American Journal of Multidisciplinary Research & Development (AJMRD)
*Volume 06, Issue 11 (**November - 2024**), PP 24-40*
ISSN: 2360-821X
www.ajmrd.com

Research Paper **Open Access**

The Current Strategies and Future Prospects for Addressing The PI3K/AKT/Mtor Pathway in Breast Cancer

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ABSTRACT: Breast cancer remains a serious global health challenge, as it is the fifth most common cause of cancer-related death and the most frequently occurring cancer in women. The PI3K/AKT/mTOR pathway is crucial for normal cell growth, survival, and division. However, in breast cancer patients, this pathway often becomes disrupted, which leads to enhanced metastasis, carcinogenesis, and treatment resistance. Hence its potential as a therapeutic target is highlighted in several breast cancer subtypes. Even with significant research efforts, there are still difficulties in transforming preclinical discoveries into effective clinical treatments. There exists a critical knowledge gap about the specific molecular mechanisms driving the route, despite some understanding of its role in breast cancer. AKT inhibitors, mTOR inhibitors, pan-PI3K inhibitors, and isoform-specific inhibitors are a few of the approaches employed to target the PI3K/AKT/mTOR system. Exploring the results of clinical trials, challenges associated with toxicity, drug resistance, and patient selection, the potential benefits of combination medications, precision medicine techniques, and recently developed diagnostic tools are important in enhanced, effective, and targeted breast cancer therapy focused on the PI3K pathway with no adverse effects. Therefore, continued research shows potential for improved treatment strategies despite various obstacles and shows improved outcomes for breast cancer patients.

Keywords - Breast carcinoma, PAM pathway, targeted molecular therapy, drug resistance, pan-PI3K *inhibitorsz*

I. INTRODUCTION

Despite advances in cancer biology and therapeutic expertise, Breast Cancer (BC) remains the most common malignancy among women and ranks as the fifth cause of cancer-related deaths worldwide (1). It is a tumor that develops in the breast cells which undergo abnormal growth and cell division. It can be developed in various parts of the breast, such as the milk-producing lobules, the ducts, or the supportive tissue (1,2). It is a heterogeneous malignancy with various subtypes (1,2).

Both the pathogenesis and progression of BC are influenced by the PI3K/AKT/mTOR signaling pathway (PAM pathway), which is essential in controlling the growth, proliferation, survival, and angiogenesis of tumor cells. This pathway is frequently activated in numerous cancers through various mechanisms making it a promising target for therapeutic interventions. Hence, the selection of the most effective therapeutic approach depends on the specific activation mechanism of the PAM pathway in a given cancer (3). Emerging as a rapidly advancing field, inhibitors designed for this pathway show potential in treatments, particularly when employed in combination with other targeted therapies. Overactivation of the PAM pathway is one of the main mechanisms targeted by several treatment modalities. Proteins linked to the PAM pathway contribute to the resistance that BC cells exhibit to anti-HER2 treatment, chemotherapy, and adaptation to estrogen deprivation during treatment in BC (4).

Applying precision medicine to breast cancer management holds great potential, yet substantial scientific and logistical obstacles hinder its adoption in clinical settings. Aside from a few established markers like ER and HER2, identifying the genetic drivers of breast cancer remains challenging, leaving a gap in confirmed oncogenic factors responsible for its development(5). Drug resistance remains a major barrier that contributes to the advancement of disease, despite the progress achieved through therapeutic methods such as targeted therapy, chemotherapy, and endocrine therapy. It is important to break down resistance mechanisms and develop practical countermeasures (5).

Only a few PI3K/AKT/mTOR inhibitors have been approved for the treatment of BC in humans, despite a large number of preclinical studies, only a limited number of PI3K/AKT/mTOR inhibitors have gained approval for human breast cancer treatment. Some examples include Alpelisib, Everolimus, and Fulvestrant with Alpelisib. This Review delves into the therapeutic prospects of drugs targeting PI3K/AKT signaling for breast cancer treatment, summarizing the most recent advances in inhibiting this pathway. The discussion encompasses the strengths and weaknesses of diverse treatment strategies directed at this pathway, identifies the cancer types that may exhibit optimal responses to these therapies, and addresses the challenges and limitations influencing their clinical development, particularly providing an overview of breast cancer, PI3K/AKT/mTOR pathway and its components, breast cancer mutations of PI3K/AKT pathway, PI3K/AKT/mTOR inhibitors in the usage, development and recent clinical findings, endocrine resistance in breast cancer and future directions in the use of this pathway as a potential therapeutic target.

1. BREAST CANCER INCIDENCE AND RISK FACTORS

In the United States, Breast Cancer ranks second in terms of cancer-related death among women and is the most common malignancy among them. One in eight women will be diagnosed with breast cancer at some point in their life, according to estimates (2). When it comes to the percentage of female cancer cases, breast cancer is only surpassed by lung cancer (1). According to global statistics, 684,000 people died from breast cancer in 2020, accounting for 2.3 million diagnoses (1). Approximately it is estimated that 2.6% of people will die from breast cancer in their lifetime (6). These figures underscore the significant impact of breast cancer on a global scale.

A complex interplay influences the onset of breast cancer, such as age, genetic predisposition, environmental factors, reproductive history, and potentially undiscovered factors (7). After gender, age plays a major part. After puberty, this cancer can strike women at any age, and the chance of getting it increases with age. Women 50 years of age and older receive the majority of breast cancer diagnoses (8). Based on SEER data, the median age at diagnosis for breast cancer was 63 years during 2016 -2022 (8). The occurrence of menarche, menopause, and oophorectomy all have an impact on the development of breast cancer (9). Because breast cancer is more common in women than in males, men are frequently underdiagnosed with the disease until it is already advanced (10). Individuals with blood group A and Rh positive may be at an increased risk (11), however, breastfeeding and full-term pregnancies serve as protective factors, lowering the risk (12).

In postmenopausal women, estrogen levels correlate with increased breast cancer risk, while antiestrogens like tamoxifen has proven to be effective in reducing the risk (13). Moreover, testosterone in postmenopausal women can also promote breast cancer development (13). Controversial associations include prolactin, IGF-1, and long-term oral contraceptive use (14). Family history, gene mutations, diabetes (especially type II), and obesity(15) are major risk factors contributing to this malignancy (16,17). Vitamin D supplements can reduce risk (18), but alcohol consumption and smoking may increase it (19). Physical activity decreases risk, but overnight work and exposure to artificial light can elevate estrogen levels and risk (20). Higher socio-economic status increases the risk, but frequent medical examinations may lead to earlier diagnosis minimizing consequences. Non-proliferative breast diseases and breast implants generally do not increase risk, but proliferative diseases, particularly with atypia, significantly enhance it (20). Increased mammographic density is a notable risk factor, and breast exposure to radiation can also elevate the risk of malignancy (21).

II. BREAST CANCER SUBTYPES

It is a markedly diverse cancer with various subtypes, classified into four groups according to the presence of specific hormone receptors as identified through immunohistochemistry. These categories include estrogen receptor-positive (ER+), progesterone receptor-positive (PR+), human epidermal growth factor receptor-positive (HER2+), and triple-negative breast cancer (TNBC), which is characterized by the absence of expression of any of the mentioned receptors (19). Estrogen receptor (ER) serves as a crucial diagnostic factor, with around 70–75% of invasive breast carcinomas exhibiting notably high ER expression (23). Progesterone receptor (PR) is present in over 50% of ER-positive patients and rarely in those with ER-negative breast cancer(24). Both ER and PR are highly expressed in breast cancer cells, serving as diagnostic and prognostic biomarkers (25). Elevated PR expression correlates positively with overall survival, time to recurrence, and time to treatment failure or progression accordingly. Conversely, lower PR levels are generally linked to a more aggressive disease course and poorer recurrence and prognosis outcomes (26).

Human Epidermal Growth Factor Receptor 2 (HER2) expression is present in 15–25% of breast tumors, and it plays an important part in deciding the course of treatment (27,28). The early emergence of HER2

overexpression in breast carcinogenesis increases the likelihood of detecting metastatic or recurring breast cancers (28). One potential real-time measure for the existence or recurrence of tumors is the serum HER2 levels. In HER2-positive cases, amplification of HER2 results in increased activation of proto-oncogenic signaling pathways, which in turn causes uncontrolled cancer cell proliferation and worse clinical outcomes. A significantly reduced disease-free period is linked to HER2 overexpression (29). A significant marker of cellular proliferation, the Ki67 antigen offers insights into therapy response, time to recurrence, and the aggressiveness of malignancy (30). To choose the best course of action and possible recurrence follow-ups, Ki67 is crucial, and it may serve as a prognostic factor, with higher expression correlating with lower survival rates (31).

Based on SEER data from 2016 to 2020, 69% of instances of breast cancer are classified as hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative. This is the most common subtype of breast cancer. Ten percent of patients are triple-negative, ten percent are HR-positive and HER2-positive, four percent are HR-negative and HER2-positive, and seven percent of cases are unknown subtypes (8,32).

Table 1. Features of different Breast Cancer Subtypes

	Luminal A	Luminal B	HER2	Triple Negative	References
Frequency	50%	15%	20%	15%	(30,31)
ER	Present	Present	Present in some	Absent	(30.31)
PR	Present	Present in some	Present in some	Absent	(30,31)
HER2	Absent	Absent	Present	Absent	(30,31)
Other Features	Slow growing	Grow faster than Luminal A	Grow faster than Luminal	High proliferation rate, alteration in DNA repair genes and increased genomic instability	(30-36)
Prognosis and relapse	Best prognosis, less incidence of relapse and high survival rate	Worse prognosis, high rate of visceral relapse and survival from diagnosis to relapse is lower	Along with HER2 targeted therapies prognosis improved and visceral relapses are more frequent	Early relapse and higher tendency to be present in advanced stages	(30-36)
Therapy	High response to hormone therapy (Tamoxifen or aromase inhibitors)	Hormonal therapy and chemotherapy	specific drugs against tHER2/neu protein (trastuzumab, trastuzumab combined with emtasin (T-DM1), pertuzumab, and tyrosine kinase inhibitors (i.e lapatinib and neratinib) along with surgery and chemotherapy	Chemotherapy/ experimental	(30-36)

III. PI3K/AKT/MTOR SIGNALING PATHWAY

An essential signaling path involved in basic physiological functions like metabolism, development, proliferation, apoptosis, and angiogenesis is the PI3K/AKT/mTOR pathway (37). In this pathway, a ligand (i.e. insulin or an insulin-like growth factor) binds to a cell-membrane receptor (i.e. tyrosine kinases or G-protein-coupled receptors). Then the activated receptor triggers PI3K (phosphatidylinositol 3-kinase), leading to the phosphorylation of (phosphatidylinositol 3,4,-diphosphate) PIP2 and the generation of (phosphatidylinositol 3,4,5-trisphosphate) PIP3. PIP3 recruits two protein kinases, AKT (protein kinase B / PKB) and PDK1 (phosphoinositide-dependent protein kinase 1), to the plasma membrane through their pleckstrin homology interaction domains (PH domains). AKT is subsequently phosphorylated by mTORC2 (mTOR complex 2) on Ser473, altering its conformation and allowing phosphorylation on Thr308 by PDK1. Once activated, AKT phosphorylates the target proteins at the cell membrane before dissociating from the membrane eventually phosphorylating other target proteins in the cytosol and cell nucleus. This phosphorylation cascade ultimately stimulates cell survival, growth, and proliferation(33).

4.1 PI3K (Phosphatidylinositol 3-Kinase)

A class of lipid kinases known as PI3Ks is essential for phosphorylating the 3′-OH group on the inositol ring of phospholipids that contain inositol. The family is made up of three classes that are involved in the phosphorylation of lipids; each class is made up of heterodimers that have p110 as the catalytic subunit and p85, p65, p55, or p101 as the regulatory subunit (31, 32). Particularly, these kinases give phosphatidylinositol 4,5-bisphosphate (PIP2) a 3′-OH group (34). Class I PI3Ks are further categorized into subclass IA proteins, consisting of one of three alternative forms of p110 (α, β, or δ) encoded by PIK3CA, PIK3CB, or PIK3CD genes respectively, combined with a regulatory subunit (p85, p65, or p55) (35). Subclass IB proteins comprise a p110γ catalytic subunit and a p101 regulatory subunit (35). Subclass IA PI3Ks are commonly involved in downstream signaling activated directly by cell surface receptors such as Receptor tyrosine kinases (RTKs), G-protein coupled receptors, and small G protein RAS, while subclass IB PI3Ks participate in signaling from GPCRs (33). An essential lipid second messenger is produced when activated PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 is located on the cytosolic side of the plasma membrane and can activate proteins containing pleckstrin homology (PH) or phenylalanine–tyrosine–valine–glutamate (FYVE) domains (36). This includes phosphoinositide-dependent kinase 1 (PDK1), AKT, and other serine/threonine kinases (37). The PH domain of AKT interacts with PIP3, leading to AKT's transient localization to the cell membrane.(38)

4.2 AKT

The protein kinase B (PKB) or AKT serine/threonine kinase, is an oncogenic protein that controls cell growth, survival, proliferation, apoptosis, and glycogen consumption (39). AKT is activated by PIP2- and PIP3-driven recruitment to the plasma membrane, where it is phosphorylated at Thr308 and Ser473. This phosphorylation then activates a variety of downstream protein substrates, including transcription factors, protein kinases, inducers of apoptosis, inhibitors of cell cycle progression, and GTPase-activation proteins (40,41). This key downstream component of the PI3K signaling pathway exists in three isoforms: AKT1 (expressed in most tissues), AKT2 (predominantly expressed in insulin-sensitive tissues like the liver, pancreas, and muscles), and AKT3 (expressed in the brain and testicles) (42).

GSK-3 is a protein kinase that phosphorylates and inhibits glycogen synthase, making it an important substrate of AKT. Many cellular signaling pathways, including the Wnt signaling system that is essential for embryonic development and the insulin-stimulated phosphatidylinositol-3–kinase-dependent route, are mediated by GSK-3 (43). GSK-3α and GSK-3β are two isoforms that have similar functions and a high degree of structural homology, particularly in the brain (43,44). Increased cellular glucose absorption and glycogen synthesis brought on by AKT's phosphorylation and inactivation of GSK-3 lower blood sugar levels (44). Various substrates including structural proteins, transcription factors involved in metabolism, and signaling proteins are used in GSK-3. Growth factors can inhibit GSK-3 by activating AKT, which has anti-apoptotic properties (45).

4.3 mTOR

The mammalian target of rapamycin (mTOR) was first discovered as the cellular target of rapamycin. It functions as an important serine/threonine kinase (46) and thereby plays a key role in regulating cell growth, proliferation, motility, survival, and the activation of gene transcription and protein synthesis in response to nutrients, growth factors, and hormones. It is an important regulator of cell growth and proliferation. Playing a part in the phosphatidylinositol 3-kinase (PI3K) cell survival pathway, it monitors nutrition availability, mitogenic signals, cellular energy, and oxygen levels. Many malignancies are associated with abnormal activation of the PI3K pathway, and increased activation is frequently associated with resistance to cancer treatments (47,48).

mTOR functions as a key junction in the PI3K pathway, acting both upstream and downstream of AKT (49). It creates two different multiprotein complexes, mTORC1 and mTORC2, which are both necessary for cell proliferation (49). Among the components of mTORC1 are mTOR, Raptor, GβL (mammalian lethal with SEC13 protein 8), and DEPTOR (domain-containing mTOR-interacting protein), which is partially inhibited by rapamycin (50). Growth factors and hormones like insulin use AKT to signal mTORC1, preventing tuberous sclerosis complex 2 (TSC2) mediated inhibition of mTORC1 which in turn activates downstream biological effects, such as mRNA translation, phosphorylating downstream targets (4E-BP1 and p70 S6 kinase), ribosome biogenesis, autophagy suppression (through Atg13 and ULK1), and activating transcription that cause increased levels of mitochondrial activity/adipogenesis (51–54).

mTORC2 is not sensitive to rapamycin and activates AKT to enhance cell survival. It is composed of mTOR, Rictor, GβL, Sin1, PRR5/Protor-1, and DEPTOR (55,56). By activating PKCα and phosphorylating SGK1, it also controls cytoskeletal dynamics, ion transport, and growth (57,58). Being a downstream target of EGFR and MET signaling, mTOR presents a potential therapeutic approach for treating a variety of cancer types.

4.4 PTEN

A key regulator in the PI3K/AKT pathway, phospholipase and tensin homolog deleted on chromosome 10 (PTEN) serves as a tumor suppressor and helps maintain cellular homeostasis (59). The phosphatase domain and the C2 domain are the two main functional domains of the PTEN structure. The phosphatase domain is responsible for the enzymatic activity of the tumor suppressor, whereas the C2 domain ensures that the catalytic domain is positioned on the plasma membrane, hence facilitating membrane interaction. A PDZ-binding protein domain found in the C-terminal tail contributes to the regulation of PTEN stability and activity(60). It functions as a lipid phosphatase, dephosphorylating phosphatidylinositol 3,4,5-trisphosphate (PIP3) and reverting it to phosphatidylinositol 4,5-bisphosphate (PIP2) to inhibit the action of phosphatidylinositol 3-kinase (PI3K) which is a key mediator of cell survival and growth (61). PTEN's role in negatively regulating the pathway contributes to the prevention of uncontrolled cell growth and tumorigenesis. Loss or inactivation of PTEN, observed in various cancers, leads to sustained PI3K/AKT signaling, promoting aberrant cell proliferation and survival, highlighting PTEN's crucial role as a tumor suppressor (62).

IV. PI3K/AKT/MTOR MUTATIONS IN BREAST CANCER

PI3K/AKT/mTOR signaling pathway is one of the most active pathways in breast cancer compared to other types of cancers (63,64). There are a variety of reasons for these mutations. Gene amplification or overexpression of receptor tyrosine kinases, including HER2, EGFR, and IGF1R, are involved in activation pathways. Moreover, activating mutations in the catalytic PI3-kinase subunit PIK3CA are frequently caused in breast cancers. These mutations occur in 36% of cases as a whole and are especially common in luminal and HER2-amplified breast cancers accounting for 29%–45% of breast cancers (63–66). Other mutations affect the pleckstrin homology domain of AKT1, which is only present in cases of breast cancer that are estrogen receptor-positive (ER+) and account for 3% of all breast cancer cases (67–69). Also, additional mutations comprise amplification of PIK3CA or AKT1-3, or they impact the PI3-kinase regulatory component PIK3R1, AKT2, or AKT3. The tumor suppressor PTEN experiences mutation or deletion in 7% of breast cancers and may also be silenced by promoter methylation. Notably, PTEN loss predominantly occurs in triple-negative breast cancers, which exhibit strong evidence of PI3-kinase pathway activation (63). In the majority of breast cancers, mutations in different genes within the PI3-kinase pathway tend to be mutually exclusive. This indicates the necessity to pinpoint distinct molecular abnormalities within specific patient subgroups to effectively choose individuals for targeted therapies.

Mainly, PIK3CA or AKT1 mutations and loss of PTEN lead to the activation of the PI3K/AKT pathway. Here, the genes encoding the catalytic subunits or regulatory subunits are mutated or amplified such as PIK3CA, PIK3CB, and PIK3R1 which encode for p110α, p110β , and p85α respectively. Out of these PIK3CA is the most frequently mutated in about 30-40% of breast cancer patients. According to a study, the 20 most frequent mutations identified to be present in exons 1,4, 7, 9, 13, and 20 are as follows (70) ;

Exon 9 - E545K, E542K, Q546K, E545A, E545G and Q546P
Exon 20 - H1047R, H1047L, G1049R, M1043I and N1044K
Exon 4 - N345K
Exon 13 - E726K
Exon 1 - Q546R, G118D, K111E, E81K and E110del
Exon 7- C420R and E453K (74)

The predominant mutations in PIK3CA were identified in exons 4, 9, and 20 (70). According to Karakas B et al. out of the three mutation hotspots (E545K, E542K, and H1047R), two are present in the helical domain of p110α and the other in the catalytic domain (71). Particularly, PIK3CA mutations are distributed among various breast cancers as follows; Luminal A 47%, Luminal B 33%, HER2 enriched 39%, and Triple Negative 8-25% (70,72).

Regarding the prognostic impact of PIK3CA mutations, there was a notable improvement in invasive disease-free survival (IDFS), particularly in advanced-age, hormone receptor-positive (HR+), and low-grade breast tumors. However, there wasn't a significant association observed with distant disease-free survival

(DDFS) or overall survival (OS) (73). Also in metastatic cancers, these mutations resulted in poor outcomes and resistance to chemotherapy. Hence, PIK3CA can be considered as a target for cancer therapy. Metastatic breast cancer patients with PIK3CA mutations in the hormone receptor-positive (HR+)/HER2-negative subtype exhibit unfavorable outcomes and resistance to chemotherapy. Conversely, individuals with PIK3CA mutated triple-negative breast cancer (TNBC) experience improved overall survival (OS) (74).

PTEN, the important tumor suppressor in the PI3K/AKT pathway also undergoes inactivation in 5-10% of breast cancer patients. The uncontrolled transmission of the PI3K signal primarily results from the inactivation of PTEN, which can occur through diverse mechanisms. These mechanisms encompass somatic mutations (including missense and nonsense mutations), deletion of the PTEN gene locus either monoallelic or biallelic, epigenetic suppression via promoter methylation, PTEN protein degradation, and post-translational modifications of PTEN protein (75). Specifically, modifications to wild-type PTEN, such as phosphorylation, mono- or poly-ubiquitination, acetylation, and oxidation, play a pivotal role in finely regulating the tumor suppressor's function. These alterations impact factors like subcellular localization, protein-protein interactions, and phosphatase activity, regardless of PTEN accumulation (76). In approximately 40%–50% of breast tumors, there is a loss of heterozygosity at the PTEN locus, while the loss of PTEN function resulting from PTEN mutations is observed in 5%–10% of breast cancer cases. Among these mutations, frameshift mutations are the most commonly identified mechanism (77,78). Partial impairment of PTEN function is adequate to facilitate tumor development, and a 50% decrease in PTEN levels is linked to a heightened acceleration of cancer progression (79). Somatic mutations in PTEN are infrequent, occurring in about 5% of sporadic breast carcinomas. However, the loss of the PTEN gene is more common, accounting for approximately 30%–40% of cases and about 20%–25% in HER2-positive breast cancers (80,81). Even though PTEN mutations are rare among breast cancer patients, up to 48% exhibit an absence of protein expression (82). Notably, the detection of PTEN through mRNA levels proves to be a reliable predictor of PI3K pathway activation compared to protein immunohistochemistry (IHC) analysis (82).

Inositol polyphosphate-4-phosphatase type II (INPP4B) is also inactivated in breast cancers mainly in triple-negative breast cancers. Here, it regulates the receptor tyrosine kinase trafficking and degradation functioning as a tumor suppressor. This subsequently leads to PI3K activation (83). In the healthy breast, INPP4B is mainly present in non-proliferative cells that express estrogen receptors (ER-positive). Suppression of the INPP4B protein in ER-positive breast cancer cells results in increased AKT phosphorylation at baseline and in response to EGF, increased cell proliferation, anchorage-independent cell growth, and the formation of xenograft tumors (84). At present, there are no specific treatments designed for tumors that experience the loss of INPP4B protein, with or without concurrent PTEN loss, which could potentially be suitable candidates for therapeutic interventions involving inhibitors targeting the PI3K pathway.

V. RESISTANCE TO ENDOCRINE THERAPY

The presence of the estrogen receptor (ER) characterizes the most common subtype of breast cancer that has been diagnosed. Endocrine therapy, which is the basis of standard treatment for this subtype of breast cancer, relies on measures that either restrict the production of estrogen or prevent it from binding to receptors (85). While endocrine therapy has shown promise for many patients, resulting in a considerable reduction in death and cancer recurrence, a notable clinical obstacle still exists (85,86). Overcoming intrinsic (de novo) or acquired resistance to endocrine therapy is the task to be addressed. These resistances are caused by a variety of complex alterations that are taking place in the tumor microenvironment. Moreover, this resistance can continue even if more anti-estrogen treatments are used (85). It was found that patients with hormone receptor-positive tumors showing elevated PI3K signaling levels, as well as those experiencing a relapse during endocrine therapy, find therapeutic benefits in interventions that target both the ER and PI3K pathways (87). While direct targeting of PI3K and mTOR achieves maximal inhibition of hormone-independent cell growth and induces apoptosis, inhibiting signaling kinases both upstream and downstream of PI3K exhibits only partial inhibitory effects. Moreover, PI3K inhibition prevents the development of hormone-independent cells, suggesting that early intervention with a combination of endocrine and PI3K-directed therapies could effectively limit the escape from anti-estrogens in patients with ER-positive breast cancer (87).

The mechanisms underlying breast cancer endocrine resistance remain largely unknown, but many studies suggest that different molecular mechanisms and signaling pathways play a role in this process e.g. changes in estrogen receptor (ER) gene expression and activity and its crosstalk with signaling pathways, mutations or dysregulation in key components of the AKT/mTOR pathway have been identified as potential contributors to endocrine therapy resistance (88,89). Epigenetic changes, such as DNA methylation and histone modifications, and ligand-independent estrogen receptor function due to mutations in the ESR1 gene have also

been suggested as factors affecting endocrine resistance in breast cancer (89,90). Thus, further studies are needed to better understand the underlying molecular mechanisms of overcoming endocrine resistance in breast cancer and to identify novel therapeutic targets.

Endocrine therapies comprise selective estrogen receptor modulators like tamoxifen, aromatase inhibitors that block estrogen synthesis, and selective estrogen receptor down-regulators such as fulvestrant (91). The primary goal is to eliminate endogenous activating ligands of estrogen receptors (90). While tamoxifen has been effective, aromatase inhibitors have become the main therapy for postmenopausal women (91).

Tamoxifen and other antiestrogens like fulvestrant function through competitive inhibition, while aromatase inhibitors such as letrozole and anastrozole block the synthesis of estrogen (91). Tamoxifen, being the pioneering therapeutic agent targeting cancer at a molecular level, has shown significant efficacy, particularly in premenopausal women with estrogen receptor-positive breast cancer. Despite its effectiveness in preventing recurrence, the estrogen receptor-positive subtype remains the most aggressive form of breast cancer (92). Tamoxifen, an anti-estrogen acting as a partial agonist, has been the standard care for premenopausal women for many decades, although aromatase inhibitors have now replaced it as the primary therapy for postmenopausal women, proving to enhance survival rates (91).

Estrogen receptor-positive breast cancers initially exhibit a low recurrence rate, but the risk increases over 3 to 5 years after initial treatment, a phenomenon known as dormancy often associated with ER-positive breast cancers and potentially influenced by the therapeutic agents used (91).

The HER2 pathway is shown to be implicated in tamoxifen resistance, with increased HER2 expression linked to resistance to hormonal therapy. In the presence of HER2, tamoxifen may function either as an agonist or antagonist, depending on the recruitment of coactivators or repressors of the estrogen receptor α transcription complex. The overexpression of AIB1 (amplified in breast cancer 1 protein), a regulator of estrogen receptor α, contributes to tamoxifen resistance (93). Furthermore, growth factor receptors such as IGF1R and EGFR can induce a lack of response to tamoxifen by leading to the activation of the MAPK and PI3K signaling pathways. The complex cross-talk between these receptors and ER involves MAPK leading to estrogen-independent phosphorylation. Here, AKT plays a crucial role in ERα (93,94). Activation of the PI3K signaling pathway and AKT phosphorylation promote estrogen-independent growth in tumor cells and resistance to anti-estrogens (93,94). Tamoxifen-resistant cells often cause overexpression of HER2, FGFR1, or loss of INPP4B. PI3KCA is more frequently affected in estrogen-positive breast cancers, while PTEN loss characterizes ER-negative breast cancers (95). Additionally, tamoxifen resistance can be influenced by dysregulated metabolism, cellular accumulation of the drug, hypermethylation of CpG islands, expression of P-glycoprotein, and histone deacetylase activity (92).

To summarize the content, the understanding of the complex interplay between that of the signaling pathways and their molecular changes involved in endocrine resistance is drastically important for developing effective therapeutic strategies against breast cancer. Combination therapies targeting multiple pathways show promise in improving treatment outcomes.

VI. DIFFERENT TYPES OF INHIBITORS IN BREAST CANCER

7.1 Pan-PI3K inhibitors

Pan-PI3K inhibitors play a role in breast cancer treatment by targeting multiple catalytic subunits of class I PI3K, including p110α, p110β, p110δ, and p110γ (96). By blocking PI3K activity across these various subunits simultaneously, pan-PI3K inhibitors aim to achieve a more comprehensive inhibition of the PI3K pathway, which is often dysregulated in breast cancer. This targeting leads to enhanced treatment efficacy. One example of a pan-PI3K inhibitor is Buparlisib (96).

Buparlisib (BKM120), developed by Novartis Pharmaceuticals is an oral pan-PI3K inhibitor (96). Clinical trials with buparlisib, including phase II/III trials like BELLE-2 and BELLE-3 were conducted. In these trials, fulvestrant was combined with buparlisib and given to post-menopausal women with HR+/HER2- metastatic breast cancer. Compared to fulvestrant alone, the studies have shown that adding buparlisib to fulvestrant leads to enhanced progression-free survival (PFS). Significant grade 3/4 adverse effects, such as transaminitis, hyperglycemia, dermatitis, and mood change would offset these favorable results. This resulted in limited drug exposure, early treatment cessation, and poor tolerability, especially in the BELLE-2 trial (97,98).

Additionally, Buparlisib was evaluated in combination with chemotherapy in the BELLE-4 trial, where

it was combined with paclitaxel as a first-line treatment for HER2- metastatic breast cancer. Unfortunately, the trial was stopped due to futility at the end of phase II, as the addition of Buparlisib to paclitaxel did not improve progression-free survival in the study population. Furthermore, Buparlisib treatment in this trial resulted in a higher frequency of serious adverse effects, leading to increased treatment discontinuation (99).

Buparlisib's overall toxicity profile, as seen in these clinical studies, included elevations in liver aminotransferase levels as well as psychological side effects such as anxiety, depression, and suicidal thoughts. The prospective use of buparlisib as the standard of care for treating breast cancer has been hampered by these side effects (100). Despite these challenges, the trials highlighted the potential benefit of PI3K inhibition in specific subgroups, such as patients with PIK3CA genetic alterations, suggesting a rationale for further exploration of PI3K inhibitors in breast cancer.

7.2 PI3K isoform-specific inhibitors

Inhibitors specific to PI3K isoforms are substances that selectively target either the p110α, p110β, p110δ, or p110γ catalytic subunits (101). In contrast to Pan-PI3K inhibitors, isoform-specific PI3K inhibitors possess the capability to achieve more precise targeting of specific elements while minimizing off-target effects (96). Alpelisib and Taselisib are examples of such inhibitors.

Alpelisib is a selective inhibitor of the p110α isoform of PI3K and has shown promise in treating hormone receptor-positive, HER2-negative advanced breast cancer with PIK3CA mutations (102). It is the first oral inhibitor to be approved by the US Food and Drug Administration (FDA) and by the European Medicines Agency (EMA). In pivotal trials like SOLAR-1, it demonstrated its efficacy when combined with fulvestrant in postmenopausal women and men with hormone receptor-positive, HER2-negative advanced breast cancer harboring PIK3CA mutations (103). Alpelisib was given regulatory approval for this particular indication after the Phase III SOLAR-1 trial, which has the identifier NCT02437318, showed that adding the medication considerably increased progression-free survival (PFS) when compared to fulvestrant alone (104). This marks a significant advancement in targeted therapy for breast cancer patients with PIK3CA mutations, highlighting the potential of Alpelisib as a valuable treatment option (102–104).

A clinical evaluation was conducted to determine the therapeutic efficacy of taselisib, a selective inhibitor that targets p110δ, in the treatment of breast cancer. The combination of Taselisib and fulvestrant in postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer was the subject of the significant SANDPIPER trial (NCT02301988). With its focus on the PI3K pathway, this Phase III trial aimed to determine whether Taselisib could enhance the effectiveness of endocrine therapy in this particular patient population (105). Clinical development did, however, face difficulties because the trial's main objective of improving progression-free survival (PFS) in comparison to fulvestrant alone was not achieved. Additionally, Taselisib showed signs of gastrointestinal and skin toxicity, which caused some patients to stop their treatment (105). Despite these setbacks, ongoing research continues to explore the potential of Taselisib and other PI3K inhibitors in refining treatment strategies for breast cancer and other malignancies with aberrant PI3K pathway activation.

7.3 AKT inhibitors

One notable AKT inhibitor is ipatasertib. It selectively inhibits AKT and has been investigated in clinical trials for breast cancer. The IPATunity130 trial (NCT03337724) is an example where ipatasertib was evaluated in combination with paclitaxel for the treatment of triple-negative breast cancer (TNBC). The trial aimed to determine whether the addition of ipatasertib to paclitaxel could improve progression-free survival (PFS) in patients with advanced or metastatic TNBC. This has entered phase I and phase II trials (106).

The PAKT trial (NCT02423603) is investigating capivasertib, another AKT inhibitor, as a treatment for hormone receptor-positive, HER2-negative breast cancer. All AKT isoforms are bound by this oral drug, which also inhibits them. In a phase I trial, it showed encouraging anticancer efficacy in individuals with solid tumors with AKT1 E17K mutations (107). The purpose of the assessment was to improve the therapy outcomes in this particular subtype of breast cancer by combining capivasertib with fulvestrant (108). Hyperglycemia, diarrhea, neutropenia, and maculopapular rash are the most frequent side effects (107). AKT inhibitors are designed to interfere with AKT-mediated oncogenic signaling, which stops cancer cells from growing and encourages cell death. AKT inhibitors' effectiveness, like that of many other targeted treatments, may change depending on the patient's unique traits and the many subtypes of breast cancer. The results of these clinical trials will offer insightful information about the safety and effectiveness of AKT inhibitors in the treatment of breast cancer, thereby opening the door for future targeted and customized therapeutic approaches (107).

7.4 mTOR inhibitors

The mammalian target of rapamycin (mTOR), a protein homologous to the p110α catalytic subunit, primarily regulates cell growth as a serine/threonine kinase. Inhibition of the PI3K/AKT/mTOR pathway has a synergistic anti-proliferative effect, and omipalisib (GSK2126458), a highly potent inhibitor of both PI3K and mTOR, belongs to the pyridinyl-benzenesulfonamide derivative class, demonstrating significant efficacy in anti-proliferative cell assays (96).

Everolimus is an mTOR inhibitor that acts by binding to the intracellular protein FKBP-12, forming a complex that inhibits mTOR or it functions as an allosteric inhibitor of mTORC1. Following the outcomes of the phase III BOLERO-2 study, regulatory approval was granted for the utilization of Everolimus in combination with Exemestane for the management of HR+/HER2− MBC which has progressed after undergoing endocrine treatment. Adverse events associated with its class include pneumonitis, anemia, stomatitis, hyperglycemia and fatigue (109).

Temsirolimus inhibits mTOR and has been studied in various cancer types. While more commonly used in other malignancies, temsirolimus has been explored in breast cancer clinical trials, particularly in the triple-negative subtype. Clinical outcomes may vary, and its efficacy in breast cancer is still an area of investigation (110). Temsirolimus acts as a selective inhibitor of mTORC1 (111). In a phase II study, it was administered at a weekly dose of 25 mg to heavily treated HR+ and/or HER2+ BC, demonstrating limited activity (112). Conversely, the phase III HORIZON trial revealed that the combination of Temsirolimus with Letrozole provided a notable advantage compared to Letrozole alone in HR+ MBC patients. However, a substantial number of grade 3 and 4 adverse events related to this class were reported.

Ridaforolimus is another mTOR inhibitor that inhibits mTOR complex 1 (mTORC1). It has been studied in clinical trials for breast cancer, both as a single agent and in combination with other therapies. Clinical data on ridaforolimus in breast cancer are limited, and its role is still being explored (113). Several other investigational mTOR inhibitors are undergoing preclinical and clinical evaluations to determine their efficacy and safety in breast cancer.

mTOR inhibitors are generally considered in advanced or metastatic breast cancer, often in combination with other agents. Adverse effects such as stomatitis, rash, and metabolic disturbances are associated with mTOR inhibitors (114).

7.5 Inhibitors of Triple Negative Breast Cancer (TNBC)

TNBC is recognized as the most aggressive subtype, constituting 15–20% of breast cancer cases, characterized by considerable heterogeneity in its mutational profile. Given the limited options for targeted therapies, conventional chemotherapy remains the cornerstone of TNBC treatment (115). About 10% of TNBC had germline mutations in either the BRCA1 or BRCA2 gene. Activating mutations in PIK3CA, which are primarily located in the p110α subunit, are the second most common molecular abnormality in TNBC, after TP53 mutations. They are present in 7–9% of initial TNBC patients, and they are likely more common in advanced TNBC cases (116). The presence of PIK3CA mutations, often coupled with inactivating changes in PTEN and activating mutations in AKT1, is observed in about 25% of TNBC cases globally (117). In this particular subtype, dysregulation of the PI3K pathway has been linked to resistance to chemotherapy, and the loss of PTEN function leads to resistance to PDL1 blockade, resulting in heightened PI3Kβ signaling. Preclinical models suggest that combining an anti-PDL1 agent with a PI3Kβ inhibitor can enhance cancer growth inhibition (118,119). Nevertheless, the precise role of PI3K pathway-targeted therapy in TNBC remains uncertain. PI3K pathway activation is more closely associated with the androgen receptor-positive subtype of TNBC and shows a weaker correlation with TNBC compared to HR-positive and HER2-positive breast cancer [62,65].

In the BELLE-4 trial, TNBC patients (constituting about 25% of the total) exhibited a tendency towards poorer prognosis in the buparlisib arm compared to the placebo arm. The inferior prognosis in the TNBC subgroup might be attributed to a shorter duration of paclitaxel exposure in the buparlisib group, implying that the toxicity of buparlisib could have compromised the proper administration of chemotherapy. Consequently, the authors failed to confirm the predictive role of PIK3CA mutations in the TNBC subtype [35]. Preclinical models have indicated that the pan-PI3Ki BKM120 sensitizes BRCA-proficient TNBC to the PARP inhibitor olaparib, demonstrating significant downregulation of BRCA1/2 expression and reduced tumor cell growth [66]. Another study highlighted the synergistic activity of buparlisib combined with olaparib in a mouse

model of breast cancer [67]. Additionally, in a phase I dose-escalation trial, Matulonis UA et al. demonstrated anticancer activity in breast cancer (54% of which were TNBC) and ovarian cancer, encompassing both germline BRCA (gBRCA)-mutated and gBRCA-wild-type patients [68].

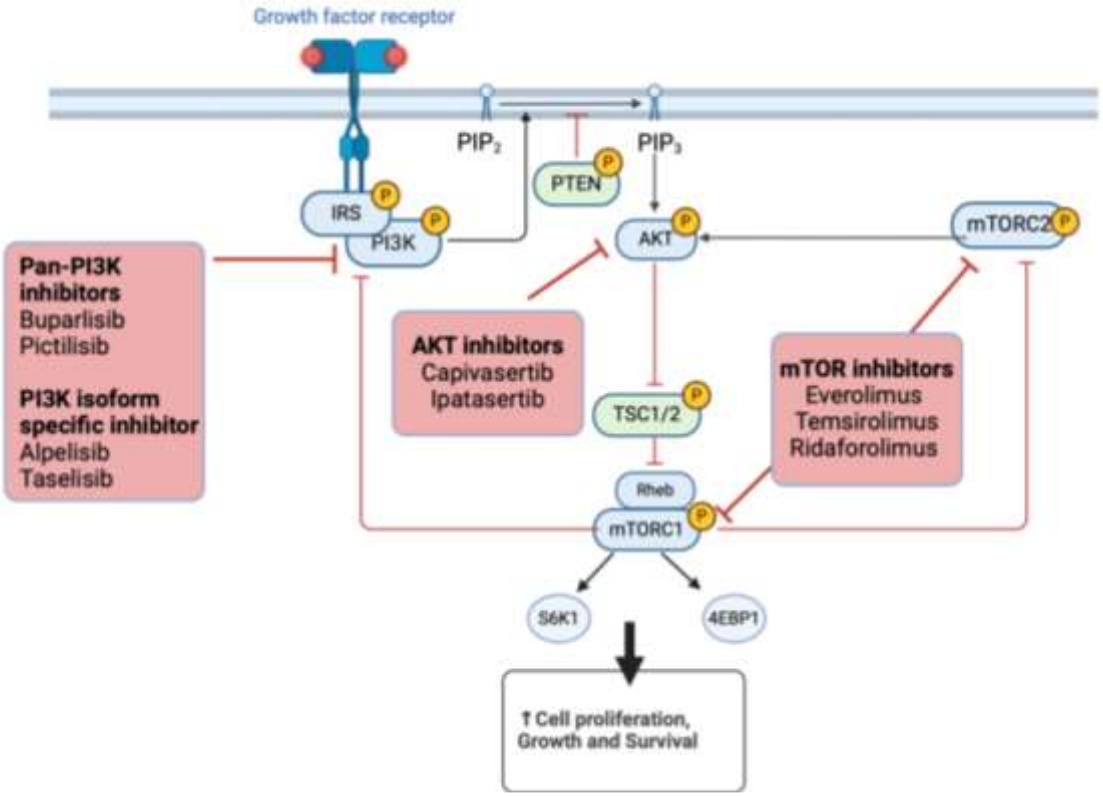

Figure 1. The PI3K/AKT/mTOR pathway and associated breast cancer inhibitors.

When the ligand (growth factor) binds to the growth factor receptor, the signaling pathway is triggered. Insulin Receptor Substrate (IRS) is recruited to the cytoplasmic region of the receptor by the ligand upon binding(120). Phosphatidylinositol 4,5-bisphosphate (PIP2) is changed into phosphatidylinositol 3,4,5-triphosphate (PIP3) when Phosphoinositide 3-Kinase (PI3K) is activated by IRS (120). Protein Kinase B (AKT) is recruited and activated in the cell membrane as a result of PIP3 accumulation (33, 37). AKT then phosphorylates TSC1/2, relieving its inhibitory impact on Rheb (Ras homolog abundant in the brain), and activating Rheb. Rapamycin's (mTOR) mammalian target is stimulated by activated Rheb(121). When mTORC1 is activated, downstream targets like p70S6 kinase and 4E-binding protein 1 (4EBP1) get phosphorylated, which ultimately helps cells proliferate, develop, and survive (122). PI3K activity is inhibited by phosphatase and Tensin homolog (PTEN), which function as a negative regulator (37). Inhibitors of PI3K, AKT, and mTOR reduce downstream signaling and inhibit tumor cell growth and survival by blocking the actions of these signaling molecules.

Table 2: Different types of inhibitors under clinical usage/ currently available for Breast Cancer targeting the PI3K/AKT/mTOR Pathway

Inhibitor type	Clinical Trial inhibitor	Breast cancer subtypes	Key Findings	References
Clinical Usage				
Pan-PI3K Inhibitors	Buparlisib (BKM120)	HR+/HER2- Metastatic Breast Cancer	- Increased PFS in BELLE-2 and BELLE-3 trials, but associated with more adverse events including transaminitis, hyperglycemia, rash, and mood disturbance. - Poor tolerability led to premature discontinuation in many patients.	(96–99)
	Pictilisib	ER+/HER2-	- FERGI trial: No significant difference in	(123,124)

	(GDC-0941)	Metastatic Breast Cancer	PFS between pictilisib and placebo. - PEGGY trial: No significant differences in terms of PFS or overall response. - Future developments suggested for more selective inhibitors.	
PI3K Isoform-Specific Inhibitors	Alpelisib (BYL719)	HR+/HER2- Metastatic Breast Cancer	- Increased PFS in SOLAR-1 trial for PIK3CA-mutant patients. - No significant improvement in PFS for PIK3CA wild-type patients. - Toxicity includes hyperglycemia, diarrhea, and rash. - FDA approval for HR+/HER2-, PIK3CA-mutated breast cancer. - Subsequent data shows clinically relevant increase in overall survival.	(107-109)
	Taselisib (GDC-0032)	ER+/HER2- Metastatic Breast Cancer	- Longer PFS in SANDPIPER trial for PIK3CA-mutated tumors. - Modest clinical benefits, questionable tolerability, and halted further investigation.	(105)
Currently Available				
AKT Inhibitors	AZD5363 (Capivasertib)	Breast Cancer with AKT E17K Mutations	Tolerated, achieved plasma levels, and modulation of AKT activity. - Proof-of-concept responses observed in PIK3CA-mutant cancers.	(111,112)
	GDC-0068 (Ipatasertib)	Triple-Negative Breast Cancer	- Dose-limiting side effects observed in phase I and II trials. - Limited selectivity due to conserved ATP-binding pocket in AKT.	(106)
mTOR Inhibitors	Everolimus (RAD001)	HR+/HER2- Metastatic Breast Cancer	- Approved by FDA in combination with exemestane for HR+/HER2- breast cancer. - Synergistic effects with tamoxifen and letrozole observed.	(114)
Dual PI3K /mTOR Inhibitors	Gedatolisib (PF-05212384)	Triple-Negative Breast Cancer	- Phase I trials ongoing for combinations with docetaxel, cisplatin, or dacomitinib in TNBC. - Manageable toxicity observed in combinations.	(125)

VII. CONCLUSION AND FUTURE PROSPECTS

The majority of the cases of breast cancer (BC) involve the PI3K/AKT/mTOR (PAM) pathway alterations. Activation of the PAM pathway has been associated with resistance to endocrine therapy in several studies. As a result, a growing number of therapeutic studies are focused on inhibitors that target this crucial signaling pathway, which is essential for cellular survival and controls essential cellular processes like metabolism and proliferation.

Among the important signaling pathways connected to treatment resistance, the PAM pathway stands out. The main reasons for its dysregulation out of many are mutations in PIK3CA, mutations in AKT, or deletion of tensin homolog (PTEN). Notably, compared to other BC subtypes, hormone receptor-positive (HR+) BC has a higher prevalence of PI3K/AKT/mTOR mutations.

In the past, research on PAM pathway inhibitors has mostly concentrated on their application as first or second-line treatments for advanced or metastatic HR-positive/HER2-negative breast cancer. However, resistance against endocrine therapy is not the only possible outcome of aberrant PAM pathway activation; resistance against anti-HER2 therapy and chemotherapy are also closely associated with it. As a result, research into the application of PAM pathway inhibitors in HER2-positive and triple-negative breast cancer is still in progress.

In summary, there are currently three main groups of PAM-specific targeted treatments that are either under study or available for usage: PI3K inhibitors (like capivasertib and ipatasertib), AKT inhibitors (like

alpelisib, taselisib, and inavolisib), and mTOR inhibitors (like everolimus). For patients with PIK3CA mutations and HR-positive/HER2-negative metastatic breast cancer, fulvestrant in conjunction with alpelisib which is the first PI3K inhibitor licensed for BC has been approved. Exemestane plus the mTOR inhibitor everolimus is authorized for postmenopausal individuals with HR-positive/HER2-negative advanced breast cancer who have not responded to letrozole or anastrozole therapy. In patients with endocrine-resistant, HR-positive/HER2-negative advanced cancer, combination therapies such as everolimus with endocrine therapy have been shown to be beneficial. These findings are consistent with phase II/III trial results.

The future prospects related to the PI3K/AKT/mTOR pathway of breast cancer treatments are dynamic and diverse. Introducing new inhibitors with improved specificity and fewer off-target effects should be explored and developed. This involves expanding our knowledge of molecular subtypes in order to customize inhibitors to particular mutations. Focusing on combination therapies that combine inhibitors with other targeted treatments should also be used as generally synergistic effects have the potential to overcome resistance mechanisms and enhance treatment outcomes. The PI3K/AKT/mTOR pathway has been identified with patient-specific mutations and activation patterns owing to advances in precision medicine techniques. Hence, treatments can be tailored based on individual profiles to maximize therapeutic responses. Research should also be conducted to identify and address resistance mechanisms associated with this pathway by looking into adaptive changes in cancers and developing strategies to counteract resistance in order to improve treatment durability. Reliable biomarkers need to be identified for predicting treatment response and resistance that will aid in patient stratification, ensuring that the right individuals receive targeted therapies, thereby maximizing efficacy. Diverse subtypes of breast cancer, including as HER2-positive and triple-negative breast tumors, should be included in clinical studies. Ultimately, a thorough evaluation of the PI3K/AKT/mTOR inhibitors' long-term safety profiles is required to guarantee their continued effectiveness without compromising the general health of the patients.

Therefore, targeting the PI3K/AKT/mTOR pathway in breast cancer holds promise, evidenced by clinical advancements. However, challenges persist, necessitating ongoing research for improved therapeutic strategies and outcomes. Thus, inhibiting this pathway represents a promising therapeutic avenue for breast cancer treatment because it can sensitize tumors to standard treatments like endocrine therapy, HER2-targeted agents, and chemotherapy. By tackling resistance mechanisms associated with activated PI3K signaling pathways in breast cancers, therapies could become more effective. Endocrine therapy combined with mTOR inhibition has already demonstrated efficacy as an approach that targets these resistant cells. To further improve outcomes for patients living with breast cancer various clinical trials are exploring novel combination strategies building upon PI3K inhibitors alongside other targeted options under investigation.

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