Evolving Targeting Therapy for BRAF-mutated Colorectal Cancer

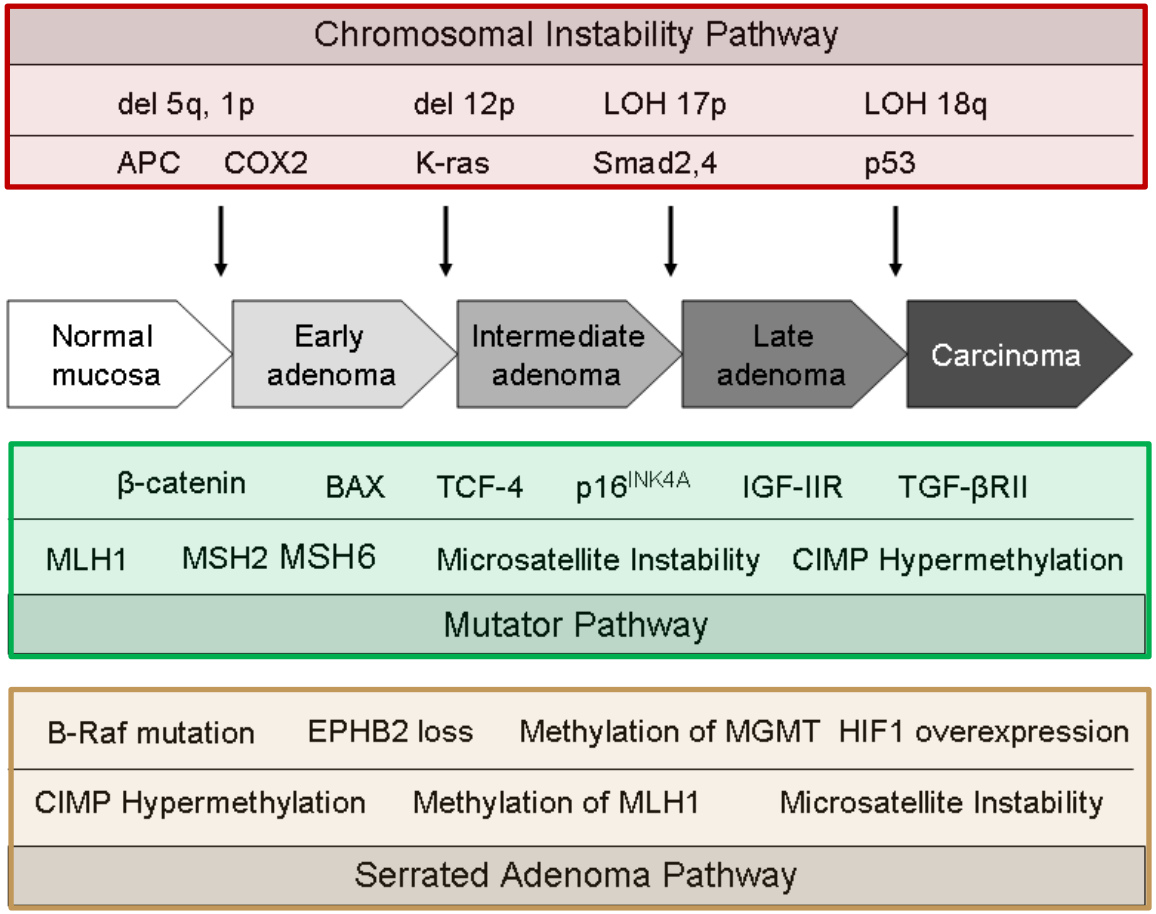
Scott Kopetz, MD, PhD.
Department of GI Medical Oncology
MD Anderson Cancer Center

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Disclosures

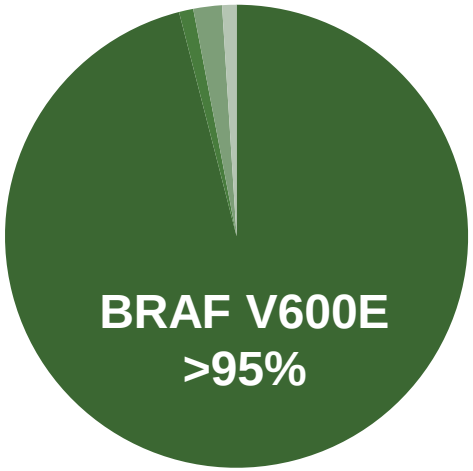
- Advisory board, research funding: Amgen, Roche/Genentech
- Research funding: Biocartis, Sysmex
- Advisory board: Taiho, BMS, Merrimack, Bayer, Array, Sanofi, GSK

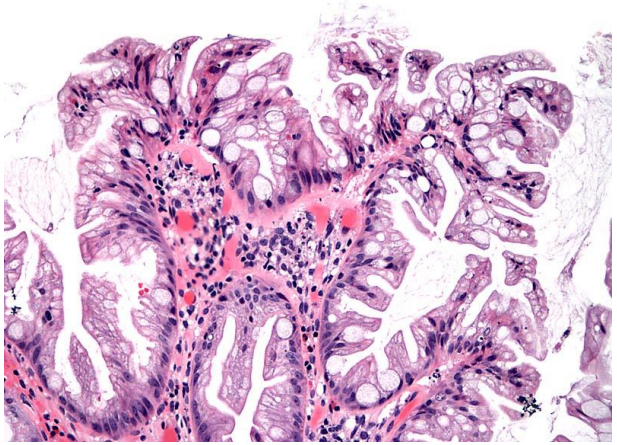
Classic Mechanisms of Carcinogenesis in Colorectal Cancer



Serrated Adenoma / BRAF^{mut} Subgroup

- BRAF mutations reflect a unique subset of CRC
  - Vast majority are BRAF V600E
  - Unique precursor lesion: Sessile serrated adenoma
  - Prognostic importance in early and late stage





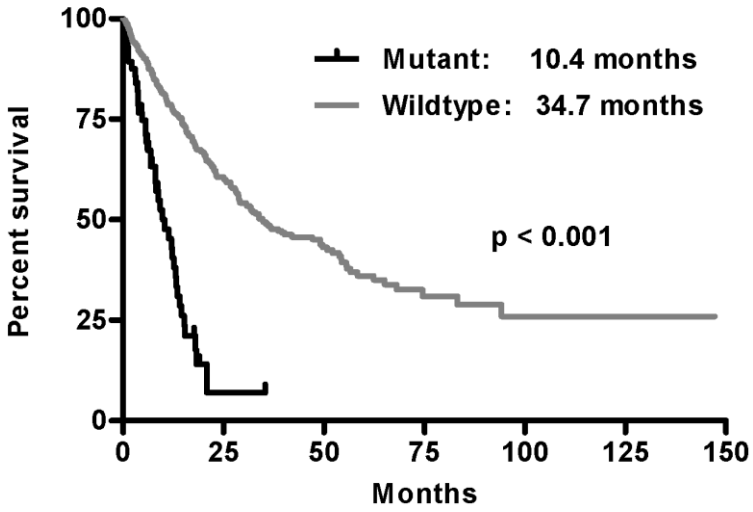
Bollag et al, Nature '10

Clinical Utility of $BRAF^{mut}$ in Standard of Care for CRC

- Determining Sporadic vs Familial MSI-H
  - Part of the recommended algorithm.
- Prognosis for Stage II / III
  - Yes, likely. Not yet in guidelines.
- Prognosis for Stage IV
  - Yes, in guidelines
- Predictive for EGFR Inhibitor sensitivity
  - Mixed data

Unique BRAF^{mut} Clinical Behavior: Metastatic Colorectal Cancer

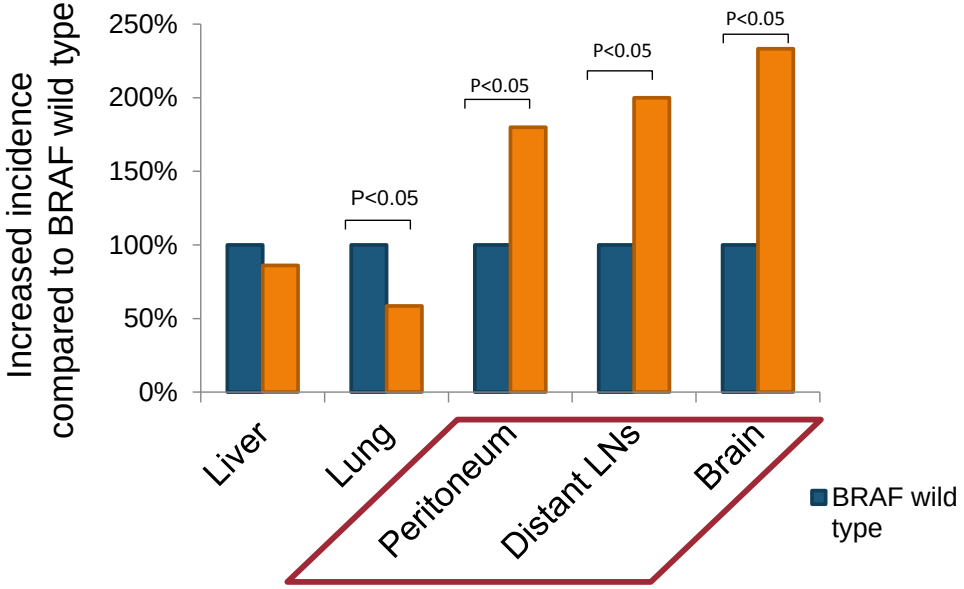
Very short overall survival



Hazard Ratio of 10.6 for OS

Less than 1 year OS

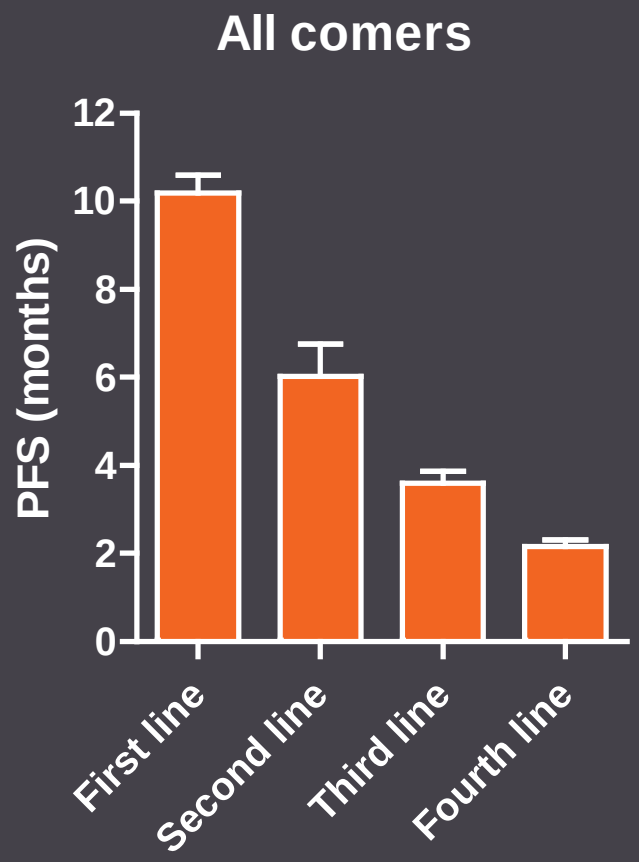
Atypical patterns of metastases

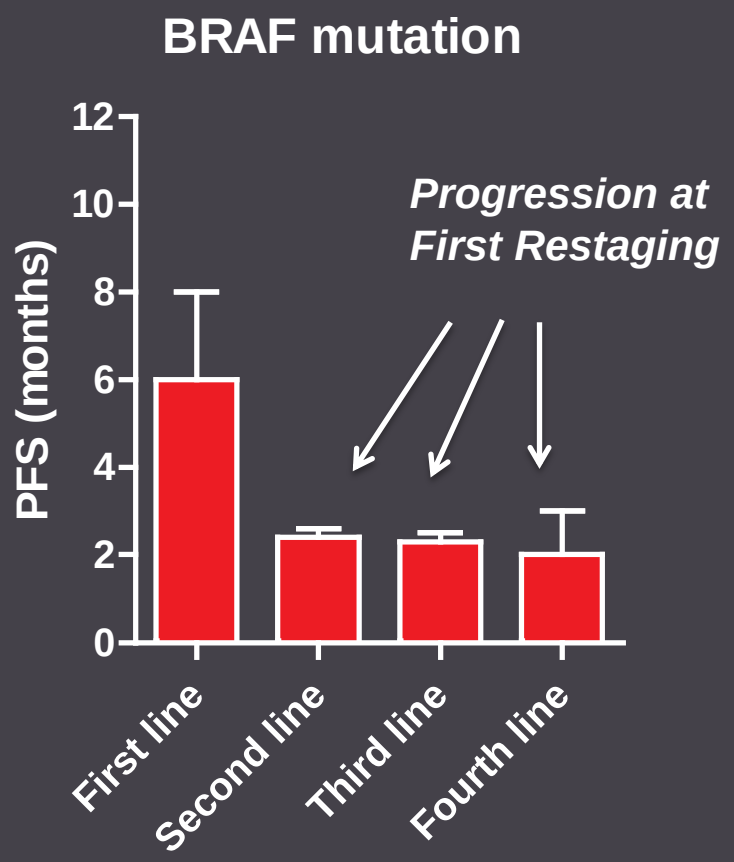


THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Morris et al , Clin Colorect al Cancer '13 Tran, Kopetz, et al, Cancer 2011

Limited Benefit of Standard of Care for BRAF^{mut} CRC Patients

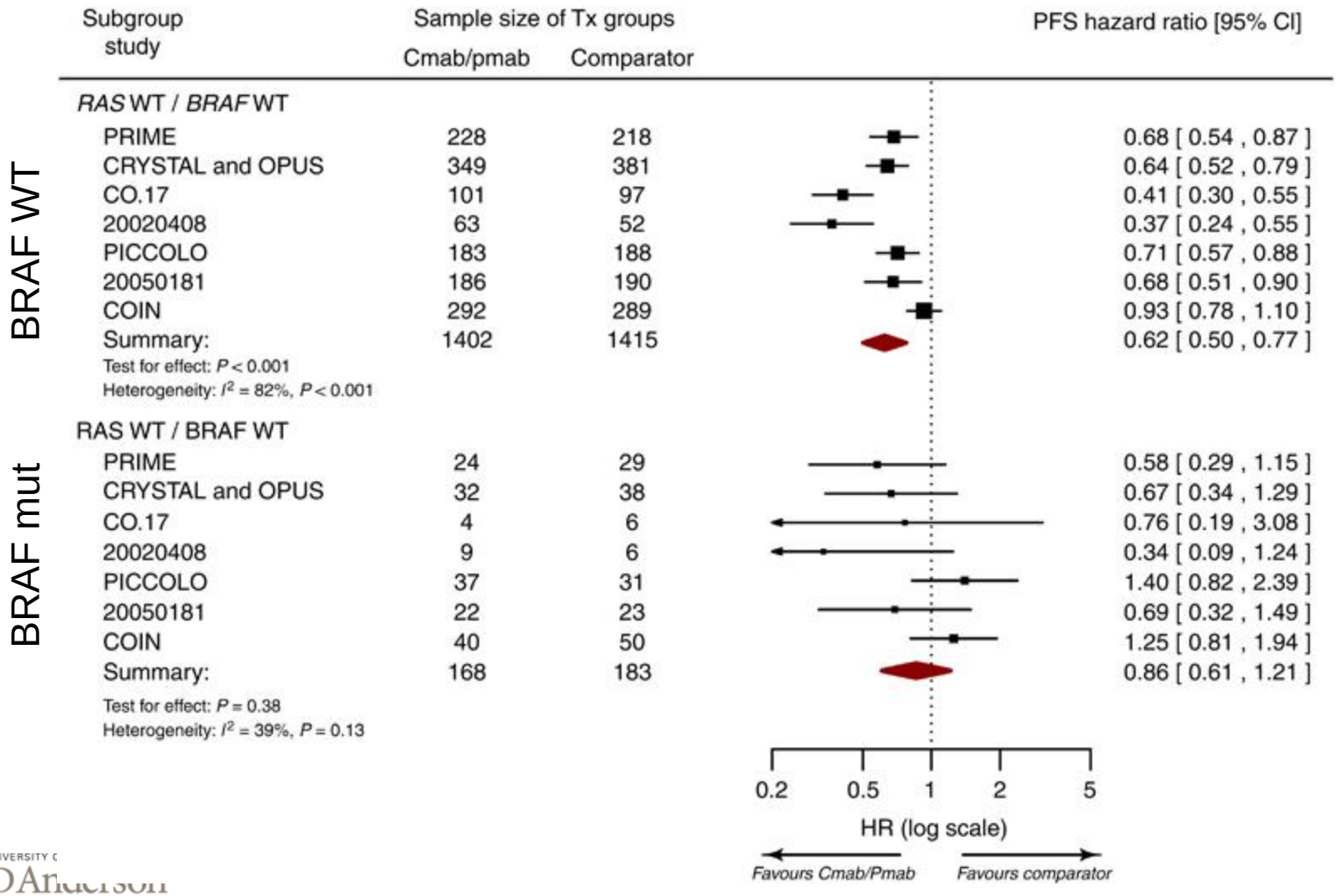




Morris, et al Clin Colorectal Cancer, '14

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

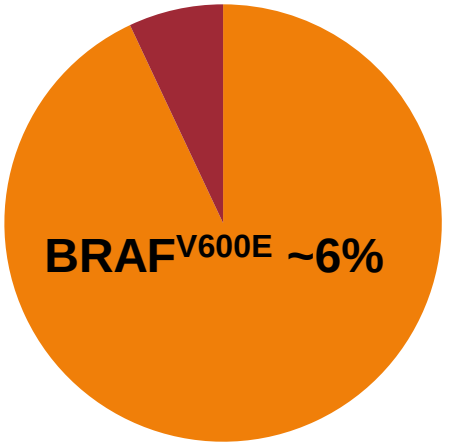
BRAF mutation and EGFR inhibition



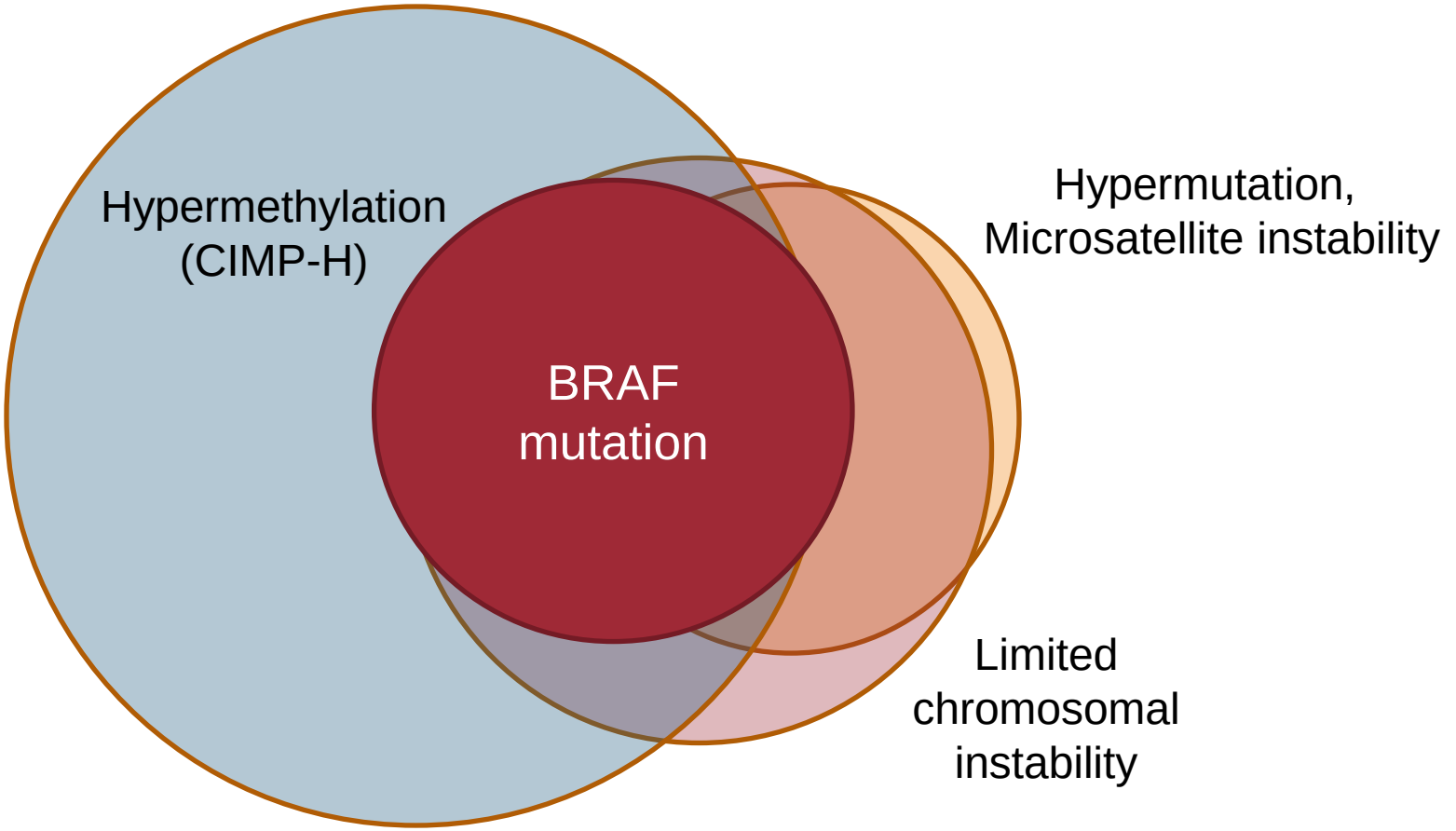
Roland, BJC '15

Why BRAF in CRC provides an example for discussion

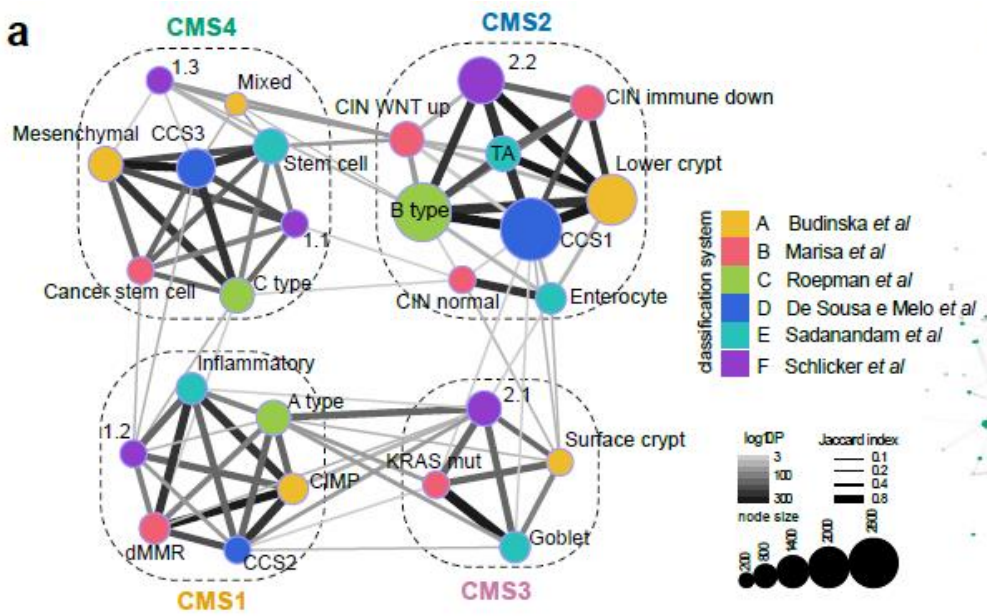
- Defines a unique molecular AND clinical subset
  - Substantial clinical need
- Compensatory activity uncovers at least two key drivers: BRAF and EGFR
- Proof of concept is established
  - With strong preclinical rationale established
  - In multiple single arm studies
  - In ongoing randomized CRC trials
- Lessons learned for iterative drug development

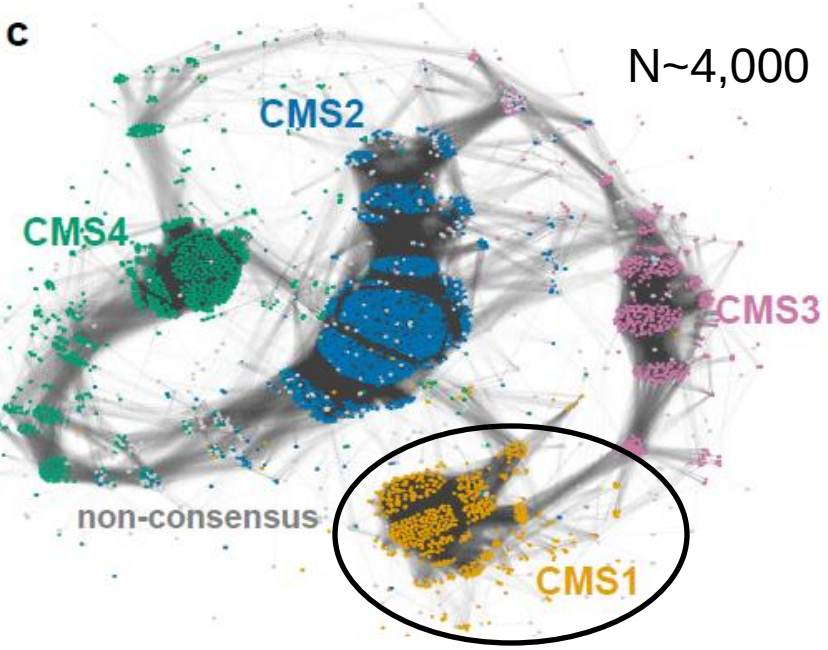


Landscape of $BRAF^{mut}$ Colorectal Cancer



Consensus Molecular Subtypes: CMS1





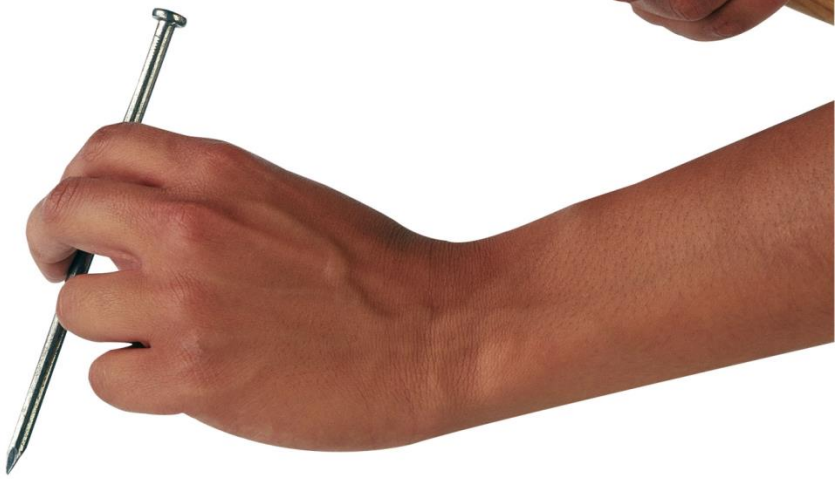
CMS1 MSI Immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
MSI, CIMP high Hypermutation	SCN high	Mixed MSI status SCNA low, CIMP low	SCN high
BRAF mutations		*KRAS* mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration TGF beta activation Angiogenesis

Guinney et al Nat Med '15

How to treat these patients?

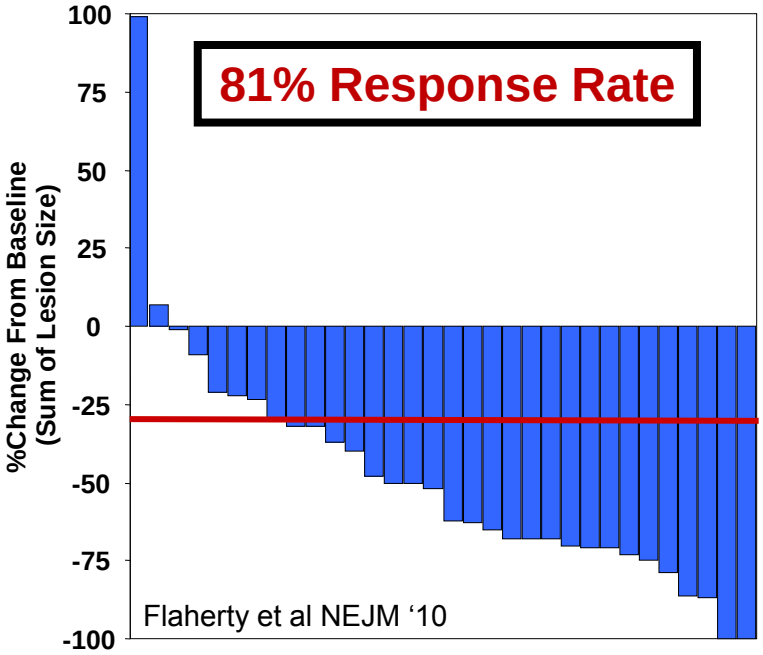
BRAF inhibitor

BRAF mutation

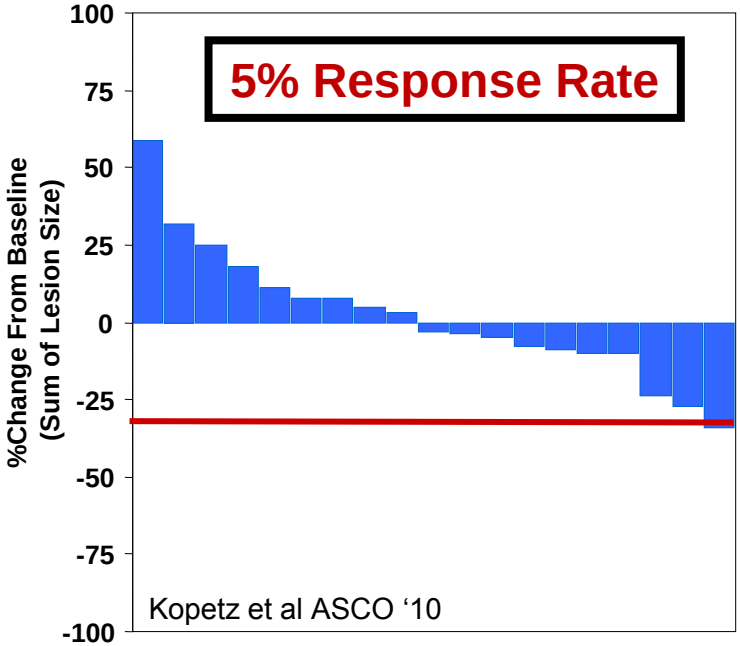


Vemurafenib (PLX4032)

Refractory Melanoma



Refractory Colorectal



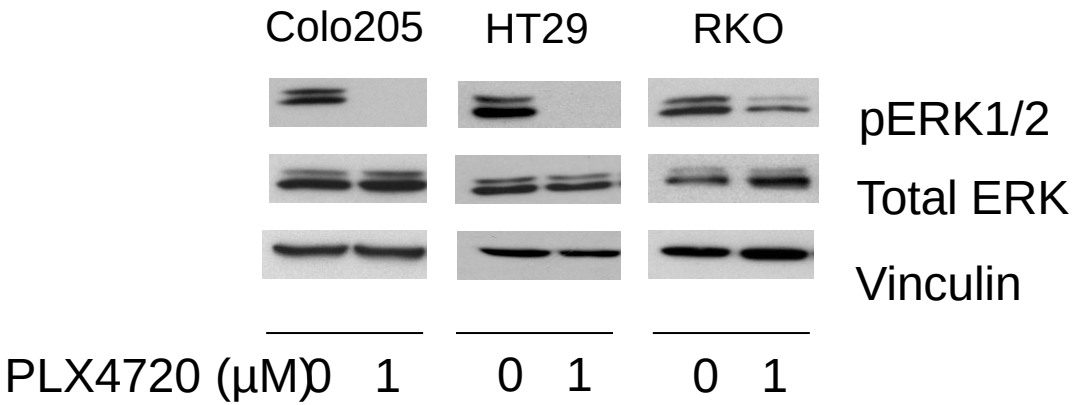
Preclinical data fails to demonstrate sufficient MAPK inhibition in CRC, unlike melanoma

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

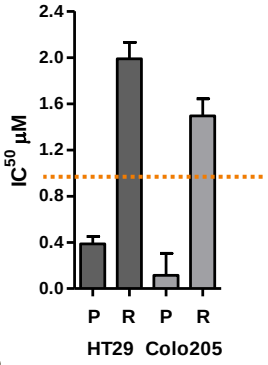
Mao, et al CCR '14

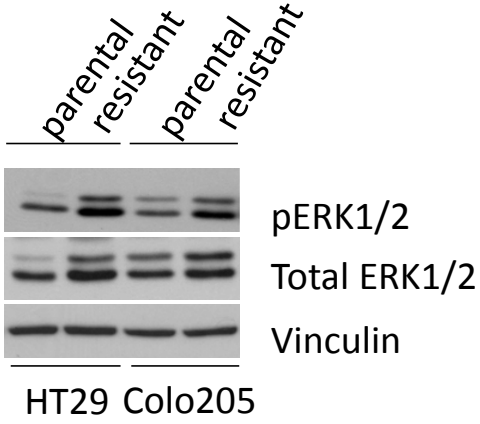
Persistent MEK activation:
Expansion from melanoma concepts

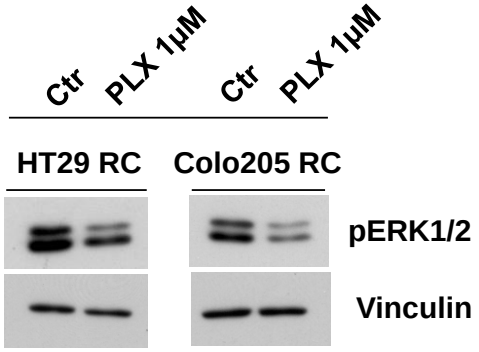
ERK inhibition is incomplete in some CRC cell lines



Acquired resistance is associated with increased pERK and incomplete inhibition







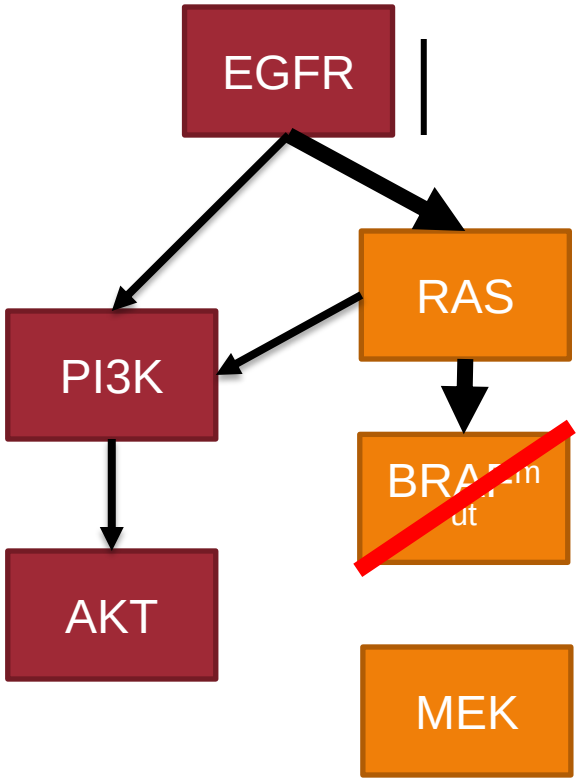
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Mao, et al CCR '

BRAF resistance through MEK reactivation

IF the problem is only incomplete MEK inhibition….

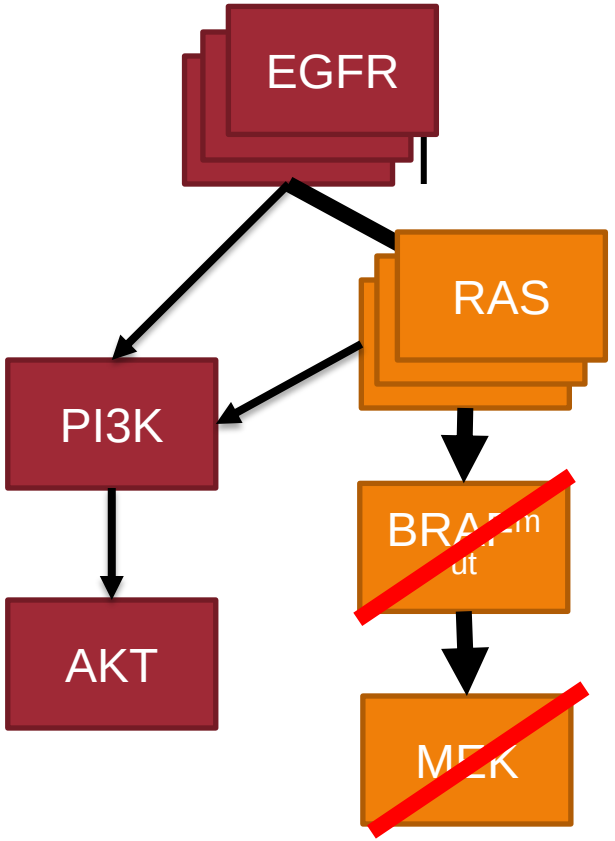
Then treat with dual inhibition of BRAF + MEK



BRAF resistance through MEK reactivation

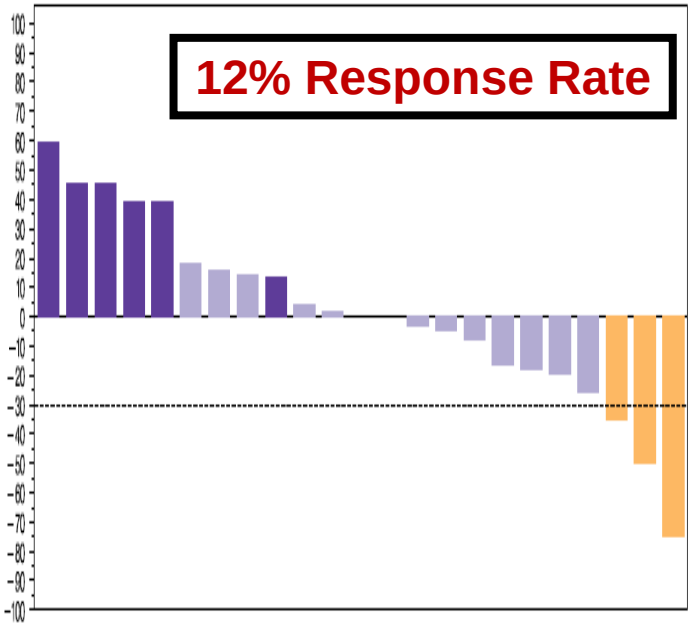
IF the problem is only incomplete MEK inhibition….

Then treat with dual inhibition of BRAF + MEK



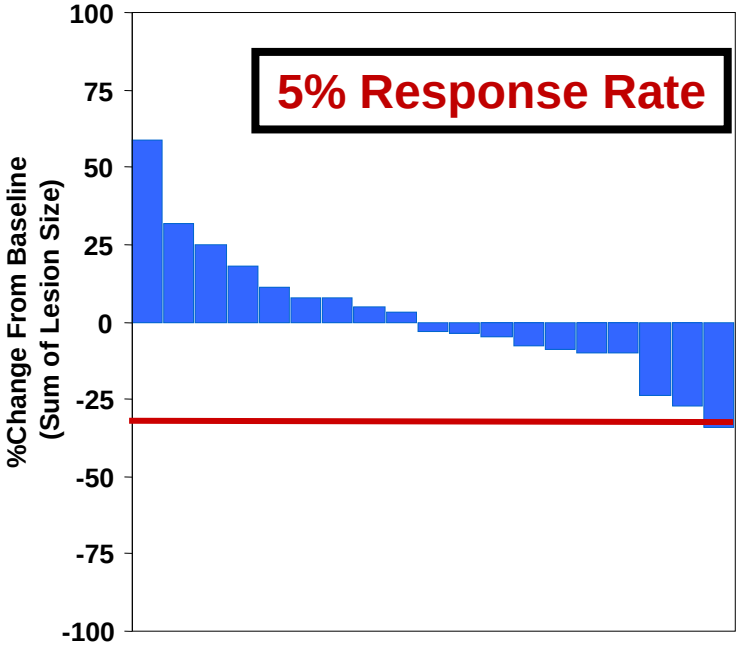
Minimal Improved Efficacy with Dual BRAF + MEK Inhibition

BRAF + MEK inhibition



GSK212 + GSK436

BRAF inhibition



Vemurafenib

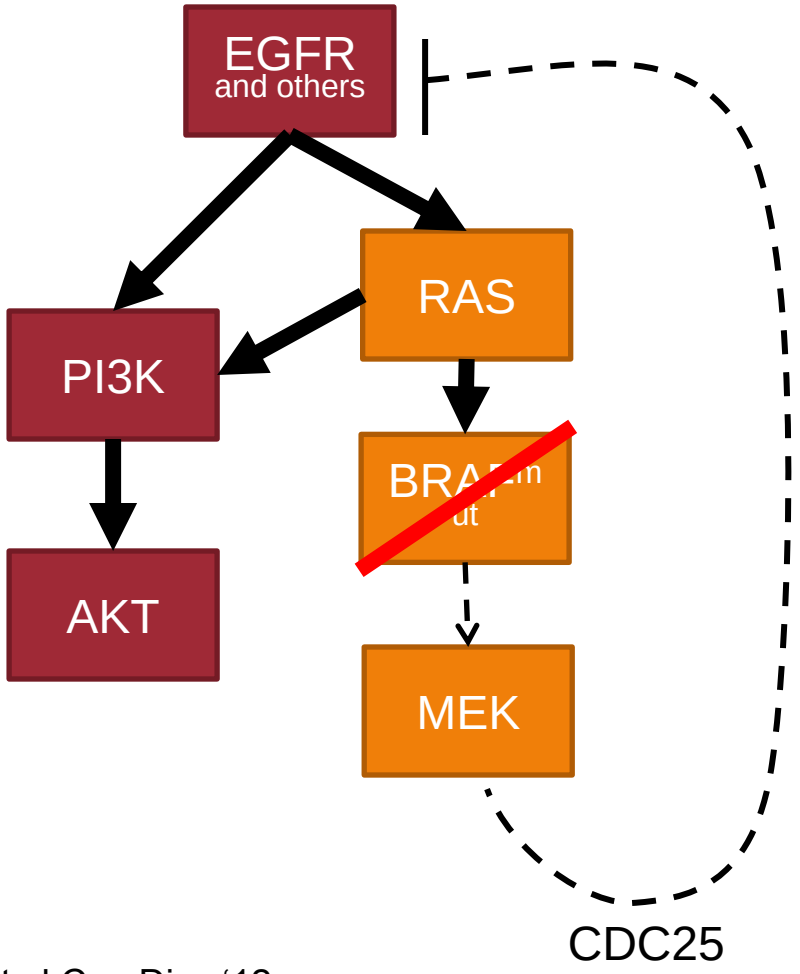
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Corcoran et al JCO '15, Kopetz et al JCO '15

Key Finding: Feedback EGFR Signaling

Perhaps the problem isn't ONLY incomplete MEK inhibition….

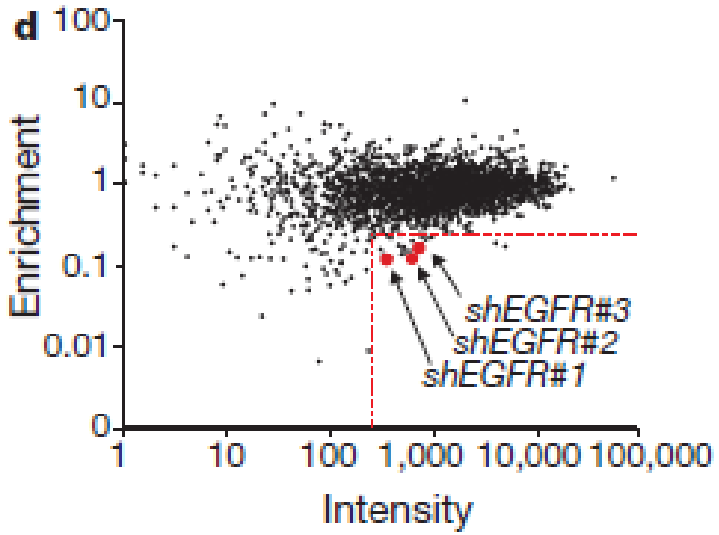
Treat with EGFR + BRAF inhibitors

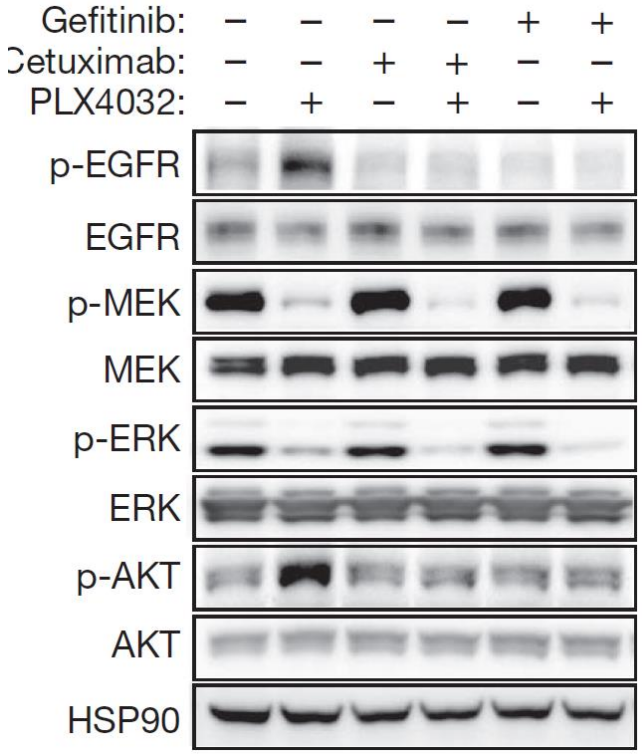


Prahallad et al Nature '12, Corcoran et al Can Disc '12

Unbiased Synthetic Lethality Screen:
EGFR Identified as a Synergistic Partner

HT29 cell line (Sensitive)





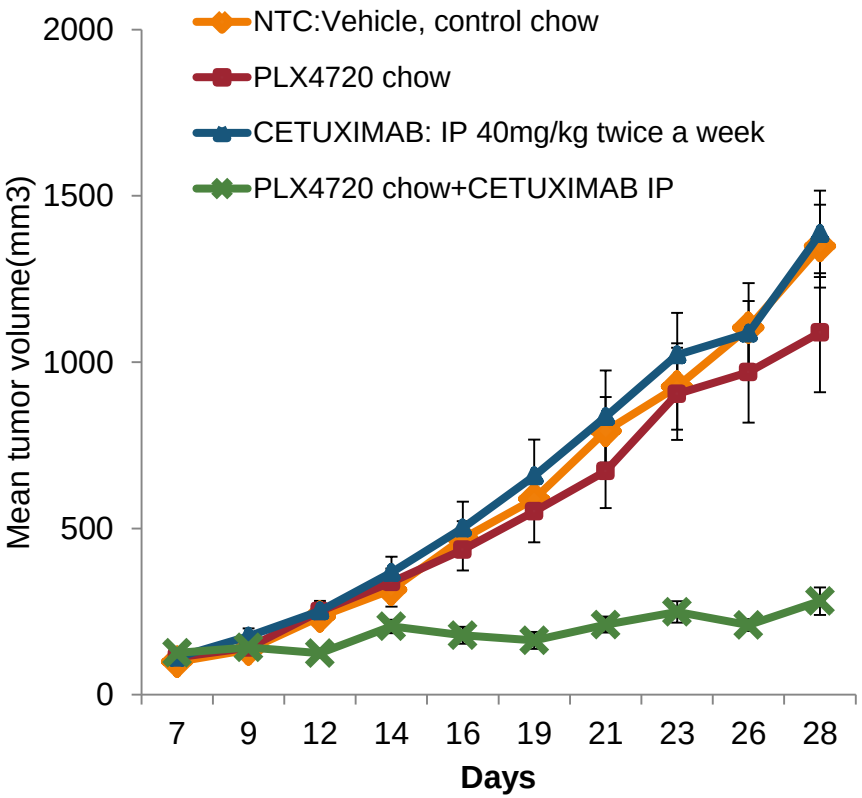
EGFR identified

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

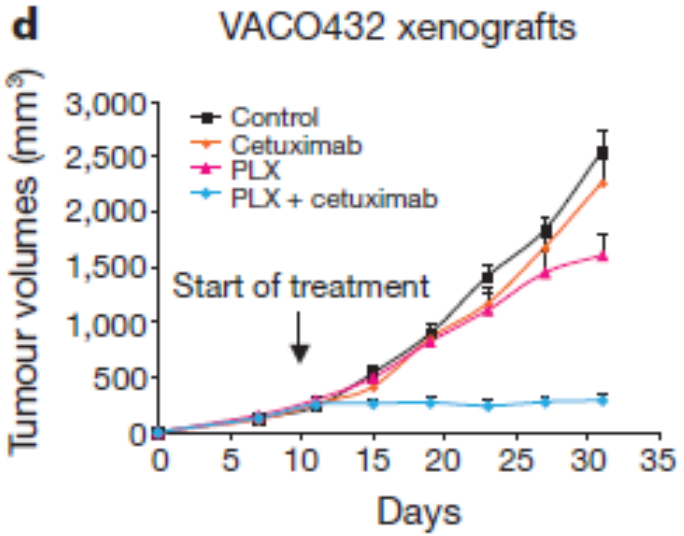
Prahallad et al Nature '12

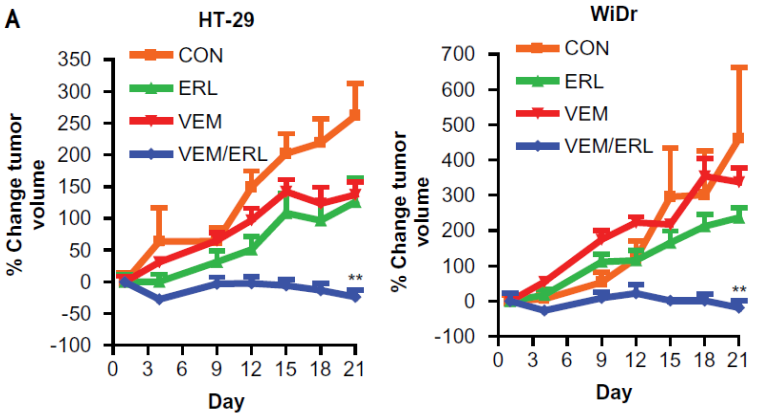
Synergy in Murine Models: BRAF + EGFR

Cell line and Patient-derived xenograft models



Kopetz, unpublished; Yang et al Can Res '11

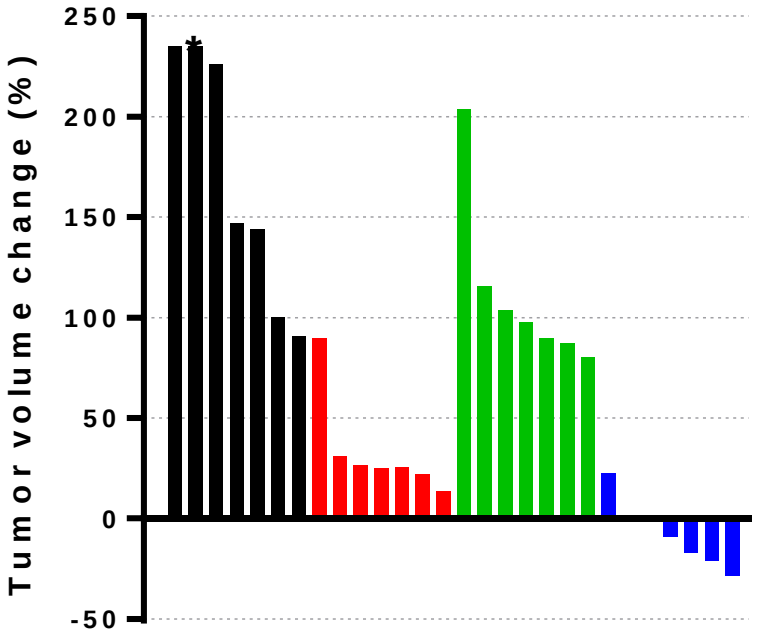


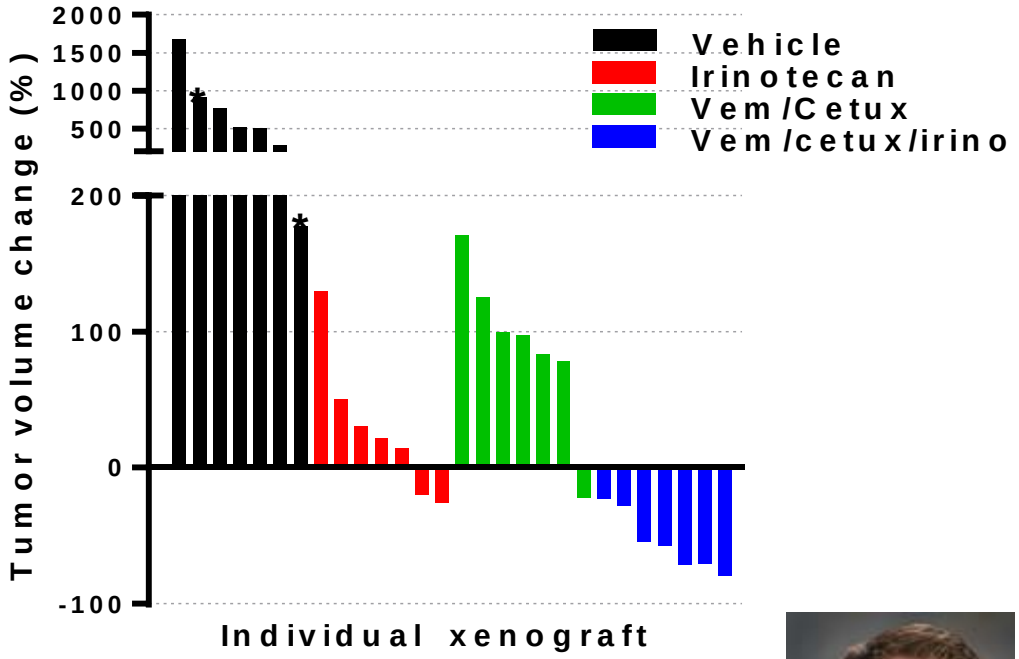


Prahallad et al Nature '12; Corcoran et al Can Disc '12

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Irinotecan combined with EGFR/BRAF inhibition induces regressions

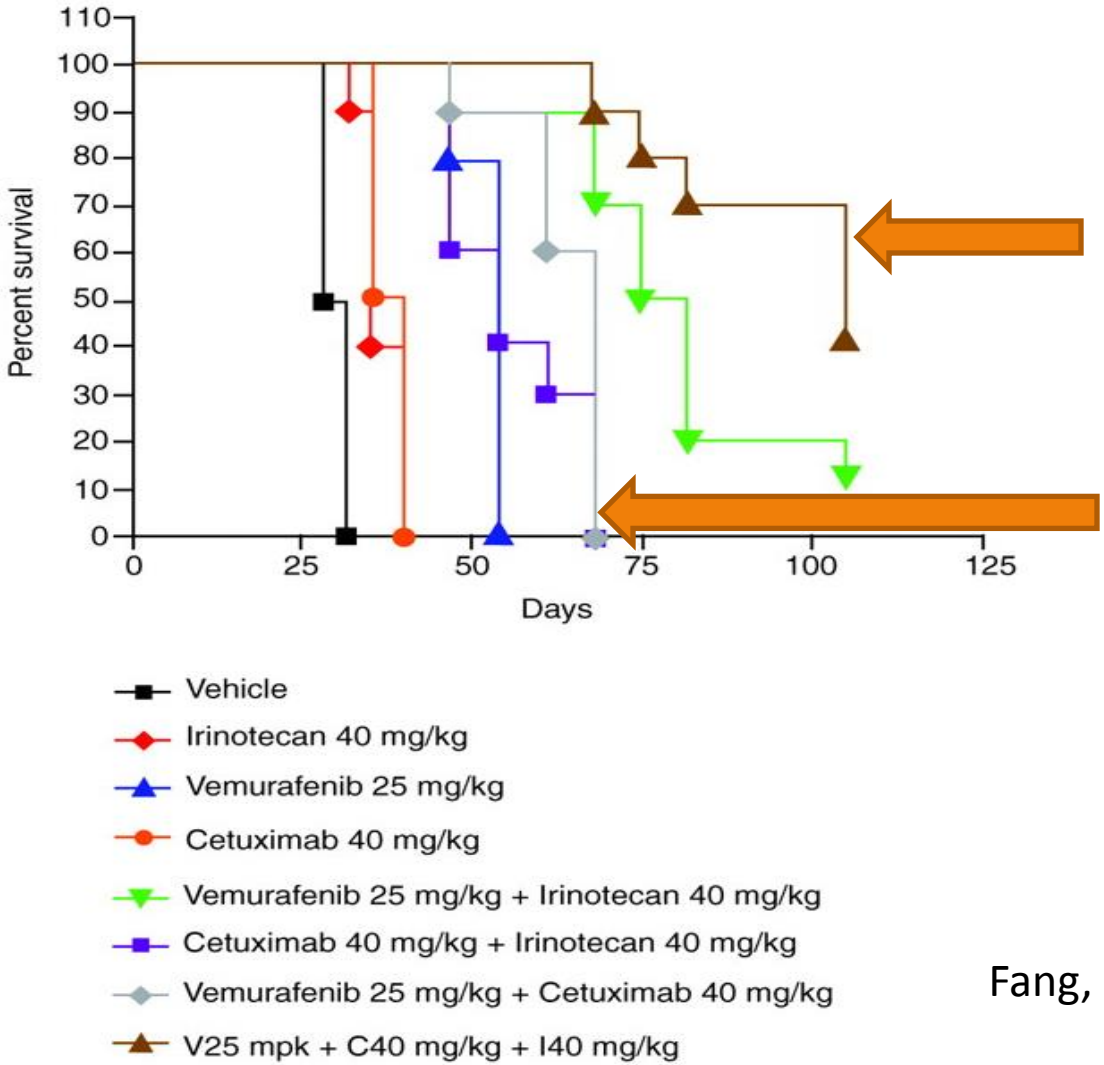




Van Morris, Alex Sorokin

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

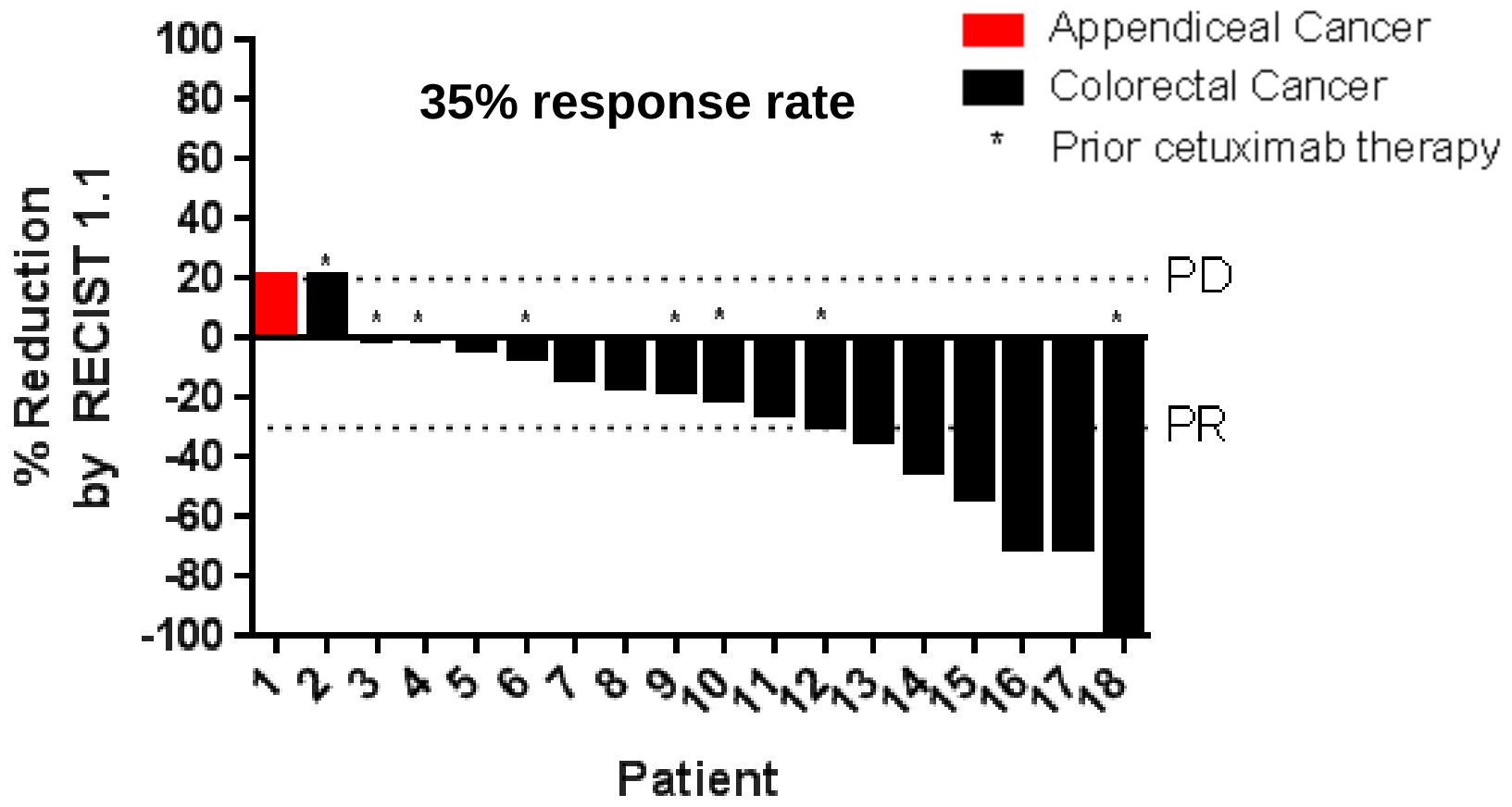
Improved ***Survival*** with Cetuximab and Vemurafenib combined with Irinotecan



Better outcomes with irinotecan

Fang, et al , Can Res, '12

Phase 1B of Cetuximab, Vemurafenib, Irinotecan: High Response Rate

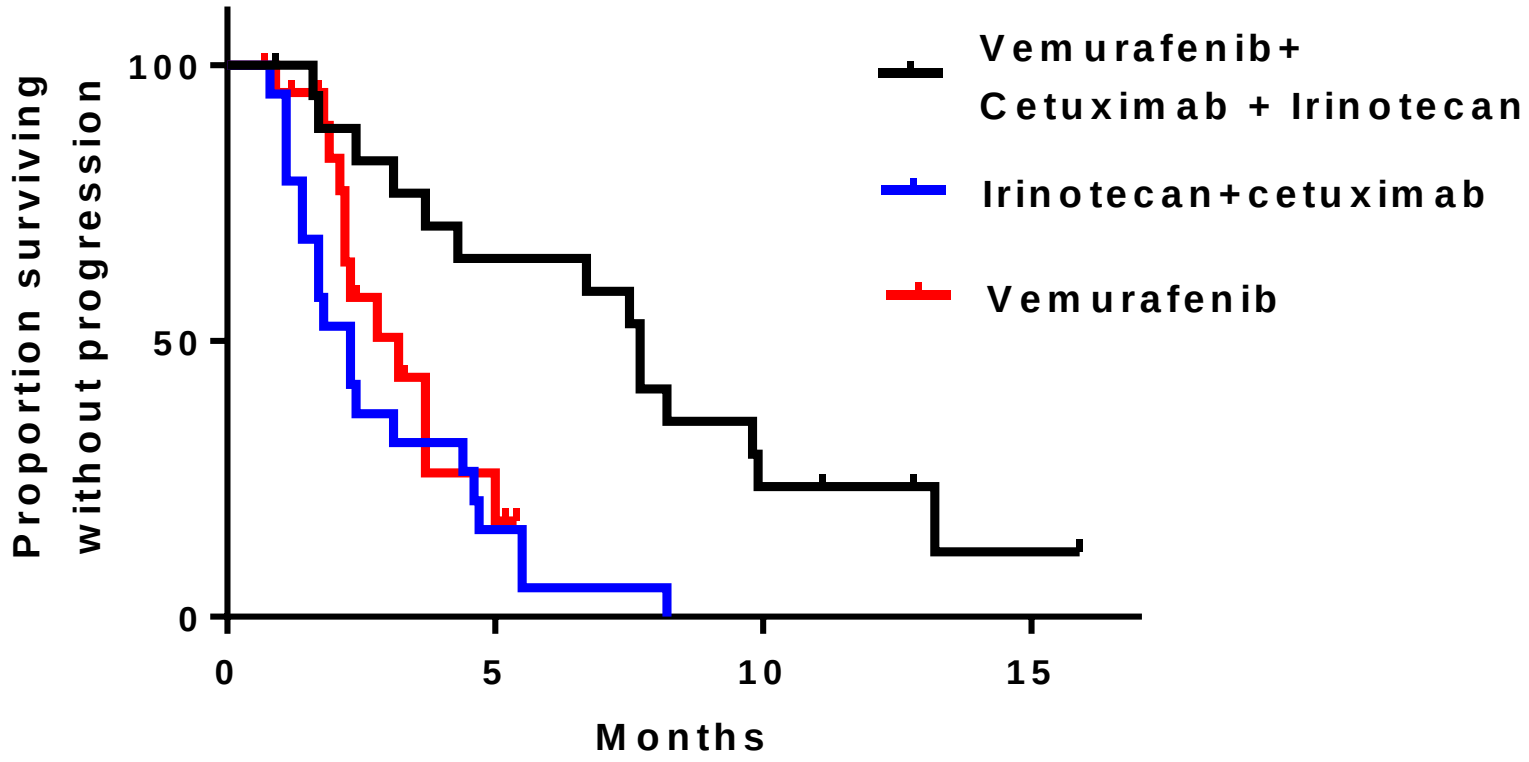


Historical response rate is <10% for cetuximab and irinotecan with PFS of 2 months.

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

David Hong et al. ASCO, ’15; Morris, CCC, ‘14

Cross-Trial Comparison: Phase 1B vs Historic Control for mBRAF CRC

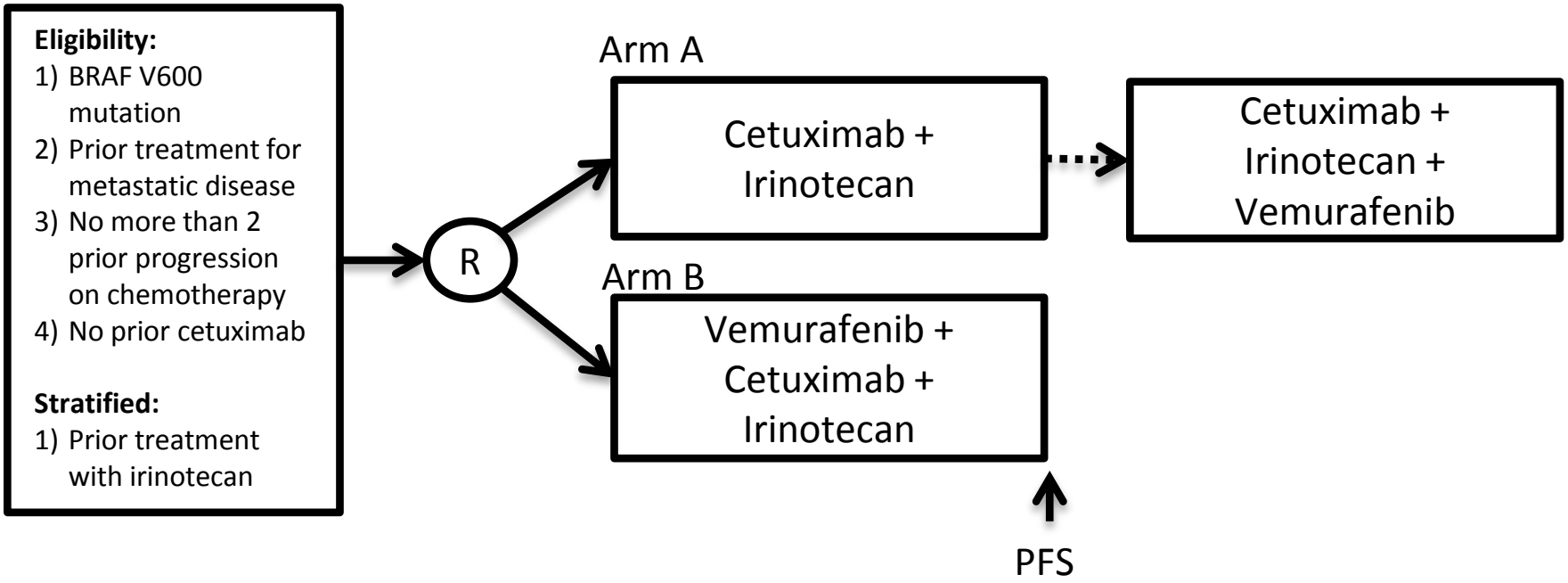


THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Van Morris

SWOG 1406: BRAF + EGFR

with availability through other cooperative groups



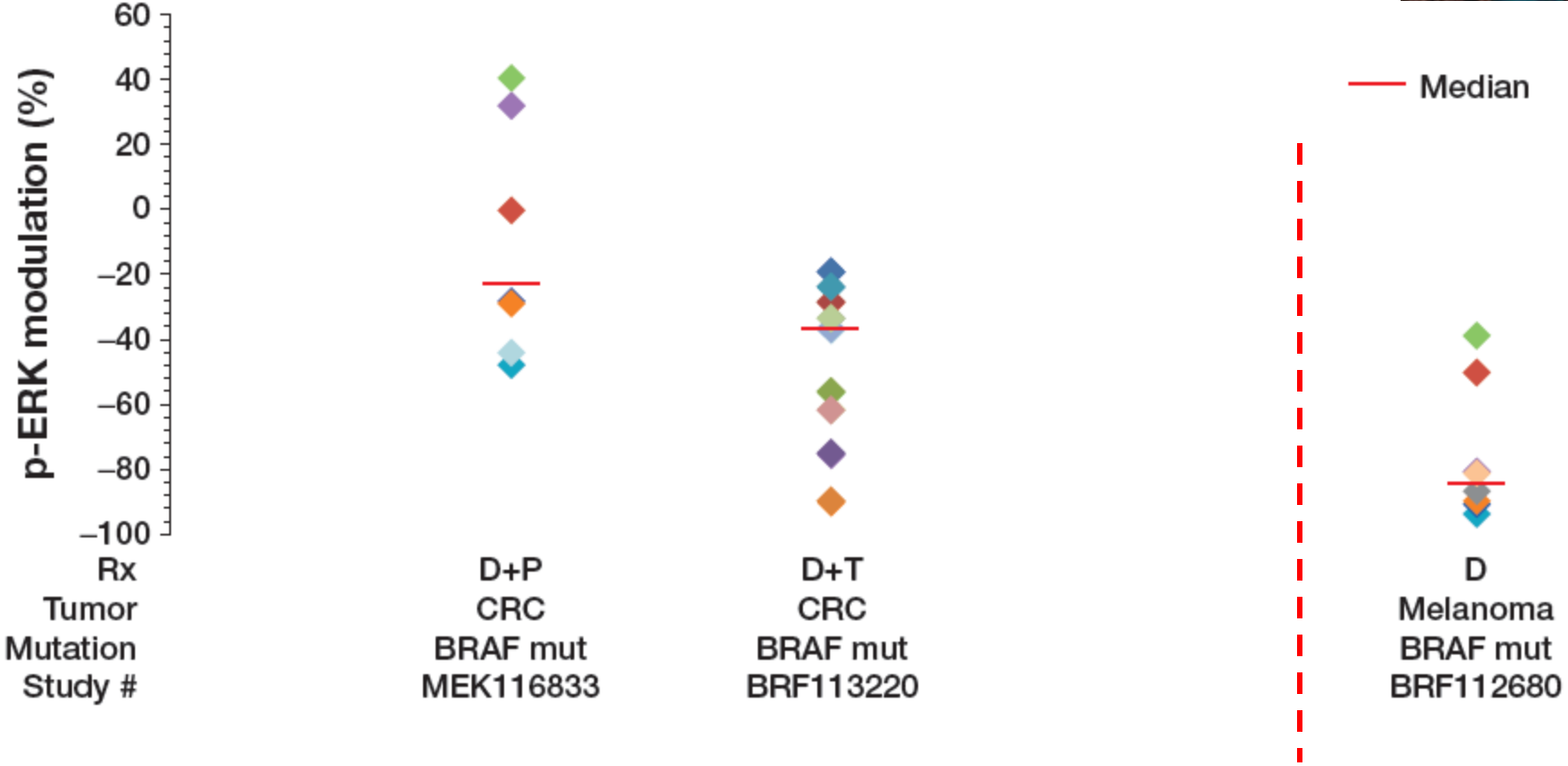
Historical response rate is <10% for cetuximab and irinotecan, with PFS of 2.4 months for $BRAF^{mut}$

Target HR 0.5 for PFS, with 2-sided alpha 5%, power 90%

N= 105 patients

Results Fall '16, Kopetz, PI

Cross-Study Comparison of Phospho-ERK Modulation



Response Rate: 13% 12%

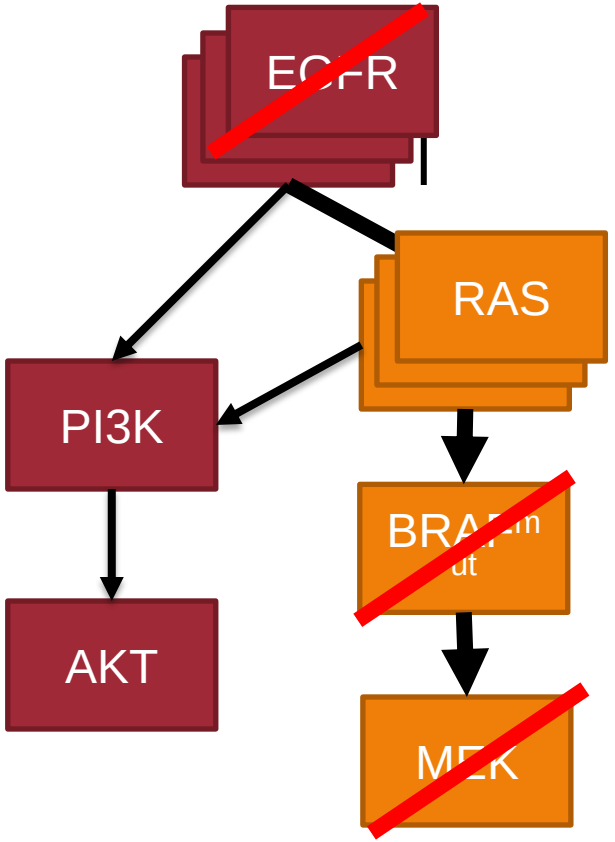
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Chloe Atreya, ASCO '15

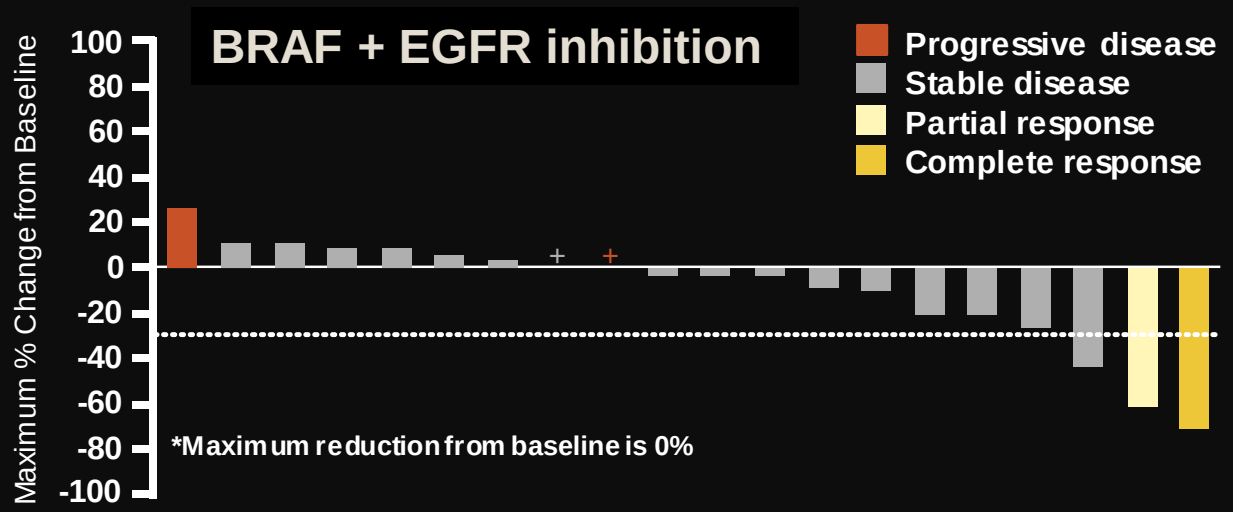
BRAF resistance through MEK reactivation

IF the problem is only incomplete MEK inhibition….

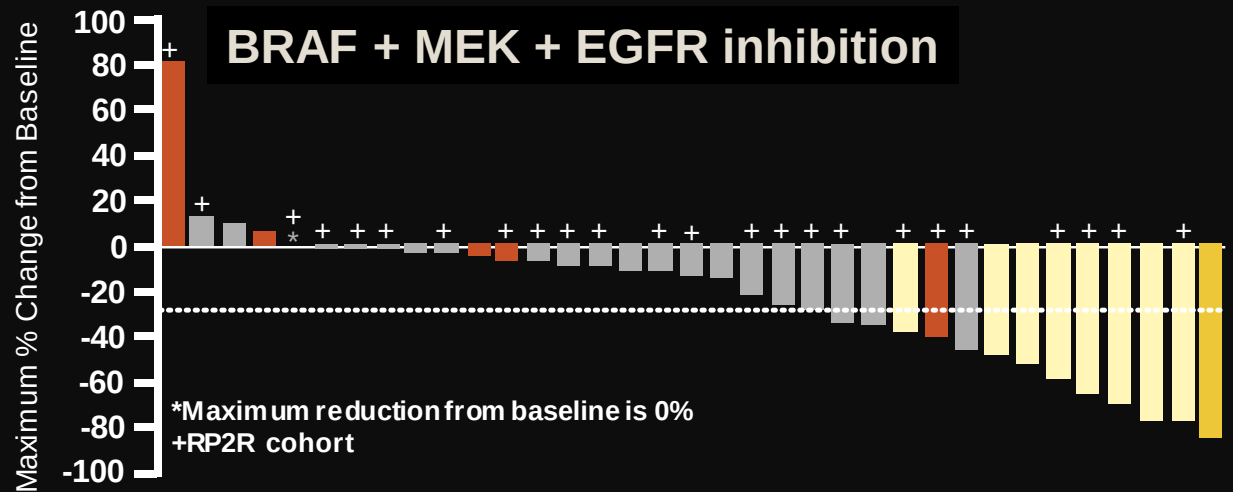
Then treat with triplet inhibition of BRAF + MEK + EGFR



Dabrafenib + Panitumumab +/- Trametinib



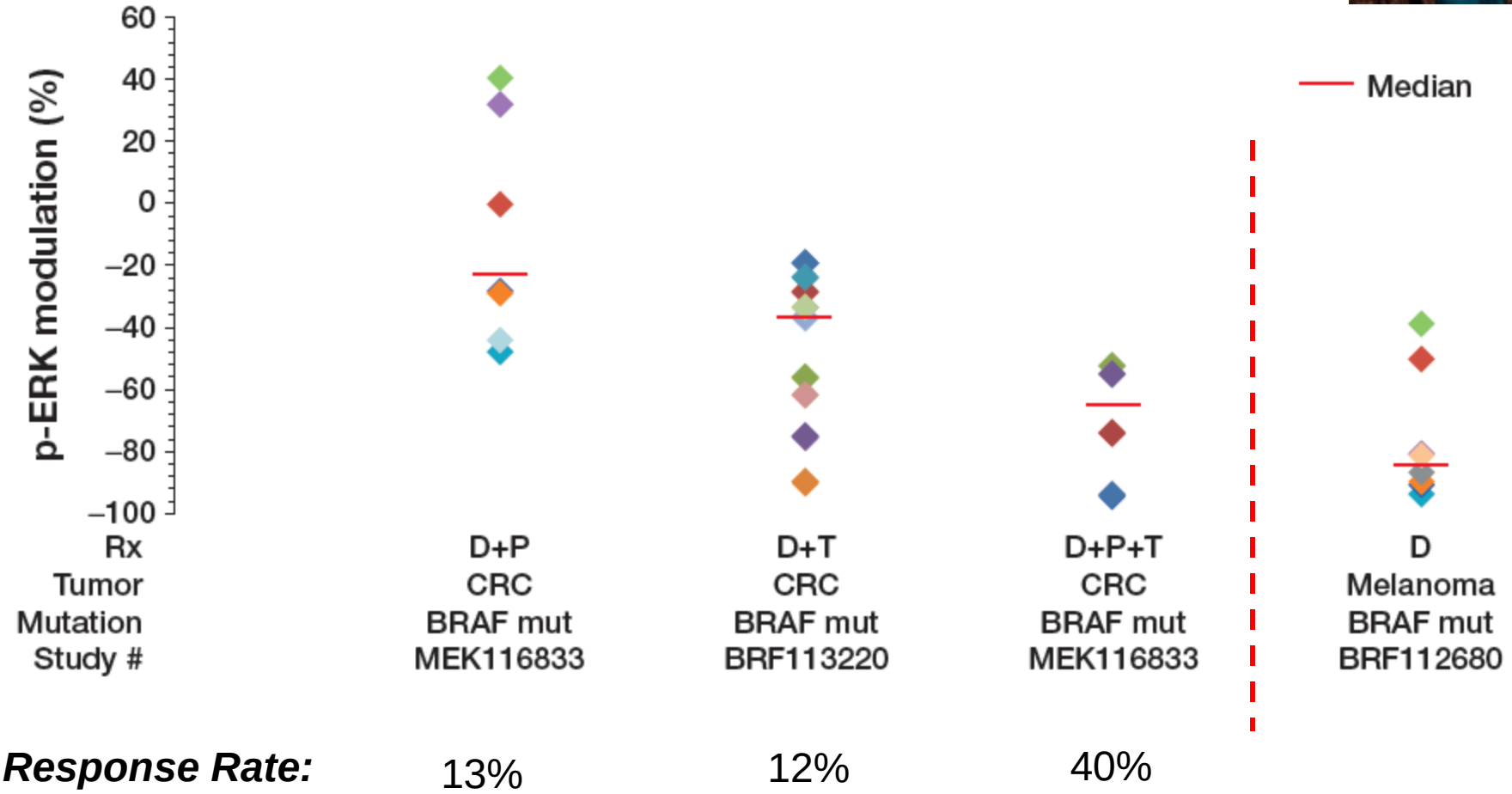
D+P (N=20)
CR+PR: 2 (**10%**)



D+P+T (N = 35)
CR+PR: 9 (**26%**)

Atreya et al ASCO ‘15

Cross-Study Comparison of Phospho-ERK Modulation

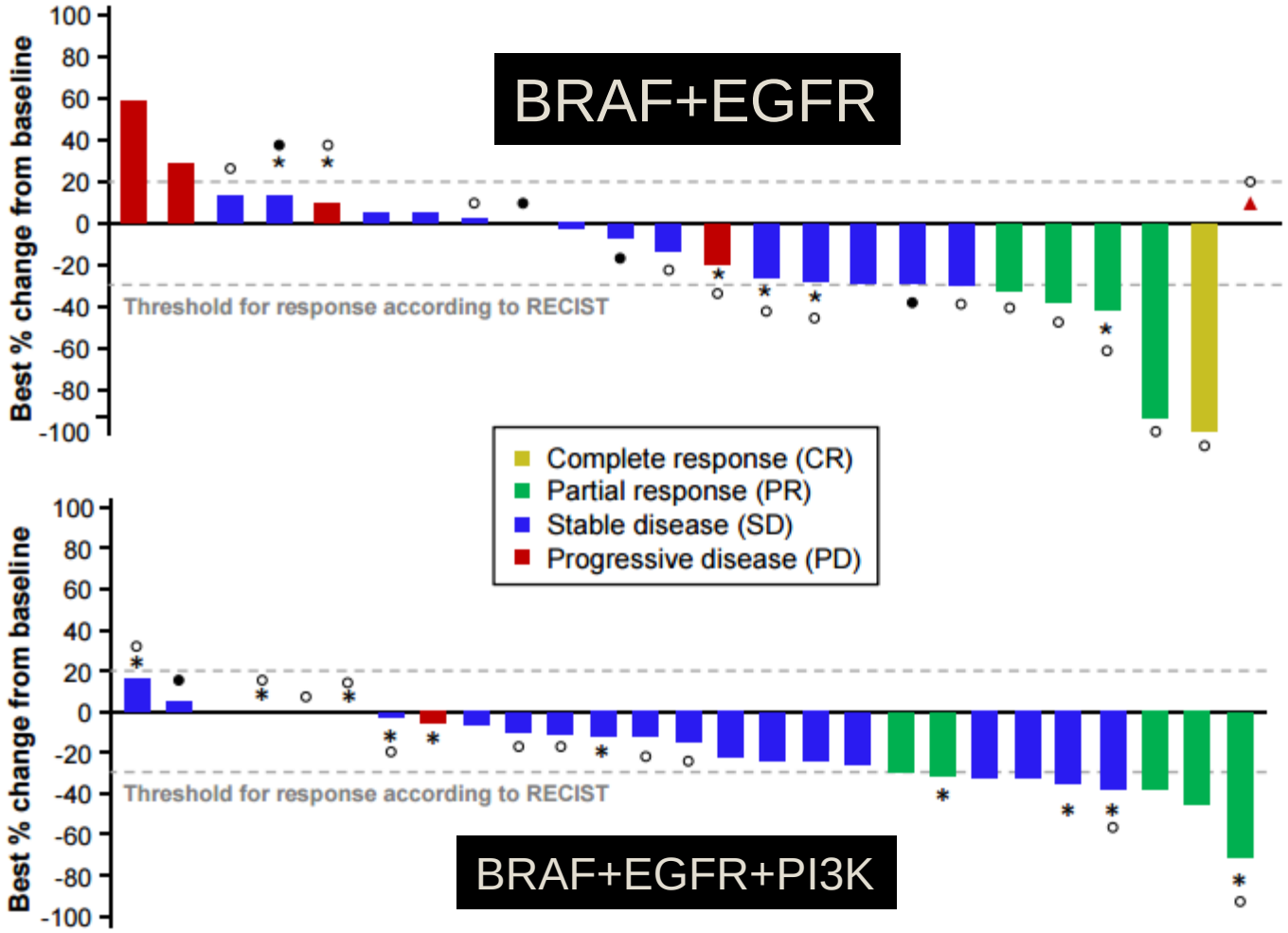


Response Rate: 13% 12% 40%

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Chloe Atreya, ASCO ‘15

Encorafenib + Cetuximab +/- BLY719



Dual Combination

PD: 4 (15%)
SD: 14 (54%)
PR: 5 (19%)[a]
CR: 1 (4%)

Triple Combination

PD: 1 (4%)
SD: 17 (61%)
PR: 9 (32%)[b]

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

See survival data update tomorrow (J. Tabernero)

Geel et al ASCO '14

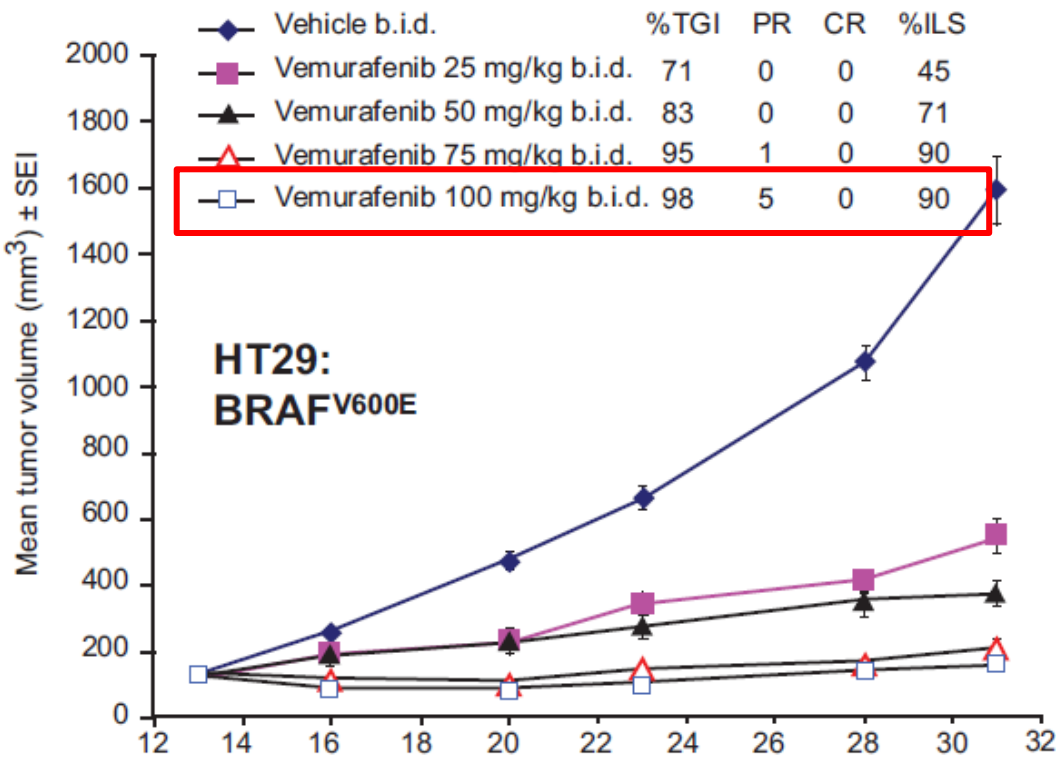
Comparison of RR and PFS for $BRAF^{mut}$ CRC

Regimen	Response	PFS	Citation
Single/Doublet RAF/MEK			
Vemurafenib	5%	2.1 months	Kopetz, JCO'15
Dabrafenib	11%	NR	Falchook, Lancet '08
Encorafenib	16%	NR	Gomez-Roca, ESMO '14
Dabr +Tramet	12%	3.5 months	Corcoran, JCO '15
Doublet with EGFR			
Vem + Panit	13%	3.2 months	Yeager et al CCR '14
Vem + Cetux	20%	3.2 months	Tabernero et al ASCO '14
Encoraf + Cetux	23%	3.7 months	Schellen et al AACR '15
Dabr + Panit	10%	3.4 months	Atreya, ASCO '15
Triplet with EGFR			
Vem + Cetux + Irino	35%	7.7 months	Hong, ASCO '15
Dabr + Tramet + Panit	26%	4.1 months	Atreya, ASCO '15
Encoraf+Cetux+Alpelisib	32%	4.3 months	Schellen et al AACR '15

Learning from BRAF Drug Development Story

- Better preclinical models
- Improving interrogation of response
- Beyond paired biopsies… improved options for interrogating biology of patients under therapy

Vemurafenib *in vivo* in colorectal cancer: Too optimistic?



Representative Cell Line Model

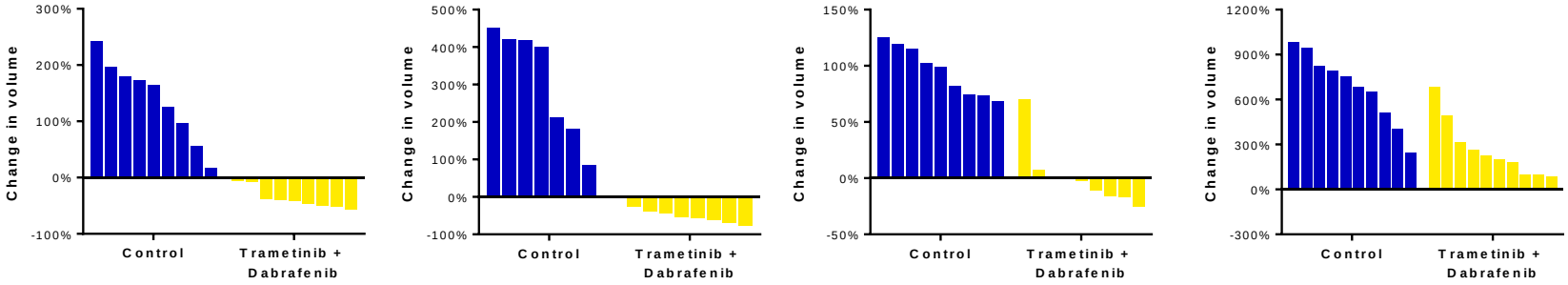
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Fang, et al , Can Res, '12

Co-clinical trials: BRAF+MEKi Study

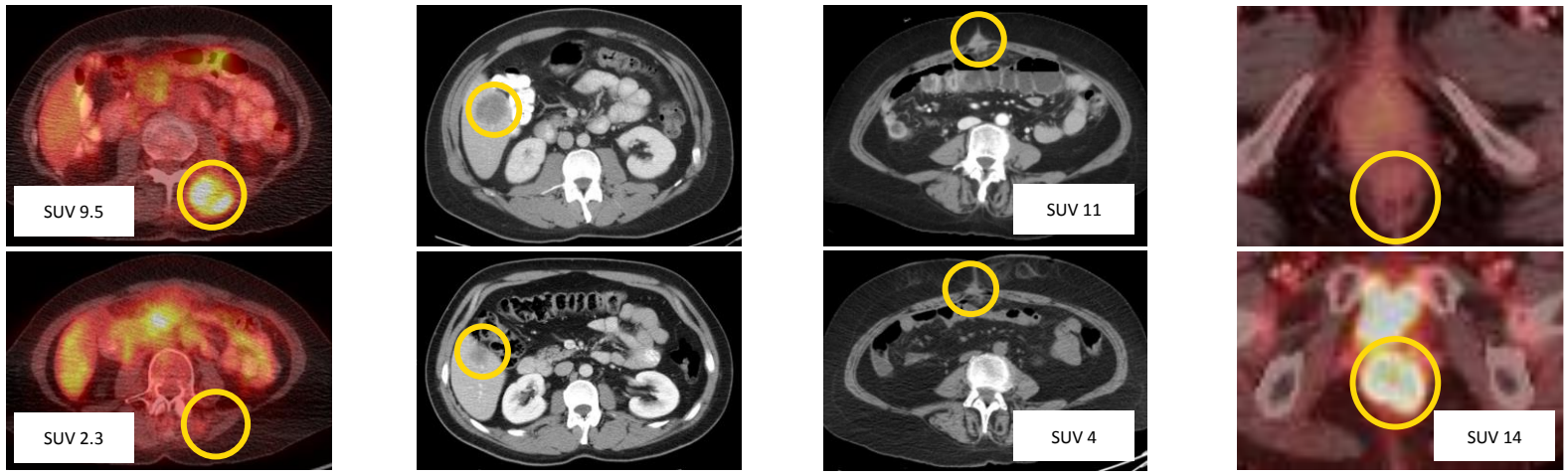
PDX response

A



Patient response

B

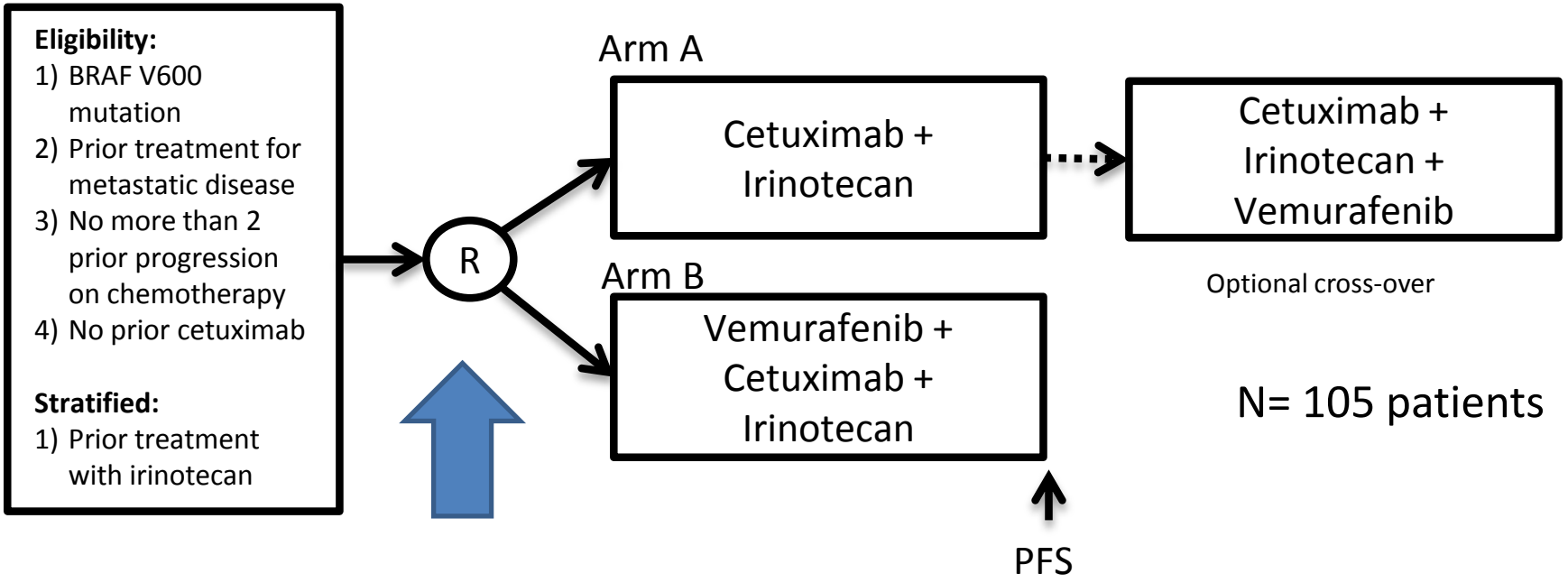


THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Corcoran, Atreya et al JCO ‘15

Prospective PDX Clinical Trial Integration:

S1406: BRAF + EGFR Inhibition in mCRC



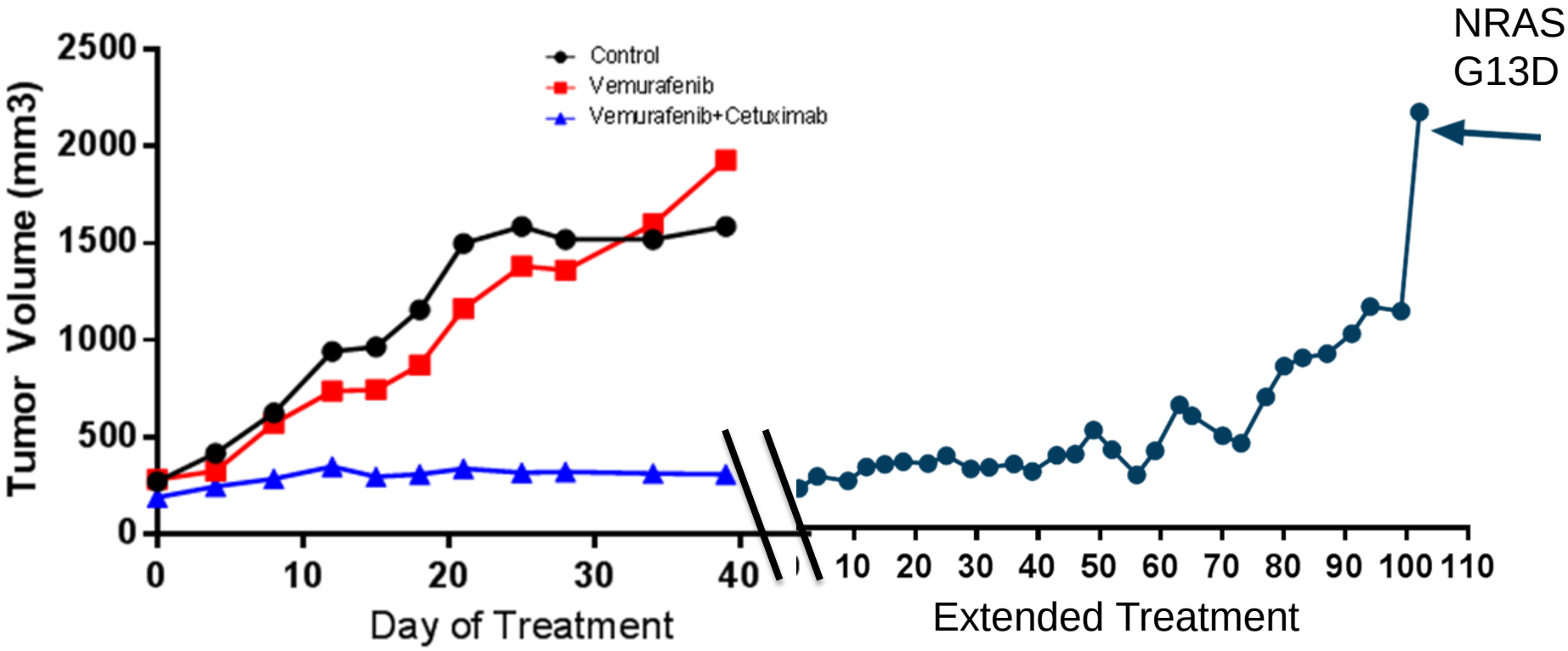
Embedded Patient-Derived Xenograft Co-Clinical Trial

- **On study biopsies to derive PDXs,** serial cfDNA
- **Co-clinical trial** to interrogate pharmacodynamics and mechanisms of resistance, and correlate outcomes

SWOG Hope, NIH R01 Funding, JAX Collaboration

MDACC, UCSF, USC, UCSD, U Colorado, Yale

Resistance to vemurafenib + cetuximab is associated with MAPK pathway mutation



Classically, KRAS and BRAF mutations are mutually exclusive

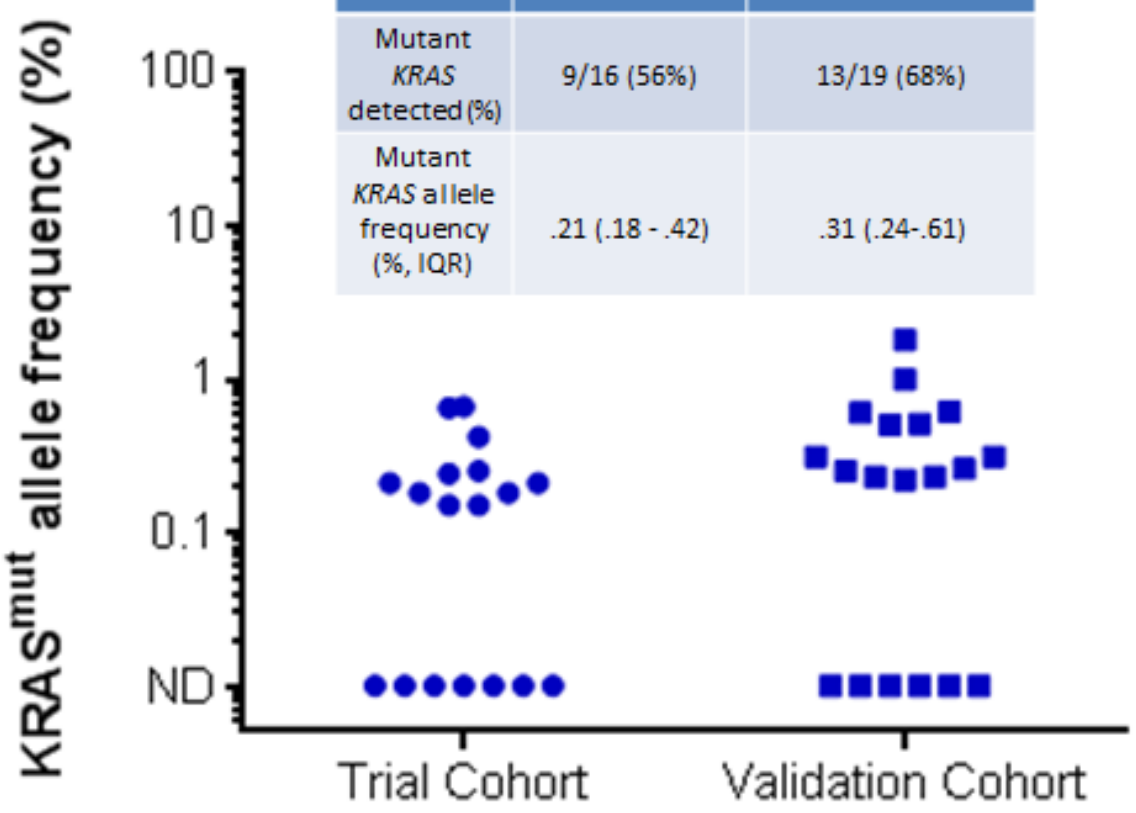
So where are these rare clones coming from?

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Kopetz, et al JCO '15

Rare KRAS^{mut} Cells Exist in BRAF^{mut} Colorectal Tumors

	Trial Cohort	Validation Cohort
Mutant *KRAS* detected (%)	9/16 (56%)	13/19 (68%)
Mutant *KRAS* allele frequency (%, IQR)	.21 (.18 - .42)	.31 (.24-.61)



Jayesh Desai
Kopetz, et al JCO '15

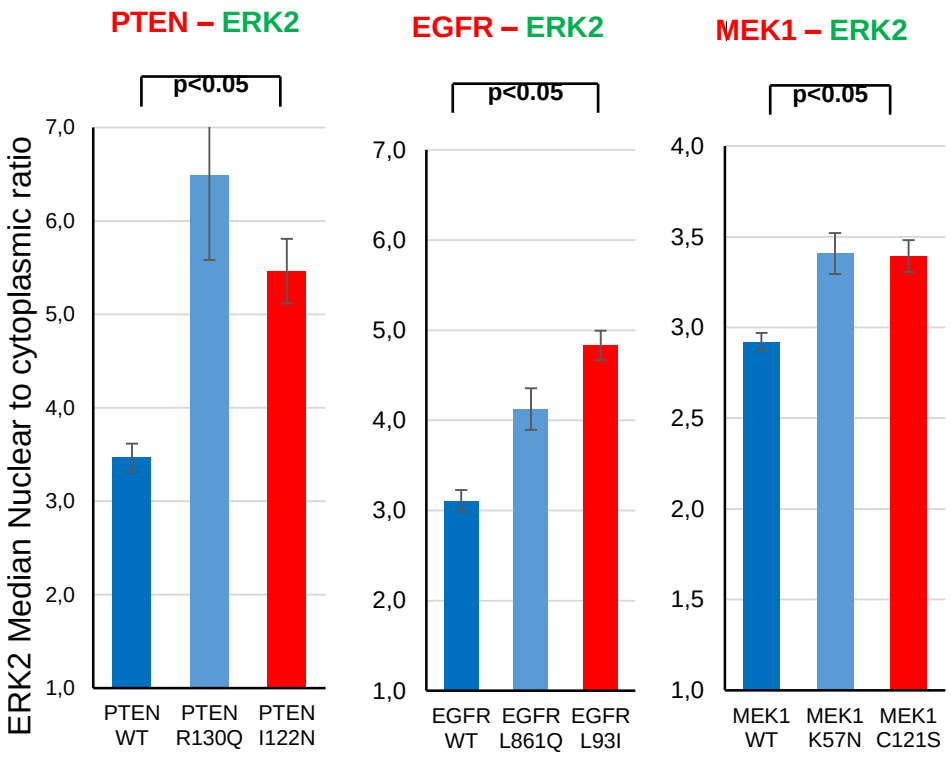
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Acquired RAS after BRAF+EGFR

- Baseline mutation analysis
  - Hotspots in AKT1, AKT2, BRAF, CDK, EGFR, ERBB2, FGFR1, F GFR3, FLT3, HRAS, JAK2, KIT, KRAS, MET, NRAS, PDGFRA, PIK3CA, RET
  - **BRAF V600E**
- Start study treatment:
  - cetuximab+ encorafenib
  - confirmed PR after 10 weeks
  - After 4 months of therapy: New progressive lesion
- Mutation analysis new lesion (same gene panel):
  - **BRAF V600E** and **KRAS G12R**

Post-progression cfDNA demonstrates clones that reactivate MAPK

Identified in cfDNA
PTEN I122N
MEK1 C121S
GNAS R201C
EGFR L93I
ARAF S490T

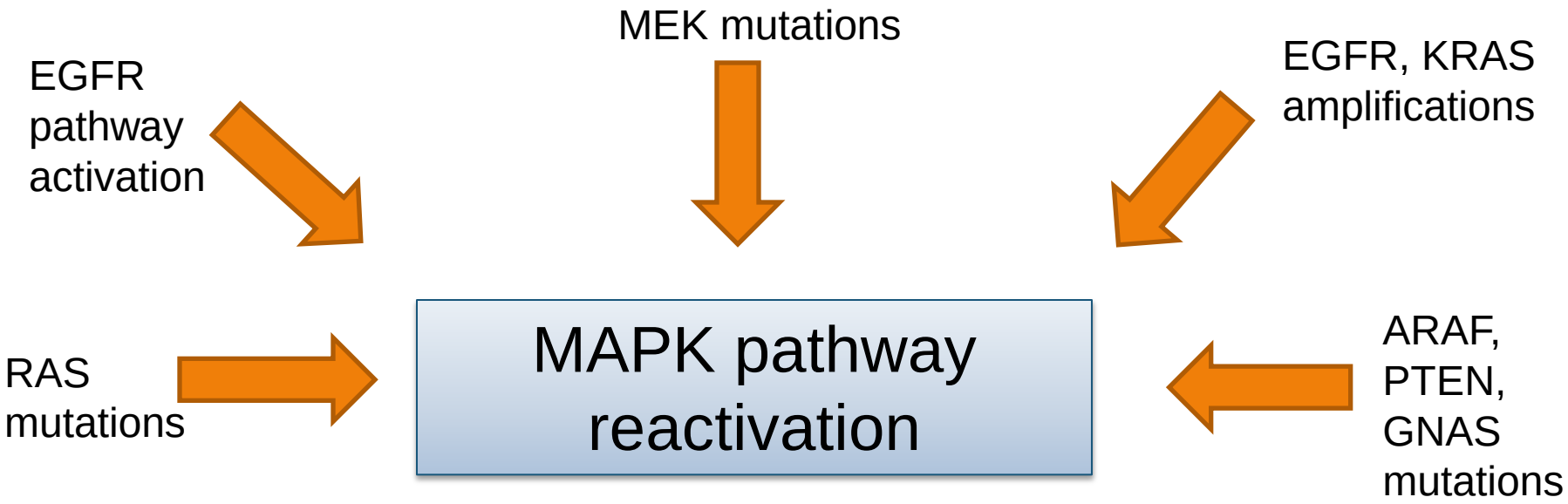


Gabi Tarnic, Novellus

If this is the case, then MEK inhibition may reverse resistance to EGFR/BRAF

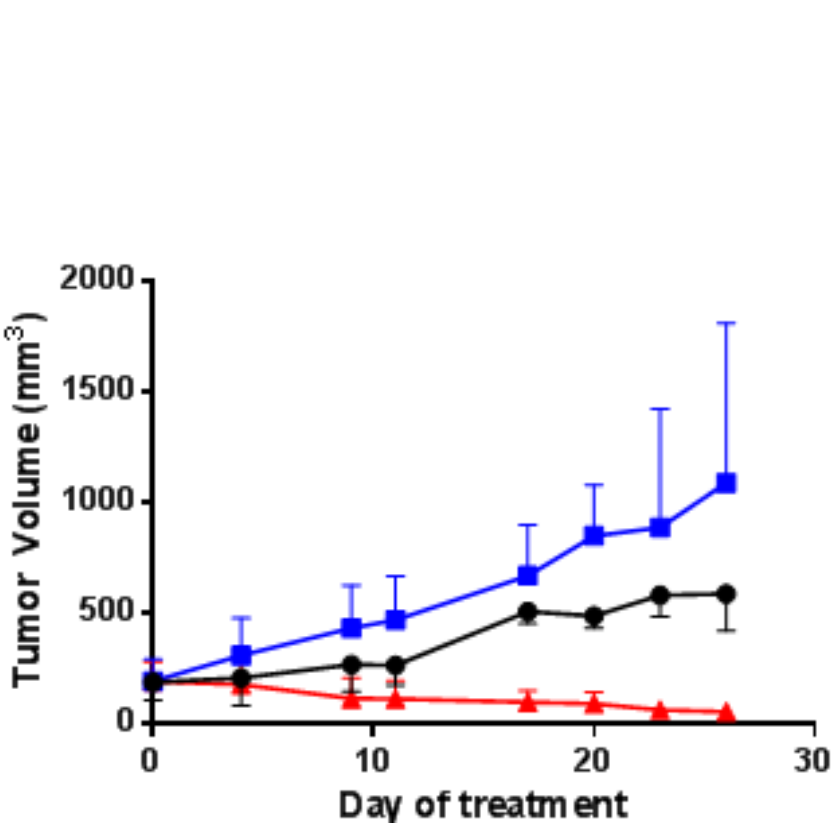
But may not substantially improve initial activity

Resistance to BRAF +/- EGFR

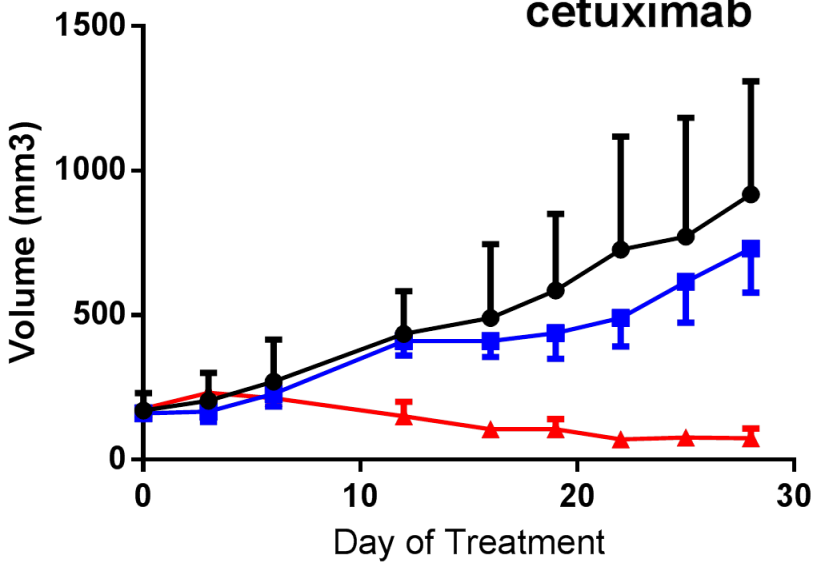


Another example of **convergent evolution** in colorectal cancer resistance to targeted therapy

PDX model: BRAF^{V600E}/KRAS^{mut}: BRAF+EGFR vs MEK+EGFR inhibition



BRAF^{V600E}/KRAS^{G12R}



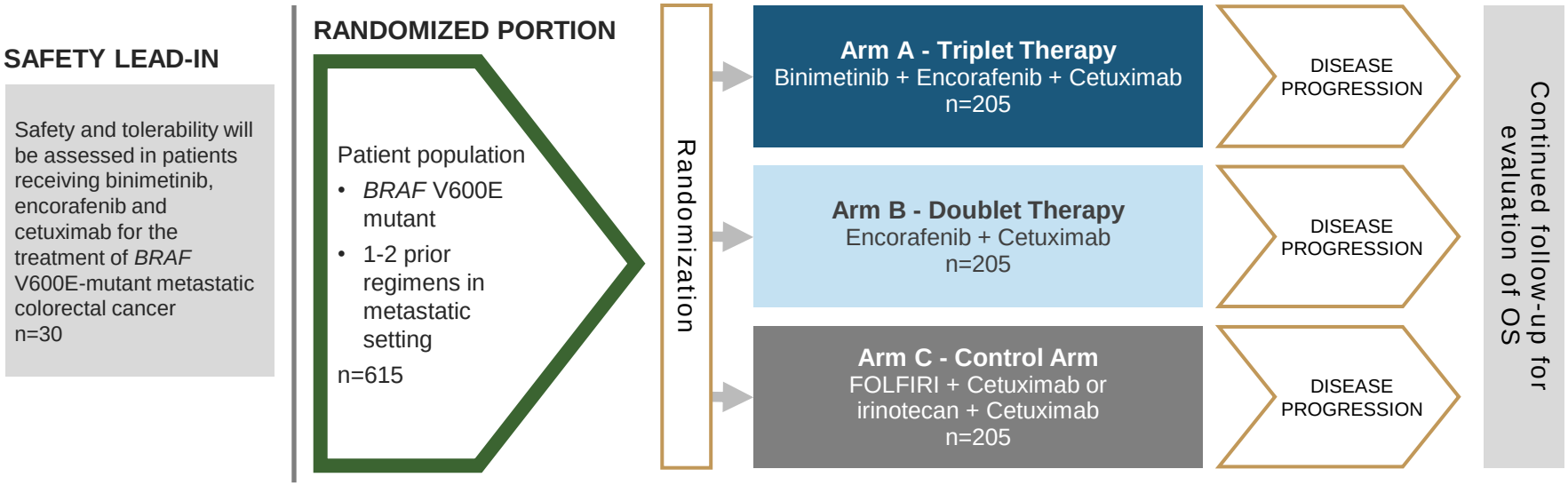
BRAF^{V600E}/KRAS^{G12D}

MEK inhibition reverses resistance to BRAF/EGFR

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Van Morris

Encorafenib + Cetuximab ± Binimetinib
Phase 3 BRAF^{mut} Colorectal Cancer Study Design

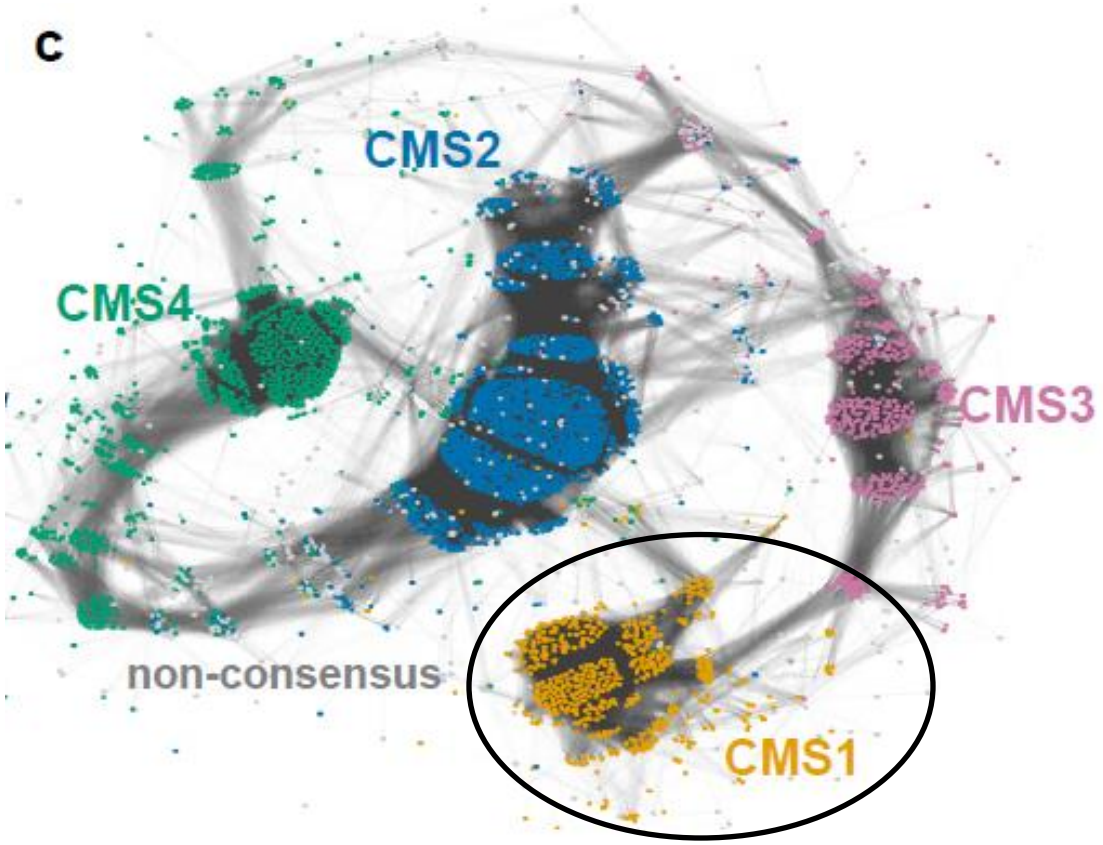


Primary Endpoint: Overall survival (OS) of the triplet therapy compared to the control arm.

Secondary Endpoints: Address efficacy of the doublet therapy compared to the control arm, and the triplet therapy compared to the doublet therapy.

Patient enrollment is expected to be completed in 2018.

Consensus Molecular Subtypes: CMS1



CMS1
MSI Immune

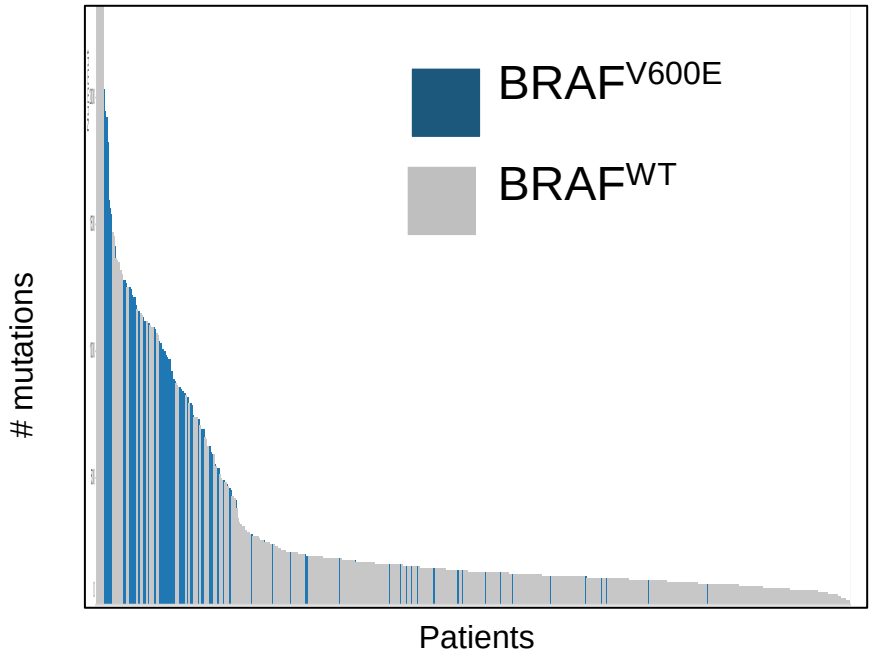
MSI, CIMP high
Hypermutation

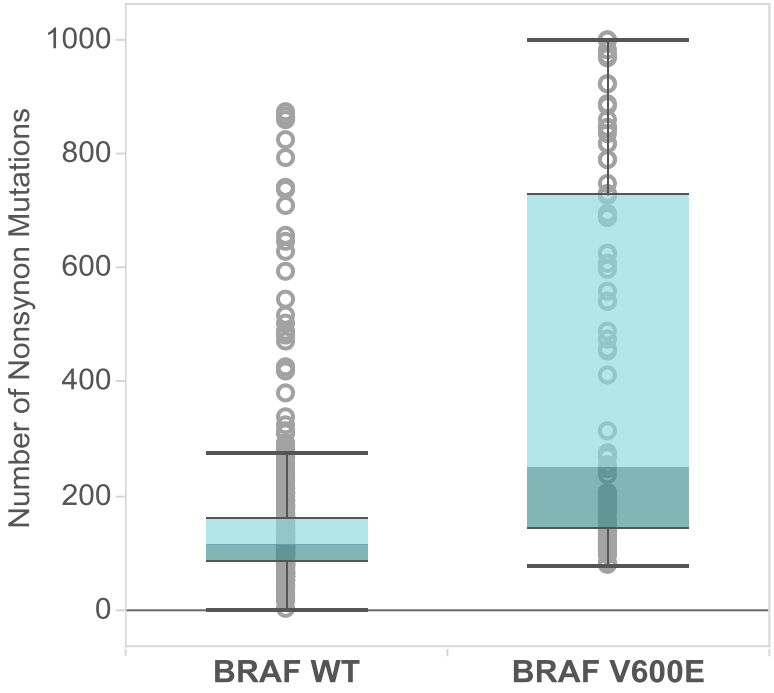
BRAF mutations

Immune infiltration
and activation

Guinney et al Nat Med '15

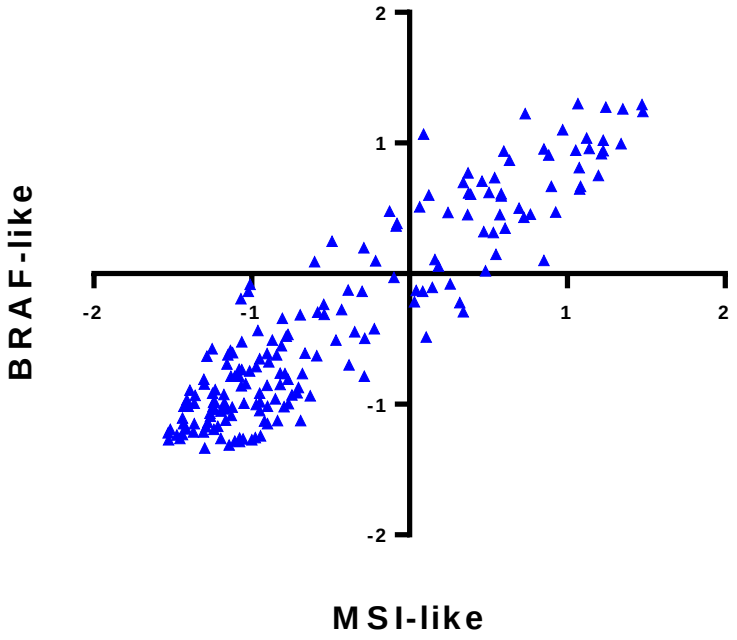
"BRAF^{mut} biology" is more than a mutated kinase

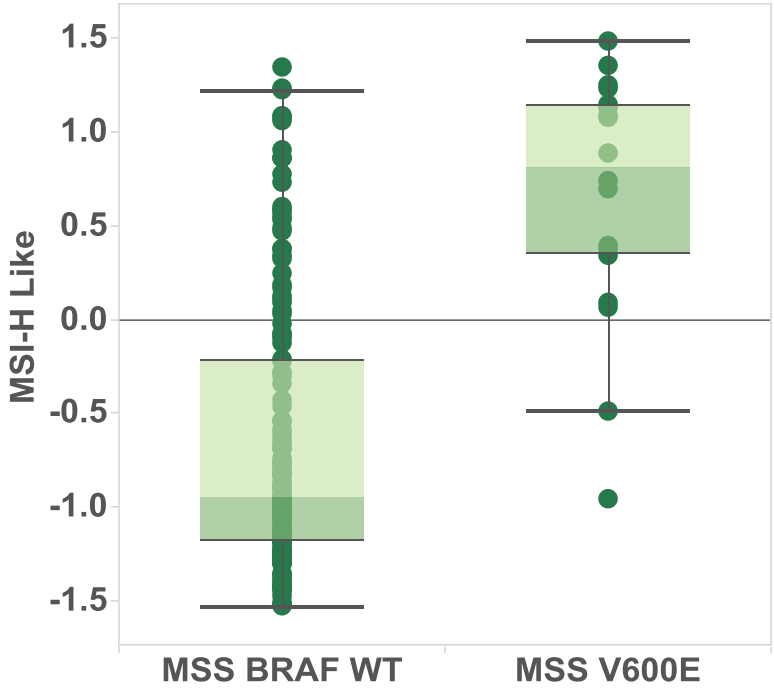




Sequencing data from NHS/HP Study (Giannakos, et al Cell Report '16)

BRAF and MSI share similar gene expression signatures





Role for immunotherapy in CMS1/BRAF mutated context?

Conclusions

- Testing for BRAF mutation is standard of care
  - Strong prognostic information that is useful for clinical management
- Patients with $BRAF^{mut}$ CRC have distinct biology and limited benefit with standard therapy
- Patients should be enrolled in clinical trials when available:
  - BRAF+EGFR+irinotecan or BRAF+EGFR+MEK appear most promising
  - Immunotherapy studies may be particularly relevant for patients with $BRAF^{mut}$ CRC (with or without MSI-H)

Acknowledgements

Kopetz Lab

- Van Morris, MD
- Feng Tian, PhD
- Camilla Jiang, MD, PhD
- Mike Lee, MD
- Jian Song, DVM
- Riham Katkhuda, MD
- Chris Lieu, MD
- Ali Kazmi, MD
- Pia Morelli, MD, PhD
- Michael Overman, MD

MDACC

- Mike Overman, MD
- Cathy Eng, MD
- Dipen Maru, MD
- Lee Ellis, MD
- Jim Abbruzzese, MD
- Atin Agarwal, MD
- Laurel Deaton
- Shanequa Manuel

MDACC Collaborators (cont)

- Yvonne Lassere
- Gerald Falchook, MD
- Robert Wolff, MD
- Xifeng Wu, PhD
- Ju-Seog Lee, PhD
- Gordon Mills, MD
- Ignacio Wistuba, MD
- George Calin, MD

Collaborators

- Garth Powis, PhD
- Bryan James PhD
- Robert Lemos
- John Mariadson, PhD
- Jayesh Desai, MD, Ludwig Aus
- Rene Bernards, NKI
- Iris Simon, Agendia
- Curt Harris, NKI
- Aaron Schetter, NKI
- Chloe Atreya, UCSF
- Ryan Corcoran

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Acknowledgements

Kopetz Lab

- Van Morris, MD
- Feng Tian, PhD
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- Michael Overman, MD


MDACC

- Mike Overman, MD
- Cathy Eng, MD
- Dipen Maru, MD
- Lee Ellis, MD
- Jim Abbruzzese, MD
- Atin Agarwal, MD
- Laurel Deaton
- Shanequa Manuel

MDACC Collaborators (cont)

- Yvonne Lassere
- Gerald Falchook, MD


THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Collaborators

- Garth Powis, PhD
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- Chloe Atreya, UCSF
- Ryan Corcoran


THE UNIVERSITY OF TEXAS MD Anderson Cancer Center