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Review

Inhibition of the PI3K/AKT/mTOR pathway in pancreatic cancer: is it a worthwhile endeavor?

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***Abstract*:** Pancreatic cancer (PC) is an aggressive disease that is challenging to treat and is associated with a high mortality rate. The most common type of PC is pancreatic ductal adenocarcinoma (PDAC), and the existing treatment options are insufficient for PDAC patients. Due to the complexity and heterogeneity of PDAC, personalized medicine is necessary for effectively treating this illness. To achieve this, it is essential to understand the mechanism of PDAC carcinogenesis. Targeted therapies are a promising strategy to improve patient outcomes. Aberrant activation of the phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) signaling pathway plays a crucial role in PC pathogenesis, from initiation to progression. This review provides a comprehensive overview of the current state of knowledge regarding the PI3K pathway in PDAC, summarizes clinical data on PI3K pathway inhibition in PDAC, and explores potential effective combinations that are a promising direction requiring further investigation in PDAC.

Keywords: clinical trials, genetic alterations, pancreatic ductal adenocarcinoma, PI3K/AKT/mTOR pathway, targeted therapy

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Introduction

Pancreatic cancer (PC) is one of the leading causes of cancer-related deaths worldwide, ranking 14th in incidence (2.6% of all cancers) and 7th in mortality (4.7% of all cancer-related deaths).[1] Pancreatic ductal adenocarcinoma (PDAC) is the most common histological type of PC, representing 90% of all PCs.[2] The pathology of this aggressive cancer is multifactorial and involves both modifiable risk factors (such as smoking, alcohol, and dietary factors) and non-modifiable factors (including gender, age, and genetic factors).[3,4]

PDAC represents a challenging neoplasm characterized by its limited therapeutic options, poor prognosis, and dismal survival.[5] Although surgery is the only curative approach for PC patients, it is usually impossible to perform optimal surgery due to the insidious onset of the disease, which results in most patients being diagnosed at an advanced stage.[6] Cytotoxic chemotherapy is the only systemic treatment currently recommended for PC patients. Olaparib, a PARP inhibitor, is the only targeted therapy that has been indicated for PC as a maintenance treatment for patients with metastatic disease who have a BRCA germline mutation.[7] However, PDAC is considered an immunologically cold tumor, which explains the inefficacy of immune checkpoint inhibitors, such as PD1/PDL1 and CTLA-4 inhibitors, in this aggressive malignancy.[8,9] Currently, PDAC management is of utmost importance for a better and more extensive understanding of PC biology and the subsequent identification of promising molecular targets.

According to recent reports, several genetic changes have been detected in PDAC. In particular, the activation of the proto-oncogene Kristen rat sarcoma viral oncogene homolog (KRAS) has been observed in approximately 90% of cases,

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and the inactivation of tumor suppressor genes, such as CDKN2A, SMAD4, and TP53, has been implicated in the tumors' proliferation and progression.[10] The activating KRAS mutation is the main oncogenic driver mutation included in the characteristic hallmarks, which occurs early in the PDAC pathogenesis process. This mutation leads to constitutive activation of downstream signaling pathways (RAS/RAF/MAPK) and phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR).[11] The PI3K signaling pathway is commonly dysregulated in PDAC cells and plays a crucial role in promoting tumor growth, survival, and metastasis.[12] Therefore, targeting the PI3K/AKT/mTOR cascade may be a potential therapeutic strategy for PDAC.

The objective of this narrative review is to provide a comprehensive overview of the current understanding of the PI3K pathway in PDAC, summarize the clinical data on PI3K pathway inhibition in PDAC, and investigate the potential of targeting the PI3K/AKT/mTOR cascade as a therapeutic strategy for this highly aggressive neoplasm.

Overview of the PI3K/AKT/mTOR pathway in PDAC

Signaling pathways are intricate networks that maintain crucial biological functions in all cell types. In tumors, these pathways are often disrupted, leading to deregulated cellular signaling implicated in various molecular hallmarks of cancer.[13] The PI3K/AKT/mTOR pathway is a key signaling pathway that is essential for cellular processes such as proliferation, survival, motility, and metabolism.[14]. Research has shown that the PI3K pathway, which is frequently activated in various types of cancer, including PC, plays a pivotal role in tumorigenesis and progression.[15] Deregulation of the PI3K pathway is frequently observed in 50% of all cancer patients and in 60% of PDAC patients.[16]

PI3K enzymes are a group of lipid kinases that catalyze the phosphatidylinositols' phosphorylation of the 3′-hydroxyl group. These enzymes are grouped into three distinct complexes (classes 1, 2, and 3) based on their structure and function.[17] Class I PI3Ks, which are composed of two subclasses (IA and IB), are the only group of PI3Ks implicated in human cancer. They are activated by various stimuli, such as receptor tyrosine kinases (RTKs), Ras, or G-protein-coupled receptors[18] (Figure 1). The composition of class IA PI3Ks consists of a regulatory p85 (with three isoforms: p85α, p85β, and p55γ) and a catalytic p110 (with three isoforms: p110α, p110β, and p110δ) subunits.[19] Upon activation, PI3K enzymes stimulate the conversion of phosphatidylinsotide-4,5-biphosphate (PIP2) to phosphatidylinsotide-3,4,5-triphosphate (PIP3). PIP3 functions as a second messenger, activating downstream effectors involved in the phosphoinositide-dependent kinase 1 (PDK1)-mediated phosphorylation of the serine-threonine kinase AKT at threonine site 308.[20] AKT activation leads to the phosphorylation of downstream components, including transcription factors, antiapoptotic proteins, and cell-cycle-related proteins. AKT, also known as protein kinase B (PKB), plays a crucial role in cell survival and growth. AKT activity is increased in PC due to its hyperphosphorylation or gene amplification.[21] Finally, mTOR is the third effector player in the PI3K signaling pathway. The role of mTOR is to regulate cell growth and apoptosis through two distinct complexes: mTORC1 (rapamycin-sensitive) and mTORC2 (rapamycin-insensitive).[22,23] mTORC1 is one of the major downstream effectors of AKT. However, mTORC2 is involved in the AKT phosphorylation on the serine residue-473. AKT activation is due to its phosphorylation mediated by PDK1 and mTORC2 on the threonine and serine sites, respectively. Thus, increased AKT activity phosphorylates the tuberous sclerosis complex 2 (TSC2) and subsequently activates the formation of the TSC2-TSC1 complex, which is directly responsible for mTORC1 activation. This complex can also bind mTORC2, leading to the promotion of its activity.[18,24]

Mutations in PI3K pathway genes and other associated regulated pathway genes are responsible for PDAC tumorigenesis. KRAS oncogenic driver mutations (75%–90% of PDAC) are the primary molecular aberration that activates the downstream PI3K signaling pathway in PDAC.[25,26] Studies have demonstrated that the PI3K pathway is activated in human PDAC and KRAS-driven mouse models of PC.[27] KRAS-activating mutations lead to overexpression of PI3KCA, which triggers acinar-to-ductal metaplasia (ADM) reprogramming through PDK1, ultimately resulting in PDAC formation.[28] The KRAS/PI3K axis plays a key role in mediating ADM, PDAC formation, and maintenance. The enhanced ducts formed from acinar cells further develop pancreatic intraepithelial neoplasia

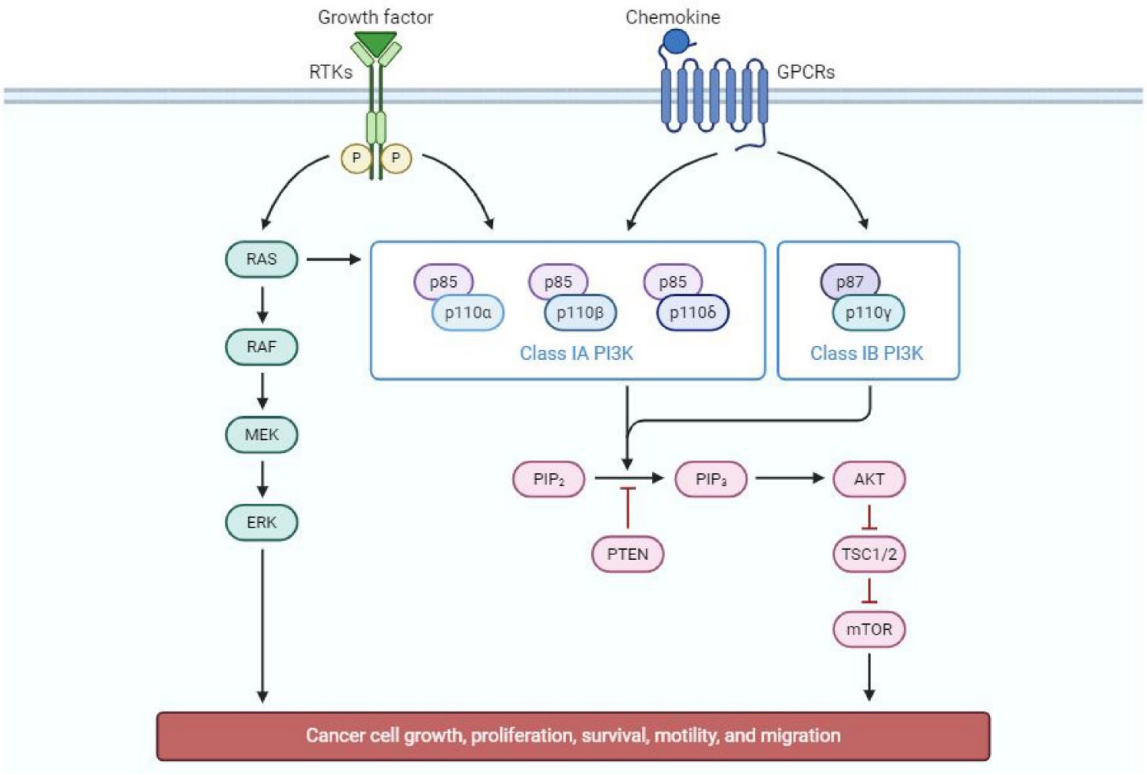

Figure 1. Overview of PI3K/AKT/ mTOR signaling pathway.
Source: Reprinted from "PI3K Pathway in Cancer," by BioRender.com (2024). Retrieved from https://app.biorender.com/biorender-templates

(PanIN) lesions in in vivo models.[29] Therefore, understanding the mechanisms and cellular functions of the PI3K pathway is crucial for the development of effective cancer therapies. Research has demonstrated that blocking the p110α PI3K isoform can prevent preneoplastic transformation induced by KRAS in animal models.[30] PIK3CA gene mutations, occurring in 3%–5% of PC patients, have been associated with an increase in ADM and PanIN in a mouse model.[31] Reactive oxygen species (ROS) are an important determinant of PC pathogenesis. ROS production is regulated by oncogenic KRAS-driven metabolic and signaling alterations. Once activated, ROS mediate the production of NADPH oxidases (NOX), which subsequently regulate ROS pro-survival activities through sustained apoptosis suppression.[32] Additionally, AKT has a direct role in the activation of NOX proteins.[33] Constitutive activation of the PI3K-effector AKT is a marker of the aggressiveness of PC. AKT2 amplification has been reported in 10%–32% of PDAC cases and contributes to the malignant phenotype.[34] Recent analysis of the human PDAC genome and genetic research on mice has revealed that PTEN gene deletion is frequently observed in PC tissues, activating the NF-κB and downstream cytokine pathways, which is linked to modifying the tumor microenvironment (TME) in PDAC.[35] When considered together, it becomes clear that the PI3K/AKT/PTEN signaling loop is a crucial signaling hub that is modified during the onset and course of PDAC.

PI3K has a crucial function in the regulation of immune cells and the coordination of interactions between cancer cells and immune cells. Additionally, it regulates the metabolic attributes of tumor cells and the TME's ability to control tumor growth and survival.[36] PDAC is a rare tumor with a higher proportion of stromal cells than tumor cells, and treatment options are limited due to the thick desmoplasia, which creates an acidic, hypoxic, and drug-impermeable TME.[37] The pancreatic TME comprises stromal cells, endothelial cells, immune cells, cancer-associated fibroblasts, and the extracellular

matrix. The dynamic nature of the TME is influenced by numerous signaling molecules released during tumor and accessory cell interactions.[38] The relationship between stromal cells and PC cells modifies intracellular signaling and metabolic pathways.[39] Cancer-associated fibroblasts secrete substances like collagen, proteoglycans, glycoproteins, and extracellular matrix constituents, enhancing cancer cell migration and proliferation while shielding them from chemotherapy drugs. The PI3K pathway is involved in the migration and proliferation of cancer-associated fibroblasts.[40] Moreover, PI3K signaling activity is crucial for PC progression, controlling macrophage motility, adhesion, metabolism, polarization, and survival.[41] Neutrophils, attracted to the stromal compartment and tumor cells by PC cells, are linked to poor prognosis and tumor development in patients with PDAC. These cells influence the migration of tumor and immune cells, accelerating cancer development through DNA damage caused by ROS.[42] The PI3K signaling pathway controls neutrophils' phagocytosis, adhesion, proliferation, survival, and chemotaxis.[43] The pancreatic TME also contains mast cells, which are associated with a worse PC patient survival rate.[44] The PI3K pathway is a crucial regulator of mast cell development, differentiation, chemotaxis, degranulation, and cytokine production,[45] as well as natural killer (NK) cell function.[34] NK cells are effector lymphocytic cells that are part of the innate immune system and are involved in the recognition and killing of tumor cells.[46] In PC, the activity of NK cells is reduced, and the decreased expression of activating killer receptors correlates with tumor progression in PC patients. By inhibiting the PI3K signaling pathway in NK cells, their function in immune surveillance can be impaired, preventing their degranulation activity and reducing NK cell-mediated lysis of tumors.[47,48] Adaptive immune responses are mostly suppressed in PC due to immunoediting, development of immune escape and immune resistance mechanisms.[49] The PI3K pathway plays a crucial role in T-cell activation, survival, and proliferation,[50] as well as the expression of the enzyme Bruton tyrosine kinase (BTK), which is essential for suppressing the growth of PC cells.[51] Finally, the PI3K cascade acts as a key regulator of angiogenesis, controlling the proliferation, survival, and maturation of endothelial cells.[52] Taken together, these studies suggest that the PI3K signaling pathway is critical for regulating pancreatic tumor biology.

Impact of targeting PI3K pathway in preclinical models of PDAC

Activation of the PI3K signaling pathway is mainly involved in the pathogenesis of PC, suggesting its potential as a promising therapeutic target for this disease. Several preclinical studies have evaluated the effects of inhibiting the PI3K cascade in PC.[53] In human PC cell lines, two distinct PI3K inhibitors (wortmannin and LY294002) were found to induce apoptosis in a dose-dependent manner.[54] In a separate study, LY294002, a specific inhibitor of the PI3K/AKT pathway, simultaneously enhanced the efficacy of nonsteroidal anti-inflammatory drugs in human PC cells by inhibiting cell cycle progression.[55] Although using PI3K pathway inhibitors as monotherapy appears to be a promising but incomplete therapeutic approach for PC, subsequent studies have investigated the potential of combining these inhibitors with other therapies to optimize their efficacy.[28] The combinatorial approach has been explored in several human and mouse models of PC. For instance, MK-2206, a pan-AKT inhibitor, was combined with a cyclin-dependent kinase (CDK) inhibitor (MK-7965, dinaciclib) in preclinical PC models using orthotopic and subcutaneous patient-derived human PC xenografts, emphasizing the antitumor effect of this combination.[56] Double inhibition of the PI3K signaling pathway at two different sites seems to be a promising therapeutic option for PC. The combination of MK-2206 (an AKT inhibitor) with buparlisib (a PI3K inhibitor) was investigated in 10 PDAC cell lines, showing promising antiproliferative effects.[57] Another interesting combination of dual inhibition of PI3K and mTOR (NVP-BEZ235) was assessed in a PC orthotopic mouse xenograft model, which showed a significant decrease in tumor growth.[58] Recently, a natural compound that inhibits both PI3K and mTOR (urolithin A) was shown to have antiproliferative and proapoptotic effects in tumor xenografts and genetically engineered mouse models in vivo.[59]

Recently, it has been observed that oncogenic KRAS activates multiple signaling networks, particularly the ERK/MAPK and PI3K/AKT/mTOR pathways, in KRAS-dependent PC. The crosstalk between these two primaries signaling pathways is clinically relevant and forms the basis for the development of combination therapies for PDAC. Inhibition of ERK represents a potential therapeutic strategy. PI3K, on the other hand, regulates the sensitivity of ERK inhibitors. Therefore,

targeting both the ERK and PI3K signaling pathways simultaneously may provide a beneficial therapeutic approach for PC.[60] Combining the inhibition of both the MAPK and PI3K pathways has demonstrated synergistic antitumor activity and a reduction in resistance in human PC cell lines.[61] Dual inhibition of PI3K (ZSTK474) and RAS/MEK (RO5126766) inhibitors decreased the viability of human PC cell lines.[62] Additionally, the combination of a MEK inhibitor (AZD6244) and a PI3K inhibitor (BKM120 or GDC-0941) increased tumor cell apoptosis in 46 human PDAC cell lines.[63] Furthermore, combining PI3K (MK-2206) and MAPK (trametinib) inhibitors with chemotherapy (nab paclitaxel and gemcitabine) in preclinical models of PDAC (PDAC cell-derived subcutaneous and PDAC patient-derived subcutaneous xenografts studies) demonstrated additive efficacy in reducing cell proliferation and inducing apoptosis.[64] Preclinical data on mutant KRAS-driven genetically engineered PC mouse models have shown an incremental benefit of the antiproliferative activity using the combination of targeted therapy (MEK and/or PI3K inhibitors) and chemotherapy (gemcitabine) compared to single-agent chemotherapy.[65] Interestingly, in vitro screens have confirmed the resistance of PDAC preclinical models to monotherapies, emphasizing the need for combination drug therapies targeting multiple pathways mainly involved in PC. Epidermal growth factor receptor (EGFR) is frequently overexpressed in PC and is associated with a poor prognosis.[66,67] Therefore, blocking EGFR signaling led to an inhibition of tumor growth and metastasis in human PC xenografts.[68] Regrettably, erlotinib's applicability for advanced PC is limited due to its restricted clinical response. Therefore, it is essential to investigate new predictive biomarkers that can identify patients with PC who would specifically benefit from erlotinib therapy and to explore potential new combination therapies.[69]

According to recent reports, the sensitivity of cell lines to the growth inhibition caused by EGFR inhibitors is influenced by the downregulation of activity in the PI3K-AKT pathway.[70] There are various mechanisms that can lead to EGFR-independent activity of the AKT pathway, such as the presence of other growth factor receptors such as insulin-like growth factor 1 receptor (IGF-1R) and fibroblast growth factor receptor (FGFR), specific mutations like constitutively activating PI3K mutations, or a lack of PTEN activity.[71] It is important to note that multiple inputs can regulate this pathway, so inhibiting EGFR alone may not be sufficient for effectively inhibiting all tumor cells, emphasizing the need for multifaceted intervention. In fact, the combination of sirolimus and erlotinib has shown synergistic inhibitory activity on tumor growth in both cell culture and in vivo xenograft models.[72] In addition, the PI3K pathway, as previously demonstrated, holds significant importance in the development of tumors and metastasis in PDAC. Furthermore, it also enables tumors to evade immune surveillance and suppress immune responses.[73] These findings offer a compelling rationale for examining the PI3K/AKT/mTOR signaling cascade in clinical settings for patients with PDAC. The PI3K/AKT/mTOR signaling pathway is of great importance in the development of PC. Several inhibitors targeting this pathway have been investigated in early-phase clinical trials for patients with advanced PC, displaying promising outcomes with certain agents.[74] However, due to the limited efficacy of single agents in targeting this pathway, the development of multidrug and multitarget combination approaches appears to be a more appealing and effective strategy for treating this aggressive disease.[75] Therefore, further investigation is needed for the following combination therapies, which show promise for clinical application: MAPK, Sonic Hedgehog pathways, or pan-histone deacetylase inhibitors in combination with PI3K/AKT/mTOR inhibitors.[76,77]

Contemporary clinical trials in PDAC targeting PI3K signaling axis

Based on preclinical data, the PI3K pathway appears to be a relevant target for PDAC management. Inhibition of this pathway can be accomplished at various points, and several drug classes that disrupt the PI3K/AKT/mTOR cascade have been evaluated in clinical research to improve PDAC treatment outcomes.[78] Notably, recent developments have led to the creation of targeted treatments that selectively inhibit PI3K, AKT, and mTOR as single agents or in combination with other therapies to enhance response rates and overcome resistance mechanisms in PDAC (Table 1).

PI3K inhibitors

Utilizing small molecules that specifically inhibit PI3K and its subsequent downstream signaling pathway offers hope for improving the management and prognosis of PDAC. Several tyrosine kinase inhibitors of PI3K have been explored in clinical trials for PDAC patients.[79]

Table 1. Clinical trials assessing PI3K/AKT/mTOR pathway inhibitors in PDAC studies.

Drug	Target	Population	*N*	Treatment regimen	Phase	Status	References
Alpelisib (BYL719)	Oral class I α-specific PI3K inhibitor	*PIK3CA*-altered advanced solid tumors	134	Alpelisib monotherapy	I	Completed	80
Alpelisib (BYL719)	Oral class I α-specific PI3K inhibitor	Locally advanced and metastatic PC	15	BYL719 in combination with gemcitabine and nab-paclitaxel	I	Completed (the study was closed prematurely due to slow accrual)	82
Buparlisib (BKM120)	Oral pan-PI3K inhibitor	Advanced solid tumors	113	Buparlisib and trametinib (MEK inhibitor) combination	Ib	Completed	84
Buparlisib (BKM120)	Oral pan-PI3K inhibitor	Advanced solid tumors with RAS/RAF alterations	89	Buparlisib in combination with Binimetinib (MEK1/2 inhibitor)	Ib	Completed	135
Buparlisib (BKM120)	Oral pan-PI3K inhibitor	Advanced refractory solid tumors	17	BKM120 plus chemotherapy (mFOLFOX6)	I	Completed	85
Sonolisib (PX-866)	Oral PI3K inhibitor	Advanced solid tumors	48	PX-866 as single agent	I	Completed	86
Copanlisib (BAY 80-6946)	Intravenous pan-class I PI3K inhibitor	Advanced solid tumors and non-Hodgkin's lymphomas	57	Copanlisib monotherapy	I	Completed	87
Pictilisib (GDC-0941)	Oral pan-class I PI3K inhibitor	Advanced solid tumors	60	Pictilisib (GDC-0941) as single agent	I	Completed	88
Pictilisib (GDC-0941)	Pan-PI3K inhibitor	Advanced solid tumors	178	Cobimetinib (MEK) and pictilisib combination therapy	I	Terminated	89
Perifosine (KRX041)	AKT inhibitor	Unreserctable locally advanced or metastatic PC	10	Perifosine monotherapy	II	Terminated for unacceptable adverse events	91
Perifosine (KRX041)	AKT inhibitor	Advanced PC	19	Perifosine as second line therapy	II	Completed	92
Afusertib (GSK2110183)	AKT inhibitor	Solid tumors and multiple myeloma	335	MEK inhibitor GSK1120212 in combination with the AKT inhibitor GSK2110183	I/II	Completed	94
Uprosertib (GSK2141795)	Oral AKT inhibitor	Advanced solid tumors	126	Uprosertib in combination with the oral MEK1/MEK2 inhibitor trametinib	I	Completed	95

(Continued)

Table 1. (Continued)

Drug	Target	Population	*N*	Treatment regimen	Phase	Status	References
Oleandrin (PBI-05204)	Oleander-derived inhibitor of AKT, FGF2, NF-κB, and p70s6k	Advanced solid tumors	46	PBI-05204 as monotherapy	I	Completed	100
Oleandrin (PBI-05204)	Oleander-derived inhibitor of AKT, FGF2, NF-κB, and p70s6k	Refractory metastatic PC	42	PBI-05204 as single agent	II	Completed	101
MK 2206	AKT inhibitor	Advanced PC	39	MK 2206 in combination with Dinaciclib (cyclin-dependent kinase inhibitor)	I	Completed	97
MK 2206	AKT inhibitor	Advanced treatment-refractory solid cancers	62	MK 2206 in combination with MEK 1/2 inhibitor (Selumetinib, AZD6244)	I	Completed	96
MK 2206	AKT inhibitor	Metastatic PC refractory to Gemcitabine-based therapy	137	MK 2206—Selumetinib combination compared to modified Folfox	II	Completed	98
LY2780301	Dual p70 S6 kinase and AKT inhibitor	Advanced tumors	80	Single-agent LY2780301	I	Completed	93
TAS0612	RSK, AKT, and S6K inhibitor	Advanced or metastatic solid tumors	100	TAS0612 as single agent	I	Recruiting (estimated study completion date: July 2027)	104
Sirolimus (AY-22989)	Oral mTOR inhibitor	Advanced cancers	57	Sirolimus in combination with Sorafenib or Sunitinib	I	Completed	106
Sirolimus (AY-22989)	Oral mTOR inhibitor	Advanced, gemcitabine-resistant PC	31	Sirolimus as monotherapy	I	Completed	105
Sirolimus (AY-22989)	Oral mTOR inhibitor	Metastatic PC	22	Metformin with or without sirolimus as maintenance therapy after induction chemotherapy	Ib	Completed	108

(Continued)

Table 1. (Continued)

Drug	Target	Population	*N*	Treatment regimen	Phase	Status	References
Nab-sirolimus	Intravenous mTOR inhibitor	Locally advanced or metastatic solid tumors and moderate hepatic impairment or normal hepatic function	28	Nab sirolimus as single agent	I	Recruiting (estimated study completion date: April 2025)	110
Nab-sirolimus	Intravenous mTOR inhibitor	Malignant solid tumors with pathogenic alterations in TSC1/TSC2 genes	120	Nab sirolimus as single-agent	II	Recruiting (estimated study completion date: December 2025)	111
Nab-sirolimus	Intravenous mTOR inhibitor	Advanced solid tumors and non-small cell lung cancer with a KRAS G12C mutation	79	Nab sirolimus in Combination with Adagrasib	I/II	Recruiting (estimated study completion date: June 2026)	112
Everolimus (RAD001)	Oral mTOR inhibitor	Gemcitabine-refractory metastatic PC	33	RAD001	II	Completed	113
Everolimus (RAD001)	Oral mTOR inhibitor	Advanced PC	31	Capecitabine and Everolimus combination treatment as first- and second-line therapy in	II	Completed	114
Everolimus (RAD001)	Oral mTOR inhibitor	Advanced PV	43	Everolimus in combination with Cetuximab and Capecitabine	I/II	Completed	115
Everolimus (RAD001)	Oral mTOR inhibitor	Recurrent or refractory advanced solid tumors	100	Combination of three inhibitors Trametinib, Everolimus, and Lenvatinib	II	Recruiting (estimated study completion date: January 2027)	116
Everolimus (RAD001)	Oral mTOR inhibitor	Solid tumors or multiple myeloma	104	VS-6766 (RO5126766) (a dual RAF/MEK inhibitor) alone and in combination with Everolimus (RAF/MEK)	I	Recruiting (estimated study completion date: May 2024)	117

(Continued)

Table 1. (Continued)

Drug	Target	Population	*N*	Treatment regimen	Phase	Status	References
Temsirolimus (CCI-779)	Intravenous mTOR inhibitor	Advanced PC	5	Temsirolimus as single agent	II	Terminated (the study was closed to accrual due to significant adverse effects resulting from study treatment)	118
Temsirolimus (CCI-779)	Intravenous mTOR inhibitor	Advanced or metastatic PC	30	Temsirolimus in combination xith Gemcitabine	I/II	Completed	119
Ridaforolimus (MK-8669)	MTOR inhibitor	Refractory advanced tumors	17	Ridaforolimus in combination with Bevacizumab	I	Completed	120
Vistusertib (AZD2014)	MTORC1/2 inhibitor	Advanced solid tumors	56	AZD2014 in monotherapy	I	Completed	121
Voxtalisib (SAR245409)	Dual inhibitor of pan-PI3K and mTORC1/2	Advanced solid cancers	83	Voxtalisib as monotherapy	I	Completed	124
Voxtalisib (SAR245409)	Dual inhibitor of pan-PI3K and mTORC1/2	Advanced solid cancers	146	Voxtalisib in combination with MEK inhibitor	Ib	Completed	125
Gedatolisib (PF05212384)	Dual inhibitor of PI3K and mTOR	Advanced solid tumors	81	Gedatolisib in combination with Irinotecan or MEK inhibitor	I	Completed	128
Gedatolisib (PF05212384)	Dual inhibitor of PI3K and mTOR	Advanced squamous cell lung, pancreatic, head and neck, and other solid tumors	96	Gedatolisib in combination with a cycline dependent kinase 4/6 (Palbociclib, PD-0332991)	I	Recruiting (estimated study completion date: January 2026)	129
Omipalisib (GSK458)	Inhibitor of pan-PI3K and mTOR	Advanced solid cancers	170	Omipalisib as single agent	I	Completed	127

KRAS, Kristen rat sarcoma viral oncogene homolog; PC, pancreatic cancer; PDAC, pancreatic ductal adenocarcinoma; PI3K/AKT/mTOR, phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin; TSC2, tuberous sclerosis complex 2.

Alpelisib (BYL719) is one of the first PI3K inhibitors to be tested in various malignancies. This PI3Kα-selective inhibitor was explored in a first-in-human phase I trial (NCT01219699) in 134 patients with PIK3CA-altered advanced solid tumors, demonstrating a safe profile and encouraging preliminary antitumor activity.[80] On April 5, 2022, alpelisib received accelerated Food and Drug Administration (FDA) approval as a treatment for adult and pediatric patients

with PIK3CA-related overgrowth spectrum (PROS).[81] Results from an in vitro study of alpelisib in PC human and murine samples led to its assessment in a phase I clinical trial (NCT02155088) in combination with chemotherapy (gemcitabine and nab paclitaxel) in 15 patients with advanced and metastatic PC. The median progression-free survival (mPFS) was 5.36 months (1.6–10 months), and the median overall survival (mOS) was 8.74 months (3.8–21.2 months). The most common adverse events (AEs) were hyperglycemia, anemia, and a decreased neutrophil count.[82]

Due to the high prevalence of resistance to targeted therapies administered as single agents, clinical investigations have been conducted to explore combinatorial approaches. As previously mentioned, the MAPK and PI3K signaling pathways are interconnected and play a crucial role in tumor initiation and progression, as well as in drug resistance mechanisms. Inhibition of one pathway can lead to compensatory activation of the other, making dual inhibition a promising strategy to overcome resistance to current therapies.[83] In an open-label phase Ib trial (NCT01155453), 113 patients with select solid tumors were administered the pan-PI3K inhibitor buparlisib (also known as BKM120) in combination with an oral MEK1/2 inhibitor (trametinib). The most frequently reported AEs were gastrointestinal and dermatologic. Although the combination showed promising activity in KRAS-mutant ovarian cancers, minimal activity was observed in PDAC patients.[84] In a phase Ib, multicenter, open-label, and basket trial (NCT01363232), 89 patients with advanced solid tumors harboring RAS/RAF alterations were evaluated for the effectiveness of buparlisib when combined with a highly potent MEK1/2 inhibitor (binimetinib). Out of these, 6 patients (7%) had PC, and at the data cutoff, 84 patients (94.4%) had discontinued study treatment due to disease progression (48.3%) and AEs (36.0%). Among the 69 patients (77.5%) who were evaluable for tumor response based on RECIST version 1.1, the combined therapy was not as effective as anticipated, with the exception of KRAS/NRAS/BRAF-mutant ovarian cancer, where significant responses were observed (partial response in 5/18 patients). Several factors may have contributed to the reduced effectiveness, including the frequent dose reductions resulting from the combination's toxicities and the consequent suboptimal pathway modulation. Additionally, the genomic context, whether truncal, shared, or private, may explain the significant differences in responses between the cancers, despite them having common driver alterations. Finally, epigenetic factors can dictate therapeutic vulnerabilities, requiring different doses of targeted therapy to achieve sufficient pathway inhibition.[85] Based on these results, further exploration of this combination may be warranted to define a better-tolerated dose and/or schedule, such as alternative scheduling with noncontinuous/pulsatile dosing of either agent, which could be explored further in RAS/BRAF-mutant tumors. The findings may inform the design of future combination therapy trials in patients with tumors harboring mutations in the PI3K and MAPK pathways. In addition, buparlisib was tested in combination with chemotherapy (mFOLFOX6) in a single-center phase I clinical trial (NCT01571024) involving 17 patients with refractory solid tumors. This combination resulted in an unconfirmed partial response in one patient and stable disease in three patients. Common AEs included neutropenia, fatigue, leukopenia, hyperglycemia, and thrombocytopenia. The increasing toxicity observed in this combination does not encourage further exploration of this treatment in gastrointestinal cancers.[85] Sonolisib or PX-866 is an oral, irreversible PI3K inhibitor that was assessed in a multicenter, open-label, and dose-escalation phase I study. This trial was the first to test PX-866 in humans and showed promising activity in 84 patients with advanced solid malignancies.[86] Copanlisib (BAY 80-6946), an intravenous pan-class I PI3K inhibitor, was evaluated in a phase I dose escalation study (NCT00962611) to assess its safety and pharmacokinetics in patients with advanced solid tumors and hematological cancers. This agent exhibited a safe profile and a preliminary antitumor effect.[87] Based on the promising results of preclinical models with pictilisib (GDC-0941), a phase I dose escalation trial was conducted in 16 patients with solid tumors, providing impetus for further investigation of this pan-class I PI3K inhibitor.[88] However, a phase Ib trial found that combining pictilisib with a MEK inhibitor (cobimetinib) did not result in higher efficacy in patients with advanced solid cancers.[89] Recently, the impact of taselisib, a selective inhibitor of PI3K, on PDAC cell proliferation was investigated. The study demonstrated a correlation between increasing taselisib concentrations and a reduction in PDAC cell viability. In addition, transcriptomic data from PDAC samples were utilized in this study to develop a risk score based

on the expression profiles of dysregulated PI3K/AKT/mTOR pathway-related genes and machine learning, which showed a significant increase in overall survival time among patients in the low-risk group. Hence, the PI3K/AKT/mTOR pathway could be harnessed to better predict individual risk scores.[90]

AKT inhibitors

AKT signaling plays a critical role in activating antiapoptotic pathways that enable cancer cells to survive. According to preclinical evidence, targeting AKT presents a promising strategy for the treatment of PC. Unfortunately, several AKT inhibitors failed to show efficacy in clinical trials. Perifosine, also known as KRX041, is an example of an AKT inhibitor that demonstrated promising results in preclinical studies but did not prove beneficial in two phase II clinical trials for patients with advanced PC.[91,92] LY2780301, another AKT inhibitor, was assessed as a single agent in a first-in-human phase I study in patients with advanced malignancies, showing minimal antitumor activity.[93]

Based on biological concepts, the PI3K/AKT/mTOR and RAF/MEK/ERK pathways are intriguing aspects of human cancer therapy. Accumulated studies on these two pathways will provide new hope for cancer patients. Inhibiting the PI3K/AKT/mTOR and MAPK/MEK/ERK pathways could have a synergistic effect. Afuresertib (GSK2110183) is an AKT inhibitor that was evaluated in combination with a MEK inhibitor (trametinib) in a phase I/II clinical trial (NCT01476137) in 20 patients with solid tumors and multiple myeloma. The purpose of this study was to determine safety and response. This trial concluded that the combination was poorly tolerated using a continuous daily dose schedule.[94] Uprosertib (GSK2141795) is another oral AKT inhibitor that failed to show clinical benefit with poor tolerance in advanced solid tumors, including PC, in combination with an oral MEK 1/2 inhibitor (trametinib) in a phase I trial.[95] MK-2206 was assessed in combination with an oral, selective MEK 1/2 inhibitor (selumetinib) in a phase I trial (NCT01021748), which involved 62 patients with advanced treatment-refractory solid malignancies and demonstrated a promising therapeutic combination option in KRAS-driven cancers.[96] Despite promising results in preclinical trials, including combination approaches with a CDK inhibitor, MK-2206 failed to show clinical benefit in a phase I study with dinaciclib (a CDK inhibitor) for patients with advanced PC.[97] In addition, this combination failed to meet its primary endpoint of improving overall survival compared to modified FOLFOX in patients with metastatic PC that had failed prior gemcitabine-based therapy in a phase II clinical trial (SWOG S1115, NCT01658943).[98] Furthermore, oleandrin, a novel plant compound derived from Nerium oleander, has been widely used as a cardiac glycoside and exhibits antitumor activity through the inhibition of phosphorylated AKT expression and downregulation of mTOR in orthotopic models of human PC.[99] In a phase I clinical trial, oleandrin demonstrated a safe profile in heavily pretreated patients with advanced solid tumors.[100] However, a phase II, single-arm trial in 42 patients with metastatic PC failed to achieve its primary endpoint of achieving 50% patient survival at 4.5 months.[101] Currently, the evaluation of novel and potent kinase inhibitors with multitargets, such as TAS0612, which inhibits RSK, AKT, and S6K, is being conducted.[102] RSK is a serine threonine kinase activated by upstream kinases of the PI3K and MAPK pathways and is implicated in various resistance mechanisms associated with single inhibition of the PI3K cascade.[103] TAS0612 is currently being explored in an ongoing phase I clinical trial (NCT04586270) in patients with advanced or metastatic malignancies.[104] The findings underscore the necessity of delving deeper into the intricate molecular mechanisms and complex signaling pathways in order to provide new therapeutic perspectives for clinicians treating PC patients. Despite the development of numerous AKT inhibitors, only a few have shown promise in preclinical studies for PC, and even fewer have been tested in clinical research. Due to their toxicity and lack of efficacy, these inhibitors are not yet approved for use in patients. Therefore, it is imperative to determine the actual impact of these drugs in a clinical setting. Thus, additional research focusing on reducing toxicity and enhancing the effectiveness of AKT-inhibitor combinations is essential.

mTOR inhibitors

Targeting mTOR has been widely investigated in the field of PC. mTOR is a serine/threonine protein kinase that is involved in tumor growth through the formation of two protein complexes, mTORC1 and mTORC2. Several mTOR

inhibitors have been evaluated in clinical settings for the treatment of PC.

Sirolimus, also known as rapamycin or AY-22989, has demonstrated promising results in preclinical studies through the inhibition of mTOR. However, in a clinical setting, this agent was investigated as a single therapy in patients with advanced PC who were refractory to gemcitabine, with marginal outcomes indicating that sirolimus monotherapy is ineffective in the treatment of PC.[105] As a result, researchers sought to combine it with other drugs. In a phase I trial, sirolimus was tested in combination with potent oral antiangiogenic kinase inhibitors (sorafenib or sunitinib) in several advanced malignancies, including PC cases, demonstrating the feasibility and safety of such a combination.[106] Another combinatorial strategy that has been investigated in the context of PC involves the combination of sirolimus and metformin. This approach was supported by preclinical evidence in PC cell lines, as it led to a synergistic effect due to enhanced inhibition of the mTOR pathway.[107] Metformin, which is an antidiabetic medication, was found to inhibit mTORC1. In a randomized, open-label phase Ib trial (NCT02048384), metformin was administered either alone or in combination with rapamycin as maintenance therapy to advanced PC patients who had previously received chemotherapy. A total of 22 patients were treated according to the protocol and were randomly assigned in a 1:1 ratio to either metformin alone (Arm A) or metformin plus rapamycin (Arm B). The results demonstrated that both treatment options had a favorable safety profile and promising outcomes, with longer-than-expected progression free survival (PFS) and overall survival (OS) in this population with poor prognosis. The median PFS for the entire cohort, Arm A, and Arm B was 3.5 (95% confidence interval (CI): 2.9–9.2), 4.0 (95% CI: 2.9 to not reached (NR)), and 3.0 months (95% CI: 2.8 to NR), respectively, and the median OS was 13.2 (95% CI: 7.8 to NR), 14.8 (95% CI: 6.2 to NR), and 9.7 months (95% CI: 9.0 to NR), for the entire cohort, Arm A, and Arm B, respectively. The study findings support further investigation of these agents in the maintenance setting. However, this trial was not designed to detect differences in clinical activity between the treatment arms. In patients with metastatic PDAC who achieve a response to chemotherapy, the administration of metformin with or without rapamycin was found to be well-tolerated and associated with better-than-expected OS. Further studies are required to prospectively evaluate the role of these agents compared to maintenance chemotherapy or observation-only approaches.[108] Nab-sirolimus, a novel and potent mTOR inhibitor, has exhibited a higher tumor inhibitory effect and more effective mTOR target suppression in preclinical models as compared to oral mTOR inhibitors.[109] Currently, nab-sirolimus is being investigated in three ongoing clinical trials, including as a single agent in locally advanced or metastatic cancers (NCT05661461),[110] in selected patients with tumors harboring pathogenic alterations in TSC1/2 genes (PRECISION-1, NCT05103358),[111] and in combination with adagrasib in tumors with KRAS G12C mutations (KRYSTAL-19, NCT05840510).[112] Everolimus (RAD001) is another oral mTOR inhibitor that has been studied in a phase II multi-institutional and single-arm trial. This trial involved 33 patients with advanced PC who had previously been unresponsive to gemcitabine. The results of the trial suggest that everolimus may have limited effectiveness when used alone and may be more effective when used in combination with other treatments.[113] In a separate phase II clinical trial, the combination of everolimus and chemotherapy (capecitabine) was analyzed in 31 patients with advanced PC. The results of this trial indicated that the combination was feasible and showed moderate effectiveness, with a disease control rate of 38%, an mPFS of 3.6 months, and an mOS of 8.9 months.[114] An open-label, multicenter, non-randomized phase I/II trial (NCT01077986) was conducted to evaluate a triple drug regimen comprising everolimus, cetuximab, and capecitabine in 43 patients with advanced PC. However, the study demonstrated the impracticality of this combination due to severe AEs.[115] Everolimus is also under exploration in an ongoing phase II clinical trial (NCT04803318) in combination with trametinib and lenvatinib for the treatment of recurrent or refractory advanced solid malignancies.[116] Another phase I trial (NCT02407509) is ongoing to explore the combination of everolimus with a dual inhibitor of RAF/MEK (VS-6766) in patients with advanced solid malignancies.[117] Moreover, in addition to the two mTOR inhibitors previously mentioned, two other inhibitors were investigated in the context of PC. The first of these is temsirolimus, an intravenous mTOR inhibitor that was tested in a phase II clinical trial (NCT0075647) involving advanced PC patients, but the results were not positive.[118] Consequently, a combination of temsirolimus and gemcitabine was studied in a phase I/II trial (ACTRN12611000643976) for PC patients.

Although the combination was found to be safe, it did not demonstrate significant efficacy.[119] The second agent is ridaforolimus (MK-8669), which was combined with bevacizumab in a phase I study (NCT00781846) involving 17 patients with refractory advanced malignancies, 2 of whom had PC. This combination showed promising outcomes in this trial.[120] Recently, a novel mTORC1 and 2 inhibitor known as vistusertib (AZD2014) was explored in a first-in-human phase I trial, suggesting activity against heavily pretreated patients with advanced solid cancers. This suggests that further investigation into mTORC inhibitors may be merited.[121]

Dual inhibitors of PI3K/mTOR pathway

The management of PDAC may benefit from a dual inhibition of PI3K and mTOR, as suggested by preclinical data demonstrating potential efficacy in PC models.[122,123]

Voxtalisib (SAR245409) is a dual inhibitor of pan-PI3K and mTORC1 and 2 that has been investigated in a first-in-human phase I trial involving 83 patients with advanced solid tumors. In this trial, voxtalisib was found to be safe, with disease stability serving as the best response in 48% of the patients analyzed.[124] Additionally, voxtalisib was studied in combination with an oral MEK inhibitor (pimasertib) in a dose-escalation and expansion phase Ib study (NCT01390818), which included 146 patients with advanced solid cancers (7 of whom had PC). However, this combination was poorly tolerated and showed a lack of clinical antitumor activity.[125] Omipalisib (GSK458) is a potent oral inhibitor of pan-PI3K and mTOR.[126] One hundred seventy patients with refractory advanced cancers (including two patients with PC) were enrolled in a dose-escalation, single-agent, and phase I study to receive omipalisib to assess its pharmacokinetics, pharmacodynamics, efficacy, and safety.[127] On the other side, gedatolisib (PF05212384) is another agent that inhibits the PI3K and mTOR pathways and was evaluated in advanced solid malignancies. In an open-label, multicenter, four-arm, dose-escalation phase I trial (NCT01347866), PF05212384 was administered in combination with chemotherapy (irinotecan) or an MEK inhibitor (PD-0325901). The results of this trial indicated the need for further investigation of gedatolisib in advanced solid tumors.[128] In a phase I clinical trial (NCT03065062) that is currently underway, the investigational drug gedatolisib is being tested in combination with a CDK4/6 inhibitor (palbociclib) in patients with advanced squamous cell lung, pancreatic, head and neck, and other solid malignancies. The study's findings are anticipated to be released in January 2026.[129]

Mechanisms of resistance to PI3K/AKT/mTOR inhibitors

Although PI3K/AKT/mTOR pathway-targeted agents have shown promising preclinical activity in PC, acquired and intrinsic resistance have significantly hindered their clinical effectiveness. To develop alternative clinical strategies, it is crucial to understand the biochemical mechanisms that lead to resistance.[74] PC cells can overcome downregulation of the PI3K pathway induced by targeted agents by activating alternate signaling pathways or maintaining or re-establishing the targeted pathway.[130] Resistance to targeted agents can be attributed to several mechanisms, including secondary target mutations, parallel signaling pathways, and amplification of downstream modifications within the same pathway.[131]

Upregulation of the PI3K/AKT/mTOR pathway due to PI3K inhibition leads to drug resistance, involving the feedback loop of RTKs, growth factors, and transcription factors like forkhead box (FOXO). FOXO suppresses RTKs or adaptors that activate the PI3K pathway, such as EGFR, IGF-1R, EGFR, FGFR, and insulin receptor (IR). By inhibiting PI3K/AKT signaling, FOXO phosphorylation is suppressed, leading to FOXO-dependent repression of RTKs and derepression of downstream molecules. This results in the activation of multiple RTKs and partial maintenance of PIP3, which ultimately leads to cell proliferation and survival.[132]

The PI3K pathway is crucial for nutrient uptake and cell survival. PC cells exhibit the "Warburg effect," which refers to increased glucose uptake and glycolytic conversion to lactate. This effect is promoted by the constitutive activation of downstream AKT signaling, which enhances glucose uptake through the GLUT family of transporters. Apart from glucose transporter guidance, it has been demonstrated that the PI3K-AKT pathway regulates multiple nodes of the glycolytic cascade, thereby ensuring the continual metabolic requirements of the cell.[133]

As previously indicated, growth factors that activate cell surface receptors, such as EGFR, FGFR, IR, and IGFR, control proliferation, migration, metabolism, and cell survival. Upon growth factor stimulation, these receptors recruit and phosphorylate insulin receptor substrate-1 (IRS-1) adaptor molecules to activate the PI3K pathway. Furthermore, the interactions between these receptors and their signaling cascades can overlap to conform to synergistic responses, where, for instance, the induction of cell cycle progression also promotes an influx in energy synthesis by altering metabolic activity.[134] Taken together, these intriguing findings demonstrate the complexity of these intrinsic feedback loops to effectively downregulate PI3K signaling. Notably, combination therapies that target PI3K, AKT, or mTOR alongside various RTK molecules effectively combat this response in preclinical studies. However, there remain limitations in the clinical setting due to primarily negative adverse effects experienced by the patients, as well as a lack of selectivity when it comes to available drugs that target RTKs specifically.

Recently, emerging evidence has demonstrated the potential role in changes in cellular plasticity and PI3K inhibitor resistance. The downregulation of several RTKs involved in PI3K signaling may result in the generation of genetically independent transcriptional programs, which lead to "drug-tolerant" cell populations. In contrast to primary drug resistance, this state allows tumor cells to survive temporarily but not proliferate during treatment. However, these drug-tolerant populations can evade initial drug therapy but do not possess the genetic mechanisms required for tumor progression. They can serve as a reservoir of tumorigenic slow-cycling cells from which secondary genetic mechanisms of acquired resistance can develop. This protective measure has been associated with a phenotypic switch, commonly referred to as cell plasticity, whereby epithelial tumors progress to a more mesenchymal state. This epithelial-mesenchymal transition has long been linked to chemoresistance. More importantly, this drug-refractory state is reversible upon drug withdrawal, highlighting the absence of genetic mutations driving this drug-tolerant state.[130]

Furthermore, mucins (MUC), which are high-molecular-weight glycoproteins, are notably overexpressed in PC. Of these, MUC1, a type I transmembrane glycoprotein, modifies the aggressiveness of PDAC by impacting metabolism and signaling through the PI3K pathway. MUC1 influences the expression and activation of several RTKs, including PDGFR, EGFR, and c-Met, to enhance cellular activities such as proliferation, dissemination, and survival. Specifically, MUC1 affects EGFR's nuclear localization, which in turn influences how EGFR interacts with transcriptionally active promoter regions. Additionally, MUC1 controls the expression of genes that confer multidrug resistance in PC cells through AKT-dependent and independent mechanisms. Considering the MUC-PI3K signaling regulatory axis as a potential treatment approach for PC may be beneficial, as it can also control MUC1-mediated resistance to chemotherapy and radiation.[34]

In general, the PI3K pathway is highly influenced by intrinsic adaptive responses that re-establish pathway activation following treatment, leading to inadequate pathway inhibition and tumor progression. This not only emphasizes the need for a deeper understanding of the complexities of PI3K signaling but also strongly supports the use of specific combinations to overcome these mechanisms of resistance.

Conclusion and prospect

Exploring the fundamental mechanisms responsible for the development of PDAC is a promising avenue for discovering targeted therapies. The PI3K/AKT/mTOR signaling pathway is a critical hub that plays a significant role in the initiation and progression of PC. It also has a crucial regulatory function in the PDAC TME, which is composed of various cellular components. Despite the development of several inhibitors that target the PI3K/AKT/mTOR pathway, the main challenge remains drug resistance, which results in suboptimal responses when these agents are used as single therapies. Results from early-phase clinical trials have demonstrated that targeting a single component of the PI3K/AKT/mTOR loop is insufficient for effectively treating this genetically diverse type of cancer. The necessity for additional research in order to determine the optimal combination of treatments that will lead to improved outcomes for patients with PDAC is evident. Furthermore, the preclinical and early-phase clinical trial data supporting the use of downstream inhibition of the PI3K/AKT/mTOR pathway (mTORC1/2 inhibitors) in PDAC

treatment presents a promising option, providing a rationale for the development of dual mTORC1/2 inhibitors as combination therapies for PDAC patients. To improve personalized management for PDAC patients, an increase in the number of clinical trials examining novel multitarget drugs and rational therapeutic combinations is recommended.

It is interesting to note that the urgent need for effective treatment methods and extending the lifespan of PDAC patients requires immediate investigation. To this end, recent advancements in genomics, transcriptomics, and artificial intelligence tools should be utilized in PC field studies. The development of risk prediction models for PDAC is essential for identifying high-risk individuals and incorporating them into individual screening programs. Additionally, innovative approaches are required to detect PC at earlier stages and prevent its occurrence. Finally, the use of in vivo research models such as human organoid models holds promise for enhancing understanding of PC pathogenesis and evaluating the efficacy and mechanisms of resistance of potential drugs and combination-based therapies in PC cells.

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Not applicable.

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Author contributions
Al Jarroudi Ouissam: Conceptualization; Visualization; Writing – original draft.

Chibani Hind: Writing – review & editing.

Brahmi Sami Aziz: Validation; Writing – review & editing.

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