

State of the art biological therapies in pancreatic cancer

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies with a five-year survival rate of approximately 5%. Several target agents have been tested in PDAC, but almost all have failed to demonstrate efficacy in late phase clinical trials, despite the better understanding of PDAC molecular biology generated by large cancer sequencing initiatives in the past decade. Erlotinib (a small-molecule tyrosine-kinase inhibitor of epidermal growth factor receptor) plus gemcitabine is the only schedule with a biological agent approved for advanced pancreatic cancer, but it has resulted in a very modest survival benefit in unselected patients. In our work, we report a summary of the main clinical trials (closed and ongoing) that refer to biological therapy evaluation in pancreatic cancer treatment.

Key words: Pancreatic cancer; Molecular characterization; Targeted therapy; Epidermal growth factor receptor inhibitors; Embryonic pathway inhibitors; Antiangiogenic therapies

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Core tip: Our study aims to give an overview of the progress made in molecular targeted therapy for pancreatic cancer in recent years and the current status of clinical trials in the field. Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies with a five-year survival rate of approximately 5%. Several target agents have been tested in PDAC but almost all have failed to demonstrate efficacy in late phase clinical trials, even with a better understanding of PDAC molecular biology generated by large cancer sequencing initiatives in the past decade. Erlotinib (small-molecule tyrosine-kinase inhibitor of epidermal growth factor receptor) plus gemcitabine is actually the only schedule

with a biological agent approved for advanced pancreatic cancer, but it resulted in a very modest survival benefit in unselected patients. In our work, we reported a summary of the main clinical trials (close and ongoing) that refer to biological therapy evaluation in pancreatic cancer treatment.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies, representing the fourth leading cause of cancer death. The five-year survival rate is approximately 5%, and surgery remains the most effective treatment^[1].

Unfortunately, only 20% of patients are suitable for radical resection, and recurrence of disease occurs in 80% of patients who undergo resection^[2].

The most important improvement concerns the conventional chemotherapy, represented by FOLFIRINOX and gemcitabine plus nab-paclitaxel regimens, but it results in a modest outcome advantage^[3,4].

No significant progress has been made in the field of targeted therapy. Erlotinib [a small-molecule tyrosine-kinase inhibitor of epidermal growth factor receptor (EGFR)] plus gemcitabine is actually the only schedule with a biological agent approved for pancreatic cancer, but it results in a very modest survival benefit in unselected patients^[5].

In recent decades, several combinations of classic chemotherapy and novel biological agents have been studied, but they have not improved overall survival, and furthermore, those trials did not use biomarkers to select responder patients^[6].

Our study aims to give an overview of the progress made in molecularly targeted therapy for pancreatic cancer in recent years and the current status of clinical trials in the field, as summarized in Tables 1-3.

MOLECULAR CHARACTERIZATION OF PDAC: HAS A BETTER UNDERSTANDING OF THE TUMOUR'S MOLECULAR BIOLOGY REALLY IMPROVED TARGETED THERAPY APPLICATIONS?

Large cancer sequencing initiatives generated a large quantity of data in the past decades. Those findings showed a complex genomic landscape characterized particularly by inter-tumoural and intra-tumoural hetero-

geneity involving genomic aberration^[7].

With the exception of the well-known KRAS, TP53, CDKN2A and SMAD4 alterations occurring at respective frequencies of 71%, 49%, 22% and 20%, a large number of genomic rearrangements with mutational frequencies less than 2% were found^[8,9].

The majority of single gene mutations in pancreatic cancer can be grouped into common cellular pathways. Jones *et al.*^[10] identified 69 mutated gene sets in most of the 24 samples analysed in their pioneering sequencing study, of which 31 could be grouped into 12 core signalling pathways. These pathways included KRAS signalling, the transforming growth factor β (TGF- β) pathway, DNA damage control, apoptosis, regulation of G1/S cell cycle transition, Hedgehog signalling, the homophilic cell adhesion pathway, integrin signalling, TGF- β signalling, Wnt/Notch signalling, and the invasion pathway^[10].

Genomic heterogeneity, a characteristic of PDAC, implies genomic instability, which is due to the acquisition of telomere dysfunction and abnormal cell-cycle control occurring predominantly in early cancer stages, but it persists after cancer dissemination, resulting in parallel evolution among different metastases. Cell clones arranging metastasis may require other driver mutations compared with primary tumour cells implementing genetic variation in pancreatic cancer^[11,12].

Given this molecular complexity, it is very difficult to separate passenger from driver mutations, to identify molecular mutations with a crucial role in pancreatic carcinogenesis that can be developed into actionable molecular targets of novel biological agents or to identify patients potentially responsive to existing agents already approved for human use in other cancers (Figure 1), and currently no predictive or prognostic biological factors are employed in clinical practice.

TARGETED THERAPY IN PDAC

EGFR pathway inhibitors

EGFR is a transmembrane receptor member of the ErbB family with a tyrosine kinase domain that is activated by many ligands including epidermal growth factor (EGF), TGF- α , heparin-binding EGF, amphiregulin, epiregulin, betacellulin and neuregulin (an epidermal growth factor). EGFR is involved in cell cycle regulation, cell survival, adhesion and differentiation through activation of the Ras/MAP kinase, phosphatidylinositol 3'-kinase (PI3K)/Akt, Janus kinase/Stat and phospholipase C/protein kinase C pathways. Several trials showed that EGFR is overexpressed in up to 90% of pancreatic cancer samples. Therefore, inhibitors targeting EGFR have been considered a promising therapeutic agent^[13].

Erlotinib is a tyrosine kinase inhibitor (TKI) molecule that competes with ATP for binding to the kinase domain, thereby blocking downstream signal transduction. A possible therapeutic role was evaluated in a large phase III trial, enrolling 569 chemotherapy naïve patients with locally advanced or metastatic pancreatic

Table 1 Principal phase III clinical trials involving targeted therapy in pancreatic cancer

Agent	Target pathway	Treatment	Setting	n	mOS (mo)	PFS (mo)	FDA approval	Ref.
Erlotinib	EGFR signaling	GEM plus erlotinib vs GEM plus P	M/LA	569	6.24 vs 5.91 (<i>P</i> = 0.038)	3.75 vs 3.55 (<i>P</i> = 0.004)	Yes	[5]
Cetuximab	EGFR signaling	GEM plus cetuximab vs GEM	M/LA	766	6.5 vs 6 (<i>P</i> = 0.14)	3.5 vs 3 (<i>P</i> = 0.058)	No	[17]
Tipifarnib	KRAS pathway	GEM plus tipifarnib vs GEM	M/LA	688	6.3 vs 6 (<i>P</i> = 0.75)	3.7 vs 3.6 (<i>P</i> = 0.72)	No	[30]
Ganitumab	IGFR pathway	GEM plus ganitumab (12 mg/kg or 20 mg/kg) vs GEM plus P	M	800	12 mg/kg arm 7.0 vs 7.2 (<i>P</i> = 0.494) 60 mg/kg arm 7.1 vs 7.2 (<i>P</i> = 0.397)	12 mg/kg arm 3.7 vs 3.6 (<i>P</i> = 0.520) 60 mg/kg arm 3.7 vs 3.7 (<i>P</i> = 0.403)	No	[35]
Bevacizumab	Angiogenesis	GEM plus bevacizumab vs GEM plus P	M/LA	602	5.7 vs 6.0 (<i>P</i> = 0.40)	4.8 vs 4.3 (<i>P</i> = 0.99)	No	[36]
Aflibercept	Angiogenesis	GEM plus aflibercept vs GEM plus P	M/LA	546	6.5 vs 7.8 (<i>P</i> = 0.203)	3.7 vs 3.7 (<i>P</i> = 0.864)	No	[38]
Axitinib	Angiogenesis	GEM plus axitinib vs GEM plus P	M/LA	632	8.5 vs 8.2 (<i>P</i> = 0.543)	4.4 vs 4.4 (<i>P</i> = 0.520)	No	[41]
Marimastat	Tumor stroma	GEM plus marimastat vs GEM	M/LA	239	5.4 vs 5.4 (NA)	3 vs 3.1 (NA)	No	[75]

GEM: Gemcitabine; P: Placebo; mOS: Median overall survival; PFS: Progression free survival; n: Number of patients enrolled; LA: Locally advanced cancer; M: Metastatic cancer; NA: Not available.

Table 2 Principal phase II clinical trials involving targeted therapy in pancreatic cancer

Agent	Target pathway	Treatment	Setting	n	Ref.
Cetuximab	EGFR signaling	GEM plus cisplatin plus cetuximab vs GEM plus cisplatin	M/LA	84	[16]
Gefitinib	EGFR signaling	GEM plus gefitinib (single arm)	M/LA	57	[18]
Trastuzumab	EGFR signaling	GEM plus trastuzumab (single arm)	M/LA	34	[20]
Trastuzumab	EGFR signaling	Capecitabine plus trastuzumab (single arm)	M/LA 2+/3+ HER-2 expression 3+ HER-2 expression or gene amplification	17 (212 screened)	[21]
Nimotuzumab	EGFR signaling	GEM plus nimotuzumab (single arm)	M/LA	18	[23]
Nimotuzumab	EGFR signaling	Nimotuzumab monotherapy (single arm)	Refractory to first line standard chemotherapy M/LA	56	[24]
Selumetinib	KRAS/MEK pathway	Capecitabine plus selumetinib vs Capecitabine	Refractory to first line standard chemotherapy M/LA	70	[31]
Trametinib	KRAS/MEK pathway	GEM plus trametinib vs GEM plus P	M/LA	160	[32]
Sorafenib	Angiogenesis	GEM plus sorafenib (single arm)	M/LA	70	[40]
RO4929097	Hedgehog signaling	RO4929097 monotherapy (single arm)	Refractory to first line standard chemotherapy M	18	[57]
Everolimus	mTOR pathway	Everolimus plus capecitabine (single arm)	M/LA	31	[67]

GEM: Gemcitabine; P: Placebo; n: Number of patients enrolled; LA: Locally advanced cancer; M: Metastatic cancer.

adenocarcinoma randomized to receive gemcitabine plus placebo or gemcitabine plus erlotinib 100-150 mg daily. The median overall survival (mOS) and progression free survival (PFS) were modestly, but statistically significantly, improved in the combination arm, 6.24 mo vs 5.91 mo (*P* = 0.038) and 3.75 mo vs 3.55 mo (*P* = 0.004), respectively^[5].

Neither EGFR status nor KRAS status analysed in the

subgroup of patients treated with erlotinib was shown to be predictive of a survival benefit in patients receiving the combination schedule^[14].

Erlotinib has been approved by the FDA in combination with gemcitabine as a first-line treatment for advanced pancreatic adenocarcinoma.

Cetuximab is a monoclonal antibody binding the extracellular domain of EGFR. After encouraging results

Table 3 Principal ongoing trials involving targeted therapy in pancreatic cancer

ClinicalTrials.gov identifier	Agent	Target	Status
NCT01728818	Afatinib	EGFR signaling	Recruiting
NCT01659502	TL-118	Angiogenesis	Not yet recruiting
NCT01621243	Necuparab	Angiogenesis	Recruiting
NCT01088815	Vismodegib	Hedgehog signaling	Recruiting
NCT01096732	Vismodegib	Hedgehog signaling	Terminated
NCT01431794	LDE-225	Hedgehog signaling	Recruiting
NCT00515866	KU-0059436	PARP inhibitor	Completed
NCT01585805	Veliparib	PARP inhibitor	Recruiting
NCT01571024	BKM120	mTOR and PI3K/ Akt pathway	Recruiting
NCT01028495	RX-0201	mTOR and PI3K/ Akt pathway	Completed
NCT01337765	BEZ235 + MEK162	mTOR and PI3K/ Akt pathway	Completed
NCT00560963	Everolimus	mTOR pathway	Completed
NCT00075647	Temsirolimus	mTOR pathway	Completed
NCT01839487	PEGPH20	Tumor stroma	Recruiting

EGFR: Epidermal growth factor receptor; mTOR: Mammalian target of rapamycin.

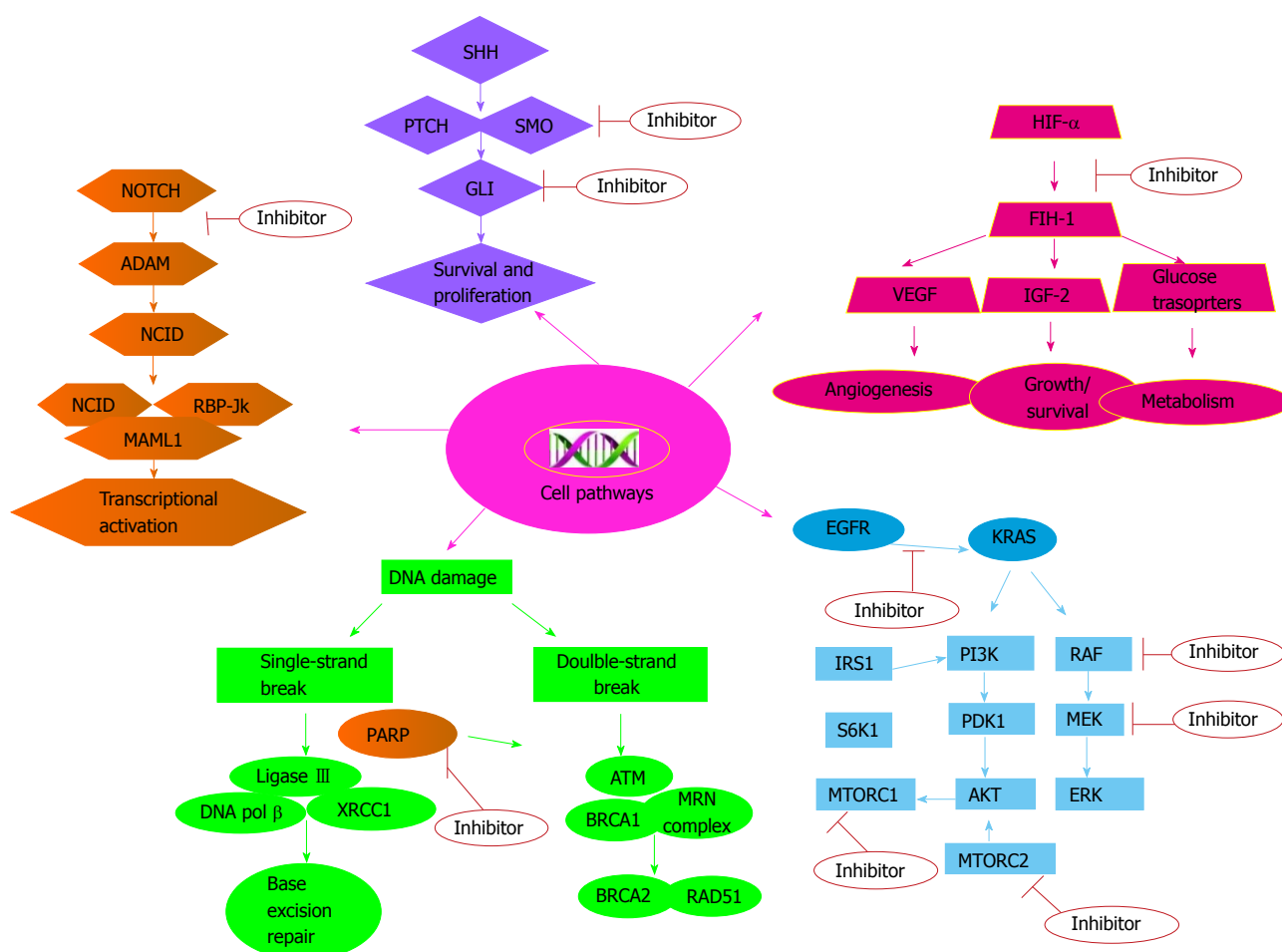


Figure 1 Principal cell signaling pathways involved in pancreatic ductal adenocarcinoma carcinogenesis and actionable molecular targets. SHH: Sonic hedgehog; PARP: Poly ADP-ribose polymerase; VEGF: Vascular endothelial growth factor; IGF: Insulin like growth factor; EGFR: Epidermal growth factor receptor; PI3K: Phosphatidylinositol 3'-kinase.

in a phase I trial, subsequent studies in association with gemcitabine-based chemotherapy have failed to demonstrate any survival benefit^[15,16].

A phase II study has evaluated the possible therapeutic role of gefitinib, a competitive inhibitor of ATP binding to the intracellular kinase domain of EGFR, in

combination with gemcitabine in inoperable or metastatic pancreatic cancer patients. The combination demonstrated promising activity with a mOS and PFS in the combination arm of 7.3 and 4.1 mo, respectively, but other evidence supporting a role of gefitinib in PDAC treatment is lacking^[17].

Another ErbB family of transmembrane tyrosine kinase receptors is HER-2, which is overexpressed in 11% of pancreatic adenocarcinoma cases. HER2-positive status has also been correlated with shorter survival^[18].

Trastuzumab plus gemcitabine was tested in 34 metastatic pancreatic cancer patients with HER-2 overexpression as determined by immunohistochemistry, and partial responses were observed in 6% of cases^[19]. Harder *et al.*^[20] in a multicentre phase II study, investigated the efficacy and toxicity of the HER2 antibody, trastuzumab, plus capecitabine in patients with pancreatic cancer and HER2 overexpression, but this treatment did not perform favourably with respect to either PFS or OS compared with standard chemotherapy.

After FDA approval of lapatinib, clinical trials have been initiated to test the effect of this HER-2 inhibitor combined with chemotherapy in pancreatic carcinoma. In particular, lapatinib was tested in combination with capecitabine as a second-line treatment in advanced pancreatic cancer with promising preliminary results. Further studies are needed to evaluate the real effectiveness and role of this molecule in the treatment of PADC^[21].

Nimotuzumab, another anti-EGFR monoclonal antibody, showed promising results^[22]. In a phase II trial where advanced pancreatic cancer patients were randomized to receive second-line monotherapy with nimotuzumab, Strumberg *et al.*^[23] showed PFS after 1 year of 10.3% and median overall survival of 18.1 wk with a tolerable toxicity profile.

Based on preclinical evidence, afatinib, an inhibitor of EGFR, HER2 and HER4, is under evaluation in an ongoing phase II trial^[24,25].

The KRAS pathway and downstream signalling cascade inhibitors

KRAS activating mutations are present in 70% to 90% of cases of pancreatic cancer. K-Ras is a GTPase protein belonging to the Ras protein family, which has oncogenic activity, and gain-of-function mutations resulting in constitutive activation promote proliferation and inhibit apoptosis through the RAF/MEK/ERK and PIK3/AKT pathways. K-Ras is very difficult to target, and no inhibitors are actually available to use in clinical practice^[26].

Preclinical study has shown that farnesylation is an important post-translational modification required for Ras activation, allowing the protein to be attached to the plasma membrane for signal transduction^[27].

After promising results in terms of anti-proliferative activity in pancreatic tumour cell lines, farnesyl-transferase inhibitors, particularly tipifarnib, failed to improve overall survival either as a single agent or in combination with gemcitabine in a phase III trial^[28,29].

Due to the difficulty of targeting Ras directly, a possible solution could be to block targets downstream of KRAS, such as the protein kinase MEK. Selumetinib is an oral small molecule that inhibits MEK1/2. In a phase II trial, patients were randomized to receive single-agent

capecitabine or selumetinib as a second-line treatment for advanced pancreatic cancer. The selumetinib arm showed a median overall survival of 5.4 mo vs 5.0 mo in the capecitabine arm, but this result was not statistically significant^[30].

Another MEK1/2 inhibitor, trametinib, was tested in pancreatic cancer in combination with gemcitabine against a regimen of gemcitabine plus placebo in a phase II randomized multicentre study. Nevertheless, no significant advantages were demonstrated in terms of overall survival or PFS^[31].

Rigosertib, a first-in-class Ras mimetic and small molecule inhibitor of multiple signalling pathways, including polo-like kinase 1 and phosphoinositide 3-kinase (PI3K), was assessed in combination with gemcitabine in patients with treatment-naïve metastatic pancreatic adenocarcinoma in a phase II/III randomized study, but the combination regimen did not improve survival or response, as recently presented at the 2015 ASCO Annual Meeting^[32].

Research in this field is in development, but the available trials have failed to show any survival benefit.

IGFR pathway inhibitors

Another possible target in ductal pancreatic cancer is represented by insulin like growth factor 1 receptor, which is highly expressed in pancreatic cells, and upon ligand binding activates several pathways involved in cell proliferation and cell survival such as the PIK3/AKT pathway^[33].

Monoclonal antibodies against IGFR (cixutumumab, ganitumab) were evaluated in PDAC treatment, but unfortunately, they failed to show a statically significant survival benefit^[34].

In particular, the phase III trial assessing ganitumab in combination with gemcitabine was closed early based on a pre-planned futility analysis: The median overall survival was 7.1 mo in the maximum dose ganitumab arm vs 7.2 mo in the placebo arm (HR, 0.97, $P = 0.397$)^[35].

Angiogenesis pathway inhibitors

Neoangiogenesis is essential for tumour progression and metastatization mechanisms. Vascular endothelial growth factor (VEGF) stimulates the proliferation of endothelial cells and is overexpressed in human pancreatic cancer. Nevertheless, neoangiogenesis inhibitors, particularly VEGF inhibitors, failed to improve overall survival in combination with gemcitabine in advanced pancreatic cancer. After encouraging results, phase III trials that tested the efficacy of bevacizumab in association with gemcitabine alone, or gemcitabine plus erlotinib, did not confirm previous findings^[36,37].

Aflibercept, a new recombinant fusion protein with extracellular portions of VEGFR-1 and VEGFR-2, which binds VEGF-A, VEGF-B and placental growth factors 1 and 2 thereby inhibiting VEGF-ligand-dependent signalling processes, suppresses tumour growth in pancreatic cell lines and xenografts. Nevertheless, a

phase III study aiming to investigate OS in metastatic pancreatic cancer patients receiving standard gemcitabine and either aflibercept or placebo demonstrated that adding aflibercept to gemcitabine did not improve OS in metastatic pancreatic cancer patients^[38].

Similarly sorafenib, an oral multikinase inhibitor of Raf-kinase, VEGF-R2/-R3 and PDGFR- β , tested alone or in combination with gemcitabine in small phase I and II trials, and axitinib, an anti-angiogenesis agent assessed in combination with gemcitabine, showed no statistically significant efficacy in a phase III trial in advanced PDAC^[39-41].

Phase II studies combining chemotherapy with promising new anti-angiogenic molecular agents, such as TL-118, a nonsteroidal anti-inflammatory oral medication, or necuparanib, which is re-engineered from heparin with possible anti-tumour activity, are underway^[42,43].

Embryonic pathway inhibitors

Hedgehog signalling has a critical role in cell proliferation and survival during embryonic development. Normal pancreatic cells silence this pathway, but pathological activation is observed in many solid tumours, particularly in PADC. Hedgehog binds to the extracellular receptor Patched, which, in the absence of Hedgehog, suppresses activation of the G-protein-coupled receptor Smoothened and upregulates glioma associated oncogene homolog1 transcriptional activity. Cancer cell lines show both Hedgehog ligand-dependent and -independent mechanisms of aberrant signalling^[44].

Bailey *et al.*^[45] showed how Sonic hedgehog (SHH) and other proteins downstream of the Hedgehog pathway, detected in precursor lesions and in PDAC primary tumour samples, contribute to the formation of the desmoplastic reaction, an important characteristic of pancreatic cancer that limits the effective delivery of anticancer agents to pancreatic cancer cells. Genetically engineered mouse models demonstrated a depletion of tumour matrix from SHH pathway inhibition, which could be a promising strategy in pancreatic cancer therapy^[46].

Vismodegib (GDC-0449), an oral small-molecule inhibitor targeting Smoothened^[47], is under assessment in open phase II trials in combination with gemcitabine in advanced cancer, in combination with gemcitabine and nab-paclitaxel in metastatic settings with promising preliminary data^[48], and as a single agent in neoadjuvant settings followed by surgery^[49-51].

The Smoothened inhibitor saridegib (IPI-926) was tested in association with gemcitabine against gemcitabine plus placebo in a randomized, double-blind, placebo-controlled phase II trial enrolling patients with metastatic disease. Unfortunately, this study was closed ahead of time due to evidence of decreased patient survival in the saridegib arm^[52].

Hedgehog inhibitors are an active research field, and several clinical trials are ongoing^[53]. Notch signalling is another embryonic pathway crucial for pancreatic organogenesis, but after pancreas development, it is

active only in a stem cell subgroup. This pathway is upregulated in PDAC and promotes tumourigenesis. Binding of Notch ligand to its receptor promotes a cascade of proteolytic cleavages, mediated by γ -secretase (presenilin). The activated form ICN (intra cellular notch) forms part of a transcription complex that, after translocating to the nucleus, regulates transcription of several genes involved in proliferation and differentiation of cells, interacting with other pathways such as Hedgehog, KRAS and NF- κ B signalling^[54,55].

RO4929097 is a selective inhibitor of the γ -secretase enzyme with anti-tumour activity in preclinical studies^[56].

A recent phase II single-arm trial assessed the possible role of RO4929097, enrolling 18 previously treated advanced PDAC patients. The treatment was well tolerated; the median survival was 4.1 mo, and the median progression-free survival was 1.5 mo^[57].

Encouraging clinical results were observed testing demcizumab, an anti- Delta-like ligand 4 antibody, plus gemcitabine and nab-paclitaxel in advanced PDAC in a phase I b trial. Further evidence is needed to confirm these preliminary data^[58].

PARP inhibitors

Mutations affecting BRCA pathway components, especially the tumour suppressor gene BRCA2, which is associated with hereditary predisposition to breast, ovarian and pancreatic cancer, promote deficiency in DNA damage repair mechanisms and genomic instability^[11].

Poly ADP-ribose polymerase (PARP) is a nuclear enzyme recruited to repair cell DNA damage, and as recent evidence showed, patients with defects in the homologous DNA recombination pathway may benefit from the use of PARP inhibitors as monotherapy or in combination with radiation or other chemotherapeutic agents. Clinical trials testing those new agents in selected patients are currently in the development phase^[59-61].

mTOR and PI3K/Akt pathway inhibitors

After activation, Ras can phosphorylate PI3K, which activates Akt, a serine/threonine kinase. Signal transduction by activated PI3K/Akt plays a role in tumour cell proliferation, survival and metabolism, usually through several downstream targets, including the mammalian target of rapamycin (mTOR)^[62].

Several trials testing PI3K/AKT axis inhibitors are currently ongoing in advanced pancreatic cancer patients after encouraging preclinical model results^[63]. These trials included the following PI3K/AKT axis inhibitors: BKM120, a PI3K inhibitor tested in combination with the mFOLFOX-6 schedule; RX-0201, an Akt antisense oligonucleotide tested in a phase II study plus gemcitabine; and BEZ235, a combined inhibitor of PI3K and mTOR assessed in a phase study in combination with the MEK inhibitor MEK162^[64-66].

Wolpin *et al.*^[67] evaluated a possible role of everolimus, an oral mTOR inhibitor, as monotherapy in 33

gemcitabine-refractory pancreatic cancer patients. The PFS and OS were 1.8 and 4.5 mo, respectively.

Recently, the results of a single arm phase II study where everolimus was tested in combination with capecitabine were published. The median OS was 8.9 mo and PFS was 3.6 mo^[68].

The results of a phase I / II study testing everolimus in combination with gemcitabine in advanced settings and the results of a phase II trial testing temsirolimus, another mTOR inhibitor, in locally advanced or metastatic settings are anticipated^[69,70].

Tumour stroma inhibitors

The stroma is a dynamic compartment of pancreatic tumours that is critically involved in tumour formation, progression and the metastasis process. Therefore, targeting stromal microenvironment elements could be an efficient therapeutic strategy in addition to previously described trials evaluating Hedgehog signalling inhibitors^[71].

After promising data derived from a preliminary clinical study on the possible role of PEGPH20, a pegylated formulation of recombinant hyaluronidase, a phase II trial is currently in the recruitment phase. The purpose of that study is to enrol untreated patients with metastatic disease to receive a combination of PEGPH20, nab-nab-paclitaxel and gemcitabine or a combination of nab-paclitaxel and gemcitabine^[72,73].

Additionally, inhibition of PDGFR, a receptor expressed in stromal cells with a critical role in recruiting pericytes and in interstitial fluid pressure in the tumour stroma, could be an interesting molecular target, as suggested by preclinical studies using an orthotopic pancreatic tumour mouse model^[74].

TKI258, a PDGFR inhibitor, is under evaluation in a phase I dose assessment for advanced pancreatic cancer patients^[75].

In the past, matrix metalloproteinase inhibitors such as marimastat were tested. Matrix metalloproteinases (MMPs) are a family of proteolytic enzymes responsible for the degradation of connective tissue proteins, and aberrant MMP expression is observed in PDAC. Nevertheless, the results of a phase III trial provided no evidence to support a combination of marimastat with gemcitabine in patients with advanced pancreatic cancer^[76].

CONCLUSION

Knowledge of the molecular biology of PDAC has important potential clinical relevance, but current efforts to improve understanding of the mutational profile of this tumour have not provided any significant advantage in the use of targeted therapy. Several agents have been tested in PDAC, but almost all have failed to demonstrate efficacy in late phase clinical trials. Only erlotinib has been approved by the FDA for advanced pancreatic cancer treatment, but the improvement of overall survival is barely 2 wk compared with gemcit-

abine alone^[5].

There could be many reasons for those unsatisfying results. First of all, the extreme genomic heterogeneity of PDAC is an important block to identifying new candidate actionable molecular targets or to testing existing biological therapies already approved for human use for other cancers. In addition, no significant results have been observed by matching targeted agents with patients harbouring the cognate molecular abnormality, such as, for example, the use of trastuzumab in HER2 overexpression cases. Due to poor results derived from targeting a single molecule, new strategies using multitargeted agents or molecular agent combinations are in the development phase in order to block more than one driving genomic aberration and to prevent or evade resistance.

Additionally, the type of chemotherapy used in combination could be a failure factor. Indeed, the majority of trials have combined target agents with gemcitabine, but actually, the first-line schedules are represented by FOLFIRINOX or gemcitabine plus Nab-paclitaxel. Therefore, greater efficacy may be obtained from the combination of target agents with those chemotherapeutic drugs.

Furthermore, most studies in which molecular or chemotherapeutic agents in pancreatic cancer were tested enrolled an unselected population of patients to treat. In the last 3 years, approximately 116 trials specific for PDAC systemic therapy were registered of which only about 8% applied criteria to select a patient subset based upon molecular biomarkers^[77].

FUTURE CHALLENGES

Most studies in which molecular or chemotherapeutic agents in pancreatic cancer were tested enrolled an unselected population of patients to treat. In the last 3 years, approximately 116 trials specific for PDAC systemic therapy were registered of which only about the 8% applied criteria to select a patient subset based upon molecular biomarkers^[77].

To stratify patients, the Australian Pancreatic Cancer Genome Initiative has started a pilot study to evaluate the feasibility of assessing a more stratified approach in the management of pancreatic cancer through predefined actionable molecular phenotypes. Patients are enrolled in this trial, called IMPaCT (Individualised Molecular Pancreatic Cancer Therapy), after a preliminary phenotype screening in order to compare the use of gemcitabine in an unselected population to a stratified approach. The aim of the study is to create a tailored approach to pancreatic cancer treatment, which seems to be one of the major challenges for the future^[78].

Finally, thanks to biotechnology advancement, biological agents can find application in cancer treatment by tumour-targeted delivery of cytotoxic drugs. Particularly, Ahn *et al.*^[79] developed antibody fragment-installed polymeric micelles *via* maleimide-thiol conjugation

for selective delivery of platinum drugs to pancreatic tumours. This antibody-drug conjugate significantly suppressed the growth of pancreatic tumour xenografts. This technology, with potential activity *in vitro* and in a mouse model, could be a promising future strategy in pancreatic cancer therapy^[79].

In conclusion, the lack of efficacy of targeted therapy in PDAC represents a challenge for the future, and more efforts are needed in order to make pancreatic cancer a curable disease.

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