



Update on Molecular Targeted Therapies for mCRC

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Viewpoint | October 2015



Brave-ish New World—What's Needed to Make Precision Oncology a Practical Reality



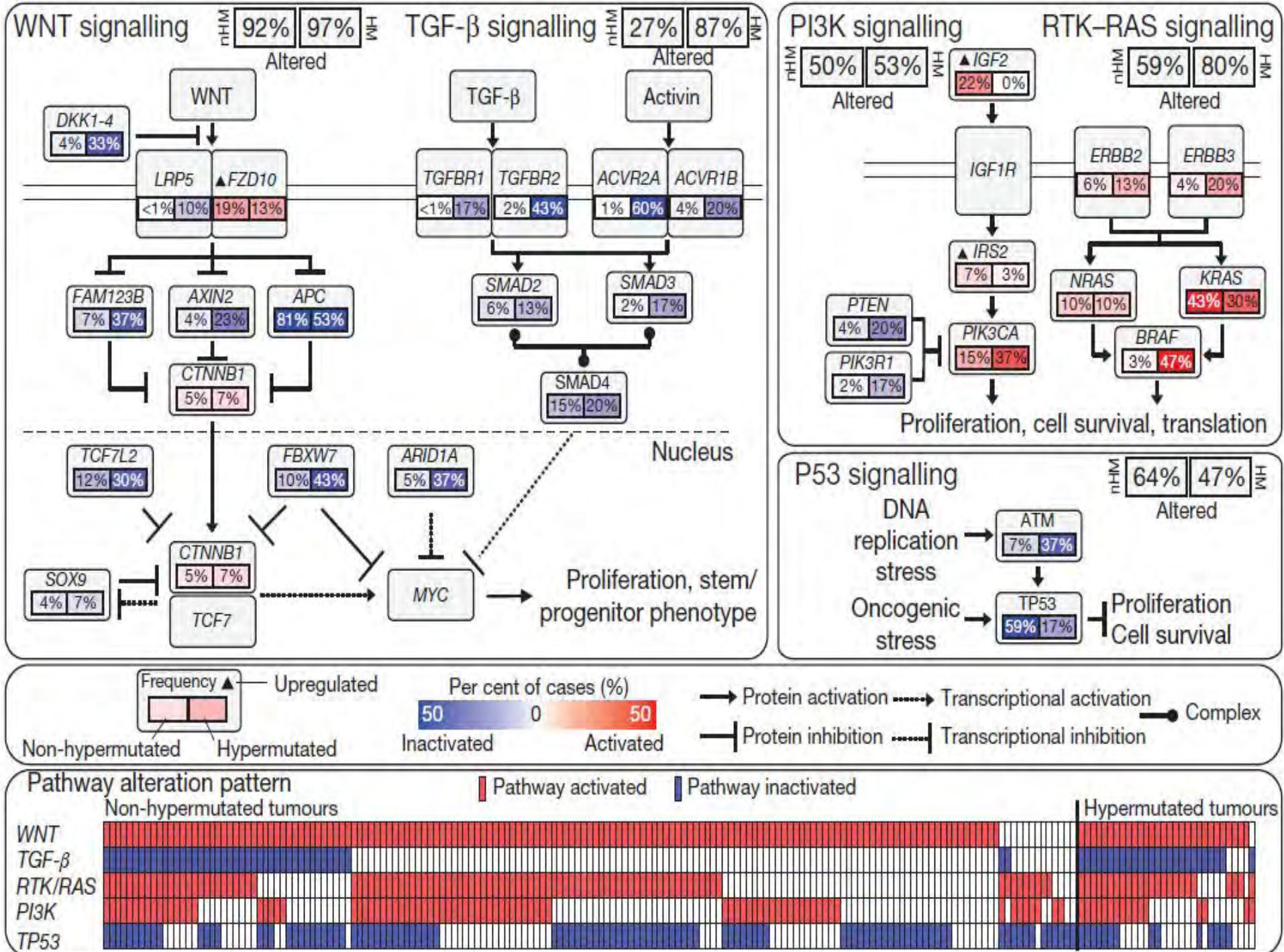
Laura E. MacConaill, PhD^{1,2}; Neal I. Lindeman, MD^{1,2}; Barrett J. Rollins, MD, PhD^{2,3}

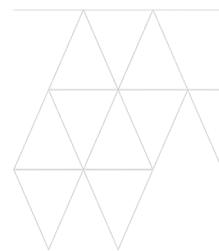


[+] Author Affiliations

JAMA Oncol. 2015;1(7):879-880. doi:10.1001/jamaoncol.2015.1540.

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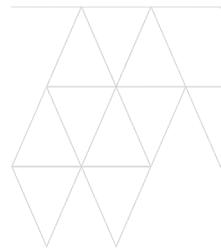
Having a biomarker for a targeted therapy is associated with significantly better outcomes

Regardless of whether the therapy is on the market or in clinical trials



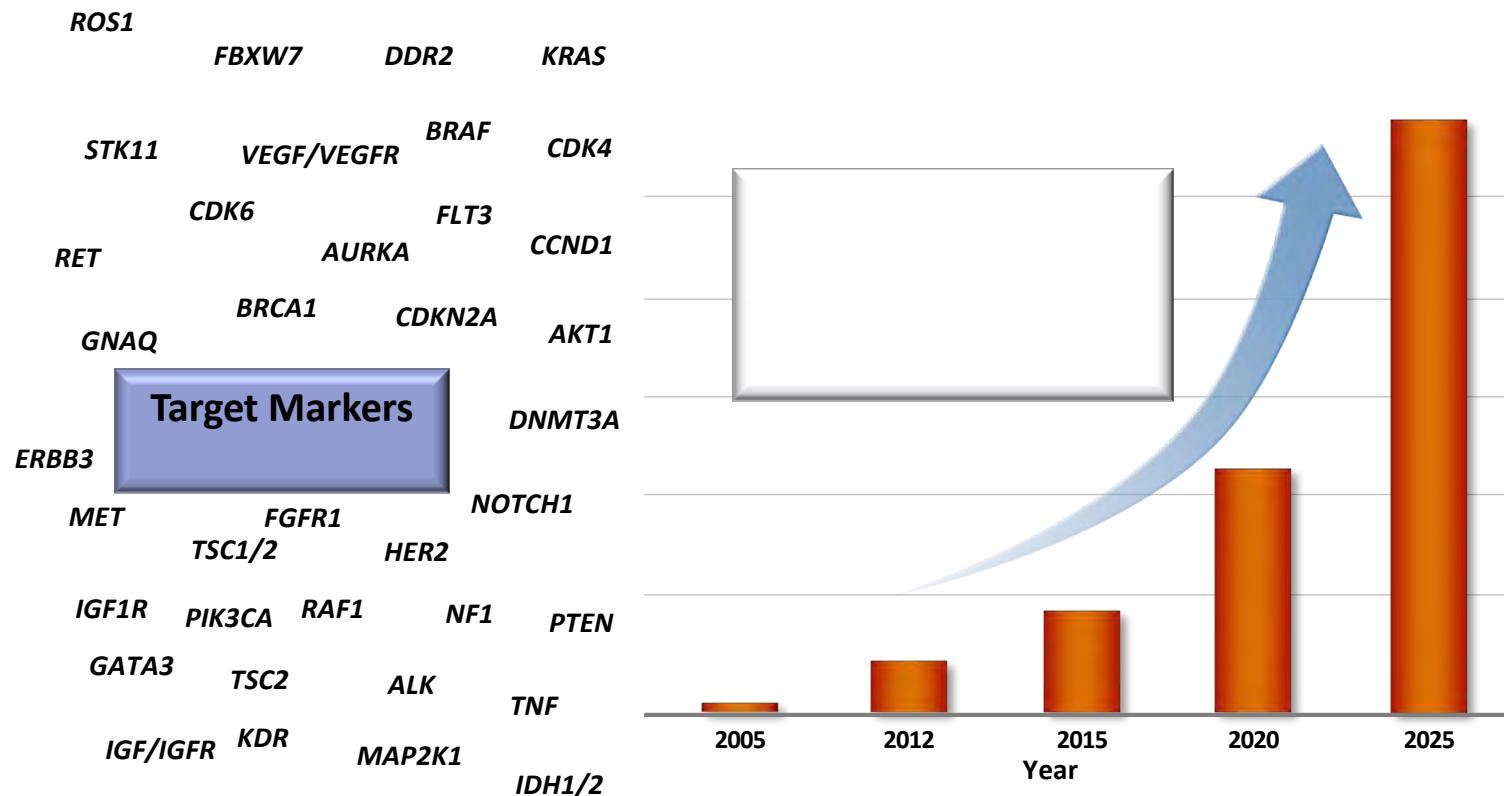
Comparisons between traditional therapies or targeted therapies selected without biomarkers vs. biomarker selected targeted therapies

1 Schwaederle M et al. JAMA Oncol. 2016;2(11):1452–1459 2 Schwaederle M et al. JCO. 2015;33(32):3817-3825 3 Jardim DL et al. J Natl Cancer Inst. 2015;107(11) 4 Barlesi F et al. The Lancet. 2016;387(10026):1415-26. All differences noted are statistically significant p<0.05.



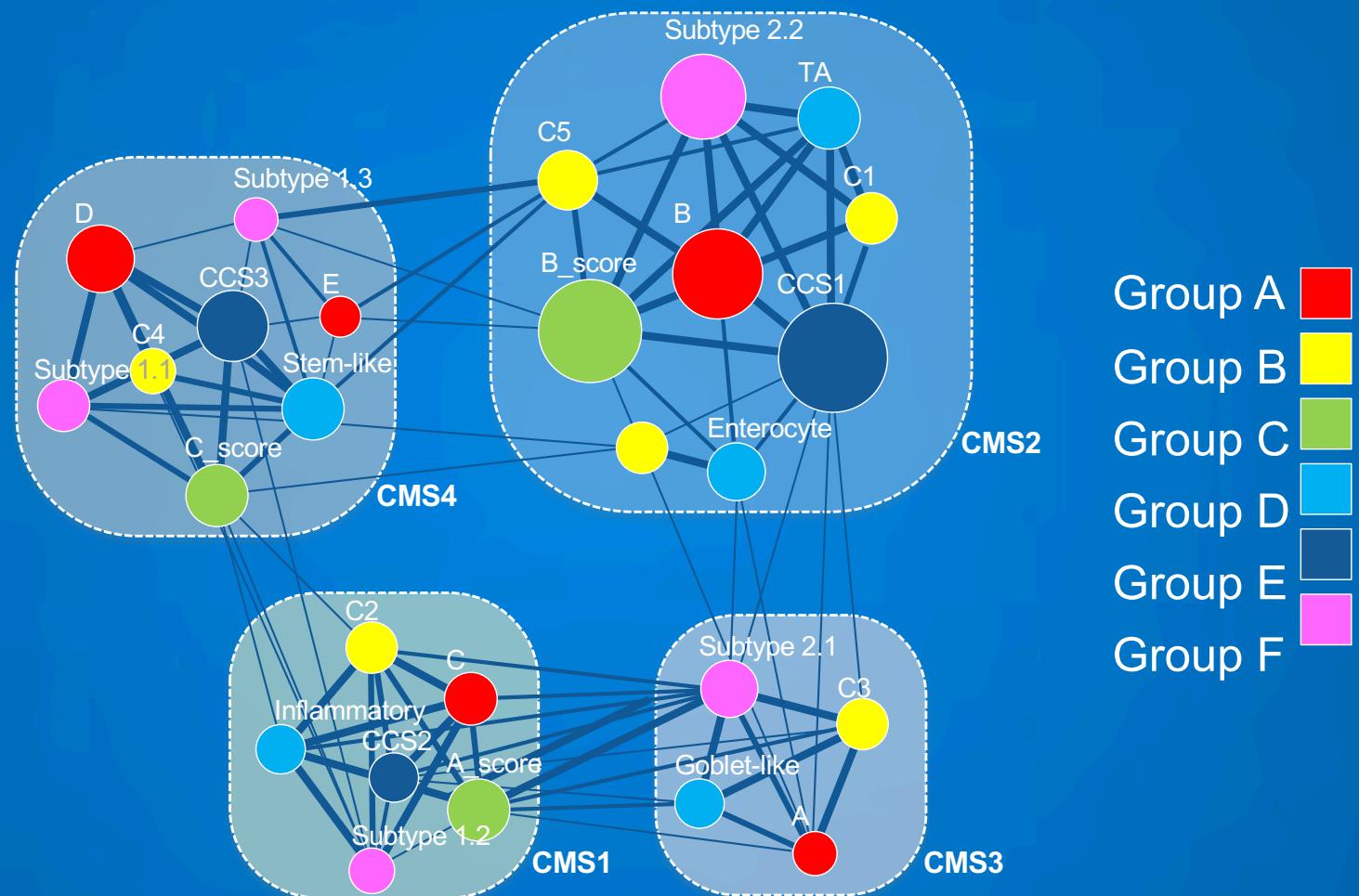
Number of Targeted Therapeutics is Rising

Knowing Which Tests to Order is the Challenge

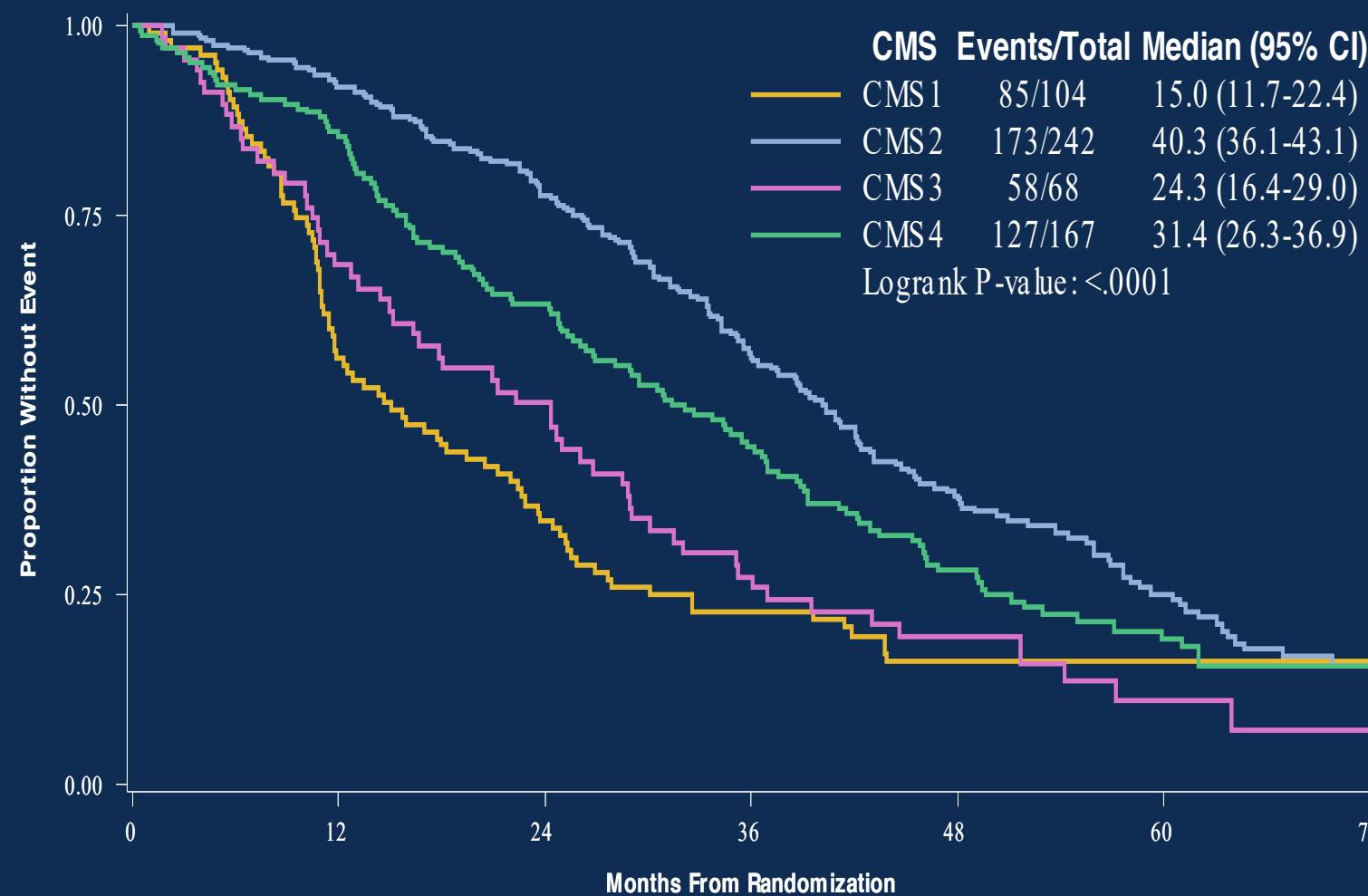


Extrapolated from BioCentury Online Intelligence Database

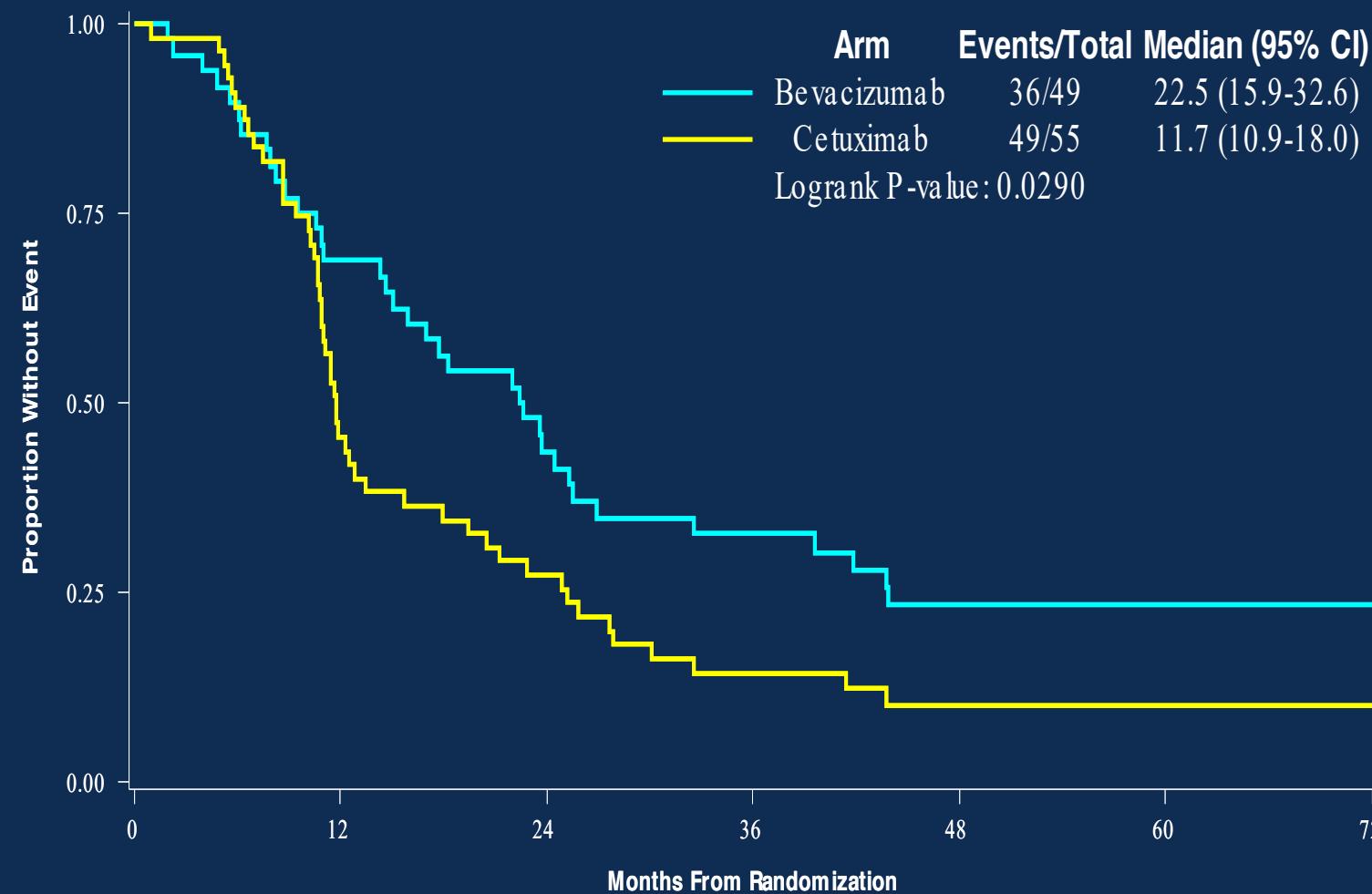
The Colorectal Cancer Subtyping Consortium (CRCSC) identifies a network of molecular subtypes



OS – All Patients by CMS Subtype



OS – CMS1 Patients by Arm



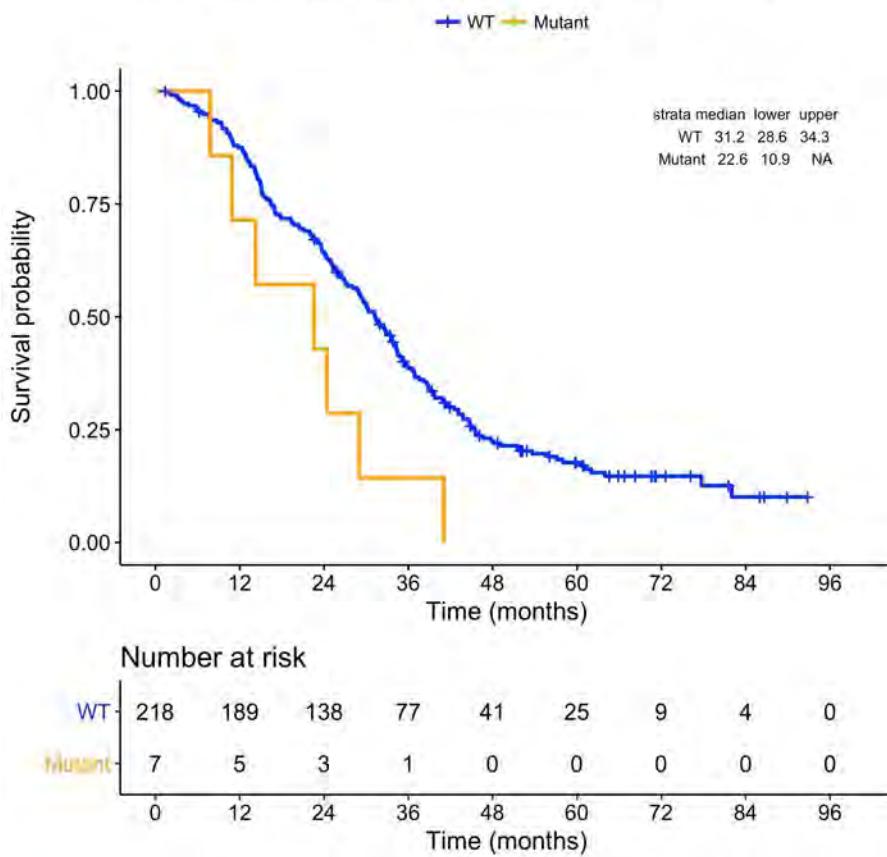
NEXT-GENERATION SEQUENCING (NGS) IN METASTATIC COLORECTAL CANCER (MCRC): NOVEL MUTATED GENES AND THEIR EFFECT ON RESPONSE TO THERAPY

Federico Innocenti, Naim Rashid, Mu Wancen, Fang-Shu Ou, Xueping Qu, Stefanie Denning, Monica Bertagnolli, Charles David Blanke, Alan P. Venook, Omar Kabbarah, Heinz-Josef Lenz

For the Alliance and SWOG

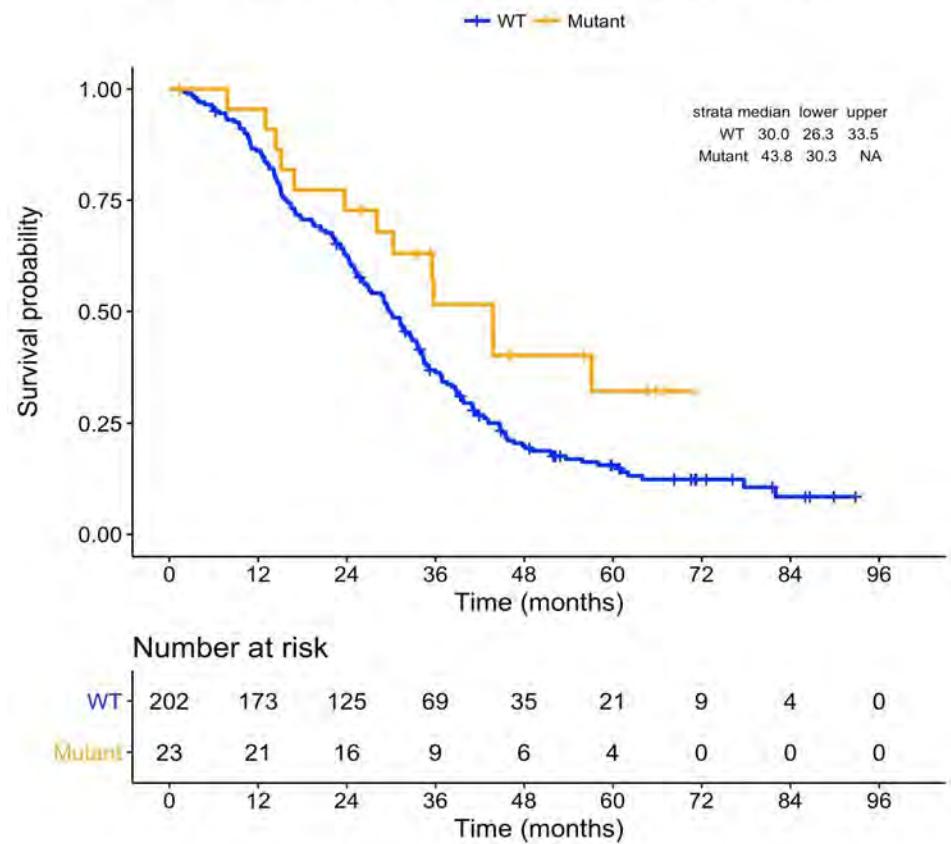
MUTATED GENES ASSOCIATED WITH OS IN THE BEVACIZUMAB ARM (N=216)

GRM3, HR= 2.34 (1.09,5.02), p=0.028, Adj. p=0.451



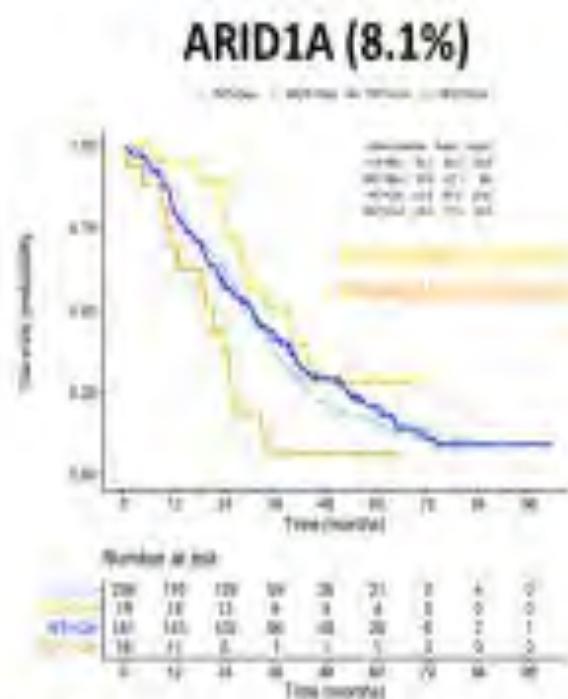
HR_{adj} 2.68 (95% CI 1.242-5.781)
P-value 0.012

LRP1B, HR= 0.55 (0.32,0.97), p=0.041, Adj. p=0.451

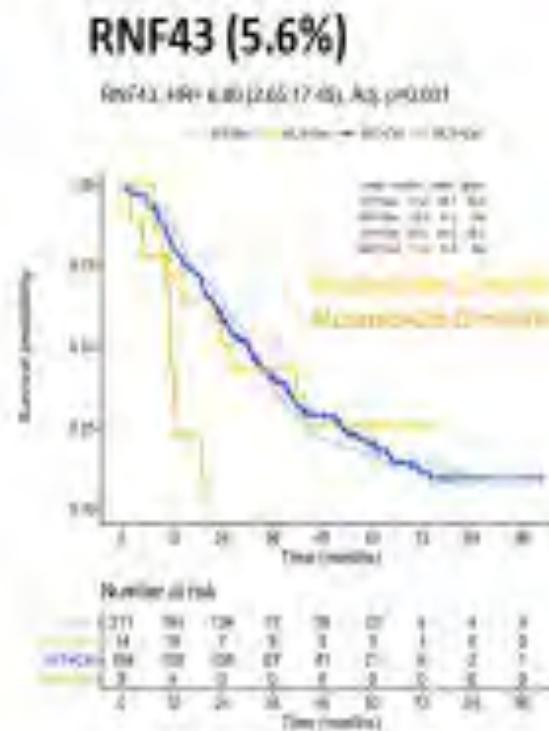


HR_{adj} 0.59 (95% CI 1.242-5.781)
P-value 0.012

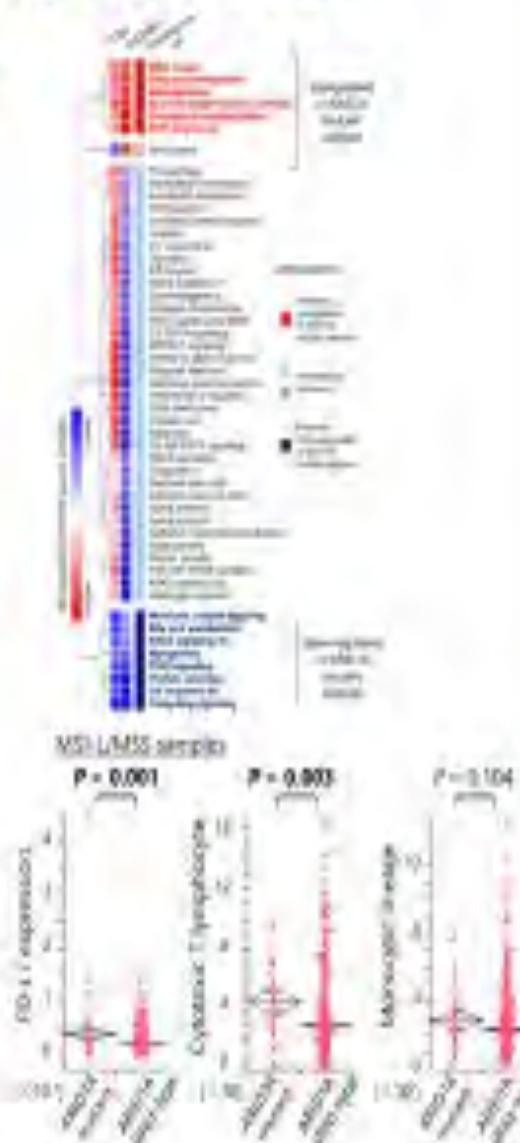
NOVEL PREDICTIVE MARKER FOR ANTI EGFR AND ANTI VEGF THERAPIES IN 80405 USING NGS



WT HR_{adj} 0.97 (95% CI 0.77-1.22)
 Mutated HR_{adj} 2.29 (95% CI 1.27-4.13)
 Interaction p 0.014

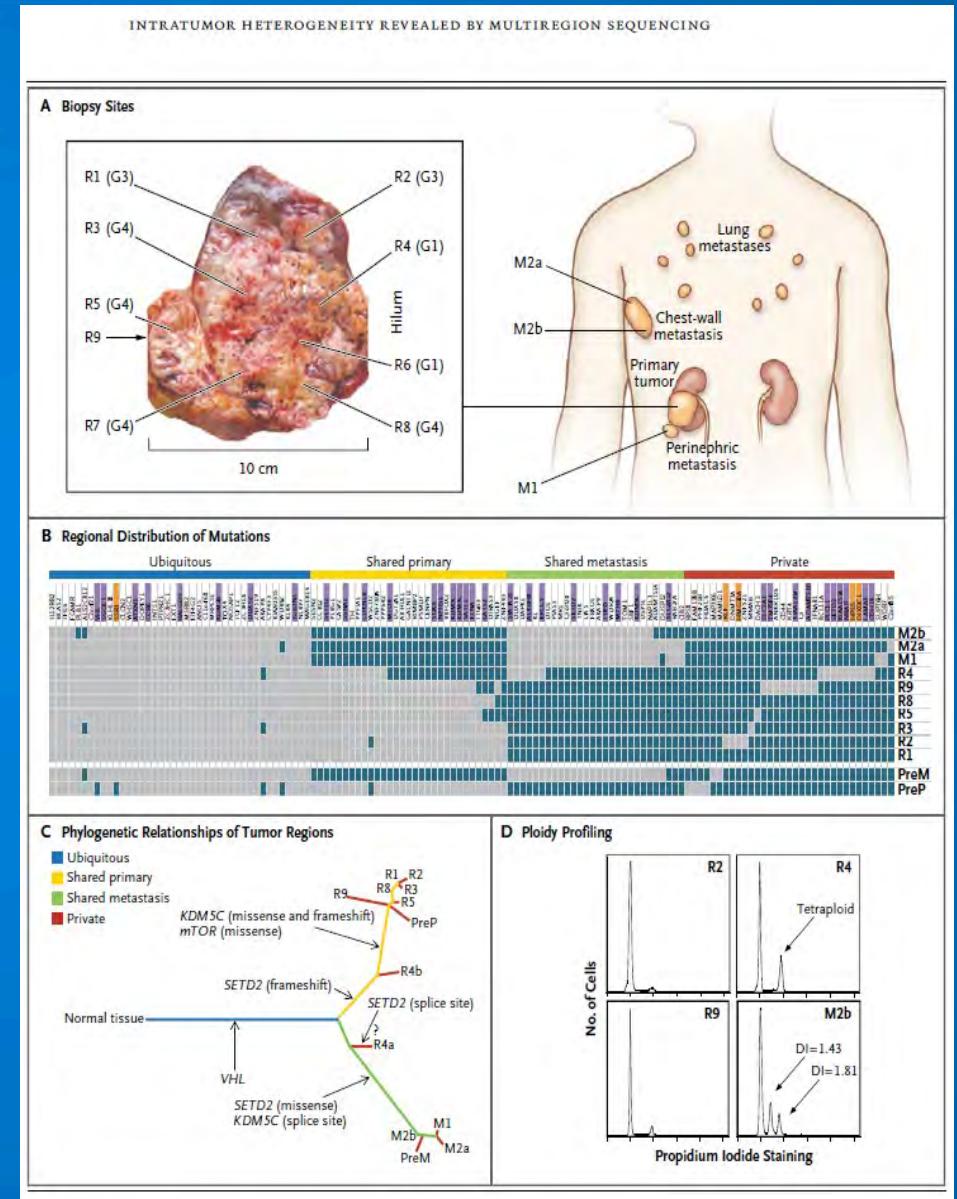


WT HR_{adj} 0.97 (95% CI 0.78-1.22)
 Mutated HR_{adj} 2.38 (95% CI 1.22-4.63)
 Interaction p 0.0003

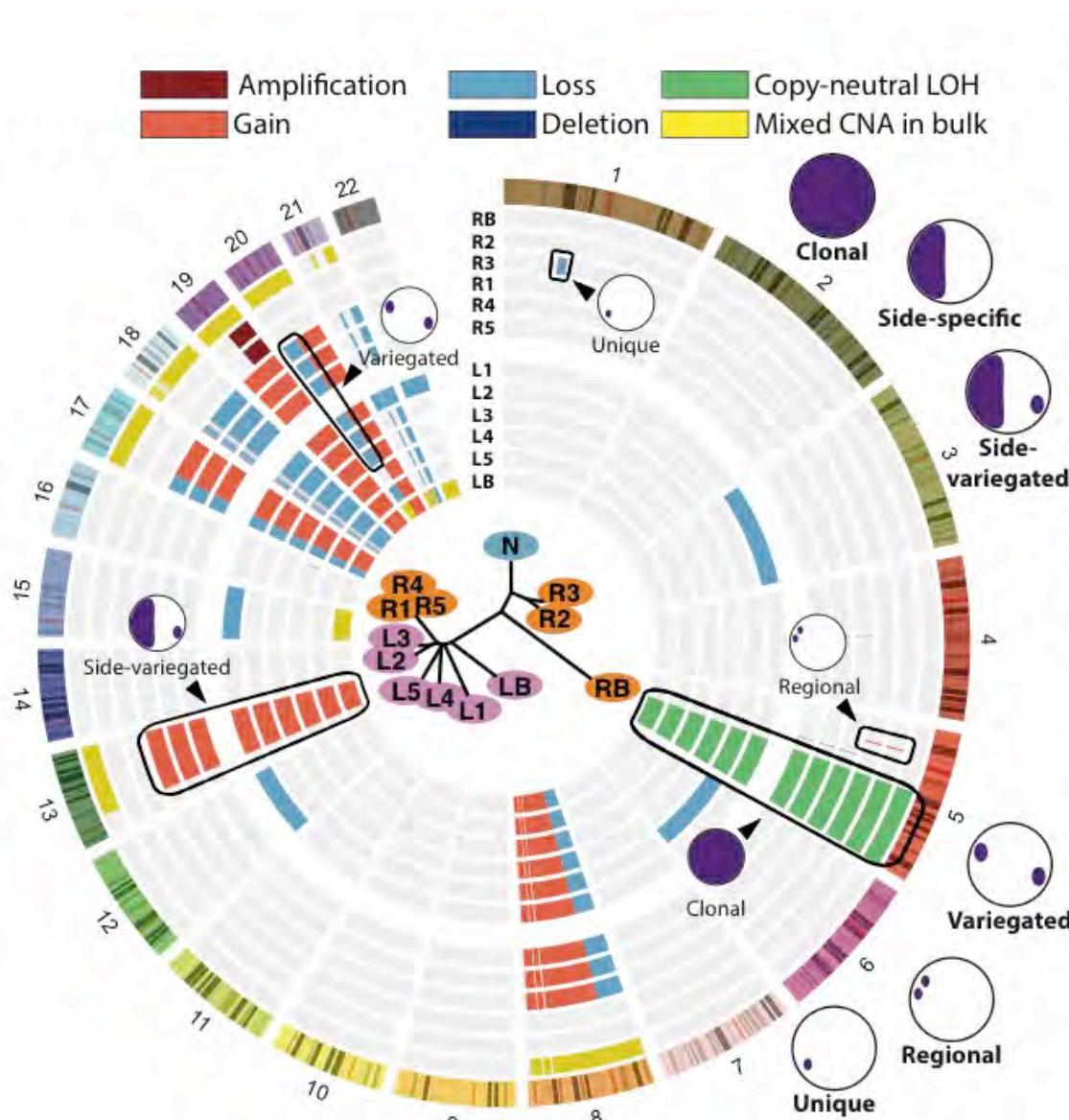


Heterogeneity also exists within individual tumors

- Ding et al., Nature 2010
 - Mutations present in 5–90% of sequencing reads from one tumor
- Navin et al., Nature 2011
 - Independent subclones coexisting in a single anatomic site in breast
- Gerlinger et al., NEJM 2012
 - Two-thirds of mutations in single biopsies were not uniformly detectable throughout all sampled regions
 - Both sensitive and resistant RNA expression patterns

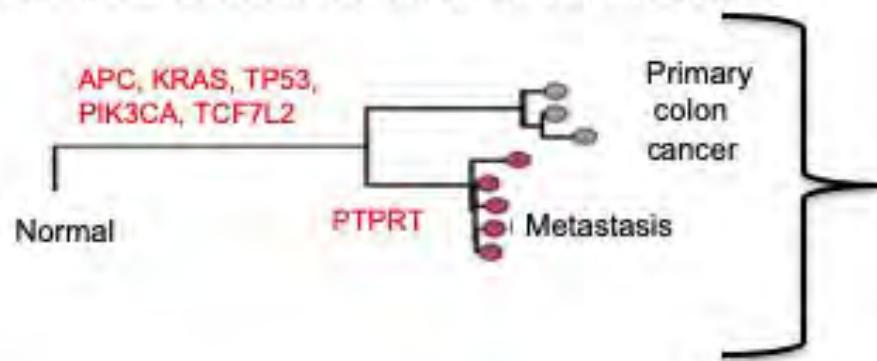


Intra-tumor copy number heterogeneity in CRC at the single gland level

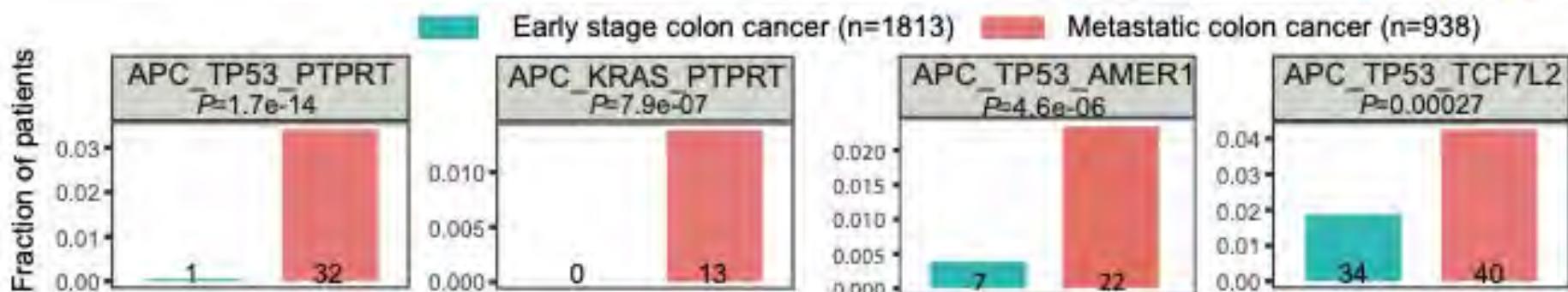
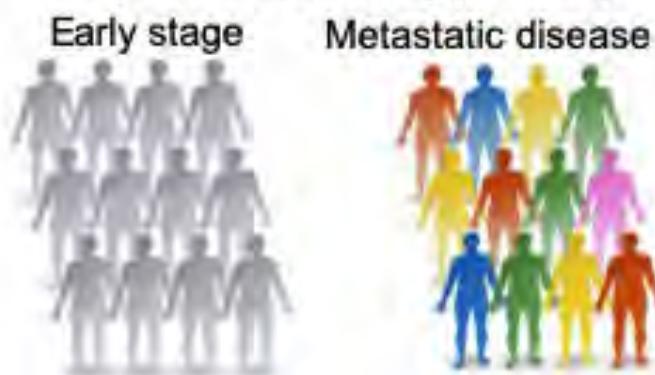


Validation of metastasis driver modules

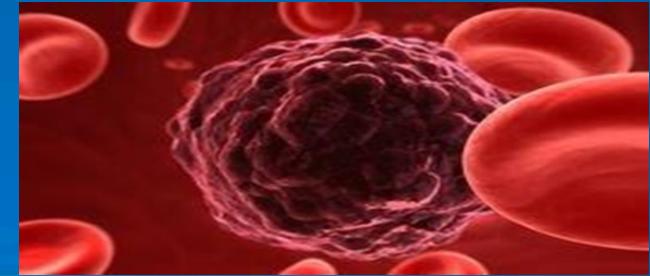
Metastasis associated early driver modules



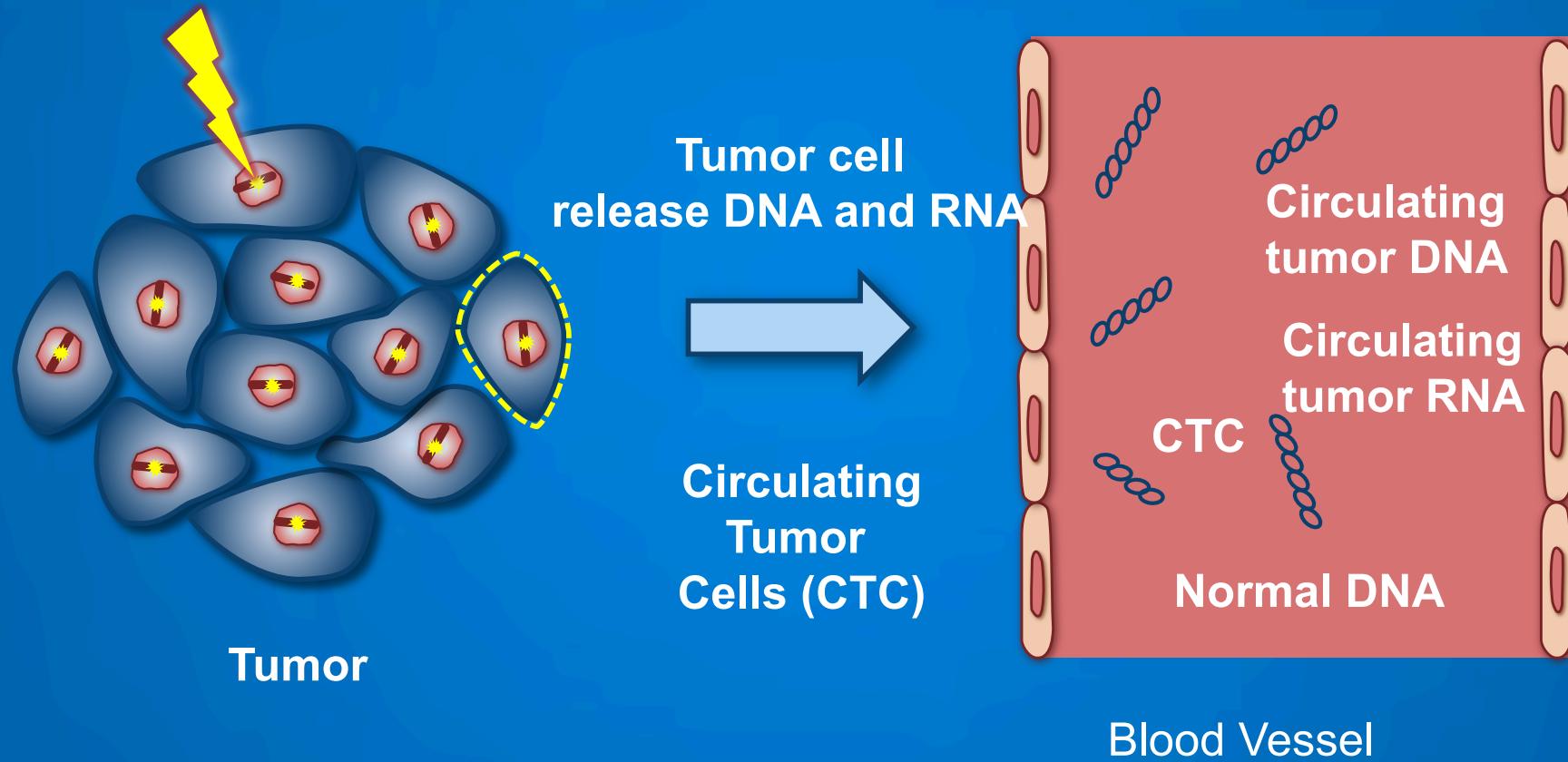
Clinically annotated CRCs with targeted sequencing (n=2751)



Liquid Biopsies

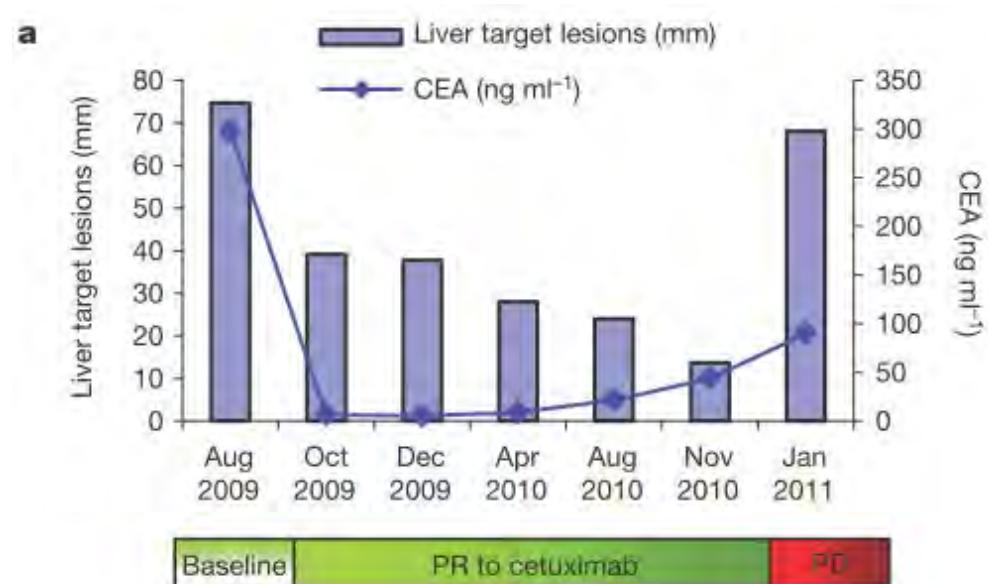


Tumor specific change (e.g. Mutation)

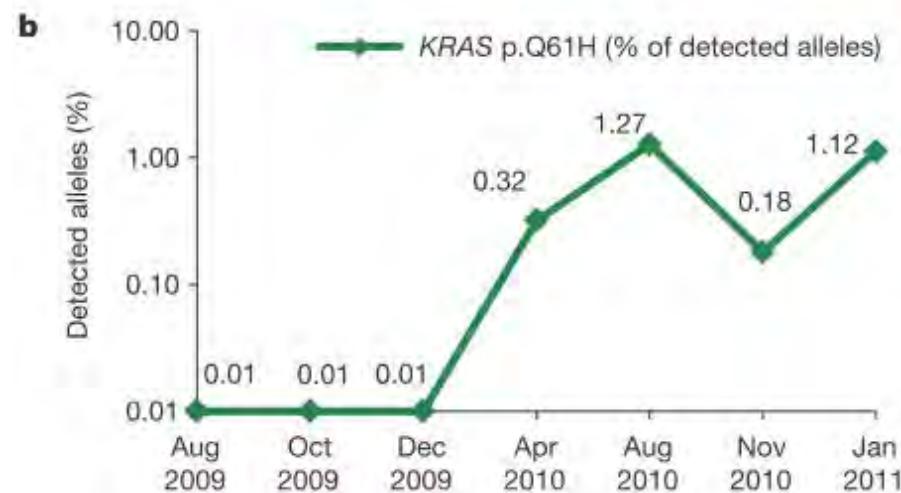


KRAS mut/ampl under pressure

Initial response to cetuximab followed by PD



Quantitative analysis of KRAS(Q61H) mutant DNA in plasma, as assessed by BEAMing



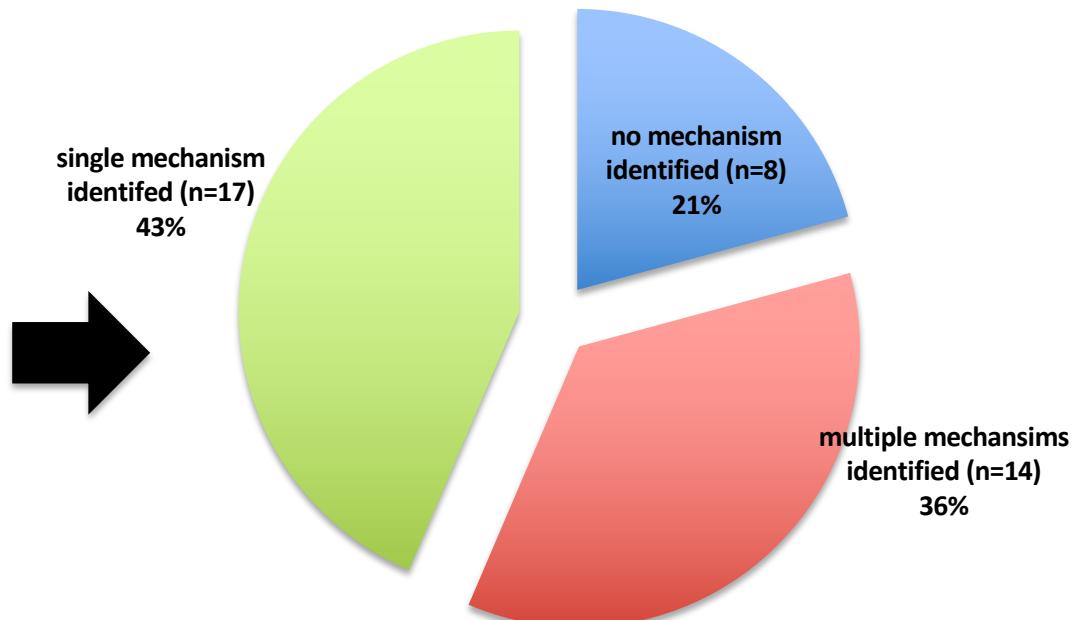
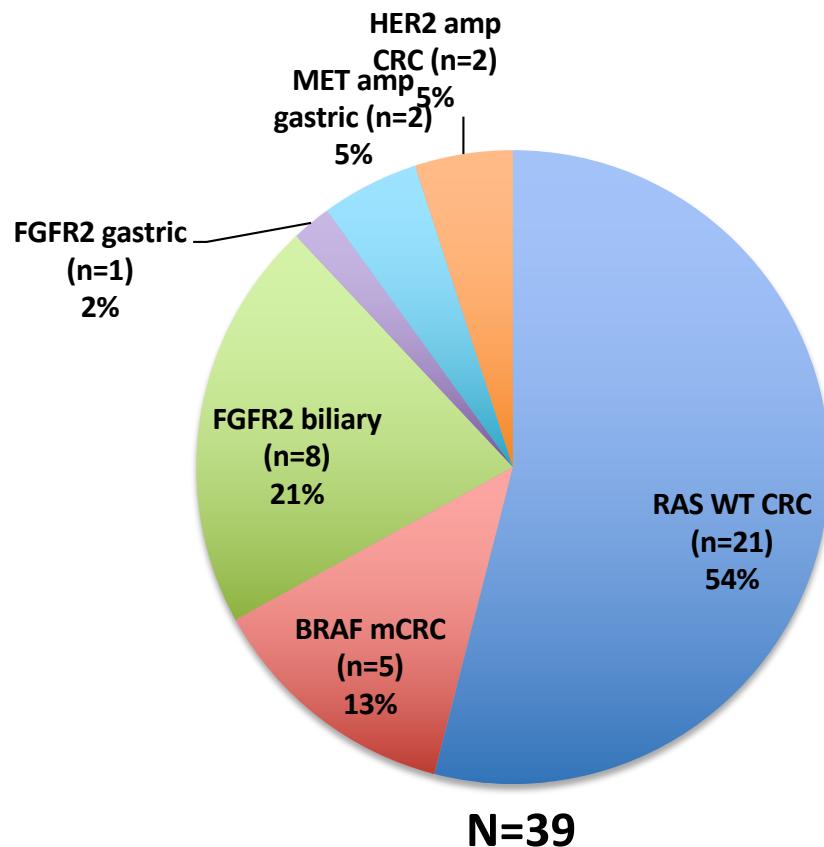
Misale S, et al. Nature 2012
Diaz E, et al. Nature 2012

PRESENTED AT:



Annual '13
Meeting

MGH GI Cancer Center Liquid Biopsy Program



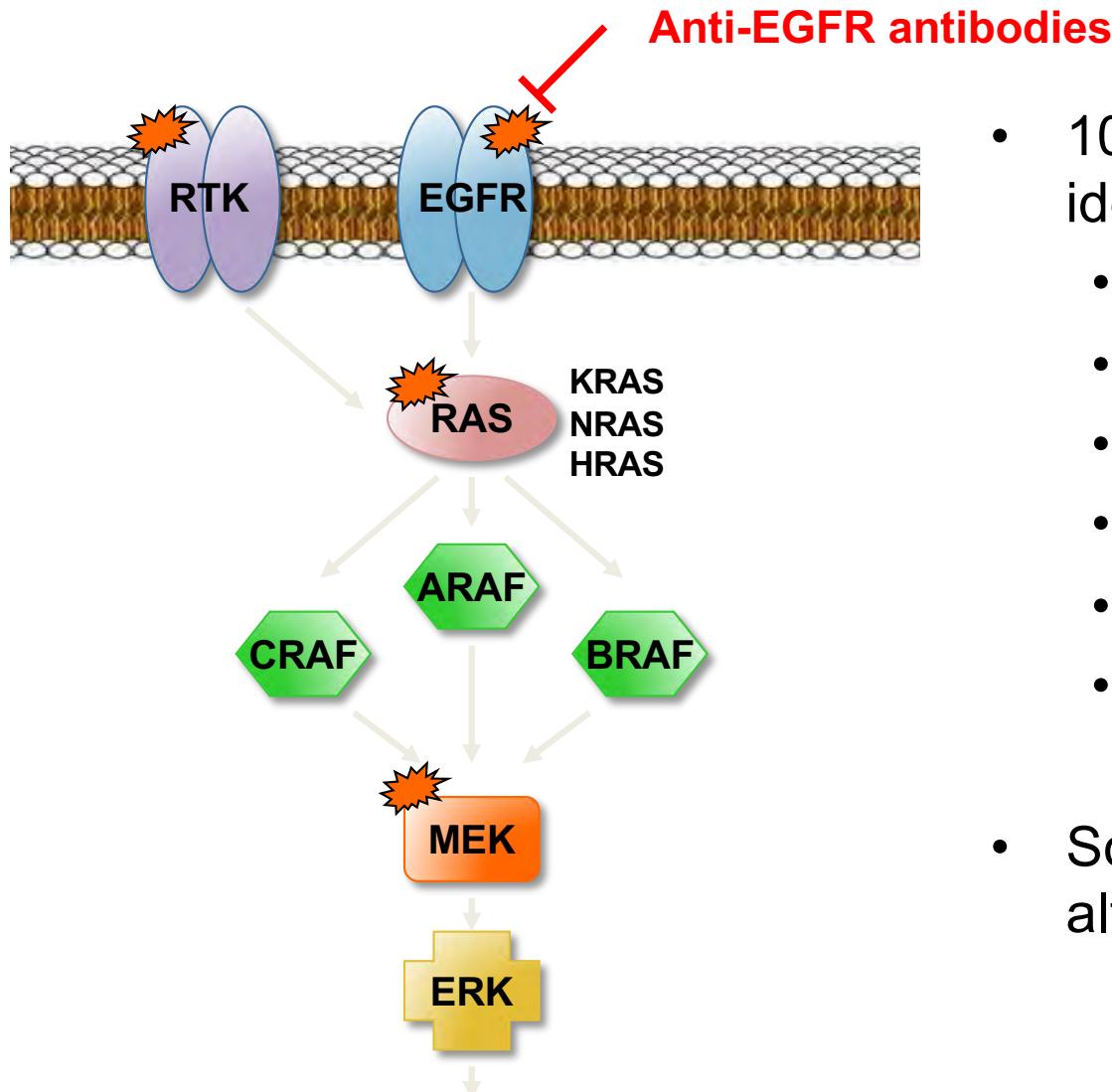
Mechanism of resistance identified in 80%

**36% with multiple resistance mechanisms
(range 2-12; median 3)**

In patients with matched tumor biopsies, ctDNA identified additional resistance mechanisms in 64%

Routine liquid biopsy assessment can effectively identify mechanisms of resistance across different tumor types and treatments

EGFR antibodies in RAS-WT CRC

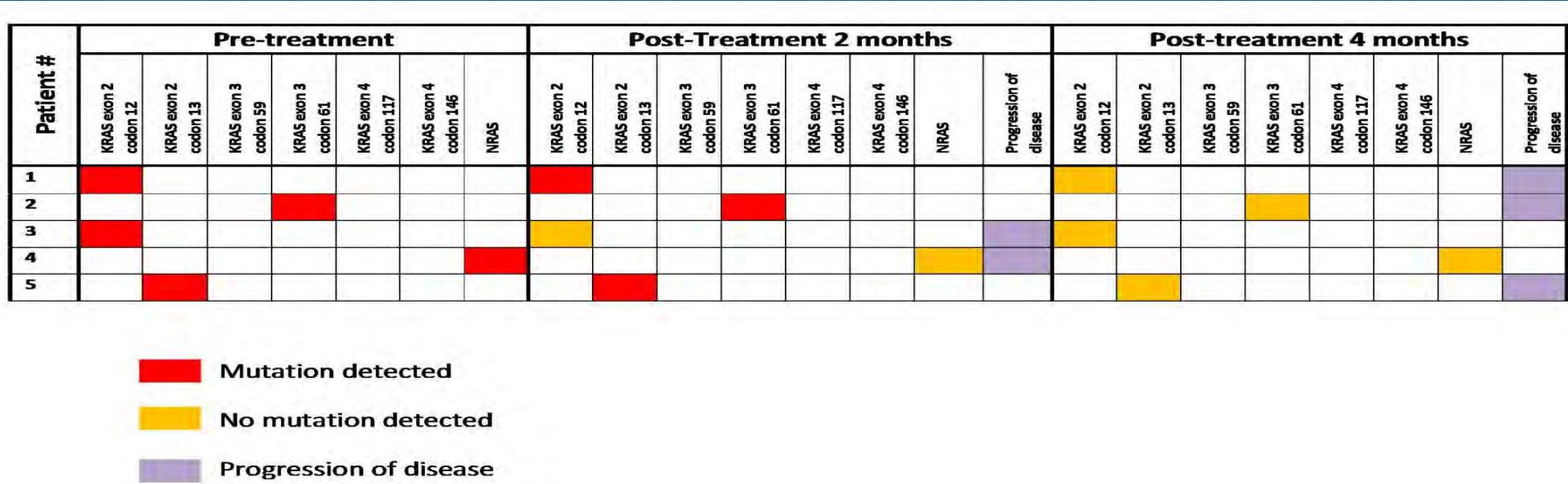


- 10 distinct resistance alterations identified across 21 patients
 - KRAS mutations
 - KRAS amplification
 - EGFR ECD mutations
 - MET amplification
 - ERBB2 amplification
 - Novel MEK1 mutation
- Some patients with 5 or more alterations present in ctDNA

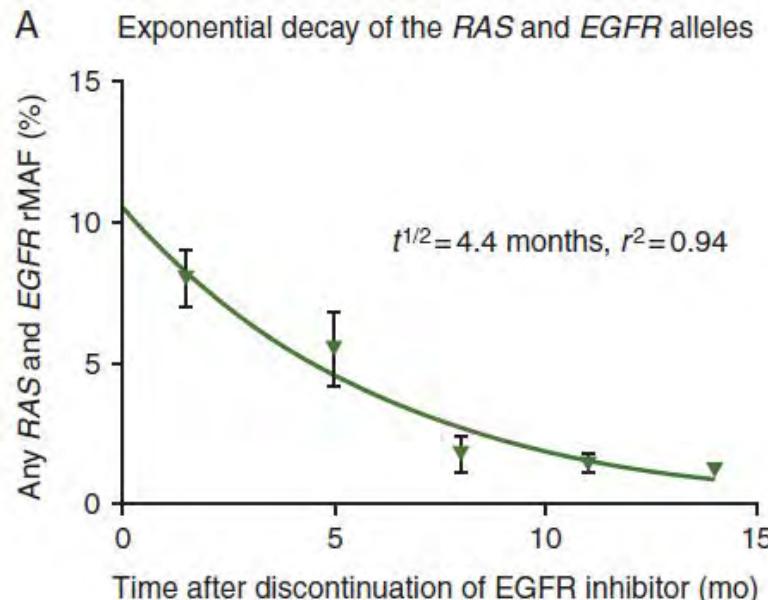
PROLIFERATION AND SURVIVAL

Interesting Findings

1. In a small series of 10 patients who all had mt ras in tissue and liquid biopsy treated with bev based chemotherapy. 5/10 changed to wt Ras under chemotherapy) Gazzaniga et al Annals of Oncology (2017) 28 (suppl_5): v573-v594)
2. Case report in JCO Precision Oncology from same group reported PR in one of this patient treated with cetuximab

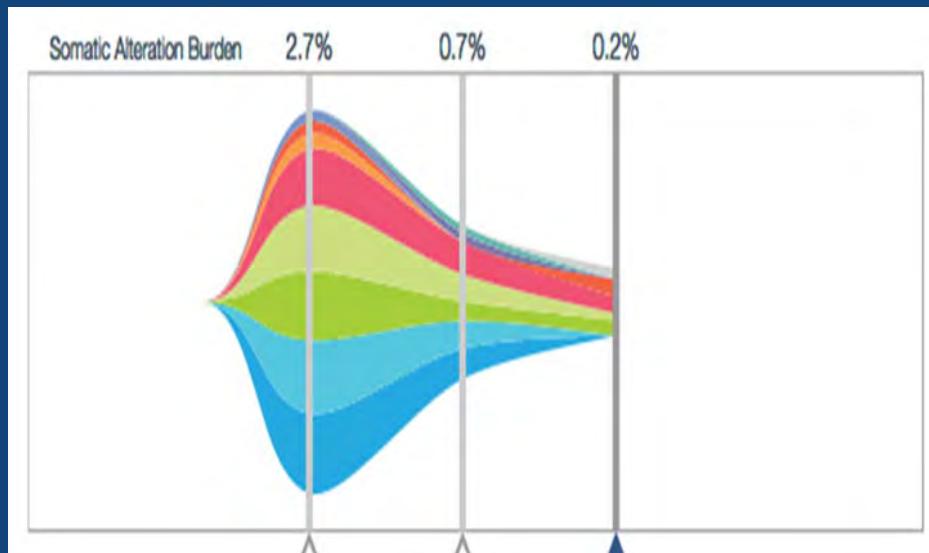


Monitoring of Resistance during anti-EGFR treatment



Parseghian et Ann Oncol. 2019 Feb 1;30(2):243-249.

Example for Monitoring for Response and Resistance Change of ctDNA levels and Loss and Gain of new ctDNA



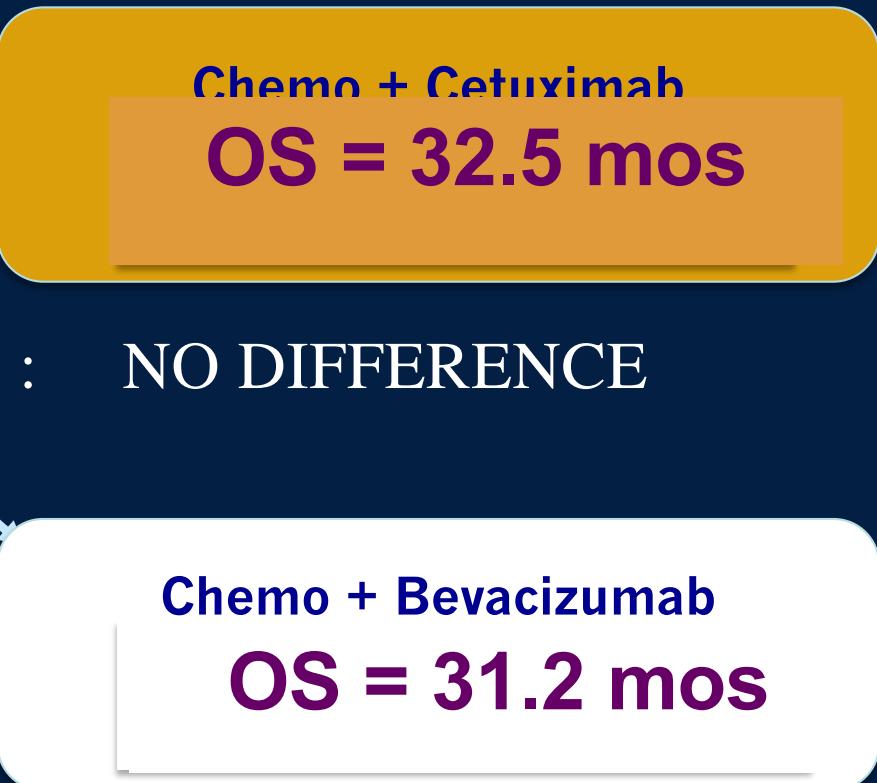
In 84 patients with metastatic CRC receiving serial monitoring, 87% had either gain (61%) or loss (63%) of clones over time

Strickler et al., *J Clin Oncol.* 35, 2017 (suppl 4S; abstract 584). Presented at GI ASCO 2017.

Heinz-Josef Lenz

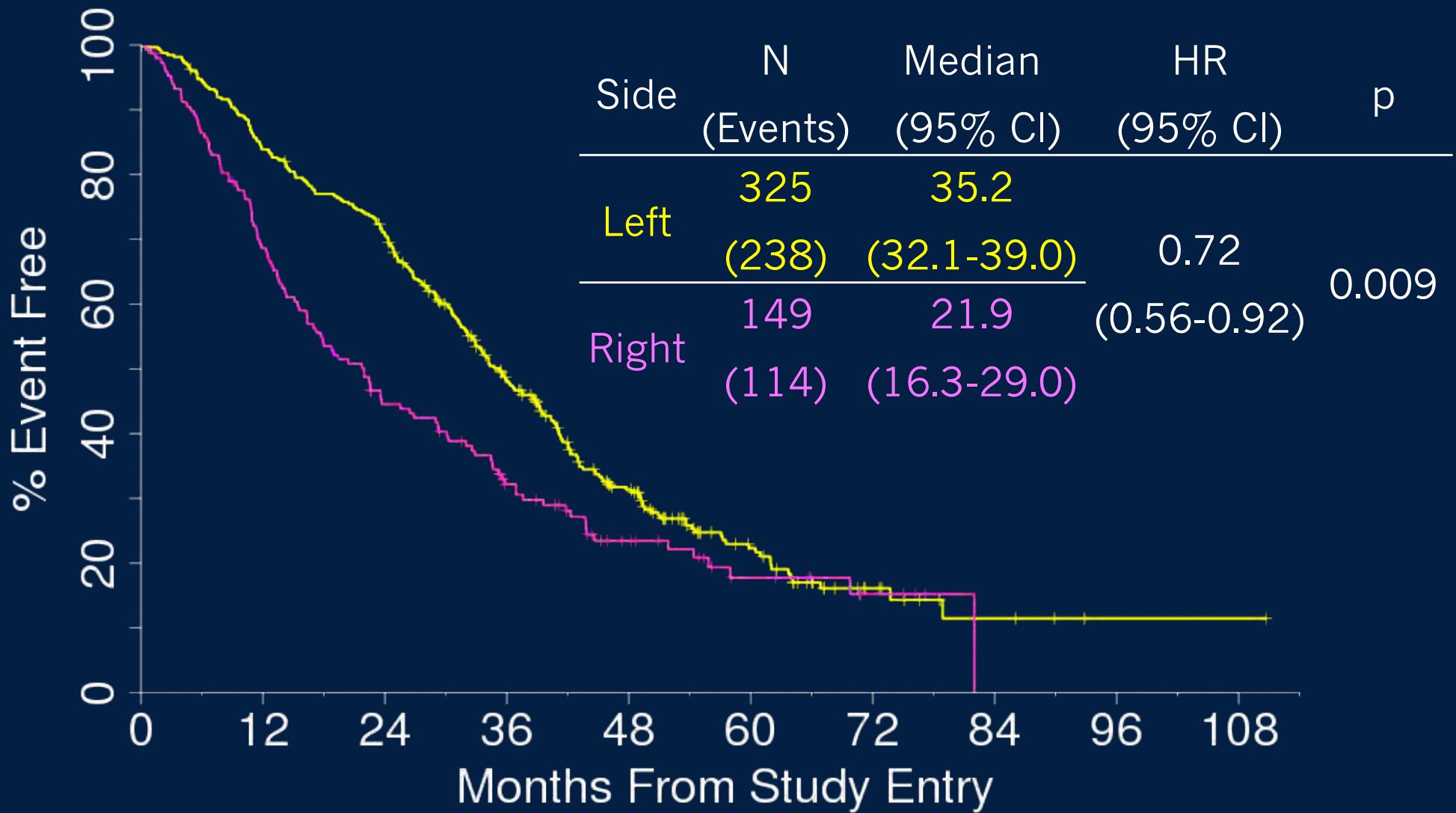
CALGB/SWOG 80405

ESMO, 2016

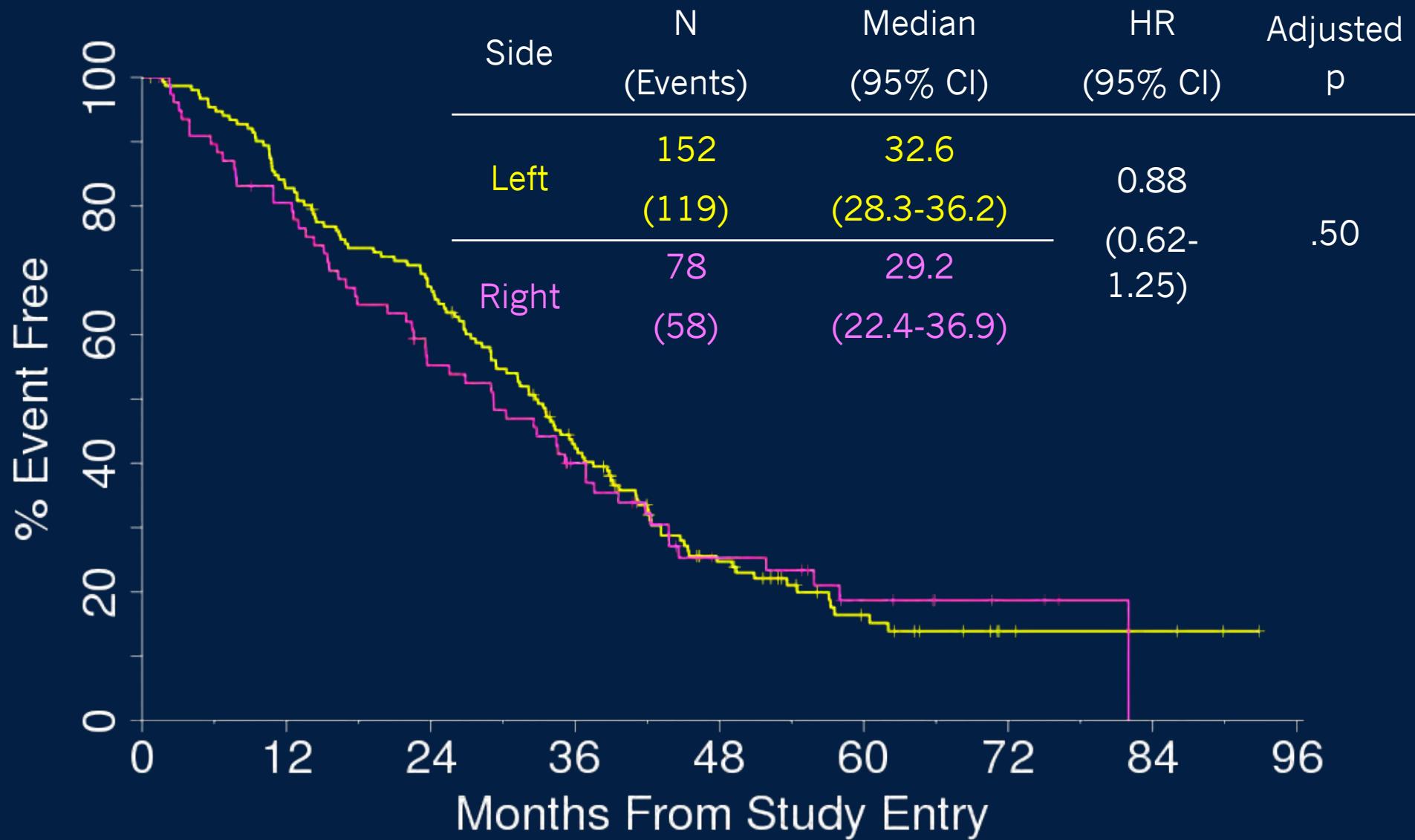


* Right or left-sided primary
Included in sidedness analysis

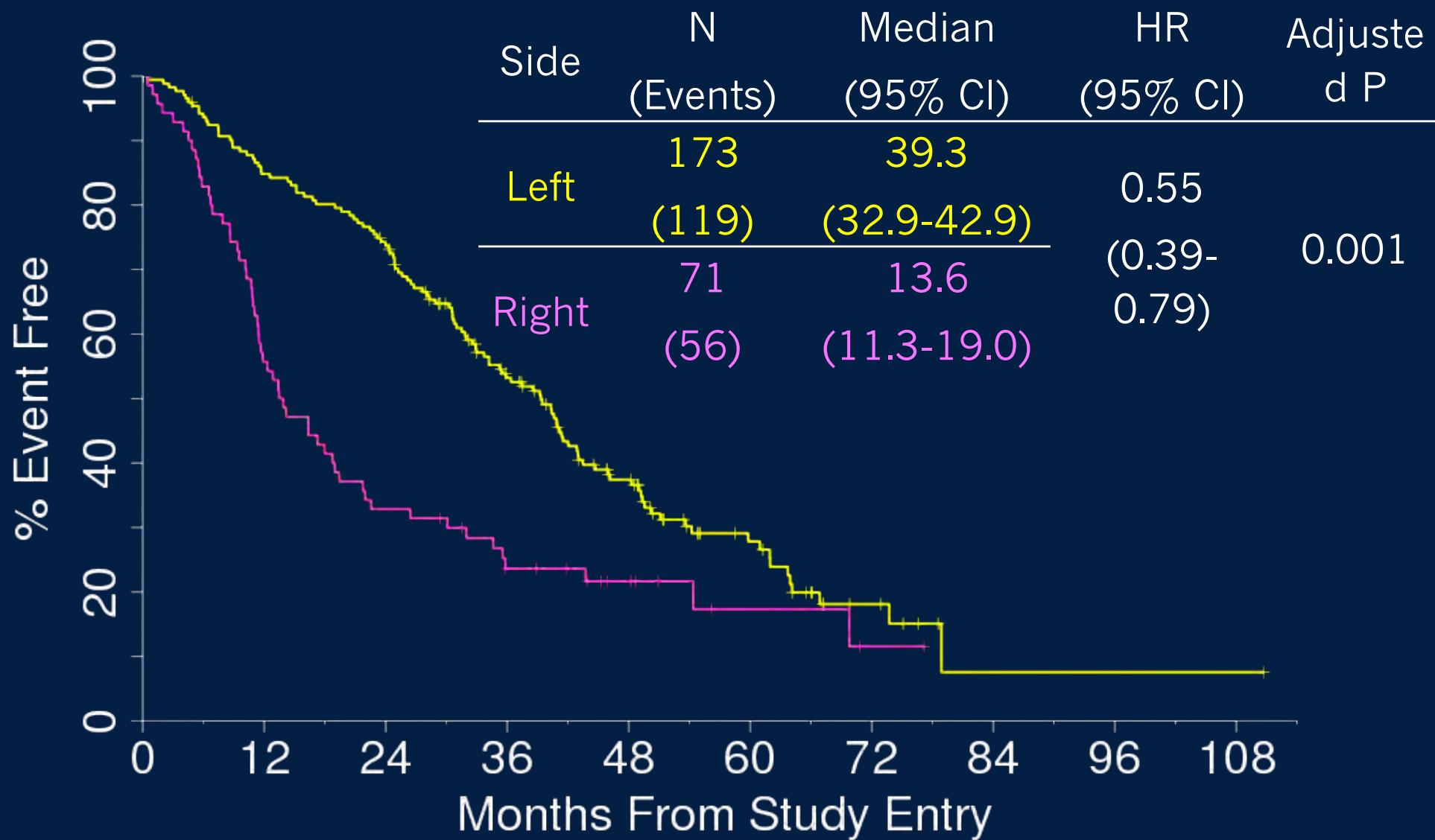
80405: Overall Survival by Sidedness (all RAS wt)



80405: OS by Sidedness (Bevacizumab)



80405: OS by Sidedness (Cetuximab)



80405: Sidedness Predictive for Biologics

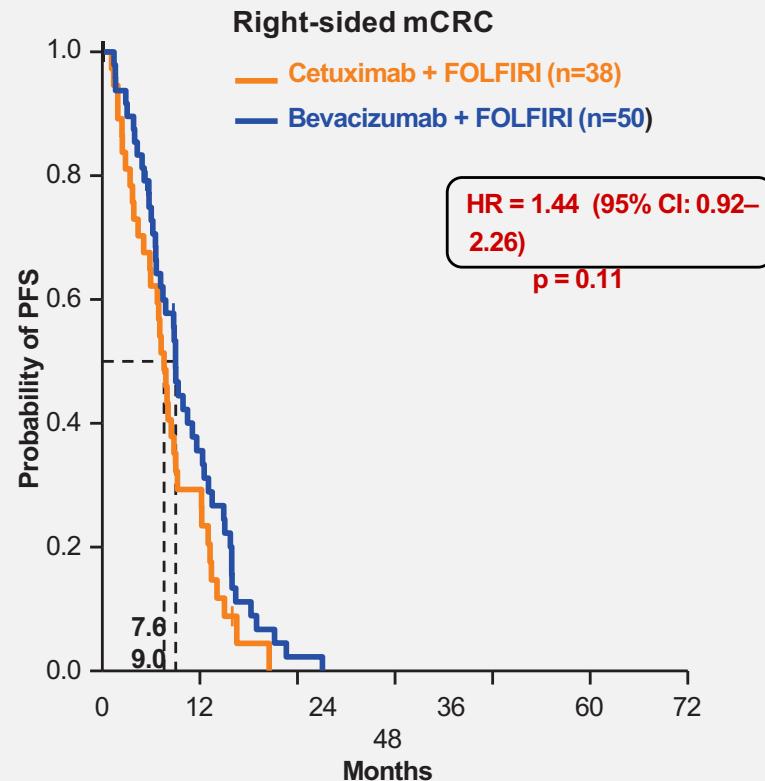
Biologic by 1° Side Interaction

BIOLOGIC	SIDE OF PRIMARY	HAZARD RATIO 95% CI	P (adjusted*)
Any biologic OS	Cetux v Bev; left Cetux v Bev; right	1.81 (1.15, 2.84)	$P_{int} = 0.009$
PFS		1.94 (1.28, 2.95)	$P_{int} = 0.001$
Cetux v Bev OS	Left	0.77 (0.59, 0.99)	0.04
PFS		0.84 (0.66, 1.06)	0.15
Cetux v Bev OS	Right	1.36 (0.93, 1.99)	0.10
PFS		1.64 (1.15, 2.36)	0.006

*Adjusted for biologic, protocol chemotherapy, prior adjuvant therapy, prior RT, age, sex, synchronous disease, in place primary, liver metastases

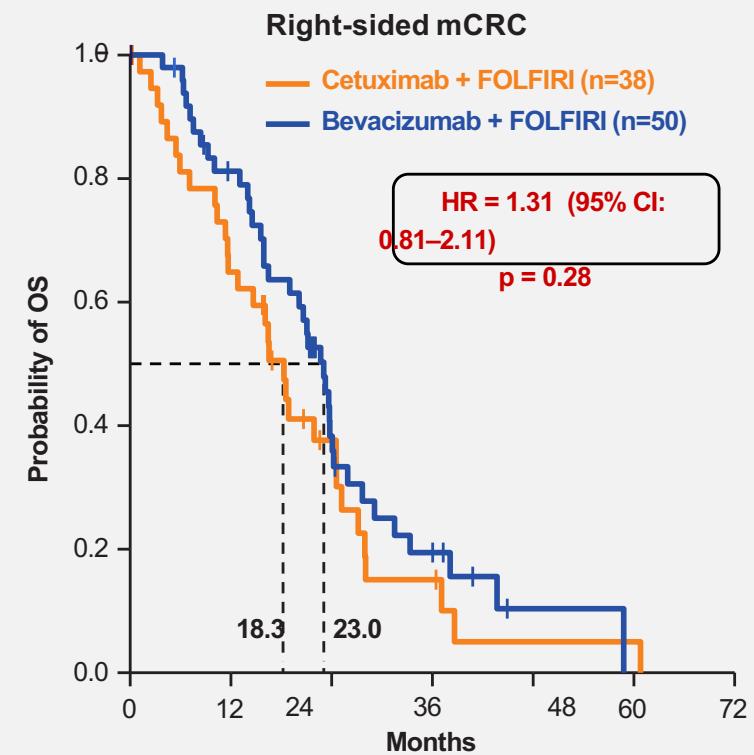
FIRE-3: Right-sided tumors

Progression-free survival



		Numbers at Risk					
Cetuximab + FOLFIRI	38	10	0	0	0	0	0
Bevacizumab + FOLFIRI	50	16	1	0	0	0	0

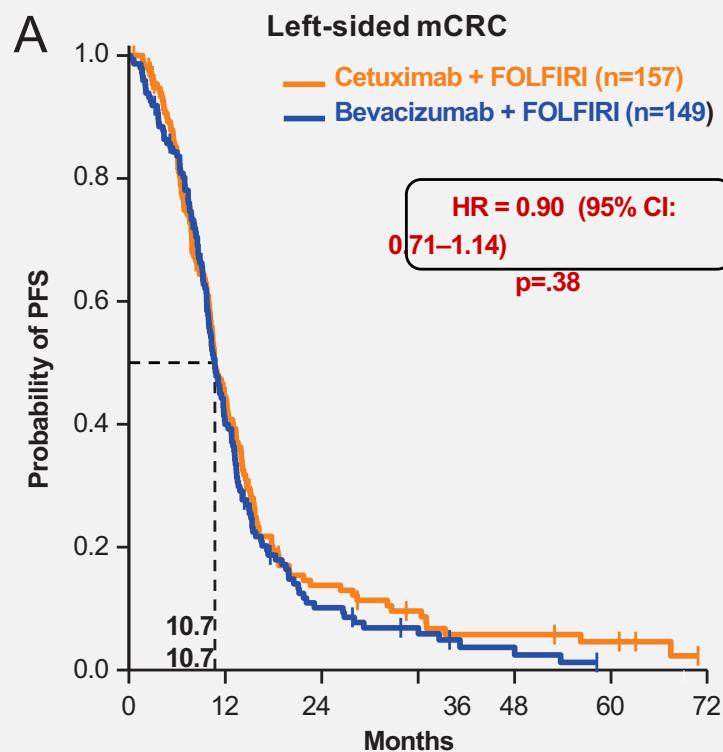
Overall survival



		Numbers at Risk							
Cetuximab + FOLFIRI	38	24	10	4	1	1	0	0	
Bevacizumab + FOLFIRI	50	37	16	7	1	0	0	0	

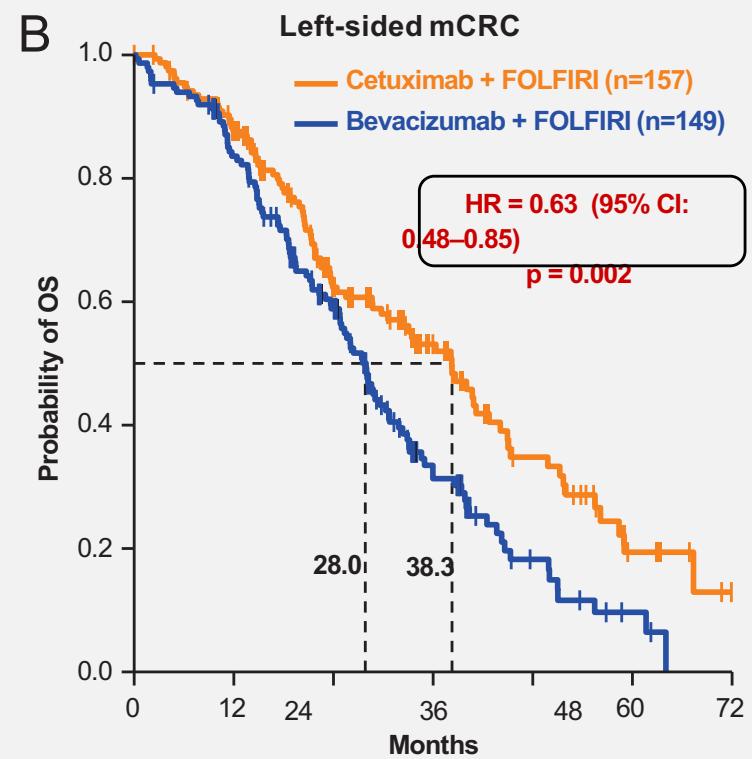
FIRE-3: Left-sided tumors

Progression-free survival



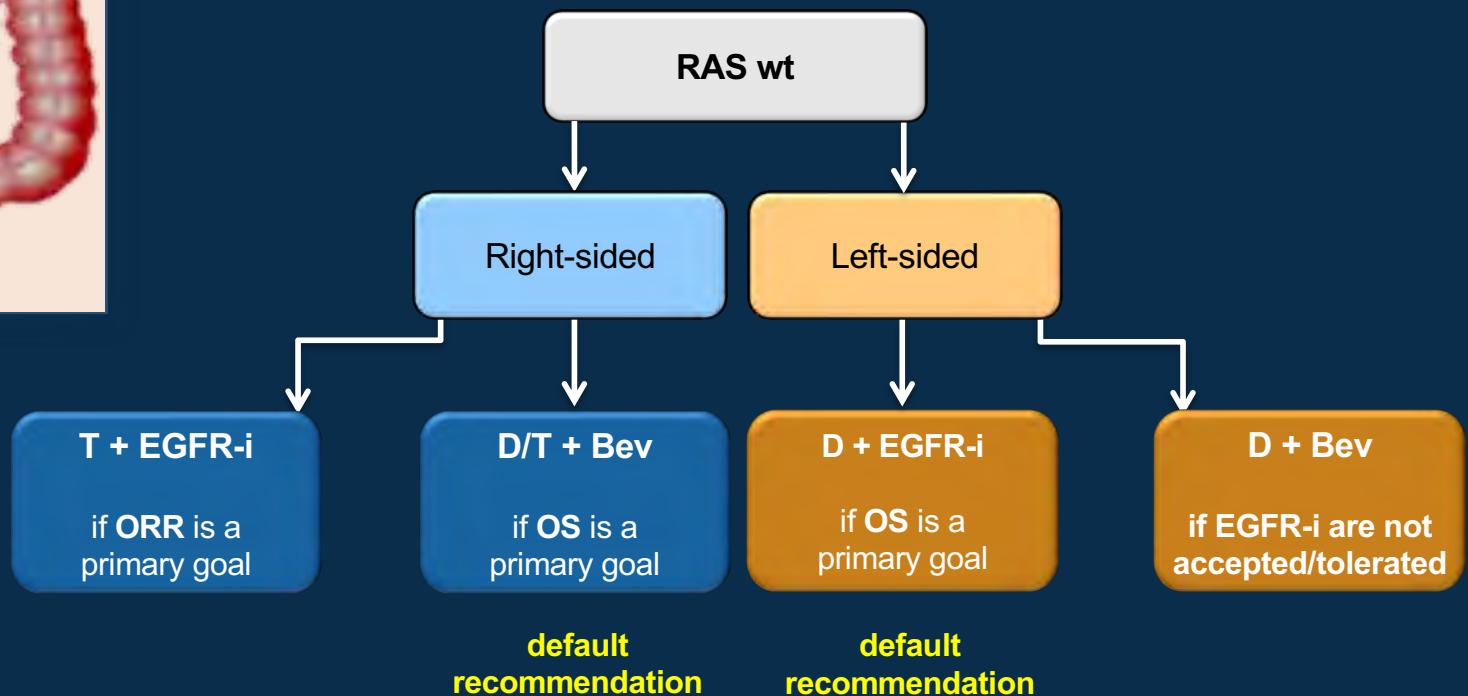
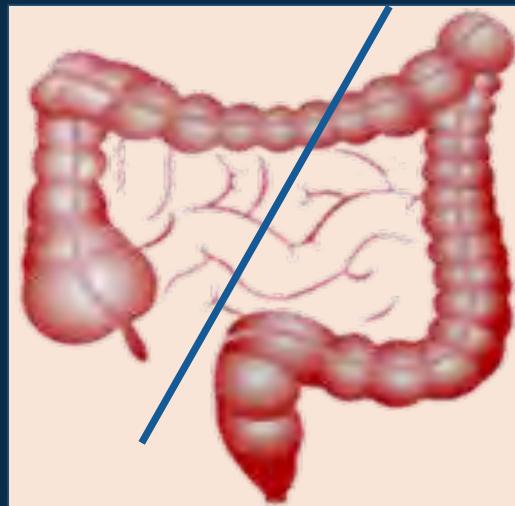
	Numbers at Risk							
Cetuximab + FOLFIRI	157	60	17	10	6	4	0	0
Bevacizumab + FOLFIRI	149	56	13	7	2	0	0	0

Overall survival



	Numbers at Risk							
Cetuximab + FOLFIRI	157	131	77	38	23	6	0	0
Bevacizumab + FOLFIRI	149	120	76	31	11	3	0	0

Left versus right colon cancer story: My Take



D: chemo doublet

T: chemo triplet

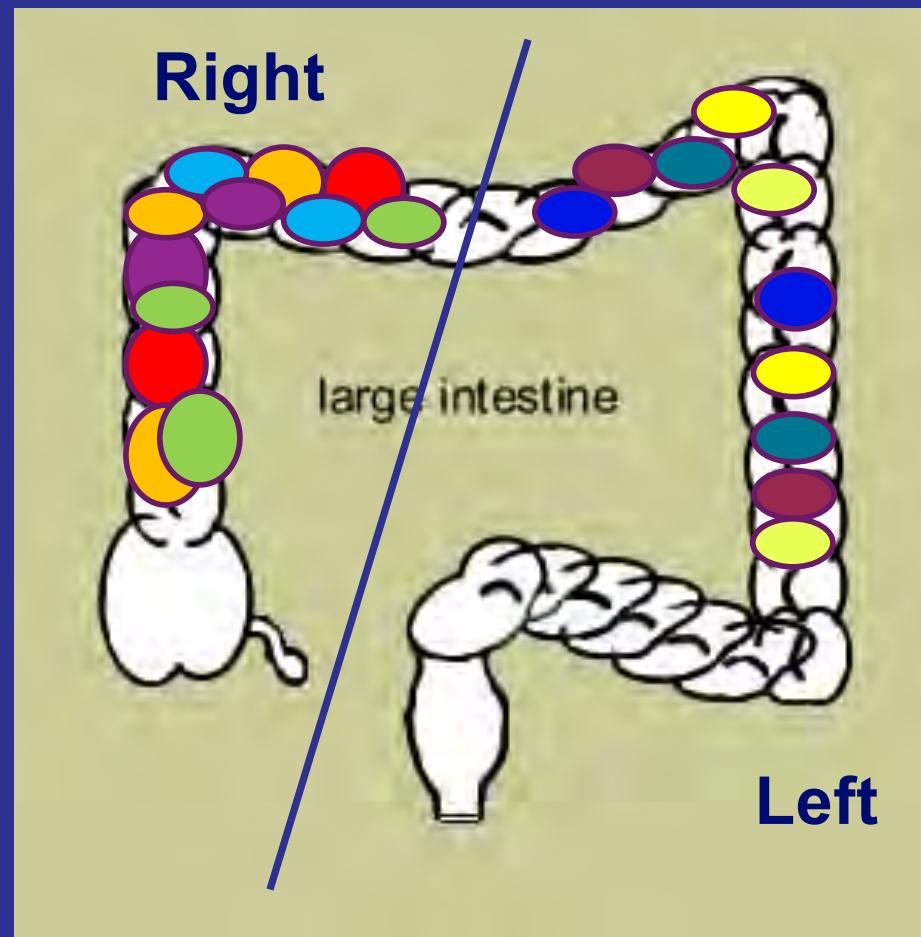
Distinct Biology of R v. L CRC

Analysis of PETACC-3 samples (n=2849)

- BRAF mut
- MSI
- KRAS
- PIK3CA
- Mucinous differentiation

High mutation Frequency

Poor Prognosis



- EREG expression
- 18q loss
- 20q Gain
- EGFR gain
- HER2 gain

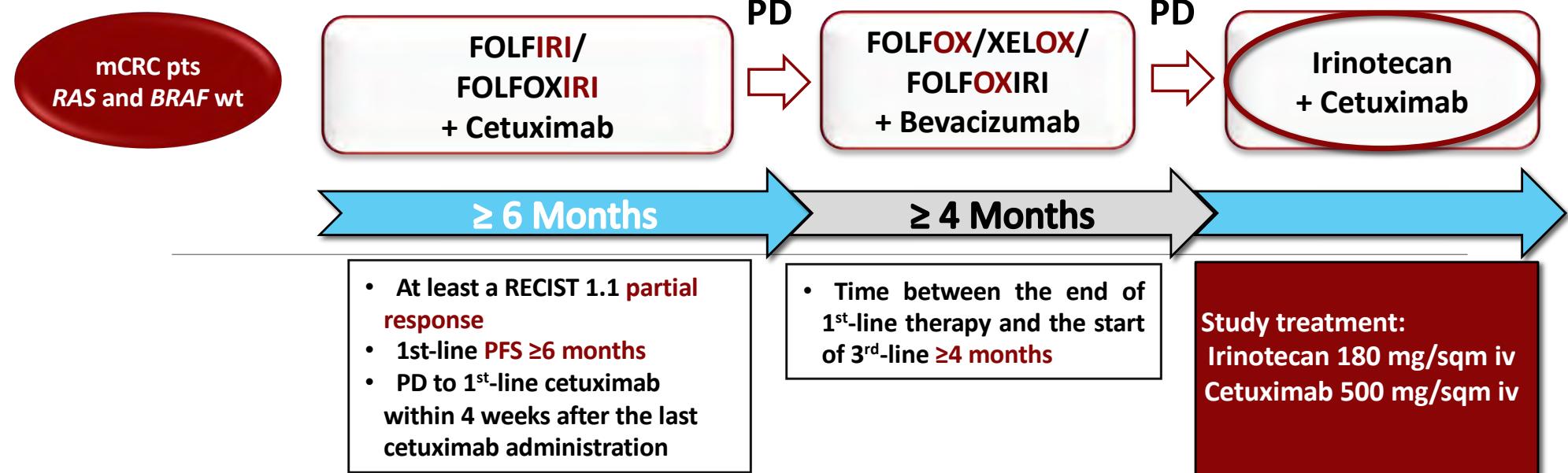
Sensitive to Cetuximab

Good Prognosis

Study Design

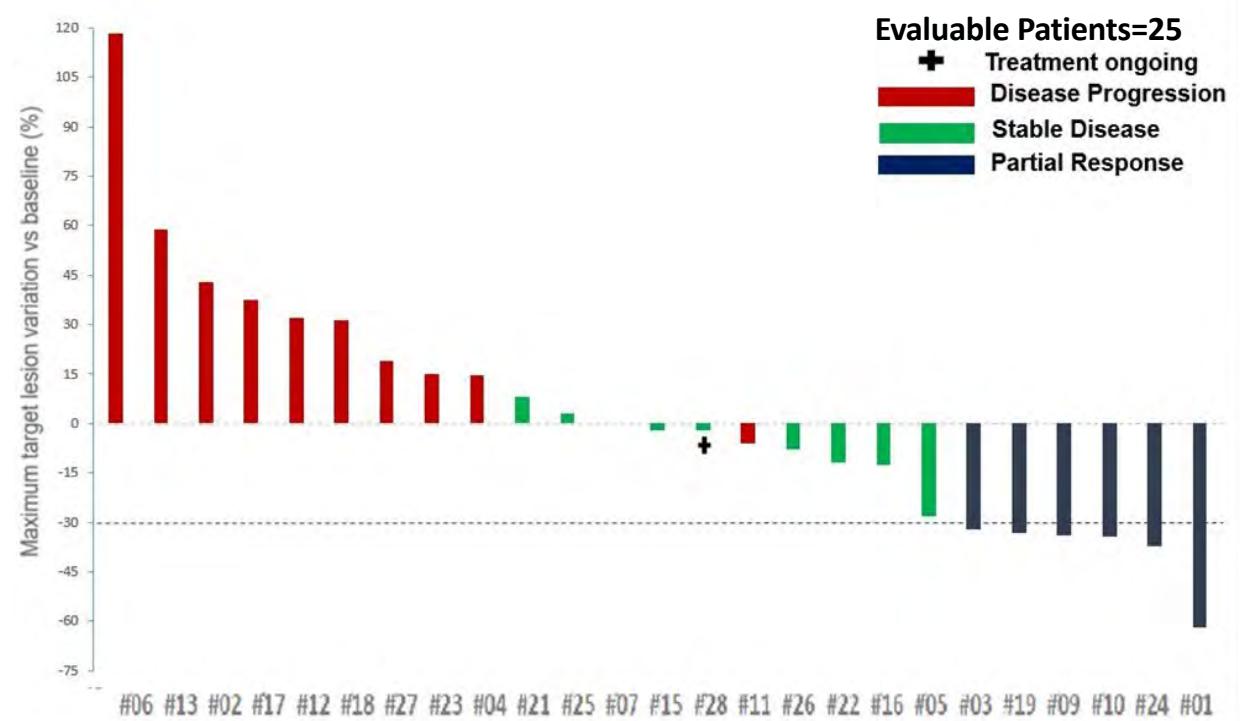
Phase II, non comparative, study

Target accrual: 27 pts

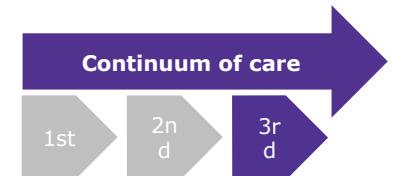


Best Response

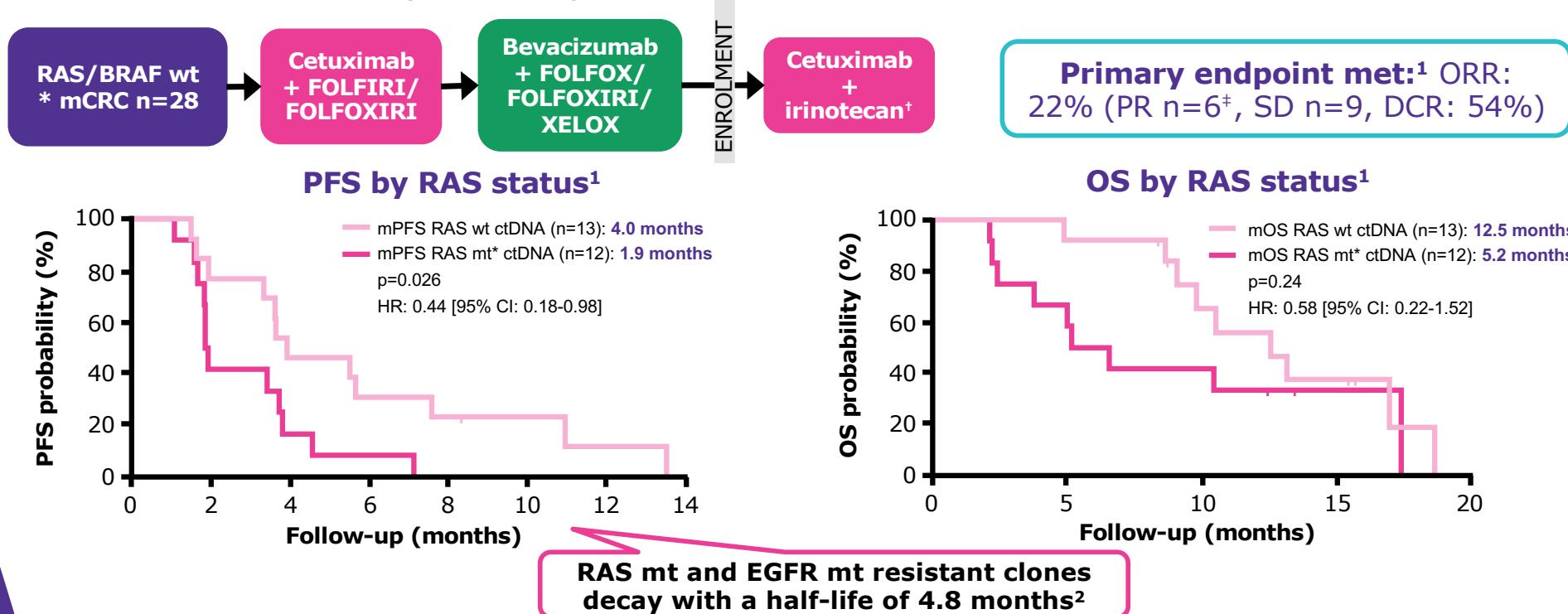
Study population	
N= 28	
No (%) [95% CI]	
Partial response	6 (21.5%)
• Confirmed Partial Response	4 (14.3%)
• Unconfirmed Partial Response	2 (7.1%)
Stable disease	9 (32.1%)
Progressive disease	13 (46.4%)
• Radiological PD	10 (35.7%)
• Clinical PD	3 (10.7%)
Response Rate	6 (21.5%) [10-40%]
Disease Control Rate	15 (53.6%) [36-70%]



The CRICKET trial further demonstrates the potential of cetuximab rechallenge in RAS wt/BRAF wt mCRC^{1*}



Phase II, multicentre, single-arm study¹



*Cetuximab is approved in patients with RAS wt mCRC. Cetuximab is not indicated for the treatment of patients with mCRC whose tumors have RAS mutations or for whom RAS tumor status is unknown³.

[†]Prior 1st line irinotecan-based and cetuximab-containing regimen with at least RECIST partial response lasting at least 6 months, and progression within 4 weeks after the last administration of cetuximab, prior 2nd line oxaliplatin-based and bevacizumab-containing treatment; [‡]2 patients had unconfirmed partial response.

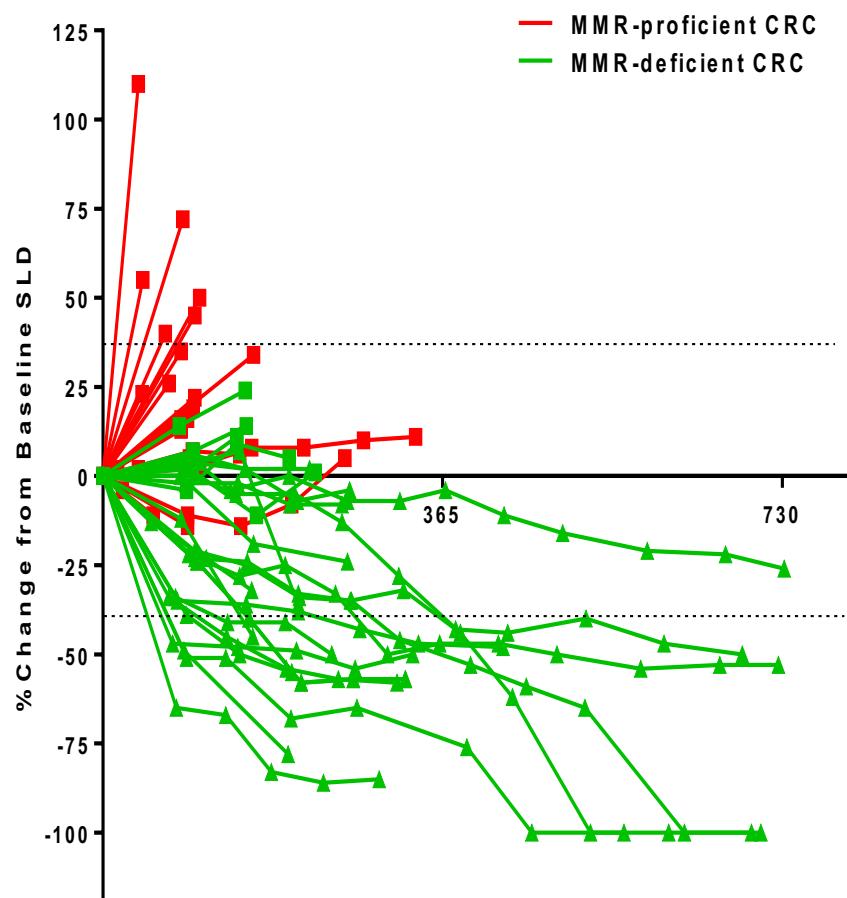
1. Rossini D, et al. ASCO 2018 Abstract 12007;
2. Parseghian C, et al. ASCO 2018 (Abstract No. 3511);
3. Erbitux SmPC Dec 2016.



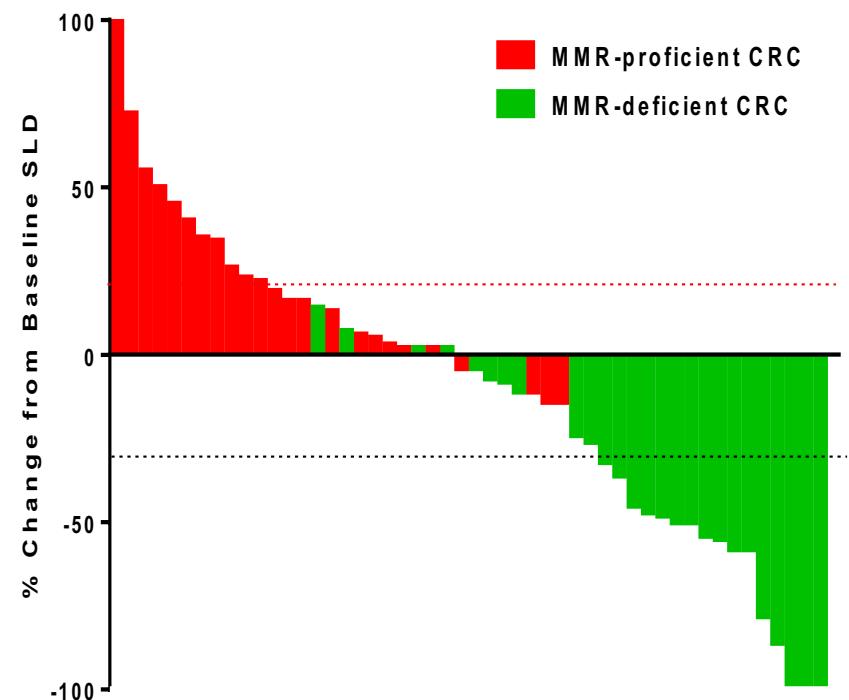
Microsatellite Instability

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

The NEW ENGLAND JOURNAL of MEDICINE



Pembrolizumab



	MMR-deficient CRC, N=28	MMR-proficient CRC, N=25
Response Rate	57%	0%
Disease Control Rate	89%	16%

Le DT, et al.
NEJM 2015
and ASCO
2016

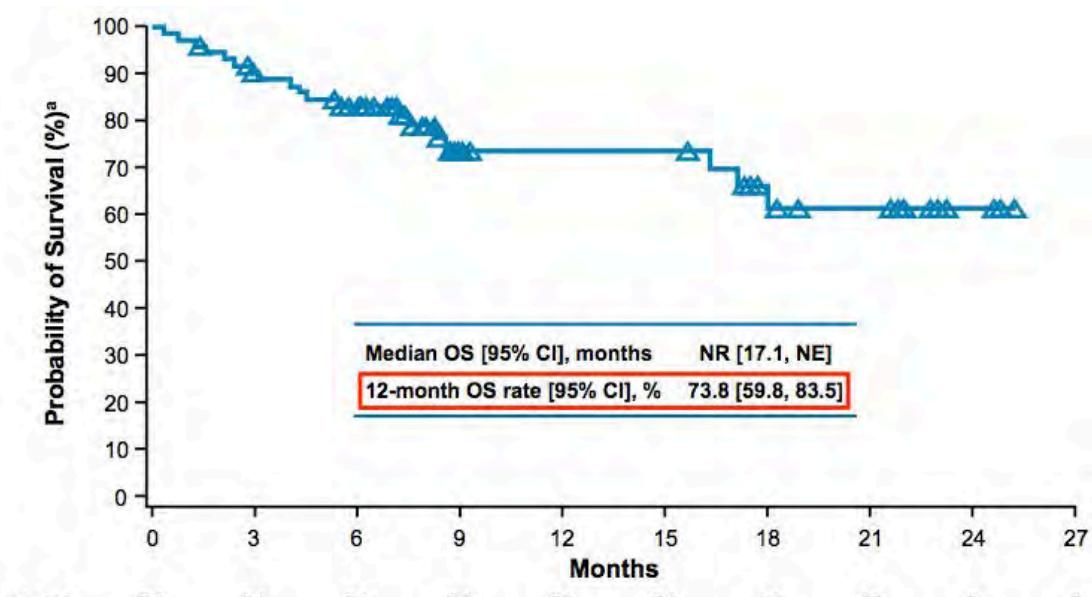
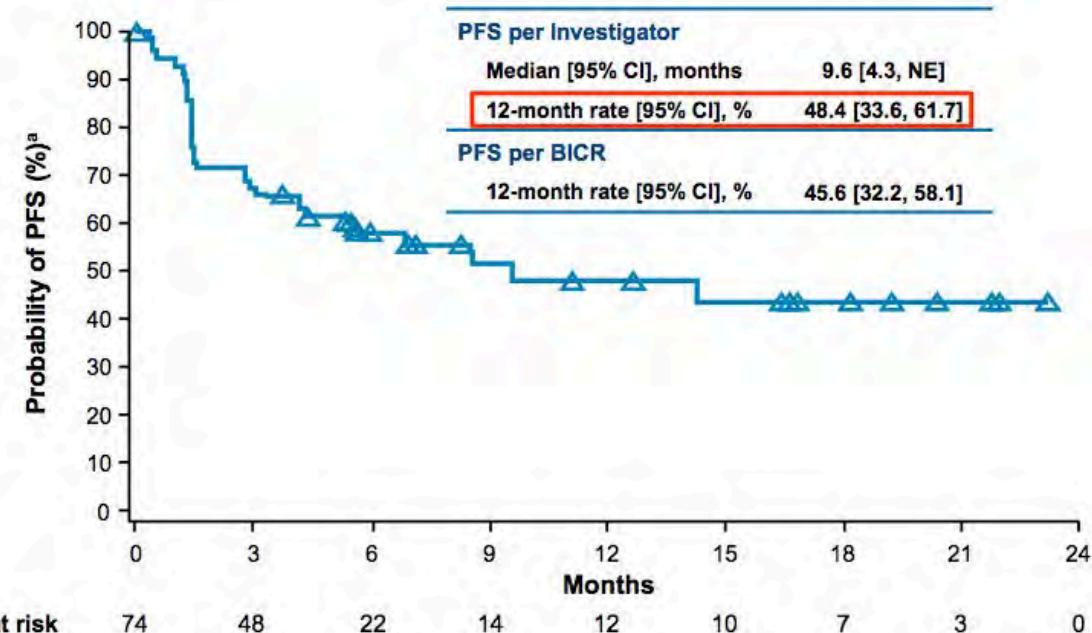
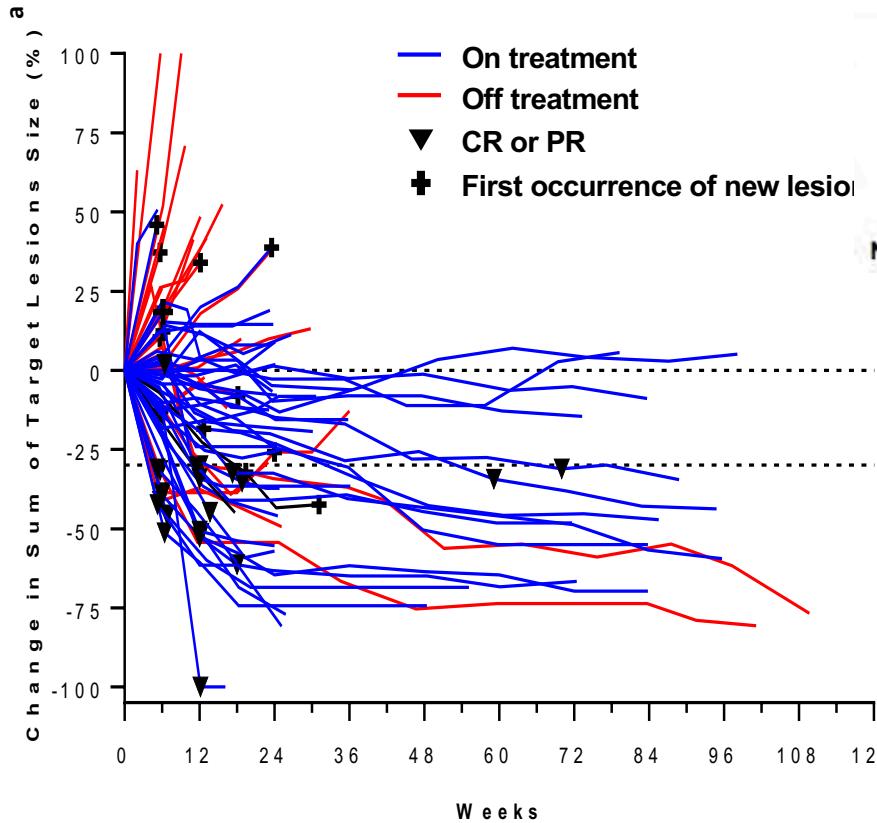
MSI-high CRC: Nivolumab Monotherapy

RR 31%

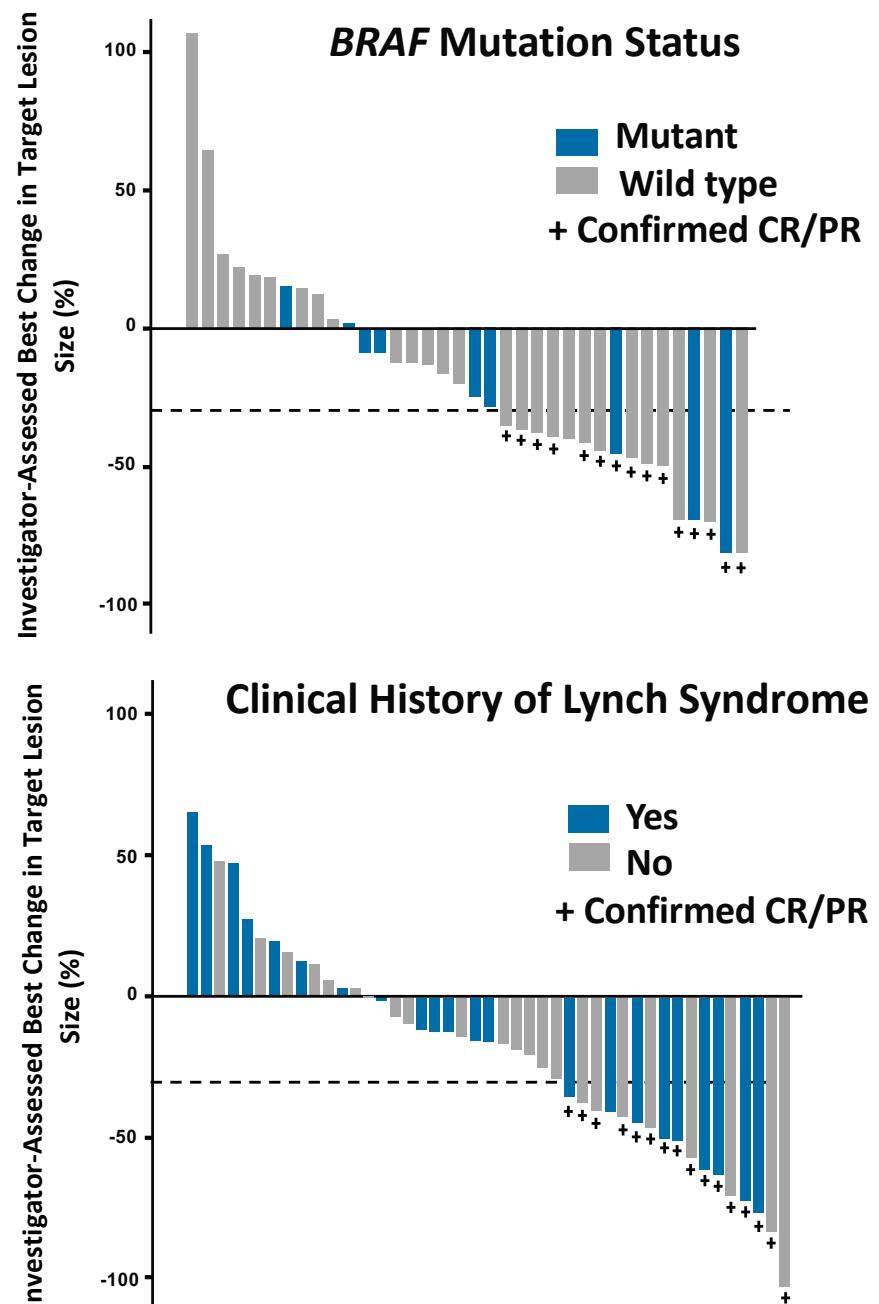
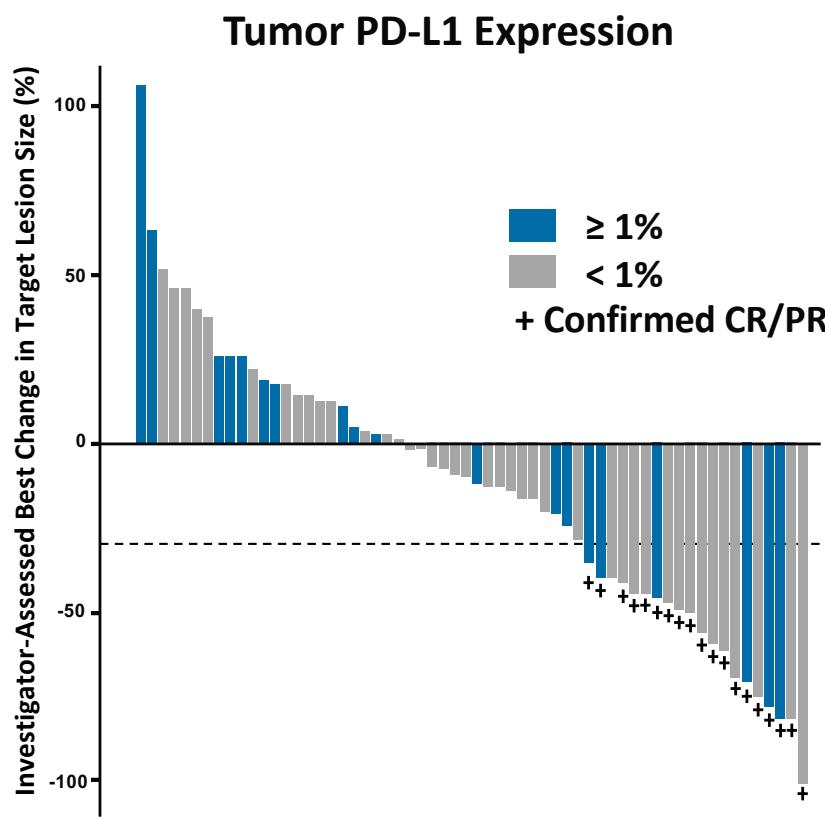
SD 39%

PD 24%

Disease Control ≥ 12 weeks in 69%



Reduction in Target Lesions Regardless of PD-L1 Expression, BRAF or Lynch History



Durable Clinical Benefit With Nivolumab Plus Low-Dose Ipilimumab as First-Line Therapy in Microsatellite Instability-High/Mismatch Repair Deficient Metastatic Colorectal Cancer

Heinz-Josef Lenz,¹ Eric Van Cutsem,² Maria Luisa Limon,³ Ka Yeung Mark Wong,⁴ Alain Hendlisz,⁵ Massimo Aglietta,⁶ Pilar García-Alfonso,⁷ Bart Neyns,⁸ Gabriele Luppi,⁹ Dana B. Cardin,¹⁰ Tomislav Dragovich,¹¹ Usman Shah,¹² Ajlan Atasoy,¹³ Roelien Postema,¹³ Zachary Boyd,¹³ Jean-Marie Ledeine,¹³ Michael James Overman,¹⁴ Sara Lonardi¹⁵

¹USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA; ²University Hospitals Gasthuisberg/Leuven and KU Leuven, Leuven, Belgium;

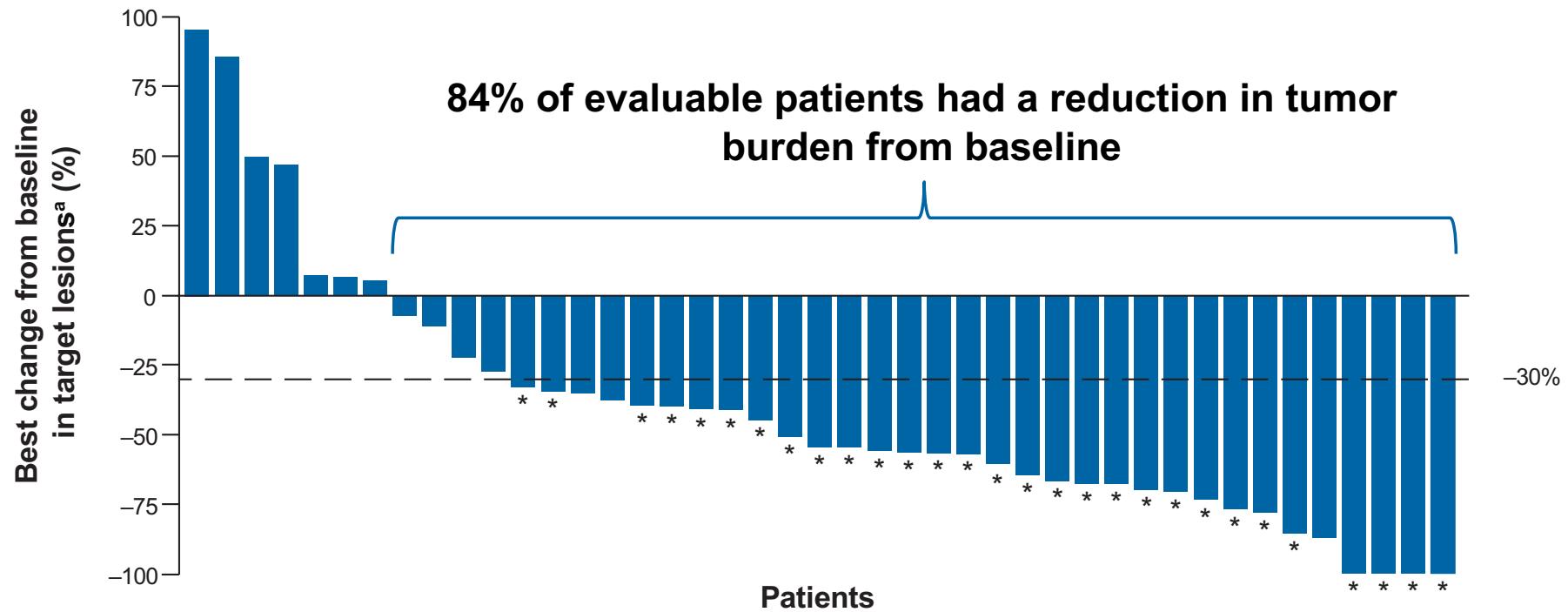
³Hospital Universitario Virgen del Rocio, Sevilla, Spain; ⁴Westmead Hospital, Sydney, Australia; ⁵Institut Jules Bordet, Brussels, Belgium; ⁶Candiolo Cancer Institute and University of Torino Medical School, Candiolo, Italy; ⁷Hospital Gral Universitario Gregorio Marañón, Madrid, Spain; ⁸University Hospital Brussels, Brussels, Belgium; ⁹University Hospital of Modena, Modena, Italy; ¹⁰Vanderbilt – Ingram Cancer Center, Nashville, TN, USA;

¹¹Banner MD Anderson Cancer Center, Gilbert, AZ, USA; ¹²Lehigh Valley Hospital, Allentown, PA, USA; ¹³Bristol-Myers Squibb, Princeton, NJ, USA;

¹⁴The University of Texas MD Anderson Cancer Center, Houston, TX, USA; ¹⁵Istituto Oncologico Vento IOV-IRCSS, Padova, Italy



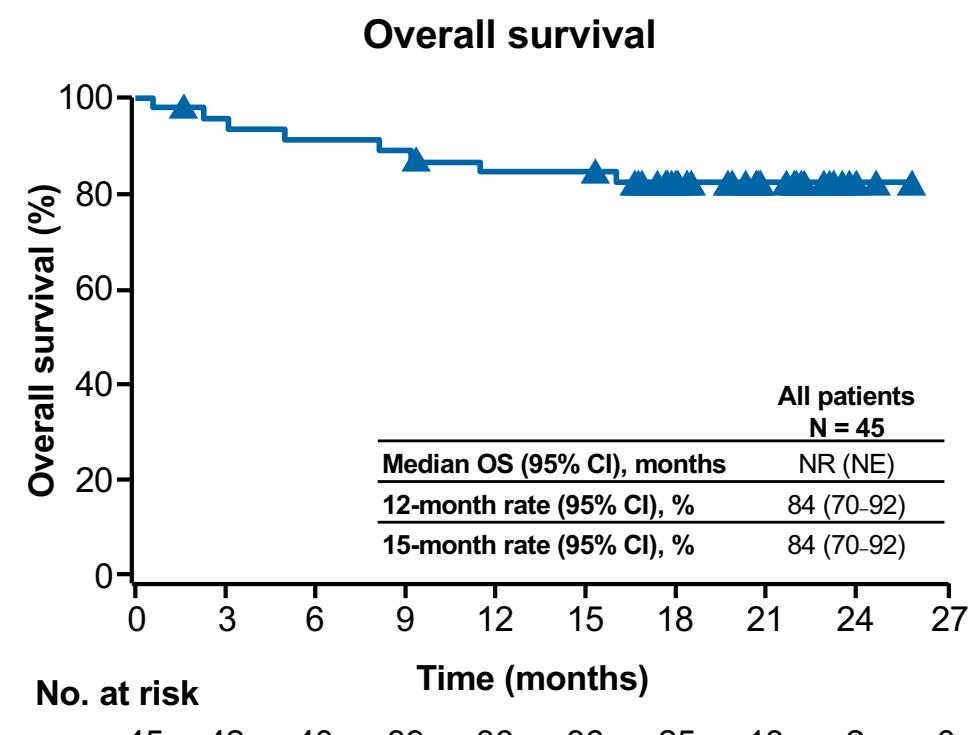
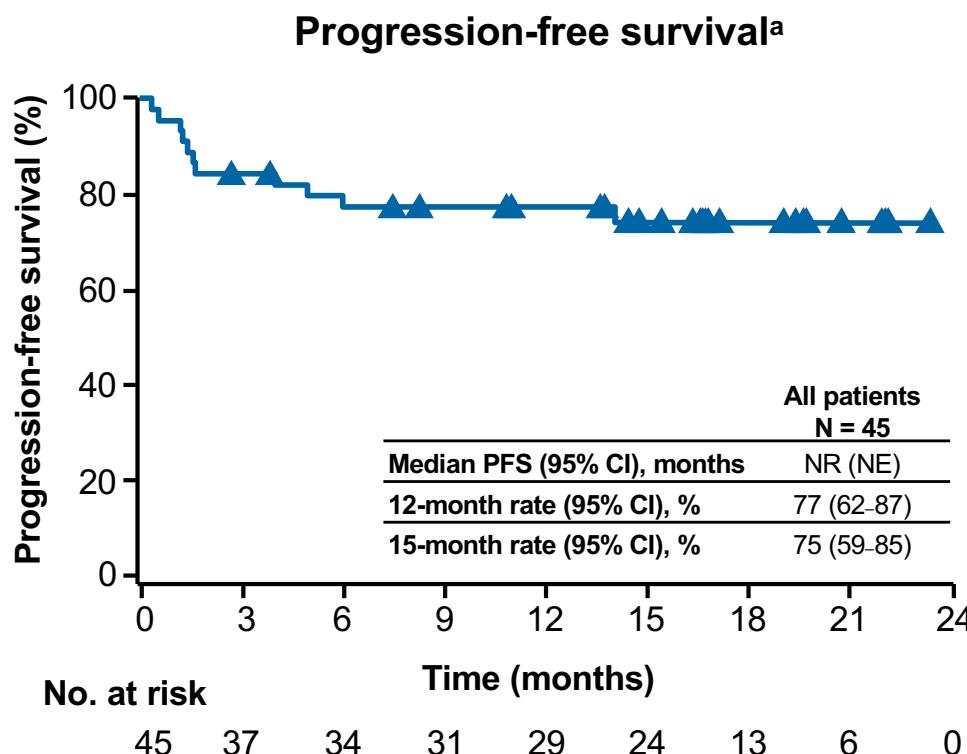
Best Change From Baseline in Target Lesions



*Confirmed response per investigator assessment.

^aEvaluable patients per investigator assessment.

Progression-Free and Overall Survival



^aPer investigator assessment.
NE, not estimable.

HER2 Overexpression

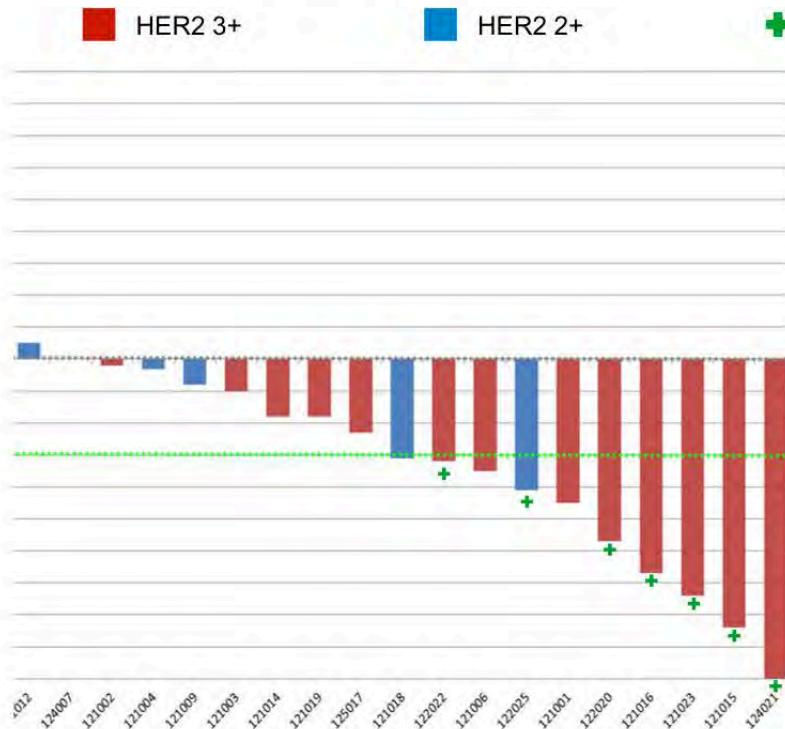
HER2/neu 3+ (2+)

HERACLES Trial

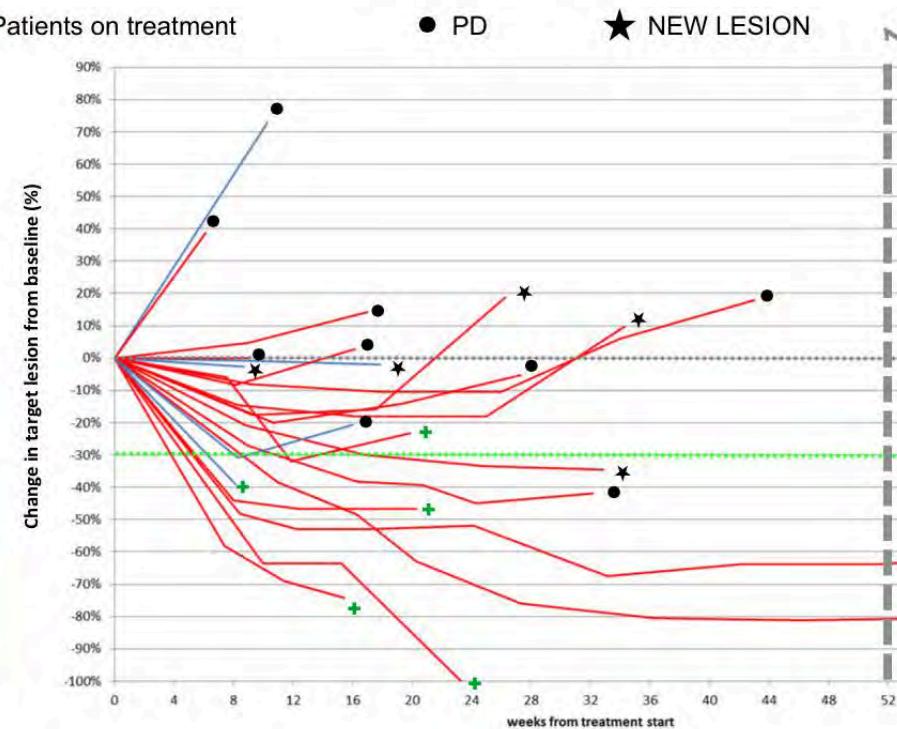
Trastuzumab + Lapatinib in HER2+ / KRAS-wt pts refractory to anti-EGFR AK

Responses by HER2 IHC Score

Waterfall plot



Spaghetti plot



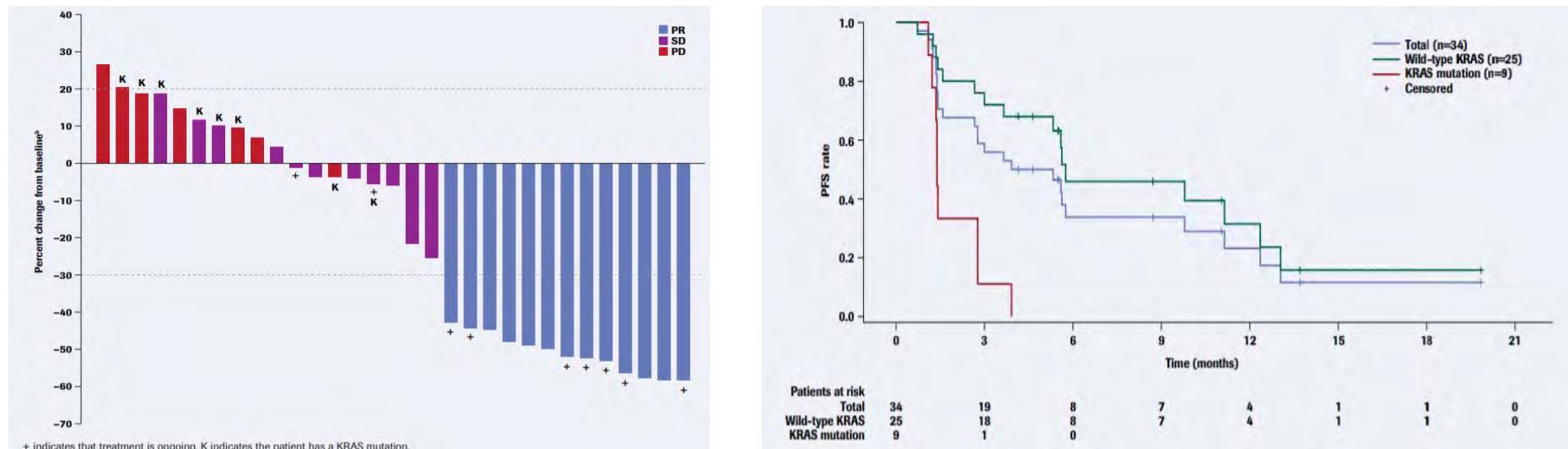
*3 patients are not shown: 122026 (IHC 2+), not assessed yet; 121011 (IHC 3+) and 121013 (IHC 3+) early clinical PD.

849 patients screened, 46 patients (5.4%) HER2+ (2+/3+); 23 patients evaluable for response
ORR 35%, DCR 78%

Siena, et al. ASCO 2015

My Pathway: Trastuzumab + Pertuzumab in HER-2 Amplified CRC

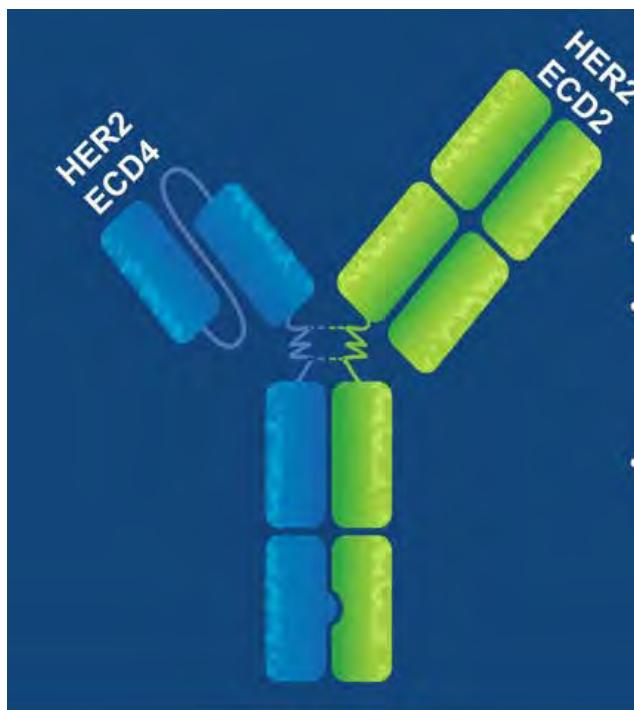
N = 34 patients



^a indicates that treatment is ongoing. K indicates the patient has a KRAS mutation.

Clinical characteristic	ORR (n=34) n (% [95% CI])	CBR (n=34) n (% [95% CI])	Median duration of clinical benefit (n=17) Months (95% CI)	Median PFS (n=34) Months (95% CI)	Median OS (n=34) Months (95% CI)
All patients (n=34)	13 (38.2 [22.2-56.4])	17 (50.0 [32.4-67.6])	10.3 (4.3-NE)	4.6 (1.6-9.8)	10.3 (7.2-22.1)
KRAS status					
Wild-type (n=25)	13 (52.0 [31.3-72.2])	17 (68.0 [46.5-85.1])	10.3 (4.3-NE)	5.7 (3.6-12.4)	14.0 (8.0-22.1)
Mutated (n=9)	0 (0 [NE-NE])	0 (0 [NE-NE])	NA	1.4 (1.1-2.8)	5.0 (1.2-10.3)
Number of prior regimens					
<4 (n=12)	4 (33.3 [9.9-65.1])	4 (33.3 [9.9-65.1])	2.8 (2.8-NE)	2.2 (1.3-5.6)	8.0 (1.8-NE)
≥4 (n=22)	9 (40.9 [20.7-63.6])	13 (59.1 [36.4-79.3])	10.3 (4.3-NE)	5.6 (2.7-12.4)	10.3 (7.2-22.1)
Tumor site ^b					
Colon, left side (n=14) ^c	6 (42.9 [17.7-71.1])	9 (64.3 [35.1-87.2])	10.4 (9.8-11.1)	9.8 (1.4-12.4)	11.5 (8.5-22.1)
Colon, right side (n=8) ^d	1 (12.5 [0.3-52.7])	1 (12.5 [0.3-52.7])	10.3 (NE-NE)	1.4 (1.1-3.9)	4.5 (1.2-14.0)
Rectum (n=11) ^e	5 (45.5 [16.7-76.6])	6 (54.5 [23.4-83.3])	5.0 (2.8-NE)	5.6 (1.3-11.1)	10.3 (1.8-NE)

ZW25: Azymetric™ Bispecific HER2-Targeted Antibody



- Designed using the Azymetric bispecific platform
- Biparatopic - simultaneously binds two HER2 epitopes
 - ECD4 (trastuzumab binding domain)
 - ECD2 (pertuzumab binding domain)
- Unique binding results in novel mechanisms of action

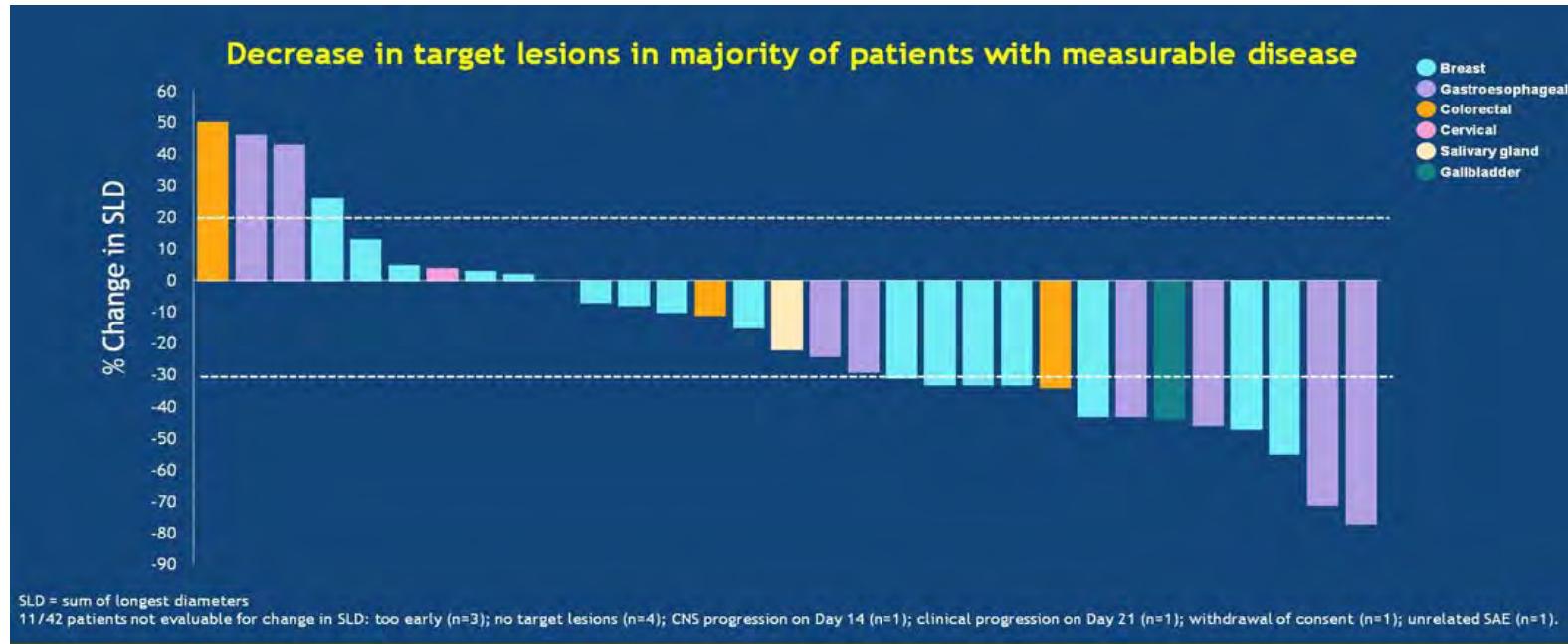
PRESENTED AT: **2018 ASCO[®]**
ANNUAL MEETING

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PRESENTED BY: Funda Meric-Bernstam

3

Change in Target Lesions Across Cancer Types



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A first in human study evaluating single agent activity in heavily pretreated HER2-expressing cancers is ongoing (NCT02892123).

DS-8201a Structure and Mechanism of Action

The diagram illustrates the structure and mechanism of action of DS-8201a. On the left, a schematic shows an antibody (red) binding to a target (blue). A cysteine residue (Cys) on the antibody is linked via a drug-linker (yellow) to a payload molecule (Exatecan derivative). The payload is a complex organic compound containing multiple rings and functional groups. To the right, a list of eight key features of DS-8201a is presented in blue boxes:

- Payload with a different mechanism of action*
- High potency of payload*
- Payload with short systemic half-life*
- Bystander effect*
- Stable linker-payload*
- Tumor-selective cleavable linker*
- High drug-to-antibody ratio*

- DS-8201a was designed with the goal of improving critical attributes of an ADC

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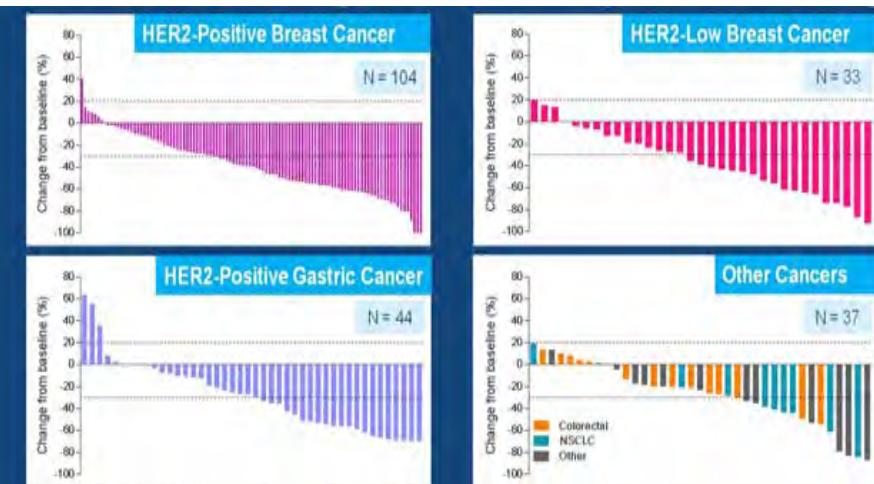
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PRESENTED BY: Hiroji Iwata, MD, PhD

3

Anti-Tumor Activity of DS-8201a

Consistent Tumor Shrinkage Across Tumor Types: (5.4 or 6.4 mg/kg)

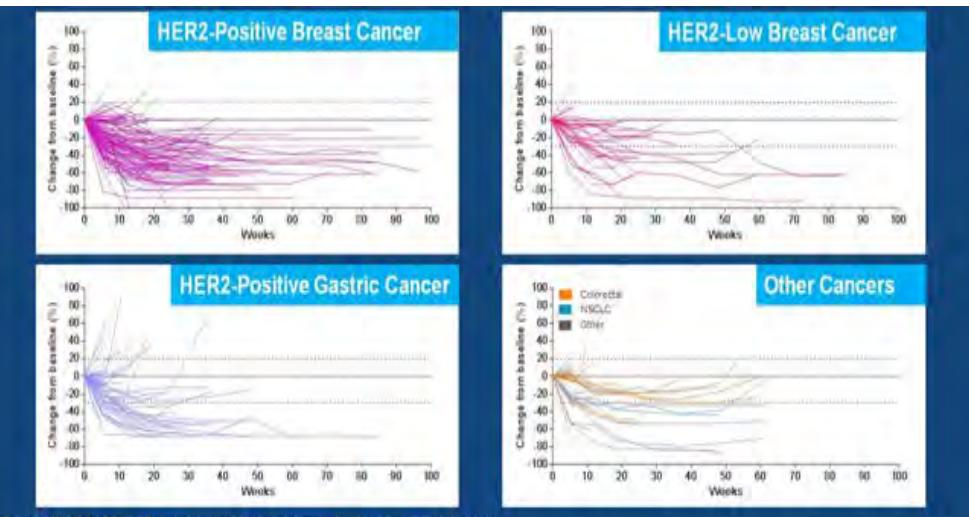


- Overall, 86.3% of subjects experienced tumor shrinkage
- Confirmed ORR* in the overall population is 49.3%

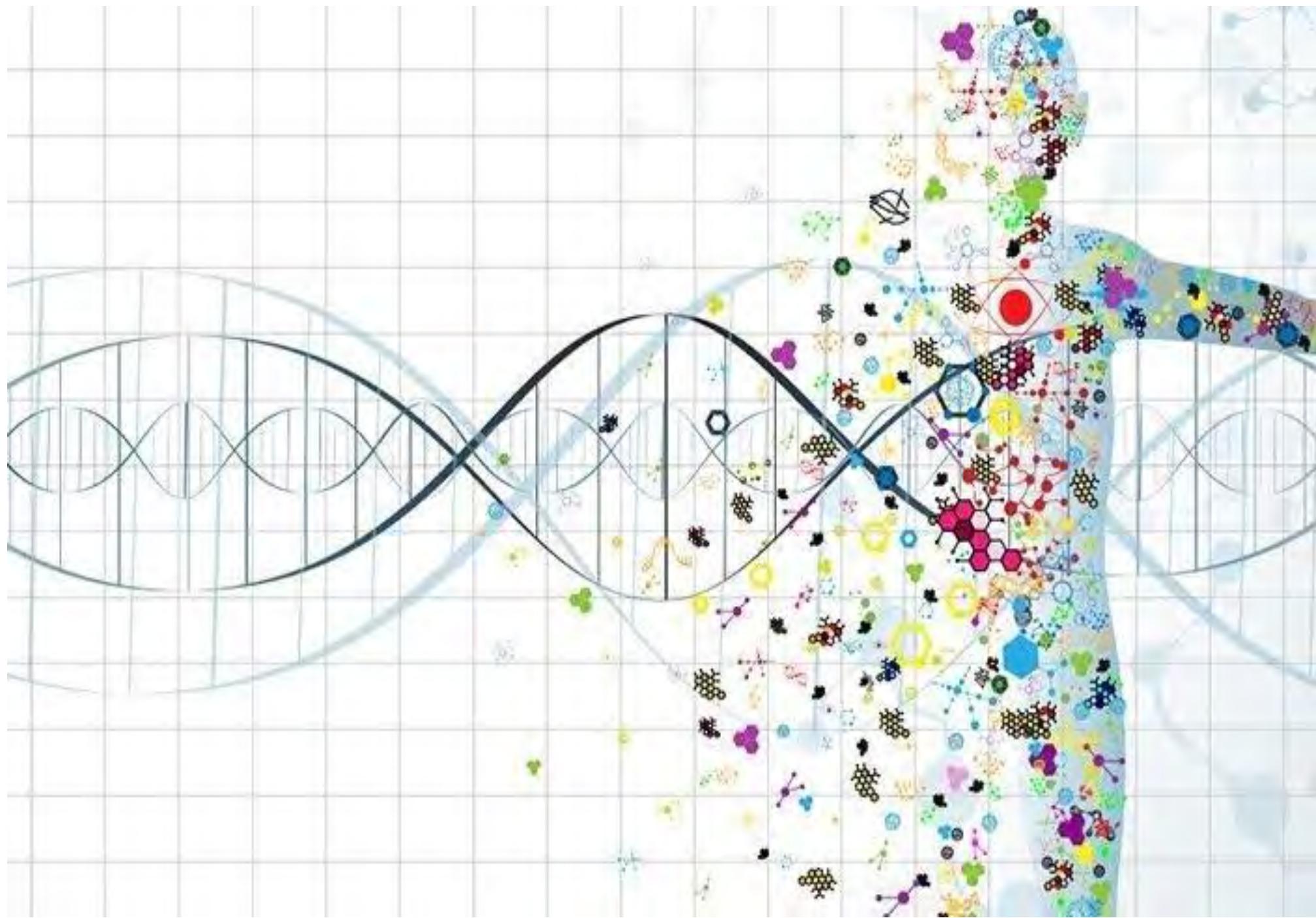
Includes subjects who had ≥1 postbaseline scan. Dotted lines denote 20% increase and 30% reduction in tumor size, respectively.

*Confirmed responses include subjects who had ≥3 consecutive scans demonstrating disease or discontinued treatment for reasons other than second neoplasm. Data cutoff: April 19, 2018.

Tumor Shrinkage Over Time by Tumor Type (5.4 or 6.4 mg/kg)



- Overall, 86.3% of subjects experienced tumor shrinkage
- 91.5% of these subjects experienced shrinkage at the time of first imaging assessment at 6 weeks



Optimal treatment of mCRC in the presence of braf

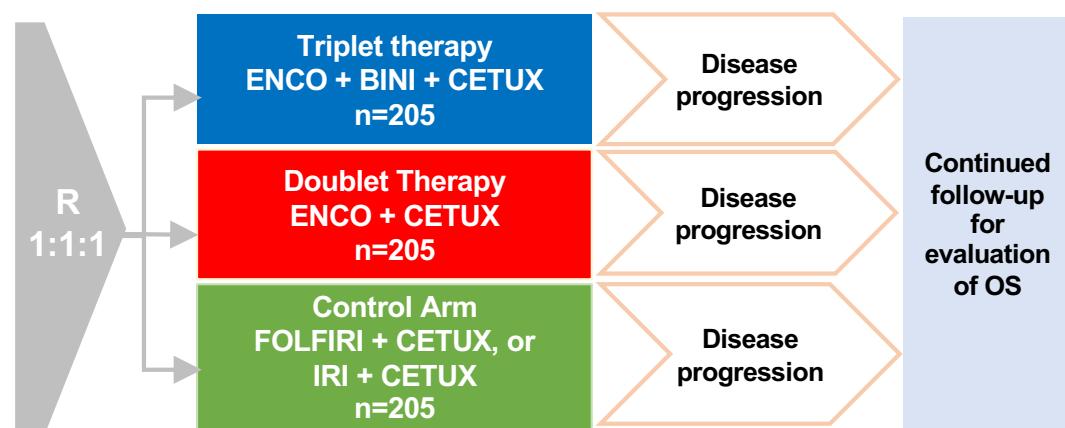
BEACON CRC Phase 3 Study Design¹

Safety Lead-in Completed

ENCO 300 mg QD
+
BINI 45 mg BID
+
CETUX 400 mg/m² (initial),
then 250 mg/m² QW

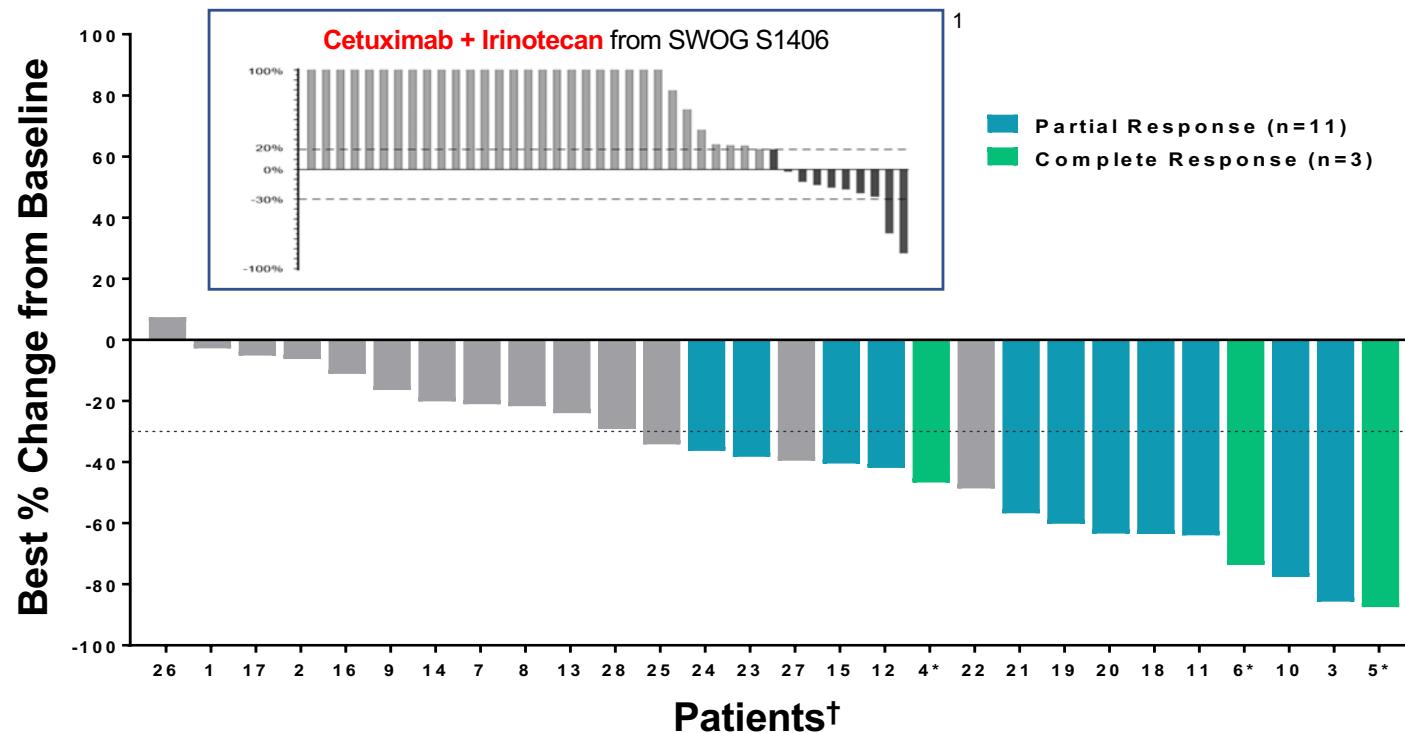
N=30

Phase 3 Currently Enrolling



1. Clinicaltrials.gov/ct2/show/NCT02928224; <https://clinicaltrials.gov/ct2/show/NCT02928224> (February 2018).

Best Percentage Change in Tumor Measurements from Baseline



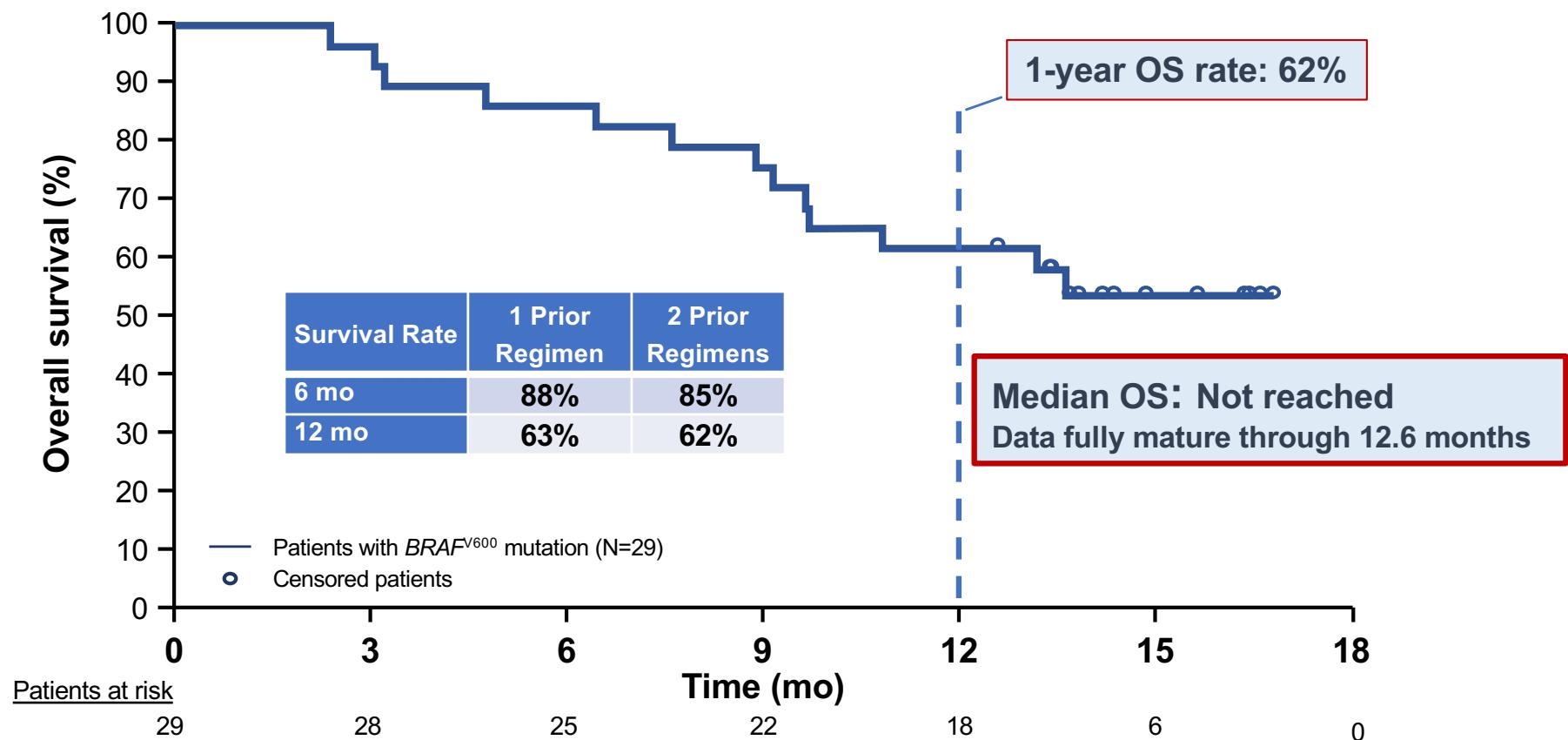
*Patients with lymph node disease with decreases in short axis dimensions consistent with RECIST 1.1 defined Complete Response.

†One patient had no baseline sum of longest diameters and is not presented.

1. Kopetz S, et al. J Clin Oncol. 2017;35:Abstr 3505, with permission.

Van Cutsem et al., ESMO GI 2018

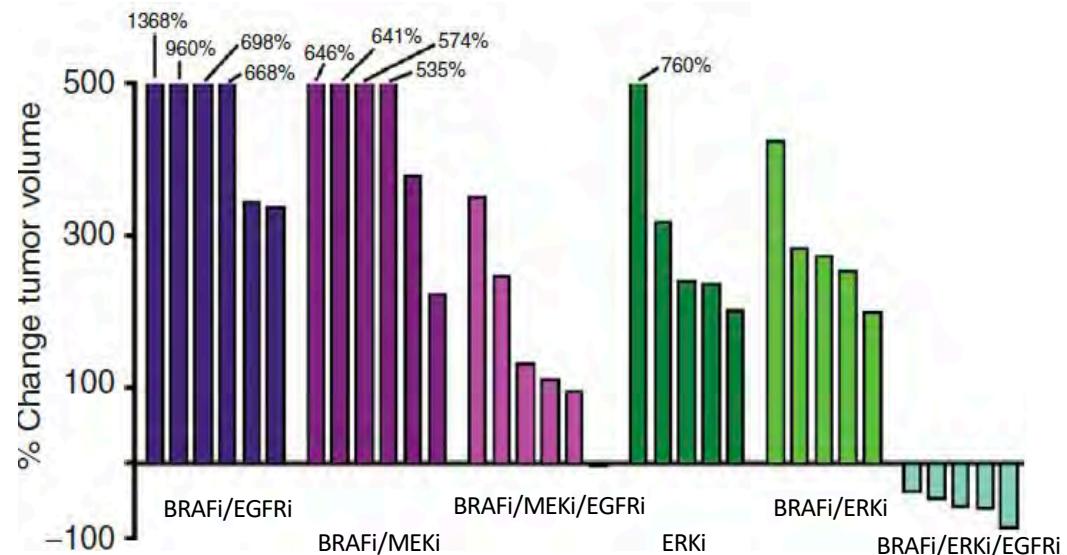
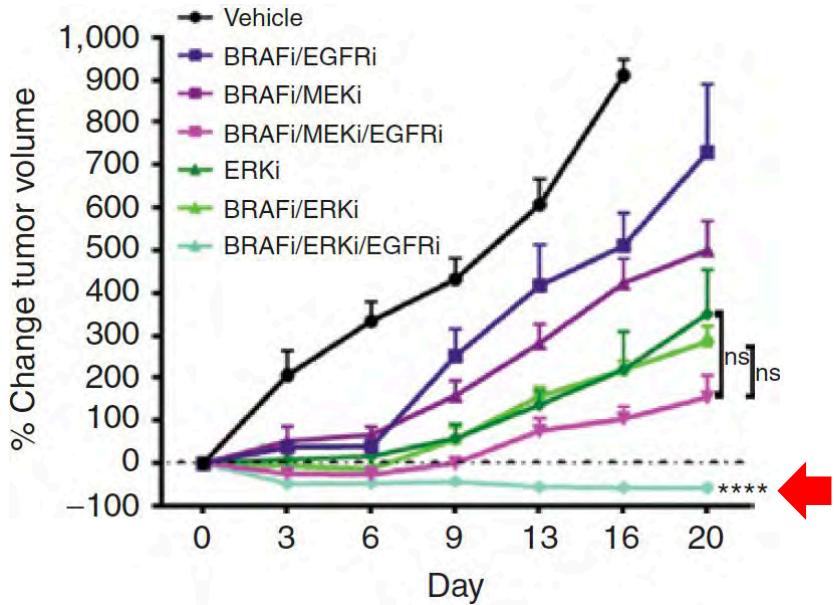
BEACON SLI: Overall Survival



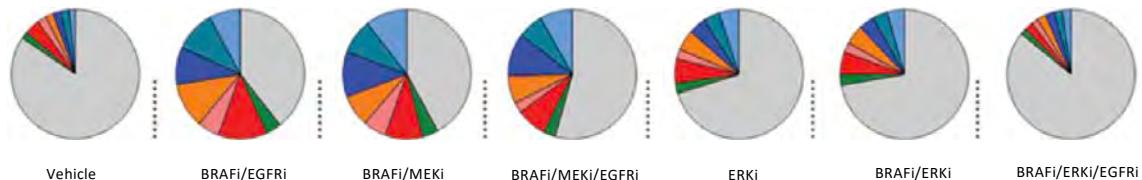
Van Cutsem et al., ESMO GI 2018

Upfront therapy to suppress resistant clones

In vivo tumor xenografts with resistant clones pooled at 1% each



Clonal abundance by 21 days



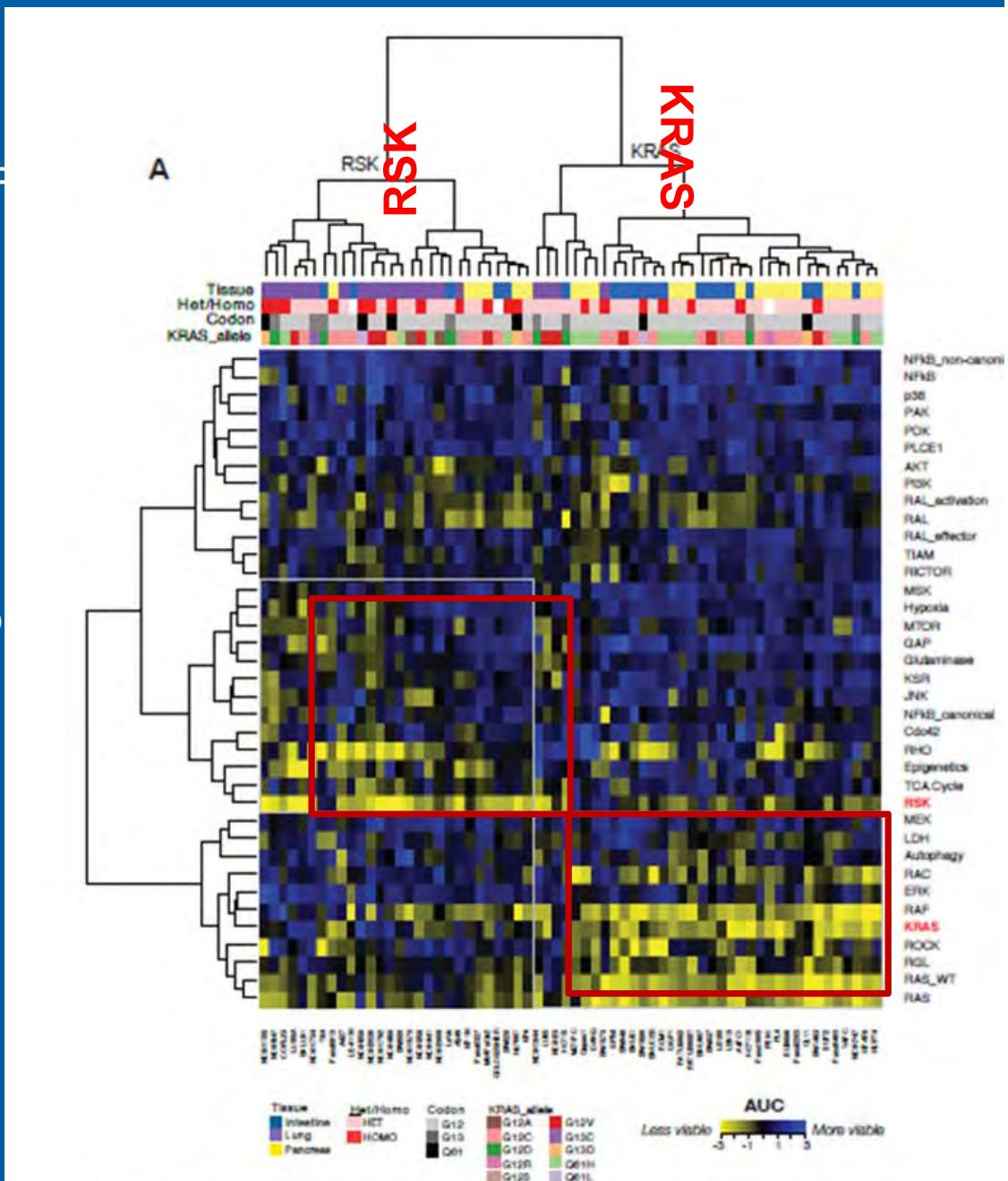
- NRAS Q61K
- KRAS G12D
- KRAS G12S
- KRAS Q61H
- MEK1 F53L
- MEK1 K57T
- MEK2 C125S

Hazar-Rethinam et al, Cancer Discovery 2018

Ras and effector dependencies

- KRAS subtype lines:
 - depend on the canonical RAS-RAF-MAPK pathway
 - upregulate genes involved in the maintenance of the epithelial phenotype
- RSK subtype lines:
 - depend on the RSK-MTOR/PI3K axis to drive aerobic metabolism to supplement glycolysis
 - express mesenchymal markers ZEB1, TGFB, TWIST

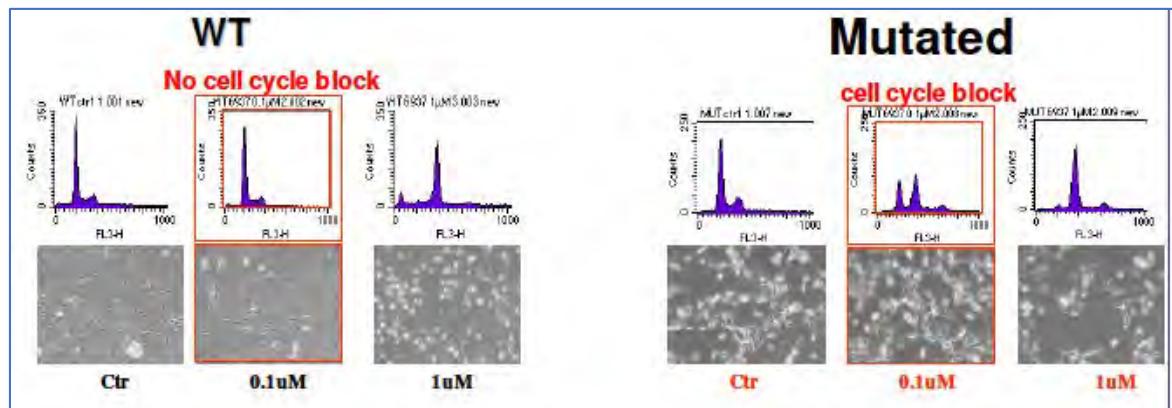
Tina Yuan, Rachel Bagni, Cyril Benes, Arnaud Amzallag, Bob Stephens, Ming Yi, FNLCR
Cell Feb 2018



Could KRAS Mutation be a Biomarker for PCM-075 Sensitivity in CRC?

Sensitivity to PLK1 inhibition in the presence of KRAS mutations in vitro

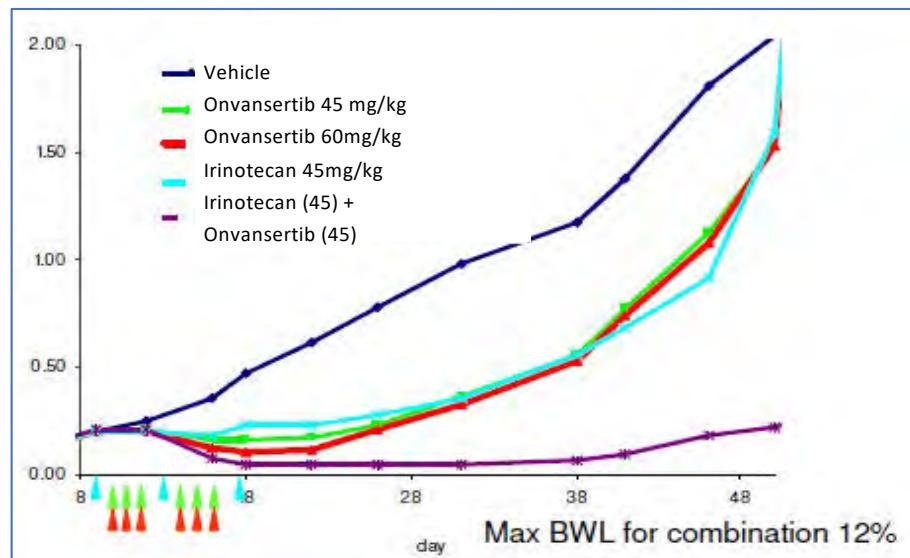
- In a genome-wide RNAi screen aimed at the identification of synthetic lethal interactions with the RAS oncogene PLK1 was identified
- KRAS mutated NIH3T3 cells showed higher sensitivity to PCM-075 compare to WT KRAS cells



Nerviano Medical Sciences (NMS)

PCM-075 in Combination with Anticancer Agents in CRC

- In the HCT116 cell line, PCM-075 was found to be synergistic in vitro with different class of drugs including:
 - the chemotherapeutic agent cisplatin
 - the active metabolite of the topoisomerase inhibitor irinotecan (SN-38)
 - the microtubule inhibitor paclitaxel
- In the HT29 xenograft model, PCM-075 was found to be:
 - **Synergistic** with the topoisomerase inhibitor irinotecan
 - **Additive** with the chemotherapeutic agent fluorouracil (5FU) or the angiogenesis inhibitor bevacizumab



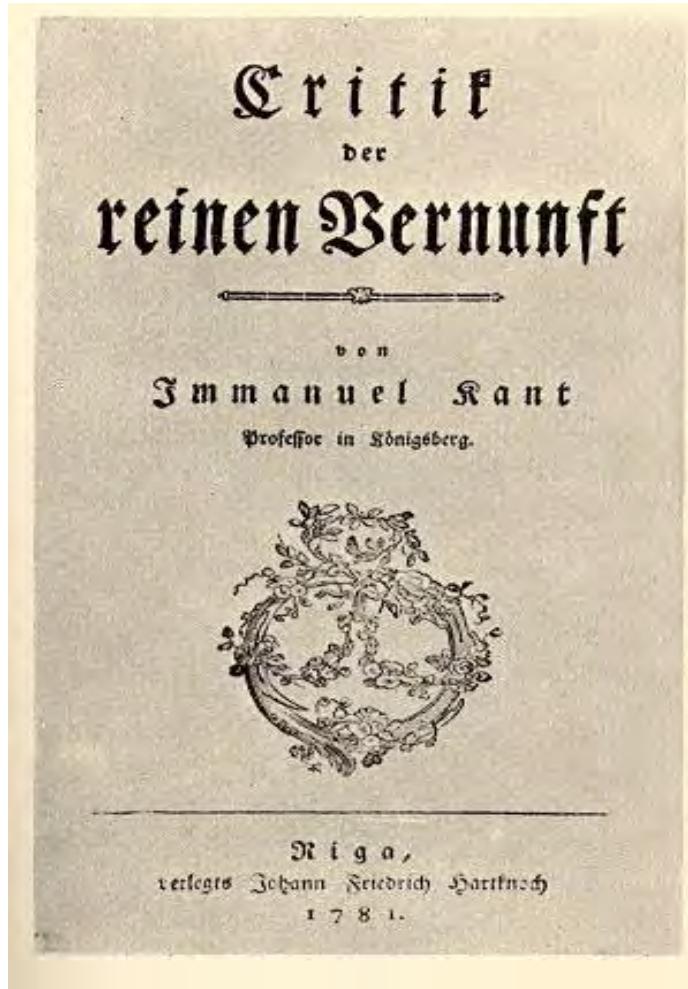


Right Treatment at the Right Time

- Genetic Testing of Tumor at time of diagnosis and if possible again at time of growth (CARIS, FOUNDATION, ORIEN)
- Genetic Testing of patients if evidence of Predisposition
- Active Monitoring with Liquid Biopsies
- Accelerating Access to Clinical Trials



Immanuel Kant (Photo from a steel engraving)



The one who knows more, may decide better