AACR American Association for Cancer Research

VIRTUAL ANNUAL MEETING II

JUNE 22-24, 2020

Drug-Anchored *in vitro* and *in vivo* CRISPR Screens to Identify Targetable Vulnerabilities and Modifiers of Response to MRTX849 in $KRAS^{G12C}$-Mutant Models

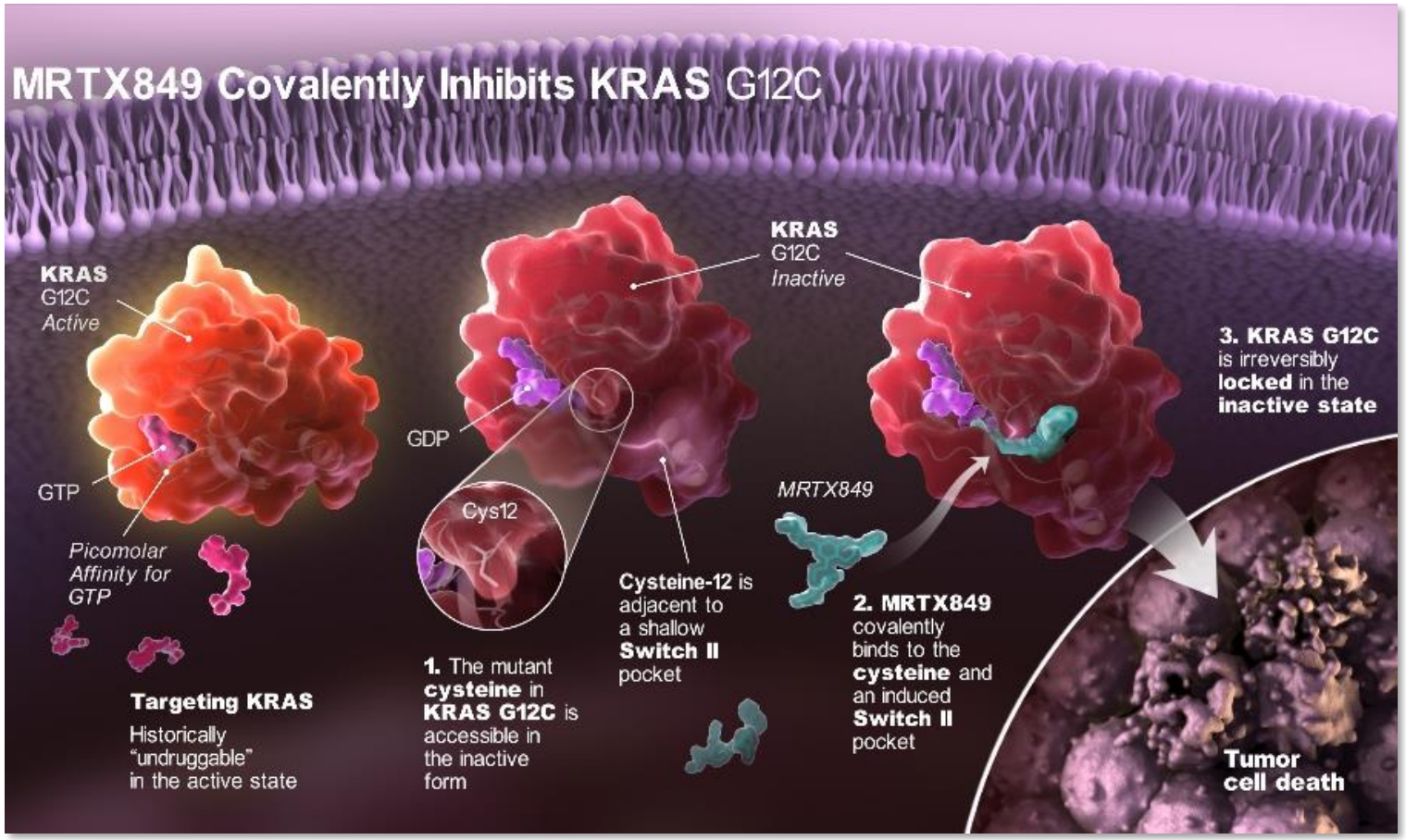
Lars Engstrom – Principal Scientist

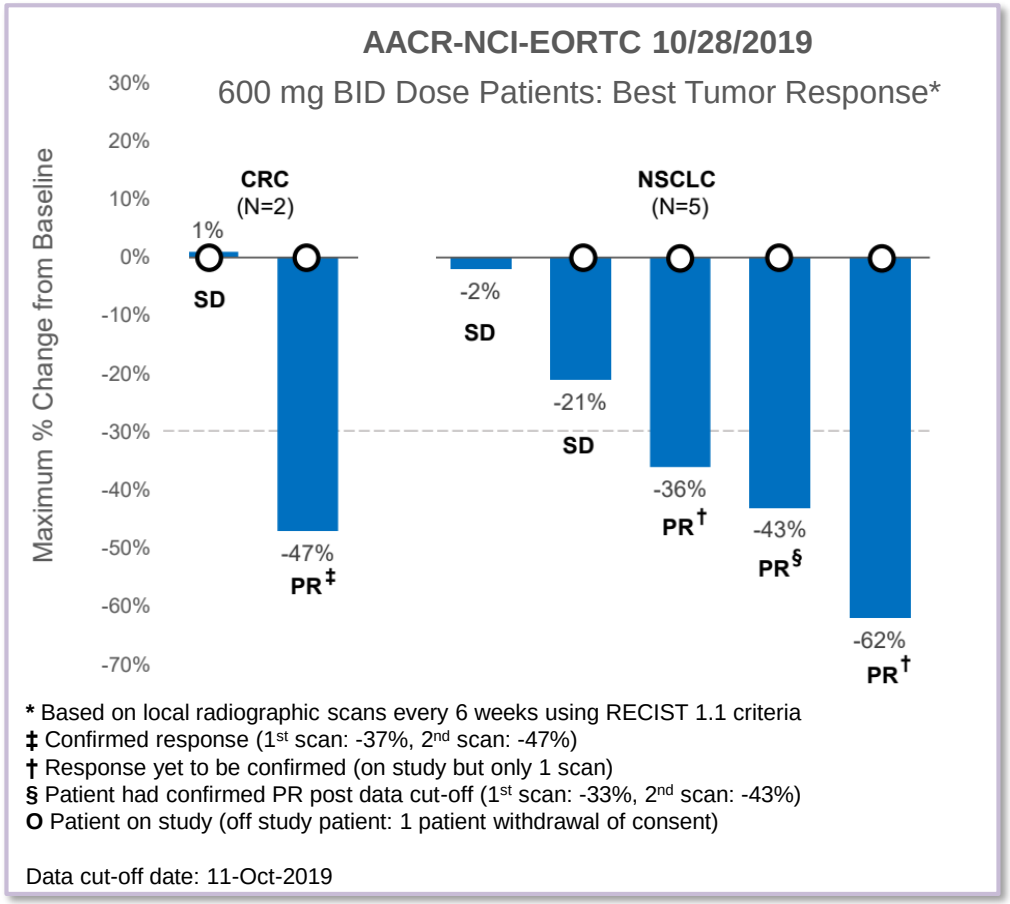
Mirati Therapeutics – San Diego, CA

Disclosures

- Lars Engstrom is an employee and stock holder of Mirati Therapeutics

MRTX849 is a Clinically Active, Irreversible, KRAS^{G12C} Inhibitor

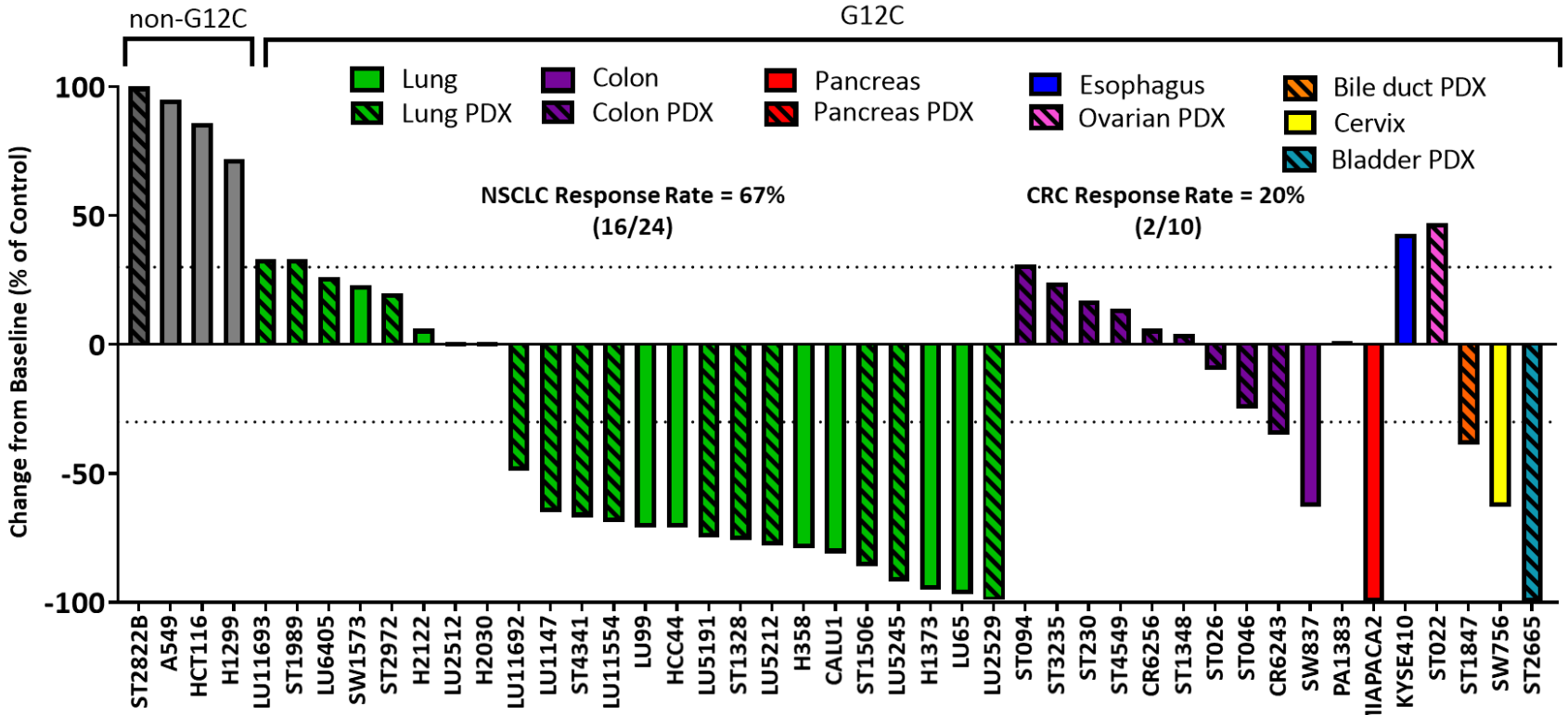


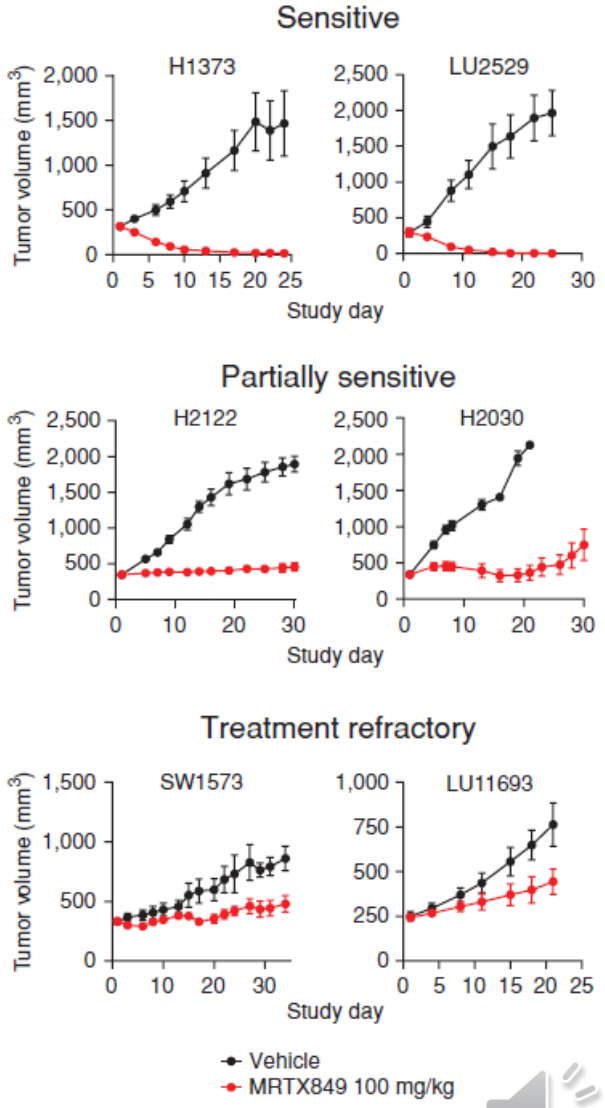


***** Based on local radiographic scans every 6 weeks using RECIST 1.1 criteria
‡ Confirmed response (1st scan: -37%, 2nd scan: -47%)
† Response yet to be confirmed (on study but only 1 scan)
§ Patient had confirmed PR post data cut-off (1st scan: -33%, 2nd scan: -43%)
O Patient on study (off study patient: 1 patient withdrawal of consent)

Data cut-off date: 11-Oct-2019

MRTX849 Demonstrates Broad Spectrum Tumor Regression in KRAS^{G12C} Nonclinical Tumor Growth Models





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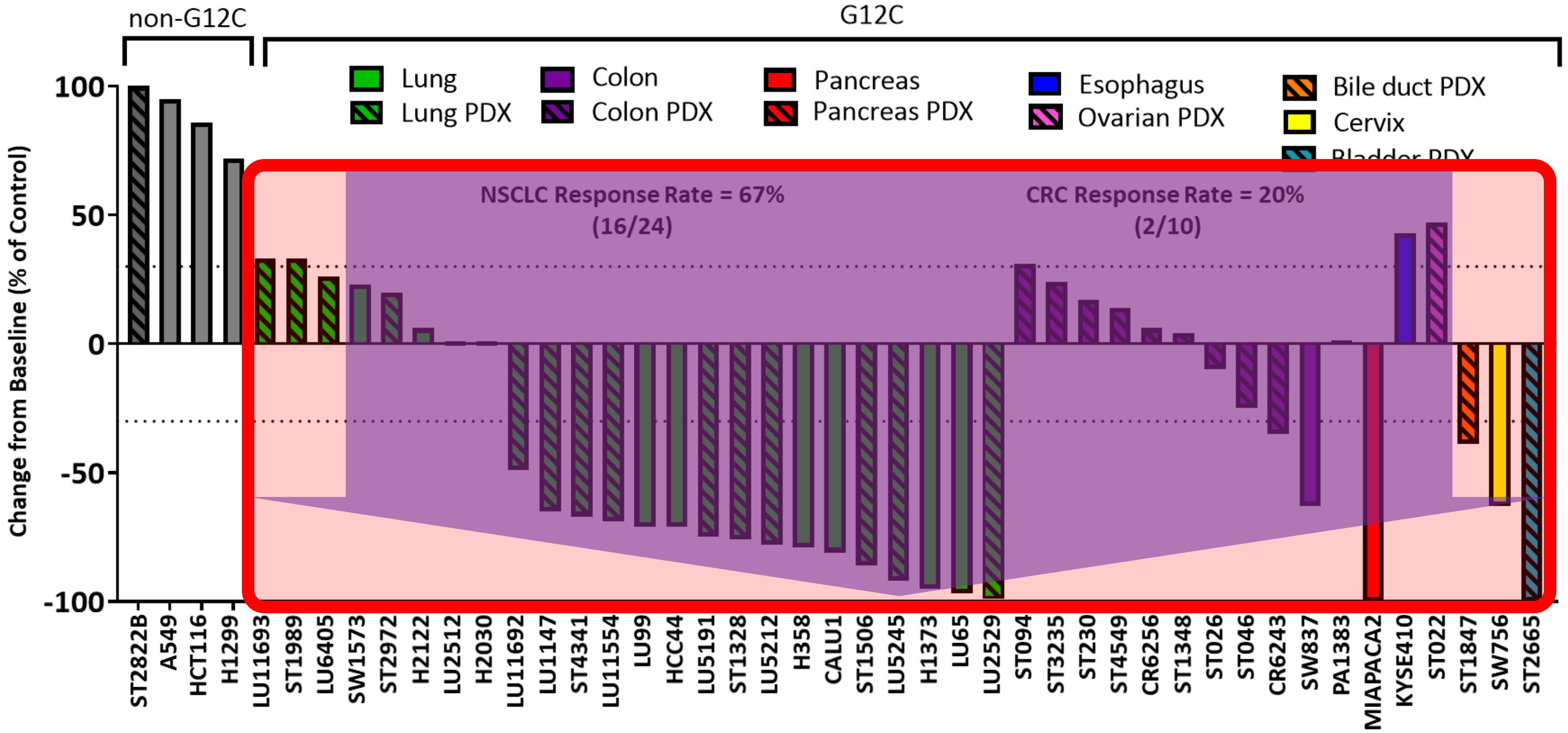
4 CDX and PDX models were treated with MRTX849 @ 100mg/kg PO, QD in all models shown. % change from baseline control was calculated on ~ day 22 post initiation of dosing.

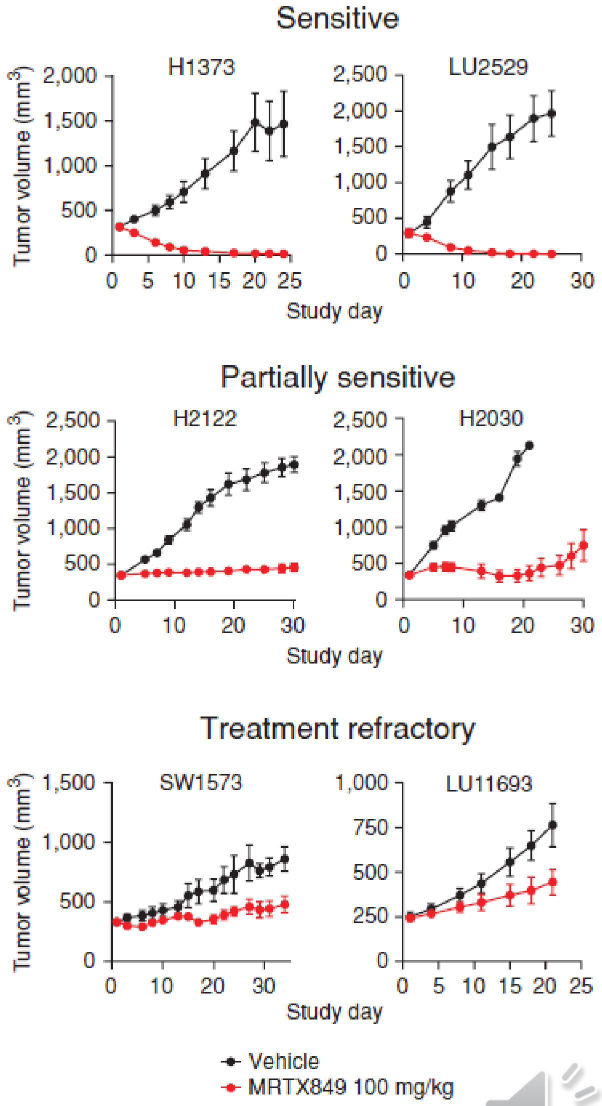
MRTX849 Demonstrates Broad Spectrum Tumor Regression in KRAS^{G12C} Nonclinical Tumor Growth Models



	LU11693	ST1989	LU6405	SW1573	ST2972	H2122	LU2512	H2030	LU11692	LU1147	ST4341	LU11554	LU99	HCC44
KRAS G12C MAF (%)	56	NA	97	100	NA	100	63	100	70	54	NA	45	54	100
KRAS CNV	NA	NA	13	2	NA	2	5	2	NA	3	NA	NA	5	2
STK11 mut	Y	NA	N	N	NA	Y	N	Y	N	Y	NA	N	N	N
KEAP1 mut	Y	NA	N	N	NA	Y	N	Y	N	N	NA	Y	N	Y
HER family	N	NA	Y	N	NA	Y	Y	N	Y	Y	NA	N	N	N
CDKN2A homodel	Y	NA	Y	Y	NA	Y	N	N	N*	N	NA	Y	Y	N

	LU5191	ST1328	LU5212	H358	CALU1	ST1506	LU5245	H1373	LU65	LU2529	ST094	ST3235	ST230	ST4549
KRAS G12C MAF (%)	100	NA	100	67	84	NA	93	99	92	100	NA	NA	NA	NA
KRAS CNV	NA	NA	NA	3	4	NA	6	3	6	4	NA	NA	NA	NA
STK11 mut	N	NA	Y	N	N	NA	N	N	Y	N	NA	NA	NA	NA
KEAP1 mut	Y	NA	Y	N	N	NA	N	N	N	N	NA	NA	NA	NA
HER family	N	NA	Y	Y	N	NA	Y	Y	N	N	NA	NA	NA	NA
CDKN2A homodel	N	NA	N	N	N	NA	N	N	N	N	NA	NA	NA	NA

	CR6256	ST1348	ST026	ST046	CR6243	SW837	PA1383	MIAPACA2	KYSE410	ST022	ST1847	SW756	ST2665
KRAS G12C MAF (%)	36	NA	NA	NA	62	57	55	98	39	NA	NA	NA	NA
KRAS CNV	2	NA	NA	NA	3	2	4	3	3	NA	NA	NA	NA
STK11 mut	N	NA	NA	NA	N	N	N	N	N	NA	NA	Y	NA
KEAP1 mut	N	NA	NA	NA	N	N	N	N	N	NA	NA	N	NA
HER family	Y	NA	NA	NA	Y	Y	Y	N	Y	NA	NA	NA	NA
CDKN2A homodel	N	NA	NA	NA	N	N	Y	Y	N	NA	NA	NA	NA



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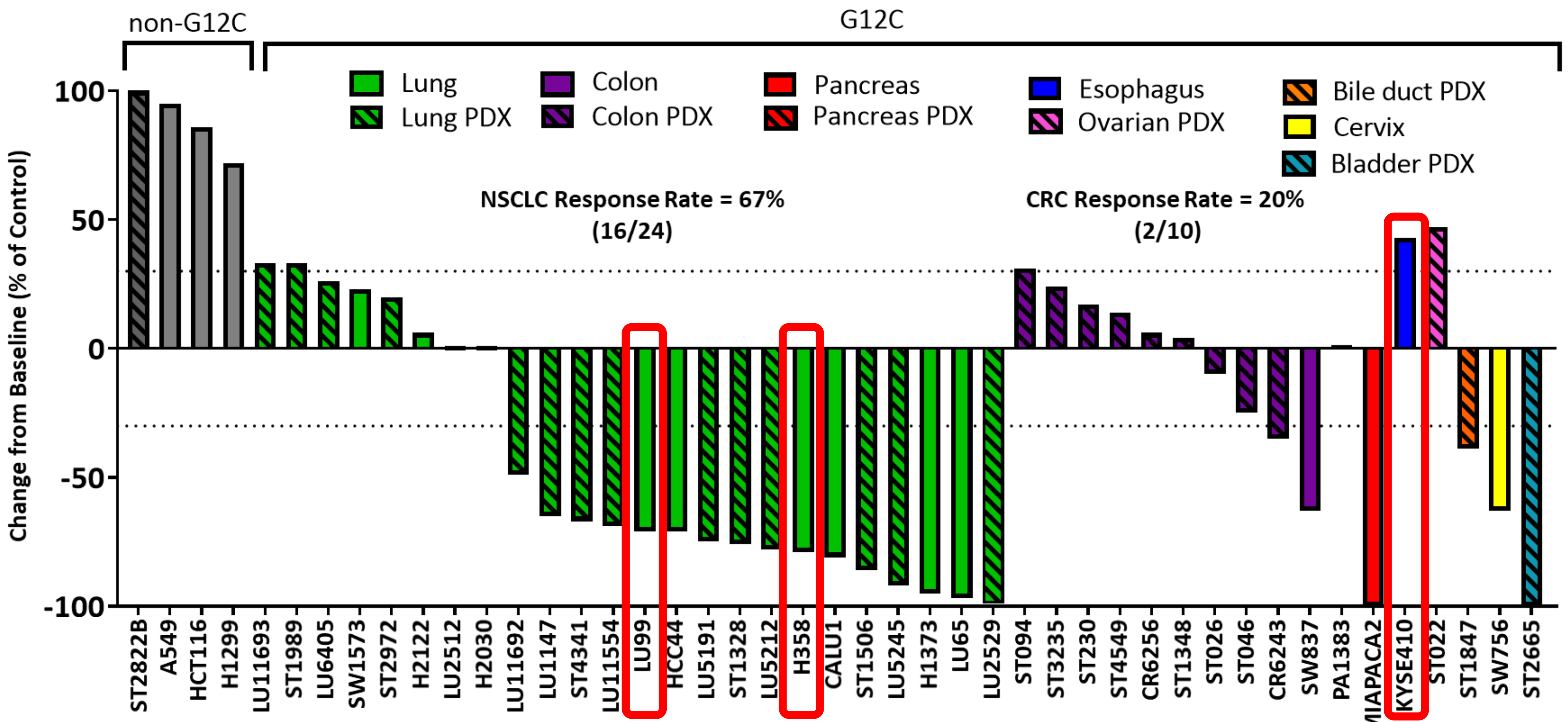
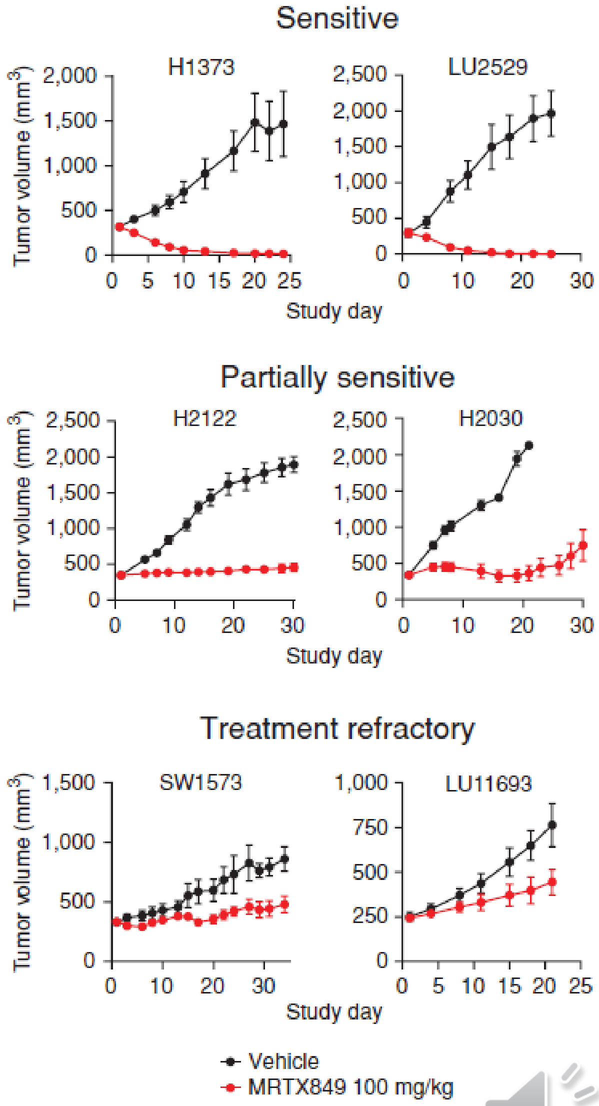
CDX and PDX models were treated with MRTX849 @ 100mg/kg PO, QD in all models shown. % change from baseline control was calculated on ~ day 22 post initiation of dosing.

MRTX849 Demonstrates Broad Spectrum Tumor Regression in KRAS^{G12C} Nonclinical Tumor Growth Models



	LU11693	ST1989	LU6405	SW1573	ST2972	H2122	LU2512	H2030	LU11692	LU1147	ST4341	LU11554	LU99	HCC44	LU5191	ST1328	LU5212	H358	CALU1	ST1506	LU5245	H1373	LU65	LU2529	ST094	ST3235	ST230	ST4549	CR6256	ST1348	ST026	ST046	CR6243	SW837	PA1383	MIAPACA2	KYSE410	ST022	ST1847	SW756	ST2665
KRAS G12C MAF (%)	56	NA	97	100	NA	100	63	100	70	54	NA	45	54	100	100	NA	100	67	84	NA	93	99	92	100	NA	NA	NA	NA	36	NA	NA	NA	62	57	55	98	39	NA	NA	NA	NA
KRAS CNV	NA	NA	13	2	NA	2	5	2	NA	3	NA	NA	5	2	NA	NA	NA	3	4	NA	6	3	6	4	NA	NA	NA	NA	2	NA	NA	NA	3	2	4	3	3	NA	NA	NA	NA
STK11 mut	Y	NA	N	N	NA	Y	N	Y	N	Y	NA	N	N	N	N	NA	Y	N	N	NA	N	N	Y	N	NA	NA	NA	NA	N	NA	NA	NA	N	N	N	N	N	NA	NA	Y	NA
KEAP1 mut	Y	NA	N	N	NA	Y	N	Y	N	N	NA	Y	N	Y	Y	NA	Y	N	N	NA	N	N	N	N	NA	NA	NA	NA	N	NA	NA	NA	N	N	N	N	N	NA	NA	N	NA
HER family	N	NA	Y	N	NA	Y	Y	N	Y	Y	NA	N	N	N	N	NA	Y	Y	N	NA	Y	Y	N	N	NA	NA	NA	NA	Y	NA	NA	NA	Y	Y	Y	N	Y	NA	NA	NA	NA
CDKN2A homodel	Y	NA	Y	Y	NA	Y	N	N	N*	N	NA	Y	Y	N	N	NA	N	N	N	NA	N	N	N	N	NA	NA	NA	NA	N	NA	NA	NA	N	N	Y	Y	N	NA	NA	NA	NA



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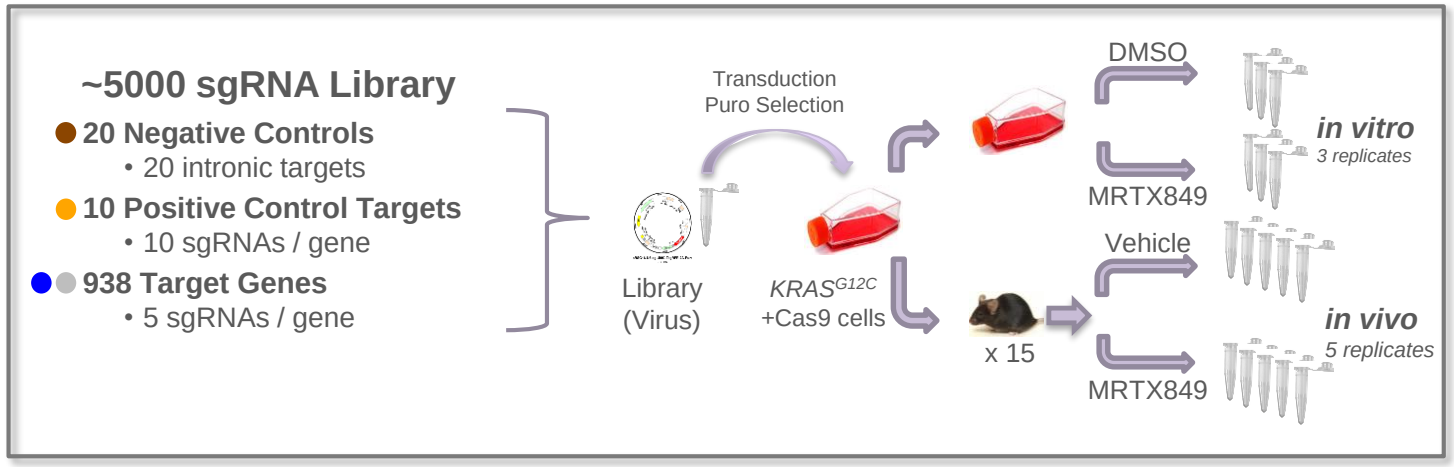
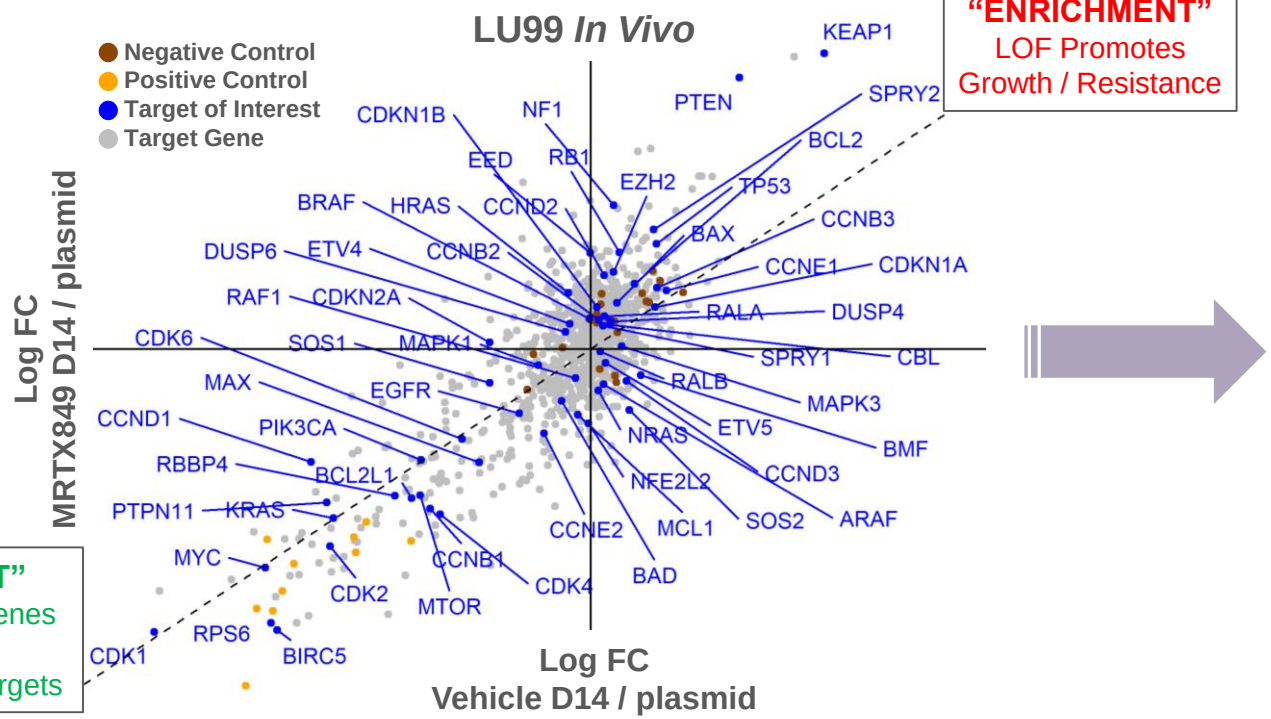
CDX and PDX models were treated with MRTX849 @ 100mg/kg PO, QD in all models shown. % change from baseline control was calculated on ~ day 22 post initiation of dosing.

Drug Anchored CRISPR Screen Reveals Drug MOA, Resistance Biomarkers & Combo Targets



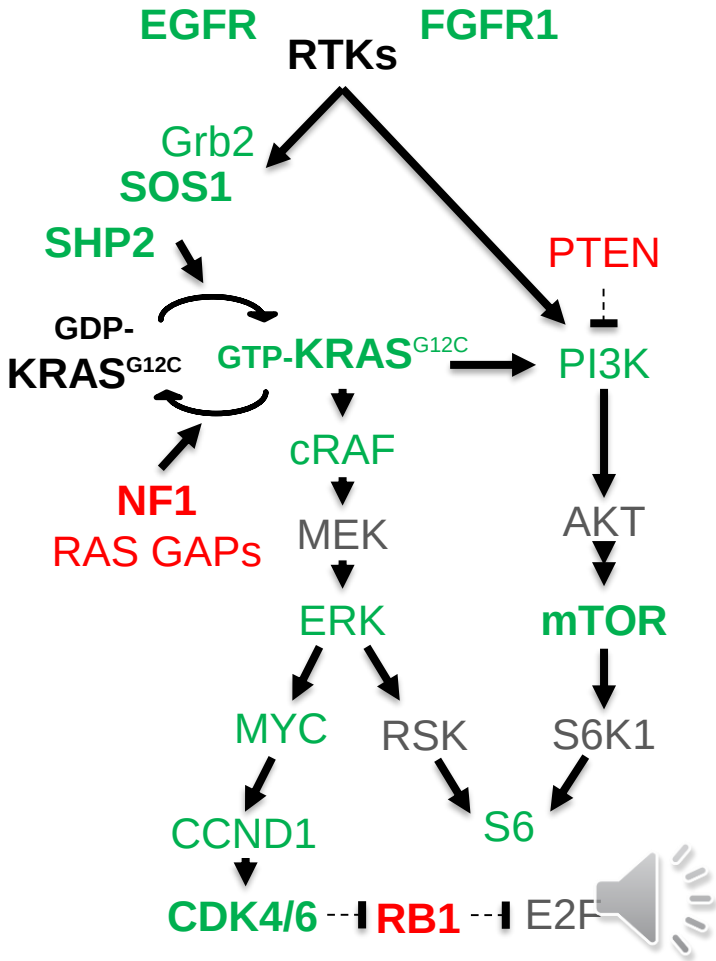


"ENRICHMENT"
LOF Promotes
Growth / Resistance

"DROP OUT"
Dependency Genes
MRTX849
Combination Targets

Combination Targets and Putative Resistance Biomarkers

TP53
KEAP1
PTPN12
PTPN14
TSC1/2



Functional Contribution of Top MRTX849 Regulated Pro-survival and Apoptosis Genes Elucidated by CRISPR Screen

Pro-Survival **Pro-Apoptosis**

CRISPR

Model		MRTX849	MYC	KRAS	BIRC5	BCL2L1	MCL1	CASP9	BCL2L11	BAX	CASP3	APAF1
LU99	In Vitro	(-)										
		+										
	In Vivo	(-)										
		+										
H358	In Vitro	(-)										
		+										
KYSE410	In Vitro	(-)										
		+										

RNAseq

Model	MRTX849	BIRC5	BCL2L1	MCL1	BAD	BMF	CASP7	CASP9	BBC3	BCL2L11	APAF1
MiaPaca2	QDx7 6hr										
H1373	QDx7 6hr										
H358	QDx7 6hr										
H2122	QDx7 6hr										
H2030	QDx7 6hr										

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log2 FC

Tumor Suppressors

Model		MRTX849	CBL	TSC2	RB1	TP53	TSC1	NF1	PTPN12	PTEN	KEAP1
LU99	In Vitro	(-)									
		+									
	In Vivo	(-)									
		+									
H358	In Vitro	(-)									
		+									
KYSE410	In Vitro	(-)									
		+									

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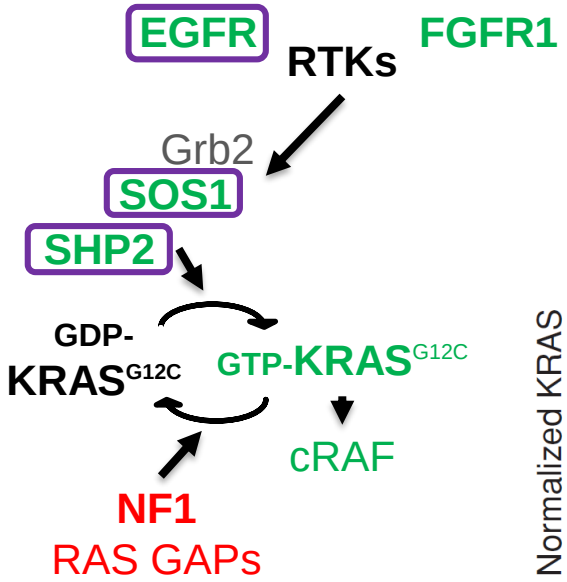
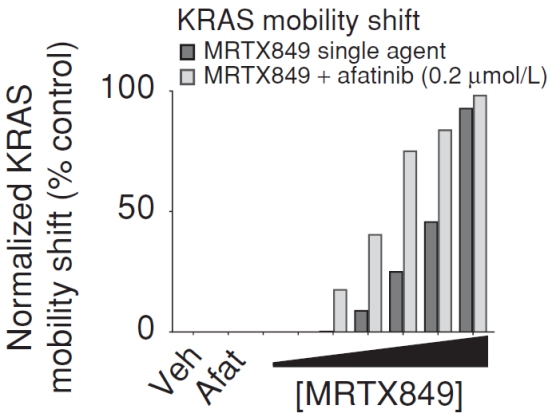
- MRTX849 treatment regulates expression of selected pro-survival and pro-apoptotic genes which correlates with tumor growth inhibition in multiple $KRAS^{G12C}$ mutant models.
- Functional role for many genes confirmed in CRISPR data
  - Pro-survival genes BIRC5/Survivin, BCL2L1, MCL1: Decreased by MRTX849 & Exhibit Dropout
  - Pro-apoptotic genes BCL2L11: Increased by MRTX849 & Exhibit Enrichment
  - Apoptotic regulators APAF1, CASP3/9 enriched in drug-treated CRISPR data, in particular
- Several tumor suppressors enriched suggesting potential for intrinsic resistance

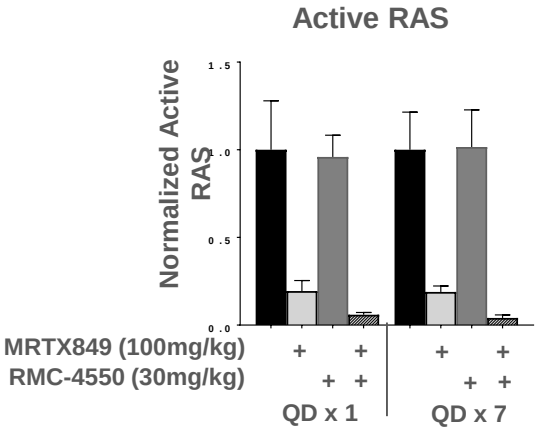
Increased KRAS^{G12C} Modification Via Upstream Combinations Improves Response



HERi -- H2122



SHP2i -- KYSE-410



Model		MRTX849	PTPN11	FGFR1	ERBB2	EGFR	FGFR3	SOS1	NF1
LU99	In Vitro	(-)							
		+							
	In Vivo	(-)							
		+							
H358	In Vitro	(-)							
		+							
KYSE410	In Vitro	(-)							
		+							

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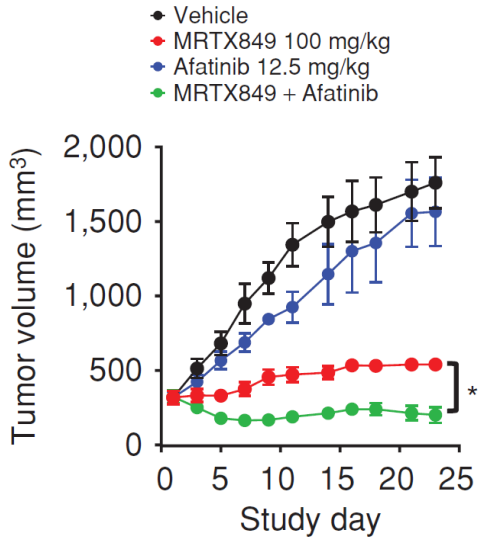
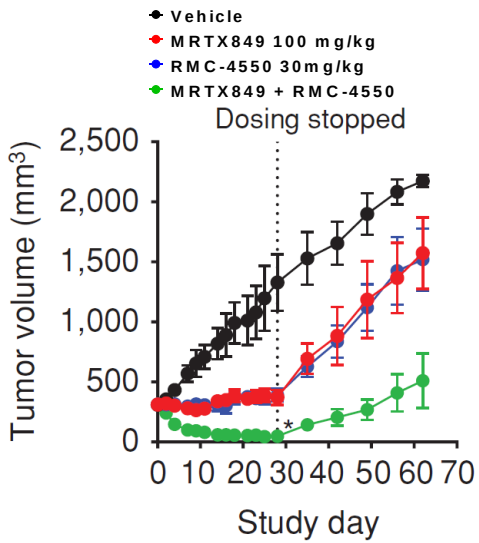
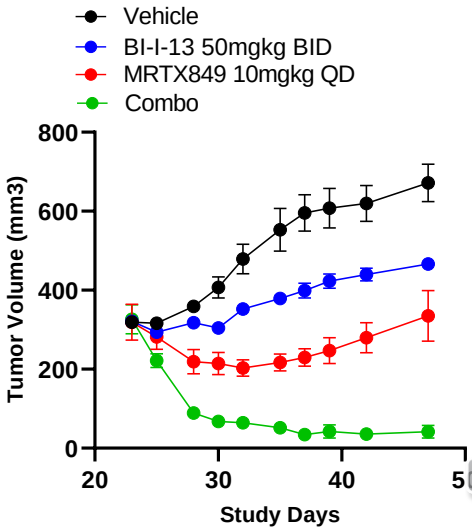
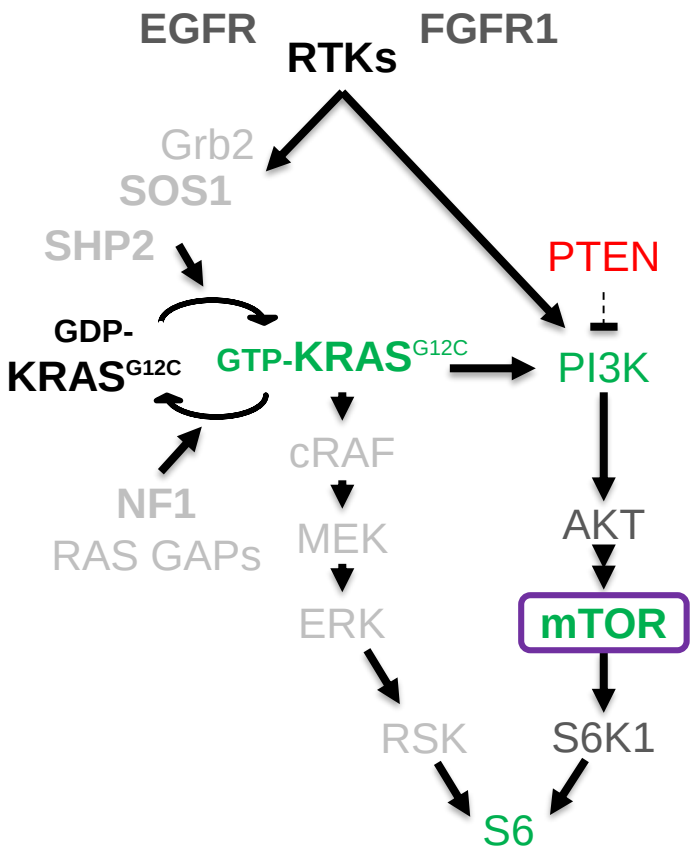




SOS1i -- MiaPaca-2



Alternative Pathway Activation Through mTOR May Contribute to Adaptive Resistance



- mTOR pathway genes drop out +/- MRTX849 treatment
- Loss of TSGs PTEN and TSC1/2 provide growth advantage
- mTOR combinations further reduce pS6 activation and leads to increased in vivo efficacy

"DROP OUT"
Dependency Genes
MRTX849
Combination Targets

Model		MRTX849
LU99	In Vitro	(-)
		+
	In Vivo	(-)
		+
H358	In Vitro	(-)
		+
KYSE410	In Vitro	(-)
		+

RPS6 EIF4E RAC1 RPTOR PTPN11 GRB2 MTOR STK11 FGFR1 PIK3CA TSC2 TSC1 PTEN

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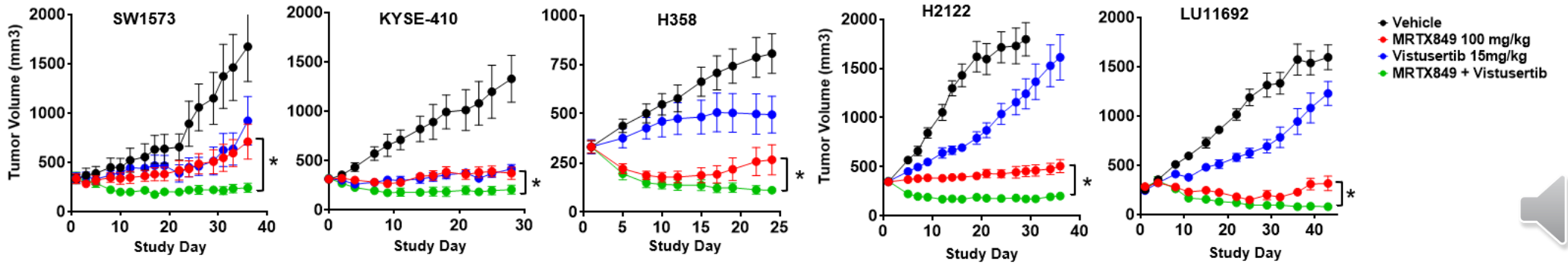
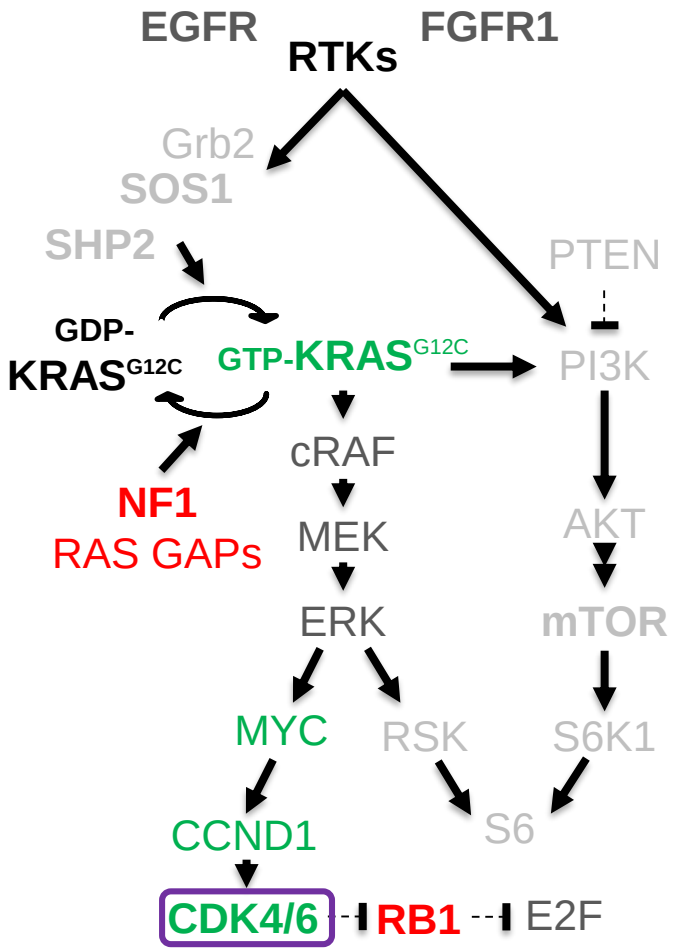
"ENRICHMENT"
LOF Promotes
Growth / Resistance



Cell Cycle Strongly Implicated in CRISPR Screens and CDK4/6 Inhibitors Augment MRTX849 In Vivo Efficacy



"DROP OUT"
Dependency Genes
MRTX849
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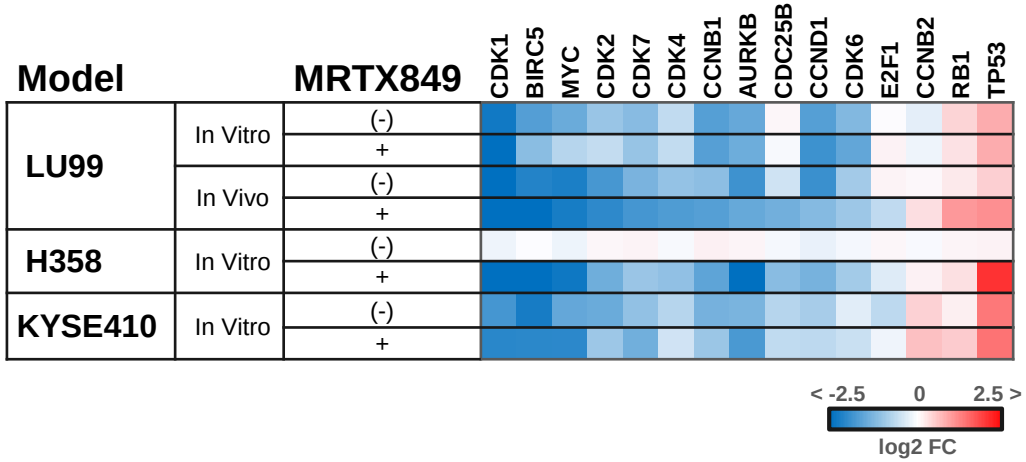

"ENRICHMENT"
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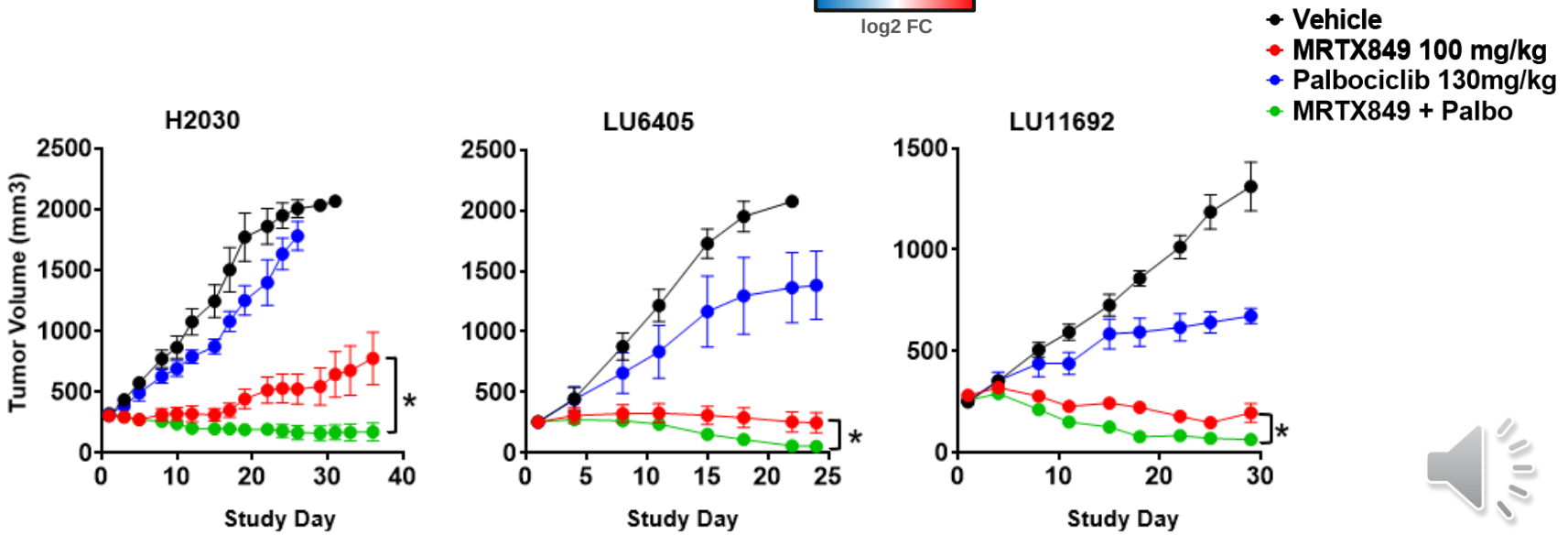

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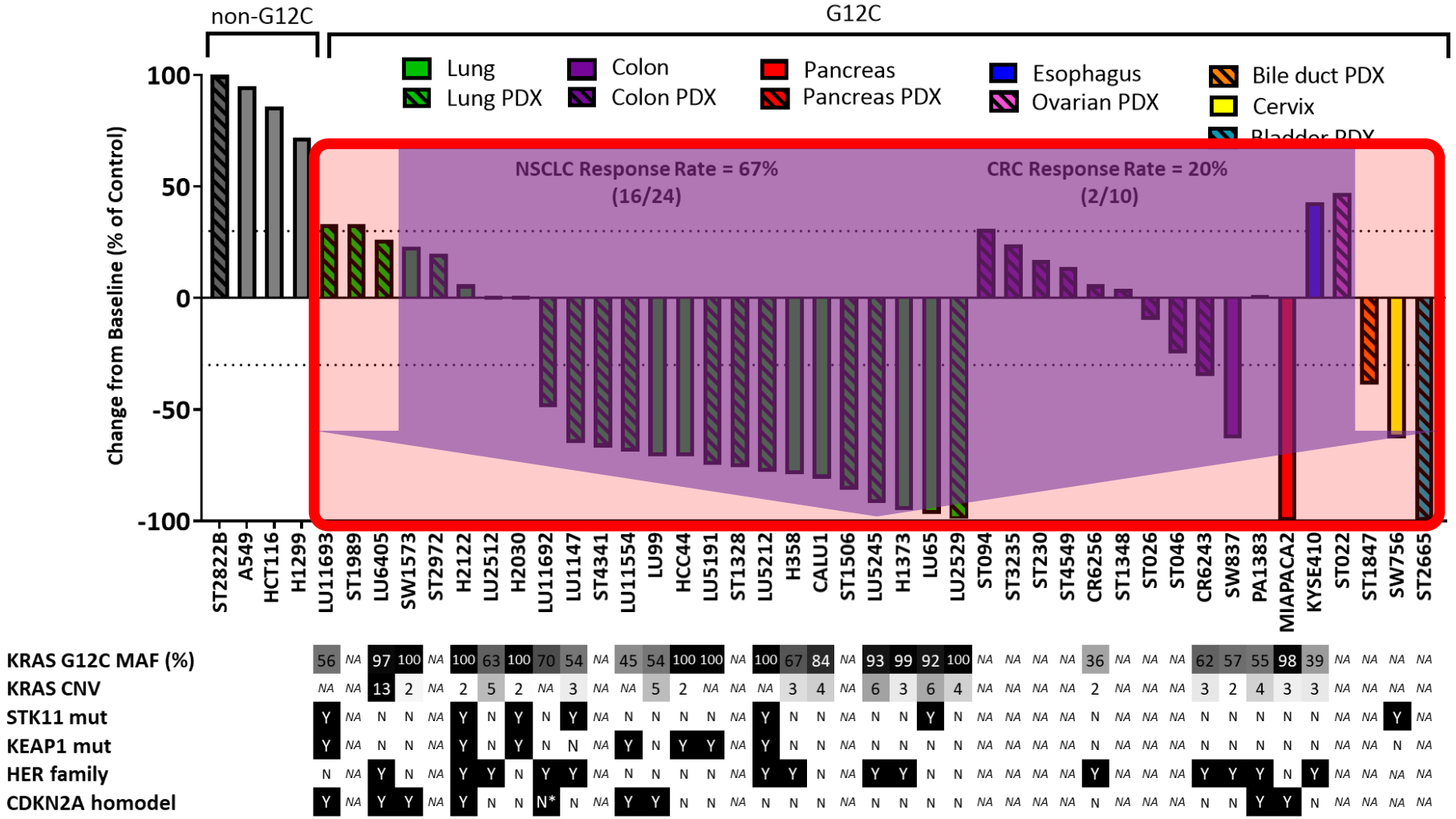
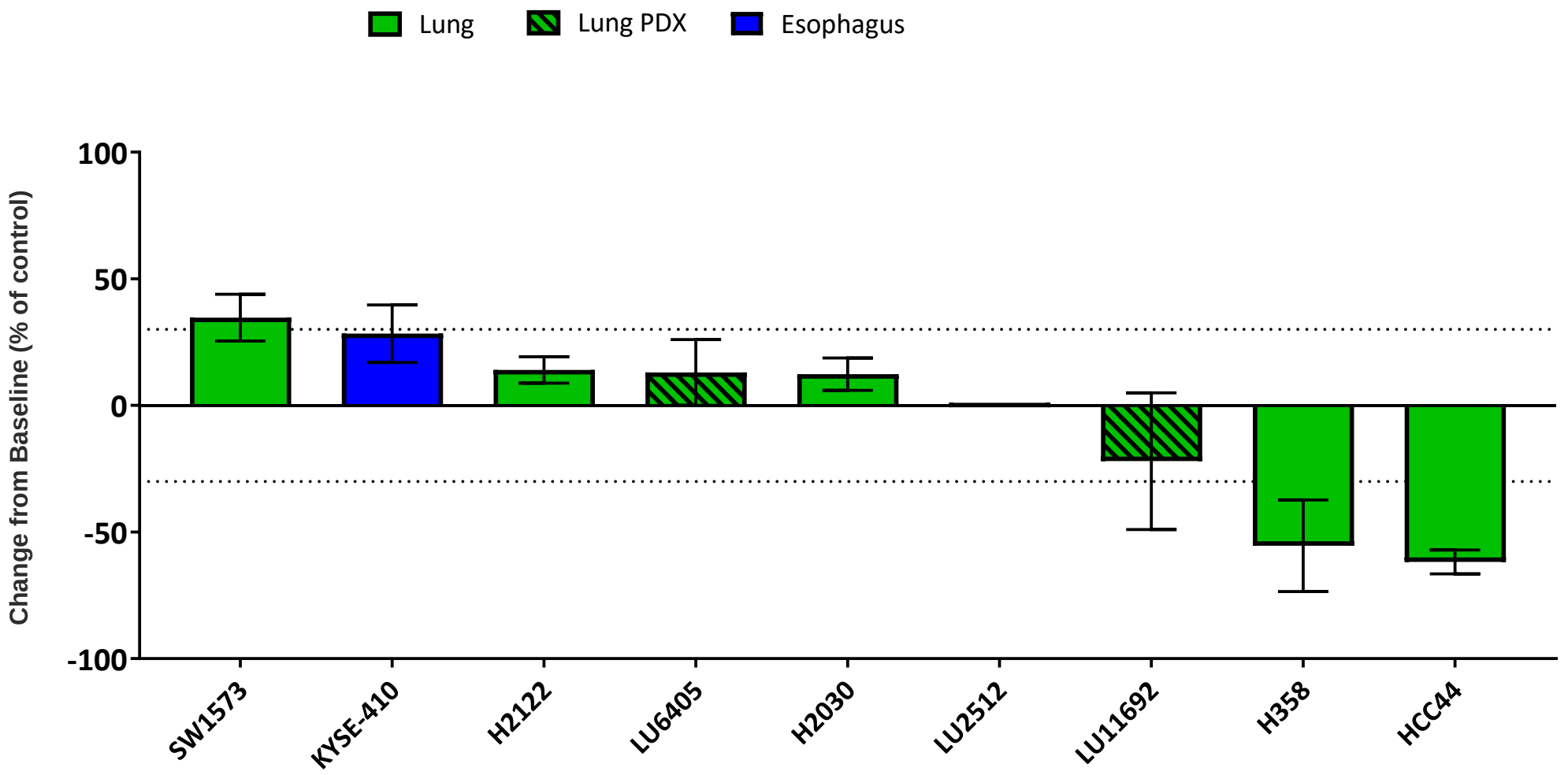


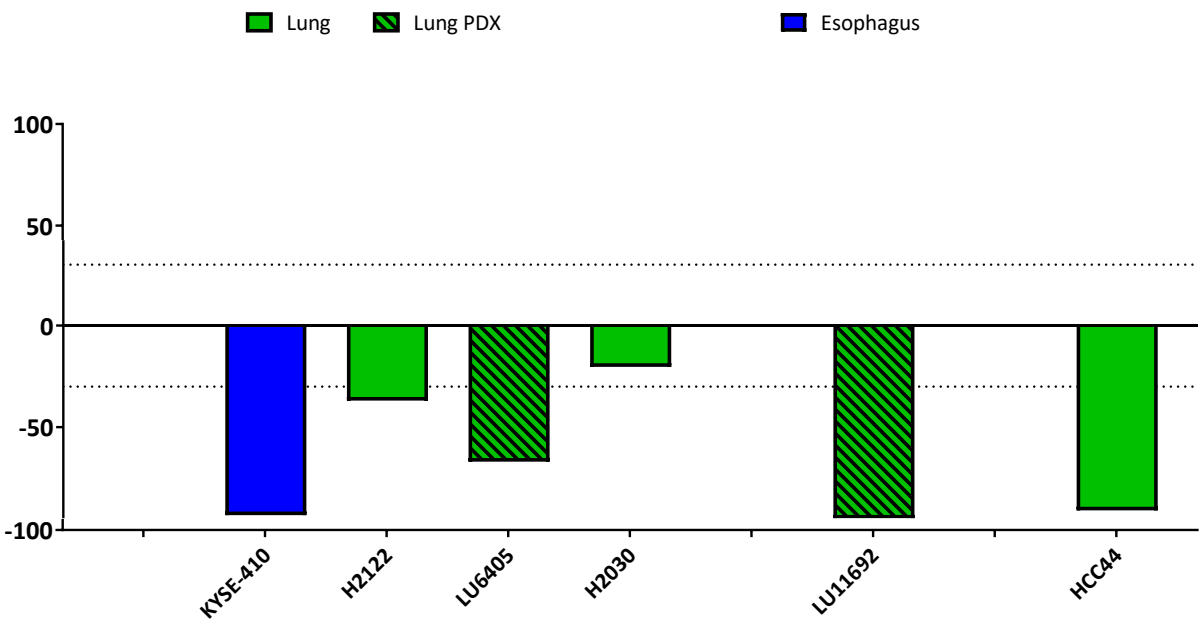
Single Agent Activity of MRTX849 in Selected Nonclinical KRAS^{G12C} Tumor Models that Exhibit Intrinsic or Adaptive Resistance



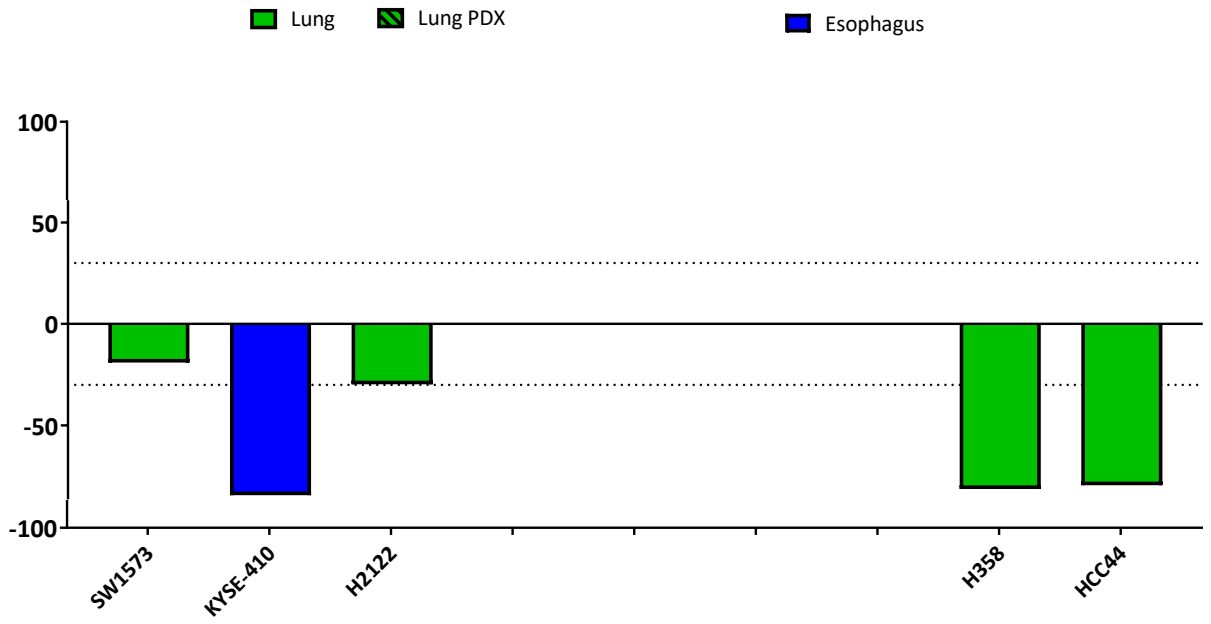
CDX and PDX models were treated with MRTX849 @ 100mg/kg PO, QD in all models shown.
% change from baseline control was calculated on ~ day 22 post initiation of dosing.

MRTX849 in Combination with HERi or SHP2i Further Inhibit KRAS^{G12C} Resulting in Dramatic Regression in Models Partially Resistant to Single Agent MRTX849

Pan-HERi Combination – Afatinib

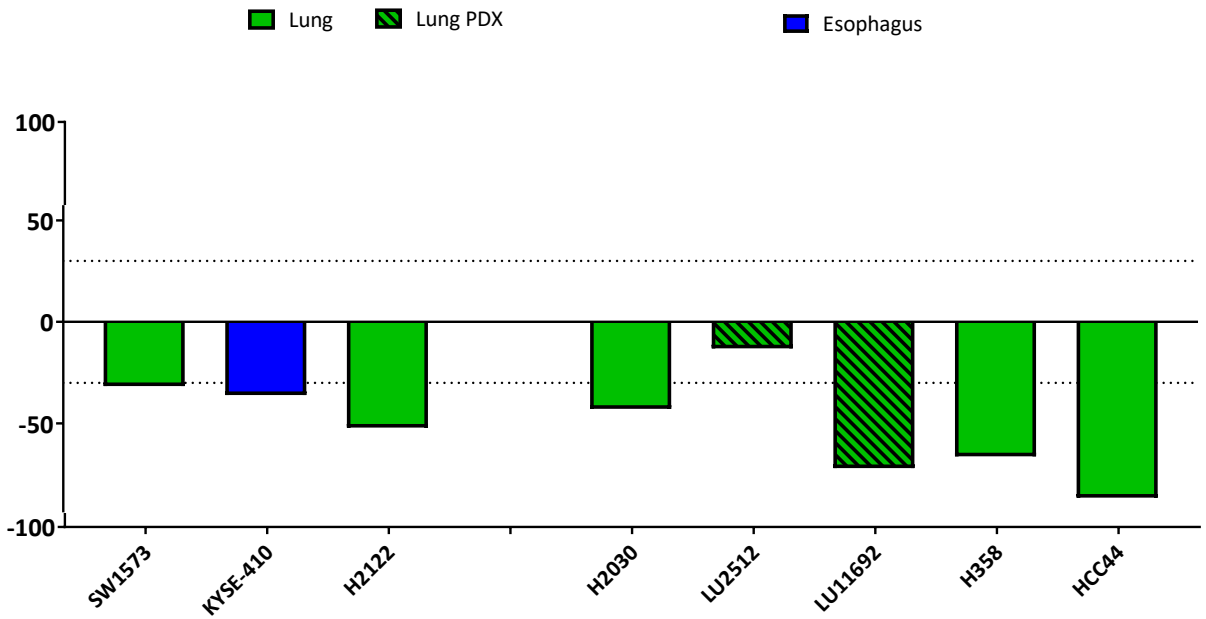


SHP2i Combination – RMC-4550

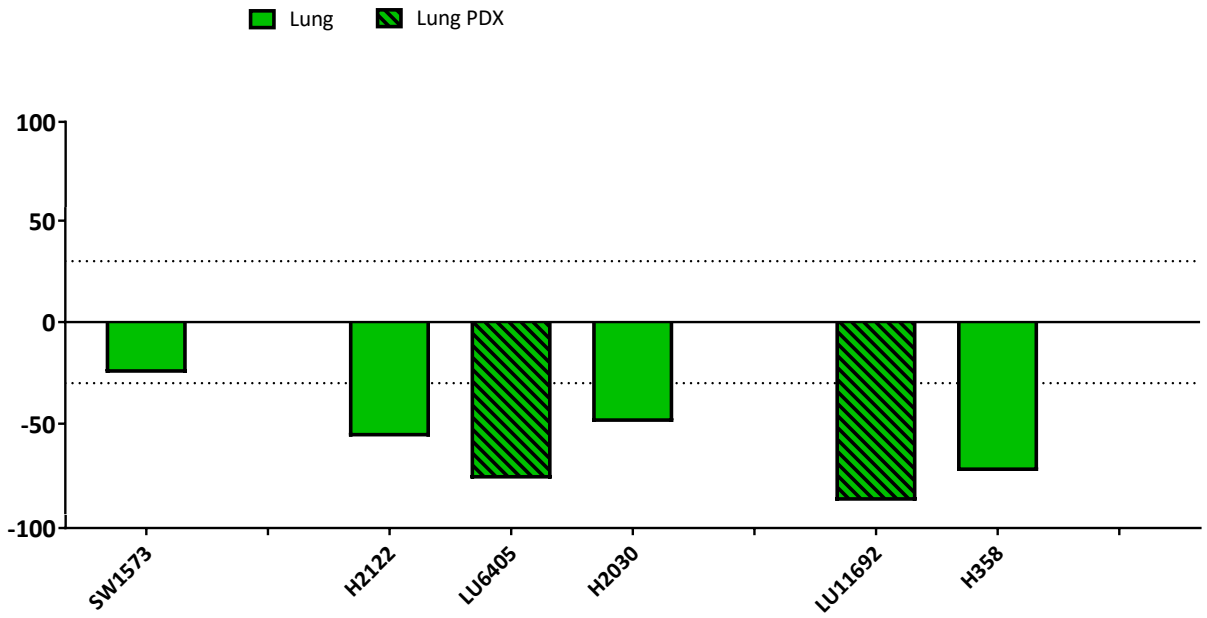


MRTX849 in Combination with Vistusertib or Palbociclib, Block Downstream Pathway Activation and Induce Dramatic Regression in Models Partially Resistant to Single Agent MRTX849

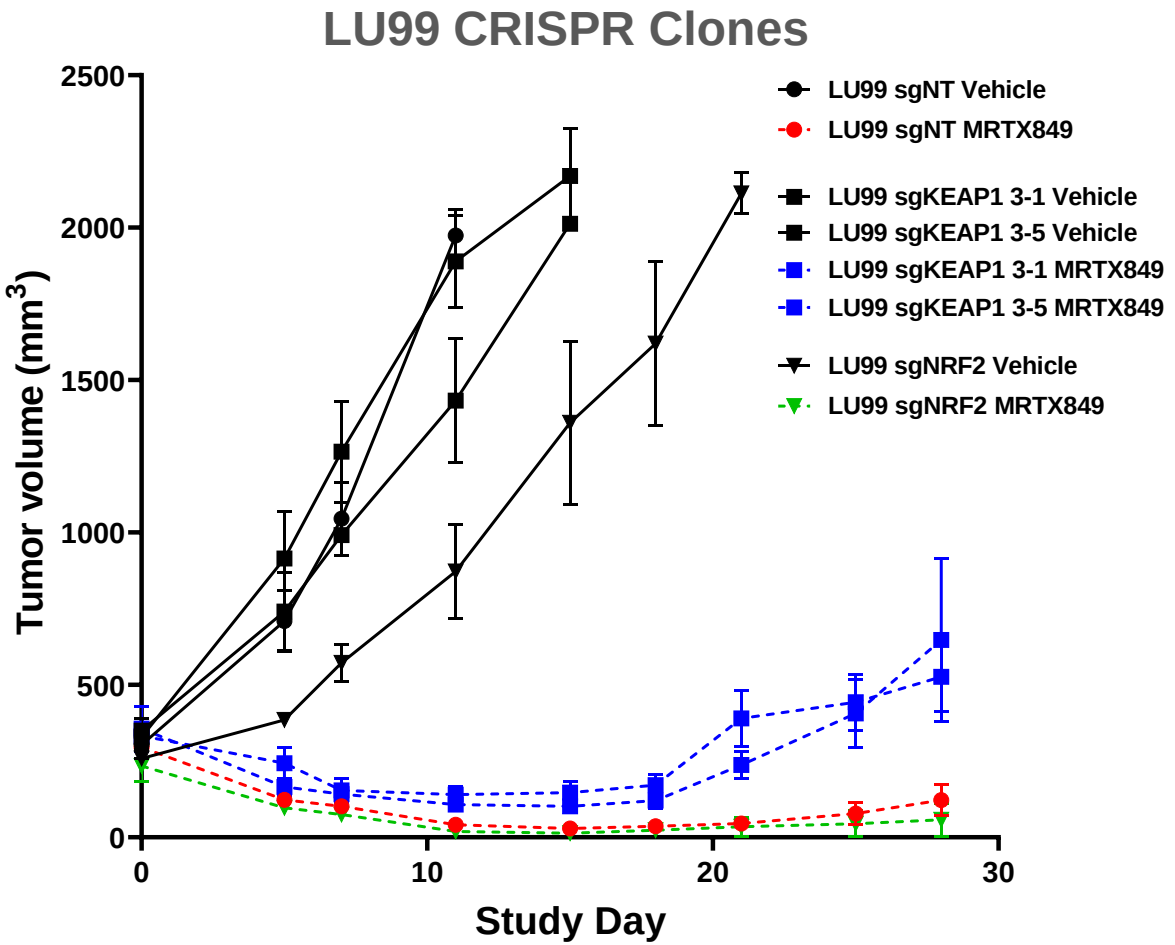
mTORi Combination – Vistusertib



CDK4/6i Combination – Palbociclib



KEAP1 KO Modifies Response to KRAS^{G12C} Inhibition and May Contribute to Adaptive Resistance



Conclusions

- MRTX849 is broadly active as a single agent across a panel of $KRAS^{G12C}$-mutant xenograft models.
- Executed MRTX849-anchored CRISPR screens targeting ~1,000 genes in 3 $KRAS^{G12C}$ cell lines, *in vitro & in vivo*.
- Tumor suppressor genes that promoted tumor growth also conferred partial drug resistance including **KEAP1**, **NF1**, **Rb1**, **TSC1/2**, and **PTEN**.
- Screened ~70 rational compounds in combination with MRTX849 across 8 lung cell lines *in vitro* that were partially MRTX849-resistant *in vivo*.
- Top combination targets validated with *in vivo* combinations are **EGFR family, SHP2, SOS1, mTOR,** and **CDK4/6.**

Acknowledgments

Mirati Therapeutics
Jamie Christensen
Pete Olson
Laura Waters
Ruth Aranda
Jill Hallin
David Briere
Andrew Calinisan
Niranjan Sudhakar
Lauren Hargis
Vickie Bowcut

Monoceros Biosystems
Adam Pavlicek
Sole Gatto
Julio Fernandez-Banet

Collaborators
Channing Der (UNC)
Adrienne Cox (UNC)
Piro Lito (MSK)
Pasi Janne (DFCI)
XenoSTART

Service Providers
Cellecta
Crown Biosciences