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MD Anderson Cancer Center
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Targeted Therapies in CRC: Opportunities and Challenges

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Disclosures

- **Ownership Interests**: Lutris, Iylon, Frontier Medicines, Xilis, Navire

- **Advisory**: Genentech, Merck, Boehringer Ingelheim, Bayer Health, Lutris, Pfizer, Mirati Therapeutics, Flame Biosciences, Carina Biotech, Frontier Medicines, Replimune, Bristol-Myers Squibb, Amgen, Tempus, Harbinger, Zentalis, AVEO, Tachyon Therapeutics, Agenus, Revolution Medicines, Kestrel Therapeutics, Regeneron, Roche

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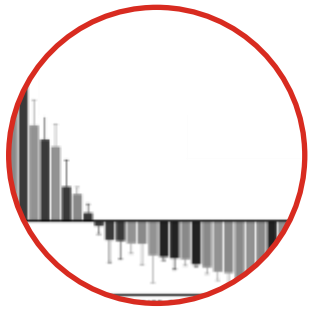
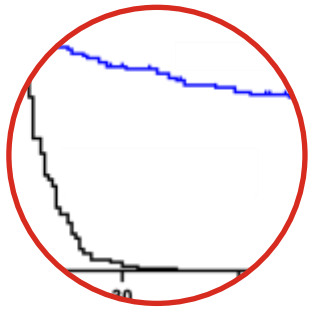
How to improve targeted therapy in CRC?



Limited response rates

- Address innate and adaptive resistance



Limited durability

- Address acquired resistance

Homeostatic Regulation

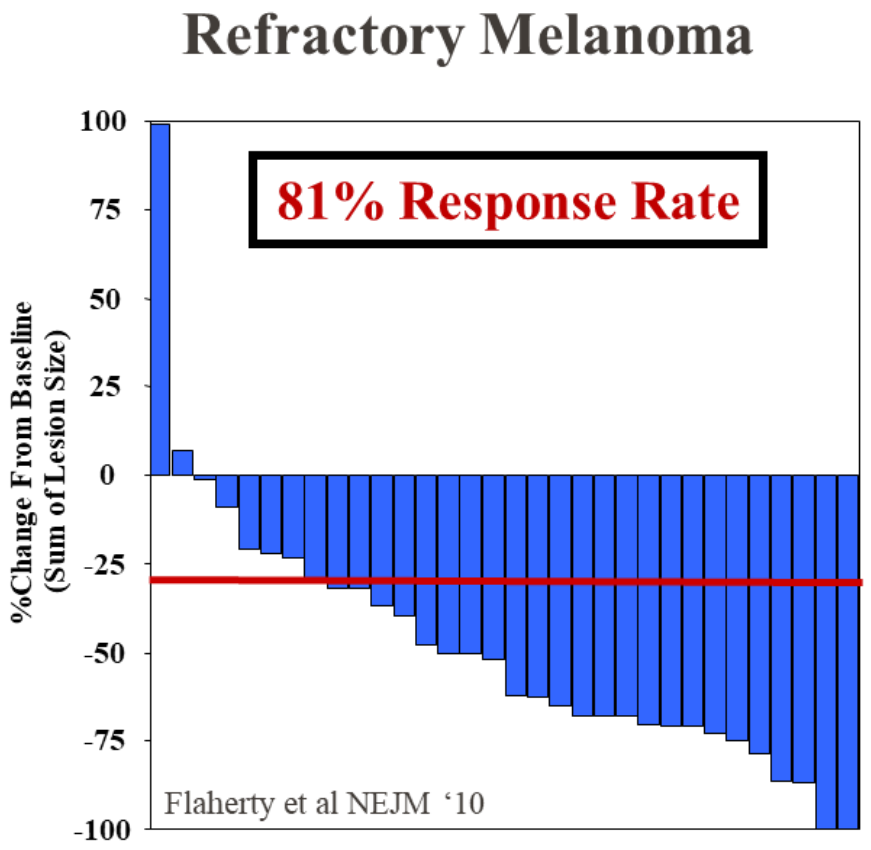
Homeostatic regulation is a critical and nearly universal feature of biological systems

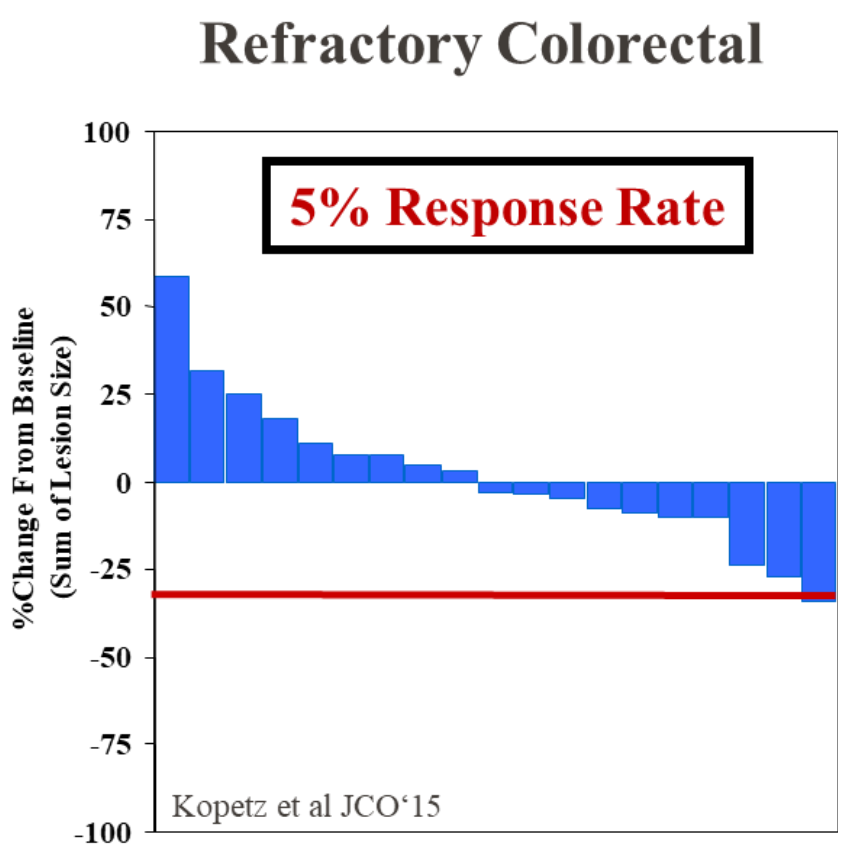
Inhibition of a single node in the pathway results in a rapid compensation in the signaling to restore homeostasis

Growth pathways like MAPK have many such feedback pathways established.

Walter B. Cannon (1871–1945) described the concept of homeostasis in human physiology. He built upon the work of Claude Bernard (“interior milieu”) and identified self-regulating processes in biology that maintained internal stability despite fluctuating conditions and external stimuli. (National Library of Medicine)

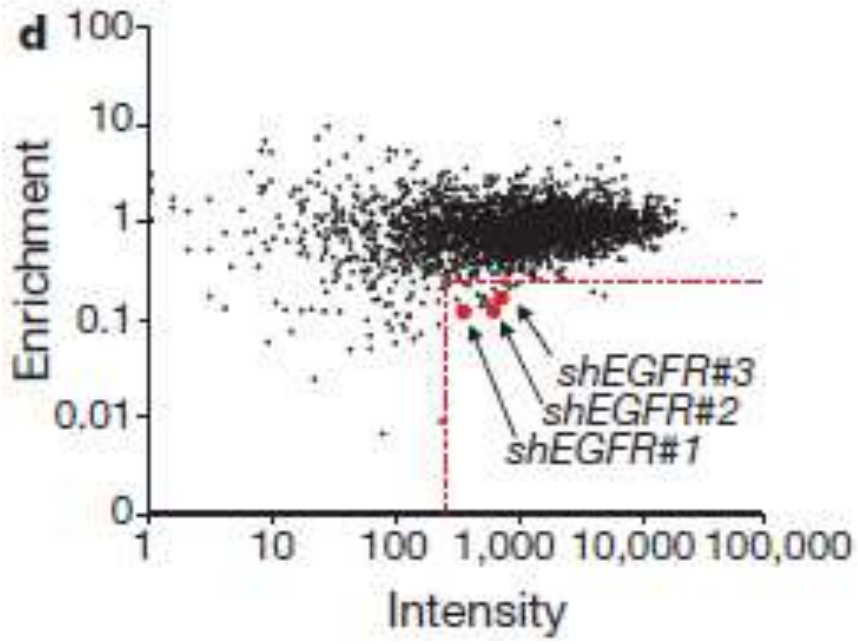
Single agent BRAF inhibition (vemurafenib)



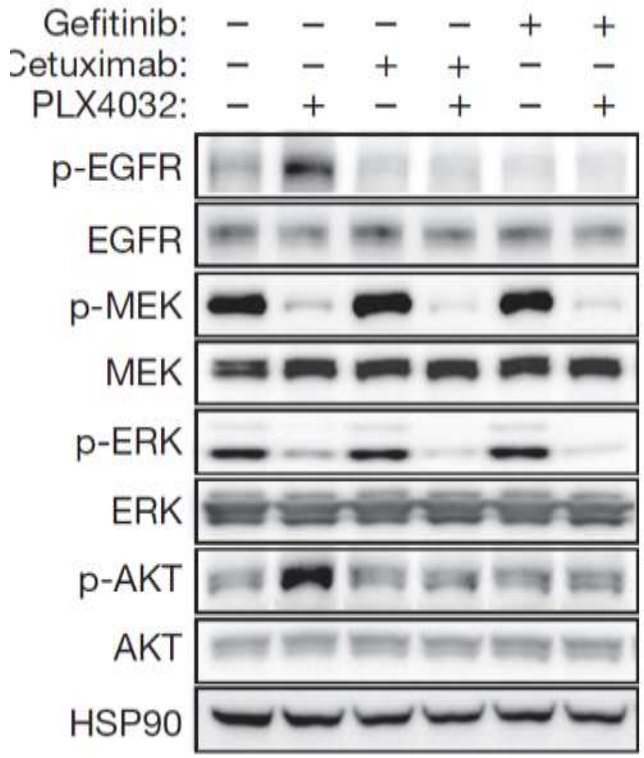


Key Lead from Unbiased Synthetic Lethality Screen:
EGFR Identified as a Synergistic Partner and Mechanism of Resistance

HT29 cell line (Sensitive)

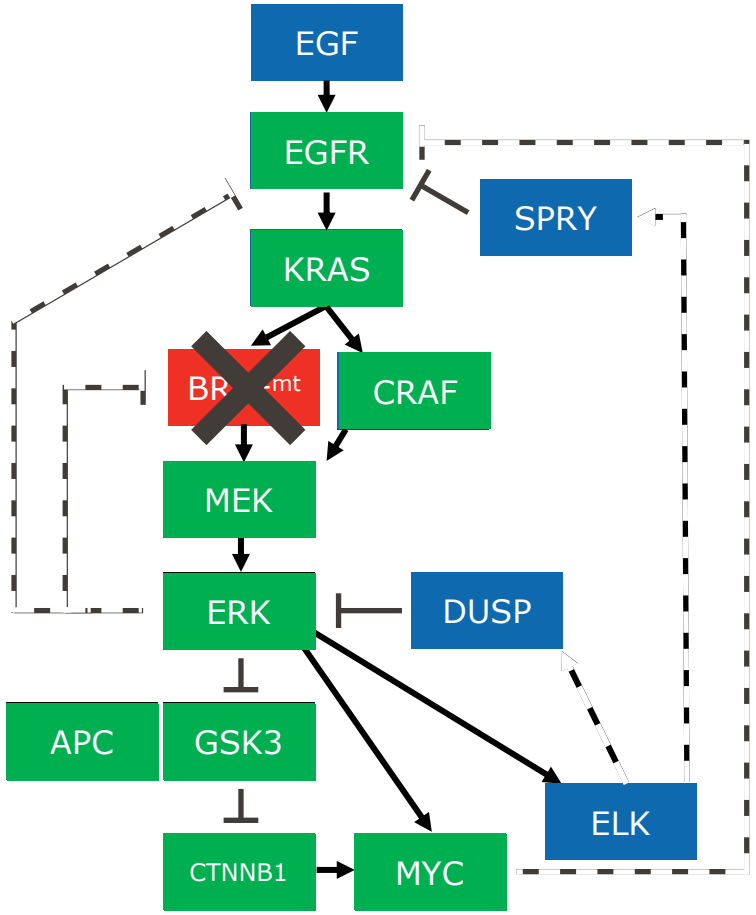


EGFR identified

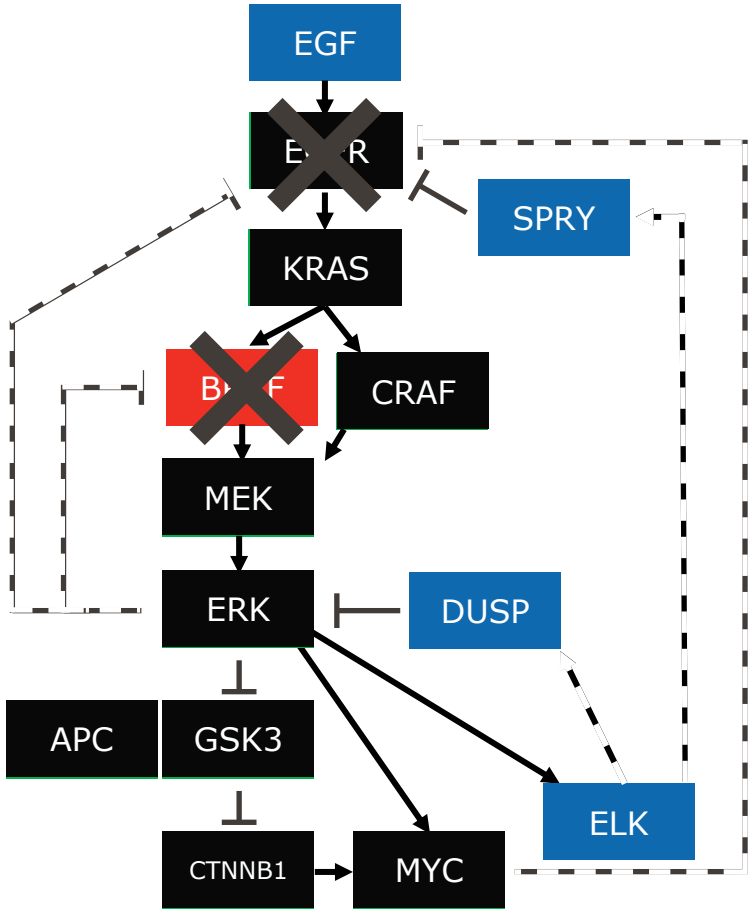


Prahallad et al Nature ’12; Corcoran et al Cancer Discovery ’12; Mao et al CCR ‘13

Targeting MAPK: Adaptive Resistance



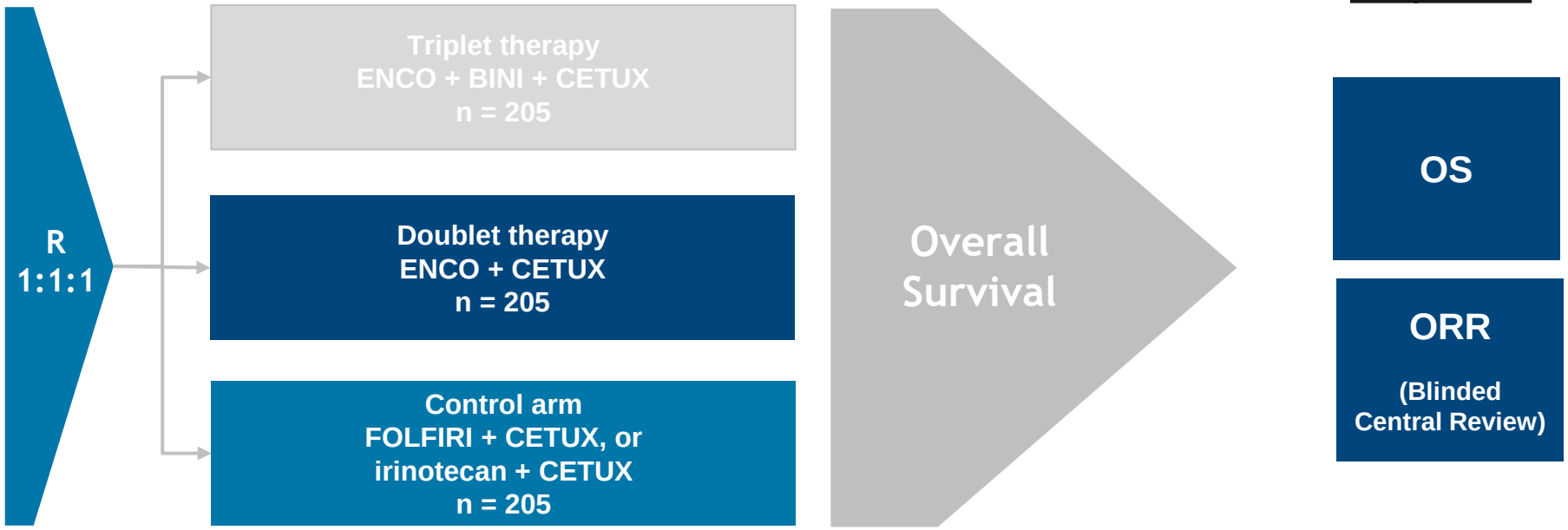
Targeting MAPK: Adaptive Resistance



BEACON Study: Encorafenib + Cetuximab in 2nd/3rd line mCRC

Patients with *BRAF*^{V600E} mCRC with disease progression after 1 or 2 prior regimens; ECOG PS of 0 or 1; and no prior treatment with any RAF inhibitor, MEK inhibitor, or EGFR inhibitor

Phase 3



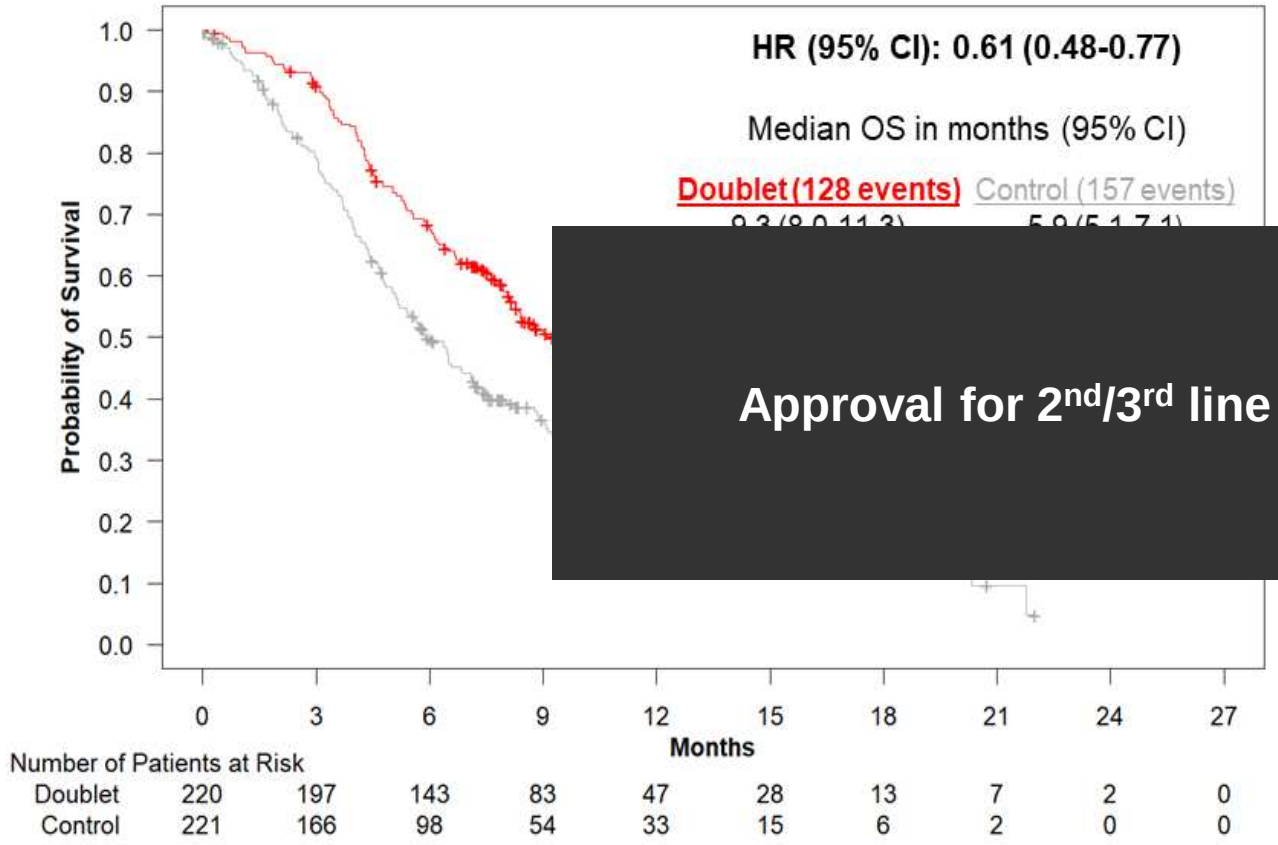
Primary Endpoints*:

- **OS**
- **ORR** (Blinded Central Review)

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

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

Encorafenib + Cetuximab Improves Overall Survival



Approval for 2nd/3rd line BRAF^{V600E} CRC

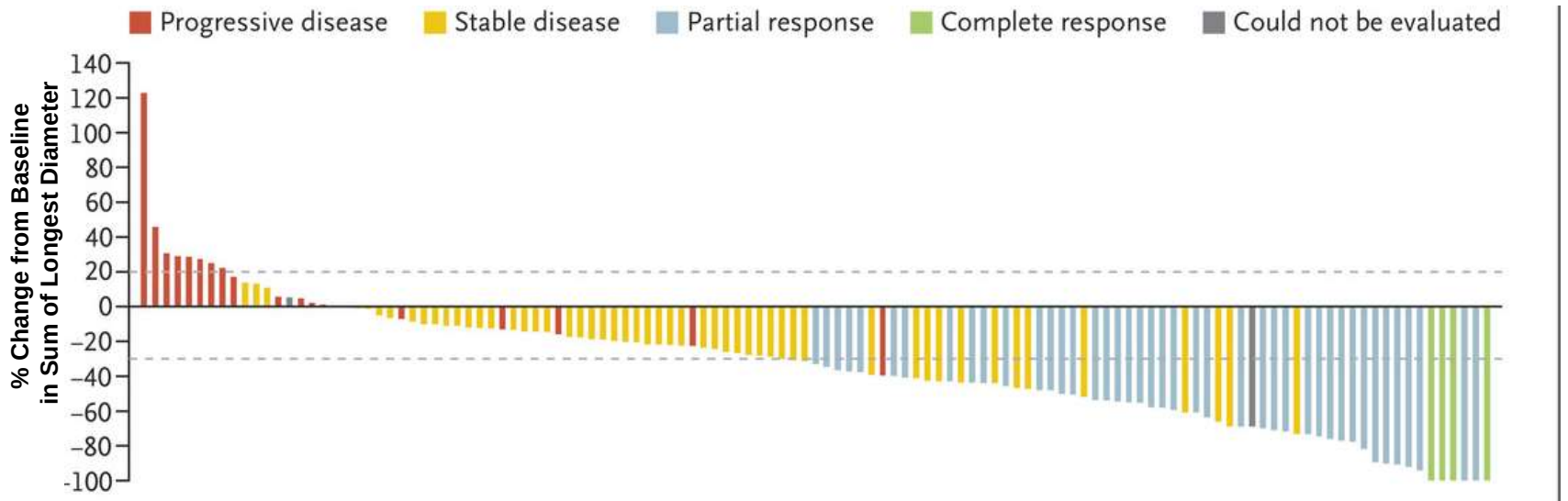
Adverse Event (Preferred term)	ENCO/CETUX N=216 Any Grade	Control N=193 Any Grade
Diarrhea	38%	49%
Dermatitis acneiform	30%	40%
Nausea	38%	44%
	27%	32%
	33%	28%
	18%	20%
	24%	28%
	19%	15%
	20%	3%
	11%	5%
Stomatitis	6%	23%
Arthralgia	23%	2%
Myalgia	15%	2%
Laboratory Abnormality**		
Hemoglobin decrease	39%	46%
Creatinine increase	54%	38%

† Kopetz et al. N Engl J Med 2019; 381:1632-1643; Tabernero et al Journal of Clinical Oncology 39, no. 4 (Feb 01, 2021) 273-284.

NSCLC and CRC Responses to G12C Inhibition: *Déjà vu*

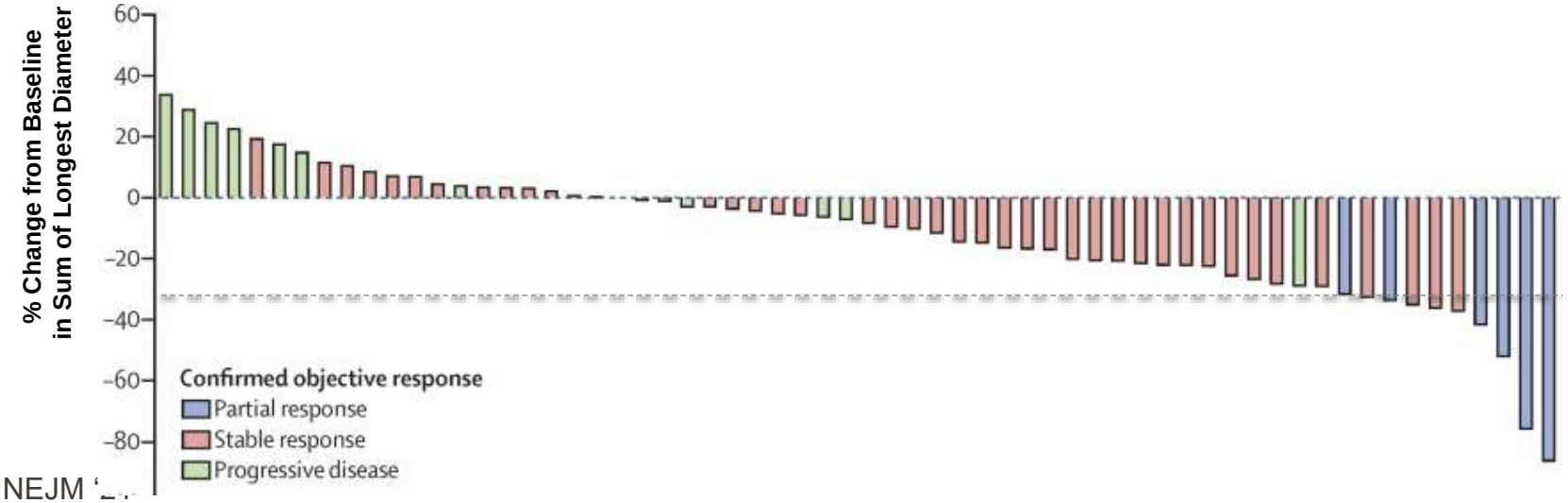
NSCLC:

37% response rate



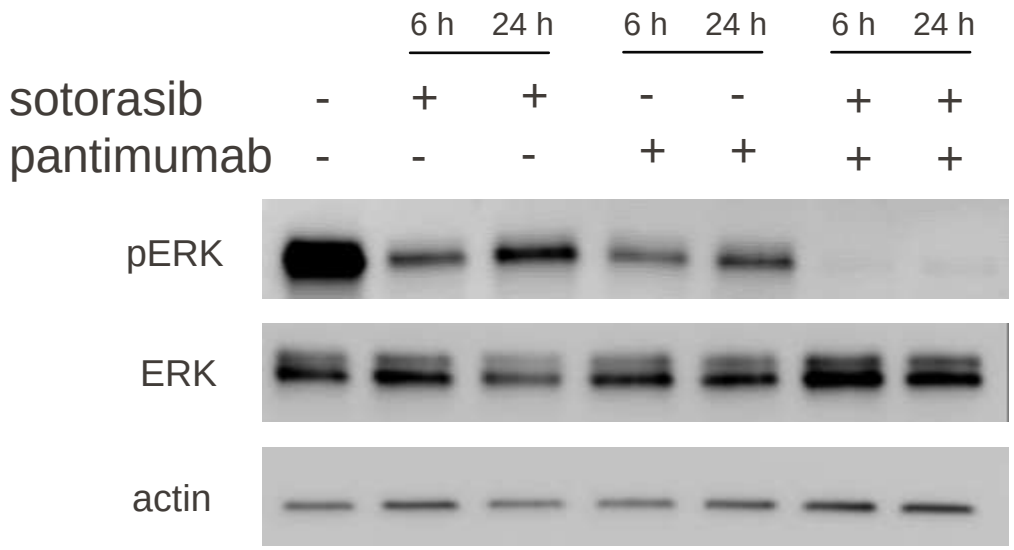
CRC:

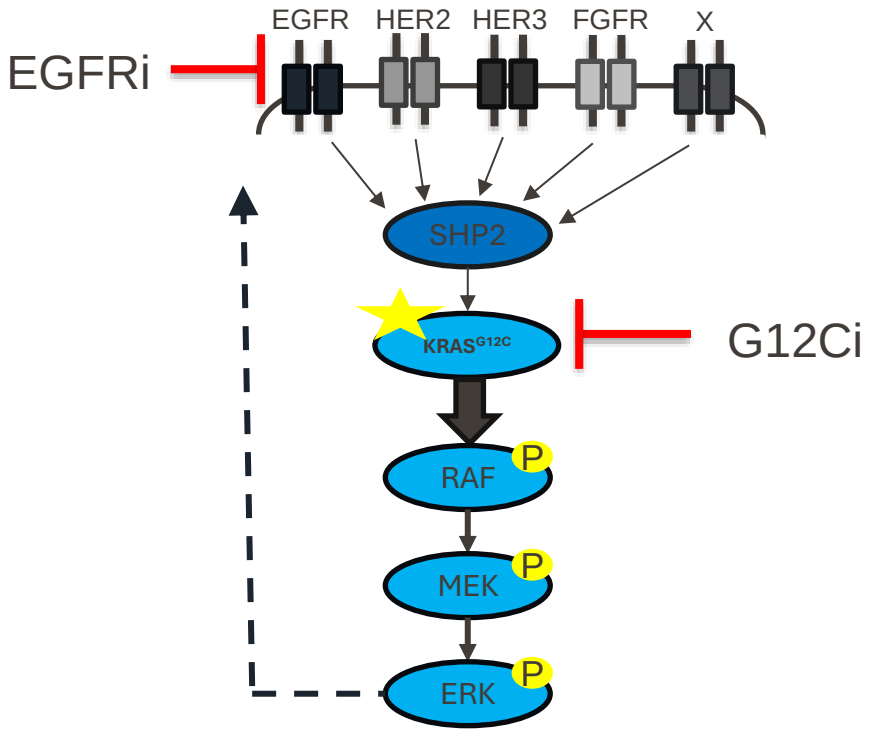
9% response rate



D. Hong et al NEJM '20; Skoulidis et al NEJM '[illegible]. Fakih, Kopetz et al Lancet Oncology '22

Adaptive resistance to KRAS^{G12C} inhibition is blocked by EGFRi



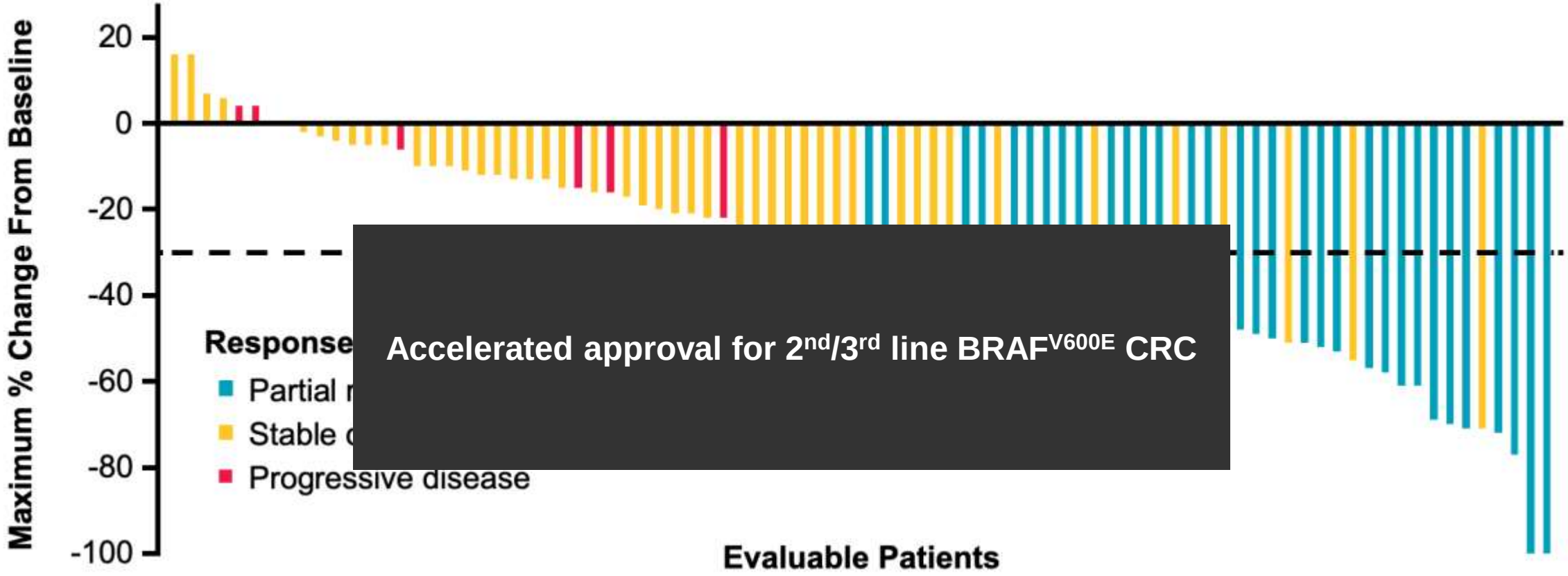


- Inhibition of G12C with sotorasib is associated with only partial pathway inhibition
- However, the pathway can be substantially inhibited with dual G12C and EGFR inhibition

See Amadio et al Cancer Discovery ‘20; Ryan et al CCR ‘20

Olu Coker

Adagrasib + Cetuximab Recently FDA Approved in mCRC



Accelerated approval for 2nd/3rd line $BRAF^{V600E}$ CRC

Confirmed objective response rate was 34.0%[a]

Disease control was observed in 80/94 patients (85.1%)

Median PFS was 6.9 months
(95% CI, 5.7–7.4)

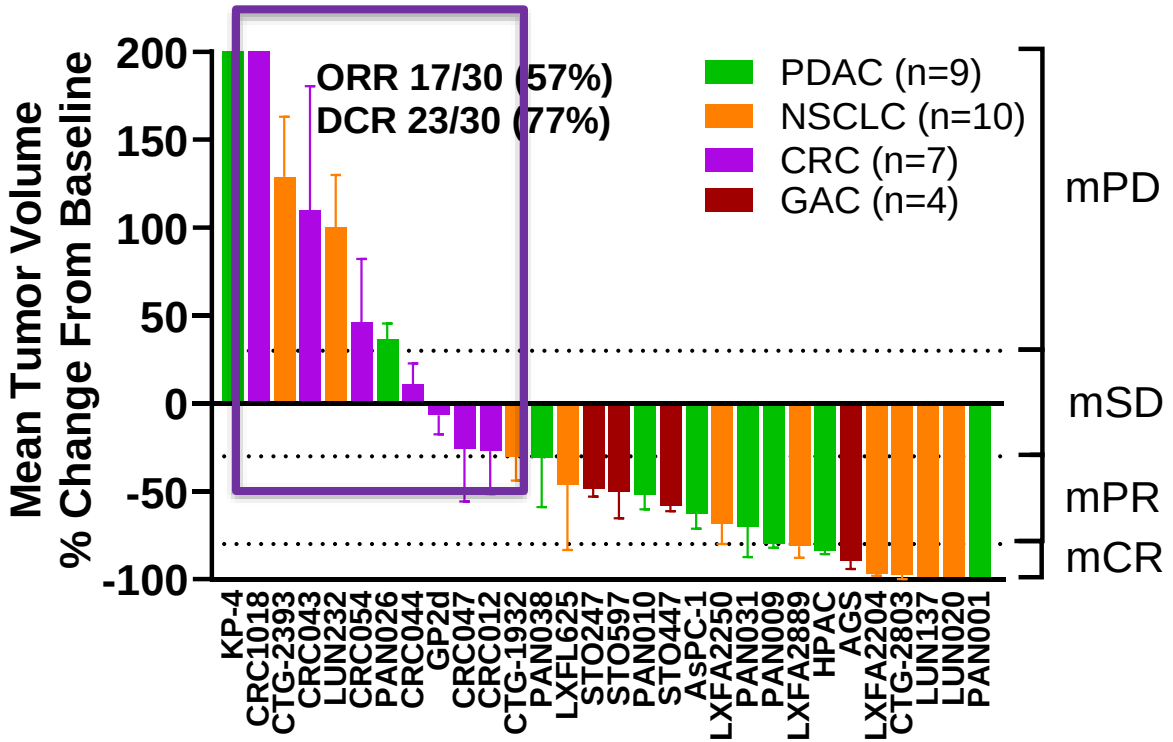
[a]ORR for the Phase 1 portion (n=32) was 43.8%; ORR for the Phase 2 portion (n=62) was 29.0%
All results are based on BICR. Waterfall plot excludes eight patients without any post-baseline scans
Data as of June 30, 2023 (median follow-up 11.9 months)

Kopetz et al AACR ’24, Yaeger et al Can Disc ‘24

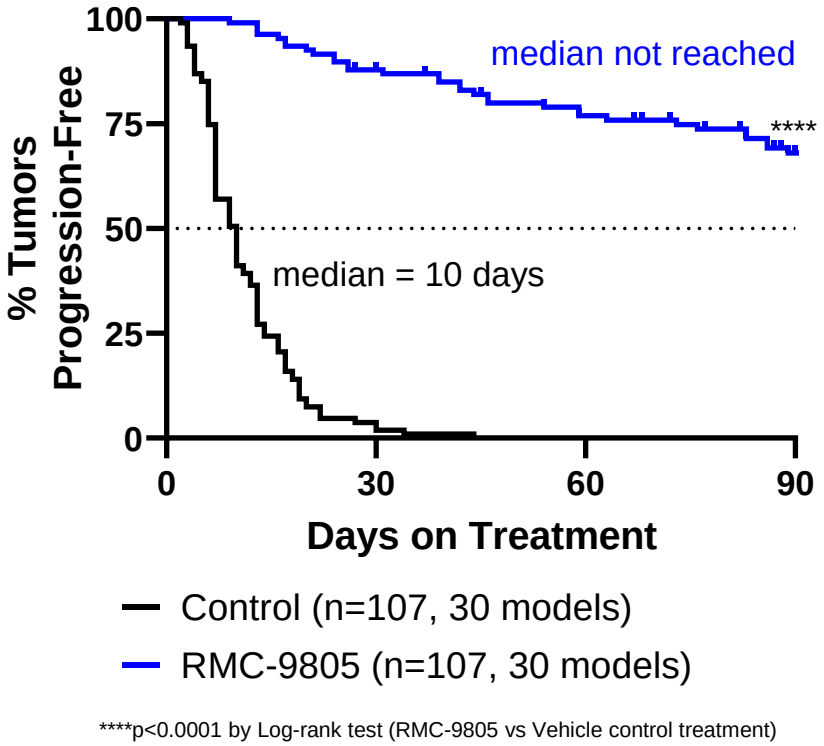
RMC-9805 Drives Deep and Durable Regressions Across Diverse KRAS^{G12D} Cancer Models *in Vivo*

AACR American Association for Cancer Research
ANNUAL MEETING 2024 • SAN DIEGO
APRIL 5-10 • AACR.ORG/AACR24 • #AACR24

Responses



Durability

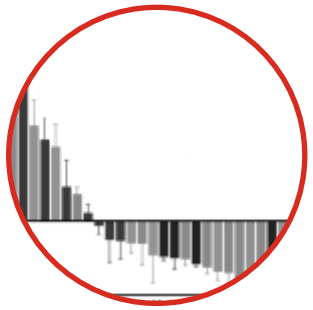


****p<0.0001 by Log-rank test (RMC-9805 vs Vehicle control treatment)

Revolution Medicines preclinical research as of 08/30/23
RMC-9805 dosed at 100 mg/kg po qd; n=2-8/group
Responses after 28 ± 2 days of treatment unless maximal tumor burden reached sooner or control tumor reached 2 doublings (4* initial TV) later
Responses assigned according to mRECIST (modified from Gao et al. Nat Med. 2015)
Progression defined as tumor doubling from baseline

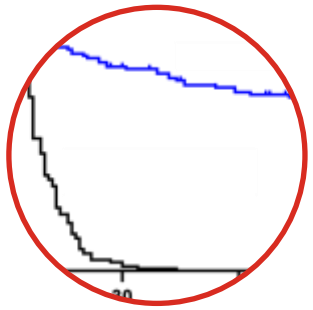
Knox et al AACR '23 NDOTH session, ND03

How to improve targeting of KRAS and BRAF tumors?



Limited response rates

- Address innate and adaptive resistance



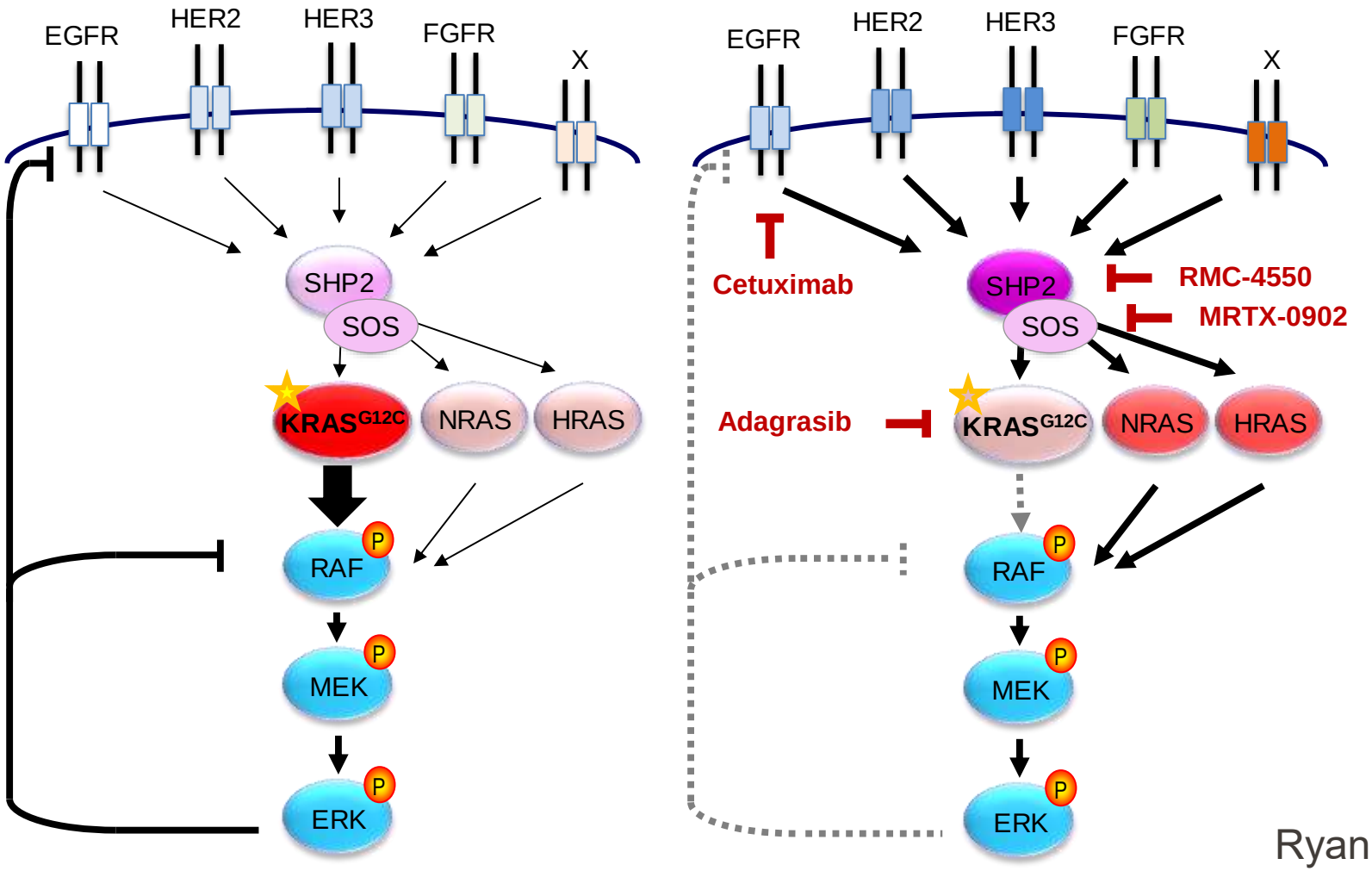
Limited durability

- Address acquired resistance

Strategies to Target Innate Resistance

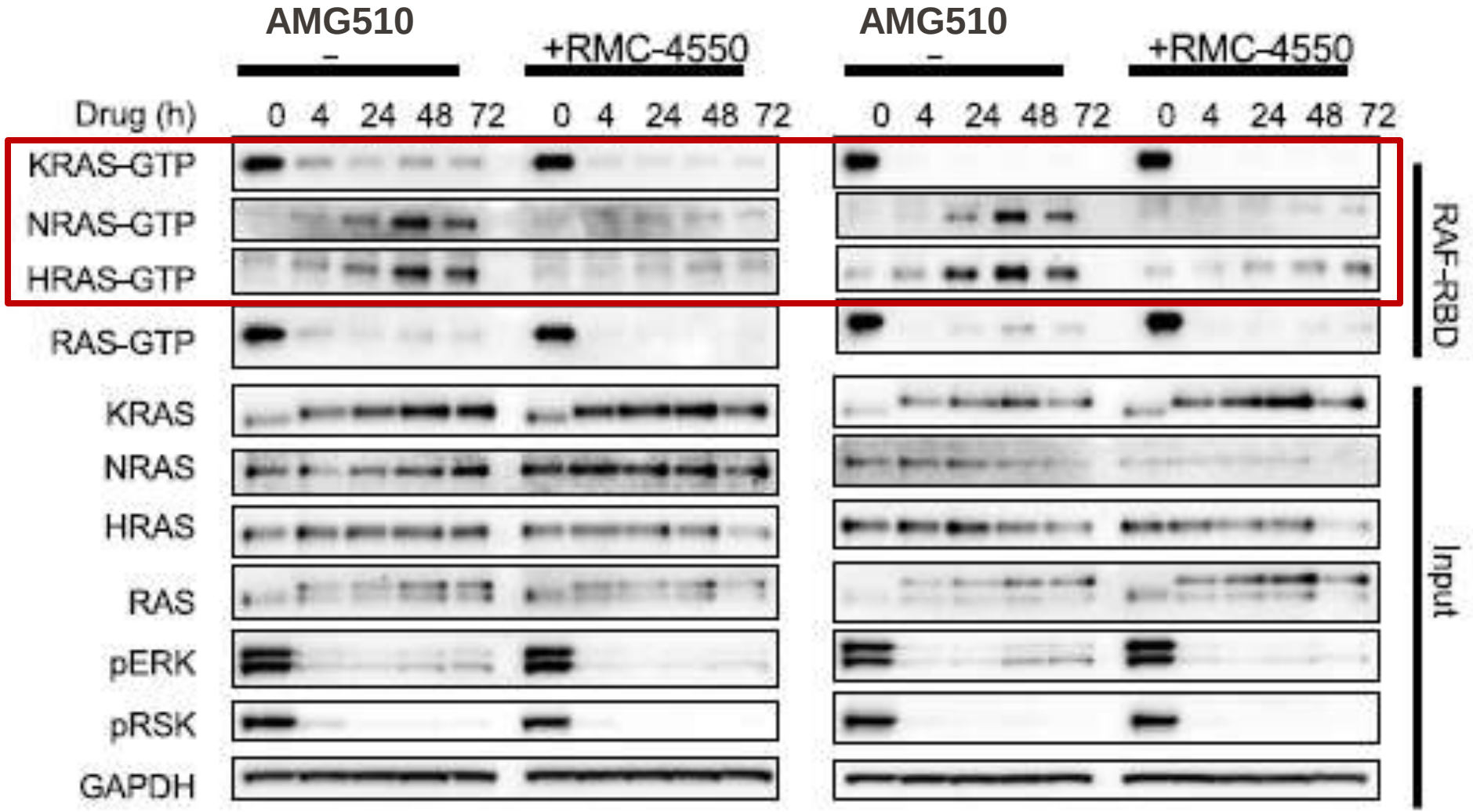
- Improving feedback inhibition: SHP2, SOSi
- Combination with cytotoxic chemotherapy
- Immunotherapy combinations
- Epigenetic combinations

But EGFR is not the only mechanism of feedback: How can you intercept feedback through multiple RTKs?



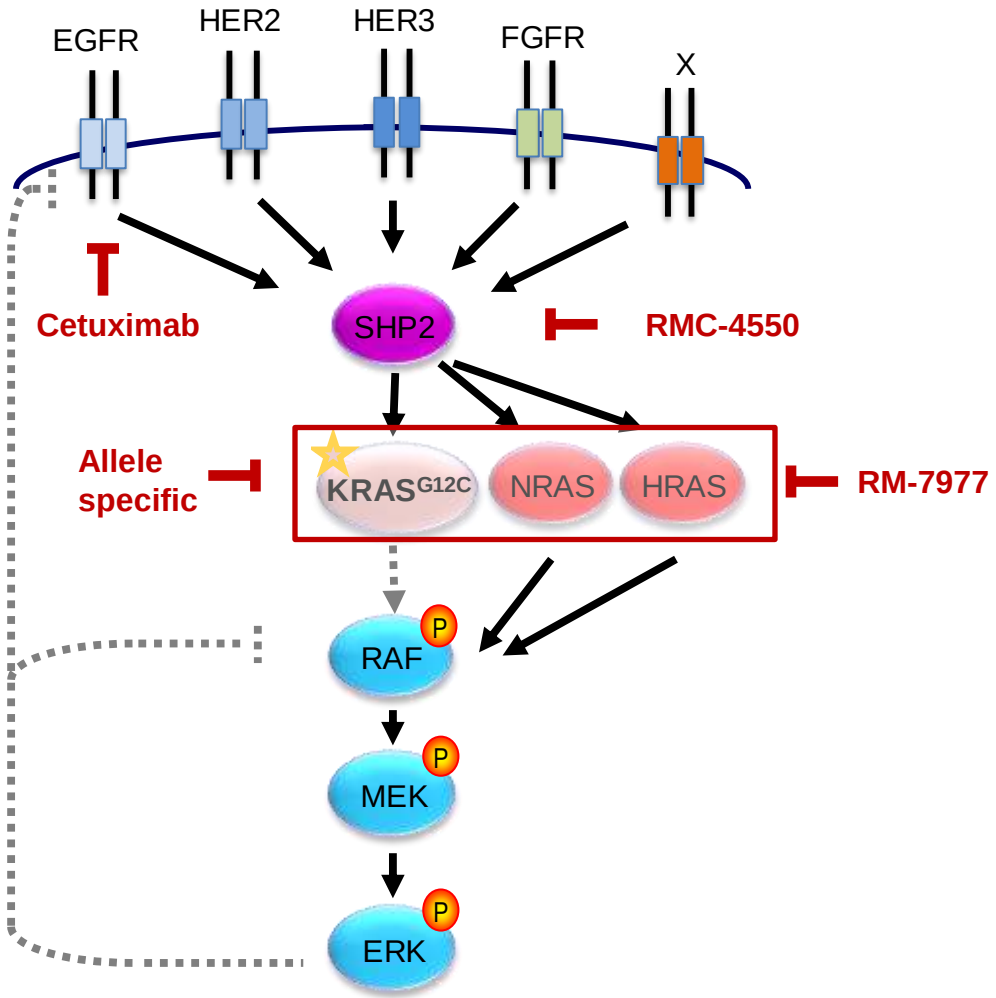
Ryan et al Cell Reports ‘22

Addition of SHP2 inhibitor blocks feedback RAS activation



Ryan et al Cell Reports ’22, with Corcoran Lab

Selection of optimal feedback inhibitor will be dependent on toxicity profiles as well as optimal pathway inhibition



The relatively toxicity and benefit of SOS and SHP2 inhibition remains to be seen.

Relying on KRAS allele-specific inhibitor therapeutic windows may be critical

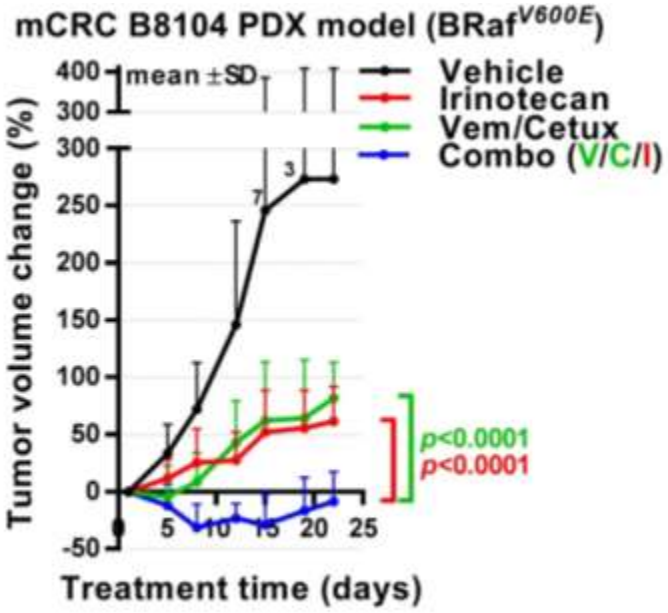
Also opportunities to explore in BRAF context

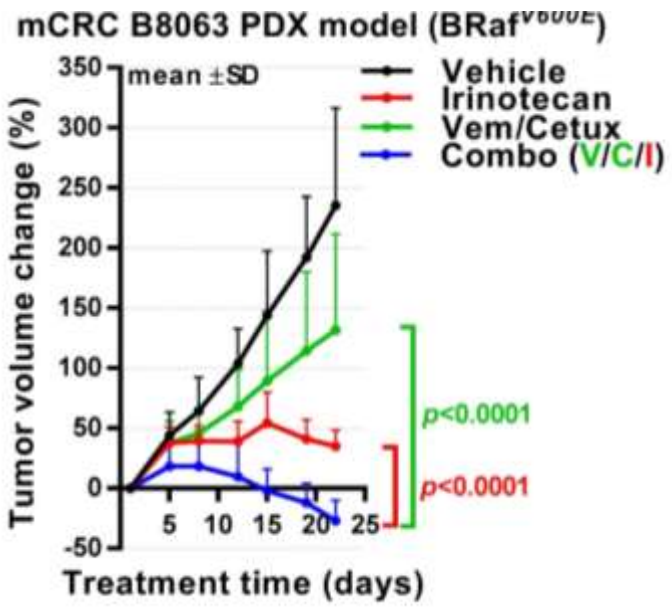
Strategies to Target Innate Resistance

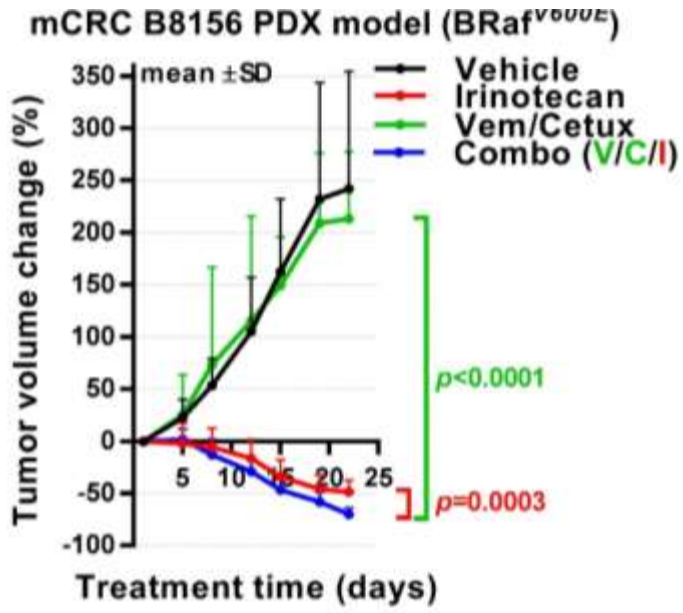
- Improving feedback inhibition: SHP2, SOSi
- Combination with cytotoxic chemotherapy
- Immunotherapy combinations
- Epigenetic combinations

Concurrent chemotherapy improves responses to BRAF + EGFR

Interrogating 3 responders from S1406 study of Vem + Cetux + Irinotecan







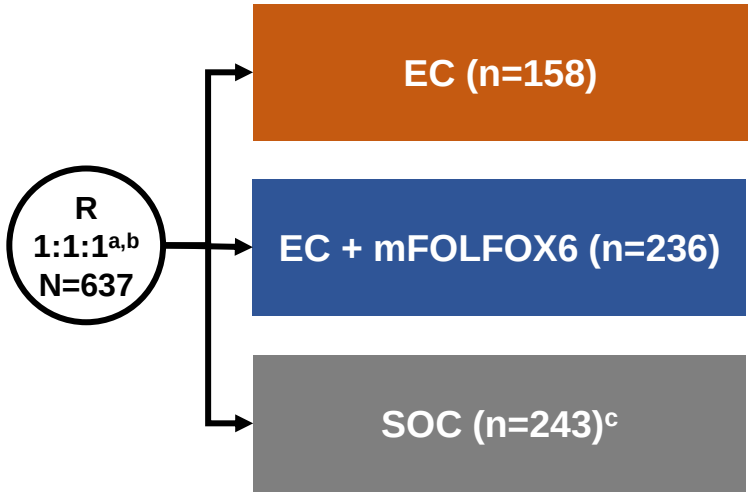
Benefit from BRAF/EGFR	Modest benefit from BRAF/EGFR	No benefit from BRAF/EGFR
Regression with the triplet	Regression with the triplet	Regression with the triplet

Hong et al Cancer Discovery ‘16

BREAKWATER: Study Design

- BREAKWATER (NCT04607421) is an open-label, multicenter, phase 3 study in first line BRAF V600E-mutant mCRC

Inclusion criteria
• Age ≥16 years (or ≥18 years based on country) • No prior systemic treatment for metastatic disease • Measurable disease (RECIST 1.1) • BRAF V600E-mutant mCRC by local or central laboratory testing • ECOG PS 0 or 1 • Adequate bone marrow, hepatic, and renal function
Exclusion criteria
• Prior BRAF or EGFR inhibitors • Symptomatic brain metastases • MSI-H/dMMR tumors (unless patients were ineligible to receive immune checkpoint inhibitors due to a pre-existing medical condition) • Presence of a *RAS* mutation



Stratified by regions (US/Canada vs Europe vs Rest of World) and ECOG PS (0 vs 1)

Dual primary endpoints:
PFS and ORR[d] by BICR
(EC + mFOLFOX6 vs SOC)

Key secondary endpoint:
OS (EC + mFOLFOX6 vs SOC)

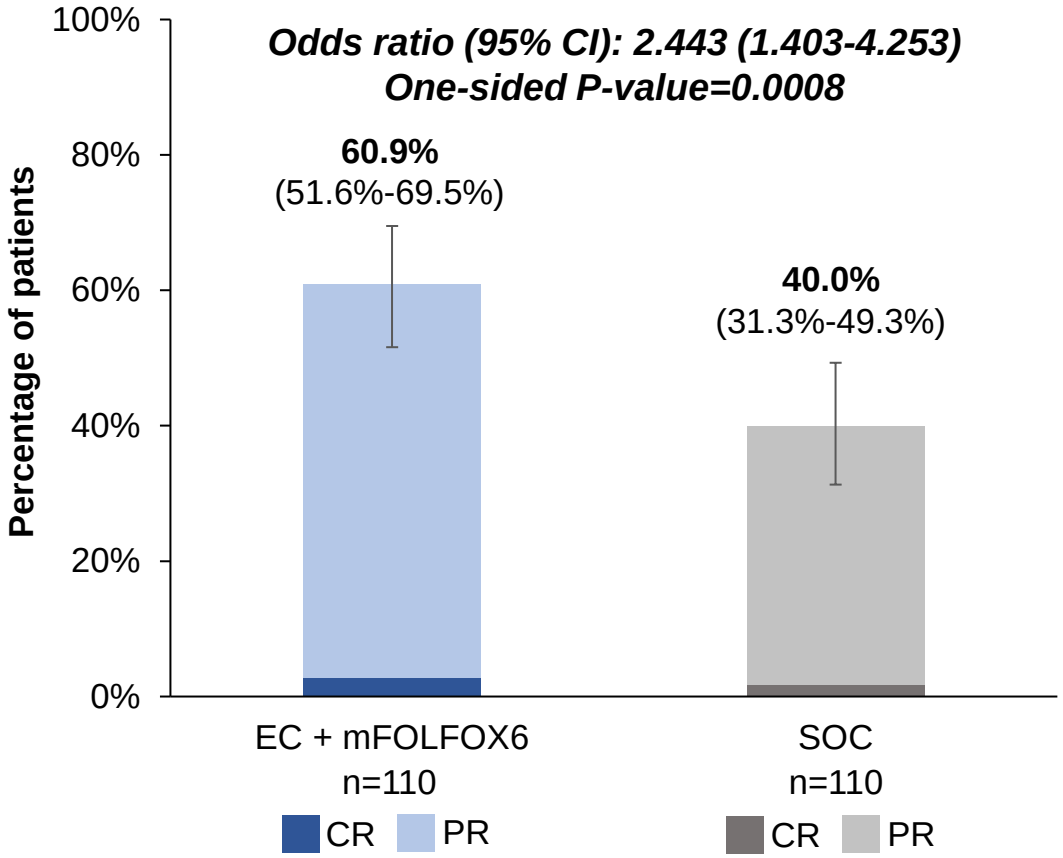
Here we present the primary analysis of ORR by BICR (one of the dual primary endpoints), an interim analysis of OS, and safety in the EC + mFOLFOX6 and SOC arms

[a]Following a protocol amendment, enrollment to the EC arm was stopped and patients were randomized 1:1 to the EC+mFOLFOX6 or SOC arms; data in the EC arm will be reported at a later date. [b]Patients were enrolled between November 16, 2021, and December 22, 2023. [c]mFOLFOX6/FOLFOXIRI/CAPOX ± bevacizumab. [d]In the first 110 patients in each of the EC+mFOLFOX6 and SOC arms.

CAPOX, capecitabine/oxaliplatin; BICR, blinded independent central review; dMMR, deficient mismatch repair; EC, encorafenib plus cetuximab; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; FOLFOXIRI, fluorouracil/leucovorin/oxaliplatin/irinotecan; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high cancer; RECIST, Response Evaluation Criteria in Solid Tumors.

Overview of Response by BICR

Confirmed ORR by BICR



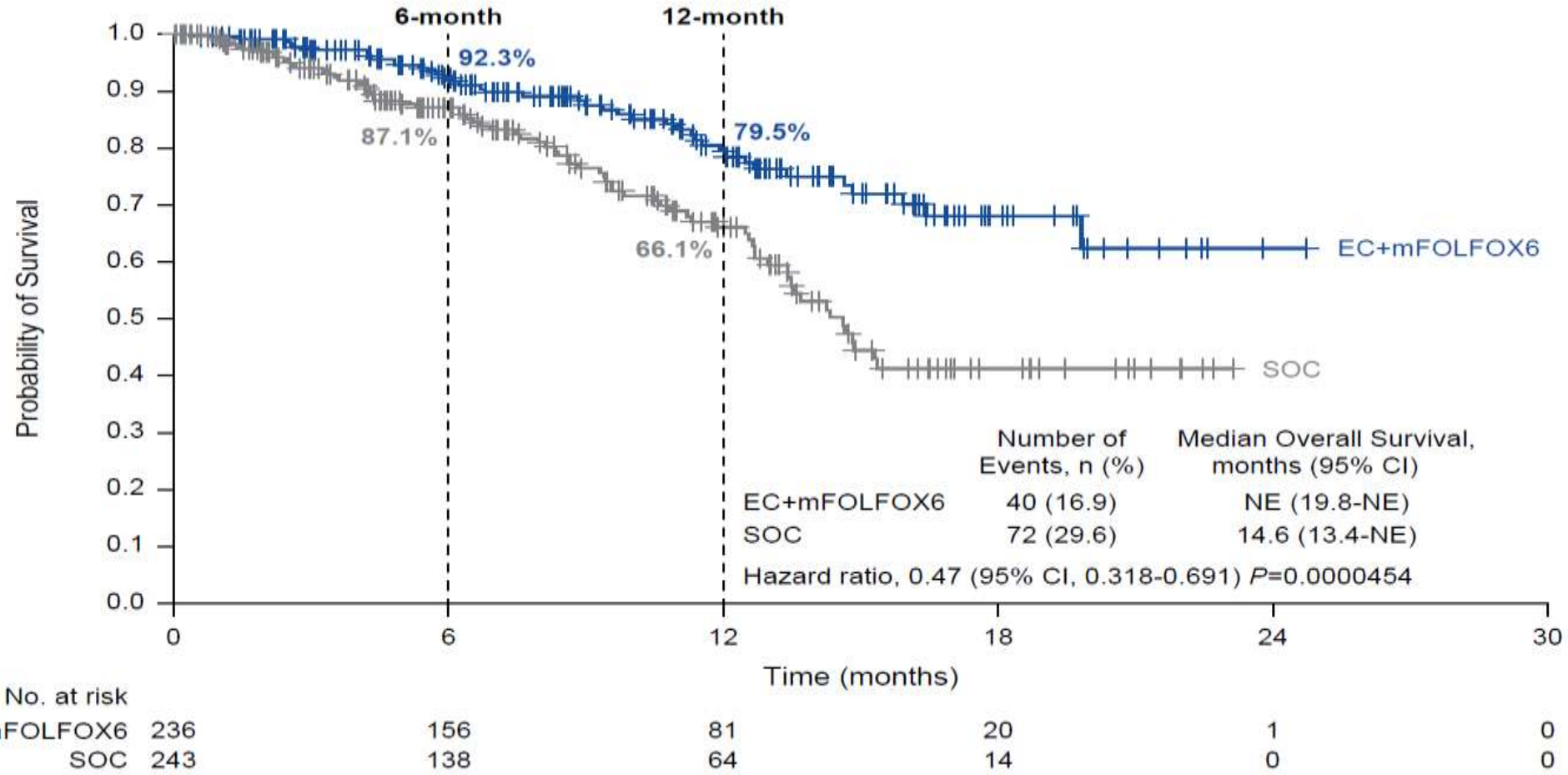
Confirmed Best Overall Response, TTR, and DOR by BICR

	EC + mFOLFOX6 n=110	SOC n=110
Confirmed best overall response, n (%)		
CR	3 (2.7)	2 (1.8)
PR	64 (58.2)	42 (38.2)
SD	31 (28.2)	34 (30.9)
Non-CR/non-PD	3 (2.7)	4 (3.6)
PD	3 (2.7)	9 (8.2)
NE	6 (5.5)	19 (17.3)
	n=67	**n=44**
TTR, median (range), weeks	7.1 (5.7-53.7)	7.3 (5.4-48.0)
Estimated DOR, median (range), months	13.9 (8.5-NE)	11.1 (6.7-12.7)
Patients with a DOR of ≥6 months, n (%)	46 (68.7)	15 (34.1)
Patients with a DOR of ≥12 months, n (%)	15 (22.4)	5 (11.4)

Data cutoff: December 22, 2023.

BICR, blinded independent central review; CR, complete response; DOR, duration of response; EC, encorafenib plus cetuximab; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; NE, not estimable; PD, progressive disease; PR, partial response; SD, stable disease; SOC, standard of care; TTR, time to response.

Interim Overall Survival[a]

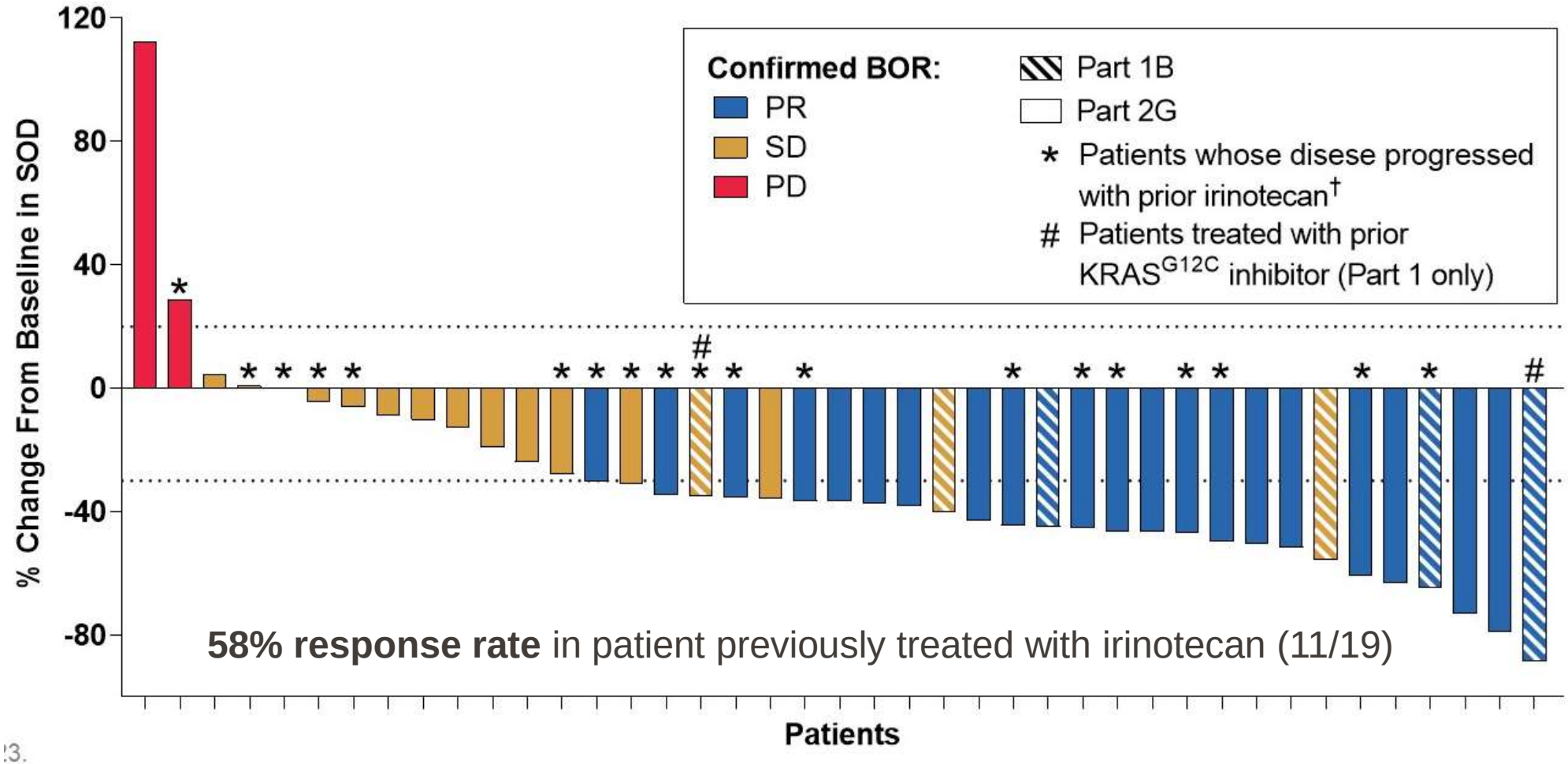


Data cutoff: December 22, 2023.

[a]OS was tested following the prespecified plan with one-sided alpha of 0.000000083, calculated as a portion of the nominal one-sided alpha of 0.001. Statistical significance was not achieved at this time.

EC, encorafenib plus cetuximab; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; NE, not estimable; SOC, standard of care.

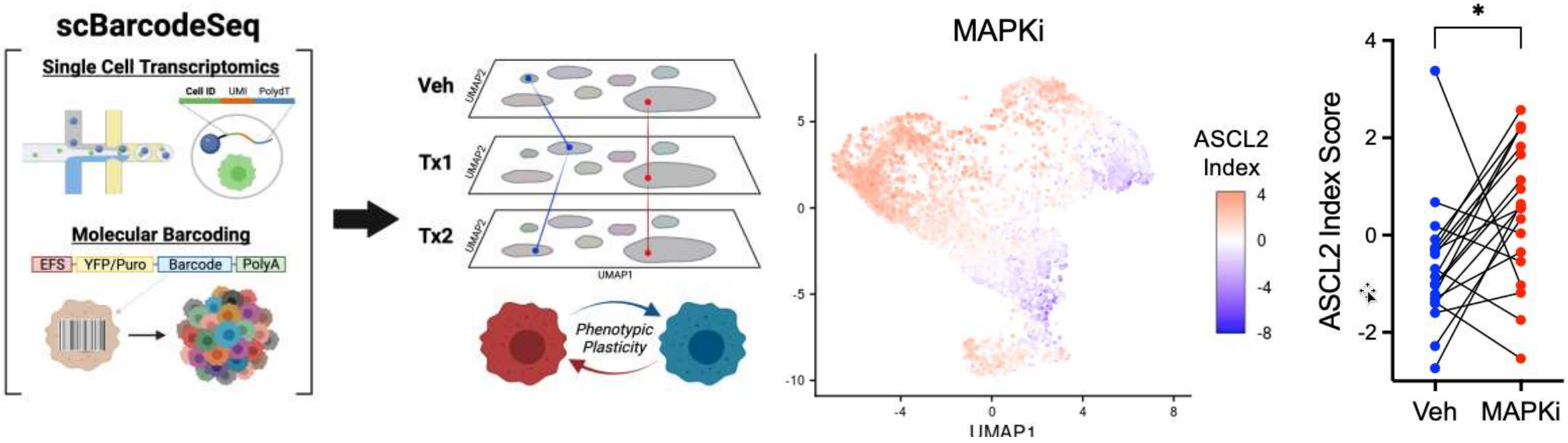
Similar seen with KRASi: Sotorasib + Panitumumab + FOLFIRI



D. Hong et al ASCO ‘23

Utilizing molecularly barcoded PDX models to track resistance

Understanding state changes vs clonal outgrowth



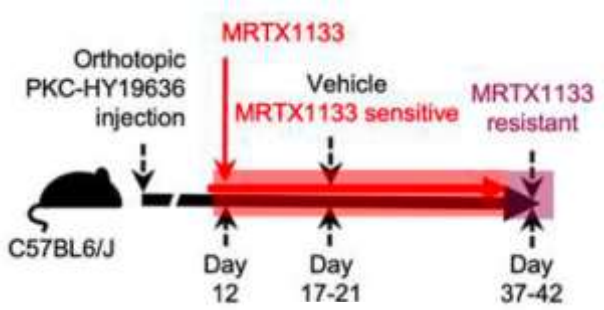
Barcoded cell demonstrate phenotype / state-change change upon MAPKi treatment

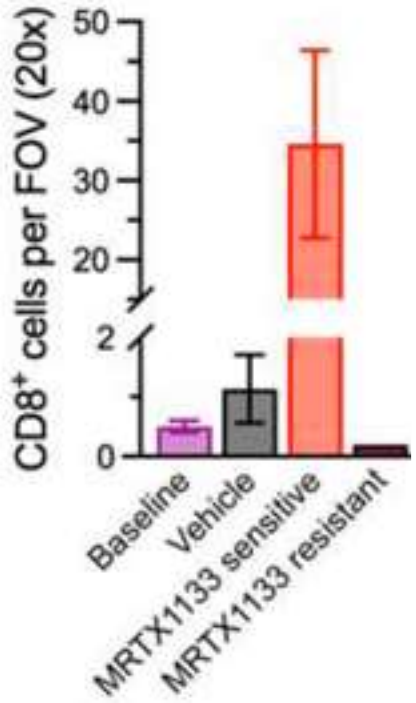
Villarreal et al AACR ‘24; Biorxiv

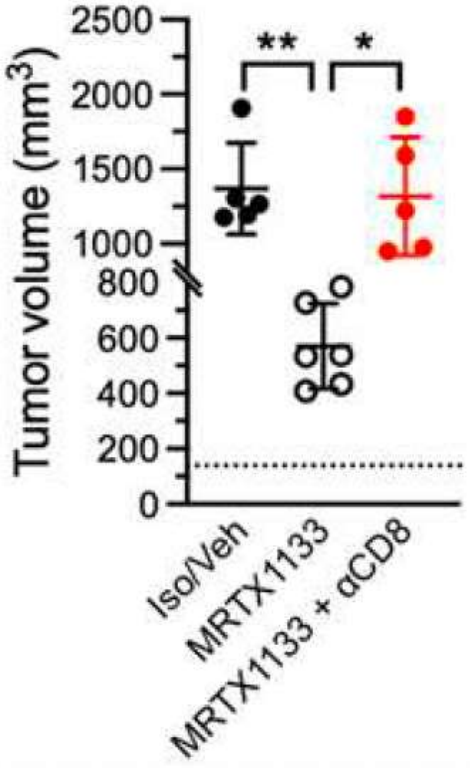
Strategies to Target Innate Resistance

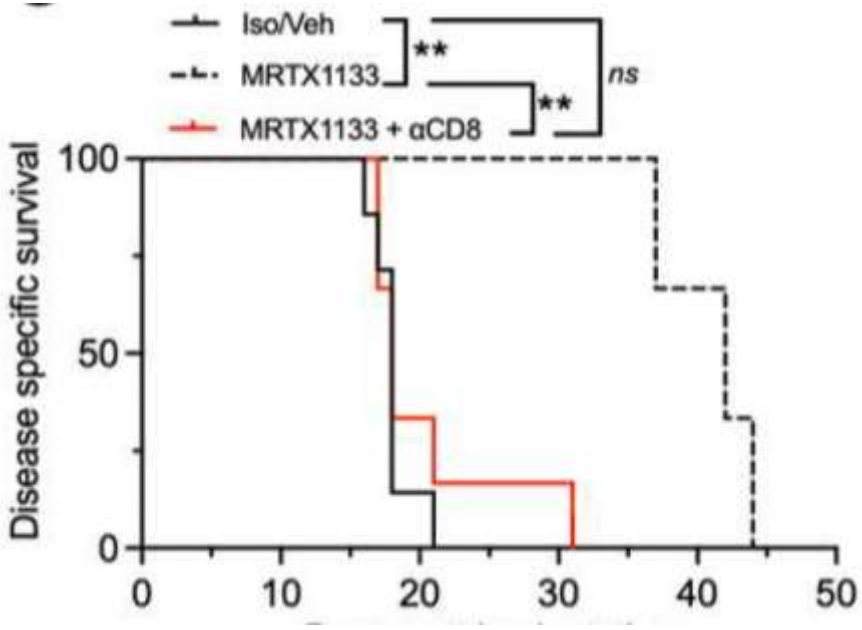
- Improving feedback inhibition: SHP2, SOSi
- Combination with cytotoxic chemotherapy
- Immunotherapy combinations
- Epigenetic combinations

CD8+ Response is Critical for KRASi Activity









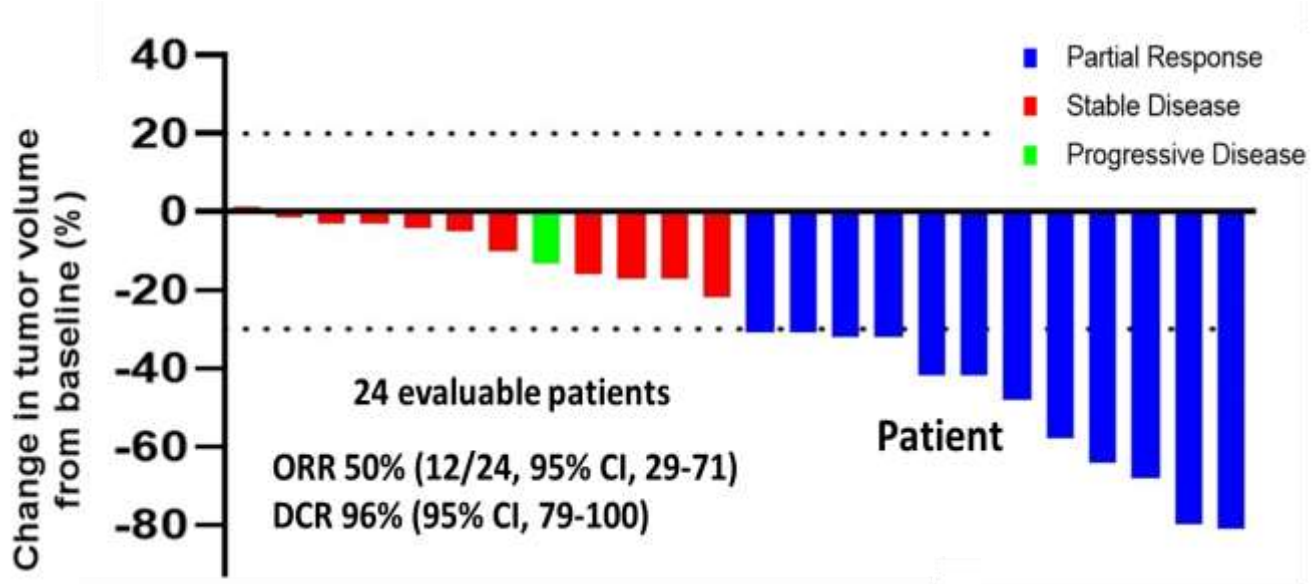
Kate McAndrews

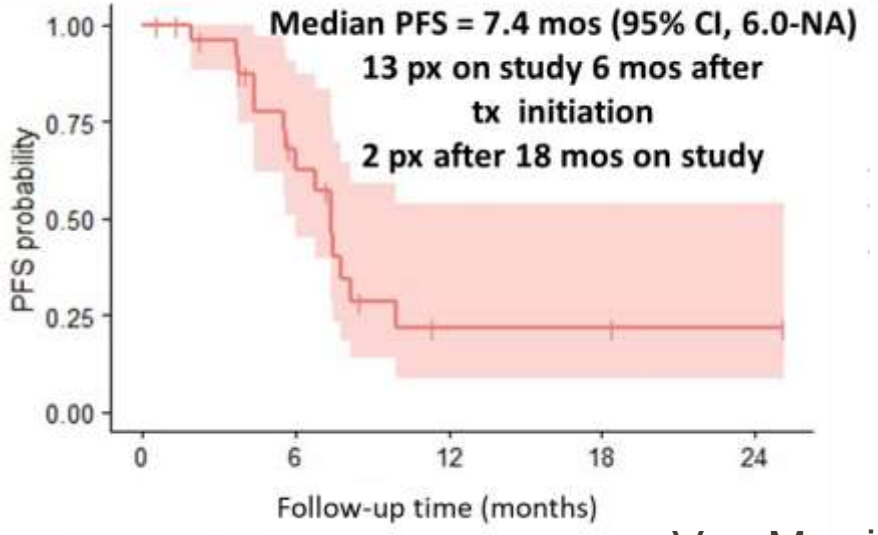
Encorafenib + cetuximab + nivolumab for MSS, *BRAF*^{V600E} metastatic CRC

- ≥1 prior line of systemic therapy
- No prior BRAF/MEK/EGFR therapy or immunotherapy allowed
- 20% historical response rate to E+C

26 patients treated

- Overall response rate **50%** (95% CI, 29-71)
- Disease control rate **96%** (95% CI, 79-100)
- Median PFS **7.4 months** (95% CI, 6.0-NA)
- Median OS **15.1 months** (95% CI, 11.2-NA)

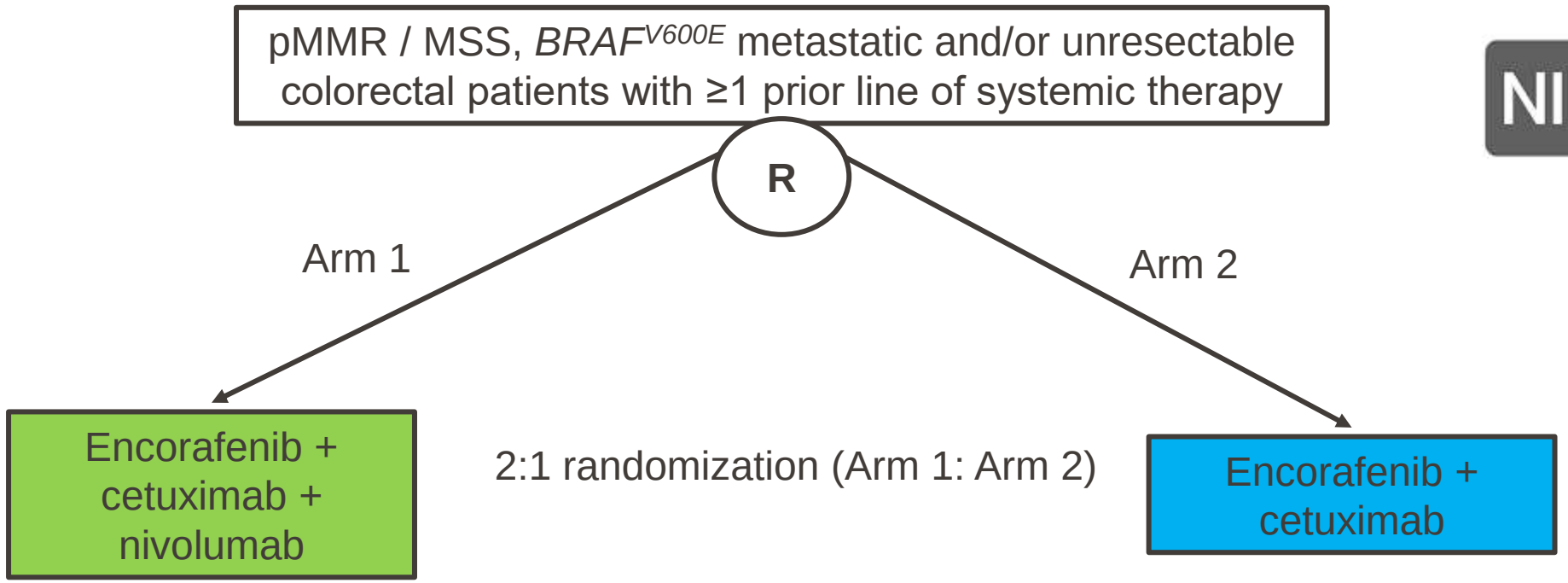




Morris VK et al, ASCO 2022

Van Morris

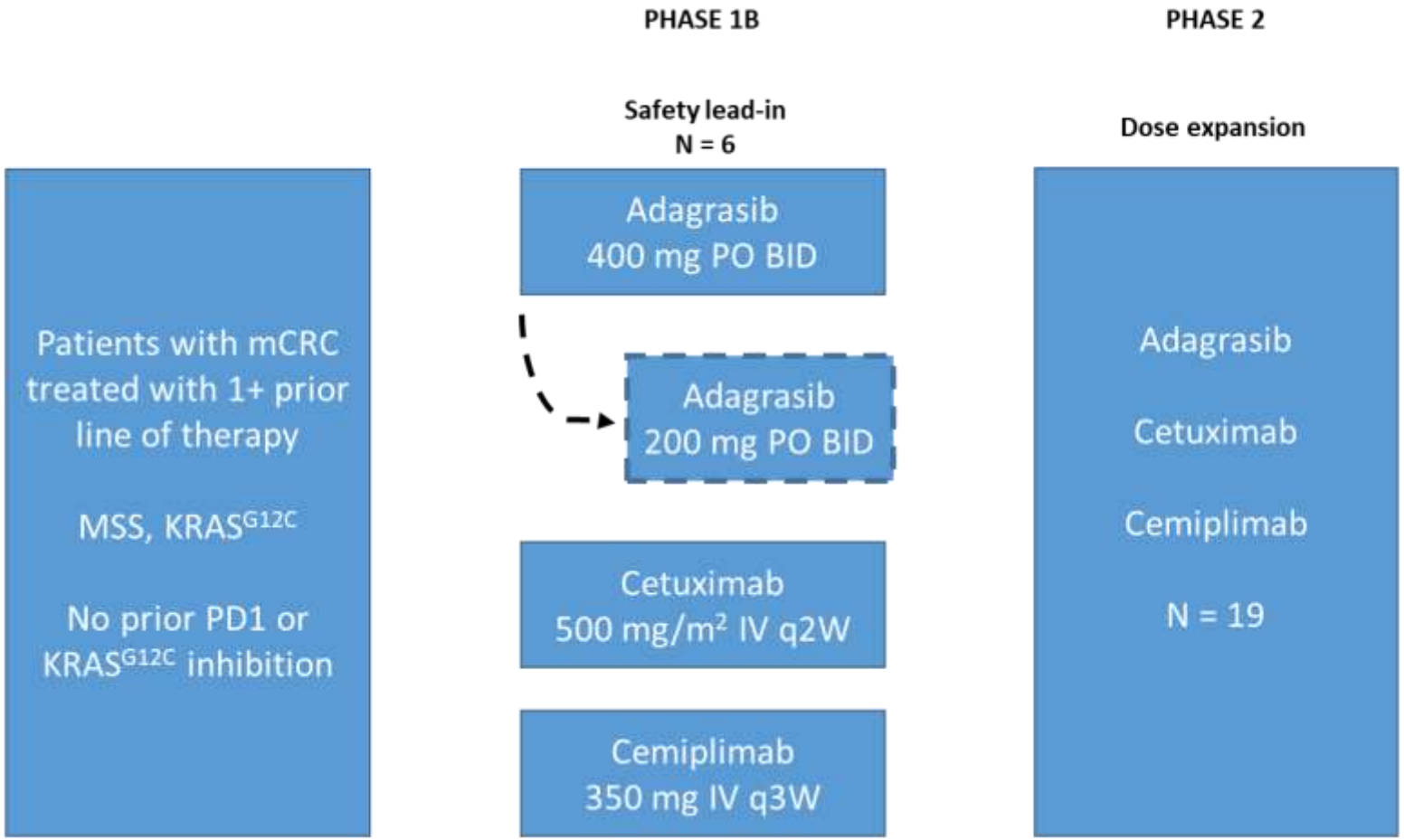
S2107 Study Schema: Encorafenib/Cetuximab +/- Nivolumab



Primary endpoint: PFS
Serial exosomal sampling

Van Morris

Combination of Adagrasib, Cetuximab, and Cemiplimab



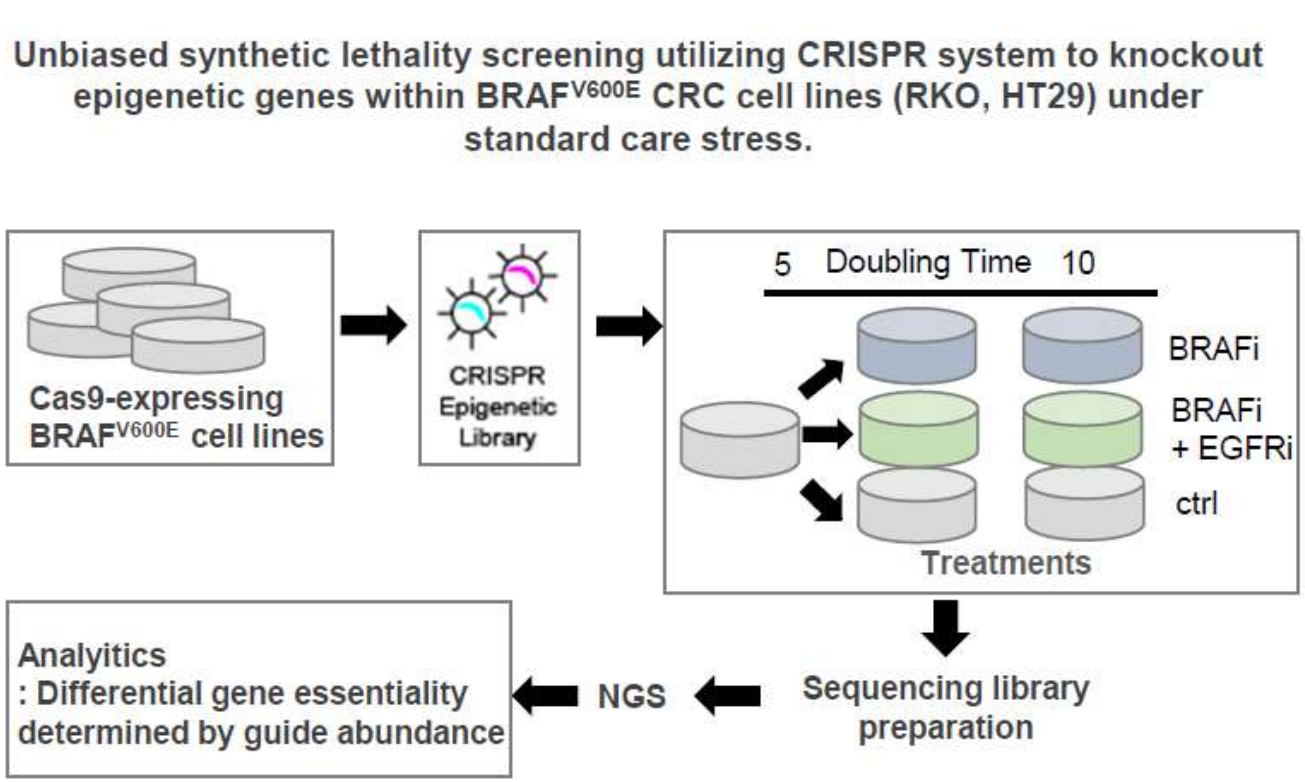
C. Parseghian, PI

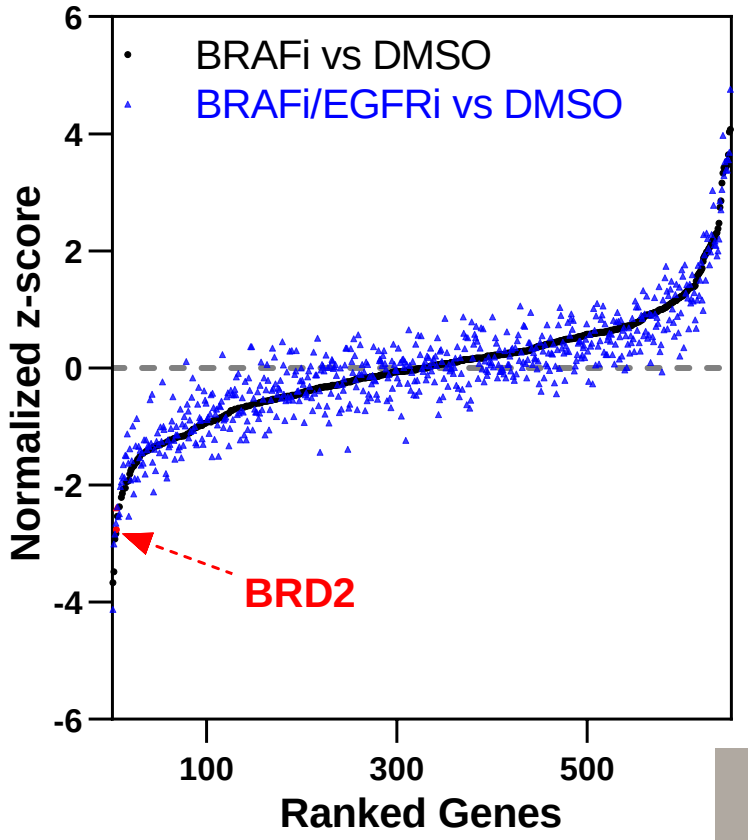
Ryan Corcoran

Strategies to Target Innate Resistance

- Improving feedback inhibition: SHP2, SOSi
- Combination with cytotoxic chemotherapy
- Immunotherapy combinations
- Epigenetic combinations

Epigenetic synthetic lethality screen identifies Bromodomain BRD2

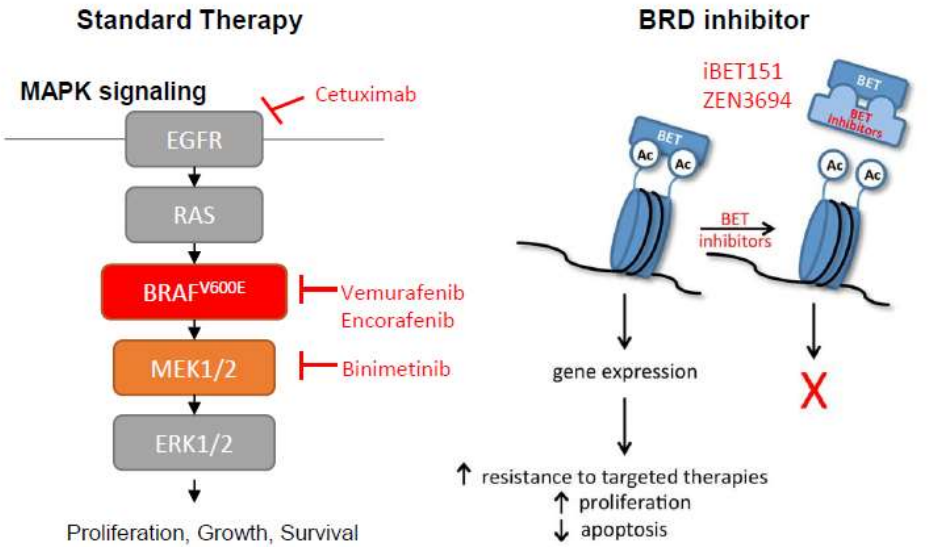




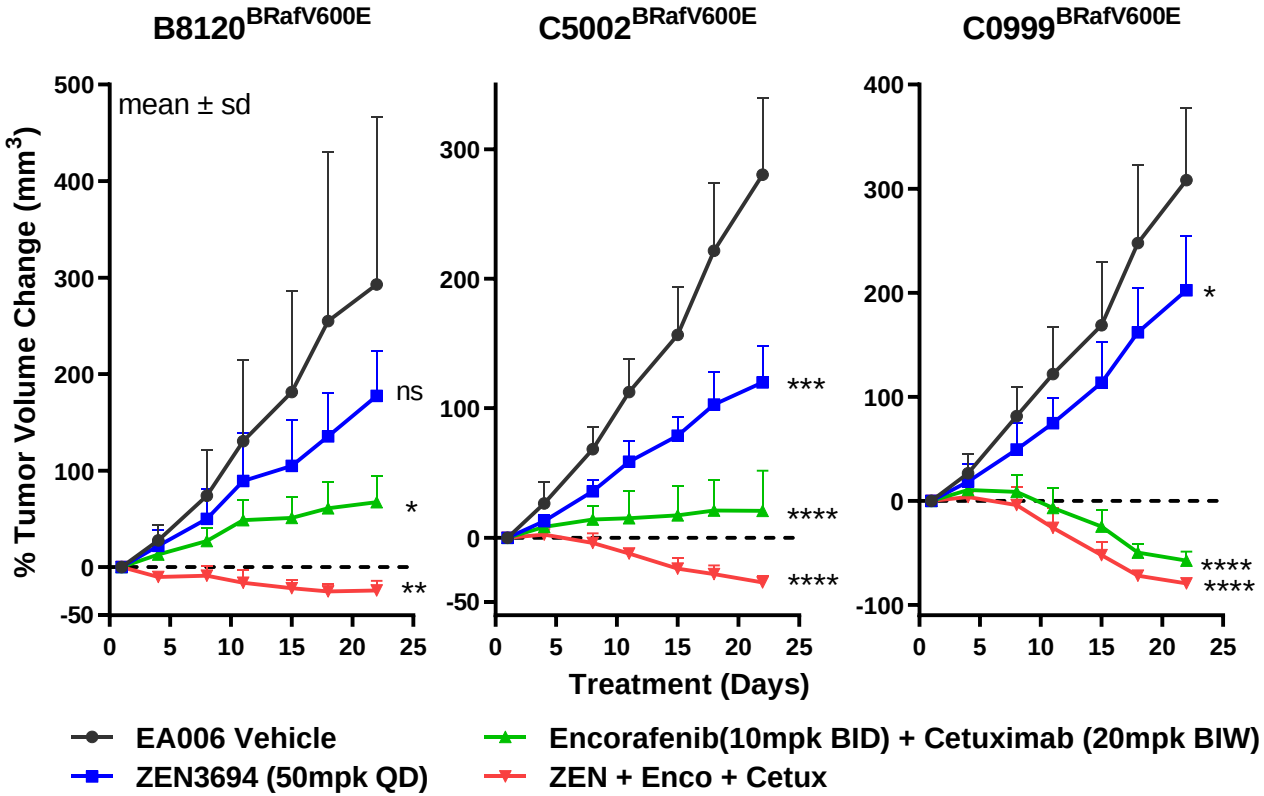
Hey Min Lee, et al AACR ’24 and Orouji et al Gut ‘21

Hey Min Lee

Bromodomain inhibition may improve efficacy of Enco / Cetux



The bromodomain and extraterminal (BET) protein family (BRD2, BRD3, BRD4, and BRDT) are epigenetic readers that, via bromodomains, regulate gene transcription by binding to acetylated lysine residues on histones.



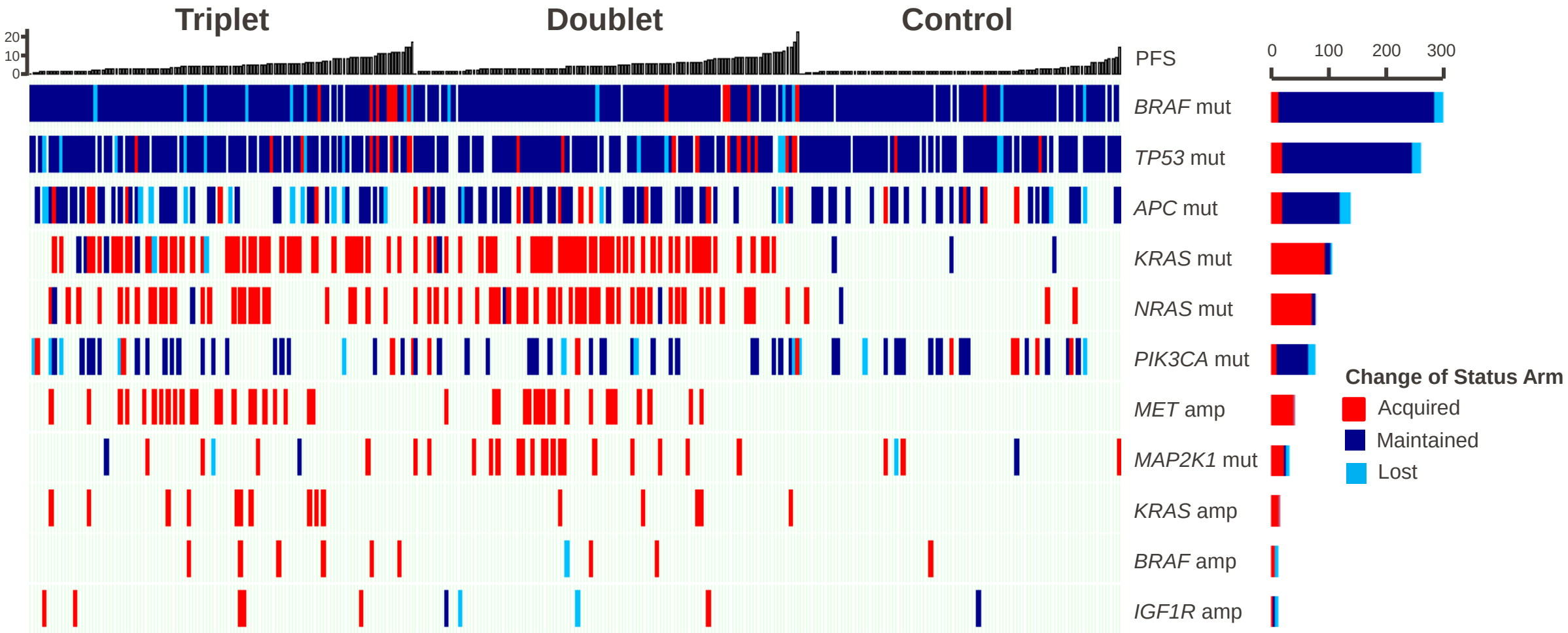
Synergy appears to be due to deeper MAPK inhibition, blunting adaptive response, and reduced MYC expression
Phase 1/2 study is being initiated through NCI ETCTN network (Encorafenib, Cetuximab, Zenith BRD inhibitor)

Hey Min Lee, et al CCR ’24 and Orouji et al Gut ‘21

Acquired Resistance

- Acquired Genomic Alterations
- Deeper inhibition of MAPK pathway
- YAP/TAZ activation
- Cellular Plasticity

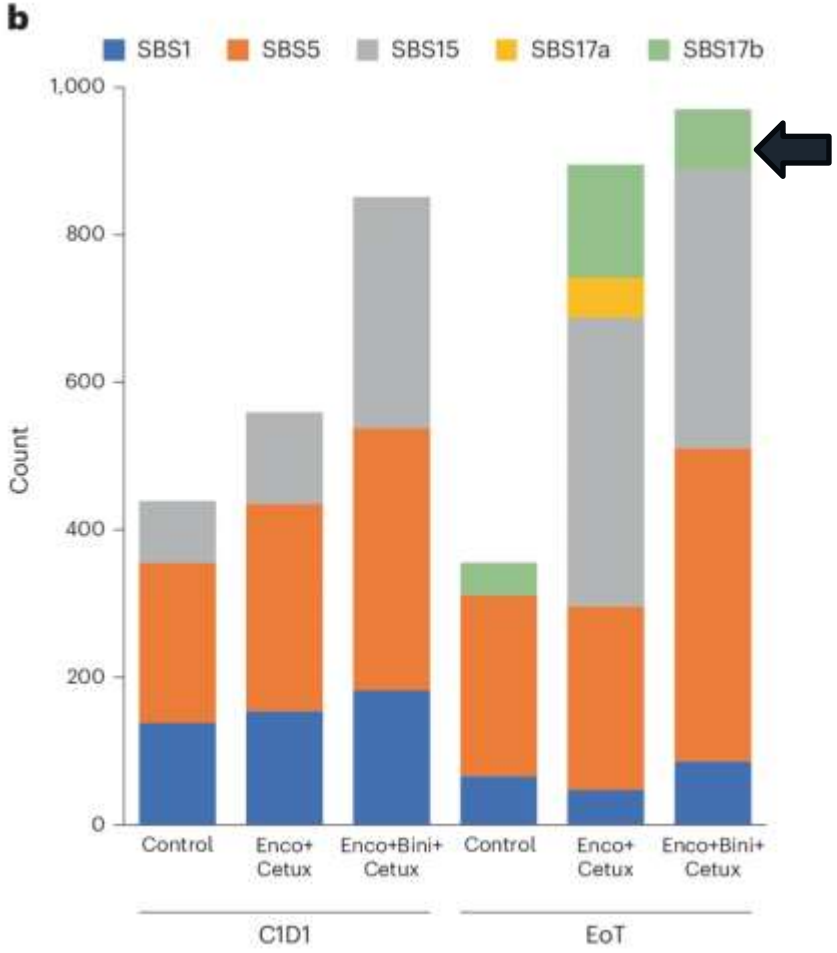
Encorafenib + Cetuximab : Key Genomic Alterations at Progression



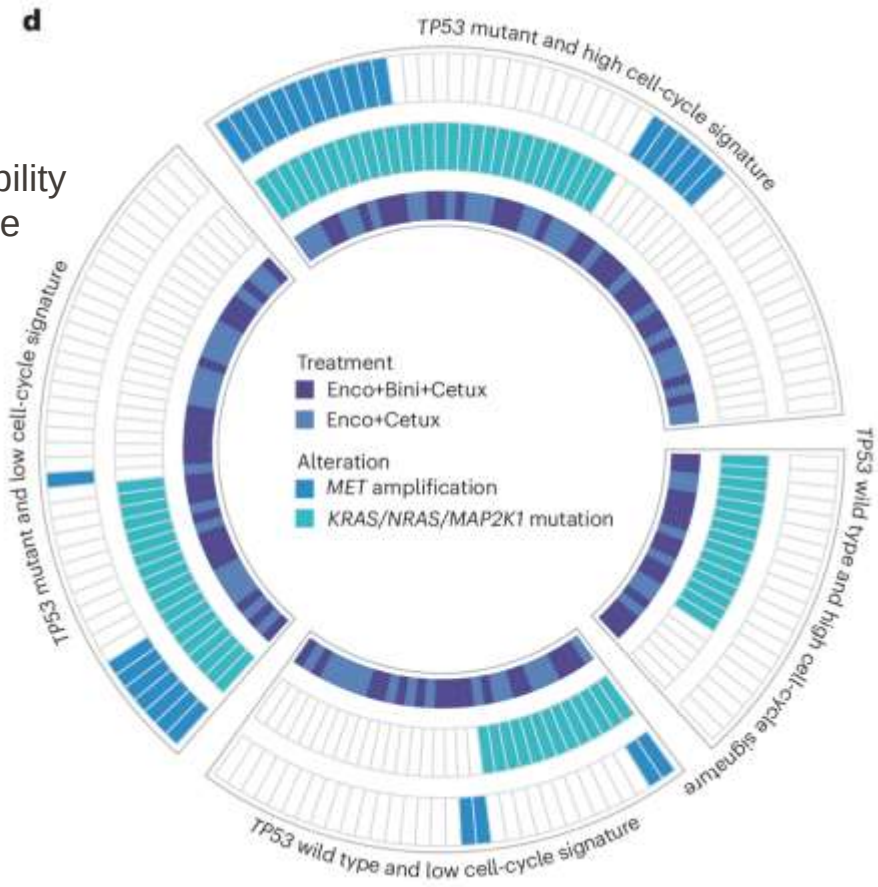
- The key acquired resistance alterations were mutations in *KRAS*, *NRAS*, and *MAP2K1*, and amplification of *MET*

Kopetz et al Nat Med ‘24

Acquired SNV through adaptive mutability, and acquired amplifications associated with TP53 mutations

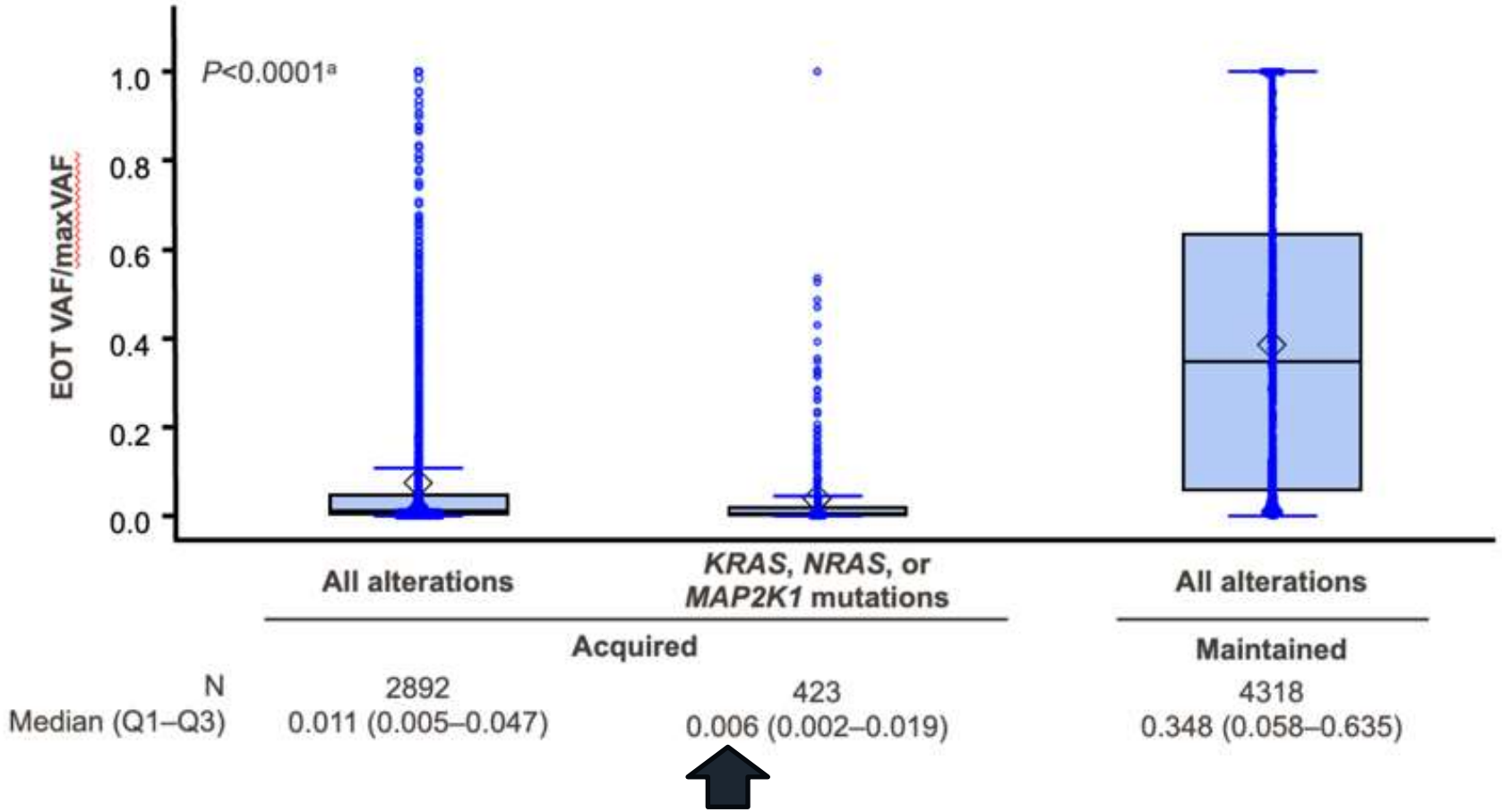


Signature of adaptive mutability with error-prone polymerases



Kopetz et al Nat Med ‘24

Acquired Alterations are Commonly Subclonal after E+C



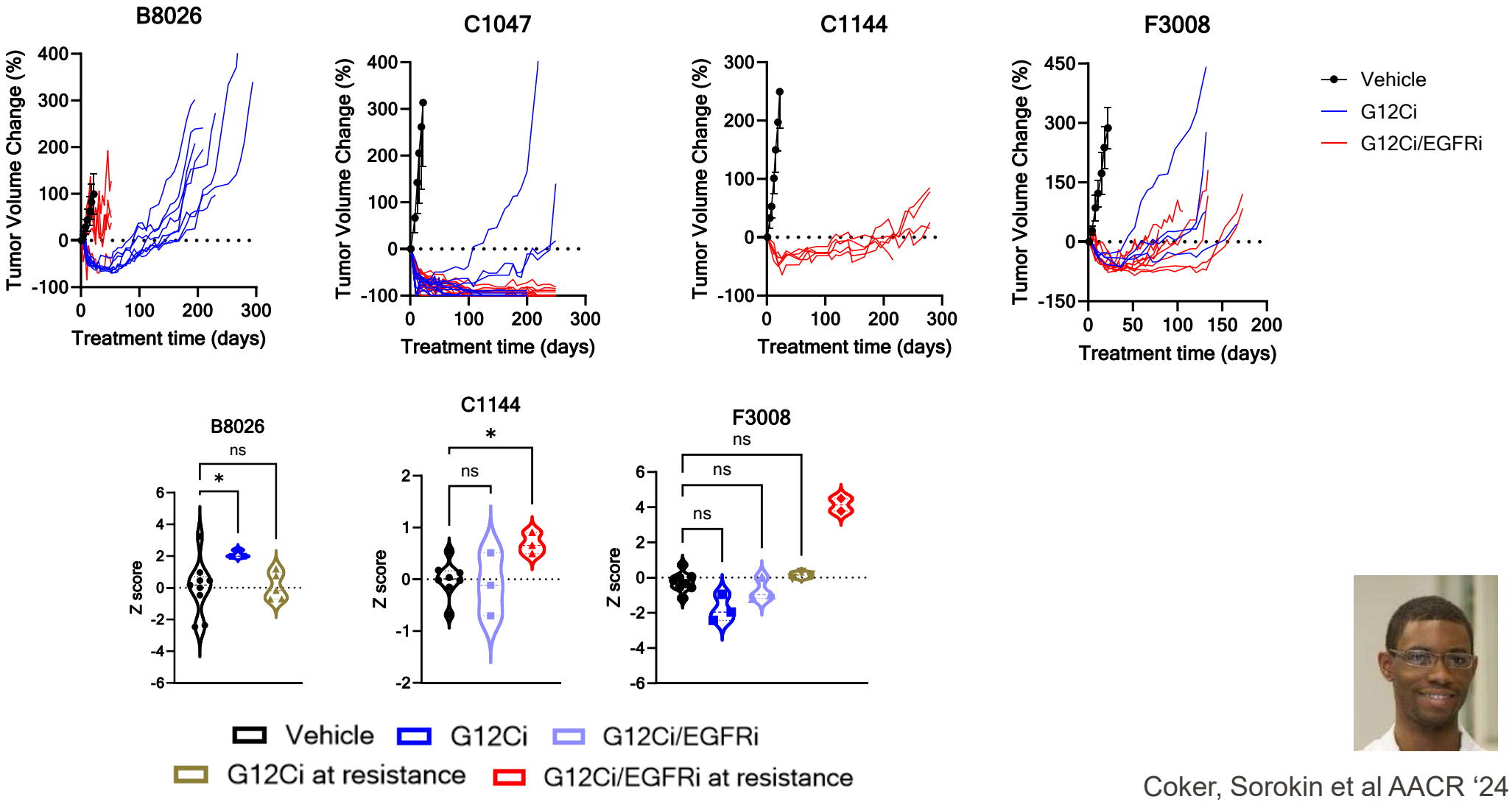
Suggests less than 1/100 cells carry the resistant clone at the time of clinical progression.

Are other mechanisms co-occurring and driving resistance?

Kopetz et al Nat Med '24

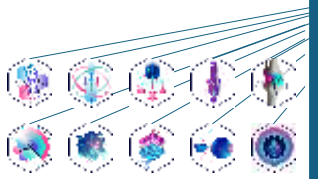
[a]*P* value for comparing between acquired (all) vs maintained (all) is based on the Wilcoxon rank-sum test (2-sided).

YAP/TAZ transcriptional program



Coker, Sorokin et al AACR '24 Poster 1704

We Don’t Fully Understand Evolution of Metastatic CRC: ASCEND



ARPA-H

Advanced Research Projects Agency for Health

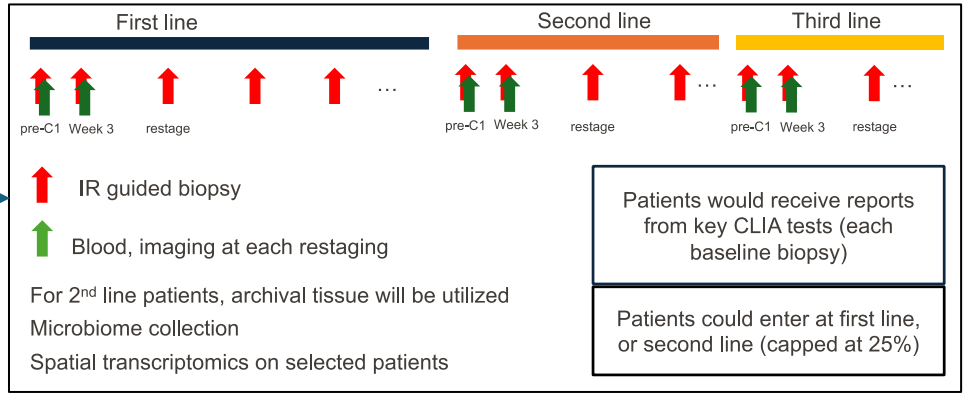
ADAPT Program

Advanced Analysis for Precision cancer Therapy

ASCEND-CRC

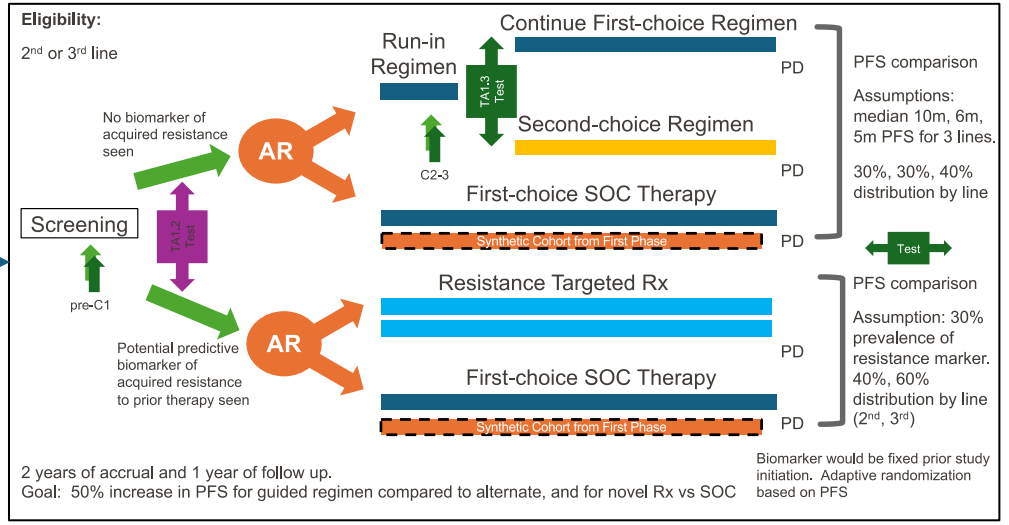
mCRC ADAPT TA2: Observational Phase 1: Years 1-3

(N=250, 8 sites)



mCRC ADAPT TA2: Interventional Phase 2: Years 3-6

Enrolling additional patients (N=300) in Phase 2



S. Kopetz, contact PI

Conclusions

- Adaptive resistance is common with targeted therapies in CRC, and combination of $BRAF^{V600E}$ and EGFR inhibition and $KRAS^{G12C}$ and EGFR inhibition are now the standard of care for patients
- Chemotherapy combinations may be compelling for biologic and clinical reasons, and worthy of further study
- Immunotherapy combinations are ongoing, but promising (even in CRC!)
- Epigenetic mechanisms have appeared in unbiased screens as modulators of innate resistance
- Acquired resistance: We may be over-attributing resistance to ctDNA detectable mechanisms, and new combinations are needed

MD Anderson

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