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BREAST CANCER (B OVERMOYER, SECTION EDITOR)

PI3K Inhibitors in Breast Cancer Therapy

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Abstract

Purpose of Review The phosphatidylinositol 3-kinase (PI3K) pathway is the most common aberrantly activated pathway in breast cancer, making it an attractive therapeutic target. In this review, we will discuss the rationale for targeting PI3K/AKT signaling and the development of PI3K/AKT inhibitors in breast cancer.

Recent Findings Although the initial clinical trials with pan-PI3K inhibitors were challenged by high toxicities and modest antitumor effect, there has been continued effort to develop agents more precisely targeting PI3K isoforms to improve therapeutic index. Alpelisib in combination with fulvestrant is now available in the clinic for postmenopausal women with advanced or metastatic hormone receptor (HR)-positive, HER2-negative, *PIK3CA*-mutated breast cancer. In addition, promising data has been observed in randomized phase II trials of AKT inhibitors in combination with fulvestrant or paclitaxel in metastatic HR-positive, HER2-negative disease and triple negative breast cancer (TNBC), respectively.

Summary The high frequency of genetic alterations in the PI3K pathway has provided the rationale for development of inhibitors targeting PI3K/AKT. Despite initial disappointment with several randomized trials of pan-PI3K inhibitors in HR-positive breast cancer, there has been continued effort to more precisely target PI3K isoforms, which has led to clinical benefit for patients with advanced breast cancer.

Keywords Breast cancer · PI3K pathway · PI3K inhibitor · AKT inhibitor · Targeted therapy

Introduction

Breast cancer is the most commonly diagnosed cancer and the second leading cause of cancer-related death in women worldwide [1]. Despite advances in prevention and therapeutics over recent decades, more than 270,000 new cases of invasive breast cancer and 42,000 breast cancer deaths are expected in the USA in 2019 [2]. Worldwide incidence of female breast cancer is predicted to reach 3.2 million new cases per year by 2050 [3].

Breast malignancies are classified into four major clinical subtypes according to hormone and growth factor receptor expression—hormone receptor-positive (HR+), HER2-positive, and triple negative breast cancer (TNBC) (i.e., negative for hormone and HER2 receptors)—and fall into four intrinsic molecular subtypes including luminal A, luminal B, HER2-enriched, and basal-like, each with distinct clinical phenotypes and outcomes [4]. Recent genomic sequencing efforts have provided further molecular characterization of breast cancer, leading to the identification of potentially actionable genetic alterations to facilitate the goal of personalized medicine.

Phosphatidylinositol 3-Kinase Pathway

Phosphatidylinositol 3-kinases (PI3Ks) are a family of intracellular heterodimeric lipid kinases that respond to nutrition, growth factor, and other environmental cues and play a critical role in regulating many biological functions, including cell growth, proliferation, survival, differentiation, metabolism, motility, genomic stability, protein synthesis, and angiogenesis. PI3K is broadly divided into three classes (I–III) based on structural and biochemical properties such as substrate specificity. Of these, class I PI3Ks are the major PI3K family

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enzymes known to drive oncogenesis. Class IA PI3Ks are heterodimers of a p110 catalytic subunit (α, β, γ, or δ) and a p85 regulatory subunit, which receive upstream activation signals from receptor tyrosine kinases (including HER, FGFR, and IGF-1) and G protein–coupled receptors. Activated PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-triphosphate (PIP3). Accumulation of PIP3 at the plasma membrane recruits protein kinase B (AKT), a central mediator of the PI3K pathway, and phosphoinositide-dependent kinase 1 (PDK1). At the plasma membrane, AKT is phosphorylated by PDK1 and PDK2 for activation then stimulates downstream effects by activating mammalian target of rapamycin (mTOR) via effects on the intermediary tuberous sclerosis complex 1/2 (TSC1/2). The tumor suppressor protein phosphatase and tensin homolog (PTEN) catalyzes the dephosphorylation of PIP3 to PIP2, thereby acting as a negative regulator of PI3K signaling [5–7] (Fig. 1).

Aberrant activation of PI3K pathway activity is frequently observed in breast cancer, leading to uncontrolled tumor cell growth and drug resistance. Mutations in *PIK3CA*, the gene encoding the p110α catalytic subunit of PI3K, are one of the most common genomic alterations in HR+ breast cancer, occurring in approximately 40% of cases [8]. The majority of these mutations cluster in the helical and kinase domain, including the three hot spot mutations (E545K, E542K, and H1047R), which activate PI3K enzyme activity, leading to constitutive, unopposed phosphorylation of AKT and its downstream effectors [9–11]. Mutations in other components of the pathway, including loss-of-function mutations in *PTEN* (2–4%) and activating mutations in *AKT1* (2–3%) and PI3K regulatory subunit α (PIK3R1) (1–2%), are less commonly observed in HR+ breast cancer but are important mechanisms activating PI3K downstream signaling. Similar findings were observed in HER2-positive breast cancer. In contrast, TNBC is more frequently associated with *PTEN* loss of expression (about 30–50%) than *PIK3CA* mutations (< 10%).

Treatment Approaches in Breast Cancer

Given that hyperactivation of the PI3K pathway is one of the most common signaling abnormalities observed in breast cancer, a substantial effort has been made to develop agents targeting this signaling cascade, particularly for HR+ breast cancer (Table 1). There are several general classes of agents that target the PI3K network: pan-PI3K inhibitors, isoform-specific PI3K inhibitors, AKT inhibitors, rapamycin analogues or mTOR inhibitors, and combined PI3K/mTOR inhibitors (which will not be discussed in this review) [12].

Hormone Receptor-Positive Breast Cancer

Approximately 70% of breast cancer cases are classified as HR+ [i.e., estrogen receptor (ER) and/or progesterone receptor (PR) positive]. While endocrine therapy remains the backbone of treatment, resistance to endocrine therapy is common and occurs invariably in the metastatic setting, leading to disease progression and death [13]. Activation of PI3K pathway signaling is an important mechanism of resistance to antiestrogen therapies; there is significant crosstalk and interdependence between PI3K and ER signaling, necessitating dual inhibition even in *PIK3CA* wild-type patients [14, 15]. In addition, preclinical studies indicate that PI3K pathway activation acts as an adaptive resistance mechanism to CDK4/6

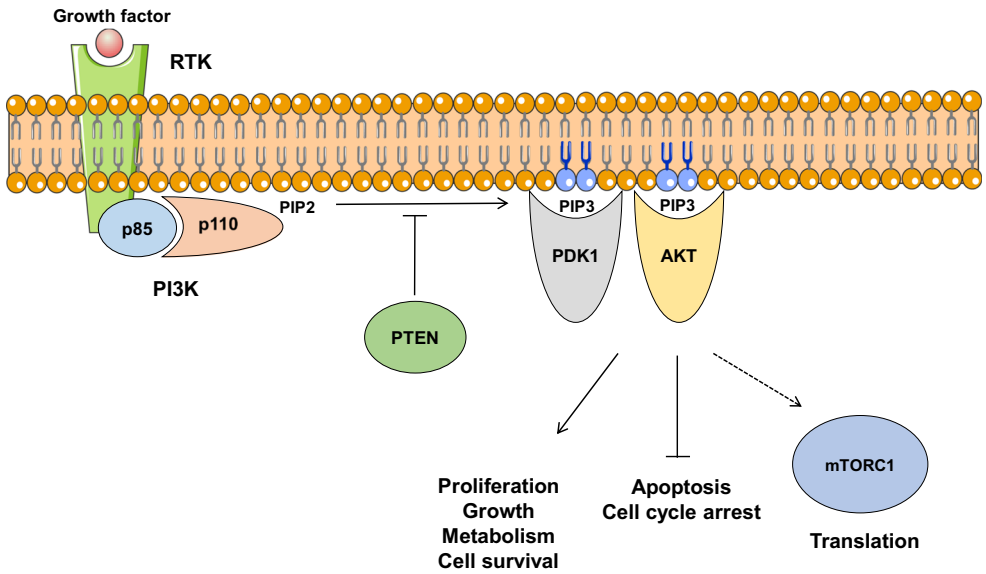

Fig. 1 PI3K signaling pathway

Table 1 Completed randomized trials of PI3K and AKT inhibitors in breast cancer

Trial	Phase	Treatment	Targeted therapy	Patient population	Outcomes (therapy vs placebo)
BELLE-2	III	Buparlisib or placebo + fulvestrant	Pan-PI3K inhibitor	HR+/HER2− locally advanced or MBC, resistant to AI ($n = 1147$)	PFS 6.9 months vs 5 months (HR 0.78; $p = 0.00021$) PFS 6.8 months vs 4 months in PI3K mutated (HR 0.76; $p = 0.014$)
BELLE-3	III	Buparlisib or placebo + fulvestrant	Pan-PI3K inhibitor	HR+/HER2− locally advanced or MBC, resistant to mTOR inhibitor ($n = 432$)	PFS 3.9 months vs 1.8 months (HR 0.67; $p = 0.0003$)
BELLE-4	II/III	Buparlisib or placebo + paclitaxel	Pan-PI3K inhibitor	HER2− locally advanced or MBC ($n = 416$)	PFS 8.0 months vs 9.2 months (HR 1.18) PFS 9.1 months vs 9.2 months in PI3K mutated (HR 1.17)
FERGI	II	Pictilisib or placebo + fulvestrant	Pan-PI3K inhibitor	Advanced or MBC, resistant to AI	PFS 6.6 months vs 5.1 months (HR 0.74; $p = 0.096$) PFS 6.5 months vs 5.1 months in PI3K mutated (HR 0.74; $p = 0.268$) PFS 5.8 months vs 3.6 months in non-PI3K mutated (HR 0.72; $p = 0.23$)
PEGGY	II	Pictilisib or placebo + paclitaxel	Pan-PI3K inhibitor	HR+/HER2− locally recurrent or MBC ($n = 183$)	PFS 8.2 months vs 7.8 months (HR 0.95; $p = 0.83$) PFS 7.3 months vs 5.8 months in PI3K mutated (HR 1.06; $p = 0.88$)
SOLAR-1	III	Alpelisib or placebo + fulvestrant	PI3Kα inhibitor	HR+/HER2− advanced BC, resistant to AI ($n = 572$)	PFS 11.1 months vs 3.7 months (HR 0.48) PFS 11.0 months vs 5.7 months in PI3K mutated (HR 0.65; $p = 0.00065$)
LORELEI	II	Taselisib or placebo + letrozole	PI3Kα inhibitor	HR+/HER2− early-stage BC, neoadjuvant ($n = 334$)	ORR 50% vs 39.3% (OR 1.55; $p = 0.049$) ORR 56.2% vs 38% in PI3K mutated (OR 2.03; $p = 0.033$) No significant difference in pCR
NEO-ORB	II	Alpelisib or placebo + letrozole	PI3Kα inhibitor	HR+/HER2− early-stage BC, neoadjuvant ($n = 257$)	ORR 43% vs 45% (*PIK3CA* mutant), 63% vs 61% (*PIK3CA* wildtype) pCR rates low in all groups
SANDPIPER	III	Taselisib or placebo + fulvestrant	PI3Kα inhibitor	HR+/HER2− locally advanced or MBC, resistant to AI ($n = 516$)	PFS 7.4 months vs 5.4 months (HR 0.70; $p = 0.0037$)
FAKTION	II	Capivasertib or placebo + fulvestrant	AKT inhibitor	HR+/HER2− advanced BC, resistant to AI ($n = 140$)	PFS 10.3 months vs 4.8 months (HR 0.57; $p = 0.0035$)
I-SPY2		MK-2206 or placebo + chemotherapy	AKT inhibitor	Invasive BC ≥ 2.5 on exam or ≥ 2 cm on imaging	Improved pCR rate
LOTUS	II	Ipatasertib or placebo + paclitaxel	AKT inhibitor	TNBC locally advanced or metastatic ($n = 124$)	PFS 6.2 months vs 4.9 months (HR 0.60; $p = 0.037$) PFS 6.2 months vs 3.7 months in *PTEN*-low tumors (HR 0.59; $p = 0.18$)

AI aromatase inhibitor, *BC* breast cancer, *HR+* hormone receptor-positive, *HER2−* HER2-negative, *HR* hazard ratio, *MBC* metastatic breast cancer, *OR* odds ratio, *ORR* overall response rate, *pCR* pathologic complete response, *PFS* progression-free survival, *TNBC* triple negative breast cancer (estrogen receptor negative, progesterone receptor negative, and HER2 negative)

inhibition, which leads to increased AKT phosphorylation and activation of CDK2, providing rationale for evaluation of inhibitors of the PI3K pathway to overcome CDK4/6 inhibitor resistance [16, 17].

Pan-PI3K Inhibitors

Pan-PI3K inhibitors inhibit the kinase activity of all four isoforms of class I PI3Ks: α, β, γ, and δ. These inhibitors encompass a broad spectrum of activity by affecting a wide range of downstream targets, though unsurprisingly with an increased risk of on- and off-target toxicities.

Several BELLE trials investigated the pan-PI3K inhibitor buparlisib. The phase III BELLE-2 trial examined the efficacy of fulvestrant plus buparlisib or placebo in women with aromatase inhibitor-refractory HR+/HER2-negative (HER2−) advanced breast cancer. The improved progression-free survival (PFS) benefit was relatively modest with the addition of buparlisib prolonging PFS by 6.9 months versus 5.0 months compared to placebo. Notably, patients with *PIK3CA* mutations detected in their circulating tumor DNA had much better outcomes if they received buparlisib rather than placebo in combination with fulvestrant (PFS 7.0 months vs 3.2 months, respectively). The most common adverse events were increased liver transaminases, hyperglycemia, and rash [18]. Another phase III trial, BELLE-3, investigated whether fulvestrant plus buparlisib was able to restore endocrine sensitivity after treatment with an mTOR inhibitor in HR+ metastatic breast cancer. Patients with *PIK3CA* mutation noted in plasma cell-free DNA who received buparlisib versus placebo had greater median PFS (4.7 months vs 1.6 months, respectively), compared to patients without *PIK3CA* mutations (3.7 months vs 2.7 months, respectively). There was some overlap in adverse events with the BELLE-2 trial including elevated transaminases and hyperglycemia as well as fatigue, hypertension, dyspnea, and pleural effusion [19]. The phase II BELLE-4 trial of patients with advanced-stage HER2−negative breast cancer demonstrated no statistically significant difference in PFS in the intention-to-treat population of buparlisib in combination with paclitaxel, nor in the subgroup of patients with *PIK3CA* mutations or *PTEN* loss [20]. More than 40% of patients in the buparlisib/paclitaxel arm experienced diarrhea, alopecia, rash, nausea, and hyperglycemia.

The phase II FERGI study on fulvestrant in combination with pictilisib, another pan-PI3K inhibitor, in HR+/HER2− breast cancer resistant to aromatase inhibitors in the adjuvant or metastatic setting found no difference in the median PFS between the pictilisib and placebo group (6.6 months vs 5.1 months, respectively), even if patients were analyzed according to the presence or absence of *PIK3CA* mutation. A subgroup analysis demonstrated that women whose cancers were both ER+ and PR+ were 56% less likely to have their disease progress if they had received the combination of pictilisib plus fulvestrant. Their median PFS was 7.4 months instead of 3.7 months seen in the placebo arm. Gastrointestinal disorders were the most common adverse event in both groups. Patients in the pictilisib arm had more skin/subcutaneous toxicities, hyperglycemia, pneumonitis, bronchopneumonia, and pleural effusions [21]. Another phase II study PEGGY failed to meet the primary endpoint, revealing no significant benefit from adding pictilisib to paclitaxel for patients with HR+/HER2− locally recurrent or metastatic breast cancer, irrespective of *PIK3CA* mutation status (median PFS 8.2 months vs 7.8 months with placebo). Hyperglycemia, hypertension, and maculopapular rash were reported in the pictilisib arm only [22].

PI3K Isoform-Specific Inhibitors

Isoform-specific inhibitors are expected to have fewer off-target adverse effects due to their enhanced selectivity. These agents target cancers that are addicted to specific PI3K isoforms. PI3Kα inhibitors selectively inhibit the class I PI3K catalytic subunit α isoform, which is often activated due to mutations in *PIK3CA*.

The α-specific PI3K inhibitors, alpelisib and taselisib, were found to exhibit promising efficacy, particularly in patients with *PIK3CA* mutations. Taselisib is technically a beta-sparing inhibitor as it selectively inhibits p110α, δ, and γ isoforms of class IA PI3K. The phase III SANDPIPER trial evaluated the effect of taselisib and fulvestrant in aromatase inhibitor-resistant *PIK3CA*-mutant locally advanced or metastatic HR+ breast cancer. There was only a 2-month benefit in median PFS compared with fulvestrant alone. Patients in the taselisib arm experienced diarrhea, hyperglycemia, colitis, and stomatitis [23]. The SOLAR-1 phase III trial demonstrated near doubling of median PFS with the addition of alpelisib to fulvestrant compared to fulvestrant therapy alone in patients with HR+/HER2− advanced breast cancer with *PIK3CA* mutations (11.0 months vs 5.7 months, respectively) [24•, 25•]. Notably, based on data from this trial, alpelisib was approved by the FDA in May 2019 for the treatment of postmenopausal women and men with HR+/HER2−, *PIK3CA*-mutated advanced or metastatic breast cancer following progression on or after an endocrine-based regimen. Alpelisib was also studied in combination with nab-paclitaxel in HER2−negative metastatic breast cancer and showed promising efficacy, particularly in patients with *PIK3CA* mutations (PFS 13.0 months vs 7.0 months with chemotherapy alone). Twenty-five percent of patients discontinued alpelisib due to adverse events including hyperglycemia, rash, and diarrhea [26].

Data in the neoadjuvant setting, in regard to the efficacy of PI3K inhibitors, have been inconsistent. Neoadjuvant treatment with taselisib in combination with letrozole demonstrated significantly improved overall response rates (50% with

taselisib vs 39.3%) in a randomized phase II study (LORELEI) involving patients with HR+/HER2− early-stage breast cancer, while the addition of alpelisib to letrozole did not improve the overall response rates in the NEO-ORB trial [27, 28].

Based on promising preclinical data, there are several studies of PI3K inhibitors, including alpelisib, buparlisib, copanlisib, pictilisib, and taselisib as well as newer agents such as gedatolisib (PI3K-mTOR inhibitor) in doublet or triplet combinations with hormonal therapy or CDK4/6 inhibitors as strategies to delay or overcome resistance to CDK4/6 inhibitors. Examples include NCT02088684, NCT02684032, NCT02626507, NCT02389842, and NCT03128619.

AKT Inhibitors

Inhibition of AKT modulates the downstream effects of PI3K. Several AKT inhibitors, including the allosteric pan-AKT inhibitor MK-2206 and the ATP-competitive pan-AKT inhibitor AZD5363, have been studied in early-phase clinical trials for the treatment of HR+ breast cancer. While MK-2206 in combination with hormonal therapy showed modest clinical activity in a phase I trial in a heterogeneous patient population with metastatic HR+/HER2− breast cancer, AZD5363 (capivasertib) demonstrated promising antitumor activity in a phase I study in patients with solid tumors harboring *AKT1* E17K mutations. Six of 20 patients with heavily pretreated metastatic HR+ breast cancer achieved partial response (4 confirmed and 2 unconfirmed) [29, 30]. A phase Ib/II randomized placebo-controlled trial of fulvestrant ± AZD5363 in postmenopausal women with aromatase inhibitor-resistant advanced breast cancer is ongoing (NCT01992952).

Recently announced results from the phase II FAKTION trial demonstrated that adding the AKT inhibitor capivasertib to fulvestrant led to a more than doubling of PFS in patients who relapsed or progressed on aromatase inhibitors (PFS 10.3 months with capivasertib vs 4.8 months). PI3K pathway activation status did not affect sensitivity to capivasertib. Dose reductions were required in nearly 40% of the study arm versus 4% in the placebo group, mostly due to rash and diarrhea [31•].

HER2-Positive Breast Cancer

HER2 is amplified/overexpressed in about 20–25% of breast cancer cases and is associated with increased tumor aggressiveness. Although trastuzumab has provided significant clinical benefits to patients with HER2-positive (HER2+) breast cancer, de novo or acquired resistance to HER2 therapies remains a major obstacle. PI3K is the major pathway downstream of HER2, and *PIK3CA* mutations occur in nearly 25% of HER2+ breast cancer cases; these mutations can confer resistance to HER2-targeted therapy and are associated with poorer outcomes [32–34]. Because HER2 mediates signal transduction through the PI3K pathway, inhibiting this signaling may be a strategy to overcome resistance and restore sensitivity to HER2-targeted therapy [35].

There has been ongoing effort to develop PI3K inhibitor combination strategies to overcome trastuzumab resistance. Pan-PI3K inhibitors (buparlisib and pilaralisib) when combined with lapatinib, trastuzumab, or trastuzumab/paclitaxel demonstrated promising efficacy and safety in early-phase trials of patients with pretreated HER2+ advanced breast cancer [36–38]. However, a phase II study of buparlisib and trastuzumab in HER2+ locally advanced or metastatic breast cancer resistant to HER2 therapy demonstrated limited efficacy [39]. Current effort is focused on isoform-selective PI3K inhibitors. Alpelisib in combination with T-DM1 was found to be tolerable and demonstrated activity in trastuzumab-resistant HER2+ breast cancer, including T-DM1-resistant disease in a phase I study [40]. Additionally, copanlisib, a pan-PI3K inhibitor, with activity predominantly against PI3Kα and δ, is being evaluated in combination with trastuzumab (NCT02705859).

TNBC

TNBC accounts for approximately 20% of breast cancer cases. Although there have been significant advances in therapeutics for HR+ and HER2+ breast cancer, targeted agents for TNBC remain limited and chemotherapy continues to be the mainstay of treatment. The relevance of PI3K/AKT/mTOR signaling in TNBC pathogenesis is supported by the frequent loss of *PTEN* and *INPP4B* phosphatases, which correlates with increased AKT phosphorylation, and the preclinical observation that *PTEN* inactivation leads to "basal-like" breast cancer in animal models [8, 41, 42]. *PIK3CA* mutations are less frequent (7–9%) in TNBC as compared to HR+ and HER2+ breast cancer, and associate commonly with luminal androgen receptor-positive subtype of TNBC [43]. Because activation of the PI3K pathway has been associated with chemotherapy resistance, studies are ongoing that evaluate combinations of PI3K pathway inhibitors with chemotherapy agents [44]. While PI3K inhibitors are still at early-stage development in TNBC, AKT inhibitors have demonstrated promising activity in combination with paclitaxel as first-line therapy in the metastatic setting.

The phase II LOTUS study of ipatasertib, an AKT inhibitor, versus placebo in combination with paclitaxel was tested in previously untreated metastatic TNBC [45]. The ipatasertib arm had significantly improved median PFS compared to the placebo arm (6.2 months vs 4.9 months, respectively). Patients were stratified based on *PTEN* status as deficient *PTEN* expression is associated with greater AKT activation. Although there was no difference in PFS in the *PTEN*-low tumors, significant differences were observed in *PI3K/AKT1/PTEN*-mutated tumors. The phase II/III trial of

ipatasertib in combination with paclitaxel in patients with *PIK3CA/AKT1/PTEN*-altered locally advanced or metastatic TNBC or HR+/HER2− breast cancer (IPATunity130) is ongoing and is a larger study that aims to confirm and build on the results of the LOTUS trial (NCT03337724).

Furthermore, the PAKT trial investigated capivasertib in combination with paclitaxel as first-line treatment for metastatic TNBC. While the median PFS was marginally longer in the experimental group, most of the benefit was seen in the 20% of patients with mutations in *PIK3CA*, *AKT1*, or *PTEN* (PFS 9.3 months vs 3.7 months in experimental vs placebo arm, respectively) [46].

In the early-stage disease setting, the I-SPY2 neoadjuvant study randomly assigned patients to standard chemotherapy—weekly paclitaxel plus doxorubicin/cyclophosphamide—with or without a novel therapy. This study has shown that neoadjuvant inhibition of AKT with the oral agent MK-2206, an allosteric AKT inhibitor, in combination with chemotherapy can increase pathologic complete response (pCR) rates in stage II–III breast cancer (pCR 40% with MK-2206 vs 22%) [47]. MK-2206 has graduated to a phase III trial based on this data.

Challenges in Targeting the PI3K Pathway and Future Directions

Although *PIK3CA* is among the most commonly mutated genes in breast cancer, effective therapeutic agents that target this aberration have proven challenging due to the complexity of this signaling pathway. More than forty inhibitors of the PI3K pathway have reached various stages of clinical development, but few have been FDA approved for clinical usage, with the exception of PI3K inhibitors idelalisib and copanlisib for hematologic malignancies and, more recently, alpelisib in breast cancer. Most PI3K inhibitors have only shown modest benefit, likely limited by lack of isoform-selective inhibition, feedback regulation, crosstalk with other signaling pathways, and tolerability. However, there are a number of early-phase trials with new combinations of PI3K-targeted agents aiming to achieve significant clinical benefit (Table 2).

Intrinsic/de novo or acquired resistance to PI3K inhibitors limits the activity of these agents as monotherapy. Continuous inhibition of the PI3K pathway leads to activation of compensatory pathways that can reduce the sensitivity to these agents; blocking one isoform can upregulate activity through other isoforms [12]. Pharmacologic inhibition of PI3K signaling can lead to rapid overexpression/activation of receptor tyrosine kinases (RTKs), including HER2 and HER3, that can activate downstream signaling pathways and curb the effectiveness of PI3K therapy [48]. Recent focus has shifted towards combination therapy with inhibitors of other signaling pathways within tumor cells including antiestrogens, upstream RTKs, and CDK4/6 to fully exploit the antitumor activity of PI3K inhibitors.

Inhibitors with increased specificity for individual isoforms of PI3K seem to have better therapeutic efficacy and improved toxicity profiles compared to non-isoform-selective agents. Isoform-specific PI3K inhibitors are distinct from pan-PI3K inhibitors as they only target specific isoforms of the PI3K p110 subunit. This achieves antitumor efficacy via blockade of relevant p110 subunits but spares irrelevant subunits, which minimizes toxicity. The primary approach explored in breast cancer has been p110α and p110β-specific inhibition. For example, taselisib demonstrated limited benefit and poor tolerability in the SANDPIPER trial, likely partly due to a lack of complete specificity for the α isoform as it also targets the δ and γ isoforms. Determining the magnitude of signaling inhibition required to produce biological and clinical effects will be critical; perhaps intermittent dosing or other scheduling alternatives may limit the on- and off-target toxicities that come with chronic inhibition [49, 50].

Another major obstacle in targeting PI3K is tolerability. The therapeutic window is narrow because normal cells also require PI3K signaling for survival and, as a consequence, severe adverse effects often manifest before full inhibition of the target in tumor cells. Pan-PI3K pathway inhibitors are associated with common, dose-dependent toxicities such as hyperglycemia, rash, fatigue, and diarrhea. p110α is crucial in mediating the cellular response to insulin, thus why interrupting this leads to hyperglycemia. Toxicity from isoform-specific PI3K inhibitors depends on their individual isoform—PI3Kα are associated with hyperglycemia and rash; PI3Kδ inhibitors are associated with gastrointestinal side effects, myelosuppression, and transaminitis; and PI3Kγ are linked with colitis [51]. In the BELLE trials, more than 20–25% of patients treated with buparlisib had severe (grade ≥ 3) adverse events, such as on-target hyperglycemia and liver toxicities [18]. Several patients had severe anxiety/depression leading to suicide attempts in the BELLE-3 trial, which is thought to be related to its penetration through the blood-brain barrier [19]. Further development of buparlisib, pictilisib, and taselisib is no longer moving forward due to their safety profile.

Patient preselection is an established concept in breast cancer treatment, such as that seen with non-response to trastuzumab in patients without *HER2* overexpression or amplification. Selecting the right patients who will benefit from superior antitumor activity from specific agents on the basis of biomarkers also proves to be an obstacle. Preclinical studies highlight that breast cancer cell lines with PI3K mutations are sensitive to PI3K pathway inhibition. Clinically, PI3Kα inhibitors and AKT inhibitors have shown promising response in patients with *PIK3CA*- and *AKT*-mutated tumors, respectively. Biomarker selection has become increasingly important in using targeted therapies and improving personalized medicine [52]. Vasan et al recent reported that double *PIK3CA* mutations in cis, which occurs in up to 15% of breast cancers, increase PI3K activity, oncogenicity, and sensitivity to PI3Kα inhibitors [53•].

Table 2 Ongoing trials of PI3K and AKT inhibitors in breast cancer

Trial	Phase	Treatment	Targeted therapy	Patient population
BYLieve				
NCT03056755	II	Alpelisib + fulvestrant/letrozole	PI3Kα inhibitor	*PIK3CA*-mutated HR+/HER2− recurrent advanced BC
SAFIR				
NCT03386162	II	Alpelisib + fulvestrant vs chemotherapy	PI3Kα inhibitor	*PIK3CA*-mutated HR+/HER2− MBC
NCT01870505	I	Alpelisib + letrozole or exemestane	PI3Kα inhibitor	HR+ locally advanced unresectable or MBC
NCT01872260	I	Alpelisib + letrozole + ribociclib	PI3Kα inhibitor	HR+/HER2− locally advanced or MBC
NCT02167854	I	Alpelisib + LJM716 (anti-HER3 antibody) + trastuzumab	PI3Kα inhibitor	HER2+ MBC
NCT02379247	I/II	Alpelisib + nab-paclitaxel	PI3Kα inhibitor	HER2− advanced or MBC
NCT01623349	I	Alpelisib + olaparib (PARP inhibitor)	PI3Kα inhibitor	Recurrent TNBC
NCT02038010	I	Alpelisib + T-DM1	PI3Kα inhibitor	HER2+ MBC who progressed on trastuzumab/taxane
NCT03006172	I/II	GDC-0077 ± palbociclib/letrozole, letrozole, fulvestrant, palbociclib/fulvestrant	PI3Kα inhibitor	*PIK3CA* mutant HR+/HER2− locally advanced or MBC
NCT02734615	I	LSZ102 + ribociclib or alpelisib	PI3Kα inhibitor (alpelisib), SERD (LSZ102)	HR+ locally advanced or MBC who have progressed after endocrine therapy
NCT03767335		MEN1611 + trastuzumab ± fulvestrant	PI3Kα inhibitor	*PIK3CA*-mutated HER2+ advanced or MBC
NCT02626507	I	Gedatolisib + palbociclib + fulvestrant	PI3K/mTOR inhibitor	HR+/HER2− BC, neoadjuvant
BEECH				
NCT01625286	I/II	AZD5363 + paclitaxel	AKT inhibitor	HR+ advanced or MBC
TAKTIC				
NCT03959891	I	Ipatasertib + fulvestrant or letrozole ± palbociclib	AKT inhibitor	HR+ MBC
IPATunity130				
NCT03337724	III	Ipatasertib + paclitaxel	AKT inhibitor	Locally advanced or metastatic TNBC and HR+/HER2− not suitable for endocrine therapy

BC breast cancer, *HR* hormone receptor (estrogen and progesterone receptors), *HR+* HR-positive, *HER2−* HER2-negative, *MBC* metastatic breast cancer, *SERD* selective estrogen receptor degrader, *TNBC* triple negative breast cancer (estrogen receptor negative, progesterone receptor negative, and HER2 negative)

Conclusion

In summary, aberrant PI3K/AKT/mTOR signaling contributes to the development of breast cancer. The high frequency of genetic alterations in this pathway has provided the rationale for the development of inhibitors targeting PI3K/AKT. Despite initial disappointment with several randomized trials of pan-PI3K inhibitors in HR+ breast cancer, there has been continued effort to more precisely target PI3K isoforms critical for the disease process, leading to the approval of alpelisib in metastatic HR+/HER2−, *PIK3CA*-mutated breast cancer. However, success of these agents in clinic requires optimizing the management of side effects and the identification of predictive markers and resistance mechanisms.

Compliance with Ethical Standards

Conflict of Interest Haley Ellis declares that she has no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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