13th Belgian Symposium on the Integration of Molecular Biology Advances into Oncology Clinical Practice

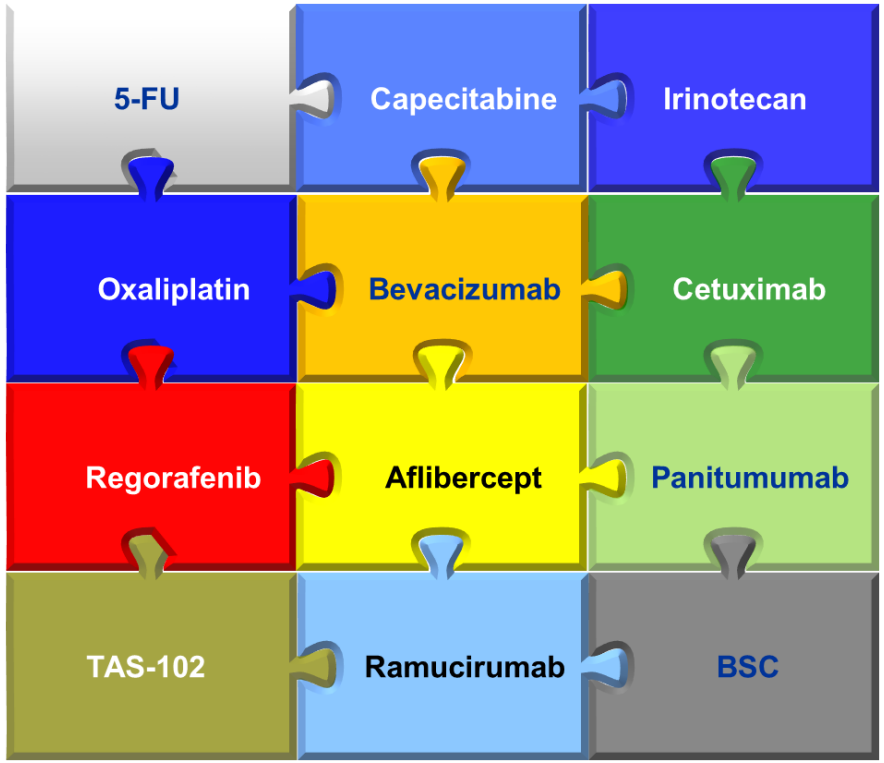
CHALLENGES IN SOLID TUMORS

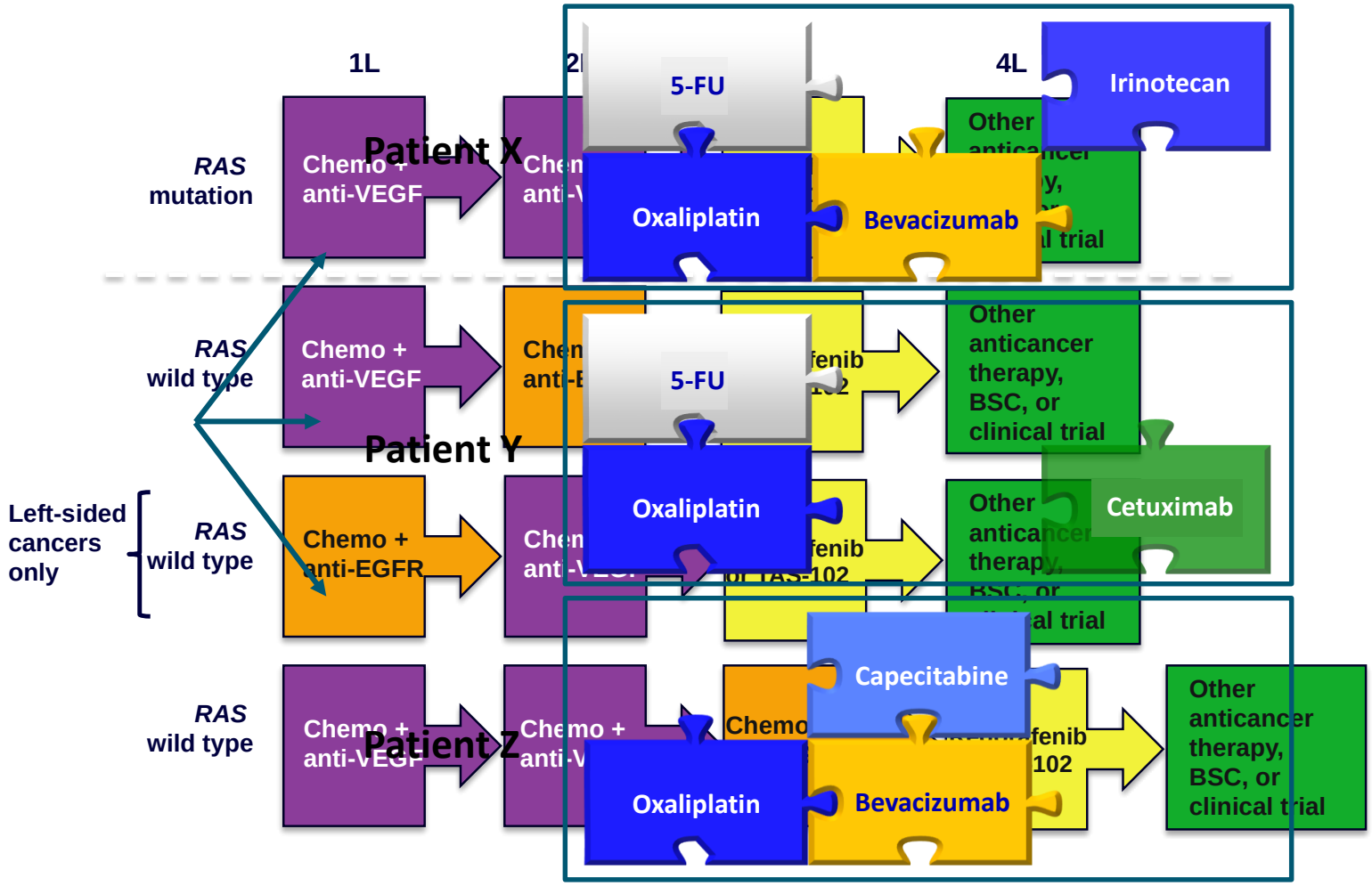
Contemporary Management of Metastatic Colorectal Cancer:

How to emerge from the status quo?

Hendlisz Alain, MD PhD
Institut Jules Bordet
Université Libre de Bruxelles

Metastatic CRC: Do We Really Personalize Therapy?





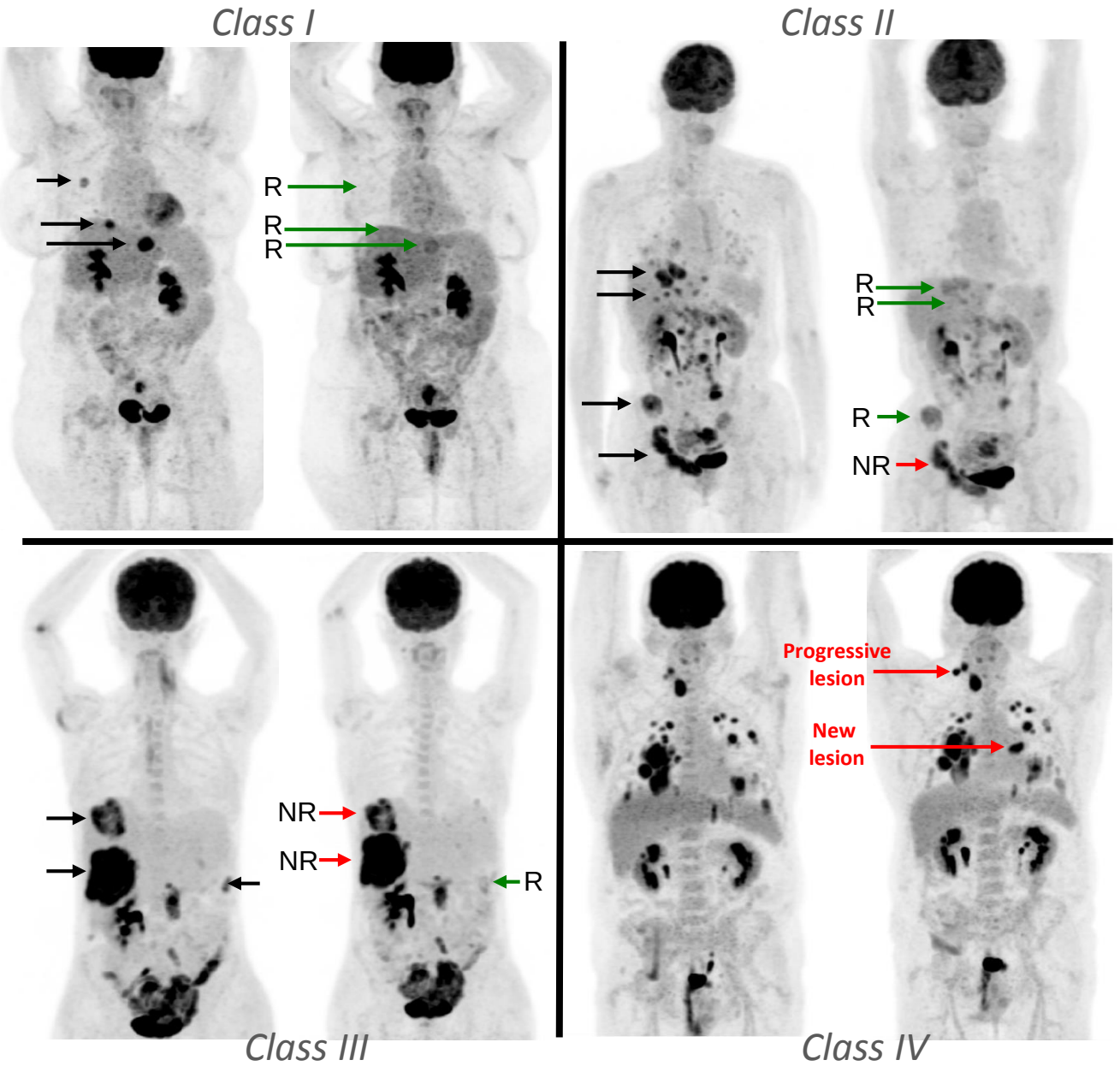
Van Cutsem et al. Ann Oncol 2016

What You See Is Not Always What You Get

BECAUSE (?)

What You Don’t See is More Important Than What You See

HETEROGENEITY in RESPONSE to THERAPY in mCRC



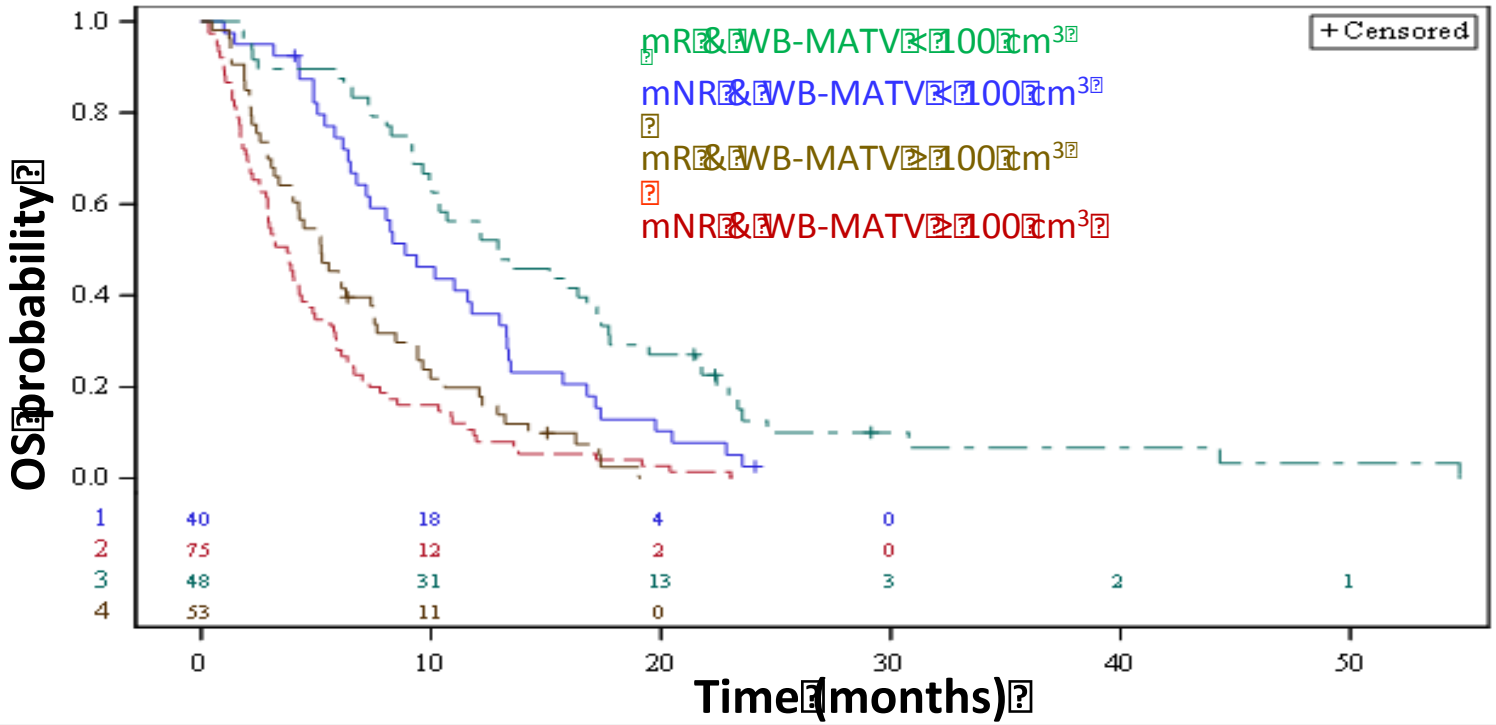
Hendlisz et al Ann Oncol 2012

Hendlisz et al PLoS One 2015

TUMOR BURDEN ADD SUBSTANTIAL INFORMATION ON TREATMENT OUTCOME

Outcome according to metabolic response & Baseline MATV

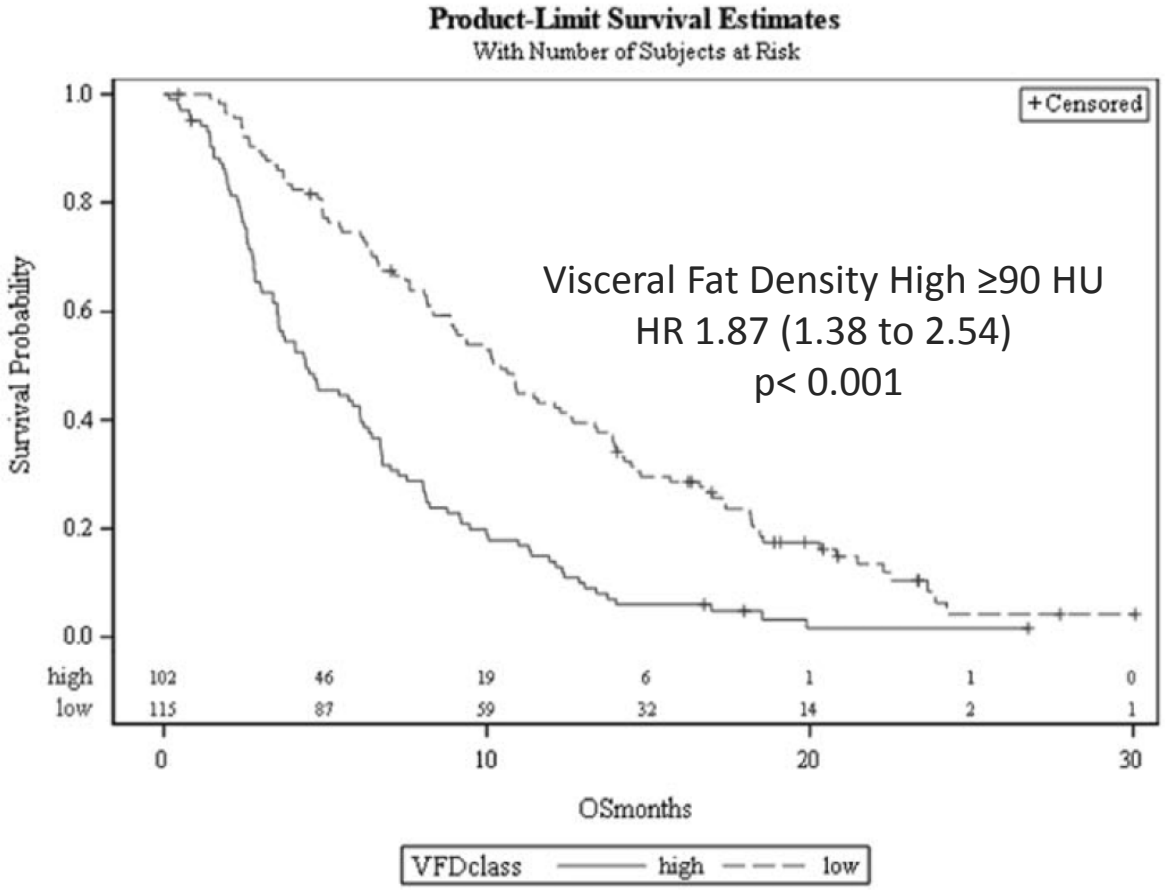
Combined analysis of 2 studies: SoMore (NCT01290926) & RegARd-C (NCT01929616)



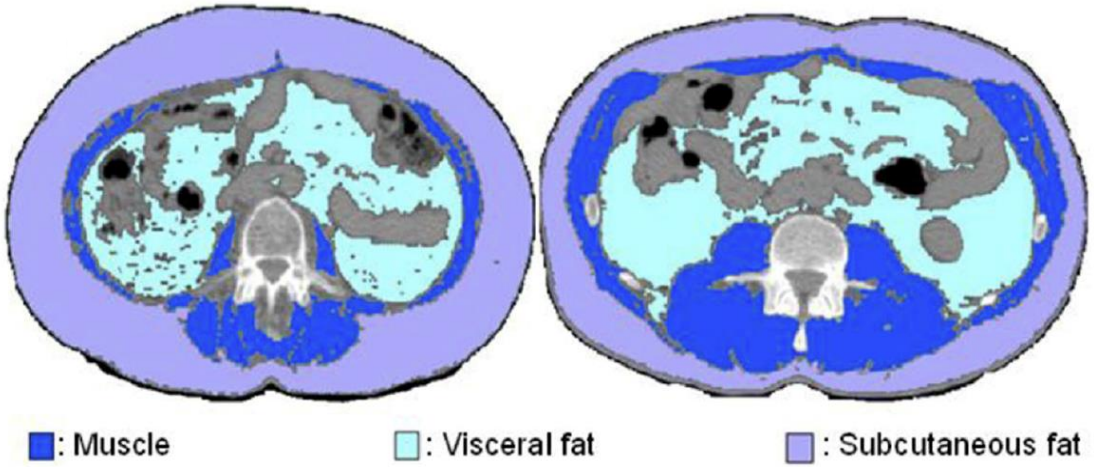
Both pre-therapeutic metabolic assessment of tumor burden (MATV)
AND dynamic metabolic assessment of response after 1 treatment course
independantly predict the outcome of patients

Woff et al. SNMMI 2019

BODY MASS COMPOSITION AS A PROGNOSTIC FACTOR

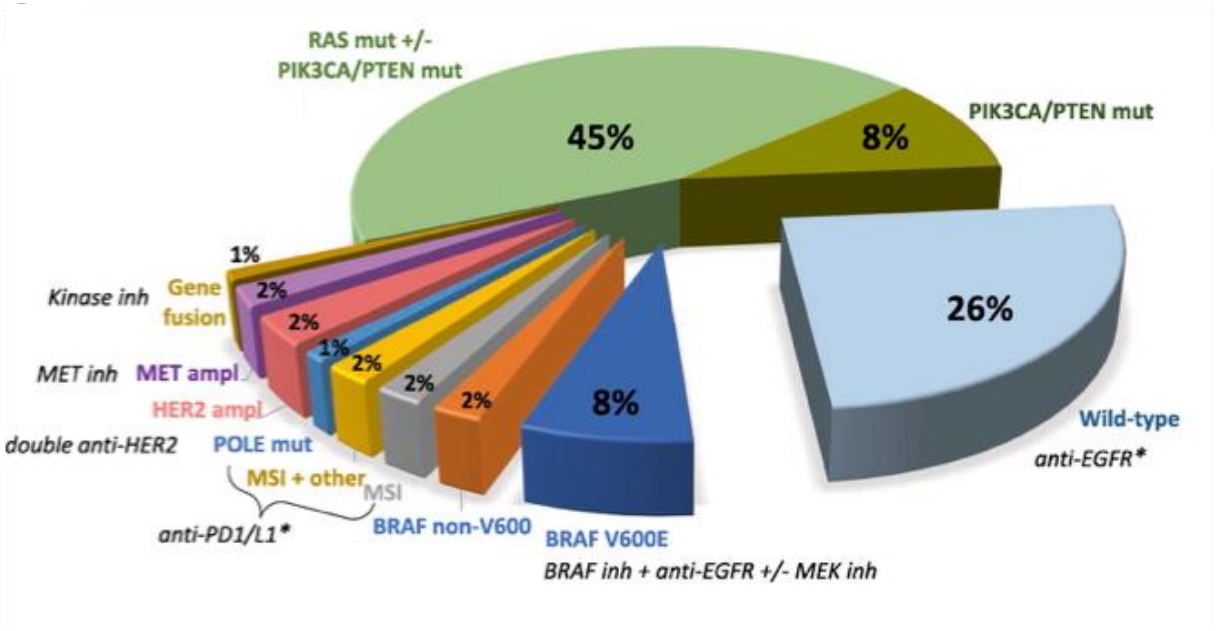


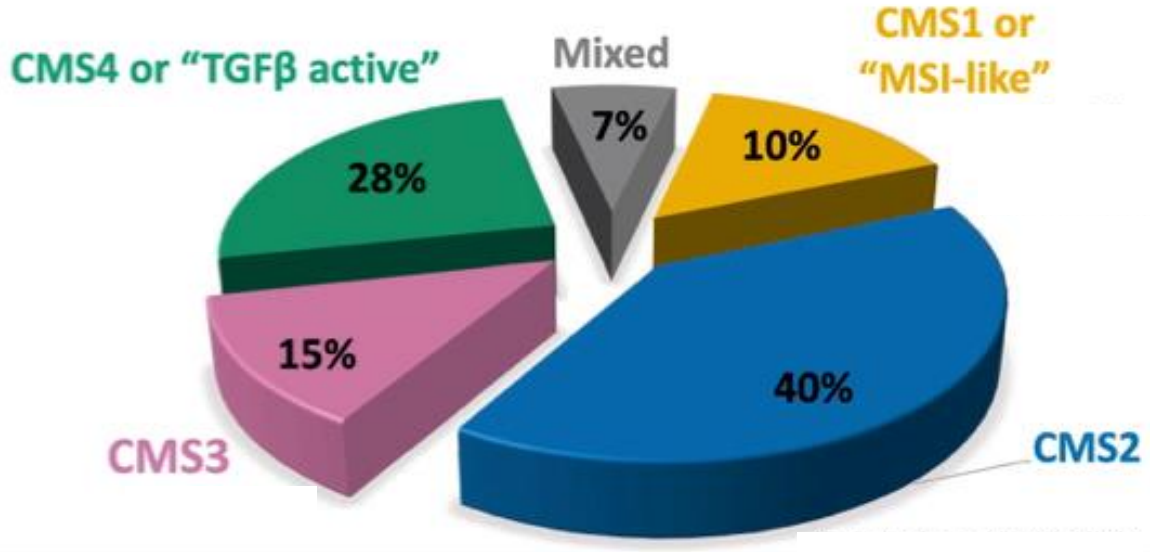
Visceral Fat Density High ≥90 HU
HR 1.87 (1.38 to 2.54)
p< 0.001



Charrette et al BMC Cancer 2019

Colon Cancer is More Than 1 Disease: Molecular Landscape



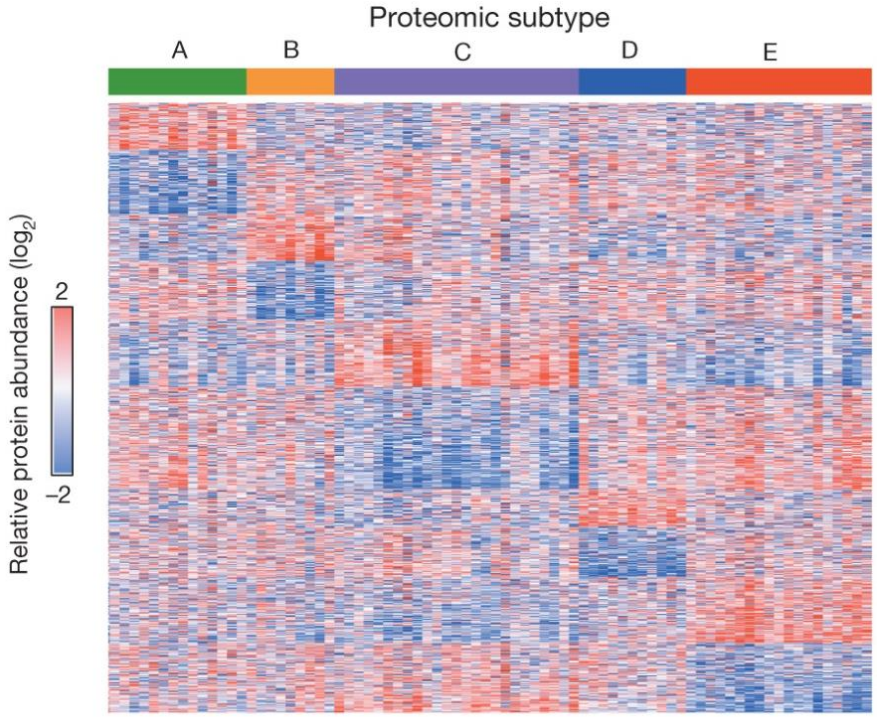


Genomics (DNA level)

Transcriptomics (RNA level)

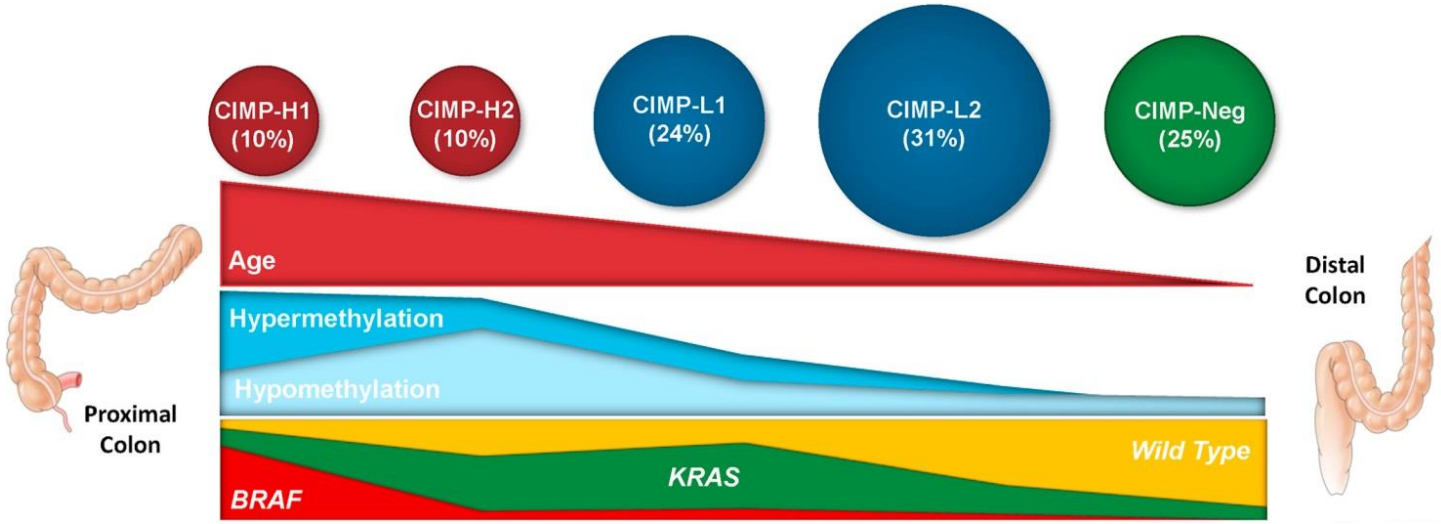
Dienstmann et al ASCO Educational Book 2018

Colon Cancer is More Than 1 Disease: Molecular Landscape



Proteomics (protein level)

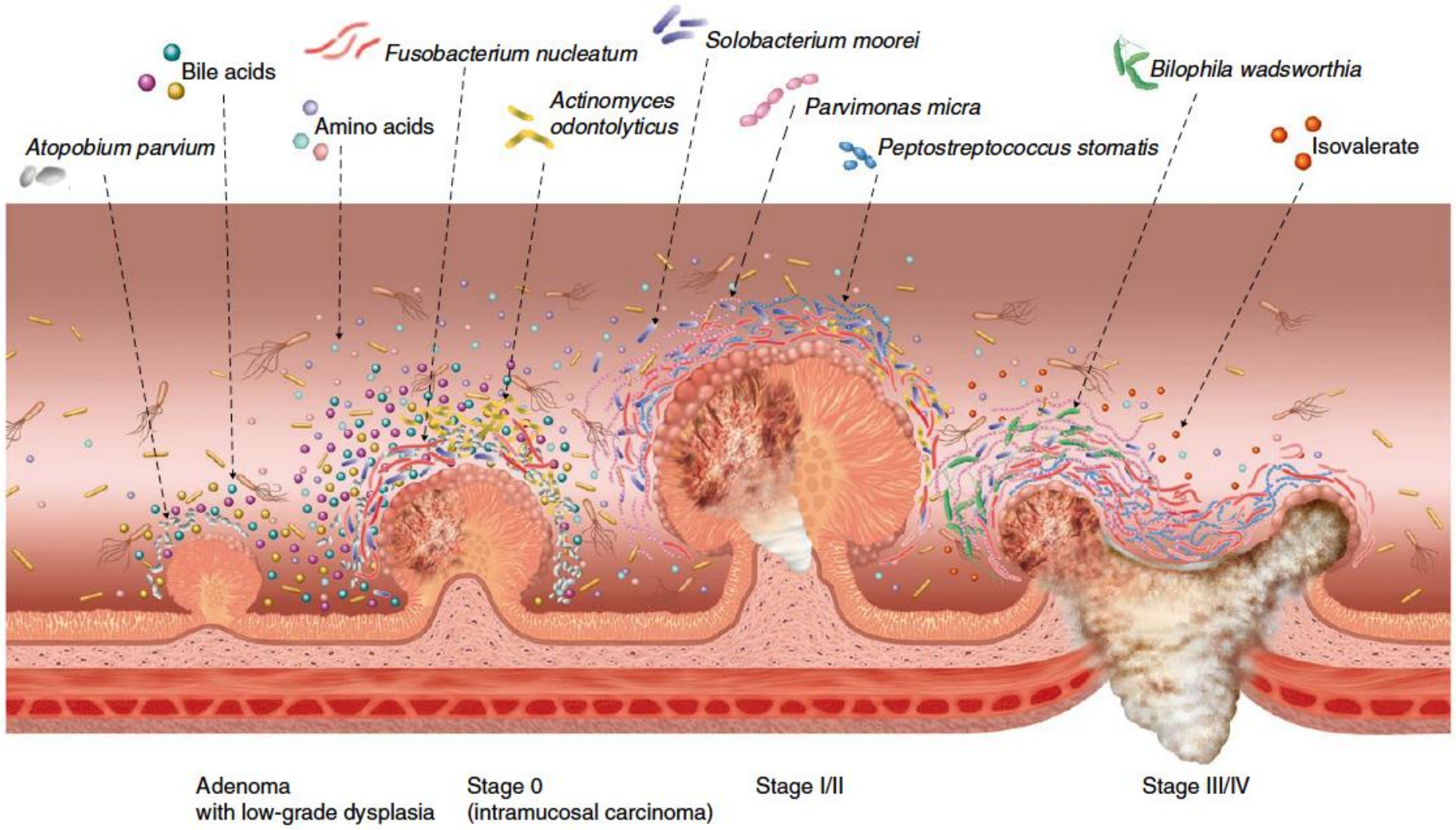
Zhang et al. Nature 2014



Epigenomics (changes in DNA and histone proteins)

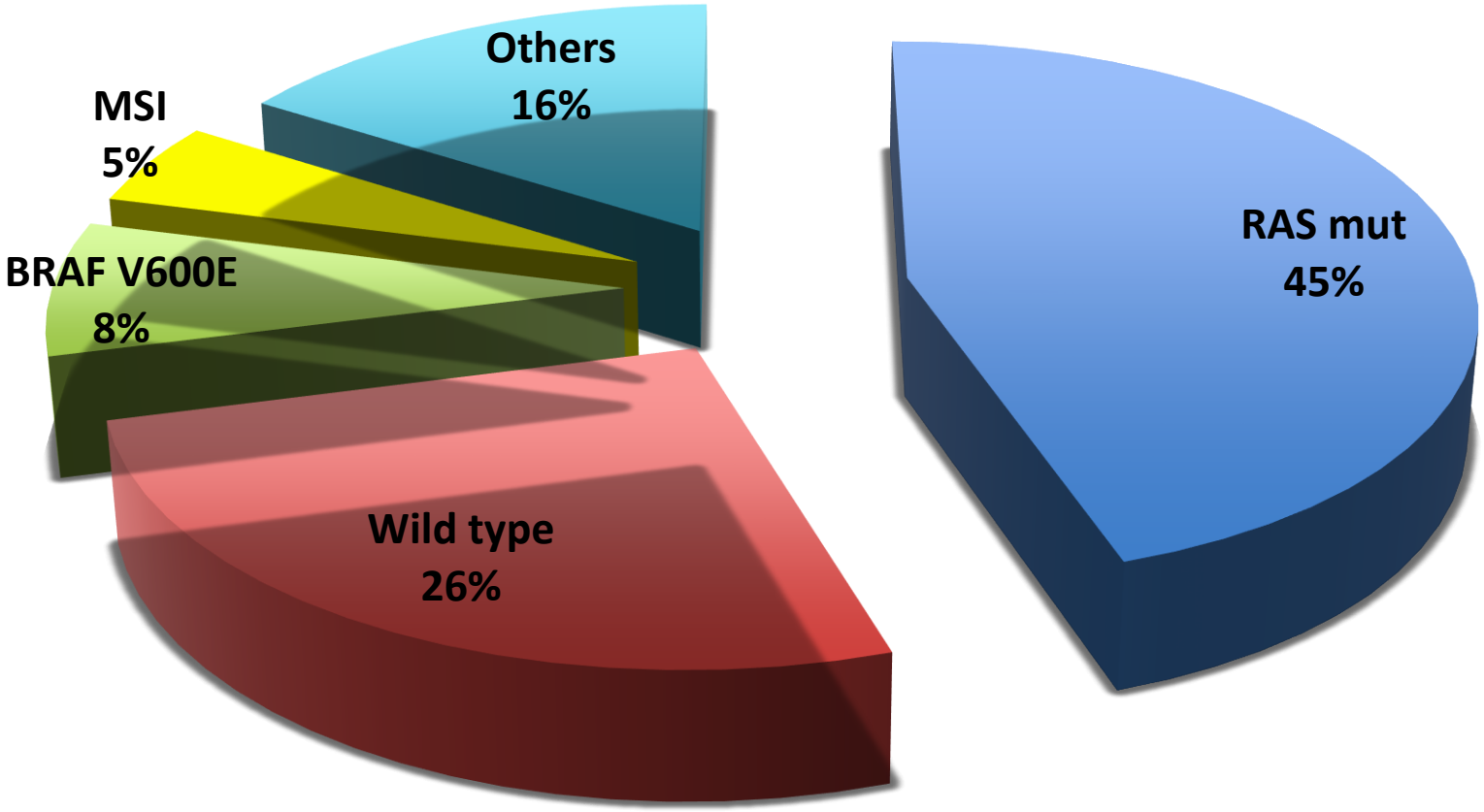
Fennell et al, Cellular and Molecular Gastroenterology and Hepatology 2019

Colon Cancer is More Than 1 Disease: Metagenomics



Yachida et al. Nature Medicine 2019

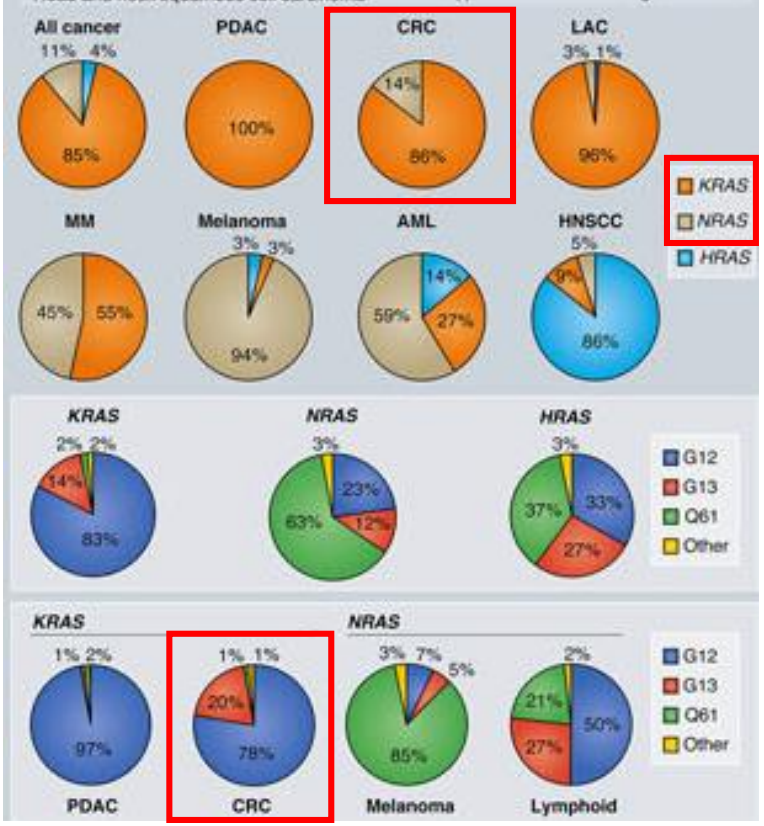
RAS-Mutated MSS mCRC

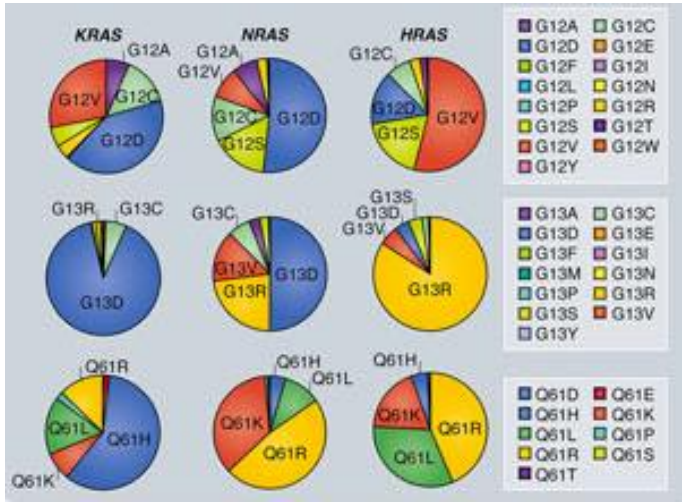


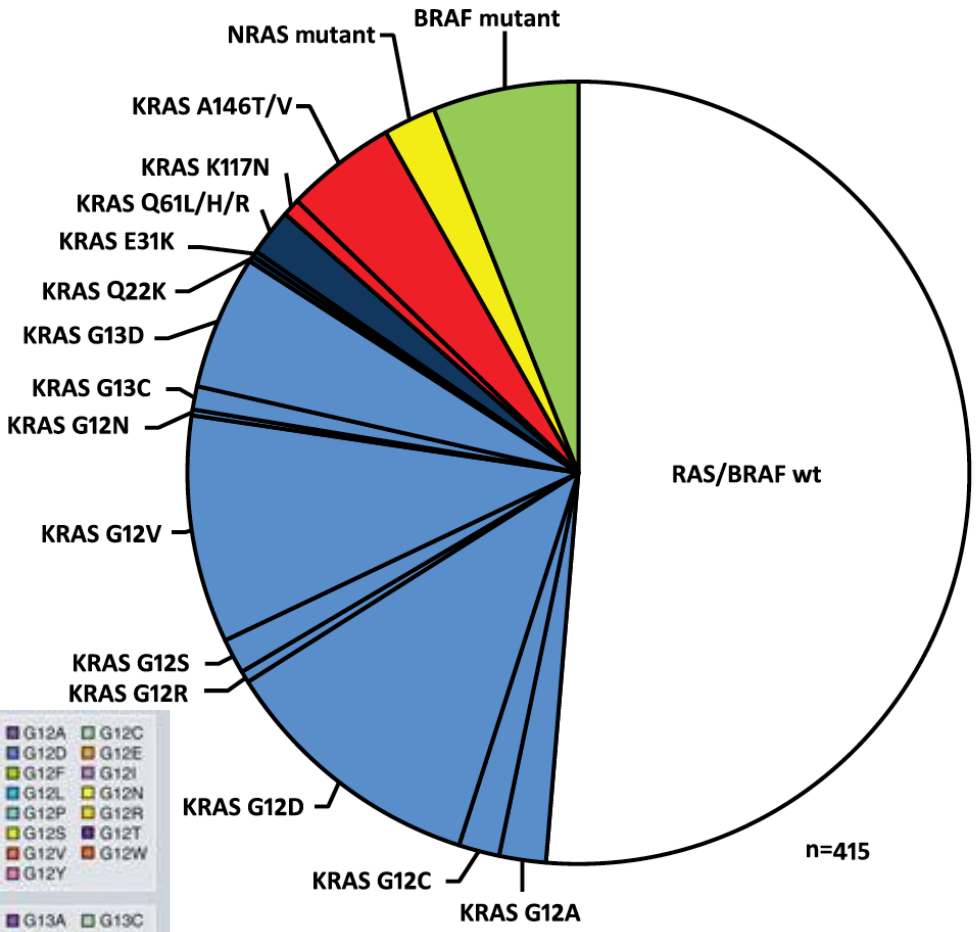
RAS mutations, deciphered

RAS mutations in cancer

Cancer	Isoform	Percentage
Pancreatic ductal adenocarcinoma	K	98
Colorectal adenocarcinoma	K	52
Multiple myeloma	K, N	43
Lung adenocarcinoma	K	32
Skin cutaneous melanoma	N	29
Uterine corpus endometrioidcarcinoma	K	25
Uterine carcinosarcoma	K	14
Thyroid carcinoma	N>H	13
Acute myeloid leukemia	N>K>H	11
Bladder urothelial carcinoma	H,K>N	11
Gastric adenocarcinoma	K	10
Cervical adenocarcinoma	K	8
Head and neck squamous cell carcinoma	H	6

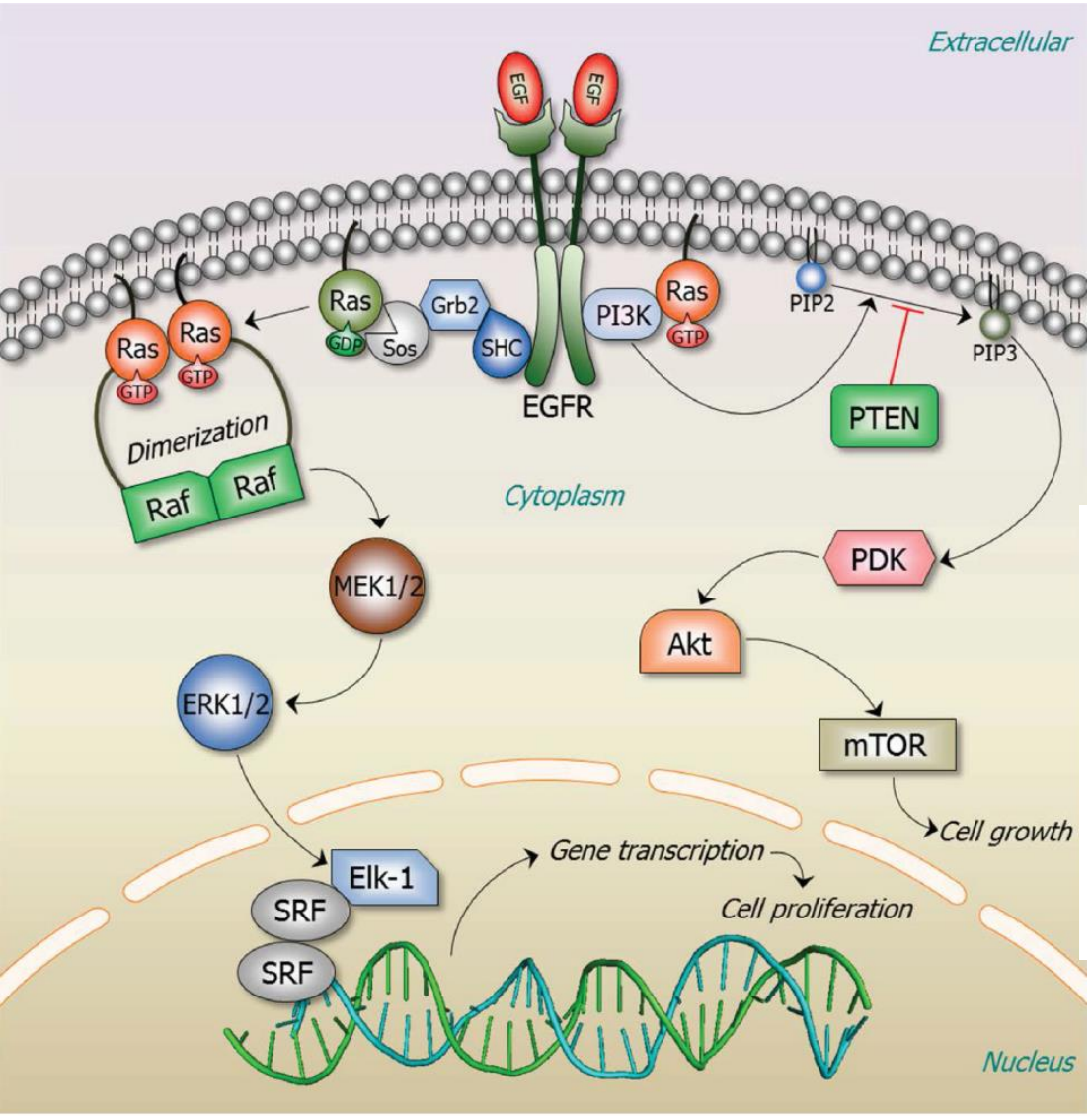




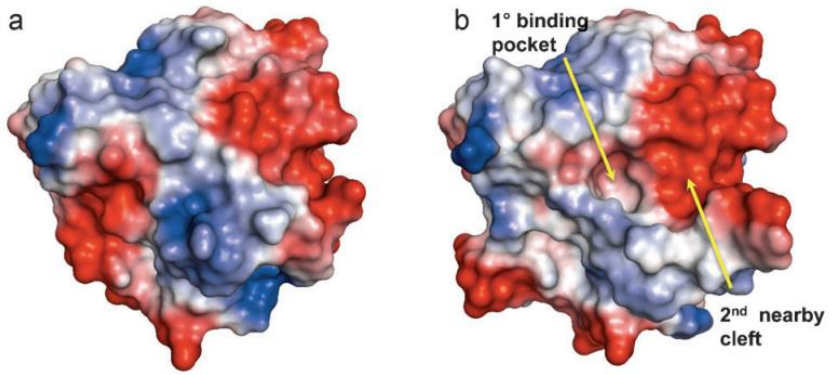


Janakiraman et al. Cancer Res 2010
Hobbs et al. J Cell Science 2016

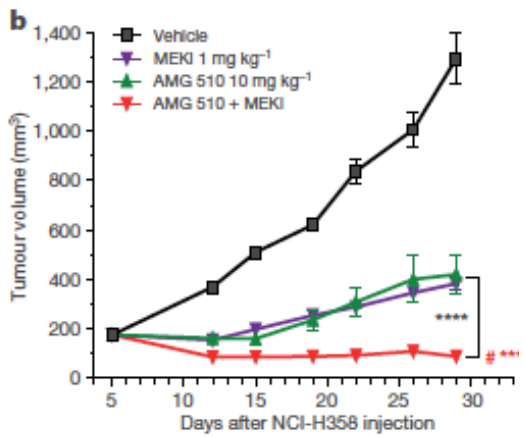
RAS… the undruggable protein

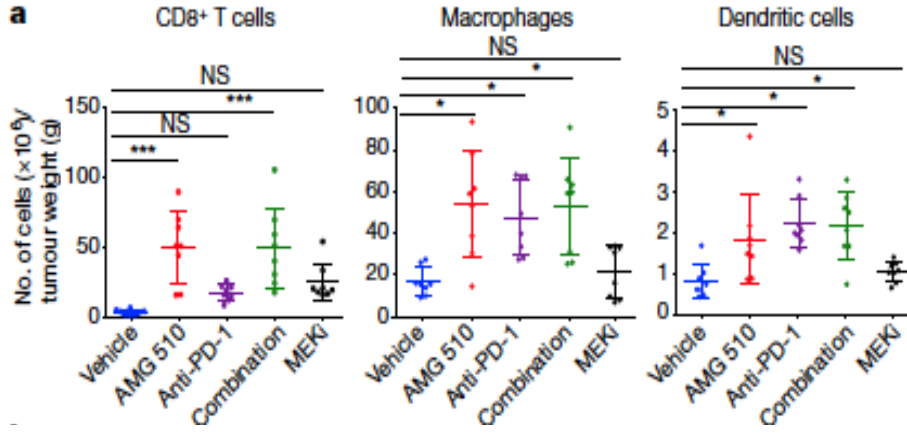


Nussinov et al. Oncotarget 2014



binds G12D & G12V Kras^{m} and inhibits SOS pathway (1)





AMG510 binds G12C and induces immunoinflammatory phenotype(2)

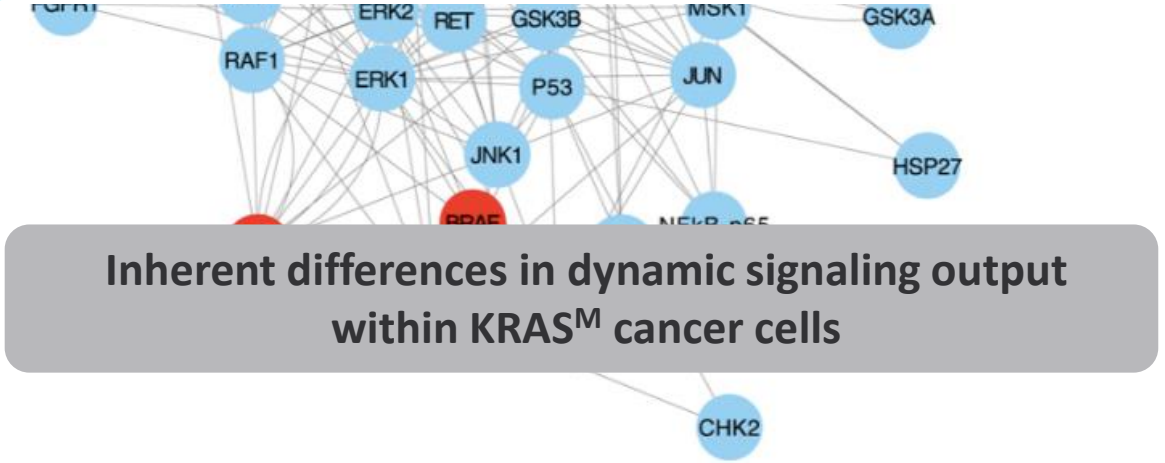
(1) Sun et al. Angew Chem Int Ed 2012
(2) Canon et al. Nature 2019

RAS^{m} … Context-Specific Signaling Patterns

Table 1. Significant differences in phosphoprotein changes between tumor types

	NSCLC vs. CRC + PDAC				CRC vs. NSCLC + PDAC				PDAC vs. NSCLC + CRC			
Drug (target)	**Increased**	**Not increased**	**Decreased**	**Not decreased**	**Increased**	**Not increased**	**Decreased**	**Not decreased**	**Increased**	**Not increased**	**Decreased**	**Not decreased**
AZD5363 (AKT)	RB		IR SRC				STAT5		IR			
Everolimus (m-TOR)			SRC S6K		MEK	RB			C-MET IRS1			
Gefitinib (EGFR)					m-TOR		IRS1					
Luminespib (HSP90)		MEK	PTEN				IGF1R IRS1		B-Catenin		C-KIT	
Pictilisib (PI3K)		m-TOR MEK	CHK1 CHK2 PTEN		GSK3B			PRAS40 AKT				
Trametinib (MEK)			PDGFRB SRC						B-Catenin CHK2			
Vemurafenib (BRAF)	FGFR1 HER3 IR STAT5			m-TOR		CHK1					PRAS40 C-KIT	

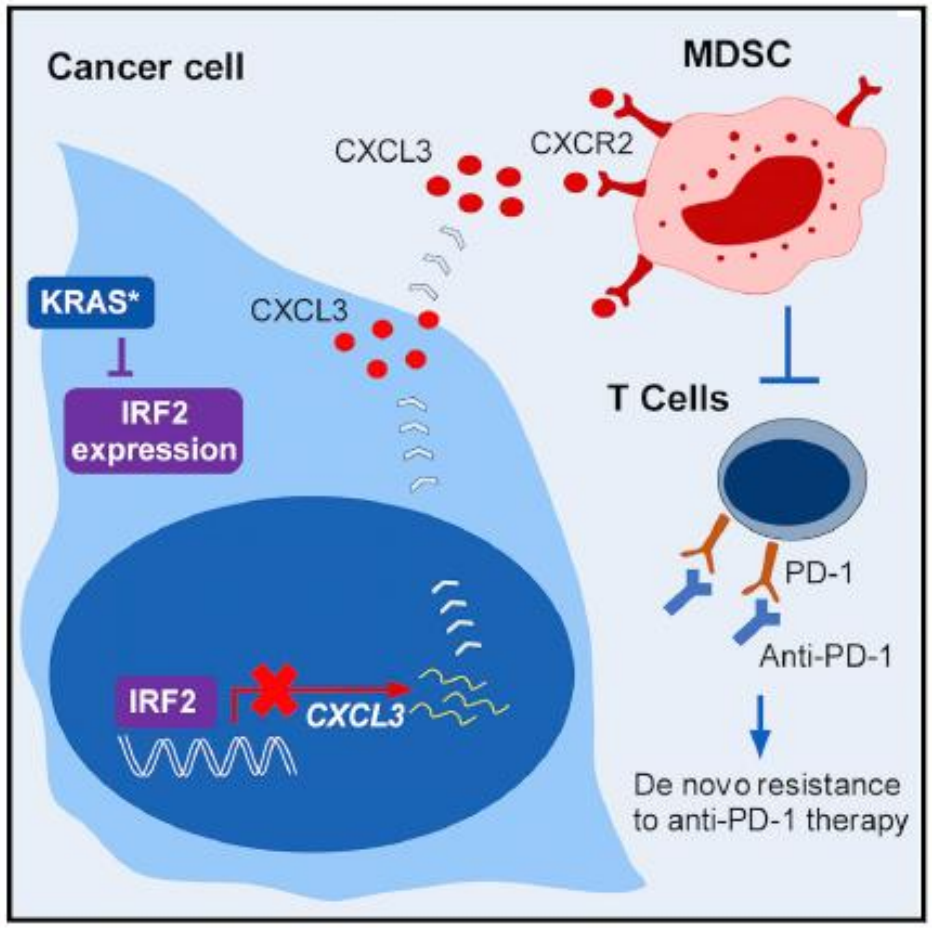
NOTE: Changes in phosphorylation of proteins that were increased or decreased upon exposure to different drugs but were significantly different from cells derived from different tumor types, i.e., NSCLC, CRC, and PDAC upon logistic regression corrected for multiple testing.



Inherent differences in dynamic signaling output within KRAS^{M} cancer cells

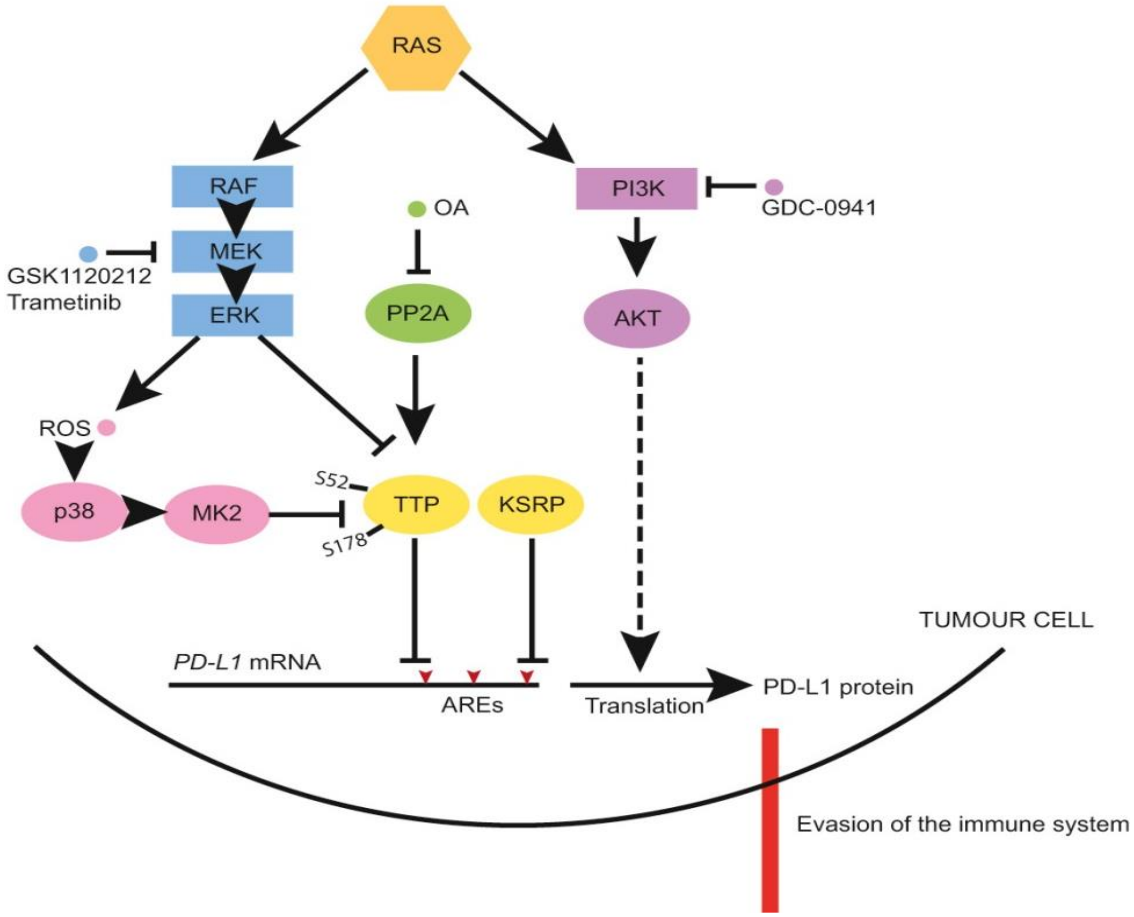
Stewart et al. Mol Cancer Ther 2019

RAS^{m} and Immune Environment



Oncogenic RAS signaling suppresses IRF2 expression
→ MDSC infiltration and T cell inhibition

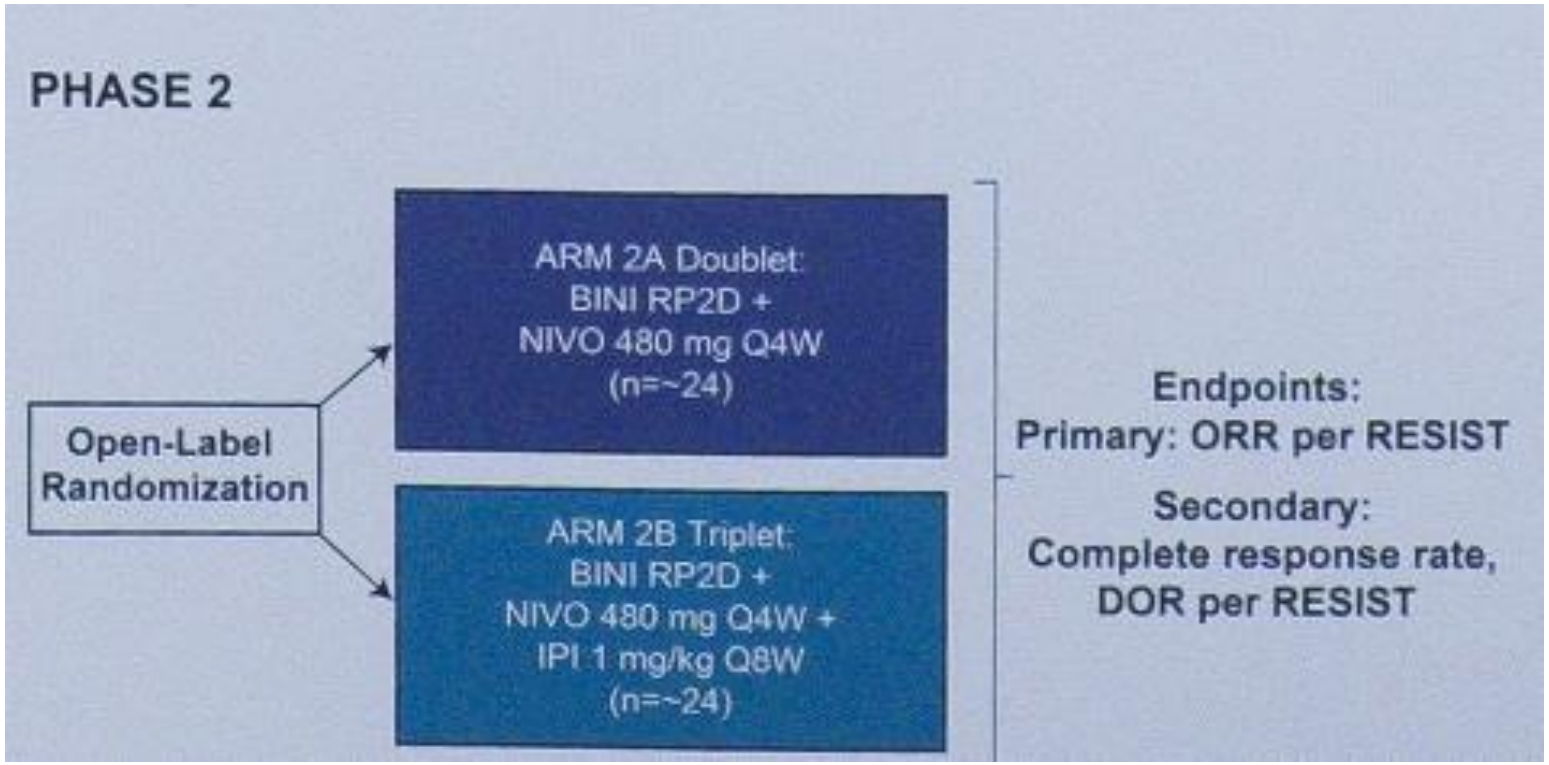
Liao et al Cancer Cell 2019



Oncogenic RAS signaling ↗ tumour cell PD-L1 expression
→ immune evasion

Coelho et al Immunity 2017

Binimetinib+Nivolumab +/-Ipilimumab in MSS RAS^{m} chemorefractory mCRC

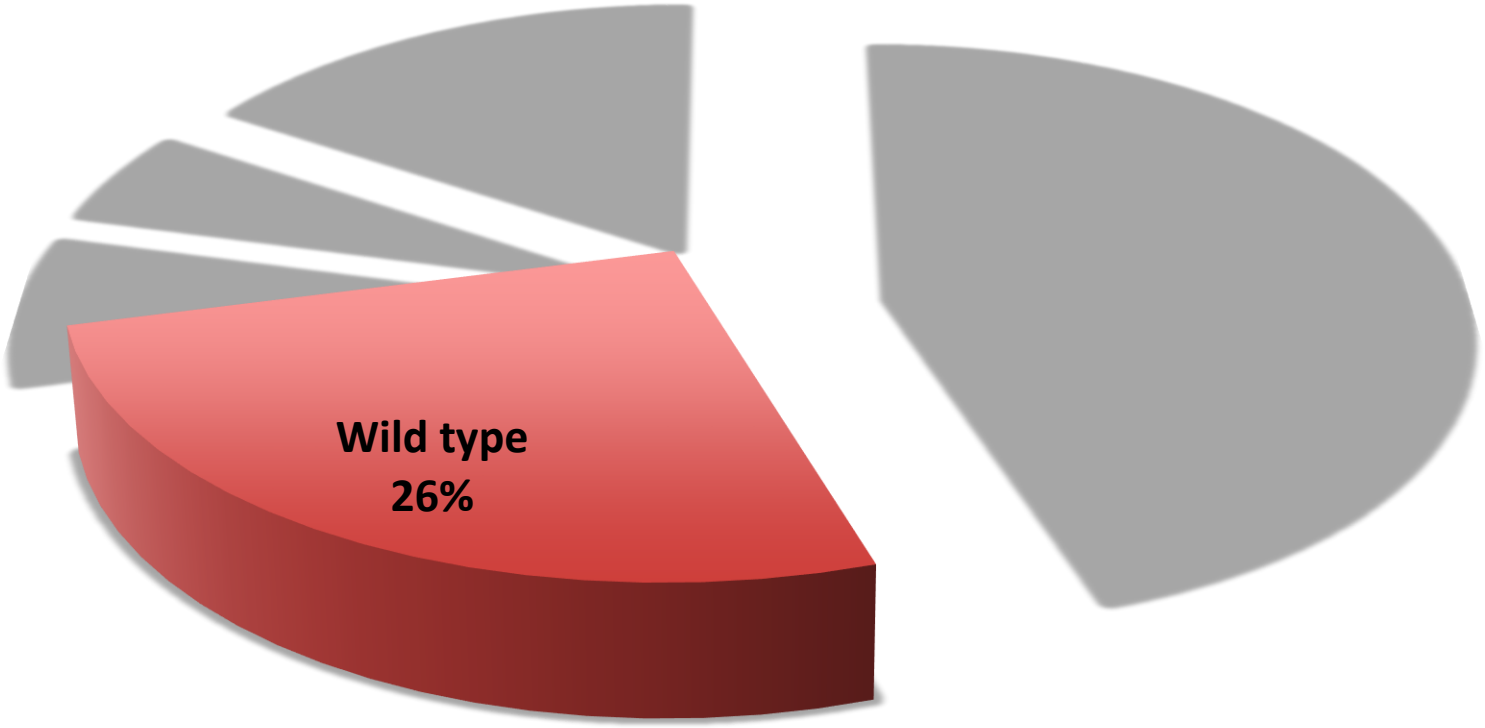


NIH U.S. National Library of Medicine

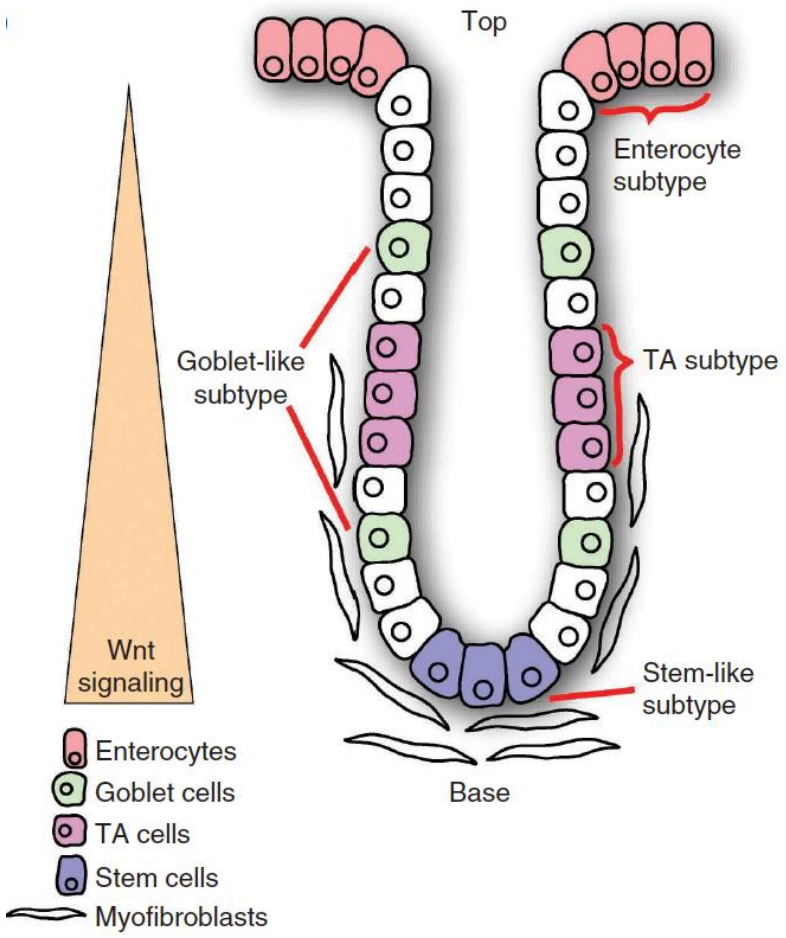
ClinicalTrials.gov

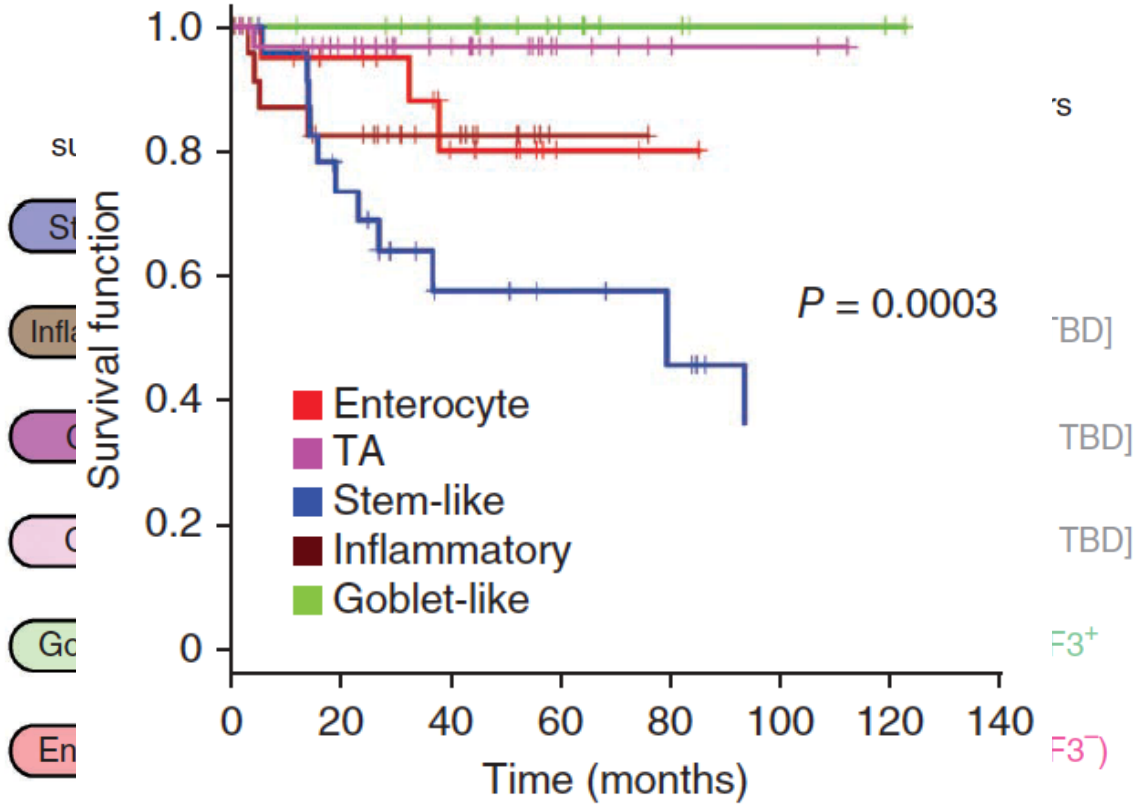
Bendell et al TPS870 ASCO GI 2018

Extended RAS/BRAF wild-type CRC



CRCAssigner subtypes (pre-Consensus Molecular Subtypes)

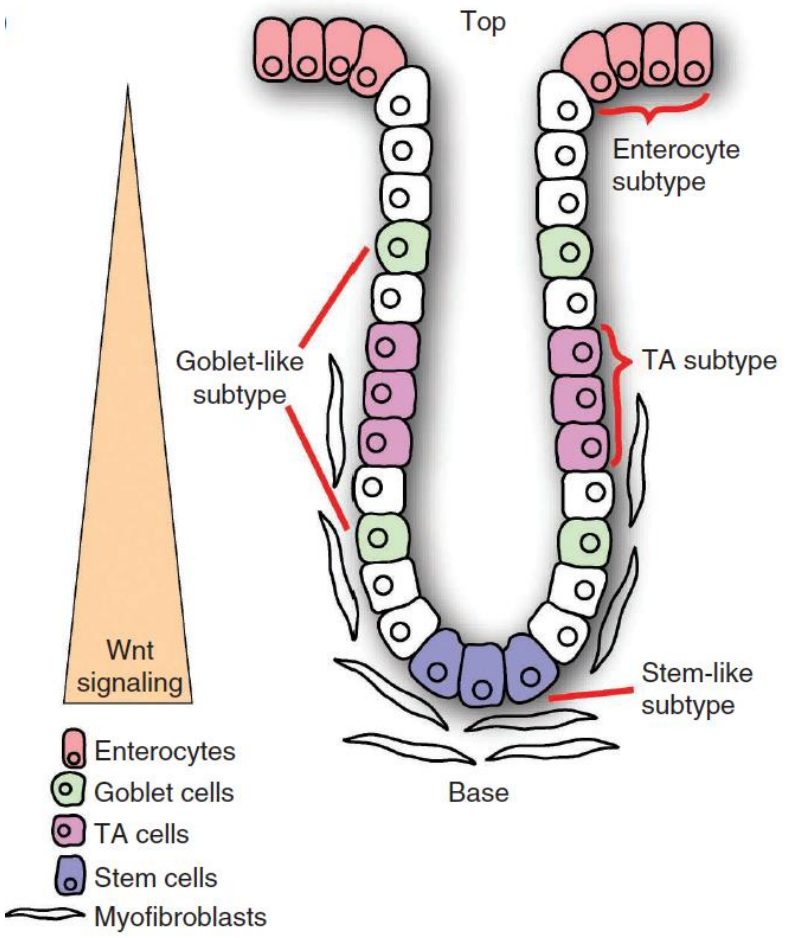


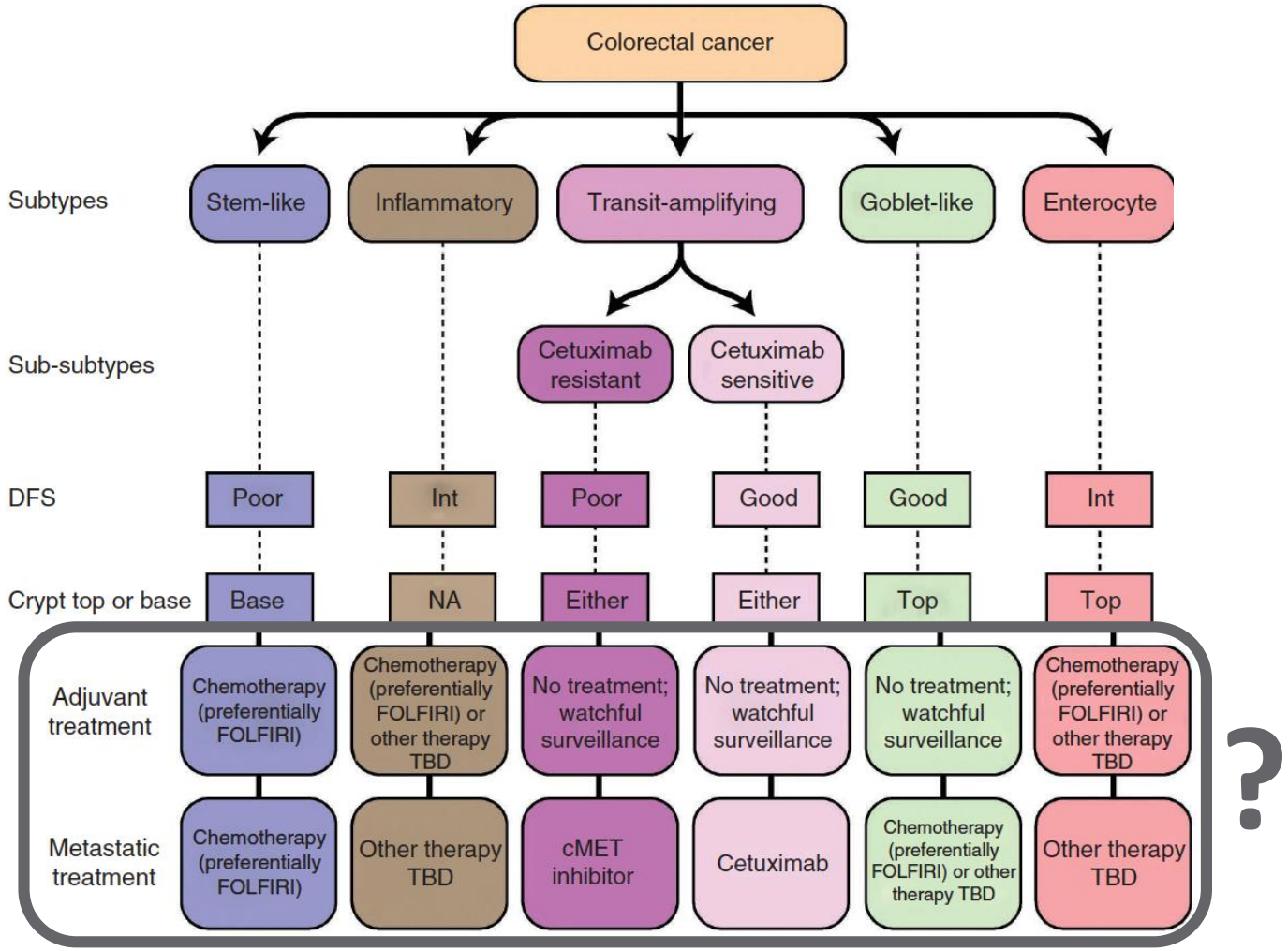


Each subtype shares similarities to distinct cell types within the normal colon crypt and shows differing degrees of 'stemness' and Wnt signaling

Sadanandam et al Nat Med 2013

CRCAssigner subtypes (pre-Consensus Molecular Subtypes)

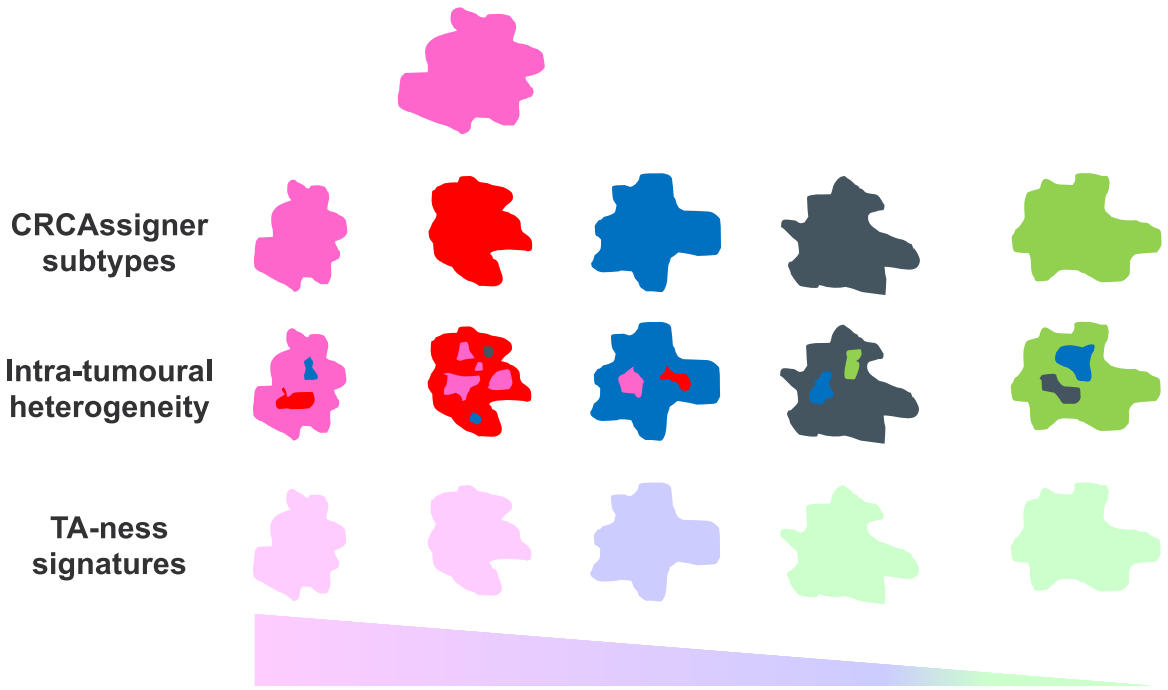


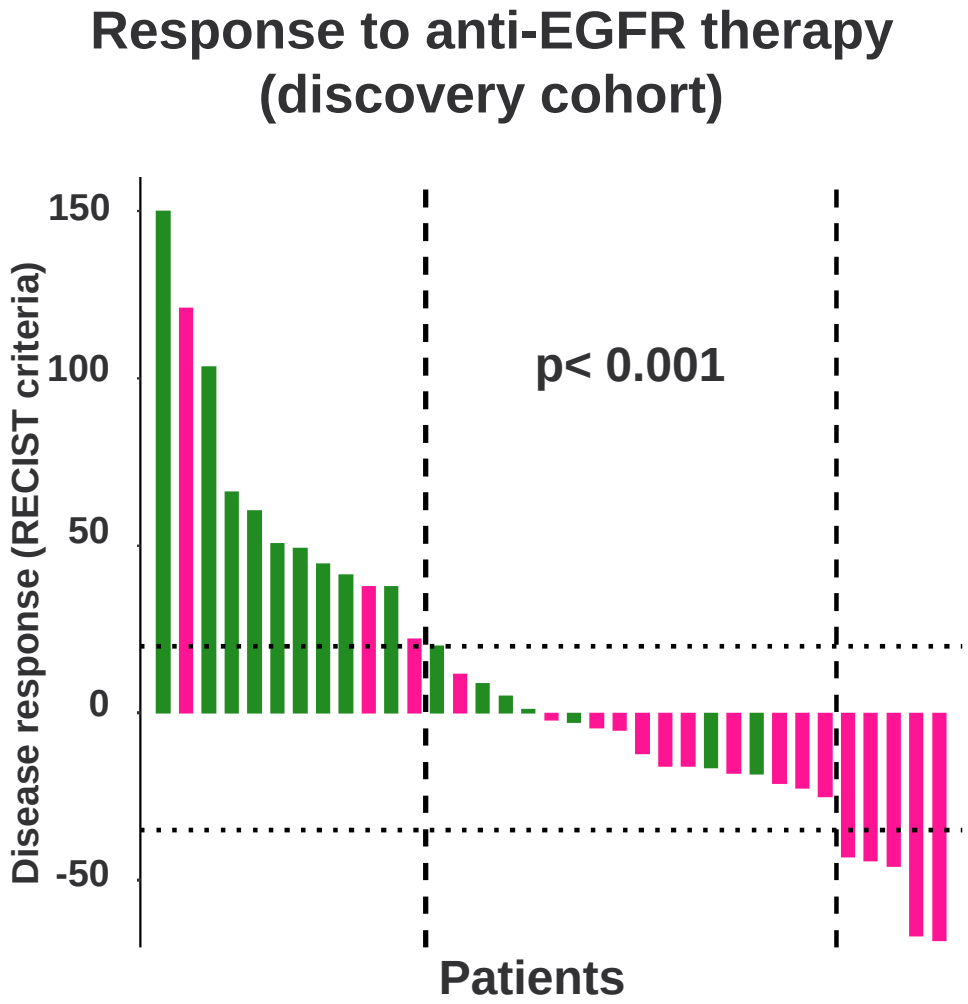


Sadanandam et al Nat Med 2013

TA-Ness signature: Subtypes within subtypes

- The TA-ness signature



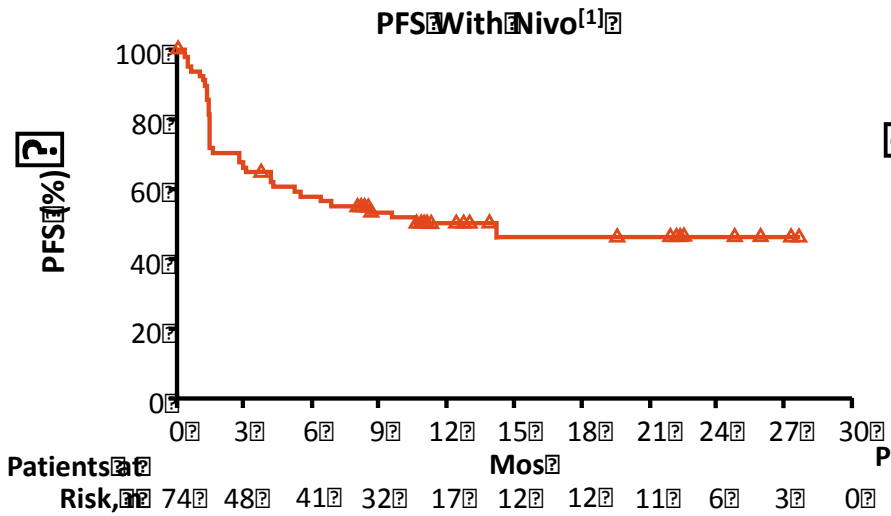


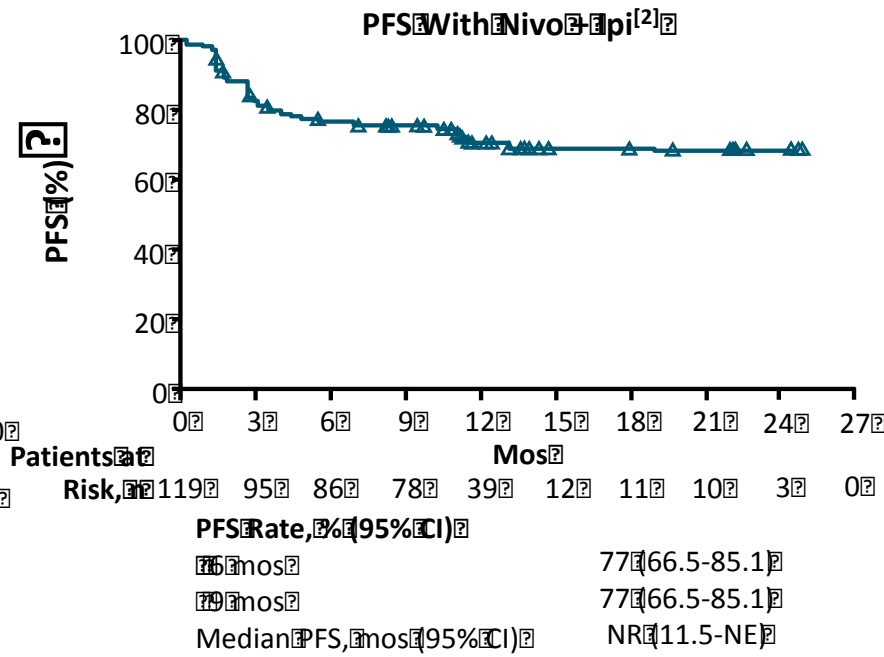
Ragulan et al Sci Rep 2019
Fontana et al ESMO 2019

MSI-H as positive predictive biomarker for immunotherapy

Nivo+ Ipi in MSI-H CRC

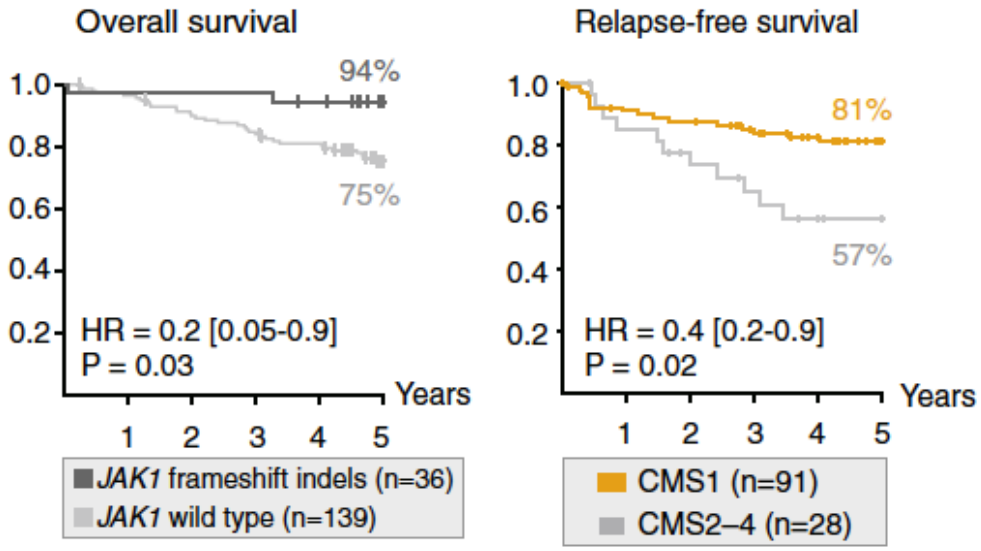
Response	Nivo 3 mg/kg + Ipi 1 mg/kg (n = 119)
ORR, % (95% CI)	55 (45.2-63.8)
Best overall response, %	
▪ CR	3
▪ PR	51
▪ Stable disease	31
▪ PD	12
▪ Not determined/reported	3
Median TTR, mos (range)	2.8 (1-14)
Median duration of response, mos (range)	NR (NE-NE)
DCR for ≥ 12 wks, % (95% CI)	80 (71.5-86.6)

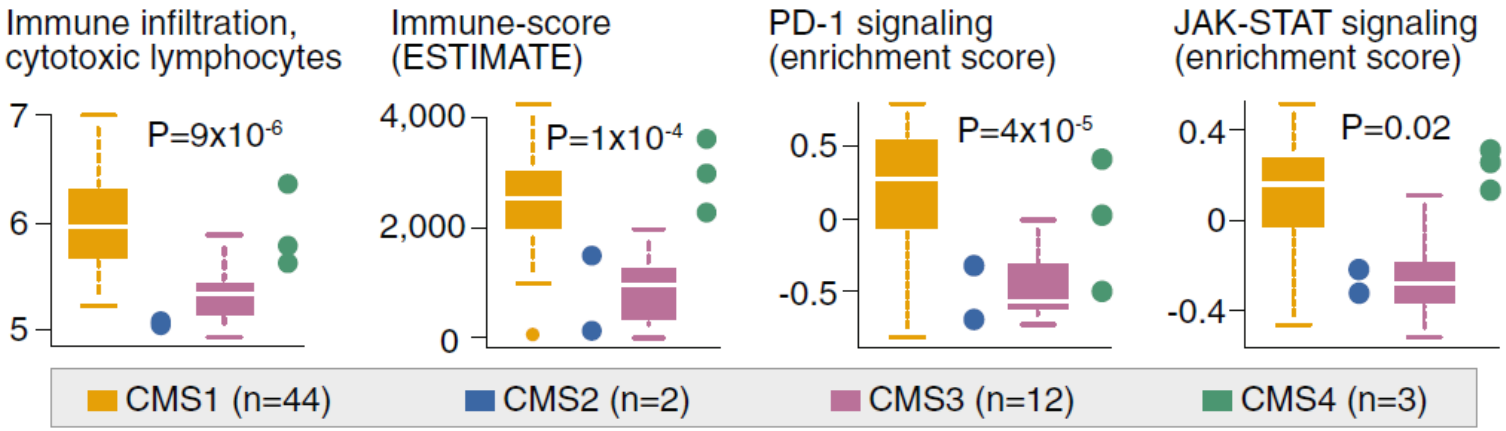




Overman et al. J Clin Oncol 2018

Transcriptional heterogeneity within MSI-H CRC





JAK1 loss-of-function mutations (20%):

- **resistance to anti-PDL1**
- **better prognosis**

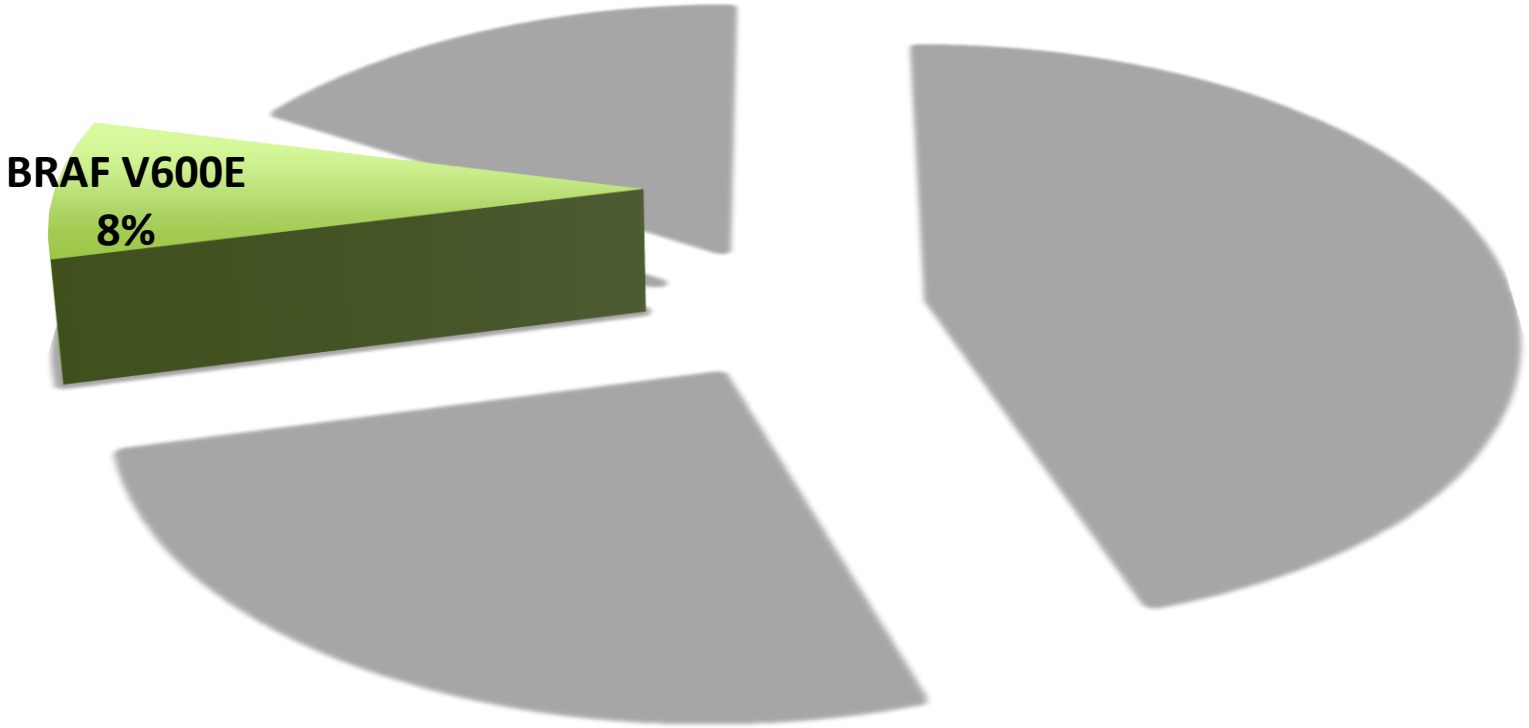
CMS1:

- **better prognosis**

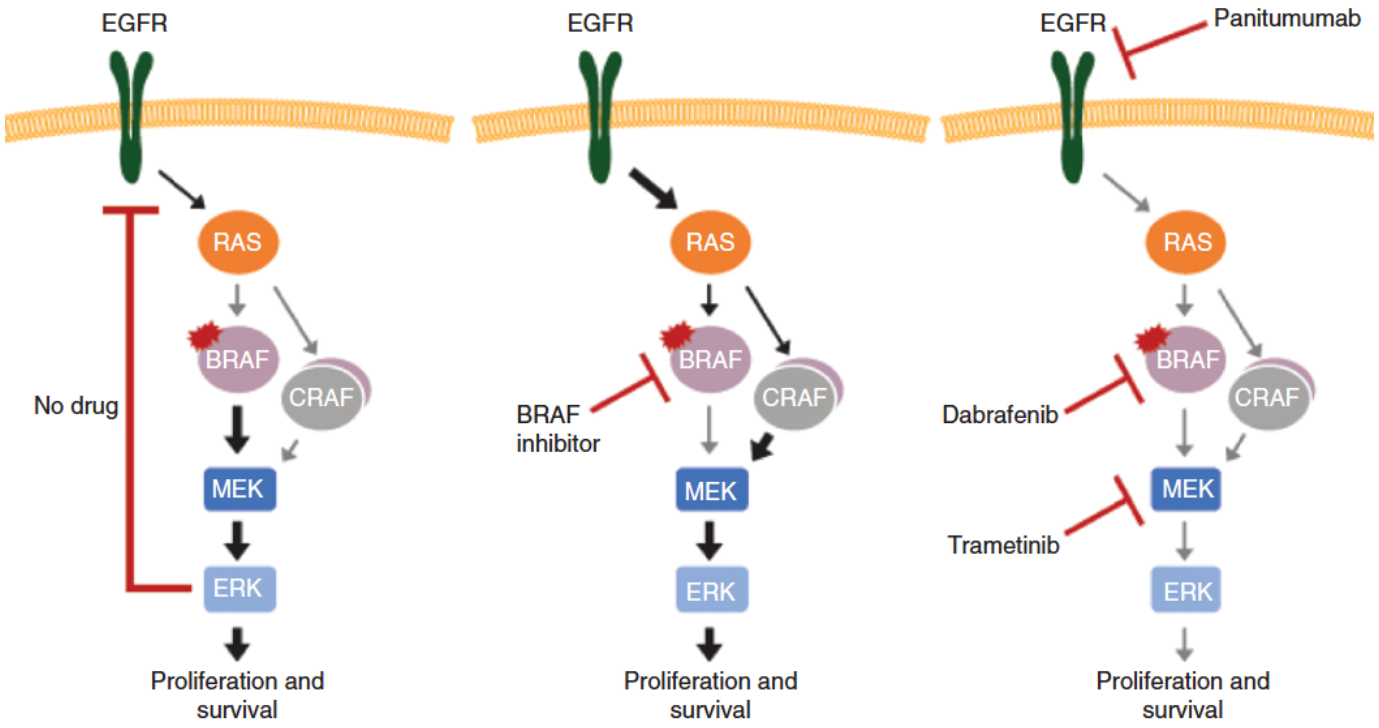
immunogenicity
MSI+CMS1 >> MSI+CMS2-4

Sveen et al Genome Med 2017

BRAF mutations



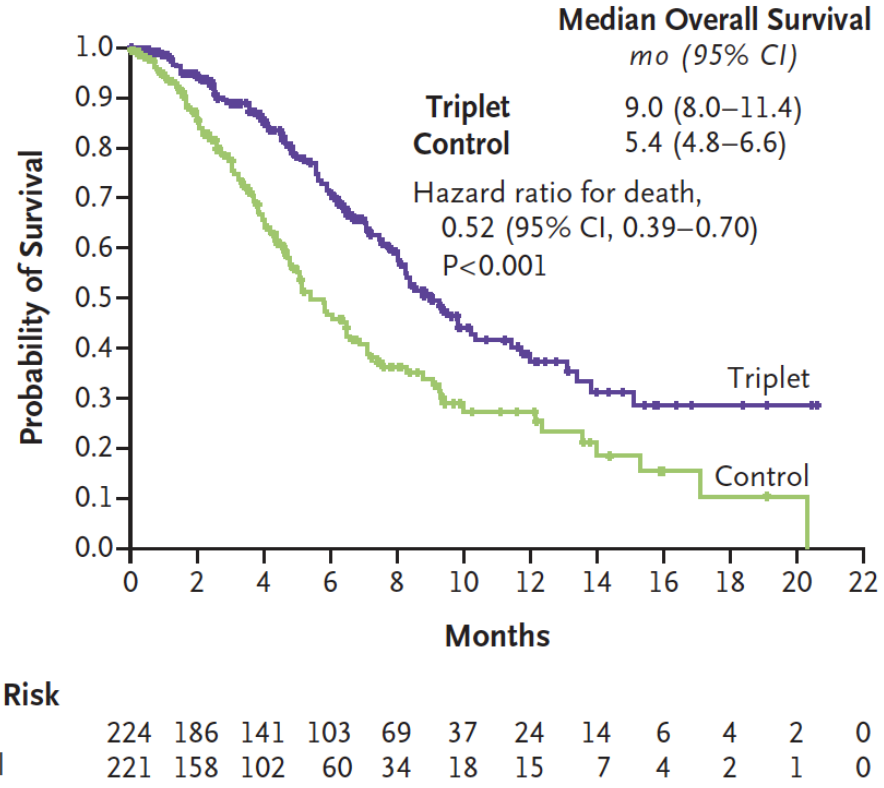
BRAF-MEK-EGFR inhibition in BRAFV600E mCRC



Combined BRAF+EGFR+MEK inhibition promising activity BRAFV600E mCRC

Corcoran et al Cancer Discovery 2018

BEACON study



No. at Risk

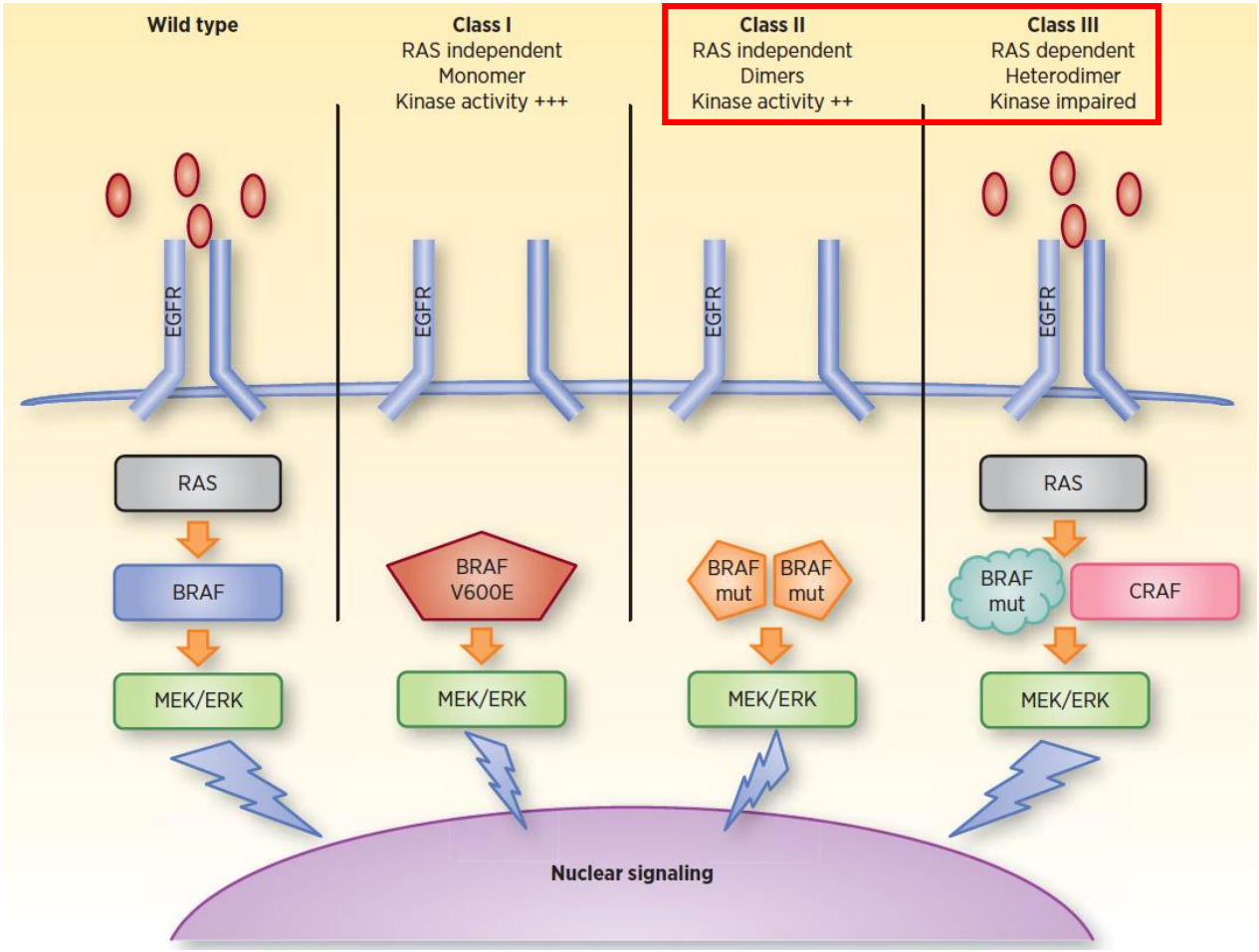
Triplet	224	186	141	103	69	37	24	14	6	4	2	0
Control	221	158	102	60	34	18	15	7	4	2	1	0

<u>Control</u> (Investigator's choice):
Iri+Cetux ou FOLFIRI+Cetux

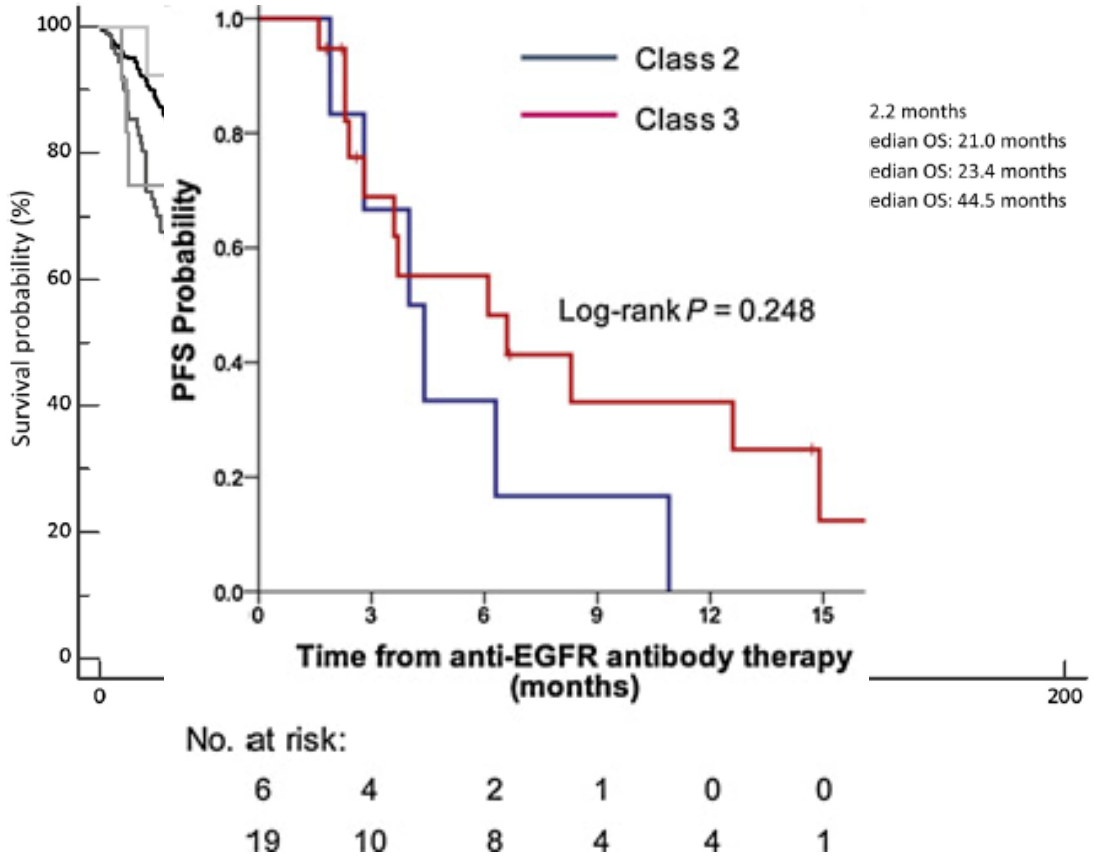
Kopetz et al, N Engl J Med 2019

V600E is not the only BRAF mutation in mCRC

2% mutations in CRC



Fontana et al. Clin Cancer Res 2019



Schirripa et al. Clin Cancer Res 2019

Yaeger et al. Clin Cancer Res 2019

CONCLUSIONS: One Size Does Not Fit All

The Path to Improvement in ColoRectal Cancer Passes Through

- Better Understanding of Tumoral Biology and Environment
- Better Definition of Response to Therapy