

Capecitabine and oxaliplatin as first and second line treatment for locally advanced and metastatic pancreatic ductal adenocarcinoma

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Background: There are limited treatment options available for patients with advanced pancreatic ductal adenocarcinoma (PDAC). We conducted a phase II study evaluating the efficacy and safety of capecitabine/oxaliplatin (CAPOX) in patients with locally advanced and metastatic PDAC treated in the first and second lines.

Methods: Forty subjects with advanced PDAC and ECOG performance status ≥ 2 were enrolled. Treatment consisted of capecitabine 2,000 mg/m² orally in two divided doses daily for 14 days and oxaliplatin 130 mg/m² intravenously day 1 every 21 days. The primary endpoint was response rate (RR); secondary endpoints included safety analysis, progression free survival (PFS) and overall survival (OS).

Results: The overall RR was 12.5% (N=3); the disease control rate was 67% (N=16). Due to the protocol definition for eligibility of response evaluation, only 60% (N=24) were evaluable for the primary endpoint. Median progression free survival (mPFS) was 3.8 months (95% CI: 1.3, 6.2); median OS (mOS) was 7.4 months (95% CI: 4.8, 12.2). The most common grade 3/4 toxicities included: fatigue (19%), nausea (17%), and diarrhea (14%).

Conclusions: CAPOX is an active regimen in patients with advanced PDAC and is associated with acceptable toxicity. Careful consideration should be given to response endpoints and outcome measures when studying this characteristically ill population.

Keywords: Pancreatic cancer; capecitabine and oxaliplatin

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Introduction

Despite recent advances in systemic therapy for advanced pancreatic ductal adenocarcinoma (PDAC), outcomes remain limited by poor survival and, for the most aggressive regimens, significant toxicities. Until 2011 when the FOLFIRINOX regimen [intravenous fluorouracil (5FU), leucovorin, oxaliplatin, and irinotecan] demonstrated

superior overall survival (OS) compared to intravenous gemcitabine alone, single agent gemcitabine was the standard of care for first line treatment (1,2). Subsequently in 2013, the combination nab-paclitaxel/gemcitabine also demonstrated better OS than gemcitabine alone (3) in the first line setting. In addition, intravenous 5FU/leucovorin and nanoliposomal irinotecan in the second-line setting

Table 1 Clinical trials evaluating the combinations of capecitabine and/or fluorouracil with oxaliplatin in advanced pancreatic ductal adenocarcinoma

Author	Year	N	1 st or 2nd line treatment	5FU or capecitabine	ORR (%)	DCR (%)	mPFS/TTP (months)	mOS (months)
Ducieux (6)	2004	31	1 st	5FU	10	NA	4.2	9.0
Tsavaris (7)	2005	30	1 st	5FU	23.3	53.3	5.5	6.3
Ghosn (8)	2007	30	1 st	5FU	27.6	62	4	7.5
Boeck (9)	2008	61	1 st	Capecitabine	13	49	4.2	8.1
Mitry (10)	2006	18	2 nd	5FU	0	17	0.9	4.9
Xiong (11)	2008	41	2 nd	Capecitabine	3	28	2.5	5.8
Novarino (12)	2009	23	2 nd	5FU	0	23.5	2.9	4.3
Yoo (13)	2009	30	2 nd	5FU	7	17	1.5	3.7
Pelzer (14)	2011	46	2 nd	5FU	0	NA	NA	4.8
Berk (15)	2012	85	2 nd	5FU and capecitabine	18	59	4	5.3
El-Hadaad (16)	2013	30	2 nd	5FU	6.7	26.7	3.3	5.5
Oettle (17)	2014	77	2 nd	5FU	NA	NA	2.9	5.9

ORR, overall response rate (% partial plus complete response per RECIST); DCR, disease control rate (ORR plus % stable disease); mPFS, median progression free survival; mTTP, median time to progression; mOS, median overall survival. Results reported in weeks converted to months using 1 week, 7 days and 4 weeks, 1 month.

after gemcitabine-based chemotherapy has recently been shown to improve survival compared to intravenous 5FU/leucovorin alone or nanoliposomal irinotecan alone (4). Due to substantial toxicities, however, many PDAC patients are not able to tolerate these regimens. In particular, questions have been raised about how much toxicity (and benefit) irinotecan contributes to the 5FU-oxaliplatin backbone in FOLFIRINOX. In addition, the continuous infusion 5FU in FOLFIRINOX may add logistical and quality of life concerns for patients. In rectal cancer, oral 5FU (capecitabine) is non-inferior compared to continuous infusion 5FU (5) and may be more convenient for patients.

The activity of infusional 5FU combined with oxaliplatin without the addition of irinotecan for advanced PDAC has been reported in several small studies (*Table 1*). Intravenous 5FU and oxaliplatin appear active in first line (FOLFOX, OFF, OXFU) and second-line (weekly oxaliplatin/5FU/leucovorin, FOLFOX) regimens (6-8,10,12-14,16,17). Median OS and response rates (RRs) were superior in the first line compared to second line studies. The combination capecitabine and oxaliplatin showed similar efficacy and toxicity profile to FOLFOX4 in a study evaluating both XELOX and FOLFOX4 in the second line (XELOX PR 18%, SD 41%, mOS 21 weeks;

FOLFOX PR 17%, SD 26%, mOS 25 weeks) (15).

Two additional small studies have evaluated capecitabine combined with oxaliplatin in advanced PDAC (*Table 1*) (16,17). The first by Xiong and colleagues was a non-randomized phase II study evaluating capecitabine and oxaliplatin (CAPOX) in subjects who had progressed on gemcitabine (n=41) (16). Results were not as encouraging as those seen in studies of oxaliplatin combined with intravenous 5FU or gemcitabine (mOS =5.75 months; PR in 1 subject; SD in 10 of 39 (26%) evaluable subjects). The side effects were manageable, however, and the study population appeared more ill than in other studies: 95% had metastatic disease and almost 30% had an Eastern Cooperative Oncology Group (ECOG) Performance Score (PS) of 2. In the same year Boeck and colleagues published a randomized three-arm phase II trial evaluating CAPOX, combination capecitabine/gemcitabine, and combination gemcitabine/oxaliplatin (17). Results for the CAPOX arm showed median progression-free survival (mPFS) 4.2 months, mOS 8.1 months, and fewer grade 3 and 4 hematologic toxicities than in the gemcitabine containing arms. The authors concluded that each regimen demonstrated similar clinical efficacy and safety profiles in this population.

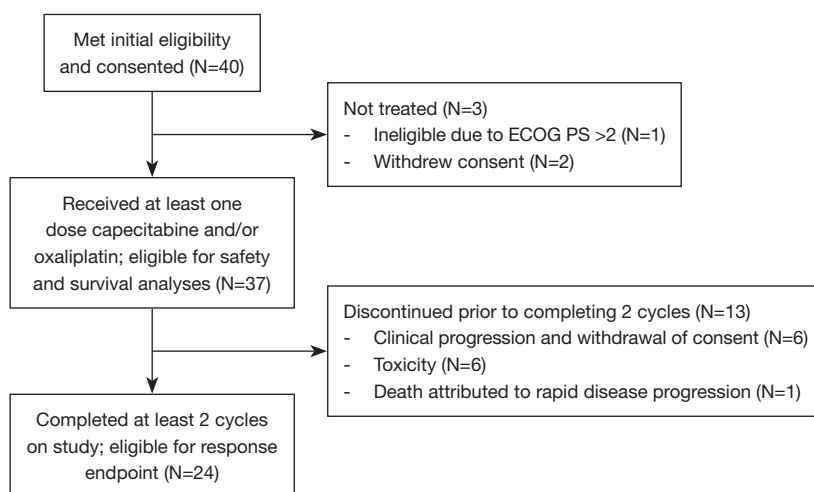


Figure 1 Consort diagram.

Given the scarcity of treatment options at the time of study initiation in the mid-2000s, we undertook a Phase II trial to assess CAPOX for first and second-line treatment in advanced PDAC. We present here the results of a multi-institutional Phase II single-arm trial that evaluated 40 patients treated with CAPOX for first or second-line treatment of locally advanced or metastatic PDAC.

Methods

Study population

Forty subjects with locally advanced or metastatic PDAC were enrolled at three academic institutions for first or second line treatment (*Figure 1*). All subjects had histologically or cytologically confirmed PDAC and had received at most one prior chemotherapy regimen for advanced disease. Previous adjuvant chemotherapy was permitted if completed more than 12 months prior to initiation of study treatment. Other eligibility criteria included ECOG PS ≤ 2 , adequate organ function and life expectancy ≥ 3 months (additional details in Supplementary 1). The Institutional Review Board approved this study, and all subjects provided written informed consent.

Treatment

Participants self-administered capecitabine 1,000 mg/m² orally twice daily (total daily dose 2,000 mg/m²), days 1–14 in 21-day cycles. Only 500 mg tablets were used, and doses were rounded to the nearest dose that could be administered with 500 mg tablets. Oxaliplatin 130 mg/m²

was administered intravenously on day 1 every 21 \pm 2 days. Treatment continued until tumor progression or toxicity requiring discontinuation of therapy. Oxaliplatin was provided by Sanofi-Synthelabo as investigational drug supply and capecitabine was prescribed commercially. Response was assessed by computed tomography (CT) or magnetic resonance imaging (MRI) every two cycles (42 \pm 2 days) using RECIST criteria (18). Complete responses (CR) and PR were confirmed by repeat scan one month later. Chemotherapy doses were modified for toxicities as outlined in the protocol (Supplementary 2). Capecitabine was held for any grade 2, 3, or 4 toxicity, and the dose was reduced when restarted after toxicity resolution. The oxaliplatin was dose-reduced for hematologic and neurologic toxicities, and the infusion was extended to six hours if a subject experienced acute laryngopharyngeal dysesthesia. Compliance with oral capecitabine was documented at each study visit by pill count.

Statistical analysis

The primary endpoint was RR, defined as objective response of measurable disease per RECIST criteria (18). Subjects were evaluable for response if two cycles of treatment on study were completed. An interim analysis was conducted after the first 12 subjects according to the Simon's 2-stage design (19). Anticipating that 10% of subjects would not be evaluable for response, a total of 40 patients were enrolled to achieve 90% power to detect 20% difference in response in target lesions, with type 1 error of 10% and alpha <5%. A two-sided 80% CI was estimated considering the two-

Table 2 Baseline characteristics

Characteristic	Number subjects, N [%]
Age in years, median [range]	61 [40–78]
Gender	
Male	19 [48]
Female	21 [53]
Race	
Asian	1 [3]
Black or African American	2 [5]
White	31 [78]
Other	3 [8]
Unknown	3 [8]
ECOG PS	
0	10 [25]
1	28 [70]
2	2 [5]
Received prior chemotherapy	
Yes	29 [72.5]
No	11 [27.5]
Stage	
Locally advanced	2 [5]
Metastatic	38 [95]
CA 19-9 (U/mL); median (range)	1,009 (3–678,332)
Number of metastatic sites, median (range)	2 (0–4)

stage design based on Atkinson and Brown methods (20). Demographics, disease characteristics and adverse events are presented for the safety population. Progression free survival (PFS) reflects time from enrollment until progression or death. Subjects who did not reach progression or were lost to follow-up were censored at the date of last progression free disease evaluation. Disease control rate included data on subjects with CR, PR, and SD. PFS and OS were calculated by the Kaplan Meier method. Subjects were included in the PFS analysis if they completed two cycles on treatment (response evaluable population); subjects were included in the OS and safety analyses if they took any capecitabine or oxaliplatin dose on study.

We also performed a post-hoc literature review to search for all advanced pancreatic cancer studies evaluating

capecitabine and oxaliplatin, and infusional 5FU and oxaliplatin. Search terms included: advanced or metastatic pancreatic cancer, 5FU, oxaliplatin, capecitabine, clinical trial. The following data was abstracted: First author, year of publication, number of subjects, line of treatment, and when available, ORR, DCR, mPFS and mOS.

Results

Patient characteristics

Forty subjects were enrolled between May 2004 and March 2010. Baseline demographics and disease characteristics are presented in *Table 2*. The majority of participants (95%) had an ECOG PS 0–1, had metastatic PDAC (95%), and had previously received gemcitabine for advanced PDAC (72.5%).

Treatment completion and toxicity

Thirty-seven subjects received at least one dose of capecitabine and/or oxaliplatin on study (safety population). The reasons for not receiving any treatment on protocol were: ineligibility due to poor performance status and withdrawal of consent. The median number of cycles per subject was 2 (range, 1–12). Among subjects evaluable for response (n=24), the most common reasons for discontinuation were disease progression (n=17; 71%), followed by toxicity (n=4; 17%), and subject and/or physician preference (n=3; 13%). Subjects not evaluable for response withdrew prior to completing two cycles due to withdrawal of consent and/or clinical progression (n=6; 46.2%), toxicity (n=6; 46.2%), and death attributed to rapid disease progression (n=1; 7.7%). Dose reductions were performed for toxicity in nine (25%) subjects and treatment holds in 16 (44%) subjects. There were 36 subjects included in the toxicity analysis as one patient was missing adverse event data. The most prevalent toxicities are reported in *Table 3*. Two subjects died during treatment, one due to a cerebrovascular ischemic event and one due to colitis.

Efficacy results

Due to the protocol definition of eligibility for evaluation of response (at least two cycles of treatment completed on study), only 24 subjects (60%) were evaluable for the primary endpoint. Four subjects were lost to follow up and were censored at the last visit.

The most frequent response was SD (n=13; 54%), and

Table 3 Adverse events (maximum grade attributable to drug)

Adverse event (n=36)	Grade 1, 2, n [%]	Grade 3, 4, n [%]	Overall, n [%]
Fatigue	19 [53]	7 [19]	26 [72]
Nausea	19 [53]	6 [17]	25 [69]
Neuropathy-sensory	21 [58]	1 [3]	22 [61]
Vomiting	15 [42]	4 [1]	19 [53]
Anorexia	15 [42]	1 [3]	16 [44]
Anemia	11 [31]	3 [8]	14 [39]
Diarrhea	8 [22]	5 [14]	13 [36]
Hand-foot skin reaction	8 [22]	1 [3]	9 [25]
Abdominal pain or cramping	4 [11]	3 [8]	7 [19]
Thrombocytopenia	7 [19]	0 [0]	7 [19]

Note: one patient who received treatment was missing safety data.

Table 4 Best recorded response

Evaluable population (N=24)	Number subjects, N [%]
CR	0 [0]
PR	3 [13]
ORR	3 [13]
SD	13 [54]
DCR	16 [67]
PD	8 [33]
Not evaluable	16 [67]

CR, complete response per RECIST; PR, partial response per RECIST; ORR, overall response rate (CR + PR); SD, stable disease per RESIST; DCR, ORR + SD; PD, progressive disease per RECIST.

three subjects experienced a PR (13%) (Table 4). At the first imaging after two cycles on treatment, 33% experienced disease progression (N=8). This result does not include those subjects who were taken off study due to clinical progression within the first two cycles as this choice was listed as 'subject or clinician preference.' The overall RR was 12.5% (80% CI: 3.5–20.1), and the disease control rate (DCR) was 67%. Twenty-four subjects were included in the PFS analysis, and 38 were included in the OS analysis. For evaluable subjects (n=24 patients with 22 PFS events), mPFS was 3.8 months (95% CI: 1.3, 6.2) (Figure 2). Among subjects treated in the first line mPFS was 4.9 months (95% CI: 1.1–NR) compared to 3.1 months (95% CI: 1.3, 6.2) among those

treated in the second line. For all treated subjects (n=37 with 24 deaths), mOS was 7.4 months (95% CI: 4.8, 12.2). Median OS among subjects treated in the first line was 8.3 months (95% CI: 2.8–NR) compared to mOS 6.9 months (95% CI: 3.6, 12.2) among those treated in the second line.

Discussion

Despite the introduction of FOLFIRINOX and nab-paclitaxel/gemcitabine into clinical practice, advanced PDAC remains a highly lethal disease, and the burdens associated with treatment remain an important issue for patients and their caregivers. Our study contributes to the capecitabine and oxaliplatin (CAPOX) literature showing that this regimen can be administered to patients with locally advanced or metastatic PDAC with encouraging DCR (67%) and acceptable toxicity in either the first- or second-line setting. Thus, CAPOX may be a reasonable choice for those patients for whom the toxicities associated with the more aggressive combination regimens is not advised. This study, however, also highlights the challenges that exist in studying patients with an inherently aggressive disease like advanced PDAC.

In this study the majority of subjects (54%) achieved SD. Furthermore, eight subjects maintained SD for greater than six months, and disease remained controlled in three subjects for greater than 10 months, which is on par with results seen for more aggressive combination regimens (2–4,21).

The RR in our study, 13%, was similar to that reported by Boeck and colleagues in the first line (13%) (9) and

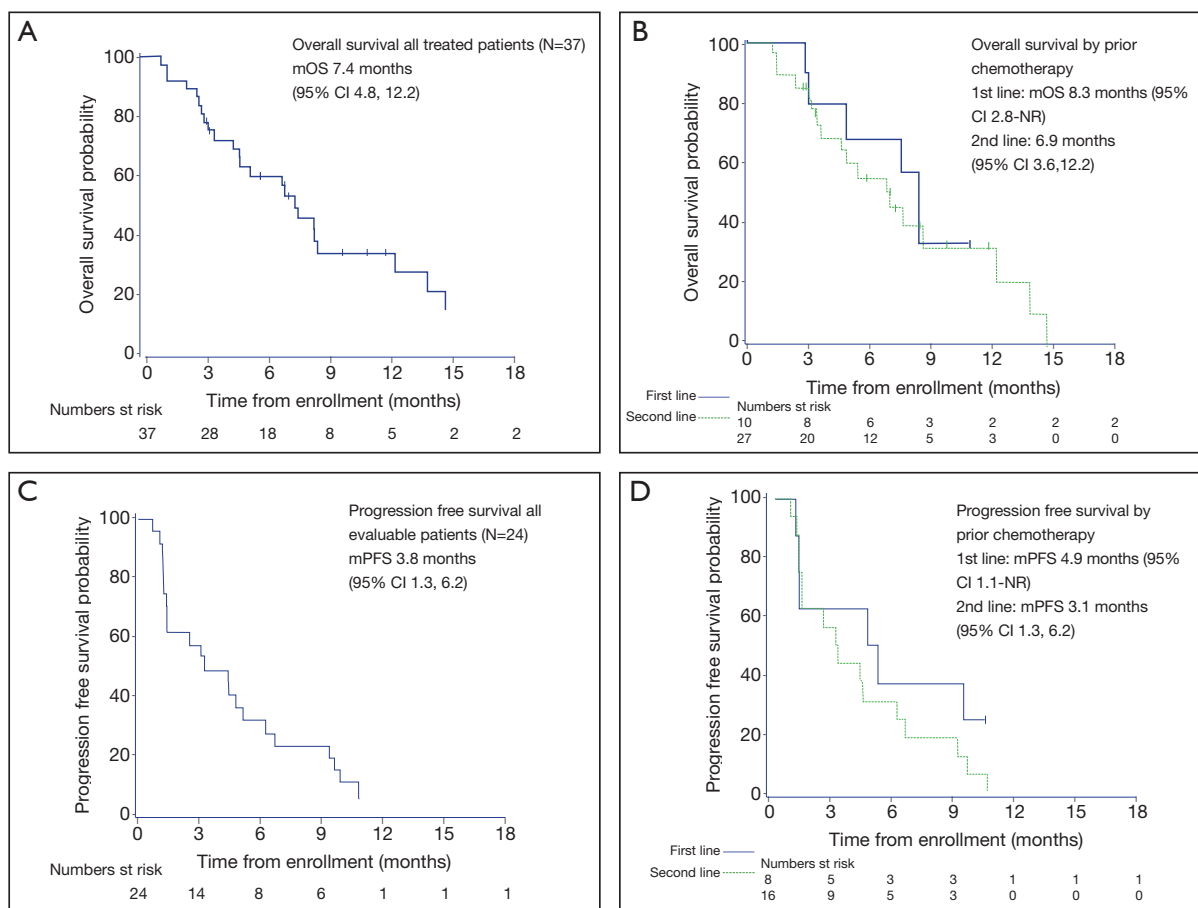


Figure 2 Kaplan-Meier estimates for overall survival and progression-free survival for all treated patients and by line of therapy. (A) Median overall survival was 7.4 months (95% CI: 4.8, 12.2); (B) median overall survival among subjects treated in the first line was 8.3 months (95% CI: 2.8–NR) and in those treated in the second line 6.9 months (95% CI: 3.6, 12.2); (C) median progression free survival was 3.8 months (95% CI: 1.3, 6.2); (D) median progression free survival among subjects treated in the first line was 4.9 months (95% CI: 1.1–NR) and in those treated in the second line 3.1 months (95% CI: 1.3, 6.2).

similar to that reported by Berk and colleagues (18%) (15). Response was greater than that reported by Xiong and colleagues evaluating CAPOX (1%) (11) and by Yoo *et al.* evaluating FOLFOX in gemcitabine refractory disease (7%) (13). Response, however, was lower than that reported by Ghosn *et al.* in their study of FOLFOX in first line therapy (27.6%) (8) (Table 1). Results were also comparable to those reported by Demols *et al.*, who assessed the benefit of oxaliplatin plus gemcitabine in subjects with gemcitabine-refractory advanced PDAC (PR 22.6%, SD 35.5%) (21) and that reported for second line 5-FU/nanoposomal irinotecan (16%) (4) by Wang-Gillam *et al.*

Median PFS (3.8 months) and mOS (7.4 months) in the current study are similar to those reported by Xiong

et al. (11) and Berk *et al.* (15), and similar to that reported for gemcitabine monotherapy in the first line setting (1). Results from studies of infusional 5FU have been variable with mOS ranging 3.7 to 9.0 months (6-8,10,12-14,16,17). Median OS was slightly lower than that reported by Boeck and colleagues for the same regimen (8.1 months) in the first-line (9), but our study also included second-line subjects. Median PFS and mOS were comparable to that reported for 5-FU/nanoposomal irinotecan in the second line (mPFS 3.1 months, mOS 6.1 months) (4).

The RR, mPFS, and mOS in this trial are substantially lower than that reported for first line FOLFIRINOX. Thus, the addition of irinotecan to the intravenous 5FU/leucovorin/oxaliplatin backbone may provide additional

benefit. However, our study does not directly compare these regimens, and the mechanism underlying this difference remains unclear. Irinotecan monotherapy has shown only modest benefit in advanced PDAC (22), and the results of other phase II studies of FOLFIRI (5FU/leucovorin, and irinotecan) and that of second line 5FU/nanoliposomal irinotecan are comparable to those reported here (4,23,24).

A substantial number of patients withdrew from this study prior to completing two chemotherapy cycles, and because of this only 24 were evaluable for response. The failure of so many patients to complete two cycles was a striking finding in and of itself. Recent trials evaluating FOLFIRINOX and nab-paclitaxel/gemcitabine included only patients with ECOG PS 0–1 (2,25), whereas this trial included patients with ECOG PS 0–2. In the current study, 5% had PS 2 while in the Xiong study 28% of subjects had PS 2 (11), and in the Boeck study 15% had KPS \leq 70% (9). This suggests that either the combination oral capecitabine may be more toxic than previously thought, or that earlier studies of 5FU and oxaliplatin were conducted in a more select patient population. It is also plausible that the prognosis for patients with poor performance status is too limited for an objective response from treatment to be documented either because of short time period of benefit or inability of the patient to tolerate treatment long enough to achieve benefit. The large number of subjects who withdrew prematurely underscores the challenge of conducting trials in this inherently sick population. Future studies in advanced PDAC should include methods that account for early progression and for assessing study populations with poor performance status, multiple comorbidities, and rapidly progressive disease.

Also potentially affecting results is the fact that 72.5% (N=29) of subjects in our study had already been treated for advanced PDAC. Previous trials in advanced PDAC have suggested that patients whose disease is refractory to first line treatment are unlikely to benefit from second line therapy. In a study of weekly 5FU/leucovorin and oxaliplatin administered in the second line after gemcitabine, Tsavaris and colleagues noted that patients who had responded to first-line gemcitabine were more likely to show response or disease stability with second line treatment (7).

The findings of this study must be considered in the context of its limitations. The primary limitation is the lower than expected number of subjects evaluable for response. In addition to potentially affecting generalizability, the small evaluable population limits the power of the study for the primary endpoint. This limitation has implications

for the design of future studies in advanced PDAC as the primary reason for non-evaluability of response was early study discontinuation. Early study discontinuation reflects both the toxicities caused by this regimen as well as the underlying disease state and poor functional status of the subjects. Alternate metrics for assessing therapeutic benefit may be important in this population such as symptom control, quality of life assessment, and earlier response endpoints. Although the study was conducted in a single geographic area, generalizability was enhanced by enrolling subjects at three different institutions.

This study shows that the combination capecitabine and oxaliplatin (CAPOX) is a reasonable treatment option for patients with advanced PDAC with acceptable toxicity and demonstrated benefit. It also adds to the body of literature supporting additional treatment strategies for patients who may not be candidates for more aggressive combination chemotherapy regimens. Finally, we emphasize the need to reassess outcome measures in advanced pancreatic cancer trials in a way that allows those patients whose disease progresses rapidly to contribute to primary endpoints.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The Institutional Review Board approved this study, and all subjects provided written informed consent.

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Supplementary 1: Eligibility criteria

- (I) Inclusion criteria:
- (i) Hematologic function: neutrophils $\geq 1.5 \times 10^9/L$, platelet $\geq 100 \times 10^9/L$;
 - (ii) Renal function: creatinine $< 1.5 \times$ upper normal limit or estimated creatinine clearance > 30 mL/min as calculated with Cockcroft-Gault equation;
 - (iii) Hepatic function: bilirubin $< 1.5 \times$ upper normal limit, ALT, AST $< 2.5 \times$ upper normal limit, alkaline phosphatase $< 2.5 \times$ upper normal limit.
- (II) Exclusion criteria:
- (i) Pregnant or lactating;
 - (ii) Serious or uncontrolled infection;
 - (iii) Prior oxaliplatin or fluoropyrimidine therapy (unless as part of adjuvant therapy completed more than 12 months prior);
 - (iv) Any active second malignancy or CNS metastases;
 - (v) Clinically significant cardiac disease;
 - (vi) Major surgery within 4 weeks of study treatment start;
 - (vii) Uncontrolled coagulopathy;
 - (viii) Malabsorption syndrome;

Any other serious uncontrolled medical condition that the investigator felt might compromise study participation.

Supplementary 2: Chemotherapy dose adjustments for toxicity*Calculation of capecitabine dose reductions*

- (I) 75% of the original dose:

If the original dose is a *total daily dose* of 2,000 mg/m² to be taken as two divided doses, then 75% of the original dose = a *total daily dose* of 1,500 mg/m² to be taken as two divided doses.

If the original dose is a *total daily dose* of 1,500 mg/m² (because of moderate renal impairment) to be taken as two divided doses, then 75% of the original dose = a *total daily dose* of 1,125 mg/m² to be taken as two divided doses.

- (II) 50% of the original dose:

If the original dose is a *total daily dose* of 2,000 mg/m² to be taken as two divided doses, then 50% of the original dose = a *total daily dose* of 1,000 mg/m² to be taken as two divided doses.

If the original dose is a *total daily dose* of 1,500 mg/m² (because of moderate renal impairment), to be taken as two divided doses, then 50% of the original.

Table S1 Capecitabine dose adjustments for non-hematologic AE's

AE incidence	Grade 2	Grade 3	Grade 4
1st appearance	Interrupt treatment until resolved to grade 0–1, then continue at same dose with prophylaxis where possible	Interrupt treatment until resolved to grade 0–1, then continue at 75% of original dose with prophylaxis where possible	Discontinue treatment unless Investigator considers it to be in the best interests of the patient to continue at 50% of original dose, once toxicity has resolved to grade 0–1
2nd appearance of same toxicity	Interrupt treatment until resolved to grade 0–1, then continue at 75% of original dose	Interrupt treatment until resolved to grade 0–1, then continue at 50% of original dose	–
3rd appearance of same toxicity	Interrupt treatment until resolved to grade 0–1, then continue at 50% of original dose	Discontinue treatment permanently (off study) unless it is considered to be by the investigator in the best interest of the patient to stay on treatment	–
4th appearance of same toxicity	Discontinue treatment permanently (off study) unless it is considered to be by the investigator in the best interest of the patient to stay on treatment	–	–

Table S2 Capecitabine dose adjustments for hematologic toxicity

Hematologic toxicity	Grade 3	Grade 4
Neutropenia and thrombocytopenia	No change	1 st occurrence—reduce to 75% of original dose of capecitabine; 2 nd occurrence—reduce to 50% of original dose of capecitabine
Anemia	Interrupt until cause is determined and treat accordingly. If the cause is determined to be other than capecitabine and the anemia has been treated accordingly, capecitabine may be resumed without dose adjustment. If the cause is determined to be capecitabine, then reduce the dose of capecitabine accordingly: 1st occurrence—reduce to 75% of original dose of capecitabine; 2nd occurrence—reduce to 50% of original dose of capecitabine	

Table S3 Oxaliplatin dose reductions

Toxicity	Reduction (mg/m ²)
Grade 4 thrombocytopenia	100
Grade 4 neutropenia	100
Grade 4 neutropenia with fever	100
Grade 3–4 mucositis	100
Grade 4 diarrhea	100
Grade 3 vomiting (occurring within 3 days of oxaliplatin dosing despite optimal antiemetic prophylaxis)	100
Grade 4 vomiting	100

Table S4 Neurological toxicity scale for oxaliplatin dose adjustments

Toxicity (Grade)	Duration of toxicity		Persistent between cycles
	1–7 days	>7 days	
Paresthesias/dysesthesias that do not interfere with function (Grade 1)	No change	No change	No change
Paresthesias/dysesthesias interfering with function, but not activities of daily living (ADL) (Grade 2)	No change	No change	100 mg/m ²
Paresthesias/dysesthesias with pain or with functional impairment that also interfere with ADL (Grade 3)	No change	65 mg/m ²	STOP—off study
Persistent paresthesias/dysesthesias that are disabling or life-threatening (Grade 4)	STOP—off study	STOP—off study	STOP—off study
ACUTE: (during or after the 2 hour infusion) laryngopharyngeal dysesthesias	Increase duration of next infusion to 6 hours	–	–