Inhibition of SOS1 by MRTX0902 Augments the Anti-tumor Response of the Targeted EGFR Inhibitor Osimertinib in NSCLC

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MIRATI THERAPEUTICS

Disclosure Information

Shilpi Khare

I have the following relevant financial relationships to disclose:

Employee of: Mirati Therapeutics

Stockholder in: Mirati Therapeutics

The investigational use of adagrasib will be discussed in this presentation.

Summary

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- The SOS1 inhibitor MRTX0902 is an effective combination partner of MRTX849 (adagrasib) in preclinical *KRAS*^{G12C}-mutant tumor models; currently being evaluated in Phase 1 clinical trials

- The combination of MRTX0902 plus adagrasib delays acquired resistance mechanisms in *KRAS*^{G12C}-mutant preclinical models

- Rational MAPK combination of MRTX0902 with osimertinib demonstrates improved efficacy in *EGFR* mutant models of NSCLC

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

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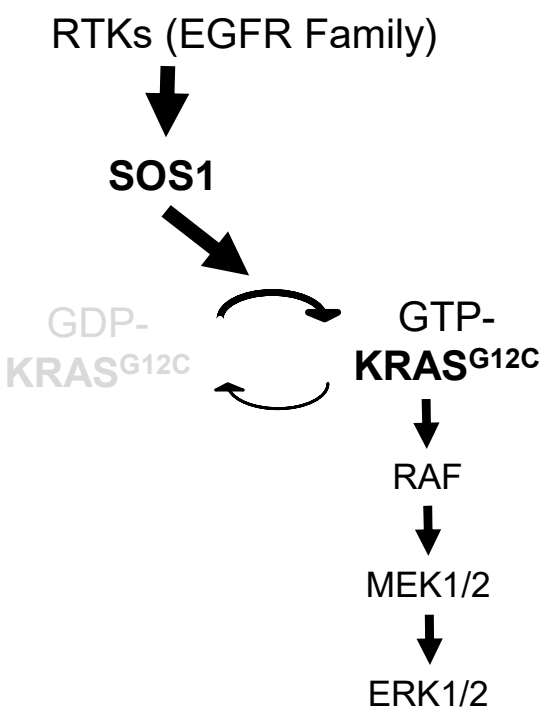
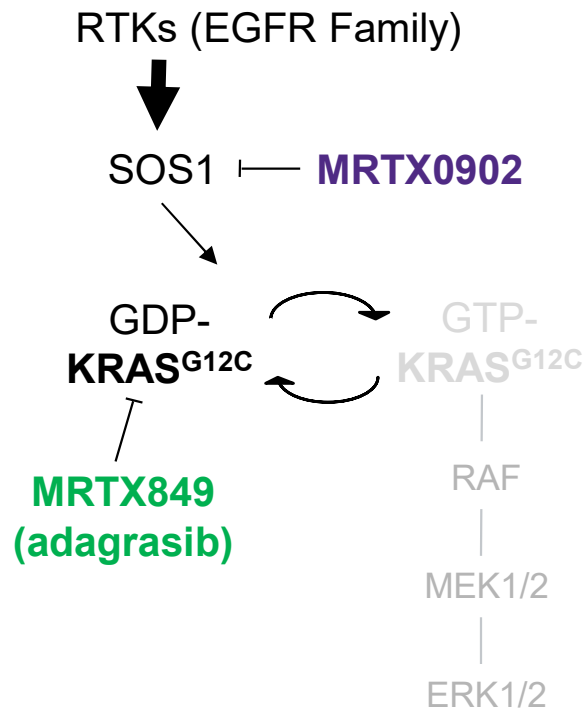
SOS1 Activates $KRAS^{G12C}$



Combination Strategy



- **SOS1** is a guanine nucleotide exchange factor (GEF) that binds to KRAS, promotes the exchange of KRAS-bound GDP for GTP, and facilitates activation of the RAF-MEK-ERK kinases
- KRAS G12C covalent inhibitors such as MRTX849 (adagrasib) bind to KRAS-GDP
- SOS1 inhibition shifts $KRAS^{G12C}$ into an inactive state and augments MRTX849 activity, leading to downregulation of KRAS-MAPK signaling
- MRTX0902 represents a potential best-in-class SOS1 inhibitor currently in Phase 1 clinical trials

Combination Treatment with MRTX0902 and MRTX849 Leads to Broad Anti-tumor Activity in *KRAS^{G12C}*-mutant Human Tumor Xenograft Models

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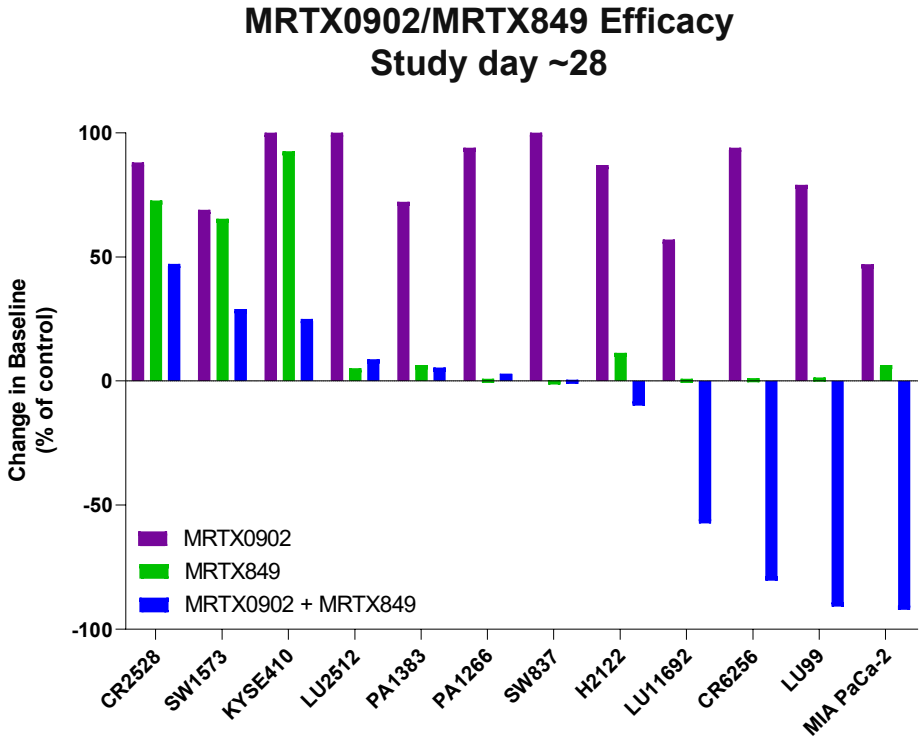

KRAS^{G12C}-mutant Cell line	Model	MRTX849 activity	MRTX0902 + MRTX849 activity
MIA PaCa-2	CDX	94% TGI*	-92% Regression*
LU99	CDX	99% TGI*	-91% Regression*
CR6256	PDX	99% TGI	-80% Regression
LU11692	PDX	99% TGI	-57% Regression
H2122	CDX	89% TGI	-10% Regression
SW837	CDX	0% Regression	-1% Regression
PA1383	PDX	94% TGI	95% TGI
PA1266	PDX	99% TGI	97% TGI
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 12 models tested

MRTX0902 Reduces DUSP6 mRNA Expression in Whole Blood

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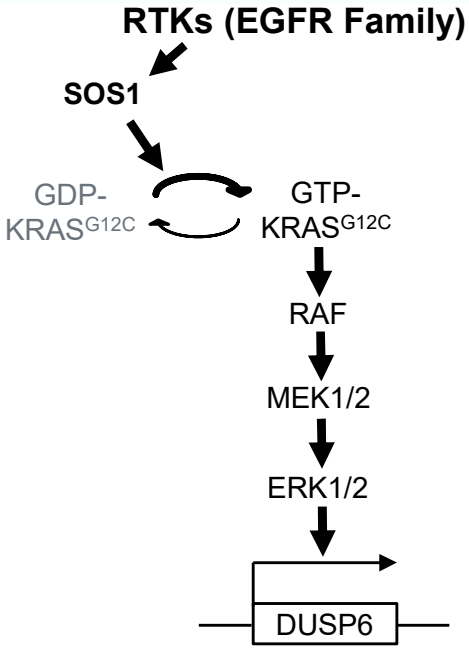
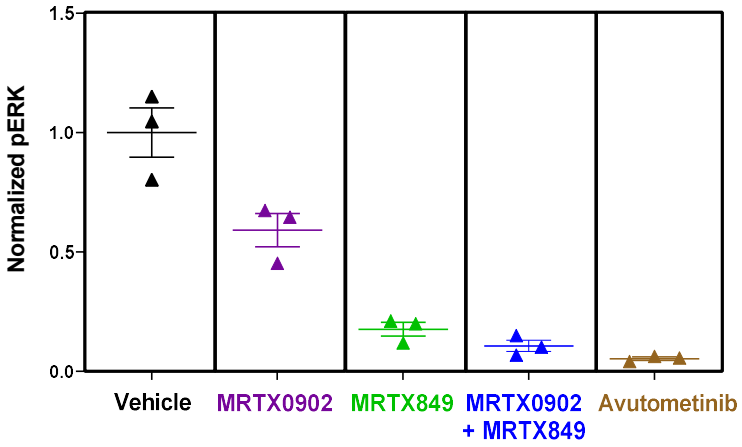
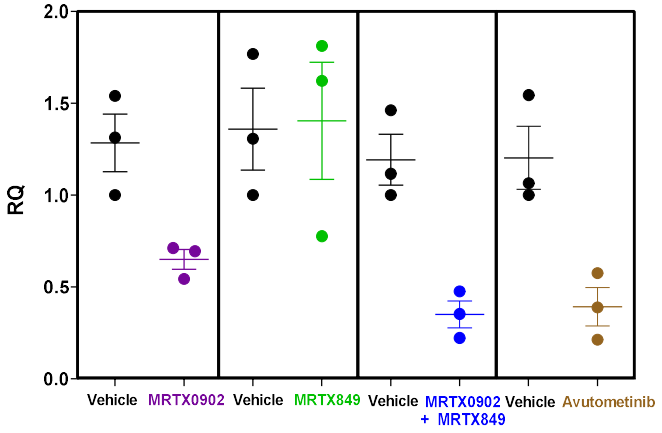


MIA PaCa-2 (KRASG12C) PD modulation (Day 6; 4 hours post-dose)





- **MRTX0902** administration results in decreased pERK in tumors and correlative reductions in blood DUSP6 transcript levels in tumor-bearing animals, comparable to levels observed following avutometinib (MEKi) treatment
- DUSP6 is a transcriptionally regulated phosphatase downstream of ERK; a validated biomarker of KRAS/MAPK pathway activity
- Data may be useful to help non-invasively determine a biologically optimized dose for MRTX0902

RTK-mediated Acquired Resistance May be Sensitive to SOS1 Inhibition

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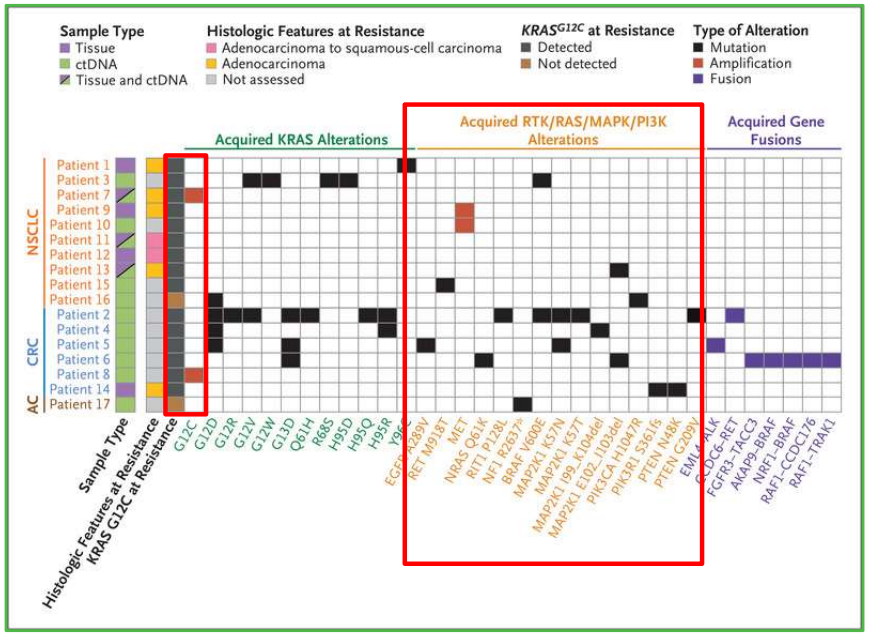
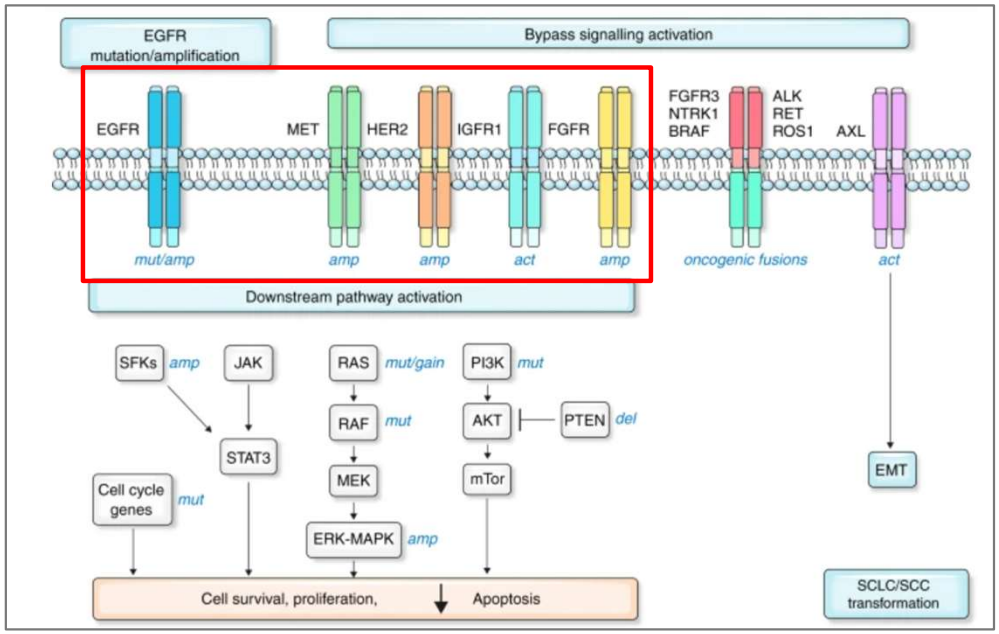
Acquired resistance to adagrasib



Awad et al., NEJM 2021

Acquired resistance to osimertinib



Leonetti et al., BJC 2019

- RTK amplification and/or mutations represent mechanisms of acquired resistance in patient biopsies
- SOS1 represents a potential universal node in cases of RTK-mediated resistance

Combination Treatment with MRTX0902 and MRTX849 has the Potential to Overcome Acquired Resistance Associated with KRAS Amplification

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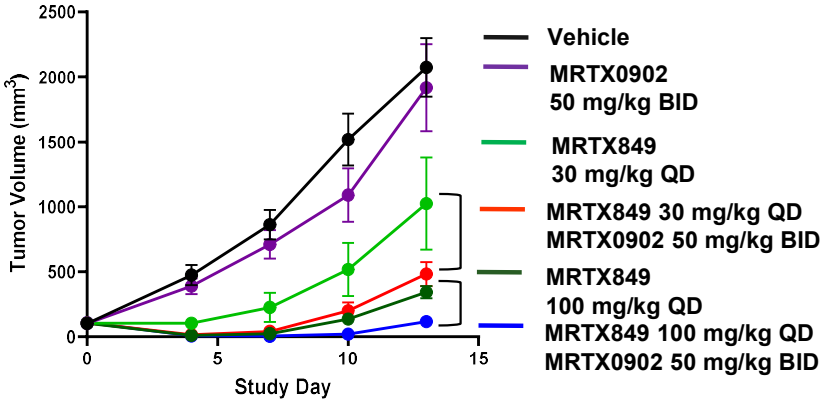
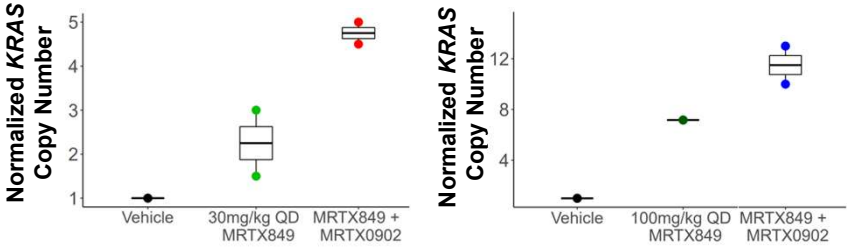
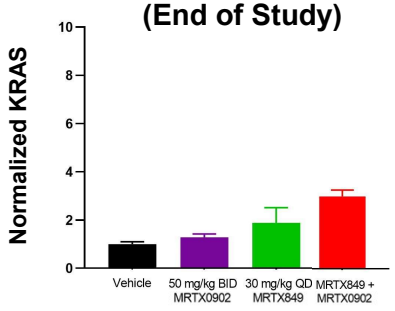
CT26 (*KRAS*^{G12C}) clone E3



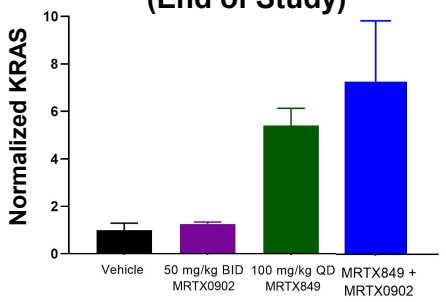
Total *KRAS*^{G12C} Gene Amplification (End of Study)

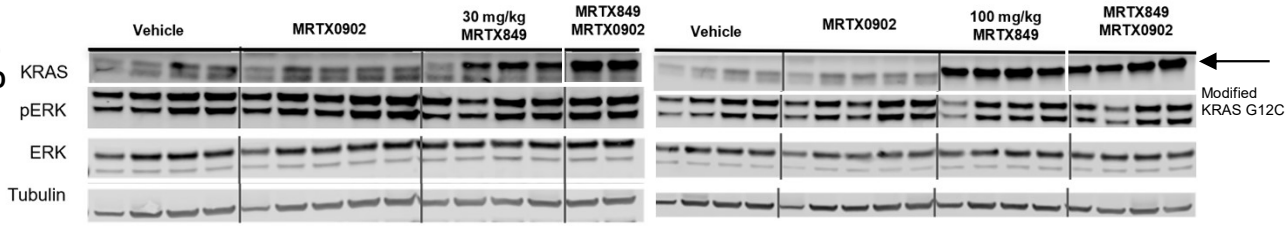


Total KRAS Expression (End of Study)



Total KRAS Expression (End of Study)





- CT26 murine tumor model treated with MRTX849 develop resistance characterized by focal amplification of *KRAS*^{G12C} on extrachromosomal DNA (*KRAS* (+) ecDNA) (Hansen *et al.* Abstract LBA005, AACR 2021)
- Combination treatment results in greater TGI and amplified mutant *KRAS* gene and KRAS protein levels compared to MRTX849 monotherapy at the end of study
- Following repeat dosing with single agent MRTX849 and combination treatment, a lack of pERK modulation is observed
- MRTX849 + MRTX0902 treatment has the potential to delay *KRAS* (+) ecDNA amplification-associated acquired resistance

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RTK-mediated Acquired Resistance May be Sensitive to SOS1 Inhibition

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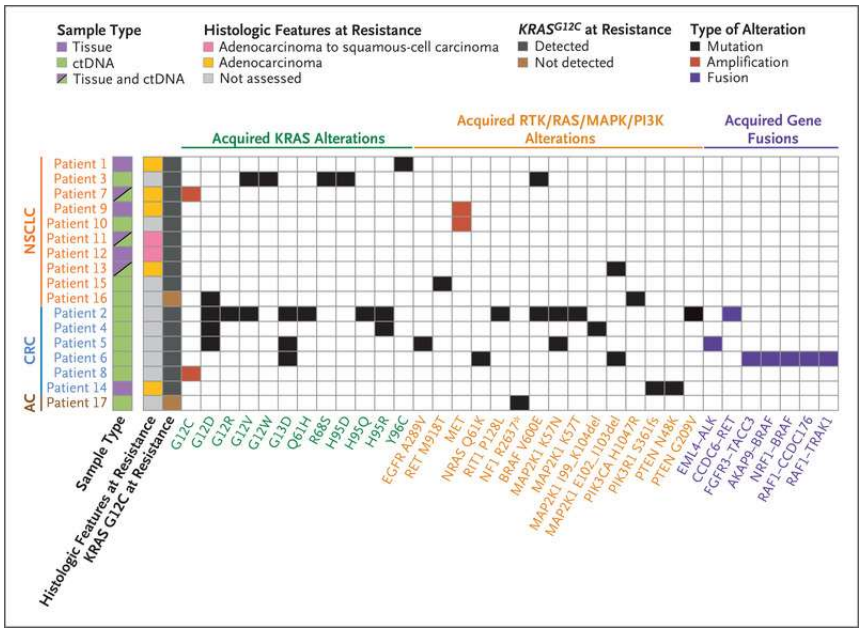
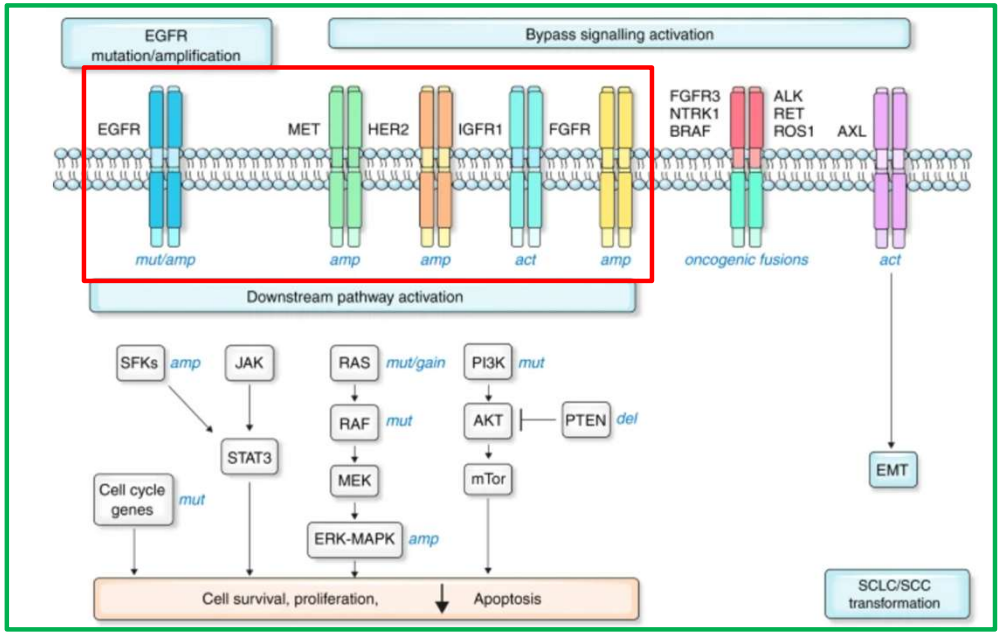
Acquired resistance to adagrasib



Awad et al., NEJM 2021

Acquired resistance to osimertinib



Leonetti et al., BJC 2019

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

Combination Treatment with MRTX0902 and Osimertinib Leads to Deeper and More Durable Suppression of MAPK and PI3K Pathway Signaling *In Vitro*

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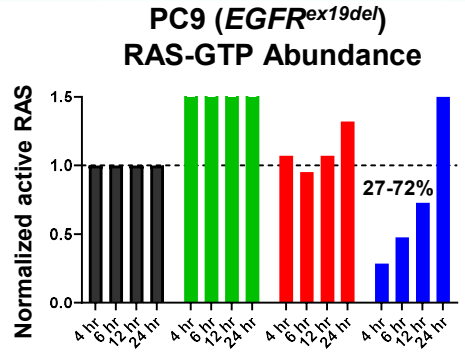

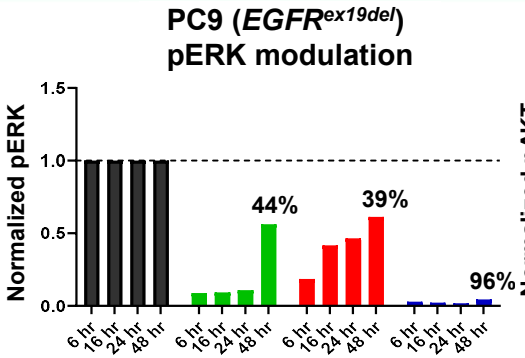

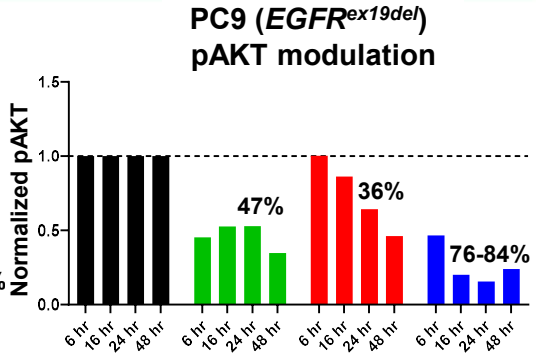

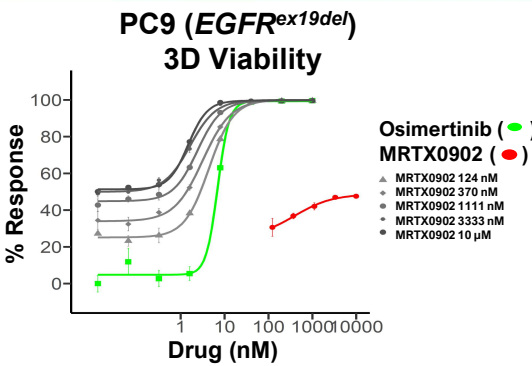

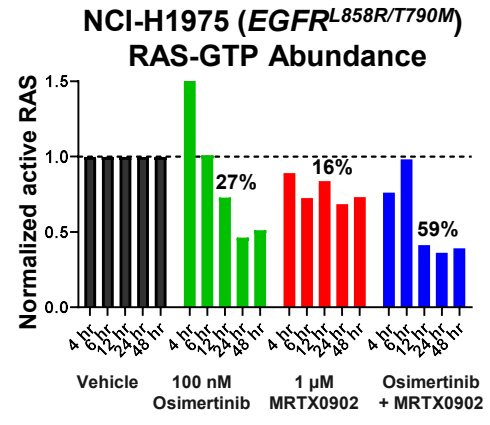

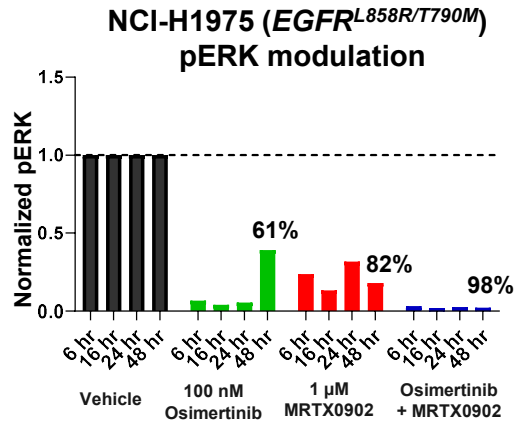

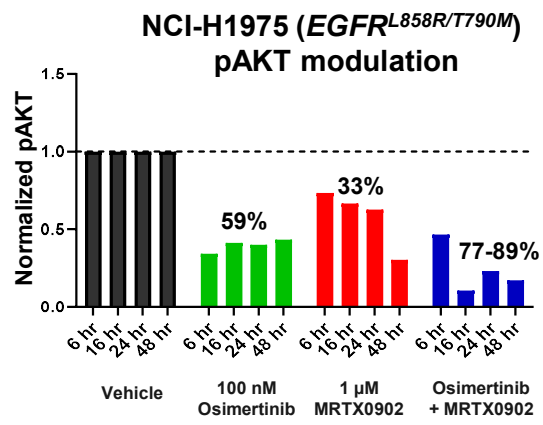

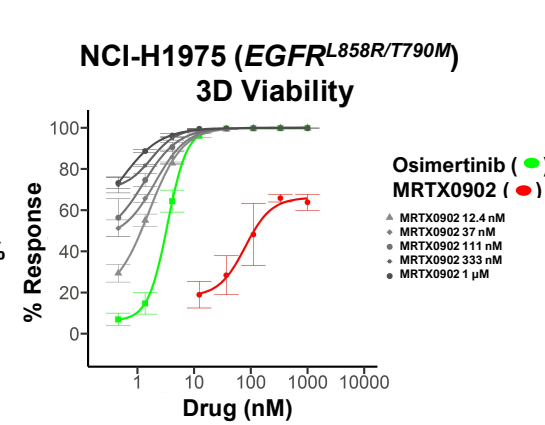

- MRTX0902 + osimertinib leads to greater reduction in activated RAS, sustained MAPK and PI3K pathway inhibition, and additive cell death in *EGFR* mutant models

Combination Treatment with MRTX0902 and Osimertinib Leads to Enhanced Apoptotic Cell Death *In Vitro*

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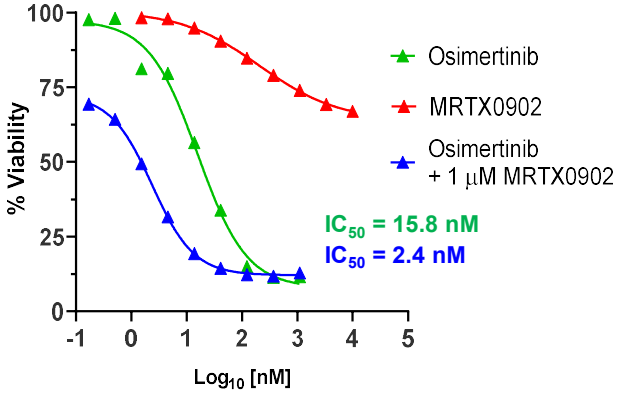
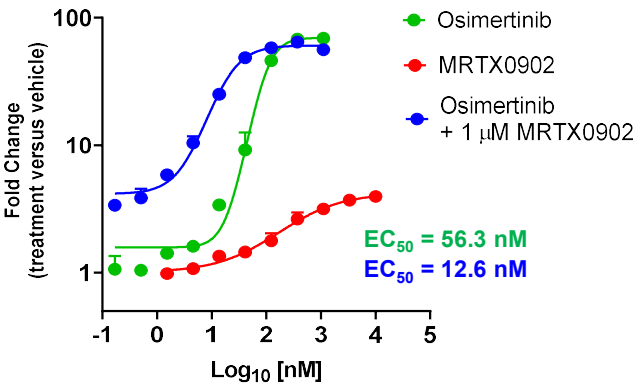
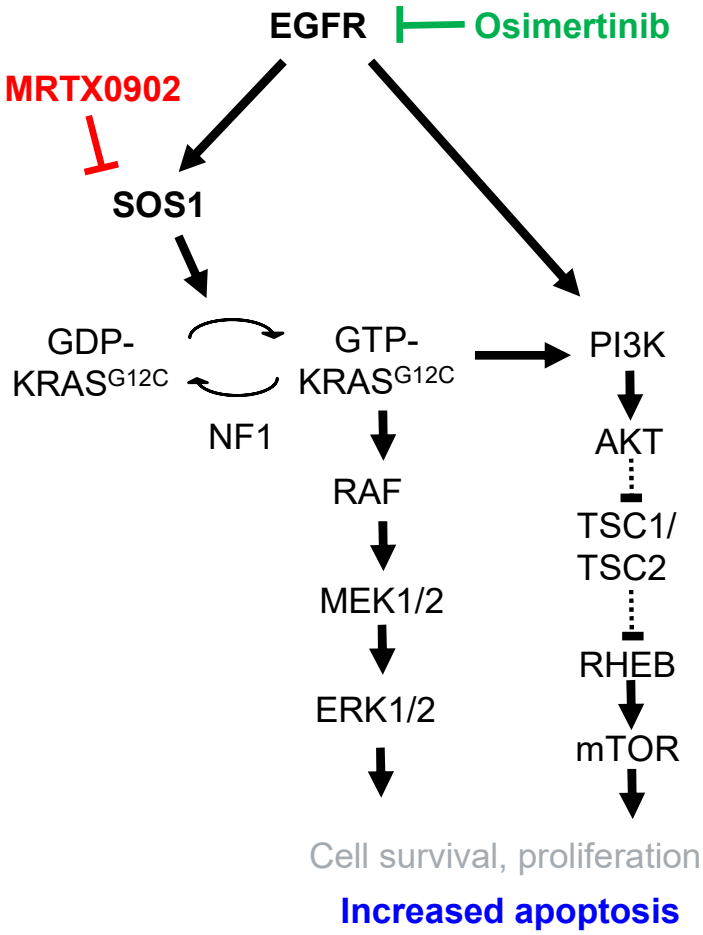
PC9 (*EGFR*^{ex19del})
3D Viability$^{(48\ hours)}$



PC9 (*EGFR*^{ex19del})
Caspase 3/7 Activity$^{(48\ hours)}$
(Normalized to % Viability)





MRTX0902 + osimertinib combination leads to:

- ~7-fold decrease in cell viability IC_{50} value versus osimertinib monotherapy
- ~5-fold greater potency versus single agent osimertinib treatment in caspase-3/7 activity assay

Combination Treatment with MRTX0902 and Osimertinib Leads to Deeper and More Durable Suppression of MAPK and PI3K Pathway Signaling *In Vivo*

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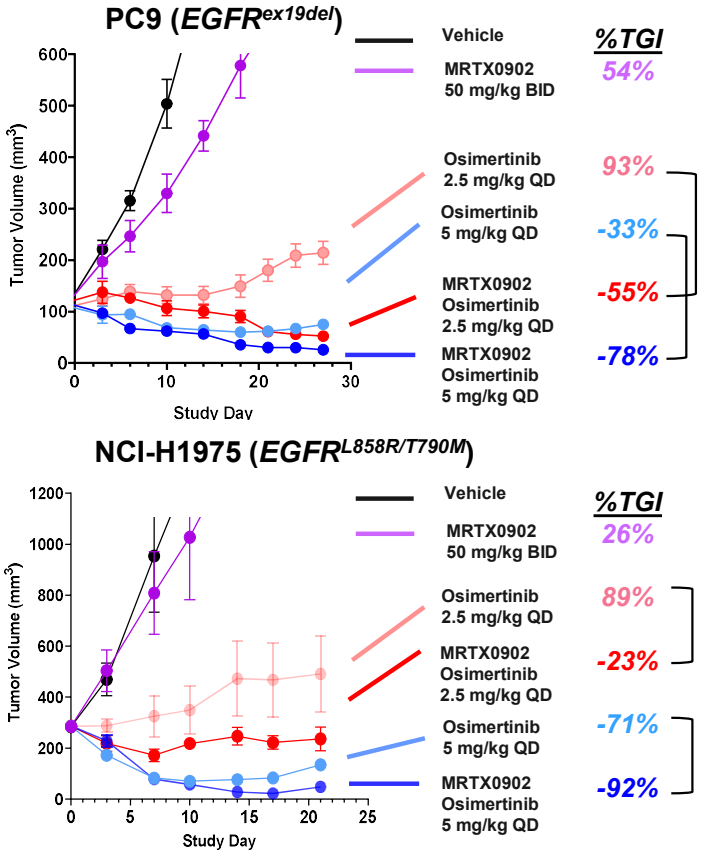

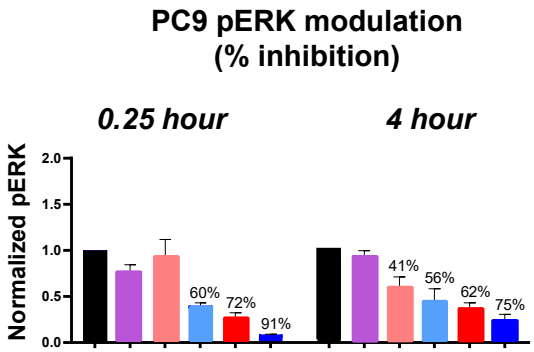

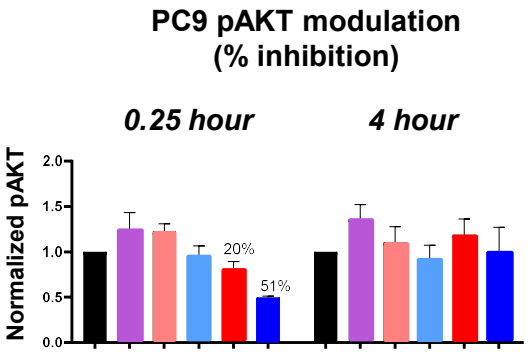

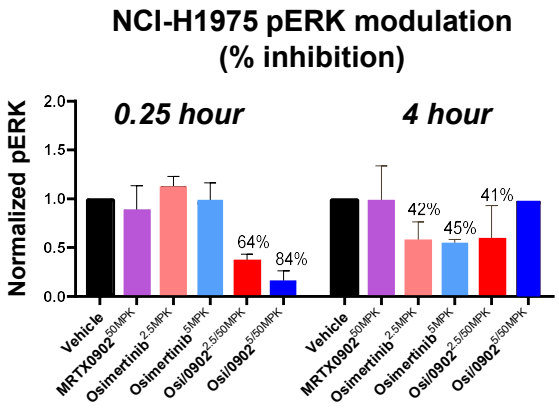

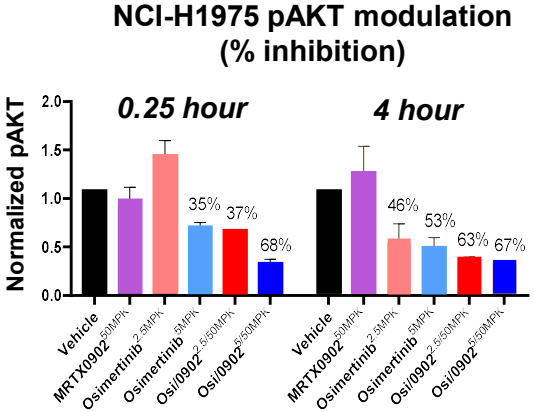

- Combination of 50 mg/kg MRTX0902 BID with osimertinib improves depth and duration of antitumor response in *EGFR* mutant models

Summary

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- The combination of MRTX0902 with MRTX849 (adagrasib) enhances the depth and durability of an anti-tumor response when compared to adagrasib monotherapy in pre-clinical *KRAS*^{G12C}-mutant tumor models

- The efficacy of MRTX0902 can be monitored via analysis of DUSP6 blood transcript levels and is currently being evaluated in Phase 1 clinical trials; additional MAPK combination testing planned

- MRTX0902 augments the *in vitro* antiproliferative and *in vivo* anti-tumor activity of the *EGFR* inhibitor osimertinib via sustained downregulation of MAPK and PI3K signaling pathways

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- **Bioinformatics:** Monoceros Biosystems