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Safety and Efficacy of Oral KRAS G12D Inhibitor INCB161734 as Monotherapy or in Combination With Cetuximab in Patients With Advanced/Metastatic Colorectal Cancer

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Declaration of Interests

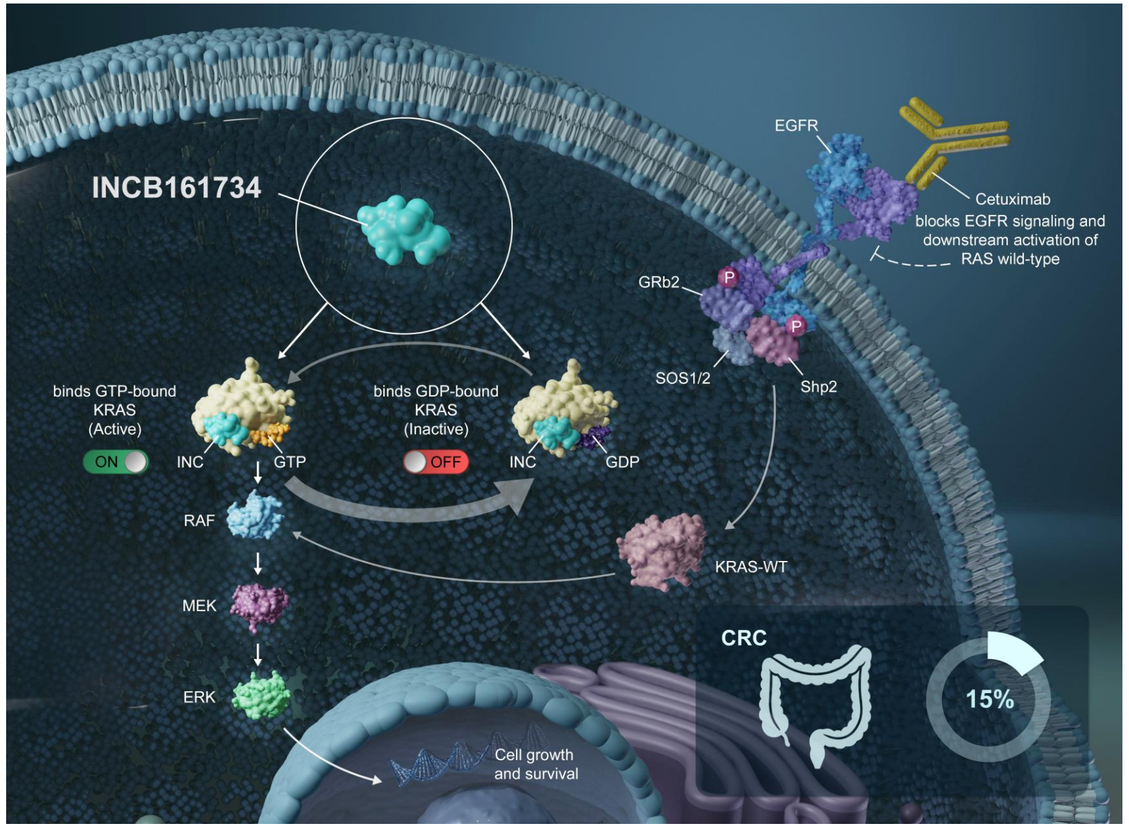
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Introduction



- CRC remains the second leading cause of cancer deaths worldwide[1]
- Despite modest survival improvements over time, outcomes remain poor for patients with advanced or metastatic CRC[2]
- *KRAS*^{G12D} mutations are oncogenic drivers in ~15% of patients with CRC[3]
- INCB161734 is a potent and selective ON/OFF oral KRAS^{G12D} inhibitor[4]
- Phase 1 results demonstrated efficacy and manageable safety in patients with *KRAS*^{G12D} advanced or metastatic solid tumours, including CRC[5]
- EGFR signalling may confer resistance to KRAS inhibition in CRC by activating RAS-MAPK signalling[6]
- Here, we report initial results of INCB161734 ± the EGFR inhibitor cetuximab in patients with advanced or metastatic CRC

1. Sung H, et al. *CA Cancer J Clin*. 2026;76:e70090. 2. Zeineddine FA, et al. *NPJ Precis Onc.* 2023;7:16. 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 916O. 6. Feng J, et al. *Oncogene*. 2023;42:1620-33.
CRC, colorectal cancer; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; GDP, guanosine diphosphate; GRb2, growth factor receptor-bound protein 2; GTP, guanosine triphosphate; INC, INCB161734; KRAS, Kirsten rat sarcoma; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma; Shp2, Src homology region 2 domain-containing phosphatase-2; SOS, son of sevenless; WT, wild type.

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INCB161734-101 (NCT06179160): INCB161734 ± Cetuximab in Patients With Metastatic CRC

Key Eligibility Criteria

- Locally advanced or metastatic CRC with *KRAS*^{G12D} mutation*
- ECOG PS 0 or 1
- Disease progression on prior standard treatment
- No prior treatment with a KRAS^{G12D} selective inhibitor

Key Endpoints

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

INCB161734 Monotherapy†

Dose Escalation (All Groups)

INCB161734
200 mg qd to 1600 mg qd

Optimization of selected RDEs

Dose Expansion (CRC)

- INCB161734 600 mg qd (n=12)
- INCB161734 1200 mg qd (n=24)

INCB161734 + Cetuximab

Cetuximab: 500 mg/m² IV administered on D1 and D15 of each 28D cycle

Dose Escalation

- INCB161734 1200 mg qd + cetuximab (n=5)
- INCB161734 600 mg qd + cetuximab (n=3)

Selected RDE
No DLTs
MTD not reached

Dose Expansion

INCB161734 1200 mg qd + cetuximab (n=20)

Data cut-off date: July 6, 2026. *Determined by local testing. †Included patients in the pharmacodynamic evaluation and food-effect cohorts.

CRC, colorectal cancer; D, day; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; KRAS, Kirsten rat sarcoma; MTD, maximum tolerated dose; ORR, objective response rate; PFS, progression-free survival; PK, pharmacokinetics; qd, daily; RDE, recommended dose for expansion.

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CRC Patient Disposition and Baseline Characteristics

- As of July 6, 2026, 24 patients with CRC received INCB161734 1200 mg qd monotherapy
  - No patients remained on treatment
  - Primary reason for discontinuation was progressive disease (n=23; 96%)*
- 25 patients received INCB161734 1200 mg qd in combination with cetuximab
  - Treatment ongoing in 6 (24%)
  - Primary reason for discontinuation was progressive disease (n=14; 56%)†
- All patients had received prior SoC chemotherapy in the metastatic setting

	INCB161734 1200 mg qd	
	Monotherapy (n=24)	**+ Cetuximab (n=25)**
Age, median (range), years	55 (32, 78)	53 (32, 77)
≥65 years, n (%)	4 (17)	7 (28)
Female, n (%)	13 (54)	16 (64)
ECOG PS, n (%)		
0	14 (58)	16 (64)
1	10 (42)	9 (36)
Liver metastases, n (%)	16 (67)	15 (60)
Total prior lines of therapy, median (min, max)	3 (1, 7)	2 (1, 7)
Prior therapy, n (%)		
5-FU/capecitabine	24 (100)	25 (100)
Oxaliplatin	21 (88)	24 (96)
Irinotecan	24 (100)	22 (88)
Anti-VEGF chemotherapy combination	24 (100)	21 (84)
Trifluridine and tipiracil	8 (33)	4 (16)
Primary site of disease, n (%)		
Right side of colon‡	3 (13)	8 (32)
Left side of colon§	19 (79)	16 (64)
Unknown	2 (8)	1 (4)

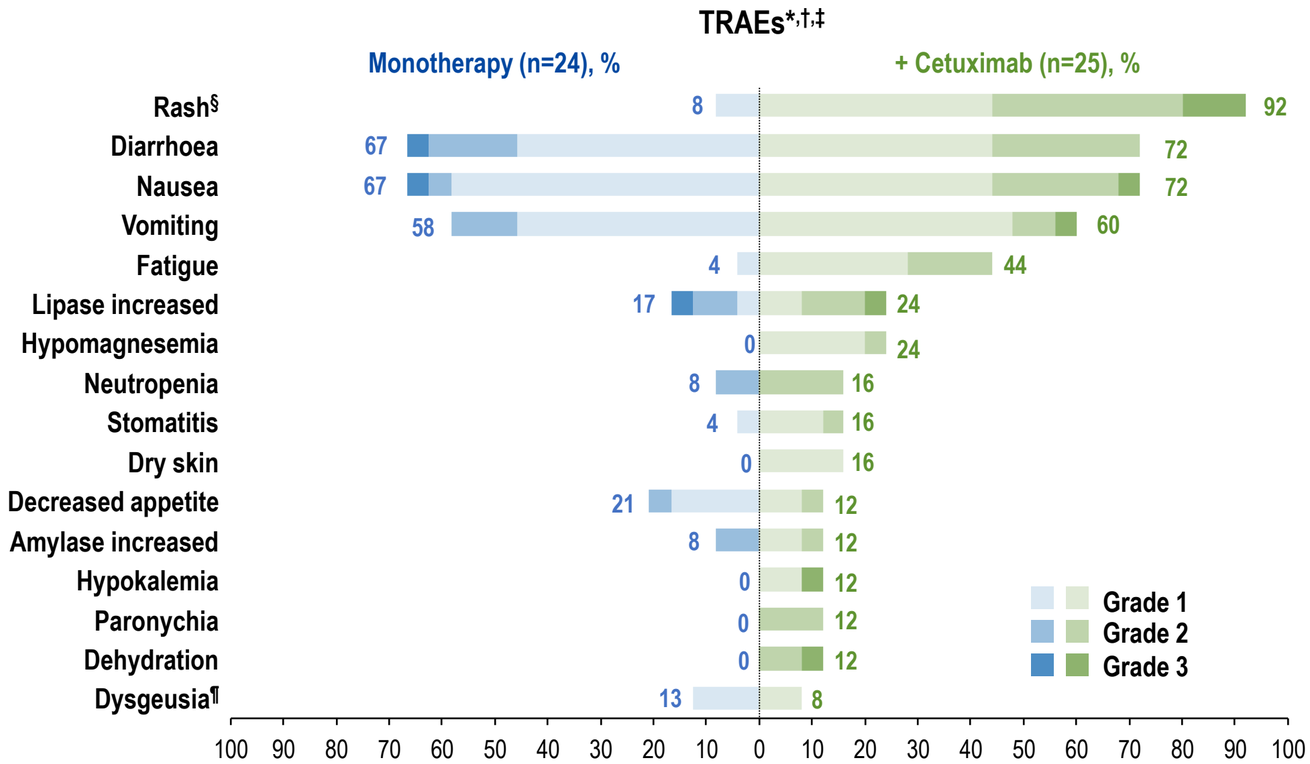
*1 patient discontinued due to patient withdrawal. †Other reasons for discontinuation were patient withdrawal (n=4) and death (n=1). ‡Includes right side of colon, caecum, and ileocaecal valve.
§Includes left side of colon, rectum, sigmoid colon, descending colon, and colon and rectum.
5-FU, 5-fluorouracil; CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; qd, daily; SoC, standard of care; VEGF, vascular endothelial growth factor.

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Safety: INCB161734 ± Cetuximab in Patients With Metastatic CRC

- TRAEs led to INCB161734 dose reductions in 8% of patients with both monotherapy and in combination with cetuximab
- No grade 4 or 5 TRAEs were observed with INCB161734 monotherapy or INCB161734 + cetuximab
- Higher incidences of rash, fatigue, and electrolyte abnormalities were observed with INCB161734 + cetuximab, consistent with the cetuximab safety profile

	INCB161734 1200 mg qd	
TRAE,*,† n (%)	**Monotherapy (n=24)**	**+ Cetuximab (n=25)**
Any TRAE	22 (92)	25 (100)
Grade 3 TRAE	2 (8)	7 (28)
TRAE leading to INCB161734		
Interruption	3 (13)	8 (32)
Reduction	2 (8)	2 (8)
Discontinuation	0 (0)	0 (0)
TRAE leading to cetuximab		
Interruption	NA	10 (40)
Reduction	NA	3 (12)
Discontinuation	NA	1 (4)



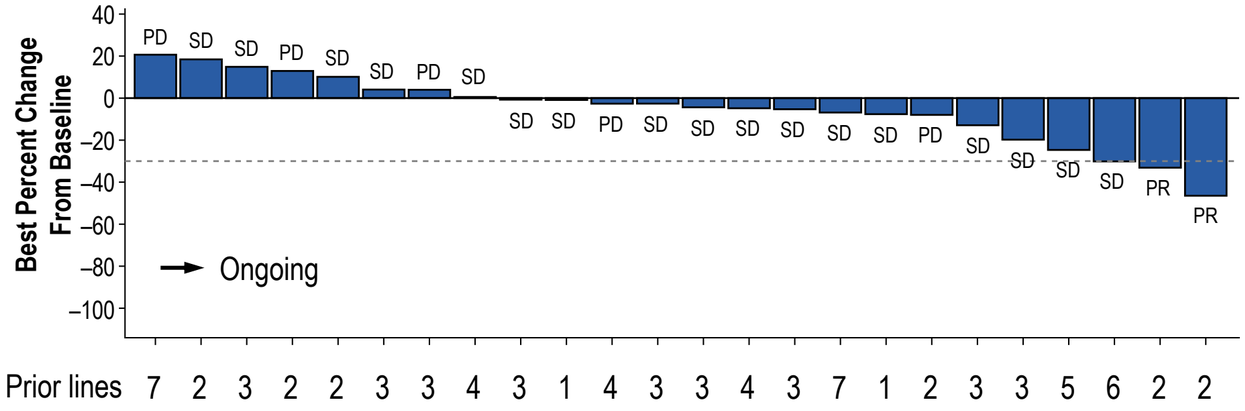
*Assessed in patients who received ≥1 dose of study drug. †Related to INCB161734 monotherapy or related to any study drug for combination therapy. ‡Occurring in ≥10% of patients in either treatment group. §Includes rash, dermatitis acneiform, rash maculo-papular, and rash pustular.
¶The maximum possible severity per CTCAE for dysgeusia is grade 2.
CRC, colorectal cancer; CTCAE, Common Terminology Criteria for Adverse Events; KRAS, Kirsten rat sarcoma; NA, not applicable; qd, daily; TRAE, treatment-related adverse event.

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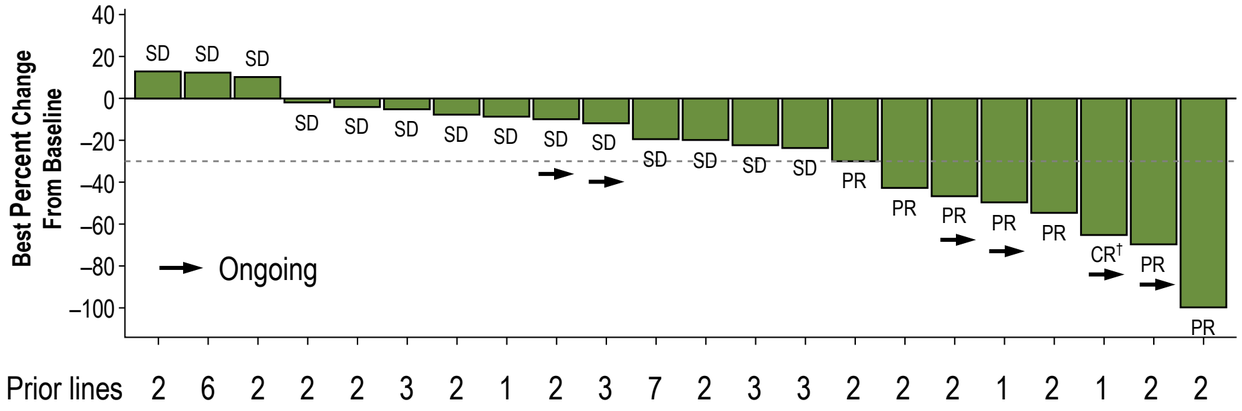
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INCB161734 in Combination With Cetuximab Showed Encouraging Antitumour Activity in Heavily Pretreated Patients With *KRAS*^{G12D}-Mutated Metastatic CRC

% (n/N)	INCB161734 monotherapy (n=24)
ORR*	8 (2/24)
DCR*	79 (19/24)



% (n/N)	INCB161734 + cetuximab (n=22)
ORR*	36 (8/22)
DCR*	100 (22/22)



*Assessed in patients who received INCB161734 at 1200 mg qd with a baseline scan and at least 1 of the following: ≥1 postbaseline scan, study discontinuation due to death or PD. Data include unconfirmed responses. †Only lymph node as target lesion and nontarget lesions.

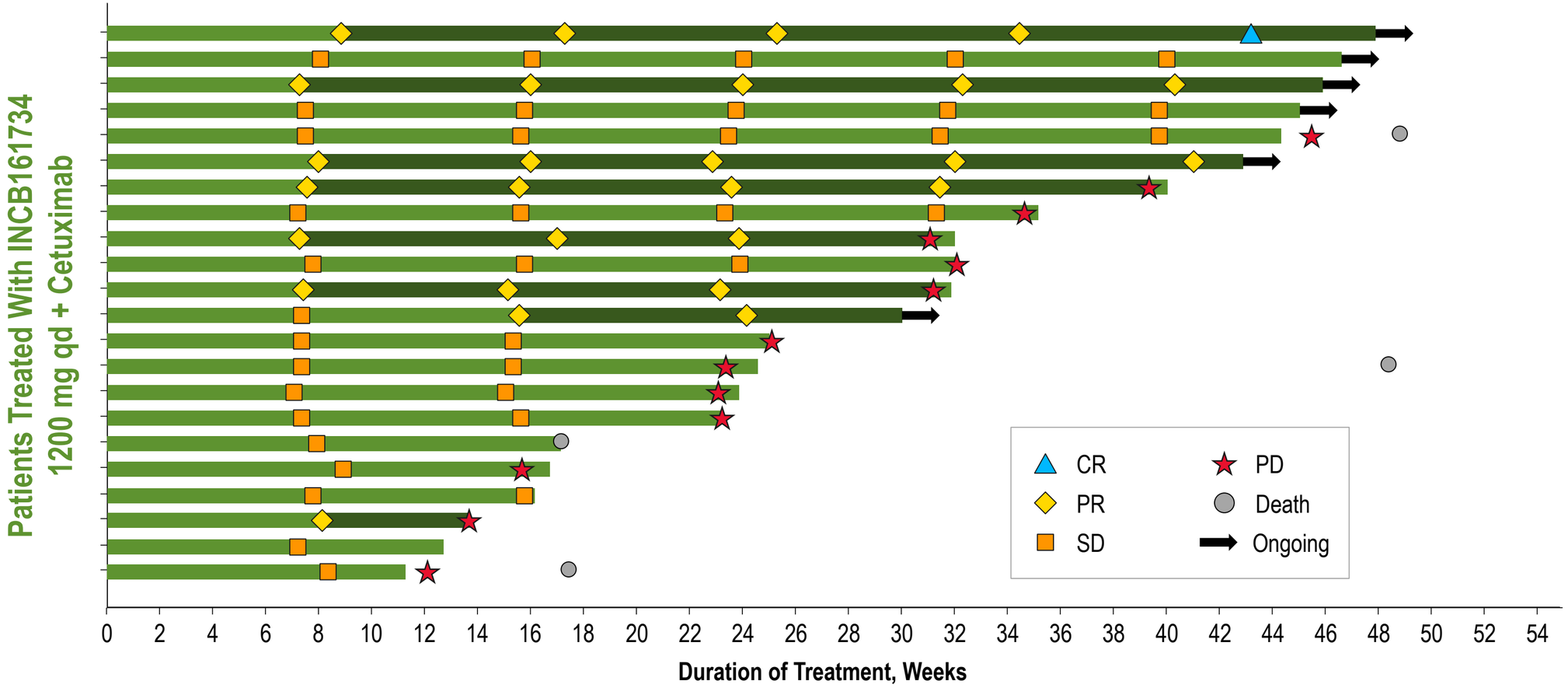
CR, complete response; CRC, colorectal cancer; DCR, disease control rate; KRAS, Kirsten rat sarcoma; ORR, objective response rate; PD, progressive disease; PR, partial response; qd, daily; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

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INCB161734 in Combination With Cetuximab Showed Durable Responses in Heavily Pretreated Patients With *KRAS*^{G12D}-Mutated Metastatic CRC

- Median PFS (95% CI) for INCB161734 1200 mg qd + cetuximab was 7.2 (5.4, NE) months



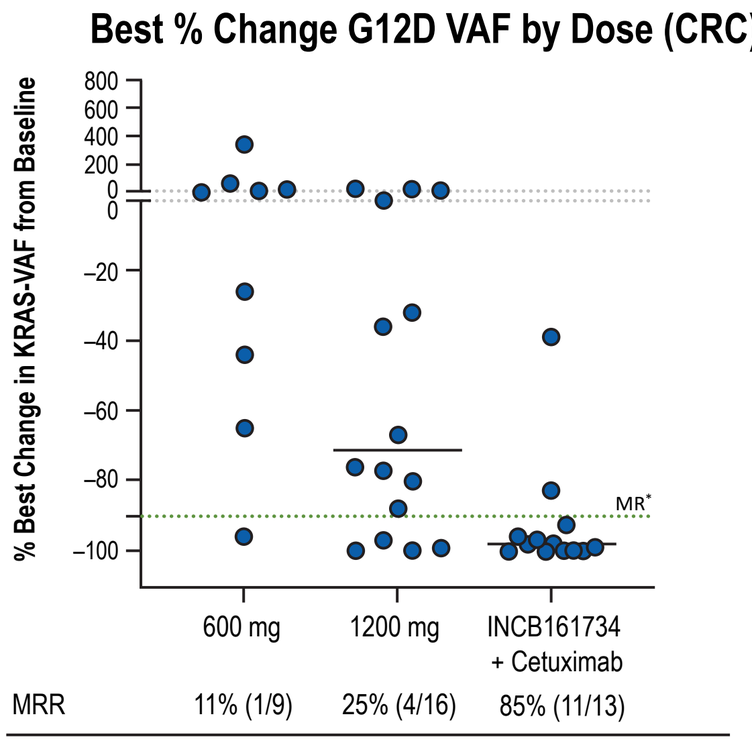
CI, confidence interval; CR, complete response; CRC, colorectal cancer; KRAS, Kirsten rat sarcoma; NE, not estimable; PD, progressive disease; PFS, progression-free survival; PR, partial response; qd, daily; SD, stable disease.

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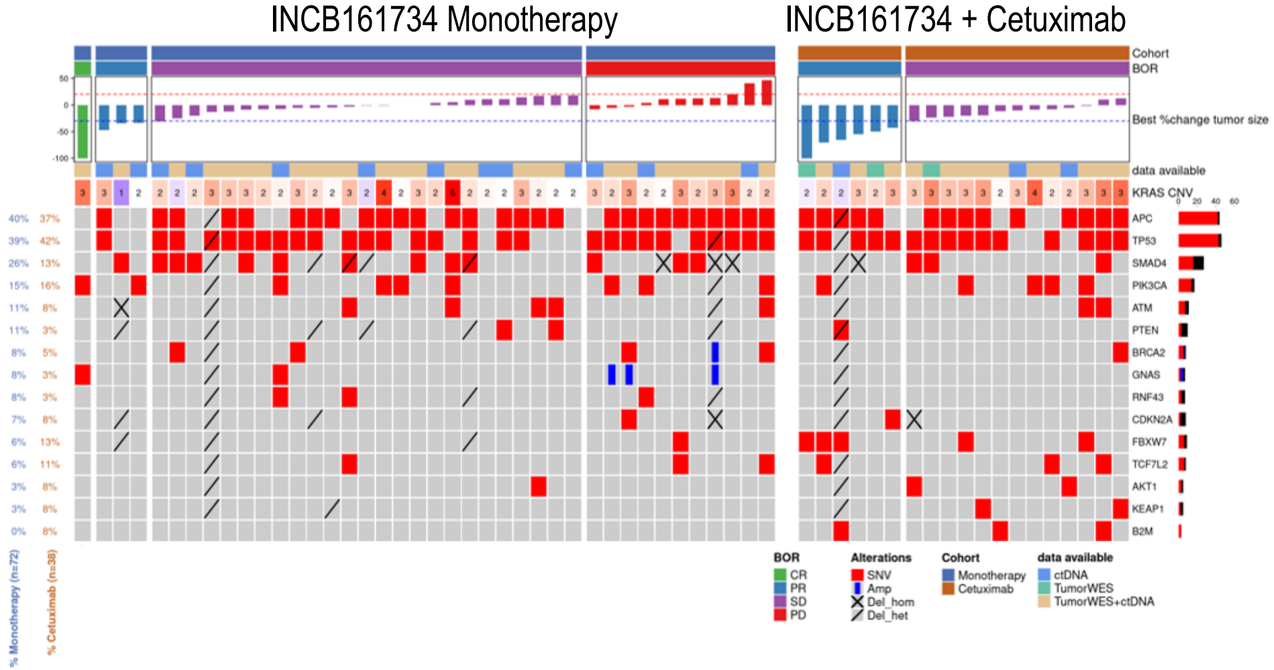
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Measurement of *KRAS*^{G12D} in Plasma ctDNA and Early Clinicogenomic Profiling in Patients With CRC

- Higher MR rates were observed in patients with INCB161734 1200 mg + cetuximab



- Baseline genomic analysis found no significant correlations for coalterations with response (ORR or DCR) for INCB161734 monotherapy or in combination with cetuximab
  - Numerically higher rates of *TP53* and *APC* mutations in monotherapy nonresponders



*MR: ≥90% reduction in *KRAS*^{G12D} VAF by week 8, assessed by ddPCR or NGS (Predicine) for all patients with baseline G12D VAF and 8-week data. Baseline NGS analysis of tumour biopsies (Caris WES) and plasma ctDNA (Predicine WES or Caris WES).
amp, amplification; BOR, best overall response; C, cycle; CR, complete response; CRC, colorectal cancer; CNV, copy number variation; ctDNA, circulating tumour DNA; D, day; DCR, disease control rate; ddPCR, droplet digital polymerase chain reaction; del, deletion; het, heterozygous; hom, homozygous; KRAS, Kirsten rat sarcoma; MR, molecular response; MRR, molecular response rate; NGS, next-generation sequencing; ORR, objective response rate; PD, progressive disease; PR, partial response; qd, daily; SD, stable disease; SNV, single nucleotide variant; VAF, variant allele frequency; WES, whole exome sequencing.

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Conclusions

- INCB161734 at 1200 mg qd as monotherapy and in combination with cetuximab had a manageable safety profile in patients with *KRAS*^{G12D} metastatic CRC
  - No DLTs were observed in combination dose escalation and MTD was not reached
  - TRAEs leading to discontinuation or dose modification were low in both groups
- Preliminary antitumour activity with INCB161734 + cetuximab demonstrated encouraging efficacy in patients with heavily pretreated *KRAS*^{G12D} metastatic CRC
  - For INCB161734 + cetuximab, ORR was 36%, DCR was 100% and median PFS was 7.2 months
- These data support further exploration of this combination in patients with *KRAS*^{G12D} metastatic CRC
- Data for INCB161734 in combination with SoC chemotherapy in patients with metastatic PDAC will also be presented at this congress (3137RO)

CRC, colorectal cancer; DCR, disease control rate; DLT, dose-limiting toxicity; KRAS, Kirsten rat sarcoma; MTD, maximum tolerated dose; ORR, objective response rate; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; qd, daily; SoC, standard of care; TRAE, treatment-related adverse event.

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