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MINIREVIEWS

Targeting *KRAS* in pancreatic adenocarcinoma: Progress in demystifying the holy grail

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Abstract

Pancreatic cancer (PC) remains one of the most challenging diseases, with a very poor 5-year overall survival of around 11.5%. Kirsten rat sarcoma virus *(KRAS)* mutation is seen in 90%-95% of PC patients and plays an important role in cancer cell proliferation, differentiation, metabolism, and survival, making it an essential mutation for targeted therapy. Despite extensive efforts in studying this oncogene, there has been little success in finding a drug to target this pathway, labelling it for decades as "undruggable". In this article we summarize some of the efforts made to target the KRAS pathway in PC, discuss the challenges, and shed light on promising clinical trials.

Key Words: Kirsten rat sarcoma virus; Targeted therapy; Pancreatic cancer; Drug resistance; Next generation sequencing; Clustered regularly interspaced short palindromic repeats

Core Tip: Kirsten rat sarcoma virus (*KRAS*) mutation is the hallmark of pancreatic cancer (PC) and an important therapeutic target. Approaches to target this oncogene has been challenging. We herein discuss the role of *KRAS* in development of PC, efforts made to target this pathway, and ongoing clinical trials.

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INTRODUCTION

In 2022, there was an estimated 62210 new pancreatic cancer (PC) cases and 49830 estimated deaths. PC is the fourth leading cause of cancer death in the United States[1]. PC is driven primarily by mutations in the Kirsten rat sarcoma virus (*KRAS*) gene, cyclin-dependent kinase inhibitor 2A, tumor protein 53, and mothers against decapentaplegic protein homolog 4. *KRAS* is one of the most frequently mutated oncogenes in human cancers. It is seen in more than 90% of PCs and more than 40% of colorectal and lung cancers[2]. 93% of all *KRAS* mutations occur at codon 12 (G12) with other common mutation sites at G13 and Q61. Missense mutation in glycine residues of G12 result in amino acid substitution, glycine substituted with aspartic acid (G12D), with valine (G12V), or with cysteine (G12C)[3]. The predominant mutation in PC is G12D followed by G12V (Figure 1)[4], but in lung cancer G12C is the most common. *KRAS* plays a major role in the development of PC and, as a result, there have been significant efforts to target the mutated *KRAS* pathway.

BACKGROUND

KRAS is a member of the rat sarcoma viral oncogene family (RAS), in addition to Neuroblastoma rat sarcoma virus and Harvey rat sarcoma virus. Identified in 1982, the *KRAS* is located on the short arm of chromosome 12[5,6]. It encodes two protein isoforms, KRAS-4B and KRAS-4A. Those are found in the inner side of the plasma membrane[7], and act as guanosine triphosphate (GTP)-binding proteins (G proteins), they bind guanine nucleotides that belong to the family of GTP-bound regulatory protein phosphatases (GTPase). An upstream signal *e.g.*, epidermal growth factor receptor (EGFR) stimulates the dissociation of guanosine diphosphate (GDP) from the GDP-bound G protein form, and allows the binding of GTP[8]. RAS functions as a binary switch, determined by two regulatory proteins called guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAP)[9]. KRAS binds to GDP in resting state due to its intrinsic GTPase activity. But with relevant stimuli, GEFs turn on signaling by catalyzing the exchange from a KRAS G-protein-bound GDP to GTP[10] (Figure 2). KRAS proteins can be activated by tyrosine kinase receptors, growth factors, chemokines, or calcium. This in turn activates multiple signaling pathways including the rapidly accelerated fibrosarcoma (RAF)-mitogen-activated protein kinase (MAPK)-extracellular regulated protein kinases (ERK) (MAPK/ERK; MEK) signaling pathway, the phosphoinositide 3-kinase (PI3K)-protein kinase (AKT)-mammalian target of rapamycin (mTOR) signaling pathway, and others. These pathways result in cell proliferation and DNA synthesis (Figure 3).

Precursor lesions of pancreatic ductal adenocarcinoma (PDAC) include pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN), and mucinous cystic neoplasm[11,12]. *KRAS* mutation was detected in 36% of PanIN-1A lesions and 87% of PanIN-2-3 lesions[13]. It was also found in 61% of patients with IPMN[14]. To study the role of *KRAS* in PC progression, scientists developed transgenic mice with inducible $KRAS^{G12D}$. Induction of oncogenic $KRAS^{G12D}$ altered normal epithelium and led to the development of precancerous lesions; on the other hand, inactivation of $KRAS^{G12D}$ in precursor lesions and during cancer progression led to disease regression[15]. These studies confirm the early role of *KRAS* mutation in the initiation and progression of precursor lesions into invasive PDAC as well as the correlation between frequency of *KRAS* mutation and degree of dysplasia.

KRAS mutation drives PC progression by resistance to apoptosis, induction of autophagy[16], immune evasion by downregulating major histocompatibility complex class I on tumor cells[17], and stimulating angiogenesis, resulting in cell survival and tumor progression.

TARGETED THERAPY

Upstream regulators

Some of the key regulators of KRAS include Son of Sevenless (SOS) and Src homology phosphatase 2 (SHP2). SOS is a GEF that activates KRAS, and SHP2 is a protein tyrosine phosphatase encoded by *PTPN11* that also promotes RAS activation, inhibiting either can delay tumor progression[18,19].

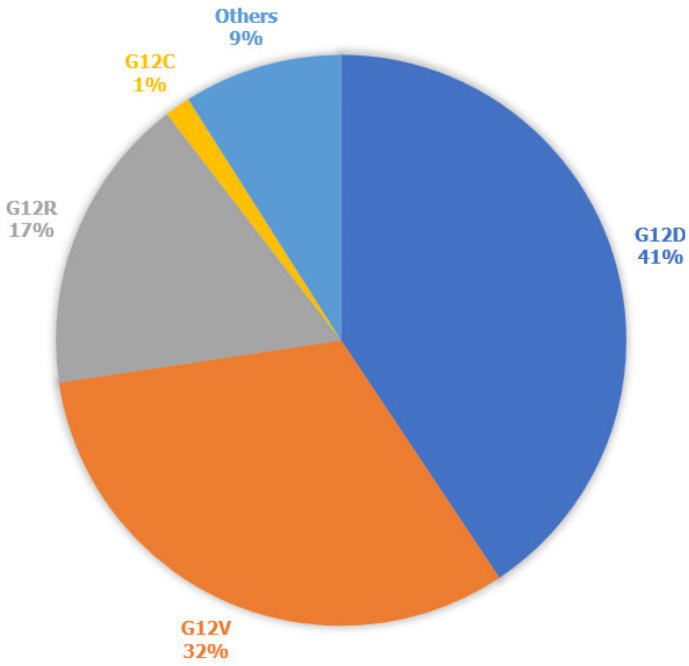

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Figure 1 Kirsten rat sarcoma virus mutations in pancreatic cancer. Types of Kirsten rat sarcoma virus (*KRAS*) mutations seen in pancreatic cancer, according to data publicly available on cBioPortal. 812 samples with altered *KRAS* collected from 5 pancreatic cancer studies. Others are A11T, A146T, A18V, G12A, G12I, G12L, G12S, G13C, G13D, G13H, G13P, G13R, L23V, Q61H, Q61K, Q61R.

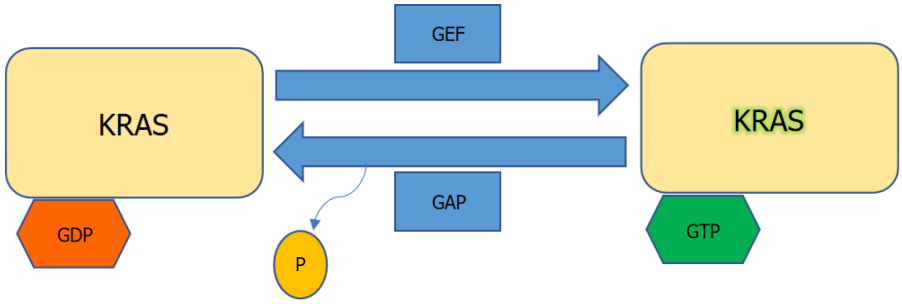

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Figure 2 Kirsten rat sarcoma virus activation. Kirsten rat sarcoma virus is activated when guanine nucleotide exchange factor displaces guanosine diphosphate from nucleotide binding site allowing guanosine triphosphate (GTP) binding and inactivated upon GTP hydrolysis by intrinsic GTP-bound regulatory protein phosphatases (GTPase) activity enhanced by GTPase activating protein. GTP: Guanosine triphosphate; GAP: GTPase activating protein; GDP: Guanosine diphosphate; GEF: Guanine nucleotide exchange factor; KRAS: Kirsten rat sarcoma virus.

BI-3406 inhibits the interaction between KRAS and SOS1 which has been shown to cause tumor regression in KRAS-driven cancer cell models. Synergy was observed with SOS1/MEK inhibitors as this combination can counteract adaptive resistance to MEK inhibitors[20]. ERAS-601 is a small molecule allosteric inhibitor of SHP2 that stops KRAS from cycling into its GTP-active state, which inhibits cellular proliferation in multiple $KRAS^{G12C}$ mutated tumor cell models[21]. Recently the Food and Drug Administration (FDA) granted fast track designation to BBP-398 (SHP2 inhibitor) in combination with Sotorasib for $KRAS^{G12C}$-mutated metastatic non-small-cell lung carcinoma (NSCLC). There is an ongoing trial to evaluate the safety and efficacy of this combination [national clinical trial (NCT) 05480865]. Combination of $KRAS^{G12C}$ inhibitor (JAB-21822) and SHP2 inhibitor (JAB-3312) showed synergistic effect in $KRAS^{G12C}$-resistant tumor cells[22], currently in phase I/II trial for PDAC (NCT05288205).

MAPK/ERK pathway

The MAPK/ERK pathway was shown in Table 1.

KRAS

Direct inhibition of the KRAS protein remains a challenge, due to its small size of 21 kDa and the lack of hydrophobic pockets on its surface. Those pockets, if found, can then be blocked by small molecules and ultimately disrupt its interaction with other proteins[23]. Several attempts have been made to directly target KRAS, but results were non-

Table 1 Kirsten rat sarcoma virus-rapidly accelerated fibrosarcoma-mitogen-activated protein kinase/extracellular regulated protein kinases-extracellular regulated protein kinases pathway inhibitors

Agent	FDA approved[1]	Clinical trials[2]		
		Conditions (phase)	Combination	NCT number
SOS inhibitors				
BI-1701963	N/A	Advanced solid tumors (I); advanced solid tumors (I); metastatic colorectal cancer (I)	Trametinib; BI 3011441; irinotecan	NCT04111458; NCT04835714; NCT04627142
SHP2 inhibitors				
ERAS-601	N/A	Advanced/ metastatic solid tumors (I)	Cetuximab, pembrolizumab	NCT04670679
JAB-3312	N/A	Advanced solid tumors (I); advanced solid tumors (I/II)	N/A; binimetinib, pembrolizumab, sotorasib, osimertinib	NCT04045496; NCT04720976
BBP-398 (IACS-15509)	(+ sotorasib) fast track designation for metastatic NSCLC	Advanced solid tumor (I); advanced NSCLC (I); advanced solid tumors (I); advanced solid tumors (I)	N/A; nivolumab; N/A; sotorasib	NCT05621525; NCT05375084; NCT04528836; NCT05480865
RLY-1971	N/A	Advanced/metastatic solid tumors (I)	N/A	NCT04252339
TNO155	N/A	Advanced solid tumors (I); advanced solid tumors (I)	EGF816 (nazartinib); spartalizumab, ribociclib	NCT03114319; NCT04000529
RMC-4630	N/A	Relapsed/refractory solid tumors (I); NSCLC (II); metastatic KRAS mutant cancers (I); relapsed/refractory solid tumors, locally advanced/metastatic EGFR positive NSCLC (I/II)	N/A; sotorasib LY3214996; cobimetinib, osimertinib	NCT03634982; NCT05054725; NCT04916236; NCT03989115
Direct KRAS inhibitors				
G12C				
Sotorasib (AMG 510, Lumakras)	Advanced NSCLC	Colorectal cancer (III); advanced solid tumors (Ib/II)	Panitumumab; N/A	NCT05198934; NCT04185883
Adagrasib (MRTX849, Krazati)	Locally advanced or metastatic NSCLC	Metastatic PC (Ib); colorectal cancer (I); solid tumors (I/II); advanced solid tumors (I); advanced/metastatic cancers (I/II)	N/A; cetuximab and irinotecan; N/A; BI-1701963; TNO155	NCT05634525; NCT05722327; NCT05162443; NCT04975256; NCT04330664
JNJ-74699157	N/A	Advanced solid tumors (I)	N/A	NCT04006301
LY3499446	N/A	Advanced solid tumors (I/II)	Abemaciclib, cetuximab, erlotinib, docetaxel	NCT04165031
GDC 6036	N/A	Advanced/metastatic solid tumors (I)	Atezolizumab, cetuximab, bevacizumab, erlotinib, GDC-1971, inavolisib	NCT04449874
D-1553	N/A	Advanced/metastatic solid tumors (I/II); NSCLC (I/II)	N/A; N/A	NCT04585035; NCT05383898
G12D				
MRTX1133	N/A	Pancreatic, lung, and colorectal cancers (I/II)	N/A	Enters phase I in 2023
Tricomplex inhibitors				
RMC-6236	N/A	Advanced solid tumors (I)	N/A	NCT05379985
RMC-6291	N/A	Advanced solid tumors (I)	N/A	NCT05462717
RAF inhibitors				
Sorafenib (BAY43-9006, NEXAVAR)	Unresectable HCC; advanced RCC; thyroid cancer	PC that cannot be removed by surgery (II); unresectable PC (I); metastatic PC (II)	Erlotinib; gemcitabine, sorafenib and radiotherapy; alone or with gemcitabine	NCT00837876; NCT00375310; NCT00114244
Vemurafenib (PLX4032, RG7204,	BRAF V600E melanoma, ECD	PC (II)	Sorafenib	NCT05068752

RO5185426, ZELBORAF)				
Dabrafenib (GSK2118436, TAFINLAR)	(+ Trametinib) BRAF V600E or V600K melanoma, NSCLC, anaplastic thyroid cancer, solid tumors	Colorectal cancer (II); advanced/metastatic BRAF V600 colorectal cancer (I)	Trametinib + PDR001; trametinib, LTT462, LXH254, TNO155, spartalizumab, tislelizumab	NCT03668431; NCT04294160
Encorafenib (BRAFTOVI)	BRAF V600E metastatic colorectal cancer	Localized colon or upper rectum cancer with BRAF V600E mutation (II)	Cetuximab	NCT05706779
Regorafenib (BAY 73-4506, STIVARGA)	Metastatic colorectal cancer; advanced GIST	Solid tumors (II)	Nivolumab	NCT04704154
Lifirafeni (BGB-283)	N/A	Advanced or refractory solid tumors (I/II)	Mirdametinib	NCT03905148
Paradox breakers				
PLX7904/ PLX8394 (PB04)	N/A	Advanced cancers (I/IIa)	N/A	NCT02012231
Pan-RAF inhibitors				
LY3009120	N/A	Advanced cancer (I)	N/A	NCT02014116
MLN2480 (BIIB-024, TAK580, Tovorafenib)	N/A	Relapsed or refractory solid tumors followed by a dose expansion in participants with metastatic melanoma (I); advanced non-hematologic malignancies (I)	N/A; MLN0128 or alisertib, or paclitaxel, or cetuximab, or irinotecan	NCT01425008; NCT02327169
HM95573 (Belvarafenib)	N/A	Locally advanced or metastatic solid tumors (I)	Cobimetinib or cetuximab	NCT03284502
BMS-908662 (XL281)	N/A	Advanced or metastatic colorectal cancer (I/II); advanced solid tumors (I)	Alone or with cetuximab; N/A	NCT01086267; NCT00451880
MEK inhibitors				
Trametinib (GSK1120212, JTP-74057)	(+Dabrafenib) BRAF V600E or V600K melanoma, NSCLC, anaplastic thyroid cancer, solid tumors	Cancers with BRAF V600E mutations (II); solid tumors (I); PC (II); metastatic PC (II); biliary tract cancer (II)	Dabrafenib; gemcitabine; SBRT + pembrolizumab; gemcitabine; N/A	NCT04439292; NCT01428427; NCT02704156; NCT01231581; NCT01943864
Cobimetinib (XL-518, GDC-0973, RG7421, Cotellic)	Histiocytic neoplasms, melanoma	PC (I); locally advanced or metastatic PC (I)	N/A; calaspargase Pegol-mknl	NCT04005690; NCT05034627
Selumetinib (AZD6244, ARRY-142886, Koselugo)	Pediatric neurofibromatosis type 1	Advanced or metastatic PC who have failed first line gemcitabine (II); locally advanced or metastatic pancreatic cancer with KRAS G12R mutations (II); metastatic pancreatic cancer previously treated with chemotherapy (II); locally advanced or metastatic PC (II)	N/A; N/A; MK2206 (Akt inhibitor) or mFOLFOX; erlotinib hydrochloride	NCT00372944; NCT03040986; NCT01658943; NCT01222689
Binimetinib (ARRY-438162, ARRY-162, MEK162, MektoviI)	Unresectable or metastatic melanoma with a BRAF V600E mutation	Advanced BRAF mutant cancers (I/II); PC with somatic BRAF V600E mutation (II); advanced solid tumors harboring RAS or BRAFV60330E mutations (I)	Encorafenib; Encorafenib; RAF 265	NCT03843775; NCT04390243; NCT01352273
Pimasertib (AS703026, SAR24550, EMD1036239, MSC1936369B)	N/A	PC (I/II)	Gemcitabine	NCT01016483
Refametinib (RDEA119, BAY86-9766)	N/A	Advanced or metastatic cancer (I); RAS-mutant hepatocellular carcinoma (II); advanced cancer (Ib)	Regorafenib; N/A; copanlisib	NCT02168777; NCT01915589; NCT01392521
E6201 (ER 806201)	N/A	BRAF V600 mutated metastatic melanoma (I); advanced solid tumors (I)	Dabrafenib; N/A	NCT05388877; NCT00794781
PD-0325901 (Mirdametinib)	N/A	Advanced cancer (I)	PF-05212384 or Irinotecan	NCT01347866
AZD8330 (ARRY-424704, ARRY-704)	N/A	Advanced malignancies (I)	N/A	NCT00454090
GDC-0623 (RG7420, G-868)	N/A	Locally advanced or metastatic solid tumors (I)	N/A	NCT01106599

RO4987655 (CH4987655, RG7167)	N/A	Advanced solid tumors (I)	N/A	NCT00817518
RO5126766 (CH5126766, RG7304)	N/A	Advanced solid tumors (I)	N/A	NCT00773526
TAK733	N/A	Advanced nonhematologic malignancies (I)	N/A	NCT00948467
ERK inhibitors				
Ulixertinib (BVD-523)	N/A	Advanced pancreatic and other solid tumors (I); metastatic PC (I); advanced MAPK pathway-altered malignancies	Palbociclib; Nab-paclitaxel and gemcitabine; N/A	NCT03454035; NCT02608229; NCT04566393
GDC-0994 (RG7842)	N/A	Locally advanced or metastatic solid tumors (I)	N/A	NCT01875705
MK-8353 (SCH900353)	N/A	Advanced/metastatic solid tumors (I); advanced malignancies (I)	Selumetinib; pembrolizumab	NCT03745989; NCT02972034
JSI-1187	N/A	Advanced solid tumors with MAPK pathway mutations (I)	Alone or with dabrafenib	NCT04418167
ERAS-007	N/A	Advanced or metastatic solid tumors (I/II); advanced gastrointestinal malignancies (I/II)	ERAS-601; encorafenib, cetuximab, palbociclib	NCT04866134; NCT05039177
Menin inhibitor				
BMF-219	N/A	NSCLC, pancreatic, colorectal cancers (I)	N/A	NCT05631574

[1]www.fda.gov.
[2]clinicaltrials.gov.
FDA: Food and Drug Administration; SOS: Son of Sevenless; KRAS: Kirsten rat sarcoma virus; HCC: Hepatocellular carcinoma; RCC: Renal cell carcinoma; ECD: Erdheim-Chester disease; GIST: Gastrointestinal stroma tumors; PC: Pancreatic cancer; RAF: Rapidly accelerated fibrosarcoma; RAS: Rat sarcoma viral oncogene family; MAPK: Mitogen-activated protein kinases; NSCLC: Non-small-cell lung carcinoma; SHP2: Src homology-2 domain-containing protein tyrosine phosphatase-2; NCT: National clinical trial; MEK: Mitogen-activated protein kinase/extracellular regulated protein kinases; N/A: Not applicable.

satisfactory[24-26]. Only recently AMG 510 (sotorasib) was developed to target G12C mutation in NSCLC without inhibiting wild-type *KRAS*[27]. Adagrasib (MRTX849) which is also a $KRAS^{G12C}$ inhibitor is well tolerated, and preliminary results showed partial response in 50% of patients with PDAC harboring this mutation[28]. However, $KRAS^{G12C}$ only occurs in 1%-2% PC and attempts to target more common *KRAS* isoforms have failed. One promising compound is MRTX1133, a small molecule that selectively inhibits $KRAS^{G12D}$ by preventing SOS-catalyzed nucleotide exchange. Subsequently, it promotes tumor regression in immunocompetent PC models and alters the tumor microenvironment by increasing tumor associated macrophages (TAM) and tumor-infiltrating cytotoxic T-cells. MRTX1133 is expected to enter phase I trial in 2023[29,30]. Other agents inhibiting G12D in the pre-clinical phase include BI-KRASG12D, JAB-22000, and ERAS-4. A new category of drugs called tricomplex inhibitors has shown promising results in pre-clinical models of $KRAS^{G12V}$ mutant cancers[31] and in a phase I trial RMC-6236 in $KRAS^{G12}$-mutant advanced solid tumors excluding G12C (NCT05379985). A recent study was able to selectively target $KRAS^{G12R}$ using a small molecule electrophile[32]. Due to the challenging nature of direct KRAS inhibition focus was shifted on downstream signaling, knowing that some of the challenges include compensation by other pathways, and that inhibiting multiple pathways can result in toxicity[33].

Multiple mechanisms are implicated in the inevitable drug resistance seen with KRAS inhibitors, either by activation of wild-type KRAS which is mediated by receptor tyrosine kinase[34], synthesizing new $KRAS^{G12C}$ proteins in response to MAPK suppression[35], or developing secondary mutations in KRAS inhibitor binding pocket[36].

RAF

With regards to drugs targeting the MAPK pathway, sorafenib was the first RAF inhibitor to be FDA-approved, initially for advanced renal cell carcinoma, followed by unresectable/metastatic hepatocellular carcinoma and metastatic differentiated thyroid cancer[37]. In a phase II trial combining sorafenib and erlotinib, 12 of the first 15 patients required dose delays or reductions due to toxicity, and the study failed to reach its primary endpoint of 8-week progression-free survival (PFS)[38]. A second-generation of RAF inhibitors (*e.g.*, vemurafenib and dabrafenib) was proven to be effective in *BRAF V600E* mutant metastatic melanoma[39]. Dabrafenib in combination with trametinib received a tumor agnostic accelerated approval for treatment of unresectable/metastatic solid tumors with *BRAF V600E* mutation that progressed on prior treatment[40]. Unfortunately, vemurafenib and dabrafenib were not as effective in *KRAS*-mutant cancers, due to compensatory ERK activation that led to enhanced tumor growth[41,42]. A third generation of RAF inhibitors called "paradox breakers" (PLX7904 and PLX8394) also blocks MEK-ERK1/2, which can overcome this resistance mechanism [43], Unfortunately, a phase I/II trial to evaluate the safety of PLX8394 was terminated due to low accrual. Recently, another group called "pan-RAF inhibitors" (LY3009120, MLN2480, and HM95573) entered phase I trials. LY3009120 is a kinase inhibitor that showed efficacy in inhibiting mutated *KRAS* and *BRAF* in preclinical models of colorectal cancer

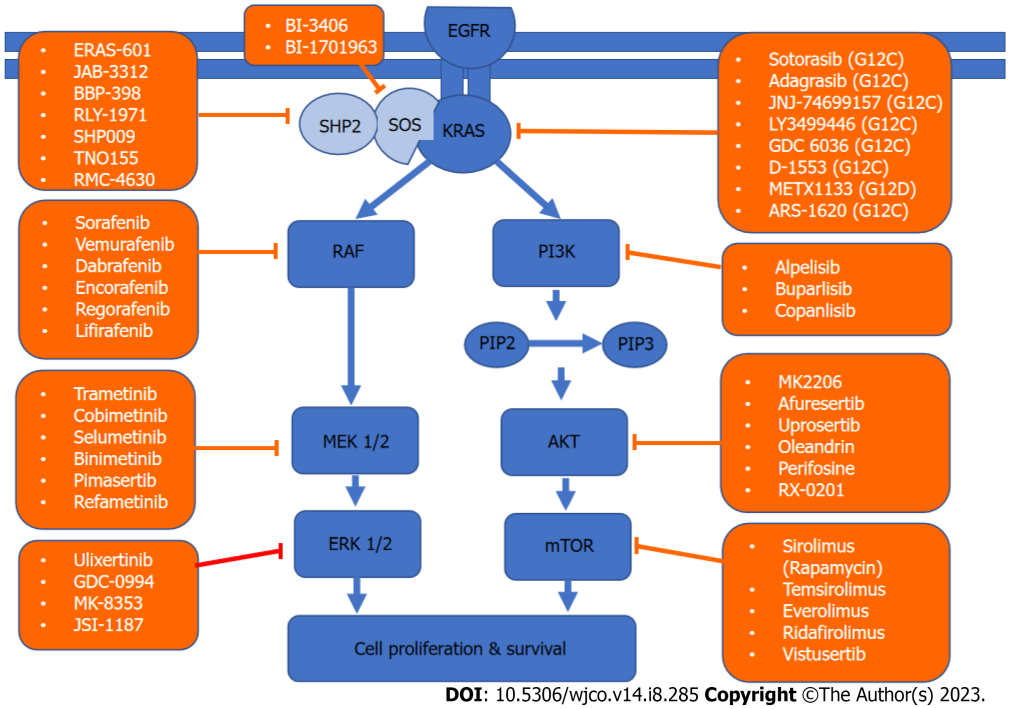

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Figure 3 Kirsten rat sarcoma virus signaling network and targeted therapy. A schematic of the two major Kirsten rat sarcoma virus pathways driving cell survival and drugs that target them. KRAS: Kirsten rat sarcoma virus; AKT: Protein kinase; EGFR: Epidermal growth factor receptor; PIP: Prolactin-induced protein; ERK: Extracellular regulated protein kinases; MEK: Mitogen-activated protein kinase/extracellular regulated protein kinases; mTOR: Mammalian target of rapamycin; PI3K: Phosphoinositide 3-kinase; RAF: Rapidly accelerated fibrosarcoma; SHP2: Src homology-2 domain-containing protein tyrosine phosphatase-2; SOS: Son of sevenless.

with minimal paradoxical MAPK activation[44,45], however, a phase I trial in advanced cancers was terminated early due to lack of sufficient clinical efficacy (NCT02014116). MLN2480 (tovorafenib) showed an acceptable safety profile[46], and HM95573 (belvarafenib) was well tolerated and showed anti-tumor activity in advanced solid tumors with RAS or RAF mutations[47]. The Yes-associated protein (YAP) is a transcription coregulator downstream from KRAS that promotes cell proliferation[48]. Combining LY3009120 and YAP-inhibitor (verteporfin) showed anti-tumor effect *in vivo* and *in vitro* by blocking compensatory activation of AKT pathway[49].

MEK

As mentioned above, trametinib is a MEK1/2 inhibitor FDA approved in combination with dabrafenib (RAF-inhibitor) as a tumor agnostic drug[50]. Trametinib was studied in combination with gemcitabine in a placebo controlled clinical trial for untreated metastatic PDAC. Unfortunately, it did not show improvement in overall survival (OS), PFS, or overall response rate (ORR)[51]. This is potentially due to a compensatory mechanism called autophagy, initiated through activation of the AKT pathway[52]. A Phase II trial of selumetinib (MEK1/2 kinase inhibitor) in PC did not show any significant difference in OS when compared to capecitabine[53], another phase II study of selumetinib targeting only PC patients with $KRAS^{G12R}$ mutation after at least two lines of prior systemic chemotherapy did not improve ORR, however, three patients had stable disease for ≥ 6 months[54]. A phase I/II trial studied the selective MEK1/2 inhibitor pimasertib in combination with gemcitabine *vs* gemcitabine alone in patients with metastatic PC. Despite the promising safety and efficacy of this combination, it did not improve PFS or OS[55]. Unfortunately, in whole there was no observed clinical benefit of MEK inhibitors in the multiple trials done in PC.

ERK

After resistance to BRAF and MEK inhibitors, the next downstream target is ERK. SCH772984[56] is a selective inhibitor of ERK1/2 that showed tumor regression in xenograft models refractory to BRAF and MEK inhibitors. Similar effects were seen with ulixertinib[57]. A phase Ib trial combining ERK1/2 inhibitor (GDC-0994) and MEK inhibitor (cobimetinib) in advanced solid tumors was terminated due to tolerability issues[58]. The ERK1/2 inhibitor JSI-1187-01 demonstrated pre-clinical efficacy in tumor models with MAPK pathway mutations, as well as synergy with BRAF inhibitors[59], and is being studied in a phase I trial (NCT04418167).

PI3K-AKT-mTOR-pathway

The PI3K-AKT-mTOR-pathway was shown in Table 2. One of the postulated reasons EGFR inhibitors and other targeted therapies develop resistance is the hyper-activation of PI3K-AKT-mTOR pathway, which can drive cancer progression and survival. PI3K is overexpressed in around 50% of patients with PC[60], and AKT2 is amplified in 10%-20% of PDAC [61]. TAM plays a role in the development of PC[62] by creating an immune-suppressive microenvironment, minimizing

Table 2 Phosphoinositide 3-kinase-protein kinase-mammalian target of rapamycin-pathway inhibitors

Agent	Combination	Phase	NCT number[1]
PI3K inhibitors (p110α) isoform			
Alpelisib (BYL719)	Gemcitabine and abraxane	I	NCT02155088
Buparlisib (BKM120)	mFOLFOX6; trametinib (MEKi)	I; I	NCT01571024; NCT01155453
Pan-PI3K inhibitors			
Copanlisib(BAY 80–6946)	N/A	I	NCT00962611
PI3K and mTOR inhibitors			
Voxtalisib (SAR245409, *XL765*)	N/A	I	NCT00485719
Dactolisib(NVP-BEZ235)	MEK162 (MEKi)	I	NCT01337765
Gedatolisib (PF-05212384, PKI-587)	Palbociclib (CDKi)	I	NCT03065062
Pan-Akt inhibitors			
MK2206	Monotherapy; dinaciclib (CDKi); selumitinib (MEKi) vs mFOLFOX6	I; I; II	NCT00848718; NCT01783171; NCT01658943
Afuresertib (GSK2110183)	Trametinib (MEKi); N/A	I; II	NCT01476137; NCT01531894
Uprosertib (GSK2141795)	Trametinib (MEKi)	I	NCT01138085
Oleandrin (PBI-05204)	N/A	II	NCT02329717
Perifosine	N/A	II; II	NCT00053924; NCT00059982
RX-0201	Gemcitabine	II	NCT01028495
Rapalogs (mTORC1 inhibitors)			
Sirolimus (rapamycin)	Sunitinib (RTKi); N/A; metformin; vismodegib (SMOi)	I; II; I/II; I	NCT00583063; NCT00499486; NCT02048384; NCT01537107
Temsirolimus (*CCI-779*, Torisel)	Lenalidomide; gemcitabine; nivolumab (PD-1i)	I; I; I/II	NCT01183663; NCT00593008; NCT02423954
Everolimus (RAD001)	Sorafenib (RTKi); trametinib (MEKi); gemcitabine; cetuximab (EGFRi) and capecitabine; N/A	I; I; I/II; I/II; II	NCT00981162; NCT00955773; NCT00560963; NCT01077986; NCT00409292
Ridafirolimus	Bevacizumab (VEGFRi)	I	NCT00781846
mTORC1/2 inhibitors			
Vistusertib (AZD2014)	N/A; selumitinib (MEKi); olaparib (PARPi)	I; II; II	NCT01026402; NCT02583542; NCT02576444

[1]clinicaltrials.gov.

PI3K: Phosphoinositide 3-kinase; NCT: National clinical trial; MEKi: Mitogen-activated protein kinase/ extracellular regulated protein kinases inhibitor; CDKi: Cyclin-dependent kinase inhibitor; RTKi: Receptor tyrosine kinase inhibitor; SMOi: Smoothened inhibitor; PD-1i: Programmed cell death receptor-1 inhibitor; EGFRi: Epidermal growth factor receptor inhibitor; VEGFRi: Vascular endothelial growth factor receptor inhibitor; mTOR: mammalian target of rapamycin; PARPi: Poly (ADP-ribose) polymerase inhibitor; N/A: Not applicable.

the antitumor effect of T-cells[63]. PI3K helps drive this immune suppression, so its inhibition can restore immune response against cancer cells as well as potentiate the effect of chemotherapy[64]. Additionally, AKT mediates an anti-apoptotic effect and plays a role in chemoresistance[65]. Phosphatase and tensin homolog is a tumor suppressor of the AKT/mTOR pathway, its loss has been implicated in PC development, recurrence, and prognosis[66], as well as acceleration of *KRAS*^{G12D}-induced PDAC in mice[67]. An *in vivo* study tested PI3Kα-specific inhibitor (BYL) in combination with an EGFR inhibitor (erlotinib) and showed reduced tumor volume and apoptosis in PDAC cell lines[68]. Currently a clinical trial combining gedatolisib (PI3K/mTOR inhibitor) with palbociclib (CDK4/6 inhibitor) in advanced squamous cell cancers of the lung, pancreas, and solid tumors is recruiting (NCT03065062). A phase I/II trial studied the safety and efficacy of combining everolimus (mTOR inhibitor), cetuximab (EGFR inhibitor), and capecitabine, however, the combination resulted in significant epidermal and mucosal toxicities with minimal efficacy[69].

Small interfering RNA, MicroRNA, and clustered regularly interspaced short palindromic repeats

Pre-clinical studies show that small interfering RNAs (siRNAs) have potential in cancer treatment. To deliver siRNAs to target cancer cells, scientists devised two unique methods, one utilized nanoparticle[70] to target lung cancer cells and another study used a biodegradable polymeric matrix (LODER) to carry the anti *KRAS*^{G12D} siRNA. This resulted in the

decrease of KRAS levels and inhibited cell proliferation[71]. MicroRNAs (miRNA) regulate cell proliferation and contribute to PC development. Depending on their role they can act as tumour suppressor or oncogenic miRNAs[72,73]. MRX34 (miRNA-34 mimic) was used in a phase I clinical trial that utilized lipid-based vesicles (NOV40) as a delivery vector, for treating patients with advanced solid tumors. miRNA-96 directly targets *KRAS* oncogene decreasing PC cell invasion and slowing tumor growth both *in vivo* and *in vitro*[74]. Clustered regularly interspaced short palindromic repeat (CRISPR) is currently being studied in *KRAS*-mutated cancers. This technology is being harnessed to target inactivated tumor suppressor genes or overactive oncogenes. In a 2018 study CRISPR-Cas13a was developed to target $KRAS^{G12D}$ mRNA. Subsequently, it also suppressed downstream ERK and AKT proteins resulting in apoptosis and significant tumor suppression *in vivo* and *in vitro*[75]. Two phase I trials utilizing the CRISPR platform are currently ongoing in PC (NCT04426669 and NCT04842812).

CONCLUSION

KRAS mutation remains the hallmark genetic aberration leading to PC. Although several studies have demonstrated positive preclinical results, the resulting clinical trial results have been largely disappointing. As we continue to have a deeper understanding of the KRAS pathway, resistance mechanisms, and the role and function of the immune system; we get closer to developing effective therapies to outsmart the scourge that is PC. Ongoing clinical trials targeting more common *KRAS* mutations in PC will hopefully lead to more effective therapy and change the outcomes for the thousands of patients affected by this disease every year.

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FOOTNOTES

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