REVOLUTION MEDICINES

Translating Frontier Oncology Targets to *Outsmart Cancer*™

Corporate Overview
Q2 2021
May 10, 2021

Legal Disclaimer

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act. All statements other than statements of historical facts contained in this presentation, including statements regarding our future results of operations and financial position, business strategy, prospective products, availability of funding, ability to maintain existing collaborations, including with Sanofi, and establish new strategic collaborations, licensing or other arrangements, the scope, progress, results and costs of developing our product candidates or any other future product candidates, the potential market size and size of the potential patient populations for our product candidates, the timing and likelihood of success of obtaining product approvals, plans and objectives of management for future operations, the scope of protection we are able to establish and maintain for intellectual property rights covering our product candidates, future results of anticipated products, are forward-looking statements and the impact of the COVID-19 pandemic on our business. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. Because forward-looking statements are inherently subject to risks and uncertainties, some of which cannot be predicted or quantified and some of which are beyond our control, you should not rely on these forward-looking statements as predictions of future events. The events and circumstances reflected in our forward-looking statements may not be achieved or occur and actual results could differ materially from those projected in the forward-looking statements. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

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' Annual Report on Form 10-Q filed with the Securities and Exchange Commission on May 10, 2021, and its future periodic reports to be filed with the Securities and Exchange Commission. 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.

Summary

- Clinical-stage precision oncology company addressing multiple, large unmet needs in RAS-addicted cancers
  - *Systematic, focused, science-driven strategy*

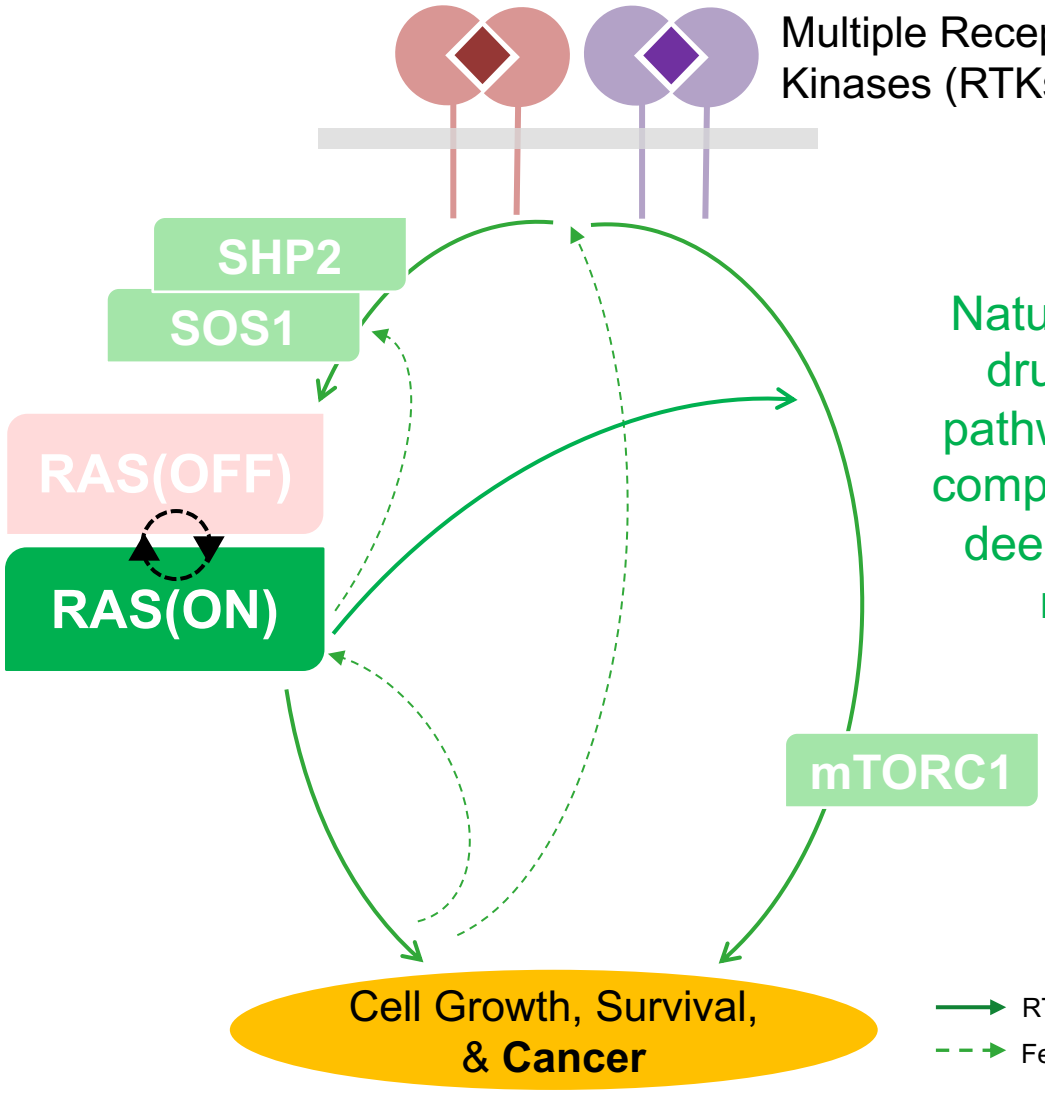
- **RAS(ON) Inhibitors** target diverse oncogenic RAS variants via highly differentiated profiles
  - ***RMC-6291 (KRAS^{G12C})*** *entered development*
  - ***RMC-6236 (RAS^{MULTI})*** *entered development*

- **RAS Companion Inhibitors** are potential backbones of targeted combinations to maximize clinical benefit
  - ***RMC-4630 (SHP2)*** *exhibits clinical activity, advancing in broad program*
  - ***RMC-5552 (mTORC1/4EBP1)*** *entered clinic*
  - ***RMC-5845 (SOS1)*** *entered development*

RAS(ON) Proteins Cause Cancer, RAS Addiction and Drug Resistance

1.
Many RAS family variants underlie addiction

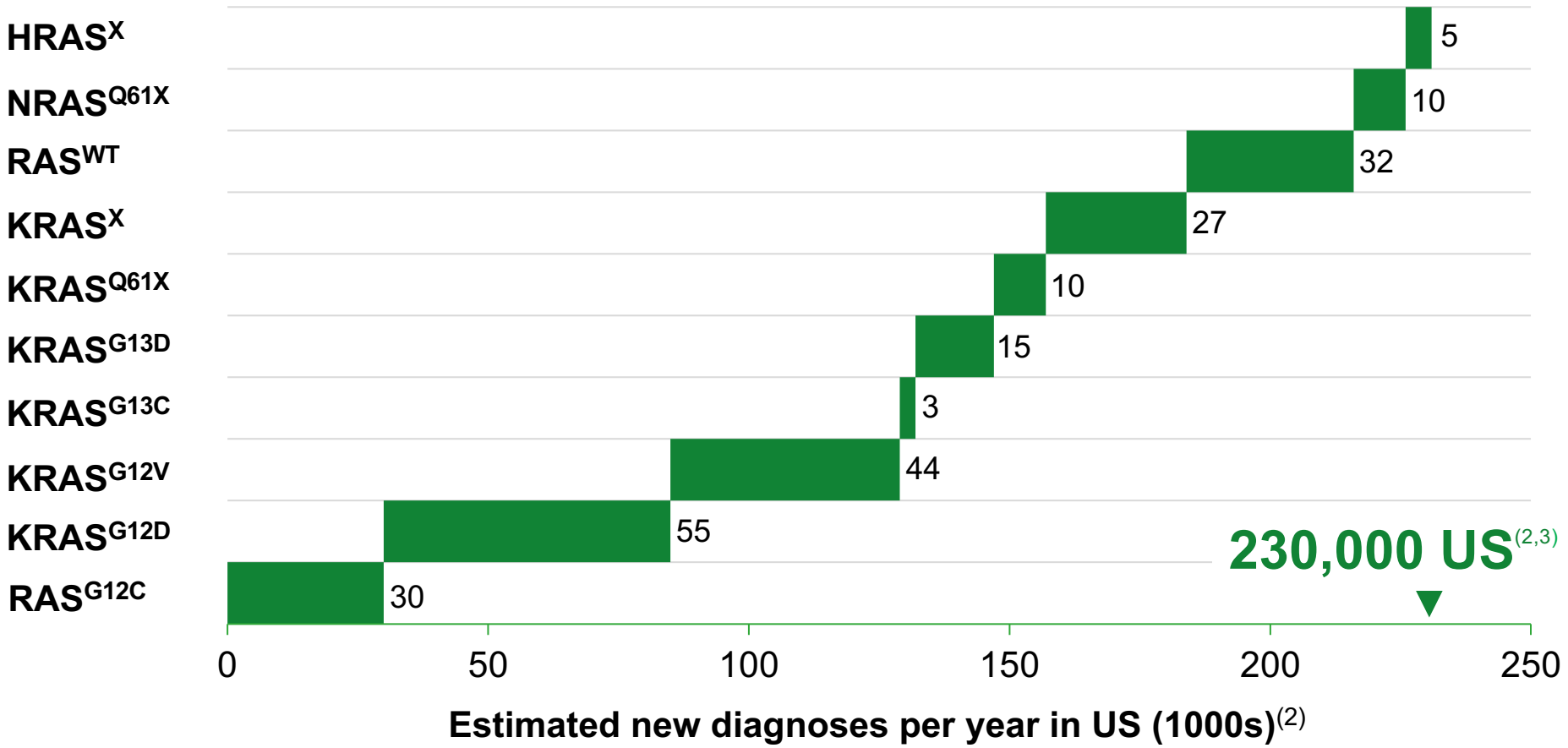
2.
RAS(ON) form drives oncogenic signaling



3.
Natural circuits are drug resistance pathways, requiring companion drugs for deep and durable responses

Targeted Therapies Needed for Common, Serious, Genetically-Defined RAS-Addicted Cancers

Tumor Addiction[1]:

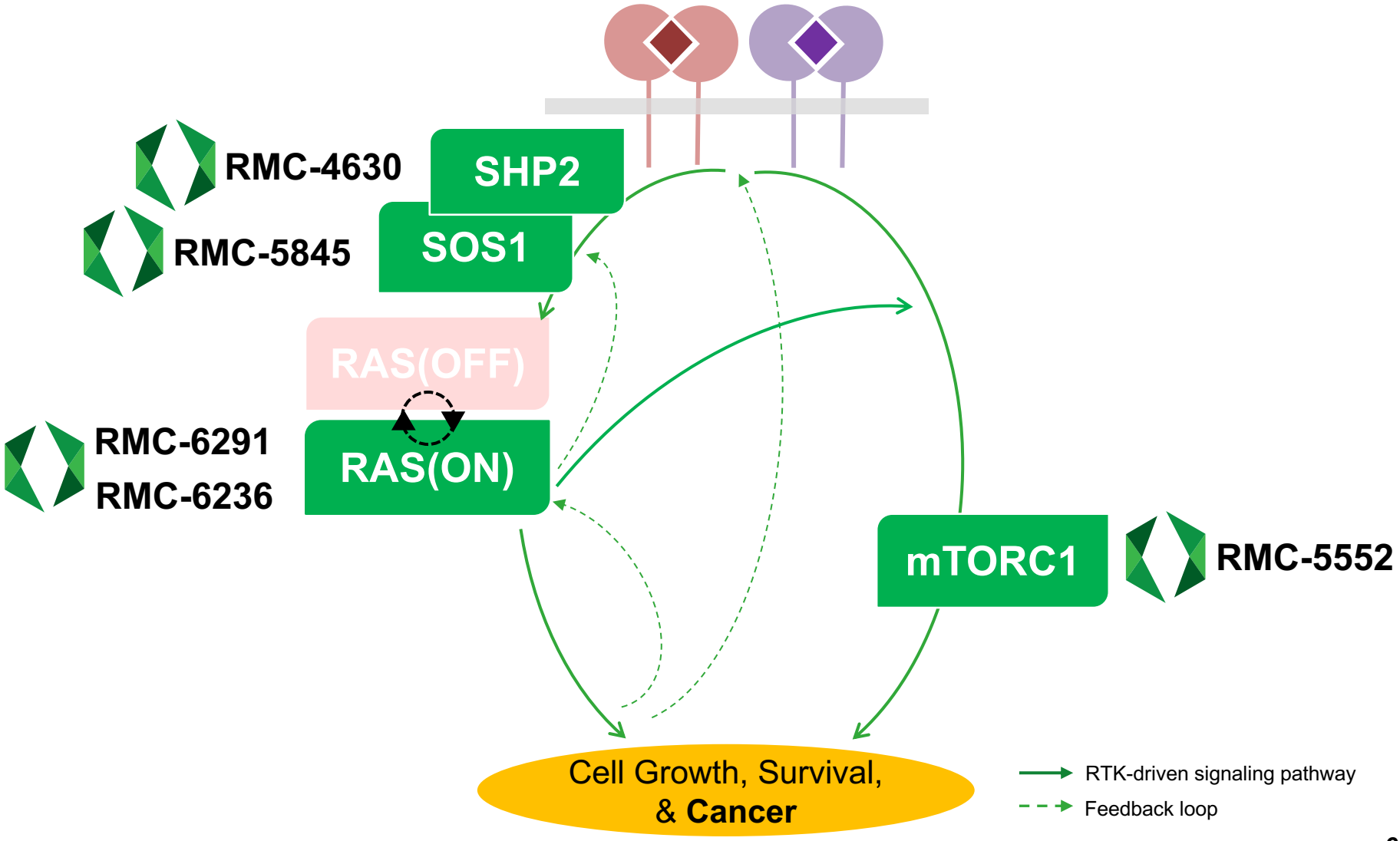


(1) $HRAS^{X}$ = all HRAS mutants; $NRAS^{Q61X}$ X = H, K, L, R, P; RAS^{WT} = $NF1^{LOF}$, RAS^{WTamp}, $BRAF^{class3,}$ and $PTPN11^{MUT}$; $KRAS^{X}$ X = G12A, G12R, G12S and A146T; $KRAS^{Q61X}$ X = H, K, L; RAS^{G12C} includes $KRAS^{G12C}$ and $NRAS^{G12C}$

(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

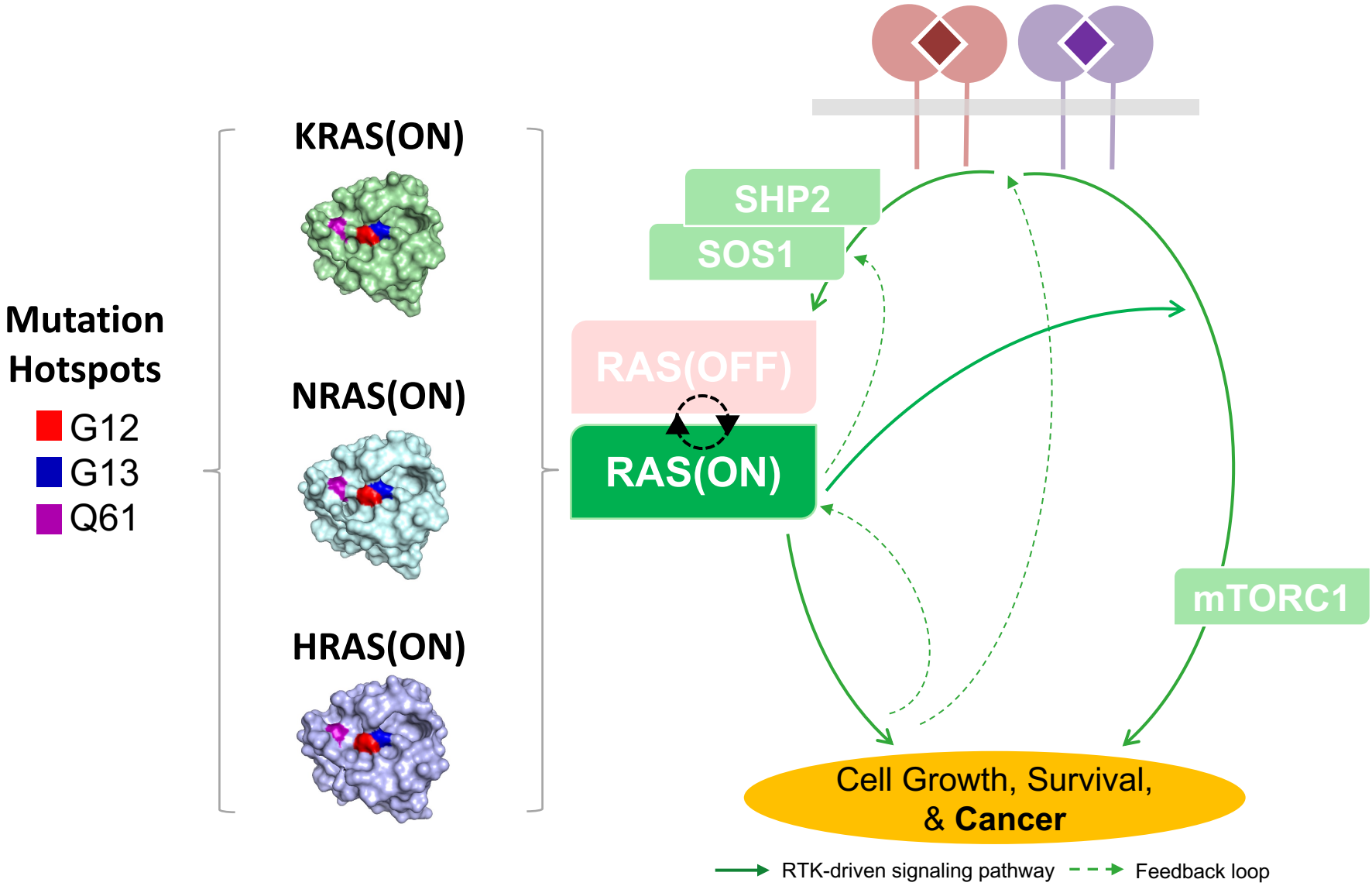
Strategic, Development-Stage Pipeline Targets Key Drivers of RAS Addiction and Resistance



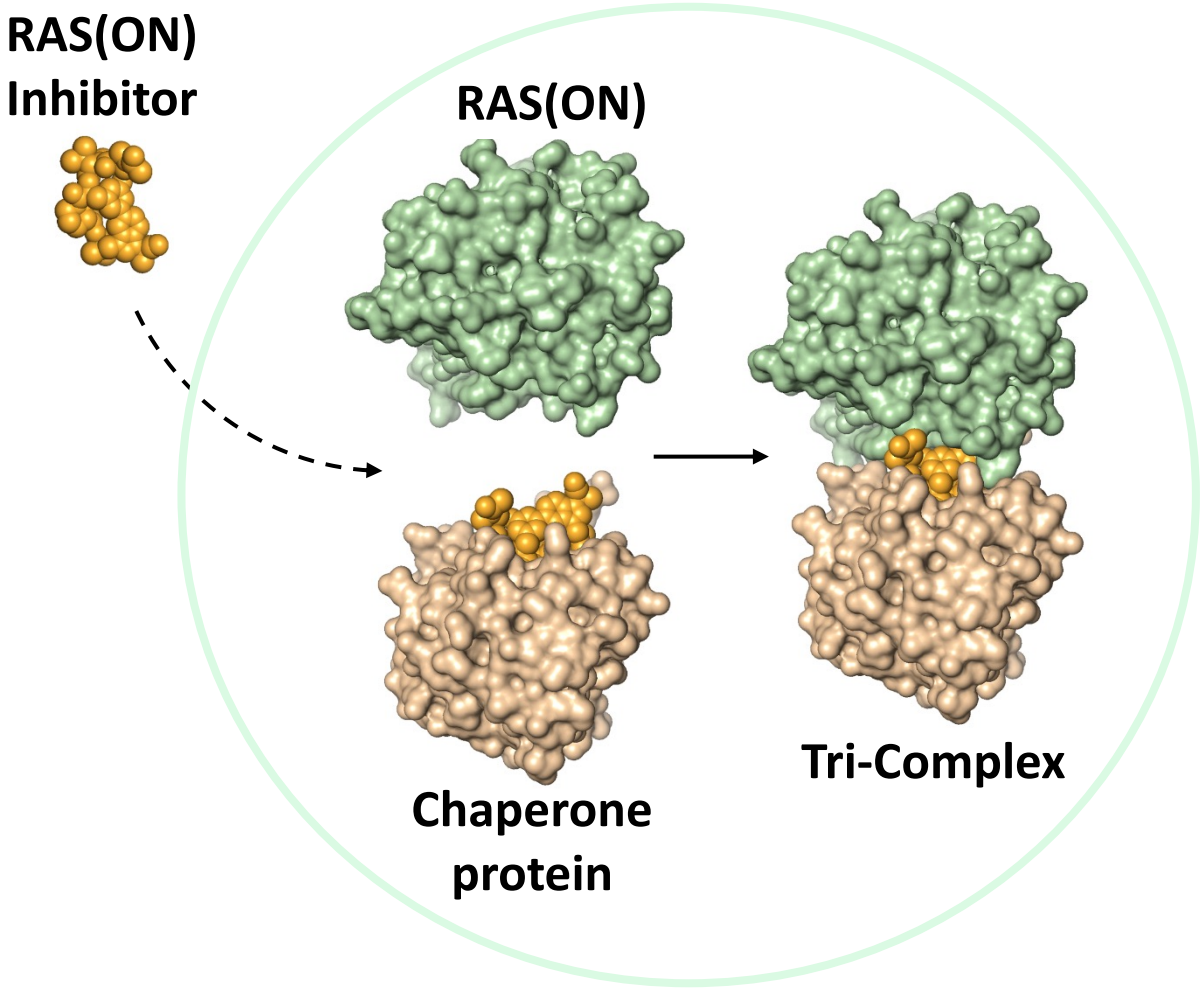
RAS(ON) Inhibitors

- RMC-6291 ($KRAS^{G12C}$)
- RMC-6236 (RAS^{MULTI})

Numerous RAS(ON) Variants Drive Cancer and RAS-Mediated Adaptive Resistance



RAS(ON) Inhibitors Block Signaling and Offer Potential Clinical Benefits



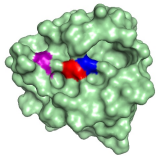
- Compelling mono and combination anti-tumor activity in preclinical *in vivo* models
- Predicted clinical benefits: range of sensitive tumor types, response rate, depth and/or duration of anti-tumor impact
- Proven reach to broad range of oncogenic RAS variants

RAS(ON) Inhibitors for Variants Driving Vast Majority of RAS-Addicted Cancers

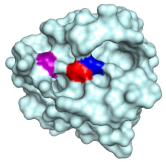
RAS variant
RAS(ON) inhibitor
Chaperone (Cyclophilin A)

RAS Variants and Inhibitors in Tri-Complexes[(1)]

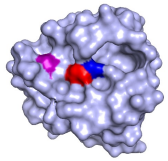
KRAS^{WT}

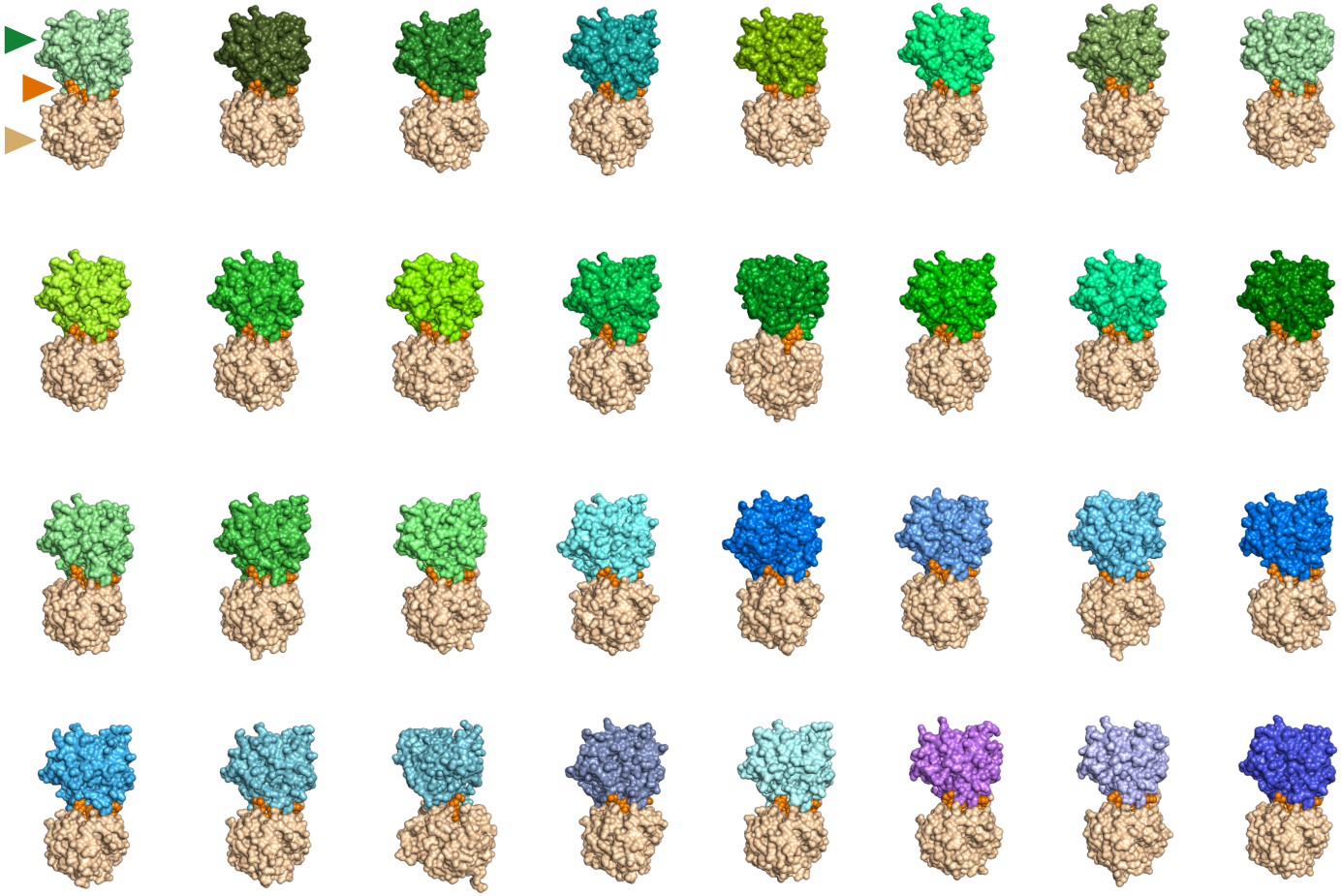


NRAS^{WT}



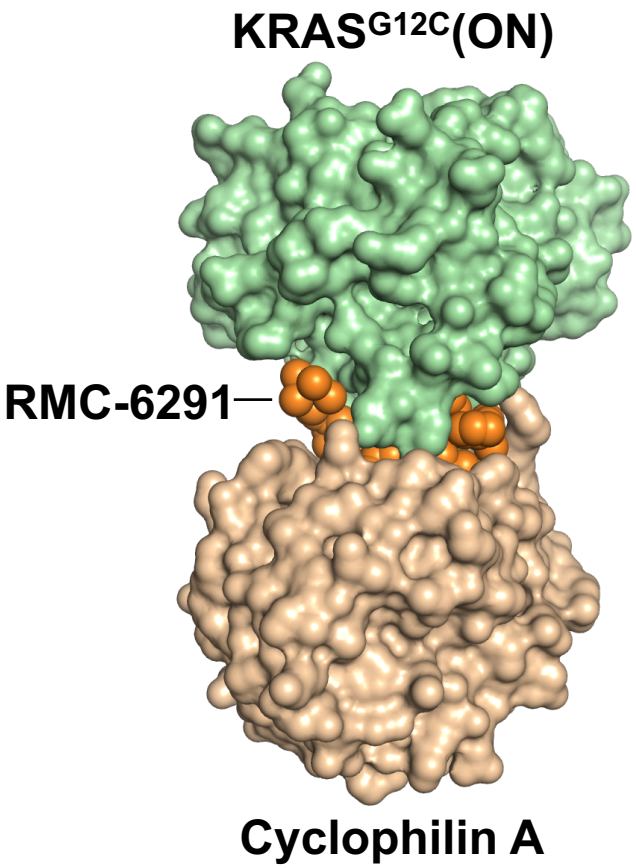
HRAS^{WT}





RVMD research
(1) Examples of surface representations of high-resolution co-crystal structures of RAS(ON) tri-complexes from RVMD collection. Some inhibitors are active against more than one RAS variant.

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

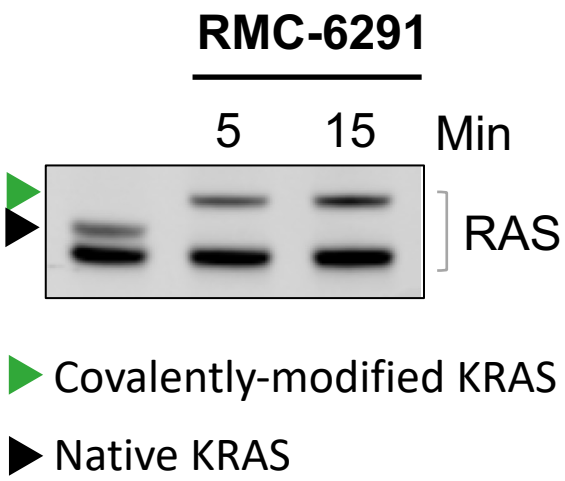


Potency for Tumor Cell Inhibition	
pERK (NCI-H358, IC_{50}, nM)[(1)]	0.7
CTG (NCI-H358, IC_{50}, nM)	0.09
Target Selectivity and Safety	
Covalent bond: k_{inact}/K_i	> 20,000
Selectivity	
• Over RAS-independent cell	> 1000X
• Over RAS^{WT}-dependent cell	> 1000X
Off-target safety panel and cysteinome screen	Low Risk
PK/ADME	
Oral %F (multiple species)	33-60
Metabolic clearance (hepatocytes, multiple species)	Low to Moderate

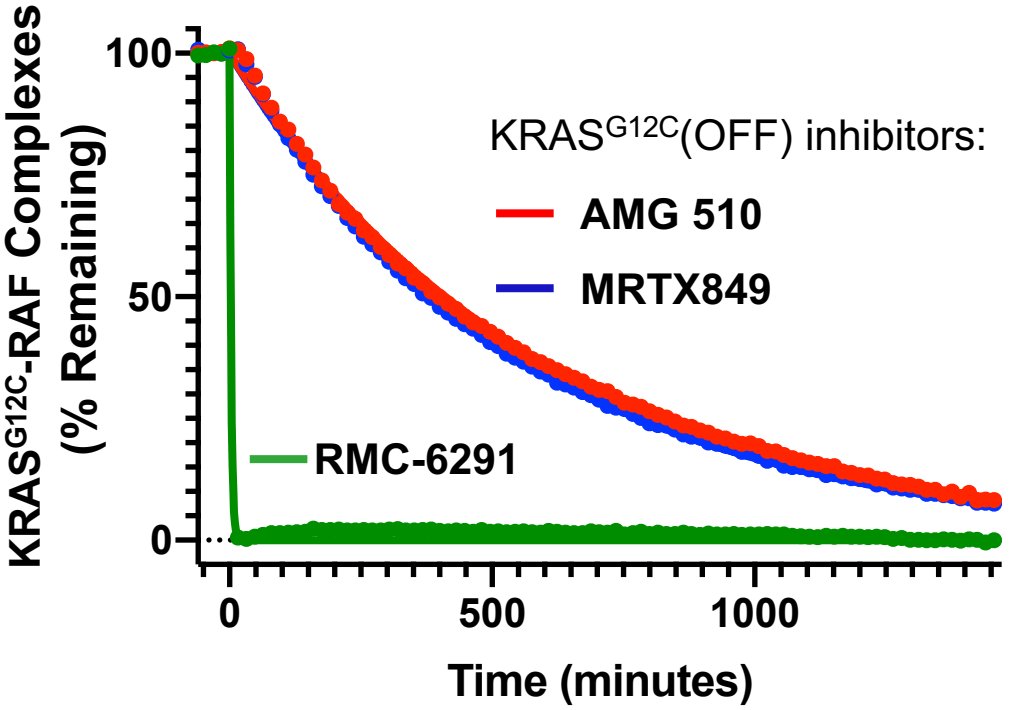
RVMD preclinical research
(1) KRAS^{G12C}-driven cell line; NRAS^{G12C}-driven line also subnanomolar

RMC-6291 Cellular Signature: Rapid Binding and Immediate Termination of RAS Signaling

$KRAS^{G12C}$ Binding

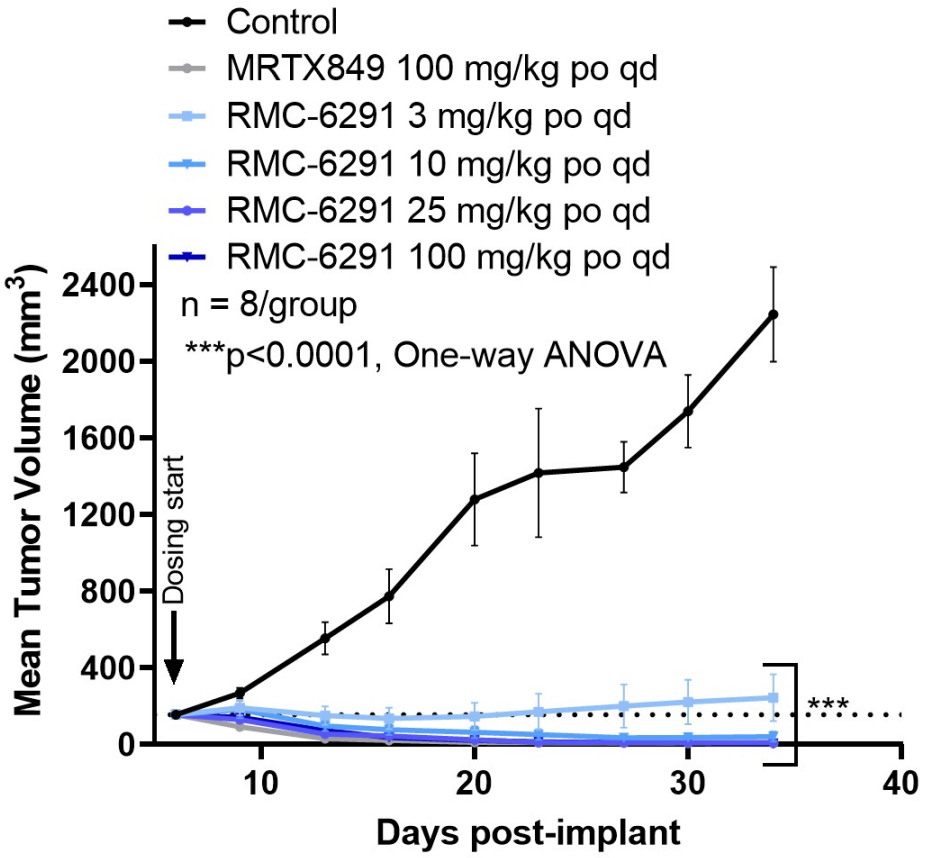


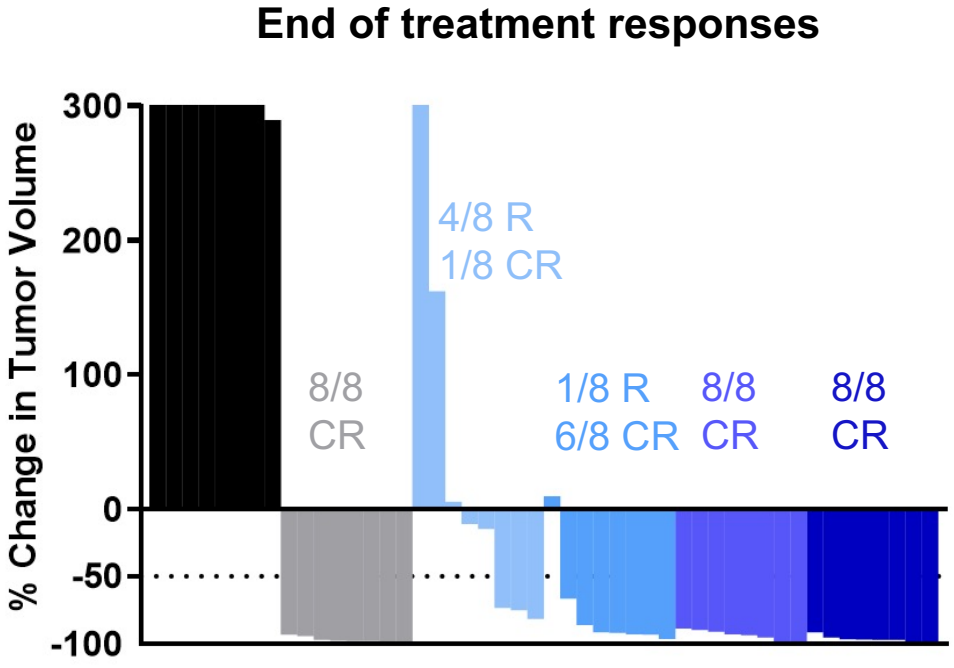
$KRAS^{G12C}$-RAF Signaling



RMC-6291: Deep Regressions of KRAS^{G12C} NSCLC Xenografts

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



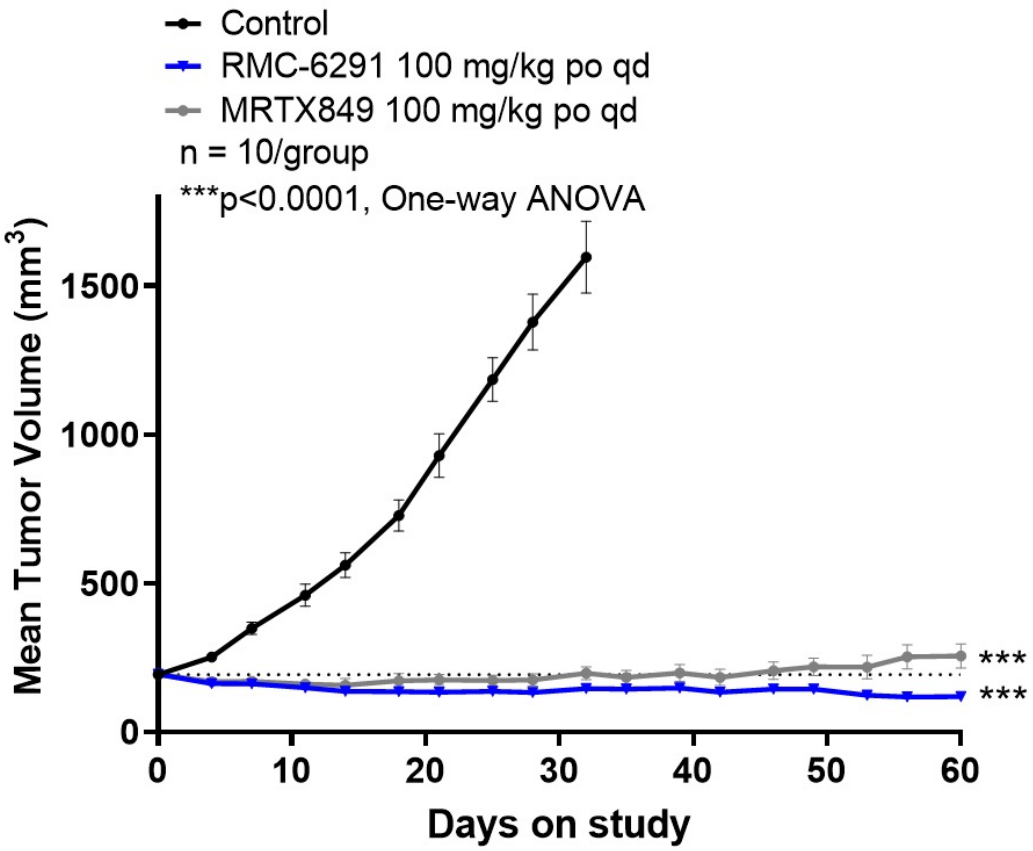


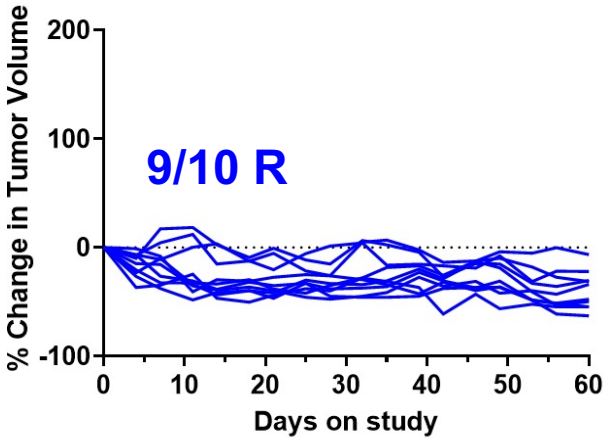
CR = number of regressions ≥80% from initial
R = tumor volume reduction ≥10% from initial
Each animal represented as a separate bar

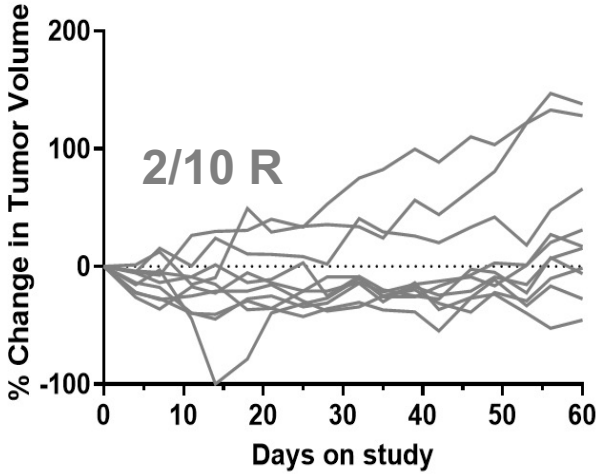
RVMD preclinical data
All treatments well tolerated
CDX = cell line-derived xenograft
NSCLC = Non-small cell lung cancer

RMC-6291: Durable Regressions of KRAS^{G12C} NSCLC Patient-Derived Xenografts

LUN092 PDX (NSCLC, KRAS$^{G12C/WT}$)







RVMD preclinical research
All treatments well tolerated
PDX = patient-derived xenograft
NSCLC = Non-small cell lung cancer

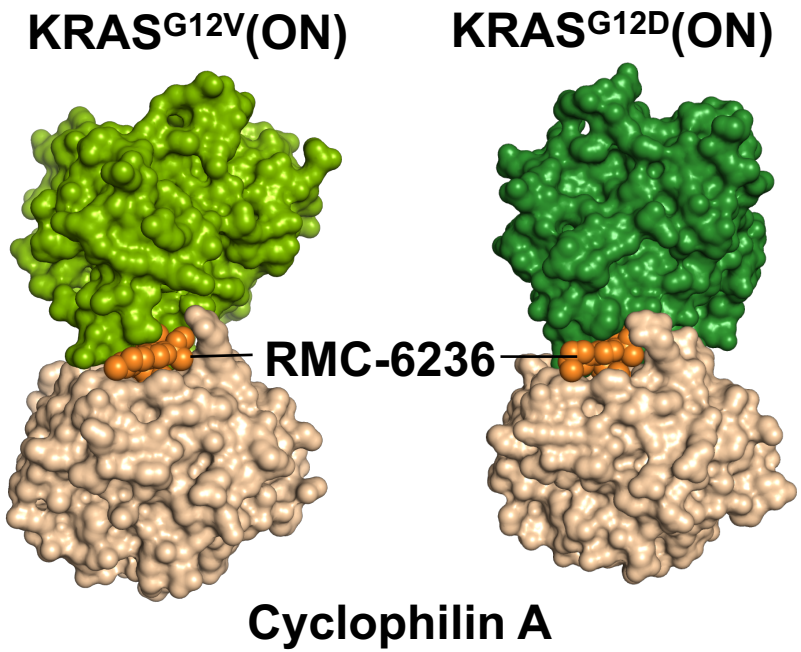
R = number of regressions ≥10% from initial
Each animal represented as a single line

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 • Dual selectivity for $KRAS^{G12C}$/$NRAS^{G12C}$ • Deep and durable responses *in vivo*

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



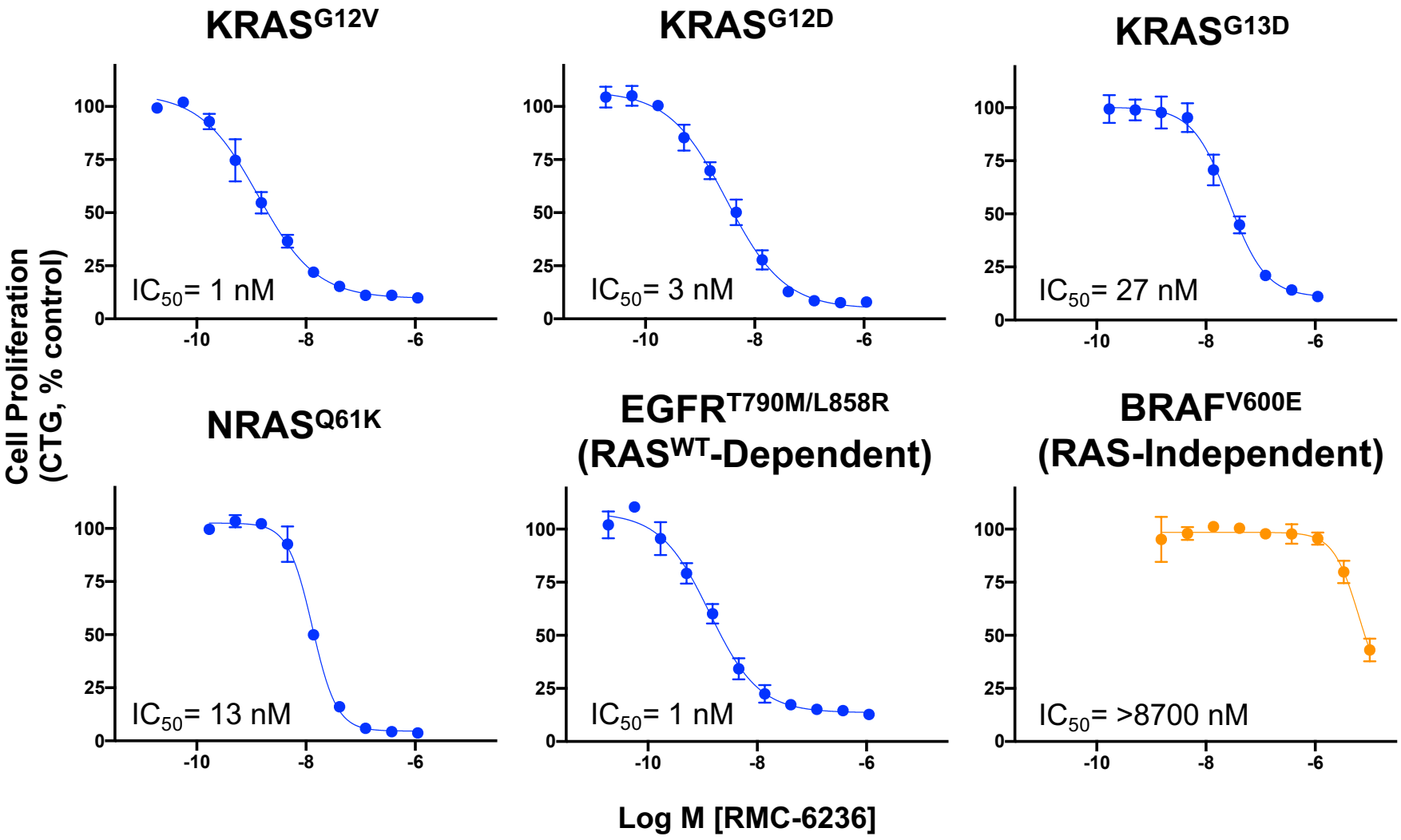
Potency for Tumor Cell Inhibition	
pERK (RAS-dependent, IC_{50}, nM)[1]	0.4-3
CTG (RAS-dependent, IC_{50}, nM)[1]	1-27

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: Potent and Selective Inhibitor of Diverse RAS-Dependent Tumor Cell Lines



Examples from RVMD preclinical research

Numerous Unmet Needs in RAS-Addicted Cancers May be Served by a RAS^{MULTI} Inhibitor

mutant-selective inhibitors unlikely

e.g., KRAS^{G12V}, KRAS^{G12A}

cancer drivers that depend on RAS^{WT}

e.g., KRAS^{WTamp}, BRAF^{class3}

Oncogenic RAS Mutants

RMC-6236

RAS^{WT} Isoforms

mutant-selective inhibitors in future^

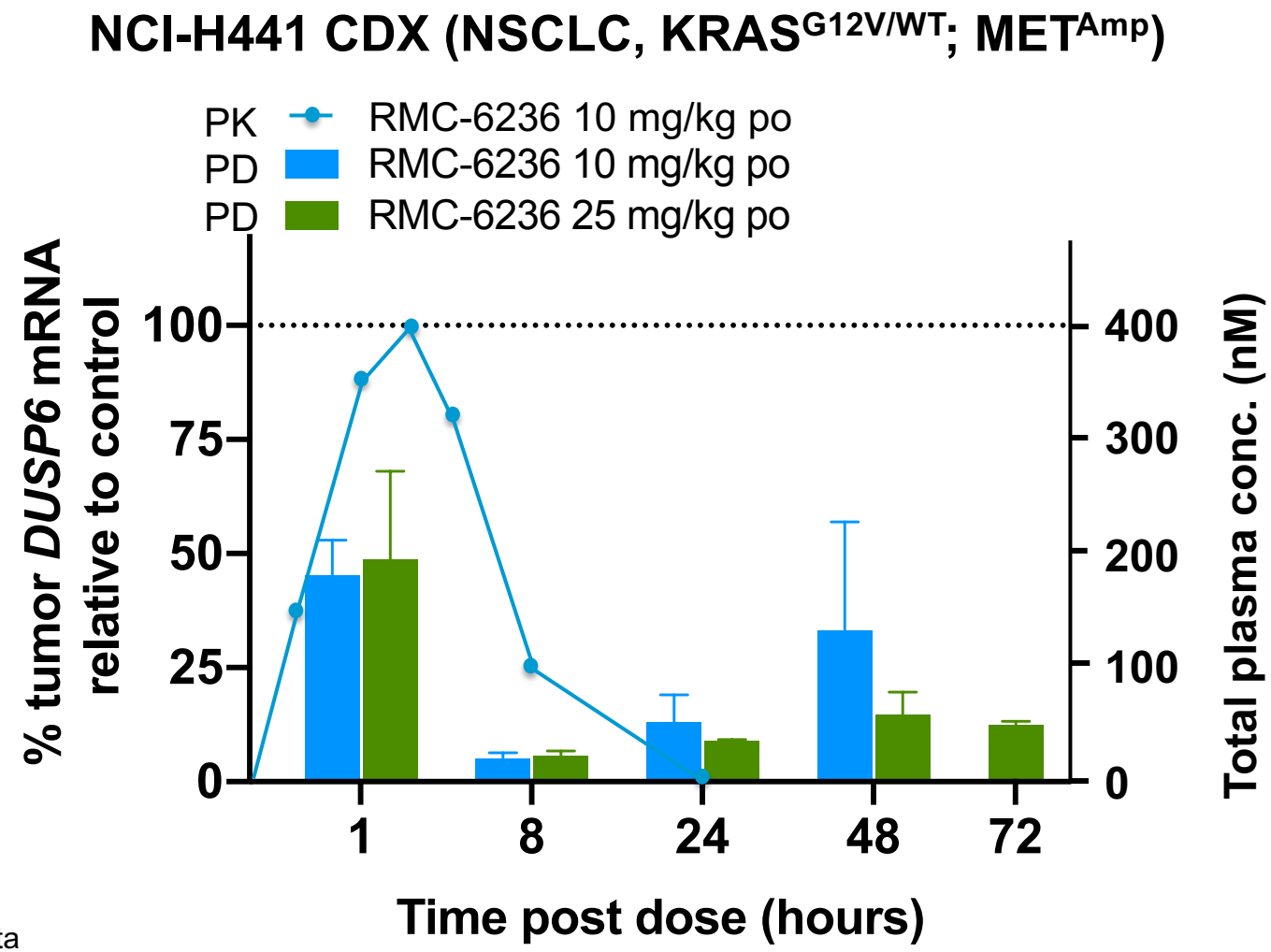
e.g., KRAS^{G12D}, KRAS^{G13C}

RAS-mediated adaptive resistance

Escape from targeted drugs

^ Parallel product paradigm

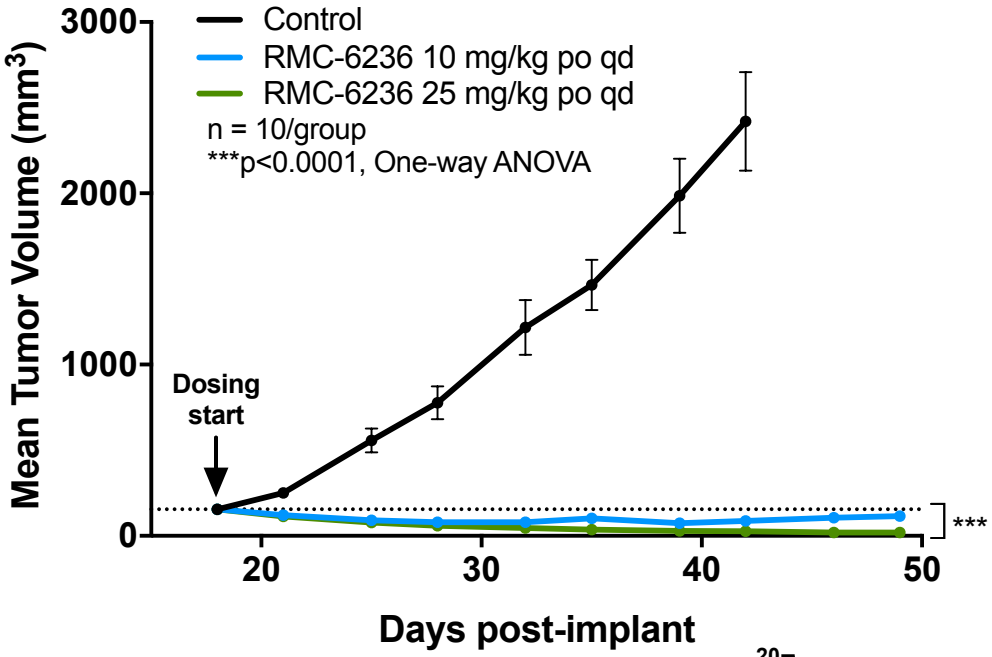
RMC-6236: Single Dose Induced Deep and Sustained RAS Pathway Inhibition *in Vivo*

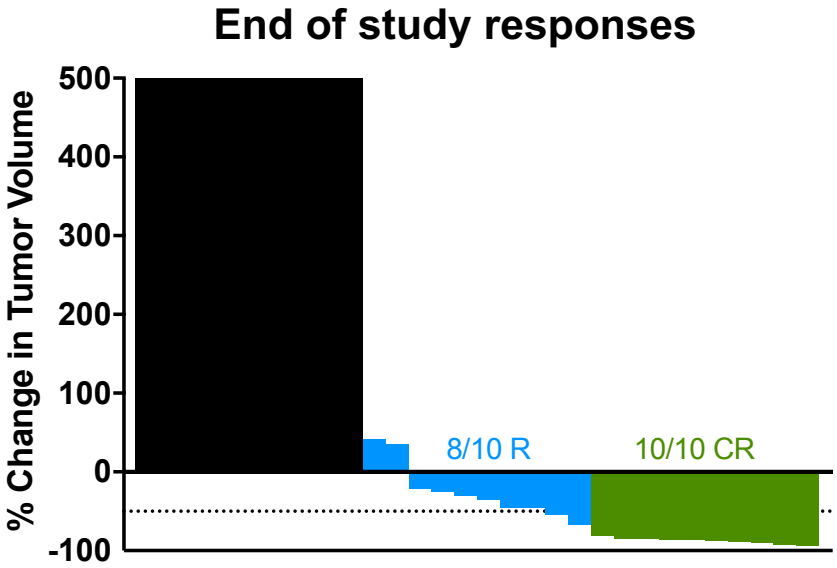


RVMD preclinical data
CDX = cell line-derived xenograft
NSCLC = Non-small cell lung cancer

RMC-6236: Deep Regressions of KRAS^{G12V} NSCLC Xenografts; Well Tolerated

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





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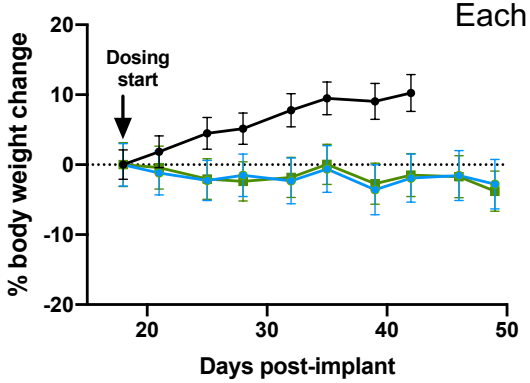
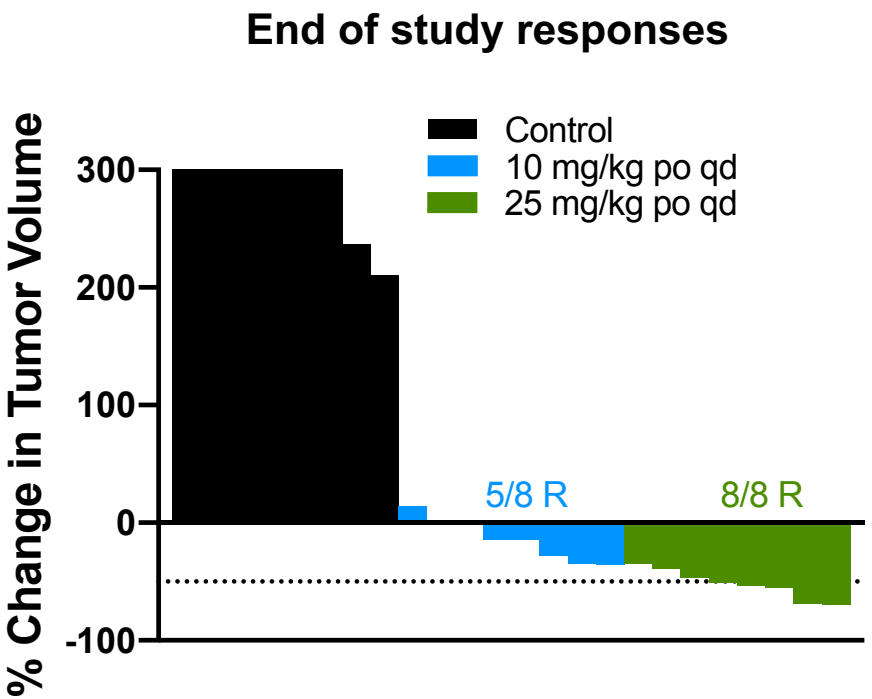
R = tumor volume reduction ≥10% from initial
Each animal represented as a separate bar



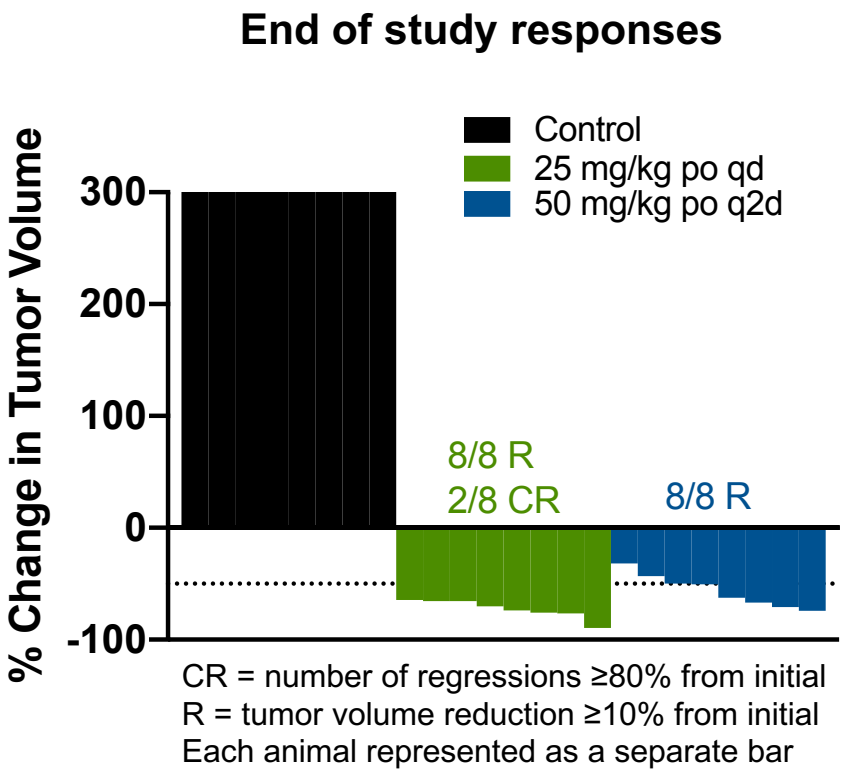
RVMD preclinical data
CDX = cell line-derived xenograft
NSCLC = Non-small cell lung cancer

RMC-6236: Deep Regressions of KRAS^{G12V} Pancreatic and Colorectal Cancer Xenografts

Capan-2 CDX (PDAC, KRAS$^{G12V/WT}$)



SW403 CDX (CRC, KRAS$^{G12V/WT}$)

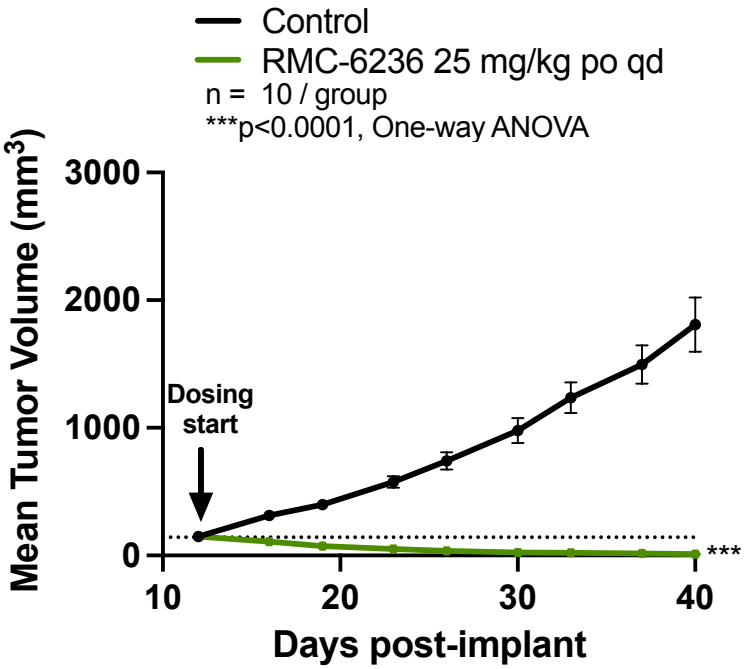


CR = number of regressions ≥80% from initial
R = tumor volume reduction ≥10% from initial
Each animal represented as a separate bar

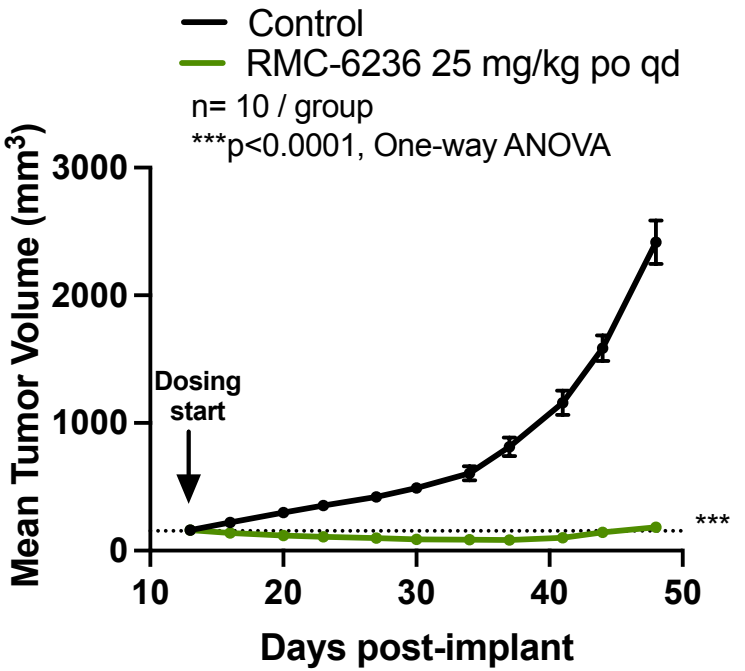
RVMD preclinical data
All treatments well tolerated
CDX = cell line-derived xenograft
PDAC = pancreatic ductal adenocarcinoma
CRC = colorectal cancer

RMC-6236: Anti-Tumor Activity in KRAS^{G12D} Pancreatic and Colorectal Cancer Xenografts

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

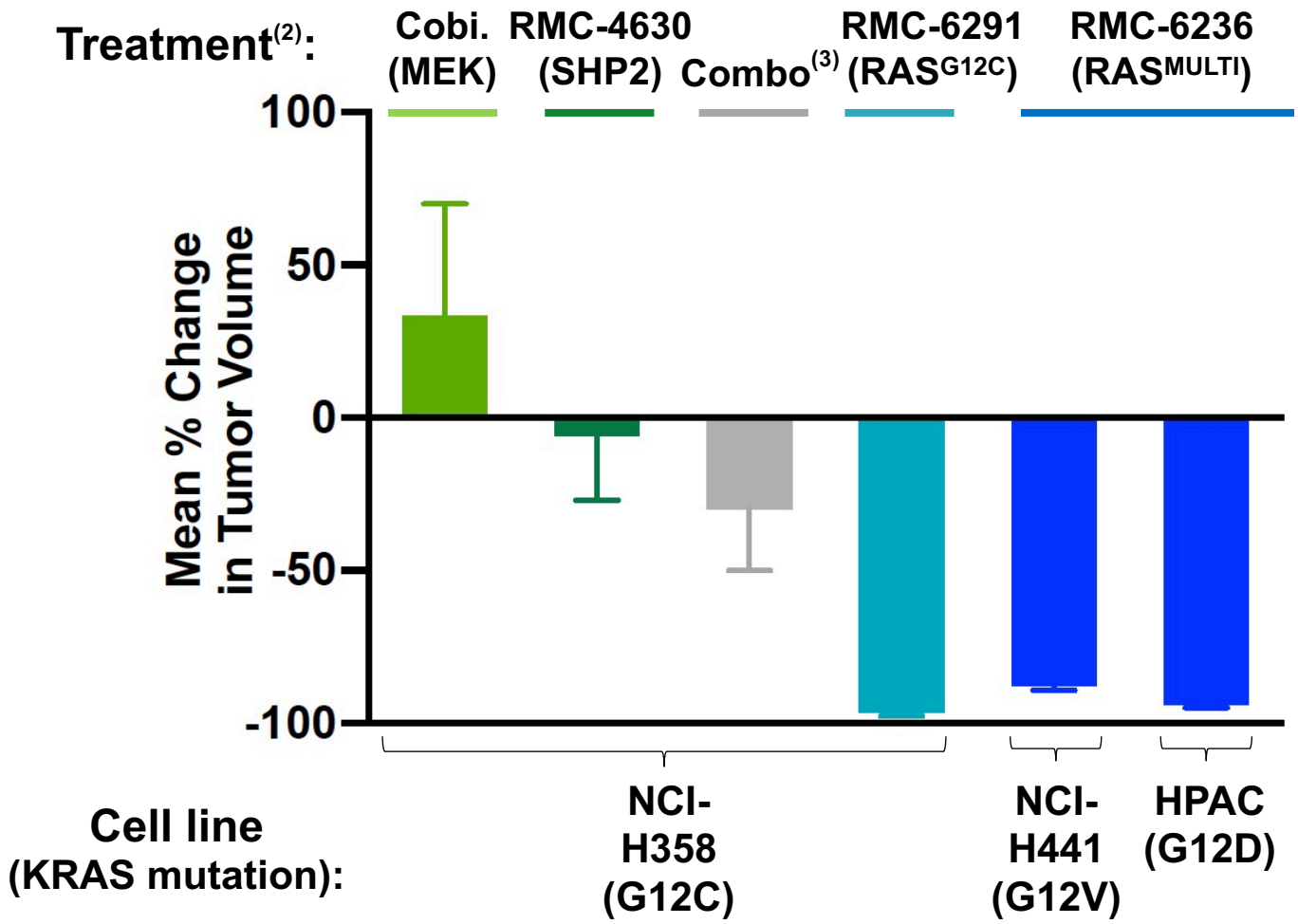


GP2d CDX (CRC, KRAS$^{G12D/WT}$)



RVMD preclinical research
All treatments well tolerated
CDX = cell line-derived xenograft
PDAC = Pancreatic ductal adenocarcinoma
CRC = colorectal cancer

Best Responses of RAS^{MUTANT} Tumor Xenografts with Tolerated[(1)] Treatment Regimens



RVMD preclinical data aggregated from representative experiments; n= 9-10 per group; error bars are SEM

(1) All body weights at end of treatment were within +/-10% of starting weights

(2) Doses (po.): Cobi. (cobimetinib) - 2.5 mg/kg/day; RMC-4630 - 30 mg/kg/day; RMC-6291 - 100 mg/kg/day; RMC-6236 - 25 mg/kg/day

(3) Combo: Cobi. (cobimetinib) - 2.5 mg/kg/day + RMC-4630 - 30 mg/kg/day

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*

Clinical	• IND submission projected 1H2022
	• Broad thesis:
	  • Sensitivity of numerous RAS genotypes across multiple patient segments
	  • Beneficial combinations with RAS Companion Inhibitors

Parallel Product Strategy for RAS(ON) Inhibitors

Development Candidate	RAS(ON) Target	Lead Status
RMC-6291	$KRAS^{G12C}/NRAS^{G12C}$	
RMC-6236	$KRAS^{G12V}$	
	$KRAS^{X}$	
	$NRAS^{Q61X}$	
	$HRAS^{X}$	
	RAS^{WT}	
	$KRAS^{G12D}$	**Lead Op.**
	$KRAS^{G13C}$	**Lead Op.**
	$KRAS^{G13D}$	
	$KRAS^{Q61H}$	

RAS^{MUTANT}-selective

RAS^{MULTI}

$HRAS^{X}$ = 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

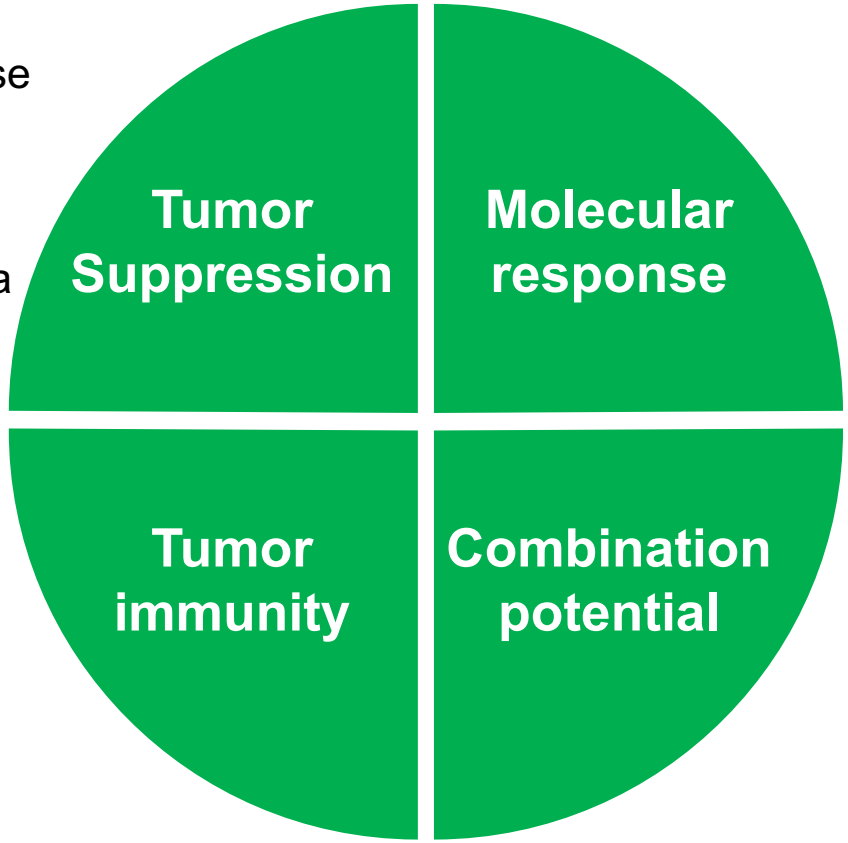
RAS Companion Inhibitors

- RMC-4630 (SHP2)
- RMC-5552 (mTORC1/4EBP1)
- RMC-5845 (SOS1)

Initial Evidence that RMC-4630 (SHP2) is an Active Anti-Tumor Drug Candidate[1]

- Clinical tumor regressions and disease control observed in $KRAS^{MUTANT}$ NSCLC[2]
- Complete and durable response observed in a $NF1^{LOF}$ uterine cancer patient[3][4]

- Evidence of favorable modulation of tumor immune microenvironment in preclinical and clinical samples[4]



- Clinical reduction in driver oncogene frequency (ctDNA) in $KRAS^{G12C}$ NSCLC and $NF1^{LOF}$ gynecologic cancers[5]

- Acceptable preclinical tolerability and additive anti-tumor effects with multiple agents
- Currently evaluating clinical tolerability and activity in combination with multiple drugs for RAS-dependent tumors, including both mutant-selective and non-mutant-selective agents

(1) RMC-4630/SAR442720 under 2018 partnership. Sanofi reimburses approved development costs and RVMD/Sanofi have 50/50 U.S. profit share.
(2) Koczywas et al. American Association for Cancer Research Annual Meeting 2021, Virtual Meeting I; April 10-15, 2021. Presentation LB001.
(3) Kelsey. 2nd Annual RAS-Targeted Drug Development Conference; September 14-16, 2020.
(4) Chen et al. American Association for Cancer Research Annual Meeting 2021, Virtual Meeting I; April 10-15, 2021. Poster LB050.
(5) Hayes et al. American Association for Cancer Research Annual Meeting 2021, Virtual Meeting I; April 10-15, 2021. Poster LB054.
ctDNA = circulating tumor DNA

SANOFI

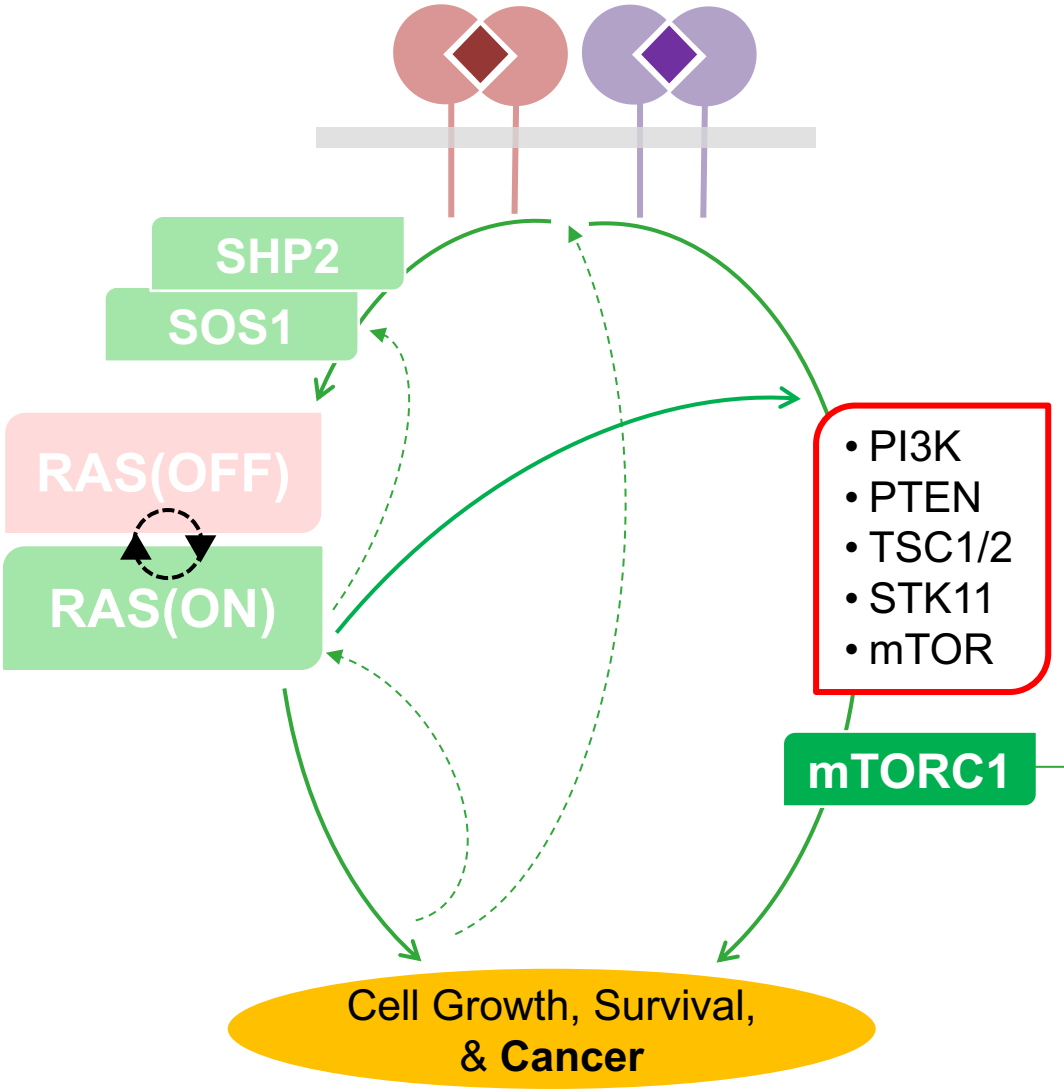
Central Clinical Thesis: RMC-4630 as Backbone for Rational, Mechanism-Based Combinations

RMC-4630 Combination Strategies		Compound	Collaborator	
"Clamp" RAS Pathway	MEK inhibitors	cobimetinib (Cotellic®)	Roche	Ph 2(1)
	ERK inhibitors	LY-3214996	Netherlands Cancer Institute	
Mutant-Selective Inhibitors	$KRAS^{G12C}$ inhibitors	sotorasib	AMGEN	Ph 1b
		TBA	AstraZeneca	
	RTK inhibitors	osimertinib (Tagrisso®)		Ph 1b(1)
Immune	Checkpoint inhibitors	pembrolizumab (Keytruda®)	SANOFI	Ph 1b

SANOFI

RMC-4630/SAR442720 under 2018 partnership
(1) Study sponsored by RVMD

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



RMC-5552

- Phase 1 dose escalation initiated
- 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

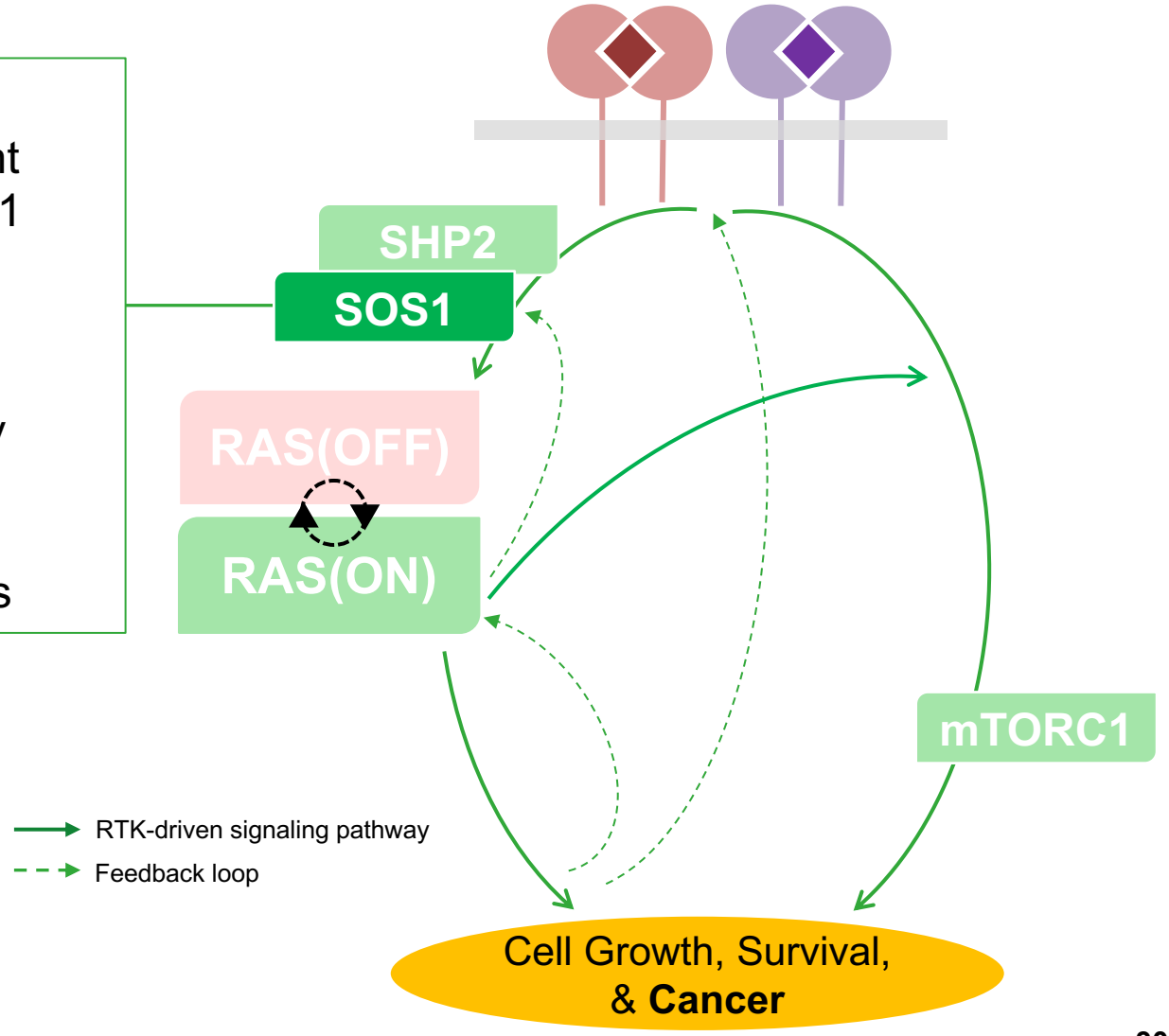
RTK-driven signaling pathway

Feedback loop

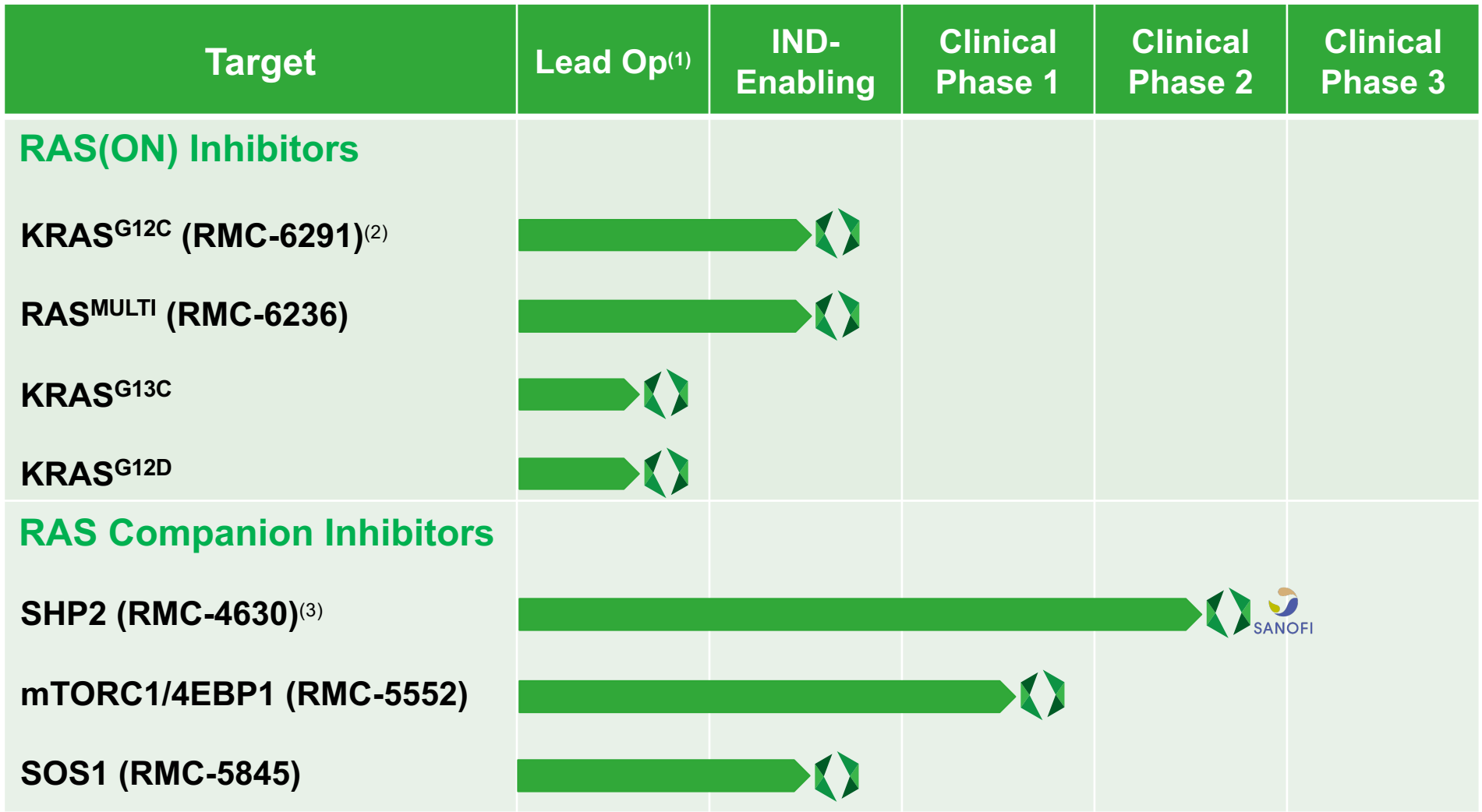
RMC-5845: Potent, Selective, Oral Inhibitor of SOS1, a Major Switch for RAS(OFF) to RAS(ON)

RMC-5845

- IND-enabling development
- Selective inhibitor of SOS1 over SOS2
- Suppresses switch from RAS(OFF) to RAS(ON)
- Well tolerated preclinically
- For select combination therapies for certain genetically-defined tumors



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)
(3) Expansion of the RMC-4630 + cobimetinib portion of RMC-4630-02 study at the recommended Phase 2 dose and schedule represents Phase 2 in this chart

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)**	
RMC-4630 monotherapy dose escalation safety data set	✓
Selection of combination dose for further testing of RMC-4630 + sotorasib	2H21
Preliminary safety and clinical activity data for RMC-4630 + cobimetinib expansion cohorts in $KRAS^{MUTANT}$ CRC	2022
RP2DS for further testing of RMC-4630 + pembrolizumab	1H21
Initial tolerability and PK data for RMC-4630 + osimertinib	2H21
• **mTORC1/4EBP1 (RMC-5552)**	
Start dosing patients with monotherapy	✓
Initial safety, PK and single agent activity data	2022
• **SOS1 (RMC-5845)**	
Submit IND	2H21

Financial Information

Financial Position	
Cash, cash equivalents and marketable securities @ 3/31/2021	**$681.6M[(1)]**

(1) Includes proceeds from the February 2021 public offering of common stock, whereby the Company issued and sold 6.7 million shares of its common stock at a price of $45.00 per share for net proceeds of $281 million, after deducting underwriting discounts and commissions and offering expenses.

Financial Guidance
2021 GAAP net loss of $170 million to $190 million[(2)]

(2) Includes non-cash stock-based compensation of $20 million to $25 million.

Translating Frontier Oncology Targets to *Outsmart Cancer*™