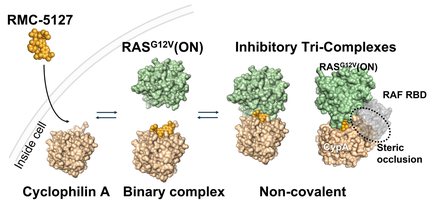
RMC-5127, a First-in-Class, Orally Bioavailable RAS(ON) G12V-Selective Tri-Complex Inhibitor, is CNS-Penetrant and Drives Regressions in Intracranially Implanted *KRAS^{G12V}* Xenograft Tumors

Zhe Chen, Andre Eriksson, Antonio Lopez Quinones, Bianca Lee, Nuntana Dinglasan, Nilufar Montazer, Jim Cregg, Anne V Edwards, Kate Sanders, Jacqueline AM Smith, David Wildes, Mallika Singh, Zhican Wang, Jingjing Jiang
Revolution Medicines, Redwood City, United States

Abstract

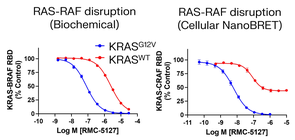
- RMC-5127 is an orally bioavailable, mutant-selective tri-complex inhibitor of the GTP-bound (ON) form of RAS^{G12V}.
- RMC-5127 drove deep suppression of RAS pathway activity, inhibited cell proliferation, and induced apoptosis in a panel of *KRAS^{G12V}* mutant human cancer cells *in vitro* but only caused submaximal inhibition in the panel of *K/N/HRAS* wildtype cancer cells, indicative of selectivity for KRAS^{G12V} over K/N/HRAS wildtype.
- Repeated oral dosing of RMC-5127 resulted in profound and durable anti-tumor activity in subcutaneous CDX and PDX models of *KRAS^{G12V}* mutant NSCLC, PDAC, and CRC *in vivo*.
- Patients with advanced cancers harboring activating mutations in RAS, particularly those with non-small cell lung cancer, often develop brain metastases.
- Dose-dependent exposure of RMC-5127 was observed in the brain of naïve mice, indicating the compound is brain penetrant.
- An intracranial xenograft model of *KRAS^{G12V}* tumors was established in immunodeficient mice to assess the CNS anti-tumor activity of RMC-5127. The intracranial tumor exposure of RMC-5127 was comparable with that observed in the brain of naïve mice at the same dose levels and was sufficient to drive robust pharmacodynamic responses in the brain tumor.
- RMC-5127 exhibited durable anti-tumor activity in the NCI-H441 intracranial model, with tumor regressions at well-tolerated doses.

Mechanism of Action



Results

1. RMC-5127 is a Potent RAS(ON) G12V-Selective Inhibitor

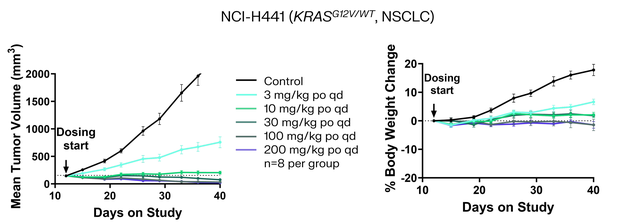


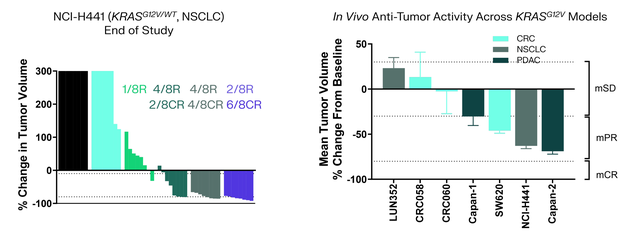
KRAS^{G12V} vs. K/N/HRAS^{WT} (1)

	RMC-5127	Trametinib (MEKi)
G12V fold sel. (EC_{50})	**26x**	3x
KRAS^{G12V} Median EC_{50} (2)	**2.1 nM**	1.7 nM
RAS^{WT} Median EC_{50} (2)	**53 nM**	4.6 nM
KRAS^{G12V} Median max. %Inhibition (3)	**93 %**	94 %
RAS^{WT} Median max. %Inhibition (3)	**53 %**	92 %

(1) Panel of *KRAS^{G12V}* mutant human cancer cells versus cells lacking RAS mutations.
(2) Median RMC-5127 concentration which gives half maximal inhibition
(3) Median maximum percentage of inhibition by RMC-5127 treatment

3. RMC-5127 Induces Profound Anti-Tumor Activity at Well-Tolerated Doses in Subcutaneous *KRAS^{G12V}* Xenograft Models *In Vivo*

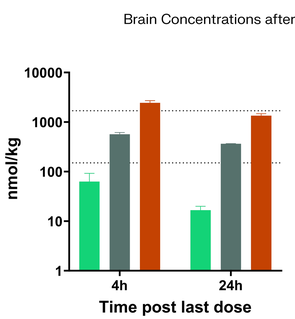




R: number of regressions >10% of initial
CR: number of regressions >80% of initial
Each mouse was represented as a separate bar.

Mouse tumor responses assigned according to mRECIST (modified from Gao et al. Nat Med. 2015): mSD = stable disease; mPR = partial response; mCR = complete response. Mouse RECIST based on response calculated as mean tumor volume % change from baseline on 28 ± 2 days of treatment.

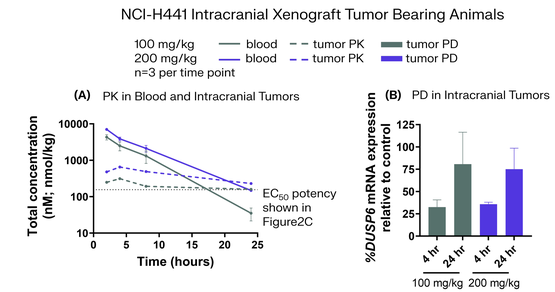
4. RMC-5127 Exhibits Dose-Dependent Exposure in the Brain of Naïve Mice



RMC-5127		
Dose (mg/kg), PO		100
Time (hour), post-dose		4
Naïve Mouse 7-day Repeat Dose	Total Brain Conc (nM)	568
	Brain Conc: Blood Conc Ratio	0.14
Tumor-Bearing Mouse Single Dose	Total Brain Conc (nM)	485
	Brain Conc: Blood Conc Ratio	0.12

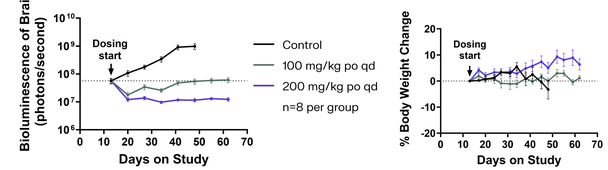
The brain exposure in naïve BALB./c mice orally dosed at 100 mg/kg is comparable with that observed in the brain of tumor-bearing mice dosed at the same level.

5. RMC-5127 Exhibits Dose-Dependent PK/PD in the Intracranially Implanted NCI-H441 Xenograft Model

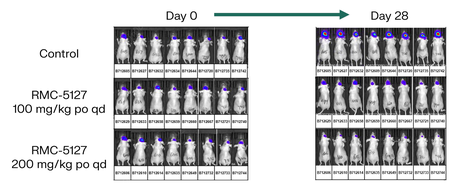


(A) Oral administration of RMC-5127 exhibits dose-dependent exposures in blood and intracranial tumors, respectively. (B) RMC-5127 inhibits MAPK pathway in the intracranial tumors at 4 hours post a single oral dose.

6. RMC-5127 Induces Durable Anti-Tumor Activity in the Intracranially Implanted NCI-H441 Xenograft Model



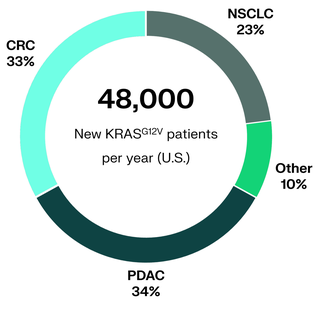
Mice in the control group were terminated early due to body weight loss.



Conclusions

- In addition to its broad anti-tumor activity in *KRAS^{G12V}* cancer models, data here demonstrate that RMC-5127 is a CNS-penetrant RAS(ON) G12V-selective inhibitor and could drive durable regressions in intracranially implanted xenograft tumors.
- Preclinical data presented here support further investigation of the potential for RMC-5127 to benefit patients with advanced RAS G12V-mutated cancers, including those with brain metastases.

RMC-5127: A Potent, Oral and RAS(ON) G12V-Selective Tri-Complex Inhibitor



Potency for Tumor Cell Inhibition	
pERK (Capan-1, IC_{50}, nM)	0.6
CTG (Capan-1, IC_{50}, nM)	2.1

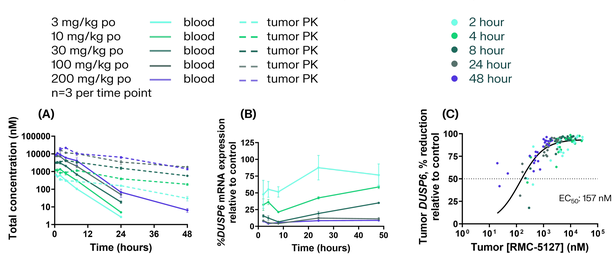
Target Selectivity and Safety	
Selectivity • Over RAS-independent cell • Over RAS^{WT}-dependent cell	> 1000X ~26X
Off-target safety panel	Low Risk

PK/ADME	
Oral bioavailability (cross species average %F)	35
Metabolic clearance (hepatocytes, multiple species)	Low to Moderate

*New patients per year rounded to nearest 1000th. Cancer type percentages may not add up to 100% due to rounding.

References: 1) Calculated 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

2. RMC-5127 Exhibits Dose-Dependent Exposure in Blood/Tumor and MAPK Pathway Inhibition



(A) RMC-5127 PK in blood and tumor post an oral single dose of RMC-5127 at indicated concentrations. Compound elimination in tumors are slower than that in blood. (B) *DUSP6* mRNA expression in tumors post a single dose of RMC-5127 at indicated concentrations. (C) Consolidated RMC-5127 PK and PD response in tumors at indicated time points. EC_{50} of RMC-5127 potency in inhibiting *DUSP6* mRNA expression is interpolated from the PK/PD relationship curve.

Abbreviations: ADME, absorption, distribution, metabolism, and excretion; PK, pharmacokinetics; PD, pharmacodynamics; CypA, Cyclophilin A

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Correspondence: jjiang@revmed.com

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