nature medicine

Article

https://doi.org/10.1038/s41591-026-04327-4

Elraglusib and chemotherapy in metastatic pancreatic ductal adenocarcinoma: a randomized controlled phase 2 trial

Received: 15 October 2025

Accepted: 9 March 2026

Published online: 14 April 2026

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Metastatic pancreatic ductal adenocarcinoma (mPDAC) is one of the leading causes of cancer-related mortality, but advances in therapeutic treatments remain limited. Elraglusib (9-ING-41), an inhibitor of GSK-3β, exhibits a multimodal mechanism of action based on antitumor activity in preclinical models of cancer, including pancreatic. The efficacy and safety of elraglusib with gemcitabine plus nab-paclitaxel (GnP) were assessed in patients with previously untreated mPDAC. In an open-label, international, multicenter, phase 2 study, patients were randomized 2:1 to weekly elraglusib/GnP or GnP alone. Primary endpoints were median overall survival (OS) and 1-year survival rate. The prespecified modified intention-to-treat population included 155 patients on elraglusib/GnP and 78 on GnP. As of the data cutoff of 27 April 2025, elraglusib/GnP improved median OS by 2.9 months and decreased the risk of death by 38% versus GnP (median OS 10.1 months versus 7.2 months, respectively (hazard ratio 0.62; 95% confidence interval 0.46 to 0.84; $P = 0.01$)). The 1-year survival rates were 44.1% versus 22.3%, respectively. The safety profile of elraglusib/GnP was manageable. The most common grade 3 or higher treatment-emergent adverse events (TEAEs) with elraglusib/GnP versus GnP alone were neutropenia (52.3% versus 30.8%), anemia (25.2% versus 29.5%) and fatigue (16.8% versus 5.1%). Explorative correlative analyses demonstrated that baseline circulating immune-related factors (that is, CXCL2 and TRAIL ligands) were associated with improved survival in the elraglusib/GnP arm. Treatment was accompanied by increases in intratumoral cytotoxic immune cell populations. Together, these findings support the clinical activity of elraglusib/GnP as first-line treatment in mPDAC and provide a biological context for the observed survival benefit. Based on the results of this phase 2 trial, a phase 3 trial is being planned. ClinicalTrials.gov registration: NCT03678883

Pancreatic cancer is the third leading cause of cancer-related mortality in the United States, fourth in the European Union and seventh worldwide[1–3]. Pancreatic ductal adenocarcinoma (PDAC) represents over 90% of all pancreatic cancers[4]. About 50% to 55% of pancreatic cancer cases are metastatic at diagnosis because of lack of specific symptoms in earlier stages[5,6]

The current first-line treatment regimens for metastatic pancreatic cancer consist of 5-fluorouracil, leucovorin, irinotecan plus oxaliplatin (FOLFIRINOX); nanoliposome irinotecan plus 5-fluorouracil, leucovorin and oxaliplatin (NALIRIFOX); or gemcitabine plus nab-paclitaxel (GnP)[4,7,8]. Some concerns include toxicity with the FOLFIRINOX and NALIRIFOX regimens, limiting their use to patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 and 1 (considered as good PS), and higher cost with NALIRIFOX[4,9,10]. Recent studies also suggested that compared with classical metastatic PDAC (mPDAC), basal mPDAC is less responsive to FOLFIRINOX[11]. GnP remains

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one of three approved first-line regimens for patients with good (0–1) or intermediate (2) ECOG PS[4,7]. Median OS with GnP treatment ranges from approximately 8 to 10 months in clinical trials and approximately 7 to 10 months in the real-world setting[9,10,12–14].

Despite the increasing incidence over the past decades and the identification of potential molecular driver alterations as targets in pancreatic cancer (for example, *BRCA1* and *BRCA2*, *PALB2*, *KRAS*, *TP53*, *CDKN2A*, dMMR/MSI-H), advances in therapeutic treatments remain limited[1]. Moreover, immunotherapy that led to positive results in other solid organ cancers has failed to improve outcomes in PDAC[15–19]. Thus, a strong need remains for new therapeutic agents to help prolong survival and improve clinical outcomes in this difficult-to-manage cancer.

Glycogen synthase kinase-3 beta (GSK-3β), a serine/threonine kinase, has been identified as a potential therapeutic target in human pancreatic cancer[20]. Elraglusib (9-ING-41) is a first-in-class, cell-permeable, ATP-competitive inhibitor of GSK-3β. In preclinical cancer models, elraglusib has contributed to a range of potential antitumor activities: inhibition of cancer cell proliferation and survival, overcoming drug resistance in tumors, inhibition of epithelial–mesenchymal transition, decrease in tumor immune evasion, activation and expansion of infiltrating $CD8^+$ T cells and natural killer (NK) cells, epigenetic control of gene expression and reduction in fibrosis[21–24]. In models of pancreatic cancer, elraglusib inhibited proliferation and survival of cancer cells, sensitized cancer cells to chemotherapy agents and prevented chemoresistance[21,25,26].

Early-phase clinical trials revealed promising results with elraglusib. In a phase 1 trial, combinations of elraglusib with a variety of chemotherapy backbones led to a median OS of 6.9 months (95% confidence interval (CI) 5.7 to 8.4 months) and an acceptable safety profile in heavily pretreated patients with relapsed or refractory solid cancers or hematological malignancies[27]. Additionally, a median OS of 4.5 months was observed among 26 patients with treatment-refractory mPDAC who received elraglusib/GnP as their third-line treatment. In a single-arm, phase 2 trial in 42 patients with previously untreated mPDAC, elraglusib/GnP led to a median OS of 11.9 months (95% CI 7.8 to 16.5) and 1-year survival rate of 48% (95% CI 32.1 to 62.3) in the intention-to-treat (ITT) population[28]. This trial established a recommended phase 2 dose for elraglusib of 9.3 mg kg^{-1} administered intravenously twice weekly when combined with GnP. Because of the promising survival trends, this trial transitioned to a phase 2 randomized trial that also explored weekly dosing of elraglusib with GnP. The key objectives of this randomized phase 2 trial were to evaluate the 1-year survival rate and the median OS and correlate efficacy parameters with tumor molecular profiles of elraglusib/GnP versus GnP in patients with previously untreated mPDAC.

Results

Patient disposition and baseline characteristics

The study was conducted at 60 sites across six countries in North America and Europe. During the selection stage, 51 patients were randomized 1:1:1 into one of the three treatment arms with 17 patients treated in each of the once-weekly elraglusib/GnP, twice-weekly elraglusib/GnP and GnP arms. Once-weekly dosing was determined to be equivalent to twice-weekly dosing based on pharmacokinetics profile, 1-year survival rate and objective response rate (ORR); thus, in addition to patient preference and improved patient compliance, elraglusib 9.3 mg kg^{-1} once weekly was selected as the preferred dosing schedule. The presented results for elraglusib/GnP focus on the once-weekly dosing of elraglusib; patients from the selection and confirmation stages are included.

Between 7 October 2021 and 9 February 2024, 286 patients enrolled in the study (171 patients in the once-weekly elraglusib/GnP arm, 17 patients in the twice-weekly elraglusib/GnP arm and 98 patients in the GnP arm); 250 patients received at least one dose of treatment (Fig. 1). The modified ITT (mITT) population included 155 patients in the once-weekly elraglusib/GnP arm, 17 patients in the twice-weekly elraglusib/GnP arm and 78 in the GnP arm (Fig. 1). At the data cutoff of 27 April 2025, the most common reasons for treatment discontinuations were progressive disease (PD) (113 patients, 45.2%), clinical progression (38 patients, 15.2%) and withdrawal by participant (33 patients, 13.2%; Fig. 1). The most common reason for study withdrawal was death (185 patients, 74.0%). Six patients in the elraglusib/GnP arm were still receiving treatment and 49 patients were in the survival follow-up (41 in the elraglusib/GnP arm and eight in the GnP arm). The rest of the results present findings related to once-weekly elraglusib/GnP and GnP arms in both the mITT and ITT populations.

The key characteristics of treated patients were a median age of 66 years (range 42–86 years), male sex in 52.4% of patients and White ethnicity in 83.2% of patients with 93.2% being non-Hispanic or Latino (Table 1). Almost all patients had metastatic disease at study entry, with approximately 73% of patients presenting with metastatic disease at initial diagnosis. The most common site of metastasis was the liver (in over 70% of patients). Most patients had an ECOG PS of 0 (41.2%) or 1 (57.2%). Elevated baseline CA 19-9 levels were reported in 88% of patients, with median CA 19-9 levels of 1,568 (range 1–381,904) in the once-weekly elraglusib/GnP arm and 1,590 (range 2–501,000) in the GnP arm. Before the study, 22.6% of patients in the once-weekly elraglusib/GnP arm and 18% in the GnP arm received prior neoadjuvant or adjuvant cytotoxic chemotherapy; 27.7% and 21.8%, respectively, received prior radiotherapy.

Efficacy

In the mITT population, the median OS was increased by 2.9 months with elraglusib/GnP compared with GnP only (median OS of 10.1 months (95% CI 7.7 to 12.5) with elraglusib/GnP versus 7.2 months (95% CI 5.7 to 9.0) with GnP (HR 0.62; 95% CI 0.46 to 0.84; $P = 0.01$; Table 2 and Fig. 2a)). A survival benefit was seen as early as 2 months (Fig. 2a) and persisted throughout the study. The hazard curves continued to diverge throughout the entire study. The 1-year landmark survival rate was 44.1% (95% CI 36.0 to 51.8) with elraglusib/GnP and 22.3% (95% CI 13.8 to 32.1) with GnP. Landmark survival rates at 18 and 24 months were 20.5% (95% CI 13.4 to 28.8) and 13.2% (95% CI 6.7 to 21.8) in the elraglusib/GnP arm and 4.4% (95% CI 0.5 to 15.5) and 0 in the GnP arm, respectively.

Similarly, elraglusib/GnP led to improvements in median OS in the ITT population, where the median OS was increased by 1.7 months with elraglusib/GnP (Table 3). The median OS was 8.9 months (95% CI 7.3 to 11.9) with elraglusib/GnP and 7.2 months (95% CI 5.7 to 8.7) with GnP (HR 0.68; 95% CI 0.51 to 0.89; $P = 0.022$) (Fig. 2b). The 1-year landmark survival rate was 42.1% (95% CI 34.4 to 49.6) with elraglusib/GnP and 22.3% (95% CI 14.5 to 31.1) with GnP. Landmark survival rates at 18 and 24 months were 19.3% (95% CI 12.6 to 27.1) and 12.4% (95% CI 6.3 to 20.6) with elraglusib/GnP and 6.2% (95% CI 1.7 to 15.2) and 3.1% (95% CI 0.3 to 12.3) with GnP, respectively.

OS benefit was observed with elraglusib/GnP across the subgroups evaluated for the presence of liver metastases, ECOG status, CA 19-9 levels at baseline, and others (Extended Data Figs. 1 and 2). The analysis of patients with liver metastases at baseline revealed a 1.7-month improvement in median OS for elraglusib/GnP in the mITT population (HR 0.62; 95% CI 0.44 to 0.87; $P = 0.008$; median OS of 8.3 months (95% CI 7.1 to 11.2) for elraglusib/GnP versus 6.6 months (95% CI 5.1 to 8.0) for GnP alone). The 1-year landmark survival rates were 39.2% with elraglusib/GnP versus 15.2% with GnP alone in this subpopulation (Supplementary Fig. 1). Among patients whose CA 19-9 levels dropped by 50% or more after one treatment cycle ($n = 30$ patients); median OS displayed numerical benefit without statistical significance toward improvement with elraglusib/GnP versus GnP (32.1 months versus 10.6 months; HR 0.32; 95% CI 0.12 to 0.87; $P = 0.089$; Supplementary Fig. 2).

Elraglusib/GnP displayed numerical benefit without statistical significance toward improvement across most secondary endpoints in the mITT population (Table 2). The median progression-free survival (PFS)

https://doi.org/10.1038/s41591-026-04327-4

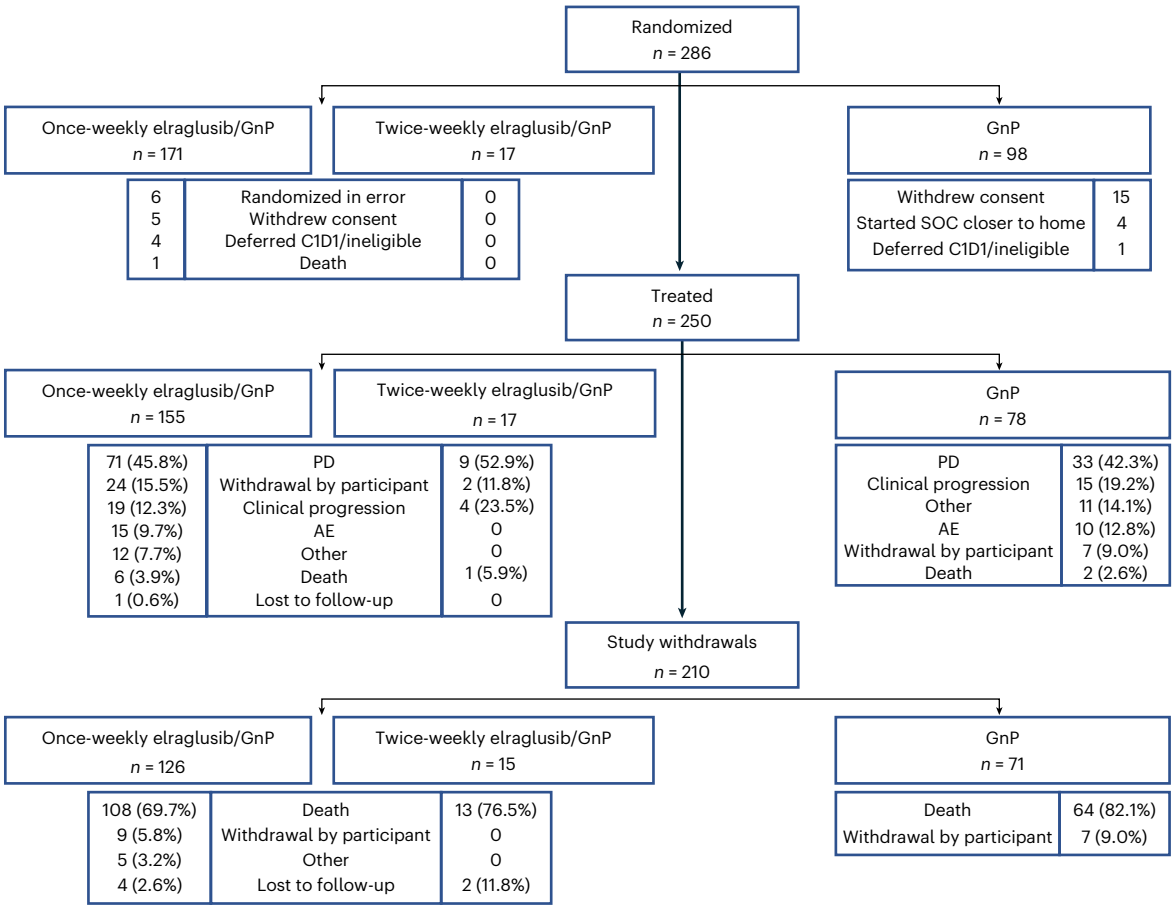

Fig. 1 | Consort diagram with patient disposition. Patient disposition throughout the study, including randomization, reasons for treatment discontinuation and reasons for study withdrawals.

was 5.6 months (95% CI 4.6 to 6.4) with elraglusib/GnP and 5.1 months (95% CI 3.2 to 6.1) with GnP (HR 0.90; 95% CI 0.68 to 1.20; $P = 0.624$; Supplementary Fig. 3). The median time to treatment failure (TTF) was 5.0 months (95% CI 3.6 to 5.6) with elraglusib/GnP and 3.4 months (95% CI 2.4 to 5.1) with GnP. ORR was observed in 44 patients (28.4%) with elraglusib/GnP and 17 patients (21.8%) with GnP (Table 2 and Supplementary Fig. 4). In the elraglusib/GnP arm, one patient achieved complete response (CR) and 43 (27.8%) patients achieved partial response (PR), including 13 patients (8.4%) with unconfirmed PR. In the GnP arm, no patients achieved CR and 17 (21.8%) patients achieved PR (confirmed and unconfirmed). The median duration of response (DOR) was 5.5 months (95% CI 3.8 to 5.8) with elraglusib/GnP and 4 months (95% CI 3.2 to 6.3) with GnP. The disease control rate (DCR) was 40.0% with elraglusib/GnP and 33.3% with GnP. Given that schedules for tumor assessment differed according to institution (assessments performed either every 8 or every 12 weeks), the DCR in our study was defined as SD, PR (including unconfirmed PR) or CR for at least 16 weeks since the first dose of the study drug, or a confirmed CR or PR.

Treatment exposure

The median duration of treatment was longer with elraglusib/GnP: 116 days (range 7–554 days; median of four treatment cycles) with elraglusib/GnP and 88 days (range 7–526 days; median of four treatment cycles) with GnP (Supplementary Table 1). More patients on elraglusib/GnP experienced dose delays or reductions (92.9% of patients on elraglusib/GnP and 84.6% of patients on GnP). Median relative dose intensities were similar for nab-paclitaxel (70% with elraglusib/GnP and 72% with GnP) and gemcitabine (74% with elraglusib/GnP and 78% with GnP). The median relative dose intensity of elraglusib was 82%.

Subsequent therapies

Subsequent systemic anticancer therapies were administered to 77 patients in the elraglusib/GnP arm and 33 in the GnP arm (Extended Data Table 1). The most common subsequent therapy was FOLFIRINOX in both treatment arms (Extended Data Table 1 and Supplementary Table 2). After transitioning to subsequent therapies, numerical benefit without statistical significance for increased median OS remained in the elraglusib/GnP arm based on the exploratory analysis: 13.3 months (95% CI 11.9 to 14.6) in the elraglusib/GnP arm versus 10.6 months (95% CI 9.0 to 12.9) in the GnP arm (HR 0.68; 95% CI 0.43 to 1.07; log-rank $P = 0.094$) among patients with subsequent therapies and 5.8 months (95% CI 4.1 to 7.1) in the elraglusib/GnP arm versus 3.4 months (95% CI 2.8 to 6.1) in the GnP arm (HR 0.69; 95% CI 0.46 to 1.03; log-rank $P = 0.064$) among patients without subsequent therapies (Extended Data Fig. 3). A large proportion of patients who did not receive subsequent therapies is still in the survival follow-up for the elraglusib/GnP arm.

Safety

Any TEAE occurred in 155 patients (100%) in the once-weekly elraglusib/GnP arm and 77 patients (98.7%) in the GnP arm, with serious TEAEs affecting a similar proportion of patients in each treatment arm (86 patients (55.5%) in the elraglusib/GnP arm and 44 patients (56.4%) in the GnP arm; Table 4). The most common TEAEs that occurred in the elraglusib/GnP arm were visual impairment ($n = 105$; 67.7% versus 9.0% with GnP), fatigue ($n = 97$; 62.6% versus 50.0% with GnP) and neutropenia ($n = 95$; 61.3% versus 41.0% with GnP), all of which occurred more frequently with elraglusib/GnP than with GnP. The most common TEAEs that were attributed to elraglusib included visual

https://doi.org/10.1038/s41591-026-04327-4

Table 1 | Patient demographics and baseline characteristics (mITT population)

Characteristic	Once-weekly elraglusib/GnP *n*=155	GnP *n*=78
Age (years)		
Mean (s.d.)	65.1 (9.1)	66.2 (9.9)
Median (range)	65.0 (42.0 to 86.0)	68.0 (42.0 to 85.0)
Sex, *n* (%)		
Female	75 (48.4)	35 (44.9)
Male	80 (51.6)	43 (55.1)
Ethnicity, *n* (%)		
White	128 (82.6)	65 (83.3)
Black or African American	7 (4.5)	6 (7.7)
Asian	5 (3.2)	2 (2.6)
Multiracial	1 (0.6)	0
Unknown/not reported	14 (9.0)	5 (6.4)
Ethnic group, *n* (%)		
Hispanic or Latino	8 (5.2)	0
Not Hispanic or Latino	141 (91.0)	77 (98.7)
Unknown/not reported	6 (3.9)	1 (1.3)
Height (in)		
Mean (s.d.)	66 (4)	67 (4)
Median (range)	67 (58 to 76)	67 (59 to 76)
Weight (lb)		
Mean (s.d.)	160.4 (37.9)	159.0 (42.2)
Median (range)	156.3 (89.3 to 335.0)	154.4 (85.3 to 343.3)
ECOG PS, *n* (%)		
0	64 (41.3)	31 (39.7)
1	89 (57.4)	45 (57.7)
2	2 (1.3)	2 (2.6)
Disease status, *n* (%)		
Metastatic at initial diagnosis	109 (70.3)	60 (76.9)
Metastatic at study entry	154 (99.4)	77 (98.7)
Site of disease/metastases, *n* (%)		
Pancreas	123 (79.4)	68 (87.2)
Liver	112 (72.3)	61 (78.2)
Lymph node	69 (44.5)	27 (34.6)
Lung	59 (38.1)	26 (33.3)
Baseline CA 19-9 (U ml^{-1}), *n* (%)	146 (94.2)	76 (97.4)
Mean (s.d.)	20,909 (54,084)	31,076 (88,065)
Median (range)	1,568 (1 to 381,904)	1,590 (2 to 501,000)
<37 U ml^{-1} (within the reference range)	17 (11.0)	11 (14.1)
≥37 U ml^{-1}	138 (89.0)	67 (85.9)

BMI, body mass index; CA, carbohydrate antigen.

impairment (66.5%), fatigue (42.6%), nausea (36.1%) and neutropenia (32.9%) (Extended Data Table 2). Elraglusib-related infusion-related reaction was reported in 24 patients (15.5%). Visual impairment and infusion-related reactions were transient.

Grade 3 or higher TEAEs were more frequent in the elraglusib/GnP arm: 139 patients (89.7%) in the elraglusib/GnP arm and 62 patients (79.5%) in the GnP arm (Table 4). The most common grade 3 or higher TEAEs with elraglusib/GnP were neutropenia (52.3% versus 30.8% with GnP), anemia (25.2% versus 29.5%) and fatigue (16.8% versus 5.1%). Of these, neutropenia and fatigue occurred more frequently with elraglusib/GnP than with GnP.

The concomitant administration of elraglusib with GnP did not increase plasma levels of nab-paclitaxel or gemcitabine (Supplementary Fig. 5). Among patients with grade 3 to 4 neutropenia, granulocyte colony-stimulating factors were administered to a similar proportion of patients: 38 (46.9%) patients on elraglusib/GnP and 11 (45.8%) on GnP. In an exploratory analysis, median OS was significantly prolonged in elraglusib/GnP-treated patients who experienced two or more grade 3 or 4 neutropenia episodes but not in GnP-treated patients (Supplementary Table 3).

TEAEs leading to treatment discontinuation were observed in 42 patients (27.1%) in the elraglusib/GnP arm and 20 patients (25.6%) in the GnP arm (Extended Data Table 3). The most common TEAEs leading to study drug discontinuation in the elraglusib/GnP arm were peripheral neuropathy (eight patients, 5.2%), infusion-related reactions (seven patients, 4.5%) and fatigue (five patients, 3.2%).

Overall, TEAEs leading to death were reported in 19 patients (12.3%) in the elraglusib/GnP arm and 13 patients (16.7%) in the GnP arm (Supplementary Table 4). The most common TEAE leading to death was disease progression. TEAEs leading to death did not overlap between the elraglusib/GnP and GnP arms except for upper respiratory hemorrhage experienced by one patient in each group. Three patients in the elraglusib/GnP arm suffered from sepsis resulting in death. Only five TEAEs leading to death were considered possibly or probably related to elraglusib: cardiac arrest (one patient), death (not otherwise specified) (one patient), dehydration (one patient), septic shock (one patient) and streptococcal sepsis (one patient). These treatment-related TEAEs leading to death occurred with once-weekly elraglusib.

Biomarker analysis

Immunophenotyping of paired tumor samples. Tumor immunophenotyping of paired pre-dose and post-dose formalin-fixed paraffin-embedded tumor samples from six patients (four patients on elraglusib/GnP and two patients on GnP) demonstrated that the percentage of CD8$^+$, granzyme B$^+$ and CD56$^+$ NK cells in the tumor parenchyma was significantly increased (by seven to 40 times) in elraglusib/GnP-treated tumors but not in GnP-treated tumors (Supplementary Table 5 and Extended Data Fig. 4). The percentage of myeloid cells, including myeloid-derived suppressor cells (MDSCs), was decreased in tumor parenchyma after treatment in both elraglusib/GnP and GnP arms.

GSK-3β expression in tumor samples

Pre-dose GSK-3β expression was analyzed in tumor samples obtained from 139 patients (98 patients on elraglusib/GnP and 41 patients on GnP). Aberrant nuclear expression of GSK-3β in 50% or more cancer cells was found in 22% and 24% of tumors in the elraglusib/GnP and GnP arms, respectively (Supplementary Fig. 6a). GSK-3β cytoplasmic overexpression in 50% or more cancer cells was detected in 78% of tumors in each arm—elraglusib/GnP (76 of 98 patients) and GnP (32 of 41 patients) (Supplementary Fig. 6b). Nuclear expression of GSK-3β or cytoplasmic overexpression of GSK-3β were not significantly correlated with clinical response or survival in the elraglusib/GnP or GnP arms.

Correlative analysis for cytokines, chemokines, soluble cell receptors or growth factors

For the analysis, blood plasma samples were available from 155 patients in the elraglusib/GnP arm and 69 patients in the GnP arm. The pre-dose analysis of 40 plasma cytokines, chemokines, soluble cell receptors

https://doi.org/10.1038/s41591-026-04327-4

Table 2 | Efficacy outcomes: OS, PFS and overall response (mITT population)

Outcome	Elraglusib/GnP *n*=155	GnP *n*=78	Effect size (95% CI)	*P*
OS				
Median OS, months (95% CI)	10.1 (7.7 to 12.5)	7.2 (5.7 to 9.0)	HR 0.62 (0.46 to 0.84)	0.010
Survival rate, % (95% CI)				
12 months	44.1 (36.0 to 51.8)	22.3 (13.8 to 32.1)		
18 months	20.5 (13.4 to 28.8)	4.4 (0.5 to 15.5)		
24 months	13.2 (6.7 to 21.8)	0		
PFS				
Median PFS, months (95% CI)	5.6 (4.6 to 6.4)	5.1 (3.2 to 6.1)	HR 0.90 (0.68 to 1.20)	0.624
Median time to treatment failure (95% CI)	5.0 (3.6 to 5.6)	3.4 (2.4 to 5.1)	HR 0.79 (0.60 to 1.05)	0.178
Overall response				
Median duration of response (95% CI)	5.5 (3.8 to 5.8)	4.0 (3.2 to 6.3)	HR 0.81 (0.43 to 1.49)	0.984
Objective response rate	44 (28.4)	17 (21.8)		0.281
Confirmed CR, *n* (%)	1 (0.6)	0		
Confirmed PR, *n* (%)	30 (19.4)	13 (16.7)		
Unconfirmed PR, *n* (%)	13 (8.4)	4 (5.1)		
Stable disease ≥16 weeks,[a] *n* (%)	23 (14.8)	11 (14.1)		
Stable disease <16 weeks, *n* (%)	27 (17.4)	16 (20.5)		
PD, *n* (%)	21 (13.5)	15 (19.2)		
Not evaluable	40 (25.8)	19 (24.4)		
Disease control rate,[a] *n* (%)	62 (40.0)	26 (33.3)		0.323

Statistical tests: log-rank tests for time-to-event variables; Cox proportional hazards model for HRs; and Cochran–Mantel–Haenszel general association tests for responder variables. All tests were two-sided. [a]Disease control is stable disease, PR or CR for at least 16 weeks since the first dose of the study drug, or a confirmed CR or PR.

or growth factors (CCSGs) identified seven CCSGs that correlated with the 1-year survival rate. When stratified according to the median value for the elraglusib/GnP arm, high levels of CXCL2 significantly correlated with and high levels of TRAIL ligand displayed numerical benefit without statistical significance toward improved OS in the elraglusib/GnP arm but not in the GnP arm (Extended Data Fig. 5)[29]. A comprehensive analysis, including optimized statistical, multivariate and machine learning models, of CCSG data with patient outcomes will be published separately.

Discussion

In this randomized phase 2 study, the combination of once-weekly elraglusib/GnP demonstrated a statistically significant improvement in survival, a 2.9-month improvement in OS in the elraglusib/GnP arm (median OS of 10.1 months versus 7.2 months with GnP; HR 0.63; $P = 0.01$). The 1-year landmark survival rate was 44.1% with elraglusib/GnP versus 22.3% with GnP in previously untreated mPDAC. A survival benefit was observed with elraglusib/GnP as early as 2 months and persisted throughout the study. Survival benefit was consistent across subgroups evaluated for the presence of liver metastases, ECOG status, CA 19-9 levels at baseline and others.

Additional numerical benefits without significance favored elraglusib/GnP over GnP across multiple endpoints, including median TTF, DOR, ORR and DCR. The OS advantage with elraglusib/GnP was observed in the absence of a significant PFS benefit (Tables 2 and 3) and persisted regardless of subsequent therapy (Extended Data Fig. 3), suggesting durable benefit beyond active treatment. Similar to many trials in advanced cancer evaluating immunomodulators, where OS benefit is often observed in the absence of a PFS benefit, this may be related to the immunomodulatory mechanism of action of GSK-3 inhibitors including elraglusib[30–32]. This disconnect may reflect delayed clinical responses but sustained OS benefit of the immune-based therapies, which often take time to mount an adequate immune response to a tumor[33,34]. This result also suggests that the survival benefit is a consequence of elraglusib's activity rather than the receipt of more doses in the elraglusib/GnP arm as the survival benefit was observed beyond treatment termination with elraglusib. For agents that mediate antitumor immunity—such as immune checkpoint inhibitors—traditional endpoints like PFS and ORR often correlate poorly with OS[33,35–37].

Our study reported a lower median OS in the GnP arm compared to historical randomized trials, where GnP typically shows an OS of approximately 8 to 10 months[8,10,13,14]. However, this finding is consistent with real-world data, where median OS is closer to 7 months when summarized across multiple studies[12]. Several factors may explain this discrepancy. Unlike many mPDAC trials, our exploratory study used broader eligibility criteria, enrolling a cohort more reflective of real-world diversity. Notably, we included patients with low albumin (<3 g dl^{-1}) and substantial tumor burden with over 25% of patients having baseline CA 19-9 > 8,000 U ml^{-1} (the upper threshold of the range reported in NAPOLI-3), features typically linked to poor prognosis[10]. Early mortality was significantly higher in the GnP arm (17.9 % within the first 2 months versus 10.9% in NAPOLI-3), probably driven by these high-risk baseline characteristics[10] (Supplementary Table 6). This early mortality probably affected both arms equally because of well-balanced baseline factors, contributing to lower median OS in the elraglusib/GnP arm also. Importantly, despite early declines, Kaplan–Meier curves diverged early and remained separated, indicating a sustained survival benefit in the elraglusib/GnP arm (Fig. 2). These results highlight the importance of considering baseline patient heterogeneity and real-world factors when interpreting survival outcomes relative to prior randomized trials and highlight the importance of including a control arm in the study to account for anticipated heterogeneity in this patient population.

https://doi.org/10.1038/s41591-026-04327-4

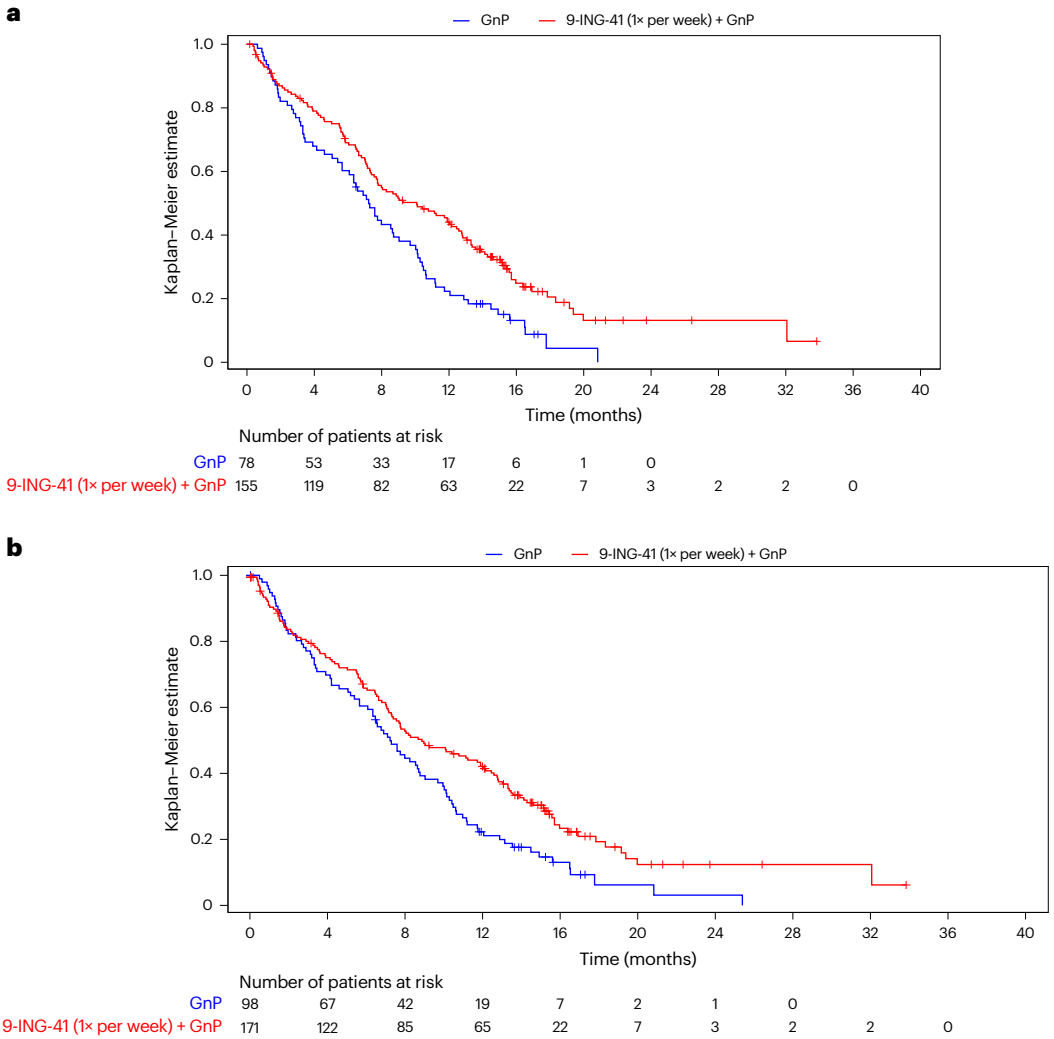

Fig. 2 | Kaplan–Meier estimates of OS in the mITT and ITT populations. a, Statistical test, log-rank stratified by center; $P = 0.010$. **b**, Statistical test, log-rank stratified by center; $P = 0.022$.

In this study, the patients had similar median relative dose intensities for nab-paclitaxel (70% with once-weekly elraglusib/GnP and 72% with GnP) and gemcitabine (74% with elraglusib/GnP and 78% with GnP) (Supplementary Table 1). These median relative dose intensities for GnP in our study were slightly lower than the median relative dose intensity for nab-paclitaxel (81%) and similar to the median relative dose intensity for gemcitabine (75%) achieved in the MPACT study[13]. The median number of treatment cycles was four in both treatment arms. To evaluate whether the observed OS benefit reflected a true treatment effect or was confounded by differential treatment duration, we performed exploratory efficacy analyses stratified according to treatment exposure as fewer than four versus four or more cycles. While the OS was shorter among patients receiving fewer than four cycles, the relative treatment benefit of elraglusib/GnP compared with GnP alone was preserved regardless of treatment duration, as reflected by similar HRs across exposure subgroups (Extended Data Table 4). These findings indicate that the OS benefit associated with elraglusib/GnP is not dependent on prolonged therapy.

Several complementary observations support that the OS improvement reflects a treatment effect rather than confounding according to treatment exposure. First, the treatment arms were well balanced at baseline and representative of a pragmatic, real-world mPDAC population, where early attrition is common. Approximately 56% of patients in the GnP arm and 50% in the elraglusib/GnP arm did not receive subsequent therapy (Extended Data Table 1). Notably, even among patients who did not proceed to second-line treatment, a numerical OS advantage was observed with elraglusib/GnP despite a relatively short treatment duration.

Second, fewer early deaths occurred within the first 2 months with elraglusib/GnP versus GnP (16.1% versus 23.1%; Supplementary Table 6), and Kaplan–Meier curves began to diverge after approximately two treatment cycles, with sustained separation thereafter (Fig. 2). Importantly, patients in the GnP arm received a similar or greater number of treatment cycles through cycle 7 (Supplementary Table 1), yet an OS advantage favoring elraglusib/GnP was already evident early in treatment, arguing against cumulative dose exposure as the primary driver of survival differences.

In addition, the OS and PFS were discordant, with no significant difference in PFS despite a statistically significant improvement in OS. Given that PFS is closely linked to treatment duration, this dissociation further supports that prolonged survival cannot be explained solely by longer exposure to therapy.

To address potential immortal time and responder biases, a landmark analysis was performed at 6 months from treatment initiation, including only patients alive at the landmark. As expected, patients remaining on treatment at 6 months demonstrated longer subsequent survival within each treatment arm. However, OS from the landmark remained longer in the elraglusib/GnP arm compared

https://doi.org/10.1038/s41591-026-04327-4

Table 3 | Efficacy outcomes: OS, PFS and overall response (ITT population)

Outcome	Once-weekly elraglusib/GnP *n*=171	GnP *n*=98	Effect size (95% CI)	*P*
OS				
Median OS, months (95% CI)	8.9 (7.3 to 11.9)	7.2 (5.7 to 8.7)	HR 0.68 (0.51 to 0.89)	0.022
Survival rate, % (95% CI)				
12 months	42.1 (34.4 to 49.6)	22.3 (14.5 to 31.1)		
18 months	19.3 (12.6 to 27.1)	6.2 (1.7 to 15.2)		
24 months	12.4 (6.3 to 20.6)	3.1 (0.3 to 12.3)		
PFS				
Median PFS (months) (95% CI)	5.5 (4.2 to 6.0)	5.4 (3.6 to 6.3)	HR 0.99 (0.76 to 1.29)	0.963
Median time to treatment failure (95% CI)	4.5 (3.3 to 5.5)	3.2 (2.1 to 4.1)	HR 0.76 (0.58 to 0.98)	0.069
Overall response				
Median duration of response (95% CI)	5.5 (3.8 to 5.8)	4.0 (3.2 to 6.3)	HR 0.81 (0.43 to 1.49)	0.984
Objective response rate	44 (25.7)	17 (17.3)		0.115
Confirmed CR, *n* (%)	1 (0.6)	0		
Confirmed PR, *n* (%)	30 (17.5)	13 (13.3)		
Unconfirmed PR, *n* (%)	13 (7.6)	4 (4.1)		
Stable disease ≥16 weeks, *n* (%)	23 (13.5)	11 (11.2)		
Stable disease <16 weeks, *n* (%)	27 (15.8)	16 (16.3)		
PD, *n* (%)	21 (12.3)	16 (16.3)		
Not evaluable, *n* (%)	56 (32.7)	38 (38.8)		
Disease control rate,[a] *n* (%)	62 (36.3)	26 (26.5)		0.102

Statistical tests: log-rank tests for time-to-event variables; Cox proportional hazards model for HRs; and Cochran–Mantel–Haenszel general association tests for responder variables. All tests were two-sided. [a]Disease control is stable disease, PR or CR for at least 16 weeks since the first dose of the study drug, or a confirmed CR or PR.

with the GnP arm, supporting a treatment effect beyond time on therapy alone (Supplementary Fig. 7). Taken together, these exploratory analyses consistently demonstrate that the OS benefit observed with elraglusib/GnP cannot be attributed to differential treatment duration, cumulative dosing or survivor bias, and instead support a true treatment-associated survival benefit in this broadly representative mPDAC population.

Overall, elraglusib/GnP provides a manageable safety profile, but elraglusib may exacerbate AEs associated with GnP. Visual impairment (attributed to elraglusib) remains the most common TEAE with elraglusib/GnP, which aligns with findings in earlier studies with elraglusib[27,28]. Most visual impairment has mild severity and primarily alters perception of contrast and color tones. This TEAE is transient (typically lasting less than 1 h) and reversible. The complete ophthalmological workup during the phase 1 study showed that elraglusib-related visual impairment did not result in any structural changes to the eye or any permanent effects on vision[27].

Furthermore, elraglusib appears to exacerbate the neutropenia associated with GnP as grade 3 or 4 neutropenia is reported more frequently with elraglusib/GnP than with GnP. To date, neutropenia has been observed primarily with elraglusib/GnP and not with elraglusib monotherapy[27,28]. The concomitant administration of elraglusib with GnP did not increase plasma levels of nab-paclitaxel or gemcitabine (Supplementary Fig. 5). Our hypothesis is that elraglusib may stimulate the proliferation of neutrophils; GnP preferentially kills these rapidly proliferating cells. In an in vivo study, the administration of a GSK-3 inhibitor improved neutrophil and megakaryocyte recovery, increased progenitors from hematopoietic stem cells (HSCs), and enhanced proliferative reconstitution of HSCs in mice transplanted with human or mouse HSCs[38]. In humans, use of lithium, an inhibitor of GSK-3, contributes to neutrophilia, which is consistent with this hypothesis[39].

Two or greater episodes of treatment-induced grade 3 to 4 neutropenia significantly correlated with better survival in the elraglusib/GnP arm but not in the GnP arm (Supplementary Table 3). Our previous study demonstrated that grade 4 neutropenia significantly correlated with objective clinical response in patients with mPDAC who received elraglusib/GnP[28]. Most patients who developed grade 3 or 4 neutropenia experienced it during cycle 1 (73.1% with elraglusib/GnP and 60.7% with GnP), which suggests a therapeutic effect rather than a dose accumulation or dose intensity effect affecting the OS.

Mechanistically, GSK-3β inhibition modulates hematopoietic progenitor differentiation but is not associated with direct marrow suppression. Accordingly, the higher rates of neutropenia observed with elraglusib/GnP probably reflect the additive myelosuppressive effects of combination therapy and longer treatment exposure among responders, rather than a specific toxicity or pharmacodynamic marker of elraglusib. Importantly, this association is exploratory and hypothesis-generating; early-onset neutropenia may serve as a pharmacodynamic correlate of adequate drug exposure or biological activity, rather than a consequence of prolonged treatment duration.

mPDAC has multiple immunomodulatory defects that lead to tumor immune resistance, including reduced infiltration with cytotoxic T and NK cells and a microenvironment dominated by helper T cells[40,41]. These defects indicate increased exhausted T cell populations, increased MDSCs, reduced ability for antigen presentation and increased immune checkpoint expression. Optimal treatments involve a combination of agents that exerts both tumor cytotoxicity (direct antitumor effect) and immune modulation (indirect antitumor

https://doi.org/10.1038/s41591-026-04327-4

Table 4 | Overview of TEAEs in 20% or more of patients (mITT population)

TEAE	Patients, *n* (%)			
	Elraglusib/GnP *n*=155		GnP *n*=78	
	Any grade	Grade 3 and higher	Any grade	Grade 3 and higher
Any TEAE	155 (100)	139 (89.7)	77 (98.7)	62 (79.5)
Serious TEAE	86 (55.5)	81 (52.3)	44 (56.4)	43 (55.1)
Leading to treatment discontinuation	42 (27.1)	26 (16.8)	20 (25.6)	16 (20.5)
Leading to death	19 (12.3)	19 (12.3)	13 (16.7)	13 (16.7)
TEAEs of any grade in 20% or more of patients				
Visual impairment[a]	105 (67.7)	1 (0.6)	7 (9.0)	0
Fatigue	97 (62.6)	26 (16.8)	39 (50.0)	4 (5.1)
Neutropenia[b]	95 (61.3)	81 (52.3)	32 (41.0)	24 (30.8)
Diarrhea	93 (60.0)	15 (9.7)	38 (48.7)	6 (7.7)
Nausea	90 (58.1)	11 (7.1)	38 (48.7)	4 (5.1)
Anemia[c]	71 (45.8)	39 (25.2)	35 (44.9)	23 (29.5)
Alopecia	71 (45.8)	0	27 (34.6)	0
Decreased appetite	65 (41.9)	9 (5.8)	19 (24.4)	6 (7.7)
Vomiting	59 (38.1)	5 (3.2)	30 (38.5)	1 (1.3)
Thrombocytopenia	58 (37.4)	17 (11.0)	25 (32.1)	6 (7.7)
Peripheral edema	56 (36.1)	3 (1.9)	25 (32.1)	0
Constipation	50 (32.3)	3 (1.9)	24 (30.8)	1 (1.3)
Abdominal pain	45 (29.0)	14 (9.0)	16 (20.5)	2 (2.6)
Pyrexia	44 (28.4)	2 (1.3)	20 (25.6)	1 (1.3)
Weight decreased	42 (27.1)	5 (3.2)	16 (20.5)	4 (5.1)
Peripheral sensory neuropathy	39 (25.2)	4 (2.6)	18 (23.1)	0
Hypokalemia	35 (22.6)	8 (5.2)	24 (30.8)	4 (5.1)
Asthenia	33 (21.3)	9 (5.8)	19 (24.4)	5 (6.4)
Dysgeusia	32 (20.6)	0	16 (20.5)	0
Infusion-related reaction	31 (20.0)	4 (2.6)	1 (1.3)	0

[a]Visual impairment includes the 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 these were counted only once. [b]Neutropenia includes neutropenia and decreased neutrophil count. [c]Thrombocytopenia includes thrombocytopenia and decreased platelet count. MedDRA, Medical Dictionary for Regulatory Activities.

effect). Elraglusib has demonstrated the ability to inhibit growth and survival of cancer cells, attenuate the unfavorable tumor immune microenvironment and decrease tumor cell resistance in a variety of preclinical models[24,30].

Targeting myeloid progenitor cells by GnP leads to a decreased number of MDSCs and neutropenia[42]. In pancreatic cancer, intratumoral MDSCs suppress the activity of T and NK cells and thus contribute to tumor resistance to immunotherapy[43–46]. Although the number of MDSCs decreased in posttreatment tumors in both elraglusib/GnP and GnP arms, the depletion of MDSCs in the elraglusib/GnP arm occurred along with concomitant increases in the percentage of tumor-infiltrating cytotoxic T cells, granzyme B^+ cells and NK cells. Given the limited number of tumor samples analyzed and the heterogeneity of PDAC, these immunophenotyping findings are exploratory and hypothesis-generating rather than statistically inferential. Nonetheless, these observations are consistent with prior preclinical and early clinical data suggesting that elraglusib may favorably modulate the tumor immune milieu when combined with GnP and warrant further evaluation in larger, prospectively designed studies.

CCSG analysis identified high levels of TRAIL (numerical benefits without statistical significance) and CXCL2 as predictors for improved survival in the elraglusib/GnP arm but not in the GnP arm. Systemic cytokines can reflect both the systemic immune/inflammatory environment and the immune status of the tumor microenvironment. Thus, identifying several pre-dose cytokine markers that predict for survival in only patients who received elraglusib/GnP is a unique finding of this study. Further, the cytokines and chemokines identified as correlating with improved survival[29] are known to mediate tumor immune suppression. For example, CXCL2 has been shown to increase intratumoral MDSC recruitment[47], which may promote resistance to checkpoint inhibitors[48]. These associations are presented descriptively with intentions to generate hypotheses regarding potential immunomodulatory effects of elraglusib, rather than to establish causal or mechanistic conclusions.

Initial limitations of this study were its open-label design and regional treatment access as several patients withdrew from the study once randomized to the control arm to pursue alternative treatment options closer to home. Patients who withdrew after randomization were asked to consent to survival follow-up, which allowed for control of selection bias relative to the primary endpoint. Despite the mITT/safety population being selected as the primary analysis set and the best suited population to represent treatment benefit, the ITT population, which includes all patients like those who withdrew after randomization and before receiving treatment, showed a statistically significant improvement in median OS and 1-year survival (Table 3). By design, the trial allowed for the inclusion of patients with poor prognostic

features, which potentially led to a higher rate of early deaths across both arms, and consequently, lower median OS for GnP compared with other randomized trials.

This open-label, randomized, phase 2 study revealed improved OS with elraglusib/GnP as first-line treatment in mPDAC when compared to the standard of care (SOC) first-line treatment, GnP. A manageable safety profile of elraglusib/GnP was confirmed and mirrors safety findings from the previous studies with elraglusib[27,28]. We hypothesize that the survival benefit will be maintained relative to the control group; therefore, direct comparison of the median OS in the elraglusib/GnP arm with other studies or other regimens (for example, FOLFIRINOX or NALIRIFOX) is inherently difficult. Although the median OS of elraglusib/GnP is relative to the median OS of GnP in this study and may shift if the median OS of GnP differs in another study, the 2.9-month survival advantage would be preserved. Supportive analysis in patients who received at least one cycle of treatment (approximately 75% of patients in this study) demonstrated that this survival improvement margin is maintained in the elraglusib/GnP arm even as survival shifts in the GnP arm (Extended Data Table 5).

Elraglusib's benign safety profile as monotherapy, and a unique mechanism of action with a multifaceted immunomodulatory component, position it as an ideal backbone agent for combination with other first-line chemotherapy regimens such as FOLFIRINOX and NALIRIFOX and immune modulators such as checkpoint inhibitors that have shown little activity to date in mPDAC[49]. A phase 2 investigator-initiated trial (NCT05077800) is exploring the combination of elraglusib with FOLFIRINOX in previously untreated mPDAC. Preliminary data on six patients treated with elraglusib/FOLFIRINOX/losartan demonstrated a PR of 20 or more months in three of six patients with extensive liver metastases and 100% DCR[50]. Other studies are underway to explore elraglusib in combination with immune checkpoint inhibitors, and phase 1 studies are being designed for an oral dosage form of elraglusib. The phase 1 study RiLEY (NCT06896188) will investigate the combination of retifanlimab, an anti-PD-1 monoclonal antibody, with elraglusib and FOLFIRINOX in advanced PDAC. Because of PDAC having multiple defects contributing to resistance to immune modulatory drugs[40,41], combinations of elraglusib with RAS or MEK inhibitors could also be potentially explored as therapeutic strategies to overcome tumor resistance and improve clinical outcomes in mPDAC. Additionally, based on the results of this phase 2 study, a phase 3 study is being planned.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-026-04327-4.

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Methods

Study design

This was an open-label, randomized, multicenter, phase 2 study to assess the efficacy and safety of elraglusib/GnP versus GnP as first-line treatment in patients with mPDAC (the 1801 study Part 3B, NCT03678883). The study followed the Pick-the-Winner adaptive trial design, which consists of a selection stage and a confirmation stage[51]. Patients enrolled from 7 October 2021 to 9 February 2024. All enrolled patients signed the informed consent form.

Ethics approval and consent

The study was performed in compliance with Good Clinical Practice and the Declaration of Helsinki (v2013). Local institutional review boards or the independent ethics committees of the participating centers approved the study protocol.

Patients

Eligible patients were aged 18 years and older, presented with previously untreated mPDAC and had at least one measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1[52] using computed tomography or magnetic resonance imaging. Patients had an ECOG PS of 0 or 1 and adequate bone marrow, liver and renal functions. Any focal radiation therapy or surgery with general anesthesia were completed 7 days before initiating study treatment; any surgery with local anesthesia was completed 3 days before treatment. Any prior chemotherapy treatments in the adjuvant or neoadjuvant setting were completed at least 6 months before study enrollment.

Key exclusion criteria included pregnancy or lactation, presence of endocrine or acinar pancreatic carcinoma or current active malignancy other than pancreatic cancer, a history of cardiovascular disease, major surgery within 7 days of enrollment, participation in another clinical trial, or rapidly progressing brain metastases or leptomeningeal involvement. Patients with stable or slowly progressing brain metastases or leptomeningeal disease were eligible to enroll if no new treatments were initiated in the prior 28 days and anticonvulsants and steroids were at stable doses for the prior 14 days (see full eligibility criteria in the protocol in the Supplementary Information). All enrolled patients signed the informed consent form within 6 weeks of initiating study treatment.

Randomization

During the selection stage of the study, patients were initially randomized in a 1:1:1 ratio to one of the three treatment arms—twice-weekly elraglusib/GnP, once-weekly elraglusib/GnP or GnP. During the confirmation stage of the study after selecting once weekly as the preferred dosing for elraglusib, patients were randomized in a 2:1 ratio to receive once-weekly elraglusib/GnP or GnP alone. Randomization for all stages of the study was stratified according to study center with a block size of three.

Procedures

During the study, intravenous elraglusib 9.3 mg kg^{-1} was administered on day 1 for the once-weekly schedule or days 1 and 4 for the twice-weekly schedule. The elraglusib's recommended phase 2 dose of 9.3 mg kg^{-1} was based on the nonrandomized, single-arm, phase 2 study[28]. GnP treatment consisted of intravenous nab-paclitaxel 125 mg m^{-2} followed by intravenous gemcitabine 1,000 mg m^2 on days 1, 8 and 15 in a 28-day cycle. Dose reductions were allowed for all treatment agents. For elraglusib, the first dose reduction was to 7.0 mg kg^{-1} dose and the second to 5.0 mg kg^{-1}. Treatment continued until disease progression (as defined in RECIST v.1.1[52]), unacceptable toxicities or the investigator's decision that a patient no longer benefited from the treatment.

Radiological tumor assessments were performed per institutional SOC using computed tomography or magnetic resonance imaging. Serum CA 19-9 levels were measured per SOC in all patients with elevated CA 19-9 at baseline and were followed for 12 months after the last dose of study treatment. During the follow-up, survival was followed in all patients for 12 months after the last dose of study treatment and then every 3 months until all patients died or the last patient was followed for 12 months. Safety assessments were performed up to 4 weeks after the last dose of the study treatment.

Study objectives and assessments

In the selection stage, the superiority of elraglusib dosing frequency was determined based on tolerability, toxicity and patient convenience.

The initial primary endpoint was the 1-year landmark survival rate in the different treatment arms. This allowed to determine the elraglusib schedule during the selection stage without waiting for OS. After the 12-month follow-up after the last treatment dose, the overall primary endpoint was the median OS, defined as the number of months from randomization to death from any cause. Additional sensitivity and exploratory analyses for OS were conducted for different patient subgroups.

Secondary endpoints included PFS, TTF, ORR, DCR, DOR and safety. PFS was defined as the time from randomization to PD or death; TTF as time from randomization to disease progression, clinical progression (for example, clinical deterioration, clinical decision because of complicating disease, worsening disease, etc.) or death; ORR as the percentage of patients with CR or PR; and DOR as the median number of months from the first documented CR or PR to disease progression. DCR was defined as the percentage of patients who achieved stable disease lasting 16 weeks or longer, CR or PR. All responses to treatment were assessed according to RECIST v.1.1[52]. TEAEs were monitored from the first dose of treatment to 30 days after the last dose, using the Common Terminology Criteria for Adverse Events v.5.0 and coded using Medical Dictionary for Regulatory Activities v.23.1[53].

The primary analysis set for the efficacy and safety analyses was the safety population (or mITT population), defined as patients who received at least one dose of the study treatment. The ITT population consisted of all randomized patients. The mITT population was selected as the primary analyses set for the efficacy analyses to account for potential patient withdrawal in the ITT population after randomization in this open-label study as described in ref. 54.

Biomarker analysis

Blood plasma samples were collected pre-dose and 3 h post-dose on day 1 of cycles 1, 2, 4 and 6 from all patients. Using a Luminex immunoassay, 40 CCSGs were measured across the plasma samples[29]. For the OS analysis, both arms were stratified according to their pre-dose levels about the median level of each CCSG in the elraglusib/GnP arm.

Optional fresh tumor biopsies were obtained within 6 weeks before the first treatment dose and after cycle 2 of treatment. Biopsy samples were fixed with formalin and embedded in paraffin within 24 h of collection. To determine the difference in the percentage of intratumoral immune cells ($CD8^+$, granzyme B^+, $CD56^+$ and $CD11b^+$) before and after treatment in elraglusib/GnP and GnP arms, immunophenotyping was performed of these biopsy tumor samples using the OmniVUE 8-Plex immunofluorescence assay (Ultivue). The percentage of intratumoral immune cells was determined by counting the total number of CD8+, granzyme B^+, $CD56^+$ or $CD11b^+$ cells within the tumor parenchyma area and by dividing the total number of cells in that same area.

GSK-3β expression was assessed using immunohistochemical staining of pre-dose formalin-fixed paraffin-embedded tumor samples. Immunohistochemical staining, histopathological evaluation and scoring were performed by Mosaic Laboratories.

Statistical analysis

The predefined sample size for the selection stage was up to 25 patients in each of the three cohorts. The planned sample size to evaluate the

primary efficacy endpoint of the 1-year survival rate was 207 evaluable patients (130 patients for elraglusib/GnP and 77 patients for GnP), which also included patients in the appropriate treatment arms from the selection stage. Primary analysis for survival and safety included all patients in the mITT analysis set. The calculation assumptions included achieving a 1-year survival rate of 55% with elraglusib/GnP and 35% with GnP (20% difference between the arms) with 80% power using a chi-squared test for equal proportions at a two-sided significance level of 0.05. Accordingly, the primary analysis was originally planned as a comparison of the 1-year survival rates. Following regulatory feedback after study initiation, the primary efficacy analysis was revised to a comparison of survival curves using a log-rank test; the sample size was not reestimated. The log-rank test was selected to appropriately account for censored survival times occurring before 1 year. In accordance with the Pick-the-Winner trial design, statistical significance for the primary endpoint was assessed at an adjusted two-sided significance level of 0.048, corresponding to a log-rank test statistic greater than 3.91 (ref. 55).

Descriptive statistics were used to summarize the efficacy and safety parameters. Categorical data were represented as frequency distributions (numbers and percentages of patients), while continuous data as the mean (s.d.) and median (range of minimum to maximum). For all time-to-event efficacy endpoints, the log-rank test statistic was used for hypothesis testing, Kaplan–Meier methodology (including figures, median, 95% CI, number of events and number censored) for the summary of variables, and Cox proportional hazards model with treatment arm as the independent variable for HRs. For continued OS, time censoring occurred on the date of the most recent assessment of any type before the loss of follow-up or the database lock. The Cochran–Mantel–Haenszel test statistic was used for the response rates. Additionally, machine-learning-based multivariate models were used for cytokine and survival correlative analysis[29].

All statistical analyses were performed using SAS v.9.4 (see the statistical analysis plan in the Supplementary Information for details on the statistical analyses).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Actuate Therapeutics is committed to sharing access to patient-level data and supporting clinical documents from eligible studies with qualified external researchers. Data will be made available after a Data Usage Agreement has been signed. Investigators and institutions who consent to the terms of the Data Usage Agreement, including but not limited to the use of these data for the purpose of a specific project and only for research purposes, and to protect the confidentiality of the data and limit the possibility of identification of participants in any way whatsoever for the duration of the agreement, will be granted access. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. Trial data availability is according to the criteria and process described at www.clinicalstudydatarequest.com. The data described in this publication will be made available for any qualified request. To submit a request for data, please contact info@actuatetherapeutics.com. Response to requests will be provided within 15 business days.

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Acknowledgements

We thank J. Afanasjeva, PharmD, for medical writing and assistance with preparing the manuscript, and A. Koukol (Actuate Therapeutics), C. Kellinger (Actuate Therapeutics), S. Smith (HiRO), M. Gonzalez Sales (Modeling Great Solutions), W. El-Deiry (Brown University) and L. Zhang (Brown University) for their contributions to this project. This work was supported by Actuate Therapeutics.

Author contributions

D.M., B.A.C., A.P.M., A.U. and T.W. conceptualized the study and developed the methodology. D.M., A.P.M. and C.S. supervised the project. D.M., R.T.S., B.A.C., Y.J., A.L.C., A.C., V.S., A.P., S.H., N.K.L., I.J.P., C.D.L., S.P., P.K., M.M., R.C., F.J.G., A.P.M. and T.S.B. were responsible for data collection. G.F., M.J. and T.W. performed the statistical analysis. D.M. and A.P.M. wrote the original draft. All authors reviewed and edited the original draft of the manuscript and reviewed the final draft to approve its submission for publication.

Competing interests

D.M. declares research funding from Amgen, Merck, Oncolytics and Rafael; scientific advisory board work for Actuate Therapeutics and Qurient; an advisory/speaker bureau for Amgen, Bristol Myers Squibb, Eisai and Exelixis; and institutional research funding from Acepodia, Actuate Therapeutics, ADC Therapeutics, Amgen, AVEO, Bayer, Blueprint Medicines, Bristol Myers Squibb, 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 Warewolf Therapeutics. R.T.S. declares institutional research funding from Lisata, Merck, Exelixis, Bristol Myers Squibb, Immuno Vaccine, Compass, Actuate, Faeth and Seagen; consultation for AstraZeneca, Boston Scientific, Genentech, Elevar, ICON Clinical Research and Foundation Medicine; and participation in advisory boards for Exelixis, Merck, AstraZeneca, Boehringer Ingelheim and Zymeworks. B.A.C. declares institutional research support from AstraZeneca, Abbvie, Actuate Therapeutics, Astellas, Agenus, Bayer, Dragonfly Therapeutics, Mink Therapeutics, Pfizer, Pyxis Oncology, Repare Therapeutics and Regeneron; and participation in advisory boards for Seattle Genetics and Eisai. A.L.C. declares consultation or participation in advisory boards for Halozyme, Seattle Genetics, Merrimack and Abbvie; institutional research funding from XBiotech, Newlink Genetics, Taiho Pharmaceutical, Immunomedics, Onconova Therapeutics, Lilly, Gilead Sciences, Genentech, Seattle Genetics, AbGenomics International, Halozyme, Novocure, Amgen, Actuate Therapeutics, Surface Oncology, Nucana, Nextrast and AstraZeneca; and travel support from Halozyme, Abbvie and Nucana. A.C. declares institutional research funding from Genentech, Merck Serono, Bristol Myers Squibb, Merck Sharp & Dohme, Roche, Beigene, Bayer, Servier, Lilly, Novartis, Takeda, Astellas, Natera and Actuate Therapeutics; and participation in advisory board or receipt of speaker fees from AbbVie, Amgen, Merck Serono, GlaxoSmithKline and Roche. V.S. declares institutional research funding from Actuate Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Clovis, Esanik, Exelixis, Fibrogen, Ipsen,

MedImmune, the National Cancer Institute, PanCAN, Cornerstone (previously Rafael), Relay, Repare, Servier, Syros and Transthera; consulting fees from Amplity (previously Lynx Group), AstraZeneca, Autem, Delcath Systems, Histosonics, Ipsen, Incyte, Rafael (previously Cornertsone), Servier and Taiho; receipt of equipment and supplies from Beigene and Cornerstone (previously Rafael); and travel support from ASCO, the Cholangiocarcinoma Foundation, Histosonics, Lynx Group/Amplity and the National Comprehensive Cancer Network. N.K.L. declares institutional research funding from Exact Sciences. C.D.L. declares institutional research funding from Servier, AstraZeneca, Genentech/Roche and Taiho. F.J.G. declares stock ownership in Actuate Therapeutics. C.S. is an employee and equity holder in Actuate Therapeutics. A.U. is an employee and equity holder in Actuate Therapeutics. T.W., G.F. and M.J. declare consulting fees from Actuate Therapeutics. A.P.M. is an employee and equity holder in Actuate Therapeutics. T.S.B.-S. declares institutional research funding from Actuate Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Clovis, Elicio, Esanik, Exelixis, Fibrogen, Jazz, Ipsen, the National Cancer Institute, PanCAN, Cornerstone (previously Rafael), Relay, Repare, RevMed, Servier and Transthera; consulting fees from AstraZeneca, Autem, Amplity (previously Lynx Group), Delcath, Elevar, HistoSonics, Incyte, Ipsen, Jazz, RevMed, Servier, Tallac and TransThera; provision of equipment/supplies from Cornerstone (previously Rafael); travel and lodging costs from ASCO, the Japanese Society of Clinical Oncology, the BinayTara Foundation, the Cholangiocarcinoma Foundation, HistoSonics, Lynx Group/Amplity, the National Comprehensive Cancer Network and the Chinese Association of Pancreatology. Y.J., A.P., S.H., I.J.P., S.P., P.K., M.M. and R.C. declare no competing interests.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-026-04327-4.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41591-026-04327-4.

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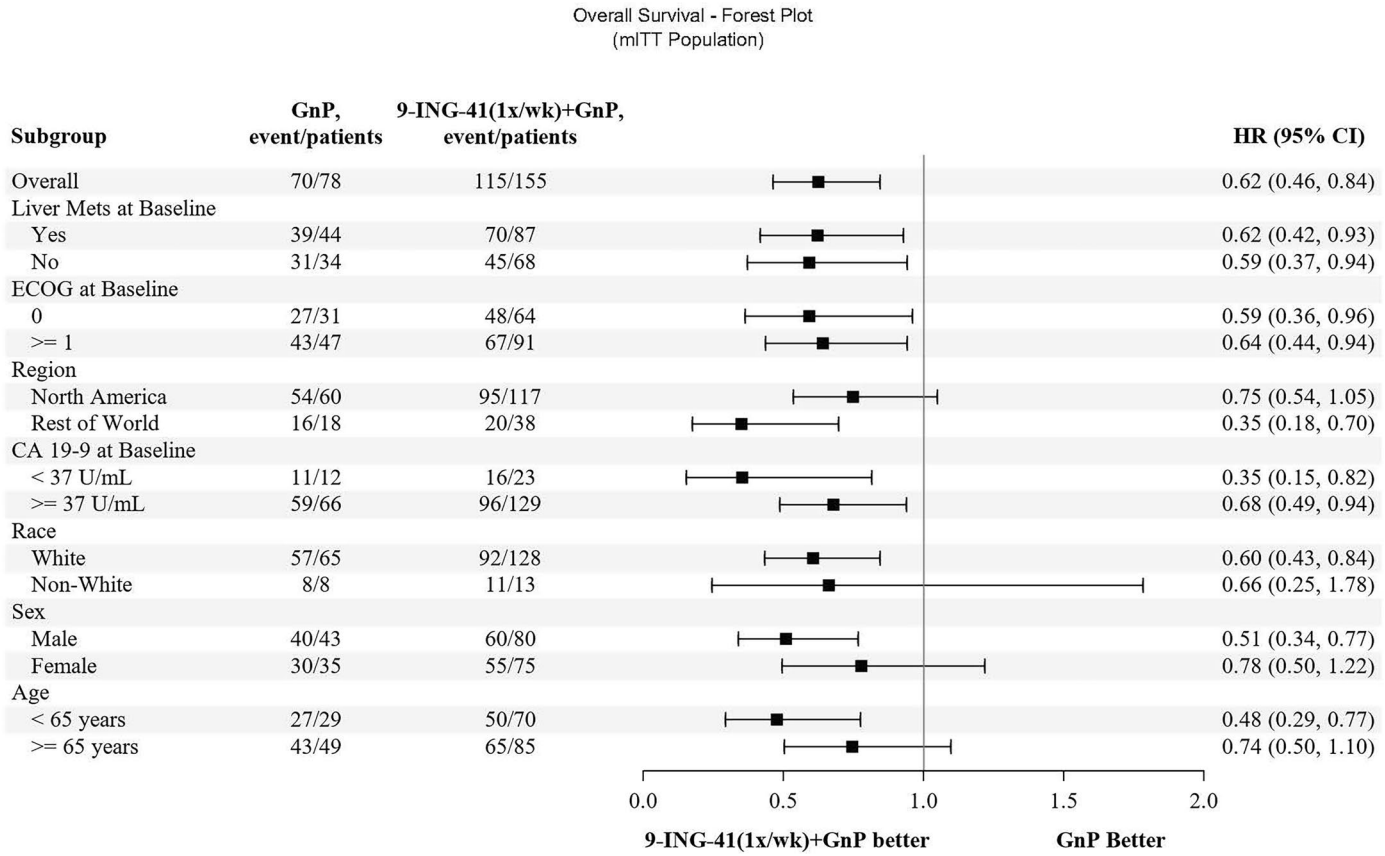
Peer review information *Nature Medicine* thanks David Chang, Mithat Gonen and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Peer reviewer reports are available. Primary Handling Editor: Ulrike Harjes, in collaboration with the *Nature Medicine* team.

https://doi.org/10.1038/s41591-026-04327-4



Extended Data Fig. 1 | Forest Plot for Overall Survival in Subgroups of the mITT population. Abbreviations: 9-ING-41, elraglusib; CA, carbohydrate antigen; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; GnP, gemcitabine plus nab-paclitaxel; HR, hazard ratio; mITT, modified intention-to-treat; wk, week.

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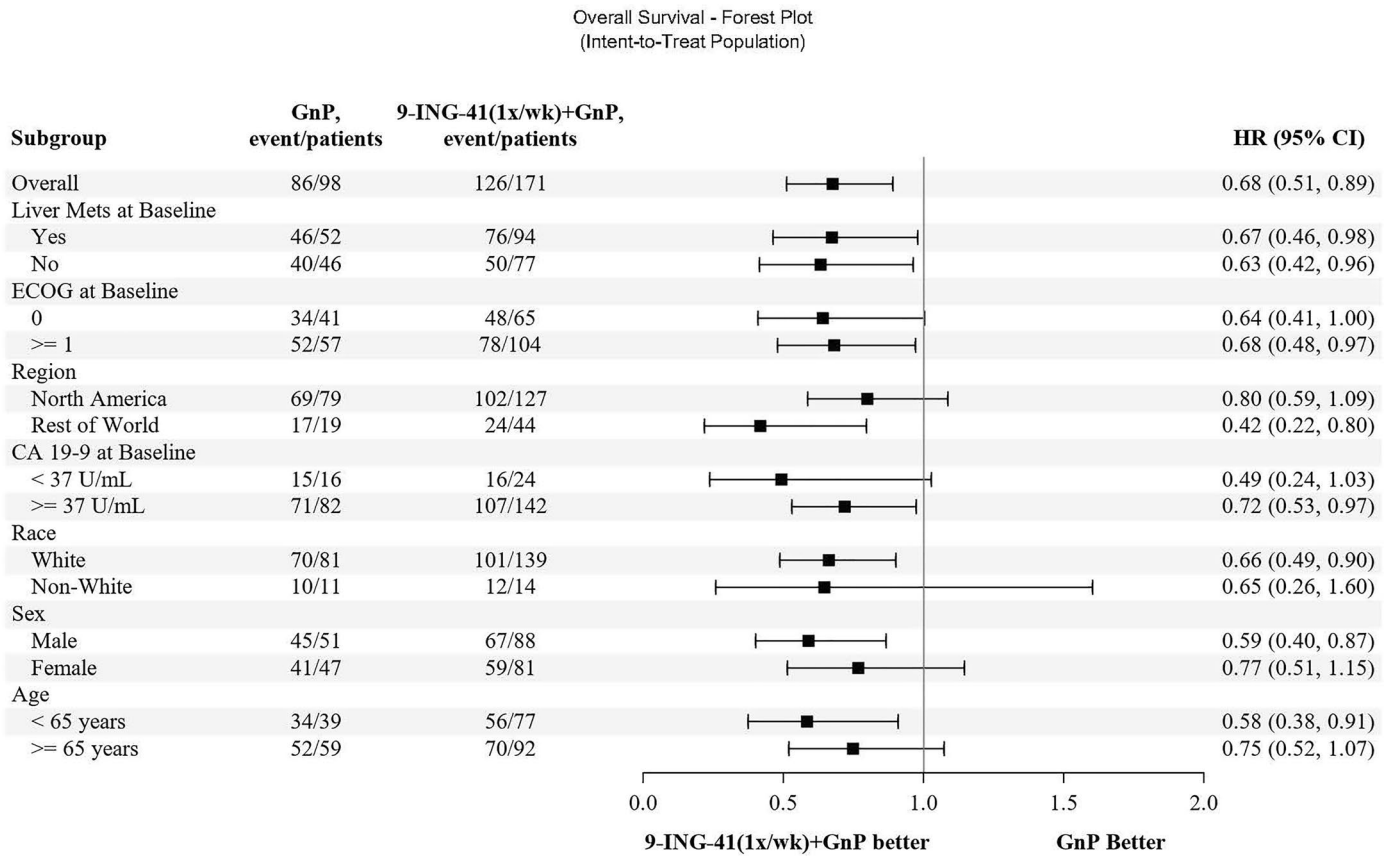

Extended Data Fig. 2 | Forest Plot for Overall Survival in Subgroups of the ITT population. Abbreviations: 9-ING-41, elraglusib; CA, carbohydrate antigen; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; GnP, gemcitabine plus nab-paclitaxel; HR, hazard ratio; ITT, intention-to-treat; wk, week.

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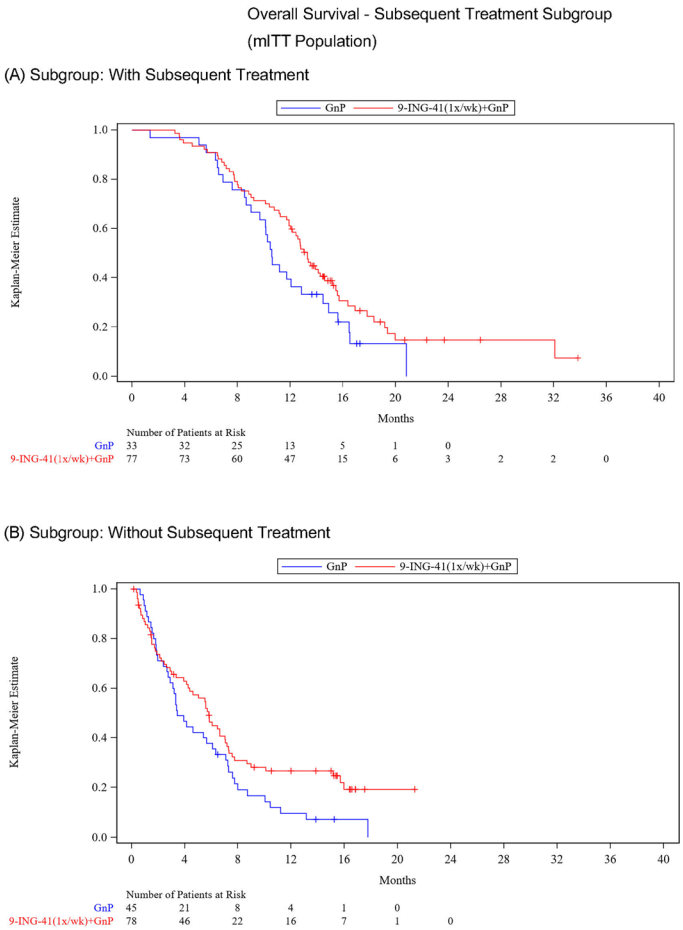
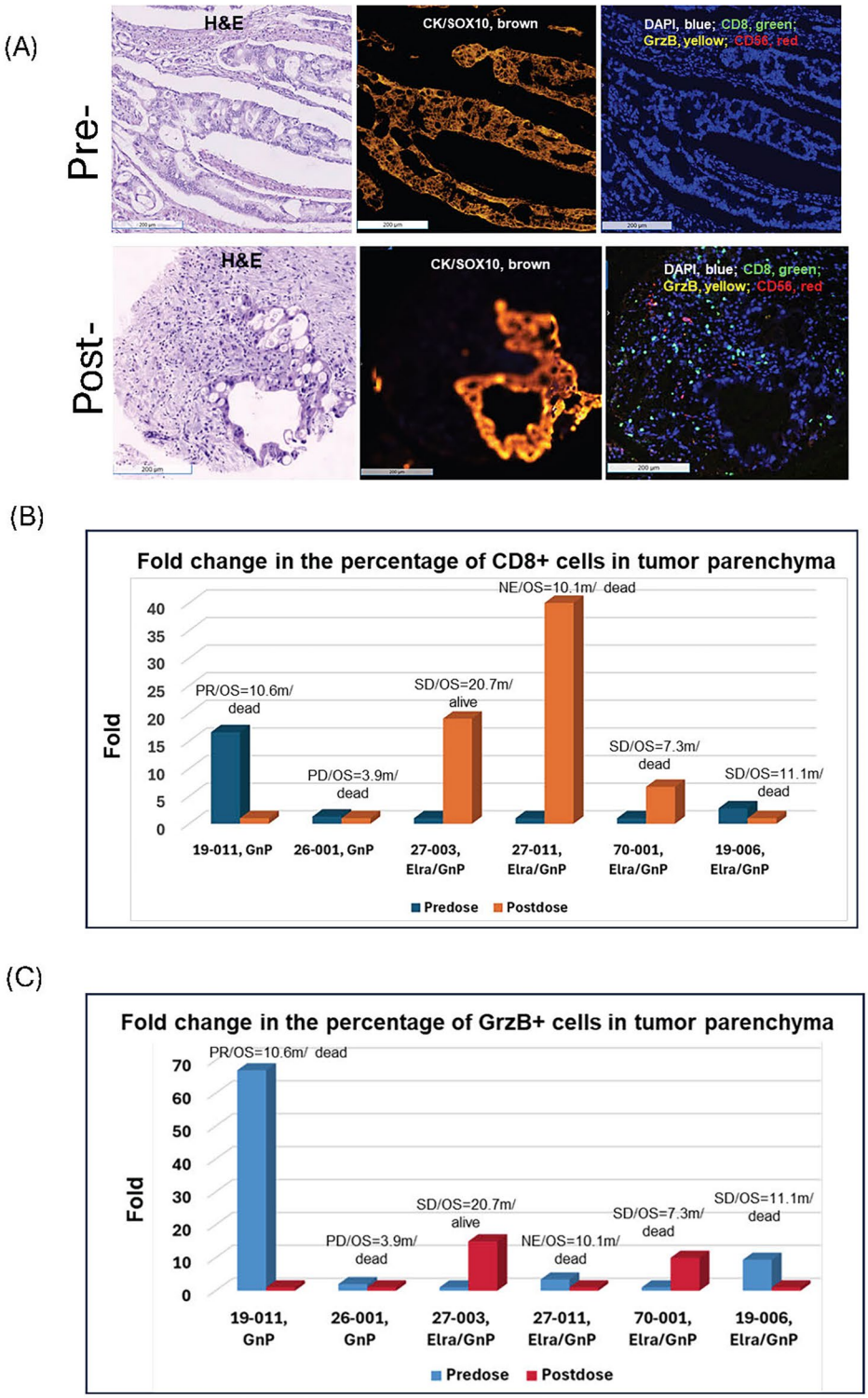


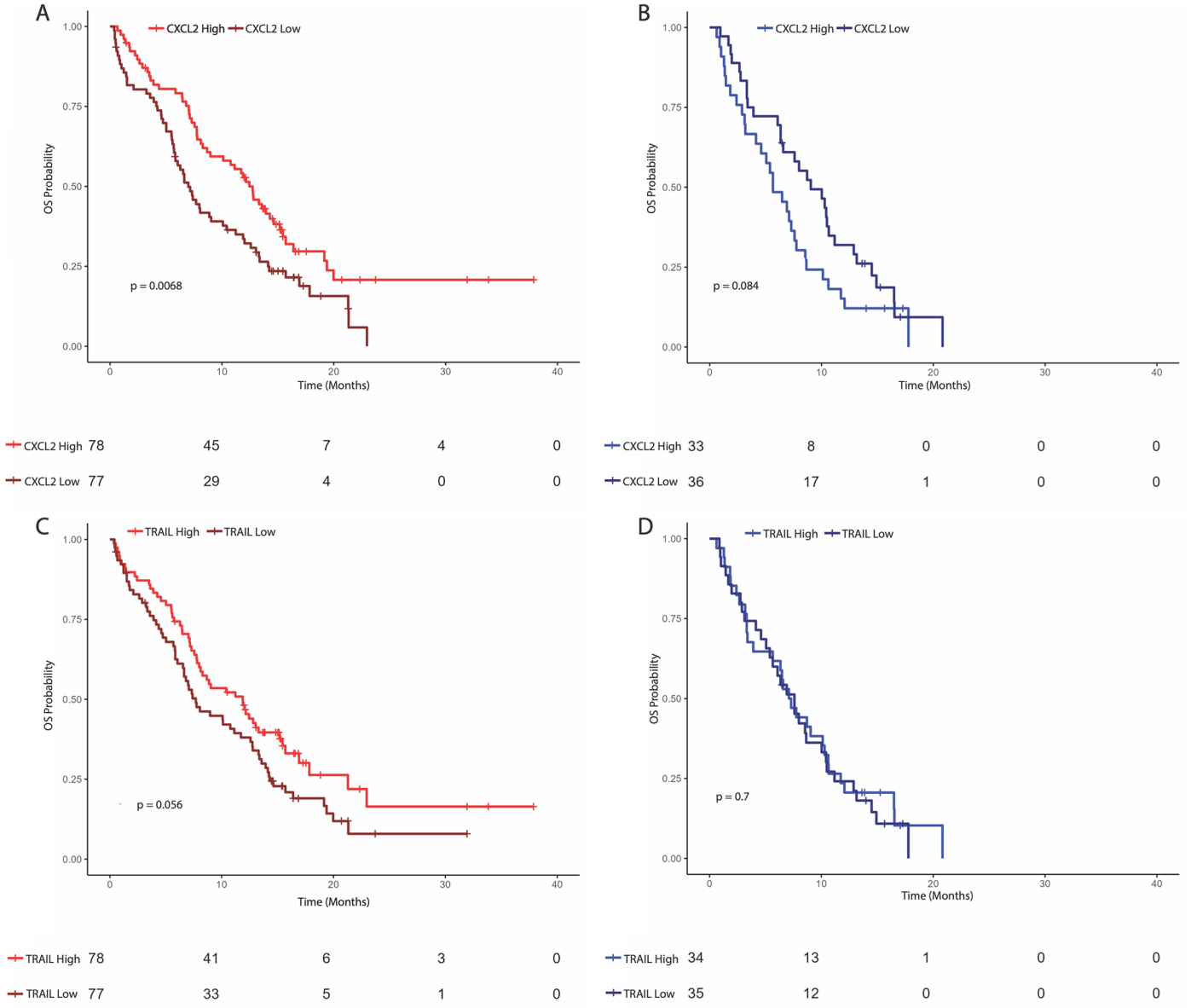
Extended Data Fig. 3 | Exploratory Analysis for Overall Survival in (A) Patients With Subsequent Treatment and (B) Patients Without Subsequent Treatment. (**A**) Statistical test: log-rank test stratified by center; p-value: p = 0.094 (**B**) Statistical test: log-rank test stratified by center; p-value: p = 0.064 Abbreviations: 9-ING-41, elraglusib; GnP, gemcitabine plus nab-paclitaxel; mITT, modified intention-to-treat; wk, week.

https://doi.org/10.1038/s41591-026-04327-4



Extended Data Fig. 4 | Immunophenotyping of Pre- and Post-treatment Tumor Samples. Representative pictures of tumor immunophenotyping analysis of pre- and post-dose tumor biopsies obtained from the patient treated with elraglusib/GnP (**A**). The percentage of CD8+ cells (**B**) and granzyme B+ immune cells (**C**) was evaluated in tumor parenchyma and compared between pre- and post-dose tumor samples in GnP and elraglusib/GnP arms. Abbreviations: CD8 + , a marker of cytotoxic T cells; CD56 + , a marker of natural killer cells; CK, cytokeratin; GrzB + , granzyme B, a marker of activated cytotoxic T cells and NK cells; GnP, gemcitabine plus nab-paclitaxel; H&E, Hematoxylin and Eosin; NE, not evaluable; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.

https://doi.org/10.1038/s41591-026-04327-4



Extended Data Fig. 5 | Overall survival of patients treated with elraglusib/GnP (A) or GnP (B) stratified about the median of the elraglusib/GnP arm as CXCL2 low or high from pre-dose samples, and overall survival of patients treated with erlaglusib/GnP (C) or GnP (D) stratified about the median of the elraglusib/GnP arm as TRAIL ligand low or high from pre-dose samples. Note: P-values were calculated using the log rank test. Abbreviations: OS, overall survival.

https://doi.org/10.1038/s41591-026-04327-4

Extended Data Table 1 | Subsequent Anti-Cancer Treatments (mITT Population)

Subsequent therapy category	Elraglusib/GnP (N=155)	GnP (N=78)
Subsequent anti-cancer therapy, n (%)	77 (50)	34 (44)
Systemic anti-cancer therapy, n (%)	77 (50)	33 (42)
FOLFIRINOX	17 (11)	10 (13)
GnP	10 (6)	4 (5)[a]
FOLFIRI	7 (5)	3 (4)
FOLFOXIRI	6 (4)	2 (3)
Liposomal irinotecan/5-FU/LV	5 (3)	2 (3)
FOLFOX	0	1 (1)
Other	32 (21)	11 (14)
Radiotherapy, n (%)	0	1 (1)[b]

[a]All 4 patients had post-treatment therapy indicated as GnP; however, treatment was determined to be first-line. [b]This patient also received anti-neoplastic therapy with radiation.
Abbreviations: 5-FU, 5-fluorouracil; FOLFIRI, leucovorin plus 5-fluorouracil plus irinotecan; FOLFIRINOX, leucovorin plus 5-fluorouracil plus irinotecan plus oxaliplatin; FOLFOX, leucovorin plus 5-fluorouracil plus oxaliplatin; FOLFOXIRI, leucovorin plus 5-fluorouracil plus oxaliplatin plus irinotecan; GnP, gemcitabine plus nab-paclitaxel; LV, leucovorin; mITT, modified intention to treat.

https://doi.org/10.1038/s41591-026-04327-4

Extended Data Table 2 | TEAEs Related to Elraglusib Occurring at an Incidence ≥10% Among Elraglusib-treated Patients (mITT Population)

MedDRA[a] Preferred Term	Elraglusib (1x/wk) +GnP (N=155) n (%)	Elraglusib (2x/wk) +GnP (N=17) n (%)	All Patients (N=250) n (%)
Any Event	148 (95.5%)	16 (94.1%)	164 (65.6%)
Visual impairment	103 (66.5%)	14 (82.4%)	117 (46.8%)
Fatigue	66 (42.6%)	9 (52.9%)	75 (30.0%)
Nausea	56 (36.1%)	5 (29.4%)	61 (24.4%)
Neutropenia	51 (32.9%)	4 (23.5%)	55 (22.0%)
Diarrhoea	45 (29.0%)	4 (23.5%)	49 (19.6%)
Thrombocytopenia	32 (20.6%)	2 (11.8%)	34 (13.6%)
Anaemia	31 (20.0%)	2 (11.8%)	33 (13.2%)
Vomiting	27 (17.4%)	2 (11.8%)	29 (11.6%)
Infusion related reaction	24 (15.5%)	3 (17.6%)	25 (10.0%)
Decreased appetite	22 (14.2%)	1 (5.9%)	25 (10.0%)
Leukopenia	18 (11.6%)	1 (5.9%)	19 (7.6%)
Weight decreased	16 (10.3%)	1 (5.9%)	17 (6.8%)

[a] MedDRA v23.1 Includes events judged possibly, probably or definitely related; excludes events judged unrelated or unlikely related. Abbreviations: GnP, gemcitabine plus nab-paclitaxel; MedDRA, Medical Dictionary for Regulatory Activities; mITT, modified intention-to-treat; TEAE, treatment-emergent adverse event; wk, week.

https://doi.org/10.1038/s41591-026-04327-4

Extended Data Table 3 | TEAEs Leading to Any Study Drug Discontinuation for >1 Patient (mITT Population)

MedDRA[a] Preferred Term	GnP (N=78) n (%)	Elraglusib (1x/wk) +GnP (N=155) n (%)	Elraglusib (2x/wk) +GnP (N=17) n (%)	All Patients (N=250) n (%)
Any Event	20 (25.6%)	42 (27.1%)	3 (17.6%)	65 (26.0%)
Neuropathy peripheral	2 (2.6%)	8 (5.2%)	1 (5.9%)	11 (4.4%)
Infusion-related reaction	0	7 (4.5%)	0	7 (2.8%)
Fatigue	2 (2.6%)	5 (3.2%)	0	7 (2.8%)
Disease progression	5 (6.4%)	2 (1.3%)	2 (11.8%)	9 (3.6%)
Asthenia	1 (1.3%)	3 (1.9%)	0	4 (1.6%)
Paraesthesia	0	3 (1.9%)	0	3 (1.2%)
Peripheral sensory neuropathy	0	3 (1.9%)	0	3 (1.2%)
Muscular weakness	1 (1.3%)	2 (1.3%)	0	3 (1.2%)
Sepsis	1 (1.3%)	2 (1.3%)	0	3 (1.2%)
Dehydration	0	2 (1.3%)	0	2 (0.8%)
Thrombocytopenia	0	2 (1.3%)	0	2 (0.8%)
Visual impairment	0	2 (1.3%)	0	2 (0.8%)
Hypotension	2 (2.6%)	0	0	2 (0.8%)
Hypoxia	2 (2.6%)	0	0	2 (0.8%)

[a] MedDRA v23.1 Abbreviations: GnP, gemcitabine plus nab-paclitaxel; MedDRA, Medical Dictionary for Regulatory Activities; mITT, modified intention-to-treat; TEAE, treatment-emergent adverse event; wk, week.

https://doi.org/10.1038/s41591-026-04327-4

Extended Data Table 4 | Overall Survival for Patients Who Received ≥4 Cycles Versus <4 Cycles of Treatment – Cox Proportional Hazards Model (mITT Population)

	GnP (N=78)	Elraglusib/GnP (N=155)
Received ≥4 Cycles Treatment, n	40	85
Median Overall Survival [95% CI] (months)	10.3 [8.6, 13.1]	14.1 [12.0, 15.7]
Received <4 Cycles Treatment, n	38	70
Median Overall Survival [95% CI] (months)	3.2 [1.9, 4.1]	4.2 [3.0, 5.7]
Overall Survival (months) - Cox Proportional Hazards Model		
Hazard Ratio [Wald 95% CI][a] for < 4 cycles		0.59 [0.39, 0.89]
Hazard Ratio [Wald 95% CI][a] for ≥ 4 cycles		0.65 [0.42, 1.00]
Treatment P-Value[a]		0.0501
Cycle group (≥4 or <4) P-Value[a]		< 0.0001
Treatment-by-cycle group interaction P-Value[a]		0.7556

[a]Cox proportional hazards model that includes treatment, cycle group (>=4 or <4), and treatment-by-cycle group interaction. Abbreviations: CI, confidence interval; GnP, gemcitabine plus nab-paclitaxel; mITT, modified intention-to-treat; NA, not available.

https://doi.org/10.1038/s41591-026-04327-4

Extended Data Table 5 | Kaplan-Meier Analysis for Patients Who Received at Least One Cycle of Treatment

	Elraglusib/GnP N=116	GnP N=58
Primary Endpoint: median OS (months) HR=0.57; log-rank p=0.018	12.5	8.5
12-month OS (%)	52.5	28.3
Events (% events)	85 (73.3%)	50 (86.2%)
18-month OS (%)	21.5	0
24-month OS (%)	12.1	0
mPFS (months) HR=0.78; P=NS	6.9	5.6
Events (% events)	105 (90.5%)	55 (94.8%)
DCR, n (%)	53.4%	44.8%
ORR, n (%)	44 (37.9%)	17 (29.3%)

Abbreviations: CI, confidence interval; DCR, disease control rate; GnP, gemcitabine plus nab-paclitaxel; HR, hazard ratio; mPFS, median progression-free survival; NS, not significant; ORR, objective response rate; OS, overall survival.

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Last updated by author(s): 2026/02/14

Reporting Summary

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For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
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☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐ A description of all covariates tested
☒	☐ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☒	☐ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Data was captured in accordance with data integrity, security, and regulatory compliance including FDA 21 CFR Part 11, ICH E9R1 and ICH E6 R2/3 Good Clinical Practice (GCP) Guidelines for the conduct of clinical trials via an electronic data capture system (EDC). Essential system requirements included user-interface specifications, role-based access control, security management, real-time validation, data encryption and audit trails documenting data entry and changes. Data entered into the system was verified by independent monitors responsible for comparing site source data consisting of patient medical records and study documentation to the data captured in the EDC. Data queries were generated to resolve identified issues. Final Data will be verified and cleaned prior to database lock whihc is planned for May 2026.
Data analysis	Data analysis was performed via SAS v9.4

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

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All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

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Actuate is committed to sharing access to patient-level data and supporting clinical documents from eligible studies with qualified external researchers. These requests are reviewed and approved on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. Trial data availability is according to the criteria and process described at www.clinicalstudydatarequest.com. The sequencing data described in this publication will be made available for any qualified request. To submit a request for data, please contact: info@actuatetherapeutics.com.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	The manuscript did not report on patient identification of sex (male/female) as treatment efficacy and safety data were not disaggregated by sex. Results are presented for the overall study population only; no formal subgroup comparisons by sex were performed for the trial. Designation of Sex (male or female) was patient self-reported at baseline for demographic purposes per requirements after patient review and execution of IRB/EC approved Informed Consent at screening. Gender data was not collected or utilized as a treatment outcome for this study.
Reporting on race, ethnicity, or other socially relevant groupings	The manuscript did not report on race, ethnicity, or other socially relevant sub groupings as treatment efficacy and safety were not disaggregated by race, ethnicity, or socially relevant subgroups. While data on participant race and ethnicity was collected as part of baseline demographic data, the study did not include a pre-specified analysis of treatment efficacy by race or ethnicity (a limitation that will be addressed in future, larger studies).
Population characteristics	Eligible patients were 18 years and older, presented with previously untreated mPDAC, and had at least 1 measurable lesion per RECIST v1.152 using a computed tomography (CT) scan or magnetic resonance imaging (MRI). Patients had ECOG PS of 0 or 1 and adequate bone marrow, liver, and renal functions. Patient disposition included: 119 female patients, 131 male patients with a median age of 66 that were randomized to treatment across 60 sites and 6 countries.
Recruitment	Eligible adult male and female patients age 18 or older who signed informed consent, meet inclusion and exclusion for the clinical trial with confirmed mPDAC and with at least 1 measurable lesion per RECIST 1.1 were randomized in a predefined scheme in a 2:1 ratio to receive either investigational product or standard of care. Recruitment was performed locally at the site level, for all regions (60 sites across six countries including the United States, Europe, and Canada) driven by site staff and investigators with experience in treating metastatic pancreatic ductal adenocarcinoma (mPDAC) who were trained trained on the clinical trial protocol. Recruitment began with the first patient enrolled in trial 07-October-2021 with first dose administered on 12-October-2021. Study accrual ended 02-February-2024, upon randomization of the last patient in the trial. The trial is currently ongoing with patients still receiving active treatment in the investigational arm.
Ethics oversight	The clinical trial was conducted in compliance with regulations including 45 CFR part 46 (Common Rule) for human research and 21 CFR Part 50, Health Canada Regulations Part C Division 5 & TCPS 2 Requirements, International Council for Harmonization E6R2/3 Good Clinical Practice (GxP),and in Compliance with (EU) No 536/2014 applicable laws and regulations, including, without limitation, data privacy laws, and clinical study disclosure laws. Data supporting the clinical trial design and Protocol were reviewed by the FDA in accordance with regulation and requirements for managing an Investigational New Drug Application (IND). The Master Protocol and Patient Informed Consent were reviewed and approved by Western Institutional Review Board (WIRB). In Canada, Ethics approval was granted by Health Canada (Clinical Trial Application), and by Regional Ethics Board (REB), governing provincial and local approval at each site performing study related activities. In Europe,the EMA Scientific, Regulatory, and Ethics review of the clinical trial data supporting the Protocol and review of the informed consent was conducted by the Reporting Member State in (Portugal, France, Spain Belgium), and by provincial/local Ethics committees covering informed consent, site suitability, and investigator qualifications for each site participating in the study prior to patient enrollment. Ethics review and approval of the Master Protocol and ICF was received in September 2021, and the protocol/ICF has been reviewed initially and annually at each of the 60 active clinical trial sites participating in the trial across six (6) countries consisting of 22 Sites using WIRB as the Central IRB Ethics review committee and 38 clinical trial sites utilizing Regional/provincial and /local Ethics or independent Institutional Review Boards.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

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Life sciences study design

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Sample size	The pre-defined sample size for the selection stage was up to 25 patients in each of the 3 cohorts. The planned sample size to evaluate the primary efficacy endpoint of 1-year survival rate was 207 evaluable patients (130 patients for elraglusib/GnP and 77 patients for GnP), which also included patients in the appropriate treatment arms from the selection stage. Primary analysis for survival and safety included all patients in the mITT analysis set. The calculation assumptions included achieving 1-year survival rate of 55% with elraglusib/GnP and 35% with GnP (20% difference between the arms) with 80% power using a chi-square test for equal proportions at a 2-sided significance level of 0.05. Accordingly, the primary analysis was originally planned as a comparison of 1-year survival rates. Following regulatory feedback after study initiation, the primary efficacy analysis was revised to a comparison of survival curves using a log-rank test; the sample size was not re-estimated. The log-rank test was selected to appropriately account for censored survival times occurring before 1 year. In accordance with the Pick-the-Winner trial design, statistical significance for the primary endpoint was assessed at an adjusted two-sided significance level of 0.048, corresponding to a log-rank test statistic greater than 3.91 . Descriptive statistics were used to summarize the efficacy and safety parameters. Categorical data were represented as frequency distributions (numbers and percentages of patients), while continuous data as mean (standard deviation) and median (range of minimum to maximum). For all time-to-event efficacy endpoints, the log-rank test statistic was used for hypothesis testing, Kaplan-Meier methodology (including figures, median, 95% CI, number of events, and number censored) for the summary of variables; and Cox proportional hazards model with treatment arm as the independent variable for hazard ratios. For continued OS, time censoring occurred on the date of the most recent assessment of any type prior to the loss of follow-up or the database lock. The Cochran-Mantel-Haenszel test statistic was used for response rates. Additionally, machine learning-based multivariate models were used for cytokine and survival correlative analysis.
Data exclusions	The following exclusion criteria were predefined by protocol to ensure patient safety: pregnancy or lactation, presence of endocrine or acinar pancreatic carcinoma or current active malignancy other than pancreatic cancer, history of cardiovascular disease, major surgery within 7 days of enrollment, participation in another clinical trial, or rapidly progressing brain metastases or leptomeningeal involvement. Patients with stable or slowly progressing brain metastases or leptomeningeal disease were eligible to enroll if no new treatments were initiated in the prior 28 days and anticonvulsants and steroids were at stable doses for the prior 14 days.
Replication	Measures for replication in the clinical trial included registration on clinicaltrials.gov, prespecified analyses outlining primary/secondary outcomes and hypotheses in the study protocol and statistical analysis plan prior to data collection, allowing for a systematic review of inclusion/exclusion criteria, randomization methods, study related procedures, safety, efficacy, and trail outcomes. Clinical trial data was collected electronically, independently verified, and analyzed via SAS Version 9.4. Categorical variables were summarized by frequency distributions (number and percentages of patients), continuous variables were summarized by mean, standard deviation, median, minimum, maximum, and time-to-event variables summarized using Kaplan-Meier methods and figures for the estimated median time. Upon completion of the trial, database lock, and CSR finalization, the study and supporting data will be reported in accordance with regulatory requirements.
Randomization	During the selection stage of the study, patients were initially randomized in 1:1:1 ratio to one of the 3 treatment arms – twice-weekly elraglusib/GnP, once-weekly elraglusib/GnP, or GnP in an open-label clinical study. During the confirmation stage of the study after selecting once weekly as the preferred dosing for elraglusib, patients were randomized at 2:1 to receive once-weekly elraglusib/GnP or GnP alone. Randomization for all stages of the study was stratified by study center with a block size of 3.
Blinding	Not applicable. Study was conducted as a randomized open-label trial.

Reporting for specific materials, systems and methods

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Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
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☒	☐ Dual use research of concern
☒	☐ Plants

Methods

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☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	ClinicalTrials.gov identifier: NCT03678883, European Clinical Trials Database (EU CT) Number:2024-518409-16-00
Study protocol	Randomized Phase 2 Study of Elraglusib (9-ING-41), a GSK-3 Inhibitor, in Combination with Gemcitabine Plus nab-Paclitaxel (GnP) Versus GnP in Previously Untreated Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC)
Data collection	Data collection is being completed in accordance FDA Regulations/Guidance, ICH E6 R2/3 Good Clinical Practice and ICH E8R1 General Considerations for Clinical Studies across sixty-two (62) University and Medical Research Centers in the US, EU (Belgium, France, Portugal and Spain) and Canada. Electronic data collection has been ongoing since October of 2021 with database close and lock projected for May of 2026.
Outcomes	Primary and Secondary Outcome measures were predefined in the clinical trial Protocol and Statistical Analysis Plan for the 1801 3B study based off data assessments from nonclinical studies and four (4) prior clinical studies conducted with elraglusib administered once weekly and twice weekly in normal healthy subjects and patients with relapsed or refractory malignancies. Elraglusib has been administered both as monotherapy and in combination with standard chemotherapy regimens, including gemcitabine and nab-paclitaxel, across a wide range of doses and schedules. The combined data from these studies support the safety, and preliminary antitumor effect observed in heavily pretreated patients receiving intravenous elraglusib, including complete and partial responses as well as durable stable disease across multiple tumor types. These findings together with favorable safety and activity of elraglusib, and survival assessments were utilized in defining primary and secondary outcomes for the study.

Plants

Seed stocks	Not Applicable
Novel plant genotypes	Not Applicable
Authentication	Not applicable

nature medicine

Supplementary information

https://doi.org/10.1038/s41591-026-04327-4

Elraglusib and chemotherapy in metastatic pancreatic ductal adenocarcinoma: a randomized controlled phase 2 trial

In the format provided by the authors and unedited

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Supplementary Table S1. Study Drug Exposure by Treatment Group (mITT Population)

	GnP (N=78)	Elraglusib (1x/w)/GnP (N=155)	Elraglusib (2x/wk)/GnP (N=17)
Treatment Cycles			
1	19 (24.4%)	37 (23.9%)	4 (23.5%)
2	14 (17.9%)	27 (17.4%)	1 (5.9%)
3-4	13 (16.7%)	18 (11.6%)	4 (23.5%)
5-6	12 (15.4%)	18 (11.6%)	2 (11.8%)
7-8	7 (9.0%)	19 (12.3%)	1 (5.9%)
9-10	6 (7.7%)	15 (9.7%)	0
>10	7 (9.0%)	21 (13.5%)	5 (29.4%)
Treatment Cycles			
n (%)	78 (100%)	155 (100%)	17 (100%)
Mean (SD)	4.7 (3.9)	5.5 (4.8)	7.1 (7.1)
Median	4	4	4
Min, Max	1, 19	1, 20	1, 27
Any Dose Delay or Reduction			
No	12 (15.4%)	11 (7.1%)	1 (5.9%)
Yes	66 (84.6%)	144 (92.9%)	16 (94.1%)
First Dose to Last Dose (days)			
n (%)	78 (100%)	155 (100%)	17 (100%)
Mean (SD)	120.1 (108.5)	152.1 (144)	203.8 (242)
Median	88	116	112
Min, Max	7, 526	7, 554	7, 973
Nab-Paclitaxel Doses			
n (%)	78 (100%)	155 (100%)	16 (94.1%)
Mean (SD)	10.4 (8.1)	11.2 (10.1)	14.6 (17)
Median	9	9	10.5
Min, Max	1, 35	1, 48	2, 69
Full Nab-Paclitaxel Doses[a]			
n (%)	75 (96.2%)	150 (96.8%)	15 (88.2%)
Mean (SD)	6.3 (4.7)	5.2 (6.1)	4.6 (6.7)
Median	5	3	2
Min, Max	1, 18	1, 44	1, 27
Average Nab-Paclitaxel Doses/Cycle			
n (%)	78 (100%)	155 (100%)	16 (94.1%)
Mean (SD)	2.3 (0.6)	2.0 (0.7)	1.9 (0.6)

Median	2.3	2	2
Min, Max	1, 3	0, 3	1, 3
Nab-Paclitaxel Dose Intensity (mg/day)			
n (%)	78 (100%)	155 (100%)	16 (94.1%)
Mean (SD)	21.9 (7.2)	19.5 (8.6)	13.8 (5.4)
Median	20.9	18.4	12.8
Min, Max	7.8, 37.2	1.5, 42.9	5.4, 26.6
Nab-Paclitaxel Relative Dose Intensity (%)			
n (%)	78 (100%)	155 (100%)	16 (94.1%)
Mean (SD)	75 (19.4)	69 (22.7)	64.3 (21.9)
Median	72	70	66
Min, Max	39.4, 107.4	6.9, 104.5	22.4, 100.8
Gemcitabine Doses			
n (%)	78 (100%)	155 (100%)	17 (100%)
Mean (SD)	10.8 (8.5)	13.2 (12.4)	15.5 (17)
Median	9	10	11
Min, Max	1, 35	1, 57	1, 69
Full Gemcitabine Doses			
n (%)	76 (97.4%)	154 (99.4%)	16 (94.1%)
Mean (SD)	7.0 (6.4)	6.5 (8.5)	7.6 (9)
Median	5	3	2.5
Min, Max	1, 32	1, 47	1, 28
Average Gemcitabine Doses/Cycle			
n (%)	78 (100%)	155 (100%)	17 (100%)
Mean (SD)	2.3 (0.6)	2.2 (0.6)	2.1 (0.5)
Median	2.5	2.3	2
Min, Max	1, 3	1, 3	1, 3
Gemcitabine Dose Intensity (mg/day)			
n (%)	78 (100%)	155 (100%)	17 (100%)
Mean (SD)	179.8 (55.1)	166.3 (59.9)	134.3 (41.6)
Median	173.1	154.2	127.9
Min, Max	65.0, 296.8	40.4, 342.9	64.3, 212.5
Gemcitabine Relative Dose Intensity (%)			
n (%)	78 (100%)	155 (100%)	17 (100%)
Mean (SD)	77.3 (18.9)	74.7 (19.1)	75.4 (17.8)
Median	78.1	74.2	72.3
Min, Max	39.4, 108.1	25.3, 103.9	44.0, 106.2
Elraglusib Doses			
n (%)	N/A	155 (100%)	17 (100%)
Mean (SD)	N/A	17.7 (17.86)	35.8 (33.61)

Median	N/A	11	21
Min, Max	N/A	1, 74	1, 104
Full Elraglusib Doses			
n (%)	N/A	152 (98.1%)	16 (94.1%)
Mean (SD)	N/A	15 (16.8)	33.8 (32.4)
Median	N/A	7	16.5
Min, Max	N/A	1, 66	2, 103
Average Elraglusib Doses/Cycle			
n (%)	N/A	155 (100%)	17 (100%)
Mean (SD)	N/A	2.8 (1)	5.1 (1.8)
Median	N/A	3	5
Min, Max	N/A	0, 4	1, 8
Elraglusib Dose Intensity (mg/day)			
n (%)	N/A	155 (100%)	17 (100%)
Mean (SD)	N/A	75.8 (28.3)	116.2 (52)
Median	N/A	75	126
Min, Max	N/A	1.5, 175.1	29.0, 198.8
Elraglusib Relative Dose Intensity (%)			
n (%)	N/A	155 (100%)	17 (100%)
Mean (SD)	N/A	77.3 (22.7)	82.8 (21.6)
Median	N/A	82	88
Min, Max	N/A	1.7, 107.7	14.0, 104.3

Abbreviations: GnP, gemcitabine plus nab-paclitaxel; mITT, modifiend intention-to-treat; N/A, not applicable; SD, standard deviation

Supplementary Table S2. Breakdown of "Other" Subsequent Treatment Category (mITT Population)

"Other" subsequent treatment	Patients, n
Elraglusib/GnP arm	**32**
5-FU	1
Atezolizumab/cabozantanib	1
FOLFIRINOX/trastuzumab	1
Gemcitabine	3[a]
Investigational	3
Irinotecan/5-FU	7
Nivolumab	1
Liposomal irinotecan	1
Liposomal irinotecan/5-FU	2
Liposomal irinotecan/oxaliplatin/5-FU	2
Liposomal irinotecan/oxaliplatin/5-FU/LV	3
Oxaliplatin/5-FU	2
Oxaliplatin/5-FU/LV	3
Tislelizumab	1
Trametinib	1
GnP arm	**11**
Capecitabine	1
chemoXRT	1
GnP/capecitabine	1
Investigational	1
Irinotecan/5-FU	1
Oxaliplatin/5-FU	2
Oxaliplatin/5-FU/LV	3
Pegylated liposomal doxorubicin/5-FU/LV	1

[a] One patient included in this group is noted to have post-treatment therapy as gemcitabine, which is first-line based on patient's history.

Abbreviations: 5-FU, 5-fluorouracil; chemoXRT, chemoradiation; FOLFIRINOX, leucovorin plus 5-fluorouracil plus irinotecan plus oxaliplatin; GnP, gemcitabine plus nab-paclitaxel; LV, leucovorin; mITT, modified intention to treat

Supplementary Table S3. Kaplan-Meier Estimates for Overall Survival Based on Neutropenia Grade 3-4 ≥ 1, 2, and 3 Episodes (mITT Population)

	Neutropenia Grade 3-4	Other (No Grade 3-4 Neutropenia)
Neutropenia Grade 3-4 ≥ 1 episode		
GnP Sample Size, n	28	50
Overall Survival - median [95% CI] (months)	9.9 [7.6, 10.6]	5.9 [3.4, 7.2]
Hazard Ratio [Wald 95% CI]		1.73 [1.07, 2.82]
Log-Rank P-Value		0.025
Elraglusib/GnP Sample Size, n	93	62
Overall Survival - median [95% CI] (months)	12.6 [9.0, 15.2]	7.2 [5.7, 9.0]
Hazard Ratio [Wald 95% CI]		1.77 [1.24, 2.52]
Log-Rank P-Value		0.001
Neutropenia Grade 3-4 ≥ 2 episodes		
GnP Sample Size, n	12	66
Overall Survival - median [95% CI] (months)	10.6 [3.2, 17.4]	6.5 [4.6, 8.0]
Hazard Ratio [Wald 95% CI]		1.79 [0.94, 3.42]
Log-Rank P-Value		0.074
Elraglusib/GnP Sample Size, n	49	106
Overall Survival - median [95% CI] (months)	13.0 [11.1, 17.8]	7.8 [6.6, 10.1]
Hazard Ratio [Wald 95% CI]		1.68 [1.14, 2.47]
Log-Rank P-Value		0.008
Neutropenia Grade 3-4 ≥ 3 episodes		
GnP Sample Size, n	8	70
Overall Survival - median [95% CI] (months)	10.4 [1.3, 17.4]	6.9 [5.4, 8.5]
Hazard Ratio [Wald 95% CI]		1.72 [0.78, 3.76]
Log-Rank P-Value		0.171
Elraglusib/GnP Sample Size, n	30	125

	Neutropenia Grade 3-4	Other (No Grade 3-4 Neutropenia)
Overall Survival - median [95% CI] (months)	17.8 [11.9, 20.7]	7.7 [6.6,10.1]
Hazard Ratio [Wald 95% CI]		2.21 [1.37, 3.58]
Log-Rank P-Value		0.001

Abbreviations: CI, confidence interval; GnP, gemcitabine plus nab-paclitaxel; mITT, modified intention-to-treat.

Supplementary Table S4. TEAEs Resulting in Death (mITT Population)

MedDRA[a] Preferred Term	GnP (N=78) n (%)	Elraglusib (1x/wk) +GnP (N=155) n (%)	Elraglusib (2x/wk) +GnP (N=17) n (%)	All Patients (N=250) n (%)
Any Event	13 (16.7%)	19 (12.3%)	3 (17.6%)	35 (14.0%)
Disease progression	7 (9.0%)	8 (5.2%)	3 (17.6%)	18 (7.2%)
Sepsis	0	3 (1.9%)	0	3 (1.2%)
Upper gastrointestinal haemorrhage	1 (1.3%)	1 (0.6%)	0	2 (0.8%)
Cardiac arrest	0	1 (0.6%)	0	1 (0.4%)
Death (not otherwise specified)	0	1 (0.6%)	0	1 (0.4%)
Dehydration	0	1 (0.6%)	0	1 (0.4%)
Febrile neutropenia	0	1 (0.6%)	0	1 (0.4%)
Ischaemic stroke	0	1 (0.6%)	0	1 (0.4%)
Septic shock	0	1 (0.6%)	0	1 (0.4%)
Streptococcal sepsis	0	1 (0.6%)	0	1 (0.4%)
Acute respiratory distress syndrome	1 (1.3%)	0	0	1 (0.4%)
Hypoxia	1 (1.3%)	0	0	1 (0.4%)
Interstitial lung disease	1 (1.3%)	0	0	1 (0.4%)
Intestinal perforation	1 (1.3%)	0	0	1 (0.4%)
Liver abscess	1 (1.3%)	0	0	1 (0.4%)

[a] MedDRA v23.1

Abbreviations: GnP, gemcitabine plus nab-paclitaxel; MedDRA, Medical Dictionary for Regulatory Activities; mITT, modified intention-to-treat; TEAE, treatment-emergent adverse event; wk, week.

Supplementary Table S5. Immunophenotyping of Paired Tumor Biopsies Collected Before and After the Treatment.

Patient No	Treatment	Response/OS/ Status (4/27/2025)	Body Site	Sample collection	CD8+ cells, percentage, tumor parenchyma	Grz B+ cells, percentage, tumor parenchyma	CD56+ cells, percentage, tumor parenchyma	CD11b+ cells, percentage, tumor parenchyma	Collection time	Treatment start	End of treatment
1	GnP	PR/10.6 m/dead	Liver	Predose	8.3	6.7	2.1	19.6	11/21/2023	12/5/2023	5/7/2024, C6W3
			Liver	Postdose	0.5	0.1	23.4	13.8	1/29/2024, **C2W3**		
2	GnP	PD/3.9 m/dead	Liver	Predose	0.4	0.4	0.7	3.8	5/31/2023	6/30/2023	9/15/2023, C4W1
			Liver	Postdose	0.3	0.2	0.9	1.5	9/19/2023, **C4W1**		
3	Elra/GnP	SD/11.1 m/dead	Pancreas	Predose	1.1	18.7	13.3	3.4	5/10/2023	6/8/2023	1/4/2024, C6W4
			Pancreas	Postdose	0.4	2	3.5	0.9	9/27/2023, **C3W4**		
4	Elra/GnP	SD/20.7 m/alive	Ileocecum/Small Bowel	Predose	0.1	0.04	0.01	1.1	5/24/2023	6/28/2023	6/19/2024, C13W3
			Under portal vein liver	Postdose	1.9	0.6	4.1	1.1	8/29/2023, **C3W1**		
5	Elra/GnP	NE/10.1 m/dead	Liver	Predose	0.01	2.4	2.4	12.2	9/21/2023	10/25/2023	1/3/2024, C3W3
			Liver	Postdose	0.4	0.7	1.8	1.8	12/15/2023, **C2W4**		
6	Elra/GnP	SD/7.3 m/dead	Liver	Predose	0.03	0.06	0.7	0	12/8/2023	12/21/2023	5/17/2024, C6W1
			Liver	Postdose	0.2	0.6	1.1	0.6	2/13/2024, **C2W3**		

Abbreviations: Elra, elraglusib; C, cycle; CD8+, a marker of cytotoxic T cells; CD11b+, a marker of myeloid cels including myeloid-derived suppressor cells; CD56+, a marker of natural killer cells; GrzB+, granzyme B, a marker of activated cytotoxic T cells and NK cells; GnP, gemcitabine plus nab-paclitaxel; NE, not evaluable; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease; W, week.

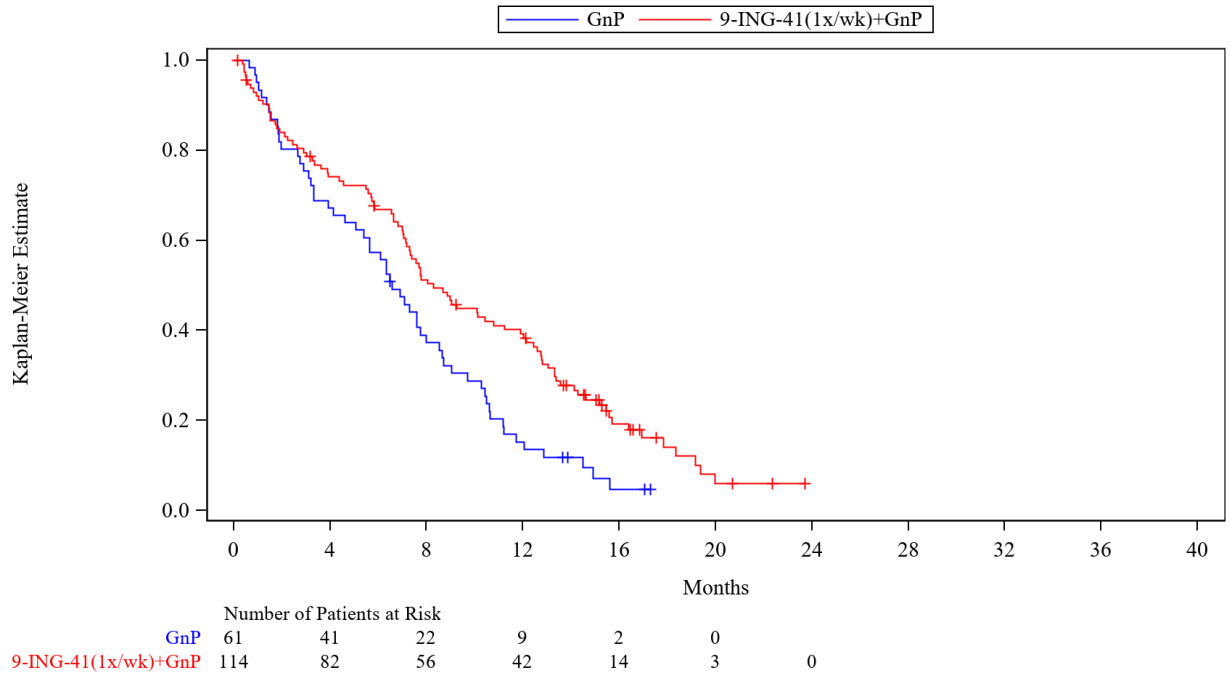
Supplementary Table S6. Deaths Occurrence Based on Treatment Month in the Study.

	Deaths n (%)	
Months	**Elraglusib/GnP (N=155)**	**GnP (N=78)**
0-2	25 (16.1%)	18 (23.1%)
3-4	12	9
5-6	17	10
7-8	19	10
9-10	6	10
11-12	12	5
13-14	9	3
15-16	9	3
17-18	1	1
19-20	3	1
31-32	1	0

Ranges include the full number shown (e.g., 0-2.99, 3-4.99, 5-6.99, etc.), data current as of 27-Mar-2025

Abbreviations: GnP, gemcitabine plus nab-paclitaxel

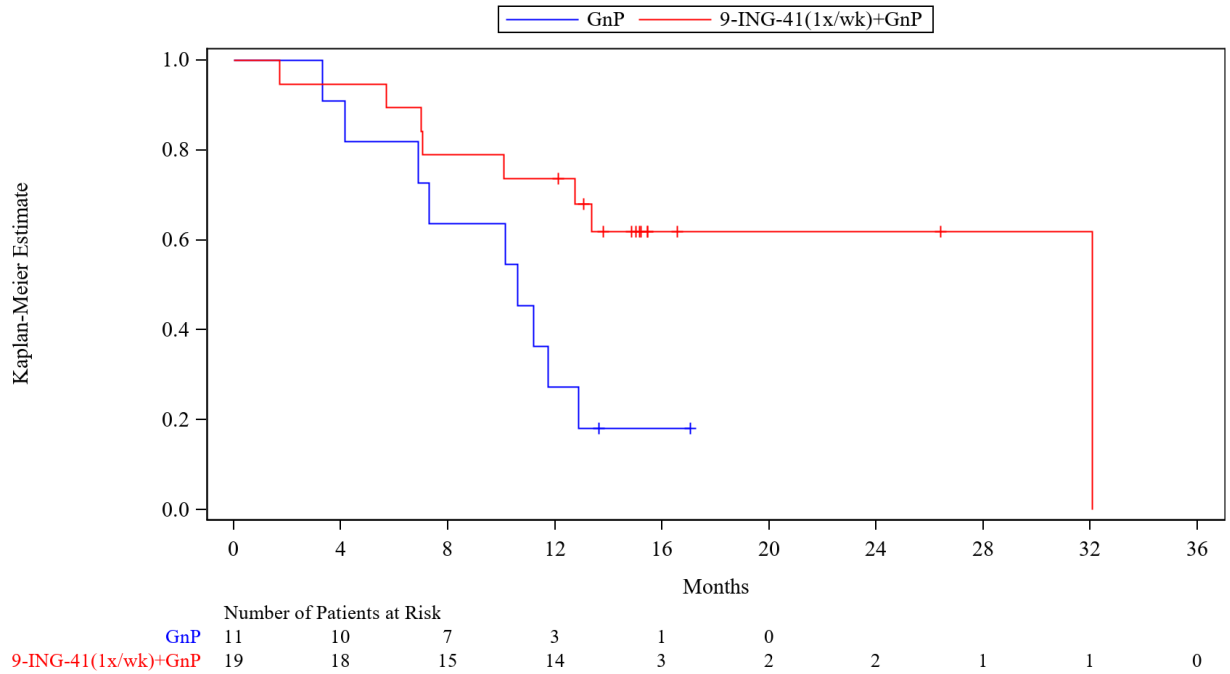
Supplementary Figures



Statistical test: log-rank test stratified by study center; p-value: p=0.008

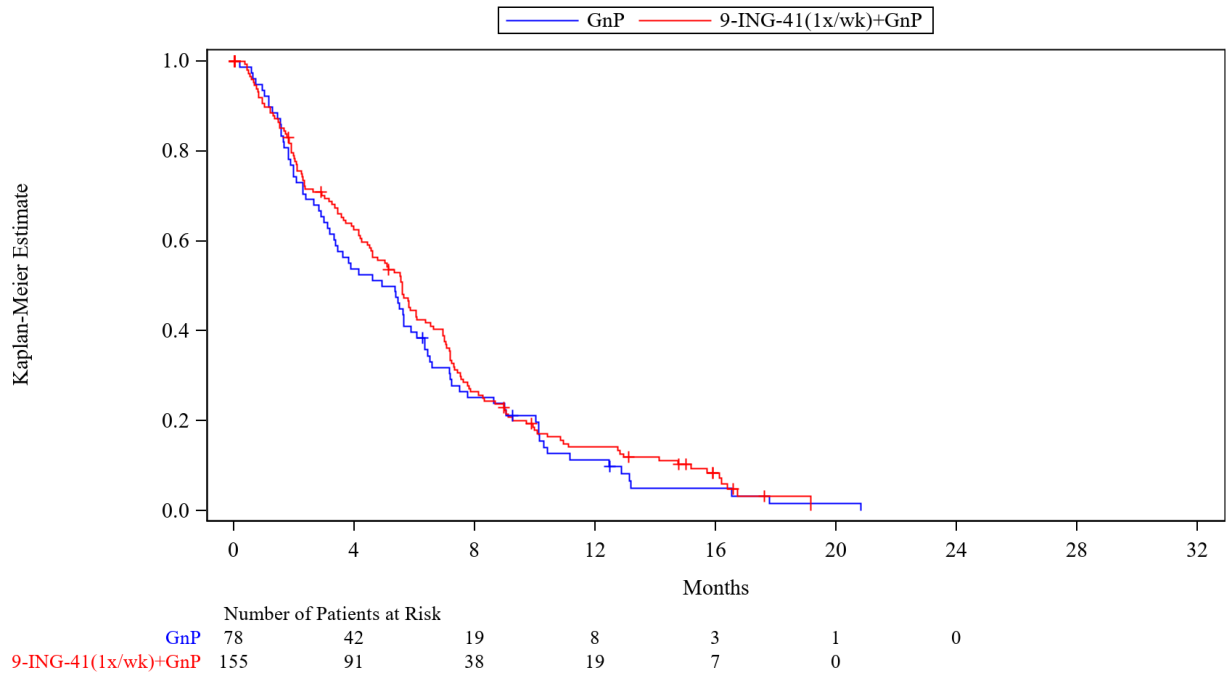
Abbreviations: 9-ING-41, elraglusib; GnP, gemcitabine plus nab-paclitaxel; mITT, modified intention-to-treat; wk, week

Supplementary Figure S1. Kaplan-Meier Estimates of Overall Survival Among Patients with Liver Metastases at Baseline (the mITT population).



Statistical test: log-rank test stratified by study center; p-value: p=0.089
Abbreviations: 9-ING-41, elraglusib; CA, carbohydrate antigen GnP, gemcitabine plus nab-paclitaxel; mITT, modified intention-to-treat; wk, week

Supplementary Figure S2. Kaplan-Meier Estimates of Overall Survival Among Patients with CA19-9 Level Reductions by ≥50% from Baseline After 1 Treatment Cycle (the mITT Population).

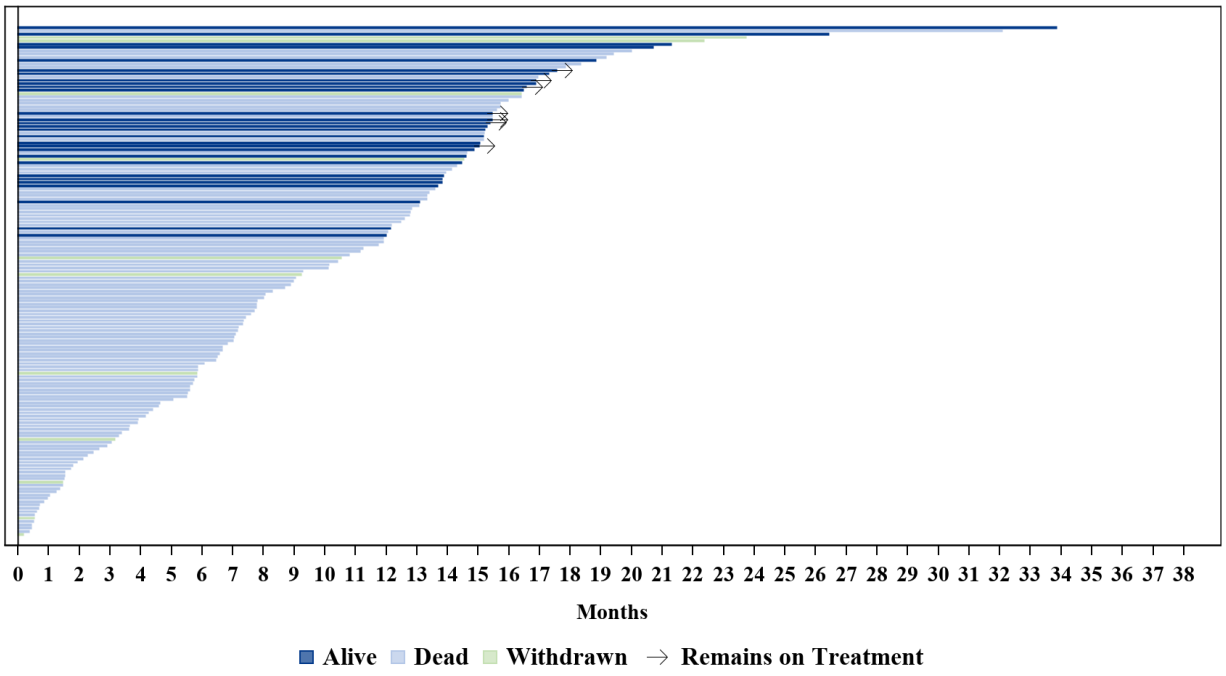


Statistical test: log-rank test stratified by center; p-value: p=0.624

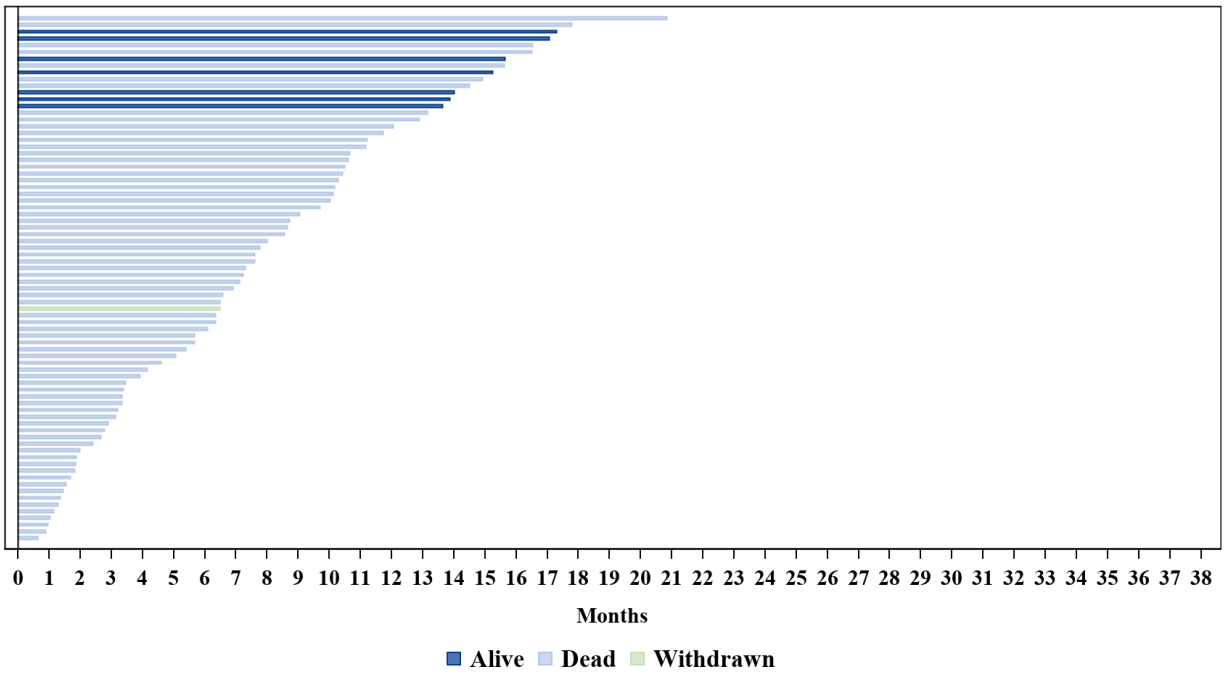
Abbreviations: 9-ING-41, elraglusib; GnP, gemcitabine plus nab-paclitaxel; mITT, modified intention-to-treat; wk, week.

Supplementary Figure S3. Kaplan-Meier Estimates of Progression-free Survival in the mITT Population.

(A)


0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38
Months
Alive
Dead
Withdrawn
Remains on Treatment

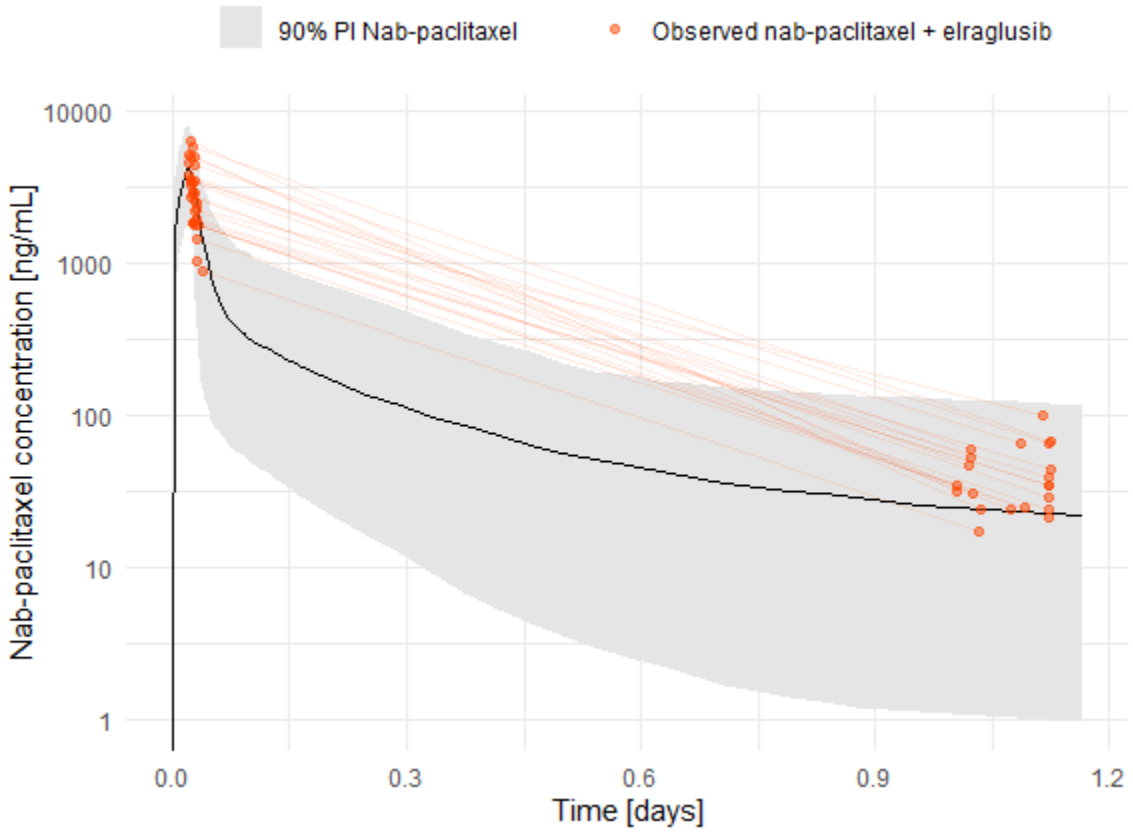
(B)



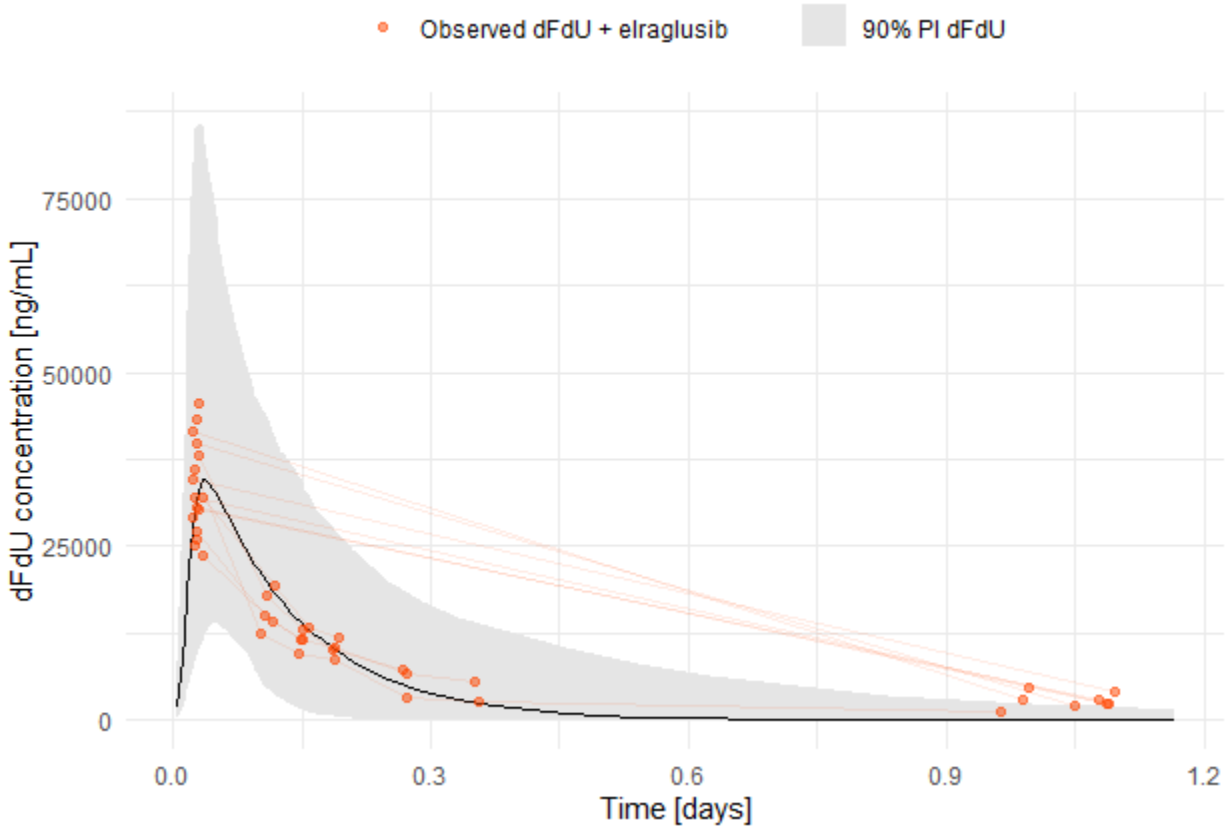
Abbreviations: GnP, gemcitabine plus nab-paclitaxel; mITT, modified intention-to-treat.

Supplementary Figure S4. Swimmer Plot of Best Overall Response for the mITT Population with Elraglusib/GnP (A) and GnP (B).

(A)


90% PI Nab-paclitaxel
Observed nab-paclitaxel + elraglusib
Nab-paclitaxel concentration [ng/mL]
10000
1000
100
10
1
0.0
0.3
0.6
0.9
1.2
Time [days]

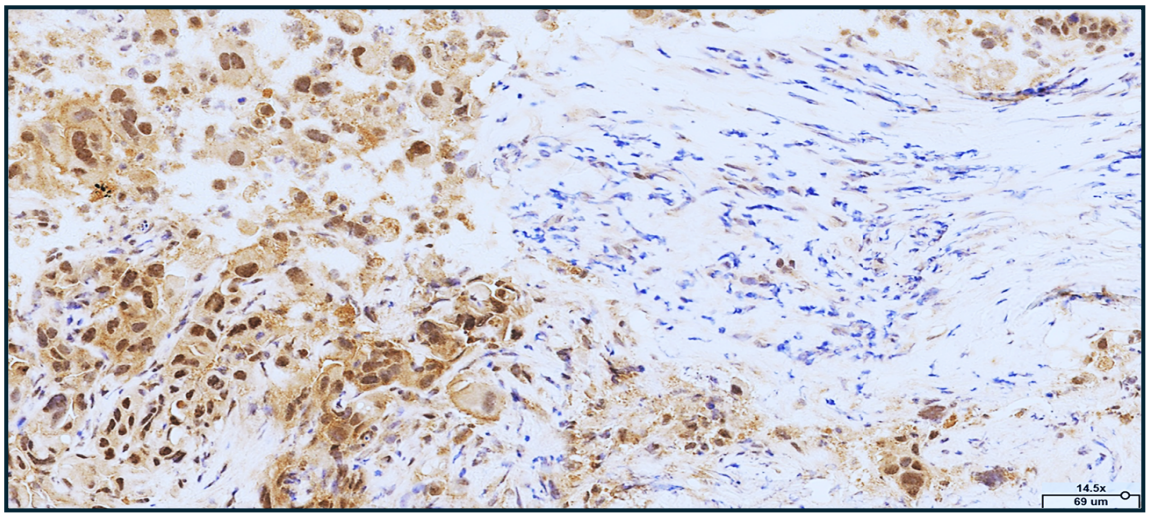
(B)



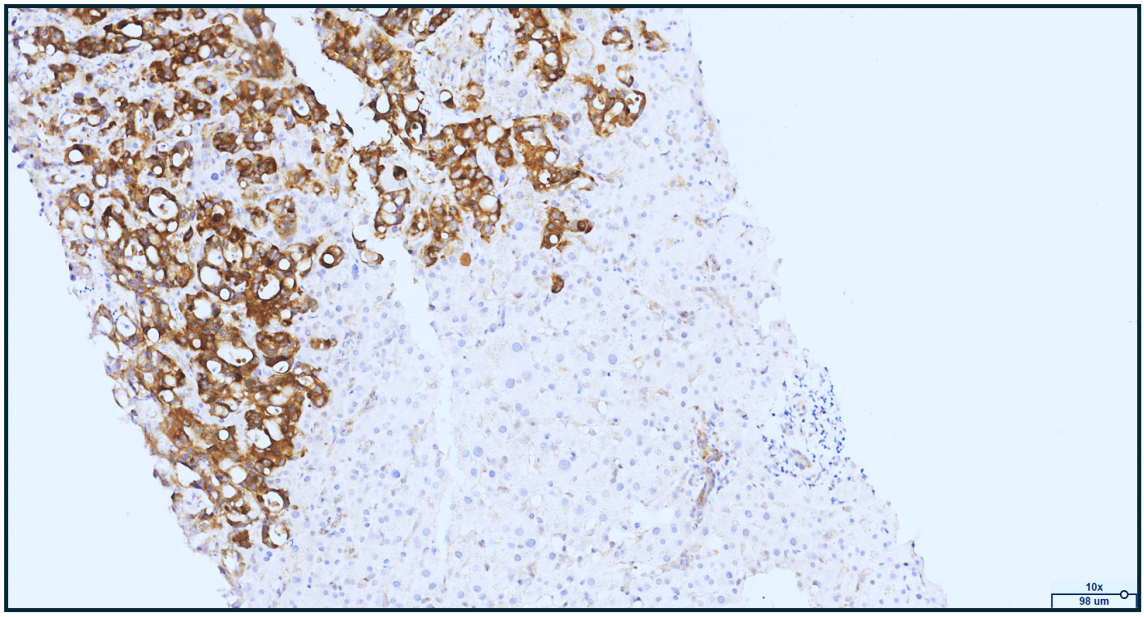
Abbreviations: dFdU, 2′,2′-difluorodeoxyuridine/metabolite of gemcitabine; PI, predicted interval

Supplementary Figure S5. Population Pharmacokinets Models for (A) Nab-paclitaxel and (B) Gemcitabine Metabolite dFdU after Co-administration with Elraglusib.

(A)

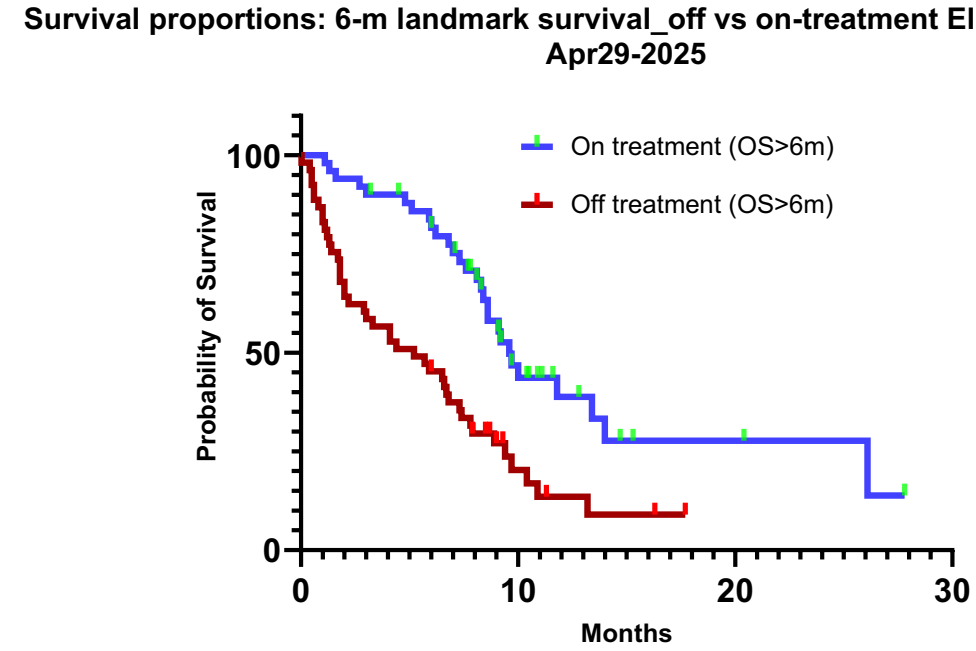


(B)



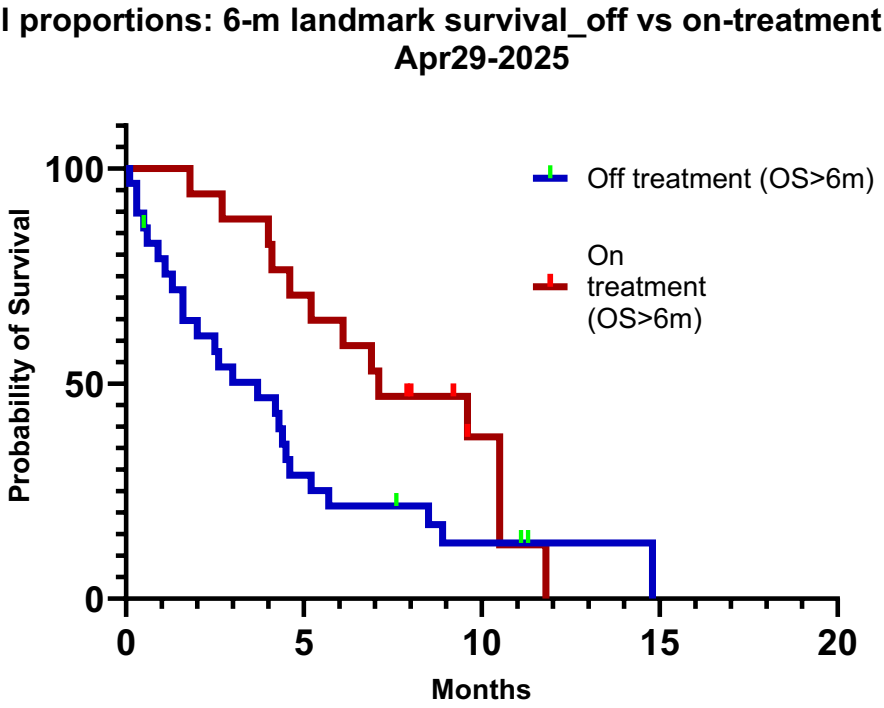
Supplementary Figure S6. Representative pictures of GSK-3β immunohistochemical staining show aberrant nuclear GSK-3β expression in cancer cells in primary PDAC (A) and cytoplasmic overexpression of GSK-3β in pancreatic cancer cells in liver metastatic lesion (B) obtained from elraglusib/GnP-treated patients.

(A)



Statistical test: log-rank test stratified by center; P-value: p<0.0001

(B)



Statistical test: log-rank test stratified by center; p-value: p=0.046

Supplementary Figure S7. Six-month Landmark Analysis for Overall Survival While On Treatment Versus Off Treatment in (A) Elraglusib/GnP Arm and (B) GnP Arm.