



Review

Targeting Akt Signaling Pathway in Cancer: Molecular Mechanisms and Advances in Therapeutic Interventions

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Abstract

The Akt/PKB (protein kinase B) is a major transducer of the phosphoinositide 3-kinase (PI3K) signaling axis, regulating key cellular processes such as growth, proliferation, apoptosis, survival, and migration in both normal and cancer cells. In normal cells, oncoproteins and tumor suppressor proteins within the Akt pathway exist in equilibrium. However, this equilibrium is disrupted in cancer cells due to activating mutations in oncoproteins and inactivating mutations in tumor suppressor proteins. This dysregulation drives tumor growth and progression, making the Akt pathway an attractive target for cancer therapies. A deeper understanding of the molecular mechanisms of the Akt signaling pathway is crucial for developing novel therapeutic agents targeting Akt and its downstream effectors for cancer treatment. This review discusses the role of Akt in cancer, current Akt-targeted agents, their limitations, and future trends.

Keywords: Akt; PI3K; cancer; cell survival; inhibitors; targeted therapy

1. Introduction

Akt, also known as Protein Kinase B (PKB), belongs to the protein kinases A, G, and C (AGC) superfamily of serine/threonine kinases [1]. Akt is one of the key kinases involved in human physiology and disease. Since the discovery of Akt as an oncogene in murine leukemia virus AKT8 and as a homolog of protein kinase C [2–4] and its subsequent identification as a downstream target of phosphoinositide 3-kinase (PI3K) [5,6], there has been a significant breakthrough in the mechanism involved in Akt signaling in cancer research [7–9].

Aberrant activation of Akt is frequently implicated in the pathogenesis of various human cancers, including solid tumors and hematologic malignancies [9–15]. It is aberrantly activated through genetic and epigenetic alterations, such as mutations and/or amplification in key regulatory components like phosphatidylinositol 3-kinase catalytic alpha (PIK3CA), phosphatase, tensin homolog (PTEN), and receptor tyrosine kinases (RTK), Akt itself, and mammalian target of rapamycin (mTOR) [9]. Once activated, Akt transmits signals from PTEN, PI3K, and RTK to downstream targets like BCL2-associated agonist of cell death (BAD), glycogen synthase 3 (GSK3), forkhead box O (FOXO) transcription factors, and mouse double minute 2 homolog (MDM2) [9,10]. This cascade of signaling events intersects with other compensatory pathways, allowing cancer cells to bypass normal regulatory mechanisms and promoting tumorigenesis [9,11].

The Akt pathway drives numerous oncogenic processes, including promoting cell survival, inhibiting apoptosis, enhancing growth and proliferation, facilitating cellular differentiation, and mediating actin cytoskeleton rearrangements [9]. It also plays an integral role in the tumor microenvironment, influencing angiogenesis, recruitment of inflammatory factors, and immune cell infiltration. These oncogenic processes collectively contribute to tumor growth, metastasis, and therapeutic resistance [9,16].

While preclinical studies have well documented the role of Akt hyperactivation in tumor initiation, disease progression, and drug resistance, clinical efforts to target Akt have faced considerable challenges [17,18]. The complexity of Akt signaling, coupled with tumor heterogeneity, feedback loops within the Akt pathway, and compensatory activation of parallel signaling networks, made it difficult to achieve sustained efficacy of Akt inhibitors in clinical trials [18,19]. These challenges underscore the urgent need to understand the intricacy of the Akt pathway to develop more effective therapeutic strategies to overcome resistance and improve the clinical outcomes of Akt-targeted therapies.

This review provides an overview of the current understanding of the Akt pathway in cancer, explores the landscape of existing Akt inhibitors against cancer, addresses their limitations, and discusses future trends in developing more effective therapies.



2. Structure, Activation, and Function of Akt

Akt has three isoforms: Akt1, Akt2, and Akt3 [1, 9]. Akt1 and Akt2 are broadly expressed, and Akt3 has a limited expression profile and is commonly expressed in brain tissue [20]. All three isoforms have an N-terminal pleckstrin homology (PH) domain, a central kinase domain (KD), and a C-terminal regulatory region (RR) with a hydrophobic motif [1,9] (Fig. 1). The PH domain binds 3-phosphoinositides such as phosphatidylinositol (4,5)-bisphosphate (PIP2) and phosphatidylinositol (3,4,5)-trisphosphate (PIP3) and plays an important role in recruiting Akt to the cell membrane. The central KD with a regulatory threonine residue in its activation loop and the C-terminal RR with a regulatory serine residue are essential for Akt kinase activation [1,9]. The PH domain also interacts with the KD and autoinhibits Akt in its basal state [9]. While the three Akt isoforms share significant sequence homology among their domains, these isoforms play non-redundant roles in cell signaling: Akt1 regulates cell survival and proliferation, Akt2 is involved in cellular metabolism and cytoskeleton dynamics, and Akt3, alongside Akt1, contributes to cell growth processes [20]. Moreover, isoform knock-out studies in mice revealed distinct physiological roles: Akt1 knock-out mice exhibit developmental defects, Akt2 knock-out mice display defects in glucose metabolism, and Akt3 knock-out mice show abnormalities in brain development [20]. Akt1 promotes cancer cell survival and proliferation and has anti-metastatic effects, while Akt2 promotes cancer cell adhesion, migration, invasion, and metastasis [21].

The Akt signaling is tightly regulated in normal cells [1,9]. As shown in Fig. 2, Akt is activated primarily through PI3K activation, which is triggered by the binding of ligands like insulin, epidermal growth factor (EGF), and other cytokines to RTKs [including the insulin growth factor 1 receptor (IGF1R), EGF receptor (EGFR), vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR)], or G-protein coupled receptors (GPCRs), cytokines receptors, intracellular tyrosine kinases and intracellular small guanosine triphosphatases (GTPases) such as rat sarcoma virus (RAS) on the plasma membrane [22]. Once activated, PI3K catalyzes the conversion of PIP2 to PIP3, and the termination of PI3K-PIP3 interaction occurs through the dephosphorylation of PIP3 back to PIP2 by PTEN [9,23]. The resulting PIP3 at the membrane serves as a docking site for kinases with PH domains, such as Akt and phosphoinositide-dependent kinase 1 (PDK1), inducing their translocation to the membrane [9,24].

Once recruited to the membrane, Akt undergoes further conformational changes through PDK1-mediated phosphorylation at its threonine 308 (Thr308) residue, and this step is sufficient for the activation of Akt [25,26]. The full activation of Akt is achieved through the mTOR complex 2 (mTORC2)-mediated phosphorylation at its serine

473 (Ser473) residue. Activated Akt then regulates various downstream targets across different cellular compartments, and this regulation influences critical cellular functions, such as cell growth, survival, proliferation, metabolism, glucose uptake, and angiogenesis [27].

As illustrated in Fig. 2, the Akt signaling is integral to regulating diverse cellular processes. Akt influences cell cycle progression via phosphorylation-mediated inhibition of cyclin-dependent kinase (CDK) inhibitors like p27^{Kip1} and p21^{Waf1}, which act as G1 checkpoint regulators [27]. Akt regulates apoptosis by inhibiting BAD, BCL-2-interacting mediator of cell death (BIM), caspase 9, and FOXO transcription factors, as well as by phosphorylating MDM2, facilitating its entry into the nucleus, which leads to p53 degradation [9]. Akt phosphorylates and inhibits the tumor suppressors tuberous sclerosis complex 1/2 (TSC1/2), which under normal conditions negatively regulates the mTOR/ribosomal protein S6 kinase (S6K) pathway, thereby activating mTOR complex 1 (mTORC1) [28]. Activated mTORC1 phosphorylates S6K polypeptide 1 (S6K1) and eukaryotic translation initiation factor 4E binding protein 1 (4EBP1), promoting protein synthesis and cellular proliferation by phosphorylation of ribosomal protein S6 (S6/RPS6) [28]. Akt also regulates cellular metabolism through modulation of its substrates like GSK3, FOXO, mTOR, and glucose transporter 1/4 (GLUT1/4); and angiogenesis by regulating vascular endothelial growth factor (VEGF) and hypoxia-inducible factor 1-alpha (HIF-1 α) [9]. While not depicted in Fig. 2, the PI3K/Akt signaling pathway exhibits extensive crosstalk with other major signaling cascades. Notably, the PI3K/Akt and RAS/Raf-1 proto-oncogene (RAF)/mitogen-activated protein kinase (MEK)/extracellular signal-regulated kinase (ERK) pathways intersect at multiple levels and often co-regulate essential cellular functions [29]. For example, RAS activation stimulates c-RAF, an Akt substrate, and initiates a kinase cascade leading to ERK activation, a pathway central to the regulation of cellular processes such as cell survival and proliferation. Interestingly, under specific conditions, Akt can inhibit the RAS/RAF/MEK/ERK pathway through phosphorylation-mediated inhibition of c-RAF [29]. Akt also modulates stress-induced mitogen-activated protein kinases (MAPKs), such as c-Jun N-terminal kinase (JNK) and p38, by phosphorylating and inhibiting apoptosis signal-regulated kinase 1 (ASK1), a MAPK kinase kinase (MAPKKK) that functions as an upstream activating kinase within the JNK and p38 pathways [30]. PI3K/Akt signaling also interacts with other key pathways, such as the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) [19], neurogenic locus notch homolog protein (NOTCH), and transforming growth factor beta (TGF β) [31]. These interactions highlight the complexity and integrative nature of PI3K/Akt signaling within the broader cellular signaling network.

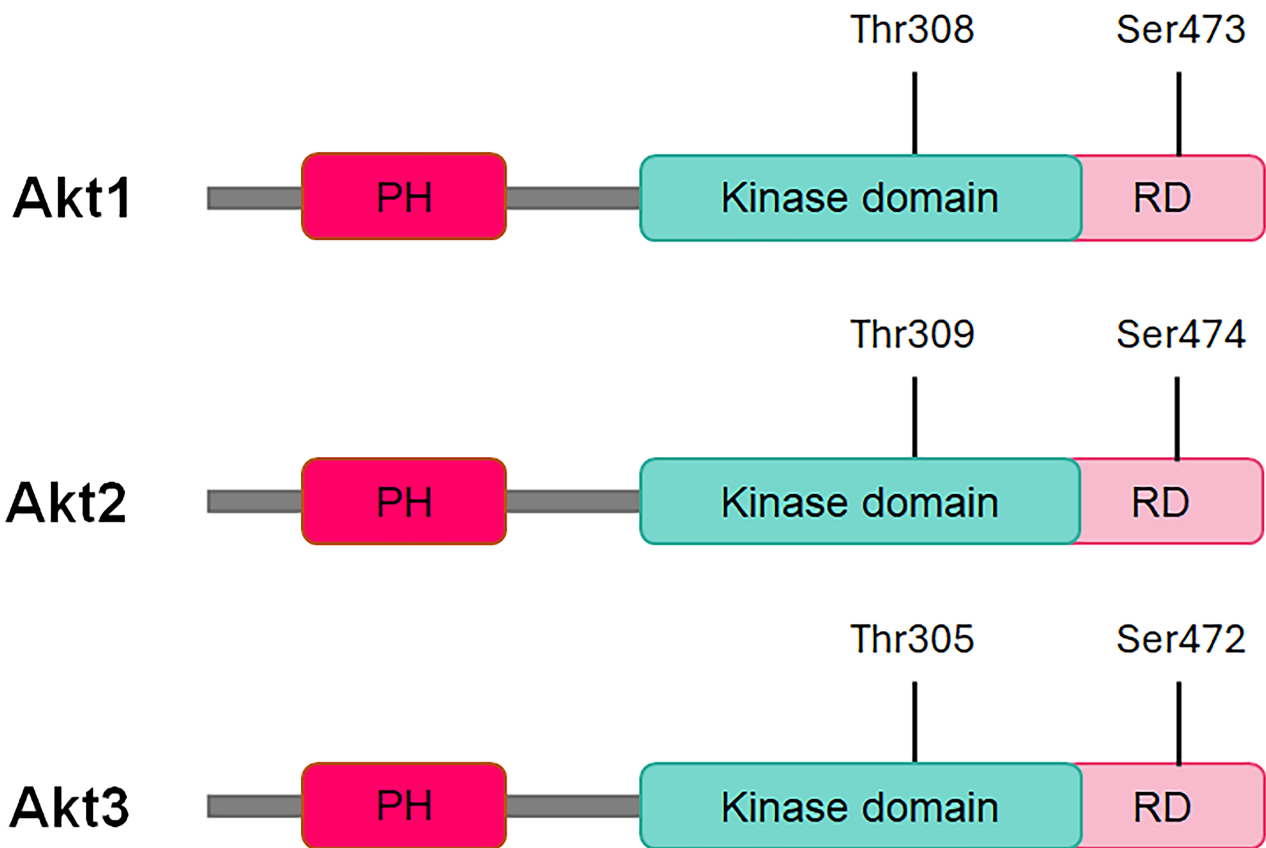


Fig. 1. Schematic of the conserved domains of Akt kinases. PH, pleckstrin domain; RD, regulatory domain; Thr, threonine; Ser, serine.

3. Deregulation of Akt in Cancer

Akt hyperactivation promotes uncontrolled cell growth, evasion of cell death, increased metabolic activity, and alteration in the tumor microenvironment and is critical for cancer progression [9,10]. Akt activation in human cancer occurs through various mechanisms, including somatic recurrent oncogenic mutation and amplifications in upstream regulators such as PI3K, PDK1, EGF receptor (EGFR), human epidermal growth factor receptor 2 (HER2/neu), or other RTKs [10]. Inactivating mutations in PTEN and PH domain leucine-rich repeat protein phosphatase (PHLPP) also contribute to Akt activation [10]. While mutations in upstream regulators most often drive Akt hyperactivation in human cancers, the three isoforms of Akt also function as oncogenes [9].

3.1 Upstream Modulators in Akt Aberrant Activation

Various upstream modulators contribute to the Akt activation in cancer cells. Somatic mutations in the *PIK3CA* gene lead to the constitutive activation of PI3K and, subsequently, Akt, independent of receptor activation [14]. *PIK3CA* mutations and/or amplifications are prevalent in cancers such as breast, cervical, colorectal, gastric, lung, and prostate cancers [32]. Overexpression of growth fac-

tor receptors, such as EGFR or HER2/neu, can also continuously activate the PI3K-Akt pathway, promoting cell survival and uncontrolled cell growth [32]. Additionally, the activation of oncogenes, such as Ras, can further activate the PI3K-Akt pathway, thereby accelerating tumorigenesis [33]. Ras mutations are prevalent in colorectal, lung, pancreatic, and ovarian cancers, where they maintain Akt activation and contribute to the sustained survival of cancer cells [33]. Furthermore, the deletion or loss-of-function mutation of *PTEN*, which normally dephosphorylates PIP3 to PIP2, results in the constitutive activation of Akt [34]. Loss of *PTEN* is commonly seen in cancers such as breast, colorectal, and prostate cancers [34]. Akt signaling also interacts with other cellular pathways, such as mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) and Notch signaling, both of which contribute to tumorigenesis and metastasis [32]. Akt can also be constitutively activated in certain hematological cancers due to chromosomal translocations that lead to the activation of upstream tyrosine kinases [11].

3.2 Akt Hyperactivation

While mutations in *AKT* genes occur less frequently compared to mutations in core Akt regulators like *PIK3CA*,

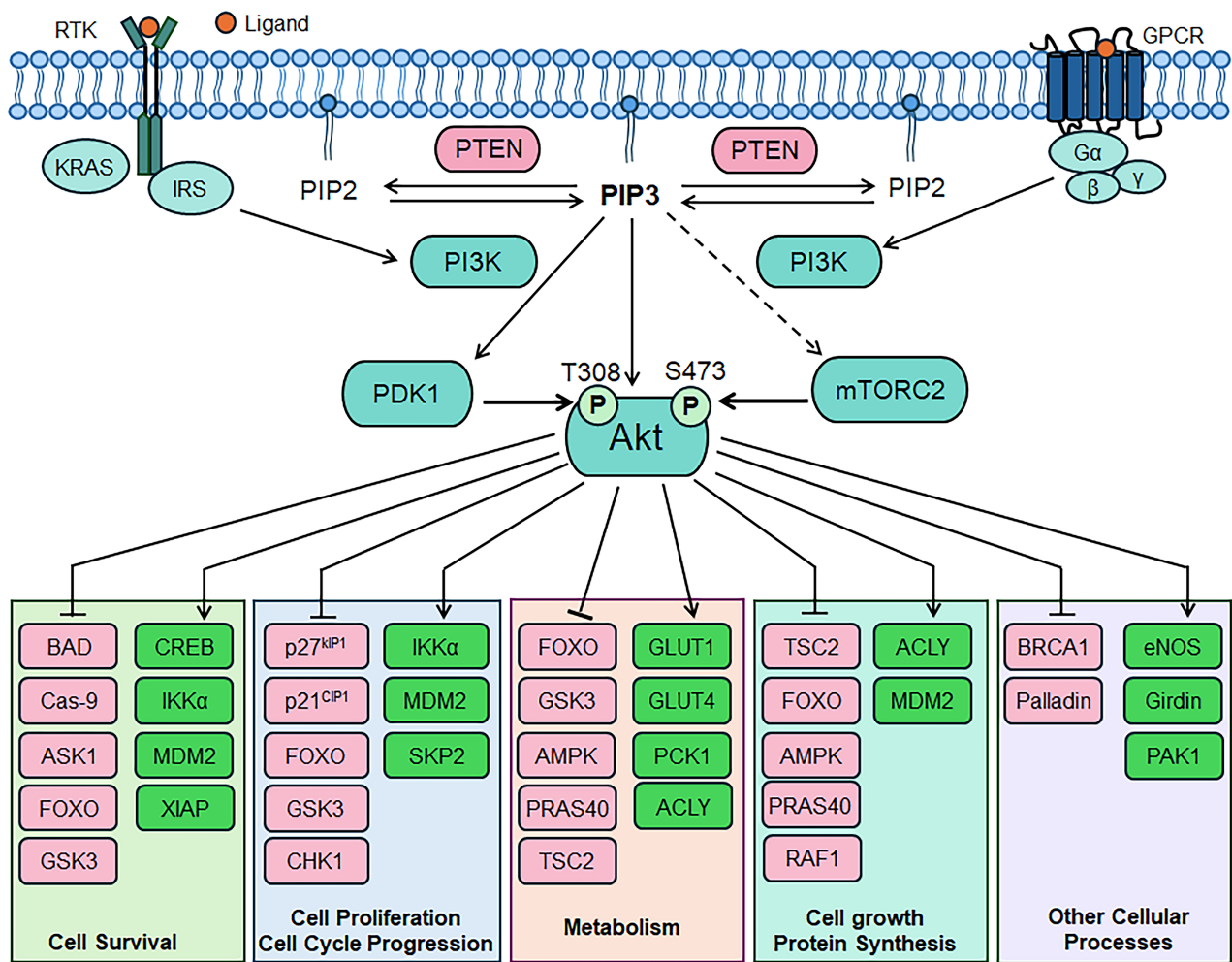


Fig. 2. Schematic of the Akt signaling cascade. ACLY, ATP-citrate lyase; AMPK, adenosine monophosphate-activated protein kinase; Akt, protein kinase B; ASK1, Apoptosis signal-regulating kinase 1; BAD, Bcl2-associated agonist of cell death; BRCA1, breast cancer type 1 susceptibility protein; Cas-9, caspase-9; CHK1, checkpoint kinase 1; CREB, cyclic adenosine monophosphate response element binding protein; eNOS, endothelial nitric oxide synthase; FOXO, forkhead box O; GLUT1, glucose transporter 1; GLUT4, glucose transporter 4; GPCR, G-protein-coupled receptor; GSK3, glycogen synthase kinase-3; IKK α , inhibitory kappa B kinase α ; IRS, insulin receptor substrate; KRAS, kirsten rat sarcoma virus; MDM2, mouse double minute 2 homolog; mTORC2, mammalian target of rapamycin complex 2; PAK1, p21-activated kinase 1; PCK1, phosphoenolpyruvate carboxykinase 1; PDK1, phosphoinositide-dependent kinase 1; PI3K, phosphatidylinositol 3-kinase; PIP2, phosphatidylinositol (4,5)-bisphosphate; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PRAS40, proline-rich Akt substrate of 40 kDa; PTEN, phosphatase and tensin homolog; RAF1, Raf-1 proto-oncogene, serine-threonine kinase; RTK, receptor tyrosine kinase; SKP2, S-phase kinase-associated protein 2; TSC2, tuberous sclerosis proteins 2; XIAP, X-linked inhibitor of apoptosis protein.

activating mutations or amplification in the *AKT* genes have been identified in various solid tumors [35]. Alterations in Akt1 and Akt2 isoforms have been implicated in various cancers, including breast, colorectal, endometrial, gastric, lung, ovarian, pancreatic, and prostate cancers, glioblastoma, and melanoma [7,35–44]. Among the Akt isoforms, Akt1 is the most mutated isoform. The *E17K* mutation in the Akt1 PH domain was the first reported somatic oncogenic mutation of any *AKT* gene [36] and is predominantly found in breast, colorectal, ovarian, and prostate cancers [36–39]. This mutation exhibits constitutive kinase activa-

tion by altering the PH domain of Akt1 and enhancing its localization to the plasma membrane, thereby promoting cancer cell proliferation, survival, and growth [36]. However, the *E17K* mutation is found to be mutually exclusive with *PI3KCA* mutation and *PTEN* loss, suggesting different yet overlapping pathways of oncogenesis [21,36].

AKT2 was the first *AKT* gene reported to be recurrently altered in human cancer through gene amplification and overexpression [7,42]. Alterations in Akt2 were observed in various cancers, including breast, colorectal, ovarian, pancreatic, and hepatocellular cancers [39,42–44].

Table 1. Akt alteration status in cancers.

Cancer type	Alterations
Breast cancer	<i>AKT1</i> Mutation [36,37] <i>AKT2</i> amplification and/or overexpression [39,43] Akt3 overexpression [46]
Brain tumors	Akt Overexpression [38]
Colorectal cancer	<i>AKT1</i> Mutation [36] <i>AKT2</i> mutation and co-amplification [7]
Endometrial cancer	<i>AKT1</i> mutation [38]
Gastric cancer	<i>AKT1</i> amplification [40]
Glioblastoma	<i>AKT1</i> mutation [41]
Hepatocellular carcinoma	Akt activation [7,47]
Melanoma	<i>AKT1</i> mutation [38] Akt3 overexpression [50,51]
Non-small cell lung cancer (NSCLC)	<i>AKT1</i> mutation [38]
Ovarian cancer	<i>AKT1</i> mutation [36] <i>AKT2</i> amplification and/or overexpression [42,44] Akt3 overexpression [48]
Pancreatic cancer	<i>AKT2</i> amplification and/or overexpression [39,42]
Prostate cancer	<i>AKT1</i> Mutation [39] Akt3 overexpression [49]
Renal cell carcinoma	Akt overexpression [41]
Thyroid cancer	Akt overexpression and overactivation [7]

In breast and ovarian cancers, overexpression of Akt2 is associated with increased invasion and metastasis potential and poor prognosis [21,44]. In pancreatic cancer, over 30% of pancreatic carcinoma samples show more than a three-fold increase in Akt2 kinase activity compared to normal pancreatic tissue, highlighting the significance of Akt2 activation in this cancer type [45]. Overexpression of Akt3 is less studied but is impactful in triple-negative breast cancer, ER-negative breast cancer, hepatitis C virus-associated hepatocellular carcinoma, ovarian cancer, prostate cancer, and melanoma [46–51]. Studies have shown that Akt3 mutations exhibit increased proliferation and pro-carcinogenic effects, but anti-metastatic effects in melanoma cells [51]. Table 1 (Ref. [7,36–44,46–51]) shows the genetic alterations of Akt isoforms in human malignancies.

4. Biological Effects of Aberrant Akt Activation

The Akt pathway is essential for normal cell survival and growth. The primary biological consequences of Akt hyperactivation, relevant to abnormal cancer cell growth, can be broadly classified into three categories: survival, proliferation, and growth [9]. Akt also had effects on tumor metabolism, angiogenesis, and invasion, contributing to cancer progression and metastasis [9].

4.1 Cell Survival and Resistance to Apoptosis

Akt has a well-established role in promoting cell survival and resisting apoptosis—one of the hallmarks of cancer [52,53]. The cell survival capability of Akt is critical

for tumor growth and contributes to the therapeutic resistance observed in many cancers. The mechanisms through which Akt modulates apoptotic and survival pathways are multifactorial, as Akt directly phosphorylates several components involved in these processes. For example, activated Akt phosphorylates and inactivates pro-apoptotic proteins such as BAD, Bcl-2-associated X protein (BAX), BIM, caspase-9, GSK3, FOXO, and endothelial nitric oxide synthase (eNOS), thereby preventing apoptosis through multiple mechanisms [54,55]. Additionally, Akt promotes cell survival through phosphorylation-mediated activation of cell survival factors, including Bcl-2 family members, MDM2, cyclic adenosine monophosphate response element binding protein (CREB), nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), and X-linked inhibitor of apoptosis protein (XIAP) [54,55]. Akt also regulates autophagy, a cellular process that allows cancer cells to survive under nutrient deprivation or stressful conditions, such as those often encountered in the pancreatic tumor microenvironment [56].

4.2 Cell Cycle Progression and Proliferation

Aberrant activation of Akt promotes cell cycle progression and proliferation primarily through phosphorylation and inhibition of specific cellular substrates [1,9]. Akt positively regulates the G1-S phase transition by phosphorylating key substrates and modulating cyclins and cyclin-dependent kinases (CDKs), leading to unchecked cell proliferation. High Akt activity is often linked to poor prognosis in various cancers, as it contributes to abnormal cell

cycle progression and tumor growth [57]. Specifically, Akt activation inhibits GSK3 kinase activity, inducing cell cycle progression via upregulation of cyclin D1 gene expression [57]. Akt directly phosphorylates cell-cycle inhibitors, p27^{Kip1} and p21^{Waf1}, sequesters them in the cytoplasm, and inhibits their binding and regulation of cyclin/CDK complex, thereby promoting cell cycle progression and tumor proliferation [7,58]. Furthermore, Akt has been shown to phosphorylate S-phase kinase-associated protein 2 (SKP2), which stabilizes SKP2 and enhances the degradation of p27^{Kip1} and p21^{Waf1}, further promoting tumorigenesis [59]. In addition to its role in cell cycle regulation, Akt is critical in stimulating protein synthesis, cell growth, and metabolic processes essential for tumor cell proliferation through its downstream target, mTOR [60,61]. The Akt-mediated modulation of key regulatory factors, such as FOXO transcription factors, MDM2, and inhibitory kappa B kinase α (IKK α), further contributes to tumor progression by regulating critical genes involved in cell cycle regulation and survival [9,62,63].

4.3 Metabolism Reprogramming

Akt plays a key role in cellular metabolism, particularly by regulating aerobic glycolysis—a hallmark of rapidly proliferating cells [64,65]. Akt regulates glucose metabolism by increasing glucose uptake into cancer cells, primarily through the translocation of the glucose transporters GLUT1/4 to the membrane, stimulating GLUT1 expression, and activating glycolytic enzymes [65]. Additionally, Akt enhances glucose influx by upregulating ectonucleoside triphosphate diphosphohydrolase 5 (ENTPD5), an endoplasmic reticulum enzyme that increases the cellular ADP:ATP ratio. This shift activates glycolytic enzymes that require ADP as a cofactor, resulting in the compensatory increase in aerobic glycolysis in cancer cells [66]. The Akt-induced phosphorylation of GSK3, a key kinase involved in the regulation of glycolytic enzymes, like glycogen synthase, enhances the cancer cell's ability to metabolize glucose rapidly [11,67]. The Akt phosphorylation of FOXO transcription factors limits their entry into the nucleus and reduces the tissue-specific metabolic changes [32]. Akt also positively regulates sterol regulatory element binding protein 1 (SREBP1), a master transcriptional regulator of lipid metabolism, which stimulates lipogenesis and blocks gluconeogenesis [65]. This occurs either through direct activation or via phosphorylation-mediated regulation of GSK3 and TORC1, leading to increased lipogenesis in cancer cells [65,68].

4.4 Angiogenesis

Aberrant activation of Akt leads to an increase in resting diameter and blood flow in the vascular endothelium [69]. Akt1 is the most predominant Akt isoform in vascular cells and is critical for VEGF-induced angiogenesis [69]. Constitutive activation of Akt1 leads to abnormal

blood vessel formation and contributes to tumor cell aberration. Akt and VEGF create an autocrine loop within the cell to regulate angiogenesis, wherein VEGF activates the Akt pathway, and Akt, in turn, regulates the expression of VEGF and its receptors [70]. Akt via mTOR signaling also induces HIF-1 α expression, which modulates key angiogenesis regulators, including VEGF, heme oxygenase 1, inducible nitric oxide, and glycolytic enzymes [70]. The Akt-mediated phosphorylation also activates eNOS, a key regulator of vascular remodeling and angiogenesis, and inhibits transcription factor FOXO1. These processes modulate angiopoietin 1 and 2 (ANG1 and ANG2) expressions, promoting endothelial cell proliferation, migration, sprouting, and aberrant blood vessel formation in the presence of VEGF, thereby supporting tumor growth [67,71]. Akt-induced activation of eNOS also increases nitric oxide production downstream of VEGF signaling, enhancing blood vessel dilation and endothelial cell migration [67]. Furthermore, Akt regulates endothelial tip formation during angiogenesis by modulating its substrates such as angiomin-like protein 1 (AMOTL1), filamin A, and vascular endothelial tyrosine phosphatase (VE-PTP) [67].

4.5 Tumor Invasion and Metastasis

Akt signaling enhances cancer cell metastatic potential by promoting processes like epithelial-mesenchymal transition (EMT) and enhancing cancer cell motility through several distinct mechanisms [16]. Specifically, Akt-mediated phosphorylation of Twist1 downregulates epithelial marker E-cadherin and upregulates mesenchymal marker N-cadherin expression. This shift promotes EMT, invasion, and metastasis via upregulation of transforming TGF β expression [16]. Akt also prevents Snail degradation through phosphorylation-mediated inhibition of GSK3 beta (GSK3 β) and activation of NF- κ B. This results in the stabilization of Snail, which inhibits E-cadherin expression and stimulates EMT [57]. Additionally, Akt hyperactivation enhances matrix metalloproteinases (MMPs) activity, which degrades the extracellular matrix and basement membrane, allowing cancer cells to invade surrounding tissues and metastasize [16,31]. Moreover, Akt also regulates the organization of actin and cellular motility by phosphorylating actin-binding protein Girdin, which is key to lamellipodia formation. Phosphorylated Girdin accumulates at the leading edge of migrating cells, facilitates lamellipodia formation, and promotes cellular motility and invasion [72]. The Akt-mediated phosphorylation of p21-activated kinase 1 (PAK1) also promotes chemotaxis, further enhancing cancer cell migration [73].

5. Recent Advances in Akt Inhibitor Research in Cancer

The Akt pathway is frequently altered in human cancers and holds promise for therapeutic interventions [10]. Akt inhibitors are broadly classified as competitive adeno-

sine triphosphate (ATP) inhibitors, allosteric inhibitors, and phosphatidylinositol analogs. Most Akt inhibitors target all three Akt isoforms and are referred to as pan-Akt inhibitors [74]. Competitive ATP inhibitors work by competing with ATP to bind to the KD of Akt and prevent its phosphorylation. Allosteric inhibitors irreversibly bind to non-catalytic sites located in the interdomain region between the KD and the PH domain and stabilize the inactive conformation of Akt. The alkyl-phospholipid compound, on the other hand, binds to the PIP3-cavity within the PH domain and prevents its translocation to the plasma membrane [75]. Several strategies have been explored to inhibit Akt signaling in cancer cells, and Akt inhibitors are currently in different stages of clinical development, either as monotherapies or combination therapies. Tables 2,3 outline select clinical trials of Akt inhibitors in cancer. Representative drugs from each category, especially those evaluated in phase III clinical trials, are discussed below.

Afuresertib (GSK2110183) is an orally available ATP-competitive pan-Akt kinase inhibitor [76]. In preclinical studies, afuresertib demonstrated a potent inhibitory effect on cell proliferation and xenograft tumor growth in a dose-dependent manner, supporting its therapeutic potential in cancer treatment [76]. Afuresertib has been investigated in multiple clinical trials, both in solid tumors, including breast, prostate, and ovarian tumors, and multiple myeloma (Tables 2,3). For instance, a phase I study of afuresertib showed favorable safety, pharmacokinetics, and clinical profile against hematologic malignancies, including multiple myeloma [76]. Furthermore, a phase I/II study of afuresertib in combination with paclitaxel and carboplatin reported positive results in platinum-resistant ovarian cancer patients, a difficult-to-treat condition [77]. A phase III trial (NCT04851613) is currently recruiting patients to evaluate the combination of afuresertib and fulvestrant in locally advanced or metastatic hormone receptor-positive (HR+)/HER2-negative (HER2-) breast cancer patients who have failed standard-of-care therapies (Table 3).

Capivasertib (AZD5363) is a potent, selective, ATP-competitive pan-Akt inhibitor [78]. Activating mutations in *PIK3CA* and *AKT1* and loss of *PTEN* have been found to significantly increase the sensitivity of tumors to capivasertib [79]. Capivasertib monotherapy has shown promise in clinical trials in advanced solid tumor patients, particularly those harboring *AKT1-E17K* mutation [79]. Capivasertib combination therapy also demonstrated clinically significant responses in Akt-mutated metastatic breast cancer patients [80,81]. Furthermore, the combination of capivasertib and paclitaxel in triple-negative breast cancer (TNBC) significantly increases progression-free survival (PFS) and overall survival (OS) compared to the combination of placebo and paclitaxel (NCT02077569) [82]. The phase III CAPItello-291 trial (NCT04305496) studied the combination of capivasertib and fulvestrant in HR+/HER2-advanced breast cancer patients refractory to aromatase in-

hibitor therapy [83]. The trial reported a statistically significant increase in the median PFS for patients receiving capivasertib and fulvestrant (7.2 months) compared to those receiving fulvestrant alone (3.6 months). Based on these findings, the Food and Drug Administration (FDA) approved capivasertib in 2023 for use in adult patients with HR+/HER2- locally advanced or metastatic breast cancer in combination with fulvestrant, marking capivasertib as the first Akt inhibitor to reach the market [84]. Other trials of capivasertib as monotherapy or combination therapies in human cancers are listed in Tables 2,3.

Ipatasertib (GDC-0068) is an ATP-competitive pan-Akt inhibitor with anti-survival and anti-proliferative effects [85]. Ipatasertib has been reported to effectively inhibit tumor growth in cancers with Akt activation due to *PTEN* loss, *PIK3CA* mutations/amplifications, or *HER2* overexpression [85]. Preclinical studies have demonstrated robust antitumor activity with ipatasertib [85]. A phase I clinical study (NCT01090960) of ipatasertib in patients with solid tumors reported that the drug was well-tolerated [86]. In the phase III IPATential150 trial (NCT03072238), adding ipatasertib to abiraterone and prednisolone significantly increased the radiographic PFS in metastatic and castration-resistant prostate cancer patients with *PTEN* loss compared to placebo and abiraterone [87]. However, in another phase III trial (IPATunity130; NCT03337724), the combination of ipatasertib and paclitaxel did not improve clinical efficacy in patients with *PIK3CA/AKT1/PTEN*-altered, HR+/HER2- breast cancer [88]. Select trials of ipatasertib in cancers are listed in Tables 2,3.

MK-2206 is an orally available allosteric inhibitor of all Akt isoforms, which prevents the translocation of Akt to the membrane, thereby blocking the activation of its downstream substrates [89]. MK-2206 exhibits higher antiproliferative activity in cancer cell lines that harbor *AKT2* amplification, *PI3KCA* mutations, *PTEN* loss/mutation, or constitutive activation of RTKs [89]. In preclinical studies, MK-2206 showed significant antitumor activity and has been extensively investigated in numerous phase I and II trials, alone or as combination therapies (Table 2). A phase I clinical trial (NCT00670488) of MK-2206 reported a favorable pharmacological activity [90]. However, phase I/II trials of MK-2206 monotherapy and/or combination therapy failed to achieve the desired clinical profile in advanced breast cancer (NCT01277757), colorectal cancer (CRC) (NCT01333475, NCT01333475), and pancreatic cancer (NCT01658943) patients [91–94].

Perifosine, a first-generation Akt inhibitor, is an orally bioavailable alkyl-phospholipid compound that prevents Akt translocation to the membrane and subsequent phosphorylation [95]. Perifosine showed promise in preclinical models [96] and has been investigated in clinical studies in several different cancers (Tables 2,3). Although perifosine monotherapy showed promising results in pediatric central nervous system tumors and solid tumors [97,98], it showed

Table 2. Select Akt inhibitors in clinical trials.

Inhibitor	Target	Mode of action	Tumor	Phase
Afuresertib (GSK2110183)	Pan-Akt	ATP-competitive	Breast, cervical, endometrial, esophageal, gastric, gastroesophageal junction, prostate, and ovarian cancers, NSCLC, solid tumors, multiple myeloma, CLL, hematologic malignancies	I/II/III
Capivasertib (AZD5363)	Pan-Akt	ATP-competitive	Breast and prostate cancers, solid tumors, B-cell non-Hodgkin lymphoma, hematological malignancies	I/II/III
Ipatasertib (GDC-0068)	Pan-Akt	ATP-competitive	Breast, head & neck, gastric, prostate, and ovarian cancers, NSCLC, solid tumors	I/II/III
Uprosertib (GSK2141795)	Pan-Akt	ATP-competitive	Endometrial cancer, melanoma, myeloma, hematopoietic and lymphoid cell neoplasm, malignant solid neoplasm	I/II
GSK690693	Pan-Akt, PKA, & PKC	ATP-competitive	Hematologic malignancies, solid tumors, lymphoma	I
LY2780301	Pan-Akt & p70S6K	ATP-competitive	Breast cancer, solid tumors, non-Hodgkin's lymphoma	I/II
MSC2363318A	Akt1/3 & p70S6K	ATP-competitive	Advanced malignancies	I
ARQ751	Pan-Akt	Allosteric	Solid tumors	I
BAY1125976	Akt1/2	Allosteric	Neoplasms	I
Miransertib (ARQ092)	Pan-Akt	Allosteric	Endometrial and ovarian cancers, solid tumors, lymphomas	I/II
MK-2206	Pan-Akt	Allosteric	Breast, colorectal, gall bladder, pancreas, prostate, oral, and ovarian cancers, NSCLC, solid tumors, melanoma, lymphomas	I/II
TAS-117	Pan-Akt	Allosteric	Solid tumors	II
Triciribine (PTX-200)	Pan-Akt	Allosteric	Acute leukemia, breast and ovarian cancers, leukemia, hematologic malignancies, metastatic cancer	I/II
Perifosine (KRX-0401)	Akt 1/2	Alkyl-phospholipids	Brain, breast, colorectal, head & neck, pancreatic, prostate, and renal cell cancers, NSCLC, solid tumors, GIST, glioblastoma, mixed glioma, multiple myeloma, sarcoma, CLL, small lymphocytic lymphoma	I/II/III

ATP, adenosine triphosphate; CLL, chronic lymphocytic leukemia; GIST, gastrointestinal stromal tumors; NSCLC, non-small cell lung cancer; PKA, protein kinase A; PKC, protein kinase C; p70S6K, p70 ribosomal S6 kinase.

Table 3. Select active or completed phase III clinical trials of Akt inhibitors in cancer.

Trial ID NCT number	Conditions	Interventions	Study status
ProBio NCT03903835	Metastatic prostate cancer	<i>Experimental:</i> Capivasertib + Docetaxel <i>Active Comparator:</i> Control: Standard Care	Recruiting
CAPItello-290 NCT03997123	Triple-negative breast cancer	<i>Experimental:</i> Capivasertib + Paclitaxel <i>Placebo Comparator:</i> Placebo + Paclitaxel	Active not recruiting
CAPItello-291 NCT04305496	Locally advanced (inoperable) or metastatic breast cancer	<i>Experimental:</i> Capivasertib + Fulvestrant <i>Placebo Comparator:</i> Placebo + Fulvestrant	Active not recruiting
CAPItello-292 NCT04862663	Locally advanced (inoperable) or metastatic breast cancer	<i>Experimental:</i> Capivasertib + Fulvestrant + Palbociclib/Ribociclib <i>Active Comparator:</i> Fulvestrant + Palbociclib/Ribociclib	Recruiting
CAPItello-281 NCT04493853	Prostate cancer	<i>Experimental:</i> Capivasertib + Abiraterone <i>Placebo Comparator:</i> Placebo + Abiraterone	Active not recruiting
CAPItello-280 NCT05348577	Prostate cancer	<i>Experimental:</i> Capivasertib + Docetaxel <i>Placebo Comparator:</i> Placebo + Docetaxel	Active not recruiting
CAPIttrue NCT06635447	Breast cancer	<i>Experimental:</i> Cohort 1 & Cohort 2 with Capivasertib + Fulvestrant	Recruiting
CAPItana NCT06764186	Locally advanced or metastatic breast cancer	Capivasertib + Fulvestrant <i>Cohort 1:</i> patients without prior fulvestrant <i>Cohort 2:</i> patients with prior fulvestrant as the first line & progressed ≥ 6 months after the first dosing of fulvestrant	Recruiting
IPATential150 NCT03072238	Metastatic prostate cancer	<i>Experimental:</i> Ipatasertib + Abiraterone <i>Active Comparator:</i> Placebo + Abiraterone	Completed
IPATunity130 NCT03337724	Breast cancer	<i>Experimental:</i> Ipatasertib + Paclitaxel <i>Placebo Comparator:</i> Placebo + Paclitaxel	Completed
NCT04177108	Triple-negative breast cancer	<i>Experimental: Cohort 1</i> Arm A: Ipatasertib + Atezolizumab + Paclitaxel Arm B: Ipatasertib + Placebo + Paclitaxel Arm C: Placebo + Placebo + Paclitaxel <i>Experimental: Cohort 2</i> Arm A: Ipatasertib + Atezolizumab + Paclitaxel Arm B: Placebo + Atezolizumab + Paclitaxel	Completed
FINER NCT04650581	Breast cancer	<i>Experimental:</i> Ipatasertib + Fulvestrant <i>Placebo Comparator:</i> Placebo	Active not recruiting
UmbrellaMAX NCT05862285	Cancer	<i>Experimental:</i> Ipatasertib + Atezolizumab <i>Experimental:</i> Tiragolumab + Atezolizumab	Recruiting
NCT04851613	Breast cancer	<i>Experimental:</i> Afuresertib + Fulvestrant <i>Placebo Comparator:</i> Placebo + Fulvestrant	Recruiting
X-PECT NCT01097018	Colorectal cancer	<i>Active Comparator:</i> Perifosine + Capecitabine <i>Placebo Comparator:</i> Placebo + Capecitabine	Completed

poor results in patients with most cancers, including breast cancers, head and neck cancers, pancreatic cancer, and metastatic melanoma [96,99]. In contrast, perifosine combination regimens have demonstrated success in metastatic CRC, relapsed or refractory multiple myeloma, and glioma [96]. Notably, a phase II trial (NCT00398879) investigating perifosine in combination with capecitabine in previously treated metastatic CRC patients showed favorable clinical results compared to the combination of placebo and capecitabine [100]. However, the combination failed to demonstrate an OS survival benefit in refractory advanced CRC in the phase III XPECT trial (NCT01097018) [101].

6. Challenges and Future Directions

The Akt signaling pathway plays a central role in promoting tumor cell survival, growth, and metastasis, making it a key target for cancer therapy [10]. Despite promising outcomes in preclinical and early clinical studies, the therapeutic success of Akt inhibitors remains limited [18]. The complex nature of the Akt signaling pathway, along with the vast array of Akt substrates (Fig. 2), often contributes to the limited efficacy of Akt monotherapy and underscores the rationale for combination strategies to target tumors driven by hyperactivated Akt signaling.

Akt isoforms exhibit distinct biological functions in cancer, which contribute to differential sensitivities to Akt inhibitors. In particular, Akt1 and Akt2 play divergent roles in regulating tumor growth, invasion, and metastasis in multiple malignancies, and their alterations have been linked to varied sensitivity of cancer cells to selective Akt inhibitors [21,102]. For example, in breast cancer, Akt1 overexpression promotes tumor growth via upregulation of cyclin D1 and S6, while Akt1 inhibition or Akt2 overexpression enhances tumor invasion and migration via modulation of focal adhesion kinase 1 (FAK1), β 1-integrin, and matrix metalloproteinase 9 (MMP9) [21,102]. These observations highlight the significance of isoform-specific biology and downstream effectors in guiding patient stratification and the development of rational combination therapies.

Resistance to Akt-mediated targeted therapy remains a significant challenge. Cancer cells may evade Akt inhibition through multiple mechanisms, including crosstalk with the RAS/RAF/MAPK/ERK pathway, where mutations in RAS/RAF may lead to ERK hyperactivation, conferring resistance [15]. Other pathways, such as JAK/STAT [19], NOTCH [31], and TGF β [103], have also been implicated in resistance to Akt inhibitors. Akt inhibition may also disrupt the negative feedback mechanism intrinsic to PI3K/Akt signaling, triggering compensatory activation of downstream effectors such as mTORC1, which further drives therapeutic resistance [7]. These adaptive responses highlight the limitations of Akt monotherapy and emphasize the need to modulate Akt pathway inhibition to improve the efficacy of therapies targeting both Akt and compensatory pathways.

Akt signaling also impacts every organ system as a result of the broad cellular and physiological effects, contributing to the on-target toxicities of pan-Akt inhibitors [104]. A notable on-target adverse effect is hyperglycemia, often observed in patients receiving PI3K or Akt inhibitors, stemming from the disruption of Akt2-mediated glucose homeostasis [104]. The mutation landscape within the Akt pathway also strongly influences therapeutic outcomes. Tumors bearing the *AKT1-E17K* mutation, which promotes constitutive membrane localization of Akt, are hypersensitive to ATP-competitive inhibitors, but not allosteric inhibitors [105,106]. While tumors harboring genetic alterations such as *PIK3CA* mutations, *PTEN* loss, or *AKT1-E17K* mutations often show increased sensitivity to Akt inhibition [36,105,106], intratumoral heterogeneity remains a formidable challenge. Studies have reported that patients receiving genetically matched therapy showed higher objective tumor response rates and improved overall survival compared to those receiving unmatched treatments [107,108].

Emerging data also highlight the critical role of the tumor microenvironment (TME) in modulating responses to Akt-targeted therapies. The PI3K/Akt pathway is essential for T cell function, proliferation, survival, and differentiation; however, its constitutive activation can drive T cells towards terminal differentiation, impairing their cytotoxic action and facilitating immune evasion [109,110]. In this context, PI3K/Akt inhibitors have been shown to enhance anti-tumor immunity, potentially overcoming resistance to immunotherapies linked to TME-induced T-cell dysfunction [111]. Notably, the incorporation of Akt inhibitors during chimeric antigen receptor (CAR) T cell expansion has been found to promote a less differentiated, memory-like phenotype, leading to improved antitumor activity [112–114]. In the stromal compartment, the Akt pathway regulates the differentiation of various cell types into cancer-associated fibroblasts (CAFs), a key component of the TME. Akt activation in CAFs drives tumor progression by regulating cell proliferation, migration, vasculogenic mimicry, and stemness [115]. Furthermore, CAF-mediated Akt phosphorylation upregulates programmed death-ligand 1 (PD-L1), aiding immune evasion [116]. Akt3-positive CAFs have been shown to exhibit immunosuppressive characteristics and may serve as a potential biomarker for assessing CAF activity [117]. Although Akt inhibitors have been extensively investigated in cancer, maximizing their utility in targeting CAF remains challenging, highlighting the need for a deeper understanding of Akt-driven heterogeneity within the TME and its implications for optimizing therapeutic strategies.

Emerging technologies are rapidly transforming the precision medicine landscape for Akt-targeted cancer therapy. Single-cell multi-omics enables high-resolution mapping of transcriptional, epigenetic, and proteomic states at the individual cell level [118], and holds great potential for

uncovering cell-specific mechanisms of Akt regulation and identifying therapeutic vulnerabilities. Spatial multi-omics builds upon this by preserving tissue architecture and allowing spatial mapping of RNA, proteins, and metabolites within intact tumor samples, and allows researchers to investigate the organization of molecular and cellular interactions within the TME [119,120]. Given the central role of the PI3K/Akt pathway in immune evasion, metabolic reprogramming, and stromal cell interactions [109,110,121], spatial multi-omics offers a powerful platform for dissecting how Akt signaling heterogeneity across distinct cellular niches within the TME.

At the computational level, AI-driven platforms are accelerating drug discovery by integrating large-scale multi-omics datasets with pharmacokinetic and pharmacodynamic modelling. These tools help predict key molecular properties such as cytotoxicity, safety, metabolic stability, and off-target effects, significantly reducing the drug development timeline and cost [122,123]. AI-guided approaches may be particularly useful for designing isoform-selective Akt inhibitors with improved efficacy and safety.

In vivo clustered regularly interspaced short palindromic repeat (CRISPR) screening represents another powerful tool for dissecting the complexities of cancer within its native physiological context [124]. These functional screens can uncover driver genes in cancer [125] as well as key mediators of resistance to cancer immunotherapy [126], thereby identifying novel therapeutic targets. When applied to Akt-targeted therapies, *in vivo* CRISPR screening can identify actionable escape pathways and guide the development of more durable and effective treatment strategies. In parallel, preclinical models, such as organoids and patient-derived xenograft (PDX), offer physiologically relevant systems for studying Akt pathway modulation, validating inhibitors, and refining biomarker-informed treatment strategies [127]. Meanwhile, plasma cell-free DNA (cfDNA) analysis offers a minimally invasive strategy for detecting actionable mutations, enabling patient stratification, guiding therapeutic decisions, and monitoring tumor evolution over time [128].

Integrating these cutting-edge methodologies has the potential to revolutionize the landscape of Akt-targeted cancer therapy. However, key challenges remain, particularly integration, standardization, and clinical interpretation of complex datasets, as well as translation across diverse patient populations. Addressing these gaps will be essential to fully realize the promise of precision oncology in targeting the Akt pathway.

7. Conclusion

The Akt signaling is a crucial regulator of cellular functions and is involved in the initiation and progression of various cancers. Targeting this pathway shows promise for cancer treatment, but challenges like feedback loops, resistance mechanisms, and tumor heterogeneity hinder ther-

apeutic success. Despite substantial progress in targeting Akt, these obstacles still impact patient outcomes in clinical trials. Future research should focus on overcoming these challenges by prioritizing the development of rational Akt-based combination therapies, refining next-generation Akt inhibitors with enhanced isoform selectivity, expanding biomarker-driven patient stratification strategies, and dissecting feedback loops and compensatory pathways contributing to resistance. Addressing these factors could translate Akt-targeted strategies into more precise, durable, and effective cancer therapies.

Author Contributions

PDL conceptualized the study design. PDL, RB, LT, and CA conducted the literature search. PDL drafted the original manuscript. All authors reviewed and edited the manuscript. All authors contributed to editorial revisions, read and approved the final version of the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

References

- [1] Manning BD, Cantley LC. AKT/PKB signaling: navigating downstream. *Cell*. 2007; 129: 1261–1274. <https://doi.org/10.1016/j.cell.2007.06.009>.
- [2] Staal SP, Hartley JW, Rowe WP. Isolation of transforming murine leukemia viruses from mice with a high incidence of spontaneous lymphoma. *Proceedings of the National Academy of Sciences of the United States of America*. 1977; 74: 3065–3067. <https://doi.org/10.1073/pnas.74.7.3065>.
- [3] Bellacosa A, Testa JR, Staal SP, Tsichlis PN. A retroviral oncogene, akt, encoding a serine-threonine kinase containing an SH2-like region. *Science (New York, N.Y.)*. 1991; 254: 274–277. <https://doi.org/10.1126/science.254.5029.274>.
- [4] Jones PF, Jakubowicz T, Pitossi FJ, Maurer F, Hemmings BA. Molecular cloning and identification of a serine/threonine protein kinase of the second-messenger subfamily. *Proceedings of the National Academy of Sciences of the United States of America*. 1991; 88: 4171–4175. <https://doi.org/10.1073/pnas.88.10.4171>.
- [5] Franke TF, Yang SI, Chan TO, Datta K, Kazlauskas A, Morrison DK, *et al*. The protein kinase encoded by the Akt proto-oncogene is a target of the PDGF-activated phosphatidylinositol 3-kinase. *Cell*. 1995; 81: 727–736. [https://doi.org/10.1016/0092-8674\(95\)90534-0](https://doi.org/10.1016/0092-8674(95)90534-0).

- [6] Burgering BM, Coffey PJ. Protein kinase B (c-Akt) in phosphatidylinositol-3-OH kinase signal transduction. *Nature*. 1995; 376: 599–602. <https://doi.org/10.1038/376599a0>.
- [7] Bellacosa A, Kumar CC, Di Cristofano A, Testa JR. Activation of AKT kinases in cancer: implications for therapeutic targeting. *Advances in Cancer Research*. 2005; 94: 29–86. [https://doi.org/10.1016/S0065-230X\(05\)94002-5](https://doi.org/10.1016/S0065-230X(05)94002-5).
- [8] Engelman JA, Luo J, Cantley LC. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. *Nature Reviews. Genetics*. 2006; 7: 606–619. <https://doi.org/10.1038/nrg1879>.
- [9] Manning BD, Toker A. AKT/PKB Signaling: Navigating the Network. *Cell*. 2017; 169: 381–405. <https://doi.org/10.1016/j.cell.2017.04.001>.
- [10] Mayer IA, Arteaga CL. The PI3K/AKT Pathway as a Target for Cancer Treatment. *Annual Review of Medicine*. 2016; 67: 11–28. <https://doi.org/10.1146/annurev-med-062913-051343>.
- [11] He Y, Sun MM, Zhang GG, Yang J, Chen KS, Xu WW, *et al.* Targeting PI3K/Akt signal transduction for cancer therapy. *Signal Transduction and Targeted Therapy*. 2021; 6: 425. <https://doi.org/10.1038/s41392-021-00828-5>.
- [12] Vivanco I, Sawyers CL. The phosphatidylinositol 3-Kinase AKT pathway in human cancer. *Nature Reviews. Cancer*. 2002; 2: 489–501. <https://doi.org/10.1038/nrc839>.
- [13] Hennessy BT, Smith DL, Ram PT, Lu Y, Mills GB. Exploiting the PI3K/AKT pathway for cancer drug discovery. *Nature Reviews. Drug Discovery*. 2005; 4: 988–1004. <https://doi.org/10.1038/nrd1902>.
- [14] Zhang Y, Kwok-Shing Ng P, Kucherlapati M, Chen F, Liu Y, Tsang YH, *et al.* A Pan-Cancer Proteogenomic Atlas of PI3K/AKT/mTOR Pathway Alterations. *Cancer Cell*. 2017; 31: 820–832.e3. <https://doi.org/10.1016/j.ccell.2017.04.013>.
- [15] Leiphrakpam PD, Are C. PI3K/Akt/mTOR Signaling Pathway as a Target for Colorectal Cancer Treatment. *International Journal of Molecular Sciences*. 2024; 25: 3178. <https://doi.org/10.3390/ijms25063178>.
- [16] Sementino E, Hassan D, Bellacosa A, Testa JR. AKT and the Hallmarks of Cancer. *Cancer Research*. 2024; 84: 4126–4139. <https://doi.org/10.1158/0008-5472.CAN-24-1846>.
- [17] Shariati M, Meric-Bernstam F. Targeting AKT for cancer therapy. *Expert Opinion on Investigational Drugs*. 2019; 28: 977–988. <https://doi.org/10.1080/13543784.2019.1676726>.
- [18] Hassan D, Menges CW, Testa JR, Bellacosa A. AKT kinases as therapeutic targets. *Journal of Experimental & Clinical Cancer Research: CR*. 2024; 43: 313. <https://doi.org/10.1186/s13046-024-03207-4>.
- [19] Britschgi A, Andraos R, Brinkhaus H, Klebba I, Romanet V, Müller U, *et al.* JAK2/STAT5 inhibition circumvents resistance to PI3K/mTOR blockade: a rationale for cotargeting these pathways in metastatic breast cancer. *Cancer Cell*. 2012; 22: 796–811. <https://doi.org/10.1016/j.ccr.2012.10.023>.
- [20] Dummler B, Hemmings BA. Physiological roles of PKB/Akt isoforms in development and disease. *Biochemical Society Transactions*. 2007; 35: 231–235. <https://doi.org/10.1042/BS T0350231>.
- [21] Riggio M, Perrone MC, Polo ML, Rodriguez MJ, May M, Abba M, *et al.* AKT1 and AKT2 isoforms play distinct roles during breast cancer progression through the regulation of specific downstream proteins. *Scientific Reports*. 2017; 7: 44244. <https://doi.org/10.1038/srep44244>.
- [22] Fresno Vara JA, Casado E, de Castro J, Cejas P, Belda-Iniesta C, González-Barón M. PI3K/Akt signalling pathway and cancer. *Cancer Treatment Reviews*. 2004; 30: 193–204. <https://doi.org/10.1016/j.ctrv.2003.07.007>.
- [23] Keniry M, Parsons R. The role of PTEN signaling perturbations in cancer and in targeted therapy. *Oncogene*. 2008; 27: 5477–5485. <https://doi.org/10.1038/onc.2008.248>.
- [24] Engelman JA. Targeting PI3K signalling in cancer: opportunities, challenges and limitations. *Nature Reviews. Cancer*. 2009; 9: 550–562. <https://doi.org/10.1038/nrc2664>.
- [25] Alessi DR, James SR, Downes CP, Holmes AB, Gaffney PR, Reese CB, *et al.* Characterization of a 3-phosphoinositide-dependent protein kinase which phosphorylates and activates protein kinase Balph. *Current Biology: CB*. 1997; 7: 261–269. [https://doi.org/10.1016/S0960-9822\(06\)00122-9](https://doi.org/10.1016/S0960-9822(06)00122-9).
- [26] Vander Haar E, Lee SI, Bandhakavi S, Griffin TJ, Kim DH. Insulin signalling to mTOR mediated by the Akt/PKB substrate PRAS40. *Nature Cell Biology*. 2007; 9: 316–323. <https://doi.org/10.1038/ncb1547>.
- [27] Hemmings BA, Restuccia DF. PI3K-PKB/Akt pathway. *Cold Spring Harbor Perspectives in Biology*. 2012; 4: a011189. <https://doi.org/10.1101/cshperspect.a011189>.
- [28] Dibble CC, Manning BD. Signal integration by mTORC1 coordinates nutrient input with biosynthetic output. *Nature Cell Biology*. 2013; 15: 555–564. <https://doi.org/10.1038/ncb2763>.
- [29] Zimmermann S, Moelling K. Phosphorylation and regulation of Raf by Akt (protein kinase B). *Science (New York, N.Y.)*. 1999; 286: 1741–1744. <https://doi.org/10.1126/science.286.5445.1741>.
- [30] Kim AH, Khursigara G, Sun X, Franke TF, Chao MV. Akt phosphorylates and negatively regulates apoptosis signal-regulating kinase 1. *Molecular and Cellular Biology*. 2001; 21: 893–901. <https://doi.org/10.1128/MCB.21.3.893-901.2001>.
- [31] Larue L, Bellacosa A. Epithelial-mesenchymal transition in development and cancer: role of phosphatidylinositol 3' kinase/AKT pathways. *Oncogene*. 2005; 24: 7443–7454. <https://doi.org/10.1038/sj.onc.1209091>.
- [32] Glaviano A, Foo ASC, Lam HY, Yap KCH, Jacot W, Jones RH, *et al.* PI3K/AKT/mTOR signaling transduction pathway and targeted therapies in cancer. *Molecular Cancer*. 2023; 22: 138. <https://doi.org/10.1186/s12943-023-01827-6>.
- [33] Mukhopadhyay S, Vander Heiden MG, McCormick F. The Metabolic Landscape of RAS-Driven Cancers from biology to therapy. *Nature Cancer*. 2021; 2: 271–283. <https://doi.org/10.1038/s43018-021-00184-x>.
- [34] Pearson HB, Li J, Meniel VS, Fennell CM, Waring P, Montgomery KG, *et al.* Identification of *Pik3ca* Mutation as a Genetic Driver of Prostate Cancer That Cooperates with *Pten* Loss to Accelerate Progression and Castration-Resistant Growth. *Cancer Discovery*. 2018; 8: 764–779. <https://doi.org/10.1158/2159-8290.CD-17-0867>.
- [35] Parsons DW, Wang TL, Samuels Y, Bardelli A, Cummins JM, DeLong L, *et al.* Colorectal cancer: mutations in a signalling pathway. *Nature*. 2005; 436: 792. <https://doi.org/10.1038/436792a>.
- [36] Carpten JD, Faber AL, Horn C, Donoho GP, Briggs SL, Robbins CM, *et al.* A transforming mutation in the pleckstrin homology domain of AKT1 in cancer. *Nature*. 2007; 448: 439–444. <https://doi.org/10.1038/nature05933>.
- [37] Rudolph M, Anzeneder T, Schulz A, Beckmann G, Byrne AT, Jeffers M, *et al.* AKT1 (E17K) mutation profiling in breast cancer: prevalence, concurrent oncogenic alterations, and blood-based detection. *BMC Cancer*. 2016; 16: 622. <https://doi.org/10.1186/s12885-016-2626-1>.
- [38] Chen Y, Huang L, Dong Y, Tao C, Zhang R, Shao H, *et al.* Effect of AKT1 (p. E17K) Hotspot Mutation on Malignant Tumorigenesis and Prognosis. *Frontiers in Cell and Developmental Biology*. 2020; 8: 573599. <https://doi.org/10.3389/fcell.2020.573599>.
- [39] Sun M, Wang G, Paciga JE, Feldman RI, Yuan ZQ, Ma XL, *et al.* AKT1/PKBalpa kinase is frequently elevated in human cancers and its constitutive activation is required for oncogenic transfor-

- mation in NIH3T3 cells. *The American Journal of Pathology*. 2001; 159: 431–437. [https://doi.org/10.1016/s0002-9440\(10\)61714-2](https://doi.org/10.1016/s0002-9440(10)61714-2).
- [40] Staal SP. Molecular cloning of the akt oncogene and its human homologues AKT1 and AKT2: amplification of AKT1 in a primary human gastric adenocarcinoma. *Proceedings of the National Academy of Sciences of the United States of America*. 1987; 84: 5034–5037. <https://doi.org/10.1073/pnas.84.14.5034>.
- [41] Kandath C, McLellan MD, Vandin F, Ye K, Niu B, Lu C, *et al*. Mutational landscape and significance across 12 major cancer types. *Nature*. 2013; 502: 333–339. <https://doi.org/10.1038/nature12634>.
- [42] Cheng JQ, Godwin AK, Bellacosa A, Taguchi T, Franke TF, Hamilton TC, *et al*. AKT2, a putative oncogene encoding a member of a subfamily of protein-serine/threonine kinases, is amplified in human ovarian carcinomas. *Proceedings of the National Academy of Sciences of the United States of America*. 1992; 89: 9267–9271. <https://doi.org/10.1073/pnas.89.19.9267>.
- [43] Bellacosa A, de Feo D, Godwin AK, Bell DW, Cheng JQ, Altomare DA, *et al*. Molecular alterations of the AKT2 oncogene in ovarian and breast carcinomas. *International Journal of Cancer*. 1995; 64: 280–285. <https://doi.org/10.1002/ijc.2910640412>.
- [44] Nakayama K, Nakayama N, Jinawath N, Salani R, Kurman RJ, Shih IM, *et al*. Amplicon profiles in ovarian serous carcinomas. *International Journal of Cancer*. 2007; 120: 2613–2617. <https://doi.org/10.1002/ijc.22609>.
- [45] Altomare DA, Tanno S, De Rienzo A, Klein-Szanto AJ, Tanno S, Skele KL, *et al*. Frequent activation of AKT2 kinase in human pancreatic carcinomas. *Journal of Cellular Biochemistry*. 2002; 87: 470–476. <https://doi.org/10.1002/jcb.10287>.
- [46] Hinz N, Jücker M. Distinct functions of AKT isoforms in breast cancer: a comprehensive review. *Cell Communication and Signaling: CCS*. 2019; 17: 154. <https://doi.org/10.1186/s12964-019-0450-3>.
- [47] Hashimoto K, Mori N, Tamesa T, Okada T, Kawauchi S, Oga A, *et al*. Analysis of DNA copy number aberrations in hepatitis C virus-associated hepatocellular carcinomas by conventional CGH and array CGH. *Modern Pathology: an Official Journal of the United States and Canadian Academy of Pathology, Inc*. 2004; 17: 617–622. <https://doi.org/10.1038/modpatho.13800107>.
- [48] Cristiano BE, Chan JC, Hannan KM, Lundie NA, Marmy-Conus NJ, Campbell IG, *et al*. A specific role for AKT3 in the genesis of ovarian cancer through modulation of G(2)-M phase transition. *Cancer Research*. 2006; 66: 11718–11725. <https://doi.org/10.1158/0008-5472.CAN-06-1968>.
- [49] Altomare DA, Testa JR. Perturbations of the AKT signaling pathway in human cancer. *Oncogene*. 2005; 24: 7455–7464. <https://doi.org/10.1038/sj.onc.1209085>.
- [50] Stahl JM, Sharma A, Cheung M, Zimmerman M, Cheng JQ, Bosenberg MW, *et al*. Deregulated Akt3 activity promotes development of malignant melanoma. *Cancer Research*. 2004; 64: 7002–7010. <https://doi.org/10.1158/0008-5472.CAN-04-1399>.
- [51] Davies MA, Stemke-Hale K, Tellez C, Calderone TL, Deng W, Prieto VG, *et al*. A novel AKT3 mutation in melanoma tumours and cell lines. *British Journal of Cancer*. 2008; 99: 1265–1268. <https://doi.org/10.1038/sj.bjc.6604637>.
- [52] Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell*. 2000; 100: 57–70. [https://doi.org/10.1016/s0092-8674\(00\)81683-9](https://doi.org/10.1016/s0092-8674(00)81683-9).
- [53] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011; 144: 646–674. <https://doi.org/10.1016/j.cell.2011.02.013>.
- [54] Mehrotra S, Languino LR, Raskett CM, Mercurio AM, Dohi T, Altieri DC. IAP regulation of metastasis. *Cancer Cell*. 2010; 17: 53–64. <https://doi.org/10.1016/j.ccr.2009.11.021>.
- [55] Agarwal E, Chaudhuri A, Leiphrakpam PD, Haferbier KL, Brattain MG, Chowdhury S. Akt inhibitor MK-2206 promotes anti-tumor activity and cell death by modulation of AIF and Ezrin in colorectal cancer. *BMC Cancer*. 2014; 14: 145. <https://doi.org/10.1186/1471-2407-14-145>.
- [56] Yang ZJ, Chee CE, Huang S, Sinicrope FA. The role of autophagy in cancer: therapeutic implications. *Molecular Cancer Therapeutics*. 2011; 10: 1533–1541. <https://doi.org/10.1158/1535-7163.MCT-11-0047>.
- [57] Tsai PJ, Lai YH, Manne RK, Tsai YS, Sarbassov D, Lin HK. Akt: a key transducer in cancer. *Journal of Biomedical Science*. 2022; 29: 76. <https://doi.org/10.1186/s12929-022-00860-9>.
- [58] Testa JR, Bellacosa A. AKT plays a central role in tumorigenesis. *Proceedings of the National Academy of Sciences of the United States of America*. 2001; 98: 10983–10985. <https://doi.org/10.1073/pnas.211430998>.
- [59] Bochis OV, Irimie A, Pichler M, Berindan-Neagoe I. The role of Skp2 and its substrate CDKN1B (p27) in colorectal cancer. *Journal of Gastrointestinal and Liver Diseases: JGLD*. 2015; 24: 225–234. <https://doi.org/10.15403/jgld.2014.1121.242.skp2>.
- [60] Inoki K, Li Y, Zhu T, Wu J, Guan KL. TSC2 is phosphorylated and inhibited by Akt and suppresses mTOR signalling. *Nature Cell Biology*. 2002; 4: 648–657. <https://doi.org/10.1038/ncb839>.
- [61] Hay N. The Akt-mTOR tango and its relevance to cancer. *Cancer Cell*. 2005; 8: 179–183. <https://doi.org/10.1016/j.ccr.2005.08.008>.
- [62] Chibaya L, Karim B, Zhang H, Jones SN. Mdm2 phosphorylation by Akt regulates the p53 response to oxidative stress to promote cell proliferation and tumorigenesis. *Proceedings of the National Academy of Sciences of the United States of America*. 2021; 118: e2003193118. <https://doi.org/10.1073/pnas.2003193118>.
- [63] Leiphrakpam PD, Brattain MG, Black JD, Wang J. TGF β and IGF1R signaling activates protein kinase A through differential regulation of ezrin phosphorylation in colon cancer cells. *The Journal of Biological Chemistry*. 2018; 293: 8242–8254. <https://doi.org/10.1074/jbc.RA117.001299>.
- [64] Elstrom RL, Bauer DE, Buzzai M, Karnauskas R, Harris MH, Plas DR, *et al*. Akt stimulates aerobic glycolysis in cancer cells. *Cancer Research*. 2004; 64: 3892–3899. <https://doi.org/10.1158/0008-5472.CAN-03-2904>.
- [65] Hoxhaj G, Manning BD. The PI3K-AKT network at the interface of oncogenic signalling and cancer metabolism. *Nature Reviews. Cancer*. 2020; 20: 74–88. <https://doi.org/10.1038/s41568-019-0216-7>.
- [66] Fang M, Shen Z, Huang S, Zhao L, Chen S, Mak TW, *et al*. The ER UDPase ENTPD5 promotes protein N-glycosylation, the Warburg effect, and proliferation in the PTEN pathway. *Cell*. 2010; 143: 711–724. <https://doi.org/10.1016/j.cell.2010.10.010>.
- [67] Revathidevi S, Munirajan AK. Akt in cancer: Mediator and more. *Seminars in Cancer Biology*. 2019; 59: 80–91. <https://doi.org/10.1016/j.semcancer.2019.06.002>.
- [68] Murugan AK. mTOR: Role in cancer, metastasis and drug resistance. *Seminars in Cancer Biology*. 2019; 59: 92–111. <https://doi.org/10.1016/j.semcancer.2019.07.003>.
- [69] Luo Z, Fujio Y, Kureishi Y, Rudic RD, Daumerie G, Fulton D, *et al*. Acute modulation of endothelial Akt/PKB activity alters nitric oxide-dependent vasomotor activity in vivo. *The Journal of Clinical Investigation*. 2000; 106: 493–499. <https://doi.org/10.1172/JCI9419>.
- [70] Semenza GL. HIF-1 and tumor progression: pathophysiology and therapeutics. *Trends in Molecular Medicine*. 2002; 8: S62–S67. [https://doi.org/10.1016/s1471-4914\(02\)02317-1](https://doi.org/10.1016/s1471-4914(02)02317-1).
- [71] Fukuhara S, Sako K, Minami T, Noda K, Kim HZ, Kodama T, *et al*. Differential function of Tie2 at cell-cell contacts and cell-substratum contacts regulated by angiotensin-1. *Nature Cell Bi-*

- ology. 2008; 10: 513–526. <https://doi.org/10.1038/ncb1714>.
- [72] Enomoto A, Murakami H, Asai N, Morone N, Watanabe T, Kawai K, *et al.* Akt/PKB regulates actin organization and cell motility via Girdin/APE. *Developmental Cell*. 2005; 9: 389–402. <https://doi.org/10.1016/j.devcel.2005.08.001>.
- [73] Zhou GL, Zhuo Y, King CC, Fryer BH, Bokoch GM, Field J. Akt phosphorylation of serine 21 on Pak1 modulates Nck binding and cell migration. *Molecular and Cellular Biology*. 2003; 23: 8058–8069. <https://doi.org/10.1128/MCB.23.22.8058-8069.2003>.
- [74] Bahrami A, Khazaei M, Hasanzadeh M, ShahidSales S, Joudi Mashhad M, Farazestanian M, *et al.* Therapeutic Potential of Targeting PI3K/AKT Pathway in Treatment of Colorectal Cancer: Rational and Progress. *Journal of Cellular Biochemistry*. 2018; 119: 2460–2469. <https://doi.org/10.1002/jcb.25950>.
- [75] Mundi PS, Sachdev J, McCourt C, Kalinsky K. AKT in cancer: new molecular insights and advances in drug development. *British Journal of Clinical Pharmacology*. 2016; 82: 943–956. <https://doi.org/10.1111/bcp.13021>.
- [76] Spencer A, Yoon SS, Harrison SJ, Morris SR, Smith DA, Brigandi RA, *et al.* The novel AKT inhibitor afuresertib shows favorable safety, pharmacokinetics, and clinical activity in multiple myeloma. *Blood*. 2014; 124: 2190–2195. <https://doi.org/10.1182/blood-2014-03-559963>.
- [77] Blagden SP, Hamilton AL, Mileshekin L, Wong S, Michael A, Hall M, *et al.* Phase IB Dose Escalation and Expansion Study of AKT Inhibitor Afuresertib with Carboplatin and Paclitaxel in Recurrent Platinum-resistant Ovarian Cancer. *Clinical Cancer Research: an Official Journal of the American Association for Cancer Research*. 2019; 25: 1472–1478. <https://doi.org/10.1158/1078-0432.CCR-18-2277>.
- [78] Davies BR, Greenwood H, Dudley P, Crafter C, Yu DH, Zhang J, *et al.* Preclinical pharmacology of AZD5363, an inhibitor of AKT: pharmacodynamics, antitumor activity, and correlation of monotherapy activity with genetic background. *Molecular Cancer Therapeutics*. 2012; 11: 873–887. <https://doi.org/10.1158/1535-7163.MCT-11-0824-T>.
- [79] Kalinsky K, Hong F, McCourt CK, Sachdev JC, Mitchell EP, Zwiebel JA, *et al.* Effect of Capiasertib in Patients With an AKT1 E17K-Mutated Tumor: NCI-MATCH Subprotocol EAY131-Y Nonrandomized Trial. *JAMA Oncology*. 2021; 7: 271–278. <https://doi.org/10.1001/jamaoncol.2020.6741>.
- [80] Smyth LM, Tamura K, Oliveira M, Ciruelos EM, Mayer IA, Sablin MP, *et al.* Capiasertib, an AKT Kinase Inhibitor, as Monotherapy or in Combination with Fulvestrant in Patients with *AKT1*^{E17K}-Mutant, ER-Positive Metastatic Breast Cancer. *Clinical Cancer Research: an Official Journal of the American Association for Cancer Research*. 2020; 26: 3947–3957. <https://doi.org/10.1158/1078-0432.CCR-19-3953>.
- [81] Schmid P, Abraham J, Chan S, Wheatley D, Brunt AM, Nemsadze G, *et al.* Capiasertib Plus Paclitaxel Versus Placebo Plus Paclitaxel As First-Line Therapy for Metastatic Triple-Negative Breast Cancer: The PAKT Trial. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2020; 38: 423–433. <https://doi.org/10.1200/JCO.19.00368>.
- [82] Robertson JFR, Coleman RE, Cheung KL, Evans A, Holcombe C, Skene A, *et al.* Proliferation and AKT Activity Biomarker Analyses after Capiasertib (AZD5363) Treatment of Patients with ER⁺ Invasive Breast Cancer (STAKT). *Clinical Cancer Research: an Official Journal of the American Association for Cancer Research*. 2020; 26: 1574–1585. <https://doi.org/10.1158/1078-0432.CCR-19-3053>.
- [83] Turner NC, Oliveira M, Howell SJ, Dalenc F, Cortes J, Gomez Moreno HL, *et al.* Capiasertib in Hormone Receptor-Positive Advanced Breast Cancer. *The New England Journal of Medicine*. 2023; 388: 2058–2070. <https://doi.org/10.1056/NEJMoa2214131>.
- [84] Mullard A. FDA approves first-in-class AKT inhibitor. *Nature Reviews. Drug Discovery*. 2024; 23: 9. <https://doi.org/10.1038/d41573-023-00202-w>.
- [85] Lin J, Sampath D, Nannini MA, Lee BB, Degtyarev M, Oeh J, *et al.* Targeting activated Akt with GDC-0068, a novel selective Akt inhibitor that is efficacious in multiple tumor models. *Clinical Cancer Research: an Official Journal of the American Association for Cancer Research*. 2013; 19: 1760–1772. <https://doi.org/10.1158/1078-0432.CCR-12-3072>.
- [86] Saura C, Roda D, Roselló S, Oliveira M, Macarulla T, Pérez-Fidalgo JA, *et al.* 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. *Cancer Discovery*. 2017; 7: 102–113. <https://doi.org/10.1158/2159-8290.CD-16-0512>.
- [87] Sweeney C, Bracarda S, Sternberg CN, Chi KN, Olmos D, Sandhu S, *et al.* Ipatasertib plus abiraterone and prednisolone in metastatic castration-resistant prostate cancer (IPATential150): a multicentre, randomised, double-blind, phase 3 trial. *Lancet (London, England)*. 2021; 398: 131–142. [https://doi.org/10.1016/S0140-6736\(21\)00580-8](https://doi.org/10.1016/S0140-6736(21)00580-8).
- [88] Turner N, Dent RA, O'Shaughnessy J, Kim SB, Isakoff SJ, Barrios C, *et al.* Ipatasertib plus paclitaxel for PIK3CA/AKT1/PTEN-altered hormone receptor-positive HER2-negative advanced breast cancer: primary results from cohort B of the IPATunity130 randomized phase 3 trial. *Breast Cancer Research and Treatment*. 2022; 191: 565–576. <https://doi.org/10.1007/s10549-021-06450-x>.
- [89] Janku F, Yap TA, Meric-Bernstam F. Targeting the PI3K pathway in cancer: are we making headway? *Nature Reviews. Clinical Oncology*. 2018; 15: 273–291. <https://doi.org/10.1038/nrclinonc.2018.28>.
- [90] Yap TA, Yan L, Patnaik A, Tunariu N, Biondo A, Fearon I, *et al.* Interrogating two schedules of the AKT inhibitor MK-2206 in patients with advanced solid tumors incorporating novel pharmacodynamic and functional imaging biomarkers. *Clinical Cancer Research: an Official Journal of the American Association for Cancer Research*. 2014; 20: 5672–5685. <https://doi.org/10.1158/1078-0432.CCR-14-0868>.
- [91] Xing Y, Lin NU, Maurer MA, Chen H, Mahvash A, Sahin A, *et al.* Phase II trial of AKT inhibitor MK-2206 in patients with advanced breast cancer who have tumors with PIK3CA or AKT mutations, and/or PTEN loss/PTEN mutation. *Breast Cancer Research*. 2019; 21: 78. <https://doi.org/10.1186/s13058-019-1154-8>.
- [92] Do K, Speranza G, Bishop R, Khin S, Rubinstein L, Kinders RJ, *et al.* Biomarker-driven phase 2 study of MK-2206 and selumetinib (AZD6244, ARRY-142886) in patients with colorectal cancer. *Investigational New Drugs*. 2015; 33: 720–728. <https://doi.org/10.1007/s10637-015-0212-z>.
- [93] Dasari A, Overman MJ, Fogelman DR, Kee BK, Menter D, Raghav KPS, *et al.* A phase II and co-clinical study of an AKT inhibitor in patients (pts) with biomarker-enriched, previously treated metastatic colorectal cancer (mCRC). *Journal of Clinical Oncology*. 2016; 34: 3563. https://doi.org/10.1200/JCO.2016.34.15_suppl.3563.
- [94] Chung V, McDonough S, Philip PA, Cardin D, Wang-Gillam A, Hui L, *et al.* Effect of Selumetinib and MK-2206 vs Oxaliplatin and Fluorouracil in Patients With Metastatic Pancreatic Cancer After Prior Therapy: SWOG S1115 Study Randomized Clinical Trial. *JAMA Oncology*. 2017; 3: 516–522. <https://doi.org/10.1001/jamaoncol.2016.5383>.
- [95] Kondapaka SB, Singh SS, Dasmahapatra GP, Sausville EA, Roy KK. Perifosine, a novel alkylphospholipid, inhibits protein kinase B activation. *Molecular Cancer Therapeutics*. 2003; 2:

1093–1103.

- [96] Richardson PG, Eng C, Kolesar J, Hideshima T, Anderson KC. Perifosine, an oral, anti-cancer agent and inhibitor of the Akt pathway: mechanistic actions, pharmacodynamics, pharmacokinetics, and clinical activity. *Expert Opinion on Drug Metabolism & Toxicology*. 2012; 8: 623–633. <https://doi.org/10.1517/17425255.2012.681376>.
- [97] Crul M, Rosing H, de Klerk GJ, Dubbelman R, Traiser M, Reichert S, *et al.* Phase I and pharmacological study of daily oral administration of perifosine (D-21266) in patients with advanced solid tumours. *European Journal of Cancer* (Oxford, England: 1990). 2002; 38: 1615–1621. [https://doi.org/10.1016/s0959-8049\(02\)00127-2](https://doi.org/10.1016/s0959-8049(02)00127-2).
- [98] Becher OJ, Millard NE, Modak S, Kushner BH, Haque S, Spasojevic I, *et al.* A phase I study of single-agent perifosine for recurrent or refractory pediatric CNS and solid tumors. *PloS One*. 2017; 12: e0178593. <https://doi.org/10.1371/journal.pone.0178593>.
- [99] Pal I, Mandal M. PI3K and Akt as molecular targets for cancer therapy: current clinical outcomes. *Acta Pharmacologica Sinica*. 2012; 33: 1441–1458. <https://doi.org/10.1038/aps.2012.72>.
- [100] Bendell JC, Nemunaitis J, Vukelja SJ, Hagenstad C, Campos LT, Hermann RC, *et al.* Randomized placebo-controlled phase II trial of perifosine plus capecitabine as second- or third-line therapy in patients with metastatic colorectal cancer. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2011; 29: 4394–4400. <https://doi.org/10.1200/JCO.2011.36.1980>.
- [101] Eng C, Bendell JC, Kopetz S, Tarco E, Xiao L, Ying J, *et al.* Impact of PI3K aberrations on efficacy of perifosine (P), x-PECT: A phase III randomized study of P plus capecitabine (PC) versus placebo plus capecitabine (C) in refractory metastatic colorectal cancer (mCRC) patients. *Journal of Clinical Oncology*. 2014; 32: 3606. https://doi.org/10.1200/jco.2014.32.15_suppl.3606.
- [102] Page N, Wappett M, O'Dowd CR, O'Rourke M, Gavory G, Zhang L, *et al.* Identification and development of a subtype-selective allosteric AKT inhibitor suitable for clinical development. *Scientific Reports*. 2022; 12: 15715. <https://doi.org/10.1038/s41598-022-20208-5>.
- [103] Zhang L, Zhou F, ten Dijke P. Signaling interplay between transforming growth factor- β receptor and PI3K/AKT pathways in cancer. *Trends in Biochemical Sciences*. 2013; 38: 612–620. <https://doi.org/10.1016/j.tibs.2013.10.001>.
- [104] Jansen VM, Mayer IA, Arteaga CL. Is There a Future for AKT Inhibitors in the Treatment of Cancer? *Clinical Cancer Research: an Official Journal of the American Association for Cancer Research*. 2016; 22: 2599–2601. <https://doi.org/10.1158/1078-0432.CCR-16-0100>.
- [105] Shrestha Bhattarai T, Shamu T, Gorelick AN, Chang MT, Chakravarty D, Gavrilu EI, *et al.* AKT mutant allele-specific activation dictates pharmacologic sensitivities. *Nature Communications*. 2022; 13: 2111. <https://doi.org/10.1038/s41467-022-29638-1>.
- [106] Schmid P, Turner NC, Barrios CH, Isakoff SJ, Kim SB, Sablin MP, *et al.* First-Line Ipatasertib, Atezolizumab, and Taxane Triplet for Metastatic Triple-Negative Breast Cancer: Clinical and Biomarker Results. *Clinical Cancer Research: an Official Journal of the American Association for Cancer Research*. 2024; 30: 767–778. <https://doi.org/10.1158/1078-0432.CCR-23-2084>.
- [107] Stockley TL, Oza AM, Berman HK, Leighl NB, Knox JJ, Shepherd FA, *et al.* Molecular profiling of advanced solid tumors and patient outcomes with genotype-matched clinical trials: the Princess Margaret IMPACT/COMPACT trial. *Genome Medicine*. 2016; 8: 109. <https://doi.org/10.1186/s13073-016-0364-2>.
- [108] Tsimberidou AM, Hong DS, Wheler JJ, Falchook GS, Janku F, Naing A, *et al.* Long-term overall survival and prognostic score predicting survival: the IMPACT study in precision medicine. *Journal of Hematology & Oncology*. 2019; 12: 145. <https://doi.org/10.1186/s13045-019-0835-1>.
- [109] Noh KH, Kang TH, Kim JH, Pai SI, Lin KY, Hung CF, *et al.* Activation of Akt as a mechanism for tumor immune evasion. *Molecular Therapy: the Journal of the American Society of Gene Therapy*. 2009; 17: 439–447. <https://doi.org/10.1038/mt.2008.255>.
- [110] Lim EL, Okkenhaug K. Phosphoinositide 3-kinase δ is a regulatory T-cell target in cancer immunotherapy. *Immunology*. 2019; 157: 210–218. <https://doi.org/10.1111/imm.13082>.
- [111] Caforio M, de Billy E, De Angelis B, Iacovelli S, Quintarelli C, Paganelli V, *et al.* PI3K/Akt Pathway: The Indestructible Role of a Vintage Target as a Support to the Most Recent Immunotherapeutic Approaches. *Cancers*. 2021; 13: 4040. <https://doi.org/10.3390/cancers13164040>.
- [112] Klebanoff CA, Crompton JG, Leonard AJ, Yamamoto TN, Chandran SS, Eil RL, *et al.* Inhibition of AKT signaling uncouples T cell differentiation from expansion for receptor-engineered adoptive immunotherapy. *JCI Insight*. 2017; 2: e95103. <https://doi.org/10.1172/jci.insight.95103>.
- [113] Zhang Q, Ding J, Sun S, Liu H, Lu M, Wei X, *et al.* Akt inhibition at the initial stage of CAR-T preparation enhances the CAR-positive expression rate, memory phenotype and in vivo efficacy. *American Journal of Cancer Research*. 2019; 9: 2379–2396.
- [114] Mehra V, Agliardi G, Dias Alves Pinto J, Shafat MS, Garai AC, Green L, *et al.* AKT inhibition generates potent polyfunctional clinical grade AUTO1 CAR T-cells, enhancing function and survival. *Journal for Immunotherapy of Cancer*. 2023; 11: e007002. <https://doi.org/10.1136/jitc-2023-007002>.
- [115] Wu F, Yang J, Liu J, Wang Y, Mu J, Zeng Q, *et al.* Signaling pathways in cancer-associated fibroblasts and targeted therapy for cancer. *Signal Transduction and Targeted Therapy*. 2021; 6: 218. <https://doi.org/10.1038/s41392-021-00641-0>.
- [116] Gao Y, Sun Z, Gu J, Li Z, Xu X, Xue C, *et al.* Cancer-Associated Fibroblasts Promote the Upregulation of PD-L1 Expression Through Akt Phosphorylation in Colorectal Cancer. *Frontiers in Oncology*. 2021; 11: 748465. <https://doi.org/10.3389/fonc.2021.748465>.
- [117] Takahashi H, Rokudai S, Kawabata-Iwakawa R, Sakakura K, Oyama T, Nishiyama M, *et al.* AKT3 Is a Novel Regulator of Cancer-Associated Fibroblasts in Head and Neck Squamous Cell Carcinoma. *Cancers*. 2021; 13: 1233. <https://doi.org/10.3390/cancers13061233>.
- [118] Liang A, Kong Y, Chen Z, Qiu Y, Wu Y, Zhu X, *et al.* Advancements and applications of single-cell multi-omics techniques in cancer research: Unveiling heterogeneity and paving the way for precision therapeutics. *Biochemistry and Biophysics Reports*. 2024; 37: 101589. <https://doi.org/10.1016/j.bbrep.2023.101589>.
- [119] Wu Y, Cheng Y, Wang X, Fan J, Gao Q. Spatial omics: Navigating to the golden era of cancer research. *Clinical and Translational Medicine*. 2022; 12: e696. <https://doi.org/10.1002/ctm2.696>.
- [120] Di Mauro F, Arbore G. Spatial Dissection of the Immune Landscape of Solid Tumors to Advance Precision Medicine. *Cancer Immunology Research*. 2024; 12: 800–813. <https://doi.org/10.1158/2326-6066.CIR-23-0699>.
- [121] Su WY, Tian LY, Guo LP, Huang LQ, Gao WY. PI3K signaling-regulated metabolic reprogramming: From mechanism to application. *Biochimica et Biophysica Acta. Reviews on Cancer*. 2023; 1878: 188952. <https://doi.org/10.1016/j.bbcan.2023.188952>.

- [122] Paul D, Sanap G, Shenoy S, Kalyane D, Kalia K, Tekade RK. Artificial intelligence in drug discovery and development. *Drug Discovery Today*. 2021; 26: 80–93. <https://doi.org/10.1016/j.drudis.2020.10.010>.
- [123] Mao Y, Shangguan D, Huang Q, Xiao L, Cao D, Zhou H, *et al.* Emerging artificial intelligence-driven precision therapies in tumor drug resistance: recent advances, opportunities, and challenges. *Molecular Cancer*. 2025; 24: 123. <https://doi.org/10.1186/s12943-025-02321-x>.
- [124] Chow RD, Chen S. Cancer CRISPR Screens In Vivo. *Trends in Cancer*. 2018; 4: 349–358. <https://doi.org/10.1016/j.trecan.2018.03.002>.
- [125] Dai M, Yan G, Wang N, Daliah G, Edick AM, Poulet S, *et al.* In vivo genome-wide CRISPR screen reveals breast cancer vulnerabilities and synergistic mTOR/Hippo targeted combination therapy. *Nature Communications*. 2021; 12: 3055. <https://doi.org/10.1038/s41467-021-23316-4>.
- [126] Manguso RT, Pope HW, Zimmer MD, Brown FD, Yates KB, Miller BC, *et al.* In vivo CRISPR screening identifies Ptpn2 as a cancer immunotherapy target. *Nature*. 2017; 547: 413–418. <https://doi.org/10.1038/nature23270>.
- [127] Tufail M, Hu JJ, Liang J, He CY, Wan WD, Huang YQ, *et al.* Predictive, preventive, and personalized medicine in breast cancer: targeting the PI3K pathway. *Journal of Translational Medicine*. 2024; 22: 15. <https://doi.org/10.1186/s12967-023-04841-w>.
- [128] Govindarajan M, Wohlmuth C, Waas M, Bernardini MQ, Kislinger T. High-throughput approaches for precision medicine in high-grade serous ovarian cancer. *Journal of Hematology & Oncology*. 2020; 13: 134. <https://doi.org/10.1186/s13045-020-00971-6>.