

# Post-hoc efficacy and biomarker analysis of elraglusib plus gemcitabine/nab-paclitaxel versus chemotherapy alone in metastatic pancreatic ductal adenocarcinoma

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## Background

Elraglusib (9-ING-41), a glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ) inhibitor, exhibits multimodal antitumor activity. In the international, open-label, randomized phase 2 1801 Part 3B study (NCT03678883), elraglusib plus gemcitabine/nab-paclitaxel (GnP) was evaluated in previously untreated metastatic pancreatic ductal adenocarcinoma (mPDAC), with patients randomized 2:1 to weekly elraglusib/GnP or GnP alone. Primary endpoints were median overall survival (mOS) and 1-year survival rate. Given balanced randomization, post-hoc analyses were performed to contextualize efficacy and identify factors associated with survival outcomes.

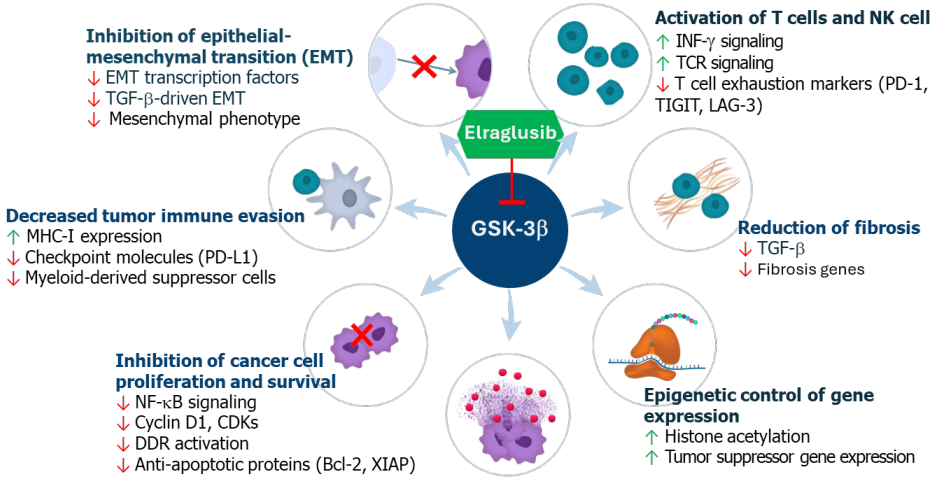


Figure 1. Multimodal MOA of elraglusib in human cancer.

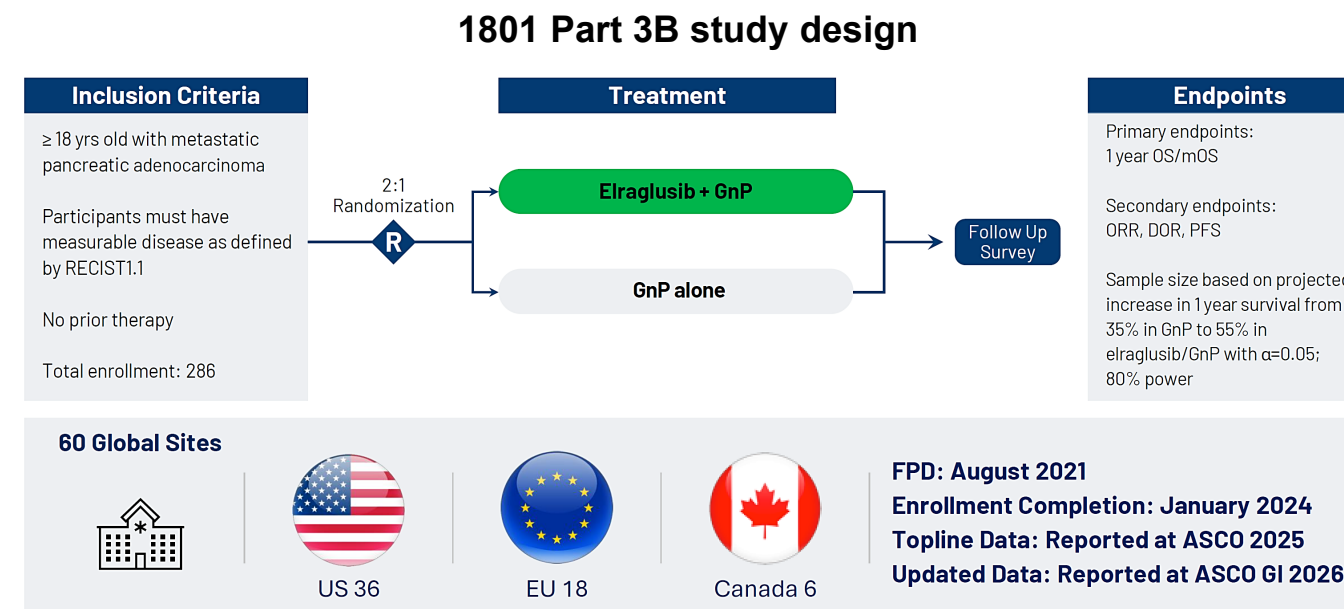
## Methods

As of the data cutoff of November 22, 2025, efficacy and safety were summarized descriptively. Time-to-event endpoints were analyzed using Kaplan–Meier estimates, log-rank testing, and Cox proportional hazards models. Response rates were compared using the Cochran–Mantel–Haenszel test. Post-hoc subgroup, sensitivity, and multivariate machine-learning analyses were performed to explore demographic, clinical, and biomarker correlates of survival; these analyses were hypothesis-generating.

## Conclusions

- Positive overall survival signals were observed in both the ITT and mITT populations, including improved 1-year OS rates versus control.
- Landmark analysis among patients completing at least one cycle demonstrated an approximately 4-month improvement in median OS (12.5 vs 8.5 months with GnP).
- The study enrolled a high-risk population, including patients with hypoalbuminemia and markedly elevated CA19-9 levels. Exploratory subgroup analyses demonstrated improved OS in patients with albumin  $\geq 3$  g/dL and CA19-9 <8000 U/mL treated with elraglusib/GnP.
- Outcomes appeared more favorable in the EU cohort versus North America, although interpretation is limited by smaller sample sizes and potential differences in patient selection.
- KRAS, TP53, CDKN2A, and SMAD4 genetic alterations were associated with worse OS only in the elraglusib/GnP arm, while lower tumor mutational burden, lower ctDNA fraction, and lower tumor grade correlated with improved OS.

## Results



Patient Baseline Characteristics	Number of patients	mOS, months		P value
		GnP	Elraglusib (1x/w)/GnP	
ECOG	0	8	12.2	0.007
	$\geq 1$	138	6.3	0.08
Albumin (baseline)	<3 g/dL	13	1.5	0.1
	$\geq 3$ g/dL	220	7.6	0.02
Liver metastasis	Present	175	6.6	0.01
	Absent	58	10.2	0.5
CA19-9 (baseline)	<8000 U/ml	165	7.8	0.01
	$\geq 8000$ U/ml	64	5.7	0.1
Region	Europe	56	5.9	0.009
	North America	177	7.6	0.1

Table 1. Subgroup analysis of OS in GnP vs elraglusib/GnP arm.

### Study 1801 Part 3B Meets Primary Endpoint of Improved Survival

Doubling of 1 year OS and 38% Reduction in Risk of Death vs GnP

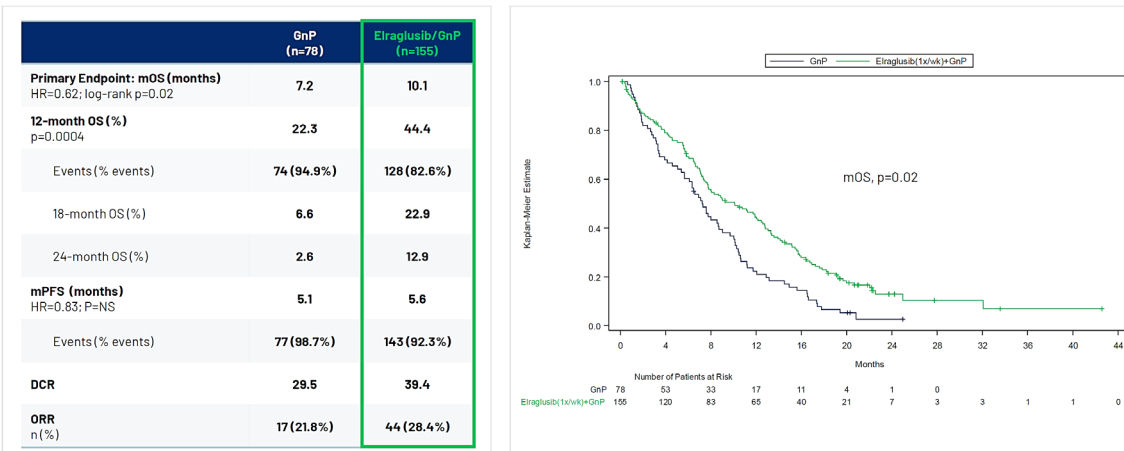


Figure 2. Analysis of clinical outcomes in GnP vs elraglusib(1x/week)/GnP arms.

### Subgroup of Patients Treated for One Cycle (4 weeks) - Significant Benefit in OS

Near Doubling of 1 year OS and 42% Reduction in Risk of Death vs GnP

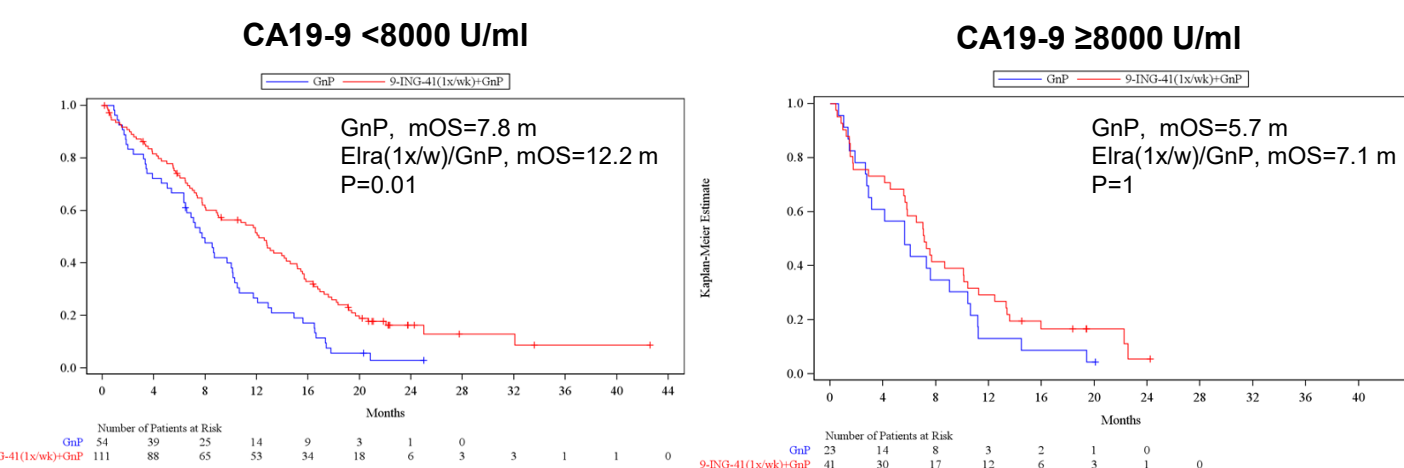
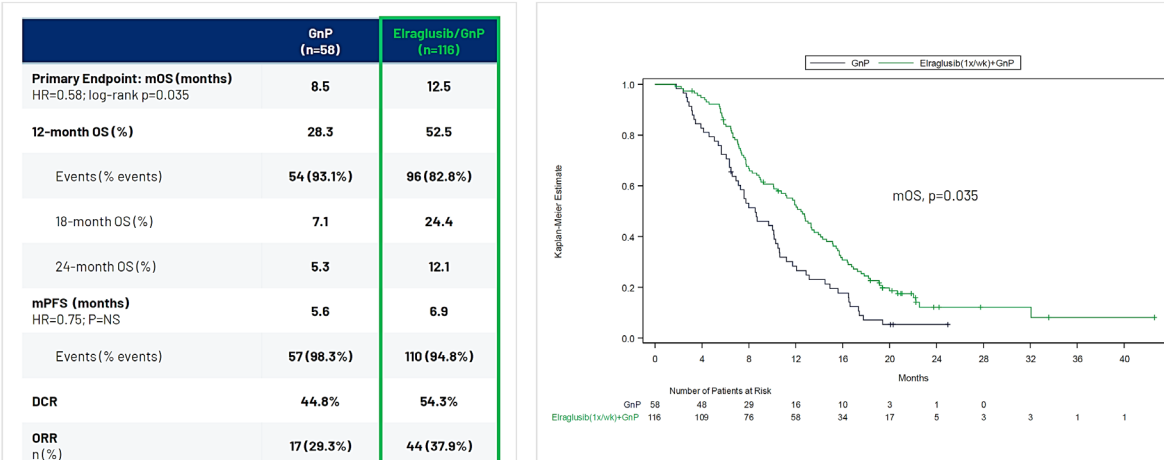


Figure 4. Analysis of OS in elraglusib(1x/w)/GnP-treated patients in North America vs Europe. In elra(1x/w)/GnP-treated patients, early mortality in North America and Europe was 15.4% and 5.3%, respectively.

## Results

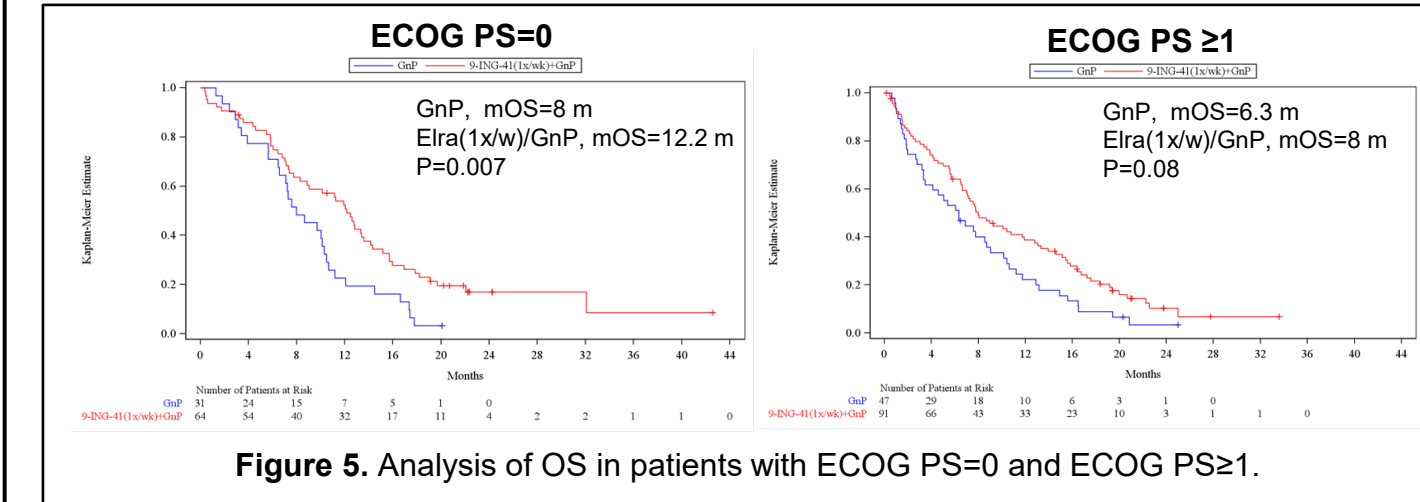


Figure 5. Analysis of OS in patients with ECOG PS=0 and ECOG PS $\geq 1$ .

Gene	Mutations in all patients, 1801 Part 3B (N=178)	GnP (N=59)				Elraglusib(1x/w)/GnP (N=119)			
		Mutations, %	mOS, months, wt	mOS, months, mut	P-value	Mutations, %	mOS, months, wt	mOS, months, mut	P-value
KRAS	80%	85% (50/59)	10.1	6.6	P=0.2	78% (93/119)	16.9	7.6	P<0.001
TP53	67%	71% (42/59)	7.6	6.2	P=0.6	66% (78/119)	13.4	7.3	P=0.002
CDKN2A	27%	34% (20/59)	7.6	6.6	P=0.6	24% (28/119)	10.4	5.8	P=0.002
SMAD4	19%	19% (11/59)	7.1	3.4	P=0.08	19% (22/119)	10.1	5.8	P=0.003
ARID1A	17%	15% (9/59)	7.6	5.7	P=0.4	19% (22/119)	8.7	7.3	P=0.2

Table 2. Mutational analysis of cfDNA obtained from patients treated with GnP and elraglusib/GnP.

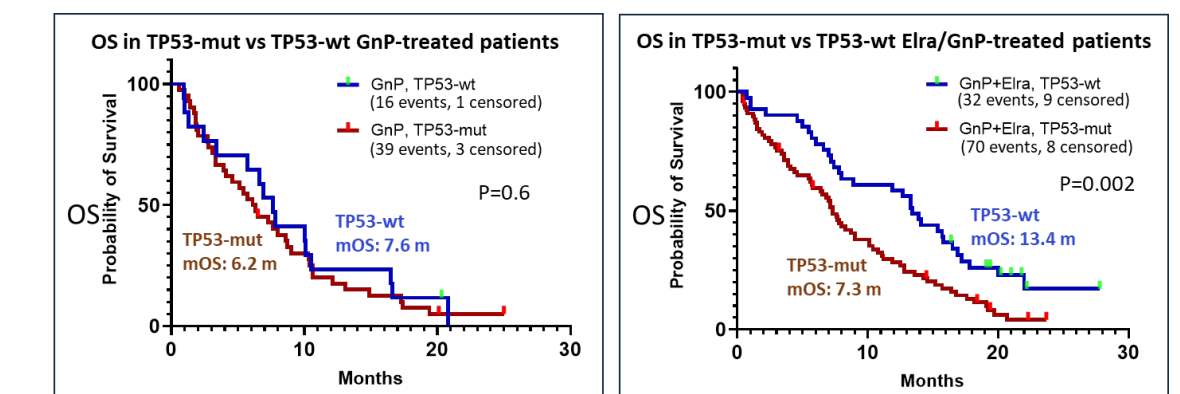


Figure 6. Analysis of TP53 mutations and OS in GnP and elraglusib/GnP arms. Survival curves were compared by log-rank (Mantel-Cox) test. Elra, elraglusib

- Pre-dose plasma samples were obtained from 178 patients with mPDAC (GnP: 59 patients; elraglusib/GnP: 119 patients). Mutational analysis of cfDNA extracted from plasma samples was performed by Tempus (Chicago, IL) using the xF+ platform.
  - Frequently mutated genes consisted of KRAS (80%), TP53 (67%), CDKN2A (27%), SMAD4 (19%), and ARID1A (17%) (Table 2).
  - KRAS, TP53, CDKN2A or SMAD4 gene mutations were correlated with worse overall survival (OS) in patients treated with elraglusib/GnP ( $p < 0.05$ ) but not in GnP-treated patients (Table 2; Fig. 6).
  - Low tumor mutational burden (TMB) and low ctDNA fraction were correlated with better OS in patients treated with elraglusib/GnP ( $P < 0.05$ ) but not in GnP-treated patients.
- Low tumor grade (Grade 1+2; mOS=14.3 m) was correlated with improved OS compared with high grade (Grade 3; mOS=7.8 m) in the elraglusib/GnP arm ( $P=0.005$ ) but not in the GnP arm.
- Pre-dose GSK-3 $\beta$  expression was analyzed in tumor samples obtained from 139 patients with mPDAC. Aberrant nuclear expression and cytoplasmic overexpression of GSK-3 $\beta$  in 50% or more cancer cells was found in 23% and 78% of tumors, respectively. Expression of GSK-3 $\beta$  was not correlated with tumor response or OS in the elraglusib/GnP or GnP arms.