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Preliminary Phase 1 Results of INCB161734, a Novel Oral *KRAS*^{G12D} Inhibitor, in Patients With Advanced or Metastatic Solid Tumors

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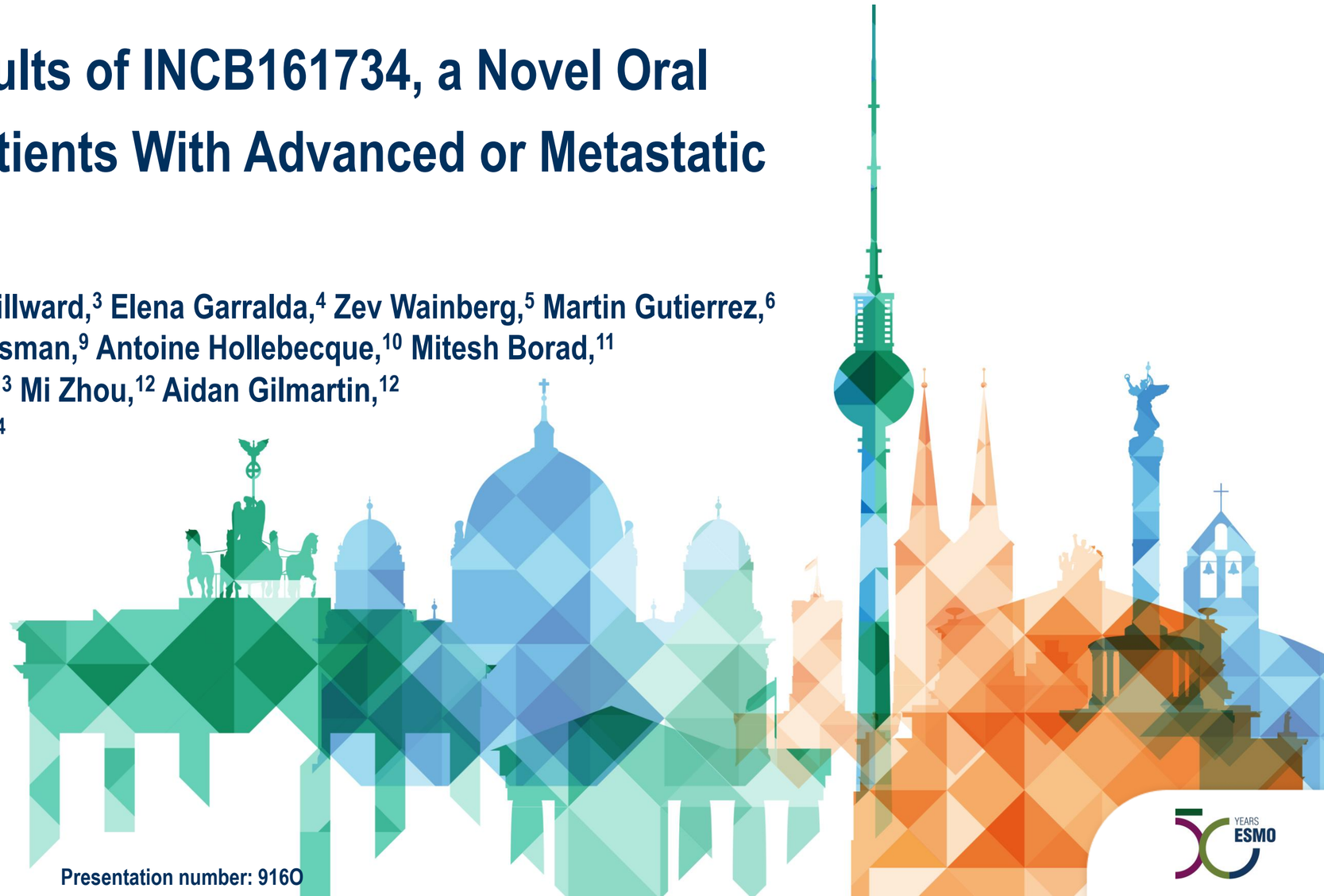

Presentation number: 916O

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Declaration of Interests

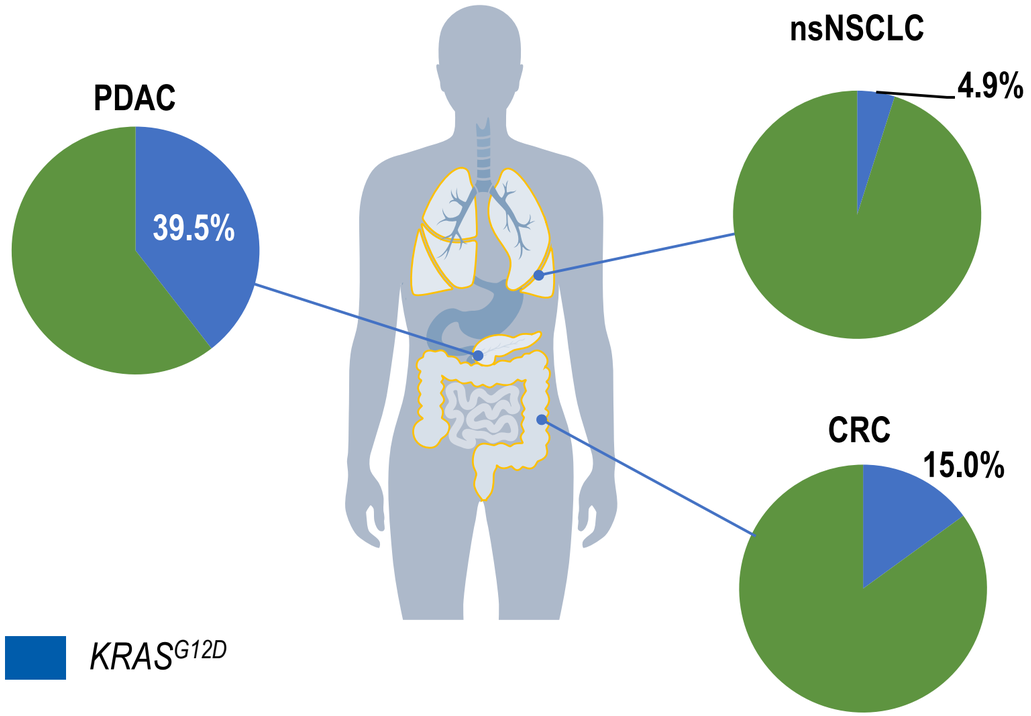
Jayesh Desai:

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*;

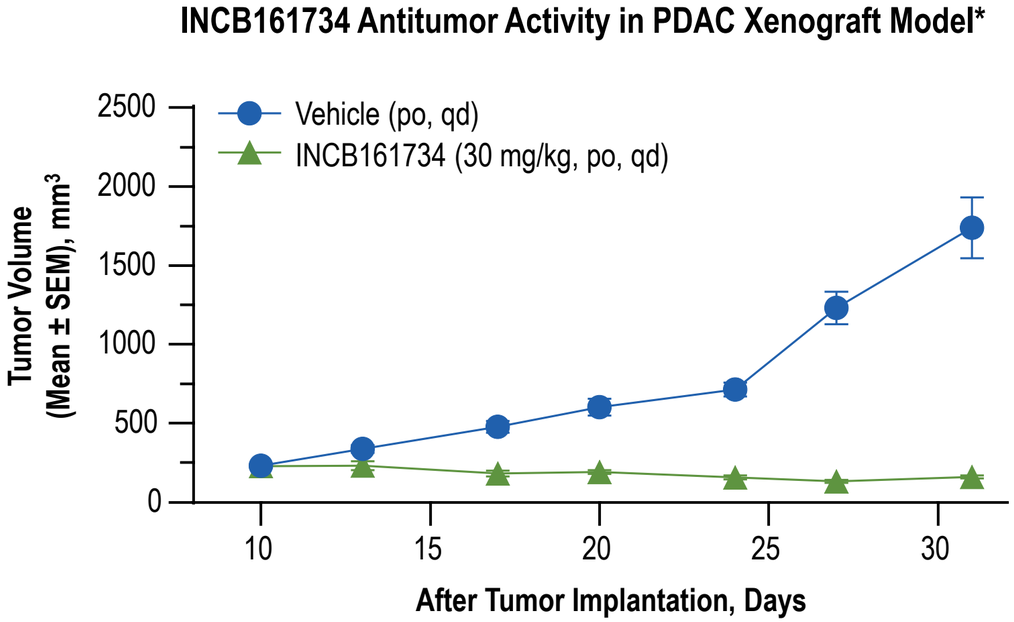
Research funding – *Amgen (Inst), AstraZeneca/MedImmune (Inst), BeiGene (Inst), Bristol Myers Squibb (Inst), Roche/Genentech (Inst), GlaxoSmithKline (Inst), Novartis (Inst), Roche (Inst)*

Introduction

- *KRAS*^{G12D} mutations are among the most common oncogenic drivers for PDAC, CRC, and nsNSCLC[1]



- 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[2]



*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

Phase 1, open-label study evaluating INCB161734 as monotherapy or in combinations

Key Inclusion Criteria

- Locally advanced or metastatic solid tumor with *KRAS*^{G12D} mutation
- Disease progression on prior standard therapy (monotherapy cohorts)
- ECOG PS 0-1
- No prior treatment with a *KRAS*^{G12D} selective inhibitor

Primary endpoint: Safety and tolerability

Secondary endpoints/objectives:
ORR, DCR, DOR, PK

INCB161734 Monotherapy*

Dose Escalation

- 1600 mg qd (n=3)
- 600 mg bid (n=7)
- 1000 mg qd (n=3)
- 600 mg qd (n=6)
- 400 mg qd (n=5)
- 200 mg qd (n=4)

PD Cohort
- 600 mg qd (n=5)
- 1000 mg qd (n=4)

Food Effect Cohort
- 1200 mg qd (n=15)

Randomized Optimization of Selected RDEs
600 mg and 1200 mg qd

Dose Expansion
- PDAC (n=40)
- CRC (n=30)
- NSCLC
- Other advanced solid tumor

Selected RP2D
1200 mg qd

INCB161734 Combinations

Dose Escalation and Expansion

+ cetuximab in CRC or PDAC
+ retifanlimab in PDAC, CRC, or NSCLC
+ GEMNabP in PDAC
+ mFOLFIRINOX in PDAC
+ cetuximab + chemotherapy in CRC
+ INCA33890† in PDAC or CRC

PDAC (n=16; enrollment ongoing)

*As of August 1, 2025. †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.

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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,† 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%). †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*^{G12D} 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)

	TRAEs*					
	All Doses (n=136)		600 mg qd (n=43)		1200 mg qd (n=67)	
TRAE, n (%)	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.

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Most Common TRAEs by Severity and INCB161734 Dose

- Gastrointestinal AEs were manageable and mostly grade 1

	Most Common TRAEs in Decreasing Order of Frequency*								
	All Doses (n=136)	600 mg qd (n=43)				1200 mg qd (n=67)			
Preferred term, n (%)	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.

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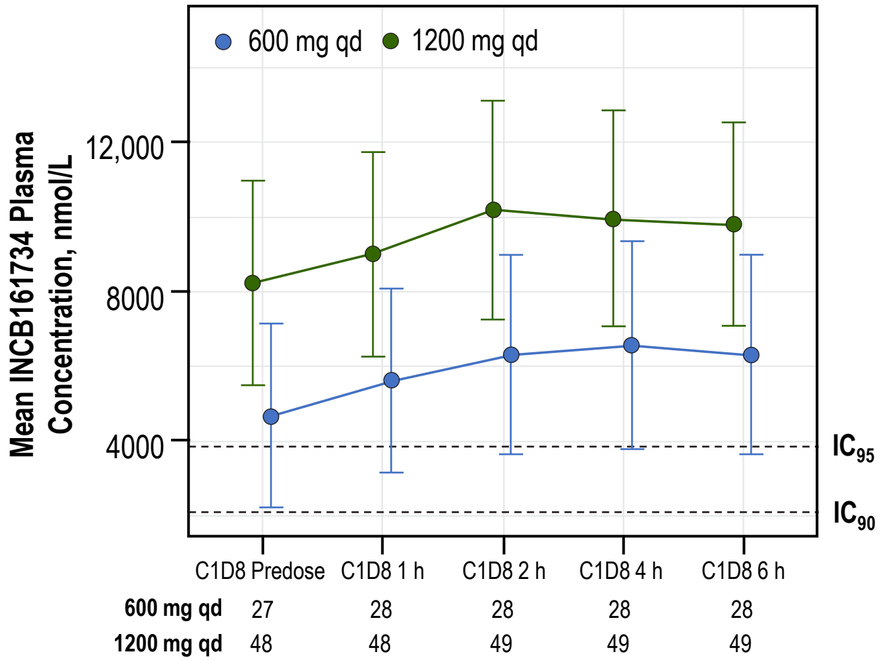
PK Analysis Supports Exposures Achieving High-Target Coverage

- 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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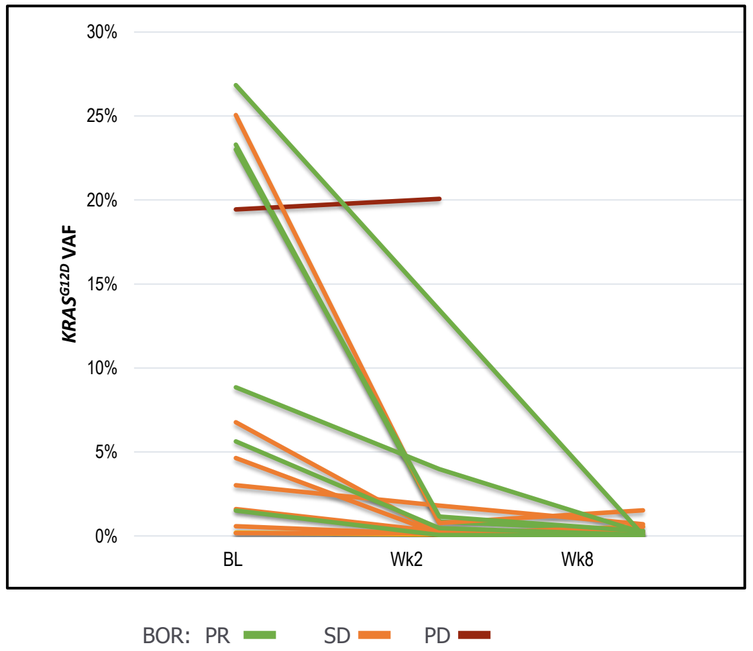
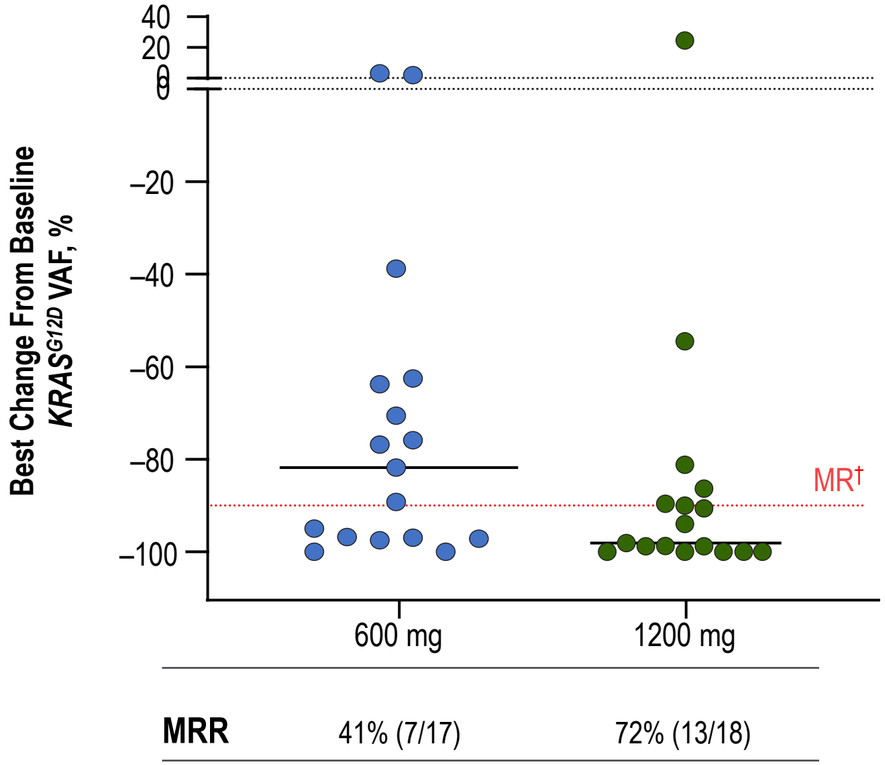
Measurement of *KRAS*^{G12D} in Plasma ctDNA Confirms Rapid Molecular Responses

- In dose escalation, INCB161734 at the ≥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, ≥600-mg dose, all tumors with detectable *KRAS*^{G12D} plasma ctDNA allele at BL. †≥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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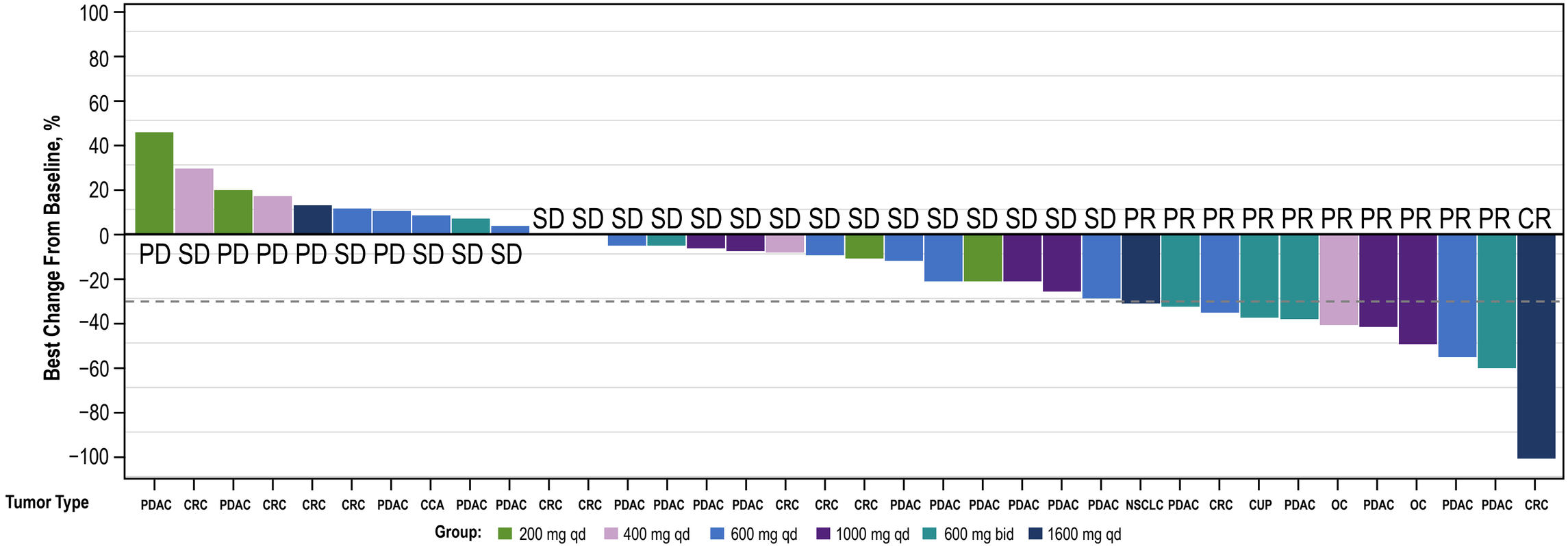
Antitumor Activity Across Cancer Types in Dose Escalation*

- Clinical responses were observed at INCB61734 doses ≥600 mg qd



*N=36 patients with ≥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.

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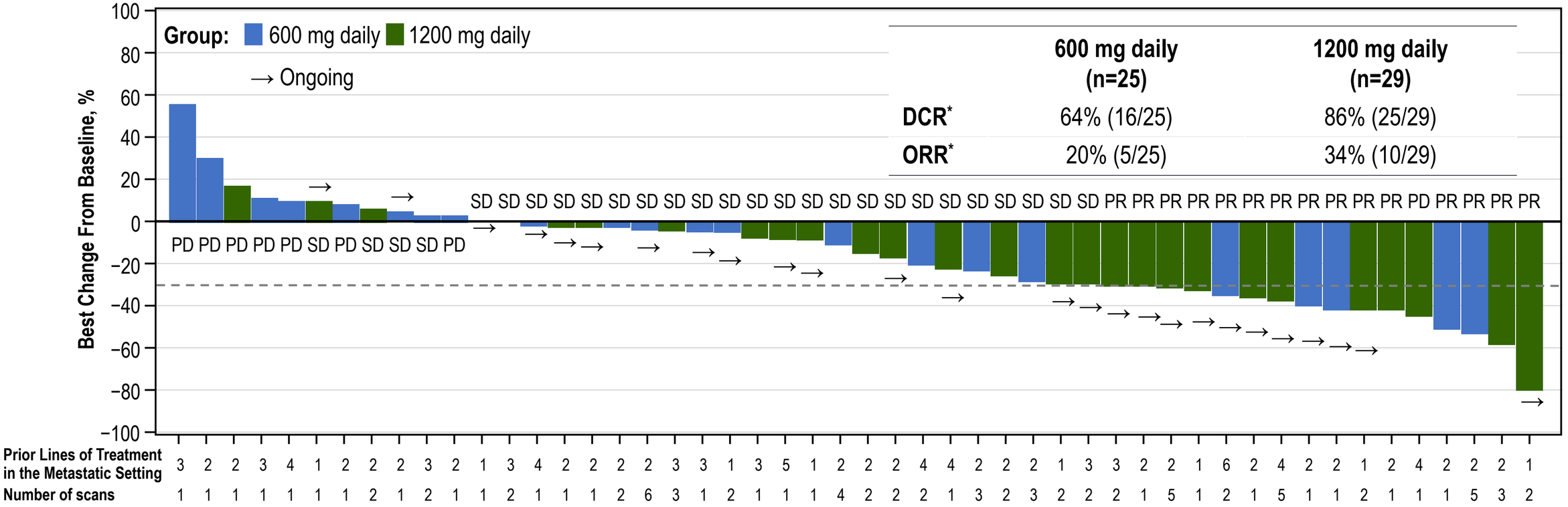
Antitumor Activity in PDAC Patients at Selected INCB61734 RDEs

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



	600 mg daily (n=25)	1200 mg daily (n=29)
DCR*	64% (16/25)	86% (25/29)
ORR*	20% (5/25)	34% (10/29)

*Investigator-assessed in patients with ≥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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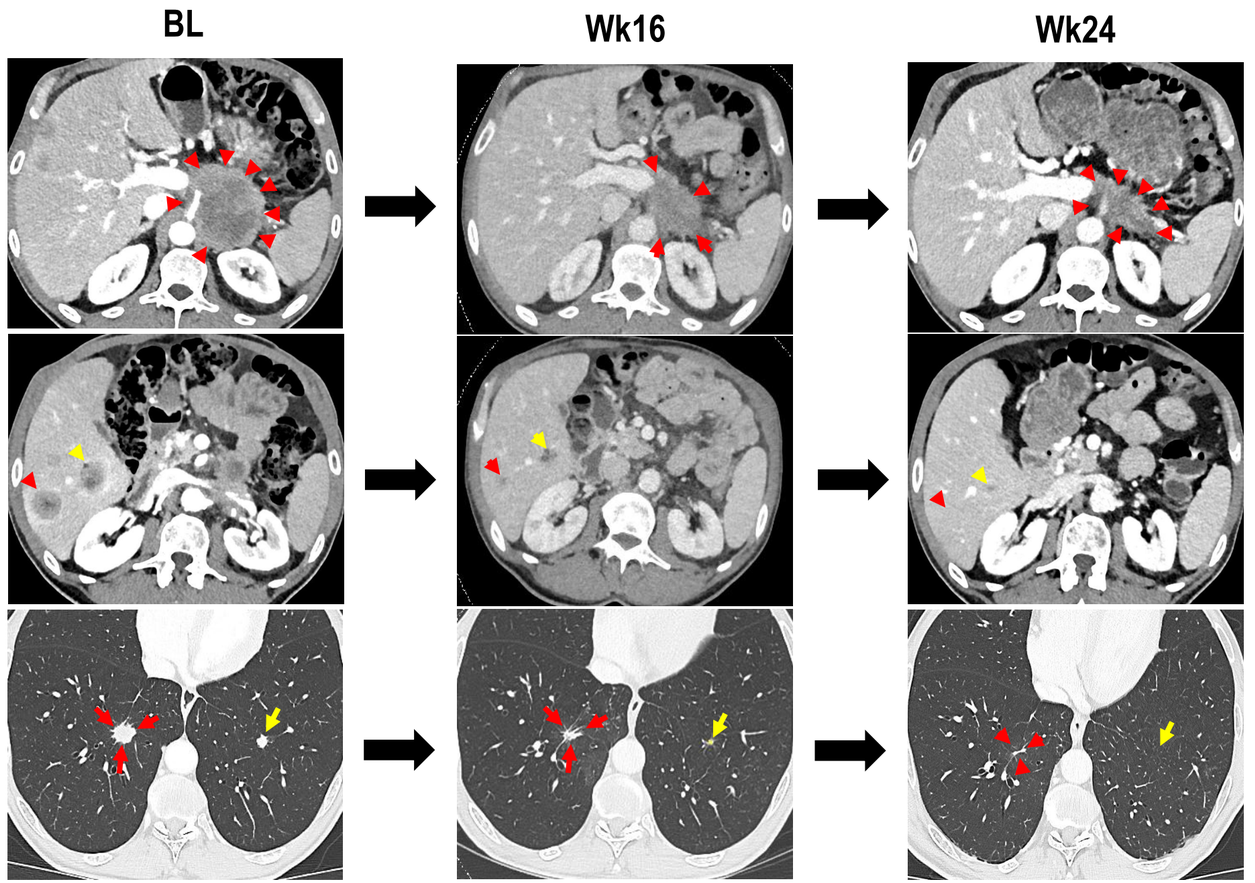
Case Report: Efficacy in Metastatic PDAC

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*^{G12D} 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*^{G12D} advanced or metastatic solid tumors
- PK and PD data indicate consistent target coverage (IC_{95}) 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

IC_{95}, 95% inhibitory concentration; mFOLFIRINOX, modified leucovorin calcium, fluorouracil, irinotecan hydrochloride, oxaliplatin; PD, pharmacodynamics; PDAC, pancreatic ductal adenocarcinoma; PK, pharmacokinetics; qd, daily.

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- 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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