

# Preliminary Phase 1 Results of INCB161734, a Novel Oral *KRAS*<sup>G12D</sup> Inhibitor, in Patients With Advanced or Metastatic Solid Tumors

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# Declaration of Interests

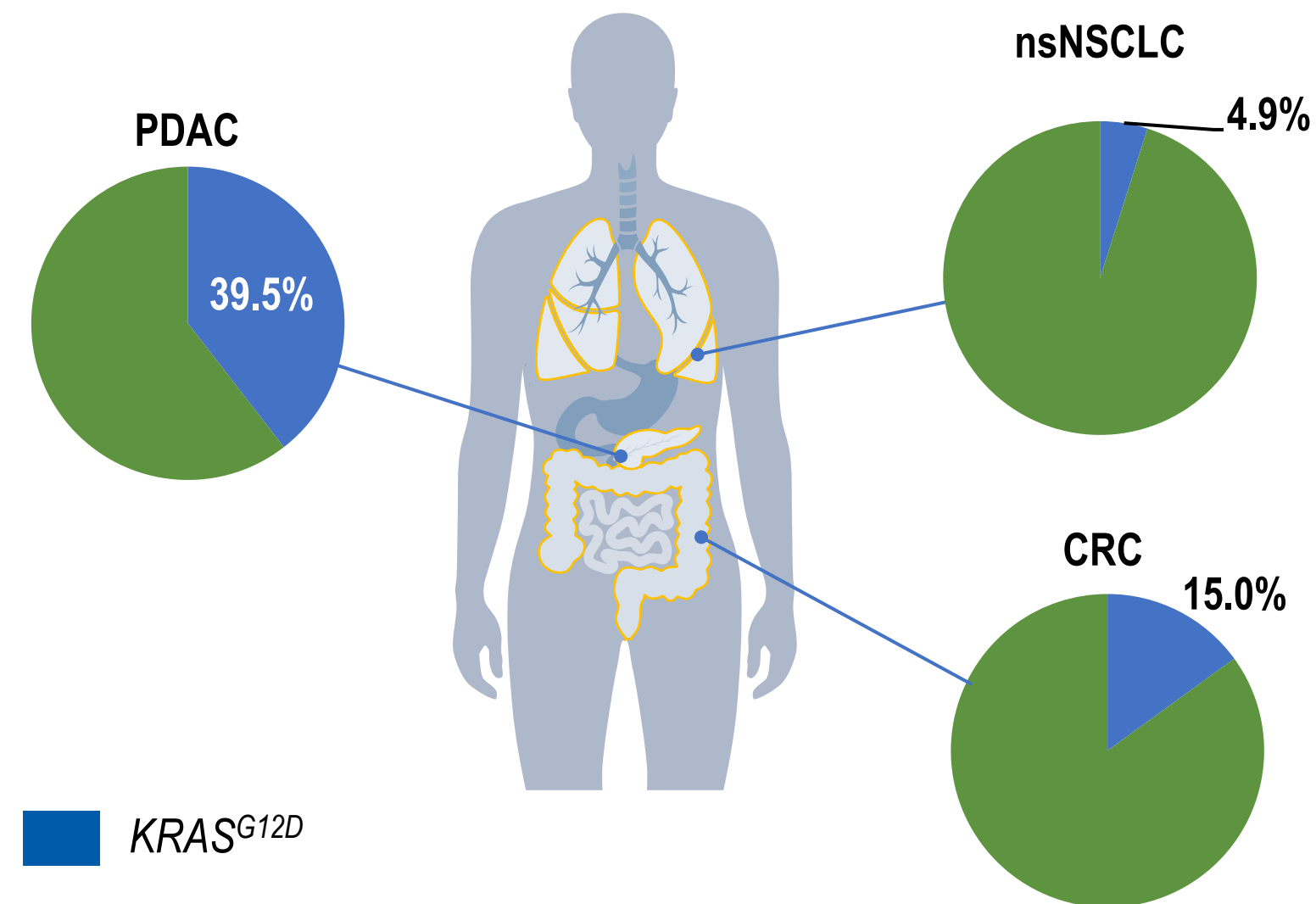
## Jayesh Desai:

Consulting or advisory role – *Amgen (Inst), Axelia Oncology, Bayer, BeiGene, Boehringer Ingelheim, Daiichi Sankyo Europe GmbH, Ellipses Pharma, GlaxoSmithKline, Incyte Corporation, Merck KGaA, Novartis, Pfizer, Pierre Fabre, Roche/Genentech;*

Research funding – *Amgen (Inst), AstraZeneca/MedImmune (Inst), BeiGene (Inst), Bristol Myers Squibb (Inst), Roche/Genentech (Inst), GlaxoSmithKline (Inst), Novartis (Inst), Roche (Inst)*

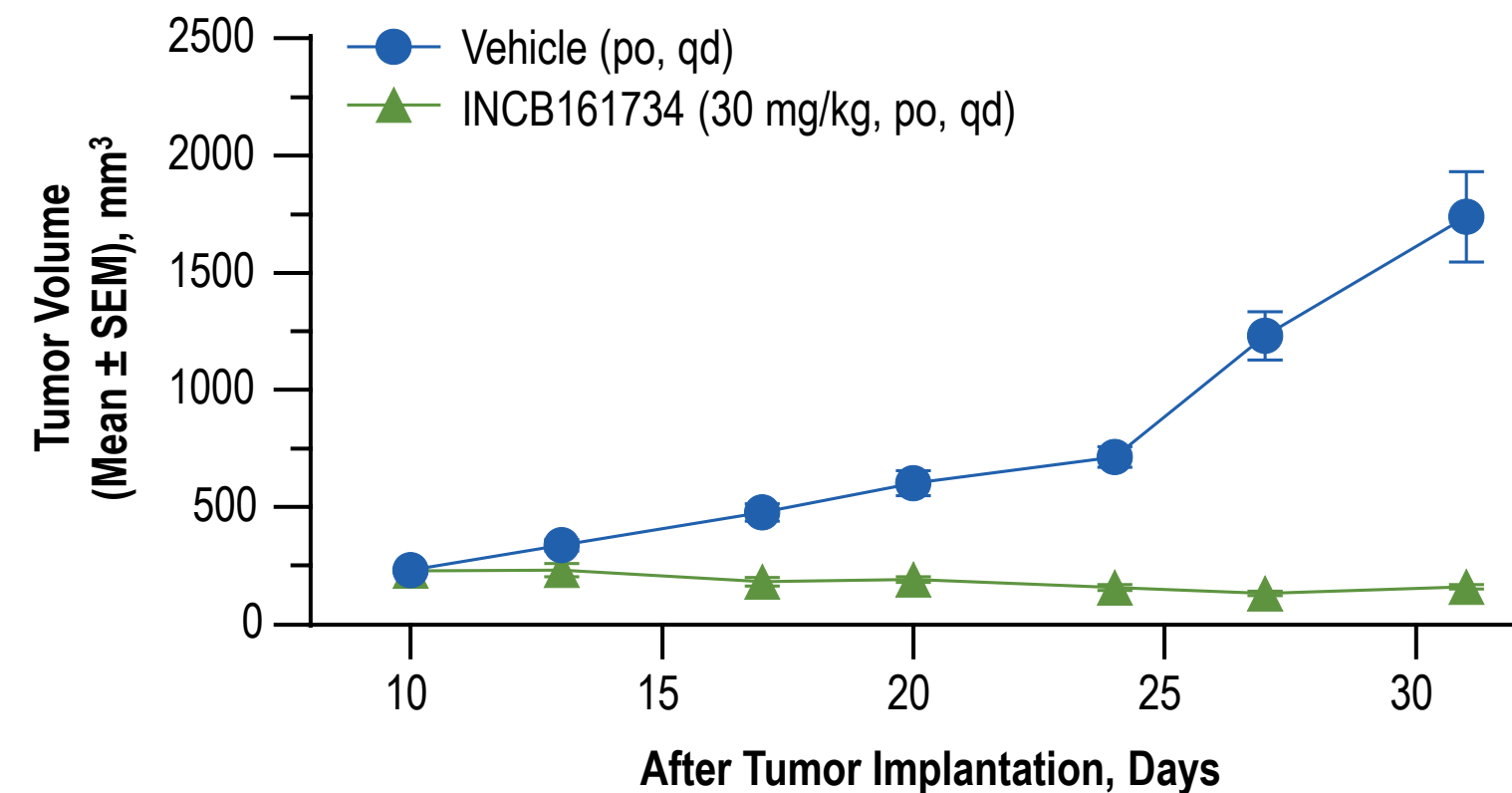
# Introduction

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



- INCB161734 is a selective noncovalent ON/OFF  $KRAS^{G12D}$  inhibitor
  - Exhibits >80-fold selectivity over  $KRAS^{WT}$
  - Binds  $KRAS^{G12D}$  at the switch II pocket with picomolar affinity
  - Demonstrates robust antitumor activity in  $KRAS^{G12D}$  xenograft and syngeneic tumors<sup>2</sup>

INCB161734 Antitumor Activity in PDAC Xenograft Model\*



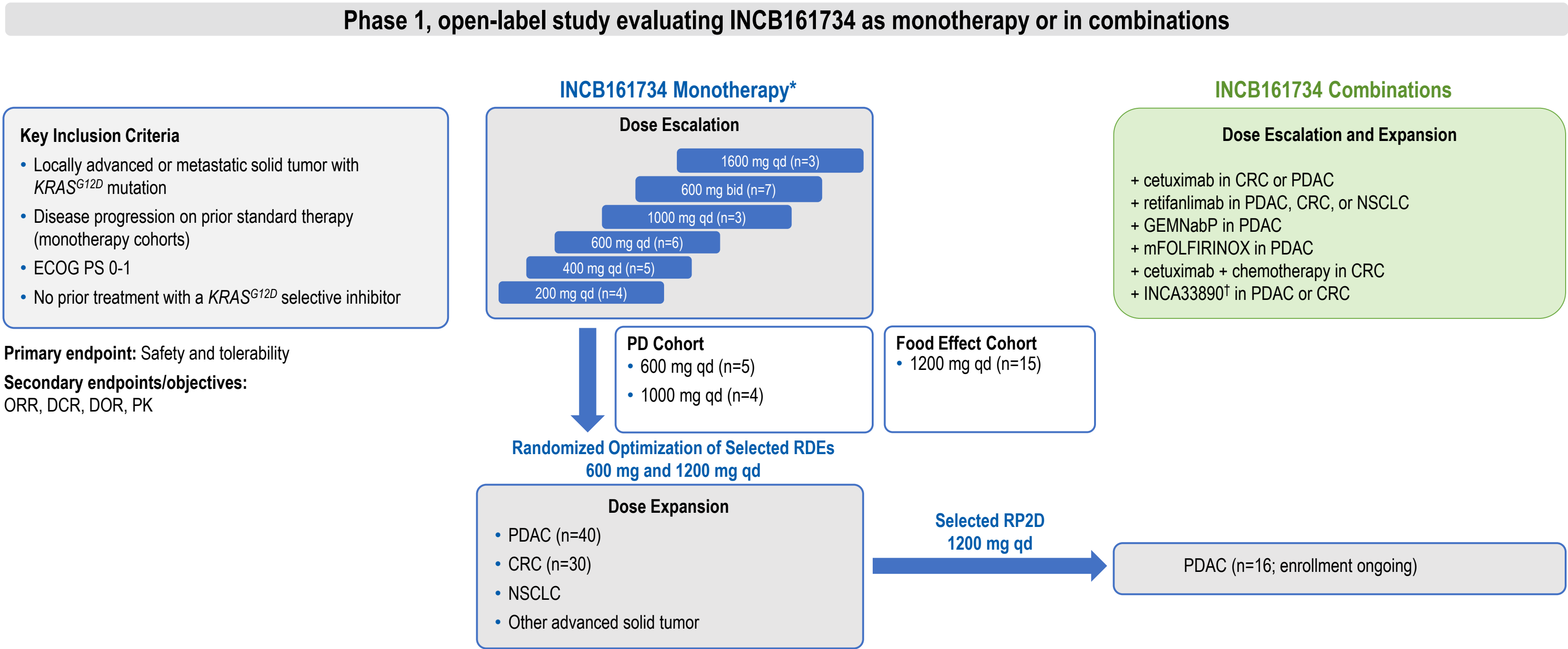
\*Panc 04.03  $KRAS^{G12D}$  (PDAC).

1. Lee JK, et al. *NPJ Precis Onc.* 2022;6:91. 2. Farren MR, et al. Presented at: AACR; 2024; San Diego, CA. Poster 5900.

CRC, colorectal cancer; nsNSCLC, non-squamous non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; po, orally; qd, daily; SEM, standard error of the mean; WT, wild type.

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# INCB161734-101 (NCT06179160): Study Design



\*As of August 1, 2025. <sup>†</sup>Oral presentation 1522MO, ESMO Congress 2025.  
bid, twice daily; CRC, colorectal cancer; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GEMNabP, nab-paclitaxel + gemcitabine; mFOLFIRINOX, modified leucovorin calcium, fluorouracil, irinotecan hydrochloride, oxaliplatin; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, pharmacodynamic; PDAC, pancreatic ductal adenocarcinoma; PK, pharmacokinetics; qd, daily; RDE, recommended dose for expansion; RP2D, recommended phase 2 dose; TEAE, treatment-emergent adverse event.

# Patient Disposition and Baseline Characteristics

- As of August 1, 2025, 138 patients were enrolled and received INCB161734 monotherapy
- Tumor types included:
  - PDAC (n=83, 60.1%)
  - CRC (n=46, 33.3%)
  - NSCLC (n=3, 2.2%)
  - OC (n=2, 1.4%)
  - AC, CCA, CUP, and GBC (all n=1, 0.7%)
- Treatment ongoing in 75 patients (54.3%)
  - Primary reason for discontinuation was disease progression (n=52; 37.7%)\*
  - No patients discontinued due to AEs

	All Patients (N=138)	PDAC (n=83)
Age, median (range), years	61 (30, 85)	63 (38, 85)
≥65 years, n (%)	49 (35.5)	37 (44.6)
Sex, female, n (%)	67 (48.6)	34 (41.0)
ECOG PS 0/1, n (%)	63 (45.7)/75 (54.3)	32 (38.6)/51 (61.4)
Liver metastases, n (%)	NA	64 (77.1)
Total prior systemic therapies, median (range)	2.0 (1, 13)	2.0 (1, 6)
Prior systemic therapies in advanced/metastatic setting, <sup>†</sup> n (%)		
1 prior line	NA	13 (15.7)
2 prior lines	NA	43 (51.8)
≥3 prior lines	NA	27 (32.5)

\*Other reasons: death (n=4; 2.9%), withdrawal (n=6; 4.3%), undefined (n=1, 0.7%). <sup>†</sup>Includes neoadjuvant or adjuvant therapy given within 6 months of advanced/metastatic disease development.

AC, appendiceal cancer; AE, adverse event; CCA, cholangiocarcinoma; CRC, colorectal cancer; CUP, cancer of unknown primary; ECOG PS, Eastern Cooperative Oncology Group performance status; GBC, gall bladder cancer; NA, not applicable; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PDAC, pancreatic ductal adenocarcinoma.

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# Safety of INCB161734 in Patients With *KRAS*<sup>G12D</sup> Mutated Advanced or Metastatic Solid Tumors

- No protocol-defined DLTs were reported in dose escalation; MTD was not reached
- No patients discontinued treatment due to TRAEs
- Most common TRAEs leading to dose reduction were nausea, decreased appetite, and fatigue (n=2 for each)

TRAE, n (%)	TRAEs*					
	All Doses (n=136)		600 mg qd (n=43)		1200 mg qd (n=67)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Any TRAE	120 (88.2)	15 (11.0)	36 (83.7)	6 (14.0)	59 (88.1)	6 (9.0)
Serious TRAE	4 (2.9)	3 (2.2)	2 (4.7)	2 (4.7)	2 (3.0)	1 (1.5)
TRAEs leading to						
Interruption	21 (15.4)	8 (5.9)	5 (11.6)	3 (7.0)	9 (13.4)	3 (4.5)
Reduction	9 (6.6)	1 (0.7)	0	0	5 (7.5)	1 (1.5)
Discontinuation	0	0	0	0	0	0

\*Assessed in patients who received ≥1 dose of study drug.  
AE, adverse event; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; qd, daily; TRAE, treatment-related adverse event.

# Most Common TRAEs by Severity and INCB161734 Dose

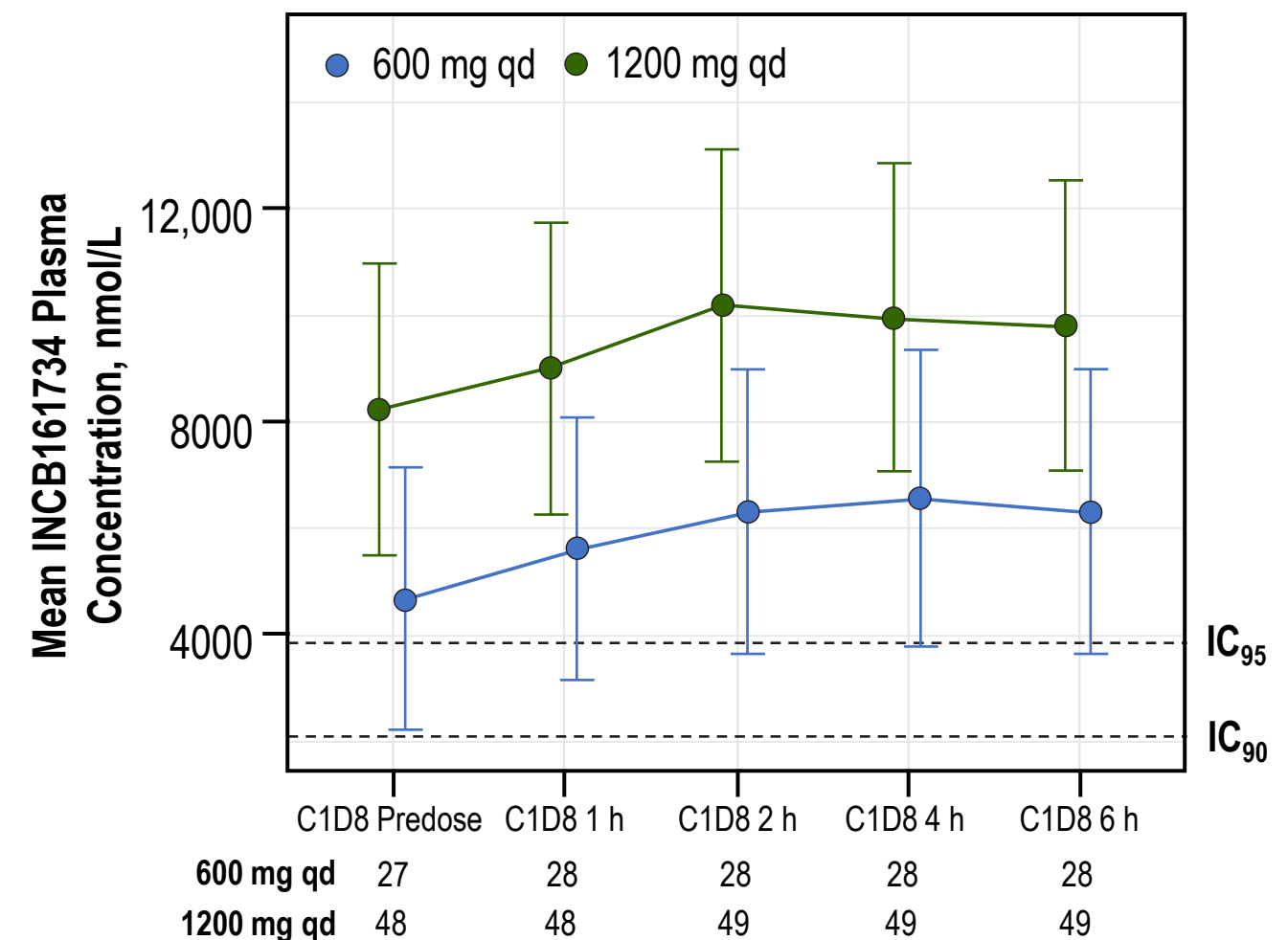
- Gastrointestinal AEs were manageable and mostly grade 1

Most Common TRAEs in Decreasing Order of Frequency*									
Preferred term, n (%)	All Doses (n=136)	600 mg qd (n=43)				1200 mg qd (n=67)			
	All Grades	All Grades	Grade 1	Grade 2	Grade ≥3	All Grades	Grade 1	Grade 2	Grade ≥3
Nausea	79 (58.1)	24 (55.8)	16 (37.2)	8 (18.6)	0	39 (58.2)	28 (41.8)	10 (14.9)	1 (1.5)
Diarrhea	69 (50.7)	19 (44.2)	14 (32.6)	4 (9.3)	1 (2.3)	36 (53.7)	29 (43.3)	6 (9.0)	1 (1.5)
Vomiting	62 (45.6)	15 (34.9)	12 (27.9)	3 (7.0)	0	35 (52.2)	26 (38.8)	9 (13.4)	0
Fatigue	24 (17.6)	6 (14.0)	4 (9.3)	2 (4.7)	0	12 (17.9)	10 (14.9)	2 (3.0)	0
Lipase increased	15 (11.0)	3 (7.0)	0	2 (4.7)	1 (2.3)	6 (9.0)	3 (4.5)	1 (1.5)	2 (3.0)
Decreased appetite	14 (10.3)	2 (4.7)	1 (2.3)	1 (2.3)	0	10 (14.9)	9 (13.4)	0 (0)	1 (1.5)
Amylase increased	10 (7.4)	1 (2.3)	0 (0)	1 (2.3)	0 (0)	4 (6.0)	1 (1.5)	3 (4.5)	0 (0)
Anemia	8 (5.9)	5 (11.6)	1 (2.3)	3 (7.0)	1 (2.3)	2 (3.0)	2 (3.0)	0 (0)	0 (0)
Dysgeusia	7 (5.1)	2 (4.7)	2 (4.7)	0 (0)	0 (0)	4 (6.0)	4 (6.0)	0 (0)	0 (0)

\*Ordered by incidence of All Grade events for All Doses; events with ≥5% incidence are presented. Review of all TEAEs did not reveal any additional AEs of significance.  
AE, adverse event; qd, daily; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

# PK Analysis Supports Exposures Achieving High-Target Coverage

- Exposure progressively increased with increasing dose
- Median  $T_{\max}$  2-4 h
- Terminal  $t_{1/2}$  approximately 20 h
- At 1200 mg qd, INCB161734 levels consistently exceeded  $IC_{95}$  at steady state
- Food effect PK analysis demonstrated modest impact of food on INCB161734 exposure



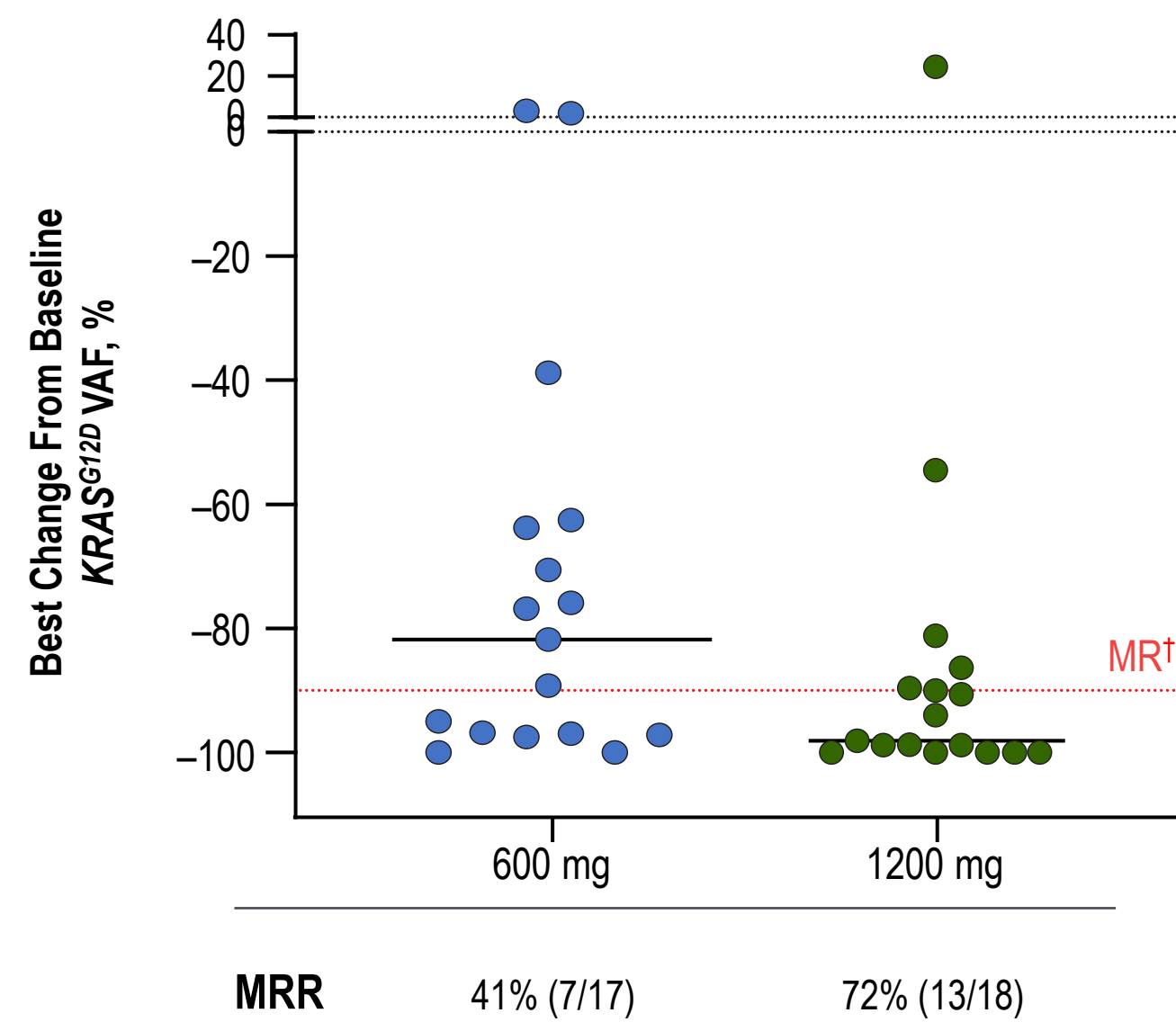
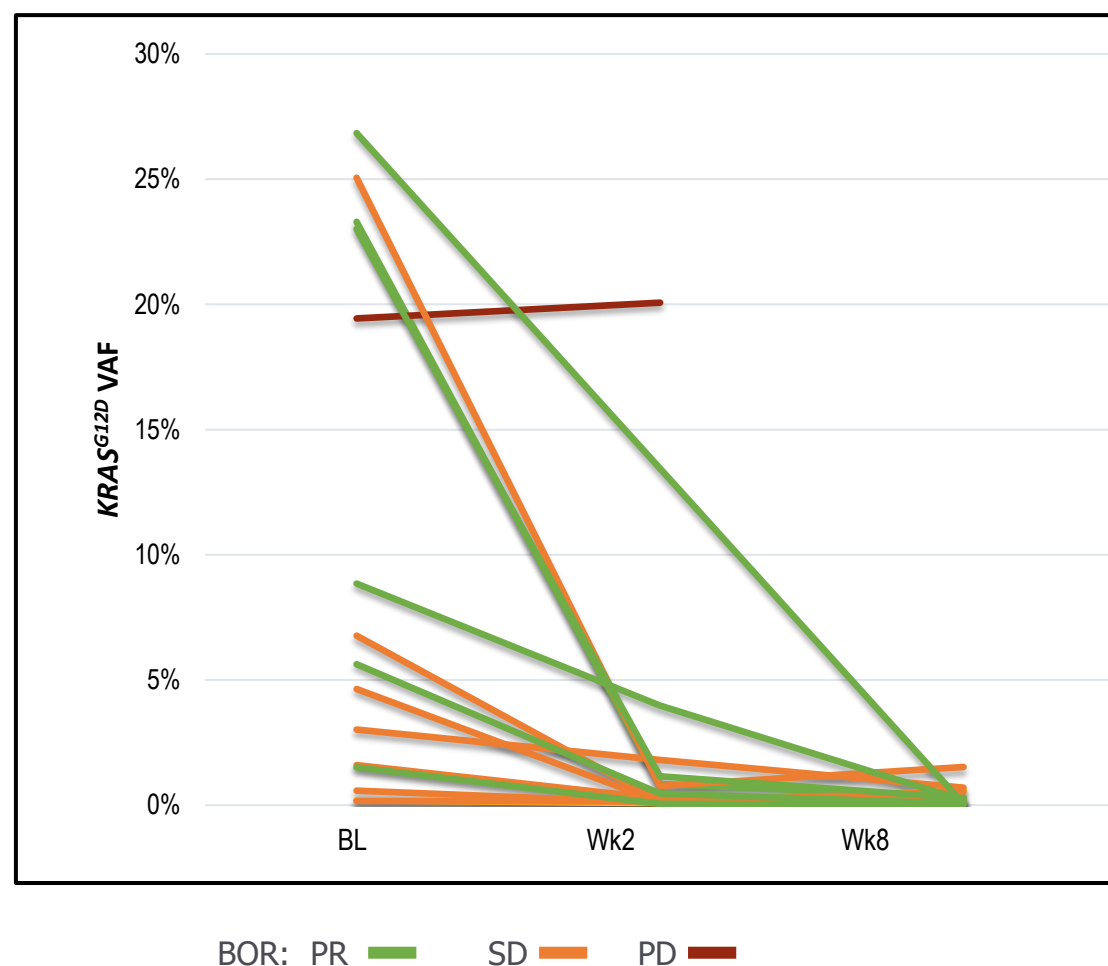
All PK data were from part 1b (monotherapy dose expansion). Error bars represent 1× standard deviation.  $IC_{90}/IC_{95}$  values were determined from in vitro human whole blood phospho-ERK assays. C, cycle; D, day; h, hour(s);  $IC_{90/95}$ , 90/95% inhibitory concentration; PK, pharmacokinetics; qd, daily;  $t_{1/2}$ , half-life;  $T_{\max}$ , time to peak concentration.

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

- In dose escalation, INCB161734 at the  $\geq 600$ -mg-qd dose caused rapid molecular responses that correlated with objective response\*
- In PDAC patients with detectable  $KRAS^{G12D}$  in plasma ctDNA, 72% receiving a 1200-mg dose had an early molecular response†



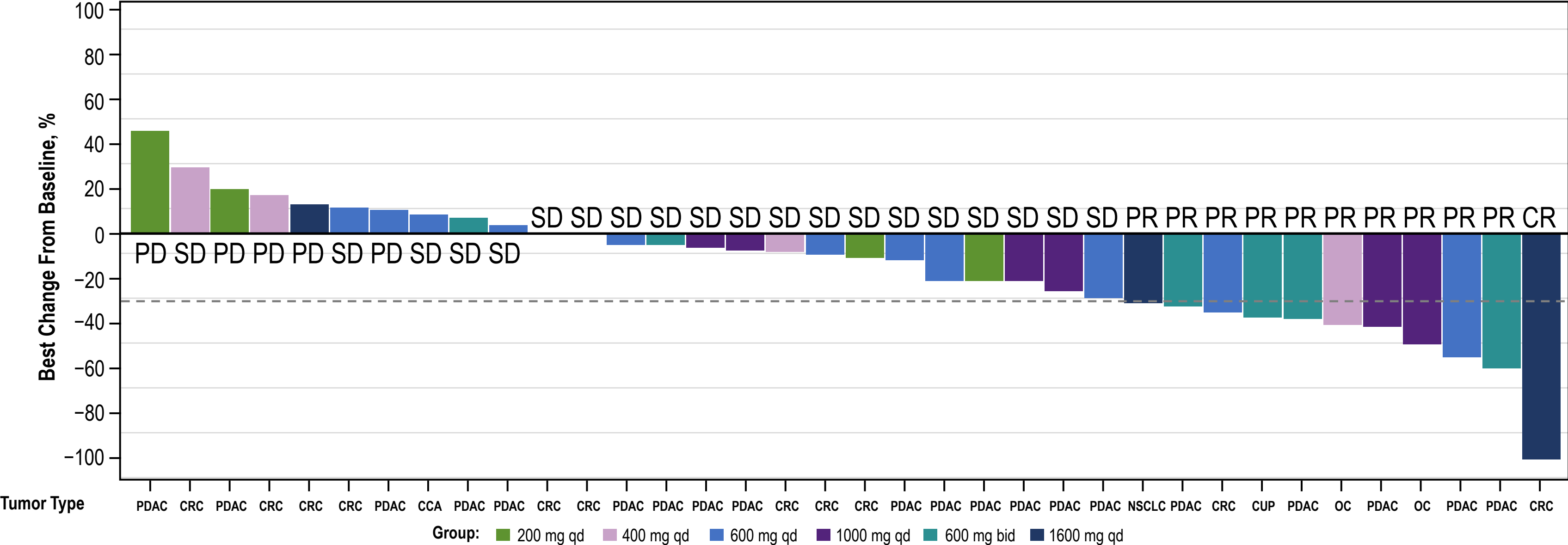
\*Dose escalation,  $\geq 600$ -mg dose, all tumors with detectable  $KRAS^{G12D}$  plasma ctDNA allele at BL. † $\geq 90\%$  reduction in  $KRAS^{G12D}$  VAF by Wk8.

BL, baseline; BOR, best overall response; ctDNA, circulating tumor DNA; MR, molecular response; MRR, molecular response rate; PD, progressive disease; PDAC, pancreatic ductal adenocarcinoma; PR, partial response; qd, daily; SD, stable disease; VAF, variant allele frequency; Wk, week.

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# Antitumor Activity Across Cancer Types in Dose Escalation\*

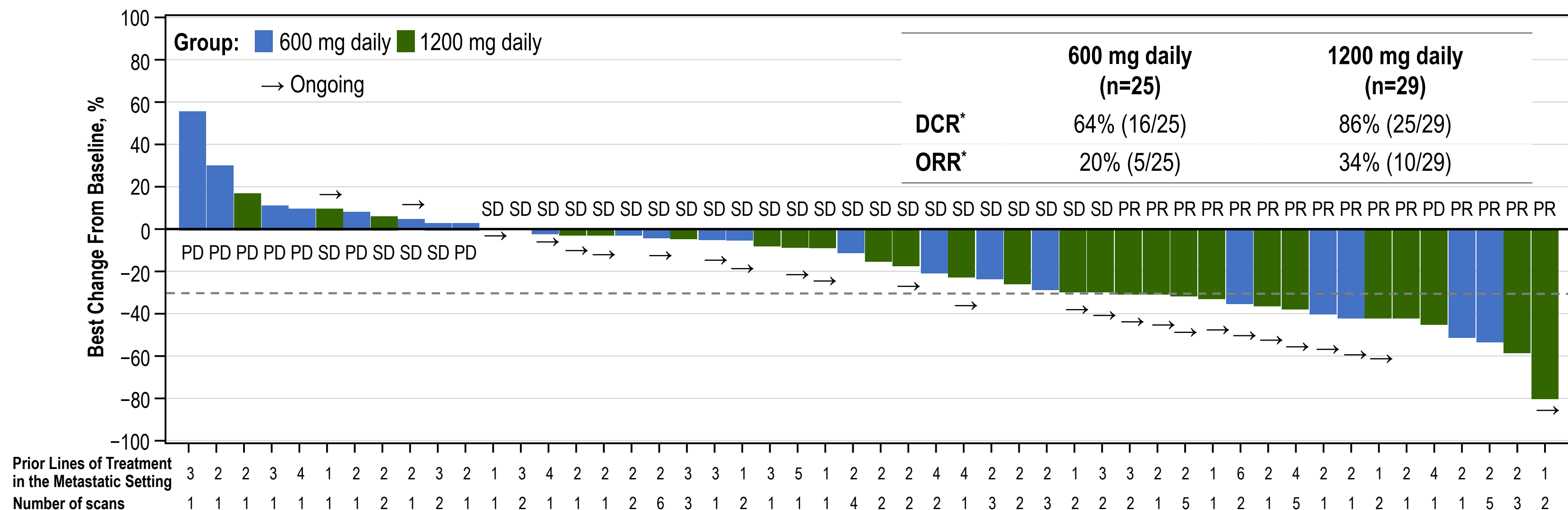
- Clinical responses were observed at INCB61734 doses  $\geq 600$  mg qd



\*N=36 patients with  $\geq 1$  postbaseline scan or clinical progression or death prior to the first RECIST assessment per investigator.  
bid, twice daily; CCA, cholangiocarcinoma; CR, complete response; CRC, colorectal cancer; CUP, cancer of unknown primary; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PD, progressive disease; PDAC, pancreatic ductal adenocarcinoma; PR, partial response; qd, daily; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

# Antitumor Activity in PDAC Patients at Selected INCB61734 RDEs

- There was a high ORR and DCR for patients with PDAC on both expansion doses



\*Investigator-assessed in patients with  $\geq 1$  postbaseline scan or clinical progression or death prior to the first RECIST assessment per investigator.

DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PDAC, pancreatic ductal adenocarcinoma; PR, partial response; qd, daily; RDE, recommended dose for expansion;

RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

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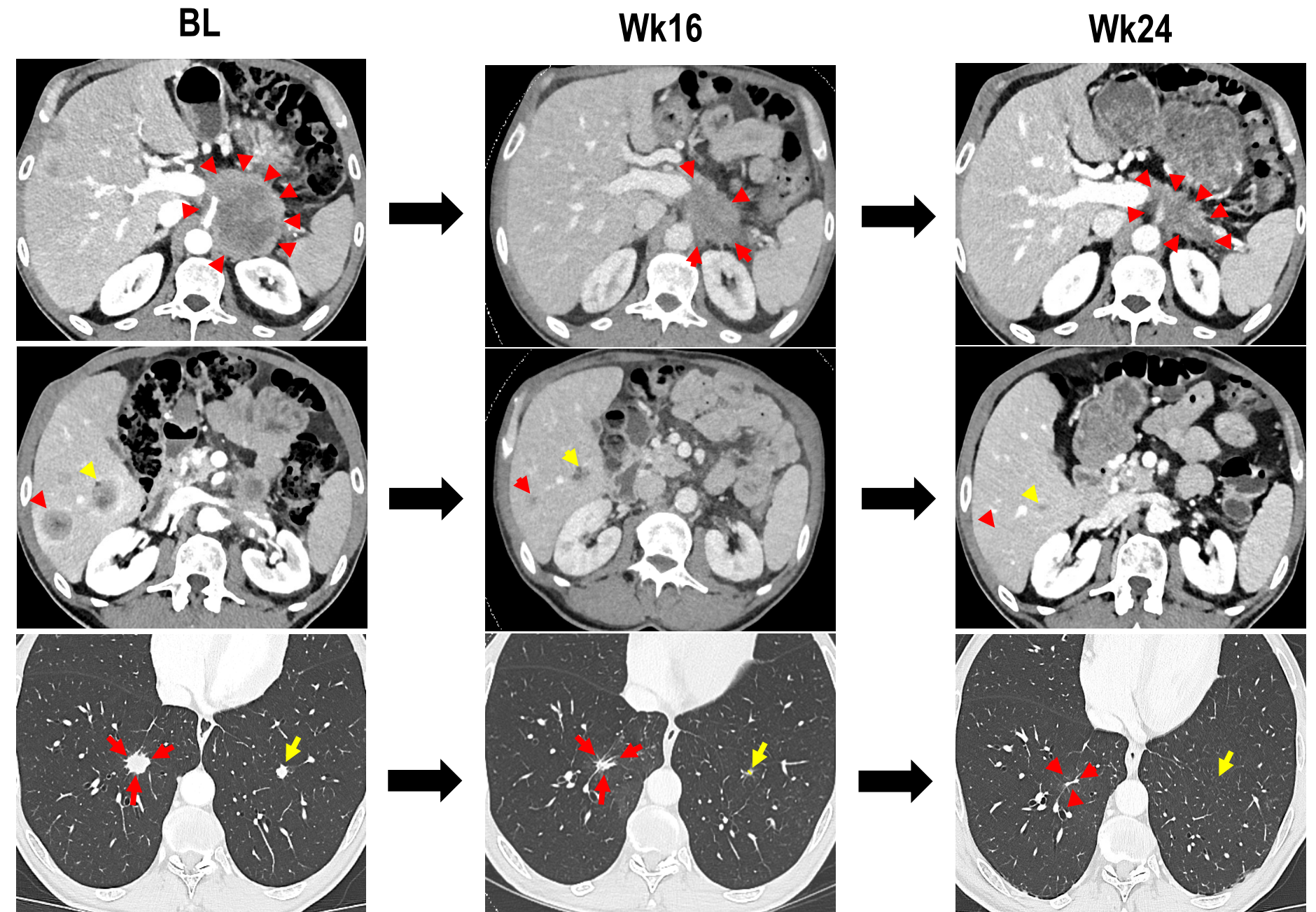
# Case Report: Efficacy in Metastatic PDAC

## Patient Baseline Characteristics

- 69-year-old man with stage IV PDAC
- Initial diagnosis in 2024
- Liver, lung, and peritoneal metastases
- Previously progressed on FOLFIRINOX

## INCB161734 Treatment Course

- 1200 mg qd without interruptions
- Deep PR of –80% in target lesion diameters at first scan and confirmed on 2 subsequent assessments
- Early molecular response was observed with undetectable *KRAS*<sup>G12D</sup> VAF at Wk4 of treatment
- Patient completed 24 Wks of treatment as of September 2025 and continues treatment



Representative images of tumor response courtesy of Dr. Antoine Hollebecque.

BL, baseline; FOLFIRINOX, leucovorin calcium, fluorouracil, irinotecan hydrochloride, oxaliplatin; PDAC, pancreatic ductal adenocarcinoma; PR, partial response; qd, daily; VAF, variant allele frequency; Wk, week.

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# Conclusions

- Results show a manageable safety profile of INCB161734 in patients with *KRAS*<sup>G12D</sup> advanced or metastatic solid tumors
- PK and PD data indicate consistent target coverage (IC<sub>95</sub>) and deep molecular responses at the 1200mg qd dose
- Clinical efficacy in heavily pretreated patients with PDAC supports continued development with INCB161734 at the 1200 mg qd dose
- Enrollment is ongoing with INCB161734 in combination with gemcitabine + nab-paclitaxel and mFOLFIRINOX in first-line metastatic PDAC



- 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 Steven Moore, PhD, of Envision Ignite, an Envision Medical Communications agency, a part of Envision Pharma Group (Fairfield, CT, USA), and funded by Incyte Corporation



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