

Pancreas adenocarcinoma: novel therapeutics

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Abstract: Pancreatic ductal adenocarcinoma (PDAC) is the third highest cause of cancer-related deaths in the US, and is projected to be second only to non-small cell lung cancer (NSCLC) by the 2020s. Current therapies have a modest impact on survival and median overall survival (mOS) across all stages of disease remains under a year. Over the last decade, however, great strides have been made in the understanding of PDAC pathobiology including the role of the tumor microenvironment (TME), DNA damage repair and mechanism of immunosuppression. Exciting novel therapeutics are in clinical development targeting the TME to increase cytotoxic drug delivery, decrease immunosuppressive cell presence and attack cancer stem cells (CSCs). Immune checkpoint inhibitors, cancer vaccines and other immunotherapies are actively being studied and novel combinations of targeted agents are being pursued. There is a sense of optimism in the oncology community that these scientific advances will translate into improved outcomes for patients with PDAC in the proximate future. In this review, we examine various novel therapeutics under clinical development with a focus on stromal disrupting agents, immunotherapeutics and DNA damage repair strategies.

Keywords: Pancreas cancer; therapeutics; tumor microenvironment (TME); immunotherapy

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the third highest cause of cancer-related deaths in the US, and is projected to be second only to non-small cell lung cancer (NSCLC) by the 2020s (1). In 2017, there are estimated to be 53,670 new cases of pancreas cancer and 43,090 deaths (2). Of these, 85% will present with unresectable disease, with a 5-year survival of 3% in patients who are metastatic at diagnosis (3). Despite these challenging figures, exciting novel therapeutics are in development and there is hope for improved outcomes in the near future.

Current therapies for metastatic PDAC

For decades, gemcitabine was a standard of care for first

line treatment of unresectable and metastatic PDAC (4). In 2007, erlotinib with gemcitabine was approved, but more recently, FOLFIRINOX (folinic acid, 5-FU, irinotecan and oxaliplatin) and gemcitabine with nab-paclitaxel (GN) have become the two upfront standards of care regimens. FOLFIRINOX demonstrated a median overall survival (mOS) of 11.2 *vs.* 6.8 months for gemcitabine (P=0.001) (PRODIGE-III-2011) (5). GN improved mOS from 6.7 to 8.5 months (P=0.001) compared to gemcitabine (MPACT-2013) (6). Recently, as second line and beyond, nano-liposomal irinotecan in combination with 5-FU and leucovorin was approved in patients previously treated with gemcitabine (NAPOLI-1-2015). Nano-liposomal irinotecan with 5-FU had a mOS of 6.1 months compared to 4.2 months for 5-FU and leucovorin alone (P=0.012) (7).

Despite studying numerous agents over the last decade,

almost none beyond cytotoxic agents have demonstrated survival benefit in late stage PDAC studies. Nonetheless, our understanding of PDAC pathobiology has evolved, including genetic basis, microenvironment and immune response.

Pathobiology

Over 90% of PDAC's are driven by early activating *KRAS* mutations (8,9). Activated *KRAS* signals through a phosphorylation cascade of RAF, MEK and ERK lead to transcription of proliferation genes. In parallel, RAS activation increases signaling through PI3K, AKT and mTOR also lead to transcription of pro-survival and proliferation genes (10). Inactivating mutations and deletions in genes that regulate the cell cycle are frequent in PDAC. In a set of 336 patients whose tumors underwent genomic profiling at Memorial Sloan Kettering Cancer Center, mutations in *TP53* were present in 72% and *CDKN2A* in 18% with 9p21 deletions involving *CDKN2A* and/or *CDKN2B* in 14%. TGF- β effector *SMAD4* was mutated in 22%. Beyond these alterations, of the 256 different mutated genes and 128 different genes with copy number alterations, only *ARID1A* was altered in >10% of PDACs, although 4.2% of these patients had germline mutations in *BRC A2* (9). These patients with germline DNA repair deficits represent an important subset with physiology that appears to predispose sensitivity to DNA damaging agents.

Histologically, PDAC is characterized by a dense stroma composing an average of 48% of tumor volume in one series (11). Stromal components include fibroblasts, hyaluronic acid (HA), collagen and other extracellular matrix proteins, inflammatory cells and cancer stem cells (CSCs). There is debate whether the stroma supports malignancy or acts as a protective barrier, however, evidence supports the stroma impairing drug delivery and supporting an immunosuppressive tumor microenvironment (TME) (12). Although PDAC is not considered an immunogenic cancer, activated CD8+ T cells are seen in the TME, but are far outnumbered by immunosuppressive inflammatory cells not seen in the normal pancreas (13). Novel therapeutics are in development targeting the stroma to improve drug delivery and the immune response. Stromal modifying therapy and immunotherapeutics as well as novel targeted agents and metabolism-directed strategies will be reviewed in detail. A selection of ongoing trials are described in *Table 1* and therapeutic targets are depicted in *Figure 1*.

Stromal targeting agents

Enzymatic stromal disruption strategies

The PDAC stroma contains an abundance of hyaluronan (HA), collagen and fibronectin, which are deposited by activated cancer-associated fibroblasts (CAFs). HA forms a gel-like, compression resistant fluid leading to increased interstitial pressures causing vessel collapse, impeding blood flow and reducing therapeutic delivery in murine PDAC models (14). A retrospective study evaluating HA levels in human PDAC found that high HA tumor staining was associated with worse overall survival (mOS 9.3 *vs.* 24.3 months; $P=0.037$) (15).

PEGPH20 is a recombinant pegylated hyaluronidase enzyme developed to target tumor stromal HA effects. In a study using KPC (*Kras*^{LSL.G12D/+}; *p53*^{R172H/+}; *PdxCre*^{tg/+}) mice, PEGPH20 administration improved vessel patency and increased intra-tumoral delivery of doxorubicin and gemcitabine. Furthermore, combination therapy with gemcitabine and PEGPH20 led to improved survival relative to gemcitabine alone (28.5 *vs.* 15 days; $P=0.002$) (16).

Early stage studies of PEGPH20 have shown promise. A phase Ib non-randomized single arm study of PEGPH20 in combination with gemcitabine as first line treatment for metastatic PDAC demonstrated a signal of interest in patients with high HA levels when compared to the low HA groups with median progression free survival (mPFS) of 7.2 *vs.* 3.5 months and mOS of 13 *vs.* 5.7 months (17).

Randomized phase II results of PEGPH20 in combination with GN compared to GN continue to demonstrate potential benefit, notably and perhaps exclusively in high HA patients. Utilizing a tissue based immunohistochemistry assay to determine HA levels, the study met the pre-specified secondary endpoint of mPFS in the high HA group (9.2 *vs.* 5.2 months; $P=0.048$). The study underwent a temporary hold due to increased thrombosis rate, both venous and arterial, in the PEGPH20 arm (43% *vs.* 25%). After resumption of the trial (stage II), high risk patients for thromboembolism were excluded and all patients were placed on low molecular weight heparin primary prophylaxis resulting in similar thrombosis rates between groups and mitigating the negative signal. It is notable, that many patients discontinued treatment during the clinical hold potentially decreasing the treatment effect in stage I analysis. In stage II (following hold and with institution of low molecular weight heparin), an improved PFS signal was observed in high HA patients and a trend

Table 1 Selected ongoing clinical trials for patients with metastatic PDAC

Category	Clinical trial identifier	Therapeutic agents	Mechanism of action	Phase	Status	Treatment line	Outcomes
Monoclonal antibodies/ antibody drug conjugates	NCT02146313	DMCU4064A	DMCU4064A: anti-MUC16 monoclonal antibody conjugated to monomethyl auristatin E	I	Recruiting	Previously treated	DLT, AE
	NCT02475213	Enoblituzumab and pembrolizumab	Enoblituzumab: anti-B7-H3 monoclonal antibody; pembrolizumab: anti-PD-1 monoclonal antibody	I	Recruiting	Previously treated	AE
	NCT02672917	MVT-5873 ± SOC chemotherapy	MVT-5873: anti-CA19-9 monoclonal antibody	I	Recruiting	1st line (w/SOC), previously treated (monotherapy)	MTD
	NCT02687230	MVT-2163 and MVF-5873	MVT-2163: anti-CA19-9 antibody conjugated to PET radiotracer; MVF-5873: anti-CA19-9 antibody	I	Recruiting	Unspecified	AE, PD/PK, imaging parameters
Checkpoint inhibitors	NCT02526017	Cabiralizumab and nivolumab	Cabiralizumab: anti-CSFR1 antibody; nivolumab: anti-PD-1 antibody	I	Recruiting	Previously treated	Phase Ia: AE, DLT; phase Ib: ORR
	NCT02558894	Durvalumab ± tremelimumab	Durvalumab: anti-PD-L1 antibody; tremelimumab: anti-CTLA-4 antibody	II	Ongoing, not recruiting	2nd line	ORR
	NCT02639026	Durvalumab and tremelimumab with radiotherapy	Durvalumab: anti-PD-L1 antibody; tremelimumab: anti-CTLA-4 antibody	I	Recruiting	Previously treated	AE
	NCT02715531	Atezolizumab and gemcitabine/nab-paclitaxel	Atezolizumab: anti-PD-L1 antibody	I	Recruiting	1st line	AE
	NCT02734160	Galunisertib and durvalumab	Galunisertib: TGF-β receptor inhibitor; durvalumab: anti-PD-L1 antibody	I	Recruiting	Previously Treated	DLT
	NCT02777710	Durvalumab and pexidartinib	Durvalumab: anti-PD-L1 antibody; pexidartinib: CSF-1 receptor antagonist	I	Recruiting	Previously treated	Part 1: DLT; part 2: ORR
	NCT02879318	Gemcitabine and nab-paclitaxel ± durvalumab and tremelimumab	Durvalumab: anti-PD-L1 antibody; tremelimumab: anti-CTLA-4 antibody	II	Recruiting	1st line	OS

Table 1 (continued)

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Category	Clinical trial identifier	Therapeutic agents	Mechanism of action	Phase	Status	Treatment line	Outcomes
Other immunotherapies	NCT02923921	FOLFOX ± AM0010	AM0010: Pegylated-IL-10	III	Recruiting	2nd line	OS
	NCT01583686	Anti-mesothelin CAR-T and aldesleukin with cyclophosphamide and fludarabine pre-conditioning	Aldesleukin: IL-2	I/II	Recruiting	Previously treated	Safety
	NCT01896869	Arm A: GVAX and ipilimumab; arm B: FOLFIRINOX	GVAX: vaccine of irradiated GM-CSF releasing PDAC cell lines Ipilimumab: anti-CTLA-4 antibody	II	Recruiting	2nd line, after FOLFIRINOX	OS
	NCT02077881	Indoximod, gemcitabine, nab-paclitaxel	Indoximod: IDO inhibitor	I/II	Recruiting	1st line	Phase I: RP2D, DLT; phase II: OS
	NCT02159716	CART-meso	CART-meso: anti-mesothelin CART-T	I	Ongoing, not recruiting	Previously treated	AE
	NCT02349724	Anti-CEA CAR-T		I	Recruiting	Previously treated	AE
	NCT02587689	anti-MUC1 CAR-T Cells		I/II	Recruiting	Previously treated	Phase I: AE; phase II: unspecified
Cancer stem cell targeted therapies	NCT02999731	Napabucasin with gemcitabine and nab-paclitaxel	Napabucasin: STAT3 transcription inhibitor	III	Not yet recruiting	1st line	OS
	NCT02050178	OMP-54F28, gemcitabine and nab-paclitaxel	OMP-54F28: frizzled receptor trap fused to Fc domain	I	Recruiting	1st line	MTD
Stromal targeting	NCT02179970	Plerixafor	Plerixafor: CXCR4 antagonist	I	Recruiting	Previously treated	AE
	NCT02583477	Durvalumab with gemcitabine/nab-paclitaxel or AZD5069	Durvalumab: anti-PD-L1 antibody; AZD5069: CXCR2 inhibitor	I/II	Ongoing, not recruiting	1st or 2nd line	Phase I: DLT; phase II: ORR
	NCT02715804	Gemcitabine/nab-paclitaxel ± PEGPH20	PEGPH20: pegylated recombinant hyaluronidase	III	Recruiting	1st line	PFS, OS
	NCT02732938	PF-04136309 with gemcitabine/nab-paclitaxel	PF-04136309: CCR2 inhibitor	II	Recruiting	1st line	DLT, PFS
	NCT02826486	BL-8040 and pembrolizumab	BL-8040: CXCR4 inhibitor; pembrolizumab: anti-PD-L1 antibody	II	Recruiting	Previously treated	ORR

Table 1 (continued)

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Category	Clinical trial identifier	Therapeutic agents	Mechanism of action	Phase	Status	Treatment line	Outcomes
Metabolism	NCT01506973	Hydroxychloroquine and gemcitabine/abraxane	Hydroxychloroquine: autophagy inhibitor	I/II	Recruiting	1st or 2nd line	Phase I: DLT, autophagy markers; phase II: OS
	NCT01835041	CPI-613 and mFOLFIRINOX	CPI-613: alpha-ketoglutarate dehydrogenase inhibitor	I	Ongoing, not recruiting	1st line	MTD
	NCT02101580	ADI-PEG and gemcitabine/nab-paclitaxel	ADI-PEG: Pegylated arginine deiminase	I	Ongoing, not recruiting	DLT cohort: 1st or 2nd line, Expansion cohort: 1st line	AE
	NCT02336087	Gemcitabine, nab-paclitaxel, metformin and dietary supplements		I	Recruiting	1st line	DLT, compliance, AE
DNA damage repair	NCT01489865	Veliparib with mFOLFOX	Veliparib: PARP inhibitor	I/II	Recruiting	Previously treated: 'BRCAness'	DLT
	NCT01585805	1st line: Gemcitabine, cisplatin ± veliparib; Previously treated: veliparib	Veliparib: PARP inhibitor	II	Recruiting	1st line in combination, previously treated in monotherapy	Part I: RP2D, ORR combination; part II: ORR veliparib alone
Targeted therapies and others	NCT02184195	Olaparib	Olaparib: PARP inhibitor	III	Recruiting	Stable on platinum x16 weeks, germline BRCA mutation	PFS
	NCT02890355	mFOLFIRI and veliparib	Veliparib: PARP inhibitor	II	Recruiting	2nd line	OS
	NCT01497392	Dovitinib, gemcitabine, capecitabine	Dovitinib: FGFR3 antagonist	I	Ongoing, not recruiting	unspecified	MTD, AE
	NCT01676259	Gemcitabine/nab-paclitaxel ± siG12D-LODER	siG12D-LODER: siRNA to KRAS G12D by local intratumoral eluter delivery	II	Not yet open	1st line	PFS
	NCT01783171	Dinaciclib and MK2206	Dinaciclib: CDK1/2/5/9 inhibitor, MK2206: AKT inhibitor	I	Ongoing, not recruiting	Previously treated	MTD
	NCT01954992	Glufosfamide vs. 5-FU	Glufosfamide: Ifosfamide linked to β-d-glucose	III	Recruiting	Previously treated with gemcitabine	OS

Table 1 (continued)

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Category	Clinical trial identifier	Therapeutic agents	Mechanism of action	Phase	Status	Treatment line	Outcomes
DNA damage repair	NCT02005315	Vantictumab, gemcitabine and nab-paclitaxel	Vantictumab: anti-frizzled Mab	I	Recruiting	1st line	MTD
	NCT02155088	BYL719 with gemcitabine and nab-paclitaxel	BYL719: PI3K α inhibitor	I	Ongoing, not recruiting	1st line	MTD
	NCT02178436	Selinexor with gemcitabine/nab-paclitaxel	Selinexor: XP01 inhibitor (inactivates CRM1-mediated nuclear protein export)	I/II	Recruiting	1st line	Phase I: MTD, AE; phase II: OS
	NCT02289898	Gemcitabine/nab-paclitaxel \pm demcizumab	Demcizumab: anti-Delta-like ligand 4 antibody	II	Ongoing, not recruiting	1st line	PFS
	NCT02352831	Tosedostat and capecitabine	Tosedostat: aminopeptidase inhibitor	I/II	Recruiting	2nd line	Phase I: DLT; phase II: PFS
	NCT02501902	Palbociclib + nab-paclitaxel	Palbociclib: CDK4/6 inhibitor	I w/MTD expansion	Recruiting	No prior treatment with study agents	DLT
	NCT02546531	Defactinib, pembrolizumab and gemcitabine	Defactinib: FAK inhibitor; pembrolizumab: anti-PD-1 antibody	I	Recruiting	Previously treated	MTD
	NCT02703571	Ribociclib and trametinib	Ribociclib: CDK 4/6 inhibitor; trametinib: MEK inhibitor	I/II	Recruiting	Previously treated	Phase I: DLT; phase II: ORR
	NCT02713529	AMG820 and pembrolizumab	AMG820: anti-CSF1R antibody; pembrolizumab: anti-PD-1 antibody	I/II	Recruiting	Previously Treated	Phase I: AE; phase II: ORR
	NCT02737228	CG200745, gemcitabine and erlotinib	CG200745: HDAC inhibitor	I/II	Recruiting	1st line	DCR
	NCT02807844	MCS110 and PDR001	MCS110: anti-macrophage CSF Mab; PDR001: anti-PD-1 antibody	I/II	Recruiting	Previously treated	Phase I: AE; phase II: ORR
	NCT02959164	Decitabine and gemcitabine	Decitabine: DNA methyltransferase inhibitor	I	Recruiting	Previously Treated	DLTs, ORR
NCT02981342	Intervention: abemaciclib with LY3023414 or galunisertib; control: gemcitabine or capecitabine	Abemaciclib: CDK4/6 inhibitor; LY3023414: dual PI3K/mTOR inhibitor; galunisertib: TGF- β receptor antagonist	II	Recruiting	Previously treated	Part I: DCR; part II: PFS	

AE, adverse events; CART, chimeric antigen receptor T-cell; CDK, cyclin dependent kinase; CSF1R, macrophage colony stimulating factor-1 receptor; DCR, disease control rate; DLT, dose limiting toxicity; FAK, focal adhesion kinase; FGFR, fibroblast growth factor receptor; HDAC, histone deacetylase; IDO, indoleamine 2,3-dioxygenase; Mab, monoclonal antibody; MTD, maximum tolerated dose; ORR, objective response rate; OS, overall survival; PARR, poly-ADP ribose reductase; PD, pharmacodynamics; PFS, progression free survival; PK, pharmacokinetic; RP2D, recommended phase 2 dose; SOC, standard of care.

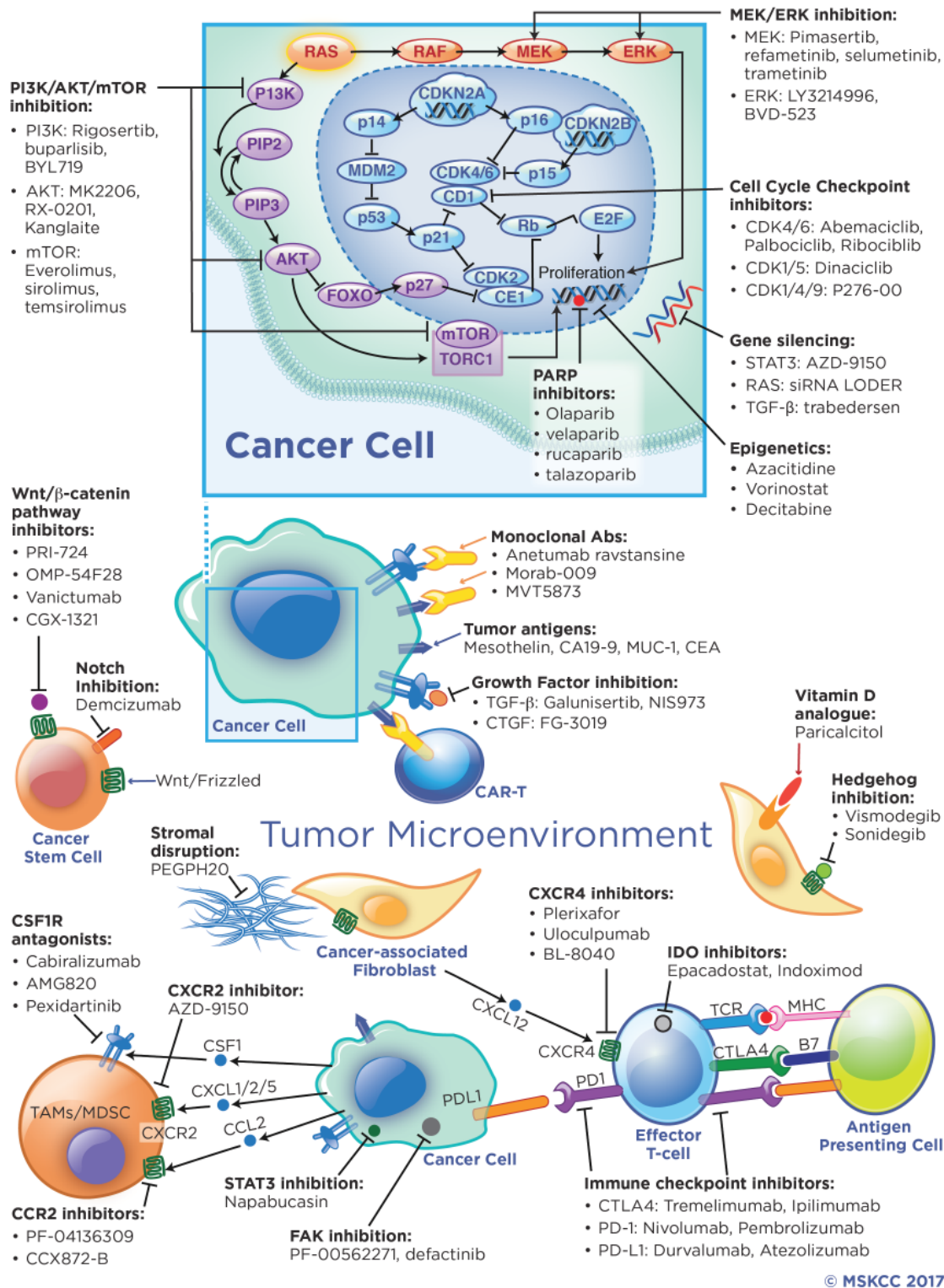


Figure 1 Tumor microenvironment and common dysregulated intracellular signaling pathways with selected novel therapeutic targets.

Table 2 Recently reported negative trials in patients with PDAC

Clinical trial identifier	Experimental therapeutic	Mechanism of action	Study agents	Treatment line	Phase	Results
NCT01956812	90Y-clivatuzumab	Anti-MUC-1 antibody labeled with yttrium-90	90Y-clivatuzumab with gemcitabine	3rd line	III	Interim analysis: futile (19)
NCT01072981	Algenpantucel-L	Allogenic pancreas cells expressing alpha-gal	Adjuvant gem with or without 5-FU chemoradiation ± algenpantucel-L	Adjuvant	III	mOS: control 30.4 months, intervention 27.3 months (20)
NCT02004262	CRS-207	Mesothelin expressing live, attenuated listeria	CRS-207 ± GVAX with cyclophosphamide vs. chemotherapy	3rd line	II	mOS (n=213): CRS-207 and GVAX 3.8 months (HR 1.52, P=0.97), CRS-207 alone 5.4 months (HR 1.05, P=0.48) and 4.6 months for chemotherapy (21)
NCT01746979	Evofofosamide	Hypoxia induced mustard pro-drug	Gemcitabine ± evofosamide	1st line	III	mOS 7.6 vs. 8.7 months (P=0.0589), 15% vs. 19% (P=0.16) (22)
NCT02202785	MLN0264	Anti-guanylyl cyclase C antibody conjugated to MMAE	MLN0264	Previously treated	II	Interim analysis (n=38): ORR 3%, SDR 24%, PDR 74% (23)
NCT01621243	Necuparanib	Heparin substance	Gemcitabine/nab-paclitaxel ± necuparanib	1st line	I/II	Interim analysis (n=117): futile (24)
NCT01959139	PEGPH20	Pegylated recombinant hyaluronidase	mFOLFIRINOX ± PEGPH20	1st line	I/II	Interim analysis: futile (25)
NCT02117479	Ruxolitinib	JAK 1/2 inhibitor	Capecitabine ± ruxolitinib	2nd line	III	Interim analysis: futile (26)

mOS, median overall survival; SDR, stable disease rate; PDR, progressive disease rate.

towards improved OS was seen in the high HA group 11.7 vs. 7.8 months (HR 0.52, 0.22–1.23) (18).

Recently, however, a phase I/randomized phase II of first line mFOLFIRINOX ± PEGPH20 (NCT01959139) in a non-biomarker selected population was stopped for futility at interim analysis (*Table 2*). The data set is being further analyzed including a retrospective analysis of tumor HA levels (25).

A phase III registration study for first line PEGPH20 in combination with GN vs. GN and placebo is recruiting in HA high patients (NCT02715804) and our group is evaluating PEGPH20 and GN in patients at higher risk for thrombosis in combination with rivaroxaban (NCT02921022).

Chemokines and the immune stroma

The immunosuppressive nature of the PDAC TME is established early in disease with interstitial aggregates of tumor-associated macrophages (TAMs), myeloid derived suppressor cells (MDSCs) and Tregs recruited from the bone marrow (13,27). Once in the microenvironment, MDSCs and TAMs inhibit proliferation and induce apoptosis of activated T-cells (27). The relatively small numbers of cytotoxic T cells in the microenvironment are rarely found in proximity to tumor epithelial cells and have down regulation of the activating T-cell co-receptor CD3 (28,29). An emerging strategy to combat the immunosuppressive TME targets the chemokine receptors that mobilize immunosuppressive cells and inhibit

migration of effector cells.

CXCR4 is a chemokine receptor expressed by effector T-lymphocytes. In the TME, the CXCR4 ligand, CXCL12, is secreted by fibroblast activation protein-alpha positive CAFs (FAP+ CAFs). In a KPC mouse model, CXCL12, coated malignant cells and appeared to exclude effector T-cells from regions with tumor epithelial cells. Depletion of CAFs or administration of the CXCR4 inhibitor, plerixafor, induced the accumulation of tumor-infiltrating lymphocytes among cancer cells and acted synergistically with PDL-1 inhibition (30). CXCR4 has also been identified on PDAC cells and PDAC stem cells as a mediator of invasion and engraftment in the pre-metastatic niche (31,32). Plerixafor is currently being evaluated in a phase I dose finding study (NCT02179970). BL-8040, a peptide inhibitor of CXCR4, is under investigation in two phase II studies in combination with pembrolizumab (NCT02907099, NCT02826486). And, ulocuplumab, an anti-CXCR4 monoclonal antibody, has been studied in combination with nivolumab in a phase I/II of metastatic PDAC and NSCLC (NCT02472977) and results are awaited.

CXCR2 and CCR2 are chemokine receptors expressed on immunosuppressive inflammatory cells. CXCR2 on MDSCs and TAMs is stimulated by CXCL1, CXCL2 and CXCL5 secreted by tumor cells and FAP+ CAFs (33). In a murine model, inhibition of CXCR2 decreased the number of myeloid cells in primary tumors and decreased metastases through prevention of metastatic niche formation (33). A phase I/II study of CXCR2 inhibitor, AZD5069, in combination with durvalumab is recruiting (NCT02583477).

CCR2 is expressed by macrophages with its ligand, CCL2, secreted by PDAC cells leading to macrophages infiltrating PDAC tumors (27). Blockade of CCR2 in mice with the novel agent, PF-04136309, decreased infiltration of inflammatory monocytes and TAMs in tumors and pre-metastatic liver and reduced tumor growth and metastases when combined with gemcitabine (27). PF-04136309 was evaluated in a phase Ib with expansion cohort in borderline resectable and locally advanced disease in combination with first line FOLFIRINOX. Sixteen of 33 patients who obtained repeat imaging had an objective response and 32 of 33 had disease control (34). A phase IB/randomized phase II study in combination with first line GN is currently underway (NCT02732938). CCR2 inhibitor, *CCX872-B*, has also demonstrated efficacy in an orthotopic mouse model decreasing tumor size by 42%

and the proportion of m-MDSCs by 45% (35). In a mostly metastatic phase I population, *CCX872-B* in combination with FOLFIRINOX had an ORR of 37% with SD of 41%. Thirteen of 21 patients with available imaging at 24 weeks were progression free (36).

Macrophages colony stimulating factor-1 (CSF-1) is over-secreted by PDAC cells and is a crucial survival factor for TAMs (37). CSF-1 receptor (CSF-1R) inhibition leads to death of CSF-1 differentiated macrophages or functional reprogramming that enhances antigen presentation and T-cell response (38). In a murine PDAC model, CSF-1 inhibition also led to increased expression of PDL-1 and CTLA-4 and therapeutic synergy with anti-PD-1 and anti-CTLA4 inhibitors (37). Four CSF-1R inhibitors are under study in early phase trials in combination with PD-1/PD-L1 inhibitors: AMG820 in combination with pembrolizumab (NCT02713529), cabiralizumab with nivolumab (NCT02526017), pexidartinib with durvalumab (NCT02777710) and MCS110 in combination with PDR001 (NCT02807844).

Indoleamine 2,3-dioxygenase (IDO)-inhibition

The enzyme IDO catabolizes tryptophan into kynurenine which is toxic to effector T cells and leads to Treg differentiation (39). In cellular assays, IDO inhibition promotes T-cell and natural killer cell growth and reduces Treg cells (40). A phase I of IDO inhibitor, epacadostat, in combination with pembrolizumab in multiple malignancies recently completed (41). Indoximod has been studied in a phase I/II study as first line treatment in combination with GN (NCT02077881). At interim analysis 11/30 patients had an objective response including one complete response (42).

Hedgehog

The hedgehog pathway is involved in cancer stemness, stromal desmoplasia and various developmental pathways (43,44). Sonic hedgehog activity is increased in the stroma and believed to activate CAFs (44,45). There is mixed data as to whether targeting the hedgehog pathway and resultant stromal desmoplasia inhibits or promotes PDAC progression (46). Early studies of smoothed inhibitors, vismodegib, saridegib and sonidegib, failed to demonstrate improved survival compared to controls (47-49). Both sonidegib and vismodegib are under study in combination with GN (NCT01431794, NCT01064622). At ASCO

2014, interim results were presented for the vismodegib study showing mPFS of 5.5 months and OS 10 of months (50).

Vitamin D

Activated pancreatic stellate cells (PSCs) are important precursors to CAFs (51). Recent data has demonstrated that vitamin D receptor (VDR) agonism modulates PSC activation reversing lipid droplet loss and expression of alpha-smooth muscle actin (52). Furthermore, incubation of PDAC cell lines in culture media from calcipotriol treated cancer-associated PSCs (CAPSCs) decreases proliferative gene expression including CXCL1, CSF2 and phospho-STAT3 relative to CAPSC culture media alone. *In vivo*, KPC mice treated with gemcitabine and calcipotriol had tumor volume decrease (70%), intratumoral gemcitabine increase and a 57% increase in survival compared to chemotherapy alone (52). Vitamin D3 has also been reported to induce differentiation of immature myeloid cells and increases in intratumoral CD4+ and CD8+ T cells in NSCLC and head and neck cancers, which may offer another mechanism of benefit in PDAC (53).

Paricalcitol is currently being studied in a single arm phase II study in combination with nivolumab, gemcitabine, nab-paclitaxel and cisplatin for first line metastatic disease (NCT02754726) and a neoadjuvant pilot in which it will be administered during a single cycle of GN versus GN alone before surgery (NCT02754726). Adverse effects as well as cellular and imaging markers will be evaluated in the latter.

Focal adhesion kinase (FAK)

FAK is a cytoplasmic tyrosine kinase with multiple functions. FAK pathways promote motility, invasion, survival and epithelial to mesenchymal transition (54). In an orthotopic mouse model of PDAC, FAK inhibition led to fewer CAFs and macrophages in the TME, smaller tumor volume, less invasion and fewer metastasis compared to controls (55). Phase I studies of PF-00562271 and GSK2256098 in combination with trametinib have completed (NCT00666926, NCT01938443). A phase II of second line GSK2256098 with trametinib and a phase I of defactinib with pembrolizumab are recruiting (NCT02428270, NCT02546531).

CSCs

The CSC theory posits that carcinogenesis is initiated by

a relatively small number of stem cells or early progenitor cells, which develop the capabilities of self-renewal and multi-lineage differentiation (56). In PDAC, stem cells are characterized by the expression of either CD44+/CD24+/ESA+ or CD133+ (\pm CXCR4+) surface markers and demonstrate resistance to gemcitabine and ionizing radiation (32,57,58).

Therapeutics aimed at these resistant cells target the Wnt/ β -catenin, notch, hedgehog and JAK/STAT pathways.

Wnt/ β -catenin

Aberrant activation of the Wnt pathway occurs in up to 65% of pancreatic cancer patients. Wnt pathway factors contribute to the epithelial-mesenchymal transition in PDAC and may be responsible for resistance to gemcitabine, DNA damage and ionizing radiation (59-61).

Inhibition of Wnt in a mouse model inhibits PanIN formation and OMP-54F8, a frizzled trap, decreased CSCs and reduced tumor growth in a patient derived xenograft greater than gemcitabine (62,63). OMP-54F8 is currently being studied in a phase I study with GN (NCT02050178). PRI-724 is a small molecule inhibitor of the Wnt target gene coactivator creb binding protein, and is the only wnt pathway inhibitor with clinical results in PDAC. In combination with gemcitabine as second line therapy, no responses were observed, but 62.5% of patients had a >30% reduction in CA19-9 and mPFS was 2 months (64). Two other wnt pathway inhibitors (CGX-1321 and Vantictumab) are in early phase clinical study (NCT02675946, NCT02005315).

Notch

Notch signaling is crucial for the embryonic development of multiple tissues including the pancreas and is upregulated in early pancreatic carcinogenesis and invasive disease (65-68). Increased notch activity facilitates the EMT and gives rise to CD44 positive pancreatic CSCs (69). Pre-clinical studies of notch inhibition including patient derived xenograft models showed promising results, however, clinical development has been more sobering (70). Tarextumab, a monoclonal antibody against notch 2/3, showed no survival benefit in a phase II study with GN and possibly worse outcomes in low notch expressers (71). Gamma secretase inhibitor, RO4929097 has been discontinued, and a phase I of MK0752 with gemcitabine had severe GI adverse effects leading to high patient withdrawal (72,73). Anti-delta-like

ligand 4 monoclonal antibody, demcizumab, continues to be studied in PDAC. In a phase I study in combination with first line GN, mPFS was 9.0 months and mOS 10.1 months, however, 2 patients developed reversible pulmonary hypertension, 1 of which developed heart failure, leading to abbreviated treatment dosing regimens of 70 days in the later cohorts (74). A randomized phase II study in combination with GN is completed and data is awaited. All arms received continuous cycles of GN until progression. One intervention arm received 3 cycles of demcizumab, the other received demcizumab for 3 cycles on, 3 cycles off and another 3 cycles on (NCT02289898).

JAK/STAT

Activation of JAK family receptors leads to phosphorylation of the STAT family transcription factors. JAK2/STAT3, in particular, is activated in PDAC with target genes including cyclin D1, p21, BCR-XL and VEGF contributing to cell cycle progression, apoptosis resistance and angiogenesis (75,76). In mice orthotopically injected with KRAS G12D shp53 cells, STAT3 knockdown leads to lower tumor volume and decreased proliferation than controls (77).

Early and mid-stage trials of JAK inhibitors showed promising initial results. In phase II, ruxolitinib and capecitabine *vs.* capecitabine and placebo demonstrated increased overall survival, 4.3 *vs.* 1.5 months, particularly in the high CRP subgroup (78). Ruxolitinib progressed to the phase III study, JANUS-1, where it again was in combination with capecitabine *vs.* capecitabine and placebo as second line treatment in patients with CRP >10. Unfortunately, as has been the case in a number of recent studies, interim analysis demonstrated futility (Table 2). Further development of ruxolitinib was discontinued in both the JANUS 1 and 2 trials (79).

Inhibition of STAT3 transcription by napabucasin has demonstrated ability to decrease relapse in PaCa-2 xenografts. Xenografts treated with gemcitabine or napabucasin for 41 days both exhibited decreased tumor growth compared to vehicle, however, when treatment was stopped tumors from gemcitabine treated mice continued to grow during the 22-day observation period, whereas napabucasin treated mice did not (80). Napabucasin has shown promising early clinical data (81). In a phase I/II in combination with paclitaxel in previously treated patients with a median of 2 prior regimens, a 52% disease control rate was achieved with mPFS of 10 weeks and mOS of 24 weeks (82). More recently in a phase Ib/II in combination

with GN as first line treatment, the intention to treat population achieved a DCR of 77% and ORR of 38% with maturing mPFS and mOS of >7.4 and >10.4 months, respectively (83). A phase III trial of napabucasin in combination with GN *vs.* GN and placebo is planned (NCT02993731). AZD-9150 is an anti-sense STAT3 inhibitor with a planned phase II in combination with durvalumab in multiple malignancies (NCT02983578).

Targeted therapy

Beyond the approval of erlotinib with gemcitabine, targeted therapy has demonstrated little efficacy in PDAC. Most targeted therapy has been directed at the RAS pathway or epidermal/platelet derived growth factor receptors (EGFR/PDGFR). RAS is a key driver of PDAC, mutated in 90–95% and found in early PanIN lesions. It or its downstream effectors, RAF, MEK and ERK, are therefore logical targets for inhibition. The most common mutations in RAS cause a constitutive activation and strategies to inhibit this activation have failed (84). Targeting RAS by inhibiting translation using small-interfering RNAs is a novel strategy to decrease RAS activity. siRNA against the G12D mutant RAS RNA by local prolonged delivery, siG12D LODER (Local Drug EluteR), has demonstrated decreased growth of human pancreatic tumor cells *in vivo* and prolonged mouse survival (85). In a phase Ib/II dose escalation 15 locally advanced, unresectable patients received siG12D LODER with a mOS of 15.12 months. Ten out of 12 patients had SD on repeat imaging and 2 had a PR (86). siRNA LODER is planned to be evaluated in locally advanced disease by intratumoral injection in a randomized phase II in combination with GN with/without LODER (NCT01676259).

MEK/ERK/MAPK, PI3K/AKT/mTOR

Given the challenges with targeting RAS, the downstream effectors MEK and ERK offer alternatives with therapeutics in development. MEK and ERK inhibitors when used as monotherapy or in combination with chemotherapy have not demonstrated benefit (87–90). MEK inhibition can lead to increased activation of PI3/AKT through hyperactivation of EGFR (91). As a result, various combination strategies have been attempted combining MEK inhibitors with PI3K, AKT and EGFR inhibitors. Unfortunately, this strategy has not seen improved outcomes and in some cases increased toxicity (92–94).

There are promising novel targets that intersect with RAS pathways including cell-cycle checkpoint inhibitors and novel kinase receptors.

Cell-cycle inhibition

Cell cycle dysregulation is a hallmark of malignancy. Cell cycle checkpoints are controlled by interactions between cyclins and corresponding cyclin dependent kinases (CDKs). p53 and CDKN2 gene mutations are common in PDAC and their protein products are intimately tied to the regulation of cyclin-D/CDK4/6 and cyclin E/CDK2 complexes which are required for progression through the G1/S checkpoint (95-97). Pre-clinical studies of multi-CDK inhibitor, daniciclib, reduced subcutaneous growth in 100% of human pancreatic cancer xenografts and combination with gemcitabine was more effective than either agent alone (98). *In vitro*, dual inhibition of CDK4/6 and PI3K/MTOR has shown synergistic effects in suppression of the cell cycle and CDK4/6 and MEK inhibition was additive (99).

Multiple CDK inhibitors are being studied in metastatic PDAC. Palbociclib is a CDK4/6 inhibitor undergoing investigation in two phase I studies—in combination with nab-paclitaxel (NCT02501902) and in combination with carboplatin or cisplatin (NCT02897375). Ribociclib and abemaciclib are in clinical study in combination with MEK and PI3K/AKT/MTOR inhibitors. Ribociclib is being evaluated in phase I/II studies in combination with everolimus (NCT02985125) and in combination with trametinib (NCT02703571) both in previously treated PDAC. Abemaciclib is being evaluated in a 4-arm phase II trial alone, in combination with PI3K/MTOR inhibitor, LY3023414, or in combination with TGF inhibitor, galunisertib (NCT02981342).

TGF-beta

Early in oncogenesis TGF- β is cytostatic and pro-apoptotic, however, later in disease TGF- β pathway activity leads to proliferation and invasiveness (100). TGF- β pathway signals through multiple SMAD proteins regulating transcription of various genes involved in cell cycle regulation and differentiation (101). SMAD4 is commonly mutated in PDAC and TGF- β stimulation of homozygous deleted SMAD4 cells leads to activation of pro-invasive and anti-apoptotic pathways including upregulation of ERK, β -catenin and p-BAD (102). In a phase I/II study

in previously treated patients, trabedersen, an antisense oligonucleotide of TGF- β 2, achieved a mOS of 13.4 months for patients administered the planned phase II dosing (n=9; 95% CI: 2.2–39.7) (103). Galunisertib, a small molecule TGF- β R1 inhibitor, achieved a mOS of 9.1 months in combination with gemcitabine *vs.* 7.59 months for gemcitabine and placebo in a recent phase II study (104). Another phase II study is planned in combination with cell cycle inhibitor, abemaciclib, as described previously, while a phase I in combination with durvalumab is recruiting (NCT02981342, NCT02734160).

Epigenetics

Epigenetic modification is a crucial method of gene control in malignancy. In PDAC, histone acetylation changes promote resistance to oxidative stress, poorer differentiation and upregulation of DNA repair genes leading to chemotherapy resistance (105). HDAC inhibitor, azacitidine, is being evaluated in a phase II study after adjuvant GN in patients with node positive disease or persistently elevated CA19-9 (NCT01845805) and a phase I study of refractory, metastatic patients in combination with nab-paclitaxel. CG200745 is in phase I/II in combination with gemcitabine and erlotinib (NCT02737228). In pre-clinical studies, CG200745 in combination with gemcitabine and erlotinib inhibited growth of xenografts and overcame gemcitabine resistance in cell lines (106). DNA methyltransferase inhibitor, decitabine is being evaluated in 3 early stage studies in combination with gemcitabine or tetrahydrouracil (NCT02959164, NCT02847000, NCT02685228).

Immunotherapy

Immunotherapy is revolutionizing cancer therapy, although impacts in PDAC remain to be realized. Various methods to utilize the immune system to target cancers are being developed with promising results in other malignancies. Immune checkpoint inhibition in melanoma and NSCLC has achieved durable responses in approximately 20–25% of patients (107,108). Chimeric antigen receptor T cells, in which a patient's own T-cells are collected, genetically altered to express a tumor antigen specific receptor and re-infused, are achieving complete responses in refractory leukemias and lymphomas (109-111). These modalities are emerging as potential treatment options in PDAC as well.

Checkpoint inhibition

Immune checkpoints consist of interactions between a series of surface proteins and their ligands to differentiate self from non-self. The classic model of effector cell stimulation involves an interaction between the MHC-presented antigen and the T-cell receptor and a costimulatory interaction between CD28 on T cells and B7 on antigen presenting cells (APCs). Additional inhibitory stimuli including PD-L1/PD-1 and CTLA-4/B7-1/2 have been identified and inhibitors developed. The PD-1 receptor is expressed on activated T cells, B cells and myeloid cells and its ligand PD-L1, is expressed on many cancers including PDAC. CTLA-4 is upregulated on activated CD4+, CD8+ and T-regulatory cells and interacts with B7 antigens on APCs (112-114). In a series of resected PDAC specimens, expression of B7-1, B7-2, PD-L1 on PDAC cells and CTLA-4 and PD-1 on tumor infiltrating immune cells were increased in both frequency (all >95%) and degree of expression (6.5 fold for CTLA-4 and 6.1 for PD-1) compared to normal control pancreas tissue. High PD-L1 expression in this series correlated with decreased survival (24 *vs.* 10 months, $P < 0.0001$) (115).

Despite excellent results in other malignancies and pre-clinical rationale in PDAC, initial clinical studies with CTLA-4 inhibitors either alone or in combination with traditional chemotherapy have had modest results. A phase II of ipilimumab administered to 20 metastatic and 7 locally advanced patients for 2 cycles did not demonstrate any responses by traditional criteria, although one patient did have a delayed response after initial progression (116). Ipilimumab and tremelimumab have both been studied in combination with gemcitabine in phase I studies with responses in 2/16 and 2/34 patients and mOS of 8.5 and 7.4 months, respectively (117,118).

Anti-PD-1 therapy has met similar challenges in a phase I with 0/14 PDAC patients demonstrating a response, whereas anti-PD-L1, durvalumab, has demonstrated only a 7% response rate (119-121). Multiple PD-1 and PDL-1 inhibitors are in early-mid phase studies alone or in combination with chemotherapy but without reported results to this point. PD-1 inhibitor, nivolumab, is in a phase II as first line with GN, cisplatin and paricalcitol (NCT02988960) and as second line with nab-paclitaxel ± gemcitabine (NCT02309177). Pembrolizumab, PD-1 inhibitor, is in phase I/II studies as first or second line in combination with GN (NCT02331251) and mFOLFOX (NCT02331251). PDL-1 inhibitor, atezolizumab, is

also being studied in a phase I in combination with GN (NCT02715531). It is noteworthy, that pembrolizumab has been approved for microsatellite instability-high and mismatch repair deficient cancers agnostic of tissue of origin (122) In PDAC specifically, a small sample of 4 mismatch repair deficient PDAC patients treated with pembrolizumab demonstrated 2 PRs and 2 SDs (123).

Due to the overall modest responses of single agent checkpoint inhibition and supporting pre-clinical evidence, the focus has shifted to combination approaches including dual checkpoint blockade, multi-modality immunotherapy, and combination with targeted therapeutics or radiation (RT). Durvalumab, and tremelimumab, are being studied in combination in phase II as first line treatment with GN versus GN (NCT02715531). They are also being studied as both first and second line treatment *vs.* durvalumab alone (NCT02527434, NCT02558894).

Dual modality immunotherapy has signaled benefit in a phase I study of ipilimumab and the cancer vaccine, GVAX, versus ipilimumab alone. mOS was 5.7 *vs.* 3.6 months (HR 0.51; $P = 0.072$) and 1-year OS (27% *vs.* 7%). Additionally, 3/15 patients had prolonged disease stabilization of 31, 71 and 81 weeks (124). GVAX consists of genetically altered allogenic PDAC cells that express GM-CSF with the aim of inducing an immune response towards the PDAC cells. Multiple combination studies with GVAX are ongoing. GVAX and ipilimumab are being studied in a phase II study *vs.* FOLFIRINOX (NCT01896869). A phase I/II of GVAX with or without nivolumab in resectable disease and a phase II of GVAX with pembrolizumab and SBRT in locally advanced disease are both recruiting (NCT02451982, NCT02648282).

The combination of checkpoint inhibitors and chemokine inhibitors is a rational combination approach. Chemokine inhibitors aim to increase the number of effector cells in the PDAC stroma and checkpoint inhibitors aim to increase effector cell activity. Indeed, KPC mice treated with CXCR2 inhibition preceding PD-1 inhibition lived longer than mice treated with vehicle followed by PD-1 inhibition (33). Similarly, a mouse model of CXCR4/CXCL12 and PD-L1 inhibition demonstrated fewer malignant cells in mouse tumors than PD-L1 alone (30). As described above, CSF1R inhibition also improves response to checkpoint blockade in murine models (37). Combination studies with these agents were described previously.

The abscopal effect is a phenomenon in which tumors outside of the field of radiation are 'treated' by radiation. The theory is that radiation causes the expression of

antigens and alteration in the TME enabling immune stimulation (125). Multiple studies are ongoing or in planning to evaluate dual checkpoint blockade and RT in the metastatic setting. Three phase I studies are recruiting or planned to evaluate various combinations of durvalumab, tremelimumab or both with RT (NCT02639026, NCT02311361, NCT02868632). Nivolumab and RT with or without ipilimumab are also recruiting (NCT02866383).

Chimeric antigen receptor T cells (CAR-T)

CAR-Ts are T cells that are genetically altered to express specific receptors for non-MHC moieties on cancer cells. When engaged, the receptor activates the T cell's cytotoxic response. CAR-Ts have shown promising results in refractory leukemia and lymphomas, but have not yielded as promising results in solid malignancies (126). In PDAC, CAR-Ts directed at various targets are being evaluated. Anti-CEA CAR-Ts are being studied in patients with CEA positive cancers with liver metastases in combination with Y90 microspheres (NCT02416466, ongoing) and by hepatic artery infusion (NCT02850536, planned). Mesothelin is an attractive target for CAR-Ts as it is highly expressed on many malignancies including 85% of PDACs (127). Three phase I studies of CAR-Ts targeting mesothelin are ongoing, but not recruiting at the University of Pennsylvania (NCT02465983, NCT02159716, NCT01897415) and a single phase I/II enrolling patients with multiple mesothelin expressing malignancies is recruiting at the National Cancer Institute (NCT01583686). Studies evaluating CAR-Ts against MUC1 (NCT02587689), prostate stem cell antigen (NCT02744287) and NK receptors (NCT03018405) are recruiting, as well. Other targets in development for CAR-Ts in PDAC include Ca19-9 and MUC16.

Monoclonal antibodies

The surface targets of CAR-Ts have also seen the development of monoclonal antibodies and antibody drug conjugates. Anetumab ravtansine is an anti-mesothelin antibody conjugated to the tubulin inhibitor DM4. This has shown strong pre-clinical results eradicating tumor in 5/6 orthogenic mice models and significantly lowering tumor volume compared to gemcitabine in patient derived xenografts (128). A phase I dose finding study in ovarian cancer, mesothelioma and pancreatic cancer was performed, however, outcomes were not reported for PDAC (NCT01439152) (129). A phase II study in pancreatic

cancer is planned. Morab-009 is an anti-mesothelin antibody that was studied in a phase II trial in combination with gemcitabine *vs.* gemcitabine alone (NCT00570713). No results have been published. SS1P is an anti-mesothelin antibody conjugated to pseudomonas toxin being studied in a phase I/II study of mesothelin expressing malignancies (NCT01362790).

MVT-5873 is an antibody targeting CA19-9. MVT-5873 has demonstrated cytotoxicity in murine xenograft models and is being studied in a phase I dose finding study evaluating MVT-5873 alone and in combination with GN for patients with CA19-9 positive malignancies (NCT00570713) (130). Preliminary data has shown acceptable toxicity with DLT of transient grade 3 AST, ALT and bilirubin elevations and potential efficacy with stable disease of >4 months in 24% of patients and Ca19-9 reductions of >50% in 48% of patients (131). MVT-5873 is being developed in parallel with MVT-2163, a radiolabeled anti-CA19-9 antibody designed as a PET imaging agent, which is in phase I in combination with MVT-5873 to evaluate pharmacokinetics and optimal timing of imaging (NCT02687230) and combined with lutetium as a radioisotope (MVT-1075; NCT03118349).

Combining immunotherapy and antibody dependent cellular cytotoxicity, enoblituzumab is an antibody with a high affinity Fc region designed to stimulate antibody dependent cytotoxicity when it binds the immune checkpoint molecule B7-H3 (132). It is being studied in phase I studies in combination with pembrolizumab (NCT02475213) and ipilimumab (NCT02381314).

Metabolism

Malignant cells commonly have different metabolic requirements than normal cells. Malignant cells tend to rely on glycolysis and anaerobic metabolism, require increased amount of glutamate and may be deficient in argininosuccinate synthase and asparagine synthetase (ASNS) (133-135). Autophagy is a key mechanism that PDAC utilizes to obtain glutamate and may be required for PDAC growth (136). Autophagy inhibitor, hydroxychloroquine, is being studied in a number of trials—as neoadjuvant therapy in a randomized trial of gemcitabine and nab-paclitaxel ± hydroxychloroquine (NCT01978184), as first or second line in combination with gemcitabine for metastatic disease (NCT01506973) and as monotherapy in previously treated metastatic patients (NCT01273805). CPI-613 inhibits mitochondrial metabolism by inhibiting

alpha-ketoglutarate dehydrogenase and pyruvate dehydrogenase and has shown efficacy in PDAC xenografts and early phase investigation (137). In a phase I trial in combination with FOLFIRINOX, an ORR of 53.9% was found comparing favorably to 31.8% for FOLFIRINOX alone in the pivotal PRODIGE study (5,138). ADI-PEG 20 inhibits argininosuccinate synthase, the activity of which is required for arginine production in PDAC cells. A phase I/IIb study of ADI-PEG with GN demonstrated promising results with a mPFS of 6.1 months, mOS 11.3 months, 45% ORR and 91% tumor regression rate in patients treated with the recommended phase II dose in the first line setting (139). A randomized phase II/III trial is in development in untreated metastatic PDAC. Eryaspase, red blood cell encapsulated L-asparaginase, hydrolyses asparagine to aspartic acid leading to asparagine depletion and impaired protein synthesis in low ASNS expressing tumors. Interestingly, in a phase IIb second line study in combination with gemcitabine or FOLFOX, eryaspase treatment improved OS in both the low ASNS (HR 0.62, P value not specified) and entire study population (HR 0.57, P=0.034) (140).

DNA repair

A small but significant subset of PDAC patients has an inheritable genetic predisposition. In a case series of 175 patients with pancreatic cancer and suspicious personal or family history who were treated at Memorial Sloan Kettering Cancer Center, a pathogenic germline mutation was found in 15.1% (BRCA2 7.4%, BRCA1 2.2%, p16 1.1%, PALB2 0.6% and Lynch syndrome 2.2%) (141). In other series of high risk patients, ATM mutations have a prevalence of 1–5.7%. In an unselected group of PDAC patients the rate of BRCA1/2 mutations is between 3.6–7%, but is significantly higher in Ashkenazi Jewish patients than non-Ashkenazi Jewish patients (12.1% *vs.* 3.7%; P=0.05) (142,143).

A majority of identified inheritable genetic mutations in PDAC affect proteins involved in homologous recombination. Homologous recombination is the highest fidelity double stranded DNA repair mechanism and is also crucial for removing DNA crosslinks. The process is initiated when the MRN (MRE11–RAD50–NBS1) complex identifies and stabilizes a double stranded DNA break. The MRN complex activates ATM leading to a complex series of interactions that require BRCA1/2 interactions with RAD51 and PALB2 to complete DNA repair (144–146). Impaired

homologous recombination leads to the use of alternative DNA repair mechanisms and the accumulation of mutations that increase the risk of carcinogenesis, but also confer an increased sensitivity to platinum agents. Platinum agents create DNA crosslinks, which require repair through HR. Indeed, a number of small case series have shown evidence that patients with BRCA-associated PDAC are responsive to platinum agents and a retrospective review of 71 patients with stage III and IV BRCA associated PDAC found improved survival in patients treated with platinum agents (22 *vs.* 9 months; P=0.039) (147–149).

Poly ADP ribose polymerase (PARP) is necessary for repair of single stranded DNA breaks, which if not repaired lead to double stranded breaks (150). Additionally, PARP is also involved in alternative double stranded DNA repair pathways in the absence of HR. In the setting of BRCA1/2 mutations, PARP inhibition leads to accumulation chromatin aberrations, cell cycle arrest and cell death (145). PARP inhibitor (PARPi) olaparib is approved in BRCA mutant ovarian cancer and in clinical development for PDAC. A phase II study of olaparib in germline BRCA (+) patients included 23 patients with PDAC and demonstrated a 22% response rate and 35% stable disease with 1 year survival of 41% (151). Olaparib is currently being evaluated in a phase III study for patients with germline BRCA mutations and metastatic disease who have had stable disease on platinum therapy for at least 16 weeks. Patients receive olaparib monotherapy maintenance or placebo after completing chemotherapy (NCT02184195). Olaparib is also being studied as second line therapy in a phase II study for patients with ‘BRCAness’—no BRCA mutation but a family history of BRCA associated cancers (NCT02677038) and a separate phase II for ‘BRCAness’ which also includes mutations in other DNA damage repair genes is being planned (NCT02511223).

The combination of platinum and PARP inhibitor is an attractive treatment regimen to exploit DNA damage repair deficits. Veliparib, is under evaluation in a 3-arm phase II study for patients with BRCA1/2 or PALB2 mutations in combination with first line gemcitabine/cisplatin *vs.* gemcitabine/cisplatin/placebo *vs.* veliparib alone (NCT01585805). A phase II evaluating second line mFOLFIRI with or without veliparib is recruiting without requirement for BRCA mutation or BRCAness (NCT02890355). A trial evaluating rucaparib as maintenance after induction platinum-based therapy in patients with deleterious germline or somatic BRCA mutations is planned.

Conclusions

Improving survival in PDAC is a critical unmet need. With increased understanding of PDAC pathobiology, novel therapeutics targeting the stroma, harnessing the power of the immune system and blocking aberrant signaling pathways have reached clinical development providing a sense of optimism that recent scientific advances will turn into clinical results. Beyond therapeutic discovery, trial design with strict success criteria is critical to expeditiously realizing these results. Rahib *et al.* investigated 32 phase III studies between 1997 and 2015, but found that half of studies with a paired phase II advanced to phase III despite a negative phase II outcome, contributing significantly to the overall 15% phase III success rate (152). Incorporating biomarkers and utilizing surrogate endpoints will also aid in maximizing therapeutic potential and identifying failing candidates early. Across multiple malignancies, Jardim *et al.* found that 57% of successful programs utilized biomarker driven patient selection, however, only 16% of failed drug programs did (153).

The application of these strategies is emerging in large collaborative trials. The Precision Promise trial is an initiative of the Pancreatic Cancer Action Network in which patients will undergo biomarker analysis with pathologic evaluation, genomic sequencing and transcriptome analysis to determine assignment in treatment arms focused on stromal disruption, DNA damage repair or immunotherapy. The trial is designed to be dynamic incorporating promising novel therapeutics and eliminating failing ones.

Still, despite optimism, with current approved treatment options, survival in PDAC remains limited, and it is recommended that all patients enroll in clinical trials with the hope, now more than ever, of improved outcomes from novel therapeutics.

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Footnote

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