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### EVIDENCE REVIEW

- 1847** Pancreatic adenocarcinoma: Beyond first line, where are we?  
*Cherri S, Noventa S, Zaniboni A*

### REVIEW

- 1864** Non-alcoholic fatty liver and chronic kidney disease: Retrospect, introspect, and prospect  
*Heda R, Yazawa M, Shi M, Bhaskaran M, Aloor FZ, Thuluvath PJ, Satapathy SK*
- 1883** Repurposing metformin for the treatment of gastrointestinal cancer  
*Cunha Júnior AD, Bragagnoli AC, Costa FO, Carnevalheira JBC*
- 1905** Mesenchymal stromal cell secretome in liver failure: Perspectives on COVID-19 infection treatment  
*Chinnici CM, Russell G, Bulati M, Miceli V, Gallo A, Busà R, Tinnirello R, Conaldi PG, Iannolo G*

### MINIREVIEWS

- 1920** Artificial intelligence applications in inflammatory bowel disease: Emerging technologies and future directions  
*Gubatan J, Levitte S, Patel A, Balabanis T, Wei MT, Sinha SR*
- 1936** Post-pancreatitis diabetes mellitus and excess intra-pancreatic fat deposition as harbingers of pancreatic cancer  
*Petrov MS*
- 1943** BRCA mutated pancreatic cancer: A change is coming  
*Rosen MN, Goodwin RA, Vickers MM*
- 1959** Metabolic and cardiovascular complications after virological cure in hepatitis C: What awaits beyond  
*Shengir M, Elgara M, Sebastiani G*

### ORIGINAL ARTICLE

#### Basic Study

- 1973** S100 calcium binding protein A6 and associated long noncoding ribonucleic acids as biomarkers in the diagnosis and staging of primary biliary cholangitis  
*Dong XH, Dai D, Yang ZD, Yu XO, Li H, Kang H*
- 1993** Long non-coding RNA TP73-AS1 promotes pancreatic cancer growth and metastasis through miRNA-128-3p/GOLM1 axis  
*Wang B, Sun X, Huang KJ, Zhou LS, Qiu ZJ*

**Retrospective Study**

- 2015** Prediction of microvascular invasion in solitary hepatocellular carcinoma  $\leq 5$  cm based on computed tomography radiomics

*Liu P, Tan XZ, Zhang T, Gu QB, Mao XH, Li YC, He YQ*

- 2025** Hepatocellular carcinoma progression in hepatitis B virus-related cirrhosis patients receiving nucleoside (acid) analogs therapy: A retrospective cross-sectional study

*Yang DH, Wang WP, Zhang Q, Pan HY, Huang YC, Zhang JJ*

**Observational Study**

- 2039** Hypophosphatemia after high-dose intravenous iron treatment in patients with inflammatory bowel disease: Mechanisms and possible clinical impact

*Detlie TE, Lindström JC, Jahnsen ME, Finnes E, Zoller H, Moum B, Jahnsen J*

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## Pancreatic adenocarcinoma: Beyond first line, where are we?

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### Abstract

Pancreatic cancer is considered one of the most aggressive cancers, with an increasing incidence in recent years. To date, chemotherapy is still the standard of care for advanced metastatic disease, unfortunately providing only a slight advantage in terms of survival. The molecular and cellular characteristics of pancreatic cancer cells, as well as the cells that characterize the pancreatic tumour microenvironment, are the basis of the mechanisms of resistance to treatment. After progression during first-line treatment, few patients are eligible for second-line treatment due to the loss of performance status. To date, a clear survival advantage has not yet been demonstrated for second-line chemotherapy. Precision medicine could be the key to increasing responses to cancer treatment and finally impacting survival in this difficult-to-treat disease. In this review, we analyze current recommendations in the second-line setting and potential future prospects.

**Key Words:** Pancreatic adenocarcinoma; Second-line; Chemotherapy; Targeted therapy; Immunotherapy

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**Core Tip:** The incidence of pancreatic ductal adenocarcinoma is increasing, with anticipation of a large impact on the population. Despite achieving a survival gain in first-line treatment in the last decade, to date, little has been achieved in second-line treatment. The molecular and genetic characteristics of this tumour represent a fundamental challenge for preclinical and clinical research. In this review, we illustrate current clinical practice in second-line treatment for advanced pancreatic adenocarcinoma and the research landscape of potential future prospects.

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## INTRODUCTION

Pancreatic cancer remains one of the deadliest malignancies, recording 432242 new deaths in 2018, with 458918 new pancreatic cancer cases reported globally[1]. Adenocarcinoma is the most common type of exocrine (non-endocrine) pancreatic cancer, accounting for over 90 percent of pancreatic cancer diagnoses. In most cases, it originates from the pancreatic ducts (ductal adenocarcinoma), in a smaller percentage of cases it can originate from the acini (acinar cell carcinoma). Rarer forms of pancreatic cancer are squamous cell carcinoma, adenosquamous carcinoma and colloid carcinoma. Despite advances in pancreatic cancer detection and management, the 5-year survival rate is still very low, only approximately 9%[2]. It is expected to become the second most common cause of cancer-related death by 2030[3]. Unfortunately, most cases are diagnosed in locally advanced or metastatic stages, for which chemotherapy remains the standard of care[4]. Progress in the treatment of pancreatic ductal adenocarcinoma (PDAC) has been very limited; in particular, gemcitabine (GEM) has been used as a monotherapy agent for first-line treatment for approximately 20 years. Subsequently, in 2011, there was a breakthrough in the treatment of metastatic PDAC (mPDAC) with the introduction of the FOLFIRINOX regimen [5-fluorouracil (5FU), folinic acid, irinotecan (IRI) and oxaliplatin (OX)] as a first-line standard of treatment[5]. However, this regimen is not suitable for all patients. Eventually, the combination of nab-paclitaxel and GEM (NabGem) also demonstrated an overall survival (OS) gain in mPDAC compared to GEM monotherapy[6]. However, no prospective randomized studies have demonstrated a benefit in terms of OS for a second-line treatment; moreover, there is currently no standard regarding the sequencing of treatments.

## CURRENT CLINICAL PRACTICE IN SECOND LINE MPDAC

### Chemotherapy

mPDAC is a biologically aggressive cancer that is often characterized by clinically evident disease progression during first-line treatment (pain, fatigue, anorexia, weight loss, constipation, fever, diabetic decompensation, *etc.*) with a deterioration of the patient performance status (PS) that limits subsequent treatments. Several complications can also arise, such as duodenal stenosis, obstruction of biliary stents and cholangitis, gastrointestinal bleeding and intestinal obstructions, which further limit the possibility of accessing second-line chemotherapy. In this context, it is not surprising that few data from large randomized trials are available. To date, there are no clear data on the superiority of a specific chemotherapy regimen due to the lack of adequate comparisons.

In advanced PDAC, the choice of which chemotherapy to use in the second-line setting basically depends on the treatments used in the first-line setting, residual toxicities (*e.g.*, peripheral neuropathy), patient PS, age and comorbidities. The ability of patients in different countries to access a specific treatment should also be considered due to the limitations of regulatory agencies.

Currently, in first-line treatment for patients with a good PS, Eastern Cooperative Oncology Group (ECOG) 0-1, two main regimens are indicated based on evidence of an OS benefit highlighted by randomized phase III trials: FOLFIRINOX and NabGem. In fact, the PRODIGE4/ACCORD11 trial showed the superiority of FOLFIRINOX over GEM in terms of OS (11.1 mo *vs* 6.8 mo), progression-free survival (PFS, 6.4 mo *vs* 3.3 mo) and the objective response rate (ORR, 31.6% *vs* 9.4%)[5], while in the Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT), NabGem showed superiority over GEM (OS 8.5 mo *vs* 6.7 mo, PFS 5.5 mo *vs* 3.7 mo, ORR 23% *vs* 7%, respectively)[6]. It is significant to consider how many patients received a subsequent therapy after progression on first-line therapy in these trials. In the PRODIGE4/ACCORD11 trial, second-line therapy was administered in approximately 50% of patients in both arms, while in the MPACT trial, second-line therapy was administered in 38% of patients in the NabGem group and in 42% of patients in the GEM group. Real-life data are very different; in fact, even in the best cases, they do not seem to include half of patients receiving second-line therapy. It is remarkable that patients

treated in high-volume centres, especially those aged < 65 years and with an ECOG PS of 0-1, receive more lines of therapy. According to Abrams *et al*[7], in the United States in 2015, approximately 56% of patients received second-line therapy and 22% received third-line therapy. The percentages reported in other recent databases are even lower: 38.2% in the United States[8], 33% in Sweden[9], and 44%-48% in British Columbia and Canada[10]. Higher percentages are reported in Austria, where the proportions of patients who had access to second- and third-line therapy were 62%-65% and 29%-37%, respectively[11].

The choice of subsequent treatment has to consider the chemotherapy drugs received in the first line. Therefore, there are two main scenarios: after a first-line treatment with GEM-based chemotherapy, the advice of the main guidelines is to choose a 5FU-based chemotherapy; in the case of a front line therapy with a 5FU-based scheme, the indication is a GEM-based therapy[12,13]. The choice between a multidrug combination regimen and monotherapy depends on the patient's PS (ECOG 0-1 or 2, respectively). A summary of the current possible options is reported in Figure 1. The study by Taieb *et al*[14] evaluated first-line and second-line treatment regimens and their geographic variation across European countries between 2014 and 2016, highlighting that the most common first-line treatments were FOLFIRINOX (35.6%), the first choice in France and in the United Kingdom; NabGem (25.7%); and GEM monotherapy (20.5%). Overall, GEM was the most frequently used second-line therapy (27.1%), followed by NabGem (17.8%), FOLFOX [5FU+ leucovorin (LV) + OX, 17.6%] and 5FU monotherapy (16.7%)[14]. It should be noted that nab-paclitaxel beyond the first line is not approved in all countries, and at that time, pegylated liposomal IRI (Nal-IRI) was not yet available.

Pancreatic cancers with specific molecular characteristics, such as microsatellite instability, fusion of the *NTRK* gene, and *BRCA 1-2* mutations, require a separate discussion. In fact, currently, it is recommended by National Comprehensive Cancer Network guidelines to evaluate at least these three genetic features, but unfortunately, this is not accessible yet for everyone in several countries.

For a better understanding of the data available in the literature, we considered the following possible scenarios: (1) Second-line chemotherapy after treatment with FOLFIRINOX; and (2) Second-line chemotherapy after GEM-based regimens (Figure 1).

### Second-line chemotherapy after treatment with FOLFIRINOX

There is no clear consensus on the second-line treatment after progression to FOLFIRINOX since no prospective randomized trials have been conducted in this setting. The choice is generally a GEM-based treatment, which could be GEM monotherapy or a GEM-based therapy. Table 1 summarizes the main second-line trials and their results, divided according to the type of study.

**GEM in monotherapy:** Only a series of retrospective studies have evaluated the efficacy of GEM as a second-line monotherapy after FOLFIRINOX failure[15,16]. The analysis conducted by Viaud *et al*[17] showed a median OS with GEM of 3.7 mo [95% confidence interval (CI): 2.5-5.2], a median PFS of 2.1 mo (95%CI: 2.0-2.6) and a disease control rate (DCR) of 40%, highlighting that age at diagnosis and PS were independently associated with OS in a multivariate analysis [hazard ratio (HR) of 1.86;  $P = 0.0055$  and 2.42;  $P < 0.0001$ , respectively] and suggesting that GEM is beneficial for patients with a good PS. A multicentre retrospective study in the same setting showed an ORR of 11% and a clinical benefit of 44% for patients, regardless of their previous response to the first-line treatment, concluding that some patients benefit from a second-line treatment[18].

**GEM based treatment:** No randomized trials have evaluated the efficacy of the NabGem combination as second-line therapy. Zhang *et al*[19] published retrospective data collected from a total of 146 patients treated with FOLFIRINOX as the first-line treatment. Of those, 30 received the NabGem combination, 8 received GEM as monotherapy, and 22 received best supportive care (BSC). The median PFS and OS were 3.61 mo and 5.69 mo in the NabGem group and 2.51 mo and 3.82 mo in the GEM monotherapy group, respectively. In a second retrospective study[10], the percentage of patients receiving NabGem compared to GEM alone was different depending on the region considered and the respective possibility for reimbursement[20]. In this study, the OS outcomes favour the NabGem combination regardless of funded access to the second-line combination. The efficacy of the combination in the second-line setting was confirmed in a third multicentre retrospective analysis, although without a comparison with GEM alone[21]. A prospective study showed that the DCR with

**Table 1 Studies of second-line treatment in metastatic pancreatic ductal adenocarcinoma**

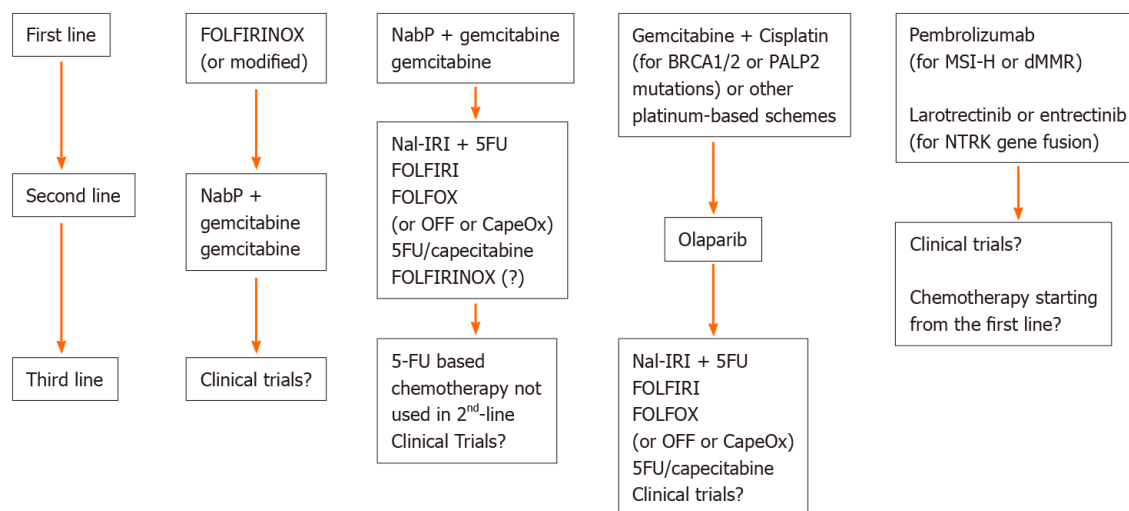
Ref.	Type of study	Patients (n)	1 <sup>st</sup> -line regimen	2 <sup>nd</sup> -line regimen	Median 2 <sup>nd</sup> -line OS (mo)	Median 2 <sup>nd</sup> -line PFS (mo)	2 <sup>nd</sup> -line ORR (%)	2 <sup>nd</sup> -line DCR (%)
Pelzer <i>et al</i> [35], 2011	Phase III	46 <sup>1</sup>	GEM monotherapy	OFF; BSC	4.8; 2.3	-	-	-
Oettle <i>et al</i> [36], 2014, CONKO-003	Phase III	160	GEM monotherapy	OFF; FF	5.9; 3.3	2.9; 2.0	-	-
Gill <i>et al</i> [37], 2016, PANCREOX	Phase III	108	GEM-based (approximately 75% monotherapy)	mFOLFOX6; FU/LV	6.1; 9.9	3.1; 2.9	13.2; 8.5	60; 63.8
Wang-Gillam <i>et al</i> [37], 2016, NAPOLI-1	Phase III	417	GEM-based <sup>2</sup>	Nal-IRI; FU/LV; Nal-IRI + FU/LV	4.9; 4.2; 6.1	2.7; 1.5; 3.1	6; 1; 16	44; 24; 52
Chung <i>et al</i> [29], 2018	Phase II	48	GEM-based	mFOLFIRINOX	9.0	5.8	18.8	62.5
Tsavaris <i>et al</i> [33], 2005	Phase II	30	GEM	OX 50 mg/mq + FU/LV (1-h iv infusion), weekly	6.25	-	23.3	53.3
Pelzer <i>et al</i> [32], 2009	Phase II	37	GEM	OFF	5.5	3.0	6	49
Yoo <i>et al</i> [34], 2009	Phase II	61	GEM-based	mFOLFIRI.3; mFOLFOX	3.9; 3.5	1.9; 1.4	0; 7	23; 17
Zaniboni <i>et al</i> [49], 2012	Phase II	50	GEM ± platinoid	FOLFIRI	5	3.2	8	36
Chung <i>et al</i> [29], 2018, SWOG S1115	Phase II	137	GEM-based	Selumetinib+ MK-2206; mFOLFOX	3.9; 6.7	1.9; 2.0	1.7; 8	22.4; 30.6
Portal <i>et al</i> [22], 2015	Prospective cohort	57	FOLFIRINOX	NabGem	8.8	5.1	17.5	58
Zaanan <i>et al</i> [47], 2014	Prospective cohort	46	GEM/FOLFIRI.3 in FIRGEM trial	FOLFOX	4.3	1.7	0	36
Wainberg <i>et al</i> [45], 2020	Meta-analysis	454	GEM-based	FOLFOX; Nal-IRI	6.3; 6.1	-	-	-
Sonbol <i>et al</i> [51], 2017	Meta-analysis	895	GEM-based	FPOX; FPIRIFP	FPIRI <i>vs</i> FP: HR OS 0.7, PFS 0.64; FPOX <i>vs</i> FP: HR OS 1.0, PFS 0.81			
Citterio <i>et al</i> [52], 2018	Meta-analysis	1587	GEM-based	FP, OX or IRI-based	Most effective IRI-based regimens (results cannot be translated into the table)			
Rahma <i>et al</i> [43], 2013	Systematic analysis	1503	GEM-based	GEM + platinum; FPOXBSC	6.0; 5.7; 2.8	4; 2.9; -	-	-
Petrelli <i>et al</i> [53], 2017	Systematic analysis	-	GEM-based	OX-based; IRI-based	5.3; 5.5	2.9; 2.7	11.9; 8.7	41.1; 29.4
Berk <i>et al</i> [48], 2012	Comparative	85	GEM-based	FOLFOX4; XELOX	5.8; 4.9	3.7; 3.7	17; 18	43; 59
Zhang <i>et al</i> [19], 2018	Retrospective	146	FOLFIRINOX	NabGem; Gem alone	5.69; 3.82	3.61; 2.51	-	-
Chae <i>et al</i> [21], 2020	Retrospective	102	FOLFIRINOX	NabGem	9.8	4.6	8.5	73.6
Viaud <i>et al</i> [17], 2017	Retrospective	96	FOLFIRINOX	GEM monotherapy	3.7	2.1	-	40
Gilabert <i>et al</i> [18], 2017	Retrospective	72	FOLFIRINOX	GEM monotherapy	-	2.5	11	-



Pointet <i>et al</i> [38], 2020	Retrospective	137	NabGem	FOLFOX; FOLFIRI; FOLFIRINOX	3.5; 9.7; 6.1	2; 6.6; 3.4	0; 9.5; 6.3	29.2; 61.9; 50
Lee <i>et al</i> [41], 2020	Retrospective	120	GEM-based	FPOX; FP	7.04; 7.43	2.89; 3.81	6.4; 5.4	52.6; 59.5
Neuzillet <i>et al</i> [50], 2012	Retrospective	63	GEM ± platinoid	FOLFIRI	6.6	3.0	7.9	39.7
Kieler <i>et al</i> [24], 2019	Retrospective	52	GEM-based	Nal-IRI + FU/LV	6.79	3.84	19.2	46.2

<sup>1</sup>The trial was prematurely stopped due to insufficient accrual.

<sup>2</sup>Approximately 45% of gemcitabine alone and 55% in combination. About 30% of patients had received ≥ 2 previous lines for metastatic disease, with 45% of patients pretreated with fluorouracil/leucovorin-based regimens. GEM: Gemcitabine; DCR: Disease control rate; BSC: Best supportive care; OFF: Oxaliplatin, folinic acid and 5-fluorouracil; 5FU: 5-Fluorouracil; OX: Oxaliplatin; LV: Leucovorin; FF: Folinic acid and 5-fluorouracil; Nal-IRI: Liposomal irinotecan; FOLFIRINOX: 5-Fluorouracil, folinic acid, irinotecan and oxaliplatin; FOLFOX: 5-fluorouracil + leucovorin + oxaliplatin; FPOX: Fluoropyrimidine and oxaliplatin-based regimens; HR: Hazard ratio; OS: Overall survival; NabGem: Nab-paclitaxel and gemcitabine; FP: Fluoropyrimidine; IRI: Irinotecan.



**Figure 1 Current therapeutic possibilities for metastatic pancreatic ductal adenocarcinoma.** NabP: Nab-paclitaxel; Nal-IRI: Nanoliposomal irinotecan; 5FU: 5-Fluorouracil; FOLFIRI: 5-Fluorouracil + irinotecan; FOLFOX: 5-fluorouracil + leucovorin + oxaliplatin; OFF: Oxaliplatin + 5-fluorouracil + folinic acid; CapeOx: Capecitabine + oxaliplatin; MSI-H: Microsatellite instability high; dMMR: DNA mismatch repair deficiency; Clinical trials?: Evaluate the availability of clinical trials suitable for the patient.

NabGem was 58% (ORR 17.5%), OS was 8.8 mo (95%CI: 6.2-9.7) and the PFS was 5.1 mo (95%CI: 3.2-6.2)[22].

To date, there are no second-line treatment recommendations after progression on the FOLFIRINOX scheme, and the use of GEM alone or in combination with nabpaclitaxel is generally dictated by patient characteristics and by the possibility of reimbursement in individual countries.

### Second-line chemotherapy after treatment with GEM based combination therapy

For patients previously treated with GEM-based regimens, the main international guidelines recommend 5FU-based therapies, which include FOLFIRI, Nal-IRI+5FU, OX, folinic acid and 5FU (OFF), FOLFOX or CapeOX and monotherapy with 5FU or capecitabine.

**Nal-IRI ± 5FU/LV:** Nal-IRI + 5FU/LV is the regimen with the most evidence and therefore a higher degree of recommendation[13]. This indication comes from the results of the NAPOLI-1 study, which compared 5FU/LV alone *vs* monotherapy with Nal-IRI or the combination of 5FU/LV + Nal-IRI in 417 patients with mPDAC and a Karnofsky PS ≥ 70 who were previously treated with GEM-based therapy[23]. In particular, 12% of patients received GEM-based therapy in the adjuvant, neoadjuvant, or locally advanced setting; 56% had received one previous line of metastatic treatment; and 32% had received two or more lines of metastatic treatment. It should be emphasized that few patients received NabGem in the first-line setting since the

GEM combination is preferred in current clinical practice, and 43% of patients had already received previous 5FU-based therapy (10% IRI and 32% platinum). Patients in the 5FU/LV + Nal-IRI group achieved a longer OS than patients in the 5FU/LV group (6.1 mo *vs* 4.2 mo;  $P = 0.012$ , HR: 0.67); however, no significant difference in OS was observed between the 5FU/LV and Nal-IRI monotherapy groups (4.2 mo *vs* 4.9 mo;  $P = 0.94$ , HR: 0.99).

These data were confirmed by a retrospective study that included 52 patients[24] and a similar Korean study[25]. However, in some countries, including Italy, this combination is not approved due to the methodological limitations of the study, such as the heterogeneity of the patient population, the study design without a comparison with the classic FOLFIRI regimen, and the inclusion of patients pretreated with 5FU or IRI[26].

**Fluoropyrimidine and OX-based regimens:** The efficacy and safety data of second-line treatment with FOLFIRINOX are based on retrospective analyses[27,28] and on some phase II studies[29,30]. In the single-arm multicentre phase 2 study performed by Chung *et al*[29] (48 patients) of modified FOLFIRINOX (IRI 120 mg/m<sup>2</sup> and OX 60 mg/m<sup>2</sup>), the ORR, DCR, median PFS and OS were 18.8%, 62.5%, 5.8 mo and 9.0 mo, respectively, with significant toxicity (neutropenia grade 3 or 4 rates of 64.6%, febrile neutropenia 16.7%). A highly toxic triplet therapy is not very suitable for second-line palliative treatment in patients with a non-optimal PS and is reserved for only a few cases. Furthermore, in a recent real-world analysis, triplet therapy with FOLFIRINOX did not seem to have an advantage over sequential chemotherapy with FOLFIRI-FOLFOX regimens[31].

For the other OX-based regimens, the data are controversial. Based on the promising results of some phase II studies[32-34], three main phase III trials have been conducted[35-37]. In the CONKO-003 trial, 160 patients were randomized to receive FF (folinic acid 200 mg/m<sup>2</sup> followed by a continuous IV infusion of fluorouracil 2000 mg/m<sup>2</sup> over 24 h on days 1, 8, 15, and 22 every 42 d) or OFF (FF and OX 85 mg/m<sup>2</sup> IV administered before FF on days 8 and 22). Compared to FF, OFF achieved a significant increase in both OS (5.9 *vs* 3.3 mo) and PFS (2.9 *vs* 2 mo)[36]. In phase III by Pelzer *et al*[35], OFF compared to BSC significantly prolonged OS (4.82 mo *vs* 2.30 mo, respectively) despite the premature closure for insufficient accrual (only 46 patients) due to the difficulty of clinicians and patients accepting BSC[35]. However, these results of the superiority of OFF over FF and BSC were not confirmed by the phase III PANCREOX trial[37]. In particular, in this study, the addition of OX to FF (in the mFOLFOX6 scheme) did not translate into an increase in OS; in contrast, it seemed detrimental (6.1 mo *vs* 9.9 mo) at the expense of increased toxicity.

In the literature, different retrospective trials and reviews have dealt with the same topic, with discordant results[38-47].

A comparative study evaluated the XELOX and FOLFOX schemes, highlighting their comparable results in terms of efficacy and toxicity profile[48].

**IRI and 5FU-based regimens (fluoropyrimidine IRI):** The use of second-line FOLFIRI in patients who progressed on first-line therapy of GEM and platinum (cisplatin or OX) was evaluated in a prospective multicentre study[49]. Among the 50 patients enrolled, four partial responses (8%) were observed with disease stability in 28% of patients, while PFS and OS were 3.2 mo and 5.0 mo, respectively. Similar results were obtained from another study that evaluated FOLFIRI after progression on GEM and platinoids[50]. Unlike the previous study, patients ( $n = 63$ ) could receive more than one treatment line in the metastatic setting. In particular, most patients had received two previous lines. DCR was achieved in 25 patients (39.7%; partial response:  $n = 5$ , stable disease:  $n = 20$ ) with FOLFIRI. The median time to progression (TTP) was 3.0 mo, and the median OS was 6.6 mo. An ECOG PS of 2 was significantly associated with a poor TTP and OS, limiting the efficacy of FOLFIRI to patients with a good PS (PS 0-1).

Some meta-analyses have concluded that fluoropyrimidine (FP) IRI (FPIRI) is superior to FP and OX-based regimens (FPOX) after first-line treatment with gem-based chemotherapy. In particular, Sonbol *et al*[51] collected randomized controlled trials comparing FP monotherapy *vs* FPOX or FPIRI and showed that FPOX or FPIRI improved PFS compared with single-agent FP, but only FPIRI reported an OS advantage. Similarly, in the network meta-analysis by Citterio *et al*[52] and the meta-analysis by Catalano *et al*[40], FPIRI seemed superior to FPOX in terms of OS. Conversely, in the systematic review of 24 studies by Petrelli *et al*[53], FPOX and FPIRI were associated with a similar efficacy, with a pooled ORR, DCR, PFS and OS of 11%, 37.9%, 2.87 mo and 5.48 mo, respectively.

In conclusion, in patients with preserved PS (ECOG PS 0-1), without relevant comorbidities, it is reasonable to propose a second-line treatment with a 5FU-based or GEM-based treatment, depending on the first-line treatment used. Within the 5FU-based regimens, any residual toxicities of the first-line treatment can lead to choose a scheme rather than another. For example, if the patient has residual neurotoxicity (*e.g.*, from Nab-paclitaxel) the choice could be FOLFIRI or Nal-IRI-5FU; if he has diarrhea or bone marrow toxicity, FOLFOX. However, some treatments, such as NabGem or Nal-IRI, are not reimbursed for the second-line in all countries, thus inevitably influencing the choice of treatment.

### Targeted therapy

The introduction of increasingly accurate techniques for molecular sequencing and a better understanding of the pathogenetic role of genes related to PDAC have led to the drafting of numerous clinical trials to study potential targeted treatments in chemorefractory disease. Studies in the literature suggest that the use of precision medicine can have a substantial effect on survival in patients affected with PDAC and that molecular-guided treatments targeting oncogenic drivers promise potential developments in clinical practice[54]. Despite countless studies, to date, few biologic treatments have been approved for advanced PDAC. In particular, the FDA (Food and Drug Administration)- and EMA (European Medicines Agency)-approved targeted drugs for second-line treatment are erlotinib, larotrectinib and entrectinib. Olaparib is approved for maintenance after response to a first-line platinum-containing agent[55].

**Erlotinib:** The approval of erlotinib, an EGFR (epidermal growth factor receptor) TK inhibitor, in combination with GEM comes from a phase III study that demonstrated a statistically significant, albeit modest, improvement in survival in PDAC compared to GEM alone[56]. These data have been confirmed in other prospective[57] and retrospective studies[58].

**Larotrectinib and entrectinib:** Fusions involving *NTRK1*, *NTRK2* and *NTRK3* lead to the expression of chimeric rearrangements in tropomyosin receptor kinases (TRKs) A, B, and C, respectively, with constitutively active kinase function. TRK fusions are oncogenic drivers in numerous cancer histotypes, including pancreatic cancer, albeit in a very low percentage of cases, approximately 0.34%[59]. A peculiarity of the studies that evaluated TRK inhibitor drugs is that the efficacy of the specific treatment on a genomic alteration is evaluated independent of the tumour histology. No randomized trials have been conducted, but the high ORR that exceeded the predetermined minimum of the investigators (30%), which was 75% for larotrectinib and 57% for entrectinib, led to the approval of these drugs. However, data from studies of these two drugs are not comparable given the heterogeneity of the study populations involved.

The approval of entrectinib for solid tumours with *NTRK* gene fusions is based on the results of three clinical trials: ALKA-372-001, STARTRK-1[60] and STARTRK-2 (NCT02568267). An integrated analysis of the following phase I and II studies included a total of 54 patients with *NTRK* fusion-positive advanced solid tumours for a total of 19 different histotypes[61]. The median follow-up was 12.9 mo and showed 50% partial responses and 7% complete responses. This response to treatment has been maintained over time with a median duration of response of 10 mo and a good toxicity profile.

The approval of larotrectinib is based on data from three multicentre, open-label, single-arm clinical studies: LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687) and NAVIGATE (NCT02576431). A pooled analysis of these studies by Hong *et al*[62] included 55 patients treated with larotrectinib. The ORR was 79% (95% CI: 72-85) in 153 evaluable patients, with a 16% complete response rate and a good safety profile.

Given the clinical benefit, even considering the low prevalence of *NTRK* fusions in patients with pancreatic cancer and the lack of easy access to Next Generation Sequencing services, patients should be tested at diagnosis for such gene alterations to guide treatment decisions as well as for gaining access to potential clinical trials.

Unfortunately, in real life clinical practice it is not possible to require such molecular insights in all patients with mPDAC due to the cost sustainability. The lack of access to these drugs in different countries represents the current gap between what precision medicine for mPDAC could be in the future and current clinical practice in different oncology contexts. The use of resources and the high costs of oncological treatments will be an increasingly important topic in the near future and it is inevitable to take this into account.

### Immunotherapy

Immunotherapy has changed the natural history of various cancer pathologies, especially melanoma and lung cancer, providing results in terms of increased OS in other neoplastic pathologies, such as cancer of the head and neck, bladder cancer, renal carcinoma, Merkel cell carcinoma and triple-negative breast tumours. However, to date, immune checkpoint inhibitors (ICI) have not shown any efficacy in controlling advanced PDAC, either in monotherapy[63,64] or in combination with chemotherapy[65,66]. Several actors are known to be responsible for the response/resistance mechanisms to ICI. Among these actors, the ability of the tumour to express antigens recognizable by the cells of the immune system and the characteristics of the tumour microenvironment in which the balance of immuno-sensitizing/immuno-suppressive factors is in favour of the latter[67]. In particular, PDAC are characterized by the presence of an abundant desmoplastic stroma composed of fibroblasts, extracellular matrix, immune cells and stellate cells. Immune cells infiltrating this stroma are mostly represented by tumour-associated macrophages, myeloid-derived suppressor cells and Treg cells, with very few effector T cells. Numerous trials are underway aimed at converting the pancreatic tumour microenvironment from immunosuppressive to immunosensitive[68,69]; however, to date, there is no indication for second-line immunotherapy treatments in chemorefractory disease. A PD-1 (programmed cell death protein 1) ICI, Pembrolizumab, has been approved by the FDA for diseases with microsatellite instability, regardless of tumour site[70]. However, this indication has not yet been approved by EMA, and in Europe, it is therefore not possible to prescribe immunotherapy in this setting outside of clinical trials.

## FUTURE DIRECTIONS

As seen from current clinical practice in second-line treatment of mPDAC, there are fundamental open questions. These questions include therapeutic possibilities for treatment after progression on TRK inhibitors in TRK fusion-positive cancers, an increase in targeted therapies, and overcoming the immuno-resistance of metastatic pancreatic disease.

### ***Therapeutic possibilities for treatment after progression on TRK inhibitors in TRK fusion-positive cancers***

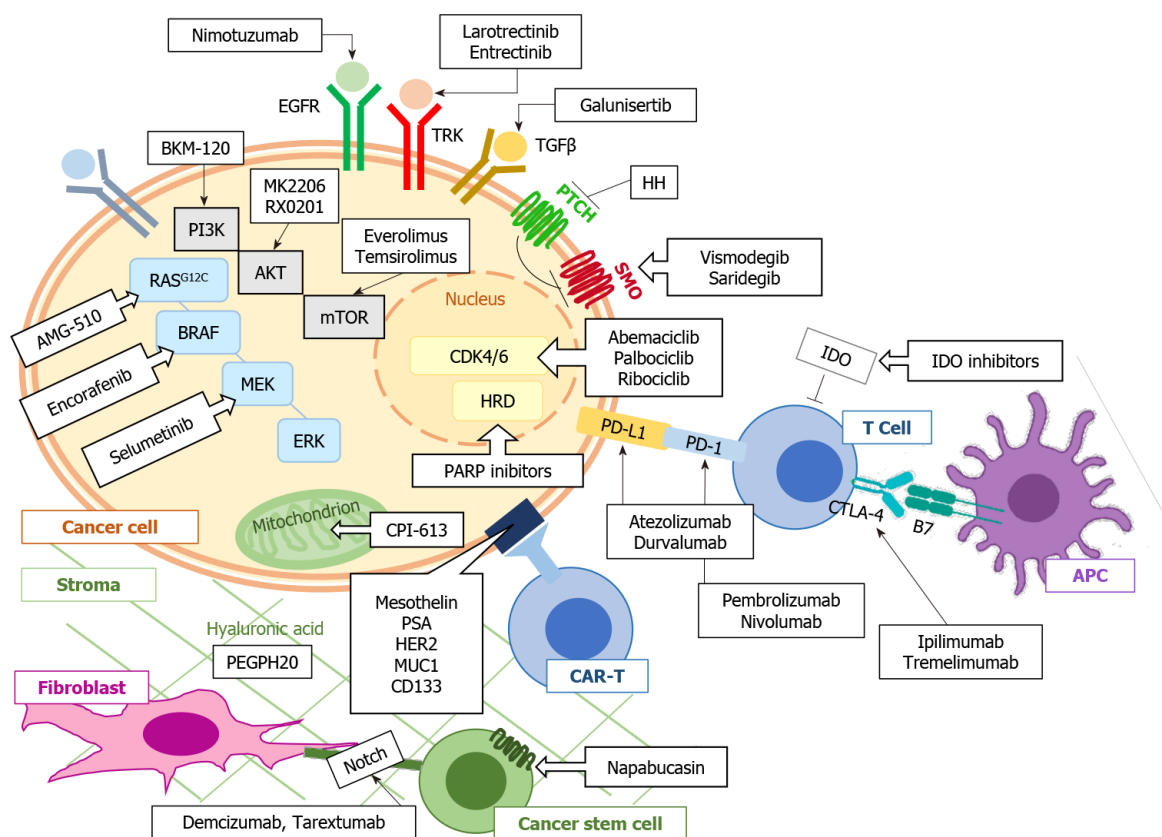
Patients may acquire resistance to first-generation TRK inhibitors; however, to date, the mechanisms of resistance to TRK inhibitor drugs are not known, and the only secondary resistance mechanism identified is the acquisition of targeted mutations in the NTRK kinase domain of the oncogenic fusion. Currently, several trials of newer molecules, such as LOXO-195[71] and TPX-00005[72], have been performed to evaluate the efficacy of targeted therapies after progression on TRK inhibitors with very promising results. Such molecules could become the second-line standard in the future after the failure of first-generation TRK inhibitors in TRK fusion-positive pancreatic adenocarcinoma.

### ***Increase of targeted therapies***

Despite the high ORR of TRK inhibitor drugs, unfortunately, the percentage of PDAC patients susceptible to this targeted treatment is extremely low. Furthermore, identification of the BRCA mutation allows the prescription of olaparib in maintenance after a response to a first-line platinum-based treatment, so there is currently no possibility of second-line targeted treatment in mutated BRCA patients[73].

To date, there are few data on the efficacy of targeted treatments in advanced PDAC; however, this deficiency should not discourage clinicians from requiring a genomic study in these patients. Indeed, knowledge of the prospective genomic profile can predict the response to chemotherapy treatment[74]. Furthermore, these data could be useful for the enrolment of second-line patients in a clinical trial. Research is currently progressing by targeting the recombination deficits of DNA as well as considering the driver genes in pancreatic carcinogenesis. Alongside drugs that target pancreatic tumour cells, there is a large amount of research addressing the peculiar tumour microenvironment that is partly responsible for the poor response to cancer treatments of advanced PDAC (Figure 2).

Regarding tumours with recombination deficiency of DNA repair, research is also underway to determine the extent of the cancer risk in patients with the so-called



**Figure 2** Main targeted drugs under study for patients with advanced pancreatic ductal adenocarcinoma. EGFR: Epidermal growth factor receptor; TGFβ: Transforming growth factor β; APC: Antigen presenting cells; PD-1: Programmed cell death protein 1; PD-L1: Programmed cell death protein ligand 1; CAR-T: Chimeric antigen receptor T cells.

‘bracness’ phenotype, or rather the genetic alterations that result in a defect in homologous recombination repair, mimicking the loss of *BRCA1* or *BRCA2*. Among these mutations is the *PALB2* mutation, which occurs in 3%-4% of familial pancreatic cancer cases[75,76]. Most studies of PARP inhibitors are conducted as maintenance after a response or stability after treatment with a platinum-based first line, *i.e.*, the current indication for olaparib. However, studies have also been conducted on the second line in patients pretreated and in progression after a first-line chemotherapy treatment[77-79]. However, in this setting, the data are currently conflicting, promising for olaparib and rucaparib and not significant for veliparib. Nevertheless, phase 3 studies are lacking.

Considering the major driver genes in pancreatic carcinogenesis, pancreatic tumours are characterized in most cases by activating mutations in *KRAS* (> 90%) and loss-of-function mutations in *TP53* (50%) and *CDKN2A* (80%). Several studies are underway with the aim of targeting such drivers; however, to date, the potential therapeutic target genes are limited to *KRASG12C* and *CDKN2A*, which are found in only a small percentage of patients. AMG 510 is a novel small molecule that specifically and irreversibly inhibits *KRASG12C* and shows antitumour activity when administered as monotherapy in pretreated patients[80,81]. Since the loss of p16INK4a is a standard feature in *KRAS*-driven PDAC, pharmacological specific inhibition of CDK4/6 represents a possible targeted treatment. However, monotherapy treatment with CDK4/6 inhibitors does not appear to be remarkably effective for pancreatic cancer[82]. It has therefore been hypothesized that the activity of CDK4/6 inhibitors can be exploited by combination therapies, such as mTOR inhibitors or chemotherapy[83]. Numerous clinical trials are currently underway (Table 2).

PI3K/Akt signalling is one of the most deregulated signalling pathways in cancer, including PDAC, and has a mediating role of the cellular signalling not only for tumour cells but also for stromal cells. Indeed, *KRAS* activates various signalling pathways of downstream effectors, including the PI3K pathway, which can, in turn, be activated by different signal transduction pathways linked to various growth factor receptors. In the last decade, there has been considerable interest in molecules inhibiting the PI3K/Akt-mediated transduction pathway, including PDAC[84,85]. One



**Table 2** Main ongoing targeted therapy studies (clinicaltrials.gov) for advanced pancreatic adenocarcinoma

Treatment	Target	Phase of study	Setting
Ribociclib plus trametinib; NCT02703571	CDK4/6	Phase I/II trial, open label single arm	Advanced or metastatic pancreatic cancer and KRAS-mutant colorectal cancer
Palbociclib + the PI3K/mTOR inhibitor, gedatolisib; NCT03065062	CDK4/6	Phase I, open label single arm	Advanced squamous cell lung, pancreatic, head and neck and other solid tumours
Abemaciclib in combination with the TGF- $\beta$ inhibitor galunisertib or other agents; NCT02981342	CDK4/6	Phase II, open label, randomized	Previously treated metastatic pancreatic ductal adenocarcinoma
BKM120 + mFOLFOX6; NCT01571024	PI3K	Phase I, open label, single arm	Advanced solid tumours including metastatic pancreatic cancer
Metformin + Gemcitabine + Erlotinib; NCT01210911	PI3K	Phase II, randomized, placebo controlled	Locally advanced or metastatic pancreatic cancer
Capecitabine + Cetuximab + Everolimus; NCT01077986	mTOR	Phase I/II, open label, single arm	Metastatic pancreatic cancer
Temsirolimus; NCT00075647	mTOR	Phase II, open label, single arm	Locally advanced or metastatic pancreatic cancer
MK2206 + Fluorouracil + Oxaliplatin + Selumetinib; NCT01658943	Akt	Phase II, open label, randomized	Metastatic pancreatic cancer
RX-0201 + Gemcitabine; NCT01028495	Akt	Phase II, open label, single arm	Metastatic pancreatic cancer
Gemcitabine $\pm$ nimotuzumab; NCT02395016	EGFR	Phase III, prospective, randomized, controlled, double-blind	Locally advanced or metastatic pancreatic cancer
MRTX849 (inhibitor of KRAS G12C) + TNO155 (inhibitor of SHP2); NCT04330664	KRASG12C	Phase I/II, open label, non-randomized	Advanced or metastatic cancer with a KRAS G12C mutation
AMG 510 Monotherapy; NCT03600883	KRASG12C	Phase I/II, open label, non-randomized	KRAS p.G12C mutant advanced solid tumours
Gemcitabine + M7824 (TGF- $\beta$ ligand trap); NCT03451773	TGF- $\beta$	Phase I/II, open label, single arm	Locally advanced or metastatic pancreatic cancer
FFX <i>vs</i> CPI-613 + mFFX; NCT03504423	CPI-613	Phase III, open-label randomized	Metastatic adenocarcinoma of the pancreas

TGF- $\beta$ : Transforming growth factor  $\beta$ .

of the major challenges contributing to the suboptimal response to PI3K inhibitor drug monotherapies is the development of resistance mechanisms. Therefore, in this case, the current standard is the identification of new targeted combination therapies[86]. Table 2 reports the current ongoing clinical trials targeting the phosphoinositide signalling cascade for the treatment of pancreatic cancer.

The transformation of growth factor beta (TGF- $\beta$ ) signalling regulates cell proliferation and plays a fundamental role in the process of metastasis, angiogenesis and escape from immune surveillance. Several TGF- $\beta$  inhibitory molecules are being studied, including oral inhibitors of the TGF- $\beta$  receptor kinase, such as galunisertib (LY2157299), which specifically downregulates SMAD2 phosphorylation, blocking the activation of the canonical pathway[87], and trabedersen (AP 12009), a TGF- $\beta$ 2-specific antisense phosphorothioate oligodeoxynucleotide[88]. For example, data from a phase Ib study using galunisertib in combination with second-line durvalumab suggests possible second-line activity of the combination[89].

CPI-613 is a new anticancer drug that selectively targets the altered form of mitochondrial energy metabolism in cancer cells, compromising the activity leading to apoptosis of cancer cells. Following the promising results of Phase I and II studies[90], a Phase III study is underway to compare this combination of FOLFIRINOX and CPI-613 with FOLFIRINOX alone.

Numerous other potential targets have been studied, such as c-KIT, VEGFR, and RET. Unfortunately, both masatinib, an anti-cKIT tyrosine kinase inhibitor, and vandetanib, an anti-VEGFR2, -RET, and -EGFR tyrosine kinase inhibitor, have failed to demonstrate a benefit over standard therapy[91,92].

A possible explanation for the failure of targeted therapies is the adaptive response to drug inhibition, for example, through the blockage of downstream signalling and the activation of other signalling transduction pathways. The future is trending towards the identification of combinations of treatments, with the aim of overcoming resistance mechanisms with an acceptable toxicity profile. Alongside this trend, there

is the need to identify predictive molecular markers of response to treatment.

### Overcome immuno-resistance of metastatic pancreatic disease

As previously reported, the initial enthusiasm for immunotherapy in advanced pancreatic cancer waned due to the not very encouraging data from early clinical trials. However, the improved understanding of resistance mechanisms has led to further clinical studies aiming to overcome the immuno-resistance of the pancreatic tumour microenvironment.

To date, data from clinical trials that evaluated the combination of ICI drugs in second-line treatment are not promising. The study conducted by O'Reilly *et al*[93] that evaluated the efficacy of the combination of durvalumab and tremelimumab in patients who progressed to first-line FP or GEM did not yield the desired results.

For the association of immunotherapy drugs with chemotherapy, the data seem to be encouraging; however, numerous association trials are also underway with cancer vaccines, adoptive T cell transfer, and direct targeted treatments in the tumour microenvironment (JAK/STAT inhibitors, CSF1R blockers, BTK inhibitors)[94].

Again, there is a lack of factors that allow us to predict the response to treatment; greater knowledge of the individual genetic characteristics together with the molecular characteristics of the disease could in the future lead to a broader selection of patients for immunotherapy treatments.

## CONCLUSION

Treatment of patients with mPDAC has improved in recent years thanks to the introduction of more effective chemotherapy regimens in the first-line setting. Consequently, the proportion of patients who are candidates for second- and third-line regimens is increasing. However, to date, chemotherapy remains the second-line standard of care, and neither personalized medicine nor immunotherapy has in fact provided important positive results in the treatment of pancreatic cancer. There are many ongoing studies aiming to overcome the multiple resistance mechanisms to treatment; however, the key to overcoming these mechanisms and providing personalized medicine to patients who have progressed to a first line of treatment is far from being identified. The small improvements shown by ongoing clinical trials could be considered a first step in what could be the future of treatment for advanced pancreatic cancer.

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