Review

Advancing Immunotherapy in Pancreatic Cancer: A Brief Review of Emerging Adoptive Cell Therapies

Deepak Sherpally * and Ashish Manne

Posted Date: 25 December 2024

doi: 10.20944/preprints202412.2086.v1

Keywords: pancreatic ductal adenocarcinoma; adoptive cell therapy; chimeric antigen receptor T cells (CAR-T); chimeric antigen receptor NK cells (CAR-NK); tumor-infiltrating lymphocytes (TIL); T cell receptor (TCR) engineered T cells; cytokine-induced killer cells (CIK); oncolytic virus

Review

Advancing Immunotherapy in Pancreatic Cancer: A Brief Review of Emerging Adoptive Cell Therapies

Deepak Sherpally [1]* and Ashish Manne [2]

[1] Department of Internal Medicine, New York Medical College/Metropolitan, New York, NY 10029, USA

[2] Department of Internal Medicine, Division of Medical Oncology at the Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, The Ohio State University Comprehensive Cancer Center, Columbus, OH 43210, USA

* Correspondence: dsherpally@nymc.edu; Tel.: (+1 212-423-6771)

Simple Summary: Pancreatic cancer is an aggressive and highly lethal malignancy with limited treatment options as it is usually detected in the advanced stage. There is an urgent need to explore new therapeutic options, and recent studies on adoptive cellular therapy (ACT) look promising, although they are in the early stages. We attempted to review the completed and ongoing studies on ACT to explore the current and future approaches to pancreatic cancer management.

Abstract: Pancreatic cancer has the lowest 5-year survival rate (13%) among major cancers and is the third leading cause of cancer-related deaths in the United States. The high lethality of this cancer is attributed to its insidious onset, late-stage diagnosis, rapid progression, and limited treatment options. Addressing these challenges requires a deeper understanding of the complex tumor microenvironment to identify novel therapeutic targets. Newer approaches like adoptive cell therapy have shown remarkable success in treating hematological malignancies but their application in solid tumors particularly pancreatic cancer is still in the early stages of development. ACT broadly involves isolating immune cells (T lymphocytes, Natural Killer cells, and macrophages) from the patient followed by genetic engineering to enhance and mount a specific anti-tumor response. Various ACT modalities are under investigation for pancreatic cancer, including chimeric antigen receptor T cells (CAR-T), chimeric antigen receptor NK cells (CAR-NK), tumor-infiltrating lymphocytes (TIL), T cell receptor (TCR) engineered T cells, cytokine-induced killer cells (CIK). Major hurdles have been identifying actionable tumor antigens and delivering focused cellular therapies to overcome the immunosuppressive and dense fibrotic stroma surrounding the pancreatic cancer. Further studies are needed to explore the limitations faced by cellular therapy in pancreatic cancer and identify novel combination treatment approaches in order to improve clinical outcomes.

Keywords: pancreatic ductal adenocarcinoma; adoptive cell therapy; chimeric antigen receptor T cells (CAR-T); chimeric antigen receptor NK cells (CAR-NK); tumor-infiltrating lymphocytes (TIL); T cell receptor (TCR) engineered T cells; cytokine-induced killer cells (CIK); oncolytic virus

1. Introduction

Pancreatic cancer is among the most lethal malignancies, representing a significant global health challenge. In 2024, it is projected to cause approximately 51,000 deaths out of 66,000 newly diagnosed cases in the United States alone [1]. With a 5-year survival rate of just 13%, pancreatic cancer has the lowest survival rate among major cancers. Its incidence is similar among African-American and Caucasian populations. Despite accounting for only 3% of new cancer diagnoses in the United States, pancreatic cancer is currently the third leading cause of cancer-related deaths and is expected to become the second in the near future [2]. Globally, the European region exhibits the highest age-standardized incidence and mortality rates, while the Southeast Asia region reports the lowest [3]. The high lethality of pancreatic cancer is attributed to its insidious onset, late-stage diagnosis,

 doi:10.20944/preprints202412.2086.v1

aggressive progression, and limited treatment options. Addressing these challenges requires a deeper understanding of the tumor microenvironment (TME) to identify novel therapeutic targets and expand treatment options, ultimately improving patient outcomes in the long term.

Pancreatic cancer risk factors are broadly categorized into modifiable and non-modifiable factors [4]. Key modifiable risk factors include smoking, excessive alcohol consumption, diets high in red or processed meats, obesity, chronic pancreatitis, and infections such as Helicobacter pylori. These factors contribute to the higher incidence observed in developed countries. Non-modifiable risk factors include advanced age, male gender, ethnicity, specific blood groups, microbiota composition, genetic predisposition, and diabetes mellitus. A comprehensive understanding of these risk factors is critical for developing effective prevention and intervention strategies.

2. Current Management of Pancreatic Ductal Adenocarcinoma

Pancreatic ductal adenocarcinomas (PDAC) account for approximately 90% of primary pancreatic cancers, with the remainder comprising less common types such as squamous, acinar, signet-ring (exocrine), ampullary, neuroendocrine, and undifferentiated carcinomas [5]. PDAC is typically stratified for risk and management using the tumor-node-metastasis (TNM) system outlined in the 8th edition of the American Joint Committee on Cancer (AJCC) staging manual [6]. While TNM staging informs treatment and prognosis, it does not include resection status, which is critical for surgical planning. Another widely used classification system focuses on tumor resectability and the presence of distant metastatic disease at diagnosis. Based on this approach, PDAC is categorized as resectable (R), borderline resectable (BR), locally advanced (LA), or metastatic [7–10]. Resectability is determined by the degree of tumor involvement with surrounding arteries and veins, typically assessed in a multidisciplinary setting. In R-PDAC, there is no tumor contact with adjacent blood vessels. BR-PDAC involves some tumor contact with blood vessels, with the expectation that systemic chemotherapy (CT) or radiation therapy (RT) can convert these cases to R-PDAC. LA-PDAC, a less clearly defined category, includes tumors with significant involvement of major arteries (e.g., celiac trunk or superior mesenteric artery interface >180°) or veins, rendering both resection and vascular reconstruction infeasible.

Following stratification, treatment plans are tailored to the disease stage. For R-PDAC and BR-PDAC, neoadjuvant chemotherapy (NAT), often combined with RT, is now preferred prior to surgical resection. In LA-PDAC, NAT helps identify patients who may benefit from subsequent surgery. For metastatic PDAC and certain LA cases, clinical trial enrollment is recommended. Systemic chemotherapy, using regimens such as FOLFIRINOX or gemcitabine/nab-paclitaxel (G/NP), remains the cornerstone of treatment for advanced PDAC. However, outcomes for metastatic PDAC remain poor, with a 5-year survival rate of only 3% [11,12].

Immunotherapy in PDAC focuses on leveraging the tumor microenvironment (TME) and the host immune system [13]. Immune checkpoint inhibitors (ICIs), targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1), have shown efficacy in mismatch repair-deficient (MMR-D) tumors, but this subgroup represents only 2% of PDAC patients [14–16]. While ICIs have revolutionized outcomes for esophageal, liver, and biliary tract cancers, their success in mismatch repair-proficient PDAC remains limited [17–26]. Emerging immunotherapy approaches, including oncolytic virus therapy (OVT), adoptive cell transfer therapy (ACT), and cancer vaccines, hold promise for all tumor types, including PDAC [20]. Among these, chimeric antigen receptor (CAR) T-cell therapy is being actively investigated as a novel therapeutic strategy in PDAC. The urgent need for new targets and treatment modalities highlights the potential of immunotherapy as a critical avenue for improving outcomes in this challenging and aggressive disease.

3. Adoptive Cell Therapy in PDAC

TME is a complex ecosystem that surrounds tumor cells, comprising various immune cell populations that play critical roles in maintaining its pro-tumorigenic nature [18]. These immune cells include lymphocytes (T and B cells), macrophages, natural killer (NK) cells, dendritic cells (DCs),

 doi:10.20944/preprints202412.2086.v1

myeloid-derived suppressor cells (MDSCs), neutrophils, and mast cells, as illustrated in Figure 1. Each cell type contributes uniquely to the dynamic interplay within the TME, promoting tumor growth, immune evasion, and resistance to therapy. Immune-related TME is important not only for the effectiveness of ICI or other cellular therapy modalities but also for the outcomes, affecting both prognosis and treatment response. High infiltration of anti-tumor immune cells significantly improved the outcomes of PDA irrespective of the ICI use [27–34].

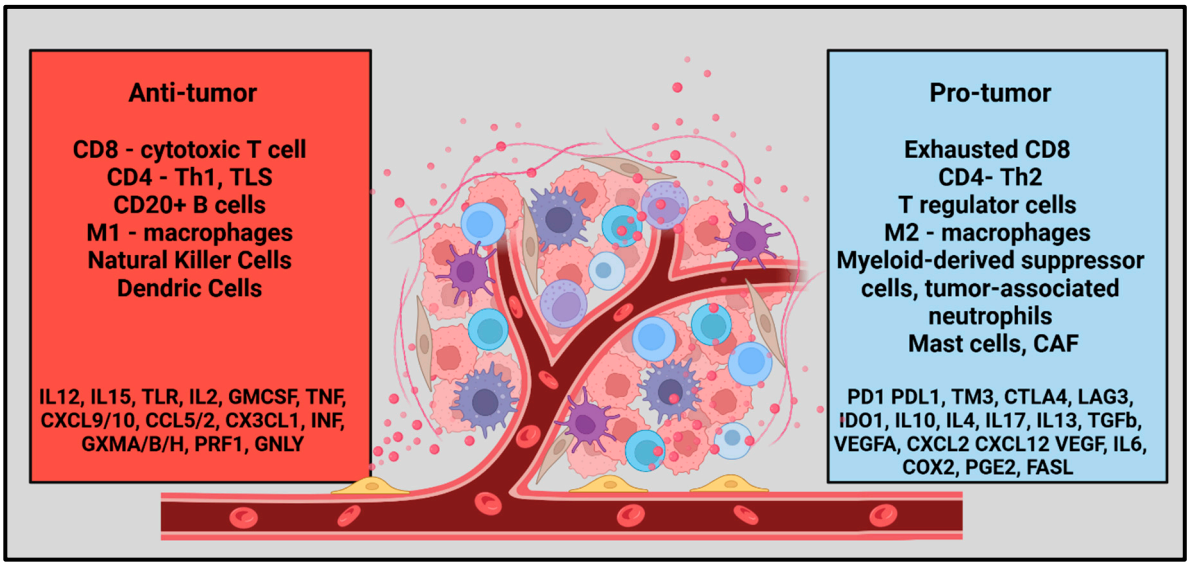

Figure 1. Summarizing the Tumor Microenvironment in Pancreatic Ductal Adenocarcinoma.

There is a growing interest in targeting TME to treat PDAC, and ACT is emerging as a key strategy in this effort [20,35]. While ACT has shown remarkable success in treating hematological malignancies, its application in solid tumors, including PDAC, remains in the early stages of development [36,37]. ACT broadly involves isolating immune cells—such as T lymphocytes, NK cells, and macrophages—from the patient, followed by their re-engineering and genetic modification to enhance their anti-tumor activity [38]. Various ACT modalities are under investigation for PDAC, including chimeric antigen receptor T cells (CAR-T), chimeric antigen receptor NK cells (CAR-NK), tumor-infiltrating lymphocytes (TILs), T cell receptor (TCR)-engineered T cells, and cytokine-induced killer cells (CIK-cells). These approaches are currently being evaluated in clinical trials to improve outcomes for this challenging malignancy. The following sections will delve deeper into these ACT modalities and their potential impact on PDAC treatment.

4. CAR- T in PDAC

CAR-T cell is a form of ACT that redirects a patient's T cells to specifically target cancer cells through genetic engineering [39]. CARs are synthetic receptors designed with four main components: an extracellular antigen-binding domain, a hinge region, a transmembrane domain, and one or more intracellular signaling domains [37]. Since the development of first-generation CARs in 1989, subsequent generations have undergone significant advancements to enhance clinical efficacy [40]. To date, five generations of CAR-T cells have been developed, each featuring modifications to the domain structure and the inclusion of additional co-stimulatory molecules. Newer generations of CAR-T cells demonstrate improved T cell activation, enhanced efficacy, and greater persistence, with the ability to rapidly expand and survive long after infusion. However, CAR-T cell therapy's success heavily depends on identifying actionable tumor-specific antigens. This remains a significant challenge for PDAC despite the therapy's transformative impact on hematological malignancies. We summarized the results of completed early-phase clinical trials (Phase I or I/II) in Table 1 and ongoing trials in Table 2.

 doi:10.20944/preprints202412.2086.v1

Table 1. Current evidence of CAR-T cell therapies in pancreatic ductal adenocarcinoma.

Trial	Target	Outcomes	Adverse effects	Notes on the target
NCT02541370* [41] (n=23)	CD-133 (B) PDAC – 7/23	PR – 2 SD – 3 PD - 2	Hyperbilirubinemia, Anemia, Leucopenia, Thrombocytopenia, Anorexia, and Mucosal hyperemia	It is a transmembrane protein and the most commonly expressed cancer stem cell marker in several cancer types [42]. Correlates with histologic type, lymphatic invasion, and metastasis in pancreatic cancer[43].
NCT02850536 [44] (n=5)	CEA	OS – 23.2m DOR – 13m	Fever, Electrolyte abnormalities, Hypertension	It can be elevated in PDAC, and a level > 7.2 ng/ml in LA PDAC is often associated with systemic disease [45–48].
NCT01897415 [49] (n=6)	Mesothelin	SD – 2 PD – 4	Abdominal pain, Back pain Dysgeusia, Gastritis	It is an important factor in pancreatic growth by promoting proliferation and inhibiting apoptosis through p53-dependent and p53-independent pathways [50,51]. Mesothelin-specific T cells were generated in 50% of pancreatic cancer patients in a study [52].
NCT02159716 [53] (n=15)	Mesothelin (B) PDAC – 5/15	PD – 3 SD - 2	Anemia, Lymphopenia, Fatigue, Dysgeusia, DIC	
NCT03874897 [54] (n=37)	Claudin 18.2 (B) PDAC – 5/37	PD – 1 SD – 3 PR – 1	Lymphopenia, Neutropenia, Anemia, Thrombocytopenia, Elevated conjugated bilirubin, Elevated aminotransferase, Hypokalemia, Pyrexia	It is a transmembrane protein that controls the paracellular space through which molecules pass in the epithelial and endothelial tissues and is essential for normal membrane barrier function [46]. It is overexpressed in various cancers and plays an important role in the progression of pancreatic neoplasms. Claudin types could be tumor-specific.
NCT05199519 [55] (n=7)	Claudin 18.2 (B) PDAC – 2/5	PR – 1 SD – 1	Neutropenia, Anorexia	
NCT01869166 [56] (n=14)	EGFR	PR – 4 SD – 8 PD - 2	Lymphocytopenia, Pleural effusion, Pulmonary interstitial exudation, Dermatitis Herpetiformis, Gastrointestinal hemorrhage	It plays a crucial role in normal cellular growth, prevention of apoptosis and development of metastasis in many types of cancer [57]. There are 4 receptors in the EGF family HER1, HER2, HER3, HER4 [58].
NCT01935843 [59] (n=11)	HER2 (B) PDAC – 2/11	SD - 2	Anemia, Lymphopenia Fever, Fatigue Transaminase elevation Gastrointestinal hemorrhage	It is a cell-membrane protein involved in promoting cell division & differentiation and contributes to tumor progression by triggering angiogenesis [60]

 doi:10.20944/preprints202412.2086.v1

* Phase I/II, B – basket trials PDAC – pancreatic ductal, adenocarcinoma, PR – partial response, SD – stable disease, PD – progressive disease, OS – overall survival, DOR – duration of response, CEA – carcinoembryonic antigen, EGFR - epidermal growth factor receptor, HER2 - human epidermal growth factor receptor 2, DIC - disseminated intravascular coagulation.

Table 2. Ongoing CAR-T Trials in Pancreatic Ductal Adenocarcinoma.

Trial	Phase	Size	Target	Primary outcome	Secondary outcomes
NCT06464965	I	30	Claudin 18.2	MTD, DLT	ORR, DCR, OS, PFS, DOR
NCT05472857	I	30		AE, MTD	ORR, DOR, DCR PFS,
NCT04404595	Ib	110		AE, MTD, DLT, ORR	ORR, DOR, DCR, PFS, OS, HRQoL
NCT04581473	I/II	192		AE, MTD, PFS	ORR, DCR, DOR, OS, PFS
NCT05393986	I	63		DLT, MTD	AE, PK, ORR, DOR, DCR, OS, PFS
NCT05275062	I	6		AE	ORR, DCR, OS, PFS, CAR -T %, Tumor marker, RR, IM92 Ab
NCT06126406	I	60	CEA	AE, DLT	DCR, AUCS, CMAX, TMAX, CEA content
NCT06043466	I	30		Dose range, , DLT, MTD	DCR, AUCS, CMAX, TMAX, CEA content
NCT06010862	I	36		AE, MTD	DCR, ORR, DOR, OS PFS, AUCS, CMAX, TMAX, CEA content
NCT05736731	I/II	160		DLT, RP2D, ORR	A2B530%, Cytokine analysis
NCT04660929	I	48	HER 2	AE, Feasibility of manufacturing, CT - 0508	ORR, PFS
NCT03740256	I	45		DLT	ORR, DCR, OS, PFS, AEs grade 3
NCT06051695	I/ II	230	Mesothelin	DLT, RP2D, ORR	A2B694 persistence, Cytokine analysis
NCT05239143	I	180	MUC1 - C	MTD, R2PD, ORR	-
NCT06158139	I	27	B7-H3	AE, CRS, Neurotoxicity	DLT, OS, PFS, DCR, ORR, B7-H3 expression
NCT02830724	I/II	124	CD 70	AE within 2 weeks, RR	AE within 6 weeks)

MTD – Maximum tolerated dose, DLT – Dose-dependent toxicity, AE – adverse events, CRS – cytokine release syndrome, RX – treatment, R2PD – recommended phase 2 dose, QOL – quality of life, ORR – Objective response rate, CR – complete response, PR – partial response, DOR – duration of overall response, DOCR – duration of overall complete response, DCR – disease control rate, RRR – radiographic response rate, OS – overall survival, PFS – progression-free survival, , RR – response rate (PR + CR). HRQoL – Health related Quality of Life, PK – pharmacokinetics, CEA – carcinoembryonic antigen, ACUS – area under the curve, CMAX – highest concentration of CEA CAR-T cells expanded, TMAX - time to reach the highest concentration.

The principal toxicities associated with CAR-T cell therapy are cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) [61]. CRS presents clinically

 doi:10.20944/preprints202412.2086.v1

with a spectrum of symptoms, ranging from mild flu-like manifestations to severe vasodilatory shock and end-organ dysfunction, potentially leading to life-threatening complications. Management of CRS involves supportive care, including symptomatic treatment, and the use of tocilizumab, an interleukin-6 (IL-6) receptor antagonist, with or without corticosteroids, depending on the severity of the condition. ICANS typically develops after the onset of CRS and exhibits a range of neurological symptoms, from temporary cognitive deficits to fatal cerebral edema. The management of ICANS is stratified by severity: mild cases are treated with supportive measures, severe cases with corticosteroids, and anti-IL-6 therapy is employed only if ICANS occurs alongside CRS. The underlying factors contributing to these toxicities include antigen overlap between cancerous and normal tissues, leading to off-target effects and an exaggerated immune response triggered by CAR-T cell activation.

5. Tumor-Infiltrating Lymphocyte Therapy (TIL) in PDAC

TIL-based ACT involves isolating TILs from tumor tissues, expanding them in vitro, and reinfusing them into patients to identify and destroy tumor cells [62]. TIL therapy, which has shown promising results in solid tumors such as melanoma, breast, and ovarian cancers, is now being investigated for PDAC [63–76]. In a meta-analysis that examined PDAC-TME, a higher CD8+ T cell subgroup was associated with significant survival benefits, highlighting the potential of TIL-therapy in PDAC [77]. TILs therapy has unique advantages, including its ability to target tumor-specific neoantigens due to the presence of multiple T-cell receptor clones, its ease of extraction from tumor tissue owing to the high number of effector memory T cells, and its low toxicity profile since it utilizes autologous cells without genetic modification [78,79]

In a study involving 17 patients, including 5 with PDAC, the best response was observed in a PDAC patient with stable disease for 17 months [79]. However, this patient, who had liver and peritoneal metastases, exhibited no response at the primary tumor site. Overall, no objective responses (OR) were recorded among the PDAC cohort, with 3 achieving stable disease (SD) and 2 progressing (PD). Progression-free survival (PFS) and overall survival (OS) for PDAC patients were 2.43 months and 14.49 months, respectively, which were worse compared to the overall study population (PFS: 2.53 months, OS: 18.86 months) [70]. Bone marrow suppression emerged as a concerning high-grade adverse event across the entire study cohort. TIL therapy for PDAC remains in its early stages, and ongoing clinical trials are summarized in Table 3. Continued research is essential to optimize this approach and improve patient outcomes with PDAC.

Table 3. Ongoing Adoptive Cell Therapy Trials in Pancreatic Ductal Adenocarcinoma.

	Trial	Phase	Size	Target	Outcomes
TIL-therapy	NCT05098197	I	50	-	TRAE, ORR, DCR, DOR, PFS, OS
	NCT03935893	II	240	-	ORR, CRR, DOR, DCR, PFS, OS
	NCT04426669	I/II	20	-	MTD, PE, AE PFS, OS
	NCT01174121	II	332	-	RR, AE Efficacy
	NCT05098197	I	50	-	TRAE, ORR, DCR, DOR, PFS, OS
Oncolytic virus	NCT03740256 (adenovirus)	I	45	HER2	DLT ORR, DCR, PFS, OS, >grade 3 AE
	NCT02705196 (adenovirus)	I/II	55		DLT ORR, OS

 doi:10.20944/preprints202412.2086.v1

	NCT05860374 (herpes virus)	I	20		TRAE, SIR, LA DCR, DOR, QoLA
	NCT05886075 (herpes virus)	I	24		AE, SIR, LA DCR, DOR, QoLA
	NCT06508307	I	21		MTD, DLT, TEAE, LA ORR, DOR, PFS Viral distribution, lymphocyte ratio, cytokine levels, immunogenicity
	NCT05076760	I	61		MTD, AE, ORR DCR, DOR, PFS, OS Exploratory biomarker analysis
CAR-NK	NCT03941457	I/II	9	ROBO1	TRAE
	NCT02839954	I/II	10	MUC1	TRAE ORR
	NCT03841110	I	64	NK cell + ICI	DLT ORR and DOR
	NCT06464965	I	30	Claudin18.2	MTD and DLT ORR, DCR, PFS, OS, and DOR
	NCT05922930	I/II		TROP2	DLT, ORR and PFS
Cytokine-induced killer (CIK) cells	NCT03509298	II	90	CIK with anti-CD3-MUC1 bispecific antibody	ORR, PFS, TTP, DCR, OS, SSR
	NCT05955157	II/III randomized	52	DC-CIK _ S-1 vs. S-1	TRAE, Hematological CBR Efficacy
T-cell receptor-engineered T-cells	NCT04809766	I	15	Mesothelin	TRAE ORR, PFS, OS
	NCT05438667	I	18	KRAS	OS, PFS, TTP, EFS, DFS, DoE AE, CMAX, TMAX, AUC, TCR-T cell number, peak value of cytokines
	NCT06487377	I	12	KRAS	DLT, TRAE, SAE ORR, DCR, DOR, TTR, OS, PFS, TCR-T cell counts, TCR gene copies, anti-drug antibodies, changes in tumor markers
	NCT04146298	I/II	30	KRAS	TRAE, ORR OS, TCR transduced T cell %
	NCT06054984	I	18	RAS/TP 53	TRAE, CMAX, TMAX, AUC ORR, DCR, PFS, OS Change in tumor size, biomarker
	NCT06043713	I	24	KRAS	AE, DLT, MTD

 doi:10.20944/preprints202412.2086.v1

					CBR, ORR, SD, ORR, PFS, OS, changes in TME
	NCT05877599	I	162	TP53	DLT, AE, SAE, TRAE, ORR, BOR, DOR, CBR, TTR, PFS
	NCT06218914	I	24	KRAS	DLT, AE, SAE ORR, BOR, DOR, CBR, TTR, PFS, OS
	NCT06105021	I/II	100	KRAS	OBD, DLT, SAE, TEAE ORR, DOR, PFS, TTR, CBR, OS
	NCT04622423	Observational	475		Tumor mutational burden, Gene expression profile, Antigenic landscape, T cell repertoire, OS, PFS, Change in tumor marker
	NCT05964361	I/II	10	WT-1	Leukapheresis %, SAE, BOR, DOR, ORR, DCR, PFS, OS, QoLA
	NCT03190941	I/II	110	KRAS	RR, TRAE
	NCT03745326	I/II	70	KRAS	RR, TRAE
	NCT04810910	I	20	Personalized Neo-antigen vaccine	TRAE, RFS, OS, CD4/CD8

TIL – tumor infiltrating lymphocytes, CAR – chimeric antigen receptor, NK – natural killer cells, TRAE – treatment related adverse events, ORR – Objective response rate, CR – complete response, PR – partial response, DOR – duration of response, OS – overall survival, PFS – progression-free survival, MTD – Maximum tolerated dose, PE - preliminary efficacy, LA – lab abnormalities, RR – response rate, DCR – disease control rate, QoLA – Quality of life assessment, SIR - Systemic Immune Response, DLT – Dose-dependent toxicity, TTP – time to progression, SSR – symptom remission rate, CBR – clinical benefit rate, Cmax – peak plasma concentration, Tmax – peak time, AUC – area under concentration, BOR - best overall response.

6. Oncolytic Virus

The development of oncolytic virus (OV) therapy began in the 1990s, but its integration into clinical practice has accelerated only within the last decade [80]. OVs are genetically engineered viruses designed to selectively infect, replicate within, and ultimately destroy cancer cells. The first OV therapy to receive regulatory approval was talimogene laherparepvec (T-VEC or OncoVEXGM-CSF), approved in 2015 for the treatment of refractory melanoma [81]. Since then, several other OVs—including H-1 parvovirus, VCN-01 adenovirus, LOAd703 adenovirus, and pelareorep reovirus—have shown promising preclinical efficacy in pancreatic cancer cell lines [82–85]. In an early clinical study reported in 2018, the HF10 virus was injected directly into the primary tumor of patients with locally advanced pancreatic ductal adenocarcinoma (PDAC), alongside systemic erlotinib and gemcitabine therapy [86]. Among the nine patients who completed the study, three achieved PR, four had SD, and two experienced disease progression (PD). Severe adverse events such as bone marrow suppression, gastrointestinal perforation, and liver dysfunction were reported but were unrelated to OV therapy.

Subsequent investigations have demonstrated the safety and potential efficacy of other OVs, such as VCN-01 and LOAd703, when combined with chemotherapy (e.g., gemcitabine/nab-paclitaxel) or immune checkpoint inhibitors (ICIs) like pembrolizumab [85,87–89]. These studies highlight the potential of OVs to act synergistically with existing therapies. OVs also enhance the effectiveness of CAR-T cell therapy in solid tumors by improving tumor-associated antigen presentation, increasing T cell infiltration and tumor penetration, and mitigating immune

 doi:10.20944/preprints202412.2086.v1

suppression within the tumor microenvironment. This combination generates a more robust and durable anti-tumor response, making OVs a promising adjunctive therapy in PDAC treatment [90]. We discussed ongoing OV therapy trials in Table 3.

7. Genetically Modified T Cell Therapy

NK cells play a pivotal role as part of the body's first line of defense against cancer. Genetically engineered NK cells have demonstrated the ability to mount specific and targeted anti-tumor responses, offering a promising avenue for cancer immunotherapy [91]. Preclinical studies involving chimeric antigen receptor NK (CAR-NK) cells targeting prostate stem cell antigen (PSCA) and mesothelin in pancreatic ductal adenocarcinoma (PDAC) have shown encouraging results, raising hope for their clinical application in select patient populations [92,93]. Compared to CAR-T cells, CAR-NK cells offer potential advantages, including reduced toxicity due to their shorter half-life and distinct cytokine profile, as well as a lower likelihood of inducing alloreactivity, making them suitable for "off-the-shelf" therapeutic products [20,94]. However, several limitations hinder their clinical implementation. These include technical challenges in manufacturing, poor tumor infiltration, and the short half-life of NK cells, which necessitates repeated administrations to sustain therapeutic effects. [95,96]. We discussed ongoing CAR-NK trials in Table 3.

In addition to NK cells, T cells can be genetically modified to express tumor-specific T-cell receptors (TCRs), enabling robust and precise anti-tumor responses [97]. Commonly targeted antigens in TCR therapy include mesothelin (MSLN), epidermal growth factor receptor (EGFR), claudin 18.2 (CLDN), CD133, and human epidermal growth factor receptor 2 (HER2). Notably, a study by Leidner et al. demonstrated that TCRs targeting mutant KRAS (KRAS12D) elicited responses in patients with metastatic PDAC, highlighting the potential of TCR-based therapies in this challenging cancer type [98]. We discussed ongoing TCR trials in Table 3.

8. Cytokine-Induced Killer (CIK) Cells

CIK cells are a heterogeneous group of CD8+ T cells that exhibit a hybrid phenotype, combining features of both T cells and natural killer (NK) cells. These cells are generated by incubating human-derived peripheral lymphocytes with anti-CD3 antibodies and cytokines [99–101]. CIK cells have shown potential to enhance the efficacy of other anti-cancer therapies, such as immune checkpoint inhibitors (ICIs) and chemotherapy, by amplifying anti-tumor responses [102].

Preclinical and clinical studies have demonstrated synergistic effects when CIK therapy is combined with chemotherapy in pancreatic cancer [100,101]. n a randomized study evaluating the addition of the chemotherapy agent S-1 to CIK therapy, a slight improvement in progression-free survival (PFS) was observed (2.5 months vs. 2.9 months, $p = 0.03$), although overall survival (OS) was comparable between the groups (6.1 months vs. 6.6 months, $p = 0.09$) [101]. Hematological toxicity was similar across both groups, but the incidence of non-infectious fever was significantly higher in the CIK group (32% vs. 3.3%, $p = 0.004$). In another study involving 47 patients with advanced pancreatic ductal adenocarcinoma (PDAC), median OS and PFS were notably higher in the group treated with dendritic cell-CIK (DC-CIK) therapy combined with S-1 (212 and 136 days, respectively) compared to those receiving DC-CIK therapy alone (128 and 85 days), chemotherapy alone (141 and 92 days), or supportive care only (52 and 43 days) [103]. These findings suggest that CIK-based therapies, particularly when combined with other modalities, hold promise for improving outcomes in advanced PDAC patients. We discussed ongoing CIK cells therapy in PDA in Table 3.

9. Conclusions

PDAC is a highly aggressive and challenging cancer that requires a multimodal approach to identify new therapeutic targets and develop innovative treatments. A comprehensive understanding of the TME in PDAC is critical to overcoming the limitations of current therapies and improving clinical outcomes. Cancer immunotherapy, particularly CAR-T therapy, has shown remarkable success in hematological malignancies and is now expanding its scope to solid tumors, including PDAC. However, the effectiveness of CAR-T therapy in PDAC is limited by factors such as

 doi:10.20944/preprints202412.2086.v1

tumor heterogeneity, T-cell exhaustion, and the suppressive influence of tumor-associated immune cells within the TME. Advances in next-generation CAR-T therapies, coupled with combination strategies integrating other treatment modalities, hold promise for addressing these challenges and unlocking the potential of CAR-T cell therapy in PDAC.

Author Contributions: Conceptualization, A.M.; resources, D.S.; writing—original draft preparation, D.S.; writing—review and editing, A.M.; visualization, A.M.; supervision, A.M. All authors have read and agreed to the published version of the manuscript.

Funding: None.

Institutional Review Board Statement: Not applicable. Institutional data was not used for this project.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: biorender.com was used to make figures.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024;74[1]:12-49.
2. Wood LD, Canto MI, Jaffee EM, Simeone DM. Pancreatic Cancer: Pathogenesis, Screening, Diagnosis, and Treatment. Gastroenterology. 2022;163[2]:386-402.e1.
3. Ilic I, Ilic M. International patterns in incidence and mortality trends of pancreatic cancer in the last three decades: A joinpoint regression analysis. World J Gastroenterol. 2022;28[32]:4698-715.
4. Hu JX, Zhao CF, Chen WB, Liu QC, Li QW, Lin YY, et al. Pancreatic cancer: A review of epidemiology, trend, and risk factors. World J Gastroenterol. 2021;27[27]:4298-321.
5. Adamska A, Domenichini A, Falasca M. Pancreatic Ductal Adenocarcinoma: Current and Evolving Therapies. Int J Mol Sci. 2017;18[7].
6. Roalsø M, Aunan JR, Søreide K. Refined TNM-staging for pancreatic adenocarcinoma – Real progress or much ado about nothing? European Journal of Surgical Oncology. 2020;46[8]:1554-7.
7. Evans DB. What Makes a Pancreatic Cancer Resectable? American Society of Clinical Oncology Educational Book. 2018[38]:300-5.
8. Vernuccio F, Messina C, Merz V, Cannella R, Midiri M. Resectable and Borderline Resectable Pancreatic Ductal Adenocarcinoma: Role of the Radiologist and Oncologist in the Era of Precision Medicine. Diagnostics (Basel). 2021;11[11].
9. Isaji S, Mizuno S, Windsor JA, Bassi C, Fernández-Del Castillo C, Hackert T, et al. International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. Pancreatology. 2018;18[1]:2-11.
10. Barcellini A, Peloso A, Pugliese L, Vitolo V, Cobianchi L. Locally Advanced Pancreatic Ductal Adenocarcinoma: Challenges and Progress. Onco Targets Ther. 2020;13:12705-20.
11. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine. New England Journal of Medicine. 2013;369[18]:1691-703.
12. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer. New England Journal of Medicine. 2011;364[19]:1817-25.
13. Dillman RO. Cancer immunotherapy. Cancer Biother Radiopharm. 2011;26[1]:1-64.
14. Nasar N, Eikenboom E, Seier K, Gonen M, Wagner A, Jarnagin WR, et al. Survival of patients with microsatellite instability-high and Lynch syndrome-associated pancreatic ductal adenocarcinomas. J Clin Oncol. 2024;42(3_suppl):640-.
15. Velcheti V, Schalper K. Basic Overview of Current Immunotherapy Approaches in Cancer. Am Soc Clin Oncol Educ Book. 2016;35:298-308.
16. Esfahani K, Roudaia L, Buhlaiga N, Del Rincon SV, Papneja N, Miller WH, Jr. A review of cancer immunotherapy: from the past, to the present, to the future. Curr Oncol. 2020;27(Suppl 2):S87-s97.

 doi:10.20944/preprints202412.2086.v1

17. Sangro B, Chan SL, Kelley RK, Lau G, Kudo M, Sukeepaisarnjaroen W, et al. Four-year overall survival update from the phase III HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. Ann Oncol. 2024;35[5]:448-57.
18. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim T-Y, et al. IMbrave150: Updated overall survival (OS) data from a global, randomized, open-label phase III study of atezolizumab (atezo) + bevacizumab (bev) versus sorafenib (sor) in patients (pts) with unresectable hepatocellular carcinoma (HCC). J Clin Oncol. 2021;39(3_suppl):267-.
19. Oh D-Y, Ruth He A, Qin S, Chen L-T, Okusaka T, Vogel A, et al. Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer. NEJM Evidence. 2022.
20. Farhangnia P, Khorramdelazad H, Nickho H, Delbandi A-A. Current and future immunotherapeutic approaches in pancreatic cancer treatment. Journal of Hematology & Oncology. 2024;17[1]:40.
21. Callahan M, Amin A, Kaye FJ, Morse MA, Taylor MH, Peltola KJ, et al. Nivolumab monotherapy or combination with ipilimumab with or without cobimetinib in previously treated patients with pancreatic adenocarcinoma (CheckMate 032). J Immunother Cancer. 2024;12[2].
22. Renouf DJ, Loree JM, Knox JJ, Topham JT, Kavan P, Jonker D, et al. The CCTG PA.7 phase II trial of gemcitabine and nab-paclitaxel with or without durvalumab and tremelimumab as initial therapy in metastatic pancreatic ductal adenocarcinoma. Nature Communications. 2022;13[1]:5020.
23. Padrón LJ, Maurer DM, O'Hara MH, O'Reilly EM, Wolff RA, Wainberg ZA, et al. Sotigalimab and/or nivolumab with chemotherapy in first-line metastatic pancreatic cancer: clinical and immunologic analyses from the randomized phase 2 PRINCE trial. Nat Med. 2022;28[6]:1167-77.
24. Bockorny B, Macarulla T, Semenisty V, Borazanci E, Feliu J, Ponz-Sarvise M, et al. Motixafortide and Pembrolizumab Combined to Nanoliposomal Irinotecan, Fluorouracil, and Folinic Acid in Metastatic Pancreatic Cancer: The COMBAT/KEYNOTE-202 Trial. Clin Cancer Res. 2021;27[18]:5020-7.
25. O'Reilly EM, Oh D-Y, Dhani N, Renouf DJ, Lee MA, Sun W, et al. Durvalumab With or Without Tremelimumab for Patients With Metastatic Pancreatic Ductal Adenocarcinoma: A Phase 2 Randomized Clinical Trial. JAMA Oncology. 2019;5[10]:1431-8.
26. Royal RE, Levy C, Turner K, Mathur A, Hughes M, Kammula US, et al. Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. J Immunother. 2010;33[8]:828-33.
27. Miksch RC, Schoenberg MB, Weniger M, Bösch F, Ormanns S, Mayer B, et al. Prognostic Impact of Tumor-Infiltrating Lymphocytes and Neutrophils on Survival of Patients with Upfront Resection of Pancreatic Cancer. Cancers (Basel). 2019;11[1].
28. Panahi M, Rezagholizadeh F, Mollazadehghomi S, Farhangnia P, Niya MHK, Ajdarkosh H, et al. The association between CD3+ and CD8+tumor-infiltrating lymphocytes (TILs) and prognosis in patients with pancreatic adenocarcinoma. Cancer Treatment and Research Communications. 2023;35:100699.
29. Orhan A, Vogelsang RP, Andersen MB, Madsen MT, Hölmich ER, Raskov H, et al. The prognostic value of tumour-infiltrating lymphocytes in pancreatic cancer: a systematic review and meta-analysis. Eur J Cancer. 2020;132:71-84.
30. Guo J, Wu M, Guo L, Zuo Q. Pretreatment blood neutrophil/lymphocyte ratio is associated with metastasis and predicts survival in patients with pancreatic cancer. Bulletin du Cancer. 2018;105[2]:146-54.
31. Ino Y, Yamazaki-Itoh R, Shimada K, Iwasaki M, Kosuge T, Kanai Y, et al. Immune cell infiltration as an indicator of the immune microenvironment of pancreatic cancer. British Journal of Cancer. 2013;108[4]:914-23.
32. Guo J, Wang S, Gao Q. An integrated overview of the immunosuppression features in the tumor microenvironment of pancreatic cancer. Frontiers in immunology. 2023;14:1258538.
33. Huber M, Brehm CU, Gress TM, Buchholz M, Alashkar Alhamwe B, von Strandmann EP, et al. The Immune Microenvironment in Pancreatic Cancer. Int J Mol Sci. 2020;21[19].
34. Galon J, Bruni D. Tumor Immunology and Tumor Evolution: Intertwined Histories. Immunity. 2020;52[1]:55-81.
35. Hartupee C, Nagalo BM, Chabu CY, Tesfay MZ, Coleman-Barnett J, West JT, et al. Pancreatic cancer tumor microenvironment is a major therapeutic barrier and target. Frontiers in immunology. 2024;15.

 doi:10.20944/preprints202412.2086.v1

36. Kirtane K, Elmariah H, Chung CH, Abate-Daga D. Adoptive cellular therapy in solid tumor malignancies: review of the literature and challenges ahead. J Immunother Cancer. 2021;9[7].
37. Sterner RC, Sterner RM. CAR-T cell therapy: current limitations and potential strategies. Blood Cancer Journal. 2021;11[4]:69.
38. Depil S, Duchateau P, Grupp SA, Mufti G, Poirot L. 'Off-the-shelf' allogeneic CAR T cells: development and challenges. Nat Rev Drug Discov. 2020;19[3]:185-99.
39. DeSelm CJ, Tano ZE, Varghese AM, Adusumilli PS. CAR T-cell therapy for pancreatic cancer. J Surg Oncol. 2017;116[1]:63-74.
40. Asmamaw Dejenie T, Tiruneh G/Medhin M, Dessie Terefe G, Tadele Admasu F, Wale Tesega W, Chekol Abebe E. Current updates on generations, approvals, and clinical trials of CAR T-cell therapy. Human Vaccines & Immunotherapeutics. 2022;18[6]:2114254.
41. Wang Y, Chen M, Wu Z, Tong C, Dai H, Guo Y, et al. CD133-directed CAR T cells for advanced metastasis malignancies: A phase I trial. Oncoimmunology. 2018;7[7]:e1440169.
42. Ding Q, Miyazaki Y, Tsukasa K, Matsubara S, Yoshimitsu M, Takao S. CD133 facilitates epithelial-mesenchymal transition through interaction with the ERK pathway in pancreatic cancer metastasis. Molecular Cancer. 2014;13[1]:15.
43. Maeda S, Shinchi H, Kurahara H, Mataki Y, Maemura K, Sato M, et al. CD133 expression is correlated with lymph node metastasis and vascular endothelial growth factor-C expression in pancreatic cancer. Br J Cancer. 2008;98[8]:1389-97.
44. Katz SC, Moody AE, Guha P, Hardaway JC, Prince E, LaPorte J, et al. HITM-SURE: Hepatic immunotherapy for metastases phase Ib anti-CEA CAR-T study utilizing pressure enabled drug delivery. J Immunother Cancer. 2020;8[2].
45. Meng Q, Shi S, Liang C, Liang D, Xu W, Ji S, et al. Diagnostic and prognostic value of carcinoembryonic antigen in pancreatic cancer: a systematic review and meta-analysis. OncoTargets and Therapy. 2017;10(null):4591-8.
46. Hall C, Clarke L, Pal A, Buchwald P, Eglinton T, Wakeman C, et al. A Review of the Role of Carcinoembryonic Antigen in Clinical Practice. Ann Coloproctol. 2019;35[6]:294-305.
47. van Manen L, Groen JV, Putter H, Vahrmeijer AL, Swijnenburg R-J, Bonsing BA, et al. Elevated CEA and CA19-9 serum levels independently predict advanced pancreatic cancer at diagnosis. Biomarkers. 2020;25[2]:186-93.
48. Kato H, Kishiwada M, Hayasaki A, Chipaila J, Maeda K, Noguchi D, et al. Role of Serum Carcinoma Embryonic Antigen (CEA) Level in Localized Pancreatic Adenocarcinoma: CEA Level Before Operation is a Significant Prognostic Indicator in Patients With Locally Advanced Pancreatic Cancer Treated With Neoadjuvant Therapy Followed by Surgical Resection: A Retrospective Analysis. Annals of Surgery. 2022;275[5]:e698-e707.
49. Watanabe K, Luo Y, Da T, Guedan S, Ruella M, Scholler J, et al. Pancreatic cancer therapy with combined mesothelin-redirected chimeric antigen receptor T cells and cytokine-armed oncolytic adenoviruses. JCI Insight. 2018;3[7].
50. Hassan R, Thomas A, Alewine C, Le DT, Jaffee EM, Pastan I. Mesothelin Immunotherapy for Cancer: Ready for Prime Time? J Clin Oncol. 2016;34[34]:4171-9.
51. Klampatsa A, Dimou V, Albelda SM. Mesothelin-targeted CAR-T cell therapy for solid tumors. Expert Opinion on Biological Therapy. 2021;21[4]:473-86.
52. Johnston FM, Tan MCB, Tan BR, Jr., Porembka MR, Brunt EM, Linehan DC, et al. Circulating Mesothelin Protein and Cellular Antimesothelin Immunity in Patients with Pancreatic Cancer. Clinical Cancer Research. 2009;15[21]:6511-8.
53. Haas AR, Tanyi JL, O'Hara MH, Gladney WL, Lacey SF, Torigian DA, et al. Phase I Study of Lentiviral-Transduced Chimeric Antigen Receptor-Modified T Cells Recognizing Mesothelin in Advanced Solid Cancers. Molecular Therapy. 2019;27[11]:1919-29.
54. QI C, Liu C, Gong J, Li J, Liu D, Wang X, et al. Claudin18.2-targeted chimeric antigen receptor T cell-therapy for patients with gastrointestinal cancers: Final results of CT041-CG4006 phase 1 trial. J Clin Oncol. 2024;42(16_suppl):2501-.

 doi:10.20944/preprints202412.2086.v1

55. Qin S, Tian W, Li M, Wei H, Sun L, Xie Q, et al. 1054P A phase Ia study to evaluate the safety, tolerability, pharmacokinetics and preliminary efficacy of a modular CLDN18.2-targeting PG CAR-T therapy (IBI345) in patients with CLDN18.2+ solid tumors. Ann Oncol. 2023;34:S638.
56. Liu Y, Guo Y, Wu Z, Feng K, Tong C, Wang Y, et al. Anti-EGFR chimeric antigen receptor-modified T cells in metastatic pancreatic carcinoma: A phase I clinical trial. Cytotherapy. 2020;22[10]:573-80.
57. Fitzgerald TL, Lertpiriyapong K, Cocco L, Martelli AM, Libra M, Candido S, et al. Roles of EGFR and KRAS and their downstream signaling pathways in pancreatic cancer and pancreatic cancer stem cells. Advances in Biological Regulation. 2015;59:65-81.
58. Oliveira-Cunha M, Newman WG, Siriwardena AK. Epidermal Growth Factor Receptor in Pancreatic Cancer. Cancers. 2011;3[2]:1513-26.
59. Feng K, Liu Y, Guo Y, Qiu J, Wu Z, Dai H, et al. Phase I study of chimeric antigen receptor modified T cells in treating HER2-positive advanced biliary tract cancers and pancreatic cancers. Protein Cell. 2018;9[10]:838-47.
60. Kumar R, Yarmand-Bagheri R. The role of HER2 in angiogenesis. Semin Oncol. 2001;28(5 Suppl 16):27-32.
61. Schmidts A, Wehrli M, Maus MV. Toward Better Understanding and Management of CAR-T Cell–Associated Toxicity. Annual review of medicine. 2021;72(Volume 72, 2021):365-82.
62. Zhao Y, Deng J, Rao S, Guo S, Shen J, Du F, et al. Tumor Infiltrating Lymphocyte (TIL) Therapy for Solid Tumor Treatment: Progressions and Challenges. Cancers. 2022;14[17]:4160.
63. Betof Warner A, Corrie PG, Hamid O. Tumor-Infiltrating Lymphocyte Therapy in Melanoma: Facts to the Future. Clinical Cancer Research. 2023;29[10]:1835-54.
64. Kazemi MH, Sadri M, Najafi A, Rahimi A, Baghernejadan Z, Khorramdelazad H, et al. Tumor-infiltrating lymphocytes for treatment of solid tumors: It takes two to tango? Front Immunol. 2022;13:1018962.
65. Rosenberg SA, Yannelli JR, Yang JC, Topalian SL, Schwartzentruber DJ, Weber JS, et al. Treatment of Patients With Metastatic Melanoma With Autologous Tumor-Infiltrating Lymphocytes and Interleukin 2. JNCI: Journal of the National Cancer Institute. 1994;86[15]:1159-66.
66. Dafni U, Michielin O, Lluesma SM, Tsourti Z, Polydoropoulou V, Karlis D, et al. Efficacy of adoptive therapy with tumor-infiltrating lymphocytes and recombinant interleukin-2 in advanced cutaneous melanoma: a systematic review and meta-analysis. Ann Oncol. 2019;30[12]:1902-13.
67. Ellebaek E, Iversen TZ, Junker N, Donia M, Engell-Noerregaard L, Met Ö, et al. Adoptive cell therapy with autologous tumor infiltrating lymphocytes and low-dose Interleukin-2 in metastatic melanoma patients. Journal of Translational Medicine. 2012;10[1]:169.
68. Ben-Avi R, Farhi R, Ben-Nun A, Gorodner M, Greenberg E, Markel G, et al. Establishment of adoptive cell therapy with tumor infiltrating lymphocytes for non-small cell lung cancer patients. Cancer Immunol Immunother. 2018;67[8]:1221-30.
69. Kradin RL, Boyle LA, Preffer FI, Callahan RJ, Barlai-Kovach M, Strauss HW, et al. Tumor-derived interleukin-2-dependent lymphocytes in adoptive immunotherapy of lung cancer. Cancer Immunol Immunother. 1987;24[1]:76-85.
70. Freedman RS, Kudelka AP, Kavanagh JJ, Verschraegen C, Edwards CL, Nash M, et al. Clinical and biological effects of intraperitoneal injections of recombinant interferon-gamma and recombinant interleukin 2 with or without tumor-infiltrating lymphocytes in patients with ovarian or peritoneal carcinoma. Clin Cancer Res. 2000;6[6]:2268-78.
71. Fujita K, Ikarashi H, Takakuwa K, Kodama S, Tokunaga A, Takahashi T, et al. Prolonged disease-free period in patients with advanced epithelial ovarian cancer after adoptive transfer of tumor-infiltrating lymphocytes. Clin Cancer Res. 1995;1[5]:501-7.
72. Pedersen M, Westergaard MCW, Milne K, Nielsen M, Borch TH, Poulsen LG, et al. Adoptive cell therapy with tumor-infiltrating lymphocytes in patients with metastatic ovarian cancer: a pilot study. Oncoimmunology. 2018;7[12]:e1502905.
73. Kverneland AH, Pedersen M, Westergaard MCW, Nielsen M, Borch TH, Olsen LR, et al. Adoptive cell therapy in combination with checkpoint inhibitors in ovarian cancer. Oncotarget. 2020;11[22]:2092-105.

 doi:10.20944/preprints202412.2086.v1

74. O'Malley D, Lee S, Psyrri A, Sukari A, Thomas S, Wenham R, et al. 492 Phase 2 efficacy and safety of autologous tumor-infiltrating lymphocyte (TIL) cell therapy in combination with pembrolizumab in immune checkpoint inhibitor-naïve patients with advanced cancers. Journal for ImmunoTherapy of Cancer. 2021;9(Suppl 2):A523-A4.
75. Li J, Chen QY, He J, Li ZL, Tang XF, Chen SP, et al. Phase I trial of adoptively transferred tumor-infiltrating lymphocyte immunotherapy following concurrent chemoradiotherapy in patients with locoregionally advanced nasopharyngeal carcinoma. Oncoimmunology. 2015;4[2]:e976507.
76. Savas P, Virassamy B, Ye C, Salim A, Mintoff CP, Caramia F, et al. Single-cell profiling of breast cancer T cells reveals a tissue-resident memory subset associated with improved prognosis. Nat Med. 2018;24[7]:986-93.
77. Orhan A, Vogelsang RP, Andersen MB, Madsen MT, Hölmich ER, Raskov H, et al. The prognostic value of tumour-infiltrating lymphocytes in pancreatic cancer: a systematic review and meta-analysis. European Journal of Cancer. 2020;132:71-84.
78. Zhao Y, Deng J, Rao S, Guo S, Shen J, Du F, et al. Tumor Infiltrating Lymphocyte (TIL) Therapy for Solid Tumor Treatment: Progressions and Challenges. Cancers (Basel). 2022;14[17].
79. Amaria R, Knisely A, Vining D, Kopetz S, Overman MJ, Javle M, et al. Efficacy and safety of autologous tumor-infiltrating lymphocytes in recurrent or refractory ovarian cancer, colorectal cancer, and pancreatic ductal adenocarcinoma. J Immunother Cancer. 2024;12[2].
80. Ajina A, Maher J. Prospects for combined use of oncolytic viruses and CAR T-cells. Journal for ImmunoTherapy of Cancer. 2017;5[1]:90.
81. Johnson DB, Puzanov I, Kelley MC. Talimogene laherparepvec (T-VEC) for the treatment of advanced melanoma. Immunotherapy. 2015;7[6]:611-9.
82. McAuliffe PF, Jarnagin WR, Johnson P, Delman KA, Federoff H, Fong Y. Effective treatment of pancreatic tumors with two multimutated herpes simplex oncolytic viruses. J Gastrointest Surg. 2000;4[6]:580-8.
83. Toda M, Martuza RL, Rabkin SD. Tumor growth inhibition by intratumoral inoculation of defective herpes simplex virus vectors expressing granulocyte-macrophage colony-stimulating factor. Mol Ther. 2000;2[4]:324-9.
84. Cho I-R, Kaowinn S, Moon J, Soh J, Kang HY, Jung C-R, et al. Oncotropic H-1 parvovirus infection degrades HIF-1α protein in human pancreatic cancer cells independently of VHL and RACK1. Int J Oncol. 2015;46[5]:2076-82.
85. Musher BL, Smaglo BG, Abidi W, Othman M, Patel K, Jawaid S, et al. A phase I/II study of LOAd703, a TMZ-CD40L/4-1BBL-armed oncolytic adenovirus, combined with nab-paclitaxel and gemcitabine in advanced pancreatic cancer. J Clin Oncol. 2022;40(16_suppl):4138-.
86. Hirooka Y, Kasuya H, Ishikawa T, Kawashima H, Ohno E, Villalobos IB, et al. A Phase I clinical trial of EUS-guided intratumoral injection of the oncolytic virus, HF10 for unresectable locally advanced pancreatic cancer. BMC Cancer. 2018;18[1]:596.
87. Bazan-Peregrino M, Garcia-Carbonero R, Laquente B, Álvarez R, Mato-Berciano A, Gimenez-Alejandre M, et al. VCN-01 disrupts pancreatic cancer stroma and exerts antitumor effects. J Immunother Cancer. 2021;9[11].
88. Garcia-Carbonero R, Bazan-Peregrino M, Gil-Martín M, Álvarez R, Macarulla T, Riesco-Martinez MC, et al. Phase I, multicenter, open-label study of intravenous VCN-01 oncolytic adenovirus with or without nab-paclitaxel plus gemcitabine in patients with advanced solid tumors. J Immunother Cancer. 2022;10[3].
89. Mahalingam D, Chen S, Xie P, Loghmani H, Heineman T, Kalyan A, et al. Combination of pembrolizumab and pelareorep promotes anti-tumour immunity in advanced pancreatic adenocarcinoma (PDAC). Br J Cancer. 2023;129[5]:782-90.
90. Ponterio E, Haas TL, De Maria R. Oncolytic virus and CAR-T cell therapy in solid tumors. Frontiers in immunology. 2024;15:1455163.
91. Froelich W. CAR NK Cell Therapy Directed Against Pancreatic Cancer. Oncology Times. 2021;43[11]:46.
92. Teng KY, Mansour AG, Zhu Z, Li Z, Tian L, Ma S, et al. Off-the-Shelf Prostate Stem Cell Antigen-Directed Chimeric Antigen Receptor Natural Killer Cell Therapy to Treat Pancreatic Cancer. Gastroenterology. 2022;162[4]:1319-33.

 doi:10.20944/preprints202412.2086.v1

93. Da Y, Liu Y, Hu Y, Liu W, Ma J, Lu N, et al. STING agonist cGAMP enhances anti-tumor activity of CAR-NK cells against pancreatic cancer. Oncoimmunology. 2022;11[1]:2054105.
94. Pan K, Farrukh H, Chittepu V, Xu H, Pan CX, Zhu Z. CAR race to cancer immunotherapy: from CAR T, CAR NK to CAR macrophage therapy. J Exp Clin Cancer Res. 2022;41[1]:119.
95. Wang K, Wang L, Wang Y, Xiao L, Wei J, Hu Y, et al. Reprogramming natural killer cells for cancer therapy. Molecular Therapy. 2024;32[9]:2835-55.
96. Liu E, Tong Y, Dotti G, Shaim H, Savoldo B, Mukherjee M, et al. Cord blood NK cells engineered to express IL-15 and a CD19-targeted CAR show long-term persistence and potent antitumor activity. Leukemia. 2018;32[2]:520-31.
97. Tsimberidou A-M, Van Morris K, Vo HH, Eck S, Lin Y-F, Rivas JM, et al. T-cell receptor-based therapy: an innovative therapeutic approach for solid tumors. Journal of Hematology & Oncology. 2021;14[1]:102.
98. Leidner R, Sanjuan Silva N, Huang H, Sprott D, Zheng C, Shih YP, et al. Neoantigen T-Cell Receptor Gene Therapy in Pancreatic Cancer. N Engl J Med. 2022;386[22]:2112-9.
99. Zhang Y, Schmidt-Wolf IGH. Ten-year update of the international registry on cytokine-induced killer cells in cancer immunotherapy. Journal of Cellular Physiology. 2020;235[12]:9291-303.
100. Choi JH, Nam GH, Hong J-m, Cho IR, Paik WH, Ryu JK, et al. Cytokine-Induced Killer Cell Immunotherapy Combined With Gemcitabine Reduces Systemic Metastasis in Pancreatic Cancer: An Analysis Using Preclinical Adjuvant Therapy-Mimicking Pancreatic Cancer Xenograft Model. Pancreas. 2022;51[9]:1251-7.
101. Wang M, Shi SB, Qi JL, Tang XY, Tian J. S-1 plus CIK as second-line treatment for advanced pancreatic cancer. Med Oncol. 2013;30[4]:747.
102. Gao X, Mi Y, Guo N, Xu H, Xu L, Gou X, et al. Cytokine-Induced Killer Cells As Pharmacological Tools for Cancer Immunotherapy. Frontiers in immunology. 2017;8:774.
103. Jiang N, Qiao G, Wang X, Morse MA, Gwin WR, Zhou L, et al. Dendritic Cell/Cytokine-Induced Killer Cell Immunotherapy Combined with S-1 in Patients with Advanced Pancreatic Cancer: A Prospective Study. Clin Cancer Res. 2017;23[17]:5066-73.