

1 **Supplemental Tables**

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3 **eTable 1: Novel Therapies in Clinical Trials in Advanced Pancreatic Cancer**

4 **eTable 2: Treatment Modalities for Pancreatic Cancer**

5 **eTable 3: Class, Adverse Effects, and Mechanism of Action of Systemic Agents**

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Clinical Trial ID	Category	Mechanism of action	Study agent(s)	Setting	Sponsor
NCT04666740	Gene targeting	PARPi in combination with PD-1 inhibition	Olaparib, pembrolizumab	Metastatic PDAC with HRD or exceptional response without HRD in maintenance.	MSK
NCT03604445		WNT pathway inhibition	BI 905677	Advanced cancers with <i>RNF43</i> mutations. Single agent	Boehringer Ingelheim
NCT03600883		<i>KRAS</i> inhibition	Sotorasib (AMG 510)	Advanced cancers with <i>KRAS</i> G12C mutation. Single or combination.	Amgen
NCT02568267		<i>TRK</i> inhibition	Entrectinib	Advanced cancers with <i>TRK</i> fusion. Single agent.	Hoffmann-La Roche
NCT02912949		<i>NRG-1</i> inhibition by bispecific antibody	Zenocutuzumab	Group G: advanced PDAC with <i>NRG1</i> fusion. Single agent.	Merus N.V.
NCT02227940		<i>ALK</i> inhibition	Ceritinib	Advanced PDAC. GN or G or cisplatin combination.	RPCI
NCT02907099	Immune TME modulation	CXCR4 antagonist	Motixafortide (BL-8040)	Advanced PDAC. Combination with PD-1 inhibitor.	MD Anderson
NCT04060342		Myeloid cell recruitment inhibition	GB1275	Advanced PDAC. Combination with PD-1 inhibitor and GN.	Gossamerbio
NCT03214250		CD40 agonist	Sotigalimab	Advanced PDAC. Combination with PD-1 inhibitor and GN.	PICI
NCT03006302		IDO1 inhibitor	Epacadostat	Advanced PDAC. Combination with pembrolizumab, CRS-207 +/- C/GVAX.	Johns Hopkins
NCT04262388		Adenosine antagonist by A2AR blockade	Oleclumab	Advanced PDAC. Combination with durvalumab.	Medimmune
NCT04104672		Adenosine antagonist by CD73 inhibition	AB680	Advanced PDAC. Combination with GN, AB680, AB122.	Arcus
NCT03766295		Mast cell inhibition	Masitinib	Advanced PDAC, Combination with G with or without masitinib.	Ab Science
NCT03504423	Metabolism	Targeting cancer metabolism	Devimistat (CPI-613)	Metastatic PDAC. Combination with mFOLFIRINOX with or without CPI-613	Rafael
NCT03435250		Metabolic synthetic lethality by MAT2A inhibition	AG-270	Advanced PDAC with <i>CDKN2A</i> or MTAP deletion with GN combination	Agios
NCT04292743		Targeting cancer amino acid metabolism	Eryaspase	Advanced PDAC in combination with mFOLFIRINOX	Erytech
NCT03816163	Protein tropism	ADCC and CDC targeting Claudin 18.2	Zolbetuximab	Metastatic PDAC. GN with or without zolbetuximab	Astellas
NCT03086369		Targeting PDGFR-a to inhibit stem cell growth	Olaratumumab	Metastatic PDAC. G with or without olaratumumab	Lilly
NCT03323944		CAR-T against mesothelin	CAR-T	Advanced PDAC. Single-agent in second-line or above.	University of Pennsylvania
NCT03269526		Bispecific Ab engaging armed T cell on EGFR.	BATs	Advanced PDAC. Single-agent in second-line or above.	MSK - University of Virginia

Abbreviations: PARPi, poly-ADP ribose polymerase inhibitor; PD-1, programmed death-1; MAT2A, methionine adenosyltransferase 2A; ADCC, antibody-dependent cytotoxicity; CDC, complement-dependent cytotoxicity; PDGFR, platelet-derived growth factor receptor; CAR-T, chimeric antigen receptor-T; B220, anti-CD3 x anti-EGFR-bispecific Antibody Armed Activated T-Cells; EGFR, epidermal growth factor receptor; CXCR4, CXC- chemokine receptor type 4; IDO1, indoleamine 2,3-dioxygenase 1; A2AR, adenosine 2 A receptor; HRD, homologous recombination deficiency; GN, gemcitabine; nab-paclitaxel; TME, tumor microenvironment; G, gemcitabine; CRS-207, attenuated listeria bacteria; C/GVAX, cyclophosphamide/GVAX vaccine; RPCI, Rosewell Park Cancer Institute; PICI, Parker Institute for Cancer Immunotherapy; MSK Memorial Sloan Kettering

27 **eTable 2: Different Treatment Modalities Available for Pancreatic Cancer**

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Surgery	Radiation	Systemic therapy	Optimal Supportive Care
Pancreaticoduodenectomy (Whipple) Distal pancreatectomy and splenectomy Central pancreatectomy	Intensity-modulated (IMRT) Stereotactic (SBRT) Ablative dose radiation	(modified) FOLFIRINOX Gemcitabine, nab-paclitaxel 5-FU/nano-liposomal irinotecan Single-agent gemcitabine or capecitabine Olaparib maintenance in germline BRCA1/2 Pembrolizumab in dMMR (mismatch repair deficiency) or TMB (tumor mutation burden) > 10 mutations/megabase	Exocrine pancreatic insufficiency: pancreas enzyme supplementation Nutritional support Diabetes management Management of jaundice: endoscopic biliary stent placement Management of duodenal obstruction: surgical bypass or enteral stent placement Treatment of thromboembolic events Psychosocial care/ counselling
Biospecimen and therapeutic clinical trials			

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eTable 3: Class, Adverse Effects, and Mechanism of Action of Systemic Agents

Agent	Route	Class	Mechanism of action	Specific adverse effects	Common adverse effects
Gemcitabine	Intravenous	Antimetabolite, Pyrimidine analog	Inhibits DNA synthesis by blocking deoxycytidine triphosphates (dCTP) incorporation	Edema, proteinuria, hematuria, hepatic dysfunction, dyspnea	fatigue, fever, infection, anemia, leukopenia, thrombocytopenia, nausea, abdominal pain, diarrhea electrolyte imbalance
Capecitabine	Oral	Antimetabolite, Pyrimidine analog	Prodrug of 5-FU, Inhibits DNA synthesis by thymidylate synthase inhibition	Mucositis, angina pectoris, vasospasm, palmar-plantar erythrodysesthesia	
5-Fluorouracil	Intravenous	Antimetabolite, Pyrimidine analog	Inhibits DNA synthesis by thymidylate synthase inhibition	Mucositis, angina pectoris, vasospasm, palmar-plantar erythrodysesthesia	
Irinotecan	Intravenous	Topoisomerase I inhibitor	Active metabolite SN-38 binds to the topoisomerase I and interferes with relieving torsional strain in DNA	Cholinergic symptoms (flushing, tearing, cramps, palpitation)	
Oxaliplatin	Intravenous	Alkylator platinum	Creates inter-strand DNA crosslinks and inhibit DNA replication and transcription	Allergic reactions, neuropathy, hepatic dysfunction.	
Albumin-bound paclitaxel	Intravenous	Taxane	Stabilizes microtubules and prevents depolymerization necessary for mitosis	Alopecia, edema, hepatic dysfunction, neuropathy	
Olaparib	Oral	PARP inhibitor	Inhibits BER accumulating single-strand DNA breaks requiring homologous repair	Fatigue, abdominal pain, respiratory tract infection	

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44 PARPi, (poly-ADP (adenosine diphosphate)–ribose polymerase) inhibitor; BER, base-excision repair