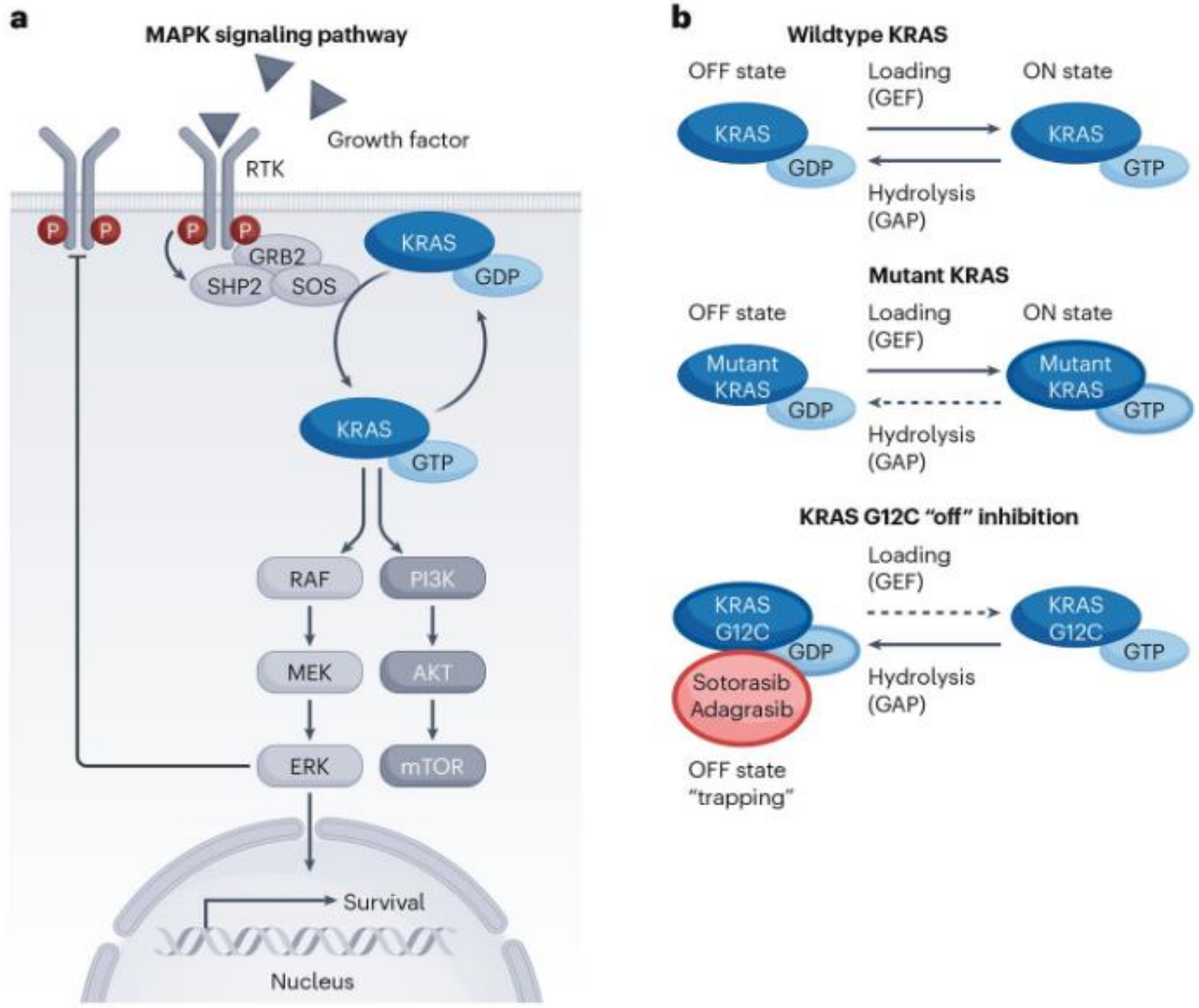
KRAS G12D inhibitor Induced Resistant Tumor Models

2026.01

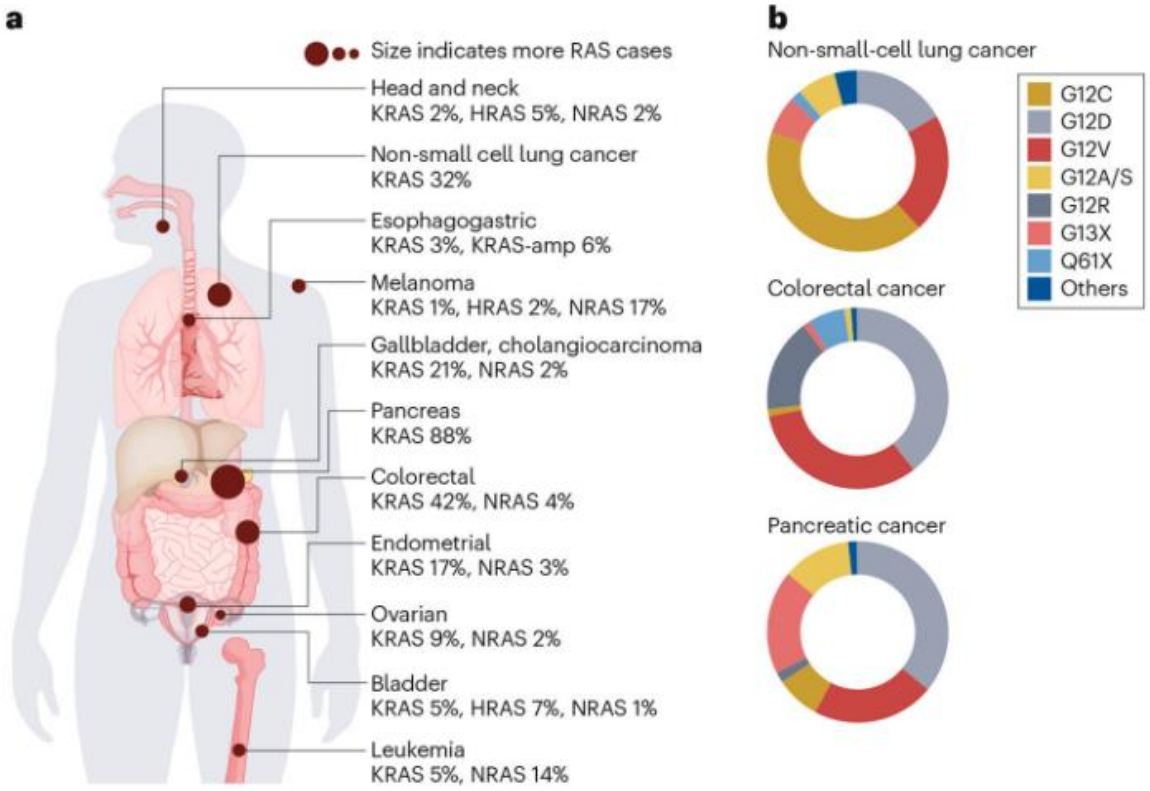
Regulation of KRAS and signal transduction pathways



- KRAS transmits environmental signals from signaling ligands and growth factor receptors, into the RAS–RAF–MEK–ERK mitogen-activated kinase signaling (MAPK) and PI3K/AKT/mTOR pathway;
- KRAS is a small membrane-bound GTP hydrolase protein which cycles between 'on' (GTP-loaded) and 'off' (GDP-unloaded) states;
- SOS1/2 are the major RAS-GEFs activated by upstream receptor tyrosine kinases (RTKs);
- Active KRAS returns to the 'off' state when GTP is hydrolyzed to GDP, a process that is driven by GTPase activating proteins (GAP) as well as its intrinsic hydrolytic activity;
- KRAS mutations act to maintain KRAS in the active 'on' state, both by reducing the intrinsic GTPase ability of the protein and by preventing the activity of GAPs.

Singhal A, Li BT, O'Reilly EM. Nat Med. 2024 Apr;30(4):969-983.

RAS mutations in cancers and KRAS inhibitors



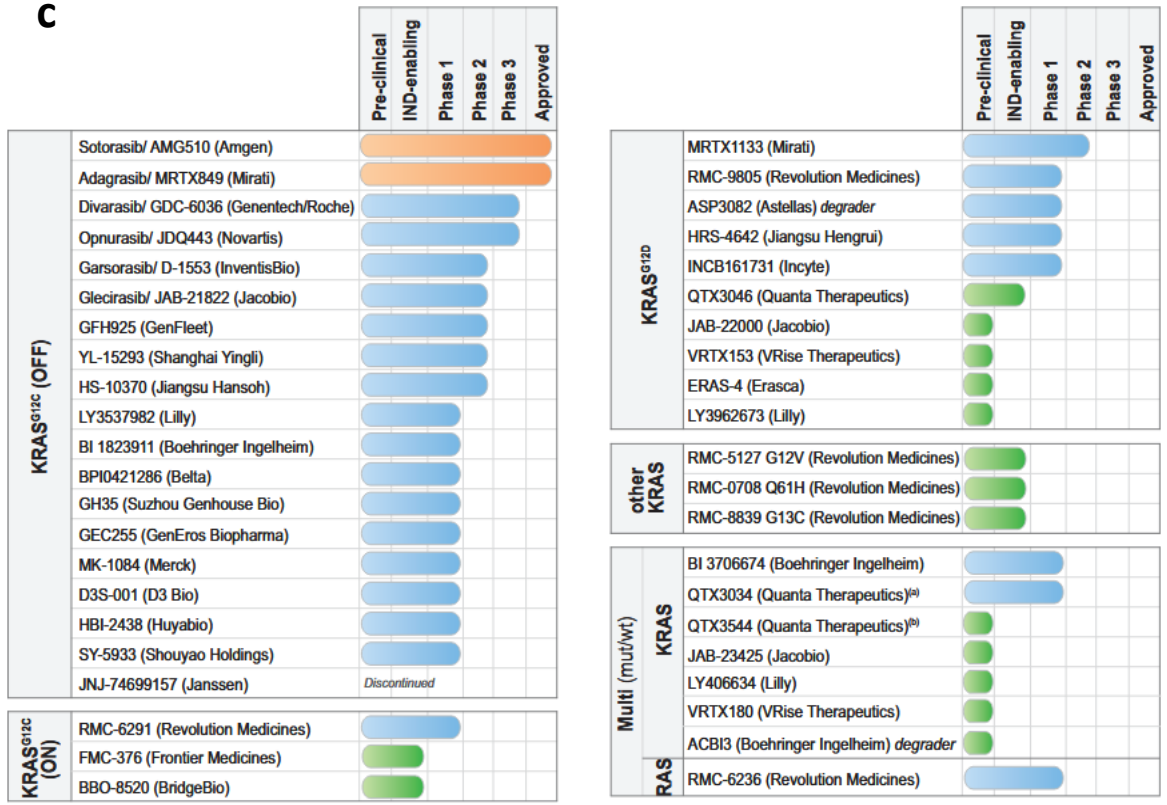
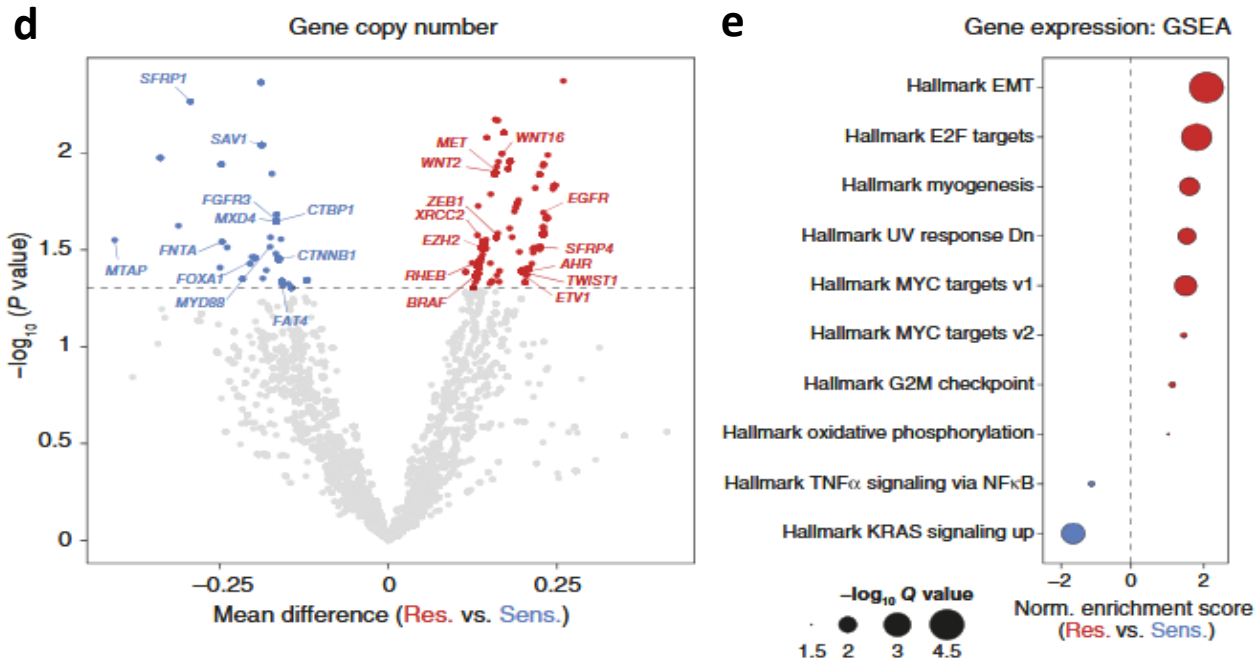


Figure a and b. Frequency of RAS mutations in major cancer types. RAS mutations exhibit significant tissue specificity, with the most common and lethal cancer types, such as colorectal cancer (CRC), pancreatic ductal adenocarcinoma (PDAC), and non-small cell lung cancer (NSCLC), being prominently associated 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.

Molina-Arcas M, Downward J. Cancer Cell. 2024 Mar 11;42(3):338-357.

Resistance to KRAS G12D inhibition and Overcoming Strategies



- **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: t**arget pEMT-associated pathways and target cell surface markers upregulated in resistant states: CLDN18.2, Netrin-1,
  - **Exploiting immune vulnerabilities**
  - **Chemotherapy combinations**

- **Mechanisms of KRAS G12D inhibitors resistance:**
  - **Genetic alterations:**
    - **KRAS amplification or secondary mutations**
    - 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**

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

Summary of KRAS G12D inhibitors induced resistant models

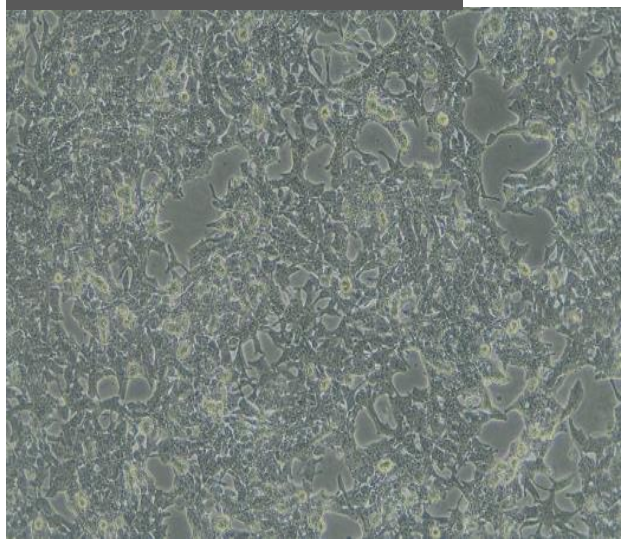
Drugs	Model ID	Cancer Type	Methods	In *vitro* validation	In *vivo* validation
MRTX1133	MRTX1133-R-GP2D	Colon Cancer	*In vitro* induced	Y	Y
	HPAC-R-MRTX1133	Pancreatic Cancer	*In vitro* induced	Y	Ongoing
	oxKPC-R-MRTX1133	Pancreatic Cancer	*In vitro* induced	Y	Y
RMC9805	RMC9805-R-KL-luc	Lung Cancer	*In vivo+In vitro* induced	Y	N

Case1: MRTX1133 induced resistant GP2D cells

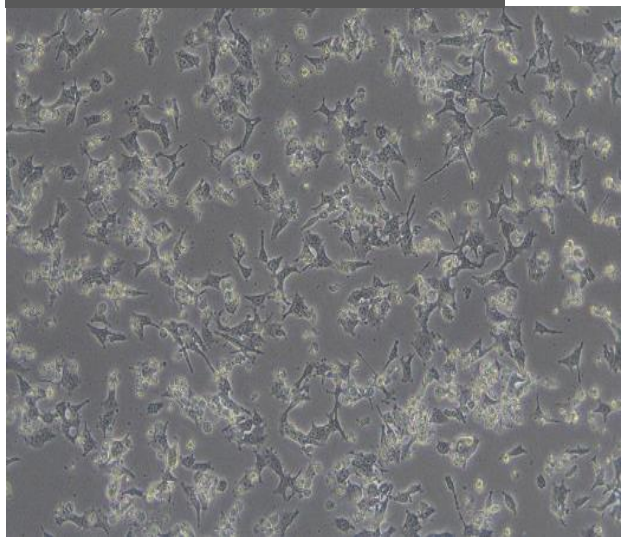
In vitro validation of MRTX1133 induced GP2D resistant cells

Cell morphology

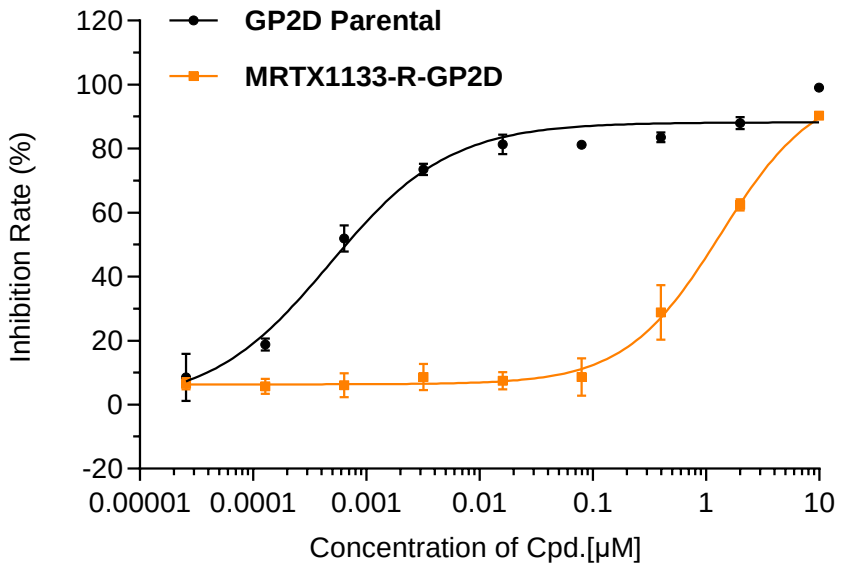
GP2D parental, 10x



MRTX1133-R-GP2D, 10x



7 day 3D CTG assay (96 well plate)



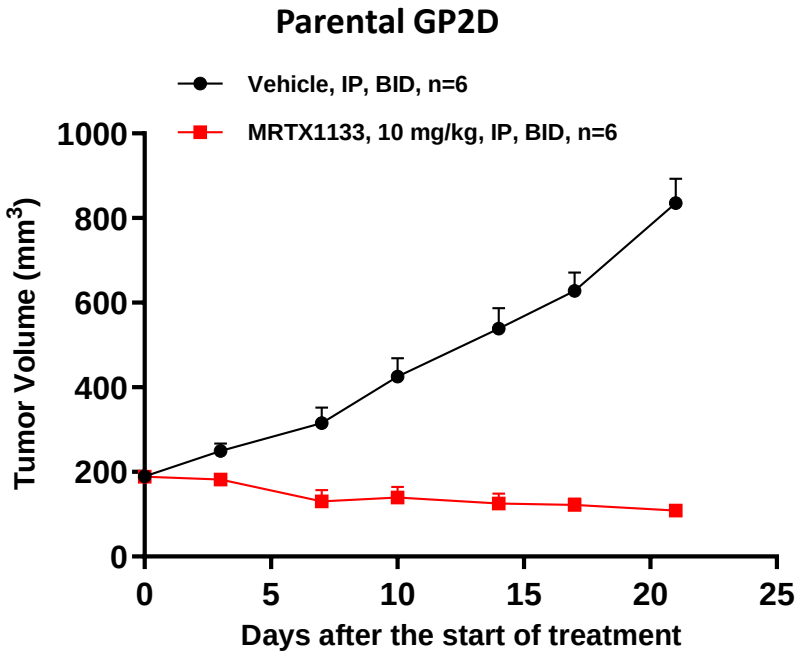
Compound	Cell line	AbsIC50 (μM)	ReIC50 (μM)	Bottom (%)	Top (%)
MRTX1133	GP2D Parental	0.0007	**0.0005**	8.54	99.09
	MRTX1133-R-GP2D	1.1764	**1.3420**	5.69	90.27

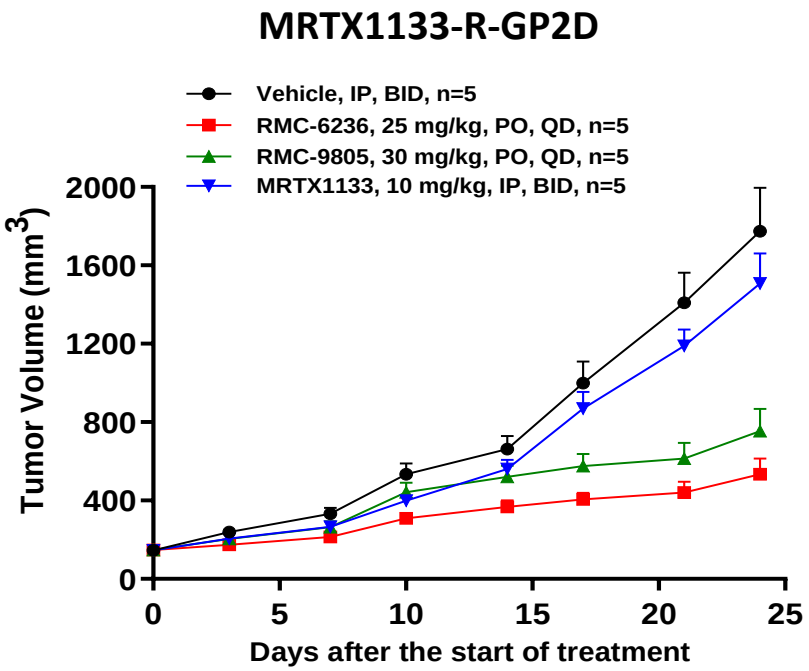
- MRTX1133-R-GP2D cell line is high sensitive to MRTX1133, with an over 2800 fold increase of IC50 value compared with GP2D parental cell line.

Case1: MRTX1133 induced resistant GP2D cells

In vivo validation of MRTX1133 induced GP2D resistant cells

Cancer type	Model ID	Mouse strain	Drug tested	Dosage	TGI (%)
Colorectal cancer	GP2D (Parental)	BALB/c nude	MRTX1133	10 mg/kg, BID	112.4%
	MRTX1133-R-GP2D	BALB/c nude	MRTX1133	10 mg/kg, BID	**-4.60%**
		BALB/c nude	RMC9805	30 mg/kg, BID	57.39%
		BALB/c nude	RMC6236	25 mg/kg, BID	72.85%





OUR COMMITMENT

Improving Health. Making a Difference.

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

https://onco.wuxiapptec.com