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ORIGINAL ARTICLE

Phase II study of elraglusib (9-ING-41), a GSK-3β inhibitor, in combination with gemcitabine plus nab-paclitaxel in previously untreated metastatic pancreatic cancer

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Introduction: The purpose of this study was to assess the efficacy and safety of elraglusib (9-ING-41), a GSK-3β inhibitor, in combination with gemcitabine/nab-paclitaxel (GnP) in previously untreated metastatic pancreatic ductal adenocarcinoma (mPDAC).

Material and methods: In a nonrandomized, Simon's two-stage, phase II study, patients with mPDAC received elraglusib 15 mg/kg on days 1 and 4 each week and GnP on days 1, 8, and 15 in a 28-day cycle. The primary endpoint was disease control rate (DCR); secondary endpoints were objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and treatment-emergent adverse events (TEAEs).

Results: A total of 42 patients, who were enrolled and treated, had a median age of 67 years and were 57.1% male. Overall, 38 patients received elraglusib at 15 mg/kg and 4 at 9.3 mg/kg with GnP. DCR was 35.7% [95% confidence interval (CI) 21.6% to 52.0%], and ORR was 26.2%. The median PFS and OS were 5.4 months (95% CI 4.4-9.2 months) and 11.9 months (95% CI 7.8-16.5 months), respectively. Most common TEAEs were visual impairment (83.3%), fatigue (69%), and nausea (66.7%). Grade $\geq$3 TEAEs occurred in 85.7% of patients and included neutropenia (52.4%), leukopenia (42.9%), and fatigue (21.4%). The dose of elraglusib was reduced to 9.3 mg/kg due to increased exacerbation of GnP-related toxicities and frequent dose interruptions and reductions of elraglusib.

Conclusions: Elraglusib/GnP showed preliminary clinical activity. In terms of safety, elraglusib resulted in a modest exacerbation of GnP-related toxicities, leading to a dose reduction of elraglusib to 9.3 mg/kg twice a week. Based on the initial efficacy and safety data, the study was amended to a randomized phase II study that will evaluate the 9.3 mg/kg dose.

Key words: GSK-3β Inhibitor, elraglusib (9-ING-41), pancreatic cancer, combination, previously untreated

INTRODUCTION

Pancreatic cancer will be diagnosed in 66 440 people in the United States and 100 152 in Europe in one year.[1,2] It is the third- or fourth-leading cause of death among cancers, depending on the region, with a 5-year survival rate of 13% overall and 3% in metastatic disease.[1,3,4]

Guidelines from the European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) recommend systemic therapy consisting of 5-fluorouracil, leucovorin, irinotecan plus oxaliplatin (FOLFIRINOX); nanoliposomal irinotecan plus 5-fluorouracil, leucovorin and oxaliplatin (NALIRIFOX); or gemcitabine plus nab-paclitaxel (GnP) for patients with advanced or metastatic pancreatic cancer with good performance status (PS). Patients with intermediate or poor PS typically receive GnP or single-agent therapy (i.e. gemcitabine, capecitabine, or 5-fluorouracil).[5,6] Treatment with the guideline-recommended regimens extends the median survival by 8-12 months.[5-9]

Glycogen synthase kinase-3 (GSK-3), a serine/threonine kinase regulating glycogen biosynthesis, emerged as a potential therapeutic target in pancreatic cancer.[10-12] GSK-3β mediates tumor cell survival and proliferation, suppresses

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apoptosis, and mediates chemotherapy resistance by regulating nuclear factor kappa B (NF-κB)-dependent gene expression.[11-17] The inhibition of GSK-3β down-regulates NF-κB activity.[11,12,16,18] GSK-3 also modulates immune checkpoint proteins and regulates tumor immune response in pancreatic cancer.[19-21]

Elraglusib (9-ING-41), a GSK-3β inhibitor, has demonstrated antitumor activity in various preclinical studies.[11,15,16,22-25] In chemoresistant cancer cells, the NF-κB pathway has increased activation, which promotes the expression of antiapoptotic molecules.[11,16,24,25] By inhibiting the expression of these antiapoptotic molecules, elraglusib may overcome NF-κB-mediated chemoresistance in human cancer. In chemoresistant tumor models of glioblastoma and breast cancer, elraglusib enhanced cytotoxic effects of chemotherapy.[15,16] In models of pancreatic cancer, the addition of elraglusib to gemcitabine led to synergistic killing of pancreatic tumor cells by blocking the phosphorylation of checkpoint kinase 1 (Chk1) and destabilizing topoisomerase IIβ binding protein (TopBP1) in the TopBP1/ataxia-telangiectasia-mutated-and-Rad3-related kinase (ATR)/Chk1 signaling cascade.[26-28] Additionally, improved survival was observed with the addition of elraglusib to gemcitabine, paclitaxel, or liposomal irinotecan in several models of pancreatic cancer.[26]

Based on extensive preclinical rationale,[15,16,22-28] elraglusib was evaluated in a phase I study as monotherapy or in combination with eight chemotherapy backbones, including GnP, in patients with advanced malignancies.[29] Evidence of antitumor activity was observed across multiple cancer histologies.[29] Elraglusib monotherapy led to an objective response rate (ORR) of 3.2%, median progression-free survival (PFS) of 1.6 months, and median overall survival (OS) of 7.7 months. In that study, 26 patients with chemorefractory metastatic pancreatic ductal adenocarcinoma (mPDAC) previously treated with GnP were rechallenged with a range of elraglusib doses (3.3-15 mg/kg) combined with GnP. These patients had a median PFS of 4.3 months and a median OS of 4.5 months, and one partial response (PR) lasted 2.2 months. Eleven patients were treated with elraglusib at the recommended phase II dose (RP2D) of 15 mg/kg in combination with GnP, leading to a disease control rate (DCR) of 57%. The combination of elraglusib/GnP appeared well tolerated at this dose.[29] Reported adverse events were those commonly associated with GnP, except for the reversible visual impairment (likely a class effect of GSK-3 inhibitors). No new safety signals were observed with elraglusib/GnP. Based on these results, a single-arm phase II study was initiated to assess the efficacy and safety of elraglusib/GnP in newly diagnosed mPDAC.

MATERIAL AND METHODS

Study design

An open-label, nonrandomized, Simon's two-stage, phase II study assessed the efficacy of elraglusib/GnP in patients with mPDAC who had not previously received systemic treatment of their metastatic disease (the 1801 study, Part 3A; NCT03678883). This study was conducted at nine sites—seven in the United States, one in Spain, and one in the Netherlands. Patients were enrolled from 20 July 2020 to 26 July 2021.

Institutional review boards or ethics committees of the respective participating centers approved the study, and all enrolled patients signed the informed consent form. The participating centers included Lifespan Cancer Institute at Rhode Island Hospital, Providence, Rhode Island, USA; INCLIVA Valencia, Valencia, Spain; Seattle Cancer Care Alliance, Seattle, Washington, USA; Vanderbilt University Medical Center, Nashville, Tennessee, USA; Northwestern University, Chicago, Illinois, USA; Sanford Health, University of South Dakota Medical Center, Sioux Falls, South Dakota, USA; University of Kansas Medical Center, Kansas City, Kansas, USA; University of Michigan, Ann Arbor, Michigan, USA; and Antoni van Leeuwenhoekziekenhuis, Amsterdam, The Netherlands. The study was conducted in compliance with Good Clinical Practice and the Declaration of Helsinki.

Patients

Eligible patients were $\geq$18 years old and presented with previously untreated advanced, recurrent, or metastatic PDAC. All patients had at least one measurable lesion per RECIST v1.1 criteria using a computed tomography (CT) scan or magnetic resonance imaging (MRI). Other eligibility criteria consisted of Eastern Cooperative Oncology Group (ECOG) PS grade 0-2 and adequate bone marrow, liver, and renal functions (see Supplementary Appendix, available at https://doi.org/10.1016/j.esmoop.2025.105122). Permitted prior therapy administered at least 6 months before study enrollment included neoadjuvant FOLFIRINOX and adjuvant 5-fluorouracil, gemcitabine, or other systemic chemotherapy.

Key exclusion criteria included pregnancy or lactation, presence of endocrine or acinar pancreatic carcinoma, history of cardiovascular disease, rapidly progressing brain metastases or leptomeningeal involvement, or major surgery within 7 days of enrollment. Patients with stable brain metastases or leptomeningeal disease were eligible.

Procedures

Treatment was administered intravenously as nab-paclitaxel 125 mg/m^2 plus gemcitabine 1000 mg/m^2 on days 1, 8, and 15 in a 28-day cycle, and elraglusib 15 mg/kg on days 1 and 4 of each week. The RP2D for elraglusib was 15 mg/kg based on the phase I study.[29]

In May 2021, the elraglusib dose was decreased to 9.3 mg/kg due to excessive patient withdrawal related to possible exacerbation of chemotherapy adverse events and increased vascular access complications, although no new safety signals related to elraglusib were observed. Doses for GnP could be altered only after an agreement between the principal investigator and the study medical monitor.

Standard CT, MRI, and/or positron emission tomography scans were carried out at baseline, followed by institutional

standard of care for tumor assessments with the earliest imaging assessment completed following two cycles after starting treatment. Treatment continued until disease progression, unacceptable toxicities, or the investigator's decision that a patient no longer benefited from treatment.

Study objectives and assessments

The primary endpoint was DCR, defined as the proportion of patients achieving stable disease (SD) for ≥16 weeks, confirmed complete response (CR), or confirmed PR according to RECIST v1.1 criteria. DCRs were calculated for patients with ≥50%, ≥90%, <50%, and <90% reductions from baseline in carbohydrate antigen (CA) 19-9 levels. The relative dose intensity was calculated as the administered cumulative dose divided by the planned cumulative dose.[30]

Secondary endpoints consisted of ORR, duration of response (DoR), PFS, OS, and treatment-emergent adverse events (TEAEs). ORR was defined as the percentage of patients achieving best CR and PR. DoR was defined as the time from tumor response to disease progression, PFS as the time from study enrollment to tumor progression or death, and OS as the time from study enrollment to death from any cause. TEAEs were recorded from the first dose of elraglusib to 30 days after the last dose and were graded using the Common Terminology Criteria for Adverse Events v4.03.

The efficacy evaluable (EE) population, also the primary analysis population, consisted of patients who had at least one postbaseline efficacy assessment on study treatment. Patients who discontinued due to disease progression or elraglusib-related toxicity before an efficacy assessment were also included. The intention-to-treat (ITT) population consisted of patients who received at least one dose of elraglusib, gemcitabine, or nab-paclitaxel.

Biomarker analysis

To assess GSK-3β expression, GSK-3β immunohistochemical (IHC) staining was carried out on formalin-fixed, paraffin-embedded tumor sections from archival tissues using Mosaic Laboratories method (Lake Forest, CA) and the Leica Bond RX (Leica Biosystems, Buffalo Grove, IL). For molecular analysis, next-generation sequencing generated genomic profiling on archival tumor and/or peripheral blood specimens. Oncoprint displayed mutations present in more than two patients and any relational patterns between mutations versus disease response.

Statistical analysis

In the original study design, ∼60 patients were expected to enroll. In Simon's two-stage design, stage 2 is initiated only if a minimum number of patients achieve disease control in stage 1.[31] According to historical data, a DCR of 50% represented the lower threshold,[8] and thus, a DCR of 65% was hypothesized for this study. Using 80% power with a one-sided significance level of 0.05, stage 1 required enrollment of up to 23 assessable patients. If more than 12 patients achieved disease control in stage 1, an additional 37 patients would be enrolled during stage 2. Otherwise, the enrollment for stage 2 would be terminated. If at least 35 out of 60 patients achieved disease control in the study, further evaluation of the treatment is warranted. However, because the study was amended to a randomized, controlled design (1801 Part B; NCT03678883), no patients were enrolled for stage 2. Thus, the data presented in this report comprise only stage 1.

Descriptive statistics were used to analyze the efficacy and safety parameters. Categorical data were summarized by frequency distributions (numbers and percentages of patients), while continuous data were represented as the number of observations, mean, standard deviation, median, minimum, and maximum. Kaplan–Meier methodology assessed time-to-event variables such as DoR, PFS, 1- and 2-year survival estimates, and OS. For estimates, two-sided 95% confidence intervals (CIs) were provided.

All statistical analyses were carried out using SAS software version 9.4 or higher.

Data availability

Actuate is committed to data transparency with qualified external researchers. The requests are approved based on scientific merit; data are anonymized in line with applicable laws and regulations; and the criteria for data availability adheres to www.clinicalstudydatarequest.com. To submit a request, please contact: info@actuatetherapeutics.com.

RESULTS

Patient disposition and baseline characteristics

A total of 42 patients were enrolled and treated: 38 patients received elraglusib at 15 mg/kg dose and 4 patients at 9.3 mg/kg dose (Figure 1). The EE population included 29 patients (25 at the 15 mg/kg dose and 4 at the 9.3 mg/kg dose), because 13 patients on elraglusib at 15 mg/kg lacked postbaseline efficacy assessment. The ITT population consisted of all 42 patients. Demographic and baseline characteristics are displayed in Table 1.

Treatment exposure

The median duration of treatment was 2.2 months: 4.4 months for the 9.3 mg/kg dose and 1.9 months for the 15 mg/kg dose. The median number of administered doses for elraglusib was 17, with 40 doses for the 9.3 mg/kg dose and 16 doses for the 15 mg/kg dose. Overall, the primary reasons for treatment discontinuation were disease progression ($n = 18$, 42.9%) and withdrawal by patient ($n = 15$, 35.7%) (Figure 1). For the elraglusib 15 mg/kg dose, the primary reasons for treatment discontinuation were disease progression ($n = 15$, 39.5%) and withdrawal by patient ($n = 14$, 36.8%).

The median relative dose intensity was 62.9% for elraglusib (73.6% for the 9.3 mg/kg dose and 59.7% for the 15 mg/kg dose), 67.7% for nab-paclitaxel, and 72.3% for gemcitabine. Furthermore, dose reductions were observed

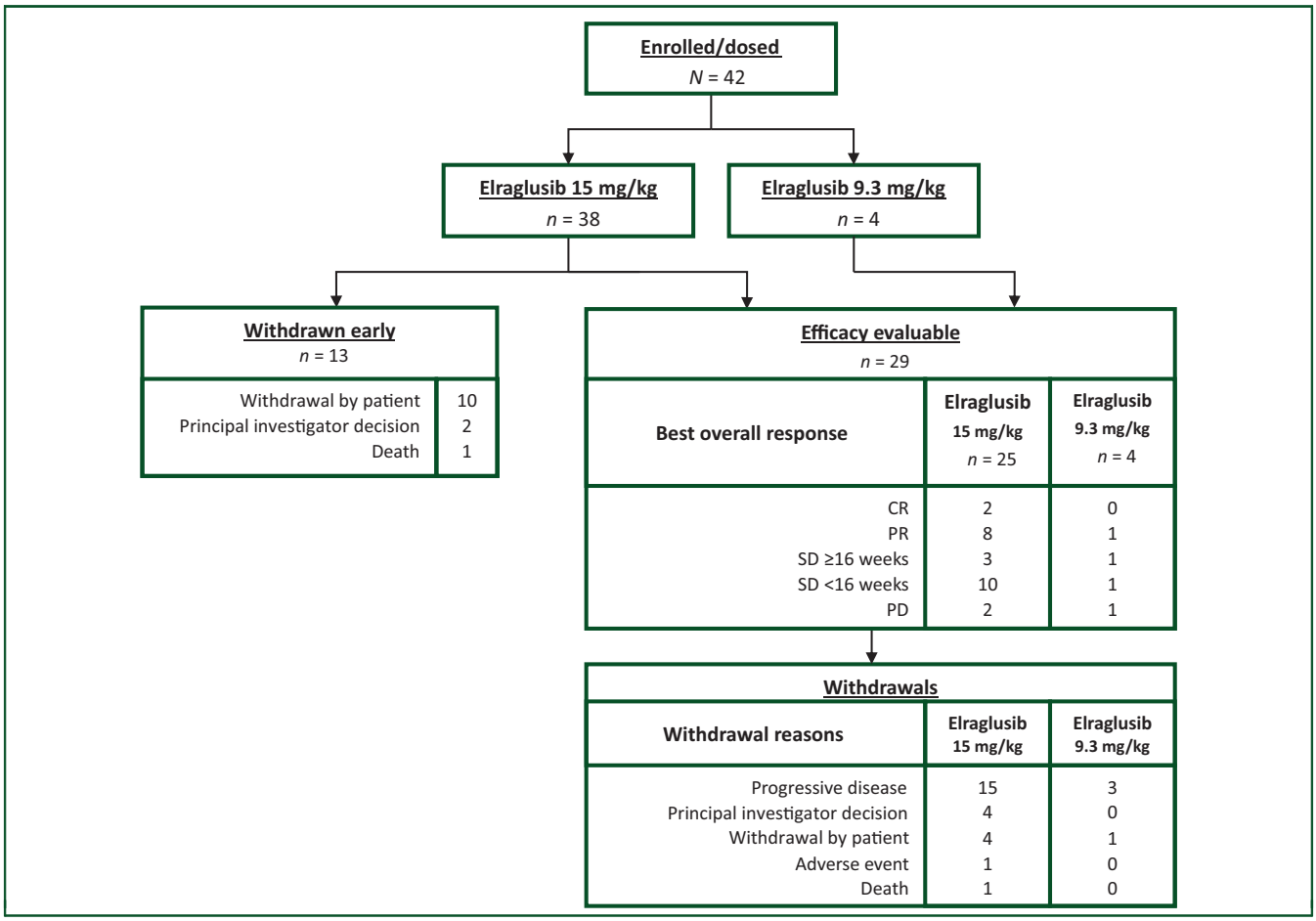

Figure 1. CONSORT diagram with reasons for treatment discontinuation and best overall response.
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

in 47.6% of treated patients for elraglusib, 52.4% for nab-paclitaxel, and 40.5% for gemcitabine.

Efficacy

DCR was 51.7% (95% CI 32.5% to 70.6%) in the EE population and 35.7% (95% CI 21.6% to 52.0%) in the ITT population (Table 2). In the EE population, the DCR was 71.4%, 100%, 33.3%, and 36.4% among patients with ≥50%, ≥90%, <50%, and <90% reductions in CA 19-9 levels from baseline, respectively (Supplementary Tables S1 and S2, available at https://doi.org/10.1016/j.esmoop.2025.105122).

The ORR was 37.9% in the EE population and 26.2% in the ITT population, with CR in two patients and PR in nine patients (Table 2). Four patients achieved SD lasting ≥16 weeks, and 11 achieved SD lasting <16 weeks. Reduction in tumor burden occurred even among patients with SD (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105122). The median DoR was 3.8 months (95% CI 1.8-12.9 months; Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2025.105122). The EE population had a median PFS of 5.4 months (95% CI 4.1-7.8 months; Figure 2A), a median OS of 15.3 months (95% CI 7.9-19.5 months; Figure 2B), a 1-year survival estimate of 56.1% (95% CI 35.7% to 72.2%), and a 2-year survival estimate of 20.1% (95% CI 7.4% to 37.2%). The ITT population had a median PFS of 5.4 months (95% CI 4.4-9.2 months; Figure 2C), a median OS of 11.9 months (95% CI 7.8-16.5 months; Figure 2D), a 1-year survival estimate of 48% (95% CI 32.1% to 62.3%), and a 2-year survival estimate of 21.4% (95% CI 10.2% to 35.4%). In the ITT population, 47.6% (20/42) of patients received a second-line treatment (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.105122). Prolonged OS was observed in patients who received second-line treatment and those who did not.

In an exploratory analysis of the ITT population, 91.7% (22/24) of patients with grade 3 or 4 neutropenia/febrile neutropenia developed neutropenia in cycle 1. Eight out of 11 patients with CR or PR had grade 3 or 4 neutropenia in cycle 1 (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2025.105122). Grade 4 neutropenia was significantly correlated ($P < 0.05$) with CR or PR in the EE population (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2025.105122).

Biomarker analysis

Total GSK-3β expression was detected in tumor tissues of 17/19 (89.5%) patients. No correlation was observed

Table 1. Patient demographics and baseline characteristics

Characteristic	ITT population ($N = 42$)
Age (years), median (range)	67 (41-85)
Sex, *n* (%)	
Male	24 (57.1)
Female	18 (42.9)
Race, *n* (%)	
White	33 (78.6)
Black or African American	3 (7.1)
Asian	2 (4.8)
Other	4 (9.5)
Ethnicity, *n* (%)	
Hispanic or Latino	2 (4.8)
Not Hispanic or Latino	37 (88.1)
Not reported	2 (4.8)
Unknown	1 (2.4)
Weight (kg), median (range)	77.8 (44.9-160.1)
Height (cm), median (range)	172 (150-190.5)
BMI, median (range)	26.1 (17.8-52.3)
ECOG performance status, *n* (%)	
0	8 (19)
1	30 (71.4)
2	4 (9.5)
Primary tumor location, *n* (%)	
Pancreas	41 (97.6)
Other (ampullary pancreatic)	1 (2.4)
Stage at diagnosis, *n* (%)	
Stage 2	2 (4.8)
Stage 3	1 (2.4)
Stage 4	38 (90.5)
Missing	1 (2.4)
Prior therapy for pancreatic cancer, *n* (%)	
No prior cytotoxic chemotherapy	34 (81.0)
Surgery	17 (40.5)
Neoadjuvant or adjuvant cytotoxic chemotherapy	8 (19.0)
Radiotherapy	4 (9.5)

ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat.

between total GSK-3β expression and response to elraglusib/GnP.

Tumor DNA genomic profiling was carried out in 10 patients with archival tumor specimens and/or peripheral blood specimens. Mutations in genes such as *TP53*, *KDM6A*, *BCLAF1*, and *KRAS* were identified in several specimens (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2025.105122).

Table 2. Response of patients with pancreatic cancer to elraglusib/GnP

Response	EE population ($N = 29$)	ITT population ($N = 42$)
Complete response (CR), *n* (%)	2 (6.9)	2 (4.8)
Partial response (PR), *n* (%)	9 (31.0)	9 (21.4)
Stable disease (SD) $\geq$16 weeks, *n* (%)	4 (13.8)	4 (9.5)
SD $<$16 weeks, *n* (%)	11 (37.9)	11 (26.2)
Progressive disease, *n* (%)	3 (10.3)	3 (7.1)
Disease control rate (CR + PR + SD $\geq$16 weeks), *n* (%)	15 (51.7)	15 (35.7)
	(95% CI 32.5% to 70.6%)	(95% CI 21.6% to 52.0%)

CI, confidence interval; EE, efficacy evaluable; GnP, gemcitabine plus nab-paclitaxel; ITT, intention-to-treat.

Safety

All patients experienced at least one TEAE, with grade 3 or higher TEAEs occurring in 85.7% of patients (Table 3). TEAEs of grade 3 or higher affecting more than 20% of patients included neutropenia ($n = 22$, 52.4%), leukopenia ($n = 18$, 42.9%), and fatigue ($n = 9$, 21.4%). Eleven grade 3 or higher TEAEs related to elraglusib were recorded in 10 patients (23.8%) (Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2025.105122). These consisted of febrile neutropenia, maculopapular rash, decreased neutrophil count, hallucination, visual impairment, anemia, fatigue, and peripheral sensory neuropathy. All were observed at the highest dose of elraglusib, 15 mg/kg. Serious TEAEs affected 73.8% of patients; only two patients (4.8%) had a serious TEAE related to elraglusib, which was febrile neutropenia (Table 3 and Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2025.105122).

The most common TEAEs were visual impairment, fatigue, nausea, diarrhea, and neutropenia (Table 3). The majority of the TEAEs were related to GnP (Supplementary Table S7, available at https://doi.org/10.1016/j.esmoop.2025.105122). TEAEs attributed to elraglusib that occurred in more than 10% of patients included visual impairment ($n = 31$, 73.8%), fatigue ($n = 13$, 31%), infusion-related reaction ($n = 5$, 11.9%), and nausea ($n = 5$, 11.9%). Visual impairment events attributed to elraglusib were mostly grade 1 (64.3% of patients), with grade 2 or 3 affecting only two (4.8%) patients each (Supplementary Table S7, available at https://doi.org/10.1016/j.esmoop.2025.105122). Visual impairment events were generally associated with changes in color perception and described as color vision change (1 patient), double vision (1 patient), photopsia (1 patient), dim vision (1 patient), visual disturbance (18 patients), blurred vision (3 patients), and transient visual impairment (13 patients). All cases attributed to elraglusib were transient and resolved within 1-2 h.

Other relevant TEAEs were port-related issues (i.e. vascular access complications and device-related thrombosis) and infusion reactions. Port-related issues were reported in five patients (nine events), all receiving elraglusib 15 mg/kg (Supplementary Table S8, available at https://doi.org/10.1016/j.esmoop.2025.105122). Eleven infusion reactions were observed in six patients: elraglusib-related in five patients (all at the 15 mg/kg dose and all grade 1 or 2 in severity) and GnP-related in one patient (Supplementary Table S7, available at https://doi.org/10.1016/j.esmoop.2025.105122).

TEAEs led to treatment discontinuation in nine patients (21.4%), all on the elraglusib 15 mg/kg dose within the first three cycles of treatment (Table 3). Only one TEAE leading to treatment discontinuation, grade 2 visual impairment, was related to elraglusib. Overall, five TEAEs resulted in the death of four patients (9.5%). One patient died due to an abscess and dehiscence at the gastroesophageal junction, one due to sepsis, and two due to disease progression. None of the TEAEs leading to death were related to elraglusib or GnP.

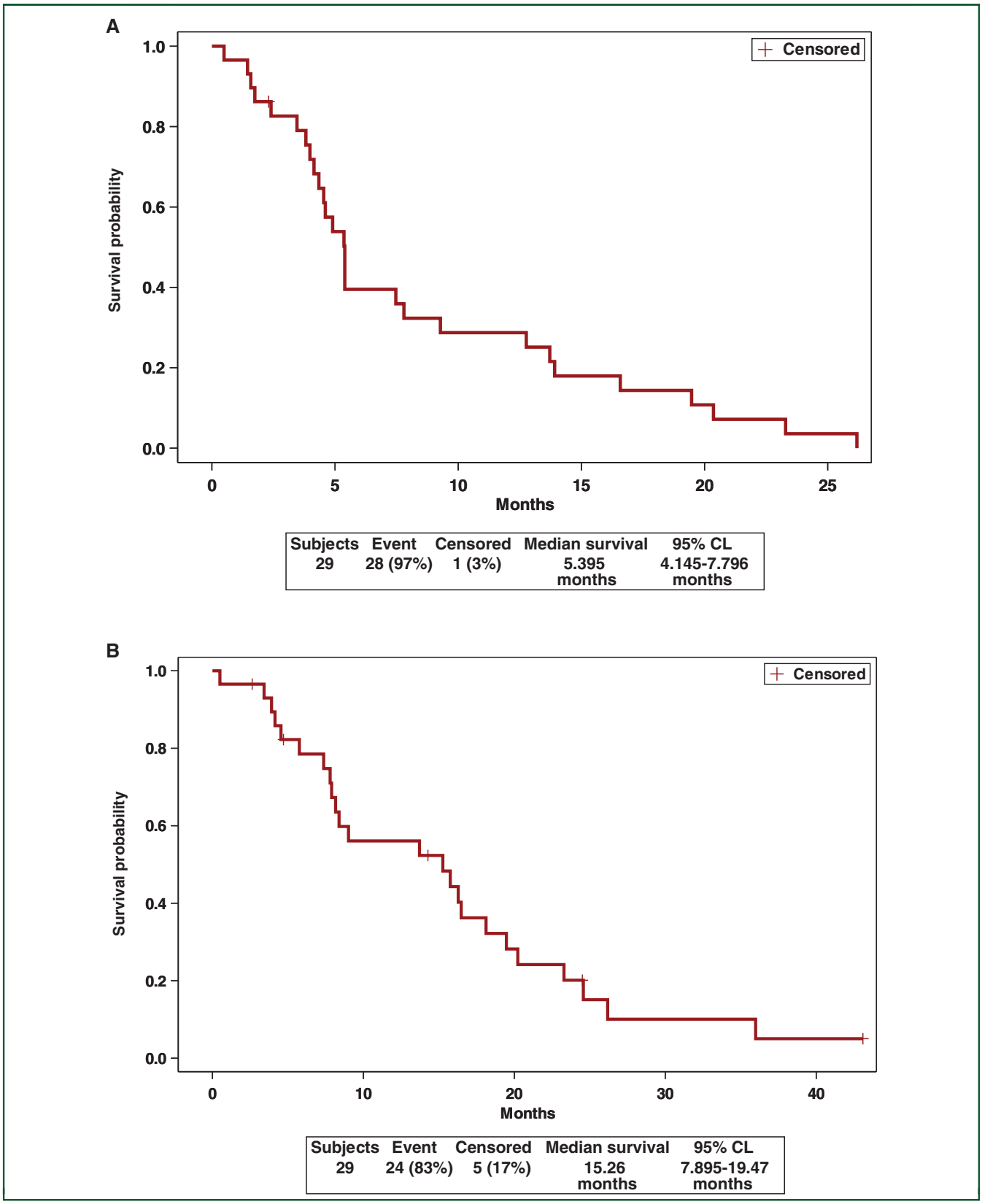

Figure 2. **Kaplan–Meier estimates of (A) progression-free survival and (B) overall survival for efficacy evaluable population; (C) progression-free survival and (D) overall survival for intention-to-treat population with elraglusib/gemcitabine plus nab-paclitaxel (GnP) in previously untreated metastatic pancreatic cancer.** CL, confidence level.

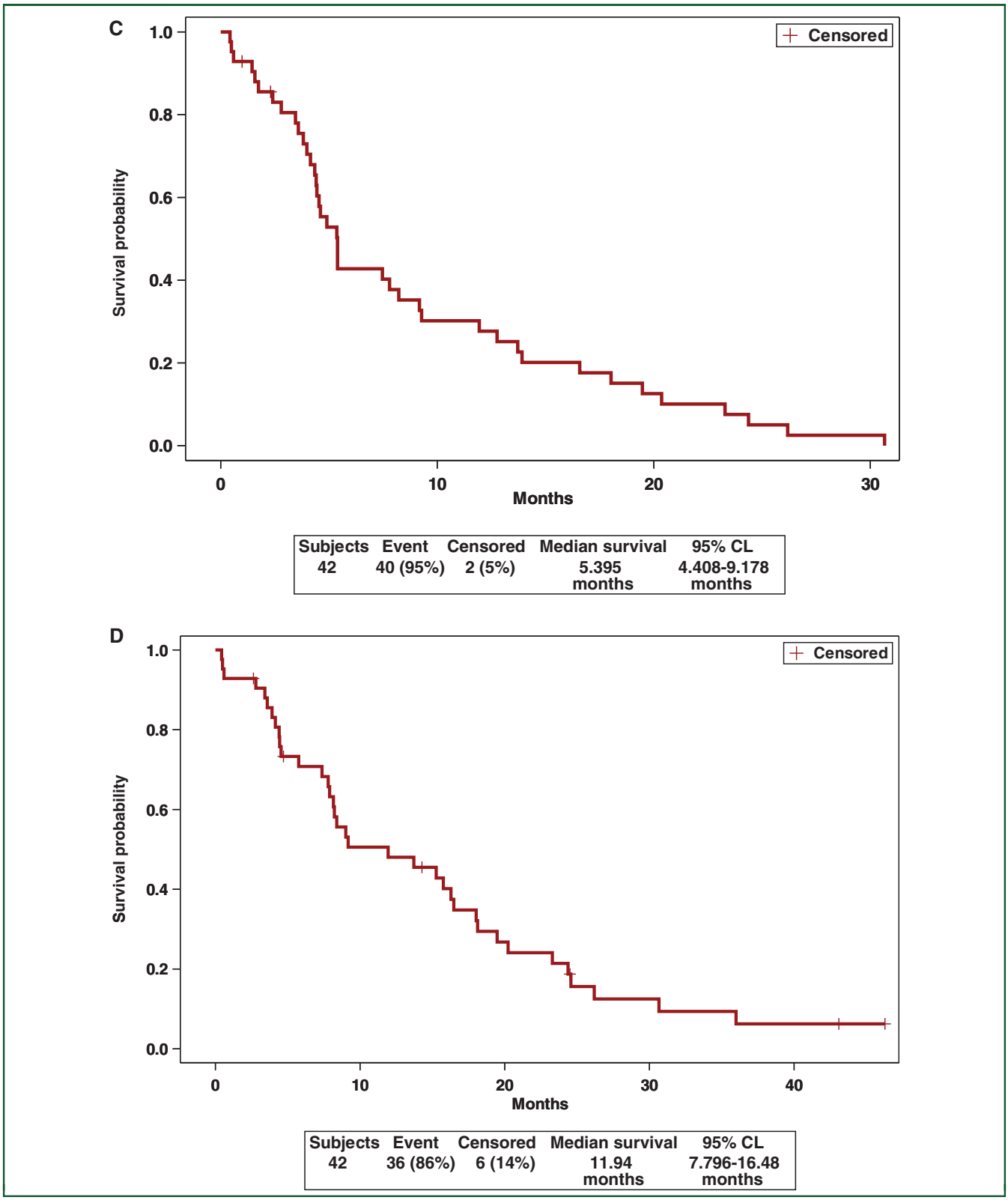

Figure 2. Continued.

The observed increase in GnP-related toxicities and the need for dose interruptions (26 patients in the 15 mg/kg group) and dose reductions of elraglusib (11 patients from 15 mg/kg to 9.3 mg/kg, 4 patients from 15 mg/kg to 12.4 mg/kg, and 2 patients from 15 mg/kg to 7 mg/kg) led to a protocol amendment to reduce elraglusib dosing to 9.3 mg/kg twice weekly for better tolerance (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.105122).

Table 3. TEAEs of any grade reported in ≥20% of patients treated with elraglusib/GnP (intention-to-treat population)

Adverse event	Patients, *n* (%) (*N* = 42)	
	Any grade	Grade ≥3
Any TEAE	42 (100.0)	36 (85.7)
Serious TEAE	31 (73.8)	27 (64.3)
Leading to treatment discontinuation	9 (21.4)	7 (16.7)
Leading to death	4 (9.5)	4 (9.5)
TEAEs of any grade in ≥20% of patients		
Visual impairment[a]	35 (83.3)	2 (4.8)
Fatigue	29 (69.0)	9 (21.4)
Nausea	28 (66.7)	1 (2.4)
Diarrhea	28 (66.7)	6 (14.3)
Neutropenia/neutrophil count decreased[b]	25 (59.5)	22 (52.4)
Decreased appetite	22 (52.4)	2 (4.8)
Abdominal pain	21 (50.0)	3 (7.1)
Leukopenia/white blood cell count decreased	21 (50.0)	18 (42.9)
Anemia	20 (47.6)	7 (16.7)
Thrombocytopenia/platelet count decreased	20 (47.6)	4 (9.5)
Constipation	20 (47.6)	0
Pyrexia	19 (45.2)	0
Vomiting	17 (40.5)	2 (4.8)
Chills	14 (33.3)	0
Insomnia	14 (33.3)	0
Myalgia	13 (31.0)	0
Hyponatremia	13 (31.0)	4 (9.5)
Headache	12 (28.6)	0
Hypokalemia	12 (28.6)	3 (7.1)
Aspartate aminotransferase increased	12 (28.6)	3 (7.1)
Muscular weakness	11 (26.2)	1 (2.4)
Dyspnea	11 (26.2)	0
Edema peripheral	11 (26.2)	0
Hypotension	11 (26.2)	1 (2.4)
Pain in extremity	9 (21.4)	0
Alopecia	9 (21.4)	0
Dysgeusia	9 (21.4)	0
Asthenia	9 (21.4)	2 (4.8)
Acute kidney injury	9 (21.4)	3 (7.1)

Additional TEAEs included febrile neutropenia in 8 (19%) patients and sepsis in 8 (19%) patients; all were grade ≥3.
GnP, gemcitabine plus nab-paclitaxel; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.
[a]Visual impairment includes MedDRA preferred terms of vision blurred, dyschromatopsia (color vision change), diplopia (double vision), photopsia, and visual impairment. Two patients reported two different TEAEs classified as visual impairment but are counted only once.
[b]Assessment of the events was made on the basis of laboratory values.

DISCUSSION

This study is the first prospective study to evaluate the clinical efficacy and safety of elraglusib/GnP in patients with previously untreated mPDAC. We report ORR of 37.9% and DCR of 51.7% with elraglusib/GnP in the EE population and ORR of 26.2% and DCR of 35.7% in the ITT population. The DCR was observed at higher rates among patients with higher reductions in CA 19-9 levels (i.e. ≥50% or ≥90%) from baseline compared with those with reductions of <50% from baseline (Supplementary Tables S1 and S2, available at https://doi.org/10.1016/j.esmoop.2025.105122). The primary endpoint could not be fully assessed, as the required 60 patient enrollment was not met and the upper DCR threshold of 65% was not achieved.

The preliminary clinical activity of elraglusib/GnP can be benchmarked against GnP in previously untreated mPDAC. The phase III MPACT study by Von Hoff et al.[8] reported an ORR of 23% (investigator-assessed ORR of 29%) and a DCR of 48% for GnP in the ITT population, and the phase III NAPOLI-3 study by Wainberg et al.[9] reported an ORR of 36% for GnP in the ITT population. While the tumor response in our study appears comparable to these large studies, up to 75% of assessable patients in our study had reduced tumor burden on the waterfall plot (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105122), demonstrating antitumor activity of the elraglusib/GnP combination. In the MPACT study, GnP led to a median PFS of 5.5 months and a median OS of 8.5 months, and the NAPOLI-3 study reported a median PFS of 5.6 months and a median OS of 9.2 months in the GnP arm.[8,9] In our study, the addition of elraglusib to GnP led to a comparable median PFS of 5.4 months for both populations—the ITT and EE. The median OS of 15.3 months and 11.9 months in the EE and ITT populations, respectively, compared favorably with these phase III studies using GnP in a similar population. Similarly, the 1-year survival estimates for OS of 56.1% (95% CI, 35.7% to 72.2%) in the EE and 48% (95% CI 32.1% to 62.3%) in the ITT populations suggest a modest numerical benefit for elraglusib/GnP in mPDAC over the 1-year historical survival estimate for GnP of 35%.[8] Additionally, the median OS for the ITT and EE populations in our study compares favorably against the reported median OS ranging from 6.9 months to 14.7 months in a meta-analysis of 22 small clinical studies using GnP as the first-line treatment of mPDAC.[32] Nevertheless, any interpretation or comparison of these efficacy analyses requires caution given the small size and lack of a control arm in our study. This further supports the decision to initiate a randomized phase II study comparing elraglusib/GnP with GnP in lieu of completing the stage 2 enrollment of Simon's two-stage design for this study.

In our study, 20/42 (47.6%) patients in the ITT population [and 17/29 (58.6%) in the EE population] received a second-line treatment. For comparison, 54% patients in the GnP arm in the NAPOLI-3 study also received a second-line treatment, with a reported median OS of 9.2 months.[9] Our ongoing randomized study will provide further insight into the combination's efficacy and the contribution of second-line treatments to overall clinical benefit.

About three out of four patients experienced a visual impairment due to elraglusib, an adverse event attributable to elraglusib and previously observed in the phase I study.[29] Reported visual impairments mostly involved visual disturbances/changes and darkened vision.[29] These were grade 1 or 2 in severity and fully resolved shortly after completion of infusion without any lasting effects. Inhibiting GSK-3β within photoreceptor cells of the retina[33] may lead to this transient and reversible visual impairment. This is likely a class effect of GSK-3β inhibitors and characterized by alterations in perception of color and contrast. Clinical studies

with another GSK-3β inhibitor, LY2090314, also previously revealed grade 1 or 2 vision disorders.[34,35]

The overall rate of grade 3 or higher TEAEs with elraglusib/GnP in our study (85.7%) was similar to previously reported rates for GnP in other randomized studies for mPDAC (83.9% in CanStem111P by Bekaii-Saab et al. and 86% in NAPOLI-3).[9,36] The incidence of individual grade 3 or higher TEAEs for elraglusib/GnP resembles the incidence patterns for GnP from phase III studies with no new unexpected safety signals for GnP (Supplementary Table S9, available at https://doi.org/10.1016/j.esmoop.2025.105122).[8,9,36]

Most grade 3 or higher TEAEs were managed by dose interruptions or reductions in either elraglusib, gemcitabine, or nab-paclitaxel (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.105122). Dose interruptions or delays were more common for elraglusib (71.4%) than for gemcitabine (59.5%) or nab-paclitaxel (61.9%). At the same time, dose reductions were less frequent for elraglusib (40.5%) than for gemcitabine (45.2%) or nab-paclitaxel (54.8%). The addition of elraglusib 15 mg/kg to GnP may have exacerbated some of the expected toxicities associated with GnP alone (Supplementary Table S9, available at https://doi.org/10.1016/j.esmoop.2025.105122), although no new safety signals were observed. Given the need for frequent dose reductions or interruption of GnP and elraglusib at the 15 mg/kg dose, the observed data may not represent the full potential of the combination in mPDAC. To address the exacerbation of toxicities, the RP2D for elraglusib was reduced to 9.3 mg/kg twice weekly for the randomized phase II study. This study will also explore the weekly dosing of elraglusib in combination with GnP.

Grade 3 or 4 neutropenia/febrile neutropenia were observed during cycle 1 in 22/42 (52%) of patients in the ITT population. Neutrophils have a short half-life and rapid turnover contributing to an early indication of myelosuppression. Dose adjustments and interruptions mitigated these neutropenia events, and only eight patients received growth factor support. Dose reductions in the chemotherapy backbone were observed in 41% versus 47% of patients for gemcitabine and 52% versus 41% for nab-paclitaxel, respectively, when compared with the MPACT study.[8] Relative dose intensities of 72% versus 75% for gemcitabine and 68% versus 81% for nab-paclitaxel were still achieved in our study compared with the MPACT study.[8]

Frequent dose interruptions and reductions were observed with elraglusib (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.105122). The initial RP2D for elraglusib of 15 mg/kg twice weekly was based on the phase I study that included 26 patients with refractory mPDAC who were previously treated with GnP.[29] Elraglusib, at doses ranging from 3.3 to 15 mg/kg twice weekly, in combination with GnP was well tolerated, justifying the 15 mg/kg RP2D in combination with GnP for the first-line setting. However, the inclusion of mPDAC patients who previously tolerated or were compliant with GnP may have contributed to a selection bias in the phase I study, and thus a RP2D of elraglusib at 15 mg/kg twice weekly may have been too high when combined with GnP in previously untreated mPDAC.

Our study included treatment-naïve patients with mPDAC, and 17/42 (40.5%) of the patients in the ITT and 17/29 (58.6%) in the EE populations required elraglusib dose reduction to improve tolerability (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.105122). This study enrolled over 80% of patients with ECOG PS $\geq$1. Dose decrease to elraglusib 9.3 mg/kg twice weekly led to a better tolerance for the four patients enrolled at this dose, contributing to the selection of an updated RP2D at 9.3 mg/kg twice weekly for the randomized study in mPDAC. Pharmacokinetic data from the phase I study demonstrated that plasma exposures at or above therapeutic levels (1 μM) were observed for >24 h at this dose of elraglusib (9.3 mg/kg).[29]

Grade 4 neutropenia significantly correlated with CR or PR in this study (Supplementary Tables S4 and S5, available at https://doi.org/10.1016/j.esmoop.2025.105122). In prior studies, Grade 3 or 4 neutropenia in cycle 1 correlated with improved survival in patients with mPDAC treated with either gemcitabine-based therapies or FOLFIRINOX.[37-41] Elraglusib inhibits the α and β isoforms of GSK-3 with similar potency but exerts antitumor effects through the β isoform. The inhibition of GSK-3α regulating the function of neutrophils may exacerbate GnP-mediated neutropenia.[42] GSK-3 inhibitors suppress the differentiation but promote the self-renewal of hematopoietic stem cells, resulting in their sensitivity to and the destruction of neutrophil precursors by cytotoxic agents such as GnP.[43] This aligns with minimal neutropenia for elraglusib monotherapy (Supplementary Table S9, available at https://doi.org/10.1016/j.esmoop.2025.105122).

Additionally, the reduction to 9.3 mg/kg twice weekly mitigated elraglusib-associated port-related issues, observed in five patients on elraglusib 15 mg/kg twice weekly (Supplementary Table S8, available at https://doi.org/10.1016/j.esmoop.2025.105122). GnP is rarely associated with port-related issues.[9] Elraglusib is a lipophilic drug, and repeated infusions over prolonged time may cause drug deposition in the port or catheter tip. Reducing to 9.3 mg/kg decreased the concentration of elraglusib in the infusion solution, helping to avoid long-term port-related issues. The randomized phase II study will provide further data regarding port-related issues. An oral form of elraglusib is in development, which may further mitigate occlusion concerns.

Our study had some limitations. The expected 60 patient enrollment was not completed, leading to the incomplete assessment of the primary endpoint. The study was non-randomized. Additionally, given the dose reductions and interruptions related to the exacerbations of GnP toxicities with the 15 mg/kg twice weekly dosing, the RP2D for elraglusib was reduced to 9.3 mg/kg twice weekly. Patients displayed better tolerance with the 9.3 mg/kg dose, and this dose is still expected to have clinical activity based on the pharmacokinetic data.[29]

Given the positive trends in the preliminary clinical activity, the randomized phase II study has been initiated to compare the efficacy and safety of elraglusib/GnP versus GnP at the reduced RP2D for elraglusib of 9.3 mg/kg in previously untreated mPDAC. The study will assess two dosing regimens of elraglusib, 9.3 mg/kg once or twice weekly, and will also evaluate predose plasma cytokine profiles and their correlations with clinical outcomes. Plasma cytokines may serve as biomarkers of immunomodulatory activity[44] and have shown predictive value in other cancer types.[45,46] Preliminary data support the predictive value of predose plasma cytokines based on our phase I and phase II studies.[47,48] Preliminary mutational analysis suggests wild-type *KRAS*, *TP53*, and *CDKN2A* genes were associated with better OS with elraglusib/GnP but not with GnP in mPDAC in the ongoing phase II study.[49] In addition, preliminary results from an ongoing study (NCT05077800) indicated tumor response with the combination of elraglusib/FOLFIRINOX and losartan in mPDAC.[50]

Conclusions

Elraglusib/GnP demonstrated preliminary evidence of benefit as first-line treatment in previously untreated mPDAC. Elraglusib resulted in a modest exacerbation of GnP-related toxicities. Given the higher-than-expected withdrawal rate related to chemotherapy adverse events, possibly compounded by elraglusib and the elraglusib-associated port-related issues at higher doses, the updated RP2D of elraglusib is 9.3 mg/kg when combined with GnP. The results of this phase II study support the ongoing randomized comparative study of elraglusib/GnP versus GnP in previously untreated mPDAC.

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DISCLOSURE

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DM: research funding from Amgen, Merck, Oncolytics, and Rafael; scientific advisory board for Actuate and Qurient; an advisory/speaker bureau for Amgen, BMS, Eisai, and Exelixis; and institutional research funding from Acepodia, Actuate Therapeutics, ADC Therapeutics, Amgen, AVEO, Bayer, Blueprint Medicines, Bristol Myers Squibb (BMS), BioNTech, Dialectic Therapeutics, Epizyme, Fujifilm, ImmuneSensor, Immune-Onc Therapeutics, Leap Therapeutics, Lycera Corp, Merck, Millennium, MiNA Alpha, NGM Biopharmaceuticals, Novartis, Oncolytics, Orano Med, Puma, Qurient, Rafael, Repare Therapeutics, Triumvira Immunologics, Vigeo Therapeutics, and Werewolf Therapeutics.

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REFERENCES

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin*. 2024;74(1):12-49.
2. European Commission. Estimates of cancer incidence and mortality in 2022, for all countries. European Cancer Information System. Available at https://ecis.jrc.ec.europa.eu/explorer.php. Accessed February 23, 2024.
3. American Cancer Society. Cancer facts & figures 2024. American Cancer Society. 2024. Available at https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2024/2024-cancer-facts-and-figures-acs.pdf. Accessed February 23, 2024.
4. Partyka O, Pajewska M, Kwaśniewska D, et al. Overview of pancreatic cancer epidemiology in Europe and recommendations for screening in high-risk populations. *Cancers (Basel)*. 2023;15(14):3634.
5. National Comprehensive Cancer Network. Pancreatic adenocarcinoma (Version 1.2024). Updated December 13, 2023. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed February 26, 2024.
6. Conroy T, Pfeiffer P, Vilgrain V, et al. Pancreatic cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34(11):987-1002.
7. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364(19):1817-1825.
8. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*. 2013;369(18):1691-1703.
9. Wainberg ZA, Melisi D, Macarulla T, et al. NALIRIFOX versus nab-paclitaxel and gemcitabine in treatment-naive patients with metastatic pancreatic ductal adenocarcinoma (NAPOLI 3): a randomised, open-label, phase 3 trial. *Lancet*. 2023;402(10409):1272-1281.
10. Woodgett JR. Molecular cloning and expression of glycogen synthase kinase-3/factor A. *EMBO J*. 1990;9(8):2431-2438.
11. Walz A, Ugolkov A, Chandra S, et al. Molecular pathways: revisiting glycogen synthase kinase-3β as a target for the treatment of cancer. *Clin Cancer Res*. 2017;23(8):1891-1897.
12. Ougolkov AV, Fernandez-Zapico ME, Savoy DN, Urrutia RA, Billadeau DD. Glycogen synthase kinase-3beta participates in nuclear factor kappaB-mediated gene transcription and cell survival in pancreatic cancer cells. *Cancer Res*. 2005;65(6):2076-2081.
13. Botrus G, Kosirorek H, Sonbol MB, et al. Circulating tumor DNA-based testing and actionable findings in patients with advanced and metastatic pancreatic adenocarcinoma. *Oncologist*. 2021;26(7):569-578.
14. Zhang JS, Herreros-Villanueva M, Koenig A, et al. Differential activity of GSK-3 isoforms regulates NF-κB and TRAIL- or TNFα induced apoptosis in pancreatic cancer cells. *Cell Death Dis*. 2014;5(3):e1142.
15. Ugolkov A, Qiang W, Bondarenko G, et al. Combination treatment with the GSK-3 inhibitor 9-ING-41 and CCNU cures orthotopic chemoresistant glioblastoma in patient-derived xenograft models. *Transl Oncol*. 2017;10(4):669-678.
16. Ugolkov A, Gaisina I, Zhang JS, et al. GSK-3 inhibition overcomes chemoresistance in human breast cancer. *Cancer Lett*. 2016;380(2):384-392.
17. Doble BW, Woodgett JR. GSK-3: tricks of the trade for a multi-tasking kinase. *J Cell Sci*. 2003;116(Pt 7):1175-1186.
18. Ougolkov AV, Bone ND, Fernandez-Zapico ME, Kay NE, Billadeau DD. Inhibition of glycogen synthase kinase-3 activity leads to epigenetic silencing of nuclear factor kappaB target genes and induction of apoptosis in chronic lymphocytic leukemia B cells. *Blood*. 2007;110(2):735-742.
19. Park R, Coveler AL, Cavalcante L, Saeed A. GSK-3β in pancreatic cancer: spotlight on 9-ING-41, its therapeutic potential and immune modulatory properties. *Biology (Basel)*. 2021;10(7):610.
20. Taylor A, Rudd CE. Small molecule inhibition of glycogen synthase kinase-3 in cancer immunotherapy. *Adv Exp Med Biol*. 2019;1164:225-233.
21. Huntington KE, Louie AD, Srinivasan PR, et al. GSK-3 inhibitor elraglusib enhances tumor-infiltrating immune cell activation in tumor biopsies and synergizes with anti-PD-L1 in a murine model of colorectal cancer. *Int J Mol Sci*. 2023;24(13):10870.
22. Pal K, Cao Y, Gaisina IN, et al. Inhibition of GSK-3 induces differentiation and impaired glucose metabolism in renal cancer. *Mol Cancer Ther*. 2014;13(2):285-296.
23. Wu X, Stenson M, Abeykoon J, et al. Targeting glycogen synthase kinase 3 for therapeutic benefit in lymphoma. *Blood*. 2019;134(4):363-373.
24. Kuroki H, Anraku T, Kazama A, et al. 9-ING-41, a small molecule inhibitor of GSK-3beta, potentiates the effects of anticancer therapeutics in bladder cancer. *Sci Rep*. 2019;9(1):19977.
25. Anraku T, Kuroki H, Kazama A, et al. Clinically relevant GSK-3β inhibitor 9-ING-41 is active as a single agent and in combination with other antitumor therapies in human renal cancer. *Int J Mol Med*. 2020;45(2):315-323.
26. Ding L, Madamsetty VS, Kiers S, et al. Glycogen synthase kinase-3 inhibition sensitizes pancreatic cancer cells to chemotherapy by abrogating the TopBP1/ATR-mediated DNA damage response. *Clin Cancer Res*. 2019;25(21):6452-6462.
27. Shimasaki T, Ishigaki Y, Nakamura Y, et al. Glycogen synthase kinase 3β inhibition sensitizes pancreatic cancer cells to gemcitabine. *J Gastroenterol*. 2012;47(3):321-333.
28. Edderkaoui M, Chheda C, Soufi B, et al. An inhibitor of GSK3β and HDACs kills pancreatic cancer cells and slows pancreatic tumor growth and metastasis in mice. *Gastroenterology*. 2018;155(6):1985-1998.e1985.
29. Carneiro BA, Cavalcante L, Mahalingam D, et al. Phase I study of elraglusib (9-ING-41), a glycogen synthase kinase-3β inhibitor, as monotherapy or combined with chemotherapy in patients with advanced malignancies. *Clin Cancer Res*. 2024;30(3):522-531.
30. Engle JA, Traynor AM, Campbell TC, et al. Assessment of adherence and relative dose intensity with oral chemotherapy in oncology clinical

trials at an academic medical center. *J Oncol Pharm Pract*. 2018;24(5):348-353.
31. Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials*. 1989;10(1):1-10.
32. Zhang Y, Xu J, Hua J, et al. Nab-paclitaxel plus gemcitabine as first-line treatment for advanced pancreatic cancer: a systematic review and meta-analysis. *J Cancer*. 2019;10(18):4420-4429.
33. Pérezleón JA, Osorio-Paz I, Francois L, Salceda R. Immunohistochemical localization of glycogen synthase and GSK3β: control of glycogen content in retina. *Neurochem Res*. 2013;38(5):1063-1069.
34. Rizzieri DA, Cooley S, Odenike O, et al. An open-label phase 2 study of glycogen synthase kinase-3 inhibitor LY2090314 in patients with acute leukemia. *Leuk Lymphoma*. 2016;57(8):1800-1806.
35. Gray JE, Infante JR, Brail LH, et al. A first-in-human phase I dose-escalation, pharmacokinetic, and pharmacodynamic evaluation of intravenous LY2090314, a glycogen synthase kinase 3 inhibitor, administered in combination with pemetrexed and carboplatin. *Invest New Drugs*. 2015;33(6):1187-1196.
36. Bekaii-Saab T, Okusaka T, Goldstein D, et al. Napabucasin plus nab-paclitaxel with gemcitabine versus nab-paclitaxel with gemcitabine in previously untreated metastatic pancreatic adenocarcinoma: an adaptive multicentre, randomised, open-label, phase 3, superiority trial. *EClinicalMedicine*. 2023;58:101897.
37. Roviello G, Ramello M, Catalano M, et al. Association between neutropenia and survival to nab-paclitaxel and gemcitabine in patients with metastatic pancreatic cancer. *Sci Rep*. 2020;10(1):19281.
38. Chen Y, Shi Y, Yan H, Wang YR, Dai GH. Timing of chemotherapy-induced neutropenia: the prognostic factor in advanced pancreatic cancer patients treated with gemcitabine/gemcitabine-based chemotherapy. *Oncotarget*. 2017;8(39):66593-66600.
39. Yamada Y, Fujii H, Watanabe D, et al. Severe neutropenia is associated with better clinical outcomes in patients with advanced pancreatic cancer who receive modified FOLFIRINOX therapy. *Cancers (Basel)*. 2018;10(11):454.
40. Kurihara T, Kogo M, Ishii M, et al. Chemotherapy-induced neutropenia as a prognostic factor in patients with unresectable pancreatic cancer. *Cancer Chemother Pharmacol*. 2015;76(6):1217-1224.
41. Kasi PM, Grothey A. Chemotherapy-induced neutropenia as a prognostic and predictive marker of outcomes in solid-tumor patients. *Drugs*. 2018;78(7):737-745.
42. Giambelluca MS, Cloutier N, Rollet-Labelle E, Boilard E, Pouliot M. Expression and regulation of glycogen synthase kinase 3 in human neutrophils. *Int J Biochem Cell Biol*. 2013;45(11):2660-2665.
43. Trowbridge JJ, Xenocostas A, Moon RT, Bhatia M. Glycogen synthase kinase-3 is an in vivo regulator of hematopoietic stem cell repopulation. *Nat Med*. 2006;12(1):89-98.
44. Hofman P, Heeke S, Alix-Panabières C, Pantel K. Liquid biopsy in the era of immuno-oncology: is it ready for prime-time use for cancer patients? *Ann Oncol*. 2019;30(9):1448-1459.
45. Chen T, Wang M, Chen Y, Cao Y, Liu Y. Advances in predictive biomarkers associated with immunotherapy in extensive-stage small cell lung cancer. *Cell Biosci*. 2024;14(1):117.
46. Almeida JS, Sousa LM, Couceiro P, et al. Peripheral immune profiling of soft tissue sarcoma: perspectives for disease monitoring. *Front Immunol*. 2024;15:1391840.
47. Weiskittel T, Huntington K, Zhang L, et al. Abstract 6426: Identification of potential immune biomarkers for GSK-3 inhibitor elraglusib (9-ING-41) in patients with relapsed/refractory metastatic cancer. *Cancer Res*. 2024;84:6426.
48. Weiskittel T, Koukol A, Kellinger C, et al. Identification of immune biomarkers in treatment-naive patients with metastatic pancreatic cancer treated with the GSK-3 inhibitor elraglusib (9-ING-41) in combination with gemcitabine/nab-paclitaxel in the 1801 phase 2 study. *J Clin Oncol*. 2024;42(suppl 16):e16331.
49. Ugolkov A, Weiskittel T, Koukol A, Kellinger C, Li H, Mazar AP. Mutational analysis of cfDNA to identify predictive biomarkers in previously untreated patients with metastatic pancreatic cancer receiving the GSK-3 inhibitor elraglusib (9-ING-41) in combination with gemcitabine/nab-paclitaxel in the 1801 phase 2 study. *J Clin Oncol*. 2024;42(suppl 16):e16306.
50. Pathak P, Lin E, Phillips I, Ting D, Weekes C. Abstract C073: FOLFIRINOX with glycogen synthase kinase-3 beta (GSK-3β) inhibitor elraglusib and transforming growth factor- β (TGFβ) inhibitor losartan in untreated metastatic pancreatic ductal adenocarcinoma (PDAC): interim analysis of safety cohort. *Cancer Res*. 2024;84:C073.

Appendix

Supplementary Information

The supplementary information provides additional information and tables and figures with more detailed data for the efficacy and safety of elraglusib.

Inclusion criteria for laboratory function within specified parameters:

a. Adequate bone marrow function: absolute neutrophil count ≥ 500/microL; hemoglobin ≥ 8.5 g/dL, platelets ≥ 75,000/microL;
b. Adequate liver function: transaminases (aspartate aminotransferase/ alanine aminotransferase [AST/ALT]) and alkaline phosphatase ≤ 3 (≤ 10 X the upper limit of normal [ULN] in the setting of liver metastasis or infiltration with malignant cells) x ULN; bilirubin ≤ 1.5 x ULN;
c. Adequate renal function: creatinine clearance ≥ 30 mL/min (Cockcroft and Gault);
d. Serum amylase and lipase ≤ 1.5 x ULN.

Supplementary Tables

Table S1. Response to Elraglusib/GnP by CA 19-9 Tumor Marker Reductions at 50% Cutoff.

Response	CA 19-9 ≥ 50% Maximum Reduction from Baseline			CA 19-9 < 50% Maximum Reduction from Baseline		
	9.3 mg/kg (N=2)	15.0 mg/kg (N=12)	Total (N=14)	9.3 mg/kg (N=2)	15.0 mg/kg (N=13)	Total (N=15)
Complete Response (CR)	0 (0%)	1 (8.3%)	1 (7.1%)	0 (0%)	1 (7.7%)	1 (6.7%)
Partial Response (PR)	1 (50.0%)	4 (33.3%)	5 (35.7%)	0 (0%)	4 (30.8%)	4 (26.7%)
Stable Disease (SD) ≥16 weeks	1 (50.0%)	3 (25.0%)	4 (28.6%)	0 (0%)	0 (0%)	0 (0%)
Stable Disease (SD) <16 weeks	0 (0%)	3 (25.0%)	3 (21.4%)	1 (50.0%)	7 (53.8%)	8 (53.3%)
Progressive Disease (PD)	0 (0%)	1 (8.3%)	1 (7.1%)	1 (50.0%)	1 (7.7%)	2 (13.3%)
Not Done	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Disease Control Rate (CR+PR+SD ≥ 16 weeks)	2 (100.0%)	8 (66.7%)	10 (71.4%)	0 (0%)	5 (38.5%)	5 (33.3%)
Exact 95% CI (Responders)	(15.8, 100)	(34.9, 90.1)	(41.9, 91.6)	(0.0, 84.2)	(13.9, 68.4)	(11.8, 61.6)

Abbreviations: CA, carbohydrate antigen; GnP, gemcitabine plus nab-paclitaxel

Table S2. Response to Elraglusib/GnP by CA 19-9 Tumor Marker Reductions at 90% Cutoff.

Response	CA 19-9 ≥ 90% Maximum Reduction from Baseline			CA 19-9 < 90% Maximum Reduction from Baseline		
	9.3 mg/kg (N=2)	15.0 mg/kg (N=5)	Total (N=7)	9.3 mg/kg (N=2)	15.0 mg/kg (N=20)	Total (N=22)
Complete Response (CR)	0 (0%)	1 (20.0%)	1 (14.3%)	0 (0%)	1 (5.0%)	1 (4.5%)
Partial Response (PR)	1 (50.0%)	3 (60.0%)	4 (57.1%)	0 (0%)	5 (25.0%)	5 (22.7%)
Stable Disease (SD) ≥16 weeks	1 (50.0%)	1 (20.0%)	2 (28.6%)	0 (0%)	2 (10.0%)	2 (9.1%)
Stable Disease (SD) <16 weeks	0 (0%)	0 (0%)	0 (0%)	1 (50.0%)	10 (50.0%)	11 (50.0%)
Progressive Disease (PD)	0 (0%)	0 (0%)	0 (0%)	1 (50.0%)	2 (10.0%)	3 (13.6%)
Not Done	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Disease Control Rate (CR+PR+SD ≥ 16 weeks)	2 (100.0%)	5 (100.0%)	7 (100.0%)	0 (0%)	8 (40.0%)	8 (36.4%)
Exact 95% CI (Responders)	(15.8, 100)	(47.8, 100)	(59.0, 100)	(0.0, 84.2)	(19.1, 63.9)	(17.2, 59.3)

Abbreviations: CA, carbohydrate antigen; GnP, gemcitabine plus nab-paclitaxel

Table S3. Dose Interruptions and Reductions for Elraglusib and GnP and Initiation Rate of Second-line Therapy

Events	**Number of patients (N=42)**
Dose interruptions/delays for elraglusib	30 (71.4%)
15 mg/kg group (n = 38)	26
9.3 mg/kg group (n = 4)	4
Dose reductions for elraglusib	17 (40.5%)
From 15 mg/kg to 9.3 mg/kg	11
From 15 mg/kg to 12.4 mg/kg	4
From 15 mg/kg to 7 mg/kg	2
Dose interruptions/delays for gemcitabine	25 (59.5%)
15 mg/kg group (n = 38)	22
9.3 mg/kg group (n = 4)	3
Dose reductions for gemcitabine	19 (45.2%)
15 mg/kg group (n = 38)	17
9.3 mg/kg group (n = 4)	2
Dose interruptions/delays for nab-paclitaxel	26 (61.9%)
15 mg/kg group (n = 38)	22
9.3 mg/kg group (n = 4)	4
Dose reductions for nab-paclitaxel	23 (54.8%)
15 mg/kg group (n = 38)	19
9.3 mg/kg group (n = 4)	4
Initiation of second-line therapy	20 (47.6%)
FOLFIRINOX	7 (16.7%)[a]
FOLFOX	6 (14.3%)[a]
FOLFIRI	2 (4.8%)
Others	5 (11.9%)[b]

[a]Includes patients on modified regimens

[b]Other treatments consisted of capecitabine (1 patient), 5-fluorouracil plus oxaliplatin (1 patient), nanoliposomal irinotecan plus 5-fluorouracil (1 patient), 5-fluorouracil plus irinotecan plus oxaliplatin (1 patient), and anti-PD-1 plus anti-TGF-β treatment (1 patient)

Abbreviations: FOLFIRI, leucovorin plus 5-fluorouracil plus irinotecan; FOLFIRINOX, leucovorin plus 5-fluorouracil plus irinotecan plus oxaliplatin; FOLFOX, leucovorin plus 5-fluorouracil plus oxaliplatin; GnP, gemcitabine plus nab-paclitaxel; PD-1, programmed death-ligand 1; TGF-β, transforming growth factor β.

Table S4. Neutropenia Grade, Time-to-Treatment Discontinuation, and Overall Survival in Patients with Clinical Response to Elraglusib/GnP

Patient	Clinical response	Neutropenia Grade	TTD (months)	OS (months)
Patient 1	PR	Grade 4	5.4	16.3
Patient 2	PR	Grade 4	4.4	8.2
Patient 3	PR	Grade 4	12.9	20.2
Patient 4	PR	Grade 4	5.6	7.9
Patient 5	PR	Grade 2	17.6	36.0
Patient 6	PR	Grade 3	3.8	4.1
Patient 7	CR	Grade 4	9.7	15.3
Patient 8	CR	Grade 4	20.4	24.6
Patient 9	PR	Grade 4	16.9	43.1
Patient 10	PR	None	5.5	8.4
Patient 11	PR	Grade 2	5.9	7.4

Abbreviations: CR, complete response; GnP, gemcitabine plus nab-paclitaxel; OS, overall survival; PR, partial response; TTD, time-to-treatment discontinuation

Table S5. Grade 4 Neutropenia is Correlated with Clinical Response in EE Population.

EE population (N=29)	Positive for Grade 4 Neutropenia (n=8)	Negative for Grade 4 Neutropenia (n=21)
Clinical response[a]	7 (87.5%)	4 (19%)
No clinical response	1 (12.5%)	17 (81%)

[a]Clinical response defined as complete or partial response

Fisher's exact test, P=0.01

Abbreviations: EE, efficacy evaluable

Table S6. TEAEs as Related to Study Treatments.

Category	Related to elraglusib	Related to gemcitabine/nab-paclitaxel
	Total (N=42)	Total (N=42)
Total Number of Related TEAEs Reported	159	588
Patients with Related TEAE	39 (92.9%)	41 (97.6%)
Patients with Serious Related TEAE	2 (4.8%)	21 (50.0%)
Patients Discontinued Due to Related TEAE	1 (2.4%)	5 (11.9%)
Patients with Grade 3 or 4 Related TEAE	10 (23.8%)	34 (81.0%)
Patient Deaths Related to Study Drug	0 (0%)	0 (0%)

Abbreviations: TEAE, treatment emergent adverse event

Table S7. Incidence of TEAEs by Grade Attributed to Study Treatment Reported ≥10% of Patients.

	Preferred Term	Total (N=42)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Related to elraglusib	Nausea	5 (11.9%)	4 (9.5%)	1 (2.4%)	0 (0%)	0 (0%)	0 (0%)
	Infusion-related reaction	5 (11.9%)	1 (2.4%)	4 (9.5%)	0 (0%)	0(0%)	0(0%)
	Fatigue	13 (31.0%)	3 (7.1%)	9 (21.4%)	1 (2.4%)	0 (0%)	0 (0%)
	Visual impairment[a]	31 (73.8%)	27 (64.3%)	2 (4.8%)	2 (4.8%)	0 (0%)	0 (0%)
Related to gemcitabine/ nab-paclitaxel	Stomatitis	5 (11.9%)	1 (2.4%)	3 (7.1%)	1 (2.4%)	0 (0%)	0 (0%)
	Hypokalemia	6(14.3%)	2 (4.8%)	2 (4.8%)	2 (4.8%)	0 (0%)	0 (0%)
	Headache	6 (14.3%)	4 (9.5%)	2 (4.8%)	0 (0%)	0 (0%)	0 (0%)
	Hyponatremia	6 (14.3%)	2 (4.8%)	1 (2.4%)	3 (7.1%)	0 (0%)	0 (0%)
	Peripheral neuropathy	6 (14.3%)	2 (4.8%)	1 (2.4%)	3 (7.1%)	0 (0%)	0 (0%)
	AST increased	7 (16.7%)	5 (11.9%)	0 (0%)	2 (4.8)	0 (0%)	0 (0%)
	Asthenia	7 (16.7%)	3 (7.1%)	3 (7.1%)	1 (2.4%)	0 (0%)	0 (0%)
	Mucosal inflammation	7 (16.7%)	4 (9.5%)	3 (7.1%)	0 (0%)	0 (0%)	0 (0%)
	Muscular weakness	7 (16.7%)	4 (9.5%)	2 (4.8%)	1 (2.4%)	0 (0%)	0 (0%)
	Peripheral edema	7 (16.7%)	7 (16.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Peripheral sensory neuropathy	7 (16.7%)	1 (2.4%)	4 (9.5%)	2 (4.8%)	0 (0%)	0 (0%)
	Rash maculo-papular	7 (16.7%)	4 (9.5%)	2 (4.8%)	1 (2.4%)	0 (0%)	0 (0%)
	Lymphocyte count decreased	8 (19.0%)	0 (0%)	3 (7.1%)	3 (7.1%)	2 (4.8%)	0 (0%)
	Alopecia	8 (19.0%)	1 (2.4%)	7 (16.7%)	0 (0%)	0 (0%)	0 (0%)
	Febrile neutropenia	8 (19.0%)	0 (0%)	0 (0%)	6 (14.3%)	2 (4.8%)	0 (0%)
	Rash	8 (19.0%)	5 (11.9%)	2 (4.8%)	1 (2.4%)	0 (0%)	0 (0%)
	Dysgeusia	9 (21.4%)	7 (16.7%)	2 (4.8%)	0 (0%)	0 (0%)	0 (0%)
	Constipation	10 (23.8%)	9 (21.4%)	1 (2.4%)	0 (0%)	0 (0%)	0 (0%)
	Myalgia	10 (23.8%)	6 (14.3%)	4 (9.5%)	0 (0%)	0 (0%)	0 (0%)
	Chills	11 (26.2%)	11 (26.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

	Preferred Term	Total (N=42)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	Vomiting	13 (31.0%)	11 (26.2%)	0 (0%)	2 (4.8%)	0 (0%)	0 (0%)
	Pyrexia	14 (33.3%)	12 (28.6%)	2 (4.8%)	0 (0%)	0 (0%)	0 (0%)
	Decreased appetite	18 (42.9%)	9 (21.4%)	8 (19.0%)	1 (2.4%)	0 (0%)	0 (0%)
	Anemia	18 (42.9%)	6 (14.3%)	7 (16.7%)	5 (11.9%)	0 (0%)	0 (0%)
	Thrombocytopenia/ platelet count decreased	19 (45.2%)	7 (16.7%)	8 (19.0%)	2 (4.8%)	2 (4.8%)	0 (0%)
	Leukopenia/white blood cell count decreased	20 (47.6%)	1 (2.4%)	2 (4.8%)	11 (26.2%)	6 (14.3%)	0 (0%)
	Nausea	24 (57.1%)	16 (38.1%)	7 (16.7%)	1 (2.4%)	0 (0%)	0 (0%)
	Diarrhea	25 (59.5%)	10 (23.8%)	9 (21.4%)	6 (14.3%)	0 (0%)	0 (0%)
	Neutropenia/neutrophil count decreased	24 (57.1%)	0 (0%)	3 (7.1%)	11 (26.2%)	10 (23.8%)	0 (0%)
	Fatigue	29 (69.0%)	6 (14.3%)	14 (33.3%)	9 (21.4%)	0 (0%)	0 (0%)

[a]Visual impairment includes vision blurred, color vision change, double vision, photopsia, and visual impairment.

Abbreviations: AST, aspartate aminotransferase; TEAE, treatment emergent adverse event

Table S8. Summary of Port-Related Issues Observed During Treatment with Elraglusib/GnP.

Patient	Study day (duration in days[a])	Dose (biweekly)	AE grade	Preferred term	Attribution	Outcome
Patient 1	5 (8)	15 mg/kg	2	Device-related infection	AE reported as superficial port infection, not related to elraglusib and not related to GnP	Resolved
Patient 2	260 (3)	15 mg/kg	2	Vascular access complication	AE reported as vascular access complication, possibly related to elraglusib and not related to GnP	Resolved
	4 (526)	15 mg/kg	2	Device-related thrombosis	AE reported as blood and lymphatic disorder, other, with clot at port prior to infusion (intermittent), possibly related to elraglusib and unlikely related to GnP	Resolved
	526 (4)	15 mg/kg	2	Vascular access complication	AE reported as vascular access complication, related to elraglusib and not related to GnP	Port replaced. Resolved.
	548 (>97)	15 mg/kg	2	Splenic vein thrombosis	AE reported as splenic vein thrombosis, unlikely	Ongoing

					related to elraglusib, possibly related to gemcitabine, unlikely related to nab-paclitaxel	
Patient 3	137 (>139)	15 mg/kg	2	Thrombosis	AE reported as thrombosis, not related to elraglusib and not related to GnP	Recovering
Patient 4	18 (>208)	15 mg/kg	2	Catheter site thrombosis	AE reported as thrombosis around PICC line, not related to elraglusib and not related to GnP	Ongoing
	18 (5)	15 mg/kg	2	Device occlusion	AE reported as vascular access complication-clogged PICC line, related to elraglusib and not related to GnP	Resolved
Patient 5	1 (142)	15 mg/kg	2	Vascular access complication	AE reported as vascular access complication (intermittent), not related to elraglusib and possibly related to GnP	Port removed. Resolved.

[a]Duration in days for port-related issues

Abbreviations: AE, adverse event; GnP, gemcitabine plus nab-paclitaxel; PICC, peripherally inserted central catheter

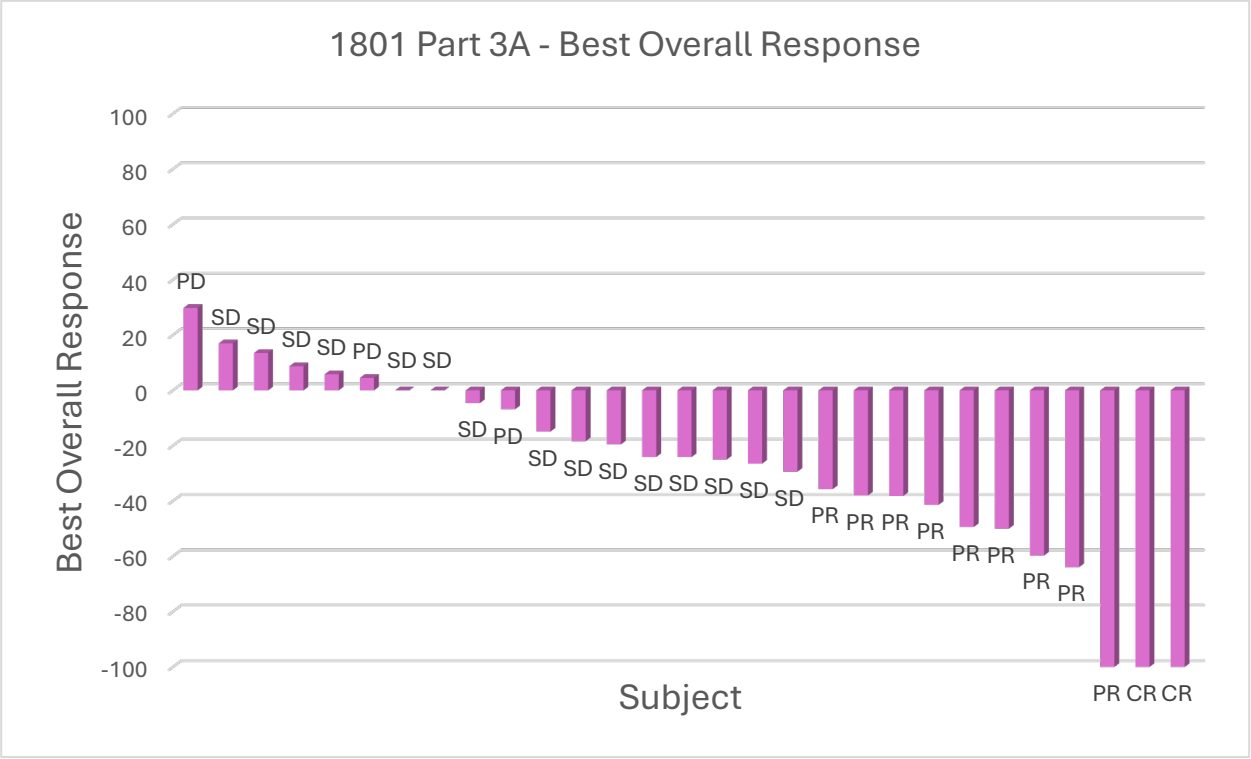
Table S9. Overview of Select Grade 3 or Higher TEAEs in Patients With mPDAC Treated With Elraglusib, Elraglusib/GnP, or GnP.

TEAEs	Elraglusib	Elraglusib/GnP	GnP		
	1801 Part 1 [29] (N=67)[a]	1801 Part 3A (N=42)	Bekaii-Saab et al. study [36] (N=547)	NAPOLI-3 [5] (N=379)	Von Hoff et al. study [8] (N=421)
Neutropenia/neutrophil count decreased	3%	52.4%	45.5%	39%	38%
Leukopenia/white blood cell count decreased	0%	42.9%	12.8%	9.2%	31%
Fatigue	3%	21.4%	NA	5.3%	17%
Anemia	6%	16.7%	19.7%	17%	13%
Febrile neutropenia	1.5%	19%	NA	2.4%	3%
Diarrhea	4.5%	14.3%	4.9%	4.5%	6%
Thrombocytopenia/platelet count decreased	0%	9.5%	NA	6.1%	13%

[a]Patients with metastatic cancer (PDAC and other histological types of solid tumors) [29]

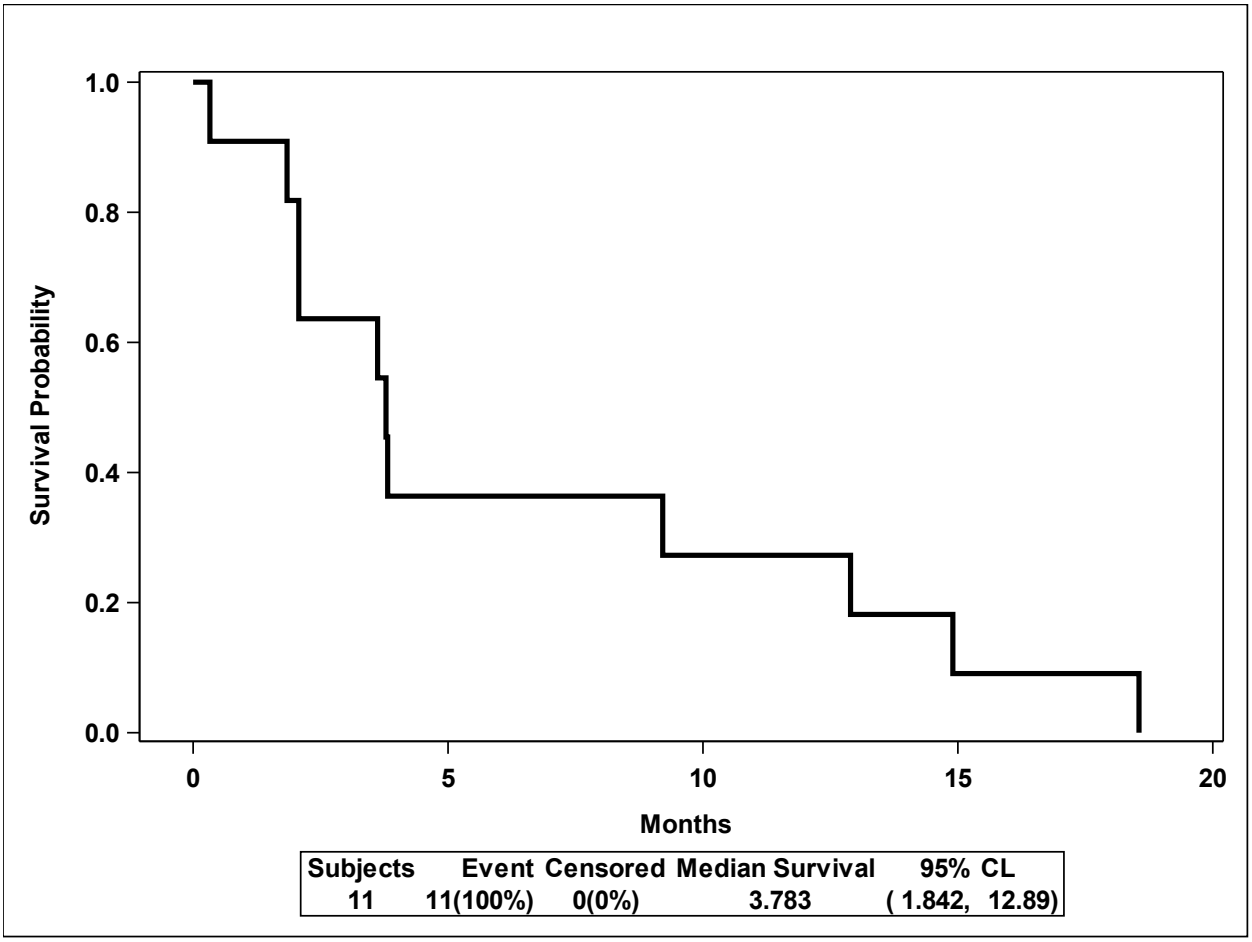
Abbreviations: GnP, gemcitabine plus nab-paclitaxel; mPDAC, metastatic pancreatic ductal adenocarcinoma; NA, not available; TEAE, treatment-emergent adverse event

Supplementary Figures



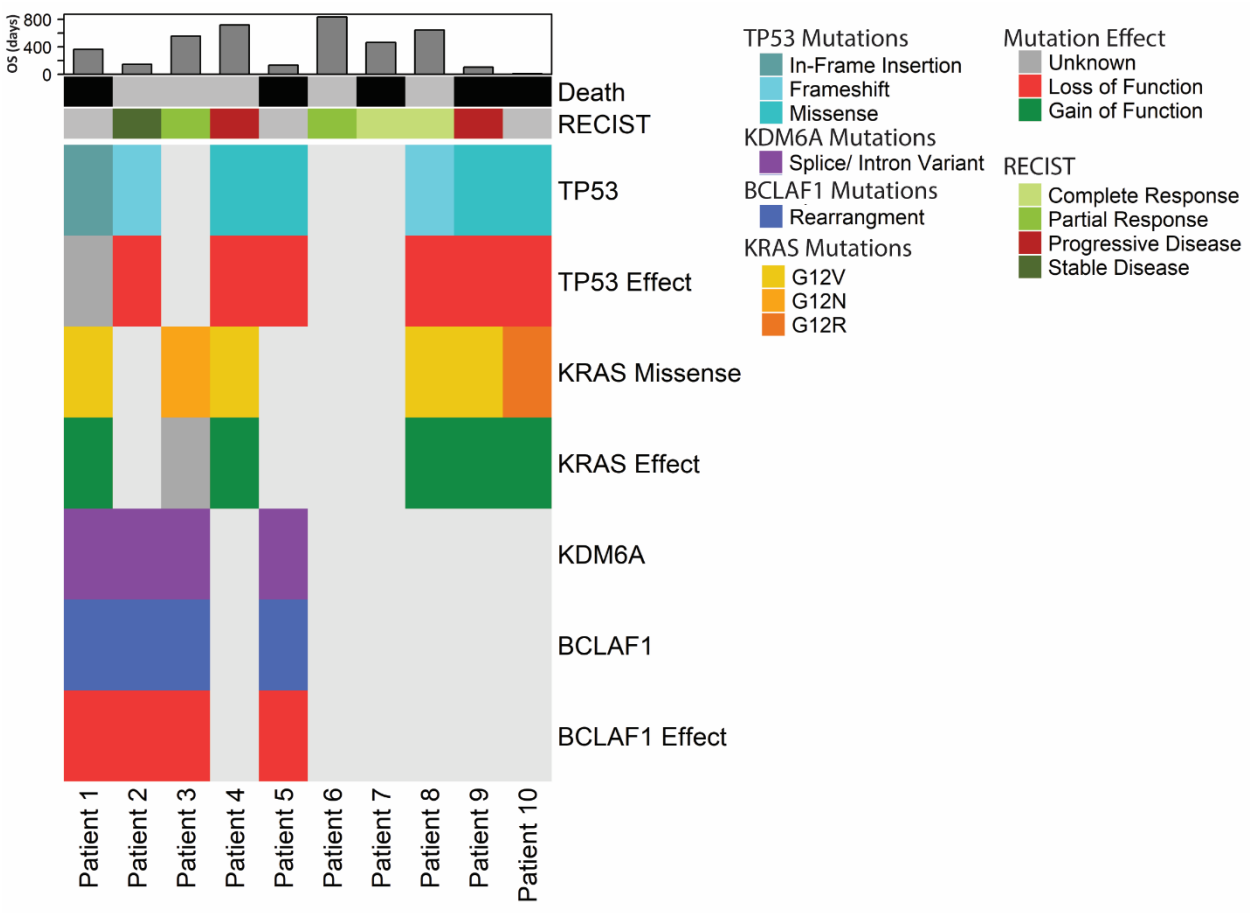
Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease

Figure S1. Best Overall Response for Efficacy Evaluable Population (N=29).



Abbreviations: CL, confidence level

Figure S2. Kaplan-Meier Estimate of the Survival Function for Duration of Response with Elraglusib/GnP in Previously Untreated Metastatic Pancreatic Cancer.



Abbreviations: OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors

Figure S3. Tumor Mutational Status (N=10) of Commonly Mutated Genes (> 2 Patients) and Their Anticipated Functional Effects.

Top bar plot annotation shows overall survival in days, the second annotation shows the death status of the patient, and the third annotation shows the RECIST response of the tumor. Figure was generated using the Complex Heatmap package in R [51].

Reference:

51. Gu Z. Complex heatmap visualization. iMeta. 2022;1(3):e43. doi:10.1002/imt2.43