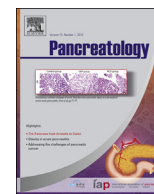


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## Review article

# Addressing the challenges of pancreatic cancer: Future directions for improving outcomes



Manuel Hidalgo <sup>a,\*</sup>, Stefano Cascinu <sup>b</sup>, Jörg Kleeff <sup>c</sup>, Roberto Labianca <sup>d</sup>, J.-Matthias Lohr <sup>e</sup>, John Neoptolemos <sup>f</sup>, Francisco X. Real <sup>g</sup>, Jean-Luc Van Laethem <sup>h</sup>, Volker Heinemann <sup>i</sup>

<sup>a</sup> Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain

<sup>b</sup> Department of Medical Oncology, University of Ancona, Ancona, Italy

<sup>c</sup> Department of General Surgery, Technische Universität München, Munich, Germany

<sup>d</sup> Ospedale Papa Giovanni XXIII, Bergamo, Italy

<sup>e</sup> Department of Clinical Science, Intervention and Technology, Karolinska Institute, Stockholm, Sweden

<sup>f</sup> National Institutes of Health Research Liverpool Pancreas Biomedical Research Unit and Cancer Research UK Liverpool Clinical Trials Unit Director, University of Liverpool and Royal Liverpool University Hospital, Liverpool, UK

<sup>g</sup> Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid and Universitat Pompeu Fabra, Barcelona, Spain

<sup>h</sup> Department of Gastroenterology-GI Cancer Unit, Erasme University Hospital, Brussels, Belgium

<sup>i</sup> Comprehensive Cancer Centre Munich, Klinikum der Universität München, Munich, Germany

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## ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC), which accounts for more than 90% of all pancreatic tumours, is a devastating malignancy with an extremely poor prognosis, as shown by a 1-year survival rate of around 18% for all stages of the disease. The low survival rates associated with PDAC primarily reflect the fact that tumours progress rapidly with few specific symptoms and are thus at an advanced stage at diagnosis in most patients. As a result, there is an urgent need to develop accurate markers of pre-invasive pancreatic neoplasms in order to facilitate prediction of cancer risk and to help diagnose the disease at an earlier stage. However, screening for early diagnosis of prostate cancer remains challenging and identifying a highly accurate, low-cost screening test for early PDAC for use in clinical practice remains an important unmet need. More effective therapies are also crucial in PDAC, since progress in identifying novel therapies has been hampered by the genetic complexity of the disease and treatment remains a major challenge. Presently, the greatest step towards improved treatment efficacy has been made in the field of palliative chemotherapy by introducing FOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan and oxaliplatin) and gemcitabine/nab-paclitaxel. Strategies designed to raise the profile of PDAC in research and clinical practice are a further requirement in order to ensure the best treatment for patients. This article proposes a number of approaches that may help to accelerate progress in treating patients with PDAC, which, in turn, may be expected to improve the quality of life and survival for those suffering from this devastating disease.

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## Introduction

Pancreatic ductal adenocarcinoma (PDAC), the most frequent form of pancreatic cancer, is a common malignancy, with around 280,000 new cases being diagnosed worldwide in 2008, and 70,000 cases seen in the European Union alone [1]. Although PDAC is the twelfth most common cancer worldwide, its low survival rate

means that it is the fourth leading cause of cancer-related death in Western countries [1–3]. Indeed, this tumour is associated with an extremely poor prognosis, as shown by a 1-year survival rate of around 18% for all stages of the disease, falling to less than 4% at 5 years [2]. The low survival rates associated with PDAC primarily reflect the fact that tumours progress rapidly with few specific symptoms and are thus at an advanced stage at diagnosis, with only 10% being operable. Therefore, it is not possible to survive PDAC in the way that colorectal or breast cancer can be survived [4].

While earlier diagnosis of the disease is clearly required to improve outcomes, more effective therapies are also urgently

\* Corresponding author. Centro Nacional de Investigaciones Oncológicas (CNIO), E-28029 Madrid, Spain. Tel.: +34 91 224 6932; fax: +34 91 224 6931.  
E-mail address: [mhidalgo@cnio.es](mailto:mhidalgo@cnio.es) (M. Hidalgo).

needed. However, progress in identifying novel therapies has been hampered by the genetic complexity of the disease and the lack of prognostic markers, underlining the need for new treatment approaches.

**Pathogenesis of pancreatic cancer**

PDAC accounts for more than 90% of all pancreatic tumours, which constitute a heterogeneous set of diseases encompassing cancers of the endocrine and exocrine pancreas. Genetic studies suggest that PDAC develops from one of three known precursor lesions – pancreatic intraepithelial neoplasias (PanINs), intraductal papillary mucinous neoplasms and mucinous cystic neoplasms – though the majority develop from PanINs, progressing from PanIN-1A and -1B through to PanIN-3 [5–7]. There is, however, some debate regarding the PanIN progression model [8,9]. Whole-exome sequencing studies have established that different precursor lesions are associated with distinct genetic alterations that mirror their histological progression (Table 1) [6,7]. Further studies into the genetic features of these initial lesions may provide an opportunity for early diagnosis of the disease while it is still in the curative stage. Genetic data have been interpreted to suggest that development of invasive disease from these precursor lesions occurs over a considerable length of time (17 years on average), with death following after 2–3 years, highlighting the importance of identifying early diagnostic markers [10–12]. Although the unavailability of early-stage tissue from patients with non-invasive precursor lesions has hampered the search for such markers, use of pancreatic cancer mouse models is likely to go some way to further the understanding of tumour initiation and progression [13,14]. Indeed, human PDAC xenografts and genetically-engineered mouse models have already been used to demonstrate the potential for the use of elevated Cath E (a protease highly and specifically expressed in PDAC) in PDAC and PanIN as an imageable, early biomarker for pancreatic cancer [15]. Nevertheless, screening for early diagnosis of pancreatic cancer remains challenging due to the low incidence of the disease, requiring a highly specific and sensitive test [16]. While focussing efforts on high-risk groups comprising those with a syndromic or familial risk of PDAC may improve accuracy, these groups represent only a minority of affected individuals [17–19]. Consequently, identifying an accurate, low-cost screening test for early PDAC for use in clinical practice remains an important unmet need. Given the cost to society, future research efforts are also likely to focus on identifying possible cancer preventative strategies. In the case of PDAC, risk factors for the disease have yet to be determined. However, the recent discovery that oncogenic K-Ras (found in almost all

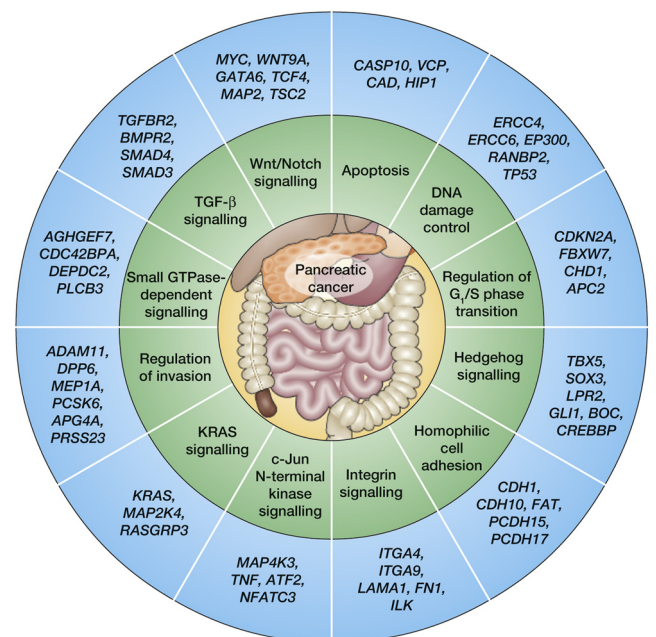
pancreatic cancers) is not constitutively active as previously thought, but requires activation by upstream stimulants [20], presents exciting possibilities for future prevention strategies. Since a large number of healthy individuals harbour Ras mutations [21], interventions aimed at reducing Ras activation is likely to have important cancer-preventive value, particularly in those with oncogenic Ras mutations [20].

Several core signalling pathways have been found to be genetically altered in PDAC, including apoptosis and Hedgehog, transforming growth factor-β (TGF-β) and KRAS signalling, with tumours containing an average of 63 alterations (Fig. 1) [22]. Key genes mutated in the majority of PDAC tumours include KRAS, TP53, SMAD4 and CDKN2A [22,23]. KRAS is an early mutation occurring in PanIN-1A lesions, suggesting that this alteration may play an important role in the initiation of many PDACs [6,24]. Mutations of CDKN2A and TP53 are also known to be involved in PDAC pathogenesis and their inactivation has been observed in around 80% and 50% of tumours, respectively [25,26]. SMAD4 inactivation is a late event present in 50–60% of tumours and may be associated with more aggressive disease [27,28]. Although the complex signalling pathways underlying the development of PDAC have yet to be fully elucidated, genomic analysis of large cohorts of patients can be used to identify common mechanisms and will be key to the development of novel therapeutic strategies for the disease [23]. The tumour microenvironment may also present an opportunity for therapeutic targeting since extensive stromal cross-talk occurs with tumour cells, with stromal–epithelial interactions contributing to tumour spread and metastases [29]. However, recent studies involving elimination of stroma-promoting Hedgehog signalling in mouse models of PDAC indicate that the role of the stroma in PDAC progression is not straight-forward, with some stromal components acting to restrain tumour growth [30]. Further studies are needed, therefore, in order to clarify the value of the stroma as a therapeutic target in PDAC. Additional research is also needed into the role of cancer stem cells (CSCs) in PDAC, since available studies suggest that a small population of these cells may be responsible for tumour initiation and propagation [31,32].

**Table 1**  
Selected somatic alterations in pancreatic ductal adenocarcinoma precursor lesions. Reproduced with permission from Macgregor-Das et al., 2013 [6].

Gene	Genetic alteration	Pathway or regulatory process	Altered in PanINs	Altered in IPMNs	Altered in MCNs
KRAS2	Activating	GTPase-dependent signalling	Yes	Yes	Yes
CDKN2A	Inactivating	Cell cycle regulation	Yes		
TP53	Inactivating	DNA damage response	Yes	Yes	Yes
SMAD4	Inactivating	TGF-β signalling	Yes	Yes	Yes
ARID1A	Inactivating	Chromatin remodelling	Yes		
MLL3	Inactivating	Chromatin remodelling	Yes		
GNAS	Activating	G protein-mediated signalling	No	Yes	
RNF43	Inactivating	Ubiquitin-dependent protein degradation	No	Yes	Yes

PanIN: pancreatic intraepithelial neoplasia; IPMN: intraductal papillary mucinous neoplasm; MCN: mucinous cystic neoplasm.



**Fig. 1.** Core signalling pathways and processes genetically altered in the majority of pancreatic cancers [22].

Furthermore, CSCs appear to be largely resistant to conventional chemotherapy and radiotherapy, suggesting that new therapies that specifically target these cells are necessary in order to improve outcomes.

**Current treatment options and unmet needs in resectable and locally advanced pancreatic cancer**

Survival rates for patients with PDAC are extremely poor, primarily due to the majority of tumours being at an advanced stage at diagnosis (Fig. 2) [33]. Indeed, only 10% of cases are resectable at presentation and more than 90% of patients undergoing potentially curative resection still die of the disease due to local recurrence and/or distant metastases in the absence of adjuvant therapy. There is a developing consensus on the definitions of an R0, R1 and R2 resection, permitting better comparison between studies [34,35]. Using a systematic approach to examining the resected specimen in the clinical pathology laboratory, a macroscopically clear resection is defined as R0 if there are no tumour cells within 1 mm of any surface, R1 if one or more tumour cells are visible within 1 mm of any surface and R2 where the resection is macroscopically incomplete. Using this definition, around 70% of macroscopically clear resections are actually R1 resections [34,35]. Nevertheless, it is apparent that survival in patients with an R0 resection is only marginally longer than in those with an R1 resection provided adjuvant chemotherapy is used [36–38].

The high rate of recurrence in PDAC is mostly caused by occult primary metastases, but may also be a result of microscopically incomplete resection and other biological features of the tumour such as frequent neural invasion [39], highlighting the importance of specialized surgeons and pathologists in the treatment of this condition. Accurate selection of the patients who are eligible for macroscopic (R0 or R1) resection with adjuvant chemotherapy is also vital, since median survival following incomplete macroscopic surgical resection (R2) of the primary tumour is comparable to that of patients with inoperable locally advanced disease treated with chemotherapy [34–38,40–42]. There is also a growing consensus on the radiological definitions of ‘resectable’, ‘borderline resectable’ and ‘unresectable’, and the National Comprehensive Cancer Network in the USA has endorsed a modified consensus from the Americas Hepato-Pancreato-Biliary Association, the Society of

Surgical Oncology and the Society for Surgery of the Alimentary Tract [43,44].

Current imaging modalities used for preoperative staging include abdominal ultrasound, computed tomography, magnetic resonance imaging and endoscopic ultrasonography. Of these, computed tomography may be the best means of assessing resectability initially based on vascular involvement, while endoscopic ultrasonography has the ability to detect small lesions and may be optimal for the diagnosis of PDAC in subjects with non-specific findings on conventional imaging [45]. Endoscopic ultrasonography combined with fine needle aspiration or needle biopsy is also becoming essential in order to obtain tumour samples for determination of the biomolecular profile that will drive outcome and treatment response [46]. Other techniques under investigation include multi-parametric imaging and functional and molecular markers. Functional markers currently being studied as indicators of disease progression include stromal changes, microvascular density and tumour metabolism [47,48]. CXCR4 is the only molecular candidate to date to correlate with rapid and metastatic progression, while for SMAD4, current data are not robust enough for identification of a locoregional recurrence pattern [49].

The poor survival rate associated with surgery alone for early-stage PDAC has led to adjuvant therapy becoming the standard of care after resection in an effort to prolong survival (Table 2) [36–38,40,50–60]. Approaches differ between Europe, where gemcitabine-based chemotherapy tends to be the standard adjuvant therapy, and the USA, where both fluoropyrimidine-based chemoradiotherapy and chemotherapy (preferentially with gemcitabine) are accepted standards. While meta-analyses of data from randomized controlled trials have shown a disease-free survival and overall survival benefit for adjuvant chemotherapy [61,62], the role of adjuvant chemoradiation is not established, with mounting evidence being non-supportive of its use [36,40,55,63,64]. Adjuvant gemcitabine does not result in longer survival than adjuvant 5-fluorouracil (5-FU) [30,46], and a 5-FU prodrug combination (S-1) has recently been shown in a study from Japan to greatly increase survival over gemcitabine [38]. The S-1 oral preparation combines tegafur (the 5-FU prodrug) with gimeracil (an inhibitor of dihydropyrimidine dehydrogenase that otherwise degrades 5-FU) and oteracil, which helps to reduce gastrointestinal-related toxicity by inhibiting 5-FU phosphorylation within the gastrointestinal lumen.

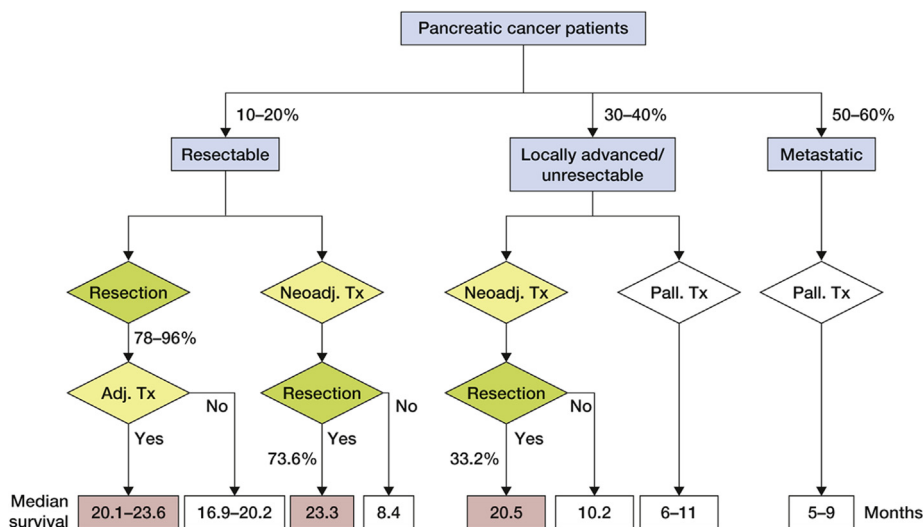


Fig. 2. Summary of survival and resection percentages for patients with pancreatic cancer. Reproduced with permission from Gillen et al., 2010 [33]. Neoadj.: neoadjuvant; Tx: treatment; Pall.: palliative; Adj.: adjuvant.

**Table 2**  
Randomized controlled trials of adjuvant therapy in patients with resectable pancreatic cancer.

Study	Treatment	N	Median survival (months)	Five-year survival (%)
Neoptolemos et al., 2001 [40]	Surgery + CRT (bolus 5-FU + EBRT)	175	15.5	NR
	Surgery + No CRT	178	16.1 ( $p = 0.235$ )	NR
Takada et al., 2002 [50]	Surgery	77	NR	18
	Surgery + CT (MF)	81	NR (NS; $p$ value NR)	11.5
Neoptolemos et al., 2004 [36]	Surgery	144	17.9	20
	vs.			
	Surgery + CRT (bolus 5-FU + EBRT)	145	15.9 ( $p = 0.05$ )	10
	Surgery	142	15.5	8
Kosuge et al., 2006 [51]	vs.			
	Surgery + CT (5-FU, 6 cycles)	147	20.1 ( $p = 0.009$ )	21
	Surgery	44	15.8	14.9
Regine et al., 2008 [52]	Surgery + CT (cisplatin/5-FU, only 2 cycles)	45	12.5 ( $p = 0.94$ )	26.4
	Surgery + CT (5-FU, 1 cycle) + CRT (5-FU + EBRT) + CT (5-FU, 3 cycles)	230	17	NR
	Surgery + CT (gemcitabine, 1 cycle) + CRT (5-FU + EBRT) + CT (gemcitabine, 3 cycles)	221	19 ( $p = 0.34$ )	NR
Neoptolemos et al., 2009 [53]	Surgery	225	16.8	NR
	Surgery + CT (5-FU, 6 cycles)	233	23.2 ( $p = 0.003$ )	NR
Ueno et al., 2009 [54]	Surgery	60	18.4	NR
	Surgery + CT (gemcitabine, 3 cycles)	58	22.3 ( $p = 0.29$ )	NR
Van Laethem et al., 2010 [55]	Surgery + CT (gemcitabine, 4 cycles)	45	24.4	NR
	Surgery + CT (gemcitabine, 2 cycles) + CRT (gemcitabine + EBRT)	45	24.3 (NS; $p$ value NR)	NR
	Surgery + CT (gemcitabine, 6 cycles)	551	23.0	16.6
Neoptolemos et al., 2010 [37]	Surgery + CT (5-FU, 6 cycles)	537	23.6 ( $p = 0.94$ )	19.2
	Surgery + CT (gemcitabine, 6 cycles)	193	11.2	NR
Uesaka et al., 2012 [56]	Surgery + CT (gemcitabine, 6 cycles)	192	23.2 ( $p < 0.0001$ )	NR
	Surgery + CT (S-1, 4 cycles)	175	20.2	12.2
Oettle et al., 2013 [57]	Surgery	179	22.8 ( $p = 0.01$ )	20.7
	Surgery + CT (gemcitabine, 6 cycles)	191	25.5	NR
Fukutomi et al., 2013 [38]	Surgery + CT (gemcitabine, 6 cycles, 24 weeks)	187	46.3 ( $p < 0.0001$ )	NR
	Surgery + CT (S-1, 4 cycles, 24 weeks)			

CRT: chemoradiotherapy; 5-FU: 5-fluorouracil; EBRT: external beam radiotherapy; NR: not reported; CT: chemotherapy; MF: mitomycin C followed by 5-FU; NS: not significant; S-1: 5-FU prodrug combination (tegafur, gimeracil and oteracil).

Valle and coworkers defined completion of all six cycles of planned adjuvant chemotherapy as a more important prognostic factor than early start of chemotherapy; a modest delay of the start of treatment until adequate recovery from surgery has taken place may increase compliance in some patients and thus prevent treatment discontinuation [65].

The early metastasizing nature of pancreatic cancer [66], along with the large proportion of patients presenting with locally advanced disease and the high frequency of microscopic incomplete resections [34,35], provides a strong rationale for neoadjuvant systemic therapy [66]. Review of the limited evidence suggests that neoadjuvant therapy does not confer a survival advantage over resection followed by adjuvant therapy for those with initially resectable tumours [33]. This is not surprising given the low effectiveness of the systemic therapy used at that time. Nevertheless, neoadjuvant approaches employing increasingly active chemotherapeutic regimens in metastatic PDAC (e.g. FOLFIRINOX [folinic acid, 5-FU, irinotecan and oxaliplatin], gemcitabine plus nab-paclitaxel and/or chemoradiotherapy) may allow downstaging of borderline resectable disease and some locally advanced cases, improving R0 resection and survival [67]. Prospective randomized studies will be required to define the potential benefit of this approach [67–70]. For those with unresectable locally advanced disease, treatment options include FOLFIRINOX, gemcitabine-based chemotherapy or chemoradiotherapy [71–77]. While chemoradiotherapy results in longer survival in patients with locally advanced PDAC compared with radiation alone or no treatment, it does not provide longer survival than systemic chemotherapy alone and increases toxicity [63,64,71,72,75,77]. Recent data from the LAP 07 study also indicate that after induction chemotherapy, further treatment with chemoradiotherapy has no benefit over continuation of chemotherapy alone in patients with locally advanced PDAC [77].

### Challenges in the treatment of metastatic disease

For patients with metastatic PDAC, the primary goals of treatment are palliation and improved survival, yet effective treatments for this population are limited, leading to extremely poor survival rates (5–9 months) [33]. Gemcitabine has been the standard treatment for metastatic disease, primarily due to its effect on symptoms and favourable toxicity profile rather than a significant effect on survival [73]. However, the combination of gemcitabine with other agents such as platinum analogues or capecitabine have not resulted in a substantive improvement, though a combination of gemcitabine and oxaliplatin may confer an additional but small survival benefit in patients with good performance status and a younger age (Table 3) [78–90]. In the UK, gemcitabine plus capecitabine is a standard of care for patients with metastatic as well as locally advanced disease [72,90,91]. FOLFIRINOX has been shown in a recent phase III study to result in longer survival compared with gemcitabine (11.1 vs. 6.8 months, respectively) as well as delaying deterioration of quality of life [69]. Additionally, a combination of gemcitabine with nab-paclitaxel improved overall survival versus gemcitabine alone in the phase III *Metastatic Pancreatic Adenocarcinoma Clinical Trial* (MPACT) (8.5 vs. 6.7 months, respectively) [70]. It should be noted, however, that the patient groups included in these trials (relatively younger patients with good performance status [0 or 1], limited volume of disease, no biliary obstruction and a relatively low proportion with pancreatic head tumours) may not be entirely representative of the patient population encountered in routine clinical practice. Furthermore, both the FOLFIRINOX and gemcitabine with nab-paclitaxel regimens are more toxic than gemcitabine alone, which may limit their use to relatively younger patients with good performance status [69,70]. Gemcitabine alone remains a standard treatment for elderly patients [92] or those with poor performance and nutritional status; appropriate identification

**Table 3**  
Randomized trials comparing gemcitabine with the combination of gemcitabine plus a platinum analogue or a fluoropyrimidine as first-line therapy in patients with metastatic pancreatic cancer.

Study	Treatment	N	ORR (%)	Median PFS/TTP (months)	Median survival (months)
<b>Gemcitabine vs. gemcitabine plus a platinum analogue</b>					
Colucci et al., 2002 [78]	Gemcitabine	54	9.2	2.0	5.0
	Gemcitabine + cisplatin	53	26.4 ( $p = 0.02$ )	5.0 ( $p = 0.048$ )	7.5
Viret et al., 2004 [79]	Gemcitabine	41	5	2.5	6.7
	Gemcitabine + cisplatin	42	7	2.2 (NS; $p$ value NR)	8.0 ( $p = 0.73$ )
Louvet et al., 2005 [80]	Gemcitabine	156	17.6	3.7	7.1
	Gemcitabine (FDR) + oxaliplatin	157	26.8 ( $p = 0.048$ )	5.8 ( $p = 0.04$ )	9.0
Heinemann et al., 2006 [81]	Gemcitabine	95	8.2	3.1	6.0
	Gemcitabine + cisplatin	95	10.2	5.3 ( $p = 0.053$ )	7.5 ( $p = 0.15$ )
Poplin et al., 2009 [82]	Gemcitabine	275	6	2.6 ( $p = 0.09$ )	4.9 ( $p = 0.015$ )
	Gemcitabine (FDR)	277	10.4	3.7	6.2
	Gemcitabine (FDR) + oxaliplatin	272	9.4	2.7	5.7
Colucci et al., 2010 [83]	Gemcitabine	199	10.1	3.9	8.3
	Gemcitabine + cisplatin	201	12.9	3.8 ( $p = 0.8$ )	7.2 ( $p = 0.38$ )
Inal et al., 2012 [84]	Gemcitabine	156	NR	8.9	12.0
	Gemcitabine + cisplatin	250		6.0 ( $p = 0.08$ )	10.5 ( $p > 0.05$ )
<b>Gemcitabine vs. gemcitabine plus a fluoropyrimidine</b>					
Berlin et al., 2002 [85]	Gemcitabine	162	5.6	2.2	
	Gemcitabine + 5-FU (bolus)	160	6.9	3.4 ( $p = 0.22$ )	5.46.7 ( $p = 0.09$ )
Scheithauer et al., 2003 [86]	Gemcitabine	42	14	4.0	8.2
	Gemcitabine + capecitabine	41	17	2.1 (NS; $p$ value NR)	9.5 (NS; $p$ value NR)
Riess et al., 2005 [87]	Gemcitabine	238	7.2	3.5 ( $p = 0.44$ )	6.2 ( $p = 0.68$ )
	Gemcitabine + 5-FU (infusional)	235	4.8	3.5	5.9
Di Costanzo et al., 2005 [88]	Gemcitabine	48	8	3.5	7.8
	Gemcitabine + 5-FU (continuous infusion)	43	11	4.5	7.5
Herrmann et al., 2005 [89]	Gemcitabine	159	7.9	4.0 ( $p = 0.207$ )	7.3 ( $p = 0.314$ )
	Gemcitabine + capecitabine	160	10.1	4.8	8.4
Cunningham et al., 2009 [90]	Gemcitabine	266	12.4	3.8	6.2
	Gemcitabine + capecitabine	267	19.1 ( $p = 0.034$ )	5.3 ( $p = 0.004$ )	7.1 ( $p = 0.08$ )

ORR: objective response rate; PFS: progression-free survival; TTP: time to progression; NS: not significant; NR: not reported; FDR: fixed dose rate; 5-FU: 5-fluorouracil.

of candidates who are suitable for monotherapy may spare unnecessary toxicity.

The combination of gemcitabine and the epidermal growth factor receptor (EGFR) inhibitor erlotinib has been approved for the treatment of metastatic disease by the US Food and Drug Administration and the European Medicines Agency following demonstration of a minimal survival benefit (6.24 vs. 5.91 months for gemcitabine) in a phase III trial [93]. However, the role of erlotinib in PDAC has been called into question due to its low clinical activity. In addition, its benefit only appears to be clinically relevant in those who develop skin rash. Increasing the dose of erlotinib until the rash occurs does not appear to be beneficial since the strategy increases toxicity but not survival. Since erlotinib-induced rash is apparent during the first 8 weeks of treatment, however, it may be possible for patients with metastatic disease to receive gemcitabine plus erlotinib, with erlotinib continuing beyond 8 weeks only in those who develop the rash [73], though these contentions require additional evidence. Although the results of initial trials with erlotinib in unselected populations have been disappointing [93], the agent may be useful in *KRAS*-mutant *p53* wild-type tumours (~15% of patients), but again prospective evidence is lacking.

Between 40% and 50% of patients with metastatic PDAC receive second-line treatment after disease progression, generally those responding to first-line therapy who have good performance status. While the optimal therapy in this setting has not been established [73], clinical activity has been reported with the combination of 5-FU and oxaliplatin and also with FOLFIRI (5-FU, irinotecan and leucovorin) [94–96]. Gemcitabine monotherapy is also reported to be an effective second-line treatment and may be useful for patients who have received first-line FOLFIRINOX [95]. In each case, optimal treatment selection for patients with metastatic disease should take into account their age and performance status, since combination therapy has no benefit for those with a performance

status  $\geq 2$  [91,92]. Nutritional support is a further important issue for such patients as it improves treatment adherence, possibly leading to improved quality of life and better outcomes. Patients with locally advanced tumours [97], as well as those who have had resection for tumours in the head of the pancreas, have reduced exocrine function and benefit from pancreatic enzyme supplementation [98]. Further randomized trials are needed in order to define the best therapy for elderly patients and for those with poor performance status or nutritional status.

### New targets for drug treatment and the promise of biomarkers in pancreatic cancer

PDAC is genetically very complex with a high diversity of mutations compared with other cancers; however, most alterations occur with very low frequency and so are challenging to exploit therapeutically. Furthermore, while *KRAS*, *p16*, *TP53* and *SMAD4* are the most commonly mutated genes in PDAC [6,22,23,28,99], no effective inhibitors of these targets have been identified to date. Nevertheless, a number of new targets are currently being investigated including genes associated with chromatin remodelling, DNA damage repair (e.g. *BRACA1* and *BRACA2*) and mutated axon guidance (e.g. *ROBO3* and *ROBO1/2*) [23,100]. The results of research with *KRAS*-driven PDAC mouse models support an important role for EGFR early during PDAC progression [101–103]. Preclinical studies suggest a role for phosphoinositide 3-kinase (PI3K) inhibitors in PDAC [104], with consideration being given to the possibility of combining PI3K inhibitors with other targeted therapies (e.g. MEK or AKT inhibitors), though toxicity may be an issue with this approach [105]. CSCs are also being investigated as a potential target in PDAC due to their putative involvement in resistance and metastases [106]. Since current chemotherapeutic agents appear to be largely ineffective at depleting the CSC pool, their combination

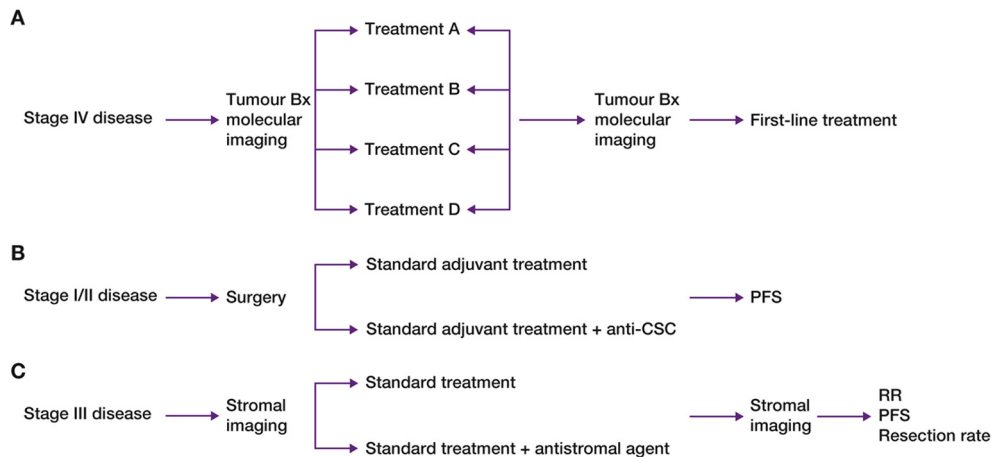
with a CSC-targeted agent may promote tumour regression. This strategy has already shown promise in preclinical models, with the combination of gemcitabine and tigatuzumab (an agonist of death receptor 5, which is enriched in pancreatic CSCs) shown to be more effective in killing both CSCs and bulk tumour cells than gemcitabine alone [106].

A further factor that may contribute to the failure of systemic therapy in PDAC is the abundant stromal content and poor blood supply associated with the disease. Moreover, it has been suggested that the tumour microenvironment may act as a pharmacological barrier, raising the possibility that it could be a therapeutic target [107,108]. A number of strategies are being investigated to target the tumour stroma and vasculature, including inhibition of TGF- $\beta$ , which plays a key role in stroma formation, the Notch/Hedgehog pathway and use of pegylated hyaluronidase to decrease intra-tumoural pressure and increase vascularization, though phase II trials with the latter were halted due to unexpected adverse events [107,109,110]. Secreted protein acidic and rich in cysteine (SPARC) is a further means of targeting the stroma in PDAC since it is over-expressed by fibroblasts in the tumour microenvironment and is inversely correlated with survival [111,112]. Nevertheless, as noted earlier, further research is required to clarify the potential of the stroma as a therapeutic target. The concept of a stromal barrier is also controversial, with a number of studies reporting that systemic drugs such as gemcitabine and larger agents are able to enter PDAC in genetically engineered mouse models of the disease [15,113], suggesting that entry of drugs into pancreatic tumours may not be a major obstacle for therapeutics.

Progress in identifying novel agents for new targets in PDAC could be accelerated by more appropriate trial design [114]. In particular, trial designs should be modified according to disease stage, with molecular imaging and repeat biopsy used to monitor disease progression (Fig. 3) [114]. In addition, there must be increased efforts to understand the molecular effects of novel drugs prior to clinical testing, with animal models such as patient-derived xenografts and genetically engineered mouse models used to screen novel drugs targeting rare mutations. The development of biomarkers that predict response to these novel agents is also crucial, though any potential markers should be evaluated carefully to ensure effective development, with validation

undertaken according to the REporting recommendations for tumour MARKer prognostic studies (REMARK) guidelines [115,116]. Further aspects that must be taken into account in biomarker development include factors associated with the drug itself, as well as its impact on the stroma and target cell. Drug levels should ideally be examined in both the tumour and blood, with germ cell single nucleotide polymorphisms (SNPs) that affect drug metabolism being considered as they can determine drug response. Stromal factors to be taken into account include the roles played by vascularity, lymphatic density, stromal volume and inflammatory infiltrate. With respect to the target cell, considerations include drug uptake and export, activation and inactivation, drug–drug interaction and other contingent factors, including genetic mutations and protein and microRNA expression.

The range of different approaches employed for biomarker discovery (e.g. Luminex multiplex technology and transcriptomic analysis) have yet to produce a biomarker used in clinical practice, though a number of promising possibilities are on the horizon. One of these biomarkers, the human equilibrative nuclear transporter type-1 (hENT1), is important for the transport of gemcitabine into and out of PDAC cells [117], and may be useful for selecting patients who would better respond to either gemcitabine- or 5-FU-based adjuvant regimens [118–120]. So far, the predictive value of hENT1 has only been shown in the setting of adjuvant therapy, while hENT1 expression was not associated with efficacy of gemcitabine applied for palliative treatment [121]; however, expression in this latter study was quantified using a different anti-hENT1 antibody from that in the adjuvant studies [118–120]. Before incorporation of hENT1 determination into clinical practice, problems associated with methodological aspects need to be resolved, particularly elucidation of the optimal anti-hENT1 antibody [120]. SPARC expression has also been proposed to correlate with increased survival in patients treated with nab-paclitaxel in a phase I/II trial [122]. However, most recent data from an evaluation of the phase III MPACT study support the notion that SPARC expression in the stroma does not serve as a predictor of treatment efficacy in patients receiving the combination of gemcitabine and nab-paclitaxel [123]. Clearly, more research is required to understand the true role of SPARC in this context.



**Fig. 3.** Potential clinical trial designs in pancreatic cancer. Reproduced with permission from Hidalgo and Von Hoff 2012 [114]. (A) Screening trial of new agents in patients with advanced disease. After a tumour biopsy with or without molecular imaging, patients are randomized to receive one of several new agents for a short period of time followed by a second tumour biopsy and appropriate imaging. Patients then proceed to receive first-line treatment. Analysis of paired tumour biopsies and molecular imaging allows the selection of molecularly active drugs to be further developed. (B) Trial design to test anticancer stem cell therapeutics. These agents are more likely to be effective in situations of minimal disease, such as in the adjuvant setting, rather than in stage IV disease. (C) Clinical trial design for drugs targeting the cancer stroma. Due to the preponderance of tumour stroma in patients with locally advanced disease this represents an ideal clinical scenario in which to test stroma-modulating drugs. Bx: biopsy; CSC: cancer stem cell; PFS: progression-free survival; RR: response rate.

To increase the identification of novel biomarkers, blood and tissue samples should be collected from all patients in clinical trials. This practice is already being performed routinely in trials conducted by the European Study Group for Pancreatic Cancer (ESPAC) [36,37,40,124], which has accumulated a wealth of samples for future analysis and provides an excellent resource for future studies of the disease.

### New approaches in drug development

The lack of effective therapies and predictive markers for PDAC has resulted in very poor survival rates for this devastating disease. Furthermore, despite being the fourth leading cause of cancer-related death, PDAC receives limited attention and research funding, and spending on it lags behind that on other cancers. Although the biology of PDAC has been well studied, progress in identifying new molecular targets has been slow and few candidate therapies are registered for the disease, possibly due to its genetic complexity and histological make-up [22,125]. However, opportunities exist for exploiting cellular therapeutic targets in PDAC including the stroma, immune system, blood vessels and cell division. The stroma in particular is a key target, since tumour–stroma interactions have been implicated in cancer cell invasion and metastases and contribute to chemoresistance [117,118]. The quest for more effective therapies for PDAC has also led to research into various immunotherapeutic strategies in an effort to reprogramme the immune system to enable more effective detection and destruction of pancreatic tumour cells. Potential immune therapies include T-cell, DNA or RNA vaccination, anti-CD40 agents, antibodies against programmed cell death protein 1 (PD1) and cytotoxic T-lymphocyte associated antigen-4 binding, and strategies aimed at targeting

TGF- $\beta$  [126–130]. TGF- $\beta$  is not only associated with stroma development [131], but is also responsible for a profound immunosuppression that is characteristic of PDAC [132]. Overcoming this immune suppression is an important challenge to be taken into account in the development of novel agents for the treatment of the disease [39]. Multi-targeted agents inhibiting the stroma, kinases and apoptosis, such as genistein, are also being investigated [133].

Opportunities for personalized medicine have begun to emerge in PDAC as a result of advances in the knowledge of PDAC biology. The importance of *SMAD4* in PDAC pathogenesis has been recognized for many years and *SMAD4* gene status of the primary carcinoma has been shown to correlate with distinct patterns of treatment failure in patients with the disease [28,134]. Furthermore, response to irinotecan has been shown to differ in *SMAD4* mutant and wild-type cancer cells, raising the possibility of personalized chemotherapy for future patients with PDAC [135]. The availability of whole genome sequencing also allows rare mutations to be identified in individual patients and targeted specifically, offering further potential for personalized medicine. However, a more structured approach to the application of this technology is needed in the future in order to maximize its potential.

### Strategies for improving pancreatic cancer outcomes across Europe

There has been little progress in improving outcomes in PDAC over the past 30 years and mortality rates closely match incidence, leading to a mortality incidence ratio of 0.98 [136]. One of the problems contributing to the limited advances in PDAC is the complex nature of the disease, with each tumour cell carrying an

**Table 4**  
Challenges in pancreatic cancer management in Europe and strategies for addressing them.

Challenge	Strategy for addressing it
<p>Management of patients with PDAC differs widely across Europe:</p> <ul style="list-style-type: none"> <li>• Platinum compounds are still used in some countries despite the lack of evidence supporting their use</li> <li>• Attitudes towards second-line therapy vary</li> <li>• Use of radiotherapy varies between countries for patients with similar clinical presentations</li> </ul>	<ul style="list-style-type: none"> <li>• Standardization of management across the region</li> <li>• Treatment selection based on evidence-based national and international guidelines</li> <li>• Harmonization of treatment guidelines in order to have a rational approach to management</li> <li>• Randomized controlled trials using a standardized protocol for pancreatic specimen examination for ease of comparison between studies</li> </ul>
<p>Treatment is dependent on the national setting and on the organization of oncology, surgery and radiotherapy services:</p> <ul style="list-style-type: none"> <li>• Molecular biological techniques are not available in all centres</li> <li>• Experienced radiologists are required for accurate staging</li> <li>• Some chemotherapy regimens require strict monitoring to avoid toxicity</li> </ul> <p>Access and funding for clinical trials is limited and varies between countries</p>	<ul style="list-style-type: none"> <li>• Referral of patients to specialist centres with surgical expertise</li> <li>• Management of patients within multidisciplinary teams comprising experts in surgery, radiotherapy, chemotherapy, molecular biology and staging</li> </ul>
<p>The majority of patients are not diagnosed with PDAC until they have advanced or metastatic disease; end of life is generally characterized by severe symptoms and poor quality of life</p>	<ul style="list-style-type: none"> <li>• Development of PDAC networks to improve access to trials and to coordinate collaboration between healthcare professionals and industry to improve outcomes</li> <li>• Cooperation between industry and academia to: <ul style="list-style-type: none"> <li>○ Ensure that trials are relevant to clinical practice</li> <li>○ Improve access to newly registered drugs (e.g. nab-paclitaxel)</li> </ul> </li> <li>• Early introduction of palliative care alongside chemotherapy to improve quality of life, mood and outcomes</li> <li>• Identification of sensitive and specific biomarkers to improve diagnosis of the disease, with prospective markers validated according to REMARK guidelines</li> </ul>
<p>The molecular biology of PDAC has been well studied but has resulted in few effective targeted therapies</p>	<ul style="list-style-type: none"> <li>• Employment of alternative strategies involving cellular therapeutic targets including the stroma, immune system, blood vessels and cell division</li> <li>• Use of personalized medicine approaches involving <i>SMAD4</i> gene status or whole genome sequencing to identify rare mutations</li> <li>• Use of PDAC mouse models to improve the understanding of tumour initiation and progression</li> </ul>

PDAC: pancreatic ductal adenocarcinoma; REMARK: REporting recommendations for tumour MARKer prognostic studies.

average of 63 mutations [22]. However, while the need for molecular characterization of different cancers is well recognized and has been highlighted by the American Society for Clinical Oncology as a key factor for accelerating progress in cancer [137], the organization and society in general have paid little attention to PDAC to date. Strategies designed to raise the profile of PDAC, in both research and clinical practice, are thus urgently needed in order to ensure the best treatment for patients. Given the increasing life expectancy of many populations worldwide, the incidence of PDAC is likely rise in the next few decades, underlining the importance of this contention.

Currently, the management of patients with PDAC differs widely across Europe. While the treatment of patients within specialist centres and management by multidisciplinary teams (MDTs) has been the norm in some countries like the UK and the Netherlands for more than a decade, in others, MDT management is not enforced and treatment within specialist centres relies on patients' proximity to these hospitals. Such variations can impact substantially on both access to clinical trials and outcome; standardization of patient management across Europe could well improve the outlook for individuals with PDAC. A further factor that may improve outcomes for patients with PDAC is the introduction of palliative care soon after diagnosis, since this approach had been shown to result in improvement in both quality of life and survival in patients with non-small cell lung cancer [138,139]. Additional approaches aimed at improving outcomes in PDAC are listed in Table 4.

## Summary

PDAC has the poorest survival rate among common cancers [3], which is primarily attributed to the advanced stage of disease in most patients at diagnosis. Therefore, there is an urgent need to discover accurate markers of pre-invasive pancreatic neoplasms in order to facilitate prediction of cancer risk and to help diagnose the disease at an earlier stage, along with the identification of an accurate, low-cost screening test for early PDAC for use in clinical practice. The development of more effective therapies is also crucial in PDAC, since new advances have been limited in recent years and treatment of the disease remains a major challenge. This article proposes a number of strategies that may help to accelerate progress in treating patients with the condition. It is hoped that incorporation of some of these approaches will go some way to improving quality of life and survival for individuals with this devastating disease.

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