The beginning of the end for KRAS cancers

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SC-US-74383

These compounds are investigational agents and have not been approved for use. The efficacy and safety of these investigational compounds have not been established.

Disclosure Information

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Norbert Kraut

I have the following relevant financial relationships to disclose:

Employee of Boehringer Ingelheim

I will not discuss off label use in my presentation

I will discuss the potential for investigational use of $KRAS^{G12D}$ inhibitors, pan-(K)RAS inhibitors and pan-KRAS PROTAC degraders

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Precision cancer therapies in 2022

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Target	Cancer types	Molecules
ALK fusion	NSCLC adeno, ALCL	crizotinib, alectinib, ceritinib, brigatinib, lorlatinib
BCR-ABL fusion	CML, Ph+ ALL	imatinib, dasatinib, nilotinib, bosutinib, ponatinib, asciminib
BRAF V600E mutation	Melanoma, hairy cell leukemia, NSCLC adeno, anaplastic thyroid, colorectal	vemurafenib, dabrafenib, encorafenib (+MEKi; +EGFRi in CRC)
BRCA mutation	Breast, epith. ovarian, fall. tube, peritoneal, prostate, pancreatic cancer	olaparib, rucaparib, talazoparib, niraparib
EGFR del19/L858R mutation	NSCLC adeno	gefitinib, erlotinib, afatinib, osimertinib, dacomitinib
EGFR T790M mutation	NSCLC adeno	osimertinib
EGFR exon 20 insertion	NSCLC adeno	amivantamab, mobocertinib
EzH2 mutation	Follicular lymphoma, epitheloid sarcoma	tazemetostat
FGFR2 fusion	Cholangiocarcinoma	pemigatinib, infigratinib
FGFR2/3 mutation or fusion	Bladder cancer	erdafitinib
FLT3 mutation	AML	midostaurin, gilteritinib
HER2 amplification	Breast cancer, gastric cancer	trastuzumab, pertuzumab, ado-trastuzumab emtansine, lapatinib, neratinib, margetuximab-cmkb, fam-trastuzumab-deruxtecan-nxki, tucatinib
IDH1 mutant, IDH2 mutant	AML	ivosidenib (IDH1), enasidenib (IDH2)
KIT/PDGFR mutation	GIST, MDS	imatinib, ripretinib
KRAS G12C mutation	NSCLC adeno	sotorasib
MET exon 14 mutation	NSCLC adeno	capmatinib, tepotinib
NF1 mutation	Neurofibromatosis type 1	selumetinib
NTRK fusion	NSCLC adeno, other (agnostic)	larotrectenib, entrectenib
PIK3CA mutation	ER/PR+, HER2- breast cancer	alpelisib
PDGFRA exon 18 mutation	GIST	avapritinib
RET fusion	NSCLC adeno, papillary thyroid cancer	selpercatinib, pralsetinib
ROS1 fusion	NSCLC adeno	crizotinib, entrectenib
VHL mutation	VHL-associated RCC, CNS hemangioblastoma, PNET	belzutifan

Impact of drugging all KRAS mutants

- Drugging all KRAS mutants has the potential to almost double the reach of Precision Oncology
- New patients per year in the U.S.:
  - **~250,000 cancer patients** (14.1%) eligible for **FDA approved precision medicines**
  - **~210,000 patients** (11.6%) with ***KRAS* mutated or amplified cancers**
- *KRASmut+* population largely non-

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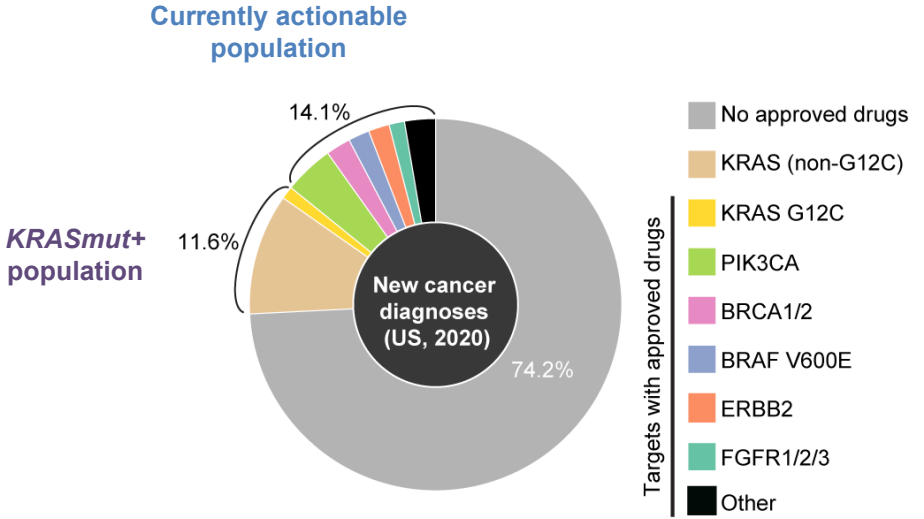
PROJECT GENIE Genomics Evidence Neoplasia Information Exchange



M Hofmann, D Gerlach, S Misale, M Petronczki and N Kraut, *Cancer Discov.* 2022

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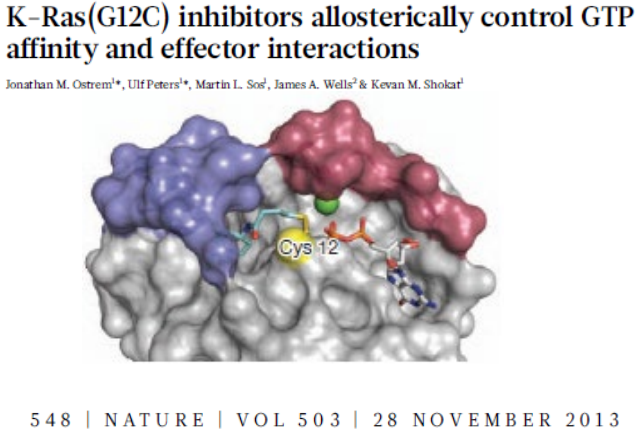
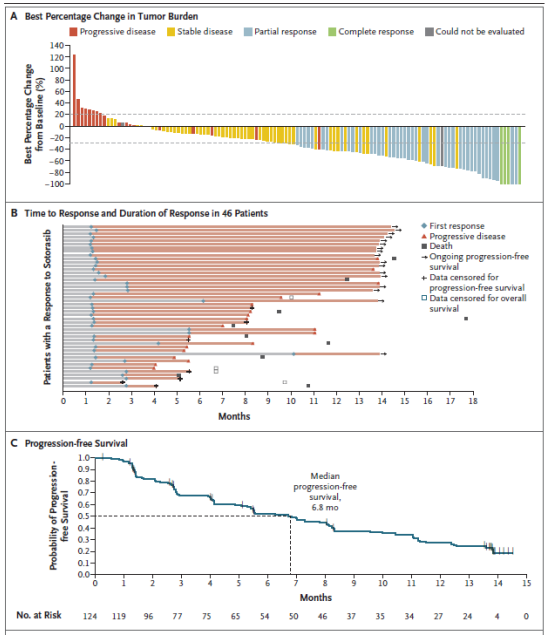
Progress in cracking KRAS





- 1982-2012: Three decades of tinkering with targeting RAS
- 2013: Direct KRAS G12C inhibition (Ostrem et al., Nature 2013)
- 2021: FDA approval of KRAS^{G12C} inhibitor sotorasib (Skoulidis et al., NEJM 2021)

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KRAS^{G12C} is an actionable cancer driver

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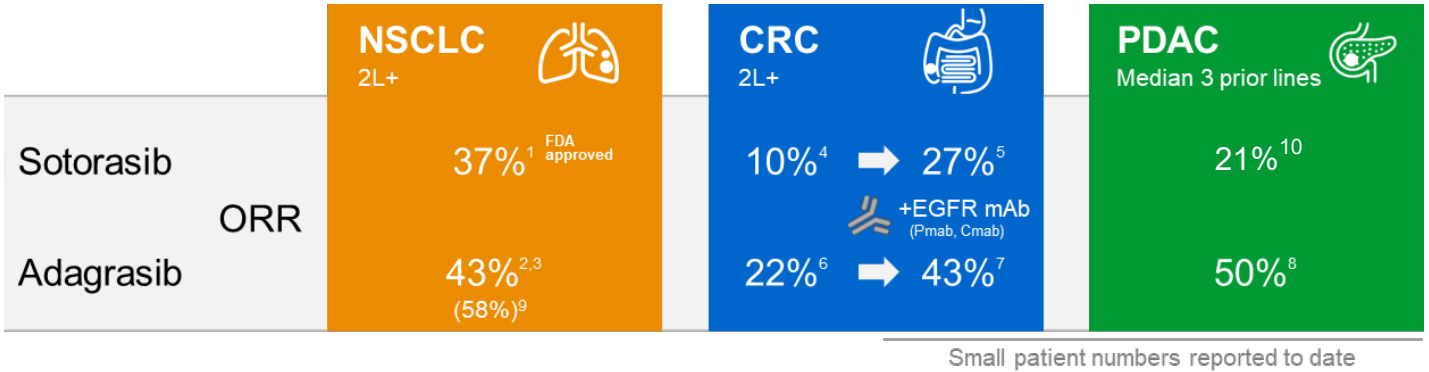
Objective Response Rates (ORR) of patients with KRAS^{G12C} mutated tumors



Mutant-selective KRAS^{G12C} inhibitors are currently changing the treatment paradigm for patients with KRAS^{G12C}-mutated cancers

[1]Skoulidis et al., NEJM 2021; Phase 2 CodeBreaK 100; DCR 81%
[2]AACR-NCI-EORTC 2020. Abstr LBA-04
[3]Mirati Therapeutics Investor Call 20th Sept 2021; Phase 1/1b, 2 KRYSTAL-1; DCR 98%
[4]ASCO 2021 Amgen investor call p23; CodeBreak100 ph 1/2, DCR 74%
[5]Fakih et al ESMO 2021 #3245; CodeBreak101 ph1b; sotorasib+panitumumab; n=26 pts, incl. 3 uPR, DCR 87%
[6]Weiss J, ESMO Sept 16-21 2021. Abstract nr LBA6; KRYSTAL-1, ph1/2; n=45 pts, incl. 1 uPR, DCR 87%
[7]Fakih M, ESMO Sept 16-21 2021. Abstract nr 434; KRYSTAL-1 ph 1/2; adagrasib+cetuximab; n=28 pts, incl. 2 uPR, DCR 100%
[8]Christensen, AACR-NCI-EORTC Molecular Targets Meeting, Oct 9, 2021; n=10 pts, incl. 1 uPR, DCR 100%
[9]Mirati Therapeutics Investor Call 8th November 2021
[10]Bekaii-Saab, ASCO-GI 2022 oral presentation

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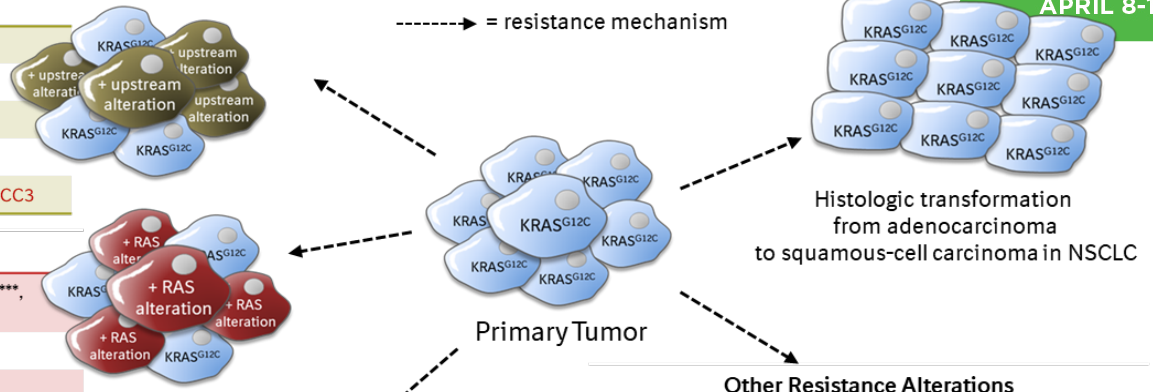
Clinical KRAS^{G12C} inhibitor resistance



Upstream Resistance Alterations

ALK	EML4-ALK
RET	RET^{M918T}, CCDC6-RET
MET	MET^{AMP}
EGFR	EGFR^{P1108L}, EGFR^{AMP}, EGFRA289V
FGFR2	FGFR2^{D304N}, FGFR2^{A68T}, FGFR2^{AMP}, FGFR3-TACC3

RAS Resistance Alterations

KRAS Secondary*	**G12D****, **G12V****, G12F***, G12W***, G12R, **G13D**, Q61H, V8I, V14I
KRAS Amplification	**G12C** and wild-type
KRAS Drug Pocket	R68S, **H95D**, H95R, Y96D, Y96C
NRAS Mutation	G13V, Q61L, **Q61K**, Q61R

Downstream Resistance Alterations

RAF	**BRAF^{V600E}**, BRAF^{K601E}, AKAP9-BRAF, NRF1-BRAF, RAF1-CCDC176, RAF1-TRAK1
MEK	**MAP2K1^{K57N}**, MAP2K1^{K57T}, MAP2K1^{Q56P}, MAP2K1$^{I99-K104}$, **MAP2K1$^{E102-I103del}$**

- Ct DNA for G12C not always detected
** mutations detected in trans
*** mutations in cis

Black indicates NSCLC only,
Red indicates CRC only,
Bold indicates both NSCLC and CRC

Other Resistance Alterations

PI3K	PIK3R1^{S361fs}, PIK3R1^{H1047R}, PTEN^{N48K}, PTEN^{E106G}, PTEN^{F200S}, PTEN^{G209V}, RICTOR^{AMP}
WNT	APC^{P1001S}, APC^{A1002G}, CTNNB1^{D546G}
Hedgehog	PTCH1^{E1257K}
Miscellaneous	SMARCA4^{R181Kfs*106}, RB1^{L60Ffs*50}, IDH2^{R172S}, IDH1^{R132C}, RIT1^{P128L}, *NF1^{R2637} observed for appendiceal cancer patient*

1. Tanaka, N., *et al.*, 2021. Cancer Discovery.
2. Awad, M.M. *et al.*, 2021., *384*(25), pp.2382-2393.
3. Zhao, Y., *et al.*, 2021. *Nature*, pp.1-5.

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Clinical combination strategies for KRAS^{G12C} inhibitors

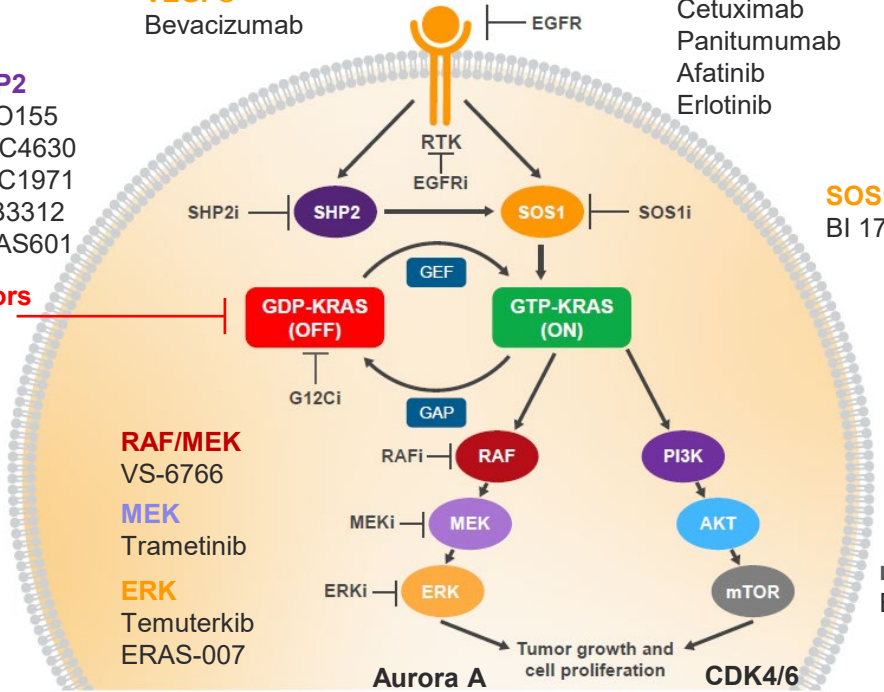
VEGF®
Bevacizumab

EGFR
Cetuximab
Panitumumab
Afatinib
Erlotinib

SHP2
TNO155
RMC4630
GDC1971
JAB3312
ERAS601

SOS1
BI 1701963

KRAS^{G12C} (OFF) inhibitors
Sotorasib
Adagrasib
D-1553
JDQ443
RG6330/GDC-6036
LY3537982
BI 1823911
JAB-21822
GFH925
GH35
MK-1084
BPI-412286
YL-15293



RAF/MEK
VS-6766

MEK
Trametinib

ERK
Temuterkib
ERAS-007

Aurora A
LY3295668

CDK4/6
Abemaciclib
Palbociclib

mTOR
Everolimus

PD-(L)1
Pembrolizumab
Tislelizumab
Atezolizumab
Sintilimab
AMG404

M Hofmann, D Gerlach, S Misale, M Petronczki and N Kraut, *Cancer Discov.* 2022 (modified); *www.clinicaltrials.gov*

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Opportunities of drugging KRAS beyond KRAS^{G12C}

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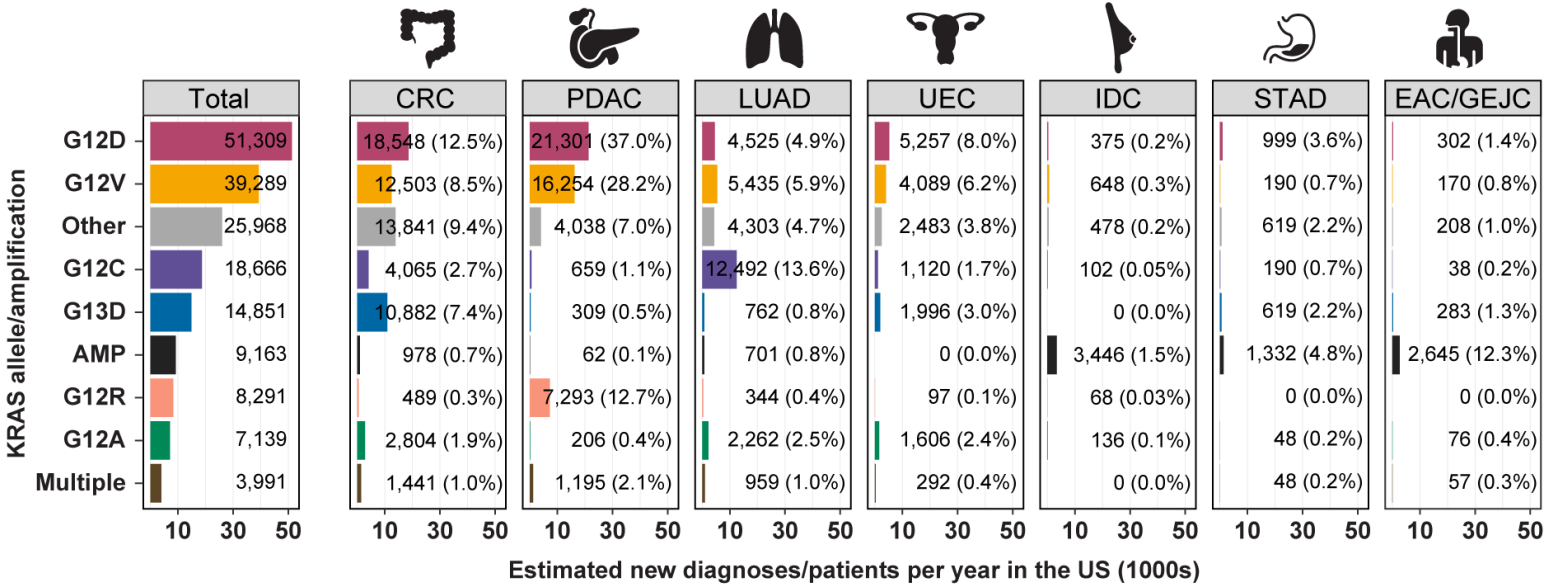
Patient numbers for distinct KRAS mutant alleles/amplification in top 7 cancer types (US)



CRC: colorectal cancer; PDAC: pancreatic ductal adenocarcinoma; LUAD: lung adenocarcinoma; UEC: undifferentiated endometrial carcinoma; IDC: invasive ductal carcinoma; STAD: stomach adenocarcinoma; EAC/GEJC: esophageal adenocarcinoma/ gastroesophageal junction cancer

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M Hofmann, D Gerlach, S Misale, M Petronczki and N Kraut, *Cancer Discov.* 2022

KRAS inhibitors in development

- More than 10 KRAS^{G12C} inhibitors in clinical development (druggability advantage of nucleophilic cysteine)
- Non-KRAS^{G12C} mutants pose significantly druggability challenges (no inherent nucleophilicity)
- All KRAS inhibitors beyond KRAS^{G12C} covered here (blue box) are at preclinical stage

Mutant-specific KRAS inhibitors

Programs (company)	IND	Target	Phase
Sotorasib/AMG 510 (Amgen)		KRAS^{G12C}	Approved
Adagrasib/MRTX849 (Mirati)			
D-1553 (InventisBio)			Clinical
JDQ443 (Novartis)			
RG6330/GDC-6036 (Roche)			
LY3537982 (Eli Lilly)			
BI 1823911 (Boehringer Ingelheim)			
JAB-21822 (Jacobio)			
GFH925 (GenFleet)			
GH35 (Genhouse Bio)			
MRTX1133 (Mirati)		KRAS^{G12D}	Preclinical
KRASG12D1-3 (Boehringer Ingelheim)			
RAS(ON) G12D (Revolution Medicines)			
RAS(ON) G13C (Revolution Medicines)		KRAS^{G13C}	

LUNA18 (Chugai), cyclic peptide pan-RAS inhibitor, Clinical

Pan-(K)RAS inhibitors

			Phase
RSC-1255 (RasCal Therapeutics)		Pan-RAS	Clinical
BI-pan-KRAS1-4 inhibitors (Boehringer Ingelheim)		Pan-KRAS: KRAS$^{G12D/V}$, KRAS wild-type	
BI-pan-KRASdegrader1 (Boehringer Ingelheim)		Pan-KRAS: KRAS$^{G12C/D/V/A}$, KRAS^{G13C}, KRAS$^{A146T/P}$, KRAS$^{Q61E/P}$, KRAS wild-type	Preclinical
RMC-6236 (Revolution Medicines)		Pan-RAS: KRAS$^{G12D/V}$, KRAS^{G13D}, KRAS^{Q61K}, RAS wild-type	

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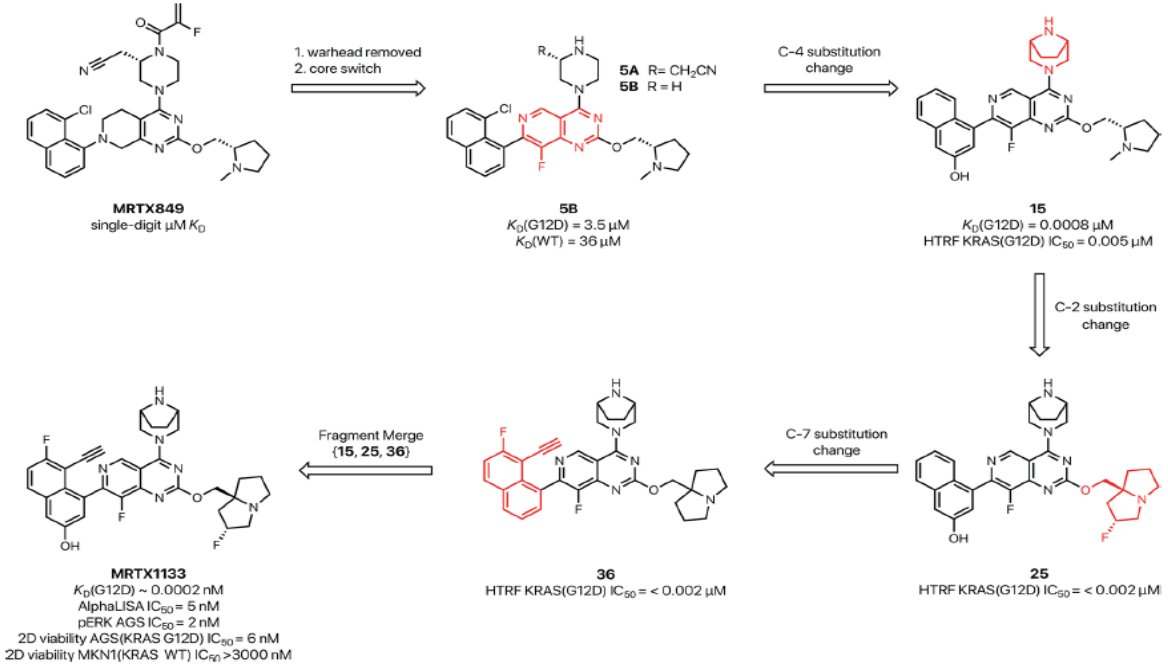
M Hofmann, D Gerlach, S Misale, M Petronczki and N Kraut, *Cancer Discov.* 2022

Mirati Therapeutics: Discovery of MRTX1133, a non-covalent inhibitor of KRAS^{G12D}

Medicinal chemistry campaign towards MRTX1133



Wang et al., *J. Med. Chem.* 2022, 65, 4, 3123; Zheng et al., *J. Med. Chem.* 2022, 65, 4, 3119

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Characterization of MRTX1133 in KRAS^{G12D} xenograft models

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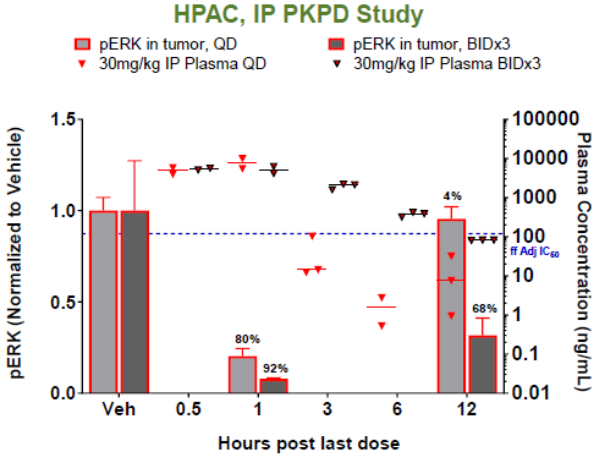
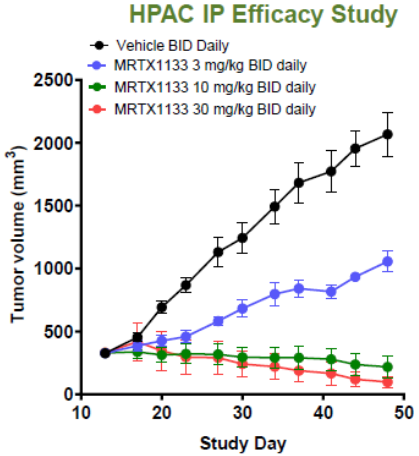
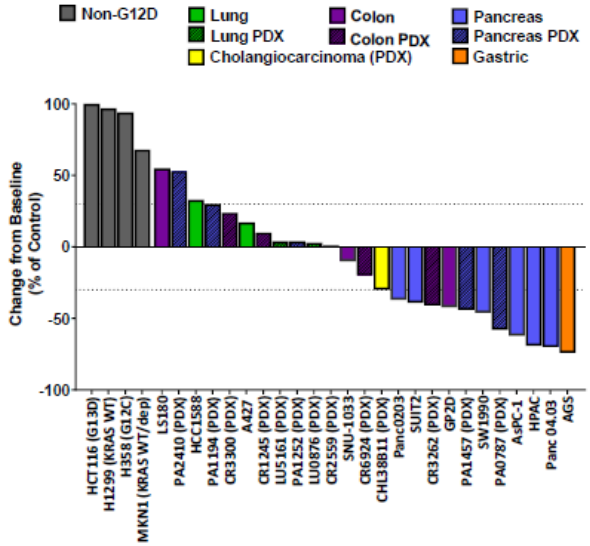
IP administration of MRTX1133 to xenograft tumor-bearing mice inhibits KRAS signaling and exhibits antitumor activity





- Near maximal pERK inhibition after a single dose of MRTX1133
- BIDx3 administration demonstrates robust pERK inhibition for entire dose interval and correlates with maximal antitumor efficacy

MRTX1133 demonstrates cytoreductive antitumor efficacy across a panel of xenograft tumor models



Limited oral bioavailability; formulations to enable IV delivery and maximize plasma exposure are being pursued

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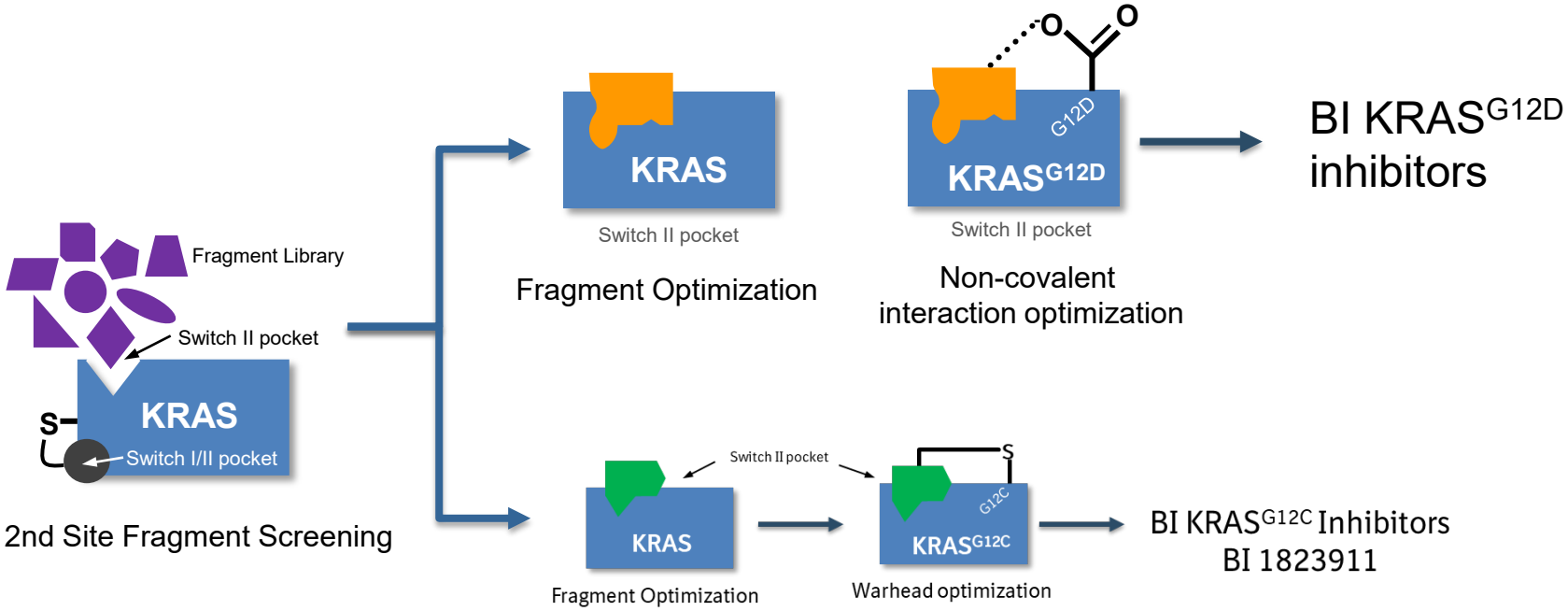
J Christensen, AACR/NCI/EORTC Conference 2021

Boehringer Ingelheim approach to KRAS^{G12D} inhibitors



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D McConnell, The Third NCI RAS Initiative Symposium 2021

Characterization of BI-KRAS^{G12D} inhibitors

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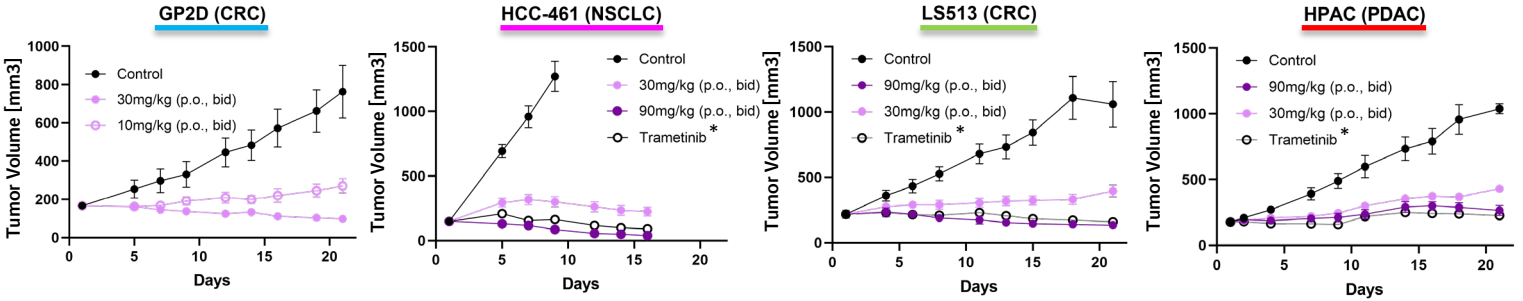
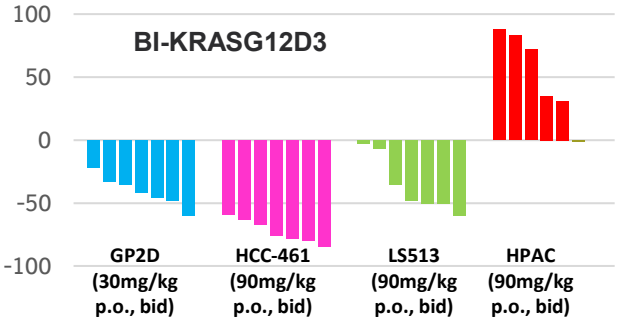
Oral administration of BI-KRASG12D3 to xenograft tumor-bearing mice exhibits biomarker modulation and antitumor activity in *KRAS^{G12D}mut* models

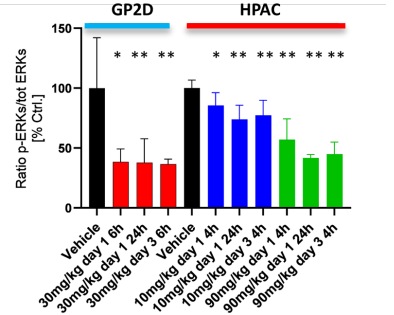


M Hofmann, RAS-Targeted Drug Development Conference, 2021; S Jurado, M. Garofalo, J. Ramharter et al unpublished

*high dose of trametinib used as positive control (0.5mg/kg bid, 5x of clin. relative dose)

Cell line, 2D proliferation	BI-KRASG12D3	MRTX1133
GP2D KRAS^{G12D} EC_{50} (nM)	10	1
ASPC-1 KRAS^{G12D} EC_{50} (nM)	53	38
ASPC-1 H95L KRAS^{G12D} EC_{50} (nM)	923	>1,000
LS513 KRAS^{G12D} EC_{50} (nM)	32	19
LS513 H95L KRAS^{G12D} EC_{50} (nM)	>1,000	>1,000
MKN-1 KRAS$^{WT\ AMP}$ EC_{50} (nM)	467	700





BI-KRASG12D3 is an orally available, mutant-selective non-covalent inhibitor of KRAS^{G12D}

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Revolution Medicines: Mutant selectivity beyond KRAS^{G12C}

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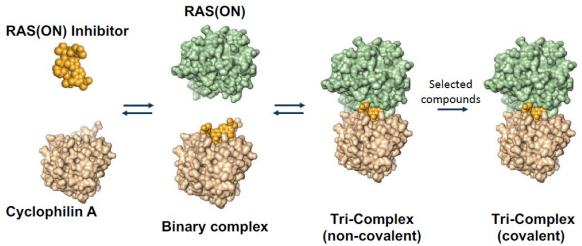
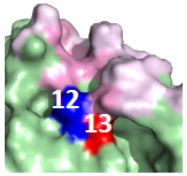
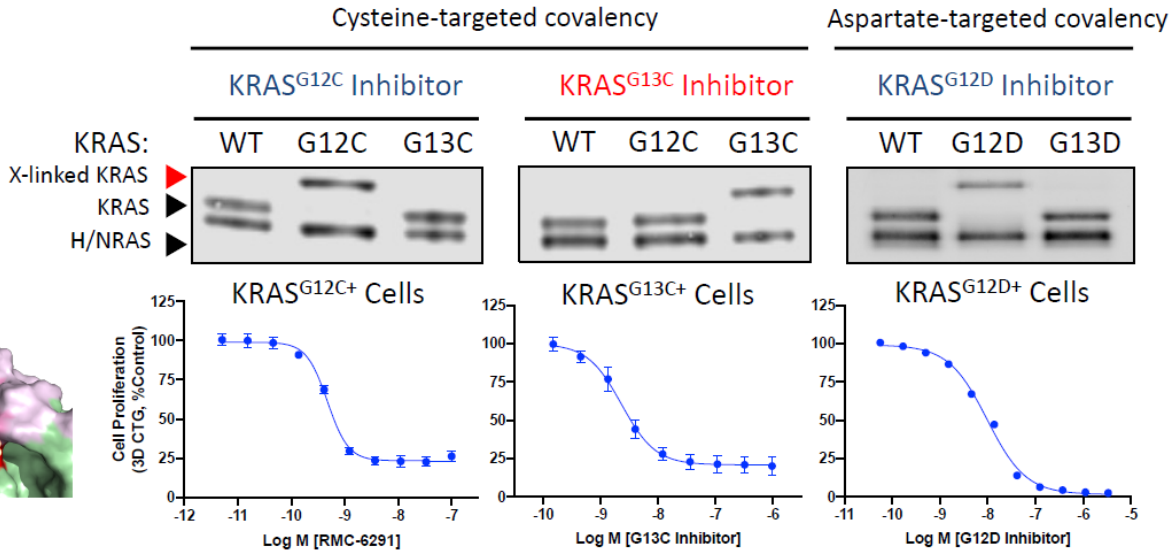
Formation of inhibitory tri-complexes





Mutant selective inhibition of KRAS^{G13C} and KRAS^{G12D}



S Kelsey, AACR-NCI-EORTC Meeting 2021; C Schulze et al., AACR Annual Meeting 2022, Abstract 3598, April 12, 2022

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RMC-9805: *In vivo* efficacy in models of KRAS^{G12D} cancers

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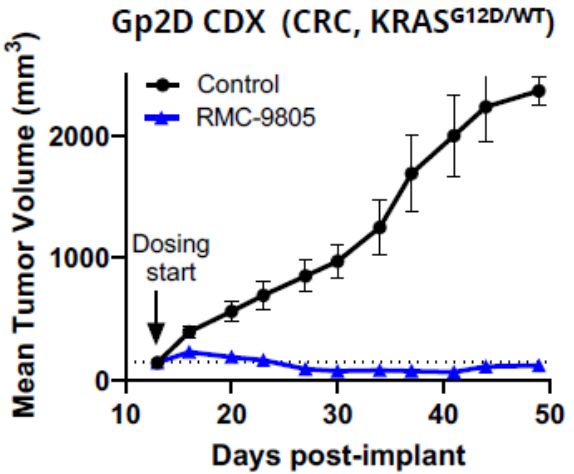
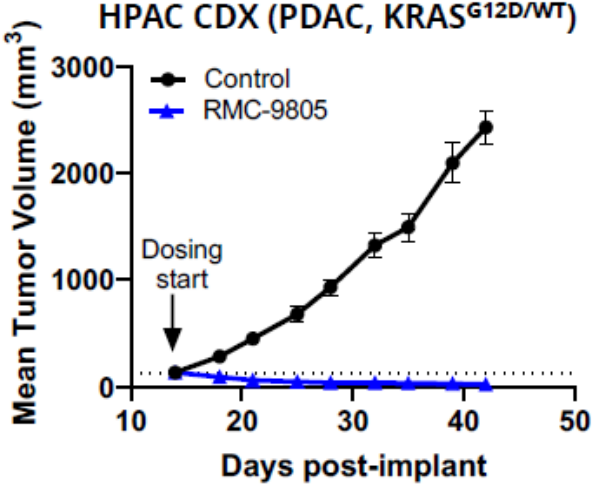


RVMD preclinical research, as of 11/05/2021
RMC-9805 dosed at 100 mg/kg pd qd; n = 10/group (top), 6/group (bottom); PDAC = pancreatic ductal adenocarcinoma; CRC = colorectal cancer



dosed at 100 mg/kg p.o. qd

RMC-9805 is an orally available, mutant-selective covalent inhibitor of KRAS^{G12D}

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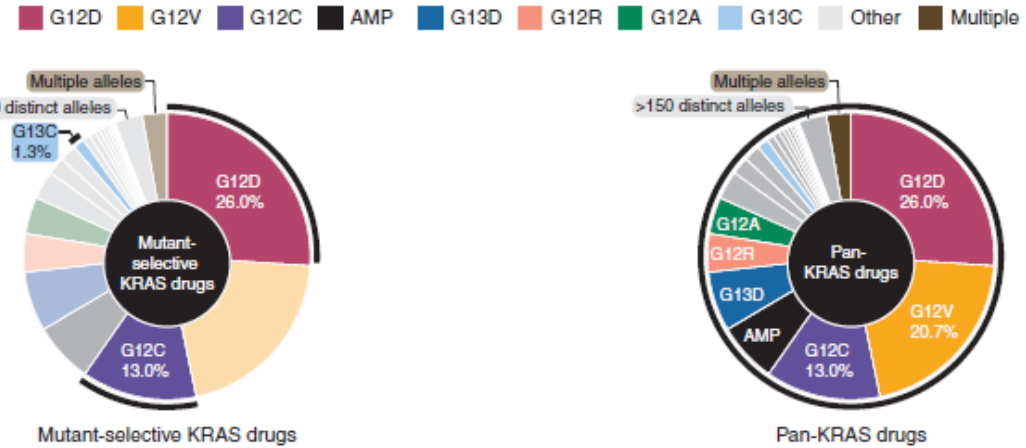
S Kelsey, Corporate Presentation 2022; JE Knox et al., AACR Annual Meeting 2022, Abstract 3596, April 12, 2022

Selectively versus broadly addressing KRAS mutants



Mutant-selective KRAS drugs

- Tolerability, low KRAS WT-mediated toxicity expected
- Combination partner with putative large therapeutic window
- Sustained target inhibition
- Early treatment lines

- Restricted patient population
- Prone to acquired on-target resistance
- NCE feasibility beyond G12D/C and G13C to be determined

Pan-KRAS drugs

- Broad patient population
- Cancers driven by KRAS WT (e.g., KRAS amplified)
- Feasibility for undrugged mutants
- Heterogenous cancers driven by multiple KRAS aberrations
- Overcome on-target KRAS resistance to allele-specific inhibitors

- KRAS WT-mediated toxicity unknown

M Hofmann, D Gerlach, S Misale, M Petronczki and N Kraut, *Cancer Discov.* 2022

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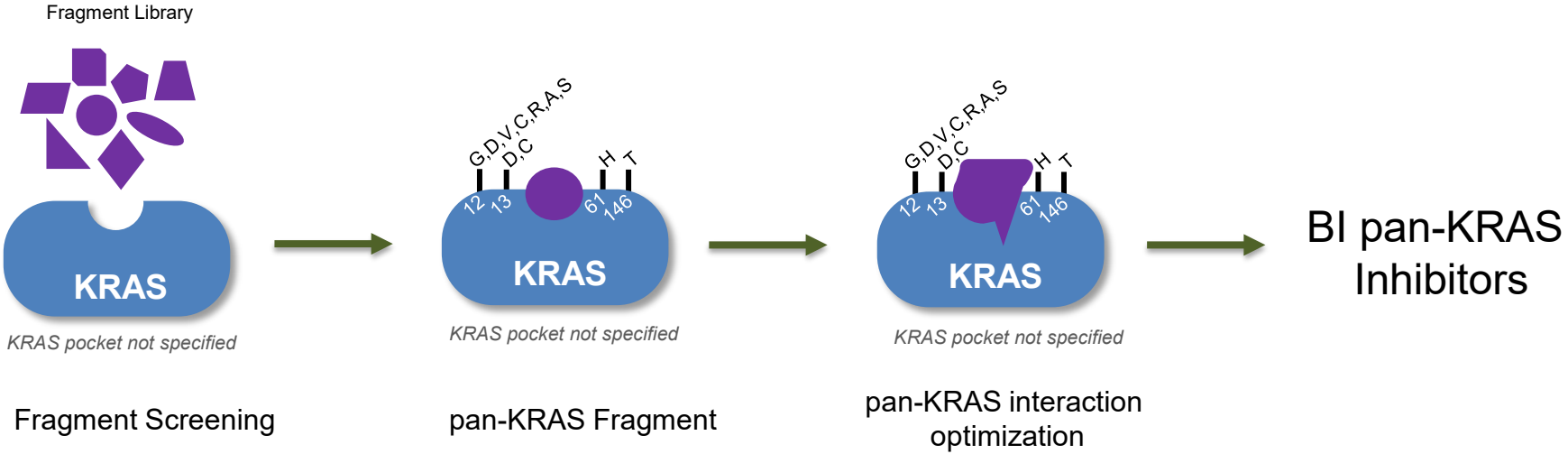
Boehringer Ingelheim approach to pan-KRAS inhibitors



Fragment Screening

pan-KRAS Fragment

pan-KRAS interaction optimization

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D McConnell, The Third NCI RAS Initiative Symposium 2021

Characterization of BI-panKRAS inhibitors

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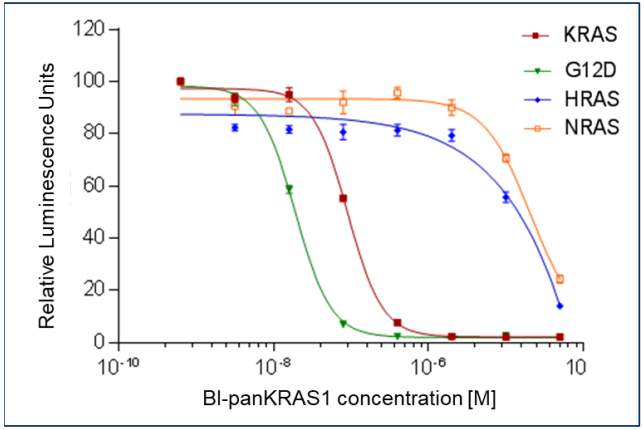
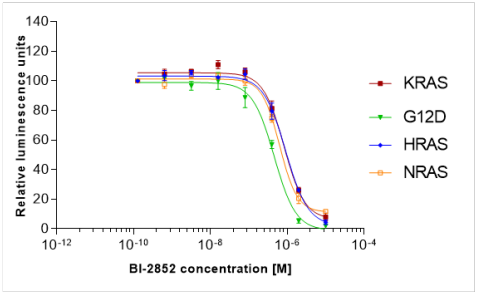
BI-panKRAS1 is isotype selective for KRAS

Pan-KRAS PPI Inhibition
(BI-panKRAS1, GDP-RAS::SOS1 AlphaScreen)

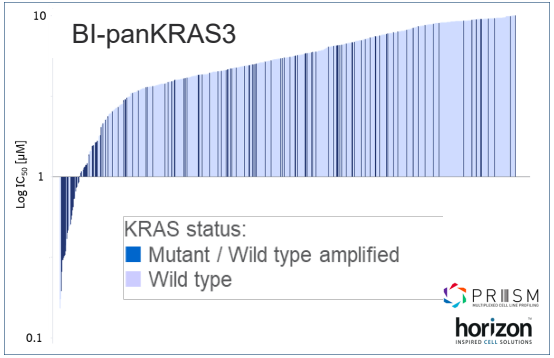


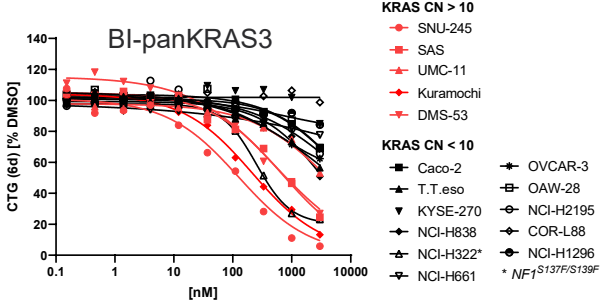
Pan-RAS PPI Inhibition
(BI-2852, GDP-RAS::SOS1 AlphaScreen)



PPI Inhibition (Alphascreen)	BI-panKRAS1	BI-2852
IC_{50} GDP-$KRAS^{G12D}$::SOS1	19 nM	820 nM
IC_{50} GDP-$KRAS^{wt}$::SOS1	91 nM	460 nM
IC_{50} GDP-$HRAS^{wt}$::SOS1	~20000 nM	920 nM
IC_{50} GDP-$NRAS^{wt}$::SOS1	~20000 nM	640 nM

BI-panKRAS3 activity on cell panel





BI-panKRAS3 is an orally available, non-covalent selective inhibitor of mutant and wild-type KRAS

These compounds are investigational agents and have not been approved for use. The efficacy and safety of these investigational compounds have not been established.

N Kraut, AACR Annual Meeting, 2021; D. Rudolph, L. Herdeis et al., unpublished

BI-panKRAS3: *In vivo* efficacy in models of KRAS$^{MUT/AMP}$ cancers

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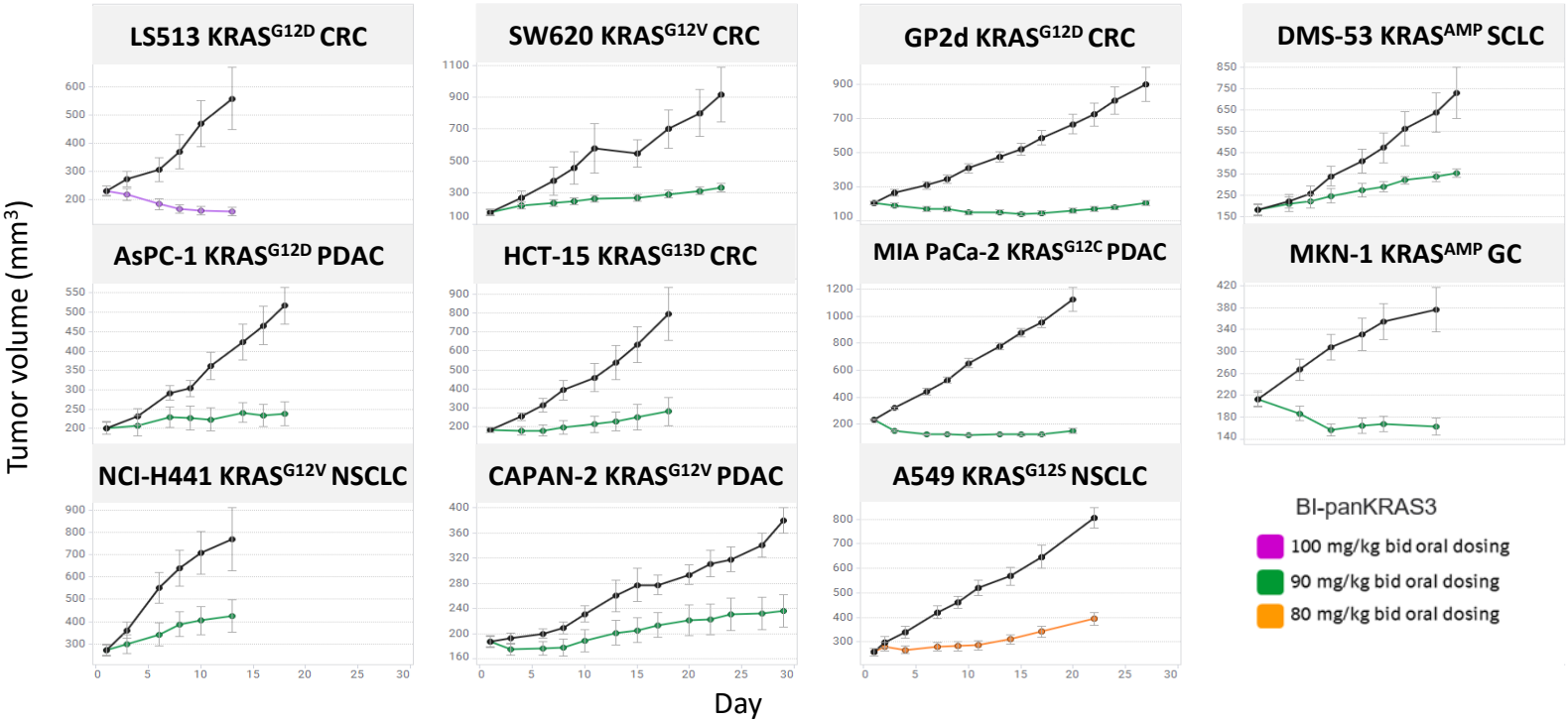

D. Rudolph, L. Herdeis et al., unpublished

These compounds are investigational agents and have not been approved for use. The efficacy and safety of these investigational compounds have not been established.

CRC=colorectal cancer; PDAC_ pancreatic cancer; NSCLC=non-small cell lung cancer; SCLC= small cell lung cancer; GC= gastric cancer

Revolution Medicines: Characterization of RAS^{MULTI} inhibitor RMC-6236

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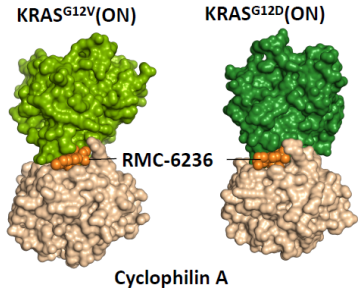
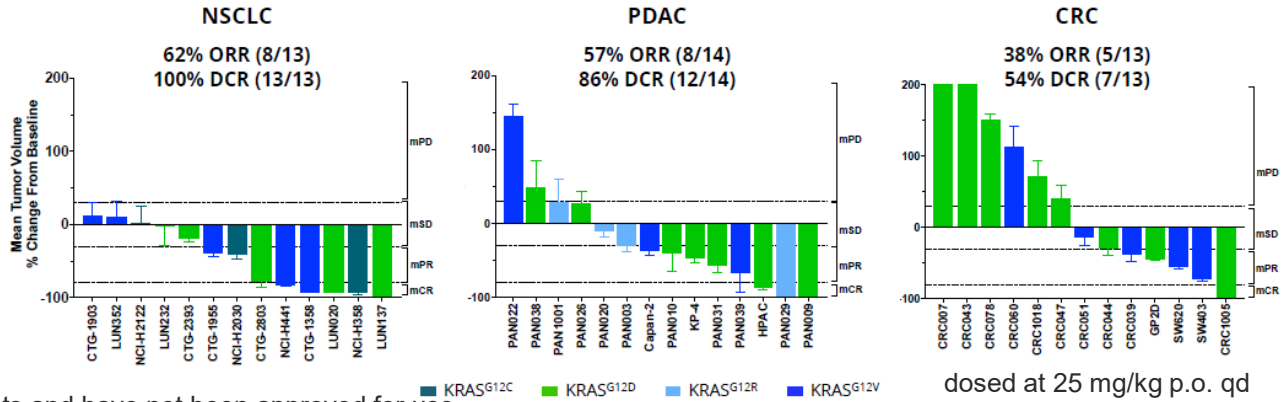


RVMD preclinical research
(1) Range reflects sensitivities across multiple RAS-variant cell lines
(2) Ratio based on cell growth assays with cell line bearing KRAS^{G12V} mutation

POTENT	Potency for Tumor Cell Inhibition
pERK (RAS-dependent, IC_{50}, nM)[1]	0.4-3
CTG (RAS-dependent, IC_{50}, nM)[1]	1-27
RAS-SELECTIVE	**Target Selectivity and Safety**
Selectivity	
• Over RAS-independent cells[2]	> 1000X
Off-target safety panel	Low Risk
ORALLY BIOAVAILABLE	**PK/ADME**
Oral %F (multiple species)	24-33
Metabolic clearance (hepatocytes, multiple species)	Low to Moderate

RMC-6236 inhibits KRAS, HRAS and NRAS

RMC-6236 is active *in vivo* in KRAS^{G12X} models

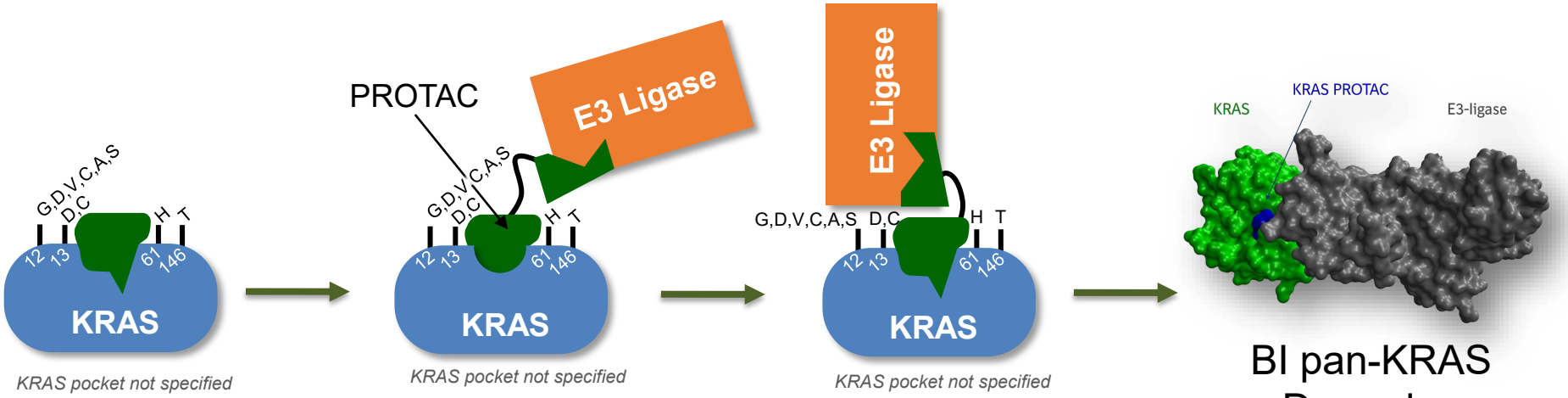


dosed at 25 mg/kg p.o. qd

These compounds are investigational agents and have not been approved for use. The efficacy and safety of these investigational compounds have not been established.

S Kelsey, AACR-NCI-EORTC Meeting 2021; Corporate Presentation 2022; M Singh et al., AACR Annual Meeting 2022, Abstract 3597, April 12, 2022

Boehringer Ingelheim approach to pan-KRAS degraders



pan-KRAS Binder

Ternary complex discovery

Ternary complex optimization

BI pan-KRAS Degraders

PROTACs = Proteolysis Targeting Chimeras

These compounds are investigational agents and have not been approved for use. The efficacy and safety of these investigational compounds have not been established.

D McConnell, The Third NCI RAS Initiative Symposium 2021

PROTACs enable irreversible KRAS inhibition by degradation

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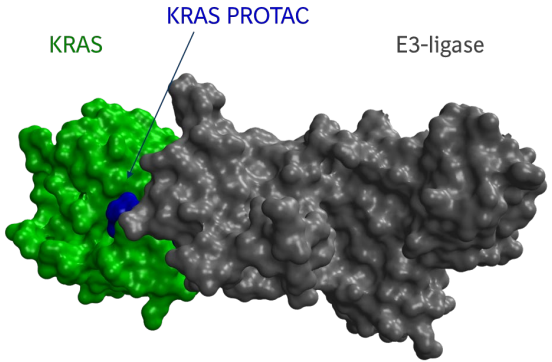
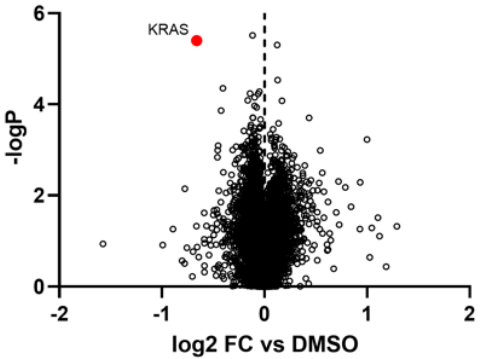
Ternary X-ray crystal structures

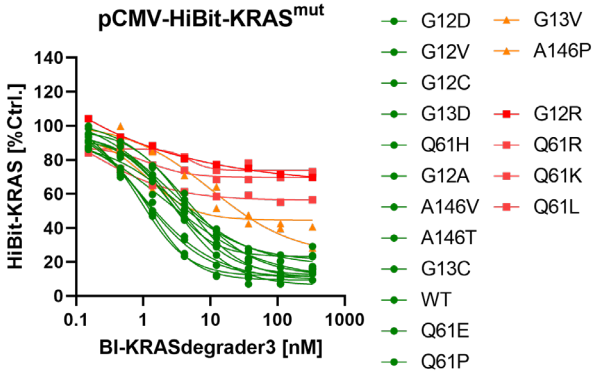


KRAS degrader selectivity

BI-KRASdegrader3, 50nM, 8h



Cellular Degradation



BI-KRASdegrader3: Preferential cellular degradation of cycling KRAS mutants

GP5d cell line transduced with HiBit-tagged KRAS

		G12D	G12V	G12C	G12R	G13D	Q61H	G12A	A146V	A146T	G13C	Q61R	WT	G13V	Q61E	Q61P	A146P	Q61K	Q61L
BI-KRASdegrader3	D_{max} [%]	87	89	93	30	79	77	88	90	84	87	45	93	72	90	90	59	32	29
	DC_{50} [nM]	1	4	1	>3k	2	3	3	1	2	4	>3k	3	10	1	1	0.2	>3k	>3k

These compounds are investigational agents and have not been approved for use. The efficacy and safety of these investigational compounds have not been established.

J. Popow, C. Kofink, A. Mantoulidis, A. Ciulli, W. Farnaby, et al. unpublished

Characterization of BI-KRASdegrader3: *In vivo* degradation and efficacy

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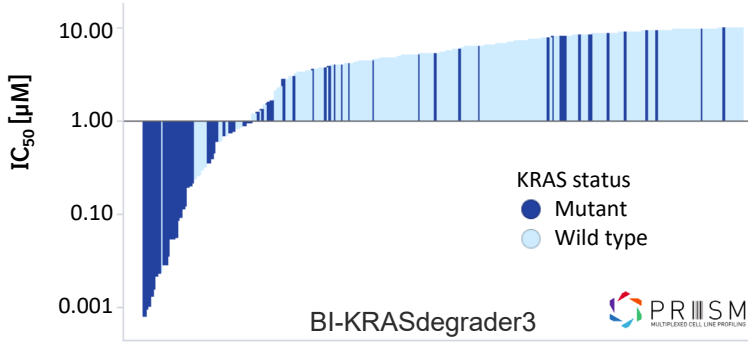
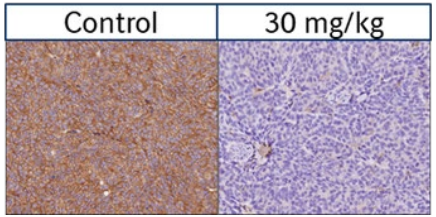
Selective activity in *KRASmut* cell lines



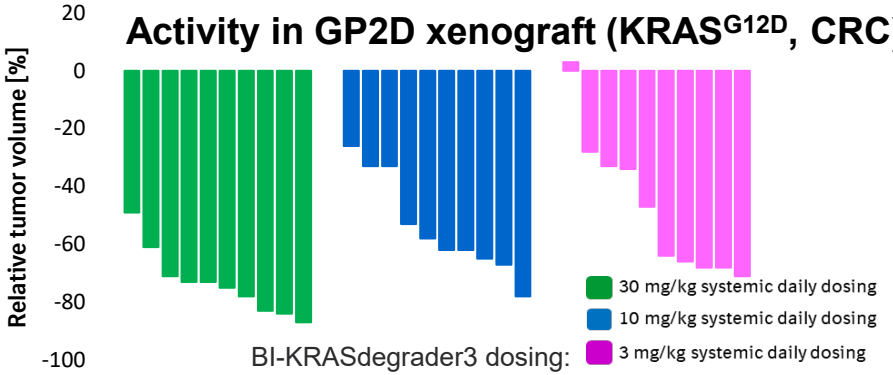
In vivo KRAS degradation



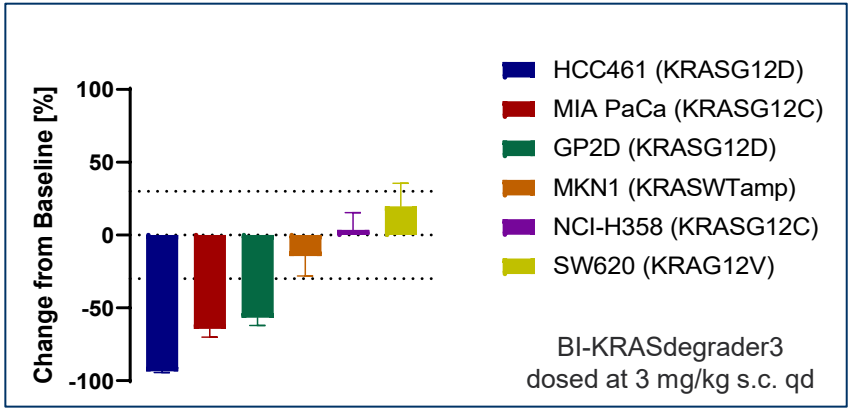
BI-KRASdegrader3:
KRAS protein levels in GP2D model after 24 hours treatment

J. Popow, C. Kofink et al. unpublished

Activity in GP2D xenograft ($KRAS^{G12D}$, CRC)



Activity across KRAS-driven xenograft models



These compounds are investigational agents and have not been approved for use. The efficacy and safety of these investigational compounds have not been established.

The beginning of the end for KRAS cancers

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Summary and conclusions:

- **Targeting KRAS has the potential to almost double the patient population eligible for precision oncology**
- **Progress in drugging other KRAS mutants with allele-specific inhibitors, eg $KRAS^{G12D}$ and $KRAS^{G13C}$– *Feasibility for other KRAS mutants to be determined***
- **Strong rationale for pan-KRAS concepts, including direct pan-(K)RAS inhibitors and pan-KRAS degraders – *Broad mutant coverage appears feasible***
- **First compounds directly targeting KRAS beyond $KRAS^{G12C}$ are expected to reach the clinic soon**
- **We are at the beginning of the end for KRAS cancers: Drugging of all the major KRAS mutant variants and advancing rational combinations for all KRAS-driven cancers is gaining traction**

These compounds are investigational agents and have not been approved for use. The efficacy and safety of these investigational compounds have not been established.

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