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REVIEW

Profile of buparlisib and its potential in the treatment of breast cancer: evidence to date

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Abstract: Alteration of the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin signaling pathway is key for the growth and survival of several cancers, including breast cancer. In addition, dysregulation of PI3K signaling may contribute to resistance to several anticancer agents. PI3K inhibitors may, therefore, be effective as antineoplastic therapy. Buparlisib is a potent and highly specific oral inhibitor of the pan-class I PI3K family. Buparlisib specifically inhibits class I PIK3 in the PI3K/AKT kinase signaling pathway in an ATP-competitive manner, thus inhibiting the production of the secondary messenger phosphatidylinositol (3,4,5)-trisphosphate and activation of the PI3K signaling pathway. This may induce inhibition of tumor cell growth and survival in susceptible tumor cell populations. Buparlisib is currently under investigation in patients with a variety of solid tumors, including breast cancer. Buparlisib has been validated as a promising anticancer agent, and tremendous efforts have been taken to develop it. However, buparlisib monotherapy has resulted in humble benefit so far. Results from studies combining buparlisib with different anticancer agents – namely, endocrine therapy, anti-HER2 therapy, and chemotherapy – have showed variable efficacy with consistent substantial toxicity.

Keywords: buparlisib, breast cancer, PI3K

Introduction

Phosphoinositide 3-kinase (PI3K) pathway, a critical signal transduction system which links oncogenes and several receptor classes to different key cellular functions, is one of the most widely activated signaling pathways in cancer.[1]

The family of lipid kinases called phosphoinositide 3-kinases (PI3Ks) plays essential regulatory roles in different cellular processes including cell survival, proliferation, differentiation, cytoskeletal organization, and glucose transport.[2–4]

There are three classes of PI3Ks which differ in their structural characteristics and substrate specificity.[5,6] Class I enzymes are the most commonly studied; they are activated directly by cell surface receptors. Furthermore, class I PI3Ks are divided into class IA enzymes, which are activated by RTKs, GPCRs, and some oncogenes such as the small G protein Ras, and class IB enzymes, which are regulated only by GPCRs.

These enzymes – through the formation of the second messenger phosphatidylinositol (3,4,5)-trisphosphate – activate many target proteins, most notably phosphoinositide-dependent kinase-1. The downstream targets of these protein kinases, such as mammalian target of rapamycin (mTOR), BCL2-associated agonist of cell death, and forkhead box O proteins, regulate proliferation, growth, and survival.[7]

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Alteration of the PI3K/AKT/mTOR pathway is key for the growth and survival of several cancers, including breast cancer (BC). Different aberrations in the PI3K signaling pathway, such as PI3K mutation/amplification, loss/mutation of the phosphatase and tensin homologue, AKT overexpression/overactivation, and modulation of tuberous sclerosis protein 1 and 2 tumor suppressors, may be often observed in BC, predominantly in hormone receptor-positive (HR+) tumors.[8] Especially, as PI3K is the most proximal component of the pathway, targeting PI3K itself rather than AKT or mTOR with PI3K inhibitors may induce pronounced inhibition of the downstream components within the pathway. Many inhibitors of mTOR have been developed for the treatment of cancers, mostly analogs of rapamycin, which specifically inhibit the activity of the TORC1 complex.[9] However, specific inhibition of TORC1 results in a feedback stimulation of AKT, thus providing an inferior therapeutic efficacy compared to inhibition of PI3K and both TORC complexes.[10] Moreover, activation of PI3K pathway may be associated with resistance to a variety of antitumor agents.[11–13]

Targeting PI3K pathway

HR+ tumor is the most frequent subtype of BC, with endocrine therapy (ET)-based regimens being its backbone of treatment.[14,15] However, HR+ BC is not homogeneous, but characterized by different genomic alterations that on one hand may affect treatment outcomes and on the other hand may offer many therapeutic opportunities with the use of targeted agents.[14,16] Of particular interest, activating PIK3CA mutations (which encode the p110α isoform of PI3K) are frequently detected in HR+ BC and are possibly associated with disease progression and resistance to ET.[14,17–19]

Roughly, 40% of human epidermal growth factor receptor 2-positive (HER2+) BCs harbor activating mutations in PIK3CA.[14] These two oncogenes have different functions and may work together to stimulate tumor growth. Several anti-HER2 agents are approved for the treatment of patients with HER2-positive BC. Nonetheless, both de novo and acquired resistance to anti-HER2 therapies may occur.[20] PIK3CA mutations might be implicated in conferring resistance to these therapies.[21–23] Given that PIK3CA-mutant BC appears to have distinct tumor biology, development of more individualized targeted therapies based on the PIK3CA genotype is awaited.

Therefore, targeting PI3K may be a valid therapeutic option in these settings. In order to maximize treatment efficacy, it would be crucial to identify those patients with PIK3CA mutations who might derive the greatest benefit from PI3K inhibitors.

Several clinical studies have been conducted – mainly in the setting of HR+/HER2− metastatic disease – to explore the combination of endocrine therapies with agents targeting PI3K/Akt/mTOR, such as PI3K inhibitors (panspecific or specific to the subunit 110 α or δ), AKT inhibitors, mTOR inhibitors, or dual inhibitors of mTOR and PI3K. Among these drugs, everolimus is the only PI3K inhibitor approved in combination with exemestane for the treatment of postmenopausal patients with endocrine-resistant HR+/HER2− BC.[24] An exploratory analysis of the BOLERO-2 study showed that the benefit of adding everolimus to ET was consistent regardless of PIK3CA alteration.[25] AZD2014 is a promising dual inhibitor of mTORC1 (rapamycin sensitive) and mTORC2 (rapamycin insensitive), which is currently under investigation in a randomized Phase II trial (MANTA).[26] Temsirolimus was tested in the Horizon study in combination with letrozole, but no benefit in terms of progression-free survival (PFS) was observed compared to letrozole alone.[27] The FERGI trial assessed the combination of pictilisib (GDC-0941), an oral inhibitor of multiple class I PI3K kinase isoforms, and fulvestrant.[28] This study demonstrated a nonsignificant benefit in terms of PFS in the pictilisib arm compared with the placebo arm (6.2 vs 3.8 months; hazard ratio, 0.77; 95% CI, 0.50–1.19), independent of PIK3CA mutation status.[28] Alternative strategies include specific inhibition of subunit α PI3K (alpelisib) or mutated PI3K (taselisib); initial results from the LORELEI study were presented at European Society for Medical Oncology 2017 and showed a benefit in terms of objective response rate for the addition of taselisib to neoadjuvant letrozole in postmenopausal patients with HR+/HER2− early BC.

Buparlisib is a potent and highly specific oral pan-class I PI3K inhibitor, which is currently under investigation in patients with a variety of solid tumors, including BC. In this article, we focus on the main characteristics of buparlisib and its potential application in the treatment of BC.

Buparlisib has demonstrated preliminary activity in preclinical models, providing a rationale for its use in clinical practice.[29] Preclinical data showed that this drug, at high concentrations, might cause cell death in various cellular systems, irrespective of the level of PI3K addiction. Moreover, this agent may interfere with microtubule assembling, inducing cell cycle arrest at G2–M phase. However, at doses and schedules used in clinical settings, these effects may not occur.[30]

In early-phase clinical studies, buparlisib showed encouraging tolerability profile, but modest clinical efficacy as a single agent.[31] As the PI3K pathway is involved in resistance to anticancer treatments, a more promising therapeutic strategy likely consists in combining buparlisib, and PI3K inhibitors in general, with other agents in order to restore sensitivity to such treatments.[32–35] Different trials testing the combination of this PI3K inhibitor with various anticancer drugs are ongoing and are summarized in Table 1.

Materials and methods

We searched PubMed for articles published anytime until September 23, 2017, using the terms "buparlisib" AND "breast cancer", and identified 45 full-text articles in English. Of these articles, 10 publications were reviews. Five publications reported original data from Phase I clinical trials involving buparlisib in BC, and one publication related to Phase III trial of buparlisib in BC was identified.

Table 1 Ongoing trials testing the combination of buparlisib with various anti-cancer drugs

Subtype	Setting	#NCT	Phase	Status	Number of patients	Treatment
HR+ HER2−	Locally advanced/metastatic BC previously treated with AI and mTOR inhibitors	NCT01633060 (BELLE-3)	III	ANR	432	BMK120/placebo + fulvestrant
	Locally advanced/metastatic BC refractory to AI	NCT01610284	III	ANR	1149	BMK120/placebo + fulvestrant
	Locally advanced/metastatic BC with prior hormonal therapy	NCT02404844 PIKTAM	II	ANR	48	BMK120 + tamoxifen
	Neoadjuvant treatment of EBC	NCT01923168	II	C	340	BYL719/placebo + letrozole BMK120/placebo + letrozole
	Metastatic BC	NCT02088684	Ib/II	ANR	70	LEE011 + BKM120 + fulvestrant LEE011 + BYL719 + fulvestrant LEE011 + fulvestrant
	Locally advanced/metastatic BC	NCT02058381 (B-YOND)	Ib	ANR	40	BYL719 or BKM120 + tamoxifen + goserelin acetate
	Metastatic BC	NCT01339442	I	C	31	BMK120 continuous or intermittent + fulvestrant
HR+ HER2+/−	Metastatic BC	NCT01248494	Ib	C	72	BEZ235 + letrozole BKM120 continuous + letrozole BMK102 intermittent + letrozole
HR+/HR− HER2+	Neoadjuvant treatment in EBC	NCT01816594 (NeoPHOEBE)	II	C	50	BKM120/placebo + trastuzumab + paclitaxel
HR+/HR− HER2−	Locally advanced/metastatic BC	NCT01572727 BELLE-4	II/III	C	416	BMK120/placebo + paclitaxel
HR+/− HER2+/−	Metastatic BC	NCT01300962	I	ANR	47	BKM120 + capecitabine BYL719 + capecitabine BKM120 + capecitabine + trastuzumab BKM120 + capecitabine + lapatinib
All subtypes	Metastatic BC with brain metastases	NCT02000882	II	R	40	BKM120 + capecitabine ± trastuzumab
TNBC	Metastatic BC	NCT01629615	II	C	50	BMK120
TNBC	Metastatic BC	NCT01790932	II	ANR	110	BMK120
TNBC Ovarian cancer	Metastatic BC	NCT01623349	I	ANR	118	BYL719 + olaparib BMK102 + olaparib
Solid tumors	Advanced solid tumors	NCT01363232	Ib	ANR	89	BKM120 + MEK162
Solid tumors	Advanced solid tumors	NCT01155453	Ib	C	113	BKM120 + GSK1120212
Solid tumors HER2+ BC	Advanced solid tumors	NCT01285466	Ib	C	110	BEZ235 + paclitaxel BKM120 + paclitaxel BEZ235 + paclitaxel + trastuzumab BKM120 + paclitaxel + trastuzumab
Solid tumors	Advanced solid tumors	NCT01576666	Ib	C	120	LDE225 + BKM120

Abbreviations: AI, aromatase inhibitors; ANR, active, not recruiting; BC, breast cancer; C, completed; EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; mTOR, mammalian target of rapamycin; R, recruiting; TNBC, triple-negative breast cancer.

HR+/HER2− BC

The combination of a PI3K inhibitor and endocrine treatment was tested in a Phase IB study of buparlisib plus letrozole in patients with HR+/HER2− metastatic BC whose disease was refractory to ET.[36] In this study, 46 patients were evaluable for response and 1 achieved complete response, 1 partial response, and 25 patients had stable disease. Clinical activity did not correlate with PIK3CA mutational status, thus suggesting that other alterations in the pathway might be responsible for PI3K pathway dependence.[36]

In the Phase III randomized, double-blind, placebo-controlled, multicenter BELLE-2 study, postmenopausal patients with HR+/HER2− metastatic BC, who had progressed on/after aromatase inhibitor therapy, were randomized 1:1 to receive either buparlisib (100 mg/day) or placebo, starting on day 15 of cycle 1, plus fulvestrant (500 mg) on days 1 and 15 of cycle 1, and thereafter on day 1 of 28-day cycles.[37]

PI3K pathway activation status (activated vs non-activated vs and unknown) and visceral disease status (present vs absent) were stratification factors. The objective of the trial was to assess the predictive value of single PI3K–AKT–mTOR pathway alterations on the clinical response of buparlisib. The primary endpoints were PFS in the overall population, in patients with known (either activated or non-activated) PI3K pathway status, and in patients with PI3K pathway activation.[37]

One thousand one hundred forty-seven patients were included in this trial; 576 received buparlisib plus fulvestrant and 571 received placebo plus fulvestrant.[37] Median PFS was 6.9 vs 5.0 months in the overall population, receiving either buparlisib or placebo, respectively (p=0.00021). Patients with known PI3K status had a median PFS of 6.8 months when treated with buparlisib and 4.5 months with placebo (p=0.0033). In patients with PI3K pathway activation, median PFS was 6.8 vs 4.0 months in the buparlisib and placebo groups, respectively (p=0.014). Patients receiving buparlisib experienced more frequently grade 3–4 increased alanine aminotransferase (25% vs 1%), increased aspartate aminotransferase (18% vs 3%), hyperglycemia (15% vs <1%), and rash (8% vs none).[37] Twenty-three percent of patients treated with buparlisib had serious adverse events as compared to 16% of patients who received placebo. Finally, this study showed that PI3K inhibition combined with ET is effective in patients with HR+/HER2− metastatic BC, but the toxicity associated with this combination is not negligible.[37]

PI3K pathway activation in preclinical models of BC is associated with tumor growth and resistance to anticancer therapies, including paclitaxel. Furthermore, buparlisib has shown synergistic activity when combined with paclitaxel in preclinical and clinical models. Therefore, the double-blind, placebo-controlled, adaptive Phase II/III BELLE-4 trial randomized (1:1) patients with untreated metastatic HER2− BC to receive either buparlisib or placebo with paclitaxel.[38] PI3K pathway activation and HR status were the stratification factors. The primary endpoint was PFS in the overall and PI3K pathway-activated populations. An adaptive interim analysis following the Phase II part of the study was planned to decide whether to go or not to Phase III (in the overall or PI3K pathway-activated population).[38] Four hundred sixteen patients were entered in the trial. At adaptive interim analysis, PFS did not increase with buparlisib over placebo, either in the overall or in the PI3K pathway-activated population. Therefore, the study was stopped for futility.[38]

HER2+ BC

The PI3K/AKT/mTOR pathway is often activated in HER2+ BC.[39] The Phase III BOLERO-1 trial combined trastuzumab and paclitaxel with or without everolimus in this setting and showed no benefit in terms of PFS in the overall population. Nevertheless, in the subgroup of patients with HR−/HER2+, there was an improvement – although not statistically significant – in median PFS of 7.2 months.[40] Moreover, in the Phase III BOLERO-3 trial, addition of everolimus to trastuzumab and vinorelbine led to an increased median PFS (from 5.78 to 7.00 months) in women with HER2+ metastatic BC.[41] A combined analysis of BOLERO-1 and BOLERO-3 demonstrated a strong positive correlation between PI3K pathway activation and PFS increase.[42] These findings pushed the investigation of PI3K inhibitors in HER+ BC.

In the CLEOPATRA study, which assessed the combination of pertuzumab, trastuzumab, and docetaxel in first-line setting,[43] PIK3CA mutation was established as a negative prognostic factor in HER2+ BC.[44] Patients with PIK3CA mutant tumors had a significantly worse PFS than those with PIK3CA non-mutant tumors.[44]

A Phase IB/II study has investigated the combination of buparlisib and trastuzumab in HER2+ BC, who previously progressed on trastuzumab.[45] In this study, buparlisib and trastuzumab combination was well tolerated, with preliminary signs of clinical activity.[45]

The Phase II NeoPHOEBE neoadjuvant study was designed to evaluate the combination of buparlisib with trastuzumab

and paclitaxel in HER2+ BC in two independent cohorts by PIK3CA mutation status; furthermore, each cohort was stratified by HR status.[46] The main objective of the trial was to assess whether PIK3CA mutation status may predict a benefit from combining anti-HER2 therapy and a PI3K inhibitor.[46] The trial was designed to enroll 256 patients. However, after enrollment of the first 50 patients, recruitment was stopped due to liver toxicity.[46] A trend toward higher objective response rate (68.8% vs 33.3%; p=0.053) and a significant decrease in Ki67 (75% vs 26.7%; p=0.021) was observed with buparlisib vs placebo in the HR+ subgroup.[46] Unfortunately, such a treatment strategy does not appear to be feasible.

Buparlisib has also been studied in combination with lapatinib in a Phase IB/II trial including patients with HER2+, trastuzumab-resistant, metastatic BC.[47] In the Phase IB part, the PI3K pathway activation status was assessed in a retrospective exploratory analysis, and evidence of PI3K pathway activation was an inclusion criterion for Phase II. Twenty-four patients were treated at five dose levels. Main drug-related adverse events included diarrhea, nausea, skin rash, asthenia, depression, anxiety, and increase in transaminases. Disease control rate was 79% (one patient with complete response and six patients with stable disease for ≥24 weeks).[47] Finally, this trial showed preliminary evidence of antitumor activity in this heavily pretreated population with manageable safety profile.

Discussion

The PI3K pathway represents both an opportunity and a challenge for cancer treatment. In this review, we have highlighted both major issues and recent progress made in the understanding of the PI3K pathway. We have analyzed both the challenges and promises for the therapeutic development of PI3K pathway inhibitors in BC.

PI3K inhibitors have been validated as promising anticancer targets, and tremendous efforts have been made to develop this class of agents for cancer therapy. However, results of these drugs used as monotherapy have been modest thus far.

Overall, results from studies combining PI3K inhibition with different anticancer agents – although with inconsistent efficacy – showed consistent substantial toxicity; hence, no further studies are being pursued.

A potential role for PI3K-targeted therapy may warrant further investigation with better-tolerated second-generation PI3K inhibitors.

Several controversies remain regarding the best treatment strategy for PI3K inhibition between pan-PI3K and isoform-selective inhibitors. Different agents/class of agents may be more active in tumors with defined molecular characteristics.

Further research is needed to assess biomarkers predictive of response to PI3K inhibitor treatment. No correlation between PI3K/AKT/mTOR pathway aberrations and clinical response has been found to date.

Finally, the potential mechanisms of PI3K inhibitor resistance are still unknown and the complexity of PI3K/AKT/mTOR pathway with extensive crosstalk with other signaling provides general possibility to overcome Pi3K inhibition. A deeper understanding of resistance mechanisms will enable rational design of combination regimens.

With the recent knowledge regarding the divergent roles of PI3K isoforms in different types of cancer, isoform-selective PI3K inhibitors have attracted increasing interest for precise cancer therapy, and over a dozen inhibitors are undergoing clinical evaluation (Table 1). Among them, CAL101 has been approved by the US Food and Drug Administration for patients with relapsed chronic lymphocytic leukemia and indolent lymphoma.

Interestingly, the PI3K pathway may be considered – at the same time – a dramatic therapeutic opportunity and a big challenge for cancer therapy with no doubt. Drugs targeting PI3K (or AKT or mTOR) are under investigation at different stages; there are potential issues associated with their toxicity and resistance. Oncogenic changes in PI3K pathway components may render cancer cells resistant to PI3K inhibition. Hence, it is important to identify new therapeutic targets for the development of agents that may either replace PI3K inhibitors or enhance the efficacy of PI3K inhibitors.

Further investigation is required to determine the best setting and the best combinations.

Disclosure

The authors report no conflicts of interest in this work.

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