Immunotherapy in pancreatic cancer—an emerging role: a narrative review

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Background and Objective: Immunotherapy is the fastest growing branch in oncology that have already revolutionized the treatment of few solid cancers. The number of immunotherapy trials for pancreatic cancer (PC) is growing but the vast number of different agents used make it difficult to comprehend a possible success trait of a certain type of immunotherapy. The aim of this review is to summarize and critically evaluate the outcome of immunotherapy trials for PC intended to aid the comprehensiveness for the treating physicians.

Methods: A PubMed search was performed to identify clinical trials in patients with PC, published in English from year 2000 to June 2021 and using combination of the terms immunotherapy, PC, and cross-checked the bibliography of the revised literature as the dublettes have been removed. Studies were divided into three groups depending on what immune components have been applied: passive products (peptides, antibodies, etc.), antigen-presenting cells, and adoptive cell transfer trials.

Key Content and Findings: The vast majority of trials, including those from most recent years, used passive products of the immune system—peptide vaccines and antibodies. The administration was often parallel to chemotherapy that was prevalently gemcitabine-based. Although immunological responses have been detected, the clinical efficacy was very limited. Trials with check point inhibitors did not show survival advantage. Dendritic cell (DC) vaccines have been associated with some clinical objective response and prolonged survival in few patients with delayed type hypersensitivity reactions. Trials with adoptive transfer therapy are lacking. The very few trials with lymphokine-activated killer (LAK)/cytokine-induced killer (CIK) cells tested only in Asian population have resulted in some clinical effects with prolonged survival. In none of the trials have the patients been preconditioned before receiving immunotherapy.

Conclusions: Although the clinical effectiveness in the majority of the reported trials has been limited, the immunological effects observed in almost all trials show a proof of concept—that immunotherapy can work. Careful re-evaluation of the clinical premises and focus on combination and cell therapy may be the way to achieve improved survival by immunotherapy in PC.

Keywords: Pancreatic cancer (PC); immunotherapy; checkpoint inhibitors; T cell; cancer vaccines

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Introduction

Pancreatic cancer (PC) is one among very few cancer types for which the prognosis has not improved much over the past decades (1). While the 5-year survival for all cancers altogether is above 60%, the survival of all-stage PC remains below 10% (1,2). Three major features of PC make it particularly difficult to treat and roadmap its dismal prognosis. The tricky anatomic location not only predefines the limitation to extend surgical resection margins, resulting in about 80% R1 resections, but is also the reason why about 30% of patients present with locally advanced disease with tumor advancement along major abdominal vessels and propagation along the rich neural routes in the area (2-4). Second, PC is prone to give early rise of metastases that can occur even before the primary tumor becomes visible to the clinician (5). This is one of the explanations why even smaller primary resectable tumors tend to recur in the majority of cases even following curative resection, leaving a 5-year chance of survival of only about 20% (2). These two major characteristics of PC are the reason why systemic oncologic treatment is making its way as the new standard in the neoadjuvant setting. Its purpose is to combat occult distant spread and/or consolidate the advanced tumor in order to select who would benefit the most from surgical resection. However, as potent and promising the new combination regimens like FOLFIRINOX or gemcitabine-nab-paclitaxel might be in prolonging life, used alone they basically never lead to cure due to the microenvironment architecture of PC.

The third unfortunate characteristic of PC is the abundant stroma that shields the tumors cells and defines its chemoresistance (6,7). The poor vascular tumor network is responsible for the ineffective drug delivery and is the driver of hypoxia which enhances endothelial-mesenchymal transformation and invasiveness of PC cells (8). The thick fibrotic stroma increases the distance between the vessels and the tumor cells and mechanically hampers the diffusion of the infused drugs, which cannot reach the cancer cells in therapeutic concentrations (9). Thus, theoretically any passively infused treatment would be doomed to failure.

The tumor microenvironment also plays an active role in carcinogenesis and tumor progression. The components of the immune system are part of this environment and depending on the immune cell composition and its balance, it can either tip over the response toward tumor antigen recognition and appropriate adoptive anti-tumoral response or aid in escaping effective tumor recognition and elimination. Manipulating the immune response towards continuous activation and tumor recognition is the basis of immunotherapy—the fastest growing branch of oncology. Immunotherapy has already revolutionized the treatment of some dismal cancer types, such as malignant melanoma or lung cancer (10,11). In particular, treatment with check point inhibitors has led to long-term survival in patients with melanoma and renal cancer (10,12,13). Inevitably, there is hope that immunotherapy may have similar significant impact on the prognosis of PC. The theoretical advantage of immunotherapy compared to cytotoxic drugs is that it will not only "work" during the treatment occasion but can perpetuate itself and be able to augment and persist during cancer recognition and elimination.

The purpose of this review is to give a comprehensive overview of the role and current attempts of immunotherapy for PC from the clinician's perspective of possible integration in treatment, to map the problematic areas and to highlight what might be opportunities for successful implementation. We present the following article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-21-174/rc).

Methods

A search in PubMed was performed to identify clinical trials in humans, published in English between January 2000 and June 2021 and using components of the immune system for immunomodulation in patients with PC. Search was performed using a combination of the search terms "immunotherapy", "pancreatic cancer", "pancreatic adenocarcinoma", "check-point inhibitors", "vaccine", "peptide vaccine", "antibody", "dendritic cells", "tumor infiltrating lymphocytes", and the bibliography of the revised literature cross-checked for additional references as the dublettes have been removed. Trials in which other products were tested, targeting signaling pathways not directly and specifically targeting the immune system were excluded.

The role of the immune system in PC

The immune system plays an active part in PC tumorigenesis throughout the stages of cancer immunoediting, from elimination, through equilibrium to the escape phase (14,15). The immune cell populations and immune mediators increase and change progressively as precursor lesions of PC evolve to invasive cancers, aiding the tumor to progress and increase its aggressiveness (16-18). The initial "good" local

inflammation is represented by players with better effector function such as $CD8^+$ and Th1 $CD4^+$ T-lymphocytes, natural killer (NK) cells, mature dendritic cells (DC), type 1 macrophages, IL-1, TNF-α, IFN-γ. It gradually becomes replaced by "bad" inflammation, sustaining cancer growth. The latter is described by regulatory (Tregs) and ineffective $CD8^+$ T-lymphocytes, immature DCs, myeloid derived suppressor cells (MDSCs), type 2 macrophages, IL-10, TGF-β (18,19). Interestingly, PC cells can mimic suppressive immune features that allow them to modulate the immune response against them. PC cells secrete inhibitory signals such as TGF-β, IL-10 and IL-6, VEGF, and express PD-L1, Fas-L, co-stimulatory molecules (B7-H3, CD40, CD40L) and can down-regulate the expression of antigens that could reveal their presence (19-21).

The typical for PC stromal reaction arises already during the early PanIN stages of tumor development (8). It not only traps and segregates immune cells from their target cancer cells, but also plays an active part in immunomodulation. PC-associated fibroblasts (CAFs), which represent the major cellular component in the desmoplastic stroma, can reduce T cell function in the stroma by receptor-mediated mechanism and promote expression of co-inhibitory markers on T cells (22,23). The stroma also recruits immunosuppressive $Foxp3^+$ $CD4^+$ T_{reg} lymphocytes and tumor-associated macrophages (TAMs) (24-26).

Extensive presence of tumor infiltrating lymphocytes (TILs) in cancerous lesions has been associated with improved survival in different cancer types (26-33). T cells are practically lacking in normal pancreas but increase in precancerous lesions and invasive cancer with grossly varying density of infiltration. A few studies point out that higher tumoral infiltration with TILs in resected pancreatic specimen, particularly by $CD8^+$ TILs, is associated with 5-survival as high as 42% (31). Co-infiltration by various populations of $CD8^+$, $CD4^+$ TILs and DCs, perhaps reflecting better crosstalk in antigen-presentation and immune recognition resulted in a survival of 48% in 5 years (31).

In contrast to for instance colorectal cancer, TILs in PC do not have a distinct distribution to center and periphery of the tumor but have a more patchy appearance (26,27,29). Whether stromal or intraepithelial TILs are more important is also uncertain (29,30,32). $CD4^+$ and $CD8^+$ TILs have been observed captured in the stromal tissue, far away from cancer cells and lacking the expression marker of memory cells, *CD45RO* (34). While some of the $CD8^+$ TILs population may still be naïve ($CD45RB^{high}$, $CD44^{low}$) as shown in mice models (17), others would have recognized a tumor antigen (35), meaning that under favorable conditions these are likely to be reacting against the cancer components that express them.

Better patient survival has been reported when high infiltration of $CD8^+$ $PD\text{-}1^+$ TILs was present, suggesting that PD-1, besides being an inhibitory marker, could also represent experienced and activated TILs recognizing a tumor target (26,36). PD-1 expression is also a possible predictive marker for success for eventual check-point inhibitor (CPI) therapy (26).

Immunotherapy for PC

Immunotherapy has been particularly successful in tumors with high-mutational load, such as malignant melanoma (37). This phenomenon provides plenty of epitopes for the immune system to target and is associated with the presence effector immune cells. Thus, the probability that any of the tumor antigens will be crucial for the cancer propagation and may induce a strong response is higher. PC is a cancer with low mutational load—in the range of 30–60 mutations compared to over 500 in melanoma (37,38). Also, with its poorer infiltration with effector T lymphocytes there are fewer potential "responders" to any immune-modulating signals. The addition of the abundant tumoral stromal reaction may hamper the delivery of any immune-stimulating drugs and the premises for success of immunotherapy in PC applied by the principles of standard oncologic treatment delivery are limited (38).

Immunotherapy runs better chances for success whenever lower tumor load is present and thus the counteractive effect of the tumor environment is lesser. Phase I and II clinical trials, just like for other types of oncologic therapy, are usually designed for patients with advanced disease who failed previous therapy attempts or are running out of therapeutic options. For cancers like PC, having already worse premises for response to immunotherapy, starting therapy too late may be particularly unlucky and predetermined to failure. Immunotherapy may also need some time to "work", since it targets the mediator (the immune system) rather than the cancer cells directly. An example for this phenomenon is the observation of pseudoprogression in some patients with melanoma treated with CPIs (39). While increase in tumor size may occur during the first weeks of treatment as a result of the beneficial inflammation that takes place,

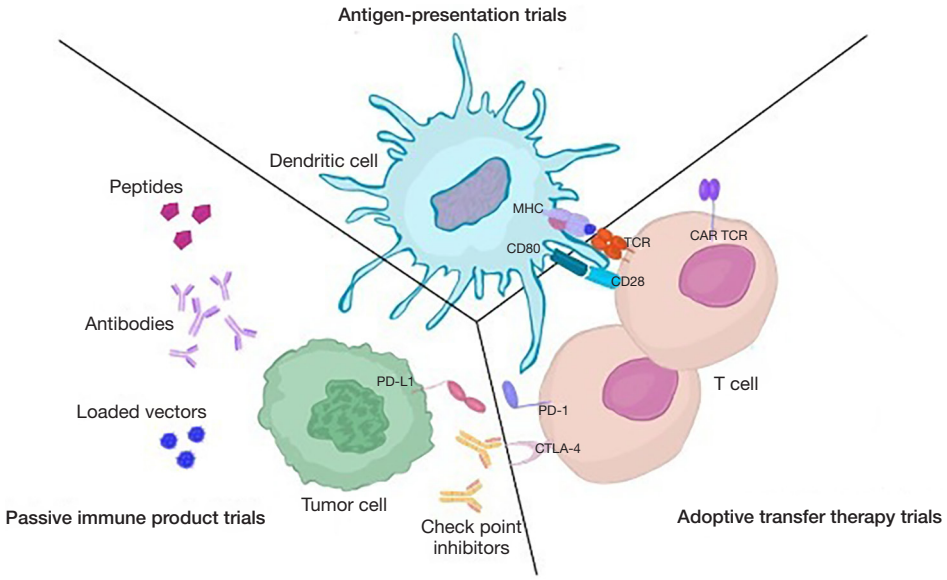

Figure 1 Type of immunotherapy trials in pancreatic cancer.

the real effect becomes obvious within a few months (40). The life expectancy of patients with PC with no treatment option is hardly that long. Although 3 months of expected survival is generally the minimum required to enter a trial, for PC patients with spread disease that is generally an overestimation (41). Fast and sudden deterioration towards lethal outcome is not unusual and may further compromise the planned delivery of treatment cycles.

Immunotherapy trials in PC

Immunotherapy may provide a variety of different options for treatment based on the parts of the immune response that are being modulated. Loaning principles from the pharmaceutical treatment, the best cost-effective result would be achieved by standardized industrially produced medication, designed to address a certain cancer target. Cancer biology, though, is characterized by complex network of mutations (not unusually private) and changes in signaling pathways that evolve during cancer progression (42). Thus, defining the target that has a central role in the particular person's tumor might be tricky and hitting only one target would mostly probably not be enough to combat the tumor. Applying a combination of drugs is quite often used in immunotherapy trials to both hit a target and to amplify the provoked response.

In order to better summarize and make a more comprehensive evaluation of the different types of immunotherapy studies in PC, we subdivided them into groups, based on what parts of the immune system have been used (*Figure 1*): (I) passive products of the immune system (tumor antigens, antibodies, interleukins)—secreted products that rely on triggering the whole chain of the immune response; (II) enhanced antigen presentation via the mediators of the immune response—DC; (III) adoptive cell transfer—reinfusion of expanded and activated effector lymphocytes—T-cells, NK cells.

Passive products of the immune system

Peptides and antibodies are the cheapest the easiest to obtain of the immunotherapy products and they have been most widely tested. They are both readily available and not cumbersome to standardize as pharmacological products. Peptides represent epitopes of a known tumor-associated antigen intended to trigger and boost the immune response against malignant cells. Antibodies are intended for receptor-mediated modulation of a signaling pathway or directly addressing immune cells. What is relied on in both cases is to unlock an effective chain of reactions, which requires the presence and adequate behavior of the other components of the adoptive response—antigen-presenting cells and T lymphocytes. The latter, though, are heavily influenced by the tumor environment.

Antigen vaccines

Boosting the reactivity of the immune system to the tumor cells by repeated exposure to foreign (cancer) antigens is the oldest concept of immunotherapy. Since cancer is derived from the own tissues and therefore prone to induce immunotolerance, tumor-associated antigens that are not present on normal cells can potentially induce immune cell reactivity. Mutations that are obliquitous in PC are most often the target of interest, such as KRAS, MUC1, survivin (43-55). Completed studies on antigen-based vaccines are summarized in *Table 1*.

Peptide vaccines

Peptide vaccines are usually administered with an adjuvant to help enhance their efficacy. They have the advantages of being easy to apply, unexpensive, and can be combined uncomplicatedly with other treatments. They are also usually well tolerated and with few side effects, usually limited to local reaction at the application site. Measurable immunologic reactions as response to their application have been registered in pretty much all trials. However, their effectiveness is limited. Clinical benefit has been observed in single cases and a near complete response has been presented in a case report (49). The exceptionally few trials making it to phase III, however, show no survival benefit from the peptide vaccination (56,58,64,67). For this reason, the interest towards peptide vaccines has been declining over the past years to being almost abandoned. Even in the adjuvant setting after resection, no impressive effect has been observed. Palmer *et al.* reported survival after resection and vaccination with seven KRAS peptides comparable to that of the patients receiving adjuvant gemcitabine, yet no control arm was present in this study (43). Also, the new current standards for adjuvant treatment with combination chemotherapy give superior results. As a proof of principle, though, immunologic response towards the vaccination agent has been induced in at least part of the patients. Some of the studies also reported a tendency for improved survival in the patients with well-developed immunologic responses (45,55-57,59,71).

Whole tumor vaccines

Another way of providing antigen stimuli is whole-tumor vaccines. They have the advantages over peptide vaccines that the cells express multiple relevant antigens. Also, the specific antigens do not have to be identified. Particularly the allogenic tumor cell lines are readily available.

Most of the trials have used GVAX, consisting of two allogenic tumor cell lines, tested both in resected and metastatic patients with evidence of immunoreactivity (*Table 1*). Le *et al.* reported that when mesothelin-expressing *Listeria monocytogenes* was added to a combination of GVAX with the immunomodulating chemotherapeutic cyclophosphamide, it almost doubled the survival of patients with metastatic PC after previous treatment failure—9.7 versus 4.6 months if treated per protocol (P=0.02) (77). Particularly, enhanced mesothelin-specific $CD8^+$ T cell responses have been linked to longer survival. In a following phase IIb RCT, however, the triple combination did not show advantage over physician's choice of single-agent chemotherapy (79). Improved survival after resection for PC have also been observed with GVAX, with a one-year survival of 93% (73). Another trial tested autologous PC stem cells in phase I but did not report survival data (78). Injection was even attempted towards lymph node groups following resection, with a median survival of 24.8 months—comparable to standard treatment (75). So far, there are no phase III trials with this type of vaccines.

Vector vaccines

A few studies aimed to enhance the antigen presentation through vector delivery—virus or attenuated bacteria (77,80-85). The vector may lead to better engagement of innate immune signals by co-stimulation and providing "danger signals" that could more effectively trigger DCs and the following cascade of T cell activation by the chosen targets such as CEA, KRAS MUC-1, etc. (80,81,84). A couple of studies have aimed at introducing oncolytic viruses locally. Although some trends towards improved survival among the responders in phase I trials (80,81) no benefit has been confirmed in phase II (84,85).

Antibody trials

Trials using antibodies have marked a peak of publication over the most recent years. Antibodies are a ready product of the immune system that can be industrially produced. The treatment protocols can be standardized as for any other pharmaceutical drug and that translates correspondingly into more straight-forward safety regulation and mass production. In this way clinical trials with antibodies are easier to convey, which explains their domination among the immunotherapy studies for PC for the last couple of years.

The most aimed targets by antibodies in PC are EGFR

Table 1 Antigen- based vaccine trials in pancreatic cancer

Author [year]	Phase	N pts PC	Type	Agent	Adjuvant	Other oncologic therapy	Stage	1st/2nd line	Median OS	Results	Comment
Gjertsen [2001] (44)	I/II	48	Peptide	KRAS	GM-CSF	n.r.	Resected, LAPC, M1	na	4.9 mo (resp); 2 mo (non)	Better survival in responders among advanced cancer pts. 1 PR	K-ras T cells accumulated in the tumor in biopsied patients with LAPC/M1
Yamamoto [2005] (50)	I	6	Peptide	MUC1	Freund's	Gem	LAPC, M1	n.r.	15.5 mo (resp); 8 mo (non)	Better survival in responders. 1 year survival 38%	1/6-anti-MUC1 IgG Ab
Scheutz [2005] (54)	I	20	Peptide, viral vector	CEA + MUC1,3	GM-CSF	n.r.	LAPC, M1	2nd	7.3 mo	Possible small benefit	PANVAC-VF
Ramanathan [2005] (51)	I	16	Peptide	MUC1	SB-AS2	Adj in 8/15: Gem + Radio/5-FU	Resected, LAPC	na	12 mo in resectable	No benefit	MUC1 humoral and T cell resp in some. NSAID and steroids- exclusion criteria
Carbone [2005] (55)	I	9/38	Peptide	P53 + KRAS	PBMCs	None	LAPC, M1	nr	n.r. for PC	Better survival in responders, all cancers	CTL response in 1/9
Wobser [2006] (49)	I	1	Peptide	Survivin	Freund's	None	M1	2nd	na	Near CR of liver mets after 6 mo, (duration 8 mo)	
Shapiro [2005] (56)	II/III RCT	383	Peptide	Gastrin-17	nr	Gem *vs.* Gem + placebo	LAPC, M1	n.r.	n.r.	n.r.	Correlation b/n anti-gastrin titers and survival
Bernhardt [2006] (57)	I/II	48	Peptide	Telomerase	GM-CSF	n.r.	LAPC, M1	n.r.	7 mo (resp); 3 mo (non)	Best survival in intermediate dose group. Better survival in responders	63% DTH and T cell
Toubaji [2008] (45)	II	5/12	Peptide	KRAS	DETOX™	None	Resected	Adj	44 mo	Tendency for improved survival	PC and CRC cancer. Vaccination after end of therapy. Immune response correlated slightly with survival
Buanes [2009] (58)	III RCT	365	Peptide	Telomerase (GV1001)	GM-CSF	Gem *vs.* Sequential Tx	LAPC, M1	1st	7.3 *vs.* 5.9 mo	No benefit	Stopped prematurely

Table 1 (*continued*)

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Author [year]	Phase	N pts PC	Type	Agent	Adjuvant	Other oncologic therapy	Stage	1st/2nd line	Median OS	Results	Comment
Yanagimoto [2010] (59)	II	21	Peptide	Personalized peptides	Freund's	Gem	LAPC, M1	1st	15.5 mo (resp); 8 mo (non)	Responders with better prognosis. 1 year survival 38%. PR 33%	Both CTL and IgG responses in 56%
Miyazawa [2010] (60)	I	21	Peptide	VEGFR2	Freund's	Gem	LAPC, M1	1st/2nd	8.7 mo	PFS 19.4 mo (1 pt)	83% Ag-specific DTH, 61% had CTL responses
Abou-Alfa [2011] (46)	I/II	24	Peptide	KRAS	GM-CSF	none	Resected	Adj	20.3 mo	Unproven efficacy; 19 mo OS if no adj chemo	KRAS mutation at codon 12. After end of therapy. 1pt with DTH. High-dose steroids/ NSAID – exclusion criteria
Wedén [2011] (47)	II	23	Peptide	KRAS	GM-CSF	None	Resected	Adj	28 mo	5 yr survival 22%. 10 yr 17% (0/87 non-vac)	All 5-year survivors were responders
Muscarella [2012] (48)	II RCT	39	Peptide	KRAS	None	Gem + vaccine *vs.* Gem + placebo	Resected	Adj	22.9 *vs.* 24.6 mo	No difference in survival	5.4 mo better survival in nonresponders
Gilliam [2012] (61)	III RCT	154	Peptide	Gastrin-17	na	No	LAPC, M1	na	5 *vs.* 2.7 mo	Improved survival with peptide and in responders: 5.8 *vs.* 2 mo (non-resp)	Peptide *vs.* placebo. Immunologic response in 74%
Brett [2002] (62)	II	30	Peptide	Gastrin-17	na	–	LAPC, M1	na	7 mo (resp) *vs.* 4 mo (non)	Improved survival in responders	67% Ab responses. More responders with higher dose
Geynisman [2013] (63)	I RCT	19	Peptide	CEA	Freund's and GM-CSF	Yes, nr	Resected LAPC, M1	na	10.9 mo	1 CR. After 32 mo, 37% alive	Randomized to receive three doses. Increased IFN-gamma response with increased dose
Kameshima [2013] (52)	I	6	Peptide	Survivin + INF-a	Freud's	No	LAPC, recurrent	na	n.r.	SD in 4, no objective responses	HLA-A*2402 positive, survivin-positive. >50% positive immunol and clinical responses

Table 1 (*continued*)

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Author [year]	Phase	N pts PC	Type	Agent	Adjuvant	Other oncologic therapy	Stage	1st/2nd line	Median OS	Results	Comment
Yamaue [2015] (64)	II/III	535	Peptide	VEGFR2	n.r.	Gem	LAPC, M1	1st	8.3 *vs.* 8.5 mo OS	No benefit. Well tolerated. Pts with injection site effect had better survival	Gem + peptide *vs.* Gem + placebo. HLA-A*24:02 genotype
Yutani [2013] (65)	II	41	Peptide	Personalized peptides	Freund's	Gem	LAPC, M1	2nd+	9.6 mo (with ChTx) *vs.* 3.1 mo (no)	No objective responses	IgG responses in 14/36 patients
Asahara [2013] (66)	I/II	29	Peptide	KIF20A	Freund's	No	LAPC, M1	na	4.8 mo *vs.* 2.8 mo (BSC)	1 CR of liver mets	Strong CTL resp to KIF epitope
Middleton [2014] (67)	III RCT	1062	Peptide	Telomerase (TeloVac)	GM-CSF	Gem+ Cap + sequent/concurr. vacc	LAPC, M1	1st	7.9 *vs.* 6.9 *vs.* 8.4 mo	No benefit	3 arms: ChTx *vs.* ChTx, followed by vaccine *vs.* ChTRx +vaccine. No corr b/n DTH and clinical resp
Nishida [2014] (68)	I	32	Peptide	WT1	Freund's	Gem	LAPC, M1	1st	8.1 mo	6 mo: 71%; 1 year: 29%	HLA-A*24:02 positivity. 58% DTH
Starodub [2015] (69)	I/II	7	Peptide	Trop-2	–	n.r.	LAPC, M1	n.r.	n.r.	No benefit	13 tumor types. Dexamethasone used
Suzuki [2014] (70)	I	9	Peptide	KIF20A	Freund's	Gem	LAPC, M1	2nd+	5.8 mo	1 year 11.1%	Enhancement of IFN-g response in 8/9
Suzuki [2017] (71)	II	68	Peptide	KIF20A, VEGFR1, VEGFR 2	Freund's	Gem	LAPC, M1	1st	9 mo	Well tolerated, no difference in 1-y survival in HLA matched and unmatched cohorts. No association response intensity and OS	In HLA-A*2402 matched pts – better OS if induced CTL responses and injection site reaction
Miyazawa [2017] (72)	II	30	Peptide	KIF20A, VEGFR1, VEGFR 2	–	Gem	Resected	Adj	15.8 mo DFS	Well tolerated. Median OS not reached at 18 mo. 1.5-y 69%. 1 PR	Injections weekly for 1 year. CTL responses in 11 pts

Table 1 (*continued*)

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Author [year]	Phase	N pts PC	Type	Agent	Adjuvant	Other oncologic therapy	Stage	1st/2nd line	Median OS	Results	Comment
Shima [2019] (53)	II RCT	94	Peptide	Survivin 2B	IFN-ß	No	LAPC, M1	2nd+	3.4 *vs.* 3.2 *vs.* 3.7 mo OS	No survival benefit of the superior S2B + IFN	HLA-A24 positive PC: 3 arms: S2b with or no IFN or placebo only. Immunologic effects observed
Palmer [2020] (43)	I/II	32	Peptide	7 KRAS peptides	Adjuvant	Gem	Resected, R0/R1	adj	33 mo OS	Survival comparable to that after adjuvant Gem	Dexamethasone used as antiemetic. Immune responses in 95%
Jaffee [2001] (73)	I	14	Whole tumor	GVAX (2 allogenic tumor cell-lines)	GM-CSF-secreting	Adj chemo-radioTh (before/after)	Resected	n.r.	n.r.	93% 1-year survival, 5 no recur 25 mo post Dg	DTH in 3 pts receiving >10×10^7 cells; 3 increased DFS
Laheru [2008] (74)	I	30	Whole tumor	GVAX	GM-CSF-secreting	No	M1	n.r.	2.3 *vs.* 4.3 mo	Survival similar to chemo alone	1. GVAX; 2. Cyclophosphamide + sequence GVAX; $CD8^+$ resp to MHC-I mesothelin epitopes in 2 (9/10 *vs.* 4/8);
Lutz [2011] (75)	II	60	Whole tumor	GVAX (inj in lymph nodes)	GM-CSF-secreting	5-FU chemoradioTx	Resected	Adj	24.8 mo	At 1 year: 85% OS, DFS 67%	8–10 weeks post res.x1 vac i.d. → 5-FU-CR → if no PD –x 4 doses. Mesothelin-specif CD8+ in HLA A1+22
Hardacre [2013] (76)	II	70	Whole tumor	Algenpantucel-L	–	Gem + 5-FU/ radiation	Resected	Adj	Not reached DFS 14 mo	1 year OS 86%	2 allo cell lines expr. α-Gal, Eosinophilia in 70%
Le [2015] (77)	II RCT	90	Whole tumor + bacteria	GVAX + Listeria monocytogenes expressing mesothelin	GM-CSF	Cyclophosphamide (Cy)	M1	2nd	6.1 *vs.* 3.9 mo OS (P=0.02)	Per protocol: 9.7 *vs.* 4.6 mo (P=0.02). Mesothelin $CD8^+$ responses - longer OS	2× Cy/GVAX + CRS-207 *vs.* 6× Cy/GVAX
Lin [2015] (78)	I	90	Whole tumor	Autologous PC stem cells	–	n.r.	all	na	n.r.	Th-1-type cytokine levels increased in medium and high-dose groups	CSC isolated from a resected tumor, culture 2–4 weeks. All received local treatment to reduce tumor burden

Table 1 (*continued*)

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Author [year]	Phase	N pts PC	Type	Agent	Adjuvant	Other oncologic therapy	Stage	1st/2nd line	Median OS	Results	Comment
Le [2019] (79)	IIb RCT	213	Whole tumor + bacteria	GVAX + Listeria monocytogenes expressing mesothelin	GM-CSF	Single agent in control arm	M1	3rd	3.7 *vs.* 5.4 *vs.* 4.6 mo OS (ns)	No better survival than chemotherapy	1:1:1 RCT: triple *vs.* Listeria *vs.* single-agent chemotherapy
Kaufman [2007] (80)	I	10	Virus	1. PANVAC-V (vaccinia v. exp CEA, MUC-1 + 3 co-stim molecules); 2. PANVAC-F (fowlpox *vs.*, same exp)	GM-CSF	n.r.	LAPC + M1 (80%)	2nd+	15.9 *vs.* 3.9 mo	Improved survival in T-cell responders *vs.* non	Ab response in 100%, TAA-T-cell response in 62.5%
Morse [2010] (81)	I	1/18	Virus	Alphavirus vector exp CEA	–	No	M1	3rd	n.r.	Liver mets resolved, T-cell resp – longer survival	Advanced cancers, infecting DCs
Le [2012] (82)	I	2/9	Bacteria	Listeria, 1 of 2 attenuated strains exp. mesothelin	–	n.r.	M1	2nd+	n.r.	3/7 lived longer than 15 mo	With liver mets, all prior GVAX. Induction of chemokines, of both lysteriolysin-O responses + anti-mesothelin T-cell resp.
Aguilar [2015] (83)	I	24	Virus	Adenovirus expressing HSV-tk gene + valacyclovir locally	Anti-herpetic prodrug	5-FU/RT as NAT	Resectable, LAPC	Adj or NAT	12 mo OS for LAPC	Slightly better than standard	Adjuvant to surgery or chemoradiation. In resected - 22 times higher infiltration with $CD8^+$; in 5/7 upregulation of PD-L1
Noonan [2016] (84)	II RCT	73	Virus	Pelareorep: oncolytic virus, KRAS	–	nPac/carboplatinum	M1	1st	4.9 *vs.* 5.2 mo PFS	No impact on survival, independent of KRAS status	ChemoTx +/– virus Immunologic effects – both proinflammatory and suppressive in circulation
Dalgleish [2016] (85)	II RCT	110	Bacteria	IMM-101: Heat-killed Mycobacterium obuense	–	Gem	LAPC, M1	1st+	6.7 *vs.* 5.6 mo OS (ns); 7 *vs.* 4.4 mo in M1 (P=0.01)	Safe and well tolerated, possible advantage in M1 pts	Combination Tx *vs.* Gem only

Ab, antibody; Adj, adjuvant therapy; BSC, best supportive care; CTL, cytotoxic lymphocyte; DC, dendritic cells; DHT, delayed-type hypersensitivity; Gem, gemcitabine; GM-CSF, granulocyte-macrophage colony-stimulating factor; GnP, gemcitabine-nab-paclitaxel; LAPC, locally advanced pancreatic cancer; M1, metastatic disease; NAT, neoadjuvant therapy; OS, overall survival; PR, partial response, RT, radiotherapy; RCT, randomized controlled trial; SD, stable disease; Tx, therapy.

and VEGF-A, which is likely due to that these antibody drugs have already been registered for treatment of other cancer types (Table S1). Whether administered alone or in combination with other targeted drugs or chemotherapy in advanced PC, so far, no improved survival has been seen in phase II and III antibody trials targeting EGFR and VEGF-A, even if applied as first-line therapy (86-91). The few combination trials with more than one of these target agents show some potential survival benefit, but have limited application due to increased toxicity (92,93). No benefit has been seen if antibody treatment has been used in conjunction to surgical resection, either (94-96). Phase II and III trials using different antibodies such as ganitumab, selumetinib, ibrutinib, tarextumab towards IGF1R, MEK, BTK, Notch2/3R (97-100) have failed to show improved survival, as well. Even targeting components of the tumor stroma, such as matrix metalloproteinase-9, have shown no convincing benefit (101).

As earlier studies have shown no benefit of solely antibody therapy, the more recent trials have focused on combination of antibody and chemotherapy. Gemcitabine has been almost exceptionally used, sometimes in combination with nab-paclitaxel (100-102). Gemcitabine has been by far surpassed by FOLFIRINOX in improving survival of patients with advanced PC, yet it is the most tolerable chemotherapeutic available. The toxicity profile of the antibody treatment, however, might restrict its co-application with the potent chemotherapy and it will be difficult to outrun its efficacy.

Checkpoint inhibitors

CPIs are a particular group of drugs, mostly antibodies, that deserve special attention. CPI treatment has become the label of practical immunotherapy as they have drastically improved the prognosis of cancers like malignant melanoma where standard treatment has failed (12). CPI block the inhibitory signals on effector T cells, such as PD-1 and CTLA-4, which are upregulated on T cells to avoid destructive immune overreaction and as a result of exhaustion in the tumor microenvironment. PD-L1 is often expressed on tumor cells and can via ligation with PD-1 on T cells directly inhibit T cell function. CTLA-4 provides an inhibitory signal to T cells after binding to the B7-1 and B7-2 on APC which hence prevents efficient T cell priming and activation.

Unlike the fantastic results that have been achieved in other cancer types, so far CPI have not proved to be particularly effective in trials with patients having advanced PC, with or without concomitant chemotherapy (*Table 2*). The reported survival has generally been no better than using single gemcitabine (121). One study reported acceptable tolerability of pembrolizumab used in the neoadjuvant setting for resectable and borderline resectable PC, but provided no survival data (110). The resectability rate was slightly higher in the CPI group—71% versus 50%, however, the groups were too small to allow for any conclusions. A study from China in cases with only local recurrence found improved survival by 2 months if CPI was used instead of gemcitabine in conjunction to radiation therapy (128).

Interestingly, a link has been reported between defective mismatch repair genes (dMMR) and response to PD-1 and PD-L1 inhibitors (117,129). In a retrospective cohort, one complete and one partial response have been seen in 7 patients receiving CPI and having dMMR, which is considerably better response rate than what all other studies have reported (117). Unfortunately, the presence of dMMR is a very rare event in patients with PC—only in 0.8% (129). Generally, CPI do not seem to have any ground-breaking effect in patients with advanced PC.

DC vaccines

The idea of using DCs in cancer vaccines follows the initial trials of antigen vaccination in an attempt to improve the immunoreactivity by correct major histocompatibility complex (MHC)-restricted antigen presentation to the effector lymphocytes and providing additional co-stimulation. This type of antigen presentation is a potent inductor of effector $CD4^+$ and $CD8^+$ lymphocytes.

In PC, DC vaccination is in many cases combined with cellular therapy—lymphokine-activated killer cells (LAK) or cytokine-induced killer cells (CIK) (*Table 3*). In the trials with vaccination with DCs only, the latter have been pulsed with peptides (130,132,136,139-141) or mRNA (135). In patients with advanced cancer, no objective responses have generally been observed (130,136,139,140). Some authors report isolated cases where partial (131) or no tumor activity was observed after longer follow up (135). Inducing specific delayed-type hypersensitivity responses by DC vaccines has been associated with improved survival (139). Interestingly, when DCs have been applied in the adjuvant setting after resection for PC, 100% of the patients survived the first year (132).

The studies combining DC vaccination with LAK cells or CIK have all been conducted in Asian population

Table 2 Clinical trials using check-point inhibitors in pancreatic cancer

Trial year	Phase	Agent type	#pts	Target	Agent	Stage	1st/2nd line	Other Th	Median OS	Result	Comment
Royal [2010] (103)	II	Ab	27	CTLA-4	Ipilimumab	LAPC, M1	2nd+	No	4.5 mo	0 response	In 1 patient - significantly delayed response-regression of prim + liver mets
Beatty [2011] (104)	I/II	Ab	21	CD40	mAb – CD40-agonist	LAPC, M1	1st	Gem	7.4 mo	Increased OS with 1.7 mo *vs.* Gem. 1 CR of liver met, 4/21 PR	CD40 activation did not trigger T cell tumor T cell infiltration (KPC model)
Brahmer [2012] (105)	I	Ab	14	PD-L1	BMS-936559	M1	2nd+	none	n.r.	No benefit. 0 response	
Le [2013] (106)	I RCT	Ab + whole Tu	30	CTLA-4	Ipilimumab	LAPC, M1	2nd+	n.r.	3.6 *vs.* 5.7 mo	In favor of combination	Ab *vs.* Ab + GVAX; ↑mesothelin-spec T cells; 1-y 7% *vs.* 27% OS
Aglietta [2014] (107)	Ib	Ab	34	CTLA-4	Tremelimumab	M1	1st	Gem	7.4 mo	6% PR	
Kalyan [2016] (108)	Ib	Ab	16	CTLA-4	Ipilimumab	LAPC, M1	1st	Gem	2.5 mo PFS	13% PR	
Duffy [2017] (109)	I	Ab	24	PD-L1, CTLA-4	Durvalumab +/– tremelimumab	M1	2nd+	SBRT	n.r.	No objective responses	
Katz [2017] (110)	I/II RCT	Ab	22	PD-1	Pembrolizumab	Resectale + BRPC	NAT	Cap+RT	n.r.	71% *vs.* 50% resection rate	Onc Tx + Ab *vs.* Onc Tx
Yamamoto [2017] (111)	I	Ab	15/96	CCR4, PD-1	Mogamulizumab, nivolumab	LAPC, M1	n.r.	n.r.	n.r.	1 PR, acceptable toxicity	Solid tumors, including PC
Cavalieri [2017] (112)	retro	Ab	2	PD-1	Pembrolizumab	n.r.	n.r.	n.r.	n.r.	1PR	GI cancers (solid) with defective MMR
O'Reilly [2019] (113)	II RCT	Ab	64	PD-L1, CTLA-4	Durvalumab +/– tremelimumab	M1	2nd	none	3.6 *vs.* 3.1 mo	3% PR. Limited efficacy	D+T *vs.* D
Naing [2018] (114)	I/II	Ab	15	PD-L1	Epacadostat durvalumab	LAPC, M1	2nd+	n.r.	n.r.	No objective responses	Solid cancer including PC
Weiss [2018] (115)	Ib/II	Ab	17	PD-1	Pembrolizumab	M1	1st/2nd	GnP	15 mo in 1st line	Slightly improved efficacy compared to literature	
Borazanci [2018] (116)	II	Ab	10	PD-1	Nivolumab	M1	1st	nPac + paricalcotol + cisplatin	8.2 mo PFS, OS not reached		

Table 2 (*continued*)

Table 2 (*continued*)

Trial year	Phase	Agent type	#pts	Target	Agent	Stage	1st/2nd line	Other Th	Median OS	Result	Comment
Hu [2018] (117)	retro		7	PD-L1, PD-1	n.r.	LAPC, M1	n.r.	n.r.	n.r.	1 CR, 2 PR	GI cancers with dMMR
Wainberg [2019] (118)	I	Ab	50	PD-1	Nivolumab	LAPC, M1	1st	GnP	9.9 mo	Feasible. Dose-limiting toxicity reached in one	
Hong [2019] (119)	Ib/II	Ab	49	BTK, PD-L1	Ibrutinib, durvalumab	LAPC, M1	2nd+	No	4.2 mo	Limited antitumor activity	Solid tumors including PC. Survival for stage III/IV PC
Doi [2019] (120)	I	Ab	15 PC	CCR4, PD-1	Mogamulizumab, nivolumab	n.r.	2nd+	No	6.5 mo	21 PR, 5 SD at	Solid tumors including PC
Kamath [2020] (121)	Ib	Ab	21	CTLA-4	Ipilimumab	M1 95%	1st/2nd	Gem	6.9 mo	Similar survival as with Gem alone	3 responders
Mahalingam [2020] (122)	Ib	Ab, oncolytic virus	11	PD-1	Pembrolizumab + pelareorep	LAPC, M1	2nd	5-FU, Gem or irinotecan	3.1 mo	1 PR for 17 mo, 3 SD	Well tolerated. Virus administered after chemo. NB PR was achieved after 6.5 mo and SD after 2 mo!
Overman [2020] (123)	II RCT	Ab	77	BTK inhibitor PD-1	Acalabrutinib +/– pembrolizumab	LAPC, M1	2nd +	No	1.4 mo PFS	No difference in OS, limited clinical effect	Median of 3 prior therapies
O'Neill [2020] (124)	Ib	Ab	10	PD-1	Nivolumab	LAPC	1st	IRE after CRT	18 mo	Well tolerated	7/10 grade 3–4 treatment events
Fumet [2020] (125)	II	PARP inhib + Ab	213	PD-L1, CTLA-4	Olaparib + durvalumab + tremelimumab	LAPC, M1	2nd	–	–	ongoing	Solid tumors. Mutation in homolog gene repair
Renouf [2020] (126)	II RCT	Ab	180	PD-L1, CTLA-4	Durvalumab + tremelimumab	M1	n.r.	GnP	5.5 *vs.* 5.4 mo PFS	No benefit	Chemo *vs.* chemo + Ab
O'Hara [2021] (127)	Ib	Ab	30	CD40, PD-1	CD40 (Sotigalimab) +/– nivolumab	M1	1st	GnP + 2 dosages of CD40 +/– Nivolumab	n.r.	Tolerability and shows clinical efficacy	4 cohorts. Shown RECIST tumor response and Immunol markers
Zhu [2021] (128)	II RCT	Ab	170	PD-1, MEK1/2	Pembrolizumab + trametinib	Local recurrence	2nd after chemo	SBRT + AB *vs.* SBRT+gem	24.9 *vs.* 22.4 mo	Better OS with Ab (P=0.0012)	mKRAS and pos. PD-L1, after 1st chemo with FFX or 5-FU

Ab, antibody; Adj, adjuvant therapy; Cap, capecitabine; CR, complete response; CRT, chemoradiotherapy; dMMR, defective mismatch repair gene; FFX, FOLFIRINOX; Gem, gemcitabine; GnP, gemcitabine-nab-paclitaxel; IRE, irreversible electroporation; LAPC, locally advanced pancreatic cancer; M1-metastatic disease; NAT, neoadjuvant therapy; nPAC, nab-paclitaxel; OS, overall survival; PARPI, poly(ADP-ribose) polymerase inhibitors; PFS, progression-free survival; PD, progressive disease; PR, partial response, RCT, randomized controlled trial: RFS, recurrence free survival; SBRT, stereotactic body radiation therapy; SD, stable disease, Tx, therapy.

Table 3 Clinical trials using dendritic cells in pancreatic cancer

Author/year	Phase	N pts PC	Type	Agent	Other oncologic therapy	Stage	$1^{st}/2^{nd}$ line	Median OS	Results	Comment
Pecher [2002] (130)	I/II	2/10	DC	MUC1 pep-DC	No	M1	1^{st}	n.r.	No benefit. All with progression	pt 2 to 10 x ↑in MUC1-$CD8^+$T cells
Mazzolini [2005] (131)	I	3/17	DC + IL-12	IL-12-secreting DCs	None	M1	2^{nd}+	n.r.	PR in 1 for more than 3 mo	Intratumoral inj, GI cancers
Lepisto [2008] (132)	I/II	10/12	DC	MUC1 pep-DC	None	Resected	Adj	26 [13–69] mo	100% 1-year survival	No difference in immune responses. No steroids, NSAID, COX2 inh
Nakamura [2009] (133)	I/II	17	DC + LAK	1. DC (loaded with Tu or peptides) + i.v./ intraperiton. act. Ly; 2. LAK alone	11 /17 chemo Tx	Reccurr, M1	$1^{st}/2^{nd}$	9 mo (DC) vs. 6 mo (LAK Tx)	9 vs. 8 mo chemo vs. immunoT: no – no diff. Longest 20 mo	DC + LAK-better effect
Hirooka [2009] (134)	I/II	5	DC + LAK	OK-432-stimulated DCs Intratumoral inj + cCD3-LAKs i.v.	Gem	LAPC	1^{st}	16 mo	3/5 responses: 1 PR (25.4 mo survival); 2 SD >6 mo; 80% 1-year OS	IFN-g producing cells ↑ after repeated Th
Suso [2011] (135)	I/II	1	DC	hTERT mRNA-DC	None	M1	2^{nd}	na	3 yrs post Tx no active disease on PET/CT	Immunol. response against hTERT-derived several Th and CTL epitopes
Rong [2012] (136)	I	7	DC	MUC1-pulsed autol DCs	None	Recurrence	2^{nd}	No benefit	PD in all within 3 mo	MUC1-expression in tumor. In 2/7 - ↑IFN-g and granzyme B Elispot assay reactivity
Kimura [2012] (137)	II	49	DC + LAK	WT1, Her2, CEA; MUC1 and Ca125 - DC LAK	Gem/ S-1	LAPC, M1	2^{nd}+	12 mo	2 CR, 5 PR, 10 SD (17/49) –with LAK; >500 days (16 mo) in 4 despite PD	↓65% Tregs
Qiu [2013] (138)	I	14	DC + CIK	α-Gal-DC, pulsed with primary PC + CIK	Gem/ Oxaliplatinum + RT	LAPC, M1	n.r.	24.7 mo in the 4 responders	2 PR	CIK derived from bone marrow stem cells. Increased CTL, activated and memory T ($CD3^+CD45RO^+$) + active T and NK ($CD3^+CD56^+$) for 6–9 mo

Table 3 (*continued*)

Table 3 (*continued*)

Author/year	Phase	N pts PC	Type	Agent	Other oncologic therapy	Stage	1st/2nd line	Median OS	Results	Comment
Koido [2014] (139)	I	10	DC	Multiple WT1-pulsed DC	Gem	M1	1st+	n.r.	No objective responses. Longer PFS and OS in class I/II vaccinated than in I or II. In 4/7 WT1-specific DHT responses, associated with prolonged OS	MHV-class I/II-restricted epitopes, WT-1-spec IFN-gamma producing CD4+ T cells significantly increased
Mayanagi [2015] (140)	I	10	DC	WT1-pulsed DC	Gem	LAPC, M1	1st	7.9 mo	No objective responses.	HLA-A*2402 Poor survival in pts with liver mets despite immunologic response
Mehrotra [2017] (141)	I/II	12	DC	Poly-ICLC (against Toll-like receptor-3), hTERT, CEA, survivin, DC	None	LAPC, M1	2nd	7.7 mo	No objective responses. In 4/8 who completed the study SD at 8 weeks	Autologous DC from HLA-A^2+ pts.; Premedication with acetaminophene + diphenhydramine. Chemo before (all) and after (6 pts). Measurable immunologic responses
Jiang [2017] (142)	II	47	DC-CIK	Dendritic cells, cytokine induced killer cells	S1	LAPC, M1	1st	7 mo in comb	Better OS in combination *vs*. DC-CIK alone (4.3 mo) or S1 (4.7 mo) or BSC (1.7 mo)	DC-CIK + S1, DC-CIK alone, S1 alone or BSC
Yanagisawa [2018] (143)	I	8	DC	WT1-pulsed DC, OK-432	S1+/– Gem	Resected	Adj	n.r.	Safe; 2-year OS 63% and better in responders than non: 71% *vs*. 0%	WT1-specific CTLs were confirmed more than once in patients who lived more than 2 years after surgery
Bassani-Sternberg [2019] (38)	Ib	3	DC + Ab + Pept + NSAID	Autologous DC, neoantigens, nivolumab, aspirin	Gem/Cap	Resected	Adj	n.r.	n.r.	5 weeks for Ag discovery + 5 weeks for manufacturing + 3 weeks after leukapheresis

Adj, adjuvant therapy; Ag, antigen; BSC, best supportive care; Cap, capecitabine; CIK, cytokine-induced killer cells; CR, complete response; CTL, cytotoxic lymphocyte; DC, dendritic cells; DHT, delayed-type hypersensitivity; Gem, gemcitabine; LAK, lymphokine-activated killer cells; LAPC, locally advanced pancreatic cancer; M1, metastatic disease; OS, overall survival; PFS, progression-free survival; PD, progressive disease; PR, partial response, RFS, recurrence free survival; RT, radiotherapy; SD, stable disease, Tx, therapy.

(133,134,137,142). Unlike the isolated DC vaccination, in these trials some objective responses were observed. Kimura *et al.* reported objective responses in 34% of the treated patients out of which two were complete responses (137). Hirooka *et al.* reported a median survival of 16 months and a 1-year survival of 80% in five patients with LAPC where DC were injected in the tumor while LAK were given intravenously—a result that can hardly be explained by the gemcitabine monotherapy that was used (134). However, larger studies are lacking.

Cellular therapy

The most efficient form of immunotherapy reported to date is adoptive cell transfer therapy using TILs (144,145). In patients with metastatic malignant melanoma, objective responses have been observed in 72% when TILs were administered after pre-conditioning chemotherapy with cyclophosphamide and fludarabine and whole-body radiation (144,146). In the patients who were found to be complete responders (impressive 22% of patients), the 3- and 5-year survival was 100% and 93%, respectively. A later randomized trial showed that these results can be achieved without radiation (147). Such results have not been achieved by any other type of oncologic therapy. The isolation of TILs, however, is a cumbersome process and has for long been impossible in PC. It was first reported by our group in 2016 that TILs from PC can be isolated using a cytokine cocktail of IL-2, IL-15, and IL-21 and expanded in sufficient amount to be sufficient for therapy (148). Another group also reported the isolation of TILs (149). So far, the data is only preclinical, but clinical trials are ongoing (150,151).

The most used immune cells for therapy are LAK cells and CIK and in combination with DC vaccination, as descried in the previous section (*Table 3*). Qiu *et al.* used autologous CIK together with pulsed DCs and reported a median survival of 24.7 months among the four responders with advanced PC (*Table 3*) (138). Chung et al reported that 60% of patients with metastatic PC were alive after 6 months after treatment with autologous CIK and not receiving any other oncologic treatment (*Table 4*) (154).

T cell therapy has also been attempted in PC, with cells derived from peripheral blood mononuclear cells (PBMCs) but without any overwhelming efficacy. Both allogeneic and autologous T lymphocytes from PBMCs sensitized to MUC-1 have been tested in resected and advanced PC (152,153). The combination of T cell and DCs has resulted in one out of 20 patients with advanced cancer with complete response, alive after 6 years (153). γδT cells retrieved and applied after resection have not proved to be of survival advantage (155). CAR-T cells for mesothelin have been tested in metastatic PC and two out of six patients have shown stable disease for 3.8 and 5.4 months without any other ongoing therapy (157). A common feature of all T cell trials is that, unlike the experience from TIL therapy, no preceding lymphodepleting treatment have been administered.

An interesting study has reported the use of allogeneic hematopoietic stem cell transplantation from HLA-identical siblings in patients with PC, analogical to its use in hematologic disease (158). Two patients receiving the treatment after radical resection for PC were both still alive after 9 years. Both cellular and humoral reactivity against two novel tumoral antigens has been observed as evidence for immunologically mediated treatment effect against cancer. Of course, larger trials are necessary before any conclusions can be drawn.

Discussion

As PC is constantly the one that fails to respond to any treatment attempts by standard oncologic means, inevitably lots of hope is brought onto immunotherapy to stop this closed cycle of desperation. The immunotherapy trials in PC have so far not shown a large-scale impact on prognosis in a broad patient cohort. Even though the clinical effects of immunotherapy have been limited, the immunological changes induced in response to treatment indicate a proof of concept—immunotherapy works. The premises for success, though, need to be diligently reevaluated.

Apparently, immunotherapy planned and delivered just like chemotherapy does not work in PC. Yet, the vast majority of the most recent trials seek to evaluate the potential efficacy of the mass-produced standardized antibody medication to an unselected cohort of patients. While CPI treatment would work in melanoma where the premises with mobilizing the infiltrating TILs, which recognize a large number of mutations, are already present in the tumors, in PC with its much fewer, scattered, and often naïve, TILs, that strategy as a single treatment option seems to be meaningless. If CPI might work in combination, for example with a stroma-targeting drug in order to aid accessibility of CPI to cancer cells in PC is unknown. However, it is the cheapest and most profitable type of treatment. But what could be the roadmap to immunotherapy's success in PC?

Table 4 Clinical trials using cellular therapy in pancreatic cancer

Author/year	Phase	N pts PC	Type	Agent	Other oncologic therapy	Stage	$1^{st}/2^{nd}$ line	Median OS	Results	Comment
Kawaoka [2008] (152)	I/II	28	T cell	Allogeneic. PBMCs stimul. with MUC-1 expressing cell line + IL-2	Intraoperative radiotherapy. No chemotherapy	Resect LAPC	1^{st}	17.8 mo Resect; 5.0 mo LAPC	1-yr: 83.3% res; 2-yr: 32.4%; 3-yr:19.4% res	Allogeneic PBMCs from healthy volunteers. Reinf. 0.6×10^{9} to 2.8×10^{10} Few times. Start 1 we postop. ↑10% effector T cells; ↓5.7% Treg
Kondo [2008] (153)	I/II	20	DC + T cell	Autologous PBMC: MUC-1 -DCs + T cells (MUC-1 sensit.)	n.r.	LAPC, M1	$1^{st}/2^{nd}$	9.8 mo (2–75 mo)	2 yr OS 20%; 3 yr OS 5%; 1 CR (lung mets, 75 mo) - high dose DC + CTLs; 5 SD	T cells were sensitized with MUC-1–producing cell line
Chung [2014] (154)	II	20	CIK	Autol. PBMCs - CIK	None	M1	2^{nd}	6.7 mo	6 mo OS: 60%; 4/12 SD; longest survivor: 22.9 mo	Ex vivo expanded. $CD8^{+}$: 86%; $CD56^{+}$: 24%. No specific pattern for responders
Aoki [2017] (155)	I	28	γδT cells	Vγ9Vδ2T cells	Gem	Resected	Adj	26 mo PFS	No benefit of T cells: the same PFS and OS	Leukapheresis after surgery, 2 weeks culture. X2 during every Gem cycle, 6 courses. Gem as immunomodulator
Lin [2017] (156)	I/II	37	NK	Allogenic NK cells	IRE	LAPC, M1	$1^{st}/2^{nd}$+	13.6 mo in LAPC; 10.2 mo in M1	Better OS in IRE-NK group *vs*. in IRE only: LAPC. 13.6 *vs*. 12.2 mo, P=0.03 M1: 10.2 *vs*. 9.1 mo, P=0.04)	Multiple NK infusions associated with better survival in LAPC
Beatty [2018] (157)	I	6	T cell	Autologous PBMCs: T cells - CARs for mesothelin	None	M1	2^{nd}+	n.r.	2 SD: 3.8 and 5.4 mo	In vitro transcribed mRNA, CAR w/both CD3-beta and 4-1BB domains. Admin. x3/week in 3 weeks

Ab, antibody; Adj-adjuvant therapy; Cap, capecitabine; CR, complete response; CRT, chemoradiotherapy; dMMR, defective mismatch repair gene; FFX, FOLFIRINOX; Gem, gemcitabine; GnP, gemcitabine-nab-paclitaxel; IRE, irreversible electroporation; LAPC, locally advanced pancreatic cancer; M1-metastatic disease; NAT-neoadjuvant therapy; nPAC, nab-paclitaxel; OS, overall survival; PARPI, poly(ADP-ribose) polymerase inhibitors; PFS, progression-free survival; PD, progressive disease; PR, partial response, RCT, randomized controlled trial: RFS, recurrence free survival; SBRT, stereotactic body radiation therapy; SD, stable disease, Tx, therapy.

PC has from baseline a lower probability of success with immunotherapy. Theoretically, adoptive transfer therapy with *ex vivo* expanded effector T lymphocytes would be the most appropriate choice to address the problem of having fewer mutations and fewer TILs. This means that the mutational profile of the individual patients' tumors, carrying quite often private mutations, needs to be outlined - by genetic sequencing and typing of the T-cell receptors of the TILs. Apparently, this is a very costly undertaking that universities must cover, since for the industry that option is unattractive. This is a major limitation of this type of treatment. Using cellular therapy against preselected tumor associated antigen (TAAs), that has been tried so far, is not even nearly effective.

Immunotherapy by itself is among the most precise and strictly targeted treatments.

Cancers have evolved in a variety of molecular mechanisms to evade the recognition by the immune system. A combined strategy, by addressing a few of these mechanisms rather than picking a single target, should result in better efficacy. For example, an autopsy investigation after a vaccine trial revealed that the tumors of patients have been largely infiltrated by lymphocytes (159). Yet, this has not been enough to change the outcome, since the tumors have been overexpressing PD-L1. Supposedly, combination with a CPI might have improved the outcome. Combination strategies are, though, much more difficult to plan, since there are a variety of parameters to control for—choice and sequence of administration of the components, dosages, timing during treatment, etc.

The right timing and route of administration during the individual treatment algorithm of each patient is another point of concern. Complementation to surgical resection would hypothetically be the best scenario as the tumor burden has been reduced the most and the mutational landscape of the whole tumor can be assessed. The generation of a good product for adoptive transfer therapy, is a time-restricted process in order to generate the most efficient young TILs (160-162). This means that reinfusion would need to be two to three weeks after surgery, but this is perhaps the most inconvenient period in terms of healing and complications. Pancreatic surgery is inevitably associated with up to 40–50% complications rate and the development of pancreatic fistula or deconditioning may hamper the process. Longer culture of the TILs may drive them to exhaustion and decrease their effectiveness. On the contrary, a patient with metastatic PC who have progressed upon previous treatment, may deteriorate fast before the immune product has been generated and thus become unsuitable for the protocol. Therefore, adaptation of the planned studies to the clinical scenarios with earlier introduction of immunotherapy, as combination in first-line palliative or neoadjuvant therapy might be worth considering.

Another critical point is the preparation of the patient before treatment. As the autopsy studies after vaccination and the earlier trials in TIL therapy in melanoma revealed, the immunosuppressive environment created and maintained by the tumor rapidly deactivates the administered boosting immune product (146,159). The key to success has been the proper preconditioning by lymphodepletion using cyclophosphamide and fludarabine in order to "create space" for the activated product to settle (146,147). None of the finished trials in PC has used this principle, except for a couple of them relying on the mild and largely insufficient effect of cyclophosphamide or gemcitabine (141,155). Furthermore, chemotherapy that is used in parallel in the prevailing number of immunotherapy studies in PC, often goes with the administration of potent corticosteroids to counteract adverse events (43,69,163). That might theoretically completely deactivate the "good" inflammation that immunotherapy pursues. The route of administration should also be carefully considered. The usual intravenous infusion (apart from DC vaccination) may lead to that a large part of the product is sequestrated when bypassing the pulmonary circulation and does not reach a more distant target in significant amount.

Despite the difficult start, immunotherapy is slowly making its way in the treatment of PC. With careful consideration of the clinical premises, choice of the immune agents and preconditioning, immunotherapy could make a treatment breakthrough in PC.

Summary

Current studies, mostly using passive immunotherapy with antibodies (including checkpoint inhibitors) and antigen vaccines, have so far not marked a major breakthrough in the treatment of patients with advanced PC. The induced immunologic responses and individual cases of success among responders show a proof of concept—that immunotherapy is an emerging option for the treatment of patients with PC. Careful planning of the studies considering the particular characteristics and premises in patients with PC might be the key to better outcome in the near future.

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Footnote

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Supplementary

Table S1 Antibody trials in pancreatic cancer

Trial (year)	Phase	#pts	Target	Agent	Stage	1st/2nd line	Other Tx	Median OS	Result	Comment
Xiong (2004)(86)	II	41	EGFR	Cetuximab	LAPC, M1	1st	Gem	7.1 mo	1-year OS 31% PR 12%, SD 63%	intratumoral EGFR expression
Van Cutsem (2009)(87)	III RCT	607	EGFR, VEGF-A	Erlotinib +Bevacizumab	M1	1st	Gem	7.1 *vs.* 6 mo	No benefit	1.Gem+Erl+Bev 2.Gem+Erl+placebo
Fujisaka (2015)(164)	I	17	mesothelin	amatuximab	nr	2nd+	no	nr	3 with SD	Mixed solid tumors Mesothelin-positive Tu on IHC
Fuchs (2015)(97)	III RCT	800	IGF1R	Ganitumab	M1	1st	Gem	7.0 *vs.* 7.1 *vs.* 7.2 mo OS	Well tolerated, no improvement of survival	Gem + 12 mg/kg, +20mg/kg *vs.* +placebo
Picozzi (2015)(165)	Ib RCT	58	MUC5ac	^{90}Yttrium-clivatuzumab tetraxetan	M1	3rd+	+/-Gem	7.9 *vs.* 3.4 mo* (p=0.004)	* for multiple cycles +Gem OS 2.7 *vs.* 2.6 mo in the whole cohorts	+/- gemcitabine Ab with isotope
Ko (2016)(88)	II	46	EGFR MEK1/2	Erlotinib Selumetinib	LAPC, M1	2nd	no	7.3 mo	No objective responses. In 38% SD in 6w+	59% with additional chemotherapy after study's discontinuation
Coveler (2016)(166)	I	35/50	SLC-44A4	ASG-5ME	M1	2nd+	no	5 mo	Well tolerated, limited tumor activity – 1PR	PC + gastric cancer Ab-drug conjugate against cell-surface target on most PC. & gastric cancers
Beg (2016)(167)	I	4/19	MUC5AC	NEO-102	LAPC, M1	2nd+	no	nr	Well tolerated, no objective responses	PC and colon cancer
Pishvaian (2016)(163)	I	6/39	CEA & CD3 epsilon TCR subunit	MEDI-565	nr	2nd+	no	nr	No objective responses. 28% of all cancer SD at best	GI tumors: Bispecific Ab Pretreated with dexamethasone
Chung (2017)(98)	II RCT	137	MEK PI3K/AKT	Selumetinib MK-2206	M1	2nd	no	3.9 *vs.* 6.7 mo	Shorter survival with immunotherapy	*vs.* oxaliplatin and fluorouracil (FOLFOX)
Benson (2017)(168)	II RCT	240	LOXL2 enzyme	Simtuzumab	M1	1st	Gem	7.6 mo *vs.* 5.9 mo *vs.* 5.7 mo OS	Well tolerated, but no improvement of clinical outcome	3 arns: Gem+Ab 700 mg *vs.* Gem-Ab 200 mg *vs.* Gem+placebo
Almhanna (2017)(169)	II	43	Guanylyl cyclase	MLN0264	LAPC, M1	2nd+	no	5.4 mo	Managable safety but low efficacy , response rate 3%	Ab-drug conjugate
Fountzilas (2017)(89)	II	18	EGFR	Erlotinib	LAPC, M1	1st, 2nd	no	3 mo	Terminated early due to futility	
Cardin (2018)(170)	I	19	Src EGFR	Dasatinib Erlotinib	LAPC, M1	1st	Gem	8 mo	No objective responses. 9 pts had SD	1-y survival 32%
Abdel-Wahab (2018)(90)	I/II RCT	45	IGF-1R EGFR	MK-0646 Erlotinib	M1	1st	Gem	10.4 (A) *vs.* 5.7 mo (C)	Best survival in MK arm, no additional benefit of Erlotinib. Low toxicity	3 arms – A: Gem + MK,B: Gem+MK+E or C: Gem+E
Maurel (2018)(96)	II	25	EGFR	Erlotinib	resected	NAT	Gem+RT	23.8 mo	Better OS for R0 *vs.* R1 resection or not resected: 65.5 mo *vs.*. 15.5 mo, P=0.01	
Dittrich (2019)(171)	Ib	30	EGFR VEGF	Erlotinib Bevacisumab	LAPC, M1	1st in M1	Cap	2.5 mo PFS	Good safety, but limited efficacy.	2 PR, 8/28 SD at 6 mo
Halfdanarson (2019)(92)	II RCT	92	EGFR	Panitumumab, Erlotinib	M1	1st	Gem	4.2 *vs.* 8.3 mo OS	Longer OS with dual inhibition, but increased toxicity	Gem +E *vs.* Gem+E+P
Mettu (2019)(93)	I	21	Src, EGFR	Dasatinib, Cetuximab	LAPC, M1	2nd+	Gem	5.8 mo	Limited clinical effect, but toxicity with both	Solid tumors Gem + Das or Gem + Das/Cet
Davis (2020)(102)	Ib	31	Wnt pathway	Vantictumab	M1	1st	GnP	10 mo	42% PR and 35.5%SD	Terminated due to pathologic-fracture related safety, Max tolerated dose not reached
Hu (2019)(100)	II RCT	177	Notch2/3R	Tarextumab	M1	1st	GnP	6.4 *vs.* 7.9 mo	No diff in OS, even somewhat better in the placebo (p=0.9)	
Wei (2019)(95)	II	114	EGFR	Erlotinib	Resected, head	NAT+ Adj	Gem	21.3 mo 25.4 mo for resected	Feasible	83/114 resected. 52% 2-year survival for resected
Lin (2019)(172)	I/II		CA125 Protease inhib.	Oregovomab Nelfinavir	LAPC	NAT	SBRT + Gem/ leucovorin/ fluoruracil	13 mo	No difference in OS/TTP Compared to a historical group with same Tx	Nelfinavir as radiosensitizer. 4/11 resected
Alewine (2020)(173)	I/II	20	mesothelin	LMB-100 (immunotoxin) + modified Pseudomonas exotoxin A	Advanced, recurrent	2nd +	nPac	nr	1PR, 7 >50% decrease of CA19-9. Not well tolerated	Ab+exotoxin Higher mesothelin expression in pts with tumor marker responses
Bendell (2020)(101)	I	36	MMP9	Andecaliximab	LAPC, M1	1st (in M1)	GnP + Ab	7.8 mo PFS	Well tolerated; PR in 44% (RECIST)	1st line in the metastatic setting
Sinn (2020)(94)	IIb RCT	122	VEGFR, PDGFR, RAF, etc	Sorafenib	Resected R1	1st	Gem	17.6 mo *vs.* 17.5 mo	No diff in RFS no OS	Gem + Ab's *vs.* Gem +placebo
Assenat (2021)(174)	II	63	HER2, EGFR	Trastusumab + Erlotinib	M1	1st	Gem + Ab	OS 7.9 mo	No control group	PFS better when grade >=2 cutaneous toxicity; HER2 and EGFR expression corr with survival on multivariate analysis
Tempero (2021)(99)	III RCT	424	BTK	Ibrutinib	M1	1st	GnP+Ab *vs.* GnP + placebo	9.7 mo *vs.* 10.8 mo	No diff in OS	More side effects and receiving lower dose chemo with Ab
Lim (2021)(91)	II RCT	65	EGFR	Erlotinib	LAPC, M1	1st	GemOx +E versus Gem +E	3.9 mo *vs.* 1.4 mo PFS, not OS (trend)	Better PFS with oxaliplatin,	Ab not tested - Erlotinib in both chemo arms, so unknown benefit

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