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APRIL 8-13, 2022 • #AACR22

MRTX0902: A SOS1 inhibitor for therapeutic intervention of KRAS-driven cancers

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Disclosure Information

Jacob Haling

I have the following relevant financial relationships to disclose:

Employee of: Mirati Therapeutics

Stockholder in: Mirati Therapeutics

KRAS/MAPK Dependency in Cancer

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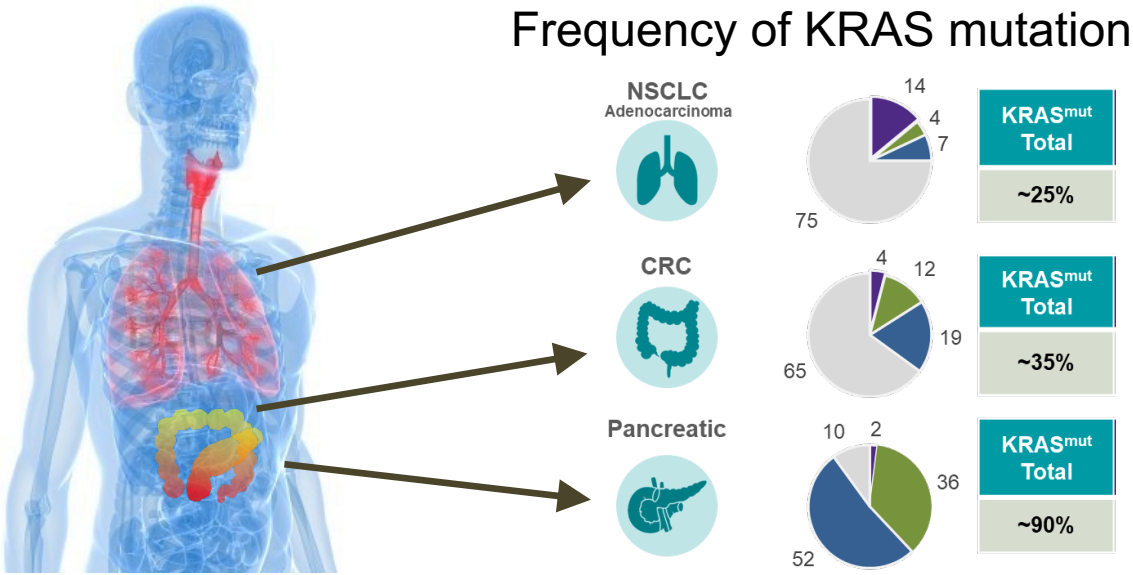

- Dysregulation of KRAS/MAPK pathway is one the most frequent causes of cancer
  >200K deaths in the US due to NSCLC, CRC, and PDAC *(2021 Estimated Deaths – NCI)*
- Targeted KRAS G12C inhibitors will improve the outcome for a subset of these patients
- Additional therapies that enhance KRAS inhibition and/or target additional mutations may increase durability of response or expand the spectrum of targetable patients

Son of Sevenless homolog 1 (SOS1) Directly Binds and Activates KRAS

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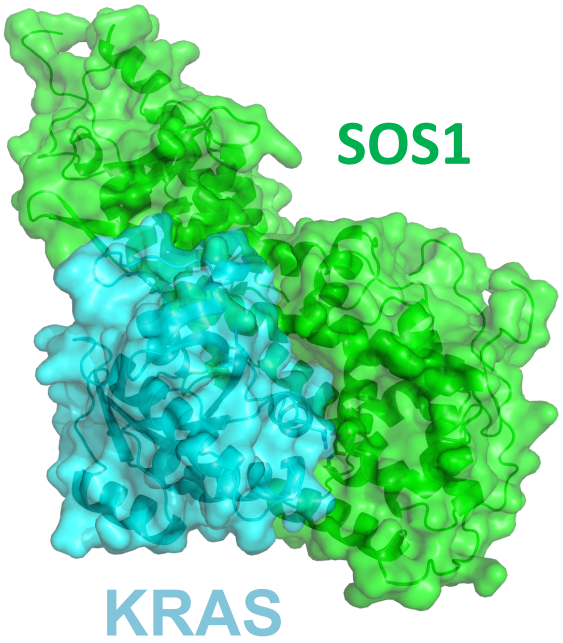
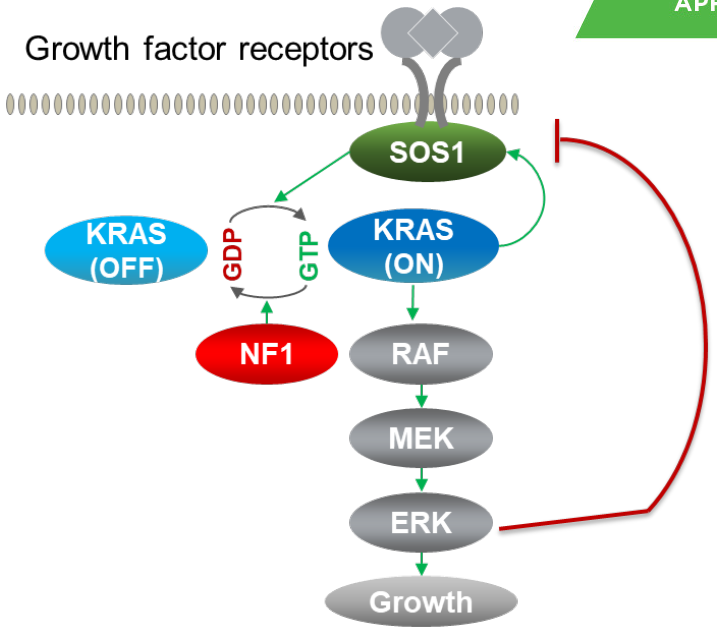
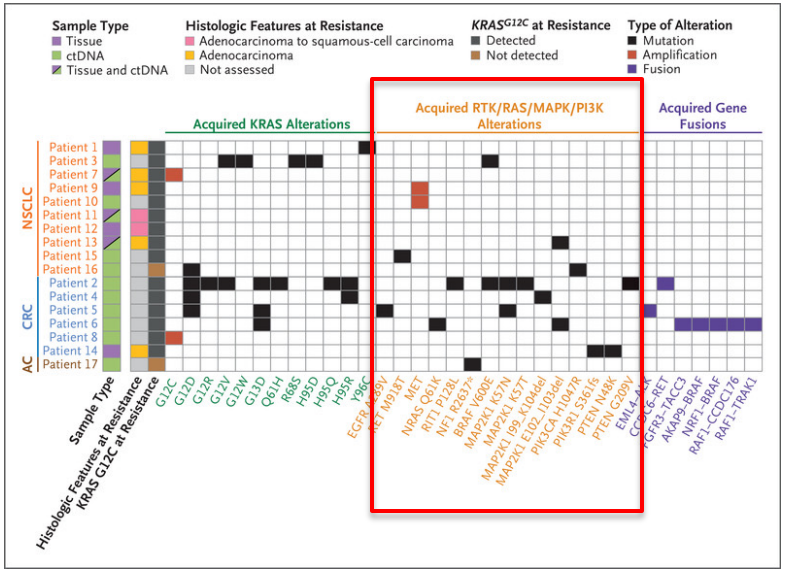




- SOS1 is a guanine nucleotide exchange factor (GEF) that binds to KRAS and promotes the exchange of KRAS-bound GDP for GTP and facilitates activation of the RAF-MEK-ERK kinases
- SOS1 mediates negative feedback inhibition upon RAF-MEK-ERK activation

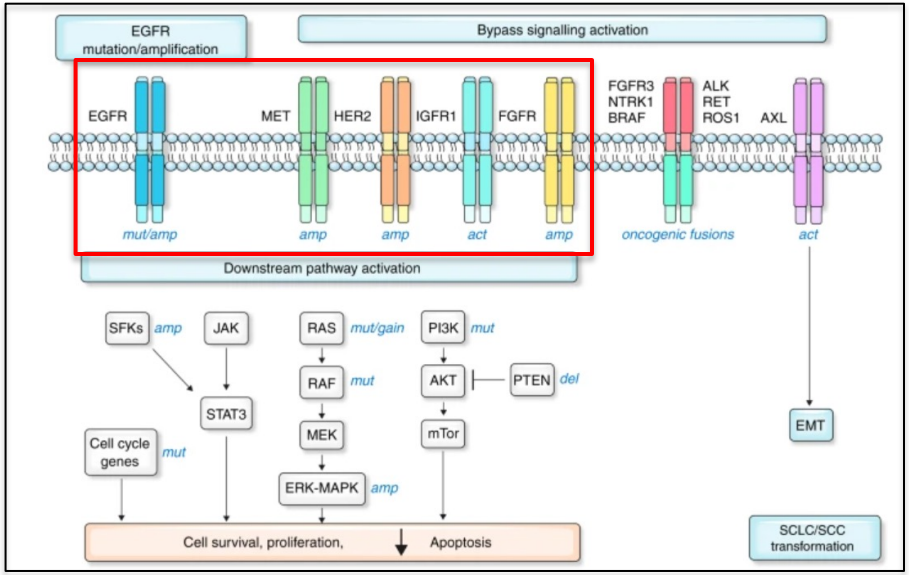
RTK-mediated Acquired Resistance may be Sensitive to SOS1 Inhibition

Acquired resistance to adagrasib



Awad et al., NEJM 2021

Acquired resistance to osimertinib



Leonetti et al., BJC 2019

- RTK amplification and/or mutations are clinically relevant mechanisms of acquired resistance
- SOS1 represents a potential universal node in cases of RTK-mediated resistance

SOS1 Inhibition Shifts KRAS^{G12C} into an Inactive State and Augments MRTX849 Activity

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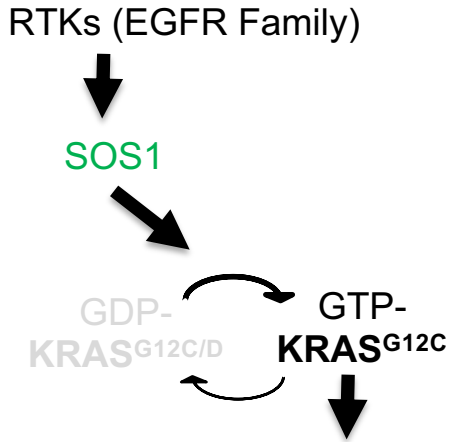
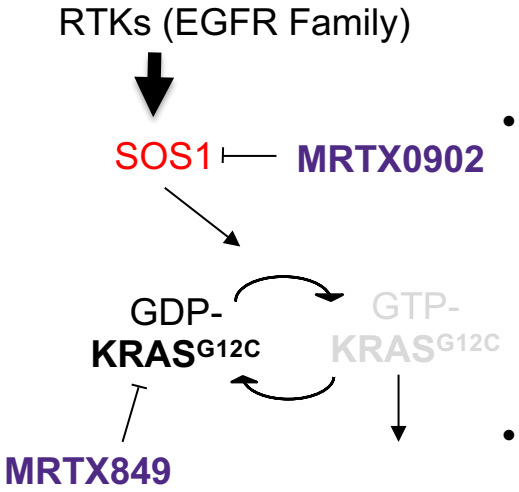
SOS1 Activates KRAS^{G12C}

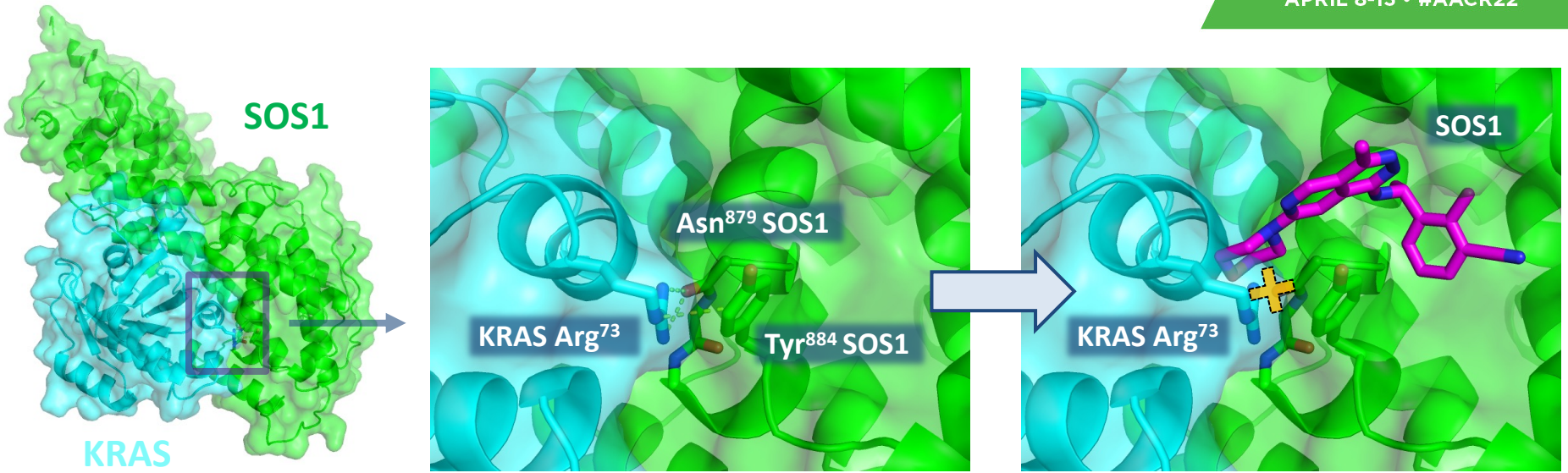


Combination Strategy



- KRAS G12C covalent inhibitors such as adagrasib bind to KRAS-GDP
- SOS1 inhibition has synergistic antitumor activity when combined with MRTX849; synergy also observed with additional KRAS inhibitors
- MRTX0902 represents a potential best-in-class SOS1 inhibitor with efficacy comparable to literature molecules

Disrupting the SOS1:KRAS Complex



- Discovery team utilized a structure-enabled approach to design Mirati SOS1 inhibitors that push into the SOS1:KRAS interface, thereby disrupting the protein-protein interaction (PPI)

SOS1 Inhibitor Optimization to MRTX0902

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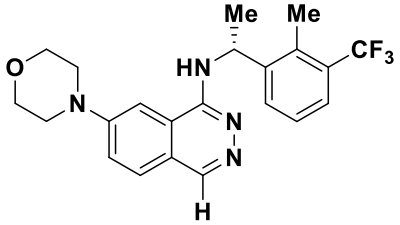
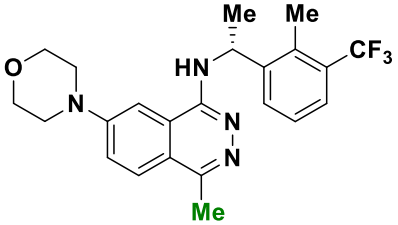
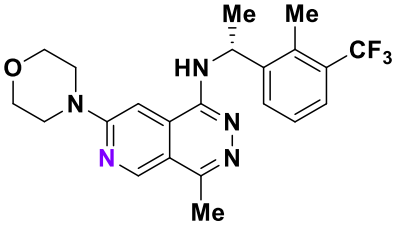


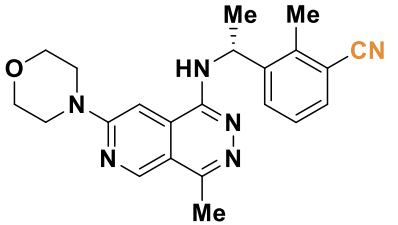
MRTX7496
pERK IC_{50} = 134 nM



MRTX9528
pERK IC_{50} = 87 nM



MRTX9416
pERK IC_{50} = 39 nM



MRTX0902
pERK IC_{50} = 33 nM

- Designed and elaborated a novel series of phthalazine based SOS1 inhibitors
- Addition of C4-substituent blocked AO metabolism without loss of cellular potency
- Azaphthalazine core increased permeability and potency, while minimizing time-dependent inhibition of CYP3A4
- Installation of nitrile on the right-hand side of the molecule further lowered CYP3A4 inhibition

MRTX0902 Meets Development Candidate Criteria

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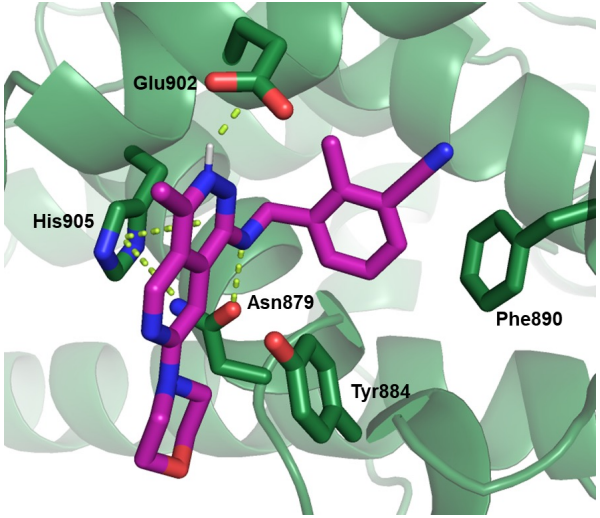
Assay	Criteria	MRTX0902
SOS1 Binding / Cell pERK IC_{50} (nM)	Potent binder with good cell activity	2 / 33
SOS2 Binding IC_{50} (nM)	Weak binder	> 100,000
In vivo Pharmacology: KRAS G12C TGI	Improved efficacy in combination with adagrasib	✓
Pharmacokinetic Profile (m/r/d/cy): Bioavailability (lowest doses)	High projected human oral bioavailability & exposure	69% / 83% / 38% / 20%
CYP3A4 Induction	Low CYP Induction risk	✓
Toxicity Assessment in Rat and Dog	≥ 1-fold safety margin	✓
Predicted human dose	< 1 g/day	✓

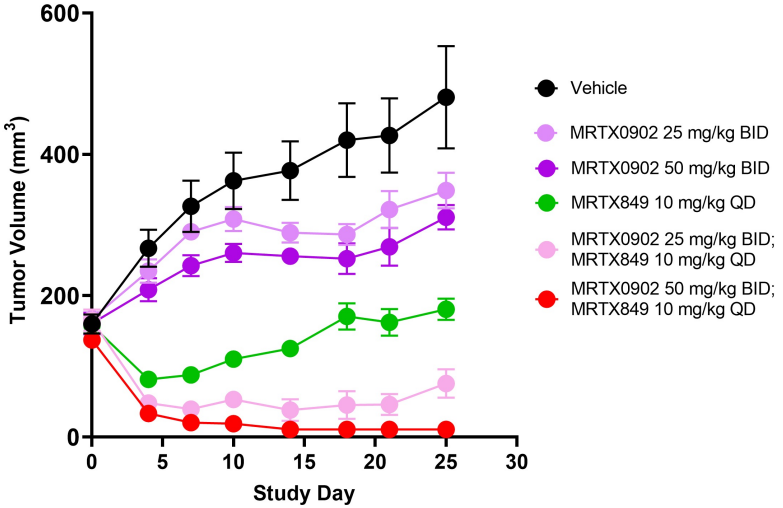
Co-Crystal Structure of SOS1:MRTX0902



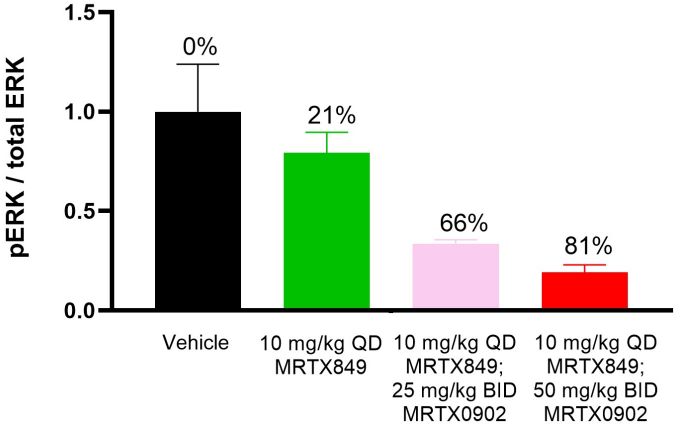
- MRTX0902 exhibits promising potency, selectivity, and exposure in preclinical species
- Regulatory toxicology (GLP) studies have completed with minimal gross observations or clinical signs at top dose levels enabling starting doses approaching efficacious dose range

MRTX0902 Demonstrates Strong In Vivo Efficacy and PD Target Modulation

MIA PaCa-2 ($KRAS^{G12C}$)



pERK Modulation in MIA PaCa-2 (4 hours post-dose)



- Combination of MRTX0902 + MRTX849 results in -92% regression, tumor free animals and correlative PD modulation
- Plasma concentration of MRTX849 remains unchanged when co-dosed with MRTX0902

MRTX0902 in Combination with MRTX849 Demonstrates Durable Regression in KRAS^{G12C} NSCLC and CRC PDX Models

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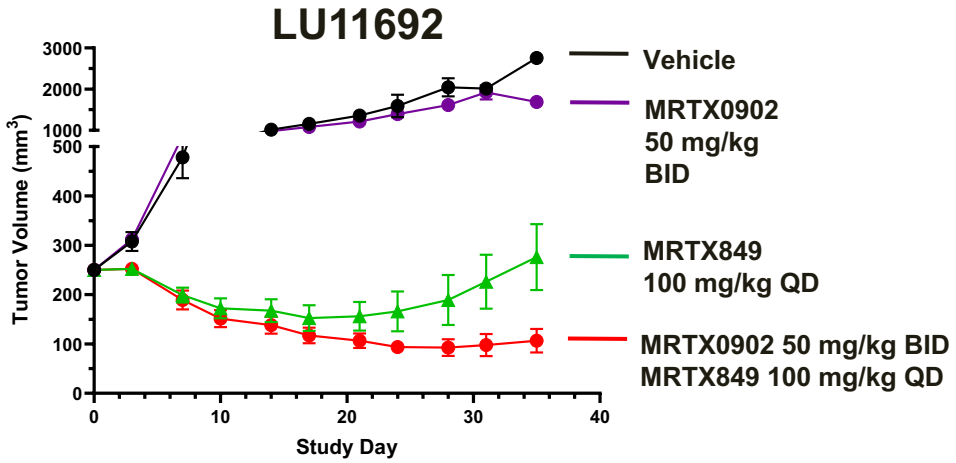

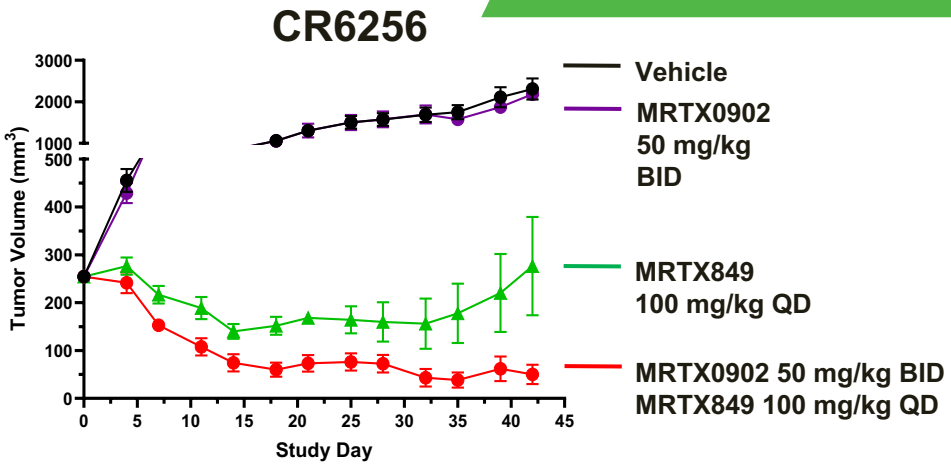

*4 of 8 animals are tumor-free (Day 11)

- Combination of MRTX0902 + MRTX849 results in sustained tumor regression in LU11692 (-57%) and CR6256 (-80%) and early onset of tumor free animals in the CR6256 model
- 100 mg/kg QD MRTX849 is the maximally efficacious preclinical dose

Combination Treatment with MRTX0902 and MRTX849 Leads to Broad Antitumor Activity in KRAS^{G12C}-Mutant Human Tumor Xenograft Models

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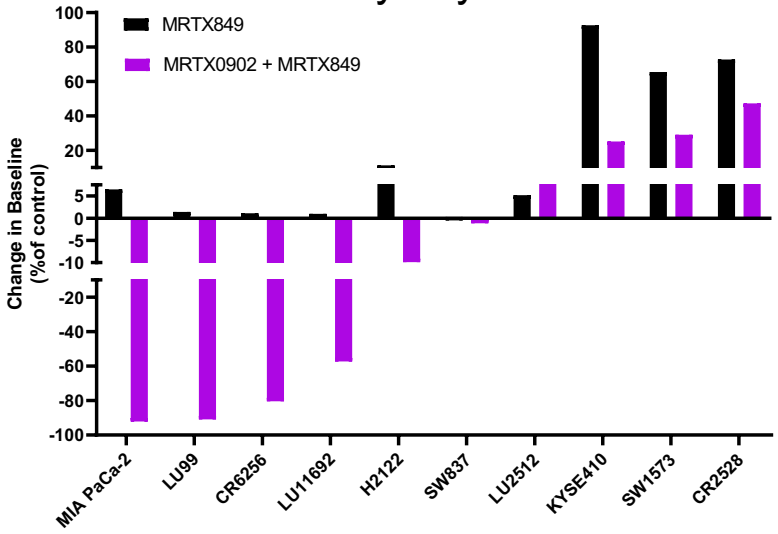
MRTX0902/MRTX849 Efficacy
Study day ~28



KRAS^{G12C} Cell line	Model	*In vivo* effect: MRTX849	*In vivo* effect: MRTX0902 + MRTX849
MIA PaCa-2	CDX	94% TGI*	-92% Regression*
LU99	CDX	99% TGI*	-91% Regression*
CR6256	PDX	99% TGI	-80% Regression
LU11692	PDX	99% TGI	-57% Regression
H2122	CDX	89% TGI	-10% Regression
SW837	CDX	0% Regression	-1% Regression
LU2512	PDX	95% TGI	91% TGI
KYSE-410	CDX	7% TGI	75% TGI
SW1573	CDX	35% TGI	71% TGI
CR2528	PDX	27% TGI	53% TGI

**Sub-efficacious dose of 10 or 30 mg/kg QD MRTX849 was tested*
Max-efficacious dose of 100 mg/kg QD MRTX849 was tested in combination with MRTX0902 unless otherwise annotated
TGI = tumor growth inhibition

- Improved efficacy observed with combination of MRTX0902 + MRTX849 in 8 of 10 models tested

Rational MAPK Combinations with MRTX0902 Demonstrate Improved Efficacy

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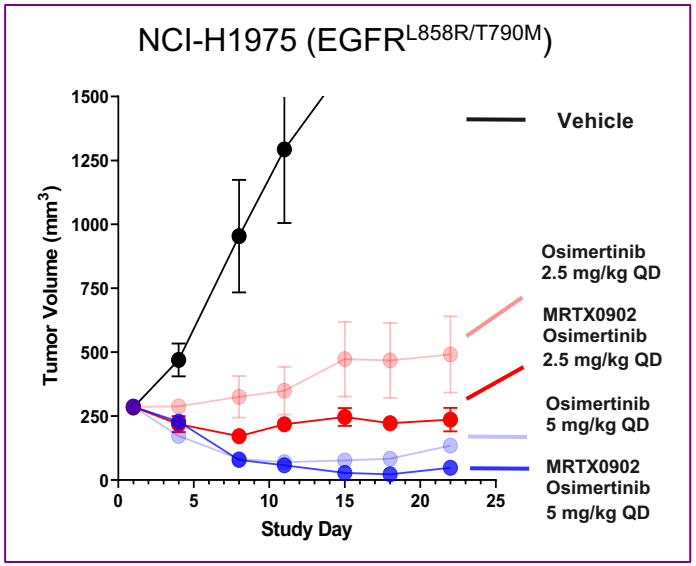
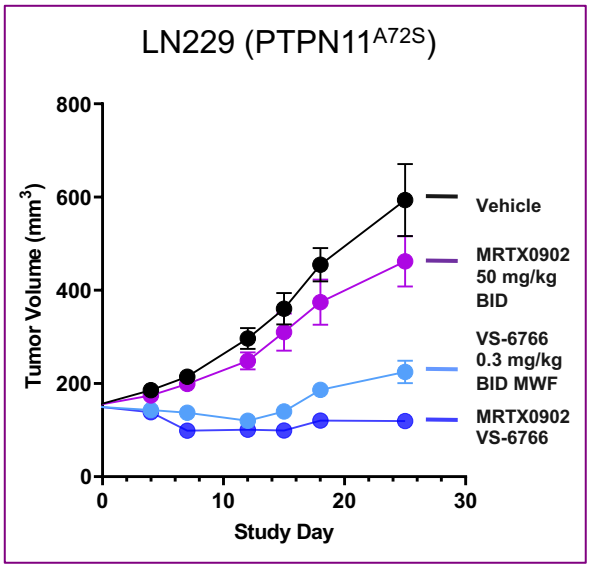
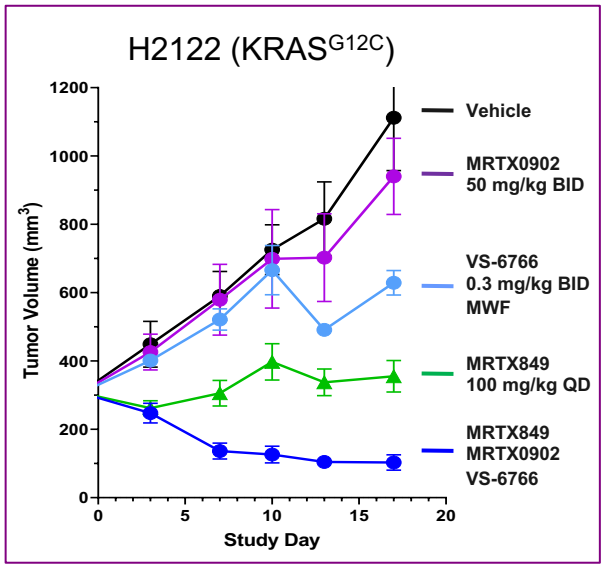
SOS1i + EGFRi



SOS1i + RAF/MEKc



SOS1i + RAF/MEKc + KRAS^{G12C}i



- Combination of 50 mg/kg MRTX0902 BID with osimertinib (EGFRi), VS-6766 (RAF/MEKc), or VS-6766 + MRTX849 improves depth of response in MAPK addicted tumor models
- Triple combination prevents feedback-mediated reactivation of the MAPK pathway

SOS1 Inhibition Prevents Feedback-mediated Reactivation of the MAPK Pathway

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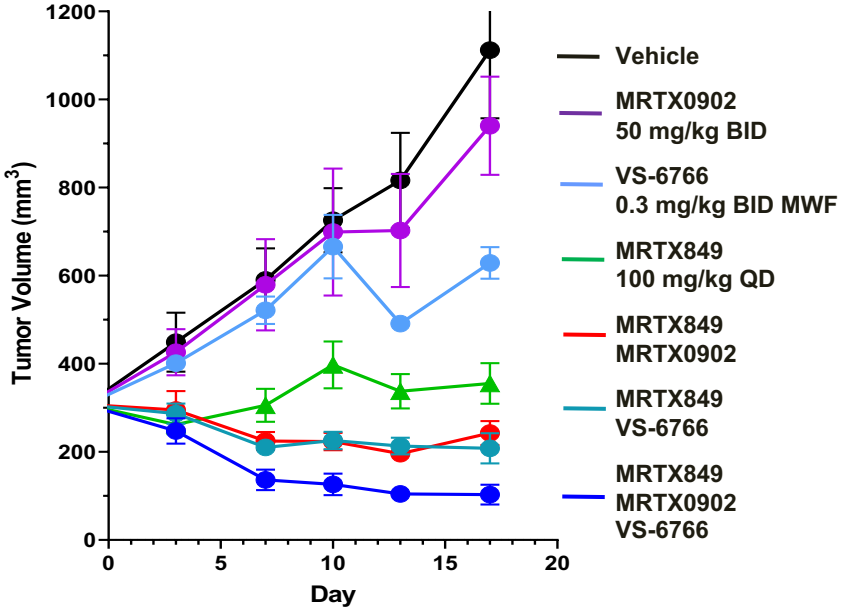
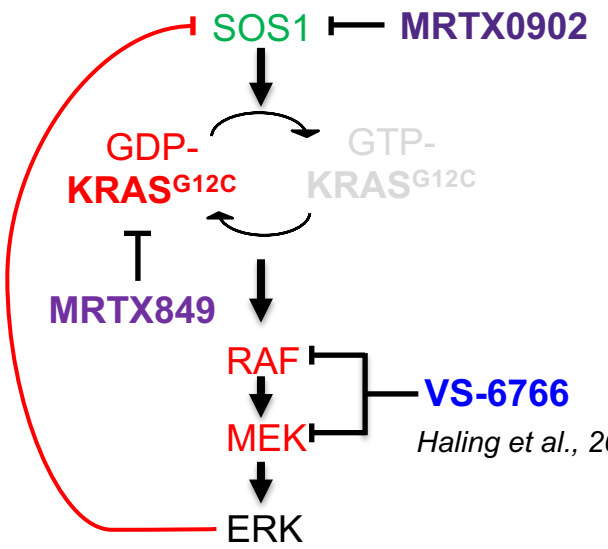
H2122 ($KRAS^{G12C}$)



Mechanism



Haling et al., 2014; Lito et al., 2014

- SOS1 inhibition prevents pathway reactivation mediated by RAF/MEK and KRAS inhibition
- Additional $KRAS^{MT}$ models are being evaluated using a similar approach with MRTX0902 combinations

Chemical Genomics Reveal Compensatory Role for SOS2

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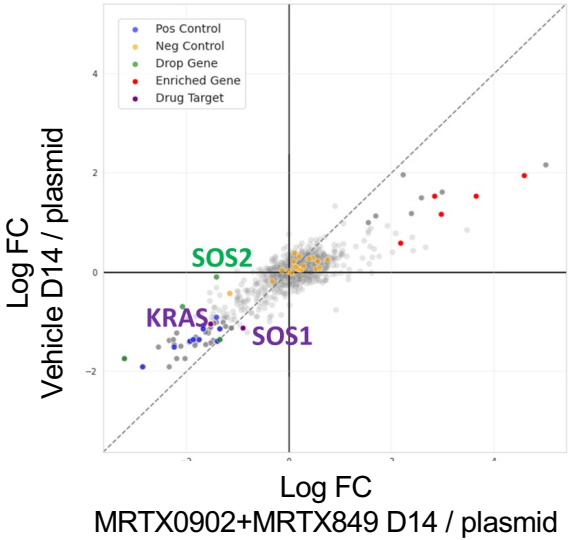
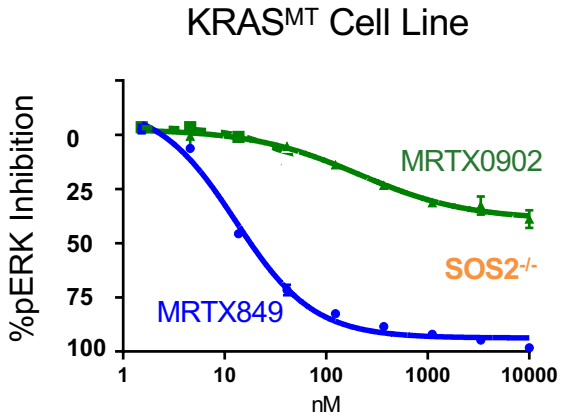
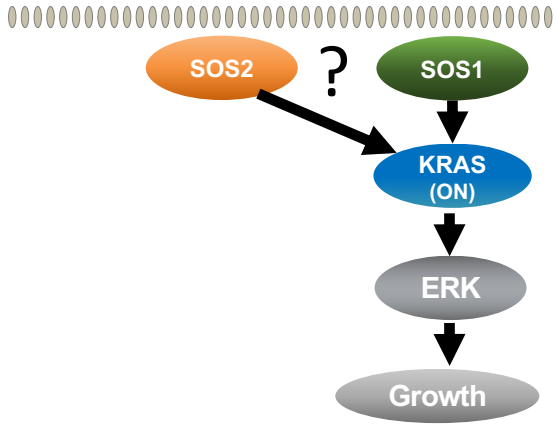
Loss of SOS2 Sensitizes LU99 to MRTX849 + MRTX0902







- SOS2, the paralog of SOS1 has some functional redundancy but is largely viewed as having a minimal role in KRAS activation
- In vitro and in vivo data suggests that SOS2 can compensate for the loss/inhibition of SOS1

Summary

- MRTX0902 was selected as the development candidate and is currently in IND-enabling studies; IND filing anticipated in 2H 2022
- MRTX0902 exhibits promising potency, selectivity, and oral exposure in preclinical species
  - Please see John Ketcham's e-poster for more; abstract # LB505
- The combination of MRTX0902 with MRTX849 enhances the depth and durability of an anti-tumor response when compared to MRTX849 alone in pre-clinical $KRAS^{G12C}$ tumor models
- Clinical development plan is to initially pursue MRTX0902/MRTX849 combination followed by additional MAPK combinations pending pre-clinical evaluations
- Compensatory role for SOS2 identified in functional genomics studies
  - Please see Shilpi Khare's poster on Wednesday April 13 for more; abstract # LB193

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