NASDAQ: MRTX

MIRATI THERAPEUTICS

Targeting the genetic and immunological drivers of cancer

The KRASG12C Inhibitor, MRTX849, Provides Insight Toward Therapeutic Susceptibility of KRAS Mutant Cancer

Presented at AACR-NCI-EORTC International Conference on Molecular Targets

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Jamie Christensen, Ph.D.

Targeting KRAS Has Been Historically Challenging

Direct, Reversible Inhibitors

- Smooth surface
- High affinity for & high intracellular concentrations of GTP/GDP

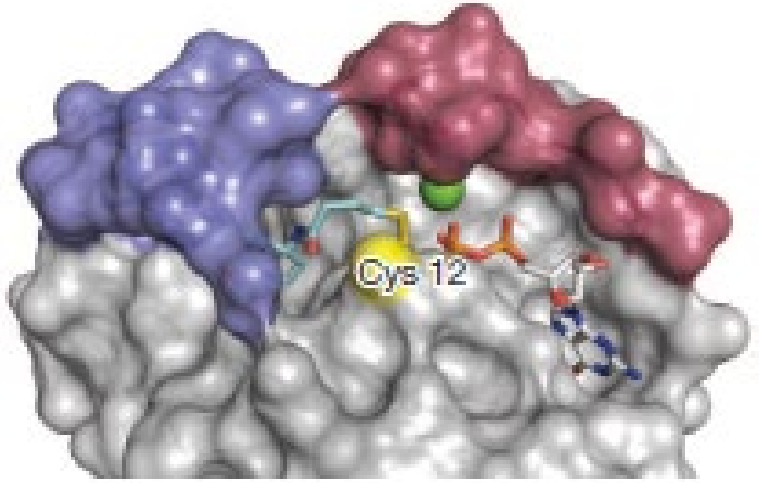
Downstream Effector Inhibitors

Raf / MEK and PI3K / AKT / mTOR

- Inhibition of WT signaling resulting in low therapeutic index
- Incomplete inhibition of signaling downstream of KRAS mut

K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions

Jonathan M. Ostrem,[1,*] Ulf Peters,[1,*] Martin L. Sos,[1] James A. Wells,[2] and Kevan M. Shokat[1]



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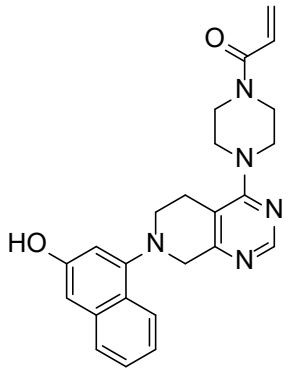
Covalent Inhibition of KRAS G12C

- Binding in the switch II pocket of GDP KRAS
- Covalent bond to cysteine 12
- Locked in the inactive conformation

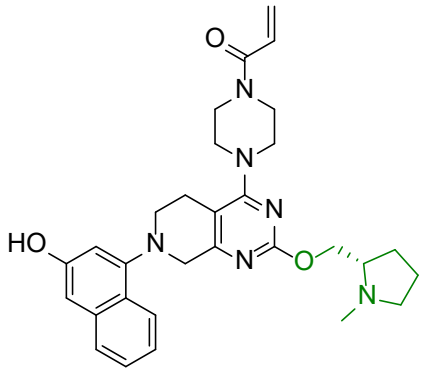
KRAS G12C Background—Reminders

- KRAS G12C mutations prevalent in (MSKCC):
  - Lung adenocarcinoma: 14%
  - CRC: 4%
  - PDAC: 2%
  - Other: gastric, uterine/endometroid, CUP. Etc
- KRAS G12C is a transversion mutation—common in smokers
- KRAS G12 mutations impair intrinsic GTPase activity and GTP hydrolysis
- Of KRAS mutations at codon 12, G12C exhibits lower intrinsic GTPase impairment and higher sensitivity to signals that modify extrinsic GTP hydrolysis

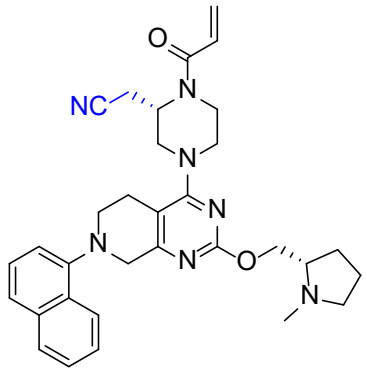
Drug Discovery Progression Toward MRTX849



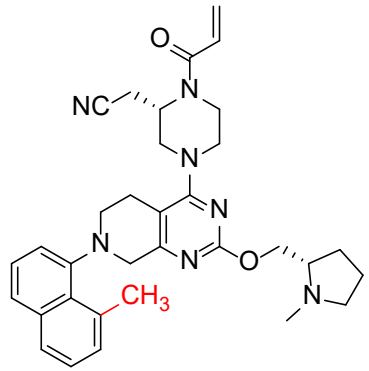
Compound 1
pERK IC_{50} = 7.6 μM[1]



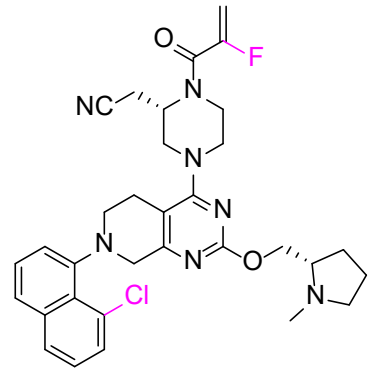
Compound 2
pERK IC_{50} = 70 nM[1]



Compound 3
pERK IC_{50} = 5 nM[1]



MRTX1257
pERK IC_{50} = 900 pM[1]
pERK IC_{50} = 6 nM[2]



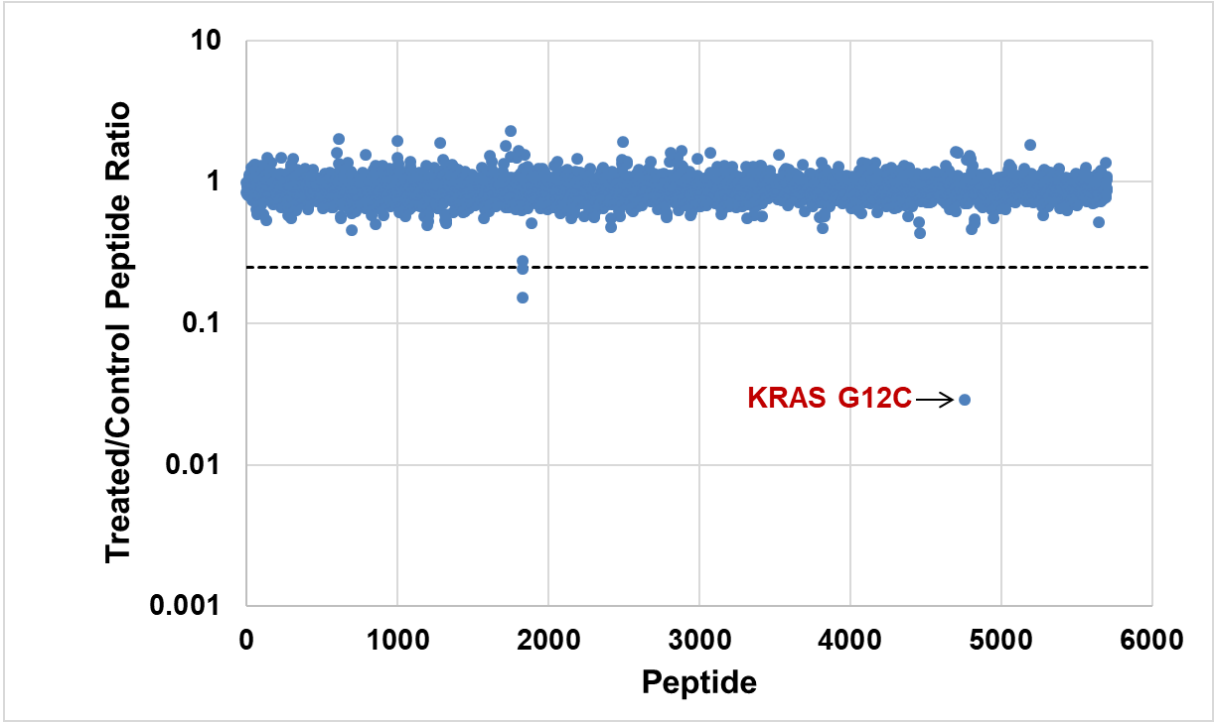
MRTX849
pERK IC_{50} = 14 nM[1]
pERK IC_{50} = 5 nM[2]

- The addition of the **C2 substituent** significantly improved solubility and cellular potency and demonstrated more rapid modification of the protein compared with compound **1**
- The **cyanomethyl substituent** on the piperazine further improved potency and allowed for the **elimination of the naphthyl 3-hydroxyl group** improving ADME properties
- **The 8-positon of the naphthyl group** to filled a hydrophobic pocket and increased potency an additional 5-fold
- **Warhead modification** and final optimization for reactivity and bioavailability provided MRTX849

[1]3 hour time point in H358 cells; [2]24 hour time point in MIA PaCa cells

MRTX849 Identified as a Potent, Selective, Orally Bioavailable Inhibitor of KRAS G12C

MW / clogP / tPSA	604/5.8/87
K_{inact}/K_I	35 +/-0.3$mM^{-1}s^{-1}$
Cellular Potency (24h, MIA PaCa)	**5 nM**
5 min/3 μM Protein Modification	66%
Hepatocyte ER% (m/h)	61 / 50
Plasma Protein Binding % (m/h)	99.0 / 98.3
F% (m/h)	**63 / 50***

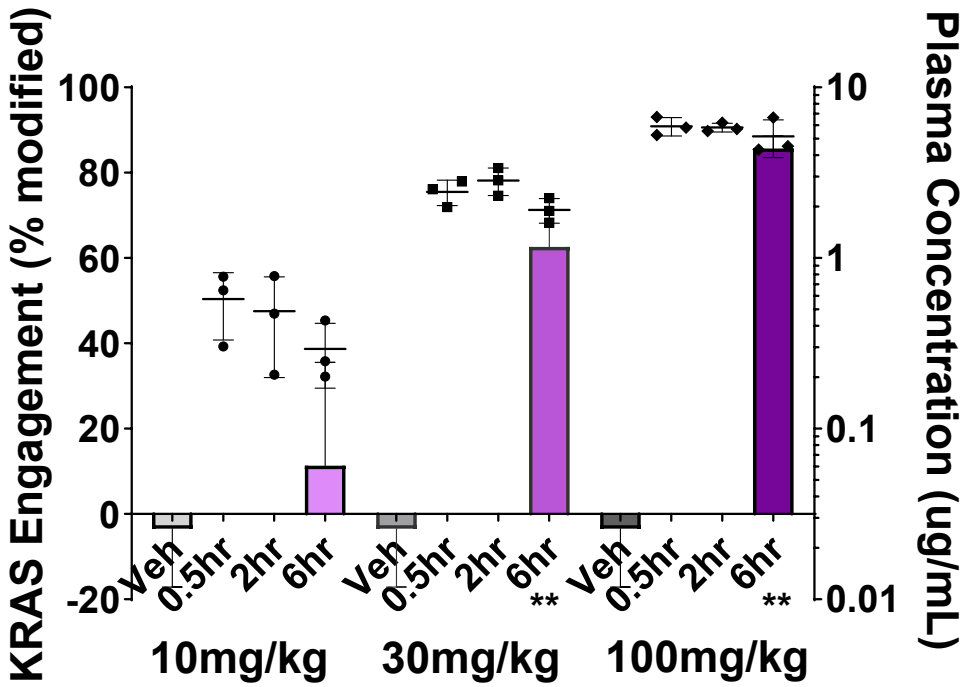


* Human projected F% from PBPK modeling

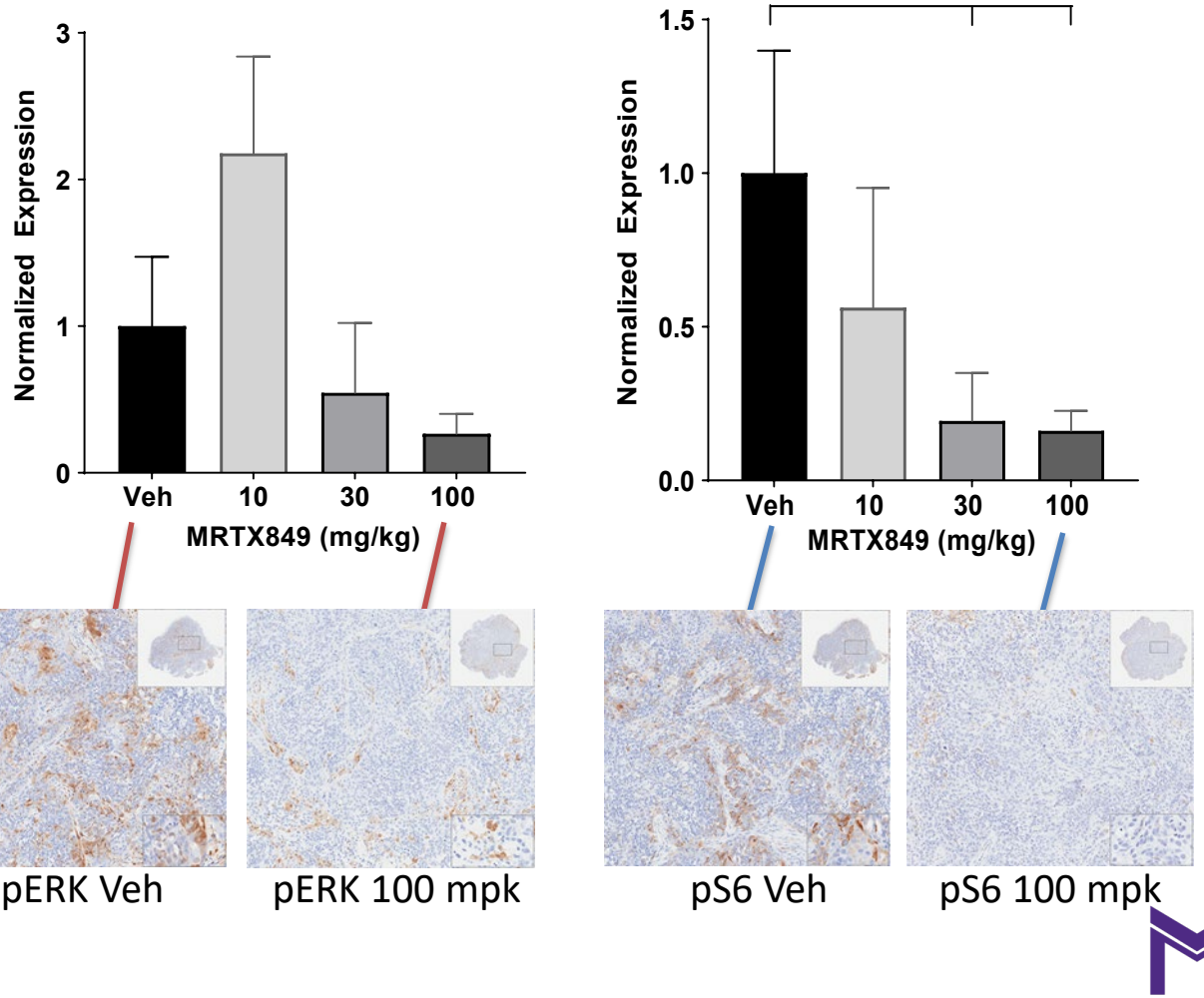
- MRTX849 only binds to **inactive, GDP-bound KRAS^{G12C}**
- Systematic adjustment of acrylamide reactivity and optimization of the naphthyl 8-substituent led to MRTX849, which shows **greater stability in whole blood and hepatocytes**
- Oral PK properties of MRTX849 improved with **50% oral bioavailability and >20 hour half-life** projected in humans. Extensive tissue distribution observed **with Vd_{ss} of > 10 L/kg** projected in humans.

MRTX849 Achieves Near Complete KRAS Modification and Inhibition In Tumors In Vivo

KRAS G12C Protein Modification after a single dose



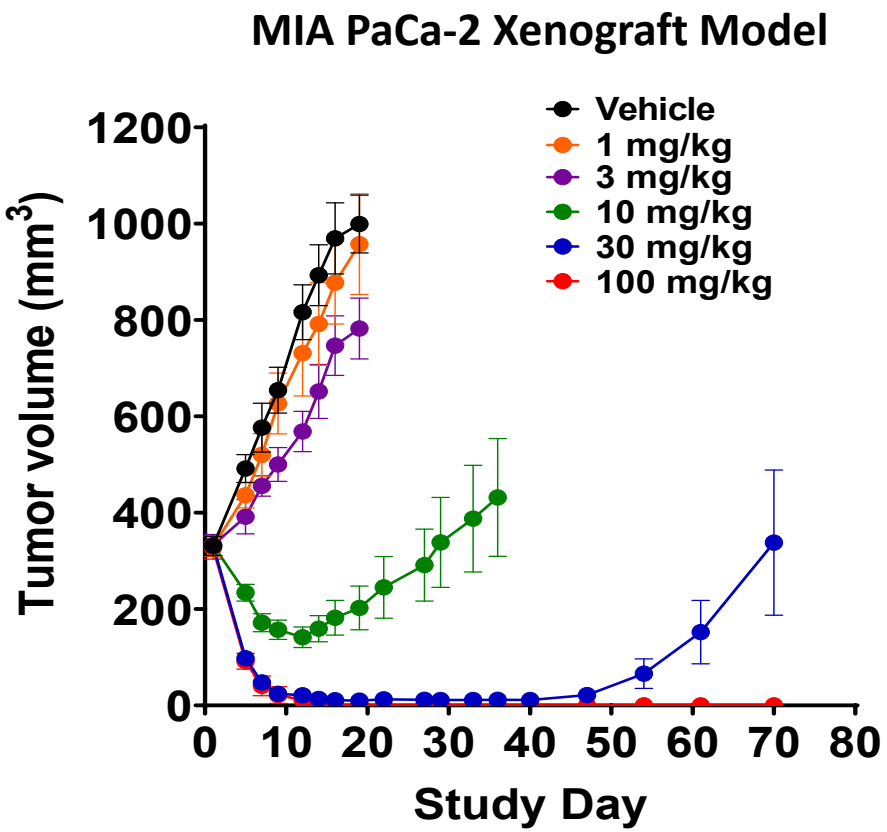
Normalized pERK and pS6 Inhibition
6 h post administration/single dose

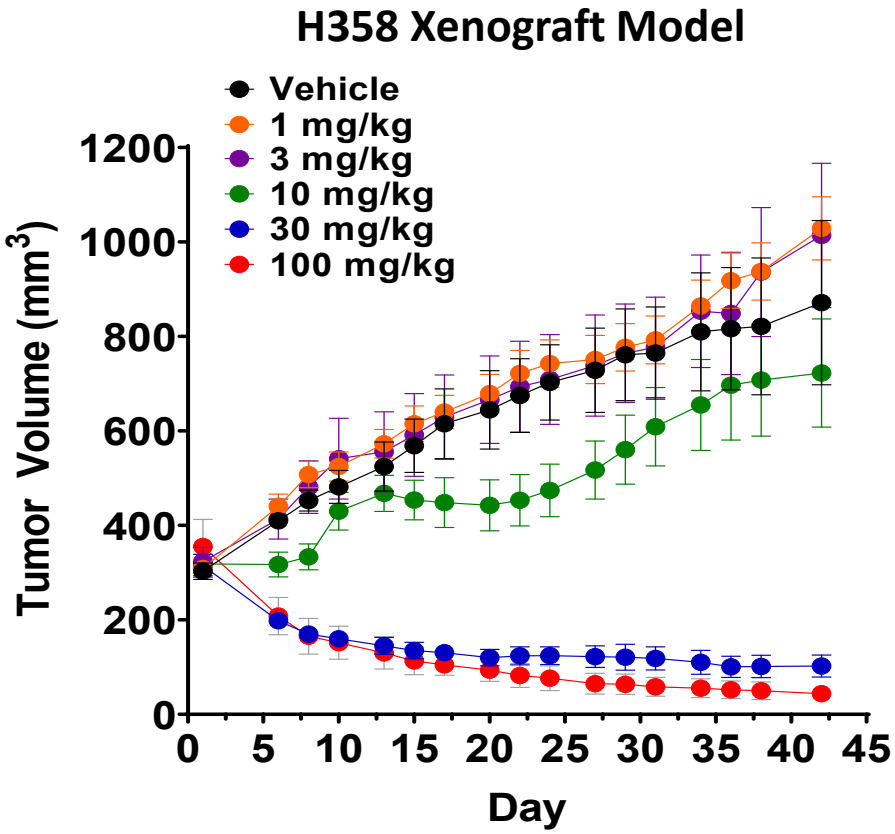


- Near complete inhibition of KRAS observed in tumor cells between 30 & 100 mg/kg—based on IHC
- No additional activity at higher doses
- Unmodifiable pool of KRAS G12C and stromal cell signaling impact magnitude of PD effect

MRTX849 Dose-dependent Anti-Tumor Efficacy

Maximally Effective Dose Confirmed Between 30-100 mg/kg





- The maximally effective dose of MRTX849 was identified as 100 mg/kg QD
- Doses of 200 mg/kg or greater were well-tolerated and did not improve antitumor activity
- Near complete target modification/inhibition correlates with maximal antitumor activity

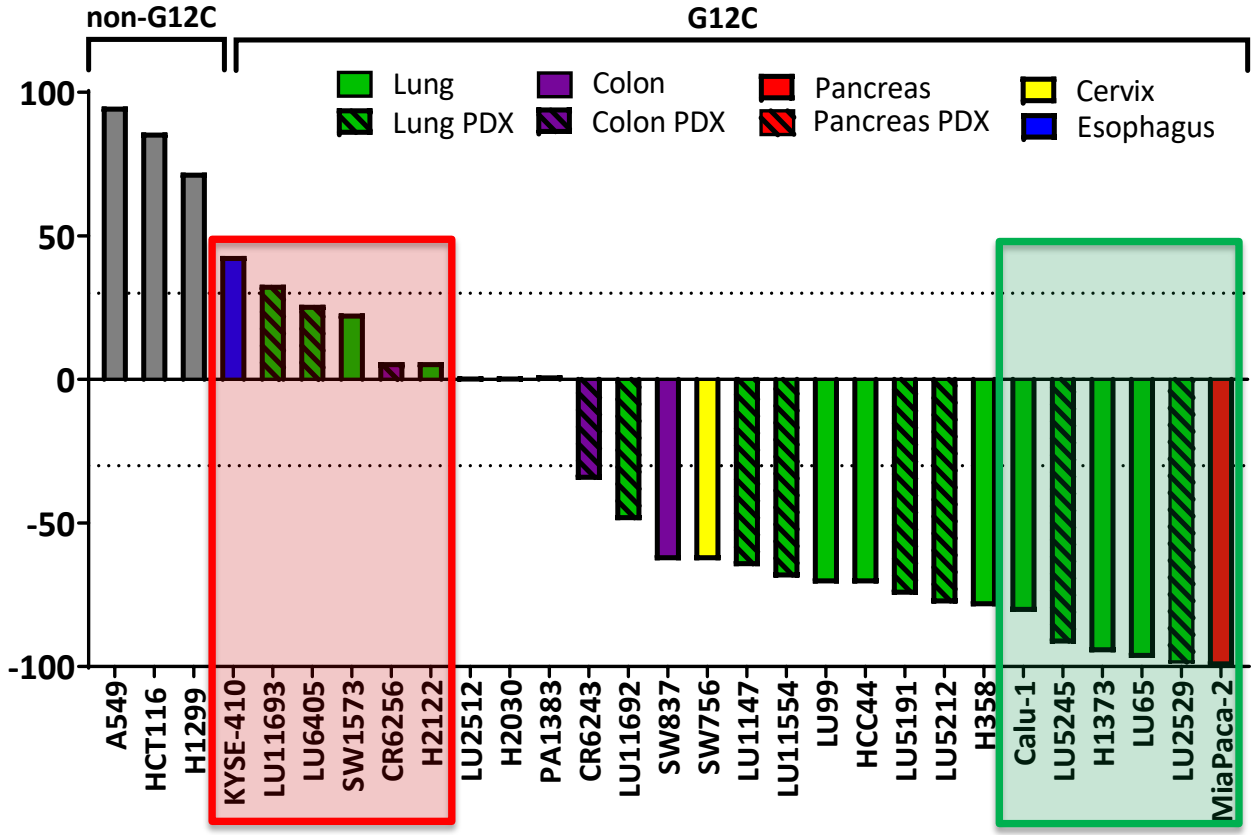
Derivation of Target Plasma Levels for MRTX849 Clinical Trials

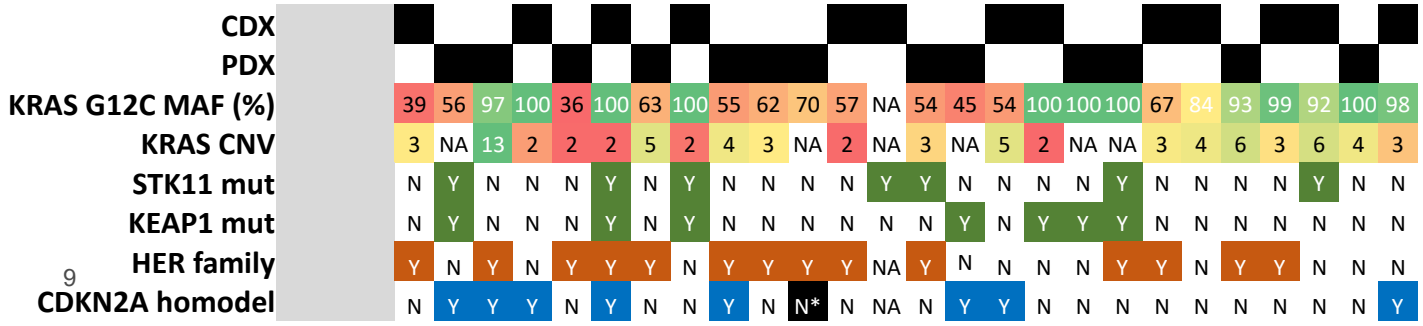
Model	Dose (mg/kg)	AUC_{0-24} (ug*h/mL)	FF adj AUC_{0-24} (ug*h/mL)	% Regression (day)	Projected Efficacious Total/FF adj AUC (human, ug*h/mL)	Projected Efficacious Total/FF adj C_{ave} (human, ng/ml)
MIA PaCa-2	10	7	0.07	-52% (13)		
MIA PaCa-2	30	24	0.24	-96% (13)	14.3	600
HCC-44	100	63	0.63	-61% (13)	37.1	1450

- AUC and C_{ave} most closely correlated with antitumor activity based on schedule dependence and infusion studies
- AUC_{0-24} and C_{ave} at 30 & 100 mg/kg, which demonstrated maximum antitumor activity in sensitive & partially sensitive models; respectively, were used for human efficacious exposure projections
- Free-fraction adjusted target $AUCs_{0-24}$ were calculated as **14.3 ug*h/mL** and **37.1 ug*h/mL**
- PBPK Link modeling approaches (PK-Sim™ or GastroPlus 9.5™) were applied to project a human efficacious target dose and exposure dose and fit human data well

MRTX849 Anti-Tumor Efficacy Across Models

Studies Designed to Identify Response/Resistance Correlates



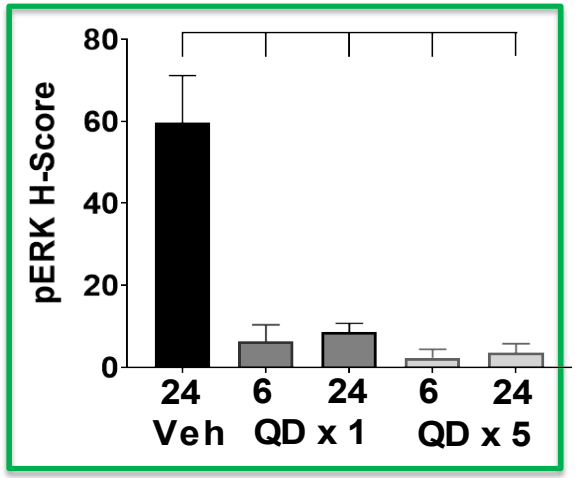


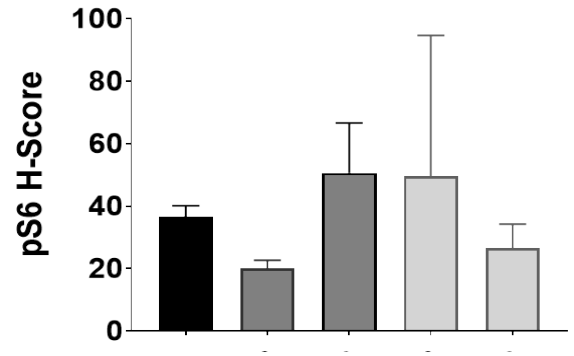
- A panel of in vivo tumor models was utilized for response correlations (obviate in vitro disconnect)
  - 100 mg/kg (max efficacious dose)
  - No significant activity in non-G12C models
- >30% tumor regression observed in ~65% of all models (17/26) suggesting potential for single agent development
- A 75% ORR In NSCLC, while CRC models were moderately responsive (BRAFi in CRC?)
- No significant correlation with co-occurring genetic alterations
- HER family score & cell cycle defects show trend
- Incomplete modification of KRAS in selected models potentially due to differences in extrinsic modulation of GTP hydrolysis

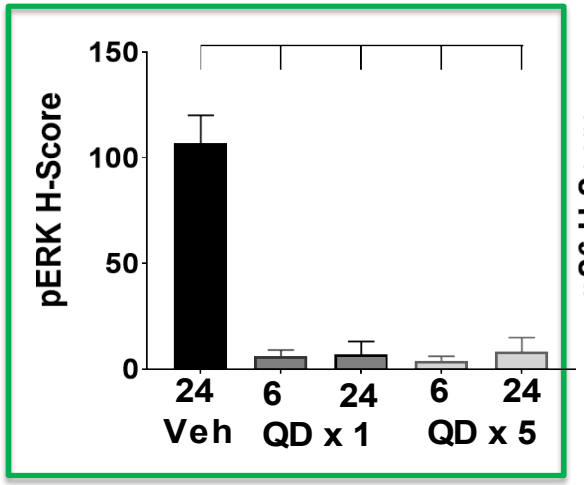
Mechanisms of Response and Resistance to MRTX849

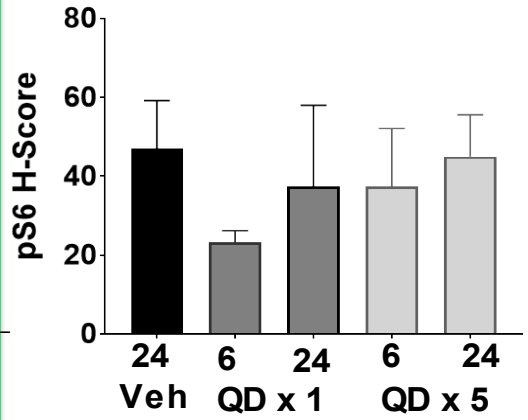
Durable Inhibition of ERK (but not S6) tracks with tumor response

MIA PaCa-2 ← **Complete Response** → **H1373**

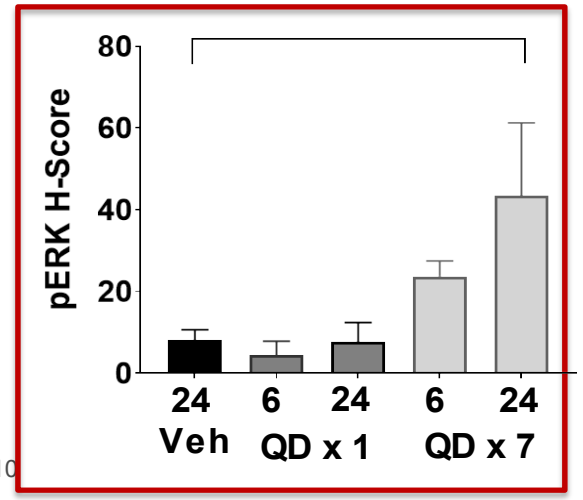


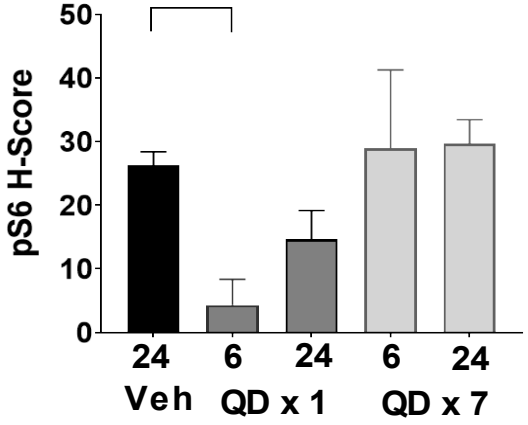


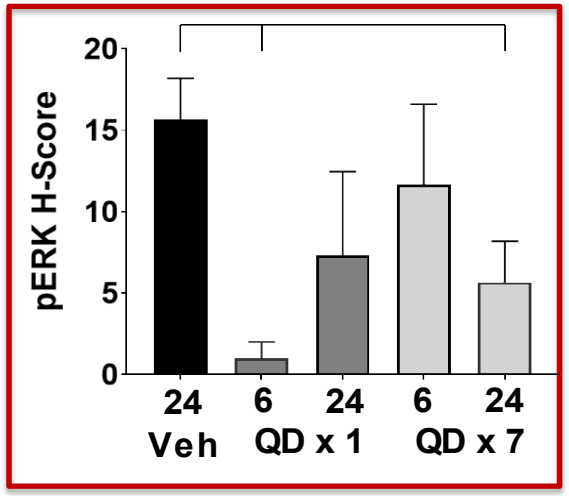


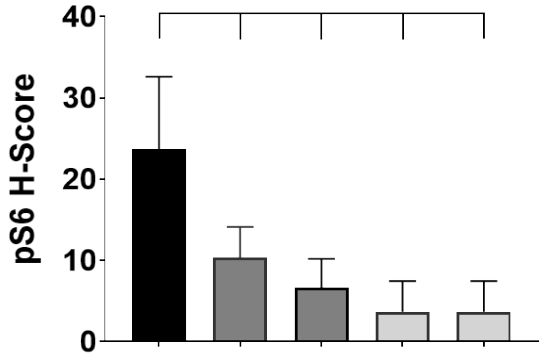


H358 ← **Partial response/Refractory** → **H2122**







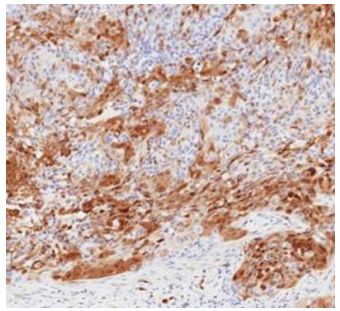


Mechanisms of Intrinsic Resistance to MRTX849

Feedback Signaling and Bypass Pathways---NCI-H358

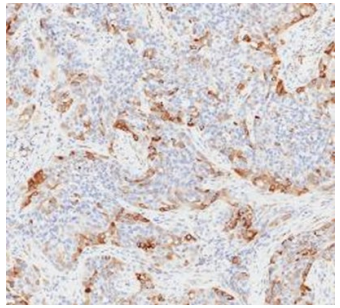
pERK

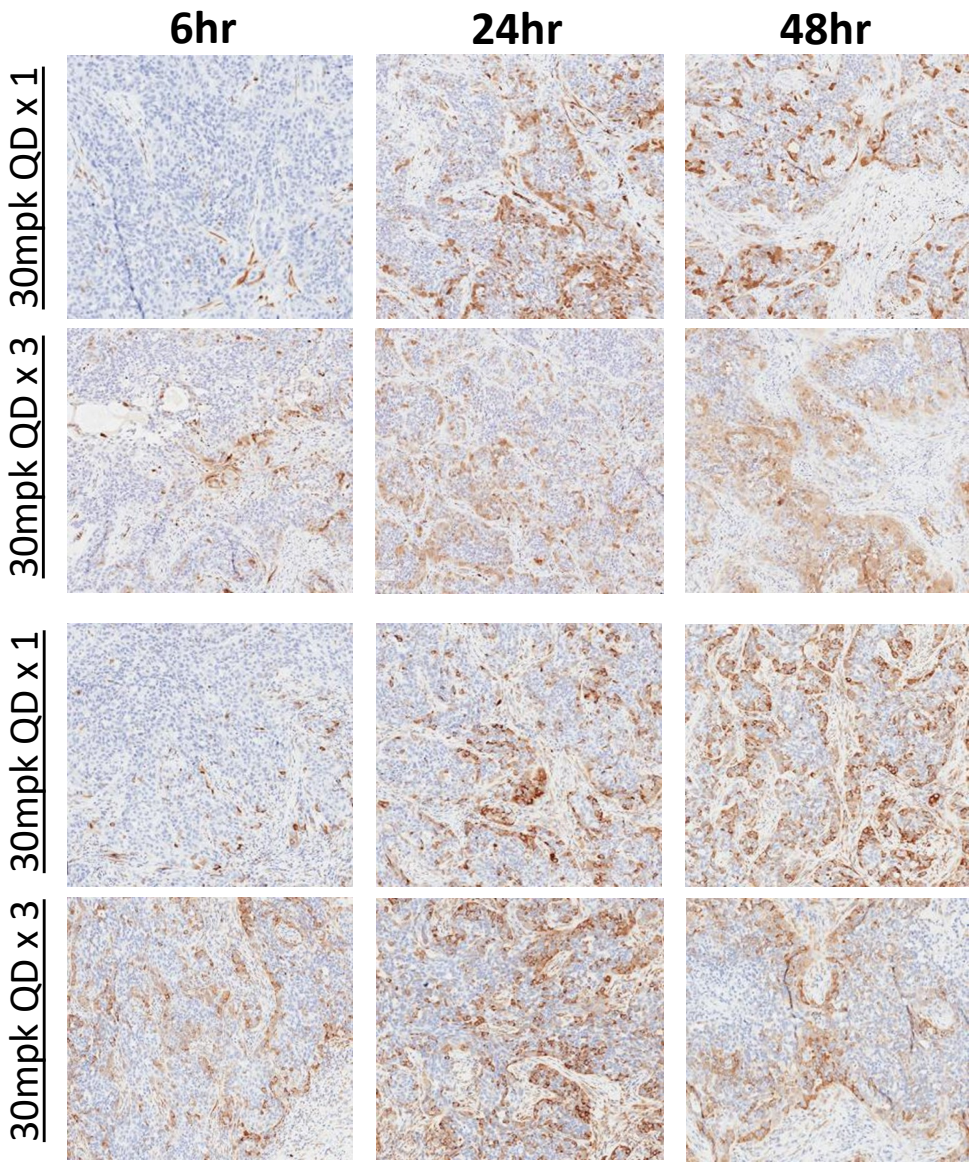
Vehicle



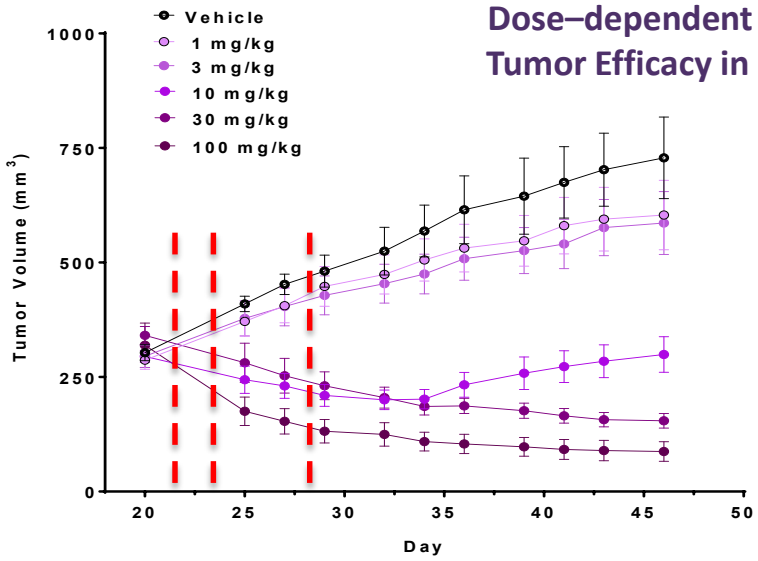
pS6

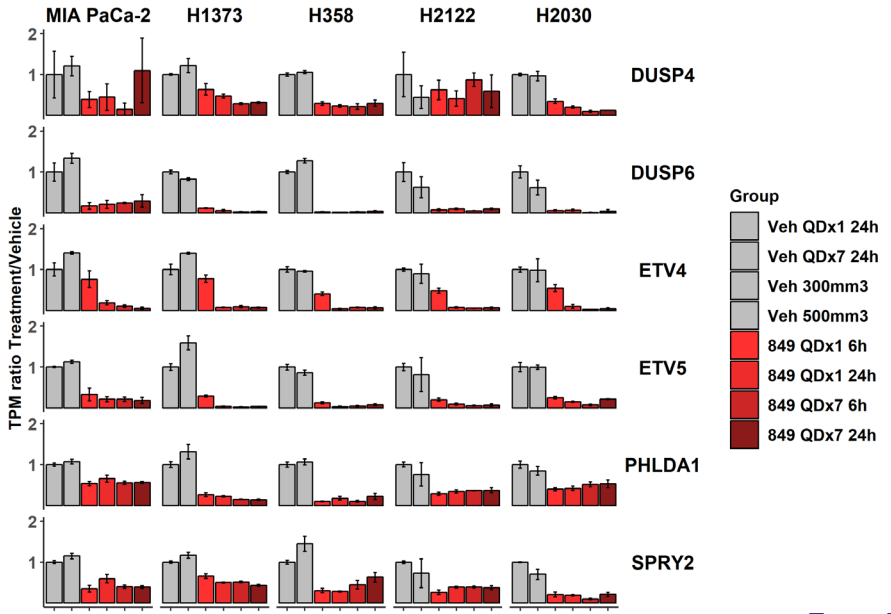
Vehicle





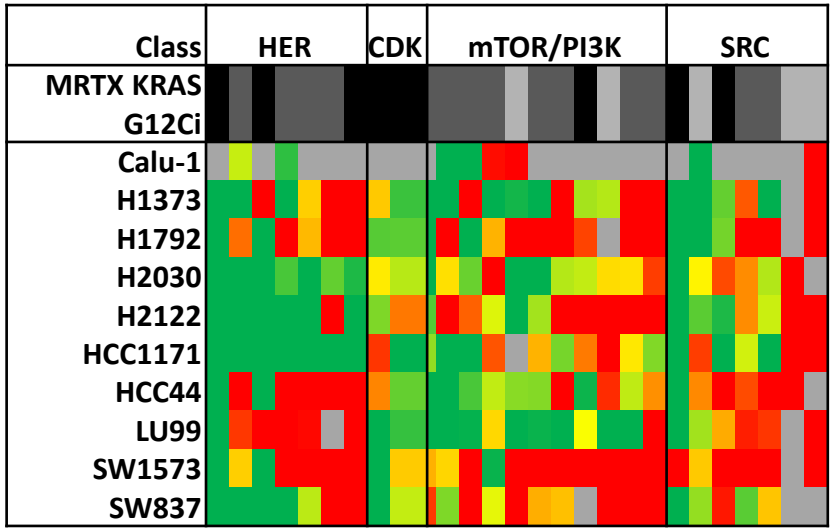
Dose–dependent Anti-Tumor Efficacy in H358



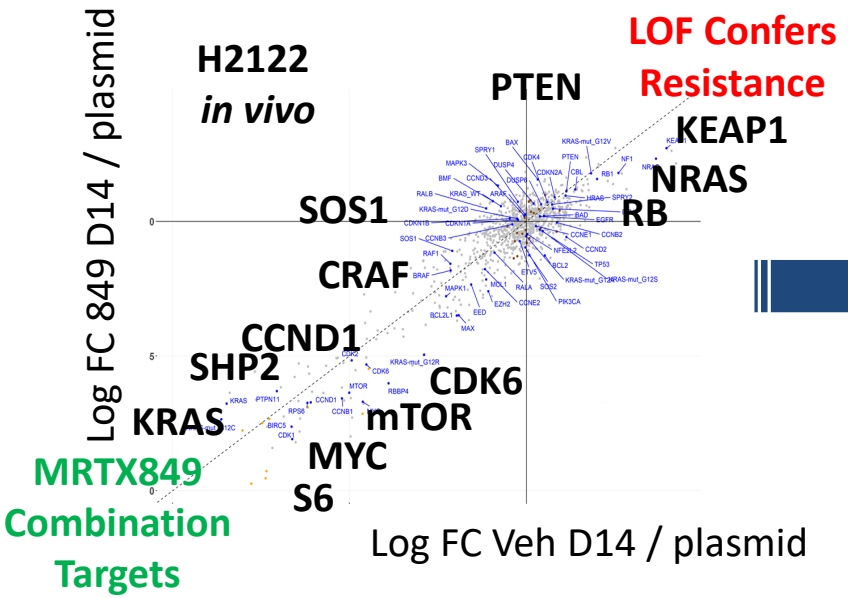


Pharmacogenomic Screens to Identify Combination Targets and Resistance Mechanisms

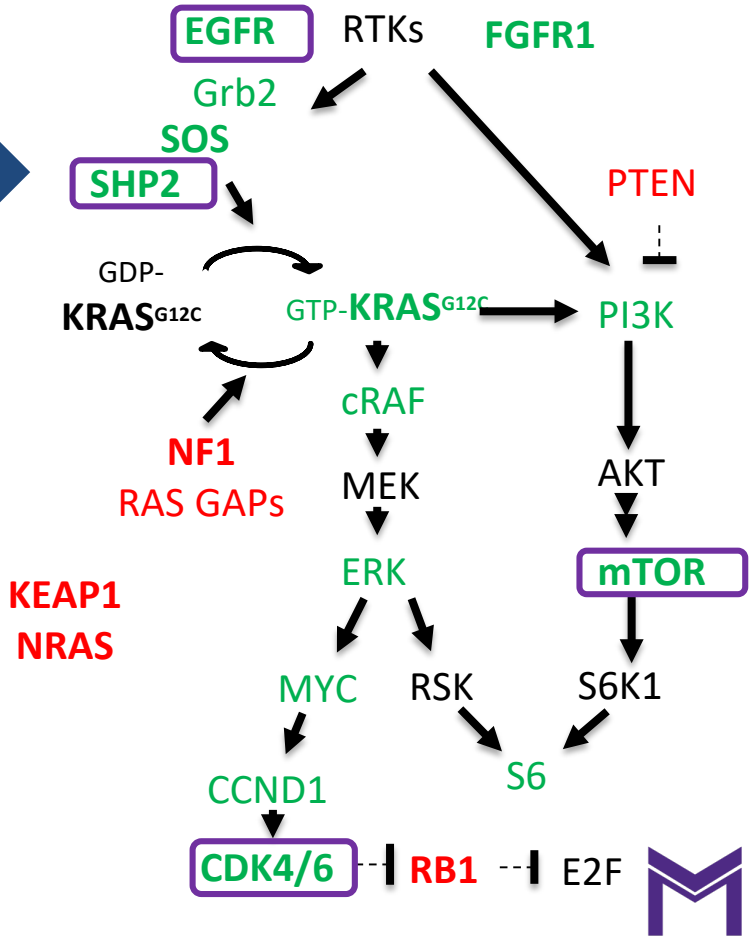
Small Mol Combo Screen



CRISPR Screens



MRTX849 Combination Targets and Resistance Gene Map



- Screened ~90 agents in combination with MRTX849 across 8 lung cell lines *in vitro* that were partially MRTX849-resistant *in vivo*.
- MRTX849-anchored CRISPR screens: ~1,000 genes, 4 $KRAS^{G12C}$ cell lines, *in vitro/in vivo*
- Top combination targets: EGFR family, FGFR1, SOS1, SHP2, mTOR, CDK4/6.
- Top resistance genes: CDKN2A, KEAP1, RB1, PTEN, NRAS.

Conclusions

- MRTX849 is a novel small molecule $KRAS^{G12C}$ inhibitor in clinical trials
- Maximal and durable inhibition of KRAS liked to defined PK parameters maximizes response
- Tumors harboring KRAS G12C are broadly dependent on KRAS for growth and survival…….
- ……However, complex signaling circuitry in some KRAS-dependent tumors can result in partial bypass of dependence
- Mechanisms are heterogeneous and relate to feedback or bypass signaling, enhanced nucleotide cycling, and KRAS-independent cell cycle transition
- Rational combination approaches provide a practical solution to address heterogeneity
- Target plasma derivation and corelative science will aid in rational development of MRTX849

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Collaborators

Channing Der (UNC)
Adrienne Cox (UNC)
Piro Lito (MSK)
Pasi Janne (DFCI)
Chip Petricoin (GMU)