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Combination Strategies to Enhance the Efficacy of SHP2 Inhibition

Mechanisms & Models of Cancer

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CSHL, August 2018

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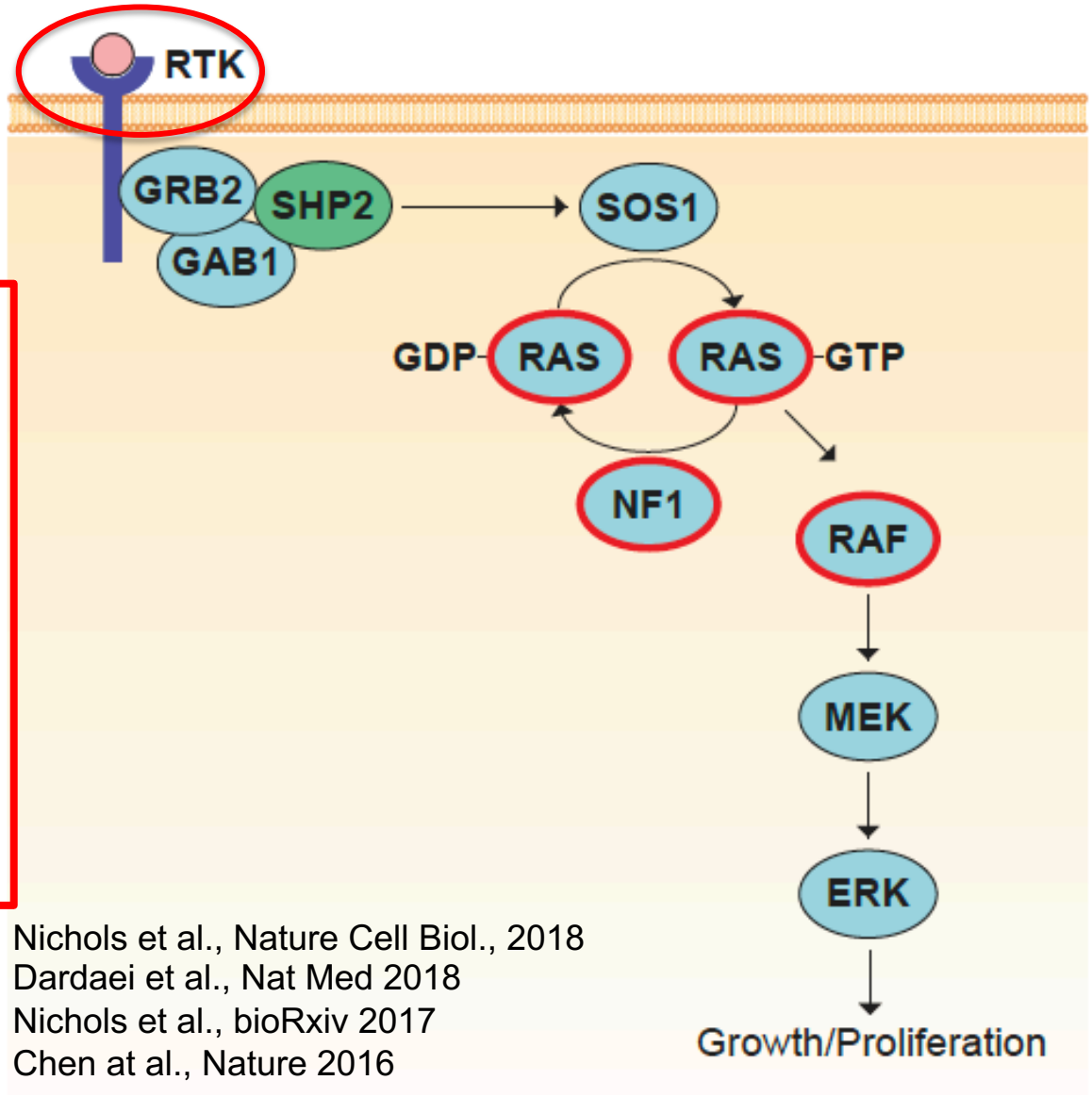
SHP2 Modulates RAS-MAPK Pathway Hyper-activation and Cell Growth Driven by Specific Oncoproteins

Oncoproteins sensitive to SHP2 inhibition

- Mutant RTKs
- RTK amplifications

- Nucleotide-cycling KRAS
- Wt KRAS amplifications

- NF1 loss of function
- BRAF class 3 mutants

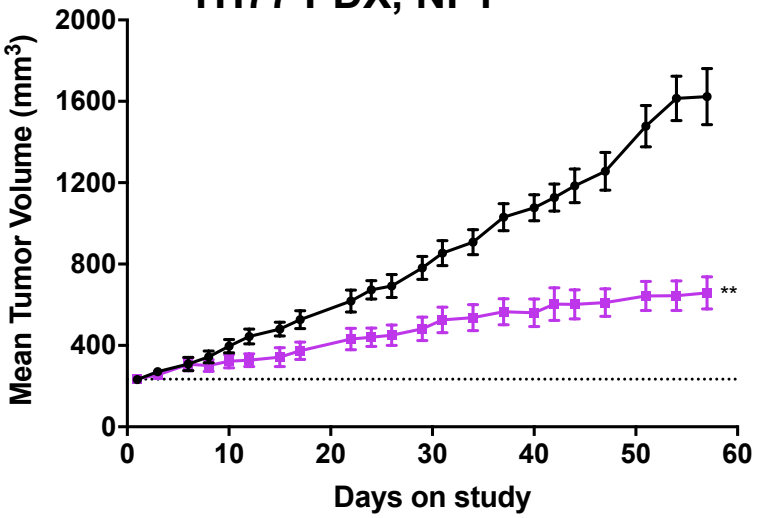


Nichols et al., Nature Cell Biol., 2018
Dardaei et al., Nat Med 2018
Nichols et al., bioRxiv 2017
Chen at al., Nature 2016

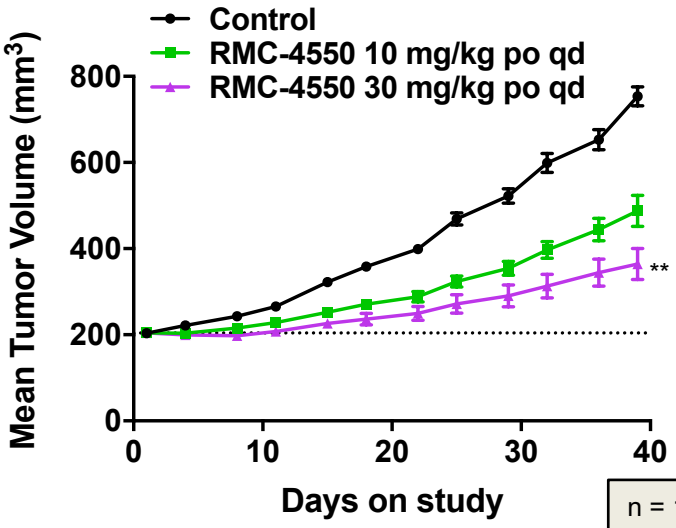
SHP2 Inhibition Efficacious in Mutant BRAF-, NF1- and Nucleotide Cycling-KRAS NSCLC PDX Models

Nichols et al., Nature Cell Biol., 2018, https://doi.org/10.1038/s41556-018-0169-1

TH77 PDX, $NF1^{S1759C\text{-}LOF}$

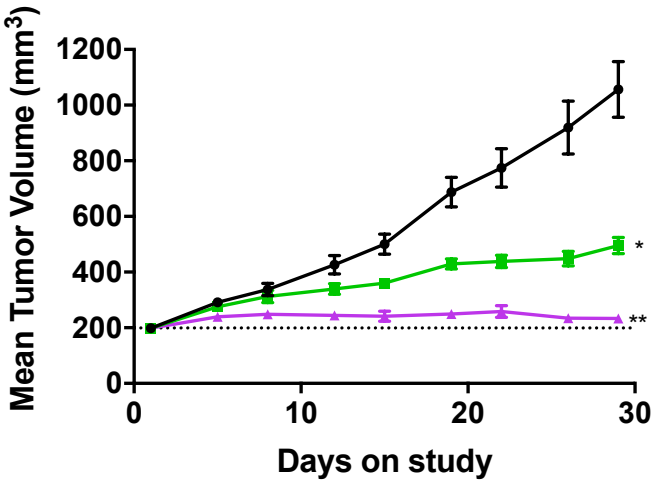


LUN037 PDX, $BRAF^{D581D\text{-}Class3}$

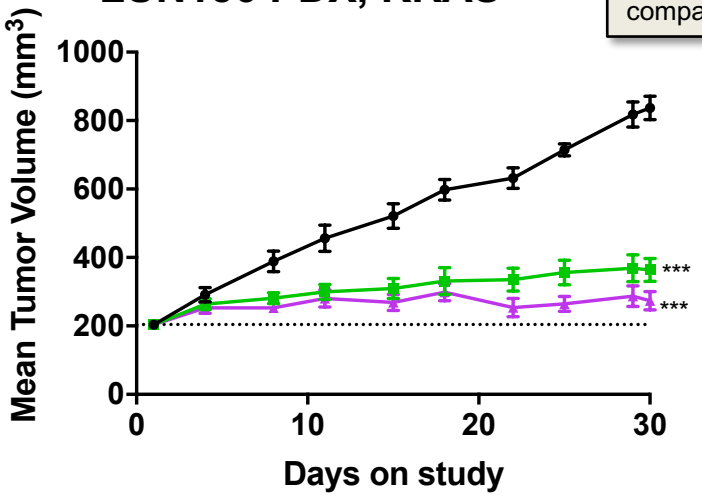


n = 10/group
***p<0.0001, **p≤ 0.001
ANOVA w multiple comparisons

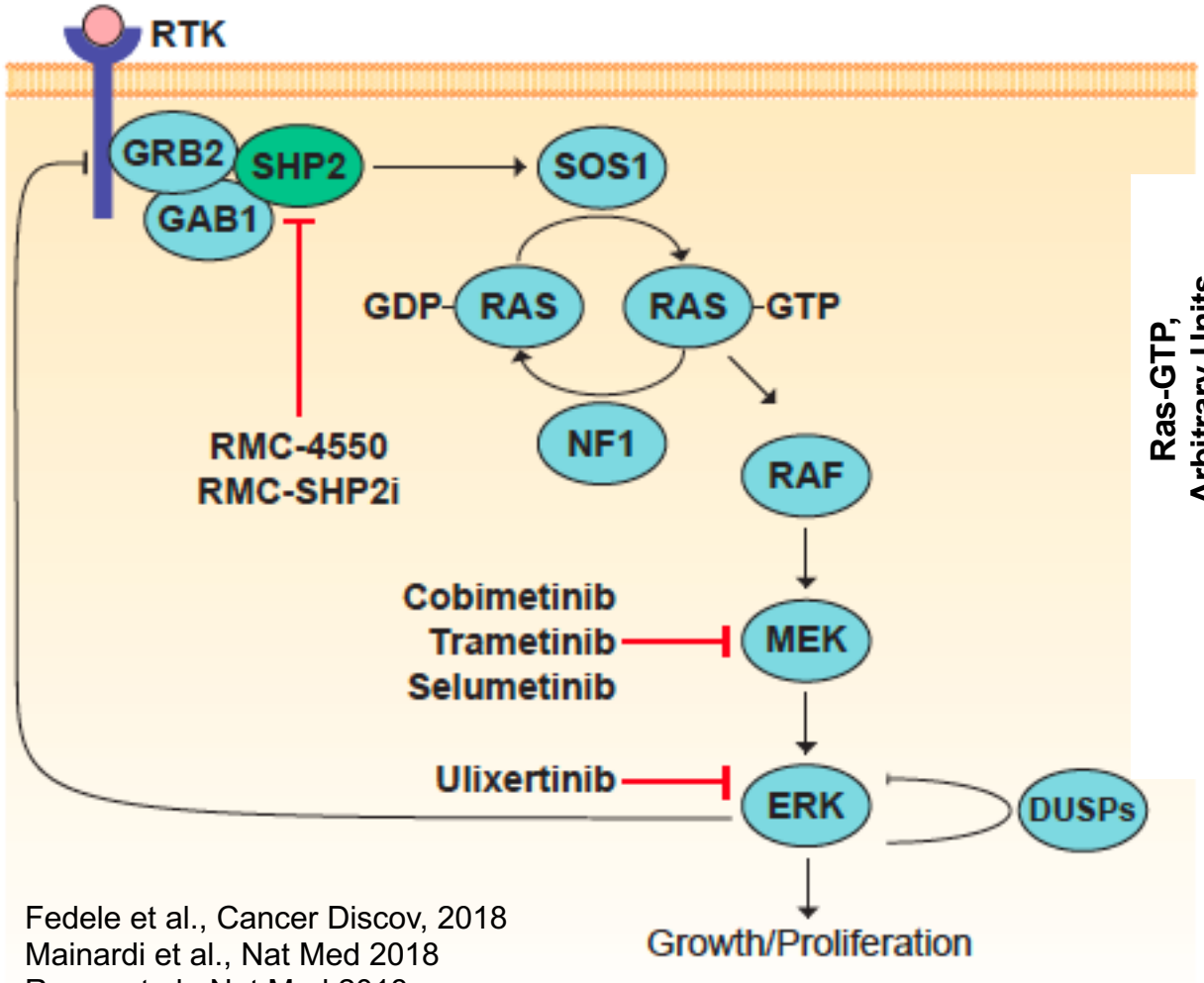
LUN092 PDX, $KRAS^{G12C}$

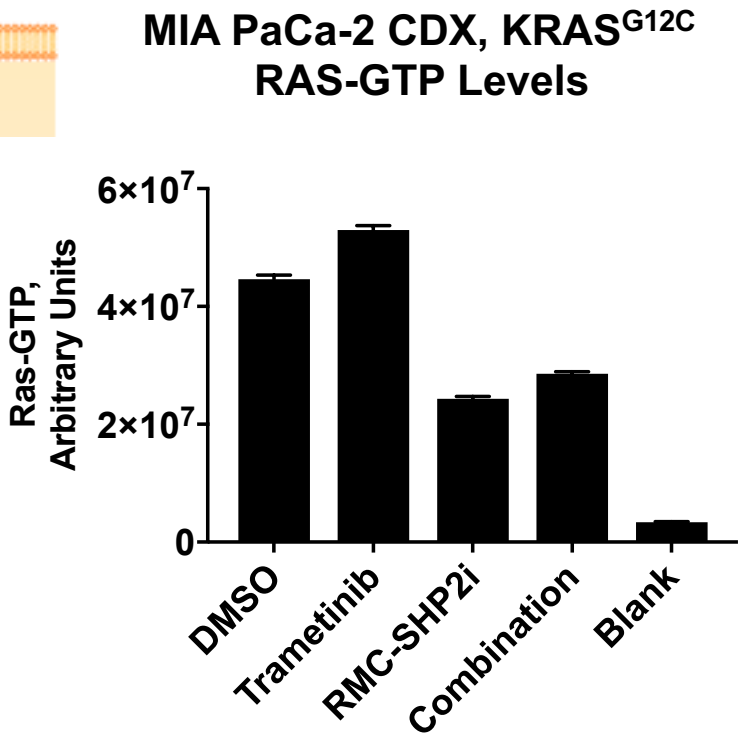


LUN156 PDX, $KRAS^{G12C}$



SHP2 Inhibition Blocks MEK Inhibitor-Driven Adaptive Resistance & Enhances Efficacy in KRAS-driven Models

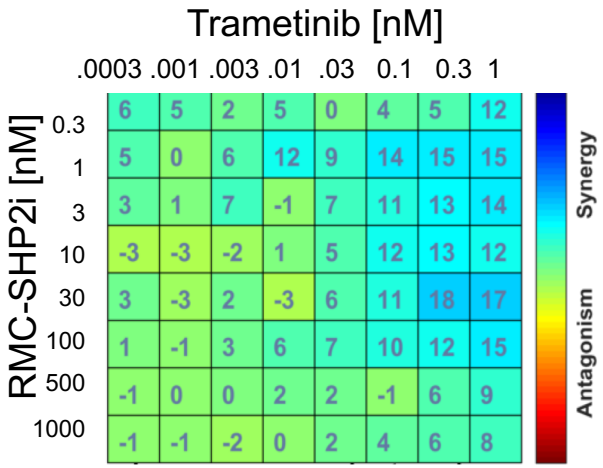




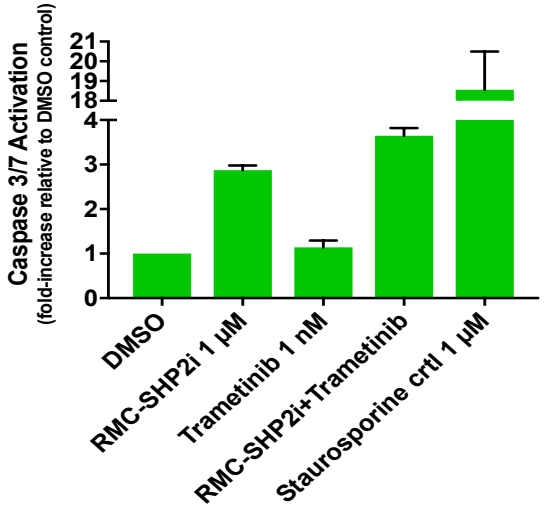
Fedele et al., Cancer Discov, 2018
Mainardi et al., Nat Med 2018
Ruess at al., Nat Med 2018
Wong et al. Nat Med 2018

SHP2 Inhibitor Exhibits Combinatorial Efficacy with a MEK Inhibitor in NCI-H358 KRAS^{G12C} Tumors

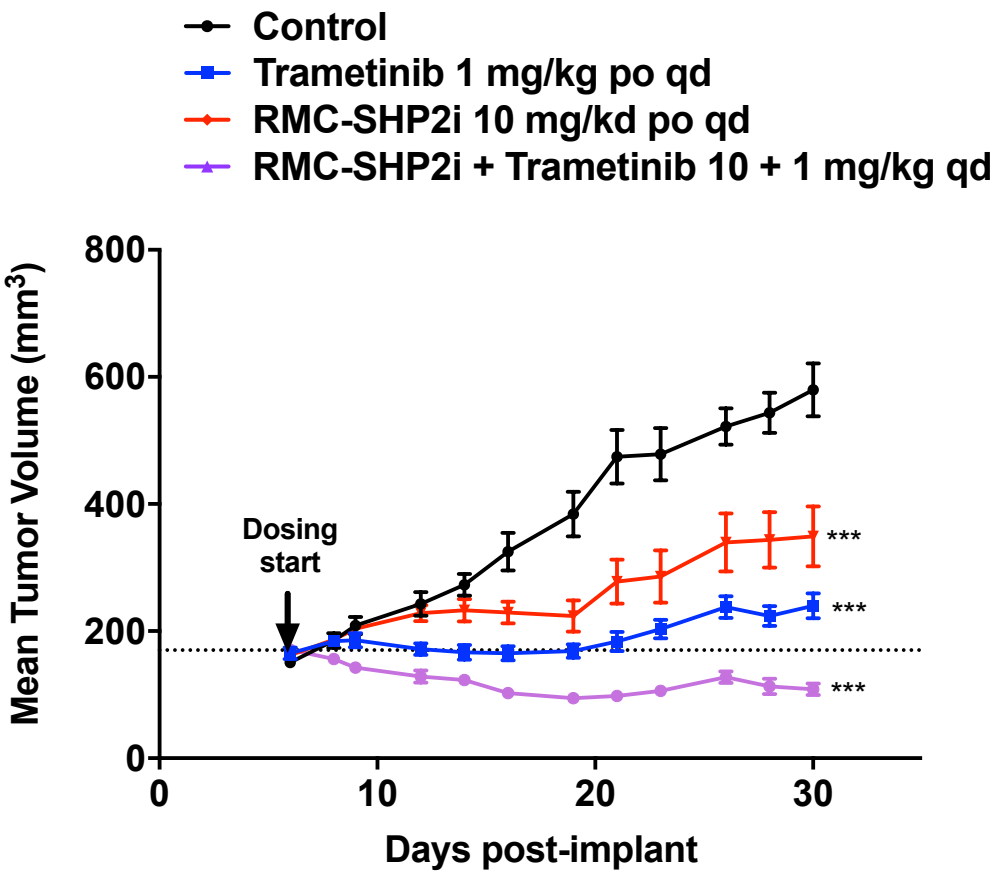
Proliferation Inhibition *in vitro* (3D)



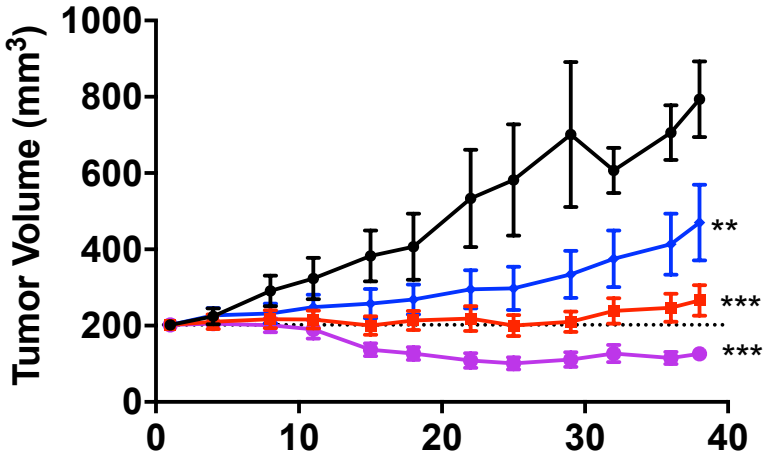
Caspase Activation (Apoptosis)

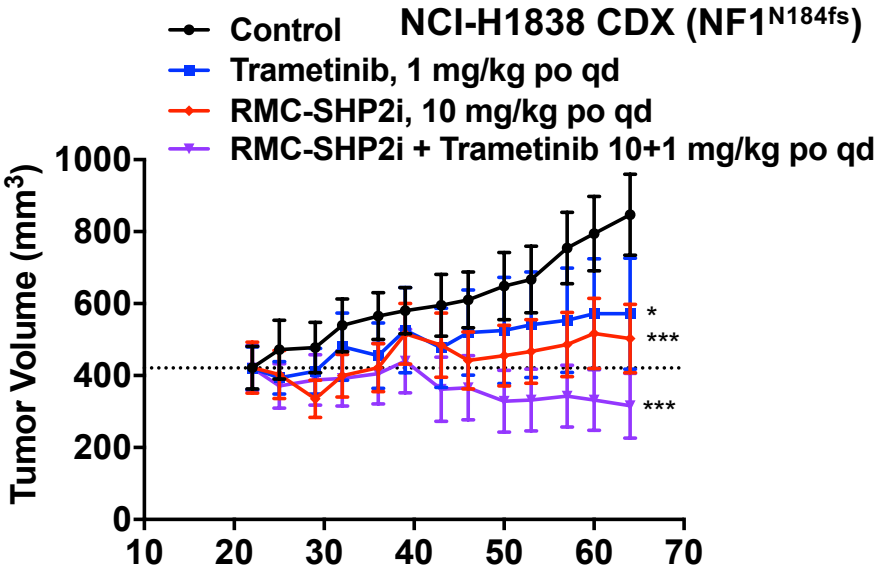


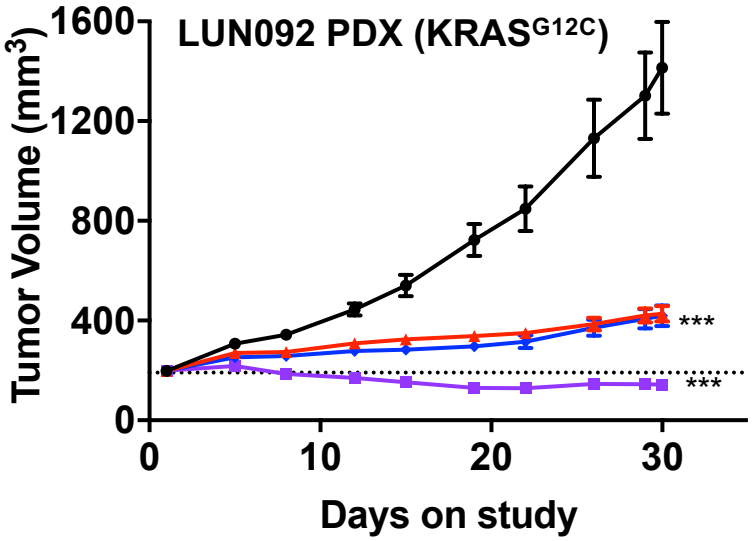
Anti-Tumor Activity *in vivo*

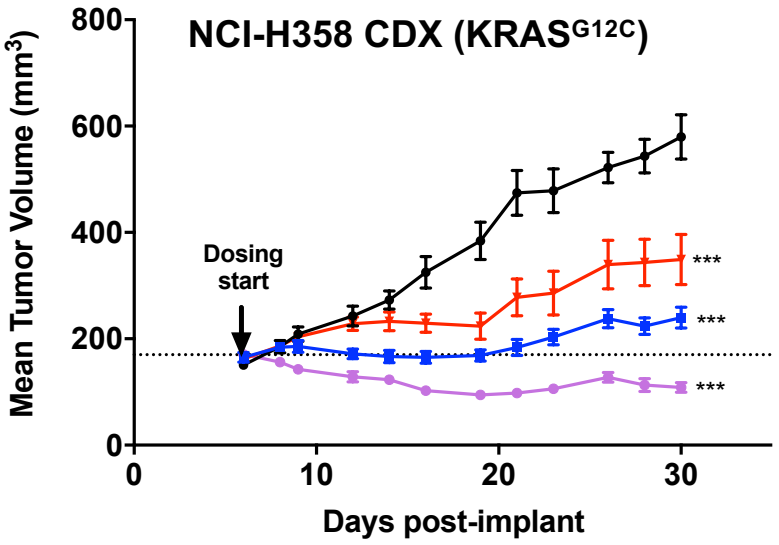


SHP2 + MEK Inhibitor Combination Drives Regressions in $NF1^{LOF}$, $BRAF^{Class3}$ and $KRAS^{G12C}$ NSCLC Models

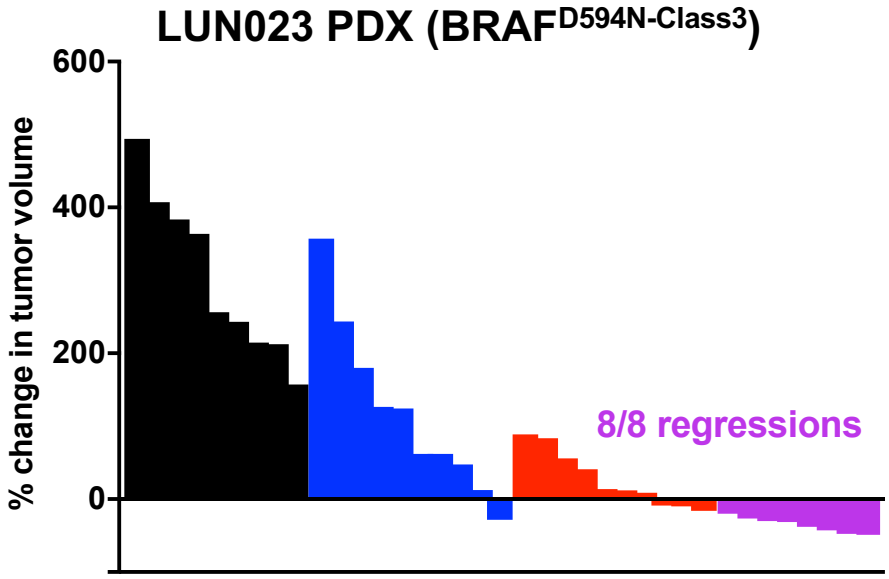


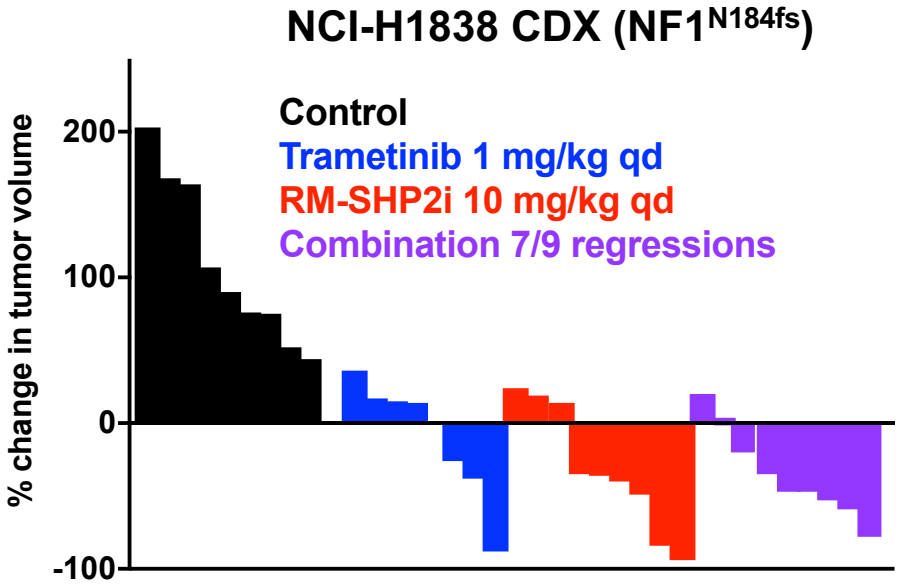


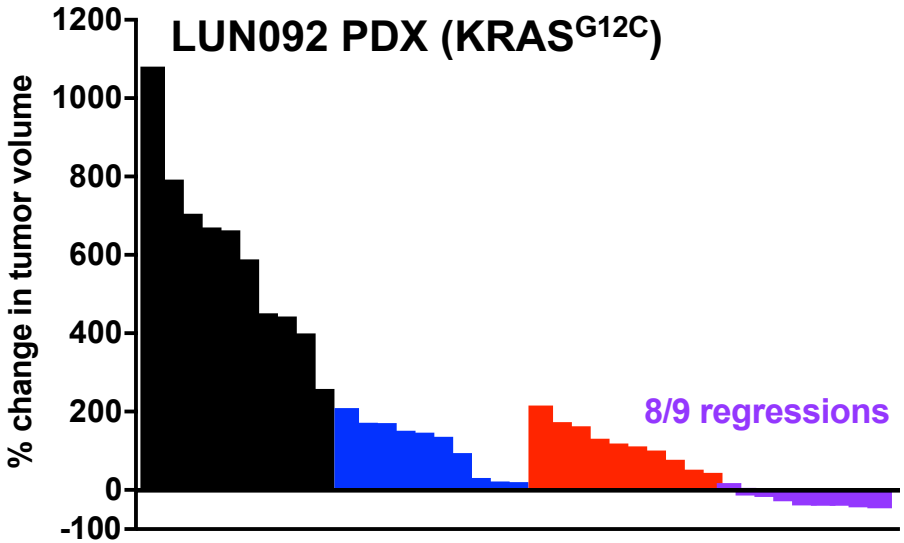


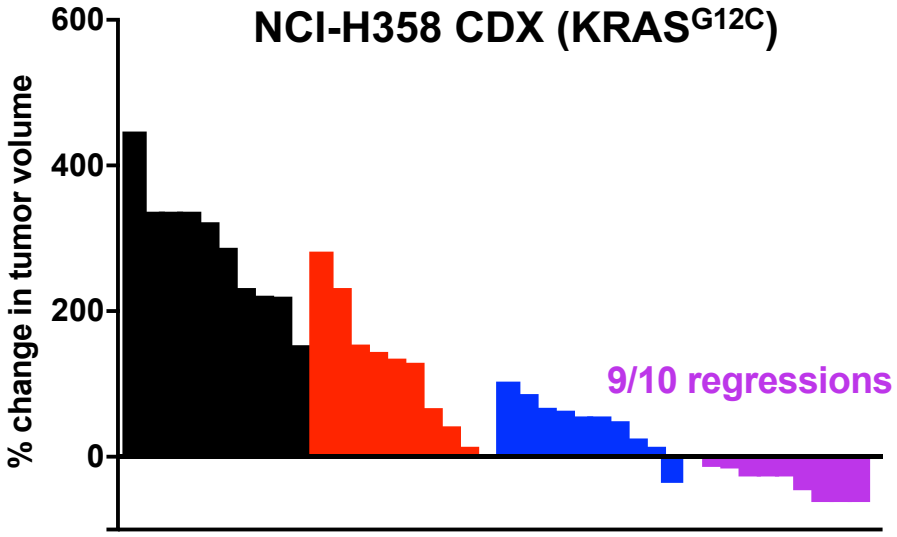


SHP2 + MEK Inhibitor Combination Drives Regressions in $NF1^{LOF}$, $BRAF^{Class3}$ and $KRAS^{G12C}$ NSCLC Models

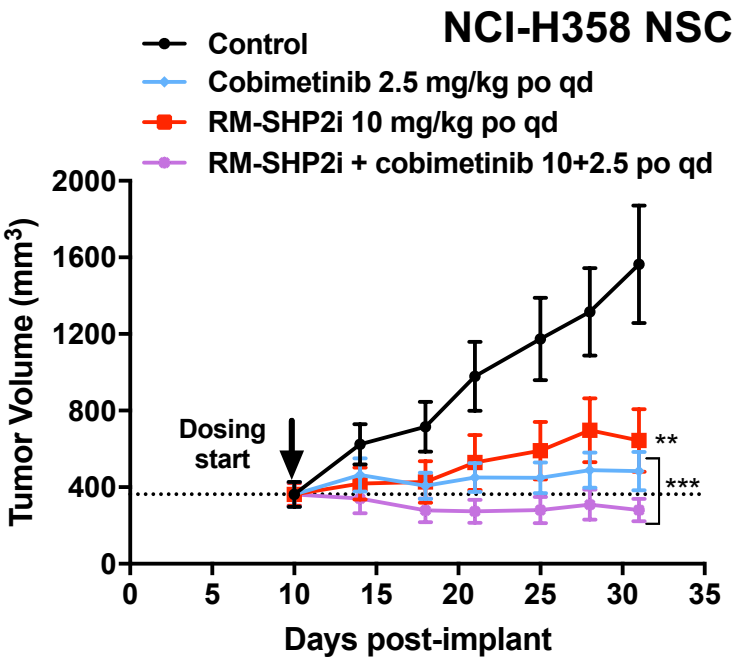


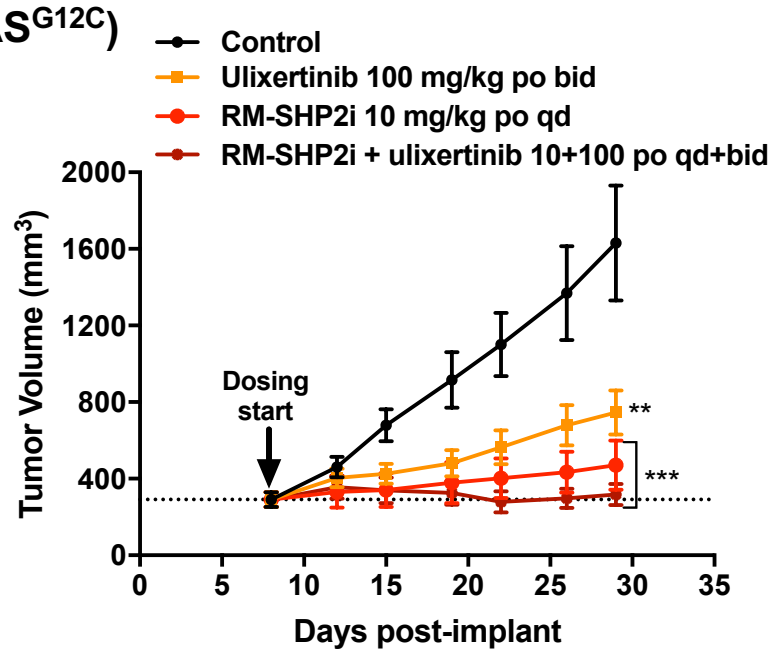


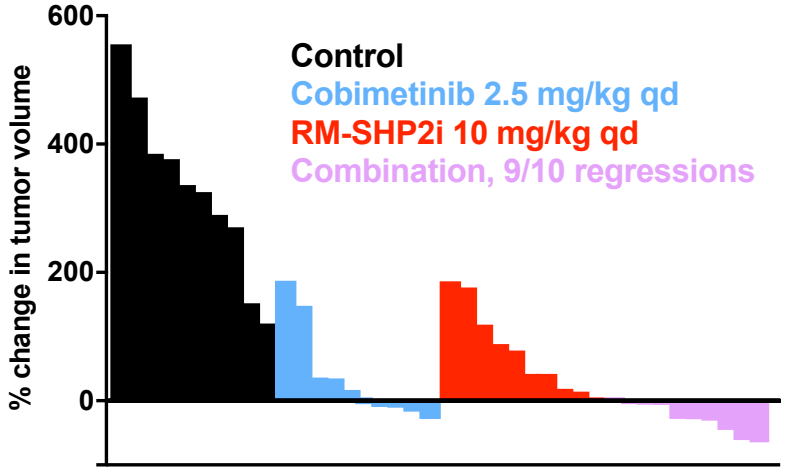


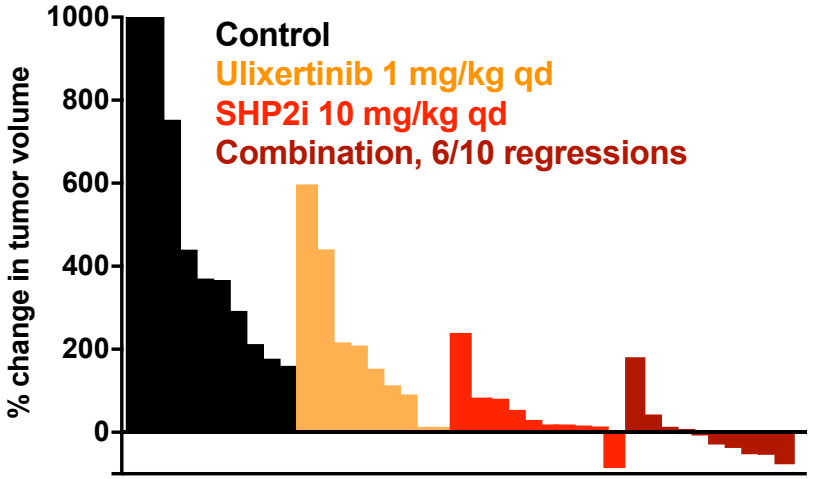


Similar Combinatorial Efficacy for SHP2 Inhibitor with an Alternate MEK Inhibitor or an ERK Inhibitor







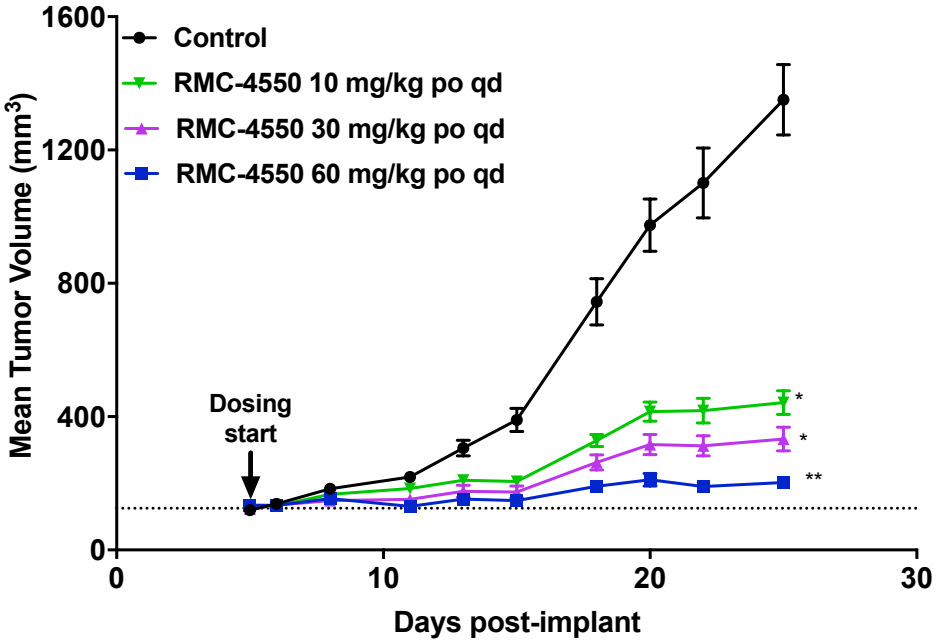


SHP2 Inhibitor Exhibits Dose-Dependent Modulation of Extent and Duration of Tumor pERK Suppression

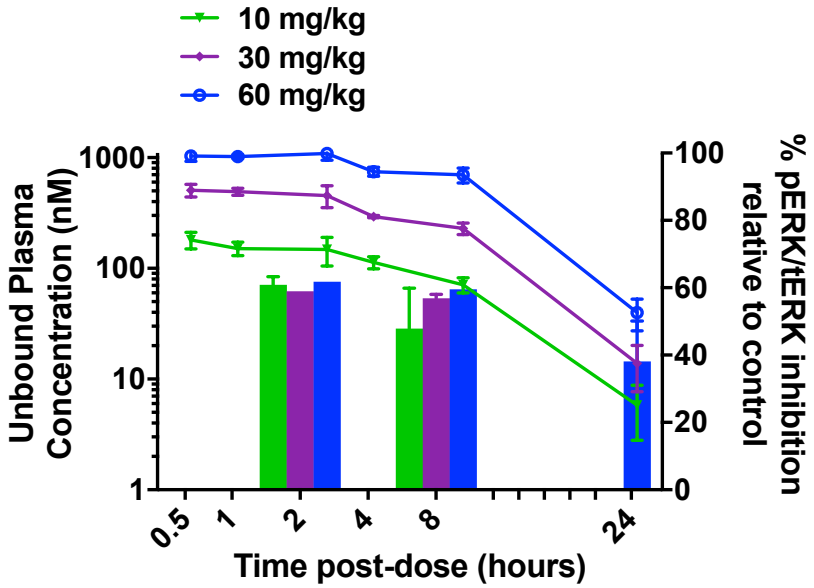
Nichols et al., Nature Cell Biol., 2018, https://doi.org/10.1038/s41556-018-0169-1

MIA PaCa-2 KRAS^{G12C} Tumor Model

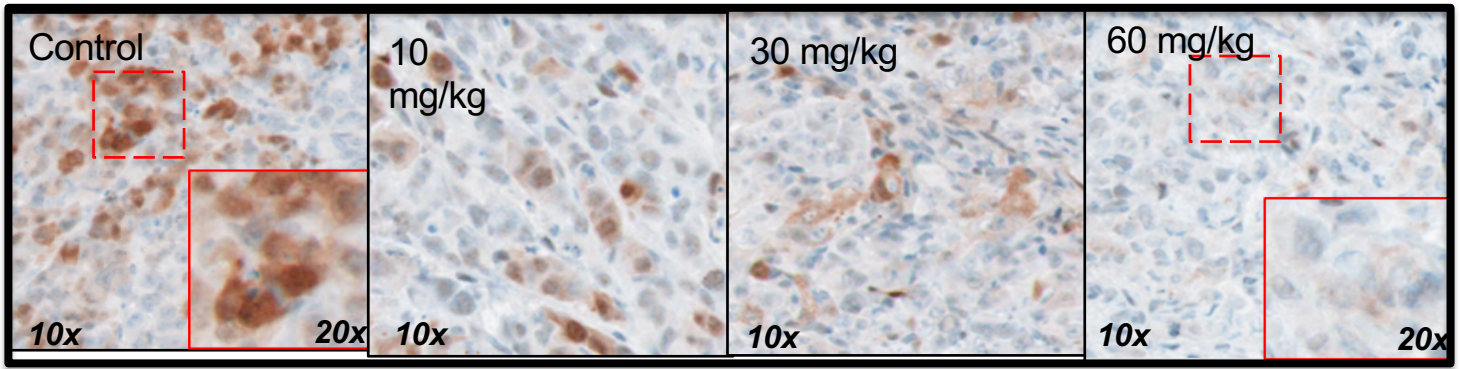
Anti-Tumor Activity



Plasma PK and Tumor pERK



pERK
1 hour post-dose



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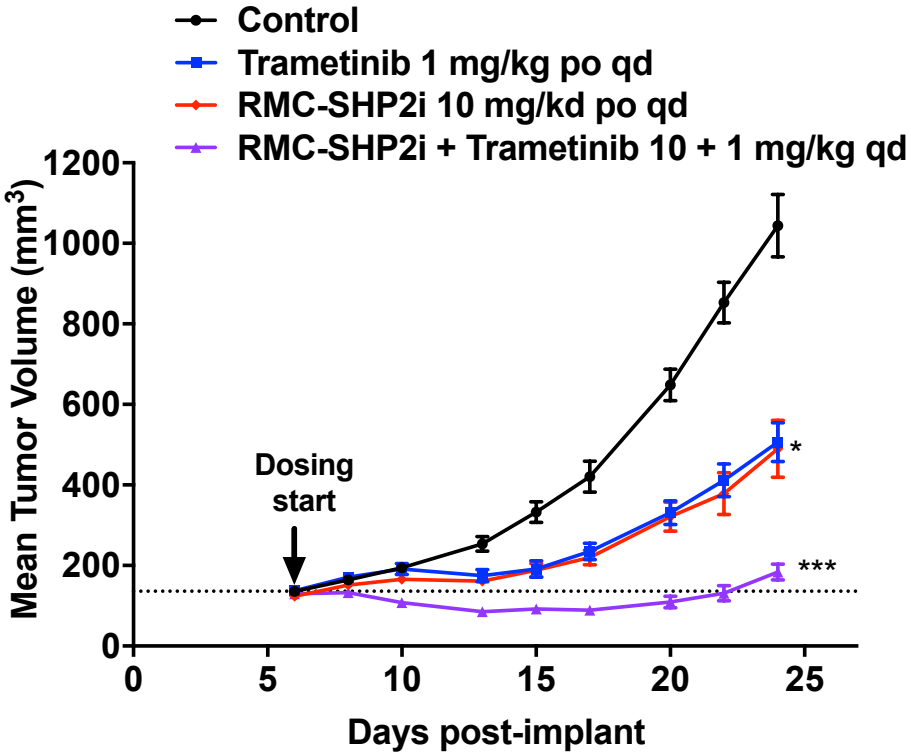
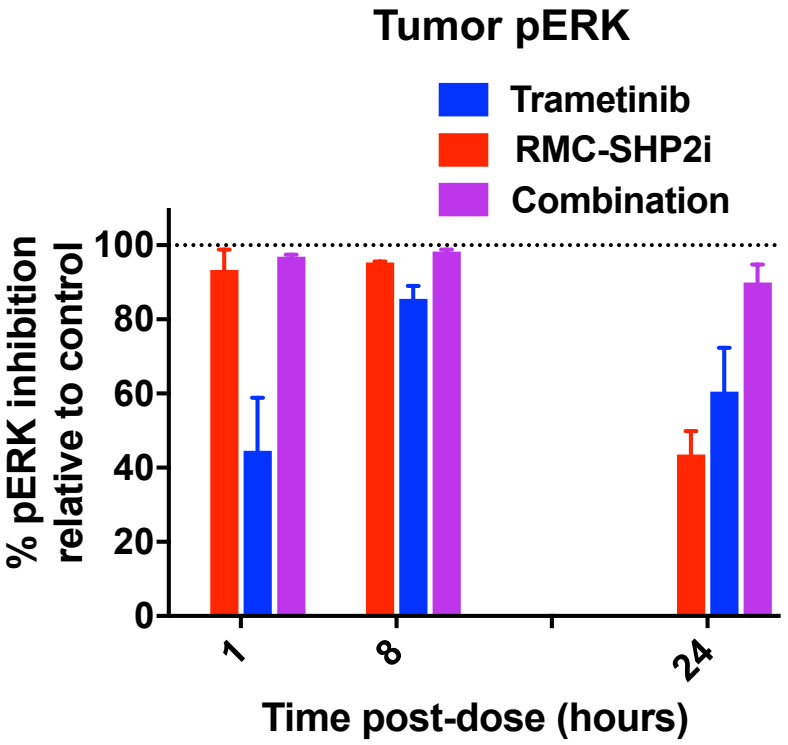
SHP2 and MEK Inhibitor Combination Increases Duration of Maximal Tumor pERK Suppression

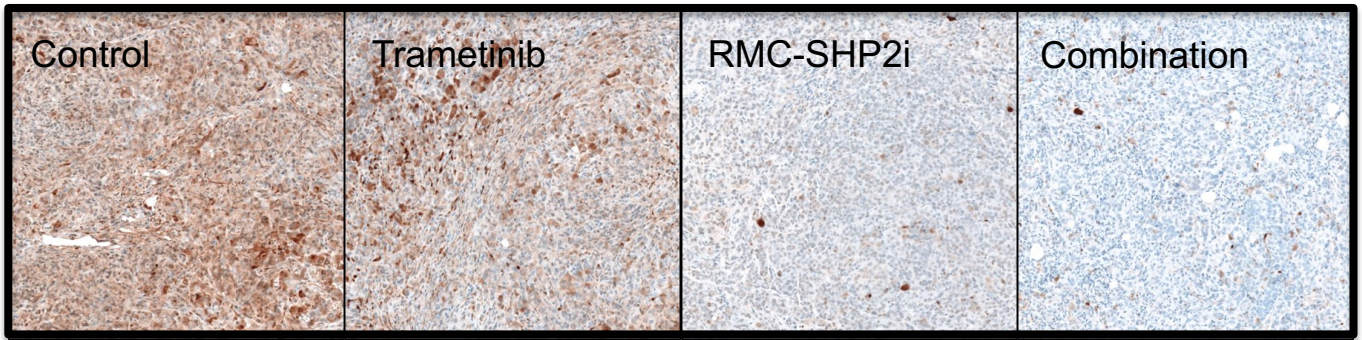
Anti-Tumor Activity



MIA PaCa-2 KRAS^{G12C} Tumor Model



pERK
1 hour post-dose



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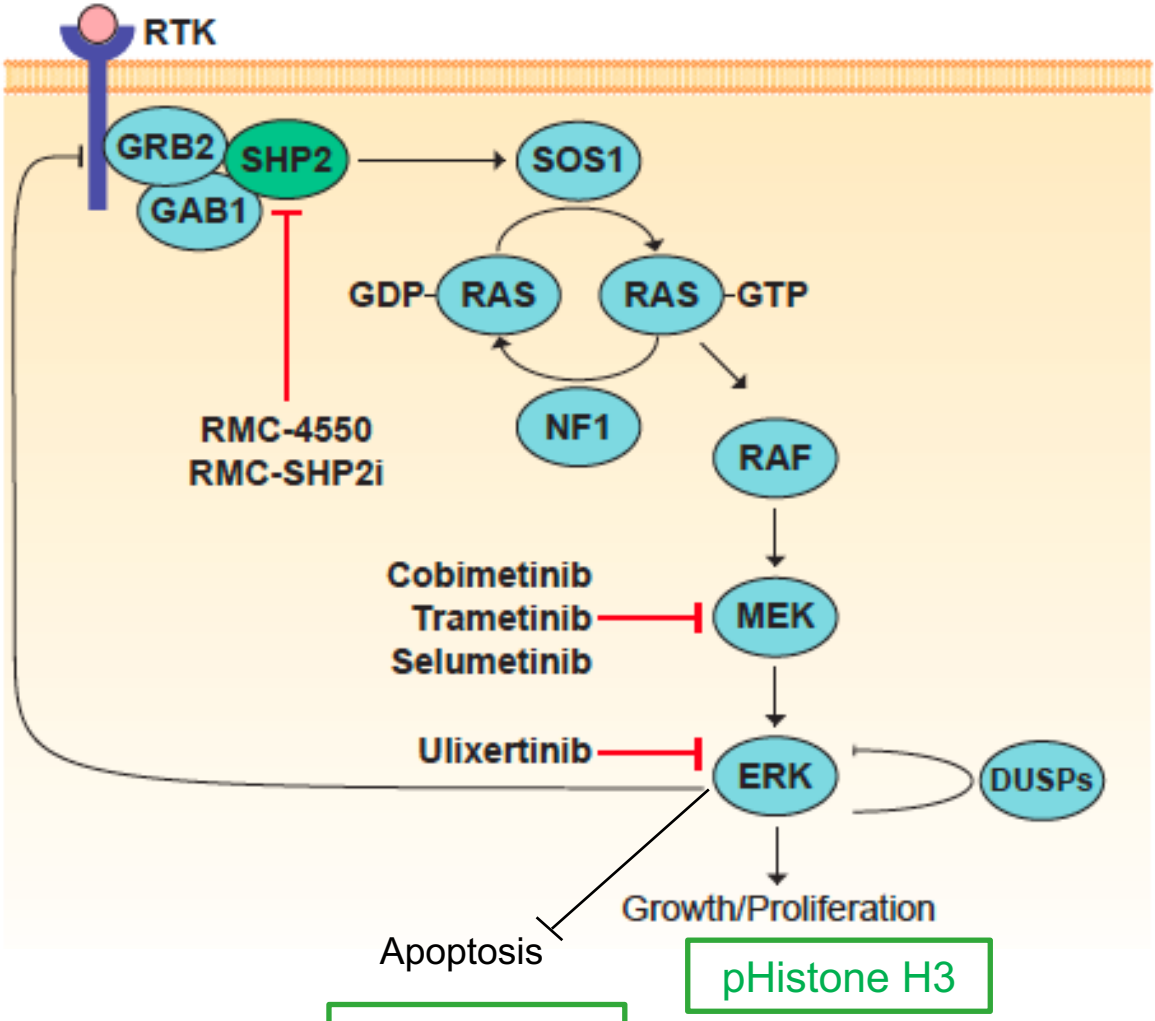
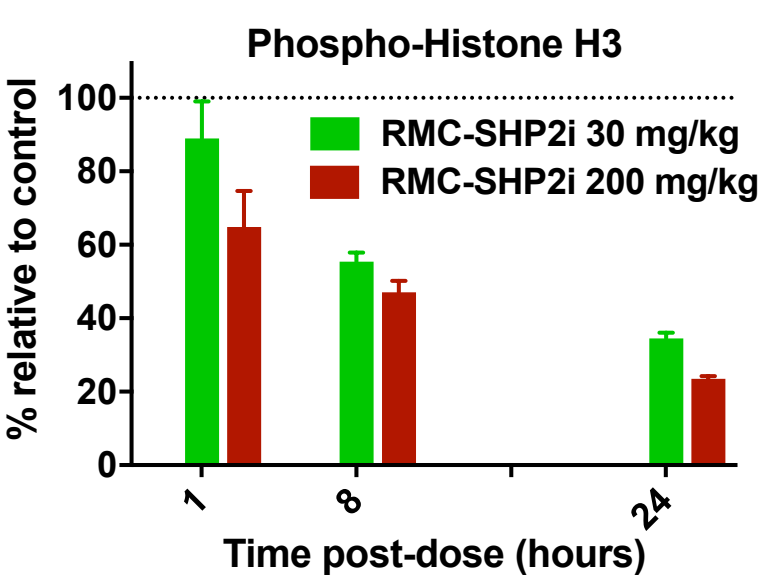
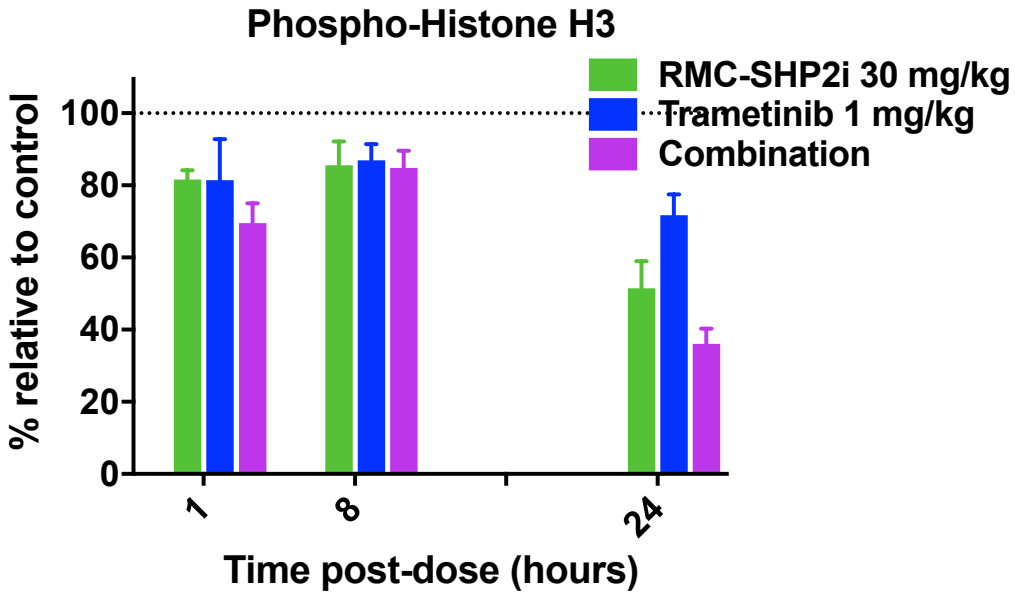
What are the Downstream Consequences of High Dose SHP2 or SHP2+MEK Inhibitor Combinations in Tumors?



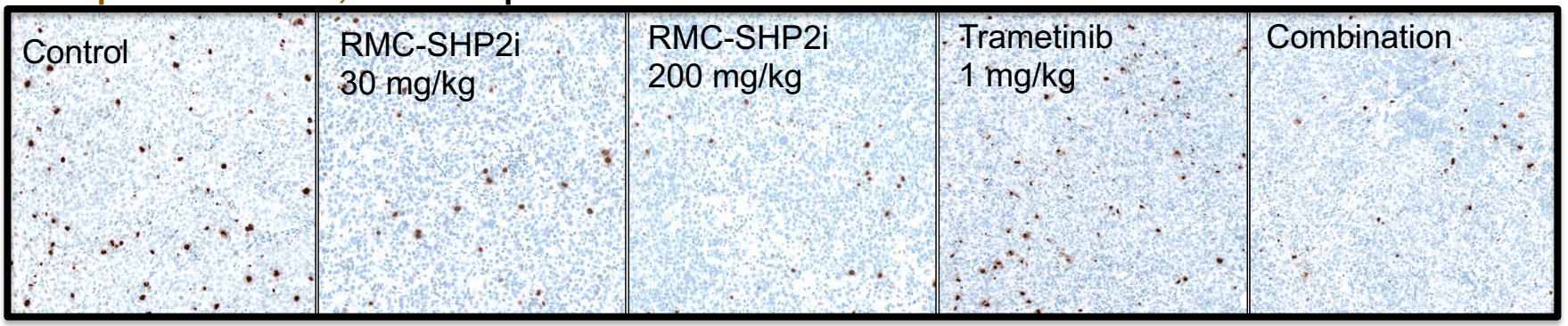
High Dose SHP2 Inhibitor or SHP2+MEK Inhibitor Combinations Inhibit Tumor Cell Proliferation

MIA PaCa-2 KRAS^{G12C} Tumor Model
N = 3/timepoint, 2 independent experiments



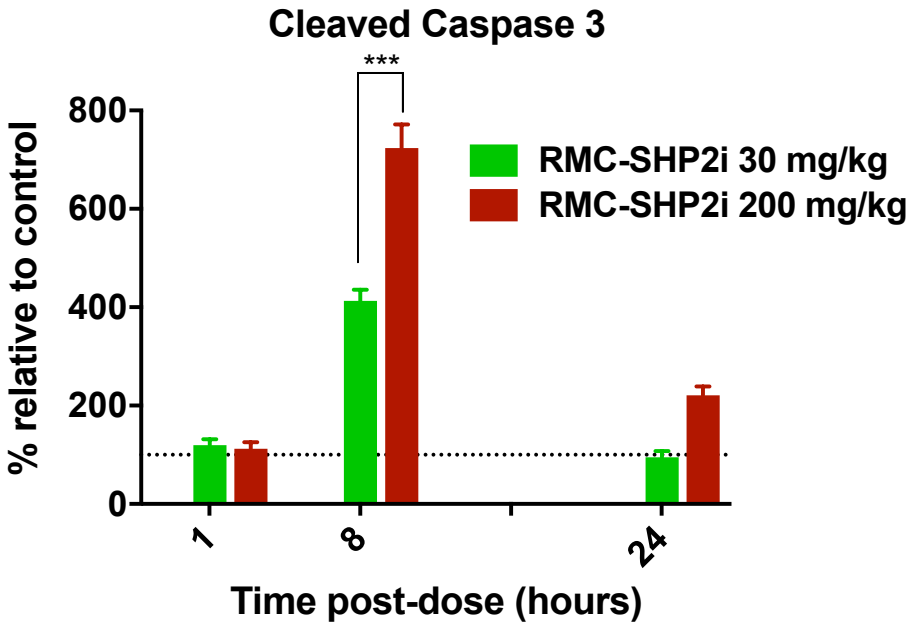


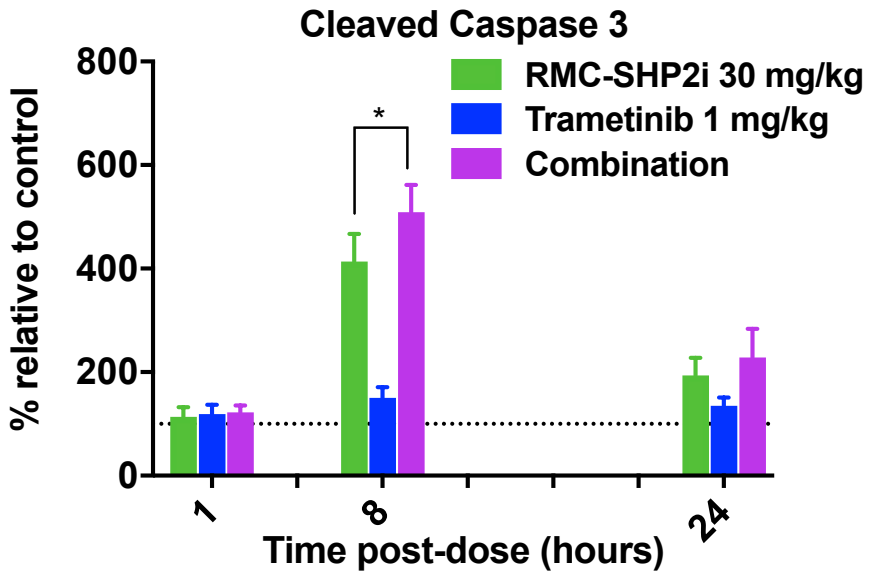
Phospho-histone H3, 24 hours post-dose



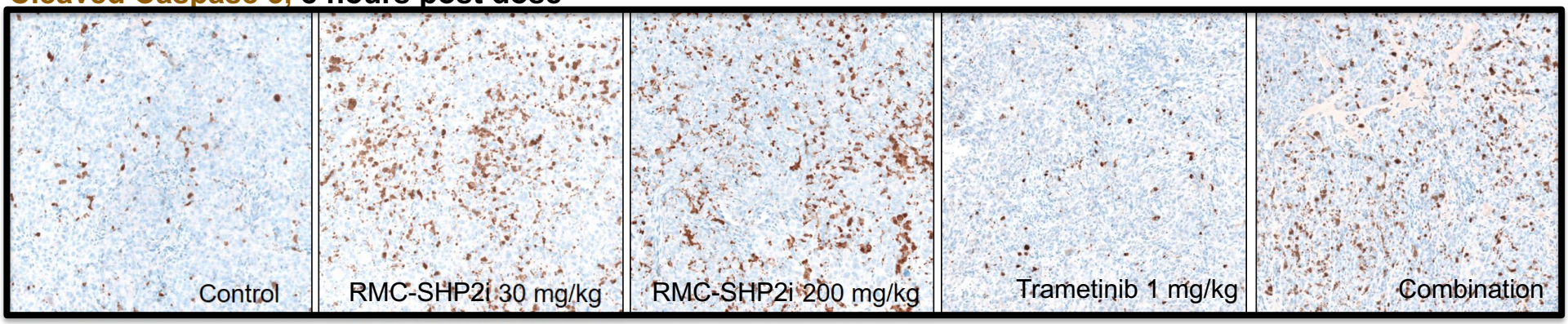
High Dose SHP2 or SHP2+MEK Inhibitor Combinations Enhance Extent and Duration of Tumor Apoptosis

MIA PaCa-2 KRAS^{G12C} Tumor Model
N = 3/timepoint, 2 independent experiments





Cleaved Caspase 3, 8 hours post dose



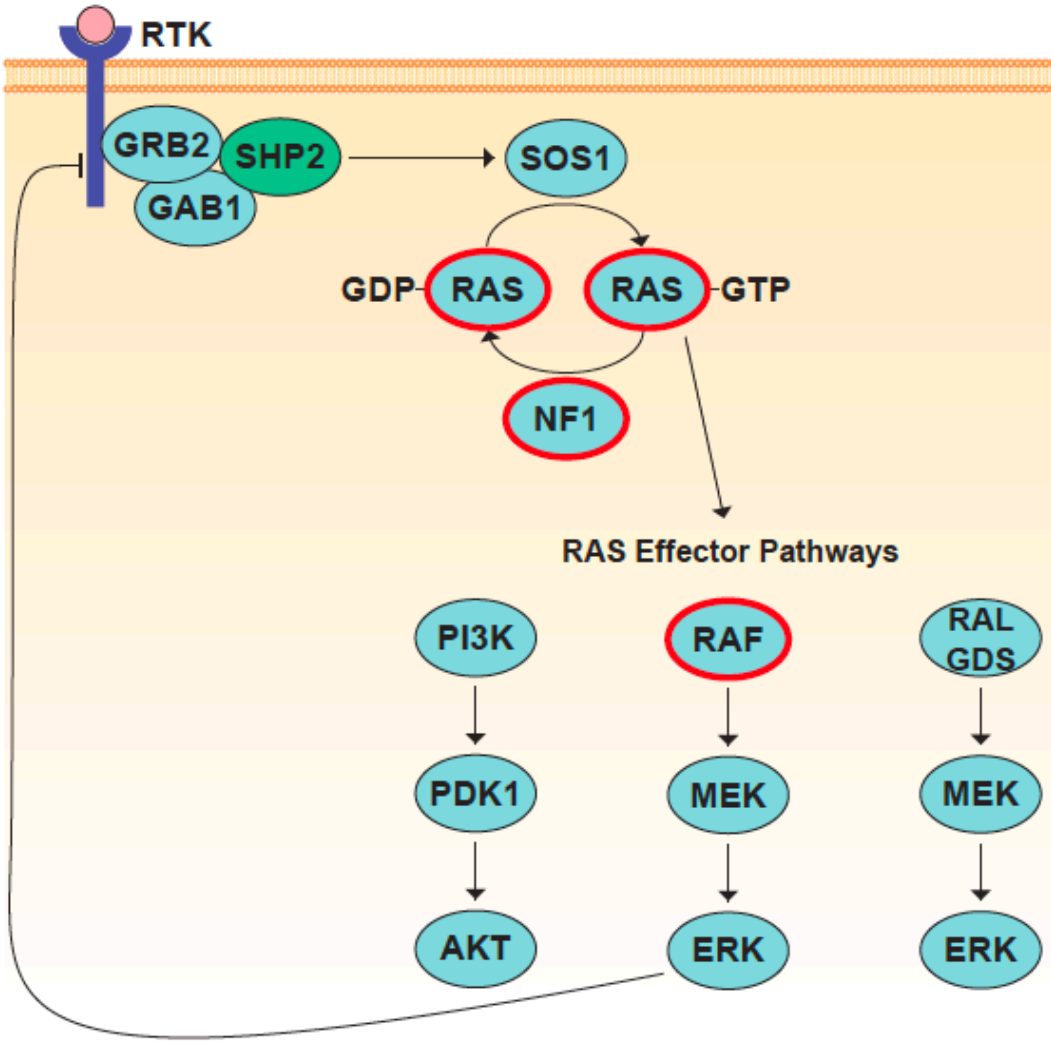
SHP2 Inhibition Drives Independent Anti-Tumor Effects and Synergizes With MEK Inhibition

Pharmacodynamic Marker	SHP2 Inhibition	MEK Inhibition	Combination
Maximal tumor pERK suppression	✓	Minimal	✓
Increased duration of pERK suppression	✓	Minimal	✓
Tumor cell apoptosis	✓	Minimal	✓
Decreased tumor cell proliferation	✓	✓	✓

SHP2 Inhibition Drives Independent Anti-Tumor Effects and Synergizes with MEK Inhibition

- Inhibition of SHP2 is sufficient to drive dose-dependent and prolonged tumor pERK suppression, increased apoptosis and decreased proliferation in $KRAS^{G12C}$ driven tumors
- In contrast, MEK inhibition alone evokes minimal inhibition of tumor pERK and drives combination effects primarily via decreased tumor cell proliferation
- Thus combinatorial effects of SHP2 and MEK inhibition cannot be restricted to SHP2-mediated abrogation of MEK-inhibitor driven adaptive feedback
- The independent anti-tumor effects of SHP2 inhibition contribute to the synergistic anti-tumor activity observed in combination with MEK inhibition in $NF1^{LOF}$, $BRAF^{Class3}$ and $KRAS^{G12C}$ tumor models

Synergistic Effects of SHP2 Inhibitor and MEK Inhibitor Likely Invoke MEK-Independent Cell Survival Pathways



SHP2 inhibitor
- ⇩ pERK
- ⇩ Proliferation
- ⇩ Upregulated RTK signaling
- ⇧ Apoptosis

+

MEK inhibitor
- ⇩ Proliferation
- ⇧ RTK signaling

⇩

SHP2 + MEK Inhibitor Combination
- ⇩ RAS/MAPK pathway = **extinction?**
- ⇩ MEK-independent pathways e.g. engage other RAS-effectors?

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Acknowledgements

TIRELESS COMMITMENT TO PATIENTS

TRANSFORMATIVE SCIENCE

OUR CORE VALUES

EXCEPTIONAL. TOGETHER.

TOTAL INTEGRITY

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