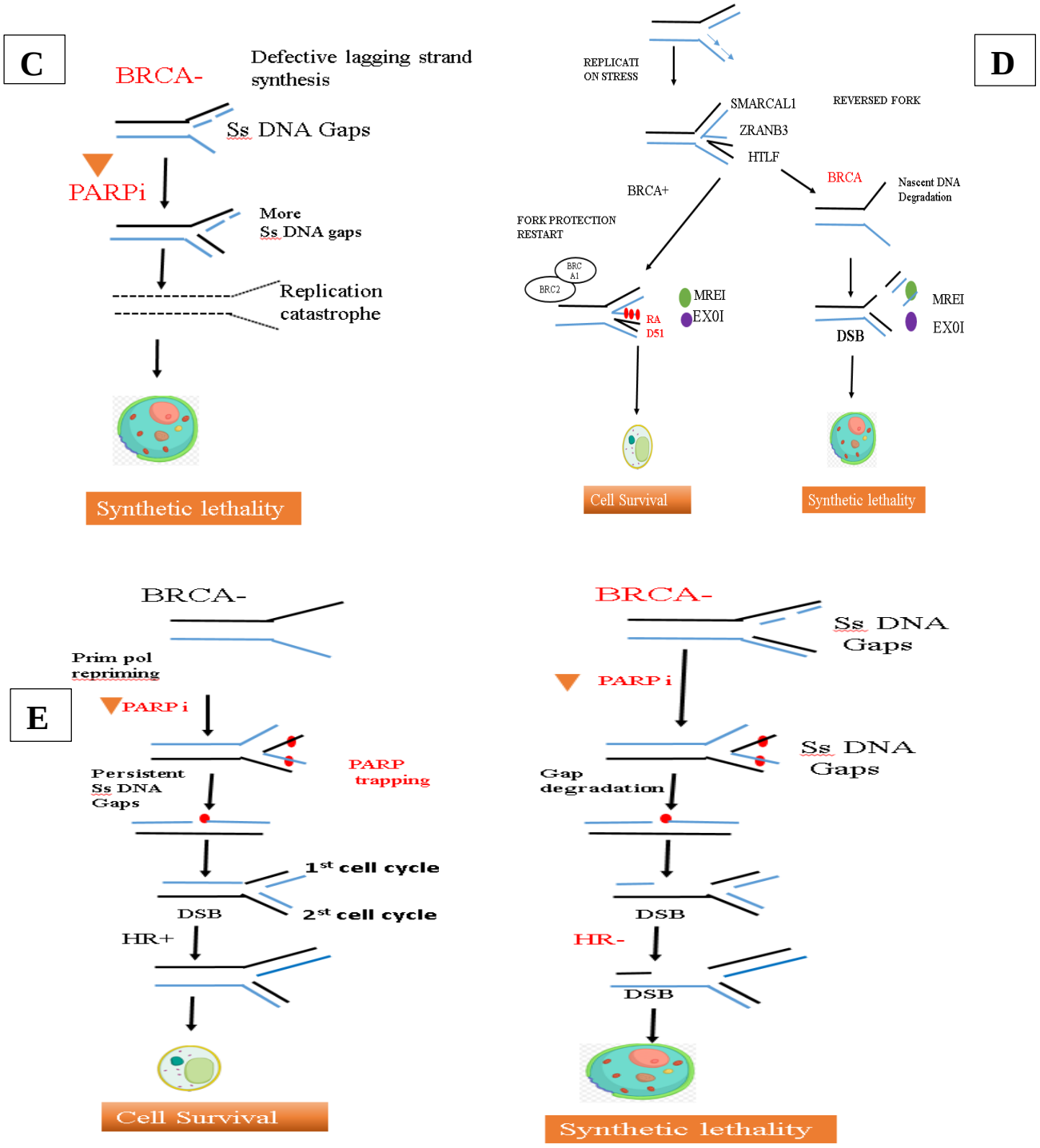
Agents	**Alternative name**	**PARP1- trapping ability (relative to olaparib (135))**	**Targets (37,40,68,136-138)**	**Producer**	**First FDA approval**
olaparib	AZD-2281,MK-7339	1	PARP1/2/3/4	LYNPARZA, AstraZeneca	2014
veliparib	ABT-888	0.2	PARP1/2/3	Abbvie	Not approved by FDA as a monotherapy
Rucaparib	AGO14699	1	PARP1/2/3/4	Rubraca, Clovis	2018
Niraparib	MK-4827		PARP1/2	Zejula, Tesaro Inc.	2017

Talazoparib	BMN-673	100	PARP1/2	Talzenna, Pfizer	2018
pamiparib	BGB-290-102	NA	PARP1/2/3	Beigene	NA(approved in China in 2021
venadaparib	1DX-1197	NA	PARP1/2	idience	NA
AZD5305	NA	NA	PARP1	AstraZeneca	NA

4.2 Emerging models: Although BRCA1/2's role in homologous recombination (HR) has been thoroughly investigated, their roles at replication forks are becoming more clear. When replication forks stall, (BRCA1 and BRCA2)are essential in halting the nucleolytic destruction of developing DNA [32]. MRE11 and EXO1 nucleases break down developing DNA in BRCA-deficient cells, and SMARCAL1, ZRANB3, and HLTF are necessary for this process to turn stalled replication forks into reversed forks. Interestingly, BRCA1-deficient cells regain fork protection when they become resistant to PARP medications. The MLL3/4 complex protein PTIP is deleted in BRCA2-deficient cells, restoring fork protection and tolerance to PARP inhibitors.These findings suggest that the greater nascent DNA degradation at reversed forks in BRCA-deficient cells exacerbates fork collapse, disrupts proper fork recovery, and causes genomic instability and cell death when PARP inhibition is used.Although BRCA1/2 mutations protects BRCA-deficient cells under stress, their vulnerability to PARP inhibitors may not be directly related to their inability to protect reversed replication forks. In cells with BRCA insufficiency, single-stranded DNA (the ssDNA) or ssDNA gaps are more common, according to new research. PrimPol-mediated repriming may be the cause of ssDNA gaps in BRCA-deficient cells, according to some research, whereas other studies explain these gaps to abnormalities in PCNA cycling and inadequate lagging strand synthesis. Specifically, incorrect processing of Okazaki fragments activates PARP1, whereas inhibition of PARP stops the lagging strand from developing during DNA replication, leading to a higher number of postreplicative single-strand nicks or gaps [33]. Double-strand breaks (DSBs) happen when imprisoned PARP1-containing ssDNA gaps persist until mitosis and the subsequent S phase. BRCA-deficient cells accumulate more DSBs all over multiple cell cycles than BRCA-proficient cells because they are unable to effectively repair gap-derived DSBs and do not initiate the replication checkpoint to slow down the cell cycle. That is important to keep in mind that the various models mentioned above might coexist. Some of these models may be connected by one underlying mechanism, even though multiple routes may contribute to the PARP inhibitor's ability to induce cell death in BRCA-deficient cells [34].

Classic models





5. CLINICAL EFFICACY

5.1 Landmark clinical trials demonstrating improved outcome

Targeted therapeutics and the use of biomarker assessment in formal treatment pose a challenge to the traditional drug development paradigm of phase I to determine the safety profile, phase II to establish the efficacy signal, and phase III for establishing definitive clinical benefit. Because they can be used to identify patients who are more likely to benefit from a specific treatment, biomarkers are an essential feature in targeted therapies[35]. In the context of personalized medicine, phase I studies to examine how to measure marker alteration in normal and tumor tissue samples, providing guidance for determining cut points and evaluating efficacy within molecularly defined subsets; phase II studies involve meticulous evaluation of the marker in the past to determine clinical value; and phase III trials are confirmatory, validating the marker

(and companion diagnostic) through extensive prospective randomized controlled trials (RCT) in a multicenter setting[36]. Therefore, the primary obstacle to the development of novel cancer treatments is the ability to recognize and evaluate activity in molecularly defined patient subsets beginning with early phase trials in order to forecast which individuals would react to a novel agent or regimen. To expedite the new medication development process and provide the appropriate therapies to the appropriate patients, design methodologies have changed over the past several years [37]. Adaptive enrichment, basket, and umbrella techniques are a class of innovative concepts for oncology-targeted therapy testing. The following topics will be covered in this review, which will illustrate the ideas with examples of ongoing or finished trials: When to use enrichment or targeted trial design strategies; (2) how to improve clinical trial efficacy by using umbrella trials to evaluate the impact of various drugs on distinct mutations (molecular subtypes) within a single tumor type; and (3) the function of basket trials in effectively screening agents to identify the "exceptional" responders, e.g., the impact of a single drug across multiple tumor types and/or histologic subtypes harboring the same mutation (molecular profile). These design techniques go against the conventional wisdom on drug development. To put these concepts into effect, cutting edge data collecting technologies, substantial multidisciplinary collaboration, and new statistical approaches are required[38]. When applicable, illustrative examples will be used to explain logistical hurdles to implementation resulting from centralized assay testing, the need for multiple specimens, multidisciplinary collaboration, and infrastructure requirements.

5.2 Combination Strategies with chemotherapy or endocrine therapy

Integrating chemotherapy with endocrine therapy has become a key approach in breast cancer treatment, aiming to enhance effectiveness and improve patient outcomes. Several strategies are employed depending on tumor characteristics and treatment goals.

Neoadjuvant Therapy: Chemotherapy is administered before surgery to shrink tumors, making them easier to remove. In hormone receptor-positive tumors, endocrine therapy can be introduced alongside or after chemotherapy to target hormone-driven cancer growth[39].

Adjuvant Therapy: Chemotherapy is given post-surgery to eliminate residual cancer cells, followed by endocrine therapy to prevent recurrence. In some high-risk cases, chemotherapy and endocrine therapy are administered concurrently[40].

Targeted Therapy: For HER2-positive breast cancer, chemotherapy is combined with HER2-targeted agents (e.g., trastuzumab) and endocrine therapy for improved efficacy. In postmenopausal women, aromatase inhibitors may be used alongside chemotherapy to enhance treatment outcomes[41].

Personalized Approaches: Advances in genetic and molecular profiling allow for biomarker-driven therapy, tailoring treatment to specific cancer characteristics such as PIK3CA mutations[42].

Clinical Trials: Ongoing research explores novel therapeutic combinations and optimized sequencing to improve efficacy and minimize toxicity

6. RESISTANCE MECHANISMS IN BREAST CANCER TREATMENT

Resistance to therapy in breast cancer can be classified into primary and acquired resistance. Primary resistance refers to cases where an immunotherapy or treatment plan is ineffective from the outset, often due to adaptive immune resistance mechanisms[43]. Acquired resistance occurs when cancer cells or bacteria develop resistance to previously effective treatments, either through genetic mutations or the uptake of resistance-conferring DNA from other cells. One major mechanism of resistance is the activation of bypass pathways, particularly in hormone receptor-positive and HER2-positive breast cancer subtypes[44]. These pathways allow cancer cells to evade the effects of therapies like endocrine therapy and targeted treatments. The PI3K/AKT/mTOR pathway is frequently implicated, where mutations in the PIK3CA gene or loss of PTEN lead to pathway overactivation, enabling continued cancer cell growth despite treatment[45]. Similarly, estrogen receptor (ER) reactivation, often through ESR1 mutations, can cause resistance to therapies like tamoxifen and aromatase inhibitors.

Alternative growth factor receptors can also contribute to resistance by triggering signaling cascades that support cancer cell survival and proliferation. The Ras/Raf/MEK/ERK pathway, when constitutively activated due to mutations in BRAF or Ras, provides another route for tumor progression independent of primary therapy[46]. Additionally, overexpression of androgen receptors (AR) in certain breast cancer subtypes allows cells to proliferate without reliance on estrogen signaling. Beyond these molecular pathways, cellular stress response and survival mechanisms enable cancer cells to withstand the effects of chemotherapy and endocrine therapy, further complicating treatment efficacy. Understanding these resistance mechanisms is crucial for developing more effective therapeutic strategies and overcoming treatment failure in breast cancer.

7. FUTURE PROSPECTS

The development of novel targets and combination approaches remains essential for enhancing existing therapies, improving efficacy, and overcoming acquired resistance[47]. Targeted therapy focuses on specific biological pathways that drive cancer progression, often involving proteins, genes, or signaling cascades. Combination therapies, which use multiple therapeutic

agents to simultaneously target different mechanisms, have shown promise in improving treatment outcomes, especially for aggressive and resistant breast cancer subtypes[48]. Overcoming resistance with next-generation agents is a critical area of ongoing research. Advances in targeted therapy include next-generation HER2 inhibitors such as neratinib and tucatinib, which are effective against trastuzumab-resistant tumors, particularly when combined with chemotherapy[49]. Similarly, PI3K inhibitors like alpelisib, used alongside HER2-targeted treatments, address pathway activation that contributes to resistance. In the field of hormonal therapy, CDK4/6 inhibitors such as palbociclib, ribociclib, and abemaciclib enhance endocrine therapy by preventing cell cycle progression in ER-positive breast cancer[50]. Additionally, selective estrogen receptor degraders (SERDs) like elacestrant offer treatment options for tumors that have become resistant to conventional endocrine therapy.

Immunotherapy has emerged as a promising strategy, particularly for triple-negative breast cancer (TNBC). Checkpoint inhibitors like pembrolizumab and atezolizumab, when combined with chemotherapy, have shown effectiveness in tumors with high PD-L1 expression[50]. Research is also exploring innovative immune techniques aimed at modifying the tumor microenvironment to enhance immune responses. The integration of immunotherapy with other modalities, such as HER2-targeted treatments and endocrine therapy, may further reduce resistance and improve clinical outcomes[51]. Biomarker-driven patient selection plays a pivotal role in personalized oncology by tailoring treatment to the molecular characteristics of each tumor. Identifying biomarkers enables clinicians to optimize therapy selection, minimize unnecessary side effects, and improve patient outcomes[52]. Advances in genomic profiling and liquid biopsy technologies provide real-time insights into resistance mechanisms, allowing for timely modifications in treatment plans. The development of multiplex biomarker panels and integration of clinical data with genomic findings enhance decision-making and enable precision medicine approaches[53].

The integration of immunotherapy with targeted therapies represents a significant advancement in cancer treatment. This approach enhances anti-tumor responses by combining immune checkpoint inhibitors with agents targeting specific mutations, such as BRAF[54]. In TNBC, combining chemotherapy with checkpoint inhibitors has demonstrated the ability to trigger immune responses while directly targeting malignant cells[55]. The continuous evolution of these integrative strategies is shaping the future of breast cancer management, offering more effective and personalized therapeutic options for patients[56].

8. CONCLUSION

The field of breast cancer treatments is always changing due to new discoveries in the field and a better comprehension of tumor biology. Patients have had better results and higher survival rates when multimodal approaches combining surgery, radiation, systemic treatments, and novel immunotherapies are used. Genomic profiling informs personalized medicine, enabling customized therapies that maximize benefits and minimize side effects. Prospective avenues for future research encompass investigating innovative drugs, combining treatments, and employing immunotherapeutic approaches to enhance outcomes, especially in complex subtypes such as triple-negative breast cancer. Investigation and clinical trials must go on to increase the efficacy of current therapies, find biomarkers for more accurate patient matching, and ultimately raise the standard of living for those with breast cancer. To optimize treatment success, a multidisciplinary approach integrating clinical, molecular, and immunotherapeutic advancements is crucial. Continued research, clinical trials, and innovation in drug discovery, treatment sequencing, and resistance mechanisms will shape the future of breast cancer therapy. By refining therapeutic strategies and leveraging precision medicine, the goal is to achieve better long-term survival, reduced toxicity, and an improved quality of life for breast cancer patients.

REFERENCES

[1] Noor F, Noor A, Ishaq AR, Farzeen I, Saleem MH, Ghaffar K, Aslam MF, Aslam S, Chen JT. Recent advances in diagnostic and therapeutic approaches for breast cancer: A comprehensive review. Current Pharmaceutical Design. 2021 Jun 1;27(20):2344-65.

[2] Núñez C, Capelo JL, Igrejas G, Alfonso A, Botana LM, Lodeiro C. An overview of the effective combination therapies for the treatment of breast cancer. Biomaterials. 2016 Aug 1;97:34-50.

[3] Haussmann J, Corradini S, Nestle-Kraemling C, Bölke E, Njanang FJ, Tamaskovics B, Orth K, Ruckhaeberle E, Fehm T, Mohrmann S, Simiantonakis I. Recent advances in radiotherapy of breast cancer. Radiation oncology. 2020 Dec;15:1-0.

[4] Liu Y, Hu Y, Xue J, Li J, Yi J, Bu J, Zhang Z, Qiu P, Gu X. Advances in immunotherapy for triple-negative breast cancer. Molecular cancer. 2023 Sep 2;22(1):145.

[5] Ye F, Dewanjee S, Li Y, Jha NK, Chen ZS, Kumar A, Vishakha N, Behl T, Jha SK, Tang H. Advancements in clinical aspects of targeted therapy and immunotherapy in breast cancer. Molecular cancer. 2023 Jul 6;22(1):105.

[6] Luque-Bolivar A, Pérez-Mora E, Villegas VE, Rondón-Lagos M. Resistance and overcoming resistance in

breast cancer. Breast Cancer: Targets and Therapy. 2020 Nov 11:211-29.

[7] Arteaga CL. Progress in breast cancer: overview. Clinical Cancer Research. 2013 Dec 1;19(23):6353-9.

[8] Herdiana Y, Husni P, Nurhasanah S, Shamsuddin S, Wathoni N. Chitosan-based nano systems for natural antioxidants in breast cancer therapy. Polymers. 2023 Jul 5;15(13):2953.

[9] Mo K, Kim A, Choe S, Shin M, Yoon H. Overview of solid lipid nanoparticles in breast cancer therapy. Pharmaceutics. 2023 Jul 31;15(8):2065.

[10] Tang, Y., Qiu, L., Li, Z., & Wang, R. (2025). Extracellular matrix shapes cancer stem cell behavior in breast cancer: A mini review. *Frontiers in Immunology*, *15*, 1503021..

[11] Li JJ, Cheng HY, Lee CH, Ng JK, Tsang JY, Tse GM. Single-cell multiplex immunocytochemistry in cell block preparations of metastatic breast cancer confirms sensitivity of GATA-binding protein 3 over gross cystic disease fluid protein 15 and mammaglobin. Cancer Cytopathology. 2025 Jan;133(1):e22910.

[12] Yersal O, Barutca S. Biological subtypes of breast cancer: Prognostic and therapeutic implications. World journal of clinical oncology. 2014 Aug 10;5(3):412.

[13] Zagami P, Carey LA. Triple negative breast cancer: Pitfalls and progress. NPJ breast cancer. 2022 Aug 20;8(1):95.

[14] Ades F, Zardavas D, Bozovic-Spasojevic I, Pugliano L, Fumagalli D, De Azambuja E, Viale G, Sotiriou C, Piccart M. Luminal B breast cancer: molecular characterization, clinical management, and future perspectives. Journal of clinical oncology. 2014 Sep 1;32(25):2794-803.

[15] Wang L, Zhang S, Wang X. The metabolic mechanisms of breast cancer metastasis. Frontiers in Oncology. 2021 Jan 7;10:602416.

[16] Malikova I, Worth A, Aliyeva D, Khassenova M, Kriajevska MV, Tulchinsky E. Proteolysis of TAM receptors in autoimmune diseases and cancer: what does it say to us?. Cell Death & Disease. 2025 Mar 5;16(1):155.

[17] Obidiro O, Battogtokh G, Akala EO. Triple negative breast cancer treatment options and limitations: future outlook. Pharmaceutics. 2023 Jun 23;15(7):1796.

[18] Broeker CD. *Comparative Genomics in Breast Cancer: Insights From Murine Models to Human Disease Mechanisms* (Doctoral dissertation, Michigan State University).

[19] Haque MA, Poullikkas T, Al-Amin Kaisar FM, Haque S, Khatun MH, Mamun A, Khan A. PHLPP1 depletion promotes tumorigenesis and stemness in triple-negative breast cancer cells through AKT signaling. Medical Oncology. 2025 Feb 20;42(3):80.

[20] Pradhan R, Dey A, Taliyan R, Puri A, Kharavtekar S, Dubey SK. Recent advances in targeted nanocarriers for the management of triple negative breast cancer. Pharmaceutics. 2023 Jan 11;15(1):246.

[21] Kotsifaki A, Alevizopoulos N, Dimopoulou V, Armakolas A. Unveiling the immune microenvironment's role in breast cancer: A glimpse into promising frontiers. International journal of molecular sciences. 2023 Oct 18;24(20):15332.

[22] Orsini A, Diquigiovanni C, Bonora E. Omics technologies improving breast cancer research and diagnostics. International Journal of Molecular Sciences. 2023 Aug 11;24(16):12690.

[23] Obidiro O, Battogtokh G, Akala EO. Triple negative breast cancer treatment options and limitations: future outlook. Pharmaceutics. 2023 Jun 23;15(7):1796.

[24] Mo K, Kim A, Choe S, Shin M, Yoon H. Overview of solid lipid nanoparticles in breast cancer therapy. Pharmaceutics. 2023 Jul 31;15(8):2065.

[25] Mo K, Kim A, Choe S, Shin M, Yoon H. Overview of solid lipid nanoparticles in breast cancer therapy. Pharmaceutics. 2023 Jul 31;15(8):2065.

[26] Herdiana Y, Husni P, Nurhasanah S, Shamsuddin S, Wathoni N. Chitosan-based nano systems for natural antioxidants in breast cancer therapy. Polymers. 2023 Jul 5;15(13):2953.

[27] Arteaga CL. Progress in breast cancer: overview. Clinical Cancer Research. 2013 Dec 1;19(23):6353-9.

[28] Poppi L. Exploring the effect of RAD51/BRCA2 inhibition to pursue synthetic lethality with PARPi in in-vitro models of pancreatic cancer.

[29] Yuan P, Ma N, Xu B. Poly (adenosine diphosphate-ribose) polymerase inhibitors in the treatment of triple-negative breast cancer with homologous repair deficiency. Medicinal research reviews. 2024 Nov;44(6):2774-92.

[30] Morganti S, Marra A, De Angelis C, Toss A, Licata L, Giugliano F, Salimbeni BT, Giachetti PP, Esposito A,

Giordano A, Bianchini G. PARP inhibitors for breast cancer treatment: a review. JAMA oncology. 2024 May 1;10(5):658-70.

[31] Duda JM. *Elucidation of the High-Grade Serous Ovarian Cancer Acetylome to Identify Novel Therapeutic Vulnerabilities* (Doctoral dissertation, University of Minnesota).

[32] Luque-Bolivar A, Pérez-Mora E, Villegas VE, Rondón-Lagos M. Resistance and overcoming resistance in breast cancer. Breast Cancer: Targets and Therapy. 2020 Nov 11:211-29.

[33] Ye F, Dewanjee S, Li Y, Jha NK, Chen ZS, Kumar A, Vishakha N, Behl T, Jha SK, Tang H. Advancements in clinical aspects of targeted therapy and immunotherapy in breast cancer. Molecular cancer. 2023 Jul 6;22(1):105.

[34] Glaviano A, Foo AS, Lam HY, Yap KC, Jacot W, Jones RH, Eng H, Nair MG, Makvandi P, Geoerger B, Kulke MH. PI3K/AKT/mTOR signaling transduction pathway and targeted therapies in cancer. Molecular cancer. 2023 Aug 18;22(1):138.

[35] Incorvaia L, Perez A, Marchetti C, Brando C, Gristina V, Cancelliere D, Pivetti A, Contino S, Di Giovanni E, Barraco N, Bono M. Theranostic biomarkers and PARP-inhibitors effectiveness in patients with non-BRCA associated homologous recombination deficient tumors: Still looking through a dirty glass window?. Cancer Treatment Reviews. 2023 Dec 1;121:102650.

[36] Llovet JM, Pinyol R, Yarchoan M, Singal AG, Marron TU, Schwartz M, Pikarsky E, Kudo M, Finn RS. Adjuvant and neoadjuvant immunotherapies in hepatocellular carcinoma. Nature Reviews Clinical Oncology. 2024 Apr;21(4):294-311.

[37] Llovet JM, Pinyol R, Yarchoan M, Singal AG, Marron TU, Schwartz M, Pikarsky E, Kudo M, Finn RS. Adjuvant and neoadjuvant immunotherapies in hepatocellular carcinoma. Nature Reviews Clinical Oncology. 2024 Apr;21(4):294-311.

[38] Zhang H, Hussin H, Hoh CC, Cheong SH, Lee WK, Yahaya BH. Big data in breast cancer: towards precision treatment. Digital Health. 2024 Nov;10:20552076241293695.

[39] Trayes KP, Sarah EH. Cokenakes. Breast cancer treatment. American family physician. 2021;104(2):171-8.

[40] Hong R, Xu B. Breast cancer: an up-to-date review and future perspectives. Cancer communications. 2022 Oct;42(10):913-36.

[41] Swain SM, Shastry M, Hamilton E. Targeting HER2-positive breast cancer: advances and future directions. Nature reviews Drug discovery. 2023 Feb;22(2):101-26.

[42] Passaro A, Al Bakir M, Hamilton EG, Diehn M, André F, Roy-Chowdhuri S, Mountzios G, Wistuba II, Swanton C, Peters S. Cancer biomarkers: emerging trends and clinical implications for personalized treatment. Cell. 2024 Mar 28;187(7):1617-35.

[43] Dong C, Wu J, Chen Y, Nie J, Chen C. Activation of PI3K/AKT/mTOR pathway causes drug resistance in breast cancer. Frontiers in pharmacology. 2021 Mar 15;12:628690.

[44] Zhong H, Zhou Z, Wang H, Wang R, Shen K, Huang R, Wang Z. The biological roles and clinical applications of the PI3K/AKT pathway in targeted therapy resistance in HER2-positive breast cancer: a comprehensive review. International Journal of Molecular Sciences. 2024 Dec 13;25(24):13376.

[45] Castel P, Toska E, Engelman JA, Scaltriti M. The present and future of PI3K inhibitors for cancer therapy. Nature cancer. 2021 Jun;2(6):587-97.

[46] Rocca A, Braga L, Volpe MC, Maiocchi S, Generali D. The predictive and prognostic role of RAS–RAF–MEK–ERK pathway alterations in breast cancer: revision of the literature and comparison with the analysis of cancer genomic datasets. Cancers. 2022 Oct 28;14(21):5306.

[47] Jin H, Wang L, Bernards R. Rational combinations of targeted cancer therapies: background, advances and challenges. Nature Reviews Drug Discovery. 2023 Mar;22(3):213-34.

[48] Lu B, Natarajan E. Combination Therapy Strategies and Advanced Biomarkers Can Potentially Enhance The Precision-Medicine Treatment of Metastatic Breast Cancer. Journal of Natural Science, Biology and Medicine. 2024 Jul;15(2):266.

[49] Guo L, Shao W, Zhou C, Yang H, Yang L, Cai Q, Wang J, Shi Y, Huang L, Zhang J. Neratinib for HER2-positive breast cancer with an overlooked option. Molecular Medicine. 2023 Oct 6;29(1):134.

[50] Pandey K, Katuwal NB, Park N, Hur J, Cho YB, Kim SK, Lee SA, Kim I, Lee SR, Moon YW. Combination of abemaciclib following eribulin overcomes palbociclib-resistant breast cancer by inhibiting the G2/M cell cycle phase. Cancers. 2022 Jan 1;14(1):210.

[51] Larroquette M, Domblides C, Lefort F, Lasserre M, Quivy A, Sionneau B, Bertolaso P, Gross-Goupil M, Ravaud A, Daste A. Combining immune checkpoint inhibitors with chemotherapy in advanced solid tumours: A review. European Journal of Cancer. 2021 Nov 1;158:47-62.

[52] Nandi D, Sharma D. Integrating immunotherapy with conventional treatment regime for breast cancer patients-an amalgamation of armamentarium. Frontiers in Immunology. 2024 Nov 1;15:1477980.

[53] Anbarasu S, Anbarasu A. Cancer-biomarkers associated with sex hormone receptors and recent therapeutic advancements: a comprehensive review. Medical Oncology. 2023 May 10;40(6):171.

[54] Idris OA, Deleon N, Gustafson M, Haj D, Zhang T. Precision Medicine Approaches in Breast Cancer: Current Strategies and Future Directions.

[55] Daly RJ, Scott AM, Klein O, Ernst M. Enhancing therapeutic anti-cancer responses by combining immune checkpoint and tyrosine kinase inhibition. Molecular cancer. 2022 Sep 29;21(1):189.

[56] Obeagu EI, Obeagu GU. Predictive models and biomarkers for survival in stage III breast cancer: a review of clinical applications and future directions. Annals of Medicine and Surgery. 2024 Oct 1;86(10):5980-7.