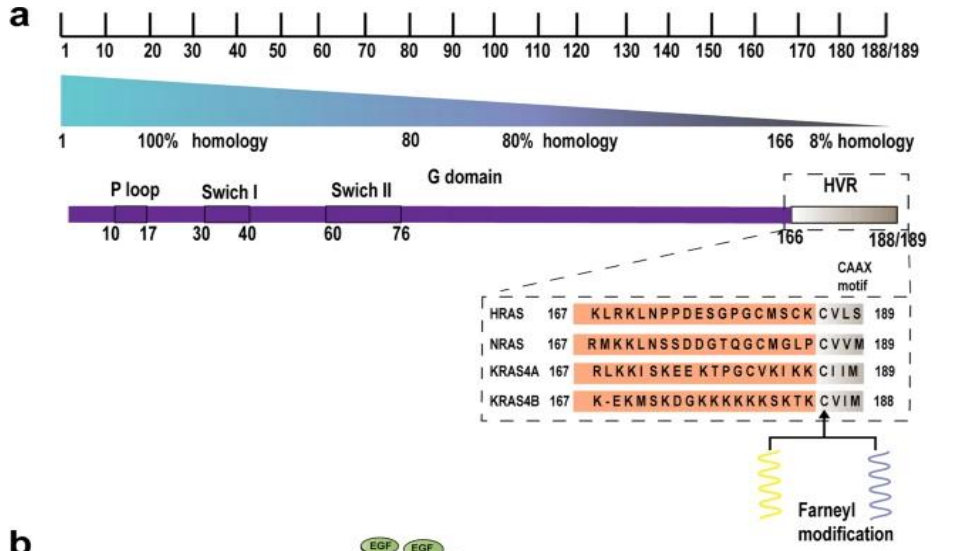
# *KRAS*-related genetically engineered cell lines and *in vivo* models

WuXi AppTec, WuXi Biology, Oncology & Immunology Unit

2023.01

# Contents

# The structure and function of *KRAS*



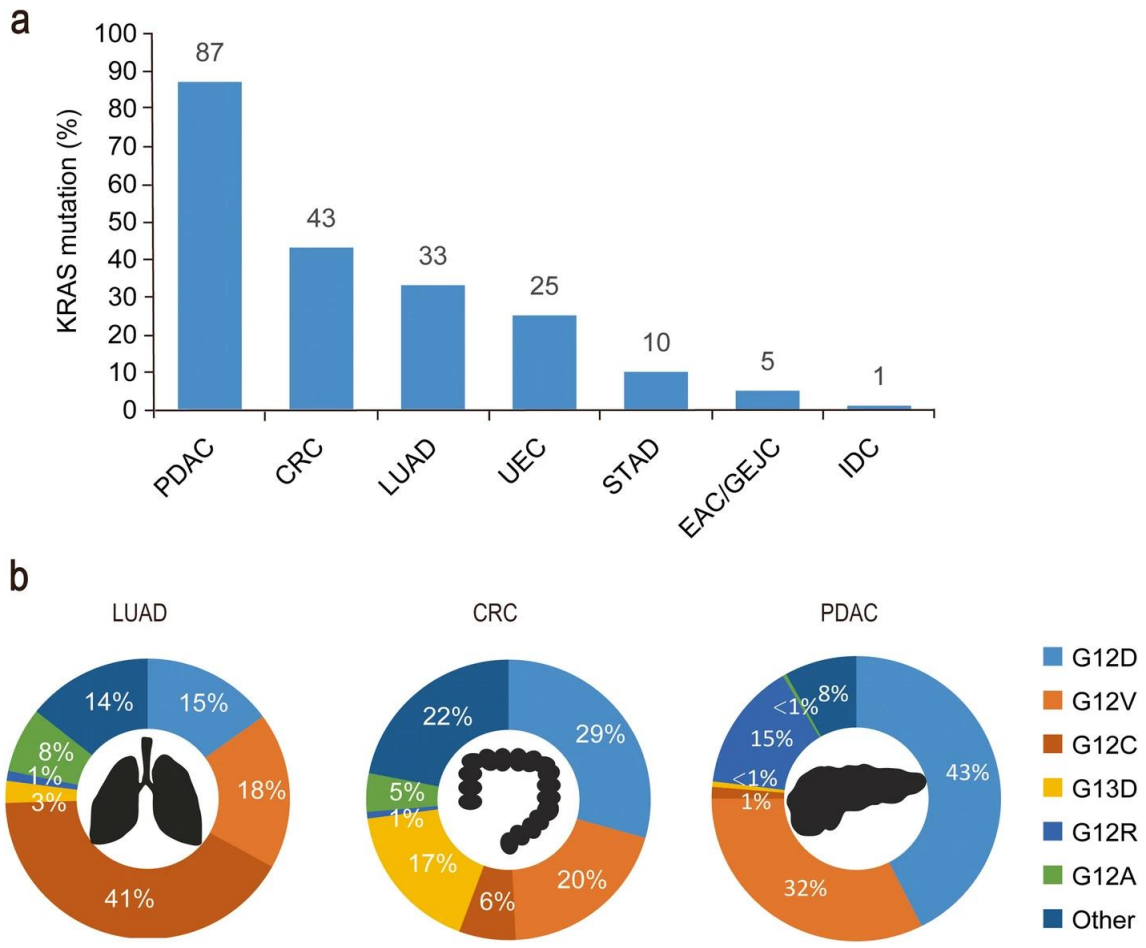

- The KRAS gene is a member of the rat sarcoma viral oncogene family (RAS), which includes two other isoforms in humans: HRAS, NRAS.

- KRAS forms two major domains: a catalytic domain called the G domain and a hypervariable region (HVR). The G domain binds guanine nucleotides and activates signalling pathway by interacting with effectors.

- The normal function of KRAS depends on the membrane localization of its post-transcriptional modification, which is mediated by a series of enzymes. KRAS functions as a guanosine diphosphate (GDP)/triphosphate (GTP) binary switch, which controls important signal transduction from activated membrane receptors to intracellular molecules. The binary switch is mainly determined by two kinds of regulatory proteins: guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs).

***Signal Transduction and Targeted Therapy*** *volume 6, Article number: 386 (2021)*

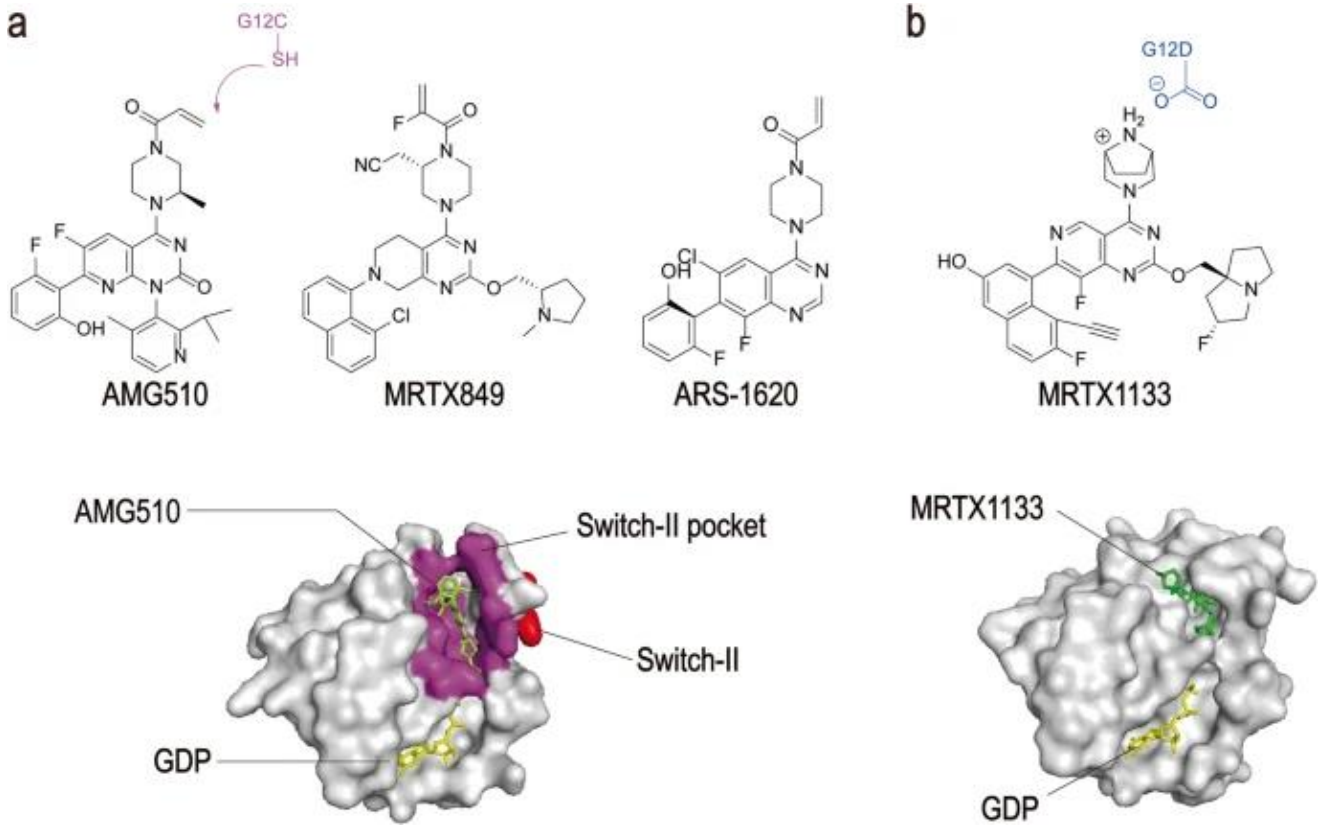
# Types and proportion of KRAS mutations in multiple human cancers




***Mol Cancer** 21, 159 (2022). https://doi.org/10.1186/s12943-022-01629-2*

- KRAS mutations are common in a variety of cancers, for example, 49% of CRC cases; ~90% of pancreatic ductal adenocarcinoma (PDAC); and 35% of lung adenocarcinomas.
- The mutant subtypes of KRAS are mainly classified as KRAS (G12D), KRAS (G12V), KRAS (G12C), KRAS (G13D), KRAS (G12R), and KRAS (G12A) mutations or KRAS wild-type amplification. Genetic alteration of G12 or G13 destroys the stability of the arginine residue hydrolysis transition state.
- The distribution of KRAS mutations varies in different human cancers, with KRAS (G12C) mutation in 41% of LUAD, whereas KRAS (G12D) and KRAS (G12V) are the two most common alleles in CRC and PDAC. Notably, other KRAS alleles such as G12R are limited in PDAC. Indeed, although the tumor type is driven by KRAS mutations, its codons and the frequency of mutations vary by tissue type.

# Targeting KRAS mutations by inhibitors



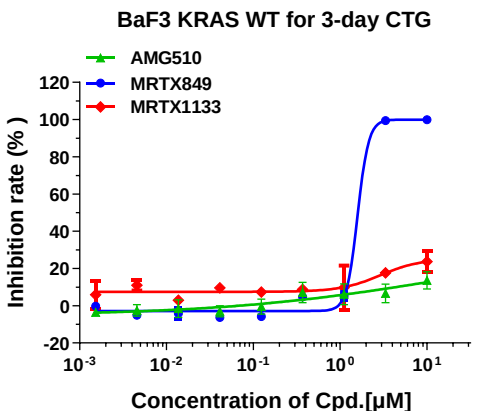

- The KRAS mutant proteins that drive cancer development are highly similar in sequence and structure based on the structural, mutational, and biochemical data of Harvey-RAS (HRAS). Direct inhibitors are most likely to bind to the catalytic domain of KRAS. However, some studies have found that KRAS mutants can be targeted by heterogeneous sites, to develop covalent inhibitors of KRAS mutants. The discovery of inhibitors that selectively target KRAS (G12C) while preserving the wild-type or other mutant KRAS is a breakthrough in the research field.

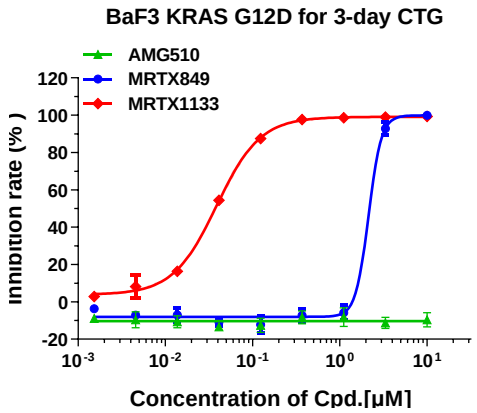
***Mol Cancer*** *21, 159 (2022). https://doi.org/10.1186/s12943-022-01629-2*

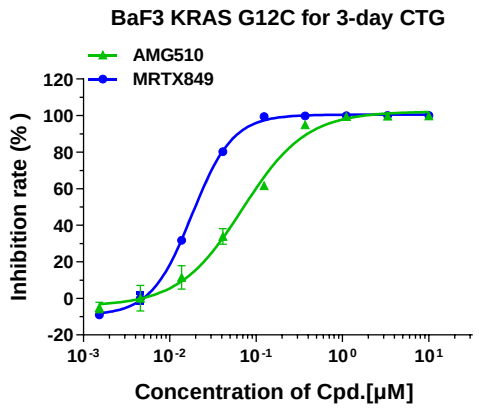
# Model summary list

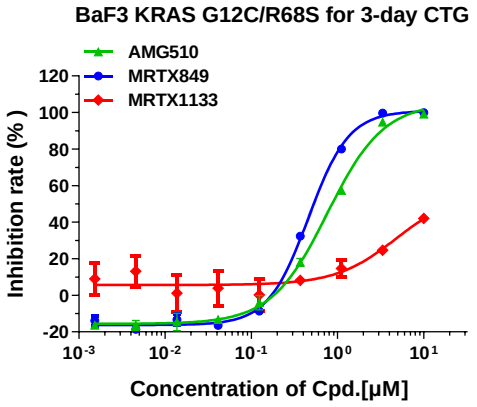
| Model ID | Description | *In vitro* validation | *In vivo* validation |
|---|---|---|---|
| Ba/F3 KRAS-WT | KRAS wild type | Yes | Yes |
| Ba/F3 KRAS-G12C | KRAS p.G12C | Yes | Yes |
| Ba/F3 KRAS-G12C/R68S | KRAS p.G12C & R68S | Yes | Yes |
| Ba/F3 KRAS-G12C/Y96D | KRAS p.G12C & Y96D | Yes | Yes |
| Ba/F3 KRAS-G12D | KRAS p.G12D | Yes | Yes |
| Ba/F3 KRAS-G12V | KRAS p.G12V | Yes | Ongoing |

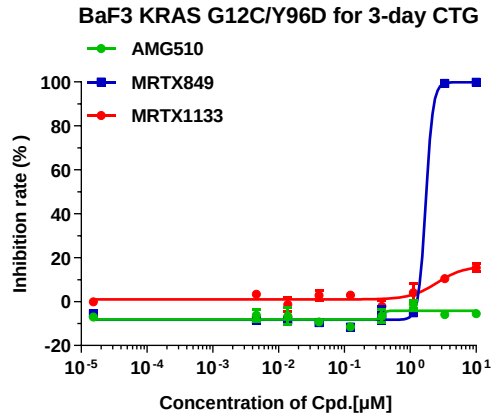
# Inhibitors in KRAS engineered Ba/F3 cells



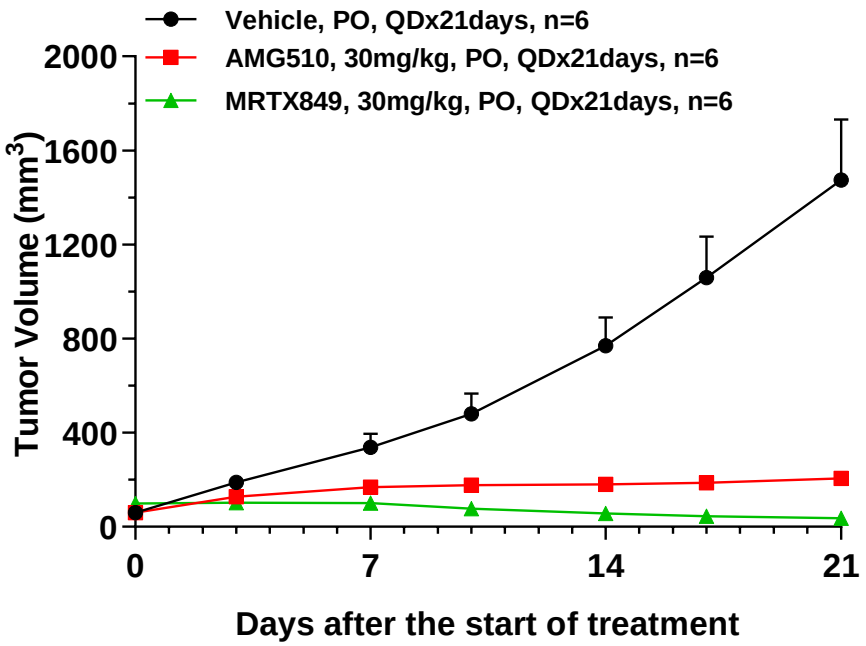



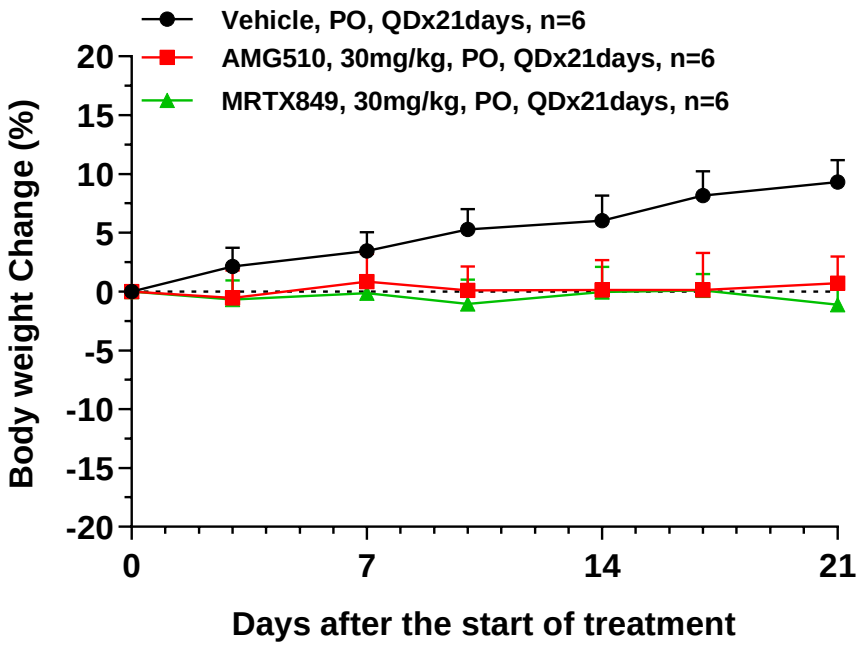




| Cell line | IC50 (nM) | | |
|---|---|---|---|
| | AMG510 | MRTX849 | MRTX1133 |
| Ba/F3 KRAS WT | NA | 1592 | NA |
| BAF3 KRAS G12D | NA | 2131 | 38.7 |
| BAF3 KRAS G12C | 72 | 20 | NA |
| Ba/F3 KRAS G12C/R68S | 763 | 459 | NA |
| Ba/F3 KRAS G12C/Y96D | NA | 1719 | NA |

# Inhibitors in Ba/F3 KRAS-G12C model

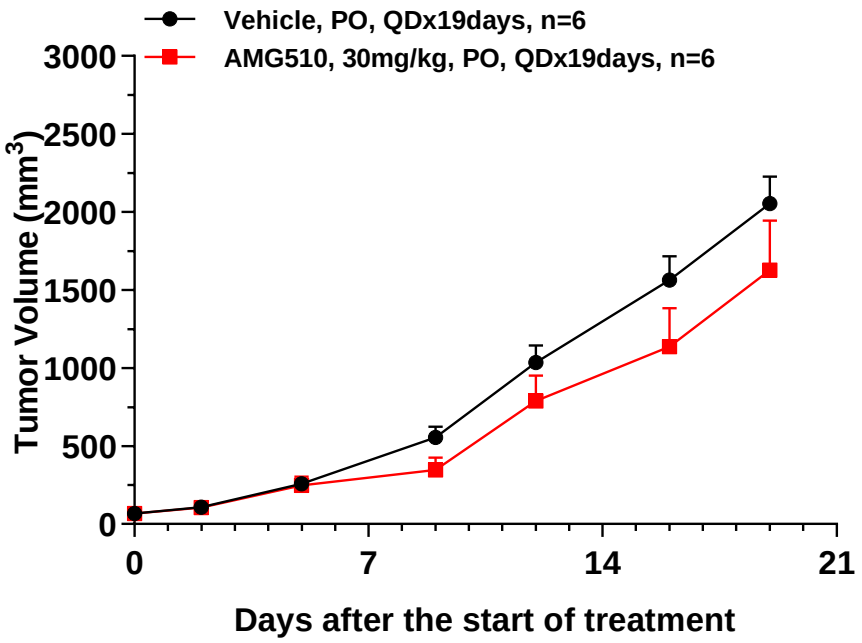
| Cell line | Model ID | Drugs tested | Dosage | TGI (%) | Model genetics |
|---|---|---|---|---|---|
| engineered murine pro-B cell line | Ba/F3 (KRAS-G12C) | AMG510<br>MRTX849 | 30 mg/kg<br>30 mg/kg | 92<br>105 | KRAS G12C |

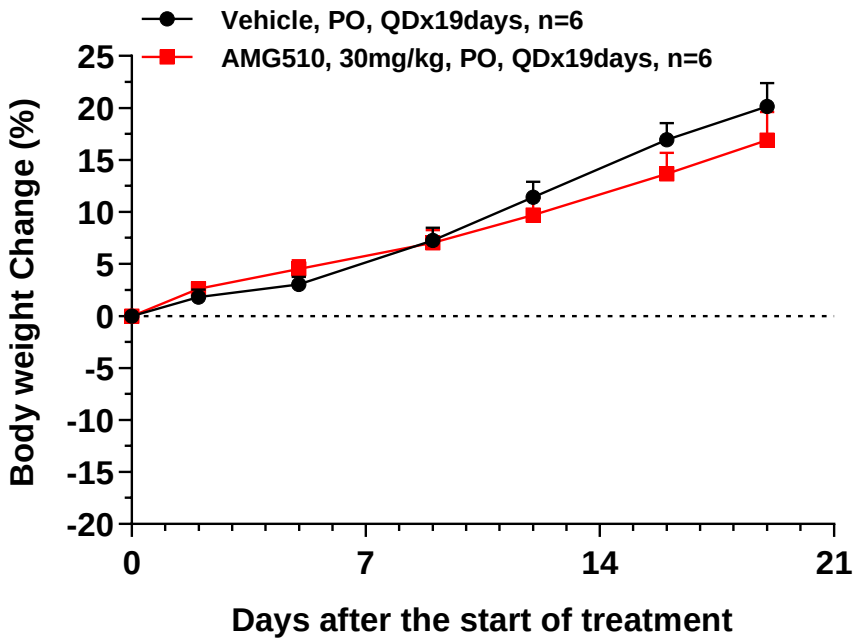


# Inhibitor in Ba/F3 KRAS-G12C/R68S model

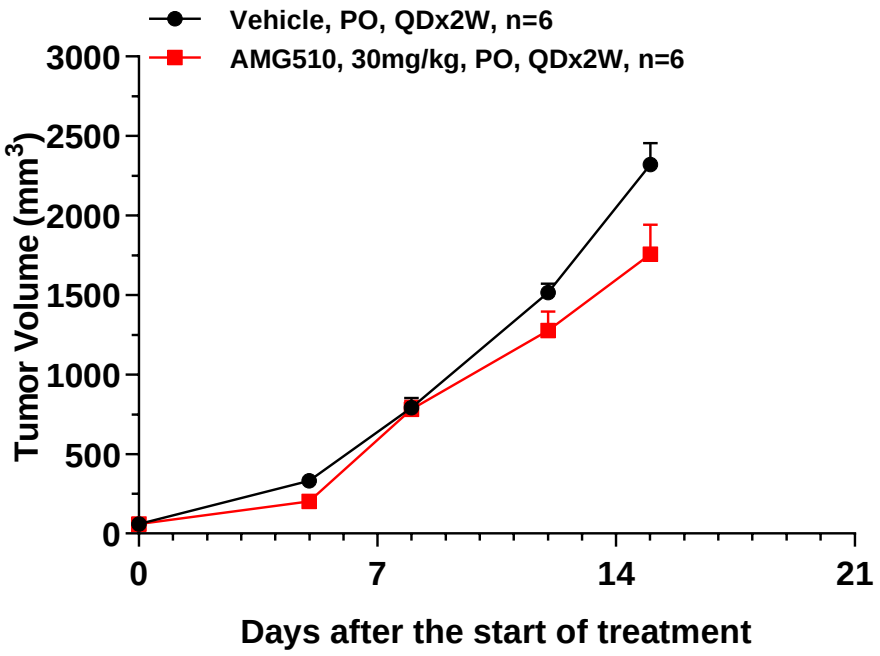
| Cell line | Model ID | Drugs tested | Dosage | TGI (%) | Model genetics |
|---|---|---|---|---|---|
| engineered murine pro-B cell line | Ba/F3 (KRAS-G12C/R68S) | AMG510 | 30 mg/kg | 22 | KRAS-G12C/R68S |

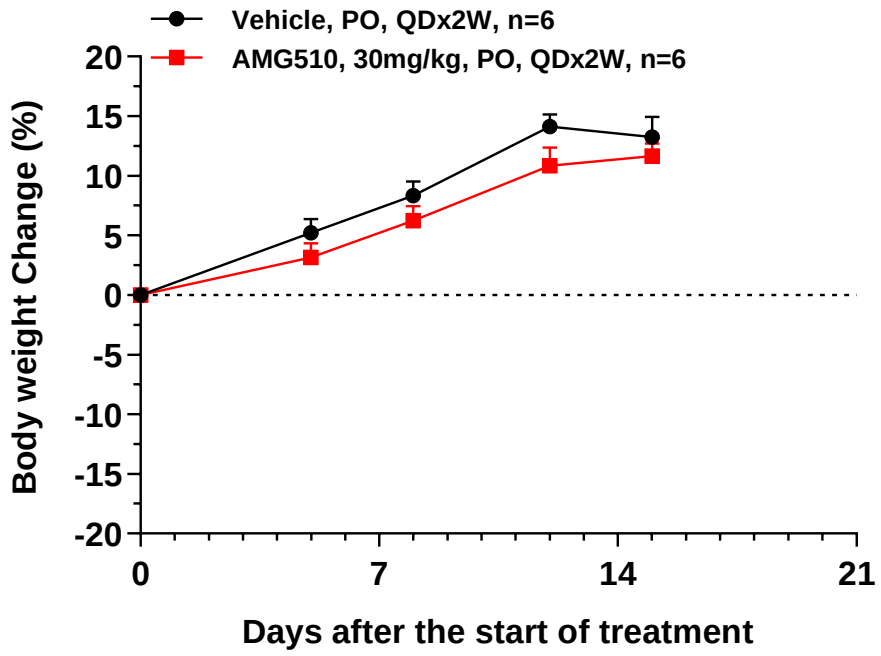


# Inhibitor in Ba/F3 KRAS-G12C/Y96D model

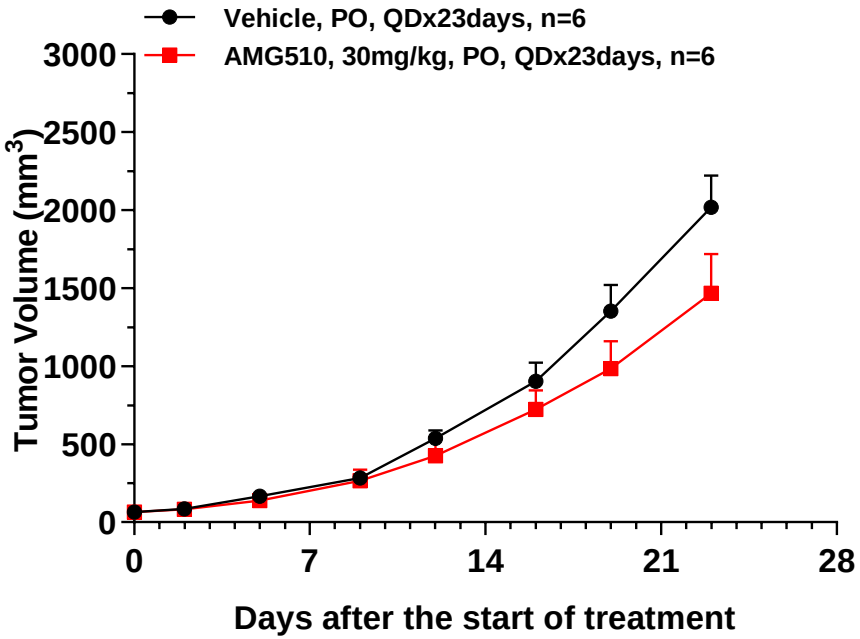
| Cell line | Model ID | Drugs tested | Dosage | TGI (%) | Model genetics |
|---|---|---|---|---|---|
| engineered murine pro-B cell line | Ba/F3 (KRAS-G12C/Y96D) | AMG510 | 30 mg/kg | 25 | KRAS-G12C/Y96D |

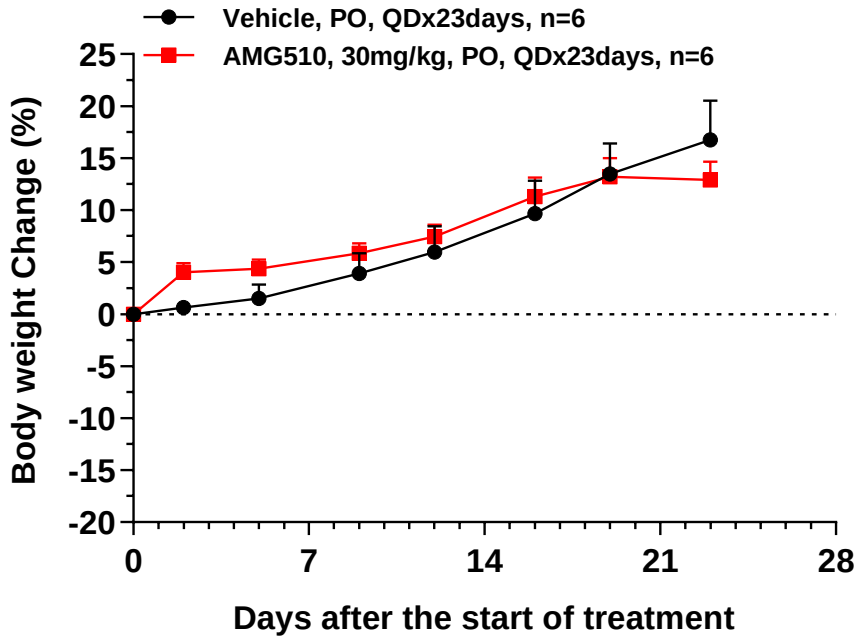


# Inhibitors in Ba/F3 KRAS wild type model

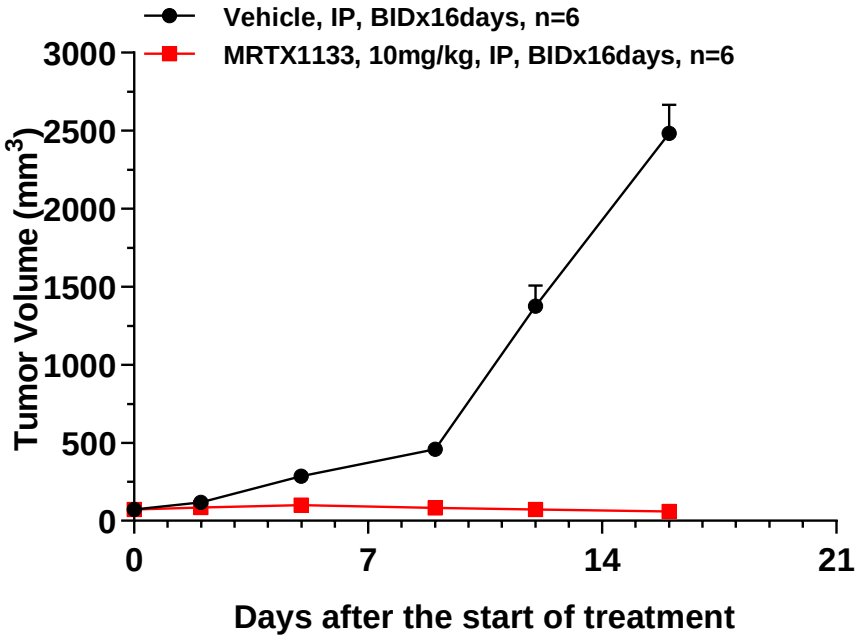
| Cell line | Model ID | Drugs tested | Dosage | TGI (%) | Model genetics |
|---|---|---|---|---|---|
| engineered murine pro-B cell line | Ba/F3 (KRAS-WT ) | AMG510 | 30 mg/kg | 28 | KRAS wild type |

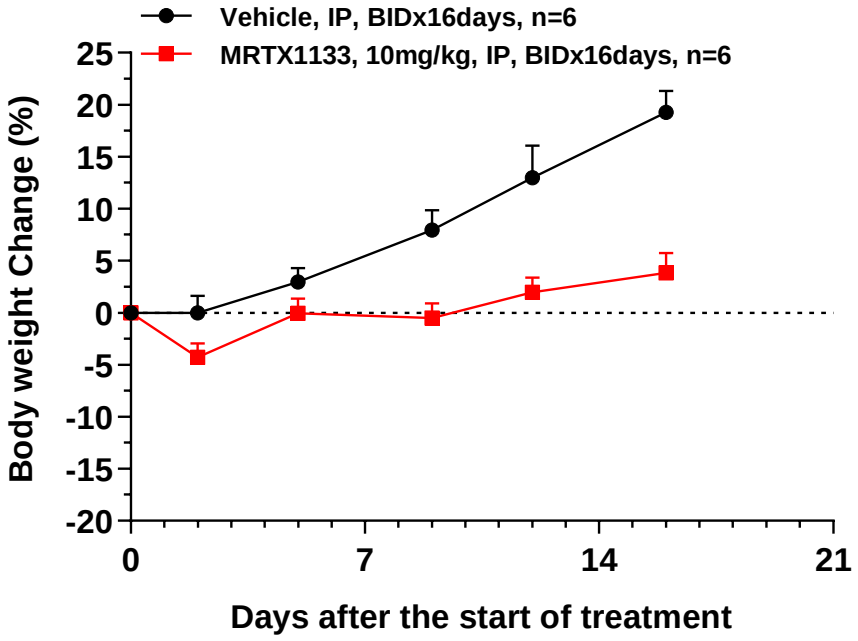


# Inhibitor in Ba/F3 KRAS-G12D model

| Cell line | Model ID | Drugs tested | Dosage | TGI (%) | Model genetics |
|---|---|---|---|---|---|
| engineered murine pro-B cell line | Ba/F3 (KRAS-G12D) | MRTX1133 | 10 mg/kg | 101 | KRAS G12D |



# OUR COMMITMENT

## *Improving Health. Making a Difference.*

**For questions and requests, please email to info_onco@wuxiapptec.com**

***https://onco.wuxiapptec.com***