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REVIEW

Targeting phosphatidylinositol 3 kinase (PI3K)-Akt beyond rapalogs

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Abstract The activation of the phosphatidylinositol 3 kinase (PI3K)-Akt pathway is a known causal mechanism of oncogenesis and resistance to cancer treatments. The process of PI3K-Akt pathway activation is complex and includes receptor tyrosine kinase(RTK) activation, PIK3CA mutations, loss of phosphatase and tensin homolog (PTEN), Akt mutations, tuberous sclerosis complex (TSC) mutations, and Ras homologue enriched in brain (RHEB) gene amplifications. The blockage of mammalian target of rapamycin (mTOR), the key downstream pathway protein, has been successful in selected cancer types, with mTOR-targeting agents available for clinical use. Other novel drugs blocking this pathway such as PI3K inhibitors, Akt inhibitors and PDK-1 inhibitors are currently only available for investigational use, but have shown promise as cancer therapies in both preclinical and early phase clinical studies. The newer generations of these inhibitors are more specific and have improved potency and safety. The combinations of targeted treatments against this pathway, blocking multiple different steps, are under preliminary investigation. Further research is needed to identify the biomarkers that predict treatment response and resistance in order to optimize personalized medicine.

Keywords PI3K · Akt · PDK-1 · Inhibitor · PTEN · mTOR

Introduction

The phosphatidylinositol 3 kinase (PI3K)-Akt pathway is one of the most popular areas for targeted cancer therapy. Both preclinical and clinical data indicate that alterations of this pathway lead to oncogenesis. Mammalian target of rapamycin (mTOR) is one of the downstream enzymes in the pathway, and two of its inhibitors, everolimus and temsirolimus, currently approved by the United States Food and Drug Administration (FDA) for commercial use against renal cell cancer (RCC), have been found to be active against multiple tumor types [1–4]. Multiple other signal transduction proteins, both upstream and downstream of mTOR, are involved in the PI3K-Akt pathway and can potentially be targeted and "drugable." mTOR as a target of inhibition has been reviewed extensively in recently published articles [5–7]. Our review will explain the PI3K-Akt pathway, including key proteins and enzymes and their relationships, followed by novel strategies other than rapamycin analogues to block the PI3K-Akt pathway.

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PI3K-AKT pathway and oncogenesis

The PI3K-Akt pathway is a common intracellular signaling pathway that can be stimulated by the activation of various receptor tyrosine kinases (RTKs), including insulin like growth factor receptor (IGF-R), epithelial growth factor receptor (EGFR), and HER-2. Over-expression and/or gene mutations of the RTKs activate downstream pathways, causing increased proliferation and cell division. The RTKs can be inhibited by small molecule tyrosine kinase inhibitors (TKIs) or monoclonal antibodies (MoAbs) and are effective for cancer treatments. However, the treatment effect is often transient in the metastatic setting, and almost all the cancers eventually progress. The mechanisms of resistance include secondary mutations in RTKs and/or activation of downstream pathways such as the PI3K-Akt and RAS-RAF-MAPK/ERK pathways. Furthermore, some cancers have primary resistance to RTK inhibitors despite

known pathway activation, which suggests that activation of the downstream signaling cascades can be the primary oncogenic event. By blocking downstream proteins at select sites or at multiple locations, resistant cancers may potentially regain sensitivity to these therapies.

Figure 1 illustrates the PI3K-Akt pathway. We will begin by explaining the key enzymes involved in the pathway.

PI3K

PI3K converts phosphatidylinositol (4,5)-bisphosphate (PIP-2) to phosphatidylinositol (3,4,5)-trisphosphate (PIP-3) by phosphorylation. There are three classes of PI3K isoforms, namely class I, II and III [8]. Class I PI3K can be further subdivided to class IA and IB, and class IA is implicated in oncogenesis in human cancers. Class IA PI3Ks are heterodimeric, being comprised of one catalytic subunit (p110α [also known as PIK3CA], p110β [PIK3CB], and p110δ [PIK3CD]), and one regulatory subunit (p85α, p85β, p55α, p55γ, and p50α). The α catalytic subunit (PIK3CA) has been most extensively studied in human cancer, and its mutations can activate the PI3K-Akt pathway and are oncogenic [9]. PIK3CA mutations are frequently found in multiple malignancies including glioblastoma, gastric, breast, and colorectal cancers, and their prevalence varies not only among different cancer types (e.g., breast versus lung), but also among different subtypes of each cancer (e.g., estrogen receptor positive versus triple negative breast cancer) [10–12]. Well over 10 different PIK3CA mutations have been discovered, and the most common mutations are H1047R, E545K and E542K [13]. Amplification of the PIK3CA gene occurs less commonly than mutations [14].

PTEN

Phosphatase and tensin homolog (PTEN), also referred to mutated multiple cancers 1 (MMAC 1) or TGF-β regulated and epithelial- cell-enriched phosphatase 1(TEP1), dephophorylates PIP-3 to PIP-2 counteracting PI3K. Inactivation or hypoactivation of PTEN causes overactivation of the PI3K-Akt pathway [10]. Germline mutations and loss of PTEN function are known to cause various syndromes including Bannayan-Zonana and Cowden syndromes [15, 16]. Patients with Cowden syndrome have up to a 90% increased risk of various malignancies, such as breast and thyroid cancers, during their lifetime [17]. Inactivation of PTEN by somatic mutations, deletions, promoter methylation and/or loss of heterozygocity (LOH) is commonly found in many cancers including prostate cancer, endometrial cancer, and glioblastoma and is associated with advanced stage of the diseases [18–23].

AKT

Akt, also known as protein kinase B (PKB), is a serine/threonine protein kinase that is activated by phosphorylation at Thr^{308} by phosphoinositide-dependent protein kinase 1 (PDK-1) and at Ser^{473} by mTOR complex 2 (mTORC2) [24]. There is some controversy if other kinases, or Akt alone, can phosphorylate Ser^{473}. The activation of both

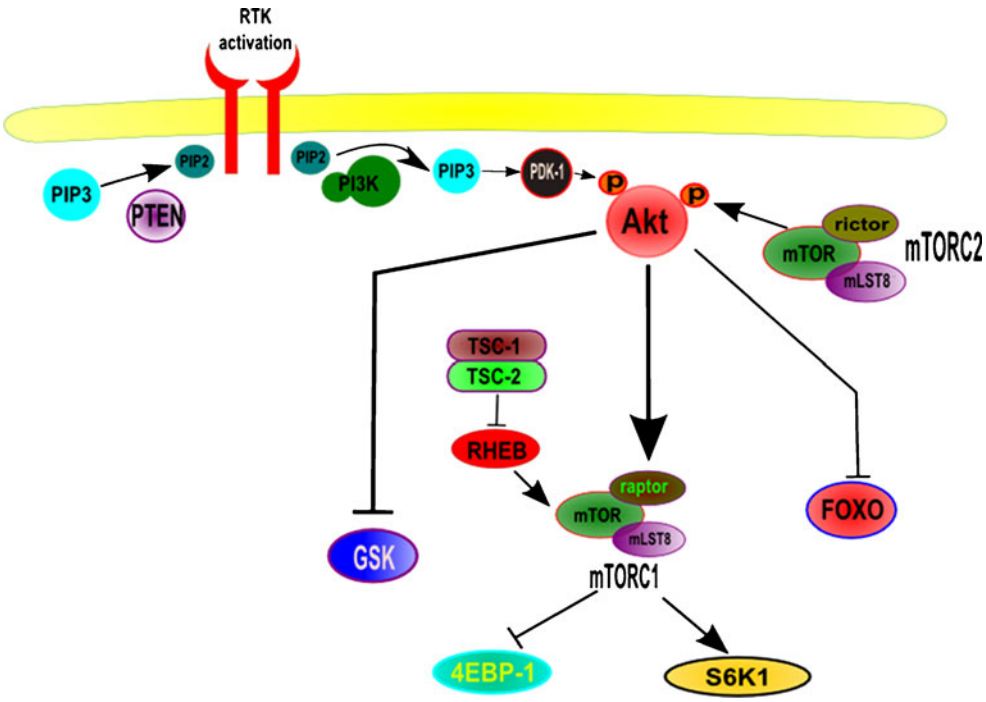

Fig. 1 PI3K-Akt pathway

kinase domains of Akt is required for its full activation [25]. The potential importance of Akt and its blockage in cancer is due to its pluri-functional role in intracellular signal transduction. Akt activates and/or inhibits multiple other proteins including BAD, FOXO and mTOR complex 1 (mTORC1). By acting on these multiple downstream pathways, Akt promotes cell survival, cell growth, cell proliferation, angiogenesis, cell migration, and invasion [26]. Akt activation is one of the important mechanisms in chemotherapy/radiotherapy resistance [27]. There are three isoforms of Akt, namely Akt1/PKBα, Akt2/PKBβ, and Akt3/PKBγ. Although their functions overlap in some areas, each has its own distinct functional role. Akt1 is vital for normal growth, Akt2 for glucose regulation, and Akt3 for brain development [28–31].

The Akt1 mutation (E17K) at the pleckstrin homology (PH) domain has been observed in breast, colorectal, and ovarian carcinomas, and the mutation was found to enhance Akt activity [32]. Although the prevalence of this Akt mutation is generally low, it has been the target of novel Akt inhibitors [33–35]. Other alterations, including Akt 1 gene amplification, Akt1 and Akt2 deletion, and Akt3 amplifications have been found, and their clinical significance in human cancers is yet to be defined [36].

The degree of Akt phosphorylation of the tumor may reflect treatment effects from upstream pathway inhibition with such treatments as trastuzumab, cetuximab, and erlotinib. The comparison of pre- and post-treatment Akt phosphorylation can indicate if the pathway is adequately suppressed by these treatments, and select markers relative to this pathway are currently under investigation as pharmacodynamic (PD) markers in the setting of early phase clinical trials.

mTOR, S6K1and 4EBP1

mTOR is a serine/threonine kinase and is structurally related to PI3K. mTOR binds to other intracellular proteins and forms two distinctive complexes, mTORC1 and mTORC2, respectively. mTORC1 is composed of mTOR, regulatory-associated protein of mTOR (raptor), and mLST8/GβL [37]. Activated mTORC1 phosphorylates ribosomal S6 kinase 1 (S6K1) and eukaryotic initiation factor 4E-binding protein (4E-BP1 or EIF4EBP-1). S6K1 promotes increased mRNA translation by phosphorylating the ribosomal protein S6. Hypophosphorylated 4E-BP protein binds to eIF4E and disrupts the interaction between ribosomes and mRNA. When hyperphosphorylated by mTOR, 4E-BP releases eIF4E and allows enhanced mRNA translation[38].

mTORC2 has been more recently discovered and consists of mTOR, rapamycin-insensitive companion of mTOR (rictor), and mLST8/GβL [39]. mTORC2 regulates cell morphology and the cytoskeleton [40]. Interestingly, mTORC2 plays a critical part in Akt activation [24]. Therefore, mTOR works both upstream and downstream of Akt in a different complex. The currently approved mTOR inhibitors—rapamycin (sirolimus), everolimus and temsirolimus—block mTORC1, only without affecting mTORC2 [41].

TSC−1/−2 and RHEB

Tuberous sclerosis complex (TSC) is a rare genetic disease caused by the germline mutation TSC-1 (hamartin) and TSC-2 (tuberin) genes. TSC patients develop variable clinical manifestations including benign tumors (hamartomas, angiofibromas, and rhabdomyoma) in the skin, kidney, lung, brain, eye, heart, and liver. Although they also have an increased risk of malignant tumors, especially renal cell carcinoma, there are still many TSC patients who do not develop malignancies [42]. This implies that TSC mutations alone are probably insufficient to cause cancer.

TSC-1 and TSC-2 form a heterodimer and function as tumor suppressors by inhibiting Ras homologue enriched in brain (RHEB), a guanosine triphosphate (GTP)-binding protein [43]. TSC has a GTPase-activating protein (GAP) domain, and exchange GTP with GDP [44]. This replacement inactivates RHEB. The functional loss of TSC by gene mutations or its promoter methylation results in RHEB overactivation [45–47].

The main role of RHEB is the activation of mTORC1, and its multiple downstream pathway proteins [48]. RHEB does not activate mTORC2 [49]. The two isoforms, RHEB 1 and RHEB 2, have been identified, and RHEB1 is most extensively studied [50]. RHEB gene amplifications can activate the pathway and have been found in prostate cancer [51]. RHEB overexpression was observed to varying degrees in human cancers including lymphoma, breast, and head/neck cancers. RHEB overexpression has been associated with aggressive disease and poor clinical outcome [52, 53]. RHEB overactivation is oncogenic and the process is mediated through mTORC1 and signal transducer and activator of transcription 3 (STAT3) [52]. In vitro studies suggest that an mTOR inhibitor can potentially induce chemotherapy sensitization in RHEB overexpressing lymphoma, but not in RHEB normoexpressing lymphoma [53].

PDK-1

PIP-3 recruits PDK-1 to the cell membrane where PDK-1 can exert its activity. PDK-1 is a serine/threonine kinase, and in the presence of PIP-3, PDK-1 phosphorylates and activates Akt[54]. Elevated phosphorylation of PDK-1 has been observed in select malignancies (i.e., breast) in patients. It is yet to be elucidated if PDK-1 overactivation is the primary oncogenic mechanism or just a consequence of upstream pathway activation [55].

GSK-3

Glycogen synthesis kinase-3 (GSK-3) has two isoforms: GSK-3α and GSK-3β. GSK-3 is known to both directly and indirectly regulate multiple intracellular proteins including transcription factors. GSK-3 not only affects glucose metabolism but also alters cell survival by inducing apoptosis [56]. Many proteins, including Akt, regulate GSK-3 by phophorylation. As GSK-3 is involved in many pathways including Wnt, Notch and Hedgehog; it is beyond this review's scope to mention the detail of GSK-3 related oncogenesis. It is, however, constitutively active and suppresses pathways such as Wnt and Hedgehog. There was concern that GSK-3 inhibitors could induce malignancies. However, preclinical data paradoxically suggest GSK-3 inhibition is indeed effective as a cancer target [57, 58]. Further research in this area will eventually elucidate the role of GSK-3 in cancer pathophysiology and treatment.

FOXO

Forkhead box (FOX) is a family of more than 100 transcription factors, and the O subgroup (FOXO) plays a key role in cell cycle control and apoptosis [59]. FOXO has four subtypes, namely FOXO1, FOXO3, FOXO4 and FOXO6. FOXO is regulated by multiple mechanisms including phosphorylation, acetylation and ubiquitination. FOXO consists of four domains, namely a DNA-binding domain (DBD), a nuclear localization signal (NLS), a nuclear export sequence (NES), and a C-terminal transactivation domain. Akt phosphorylates FOXO at multiple domains and prevents FOXO from binding to DNA.

Rationale of blocking PI3K-AKT pathway

Although the PI3K-Akt signaling pathway is complex and blocking the pathway can potentially cause significant adverse effects on cell regulation, there are multiple scientific grounds to support this strategy in cancer therapy. As PI3K-Akt pathway activation is one of the important mechanisms of resistance to cytotoxic chemotherapies, hormonal therapies, biological treatments and radiotherapy, pathway inhibition can potentially overcome resistance [27].

We will first summarize the various topics of the pathway blockade, followed by class-specific compound discussions.

Upstream receptors. What receptors activate the PI3K-Akt pathway?

HER family (or ErbB family), platelet-derived growth factor receptor (PDGFR), and insulin-like growth factor (IGFR) receptors are the transmembrane receptors, which are well known to activate the PI3K-Akt pathway. Many other receptors including fibroblast growth factor receptor (FGFR), vascular endothelial growth factor receptor (VEGFR), cMET/hepatocyte growth factor receptor (HGFR), T cell receptor and Notch have also been found to use the PI3K-Akt signaling cascade for cell proliferation, growth, and migration [60–64]. Overexpression of those receptors is one of the plausible oncogenic processes in many types of cancers. Direct receptor blockade by MoAb and/or TKI is the easiest method of inhibiting receptor-mediated tumor growth. However, the activation or overexpression of alternative pathways can occur when treatment resistance emerges. The blockade of common downstream intracellular pathways such as PI3K-Akt and/or RAS/RAF/MAPK can potentially overcome the treatment resistance.

Crosstalk with other pathways

Transmembrane receptors, upon activation, can stimulate multiple other intracellular pathways such as RAS/RAF/MAPK and JAK-STAT pathways. In some cancers the primary oncogenic event is the mutational activation of the pathway's protein enzymes.

The best-described example is the V600E BRAF mutation, which occurs in approximately 60% of melanoma patients [65]. BRAF inhibition, or its downstream protein MEK inhibition, can suppress the pathway. The proof of concept was observed in the phase I clinical study, where almost 70% of melanoma patients with such BRAF mutations responded to BRAF or MEK inhibitors [66, 67]. However, resistance can occur and one of the main causes is the crosstalk between RAS/RAF/MAPK and PI3K-Akt pathways. BRAF or MEK inhibitor-resistant melanoma was found to have Akt upregulation [68]. BRAF-resistant melanoma cells do not appear sensitive to downstream MEK inhibition, but potentially susceptible to PI3K inhibition. This is currently an area of intense research and multiple combination phase I studies are ongoing to prove this concept in the clinical setting.

mTOR inhibitors resistance and the role of PI3K or Akt inhibition

Currently mTOR inhibitors are the only commercially available agents for PI3K-Akt pathway blockade. Clinical response rates to mTOR inhibitor monotherapy in renal cell cancer are approximately 3–8% [1, 2]. mTOR inhibition can cause paradoxical activation of IGF-1 and its downstream pathway (i.e., PI3K-Akt pathway) by releasing physiological negative feedback inhibition [69, 70]. In a preclinical setting, the combination of mTOR inhibitors with IGF-1R inhibitors or Akt inhibitors has shown greater activity than either agent

used alone [70]. A more in-depth discussion of the relevance of mTOR inhibitor resistance is reviewed by Carew et al. [71].

What is the best combination?

It is clear that blockage of one pathway or target is not the ultimate solution. Even in very oncogene-addicted cancers, blockage of a single pathway can yield transient clinical benefit, but eventually results in resistance, often due to bypass mechanisms. What is the best combination? Is it mTOR+PI3K, MEK+PI3K, or BRAF+Akt inhibitors? The answer could be all or none of them. Clearly, the diverse biology of cancer cannot be generalizable even in the same histological type. Treating cancer patients based on traditional organ-specific strategies does work, but in the majority of cases of metastatic disease results in relatively ineffective treatment. Even if the primary oncogenic events are the same, the subsequent resistant mechanisms may be quite different. Various mechanisms of EGFR TKI resistance in lung adenocarcinoma—including T790M secondary mutations or MET protoncogene amplification—and dozens of different secondary mutations in chronic myeloid leukemia (CML) after imatinib failure clearly illustrate the diversity and complexity of resistance, and demonstrate great need for an individual approach to treatment [72–74]. Multiple tissue samplings at the time of diagnosis and at the time of disease progression will potentially be one of the tools needed to identify individual mechanisms of treatment resistance. Circulating tumor cells, if obtainable, may one day replace the need for invasive biopsies as technological advances improve their identification and sensitivity.

PI3K inhibitors

Dual PI3K and mTOR inhibitors

Like other kinase inhibitors, the mechanism of PI3K inhibition is mediated through the blockage of the adenosine triphosphate (ATP)-binding pocket of the catalytic subunit [75]. More than ten PI3K inhibitors have been developed and tested. It is not uncommon to observe one kinase inhibitor possessing inhibitory activities against multiple different kinases [76]. mTOR belongs to a family of PI3K-related kinases (PIKKs) and it shares structural similarity with PI3K [77]. More specifically, mTOR contains HEAT (Huntingtin, EF3, A subunit of PP2A and TOR) repeats, and its three dimensional structure resembles the PI3K catalytic subunit [77, 78]. Therefore, many but not all PI3K inhibitors have mTOR inhibitory potency.

There are potential advantages of dual mTOR and PI3K blocking agents over pure PI3K inhibitors. In some cancers, alterations of PDK-1, Akt, TSC, or RHEB are the oncogenic processes. They are located downstream of PI3K and PI3K inhibition alone is unlikely to suppress the downstream pathway activation. However, as they sit upstream of mTOR, the mTOR inhibitory component of dual PI3K-mTOR inhibition can be effective for those select cancers. Additionally, the crosstalk between the RAS/RAF/MAPK and PI3K-Akt pathways occurs at the level of Akt. Potential disadvantages are side effects due to multi-blockade and the resultant inability to increase the dose high enough to get adequate tumor-drug exposure to cause cell death. Further basic and clinical research will elucidate the difference between dual blockade and pure PI3K inhibitors.

The PI3K inhibitor prototypes are **LY294002** and **wortmannin.** The naturally occurring flavonoid **quercetin** is found in many vegetables and fruits. It has potent PI3K inhibitory activity. LY294002 is a quercetin derivative and has higher potency for PI3K inhibition [79]. In both in vitro and in vivo studies, LY 294002 has reversed paclitaxel resistance in ovarian cancer, and the combination of paclitaxel with LY294002 has demonstrated synergy [80]. However, poor bioavailability has precluded further development of LY294002. **SF1126** is a prodrug of LY294002 that is linked with an integrin antagonist. This enhances delivery of LY294002 to targeted cells. After IV administration, SF1126 is hydrolyzed in a pH-dependent manner. In a phase I study, SF1126 was well tolerated and anticancer activity was observed [81].

Wortmannin is a fungal metabolite and is a potent irreversible PI3K inhibitor [75, 82]. Wortmannin is an unstable compound, less active in vivo than in vitro, and is presently not in clinical use [83]. To overcome its pharmacological problems, multiple derivatives have been developed. **PX-866**, the most potent wortmannin derivative currently available, recently completed phase I investigation in solid tumor malignancies and was well tolerated with a 20% stable disease rate [84]. The agent is currently under clinical investigation in combination with cytotoxic chemotherapies [85].

BEZ 235 is an oral potent dual PI3K and mTOR inhibitor. In addition to mTORC 1, BEZ 235 also inhibits mTORC2. In a phase I study, a partial response was observed in a lung cancer patient with Cowden syndrome and in an ER(+) breast cancer patient [86]. Additionally, 24% of patients had stable disease (SD)≥4 months. Although these results are encouraging, once again it can be observed that monotherapy with many agents of this class will be insufficient for most metastatic patients. Unlike BKM 120 (see below), hyperglycemia was not observed.

More specific PI3K inhibitors

BKM 120 is a specific PI3K inhibitor [87]. Its antitumor activity was observed initially in a xenograft model of

PIK3CA mutated breast cancer [88]. In a phase I study, a partial response (PR) was observed in a triple-negative breast cancer patient whose tumor harbored the KRAS mutation [89]. KRAS is known to activate not only the Ras-RAF-MAPK pathway but also PI3K[90]. This KRAS-PI3K crosstalk is a known mechanism of resistance to MEK inhibitors and the preliminary positive response in this KRAS-mutated patient lends consideration for the possible use of PI3K inhibitors in combination with MEK inhibitors [91]. Only one colorectal patient in the study carried PIK3CA mutation and did not respond to the BKM120 compound. The dose-limiting toxicities included grade 4 hyperglycemia, grade 3 mood alteration, and rash. The mood alteration from PI3K inhibitors was somewhat unexpected, but was explainable. PI3K inhibition can cause insulin resistance. This resistance was associated with increased risk of neurocognitive dysfunction including Alzheimer's disease [92]. In an animal model study, PI3K inhibition caused depression and anxiety [93].

XL147 (SAR 245408) is another oral PI3K inhibitor. XL147 was investigated as a single agent and in combination with carboplatin plus paclitaxel, and with erlotinib [94–96]. The agent was well tolerated, and a partial response was observed in a lung cancer patient in a monotherapy study [94]. XL765 (SAR245409) is an oral PI3K and TORC1/2 inhibitor. XL765 is well tolerated, both as a single agent as well as in combination with erlotinib or temozolomide (TMZ) [97–99]. **GDC-0941**, another PI3K inhibitor, has demonstrated improved bioavailability relative to its prototype compounds, PI-103, PI- 540 and PI-620 [100]. In phase I studies, a partial response has been reported in a breast cancer patient and prolonged SD was achieved in multiple ovarian cancer patients [101, 102].

Other PI3K inhibitors

CAL-101 is a p110δ specific PI3K inhibitor, while all the other PI3K inhibitors are p110α inhibitors. Unlike p110α, which is expressed ubiquitously in many tissues, p110δ is exclusively found in leukocytes, making this agent potentially useful for the treatment of hematological malignancies [103]. Chronic lymphocytic leukemia (CLL) cells express higher p110δ compared to normal B-cells. CAL-101 induced apoptosis in CLL cells without affecting normal B-cells [104]. In phase I studies, single agent CAL-101 showed high response rates of 62% in heavily pretreated indolent non-Hodgkin's lymphoma patients and in 33% of CLL patients [105, 106]. The clinical study results and main pharmacological actions of notable P13K inhibitors are summarized in Table 1 [81, 85, 86, 89, 94, 97, 101, 102, 105–112].

AKT inhibitors

Alkyl-lysophospholipids (ALPs) are synthetic lipids and cannot be properly degraded by phospholipase, resulting in abnormal accumulation in the cell membrane, disruption of cell metabolism, and cell death [113]. ALP also has Akt inhibitory activity and anti-neoplastic properties [114]. **Miltefosine** is one of the ALPs and is very effective in the treatment of visceral leishmaniasis [115]. It is available as both a topical solution as well as an oral agent. Topical miltefosine can effectively treat cutaneous breast cancer metastasis [116]. Oral miltefosine was evaluated for cancer treatment and the dose was 3–4 times higher than the dose used for the treatment of leishmaniasis. Responses were observed in a fraction of patients, however toxicities including nausea, vomiting, and kidney impairment precluded further development of this medication as an anti-neoplastic agent [117]. **Perifosine** is structurally related to miltefosine, but has a superior safety profile. Perifosine does not inhibit Akt directly, but inhibits Akt translocation to the cell membrane, which is necessary for Akt phosphorylation and activation [118]. Perifosine has been studied in many phase I and phase II studies. Although the agent was well tolerated, perifosine did not exhibit antitumor activity in melanoma, squamous cell carcinoma of the head and neck, or breast cancer as a single agent [119–121]. In contrast, durable responses were observed in heavily pretreated Waldenstrom's macroglobulinemia (WM), chronic lymphocytic leukemia (CLL), and soft tissue sarcoma patients [122–124]. Multiple combination studies with various agents are ongoing.

Triciribine, also known as Akt/protein kinase B signaling inhibitor-2 (API-2), is a potent and specific Akt inhibitor [125]. Tricibirine has been around for over 20 years and has been used in phase I and phase II studies. At high doses, it has clearly shown anti-neoplastic activity as a single agent, including one complete response in metastatic squamous cell carcinoma of cervix [126]. Due to its significant side effect profile, including hepatotoxicity, hyperglycemia, and hypocalcemia, its clinical use has been limited.

MK2206, an allosteric Akt inhibitor, has high inhibitory potency against both Akt1 and Akt2 with less activity toward Akt3. In a phase I study with single agent MK2206, SD was observed in 16% of refractory solid tumor patients and a minor response was observed in a patient who had chemo-refractory pancreatic cancer with PTEN loss [127]. In vitro studies suggest enhanced effects when MK2206 is used in combination with other cytotoxic agents [128]. Currently, multiple studies with various drug combinations, including both targeted and cytotoxic agents, are ongoing. The summary data of Akt inhibitors are presented in Table 1 [122–124, 126, 127, 129–131].

Table 1 Summary of PI3K inhibitors, Akt inhibitors and PDK-1 inhibitors

Drug Class	Drug [reference]	Other target action	Mode of admin.	Clinical Efficacy[a]	DLT (notable non-DLT toxicities)	Current phase of clinical studies and combination use
PI3K inhibitor	Quercetin [107]	PI4K	IV, oral	AFP decrease in HCC and CA-125 decrease in ovarian Ca	Nephrotoxicity	Chemoprevention No therapeutic trials
	wortmannin	mTOR, PI4K				Not in clinical use
	LY294002 [108]	mTOR, PI4K DNA-PK PIM1, PLK1, CK2, ATM				Not in clinical use
	BKM120 [89]		oral	PR in breast Ca. 42% SD	hyperglycemia, rash, epigastralgia mood alteration, pruritus	Phase I/II AI, trastuzumab, MEK inhibitor
	BEZ 235 [86, 108]	mTOR DNA-PK	oral	PR in lung and breast Ca 24% SD	No DLT (fatigue, diarrhea)	Phase I/II AI, trastuzumab
	XL147 (SAR245408) [94]		oral	PR in lung 17% SD	Rash, Hypersensitivity (nausea, fatigue, diarrhea)	Phase I/II
	XL 765 (SAR245409) [97]	mTOR	oral	14% SD	nausea, vomiting, rash, fatigue, hypophosphatemia, abnormal EKG, transaminitis	Phase I AI, temozolomide, erlotinib
	SF1126 [81]	mTOR (TORC1/TORC2), DNA-PK PIM1, PLK1, CK2, ATM	IV	21% SD	Diarrhea (nausea, vomiting, fever, fatigue)	Phase I
	GDC-0941 [101, 102, 108]	mTOR DNA-PK	oral	PR in breast Ca 16-21% SD	Headache Pleural effsion Decreased DLCO (nausea,vomiting, diarrhea, dysguesia)	Phase I MEK inhibitor Trastuzumab Erlotinib Carbo/Pac/Bev
	GDC-0980 [109]	mTOR	oral	23% SD	No DLT (nausea, diarrhea, fatigue, flatulence)	Phase I Pac/Bev/trastuzumab
	PX 866 (wortmannin analogue) [85]	mTOR	oral	22% SD	diarrhea increased AST (nausea, vomiting, fatigue)	Phase I cetuximab, docetaxel
	CAL −101 (p110δ inhibitor) [105, 106]		oral	33% PR in CLL 62% PR in indolent NHL	33% AST/ALT elevation (cytopenia)	Phase I Benda/rituximab ofatumumab
	PF-04691502 [110]	mTOR	oral			Phase I
	BGT226	mTOR	oral			Phase I
	GSK2126458 [111]	mTOR	oral			Phase I
	ZSTK474 [108, 112]	mTOR DNA-PK	oral			Phase I
	XL-499 IC486068 (p110δ inhibitor)					preclinical

Table 1 (continued)

Drug Class	Drug [reference]	Other target action	Mode of admin.	Clinical Efficacy[a]	DLT (notable non-DLT toxicities)	Current phase of clinical studies and combination use
Akt inhibitor	Triciribine (APL-2) [126, 129]		IV	PR and CR in cervical SCC	Hepatotoxicity Hypocalcemia hyperglycemia	Phase I
	MK2206 [127]		oral	16% SD	Rash, hyperglycemia Pruritus, diarrhea (nausea, fatigue,)	Phase I Carbo/Pac Docetaxel Trastuzumab, lapatinib MEK inhibitor Gefitinib IGF-1R MoAb
	Perifosine [122–124, 130]	Cell membrane	oral	6% PR in WM PR in CLL PR in sarcoma	Fatigue diarrhea	Phase I/II/III VEGF TKIs Bortezomib Various cytotoxic agents mTOR inhibitors imatinib
	GSK690693 [131]	PAK6, PKCη PKCθ, PrkX	IV			Preclinical
	XL418	S6K				preclinical
	A443654					preclinical
	PX-316					preclinical
PDK-1 inhibitor	OSU-03012					preclinical
	BX912 [142]	PKA				preclinical
	BX320 [143]					preclinical
	BX795 [144]					preclinical
	GSK2334470 [145]					preclinical
	BAG956 [144]	PI3K				preclinical
	dibenzo [c,f][2, 7] naphthyridines [145]					preclinical

[a] Efficacy is single agent response. If cancer subtype is not specified, efficacy was observed unselected solid malignancy patients.

AFP alpha fetoprotein, *AI* aromatase inhibitor, *Benda* bendamustine, *Bev* bevacizumab, *Ca* carcinoma, *Carbo* carboplatin, *CLL* chronic lymphocytic leukemia, *CR* complete response, *DLCO* Diffusing Capacity of the Lung for Carbon Monoxide, *DLT* dose-limiting toxicities, *HCC* hepatocellular carcinoma, *IGF-1R* insulin like growth factor 1 receptor, *IV* intravenous, *K* kinase, *MoAb* monoclonal antibody, *mTOR* mammalian target of rapamycin, *NHL* non-Hodgkin's lymphoma, *Pac* paclitaxel, *PI* Phosphatidylinositol, *PIM-1* Proto-oncogene serine/threonine-protein kinase pim-1, *PKA* protein kinase A, *PR* partial response, *SD* stable disease, *S6K* ribosomal S6 kinase, *TKIs* tyrosine kinase inhibitors, *TORC* mammalian target of rapamycin complex, *VEGF* vascular endothelial growth factor, WM waldenstrom's macroglobulinemia

PDK-1 inhibitors

Table 1 summarizes PDK1 inhibitors. PDK1 inhibitors are still in the preclinical drug development stage, but are worth mentioning. **Celecoxib** is a cyclooxygenase −2 (COX-2) inhibitor and has anti-inflammatory activity. Celecoxib also has moderate PDK-1 inhibitory action, and can induce apoptosis in cancer cells [132]. However, because of its low potency, celecoxib at currently approved dosages for inflammation does not have clinically meaningful antitumor effects [133, 134]. **OSU-03012** is a celecoxib derivative and has a twenty-fold greater inhibitory potency against PDI-K compared with celecoxib [135]. In vitro studies have demonstrated cytotoxicity against various cancer cell lines including those of CLL, glioblastoma, lymphoma, myeloma, breast, and pancreatic cancers [136–138].

UCN-01, 7-Hydroxystaurosporine, is a multi-kinase inhibitor whose targets include PKCα, PKCβ, PKCγ, Chk1 as well as PDK-1 [139]. Multiple studies have confirmed its antitumor potency, and several trials are currently ongoing in different phases of clinical investigation [140]. However, more recent data has indicated its main mechanism of anticancer activity is through Chk1 inhibition, and its role as a PDK-1 inhibitor is not yet defined [141]. Currently investigated PDK-1 inhibitors are listed in Table 1 [142–145].

Unanswered questions and future directions

The obvious and yet most difficult question is which agent or agents will be the champion in each class and why. Most of the new agents currently under clinical investigation are safe and well tolerated. Their side effect profiles, which include hyperglycemia, pulmonary toxicity and mood alteration, may limit their clinical use in certain population groups such as those with diabetes, chronic obstructive pulmonary disease, and depression, respectively. Most of the agents demonstrated, at best, only cytostatic activity with an occasional response. Except for one case involving a KRAS-mutated breast cancer patient who responded to BKM120, there have been no relevant potential predictive biomarkers seen clinically. Like other targeted agents, these agents will most likely show activity in selected patient populations with specific molecular alterations, and in drug combinations. The importance of simultaneous development of predictive biomarkers cannot be overemphasized. Additionally, a more effective and efficient way to screen for appropriate patient selection is needed. Some pathway alterations, such as the Akt1 mutation, are generally uncommon. If the association of clinical characteristics with molecular characteristics can be identified, screening strategies will be more efficient.

Although our understanding of PI3K-Akt and its surrounding pathways has improved, further elucidation (especially its crosstalk with other signaling cascades and defining appropriate patient subsets), is critical if we are to more definitively define its role in cancer treatment. The early therapeutics team at MD Anderson has presented an initial and updated response profile of patients treated with inhibitors of the PI3K pathway. They looked at response primarily of monotherapy treatment in patients preselected by either a PIK3CA mutation or PTEN deletion [146]. Although preliminarily, extremely positive results relative to mutational status, the most recent presentation showed <25% response. Although still encouraging, it demonstrates to the cancer community the importance of the next steps of PIK3CA mutations. We have to think and act smarter but to do that we will also need to gather the facts, as difficult as it may be. Even when we harvest fresh tissue, it is unknown how reflective its expression profile is relative to other disease sites within the same patient. However, when we finally define the keys to therapeutic success, we must be prepared to act: we must continue to develop in parallel the necessary pharmacodynamic tools and clinical drug combinations so as to be able to tackle the results head on and hopefully make a difference in the treatment of this disease both collectively, as well as one patient at a time.

Conflict of interest statement Although the authors have not received and will not receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this manuscript, benefits have been or will be received but are directed solely to a research fund, foundation, educational institution or other non-profit organization with which one or more of the authors is(are) associated.

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