REVOLUTION MEDICINES

Translating Frontier Oncology Targets to *Outsmart Cancer*™

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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 filed with the Securities and Exchange Commission on November 12, 2020, 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.

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Summary

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

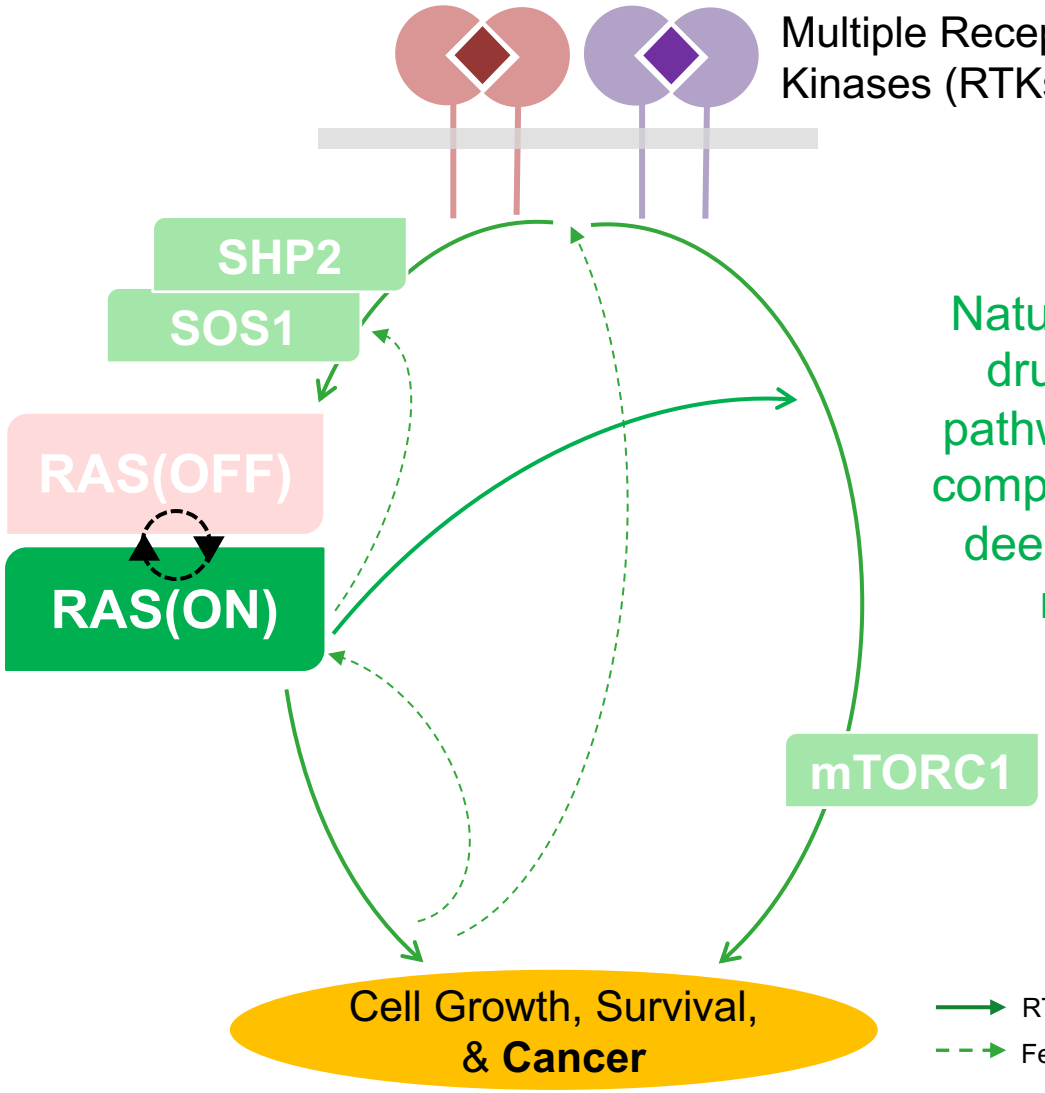
- **RAS(ON) Inhibitors** target diverse oncogenic RAS variants via highly differentiated profiles
  - ***RMC-6291 (KRAS^{G12C})*** *enters development*
  - ***RMC-6236 (RAS^{MULTI})*** *enters development*

- **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)*** *prepares to enter clinic*
  - ***RMC-5845 (SOS1)*** *enters development*

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

1.
Many RAS family variants underlie addiction

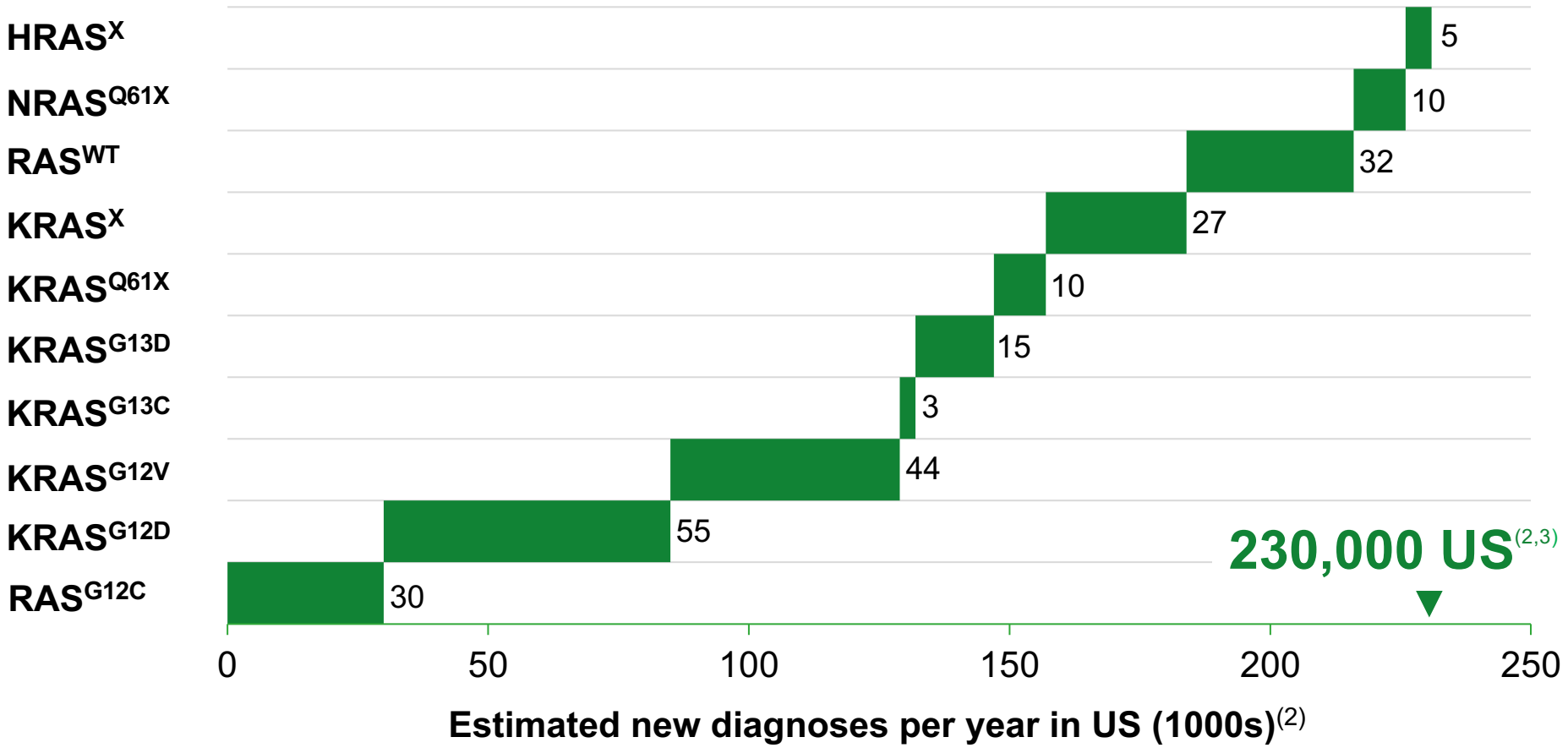
2.
RAS(ON) form drives oncogenic signaling



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]:

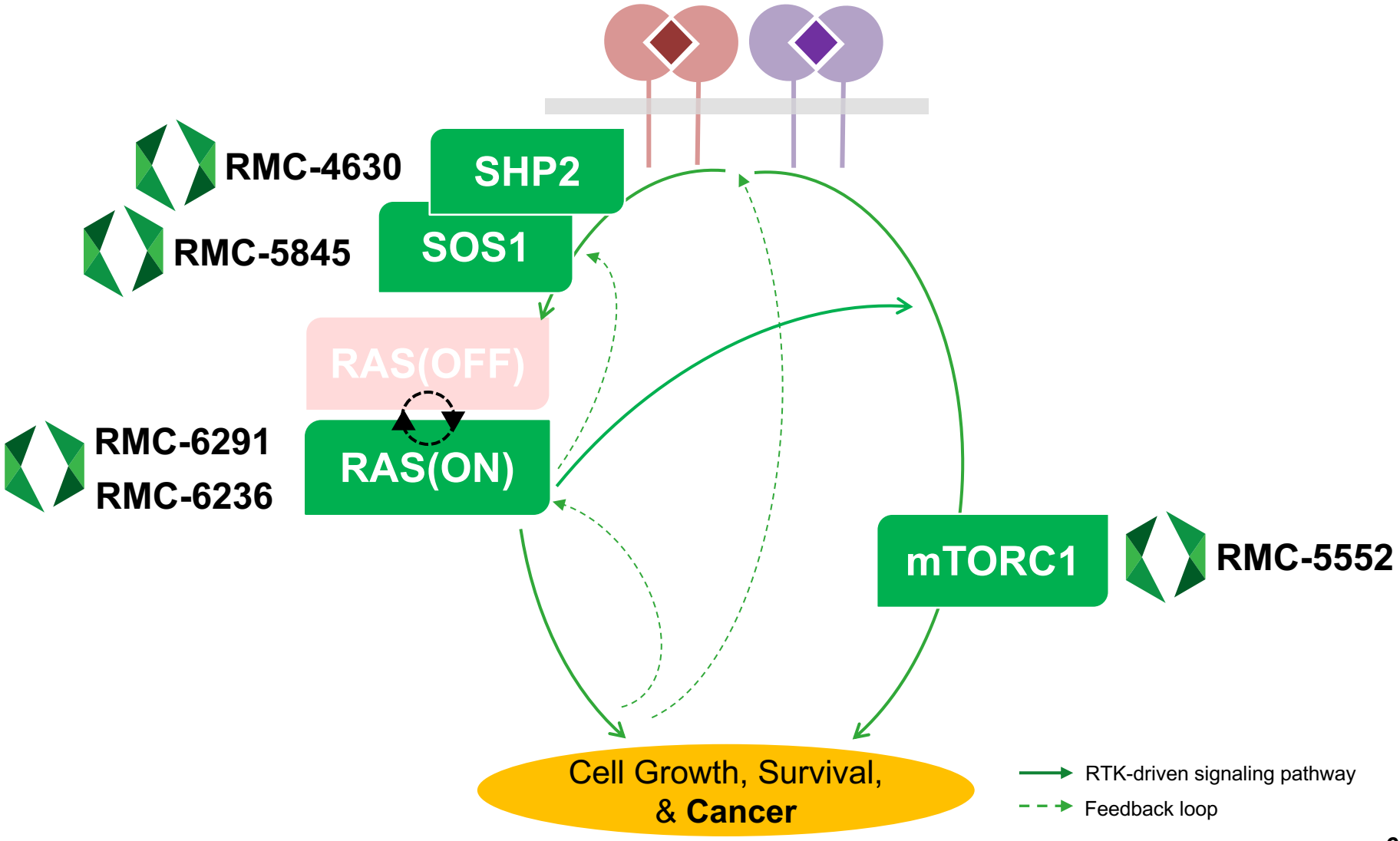


(1) $HRAS^{X}$ = all HRAS mutants; $NRAS^{Q61X}$ X = H, K, L, R, P; RAS^{WT} = $NF1^{LOF}$, RAS^{WTamp}, $BRAF^{class3,}$ and $PTPN11^{MUT}$; $KRAS^{X}$ X = G12A, G12R, G12S and A146T; $KRAS^{Q61X}$ X = H, K, L; RAS^{G12C} includes $KRAS^{G12C}$ and $NRAS^{G12C}$

(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

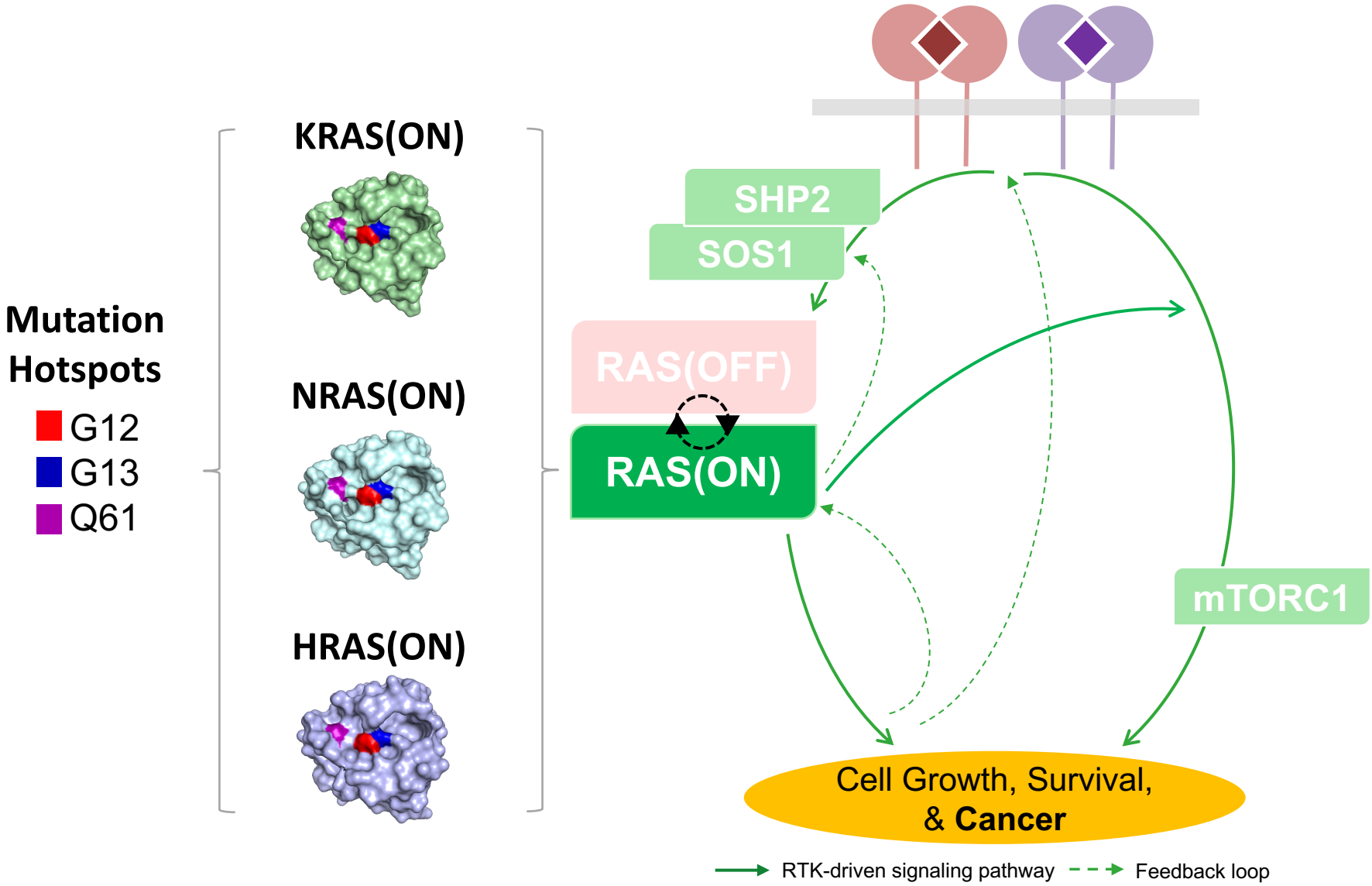
Strategic, Development-Stage Pipeline Targets Key Drivers of RAS Addiction and Resistance



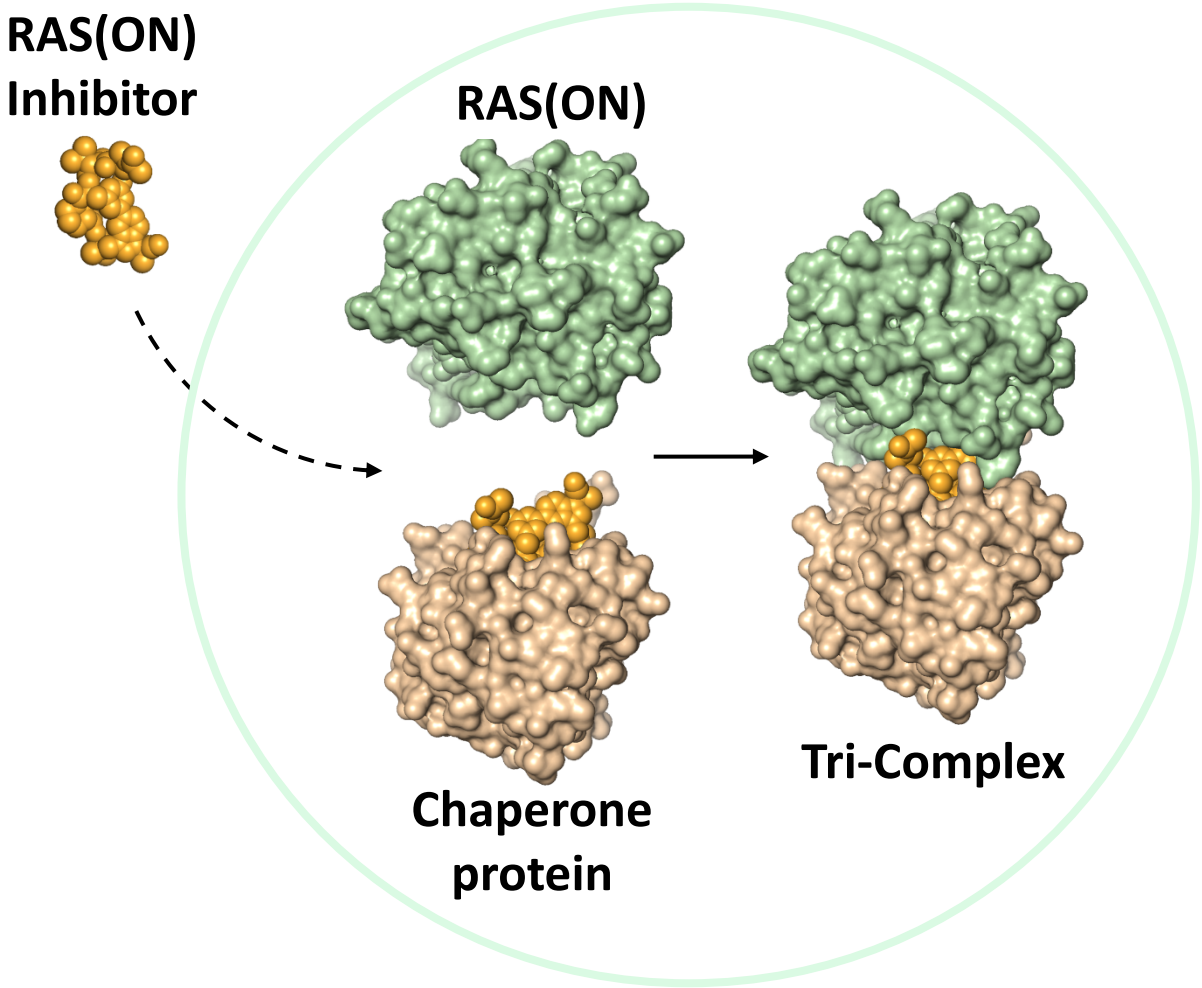
RAS(ON) Inhibitors

- 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



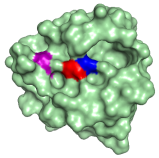
- Compelling mono and combination anti-tumor activity in preclinical *in vivo* models
- Predicted clinical benefits: range of sensitive tumor types, response rate, depth and/or duration of anti-tumor impact
- Proven reach to broad range of oncogenic RAS variants

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

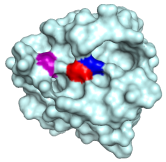
RAS variant
RAS(ON) inhibitor
Chaperone (Cyclophilin A)

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

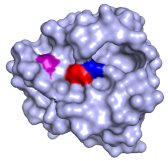
KRAS^{WT}

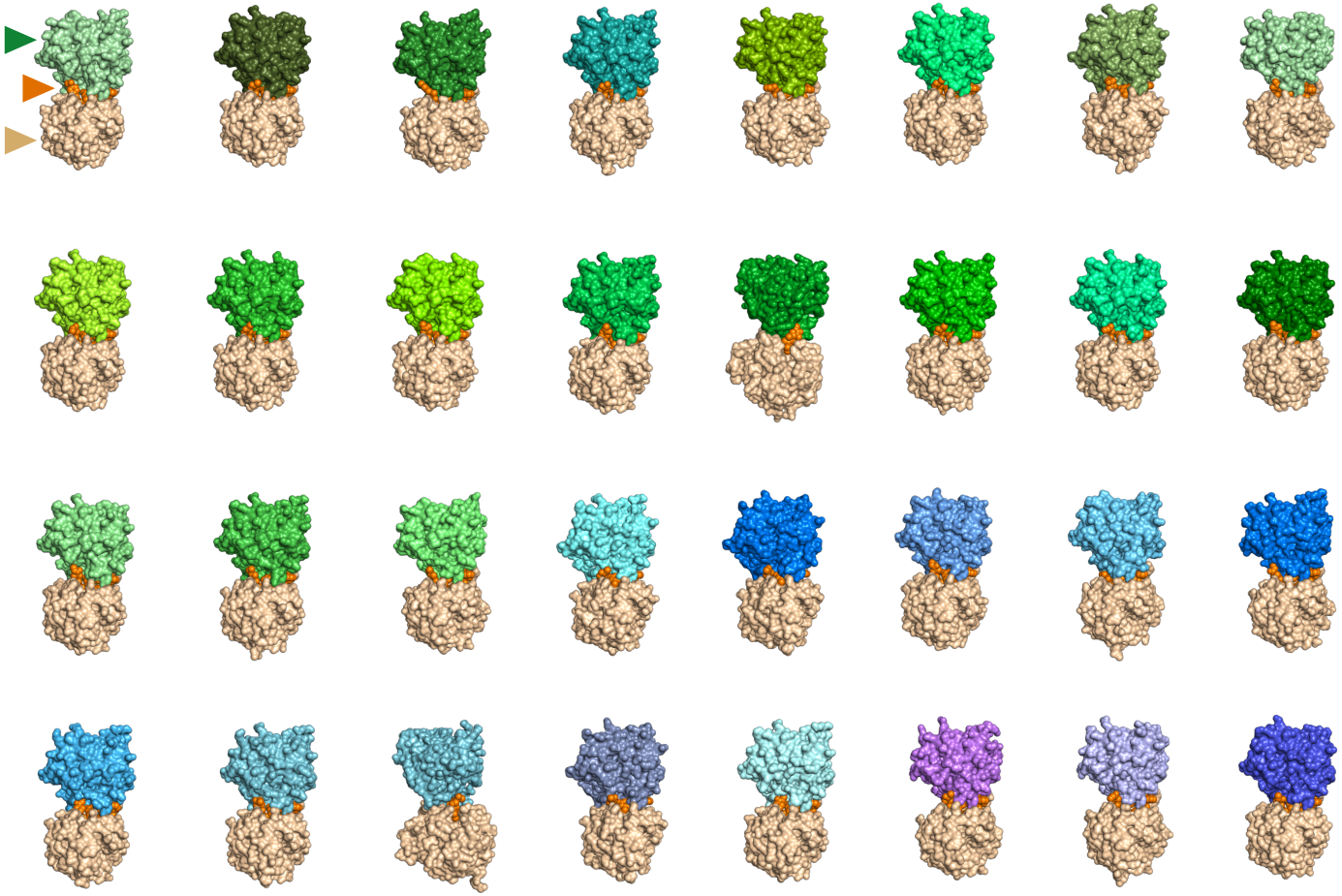


NRAS^{WT}



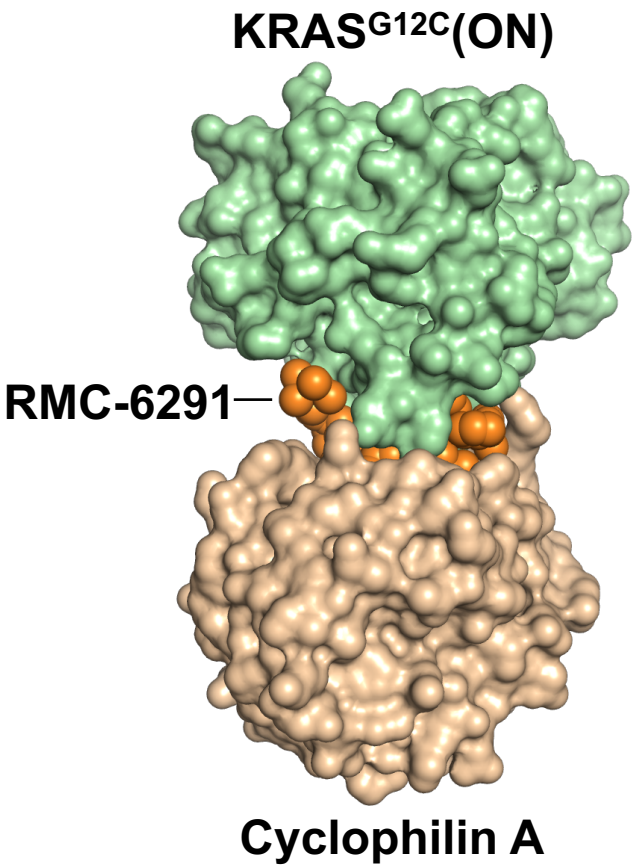
HRAS^{WT}





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, Highly Potent, Oral and Selective Tri-Complex Inhibitor of $KRAS^{G12C}$(ON)

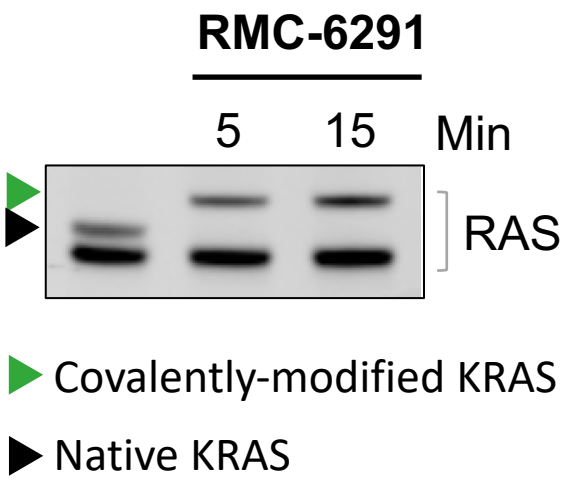


Potency for Tumor Cell Inhibition	
pERK (NCI-H358, IC_{50}, nM)(1)	0.7
CTG (NCI-H358, IC_{50}, nM)	0.09
Target Selectivity and Safety	
Covalent bond: k_{inact}/K_i	> 20,000
Selectivity	
• Over RAS-independent cell	> 1000X
• Over RAS^{WT}-dependent cell	> 1000X
Off-target safety panel and cysteinome screen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

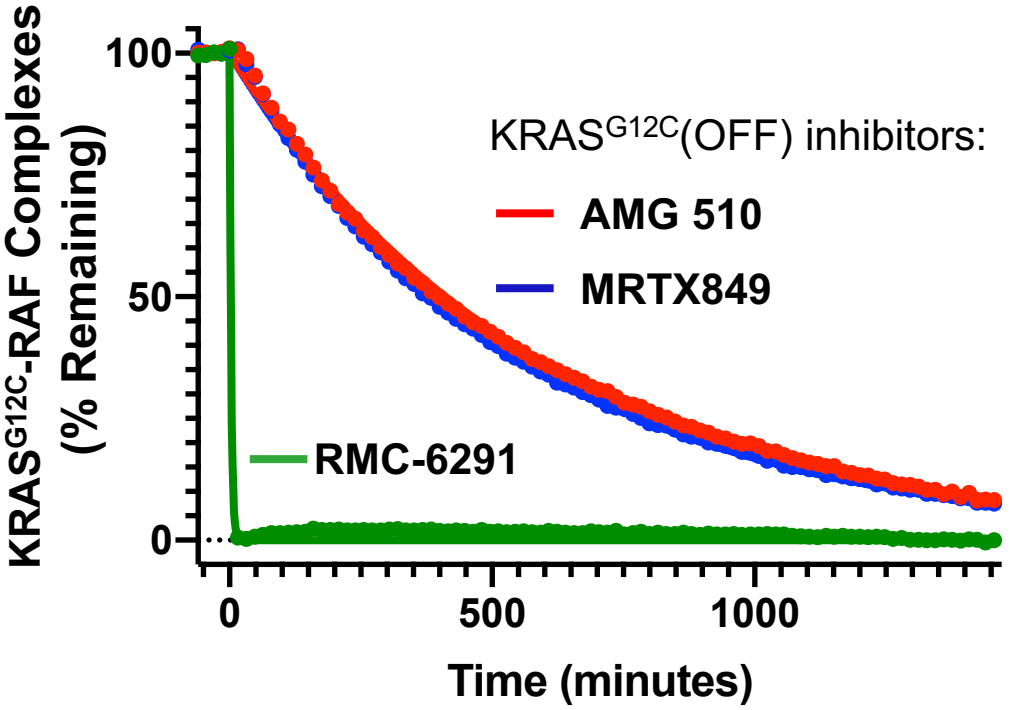
RVMD preclinical research
(1) $KRAS^{G12C}$-driven cell line; $NRAS^{G12C}$-driven line also subnanomolar

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

$KRAS^{G12C}$ Binding

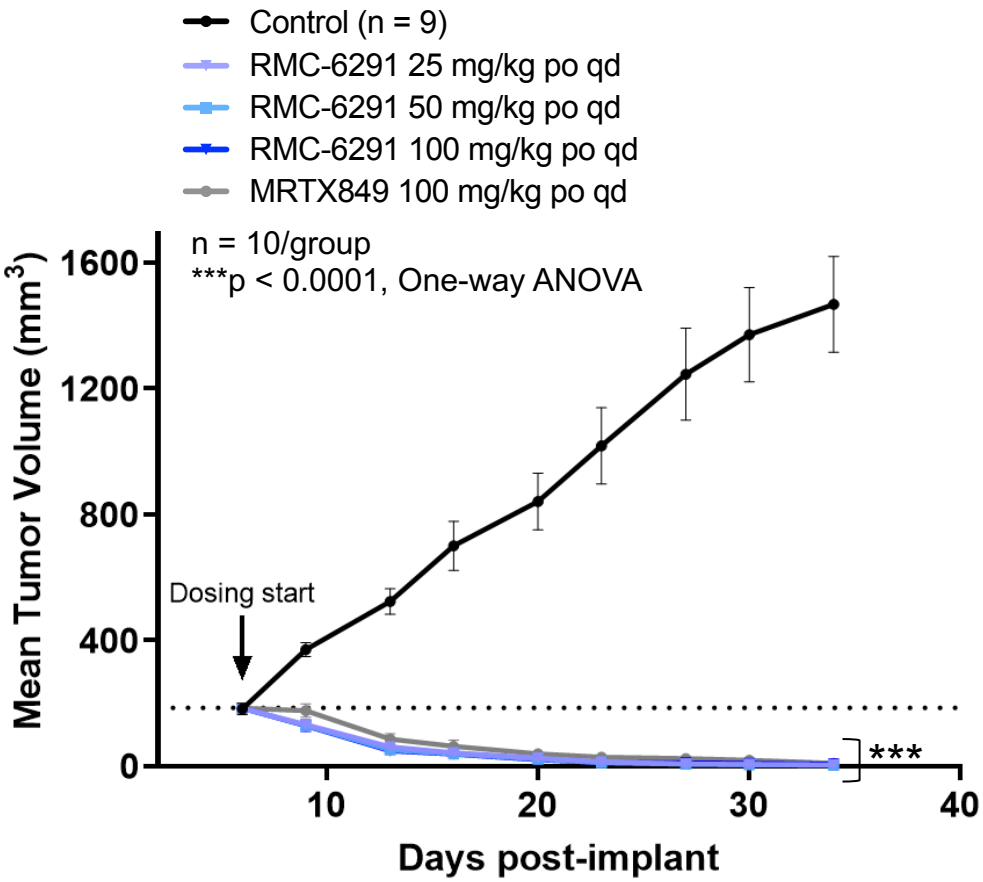


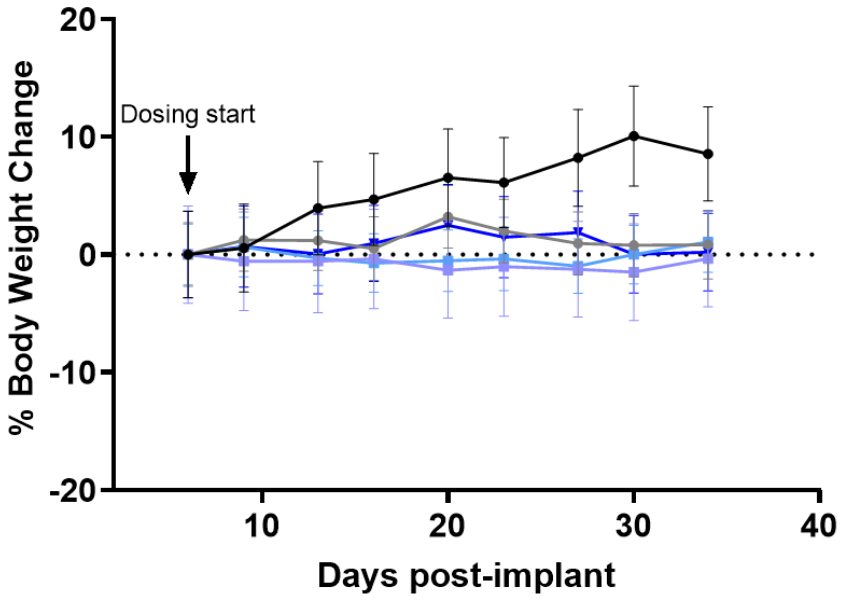
$KRAS^{G12C}$-RAF Signaling



RMC-6291: Deep Regressions of KRAS^{G12C} Tumor Xenografts; Well Tolerated

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





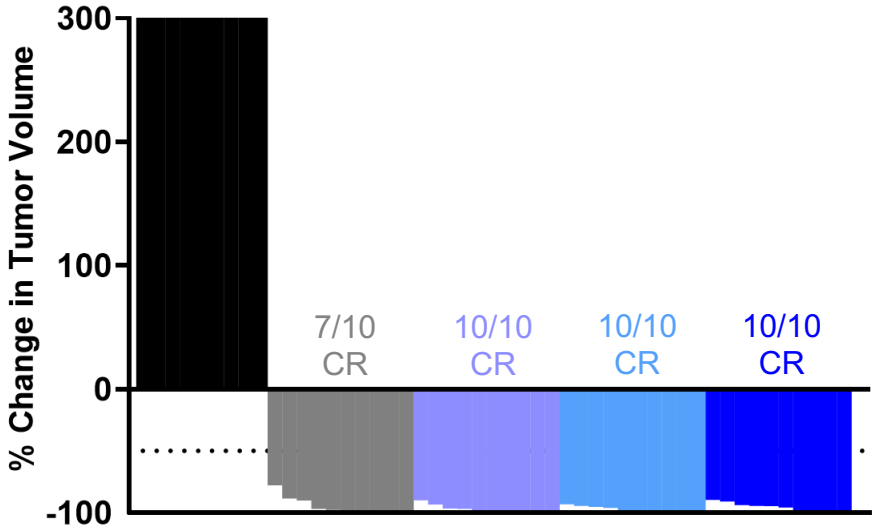
RVMD preclinical data
CDX = cell line-derived xenograft
NSCLC = Non-small cell lung cancer

RMC-6291: Exceptional Response Depth and Durability in KRAS^{G12C} Tumor Xenografts

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

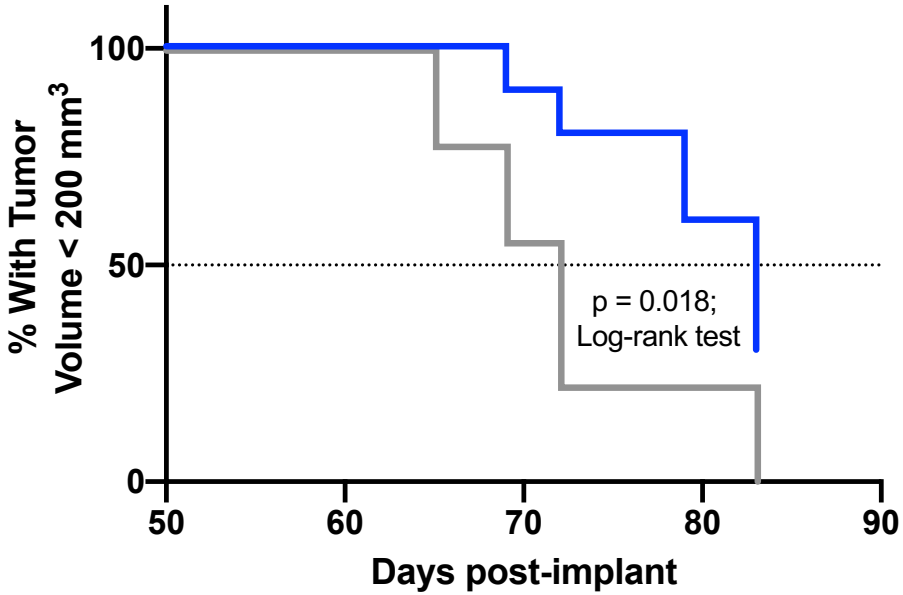
- Control
- RMC-6291 25 mg/kg po qd
- RMC-6291 50 mg/kg po qd
- RMC-6291 100 mg/kg po qd
- MRTX849 100 mg/kg po qd

End of treatment responses



CR = number of regressions ≥ 80% from initial
Each animal represented as a separate bar

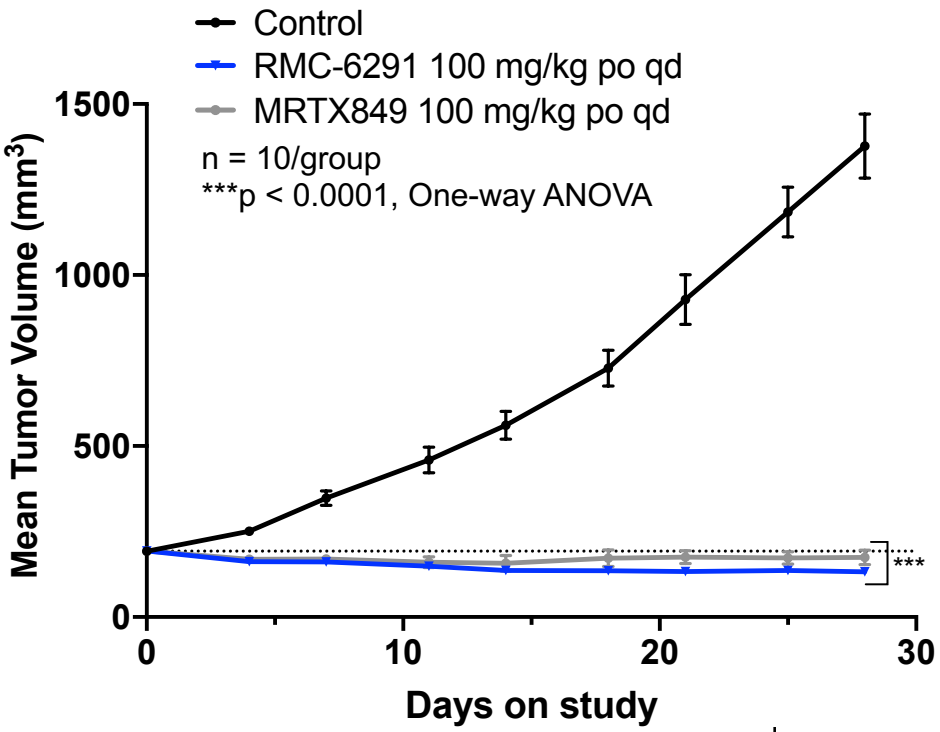
Post-treatment re-growth

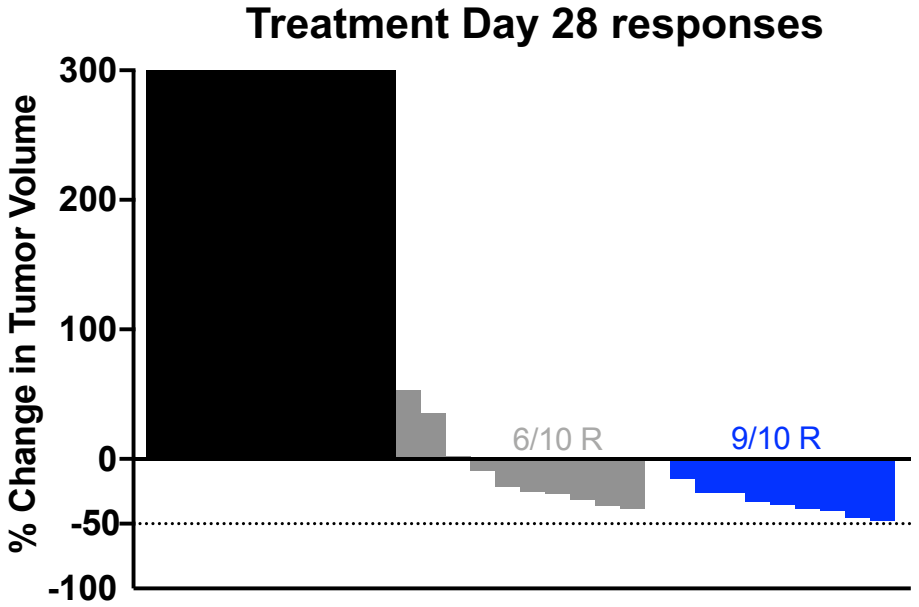


RVMD preclinical data
CDX = cell line-derived xenograft
NSCLC = Non-small cell lung cancer

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

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





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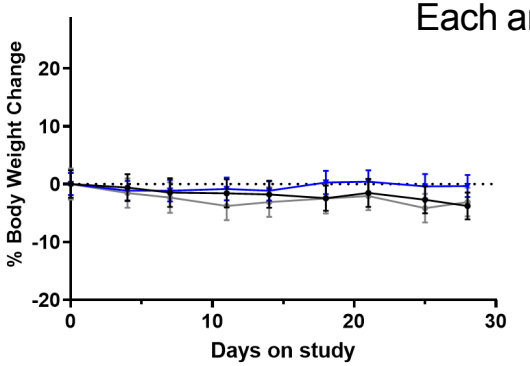


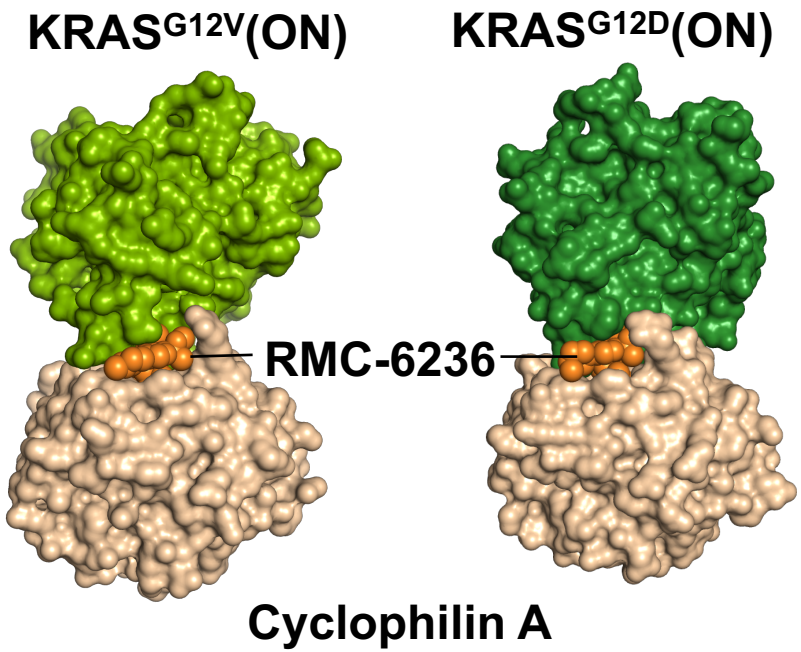
RVMD preclinical research
PDX = patient-derived xenograft
NSCLC = Non-small cell lung cancer

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, Highly Potent, Oral, RAS-Selective Tri-Complex RAS^{MULTI}(ON) Inhibitor



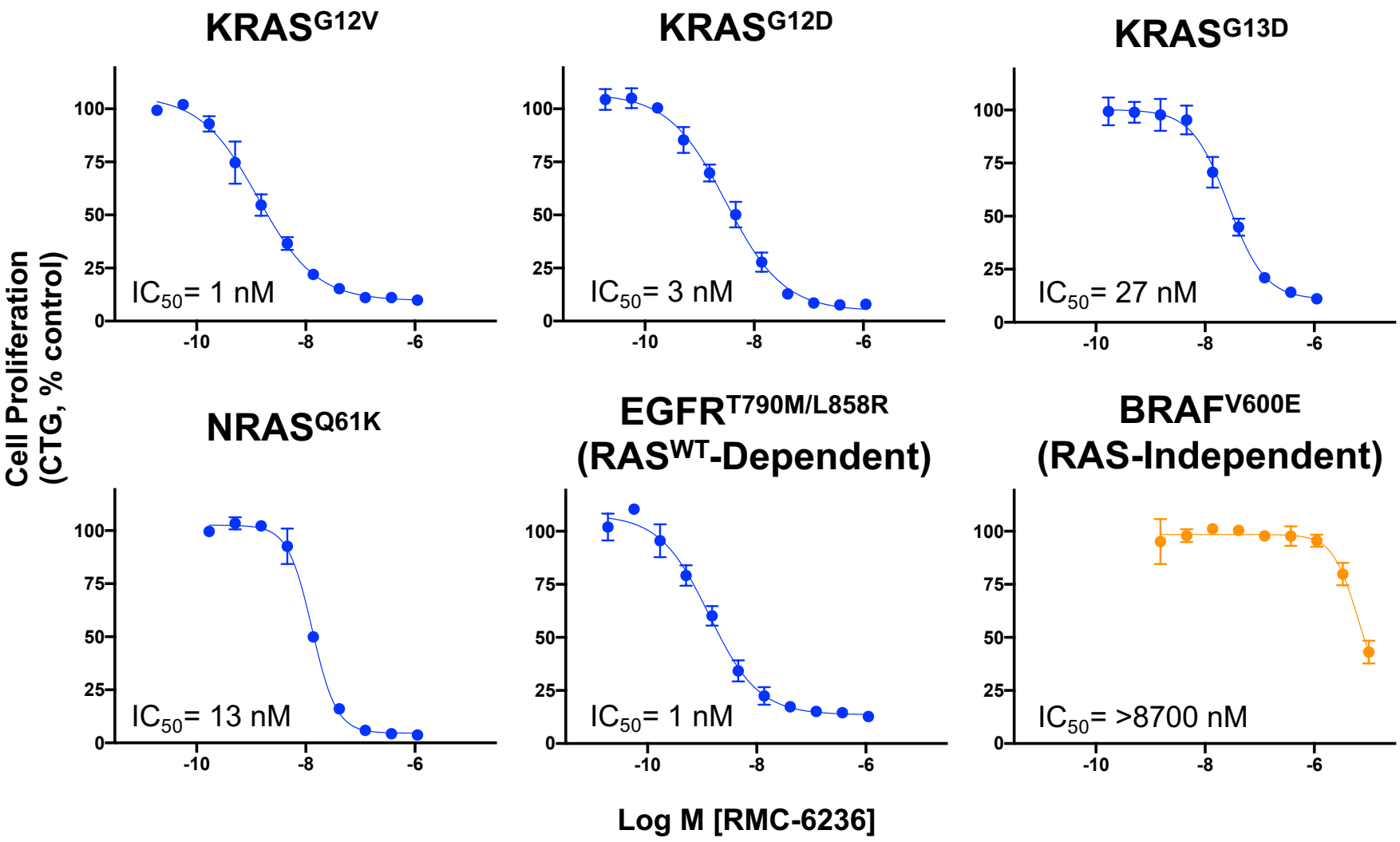
Potency for Tumor Cell Inhibition	
pERK (RAS-dependent, IC_{50}, nM)[1]	0.4-3
CTG (RAS-dependent, IC_{50}, nM)[1]	1-27

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

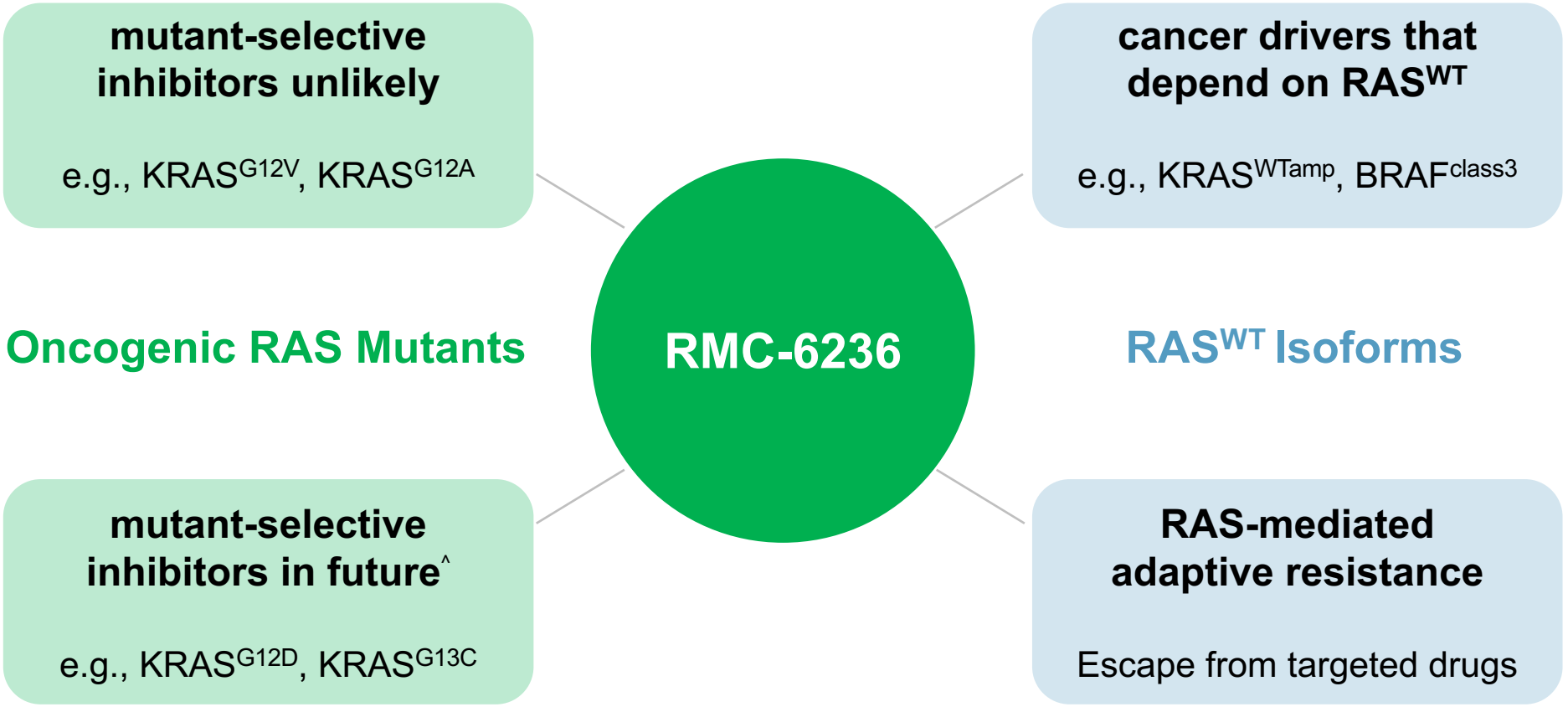
RVMD preclinical research
(1) Range reflects sensitivities across multiple RAS-variant cell lines
(2) Ratio based on cell growth assays with cell line bearing KRAS^{G12V} mutation

RMC-6236: Potent and Selective Inhibitor of Diverse RAS-Dependent Tumor Cell Lines



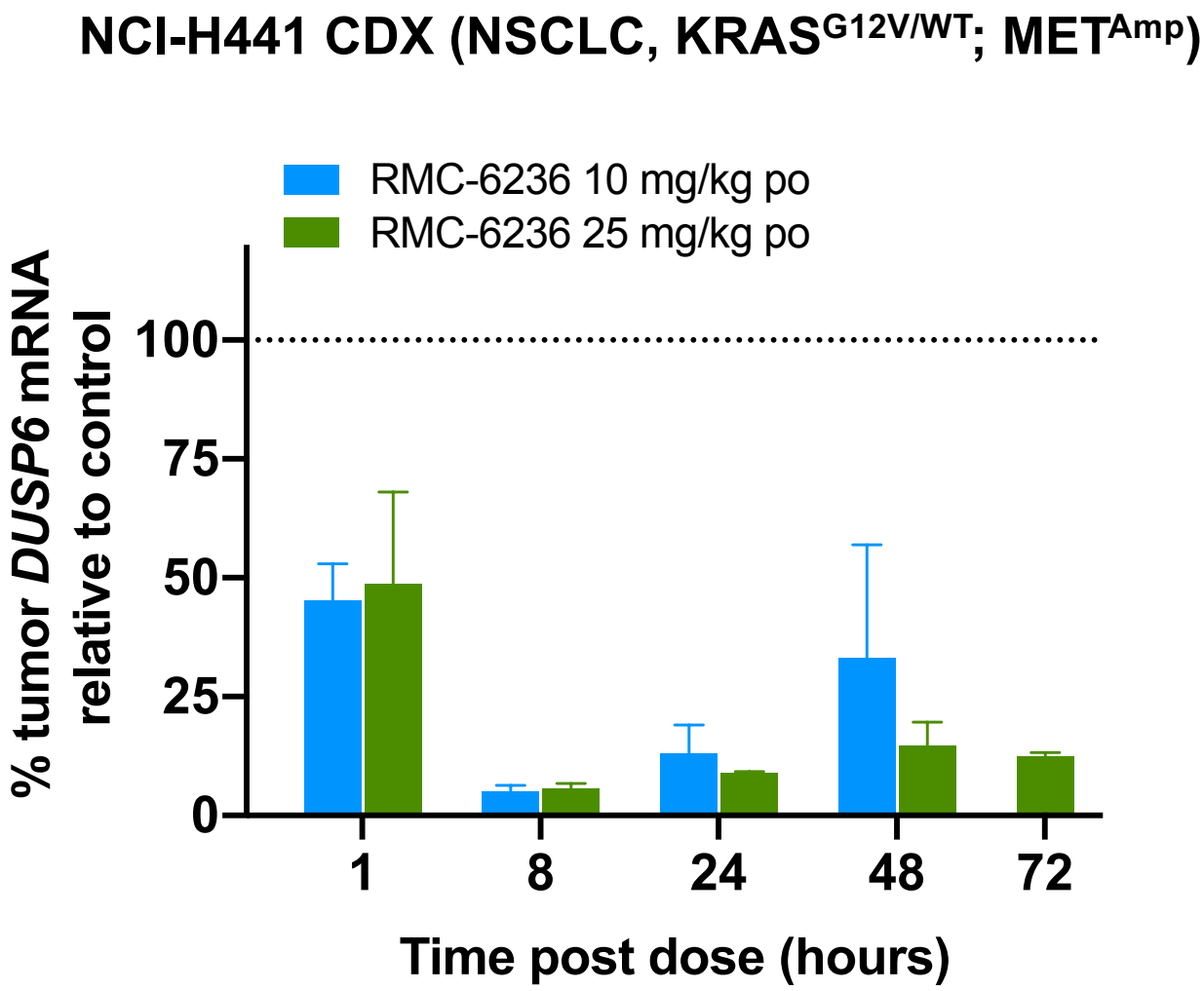
Examples from RVMD preclinical research

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



^ Parallel product paradigm

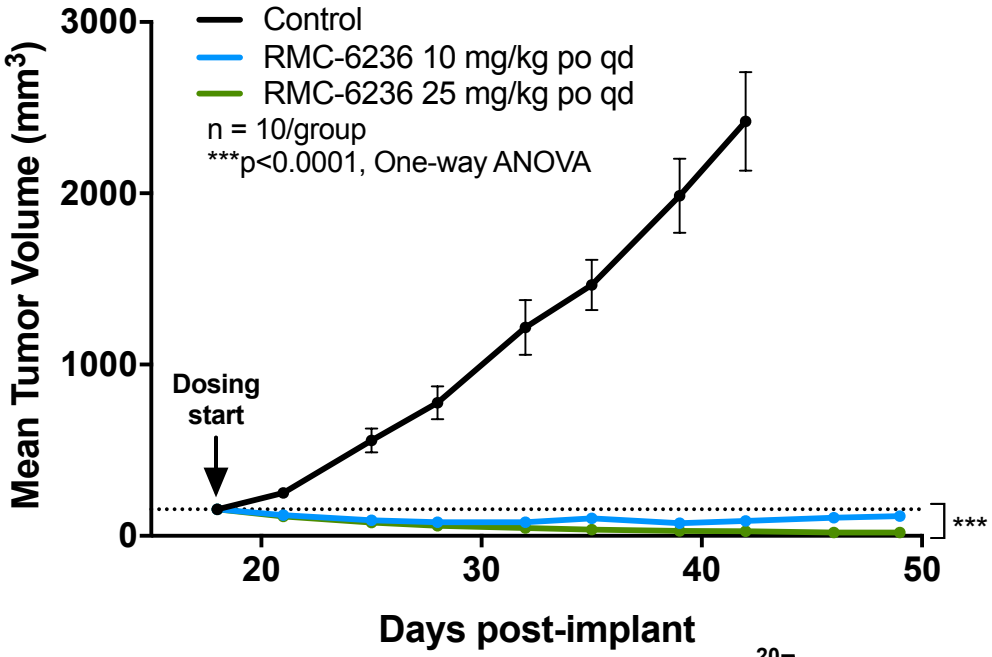
RMC-6236: Single Dose Induces Deep and Sustained RAS Pathway Inhibition *in Vivo*

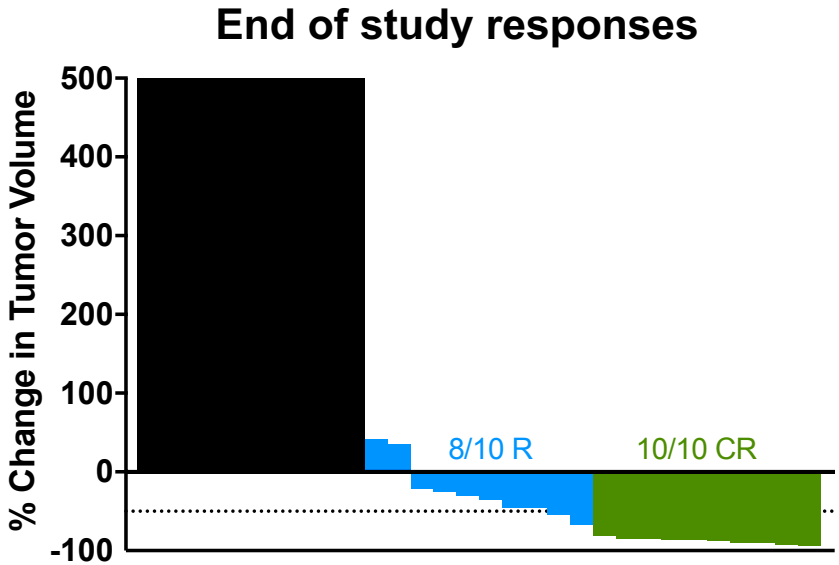


RVMD preclinical data
CDX = cell line-derived xenograft
NSCLC = Non-small cell lung cancer

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

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





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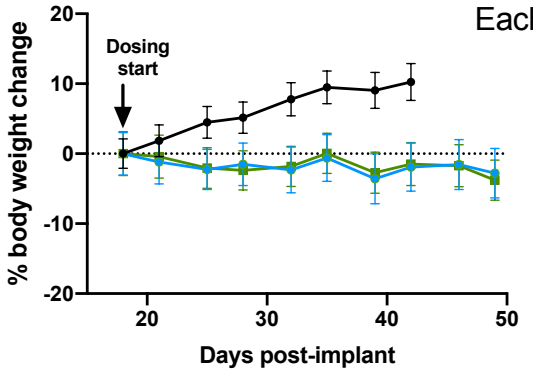
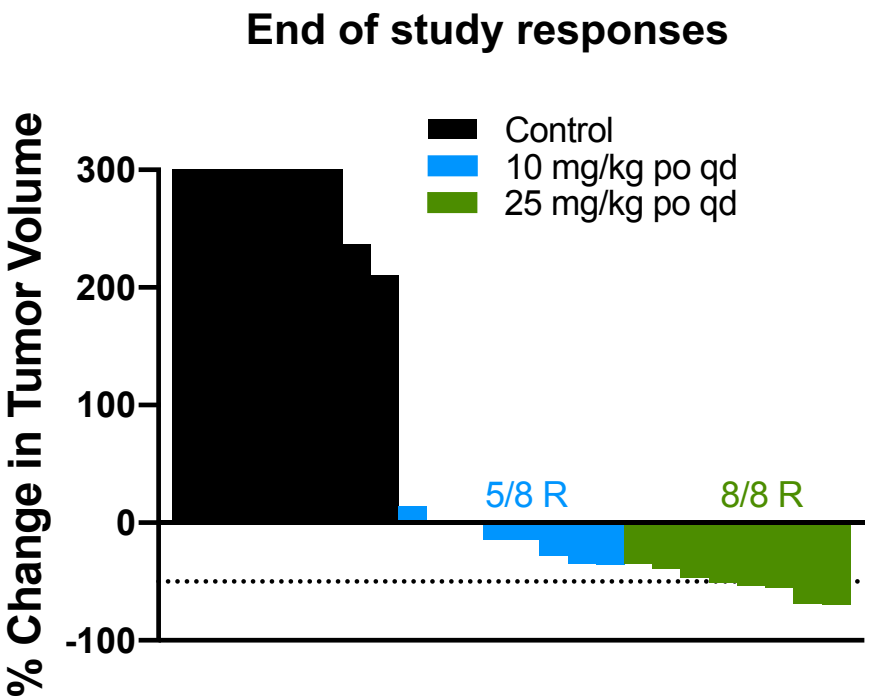
Each animal represented as a separate bar



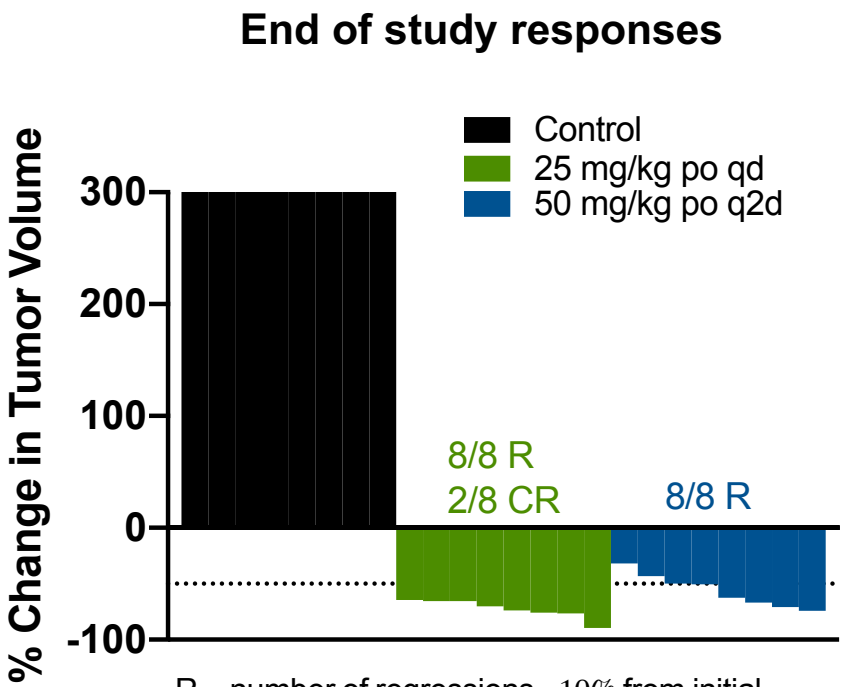
RVMD preclinical data
CDX = cell line-derived xenograft
NSCLC = Non-small cell lung cancer

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

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



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

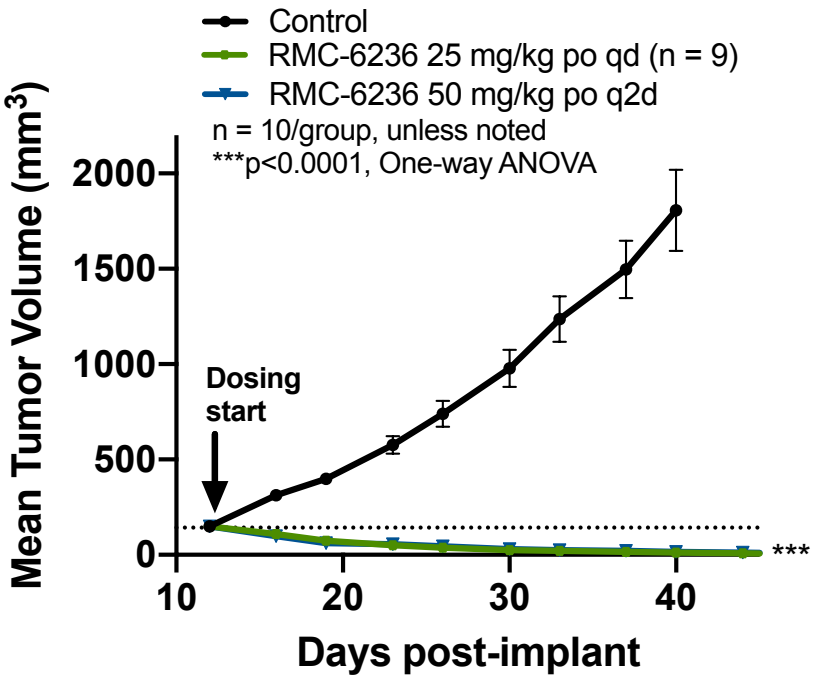


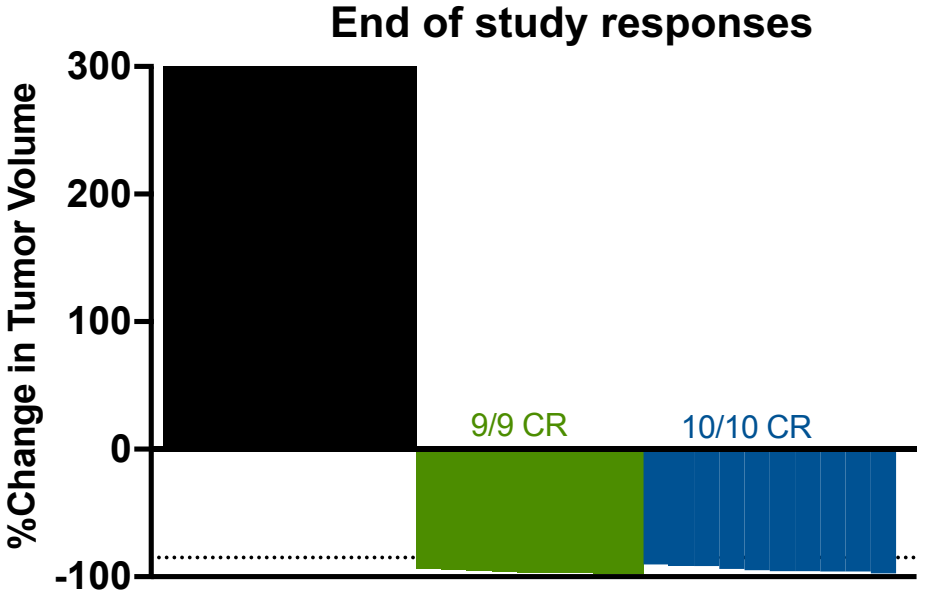
R = number of regressions >10% from initial
CR = number of regressions ≥80% from initial
Each animal represented as a separate bar

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

RMC-6236: Deep Regressions of KRAS^{G12D} Pancreatic Cancer Xenografts

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





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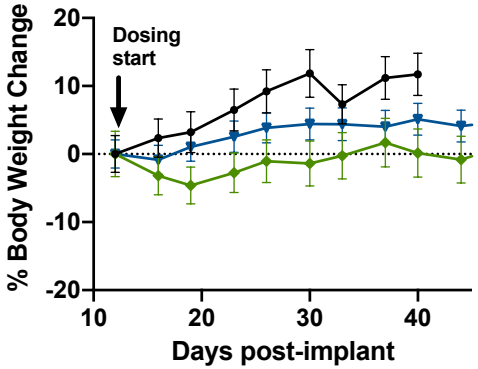


RVMD preclinical data
CDX = cell line-derived xenograft
PDAC = Pancreatic ductal adenocarcinoma

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

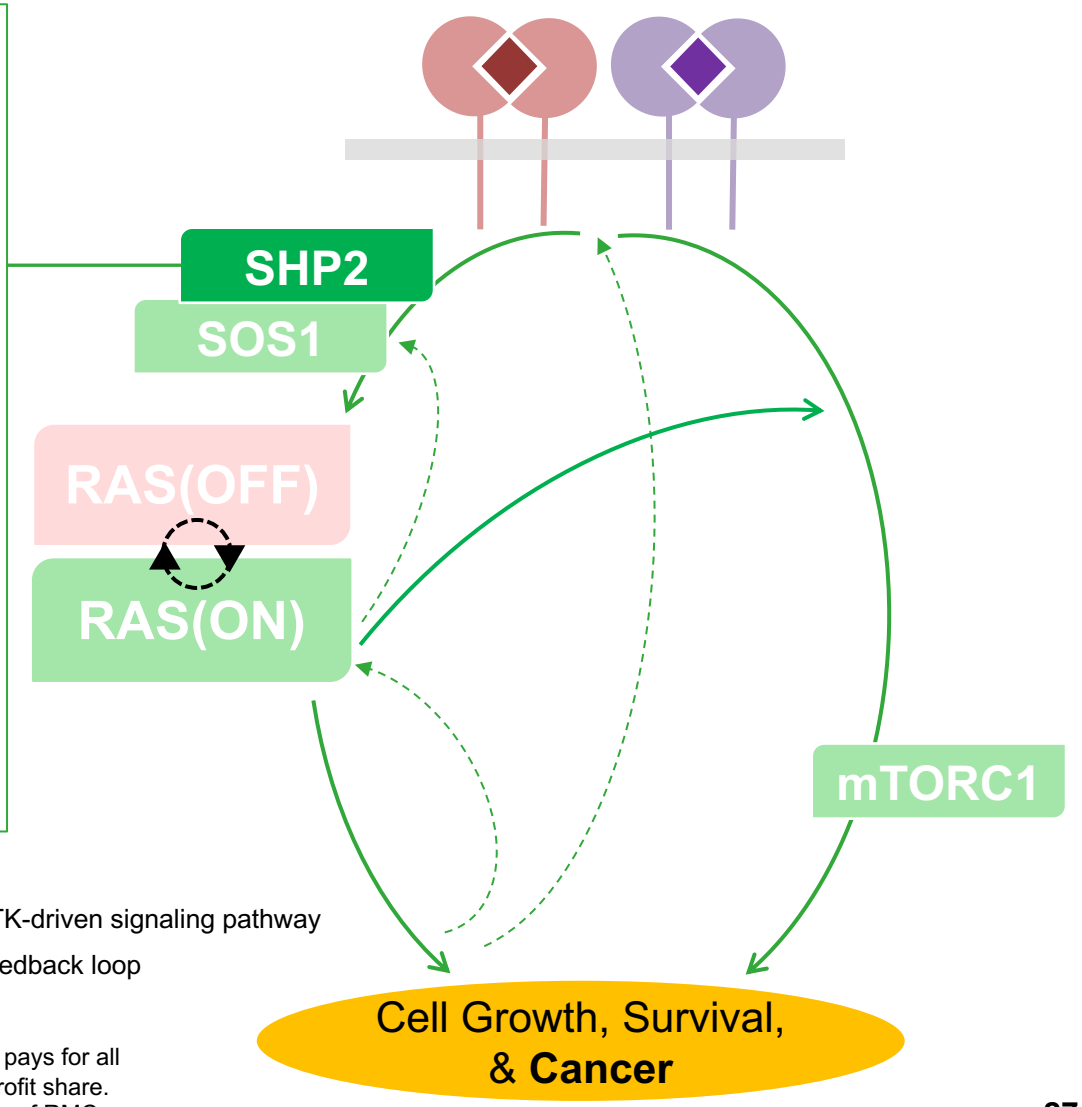
RAS Companion Inhibitors

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

RMC-4630: Potent, Oral Inhibitor of SHP2 – Master Regulator of RAS Signaling Pathway

RMC-4630[1]

- Clinical Phase 2[2]
- Monotherapy and backbone for targeted combinations
- Initial monotherapy activity in multiple cancers and genotypes
  - *Expansion at RP2DS underway*
- Initial combo activity with MEK inhibitor in RAS^{MUTANT} colorectal cancer
  - *Expansion at RP2DS underway*
- Initial clinical evidence of enhanced immune infiltration in tumors



(1) RMC-4630/SAR442720. Under 2018 partnership, Sanofi pays for all development costs and RVMD/Sanofi have 50/50 U.S. profit share.
(2) Expansion at RP2DS for RMC-4630 + cobimetinib portion of RMC-4630-02 study represents Phase 2

SANOFI

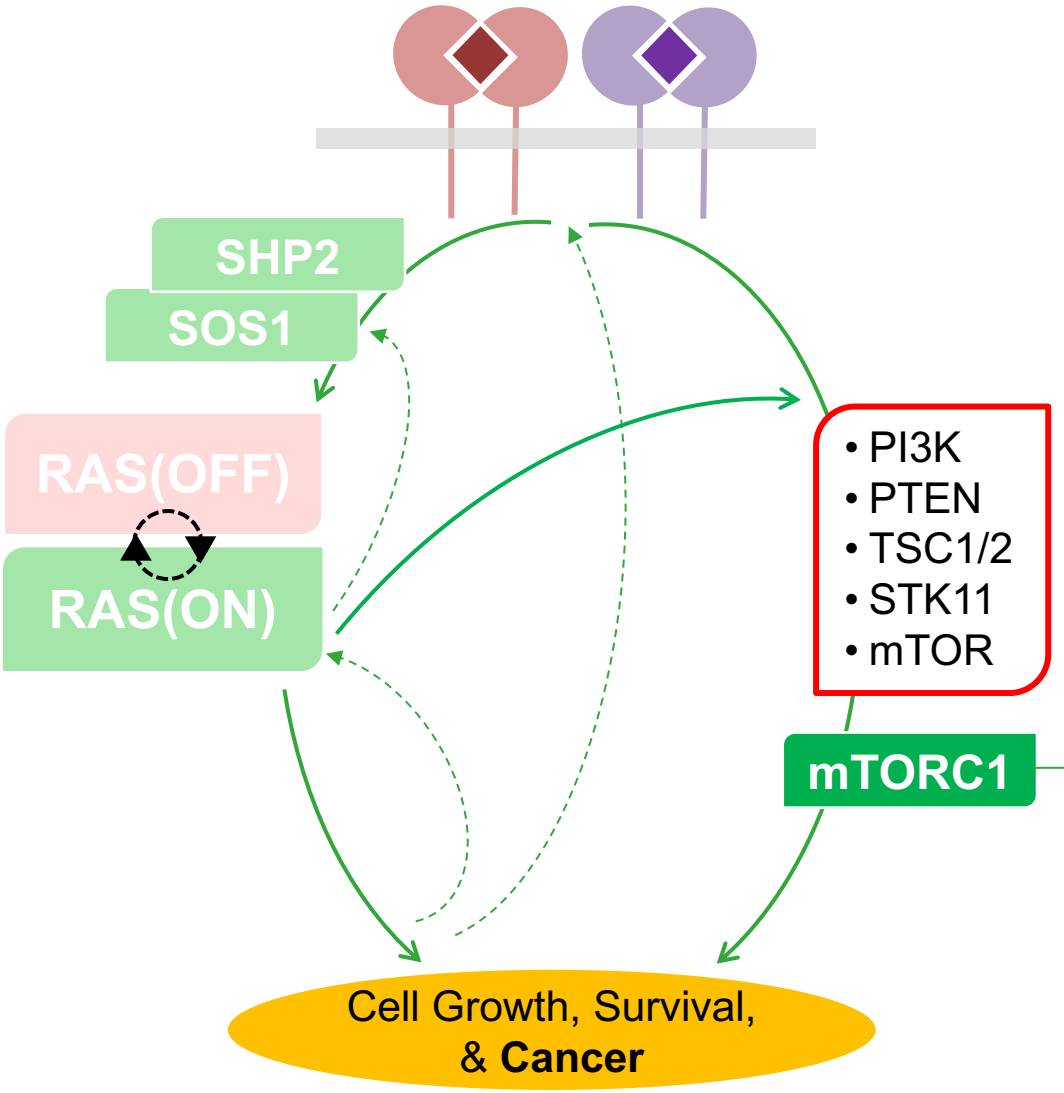
Central Clinical Thesis: RMC-4630 as Backbone for Rational, Mechanism-Based Combinations

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 / AMG 510	AMGEN	Ph 1b
		TBA	AstraZeneca	
	RTK inhibitors	osimertinib (Tagrisso®)		Ph 1b[1]
Immune	Checkpoint inhibitors	pembrolizumab (Keytruda®)	SANOFI	Ph 1b

SANOFI

(1) Study sponsored by RVMD

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



RMC-5552

- Phase 1 trial initiation pending
- 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

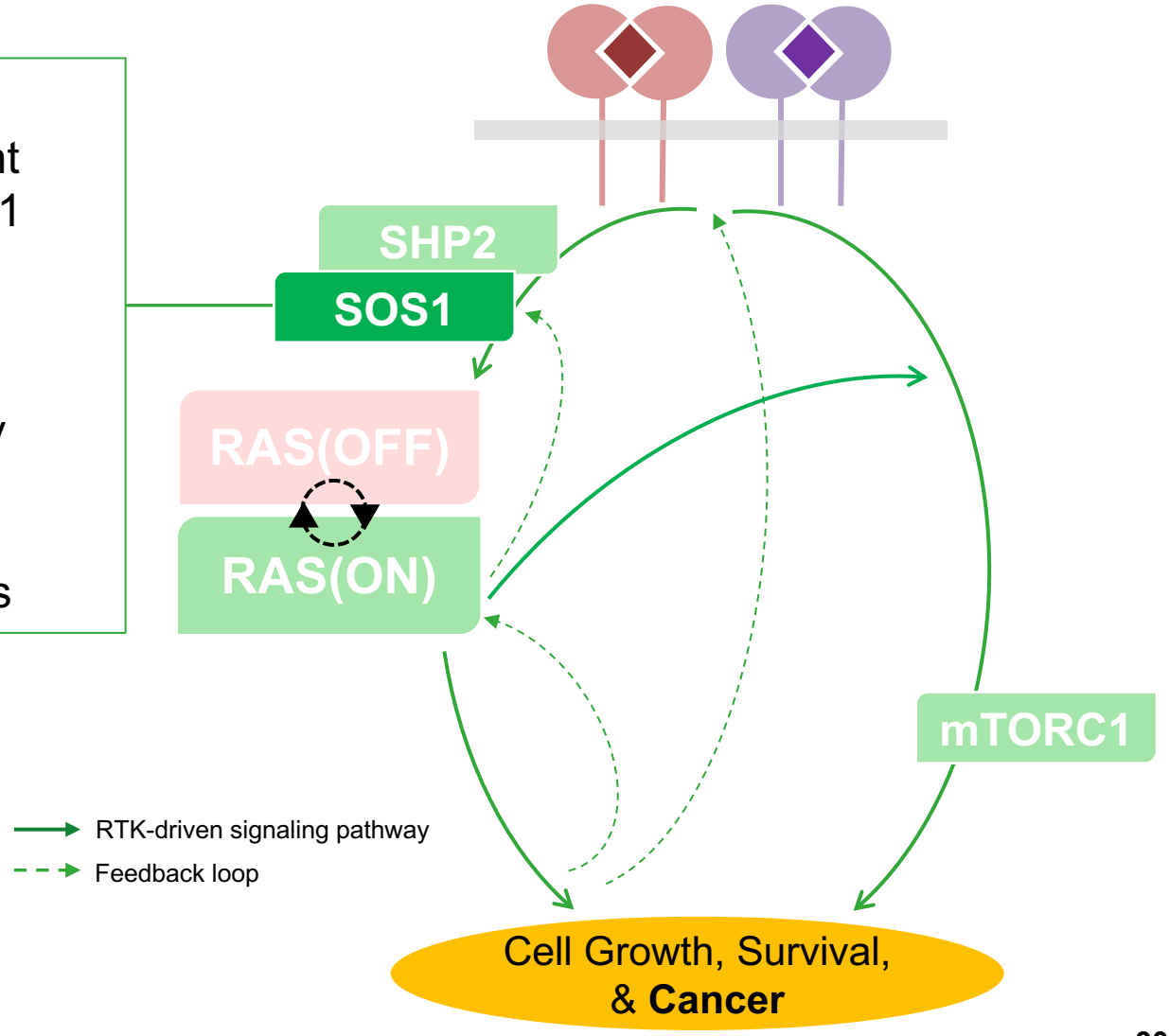
RTK-driven signaling pathway

Feedback loop

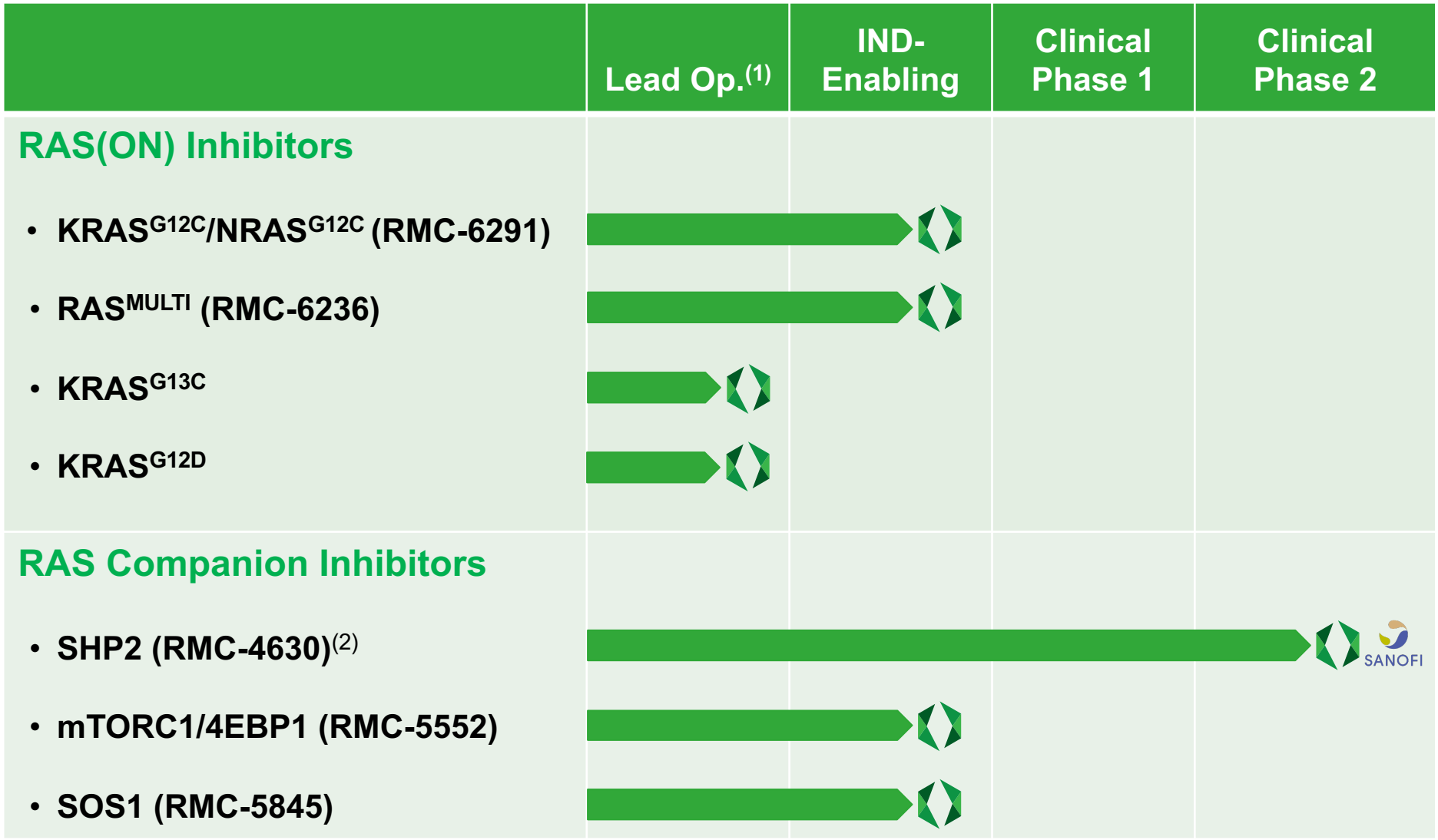
RMC-5845: Potent, Selective, Oral Inhibitor of SOS1, a Major Switch for RAS(OFF) to RAS(ON)

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) Expansion at RP2DS for RMC-4630 + cobimetinib portion of RMC-4630-02 study represents Phase 2

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	1H21
RP2DS for further testing of RMC-4630 + AMG 510	1H21
Preliminary clinical activity data for RMC-4630 + AMG 510	2H21
Preliminary safety and clinical activity data for RMC-4630 + cobimetinib expansion cohorts in RAS^{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	1H21
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 @ 9/30/2020	$466.1M(1)

(1) Includes $167.8 million in net proceeds from the July 2020 public offering of common stock.

Translating Frontier Oncology Targets to *Outsmart Cancer*™