Therapeutic developments in pancreatic cancer: current and future perspectives

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Abstract | The overall 5-year survival for pancreatic cancer has changed little over the past few decades, and pancreatic cancer is predicted to be the second leading cause of cancer-related mortality in the next decade in Western countries. The past few years, however, have seen improvements in first-line and second-line palliative therapies and considerable progress in increasing survival with adjuvant treatment. The use of biomarkers to help define treatment and the potential of neoadjuvant therapies also offer opportunities to improve outcomes. This Review brings together information on achievements to date, what is working currently and where successes are likely to be achieved in the future. Furthermore, we address the questions of how we should approach the development of pancreatic cancer treatments, including those for patients with metastatic, locally advanced and borderline resectable pancreatic cancer, as well as for patients with resected tumours. In addition to embracing newer strategies comprising genomics, stromal therapies and immunotherapies, conventional approaches using chemotherapy and radiotherapy still offer considerable prospects for greater traction and synergy with evolving concepts.

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Pancreatic cancer therapy remains a formidable challenge. Partially as a result of improvements in the treatment of other cancers and an ageing population, pancreatic cancer will probably become the second leading cause of cancer-associated mortality within the next decade in Western countries[1]. Worldwide, the incidence of pancreatic cancer is predicted to be ~420,000 by the year 2020, with an associated mortality of around 410,000 (REF.[2]). Our ever-growing understanding of the complex genetic, epigenetic and metabolic alterations as well as of the equally complex interplay of cancer cells with stromal cells, immune cells and endothelial cells has not yet resulted in a dramatic change in the overall outcome for patients with pancreatic cancer[3]. Challenges include identification of at-risk populations for screening and prevention, early detection by advanced imaging and novel cancer (bio)markers and most notably better therapeutic options that overcome the resistance of pancreatic cancer to current treatment modalities, including chemotherapy, radiotherapy and targeted therapies. Here, we provide a perspective on current and future pancreatic cancer therapies.

Surgery and conventional therapy

Adjuvant therapy: a step change. Surgery remains the only chance for cure of pancreatic cancer (FIG. 1), and the approach has evolved from a high-risk procedure a few decades ago to a challenging yet relatively safe procedure in experienced centres today[3,4]. Surgery alone, however, is not enough, as >90% of patients relapse and die of their disease after potentially curative surgery without additional therapy[3]. Adjuvant treatment strategies have therefore been evaluated during the past several decades (TABLE 1).

In a trial carried out in the 1970s, the Gastrointestinal Tumour Study Group compared observation after surgery with adjuvant 5-fluorouracil (5-FU)-based radiation after surgery, followed by weekly 5-FU for 2 years or until recurrence in 43 patients, and demonstrated a substantial difference in favour of the treatment arm[5]. Although this trial is now several decades old, it has influenced patient care until today, especially in the USA. From the 1980s to the 1990s, the European Organisation for Research and Treatment of Cancer trial compared adjuvant radiotherapy and 5-FU with observation. No survival benefit for this treatment, either in the

Key points

- Pancreatic cancer is currently the fourth leading cause of cancer-associated mortality and is projected to be the second leading cause within the next decade in Western countries.
- For resectable tumours, surgery followed by adjuvant chemotherapy (gemcitabine plus capecitabine) is the standard of care; median survival in these patients is 26 months, with a 5-year survival of 30%.
- For borderline resectable and locally advanced, unresectable tumours, neoadjuvant protocols are utilized, with a shift towards chemotherapy rather than radiochemotherapy, although good evidence from randomized controlled trials is lacking.
- In the metastatic setting, FOLFIRINOX and nab-paclitaxel–gemcitabine are standard treatment options in patients with good performance status; both combinations have shown a survival advantage over previously standard gemcitabine monotherapy.
- Second-line therapies, notably nanoliposomal irinotecan plus 5-fluorouracil–folinic acid, might prolong survival after first-line gemcitabine failure.
- Pathway-specific targeted therapies have failed to provide clinically relevant benefits; therapies targeting the stroma as well as immunotherapies hold promise for the future but are currently not standard of care.

pancreatic head cancer subgroup or in the whole cohort, was found[6].

The ESPAC-1 trial randomized 541 patients into a two-by-two factorial design (70 patients to 5-FU-based chemoradiotherapy, 74 to 5-FU chemotherapy, 72 to both treatments and 69 to observation), a further 68 patients to chemoradiotherapy or no chemoradiotherapy and 188 to chemotherapy or no chemotherapy. The trial showed no benefit for chemoradiation but a potential benefit for chemotherapy[7]. Follow-up analysis of the patients randomly assigned within the two-by-two factorial design[8] demonstrated a benefit of adjuvant chemotherapy (5-FU) following R0 or R1 resection of pancreatic cancer. Although several radiooncologists have criticized the chemoradiotherapy given in the ESPAC-1 trial, the survival data based on intention-to-treat analysis in ESPAC-1 are broadly similar to the per-protocol treatment with chemoradiation in the RTOG 97–04 trial[9]. In the ESPAC-1 trial, patients in the two-by-two factorial design part of the trial given 5-FU-based chemoradiotherapy plus 5-FU–folinic-acid (FA) chemotherapy had a median survival of 19.9 months[8] (TABLE 1). This survival is comparable to a median survival of 16.9 months in those given 5-FU-based chemoradiotherapy plus 5-FU–FA chemotherapy and a median survival of 20.5 months with 5-FU-based chemoradiotherapy plus gemcitabine chemotherapy in the RTOG 97–04 trial[9].

The CONKO-001 trial similarly showed a clear benefit of adjuvant gemcitabine versus observation after pancreatic cancer resection[10,11]. Subsequently, the ESPAC-3 trial compared 5-FU with gemcitabine as adjuvant therapy and showed no survival benefit for gemcitabine compared with 5-FU, although treatment-related serious adverse events were higher in the 5-FU group than the gemcitabine group[12]. A retrospective analysis of ESPAC-3 suggested that tumour expression of equilibrative nucleoside transporter 1 (ENT1; also known as SLC29A1), a key mediator of cellular uptake of gemcitabine, might predict benefit from adjuvant gemcitabine. These results suggest a role for tumour ENT1 expression in stratifying adjuvant chemotherapy decisions, although prospective validation is required[13]. Stratification might be further refined by the integration of other components of key drug metabolic pathways such as cytidine deaminase (gemcitabine catabolism)[14] and dihydropyrimidine dehydrogenase (5-FU metabolism)[15], paving the way for more personalized biomarker-driven approaches to adjuvant chemotherapy. Importantly, completion of all six cycles of chemotherapy was an important prognostic factor[16]. The addition of erlotinib (a small molecule inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase) to gemcitabine did not improve survival in patients with R0 resected pancreatic cancer[17]. In a trial of this patient group conducted in Japan (with 69% of patients having an Eastern Cooperative Oncology Group (ECOG) performance status of 0 and other favourable prognostic factors), S-1 (a combination of tegafur, gimeracil and oteracil potassium) was superior to gemcitabine as adjuvant therapy, with more than 40% 5-year survival for the S-1 group versus 24% in the gemcitabine group[18]. This finding remains to be confirmed in non-Asian populations.

The most recent ESPAC-4 trial, published in 2017, compared gemcitabine with gemcitabine–capecitabine combination therapy in patients with R0 or R1 resected pancreatic cancer[19] (FIG. 1). This trial demonstrated the superiority of gemcitabine–capecitabine in the adjuvant setting, with 5-year survival approaching 30%, even though ~80% of the tumours were N1 (lymph node positive) and 60% were R1 (<1 mm of the tumour margin), and only 42% of patients had a performance status of 0. The trial was also more inclusive in terms of no postoperative CT scan or CA19-9 cut-off levels. The improved survival results were achieved without a marked increase in overall toxicity and were manageable with protocol-driven capecitabine dose reduction when required. This approach resulted in an acceptable level of toxicity, as shown in the previous phase III trial in advanced and metastatic pancreatic cancer[20]. Grade 3 or 4 neutropenia was more common in the gemcitabine–capecitabine group (38%) than in the gemcitabine group (24%), but the rate of febrile neutropenia was low in both groups, and there were fewer other infective manifestations in the gemcitabine–capecitabine group (3%) than the gemcitabine alone group (7%). As expected, more grade 3 and 4 diarrhoea events occurred in the gemcitabine–capecitabine group (5%) than with gemcitabine alone (2%). The only grade 3 and 4 hand–foot syndrome events occurred with the combination chemotherapy, but only 7% of patients were affected, and the events were generally manageable with capecitabine dose modification. The ESPAC-4 trial set the standard and benchmark for adjuvant combination cytotoxic therapy, and thus gemcitabine–capecitabine is recommended over other adjuvant therapy regimens in the 2017 American Society of Clinical Oncology (ASCO) Clinical Practice Guideline update for potentially curable pancreatic cancers[21]. The results of the ongoing adjuvant trials using nab-paclitaxel (nanoparticle albumin–bound paclitaxel) plus gemcitabine (APACT; NCT0196443) and modified FOLFIRINOX (mFOLFIRINOX) (PRODIGE; NCT01526135) are pending.

Hand–foot syndrome
A condition that can occur after chemotherapy in which there is redness, swelling, numbness and/or skin peeling on the palms of the hands and the soles of the feet.

FOLFIRINOX
A therapy combination including folinic acid, 5-fluoruracil, irinotecan and oxaliplatin.

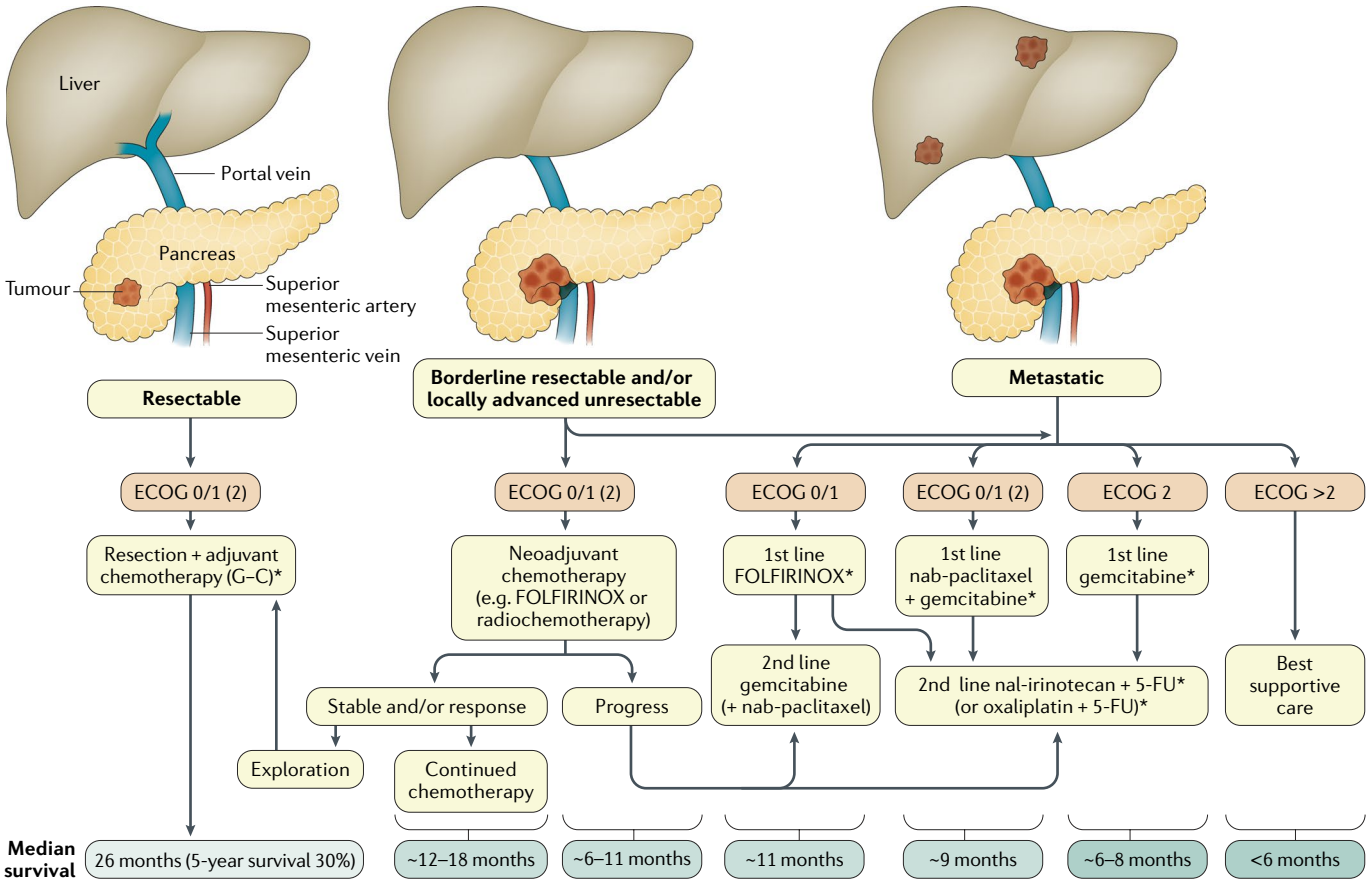

Fig. 1 | **Suggested treatment algorithm for patients with pancreatic cancer.** Patients are stratified according to tumour stage (resectable, borderline resectable and locally advanced unresectable, metastatic) and performance status (defined by the Eastern Cooperative Oncology Group (ECOG) score). Median survival values are) estimates from published data, mainly from small, single-arm or retrospective trials. In the metastatic setting, survival data are from trials of first-line therapy. This treatment algorithm represents the expert opinion of the authors. 5-FU, 5-fluorouracil; FOLFIRINOX, folinic acid, fluorouracil, irinotecan and oxaliplatin; G–C, gemcitabine–capecitabine; nab, nanoparticle albumin-bound; nal, nanoliposomal. *Approaches are based on evidence from RCTs. Other depicted treatment algorithms are current approaches, but they are not evidence based and are not standard of care worldwide.

Neoadjuvant therapy. An emerging strategy for pancreatic cancer, especially for borderline resectable[22], but also for resectable as well as locally advanced unresectable cancers, is neoadjuvant or perioperative therapy[23] (FIG. 1). For many decades, high-quality data from randomized controlled trials (RCTs) in the neoadjuvant setting were lacking, partly because of difficulties in trial design and recruiting patients. Indeed, the first randomized trial for neoadjuvant chemoradiotherapy in pancreatic cancer had to be closed early owing to poor patient recruitment and results that were not statistically significant[24]. Currently, several randomized phase III trials are underway that will hopefully provide data on this concept. In patients with resectable tumours, for example, the NEOPAC study analyses adjuvant gemcitabine versus neoadjuvant gemcitabine–oxaliplatin plus adjuvant gemcitabine[25], whereas the NEOPA trial tests neoadjuvant chemoradiotherapy versus upfront surgery[26]. Similarly, the PREOPANC trial analyses the same concept for resectable as well as borderline resectable pancreatic cancers[27]. The ESPAC-5F trial compares, in a four-arm design, immediate surgery, neoadjuvant chemoradiotherapy, gemcitabine–capecitabine and FOLFIRINOX in patients with borderline resectable pancreatic cancer[28]. An interim analysis published in abstract form (55 patients randomized) of a phase II/III RCT (NCT01458717) comparing neoadjuvant chemoradiation with gemcitabine with adjuvant chemoradiation with gemcitabine in borderline resectable pancreatic cancer demonstrated a median survival of 23 months for neoadjuvant therapy and 11 months for upfront surgery ($P = 0.011$)[29]. Of note, adjuvant chemoradiation is not considered effective[8], and the median survival in the upfront surgery group is much lower than would be expected in this group of patients and even less than in patients with locally advanced and/or metastatic disease who underwent neoadjuvant therapy[30].

With more active chemotherapeutic regimens available, most notably FOLFIRINOX[31,32], there has been a shift away from chemoradiotherapy towards chemotherapy in the neoadjuvant setting (FIG. 1). A number of centres have reported high resection rates even in locally advanced, unresectable cases following neoadjuvant

FOLFIRINOX therapy[33–35] (up to 60% in one report, although 50% of the tumours were initially unresectable because of distant metastasis[30]). Importantly, response to therapy is not reflected by imaging[36], highlighting the need for multidisciplinary discussions and, on a case-by-case decision, surgical exploration.

There is hope that with more active and evidence-based treatment options becoming available, an increased proportion of patients with borderline resectable or locally advanced unresectable tumours[22] will have their disease resected, substantially increasing the overall number of patients who can be offered the only chance for cure.

Local therapies for unresectable tumours

A sizeable proportion of patients with pancreatic cancer, estimated at around 30–40%, present with borderline resectable or locally advanced unresectable tumours[3]. Although borderline resectable tumours are candidates either for upfront surgery or neoadjuvant

Table 1 | **Randomized clinical trials of adjuvant therapy for pancreatic cancer**

Trial name	Resection margin	Treatment arms	*n*	Median survival in months (*P* value)	5-year overall survival % (95% CI; *P* value)	Refs
GITSG	R0	Observation	22	11	ND	5
		5-FU-based radiation followed by 5-FU	21	20 ($P=0.035$)	ND	
EORTC[a]	R0/R1	Observation	54	12.6	10.0 (0–20.0)	6
		5-FU-based chemoradiation	60	17.1	20.0 (5.0–35.0; $P=0.099$)	
RTOG 97-04	R0/R1	5-FU, 5-FU-based radiation and 5-FU	230	16.9	ND	9
		Gemcitabine, 5-FU-based radiation and gemcitabine	221	20.5 ($P=0.9$)	ND	
ESPAC-1 (all patients)	R0/R1	No chemoradiotherapy	178	16.1	19.5	7,8
		Chemoradiotherapy	175	15.5 ($P=0.235$)	10.3	
		No chemotherapy	235	14.0	9.9	
		Chemotherapy	238	19.7 ($P=0.0005$)	23.3	
ESPAC-1 (2 × 2 only)	R0/R1	No chemoradiotherapy	144	17.9	19.6	7,8
		Chemoradiotherapy	145	15.9 ($P=0.05$)	10.8 (6.1–17.0)	
		No chemotherapy	142	15.5	8.4 (3.8–14.1)	
		Chemotherapy	147	20.1 ($P=0.009$)	21.1 (14.6–28.5)	
		Observation	69	16.9	10.7	
		Chemoradiotherapy	73	13.9	7.3	
		Chemotherapy	75	21.6	29.0	
		Chemoradiotherapy + chemotherapy	72	19.9	13.2	
CONKO-001	R0/R1	Observation	175	20.2	10.4 (5.9–15.0)	10,11
		Gemcitabine	179	22.8	20.7 (14.7–26.6; $P=0.01$)	
ESPAC-3	R0/R1	Gemcitabine	539	23.6	17.5 (14.0–21.2)	12
		5-FU	551	23.0	15.9 (12.7–19.4; $P=0.39$)	
CONKO-005	R0	Gemcitabine	217	26.5	19%	17
		Gemcitabine + erlotinib	219	24.6 (NS)	28%	
IMPRESS	R0/R1	Gemcitabine +/– radiochemotherapy	722 (*n* per arm not published)	30.4	ND	NCT01072981
		Gemcitabine + /– radiochemotherapy + algenpantucel-L		27.3 (NS)	ND	
JASPAC-01	R0 (R1)[b]	Gemcitabine	190	25.5	24.4 (18.6–30.8)	18
		S-1	187	46.5	44.1 (36.9–51.1; $P<0.0001$)	
ESPAC-4	R0/R1	Gemcitabine	366	25.5	16.3 (10.2–23.7)	19
		Gemcitabine + capecitabine	365	28.0	28.8 (22.9–35.2; $P=0.032$)	
RTOG 0848	R0/R1	Gemcitabine (+/– erlotinib[c]) +/– chemoradiotherapy	952	NA	NA	NCT01013649
APACT	R0/R1	Gemcitabine +/– nab-paclitaxel	800	NA	NA	NCT01964430
PRODIGE/ UNICANCER	R0/R1	mFOLFIRINOX versus gemcitabine	490	NA	NA	NCT01526135

5-FU, 5-fluorouracil; mFOLFIRINOX, modified FOLFIRINOX; NA, not applicable; nab, nanoparticle albumin-bound; ND, not determined; NS, not significant; S-1, tegafur, gimeracil and oteracil potassium. [a]Only pancreatic head cancers. [b]R0 was stated as inclusion criteria, yet 13% of cases included were R1. [c]This arm has been closed.

Table 2 | **Local ablative therapies for pancreatic cancer**

Local ablative therapy	Method of action	Delivery: laparotomy	Deleivery: percutaneous and/or endoscopic ultrasonography	Invasiveness of procedure
Stereotactic body radiation	Radiation, apoptosis and non-apoptotic cell death	NA	NA	–
Radiofrequency ablation	Thermal damage: heat and coagulative necrosis	+++	++/+	+++
Irreversible electroporation	Electroporation and apoptosis	+++	+	+++
High-intensity focused ultrasound	Thermal damage: heat and coagulative necrosis	NA	NA/+	–
Photodynamic therapy	Nonthermal cytotoxic effects and necrosis	NA	++/+	++
Microwave ablation	Thermal damage: heat and coagulative necrosis	+++	++/+	+++
Cryoablation	Thermal damage: cold and necrosis	+++	++/+	+++
I^{125} seed implantation	Radiation, apoptosis and non-apoptotic cell death	+++	++/+	+++

Owing to the heterogeneity of the clinical data, there are no comparable outcome data. Level of invasiveness of delivery method and procedure: –, none; +, minor; ++, moderate; +++, major. NA, not applicable.

treatment protocols (as discussed in the previous section), treatment for locally advanced tumours is more complex and less evidence based. There is general agreement that these tumours should initially be treated with systemic (induction) chemotherapy[37], the argument being that a relevant number of these tumours have already metastasized and that local therapies would be of questionable benefit in those cases. If the tumours do not show metastatic progression after initial systemic therapy, local therapies are considered to be an option for tumour control and/or symptom relief, although there is no evidence from RCTs supporting this approach. Enthusiasts for chemoradiation[38] suggest that in the era of more effective systemic therapies (such as FOLFIRINOX and nab-paclitaxel–gemcitabine) and with newer radiotherapy techniques and novel radiosensitizers, further trials of this approach are warranted. Other methods for loco-regional therapy include irreversible electroporation (IRE), radiofrequency ablation (RFA), stereotactic body radiation (SBRT), high-intensity focused ultrasound (HIFU) and others (reviewed in REFS[39–41]) (TABLE 2). RFA and SBRT are the best studied modalities in locally advanced pancreatic cancer. RFA is usually carried out during open surgery or guided by endoscopic ultrasonography, and mortality is reported to be 0–3%, with relevant morbidity in the range of 4–28%. SBRT has been studied with varying techniques and radiation doses applied, and morbidity has been reported in up to 25% of patients[41]. IRE is a method that has gained interest, as it is thought to be able to destroy tumour tissue in the vicinity of critical structures, such as vasculature, that other methods relying on thermal effects like RFA cannot. Morbidity and mortality are within the range of what has been reported for RFA and SBRT; importantly, IRE can also be carried out percutaneously under CT guidance. HIFU has been less well studied, and marked local tissue destruction is a potential adverse event[42,43]. Even less is known about other potential local options[39–41].

Studies analysing local ablative therapies have reported tumour regression, prolonged survival and symptom control as well as tumour resection in a number of patients. However, efficacy data are heavily biased in the published patient cohorts, and thus conclusive data regarding the effects of local ablative therapies in pancreatic cancer are sparse owing to the lack of RCTs. It should be stressed that these are currently not established procedures. Nonetheless, as more solid data become available, these modalities might offer new options in the multimodal therapy of patients with locally advanced pancreatic cancer.

Palliative therapy: incremental progress

Patients with distant metastases and/or local irresectability generally qualify for systemic palliative chemotherapy. Until 2011, monotherapy with gemcitabine remained the standard of care on the basis of a trial by Burris et al. that compared gemcitabine monotherapy with 5-FU monotherapy. The study showed a significant clinical benefit but only marginally extended survival in favour of gemcitabine[44]. Combinations of gemcitabine with a second cytotoxic drug or various targeted agents have been extensively evaluated in the past few years. Most of these trials, however, proved to be futile, leaving gemcitabine as the sole standard of care. The situation changed in 2011, when the PRODIGE 4/ACCORD 11 trial demonstrated a clinically meaningful survival advantage of the gemcitabine-free FOLFIRINOX regimen over gemcitabine in patients with metastatic pancreatic cancer (11.1 versus 6.8 months median overall survival)[45]. In 2013, another combination therapy entered the stage, with the phase III MPACT trial reporting the results of nab-paclitaxel in combination with gemcitabine in patients with metastatic pancreatic cancer[46]. In contrast to conventional

Irreversible electroporation
(IRE). A nonthermal ablation technique that uses short (microsecond) pulses of high voltage electrical current to create permanent, lethal nanopores in the cell membrane.

Radiofrequency ablation
(RFA). An ablation technique that uses heat generated from medium frequency alternating current.

Stereotactic body radiation
(SBRT). A specialized type of external beam radiation therapy that uses focused radiation beams to precisely target a tumour that is well defined by detailed imaging scans.

High-intensity focused ultrasound
(HIFU). A procedure that uses an acoustic lens to concentrate multiple intersecting beams of ultrasound on a target.

Table 3 | **Phase III randomized clinical trials of second-line chemotherapy for pancreatic cancer**

Study	Regimes	*n*	Median survival (months)	*P* value	Refs
CONKO-003 (2011)	Oxaliplatin, 5-FU–FA	23	4.8	0.008	[53]
	BSC	23	2.3		
CONKO-003 (2014)	Oxaliplatin, 5-FU–FA	76	5.9	0.01	[54]
	5-FU–FA	84	3.3		
PANCREOX (2014)	FOLFOX6	54	6.1	0.02	[55]
	5-FU–FA	54	9.9		
NAPOLI-1 (2016)	nal-irinotecan plus 5-FU–FA combination	117	6.1	0.012	[56]
	5-FU–FA combination therapy control	119	4.2	0.94	
	nal-irinotecan monotherapy	151	4.9		
	5-FU–FA monotherapy control group	149	4.2		
No formal name	Glufosfamide versus 5-FU–FA	480	NA	NA	NCT01954992[a]
No formal name	nab-paclitaxel + gemcitabine versus oxaliplatin + 5-FU–FA	300	NA	NA	NCT02506842[a]

5-FU, 5-fluorouracil; BSC, best supportive care; FA, folinic acid; FOLFOX6, 5-fluoruracil, folinic acid and oxaliplatin; NA, not applicable; nab, nanoparticle albumin-bound; nal, nanoliposomal. [a]Trial ongoing.

paclitaxel, which requires a castor oil-based solvent that frequently leads to infusion hypersensitivity reactions, nab-paclitaxel represents a solvent-free, albumin-bound and water-soluble formulation of paclitaxel. This novel formulation reduces the risk of hypersensitivity reactions and neutropenia, with no need for pre-medication with antihistamines and systemic steroids, as is required for conventional paclitaxel[47]. The MPACT trial revealed a survival benefit for nab-paclitaxel–gemcitabine over gemcitabine monotherapy (median overall survival 8.7 versus 6.6 months)[48,49].

Although both trials generally included younger patients with good performance status, the patient populations in the PRODIGE 4/ACCORD 11 and the MPACT trials showed distinct differences in mean patient age, metastatic sites, serum CA19-9 levels and ECOG status; these differences preclude any head-to-head comparison between the trial results, although the gemcitabine control arm performed similarly in both trials, suggesting broadly similar patient demographics. Both available combination regimens for first-line therapy of metastatic pancreatic cancer, FOLFIRINOX and nab-paclitaxel–gemcitabine, are associated with a substantial toxicity profile. Neutropenia occurs in ~47.5% of patients treated with FOLFIRINOX and in 38% of patients treated with nab-paclitaxel–gemcitabine, with 5.4% and 3% febrile neutropenia, respectively[45,48]. Patients must be carefully selected for combination therapies. FOLFIRINOX is mainly reserved for patients with an ECOG performance status of 0 or 1 without limiting comorbidities. The combination of nab-paclitaxel–gemcitabine can also be considered in selected patients with ECOG 2 performance status, although only a small number of such patients were included in the randomized trial, and thus this recommendation is not evidence based. In the ASCO Clinical Practice Guidelines for metastatic pancreatic cancer[50], both regimens are currently recommended for patients with ECOG performance status 0–1, and gemcitabine alone is recommended for patients with ECOG performance status 2.

Of note, both FOLFIRINOX and nab-paclitaxel–gemcitabine combination therapies have been evaluated in randomized clinical trials for patients with metastatic disease only. Large randomized clinical trials evaluating both protocols for locally advanced disease with or without the addition of sequential chemoradiation are ongoing (for instance, the NEOLAP study NCT02125136). Nevertheless, both intensified combination chemotherapy protocols are frequently used in an attempt to downstage locally advanced tumours either with chemotherapy alone or with a sequential approach, in which induction chemotherapy is followed by chemoradiation or other local therapies (as described earlier) in patients without evidence of progression during induction chemotherapy. The only RCT on this topic (LAP07) did not demonstrate a survival benefit of chemoradiation (54 Gy plus capecitabine) compared with chemotherapy alone (gemcitabine or gemcitabine–erlotinib; 15.2 versus 16.5 months, $P = 0.83$) in patients with locally advanced disease who were stable following induction chemotherapy with gemcitabine or gemcitabine–erlotinib. However, local progression was reduced in the chemoradiation arm (32% versus 46%, $P = 0.03$)[51].

Second-line therapy: a new beginning

Most pancreatic cancers progress within a few months during or after first-line palliative chemotherapy despite the use of intensified protocols, making second-line chemotherapy important in a large proportion of patients. Around 16–86% of patients undergo second-line therapy[52]; in the ACCORD/PRODIGE 4 trial, ~50% of patients (165 of 342) underwent second-line chemotherapy, with a median survival of 4.4 months[45]. Despite the unmet need for evidence-based second line therapies, only a few phase III RCTs have been carried out (TABLE 3). The first phase III RCT compared best

Nanoliposomal irinotecan
An artificial, nanosized liposomal delivery system for irinotecan that is designed to keep irinotecan in circulation for longer than free irinotecan.

supportive care to oxaliplatin, 5-FU and FA (OFF) in 46 patients[53]. The trial started in 2002 and had to be stopped in 2003 because of low recruitment. Nonetheless, the OFF regimen was associated with significantly increased second-line survival (4.8 versus 2.3 months, $P=0.008$). The follow-up trial compared OFF with 5-FU–FA and demonstrated that in patients with gemcitabine refractory pancreatic cancer, OFF is superior to 5-FU–FA (median survival 5.9 versus 3.3 months, $P=0.01$) and that the addition of oxaliplatin did not result in clinically relevant increased toxicity[54]. By contrast, the PANCREOX trial did not show a benefit of the addition of oxaliplatin (FOLFOX6) to 5-FU–FA (median survival 6.1 versus 9.9 months, $P=0.02$), with increased toxicity being observed in the FOLFOX6 arm, although this trial was also very small ($n=56$ per arm) and to date has only been published in abstract form[55]. A phase III randomized clinical trial published in 2016 demonstrated that nanoliposomal irinotecan plus 5-FU–FA significantly increased survival compared with 5-FU–FA (6.1 versus 4.2 months, $P=0.012$) in patients previously treated with a gemcitabine-based regimen[56]. Most studies carried out to date have evaluated second-line regimens after gemcitabine-based therapy failure. FOLFIRINOX is an active and more frequently used regimen in fit patients (ECOG performance status 0–1)[45]; however, data regarding second-line therapy following this regimen are sparse. In a prospective multicentre cohort study, 57 patients were treated with nab-paclitaxel and gemcitabine following FOLFIRINOX, with a median survival of 8.8 months and an acceptable toxicity profile[57].

There is now evidence from phase II and III trials[52] that second-line therapy is effective and well tolerated in patients who maintain good performance status despite progression on first-line treatment. Median survival after disease progression with first-line chemotherapy has increased over the past decades from ~2–3 months to 4–5 months and to >6 months in trials conducted in the past few years[52,56]. Owing to the emergence of more active first-line therapies such as FOLFIRINOX, novel second-line therapies have to be established and evaluated (TABLE 4). As of now, nanoliposomal irinotecan (or oxaliplatin) and/or 5-FU–FA seems to be the best option in patients treated with first-line gemcitabine-based therapy, whereas a gemcitabine-based regimen (for example, nab-paclitaxel plus gemcitabine or single-agent gemcitabine, depending on performance status) might be an option after first-line FOLFIRINOX failure, although randomized trials to confirm this suggestion are required[50,58] (FIG. 1).

Targeted therapies: failures and hope

Numerous targeted agents have been evaluated alone or in combination with chemotherapy in metastatic pancreatic cancer. Unfortunately, most agents have so far failed to improve patient survival. The long list of targeted compounds tested in trials and found to be futile includes antiangiogenic drugs, such as the vascular endothelial growth factor (VEGF) inhibitors bevacizumab and aflibercept[59,60], and multikinase inhibitors with antiangiogenic activity, such as sunitinib, sorafenib and axitinib[61–64]. It can be speculated that the futility of all antiangiogenetic approaches tested so far is due to the largely hypovascular nature of the stroma surrounding cancer cells in this disease[63]. In the past few years, other compounds targeting important signalling cascades in pancreatic cancer have proved futile in randomized trials with gemcitabine as the chemotherapeutic backbone; these therapies include the anti-insulin-like growth factor 1 receptor antibodies ganitumab and cixutumumab[65,66], the multi-kinase inhibitor masitinib[67] and the phosphoinositide 3-kinase (PI3K) inhibitor rigosertib[68]. The results of these trials have been reviewed elsewhere[69].

The only targeted agent to have exhibited a statistically significant, yet clinically marginal, effect on patient survival is erlotinib. Moore et al. reported in a randomized trial that the combination of gemcitabine and erlotinib conferred a mean survival benefit of ~2 weeks over gemcitabine alone[70]. This marginal benefit clearly raises questions about the clinical significance of erlotinib. It can be speculated that owing to the high percentage of activating *KRAS* mutations, which occur in up to 90% of patients

Table 4 | **Phase II trials of second-line (chemo)therapy for pancreatic cancer published in the past few years**

Study phase	Year	Regimes	*n*	Median survival in months (*P* value)	Refs
Phase II (RCT)	2015	Capecitabine + ruxolitinib	64 (31[a])	4.5 versus 4.3 (NS)	134
		Capecitabine + placebo	63 (29[a])	2.7 versus 1.8[a] ($P=0.011$)	
Phase II (RCT)	2015	mFOLFOX	60	7.5 versus 4 (NS)	140
		MK-2206 + selumetinib	53		
Phase II (RCT)	2014	S-1 + folinic acid	45	6.3 versus 5.5 (NS)	141
		S-1	47		
Phase II	2015	Lapatinib and capecitabine	17	5.2	142
Phase II	2014	Vatalanib	67	~4.0	143
Phase II	2014	Capecitabine and docetaxel	43	5.3	144
Phase II	2014	PHY906 and capecitabine	25	5.0	145

mFOLFOX, modified FOLFOX (5-fluorouracil, folinic acid and oxaliplatin); NS, not significant; S-1, tegafur, gimeracil and oteracil potassium; RCT, randomized controlled trial. [a]In patients with a serum C-reactive protein (CRP) level above the median of the study population (13 mg/l).

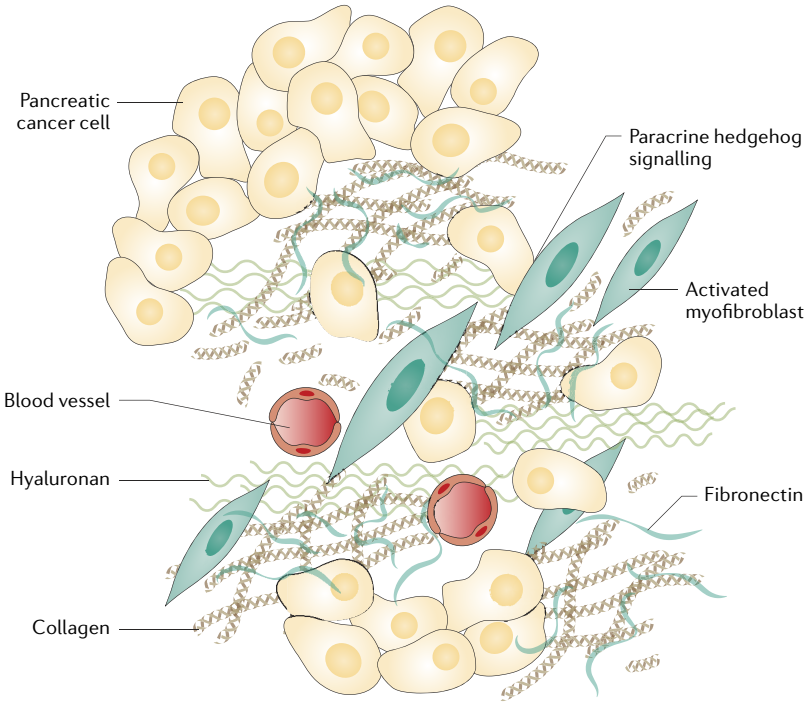

Fig. 2 | **The microenvironment of pancreatic tumours.** The pancreatic tumour microenvironment contains an abundant fibrotic stroma that includes a variety of cell types as well as extracellular matrix components, such as collagen, fibronectin and hyaluronic acid (hyaluronan).

with pancreatic cancer, pharmacological inhibition of EGFR upstream of GTPase KRAS is only minimally effective in this cancer type[63]. Notably, a subgroup of patients who develop a skin rash (grade ≥2 on the National Cancer Institute Common Toxicity Criteria version 2.0)[71] upon erlotinib treatment showed a median survival of almost 12 months. Although the underlying molecular mechanisms behind this striking observation remain to be fully elucidated, skin rash can be generally considered as a positive predictive marker for response to anti-EGFR therapy across tumour entities[72]. Unfortunately, predictive biomarkers to prospectively identify these responding patients have not been forthcoming. A common challenge to correlative research in such large, multicentre trials is the limited availability of good quality tissue samples, an issue that should be addressed to further develop stratified or personalized approaches for pancreatic cancer.

The failure of targeted therapies to improve the outcome of advanced pancreatic cancer in unselected patient populations might be explained by both the high molecular heterogeneity of this disease and the high content of surrounding stromal and inflammatory components that affect signalling pathways and drug accessibility, half-life and metabolism. In addition to addressing the crosstalk with mesenchymal and inflammatory stromal components (discussed in the next section) mediating therapy resistance, advances in determining the key molecular drivers of each tumour in a precision medicine approach will hopefully overcome the disappointing performance of targeted approaches observed in unselected populations of patients with advanced pancreatic cancer.

Cancer-associated fibroblasts
(CAFs). Fibroblasts within the tumour microenvironment that promote tumorigenic features by initiating the remodelling of extracellular matrix or by secreting cytokines.

Stroma targeting: learning the hard way

The pancreatic tumour microenvironment has attracted much interest in the past decade, with particular attention focused on its role as a determinant of therapy response. The plentiful fibrotic stroma associated with pancreatic cancer contains a variety of cell types, including cancer-associated fibroblasts (CAFs), inflammatory cells, blood vessels and nerve cells. The stroma also comprises a variety of extracellular matrix components, with pancreatic CAFs activated to produce collagen, fibronectin, laminin and hyaluronic acid[73] (FIG. 2).

Exploiting the stroma to enhance chemotherapeutic drug delivery is an attractive prospect. Secreted protein acidic and rich in cysteine (SPARC) is a matricellular protein produced by CAFs that is known to bind albumin. Consequently, it was proposed that SPARC might enrich the concentration of nab-paclitaxel within the pancreatic cancer microenvironment, thereby increasing its antitumour activity. As mentioned earlier, the combination of gemcitabine plus nab-paclitaxel led to improved survival compared with gemcitabine monotherapy[48]. However, no association was established between stromal SPARC levels and overall survival in either treatment arm[74].

The deposition of extracellular matrix components alters the physical nature of the developing pancreatic tumour, causing stiffness and increasing hydrostatic pressures. Furthermore, pancreatic tumours are poorly vascularized[73]. The combination of increased hydrostatic pressure within pancreatic tumours and poor vascularization is believed to create a barrier to drug uptake, and several approaches aimed at challenging this stromal barrier to enhance drug delivery to pancreatic ductal adenocarcinoma (PDAC) tumour cells have been tested. Systemic administration of the modified hyaluronidase molecule PEGPH20 into mice with established pancreatic tumours decreased tumoural hyaluronic content, reduced interstitial fluid pressures and increased the number of functioning tumour blood vessels[75,76]. This promising preclinical data led to clinical trials in which PEGPH20 is combined with nab-paclitaxel and gemcitabine or with FOLFIRINOX (NCT01839487 and NCT01959139, respectively). Interim analysis of the nab-paclitaxel and gemcitabine trial, published in abstract form, showed that patients with high levels of tumoural hyaluronic acid had a progression-free survival of 9.2 months when treated with the combination that included PEGPH20 compared with 4.3 months if given paclitaxel and gemcitabine only[77].

Pancreatic stellate cells (PSCs) are a form of fibroblast that become activated in the developing pancreatic tumour, leading to the hypothesis that reversing activated PSCs to a quiescent phenotype might decrease fibrosis and improve drug delivery[78]. PSCs express high levels of vitamin D receptor. Treatment with calcipotriol, a ligand for this receptor, was associated with the reversion of activated PSCs to a quiescent state in cell culture and in a preclinical model led to decreased fibrosis and enhanced tumour uptake of gemcitabine[79].

However, targeting the fibroblastic components of PDAC needs to be approached with caution. Hedgehog signalling between cancer cells and CAFs promotes stromal desmoplasia[80]. In a mouse model, short-term pharmacological inhibition of the sonic hedgehog (SHH) pathway using the Smoothened homologue (SMO) inhibitor IPI-926 inhibited myofibroblast growth and collagen deposition, increased tumour vascularity and enhanced gemcitabine delivery to pancreatic tumours[81]. However, the use of combined IPI-926 and gemcitabine in patients failed to confirm improved survival over gemcitabine monotherapy, and the trial was halted early because of an increased rate of progressive disease in the treatment arm. It has since been demonstrated that longer-term IPI-926 administration decreased stromal content and increased vascularization of pancreatic tumours in a preclinical mouse model, but surprisingly, these tumours showed accelerated growth and increased metastasis[82]. Likewise, genetically eliminating stromal fibroblasts caused an aggressive tumour phenotype and decreased survival[83]. Thus, the stroma seems to (at least in part) protect against tumour progression, yet at the same time, it creates an environment that impairs drug delivery to the tumour. More research is required to understand how to optimally target the stroma so as not to compromise its protective role.

The hypoxic nature of the pancreatic tumour microenvironment offers the possibility of selectively targeting cancer cells. Evofosfamide is a prodrug that, under hypoxic conditions, releases the DNA alkylating agent bromo-isophosphoramide mustard, which inhibits DNA replication by forming DNA crosslinks and interferes with DNA transcription. In the phase III MAESTRO clinical trial, 693 patients with locally advanced unresectable or metastatic pancreatic cancer were randomly assigned to combined evofosfamide and gemcitabine versus combined placebo and gemcitabine (NCT01746979). Despite a statistically significant improvement in median progression-free survival from 3.7 months with the placebo-containing combination to 5.5 months with the evofosfamide-containing combination (HR = 0.77; 95% CI 0.65–0.92, $P = 0.004$), the slight improvement in median overall survival for patients who received evofosfamide–gemcitabine (8.7 months) compared with patients who received placebo–gemcitabine (7.6 months) did not reach statistical significance (HR = 0.84; 95% CI 0.71–1.01, $P = 0.059$)[84].

Immunotherapies: great promise

A key reason why cancer cells can survive and establish tumours is that they can suppress the immune response, either directly or via other cells in the tumour microenvironment. This property has now been defined as one of the hallmarks of cancer[85]. Immune response also predicts survival in pancreatic cancer, suggesting that manipulation of this feature might be of clinical benefit[86].

Inhibition of proteins involved in T cell checkpoints, such as cytotoxic T lymphocyte protein 4 (CTLA4; targeted by ipilimumab) and programmed cell death protein 1 (PD-1; targeted by nivolumab and pembrolizumab) shows enormous promise in a number of cancer types, most notably, malignant melanoma[87]. However, to date, pancreatic cancer has proved refractory to this approach using these agents, probably reflecting the immunosuppressive nature of the pancreatic cancer microenvironment. Mechanisms by which cancer suppresses the immune response include activation of regulatory T cells (T_{reg} cells)[88] or myeloid-derived suppressor cells (MDSCs)[89], inhibition of effector T cells (T_{eff} cells)[90] or antigen-presenting cells (APCs)[91] and modulation of macrophage populations within the tumour[92]. Cancer also includes the establishment of a barrier to entry of T_{eff} cells into the tumour milieu[93]. Immunotherapy to reverse these effects has been successful in many tumour types, a notable exception to date being pancreatic cancer[94].

The simplest form of the immunotherapy approach is a cancer vaccine using a tumour-specific antigen[95]. Unfortunately, such direct approaches have as yet proved ineffective in pancreatic cancer[94]; for example, the Telovac trial (which used a vaccine (GV1001) made of fragments of telomerase) gave no survival benefit in patients with advanced pancreatic cancer[96]. Other trials, such as the GTPase RAS peptide vaccine TG01/GM-CSF[97], are ongoing. An early-phase trial of the TG01/GM-CSF vaccine in combination with gemcitabine in the adjuvant setting has reported an encouraging median survival of 33 months, although this study was small ($n = 19$), and larger, randomized trials are required[98].

Adoptive immunotherapy approaches. Adoptive approaches involve injecting immune cells into patients. One method could be using T cells isolated from the patient: tumour-infiltrating T cells have been shown to respond to tumour antigens and to possess an ability to migrate from the vasculature into the tumour microenvironment. Therefore, expanding tumour-infiltrating T cells ex vivo and injecting them back into the patient could be beneficial[99]. Similarly, extracting APCs (for example, dendritic cells) and challenging them ex vivo with an appropriate antigen could provide an agent to stimulate an antitumour immune response, for example, Sipuleucel-T in prostate cancer[100]. Another approach is to generate a cell line that will express HLA-DR and, because the cell line is not autologous, proteins such as telomerase reverse transcriptase (TERT), which will stimulate an immune response when these cells are administered to the patient. Phase II clinical trials with one such agent (ACIT-1) are underway in pancreatic cancer (NCT03096093). Alternatively, immune cells could be engineered to replace compromised lymphocytes. The use of T cells with engineered T cell receptors has showed promise in cell culture and mouse models[101], but the technology has largely proved ineffectual or harmful in clinical trials[102]. In this context, chimeric antigen receptor (CAR)-T cells have shown greater promise[103]. These are T cells engineered in vitro to express a protein-binding domain on their surface, typically in the form of a single-chain variable fragment (ScFv), which is grafted onto T cell stimulatory domains[104]. A cancer-cell-specific surface protein is selected as a target to produce a therapeutic that can be both specific and effective, particularly enabling lymphodepletion to remove T_{reg} cells and

T cell checkpoints
Molecules in the immune system that can either turn up (via co-stimulatory pathways) or turn down (via inhibitory pathways) immune responses

Regulatory T cells
(T_{reg} cells). A subpopulation of T cells that modulate immune system function, maintain self-tolerance and prevent autoimmune disease.

Myeloid-derived suppressor cells
A heterogeneous group of immune cells of myeloid lineage (derived from bone marrow stem cells), they are strongly immunosuppressive rather than immunostimulatory.

Effector T cells
A subpopulation of T cells that have an important role in executing immune functions, including releasing T cell cytokines.

Antigen-presenting cells
(APCs). Cells that display antigens complexed with major histocompatibility complexes on their cell surfaces.

reduce competition for stimulatory cytokines. Further advances, including engineering CAR-T cells to produce appropriate cytokines or suicide cassettes to limit toxicity, are in development[105].

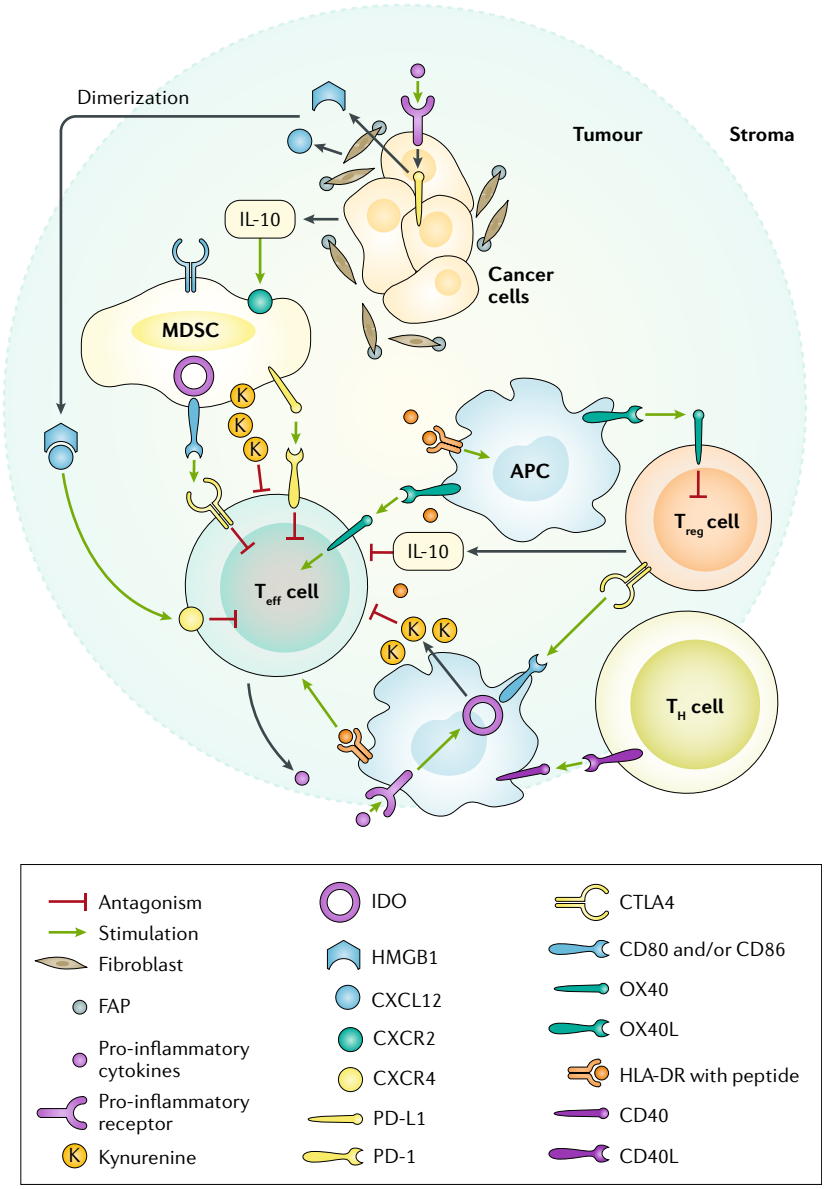

Fig. 3 | **Tumour antigens and the role of regulatory and effector T cells in pancreatic cancer.** Proteins released by cancer cells should activate antigen-presenting cells (APCs), stimulating effector T (T_{eff}) cells. This immune response will be facilitated by T helper (T_H) cells via CD40 on APCs. As well as activating T_{eff} cells, APCs express the OX40 ligand (OX40L; also known as TNFSF4), which also suppresses regulatory T (T_{reg}) cells. Negative feedback loops would naturally dampen this effect through expression of cytotoxic T lymphocyte antigen 4 (CTLA4) on activated T_{eff} cells, expression of programmed cell death 1 ligand 1 (PD-L1) on myeloid-derived suppressor cells (MDSCs) and activation of indoleamine 2,3-dioxygenase (IDO) in APCs, which stimulates release of the T_{eff} cell inhibitor kynurenine. Among other effects, CTLA4 also causes release of kynurenine from MDSCs and APCs via CD80 or CD86 and IDO. To overcome the antitumour immune response, cancer cells release IL-8 and other cytokines that stimulate MDSCs. They also release high-mobility group protein B1 (HMGB1), which combines with CXC-chemokine ligand 12 (CXCL12) produced by prolyl endopeptidase fibroblast activation protein (FAP)-expressing tumour-associated fibroblasts to inhibit T_{eff} cells via CXC-chemokine receptor 4 (CXCR4). Pro-inflammatory cytokines released by T_{eff} cells induce cancer cell PD-L1 expression, which inhibits effector T cell function by binding programmed cell death protein 1 (PD-1). CD40L, CD40 ligand.

Immune checkpoint modulation. Cancer activates inhibitors of T_{eff} cells, including increasing the number of MDSCs via activation of MDSC-expressed CXC-chemokine receptor 2 (CXCR2) with IL-8 (REF.[106]). MDSCs can be targeted with agents such as the cGMP-specific 3′,5′-cyclic phosphodiesterase (PDE5A) inhibitor tadalafil[107,108]. MDSCs activate PD-1 by expressing its ligand (programmed cell death 1 ligand 1 (PD-L1))[109]. PD-L1 is also expressed on the surface of the cancer cells themselves[110] and on M2 macrophages[111]. Antagonists of PD-1 (such as nivolumab) or PD-L1 (such as durvalumab) at least partly counteract cancer-induced immune suppression[100].

The CD28 homologue CTLA4 is expressed on both T_{eff} cells and T_{reg} cells and negatively regulates activation, possibly via competitive inhibition of CD28 (REF.[112]). In addition, indoleamine 2,3-dioxygenase (IDO), expressed in APCs and MDSCs, is activated by CTLA4 as a result of binding to CD80 and/or CD86, increasing levels of kynurenine and decreasing tryptophan[113] (FIG. 3). Depletion of tryptophan is directly immunosuppressive in APCs, and kynurenine also acts to inhibit T_{eff} cells via their aryl hydrocarbon receptors[113,114]. CTLA4 can be directly inhibited with agents such as ipilimumab[115], and IDO can be inhibited with compounds such as indoximod[116]. As an alternative to inhibiting immunosuppressors, agonists of stimulatory proteins on T_{eff} cells or APCs have the potential to restore immune response. For instance, MOXR0916 stimulates OX40 (also known as TNFRSF4) on T_{eff} cells[117], whereas CP-870,893 (a CD40 agonist monoclonal antibody) stimulates CD40 on APCs[118]. To date, none of these antagonists or agonists have proved successful in the treatment of pancreatic cancer, although CD40 activation (using CP-870,893) together with gemcitabine resulted in partial response in 4 of 21 patients with pancreatic cancer, potentially by influencing the immune reaction and fibrosis via tumour-associated macrophages[119]. A clinical trial of RO7009789 (a CD40 agonist monoclonal antibody) with nab-paclitaxel plus gemcitabine used as a neoadjuvant is underway (NCT02588443).

Macrophage targeting. Another way that cancer evades immune recognition is to promote the differentiation of macrophages into cells that promote cell growth and repair pathways (M2 macrophages) rather than growth inhibitory killer macrophages (M1 macrophages) (FIG. 4). M2 macrophages can suppress T_{eff} cells by secreting IL-10 and by producing carbon monoxide via the enzyme haem oxygenase, which can be chemically inhibited with imidazole–dioxolanes[120]. Innate immunity can also be improved by increasing the proportion of M1 macrophages, an approach known as macrophage innate conversion[92].

Activation of Toll-like receptor 7 (TLR7), which is expressed on macrophages and MDSCs, promotes macrophage differentiation towards an M1 phenotype, and the receptor can be stimulated by agents such as imiquimod[121]. However, TLR7 is present on numerous cell types, and the result of treatment with an agonist

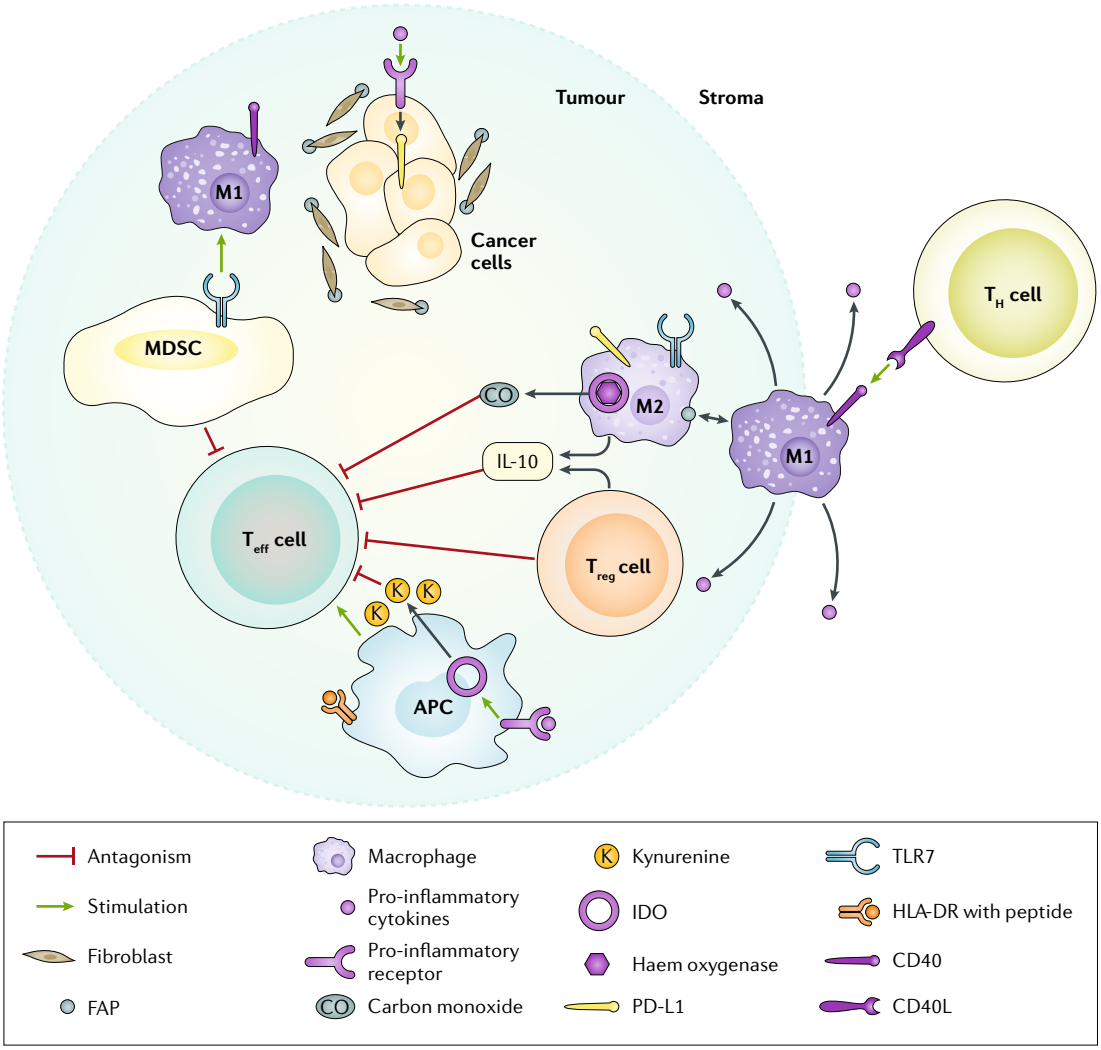

Fig. 4 | **Macrophages in the pancreatic tumour microenvironment.** M2 macrophages contribute to immune suppression by expressing programmed cell death 1 ligand 1 (PD-L1) and IL-10 and producing carbon monoxide via haem oxygenase. By contrast, M1 macrophages do not express PD-L1 or prolyl endopeptidase fibroblast activation protein (FAP) and express pro-inflammatory cytokines that in most respects aid the immune response. Differentiation towards an M1 phenotype is controlled by Toll-like receptor 7 (TLR7), which is expressed by myeloid-derived suppressor cells (MDSCs) and M2 macrophages. Pro-inflammatory activation of M1 macrophages is also supported by T helper (T_H) cells via CD40. APC, antigen-presenting cell; CD40L, CD40 ligand; IDO, indoleamine 2,3-dioxygenase; T_{eff}, effector T; T_{reg}, regulatory T.

Suicide cassettes
Components of vector DNA consisting of a suicide gene and regulatory sequence to be expressed by a transfected cell, which cause the transfected cell to undergo apoptosis.

Kynurenine
A metabolite of tryptophan produced by indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO).

Neo-antigen
A new antigen expressed exclusively by tumour cells that is generated by the progressive mutational process that drives cancer evolution.

is consequentially complex. Indeed, inhibition rather than activation of the receptor has been suggested for prevention and treatment of pancreatic cancer[122].

Future directions for immunotherapy. The failure of immunotherapy in treating pancreatic cancer might reflect the efficient exclusion of T_{eff} cells from the tumour microenvironment in this form of cancer. This exclusion might relate to a subclass of CAFs that express prolyl endopeptidase fibroblast activation protein (FAP), which is expressed on fibroblasts and some macrophages. Depletion of macrophage or fibroblast FAP-expressing cells restores immune control in mouse cancer models, suggesting they both have a role in cancer immunosuppression[123]. FAP-positive fibroblasts express CXC-chemokine ligand 12 (CXCL12), which can form a dimer with high-mobility group protein B1 (HMGB1; expressed by pancreatic cancer cells) that activates the suppressor CXCR4 on T_{eff} cells. In mouse models of pancreatic cancer, inhibition of CXCR4 using plerixafor (AMD3100) led to T_{eff} cell accumulation in the tumour[93]. However, the failure of this approach when using the combination of the CXCR4 inhibitor ulocuplumab with an anti-PD-1 therapy, nivolumab, in a phase I/II clinical trial including patients with pancreatic cancer calls this strategy into question (NCT02472977). In some gastrointestinal cancers (such as colon or gastric cancers), response to checkpoint inhibitors is restricted to patients with DNA mismatch repair defects (presumably as a result of the increased rate of neo-antigen generation in these tumours), suggesting that this feature could be a potential predictive biomarker for checkpoint inhibitor therapy[124]. However, this property probably applies to only a small proportion of pancreatic cancers and is yet to be validated in this setting.

Checkpoint inhibitors and other forms of immunotherapy do promise much for the future treatment of pancreatic cancer, but as seen in FIGS 3–5, millions of years of evolution have led to an extremely complex regulatory network to ensure that the immune response is measured. Therapeutic intervention to restore immune response is likely to lead to beneficial effects and adverse consequences, including diabetes and pancreatitis[125].

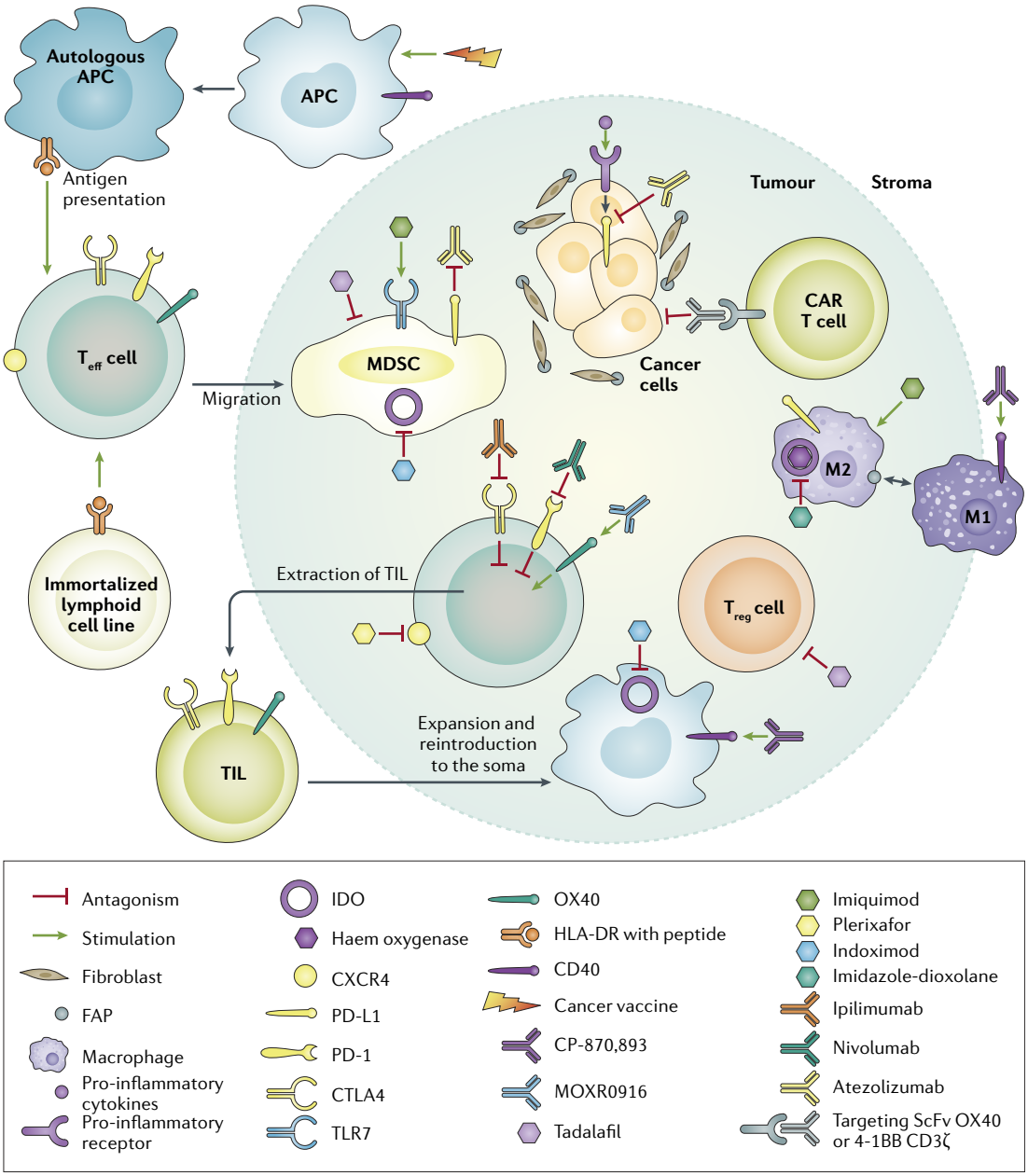

Fig. 5 | **Drugs to modulate immune function in pancreatic cancer.** A large number of agents have been developed to overcome immunosuppression. CP-870,893 is an agonist antibody for CD40, which is expressed by M1 macrophages and antigen-presenting cells (APCs). MOXR0916 is an agonist for OX40 (also known as TNFRSF4), which is present on effector T (T_{eff}) cells. Tadalafil is an inhibitor of phosphodiesterase and so inhibits the activity of myeloid-derived suppressor cells (MDSCs) and regulatory T (T_{reg}) cells. Imiquimod is an agonist of Toll-like receptor 7 (TLR7), which promotes macrophage polarization towards an M1 phenotype. Plerixafor inhibits CXC-chemokine receptor 4 (CXCR4), a protein that negatively regulates T_{eff} cell immune function. Indoleamine 2,3-dioxygenase (IDO), which is expressed by APCs and MDSCs, can be inhibited with indoximod. Imidazole-dioxolane inhibits haem oxygenase present in M2 macrophages. The T_{eff} cell immune checkpoint proteins cytotoxic T lymphocyte antigen 4 (CTLA4), programmed cell death protein 1 (PD-1) and programmed cell death 1 ligand 1 (PD-L1) are inhibited by ipilimumab, nivolumab and atezolizumab, respectively. Chimeric antigen receptor (CAR)-T cells directly target cancer cells via engineered single-chain variable fragments (ScFv), which specifically bind proteins on the surface of cancer cells. Cancer vaccines, autologous APCs and immortalized lymphoid cell lines can be used to activate T_{eff} cells. Tumour-infiltrating lymphocytes (TILs) are taken from the tumour and are amplified before being reintroduced. FAP, fibroblast activation protein.

Abscopal effects
A phenomenon whereby local radiotherapy causes regression of not only the targeted tumour but also distant tumours.

Intensity-modulated radiation therapy
A high-precision conformal radiotherapy approach to deliver precise radiation doses to a malignant tumour or specific areas within the tumour.

Balancing the therapy will be difficult and will probably require multiple agents; trials of combinations are underway, and the results will need to be carefully monitored[126]. Another question is how checkpoint inhibitors will interact with other treatment options. As both chemotherapy and radiotherapy target dividing cells, and cell division is a feature of both cancer and the immune response to cancer, theoretical relationships between treatment and immunity have never been in short supply. Negative effects that result from a reduction in T cells[127] and positive bystander or abscopal effects owing to release of cancer-related proteins[128] have been proposed, and in vitro and animal model experiments have been presented to support both possibilities. Empirical evidence in a clinical setting has been much more difficult to obtain and interpret. When that evidence is available, it seems that chemotherapy with agents such as gemcitabine and/or capecitabine reduces the immune response to a much smaller degree than feared, yet it improves cancer immunity much less than hoped for[129]. The relationship between the level and method (for example, SBRT versus intensity-modulated radiation therapy) of radiation applied and toxicity is complex for both cancer and immune cells. High radiation doses might induce release of factors such as TNF, tumor necrosis factor ligand superfamily member 10 (TNFSF10, also known as TRAIL), prostate apoptosis response 4 protein (PAR4; also known as PAWR) and ceramide that can increase distant immune responses[130], although there is no evidence to support this effect as yet in the treatment of pancreatic cancer.

Precision medicine: opportunities and obstacles

Precision medicine is an emerging concept in oncology that offers improved outcomes by individualizing patient therapy. The key principle is to select the best therapy or combination therapy in a patient-specific fashion[131]. This approach would not only take into account targetable alteration of a specific tumour but also drug delivery, drug metabolism and adverse effects for a specific patient. There are a number of obstacles to developing and implementing precision medicine for pancreatic cancer. The incidence for targetable genetic alteration varies and in general is considerably lower than the tumour incidence, highlighting the need for validated and accurate biomarkers for enrichment of eligible patients. Sampling bias is a potential problem, as tumour heterogeneity means that single biopsy samples might not accurately capture tumour subtype. Furthermore, there is the need to base individual therapies on evidence, necessitating a shift in current preclinical analysis[132] as well as trial designs and evidence generation (reviewed in REF.[131]). The necessary trial designs include basket trials that test drugs in different cancers that share common alterations and umbrella trials that test different drugs targeting different alterations in a single tumour type. The first umbrella trial on precision medicine in pancreatic cancer — the Individualized Molecular Pancreatic Cancer Therapy (IMPaCT) trial[133] — highlighted the difficulties of this approach. The aim of the trial was to assess standard chemotherapy (gemcitabine) versus personalized therapy in patients with pancreatic cancer. Patients with tumour mutations in homologous recombination and DNA damage repair genes (*BRCA1*, *BRCA2*, *PALB2* or *ATM*), with amplified *ERBB2* (also known as *HER2*) or with absence of mutations in *KRAS* would receive targeted treatment. Of 93 patients considered, 76 were screened and 22 eligible patients were identified. However, for various reasons, none of these patients has been successfully treated within the IMPaCT study[133].

The UK Precision-Panc trial and the University of Toronto-initiated COMPASS trial (NCT02750657) are other platforms for adaptive trials in pancreatic cancer. These studies utilize cancer sequencing data to detect actionable drug targets and tumour subclasses and also initially aim to define a subgroup of patients with deficient DNA repair mechanisms who might be more responsive to platinum-based chemotherapy. To date, this level of sequencing has been limited to resection specimens from a subgroup of patients with sufficiently cellular tumours undergoing surgical resection. The ability to deliver this depth of tumour analysis in a timely manner using biopsy material in a multicentre trial setting might be challenging.

There are several individualized treatment options available for patients with pancreatic cancer, although most of them are not based on data from controlled clinical trials. For example, patients with evidence of systemic inflammation (as determined by elevated serum C-reactive protein (CRP) levels) seem to benefit from combination therapy comprising the Janus kinase 1 (JAK1)–JAK2 inhibitor ruxolitinib and capecitabine[134]. Patients with high tumour peroxisomal acyl-CoA oxidase 1 expression might benefit from therapy with the tyrosine kinase inhibitor masitinib with gemcitabine[67]. Similarly, patients with high tumour levels of hyaluronic acid respond better to a pegylated recombinant human hyaluronidase-based therapy[77]. The biomarker-enriched phase III trial to determine whether this response translates into survival benefit in patients with tumours expressing high hyaluronic acid levels is ongoing. Furthermore, in the adjuvant setting, ENT1 has been shown to be a predictive marker in patients treated with gemcitabine but not 5-FU[13]. Pancreatic cancer stromal SPARC expression had initially been suggested as a marker for nab-paclitaxel response[46]; however, no statistically significant associations between SPARC levels and drug efficacy have been shown[74]. In the past few years, large-scale genomic analyses have revealed several potential targets for personalized therapy and pancreatic cancer subgroups. Most notably, the unstable subtype of pancreatic cancer that co-segregated with inactivation of DNA maintenance genes (discussed earlier in the context of the IMPaCT trial) and a signature of DNA damage repair deficiency in tumours correlated with response to platinum-based therapies or poly(ADP-ribose) polymerase (PARP) inhibitors[135–137]. The very small percentage of patients with *BRAF* (and not *KRAS*) mutations might benefit from serine/threonine-protein kinase BRAF inhibitors[138]. Further, transcriptome classification revealed an immunogenic subtype with upregulation of CTLA4 and PD-1 that might be targeted by immune modulation therapies[139].

Conclusions

Pancreatic cancer remains a challenging disease to treat. Although it is predicted to become the second leading cause of cancer-associated mortality within the next decade, there has been steady progress in improving outcomes during the past years. In part because of better perioperative care and more effective adjuvant treatments, survival has more than doubled, with a robust 30% 5-year survival following tumour resection and adjuvant therapy. Similarly, a substantial percentage of patients (up to 50% or more) with borderline resectable and locally advanced unresectable tumours can currently be offered surgery following neoadjuvant protocols. After a prolonged period of stagnation, we now also see improvements in the therapy of metastatic disease with two combination therapies, which (in the best scenario) almost double median survival. Finally, there are evidence-based options for second-line therapy available for patients with good performance status who progress after first-line therapy.

Many challenges remain; the overall prognosis of pancreatic cancer — for patients at all stages combined — remains poor. There had been much hope that pathway-specific targeted therapies would yield improvements in outcomes. However, we have witnessed several failures, either in terms of clinically irrelevant benefits or non-statistically significant effects. Prominent examples include EGFR blockade and antiangiogenic therapy. Similarly, initial attempts to target the tumour stroma or to use the hypoxic microenvironment as a target have failed. These failures might be explained by the high molecular heterogeneity and the surrounding stromal and inflammatory components of pancreatic cancer that influence signalling pathways, drug accessibility and metabolism.

In addition, immunotherapies have been successful in several human tumour entities and promise much for the future treatment of pancreatic cancer. However, the immune response is an extremely complex regulatory network, and there has been no breakthrough yet for immunotherapy in this disease.

There have been tremendous improvements in our understanding of the complex molecular makeup of pancreatic cancer and its peculiar microenvironment. The key will be to translate this knowledge into clinical care by identifying subgroups of patients who benefit from certain therapies — that is, to establish precision medicine for pancreatic cancer. This approach requires novel trial designs and interdisciplinary cooperation. The first clinical studies have been initiated along these lines, but it remains a challenge for the future to define subpopulations of patients with pancreatic cancer for whom specific therapies are available and deliverable and to test this approach within well-designed, cost-effective trials.

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