Colorectal Cancer: State of the Science

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

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

Example of Panel of Genes Tested Using an NGS-Based Approach[1]

Take home: NGS may be the most efficient method for capturing TRK fusions, particularly useful in settings where pretest probability is low

Current Gene List Entire coding sequence (base substitutions, indels, copy number alterations)									Select rearrangements
ABL1	ABL2	ACVR1B	AKT1	AKT2	AKT3	ALK	AMER1(FAM123B)	APC	ALK
AR	ARAF	ARFRP1	ARID14	ARID1B	ARID2	ASXL1	ATM	ATR	BCL2
ATRX	AURKA	AURKB	AXIN1	AXL	BAP1	BARD1	BCL2	BCL2L1	BCR
BCL2L2	BCL6	BCOR	BCORL1	BLM	BRAF	BRCA1	BRCA2	BRD4	BRAF
BRIP1	BTG1	BTK	C11orf30 (EMSY)	CARD11	CBFB	CBL	CCND1	CCND2	BRAC1
CCND3	CCNE1	CD274 (PD-L1)	CD79A	CD79B	CDC73	CDH1	CDK12	CDK4	BRCA2
CDK6	CDK8	CDKN1A	CDKN1B	CDKN2A	CDKN2B	CDKN2C	CEBPA	CHD2	BRD4
CHD4	CHEK1	CHEK2	CIC	CREBBP	CRKL	CRLF2	CSF1R	CTCF	EGFR
CTNNA1	CTNNB1	CUL3	CYLD	DAXX	DDR2	DICER1	DNMT3A	DOT1L	ETV1
EGFR	EP300	EPHA3	EPHA5	EPHA7	EPHB1	ERBB2	ERBB3	ERBB4	ETV4
ERG	ERRFI1	ESR1	EZH2	FAM46C	FANCA	FANCC	FANCD2	FANCE	ETV5
FANCF	FANCG	FANCL	FAS	FAT1	FBXW7	FGF10	FGF14	FGF19	ETV6
FGF23	FGF3	FGR4	FGF6	FGFR1	FGFR2	FGFR3	FGFR4	FH	FGFR1
FLCN	FLT1	FLT3	FLT4	FOXL2	FOXP1	FRS2	FUBP1	GABRA6	FGFR2
GATA1	GATA2	GATA3	GATA4	GATA6	GID4 (C17orf39)	GLI1	GNA11	GNA13	FGFR3
GNAQ	GNAS	GPR124	GRIN2A	GRM3	GSK3B	H3F3A	HGF	HNF1A	KIT
HRAS	HSD3B1	HSP90AA1	IDH1	IDH2	IGF1R	IGF2	IKBKE	IKZF1	MSH2
IL7R	INHBA	INPP4B	IRF2	IRF4	IRS2	JAK1	JAK2	JAK3	MYB
JUN	KAT6A (MYST3)	KDM5A	KDM5C	KDM6A	KDR	KEAP1	KEL	KIT	MYC
KLHL6	KMT2A (MLL)	KMT2C (MLL3)	KMT2D (MLL2)	KRAS	LMO1	LRP1B	LYN	LZTR1	NOTCH2
MAGI2	MAP2K1 (MEK1)	MAP2K2 (MEK2)	MAP2K4	MAP3K1	MCL1	MDM2	MDM4	MED12	NTRK1
MEF2B	MEN1	MET	MITF	MLH1	MPL	MRE11A	MSH2	MSH6	NTRK2
MTOR	MUTYH	MYC	MYCL (MYCL1)	MYCN	MYD88	NF1	NF2	NFE2L2	PDGFRA
NFKBIA	NKX2-1	NOTCH1	NOTCH2	NOTCH3	NPM1	NRAS	NSD1	NTRK1	RAF1
NTRK2	NTRK3	NUP93	PAK3	PALB2	PARK2	PAX5	PBRM1	PDCD1LG2 (PD-L2)	RARA
PDGFRA	PDGFRB	PDK1	PIK3C2B	PIK3CA	PIK3CB	PIK3CG	PIK3R1	PIK3R2	RET
PLCG2	PMS2	POLD1	POLE	PPP2R1A	PRDM1	PREX2	PRKAR1A	PRKCI	ROS1
PRKDC	PRSS8	PTCH1	PTEN	PTPN11	QKI	RAC1	RAD50	RAD51	TMPRSS2
RAF1	RANBP2	RARA	RB1	RBM10	RET	RICTOR	RNF43	ROS1	
RPTOR	RUNX1	RUNX1T1	SDHA	SDHB	SDHC	SDHD	SETD2	SF3B1	
SLIT2	SMAD2	SMAD3	SMAD4	SMARCA4	SMARCB1	SMO	SNCAIP	SOCS1	
SOX10	SOX2	SOX9	SPEN	SPOP	SPTA1	SRC	STAG2	STAT3	
STAT4	STK11	SUFU	SYK	TAF1	TBX3	TERC	TERT (Promoter only)	TET2	
TGFBR2	TNFAIP3	TNFRSF14	TOP1	TOP2A	TP53	TSC1	TSC2	TSHR	
U2AF1	VEGFA	VHL	WISP3	WT1	XPO1	ZBTB2	ZNF217	ZNF703	

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

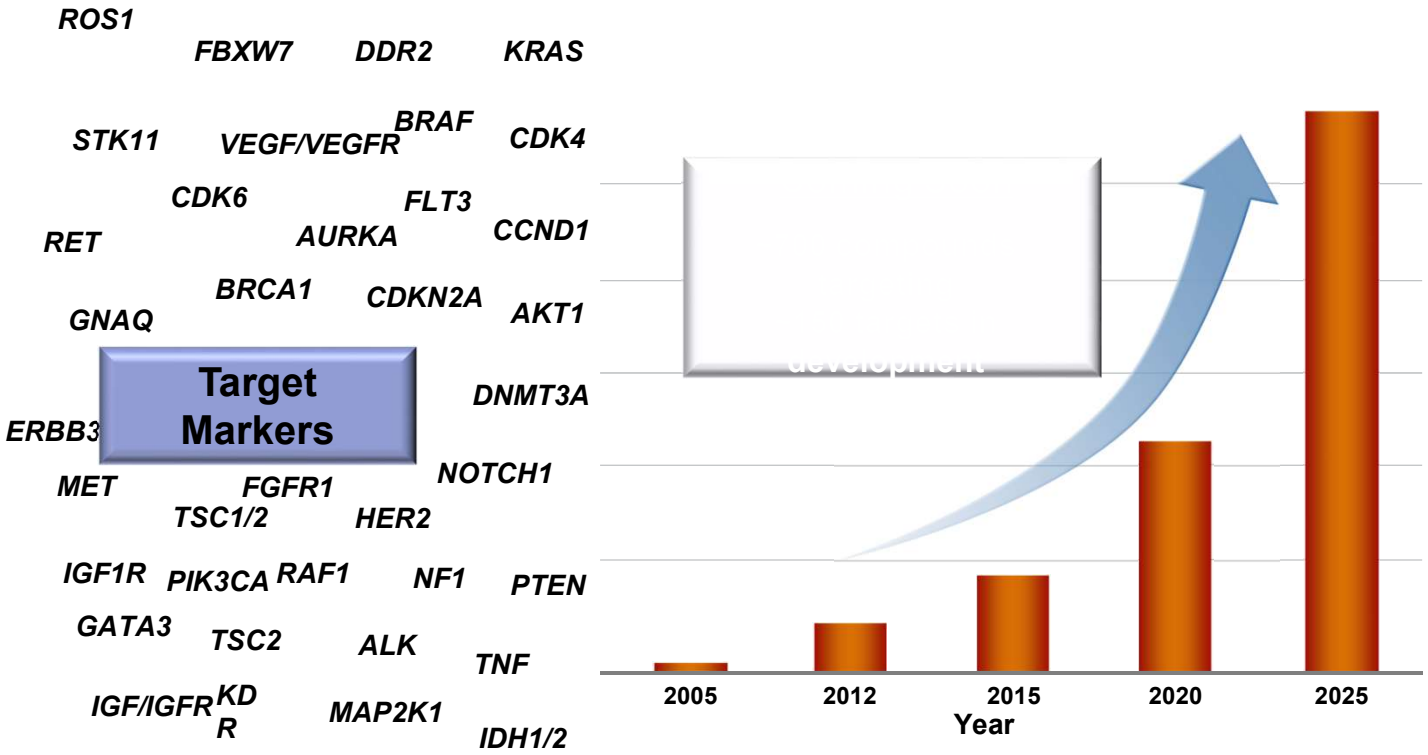
			Increase in Overall Survival	Increase in Progression-Free Survival	Increase in Response Rate
Phase I **Studies**	n = 13'203	JAMA Oncology		**2.75** months from 2.95 to 5.7	**25.7%** from 4.9% to 30.6%
Phase II **Studies**	n = 32'149	Journal of Clinical Oncology	**4.8** months from 8.9 to 13.7	**3.2** months from 2.7 to 5.9	**20.5%** from 10.5% to 31.0%
Phase III **Studies**	n = 38'104	JNCI	**5.8** months from 13.5 to 19.3	**2.8** months from 5.5 to 8.3	**25.0%** from 23.0% to 48.0%
NSCLC – In Practice	n = 17'664	The Lancet	**4.7** months from 11.8 to 16.5	**2.9** months from 7.1 to 10.0	1st line: 4.0% from 33.0% to 37.0% 2nd line: 8.0% from 9.0% to 17.0%

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



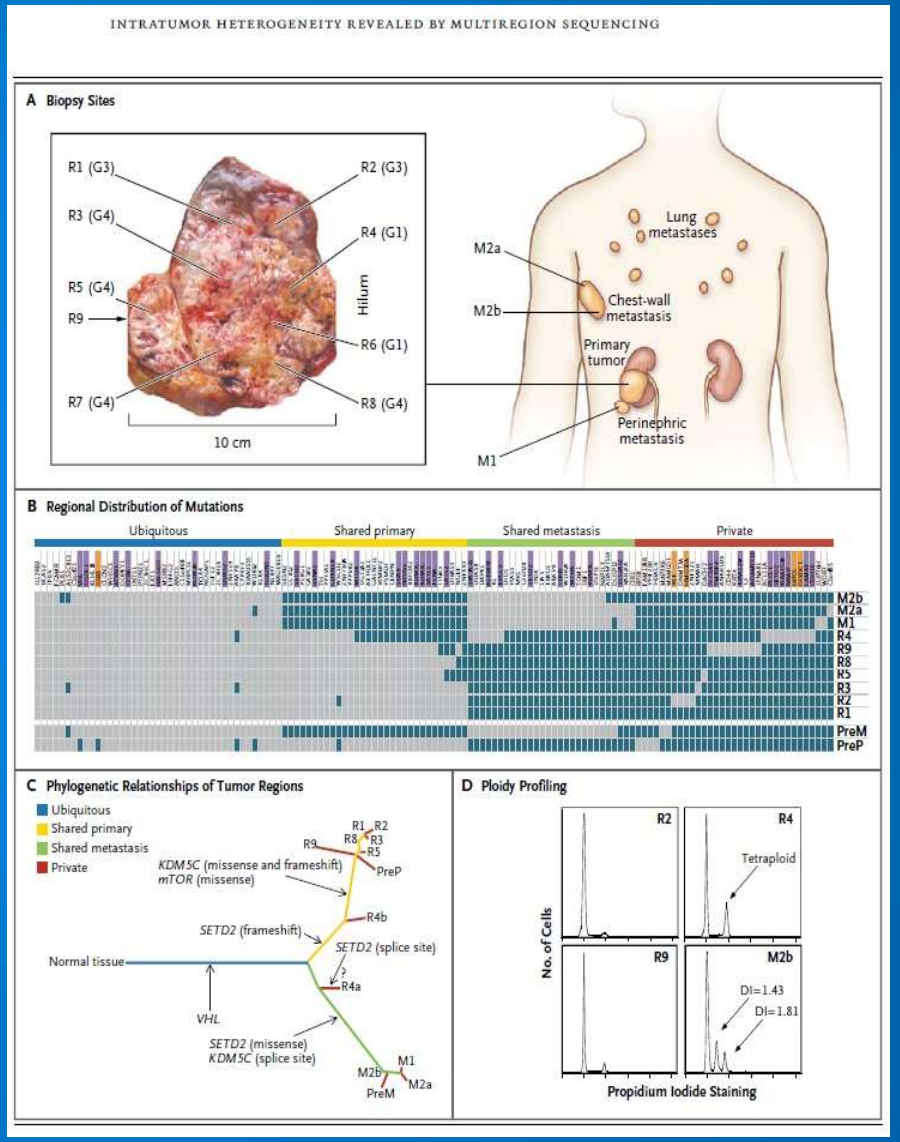
Extrapolated from BioCentury Online Intelligence Database

New Science in Colorectal

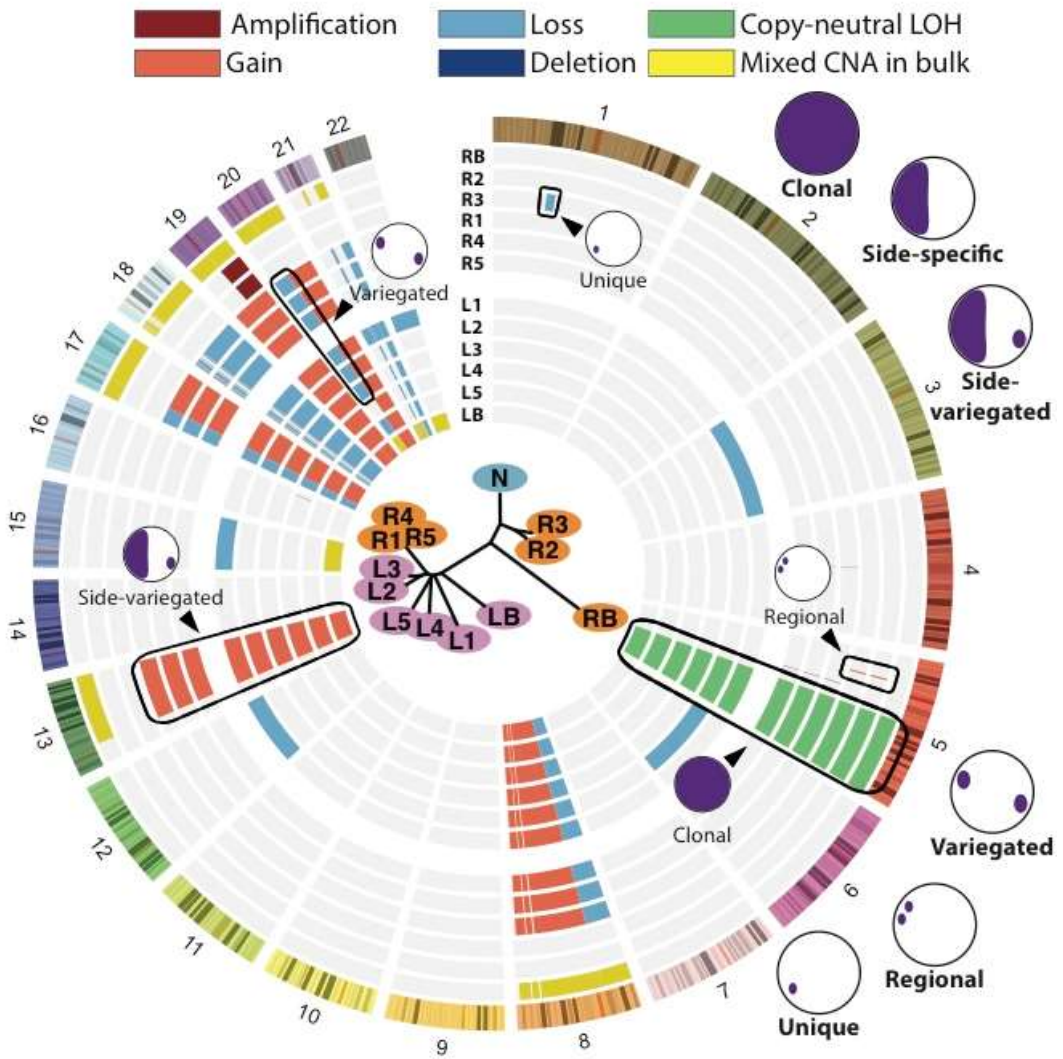
- New INSIGHTS into Molecular Features
- Acceptable to look for the Needle in the Haystack
- MSI
- HER2
- BRAF
- RAS
- PI3K

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

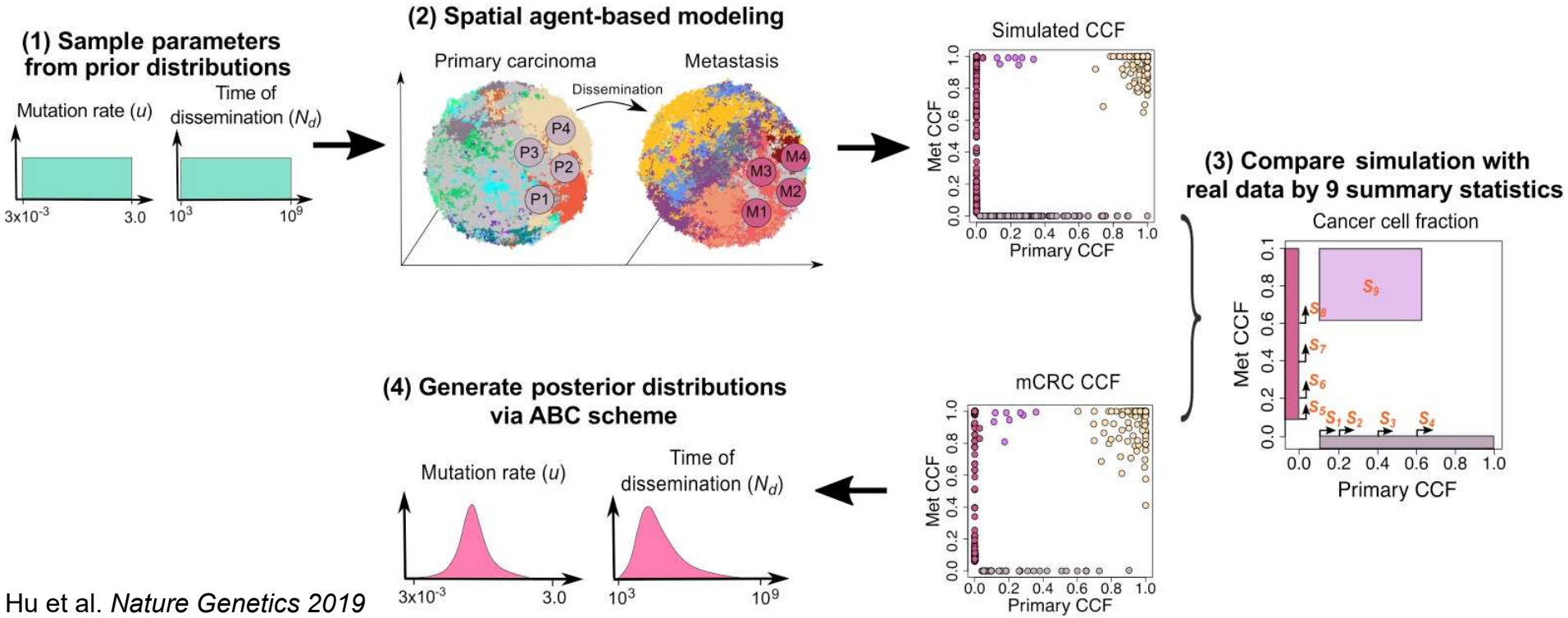


Intra-tumor copy number heterogeneity in CRC at the single gland level



Curtis et al Nature Genetics 2016

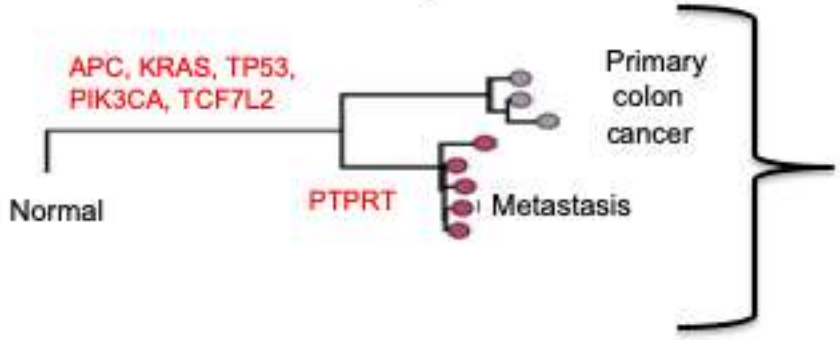
Spatial Computational Inference of MEtastatic Timing (SCIMET)



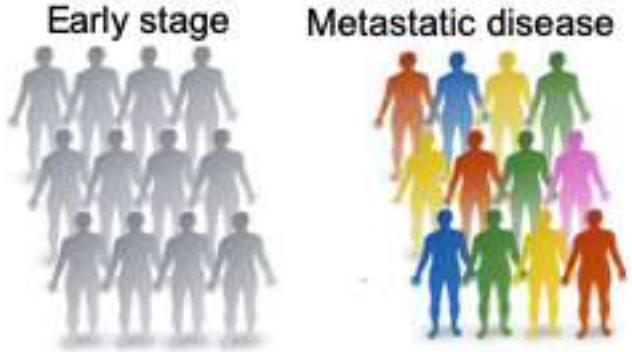
Hu et al. *Nature Genetics 2019*

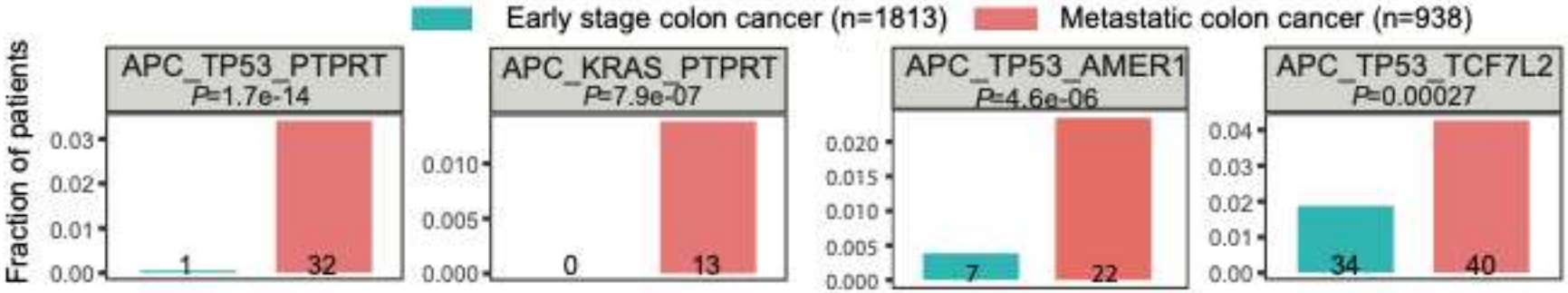
Validation of metastasis driver modules

Metastasis associated early driver modules



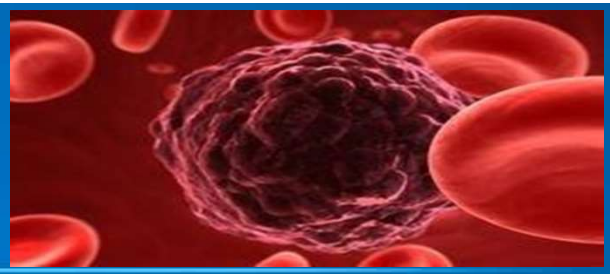
Clinically annotated CRCs with targeted sequencing (n=2751)



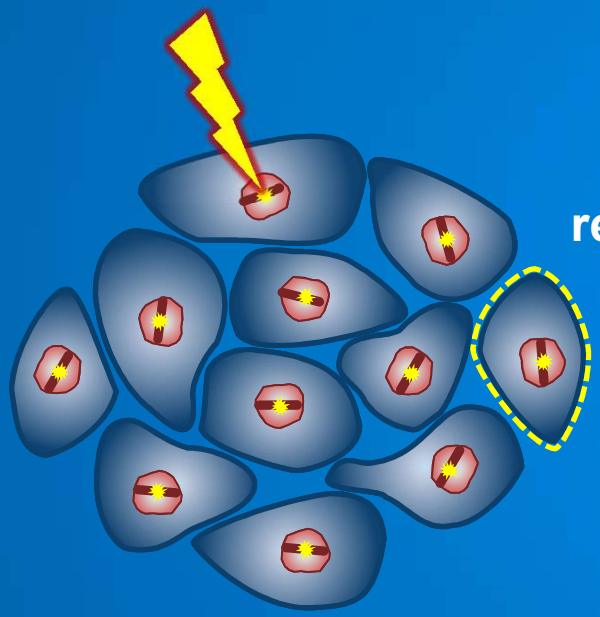


Hu…Curtis *Nature Genetics 2019*

Liquid Biopsies



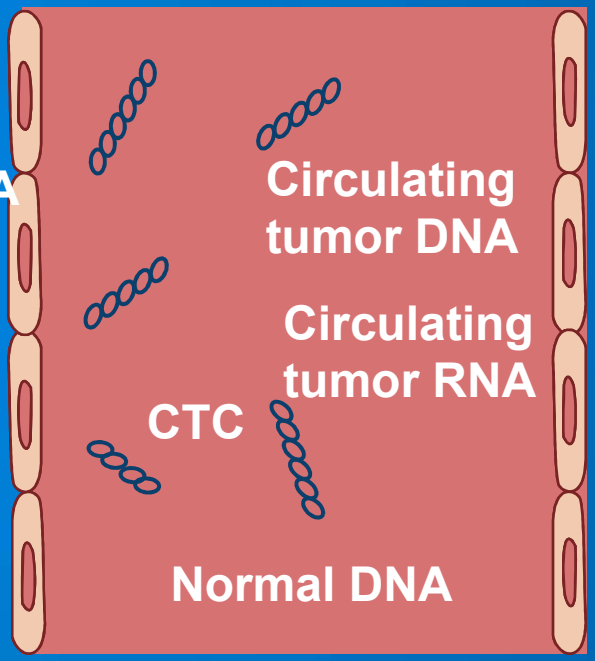
Tumor specific change (e.g. Mutation)



Tumor

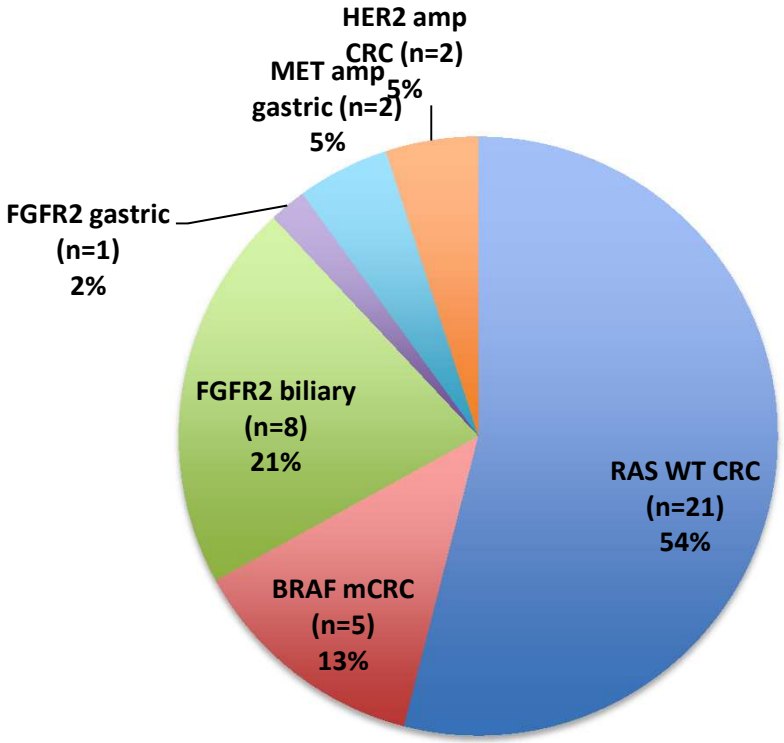
Tumor cell release DNA and RNA

Circulating Tumor Cells (CTC)

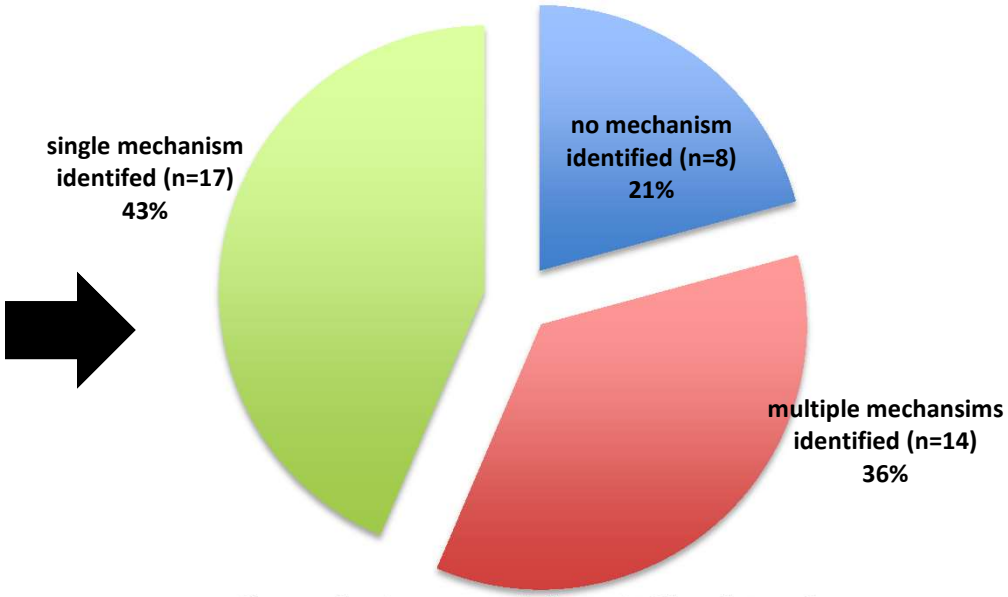


Blood Vessel

MGH GI Cancer Center Liquid Biopsy Program



N=39



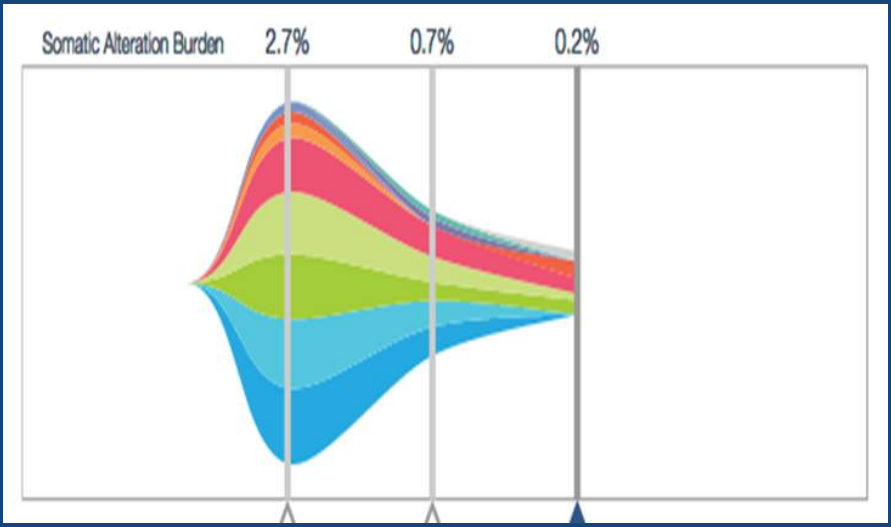
Mechanism of resistance identified in 80%

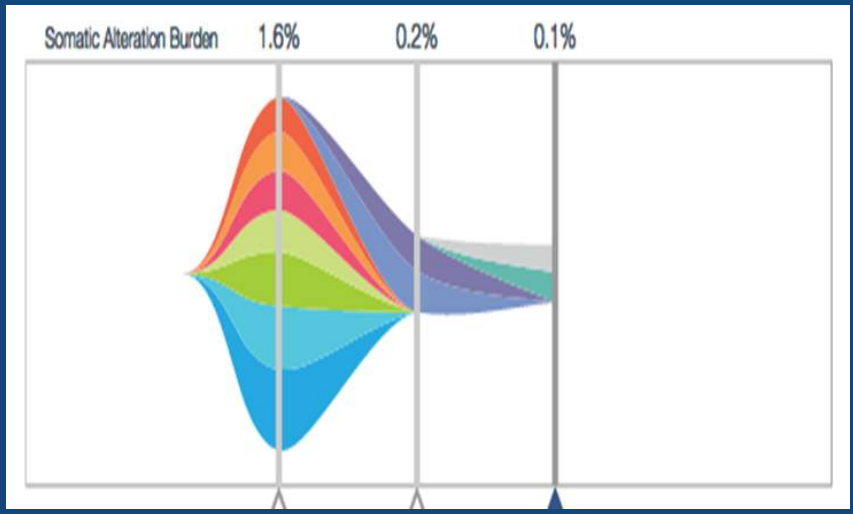
Routine liquid biopsy assessment can effectively identify mechanisms of resistance across different tumor types and treatments

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

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

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





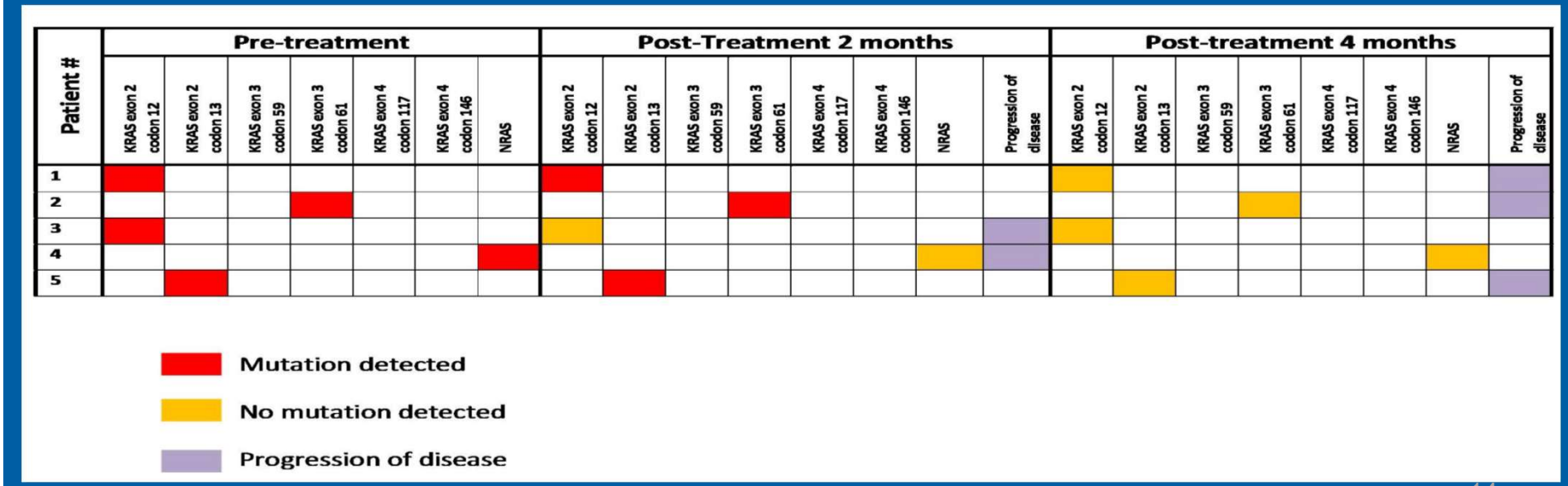
In 84 patients with metastatic CRC receiving serial monitoring, 87% had either gain (61%) or loss (63%) of clones over time

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

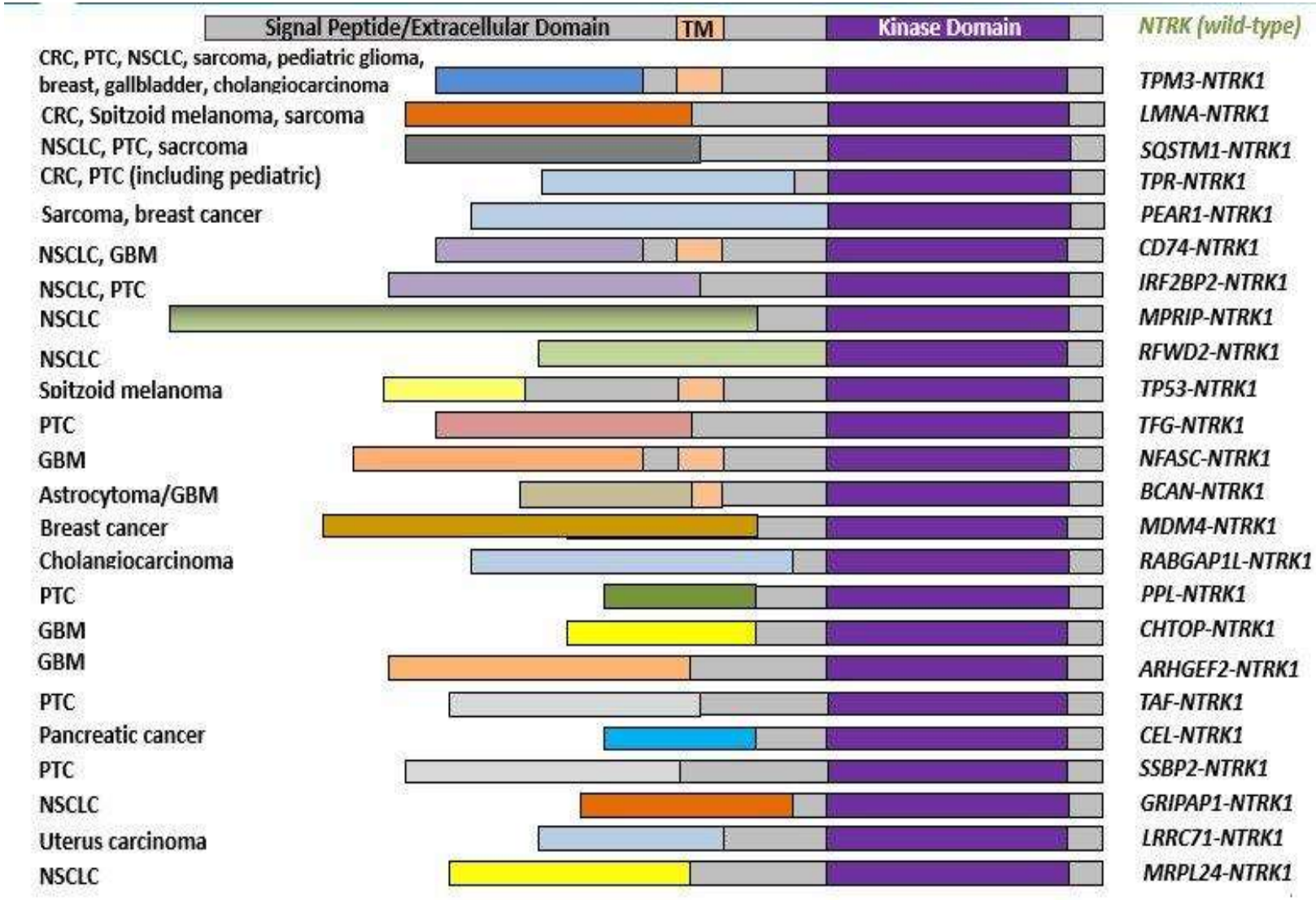
Heinz-Josef Lenz

Interesting Findings

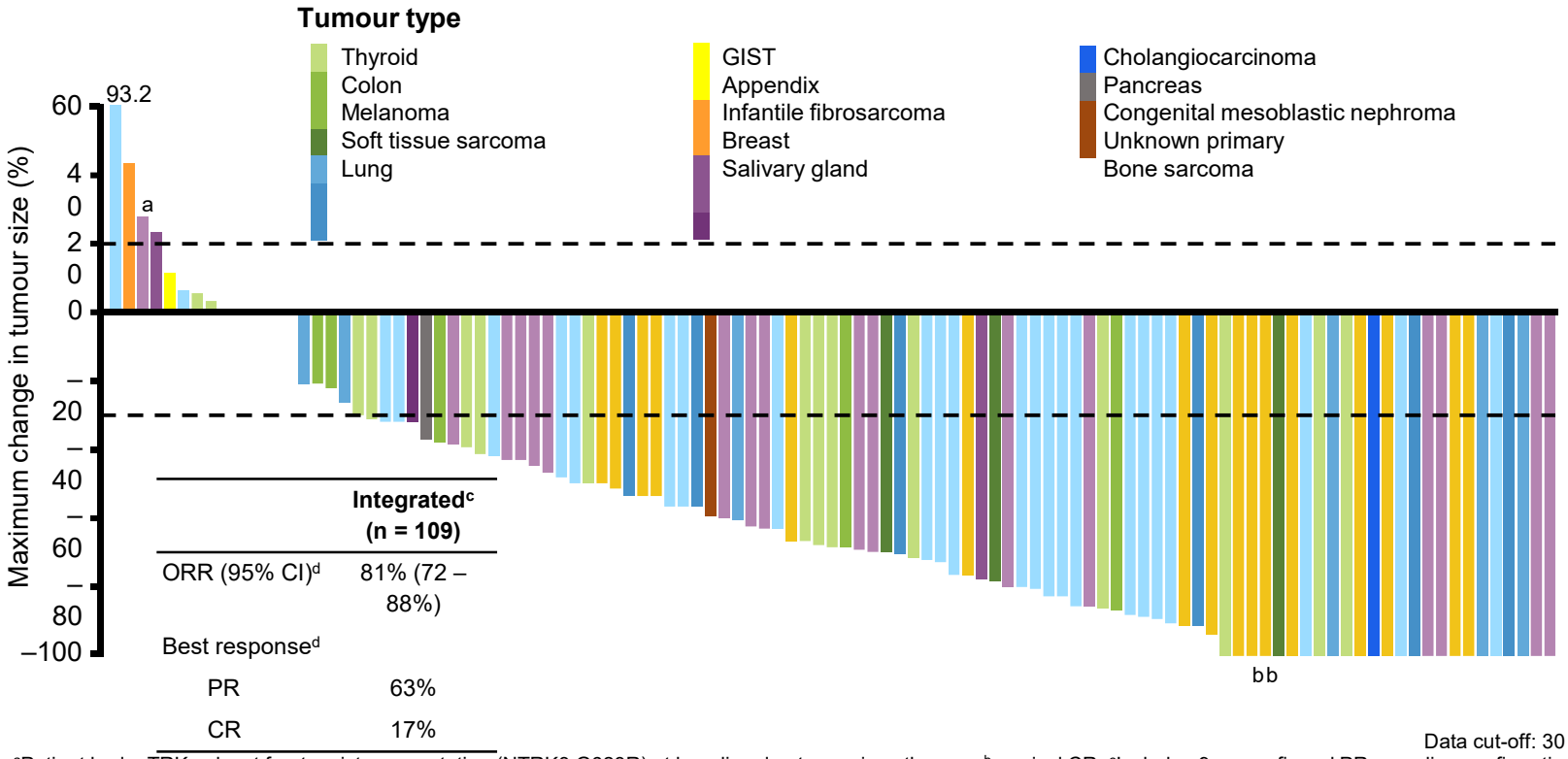
1. In a small series of 10 patients who all had mt ras in tissue and liquid biopsy treated with bev based chemotherapy. 5/10 changed to wt Ras under chemotherapy) Gazzaniga et al Annals of Oncology (2017) 28 (suppl_5): v573-v594)
2. Case report in JCO Precision Oncology from same group reported PR in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




Can you find **Trump** in this pile of Oompa Loompas?



Integrated dataset: Larotrectinib is efficacious across tumour types



Data cut-off: 30 July 2018.

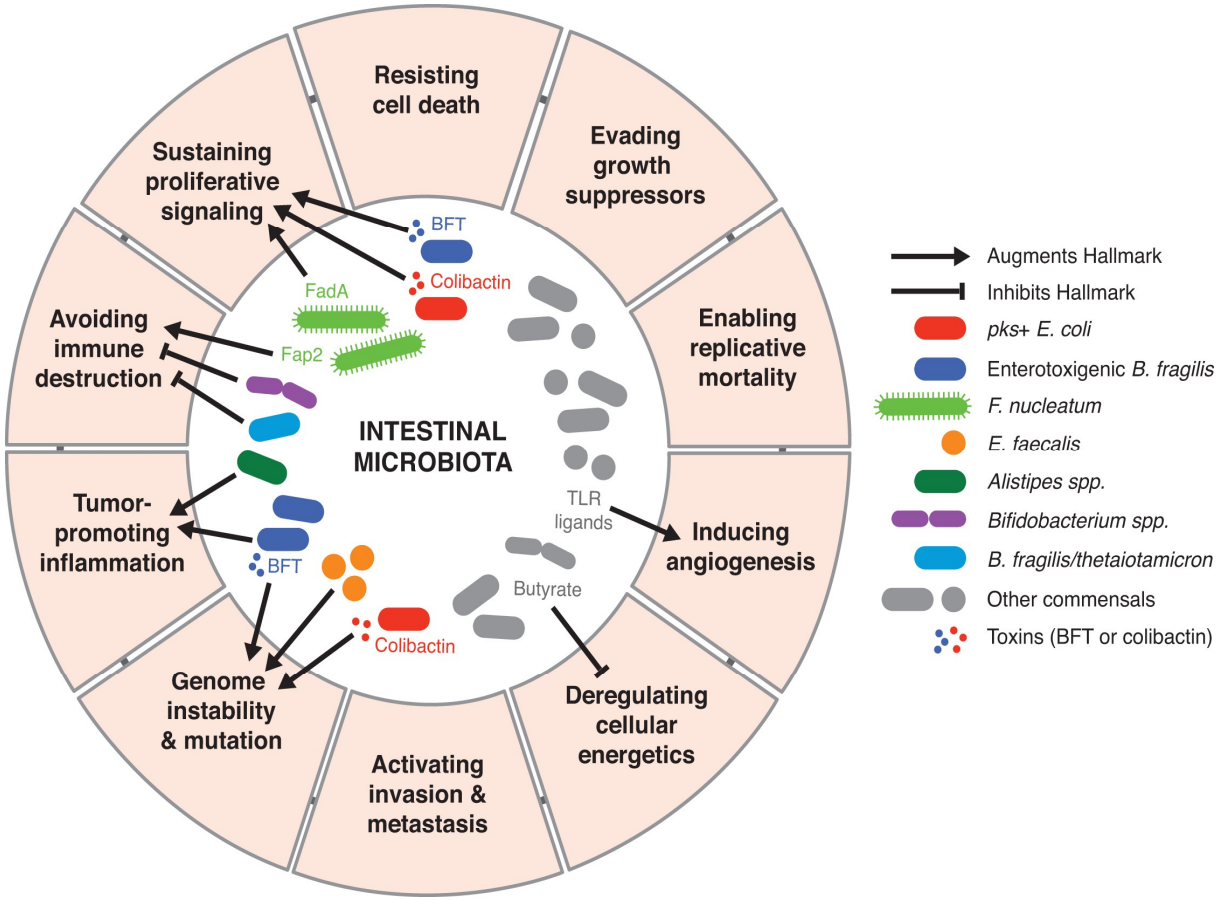
[a]Patient had a TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to previous therapy; [b]surgical CR; [c]Includes 9 uncomfirmed PRs pending confirmation; does not include 13 patients continuing on study and awaiting initial response assessment; [d]RECIST 1.1.

CI: confidence interval; CR: complete response; GIST: gastrointestinal stromal tumour; ORR: objective response rate; PR: partial response.

Lassen U. et al. (2018) presented at ESMO Congress 2018, Abstract 409O.

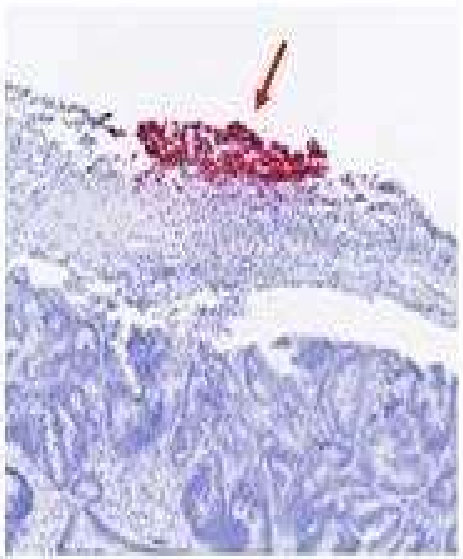
THE MICROBIOME MODULATES CANCER

Microbial-derived signals modulate many of the hallmarks of cancer through various mechanisms

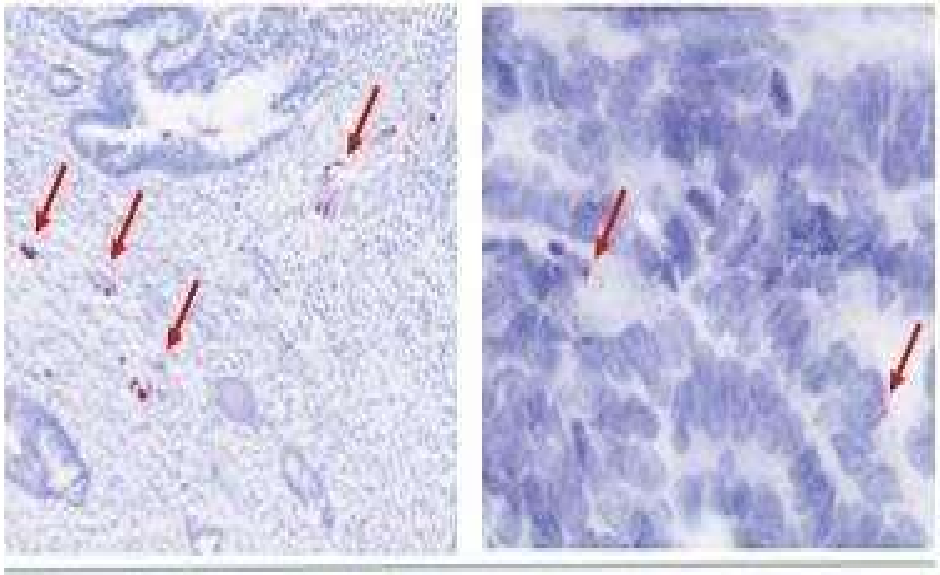


Tumor-associated bacteria hitches a ride to metastatic sites

Fusobacterium nucleatum (FN) in colorectal cancer: 1 red dot = 1 bacteria RNA molecule



FN in Biofilm in primary tumor



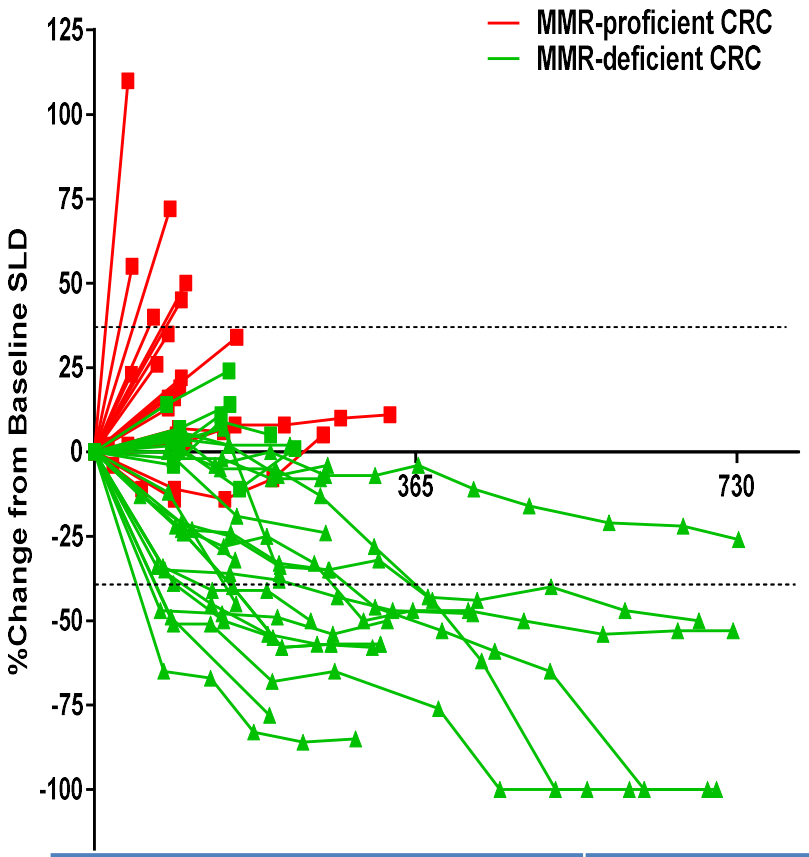
Invasive FN colonizing tumor cells

Nuciforo et al Science 2017

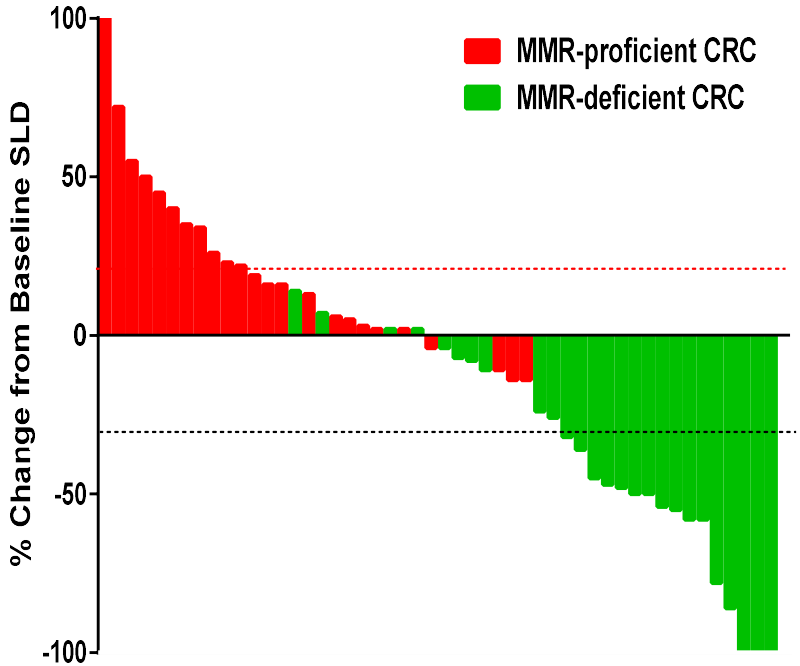
Microsatellite Instability

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

The NEW ENGLAND JOURNAL of MEDICINE



Pembrolizumab



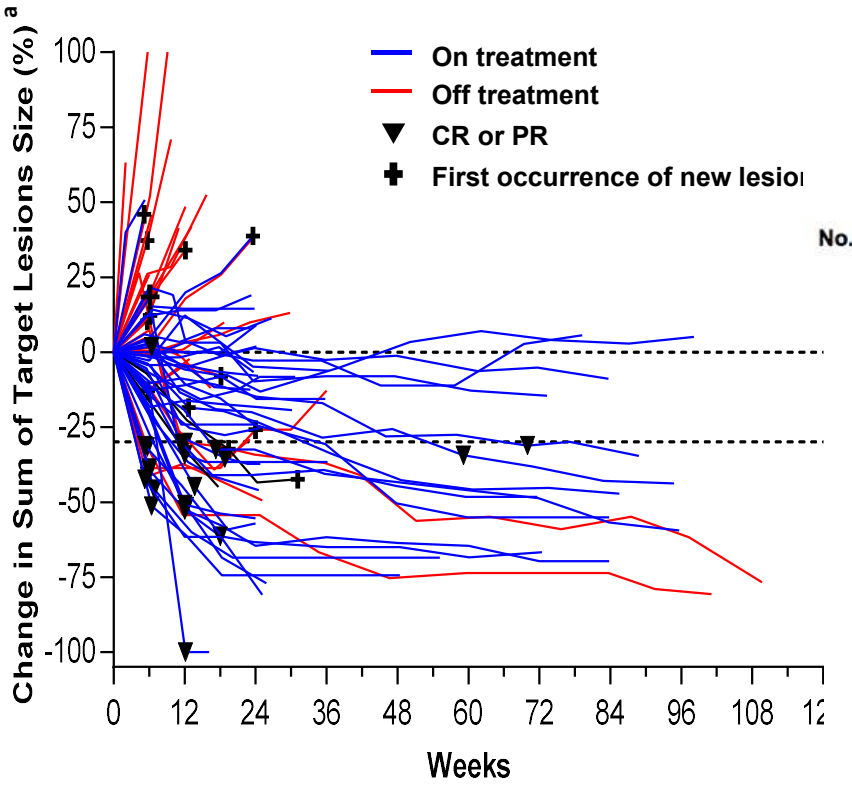
	MMR-deficient CRC, N=28	MMR-proficient CRC, N=25
Response Rate	**57%**	0%
Disease Control Rate	**89%**	16%

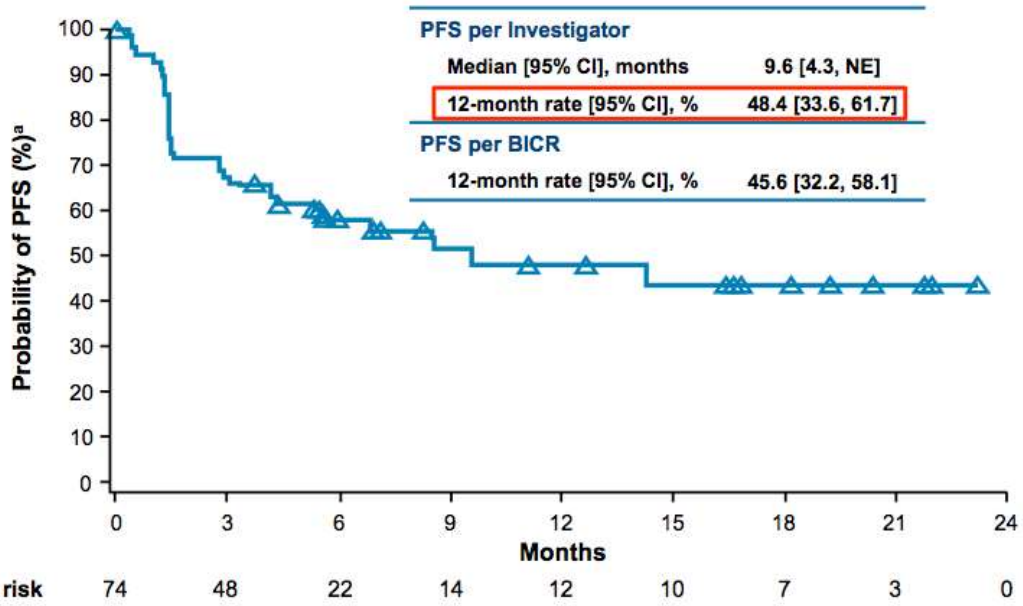
Le DT, et al. NEJM 2015 and *ASCO 2016*

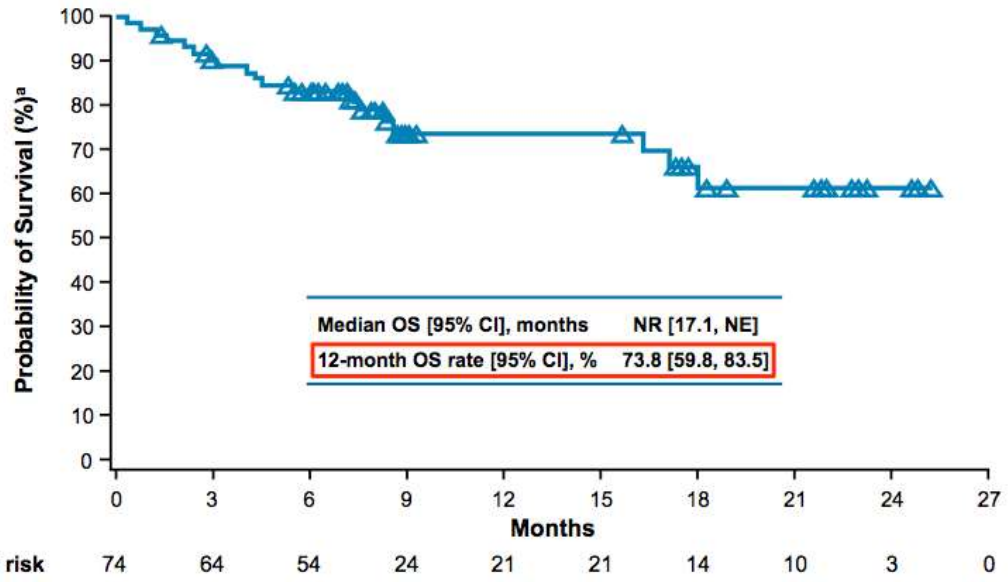
MSI-high CRC: Nivolumab Monotherapy

RR 31%
SD 39%
PD 24%

Disease Control ≥12weeks in 69%

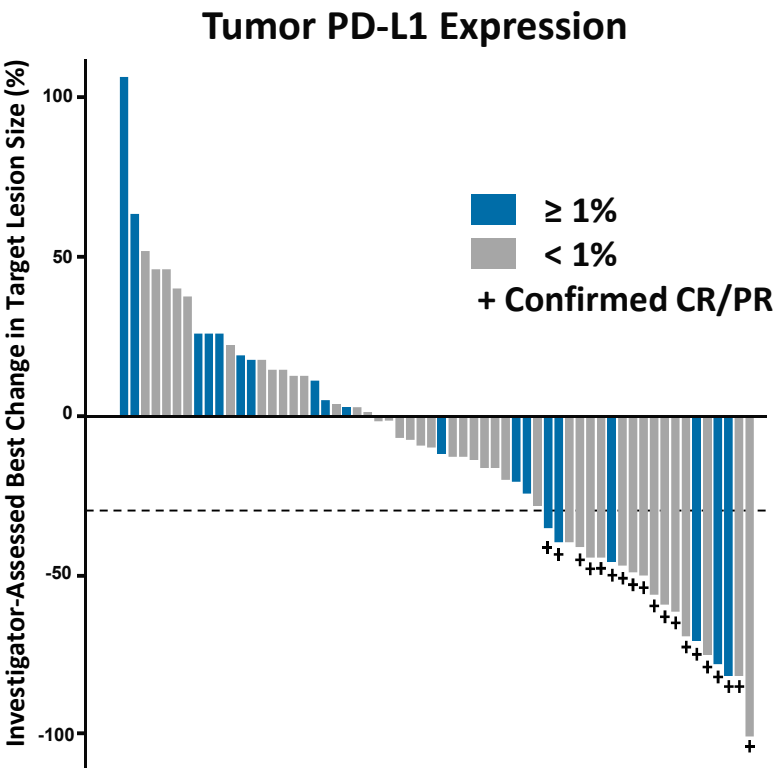


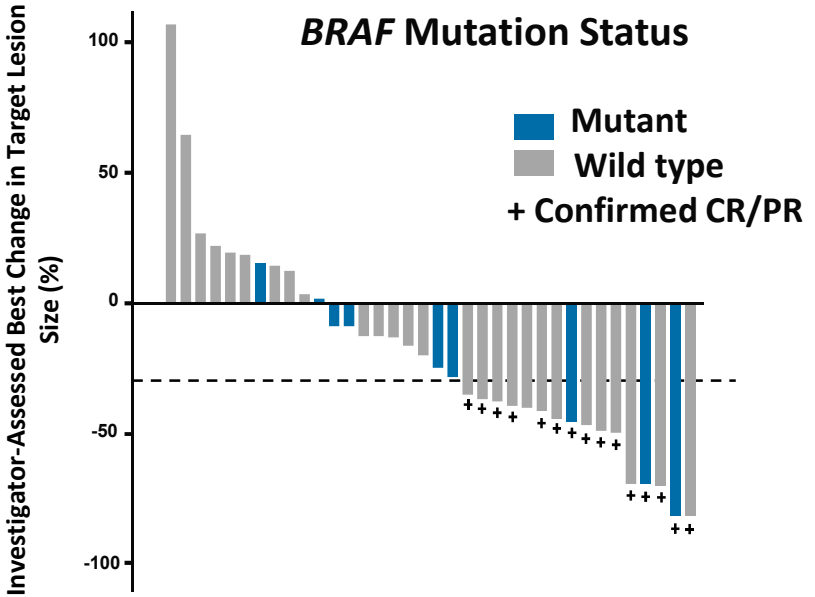


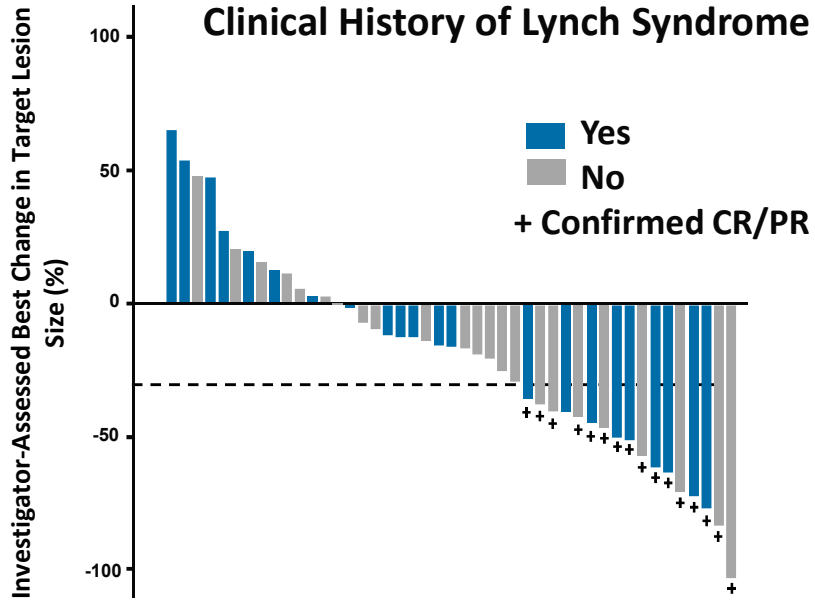


Overman et al. Lancet Oncology 2017

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







Overman et al. Lancet Oncology 2017

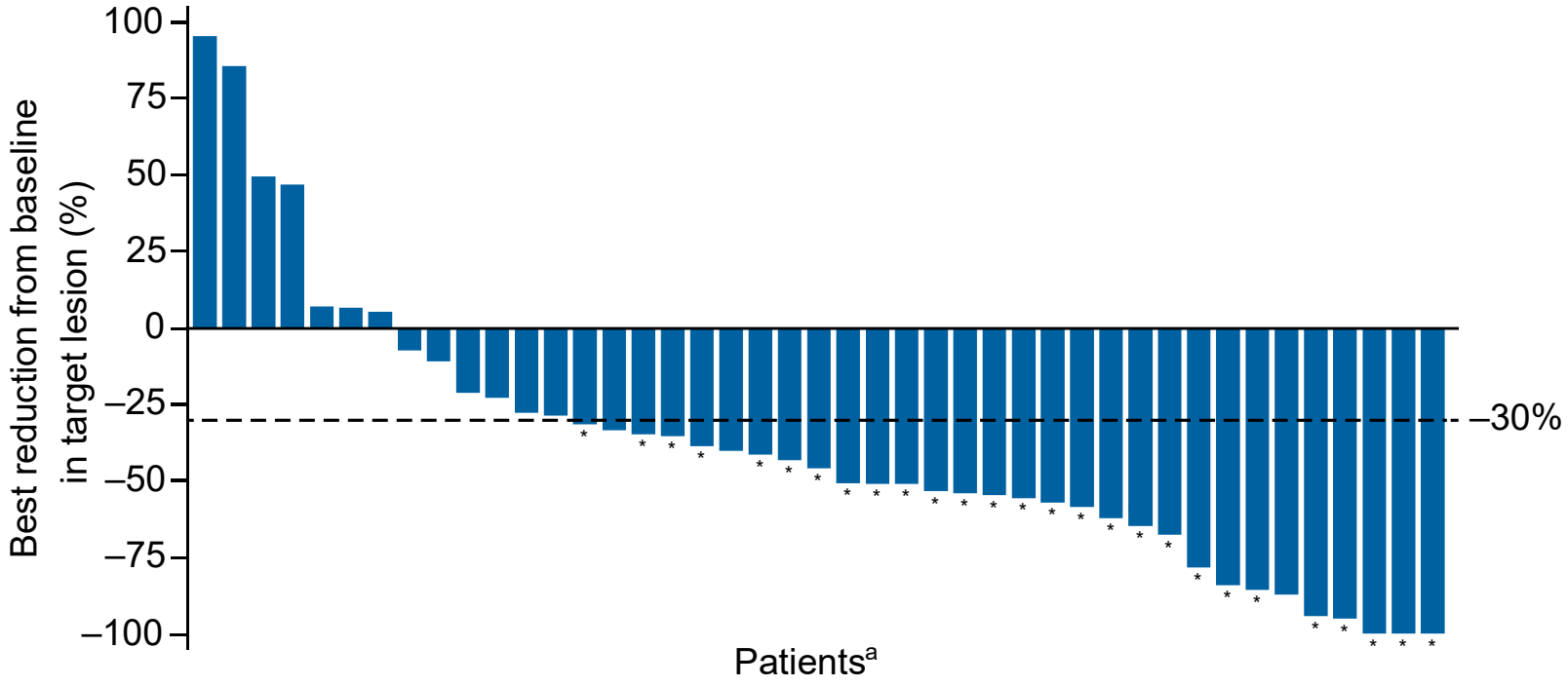
MUNICH 2018 ESMO congress

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 Lonardi[15]

[1]USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [2]University Hospitals Gasthuisberg/Leuven and KU Leuven, Leuven, Belgium; [3]Hospital Universitario Virgen del Rocio, Sevilla, Spain; [4]Westmead Hospital, Sydney, Australia; [5]Institut Jules Bordet, Brussels, Belgium; [6]Candiolo Cancer Institute and University of Torino Medical School, Candiolo, Italy; [7]Hospital Gral Universitario Gregorio Marañon, Madrid, Spain; [8]University Hospital Brussels, Brussels, Belgium; [9]University Hospital of Modena, Modena, Italy; [10]Vanderbilt – Ingram Cancer Center, Nashville, TN, USA; [11]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [12]Lehigh Valley Hospital, Allentown, PA, USA; [13]Bristol-Myers Squibb, Princeton, NJ, USA; [14]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [15]Istituto Oncologico Vento IOV-IRCSS, Padova, Italy

Best Reduction in Target Lesions

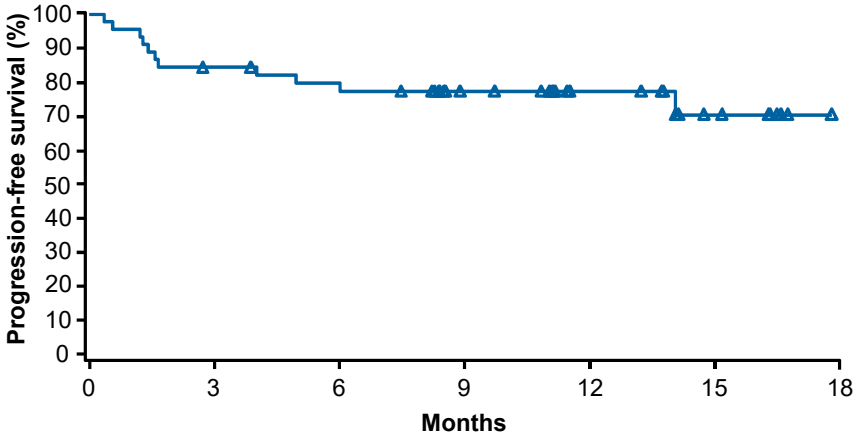


- 84% of patients had a reduction in tumor burden from baseline

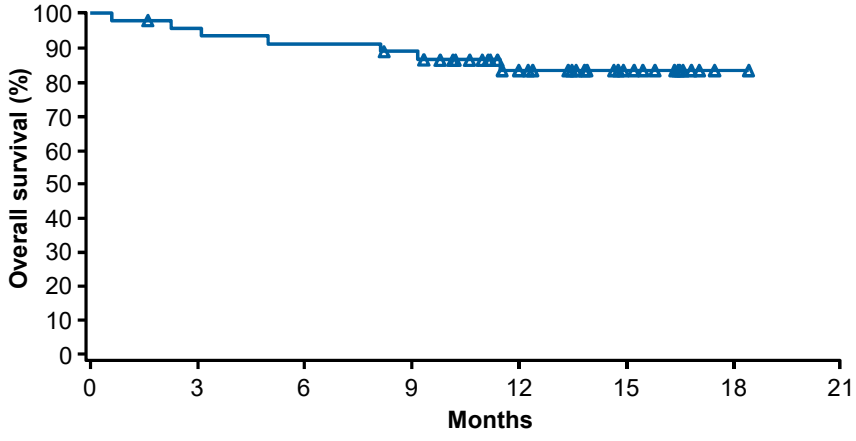
*Confirmed response per investigator assessment
[a]Evaluable patients per investigator assessment

Progression-Free and Overall Survival

PFS[a]	NIVO3 (Q2W) + IPI1 (Q6W) N = 45
Median PFS, months (95% CI)	NR (14.1–NE)
9-mo rate (95% CI), %	77 (62.0–87.2)
12-mo rate (95% CI), %	77 (62.0–87.2)



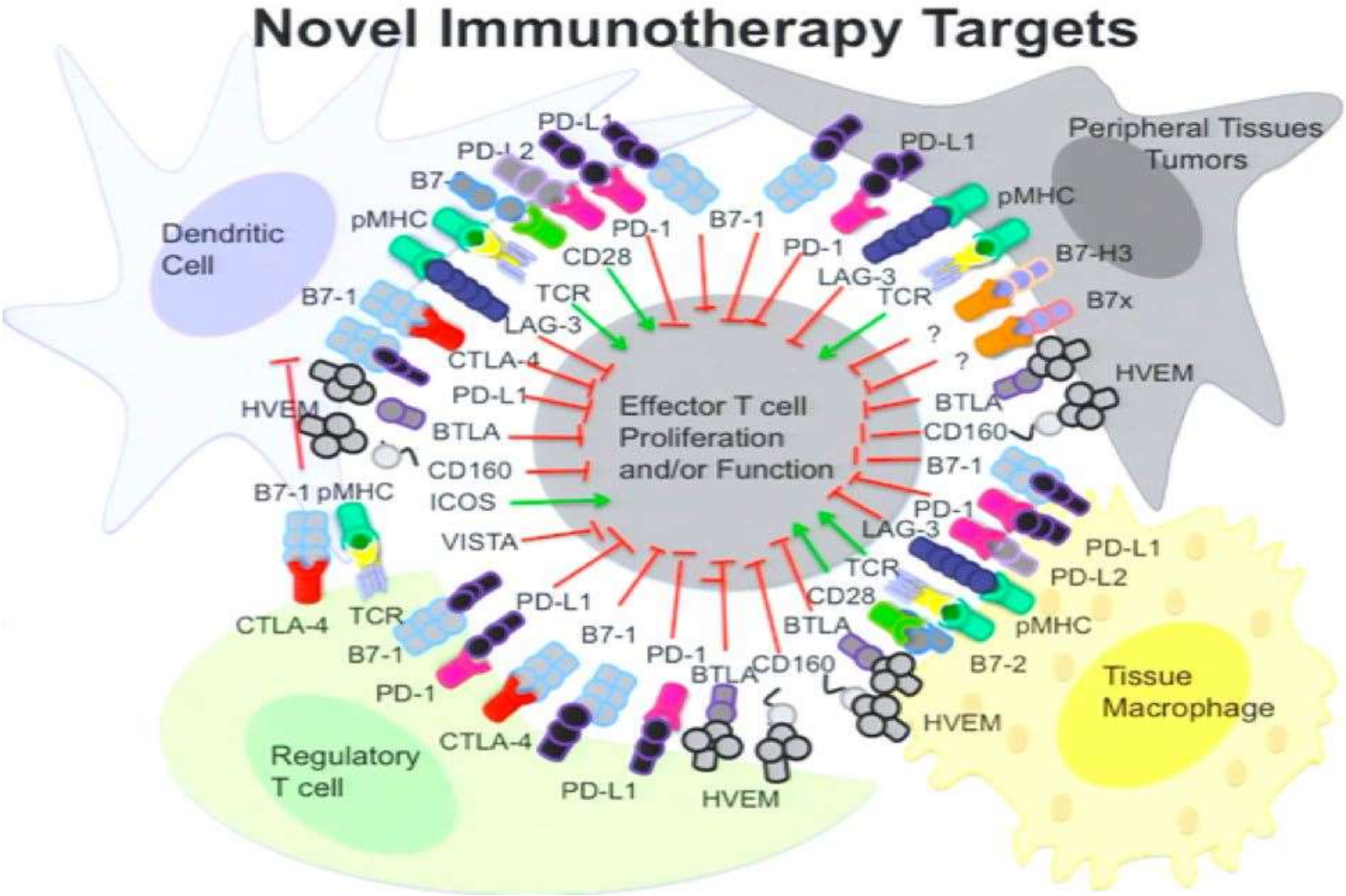
OS[a]	NIVO3 (Q2W) + IPI1 (Q6W) N = 45
Median OS, months (95% CI)	NR (NE)
9-mo rate (95% CI), %	89 (74.9–95.1)
12-mo rate (95% CI), %	83 (67.6–91.7)



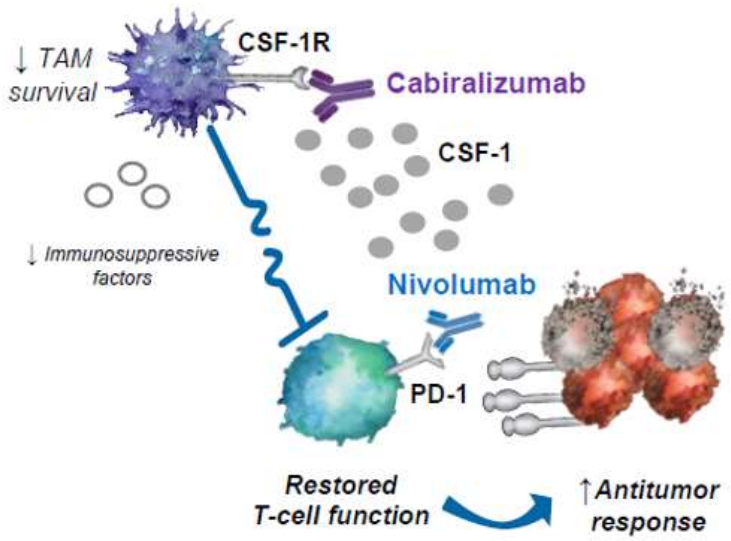
No. at risk							
	45	37	34	24	15	7	7
	45	42	40	38	24	13	1	0

[a]Per investigator assessment.
mo = month; NE = not estimable; NR = not reached

Harnessing the Immune System



BMS/Five Prime FIH Cabiralizumab + Nivolumab Rationale



- TAMs inhibit antitumor T-cell activity in the tumor microenvironment[1,2]
  - In pancreatic and other cancers, high levels of TAMs are associated with poor prognosis[3-5]
  - Signaling through the CSF-1 receptor promotes the maintenance and function of TAMs[1,2]
- Cabiralizumab is a humanized IgG4 mAb that blocks CSF-1R[6] and depletes TAMs
- Preclinical data suggest that CSF-1R inhibition synergizes with PD-1 blockade to enhance antitumor activity[7]

CSF-1 = colony stimulating factor 1; TAM = tumor-associated macrophage; IgG = immunoglobulin G, mAb = monoclonal antibody; PD-1 = programmed death-1

1. Ries CH, et al. *Cancer Cell* 2014;25:846–859. 2. Cannarile M, et al. *J ImmunoTher Cancer* 2017;5:53. 3. Hu H, et al. *Tumour Biol* 2016;37:8657–8664. 4. Kurahara H, et al. *J Surg Res* 2011;167:e211–e219. 5. Goswami KK, et al. *Cell Immunol* 2017;316:1–10. 6. Bellovin D, et al. *Cancer Res* 2017;77 (13 suppl) [abstract 1599]). 7. Zhu Y, et al. *Cancer Res* 2014;74:5057–5069.

Zev A. Wainberg, et al.

High Unmet Medical Need Remains in Later-Line MSS mCRC – Multiple Combinations With Approved Immune Checkpoint Inhibitors Are Currently Being Explored

	Anti–PD-L1s			Anti–PD-1s	
	Atezolizumab	**Durvalumab**	**Avelumab**	**Nivolumab**	**Pembrolizumab**
Other IOs		Treme ± RT		Ipi ± RT Dara	AZA + epacadostat (IDO-1) Navarixin (CXCR2) Maraviroc (CCR5R) Poly-ICLC (TLR-3)
Antiangiogenics	Bevacizumab + cobimetinib (MEK)	Cediranib			
Other Targeted	Cobimetinib (MEK) CEA-TCB (CEA)		eFT508 (MNK1/2) Regorafenib (RTK)	Ipi + cobimetinib (MEK) Binimetinib (MEK) + Ipi Regorafenib (RTK)	
Epigenetic					Romidepsin (HDAC1/2) and/or AZA
Cytotoxic				TAS-102	
Other	Bevacizumab + CT	AZA		Ipi + panitumumab (EGFR)	Bevacizumab + CT

Aza, azacytidine; Dara, daratumumab (anti-CD38); Ipi, ipilimumab (anti–CTLA-4); RT, radiation therapy; Treme, tremelimumab (anti–CTLA-4).

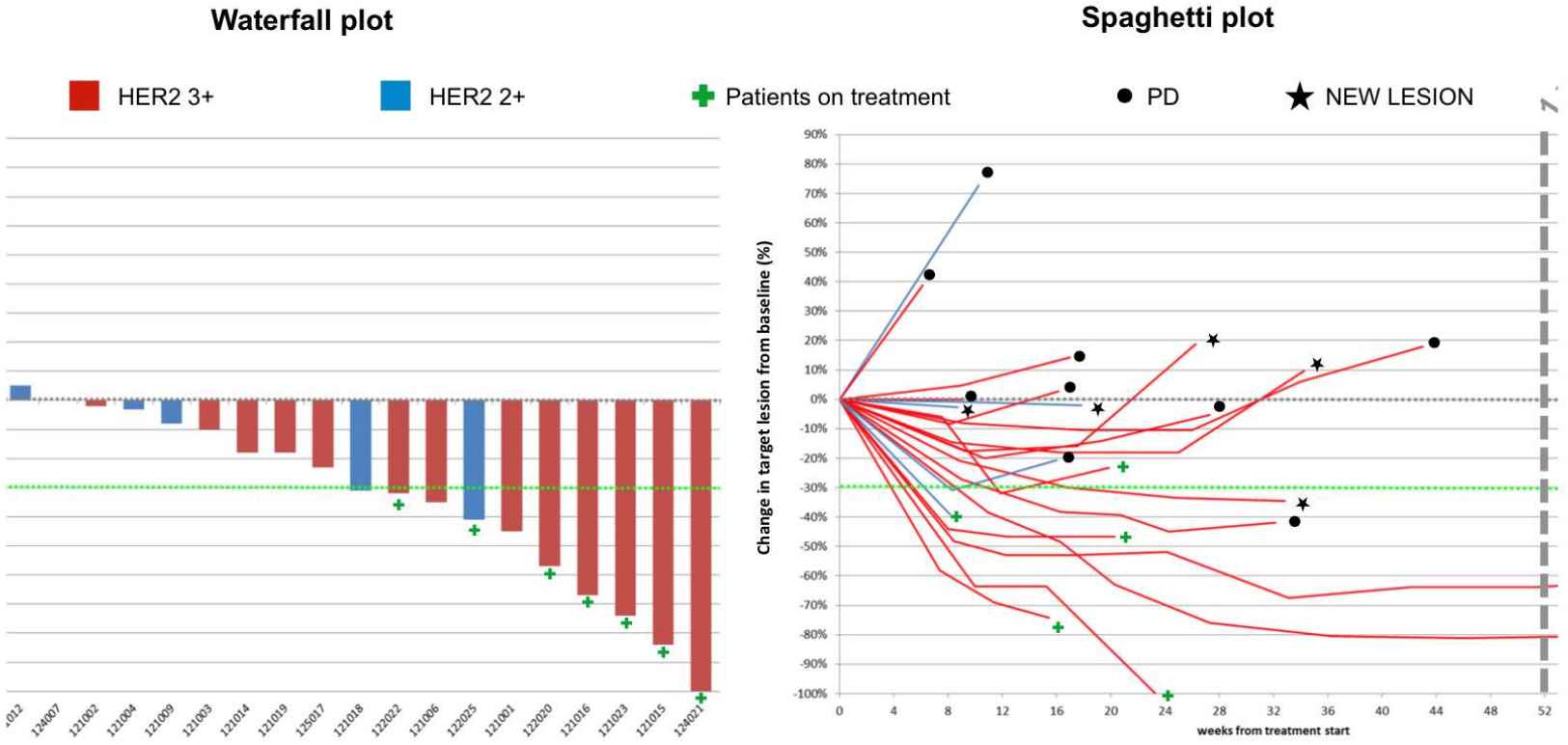
1. NCT02701400. Accessed at https://clinicaltrials.gov/ct2/show/NCT02701400; 2. NCT03104439. Accessed at https://clinicaltrials.gov/ct2/show/NCT03104439; 3. NCT02959437. Accessed at https://clinicaltrials.gov/ct2/show/NCT02959437;
4. NCT03473925. Accessed at https://clinicaltrials.gov/ct2/show/NCT03473925; 5. NCT03274804. Accessed at https://clinicaltrials.gov/ct2/show/NCT03274804; 6. NCT02834052. Accessed at https://clinicaltrials.gov/ct2/show/NCT02834052;
7. NCT02876224. Accessed at https://clinicaltrials.gov/ct2/show/NCT02876224; 8. NCT02484404. Accessed at https://clinicaltrials.gov/ct2/show/NCT02484404; 9. NCT02650713. Accessed at https://clinicaltrials.gov/ct2/show/NCT02650713;
11. NCT03258398. Accessed at https://clinicaltrials.gov/ct2/show/NCT03258398; 12. NCT03475953. Accessed at https://clinicaltrials.gov/ct2/show/NCT03475953; 13. NCT02060188. Accessed at https://clinicaltrials.gov/ct2/show/NCT02060188;
14. NCT03271047. Accessed at https://clinicaltrials.gov/ct2/show/NCT03271047; 15. NCT02512172. Accessed at https://clinicaltrials.gov/ct2/show/NCT02512172; 16. NCT02860546. Accessed at https://clinicaltrials.gov/ct2/show/NCT02860546;
17. NCT02982694. Accessed at https://clinicaltrials.gov/ct2/show/NCT02982694; 18. NCT02982694. Accessed at https://clinicaltrials.gov/ct2/show/NCT02982694; 19. NCT03442569. Accessed at https://clinicaltrials.gov/ct2/show/NCT03442569;
20. NCT03396926. Accessed at https://clinicaltrials.gov/ct2/show/NCT03396926; 21. NCT03406871. Accessed at https://clinicaltrials.gov/ct2/show/NCT03406871; 22. NCT02811497. Accessed at https://clinicaltrials.gov/ct2/show/NCT02811497.

HER2 Overexpression
HER2/neu 3+ (2+)

HERACLES Trial

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

Responses by HER2 IHC Score



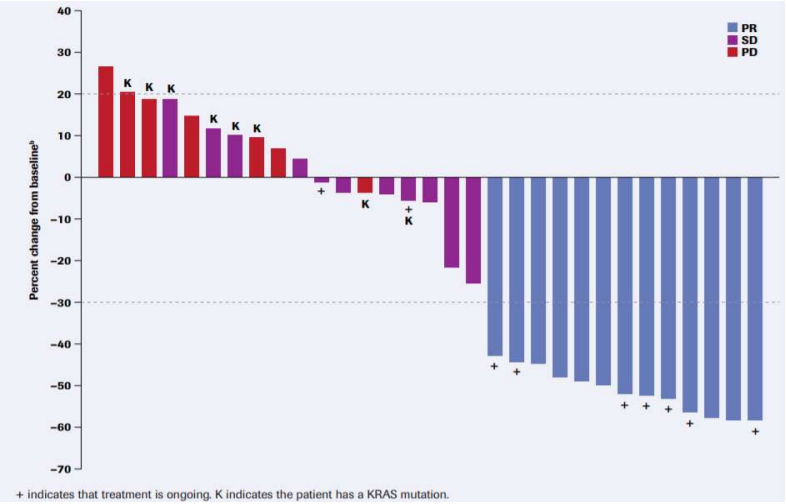
*3 patients are not shown: 122026 (IHC 2+), not assessed yet; 121011 (IHC 3+) and 121013 (IHC 3+) early clinical PD.

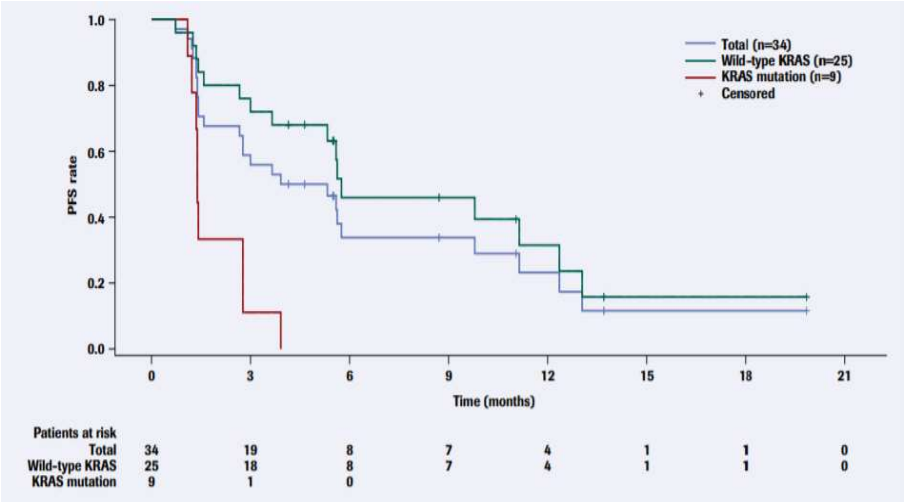
849 patients screened, 46 patients (5.4%) HER2+ (2+/3+); 23 patients evaluable for response
ORR 35%, DCR 78%

Siena, et al. ASCO 2015

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

N = 34 patients

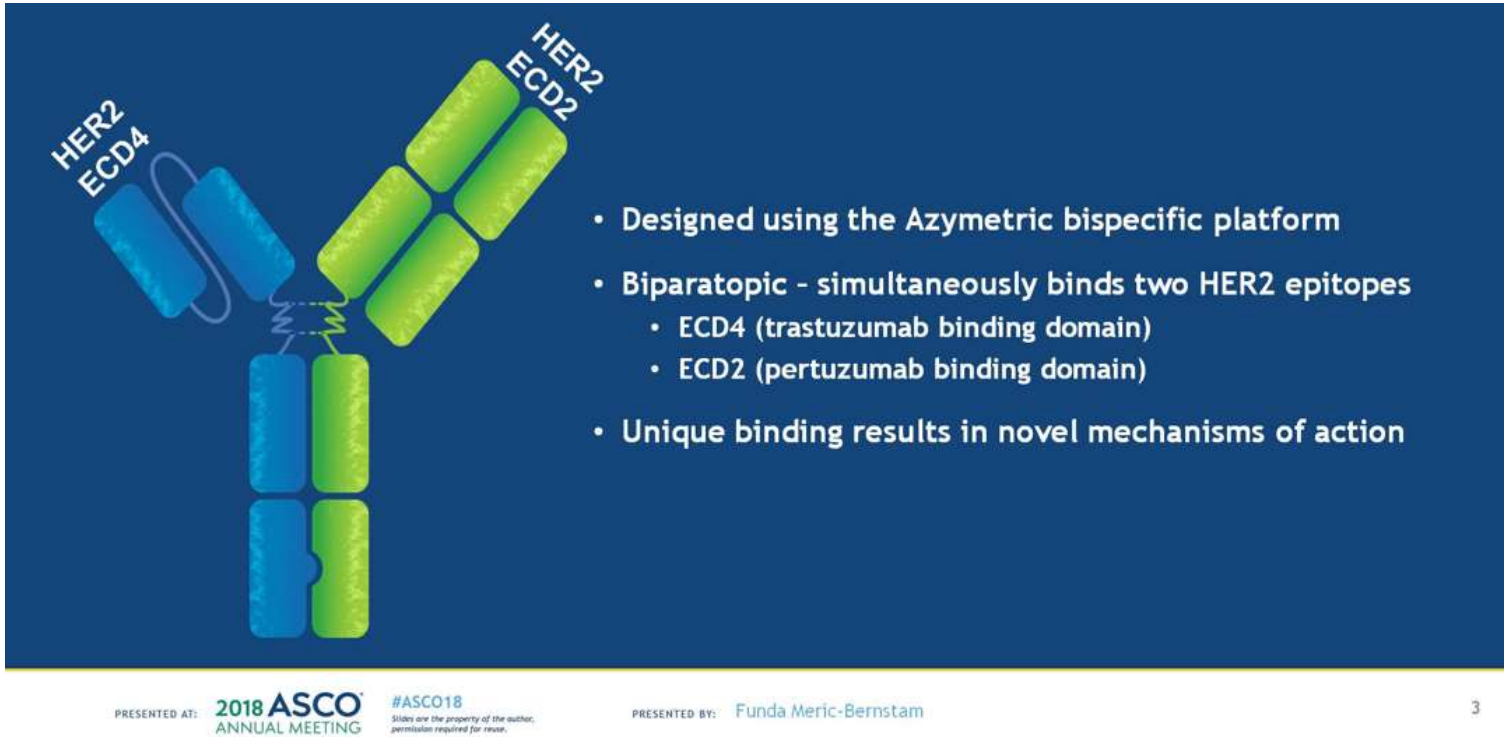




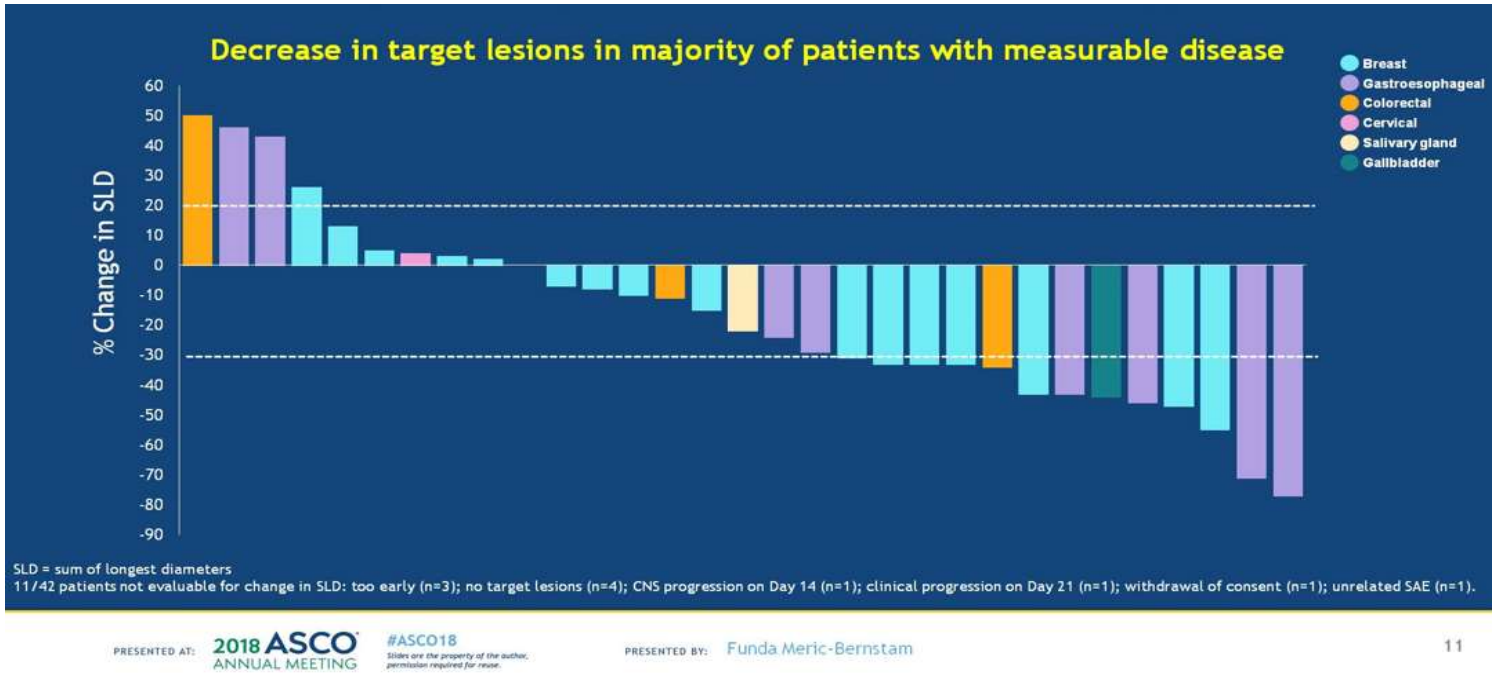
Clinical characteristic	ORR (n=34) n (% [95% CI])	CBR (n=34) n (% [95% CI])	Median duration of clinical benefit (n=17) Months (95% CI)	Median PFS (n=34) Months (95% CI)	Median OS (n=34) Months (95% CI)
All patients (n=34)	13 (38.2 [22.2-56.4])	17 (50.0 [32.4-67.6])	10.3 (4.3-NE)	4.6 (1.6-9.8)	10.3 (7.2-22.1)
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)

Hurwitz, H. GI ASCO 2018

ZW25: Azymetric™ Bispecific HER2-Targeted Antibody

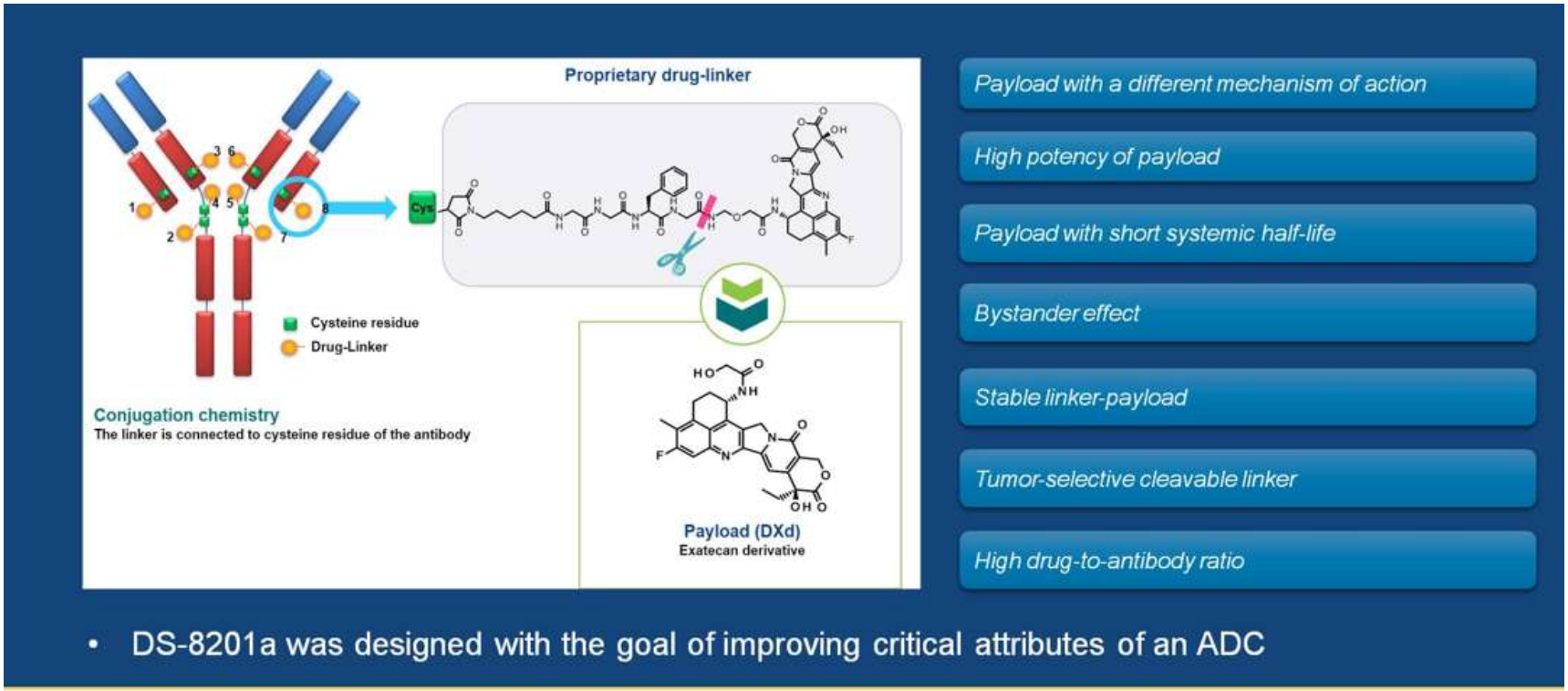


Change in Target Lesions Across Cancer Types



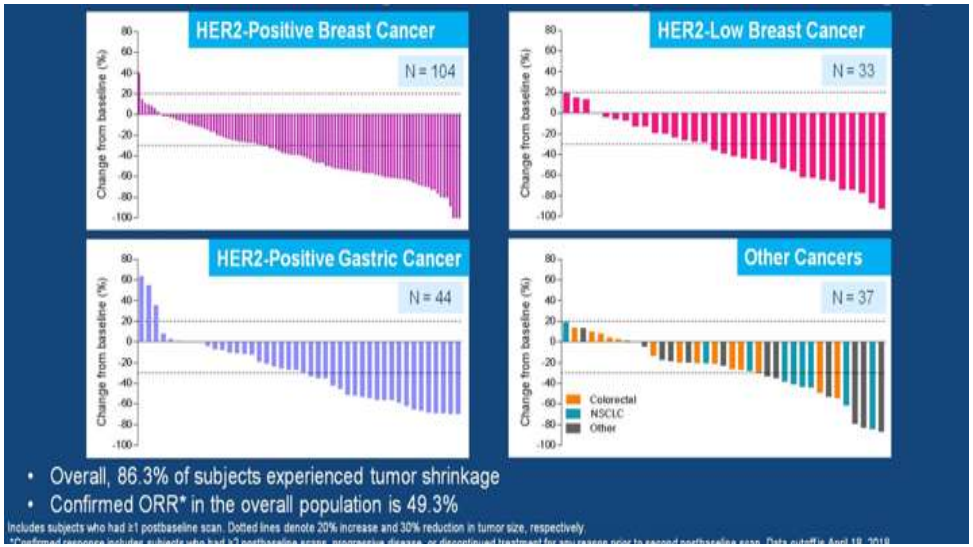
A first in human study evaluating single agent activity in heavily pretreated HER2-expressing cancers is ongoing (NCT02892123).

DS-8201a Structure and Mechanism of Action

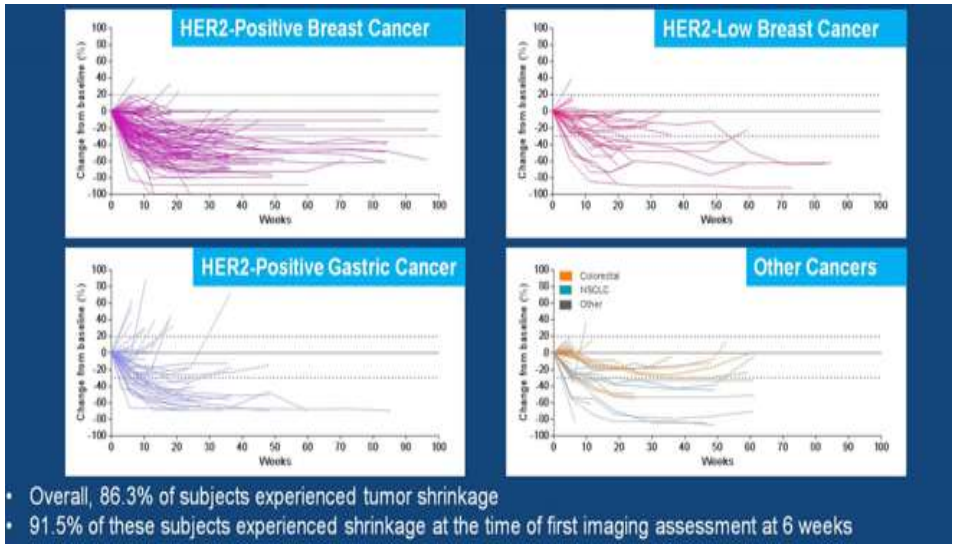


Anti-Tumor Activity of DS-8201a

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

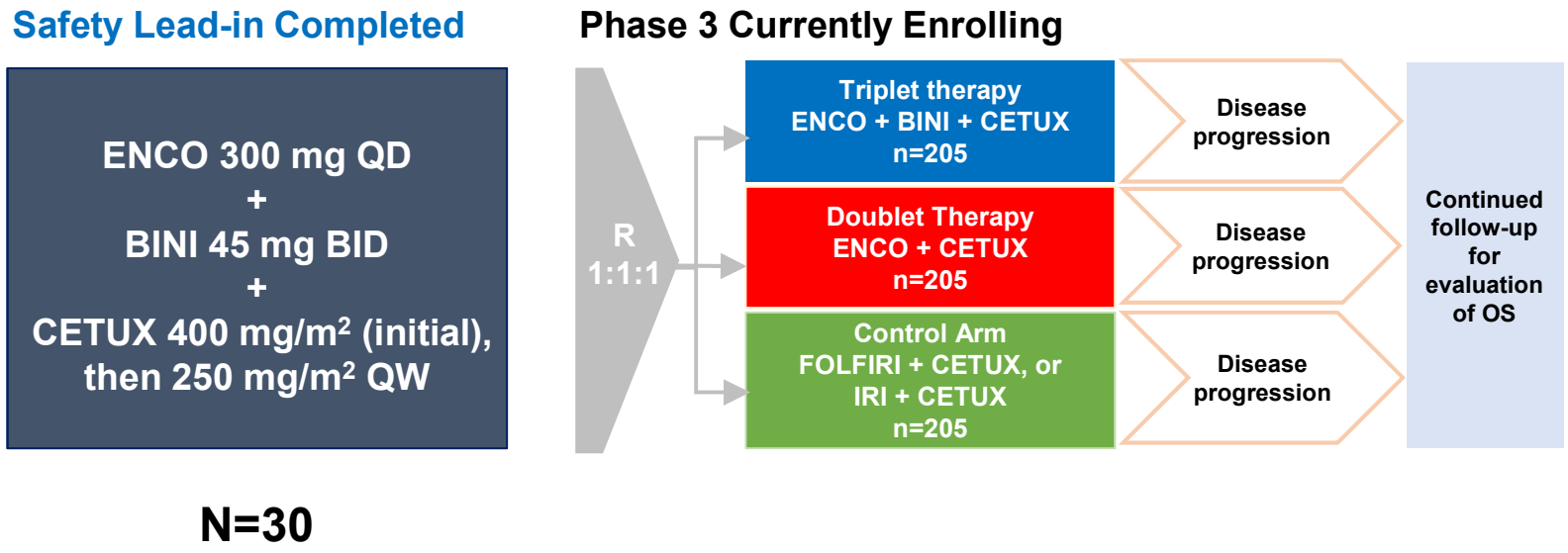


Tumor Shrinkage Over Time by Tumor Type (5.4 or 6.4 mg/kg)



Braf mutations

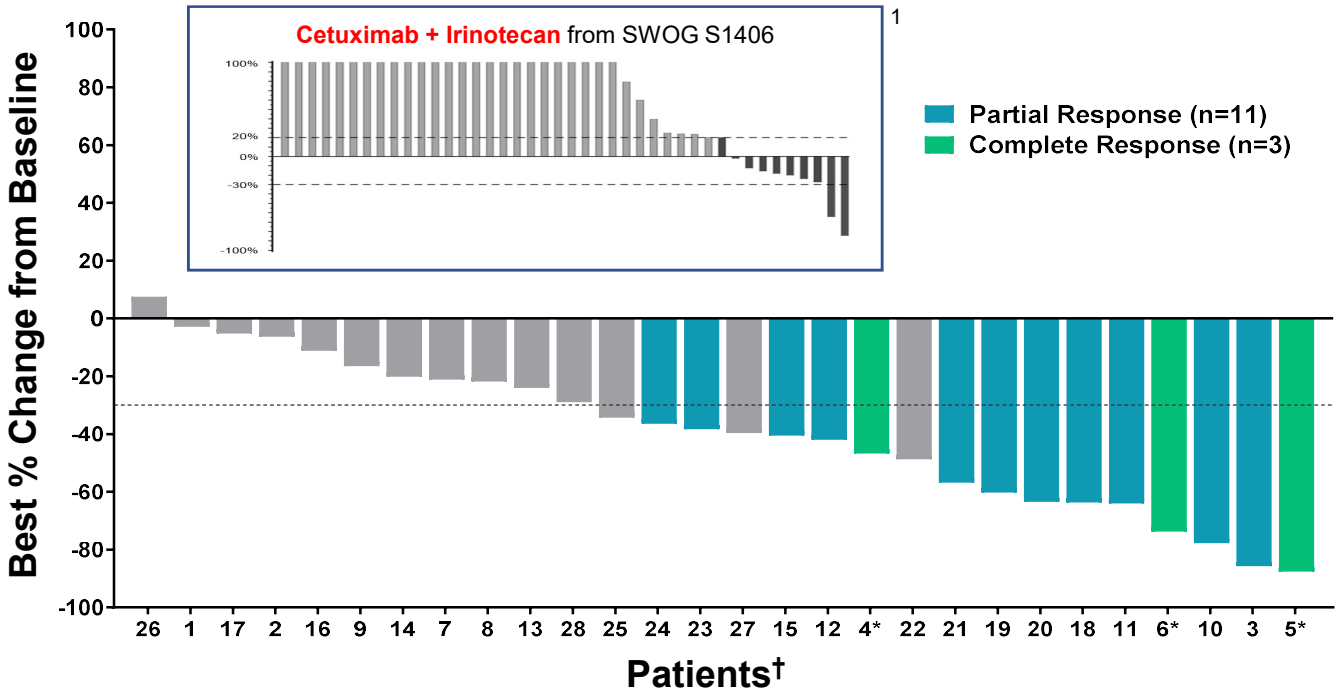
BEACON CRC Phase 3 Study Design[1]



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

Van Cutsem et al., ESMO GI 2018

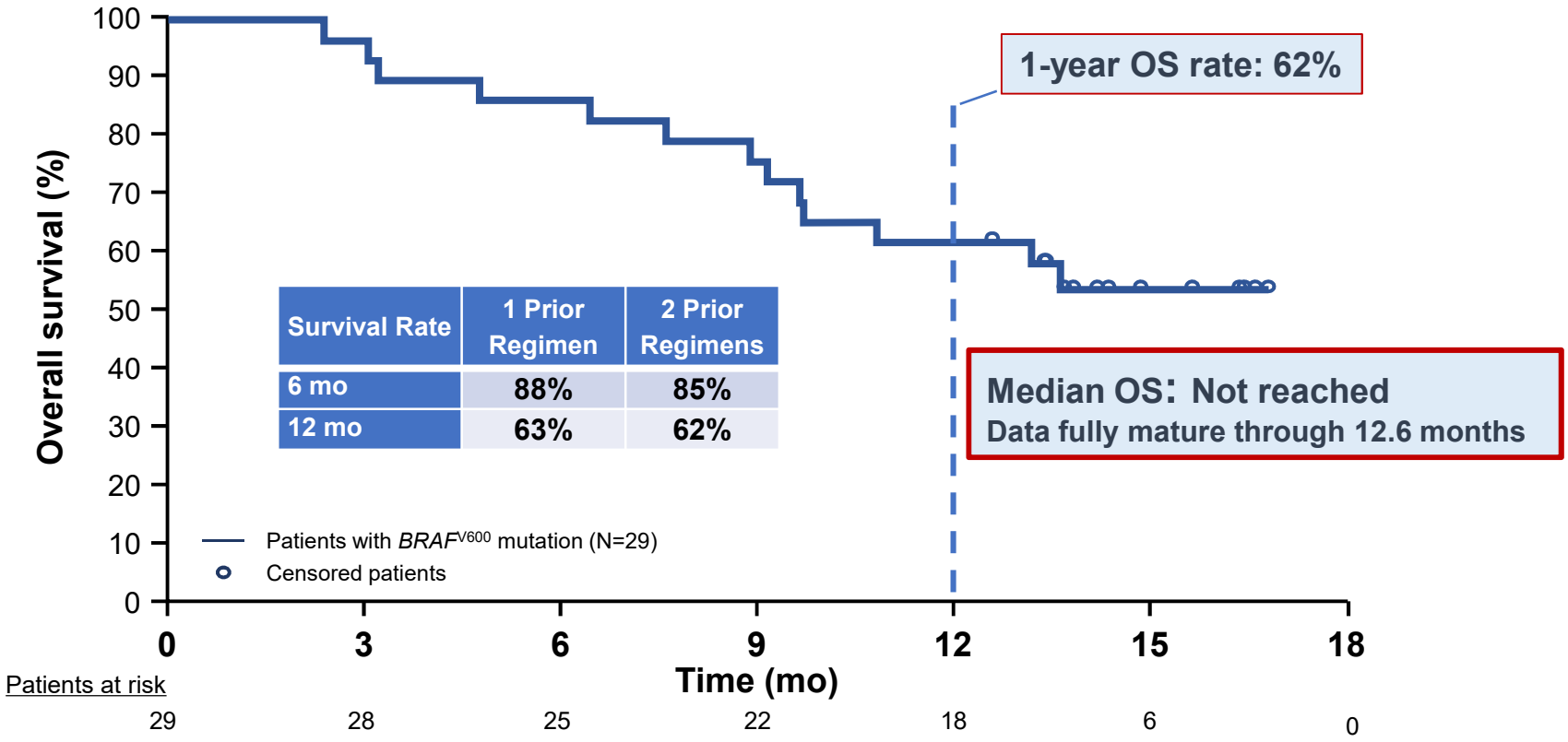
Best Percentage Change in Tumor Measurements from Baseline



*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

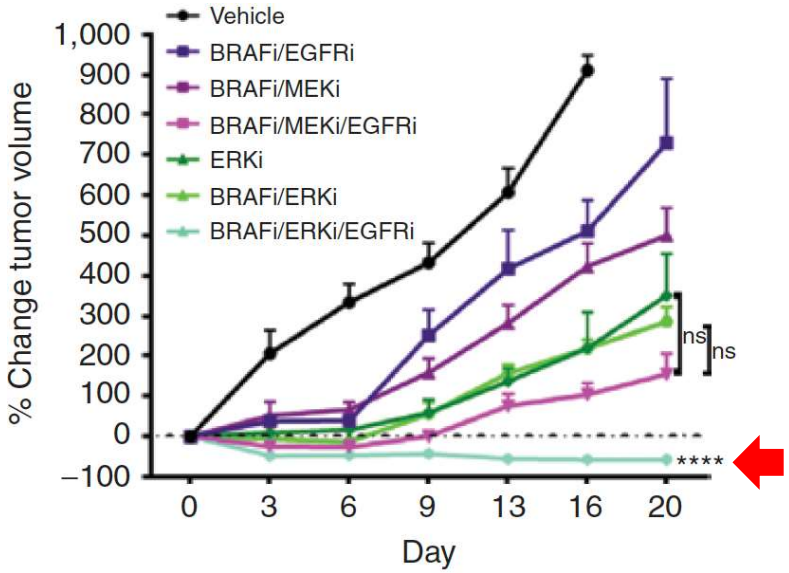
BEACON SLI: Overall Survival

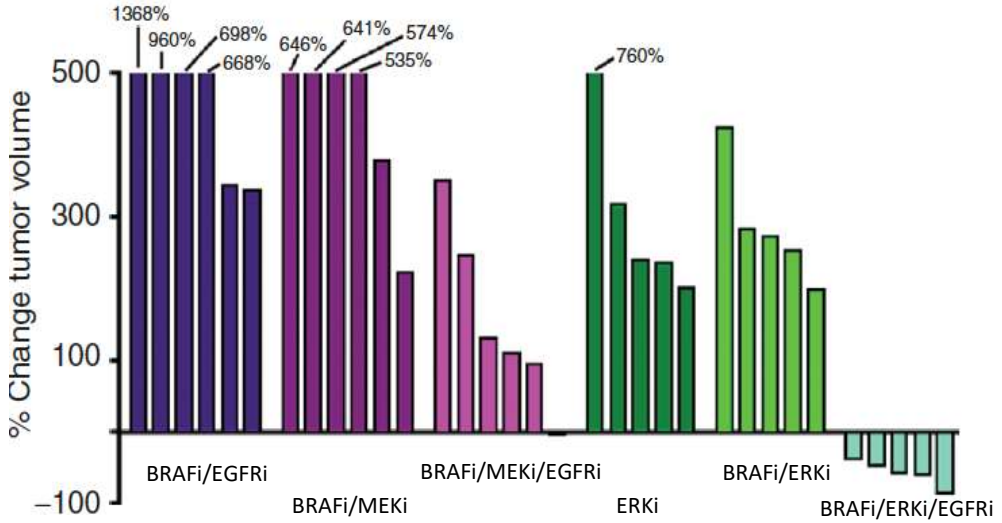


Van Cutsem et al., ESMO GI 2018

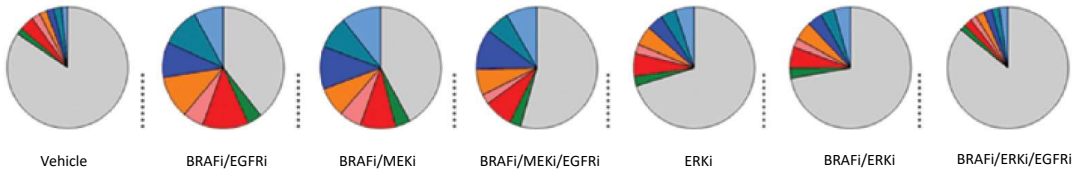
Upfront therapy to suppress resistant clones

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



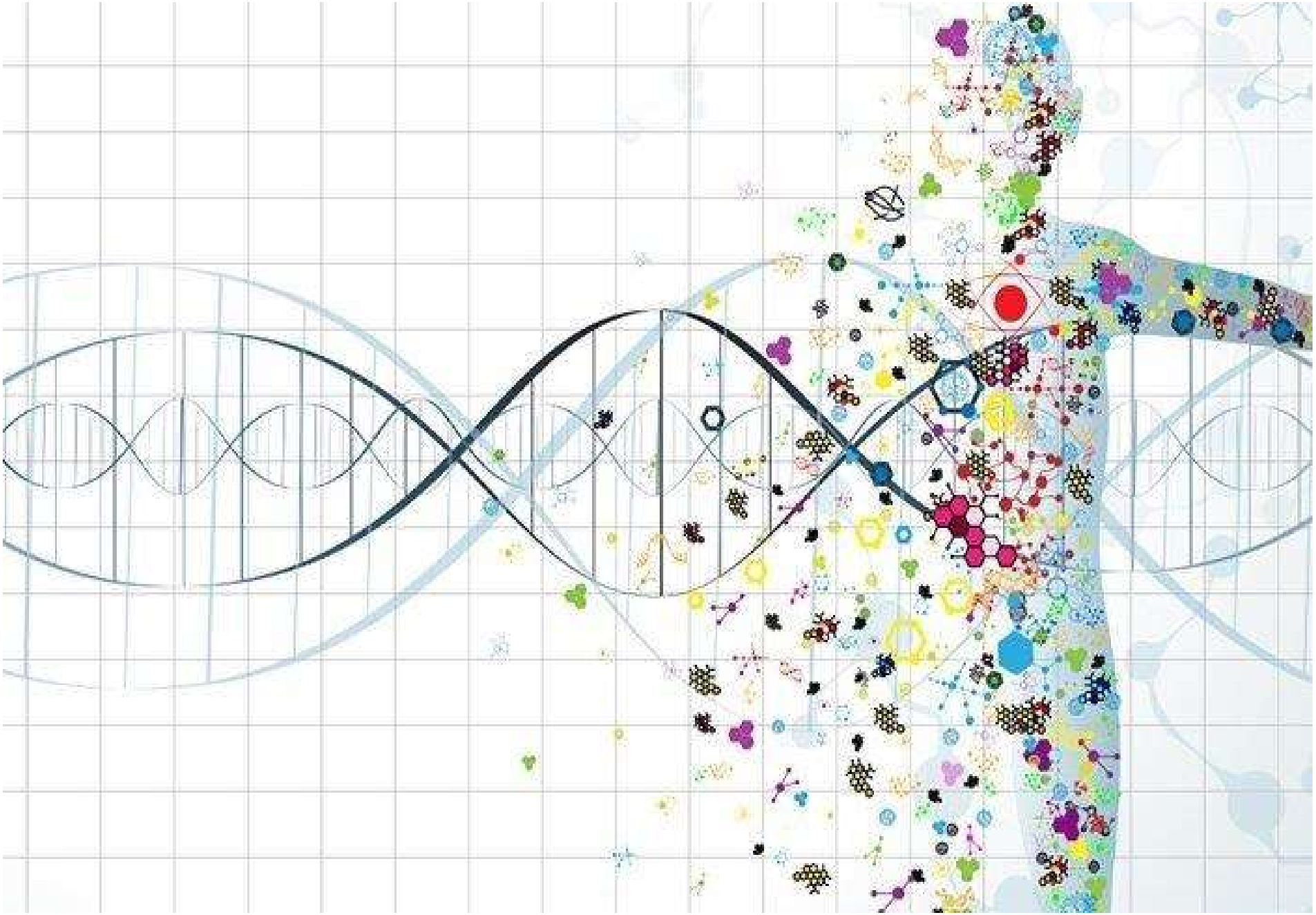


Clonal abundance by 21 days



MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

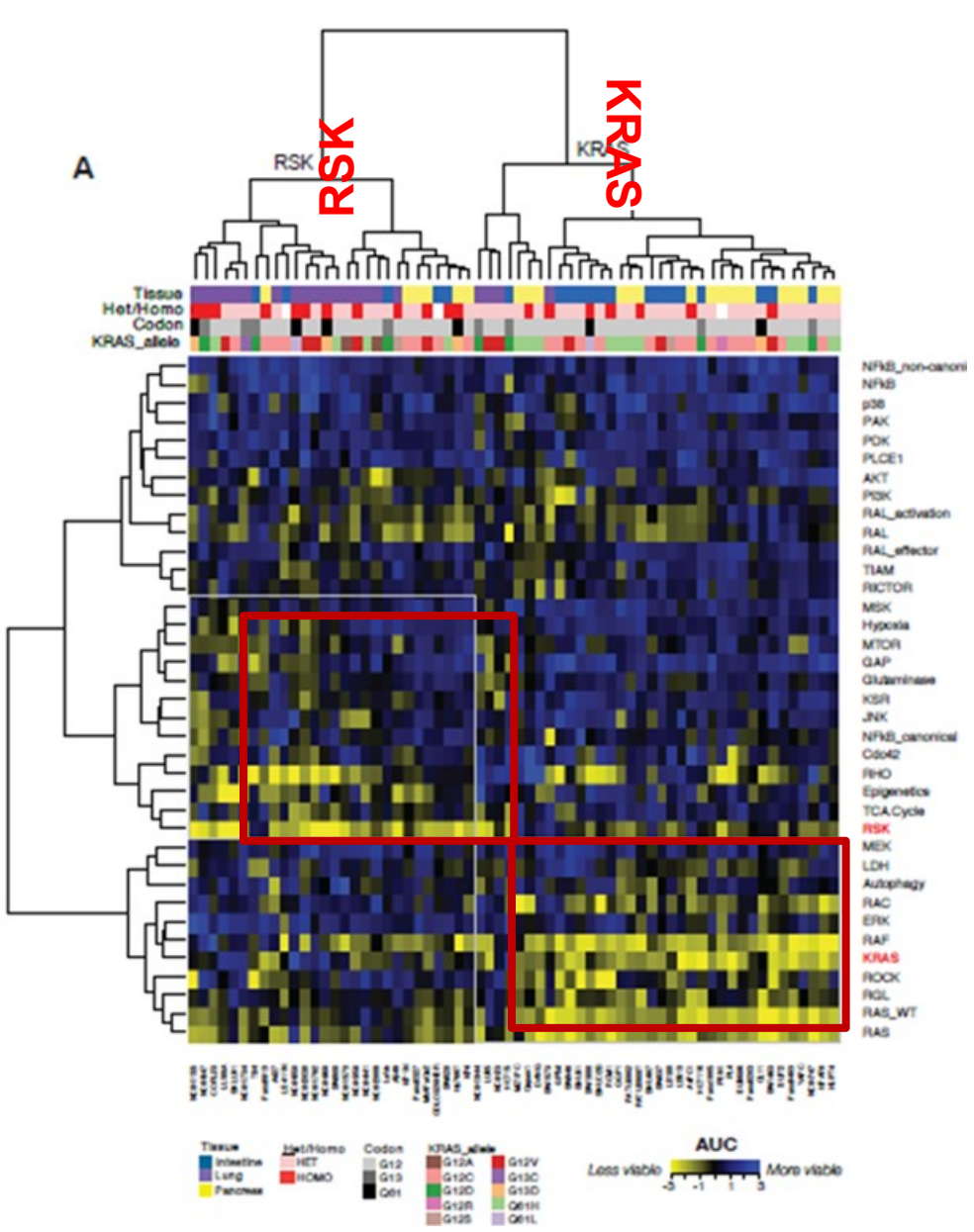
Hazar-Rethinam et al, Cancer Discovery 2018

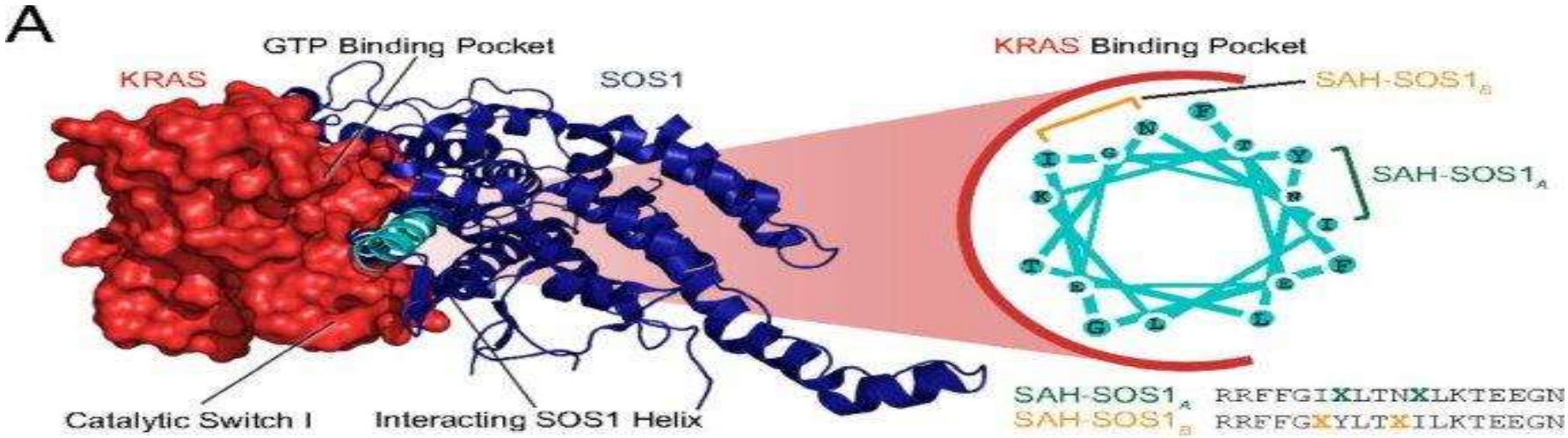


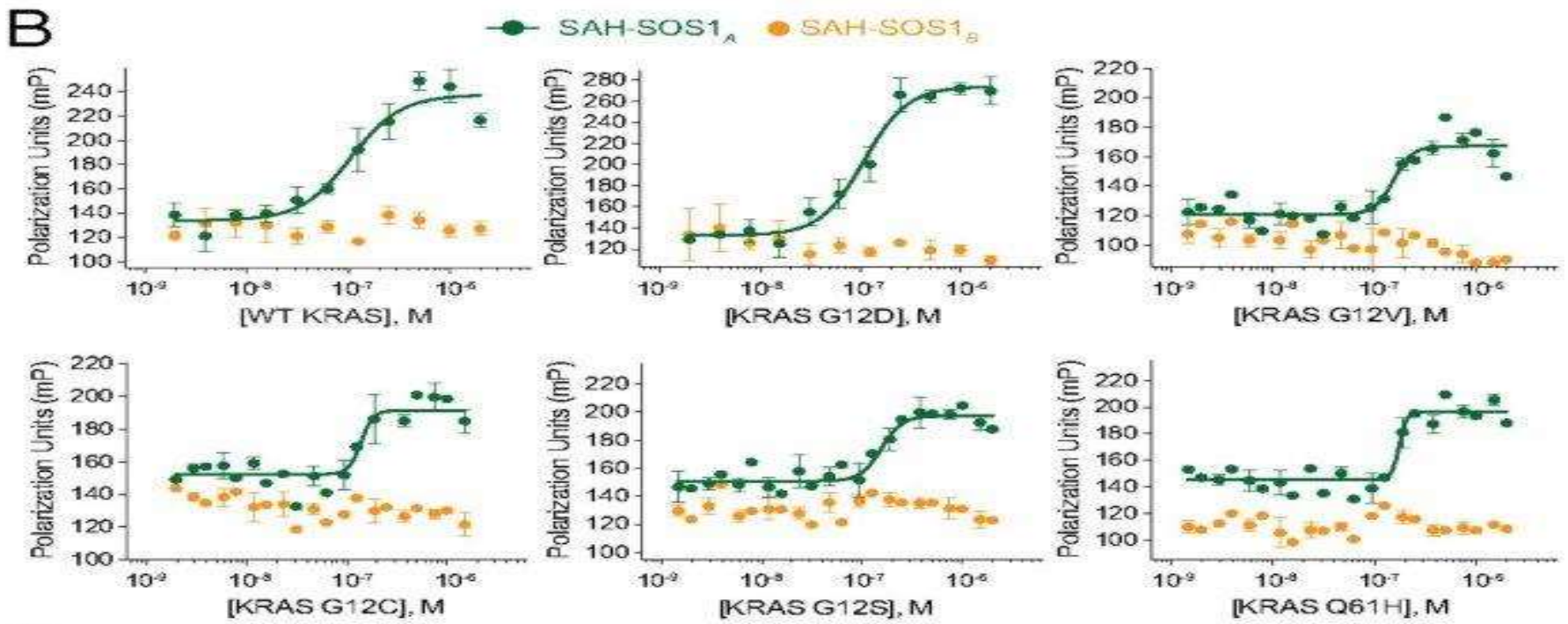
Ras and effector dependencies

- 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





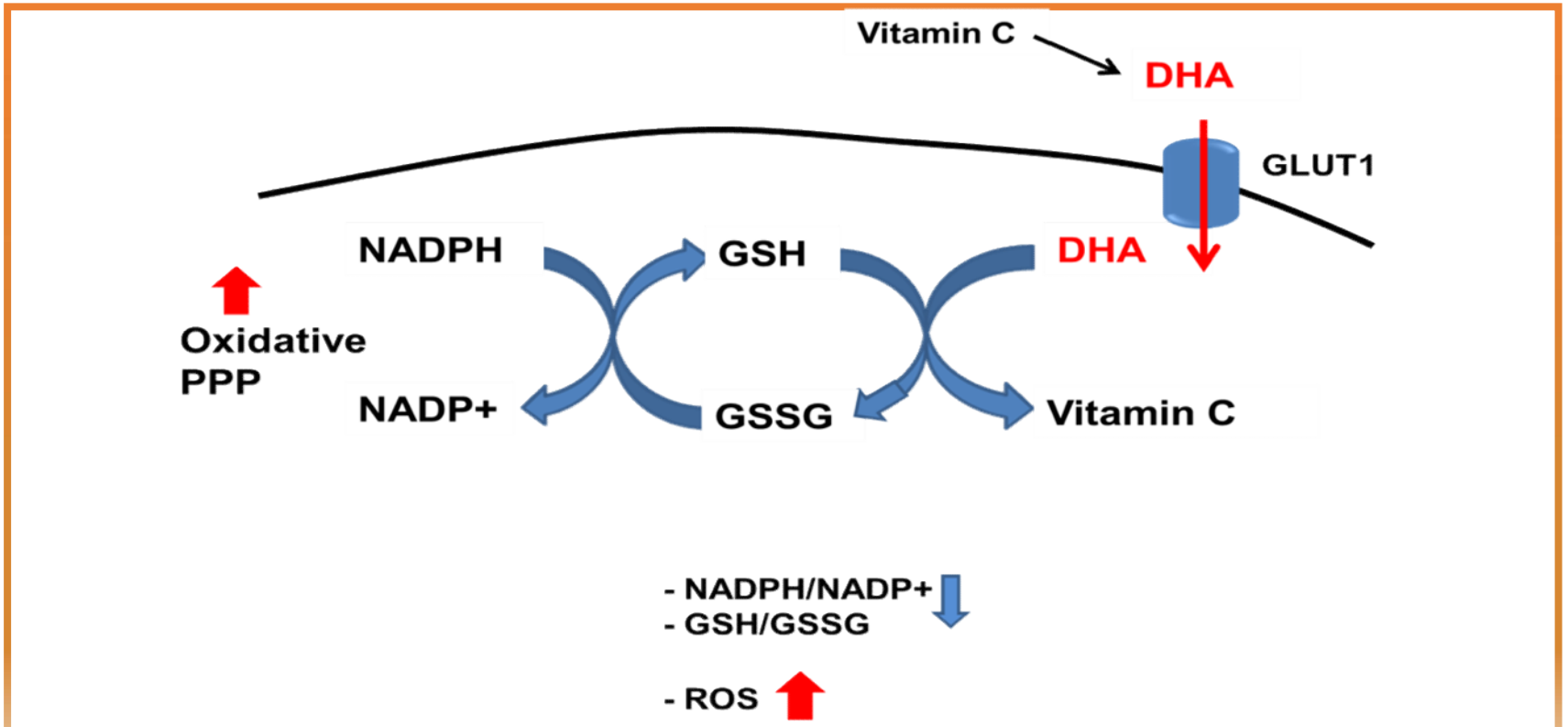


C

EC_{50}, nM	WT	G12D	G12V	G12C	G12S	Q61H
$SAH\text{-}SOS1_A$	106 ± 16	109 ± 13	154 ± 15	140 ± 17	155 ± 15	175 ± 22
$SAH\text{-}SOS1_B$	> 4000	> 4000	> 4000	> 4000	> 4000	> 4000

KRAS or BRAF mutant CRC cells rewire glucose metabolism by upregulating GLUT1 expression

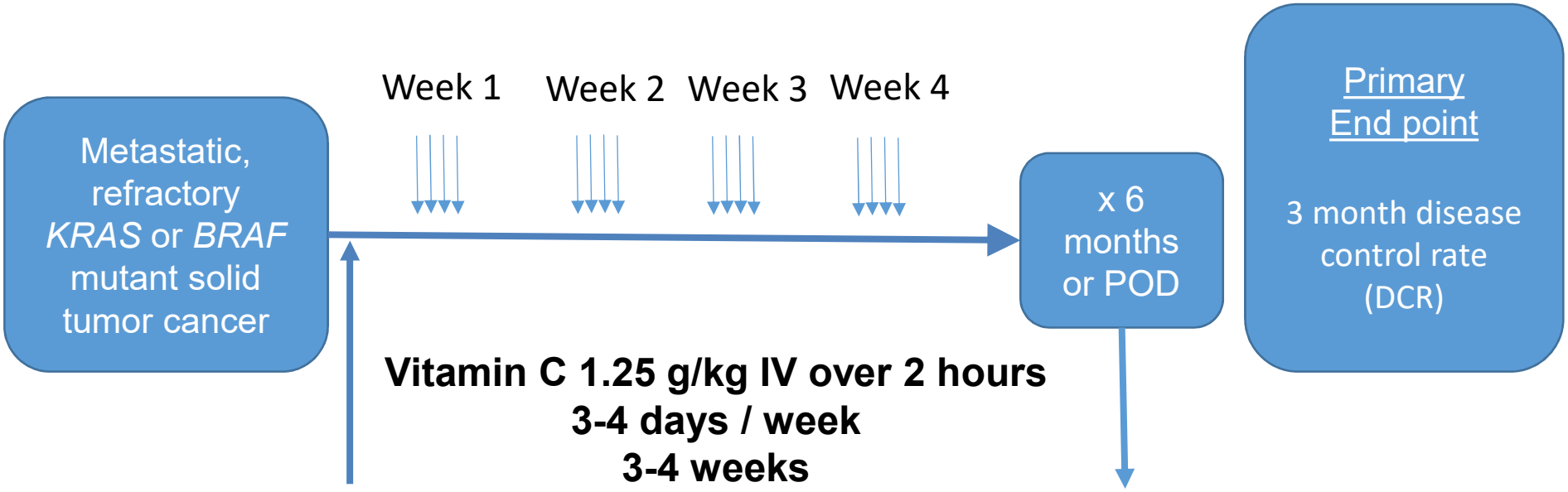
We developed a strategy for targeting KRAS or BRAF-mutant cancers by exploiting the selective high expression of GLUT1 and the high levels of reactive oxygen species (ROS) produced in these cells with vitamin C



Our preclinical studies have shown that ascorbate selectively kills KRAS and BRAF mutant CRC cells in culture and genetically engineered mouse models

SUB AIM 1.1: Clinical and translational evaluation of high dose Ascorbate in KRAS/BRAF mutant tumors

Phase II Pilot Study: Cohort B

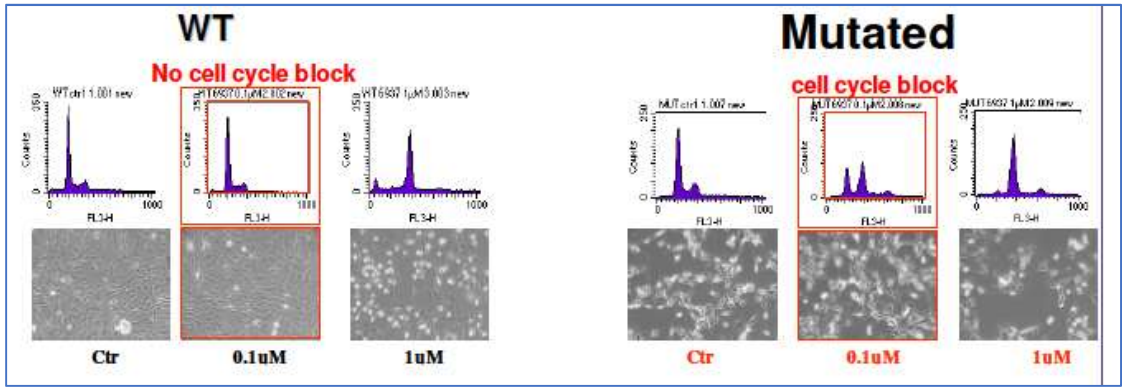


Biostats: 30% 3-month DCR vs. < 10%
90% power, one-sided alpha 0.1 requires 25 evaluable patients

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

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

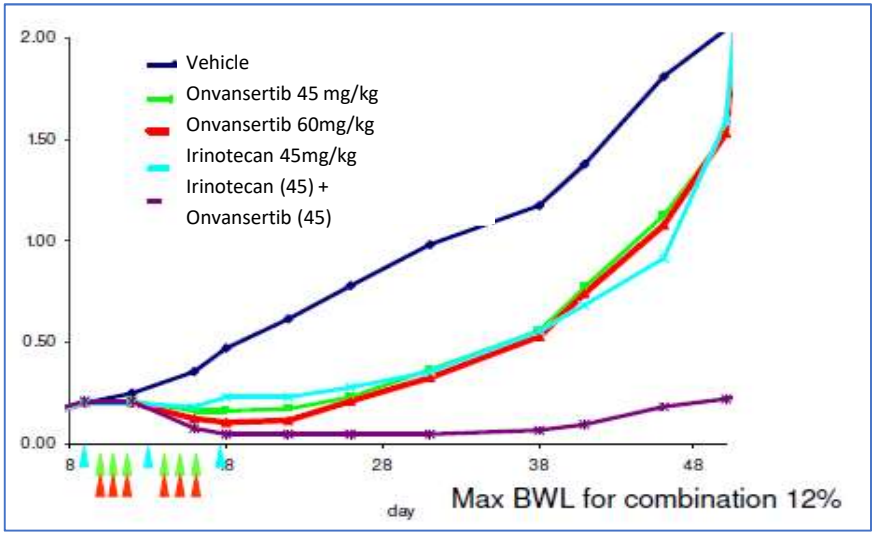
- In a genome-wide RNAi screen aimed at the identification of synthetic lethal interactions with the RAS oncogene PLK1 was identified
- KRAS mutated NIH3T3 cells showed higher sensitivity to PCM-075 compare to WT KRAS cells



Nerviano Medical Sciences (NMS)

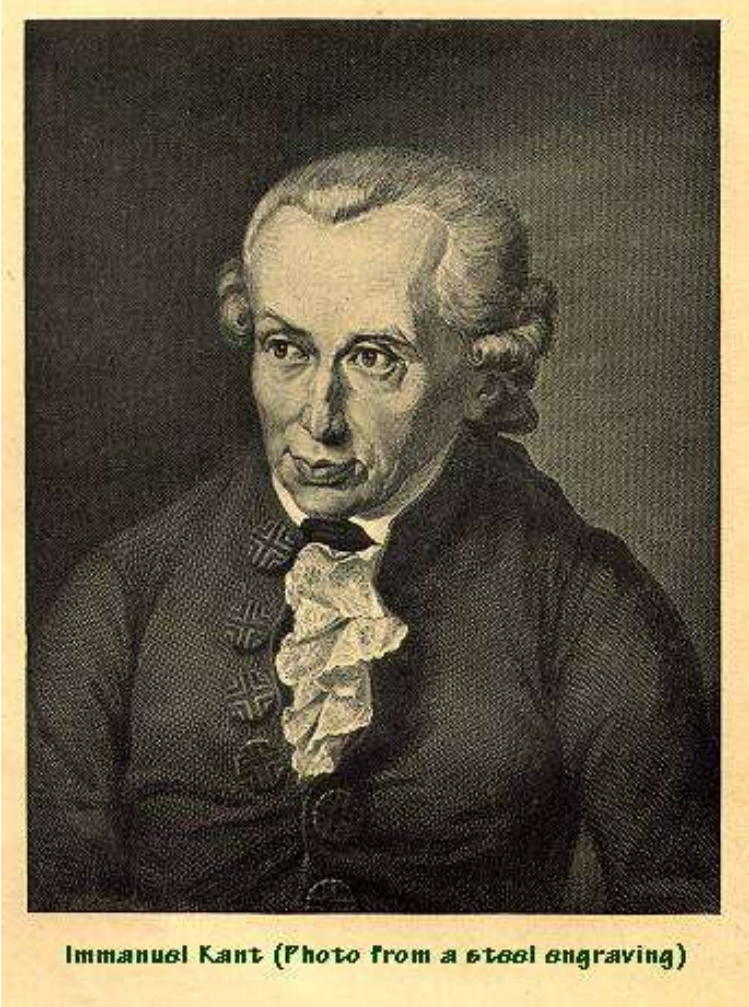
PCM-075 in Combination with Anticancer Agents in CRC

- **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



Our Goal: Right Treatment Right Time

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



Immanuel Kant (Photo from a steel engraving)

The one who knows more, may decide better