

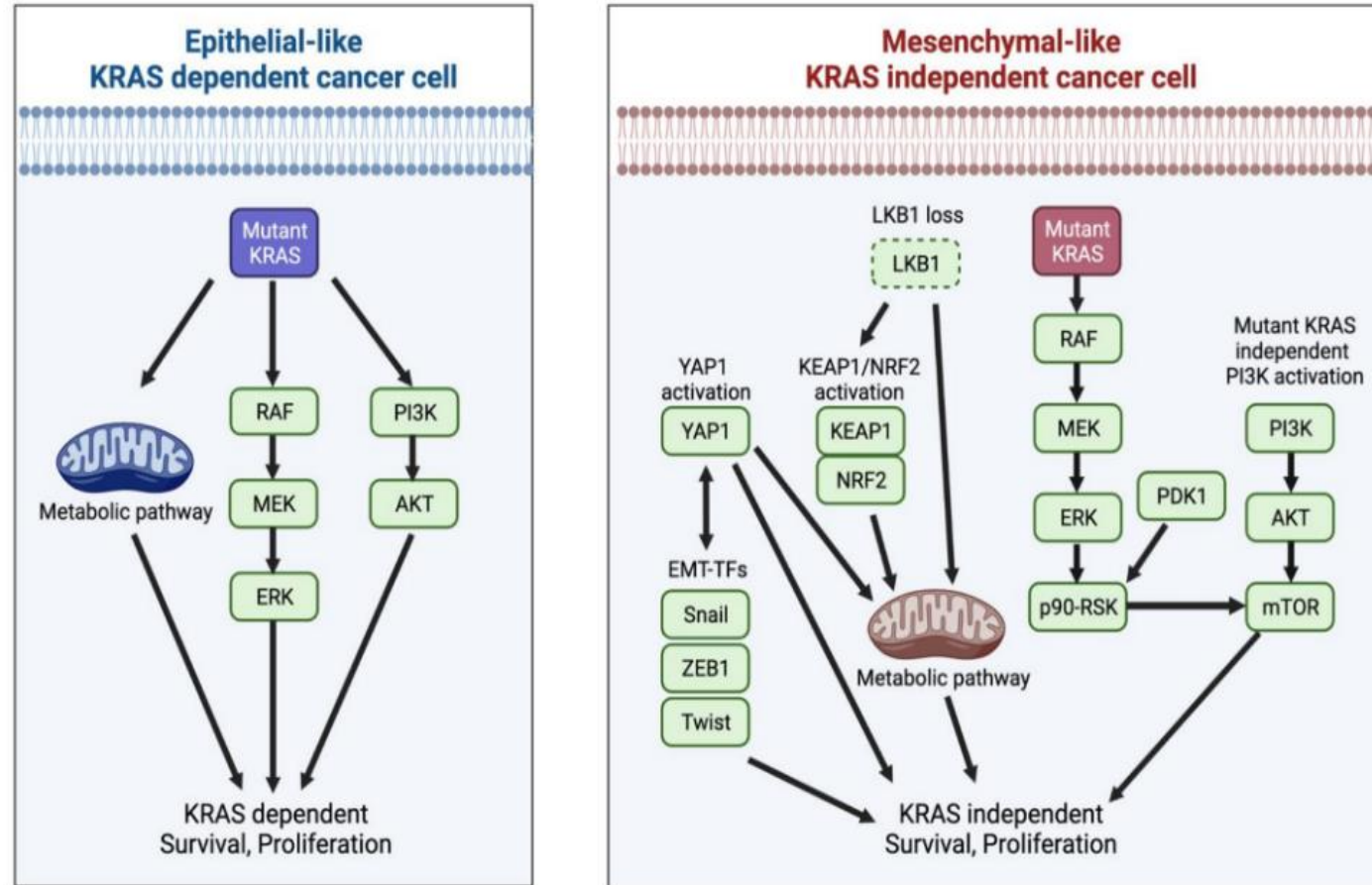
RMC-9805 induced resistant KL-Luc model



2026.06

Escaping mechanisms of KRAS dependency and independency

KRAS mutation and LKB1 Loss in cell survival



- ◆ Mechanisms of KRAS dependency:
 - Inhibits apoptosis
 - Promotes proliferation
 - Drives metabolic reprogramming and alters TME (tumor microenvironment) through upregulation of GLUT1, Hexokinase 1/2, and PFK1 as well as hexosamine Biosynthesis Pathway activation
- ◆ Mechanisms of KRAS Independency:
 - Activation of YAP1 and/or RSK–mTOR pathways
 - Co-mutations in **STK11 (LKB1)**, **KEAP1**, and **NFE2L2 (NRF2)**
 - Enhanced glutaminolysis
 - EMT phenotype emergence

Adachi Y, Kimura R. *Cancers (Basel)*. 2021 Oct 11;13(20):5081

RAS mutations in major cancer types and KRAS inhibitors

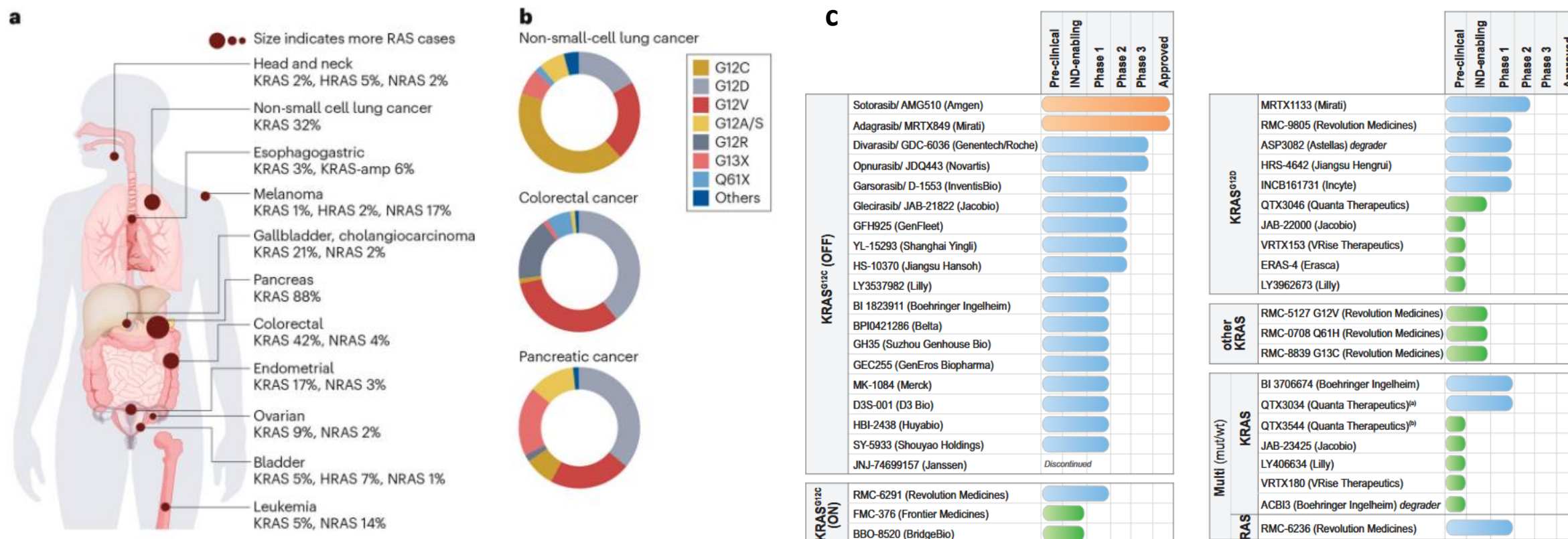
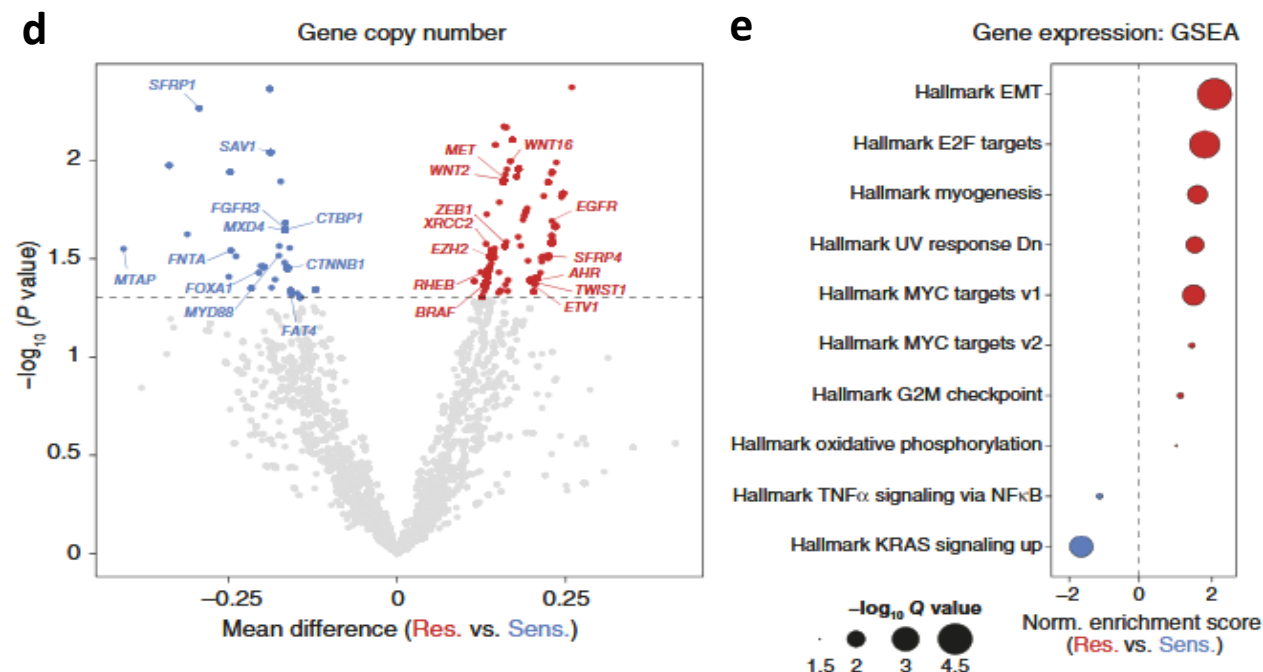


Figure a and b. Frequency of RAS mutations in major cancer types. RAS mutations exhibit significant tissue specificity, with the most common and lethal cancer types, such as colorectal cancer (CRC), pancreatic ductal adenocarcinoma (PDAC), and non-small cell lung cancer (NSCLC), being prominently associated with KRAS mutations (43%, 85%, and 31%, respectively). KRAS G12C is the most common allele in NSCLC; KRAS G12D and KRAS G12V are the two most common alleles in CRC and PDAC. **Figure c.** Mutant-specific and multi-(K)RAS inhibitors in clinical trials or pre-clinical development.

KRAS G12D resistance & overcoming strategies



Mechanisms of KRAS G12D inhibitors resistance:

➤ Genetic alterations:

- KRAS amplification
- Amplifications: RTKs (EGFR, ERBB family, FGFR, MET), MYC, CDK6, YAP1
- Mutations: PIK3CA, secondary KRAS mutations

➤ Adaptive signaling

- RTK-driven feedback activation (EGFR/ERBB family, other RTKs)
- PI3K–AKT–mTOR pathway activation
- MAPK pathway rebound
- ABC transporter-mediated efflux pathway

➤ Cell state plasticity

- EMT/pEMT programs: transition from classical to mesenchymal/pEMT states
- pEMT features: MYC & mTORC1 activation, OXPHOS, stress response pathways

➤ Tumor microenvironment (TME) influence

■ Strategies to Overcome KRAS G12D Resistance

- **Targeting genetic alterations:** next-generation KRAS G12D inhibitors; Target amplified oncogenes: SHP2 or SOS1 inhibitors
- **Counteracting adaptive signaling:** Combination therapies to block feedback loops
- **Addressing cell state plasticity:** target pEMT-associated pathways and target cell surface markers upregulated in resistant states: CLDN18.2, Netrin-1,
- **Exploiting immune vulnerabilities**
- **Chemotherapy combinations**

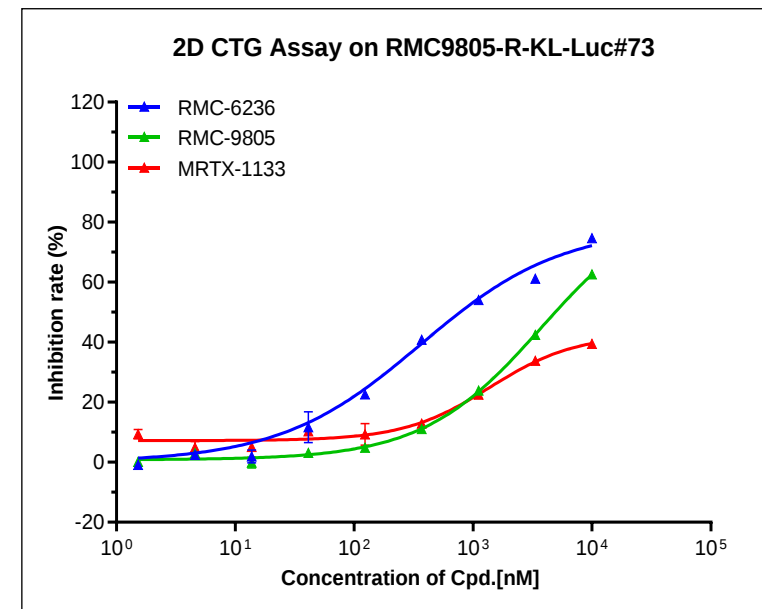
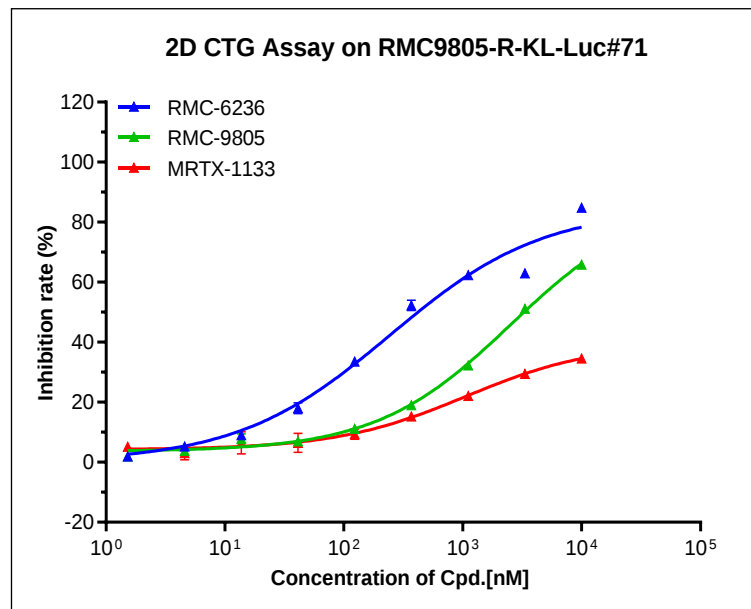
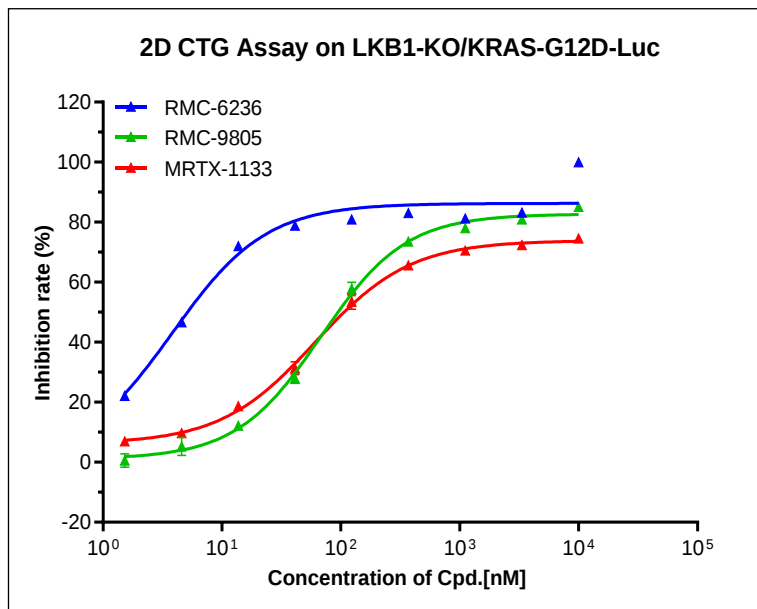
Dilly J, Hoffman MT. Cancer Discov. 2024 Nov 1;14(11):2135-2161

Summary of RMC-9805 induced resistant model

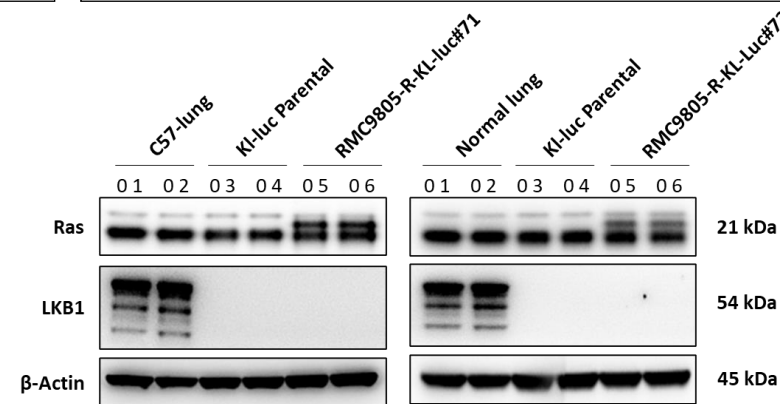
Model ID	Cancer type	Drugs tested	Target	Status
RMC-9805 resistant KP4	Pancreatic cancer	RMC-9805	KRAS G12D	Ongoing
RMC-9805 resistant KL-luc	Lung cancer	RMC-9805	KRAS G12D	Ongoing

Establishment of RMC-9805 induced resistant KL-Luc #71 and #73 cells

In vitro validation of RMC-9805 induced KL-Luc resistant cells



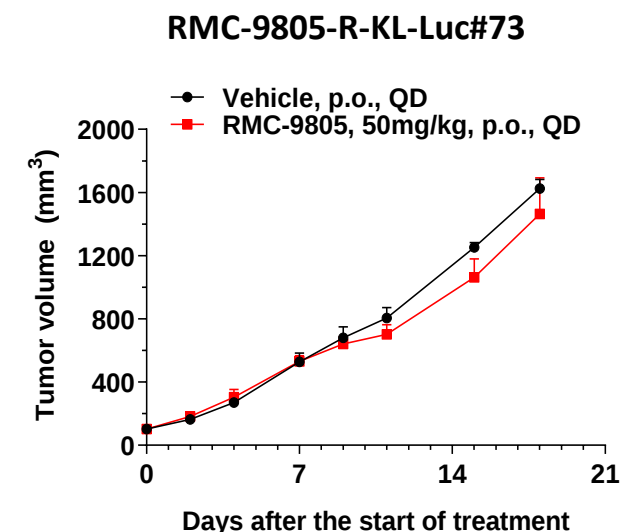
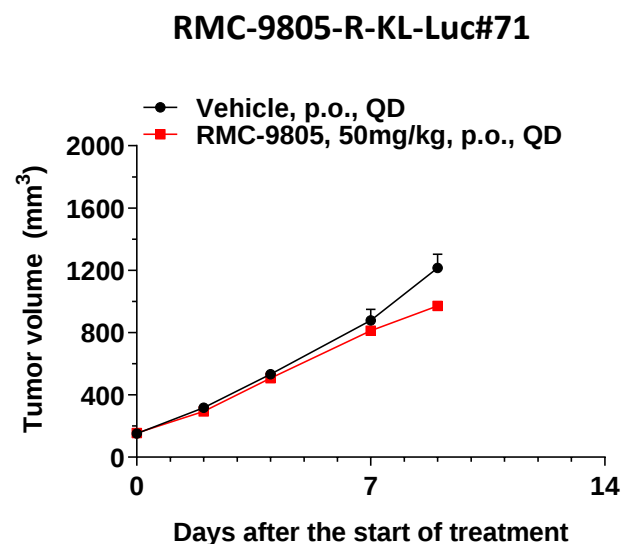
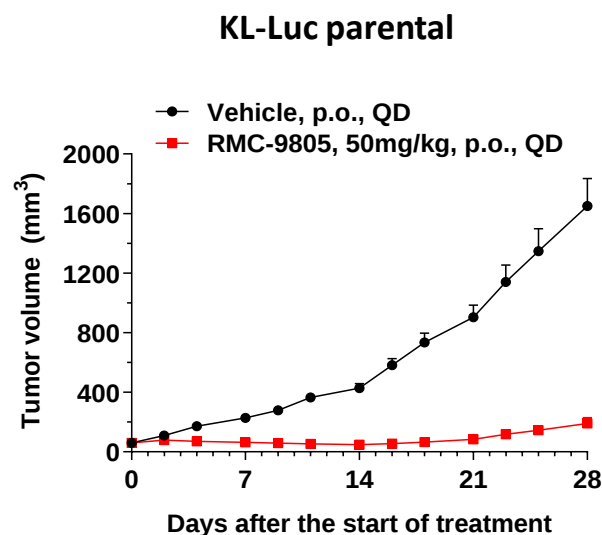
Cell line	Compounds	AbiC50 (nM)	RelC50 (nM)	Top(%)	Bottom (%)
KL-Luc Parental	RMC-6236	5.13	3.84	99.96	22.11
	RMC-9805	94.62	67.99	85.06	0.52
	MRTX-1133	106.58	60.84	74.53	7.01
RMC9805-R-KL-Luc#71	RMC-6236	420.08	245.2	84.80	1.95
	RMC-9805	3274.95	2514	65.88	1.93
	MRTX-1133	\	1063	34.58	3.04
RMC9805-R-KL-Luc#73	RMC-6236	778.92	361.4	74.66	-0.88
	RMC-9805	4911.69	3756	62.64	-0.22
	MRTX-1133	\	1375	39.41	3.58



Establishment of RMC-9805 induced resistant KL-Luc#71 and #73 cells

In vivo validation of KL-Luc parental and RMC-9805 induced KL-Luc resistant model

Model	Drugs	Schedule	TGI
KL-Luc parental	RMC-9805	50mg/kg, PO, QD	91.80%
RMC-9805-R-KL-Luc#71	RMC-9805	50mg/kg, PO, QD	23.24%
RMC-9805-R-KL-Luc#73	RMC-9805	50mg/kg, PO, QD	10.62%



RMC9805-R-KL-Luc#71 and RMC9805-R-KL-Luc#73 established tumor models showed resistant to RMC-9805 (50 mg/kg) .



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For questions and requests, please email to Pharmacology-BD-Translation@wuxiapptec.com



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