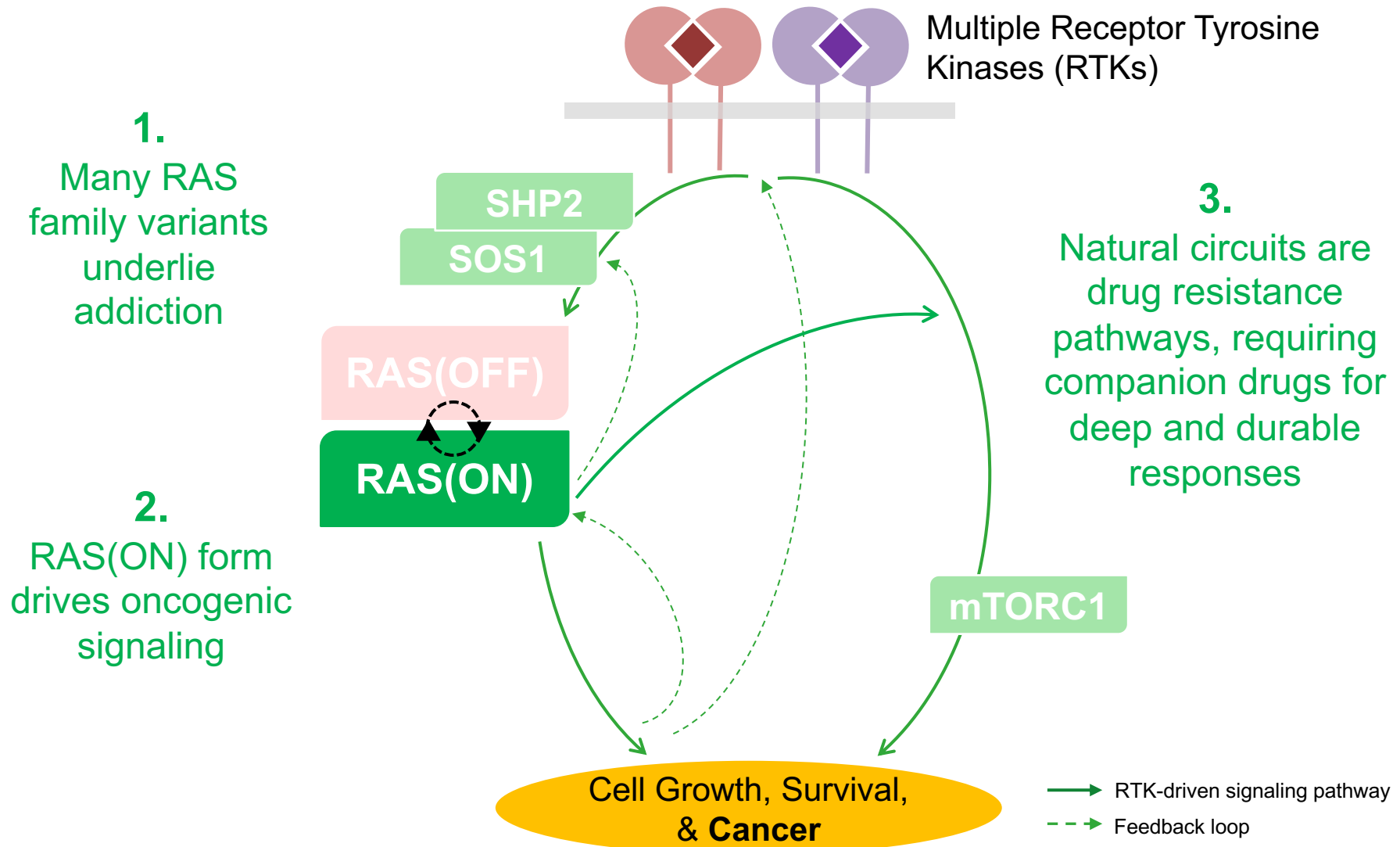# REVOLUTION
MEDICINES

Drugging the RAS(ON) Form of Diverse Oncogenic RAS Mutations

RAS Targeted Drug Discovery:
Expanding RAS Druggability Beyond G12C
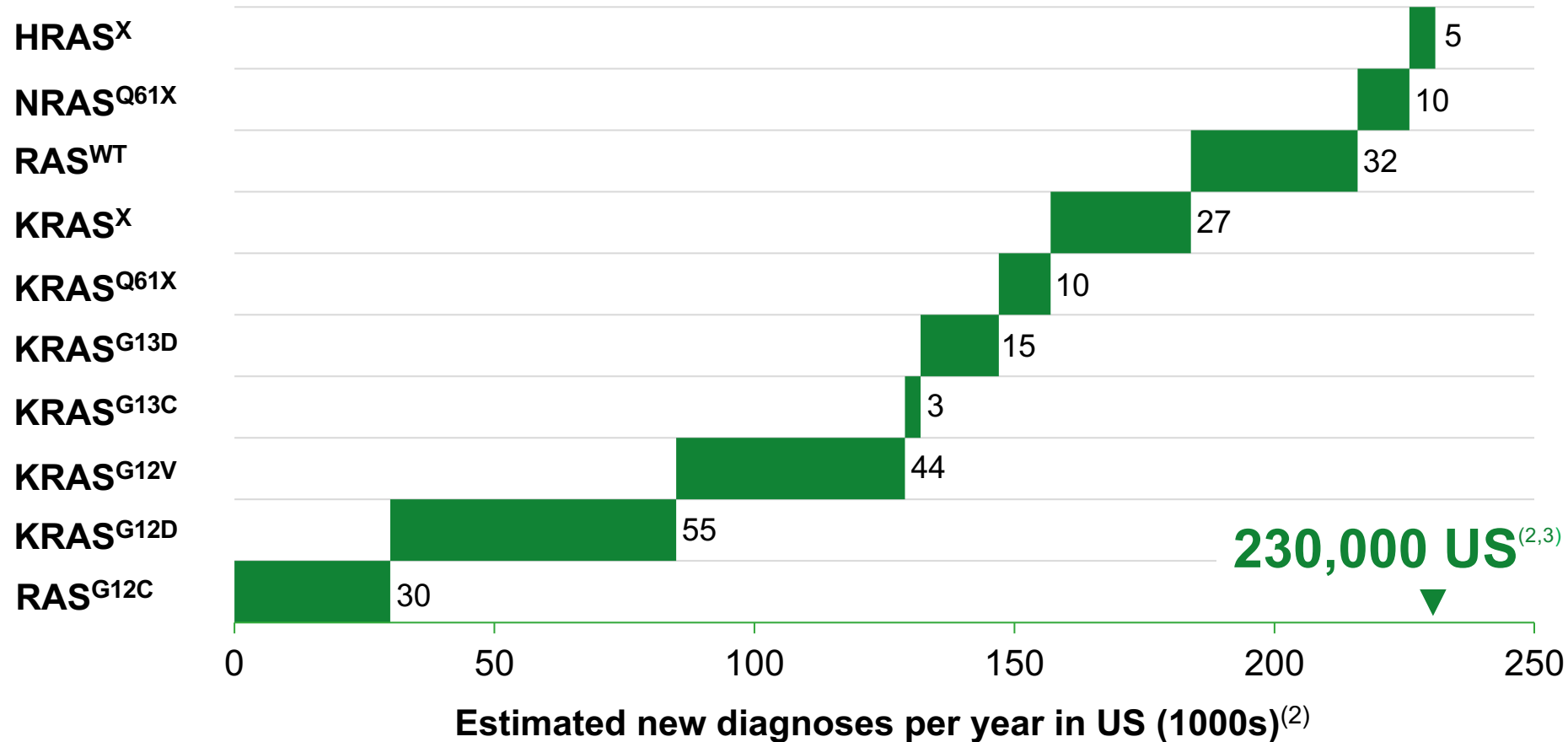
February 2021

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

Multiple Receptor Tyrosine Kinases (RTKs)

1.
Many RAS family variants underlie addiction

SHP2

SOS1

RAS(OFF)

RAS(ON)

2.
RAS(ON) form drives oncogenic signaling

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

mTORC1

Cell Growth, Survival, & **Cancer**

→ RTK-driven signaling pathway

⇢ Feedback loop

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

Tumor Addiction[1]**:**

Tumor Addiction[1]	Estimated new diagnoses per year in US (1000s)[2]
HRAS^X	5
NRAS^{Q61X}	10
RAS^{WT}	32
KRAS^X	27
KRAS^{Q61X}	10
KRAS^{G13D}	15
KRAS^{G13C}	3
KRAS^{G12V}	44
KRAS^{G12D}	55
RAS^{G12C}	30

230,000 US[2,3]

Estimated new diagnoses per year in US (1000s)[2]

(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

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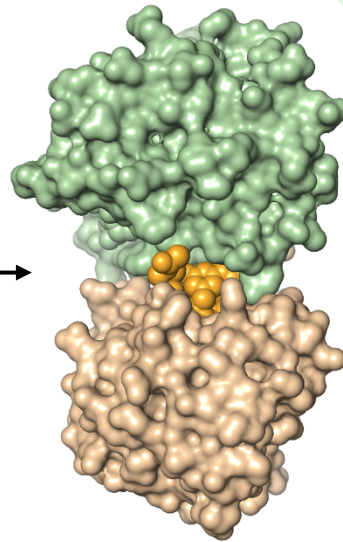

RAS(ON) Inhibitor

RAS(ON)
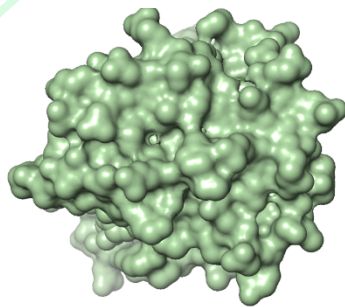
Chaperone protein

Tri-Complex

- 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

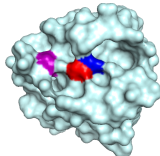# RAS(ON) Inhibitors for Variants Driving Vast Majority of RAS-Addicted Cancers

▶ RAS variant

▶ RAS(ON) inhibitor

▶ Chaperone (Cyclophilin A)

KRAS[WT]

NRAS[WT]

HRAS[WT]

RAS Variants and Inhibitors in Tri-Complexes[1]
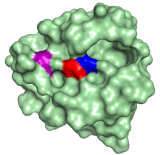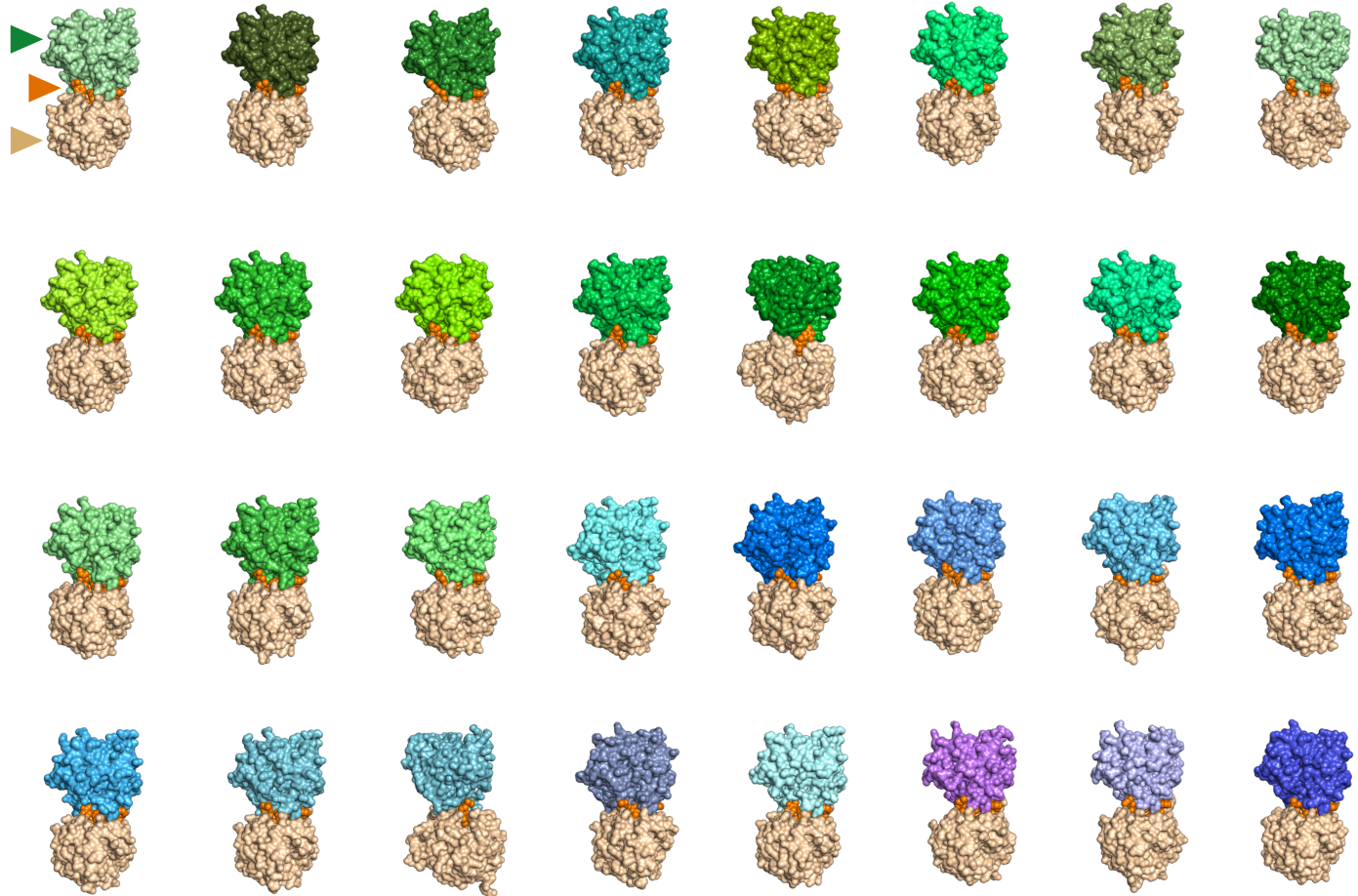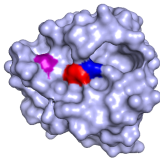
RMC-6291: First-in-Class, Highly Potent, Oral and Selective Tri-Complex Inhibitor of KRAS[G12C](ON)

KRAS[G12C](ON)

RMC-6291—

Cyclophilin A
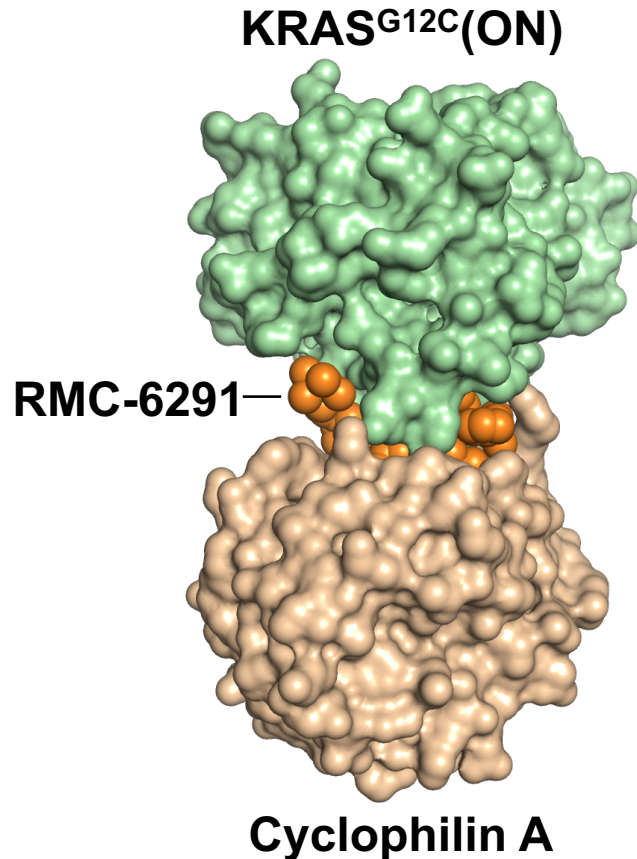
Potency for Tumor Cell Inhibition	
pERK (NCI-H358, IC_{50}, nM)[1]	0.7
CTG (NCI-H358, IC_{50}, nM)	0.09

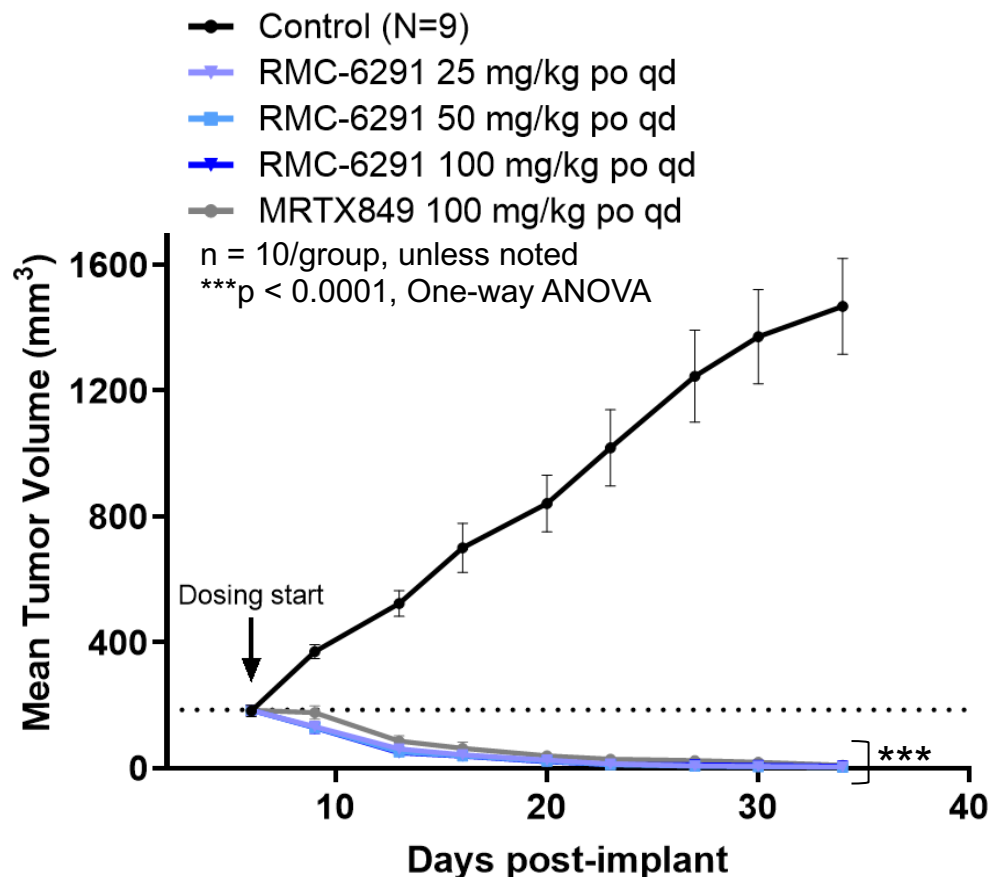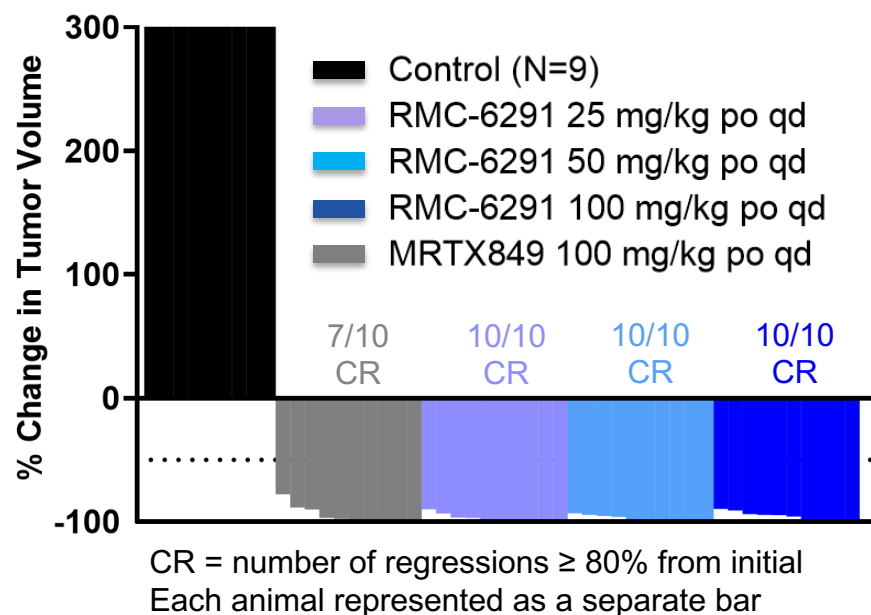| Target Selectivity and Safety	
Covalent bond: k_{inact}/K_i	> 20,000
Selectivity	
• Over RAS-independent cell	> 1000X
• Over RAS[WT]-dependent cell	> 1000X
Off-target safety panel and cysteinome screen	Low Risk

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: Deep Regressions of KRAS^{G12C} Tumor Xenografts

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

RVMD preclinical data
CDX = cell line-derived xenograft
NSCLC = Non-small cell lung cancer
Animals in each arm tolerated dosing well as determined by body weight assessments

KRAS^{G12C}(ON) Inhibitors Drive Superior Inhibition of Oncogenic KRAS^{G12C}

In multiple preclinical studies RVMD tri-complex KRAS^{G12C}(ON) inhibitors showed superiority over KRAS^{G12C}(OFF) inhibitors:

✓ Increased durability of pathway and cell growth inhibition in NSCLC and CRC cells *in vitro*

✓ Increased durability of pathway inhibition following RTK stimulation

✓ Immediate termination of RAS(ON) signaling, versus slower time-course to trap RAS(OFF)

✓ Improved anti-tumor activity in PDX models with KRAS^{G12C}

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

KRAS^{G12V}(ON) **KRAS^{G12D}(ON)**

RMC-6236

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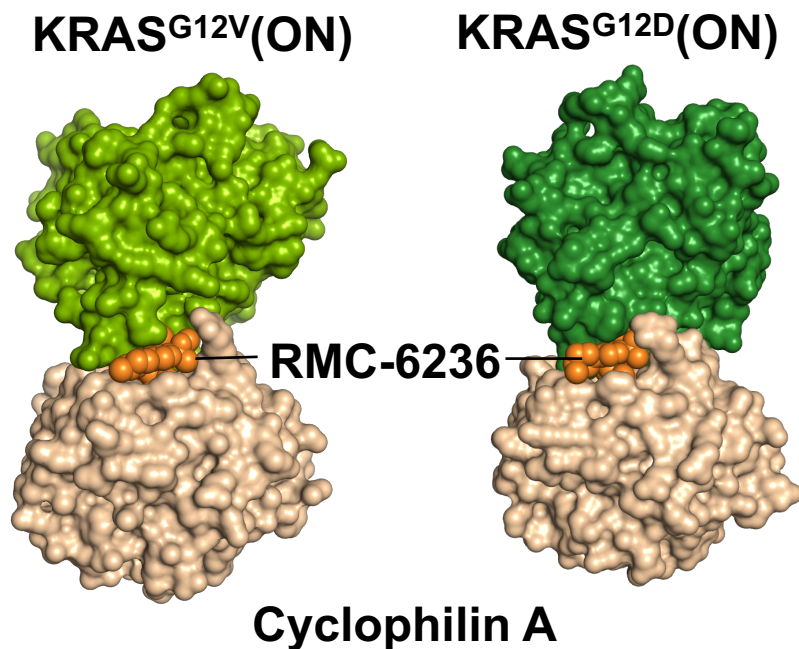
Potency for Tumor Cell Inhibition	
pERK (RAS-dependent, IC_{50}, nM)[1]	0.4-3
CTG (RAS-dependent, IC_{50}, nM)[1]	1-27

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

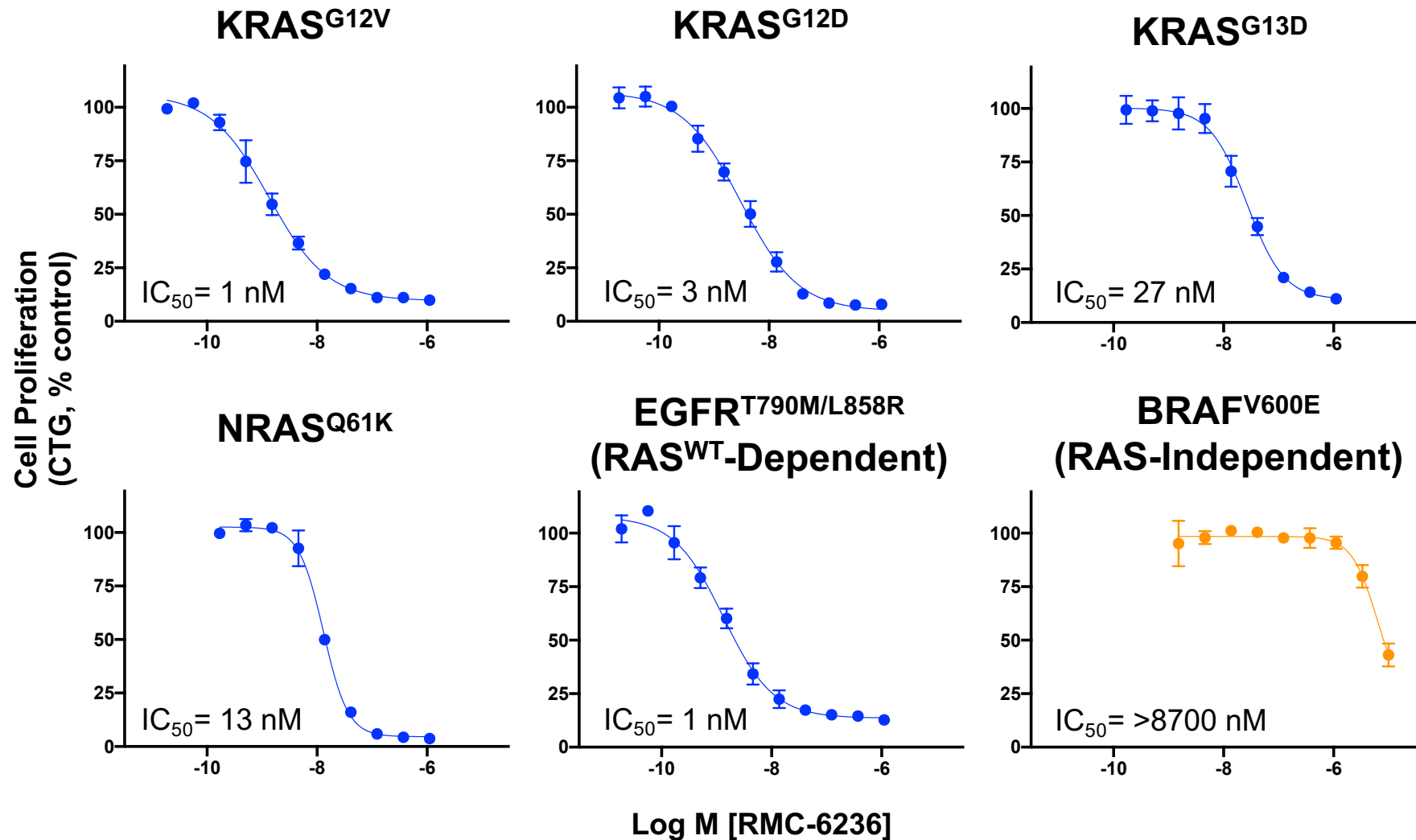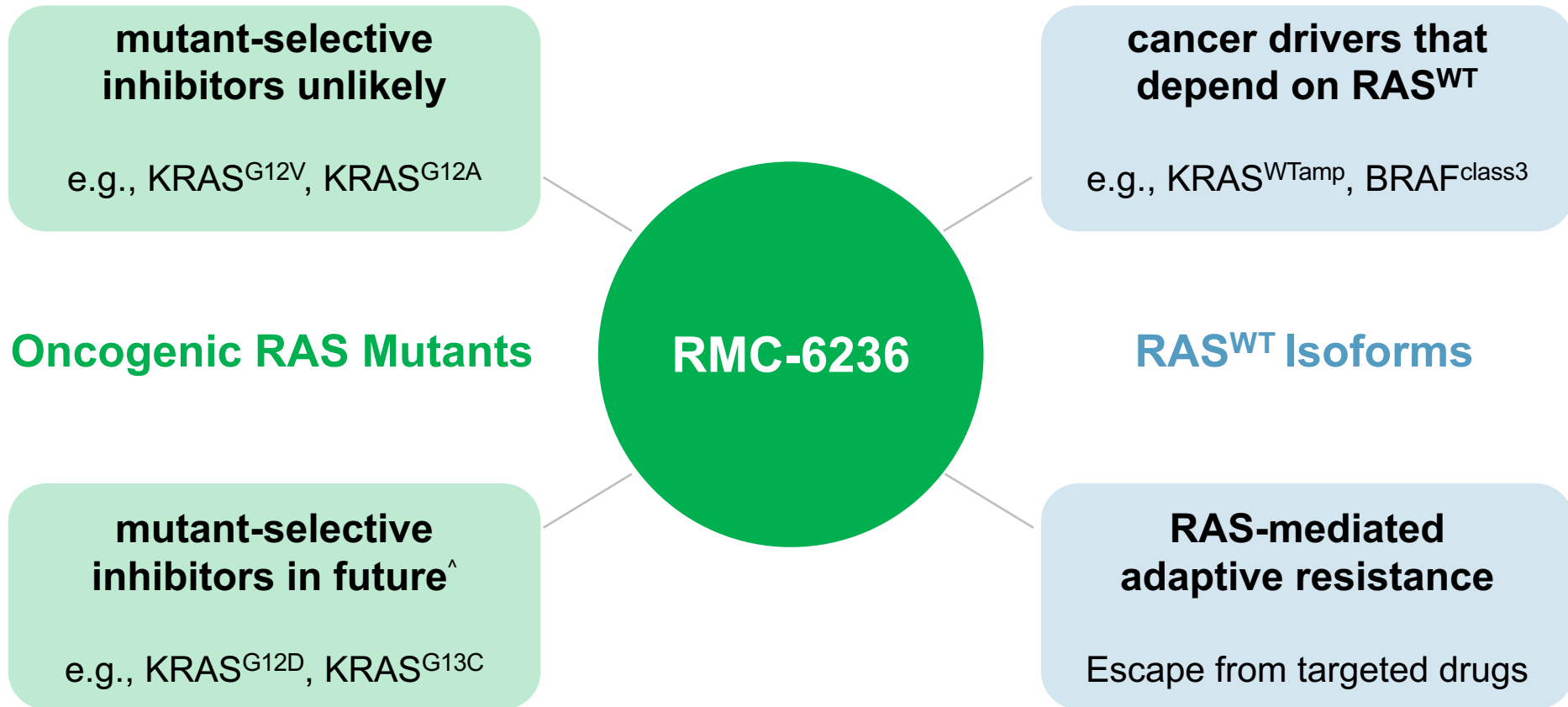| PK/ADME	
Oral %F (multiple species)	24-33
Metabolic clearance (hepatocytes, multiple species)	Low to Moderate

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

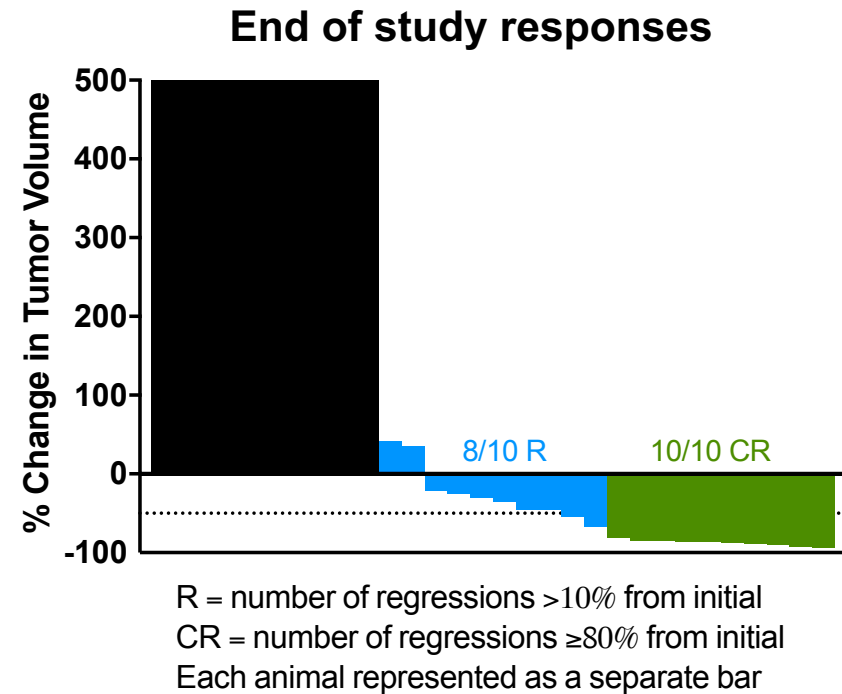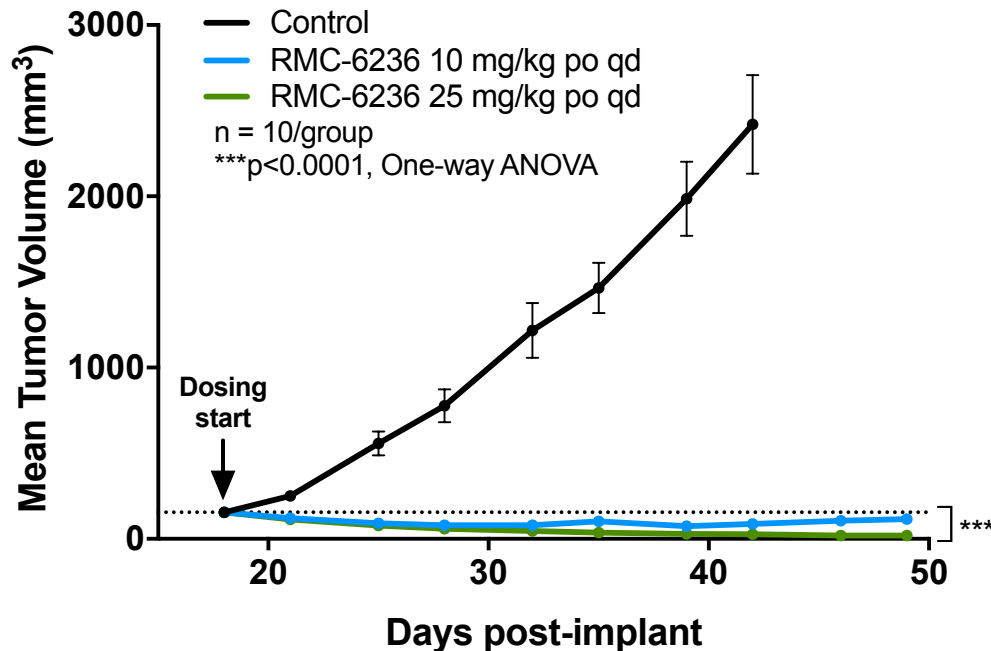# RMC-6236: Potent and Selective Inhibitor of Diverse RAS-Dependent Tumor Cell Lines

Examples from RVMD preclinical research

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

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: Deep Regressions of KRAS^{G12V} NSCLC Xenografts

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

n = 10/group
***p<0.0001, One-way ANOVA

End of study responses

8/10 R

10/10 CR

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
NSCLC = Non-small cell lung cancer

RMC-6236: Favorable Tolerability

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

Legend:
- Control
- RMC-6236 10 mg/kg po qd
- RMC-6236 25 mg/kg po qd

n = 10/group
***p<0.0001, One-way ANOVA

X-axis: Days post-implant
Y-axis: % body weight change

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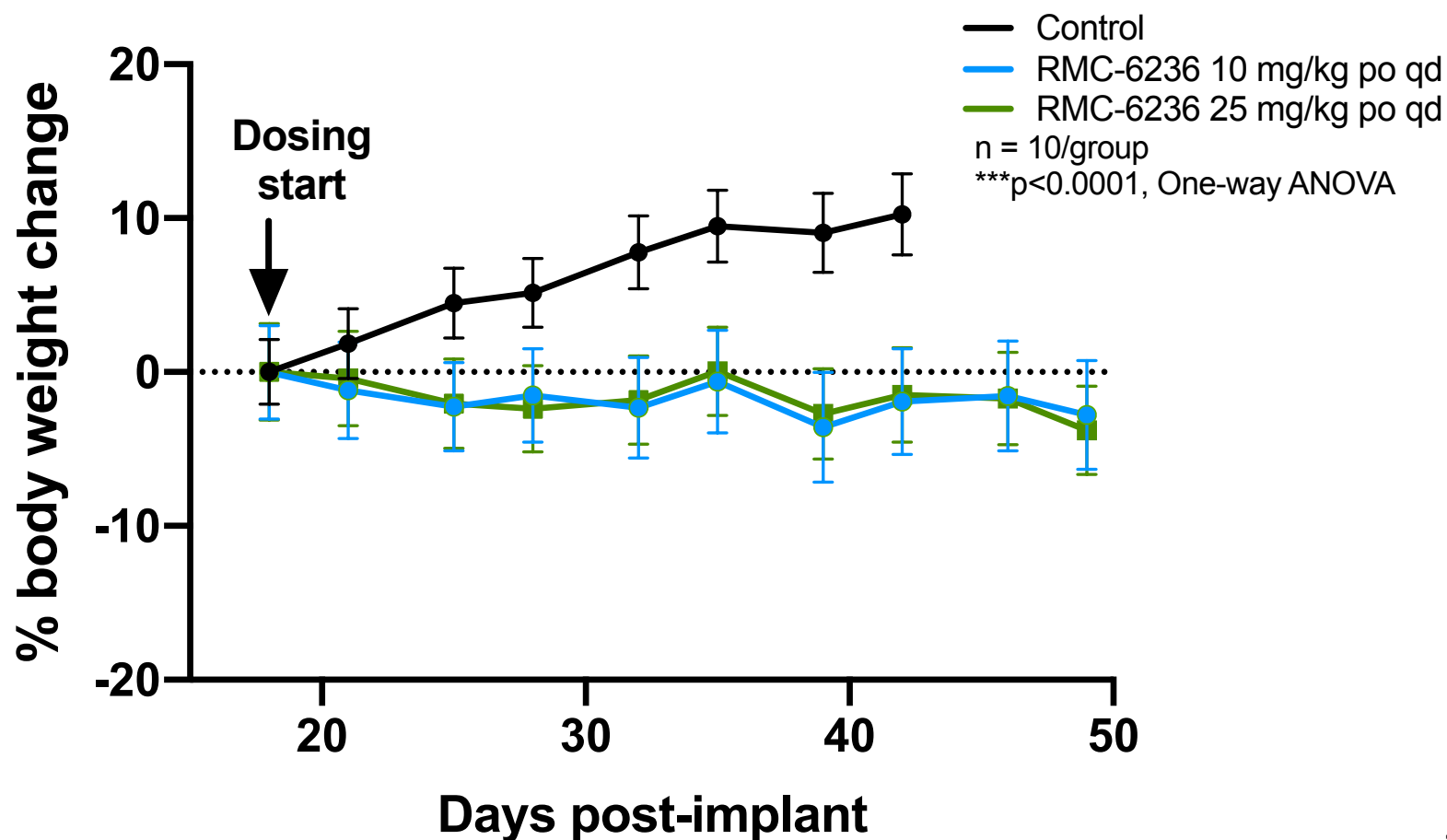
RMC-6236: Deep Regressions of KRAS^{G12V} Pancreatic and Colorectal Cancer Xenografts

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

End of study responses

Legend:
- ■ Control
- ■ 10 mg/kg po qd
- ■ 25 mg/kg po qd

5/8 R (blue)
8/8 R (green)

Y-axis: % Change in Tumor Volume (300, 200, 100, 0, -100)
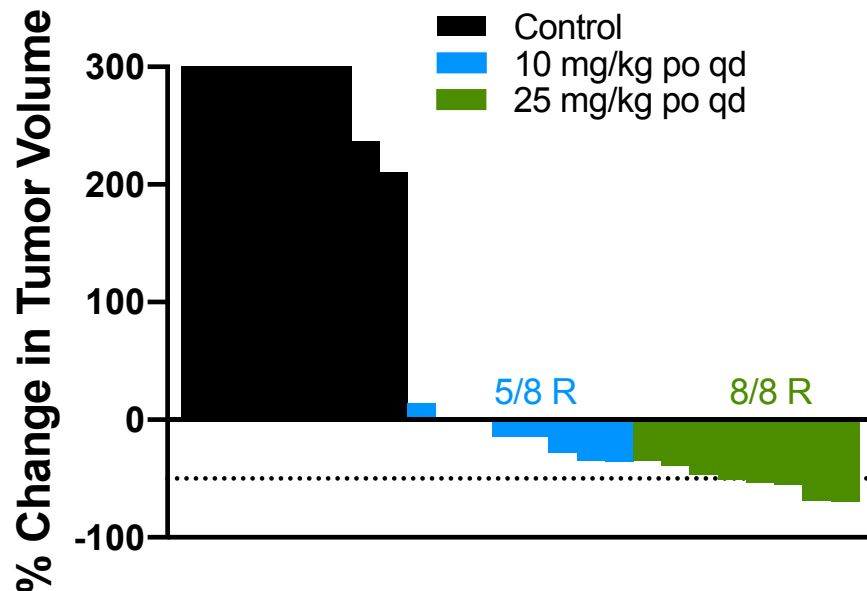
SW403 CDX (CRC, KRAS$^{G12V/WT}$)

End of study responses
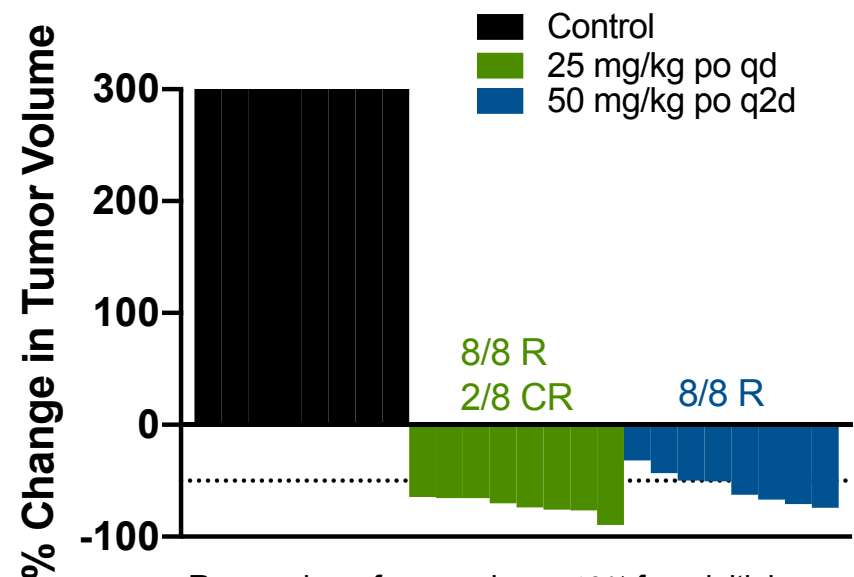
Legend:
- ■ Control
- ■ 25 mg/kg po qd
- ■ 50 mg/kg po q2d

8/8 R
2/8 CR
8/8 R

Y-axis: % Change in Tumor Volume (300, 200, 100, 0, -100)

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

RAS Mutant-Selective versus RAS^{MULTI} Inhibitors

Mutant Selective

RAS^{MULTI}

Desirability (arrow pointing up)

Permits deep and sustained target coverage

Combinability

Low RAS^{WT}-mediated toxicity

Generally restricted to one RAS mutation

Permits escape via RAS^{WT}

Activity against many RAS mutations

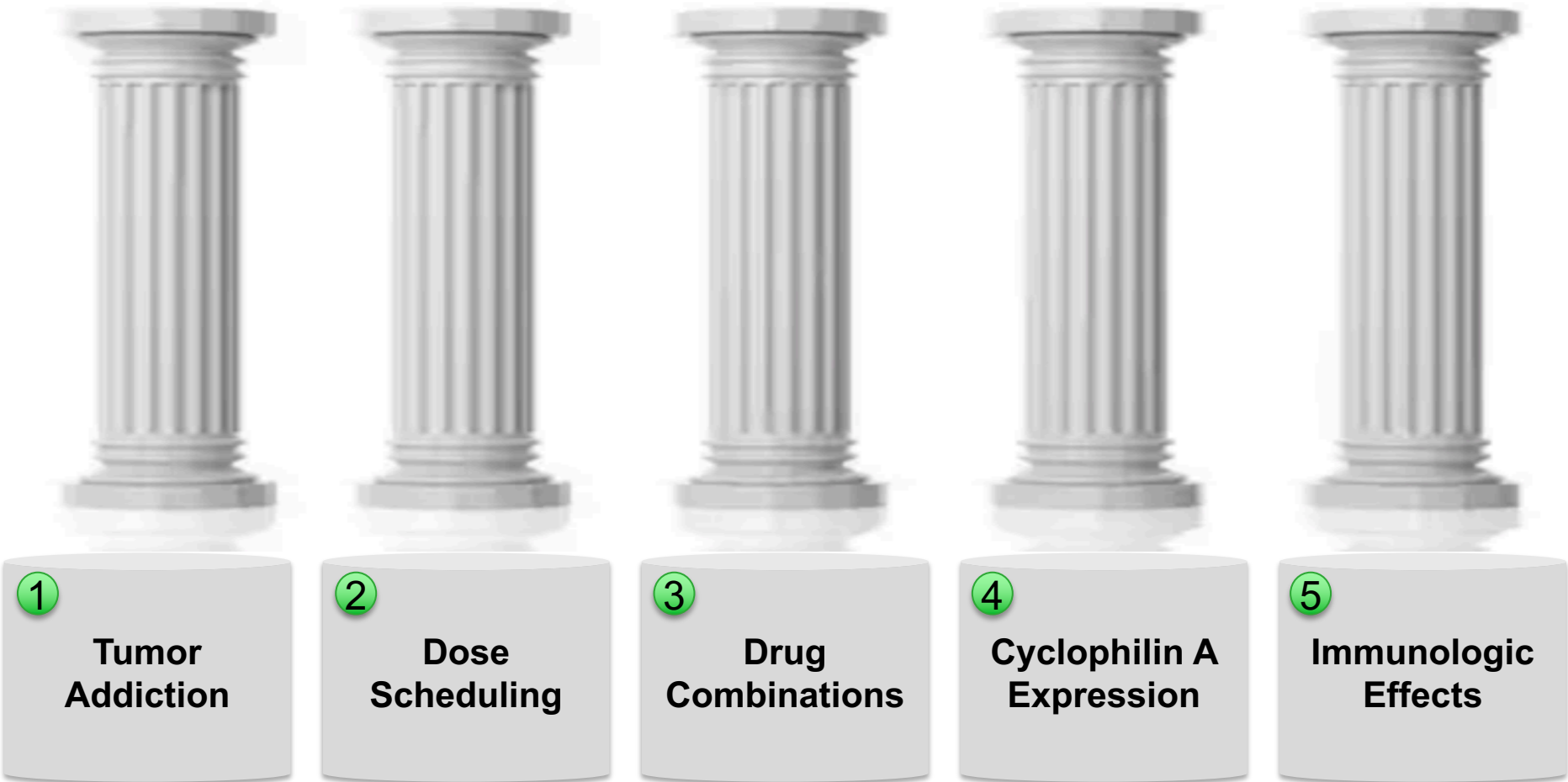Abrogates escape via RAS^{WT} signaling ('RAS^{WT} –Mediated Adaptive Resistance')

Depth and duration of target inhibition constrained by toxicity
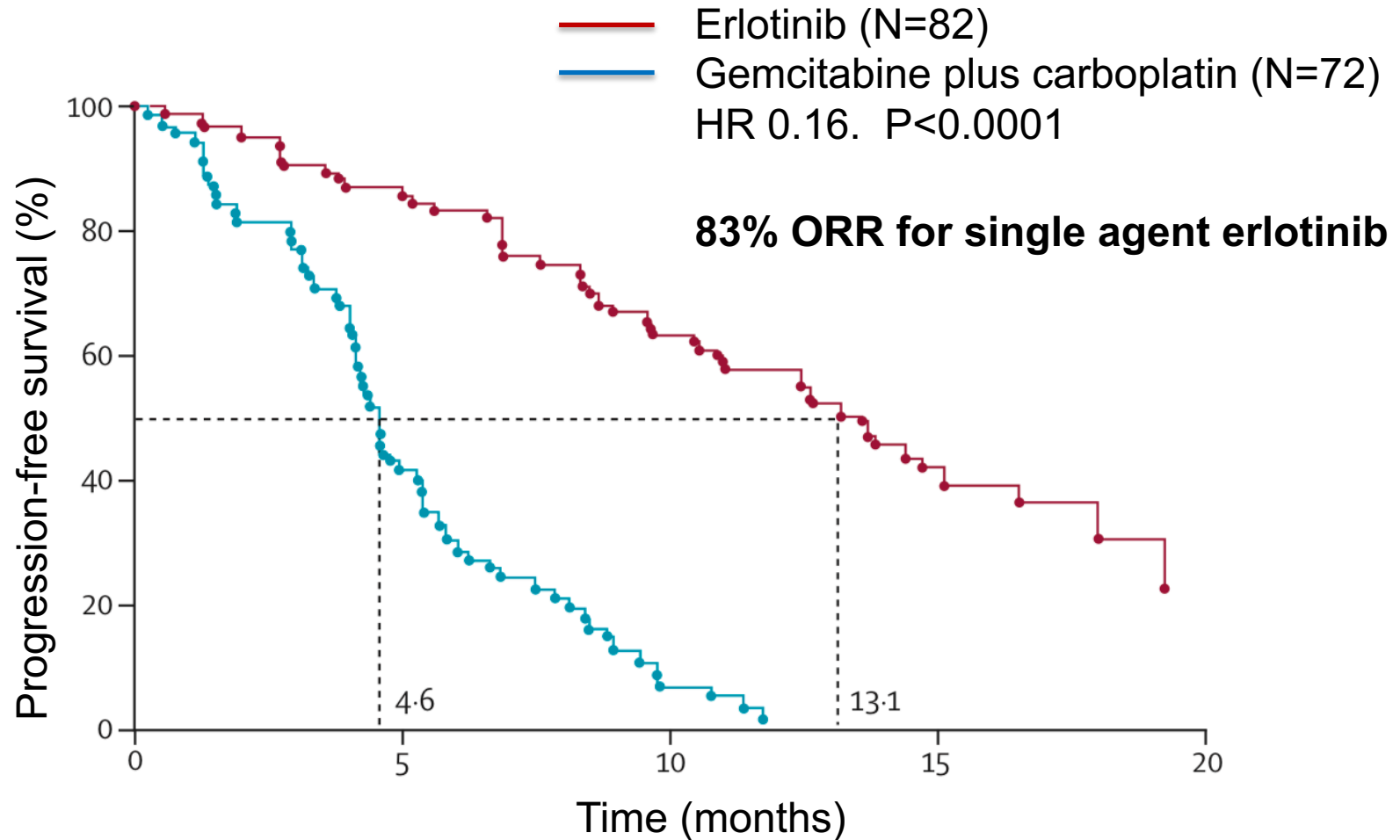
Requires care in selecting optimal drug combinations

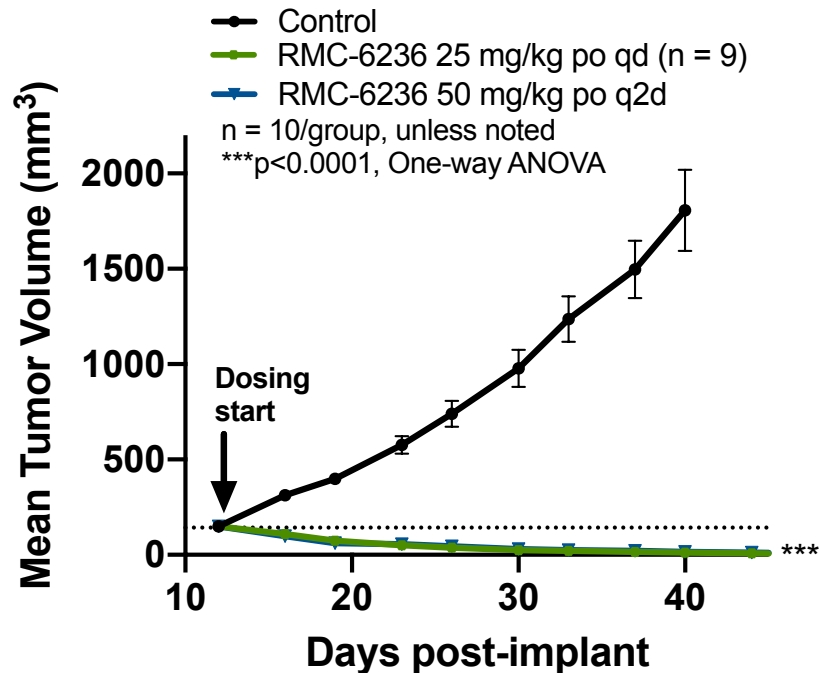# Optimizing Therapeutic Index with RAS^{MULTI} Inhibitors

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

Therapeutic Index Precedent Set By Inhibition of EGFR^{MUT} NSCLC Despite EGFR^{WT} Activity

Erlotinib (N=82)
Gemcitabine plus carboplatin (N=72)
HR 0.16. P<0.0001

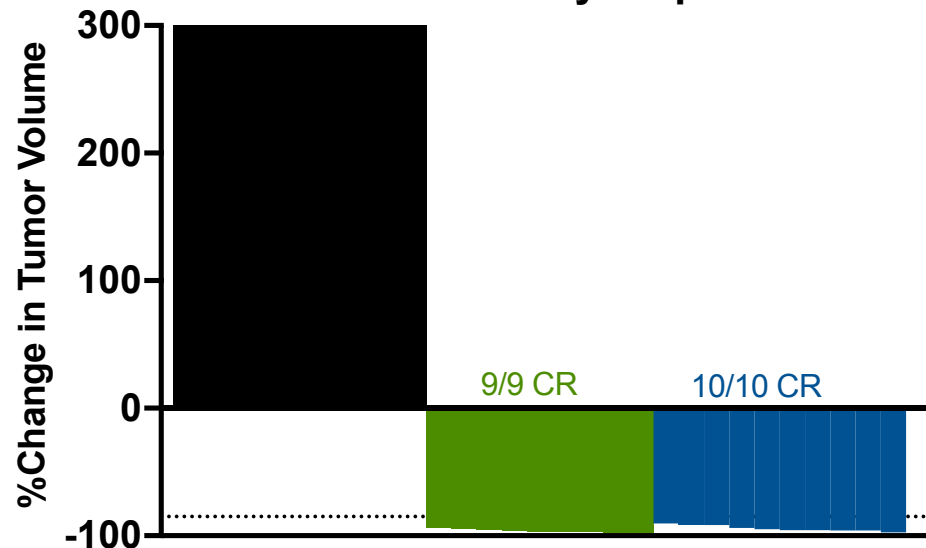**83% ORR for single agent erlotinib**

From: Zhou et al. Lancet Oncol 2011

RMC-6236: Intermittent Dosing Efficacious in KRAS^G12D Pancreatic Cancer Xenografts

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

Control
RMC-6236 25 mg/kg po qd (n = 9)
RMC-6236 50 mg/kg po q2d
n = 10/group, unless noted
***p<0.0001, One-way ANOVA

Dosing start

Mean Tumor Volume (mm^3)
Days post-implant

End of study responses

%Change in Tumor Volume

9/9 CR   10/10 CR

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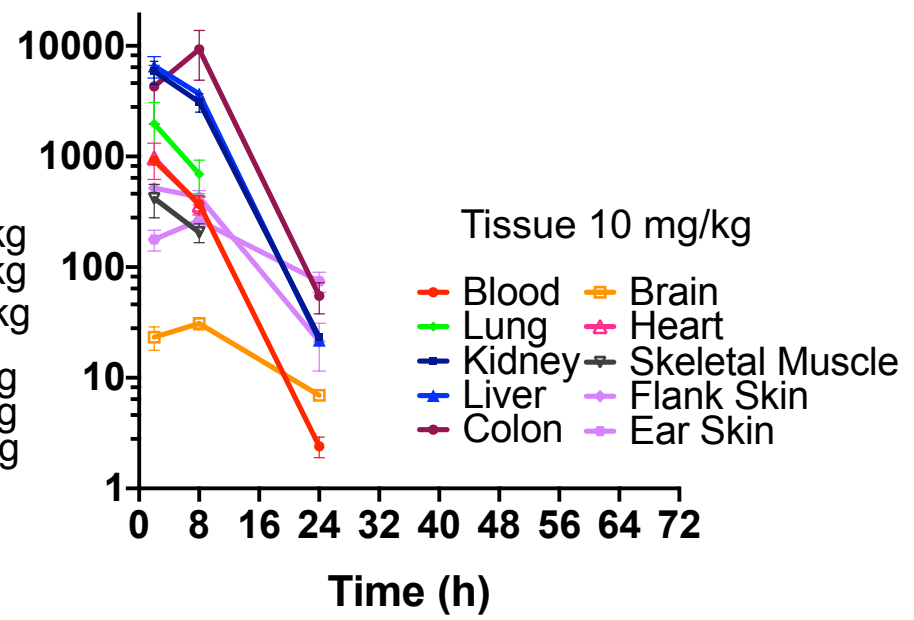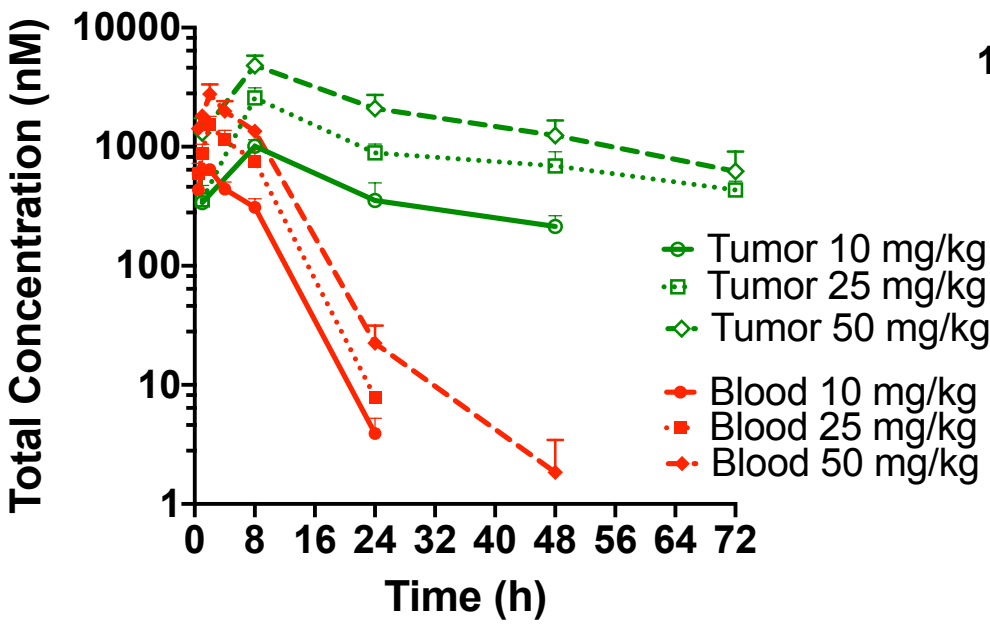Each animal represented as a separate bar

Dosing start
% Body Weight Change
Days post-implant
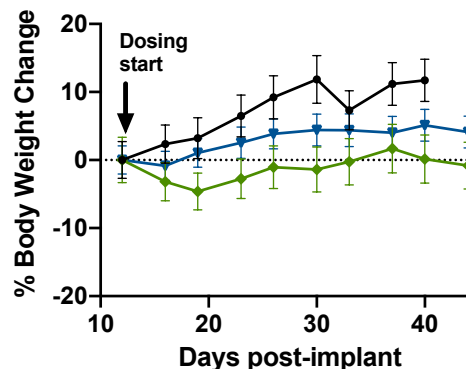
Sustained RMC-6236 Exposure In Tumor versus Transient Exposure in Normal Tissues
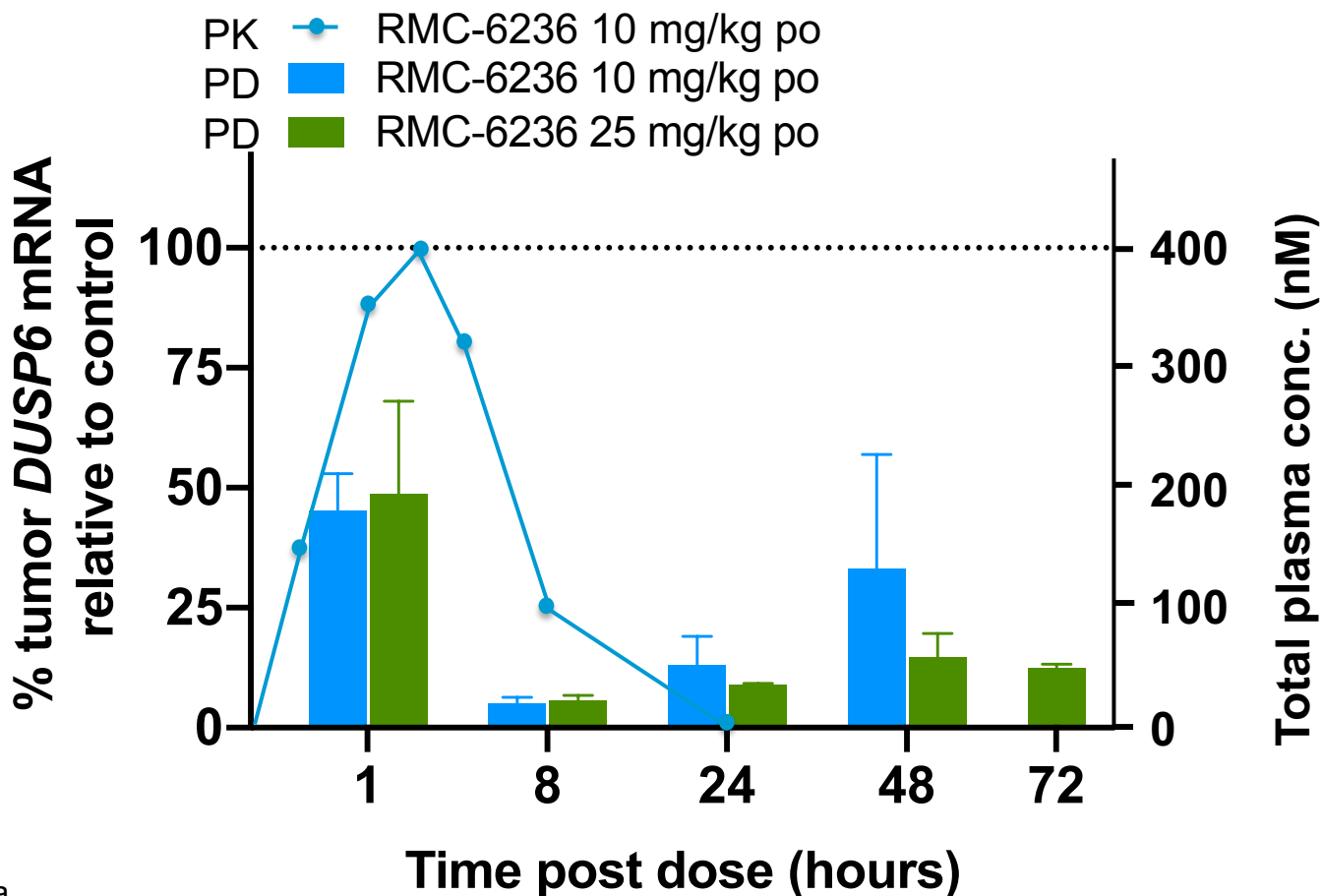

Single Dose in Tumor-Bearing Mice

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

Single Dose in Non-Tumor-Bearing Mice

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

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

PK — RMC-6236 10 mg/kg po
PD RMC-6236 10 mg/kg po
PD RMC-6236 25 mg/kg po

% tumor *DUSP6* mRNA relative to control

Total plasma conc. (nM)

Time post dose (hours)

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

High Affinity for Cyclophilin A Permits Sustained RAS Pathway Suppression
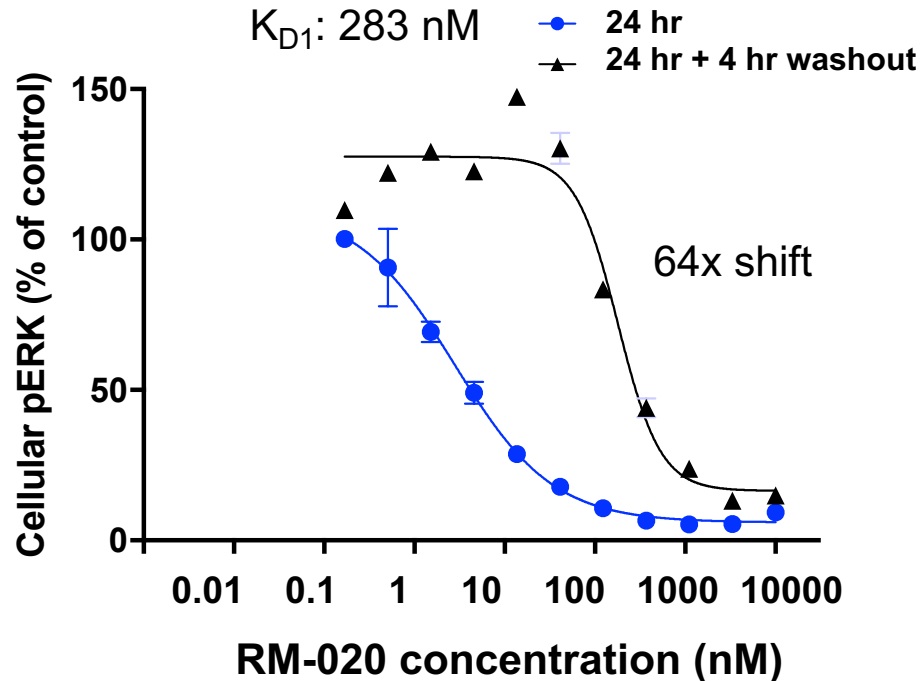

SW480
(CRC, KRAS$^{G12V/G12V}$)

RAS(ON) Inhibitor

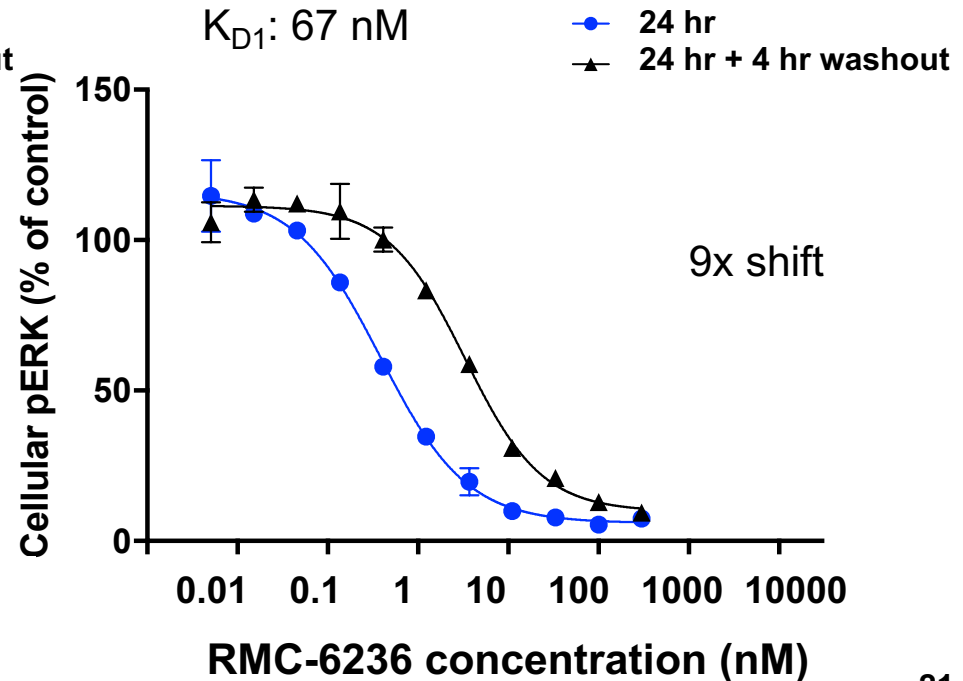Cyclophilin A Chaperone
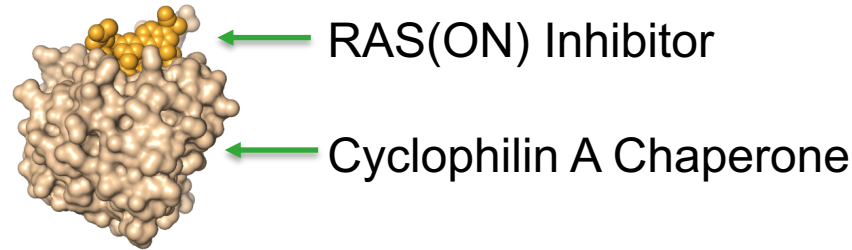
Low Cyclophilin A Affinity

RM-020
K_{D1}: 283 nM

- ● 24 hr
- ▲ 24 hr + 4 hr washout

64x shift

High Cyclophilin A Affinity

RMC-6236
K_{D1}: 67 nM

- ● 24 hr
- ▲ 24 hr + 4 hr washout

9x shift

Human Tumors may have Relatively High Cyclophilin A Levels versus Normal Tissues

Colon cancer
(45% of which is RAS^{MUT})

NSCLC
(35% of which is RAS^{MUT})

Endometrial cancer
(17% of which is RAS^{MUT})
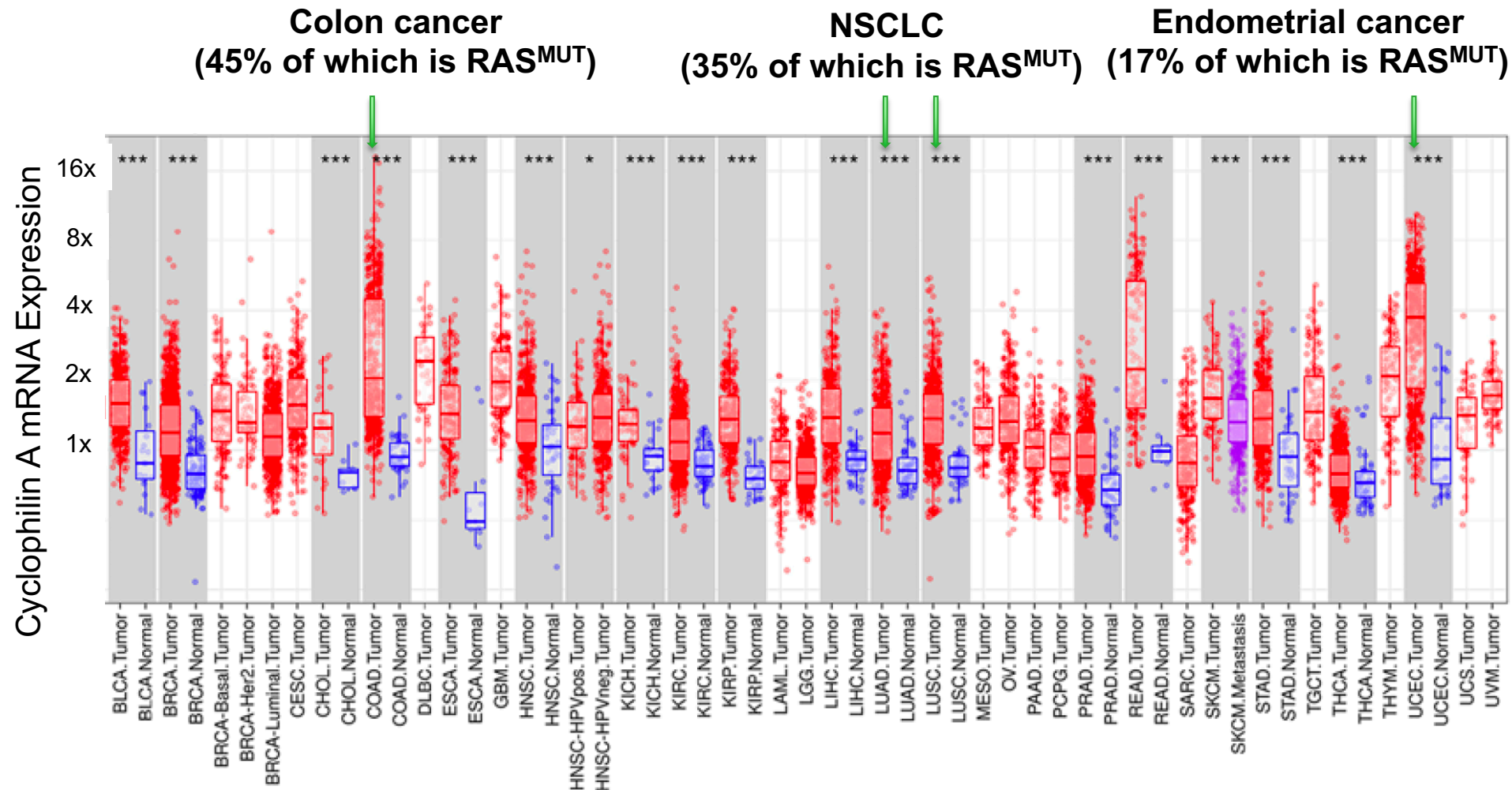
Figure from Wang et al, Onc Lett 2019
RAS^{MUT} incidence from Foundation Medicine
Insights August 2020

Tumor   Normal tissue

RMC-4630

RMC-5845

SHP2

SOS1

RAS(OFF)

RMC-6291
RMC-6236

RAS(ON)

mTORC1

RMC-5552

Cell Growth, Survival, & **Cancer**

RTK-driven signaling pathway

Feedback loop
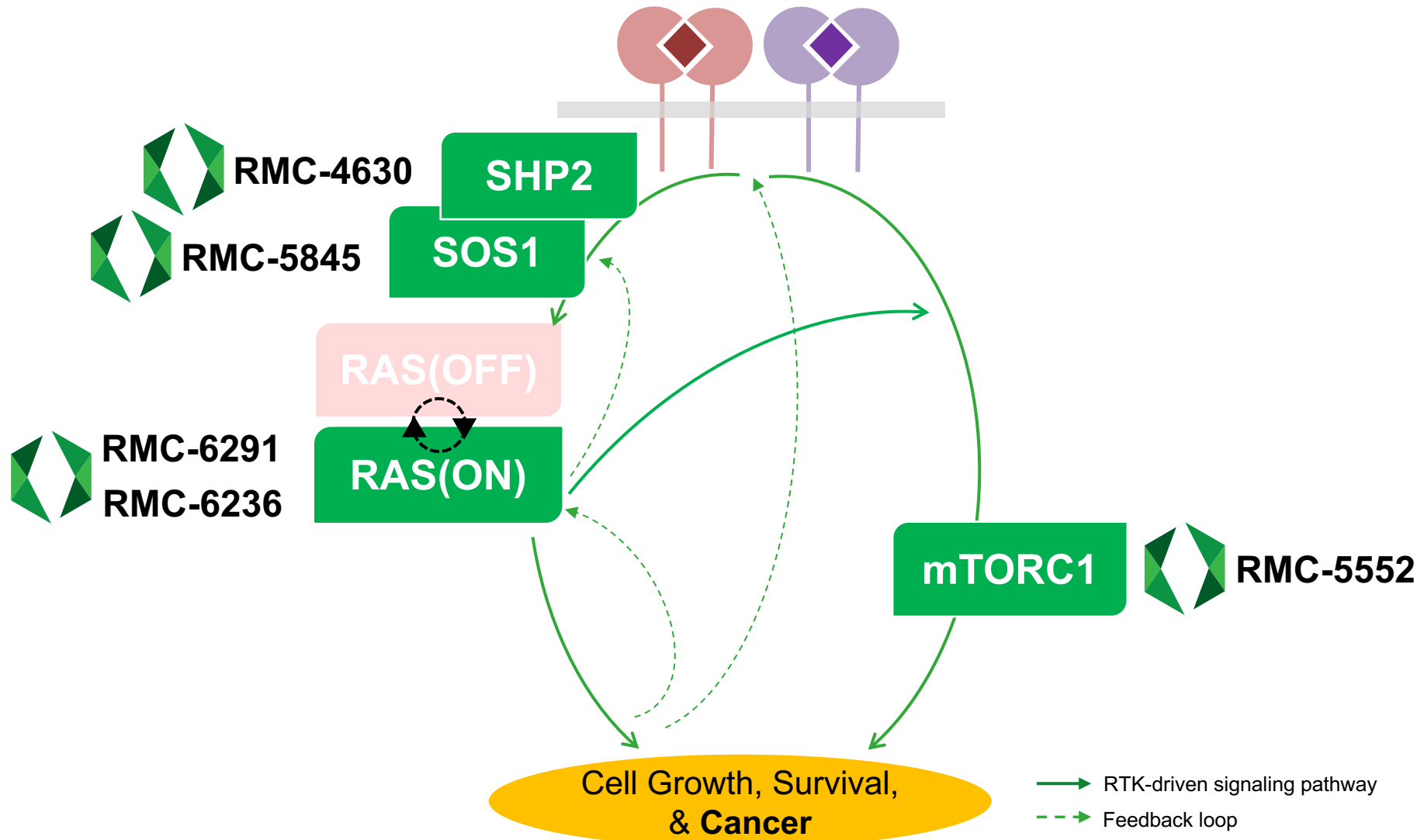
Translating Frontier Oncology Targets to *Outsmart Cancer*™