

# Current status and dilemma of second-line treatment in advanced pancreatic cancer: is there a silver lining?

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**Abstract:** Pancreatic cancer remains one of the most lethal malignant diseases worldwide. The majority of patients present with advanced disease and, therefore, need palliative chemotherapy. Some chemotherapeutic regimens have been well established as first-line therapies and have been shown to increase survival; however, almost all patients with advanced pancreatic cancer will experience disease progression after first-line therapy. Nevertheless, many patients who retain good performance status after initial treatment remain good candidates for additional therapy. Historically, few studies have assessed second-line therapy, with most reports representing small phase II trials with variable findings; however, clinical research for second-line treatment has increased in the past decade, and several randomized controlled trials using different regimens have been published. The current literature shows varying results on treatment efficacy and tolerability. Thus, we reviewed the published data on the use of chemotherapy in the second-line setting for the treatment of advanced pancreatic cancer.

**Keywords:** pancreatic cancer, second-line, chemotherapy, targeted therapy

## Introduction

Pancreatic cancer is a highly lethal disease, for which the 5-year relative survival rate is approximately 7%–8%.<sup>1,2</sup> It remains the fourth leading cause of cancer-related deaths, with approximately 43,090 deaths estimated in the US in 2017.<sup>3</sup> Most patients (approximately 80%) are ineligible for potential curative resection at diagnosis.<sup>4</sup> In these cases, pancreatic cancer is diagnosed at an advanced stage – either as locally advanced pancreatic cancer (LAPC) or as metastatic disease – with a median overall survival (OS) of 9–15 and 6–9 months, respectively.<sup>5</sup> Gemcitabine has been the standard first-line treatment in this advanced setting for over a decade.<sup>6</sup> However, since 2011, new chemotherapeutic regimens (FOLFIRINOX and nab-paclitaxel plus gemcitabine) have shown improved survival benefit over gemcitabine monotherapy and are the most commonly administered first-line therapies in patients with good performance status.<sup>7,8</sup> Therefore, gemcitabine monotherapy is now more frequently used as an option for patients with advanced pancreatic cancer who have poor performance status. Nonetheless, almost all patients will inevitably experience disease progression during or following first-line therapy and, beyond first-line treatment, approximately half of all patients with advanced pancreatic cancer remain in good general condition and, therefore, may receive subsequent therapies.<sup>9</sup>

Historically, multiple phase II studies have used various single agents or combination regimens in the second-line setting to improve survival, although most

of these attempts have been in vain. However, in recent years, second-line chemotherapies have been developed using different regimens as standards. Several randomized phase III trials, including NAPOLI-1, CONKO-003, and PANCREOX, have shown promising results in improving survival, thus representing potential second-line options for patients with gemcitabine-resistant pancreatic cancer.<sup>10–12</sup> However, reflecting the contradictory results on treatment efficacy and tolerability and criticisms on selective enrollment and study biases, the optimal second-line strategy for pancreatic cancer remains unknown.

In this review, we summarize current second-line chemotherapy options, second-line targeted therapies, and the most promising second-line agents to highlight state-of-the-art and future directions of second-line treatment in advanced pancreatic cancer.

## Search strategy and selection criteria

The data for this review were identified through searches of PubMed and references from relevant articles published in the English language using the following search terms: “advanced pancreatic cancer”, “inoperable pancreatic adenocarcinoma”, “gemcitabine-refractory pancreatic cancer”, “second-line therapy”, “second-line treatment”, and “second-line chemotherapy”. Abstracts from the annual meetings of the American Society of Clinical Oncology and European Society of Medical Oncology were also screened for additional studies. Only prospective clinical trials published between 1997 and 2017 were included. Studies were also required to meet the inclusion criteria that the first-line therapy was either a gemcitabine-based regimen (gemcitabine monotherapy or gemcitabine-containing combination therapy) or FOLFIRINOX. Abstracts and reports from meetings were included only when they directly associated with previously published work. The PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) flow diagram for this review is shown in Figure 1.

## Second-line chemotherapy in advanced pancreatic cancer: yes or no?

Does the benefit of chemotherapy continue with disease progression during or after first-line treatment? Two randomized phase III trials compared second-line treatments with best supportive care (BSC). In the first study by Ciuleanu et al, 303 patients with previously gemcitabine-treated metastatic pancreatic adenocarcinoma were randomized to glufosfamide or BSC.<sup>13</sup> The median survival was 105 days (3.5 months) for glufosfamide and 84 days (2.8 months) for BSC, with an 18%

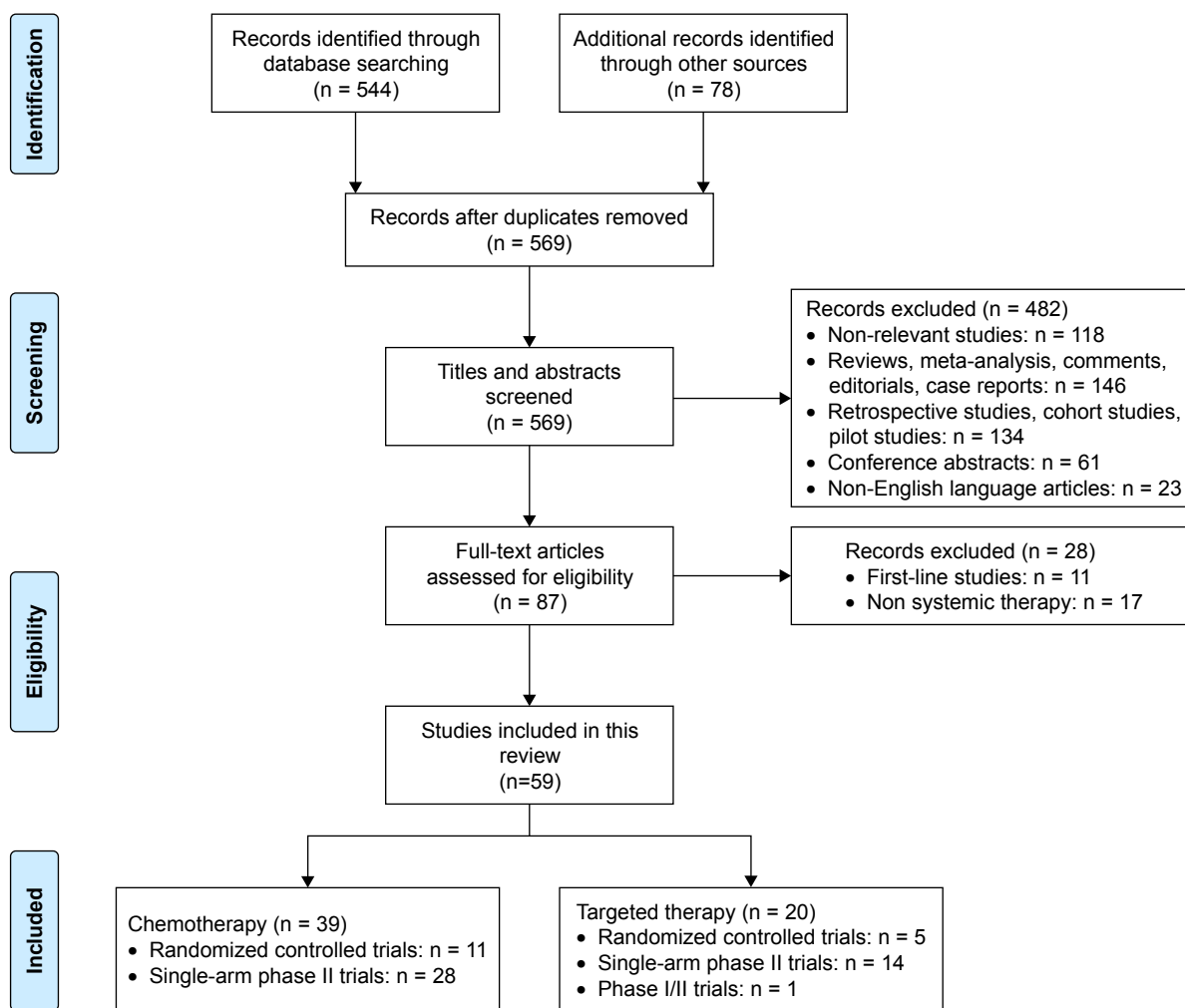
increase in OS for glufosfamide, which was not statistically significant (HR 0.85; 95% CI 0.66–1.08;  $P = 0.19$ ), suggesting low activity of glufosfamide in this refractory patient population. The second study by the German CONKO-study group randomized patients in a 1:1 ratio to oxaliplatin plus folinic acid and 5-fluorouracil (OFF) or BSC.<sup>14</sup> Calculations were undertaken with a total of 165 patients to demonstrate a doubling of survival time after progression on first-line gemcitabine therapy. However, after inclusion of 46 patients (23 in each arm), the trial was terminated early due to insufficient accrual (lack of acceptance of BSC by patients and physicians). Although no confirmed response better than stable disease was observed, OFF as second-line chemotherapy significantly prolonged survival time compared to BSC alone (4.82 vs 2.30 months,  $P = 0.008$ ; Table 1).

These two studies did not yield sufficient evidence to demonstrate the necessity of second-line chemotherapy (partly because one study used glufosfamide, which was not commonly used in the treatment of pancreatic cancer, and the other study was prematurely closed); however, this treatment may have a survival benefit in this patient population. Further trials in the second-line setting are needed, comparing active treatment with BSC to ensure that patients do not receive unnecessary toxicity without any benefit. That is, from an ethical perspective, patient-centered decision-making becomes the highest priority. Therefore, a comprehensive assessment considering performance status, comorbidities, expected toxicities, cost-effectiveness, and patient preference is required.

## Second-line single-agent chemotherapy: one is all?

A summary of the prospective clinical trials on second-line single-agent chemotherapy is shown in Table 2. All of these trials were phase II studies. Although few patients showed an objective response (range 0–15%), the disease control rate ranged from 16.7% to 58%, and the median second-line survival ranged from 3.5 to 7.6 months.

Based on the data of increased cytotoxic activity of oxaliplatin in pancreatic cell lines with microsatellite instability, Androulakis et al conducted a phase II trial that enrolled 18 advanced pancreatic cancer patients with a previous history of gemcitabine-based chemotherapy treatment.<sup>15</sup> Oxaliplatin was administered at 130 mg/m<sup>2</sup> every 3 weeks. The study failed to induce an objective response, and three patients had stable disease for over 2 months. Hematological toxicity was mild, with no grade 3 or 4 toxic effects reported.



**Figure 1** PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) flow diagram of study selection.

In patients with advanced pancreatic cancer, first-line chemotherapy with pemetrexed has shown clinical activity as a single agent as well as in combination with gemcitabine. Based on this result, a multicenter phase II trial was conducted to evaluate the efficacy and safety of pemetrexed as a second-line treatment in patients with advanced pancreatic cancer who had progressed on single-agent gemcitabine or gemcitabine-based first-line chemotherapy.<sup>16</sup> A total of 52 patients received pemetrexed at 500 mg/m<sup>2</sup> intravenously every 3 weeks. The response rate was 3.8% (95% CI 0.5%–13.2%). At a median follow-up of 20 weeks, the median time to progression (TTP) was 7 weeks, and the median OS was 20 weeks. The most frequent hematological grades 3 and 4 toxic effects included neutropenia (17.3%), thrombocytopenia (5.8%), and anemia (3.8%). The most frequent non-hematological toxic effects (any grade) were diarrhea, nausea, and stomatitis/pharyngitis (23.1% each). The authors concluded that pemetrexed is a safe treatment

option with limited activity in the second-line setting after gemcitabine failure.

Second-line chemotherapy with single-agent tegafur/gimeracil/oteracil (S-1) in patients with gemcitabine-resistant advanced pancreatic cancer has also been assessed. Morizane et al examined S-1 treatment at 40 mg/m<sup>2</sup> twice a day for 4 weeks on a 6-week cycle and showed that the response rate was 15% with a median progression-free survival (PFS) of 2.0 months and a median OS of 4.5 months.<sup>17</sup> The toxicity was tolerable, and no life-threatening toxicities were observed. Another study using the same regimen showed a similar response rate of 9.5%, and PFS and OS were 4.1 and 6.3 months, respectively.<sup>18</sup> Moreover, the toxicity profile was similar.

Irinotecan monotherapy has been tested in patients with previously untreated advanced pancreatic cancer, and the activity observed with irinotecan was at least equivalent to, if not better than, that of gemcitabine. Based on these data, Yi et al initiated a phase II study of single-agent irinotecan

**Table 1** Randomized controlled trials evaluating second-line chemotherapy in gemcitabine-refractory advanced pancreatic cancer

Study	Treatment	No of patients	Median age	ECOG 0-1 (%) / KPS 90-100 (%)	Metastatic disease (%)	Response rate	Median response duration	Median PFS	Median OS
Ioka et al <sup>47</sup>	S-1 + irinotecan	60	62	100	100	ORR 18.3%	TTF 2.1 months	3.5 months	6.8 months
	S-1	67	65	100	100	ORR 6.0%	TTF 1.8 months	1.9 months	5.8 months
Ueno et al <sup>45</sup>	SL	69	65	100	NR	ORR 27.5%	TTF 3.7 months	3.8 months	6.3 months
	S-1	71	64	100	NR	ORR 19.7%	TTF 2.4 months	2.7 months	6.1 months
Gill et al <sup>12</sup>	mFOLFOX6	54	65	88.9	92.6	CR 0%; PR 13.2%; SD 44.7%	TTP 2.2 months	3.1 months	6.1 months
	FULV	54	67	94.4	94.4	CR 0%; PR 8.5%; SD 55.3%	TTP 3.8 months	2.9 months	9.9 months
Wang-Gillam et al <sup>11</sup>	Nanoliposomal irinotecan plus FU/LV	117	63	59	100	ORR 16%	TTF 2.3 months	3.1 months	6.1 months
	Nanoliposomal irinotecan	151	65	57	100	ORR 6%	TTF 1.7 months	2.7 months	4.9 months
	FF	149	63	51	100	ORR 1%	TTF 1.4 months	1.6 months	4.2 months
Ohkawa et al <sup>46</sup>	S-1 + oxaliplatin	136	65	100	100	ORR 20.9%	NR	3.0 months	7.4 months
	S-1	132	63.5	100	100	ORR 11.5%	NR	2.8 months	6.9 months
Oettle et al <sup>10</sup>	OFF	76	62	53.9	88.2	CR 1.3%	TTP 2.9 months	2.9 months	5.9 months
	FF	84	61	47.6	88.1	CR 1.2%	TTP 2.0 months	2.0 months	3.3 months
Ge et al <sup>44</sup>	SL	45	NR	NR	100	NR	NR	3.0 months	6.3 months
	S-1	47	NR	NR	100	NR	NR	1.9 months	5.5 months
Pelzer et al <sup>13</sup> (terminated)	OFF	23	60	47.8	73.9	CR 0%; PR 0%	NR	NR	4.82 months
	BSC	23	61	52.2	69.6	CR 0%; PR 0%	NR	NR	2.30 months
Ciuleanu et al <sup>14</sup>	Glufosfamide	148	58	40	100	CR 0%; PR 2.1%; SD 31%	NR	46 days	105 days
	BSC	155	57	44	100	CR 0%; PR 0.7%; SD 19%	NR	43 days	84 days
Yoo et al <sup>47</sup>	mFOLFIRI,3	31	55	100	NR	PR 0%; SD 23%; PD 68%	NR	8.3 weeks	16.6 weeks
	mFOLFOX	30	55	97	NR	PR 7%; SD 10%; PD 70%	NR	6.0 weeks	14.9 weeks
Ulrich-Pur et al <sup>35</sup>	Raltitrexed plus irinotecan	19	63	21	100	PR 16%; SD 32%	RD 14 weeks	4.0 months	6.5 months
	Raltitrexed	19	60	21	100	PR 0%; SD 37%	RD 11 weeks	2.5 months	4.3 months

**Notes:** FU/LV = leucovorin 400 mg/m<sup>2</sup> on Day 1, fluorouracil 400 mg/m<sup>2</sup> bolus on Day 1, followed by fluorouracil 2,400 mg/m<sup>2</sup> continuous infusion for 46 hours every 14 days. mFOLFOX6 = FU/LV plus oxaliplatin 85 mg/m<sup>2</sup> on Day 1 every 14 days. FF = intravenous folic acid 200 mg/m<sup>2</sup> and continuous infusion of fluorouracil 2,000 mg/m<sup>2</sup> over 24 hours on days 1, 8, 15, and 22 of a 6-week cycle. OFF = FF plus oxaliplatin 85 mg/m<sup>2</sup> on days 8 and 22. mFOLFIRI,3 = irinotecan 70 mg/m<sup>2</sup> on Day 1, leucovorin 400 mg/m<sup>2</sup> on Day 1, fluorouracil 2,000 mg/m<sup>2</sup> over 46 hours from Day 1, followed by irinotecan 70 mg/m<sup>2</sup> every 2 weeks. mFOLFOX = oxaliplatin 85 mg/m<sup>2</sup> on Day 1, leucovorin 400 mg/m<sup>2</sup> on Day 1, followed by fluorouracil 2,000 mg/m<sup>2</sup> over 46 hours every 2 weeks.

**Abbreviations:** BSC, best supportive care; CR, complete response; ECOG, Eastern Oncology Cooperative Group; KPS, Karnofsky performance status; NR, not reported; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; S-1, tegafur/gimeracil/oteracil; SL, S-1 plus leucovorin; TTF, time to progression.

**Table 2** Single-armed phase II clinical trials evaluating second-line single-agent chemotherapy in advanced pancreatic cancer

Study	Treatment	No of patients*	ECOG 0–1 (%) / KPS 90–100 (%)	Metastatic disease (%)	Response rate	Median survival
Hosein et al <sup>22</sup>	Nab-paclitaxel 100 mg/m <sup>2</sup> on days 1, 8, and 15 of a 28-day cycle	19	79	95	CR 0%; PR 5%; SD 32%	OS 7.3 months; PFS 1.7 months
Ko et al <sup>20</sup>	Nanoliposomal irinotecan 120 mg/m <sup>2</sup> every 3 weeks	40	60	100	PR 7.5%; SD 42.5%; PD 25.0%	OS 5.2 months; PFS 2.4 months
Sudo et al <sup>18</sup>	S-1 40 mg/m <sup>2</sup> orally, twice a day for 4 weeks on a 6-week cycle	21	71.4	95	PR 9.5%; SD 43%	OS 6.3 months; PFS 4.1 months
Yi et al <sup>19</sup>	Irinotecan 150 mg/m <sup>2</sup> every 2 weeks	33	94	100	PR 9%; SD 39%	OS 6.6 months; PFS 2.0 months
Morizane et al <sup>17</sup>	S-1 40 mg/m <sup>2</sup> orally, twice a day for 4 weeks on a 6-week cycle	40	90	100	CR 0%; PR 15%; SD 43%; PD 38%	OS 4.5 months; PFS 2.0 months
Boeck et al <sup>21</sup>	Capecitabine 1,250 mg/m <sup>2</sup> orally, twice a day for 2 weeks on a 3-week cycle	39	51	97	PR 0; SD 39%; PD 31%	OS 7.6 months
Boeck et al <sup>16</sup>	Pemetrexed 500 mg/m <sup>2</sup> every 3 weeks	52	94.2	88.5	PR 3.8%; SD 19.2%; PD 59.6%	OS 20 weeks
Androulakis et al <sup>15</sup>	Oxaliplatin 130 mg/m <sup>2</sup> every 3 weeks	18	72	72	CR 0%; PR 0%; SD 16.7%	OS 3.5 months

**Notes:** \*All patients were previously treated with first-line gemcitabine monotherapy or gemcitabine-based combination therapy.

**Abbreviations:** CR, complete response; ECOG, Eastern Oncology Cooperative Group; KPS, Karnofsky performance status; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; S-1, tegafur/gimeracil/oteracil.

as second-line chemotherapy in patients with advanced pancreatic cancer.<sup>19</sup> Among 33 patients, three patients showed a partial response, and 13 patients with stable disease were observed. The median PFS and OS were 2.0 and 6.6 months, respectively. Toxicity profiles were generally manageable, and there was no treatment-related death. Nanoliposomal irinotecan is a liposomal nanoparticle that encapsulates free irinotecan. This structure protects the irinotecan base from being converted to its active metabolite, SN-38, which enables a longer duration of the drug in circulation – thus increasing and prolonging the intratumoral levels of irinotecan and SN-38. In a phase II study of 40 patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based therapy, the administration of nanoliposomal irinotecan at 120 mg/m<sup>2</sup> every 3 weeks resulted in a median OS of 5.2 months, 1-year survival of 25%, and a manageable toxicity profile.<sup>20</sup>

Capecitabine, a prodrug of fluorouracil, has shown single-agent activity in the first-line treatment of patients with advanced pancreatic cancer. Boeck et al also examined capecitabine as salvage chemotherapy in gemcitabine-pretreated patients.<sup>21</sup> This agent was orally administered to 39 patients at a dose of 1,250 mg/m<sup>2</sup> twice daily for 14 days, followed by 7 days of rest. After a median follow-up of 6.6 months, 27 patients were evaluated for their response: no complete or partial responses were observed, but 15 patients (39%) had stable disease. The median TTP was 2.3 months, and the median OS was 7.6 months. Predominant grades 2 and 3 toxicities included hand–foot syndrome (28%), anemia

(23%), leg edema (15%), diarrhea (13%), nausea/vomiting (10%), and leukocytopenia (10%).

Nab-paclitaxel – which can breach the blood–stroma barrier to reach tumor cells – was also tested in the second-line setting for advanced pancreatic cancer prior to the phase III MAPCT trial.<sup>22</sup> Patients received nab-paclitaxel at 100 mg/m<sup>2</sup> for over 30 minutes on days 1, 8, and 15 of a 28-day cycle. Among the 19 treated patients, one patient had a confirmed partial response and 6 patients had stable disease as their best response. The median PFS and OS were 1.7 and 7.3 months, respectively. Grades 3 and 4 neutropenia, neutropenic fever, and anemia occurred in 32%, 11%, and 11% of patients, respectively.

In summary, single-agent chemotherapy may constitute a feasible treatment option with acceptable activity and tolerable toxicity for patients with gemcitabine-refractory pancreatic cancer. In view of the favorable toxicity profile, single agents combined with other agents might improve the therapeutic results.

## Second-line combination chemotherapy: it takes two to tango?

As a patient's performance status often rapidly declines when the tumor is locally or systemically progressing, it can be difficult to administer second-line combination chemotherapy in pancreatic cancer. However, it is reasonable to consider salvage chemotherapy in a selective patient population. Several clinical trials have evaluated the efficacy and safety of different combination regimens in patients with advanced

pancreatic cancer previously treated with gemcitabine-based therapies, with some combinations yielding promising results (Tables 1 and 3).

## Platinum-based regimens

Many studies have used oxaliplatin as part of a combination regimen – the most commonly used being oxaliplatin plus infusional fluorouracil. The OFF regimen administered on a 6-week cycle was feasible and active, with an acceptable toxicity profile.<sup>23</sup> As discussed earlier, the OFF regimen as second-line therapy showed a survival benefit compared with BSC in gemcitabine-refractory disease.<sup>14</sup> The German CONKO-study group further conducted a randomized phase III trial comparing OFF to folinic acid and fluorouracil (FF) and showed that the OFF regimen was associated with a significantly improved OS (5.9 vs 3.3 months;  $P = 0.010$ ) and PFS (2.9 vs 2.0 months;  $P = 0.019$ ).<sup>10</sup> The addition of oxaliplatin to FF increased neurotoxicity (mostly, grades 1 and 2) but was well tolerated. However, the results of a more recent randomized phase III trial (PANCREOX) using a biweekly infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX) schedule were disappointing, with similar PFS (3.1 vs 2.9 months;  $P = 0.99$ ) and shorter OS (6.1 vs 9.9 months;  $P = 0.02$ ) in the modified FOLFOX6 group versus the infusional fluorouracil/leucovorin (FU/LV) group.<sup>12</sup> Moreover, the response rates were not significantly different between groups (13.2% vs 8.5%;  $P = 0.361$ ). The tolerability of the infusional FU/LV group was remarkably better than that of the modified FOLFOX6 group, with a nearly six-fold lower incidence of grades 3/4 adverse events (11% vs 63%).

Other oxaliplatin–fluoropyrimidine combinations have also been evaluated in small phase II studies. In a comparable regimen to OFF, Tsavaris et al used weekly 50 mg/m<sup>2</sup> oxaliplatin, 50 mg/m<sup>2</sup> leucovorin, and 500 mg/m<sup>2</sup> fluorouracil treatments and achieved a median OS of 25 weeks.<sup>24</sup> Novarino et al administered 40 mg/m<sup>2</sup> oxaliplatin, 250 mg/m<sup>2</sup> leucovorin, and 500 mg/m<sup>2</sup> fluorouracil weekly for a treatment period of 3 weeks on a 4-week cycle, resulting in a median OS of 17.1 weeks.<sup>25</sup> In a similar study conducted by El-Hadaad and Wahba, the median OS was 22 weeks.<sup>26</sup> Additionally, a small phase II trial in Korea randomly assigned patients to receive 85 mg/m<sup>2</sup> oxaliplatin, 400 mg/m<sup>2</sup> leucovorin, and 2,000 mg/m<sup>2</sup> fluorouracil (modified FOLFOX) or 70 mg/m<sup>2</sup> irinotecan, 400 mg/m<sup>2</sup> leucovorin, and 2,000 mg/m<sup>2</sup> fluorouracil (modified FOLFIRI.3).<sup>27</sup> However, the efficacy was modest, and the median OS was 14.9 and 16.6 weeks for modified FOLFOX and modified FOLFIRI.3, respectively.

**Table 3** Single-armed phase II clinical trials evaluating second-line combination chemotherapy in advanced pancreatic cancer

Study	Treatment	No of patients*	ECOG 0–1 (%) / KPS 90–100 (%)	Metastatic disease (%)	Response rate	Median response duration	Median survival
Ettrich et al <sup>32</sup>	Docetaxel 75 mg/m <sup>2</sup> on Day 1 + oxaliplatin 80 mg/m <sup>2</sup> on Day 2 on a 21-day cycle	44	69.7	81.8	CR 0%; PR 15.9%; SD 31.8%; PD 52.3%	NR	OS 10.1 months; PFS 1.82 months
Braghiroli et al <sup>49</sup>	Metformin 850 mg orally, three times a day plus paclitaxel 80 mg/m <sup>2</sup> weekly for 3 weeks on a 4-week cycle	20	60	100	SD 31.6%	TTP 44 days	OS 4.3 months; PFS 1.5 months
Soares et al <sup>53</sup>	Docetaxel 30 mg/m <sup>2</sup> on days 1 and 8 plus capecitabine 800 mg/m <sup>2</sup> orally, twice a day on days 1–14 on a 21-day cycle	42	74	100	CR 0%; PR 14.3%; SD 59.5%; PD 26.2%	TTF 3.0 months	OS 5.3 months; PFS 3.7 months
El-Hadaad and Wahba <sup>26</sup>	Oxaliplatin 85 mg/m <sup>2</sup> on days 1 and 15, leucovorin 20 mg/m <sup>2</sup> and 5-FU 500 mg/m <sup>2</sup> on days 1, 8, and 15 every 3 weeks	30	83.3	20	PR 6.7%; SD 20%; PD 40%	RD 13 weeks	OS 22 weeks
Kim et al <sup>33</sup>	S-1 40–60 mg orally, twice a day on days 1–14 plus cisplatin 60 mg/m <sup>2</sup> on Day 1 on a 21-day cycle	11	81.8	81.8	CR 0%; PR 0%; SD 9.1%	TTP 44 days	OS 81 days
Zaniboni et al <sup>38</sup>	Irinotecan 180 mg/m <sup>2</sup> on Day 1, leucovorin 200 mg/m <sup>2</sup> on days 1 and 2, 5-FU 400 mg/m <sup>2</sup> bolus on days 1 and 2, and 5-FU 600 mg/m <sup>2</sup> continuous infusion for 22 hours on days 1 and 2 every 2 weeks	50	100	74	PR 8%; SD 28%; PD 52%	NR	OS 5.0 months; PFS 3.2 months
Katopodis et al <sup>42</sup>	Capecitabine 800 mg/m <sup>2</sup> orally, twice a day on days 1–14 plus docetaxel 75 mg/m <sup>2</sup> on Day 1 on a 21-day cycle	31	93.6	96.8	PR 9.7%; SD 22.6%; PD 67.6%	TTP 2.37 months	OS 6.3 months; PFS 2.4 months

Cereda et al <sup>48</sup>	Mitomycin 8 mg/m <sup>2</sup> on Day 1 plus ifosfamide 2,500 mg/m <sup>2</sup> and mesna 3,000 mg/m <sup>2</sup> on days 1–3 on a 28-day cycle	20	60	100	PR 5%; SD 10%; PD 85%	NR	OS 3.7 months; PFS 1.7 months
Pelzer et al <sup>23</sup>	Oxaliplatin 85 mg/m <sup>2</sup> on days 8 and 22, folinic acid 500 mg/m <sup>2</sup> and 5-FU 2,600 mg/m <sup>2</sup> on days 1, 8, 15, and 22 every 6 weeks	37	NR	100	CR 2.7%; PR 2.7%; SD 43.2%; PD 51%	TTP 12 weeks	OS 22 weeks
Novarino et al <sup>25</sup>	Oxaliplatin 40 mg/m <sup>2</sup> , 5-FU 500 mg/m <sup>2</sup> , and leucovorin 250 mg/m <sup>2</sup> weekly for 3 weeks on a 4-week cycle	23	74	69.5	ORR 0%; SD 23.5%; PD 76.5%	TTP 11.6 weeks	OS 17.1 weeks
Kim et al <sup>41</sup>	5-FU 1,000 mg/m <sup>2</sup> on days 1–3 plus paclitaxel 175 mg/m <sup>2</sup> on Day 1 on a 28-day cycle	28	46.4	93	PR 10%; SD 20%; PD 70%	TTP 2.5 months	OS 7.5 months
Xiong et al <sup>28</sup>	Oxaliplatin 130 mg/m <sup>2</sup> on Day 1 plus capecitabine 1,000 mg/m <sup>2</sup> orally, twice a day on days 1–14 every 3 weeks	39	71.4	95	PR 2.6%; SD 26%	NR	OS 23 weeks; PFS 9.9 weeks
Ko et al <sup>37</sup> (unacceptable toxicity)	Docetaxel 65 mg/m <sup>2</sup> plus irinotecan 160 mg/m <sup>2</sup> every 3 weeks	14	93	100	PR 0%; SD 21.4%; PD 64.3%	TTF 36 days; TTP 49 days	OS 134 days
Reni et al <sup>30</sup>	Raltitrexed 3 mg/m <sup>2</sup> plus oxaliplatin 130 mg/m <sup>2</sup> every 3 weeks	41	61	100	PR 24%; SD 27%; PD 37%	NR	OS 5.2 months; PFS 1.8 months
Stathopoulos et al <sup>34</sup>	Gemcitabine 1,000 mg/m <sup>2</sup> on days 1 and 15 plus lipoplatin 25–125 mg/m <sup>2</sup> on days 1 and 15 on a 28-day cycle	24	50	79.2	CR 0%; PR 8.3%; SD 58.3%	NR	OS 4 months
Demols et al <sup>31</sup>	Gemcitabine 1,000 mg/m <sup>2</sup> on Day 1 plus oxaliplatin 100 mg/m <sup>2</sup> on Day 2 every 2 weeks	33	87.9	65	PR 22.6%; SD 38.7%; PD 38.7%	TTP 4.2 months	OS 6 months
Tsavaris et al <sup>24</sup>	Oxaliplatin 50 mg/m <sup>2</sup> , leucovorin 50 mg/m <sup>2</sup> , and 5-FU 500 mg/m <sup>2</sup> weekly	30	NR	97	PR 23.3%; SD 30.0%; PD 46.7%	RD 22 weeks; TTP 22 weeks	OS 25 weeks
Cantore et al <sup>29</sup>	Oxaliplatin 60 mg/m <sup>2</sup> on days 1 and 15 plus irinotecan 60 mg/m <sup>2</sup> on days 1, 8, and 15 on a 28-day cycle	30	30	100	PR 10%; SD 23%; PD 33%	TTP 4.1 months	OS 5.9 months
Reni et al <sup>36</sup>	Mitomycin 6 mg/m <sup>2</sup> on Day 1 plus docetaxel and irinotecan on days 2 and 8 with escalating doses every 4 weeks	15	27	100	CR 0%; PR 0%; SD 23%; PD 77%	TTP 1.7 months	OS 6.1 months
Rothenberg et al <sup>40</sup>	Eniluracil 50 mg orally on days 1–7 plus 5-FU 20 mg/m <sup>2</sup> orally on days 2–6 on a 28-day cycle	48	77	100	PR 2%	NR	OS 3.4 months

**Notes:** \*All patients were previously treated with first-line gemcitabine monotherapy or gemcitabine-based combination therapy.

**Abbreviations:** CR, complete response; ECOG, Eastern Oncology Cooperative Group; KPS, Karnofsky performance status; NR, not reported; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RD, response duration; SD, stable disease; S-I, tegafur/gimeracil/oteracil; TTF, time to treatment failure; TTP, time to progression; 5-FU, 5-fluorouracil.

A phase II study assessed the activity and safety profile of a combination of capecitabine and oxaliplatin.<sup>28</sup> A total of 39 patients received this regimen as a second-line treatment. One patient (2.6%) showed a partial response, and ten patients had stable diseases (26%). The median PFS and OS were 9.9 and 23 weeks, respectively, and the toxic effects were generally manageable.

Oxaliplatin in combination with agents other than fluoropyrimidine has also been tested as a second-line regimen for advanced pancreatic cancer. A phase II trial evaluated oxaliplatin in combination with irinotecan in 30 patients.<sup>29</sup> Three patients (10%) showed a partial response, and seven patients (23%) had stable disease. The median TTP was 4.1 months, and the median OS was 5.9 months, with a 1-year survival rate of 23.3%. Grades 3 and 4 adverse events included leukopenia (6%), neuropathy (6%), and diarrhea (3%). Reni et al treated 41 patients, who previously received gemcitabine in the first-line setting, with oxaliplatin at 130 mg/m<sup>2</sup> and raltitrexed at 3 mg/m<sup>2</sup> every 3 weeks as salvage chemotherapy.<sup>30</sup> The results showed a partial response in 24% of patients and a median OS of 5.2 months. Neutropenia was the most common toxic effect, occurring in 12% of patients. Demols et al evaluated the activity and tolerability of gemcitabine and oxaliplatin (GEMOX) in patients who had progressed during or following gemcitabine therapy.<sup>31</sup> The study showed a response rate of 22.6% in 31 assessable patients. The median response duration and TTP were 4.5 and 4.2 months, respectively, and the median OS was 6 months (range 0.5–21). Grades 3 and 4 toxicities occurred in 16 patients (48%). Recently, Ettrich et al conducted a phase II trial examining the activity of the docetaxel and oxaliplatin (DocOx) combination as a second-line treatment for advanced pancreatic cancer.<sup>32</sup> Tumor response was achieved in 15.9% of the patients, with a disease control rate of 48% after the first two treatment cycles. The median PFS was 1.8 months, and the median OS was 10.1 months. Notably, grades 3 and 4 neutropenia developed in 63.6% of patients, and diarrhea developed in 11.4% of patients. However, all toxicities were manageable. Thus, the data obtained using the DocOx protocol were consistent with other second-line protocols, including the OFF regimen, indicating DocOx as an option for patients with chemorefractory pancreatic cancer.

Cisplatin-based regimens have also been investigated as second-line chemotherapy after gemcitabine failure. Kim et al conducted a phase II study examining cisplatin plus S-1 as a second-line palliative chemotherapy for patients with gemcitabine-refractory pancreatic cancer.<sup>33</sup> The study was

terminated early after the enrollment of 11 patients due to severe toxicity. The median TTP was 44 days (1.4 months), and the median OS was 81 days (2.7 months). The most common grades 3 and 4 toxicities included fatigue (27.3%), nausea (27.3%), and anorexia (18.2%). Stathopoulos et al tested lipoplatin – a liposomal cisplatin aimed at the avoidance of renal toxicity – combined with gemcitabine in pretreated patients with advanced pancreatic cancer.<sup>34</sup> The objective response rate data showed a partial response in two of the 24 patients examined (8.3%) and stable disease in 14 patients (58.3%). The median survival from the beginning of second-line treatment was 4 months.

## Irinotecan-based regimens

Irinotecan-based chemotherapeutic regimens are options in the second-line setting for patients who progressed during gemcitabine-based treatment. In Austria, Ulrich-Pur et al conducted a phase II trial involving 38 patients who were pretreated with gemcitabine.<sup>35</sup> The patients were randomized to 3-weekly courses of irinotecan at 200 mg/m<sup>2</sup> on Day 1 plus raltitrexed at 3 mg/m<sup>2</sup> on Day 2, or raltitrexed at 3 mg/m<sup>2</sup> on Day 1 only. The superior response rate in the combination group (16% vs 0%) led to the termination of the trial in the first stage of accrual. The median PFS (4.0 vs 2.5 months) and the median OS (6.5 vs 4.3 months) were also superior in the combination group. Grades 3 and 4 toxic effects were comparable between the two groups. A study in Italy evaluated the activity of mitomycin, docetaxel, and irinotecan (MDI) on metastatic pancreatic adenocarcinoma following gemcitabine-containing chemotherapy.<sup>36</sup> The median TTP was 1.7 months, and the median OS was 6.1 months, with no objective response observed. Ko et al tested a regimen using irinotecan and docetaxel and showed a disease control rate of 21.4%. The median OS was 134 days (4.5 months), with a 6-month survival rate of 36%.<sup>37</sup> However, 12 of the 14 patients experienced grades 3 and 4 toxic effects, with neutropenia/leukopenia (42.9%) being the most common grades 3 and 4 toxicity. The FOLFIRI regimen has also been tested in a prospective multicenter study.<sup>38</sup> Among the 50 enrolled patients, four partial responses (8%) and 14 stable diseases (28%) were observed. The median PFS and OS were 3.2 and 5.0 months, respectively. Grades 3 and 4 neutropenia and diarrhea occurred in ten (20%) and six (12%) patients, respectively.

An open-labeled, multicenter, phase III trial (NAPOLI-1) assessed the effect of nanoliposomal irinotecan alone and in combination with FF in patients with metastatic pancreatic ductal adenocarcinoma previously treated with



gemcitabine-based therapy.<sup>11</sup> Patients were randomly assigned to receive either 120 mg/m<sup>2</sup> nanoliposomal irinotecan every 3 weeks or FF weekly for 4 weeks in a 6-week cycle. Safety data from a concurrent study in patients with metastatic colorectal cancer treated with a combination of 80 mg/m<sup>2</sup> nanoliposomal irinotecan and FF every 2 weeks were demonstrated; thus, the study protocol was amended to add this regimen as a third arm. The median OS in patients assigned to the nanoliposomal irinotecan combination regimen was 6.1 months versus 4.2 months with FF alone (HR = 0.67; *P* = 0.012). The median OS did not differ between nanoliposomal irinotecan alone and FF (HR = 0.99; *P* = 0.94). The most frequent grades 3 and 4 adverse events in the nanoliposomal irinotecan combination group were neutropenia (27%), diarrhea (13%), vomiting (11%), and fatigue (14%). The US Food and Drug Administration rapidly approved nanoliposomal irinotecan plus FF as second-line therapy for metastatic pancreatic ductal adenocarcinoma.

## Fluorouracil-based regimens

Fluorouracil in combination with oxaliplatin or irinotecan formulations has been well studied, with the combination of fluorouracil and irinotecan formulations appearing to be appropriate as second-line treatment.<sup>39</sup> Besides, fluorouracil combined with agents other than oxaliplatin and irinotecan has also been tested. An early phase II trial assessed the combination of eniluracil – a potent irreversible inactivator of dihydropyrimidine dehydrogenase – and fluorouracil.<sup>40</sup> Among 48 patients with gemcitabine-refractory metastatic pancreatic cancer, one patient (2%) had a confirmed partial response. The median OS was 3.4 months, and grades 3 and 4 toxicity occurred in 31 out of 48 (65%) patients. The researchers therefore concluded that fluorouracil plus eniluracil has limited activity in patients with advanced pancreatic cancer and is associated with a high frequency of grades 3 and 4 toxic effects. Kim et al studied the combination of fluorouracil and paclitaxel in 28 patients with a history of previous gemcitabine-based chemotherapy, 20 of whom were assessable.<sup>41</sup> The study showed a partial response rate of 10% and stable disease in 20% of patients. The median TTP and OS were 2.5 and 7.6 months, respectively. Furthermore, the combination of capecitabine and docetaxel has been studied because there are preclinical data showing synergy between these agents. A phase II study that enrolled 31 patients showed that the combination of capecitabine with docetaxel was moderately active in pretreated advanced pancreatic cancer with a partial response rate of 9.7% and stable disease in 22.6% of patients.<sup>42</sup> The median

PFS and OS were 2.4 and 6.3 months, respectively. The most common grades 3 and 4 toxic effect was neutropenia (32.2%). Moreover, the researchers reported that 20% of patients had pain control, and 38.7% of patients maintained their body weight. In another phase II study, a similar regimen, but with different dosing, showed a median PFS and OS of 3.7 and 5.3 months, respectively.<sup>43</sup> A total of 14% of patients showed an objective response, and as many as 59% of patients had stable disease for two cycles. Treatment was generally well tolerated, but one patient died, with the cause of death being possibly related to treatment.

Based on preclinical data indicating that leucovorin could enhance the efficacy of S-1, Ge et al conducted a phase II trial enrolling 92 patients with gemcitabine-refractory advanced pancreatic cancer.<sup>44</sup> The patients were randomly assigned to S-1 in combination with leucovorin or S-1 alone. The study showed no significant differences in the median OS (5.5 vs 6.3 months), median PFS (1.9 vs 3.0 months), and overall response rate (4.7% vs 8.3%) between the two groups. Grades 3 and 4 toxic effects were significantly higher in the S-1 plus leucovorin group than in the S-1 group. Based on these efficacy data, the researchers concluded that, compared with S-1, S-1 plus leucovorin did not improve survival in this patient population. Another similar study showed a higher disease control rate in the S-1 plus leucovorin group, but comparable OS in the two groups.<sup>45</sup> Randomized trials from Japan comparing the efficacy and safety of S-1 plus oxaliplatin (or S-1 plus irinotecan) with that of S-1 alone also showed no significant improvement in OS and PFS.<sup>46,47</sup>

## Other regimens

Cereda et al conducted a phase II trial exploring the activity of the combination of mitomycin and ifosfamide as salvage therapy in patients with gemcitabine-resistant metastatic pancreatic cancer.<sup>48</sup> The study showed a partial response rate of 5% (one patient) and stable disease in 10% of patients. However, grades 3 and 4 toxicities, including neutropenia in 80% of patients, were poorly tolerated, leading to the premature termination of this trial. Braghiroli et al tested the combination of paclitaxel and metformin for patients with gemcitabine-refractory pancreatic cancer based on preclinical data demonstrating synergism in this combination.<sup>49</sup> The disease control rate was 31.6% (6 patients), with a median OS and PFS of 128 and 44 days, respectively. Treatment-related grades 3 and 4 toxicities were observed in eight patients (40%), with the most common toxicity being diarrhea. The study failed to meet its primary endpoint and was, therefore, terminated in the first phase.

## Second-line targeted therapy: going beyond cytotoxic chemotherapy?

Targeted agents have been extensively assessed in the first-line setting in pancreatic cancer. Disappointingly, multiple studies have failed to show any improvement in survival. One exception is the combination of gemcitabine and the EGFR tyrosine kinase inhibitor (TKI) erlotinib, which gained regulatory approval following a small but statistically significant improvement (10-day) in median survival compared with gemcitabine alone in a large, randomized phase III trial.<sup>50</sup> Despite the lack of activity of targeted agents in the first-line setting, investigators have tested new drugs or drug combinations to improve survival for patients with advanced pancreatic cancer following first-line therapy (Table 4).

### EGFR inhibitors

Erlotinib – the most studied targeted agent – has been evaluated in the setting of gemcitabine-refractory metastatic pancreatic cancer in patients. A phase II trial of erlotinib dose-escalation to induce rash in non-selected patients with advanced pancreatic cancer showed a correlation between rash and disease control, with 47% of evaluable patients with grade 2 or 3 rash showing stable disease over 8 weeks versus 9% of patients with grade 0 or 1 rash ( $P = 0.017$ ).<sup>51</sup> However, there was no difference in survival based on rash, with a median OS of 3.9 months for patients who developed grade 2 or 3 rash versus 3.8 months for patients with grade 0 or 1 rash ( $P = 0.12$ ). In addition, no differences in median TTP by degree of rash were noted ( $P = 0.25$ ). Erlotinib combined with chemotherapeutic drugs or other targeted agents has also been tested in the second-line setting. A phase II trial studied erlotinib in combination with capecitabine in 30 gemcitabine-refractory patients and showed an overall objective radiologic response rate of 10% and median survival duration of 6.5 months.<sup>52</sup> In another phase II trial, the safety and efficacy of selumetinib, a MEK 1/2 inhibitor, plus erlotinib in patients with previously treated advanced pancreatic cancer were evaluated on the basis of preclinical evidence of synergistic activity between MEK and EGFR inhibitors.<sup>53</sup> This dual-targeted therapeutic strategy showed modest antitumor activity in pancreatic cancer, with a disease control rate of 41% and a median OS of 7.3 months. Dual inhibition of the EGFR and VEGF pathways using the combination of erlotinib and bevacizumab has also been tested for gemcitabine-refractory metastatic pancreatic cancer.<sup>54</sup> With a median OS of 102 days and median TTP of 40 days, the authors concluded that this “targeted-only” approach was relatively ineffective for this patient population. Everolimus,

an mammalian target of rapamycin (mTOR) inhibitor, and erlotinib in combination were also evaluated as another dual-targeted regimen.<sup>55</sup> The researchers reported a median OS of 87 days (2.9 months), with no objective response or disease stability.

Gefitinib, another EGFR TKI, was shown to enhance the activity of various cytotoxic agents, including taxanes, in preclinical studies. Ignatiadis et al, therefore, conducted a phase II trial using a gefitinib and docetaxel combination as second-line treatment in patients with advanced pancreatic cancer.<sup>56</sup> The study enrolled 26 patients and showed a median OS of 2.9 months, with 34.6% of patients developing grade 3/4 neutropenia (only one developed febrile neutropenia). A similar study done by Brell et al also showed limited efficacy. Notably, febrile neutropenia was observed in 11 patients (27%).<sup>57</sup>

Lapatinib is a TKI that binds to both EGFR and HER-2, which is overexpressed in 20% of patients with pancreatic cancer. Lapatinib leads to cell-growth arrest by the dual inhibition of EGFR and HER-2 and apoptosis via the inhibition of HER-2. Based on preclinical data suggesting augmented inhibition of tumor progression by targeting EGFR and HER-2 in xenograft models, Wu et al treated 17 patients with metastatic pancreatic cancer, who had progressed during first-line gemcitabine-based therapy, with capecitabine at 1,000 mg/m<sup>2</sup> on days 1–14 in combination with lapatinib 1,250 mg daily on a 21-day cycle.<sup>58</sup> A disease control rate of 35.3% was achieved, with median PFS and OS rates of 2.6 and 5.2 months, respectively. Furthermore, the researchers observed that a subset of patients who responded to the lapatinib and capecitabine showed prolonged PFS (4.0 months) and OS (8.3 months).

### VEGF and VEGFR inhibitors

Bevacizumab – an anti-VEGF monoclonal antibody – has been approved for the treatment of various solid tumors (colon cancer, non-small-cell lung cancer, and renal cancer) and a specific eye disease. A previous phase III trial comparing gemcitabine plus bevacizumab with gemcitabine alone in the first-line setting showed no improvement in OS with the addition of bevacizumab to gemcitabine.<sup>59</sup> In the second-line setting, patients with gemcitabine-refractory metastatic pancreatic adenocarcinoma were randomized to receive bevacizumab alone or bevacizumab in combination with docetaxel.<sup>60</sup> The median PFS and OS were 43 days (1.4 months) and 165 days (5.5 months) in the combination group and 48 days (1.6 months) and 125 days (4.2 months) in the single-agent group. No confirmed objective responses

Table 4 Targeted agents tested in advanced pancreatic cancer in the second-line setting

Study	Study design	Treatment	No of patients*	ECOG 0-1 (%) / KPS 90-100 (%)	Metastatic disease (%)	Response rate	Median PFS	Median OS
Chung et al <sup>64</sup>	Randomized phase II	Selumetinib plus MK-2206	58	100	74	PR 1.7%; SD 20.7%	1.9 months	3.9 months
Ko et al <sup>53</sup>	Single-arm phase II	mFOLFOX	62	100	63	PR 6.5%; SD 22.6%	2.0 months	6.7 months
Hurwitz et al <sup>65</sup>	Randomized phase II	Selumetinib plus erlotinib Ruxolitinib plus capecitabine	46 64	100 46.9	96 100	SD 41% CR 1.6%; PR 6.3%; SD 32.8%; PD 37.5%	1.9 months 1.7 months	7.3 months 4.5 months
Wu et al <sup>68</sup>	Single-arm phase II	Capecitabine	63	42.9	100	CR 0%; PR 1.6%; SD 34.9%; PD 33.3%	1.5 months	4.3 months
Dragovich et al <sup>62</sup>	Single-arm phase II	Lapatinib plus capecitabine	17	88	100	CR 0%; PR 0%; SD 35.3%; PD 35.3%	2.6 months	5.2 months
Renouf et al <sup>51</sup>	Single-arm phase II	Vatalanib	65	95	92	PR 3.1%; SD 27.7%; PD 52.3%	2 months	NR
Bodoky et al <sup>63</sup>	Randomized phase II	Erlotinib Selumetinib	49 32	80.4 NR	88.2 100	SD 32% PR 5%; SD 32%; PD 61%	NR 2.1 months	3.78 months 5.4 months
Arcaroli et al <sup>68</sup>	Single-arm phase II	Capecitabine	38	NR	100	PR 9%; SD 28%; PD 63%	2.2 months	5.0 months
Astsaturou et al <sup>60</sup>	Single-arm phase II	Saracatinib	19	100	100	CR 0%; PR 0%; SD 10.5%; PD 89.5%	1.6 months	2.5 months
Ramanathan et al <sup>72</sup>	Randomized phase II	Bevacizumab Bevacizumab plus docetaxel PX-12 (54 mg/m <sup>2</sup> ) PX-12 (128 mg/m <sup>2</sup> )	16 16 9 7	100 100 60 57	100 100 NR	PD 87.5% PD 81.25% SD 22.2%; PD 77.8% PD 100%	43 days 48 days 0.9 months 0.6 months	165 days 125 days 3.2 months for all
Javle et al <sup>55</sup>	Single-arm phase II	Everolimus plus erlotinib	15	100	100	PD 93.75%	49 days	87 days
Chawla et al <sup>71</sup>	Phase I/II	Rexin-G (dose 1) Rexin-G (dose 2)	6 7	100 100	100 100	PR 11.1%; SD 88.9%	3 months 7.65 months	4.3 months 9.2 months
Ko et al <sup>54</sup>	Single-arm phase II	Bevacizumab plus erlotinib	36	100	100	PR 2.8%; SD 19%	NR	102 days
O'Reilly et al <sup>61</sup>	Single-arm phase II	Sunitinib	77	88.3	100	CR 0%; PR 1.4%; SD 20.3%; PD 54%	1.31 months	3.68 months
Brell et al <sup>57</sup>	Single-arm phase II	Gefitinib plus docetaxel	41	92.7	NR	PR 2%; SD 46%; PD 37%	1.8 months	4.5 months
Wolpin et al <sup>67</sup>	Single-arm phase II	Everolimus	33	100	100	CR 0%; PR 0%; SD 21%; PD 67%	1.8 months	4.5 months
Pino et al <sup>70</sup>	Single-arm phase II	Capecitabine plus celecoxib	35	74	94	PR 9%; SD 29%; PD 65.7%	17 weeks	19 weeks
Carvajal et al <sup>69</sup>	Single-arm phase II	Flavopiridol plus docetaxel	10	NR	100	SD 33%; PD 67%	NR	4.2 months
Kulke et al <sup>52</sup>	Single-arm phase II	Capecitabine plus erlotinib	30	100	100	PR 10%	3.4 months	6.5 months
Ignatiadis et al <sup>56</sup>	Single-arm phase II	Gefitinib plus docetaxel	26	92.3	NR	SD 19.2%; PD 65.3%	NR	2.9 months

Notes: \*All patients were previously treated with first-line gemcitabine monotherapy or gemcitabine-based combination therapy.

Abbreviations: CR, complete response; ECOG, Eastern Oncology Cooperative Group; KPS, Karnofsky performance status; NR, not reported; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PX-12, inhibitor of Thioredoxin-1; SD, stable disease.

were observed, and the study was terminated according to the early termination rule for futility.

Sunitinib is an oral, small-molecule, multi-targeted receptor TKI that inhibits VEGFR, PDGFR, kit, RET, and FLT3. The Cancer and Leukemia Group B conducted a phase II study evaluating sunitinib in 77 patients with progressive metastatic pancreatic cancer following prior gemcitabine-based therapy.<sup>61</sup> The disease control rate was 21.7%: one patient (1.4%) had a partial response, and 15 patients had stable disease (20.3%). The PFS was 1.31 months and OS was 3.68 months. Although the study met its primary endpoint (disease control rate), the researchers concluded that sunitinib had minimal activity and moderate toxicity in a population of patients with gemcitabine-refractory pancreatic cancer.

Vatalanib is an orally active TKI with high receptor-binding affinity for VEGFR, PDGFR, c-Kit, and c-Fms. In preclinical orthotopic pancreatic models, vatalanib showed significant antitumor activity and it was correlated with decreased microvessel density. As vatalanib targets multiple targets implicated in pancreatic cancer survival and angiogenesis and shows promising preclinical activity, a phase II study investigating the efficacy and tolerability of vatalanib in patients with gemcitabine-refractory advanced pancreatic cancer was conducted.<sup>62</sup> The study resulted in a 6-month survival rate of 29%, with a median PFS of 2 months. The most common grade 3/4 adverse events included hypertension (20%), fatigue (17%), abdominal pain (17%), and elevated alkaline phosphatase (15%). Changes in biomarkers, including soluble VEGF and VEGFR, did not correlate with the response to vatalanib.

## Ras pathway inhibitors

The Ras pathway represents a growth-promoting pathway that is associated with pancreatic cancer through mutations in the *KRAS* and *BRAF* genes. Activating *KRAS* mutations are observed in >90% of pancreatic adenocarcinomas. Reflecting the complexity of directly targeting *KRAS*, drug development efforts have focused on downstream components of the Ras pathway, such as MEK. Selumetinib is an oral MEK1/2 inhibitor, and a free-base suspension of selumetinib has demonstrated preclinical activity in a range of tumors, including human pancreatic tumors. In a randomized phase II study, 70 patients with metastatic pancreatic cancer, who failed first-line therapy, were administered either selumetinib or capecitabine.<sup>63</sup> The median OS was 5.4 months in the selumetinib group and 5.0 months in the capecitabine group ( $P = 0.92$ ). The median PFS was 2.1 and 2.2 months in the selumetinib and capecitabine groups, respectively ( $P = 0.41$ ). Serious adverse events were recorded in 43% of patients in the selumetinib group and 25% in the capecitabine group.

These researchers concluded that although selumetinib is a well-tolerated second-line option for metastatic pancreatic cancer patients with failed first-line gemcitabine treatment, selumetinib is not significantly different from capecitabine in terms of OS in this patient population. Furthermore, the dual-targeted therapeutic strategy using selumetinib and MK-2206 failed to improve OS in the second-line setting.<sup>64</sup>

## Janus kinase inhibitors

Emerging evidence supports a role for Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling in the pathogenesis and clinical course of pancreatic cancer. In a randomized phase II study, the JAK1/JAK2 inhibitor ruxolitinib was evaluated in combination with capecitabine versus placebo plus capecitabine in patients who experienced treatment failure with gemcitabine.<sup>65</sup> No difference in survival was observed in the intention-to-treat population. However, in a prespecified subgroup analysis, patients with a C-reactive protein (CRP) level greater than 13 mg/L showed an improvement in median OS (2.7 vs 1.8 months;  $P = 0.011$ ). This finding led to the design of two randomized phase III trials (JANUS1 and JANUS2) for the second-line treatment of advanced pancreatic cancer. However, both JANUS1 and JANUS2 studies were terminated due to the lack of efficacy (no survival benefit for ruxolitinib plus capecitabine).<sup>66</sup>

## Phosphoinositide-3-kinase (PI3K)–mTOR pathway inhibitors

The PI3K/Akt/mTOR pathway is activated in half of pancreatic cancers, and inhibition of this pathway has been found to have antitumor effects in preclinical studies. Wolpin et al conducted a phase II trial evaluating the efficacy and safety of everolimus, an oral mTOR inhibitor, in patients who experienced treatment failure on first-line therapy with gemcitabine.<sup>67</sup> Although treatment with everolimus was well tolerated, no complete or partial responses were observed, and only seven of 33 patients (21%) had stable disease at the first restaging scans performed at 2 months. The median PFS and OS was 1.8 and 4.5 months, respectively.

Src, a nonreceptor tyrosine kinase, interacts with the PI3K regulatory subunit p85 to yield an increase in Akt activation. The oral Src inhibitor saracatinib exhibited antitumor activity in preclinical models of pancreatic cancer. In a phase II clinical trial of saracatinib in patients previously treated for pancreatic cancer, saracatinib was administered orally and continuously in 28-day cycles.<sup>68</sup> As only two patients (11%) patients survived for at least 6 months, the study was amended as a biomarker-driven trial. However,

of the 47 patients screened, only one patient was biomarker positive. Reflecting the low frequency of biomarker-positive patients, the study was eventually terminated.

Some other targeted agents, including flavopiridol (CDK inhibitor), celecoxib (selective COX-2 inhibitor), Rixin-G (targeted gene therapy vector), and PX-12 (inhibitor of thioredoxin-1), have been tested as either single agents or in combination with cytotoxic therapy in the second-line setting.<sup>69–72</sup> However, most of these drugs resulted in minimal or modest antitumor activity, except for Rixin-G. As a tumor-targeted retrovector bearing a cytotoxic cyclin G1 product, Rixin-G is a paradigm in the length of time to bring new therapeutics to bedside. It is the first targeted gene therapy vector to gain fast-track designation and orphan drug priorities for multiple cancer indications in the USA. As for pancreatic cancer, Rixin-G showed promise in the treatment of gemcitabine-resistant metastatic pancreatic cancer, as it produces an almost 10-month survival benefit. A pivotal phase II/III two-arm randomized study has been planned to confirm the OS benefit of Rixin-G as monotherapy versus the physician's choice of therapy in gemcitabine-refractory pancreatic cancer.

Overall, using single or combination targeted agents in the second-line setting has yielded rare responses, short PFS and OS times, and has limited the value with this strategy. Slightly more activity has been observed for combining a targeted agent with cytotoxic therapy in the refractory disease setting, although the benefit may relate to the cytotoxic backbone. In addition, an assessment of biomarkers that might identify the patient subsets most likely to benefit from targeted therapy is needed.

## Treatment effect trends over time

The above-summarized trials with available data were analyzed for treatment effect trends over time. The outcome trends over time were analyzed through the locally estimated scatterplot smoothing (LOESS) method using SPSS 19.0 software (IBM Corporation, Chicago, IL, USA). The median OS, PFS, and response rates of each regimen were plotted over time based on the year the studies were initiated. Regrettably, the median OS, PFS, and response rates remained unchanged over time (Figure 2).

## Future perspectives: every cloud has a silver lining

### Ongoing trials in the second-line setting: finding diamonds in the rough

As the search continues for strategies to refine approaches in treating patients with pancreatic cancer, and only a

few studies have focused on second-line therapy. This phenomenon is attributed to the poor performance status of the patients and limited survival benefit of testing agents or regimens after progression of first-line therapy. Nonetheless, there are still some novel noncytotoxic agents showing therapeutic potentials in this setting (Table 5).

Acalabrutinib, a selective second-generation BTK inhibitor, showed promising antitumor effects in combination with pembrolizumab.<sup>73</sup> A phase II study evaluating acalabrutinib alone or in combination with pembrolizumab is currently ongoing. Preliminary results of the first 58 treated patients revealed that the combination of acalabrutinib and pembrolizumab has a favorable benefit/risk profile and encouraging antitumor activity in pretreated metastatic pancreatic cancer, particularly in a subpopulation of patients with familial pancreatic cancer.

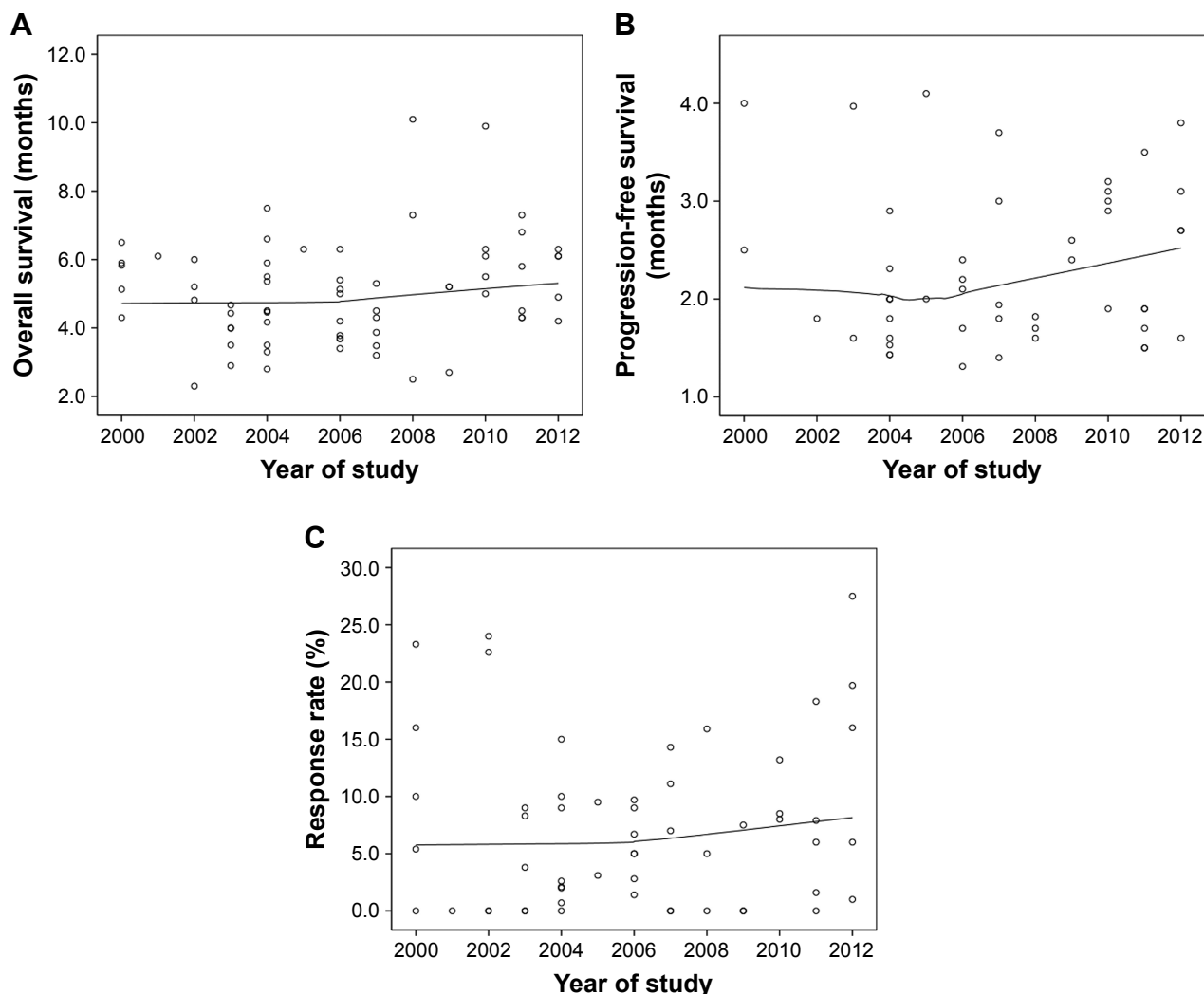
ERY-ASP – a new investigational medicinal product composed of *Escherichia coli* L-asparaginase encapsulated in erythrocytes – has shown potential efficacy in a subgroup of patients with pancreatic cancer with null/low asparagine synthetase (79.4%).<sup>74</sup> In an ongoing phase II trial, the combination of ERY-ASP plus cytotoxic chemotherapy versus chemotherapy alone is currently being tested.

Similarly, poly (ADP-ribose) polymerase (PARP) inhibitors also hold promise in the treatment of pancreatic cancer. Several trials investigating PARP inhibitors that include olaparib, veliparib, and rucaparib are underway for patients with pretreated advanced pancreatic cancer. Some have, shown encouraging results in patients with a germline *BRCA1/2* mutation.

In immunotherapy studies, AM0010 – a pegylated recombinant human interleukin 10 – has shown evidence of antitumor activity as salvage therapy in metastatic pancreatic adenocarcinoma. In a phase Ib study, AM0010 plus FOLFOX resulted in a median PFS of 3.5 months and a median OS of 10.0 months. The observed immune activation, including clonal T-cell expansion and prolonged objective tumor responses, is encouraging, and this regimen is currently being studied in a phase III trial. Besides, pembrolizumab, a type of immunotherapy that works by blocking the programmed death receptor-1 (PD-1) pathway, has been recommended to treat microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors in the second-line setting.<sup>75</sup>

## Sequential strategy: improving efficacy of treatment

To date, the optimum sequential chemotherapy strategy remains an unanswered question in the management of



**Figure 2** The treatment outcome trends over time plotted against the year of the studies including overall survival (A), progression-free survival (B), and response rate (C).

advanced pancreatic cancer. Because of a lack of relative clinical trials, no clear evidence is available for second-line chemotherapy after FOLFIRINOX or gemcitabine plus nab-paclitaxel first-line regimens. Moreover, the benefit of

FOLFIRINOX, followed by gemcitabine plus nab-paclitaxel versus the reverse sequence, also remains unknown. Recent data from a non-randomized cohort study suggest that the administration of nab-paclitaxel and gemcitabine in patients

**Table 5** Selected ongoing phase II or III clinical trials in patients with pretreated advanced pancreatic cancer

Clinical trial identifier	Type of study	Regimen	No of patients	Primary endpoint
NCT02726854	Phase II	Apatinib	30	PFS, ORR
NCT02967770	Randomized phase II	MTT vs SOC	58	PFS
NCT02558868	Randomized phase II	Oxaliplatin + irinotecan vs irinotecan	80	OS
NCT02195180	Randomized phase II	ERY-ASP + GEM/FOLFOX4 vs GEM/FOLFOX4	141	PFS
NCT02677038	Phase II	Olaparib	24	ORR
NCT02042378	Phase II	Rucaparib	19	ORR
NCT02890355	Randomized phase II	Veliparib + mFOLFIRI vs FOLFIRI	143	OS
NCT01954992	Randomized phase III	Glufosfamide vs 5-FU	480	OS
NCT02923921	Randomized phase III	AM0010 + FOLFOX vs FOLFOX	566	OS
NCT01834235	Randomized phase II	NPC-1C + GEM + ABX vs GEM + ABX	81	OS, safety, and tolerability
NCT02362048	Randomized phase II	ACP-196 vs ACP-196 + pembrolizumab	73	Treatment emergent adverse events

**Abbreviations:** MTT, molecularly tailored therapy; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SOC, standard of care; 5-FU, 5-fluorouracil; GEM, gemcitabine; ERY-ASP, L-asparaginase encapsulated in erythrocytes; NPC-1C, ensituximab; ABX, nano albumin bound-paclitaxel; ACP-196, acalabrutinib; FOLFOX, folinic acid + fluorouracil + oxaliplatin; FOLFIRI, folinic acid + fluorouracil + irinotecan.

refractory to the FOLFIRINOX regimen might be a successful strategy to delay tumor progression, as documented by a disease control rate of 58%.<sup>76</sup> Median PFS and OS from the start of second-line therapy were 5.1 and 8.8 months, respectively. However, these exciting results were associated with a high rate of toxicity; grades 3 and 4 toxicity occurred in 40% of the patients, mostly neutropenia and neurotoxicity. Moreover, a retrospective study using the same sequence observed similar results.<sup>77</sup> Therefore, to reduce cumulative toxic effects, optimize dose intensity, and increase efficacy, further investigation in therapeutic sequences is needed.

## Maintenance therapy in advanced disease: new life for an old idea

With the success of more effective regimens in patients with advanced disease, questions concerning how best to manage the treatment-free interval prior to disease progression have been raised. Therapeutic strategies, such as maintenance therapy, may represent potential means to improve clinical outcomes in advanced pancreatic cancer. Although well established for the treatment of certain hematologic malignancies, maintenance therapy has only recently been tested as a treatment paradigm for metastatic pancreatic adenocarcinoma. In the Pancreatic AdenoCarcinoma Trials - 12 (PACT-12) trial, 55 patients without evidence of progression after 6 months of initial chemotherapy (mostly, gemcitabine combinations) were randomized to sunitinib or observation.<sup>78</sup> Median OS was 9.2 months in the observation group versus 10.6 months in the sunitinib group, which was not statistically significant (HR 0.71; 95% CI 0.40–1.26;  $P = 0.11$ ) and precluded strong conclusions; however, the 1- and 2-year survival rates were 35.7% and 7.1% in the observation arm and 40.7% and 22.9% in the sunitinib arm, suggesting that a subset of patients may benefit from maintenance therapy. Although sunitinib proved inactive in second-line therapy of pancreatic cancer, the intriguing results of the PACT-12 trial suggest that this drug may impact the disease course when administered as maintenance treatment in patients achieving disease control with first-line chemotherapy. Alternatively, it is likely that as more active agents against pancreatic cancer become available, maintenance therapy may potentially achieve even more exciting results.

## OS prediction for second-line chemotherapy: better patient selection

Currently, the vast majority of clinical trials evaluating second-line regimens have used the Eastern Oncology Cooperative Group or Karnofsky performance status score and other “pragmatic parameters” (eg, age, duration of

first-line therapy) to select candidates. This selection not only generates considerable heterogeneity in survival in patients who receive second-line chemotherapy between studies but also is unable to determine which patients might benefit from second-line chemotherapy. A retrospective study from the CONKO study group revealed that a prognostic score which included Karnofsky performance status, carbohydrate antigen 19-9 levels at start of second-line therapy, and the duration of first-line therapy was able to identify three subgroups in the second-line setting.<sup>79</sup> The modified Glasgow Prognostic Score – a systemic inflammation-based prognostic system which incorporated CRP and albumin – has also been shown to be reliable indicator of OS in the setting of second-line therapy.<sup>65</sup> In a prospective population-based cohort study, Vienot et al developed and validated a prognostic nomogram and score to predict OS in patients with advanced pancreatic cancer who received second-line chemotherapy in routine clinical practice using a broad spectrum of parameters (age, smoking status, liver metastases, performance status, pain, jaundice, ascites, duration of first-line, and type of second-line regimen).<sup>80</sup> This score classified patients into low-, intermediate-, and high-risk groups with median OS of 11.3, 3.6, and 1.4 months, respectively. Although the study did not evaluate albumin or serum CRP because of the high rate of missing data, this prognostic nomogram and score represents the most comprehensive scoring system reported thus far, which accurately predicts OS prior to the administration of second-line chemotherapy and may help clinicians in their therapeutic decisions. In addition, this tool may be beneficial for better selection of patients for treatment, for stratified random assignment to ensure well-balanced treatment groups, and for the potential optimization of clinical trial design. Furthermore, the development of risk-adapted strategies for second-line management in the future could be considered in the different risk groups identified.

## Conclusion

If disease progression occurs after administration of first-line therapy, survival remains short for patients with pancreatic cancer, and the outcome with second-line chemotherapy remains unsatisfactory, with a low response rate. The current treatment options vary in terms of drugs and dosages with different survival benefits. The only way to move forward in meaningful ways will be to identify new and more effective therapeutic alternatives that emerge from phase I/II clinical trials. Any therapy should be individualized and based on performance status, comorbidities, expected toxicities, and patient preference. More broadly, with a greater understanding of pancreatic cancer tumor biology, coupled with the

growing availability of non-cytotoxic agents and interest by academia and pharmaceutical companies to meet the challenge, better systemic treatments of pancreatic cancer beyond conventional chemotherapy are anticipated in the near future. Due to the heterogeneity of pancreatic cancer per se, each novel therapy may exclusively be limited to a distinct subset of individuals. In addition, there is a need to assess biomarkers that might identify the patient subsets that will most likely benefit from second-line therapy.

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## Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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