Review Article

Current and future systemic treatment options in metastatic pancreatic cancer

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Abstract: Although pancreatic adenocarcinoma is the fourth leading cause of cancer death, only modest improvement has been observed in the past two decades, single agent gemcitabine has been the only standard treatment in patients with advanced disease. Recently newer agents such as nab-paclitaxel, nimotuzumab and regimens such as FOLFIRINOX have been shown to have promising activity being superior to gemcitabine as a single agent. With better understanding of tumour biology coupled with the improvements in targeted and immunotherapies, there is increasing expectation for better response rates and extended survival in pancreatic cancer.

Keywords: Pancreatic cancer treatment; nabpaclitaxel; FOLFINOX; targeted therapy; immunotherapy

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Introduction

Pancreatic adenocarcinoma is the fourth most-frequent cause of tumor related death in western world (1). Median survival is 4 to 6 months and median 5-year survival is less than 5% (2). Great majority of the patients with pancreatic adenocarcinoma presents at advanced stage, either with metastatic or locally advanced disease. Actuarial 5-year survival rate for early stage operable disease with adjuvant treatment is around 20% (3,4). However, 70% of them recurs and need palliative treatment. Standard treatment of metastatic and locally advanced pancreatic cancer patients who cannot be treated with chemoradiation or surgery is chemotherapy. Pancreatic cancer is a well-known relatively chemo-refractory disease. Evidence changed in recent years from single agent gemcitabine treatment to combination regimens. FOLFIRINOX and gemcitabine plus nab-paclitaxel became two standard options for metastatic pancreatic cancer for patients with good performance status (5,6). Targeted agents, immunotherapy and vaccines are the most popular fields of clinical trials in advanced pancreatic cancer and we will reach a bulk of new clinical data in the treatment of metastatic pancreatic cancer in near future.

Cytotoxic therapy

Cytotoxic chemotherapy is the standard treatment option for metastatic and locally advanced pancreatic cancer patients cannot be treated with surgery or radiochemotherapy. Chemotherapy trials had been failed to show benefit for a long time in the past. In 1997 gemcitabine monotherapy became the standard treatment with the landmark study by Burris *et al.* (7). Gemcitabine (n=63) monotherapy was compared with weekly blous 5-fluorouracil (n=63) and modest survival benefit was shown in gemcitabine group (5.6 *vs.* 4.4 months). But clinical benefit was evident regarding performance status and pain control in gemcitabine group. Gemcitabine was used as the standard treatment for many years due to good patient tolerance and improved quality of life in metastatic cancer patients. Several agents including capecitabine, irinotecan, oxaliplatin and cisplatin were tested in combination with gemcitabine but survival benefit could not be shown in any of those phase III studies (8-11). Several targeted agents

were also studied in combination with gemcitabine in phase II or III trials. Studies of vismodegib, masitinib, sorafenib, AMG479 and IPI926 in combination with gemcitabine failed to show survival benefit (12-16). Significant phase III studies of gemcitabine were summarized in *Table 1*. A small survival benefit was shown with platinum derivatives and capecitabine when added to gemcitabine in meta-analyses due to underpowered studies to show small differences (18,19). Additional toxicity came with this marginal survival benefit with gemcitabine and platinum or capecitabine combinations.

Combination therapy for advanced pancreatic cancer was controversial until year 2011. Prodige 4-ACCORD 11 randomized phase III trial compared FOLFIRINOX regimen with gemcitabine in good performance status, 336 untreated, metastatic pancreatic adeno cancer patients (5). Inclusion criteria were strict as permitting patients up to age of 75 years, with ECOG performance status 0 or 1, nearly normal bilirubin, good bone marrow and renal function, and without a history of heart disease. This study met the primary endpoint of OS as 11.1 *vs.* 6.8 months in FOLFIRINOX and gemcitabine arms, respectively (HR=0.57, P=0.0001). ORR (31.6% *vs.* 9.4%, P=0.0001) and PFS (6.4 *vs.* 3.3 months, P=0.001) was also superior in FOLFIRINOX compared to gemcitabine group consistent with OS results. These better survival rates and responses came with the expense of excess toxicity. Febrile neutropenia (5.4% *vs.* 0.6%, P=0.009), thrombocytopenia (9.1 *vs.* 2.4, P=0.008), peripheral neuropathy (9% *vs.* 0%, P=0.001), vomiting (14.5% *vs.* 4.7%, P=0.002), diarrhea (12.7 *vs.* 1.2, P=0.0001), thromboembolic events (6.6% *vs.* 4.1%) and growth factor support (42.5% *vs.* 5%) rates were higher in FOLFIRINOX compared to gemcitabine group. But elevated LFTs were higher in gemcitabine group (20.8% *vs.* 7.3%). FOLFIRINOX combination regimen was approved for the first line treatment of metastatic pancreas adenocarcinoma patients with good performance status regarding results of this trial.

Chemoresistance of pancreatic cancer is partly attributed to stroma rich characteristic of the tumor. Albumin-bound paclitaxel (nab-paclitaxel) was shown to bind to protein SPARC (secreted protein acidic and rich in cysteine) also known as osteonectin, which is overexpressed by fibroblasts in the pancreatic cancer microenvironment (20,21). Thus nab-paclitaxel renders an effective amount of cytotoxicity by depleting tumor stroma. The molecular mechanism of nab-paclitaxel is not fully understood and simply albumin avidity of tumor cells might deliver a high concentration of chemotherapeutic in the tumoral tissue. Nab-paclitaxel came as another combination option with gemcitabine for patients with advanced stage pancreatic cancer. After the impressive response rate (48%) and survival of 12 months from the phase I-II trial, phase III trial was conducted (22). The MPACT trial compared gemcitabine plus nab-paclitaxel with gemcitabine in 861 untreated metastatic pancreatic adeno cancer patients (6). This study also met the primary endpoint of OS and nab-paclitaxel was the first agent showed OS increment with addition to gemcitabine (8.5 *vs.* 6.7 months, HR=0.72, P=0.000015). One year survival rate (35% *vs.* 22%), PFS (5.5 *vs.* 3.7) and ORR (23% *vs.* 7%) were higher in gemcitabine plus nab-paclitaxel compared to gemcitabine group. Toxicity related deaths were similar in groups (4% for each) but grade 3-4 neutropenia (38% *vs.* 20%), fatigue (17% *vs.* 7%), neuropathy (17% *vs.* <1%) were higher in combination group. In the subgroup analyses patients with poorer performance status (KPS 70-80) and more bulky disease (liver metastases, >3 metastatic sites and >59XULN CA19.9 level) much benefited from the gemcitabine plus nab-paclitaxel combination regimen.

Table 1 Gemcitabine based phase III studies for palliative setting in pancreatic cancer

Treatment	N	Response rate (%)	Overall survival (months)	P	Reference
Gemcitabine	63	5.4	5.65	0.0025	(7)
Bolus 5FU	63	0	4.41		
Gemcitabine	284	8.0	5.91	0.038	(17)
Gemcitabine + erlotinib	285	8.6	6.24		
Gemcitabine	266	12.4	6.2	0.02	(18)
Gemcitabine + capecitabine	267	19.1	7.1		
Gemcitabine	430	7	6.7	0.000015	(6)
Gemcitabine + nab-paclitaxel	431	23	8.5		

Treatment selection

Decision of two new standard options for metastatic pancreatic adenocarcinoma might be given according to age (number of patients >70 was lower in Prodige4 ACCORD 11 trial), performance status (MPACT trial consisted a broader spectrum for performance status; KPS 70-100),

patients preference of treatment routes and frequency (46 hours infusional 5-fluorouracil *vs*. weekly nab-paclitaxel treatment) and toxicity profiles (increased hematologic toxicity, febrile neutropenia, diarrhea, fatigue and growth factor support need in FOLFIRINOX regimen and alopecia in nab-paclitaxel combination treatment). Patients who will not tolerate the FOLFIRINOX combination chemotherapy or who do not want a central access might be good candidates for gemcitabine plus nab-paclitaxel study. However gemcitabine monotherapy must be kept in mind as the oldest standard for patients cannot receive FOLFIRINOX or nab-paclitaxel.

Drug sensitivity model for gemcitabine, irinotecan, oxaliplatin, nab-paclitaxel, 5-fluorouracil and oxaliplatin was generated with pharmacogenomic studies in pancreatic cancer cell lines according to genetic expression of molecular pathways i.e., the transforming growth factor B (TGF-B), hedgehog and jak-stat (8,23-26). Sangar *et al*. validated this pharmacogenomic test in a phase II trial in pancreatic adenocarcinoma patients (n=20) and patients sensitive to drug had longer TTP compared to intermediate sensitive and resistant patients (7.3 *vs*. 5.3 *vs*. 3.7 months) according to pharmacogenomic analysis (27). Pharmacogenomic test was shown to be predictive for treatment efficacy regarding TTP. Future studies with this pharmacogenomic tests might help 1st and 2nd line treatment decisions and treatment choice of nab-paclitaxel plus gemcitabine or FOLFIRINOX as the 1st line treatment. A high SPARC expression is associated with improved response to nab-paclitaxel and pre-treatment pharmacogenomic testing of SPARC might be useful for choosing patients for gemcitabine plus nab-paclitaxel treatment (22). There are a number of ongoing trials mostly with gemcitabine chemotherapy backbone on the first line treatment of advanced pancreatic cancer listed in *Table 2* and a third treatment option might come from these trials.

Data on second line treatment of metastatic pancreatic cancer is sparse. The only second line, randomized phase III study in advanced pancreatic cancer tested FOLFOX versus best supportive care after first line treatment with gemcitabine failure. This study demonstrated a median second line survival benefit of 4.82 months compared to 2.30 months with best supportive care (53). That might be a good option in fit patients progressed on gemcitabine treatment. In FOLFIRINOX trial 47% of the patients were treated with second line therapy and most of them received gemcitabine (5). Thus gemcitabine might be an option patients progressed on FOLFIRINOX treatment. Ongoing trials for the second line treatment of advanced pancreatic cancer are summarized in *Table 3*.

Targeted therapy

During last 10 years various targeted agents were tested alone or in combination with gemcitabine for treatment of advanced pancreatic cancer. But all but one failed to improve patients' survival significantly. Erlotinib, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor was the first agent achieved survival benefit when added to gemcitabine (17). However the difference was minimal (6.24 *vs*. 5.91 months, P=0.038) and raised the question of clinical significance. A prolonged survival of 10.5 months was seen in a subgroup of patients who developed grade 2 or severe skin rash. Skin rash was the most important adverse effect. Skin rash was proposed as a predictive marker for erlotinib benefit (60). However it is not clearly defined as a predictive tool. The EGFR monoclonal antibody cetuximab and VEGF antibody bevacizumab were failed in phase III studies of advanced pancreatic cancer (61,62). Another EGFR monoclonal antibody nimotuzumab in combination with gemcitabin had shown better overall survival compared to gemcitabine plus placebo (8.7 *vs*. 6.1 months) with tolerable toxicity in a recent phase II trial in first line treatment of locally advanced or metastatic pancreas cancer patients (63). Other members of small molecule tyrosine kinase inhibitors axitinib, sorafenib and tipifarnib (a farnesyl transferase inhibitor) with combination of gemcitabine were compared with single agent gemcitabine in different phase III trials. But they were also failed to show any benefit in treatment of advanced pancreatic cancer (64-66). Masitinib a c-kit inhibitor of mast cell function, marimastat an agent against secreted matrix proteases were also tested in phase III randomized trials with or without gemcitabine. However no survival benefit was seen with adding these agents to gemcitabine in advanced pancreatic cancer (67,68).

Insulin like growth factor 1 receptor (IGF1R) is highly expressed in pancreatic cancer and takes role in downstream signalling cascades for cancer cell survival and proliferation thorough a KRAS-dependent and independent pathway. It was another target for drug development for several solid tumors and also pancreatic cancer. However IGF1 R inhibitor AMG-479 and monoclonal antibody cixutumumab failed to show a survival benefit (15,69).

K-ras is a major driver in pancreatic cancer and mutated in 90% of the cases. It causes an uncontrolled activity of downstream pathway of raf, MEK and ERK,

Table 2 Ongoing first line trials on advanced pancreatic cancer

Target	Phase	N	Treatment	Reference
Mitotic inh; polo like kinase	II-III	150-650	Gem +/- Rigosertib	(28)
Hypoxia	III	660	Gem +/- TH302	(29)
hENT1	III	175	Gem *vs*. FOLFOX (hENT1 high *vs*. low)	(30)
Hyaluronan	II	132	Gem + Nab-pacl +/- PEGPH20	(31)
Antistromal	II	148	Gem + Nab-pacl +/- M402	(32)
TGF-B	I-II	168	Gem +/- LY2157299	(33)
Hedgehog	II	80	Gem + Nab-pacl + Vismodegib	(34)
	II	106	Gem +/- Vismodegib	(35)
	I-II	25	Gem + Vismodegib	(36)
	I	40	FOLFIRINOX + LDE225	(37)
	II	122	Gem +/- IPI-926	(16)
Notch inh. Stem cells	II	140	Gem + Nab-pacl +/- OMP59R5	(38)
Notch inh.	I	60	Gem + MK0752	(39)
HSP27	II	132	Gem + Nab-pacl +/- 068-428	(40)
Mek	II	174	Gem +/- MSC19363699D	(41)
Akt	II	31	Gem +/- RX-0201	(42)
EGFR, HER2,4	II	117	Gem +/- Afatinib	(43)
Angiogenesis	II	80	Gem +/- TL-118	(44)
Myostatin	II	120	LY249555 + Chemo	(45)
Ras	II	70	Pacl + carbo +/- Reovirus	(46)
PARPI (BRCA +)	II	70	Gem + Cisp +/- Veliparib	(47)
mTOR + tyrosine kinase	II	120	Gem, erlotinib +/- metformin	(48)
mTOR	I-II	21	Gem + Everolimus	(49)
Stem cells	II	82	PEXG +/- Metformin	(50)
HDAC	I-II	50	Radiotherapy + cape +/- vorinostat	(51)
DNA-methylation	I	30	Gem + 5-Azacytidine	(52)

TGF-B, transforming growth factor B.

Table 3 Ongoing trials beyond first line on advanced pancreatic cancer

Target	Phase	N	Treatment	Reference
Liposomal irinotecan	III	405	MM-198 +/- 5-FU/LV	(54)
JAK1,2	III	138	Capecitabine +/- ruxolitinib	(55)
Ifosfamide conjugate	III	480	5FU/LV (bolus) *vs*. glufosfamide	(56)
MEK, AKT	III	133	FOLFOX *vs*. selumetinib + MK2206	(57)
MEK, tyrosine kinase	II	46	Erlotinib + AZD6244	(58)
mTOR, VEGFR, tyrosine kinase	II	12	Sorafenib + everolimus	(59)

leading to tumor cell proliferation and survival. Mitogen activated protein kinase MEK is an important druggable target in pancreatic carcinoma in which activating K-ras mutation is seen frequently. Trametinib (GSK1120212) a MEK inhibitor failed to show survival benefit when added to gemcitabine in advanced pancreatic cancer (70).

Another MEK inhibitor MSC1936369B is being tested in combination with gemcitabine in first line treatment of advanced pancreatic cancer in a phase II trial (41). A phase II study is evaluating another MEK inhibitor AZD6244 in combination with tyrosine kinase inhibitor erlotinib in second line treatment of advanced pancreatic cancer (58).

The PI3K/Akt and mTOR pathway takes role in tumor cell proliferation, survival and metabolism is another therapeutic target in advanced pancreatic cancer. Increased activity of PI3K/Akt and mTOR pathway might take an important role in resistance of drugs effecting ras-raf-MEK and ERK pathway. A phase II study of an Akt antisense oligonucleotide, RX-0201 in combination with gemcitabine is completed and results are awaited (42). A study of PI3K inhibitor BKM120 in combination with mFOLFOX-6 regimen in advanced stage solid tumors including pancreatic cancer is going on (71). The BEZ235 is a combined inhibitor of PI3Kand mTOR. A phase I study of BEZ235 in combination with the MEK inhibitor MEK162 with the strategy of hitting two pathways at the same time is completed in advanced solid tumor patients carrying K-ras, Nras and/or Braf mutations including pancreatic cancer and results are awaited (72). The study of mTOR inhibitor everolimus monotherapy by Wolpin *et al*. had shown a PFS and OS of 1.8 and 4.5 months respectively in gemcitabine refractory pancreatic cancer patients (73). Another phase II study of everolimus in combination with erlotinib in previously treated advanced pancreatic cancer patients was terminated due to futility and significant adverse effects (74). A phase II trial of the other mTOR family member temsirolimus is completed in locally advanced or metastatic pancreas cancer patients and results are pending (75). A phase I and II combination study of everolimus and sorafenib in advanced solid tumor patients including pancreas cancer refractory to gemcitabine was completed and results are also pending (76). A phase I/II study of everolimus in combination with gemcitabine in advanced pancreas cancer patients is completed and results are awaited (49). A list of novel therapeutic targets and drugs is given in *Table 4*.

A commonly used oral antidiabetic drug metformin was shown to activate adenosine monophosphate-activated protein kinase (AMPK).The AMPK inhibits mTOR pathway by phosphorylation and stabilization of the tumor suppressor gene TSC2 (86). One of the mechanisms for TKI-resistance is hyperactivation of mTOR pathway. Blocking the mTOR pathway might be a good strategy for overcoming TKI resistance. A phase II randomized study of metformin in combination with erlotinib and gemcitabine compared to placebo in advanced pancreatic cancer patients is going on (48).

Novel therapeutics

Pancreas cancer has an extensive stromal tissue which is a unique histological feature. This dominant desmoplastic tissue might contribute the weak penetration of the applied drugs and act as a protective barrier from the treatments. It was hypothesized as a chemoresistance mechanism of pancreas carcinoma (87). Sonic hedgehog pathway takes an important role for stimulating stromal reaction. Vismodegib an hedgehog inhibitor is the first drug approved in advanced and metastatic basal cell skin carcinoma (88). Various clinical trials of vismodegib in combination with gemcitabine and gemcitabine plus nab-paclitaxel are ongoing in recurrent or advanced pancreatic cancer patients (34-36). Another hedgehog inhibitor IPI-926 or placebo in combination with gemcitabine is studied in a phase II randomized study in metastatic pancreas cancer patients (16). This study is completed and results are pending. Hedgehog inhibitor LDE225 is tested in combination with FOLFIRINOX in untreated advanced pancreatic cancer patients and the study is ongoing (37).

The Notch pathway is thought to take role in pancreas carcinogenesis and Notch ligand and receptor are shown to be highly expressed in pancreas cancer (89,90). OMP-59R5 is a fully human monoclonal antibody that targets the Notch2 and Notch3 receptors. It downregulates Notch pathway signaling and affects pericytes, tumor stroma and microenvironment and thought to have anti-cancer stem cell effect. The ALPINE trial testing OMP-59R5 with gemcitabine and Nab-paclitaxel in first-line advanced pancreatic cancer patients showed well tolerability and responses (PR=46%, DCR=77%) in early phase I results (91). Gamma secretase is an enzyme causes proteolytic cleavage and release of the intracellular domain of the Notch and activates Notch signalling pathway. A phase II study of gamma-secretase inhibitor RO4929097 monotherapy is going on in pretreated metastatic pancreas cancer patients (92). Another gamma-secretase inhibitor MK0752 and gemcitabine combination are being tested for first line treatment of stage III and IV pancreas cancer patients (39).

Histone de-acetylation (HDAC) and DNA hypermethylation are two major epigenetic changes cause tumor supressor gene silencing and tumor cell proliferation,

Table 4 Summary of novel therapeutic agents

Drug	Class	Target-pathway	Reference
Tipifarnib	FT inhibitor	RAS, RAF, MEK	(66)
Selumetinib	C-met inh		(77)
Erlotinib	TKI	EGFR	(17)
Everolimus, temsirolimus	MTOR inh	MTOR/PI3K/AKT/MEK	(49)
Metformin	AMPK act.		(48)
MK-2206	AKT		(57)
RX-0201	AKT		(42)
XL765	PI3K/MTOR		(78)
BKM120	PI3K		(71)
MSC1936369D	MEK		(41)
Vismodegib	Small molecule Shh inh	Hedgehog	(34-36)
Saridegib (IPI-926)			(16)
LDE-225			(37)
R04929097	Gamma secretase inh	Notch	(79)
MK0752	Gamma secretase inh		(39)
OMP59R5	Notch2/3 Antibody (antiSC)		(38)
Vorinostat	HDAC inh	HDAC	(51)
5-Azacytidine	DNA-methyltransferase inh.	DNA-methyltransferase	(52)
AGS-1C4D4	Antibody to PSCA	PSCA	(80)
LY2157299	TGF-B type-1 receptor inh.	TGF-B	(33)
Dasatinib, Saracatinib	SRC,bcr-abl inh	SRC	(81,82)
Olaparib, veliparib	PARP inh	PARP/BRCA/PALB2, Fanconi pathway	(47,83)
Ipilimumab, nivolumab	Check point inh	Immune/AntiCTLA-4, AntiPD-1	(84,85)

TGF-B, transforming growth factor B.

growth and progression. Vorinostat, HDAC inhibitor is being tested in locally advanced pancreas cancer patients in combination with capecitabine and radiotherapy in a phase I and II study (51). The chemical cytosine analogue 5-azacitidine inhibits DNA methyltransferase and a phase I study in combination with gemcitabine is going on in first line treatment of advanced pancreatic cancer patients (52).

TGF-B is another regulator pathway of stromal reaction and TGF-B takes role in stimulating stromal reaction, invasion, metastasis and promoting angiogenesis in pancreas cancer (93). Trabedersen, an antisense oligodeoxynucleotide which inhibits TGF-B2 expression was shown to have good efficacy and safety profile in the second line treatment of pancreas cancer patients (n: 37; median OS, 13.4 months) (94). A phase II study of gemcitabine in combination with a specific type 1 receptor inhibitor of TGF-beta, LY2157299 or placebo is recruiting patients (33).

Pancreas cancers are rich of tumor stroma and have a high level of hyaluronan. PEGPH20 degrades hyaluronan, reduces interstitial fluid pressure and facilitates drug delivery (95,96). It has shown to improve efficacy when used with cytotoxics. A phase IB trial of gemcitabine plus PEGPH20 had shown promising efficacy and phase II and III trials of gemcitabine + nabpaclitaxel ± PEGPH20 (HALOZYME) and FOLFIRINOX +/- PEGPH20 (SWOG-NCI) are planned (97,98).

The DNA double-strand breaks (DSBs) are mainly repaired by homologous recombination, a process mediated by BRCA1 and BRCA2 proteins which sustains genomic stability and cell survival (99). Alternative poly (ADP-ribose) polymerase (PARP) pathway takes the main role for DNA repair when BRCA dysfunction occurs. PARP is a critical enzyme of cell proliferation and DNA repair mediates repair of DNA single strand breaks (SSB), and rescues

tumor cells from DNA damage. PARP represents a good therapeutic target in BRCA mutated/dysfunctional tumors. Inhibition of PARP-1 activity prevents the recruitment of DNA repair enzymes and leads to failure of SSB repair. DNA single strand breaks accumulate, induce formation of DNA replication fork arrests, and form DSBs (100). In the combined absence of PARP activity and BRCA1 or BRCA2 activity, both repair pathways are disabled; DNA DSBs cannot be repaired properly. DSBs can induce genomic instability and ultimately lead to tumor cell death. PARP inhibitors have shown efficacy in BRCA mutated ovary and breast cancer patients (101-105). A 5% to 7% of pancreatic cancer patients show germline mutations of BRCA 1 or 2. Preclinical data showed susceptibility to alkylating agents and Parp inhibitor in Capan-1 BRCA 2 deficient pancreatic cancer cell line (106). A randomized phase II study of gemcitabine + cisplatin +/- veliparib in BRCA 1-2 and PALP-2 mutated locally advanced or metastatic pancreatic cancer patients is being continued (47). The second part of this trial which is a single arm phase II, is going on in previously treated pancreatic cancer patients. Novel agents on the treatment of advanced pancreatic cancer are summarized in *Table 4*.

Platinum compounds directly bind to DNA and causes double strand breaks. A dysfunction in BRCA1 and its pathway is associated with a specific DNA-repair defect that sensitizes cells to platinum drugs in animal models (107,108). Platinum compounds showed high responses in triple negative breast cancer which share similar features with BRCA deficient patients (109,110).

Immunotherapies

Immunologic treatments are increasingly studied in last few years in various tumors in medical oncology. Unmet medical need in pancreatic cancer directed researchers to investigate new pancreatic cancer treatments and also immunological approaches. After the first positive results of ipilimumab came from phase III study of metastatic malignant melanoma, interest on immunological treatments increased. Immunologic treatments might be classified as passive immunotherapy approaches as the use of antibodies or *in vitro* generated effector cells, and vaccination for stimulating antitumoral response. There are different ways of delivering vaccines. Dendritic cell (DC) vaccines combine tumoral antigen with DCs for presenting them to effector T cells. Viral or bacterial DNA is inserted to human cells to modulate cell-mediated immunity by the DNA vaccines. Peptides are inserted to human cells by T-cell receptor peptide vaccines for increasing cell mediated immunological response. DCs are the most potent antigen presenting cells. They can cause a high antigenic response via stimulating T and B cells. Kimura *et al.* showed DC vaccine plus lymphokine activated killer cell treatment and chemotherapy prolonged overall survival compared to patients received only DC vaccine or chemotherapy (111). Carcinoembryonic antigen (CEA) is an oncofetal antigen that is expressed in epithelial malignancies and pancreatic cancer. It is one of the highly expressed antigens in pancreatic cancer might be used with DCs for vaccine treatment of pancreatic cancer (112). MUC1 is another protein which is highly expressed in pancreatic cancer (113). Phase I and II studies of MUC1 antigen pulsed DC vaccines showed hopeful results in advanced pancreatic cancer (114,115). A phase I study in advanced pancreatic cancer with vaccine containing vaccinia virus expressing CEA and MUC1 and costimulatory molecules showed well tolerability an overall survival advantage in immune responsive patients (116). But a phase III trial of fowlpox viruses expressing CEA and MUC1 and costimulatory molecules failed to improve overall survival when compared to chemotherapy or best supportive care in palliative setting in pancreatic cancer patients (117). Heat shock proteins are a family of chaperone proteins expressed in all species which are induced by stress conditions. They are presented within HLA class I complex on the cell surface. HSPPC-96 is a HSP-based vaccine used in a small study of resected pancreas cancer patients with tolerable toxicity profile and long survival durations in some patients (118).

Algenpantucel-L is an irradiated, live combination of two human allogeneic pancreatic cancer cell lines. These cells express the murine enzyme alpha-1,3-galactosyl transferase (alpha-GT) which directs the synthesis of alpha-galactosyl epitopes on surface proteins and glycolipids of such cell lines. Alpha-Ga1 epitopes are absent in humans but large amount of alpha-Ga1 antibodies exists (119). Alpha-Ga1 antibodies and alpha Ga1 epitopes in algenpantucel–L activates complement mediated lysis and antibody dependent cell mediated toxicity against algenpantucel-L cells (120). Phase II adjuvant study of algenpantucel in combination with radiation plus 5-fluorouracil and gemcitabine treatments in resected pancreatic cancer patients reached a one year DFS of 62% and OS of 86% meeting primary and secondary endpoints (121). This promising result in the adjuvant setting was one of the important factors directing researchers' focus on vaccine trials in pancreatic cancer.

Granulocyte monocyte colony stimulating factor (GM-CSF) is a potent cytokine able to mobilize monocytes, eosinophils and lymphocytes to the tumor sites. Early studies have shown the efficacy of GM-CSF vaccine in resected pancreatic cancer patients and trials in metastatic pancreas cancer with GM-SCF are ongoing (122).

K-ras mutations are found in up to 90% of pancreatic cancers (123). K-ras mutation is specific for tumor cells and is not present in normal cells. These mutations can be targets for a specific T cell mediated toxicity. A phase I/II trial of synthetic mutant ras peptides with GM-CSF showed a prolonged survival in immune responders compared to nonresponders (5 *vs*. 2 months) in advanced pancreatic cancer patients (124). Median survival was also longer for also immune responders among resected pancreatic cancer patients (Median OS: 20% *vs*. 0%, for 10 years).

Telomerase is a ribonucleotide enzyme that is expressed in almost all of the cancer but not in normal cells (125). Telomerase maintains telomers which exist at the end of the chromosomes and elicits stability. It is generally activated in cancer cells and was shown to be expressed in pancreatic cancer (126). A telomerase peptide vaccine GV1001 with GM-CSF was shown to prolong survival in unresectable pancreatic cancer patients in a phase I-II study (127). However, phase III study of GV1001 with gemcitabine sequential combination versus gemcitabine was closed due to lack of survival advantage in unresectable pancreas cancer patients (128,129). Another phase III study of capecitabine plus gemcitabine with or without GM-CSF plus GV1001 in locally advanced or metastatic pancreatic cancer patients was completed and results are awaited (130). Ongoing phase II vaccine trials are summarized in *Table 5*.

Pancreatic cancer is one of the immunologically quiescent tumors. Effector T cell infiltration is not a natural response for pancreatic cancer. But immune system can be provoked. Gemcitabine plus CD40 agonist activating T cells has been shown to reduce tumor burden in advanced pancreatic cancer patients in a phase I study (150). Zheng *et al*. studied a vaccine with or without intravenous low dose or oral metronomic cyclophosphamide in pancreatic cancer patients in a three arm neoadjuvant and adjuvant study (151). Cyclophophamide was used to deplete regulatory T cells. Intratumoral and peritumoral lymphoid aggregates were found in surgical specimens of the vaccinated patients (152). Lymphoid aggregates in pancreatic adenocarcinomas consisted organized T and B cell zones and germinal center like structures. PD-L1 expressing and PD-1 positive cells were upregulated in lymphoid aggregates but not in pancreatic adenocarcinomas without T cell infiltration. Vaccines can induce tumor infiltrating lymphocytes in non-immunogenic tumors. These tumor infiltrating lymphocytes can secrete IFN-gamma and other cytokines that up-regulate PD-1 and PD-L1 pathway. But vaccine induced T cells might be downregulated by the suppressive mechanisms within the tumor. Thus vaccines must be given with agents modulate these suppressive mechanisms and activate T cell response. Anti-PD-1 antibody was shown to enhance infiltration of vaccine induced tumor specific infiltrating lymphocytes active against mesothelin epitope in a preclinical pancreatic cancer model (153).

Modulating regulatory pathways might be another strategy to enhance vaccine's efficacy in pancreatic cancer. Ipilimumab an anti-CTLA4 antibody (Four, 3 weekly, 10 mg/kg induction doses and maintenance q 12 weeks if stable disease or better response is seen at week 22) was given alone or with vaccine to metastatic pancreatic cancer patients in a phase 1B study (154). Thirty metastatic pancreatic patients received two or more lines of chemotherapy were included to this study. Overall survival was longer in ipilimumab + GVAX than ipilimumab alone treated patients (5.5 *vs*. 3.3 months). Twelve month OS and response rate was also higher in the combination arm (27% *vs*. 7% and 45% *vs*. 0%, respectively). Survival was found to be correlated with CD8+, mesothelin specific T cell quantity. Phase II study of this protocol is under development due to this promising result. Targeting more than one checkpoint pathway at the same time might be another option for getting increased efficacy. Anti-PD-1 agent nivolumab and anti-CTLA-4 agent ipilimumab was given concomitantly to malignant melanoma patients and a higher response with the cost of increased toxicity was seen compared to response rate in single agent ipilimumab studies (40% *vs*. 32% for responses and 14% *vs*. 51% for grade 3-5 toxicity) (155,156). Regarding the low amount of T cells in pancreatic cancer microenvironment, combining these immune checkpoint pathway modulators might not be a beneficient strategy due to increased toxicity. Listeria monocytogenes, peptide, DNA, and DC based vaccines are the new vaccines might induce T cells better. Vaccines and immune checkpoint inhibitors as anti-CTLA-4 plus GVAX and anti-PD-1 plus GVAX prime/Listeria boost are the emerging combination strategies. Targeting methylation might unchain the anti-inflammatory signals with hypomethylating strategy and combination with immune checkpoint inhibitors might increase the efficacy. Engineered T cells targeting pancreatic cancer antigens is

Table 5 Ongoing phase II and III vaccine trials in advanced pancreatic cancer

Target		Phase	N	Line	Treatment	Reference
Telomerase	Advanced	III	1110	1st	Capecitabine + Gemcitabine +/- GMCSF + GV1001	(130)
CEA, MUC1	Advanced	III	250	2nd (after gem failure)	PANVAC-F *vs*. BSC *vs*. CT	(131)
Alpha-Ga1	Borderline resectable/ Locally advanced unresectable	III	280	1st/2nd and adjuvant	FOLFIRINOX + Algenpantucel-L→PD; Gem + Nab-Pacl. + Algenpantucel-L →No distant mets;5-FU / Cape + RT + Algenpantucel-L	(132)
GMCSF transduced whole tumor cell	Metastatic	II	92	Maintenance	FOLFIRINOX (If non-progressive)→Ipilimumab + GVAX	(133)
GMCSF transduced whole tumor cell	Metastatic	II	90	1st/2nd	GVAX + cyclophosphamide or GVAX + cylophosphamide + CRS-207 (attenuated Listeria monocytogenes)	(134)
GMCSF transduced whole tumor cell	Metastatic	II	240	2nd line or beyond	GVAX + cyclophosphamide + CRS-207 or CRS207 or Gem/Cape/5-FU/Iri/Erlo	(135)
CEA	Advanced/ metastatic	I/II	28	2nd or beyond	AVX701	(136)
Whole tumor cell	Advanced	II	40	1st or beyond	IFNα or IFN_{γ} treated tumor cell vaccine+ GMCSF + cylophosphamide	(137)
Whole tumor cell	Advanced	II	14	1st line or beyond	IFNα treated tumor cell vaccine+ GMCSF + cylophosphamide	(138)
CEA	Advanced/ metastatic	II	24	1st or beyond	ALVAC-CEA + IL-2 + GMCSF	(139)
RAS	Stage II/III/IV	II	NA	1st or beyond	DETOX-PC + IL-2 + GMCSF	(140)
CEA peptide -1-6D	II/III/IV	II	7	Maintenance	Standart tx (if non progressive)→Cap1-6-D + GMCSF + incomplete Freund's adjuvant	(141)
Whole cell	II/III/IV	II	NA	1st line or beyond	Allogeneic tumor cell vaccine (incubated with IFNα) + GMCSF + cyclophosphamide	(138)
Plasmid DNA pancreatic tumor cell	III/IV	II	60	1st line or maintenance	Vaccine + cyclophosphamide + GMCSF	(142)
MUC1	Adjuvant/ Unresetbale	II	25	1	Vaccine (MUC-1 antigen + SB AS-2 adjuvant)	(143)
CEA /Modified CEA	Adjuvant/locally advanced	II	15	Adjuvant/1	Vaccine (CEApeptide/Modified CEA –CAP1-6D)	(144)
VEGFR1 and VEGFR2 epitope	Locally advanced/ metastatic	I/II	17	1st	Vaccine (VEGFR1-1084, VEGFR2-169) + Gem	(145)
Cancer stem cell	Metastatic	I/II	40	1st line or beyond	Cancer stem cell vaccine	(146)
Survivin (HLA-A1, A2, B35)	Metastatic	I/II	70	1st line or beyond	Survivin HLA-A1, A2, B35 epitope vaccine	(147)
DC	Unresectable	I/II	30	1st line or beyond	İntratumoral DC vaccine	(148)
Plasmid DNA (DTA-H19)	Locally advanced	II	70	1st line	Intratumoral BC-819 (Plasmid DNA accine against DTA-H19)	(149)

another emerging era of treatment in advanced pancreatic cancer.

Combining two vaccines might be another strategy to enhance efficacy. GVAX is a DC vaccine which is exposed to whole pancreatic cancer cell irradiated and incubated with GMCF. CRS 207 is a Listeria based vaccine in which a tumor specific antigen mesothelin is incorporated to the Listeria's chromosome and of which two virulence genes (actA, inlB) were deleted. Listeria is an intracellular microorganism and it secretes and expresses tumor antigens inside the antigen presenting cells. Induction of robust innate and antigen specific adoptive immunity occurs by this way. GVAX alone or in combination with CRS207 was given to advanced pancreatic cancer patients (2 to 1 randomization; n=90) who have failed or refused previous chemotherapy (85). Median OS was higher in combination compared to GVAX alone arm (6.1 *vs*. 3.9 months, P=0.0172, HR=0.59). Overall survival benefit was more clear among patients treated as 3rd line (5.7 *vs*. 3.9 months, P=0.0003, HR=0.29). Immunotherapy might be synergistic with different combinations of treatment i.e. chemotherapy and targeted agents.

A randomized phase II study of gemcitabine with or without AGS-1C4D4, a fully human monoclonal antibody to prostate stem cell antigen (PSCA) showed better 6-month survival rates in combination (n=133; 60.9%) versus gemcitabine arm (n=63; 44.4%) in metastatic pancreatic cancer (157). Median survival was and response rate were also higher in the combination group (7.6 *vs*. 7.6 months and 21.6% *vs*. 13.1%, respectively). The 6-month SR was higher in PSCA-positive subgroup (79.5% *vs*. 57.1%).

Immunotherapy might be a promising treatment option for pancreatic cancer. Immunologic treatments have no potential side effects like conventional chemotherapeutics have unique toxicity profile like autoimmune phenomena. There is no phase III data of immunological treatment showing benefit in metastatic pancreas cancer. Absence of pancreatic cancer cell specific antigen and immunological quiescent microenvironment of pancreas cancer are difficulties for investigations on immunologic treatment approaches. Combinations of active and passive immunologic treatments, targeted agents and conventional chemotherapies might be important strategies for increasing efficacy.

In conclusion, FOLFIRINOX and gemcitabine + Nab-paclitaxel are new standard combinations in frontline setting. However they can be integrated to all disease settings in clinical practice. Gemcitabine + nab-paclitaxel combination seems to be more tolerable and might be given to patients with a broader spectrum of performance status. Trials are ongoing with addition of various targeted agents with these two standard chemotherapy backbones. Data for second and third line treatment are emerging. Treatment agents targeting stroma, immune pathways and inflammation are under development.

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