

# Current concepts and novel targets in advanced pancreatic cancer

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## ABSTRACT

Pancreatic cancer remains one of the most aggressive tumours with a 5-year survival rate of less than 5%. The dismal prognosis of this tumour entity that is associated with a high degree of drug resistance has not changed over the past decades. Since 1997, gemcitabine-based regimens have been the therapy of choice for advanced pancreatic cancer. Recently, however, new combination chemotherapy regimens achieved a significant survival benefit compared to gemcitabine-based therapies. In addition, novel approaches to improve drug delivery are currently being developed, and new drugs targeting signalling pathways both within the tumour cells and the tumour microenvironment are undergoing preclinical and clinical validation. Furthermore, efforts are being made to identify predictive markers for individualised treatment approaches based on molecular tumour characteristics. This review provides an overview on current and emerging concepts as well as novel targets for systemic treatment of advanced pancreatic cancer. Combination therapies incorporating drugs directed against these new targets may open new avenues for improving the efficacy of current treatment approaches and overcoming the devastating prognosis of pancreatic cancer patients.

## INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is associated with a 5-year survival rate of less than 5% and a median survival of 6 months after diagnosis, thereby exhibiting the poorest prognosis of all solid tumours.<sup>1,2</sup> It is characterised by a high propensity for local invasion and distant metastasis as well as a largely drug-resistant phenotype. At presentation, only approximately 20% of PDAC patients qualify for surgical resection in curative intent. Even for those, the 5-year survival rate rarely exceeds 20% due to early relapse or metastatic spread of the disease. The vast majority of patients, however, already present with locally advanced or metastatic disease, which is associated with an extremely poor prognosis.<sup>3</sup>

The current management of PDAC is guided by tumour stage, comorbidities and performance status of the patients. Surgical resection followed by a 6-month-course of adjuvant gemcitabine-based chemotherapy is the standard of care for early-stage disease (figure 1).<sup>3</sup> In contrast, patients with metastatic disease are candidates for systemic palliative chemotherapy. For patients with locally advanced disease without evidence of metastasis, optimal treatment remains to be defined, with chemotherapy alone as well as chemoradiation to be considered (figure 1).

This review focuses on current and emerging therapeutic concepts for patients presenting with metastatic or locally advanced disease, for which surgery in curative intent is not an option.

## CURRENT MANAGEMENT Metastatic disease

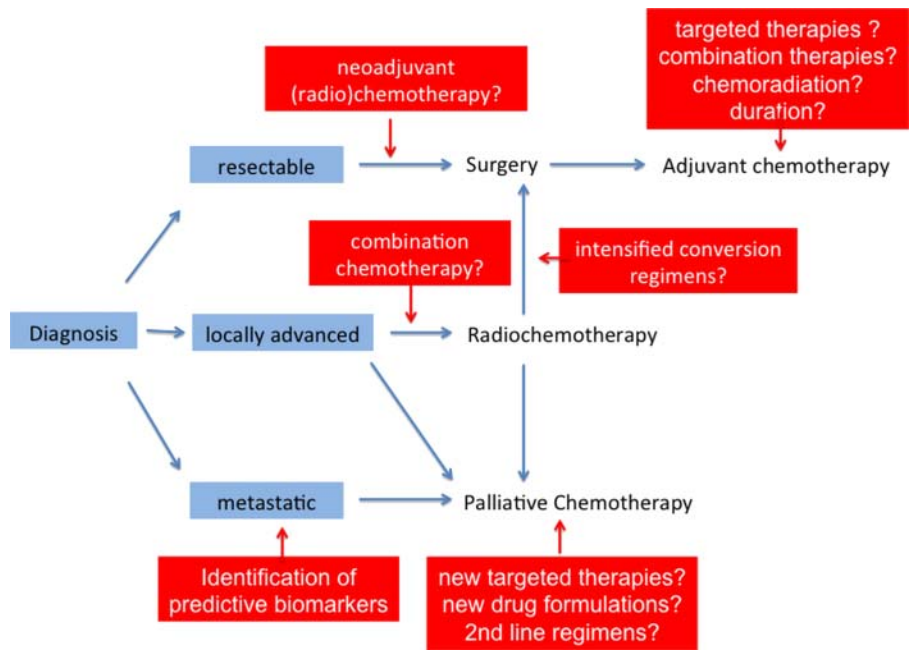
Since 1997, the nucleoside analogue gemcitabine has been established as standard of care in metastatic PDAC. Burris *et al*<sup>4</sup> published the results of a phase III trial comparing 5-fluorouracil (5-FU), which had been used frequently by that time, with gemcitabine as a single agent administered as a weekly intravenous injection. Treatment with gemcitabine resulted in a superior clinical response compared to 5-FU and was associated with a significant, but modest survival benefit (median survival 5.65 vs 4.41 months). In addition, the clinical benefit response, a composite score for pain (analgesic consumption and pain intensity), Karnofsky performance score and weight, was in favour of gemcitabine leading to US Food and Drug Administration approval and the establishment of gemcitabine as standard of care in first-line palliative therapy for advanced PDAC.<sup>3</sup>

Over the past decade, numerous trials have been conducted to improve the outcome in patients with metastatic disease by combination therapies using gemcitabine as backbone. Most trials used a second cytotoxic agent such as 5-FU,<sup>5</sup> capecitabine,<sup>6</sup> oxaliplatin,<sup>7,8</sup> cisplatin,<sup>9,10</sup> irinotecan,<sup>11</sup> exatecan<sup>12</sup> or pemetrexed<sup>13</sup> administered in combination with gemcitabine. However, despite a modest improvement in progression-free survival in some trials, a significant benefit in overall survival could not be demonstrated for any of these combination therapies.<sup>3</sup>

Despite these discouraging results of single trials, a recent meta-analysis by Heinemann *et al*<sup>14</sup> suggests a benefit of combination therapies in patients with good performance status. By analysing 15 randomised trials of combination therapies, the authors showed a significant survival benefit when gemcitabine was combined with either a platinum derivative or fluoropyrimidines. This was, however, restricted to patients with good performance status. Another meta-analysis by Sultana *et al*<sup>15</sup> confirmed the benefit of combination therapy with gemcitabine and a platinum compound. In that meta-analysis, however, combination with fluoropyrimidines only resulted in improved survival when the oral analogue capecitabine was used as the partner drug. Taken together, these data indicate that there might be a

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**Figure 1** Overview on current stage-dependent treatment strategies and new approaches for improvement of pancreatic cancer therapy.



significant, albeit small, survival benefit for gemcitabine-based combination therapies in patients with good performance status.

Conroy *et al*<sup>16</sup> recently reported the first significant improvement in overall survival using a gemcitabine-free combination therapy regimen. In the landmark PRODIGE trial published in 2011, the authors used the FOLFIRINOX protocol (folinic acid, fluorouracil, irinotecan and oxaliplatin), which resulted in a remarkably improved overall survival of 11.1 months compared to 6.8 months in the control arm using gemcitabine alone.<sup>16</sup> As expected, the side effects of this new combination regimen were significant, including a grade 3 and 4 neutropenia rate of 45.7%. Interestingly, pancreatic head tumours requiring biliary stents accounted for only 14.3% of all patients, which might explain the low observed incidence of cholangitis. Taken together, this new regimen represents a new treatment standard for patients with metastatic PDAC that should be preferred to gemcitabine-based combination regimens in carefully selected patients with good performance status and without contraindications.

### Second-line therapy in metastatic disease

Only a few trials have evaluated the use of second-line regimens after the failure of first-line therapy. The only randomised trial in this context tested the combination of oxaliplatin and 5-FU versus best supportive care after failure of gemcitabine-based first-line therapy. Although the trial was prematurely terminated due to insufficient accrual, the oxaliplatin and 5-FU protocol resulted in a significantly prolonged median second-line survival of 4.82 months compared to 2.30 months with best supportive care.<sup>3 17</sup> This suggests that a sequential administration of a 5-FU and platinum-based combination regimen after gemcitabine-based monotherapy is able to provide a survival benefit.<sup>3</sup>

### Targeted therapies in metastatic disease

During the past decade, numerous targeted agents have been evaluated alone or in combination with chemotherapy in metastatic PDAC. Unfortunately, most agents have so far failed to

improve patient survival significantly. The long list of agents tested in trials as futile include antiangiogenic drugs such as the vascular endothelial growth factor (VEGF) antibody bevacizumab and multikinase inhibitors with antiangiogenic activity such as axitinib, sunitinib and sorafenib.<sup>18–20</sup> The same applies for various other targeted agents directed against secreted matrix proteases<sup>21</sup> or against intracellular targets such as farnesyl transferase inhibitors.<sup>22</sup>

To date, inhibition of the epidermal growth factor receptor (EGFR) pathway by the small molecule inhibitor erlotinib represents the only targeted therapy approved for metastatic PDAC. A trial conducted by the National Cancer Institute of Canada Clinical Trials Group demonstrated a small, but significant benefit in median overall survival of approximately 2 weeks in patients receiving erlotinib in combination with gemcitabine compared to patients treated with gemcitabine plus placebo.<sup>23</sup> This marginal benefit clearly raises questions about the clinical significance of erlotinib. However, in a small subgroup of patients who developed grade II or more skin rash as a side effect of erlotinib treatment, a prolonged median survival of 10.5 months was observed—almost the median survival that has been described with FOLFIRINOX treatment.<sup>23</sup> The underlying molecular mechanisms behind this striking observation remain to be fully elucidated. At this point, it is not entirely clear whether the erlotinib-induced rash is predictive of treatment response to erlotinib or serves merely as a prognostic factor reflecting a more favourable tumour biology.<sup>24</sup> In view of these data, it is presently recommended to stop erlotinib and to continue gemcitabine as monotherapy in the absence of skin toxicity.

### Locally advanced pancreatic cancer

Locally advanced pancreatic cancer (LAPC) is defined as surgically unresectable disease without evidence of distant metastases.<sup>25</sup> The optimal treatment for these patients remains to be defined. In addition to systemic chemotherapy, chemoradiation has to be considered in order to achieve locoregional control.<sup>26</sup> In contrast, radiotherapy alone has been largely abandoned since early studies demonstrated a lack of benefit from radiation

alone compared to chemoradiation.<sup>27 28</sup> The impact of chemoradiation versus chemotherapy alone on the survival of patients presenting with locally advanced disease still has to be clarified. Several small early studies using older radiation techniques and chemotherapy regimens resulting in high toxicities may no longer be representative of state-of-the-art clinical care.<sup>29–31</sup> However, recent studies continue to produce conflicting data. A randomised trial conducted by French groups used a fairly aggressive regimen including 60 Gy of radiation combined with simultaneous continuous infusions of 5-FU and cisplatin. Compared with gemcitabine alone, survival was significantly inferior in the chemoradiation group (8.6 vs 13 months).<sup>32</sup> In contrast, a recent trial conducted by the Eastern Cooperative Oncology Group compared a less toxic regimen consisting of radiotherapy (50.4 Gy) and gemcitabine (600 mg/m<sup>2</sup> per week) with gemcitabine alone. In that study, radiochemotherapy resulted in a slight, but significant, survival benefit (11.1 months (95% CI 7.6 to 15.5 months) vs 9.2 months (95% CI 7.9 to 11.4 months), one-sided  $p=0.017$ ).<sup>33</sup>

In light of these conflicting data, it has to be taken into account that approximately 30% of the patients treated with chemoradiation for LAPC develop metastatic disease soon after diagnosis and may thus have little benefit from this type of therapy.<sup>34</sup> Therefore, a sequential approach has been proposed consisting of an initial chemotherapy regimen followed by restaging and subsequent chemoradiation only for those patients with no evidence of early metastatic progression, thus avoiding unnecessary toxic treatment.<sup>34</sup>

The ongoing GERCOR LAP-07 study, a multi-institutional phase III trial, was designed to test the impact of this sequential approach on survival (<http://www.clinicaltrials.gov>, identifier code NCT00634725). Patients are randomly assigned to receive either gemcitabine alone or gemcitabine/erlotinib. After 4 months of chemotherapy, patients with stable disease are randomly assigned a second time either to continue their chemotherapy or to receive chemoradiation to 54 Gy with concurrent capecitabine. The results of this largest randomised trial in LAPC are eagerly awaited.<sup>35</sup>

Current trial concepts are not only aiming to identify the optimal sequence of radiation and chemotherapy but also to define the most efficient chemotherapy regimens in LAPC. Given the profound impact of the FOLFIRINOX regimen in metastatic PDAC, it may be speculated that an intensified chemotherapy preceding chemoradiation might also be of benefit to patients with locally advanced tumours.

In addition, it remains unclear to date which drug is most effective as radiosensitiser given concurrently with radiation. Earlier studies have established chemoradiation with 5-FU as standard. Based on in-vitro data indicating that gemcitabine is a more potent radiosensitiser compared to 5-FU, several smaller trials using gemcitabine together with radiotherapy revealed a trend towards better survival compared to 5-FU;<sup>36</sup> however, at the cost of a higher systemic toxicity. Therefore, efforts have been made to decrease toxicity by reducing the dose of gemcitabine<sup>37</sup> or by improving the radiotherapy techniques.<sup>26 38</sup> Currently, 5-FU or gemcitabine at a reduced dose are equally applied as radiosensitiser.

### Neoadjuvant therapy in LAPC

Radiochemotherapy as well as intensified chemotherapy with or without subsequent chemoradiation are concepts that may offer the possibility of downstaging patients to achieve secondary resectability in locally advanced or borderline resectable cases. Several retrospective and small prospective trials indicate

that a subgroup of patients who are initially unresectable can successfully undergo resection after neoadjuvant therapy. According to recent meta-analyses by Gillen *et al*<sup>39</sup> and Assifi *et al*<sup>40</sup> approximately one-third of pancreatic cancer patients initially staged as unresectable or borderline resectable had resectable tumours following neoadjuvant chemoradiation, with survival rates comparable to initially resectable patients. Chemotherapeutic regimens included gemcitabine, 5-FU (and oral analogues), mitomycin C and platinum compounds. In the meta-analysis by Gillen *et al*,<sup>39</sup> however, neither increased resection frequencies nor improved survival by neoadjuvant therapy were observed in patients with initially resectable tumours. These meta-analysis data demonstrating a survival benefit of neoadjuvant chemoradiation in patients with LAPC could be corroborated by a recent large retrospective series reported on 215 patients with LAPC at a single institution.<sup>41</sup> In that series, radiotherapy was delivered with a median dose of 52.2 Gy in single fractions of 1.8 Gy, with gemcitabine being applied concomitantly at a dose of 300 mg/m<sup>2</sup> weekly. Following radiochemotherapy, 26% of the patients could be resected and had a median overall survival of 22 months, which was similar to patients with primary resection.<sup>41</sup>

As discussed above, a sequential approach with upfront chemotherapy followed by radiochemotherapy after restaging might prevent unnecessary radiotherapy in patients with early metastatic disease. However, evidence for this approach is limited and further trials for patients with locally advanced tumours are urgently required (NCT01359007).

### EMERGING CONCEPTS

#### Improving drug delivery

The impact of current chemotherapeutic regimens on the overall survival of pancreatic cancer patients is clearly unsatisfying. Several new approaches aim to improve the delivery of known chemotherapeutic agents into the tumour. Based on recent preclinical data in mouse models that will be discussed below in detail, it has been hypothesised that currently available cytotoxic drugs can not access tumour cells at an effective concentration due to the extensive hypovascular stroma reaction that acts as a fence around tumour cells protecting them from therapeutic agents administered to the systemic circulation.<sup>42</sup> Therefore, numerous efforts have been made to improve drug formulations in the aim of enhancing accessibility to the tumour cells.

Nanoparticle albumin-bound (nab)-paclitaxel is an albumin-stabilised paclitaxel formulation that was initially developed to avoid toxicities associated with oil-based solvents required to solubilise paclitaxel. Nab-paclitaxel has been approved in patients with metastatic breast cancer. In addition, it has shown promising activity in a recent phase I/II trial with pancreatic cancer patients,<sup>43</sup> and several trials using nab-paclitaxel in combination chemotherapies are currently ongoing (NCT01161186, NCT01470417, NCT01010945). The molecular mechanism of nab-paclitaxel has not been fully elucidated. In addition to the hypothesis that the tumour cells themselves are albumin-avid leading to enhanced tumoral concentration, it has been hypothesised that secreted protein, acidic and rich in cysteine, also known as osteonectin, which is highly expressed and secreted by pancreatic peritumoral fibroblasts, may serve as an albumin-binding protein that sequesters nab-paclitaxel and concentrates the drug intratumorally.<sup>44</sup> Interestingly, a recent preclinical study that used a combination of nab-paclitaxel and gemcitabine in a genetic mouse model of pancreatic cancer<sup>45</sup> showed that coadministration of nab-paclitaxel and gemcitabine

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uniquely led to tumour regression that was associated with increased intratumoral gemcitabine levels and a marked decrease in cytidine deaminase, the primary gemcitabine metabolising enzyme. The authors could demonstrate that paclitaxel reduced the levels of cytidine deaminase protein in cultured cells through reactive oxygen species-mediated degradation,<sup>45</sup> which suggests a synergistic effect of (nab)paclitaxel and gemcitabine in combination regimens.

In addition to (nab)paclitaxel, several other formulations have been developed in order to facilitate drug delivery to the tumour, among them coating drugs with liposomal phospholipid vesicles: EndoTAG-1 is a novel cationic liposomal formulation of paclitaxel, which targets tumour endothelial cells that express negatively charged cell-surface molecules. Therapy with cationic liposomal paclitaxel led to reduced tumour vessel density and endothelial cell mitosis resulting in diminished tumour perfusion and growth.<sup>46</sup> A randomised phase II trial showed significantly improved survival in patients treated with liposomal paclitaxel in combination with gemcitabine compared to gemcitabine alone.<sup>47</sup> Similarly, a liposomal formulation of irinotecan (PEP02) has shown activity in gemcitabine-refractory pancreatic cancer.<sup>48</sup> Further trials are warranted to investigate the activity of liposomal formulations and other modifications aiming to improve drug delivery in pancreatic cancer.

### Novel targeted approaches

In addition to improving drug delivery, novel targeted therapies are urgently needed. So far, targeted agents have largely failed to provide a substantial survival benefit in advanced pancreatic cancer. Therefore, it is of utmost importance to identify novel candidates for drug development that are able to impact significantly on the outcome of this disease. Most novel compounds can be classified functionally into four main groups: (1) drugs interfering with downstream signalling cascades within the tumour cells; (2) drugs targeting the stromal response; (3) drugs modulating tumour vasculature thereby enhancing drug delivery; and (4) drugs targeting the immune response (figure 2).

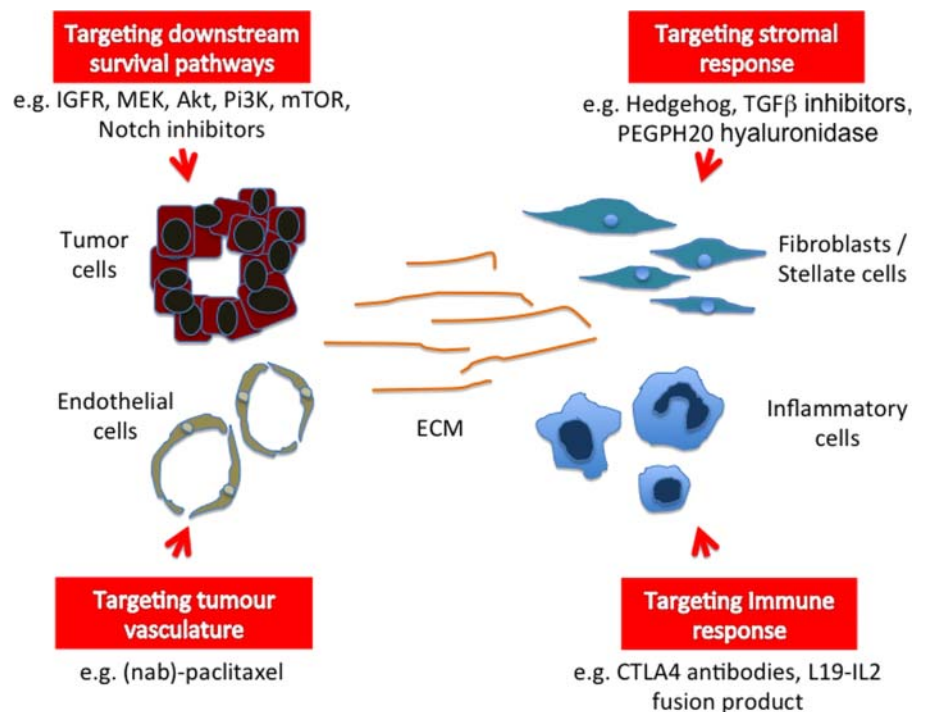
### Targeting survival and angiogenesis pathways

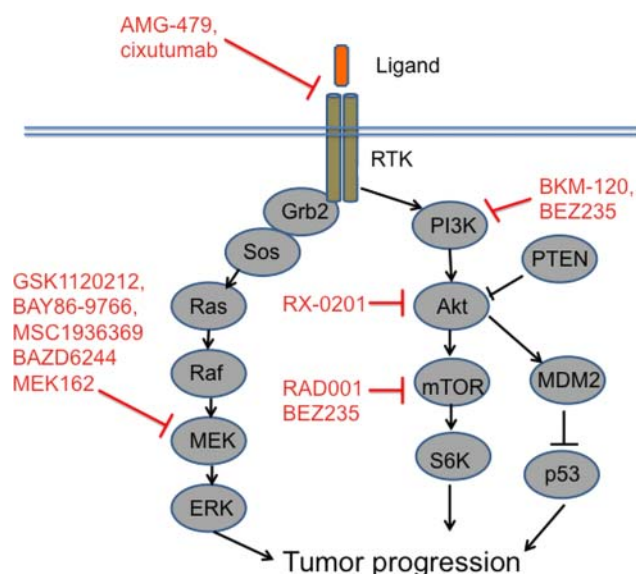
Therapeutic inhibition of receptor tyrosine kinases such as EGFR and VEGFR regulating tumour cell survival, proliferation and angiogenesis both by monoclonal antibodies and small molecule inhibitors has been evaluated extensively and approved for clinical use in several solid tumours including colon cancer.<sup>49</sup> In pancreatic cancer, however, EGFR inhibition with the small molecule inhibitor erlotinib is the only targeted approach that has been approved for clinical use, but only provides a marginal survival benefit, as discussed above.<sup>23</sup> Although robust data on the role of activating K-Ras mutations as predictors of response to EGFR inhibitors in pancreatic cancer are missing, it may be speculated that due to the high percentage of activating K-Ras mutations occurring in up to 90% of pancreatic cancer patients, pharmacological inhibition of EGFR upstream of K-Ras remains only marginally effective in this cancer type.

Targeting VEGF by the monoclonal antibody bevacizumab has also been demonstrated as ineffective in pancreatic cancer.<sup>18</sup> In addition, antiangiogenic multikinase inhibitors such as axitinib targeting the VEGF family,<sup>50</sup> sorafenib targeting VEGF receptor, platelet-derived growth factor receptor and Raf<sup>51</sup> as well as the VEGF inhibitor aflibercept<sup>52</sup> have all shown negative results in recent randomised trials. It can be speculated that the futility of all antiangiogenic approaches tested so far is due to the largely hypovascular nature of the stroma surrounding cancer cells in this disease. In line with the disappointing clinical data, recent reports in genetically engineered mouse models suggest that decreasing the stromal density by the inhibition of stromal signalling pathways leads to enhanced intratumoural perfusion. This improves rather than impairs the efficacy of chemotherapy by facilitating drug accessibility to the tumour cells.<sup>53</sup>

Despite these disappointing results with anti-EGFR and anti-VEGF approaches, several novel targets within receptor tyrosine kinase signalling cascades are under evaluation in clinical trials. Among those are components of the insulin-like

**Figure 2** Schematic overview of different therapeutic approaches for advanced pancreatic cancer. CTLA-4, cytotoxic T lymphocyte-associated antigen 4; ECM, extracellular matrix; IGFR, insulin-like growth factor receptor; IL2, interleukin 2; nab, nanoparticle albumin-bound; mTOR, mammalian target of rapamycin; PEGPH20, PEGylated human recombinant PH20 hyaluronidase; TGF $\beta$ , transforming growth factor  $\beta$ .





**Figure 3** Schematic overview of major survival and proliferation pathways and targeted agents currently evaluated in pancreatic cancer. mTOR, mammalian target of rapamycin; PTEN, phosphatase and tensin homologue; RTK, receptor tyrosine kinase.

growth factor 1 receptor (IGF1R) pathway. IGF1R mediates a strong survival effect through both K-Ras-dependent and independent downstream signalling cascades and is highly expressed in pancreatic cancer tissues (figure 3). IGF1R therefore represents a promising survival target, which might be functionally relevant even in K-Ras mutated tumours.<sup>54</sup> Currently, several monoclonal antibodies targeting IGF1R, among them AMG-479, are under investigation in clinical trials (table 1). Unfortunately, the IGF1R inhibitor cixutumumab (IMC-A12) has already failed to show an effect on progression-free or overall survival in a recent randomised phase II trial when administered in combination with erlotinib and gemcitabine.<sup>55</sup> In addition, another trial exploring the IGF1R inhibitor AMG-479 has very recently been stopped after an interim analysis revealed that the trial was unlikely to meet its efficacy endpoint.

Activated K-Ras belongs to the predominant oncogenes in pancreatic adenocarcinomas that are mutated in a high percentage of cases. This mutation can already be detected in early pre-invasive lesions during pancreatic carcinogenesis.<sup>56</sup> Earlier efforts to target K-Ras by farnesyltransferase inhibitors have failed.<sup>22</sup> In addition to preclinical research evaluating K-Ras as target using newer molecules, numerous trials are currently investigating kinases acting downstream of mutant K-Ras as therapeutic targets to overcome K-ras-induced drug resistance. The mitogen-activated protein kinase MEK belongs to the most important downstream effectors of K-Ras signalling, and has been shown to mediate K-Ras induced effects on proliferation and survival (figure 3). MEK inhibition therefore represents an innovative therapeutic avenue particularly in tumours carrying an activating K-Ras mutation. Several small molecule inhibitors have been developed and have been validated in vitro for their therapeutic efficacy in pancreatic cancer cells, including the compounds GSK1120212, BAY86-9766, MSC1936369B and AZD6244. Based on promising preclinical data, phase II trials with GSK1120212 and MSC1936369B in combination with gemcitabine in advanced pancreatic cancer are currently in progress (table 1). In addition, AZD6244 is being tested in

**Table 1** Overview of selected targeted therapies currently under investigation in clinical trials

	Compound	Clinical trial
<b>Survival signalling</b>		
IGF1R	AMG-479	NCT01231347
MEK	GSK1120212	NCT01231581
	MSC1936369B	NCT01016483
	AZD6244	NCT01222689
	MEK162	NCT01363232
PI3K	BKM120	NCT01571024
	BEZ235	NCT01337765
	RX-0201	NCT01028495
AKT/PKB	RAD001	NCT00560963
mTOR	RAD001	NCT01077986
<b>Immune response</b>		
CTLA-4	Ipilimumab	NCT01473940
	Tremelimumab	NCT00556023
CD40	CP870,893	NCT01456585
<b>Stromal response</b>		
Fibronectin ED-B	L19-IL2	NCT01198522
TGFβRI	LY2157299	NCT01373164
Hyaluronan	PEGPH20	NCT01453153
<b>Oncofetal pathways</b>		
γ-Secretase (Notch pathway)	RO4929097	NCT01232829
	MK0752	NCT01098344
<b>Epigenetics</b>		
HDAC	Vorinostat	NCT00948688
DNA methyltransferase	5-Azacitidine	NCT01167816

CTLA-4, cytotoxic T lymphocyte-associated antigen 4; HDAC, histone deacetylases; IGF1R, insulin-like growth factor 1 receptor; mTOR, mammalian target of rapamycin; TGFβRI; transforming growth factor β type I receptor.

combination with the EGFR inhibitor erlotinib in patients with pancreatic cancer refractory to gemcitabine (table 1).

The PI3K/Akt signalling pathway represents another promising candidate whose inhibition might offer a significant therapeutic potential.<sup>57</sup> PI3K/Akt is implicated in the progression of numerous human malignancies including pancreatic cancer by enhancing tumour cell proliferation, survival and metabolism. Activation of PI3K/Akt by upstream signals through receptor tyrosine kinases such as IGF1R has been reported in a high proportion of pancreatic cancers and serves as an independent negative prognostic factor (figure 3).<sup>58</sup> In addition, its activity may be dependent on the phosphatase and tensin homologue, which normally inactivates Akt but whose expression is frequently lost in pancreatic cancers.<sup>59</sup>

Various small molecules have been identified as potential inhibitors of PI3K/Akt signalling, some of which are being evaluated in clinical trials as monotherapy or in combination with chemotherapeutic agents. Among them, the Akt antisense oligonucleotide RX-0201 is being tested in a phase I/II trial in patients with metastatic pancreatic cancer<sup>60</sup> (table 1). PI3K inhibitors such as BKM120 or the combined PI3K/mammalian target of rapamycin (mTOR) inhibitor BEZ235 are currently being evaluated in phase I trials in combination with two different MEK inhibitors GSK1120212 and MEK162 in advanced solid tumours including pancreatic cancer carrying K-Ras, N-Ras and/or B-Raf mutations (table 1). This approach aims to overcome drug resistance mediated by upstream mutations of Ras and/or Raf through simultaneous blockade of the two major downstream cascades, MEK/ERK and PI3K/Akt signalling. The results of this combined approach are eagerly awaited.

mTOR represents another promising target for therapeutic intervention. A serine/threonine kinase like Akt, it is activated

by PI3K/Akt signalling and is known as a regulator of gene transcription and cell cycle progression (figure 3). Although a recent phase II trial using the mTOR inhibitor RAD001 as monotherapy had minimal clinical activity in patients with gemcitabine-refractory metastatic pancreatic cancer,<sup>61</sup> trials testing the effect of mTOR inhibition in combination with cytotoxic drugs or EGFR inhibitors are currently ongoing (table 1). Interestingly, metformin, a commonly used antidiabetic drug, is known to inhibit the mTOR pathway through activation of the AMP-activated protein kinase (AMPK) that negatively regulates mTOR activity via phosphorylation and stabilisation of the tumour suppressor gene TSC2.<sup>62</sup> Based on these preclinical findings and supported by epidemiological studies suggesting that use of the antidiabetic drug metformin might be associated with a reduced life-time risk of developing cancers,<sup>63 64</sup> metformin is currently being tested in a randomised phase II trial together with gemcitabine and erlotinib in patients with advanced pancreatic cancer (NCT01210911). In this context, tumour cell metabolism has gained increasing interest as a potential therapeutic avenue with several preclinical studies investigating the feasibility of interfering with glucose and glutamine utilisation,<sup>65</sup> and trials aiming to investigate interference with tumour cell metabolism and to use metabolic profiles to predict therapeutic outcome (NCT01196247).

Poly (ADP-ribose) polymerase (PARP) is a family of proteins involved in a number of cellular processes mainly involving DNA repair and apoptosis. Sensitivity to therapeutic PARP inhibition is known to be associated with defects in the breast cancer DNA repair pathway. A subset of pancreatic cancer patients including a proportion of patients with familial pancreatic cancer, have defects in the breast cancer DNA repair pathway or other defects in homologous repair. These cancers might respond to PARP inhibitors when given in combination with the DNA damaging agents. One ongoing trial is currently evaluating the PARP inhibitor olaparib in combination with cisplatin and irinotecan (NCT01296763). Moreover, several groups are investigating another PARP inhibitor, veliparib, with different drug combinations for advanced pancreatic cancer (NCT01489865, NCT01585805).

### Targeting the immune response

In recent years, evidence has accumulated indicating that local and systemic immune response represents a major determinant of tumour resistance and progression.<sup>66</sup> In contrast to targeted approaches that aim to inhibit molecular pathways crucial for tumour growth and maintenance, immunotherapy endeavours to stimulate a host immune response that results in long-term tumour destruction.<sup>67</sup> The stroma of pancreatic cancer is particularly rich in inflammatory cells that are proposed to mediate drug resistance and tumour progression.<sup>68</sup> Therefore, immune cells such as T cells and macrophages infiltrating the peritumoral stroma represent a promising target for immunotherapeutic approaches.

T-cell-mediated immunity includes multiple sequential steps that are regulated by counterbalancing stimulatory and inhibitory signals that fine-tune the response.<sup>66</sup> Inhibitory pathways are referred to as immune checkpoints that are crucial for maintaining self-tolerance and modulating the duration and amplitude of physiological immune responses. It has been recognised that many tumours co-opt certain immune checkpoint pathways as a major mechanism of immune resistance, particularly against T cells that are specific for tumour antigens.<sup>66</sup> Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) is one of these immune checkpoints that plays a critical role in

regulating and limiting immune responses and can be blocked by specific antibodies such as ipilimumab, a fully human antibody. Binding to CTLA-4 blocks its activity, thereby sustaining an active immune response in its attack on cancer cells. After successful clinical trials and approval of ipilimumab for advanced melanoma, early phase trials are currently underway in pancreatic cancer for ipilimumab and a second monoclonal antibody targeting CTLA-4, tremelimumab (table 1). It remains to be seen whether the therapeutic efficacy of this immunotherapeutic approach demonstrated in melanoma can be extended to pancreatic cancer.

Another promising target in this context was recently published in a study by Beatty *et al.*<sup>69</sup> In this paper, the authors tested the combination of an agonist CD40 antibody with gemcitabine in a phase I trial with patients with advanced pancreatic cancer. CD40 is a tumour necrosis factor receptor superfamily member that has been shown to be a key regulatory step in the development of T-cell-dependent antitumor immunity, which relies on CD40-mediated 'licensing' of antigen-presenting cells for tumour-specific T-cell priming and activation.<sup>69</sup> Treatment with the CD40 agonist CP870,893 resulted in tumour regression in some patients, in particular in those with macrophage-dominated inflammatory tumour infiltrates. The authors reproduced this treatment effect in a genetically engineered mouse model of pancreatic cancer and found unexpectedly that CD40-induced tumour regression required macrophages rather than T cells or gemcitabine. CD40-activated tumoricidal macrophages rapidly infiltrated tumours and facilitated the depletion of tumour stroma.<sup>69</sup> Following these results, the effect of the CD40 agonist CP870,893 is currently being tested in a neoadjuvant and adjuvant setting in patients with resectable pancreatic cancer (table 1).

In addition to enhancing the systemic immune response, attracting selected antitumour cytokines to the site of the tumour is a promising concept that is currently under intense preclinical and clinical investigation. One of the most tumour-selective antigens that can be used to guide cytokines to the site of the tumour is the extracellular matrix (ECM) protein ED-B of fibronectin. Expression of ED-B itself is associated with neoangiogenesis and tumour growth. A human single-chain Fv antibody fragment L19 has recently been generated, which displays high binding affinity for ED-B.<sup>70</sup> This antibody fragment can be linked to interleukin (IL)-2, one of the most potent antitumour cytokines, which is, however, too toxic for systemic administration and is only suitable for local therapy.<sup>71</sup> The fusion product consisting of the ED-B antibody fragment L19 and IL-2 (L19-IL2) is currently being tested in a phase I/II trial in pancreatic cancer (table 1). The targeted accumulation of IL-2 to the tumour microenvironment by conjugating it to the tumour-selective L19 antibody appears to be an attractive concept to enhance the therapeutic index of IL-2.<sup>70</sup>

### Targeting the stromal reaction

The extensive desmoplastic reaction that comprises up to 90% of the tumour volume is the predominant histological feature of pancreatic cancer. The stroma consists of a variety of cellular components such as inflammatory cells, stellate cells and activated fibroblasts that are embedded within a dense extracellular matrix.<sup>72 73</sup> Over decades, the majority of research efforts had focussed on the tumour cells thereby largely neglecting the impact of the stromal response. Only recently, the role of the stroma as a barrier fencing off the tumour cells against systemically applied drugs has been recognised.<sup>73</sup> Furthermore, it was hypothesised that inefficient drug delivery due to the intense

stromal reaction may be an important contributor to chemoresistance in pancreatic cancer.<sup>53 73</sup>

During recent years, several landmark papers have investigated the impact of stroma-related signalling pathways on desmoplastic reaction, tumour progression and drug resistance in genetically engineered mouse models. Inhibition of these pathways is considered a promising tool to decrease stromal density and to facilitate the access of cytotoxic drugs to the tumour cells. The sonic hedgehog pathway is one of the predominant signalling cascades known to stimulate stromal reaction. In a genetic mouse model, systemic administration of the hedgehog inhibitor IPI926 resulted in a significant depletion of tumour-associated stroma. This was associated with an increase in the intratumoral vascular density, enhanced concentration of the coadministered cytotoxic agent gemcitabine and increased survival of the animals.<sup>53</sup> Based on these preclinical data, trials investigating hedgehog inhibitors have been initiated in patients with advanced pancreatic cancer, among them trials evaluating the hedgehog inhibitor IPI926. Recently, however, this trial was stopped. According to a preliminary press release, an interim analysis found that overall survival in patients on the gemcitabine plus IPI926 arm was inferior compared to gemcitabine plus placebo (<http://phx.corporate-ir.net>). Despite these sobering results, further clinical trials evaluating other hedgehog inhibitors such as GDC-0449 in combination with gemcitabine or LDE225 in combination with FOLFIRINOX or gemcitabine are still ongoing (table 1).

The transforming growth factor  $\beta$  (TGF $\beta$ )-dependent signalling cascade is known as another key pathway implicated in stromal reaction.<sup>74</sup> TGF $\beta$  plays a crucial role in promoting stroma production and invasion, metastasis, angiogenesis and escape from immunosurveillance in pancreatic cancer.<sup>75</sup> Several drugs have been developed to target TGF $\beta$  signalling, among them the antisense oligodeoxynucleotide trabedersen (AP 12009), which specifically inhibits TGF $\beta$ 2 expression. This compound demonstrated an excellent safety profile and encouraging survival results when administered as monotherapy in refractory solid tumours including pancreatic cancer<sup>76</sup> (table 1).

TGF $\beta$  signalling is induced after TGF $\beta$  binds as dimers to the TGF $\beta$  type II receptor, which recruits and phosphorylates the TGF $\beta$  type I receptor. During recent years, efforts have been made to develop compounds that bind to and inhibit TGF $\beta$  receptors. A phase I/II trial is currently ongoing that tests the impact of LY2157299, a small molecule that has been designed to inhibit TGF $\beta$  type I receptor selectively, in combination with gemcitabine for patients with advanced or metastatic pancreatic cancer (table 1).

In addition to targeting stromal-related signalling pathways, acellular matrix components are currently being evaluated as targets for therapeutic intervention: Two groups recently identified hyaluronan, a non-sulphated glycosaminoglycan, as highly abundant in the extracellular matrix of both human and murine pancreatic cancer tissues.<sup>77 78</sup> In a genetically engineered mouse model the authors could show that a PEGylated human recombinant PH20 hyaluronidase (PEGPH20) enzymatically depletes hyaluronan, thereby inducing re-expansion of tumour blood vessels and increasing the concentration of gemcitabine within the tumour, which resulted in significantly diminished tumour growth and prolonged survival in mice. Based on these promising preclinical data, a phase 1b/2 trial comparing PEGPH20 combined with gemcitabine versus gemcitabine alone is currently recruiting to evaluate the impact of depleting hyaluronan in patients with metastatic pancreatic cancer (table 1).

### Targeting oncofetal signalling

Signalling pathways that are essential for embryonic development and tissue homeostasis are frequently reactivated in cancers. These developmental or oncofetal signals have been demonstrated to accelerate tumour progression and mediate resistance to chemotherapy in pancreatic cancer.<sup>79</sup> A recent study by Jones *et al*<sup>80</sup> using a comprehensive genome sequencing approach revealed 12 major signalling pathways that are genetically affected in pancreatic cancer. Interestingly, four of them have been implicated in embryonic development: Notch, Hedgehog, TGF $\beta$  and Wnt $\beta$ -catenin pathways are altered in the majority of cases.<sup>80</sup> Accumulating evidence indicates that these genetic alterations translate into functional reactivation of these pathways in both human tumours and murine models.<sup>81 82</sup>

The Hedgehog and TGF $\beta$  signalling pathway are also major determinants of the stromal reactions and have been discussed above. The Notch pathway is thought to maintain pancreatic progenitor cells in an undifferentiated state by enhancing their survival and persistence, in analogy to its function during embryogenesis.<sup>81</sup> Both the Notch ligand and receptor are highly expressed in pancreatic cancer.<sup>83</sup> In a genetic mouse model, Notch activation has been shown to synergise with K-Ras in inducing pancreatic intraepithelial neoplasias and invasive carcinoma,<sup>84</sup> making the Notch pathway a promising therapeutic target. Various inhibitors have been developed at different levels of the pathway, including inhibitors of the enzyme  $\gamma$ -secretase that plays a key role in the activation of Notch signalling by proteolytic cleavage and release of the intracellular domain of Notch.<sup>81</sup> Currently, trials evaluating the  $\gamma$ -secretase inhibitors RO4929097 and MK0752 in patients with metastatic pancreatic cancer are ongoing (table 1).

### Targeting epigenetic changes

In contrast to genetic alterations leading to altered expression or activity of proteins, epigenetic alterations are heritable, yet not accompanied by changes in DNA sequence. In contrast to genetic mutations, epigenetic changes are potentially reversible and therefore amenable to therapeutic interventions. During recent years, various epigenetic mechanisms affecting gene expression at the chromatin level have been implicated in carcinogenesis and tumour progression of many human malignancies including pancreatic cancer, among them DNA methylation and histone acetylation as most prominent and therapeutically exploitable features.<sup>85</sup>

Acetylation of histones removes the positive charge on the histones, leading to a more relaxed chromatin structure (euchromatin) that is associated with transcriptionally active DNA. This relaxation can be reversed by histone deacetylases (HDAC). HDAC activity leads to reduced transcription of multiple genes, among them several crucial tumour suppressor genes. This results in enhanced proliferation, resistance to apoptosis and tumour progression. In pancreatic cancer, several members of the HDAC family such as HDAC2 and HDAC6 are highly expressed and are known to mediate resistance to apoptosis.<sup>86 87</sup> Several drugs inhibiting HDAC such as vorinostat have been developed and demonstrate significant antitumour activity in a variety of malignancies.<sup>88</sup> In pancreatic cancer, vorinostat is currently being evaluated in combination with radiation therapy and chemotherapy in two trials enrolling patients with locally advanced disease (table 1).

In contrast to histone acetylation that activates gene transcription, DNA methylation is associated with gene silencing.

Globally, the DNA of cancer cells is considered to be hypomethylated. This is associated with genomic instability and transcription of silenced transposable sequences.<sup>89</sup> However, the CpG islands of multiple promoter regions of tumour suppressor genes frequently undergo DNA hypermethylation, leading to gene silencing and promotion of cancer development.<sup>89</sup> DNA hypermethylation of tumour suppressor genes is therefore an attractive target for therapeutic intervention. 5-Azacytidine is a chemical cytosine analogue known to inhibit DNA methyltransferase at low doses. Based on promising in-vitro data,<sup>90</sup> a phase I trial of 5-azacytidine plus gemcitabine in patients with advanced pancreatic cancer is currently recruiting (table 1). It remains to be determined whether the net effect of a drug like 5-azacytidine on hypermethylated tumour suppressors outweighs potentially harmful interference with methylation signatures of other genes in humans.

### THE CHALLENGE: DEFINING PERSONALISED THERAPIES

The ultimate goal to overcome the appalling resistance of pancreatic cancer to numerous systemic therapeutic approaches may be achieved not only by successfully developing new targeted agents but also by defining which patient subgroups might obtain the greatest benefit from them. Accumulating evidence indicates that PDAC is characterised by a marked genetic heterogeneity. By combining comprehensive transcriptional and genomic analyses, Jones *et al*<sup>80</sup> defined a core set of 12 cellular signalling pathways and processes that were each genetically altered in the majority of investigated PDAC cases. However, for each individual case, the genes and pathways affected varied considerably, suggesting that an individualised approach to therapy is likely to be required.<sup>5</sup>

Facing the long list of futile clinical trials using targeted therapies, it may be speculated that some of the agents that failed to benefit unselected populations of patients with PDAC might have had an impact in a more individualised strategy using selected patients with distinct molecular subtypes responsive to a given targeted agent.

Based on transcriptional profiles of PDAC tissues, Collisson and coworkers<sup>91</sup> recently defined three PDAC subtypes (classic, quasimesenchymal and exocrine-like), which differed significantly in clinical outcome and therapeutic response to gemcitabine and erlotinib. Although currently not ready for routine clinical use, the gene signatures for these subtypes may have utility in stratifying patients for subtype-specific therapies.

### CONCLUSIONS

Numerous novel therapeutic avenues targeting tumour cells, tumour vasculature or stromal response are currently under evaluation in clinical trials. To date, it is unclear which of these avenues—if any—can be translated into clinical routine care for patients with advanced pancreatic cancer. Generally, clinical trials for pancreatic cancer face several obstacles such as short overall survival time and heterogeneity of the disease. Apart from the marginal benefit demonstrated by erlotinib, all trials testing novel targeted approaches have failed so far. The advent of the FOLFIRINOX regimen has significantly widened the armamentarium of chemotherapeutic options that had been largely restricted to gemcitabine-based regimens before. In clinical practice, treatment choice between aggressive combination therapy and gemcitabine has to be made individually depending on the patient's performance status and comorbidities. For locally advanced disease, chemoradiation is an option to improve local control although data in this regard are

conflicting. In addition, the right timing of chemoradiation remains to be defined (figure 1).

Despite some improvements in chemotherapeutic strategies, the prognosis of advanced pancreatic cancer still remains appalling. In order to develop new therapeutic strategies successfully for this disease, preclinical and clinical research has to focus on three main areas essential to overcome drug resistance: (1) optimisation of drug delivery; (2) identification of novel targets; and (3) identification of molecular markers to individualise therapy decisions.

Numerous novel compounds with promising preclinical efficacy data are currently being evaluated in clinical trials. Given the long list of futile trials with novel targeted agents in the past, it remains speculative at present which—if any—of these agents will be able to make a difference in improving the prognosis of patients with advanced pancreatic cancer. Most of the drugs that are currently in clinical evaluation have been identified and preclinically validated in xenograft models using human pancreatic cancer cell lines injected orthotopically or subcutaneously into immune-deficient mice. However, given the high stroma content and the strong immune infiltration frequently detected in endogenous pancreatic tumours, the transferability of most in-vitro data and xenograft studies to the human situation is very limited. Therefore, future preclinical testing of therapeutic strategies should be performed in appropriate genetically engineered mouse models that recapitulate the genetic and morphological characteristics of the human disease. Using these models, the impact of novel agents not only on tumour cells but also on the tumour microenvironment can be evaluated in detail in a preclinical setting.

Finally, molecular markers are urgently needed that are able to predict therapeutic responsiveness or resistance to a given drug in an approach towards a personalised medicine. In contrast to other solid tumours, predictive biomarkers suitable for use in clinical routine are largely missing in pancreatic cancer. All future trials evaluating novel agents should be accompanied by comprehensive translational programmes aiming to identify predictive biomarkers, either in the tissue or in body fluids that are easier to access and to monitor during therapy.

It will be the combination of innovative therapeutic strategies and optimised patient selection that hopefully will be able to make a difference and finally translate into a clinically significant benefit for patients with advanced pancreatic cancer.

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## Current concepts and novel targets in advanced pancreatic cancer

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