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Targeting AKT for cancer therapy

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Abstract

Introduction—Targeted therapies in cancer aim to inhibit specific molecular targets responsible for enhanced tumor growth. AKT/PKB (protein kinase B) is a serine threonine kinase involved in several critical cellular pathways including survival, proliferation, invasion, apoptosis, and angiogenesis. Although phosphatidylinositol-3 kinase (PI3K) is the key regulator of AKT activation, numerous stimuli and kinases initiate pro-proliferative AKT signaling which results in the activation of AKT pathway to drive cellular growth and survival. Activating mutations and amplification of components of the AKT pathway are implicated in the pathogenesis of many cancers including breast and ovarian. Given its importance, AKT, it has been validated as a promising therapeutic target.

Areas covered—This article summarizes AKT's biological function and different classes of AKT inhibitors as anticancer agents. We also explore the efficacy of AKT inhibitors as monotherapies and in combination with cytotoxic and other targeted therapies.

Expert opinion—The complex mechanism following AKT inhibition, requires the addition of other therapies to prevent resistance and improve clinical response Further studies are necessary to determine additional rational combinations that can enhance efficacy of AKT inhibitors, potentially by targeting compensatory mechanisms, and/or enhancing apoptosis. The identification of biomarkers of response is essential for the development of successful therapeutics.

Keywords

AKT activation; tumorigenicity; breast and ovarian cancer; AKT inhibitors; targeted therapy; combinational therapy

1. Introduction

Breast and ovarian cancers are two of the most frequent malignancies in women, with breast cancer being the second and ovarian cancer being the fifth leading causes of cancer-related death in women[1, 2]. Although endocrine therapy and chemotherapy are effective, many

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Declaration of interest

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tumors have intrinsic or acquired resistance to standard therapies[3, 4]. Extensive research has revealed many potential cellular processes such as epigenetic, genomic change, DNA repair and molecular cross talk that underlie therapeutic resistance[5, 6]. Determining targetable molecular biomarkers as alternative or combinational treatments can add to the clinical efficacy of the current therapies and overcome potential resistance.

Over the past few decades, molecular characterization of differentially expressed genes in breast and ovarian cancer patients has demonstrated that novel molecular targeted therapies were successful approaches[7, 8]. Genomic alterations in the phosphatidylinositol 3-kinase (PI3K)/AKT pathway have been reported in several types of cancer, including breast and ovarian[9, 10]. AKT, also known as protein kinase B (PKB), is a critical growth regulator in PI3K signaling, that phosphorylates over 9,000 proteins[11, 12] and is an attractive therapeutic target in cancer. Targeting AKT with the available small molecule inhibitors may enhance approved or investigational anticancer treatments[13]. In this review, the biological function and activation of AKT and its contribution to tumor development and progression are explained. Furthermore, the efficacy of clinically relevant AKT inhibitors as monotherapy and in combination with cytotoxic and other targeted therapies in the treatment of breast and ovarian cancers are discussed.

2. AKT function and structure

AKT is a serine threonine kinase that mediates various biological functions (Figure 1) such as cell proliferation, survival, glucose metabolism, protein synthesis, genome stability, and inhibition of apoptosis in response to different growth factors and extracellular stimuli[14, 15]. Besides its pivotal role in normal cellular physiology, many studies have demonstrated the activation of AKT cascade in various types of human cancer that often results in tumor aggressiveness and drug resistance[16, 17]. Several pathways regulated by AKT are implicated in cancer-associated phenotypes. AKT inactivates pro-apoptotic proteins, such as BCL-2-antagonist of cell death (BAD) and procaspase-9, to block apoptosis. During cell cycle progression, AKT phosphorylates and inhibits glycogen synthase kinase 3β (GSK3β) to prevent cyclin D1 degradation[18, 19, 20].

There are three *AKT* isoforms in humans: *AKT1* (PKB-α), *AKT2* (PKB-β) and *AKT3* (PKB-γ) that share a common structure and a similar activation mechanism[21]. The pleckstrin homology (PH) domain at the N-terminus of AKT interacts with membrane lipids to facilitate AKT recognition and membrane translocation by upstream kinases[22]. The center catalytic region of the protein is the kinase domain, which contains a threonine residue that needs to be phosphorylated for AKT activation[23]. The C-terminal regulatory hydrophobic region of AKT contains a conserved serine residue required for the kinase phosphorylation and activation[24]. All three AKT isoforms share 80% homology in their amino acid sequences with isoform-specific functions[25]. While AKT1 is mainly involved in regulating cell growth and division, AKT2 plays an important role in cellular energy and metabolism[26]. AKT3, the least studied AKT isoform, has been proposed as critical for brain development and the viability of malignant glioma cells[27].

3. AKT activation mechanism and signaling pathway

The main event that triggers AKT activation is the binding of ligands to cell membrane receptors. These ligands include growth factors such as IGF-1 (insulin-like growth factor 1) and PDGF (platelet-derived growth factor), cytokines, hormones, and mitogens[28, 29]. Identical mechanisms downstream of PI3K pathway, as the key element of the AKT signaling cascade, activate all three AKT isoforms [14]. Upon growth factor binding to receptor tyrosine kinase (RTK), the regulatory subunit of PI3K (p85) is targeted to phosphotyrosine-containing cytoplasmic domains of activated RTK. This leads to the activation of the catalytic domain of PI3K (p110), which then recruits AKT to the plasma membrane by binding the PH domain to membrane lipids[30]. The AKT undergoes a conformational change, resulting in the phosphorylation of Thr308 residue by phosphoinositide-dependent kinase-1 (PDK1) and phosphorylation of Ser473 by target of rapamycin complex 2 (mTORC2) of the mammalian target of rapamycin (mTOR) kinase[31, 32]. In addition to mTORC2, multiple different kinases, including DNA-PK (DNA-dependent protein kinase) which is a PI3K-like kinase (PIKK), are responsible for phosphorylation and activation of AKT at Ser473[33].

Once phosphorylated, activated AKT translocate to various intracellular locations, where it phosphorylates and modulates the function of numerous substrates. Many of these are involved in cancer initiation and progression[34]. Tumor suppressors phosphatase and tensin homolog (PTEN) and PH domain leucine-rich-protein phosphatase (PHLPP) negatively regulate AKT through dephosphorylation[35]. PTEN dephosphorylates PIP3 component of PI3K back to PIP2 and PHLPP removes phosphate group from AKT at S473 residue[36].

Activated AKT phosphorylates a variety of protein substrates involved in survival and cellular growth. mTOR, the main downstream target of PI3K/AKT signaling, is a key cell metabolism regulator that once activated phosphorylates ribosomal protein S6 kinase (p70S6K) and eIF4E binding-protein-1 (4E-BP1) to promote protein synthesis. Tuberous sclerosis complex 1 and 2 (TSC1 and TSC2) tumor suppressors, which are negative regulators of mTOR/S6K pathway, are phosphorylated by AKT, resulting in their inhibition[37, 38]. In addition, AKT phosphorylates the proline-rich AKT substrate of 40 kDa (PRAS40) at Thr246 and the yes-associated protein (YAP) at Ser127 to induce their interactions with 14–3-3. These interactions correlate with their inactivations[39, 40, 41]. AKT exerts its effect on cell cycle progression by phosphorylating and inhibiting cyclin dependent kinase inhibitors, p21 and p27, which function as G1 checkpoints to arrest cell cycle[38]. AKT regulates apoptosis through inhibition of BAD, BCL-2-like protein 11 (BIM), caspase 9, and forkhead box protein O1 (FoxO1)[42, 43, 44, 45]. It also phosphorylates MDM2, allowing its entry into the nucleus. This results in p53 degradation[46, 47, 48].

4. AKT activation in breast and ovarian cancers

Aberrant expression of AKT has been observed in a variety of human cancers such as breast, lung, ovarian, pancreatic, and gastric carcinomas[49]. *AKT1* amplification, unlike other AKT isoforms, is commonly reported in cancer. However, an activating somatic mutation in

the PH domain of *AKT1* has been identified in 8.2% of breast, 2% of ovarian and 5.9% of colorectal cancers[50]. The *AKT1-E17K* mutation plays a crucial role in cancer development as it has been shown to express as mutually exclusive to the *PIK3CA* mutation and *PTEN* loss. *AKT1-E17K* stimulates AKT membrane localization, induction of cellular transformation, and leukemia in mice[50]. The first genomic alteration in the *AKT* family was observed in *AKT2*. A large-scale multicenter study identified *AKT2* overexpression in 12% (16 of 132) of ovarian and 3% (3 of 106) of breast carcinomas[7]. Interestingly, *AKT2* amplification was more frequent in high grade ovarian tumors and correlated with a poor prognosis for patients[51]. Furthermore, overexpression studies of AKT2 showed increased invasion and metastasis of human breast and ovarian cancer cells[52].

The function of *AKT3*, the least studied isoform in the *AKT* family, in cancer initiation and progression is unknown. TCGA analysis has reported the upregulation of *AKT3* mRNA in 28% of triple negative breast cancer (TNBC)[53]. In a recent study, targeted exome-sequencing has identified a novel *AKT3* mutation in a human epidermal growth factor receptor 2 (HER2) amplified breast cancer patient with acquired resistance to trastuzumab[54]. Additionally, 20% of ovarian tumor subtypes and 40% of primary melanomas exhibited increased AKT3 expression[27, 55]. AKT3 induces G2/M transition during cell cycle progression in ovarian cancer cell lines[55].

5. AKT inhibitors as anticancer treatments

Inhibiting AKT as the central component of frequently disrupted PI3K/AKT signaling has long been an attractive therapeutic approach in cancer. Several compounds for targeting AKT are in clinical development (Table. 1). There are two classes of AKT inhibitors: ATP-competitive and allosteric inhibitors. The ATP-competitive inhibitors bind to the active site of AKT, blocking ATP binding; whereas, allosteric inhibitors bind to the PH domain, preventing AKT phosphorylation and activation[56]. Although the three AKT isoforms have structural similarity, there are differences in their functions, tissue distribution and substrate specificity[57]. Consequently, the impact of novel therapeutics on different isoforms *in vivo* needs further study.

5.1 Ipatasertib (GDC-0068)

Ipatasertib (GDC-0068), a potent and selective ATP-competitive AKT1, 2 and 3 inhibitor, was discovered during a structural based optimization design[58]. Ipatasertib treatment inhibits AKT signaling and cell cycle in human cancer cell lines and induces a robust antitumor response in PIK3CA/AKT driven tumor xenograft models[59].

A first monotherapy of ipatasertib in human demonstrated robust and safe targeting of AKT with downregulation of AKT pathway targets in patients with diverse solid tumors (Figure 2A)[60]. Ipatasertib was well tolerated in this phase I, with most common adverse events being gastrointestinal and grade 1–2. The study also demonstrated that ipatasertib ≥200 mg daily in patients resulted in exposure corresponding to concentrations that resulted in over 90% tumor growth inhibition (TGI_{90}) in preclinical xenograft models with *PTEN*-null status. Pharmacodynamic studies in platelet rich plasma (pGSK3β, not shown) and paired

pre-treatment and on-treatment biopsies (pPRAS40, pGSK3β, p4E-BP1 and pmTOR) confirmed target inhibition (Figure 2B).

A phase Ib trial of ipatasertib and paclitaxel combination showed a good safety profile with antitumor activity seen in TNBC and HER2-negative breast patients, harboring PIK3K/AKT pathway activation[61]. Furthermore, the addition of ipatasertib to paclitaxel in a phase II trial was associated with improved progression-free survival in metastatic TNBC patients[62]. In this randomized placebo-controlled, double-blind phase II trial, patients with measurable and inoperable locally advanced or metastatic TNBC previously untreated with systemic therapy were treated with paclitaxel plus ipatasertib and paclitaxel plus placebo. Median progression-free survival in the intention-to-treat population was 6.2 months (95% CI 3.8—9.0) with ipatasertib plus paclitaxel versus 4.9 months (3.6–5.4) with placebo plus paclitaxel (hazard ratio 0.60, 95% CI 0.37–0.98, p= 0.037) (Figure 3A). Notably, the effect of ipatasertib in patients with PTEN-low tumors by immunohistochemistry (IHC) was not greater than those with non-PTEN-low tumors. However, efficacy in the patients with *PIK3CA/AKT1/PTEN*-altered tumors on next generation sequencing (NGS) showed an encouraging progression-free survival (HR of 0.44 and an increase of 4.1 months in the median progression-free survival) with a median of 9.0 months in the ipatasertib group, versus 4.9 months in the placebo group (Figure 3B). These results are encouraging for the utility of NGS for patient selection to benefit AKT inhibitors. The lack of enhanced efficacy when using only PTEN loss by IHC as a stratifier may be due to other mechanisms of pathway alteration diluting the effect. However, PTEN IHC may also have additional challenges as a predictive marker as previous studies have reported a high rate of discordance between primary and metastasis[63], suggesting tumor heterogeneity and/or PTEN status evolution.

5.2 Capivasertib (AZD5363; AstraZeneca)

Capivasertib (AZD5363) is an ATP-competitive inhibitor that inhibits all three AKT isoforms with a potency of ≤10 nM in cell-free assays and good preclinical drug metabolism and pharmacokinetics properties[64]. In preclinical studies, capivasertib inhibits phosphorylation of PRAS40 and GSK3β (AKT substrates) as well as S6 and 4E-BP1; however, it increases the phosphorylation of AKT at Ser473 and Thr308[65]. In a standard growth assay using a panel of 182 tumor cell lines, capivasertib inhibits the proliferation of 41 cell lines with most sensitivity observed in breast cancer cells (63%)[64]. Additionally, activating mutations in *PIK3CA* and *AKT1* or loss of the *PTEN* tumor suppressor gene significantly enhanced capivasertib sensitivity.

Capivasertib monotherapy shows encouraging clinical efficacy in various *AKT1-E17K* mutant solid tumors, including ER-positive breast, cervical, and ovarian cancer. In a phase I study, capivasertib as a single drug resulted in partial response in two patients, one with breast and the other one with ovarian cancer, both with *AKT1-E17K* mutation[66]. In a multihistology basket study of capivasertib in patients with advanced solid tumors with *AKT1-E17K* mutation, median progression-free survival was 5.5 months, 6.6 months, and 4.2 months in patients with ER-positive breast cancer, gynecologic, and other solid tumors respectively[67]. In an exploratory biomarker analysis, the presence of coincident PI3K

pathway hotspot mutations enhanced efficacy (HR 0.21, p=0.045). Recently in the NCI-MATCH trial, capivasertib caused partial responses or stable disease in nearly 70% of the patients with metastatic *AKT1*-mutant tumor[68]. Notably in this study, ER-positive patients were allowed to continue endocrine therapy. Overall, studies to date suggest that capivasertib is an active agent especially in tumors with *AKT1-E17K* mutation.

There are several ongoing phase I and II clinical studies determining capivasertib therapeutic effect as a single agent or in combination with other drugs in breast and ovarian cancers. The combination of capivasertib with estrogen receptor antagonist fulvestrant in *AKT1* or *PTEN*-mutant ER-positive metastatic breast cancer is currently in clinical development[69]. Recently, in a phase II trial of postmenopausal women with ER-positive and HER2-negative endocrine resistant advanced breast cancer(), the addition of capivasertib to fulvestrant resulted in significantly longer progression-free survival compared to placebo with fulvestrant (PFS 10.3 months vs 4.8 months; Hazard Ratio (HR) 0.57; 95% CI: 0.39 to 0.84; one-sided p = 0.0017; two-sided 0.0035), with a trend toward improved survival (26 vs 20 months)[70].

Moreover, the combination of capivasertib with paclitaxel in a phase II trial of metastatic TNBC demonstrated longer progression-free survival and a significant increase in overall-survival[71]. This combination is being further explored as a first line therapy for TNBC. Combination with targeted therapy is also being explored. Phase I expansion of PARP inhibitor olaparib and capivasertib indicated evidence of antitumor activity in ovarian, endometrial, and TNBC with 50% overall response rate observed in endometrial cancer cohort[72].

5.3 ARQ751 and ARQ092

ARQ092 and its analog ARQ751 are highly potent allosteric inhibitors of all three AKT isoforms and *AKT-E17K*. ARQ092 and ARQ751 dephosphorylate active AKT and prevent its plasma membrane localization[73, 74]. Both compounds exhibited strong antitumor activity across several tumor types, being most potent in breast, endometrial, leukemia, and colorectal cancer cell lines [74].

In a phase I study of ARQ092 in subjects with advanced solid tumors, two patients with activating mutation in *PIK3CA* gene experienced durable partial responses[75] and antitumor activity was observed in patients harboring *AKT1-E17K* and *PIK3CA-H1047R* mutations in a phase Ib trial[76]. Results from another phase Ib study of ARQ092 in combination with carboplatin plus paclitaxel demonstrated encouraging clinical activity in ovarian patients. Two ovarian cancer patients, pretreated with carboplatin and paclitaxel, achieved complete response (*AKT-E17K* mutant) and partial response (unknown *AKT* mutant)[77]. Ongoing ARQ751 phase I dose escalation study in patients with advanced solid tumors with *AKT-1*, *2*, and *3* genomic alterations, PI3K activating mutations, *PTEN*-null, and other *PTEN* actionable mutations demonstrated a manageable safety profile[78]. Interestingly, a non-oncological phase I trial of ARQ092 is also being conducted for the treatment of Proteus syndrome in children and adults patients[79].

5.4 Afuresertib (GSK2110183) and Uprosertib (GSK2141795)

Afuresertib (GSK2110183) and uprosertib (GSK2141795) are potent ATP-competitive inhibitors of AKT1, 2, and 3 that demonstrate more sensitivity in hematological cell lines[80]. Afuresertib, which has more potency against AKT1, is shown to be safe and well-tolerated with manageable adverse events, including hyperglycemia in a clinical study[81]. Single agent activity was observed with afuresertib in patients with multiple myeloma[81]. A phase I/II clinical study on afuresertib, in combination with paclitaxel and carboplatin, showed favorable activity in patients with platinum-resistant ovarian cancer[82]. Continuous daily dosing of afuresertib was poorly tolerated in combination with MEK inhibitor trametinib in a phase I study of patients with solid tumors. However, an intermittent dose schedule of afuresertib with trametinib provided a more tolerable safety profile[83]. Uprosertib, a close analog of afuresertib, has more inhibition potency with greater off-target effects. In a phase I study, uprosertib was safe and well-tolerated, with preliminary clinical activity seen as monotherapy in patients with *PIK3CA* mutation or *PTEN* loss[84].

5.5 MK-2206

Allosteric AKT inhibitor, MK-2206 (Merck), predominantly inhibits AKT1 and 2 with preclinical single agent activity that prevents phosphorylation of downstream AKT signaling in a range of cancer cell lines[85]. The anti-proliferative effect of MK-2206 was greater in tumor cell lines having *AKT2* amplification, *PIK3CA* mutation, *PTEN* loss/mutation, or RTK (such as HER2) constitutive activation[85, 86].

In spite of promising preclinical antitumor activity in the diseases, MK-2206 has shown limited efficacy in monotherapy in phase II trials[87]. MK-2206 has been investigated in a phase II trial for the treatment of platinum-resistant ovarian, primary peritoneal or fallopian tube cancers, as well as breast cancer with *PIK3CA/AKT* mutations or *PTEN* loss. MK-2206 was also tested in a Phase II trial in advanced breast cancer patients selected for *PIK3CA/AKT1* mutations or *PTEN* loss/*PTEN* mutation[88]. In spite of the fact that preclinical models with *PIK3CA/AKT* and *PTEN* alterations showed antitumor efficacy of MK-2206, MK-2206 monotherapy has limited clinical activity in these biomarker-selected, metastatic breast cancer patients. Notably, MK-2206 treatment was associated with a significant decline in pAKT-S473 and pAKT-T308 and PI3K activation score in peripheral blood mononuclear cells (PBMC) and platelet-rich plasma (PRP), but pathway inhibition was not observed upon comparison of pre-treatment and on-treatment tumor biopsies. By IHC, there was no significant decrease in median pAKT-S473 or Ki-67 staining in the overall cohort, but a drop was observed in the two patients with clinical benefit (one with partial response, one with prolonged stable disease). This suggests that there may be inadequate target inhibition at tolerable doses in heavily pre-treated patients with pathway activation.

In a preclinical breast cancer model, upregulation of AKT3 due to epigenetic reprogramming conferred resistance to MK-2206, which was reversible upon drug removal[89]. Therefore, attempts were focused on combinational therapies. The evaluation of MK-2206 treatment alone or in combination with trastuzumab or lapatinib (HER inhibitors) in several phase I studies of HER2-positive breast cancer showed antitumor

activity[90]. Phase I trial of MK-2206 combined with trastuzumab or lapatinib was tolerated with clinical efficacy in HER2-positive breast cancer.

The combination of MK-2206 and paclitaxel in breast cancer and solid tumors was well-tolerated with evidence of antitumor activity[91]. In the adaptive neoadjuvant I-SPY2 trial, the combination of MK-2206 with paclitaxel improved the predicted pathologic response rates in several HR-negative and HER2-positive breast cancers compared to standard chemotherapy[92].

MK-2206 was also assessed in ER-positive breast cancer patients in a window-of-opportunity trial and a neoadjuvant trial in combination with endocrine therapy, both with concerns raised about tolerability[93, 94]. Both of these trials performed pharmacodynamics analysis of pretreatment and on-treatment tumor samples and also suggested that there may be suboptimal target inhibition at clinically achievable doses[95].

5.6 Perifosine

Perifosine is a relatively non-selective AKT allosteric inhibitor that disrupts the interaction between AKT and phospholipids in the plasma membrane and triggers apoptosis *in vitro* and *in vivo* of human tumor models[96]. Although perifosine displayed significant anti-proliferative activity in preclinical studies, no objective response was observed in a phase II trial of perifosine in pretreated metastatic breast cancer patients[97]. Perifosine plus docetaxel was also assessed in a phase I study in platinum-resistant epithelial ovarian cancer patients[98]. The combination demonstrated evidence of efficacy with acceptable safety profile, but progression-free survival and overall-survival was 1.9 and 4.5 months respectively. One patient with a *PTEN* mutation achieved partial remission (PR) for 7.5 months, suggesting that targeting AKT with next generation inhibitors in ovarian cancer having PI3K pathway alterations may be warranted.

5.7 BAY1125976

BAY1125976 is a potent and selective allosteric AKT1 and 2 inhibitor with anti-proliferative activity in a panel of human cancer cell lines—particularly breast and prostate cancer cells[99]. It was also well tolerated *in vivo* with antitumor efficacy observed in tumor models having PI3K/AKT pathway alterations, including *AKT1-E17K* and *PTEN*-loss. BAY1125976 is currently in early phase clinical trials (ClinicalTrials.gov Identifier:).

5.8 Triciribine (PTX-200)

Triciribine phosphate monohydrate (TCN-PM) is an allostericinhibitor of all AKT isoforms which binds to the PH domain and prevents AKT phosphorylation and subsequent activation[100]. In preclinical testing, it has been shown to inhibit AKT phosphorylation, cause cell cycle arrest, and induce apoptosis[101, 102]. The combination treatment of triciribine with gemcitabine in pancreatic cancer cells augmented the antitumor activity and overcame the resistance mediated by AKT activation[103].

Preliminary evidences from phase I studies in patients with solid tumors containing activated AKT and advanced hematologic malignancies indicated that triciribine reduced AKT

phosphorylation levels, but its efficacy as a single agent was limited due to toxicity[104, 105]. The clinical activity of carboplatin plus triciribine in patients with platinum-resistance recurrent ovarian cancer is being explored in ongoing studies (ClinicalTrials.gov Identifier:).

5.9 TAS-117

TAS-117 is a highly potent and selective allosteric AKT inhibitor with a high affinity for AKT1, 2, and 3. TAS-117 induced a significant growth inhibition in multiple myeloma cell lines with high level of baseline AKT phosphorylation[106]. *In vivo*, TAS-117 was effective in combination with chemotherapeutic agents and greatly improved the sensitivity of carboplatin or irinotecan in a human ovarian cancer cell line-derived (A2780A) xenograft model[107]. Phase II trial of TAS-117 in subjects with advanced solid tumors having PI3K/AKT pathway aberrations is under investigation (ClinicalTrials.gov Identifier:).

5.10 LY2780301

LY2780301 is a highly selective and potent ATP-competitive dual inhibitor of p70S6K and AKT that exhibited anti-proliferative activity in a broad range of cancer cell lines with effective tumor growth inhibition in xenograft models of A2780 (ovarian), HCT116 (colon), H460 (lung), and PC3 (prostate). (Data on File from Eli Lilly Company).

A phase I trial of LY2780301 in patients with advanced or metastatic cancers was conducted to determine the recommended phase II dose as a single agent[108]. Among patients receiving 500 mg daily, more than 50% exhibited reduced S6 phosphorylation in skin biopsies on Day 8 of treatment. However, this effect was not maintained with any correlation of pharmacokinetics and S6 phosphorylation levels the in skin. The pharmacokinetic and drug interaction of LY2780301 in combination with paclitaxel is being examined in women with HER2-negative metastatic breast cancer[109]. Combining LY2780301 and paclitaxel in a recent phase Ib/II trial of HER2-negative, locally advanced or metastatic breast cancer patients, showed preliminary evidences of efficacy, independently of PI3K/AKT activation (ClinicalTrials.gov Identifier:). The addition of LY2780301 to gemcitabine in another phase Ib dose escalation study of patients with PI3K/AKT pathway alterations demonstrated acceptable toxicity with 74% disease control at cycle 2, and a 5% partial response rate (responses in breast and cervical cancer)[110].

5.11 MSC2363318A

MSC2363318A is a selective and potent ATP-competitive inhibitor of p70S6K, AKT1 and 3 with strong growth inhibition activity in many solid tumor cell lines especially those with molecular alterations in PI3K/AKT pathway[111]. Evaluation of MSC2363318A in patient-derived xenograft models of breast cancer suggested that dual p70S6K/AKT inhibitor may improve AKT pathway inhibition by blocking the negative AKT activation emanating through the negative feedback loop[112]. The unique capacity of MSC2363318A to pass the blood-brain barrier[111] allows clinical investigations of cancers with PI3K/AKT pathway dysregulation that involved central nervous system malignancies. MSC2363318A alone and in combination with trastuzumab and tamoxifen has been investigated in a phase I dose escalation study of patients with advanced malignancies[113].

5.12 Cenisertib (R763/AS703569)

Cenisertib is a potent inhibitor of Aurora kinases that blocks the kinase activity of AKT as well as FLT3, VEGFR2, LYN, BTK, and KIT and induces growth inhibition, apoptosis and cell cycle arrest in various cancer cell lines both *in vitro* and *in vivo* [114, 115]. Data from two phase I trials in advanced solid tumors (two arm trial) and hematological malignancies indicated that cenisertib was well tolerated with early evidence of activity observed in patients with leukemia[116, 117]. The combination of cenisertib with gemcitabine in subjects with advanced solid tumors is in phase I clinical study[118].

6. Conclusions

Over the past few decades, a growing body of literature has emphasized the key role of AKT during tumor development, survival, and progression. In fact, AKT hyperactivation contributes to many hallmarks of cancer, such as evading apoptosis, self-sufficiency in growth, invasion, and metastasis[119]. Given the role of AKT as an attractive target, several small molecule inhibitors have been discovered and progressed in trial studies. However, none of the AKT inhibitors have been approved for clinical use to date. The structural similarity between AKT isoforms and the off-target inhibition of AGC kinase family hindered the discovery of selective and efficacious compounds inhibiting AKT. First generation AKT inhibitors exhibited limited clinical efficacy as single agent and have limitations due to toxicity. Clinical trials that are designed based on mechanistic insights of AKT pathway and combinational treatments will provide a better clinical perspective of AKT inhibitors and use the full potential of these compounds.

7. Expert opinion

One of the main goals of translational research in the era of precision medicine is the identification of targeted agents and their predictive biomarkers for the development of successful therapeutic strategies. Identification and validation of potential biomarkers in response to AKT inhibitors treatment is increasingly essential to design trials for novel targeting agents and pave the way for clinical practice of these compounds. Several studies have indicated that genomic aberrations in PI3K/AKT pathway are associated with sensitivity to AKT inhibitors[120]. These observations suggest that genomic alterations in this pathway (activating *AKT* and *PIK3CA* mutations, and inactivating *PTEN* mutations) are candidates for biomarkers of response to AKT inhibitors. In contrast, PTEN loss by IHC may be less robust as a biomarker. The expression of PTEN may be lost due to non-genomic mechanisms; therefore, DNA sequencing in addition to IHC quantification will provide more extensive insight.

In the clinic, the *AKT1-E17K* mutation, which occurs at a relatively low rate in breast and ovarian tumors, is shown to be a strong predictive biomarker of response to AZD5363 monotherapy[67]. The fact that *AKT1-E17K* presents at a low frequency should not minimize its potent biological effect during tumorigenicity and potential impact on outcomes in patients with tumors bearing this mutation. Although accumulation of sequencing data has identified more *AKT* mutations, most of these alterations do not activate pathway signaling or affect growth compared to a wild type. In a functional

characterization study of more than twenty AKT mutations, E17K (*AKT1* and *AKT2*), L52R, Q79K, and D323H (*AKT1*) were the only mutants that showed pathway activations. Therefore, the majority of AKT variants identified by clinical tumor sequencing are passenger mutations with few functional consequences[121]. In addition to analysis of somatic alterations in PI3K/AKT pathway, transcriptomic and proteomic signatures of AKT inhibitors sensitivity also need to be explored to better select patients that may benefit from AKT inhibitors.

Despite the development of a large number of compounds with promising results for inhibiting AKT, there is a gap between preclinical data and the lack of a clinically effective AKT inhibitor. Although AKT inhibitors have compelling antitumor activity in tumors having specific genetic alterations, the complex cellular function of AKT and activation of potential feedback signaling limit the efficacy of AKT as a single agent. AKT inhibitors have been shown to improve the therapeutic effect of standard anticancer agents in several preclinical studies. Therefore, combinational therapy approaches appeared to be a major research direction for the clinical utilization of AKT inhibitors.

The antitumor activity of ipatasertib and paclitaxel combination seen in patients with TNBC harboring PIK3K/AKT pathway activation supports the hypothesis that PI3K/AKT activation predicts sensitivity to AKT inhibitors[62]. The efficacy seen with capivasertib and paclitaxel also support the hypothesis that targeting AKT in tumors with PI3K pathway alterations can enhance chemosensitivity and improve clinical outcomes. Further studies are necessary to determine additional rational combinations that can enhance efficacy of AKT inhibitors, potentially by targeting compensatory mechanisms, and/or enhancing apoptosis.

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Article highlights

- Aberrant activation of AKT plays an important role in the pathogenesis of many human tumors, including breast and ovarian cancers.
- Many compounds have been developed to inhibit AKT as a validated therapeutic target.
- Tumors with PI3K/AKT pathway genomic alterations demonstrated more sensitivity to AKT inhibitions.
- Combining AKT inhibitors with other therapeutic agents can greatly enhance the efficacy of these inhibitors.
- the identification of targeted agents and their predictive biomarkers is necessary for the development of successful therapeutic strategies.

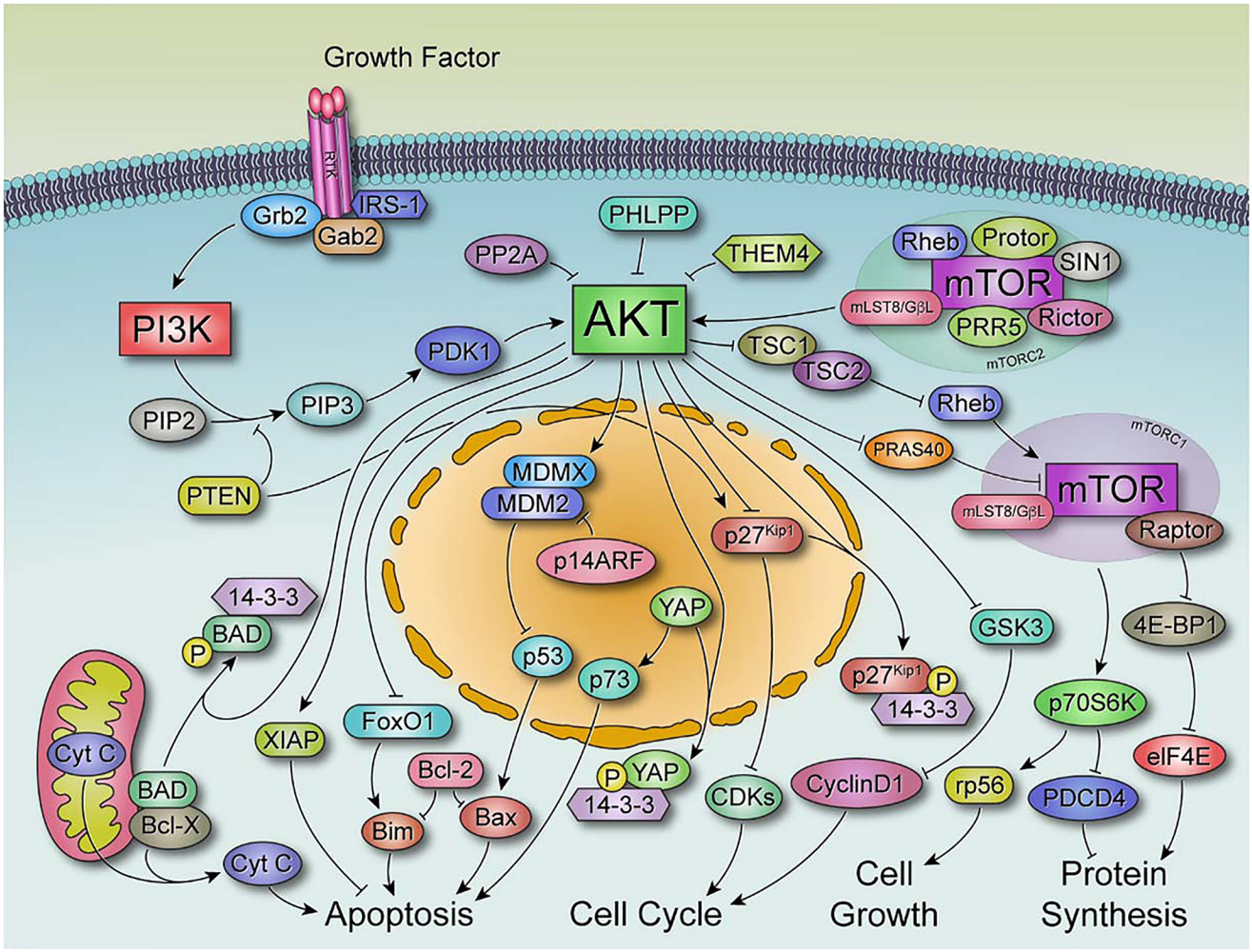

Figure 1.

Representation of AKT pathway and downstream effectors. Shown are the key molecular targets involved in AKT signaling. Upon growth factor binding to receptor tyrosine kinase (RTK), phosphoinositol bisphosphate (PIP2) is converted to phosphoinositol trisphosphate (PIP3), which recruits AKT and phosphoinositide-dependent kinase-1 (PDK1) to the plasma membrane by binding the PH domain to membrane lipids. PDK1 and mammalian target of rapamycin complex 2 (mTORC2) phosphorylate AKT, resulting in full activation of AKT. Phosphatase and tensin homolog (PTEN) and PH domain leucine-rich-protein phosphatase (PHLPP) negatively regulate AKT through dephosphorylation of PIP3 and AKT (serine-473 residue) respectively. Once activated AKT phosphorylates and inhibits the proline-rich AKT substrate of 40 kDa (PRAS40) and tuberous sclerosis complex 1 and 2 (TSC1 and TSC2) to promote protein synthesis. AKT blocks apoptosis through inhibition of BCL-2-antagonist of cell death (BAD), BCL-2-like protein 11 (BIM), and forkhead box protein O1 (FoxO1). It also phosphorylates MDM2, resulting in p53 degradation. AKT prevents cell cycle arrest and cyclin D1 degradation by phosphorylating and inhibiting cyclin dependent kinase inhibitor p27, and glycogen synthase kinase 3β (GSK3β).

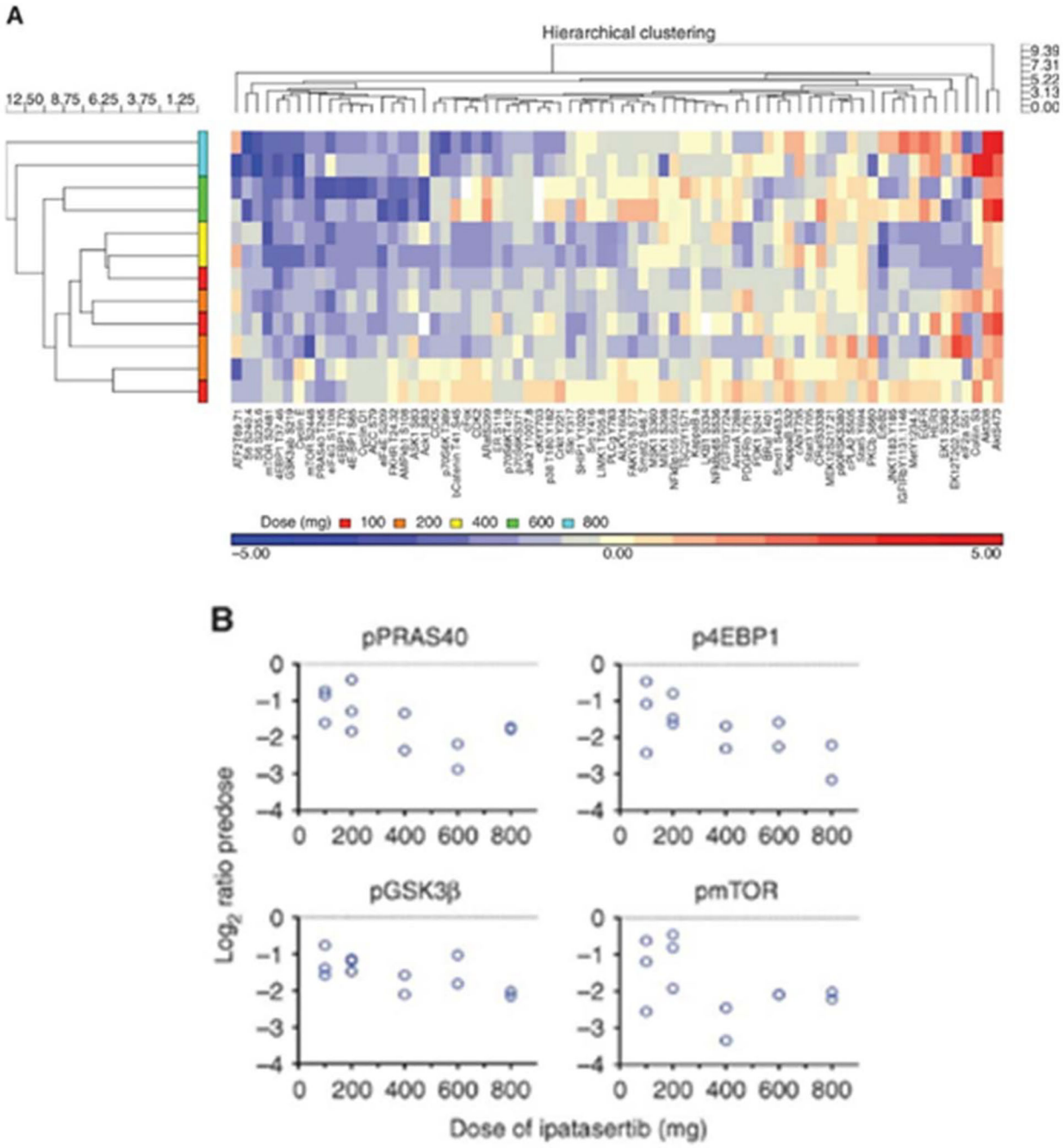

Figure 2.

Pharmacodynamic effects of AKT inhibition. Patients undergoing treatment with ipatasertib underwent pre-treatment and on-treatment tumor biopsies. Pharmacodynamics effects were evaluated with reverse phase protein array for multiple AKT pathway targets. A) Ipatasertib caused accumulation of AKT phosphorylation (Threonine-308 and Serine-473) and downregulation of multiple AKT targets such as B) proline rich AKT substrate of 40 kDa (PRAS40), eIF4E binding-protein-1 (4E-BP1), glycogen synthase kinase 3β (GSK3β), and mammalian target of rapamycin (mTOR) in a dose-dependent manner. Figure was reprinted with permission from "*A First-in-Human Phase I Study of the ATP-Competitive AKT*

Inhibitor Ipatasertib Demonstrates Robust and Safe Targeting of AKT in Patients with Solid Tumors" by Cristina Saura, 2016. Cancer Discovery, Volume 7, Pages 102–113.

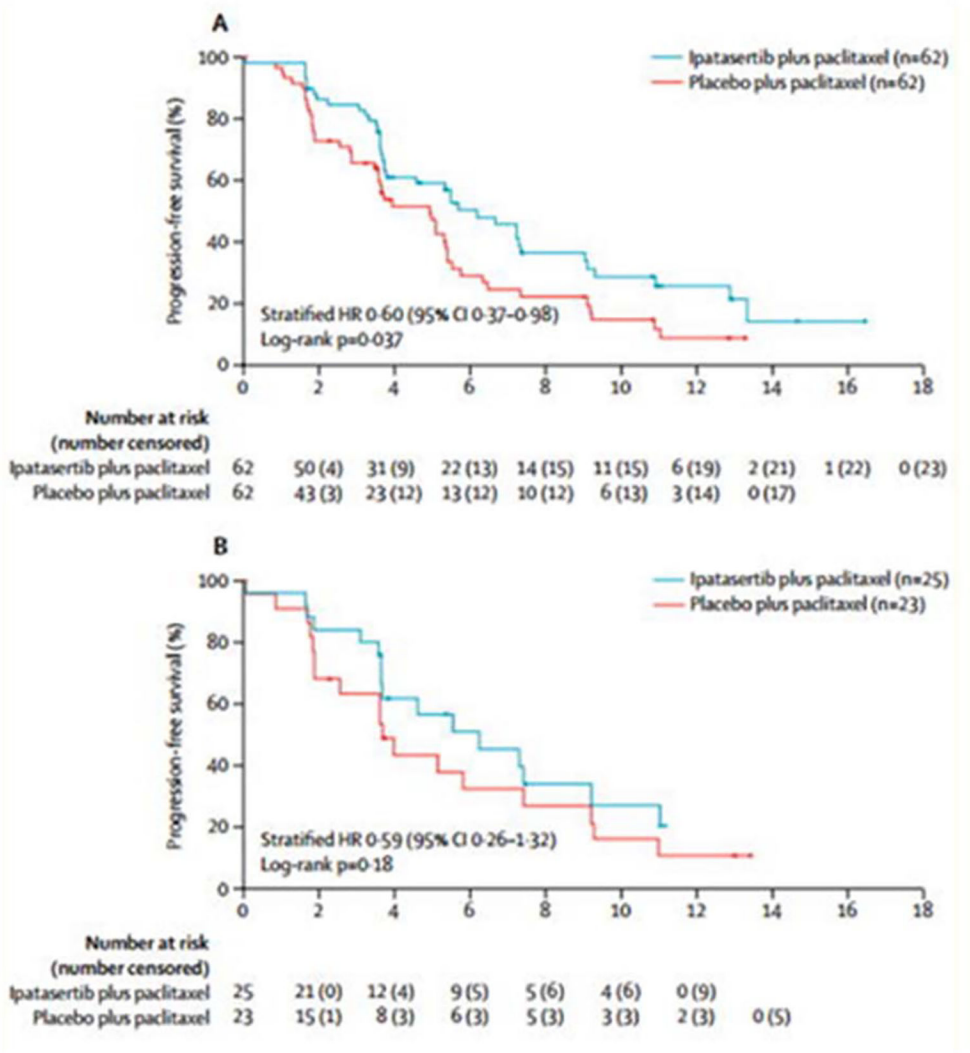

Figure 3.

Progression-free survival (PFS) in randomized clinical trial of ipatasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple negative breast cancer. A) PFS in the intention-to-treat population unselected by biomarker, and B) PFS in patients with tumors bearing *PIK3CA*/*AKT1*/ phosphatase and tensin homolog (*PTEN*) alterations. Figure was reprinted with permission from "*Ipatasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (LOTUS): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial"* by Sung-Bae Kim, 2017. The Lancet Oncology, Volume 18, Pages 1360–1372.

Table 1.

Drugs targeting AKT in clinical trials.

Inhibitor	Class	Target	Status
Ipatasertib (GDC-0068)	ATP-competitive	AKT1, 2 and 3	Phase I/Phase II/ Phase III clinical trials
Capivasertib (AZD5363)	ATP-competitive	AKT1, 2 and 3	Phase I/Phase II clinical trials
ARQ751 and ARQ092	Allosteric	AKT1, 2 and 3	Phase I clinical trials
Afuresertib (GSK2110183) and Uprosertib (GSK2141795)	ATP-competitive	AKT1, 2 and 3	Phase I/Phase II clinical trials
MK-2206	Allosteric	AKT1 and 2	Phase I/Phase II clinical trials
Perifosine	Allosteric	AKT1, 2 and 3	Phase I clinical trials
BAY1125976	Allosteric	AKT1 and 2	Phase I clinical trials
Triciribine	Allosteric	AKT1, 2 and 3	Phase I clinical trials
TAS-117	Allosteric	AKT1, 2 and 3	Phase II clinical trials
LY2780301	ATP-competitive	AKT1, 2, 3 and p70S6K	Phase I clinical trials
MSC2363318A	ATP-competitive	AKT1, 3 and p70S6K	Phase I clinical trials
Cenisertib (R763/AS703569)	ATP-competitive	AKT, FLT3, VEGFR2, LYN, BTK and KIT	Phase I clinical trials