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Combination of RAS(ON) G12C-Selective and Multi-Selective Tri-Complex Inhibitors Overcomes Resistance and Prolongs Durability in Preclinical Models of $KRAS^{G12C}$ NSCLC

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Revolution Medicines

Disclosure Information

Xing Wei

I have the following relevant financial relationships to disclose:

Employee of: Revolution Medicines

Stockholder in: Revolution Medicines

Excessive RAS(ON) Signaling Drives 30% of Human Cancers, Targeted by RAS(ON) Inhibitors

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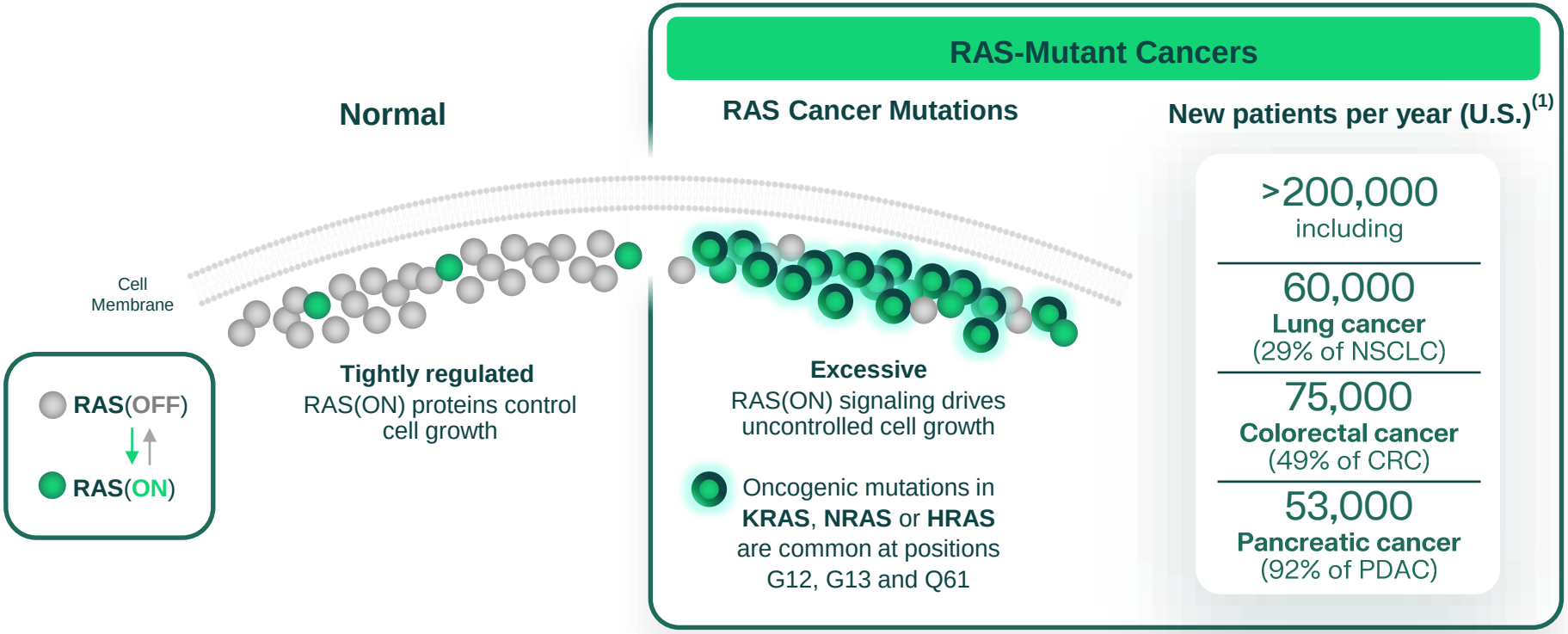

(1) Estimated using tumor mutation frequencies from Foundation Medicine Insights March 2022 and scaled to estimated patient numbers using cancer incidence from ACS Cancer Facts and Figures 2023

Complementary RAS(ON) Inhibitors Designed for Monotherapy and Combination Strategies Against RAS-Addicted Cancers

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RMC-6236
RAS(ON) multi-selective inhibitor

- Noncovalent, selective inhibitor with potent activity vs mutant and wild-type RAS(ON) proteins
- Orally bioavailable, generally well-tolerated in patients at active doses
- Clinical monotherapy anti-tumor activity observed across diverse RAS cancer mutations†
- Potential backbone of RAS(ON) inhibitor doublets with RAS(ON) mutant-selective inhibitors

†NCT05379985

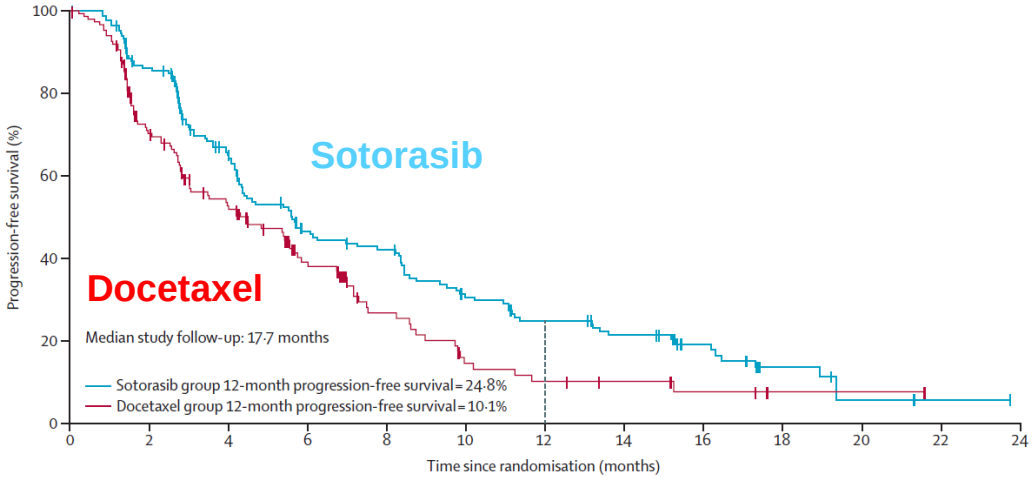
RMC-6291
RAS(ON) G12C-selective inhibitor

- Covalent and highly selective inhibitor of RAS^{G12C}(ON) proteins
- Orally bioavailable, generally well-tolerated in patients at active doses
- Promising and differentiated initial monotherapy clinical profile in previously treated $KRAS^{G12C}$ NSCLC‡
- Potentially complementary to RAS(ON) multi-selective inhibitor in RAS(ON) inhibitor doublets

‡NCT05462717

Unmet Medical Need for Improved Clinical Outcomes for KRAS^{G12C} NSCLC Patients

All Tumors Eventually Progress on KRAS^{G12C}(OFF) Inhibitor Treatment



De Langen et al. Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with KRAS^{G12C} mutation: a randomized, open-label, phase 3 trial. *The Lancet* 2023

	mPFS (95%CI)	mDoR (95%CI)	ORR (95%CI)
Sotorasib[(1)]	5.6 months (4.3 - 7.8)	8.6 months (7.1 - 18.0)	28.1% (21.5 - 35.4)
Adagrasib[(2)]	6.5 months (4.7 - 8.4)	8.5 months (6.2 - 13.8)	42.9% (33.5 – 52.6)

(1) De Langen et al., *Lancet.* 2023
(2) Jänne et al., *New Engl J Med.* 2022

RMC-6291: Active in KRAS^{G12C} NSCLC Previously Treated with or Naïve to KRAS^{G12C}(OFF) Inhibitors

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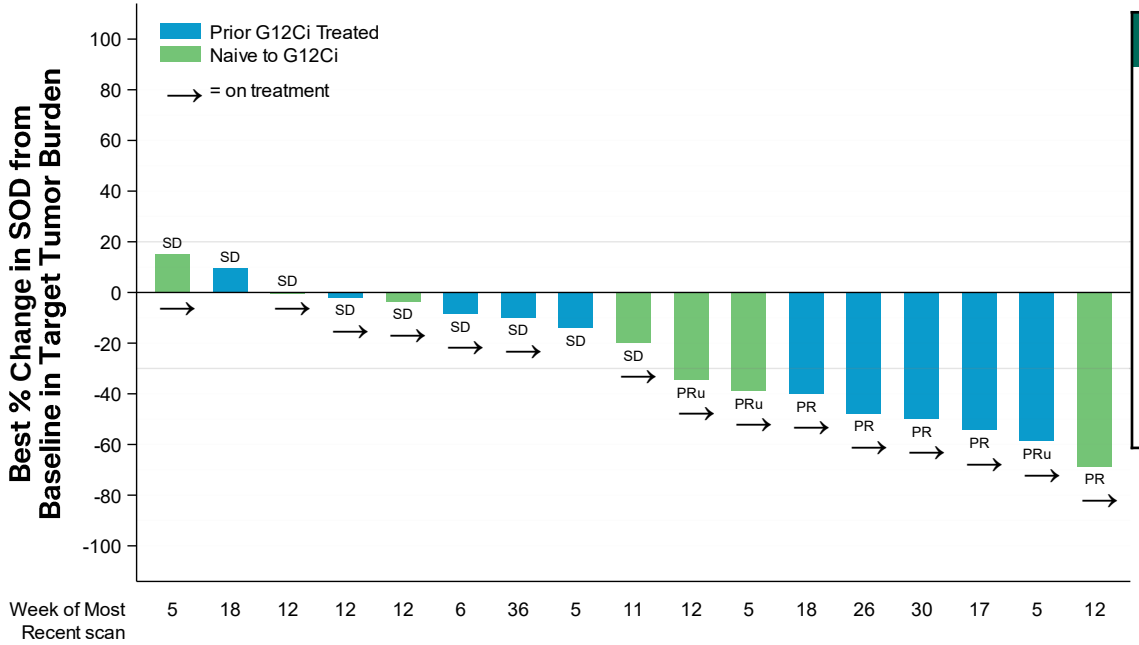
Evaluable for Efficacy* (n=17)



Tumor Response (per RECIST 1.1)		
Best overall response	**Prior G12Ci (n=10)**	**Naïve to G12Ci (n=7)**
Partial response†	5 (50)	3 (43)
Stable disease	5 (50)	4 (57)
Progressive disease	0	0
ORR	5 (50)	3 (43)
DCR††	10 (100)	7 (100)

All data are n (%)
†PR includes 5 confirmed and 3 unconfirmed
†† DCR=SD+PR+CR

*All treated patients who received a first dose of RMC-6291 at least 8 weeks prior to data extract date

Data Extracted 05 October 2023
Jänne et al. presented at AACR-NCI-EORTC 2023

RAS(ON) Inhibitors May Address Multiple Mechanisms of Clinical Resistance to KRAS^{G12C}(OFF) Inhibitors

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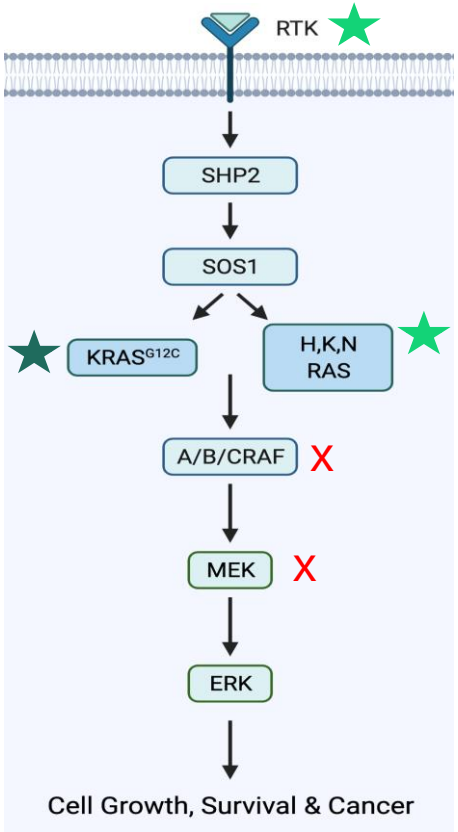
Upstream activation
RTK alterations



Mutant RAS amplification
SWII binding pocket mutations

WT RAS activation
Oncogene switch mutations

Downstream pathway activation (X)

RAS(ON) Rescue Mechanisms

- Potential sensitivity to RMC-6236
- Potential sensitivity to RMC-6236 or RMC-6291

Schulze, et al. *Science* 2023
Holderfield et al. *Nature* 2024

Awad and Aguirre et al., *New Engl J Med.* 2021
Tanaka et al. *Cancer Discovery* 2021
Zhao et al., *Nature* 2022
Sacher et al., *NEJM* 2023

RAS(ON) Inhibition Overcomes RTK-Mediated Clinical Resistance Mechanisms in Preclinical Models

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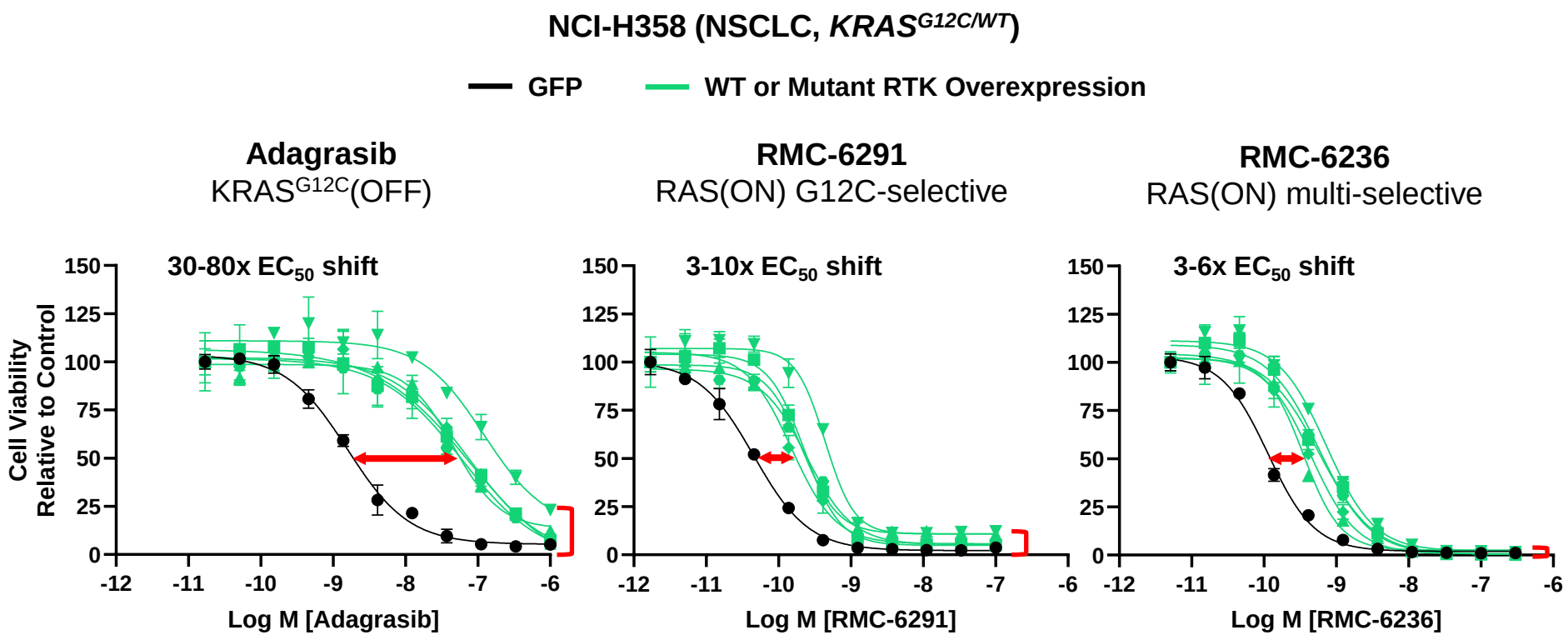

RTK overexpression includes EGFR, EGFR A289V, FGFR2, HER2 and RET M918T

RAS(ON) Inhibitor Doublet Drives Deep and Durable Tumor Regression and RAS Pathway Suppression in Xenografts

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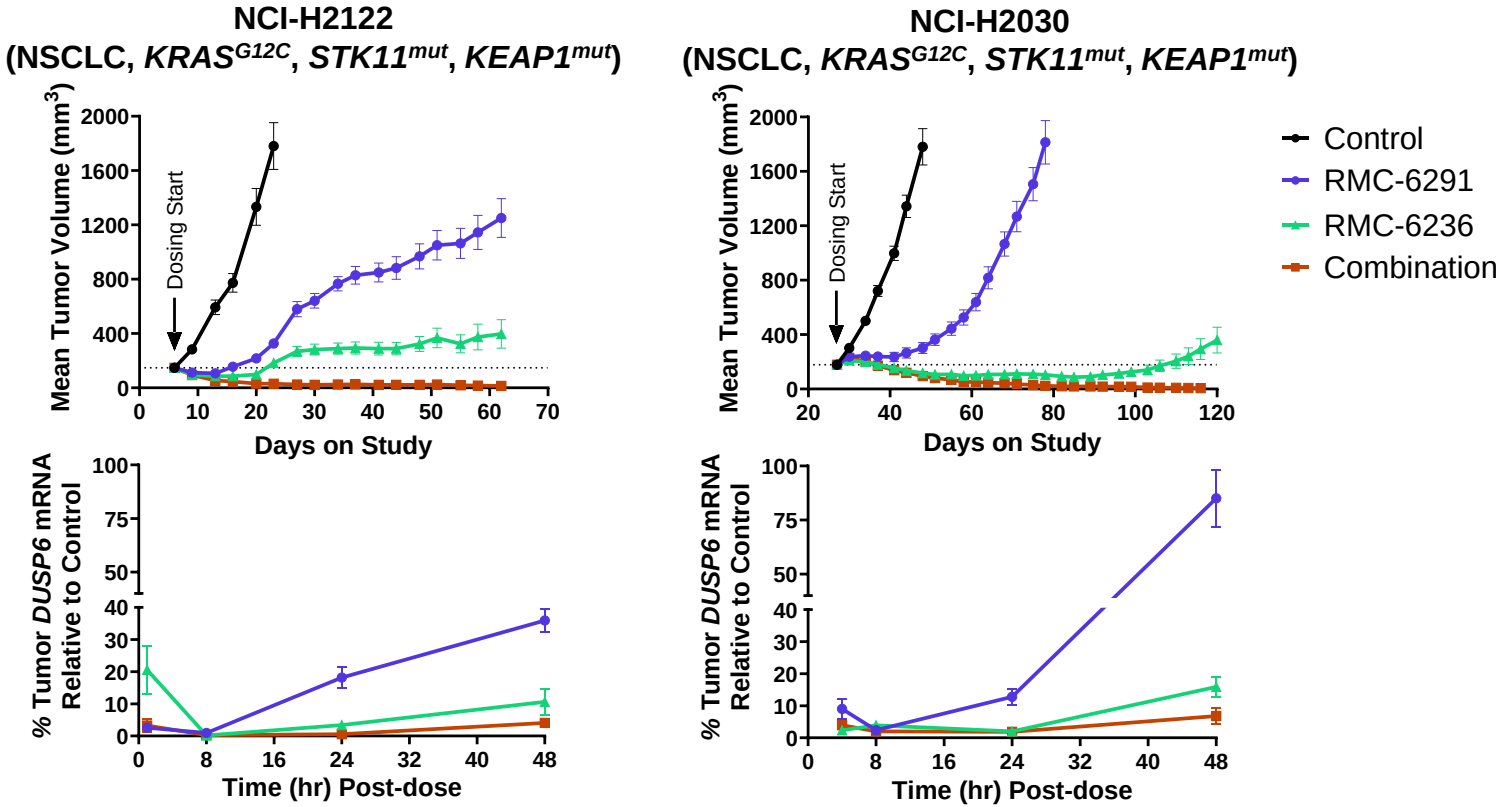
Tumor Volume

Pharmacodynamic Modulation of RAS Signaling in Tumors



RMC-6291 dosed at 100 mg/kg PO QD
RMC-6236 dosed at 25 mg/kg PO QD

RAS(ON) Inhibitor Doublet Induces Increased Apoptosis in KRAS^{G12C} NSCLC Xenograft Tumors

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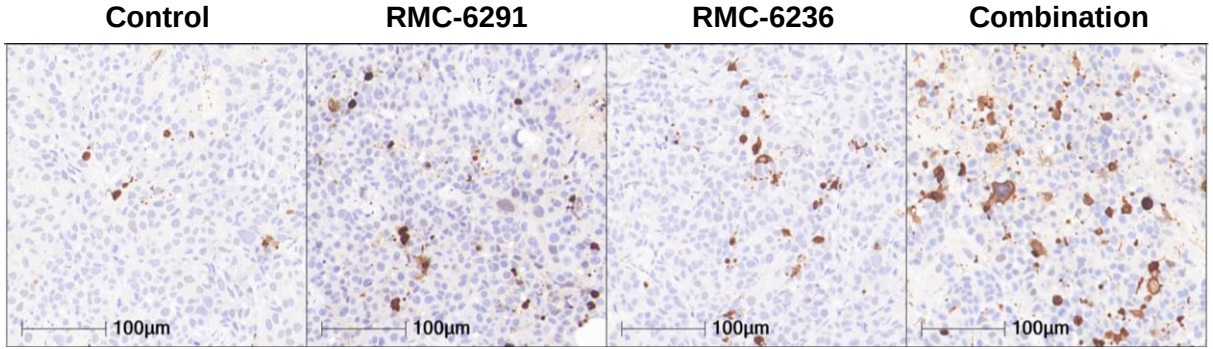
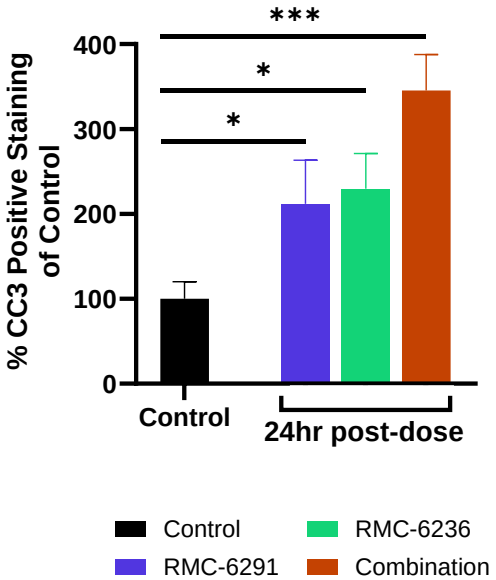
NCI-H2030
(NSCLC, *KRAS^{G12C}*, *STK11^{mut}*, *KEAP1^{mut}*)

Induction of Apoptosis (Cleaved Caspase-3)





RMC-6291 dosed at 100 mg/kg PO; RMC-6236 dosed at 25 mg/kg PO
n=3 per time point
*p<0.05, ***p<0.001 by t test (control vs treatment post single dose)

RAS(ON) Inhibitor Doublet Highly Active in KRAS^{G12C} NSCLC Xenografts Refractory to Mutant-Selective Inhibitors

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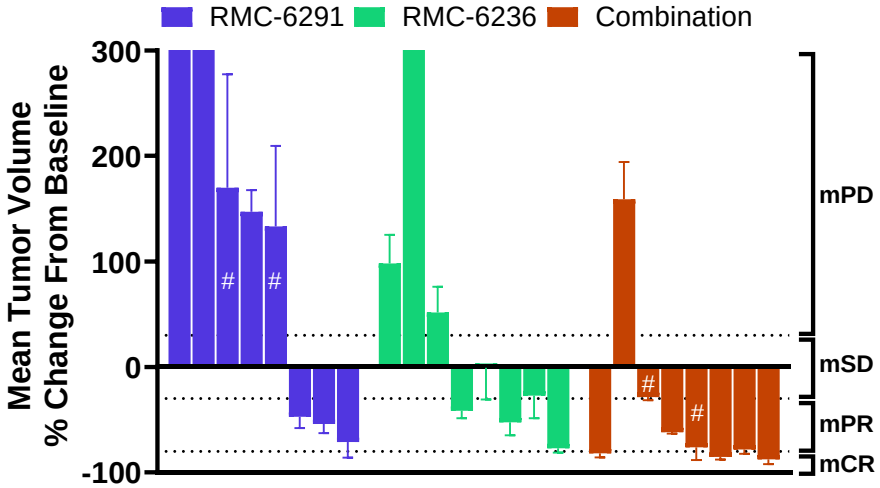
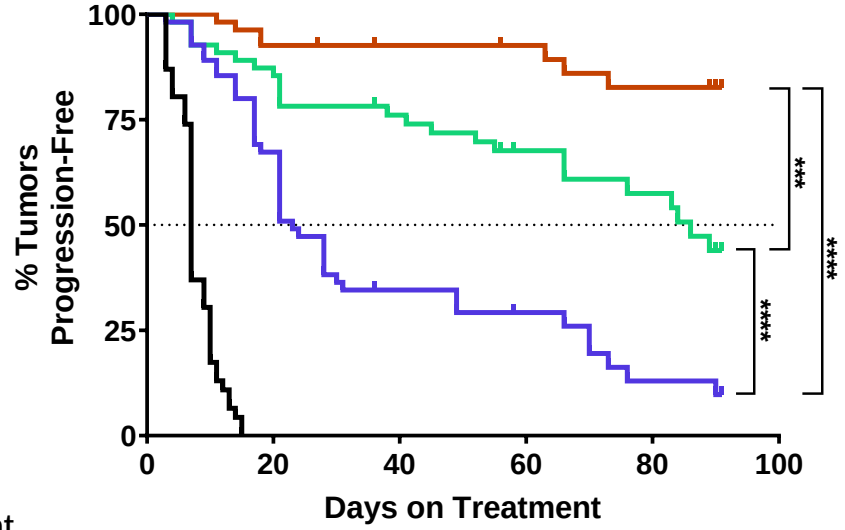
Improved Responses



Prolonged Durability



All treatments tolerated based on body weight assessment

n=3-15 per group
RMC-6291 dosed at 100 or 200# mg/kg PO QD; RMC-6236 dosed at 25 mg/kg PO QD
Xenografts in each treatment from left to right: NCI-H2122, CTG-2026, CTG-2536, NCI-H2030, LXFA-1335, LUN055, CTG-2579 and LUN092
***p<0.001; ****p<0.0001 by Log-rank test for indicated comparisons in KM analysis

- Control, n=46, median 7d
- RMC-6291, n=55, median 23d
- RMC-6236, n=55, median 86d
- Combination, n=54, median not reached

Summary

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- RAS(ON) multi-selective (RMC-6236) and RAS(ON) G12C-selective (RMC-6291) inhibitors, as single agents or in combination, may address multiple mechanisms of both intrinsic and acquired resistance to $KRAS^{G12C}$(OFF) inhibitors.
- The doublet of RMC-6236 and RMC-6291 leads to more durable RAS pathway suppression and increased induction of apoptosis in $KRAS^{G12C}$ NSCLC xenograft tumors *in vivo* compared to single agents.
- RMC-6236 and RMC-6291 demonstrate combinatorial benefits in both depth and durability of response in $KRAS^{G12C}$ NSCLC xenograft models that are refractory to mutant-selective inhibitors.
- A Phase 1b clinical trial combining RMC-6236 with RMC-6291 in patients with $KRAS^{G12C}$ solid tumors is currently underway (NCT06128551).

Acknowledgements

- The patients and investigators who are making clinical evaluation of RMC-6236 and RMC-6291 possible
- Revolution Medicines Research and Development Teams