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Safety and Efficacy of INCB161734, a Novel Oral KRAS G12D Inhibitor, in Combination With Chemotherapy in Patients With Advanced/Metastatic Pancreatic Ductal Adenocarcinoma

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Declaration of Interests

Antoine Hollebecque:

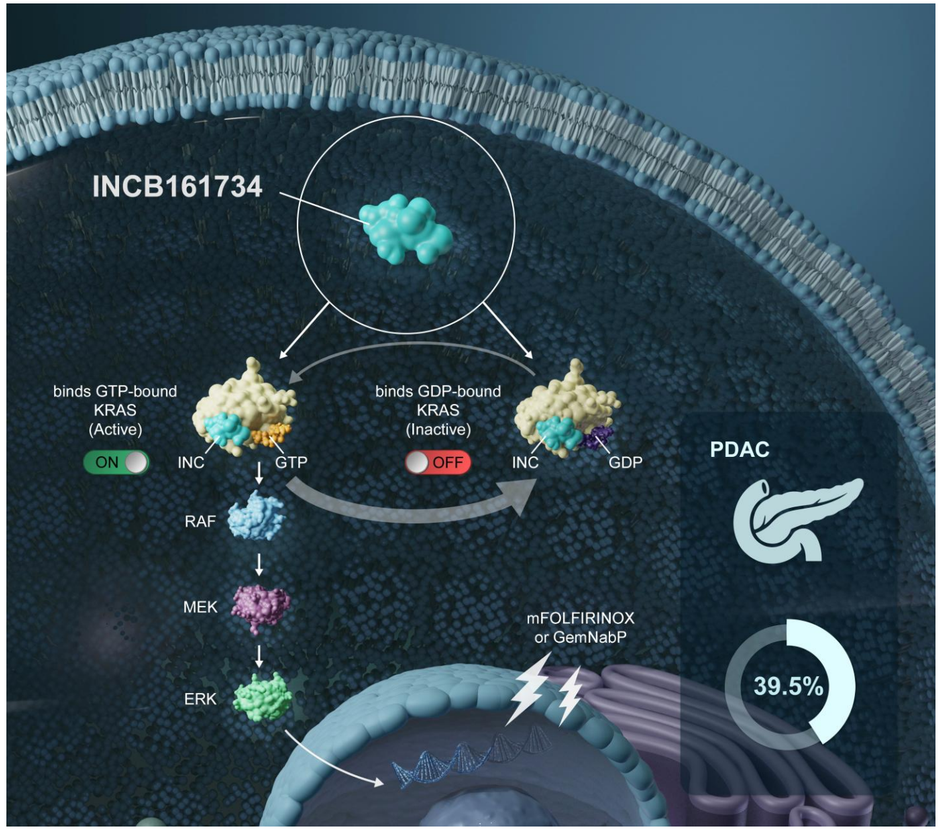
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Introduction



- PDAC is the sixth leading cause of cancer deaths worldwide[1]
  - 1L chemotherapies for patients with mPDAC have limited benefit[2]
- PDAC is primarily a KRAS-driven cancer[3]
  - *KRAS*^{G12D} is the most frequent oncogenic driver, occurring in ~40% of patients
- INCB161734 is a potent and selective ON/OFF oral KRAS^{G12D} inhibitor[4]
- Phase 1 results demonstrated INCB161734 monotherapy efficacy and manageable safety in patients with *KRAS*^{G12D} solid tumours, including mPDAC[5]
- INCB161734 1200 mg qd was tolerable when combined with SoC chemotherapy in patients with mPDAC[6]
- Here, we report updated efficacy and safety data for INCB161734 in combination with SoC chemotherapy in patients with *KRAS*^{G12D} mPDAC

1. Sung H, et al. *CA Cancer J Clin*. 2026;76:e70090. 2. Koopman M, et al. *ESMO Gastrointest Oncol*. 2025;9:100214. 3. Lee JK, et al. *NPJ Precis Onc*. 2022;6:91. 4. Farren MR, et al. Presented at: AACR 2024; San Diego, CA, USA. Poster 5900. 5. Desai J, et al. Presented at: ESMO 2025; Berlin, Germany. Oral 9160. 6. Wainberg Z, et al. Presented at: ASCO GI 2026; San Francisco, CA, USA. Oral 654.

1L, first-line; ERK, extracellular signal-regulated kinase; GDP, guanosine diphosphate; GEMNabP, nab-paclitaxel + gemcitabine; GTP, guanosine triphosphate; INC, INCB161734; KRAS, Kirsten rat sarcoma; MEK, mitogen-activated protein kinase kinase; mFOLFIRINOX, modified leucovorin calcium, fluorouracil, irinotecan hydrochloride, oxaliplatin; mPDAC, metastatic pancreatic ductal adenocarcinoma; PDAC, pancreatic ductal adenocarcinoma; qd, daily; RAF, rapidly accelerated fibrosarcoma; SoC, standard of care.

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Phase 1 Evaluation of INCB161734 Plus SoC Chemotherapy in mPDAC (NCT06179160)

Key Eligibility Criteria

- Locally advanced or metastatic PDAC with *KRAS*^{G12D} mutation*
- ECOG PS 0 or 1
- No prior treatment with a KRAS^{G12D} selective inhibitor
- Dose escalation: ≤1 prior systemic regimen in the metastatic setting†
- Dose expansion: no prior regimen in the metastatic setting†

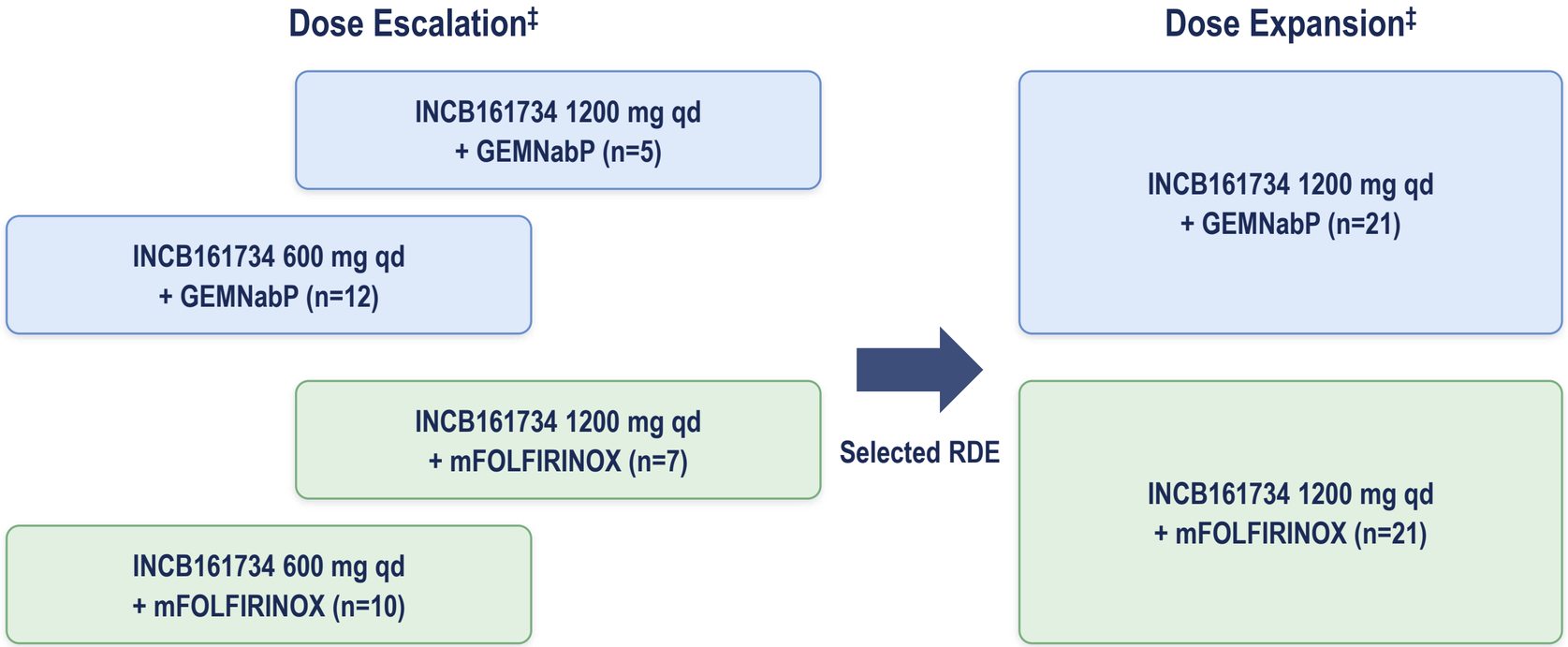
Key Endpoints

- Safety and tolerability
- Efficacy (ORR, DCR, DOR, and PFS)

Chemotherapy Regimens

GEMNabP: D1, D8, D15 of 28D cycle. Gemcitabine 1000 mg/m², nab-paclitaxel 125 mg/m²

mFOLFIRINOX: D1, D15 of 28D cycle. Oxaliplatin 85 mg/m², leucovorin 400 mg/m², irinotecan 150-180 mg/m², fluorouracil 2400 mg/m²



Data cut-off date: July 6, 2026. *Determined by local testing. †Neoadjuvant or adjuvant therapy may be counted as 1 line of therapy if recurrence/development of metastatic disease occurred within 6 months of the last dose of therapy; patients who received no standard systemic therapy for PDAC may have received ≤1 cycle of GEMNabP or mFOLFIRINOX before enrolling. ‡Treated until start of new anticancer therapy, disease progression, unacceptable toxicity, death, withdrawal of consent, discontinuation or the end of the study.
D, day; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GEMNabP, nab-paclitaxel + gemcitabine; KRAS, Kirsten rat sarcoma; mFOLFIRINOX, modified leucovorin calcium, fluorouracil, irinotecan hydrochloride, oxaliplatin; mPDAC, metastatic pancreatic ductal adenocarcinoma; ORR, objective response rate; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; qd, daily; RDE, recommended dose for expansion; SoC, standard of care.

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Patient Disposition and Baseline Characteristics

- As of July 6, 2026, 54 patients with mPDAC received INCB161734 1200 mg qd in combination with chemotherapy
- 26 patients received INCB161734 in combination with GEMNabP
  - Median (range) duration of INCB161734 treatment was 7.6 (0.5, 9.1) months
  - Treatment ongoing in 16 (62%)
  - Primary reason for discontinuation was progressive disease (n=8; 31%)*
- 28 patients received INCB161734 in combination with mFOLFIRINOX
  - Median (range) duration of INCB161734 treatment was 7.0 (0.6, 11.7) months
  - Treatment ongoing in 23 (82%)
  - Primary reason for discontinuation was progressive disease (n=4; 14%)†

	INCB161734 1200 mg qd	
	GEMNabP (n=26)	**mFOLFIRINOX (n=28)**
Age, median (range), years	62 (35, 77)	63 (37, 77)
≥65 years, n (%)	11 (42)	13 (46)
ECOG PS, n (%)		
0	13 (50)	12 (43)
1	13 (50)	16 (57)
Metastatic disease at diagnosis, n (%)	12 (46)	25 (89)
Liver metastases, n (%)	22 (85)	24 (86)
Prior neoadjuvant/adjuvant therapy, n (%)	10 (38)	3 (11)
Total prior systemic therapy, n (%)		
0	14 (54)	24 (86)
1	12 (46)	3 (11)
2	0	1 (4)
Prior lines of systemic therapy in the metastatic setting, n (%)		
0	24 (92)	26 (93)
1	2 (8)	2 (7)

*2 patients discontinued with the primary reason of adverse event. †1 patient discontinued with the primary reason of adverse event.

ECOG PS, Eastern Cooperative Oncology Group performance status; GEMNabP, nab-paclitaxel + gemcitabine; KRAS, Kirsten rat sarcoma; mFOLFIRINOX, modified leucovorin calcium, fluorouracil, irinotecan hydrochloride, oxaliplatin; mPDAC, metastatic pancreatic ductal adenocarcinoma; qd, daily.

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Safety: INCB161734 in Combination With GEMNabP

	INCB161734 1200 mg qd + GEMNabP (n=26)
Any TRAE, n (%)*	26 (100)
TRAE leading to INCB161734	
Interruption	19 (73)
Reduction	6 (23)
Discontinuation	1 (4)
TRAE leading to chemotherapy (any component)†	
Interruption	22 (85)
Reduction	18 (69)
Discontinuation	8 (31)
RDI, median %‡	
INCB161734	85
GEMNabP (cycles 1-4)	69
GEMNabP†	49

	INCB161734 1200 mg qd + GEMNabP (n=26)		
TRAE, n (%)§	Any grade	Grade 1/2	Grade ≥3
Diarrhoea	17 (65)	16 (62)	1 (4)
Nausea	17 (65)	16 (62)	1 (4)
Decreased neutrophil count¶	17 (65)	2 (8)	15 (58)
Anaemia	15 (58)	5 (19)	10 (38)
Vomiting	12 (46)	9 (35)	3 (12)
Fatigue	12 (46)	7 (27)	5 (19)
Pyrexia	10 (38)	9 (35)	1 (4)
Decreased platelet count‖	9 (35)	4 (15)	5 (19)
Alopecia	7 (27)	7 (27)	0
Decreased appetite	7 (27)	7 (27)	0
ALT increased	6 (23)	6 (23)	0
Dysgeusia**	6 (23)	6 (23)	NA
Oedema peripheral	6 (23)	6 (23)	0
Peripheral sensory neuropathy	6 (23)	6 (23)	0

*Assessed in patients who received ≥1 dose of study drug. †Median duration of treatment was 7.6 months. ‡Chemotherapy dose intensity was derived as the minimum RDI among all chemotherapy components. §Includes any-grade TRAEs that occurred in ≥20% of patients. ¶Includes neutropenia and neutrophil count decreased. ‖Includes thrombocytopenia and platelet count decreased. **The maximum possible severity per CTCAE for dysgeusia is grade 2.
ALT, alanine aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; GEMNabP, nab-paclitaxel + gemcitabine; NA, not applicable; qd, daily; RDI, relative dose intensity; TRAE, treatment-related adverse event.

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Safety: INCB161734 in Combination With mFOLFIRINOX

	INCB161734 1200 mg qd + mFOLFIRINOX (n=28)
Any TRAE, n (%)*	28 (100)
TRAE leading to INCB161734	
Interruption	11 (39)
Reduction	6 (21)
Discontinuation	0
TRAE leading to chemotherapy (any component)†	
Interruption	22 (79)
Reduction	16 (57)
Discontinuation	9 (32)
RDI, median %‡	
INCB161734	77
mFOLFIRINOX (cycles 1-4)	67
mFOLFIRINOX†	53

	INCB161734 1200 mg qd + mFOLFIRINOX (n=28)		
TRAE, n (%)§	Any grade	Grade 1/2	Grade ≥3
Diarrhoea	19 (68)	16 (57)	3 (11)
Nausea	18 (64)	17 (61)	1 (4)
Vomiting	16 (57)	14 (50)	2 (7)
Decreased neutrophil count¶	16 (57)	6 (21)	10 (36)
Fatigue	15 (54)	12 (43)	3 (11)
Anaemia	11 (39)	8 (29)	3 (11)
Decreased platelet count‖	9 (32)	4 (14)	5 (18)
Peripheral sensory neuropathy	9 (32)	9 (32)	0
Decreased appetite	7 (25)	7 (25)	0
Dysgeusia**	7 (25)	7 (25)	NA

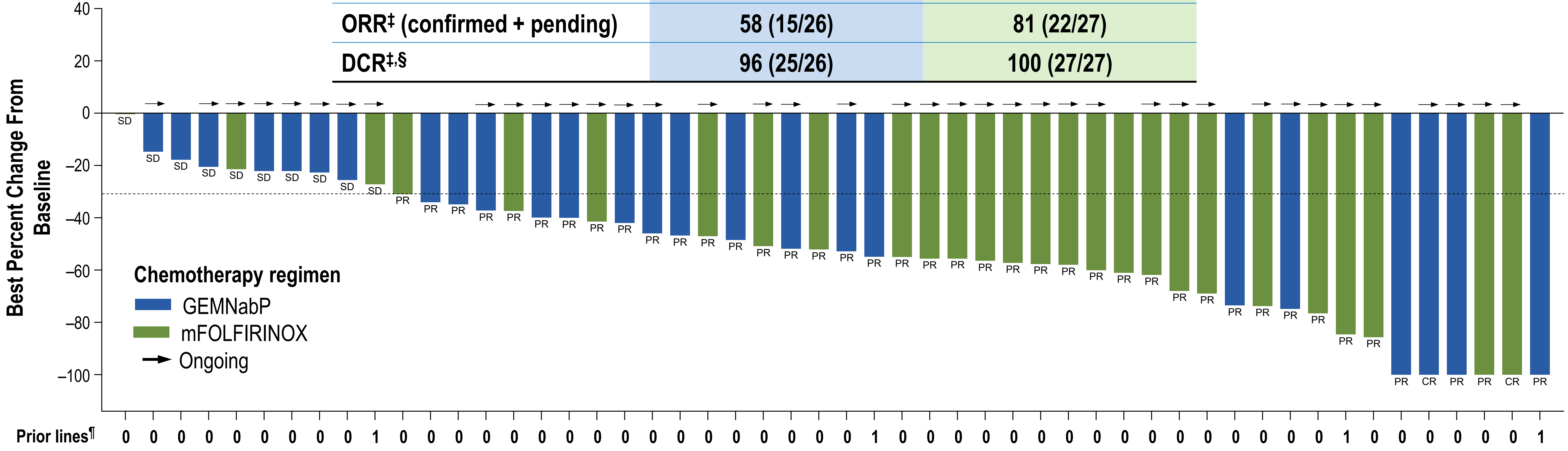
- The safety profile of INCB161734 + GEMNabP or mFOLFIRINOX was broadly consistent with the established profiles of the SoC regimens
- No fatal TRAEs were recorded

*Assessed in patients who received ≥1 dose of study drug. †Median duration of treatment was 7.0 months. ‡Chemotherapy dose intensity was derived as the minimum RDI among all chemotherapy components. §Includes any-grade TRAEs that occurred in ≥20% of patients. ¶Includes neutropenia and neutrophil count decreased. ‖Includes thrombocytopenia and platelet count decreased. **The maximum possible severity per CTCAE for dysgeusia is grade 2.
CTCAE, Common Terminology Criteria for Adverse Events; GEMNabP, nab-paclitaxel + gemcitabine; mFOLFIRINOX, modified leucovorin calcium, fluorouracil, irinotecan hydrochloride, oxaliplatin; NA, not applicable; qd, daily; RDI, relative dose intensity; SoC, standard of care; TRAE, treatment-related adverse event.

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Antitumour Activity of INCB161734 + SoC Chemotherapy in Patients With mPDAC

	INCB161734 1200 mg qd	
Response, % (n/N)	GEMNabP (n=26)*	mFOLFIRINOX (n=27)†
ORR‡,§	69 (18/26)	89 (24/27)
ORR‡ (confirmed + pending)	58 (15/26)	81 (22/27)
DCR‡,§	96 (25/26)	100 (27/27)



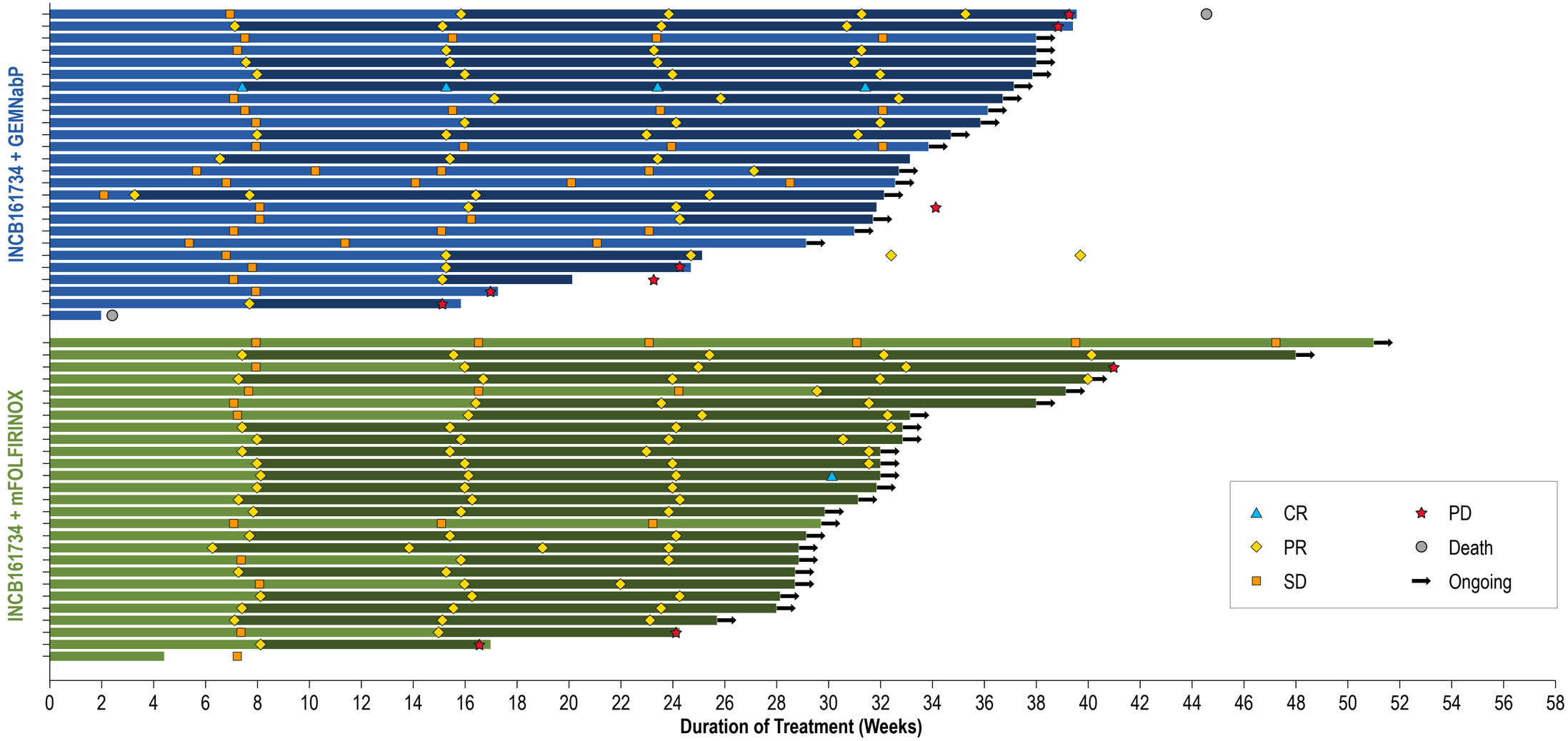
- Median duration of efficacy follow-up was 7.2 months for INCB161734 + GEMNabP and 5.6 months for INCB161734 + mFOLFIRINOX‖
- Plasma ctDNA analysis demonstrated high rates of rapid molecular responses for INCB161734 + GEMNabP (74%) and mFOLFIRINOX (69%)**

*1 patient receiving INCB161734 + GEMNabP was included in the efficacy evaluable population but was not included in the waterfall plot due to death before the first scan. †1 patient was removed from the efficacy evaluable population due to an early adverse event.
‡Assessed in patients with a baseline scan and at least 1 of the following: ≥1 postbaseline scan or discontinued treatment due to death or PD. §Data include unconfirmed responses. ¶In the advanced/metastatic setting. ‖Calculated by the reverse Kaplan-Meier method.
**Molecular response: ≥90% reduction in *KRAS*[G12D] VAF by week 8, assessed by ddPCR or NGS (Predicine) for all patients with baseline G12D VAF and week 8 data.
CR, complete response; ctDNA, circulating tumour DNA; DCR, disease control rate; ddPCR, droplet digital polymerase chain reaction; GEMNabP, nab-paclitaxel + gemcitabine; mFOLFIRINOX, modified leucovorin calcium, fluorouracil, irinotecan hydrochloride, oxaliplatin; mPDAC, metastatic pancreatic ductal adenocarcinoma; NGS, next-generation sequencing; ORR, objective response rate; PD, progressive disease; PR, partial response; qd, daily; SD, stable disease; SoC, standard of care; VAF, variant allele frequency.

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Durable Benefit With INCB161734 + SoC Chemotherapy in mPDAC

- PFS at 6 months was 80% for INCB161734 + GEMNabP and 90% for INCB161734 + mFOLFIRINOX



Assessed in patients with a baseline scan and at least one of the following: ≥1 postbaseline scan or discontinued treatment due to death or PD.
CR, complete response; GEMNabP, nab-paclitaxel + gemcitabine; mFOLFIRINOX, modified leucovorin calcium, fluorouracil, irinotecan hydrochloride, oxaliplatin; mPDAC, metastatic pancreatic ductal adenocarcinoma; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SoC, standard of care.

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Conclusions

- The favourable safety and tolerability profile for INCB161734 1200 mg qd + GEMNabP or mFOLFIRINOX in patients with mPDAC was broadly consistent with the established profiles of the SoC regimens
  - GI TRAEs were mostly grade 1/2 and improved during treatment
  - The incidence of TRAEs leading to INCB161734 treatment discontinuation was low
- Deep and durable treatment responses were observed
  - ORR (DCR) was 69% (96%) for INCB161734 + GEMNabP and 89% (100%) for INCB161734 + mFOLFIRINOX
  - 6-month PFS landmark rates were 80% for INCB161734 + GEMNabP and 90% for INCB161734 + mFOLFIRINOX
- Encouraging clinical efficacy supports the ongoing global phase 3 DAWN-303 trial evaluating SoC chemotherapy in combination with INCB161734 or placebo in patients with 1L mPDAC (NCT07522073)
  - DAWN-303 is actively enrolling globally

1L, first-line; DCR, disease control rate; GEMNabP, nab-paclitaxel + gemcitabine; GI, gastrointestinal; KRAS, Kirsten rat sarcoma; mFOLFIRINOX, modified leucovorin calcium, fluorouracil, irinotecan hydrochloride, oxaliplatin; mPDAC, metastatic pancreatic ductal adenocarcinoma; ORR, objective response rate; PFS, progression-free survival; qd, daily; SoC, standard of care; TRAE, treatment-related adverse event.

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