AACR-NCI-EORTC Virtual International Conference on
MOLECULAR TARGETS AND CANCER THERAPEUTICS
October 7-10, 2021

Discovery and Development of RAS(ON) Inhibitors Beyond KRAS^{G12C}

Steve Kelsey MD FRCP FRCPath
Revolution Medicines
Redwood City CA

Steve Kelsey

I have the following financial relationships to disclose:

Stockholder in: Revolution Medicines

Employee of: Revolution Medicines

I will not discuss off label use in my presentation.

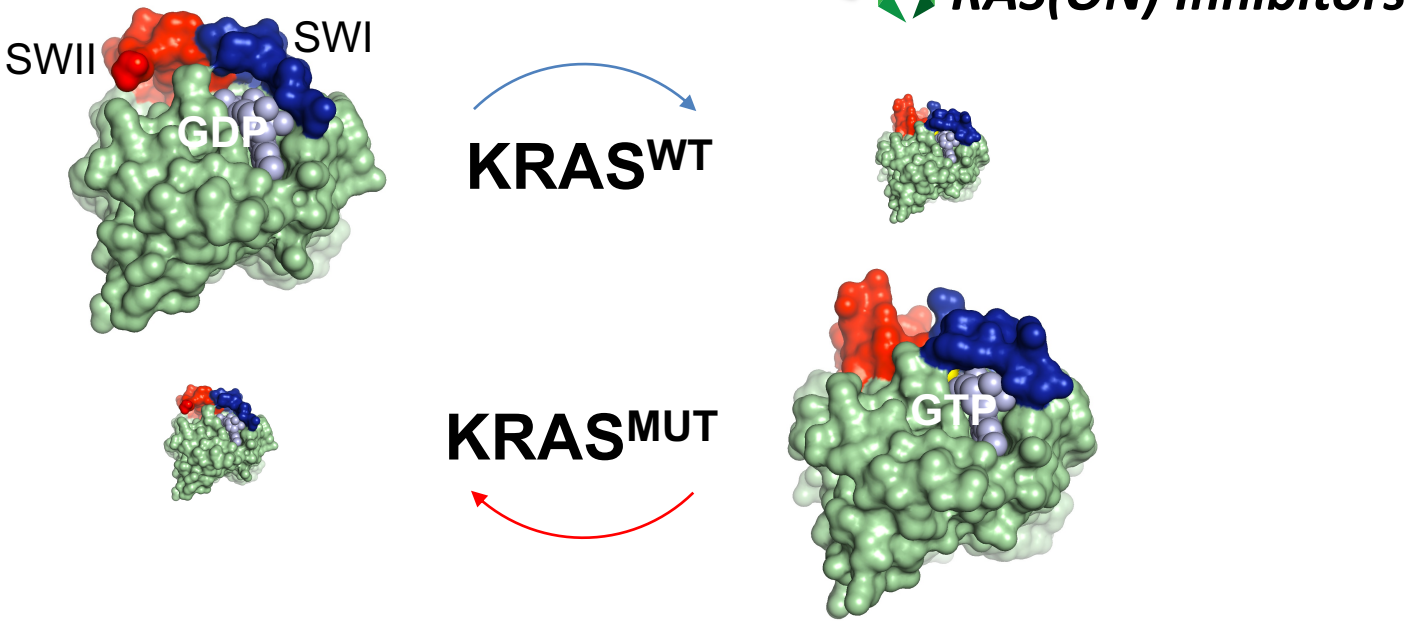
I will discuss the potential for investigational use of RAS(ON) inhibitors and Companion inhibitors in my presentation

$KRAS^{MUT}$ Cancer Cells are Addicted to, and Tenaciously Maintain, High Levels of RAS(ON)

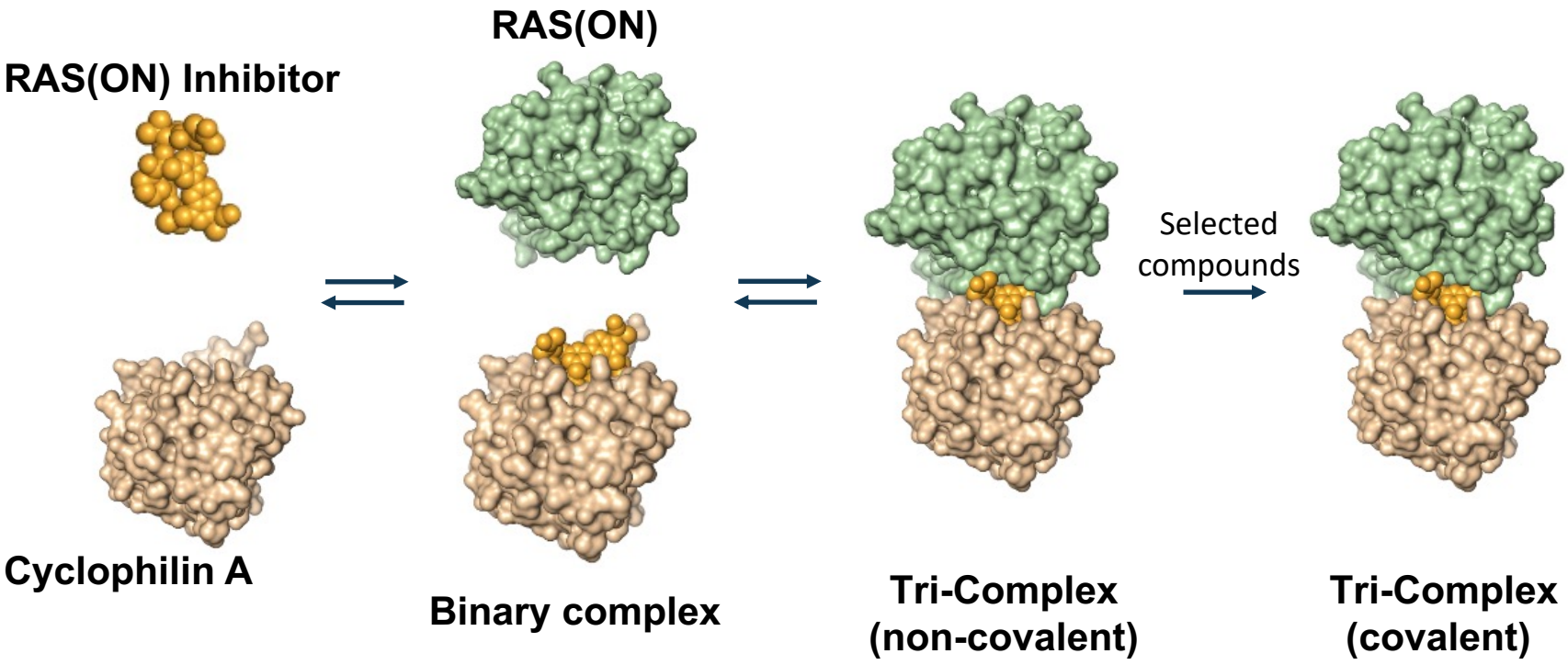
KRAS(OFF) - inactive

KRAS(ON) - active

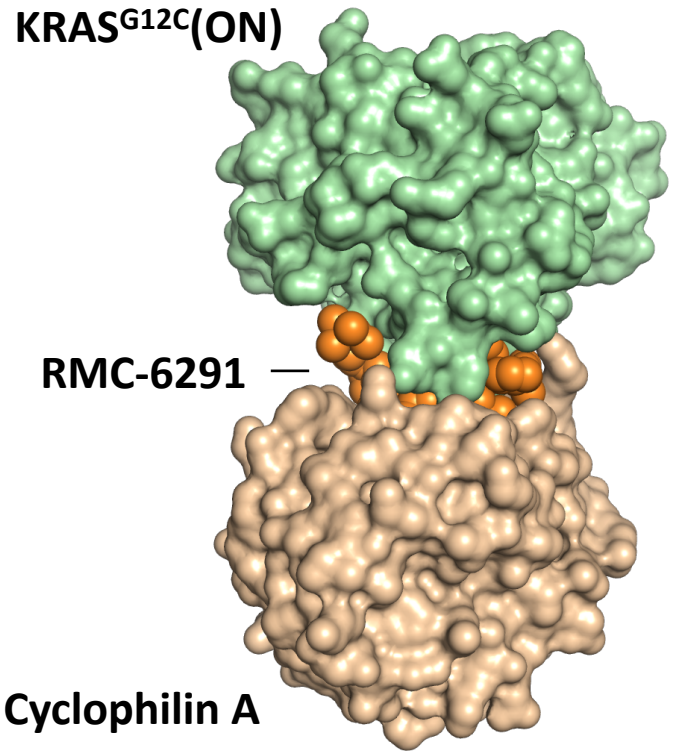
RAS(ON) Inhibitors



RAS(ON) Inhibitors Block Signaling Directly through Formation of Inhibitory Tri-Complexes



RMC-6291: First-in-Class, Potent, Oral and Selective Tri-Complex Inhibitor of $KRAS^{G12C}$(ON)

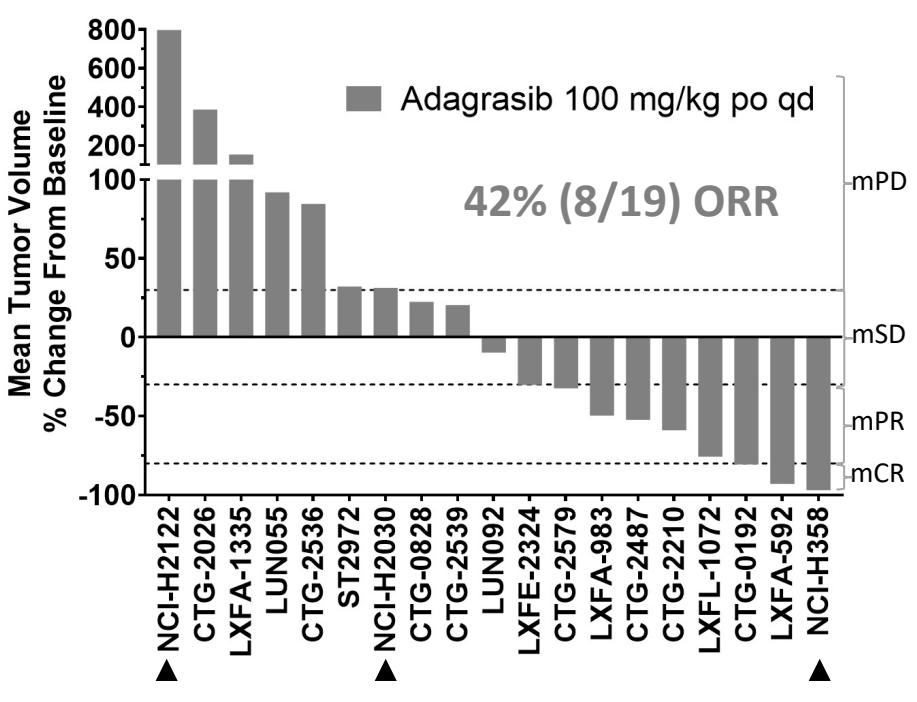


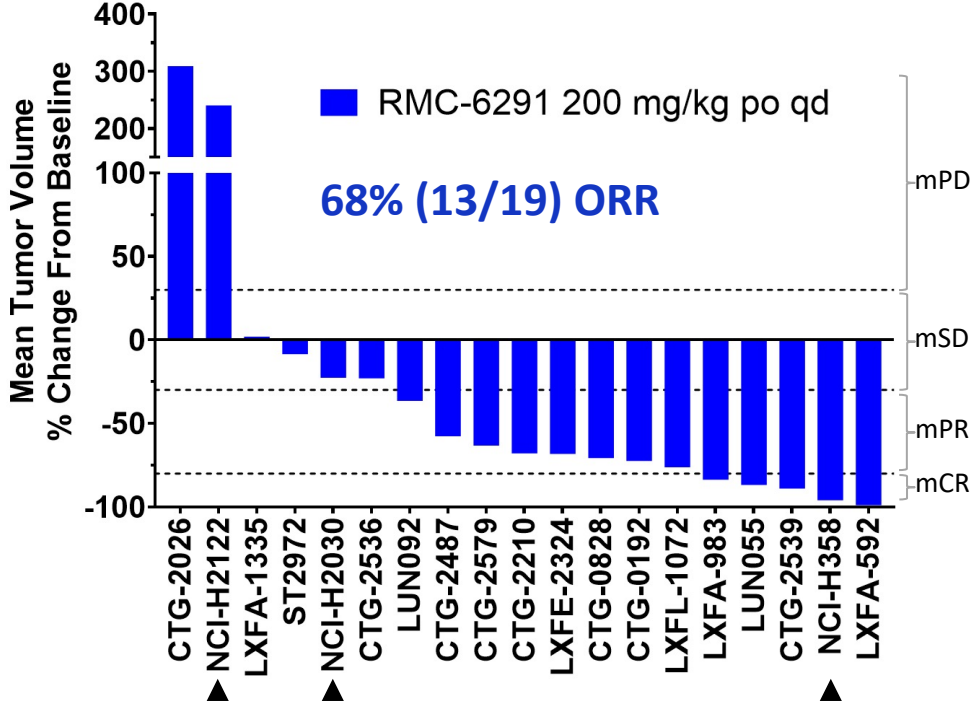
Potency for Tumor Cell Inhibition	
pERK (NCI-H358, IC_{50}, nM)(1)	0.7
CTG (NCI-H358, IC_{50}, nM)	0.09
Target Selectivity and Safety	
Covalent bond: k_{inact}/K_i ($M^{-1}s^{-1}$)	289,000
Selectivity	
• Over RAS-independent cell	> 1000X
• Over RAS^{WT}-dependent cell	> 1000X
Off-target safety panel and cysteinome screen	Low Risk
PK/ADME	
Oral %F (multiple species)	33-60
Metabolic clearance (hepatocytes, multiple species)	Low to Moderate

RVMD preclinical research; (1) $KRAS^{G12C}$-driven cell line; $NRAS^{G12C}$-driven line also subnanomolar

Superior Outcomes with RMC-6291, KRAS^{G12C}(ON) Inhibitor, in KRAS^{G12C} NSCLC PDX Models

Tumor Responses in 19 NSCLC KRAS^{G12C} Xenografts





▲Denotes CDX model; all others are PDX. Responses assigned according to mRECIST (modified from Gao et al Nat Med. 2015).

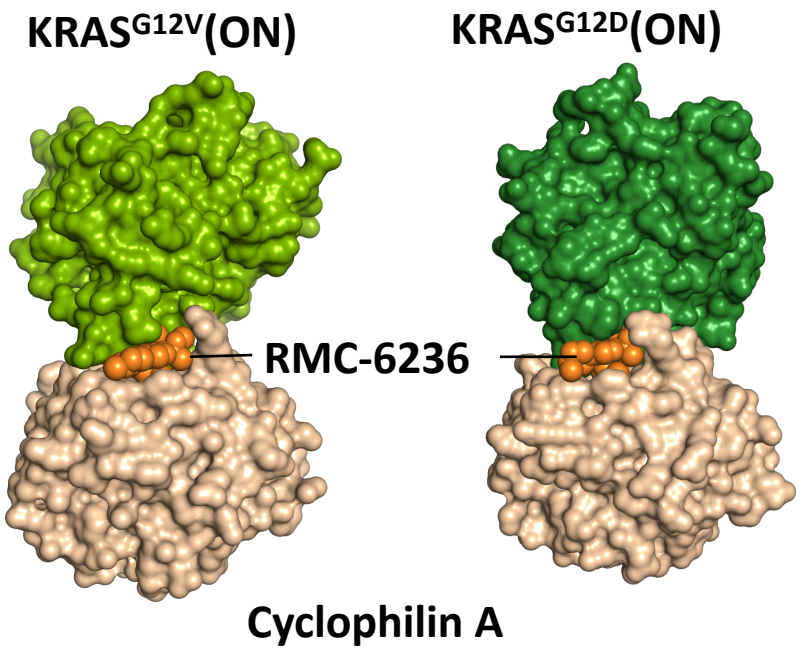
Beyond KRAS^{G12C}: Mutant Selectivity versus RAS^{MULTI} Inhibitors

RAS^{MULTI} and RAS^{MUTANT}-Selective Inhibitors Display Complementary Profiles[1] and Trade-offs

RAS^{MUTANT}-Selective Inhibitor	RAS^{MULTI} Inhibitor
Selectivity for mutation in tumor permits high inhibitor doses, providing deep and sustained target coverage with good tolerability	Serves multiple patient sub-populations
Expected to combine well with RAS Companion Inhibitors	Suppresses diverse RAS variants (including wild-type) that can cause resistance
	Possibly may be useful as a RAS Companion Inhibitor
Different compounds needed for different RAS genotypes	On-target normal tissue effects will be dose-limiting and may constrain depth and/or duration of target coverage
Likely requires a RAS Companion Inhibitor	

(1) RVMD preclinical research

RMC-6236: First-in-Class Tri-Complex RAS^{MULTI}(ON) Inhibitor

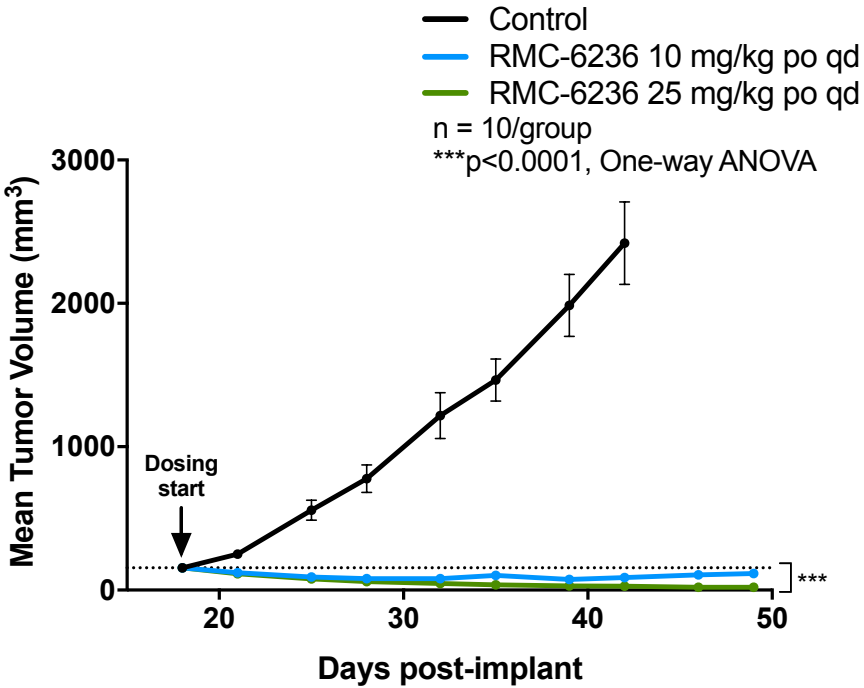


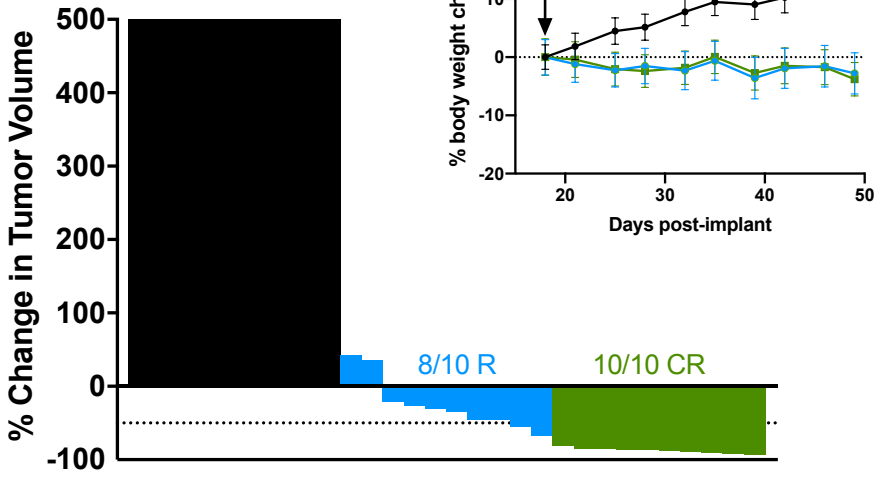
POTENT	**Potency for Tumor Cell Inhibition**
pERK (RAS-dependent, IC_{50}, nM)(1)	0.4-3
CTG (RAS-dependent, IC_{50}, nM)(1)	1-27
RAS-SELECTIVE	**Target Selectivity and Safety**
Selectivity • Over RAS-independent cells(2)	> 1000X
Off-target safety panel	Low Risk
ORALLY BIOAVAILABLE	**PK/ADME**
Oral %F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

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

RMC-6236 Induces Regressions of KRAS^{G12V} NSCLC Tumors

NCI-H441 (NSCLC, KRAS$^{G12V/WT}$; MET^{Amp})

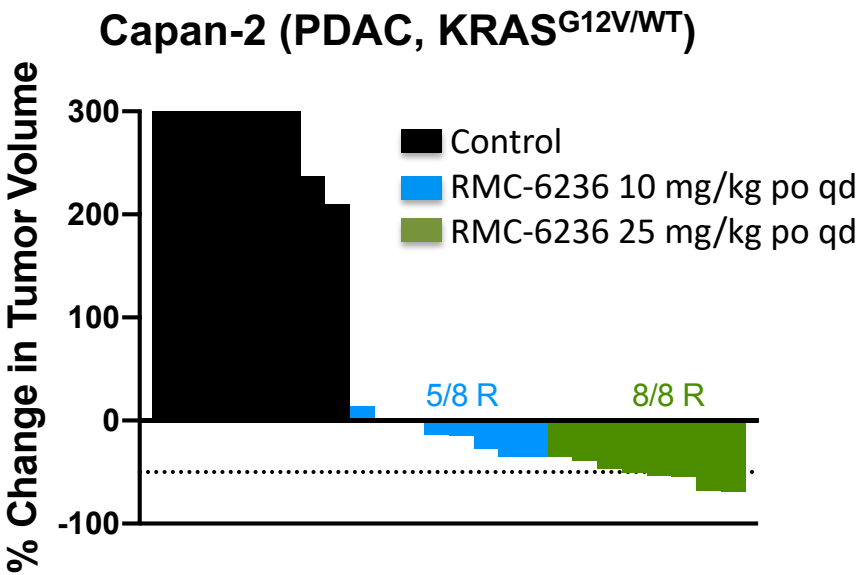


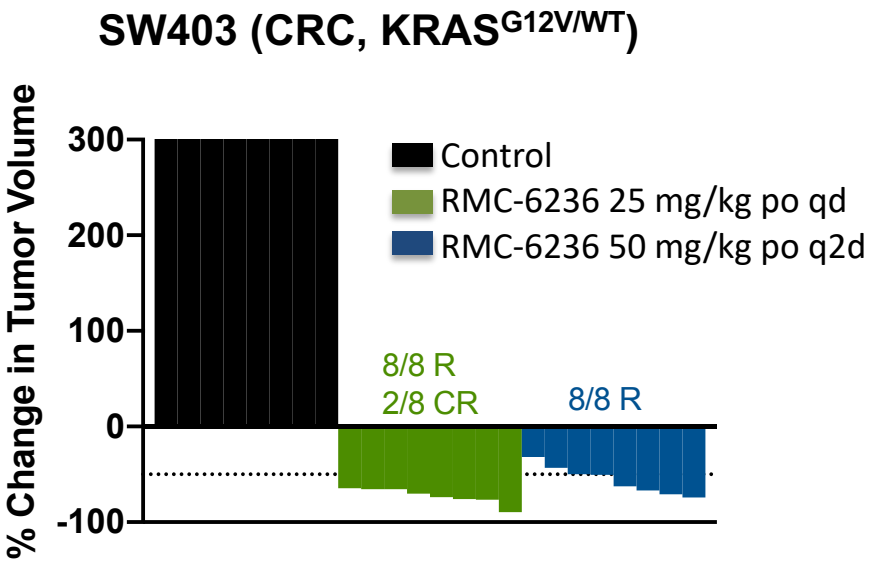


CR = number of regressions ≥80% from initial
R = tumor volume reduction ≥10% from initial
Each animal represented as a separate bar

RVMD preclinical data

RMC-6236 Induces Regressions of KRAS^{G12V} Pancreatic and Colorectal Tumors

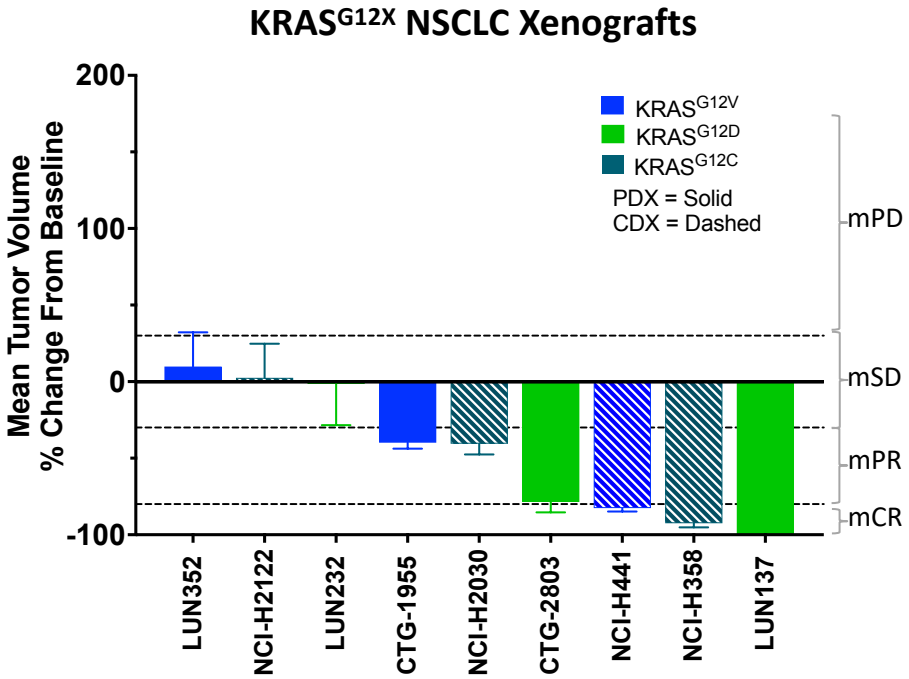


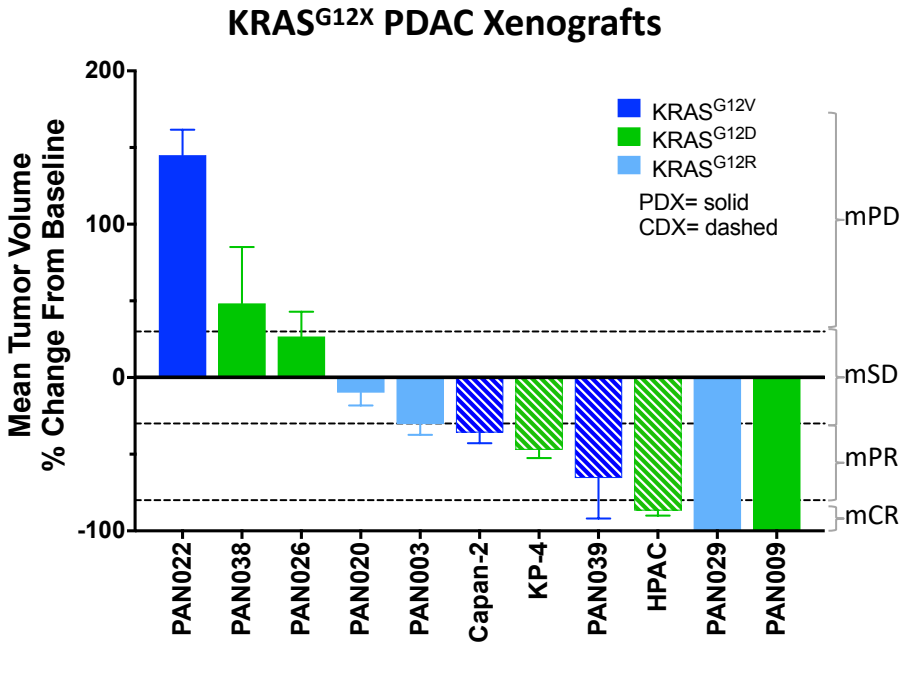


CR = number of regressions ≥80% from initial
R = tumor volume reduction ≥10% from initial
Each animal represented as a separate bar

RVMD preclinical data

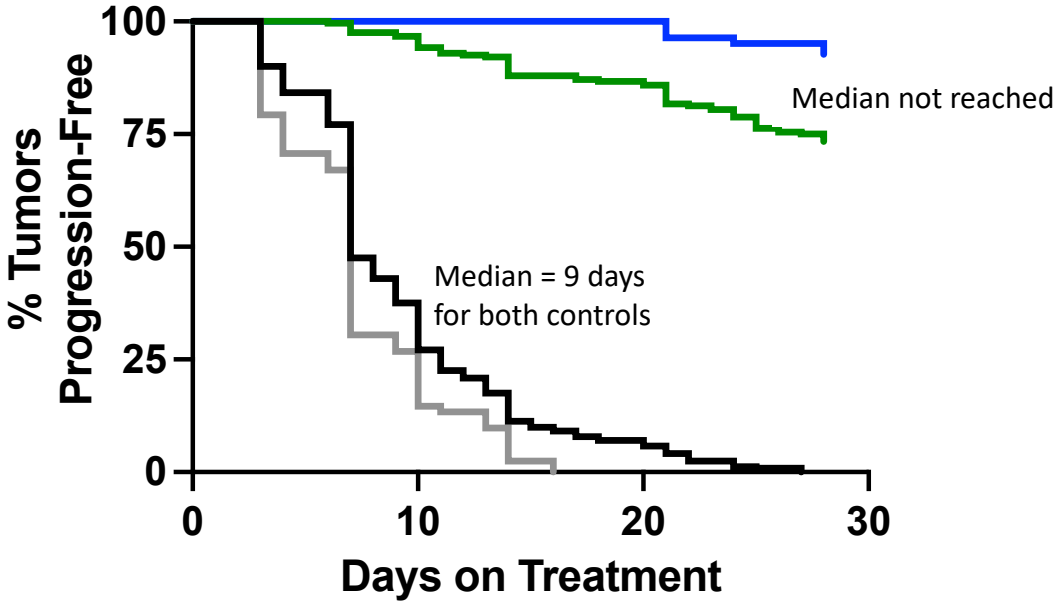
RMC-6236 Exhibits Significant Anti-Tumor Activity in KRAS^{G12X} Tumor Models *in Vivo*





RVMD preclinical data

RMC-6236 Significantly Extends Time to Tumor Doubling Across Xenograft Models



KRAS^{G12X} RMC-6236 25 mg/kg po qd

All RAS Pathway^{MUT} RMC-6236 25 mg/kg po qd

KRAS^{G12X} control

All RAS Pathway^{MUT} control

Progression defined as tumor doubling from baseline over 28 days

p<0.0001 by Log-rank test (control vs treated)

KRAS^{G12X} n = 154
Other RAS and RAS Pathway mutations n = 86
All RAS Pathway^{MUT} includes both groups n = 240

RVMD preclinical data
as of July 25, 2021

RMC-6236 Active Against KRAS^{G12C}(OFF) Inhibitor "RAS Oncogene Switch" Resistance Mutations

KRAS^{G12}	G12A	G12C	G12D	G12E	G12F	G12H	G12I	G12K	G12L	G12M	G12N	G12P	G12Q	G12R	G12S	G12T	G12V	G12W	G12Y
Clinical resistance		■			■									■			■	■	
RMC-6236	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

KRAS^{G13}	G13	G13D
Clinical resistance		■
RMC-6236	+	+

NRAS^{Q61}	Q61	Q61K
Clinical resistance		■
RMC-6236	+	+

\+ Active against mutation

■ Resistance mutation reported in clinic

RVMD preclinical research

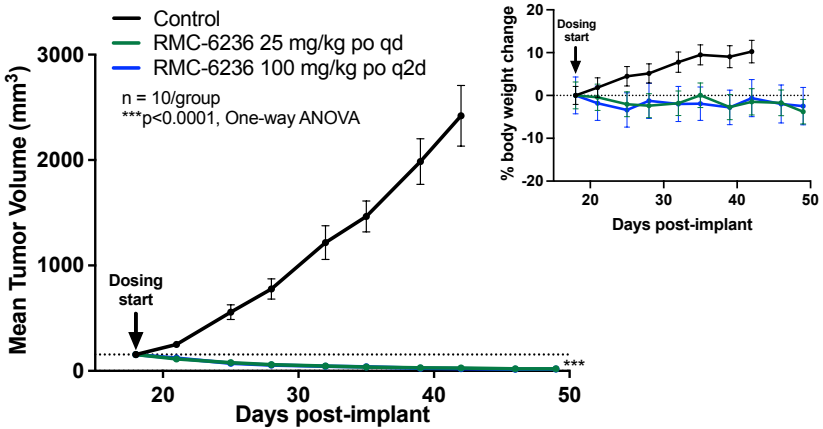
KRAS^{G12} mutations assessed bv cellular RAS/RAF disruption assay; KRAS^{G13}, NRAS^{Q61} and BRAF^{V600} mutations assessed by cell proliferation assay

Nichols. RMC-6291: Biological Features of Targeting KRAS^{G12C}(ON) and Potential Application to Overcoming Drug Resistance in RAS-Addicted Tumors. The Third RAS Initiative Symposium. May 24 – 26, 2021.

Optimizing Therapeutic Index with RAS^{MULTI} Inhibitors

1. Tumor Addiction
2. Dose Scheduling
3. Cyclophilin A Expression
4. Immunologic Effects
5. Drug Combinations

NCI-H441 CDX (KRAS^{G12V}/WT; MET^{Amp}, NSCLC)



RVMD preclinical data

Cyclophilin A Expression Across 16 Different Tumors

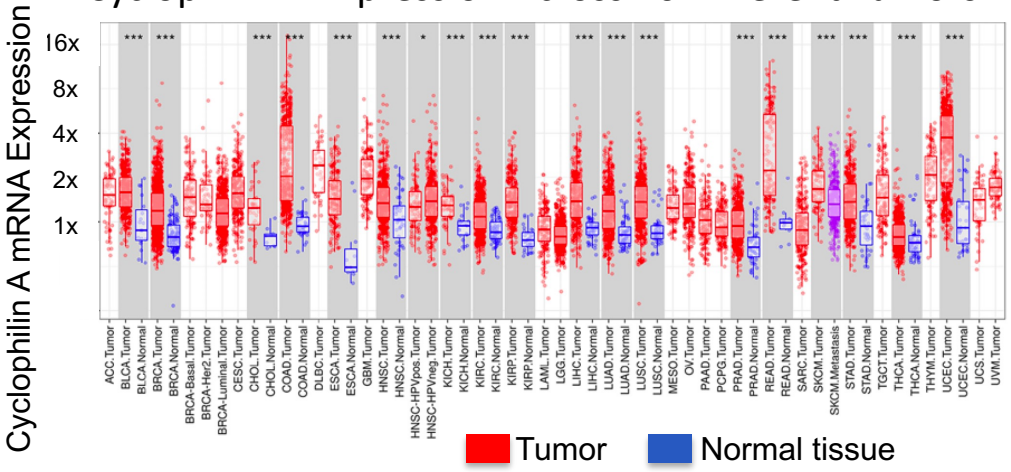
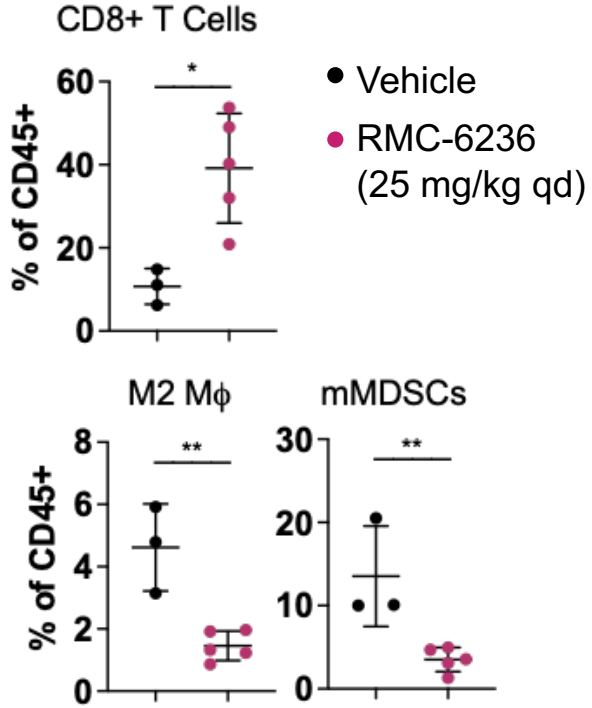


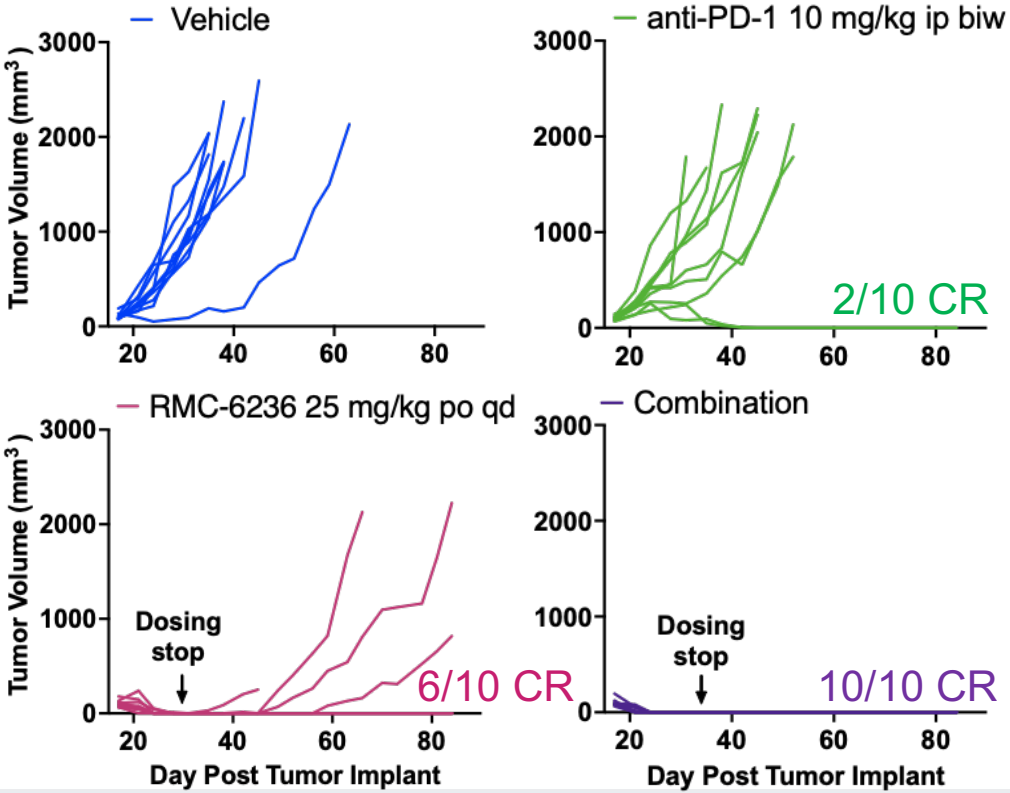
Figure from Wang et al, Onc Lett 2019

RMC-6236 Induces Anti-Tumor Immunity *in Vivo* and is Additive to Checkpoint Inhibition

Favorable Transformation of TME



Durable CRs in Combination with anti-PD-1



RVMD preclinical research
CT26 cell line engineered to express $KRAS^{G12C}$

Mutant Selectivity Beyond KRAS^{G12C}

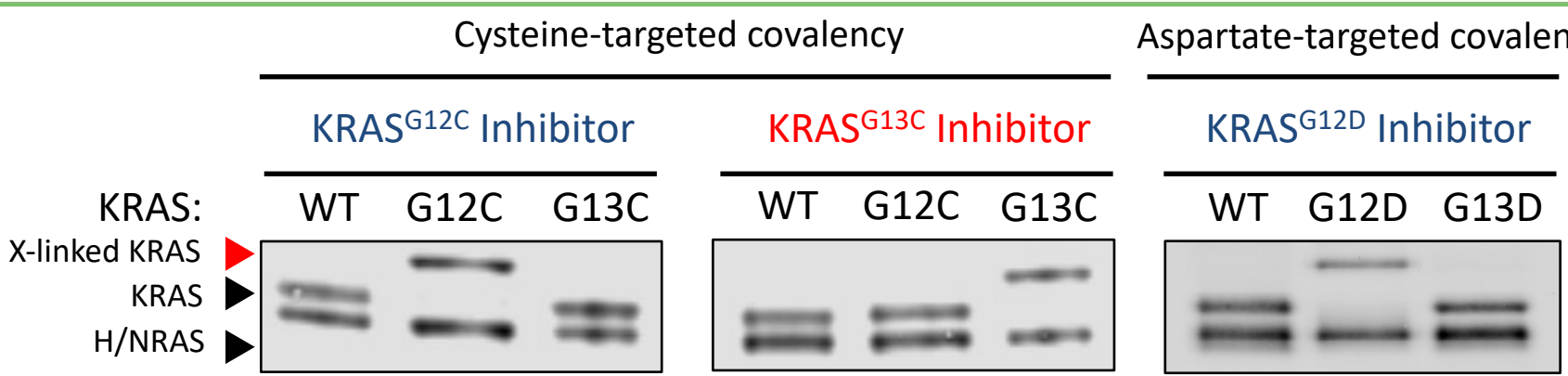
Cysteine-targeted covalency

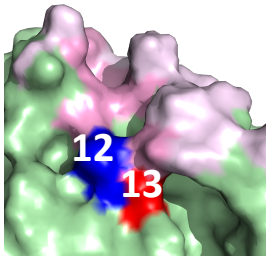
Aspartate-targeted covalency

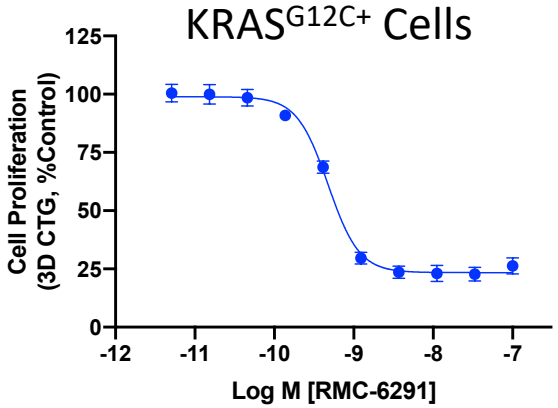
KRAS^{G12C} Inhibitor

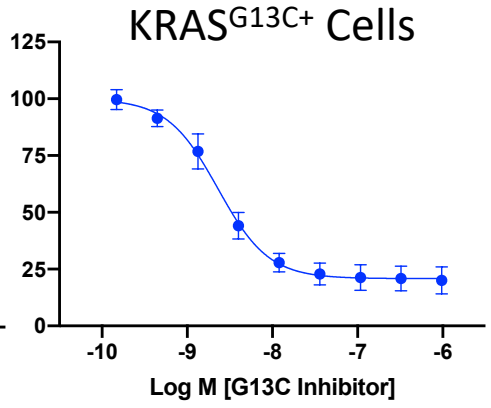
KRAS^{G13C} Inhibitor

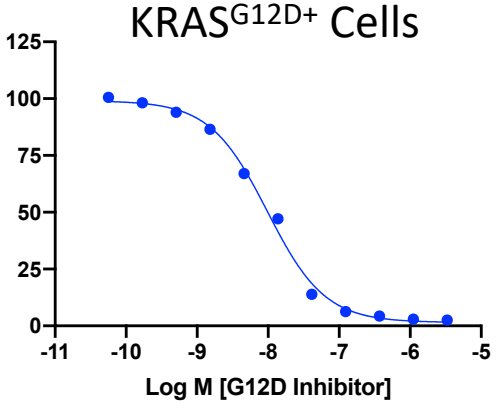
KRAS^{G12D} Inhibitor









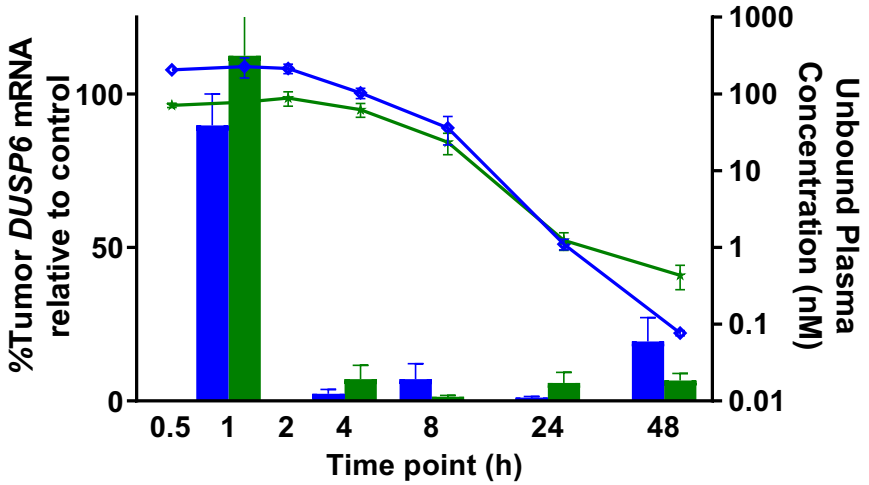


PD Effects with Potent, Orally Bioavailable, Selective, Covalent Inhibitors of KRAS^{G12D}(ON)

Single Dose PK/PD
HPAC CDX (PDAC, KRAS$^{G12D/WT}$)

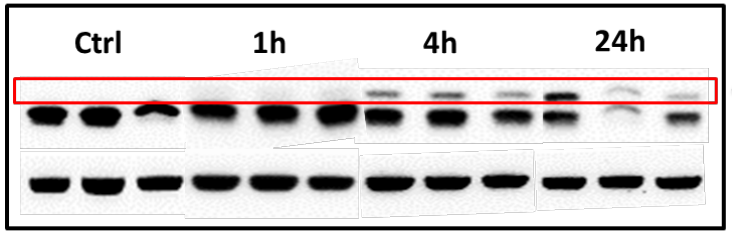
RM-036 100 mg/kg po
RM-037 100 mg/kg po

Tumor PD: Bars
Plasma PK: Lines

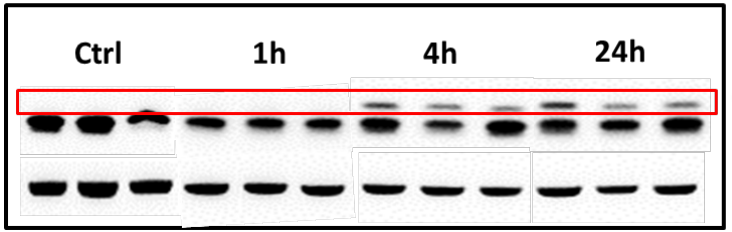


KRAS Target Engagement

RM-036

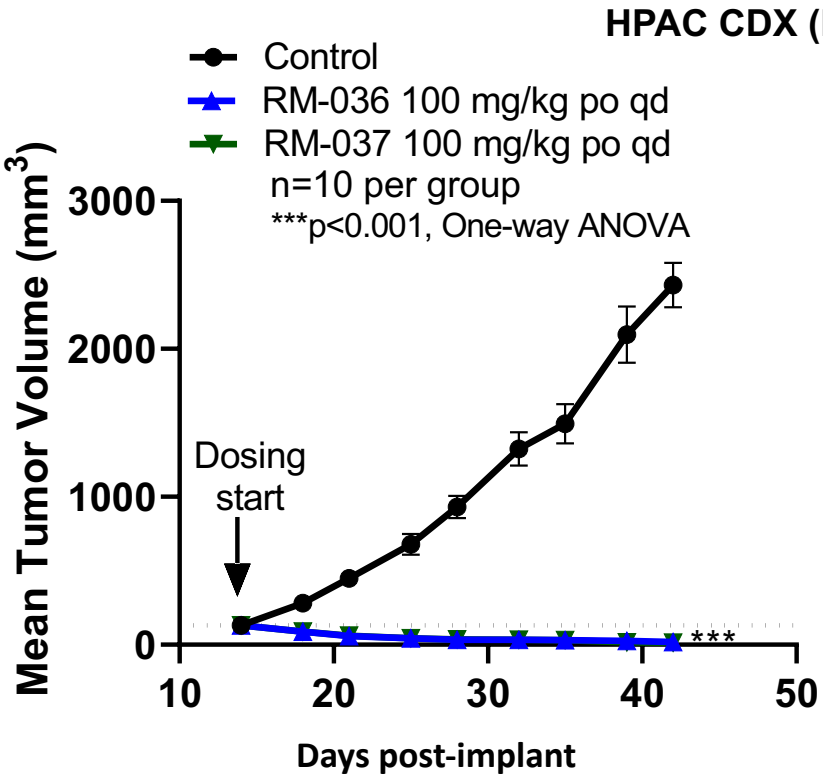


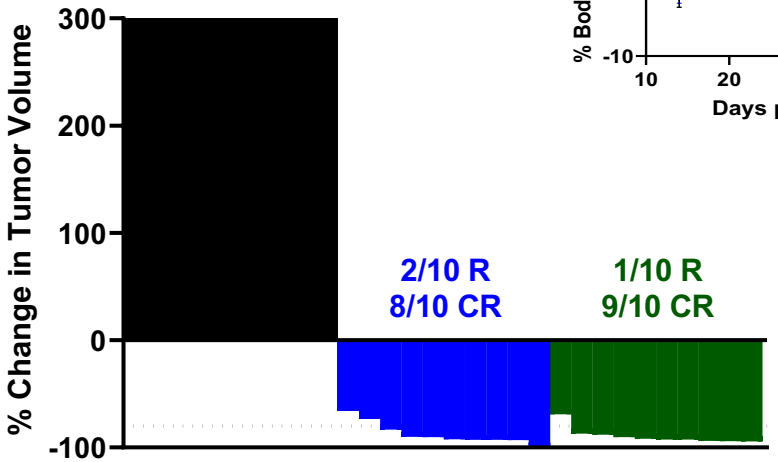
RM-037

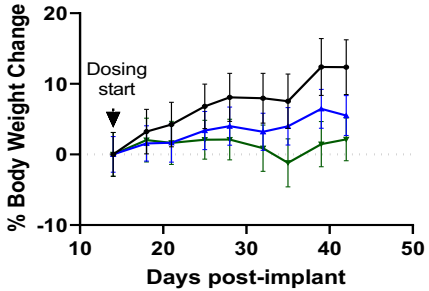


RVMD preclinical data

Tumor Regressions with Orally Bioavailable, Covalent Inhibitors of KRAS^{G12D}(ON)





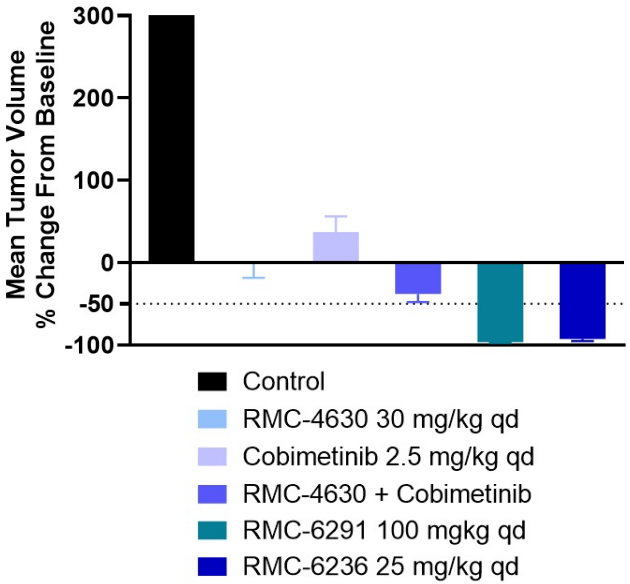


RVMD preclinical data

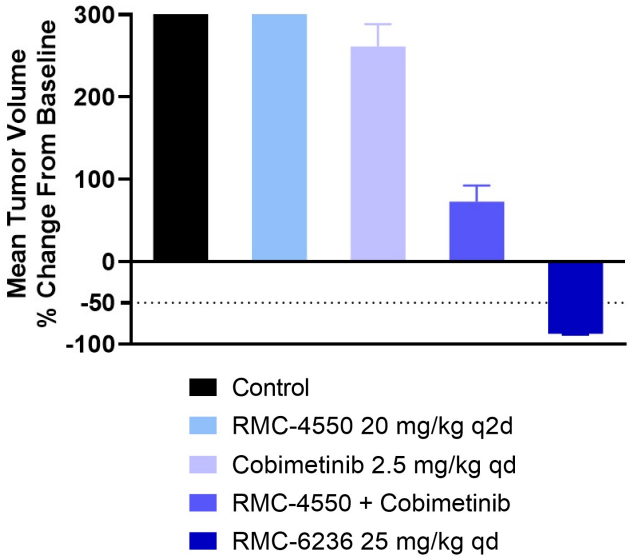
Direct Inhibition of RAS^{MUT} Drivers is More Effective than Indirect Pathway 'Clamping'

Preclinical RAS^{MUT} *In Vivo* Tumor Models

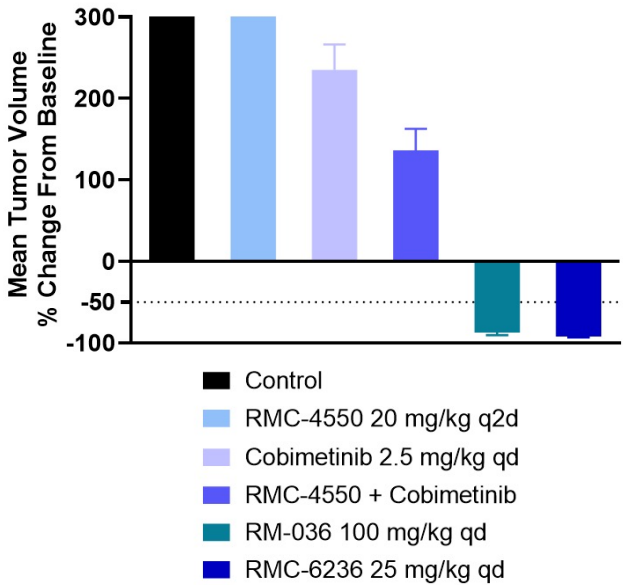
NCI-H358 CDX (NSCLC, KRAS^{G12C})



NCI-H441 CDX (NSCLC, KRAS^{G12V})

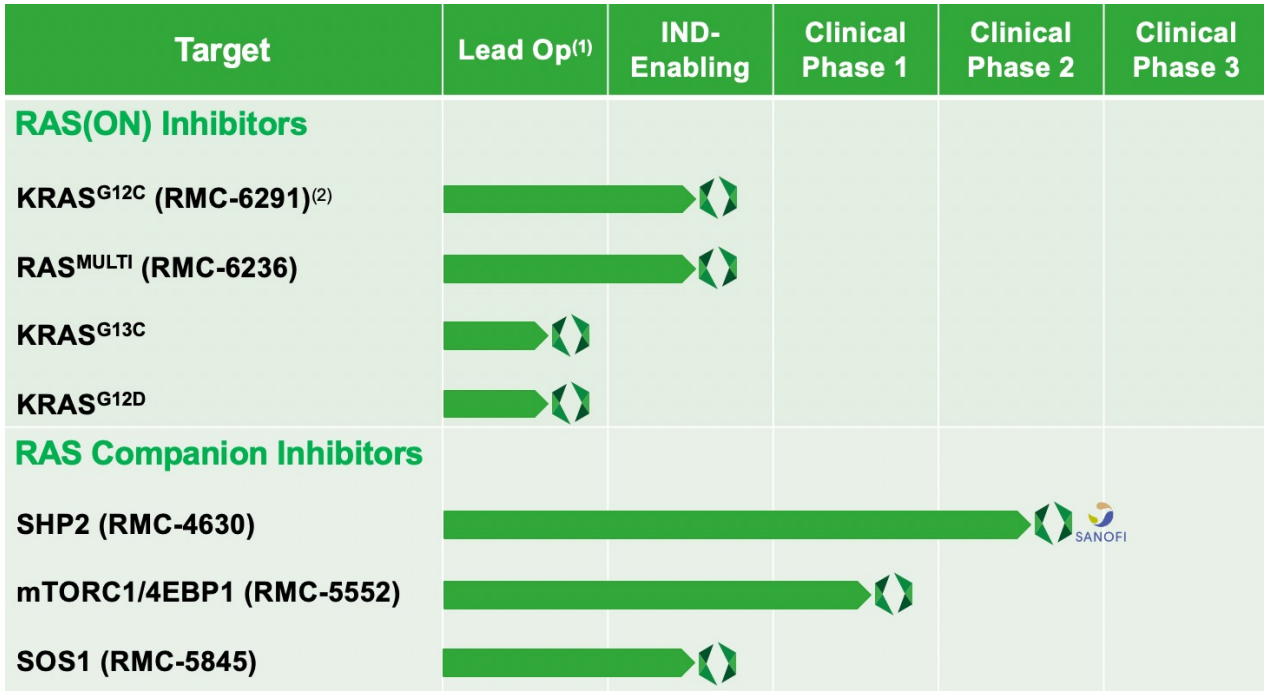


HPAC CDX (PDAC, KRAS^{G12D})



RVMD preclinical data
Compiled from multiple experiments

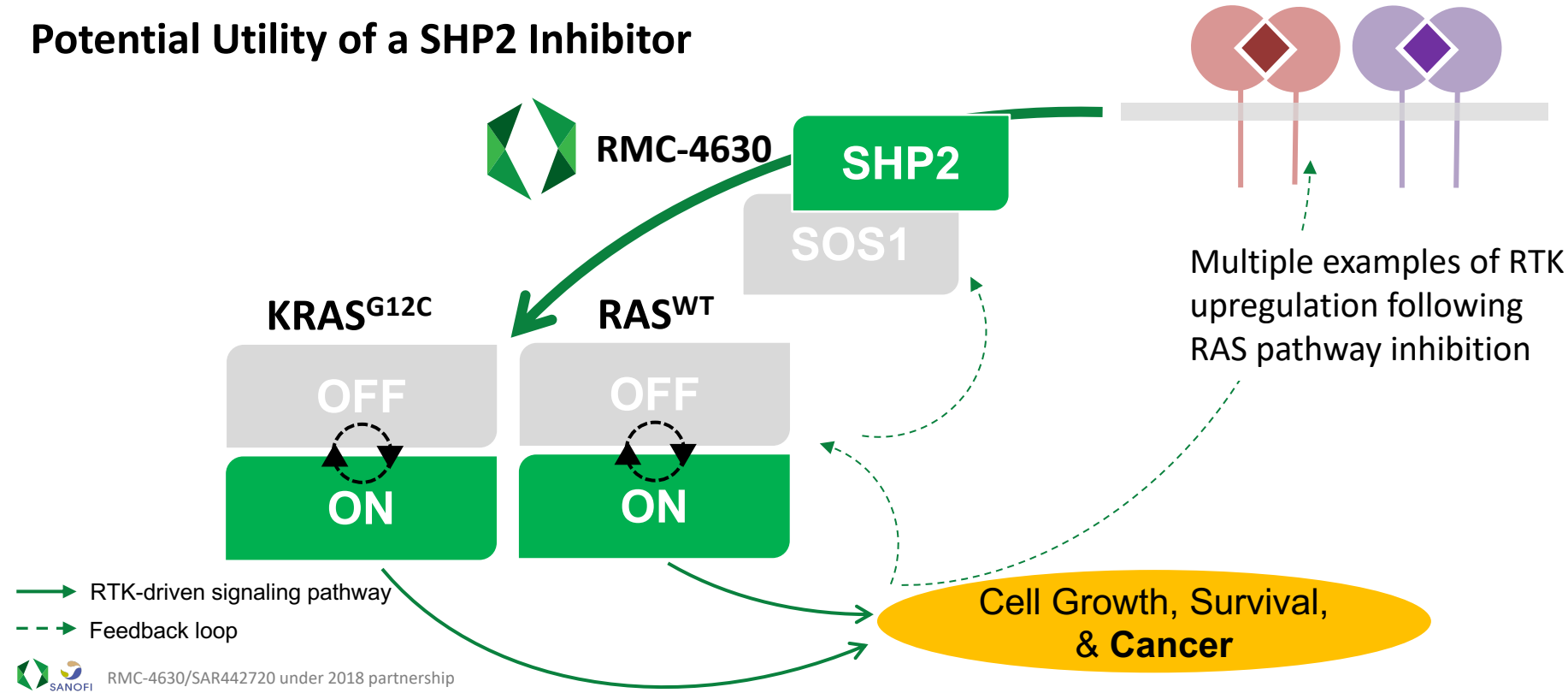
Strategic RVMD Pipeline of Targeted Drugs to Defeat RAS-Addicted Cancers



(1) Entry into Lead Optimization stage requires drug-like molecules exhibiting preclinical *in vivo* activity
(2) RMC-6291 inhibits both $KRAS^{G12C}$(ON) and $NRAS^{G12C}$(ON)

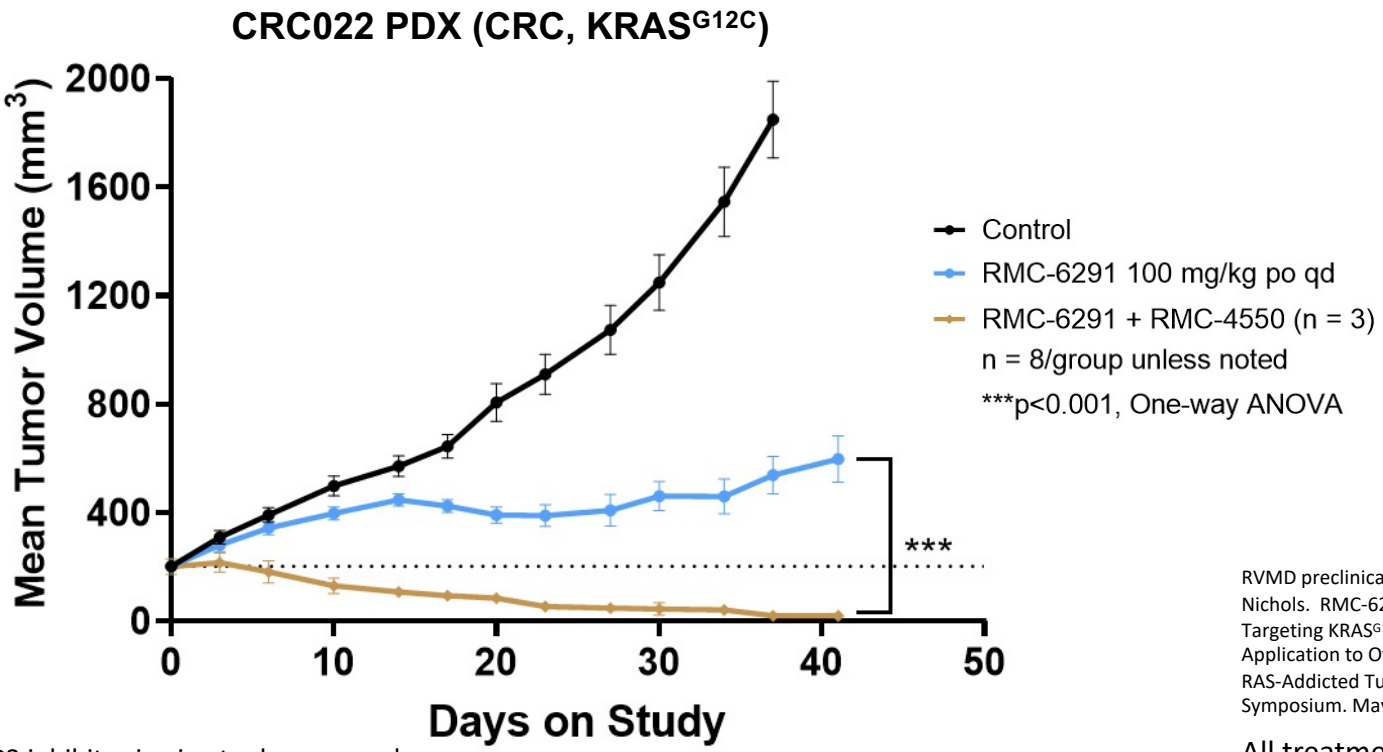
RTK Activation Can Increase Activity of Mutant *and* Wild-type KRAS

Potential Utility of a SHP2 Inhibitor



RMC-4630/SAR442720 under 2018 partnership

Combination of RMC-6291 with SHP2 Inhibitor Induces Regressions in Resistant CRC



RMC-4550 is a SHP2 inhibitor in vivo tool compound

RVMD preclinical research
Nichols. RMC-6291: Biological Features of Targeting KRASG12C(ON) and Potential Application to Overcoming Drug Resistance in RAS-Addicted Tumors. The Third RAS Initiative Symposium. May 24 – 26, 2021.

All treatments well tolerated

Clinical Combinations of RMC-4630 with KRAS^{G12C} Inhibitors is High Priority

Study	Sponsor	SHP2 Inhibitor	Combined with	Indications	Status	Geography
CodeBreaK101c Phase 1b	Amgen	RMC-4630	Sotorasib	2L+ NSCLC, CRC, other	Ongoing dose escalation – currently at 'target' dose 200mg D1D2	US
RMC-4630-03 Phase 2	**Revolution Medicines**	**RMC-4630**	**Sotorasib**	**2-4L NSCLC**	**Site initiation underway**	**Global**
TBD	Revolution Medicines	RMC-4630	RMC-6291	TBD	Planned	TBD

RMC-4630/SAR442720 under 2018 partnership

Acknowledgments

Everybody at Revolution Medicines

Sanofi

Amgen

Numerous academic collaborators