REVOLUTION MEDICINES

Translating Frontier Oncology Targets to *Outsmart Cancer*™

November 10, 2021

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For a further description of the risks and uncertainties that could cause actual results to differ from those anticipated in these forward-looking statements, as well as risks relating to the business of Revolution Medicines in general, see Revolution Medicines' Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on November 10, 2021, and its future periodic reports to be filed with the Securities and Exchange Commission. The information included in these materials is provided as part of an oral presentation on November 10, 2021 and is qualified as such. Except as required by law, Revolution Medicines undertakes no obligation to update any forward-looking statements or other information contained herein to reflect new information, events or circumstances, or to reflect the occurrence of unanticipated events.

This presentation concerns anticipated products that are under clinical investigation and which have not yet been approved for marketing by the U.S. Food and Drug Administration (FDA). It is currently limited by Federal law to investigational use, and no representation is made as to its safety or effectiveness for the purposes for which it is being investigated.

Precision Oncology Developing Next-Generation Targeted Therapies for RAS-Addicted Cancers

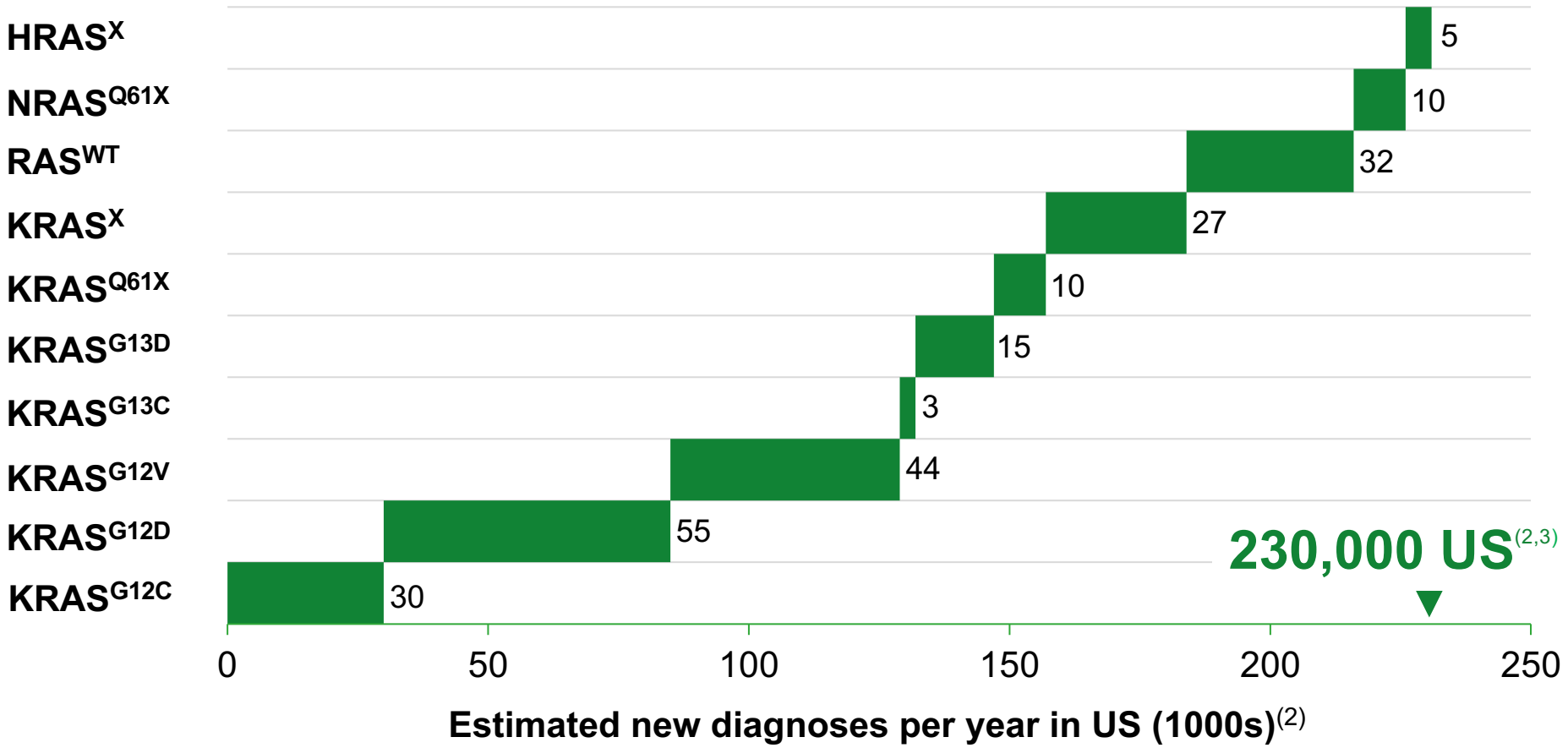
- **High unmet clinical needs remain among patients with wide range of RAS-addicted tumors**
  - Enhance clinical benefit for those with $KRAS^{G12C}$ tumors
  - Address large opportunity in other unserved RAS^{MUTANT} tumors

- **Increase response rates and durability in $KRAS^{G12C}$ tumors beyond benchmarks established with first-generation inhibitors**
  - $KRAS^{G12C}$(ON) inhibitor with robust profile: RMC-6291
  - RAS Companion Inhibitors: RMC-4630, RMC-5552 and RMC-5845

- **Deliver treatments for RAS^{MUTANT} tumors beyond $KRAS^{G12C}$**
  - RAS^{MULTI}(ON) inhibitor: RMC-6236
  - Pipeline of additional RAS^{MUTANT}-selective inhibitors
  - RAS Companion Inhibitors

Large Unmet Needs in RAS-Addicted Cancers Driven by Diverse RAS Variants

Tumor Addiction[1]:

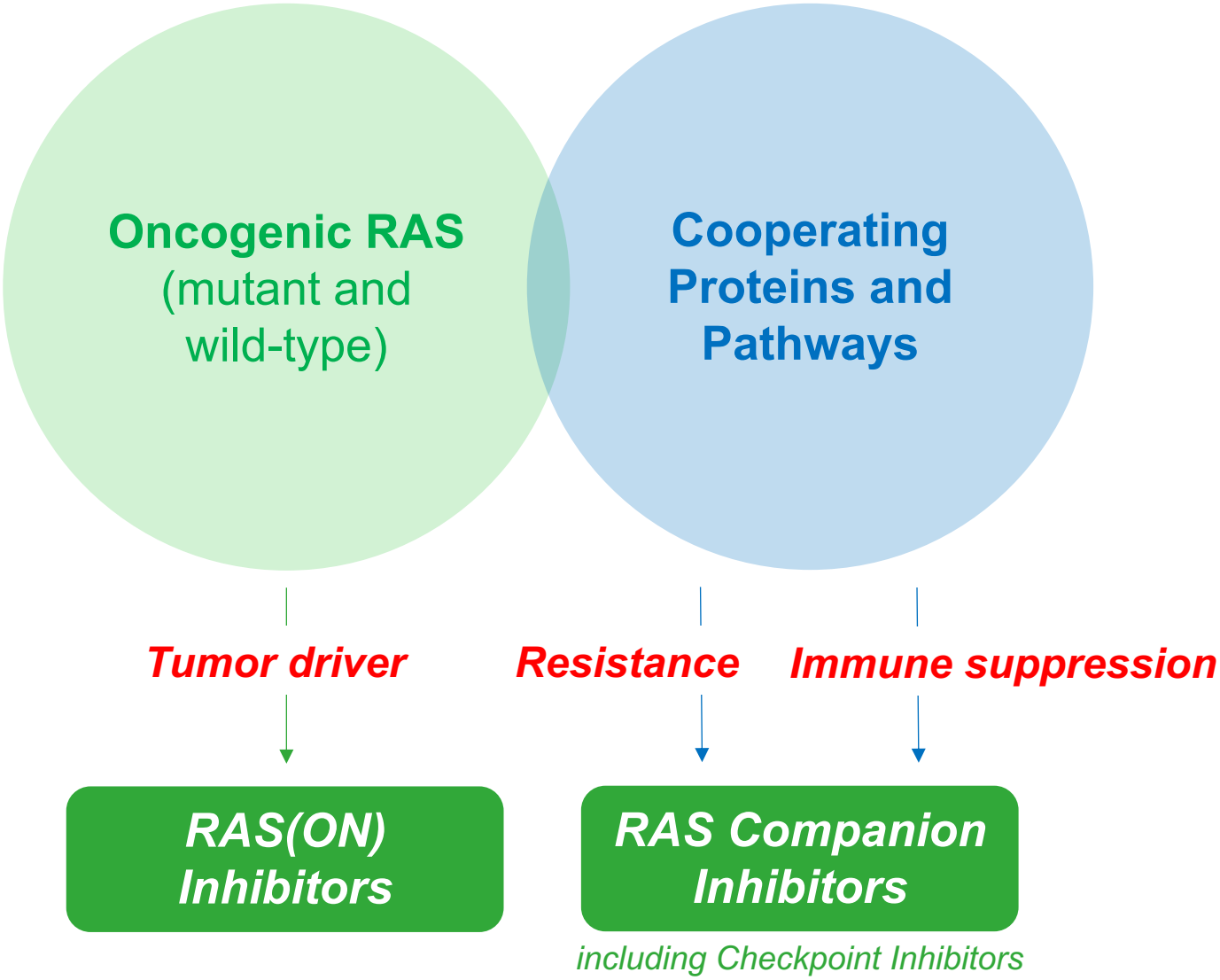


(1) $HRAS^{X}$ = all HRAS mutants; $NRAS^{Q61X}$ X = H, K, L, R, P; RAS^{WT} = $NF1^{LOF}$, RAS^{WTamp}, $BRAF^{class3,}$ and $PTPN11^{MUT}$; $KRAS^{X}$ X = G12A, G12R, G12S and A146T; $KRAS^{Q61X}$ X = H, K, L; RAS^{G12C} includes $KRAS^{G12C}$ and $NRAS^{G12C}$

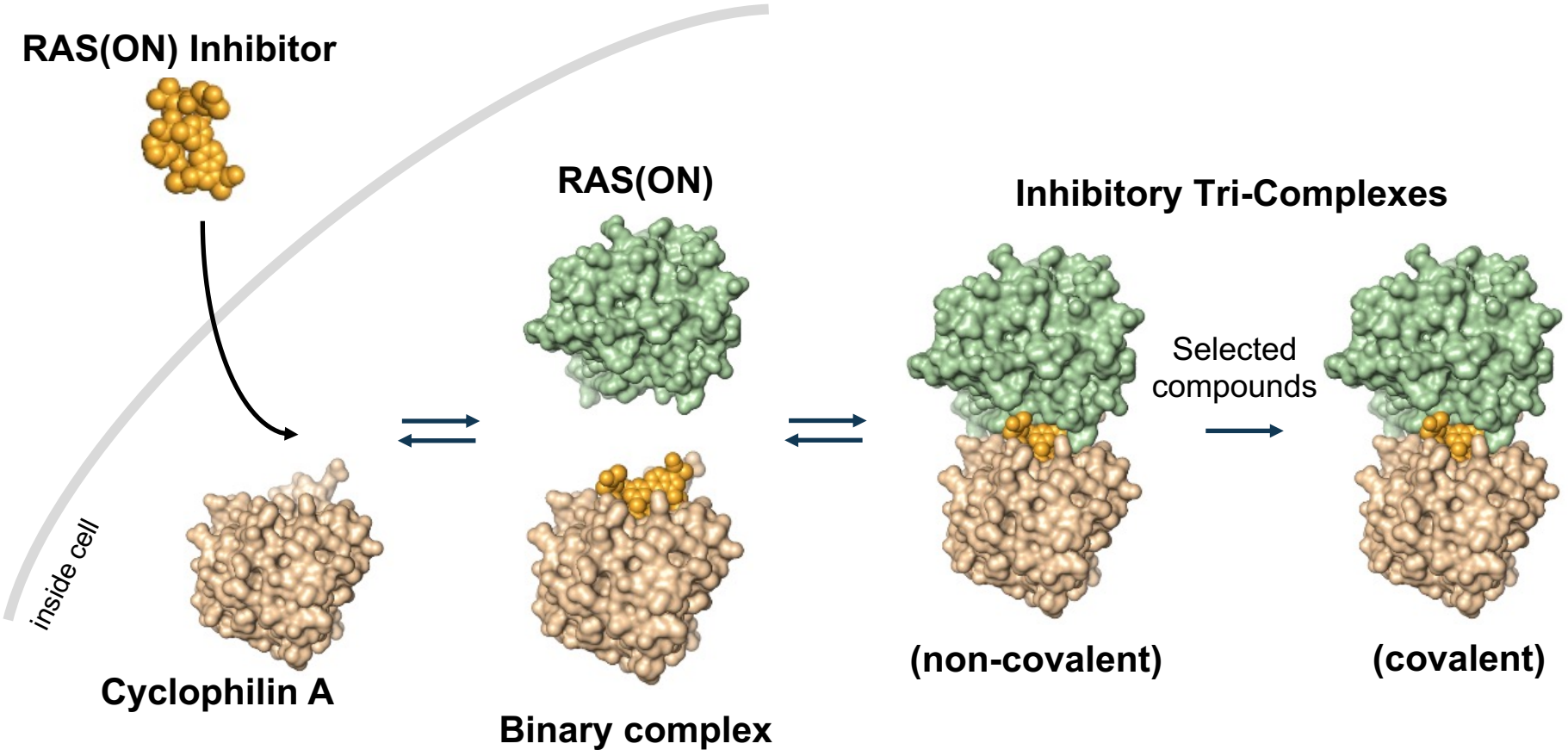
(2) Calculated using tumor mutation frequencies from Foundation Medicine Insights August 2020 and scaled to estimated patient numbers using cancer incidence from ACS *Cancer Facts and Figures* 2020. Includes 12 major types: non-small cell lung cancer, colorectal, pancreatic adenocarcinoma, renal, gastroesophageal, head and neck squamous cell, ovarian and biliary cancers, acute myeloid leukemia, and advanced melanoma, bladder and uterine/endometrial cancers causing mortality.

(3) Est. worldwide annual incidence of RAS-mutated cancers is 3.4 million per Prior et al., *Cancer Research* 2020

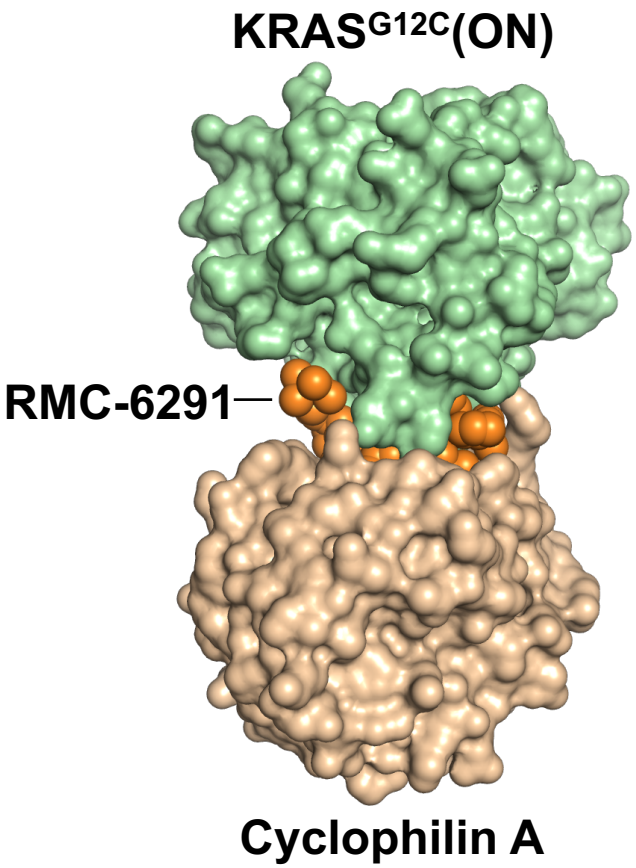
Our Approach: RAS(ON) Inhibitors as Nucleus of Combination Treatment Strategies



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



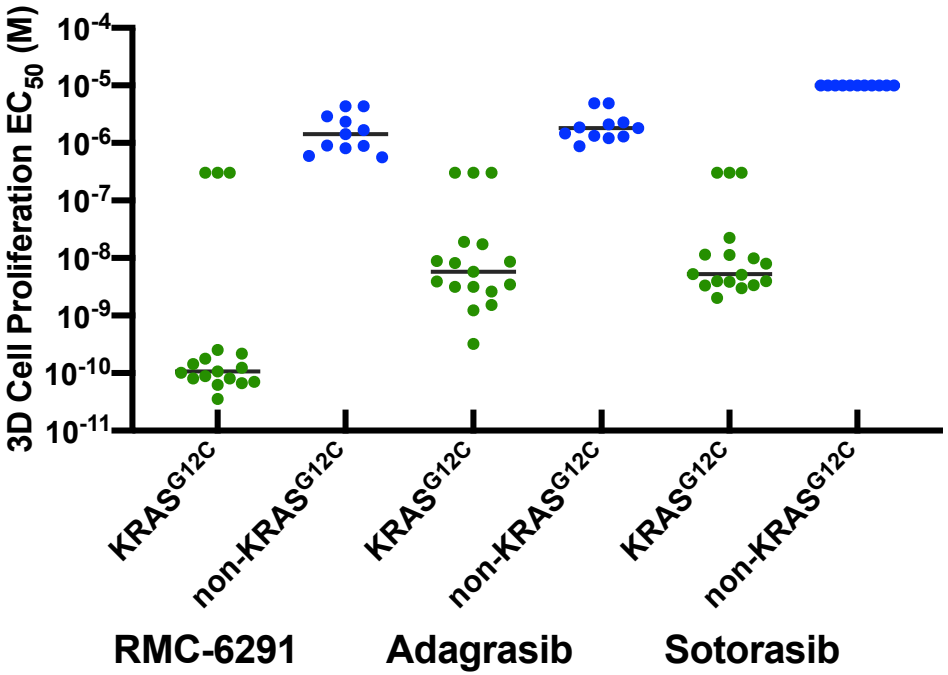
RMC-6291: First-in-Class, Potent, Oral and Selective Tri-Complex Inhibitor of KRAS^{G12C}(ON)



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

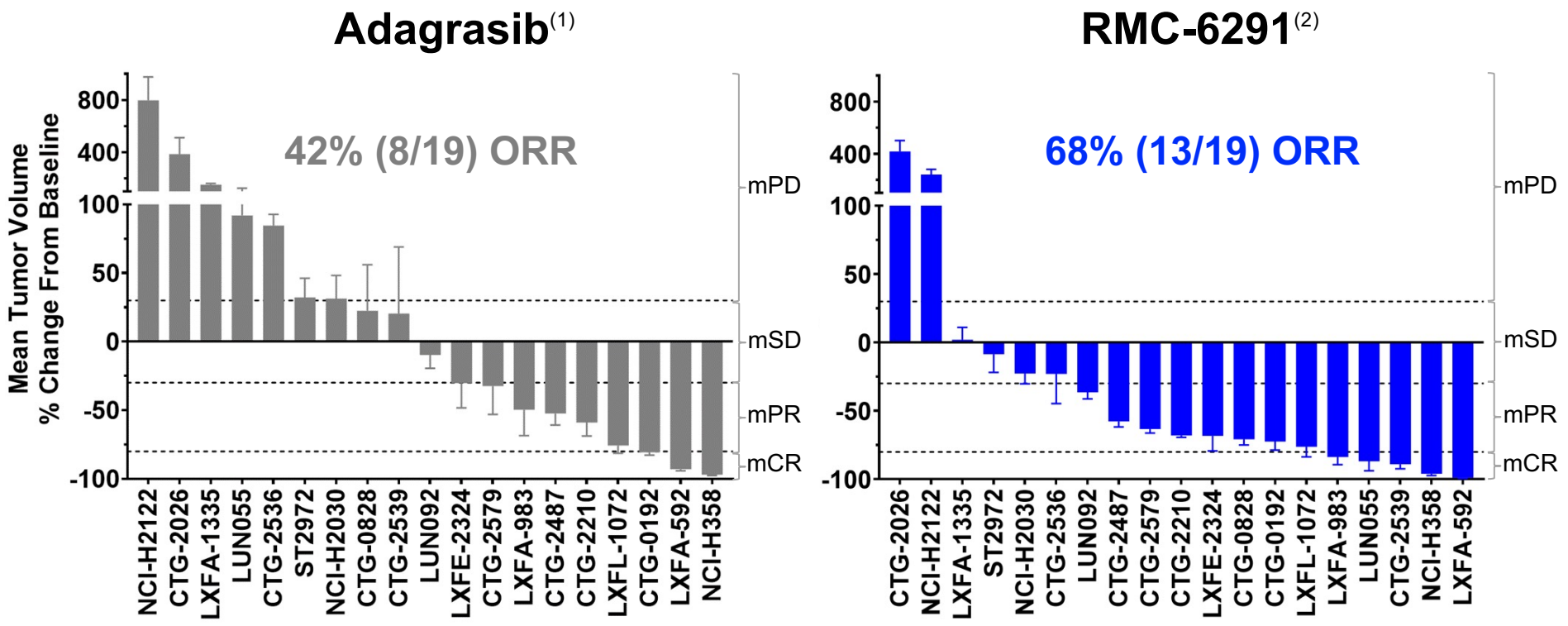
RVMD preclinical research
(1) $KRAS^{G12C}$-driven cell line; $NRAS^{G12C}$-driven line also subnanomolar

RMC-6291 is a Highly Potent and Selective Inhibitor of KRAS^{G12C}



Median EC_{50} values (nM)			
	RMC-6291	**Adagrasib**	**Sotorasib**
KRAS^{G12C}	0.1	5.8	5.2
non-KRAS^{G12C}	1,400	1,800	>10,000
Selectivity (fold)	12,700	310	>1,900

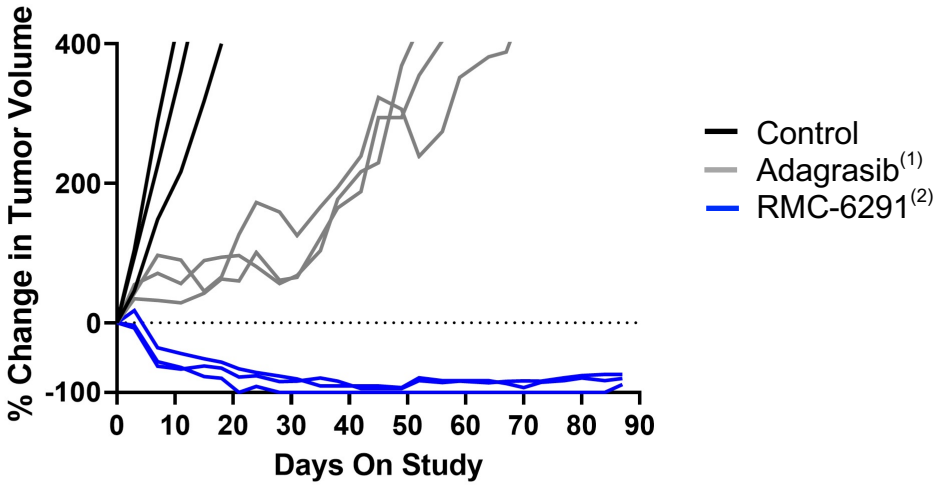
Superior Outcomes with RMC-6291 in Mouse Clinical Trial with KRAS^{G12C} NSCLC Xenografts



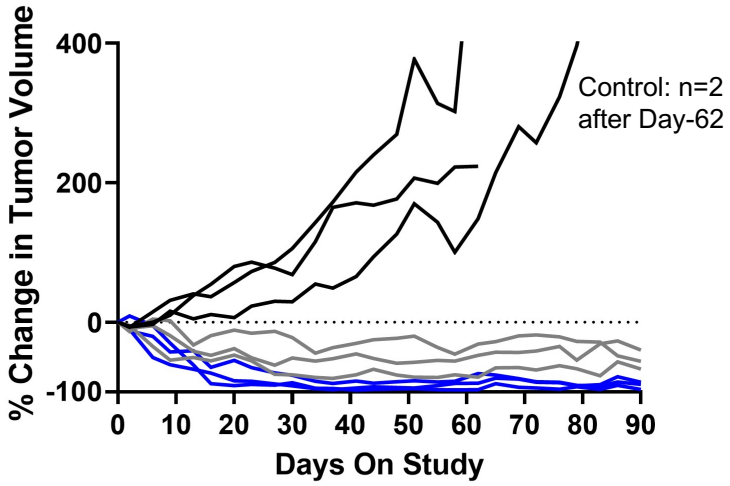
RVMD preclinical research, as of 07/28/21
(1) 100 mg/kg po qd; (2) 200 mg/kg po qd
NSCLC = Non-small cell lung cancer
PDX = patient-derived xenograft; CDX = cell line-derived xenograft
All models are PDX except for CDX models NCI-H2122, NCI-H2030, and NCI-H358
Responses assigned according to mRECIST (modified from Gao et al Nat Med. 2015):
mPD = progressive disease; mSD = stable disease; mPR = partial response; mCR = complete response

RMC-6291 May Improve on the KRAS^{G12C}(OFF) Inhibitor Class Across Three Parameters in NSCLC

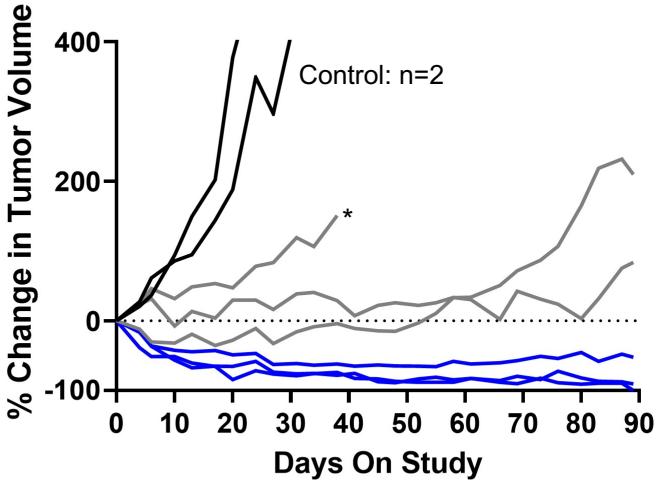
Increased Rate of Response[(a)]



Increased Depth of Response[(b)]

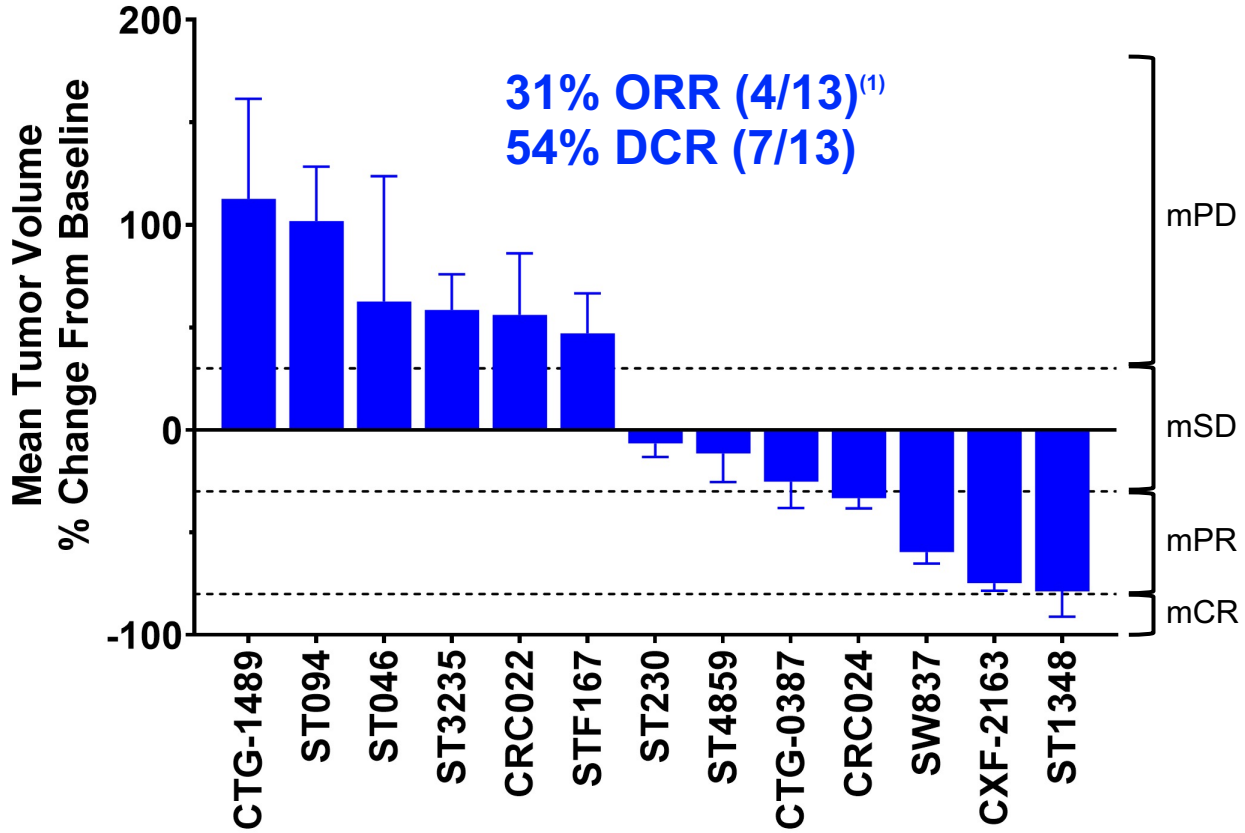


Increased Durability of Response[(c)]



RVMD preclinical research
(1) 100 mg/kg po qd; (2) 200 mg/kg po qd
n= 3/group unless noted
NSCLC = Non-small cell lung cancer
PDX = patient-derived xenograft
PDX Models: (a) LUN055; (b) LXFA-983; (c) CTG-0828
* 1 mouse taken down due to TV > 800 mm^3

RMC-6291 Shows Anti-tumor Activity in Mouse Clinical Trial with KRAS^{G12C} CRC Xenograft Models



RVMD preclinical research, as of 10/15/21
RMC-6291 dosed at 200 mg/kg po qd
CRC = colorectal cancer
PDX = patient-derived xenograft; CDX = cell line-derived xenograft
All models are PDX except for CDX model SW837
Responses assigned according to mRECIST (modified from Gao et al. Nat Med. 2015):
mPD = progressive disease; mSD = stable disease; mPR = partial response; mCR = complete response
(1) Adagrasib: 23% ORR in these models; 22% ORR in Phase 1/2 KRYSTAL-1 trial in CRC reported at ESMO 2021;
Sotorasib: 9.7% ORR in CodeBreaK 100 CRC trial reported in Amgen corporate press release 9/16/2021

RMC-6291 Active Against All Reported Second-Site KRAS^{G12C}(OFF) Inhibitor Resistance Mutations

	Y96	Y96C	Y96D	Y96F	Y96H	Y96N	Y96S	H95D	H95L	H95N	H95P	H95Q	H95R	H95Y	R68G	R68K	R68M	R68S	R68T	R68W
Clinical resistance		■	■					■				■	■					■		
RMC-6291	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adagrasib	+	-	-	+	-	-	-	-	-	-	-	-	-	+	-	+	+	+	+	+
Sotorasib	+	-	-	+	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+

+ Active
- Inactive

RVMD preclinical research
Mutations assessed bv cellular RAS/RAF disruption assay

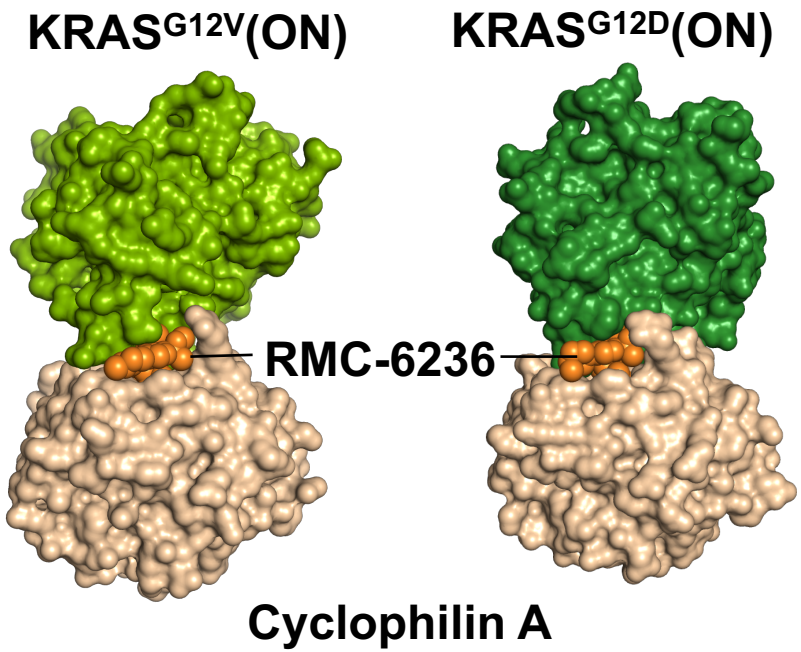
Nichols. RMC-6291: Biological Features of Targeting KRAS^{G12C}(ON) and Potential Application to Overcoming Drug Resistance in RAS-Addicted Tumors. The Third RAS Initiative Symposium. May 24 – 26, 2021.
Awad et al. Mechanisms of acquired resistance to KRAS G12C inhibition in cancer. AACR Annual Meeting 2021. April 10, 2021.
Tanaka et al. Clinical acquired resistance to KRASG12C inhibition through a novel KRAS switch-II pocket mutation and polyclonal alterations converging on RAS-MAPK reactivation. Cancer Discovery. April 6 2021. DOI: 10.1158/2159-8290.CD-21-0365
Revolution Medicines Science Talk: Emerging Insights about RAS-Addicted Cancers, Drug Resistance and Treatment Strategies. June 17, 2021.

RMC-6291: Best-in-Class Preclinical Profile Predicts Best-in-Class Clinical Profile

	RMC-6291
Status	• IND-enabling development
Preclinical	• RAS(ON) binding and mechanism of action • Subnanomolar potency • Deep and durable responses *in vivo* • Increased response rate in preclinical models of $KRAS^{G12C}$ NSCLC • Overcomes clinically-observed second-site resistance mutations • Low susceptibility to increased flux driving $KRAS^{G12C}$(OFF) to $KRAS^{G12C}$(ON)

Clinical	• IND submission projected 1H2022
	• Superiority thesis:
	  • Range of sensitive tumor types, response rate, depth and/or duration
	  • Beneficial combinations with RAS Companion Inhibitors

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



Potency for Tumor Cell Inhibition	
pERK (RAS-dependent, IC_{50}, nM)[1]	0.4-3
CTG (RAS-dependent, IC_{50}, nM)[1]	1-27

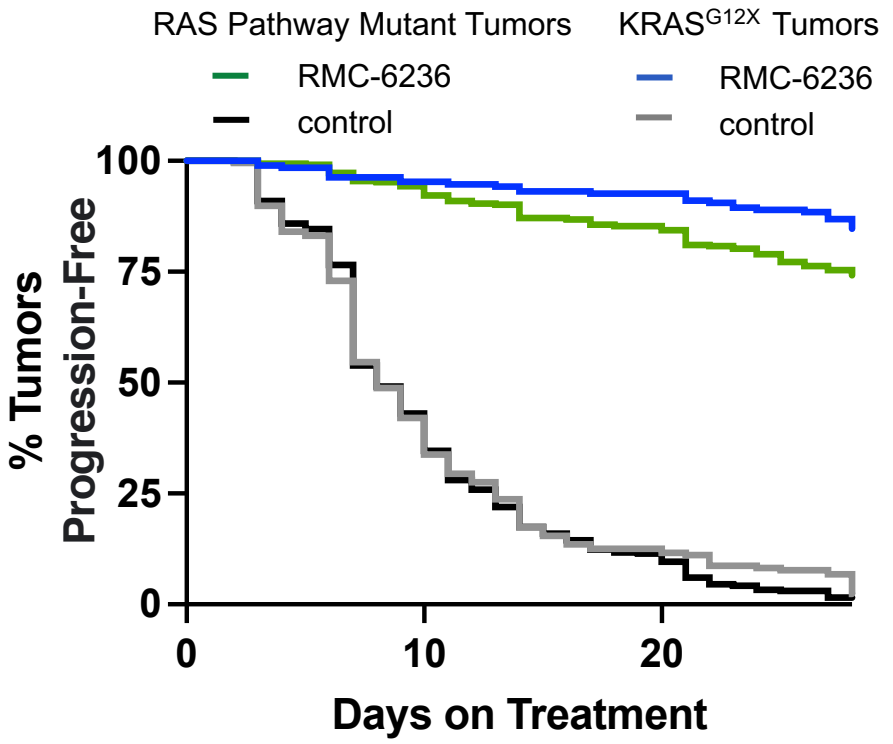
Target Selectivity and Safety	
Selectivity	
• Over RAS-independent cells[2]	> 1000X
Off-target safety panel	Low Risk

PK/ADME	
Oral %F (multiple species)	24-33
Metabolic clearance (hepatocytes, multiple species)	Low to Moderate

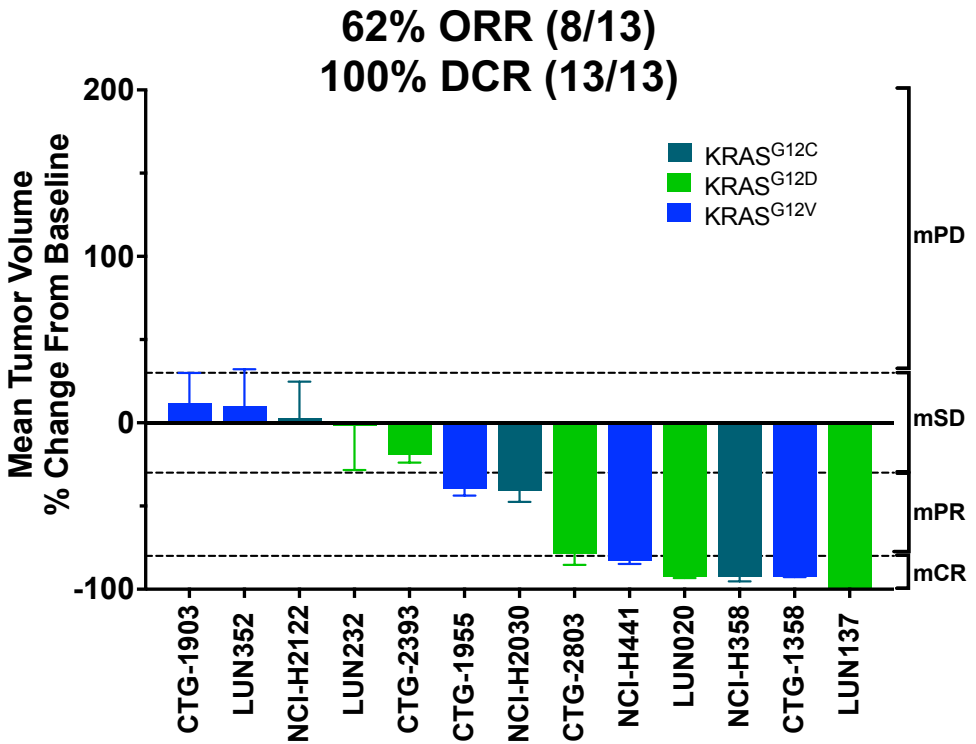
RVMD preclinical research
(1) Range reflects sensitivities across multiple RAS-variant cell lines
(2) Ratio based on cell growth assays with cell line bearing KRAS^{G12V} mutation

RMC-6236 is Highly Active Across Tumor Models with Diverse RAS Drivers *in Vivo*

Diverse RAS Pathway Mutant Tumors Models

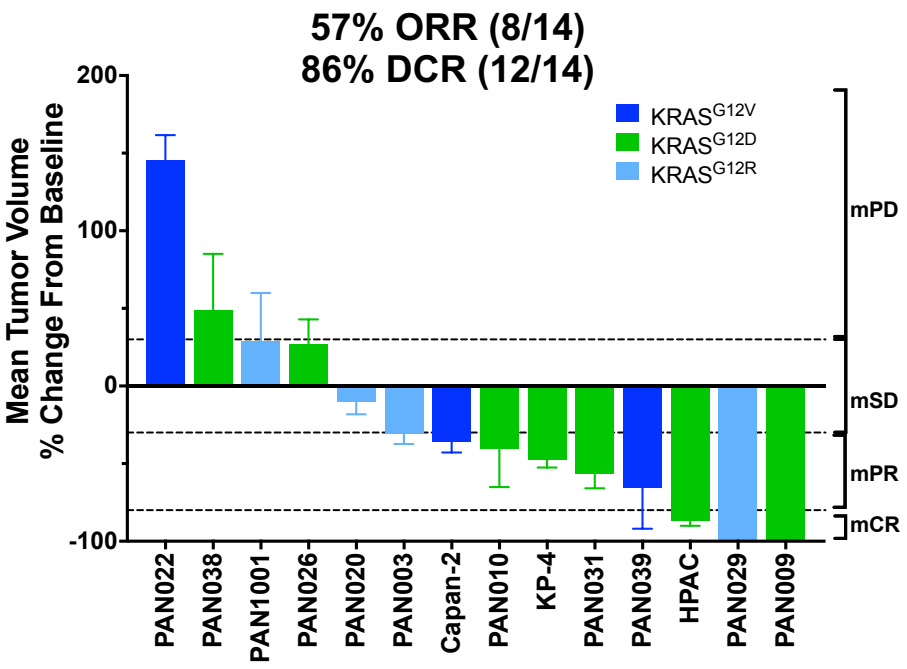


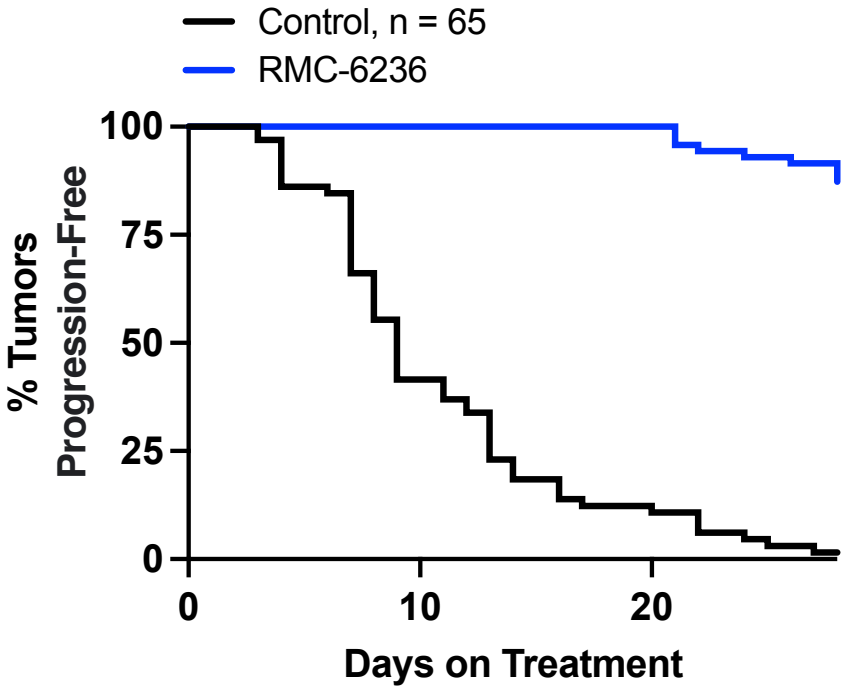
KRAS^{G12X} NSCLC Models



RVMD preclinical research, as of 10/12/21
RMC-6236 dosed at 25 mg/kg po qd
(Left) KRAS^{G12X} Tumors, where X = D,V,C, A or R: n = 207
RAS Pathway Mutant Tumors includes KRAS^{G12X} and other RAS and RAS pathway mutant tumors: KRAS^{G13C}, KRAS^{G13D}, KRAS^{K117N}, KRAS^{Q61H}, NF1^{LOF}, PTPN$^{E76K\ or\ G503V}$, BRAF$^{Class\ 3\text{-}mutant}$, and KRAS$^{WT\text{-}Amp}$: n = 332
K-M progression defined as tumor doubling from baseline over 28 days
$p<0.0001$ by Log-rank test (control vs active treatment)
(Right) NSCLC = Non-small cell lung cancer
PDX = patient-derived xenograft; CDX = cell line-derived xenograft
All models are PDX except for CDX models NCI-H2122, NCI-H2030, NCI-H441, and NCI-H358
Responses assigned according to mRECIST (modified from Gao et al Nat Med. 2015):
mPD = progressive disease; mSD = stable disease; mPR = partial response; mCR = complete response

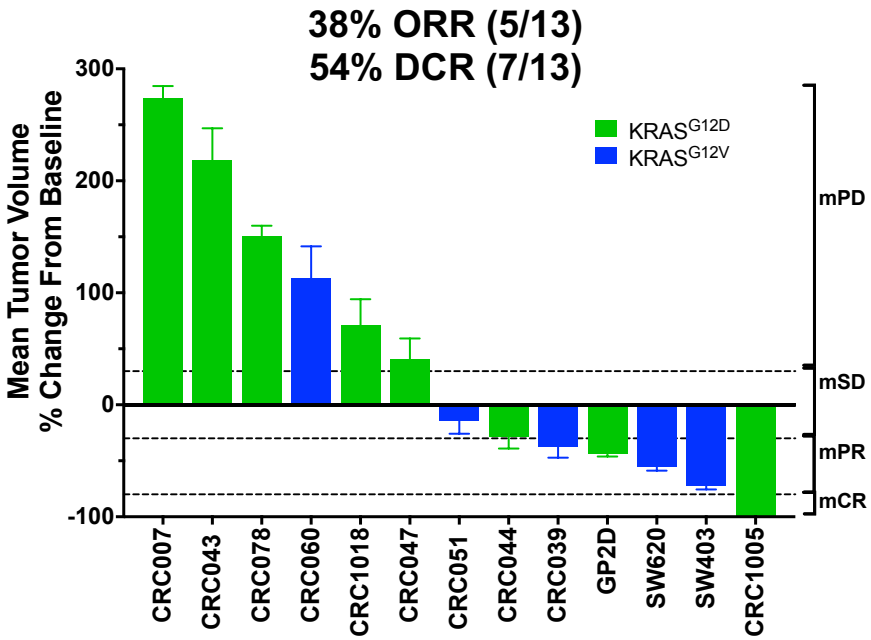
RMC-6236 Drives Regressions in KRAS^{G12X} PDAC Tumor Models *in Vivo*

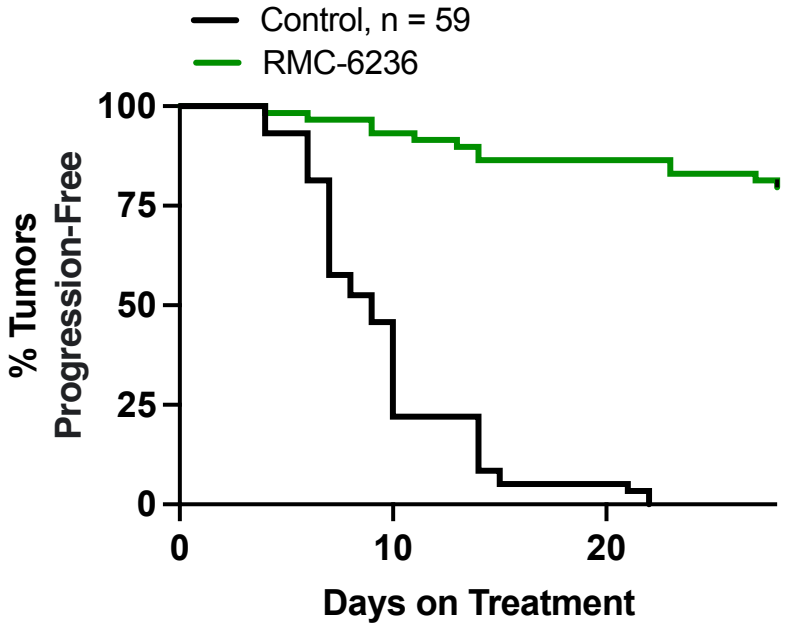




RVMD preclinical data, as of 10/12/21
RMC-6236 dosed at 25 mg/kg po qd
PDAC = pancreatic ductal adenocarcinoma
(Left) PDX = patient-derived xenograft; CDX = cell line-derived xenograft
All models are PDX except for CDX models Capan-2, KP-4, and HPAC
Responses assigned according to mRECIST (modified from Gao et al Nat Med. 2015):
mPD = progressive disease; mSD = stable disease; mPR = partial response; mCR = complete response
(Right) K-M progression defined as tumor doubling from baseline over 28 days

RMC-6236 Drives Regressions in KRAS^{G12X} CRC Tumor Models *in Vivo*

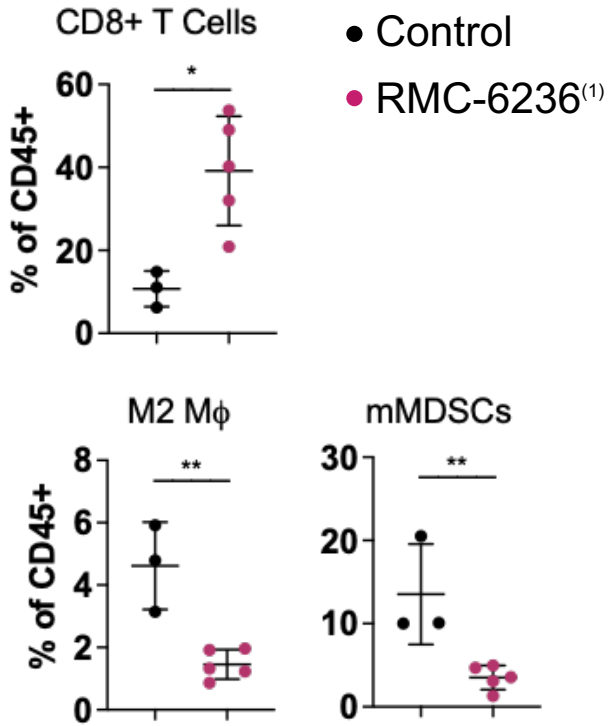




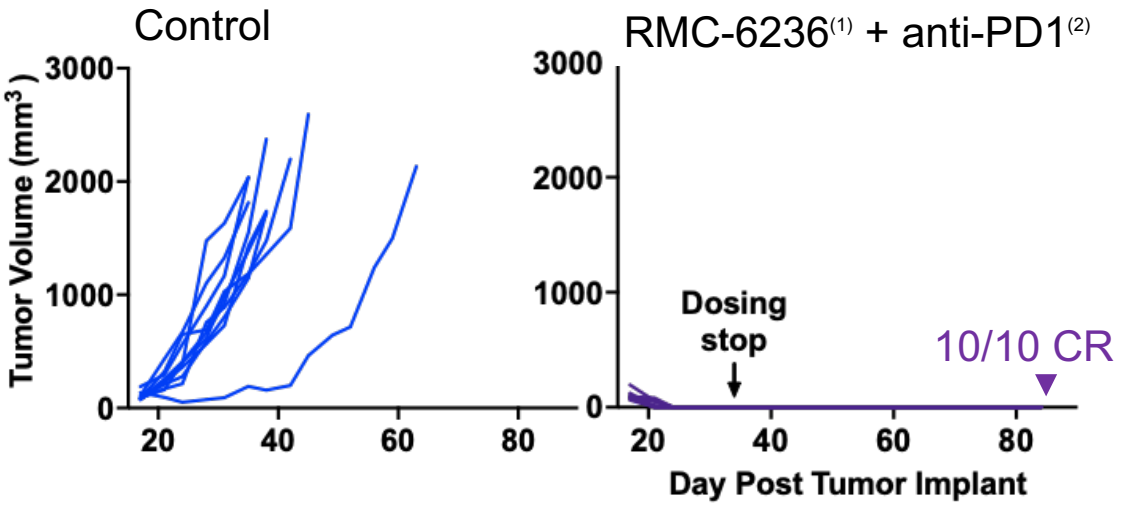
RVMD preclinical data, as of 10/12/21
RMC-6236 dosed at 25 mg/kg po qd
CRC = colorectal cancer
(Left) PDX = patient-derived xenograft; CDX = cell line-derived xenograft
All models are PDX except for CDX models GP2D, SW620, and SW403
Responses assigned according to mRECIST (modified from Gao et al. Nat Med. 2015)
mPD = progressive disease; mSD = stable disease; mPR = partial response; mCR = complete response
(Right) K-M progression defined as tumor doubling from baseline over 28 days

RMC-6236 Promotes Anti-Tumor Immunity *in Vivo* and is Strongly Additive with Checkpoint Inhibitor

Favorable Transformation of Tumor Immune Microenvironment

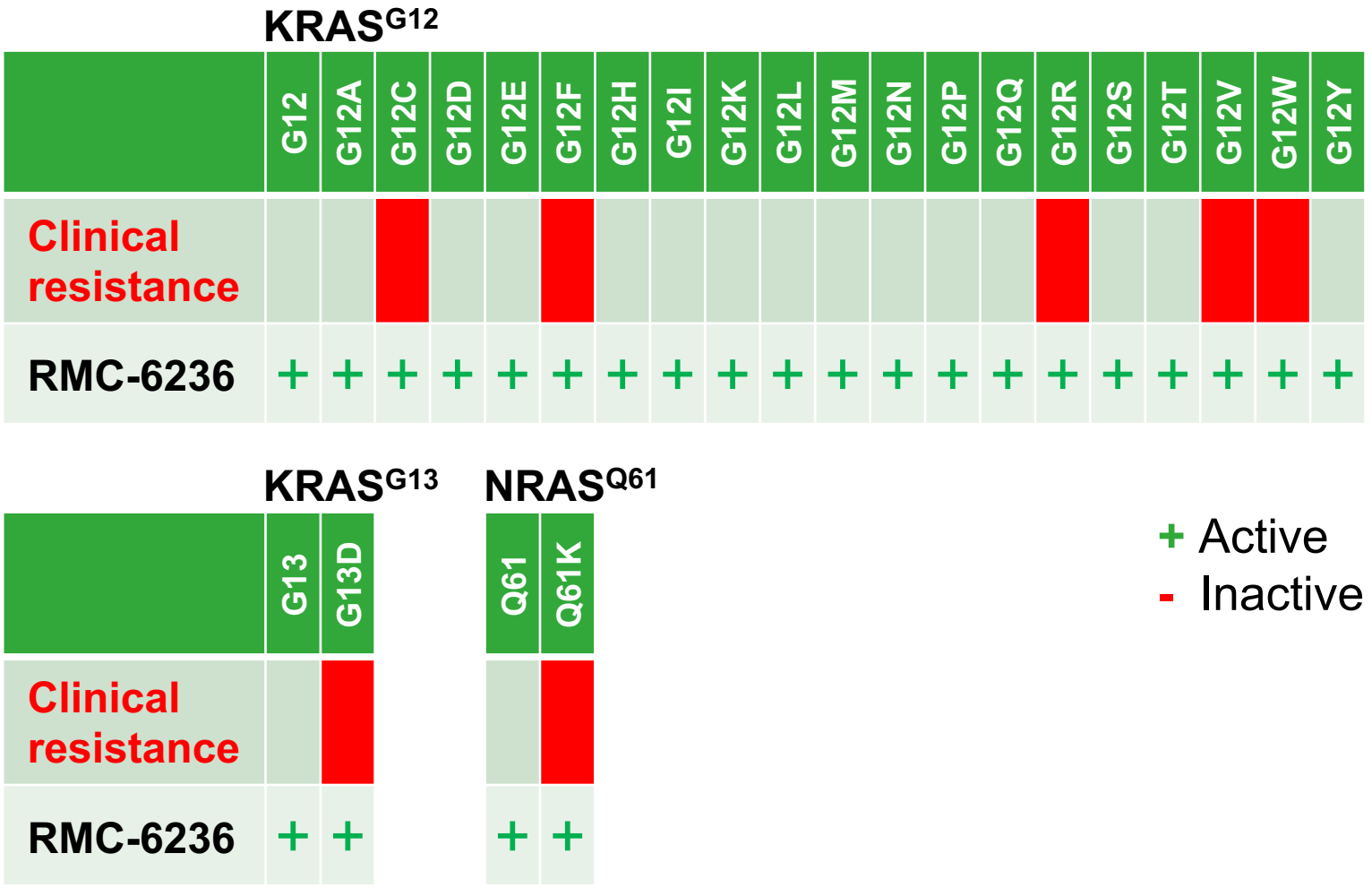


Durable Complete Responses with Combination



RVMD preclinical research
Syngeneic tumor model with CT26 cell line engineered to express $KRAS^{G12C}$
(1) 25 mg/kg po qd; (2) 10 mg/kg ip biw

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



RVMD preclinical research

KRAS^{G12} mutations assessed by 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.

Awad et al. Mechanisms of acquired resistance to KRAS G12C inhibition in cancer. AACR Annual Meeting 2021. April 10, 2021.

Tanaka et al. Clinical acquired resistance to KRASG12C inhibition through a novel KRAS switch-II pocket mutation and polyclonal alterations converging on RAS-MAPK reactivation. Cancer Discovery. April 6 2021. DOI: 10.1158/2159-8290.CD-21-0365

Revolution Medicines Science Talk: Emerging Insights about RAS-Addicted Cancers, Drug Resistance and Treatment Strategies. June 17, 2021.

RMC-6236: Predicted to Serve Multiple, Large Unmet Needs Based on Preclinical Profile

	RMC-6236
Status	• IND-enabling development
Preclinical	• RAS(ON) binding and mechanism of action • Low nanomolar potency • Selective for RAS family • Deep and durable responses *in vivo* • Overcomes clinically-observed switch mutations • Induces anti-tumor immunity and shows combinatorial anti-tumor effect with checkpoint inhibitor

Clinical	• IND submission projected 1H2022
	• Broad thesis:
	  • Sensitivity of numerous RAS genotypes across multiple patient segments
	  • Beneficial combinations with RAS Companion 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 Expected to combine well with RAS Companion Inhibitors	Serves multiple patient sub-populations 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 Likely requires a RAS Companion Inhibitor	On-target normal tissue effects likely will be dose-limiting and may constrain depth and/or duration of target coverage

(1) RVMD preclinical research

Parallel Product Strategy for RAS(ON) Inhibitors

Mutant-selective (undisclosed)

TBN ($KRAS^{G13C}$-selective)

TBN ($KRAS^{G12D}$-selective)

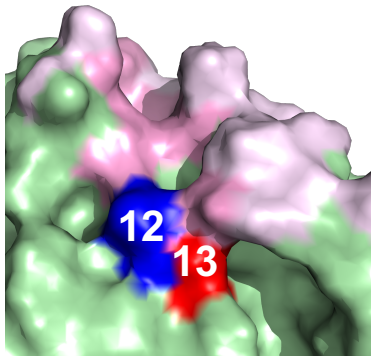
Mutant- selective (undisclosed)

RMC-6291 ($KRAS^{G12C}$-selective)

RMC-6236 (RAS^{MULTI})

TBN = to be named

Distinctive Covalent Tri-Complex Inhibitors with Exquisite KRAS^{MUTANT}(ON) Selectivity



Cysteine-targeted

Aspartate-targeted

KRAS^{G12C} Inhibitor

KRAS^{G13C} Inhibitor

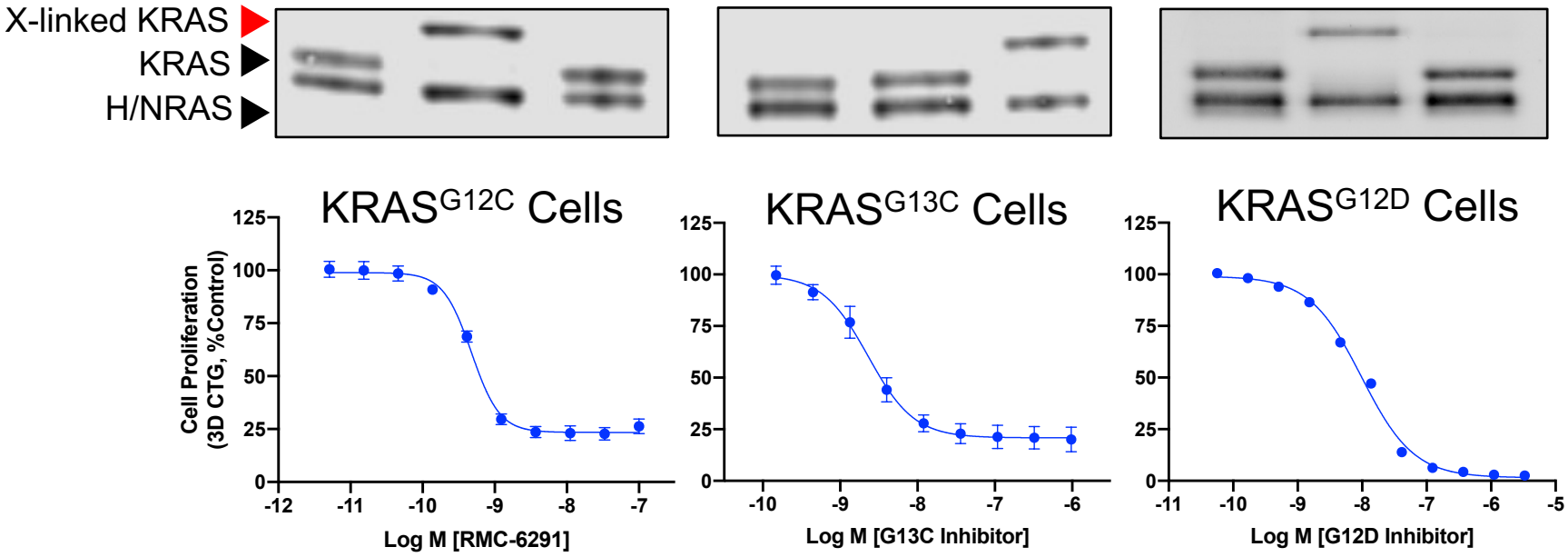
KRAS^{G12D} Inhibitor

KRAS: WT G12C G13C WT G12C G13C WT G12D G13D

X-linked KRAS

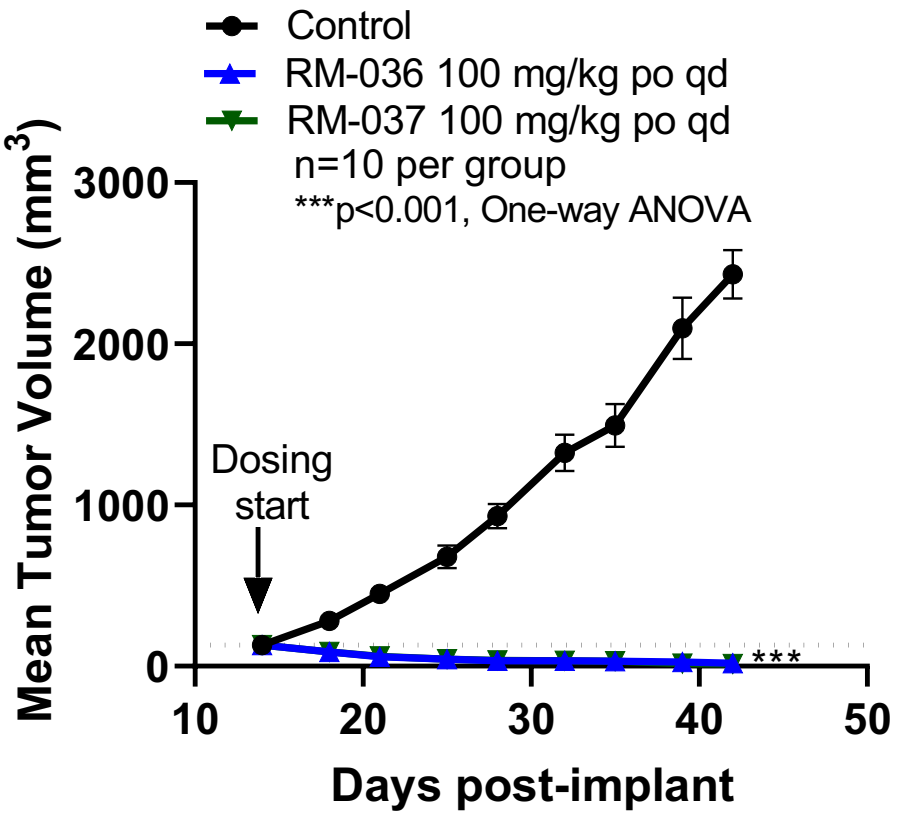
KRAS

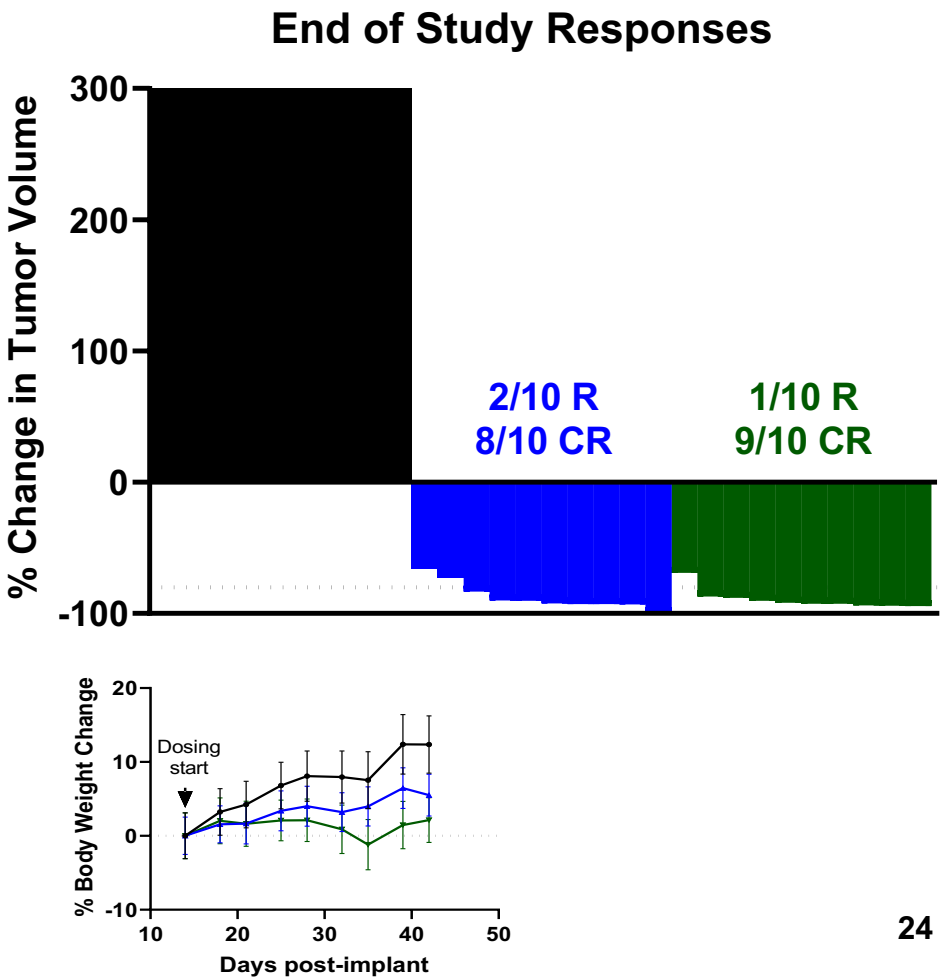
H/NRAS



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

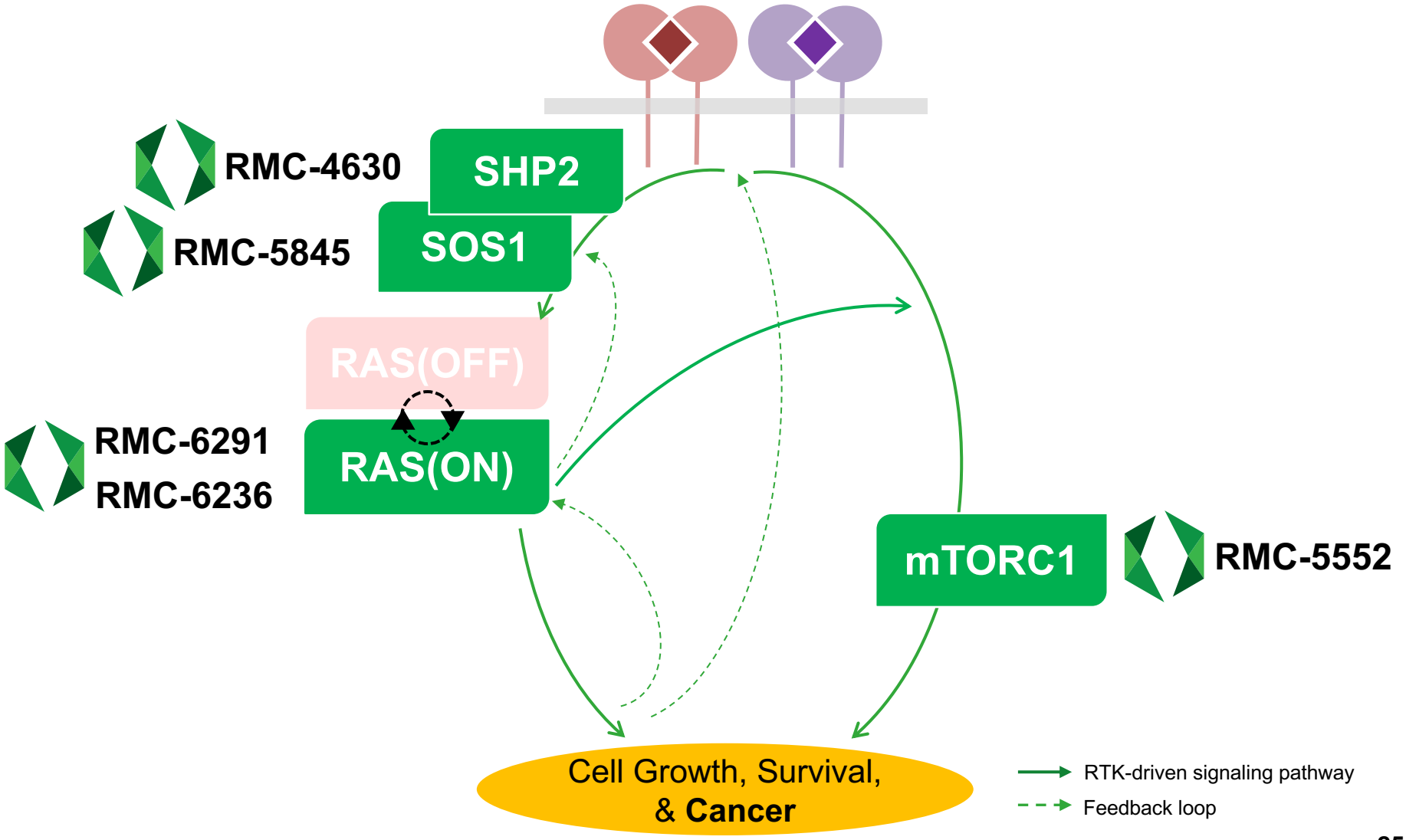
HPAC CDX (PDAC, KRAS$^{G12D/WT}$)





RVMD preclinical research
PDAC = pancreatic ductal adenocarcinoma
CDX = cell line derived xenograft
R = tumor regressions >10% reduction from initial volume
CR = tumor regressions ≥ 80% reduction from initial volume
Each animal represented as a separate bar

Strategic, Development-Stage Pipeline Targets Key Drivers of RAS Addiction and Resistance



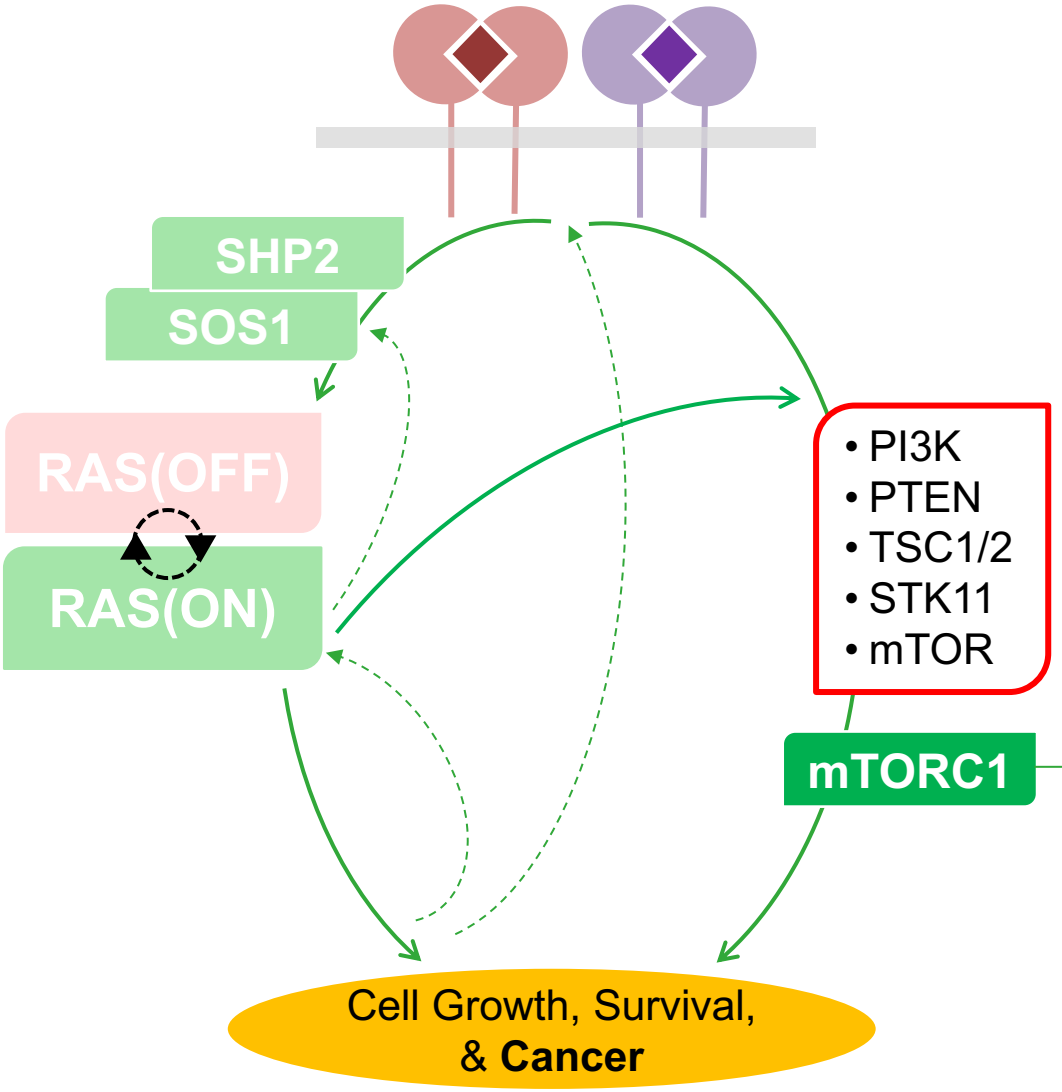
Priority Clinical Combination Studies with RMC-4630

	Study	Sponsor	Combined with	Indication(s)	Status
$KRAS^{G12C}$	CodeBreaK 101c (US)	Amgen	sotorasib	2L+ solid tumors	Dose escalation evaluating RMC-4630 at target dose (200 mg D1D2)
	RMC-4630-03 (Global)	RevMed	sotorasib	2L+ NSCLC	Actively recruiting
	TCD16210 (Global)	Sanofi	adagrasib	2L+ NSCLC	In preparation
	TBD	RevMed	RMC-6291	TBD	Planning
$KRAS^{MUTANT}$	TCD16210 (Global)	Sanofi	Pembro-lizumab	1L $PDL1^{+}$ NSCLC	Planning Phase 2 expansion

SANOFI

RMC-4630/SAR442720 under 2018 partnership

RMC-5552: Potent, Selective Inhibitor of Hyperactivated mTORC1 Signaling in Cancer



RMC-5552

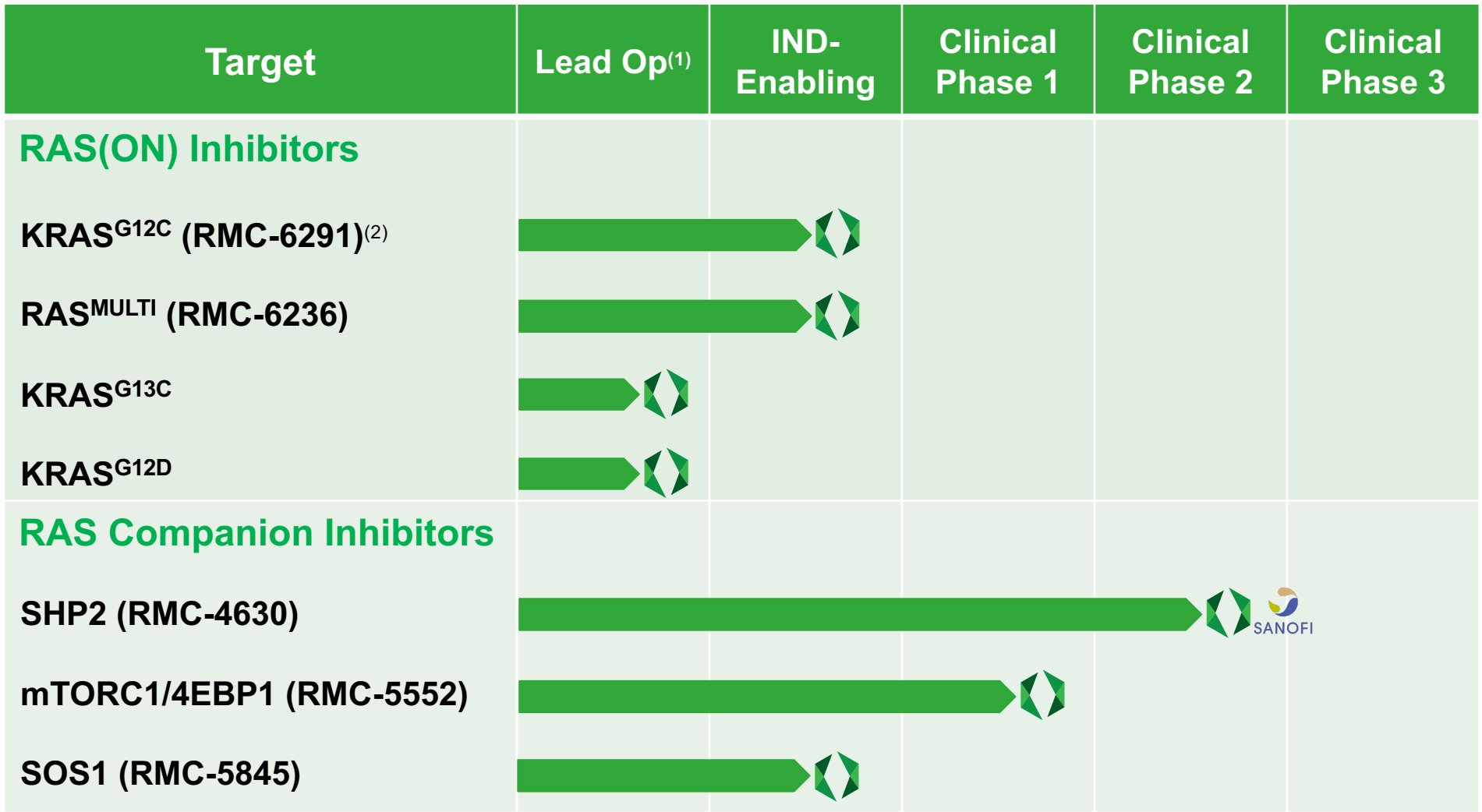
- Phase 1 dose escalation underway
- Monotherapy for tumor genotypes linked to hyperactivated mTORC1
- Combinations with RAS inhibitors for patients with cancers harboring RAS/mTOR signaling co-mutations

Genomic alterations of these proteins hyperactivate mTORC1 and can drive cancer

RTK-driven signaling pathway

Feedback loop

Expansive and 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)

Corporate Milestones

Milestone	Expected
RAS(ON) Inhibitors	
• **$KRAS^{G12C}$/$NRAS^{G12C}$ (RMC-6291)**	
Submit IND	1H22
• **RAS^{MULTI} (RMC-6236)**	
Submit IND	1H22
• **Nominate third Development Candidate**	2H21
RAS Companion Inhibitors	
• **SHP2 (RMC-4630)**	
Selection of dose for further testing of RMC-4630 + sotorasib (CodeBreaK 101c)	2H21
FPI RMC-4630-03 (RMC-4630 + sotorasib)	2H21
Preliminary findings from RMC-4630-03 (RMC-4630 + sotorasib)	2H22
• **mTORC1/4EBP1 (RMC-5552)**	
Initial safety, PK and single agent activity data	2022
• **SOS1 (RMC-5845)**	
IND-ready	2H21

Financial Information

Financial Position	
Cash, cash equivalents and marketable securities @ 9/30/2021	$608.7 million

Financial Guidance
2021 GAAP net loss of $170 million to $190 million[(1)]

(1) Includes non-cash stock-based compensation of approximately $20 million.

Translating Frontier Oncology Targets to *Outsmart Cancer*™