On a Journey to Erase Cancer

Erasca AACR Investor Presentation

April 2022

CONFIDENTIAL

Disclaimer: Forward Looking Statements & Market Data

We caution you that this presentation contains forward-looking statements. All statements other than statements of historical facts contained in this presentation, including statements regarding our future results of operations and financial position, business strategy, research and development plans, the anticipated timing, costs, design and conduct of our ongoing and planned preclinical studies and clinical trials for our product candidates, the potential benefits from our current or future arrangements with third parties, the timing and likelihood of success of our plans and objectives, and future results of anticipated product development efforts, are forward-looking statements. In some cases, you can identify forward-looking statements by terms such as “may,” “will,” “should,” “expect,” “plan,” “anticipate,” “could,” “intend,” “target,” “project,” “contemplates,” “believes,” “estimates,” “predicts,” “potential” or “continue” or the negative of these terms or other similar expressions. The inclusion of forward-looking statements should not be regarded as a representation by us that any of our plans will be achieved. Actual results may differ from those set forth in this presentation due to the risks and uncertainties inherent in our business, including, without limitation: our approach to the discovery and development of product candidates based on our singular focus on shutting down the RAS/MAPK pathway, a novel and unproven approach; we are early in our development efforts and have only two product candidates in early clinical development and all of our other development efforts are in the preclinical or development stage; potential delays in the commencement, enrollment, and completion of clinical trials and preclinical studies; our dependence on third parties in connection with manufacturing, research, and preclinical and clinical testing; unexpected adverse side effects or inadequate efficacy of our product candidates that may limit their development, regulatory approval, and/or commercialization, or may result in recalls or product liability claims; unfavorable results from preclinical studies or clinical trials; results from preclinical studies or early clinical trials not necessarily being predictive of future results; the inability to realize any benefits from our current licenses and acquisitions and any future licenses, acquisitions, or collaborations, and our ability to fulfill our obligations under such arrangements; regulatory developments in the United States and foreign countries; our ability to obtain and maintain intellectual property protection for our product candidates and maintain our rights under intellectual property licenses; our ability to fund our operating plans with our current cash, cash equivalents, and investments; our ability to maintain undisrupted business operations due to the COVID-19 pandemic, including delaying or disrupting our clinical trials, manufacturing, and supply chain; and other risks described in our prior filings with the Securities and Exchange Commission (SEC), including under the heading “Risk Factors” in our quarterly report on Form 10-Q for the three months ending on June 30, 2021, and any subsequent filings with the SEC. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof, and we undertake no obligation to update such statements to reflect events that occur or circumstances that exist after the date hereof. All forward-looking statements are qualified in their entirety by this cautionary statement, which is made under the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions, and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk. These and other factors could cause results to differ materially from those expressed in the estimates made by the independent parties and by us.

Agenda

- Clinical development plan overview
- Clinical development in GI malignancies
  - Erasca's 2022 AACR posters
  - Discussant: Scott Kopetz, MD, PhD
- Erasca's 2022 AACR posters supporting clinical development in other indications
  - Head and neck squamous cell carcinoma
  - Non-small cell lung cancer
  - Hematological malignancies
  - Tissue agnostic indications
- Q&A

~5.5m lives at stake annually worldwide with RAS/MAPK pathway alterations; 90+% of unmet needs are “blue ocean” with limited/no treatment options

New cases estimated worldwide per annum (thousands; numbers may not add up due to rounding)

ALTERATIONS	GBM	HNSCC	NSCLC	CRC	MELANOMA	PDAC	OTHER SOLID TUMORS	AML	US	EU	ROW	GLOBAL
EGFR*/FLT3	125	513	184	338	-	-	-	61	82	222	917	1,220
NF1	25	58	98	35	33	1.9	434	3.2	75	159	453	687
KRAS G12C	-	2.8	240	57	-	5.0	45	0.1	36	82	232	350
Other KRAS	0.5	14.1	252	703	1.6	420	527	4.7	179	470	1,273	1,922
NRAS	0.5	8.4	11.7	72	71	1.0	116	13.8	42	82	170	295
HRAS	0.2	45	7.8	0.4	3.0	0.2	57	-	11	24	80	114
BRAF V600E/K	2	1.9	23	180	93	1.4	158	0.4	63	127	271	461
Other BRAF	0.5	4.7	33	24	9.7	0.8	87	0.2	18	39	103	160
MEK	0.2	1.9	11.7	8.8	4.6	0.2	22	-	5	11	33	50
Co-occurring activating MAPK pathway alterations**	1.4	10.3	62	59	37	7.1	84	3.0	33	69	162	264
US	12	29	93	114	77	51	153	11	542			
EU	34	76	194	398	116	124	324	18		1,285		
Rest of World	109	555	635	964	60	264	1,053	57			3,696	
Global	155	660	923	1,476	253	438	1,530	86				5,522

Blue ocean opportunities Red ocean opportunities

* Post-Osimertinib resistant population shown for EGFRm NSCLC except for SCLC transformation
** Co-occurring activating MAPK pathway alterations exclude EGFR overexpression
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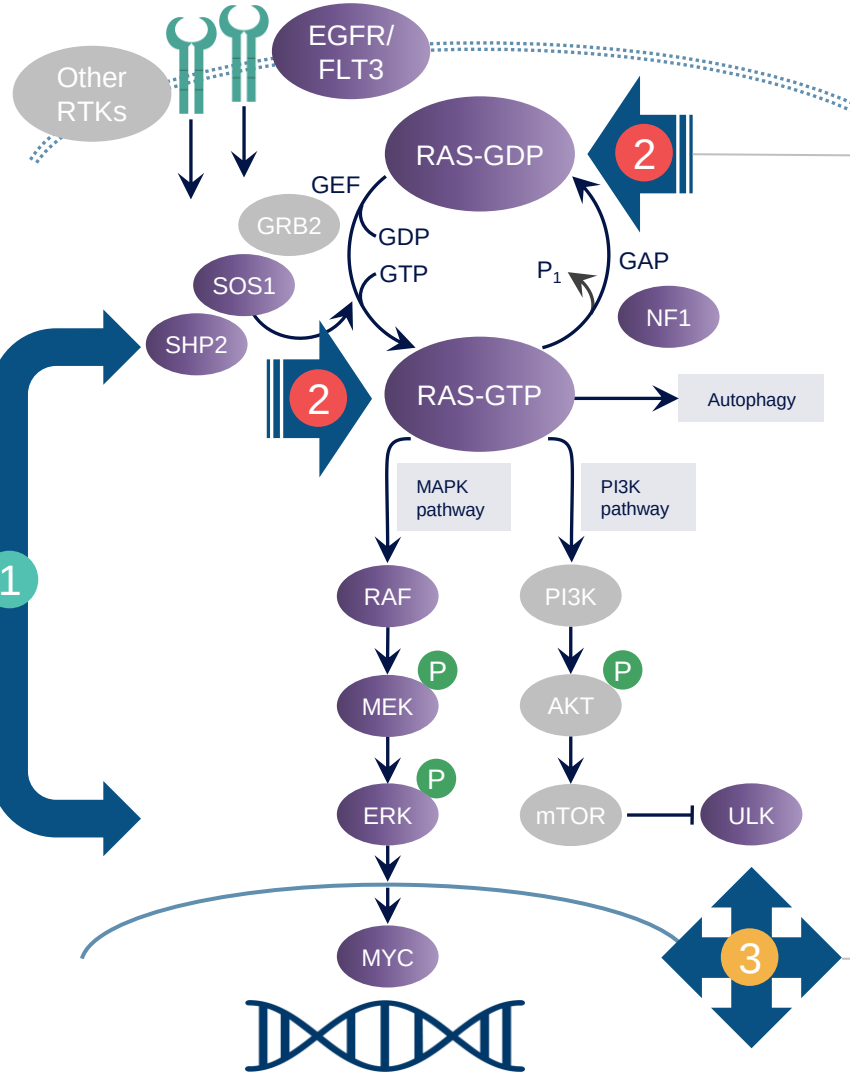
ERASCA

Our singular focus is on the RAS/MAPK pathway

Our Strategy

Comprehensively shut down the RAS/MAPK pathway



1

Target upstream and downstream RAS/MAPK nodes with single agents and clamp oncogenic drivers (MAPKlamp™) with combinations (e.g., **ERAS-007 ERKi** and **ERAS-601 SHP2i**)

2 **Target RAS directly** with single agents (e.g., **ERAS-3490 CNS-penetrant KRAS G12Ci**) and combinations with upstream, downstream, and escape route targeted therapies

3 **Target escape routes** enabled by other proteins or pathways to further disrupt RAS/MAPK pathway signaling

Erasca's clinical development plan targets multiple indications

Alterations	GBM	HNSCC	NSCLC	CRC	Melanoma	PDAC	Other solid tumors	AML
EGFR*/FLT3	125	513	184	338	-	-	-	61
NF1	25	58	98	35	33	1.9	434	3.2
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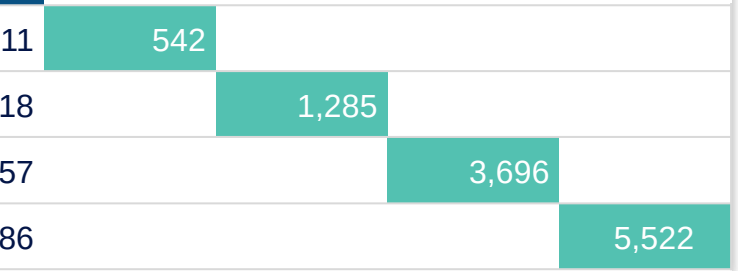
Clinical Development Plan



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Blue ocean opportunities Red ocean opportunities

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Erasca's clinical development plan targets multiple indications – CRC, PDAC

Alterations	GBM	HNSCC	NSCLC	CRC	Melanoma	PDAC	Other solid tumors	AML
EGFR*/FLT3	125	513	184	338	-	-	-	61
NF1	25	58	98	35	33	1.9	434	3.2
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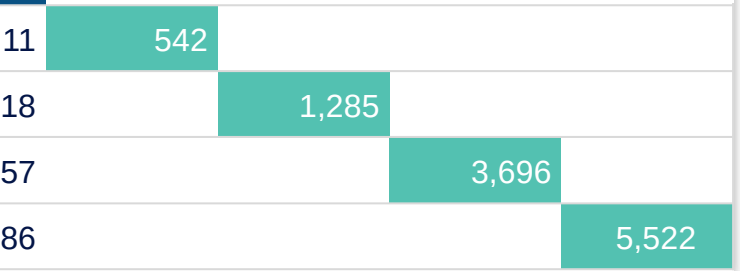

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Erasca's clinical development plan targets multiple indications – HNSCC

Alterations	GBM	HNSCC	NSCLC	CRC	Melanoma	PDAC	Other solid tumors	AML
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NF1	25	58	98	35	33	1.9	434	3.2
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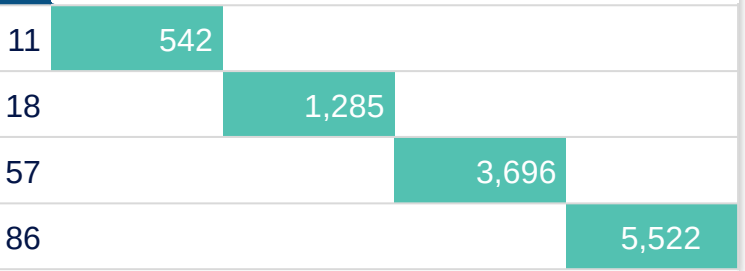

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Erasca's clinical development plan targets multiple indications – NSCLC

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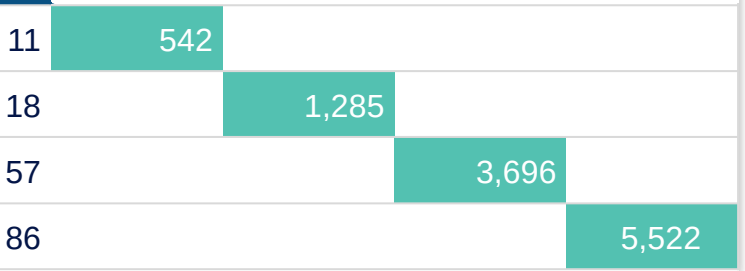
④ **FLAGSHP-1:** 601 + cetuximab (HPV-negative HNSCC)
⑤ **HERKULES-2:** 007 + osimertinib
⑥ **HERKULES-2:** 007 or 601 + sotorasib; **Future 3490 trial(s)**



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Erasca's clinical development plan targets multiple indications – AML

Alterations	GBM	HNSCC	NSCLC	CRC	Melanoma	PDAC	Other solid tumors	AML
EGFR*/FLT3	125	513	184	338	-	-	-	61
NF1	25	58	98	35	33	1.9	434	3.2
KRAS G12C	-	2.8	240	57	-	5.0	45	0.1
Other KRAS	0.5	14.1	252	703	1.6	420	527	4.7
NRAS	0.5	8.4	11.7	72	71	1.0	116	13.8
HRAS	0.2	45	7.8	0.4	3.0	0.2	57	-
BRAF V600E/K	2	1.9	23	180	93	1.4	158	0.4
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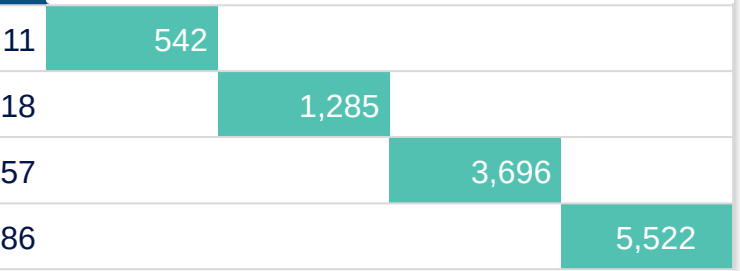
4. **FLAGSHP-1:** 601 + cetuximab (HPV-negative HNSCC)
5. **HERKULES-2:** 007 + osimertinib
6. **HERKULES-2:** 007 or 601 + sotorasib; **Future 3490 trial(s)**
7. **HERKULES-4:** 007 or 601 + gilteritinib



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Erasca's clinical development plan targets multiple indications – tissue agnostic

Alterations	GBM	HNSCC	NSCLC	CRC	Melanoma	PDAC	Other solid tumors	AML
EGFR*/FLT3	125	4 513	5 184	338	-	-	-	7 61
NF1	25	58	98	35	33	1.9	434	3.2
KRAS G12C	-	2.8	6 240	57	-	5.0	45	0.1
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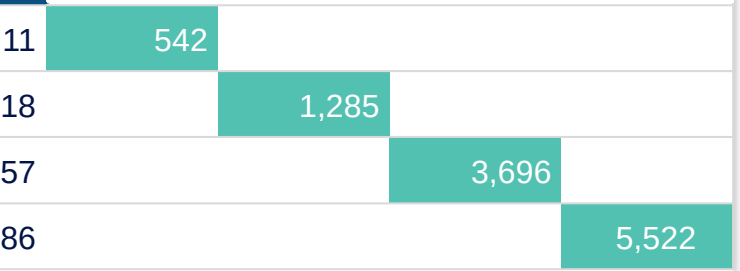
5. **HERKULES-2:** 007 + osimertinib
6. **HERKULES-2:** 007 or 601 + sotorasib; **Future 3490 trial(s)**
7. **HERKULES-4:** 007 or 601 + gilteritinib
8. **HERKULES-1:** 007 + 601 (our first MAPKlamp)



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Erasca's clinical development plan generates multiple ways to win for patients

Indication	RAS/MAPK altered solid tumors	EGFRm NSCLC post-osi	KRAS G12C NSCLC	BRAFm CRC EC-naïve	BRAFm CRC EC-treated	KRASm/ NRASm CRC	KRASwt/ NRASwt/ BRAFwt 3L CRC	HPV-negative HNSCC	FLT3m AML	EGFR altered rGBM
Benchmark	SOC is largely chemo	ORR 29%, mDOR 4.2 mos.	ORR 36%, mDOR 10 mos.	ORR 20%, mDOR 6.1 mos.	ORR ~2%, mDOR NA	ORR ~2%, mDOR NA	ORR 20%, mDOR 5.4 mos.	ORR 13%, mDOR 5.8 mos.	CR/CRh 23%, mDOR 7.4 mos.	ORR 26%, mDOR 4.2 mos.
Regimen tested	ERAS-007 + ERAS-601 (our first MAPKlamp)	ERAS-007 + osimertinib (osi)	ERAS-007 or ERAS-601 + sotorasib	ERAS-007 + encorafenib + cetuximab (EC)	ERAS-007 + EC	ERAS-007 + palbociclib	ERAS-601 + cetuximab	ERAS-601 + cetuximab	ERAS-007 or ERAS-601 + gilteritinib	ERAS-801 monotherapy
	ERAS-007 (alternative schedules)		ERAS-3490							
	ERAS-601 (alternative schedules)									
Erasca trial(s)	HERKULES-1	HERKULES-2 Sub-study 1	HERKULES-2 Sub-study 2	HERKULES-3 Sub-study 1	HERKULES-3 Sub-study 1	HERKULES-3 Sub-study 2	FLAGSHP-1	FLAGSHP-1	HERKULES-4	THUND-ERBBOLT-1
	FLAGSHP-1		ERAS-3490 Ph 1 trial (in future)							

100% of CRC

Erasca presented six posters at AACR featuring data supporting best-in-class potential and clinical development plans for ERAS-007, -601, and -3490

Abstract Number	Abstract Title
2672	ERAS-007 is a selective ERK1/2 inhibitor with preclinical activity across RAS/MAPK pathway-driven CRC models
2671	ERAS-601, a potent allosteric inhibitor of SHP2, demonstrates compelling single agent anti-tumor activity in RAS/MAPK-driven tumor models
2670	ERAS-601, a potent allosteric inhibitor of SHP2, synergistically enhances the efficacy of sotorasib/adagrasib and cetuximab in NSCLC, CRC, and HNSCC tumor models
3345	ERAS-601, a potent allosteric inhibitor of SHP2, synergistically enhances the activity of a FLT3 inhibitor, gilteritinib, in FLT3-mutated AML tumor models
2669	ERAS-007 (ERK1/2 inhibitor) + ERAS-601 (SHP2 inhibitor) exhibit nonclinical combination activity across KRAS mutated NSCLC, CRC, and PDAC tumor models
2675	Discovery of potent CNS-penetrant covalent KRAS G12C inhibitors

Erasca's clinical development plan generates multiple ways to win for patients

Indication	RAS/MAPK altered solid tumors	EGFRm NSCLC post-osi	KRAS G12C NSCLC	BRAFm CRC EC-naïve	BRAFm CRC EC-treated	KRASm/ NRASm CRC	KRASwt/ NRASwt/ BRAFwt 3L CRC	HPV-negative HNSCC	FLT3m AML	EGFR altered rGBM
Benchmark	SOC is largely chemo	ORR 29%, mDOR 4.2 mos.	ORR 36%, mDOR 10 mos.	ORR 20%, mDOR 6.1 mos.	ORR ~2%, mDOR NA	ORR ~2%, mDOR NA	ORR 20%, mDOR 5.4 mos.	ORR 13%, mDOR 5.8 mos.	CR/CRh 23%, mDOR 7.4 mos.	ORR 26%, mDOR 4.2 mos.
Regimen tested	ERAS-007 + ERAS-601 (our first MAPKlamp)	ERAS-007 + osimertinib (osi)	ERAS-007 or ERAS-601 + sotorasib	ERAS-007 + encorafenib + cetuximab (EC)	ERAS-007 + EC	ERAS-007 + palbociclib	ERAS-601 + cetuximab	ERAS-601 + cetuximab	ERAS-007 or ERAS-601 + gilteritinib	ERAS-801 monotherapy
	ERAS-007 (alternative schedules)		ERAS-3490							
	ERAS-601 (alternative schedules)									
Erasca trial(s)	HERKULES-1	HERKULES-2 Sub-study 1	HERKULES-2 Sub-study 2	HERKULES-3 Sub-study 1	HERKULES-3 Sub-study 1	HERKULES-3 Sub-study 2	FLAGSHP-1	FLAGSHP-1	HERKULES-4	THUND-ERBBOLT-1
	FLAGSHP-1		ERAS-3490 Ph 1 trial (in future)							

Indications and regimens supported by Erasca's 2022 AACR data

100% of CRC

Agenda

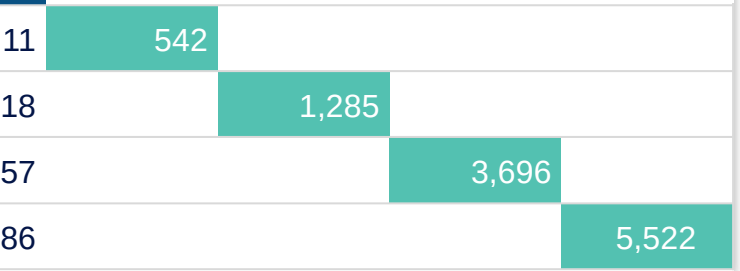
- Clinical development plan overview
- Clinical development in GI malignancies
  - Erasca's 2022 AACR posters
  - Discussant: Scott Kopetz, MD, PhD
- Erasca's 2022 AACR posters supporting clinical development in other indications
  - Head and neck squamous cell carcinoma
  - Non-small cell lung cancer
  - Hematological malignancies
  - Tissue agnostic indications
- Q&A

Erasca's clinical development plan targets multiple indications

Alterations	GBM	HNSCC	NSCLC	CRC	Melanoma	PDAC	Other solid tumors	AML
EGFR*/FLT3	125	513	184	338	-	-	-	61
NF1	25	58	98	35	33	1.9	434	3.2
KRAS G12C	-	2.8	240	57	-	5.0	45	0.1
Other KRAS	0.5	14.1	252	703	1.6	420	527	4.7
NRAS	0.5	8.4	11.7	72	71	1.0	116	13.8
HRAS	0.2	45	7.8	0.4	3.0	0.2	57	-
BRAF V600E/K	2	1.9	23	1 180	93	1.4	158	0.4
Other BRAF	0.5	4.7	33	24	9.7	0.8	87	0.2
MEK	0.2	1.9	11.7	8.8	4.6	0.2	22	-
Co-occurring activating MAPK pathway alterations**	1.4	10.3	62	59	37	7.1	84	3.0
US	12	29	93	114	77	51	153	11
EU	34	76	194	398	116	124	324	18
Rest of World	109	555	635	964	60	264	1,053	57
Global	155	660	923	1,476	253	438	1,530	86

Clinical Development Plan

① **HERKULES-3:** 007 + encorafenib & cetuximab (EC)



Blue ocean opportunities Red ocean opportunities

* Post-Osimertinib resistant population shown for EGFRm NSCLC except for SCLC transformation

** Co-occurring activating MAPK pathway alterations exclude EGFR overexpression

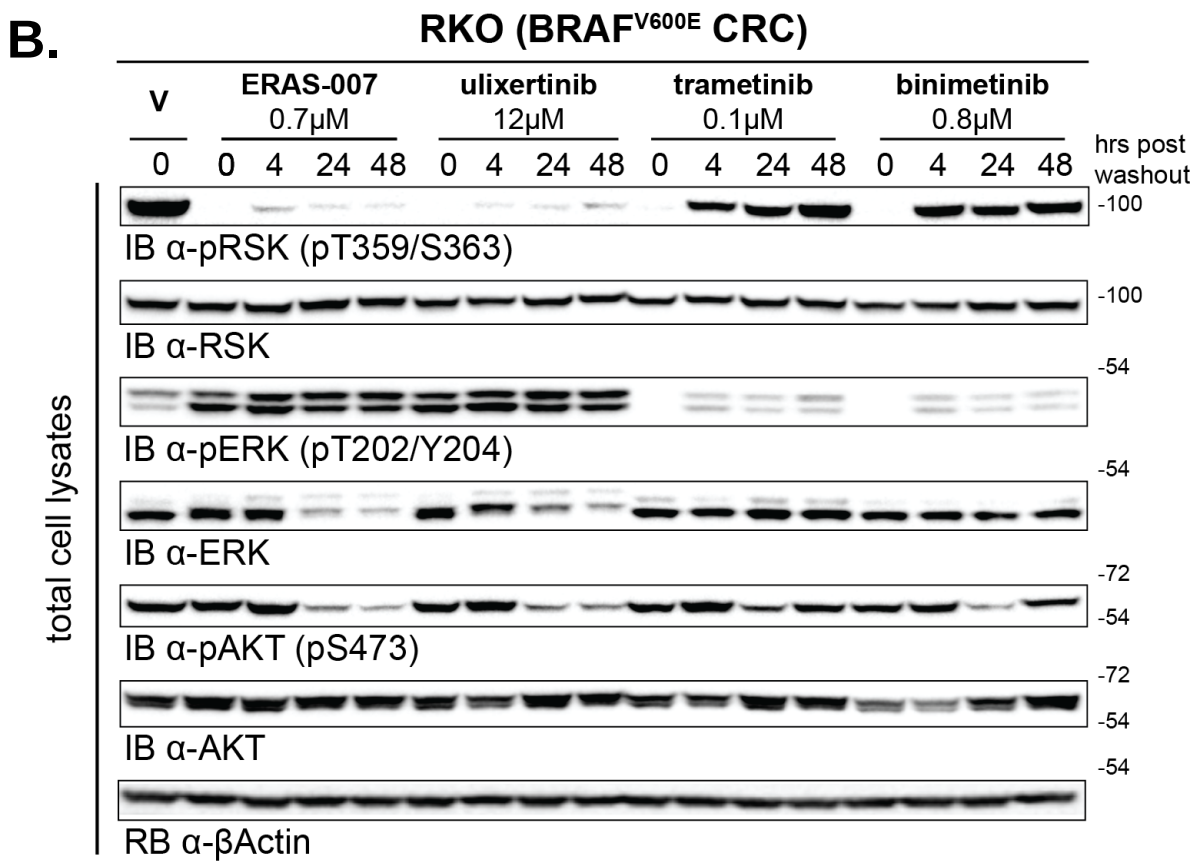
[1] Triple wildtype CRC is KRASwt, NRASwt, and BRAFwt

Source: SEER database (2020), ECIS database (2020), GLOBOCAN database (2020), The AACR Project GENIE Consortium version 8.1 (2020), TCGA Research Network: https://www.cancer.gov/tcga, Tyner JW et al. (2018) PMID: 30333627, Brenner CW et al (2013) PMID: 24120142, Chen J et al. (2020) PMID: 32015526, and Ostrom QT, et al. (2020) PMID: 33123732

ERAS-007 exhibits both long biophysical target residence time and sustained RAS/MAPK pathway inhibition relative to other ERK and MEK inhibitors

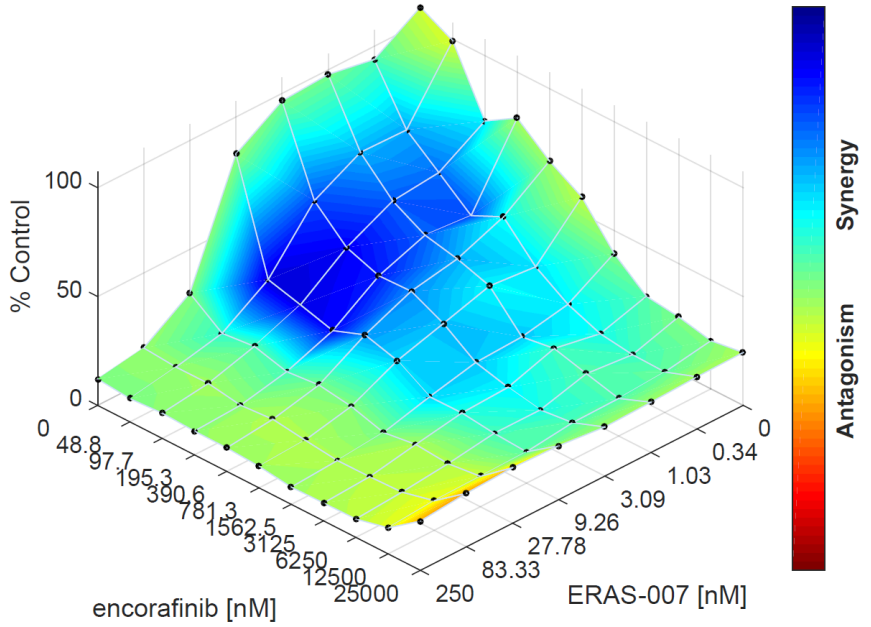
Compound	ERK2 residence time (τ) (min)	pRSK IC_{50} in RKO (nM)
ERAS-007	550	7.0
ulixertinib	16	116.8
trametinib	<0.03	1.3
binimetinib	<0.03	8.3

- ERK2 residence time was determined for ERKi(s), ERAS-007 and ulixertinib, and MEKi(s), trametinib and binimetinib, by BLI and SPR, respectively
- ERAS-007 had a target residence time of 550 min
- In cellular signaling assays, ERAS-007 exhibited sustained RAS/MAPK inhibition in the $BRAF^{V600E}$ CRC cell line, RKO



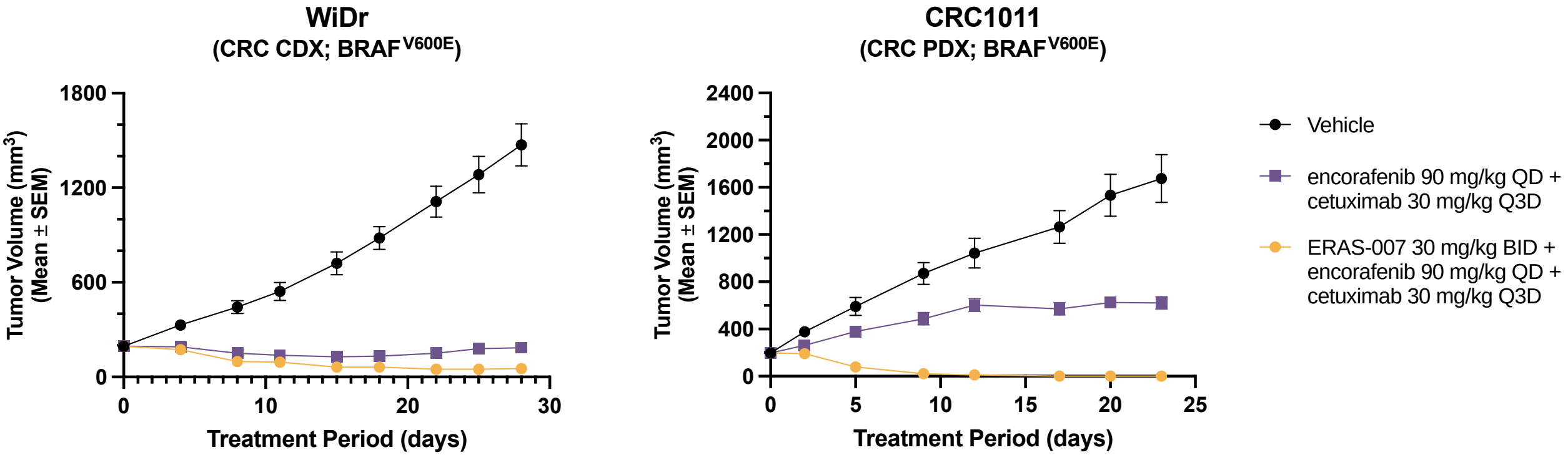
ERAS-007 inhibits cellular proliferation and exhibits combination activity with encorafenib in BRAF^{V600E} CRC cell lines

Cell Line	3D Cell Viability ERAS-007 IC_{50} (nM)
RKO	13.63
WiDr	8.35
HT-29	12.07
MDST8	3.81
LIM2405	0.81



- ERAS-007 exhibits monotherapy activity across BRAF^{V600E} CRC cell lines in 3D cell viability assays
- ERAS-007 and encorafenib exhibit synergy in the RKO cell line in 3D cellular format

ERAS-007 in combination with encorafenib ± cetuximab (EC) demonstrates efficacy in BRAF^{V600E} CRC CDX and PDX models



- The triple combination demonstrated superior activity and was statistically significant relative to the standard of care EC combination
- The triplet was well tolerated based on body weight loss and health observations

Erasca's clinical development plan targets multiple indications

Alterations	GBM	HNSCC	NSCLC	CRC	Melanoma	PDAC	Other solid tumors	AML
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Clinical Development Plan

① **HERKULES-3:** 007 + encorafenib & cetuximab (EC)

② **HERKULES-3:** 007 + palbociclib

US	542
EU	1,285
Rest of World	3,696
Global	5,522

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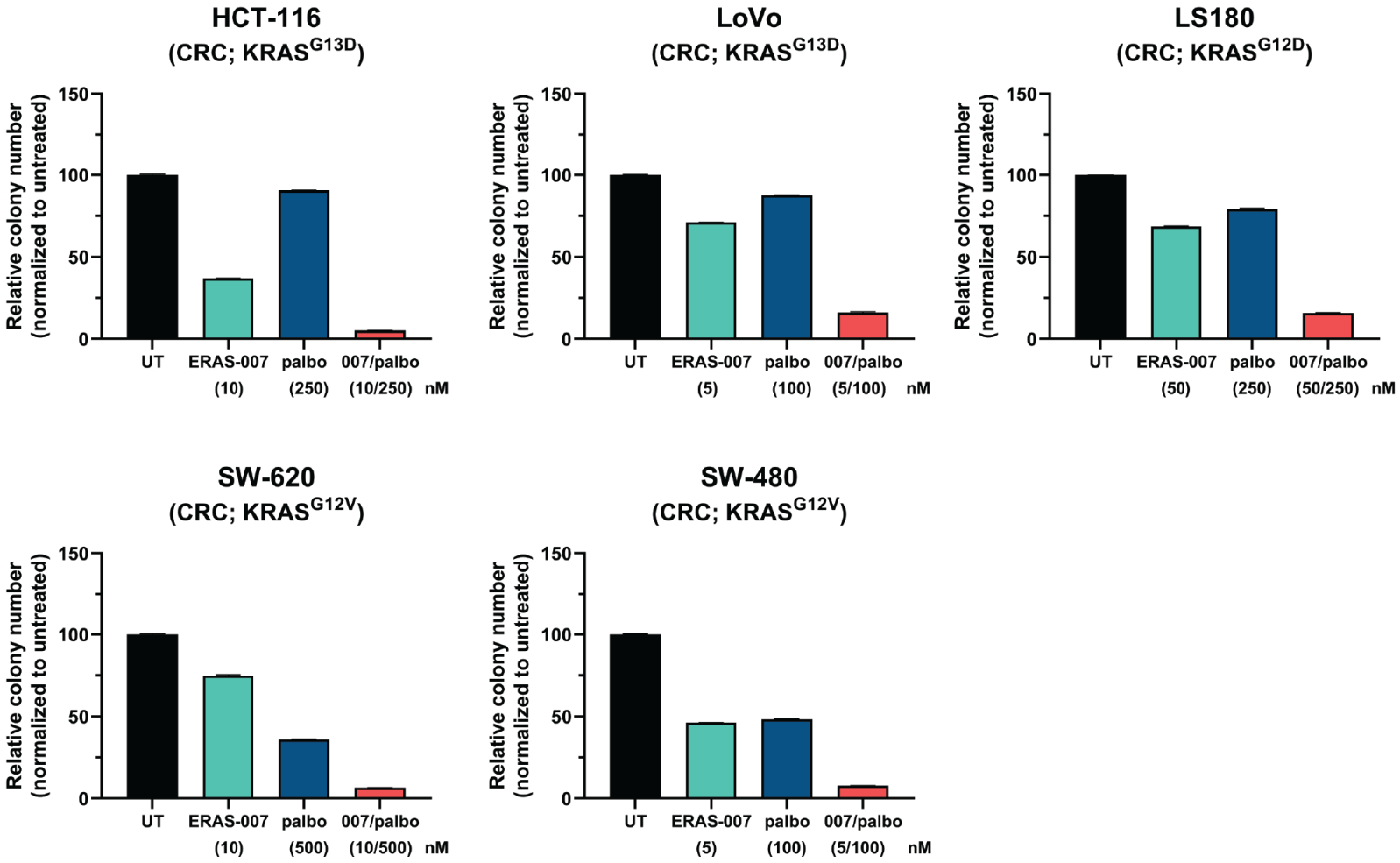
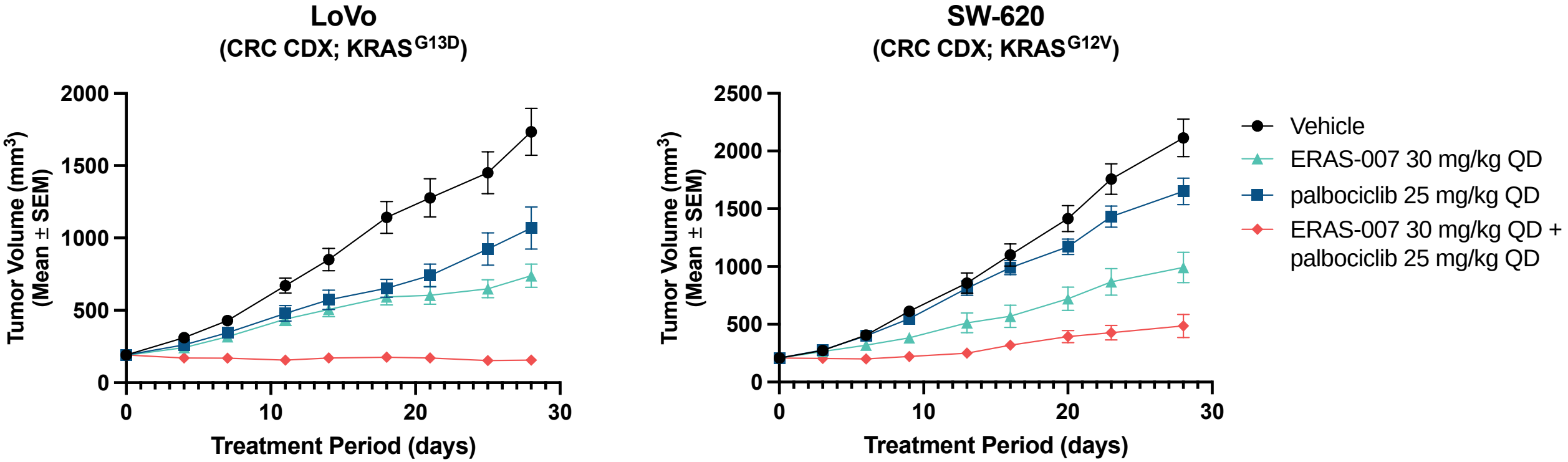
ERAS-007 and palbociclib demonstrate combination benefit *in vitro* across multiple KRAS^{mut} CRC models



- KRAS^{mut} cell lines were treated for 14 days with ERAS-007, palbociclib, or the combination
- Clonogenic assays were quantitated by crystal violet
- Significant combination activity was observed across multiple KRAS^{mut} CRC models

ERAS-007 in combination with palbociclib demonstrates *in vivo* efficacy in $KRAS^{mut}$ CRC models



- ERAS-007 in combination with palbociclib demonstrated superior activity and was statistically significant relative to the monotherapy groups
- The combination was well tolerated based on body weight loss and health observations

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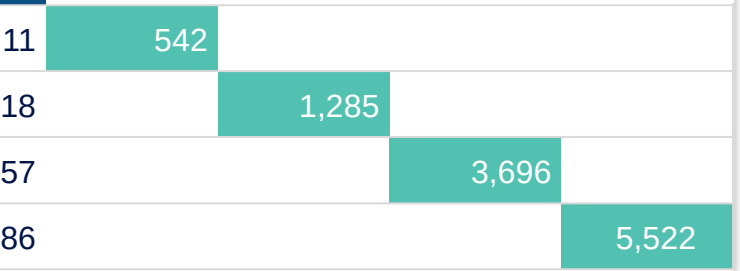
3

Clinical Development Plan

1. **HERKULES-3:** 007 + encorafenib & cetuximab (EC)
2. **HERKULES-3:** 007 + palbociclib
3. **FLAGSHP-1 / HERKULES-3:** 601 + cetuximab (triple WT CRC[1])



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ERAS-601 demonstrates high potency and selectivity against SHP2

Compound	Biochemical SHP2 inhibition IC50 (nM)
ERAS-601	4.6

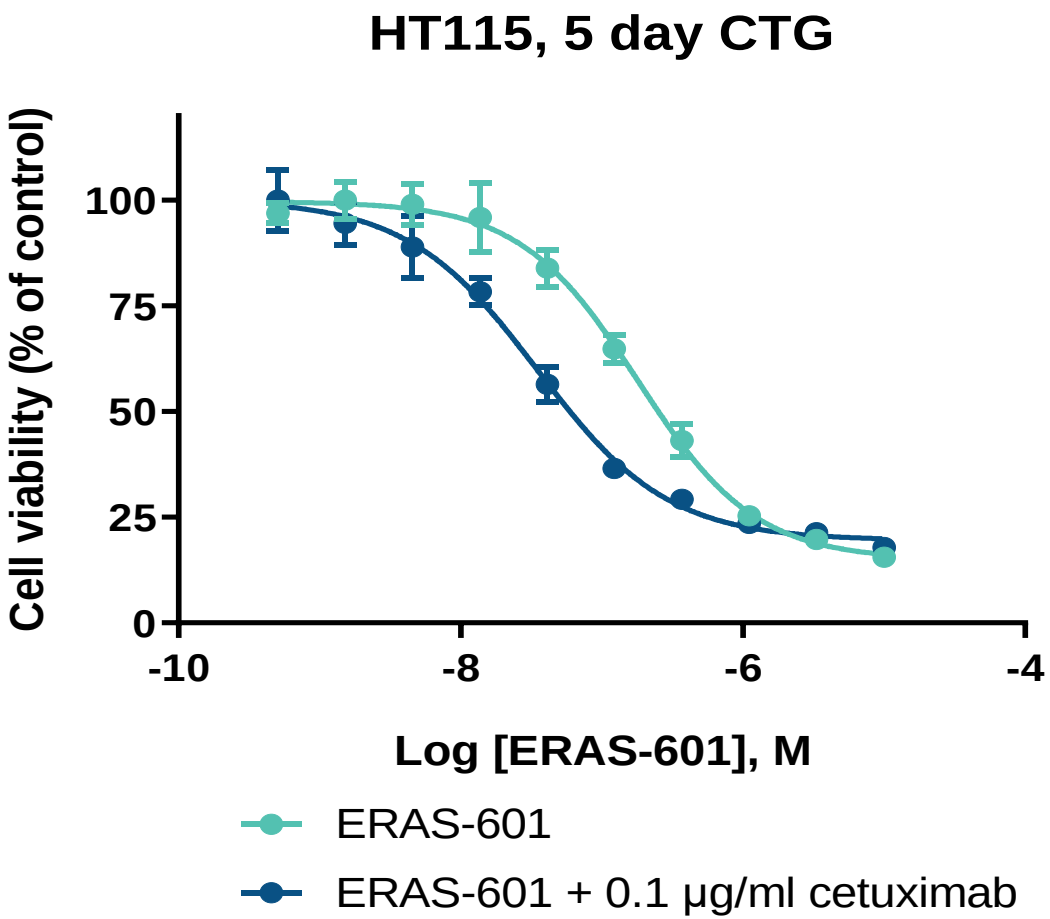
ERAS-601

demonstrated no off-target activity in 300 kinase (<30% inhibition @ 1μM) and 12 phosphatase panels (IC50 >10μM)

	Cell Line	Cancer Type	IC_{50} (nM)	
			ERAS-601	RMC-4550[1]
KRAS G12C	HCC44	NSCLC	48	95
	MIA PaCa-2	Pancreatic	6	17
	NCI-H1373	NSCLC	64	474
	NCI-H1792	NSCLC	40	27
	NCI-H2122	NSCLC	259	1,876
	NCI-H358	NSCLC	12	49
	SW1573	NSCLC	104	298
BRAF class III	NCI-H1666	NSCLC	19	51
	NCI-H508	CRC	95	208
NF1 LoF	MeWo	Melanoma	56	241
wtEGFR amplification	KYSE-520	Esophageal	119	440

[1]RMC-4550 is Revolution Medicine's SHP2i tool compound and is believed to behave similarly to their clinical compound, RMC-4630 (per company disclosure); LoF = loss of function; wtEGFR = wildtype EGFR

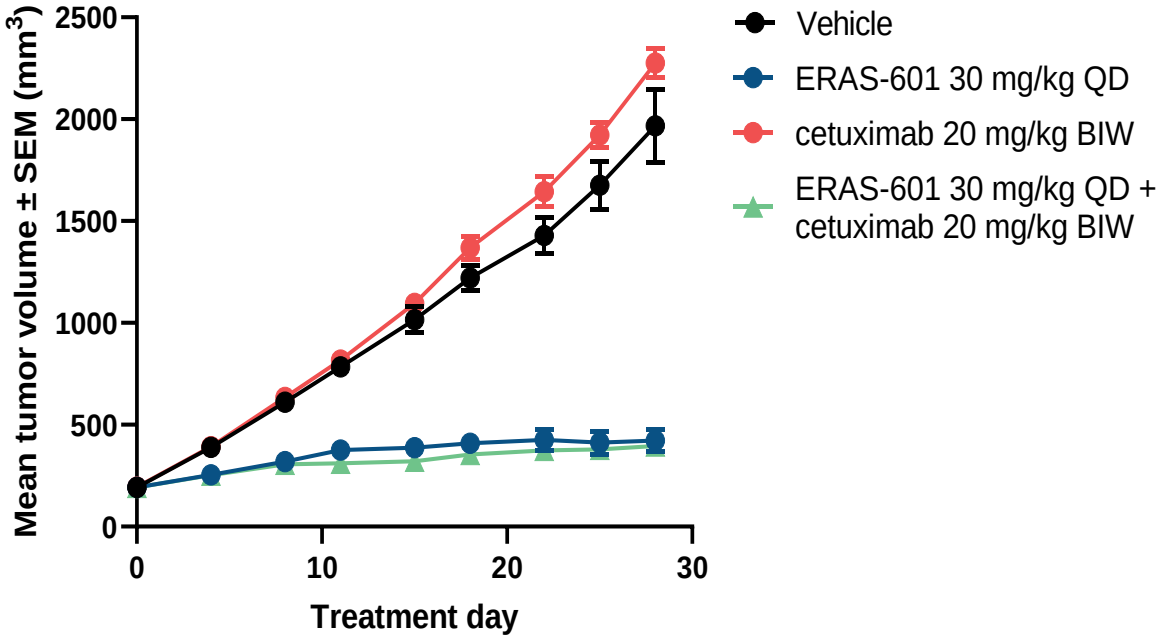
A low dose of cetuximab enhances ERAS-601's in vitro activity in the triple wild-type CRC cell line HT115



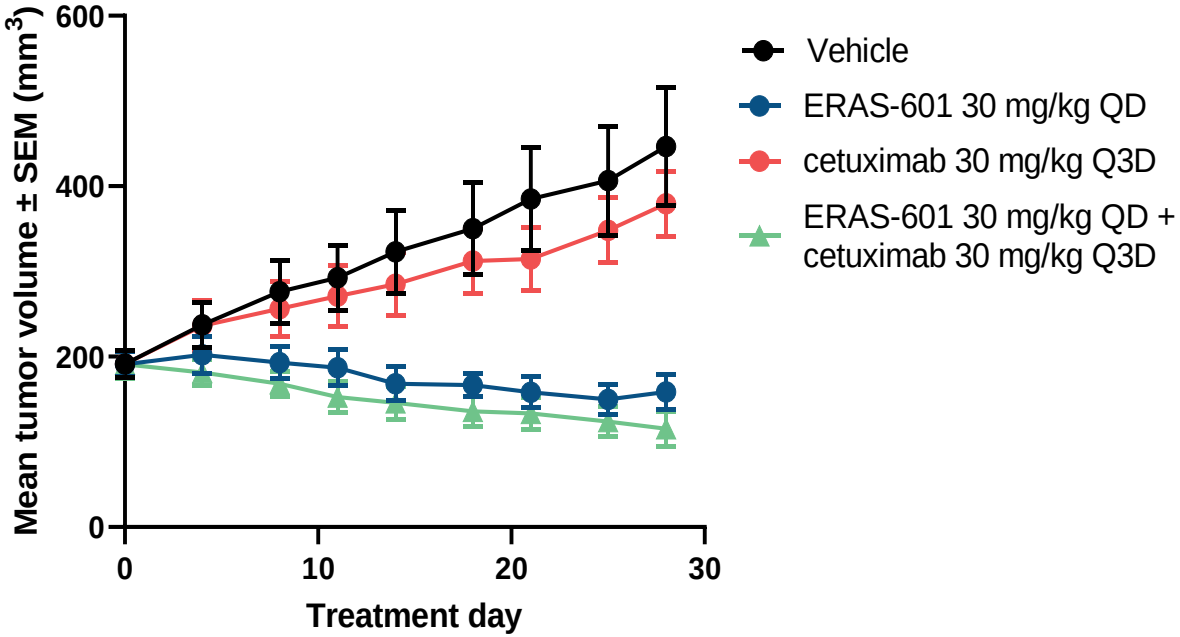
Treatment	2D CTG IC50, nM
ERAS-601	180
ERAS-601 + 0.1 µg/mL cetuximab	35

ERAS-601 and cetuximab demonstrated combination benefit in triple wild-type CRC models in vivo

Triple wild-type CRC PDX CRC049



Triple wild-type CRC PDX CRC1023



- ERAS-601 in combination with cetuximab demonstrated superior activity in triple wild-type CRC and was statistically significant relative to the monotherapy groups
- The combination was well tolerated based on body weight loss and health observations

Conclusions

ERAS-007

- ERK inhibitor amenable to intermittent dosing due to its potency and long target residence time
- Demonstrates promising nonclinical activity as a monotherapy and in combinations with encorafenib ± cetuximab and palbociclib in $BRAF^{V600E}$ and $KRAS^{mut}$ CRC models, respectively
- ERAS-007 in combination with encorafenib + cetuximab and palbociclib is currently being evaluated in the HERKULES-3 phase 1b/2 master protocol

ERAS-601

- Potent allosteric inhibitor of SHP2
- Combination of ERAS-601 with cetuximab enhances anti-proliferative activity in vitro and achieves tumor growth inhibition superior to respective monotherapies in triple wild-type CRC CDX and PDX models
- ERAS-601 + cetuximab combination in triple wild-type CRC is being evaluated in FLAGSHP-1 phase 1 trial

Agenda

- Clinical development plan overview
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THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Leveraging Adaptive Response in CRC

Scott Kopetz, MD, PhD
Professor, Deputy Chair, GI Medical Oncology

Disclosures | Scott Kopetz, MD, PhD

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Roche/Genentech, EMD Serono/Merck KGA,
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Symphogen, Biocartis, Amgen, Novartis, Lilly,
Boehringer Ingelheim, Boston Biomedical,
Pierre Fabre, AstraZeneca/Medimmune,
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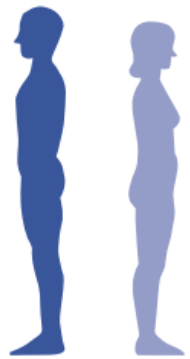
Novartis, Boehringer Ingelheim

CRC is a Leading Cause of New Cancer Cases and Deaths

Leading Sites of New Cancer Cases and Deaths – 2022 ACS Estimates

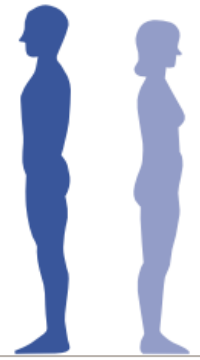
Estimated New Cases

Male			Female		
Prostate	268,490	27%	Breast	287,850	31%
Lung & bronchus	117,910	12%	Lung & bronchus	118,830	13%
Colon & rectum	80,690	8%	Colon & rectum	70,340	8%
Urinary bladder	61,700	6%	Uterine corpus	65,950	7%
Melanoma of the skin	57,180	6%	Melanoma of the skin	42,600	5%
Kidney & renal pelvis	50,290	5%	Non-Hodgkin lymphoma	36,350	4%
Non-Hodgkin lymphoma	44,120	4%	Thyroid	31,940	3%
Oral cavity & pharynx	38,700	4%	Pancreas	29,240	3%
Leukemia	35,810	4%	Kidney & renal pelvis	28,710	3%
Pancreas	32,970	3%	Leukemia	24,840	3%
All sites	**983,160**		**All sites**	**934,870**	



Estimated Deaths

Male			Female		
Lung & bronchus	68,820	21%	Lung & bronchus	61,360	21%
Prostate	34,500	11%	Breast	43,250	15%
Colon & rectum	28,400	9%	Colon & rectum	24,180	8%
Pancreas	25,970	8%	Pancreas	23,860	8%
Liver & intrahepatic bile duct	20,420	6%	Ovary	12,810	4%
Leukemia	14,020	4%	Uterine corpus	12,550	4%
Esophagus	13,250	4%	Liver & intrahepatic bile duct	10,100	4%
Urinary bladder	12,120	4%	Leukemia	9,980	3%
Non-Hodgkin lymphoma	11,700	4%	Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,710	3%	Brain & other nervous system	7,570	3%
All sites	**322,090**		**All sites**	**287,270**	



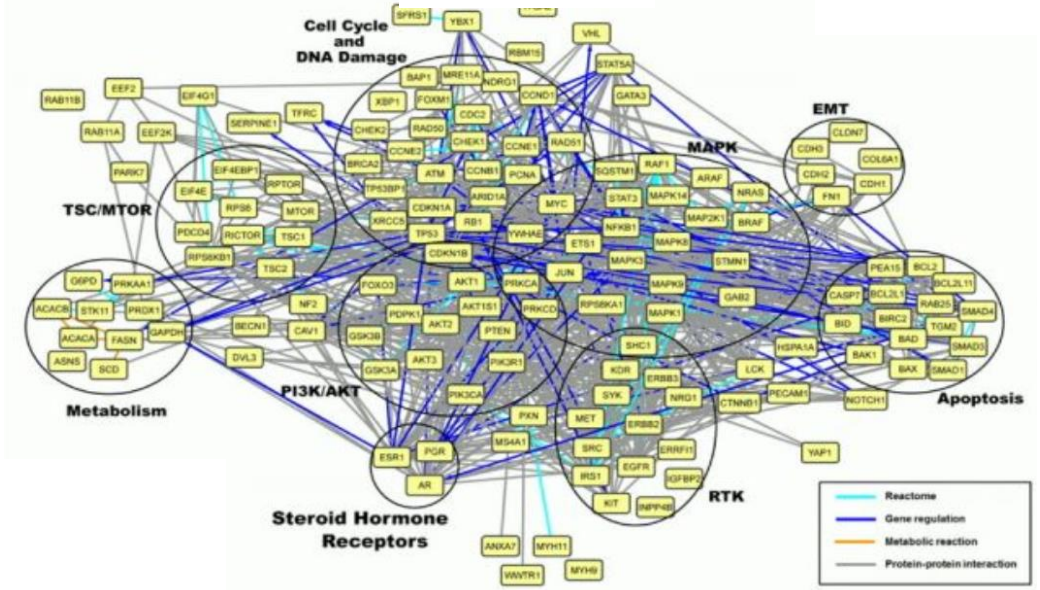
Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

CRC Treatment Landscape – Unmet Needs Still Remain

Colorectal cancer remains the most common tumor type enrolled onto Phase 1 studies

Line of Therapy	1L *95% of Stage IV patients*	2L	3L
Current Treatment Landscape	Fluorouracil + oxaliplatin ± irinotecan	Fluorouracil-based chemotherapy + bevacizumab Irinotecan or oxaliplatin based on 1L treatment	Targeted Therapy or Chemotherapy Regorafenib TAS-102
Tumor Heterogeneity	If RAS wild type and left-sided tumor, anti-EGFR (eg, cetuximab) can replace bevacizumab PD1 for MSI-H	Tumors harboring BRAF V600E or HER2 amplifications treated with respective targeted therapies	
Survival Rates	~24-30 mos mOS ~12 mos mPFS	~12-18 mos mOS ~6 mos mPFS	~6-9 mos mOS ~2 mos mPFS

Treatment Durability in CRC is Limited by Adaptive Resistance



Homeostatic regulation is a critical and nearly universal feature of biological systems

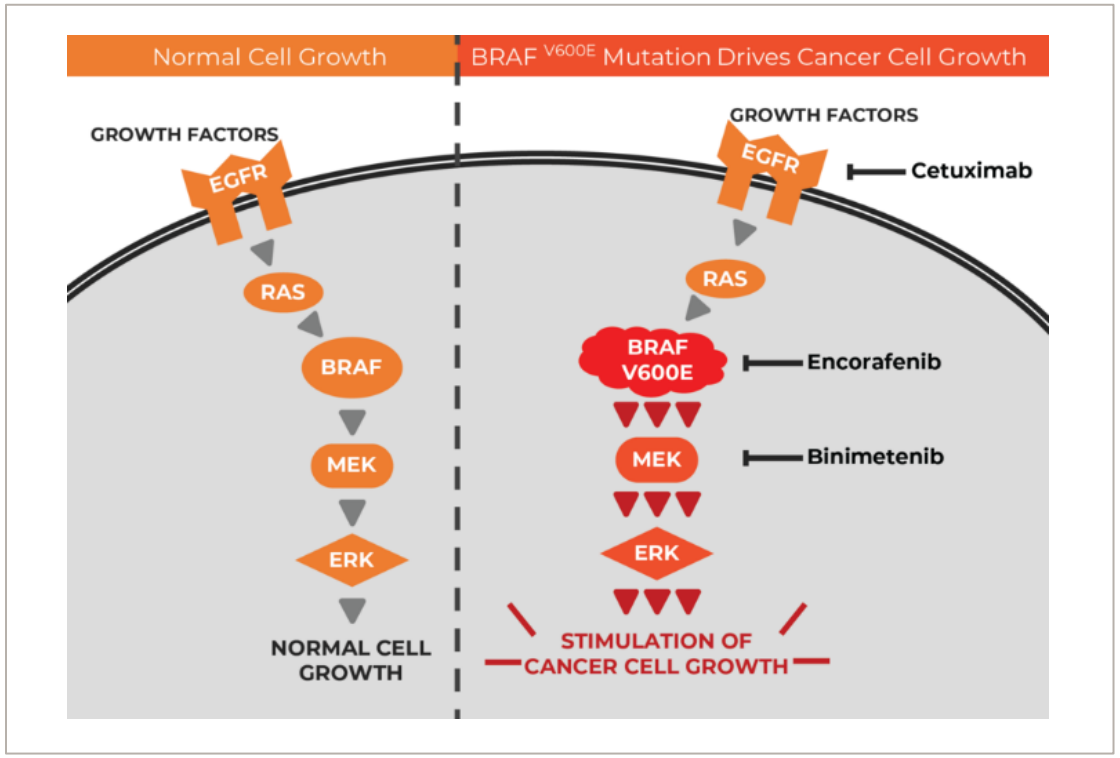
Growth pathways like MAPK have a number of such feedback networks established

Inhibition of a single node in the pathway results in a rapid compensation in the signaling to restore homeostasis

Tackling Adaptive Resistance in CRC: Two Examples

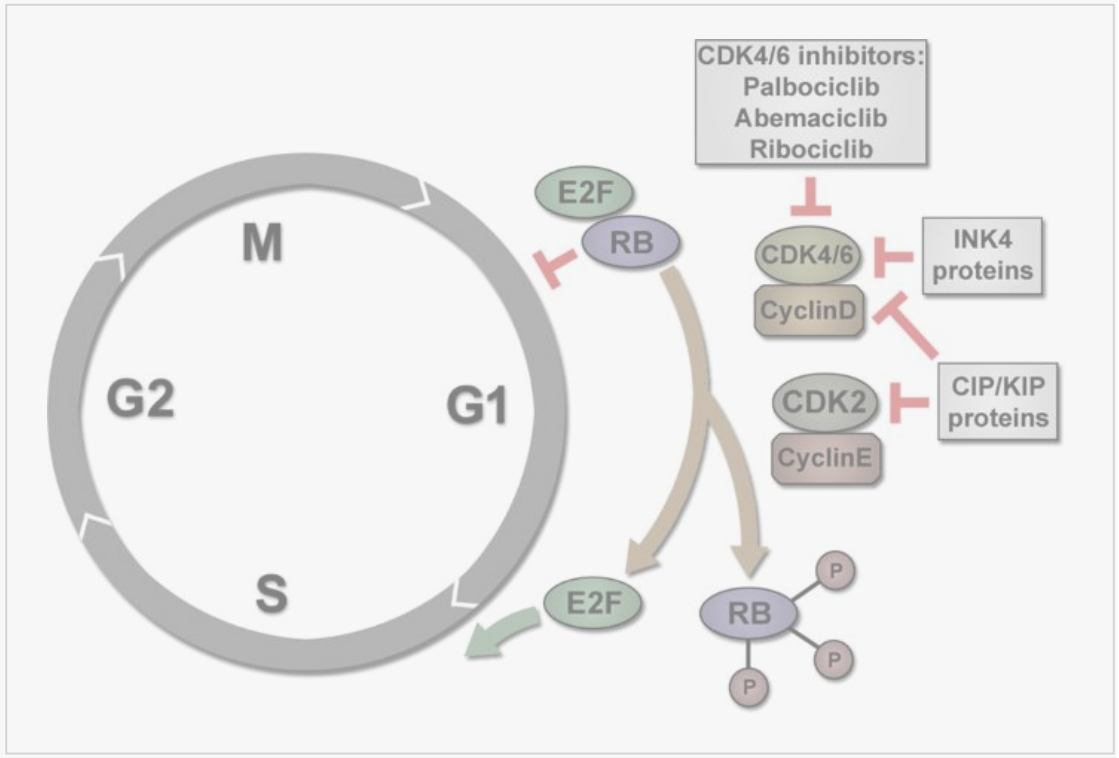
BRAF

BRAF + EGFR in $BRAF^{V600E}$



BRAF and EGFR drive cell differentiation, proliferation and survival through MAPK pathway

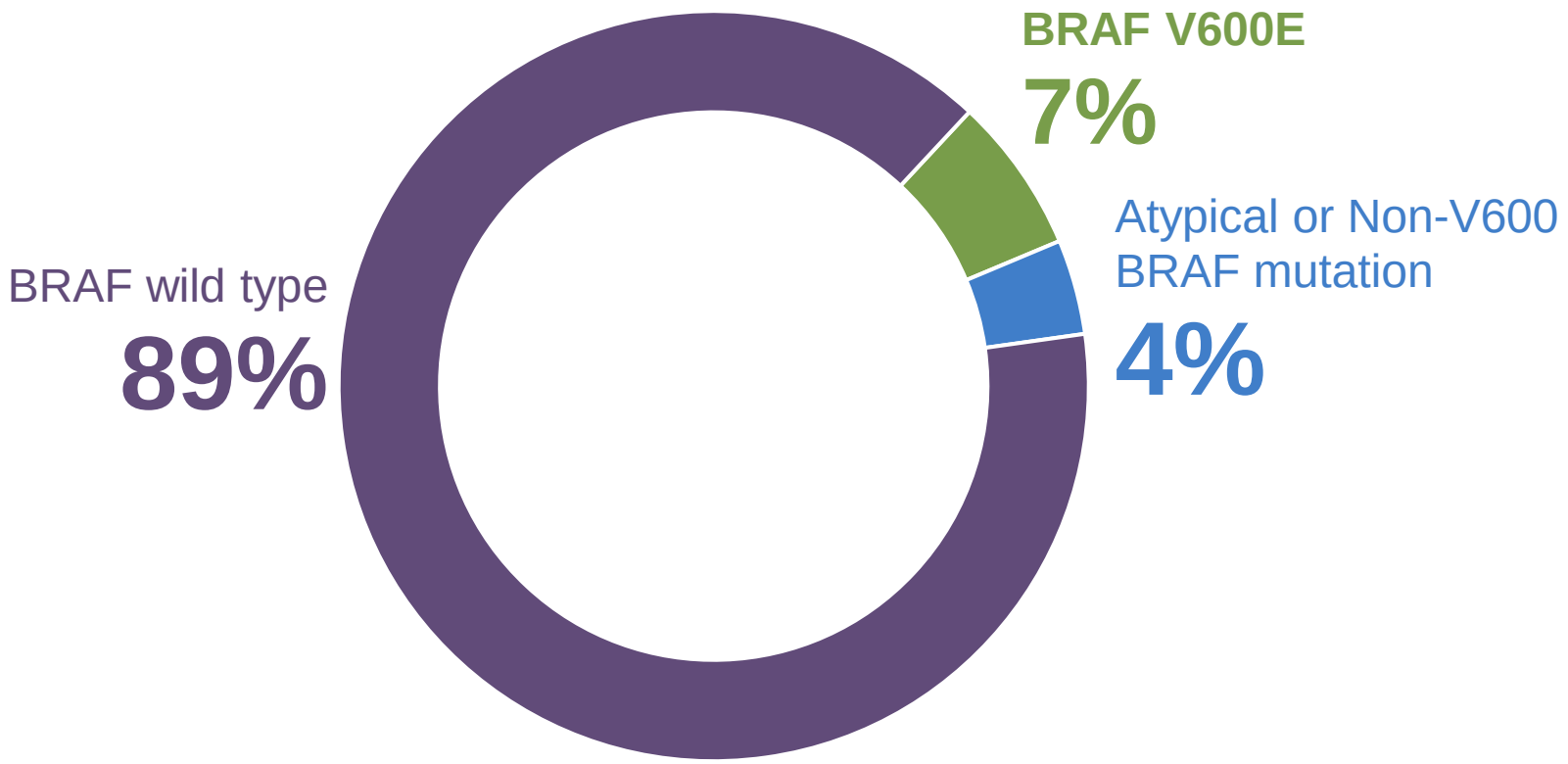
MEK + CDK4/6 in $KRAS^{mut}$



“BRAF Mutations”: V600E and Atypical / Non-V600E

~10%

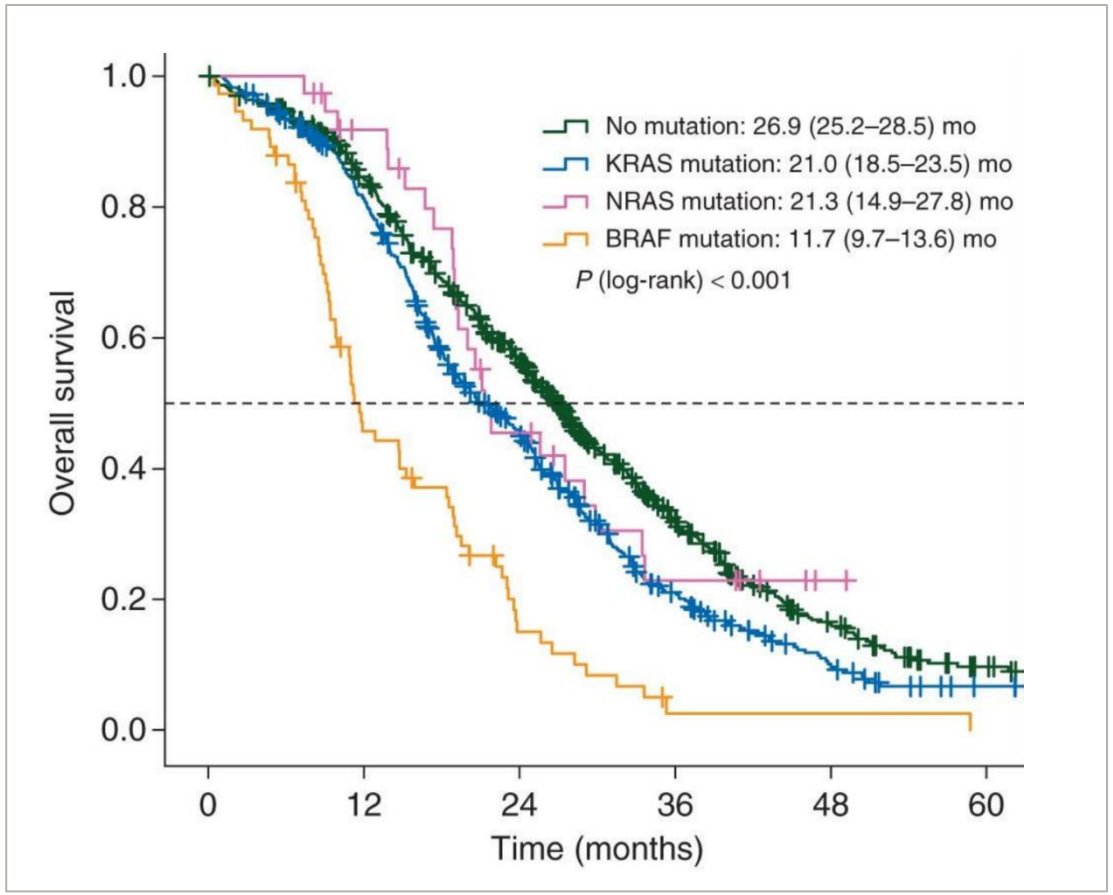
of all CRC patients have a BRAF mutation



Cbioportal; referencing Cancer Cell ‘18

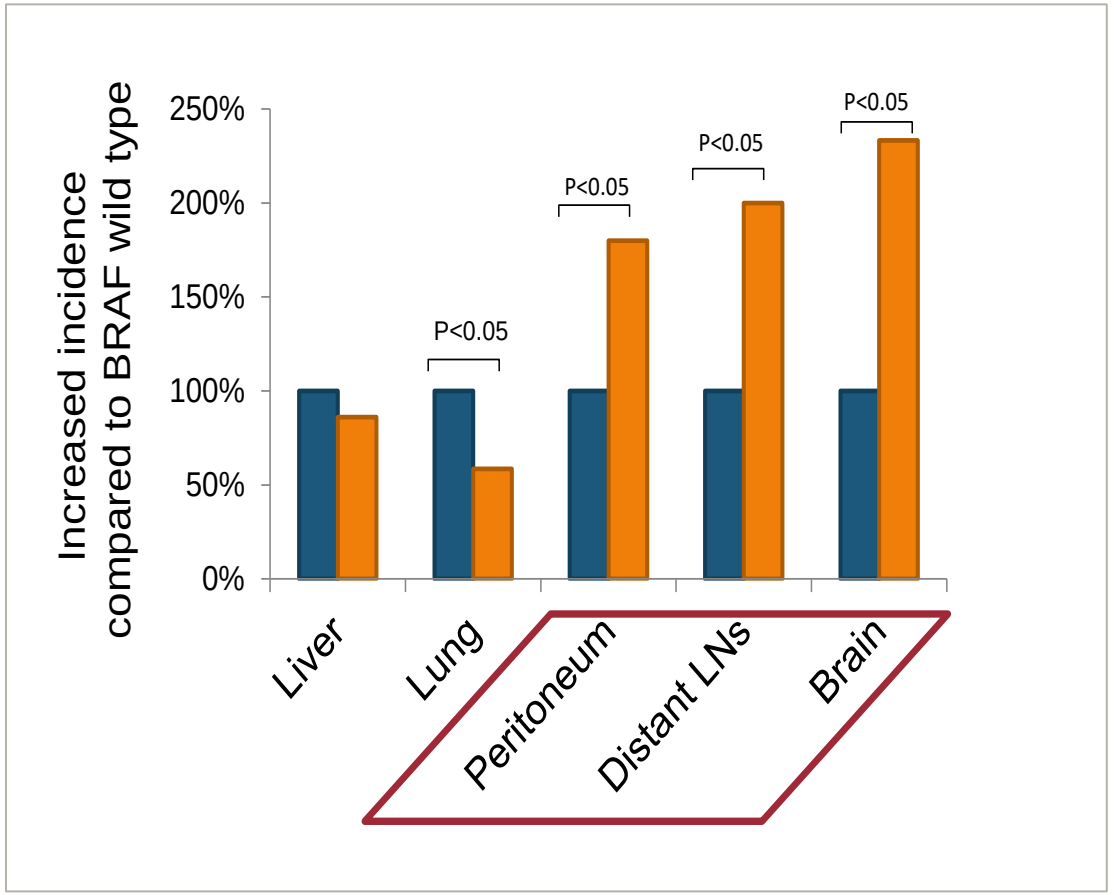
$BRAF^{V600E}$: Poor OS and Atypical Metastases

Overall Survival



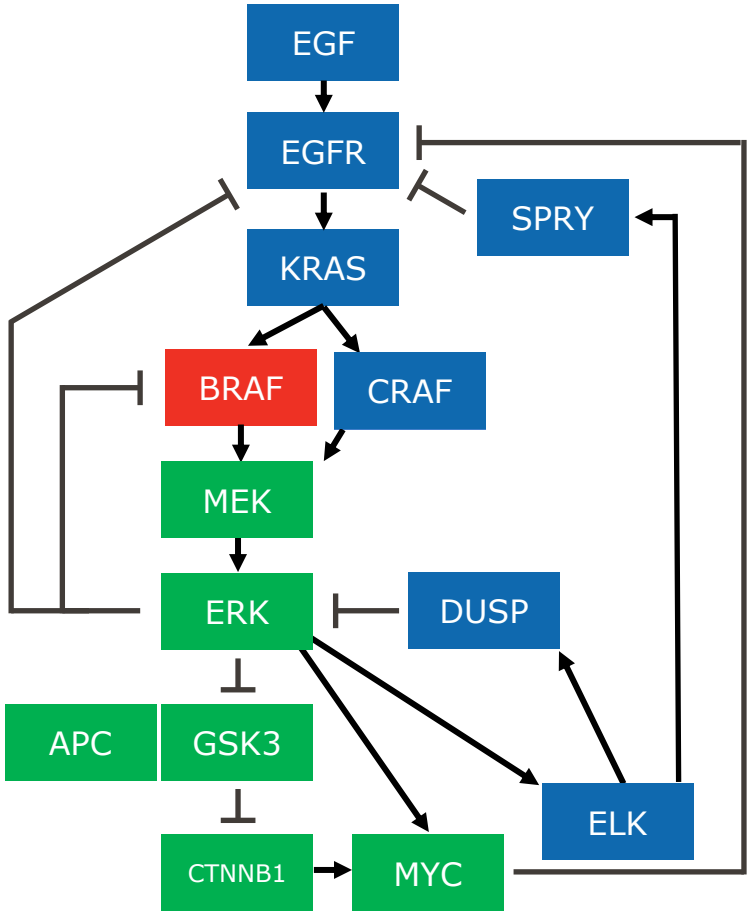
Modest et al Ann Onc '16

Cancer Incidence vs BRAF WT



Morris et al , Clinical Colorectal Cancer '13

Targeting MAPK: Adaptive Resistance with BRAF Inhibition



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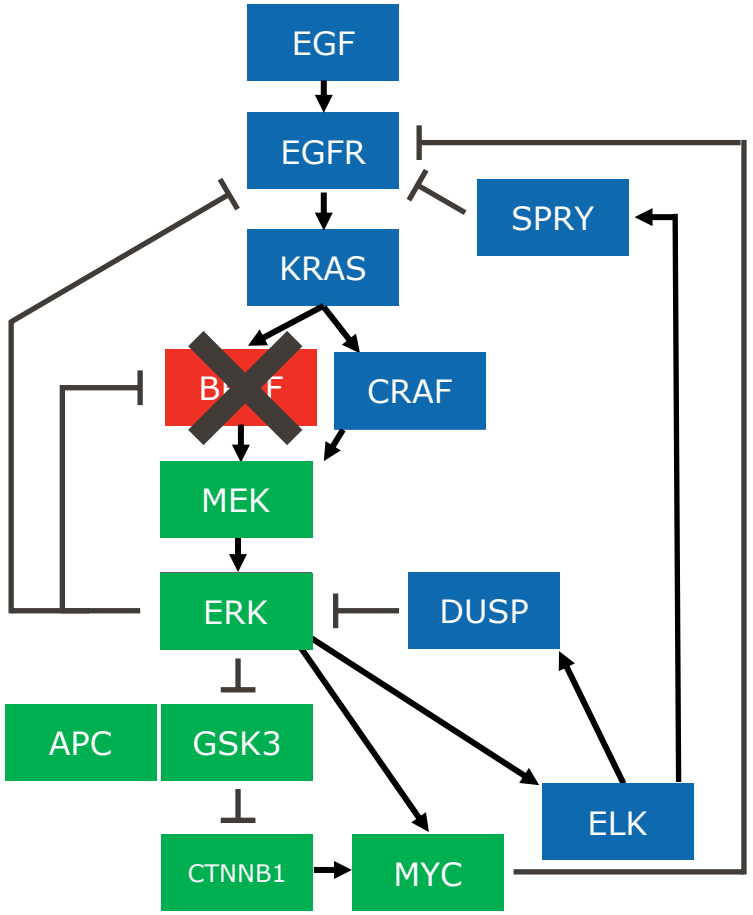
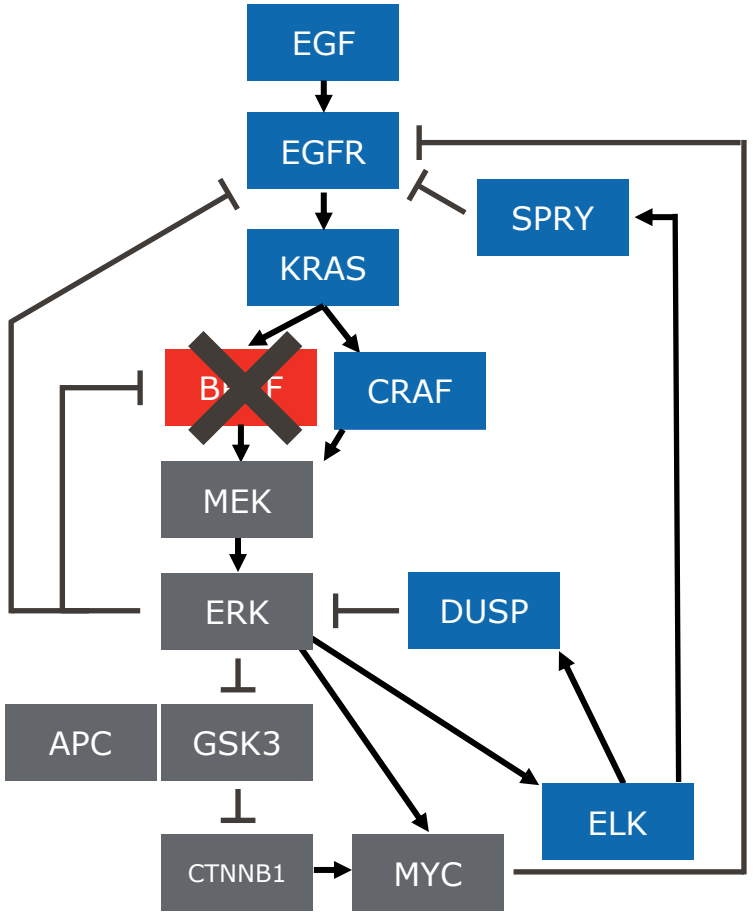


Targeting MAPK: Adaptive Resistance with BRAF Inhibition



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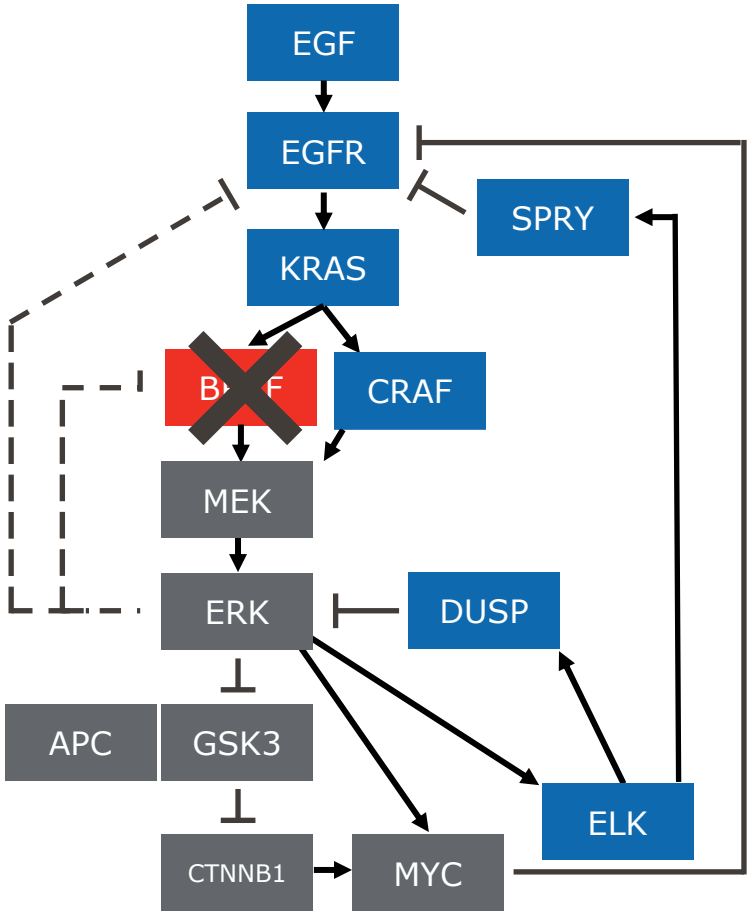

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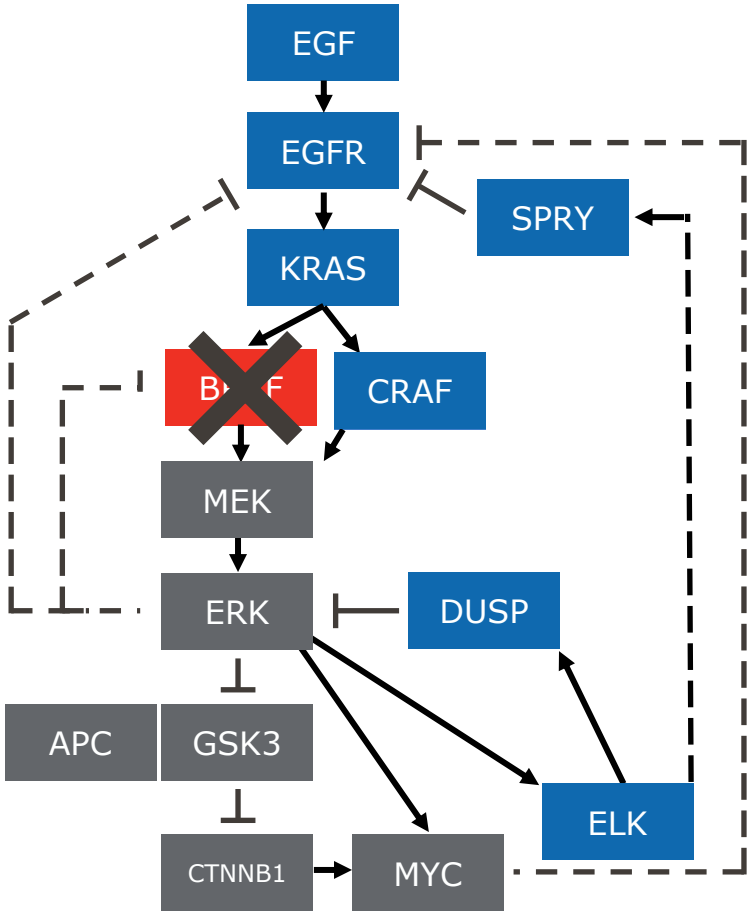

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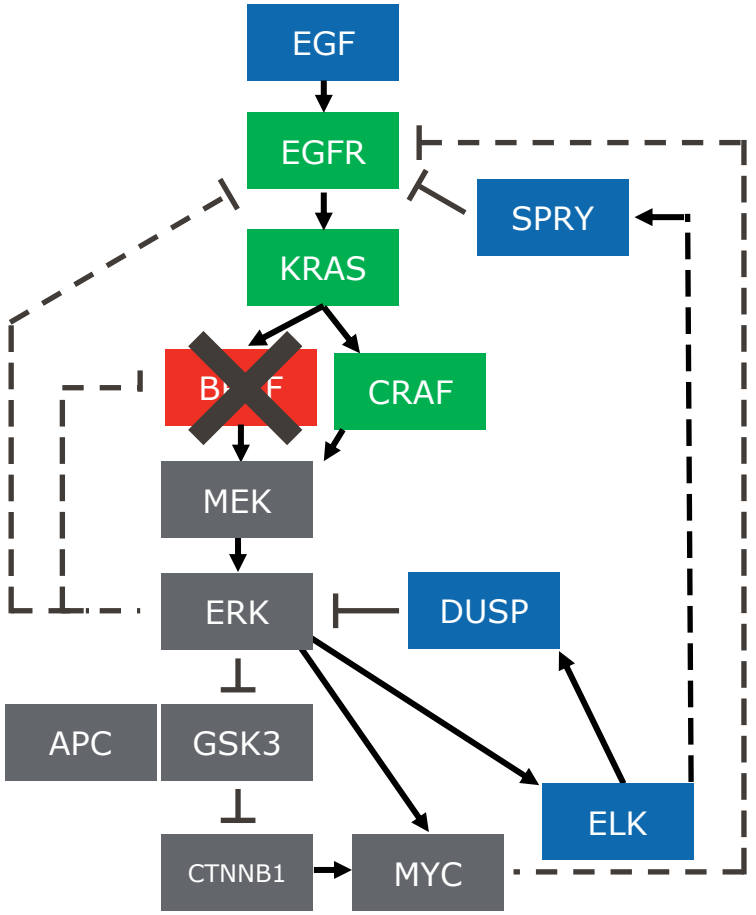

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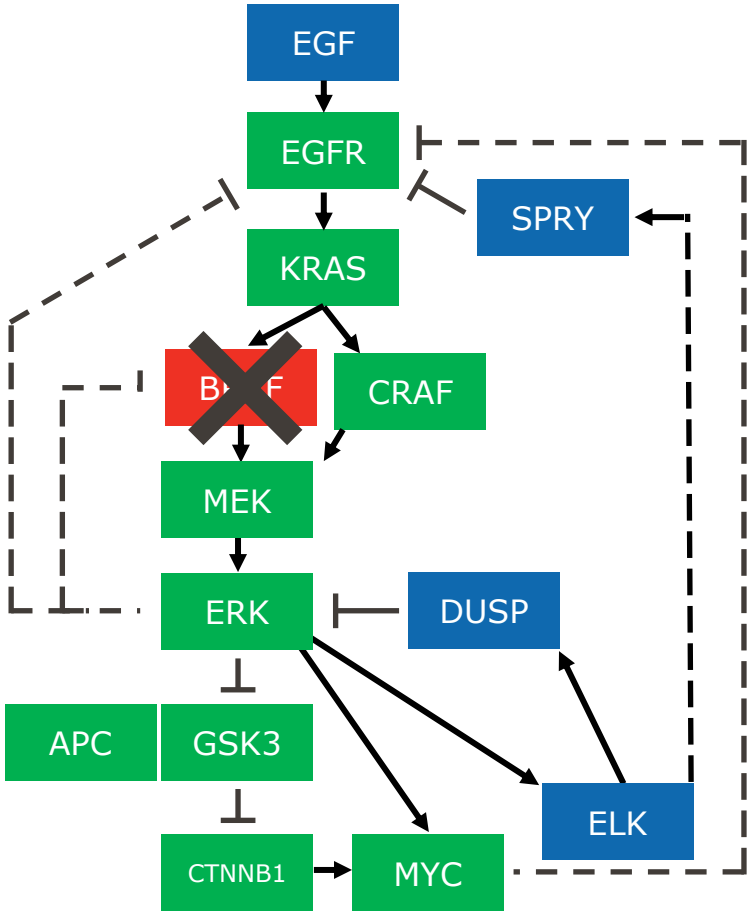
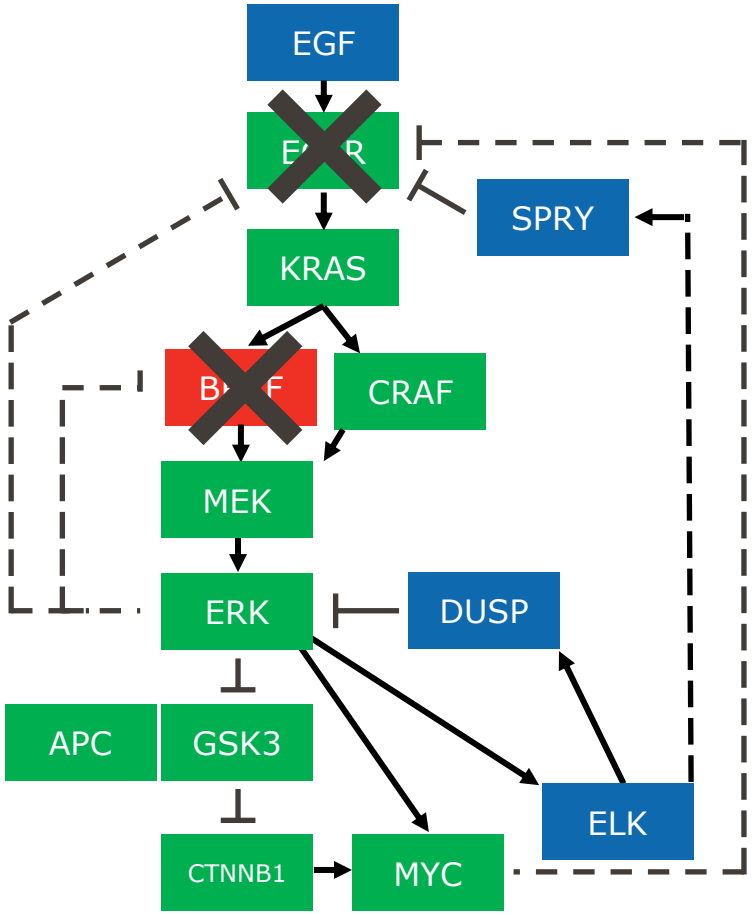


Preventing Adaptive Resistance by Inhibiting EGFR Feedback



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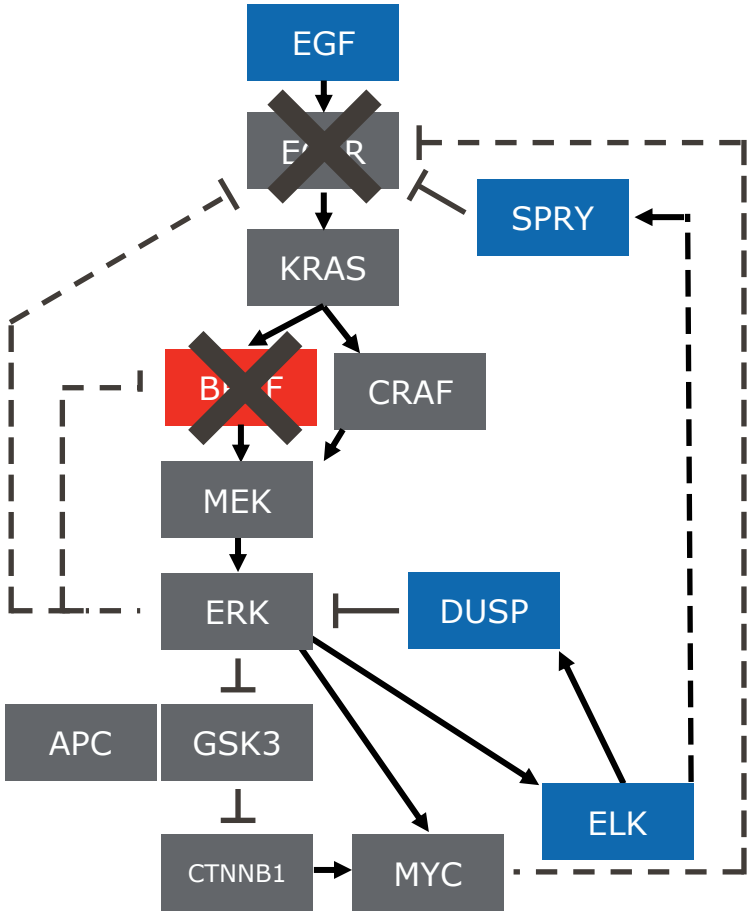
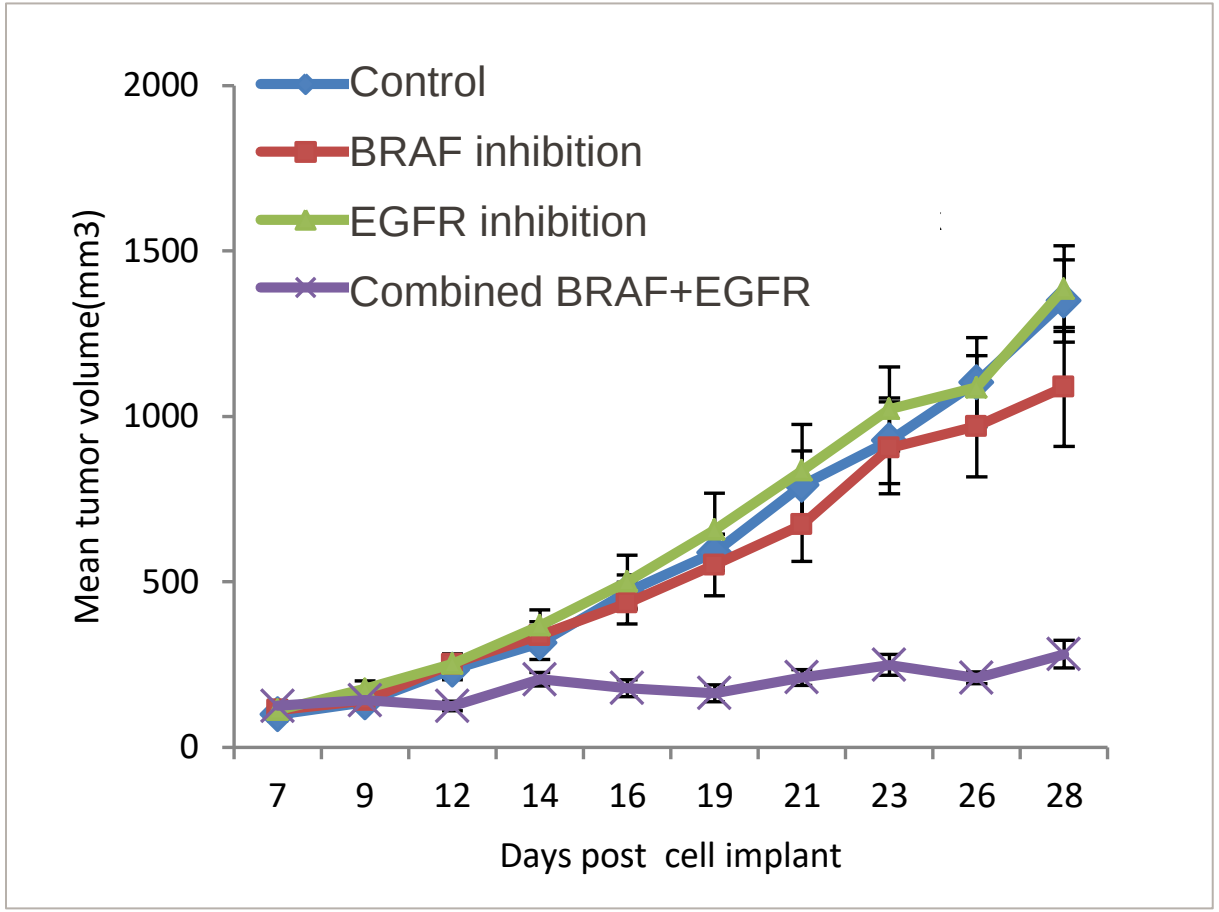
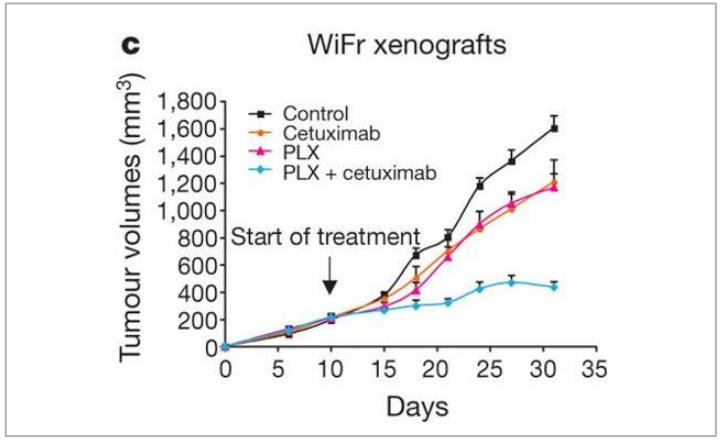
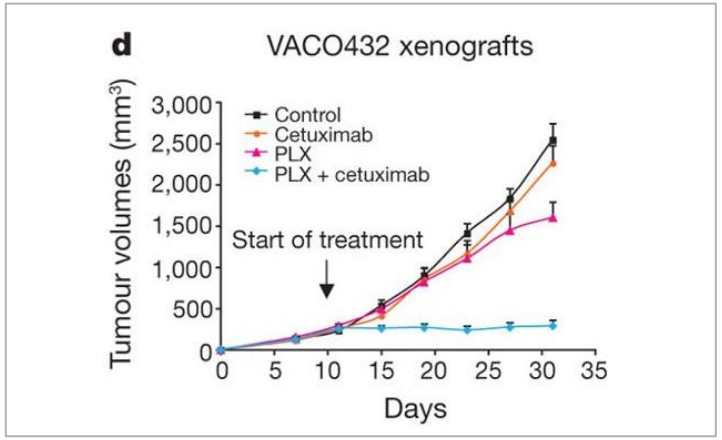


BRAF + EGFR Feedback Inhibition: High Response Rates



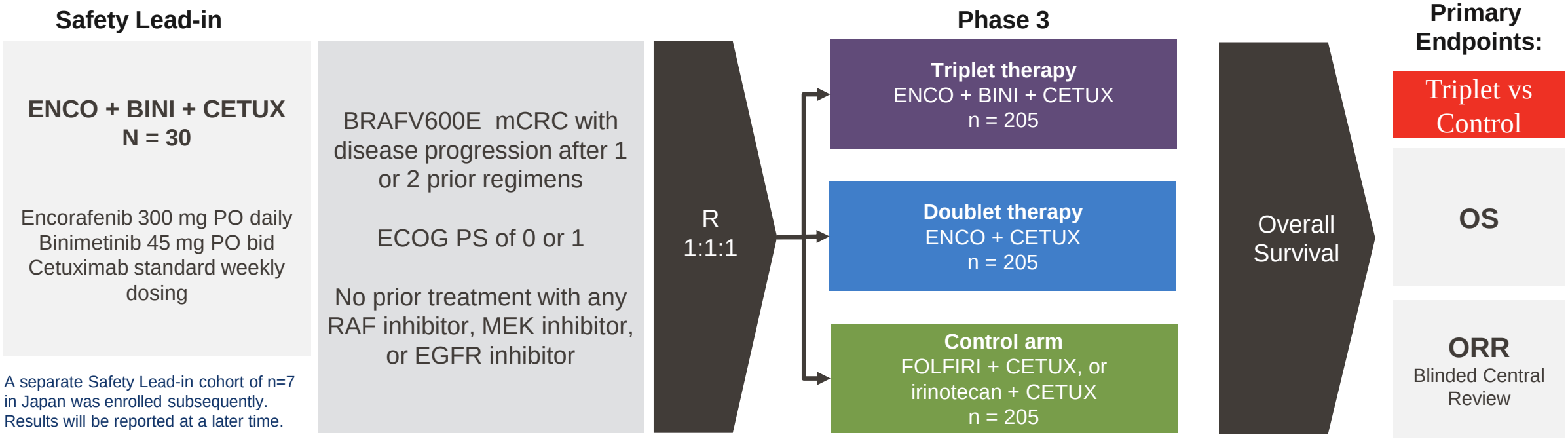




Feng Tian, Van Morris

BEACON Study Design

Results of Safety Lead-In led to the introduction of an additional primary endpoint of ORR and an interim OS analysis to allow for early assessment

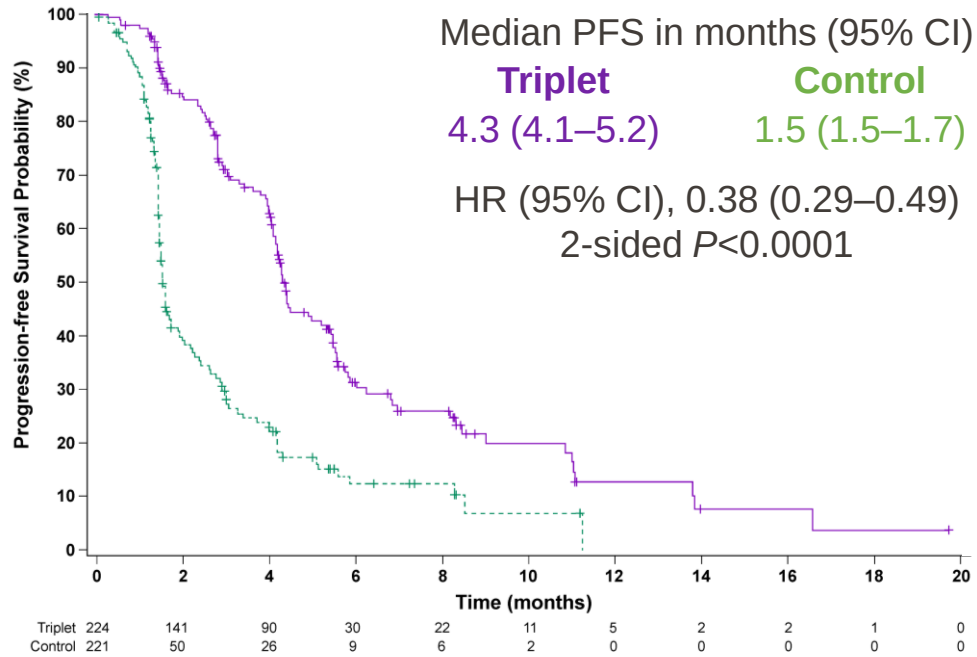


Randomization was stratified by ECOG PS (0 vs. 1), prior use of irinotecan (yes vs. no), and cetuximab source (US-licensed vs. EU-approved).

Secondary Endpoints: Doublet vs Control OS & ORR, PFS, Safety

PFS Still 4 months, and not Improved with Addition of MEKi

Triplet vs Control

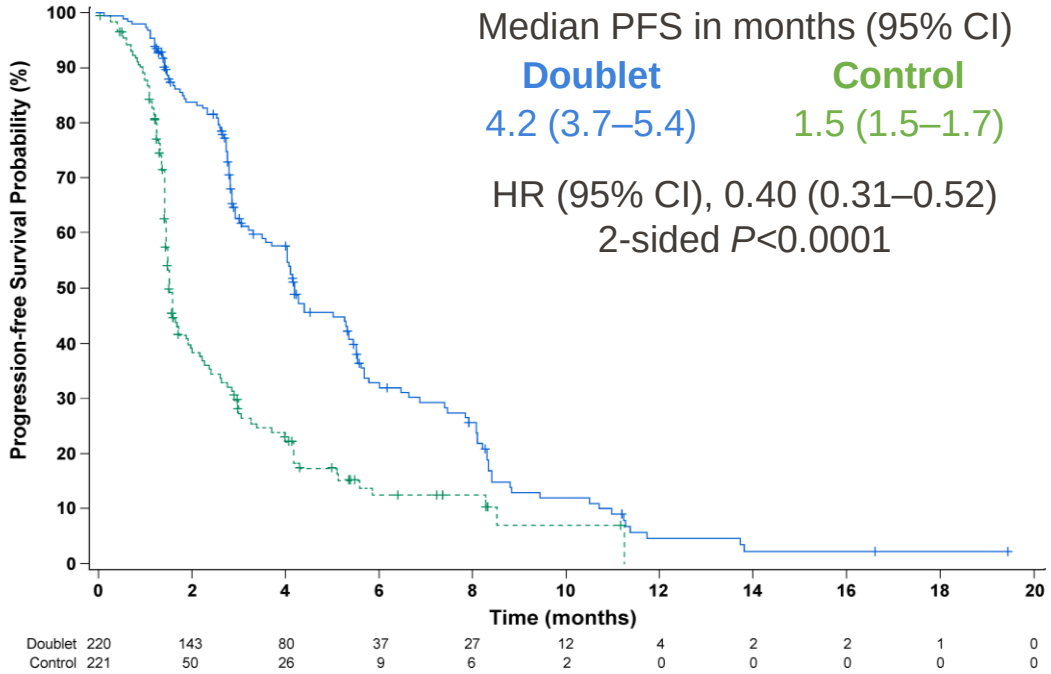


Median PFS in months (95% CI)

Triplet	Control
4.3 (4.1–5.2)	1.5 (1.5–1.7)

HR (95% CI), 0.38 (0.29–0.49)
2-sided *P*<0.0001

Doublet vs Control



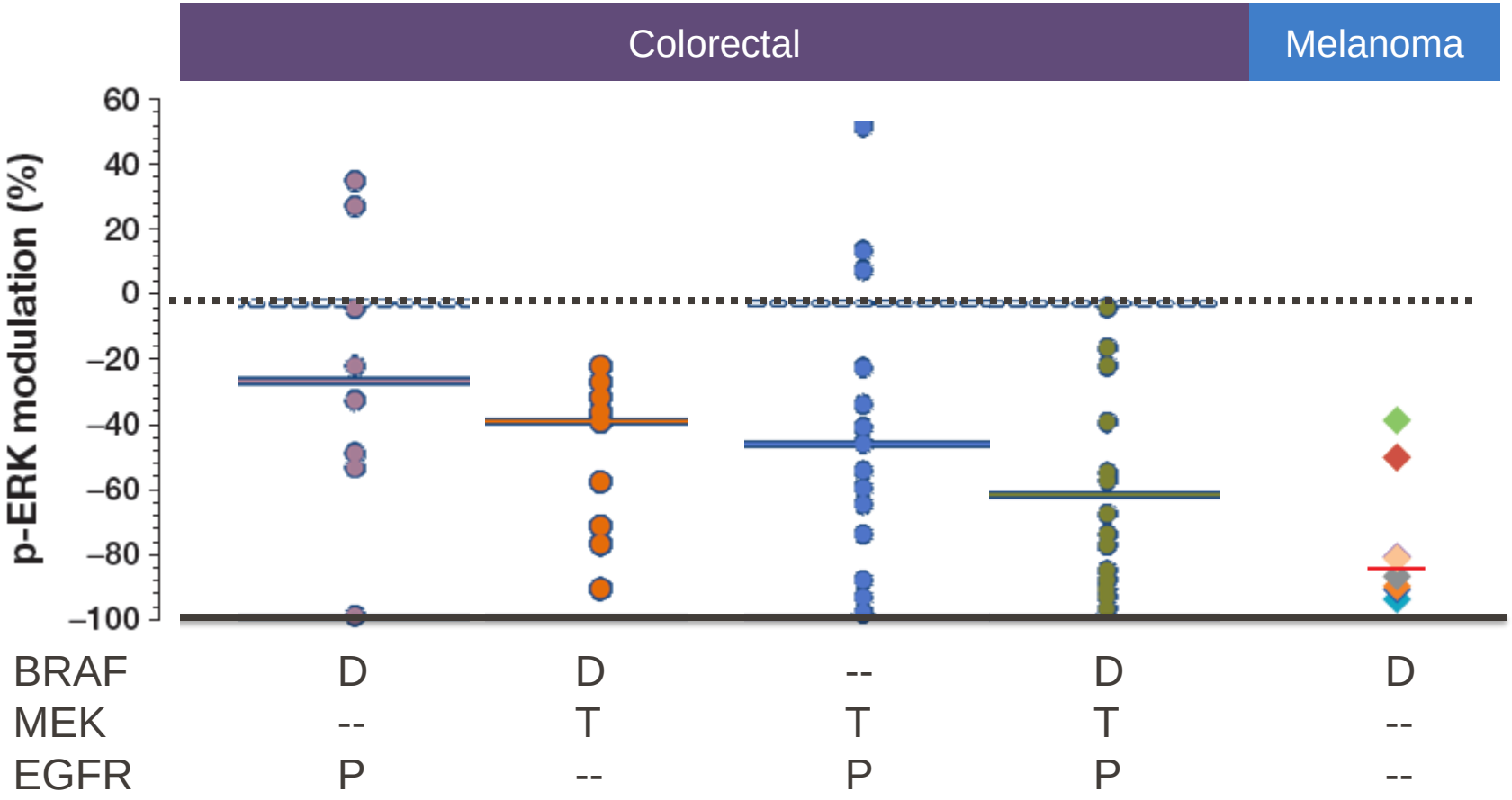
Median PFS in months (95% CI)

Doublet	Control
4.2 (3.7–5.4)	1.5 (1.5–1.7)

HR (95% CI), 0.40 (0.31–0.52)
2-sided *P*<0.0001

*PFS by BICR (blinded independent central review)

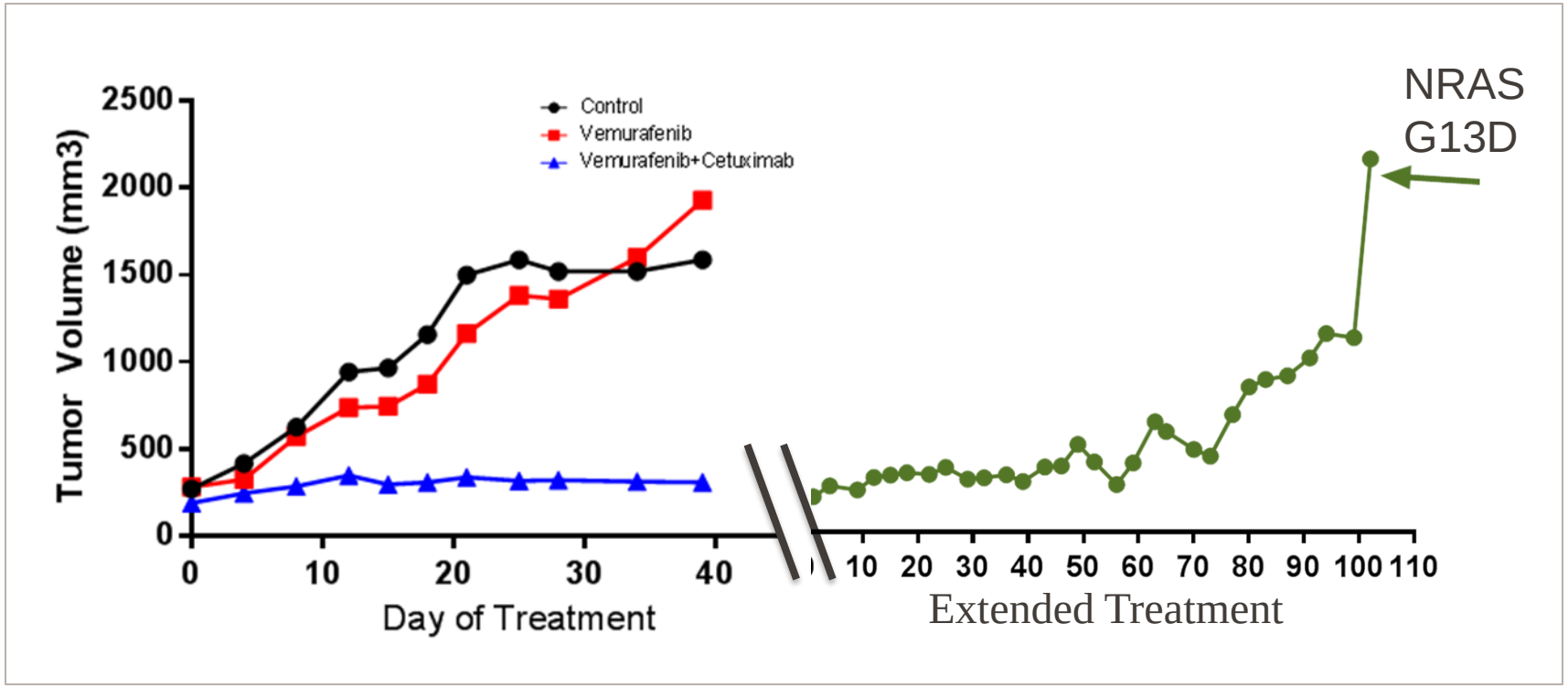
Cross-Study Comparison: Combination Therapy Does Not Inhibit pERK to Level Seen in Melanoma



Atreya et al ASCO ‘16, Updated Corcoran et al Cancer Discovery ‘18

Resistance to BRAFi + Cetuximab is Associated with MAPK Pathway Reactivation

Tumor Volume



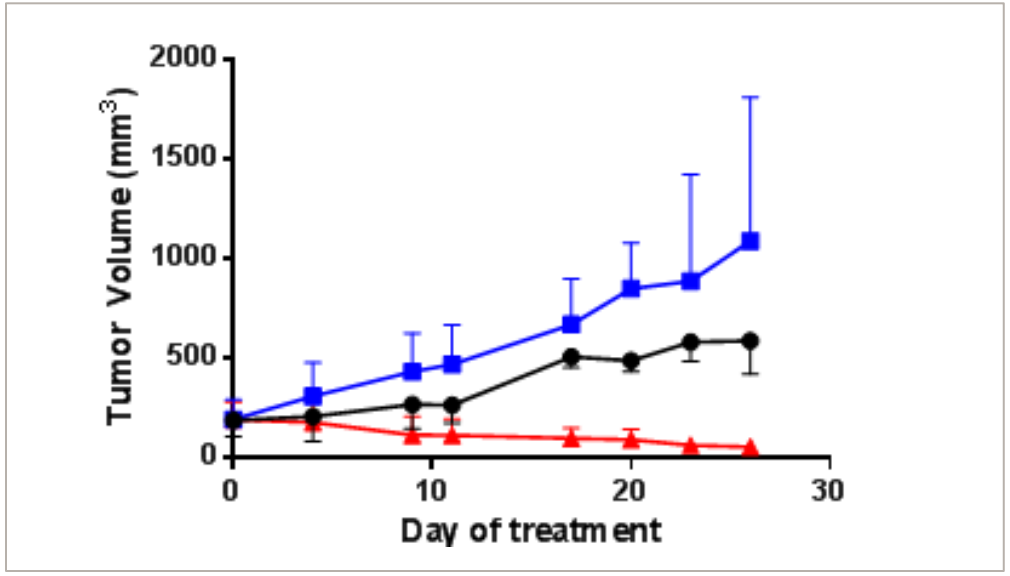
PDX	Acquired Mutation
1	KRAS G12D
2	KRAS G12R
3	NRAS G12D
4	MEK1 L42F
5	MEK1 F53V
6	MEK1 E203K
7	EGFR Y869C
8	NRAS G13D

Kopetz et al JCO ‘15

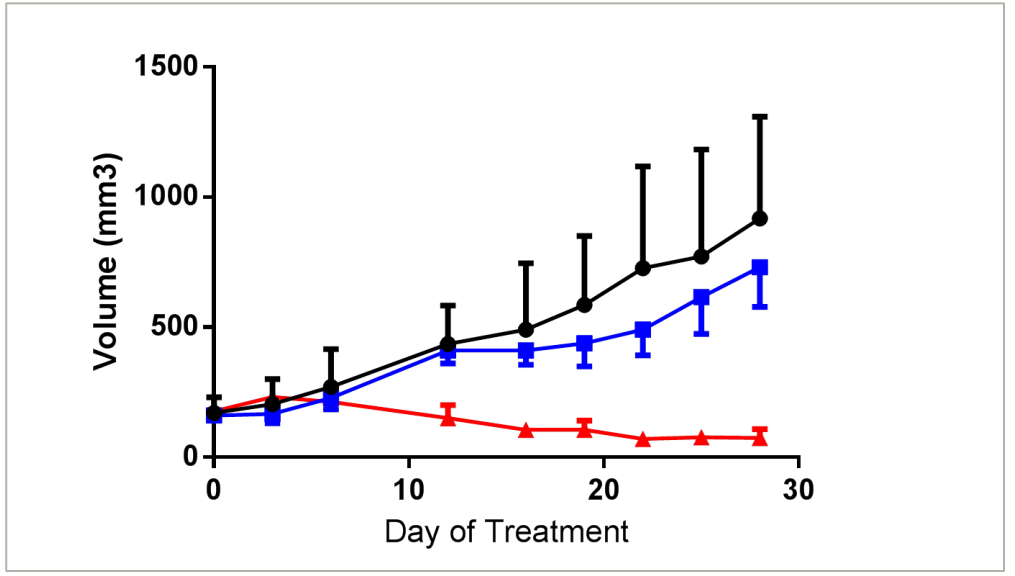
$BRAF^{V600E}/KRAS^{mut}$: High Dose MEK+EGFR Inhibition

PDX model

$BRAF^{V600E}/KRAS^{G12R}$



$BRAF^{V600E}/KRAS^{G12D}$

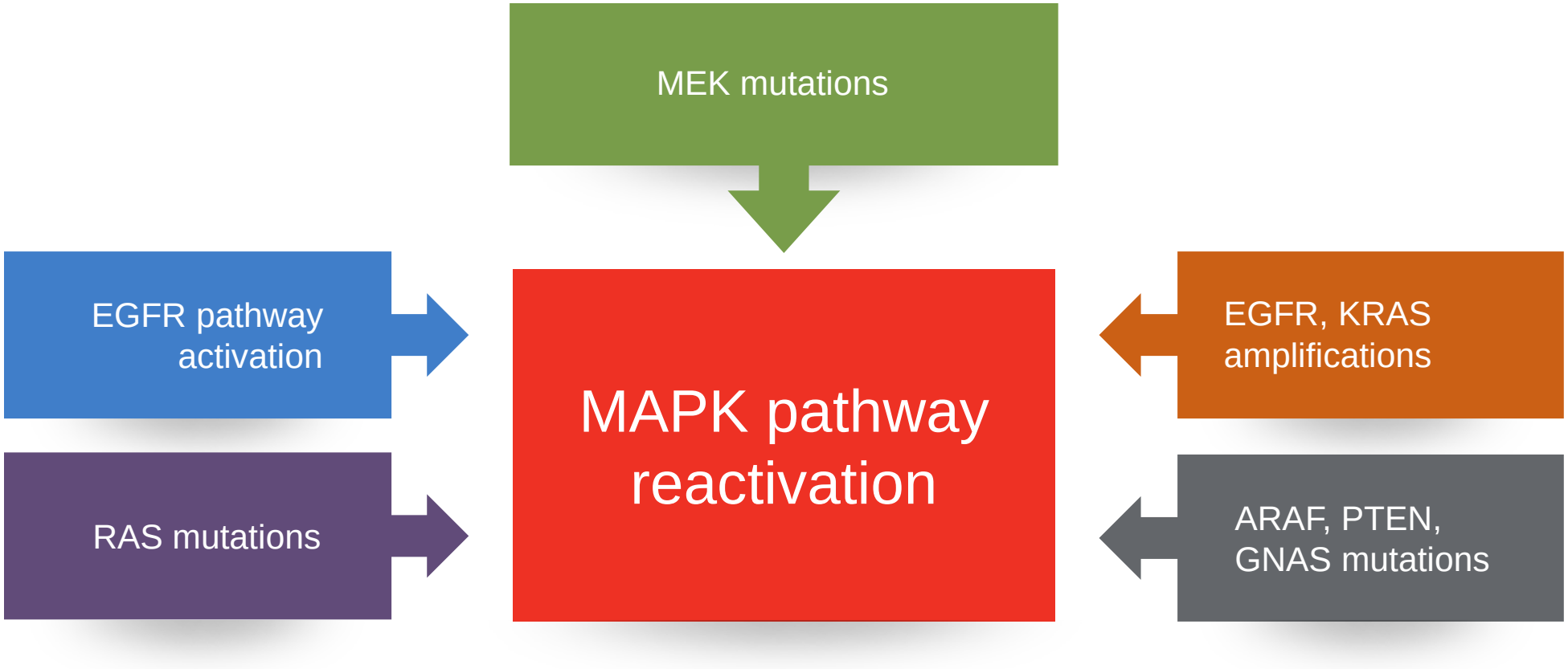


Control
Vemurafenib +cetuximab
Trametinib + cetuximab

These acquired RAS models are **still sensitive to high dose MAPK inhibition**

Resistance to BRAF + EGFR

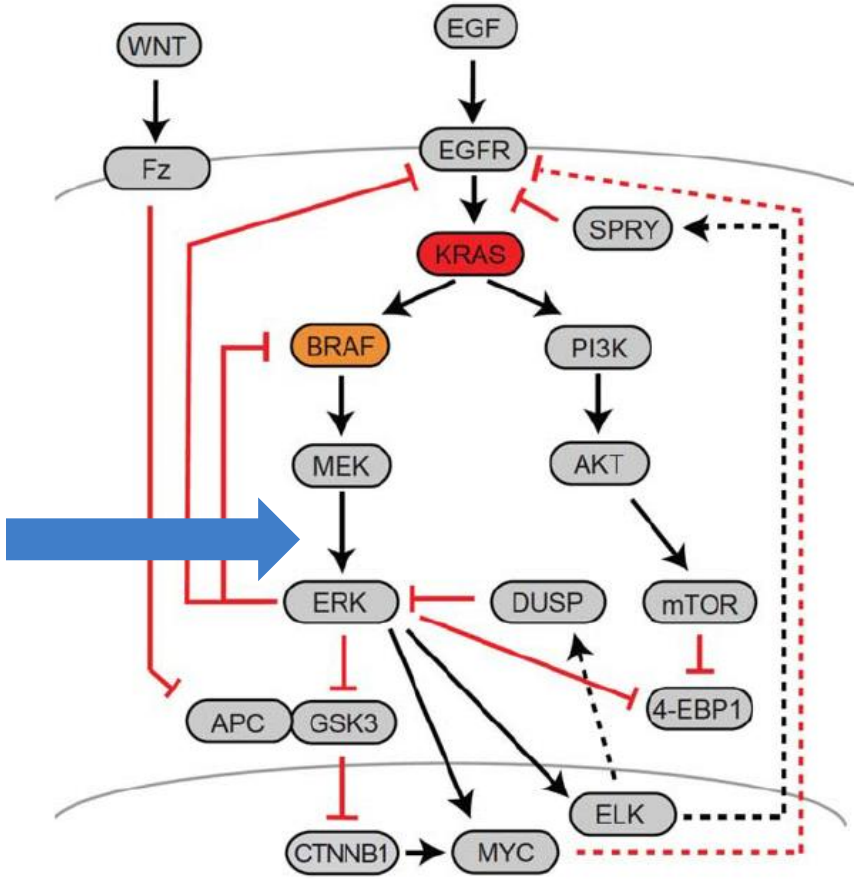
*Another example of **convergent evolution** in colorectal cancer resistance to targeted therapy*



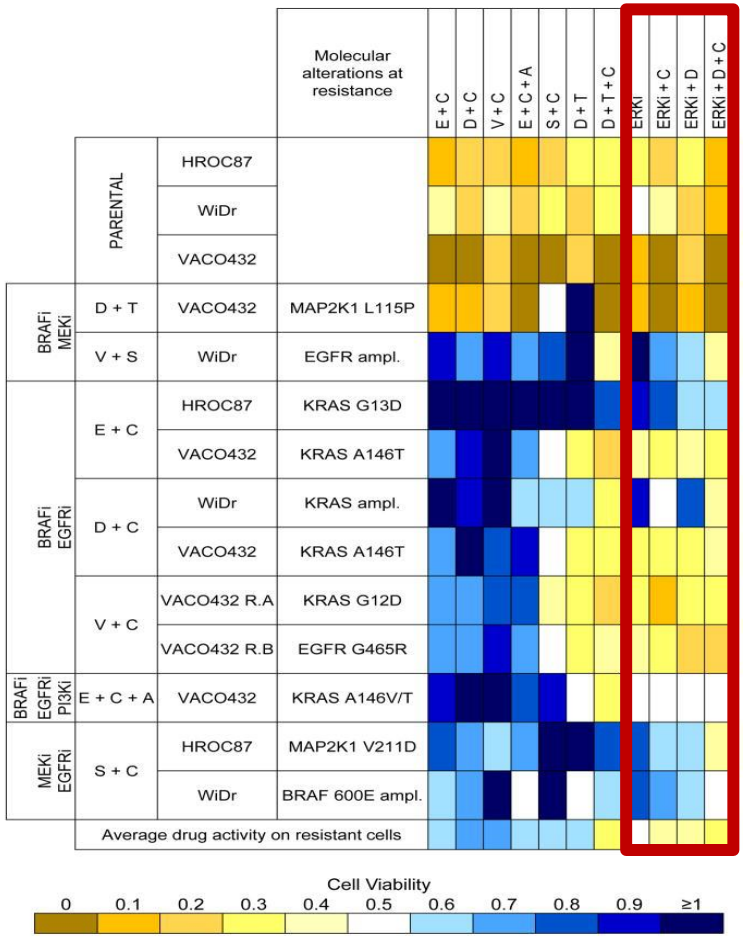
Ahronian et al Cancer Discovery ‘15; Misale et al Nat Comm ‘15

ERK Inhibition to Intercept MAPK Reactivation

Inhibition Nodes for MAPK Reactivation



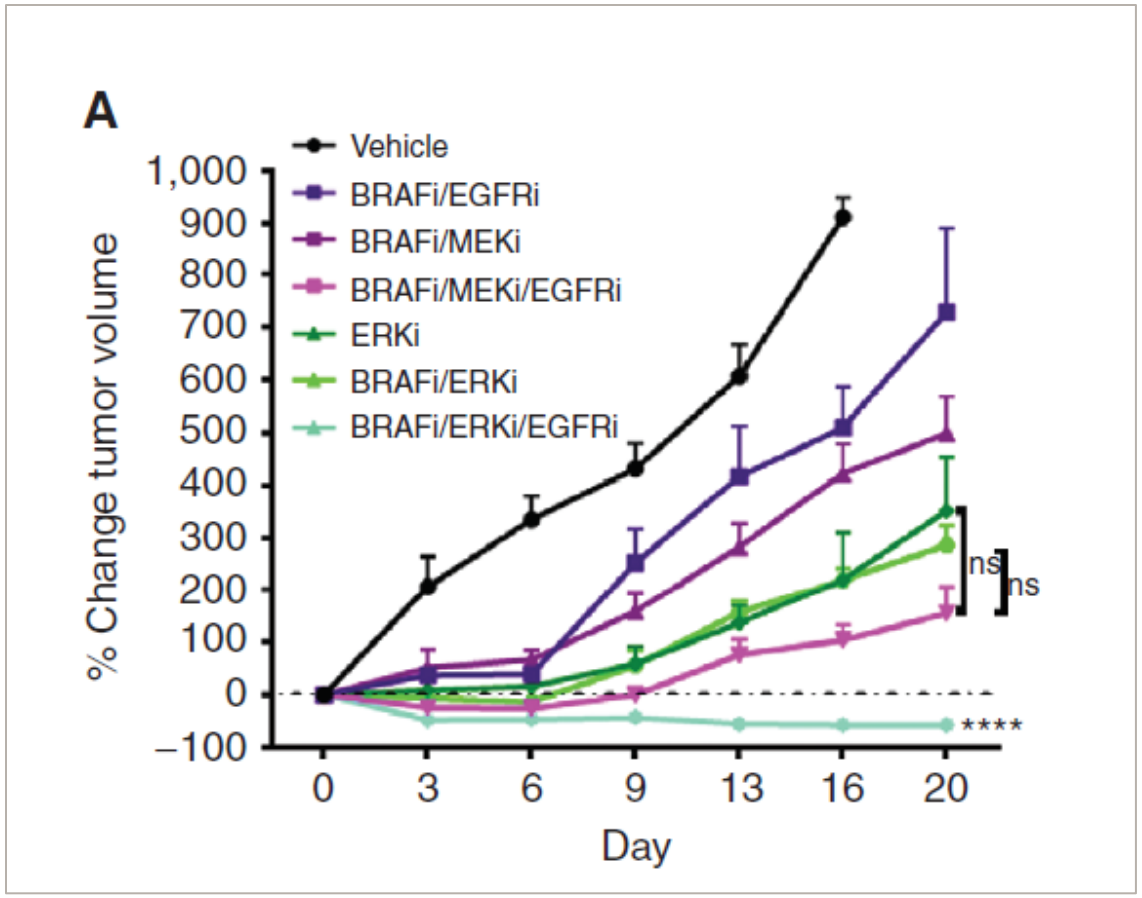
Cell Death by Molecular Resistant Alterations After Combination Treatment

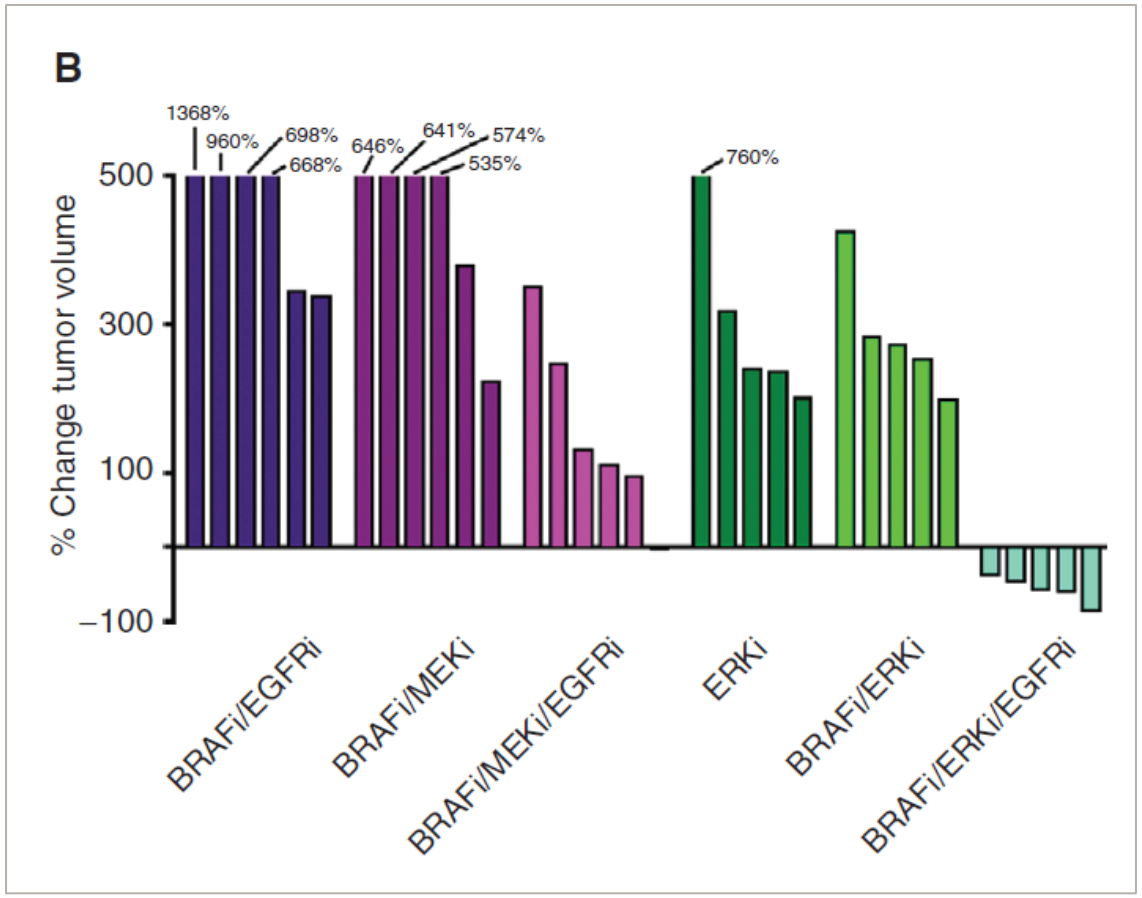


Oddo et al Can Res ‘16

ERK Inhibition, Combined with BRAF and EGFR, May Delay Development of MAPK Reactivation

Change in tumor volume

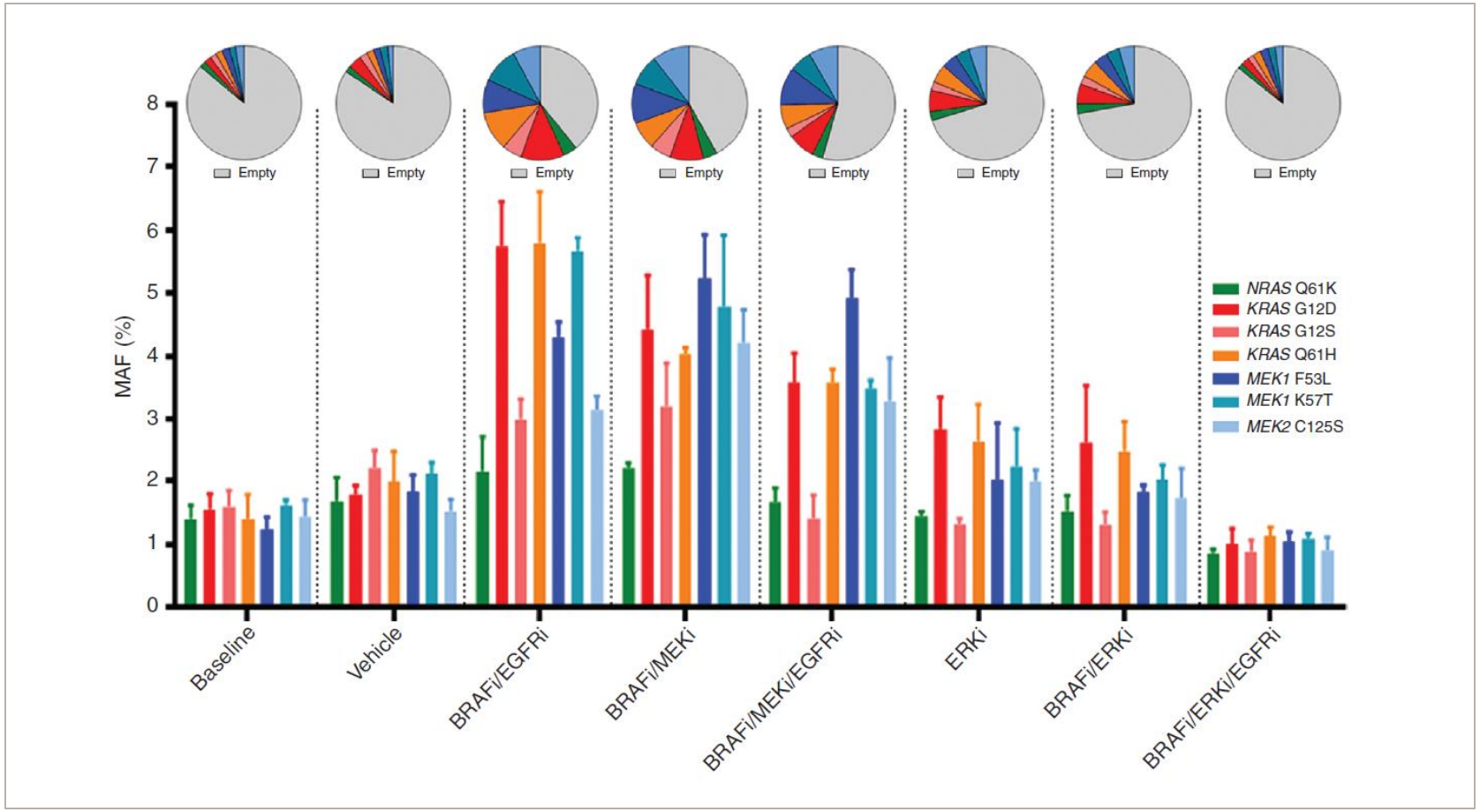




Hazar-Rethinam et al CCR ‘18

ERK, BRAF, EGFR: Suppression of RAS Outgrowth

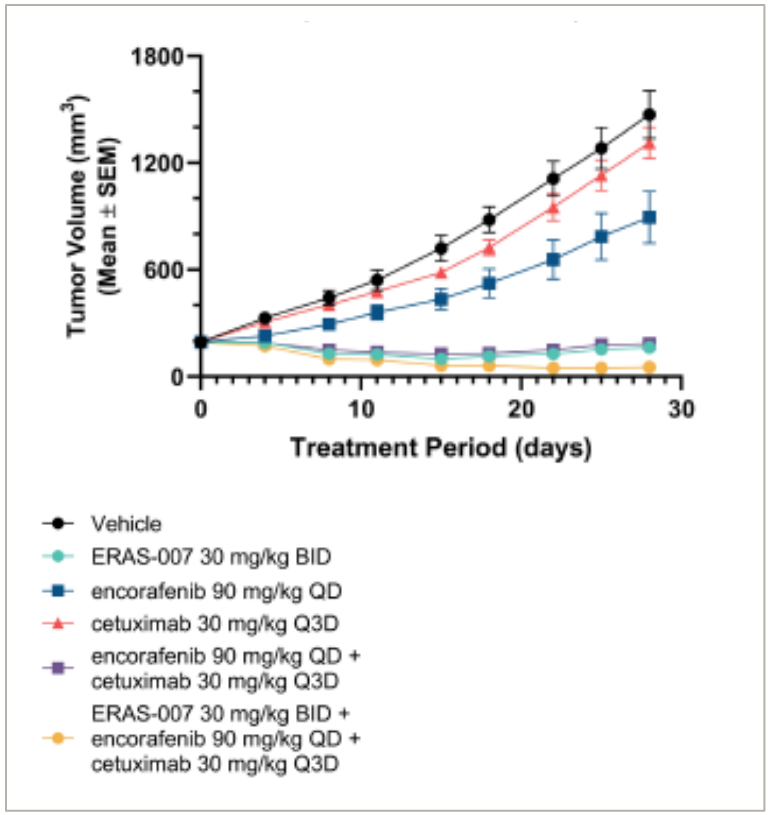
Rationale for triple combination of BRAF/ERK/EGFR inhibition

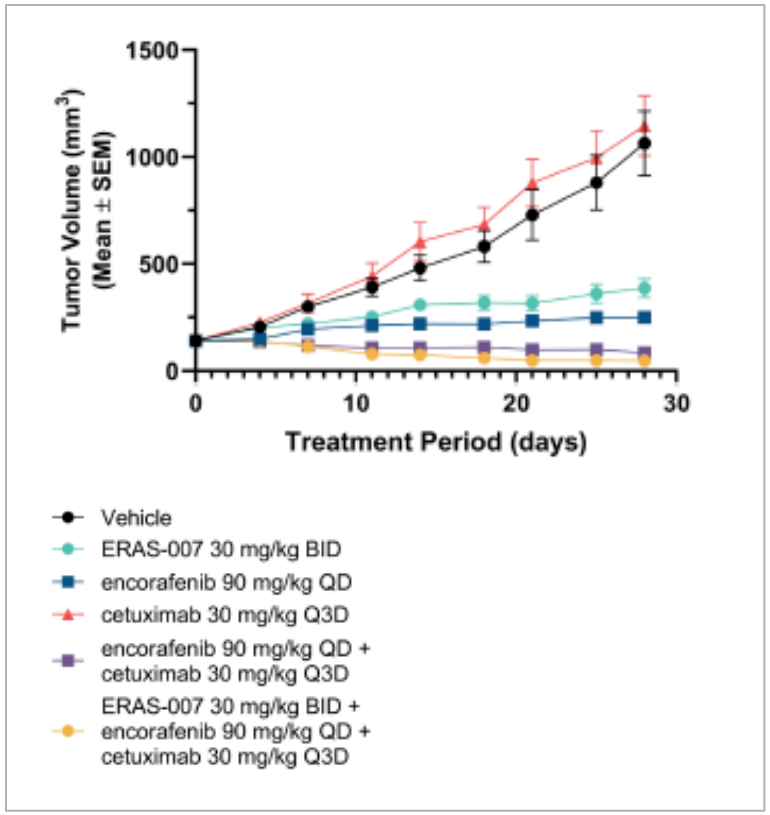


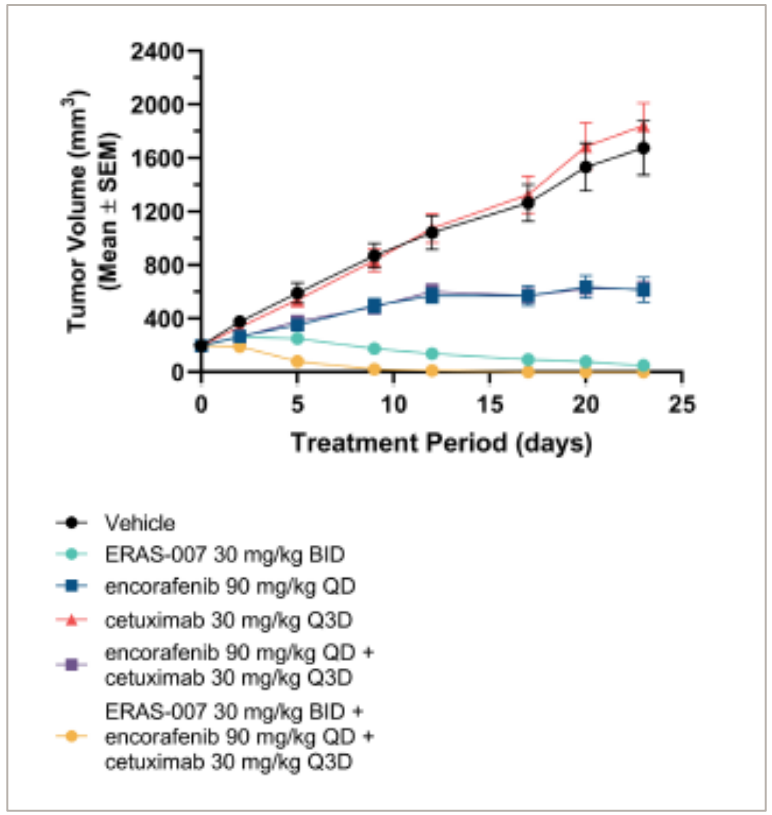
Hazar-Rethinam et al CCR ‘18

In vivo Data Support Efficacy of ERAS-007 in Combination

WiDr	CR0004	CRC1011
CRC CDX; BRAF^{V600E}	*CRC CDX; BRAF^{V600E}*	*CRC PDX; BRAF^{V600E}*





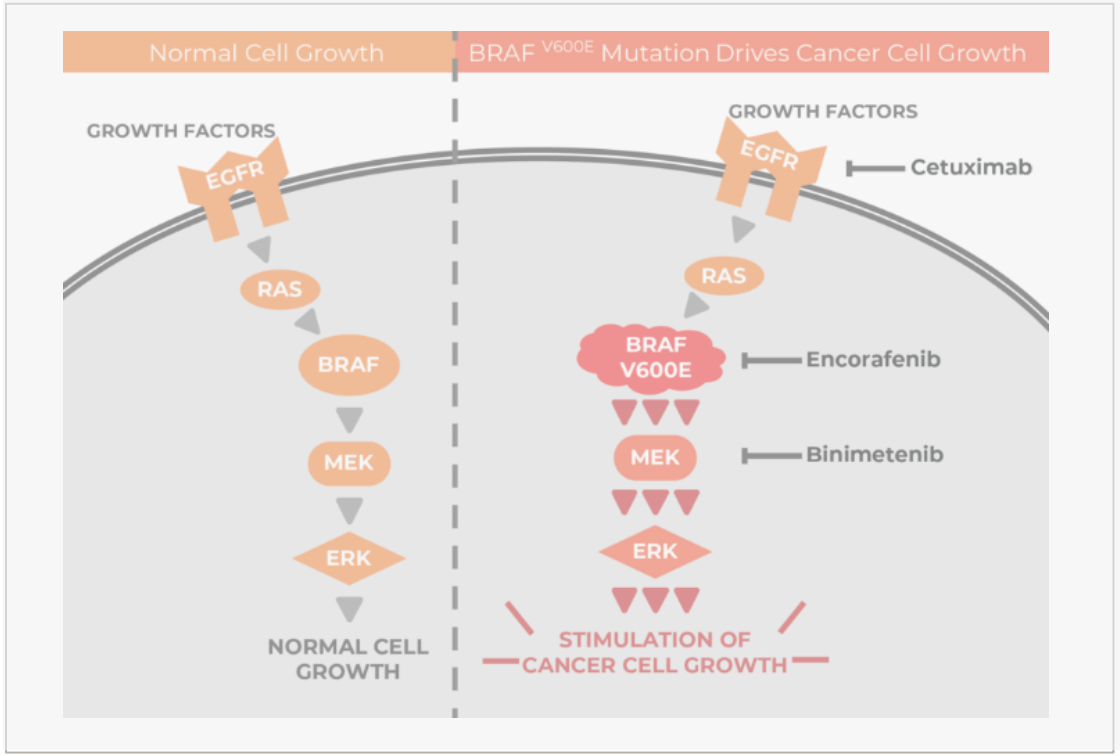


Erin D. Lew et al, AACR 2672, ERAS-007 is a selective ERK1/2 inhibitor with preclinical activity across RAS/MAPK pathway-driven CRC models

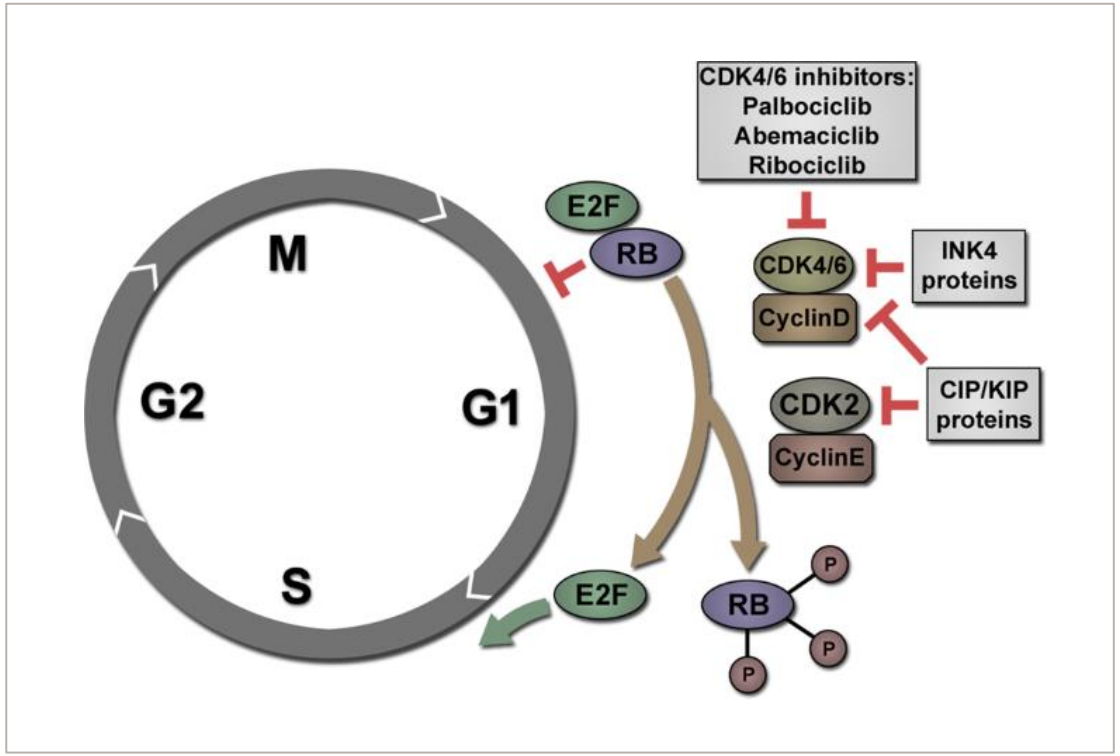
Tackling Adaptive Resistance in CRC: Two Examples

MEK/ERK

BRAF + EGFR in $BRAF^{V600E}$

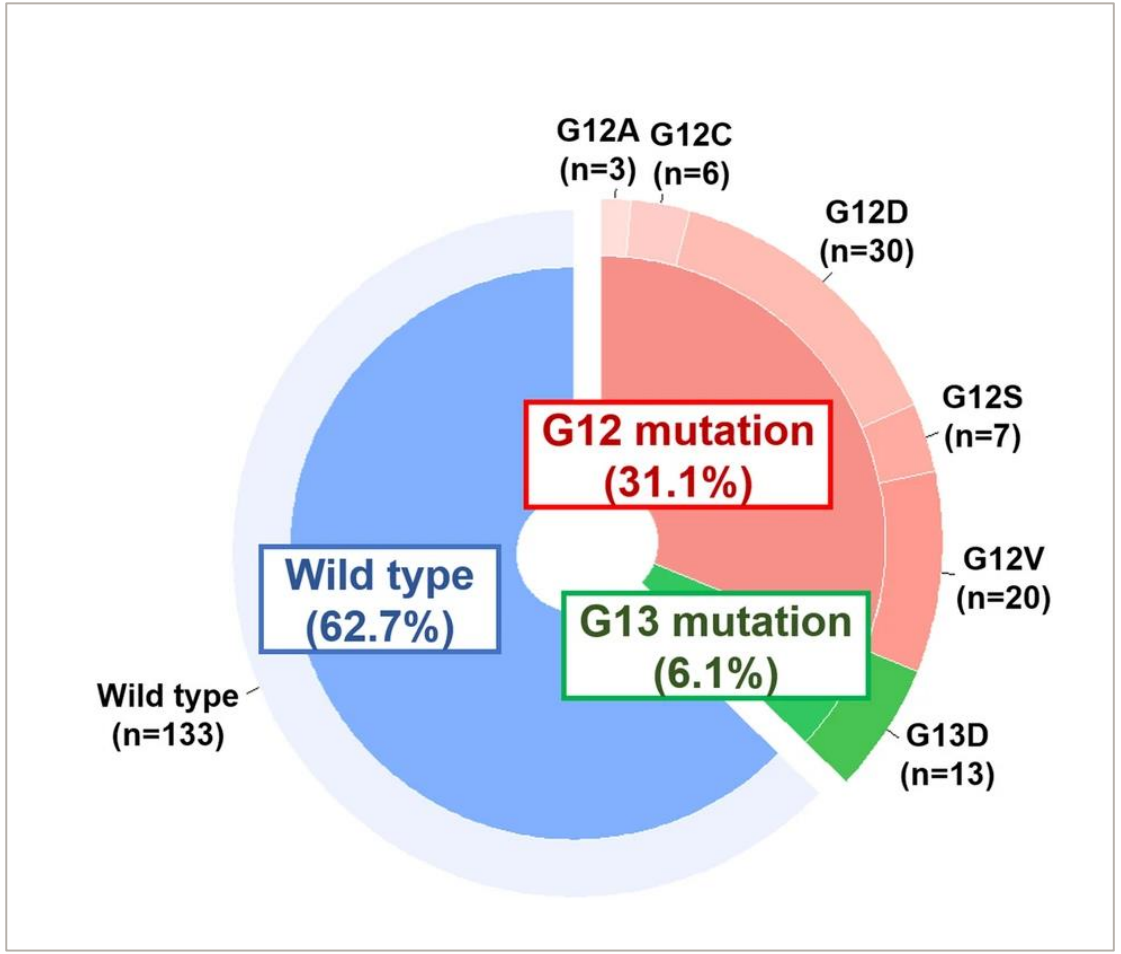


MAPKi + CDK4/6 in $KRAS^{mut}$



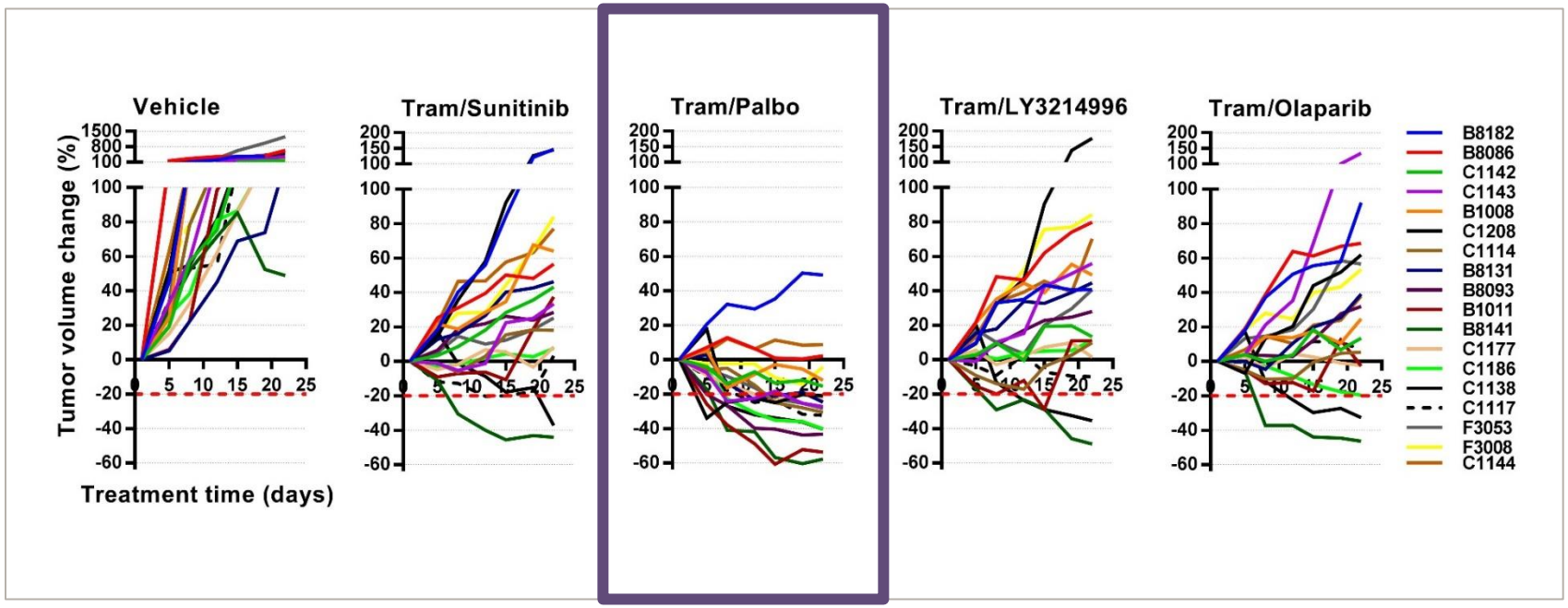
RAS Mutated CRC Remains a Critical Unmet Need

- There are **no directed therapies** available, aside from 2-3% of patients with KRAS G12C
- RAS mutations (KRAS/NRAS) **define lack of benefit** from anti-EGFR antibodies
- **~50% of patients** have RAS mutations (40-45% KRAS, 5-10% NRAS) = 25,000 mCRC pts/yr in US alone

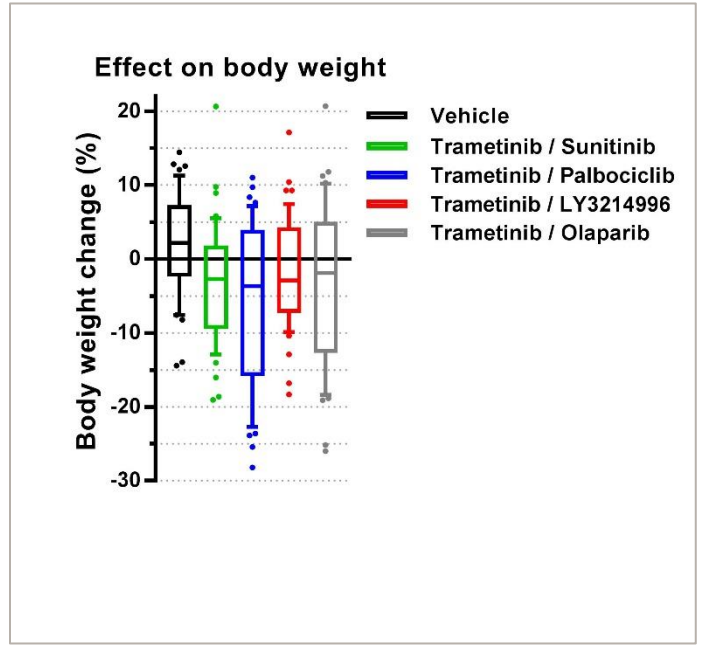


Evaluating MEK Inhibitor-Based Combinations: 2nd Stage Results

PDX models

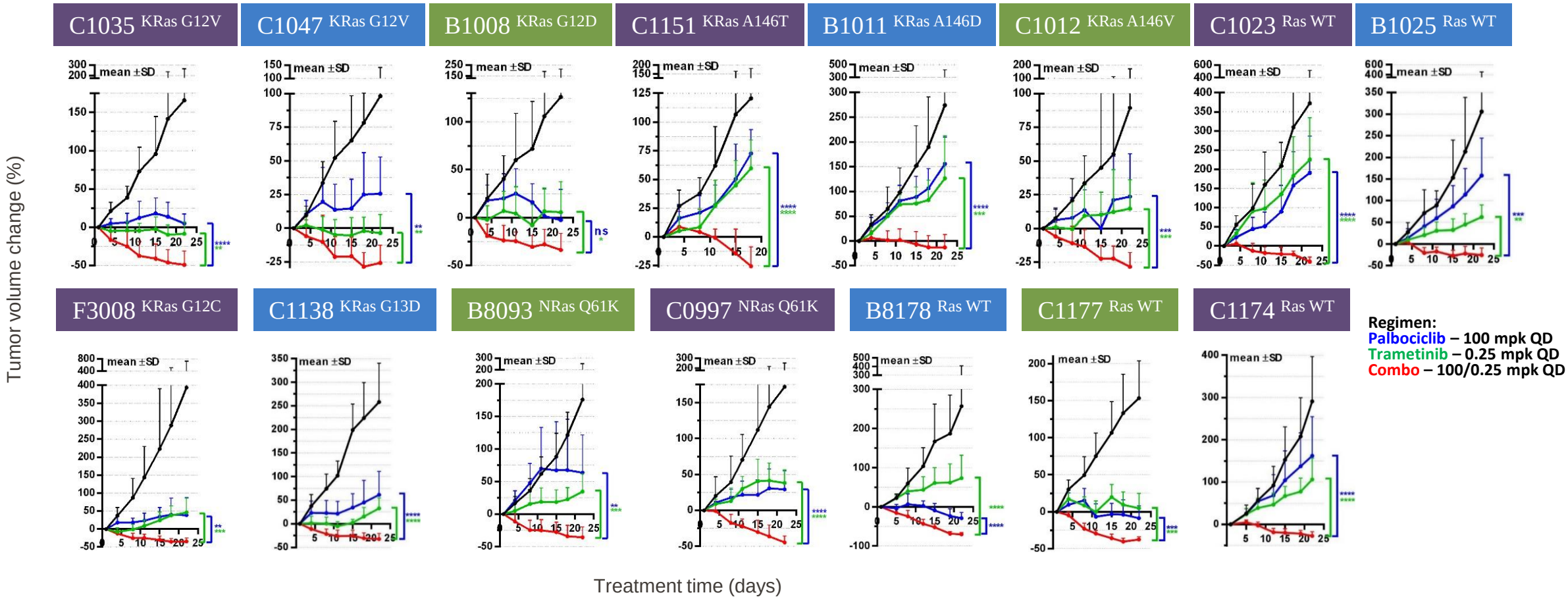


Further Investigation



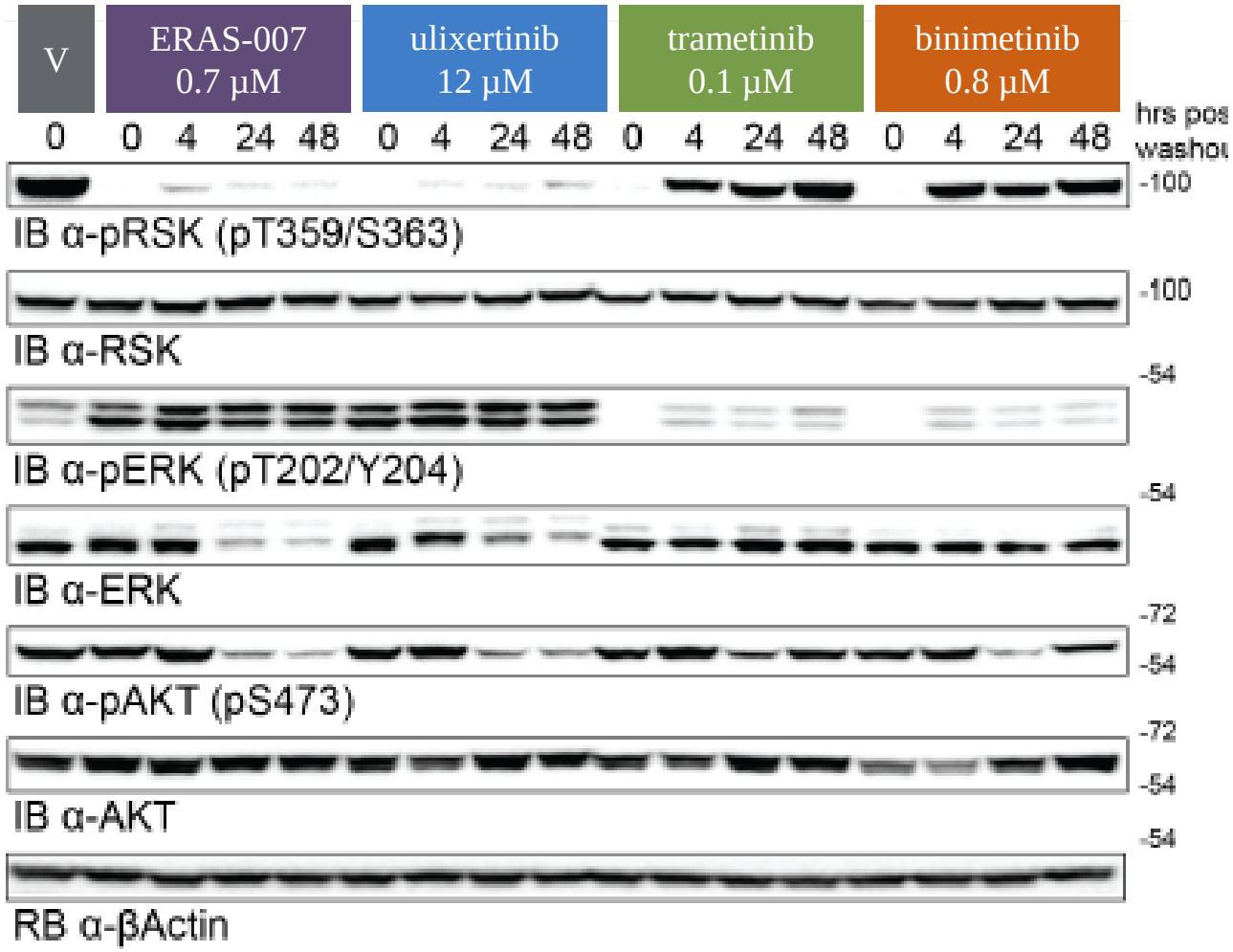
MEK + CDK4/6i Inhibition: Superior Activity to Monotherapies

PDX models



Inhibition of MEK and CDK4/6 represents highly active combination regimen ***in vivo***

Reactivation of MAPK Pathway Occurs Rapidly with MEKi



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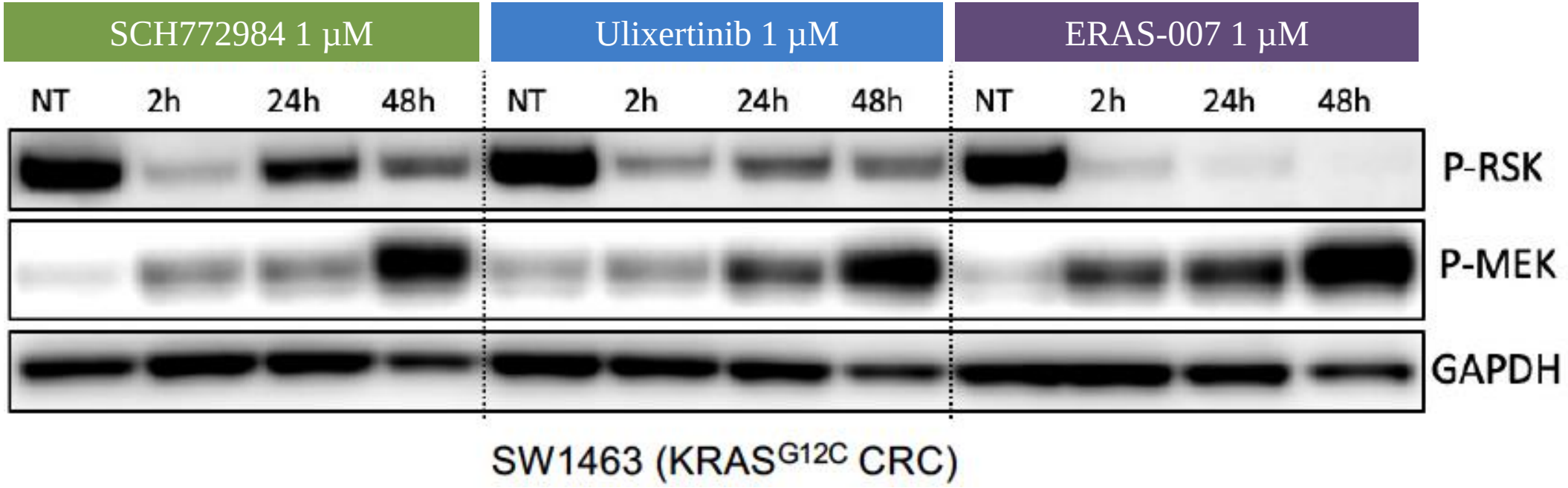
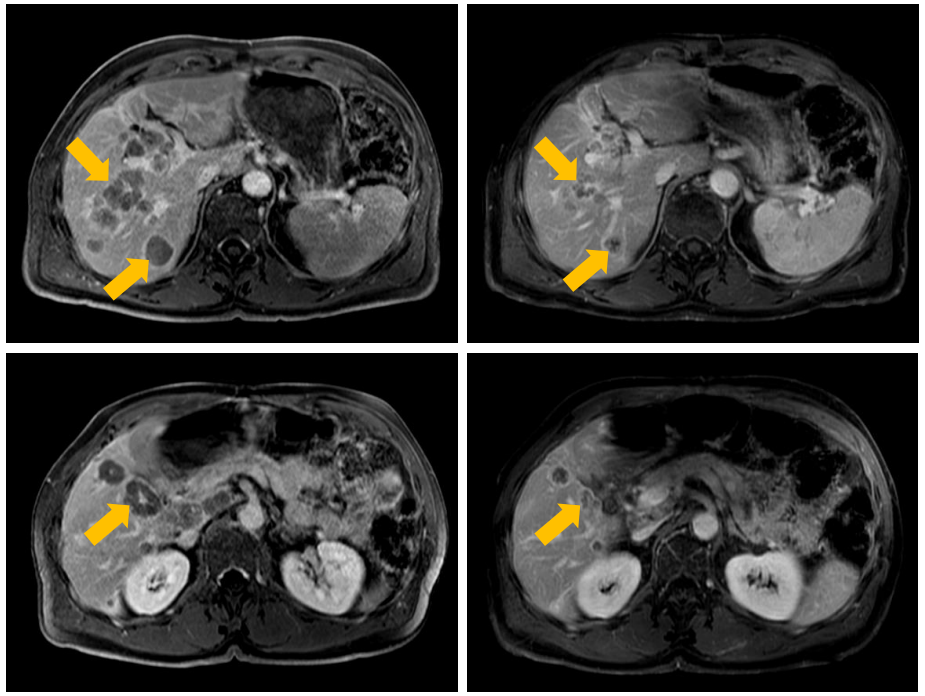
Durability of Pathway Inhibition with ERAS-007

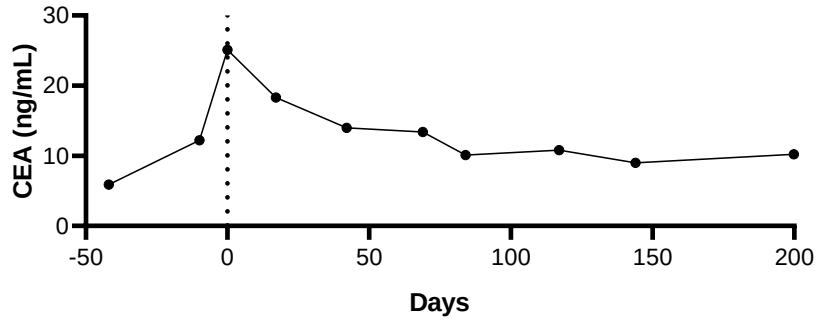


Data from Erasca/R. Corcoran

Case Study: Patient Response with MEKi + CDK4/6i

69 yo M w/KRAS G12D mutated, right sided mCRC s/p 1st restaging after 2 cycles





2 Target lesions – segment VIII & IVb PR = 45.8% reduction by RECIST 1.1

Patient of B. Johnson

Case Study: Patient Response with MEKi + CDK4/6i

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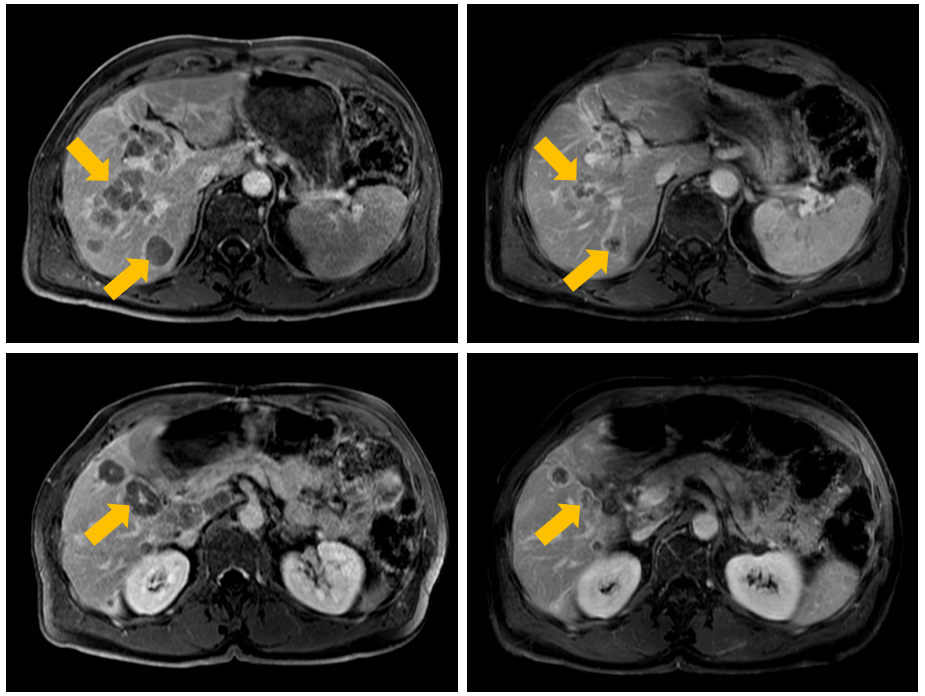
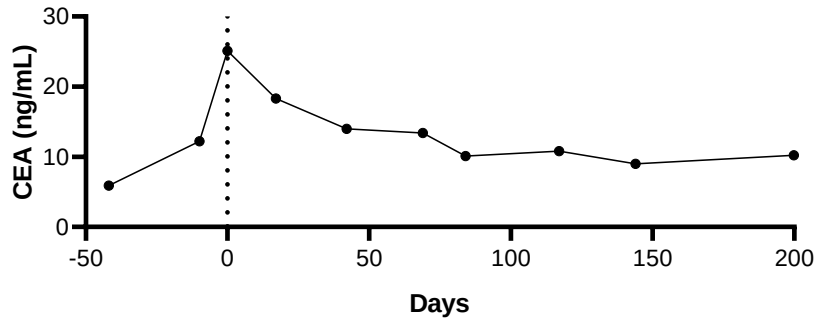




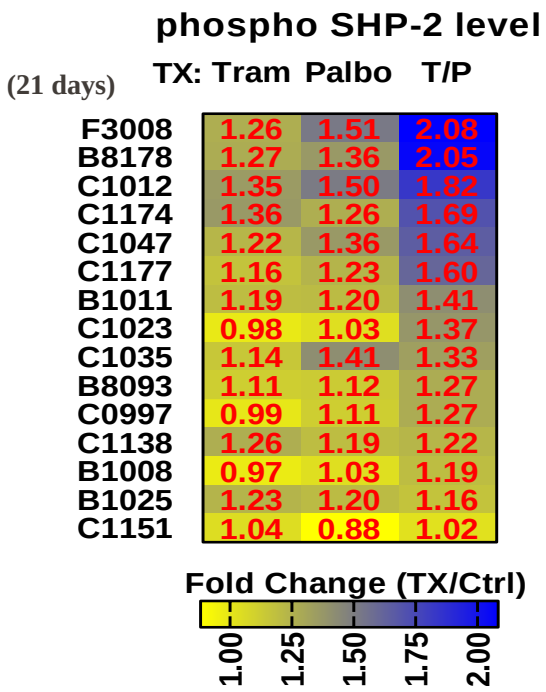
2 Target lesions – segment VIII & IVb PR = 45.8% reduction by RECIST 1.1

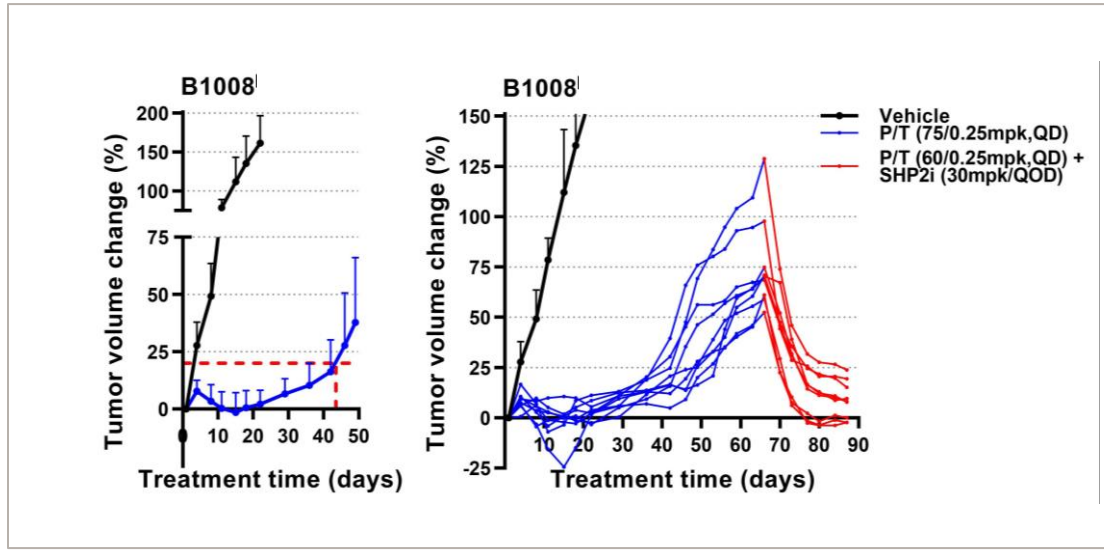
But what will be the durability of the response?

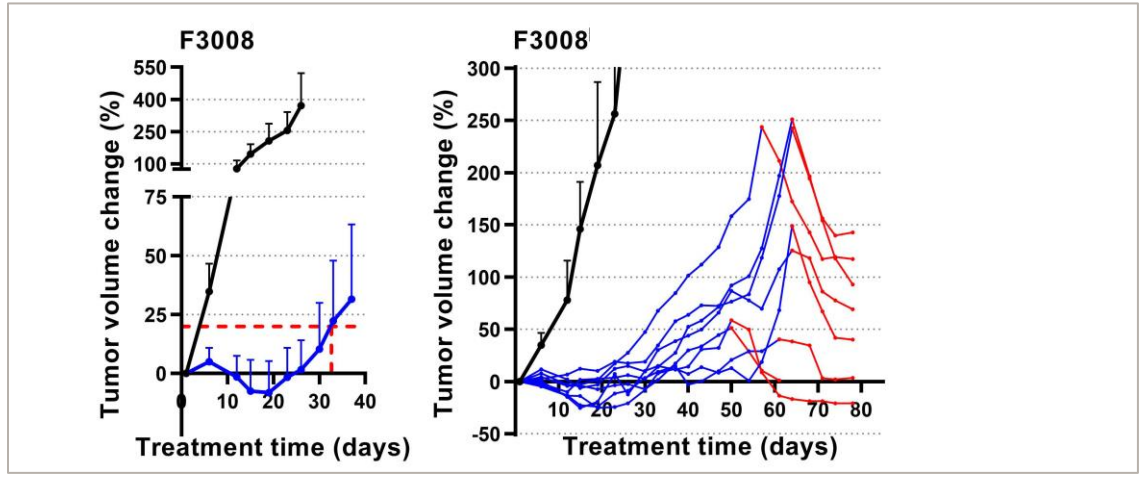
Patient of B. Johnson

SHP2 Inhibition Reverses Adaptive Resistance to MEK/CDK

Acquired Progression on MEK+CDK4/6 is associated with SHP2 activity and sensitivity to inhibition

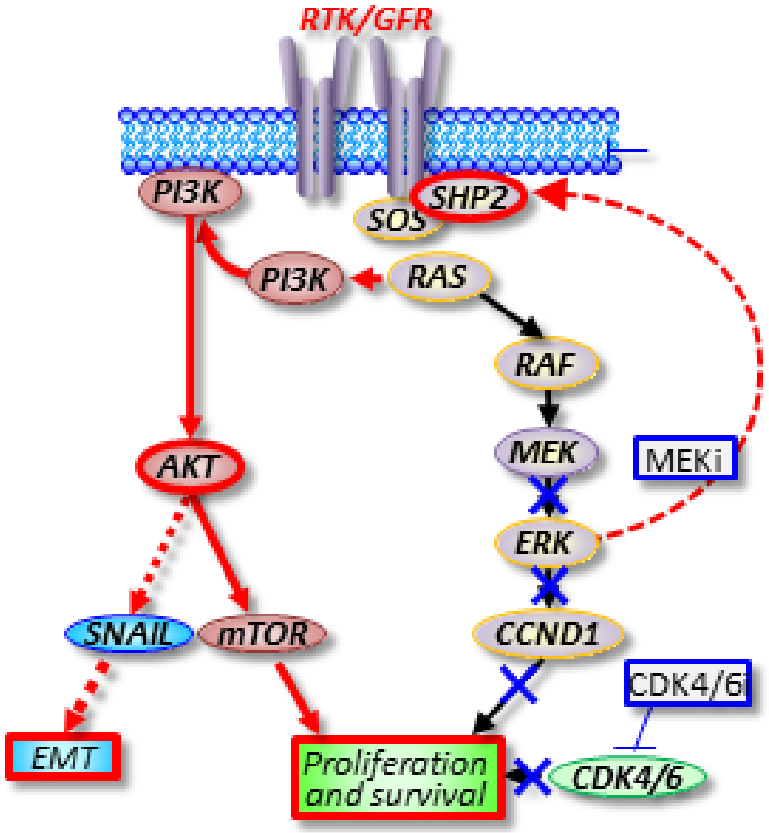




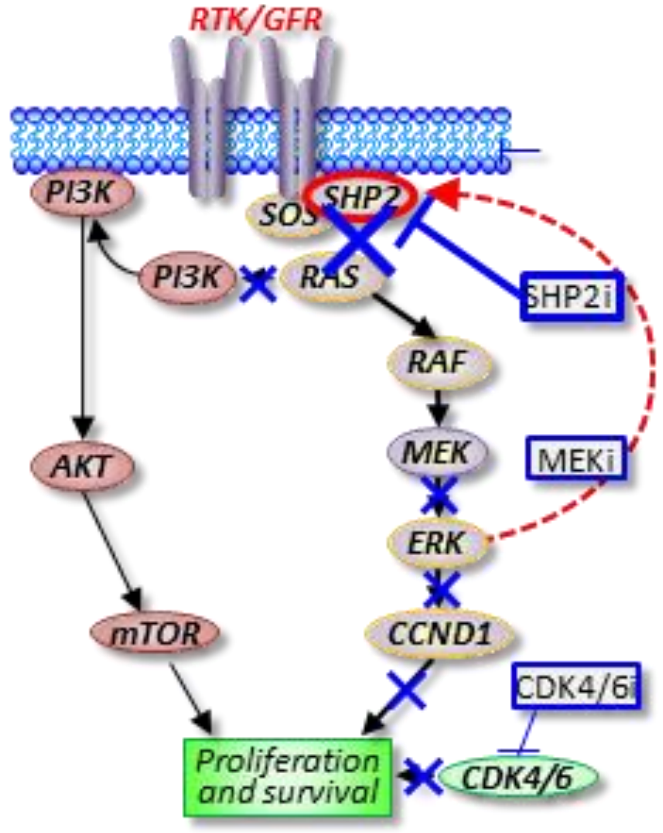


Adaptive Feedback Mechanism

MEK Inhibition



MEK + SHP2 Inhibition



Conclusions: Adaptive resistance supports combination approach

1

Adaptive resistance is common with targeted therapies in CRC, and MAPK pathway dependency is commonly maintained.

2

Optimal BRAF inhibition with **BRAF+EGFR** is currently the standard of care, but resistance develops.

Resistance involved MAPK pathway reactivation, and ERKi may provide an opportunity

3

MEK + CDK4/6 inhibition is a promising combination.

Preclinical data support the potential of ERK + CDK4/6 to improve upon this activity

4

Rational **doublets and triplets** may be active in many settings, following the principles of combinatorial adaptive resistance therapy

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Funda Meric, MD
Tony Saab, MD
Chloe Atreya, MD
Geoff Shapiro, MD
Ryan Corcoran, MD, PhD

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THE HOPE FOUNDATION FOR CANCER RESEARCH
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS
Federally Funded Research
PDXNet

Agenda

- Clinical development plan overview
- Clinical development in GI malignancies
  - Erasca's 2022 AACR posters
  - Discussant: Scott Kopetz, MD, PhD
- Erasca's 2022 AACR posters supporting clinical development in other indications
  - Head and neck squamous cell carcinoma
  - Non-small cell lung cancer
  - Hematological malignancies
  - Tissue agnostic indications
- Q&A

Erasca's clinical development plan targets multiple indications

Alterations	GBM	HNSCC	NSCLC	CRC	Melanoma	PDAC	Other solid tumors	AML
EGFR*/FLT3	125	④ 513	184	338	-	-	-	61
NF1	25	58	98	35	33	1.9	434	3.2
KRAS G12C	-	2.8	240	57	-	5.0	45	0.1
Other KRAS	0.5	14.1	252	703	1.6	420	527	4.7
NRAS	0.5	8.4	11.7	72	71	1.0	116	13.8
HRAS	0.2	45	7.8	0.4	3.0	0.2	57	-
BRAF V600E/K	2	1.9	23	180	93	1.4	158	0.4
Other BRAF	0.5	4.7	33	24	9.7	0.8	87	0.2
MEK	0.2	1.9	11.7	8.8	4.6	0.2	22	-
Co-occurring activating MAPK pathway alterations**	1.4	10.3	62	59	37	7.1	84	3.0
US	12	29	93	114	77	51	153	11
EU	34	76	194	398	116	124	324	18
Rest of World	109	555	635	964	60	264	1,053	57
Global	155	660	923	1,476	253	438	1,530	86

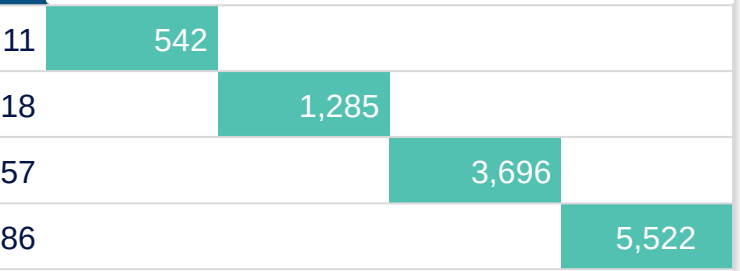
Clinical Development Plan

① **HERKULES-3:** 007 + encorafenib & cetuximab (EC)

② **HERKULES-3:** 007 + palbociclib

③ **FLAGSHP-1 / HERKULES-3:** 601 + cetuximab (triple WT CRC[1])

④ **FLAGSHP-1:** 601 + cetuximab (HPV-negative HNSCC)



Blue ocean opportunities Red ocean opportunities

* Post-Osimertinib resistant population shown for EGFRm NSCLC except for SCLC transformation

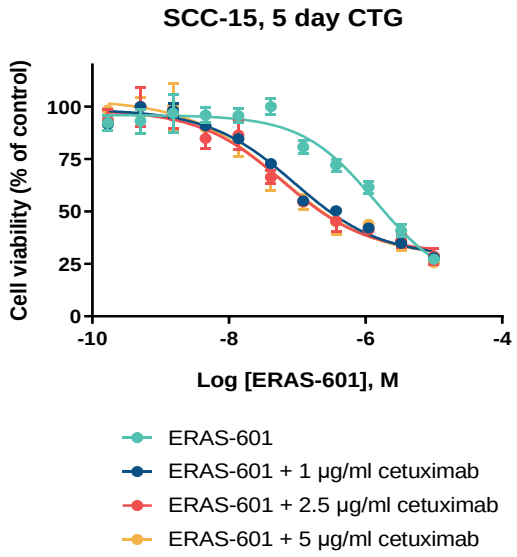
** Co-occurring activating MAPK pathway alterations exclude EGFR overexpression

[1] Triple wildtype CRC is KRASwt, NRASwt, and BRAFwt

Source: SEER database (2020), ECIS database (2020), GLOBOCAN database (2020), The AACR Project GENIE Consortium version 8.1 (2020), TCGA Research Network: https://www.cancer.gov/tcga, Tyner JW et al. (2018) PMID: 30333627, Brenner CW et al (2013) PMID: 24120142, Chen J et al. (2020) PMID: 32015526, and Ostrom QT, et al. (2020) PMID: 33123732

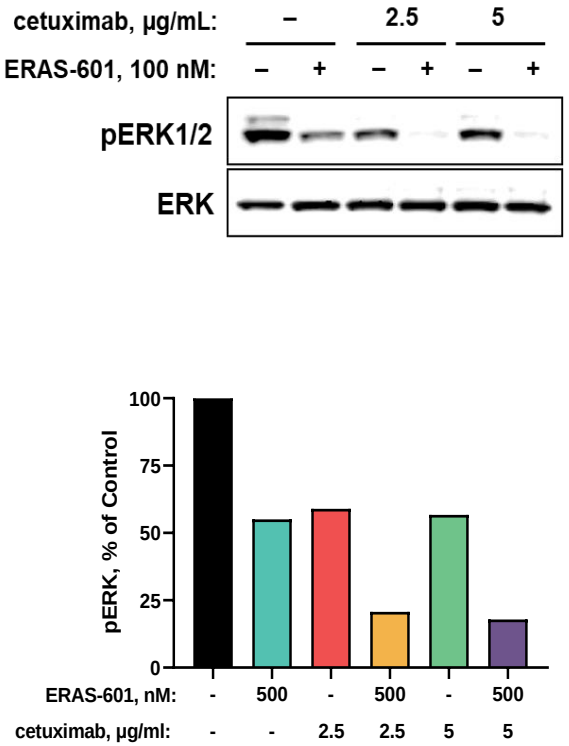
ERAS-601 and cetuximab demonstrated combination benefit in HPV-negative head and neck squamous cell carcinoma (HNSCC) in vitro and in vivo

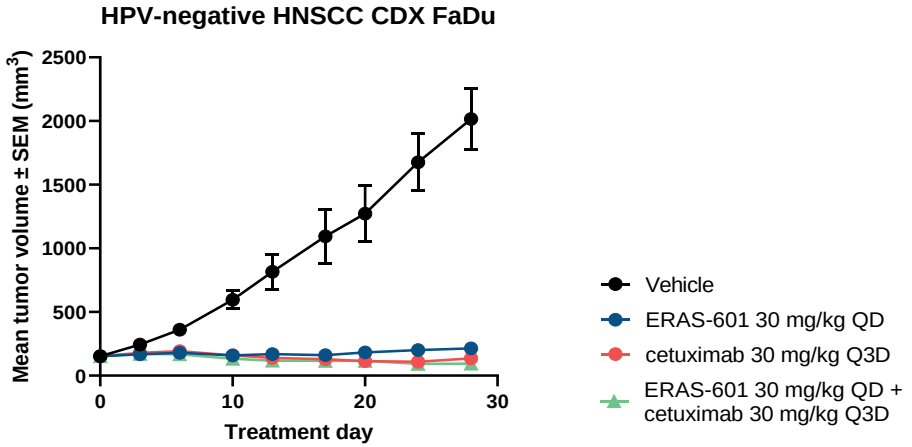
A.



Treatment	2D CTG IC50, nM
ERAS-601	1,406
ERAS-601 + 1 µg/ml cetuximab	91
ERAS-601 + 2.5 µg/ml cetuximab	61
ERAS-601 + 5 µg/ml cetuximab	55

B.





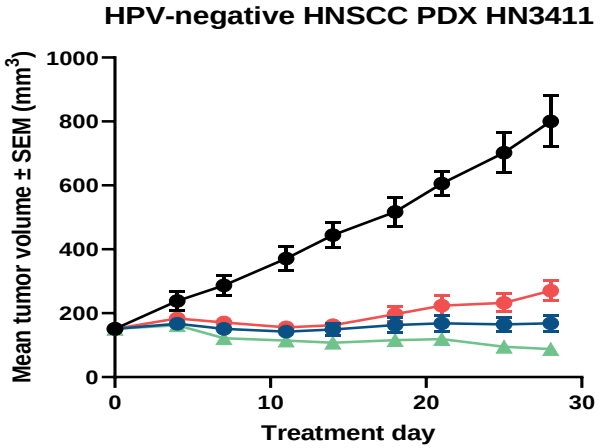


Figure 6. Combination of ERAS-601 and cetuximab in HPV-negative HNSCC. A. SCC-15 cells were treated with ERAS-601 alone or cotreated with indicated suboptimal concentrations of cetuximab. The cellular proliferation was assessed in a 5 day 2D CellTiter-Glo assay. IC50 values are summarized in the table. **B.** Cal-27 cells were treated with ERAS-601 and cetuximab for 6 hours and cell lysates were immunoblotted with the indicated antibodies. The graph shows the quantification of ERK1/2 phosphorylation.

Figure 7. In vivo efficacy of ERAS-601 with cetuximab combination in HPV-negative HNSCC xenografts. Immunodeficient mice bearing the indicated tumor xenografts were dosed orally with ERAS-601 or intraperitoneally with cetuximab as indicated. Tumors were measured on the indicated days and mean tumor volumes were plotted. *SEM*, standard error of the mean.

Conclusions

- Combination of ERAS-601 with cetuximab enhances in vitro anti-proliferative activity in HPV-negative head and neck squamous cell carcinoma (HNSCC) models
- ERAS-601 shows compelling activity both as a monotherapy and in combination with cetuximab in HPV-negative HNSCC CDX and PDX models
- ERAS-601 + cetuximab combination in HPV-negative HNSCC is being evaluated in FLAGSHP-1 phase 1 clinical trial

Agenda

- Clinical development plan overview
- Clinical development in GI malignancies
  - Erasca's 2022 AACR posters
  - Discussant: Scott Kopetz, MD, PhD
- Erasca's 2022 AACR posters supporting clinical development in other indications
  - Head and neck squamous cell carcinoma
  - Non-small cell lung cancer
  - Hematological malignancies
  - Tissue agnostic indications
- Q&A

Erasca's clinical development plan targets multiple indications

Alterations	GBM	HNSCC	NSCLC	CRC	Melanoma	PDAC	Other solid tumors	AML
EGFR*/FLT3	125	513	184	338	-	-	-	61
NF1	25	58	98	35	33	1.9	434	3.2
KRAS G12C	-	2.8	6 240	57	-	5.0	45	0.1
Other KRAS	0.5	14.1	252	703	1.6	420	527	4.7
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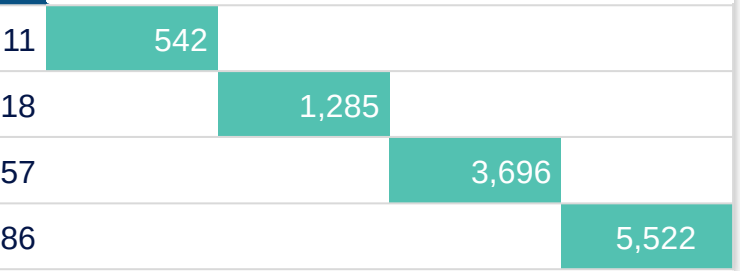
④ **FLAGSHP-1:** 601 + cetuximab (HPV-negative HNSCC)
⑤ **HERKULES-2:** 007 + osimertinib
⑥ **HERKULES-2:** 007 or 601 + sotorasib; **Future 3490 trial(s)**



Blue ocean opportunities Red ocean opportunities

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We have developed CNS-penetrant KRAS G12C inhibitors ("ERAS G12Ci's") to target KRAS G12C mutant tumors that metastasize to the brain, such as NSCLC

Parameter	3490	3537	3788	4926	Reference compounds[1]
P-gp substrate ratio[2]	↑ 1.5	↑ 5.0	↑ 4.0	↑ 3.5	30.9[3]
Rat brain / plasma (%)	↑ 52%	↑ 68%	↑ 11%	↑ 21%	1 - 6%
Rat brain concentration (ng / g)	↑ 156	↑ 290	↑ 91	↑ 170	6 - 36
Mouse AUC_{po}/D (hr*kg*ng/mL/mg)	↑ 693	↔ 535	↔ 326	↔ 614	102 - 637

Arrows indicate change in values relative to sotorasib and adagrasib, whose values are listed in the reference compounds column

[1] The reference compounds are sotorasib and adagrasib

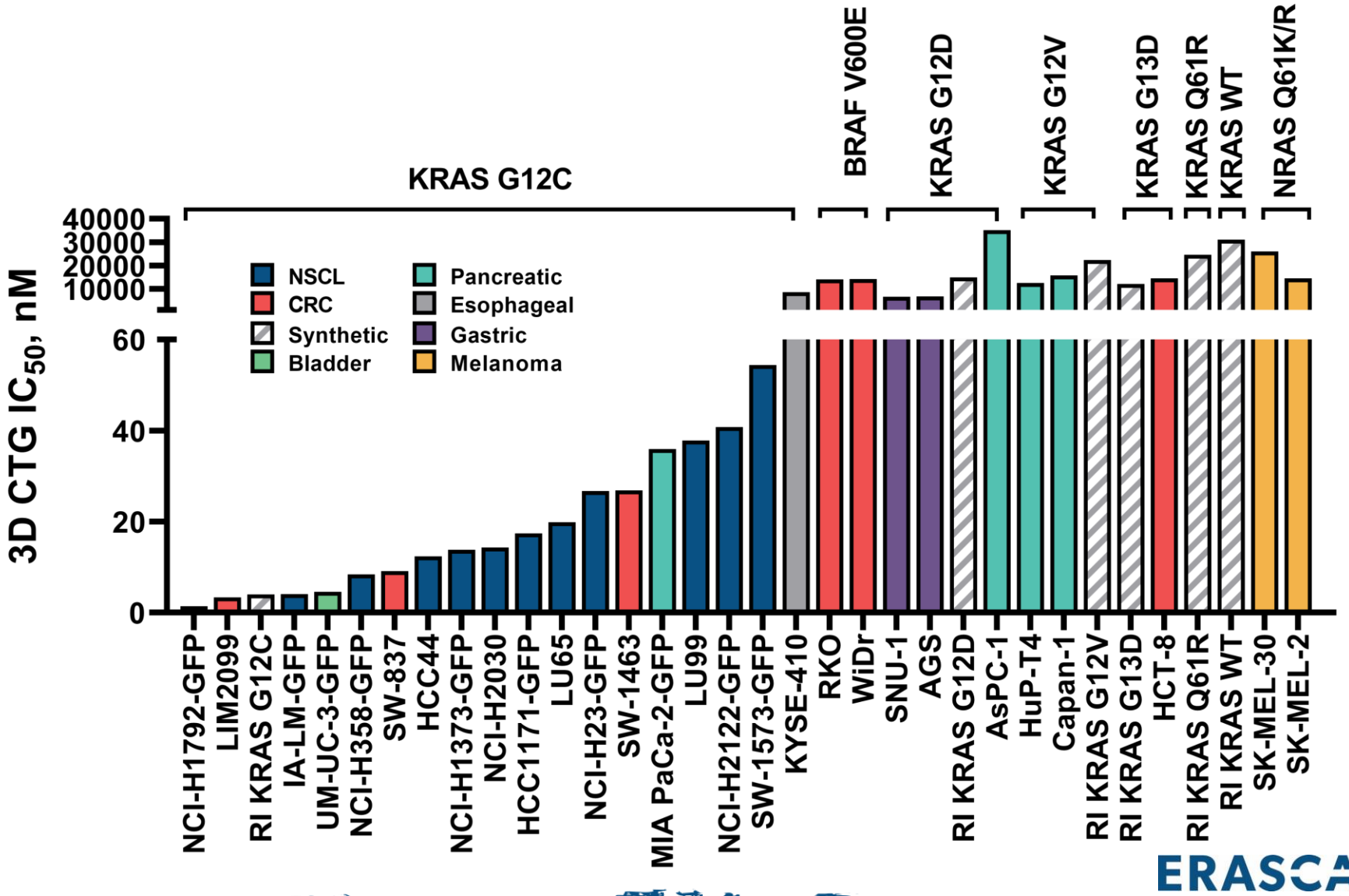
[2] P-gp substrate ratios were characterized in a P-gp expressing MDCK cell line. Per compound, a P-gp substrate ratio was calculated by dividing its efflux ratio in absence of a P-gp inhibitor by its efflux ratio in presence of a P-gp inhibitor. Compounds with lower P-gp substrate ratios are less likely to be P-gp substrates

[3] The P-gp substrate ratio was characterized for a single reference compound.

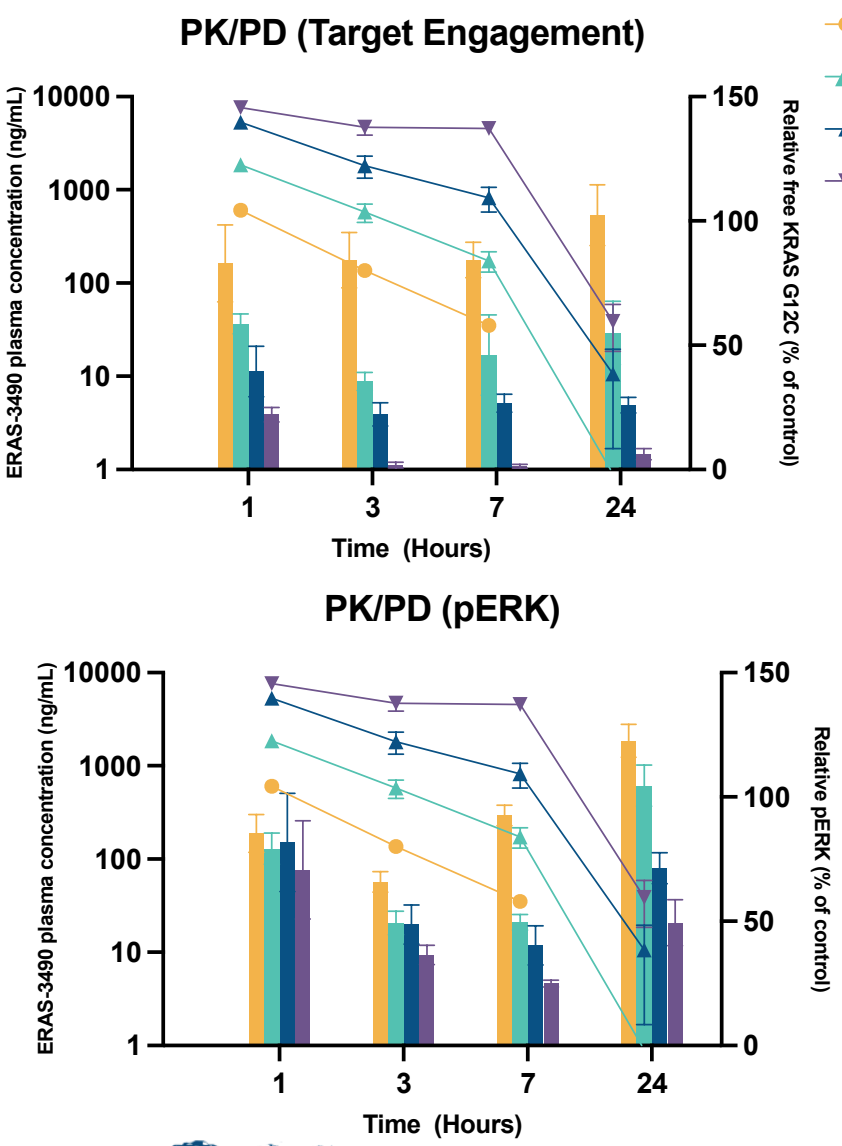
ERASCA

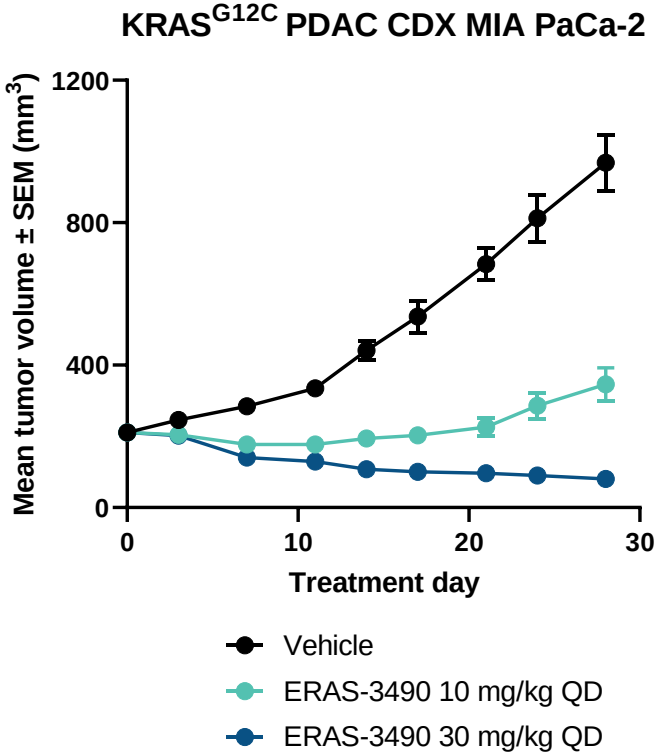
ERAS-3490, a KRAS G12Ci, selectively inhibited cell viability in a panel of 19 $KRAS^{G12C}$ cell lines and not in 15 non-$KRAS^{G12C}$ cell lines

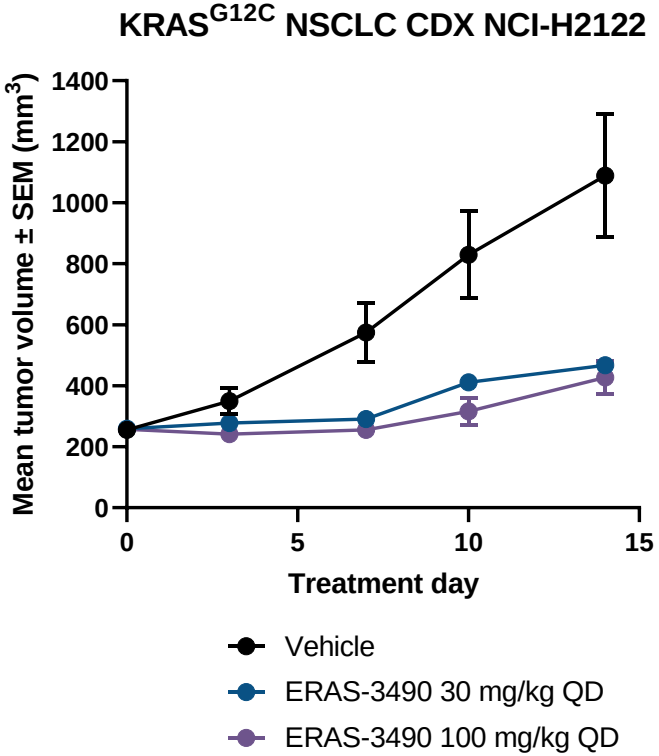
- >950-fold selectivity when comparing all non-$KRAS^{G12C}$ cell lines to all $KRAS^{G12C}$-harboring cell lines
- ERAS-3490 exhibited >7,000-fold selectivity for $KRAS^{G12C}$ versus $KRAS^{WT}$ based on RAS initiative cell lines



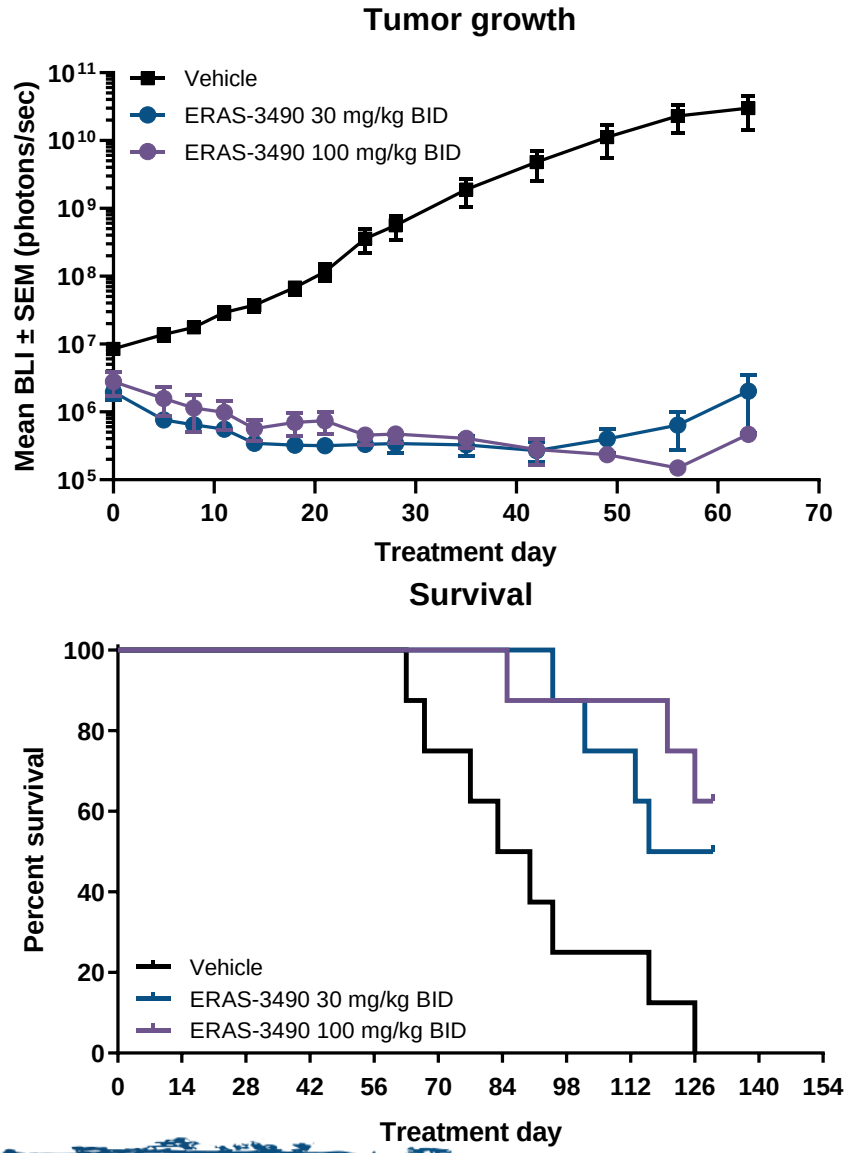
ERAS-3490 exhibited dose dependent activity in a MIA PaCA-2 PK/PD study and showed significant TGI in two KRAS^{G12C} CDX models

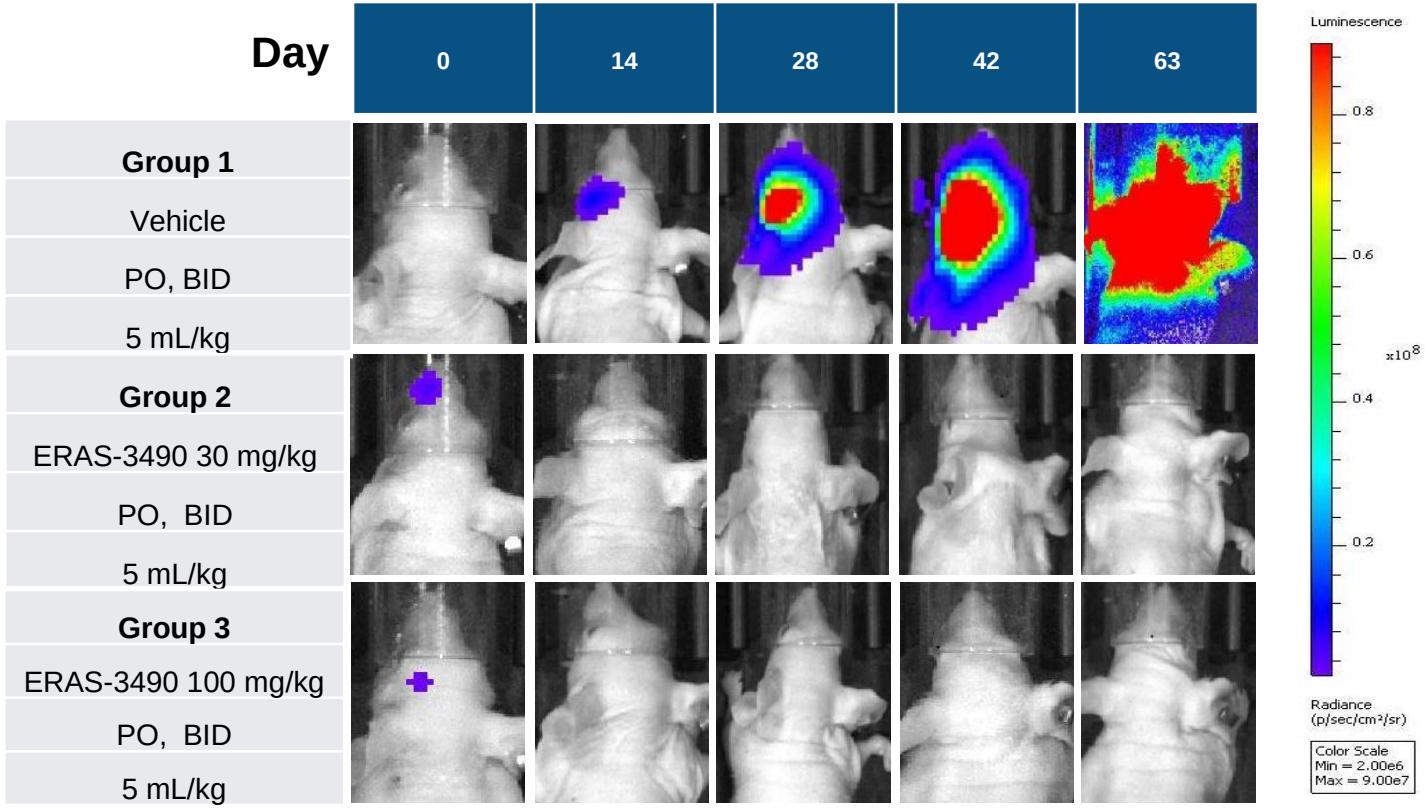






ERAS-3490 showed significant tumor regression and dose dependent survival benefit in an ongoing in vivo study intended to model NSCLC CNS metastases





ERAS-601 combined with sotorasib or adagrasib synergistically inhibited cell viability in KRAS^{G12C} mutant cells

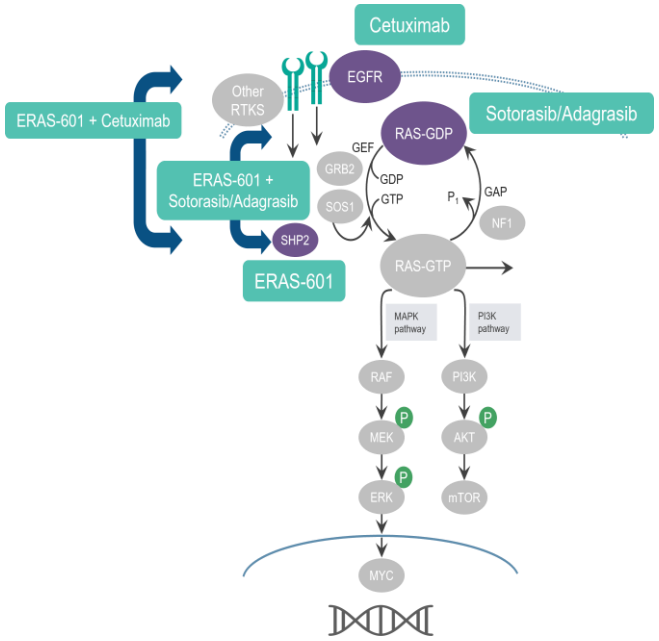


Figure 1. Schematic representation of ERAS-601 with sotorasib or adagrasib combination and ERAS-601 with cetuximab combination

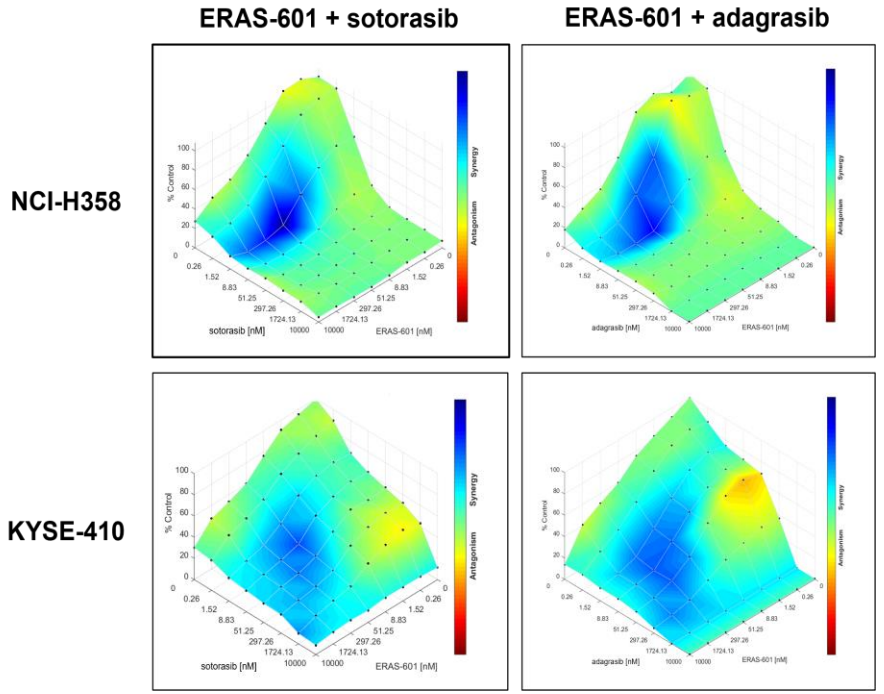
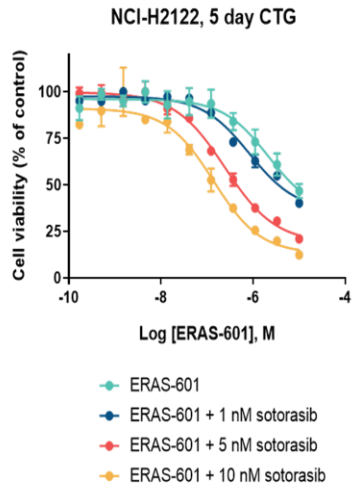


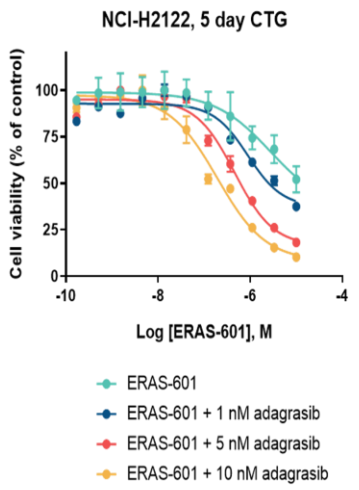
Figure 2. Combination analysis of ERAS-601 with KRAS^{G12C} inhibitors. NCI-H358 KRAS^{G12C} and KYSE-410 KRAS^{G12C} cell lines were treated with ERAS-601 and sotorasib or adagrasib. The proliferation was assessed in a 5 day 3D CellTiter-Glo assay and synergy plots were generated using Combenefit software.

A.



Treatment	2D CTG IC50, nM
ERAS-601	2,181
ERAS-601 + 1 nM sotorasib	834
ERAS-601 + 5 nM sotorasib	246
ERAS-601 + 10 nM sotorasib	139

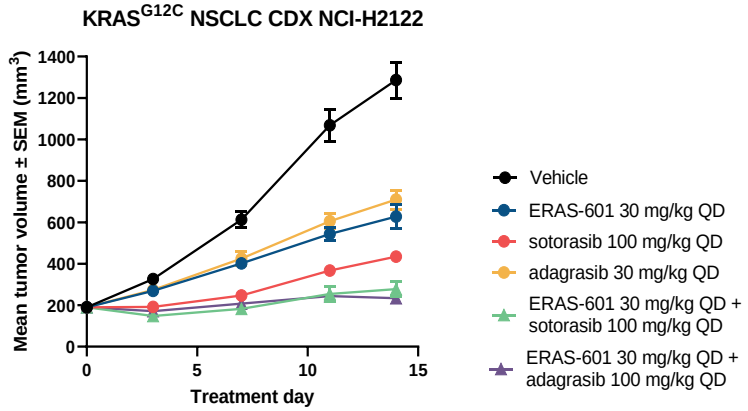
B.



Treatment	2D CTG IC50, nM
ERAS-601	2,785
ERAS-601 + 1 nM adagrasib	888
ERAS-601 + 5 nM adagrasib	460
ERAS-601 + 10 nM adagrasib	190

Figure 3. Cotreatment of ERAS-601 with sotorasib/adagrasib in the NCI-H2122 KRAS^{G12C} cell line. The cells were treated with ERAS-601 alone or cotreated with indicated concentrations of sotorasib (**A**) or adagrasib (**B**). The cellular proliferation was assessed in a 5 day 2D CellTiter-Glo assay. IC50 values are summarized in the tables.

ERAS-601 combined with sotorasib or adagrasib demonstrated in vivo combination benefit in KRAS^{G12C} mutant NSCLC and CRC CDX and PDX models



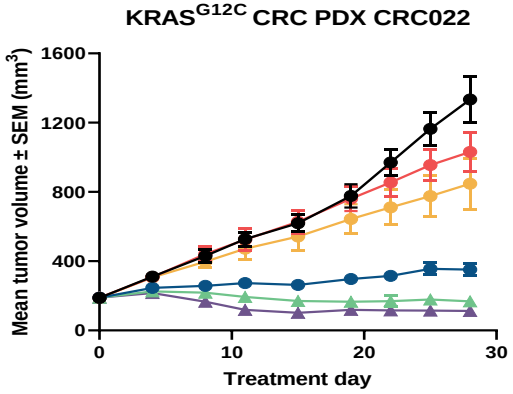
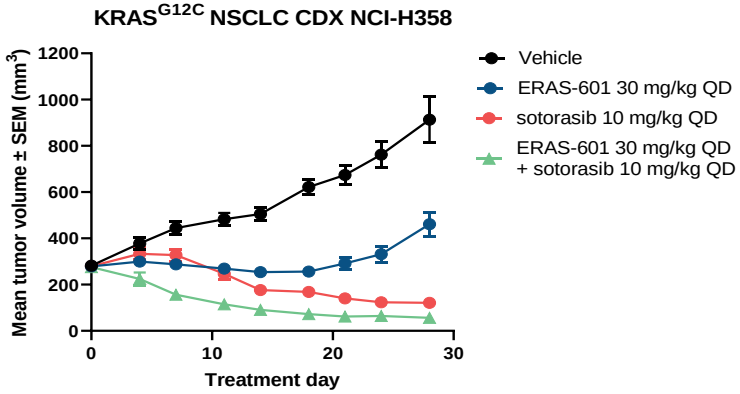
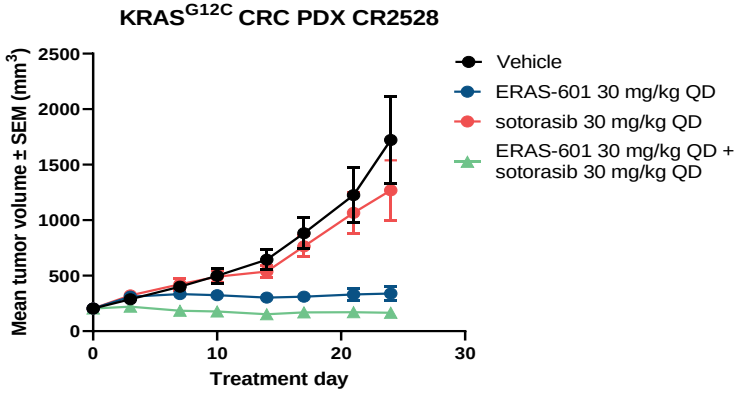
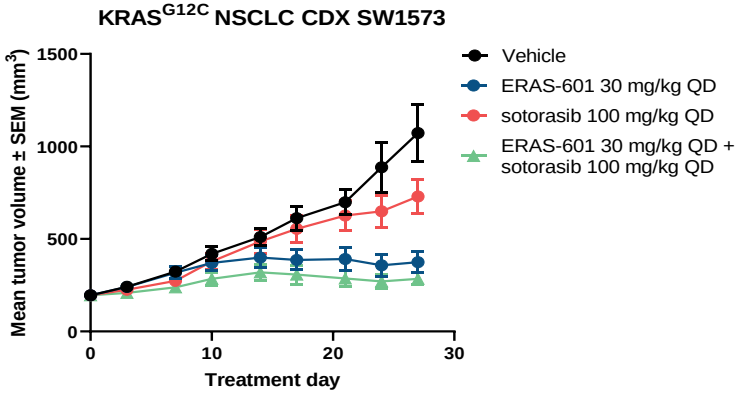


Figure 4. In vivo efficacy of ERAS-601 with sotorasib/adagrasib combination in KRAS^{G12C} mutant xenografts. Immunodeficient mice bearing the indicated tumor xenografts were orally dosed with indicated single agent and combination treatments. Tumors were measured on the indicated days and mean tumor volumes were plotted. *SEM*, standard error of the mean.







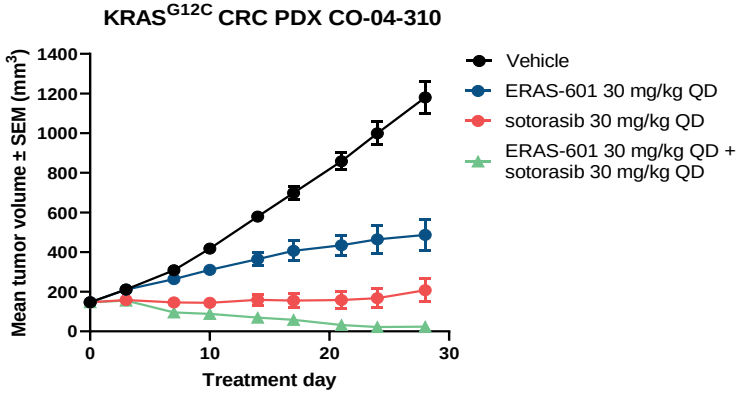


Figure 5. In vivo efficacy of ERAS-601 with sotorasib combination in KRAS^{G12C} mutant xenografts. Immunodeficient mice bearing the indicated tumor xenografts were orally dosed with indicated single agent and combination treatments. Tumors were measured on the indicated days and mean tumor volumes were plotted. *SEM*, standard error of the mean.

Conclusions

ERAS-3490

- ERAS G12Ci's show promising CNS penetration potential, potency, and selectivity in $KRAS^{G12C}$ cells in vitro and in vivo
- An example CNS-penetrant ERAS G12Ci, ERAS-3490, shows both significant tumor regression and survival benefit in a $KRAS^{G12C}$ NSCLC brain metastases model
- ERAS-3490 is on track for an IND filing in the second half of 2022

ERAS-601 + $KRAS^{G12C}$ inhibitor combinations

- ERAS-601 synergizes with KRASG12C inhibitors in vitro
- ERAS-601 + $KRAS^{G12C}$ inhibitor combinations show superior tumor growth inhibition to respective monotherapies in $KRAS^{G12C}$ NSCLC and CRC CDX and PDX models
- ERAS-601 in combination with sotorasib is being evaluated in the HERKULES-2 master protocol

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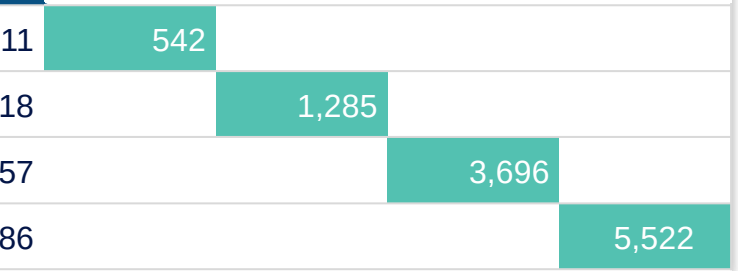
⑤ **HERKULES-2:** 007 + osimertinib
⑥ **HERKULES-2:** 007 or 601 + sotorasib; **Future 3490 trial(s)**
⑦ **HERKULES-4:** 007 or 601 + gilteritinib



Blue ocean opportunities Red ocean opportunities

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ERAS-601 and gilteritinib combination demonstrated combination benefit in FLT3-ITD mutated AML cells in vitro

The combination of ERAS-601 with gilteritinib synergistically inhibited cellular viability in FLT3-ITD mutated AML cells

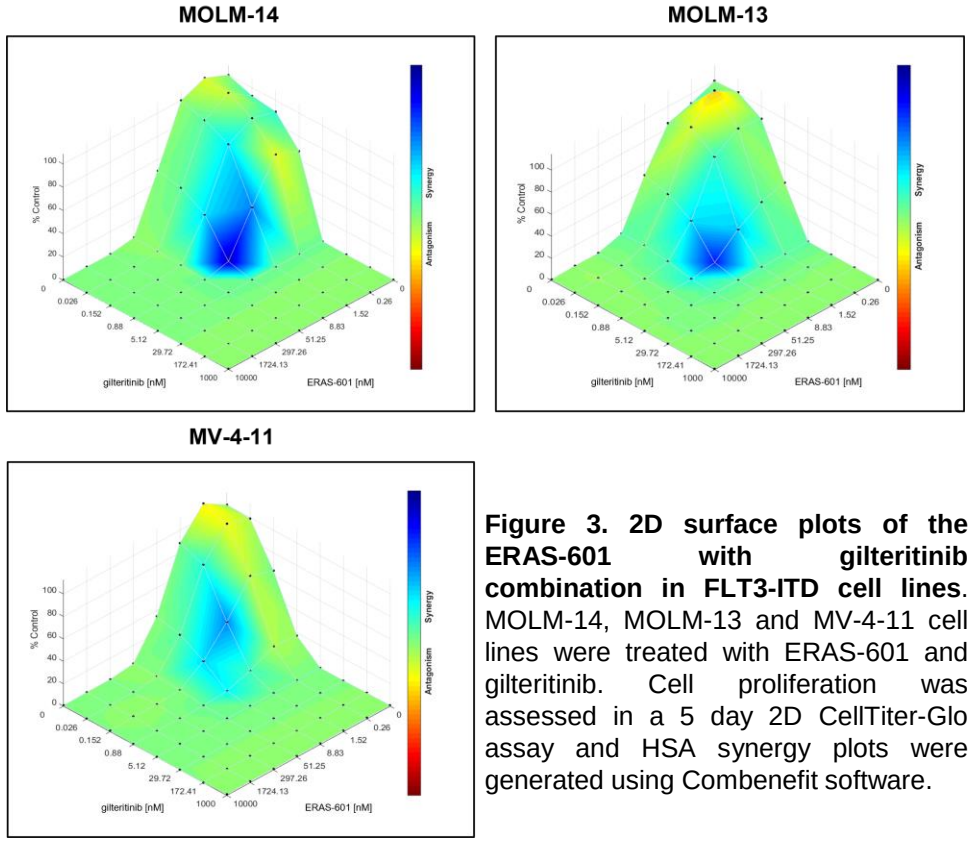


Figure 3. 2D surface plots of the ERAS-601 with gilteritinib combination in FLT3-ITD cell lines. MOLM-14, MOLM-13 and MV-4-11 cell lines were treated with ERAS-601 and gilteritinib. Cell proliferation was assessed in a 5 day 2D CellTiter-Glo assay and HSA synergy plots were generated using Combenefit software.

The combination of ERAS-601 with gilteritinib showed enhanced inhibition of ERK1/2 phosphorylation in FLT3-ITD mutated AML cells

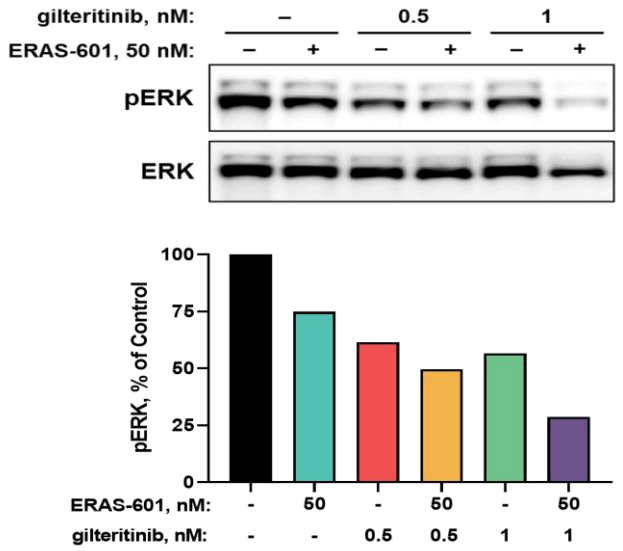


Figure 4. Assessment of ERK1/2 signaling following ERAS-601 and gilteritinib treatment. The FLT3-ITD mutated AML cell line MOLM-14 was treated with ERAS-601 alone and ERAS-601 with gilteritinib combination for 6 hours and cell lysates were harvested. *Top panel*, immunoblot of pERK1/2 and total ERK. *Bottom panel*, quantitation plot of pERK1/2 after being normalized to total ERK.

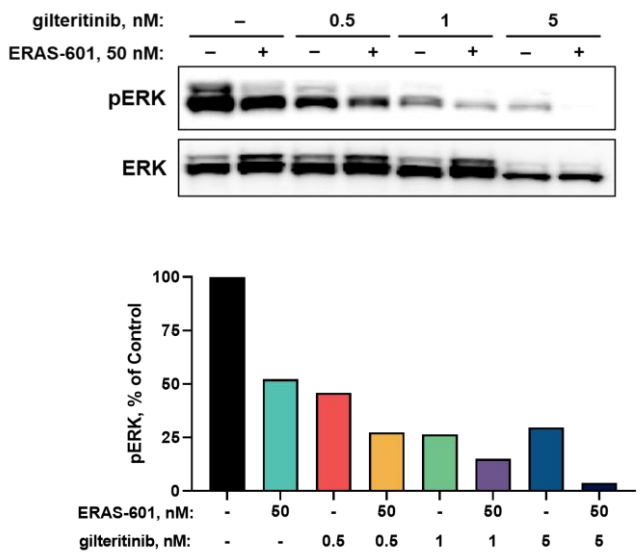


Figure 5. Assessment of ERK1/2 signaling following ERAS-601 and gilteritinib treatment. The FLT3-ITD mutated AML cell line MV-4-11 was treated with ERAS-601 alone and ERAS-601 with gilteritinib combination for 6 hours and cell lysates were harvested. *Top panel*, immunoblot of pERK1/2 and total ERK. *Bottom panel*, quantitation plot of pERK1/2 after being normalized to total ERK.

The combination of ERAS-601 with gilteritinib achieved durable tumor growth inhibition in a FLT3-ITD mutated AML-subcutaneous CDX model MOLM-13

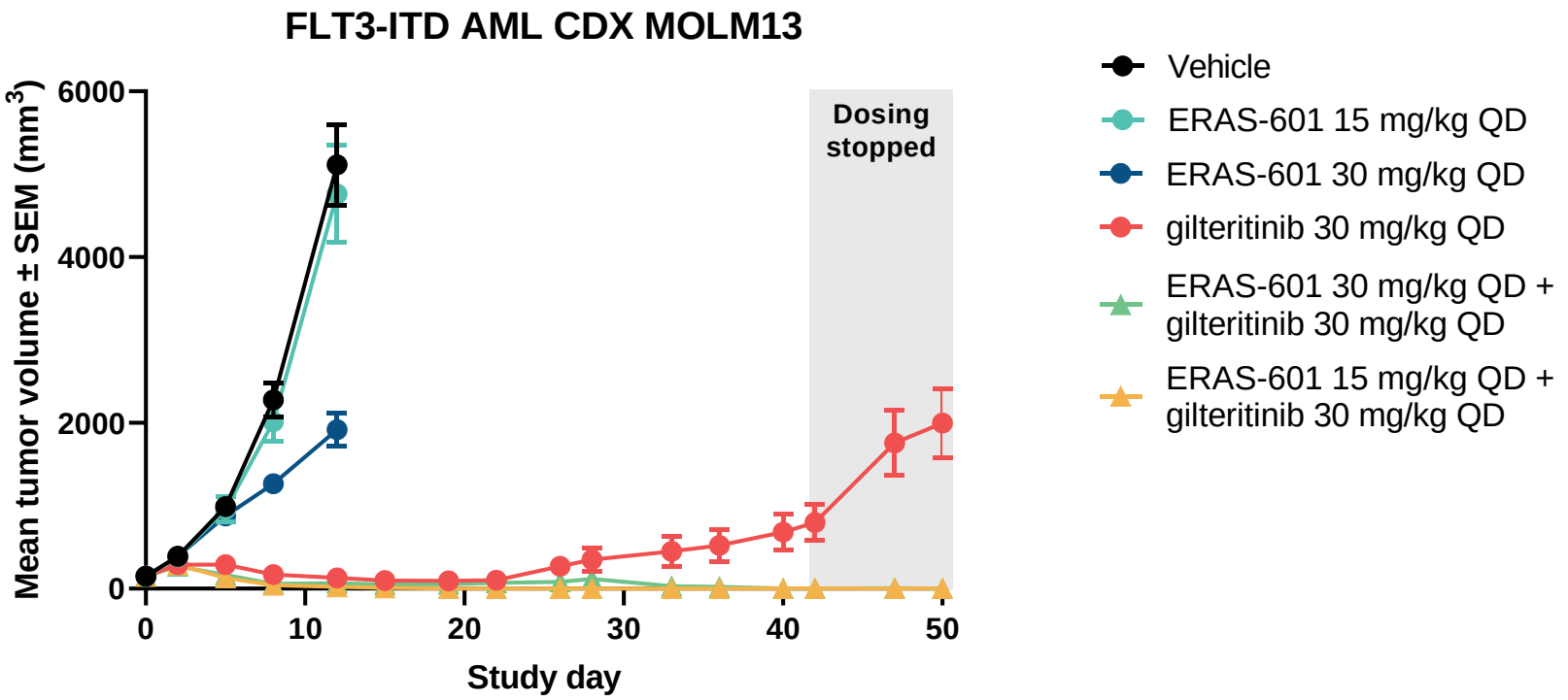


Figure 6. In vivo efficacy of ERAS-601 with gilteritinib combination in a FLT3-ITD mutant subcutaneous xenograft. Immunodeficient mice bearing MOLM-13 tumor xenografts were orally dosed with indicated single agent and combination treatments. Tumors were measured on the indicated days and mean tumor volumes were plotted. *SEM*, standard error of the mean.

Combination of ERAS-601 with gilteritinib achieved superior tumor growth inhibition to respective monotherapies in a FLT3-ITD mutated AML engrafted CDX model MOLM-13-Luc

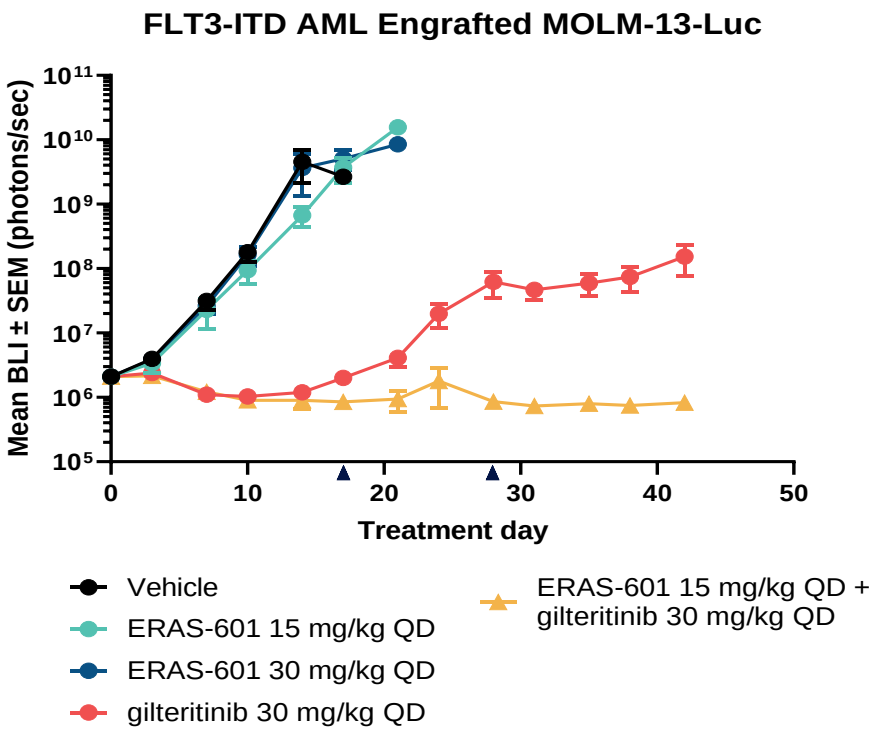


Figure 7. In vivo efficacy of ERAS-601 with gilteritinib combination in a FLT3-ITD mutant engraftment model. Immunodeficient mice harboring engrafted luciferase labeled MOLM-13 cells ("MOLM-13-Luc") were orally dosed with indicated single agent and combination treatments. Bioluminescence intensity (BLI) was measured following luciferin injection on the indicated days and mean BLI was plotted. *SEM*, standard error of the mean.

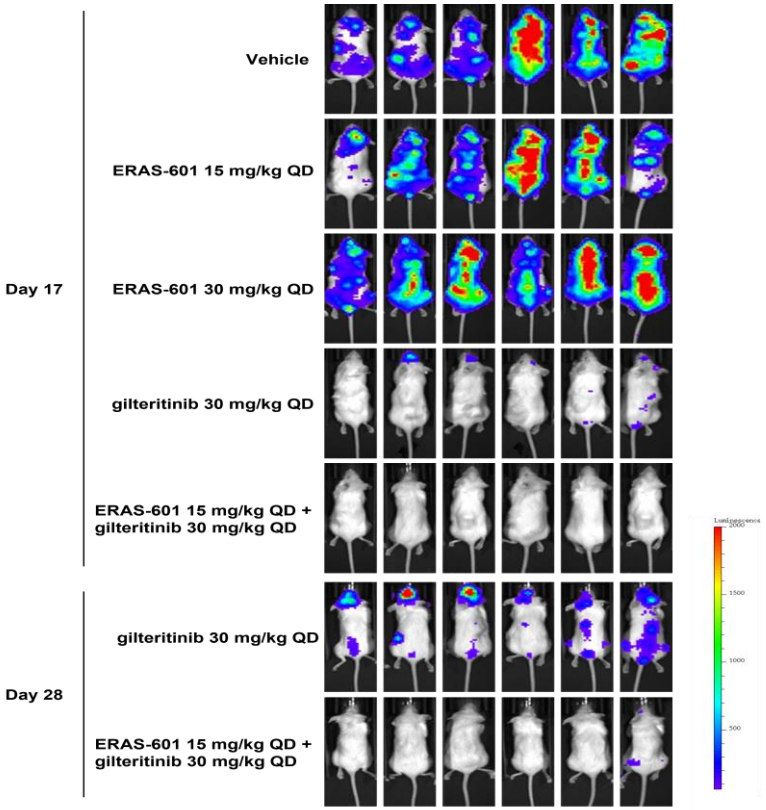


Figure 8. Bioluminescent images of ERAS-601 with gilteritinib combination efficacy in a FLT3-ITD mutant engraftment model. Immunodeficient mice harboring engrafted luciferase labeled MOLM-13 cells ("MOLM-13-Luc") were orally dosed with indicated single agent and combination treatments. The figure shows representative bioluminescence images of tumor-bearing mice at day 17 and day 28.

Conclusions

- Combination of ERAS-601 with gilteritinib enhances the inhibition of RAS/MAPK pathway signaling and cellular proliferation in FLT3-ITD mutant AML cellular models
- ERAS-601 + gilteritinib achieves more durable tumor growth inhibition than respective gilteritinib and ERAS-601 monotherapies in the FLT3-ITD mutant CDX AML MOLM-13 subcutaneous model and MOLM13-Luc AML engraftment model
- These data support the clinical development of ERAS-601 in combination with gilteritinib in FLT3-altered AML in the HERKULES-4 Phase 1b/2 master protocol

Agenda

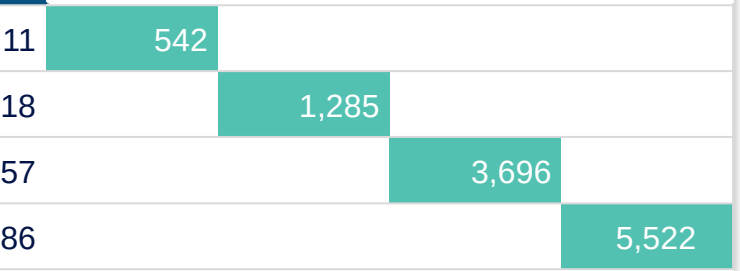
- Clinical development plan overview
- Clinical development in GI malignancies
  - Erasca's 2022 AACR posters
  - Discussant: Scott Kopetz, MD, PhD
- Erasca's 2022 AACR posters supporting clinical development in other indications
  - Head and neck squamous cell carcinoma
  - Non-small cell lung cancer
  - Hematological malignancies
  - Tissue agnostic indications
- Q&A

Erasca's clinical development plan targets multiple indications

Alterations	GBM	HNSCC	NSCLC	CRC	Melanoma	PDAC	Other solid tumors	AML
EGFR*/FLT3	125	513	184	338	-	-	-	61
NF1	25	58	98	35	33	1.9	434	3.2
KRAS G12C	-	2.8	240	57	-	5.0	45	0.1
Other KRAS	0.5	14.1	252	703	1.6	420	527	4.7
NRAS	0.5	8.4	11.7	72	71	1.0	116	13.8
HRAS	0.2	45	7.8	0.4	3.0	0.2	57	8 -
BRAF V600E/K	2	1.9	23	180	93	1.4	158	0.4
Other BRAF	0.5	4.7	33	24	9.7	0.8	87	0.2
MEK	0.2	1.9	11.7	8.8	4.6	0.2	22	-
Co-occurring activating MAPK pathway alterations**	1.4	10.3	62	59	37	7.1	84	3.0
US	12	29	93	114	77	51	153	11
EU	34	76	194	398	116	124	324	18
Rest of World	109	555	635	964	60	264	1,053	57
Global	155	660	923	1,476	253	438	1,530	86

Clinical Development Plan

1. **HERKULES-3:** 007 + encorafenib & cetuximab (EC)
2. **HERKULES-3:** 007 + palbociclib
3. **FLAGSHP-1 / HERKULES-3:** 601 + cetuximab (triple WT CRC[1])
4. **FLAGSHP-1:** 601 + cetuximab (HPV-negative HNSCC)
5. **HERKULES-2:** 007 + osimertinib
6. **HERKULES-2:** 007 or 601 + sotorasib; **Future 3490 trial(s)**
7. **HERKULES-4:** 007 or 601 + gilteritinib
8. **HERKULES-1:** 007 + 601 (our first MAPKlamp)



Blue ocean opportunities Red ocean opportunities

* Post-Osimertinib resistant population shown for EGFRm NSCLC except for SCLC transformation
** Co-occurring activating MAPK pathway alterations exclude EGFR overexpression
[1] Triple wildtype CRC is KRASwt, NRASwt, and BRAFwt
Source: SEER database (2020), ECIS database (2020), GLOBOCAN database (2020), The AACR Project GENIE Consortium version 8.1 (2020), TCGA Research Network: https://www.cancer.gov/tcga, Tyner JW et al. (2018) PMID: 30333627, Brenner CW et al (2013) PMID: 24120142, Chen J et al. (2020) PMID: 32015526, and Ostrom QT, et al. (2020) PMID: 33123732

ERAS-007 + ERAS-601 MAPKlamp combination demonstrated superior colony growth inhibition over single agent treatment in KRAS mutant NSCLC, CRC, and PDAC cell lines

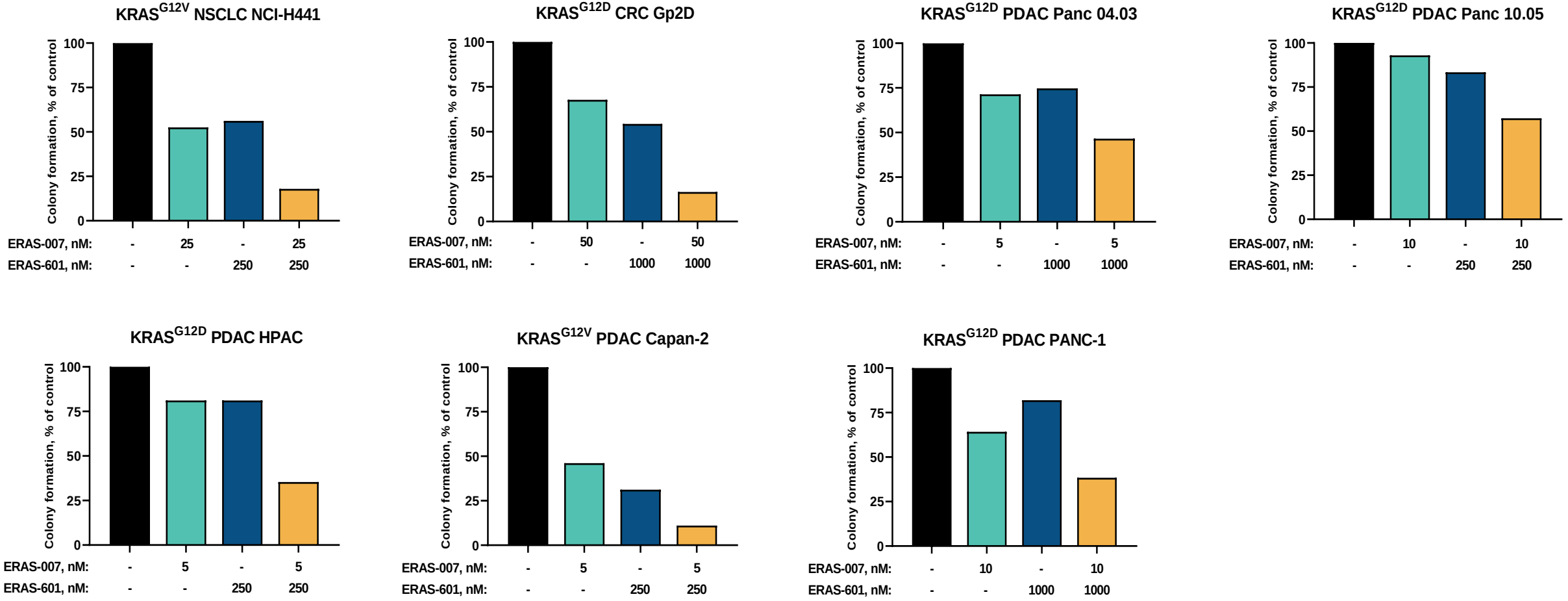


Figure 3. Colony formation assay. KRAS mutant NSCLC, CRC, and PDAC cell lines were seeded for colony formation assays. Cells were then treated with either ERAS-007, ERAS-601, or the ERAS-007 + ERAS-601 MAPKlamp combination. After 14 days, colony formation was quantified by the crystal violet staining method.

ERAS-007 + ERAS-601 MAPKlamp combination showed combination benefit in KRAS mutant CRC and NSCLC CDX models

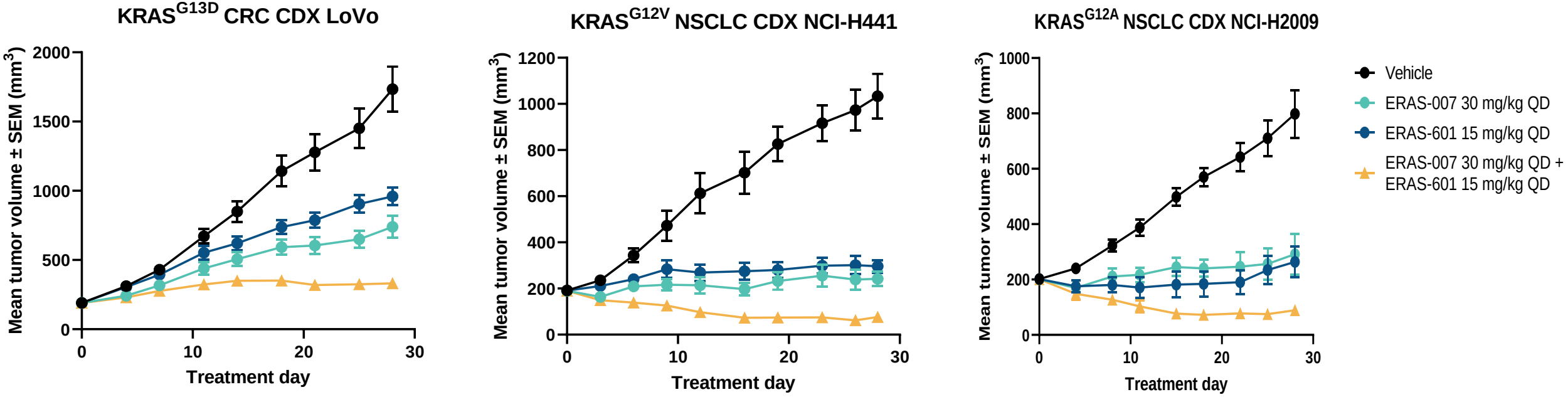


Figure 4. In vivo efficacy of ERAS-007, ERAS-601, or the ERAS-007 + ERAS-601 MAPKlamp combination in KRAS mutant models. Immunodeficient mice bearing the indicated tumor xenografts were orally dosed with vehicle, ERAS-007 at 30 mg/kg QD, ERAS-601 at 15 mg/kg QD, and ERAS-007 at 30 mg/kg QD combined with ERAS-601 at 15 mg/kg QD. Tumors were measured on the indicated days and mean tumor volumes were plotted. *SEM,* standard error of the mean.

The ERAS-007 + ERAS-601 MAPKlamp combination also showed combination benefit in KRAS mutant PDAC PDX models

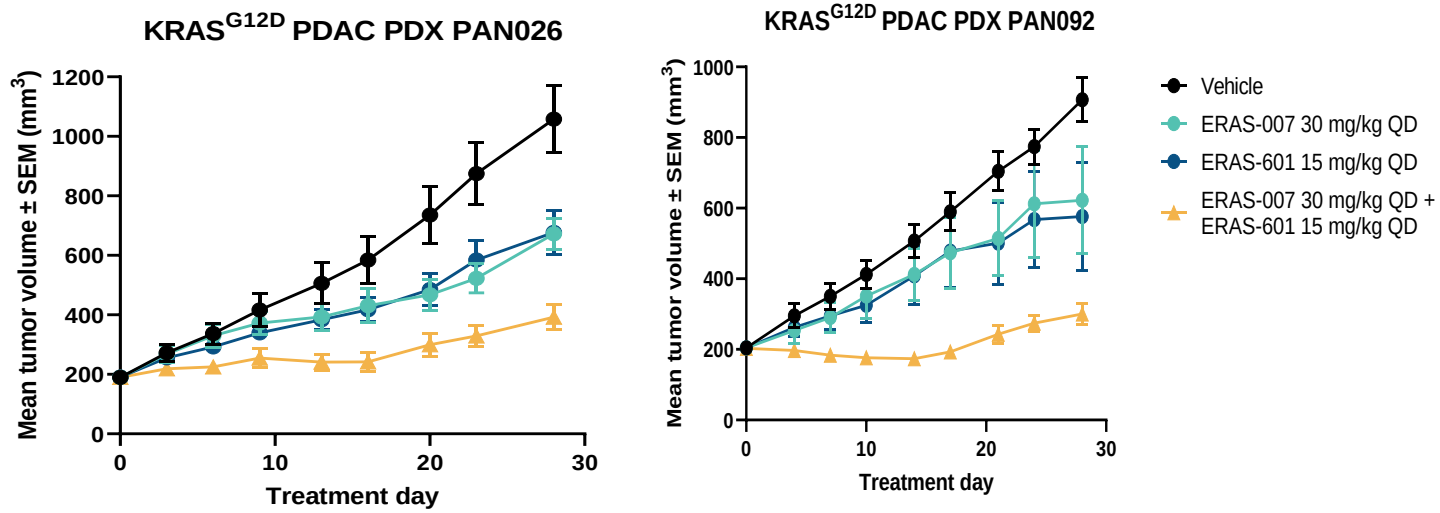


Figure 4. In vivo efficacy of ERAS-007, ERAS-601, or the ERAS-007 + ERAS-601 MAPKlamp combination in KRAS mutant models. Immunodeficient mice bearing the indicated tumor xenografts were orally dosed with vehicle, ERAS-007 at 30 mg/kg QD, ERAS-601 at 15 mg/kg QD and ERAS-007 at 30 mg/kg QD combined with ERAS-601 at 15 mg/kg QD. Tumors were measured on the indicated days and mean tumor volumes were plotted. *SEM,* standard error of the mean.

Mutation	Model ID	Tumor type	Model Type	Anti-tumor efficacy, % TGI		
				ERAS-601 15 mg/kg QD	ERAS-007 30 mg/kg QD	ERAS-601 15 mg/kg QD + ERAS-007 30 mg/kg QD
KRAS^{G12D}	PAN026	Pancreatic	PDX	44%	44%	77%**
	PAN092	Pancreatic	PDX	47%	41%	86%
KRAS^{G13D}	LoVo	CRC	CDX	50%	64%	91%**
KRAS^{G12V}	NCI-H441	NSCLC	CDX	87%	94%	114%**
KRAS^{G12A}	NCI-H2009	NSCLC	CDX	90%	85%	119%*

Table 1. ERAS-007 + ERAS-601 MAPKlamp combination in vivo activity summary across 5 KRAS mutant models
ERAS-601 + ERAS-007 MAPKlamp combination exhibited superior TGI relative to ERAS-601 and ERAS-007 monotherapies in 5 KRAS mutant CDX and PDX models. *p-values < 0.05 **p-values < 0.01 ***p-values < 0.001 (p-values assessed relative to ERAS-601 and ERAS-007 monotherapies).

Conclusions

- ERAS-007 + ERAS-601 MAPKlamp combination enhances inhibition of RAS/MAPK pathway signaling by simultaneously inhibiting the terminal node of the RAS/MAPK pathway, ERK1/2, and an upstream node, SHP2
- This MAPKlamp combination enhances the inhibition of colony growth in KRAS mutant NSCLC, CRC, and PDAC cell lines in vitro
- In vivo, ERAS-007 + ERAS-601 MAPKlamp demonstrates superior tumor growth inhibition and tumor regression relative to either agent alone in KRAS mutant NSCLC, CRC, and PDAC xenografts
- These data support the clinical development of the ERAS-007 + ERAS-601 MAPKlamp combination

Q&A

ERASCA

Thank You!