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Systematic or Meta-analysis Studies

Checkpoint inhibitors in pancreatic cancer

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ABSTRACT

Introduction: Immune checkpoint inhibitors, targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and the programmed cell death protein-1 (PD-1)/programmed cell death ligand-1 (PD-L1) pathways have shown remarkable potential in several types of cancer. In this review we summarize published and ongoing studies on checkpoint inhibitors in pancreatic cancer (PC).

Methods: We conducted a systematic literature search using Medline and Embase up to November 2018; additional data from a search on clinicaltrials.gov were included. Endpoints of interest encompassed overall survival (OS), progression free survival (PFS) and response rates.

Results: Full-length articles constituted a minority of included records. Furthermore, few patients were enrolled, and only few phase II studies were identified.

Disappointing limited activity was demonstrated with single-agent checkpoint inhibitors in PC. A small number of studies on combination therapy showed promise with regards to response. But overall, PC patients treated with checkpoint inhibitors were not shown to elicit improvement in response rates or overall survival.

Conclusion: Checkpoint inhibition monotherapy has failed to elicit efficacy in patients with pancreatic cancer. Combination regimens including chemotherapy have shown initial promise, but these results need to be verified. Numerous studies on checkpoint inhibition in PC are ongoing.

Introduction

In 2016 pancreatic cancer (PC) moved from 4th [1,2] to 3rd leading cause of cancer death in the US, surpassing breast cancer [3]. PC is projected to be the second leading cause of cancer related death in 2020 [4,5]. Over 90% of PC cases develop in the exocrine tissue. Pancreatic adenocarcinomas compromise most of the exocrine tumors and of these the pancreatic ductal adenocarcinoma (PDAC) is the most frequent histological subtype [6]. About half of patients with PC present with distant metastases while approximately a third present with locally advanced disease [7]. A small portion of PC patients have tumors characterized by defective mismatch repair with possible implication for treatment strategy [8,9].

Surgery is the only potentially curative treatment of PC [10]. However, less than 20% of patients are eligible for this intervention [2]. Even after radical resection, the recurrence rate is high [11], and the majority of patients relapse within two years. Adjuvant treatment with modified FOLFIRINOX (5-fluorouracil (5-FU), leucovorin, irinotecan, oxaliplatin) results in the longest overall survival (OS) yet reported after resection, with 63% being alive after three years [12]. In most instances, palliative chemotherapy is the only treatment option [13]. The choice of treatment for metastatic PC is guided by the patients' performance status, and current recommendations include FOLFIRINOX, gemcitabine plus nab-paclitaxel or gemcitabine monotherapy [13]. The combination of Onivyde (irinotecan liposome), 5-FU and leucovorin is approved by European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) after gemcitabine-based therapy [14–16]. The overall 5-year survival rate for PC is 8% [2] and significant improvement in survival over the past decades has remained absent despite introduction of new regimens [17]. Thus, the need for novel therapies is warranted. Current approaches include investigation of immunotherapy combinations, targeting of DNA repair, stroma, and tumor metabolism and the identification of clinically useful biomarkers.

Immune therapy and its implications for treatment is a topic of interest and a possible way to improve the prognosis of PC. It is an investigational field that encompasses targeted therapies and anti-tumor vaccination [18]. The present review investigates the status in the field of immune checkpoint therapy in patients with PC.

Checkpoint inhibition

The term 'immune checkpoints' refers to the regulatory mechanisms

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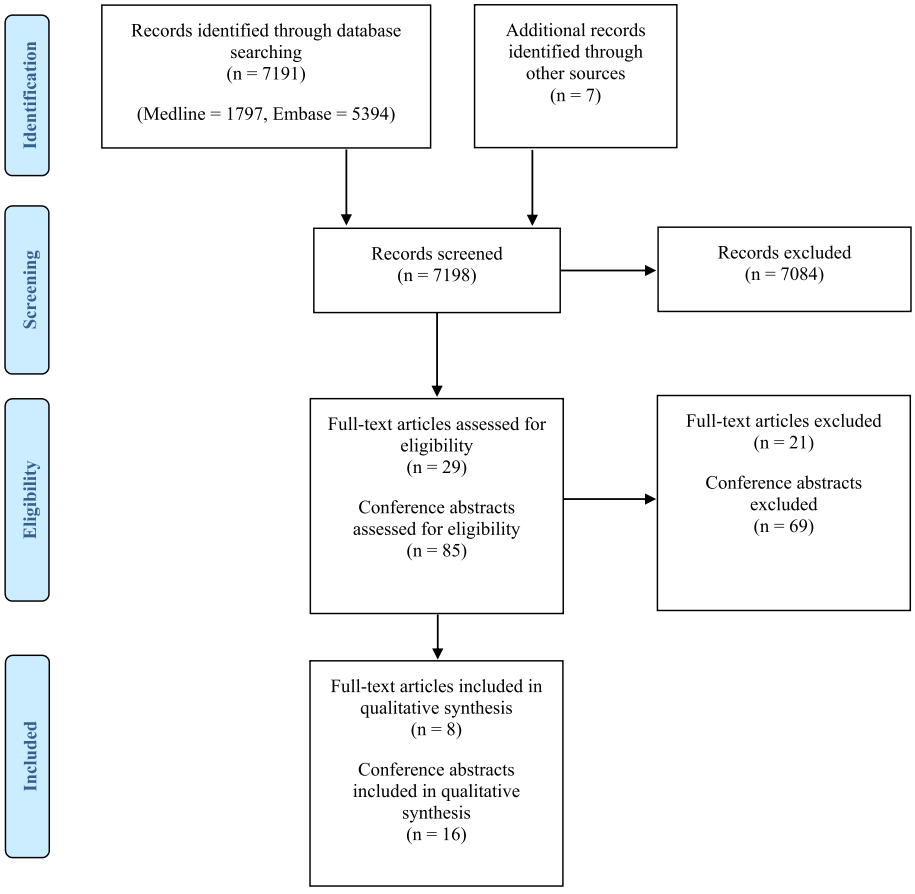

Fig. 1. PRISMA 2009 Flow Diagram.

used to modulate T-cell immune responses [19]. It has been theorized that tumor cells exploit the inhibitory effect of checkpoint regulation to escape immune responses. The rationale behind targeting immune checkpoints is that blockade of the inhibitors ('releasing the brakes') harnesses the endogenous anti-tumor response of the immune system to combat the disease [19]. Several antibodies against immune checkpoints have been approved and others are being investigated. Frequently studied targets of these antibodies are cytotoxic T lymphocyte protein 4 (CTLA-4), programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1). CTLA-4 is a receptor with an inhibitory role for T lymphocyte activation [20]. Thus, blockade of CTLA-4 increases and activates T cells [21]. PD-1 is expressed on T lymphocytes, among other immune cells, and PD-L1 is one of its ligands. The binding of PD-1 and PD-L1 causes an inhibitory signal in T cells. Conversely, an inhibition of PD-1/PD-L1 binding leads to T cell activation and an amplified immune response [22–24].

The lymphocyte activation gene-3 (LAG-3) is the third checkpoint receptor protein to be targeted in the clinic and is proposed to modulate T cell activity through the binding to MHC class II-molecules. There is, however, conflicting evidence regarding the role of LAG-3 in immune modulation. Mice lacking LAG-3 have been found to have normal T cell function [25], but later research still suggests a role for LAG-3 in T cell inhibition [26,27].

Methods

Studies were identified by searching the Medline (1966-present) and Embase (1974-present) databases. We used the following search terms: (1) pancreas cancer and checkpoint inhibitors – including names for specific drugs (ipilimumab, tremelimumab, nivolumab, pembrolizumab, pidilizumab, AMP-224, atezolizumab, durvalumab, avelumab, MEDI4736, IMP321, MEDI6469, relatlimab, spartalizumab), and (2) microsatellite-instable tumors and checkpoint inhibitors. The searches were last performed on November 8th 2018. The reference lists from articles were screened for relevant studies as well.

In addition to the search for completed studies, searches for ongoing clinical trials were made on clinicaltrials.gov. All search strings are shown in Appendix A.

Two authors (AH and DN) screened titles and abstracts for relevant articles. Prospective clinical studies involving checkpoint inhibitors in the treatment of PC were included. Regarding microsatellite-instable tumors, retrospective studies were included as well. Trials with 'solid tumors' were excluded if data for PC patients could not be identified separately. Also, studies on pancreatic neuroendocrine tumors were excluded, as well as studies investigating only indoleamine 2,3-dioxygenase (IDO) inhibitors (or other amino acid degrading enzyme inhibitors). Reviews, case reports, records including less than two PC patients, letters to the editor and editorials were excluded as well. Conference abstracts and preliminary data from studies were included if the inclusion criteria were met, but only if no full-length article was available. In cases where multiple articles or abstracts, utilizing the same data, were published the latest published version was used.

The ongoing trials investigating regimens involving checkpoint inhibitors in the treatment of PC were included. Trials were excluded if the anticipated number of PC patients was prespecified to less than 10.

Data variables that were extracted from studies included: study design, treatment, patient characteristics, number of patients and data on efficacy. Efficacy variables of interest were OS, progression free survival (PFS), time to progression (TTP), objective response rate (ORR), number of patients with complete (CR) or partial response (PR) and number of patients with stable disease (SD). Efficacy measures were calculated based on total number of included patients.

Table 1
Checkpoint inhibitors in pancreatic cancer – published trials.

Trial	Phase	Therapy	Setting	Number of patients	Response	Median PFS/OS in months
Monotherapy						
Royal[29]	II	Ipilimumab	Locally advanced/metastatic 74% pre-treated	27	0% RR 1 delayed response	OS: 4.5
Brahmer[30]	I	BMS-936559	Advanced Pre-treated	14	0% RR	NR
O'Reilly[31] (CA)	II Randomized	Durvalumab vs. Durvalumab + tremelimumab	Metastatic 2nd-line	33	6% DCR	OS: 3.6
				32	9% DCR 3% PR	OS: 3.1
Combination therapy						
CTLA-4 plus PD-1/PD-L1 inhibition						
Duffy[32] (CA)	Pilot study	Durvalumab	Metastatic Pre-treated	24	21% SD	NR
		Durvalumab + tremelimumab + SBRT				
Renouf[33] (CA)	II (safety part)	Durvalumab + tremelimumab + gemcitabine + nab-paclitaxel	Metastatic No prior treatment	11	73% PR 100% DCR	PFS 7.9 (95% CI 3.5–9.2)
Checkpoint inhibition combined with chemotherapy						
Katz[34] (CA)	Ib/II	Pembrolizumab + capecitabine + RT vs. Capecitabine + RT	50% resectable/ 50% borderline resectableNeoadjuvant	14	71% underwent surgery	NR
	randomized			8	50% underwent surgery	
Aglietta[35]	Ib dose escalation	Gemcitabine - > tremelimumab (different doses)	Metastatic No prior treatment	34	21% SD 6% PR	OS: 7.4 (95% CI 5.8–9.4)
Kalyan[36] (CA)	Ib	Ipilimumab + gemcitabine	Advanced	16	13% PR	PFS: 2.5 (95% CI 0.8–4.8)
			No prior gemcitabine in advanced setting		31% SD	OS: 8.5 (95% CI 2.2–10.3)
Weiss[39]	Ib/II	Pembrolizumab + gemcitabine + nab-paclitaxel	Metastatic No prior treatment	12	25% PR 67% SD	PFS: 9.1 (95% CI 4.9–15.3) OS: 15.0 (95% CI 6.8–22.6)
			Pre-treated	5	40% SD	NR
Mahalingam[40] (CA)	II	Pembrolizumab + reolysin + 5-FU Pembrolizumab + reolysin + gemcitabine Pembrolizumab + reolysin + irinotecan	Metastatic 2nd line	11	9% PR 18% SD	NR
Wainberg[41] (CA)	I	Nivolumab + nab-paclitaxel + gemcitabine	Locally advanced/metastatic No prior treatment 24% had ≥ 1% PD-L1 expression 12% had ≥ 5% PD-L1 expression	50	2% CR 16% PR 46% SD	PFS: 5.5 OS: 9.9
Borazanci[42] (CA)	II, pilot	Nivolumab + nab-paclitaxel + cisplatin + gemcitabine + paricalcitol	Metastatic 1st line	10	80% PR 100% DCR	PFS: 8.2
O'Hara[43](CA)	Ib	Gemcitabine + nab-paclitaxel + APX005M (anti-CD40 antibody) +/- nivolumab	Metastatic No prior treatment	30	47% PR 27% SD	NR
Wang-Gillam[44]	I dose escalation		Advanced 1st line			
		Gemcitabine		6	83% SD	OS: 16.7 TTP: 10.2
		Gemcitabine + 0.5 mg IMP321		6	33% SD	OS: 5.6 TTP: 2.0
		Gemcitabine + 2.0 mg IMP321		5	60% SD	OS: 6.4 TTP: 5.3
Checkpoint inhibition combined with other immunotherapy						

(*continued on next page*)

Table 1 (*continued*)

Trial	Phase	Therapy	Setting	Number of patients	Response	Median PFS/OS in months
Le[45]	Ib	Ipilimumab vs. Ipilimumab + vaccine	Advanced/metastatic Pre-treated	15	13% SD	OS: 3.6 (95% CI 2.5–9.2)
	randomized			15	20% SD	OS: 5.7 (95% CI 4.3–14.7)
Overman[46] (CA)	II	Acalabrutinib vs. Pembrolizumab + acalabrutinib	Metastatic Pre-treated	26	15% SD	NR
	randomized			32	9% PR 16% SD	
Nesselhut[47] (CA)	Pilot study	Nivolumab + dendritic cells	Metastatic	7	29% PR	NR
Yamamoto[48] (CA)	I	Nivolumab + mogamulizumab (anti-CC-chemokine receptor 4 antibody)	Advanced/metastatic	15	7% PR 33% SD	NR
Wainberg[49] (CA)	I dose escalation	Nivolumab + cabiralizumab (antibody directed against CSF-1 receptor)	Advanced Pre-treated	31 evaluable	10% PR* 3% SD*	NR
Overman[50] (CA)	I/II	Oleclumab (antibody targeting CD73) +/- durvalumab	Advanced Pre-treated	20	10% PR 15% SD	NR
Naing[51] (CA)	I/II	Durvalumab + epacadostat	Advanced Pre-treated	15	27% SD	NR
Checkpoint inhibition in PC with microsatellite instability/defective mismatch repair						
Cavalieri[55] (CA)	Retrospecti-ve	Pembrolizumab	dMMR	2	50% PR 50% SD	NR
Le[9]	II	Pembrolizumab	Advanced	8	25% CR	NR
			Pre-treated dMMR/MSI positive		37% PR	
					12% SD	
Hu[56]	Retrospecti-ve	PD-L1 inhibitor + IDO1 (amino acid degrading enzyme) inhibitor or PD-1 inhibitor	Advanced	7	14% CR	NR
			Pre-treated		29% PR	
			dMMR		14% SD	

CA: conference abstract, CI: confidence interval, CR: complete response, DCR: disease control rate, dMMR: defective mismatch repair, NR: not reported, OS: overall survival, PC: pancreatic cancer, PD: disease progression, PFS: progressive free survival, PR: partial response, RT: radiotherapy, SBRT: stereotactic body radiation therapy, SD: stabile disease, TTP: time to progression.

* Calculated based on number of evaluable patients, since total number of included patients was not reported.

For ongoing trials, the following data were extracted: study design, patient characteristics, treatment, number of patients, estimated study completion date, study status and primary outcome measures.

Results

The primary search (1) yielded 5548 results (Medline 1363, Embase 4185). The search on microsatellite-instable tumors and checkpoint inhibitors (2) yielded 1643 results (Medline 434, Embase 1209). In addition, six abstracts and one article were identified by reading relevant publications. In total, 7198 records were identified and screened. Eighty-five conference abstracts and 29 articles were assessed for eligibility. In the end, a total of 16 abstracts and eight articles were included in the review (Fig. 1). All included records are summarized in Table 1.

Monotherapy

CTLA-4 inhibitors

Ipilimumab and tremelimumab are human monoclonal CTLA-4-blocking antibodies. Ipilimumab is approved for the treatment of melanoma by the EMA and for the treatment of melanoma and renal cell carcinoma (in combination with nivolumab) by FDA. Tremelimumab is being investigated in trials with several tumor types [28].

We found a single phase II study in which patients with locally advanced or metastatic PC received monotherapy with ipilimumab [29]. Among twenty-seven included patients 74% had received prior gemcitabine-based chemotherapy. No responders were observed by the evaluation criteria, but a delayed response by one subject was reported in which initial progression was followed by regression of both the primary tumor and metastases. Median OS was 4.5 months (Table 1).

PD-1/PD-L1 inhibitors

Pembrolizumab, nivolumab and pidilizumab are humanized monoclonal antibodies targeting PD-1 and thereby inhibiting the interaction of PD-1 and its ligands PD-L1 and PD-L2. Durvalumab, avelumab, atezolizumab as well as BMS-936559 and spartalizumab are human monoclonal antibodies that bind to PD-L1 and block the interaction of PD-1 and CD80 (B7.1) with PD-L1. PD-1/PD-L1 inhibitors are approved by either the FDA, EMA or both for the treatment of various malignancies, the range of which includes melanoma, non-small cell lung cancer, urothelial carcinoma, Merkel cell carcinoma, head and neck squamous cell cancer, classical Hodgkin lymphoma and renal cell carcinoma. Pidilizumab, spartalizumab and BMS-936559 are investigational drugs.

Regarding PD-1/PD-L1 inhibitor monotherapy, two studies on advanced PC were identified. Brahmer et al. [30] tested anti-PD-L1 antibody BMS-936559 in a phase I trial involving 207 patients with different types of advanced cancer. No objective response was reported for 14 patients with PC (Table 1). Preliminary results from part A of a randomized phase II trial on 65 patients with metastatic PC, who had failed first line 5-FU- or gemcitabine-based therapy, were available [31]. Patients were randomized to receive either durvalumab monotherapy or durvalumab in combination with tremelimumab. Median OS was 3.6 and 3.1 months, and disease control rate (DCR, defined as SD + PR + CR) was 6% and 9%, respectively (Table 1).

Ongoing studies

A single randomized phase II study on durvalumab versus observation after R0/R1 resection following neoadjuvant chemotherapy in patients with borderline resectable PC is ongoing (Table 2).

CTLA-4 plus PD-1/PD-L1 inhibition

In a dual inhibition setting, two studies on metastatic PC were found. Results from a pilot study on patients with metastatic PC refractory to chemotherapy included two cohorts treated with checkpoint inhibitors [32]. One cohort received durvalumab monotherapy and the other received combined durvalumab and tremelimumab in combination with stereotactic body radiation at two different schedules (8 Gy/single fraction or 25 Gy in 5 fractions). Twenty-four patients were treated in total. Twenty-one percent, across both cohorts, had SD (Table 1).

The Canadian Cancer Trials Group has published preliminary results from a phase II study with 11 patients with metastatic PC [33]. Patients were planned to be randomized to gemcitabine plus nab-paclitaxel or gemcitabine, nab-paclitaxel, durvalumab and tremelimumab as first line treatment. DCR of 100% including PR of 73% was achieved in patients enrolled in the safety part of the study (Table 1).

Ongoing studies

Seven ongoing studies on dual inhibition in advanced PC were found. Three studies investigate durvalumab + tremelimumab, two of them in combination with radiotherapy. Three ongoing studies evaluate nivolumab + ipilimumab + either radiotherapy, CRS-207 (Listeria-based cancer vaccine) with or without GVAX (irradiated, allogeneic pancreatic cancer cells) and low-dose cyclophosphamide. Lastly, a study compares nivolumab + niraparib (inhibitor of poly (ADP-ribose) polymerase (PARP) types 1 and 2) to ipilimumab + niraparib (Table 2).

Checkpoint inhibition combined with chemotherapy

A single study evaluated pembrolizumab in combination with chemotherapy in the neoadjuvant setting. Patients with resectable/borderline resectable PC were randomized to radiotherapy followed by pembrolizumab in combination with capecitabine or radiotherapy followed by capecitabine [34]. Twenty-two patients were enrolled. Totally, 70% of patients in the pembrolizumab arm underwent surgery compared to 50% of patients in the arm not receiving pembrolizumab (Table 1).

In the advanced setting, eight records were identified, two of which investigated CTLA-4 inhibitors while six investigated PD-1/PD-L1 inhibitors.

Tremelimumab and ipilimumab in combination with gemcitabine have both been evaluated in phase Ib settings, in trials that enrolled 34 (chemotherapy-naive) and 16 (no prior gemcitabine for advanced disease) patients, respectively [35,36]. OS was 7.4 months (95% confidence interval (CI) 5.8–9.4) and 8.5 months (95% CI 2.2–10.3), respectively. In the tremelimumab trial 6% achieved PR and 21% achieved SD (> 10 weeks), while 13% had PR and 31% had SD in the ipilimumab trial. Thus, both RR and DCR were similar to efficacy rates observed in patients receiving gemcitabine monotherapy (RR: 4–15% [18], DCR: 33–51% [37,38]) (Table 1).

Pembrolizumab was combined with gemcitabine and nab-paclitaxel in a phase Ib/II study on 17 patients with metastatic PC [39]. Fifteen patients were evaluable for efficacy and five patients had received prior chemotherapy. For the chemotherapy naive patients, median PFS was 9.1 months (95% CI 4.9–15.3) and OS was 15 months (95% CI 6.8–22.6). PR and SD were 25% and 67%, respectively. Thus, no patients had progressive disease (PD). Response for the previously treated group was 40% SD (Table 1).

A combination of pembrolizumab, reolysin (a reovirus with potential oncolytic activity) and either 5-FU, gemcitabine or irinotecan were given to patients with metastatic PC who had progressed after first line treatment [40]. Eleven patients were included, the majority died due to PD and only five patients were evaluable for efficacy. Nine percent had PR and 18% had SD (Table 1).

Nivolumab was combined with gemcitabine plus nab-paclitaxel in a phase I setting [41]. Forty-two patients with advanced PC out of 50 enrolled were evaluable for response. All patients were treatment naive. PFS and OS were 5.5 and 9.9 months, respectively. Two percent CR, 16% PR and 46% SD were reported (Table 1).

The combination of nivolumab, nab-paclitaxel, cisplatin, gemcitabine and paricalcitol (D-vitamin analog) was tested in a phase II pilot trial on ten patients with untreated metastatic PC [42]. PFS was 8.2 months. The preliminary results showed a DCR of 100%, including 80% PR and 20% SD (Table 1).

In a multi-center phase I study on untreated patients with PC, regimens of gemcitabine, nab-paclitaxel and APX005M (CD40 antibody) with and without nivolumab were tested [43]. Thirty patients were treated. Best responses across all cohorts included 47% PR and 27% SD (Table 1).

Lastly, Wang-Gillam et al. carried out a phase I dose escalation study in which treatment-naive patients with advanced PC were treated with gemcitabine monotherapy or gemcitabine in combination with IMP321 (soluble form of LAG-3) administered at two dose levels [44]. Seventeen patients were enrolled, six receiving only gemcitabine, six receiving gemcitabine plus 0.5 mg IMP321, and five patients receiving gemcitabine + 2.0 mg IMP321. The best responses observed were 83% SD in the gemcitabine only cohort, 33% SD in the 0.5 mg IMP321 cohort, and 60% SD in the 2.0 mg IMP321 cohort. However, no additional activity was observed for the combination of IMP321 with gemcitabine. Median OS was 16.7 months, 5.6 months and 6.4 months in the gemcitabine only cohort, 0.5 mg IMP321 cohort and 2.0 mg IMP321 cohort, respectively (Table 1).

Ongoing studies

Five studies on resectable or potentially resectable PC were found. Two investigate pembrolizumab while the other two investigate avelumab and three investigate nivolumab. Checkpoint inhibitors are combined with chemotherapy, radiotherapy, vaccination and paricalticol among others.

In the advanced setting, 11 different trials on ipilimumab, avelumab, pembrolizumab, nivolumab and durvalumab are ongoing and regimens include radiotherapy, vaccination and treatment with other antibodies than checkpoint inhibitors (Table 2).

Checkpoint inhibition combined with other immunotherapy

We found six studies on checkpoint inhibition in advanced setting. One trial incorporated ipilimumab, and five trials included PD-1/PD-L1 inhibitors.

Le et al. conducted a phase Ib study in which patients with previously treated locally advanced or metastatic PC were randomized to ipilimumab monotherapy or a vaccine consisting of modified allogenic pancreatic tumor cells (GVAX) followed by ipilimumab [45]. OS was 3.6 months (CI 2.5–9.2) in the ipilimumab monotherapy arm versus 5.7 months (95% CI 4.3–14.7) in the GVAX plus ipilimumab arm. There was no statistically significant difference in OS between the two arms. Totally, 13 and 20 percent of the patients obtained SD in the ipilimumab and the vaccine plus ipilimumab arm, respectively (Table 1).

In a randomized phase II study [46] previously treated patients with metastatic PC were randomized to monotherapy with acalabrutinib (bruton tyrosine kinase inhibitor) or combination therapy with pembrolizumab + acalabrutinib. Fifty-eight patients were treated and 44 patients were evaluable for response. Fifteen percent SD were observed in patients receiving monotherapy while 9% PR and 16% SD were observed in patients receiving combination therapy (Table 1).

Nivolumab + either a vaccine made from dendritic cells, mogamulizumab (antibody targeting CC chemokine receptor 4) or cabiralizumab (anti-CSF-1 receptor) were evaluated in three different phase I/pilot trials [47–49]. Between 7 and 31 patients with advanced PC were enrolled and PR was observed in 7–29%, while 3–33% had SD

Table 2
Checkpoint inhibitors in pancreatic cancer – Ongoing trials.

Clinical Trial.gov identifier	Phase	Therapy	Setting	Number of patients	Primary outcome	Estimated completion date, status
Monotherapy						
NCT03038477	II Randomized	Durvalumab vs. observation	Borderline resectable Adjuvant	114	DFS	December 2019 Suspended
CTLA-4 plus PD-1/PD-L1 inhibition						
NCT02868632	I	Durvalumab + SBRT Tremelimumab + SBRT Durvalumab + tremelimumab + SBRT	Unresectable non-metastatic 1st-line	36	OS	February 2020 Recruiting
NCT02311361	I/II	Tremelimumab + SBRT Durvalumab + SBRT Durvalumab + tremelimumab + SBRT	Unresectable metastatic Pre-treated	70	Safety	December 2019 Recruiting
NCT02527434	II	Tremelimumab - > sequenced to durvalumab or to durvalumab + tremelimumab after progressive disease	Metastatic (other solid tumors) Pre-treated	64	ORR	December 2018 Active, not Recruiting
NCT03404960	Ib/II Randomized	Nivolumab + niraparib vs. Ipilimumab + niraparib	Locally advanced or metastatic Pre-treated with platinum-based therapy without PD	84	PFS	June 2021 Recruiting
NCT02866383	II Randomized	Nivolumab + SBRT vs. Nivolumab + ipilimumab + SBRT	Metastatic Pre-treated	80	CBR	November 2020 Recruiting
NCT03190265	II Randomized	Nivolumab + ipilimumab + cyclophosphamide + GVAX + CRS-207 (Listeria-based cancer vaccine) vs. Nivolumab + ipilimumab + CRS-207	Metastatic Pre-treated	63	ORR	October 2019 Recruiting
NCT03104439	II	Nivolumab + ipilimumab + radiotherapy	Advanced (including CRC) Pre-treated	80	DCR	October 2024 Recruiting
Checkpoint inhibition combined with chemotherapy (among others)						
NCT03344172	II Randomized	Avelumab + gemcitabine + nab-paclitaxel + hydroxychloroquin vs. Gemcitabine + nab-paclitaxel + hydroxychloroquin (4-aminoquinoline)	Resectable or borderline resectable Pre-operative	120	Histologic response	January 2021 Recruiting
NCT02930902	Ib	Pembrolizumab + paricalcitol (vitamin D analog) Pembrolizumab + paricalcitol + gemcitabine + nab-paclitaxel	Resectable Preoperative	30	Safety TIL	February 2020 Recruiting
NCT02305186	I/II Randomized	Pembrolizumab + capecitabine + RT vs. Capecitabine + RT	Resectable or borderline resectable Neoadjuvant	56	Safety TIL	June 2019 Recruiting
NCT02451982	I/II Randomized	Nivolumab + cyclophosphamide + GVAX vs. Nivolumab + cyclophosphamide + GVAX + urelumab vs. Cyclophosphamide + GVAX	Stage I or II Preoperative	75	IL17A level	February 2020 Recruiting
NCT03161379	II	Nivolumab + cyclophosphamide + GVAX + SBRT	Borderline resectable Neoadjuvant	50	Pathologic response	September 2019 Recruiting
NCT01473940	I	Ipilimumab + gemcitabine	Unresectable stage III or IV No prior chemotherapy in advanced setting	21	Safety	April 2018 Active, not recruiting
NCT03098160	I	Ipilimumab + evofosfamide	Locally advanced or metastatic (other solid tumors) Pre-treated	69	Recomended dose	April 2019 Recruiting
NCT03329248	Ib/II	Avelumab + adaptive T-cell Therapy (Adenovirus, Yeast, fusionpProtein vaccine) + haNK (high-affinity natural killer cell therapy) + chemotherapy + SBRT	Advanced Pre-treated	80	Safety ORR	December 2019 Active, not recruiting
NCT03387098	I/II	Avelumab + adaptive T-cell Therapy (Adenovirus, Yeast, fusionpProtein vaccine) + haNK (high-affinity natural killer cell therapy) + chemotherapy + SBRT	Advanced Pre-treated	173	Safety ORR	December 2019 Recruiting
NCT03153410	I	Pembrolizumab + cyclophosphamide + GVAX + IMC-CS4 (antibody against CSF-1R)	Borderline resectable Prior treatment with chemo/radiotherapy	12	Safety CD8 T cell density	September 2020 Recruiting
NCT02648282	II	Pembrolizumab + cyclophosphamide + GVAX + SBRT	Locally advanced After 4 cycles mFOLFIRINOX or Gemcitabine/ Abraxane-based chemotherapy	54	Distant metastases free survival	July 2020 Recruiting
NCT02009449	I	Nivolumab & pembrolizumab 23 drug regimens including AM0010 (PEGylated human interleukein-10), pazopanib (protein kinase inhibitor of VEGFR1-3, c-kit and PDGF-R), and various chemotherapy drugs	Advanced PC (other solid tumors)	350	Safety & tolerability PK	March 2020 Active, not recruiting

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Table 2 (*continued*)

Clinical Trial.gov identifier	Phase	Therapy	Setting	Number of patients	Primary outcome	Estimated completion date, status
NCT02309177	I Randomized	Nivolumab + nab-paclitaxel vs. Nivolumab + nab-paclitaxel + gemcitabine	Locally advanced or metastatic (other solid tumors) 1st-line (gemcitabine cohort) 2nd-line (nab-paclitaxel + gemcitabine cohort)	118	Safety & tolerability	October 2018 Completed
NCT03336216	II Randomized	Nivolumab + cabiralizumab (anti-CSF-1 receptor) vs. Nivolumab + cabiralizumab + gemcitabine + nab-paclitaxel / 5-fluorouracil + leucovorin + oxalipatin vs. Gemcitabine + nab-paclitaxel / 5-fluorouracil + leucovorin + irinotecan hydrochloride (or onivyde)	Locally advanced or metastatic 2nd-line	160	PFS	December 2020 Recruiting
NCT03376659	I/II	Durvalumab + CV301 (vaccine-based immunotherapeutic targeting tumor-associated antigens, CEA and MUC-1) + capecitabine + bevacizumab Durvalumab + CV301 + capecitabine	Metastatic (including CRC) Maintenance after 1st-line	54	PFS Recommended dose	December 2023 Recruiting
NCT03214250	I/II Randomized	APX005M (anti-CD40 antibody) + gemcitabine + nab-paclitaxel APX005M + gemcitabine + nab-paclitaxel + nivolumab	Metastatic 1st-line	105	Safety OS	September 2022 Recruiting
Checkpoint inhibition combined other therapy						
NCT03373188	I Randomized	Nivolumab + anti-SEMA4D monoclonal antibody VX15/2503 + surgery vs. Ipilimumab + anti-SEMA4D monoclonal antibody VX15/2503 + surgery vs. Anti-SEMA4D monoclonal antibody VX15/2503 + surgery vs.Surgery	Resectable (other solid tumors) Preoperative	32	CD8 T cell density	December 2022 Recruiting
NCT01896869	II Randomized	Ipilimumab + GVAX vs. FOLFIRINOX	Metastatic Pre-treated with 8–12 doses of FOLFIRINOX without PD	83	OS	December 2019 Suspended (On hold during interim analysis)
NCT03193190	Ib/II Randomized	Cohorte 1: Atezolizumab + selicrelumab (CD40 agonist) + gemcitabine + nab-paclitaxel vs. Atezolizumab + selicrelumab + bevacizumab + gemcitabine + nab-paclitaxel vs. Atezolizumab + bevacizumab + gemcitabine + nab-paclitaxel vs. Atezolizumab + emactuzumab (antibody directed against the CSF-1R) + gemcitabine + nab-paclitaxel vs. Gemcitabine + nab-paclitaxel Cohorte 2: Atezolizumab + cobimetinib (inhibitor of mitogen-activated protein kinase kinase 1) vs. Atezolizumab + PEGPH20 (recombinant hyaluronidase) vs. Atezolizumab + BL-8040 (inhibitor of CXC Chemokine Receptor 4) vs. Atezolizumab + RO6874281 (engineered variant of interleukin-2 targeting fibroblast activation protein) vs. Atezolizumab + emactuzumab vs. Gemcitabine + nab-paclitaxel or mFOLFOX6	Metastatic Cohort 1: 1st-line Cohort 2: 2nd-line	205	ORR Safety	September 2020 Recruiting
NCT03481920	I	Avelumab + PEGPH20 (recombinant hyaluronidase)	Advanced	24	ORR Safety	August 2019 Recruiting
NCT02600949	I	Pembrolizumab + vaccine (made from tumor cells) Vaccine	Metastatic (other solid tumors)	60	Toxicity Vaccine development	May 2022 Recruiting
NCT02546531	I	Pembrolizumab + defactinib (focal adhesion kinase inhibitor) + gemcitabine	Advanced	50	Recomended dose	July 2020 Recruiting
NCT02646748	I	Pembrolizumab + itacitinib (JAK1 inhibitor) Pembrolizumab + INCB050465 (inhibitor of phosphoinositide-3 kinase)	Advanced or metastatic (other solid tumors)	237	Safety	August 2019 Recruiting
NCT02009449	I	Pembrolizumab + AM0010 (conjugate of IL-10 and polyethylene glycol)	Advanced (other solid tumors)	350	PK Safety	March 2020 Active, not recruiting
NCT03454451	I Randomized	Pembrolizumab + CPI-006 (inhibitor of CD73 and adenosine production) vs. CPI-006	Advanced (other solid tumors)	378	AE's DLTs Dose level	December 2023 Recruiting
NCT02713529	Ib/II	Pembrolizumab + AMG820 (antibody against colony-stimulating factor-1 receptor c-fms)	Advanced (other solid tumors)	116	AE's ORR	May 2020 Active, not recruiting
NCT03168139	I/II	Pembrolizumab + olaptesed pegol (targets chemokine stromal cell-derived factor 1)	Stage IV with liver metastases (other solid tumors)	20	PK Safety	March 2022 Recruiting

(*continued on next page*)

Table 2 (*continued*)

Clinical Trial.gov identifier	Phase	Therapy	Setting	Number of patients	Primary outcome	Estimated completion date, status
NCT02758587	I/II	Pembrolizumab + defactinib (focal adhesion kinase inhibitor)	Advance (other solid tumors)	59	AE's	December 2021 Recruiting
NCT03264404	II	Pembrolizumab + azacitidine (pyrimidine nucleoside analogue of cytidine)	Advanced	31	PFS	September 2019 Recruiting
NCT02907099	II	Pembrolizumab + BL-8040 (inhibitor of CXC Chemokine Receptor 4)	Metastatic 2nd-line	15	ORR	December 2019 Recruiting
NCT02826486	II	Pembrolizumab + BL-8040 (inhibitor of CXC Chemokine Receptor 4)	Metastatic Pre-treated	37	ORR	December 2018 Active, not recruiting
NCT01174121	II	Pembrolizumab + TIL TIL	Metastatic (other solid tumors) Pre-treated	332	Tumor regression	December 2024 Recruiting
NCT03432676	II	Pembrolizumab + epacadostat (inhibitor of indoleamine 2,3-dioxygenase)	Advanced with chromosomal instability/ homologous recombination repair deficiency Pre-treated	21	OR	April 2021 Withdrawn
NCT02362048	II Randomized	Pembrolizumab + acalabrutinib (inhibitor of Bruton's tyrosine kinase) vs. Acalabrutinib	Metastatic Pre-treated	73	AE's	September 2017 Active, not recruiting
NCT03331562	II Randomized	Pembrolizumab + paricalcitol (vitamin D analog) vs. Pembrolizumab + placebo	Metastatic 2nd-line	24	Disease progression	December 2019 Recruiting
NCT03006302	II Randomized	Pembrolizumab + epacadostat (inhibitor of indoleamine 2,3-dioxygenase) + CY + GVAX + CRS-207 (Listeria-based cancer vaccine) vs. Pembrolizumab + epacadostat + CRS-207	Metastatic 2nd-line	70	Recomended dose Survival	June 2023 Recruiting
NCT02526017	I	Nivolumab + cabiralizumab (anti-CSF-1 receptor) Cabiralizumab	Advanced (other solid tumors) Pre-treated	295	ORR Recomended dose Safety	March 2020 Active, not recruiting
NCT03184870	I/II	Nivolumab + BMS-813160 (antagonist of C-C chemokine receptor types 2 and 5) BMS-813160	Metastatic (including CRC)	260	AE's Death ORR PFS	December 2021 Recruiting
NCT03098550	I/II	Nivolumab + daratumumab (antibody against glycoprotein CD-38)	Metastatic (other solid tumors)	120	AE's Laboratory abnormalities	August 2020 Active, not recruiting
NCT02465060	II	Nivolumab + various biological drugs	Advanced (other solid tumors) Pre-treated	6452	ORR	June 2022 Recruiting
NCT03250273	II	Nivolumab + entinostat (inhibitor of histone deacetylase)	Metastatic or unresectable (other solid tumors)	54	ORR	November 2020 Recruiting
NCT02777710	I	Durvalumab + pexidartinib (tyrosine kinase inhibitor of KIT, CSF1R and FLT3)	Advanced or metastatic (other solid tumors) Pre-treated	58	DLTs ORR	June 2019 Recruiting
NCT02734160	Ib	Durvalumab + galunisertib (tyrosine kinase transforming growth factor-beta receptor type 1 antagonist)	Metastatic	37	DLTs	June 2019 Recruiting
NCT02403271	Ib/II	Durvalumab + ibrutinib (Bruton's tyrosine kinase inhibitor)	Stage III or IV (other solid tumors) Pre-treated	124	AE's ORR	August 2017 Completed
NCT03245541	I/II	Durvalumab + stereotactive ablative radiatiotherapy	Locally advanced unresectable or borderline resectable Pre-treated Preoperative	30	DLTs PFS Resectability	September 2021 Recruiting
NCT02983578	II	Durvalumab + AZD9150 (antisense oligonucleotide targeting signal transducer and activator of transcription 3)	Advanced Pre-treated	75	DCR Tumor biomarker	March 2021 Recruiting

AE's: adverse events, CBR: clinical benefit rate, CRC: Colorectal Cancer, CSF-1R: colony stimulating factor 1 receptor, DCR: disease control rate, DFS: disease free survival, DLTs: dose limiting toxicities, GVAX: autologous vaccine made from modified pancreatic cancer cells, OR: objective response, ORR: objective response rate, OS: overall survival, PC: pancreatic cancer, PD: progressive disease, PK: Pharmacokinetic, PFS: progressive free survival, SBRT: stereotactic body radiation therapy, TIL: tumor infiltrating lymphocytes, VEGF: vascular endothelial growth factor.

(Table 1).

Preliminary results were published from a phase I study on oleclumab (antibody that binds to CD73 and inhibits adenosine production) with or without durvalumab [50]. Out of 20 evaluable patients with advanced PC, 10% had PR and 15% had SD.

Finally, durvalumab was combined with the IDO inhibitor epacadostat in a phase I/II study from which preliminary results have been published [51]. Fifteen patients with advanced PC were included and 27% had SD.

Ongoing studies

One randomized phase I trial is investigating the effect of nivolumab or ipilimumab plus a potentially immune enhancing antibody (anti-SEMA4D monoclonal antibody VX15/2503) in patients with surgically resectable PC.

In advanced or metastatic PC, ipilimumab, atezolizumab and avelumab are investigated in three separate trials, but pembrolizumab is the most frequently investigated checkpoint inhibitor (16 trials), and it is among other things combined with epacadostat in two different studies.

Other frequently used drugs are nivolumab and durvalumab with five studies in progress for each drug (Table 2).

Checkpoint inhibition in pancreatic tumors with microsatellite instability/ defective mismatch repair

Microsatellites are a class of DNA-segments characterized by small repeat segments scattered throughout the genome. The instability at these DNA-sites (microsatellite instability, MSI) has been proposed as a significant factor in other cancer types e.g. colorectal cancer [52,53]. Tumor cells with a high number of alterations in the microsatellite loci have been shown to have errors in the cellular mismatch repair machinery, suggesting a link between MSI and defective mismatch repair (dMMR) [54].

Data from a retrospective study regarding various gastrointestinal malignancies with dMMR has been presented [55]. The research group identified nine patients who had received pembrolizumab. Two of the identified patients had PC. One PC patient had PR (duration = 11 months) and the other had SD (duration = 5 months) (Table 1).

From a study on dMMR/MSI positive tumors, eight patients with PC who received pembrolizumab was identified [9]. All had advanced disease and had been treated prior to inclusion in the trial. A DCR of 75% was achieved, including 25% CR, 37% PR and 12% SD (Table 1).

More recently, Hu et al. analyzed MSI status in 833 patients with PC. Only 7 cases of dMMR were detected (0.8%) [56]. All patients were found to have Lynch Syndrome. Four (57%) were found to have benefit of mono- or combination therapy with a PD-1 or PD-L1 inhibitor (1 CR, 2 PR, 1 SD) (Table 1).

Discussion

In general, the level of evidence is low when considering the effect of checkpoint inhibitors in the treatment of PC. Often, a very small number of patients were enrolled in the studies and overall, few prospective studies have been published. Thus, any conclusions based on this literature involves a significant amount of uncertainty. Even so, the potential for checkpoint inhibition monotherapy in PC seems limited, as a significant effect on clinical response and survival is lacking. This notion is supported elsewhere [18,24,57,58] and is reflected in the fact that very few ongoing studies utilize monotherapy (see Table 2). More attention has been given to checkpoint inhibitors combined with other modalities, but no clear strategy stands out. Methods to improve checkpoint inhibition regimens include targeting both CTLA-4 and the PD-1/PD-L1 pathways simultaneously. Indeed, a very high DCR was found in treatment-naive patients who were given durvalumab, tremelimumab, nab-paclitaxel and gemcitabine [33], but similar results were not found in previously treated patients receiving durvalumab, tremelimumab and radiotherapy [32]. A comparably high DCR was shown in untreated patients with metastatic PC receiving gemcitabine, nab-paclitaxel, paricalcitol and nivolumab [42]. Another interesting result was reported by Katz et al. in a study on resectable disease, where 71% of patients receiving neoadjuvant pembrolizumab, capecitabine and radiotherapy underwent surgery opposed to only 50% of the patients who received capecitabine and radiotherapy. One study [39] found a higher OS in chemotherapy-naive patients receiving combination of pembrolizumab, gemcitabine and nab-paclitaxel than the OS reported in patients receiving FOLFIRINOX [37].

These findings could indicate a possible effect of adding checkpoint inhibitors to standard PC treatment. But to what degree these results should be attributed to checkpoint inhibition remains to be shown in randomized studies with a greater number of patients included. Even given a possible effect of targeting multiple checkpoints, the risk of adverse side effects, which have been highlighted as being more frequent and more severe when combining checkpoint inhibitors, should be considered [59].

Immunogenicity

The tumor microenvironment in pancreatic cancer

The stroma in PC consists of cells, such as pancreatic stellate cells (PSCs) and immune cells, acellular components, blood vessels and nerves [60]. The relationship between these cellular and acellular elements is intricate. PSCs are thought to inhibit immune response, both by reducing CD8 + T-cell infiltration and promoting regulatory T cell (Treg) infiltration into the tumor milieu [61,62]. However, the tumor-promoting effect of PSCs might be time and context dependent and thus complicated [63]. Tregs are capable of immune regulation and are considered immunosuppressive cells, a group that also include PSCs as well as myeloid derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs) and mast cells. These cells can induce a favorable environment for cancer by inhibiting the immune system – via either checkpoint molecules or a more general anti-inflammatory effect – or by providing cytokines and growth factors that sustain tumor cells directly. The immunosuppressive cells can also promote angiogenesis [64,65].

Because PC has been described as a tumor type with an abundance of immunosuppressive mechanisms [57], attention has been drawn to this complex PC tumor microenvironment (TME) since it is thought to serve as an obstacle to successful systemic therapy [60]. Bailey et al. classified PC into four types based on expression patterns, and one subtype (the “immunogenic”) was characterized by upregulation of acquired immune suppression networks [66]. It has been hypothesized that a non-immunogenic TME contributes to a dampened immune response, exemplified by a low number of infiltrating T cells in PC compared to other solid malignancies [67]. This theory is supported by the fact that a research group found tumor infiltrating lymphocytes (TILs) being trapped in peritumoral tissues, thus, not being able to reach tumor cells [68]. On the other hand, high quality neo-antigen presentation in the TME (as opposed to just high quantity) identified long term PC survivors, and it has been hypothesized that targeting such neo-antigens can improve efficacy of checkpoint inhibitors in PC [69].

Interestingly, the focus on the TME has challenged the idea of traditional radio-chemotherapy as having only an immune suppressing effect. This leads to the notion that this treatment could also promote immune response via influence of the microenvironment. Chemotherapeutic drugs, such as gemcitabine and paclitaxel and radiotherapy have been able to facilitate tumor immunogenicity. The “abscopal effect” refers to the possibility of inducing an enhanced immune response because of antigens released from destroyed tumor cells

due to radiation [70]. This leaves a hypothetical role for checkpoint inhibition given in a combination with chemotherapy or radiation [71,72].

Antigenicity

It has been proposed that cancer cells characterized by dMMR express more immunogenic antigens and thus are more susceptible to immune therapy [18]. Interestingly, it has been shown that dMMR status predicts response to PD-1 blockade in solid tumors [9].

A link between MSI/dMMR and the targets of checkpoint inhibition has been established. Colorectal cancer tumor cells with MSI/dMMR contained a high infiltration of cytotoxic T lymphocytes (CTLs) and the MSI tumors even had upregulated expression of PD-1, PD-L1, CLTA-4 and LAG-3 [73]. Mismatch-repair status has been found to predict clinical benefit from pembrolizumab in a phase II study [74] on metastatic carcinomas (involving both colorectal cancer with and without dMMR as well as other carcinomas with dMMR). In addition, pembrolizumab and nivolumab are FDA-approved for the treatment of tumors with dMMR or MSI [75,76]. Tumor mutational burden (TMB) is a metric related, but not identical, to MSI-status, which has been hypothesized to predict response to checkpoint inhibition [77]. Interestingly, a higher TMB was associated with better response in non-small cell lung cancer patients receiving pembrolizumab [78], and with clinical benefit in malignant melanoma patients receiving either ipilimumab or tremelimumab [79]. A high degree of mutation, as seen in tumors with dMMR or high TMB, has been theorized to elicit an anti-tumor immune response directed against neoantigens on cancer cells which could be enhanced with immune checkpoint blockade [74]. In PC, dMMR was present in only 1.6% of tumors [8], and PC was also shown to have a low TMB compared to other malignancies [77]. Thus, future efforts must be supportive on better understanding and modulation of mutation associated neoantigen-specific immunity.

PD-L1 expression

A possible role for PD-L1 as a predictive biomarker in treatment with PD-1/PD-L1 inhibiting antibodies is being investigated. A recent meta-analysis of patients with malignant melanoma or non-small cell lung cancer demonstrated a significant association between the expression of PD-L1 and response to PD-1/PD-L1 blockade. In PC, TILs have been inversely correlated with PD-L1 expression, and several study groups found a correlation between PD-L1 expression and poor prognosis [80–82]. But studies showing a correlation between PD-L1 expression and response to checkpoint inhibition treatment in PC are lacking. Of note, PD-L1 expression in various tumors normally considered for checkpoint inhibition therapy ranged widely between 14 and 100%. Also, consensus for a cut-off value for determining whether a tumor is PD-L1-positive or -negative does not exist, which presents a challenge in comparing studies utilizing different values. High PD-L1 expression does not guarantee response and low or no PD-L1 expression does not exclude the possibility of response in tumors [83]. These issues has led to the investigation of PD-L1 expression in exosomes, which has been found to be associated with response to PD-1 blockade [84].

Other targets for immune therapy

Arginase (ARG) and IDO are two amino acid degrading enzymes that, like immune checkpoints, have influence on immunogenic tolerance and contribute to T-cell functionality. These enzymes are theorized to have negative regulatory roles in the TME and they could be considered targets for therapy [85]. Indeed, the IDO1-inhibitor epacadostat was included in a completed study [51] (Table 1) as well as in two ongoing studies (Table 2. NCT03006302, NCT03432676) in advanced PC.

The increased activity of T cells caused by oleclumab (MEDI9447) has already led to inclusion of this adenosine-decreasing drug into clinical trials [50,86]. Noteworthy monoclonal antibodies with T cell modulating and potential anti-neoplastic effect include urelumab, varlilumab and zanolimumab [87–92]. The antibody FG-3019 targets connective tissue growth factor and has been tested in PC patients [93,94].

Conclusion

The literature in this field compromise relatively few studies that furthermore often include a small number of patients. Monotherapy with checkpoint inhibitors in PC has failed to elicit a significant response. Furthermore, when looking at different combination regimens most of the studies do not find an improvement in survival compared to standard of care. Even so, a few studies point to a possible effect of implementing immunotherapy in combination with chemotherapy and/or radiation, since a few cases of high DCR and also occasional high ORR were reported. The idea of chemo-radiotherapy as a booster of immune response supports such combination regimens, and ongoing studies on checkpoint inhibitors in PC are numerous. Finally, identification of biomarkers that differentiate tumors based on their responsiveness to immunotherapy could be a way to improve the efficiency of this treatment.

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Declaration of Competing Interest

All authors declare no conflicts of interest.

Appendix A:. Search strings

Medline searches
Pancreas cancer and checkpoint inhibitors:

((((((((((((((((((((((((((((((((((((immunotherapy[MeSH Terms]) OR immunotherap*) OR checkpoint inhib*)) OR ipilimumab) OR tremelimumab) OR nivolumab) OR pembrolizumab) OR pidilizumab) OR AMP-224) OR atezolizumab) OR durvalumab) OR avelumab) OR MEDI4736) OR IMP321) OR MEDI6469) OR relatlimab) OR BMS-986016) OR spartalizumab) OR PDR001))) AND Humans[Mesh] AND English[lang])) AND ((Pancreatic neoplasms[MeSH Terms]) OR ((((((((((Cancer*) OR carcinoma[MeSH Terms]) OR Carcinoma*) OR malign*) OR tumor*) OR adenocarcinoma[MeSH Terms]) OR adenocarcinom*) OR neoplasms[MeSH Terms]) OR neoplasm*)) AND ((pancrea*) OR pancreas[MeSH Terms])))) AND Humans[Mesh] AND English[lang])) AND ((Pancreatic neoplasms[MeSH Terms]) OR ((((((((((Cancer*) OR carcinoma[MeSH Terms]) OR Carcinoma*) OR malign*) OR tumor*) OR adenocarcinoma[MeSH Terms]) OR adenocarcinom*) OR neoplasms[MeSH Terms]) OR neoplasm*)) AND ((pancrea*) OR pancreas[MeSH Terms])))) AND Humans[Mesh] AND English[lang])) AND Humans[Mesh] AND English[lang]) AND Humans[Mesh] AND English[lang])

MSI/dMMR and checkpoint inhibitors:

((((((((((((((dna mismatch repair[MeSH Terms]) OR (((dna) AND mismatch) AND repair)) OR dna mismatch repair) OR ((mismatch) AND repair))) OR ((mismatch repair) AND deficient)) OR microsatellite instability[MeSH Terms])) OR ((microsatellite) AND instability)) OR microsatellite instability)) AND ((((((((((((((immunotherapy[MeSH Terms]) OR immunotherap*) OR checkpoint inhibit*) OR ipilimumab) OR tremelimumab) OR nivolumab) OR pembrolizumab) OR pidilizumab) OR AMP-224) OR atezolizumab) OR durvalumab) OR avelumab) OR MEDI4736) OR IMP321) OR MEDI6469) OR relatlimab) OR BMS-986016) OR spartalizumab) OR PDR001)

Embase searches
Pancreas cancer and checkpoint inhibitors:

1	MEDI6469.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	25	BMS-986016.mp. or relatlimab/
2	IMP321.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	26	spartalizumab.mp. or spartalizumab/
3	MEDI4736.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word	27	PDR001.mp.
4	avelumab/	28	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
5	avelumab.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	29	carcinoma/ or solid malignant neoplasm/ or adenocarcinoma/
6	durvalumab/	30	malignant neoplasm/ or neoplasm/ or solid malignant neoplasm/
7	durvalumab.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	31	cancer.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
8	atezolizumab/	32	carcinoma.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
9	atezolizumab.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	33	malignan*.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
10	AMP-224.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	34	tumor.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
11	pidilizumab/	35	adenocarcinoma.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
12	pidilizumab.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	36	neoplasm*.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
13	pembrolizumab/	37	29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
14	pembrolizumab.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	38	pancreas/
15	nivolumab/	39	pancrea*.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
16	nivolumab.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	40	38 or 39
17	ticilimumab/	41	pancreas tumor/ or pancreas cancer/
18	tremelimumab.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	42	pancreas cancer/
19	ipilimumab/	43	pancreas adenocarcinoma/ or pancreas carcinoma/
20	ipilimumab.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	44	pancreatic neoplasm*.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
21	immunotherapy/ or biological therapy/ or cancer immunotherapy/	45	37 and 40
22	immunotherap*.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	46	41 or 42 or 43 or 44 or 45
23	checkpoint inhibit*.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	47	28 and 46
24	relatlimab.mp. or relatlimab/	48	limit 47 to (human and english language)

MSI/dMMR and checkpoint inhibitors:			
1	MEDI6469.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	25	relatlimab.mp. or relatlimab/
2	IMP321.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	26	BMS-986016.mp. or relatlimab/
3	MEDI4736.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word	27	spartalizumab.mp. or spartalizumab/
4	avelumab/	28	PDR001.mp.
5	avelumab.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	29	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
6	durvalumab/	30	microsatellite instability/
7	durvalumab.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	31	microsatellite instability.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
8	atezolizumab/	32	mismatch repair/
9	atezolizumab.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	33	mismatch repair deficient.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
10	AMP-224.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	34	30 or 31 or 32 or 33
11	pidilizumab/	35	29 and 34
12	pidilizumab.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	36	
13	pembrolizumab/	37	
14	pembrolizumab.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	38	
15	nivolumab/	39	
16	nivolumab.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	40	
17	ticilimumab/	41	
18	tremelimumab.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	42	
19	ipilimumab/	43	
20	ipilimumab.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	44	
21	cancer immunotherapy/ or immunotherapy/	45	
22	biological therapy/	46	
23	immunotherap*.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	47	
24	checkpoint inhibit*.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	48	

Clinicaltrials.gov – Searches

The searches on ongoing clinical trials regarding (1) pancreas cancer and (2) microsatellite-instable/tumors with mismatch repair deficiency were conducted as such: the keywords entered as 'condition or disease' (namely, (1): "pancreas cancer" and (2): both "microsatellite instability" and "dMMR") were one by one paired with each and every one of 16 keywords entered as 'other terms' (namely, "immunotherapy", "checkpoint inhibitor", "ipilimumab", "tremelimumab", "nivolimumab", "pembrolizumab", "pidilizumab", "AMP-224", "atezolizumab", "durvalumab", "avelumab", "MEDI4736", "IMP321", "MEDI6469", "relatlimab", "BMS-986016").

References

[1] Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Euro J Cancer (Oxford, England: 1990) 2013;49:1374–403.

[2] American Cancer Society. Cancer Facts & Figures (2018). https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2018.html. Accessed December 18, 2018.

[3] Pancreaticic cancer action network. Pancreatic cancer facts (2016). https://www.pancan.org/wp-content/uploads/2016/02/2016-GAA-PC-Facts.pdf. Accessed December 18, 2018.

[4] Pancreatic cancer action network. The alarming rise of pancreatic cancer deaths in the united states: why we need to stem the tide today (2012). https://www.pancan.org/wp-content/uploads/2013/01/incidence_report_2012_executive_summary.pdf. Accessed December 18, 2018.

[5] Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014;74:2913–21.

[6] American Cancer Society. Types of pancreatic cancer (2018). https://www.cancer.org/cancer/pancreatic-cancer/about/what-is-pancreatic-cancer.html#references. Accessed December 18, 2018.

[7] L. SR, D. MK, Ahmedin J. Cancer statistics. CA Cancer J Clin 2017;67(2017):7–30.

[8] Lupinacci RM, Goloudina A, Buhard O, Bachet JB, Marechal R, Demetter P, et al. Prevalence of microsatellite instability in intraductal papillary mucinous neoplasms of the pancreas. Gastroenterology 2018;154:1061–5.

[9] Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, et al. Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017;357:409–13.
[10] Seufferlein T, Bachet JB, Van Cutsem E, Rougier P. Pancreatic adenocarcinoma: ESMO-ESDO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol: Offic J Euro Soc Med Oncol 2012;23(Suppl 7):vii33–40.
[11] Schorn S, Demir IE, Samm N, Scheufele F, Calavrezos L, Sargut M, et al. Meta-analysis of the impact of neoadjuvant therapy on patterns of recurrence in pancreatic ductal adenocarcinoma. BJS Open 2018;2:52–61.
[12] Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC-c, Raoul J-L, et al. Unicancer GI PRODIGE 24/CCTG PA.6 trial: a multicenter international randomized phase III trial of adjuvant mFOLFIRINOX versus gemcitabine (gem) in patients with resected pancreatic ductal adenocarcinomas. J Clin Oncol 2018;36:LBA4001.
[13] Ducreux M, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goéré D, et al. Cancer of the pancreas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up†. Ann Oncol 2015;26:v56–68.
[14] Wang-Gillam A, Li C-P, Bodoky G, Dean A, Shan Y-S, Jameson G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet 2016;387:545–57.
[15] U.S. Food and drug administration. Highlights of prescribing information on ONIVYDE™ (irinotecan liposome injection), (2015).
[16] European Medicines Agency. Summary of Europen public assessment report (EPAR) for Onivyde (irinotecan). (2016).
[17] M.K. Siegel RL, Jemal A, Cancer statistics, 2016. CA Cancer J Clin. 2016 Jan-Feb;66(1):pp. 7–30. doi: 10.3322/caac.21332. Epub 2016 Jan 7.
[18] Chiaravalli M, Reni M, O'Reilly EM. Pancreatic ductal adenocarcinoma: state-of-the-art 2017 and new therapeutic strategies. Cancer Treat Rev 2017;60:32–43.
[19] Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:252.
[20] Tivol EA, Borriello F, Schweitzer AN, Lynch WP, Bluestone JA, Sharpe AH. Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4. Immunity 1995;3:541–7.
[21] European Medicines Agency. Summary of European public assessment report (EPAR) for Yervoy (ipilimumab), (Updated December, 2017).
[22] Borch TH, Donia M, Andersen MH, Svane IM. Reorienting the immune system in the treatment of cancer by using anti-PD-1 and anti-PD-L1 antibodies. Drug Discov Today 2015;20:1127–34.
[23] Schildberg Frank A, Klein Sarah R, Freeman Gordon J, Sharpe Arlene H. Coinhibitory pathways in the B7-CD28 ligand-receptor family. Immunity 2016;44:955–72.
[24] Belinda Lee RH, Wong Hui-Li, Tie Jeanne, Putoczki Tracy, Tran Ben, Gibbs Peter, Cristie Michael. Emerging biomarkers for immunomodulatory cancer treatment of upper gastrointestinal. Pancreatic Hepatic Cancers 2017.
[25] Miyazaki T, Dierich A, Benoist C, Mathis D. Independent modes of natural killing distinguished in mice lacking Lag3. Science 1996;272:405.
[26] Workman CJ, Dugger KJ, Vignali DAA. Cutting edge: molecular analysis of the negative regulatory function of lymphocyte activation gene-3. J Immunol 2002;169:5392–5.
[27] J. WC, A. VDA. The CD4-related molecule, LAG-3 (CD223), regulates the expansion of activated T cells. Eur J Immunol 2003;33:970–9.
[28] Comin-Anduix B, Escuin-Ordinas H, Ibarrondo FJ. Tremelimumab: research and clinical development. OncoTargets Therapy 2016;9:1767–76.
[29] Royal RE, Levy C, Turner K, Mathur A, Hughes M, Kammula US, et al. Phase 2 trial of single agent ipilimumab (Anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. J Immunother 2010;33:828–33.
[30] Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. New England J Med 2012;366:2455–65.
[31] O'Reilly EM, Oh D-Y, Dhani N, Renouf DJ, Lee MA, Sun W, et al. A randomized phase 2 study of durvalumab monotherapy and in combination with tremelimumab in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC): ALPS study. J Clin Oncol 2018;36:217-217.
[32] Duffy AG, Makarova-Rusher OV, Kleiner DE, Alewine C, Figg WD, Steinberg SM, et al. A pilot study of immune checkpoint inhibition in combination with radiation therapy in patients with metastatic pancreatic cancer. J Clin Oncol Conf 2017;35.
[33] Renouf DJ, Dhani NC, Kavan P, Jonker DJ, Wei AC-c, Hsu T, et al. The Canadian cancer trials group PA.7 trial: results from the safety run in of a randomized phase II study of gemcitabine (GEM) and nab-paclitaxel (Nab-P) versus GEM, nab-P, durvalumab (D), and tremelimumab (T) as first-line therapy in metastatic pancreatic ductal adenocarcinoma (mPDAC). J Clin Oncol 2018;36:349-349.
[34] Katz MHG, Varadhachary GR, Bauer TW, Acquavella N, Merchant NB, Le TM, et al. Preliminary safety data from a randomized multicenter phase Ib/II study of neoadjuvant chemoradiation therapy (CRT) alone or in combination with pembrolizumab in patients with resectable or borderline resectable pancreatic cancer. J Clin Oncol Conf 2017;35.
[35] Aglietta M, Barone C, Sawyer MB, Moore MJ, Miller WH, Bagala C, et al. A phase I dose escalation trial of tremelimumab (CP-675,206) in combination with gemcitabine in chemotherapy-naive patients with metastatic pancreatic cancer. Ann Oncol 2014;25:1750–5.
[36] Kalyan A, Kircher SM, Mohindra NA, Nimeiri HS, Maurer V, Rademaker A, et al. Ipilimumab and gemcitabine for advanced pancreas cancer: a phase Ib study. J Clin Oncol Conf 2016;34.
[37] Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817–25.
[38] Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369:1691–703.
[39] Weiss GJ, Blaydorn L, Beck J, Bornemann-Kolatzki K, Urnovitz H, Schutz E, et al. Phase Ib/II study of gemcitabine, nab-paclitaxel, and pembrolizumab in metastatic pancreatic adenocarcinoma. Invest New Drugs 2018;36:96–102.
[40] Mahalingam D, Fountzilas C, Moseley JL, Noronha N, Cheetham K, Dzugalo A, et al. A study of REOLYSIN in combination with pembrolizumab and chemotherapy in patients (pts) with relapsed metastatic adenocarcinoma of the pancreas (MAP). J Clin Oncol Conf 2017;35.
[41] Wainberg ZA, Hochster HS, Kim E, George B, Kalyan A, Chiorean EG, et al. Phase I study of nivolumab (nivo) + nab-paclitaxel (nab-P) + gemcitabine (Gem) in advanced pancreatic cancer (APC). J Clin Oncol 2019;37(4_suppl):298-298.
[42] Borazanci EH, Jameson GS, Borad MJ, Ramanathan RK, Korn RL, Caldwell L, et al. A phase II pilot trial of nivolumab (N) + albumin bound paclitaxel (AP) + paricalcitol (P) + cisplatin (C) + gemcitabine (G) (NAPPCG) in patients with previously untreated metastatic pancreatic ductal adenocarcinoma (PDAC). J Clin Oncol 2018;36:358-358.
[43] O'Hara MH, O'Reilly EM, Rosemarie M, Varadhachary G, Wainberg ZA, Ko A, et al. CT004 - A phase Ib study of CD40 agonistic monoclonal antibody APX005M together with gemcitabine (Gem) and nab-paclitaxel (NP) with or without nivolumab (Nivo) in untreated metastatic ductal pancreatic adenocarcinoma (PDAC) patients. AACR Ann Meet 2019.
[44] Wang-Gillam A, Plambeck-Suess S, Goedegebuure P, Simon PO, Mitchem JB, Hornick JR, et al. A phase i study of IMP321 and gemcitabine as the front-line therapy in patients with advanced pancreatic adenocarcinoma. Invest New Drugs 2013;31:707–13.
[45] Le DT, Lutz E, Uram JN, Sugar EA, Onners B, Solt S, et al. Evaluation of ipilimumab in combination with allogeneic pancreatic tumor cells transfected with a GM-CSF gene in previously treated pancreatic cancer. J Immunother 2013;36:382–9.
[46] Overman MJ, Lopez CD, Benson AB, Neelapu SS, Mettu NB, Ko AH, et al. A randomized phase 2 study of the Bruton tyrosine kinase (Btk) inhibitor acalabrutinib alone or with pembrolizumab for metastatic pancreatic cancer (mPC). J Clin Oncol Conf 2016;34.
[47] Nesselhut J, Marx D, Lange H, Regalo G, Cillien N, Chang RY, et al. Systemic treatment with anti-PD-1 antibody nivolumab in combination with vaccine therapy in advanced pancreatic cancer. J Clin Oncol Conf 2016;34.
[48] Yamamoto N, Muro K, Ishii H, Kato T, Tsushima T, Takenoyama M, et al. Anti-CC-chemokine receptor 4 (CCR4) antibody mogamulizumab (Moga) and nivolumab (Nivo) combination phase I study in patients with advanced or metastatic solid tumors. Ann Oncol 2017;28(Supplement 5):v611.
[49] P.-P.S. Wainberg Z., Luke J., Kim E., Thompson J., Pfanzelter N., Gordon M., Rasco D., Weise A., Hodi F.S., Inamdar S., Perna S., Ma C., Powers J., Carleton M., Xiang H., Zhou L., Collins H., Lee Y., Lee J., Johnson J., Britten C., Ghoddusi M., First-in-human phase 1 dose escalation and expansion of a novel combination, anti-CSF-1 receptor (cabiralizumab) plus anti-PD-1 (nivolumab), in patients with advanced solid tumors., (2017).
[50] Overman MJ, LoRusso P, Strickler JH, Patel SP, Clarke SJ, Noonan AM, et al. Safety, efficacy and pharmacodynamics (PD) of MEDI9447 (oleclumab) alone or in combination with durvalumab in advanced colorectal cancer (CRC) or pancreatic cancer (panc). J Clin Oncol 2018;36:4123-4123.
[51] Naing A, Powderly JD, Falchook G, Creelan B, Nemunaitis J, Lutzky J, et al. Abstract CT177: epacadostat plus durvalumab in patients with advanced solid tumors: preliminary results of the ongoing, open-label, phase I/II ECHO-203 study. Cancer Res 2018;78. CT177-CT177.
[52] Thibodeau SN, Bren G, Schaid D. Microsatellite instability in cancer of the proximal colon. Science 1993;260:816–9.
[53] N. The Cancer Genome Atlas, Comprehensivemolecular characterization of human colon and rectal cancer, Nature, 487 (2012) pp. 330–337.
[54] Parsons R, Li G-M, Longley MJ, Fang W-H, Papadopoulos N, Jen J, et al. Hypermutability and mismatch repair deficiency in RER+ tumor cells. Cell 1993;75:1227–36.
[55] Cavalieri CC. Pembrolizumab in gastrointestinal (GI) malignancies with defective DNA mismatch repair (dMMR): a single institution experience. J Clin Oncol Conf 2017;35.
[56] Hu ZI, Shia J, Stadler ZK, Varghese AM, Capanu M, Salo-Mullen E, et al. Evaluating mismatch repair deficiency in pancreatic adenocarcinoma: challenges and recommendations. Clin Cancer Res 2018;24(6):1326–36.
[57] U.M. Kieler M, Bianconi D, Prager G, Challenges and perspectives for immunotherapy in adenocarcinoma of the pancreas: The cancer immunity cycle; 2018.
[58] Kabacaoglu D, Ciecielski KJ, Ruess DA, Algül H. Immune checkpoint inhibition for pancreatic ductal adenocarcinoma: current limitations and future options. Front Immunol 2018;9:1878.
[59] Hassel JC, Heinzerling L, Aberle J, Bähr O, Eigentler TK, Grimm M-O, et al. Combined immune checkpoint blockade (anti-PD-1/anti-CTLA-4): evaluation and management of adverse drug reactions. Cancer Treat Rev 2017;57:36–49.
[60] Feig C, Gopinathan A, Neesse A, Chan DS, Cook N, Tuveson DA. The pancreas cancer microenvironment. Clin Cancer Res: Offic J Am Assoc Cancer Res 2012;18:4266–76.
[61] Ansari D, Carvajo M, Bauden M, Andersson R. Pancreatic cancer stroma: controversies and current insights. Scand J Gastroenterol 2017;52:641–6.
[62] Ene-Obong A, Clear AJ, Watt J, Wang J, Fatah R, Riches JC, et al. Activated pancreatic stellate cells sequester CD8+ T cells to reduce their infiltration of the juxtatumoral compartment of pancreatic ductal adenocarcinoma. Gastroenterology

2013;145:1121–32.
[63] Pothula SP, Xu Z, Goldstein D, Pirola RC, Wilson JS, Apte MV. Key role of pancreatic stellate cells in pancreatic cancer. Cancer Lett 2016;381:194–200.
[64] Kunk PR, Bauer TW, Slingluff CL, Rahma OE. From bench to bedside a comprehensive review of pancreatic cancer immunotherapy. J ImmunoTher Cancer 2016;4:14.
[65] Skelton RA, Javed A, Zheng L, He J. Overcoming the resistance of pancreatic cancer to immune checkpoint inhibitors. J Surg Oncol 2017;116:55–62.
[66] Bailey P, Chang DK, Nones K, Johns AL, Patch A-M, Gingras M-C, et al. Genomic analyses identify molecular subtypes of pancreatic cancer. Nature 2016;531:47.
[67] Beatty GL, Gladney WL. Immune escape mechanisms as a guide for cancer immunotherapy. Clin Cancer Res: Offic J Am Assoc Cancer Res 2015;21:687–92.
[68] von Bernstorff W, Voss M, Freichel S, Schmid A, Vogel I, Jöhnk C, et al. Systemic and local immunosuppression in pancreatic cancer patients. Clin Cancer Res 2001;7:925s–32s.
[69] Balachandran VP, Łuksza M, Zhao JN, Makarov V, Moral JA, Remark R, et al. Identification of unique neoantigen qualities in long-term survivors of pancreatic cancer. Nature 2017;551:512.
[70] I.A. Voutsadakis, Immune blockade inhibitors and the radiation abscopal effect in gastrointestinal cancers, 2018.
[71] Tsuchikawa T, Takeuchi S, Nakamura T, Shichinohe T, Hirano S. Clinical impact of chemotherapy to improve tumor microenvironment of pancreatic cancer. World J Gastrointest Oncol 2016;8:786–92.
[72] Zheng Y, Dou Y, Duan L, Cong C, Gao A, Lai Q, et al. Using chemo-drugs or irradiation to break immune tolerance and facilitate immunotherapy in solid cancer. Cell Immunol 2015;294:54–9.
[73] Llosa NJ, Cruise M, Tam A, Wicks EC, Hechenbleikner EM, Taube JM, et al. The vigorous immune microenvironment of microsatellite instable colon cancer is balanced by multiple counter-inhibitory checkpoints. Cancer Discov 2015;5:43–51.
[74] Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509–20.
[75] FDA, FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication; 2017.
[76] U.S. Food and drug administration. Highlights of prescribing information on OPDIVO(nivolumab), (Updated December, 2017).
[77] Chalmers ZR, Connelly CF, Fabrizio D, Gay L, Ali SM, Ennis R, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Med 2017;9:34.
[78] Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, et al. Mutational landscape determines sensitivity to PD-1 blockade in non–small cell lung cancer. Science 2015;348:124–8.
[79] Snyder A, Makarov V, Merghoub T, Yuan J, Zaretsky JM, Desrichard A, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med 2014;371:2189–99.
[80] Birnbaum DJ, Finetti P, Lopresti A, Gilabert M, Poizat F, Turrini O, et al. Prognostic value of PDL1 expression in pancreatic cancer. Oncotarget 2016;7:71198–210.
[81] Nomi T, Sho M, Akahori T, Hamada K, Kubo A, Kanehiro H, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. Clin Cancer Res 2007;13:2151–7.
[82] N.A.G. Martin Loos, Jörg Kleeff, Thomas Giese, Matthias M. Gaida, Frank Bergmann, Melanie Laschinger, Markus W.Büchler and Helmut Friess, Clinical significance and regulation of the costimulatory molecule B7-H1 in pancreatic cancer, 2008.
[83] Patel SP, Kurzrock R. PD-L1 expression as a predictive biomarker in cancer immunotherapy. Mol Cancer Ther 2015;14:847–56.
[84] Del Re M, Marconcini R, Pasquini G, Rofi E, Vivaldi C, Bloise F, et al. PD-L1 mRNA expression in plasma-derived exosomes is associated with response to anti-PD-1 antibodies in melanoma and NSCLC. Br J Cancer 2018;118:820.
[85] Mondanelli G, Ugel S, Grohmann U, Bronte V. The immune regulation in cancer by the amino acid metabolizing enzymes ARG and IDO. Curr Opin Pharmacol 2017;35:30–9.
[86] National cancer institute, NCI drug dictionary: anti-CD73 monoclonal antibody MEDI9447. https://www.cancer.gov/publications/dictionaries/cancer-drug/def/anti-cd73-monoclonal-antibody-medi9447. Accessed November 12, 2018.
[87] Burris HA, Infante JR, Ansell SM, Nemunaitis JJ, Weiss GR, Villalobos VM, et al. Safety and activity of varlilumab, a novel and first-in-class agonist anti-CD27 antibody, patients with advanced solid tumors. J Clin Oncol 2017;35:2028–36.
[88] National cancer institute, NCI drug dictionary: urelumab, https://www.cancer.gov/publications/dictionaries/cancer-drug/def/urelumab. Accessed November 12, 2018. .
[89] National cancer institute, NCI drug dictionary: varlilumab. https://www.cancer.gov/publications/dictionaries/cancer-drug/def/varlilumab. Accessed November 12, 2018.
[90] National cancer institute, NCI drug dictionary: zanolimumab. https://www.cancer.gov/publications/dictionaries/cancer-drug/def/zanolimumab. Accessed November 12, 2018.
[91] Kim YH, Duvic M, Obitz E, Gniadecki R, Iversen L, Österborg A, et al. Clinical efficacy of zanolimumab (HuMax-CD4): two phase 2 studies in refractory cutaneous T-cell lymphoma. Blood 2007;109:4655–62.
[92] Segal NH, Logan TF, Hodi FS, McDermott D, Melero I, Hamid O, et al. Results from an integrated safety analysis of urelumab, an agonist anti-CD137 monoclonal antibody. Clin Cancer Res 2017;23:1929–36.
[93] National cancer institute, NCI drug dictionary: anti-CTGF monoclonal antibody FG-3019. https://www.cancer.gov/publications/dictionaries/cancer-drug/def/anti-ctgf-monoclonal-antibody-fg-3019. Accessed November 12, 2018.
[94] P.J. Picozzi VJ, Koong A, McMullen AD, Gadea P, Williams D, et al., FG-3019, a human monoclonal antibody to CTGF, with gemcitabine/erlotinib in patients with locally advanced or metastatic pancreatic ductal adenocarcinoma. 2013 ASCO Gastrointestinal Cancers Symposium, abstract 213, San Francisco, CA, USA., (2013).