Selective Inhibition of the Active State of KRAS^{G12V} with the Non-Covalent, Tri-Complex Inhibitor RMC-5127

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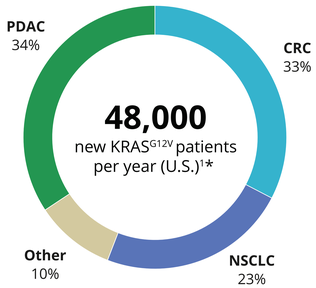
Abstract

- KRAS^{G12V} mutations are found in multiple cancers, and successful targeting of KRAS^{G12V}-mutant tumors represents an important unmet medical need.
- We previously applied our tri-complex inhibitor platform, which utilizes chemical remodeling of the cellular chaperone cyclophilin A (CypA) to bind to undruggable surfaces, to design mutant-selective inhibitors targeting KRAS^{G12C}, KRAS^{G13C}, KRAS^{G12D}, and KRAS^{Q61H}, in addition to the RAS^{MULTI} inhibitor RMC-6236.
- RMC-5127 binds to CypA with high affinity, creating a neomorphic interface that forms a selective, non-covalent interaction with KRAS^{G12V}(ON).
- The resulting tri-complex sterically blocks effector binding to KRAS^{G12V}(ON), thereby inhibiting downstream signaling.
- RMC-5127 potently suppresses ERK phosphorylation in KRAS^{G12V}-mutant cancer cells, and is infinitely selective for KRAS^{G12V} over RAS^{WT}-driven cancer cell lines due to a limiting cellular concentration of CypA.
- In preclinical species, RMC-5127 shows good bioavailability, dose-proportional exposure, and low clearance, allowing for oral dosing.
- In human xenograft tumors harboring KRAS^{G12V} mutations, a single dose of RMC-5127 induces dose-dependent, deep, and durable suppression of RAS pathway signaling *in vivo*.
- Repeated daily oral administration of RMC-5127 is well tolerated and demonstrates profound anti-tumor activity in these preclinical models.

RMC-5127: A Potent, Oral, and Selective Tri-Complex Inhibitor of KRAS^{G12V}(ON)



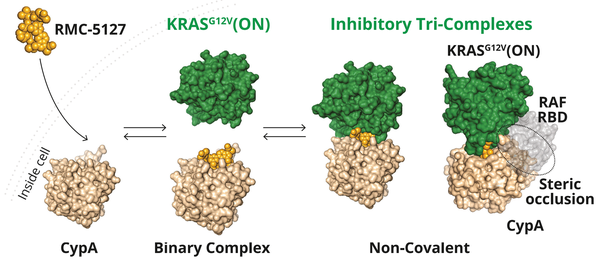
*New patients per year rounded to nearest 1000th. Cancer type percentages may not add up to 100% due to rounding.

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

Target Selectivity and Safety	
Selectivity • Over RAS-independent cells • Over RAS^{WT}-dependent cells	 >1000× 26×
Off-target safety panel	Low risk

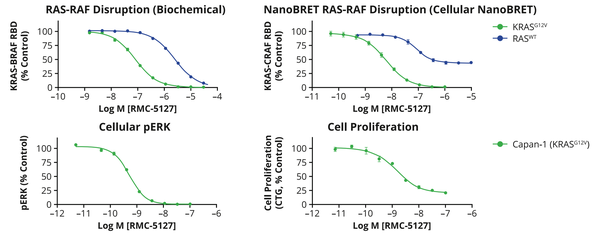
PK/ADME	
Oral bioavailability (cross-species average %F)	35
Metabolic clearance (hepatocytes, multiple species)	Low to moderate

Mechanism of Action

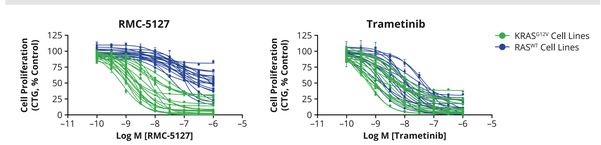


Results

RMC-5127 is a Selective and Potent Inhibitor of KRAS^{G12V}

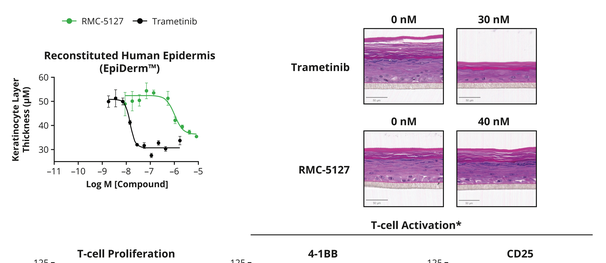


RMC-5127 is Selective for KRAS^{G12V} Over RAS^{WT}-Dependent Cancer Cell Lines



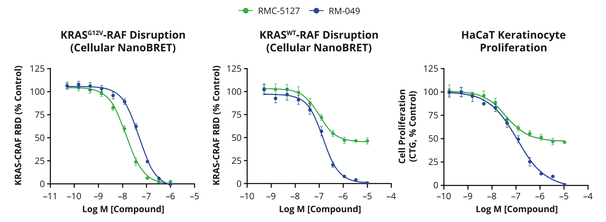
	G12V Fold Selectivity (EC_{50})	Median EC_{50}		Maximum % Inhibition	
		KRAS^{G12V}	RAS^{WT}	KRAS^{G12V}	RAS^{WT}
RMC-5127 (KRAS^{G12V}[ON])	26×	2.1 nM	53 nM	93%	53%
Trametinib (MEK)	3×	1.7 nM	4.6 nM	94%	92%

RMC-5127 Shows Negligible Activity in Non-Cancer Cells



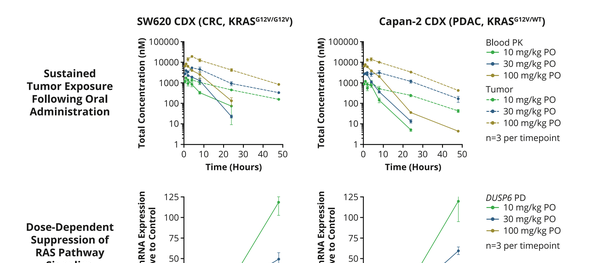
*T-cell data was pooled from two donors.

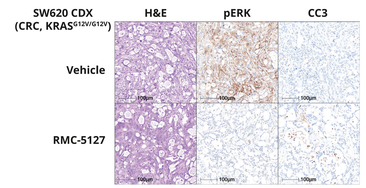
Submaximal Inhibition of RAS^{WT} by RMC-5127 is a Function of Tri-Complex Mechanism of Action



- Cellular CypA concentration puts an upper bound on the active binary complex concentration.
- Affinity (K_D) of the RMC-5127:CypA binary complex for KRAS^{WT} is 2.8 µM, close to the concentration of CypA (~10 µM)[2]. Therefore, complete saturation of CypA with RMC-5127 is insufficient to fully inhibit KRAS^{WT}.
- The analog RM-049 exhibits similar G12V selectivity to RMC-5127 but has ~10× greater potency, with a K_D of the RM-049:CypA binary complex for KRAS^{WT} of 0.27 µM, and can fully inhibit KRAS^{WT}.

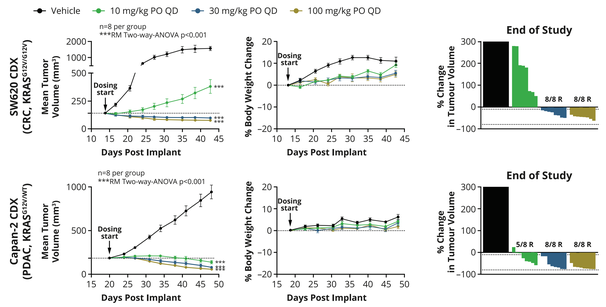
RMC-5127 Exhibits Favorable PK/PD Profile in Preclinical Models





Representative images of IHC staining shown in CDX tumors after a single dose of RMC-5127 (100 mg/kg). Images for H&E and pERK are from 8-hour-treated mice, and images for CC3 are from 24-hour-treated mice.

RMC-5127 Drives Tumor Regression at Well-Tolerated Doses



References: 1. Calculated using tumor mutation frequencies from Foundation Medicine Insights March 2022, and scaled to estimate patient numbers using cancer incidence from American Cancer Society Cancer Facts and Figures 2023; 2. Concurrent inhibition of oncogenic and wild-type RAS-GTP for cancer therapy. (Holderfield M, et al. pre-print, 2023).

Abbreviations: 4-1BB, tumor necrosis factor receptor superfamily member 9; ADME, absorption, distribution, metabolism, and excretion; ANOVA, analysis of variance; BRET, bioluminescence resonance energy transfer; CC3, cleaved caspase 3; CD25, cluster of differentiation 25; CDX, cell line xenograft; CRC, colorectal cancer; CTG, CellTiter-Glo®; CypA, cyclophilin A; DUSP6, dual specificity phosphatase 6; EC_{50}, half maximal effective concentration; ERK, extracellular signal-regulated kinase; IC_{50}, half maximal inhibitory concentration; IHC, immunohistochemistry; KRAS, Kirsten rat sarcoma viral oncogene homolog; NSCLC, non-small cell lung cancer; PD, pharmacodynamic; PDAC, pancreatic ductal adenocarcinoma; pERK, phosphorylated ERK; PK, pharmacokinetic; PO, by mouth; QD, once daily; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma; RBD, RAS-binding domain; WT, wild-type.

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