

# Preliminary Phase 1 Results of INCB161734, a Novel Oral Kirsten Rat Sarcoma (KRAS) G12D Inhibitor, as Monotherapy or in Combination With Chemotherapy for Advanced/Metastatic Pancreatic Ductal Adenocarcinoma (PDAC)

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Abstract number 654. Presented at the ASCO GI Symposium 2026 • San Francisco, CA, USA • January 8-10, 2026

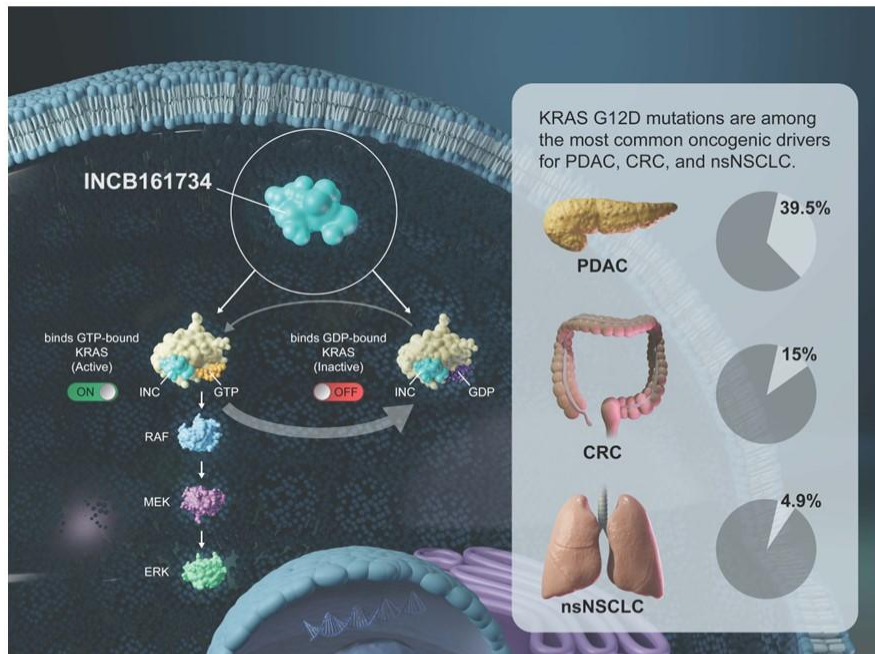
# Key Takeaway Points

- INCB161734 monotherapy demonstrates a favorable safety and efficacy profile at the RP2D of 1200 mg qd
- INCB161734 at 1200 mg qd demonstrates tolerability with SoC chemotherapy (GEMNabP or mFOLFIRINOX) in patients with metastatic PDAC, without compromising chemotherapy dose intensity or schedule

GEMNabP, nab-paclitaxel + gemcitabine; mFOLFIRINOX, modified leucovorin calcium, fluorouracil, irinotecan hydrochloride, oxaliplatin; PDAC, pancreatic ductal adenocarcinoma; qd, daily; RP2D, recommended phase 2 dose; SoC, standard of care.

# Introduction

- $KRAS^{G12D}$  mutations are among the most common oncogenic drivers for PDAC, CRC, and nsNSCLC<sup>1</sup>



- INCB161734 is a novel, selective ON/OFF oral  $KRAS^{G12D}$  inhibitor:
  - Exhibited >80-fold selectivity over  $KRAS^{WT}$
  - Demonstrated robust monotherapy antitumor activity and enhanced tumor growth inhibition when combined with chemotherapy in murine models with  $KRAS^{G12D}$  xenograft and syngeneic tumors
- Initial phase 1 results demonstrated a manageable safety profile in patients with  $KRAS^{G12D}$  advanced or metastatic solid tumors<sup>2</sup>

1. Lee JK, et al. *NPJ Precis Onc.* 2022;6:91. 2. Desai J, et al. Presented at: ESMO 2025; Berlin, Germany; oral 9160.

CRC, colorectal cancer; ERK, extracellular signal-regulated kinase; GDP, guanosine diphosphate; GTP, guanosine triphosphate; INC, INCB161734; MEK, mitogen-activated protein kinase kinase; nsNSCLC, non-squamous non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; RAF, rapidly accelerated fibrosarcoma; WT, wild type.

# INCB161734-101 (NCT06179160): Study Design

## Key Eligibility Criteria (All Groups)

- Locally advanced or metastatic solid tumor with KRAS<sup>G12D</sup> mutation
- ECOG PS 0 or 1
- No prior treatment with a KRAS<sup>G12D</sup> selective inhibitor

## Key Eligibility Criteria (Chemotherapy Combinations in PDAC)

- Dose escalation: ≤1 prior systemic regimen in the metastatic setting<sup>†</sup>
- Dose expansion: no prior regimen in the metastatic setting<sup>†</sup>

## INCB161734 Monotherapy\*

### Dose Escalation<sup>‡</sup>

200 mg → 1600 mg qd (n=28)



Randomized Optimization  
of Selected RDEs

### Dose Expansion 600 mg/1200 mg qd

PDAC<sup>§</sup>  
600 mg qd (n=25)  
1200 mg qd (n=61)

**Primary Endpoint:**  
Safety and tolerability

**Secondary  
Endpoints/Objectives:**  
ORR, DCR, DOR, PK

## INCB161734 + SoC Chemotherapy in PDAC\*

### Dose Escalation INCB161734 600/1200 mg qd

+ GEMNabP (n=17)

+ mFOLFIRINOX (n=16)



Selected RDE

### Dose Expansion INCB161734 1200 mg qd

+ GEMNabP (target n~20)

+ mFOLFIRINOX (target n~20)

## Chemotherapy Regimens

**GEMNabP:** D1, D8, D15 of 28D cycle. Gemcitabine 1000 mg/m<sup>2</sup>, nab-paclitaxel 125 mg/m<sup>2</sup>

**mFOLFIRINOX:** D1, D15 of 28D cycle. Oxaliplatin 85 mg/m<sup>2</sup>, leucovorin 400 mg/m<sup>2</sup>, irinotecan 150-180 mg/m<sup>2</sup>, fluorouracil 2400 mg/m<sup>2</sup>

\*As of November 11, 2025. <sup>†</sup>Neoadjuvant or adjuvant therapy may be counted as 1 line of therapy if recurrence/development of metastatic disease occurred within 6 months of last dose of therapy; patients who received no standard systemic therapy for PDAC may have received ≤1 cycle of GEMNabP or mFOLFIRINOX before enrolling, with last dose ≥7 days before cycle 1, day 1. <sup>‡</sup>Included doses of 200-1600 mg qd and 600 mg bid. Additional cohorts of patients included the pharmacodynamic evaluation cohort (n=9) and the food-effect cohort (n=17). <sup>§</sup>Included patients in the pharmacodynamic evaluation and food-effect cohorts.

bid, twice daily; CRC, colorectal cancer; D, day; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GEMNabP, nab-paclitaxel + gemcitabine; mFOLFIRINOX, modified leucovorin calcium, fluorouracil, irinotecan hydrochloride, oxaliplatin; ORR, objective response rate; PDAC, pancreatic ductal adenocarcinoma; PK, pharmacokinetics; qd, daily; RDE, recommended dose for expansion; SoC, standard of care.

# PDAC Patient Disposition and Baseline Characteristics

- As of November 11, 2025, 61 patients with PDAC received single agent INCB161734 1200 mg qd
  - Treatment ongoing in 42 (69%)
  - Primary reason for discontinuation was disease progression (n=14; 23%)
- 28 patients received INCB161734 in combination with GEMNabP
  - Treatment ongoing in 24 (86%)
  - Primary reason for discontinuation was withdrawal by patient (n=2; 7%)
- 16 patients received INCB161734 in combination with mFOLFIRINOX
  - Treatment ongoing in 12 (75%)
  - Primary reason for discontinuation was disease progression (n=3; 19%)

	INCB161734 1200 mg qd Monotherapy (n=61)	INCB161734 600/1200 mg qd	
		GEMNabP (n=28)	mFOLFIRINOX (n=16)
Age, median (range), years	63 (38, 85)	65 (40, 79)	61 (34, 72)
≥65 years, n (%)	27 (44.3)	14 (50.0)	7 (43.8)
Liver metastases, n (%)	43 (70.5)	24 (85.7)	12 (75.0)
Total prior lines of therapy, median (min, max)	2 (1, 6)	1 (0, 2)	1 (0, 2)
Prior neoadjuvant/adjuvant therapy, n (%)	27 (44.3)	12 (42.9)	3 (18.8)
Prior systemic therapies in the metastatic setting, n (%)			
0 prior lines	0 (0)	15 (53.6)	11 (68.8)
1 prior line	20 (32.8)	13 (46.4)	5 (31.3)
2 prior lines	26 (42.6)	0 (0)	0 (0)
≥3 prior lines	15 (24.6)	0 (0)	0 (0)
KRAS <sup>G12D</sup> molecular test for enrollment (%)		NGS-tissue (70.2), NGS-blood (21.3), PCR-tissue (4.3), PCR-blood (4.3)	

GEMNabP, nab-paclitaxel + gemcitabine; max, maximum; mFOLFIRINOX, modified leucovorin calcium, fluorouracil, irinotecan hydrochloride, oxaliplatin; min, minimum; NGS, next-generation sequencing; PCR, polymerase chain reaction; PDAC, pancreatic ductal adenocarcinoma; qd, daily.

# INCB161734 Was Well Tolerated as 1200 mg qd Monotherapy in Patients With *KRAS*<sup>G12D</sup>-Mutated PDAC

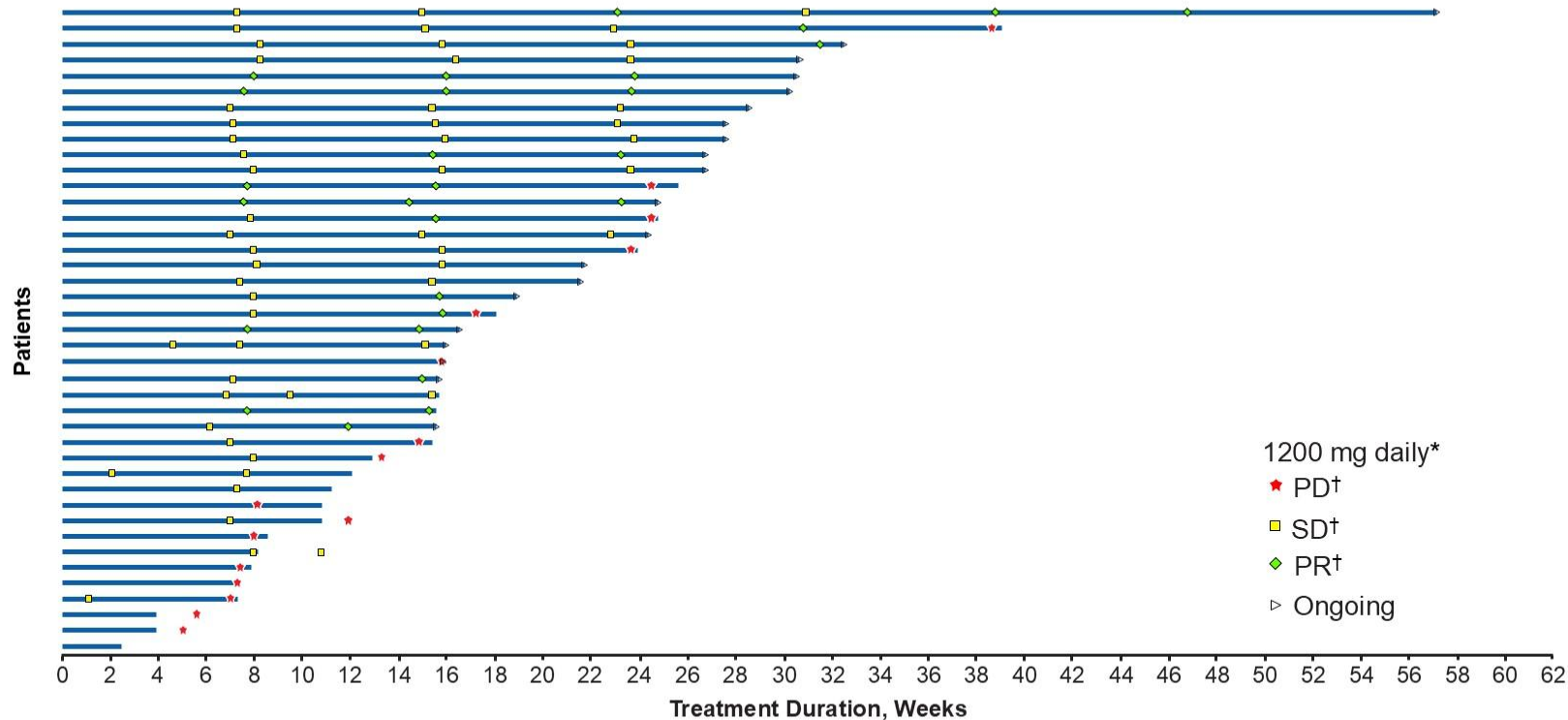
- 2 patients (3%) discontinued treatment due to TRAEs
- 6 patients (10%) had dose reductions due to TRAEs
  - Most common TRAE leading to dose reduction was fatigue (n=2)
- 13 patients (21%) had dose interruption due to TRAEs
- Gastrointestinal TRAEs were mostly grade 1, manageable with concomitant medication, and improved after cycle 1
  - Vomiting was mainly limited to the first cycle of treatment

TRAE, <sup>†</sup> n (%)	TRAEs*			
	1200 mg qd (n=61)			
	All Grades	Grade 1	Grade 2	Grade ≥3
Any TRAE	55 (90.2)	19 (31.1)	24 (39.3)	12 (19.7)
Nausea	36 (59.0)	24 (39.3)	11 (18.0)	1 (1.6)
Vomiting	35 (57.4)	27 (44.3)	8 (13.1)	0 (0)
Diarrhea	33 (54.1)	26 (42.6)	6 (9.8)	1 (1.6)
Fatigue	20 (32.8)	15 (24.6)	4 (6.6)	1 (1.6)
Decreased appetite	9 (14.8)	8 (13.1)	0 (0)	1 (1.6)
Selected TRAEs				
Thrombocytopenia	4 (6.6)	4 (6.6)	0 (0)	0 (0)
Neutropenia	4 (6.6)	1 (1.6)	2 (3.3)	1 (1.6)
Anemia	4 (6.6)	2 (3.3)	0 (0)	2 (3.3)

\*Assessed in patients who received ≥1 dose of study drug. †Includes only TRAEs that occurred in ≥10% of patients receiving the indicated dose, except for selected TRAEs. PDAC, pancreatic ductal adenocarcinoma; qd, daily; TRAE, treatment-related adverse event.



# Swimmer Plot Indicates Clinical Benefit Is Durable in Heavily Pretreated Patients With PDAC

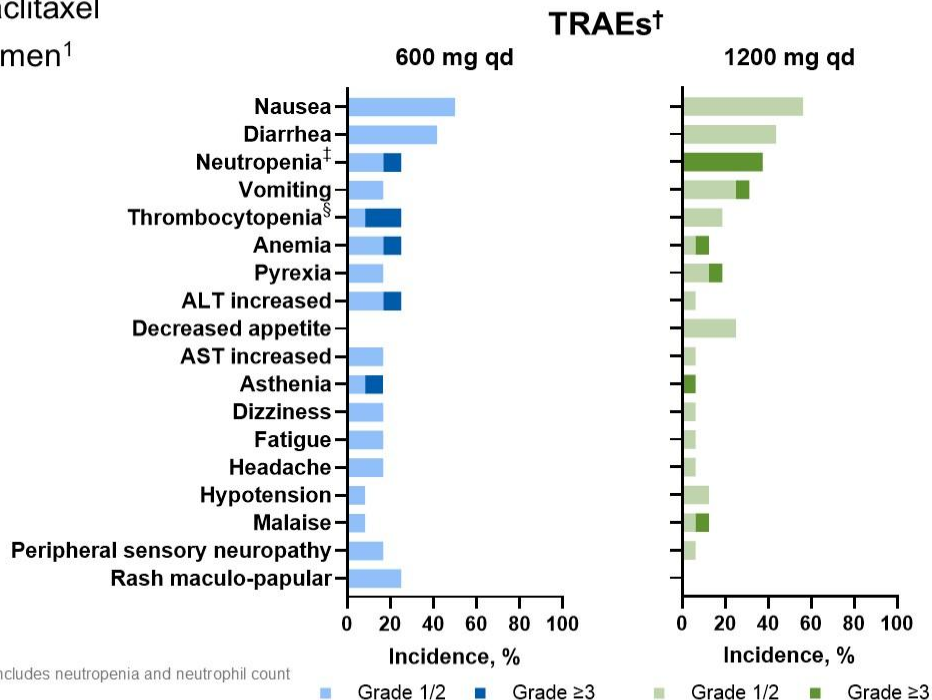


\*NCB161734 600 mg bid or 1200 mg qd. †Investigator-assessed per RECIST v1.1 in patients with a baseline scan who either completed  $\geq 2$  postbaseline scans or discontinued due to clinical progression or death. bid, twice daily; PD, progressive disease; PDAC, pancreatic ductal adenocarcinoma; PR, partial response; qd, daily; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

# INCB161734 in Combination With GEMNabP Was Well Tolerated Without Compromising Chemotherapy Dose Intensity

- 46% of patients were 2L and had received prior systemic chemotherapy
- Median RDI was 74% for both gemcitabine and nab-paclitaxel
  - Comparable to previous reports for GEMNabP regimen<sup>1</sup>

TRAE,* n (%)	GEMNabP	
	600 mg qd (n=12)	1200 mg qd (n=16)
	All Grades	All Grades
Any TRAE	12 (100)	14 (87.5)
TRAE leading to INCB161734		
Interruption	7 (58.3)	7 (43.8)
Reduction	0 (0)	1 (6.3)
Discontinuation	0 (0)	0 (0)
TRAE leading to chemotherapy		
Interruption	8 (66.7)	6 (37.5)
Reduction	3 (25.0)	7 (43.8)
Discontinuation	1 (8.3)	0 (0)



1. Von Hoff DD, et al. *N Engl J Med*. 2013;369(18):1691-1703.

\*Assessed in patients who received  $\geq 1$  dose of study drug. <sup>†</sup>Including only TRAEs that occurred in  $\geq 10\%$  of patients. <sup>‡</sup>Includes neutropenia and neutrophil count decreased. <sup>§</sup>Includes thrombocytopenia and platelet count decreased.

2L, second-line; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GEMNabP, nab-paclitaxel + gemcitabine; qd, daily; RDI, relative dose intensity; TRAE, treatment-related adverse event.

# INCB161734 in Combination With mFOLFIRINOX Was Well Tolerated Without Compromising Chemotherapy Dose Intensity

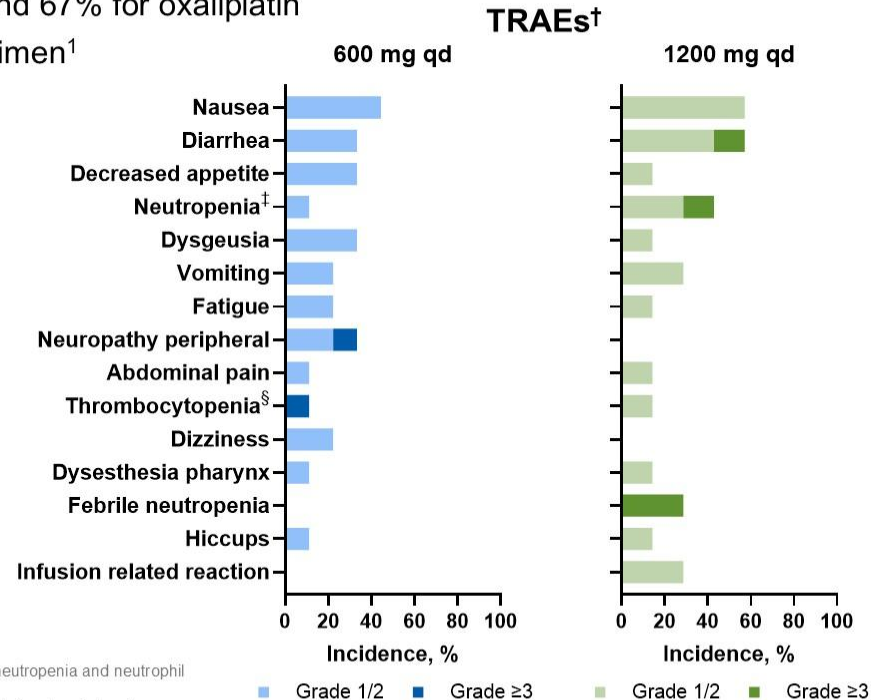
- 31% of patients were 2L and had received prior systemic chemotherapy
- Median RDI was 76% for fluorouracil, 67% for irinotecan, and 67% for oxaliplatin
  - Comparable to previous reports for mFOLFIRINOX regimen<sup>1</sup>

TRAE,* n (%)	mFOLFIRINOX	
	600 mg qd (n=9)	1200 mg qd (n=7)
	All Grades	All Grades
Any TRAE	8 (88.9)	5 (71.4)
TRAE leading to INCB161734		
Interruption	4 (44.4)	3 (42.9)
Reduction	0 (0)	0 (0)
Discontinuation	0 (0)	0 (0)
TRAE leading to chemotherapy		
Interruption	3 (33.3)	4 (57.1)
Reduction	1 (11.1)	4 (57.1)
Discontinuation	2 (22.2)	2 (28.6)

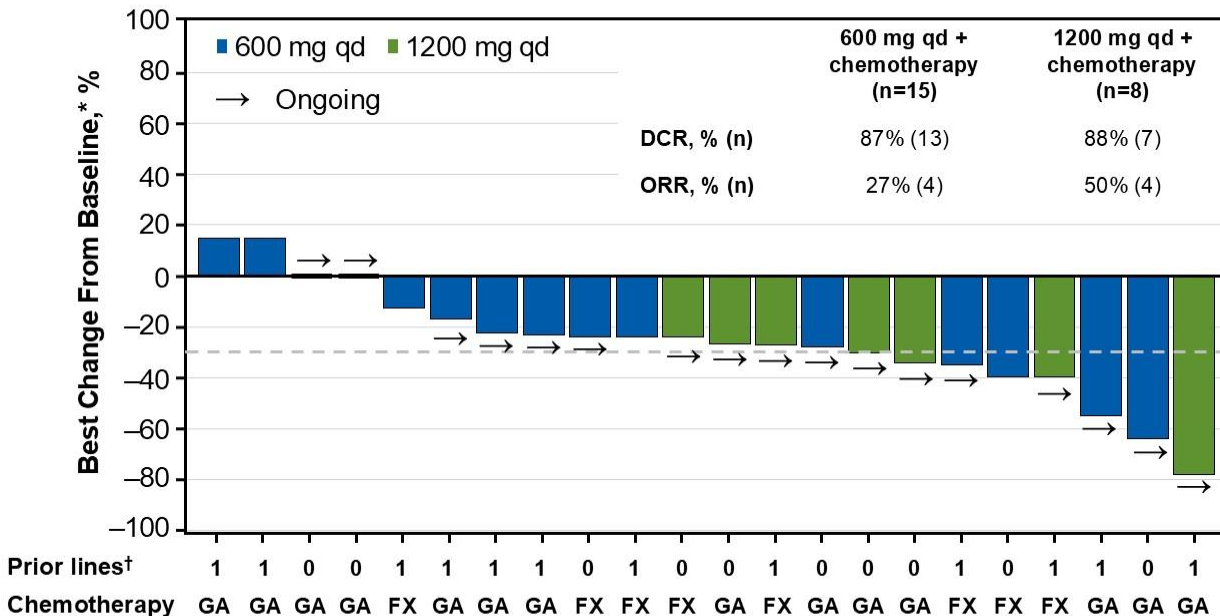
1. Conroy T, et al. *N Engl J Med*. 2018;379(25):2395-2406.

\*Assessed in patients who received  $\geq 1$  dose of study drug. †Including only TRAEs that occurred in  $\geq 10\%$  of patients. ‡Includes neutropenia and neutrophil count decreased. §Includes thrombocytopenia and platelet count decreased.

2L, second-line; mFOLFIRINOX, modified leucovorin calcium, fluorouracil, irinotecan hydrochloride, oxaliplatin; qd, daily; RDI, relative dose intensity; TRAE, treatment-related adverse event.



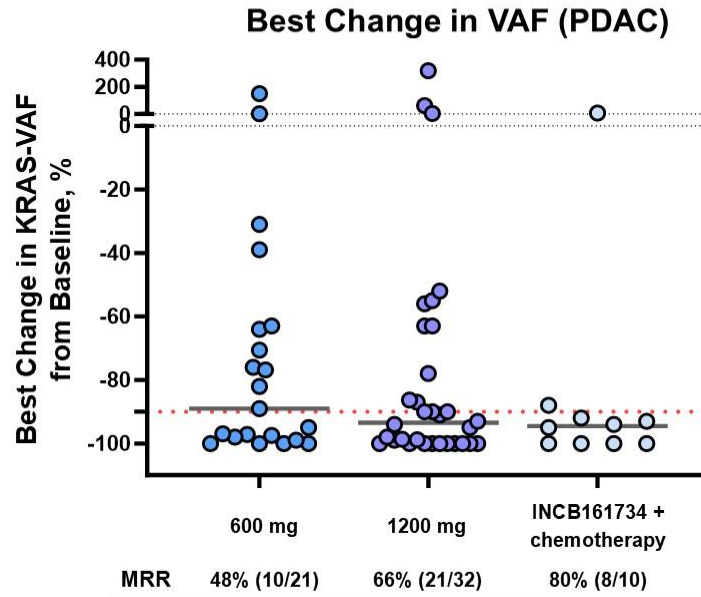
# INCB161734 With SoC Chemotherapy Showed Encouraging Antitumor Activity in Patients With 1L or 2L Metastatic PDAC



\*Investigator-assessed per RECIST v1.1 in patients with  $\geq 1$  postbaseline scan or who discontinued due to clinical progression or death. Missing data: death before first scan (n=1). †In the advanced/metastatic setting. 1L, first-line; 2L, second-line; DCR, disease control rate; FX, modified leucovorin calcium, fluorouracil, irinotecan hydrochloride, oxaliplatin; GA, nab-paclitaxel + gemcitabine; ORR, objective response rate; PDAC, pancreatic ductal adenocarcinoma; qd, daily; RECIST, Response Evaluation Criteria in Solid Tumors; SoC, standard of care.

# Measurement of $KRAS^{G12D}$ in Plasma ctDNA Confirmed Rapid Molecular Responses

- INCB161734 at  $\geq 600$  mg qd dose caused rapid molecular responses
- In patients with PDAC with detectable  $KRAS^{G12D}$  in plasma ctDNA (79%), 66% receiving a 1200 mg dose had an early MR\*
- INCB161734 chemotherapy combinations (GEMNabP or mFOLFIRINOX) showed increased MR

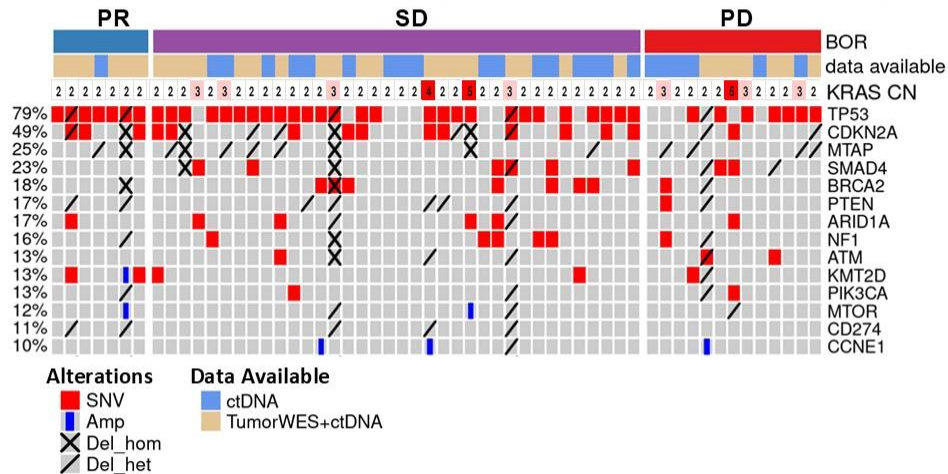


\* $\geq 90\%$  reduction in  $KRAS^{G12D}$  VAF by week 8, assessed by ddPCR.

ctDNA, circulating tumor DNA; ddPCR, droplet digital polymerase chain reaction; GEMNabP, nab-paclitaxel + gemcitabine; mFOLFIRINOX, modified leucovorin calcium, fluorouracil, irinotecan hydrochloride, oxaliplatin; MR, molecular response; MRR, molecular response rate; PDAC, pancreatic ductal adenocarcinoma; qd, daily; SD, stable disease; VAF, variant allele frequency.

# Early Clinicogenomic Profiling in PDAC

## Baseline Genomic Profiles (Tissue + Plasma ctDNA NGS)



## Longitudinal Plasma Measures of *KRAS* CN (ctDNA)



- From early baseline NGS analysis\*: no significant correlations of baseline co-alterations with BOR, but some nonsignificant associations:
  - SMAD4*, *ATM*, *KRAS* CN gain was more common among patients who did not achieve response

- KRAS* CN gain from baseline to EOT was detected in 1 patient with PR and 5 patients with SD as BOR, suggesting a possible acquired resistance mechanism

\*Dose escalation and dose expansion, all available patients with  $\geq 600$  mg dose; includes known or likely pathogenic variants occurring in  $\geq 10\%$  of patients. Tissue NGS (Caris); plasma ctDNA NGS (dose escalation: Predicine WES; dose expansion: Caris WES).

Amp, amplification; BOR, best overall response; CN, copy number; ctDNA, circulating tumor DNA; EOT, end of treatment; NGS, next-generation sequencing; PD, progressive disease; PDAC, pancreatic ductal adenocarcinoma; PR, partial response; SD, stable disease; SNV, single nucleotide variant; VAF, variant allele frequency.

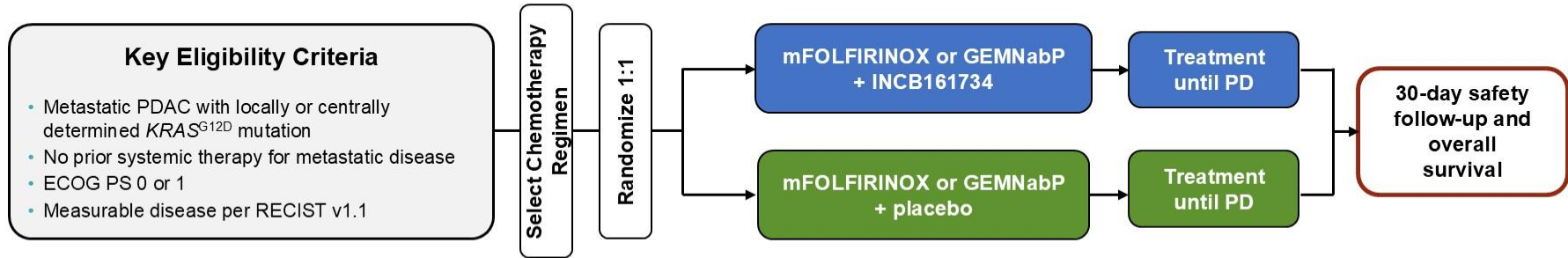
# Conclusions

- Results show a favorable safety profile of INCB161734 as monotherapy at 1200 mg qd, with few dose interruptions and reductions
  - GI TRAEs were mostly grade 1 and improved during treatment
- Safety data of INCB161734 at RP2D of 1200 mg qd in combination with GEMNabP or mFOLFIRINOX in patients with *KRAS*<sup>G12D</sup> advanced or metastatic PDAC indicates feasibility of the combination without compromising dose intensity of chemotherapy
- Deep molecular responses were observed in patients with PDAC who received INCB161734 as monotherapy and in combination with GEMNabP or mFOLFIRINOX
- Encouraging clinical efficacy supports initiation of a phase 3 trial in patients with 1L metastatic PDAC

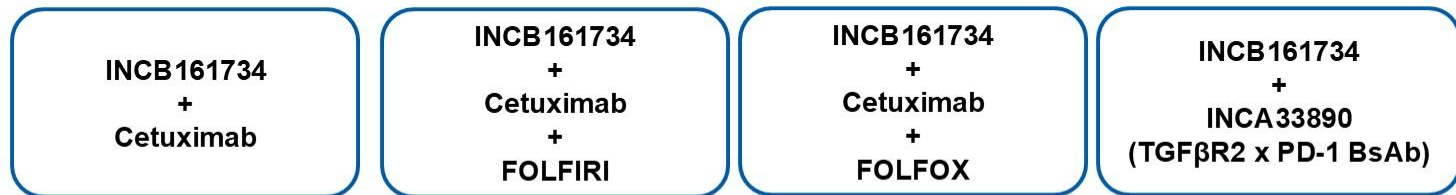
1L, first-line; GEMNabP, nab-paclitaxel + gemcitabine; GI, gastrointestinal; mFOLFIRINOX, modified leucovorin calcium, fluorouracil, irinotecan hydrochloride, oxaliplatin; PDAC, pancreatic ductal adenocarcinoma; qd, daily; RP2D, recommended phase 2 dose; TRAE, treatment-related adverse event.

# Future Direction

- DAWN-303 global phase 3 study in patients with 1L metastatic PDAC initiating in 2026



- Additional combination therapies are being explored in patients with CRC in the phase 1 study



1L, first-line; BsAb, bispecific antibody; CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFIRI, folinic acid, 5-fluorouracil, and irinotecan; FOLFOX, folinic acid, 5-fluorouracil, and oxaliplatin; GEMNabP, nab-paclitaxel and gemcitabine; mFOLFIRINOX, modified leucovorin calcium, 5-fluorouracil, irinotecan, oxaliplatin; PD-1, programmed cell death protein 1; PD, progressive disease; PDAC, pancreatic ductal adenocarcinoma; RECIST, Response Evaluation Criteria in Solid Tumors; TGFβR2, transforming growth factor beta receptor type 2.

# Acknowledgments

The authors wish to thank the patients and their families, the investigators, and the site personnel who participated in this study.

This study was sponsored by Incyte Corporation (Wilmington, DE, USA).

Medical writing assistance was provided by Alasdair Gunn, DPhil, of Envision Ignite, an Envision Medical Communications agency, a part of Envision Pharma Group (Fairfield, CT, USA), and funded by Incyte.