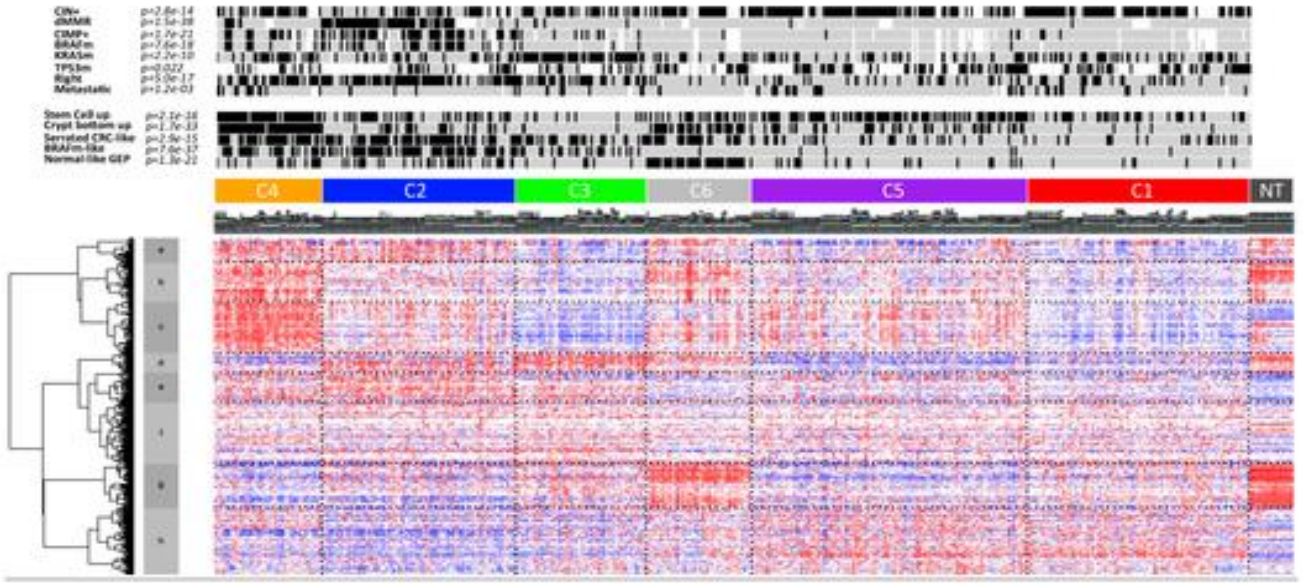
A molecular taxonomy of colorectal cancer



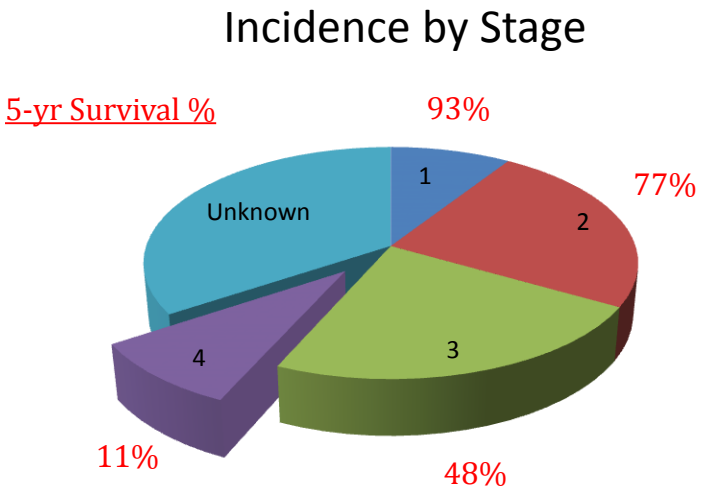
Ultan McDermott
Wellcome Trust Sanger Institute

Disclosures

- Founder and consultancy, 14M Genomics

wellcome trust sanger institute

Progress in metastatic CRC



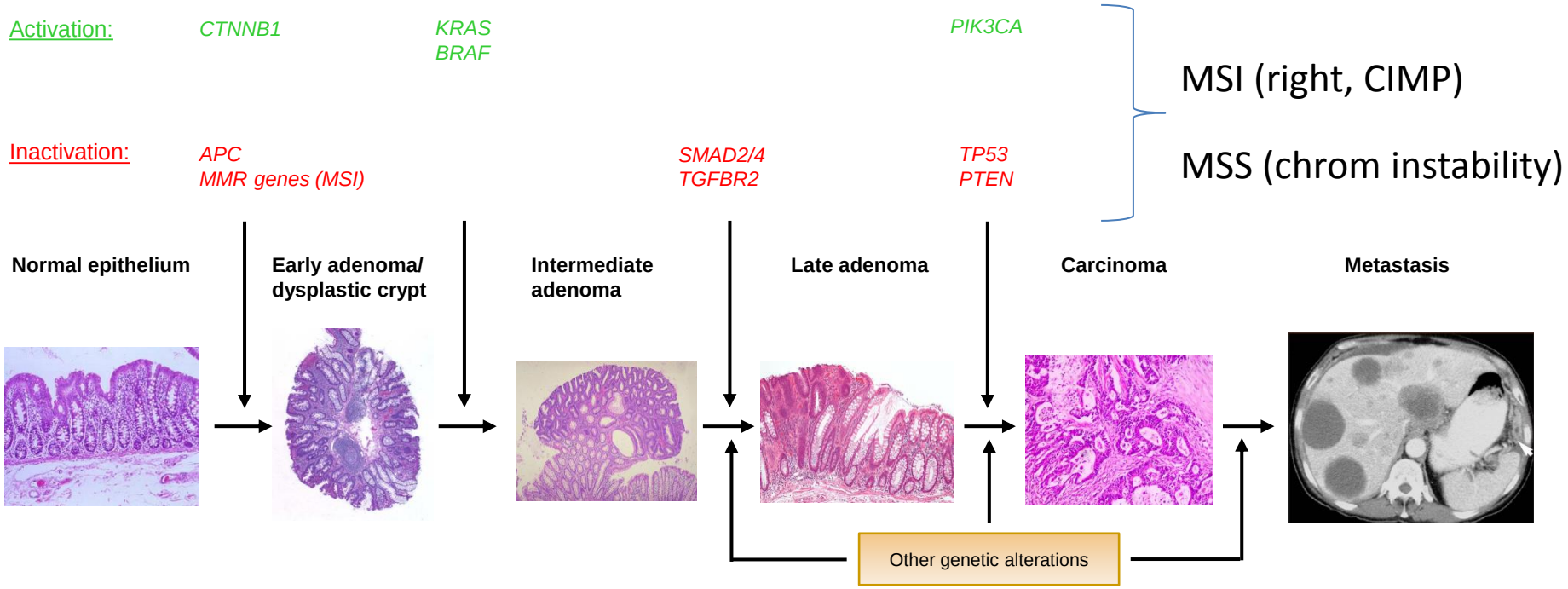
Percent Surviving 5 Years

64.7%

Main chemotherapy regimens:	FOLFOX6 (Oxaliplatin/5FU) 2-weekly FOLFIRI (Irinotecan/5FU) 2-weekly
Biologics:	Cetuximab (EGFR mAb) Bevacizumab (VEGFR mAb) Regorafenib (multi-kinase) Aflibercept (VEGF)

wellcome trust sanger institute

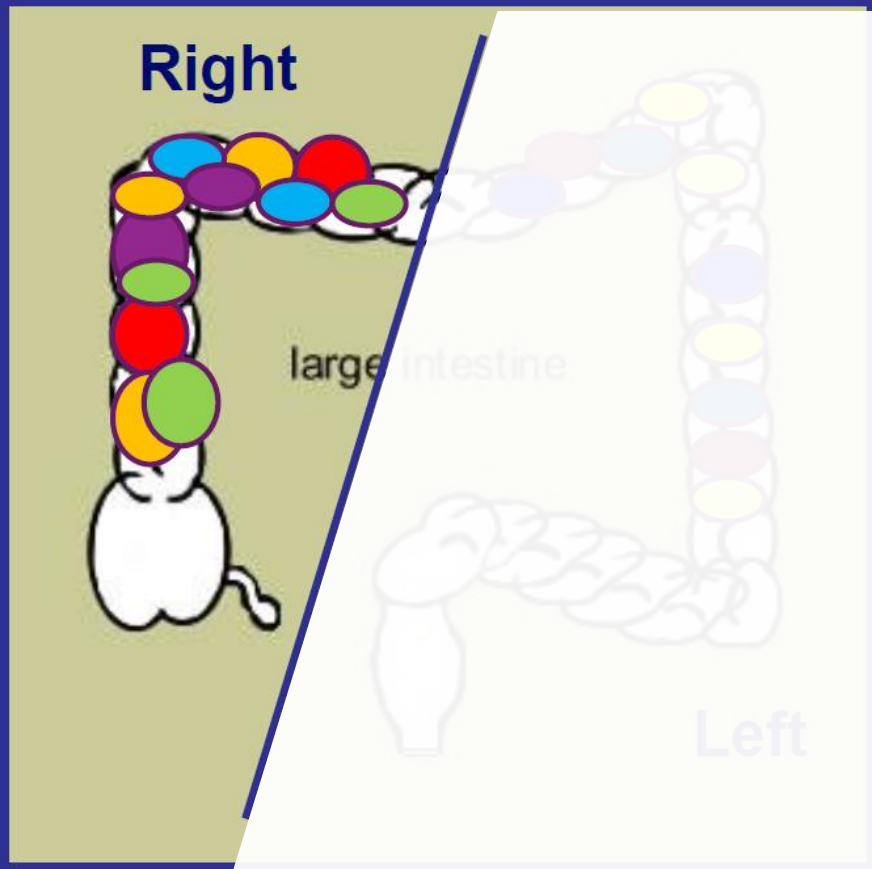
The adenoma-carcinoma sequence



Right versus Left Colon Cancer

Analysis of PETACC-3 samples (n=2849)

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



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

High mutation Frequency

Poor Prognosis

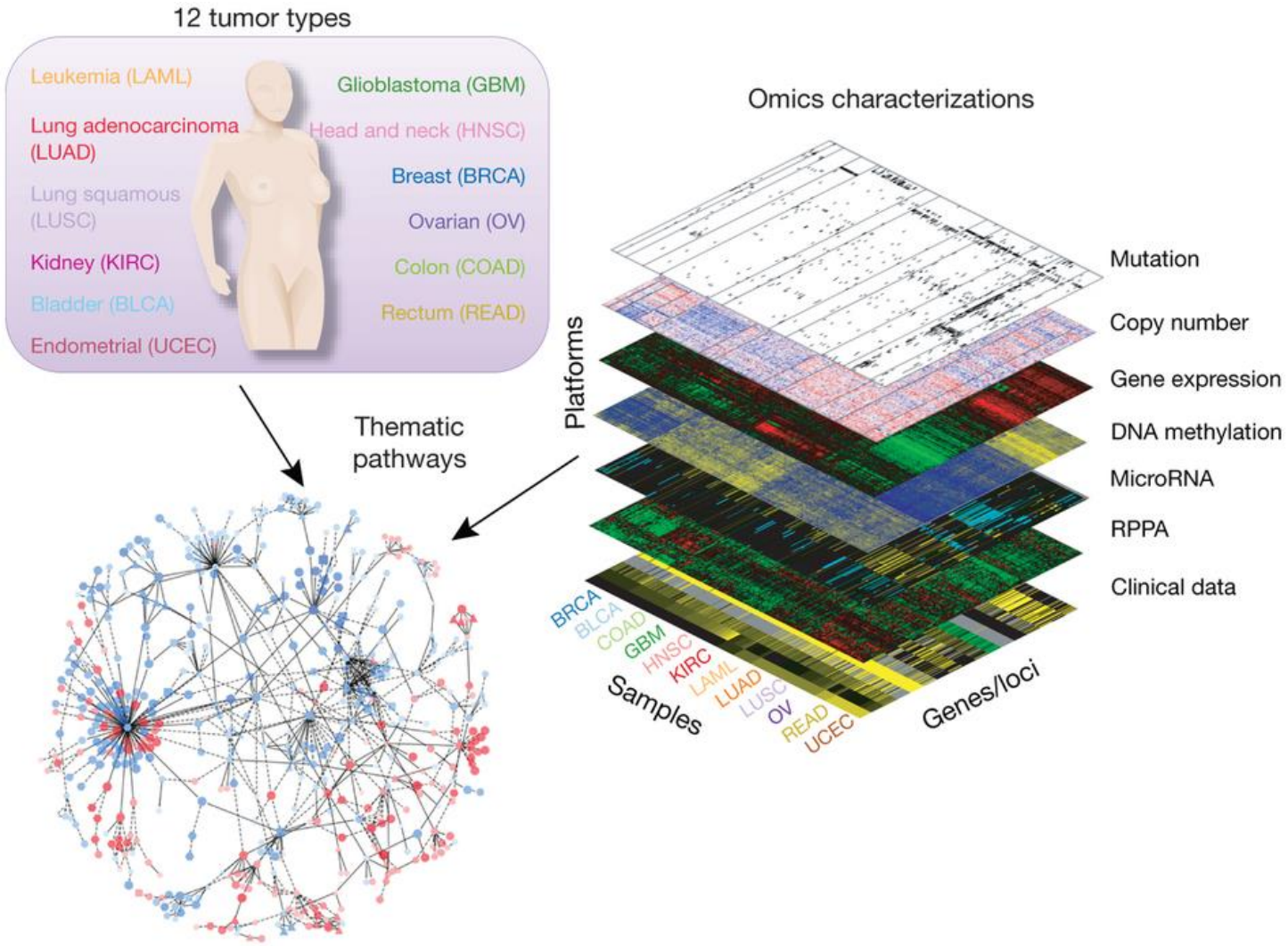
Sensitive to Cetuximab

Good Prognosis

Missiaglia, ASCO 2013

wellcome trust sanger institute

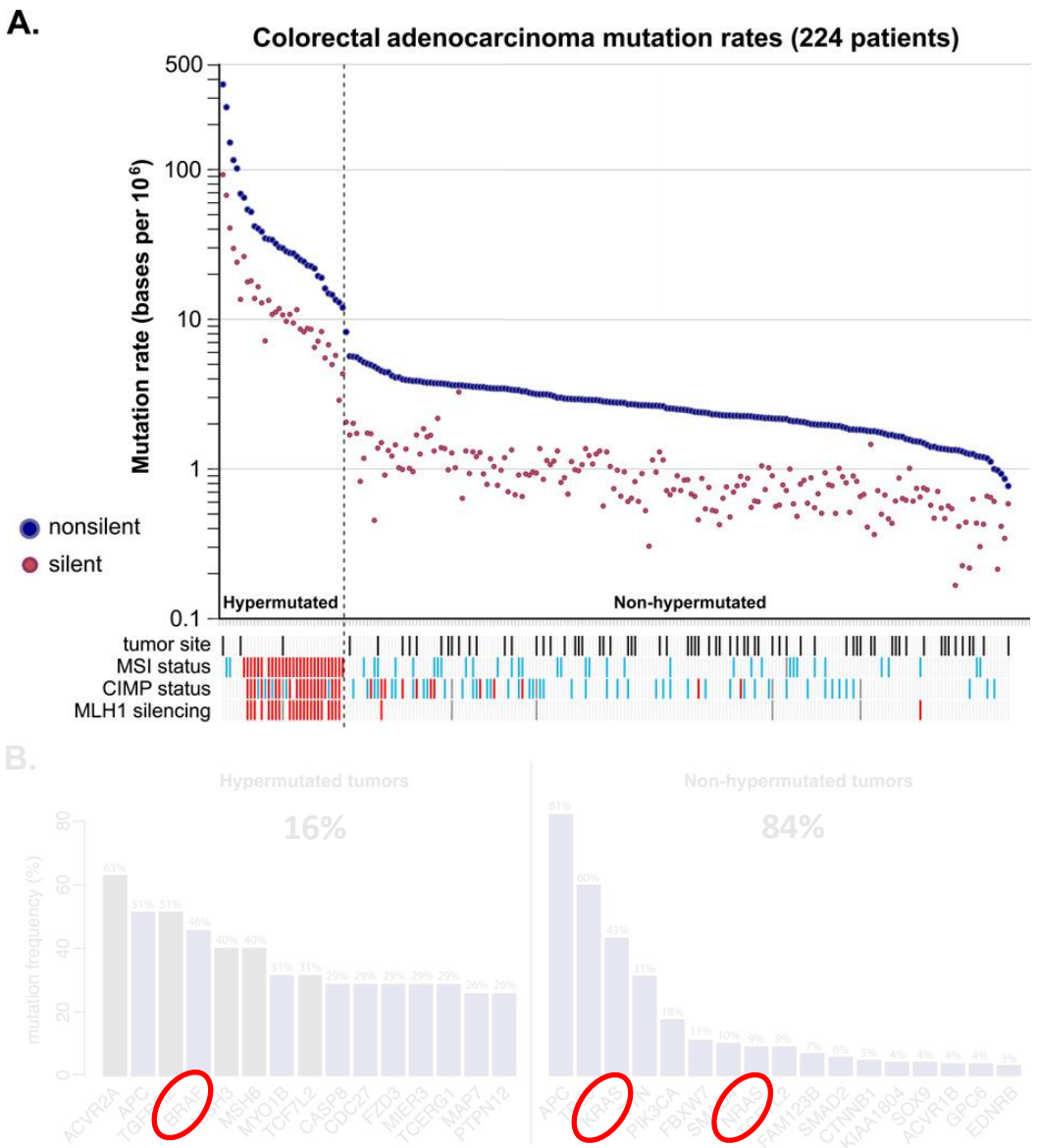
Adding ‘omics to classifying cancer



Nature Genetics **45**, 1113–1120 (2013)

wellcome trust sanger institute

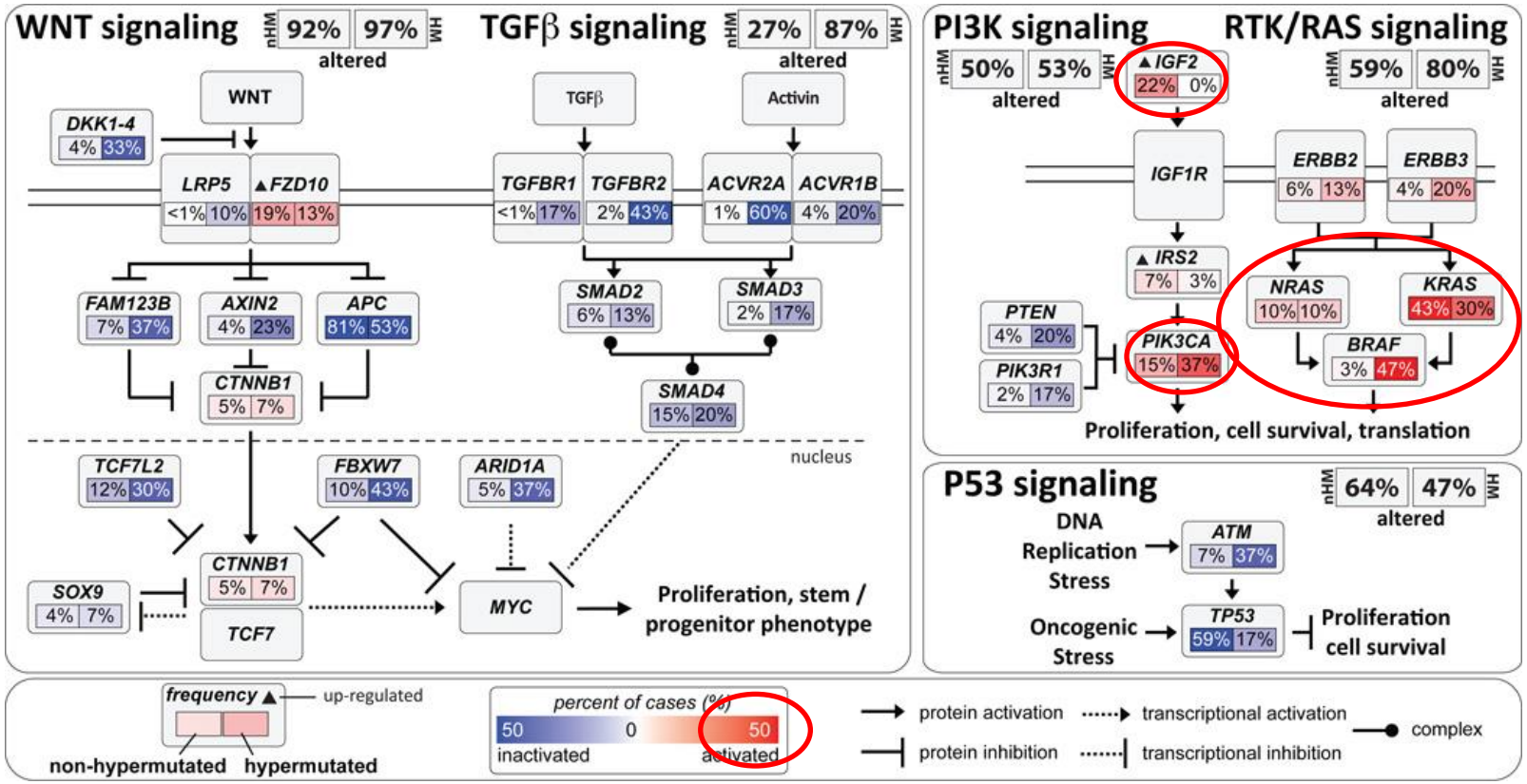
Mutation frequencies in colorectal cancer



Nature **487**, 330-337 (2012) doi:10.1038/nature11252

wellcome trust sanger institute

Pathways in colorectal cancer

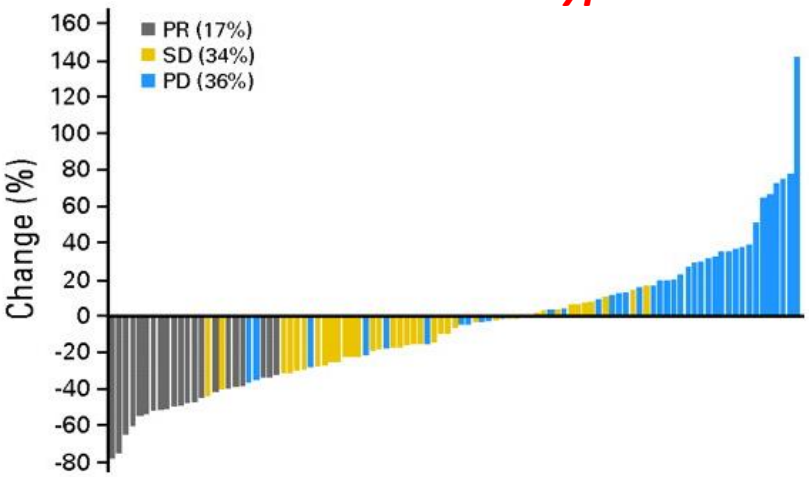


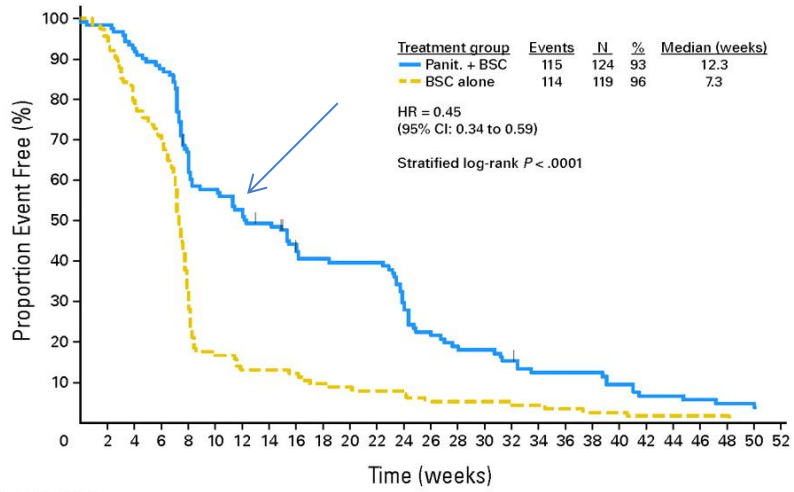
Nature **487**, 330-337 (2012) doi:10.1038/nature11252

wellcome trust sanger institute

EGFR therapy and KRAS in colorectal cancer

KRAS wild-type

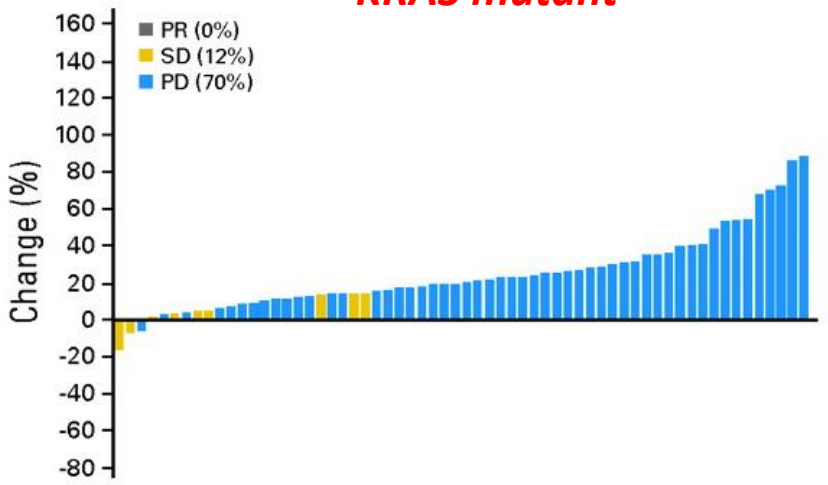


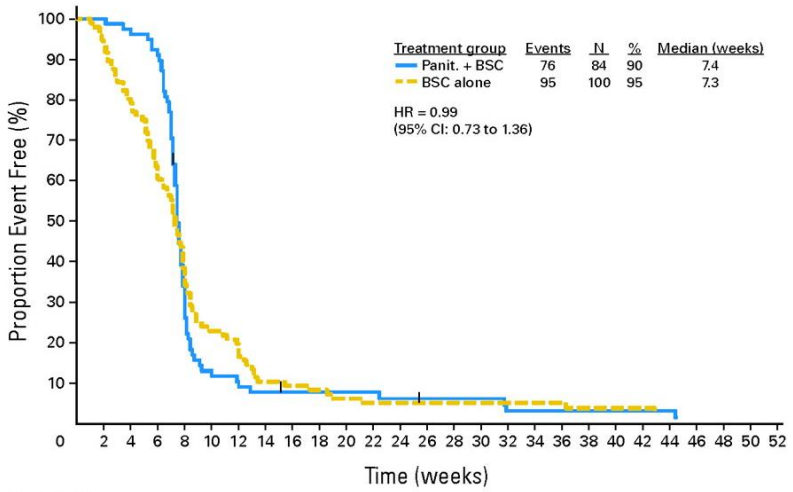


No. of patients at risk

Panit + BSC	124	119	112	106	80	69	63	58	50	45	44	44	33	25	21	20	17	13	13	13	10	7	7	6	5	5
BSC alone	119	109	91	81	38	20	15	15	14	11	10	9	9	6	6	6	6	5	4	3	3	2	2	2	2	1

KRAS mutant





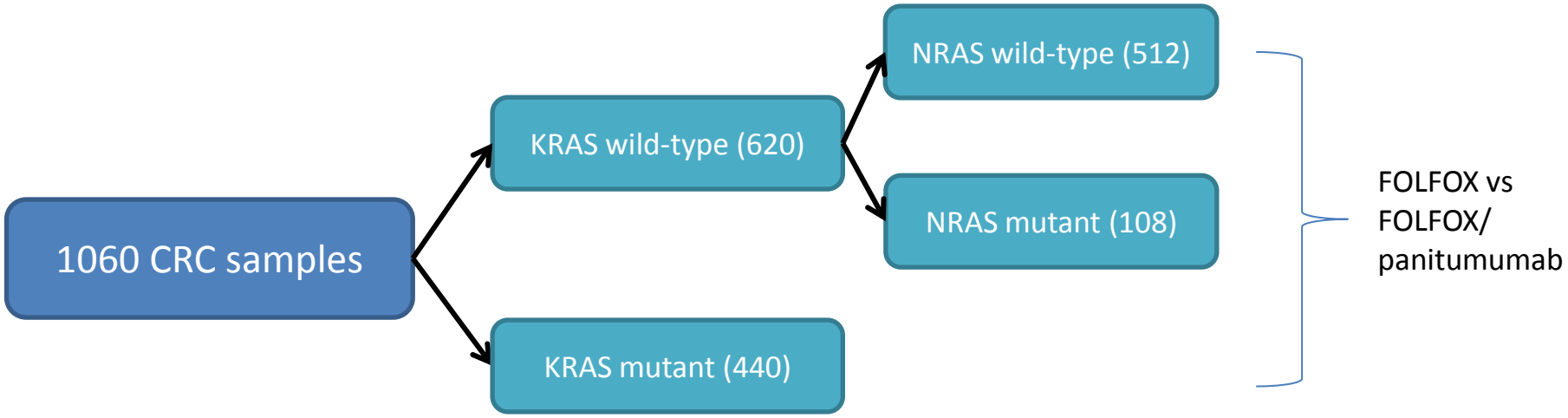
No. of patients at risk

Panit + BSC	84	78	76	72	26	10	8	6	5	5	5	5	4	4	4	4	2	2	2	2	2	2	1	1	1
BSC alone	100	91	77	61	37	22	19	10	9	8	6	5	5	4	4	4	4	4	4	3	3	3	2	2	2	2

JCO **26**:1626-1634 (2008)

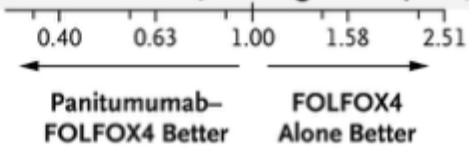
wellcome trust sanger institute

RAS mutations in colon cancer



B Overall Survival

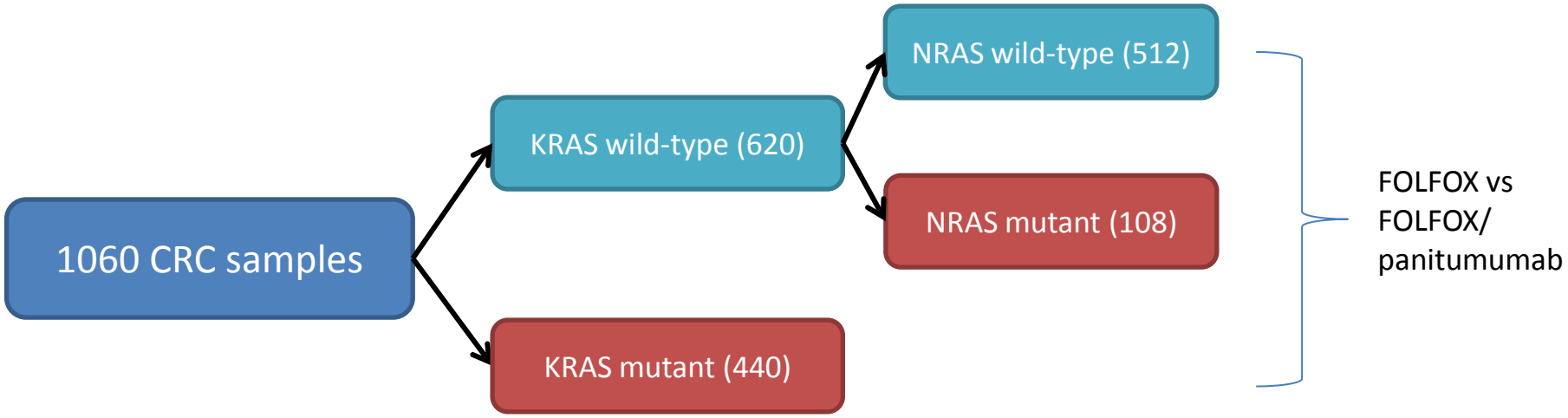
Subgroup	No.	Hazard Ratio for Death from Any Cause (95% CI)
Primary analysis		
Nonmutated *KRAS* exon 2	656	0.83 (0.67–1.02)
Mutated *KRAS* exon 2	440	1.24 (0.98–1.57)
Prospective–retrospective analysis		
Nonmutated *RAS*	512	0.78 (0.62–0.99)
Mutated *RAS*	548	1.25 (1.02–1.55)
Nonmutated *KRAS* exon 2, mutated other *RAS*	108	1.29 (0.79–2.10)



N Engl J Med **369**:1023-103 (2013)

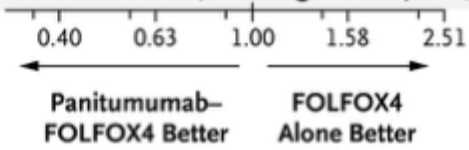
wellcome trust sanger institute

RAS mutations in colon cancer



B Overall Survival

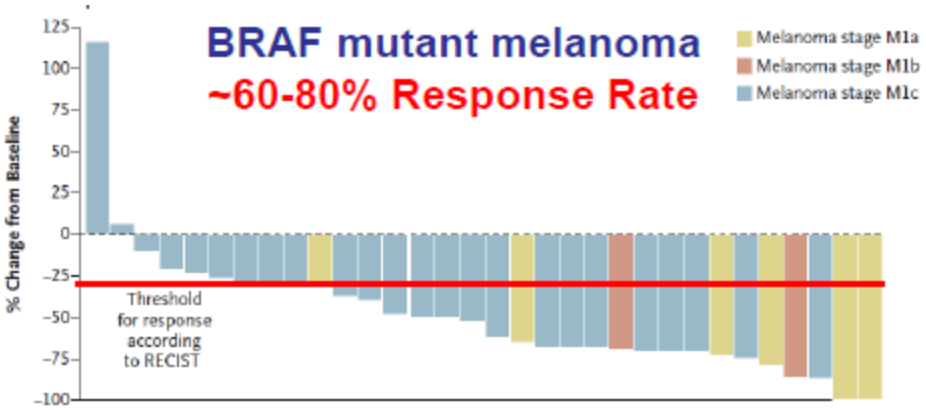
Subgroup	No.	Hazard Ratio for Death from Any Cause (95% CI)
Primary analysis		
Nonmutated *KRAS* exon 2	656	0.83 (0.67–1.02)
Mutated *KRAS* exon 2	440	1.24 (0.98–1.57)
Prospective–retrospective analysis		
Nonmutated *RAS*	512	0.78 (0.62–0.99)
Mutated *RAS*	548	1.25 (1.02–1.55)
Nonmutated *KRAS* exon 2, mutated other *RAS*	108	1.29 (0.79–2.10)

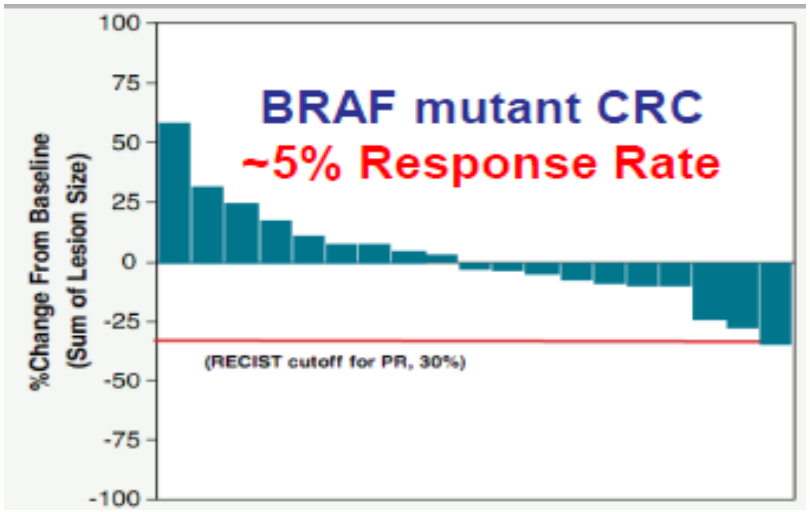


N Engl J Med **369**:1023-103 (2013)

wellcome trust sanger institute

BRAF mutant colon cancer





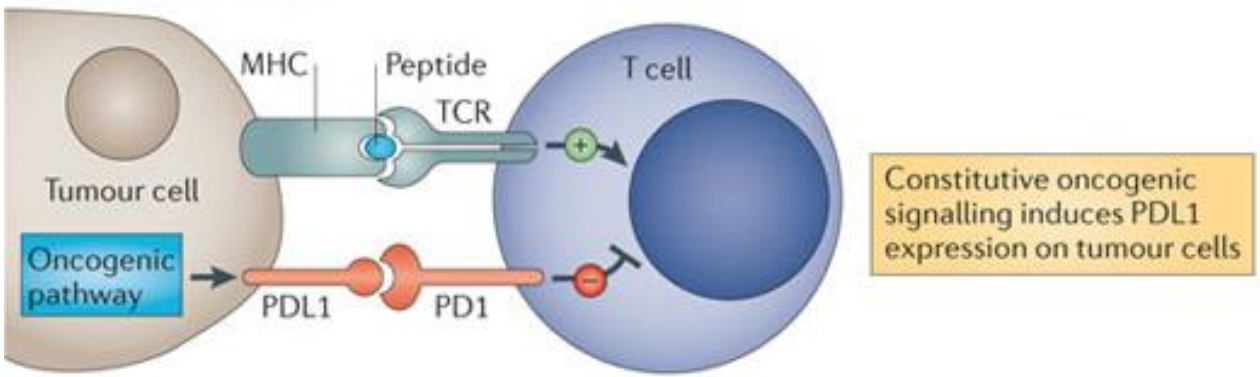
BRAF mutant colon cancer – BRAF/EGFR vs BRAF/MEK/EGFR

- 19 patients ; Phase I/II
- **BRAF/MEK/EGFR** triplet = 4/6 patients achieved partial responses and 2 pts with stable disease
- **BRAF/EGFR** doublet = 7/8 achieved SD as the best overall response.

1. *N Engl J Med* **363**;809-19 (2010)
2. *ASCO* abstract 3534 (2010)
3. *Nature* 000, 1-5 (2012) doi:10.1038/nature10868

wellcome trust sanger institute

Immune-checkpoint ligands on tumour cells



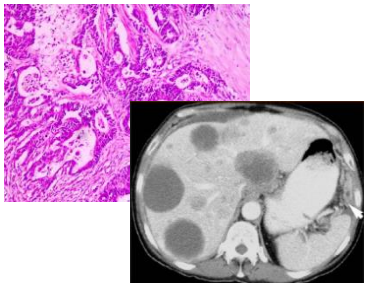
Response of metastatic colorectal cancer to anti-PD-1 therapy

Colon cancer subtypes (n=87)	PD-1 expression (TILs) (%)	PD-L1 (tumour cells) (%)
MSS colon cancers (n=60)	39%	13%
MSI-H colon cancers (n=27)	77%	38%

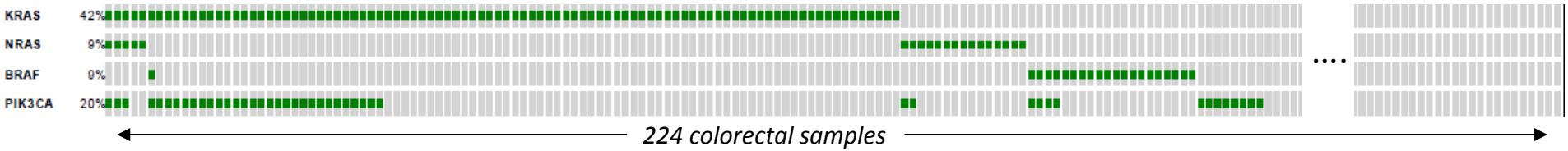
Gatalica *et al*, 2014 ASCO Annual Meeting.

wellcome trust sanger institute

Molecular stratification of colon cancer



KRAS/NRAS/BRAF wild-type	EGFR inhibitors
BRAF mutant	BRAF/MEK/EGFR inhibitors
KRAS mutant	EGFR/MEK inhibitors IGF1R/MEK inhibitors
Microsatellite instability	Anti-PD-1 or PD-L1 mAb



wellcome trust sanger institute

Genomically driven clinical trials

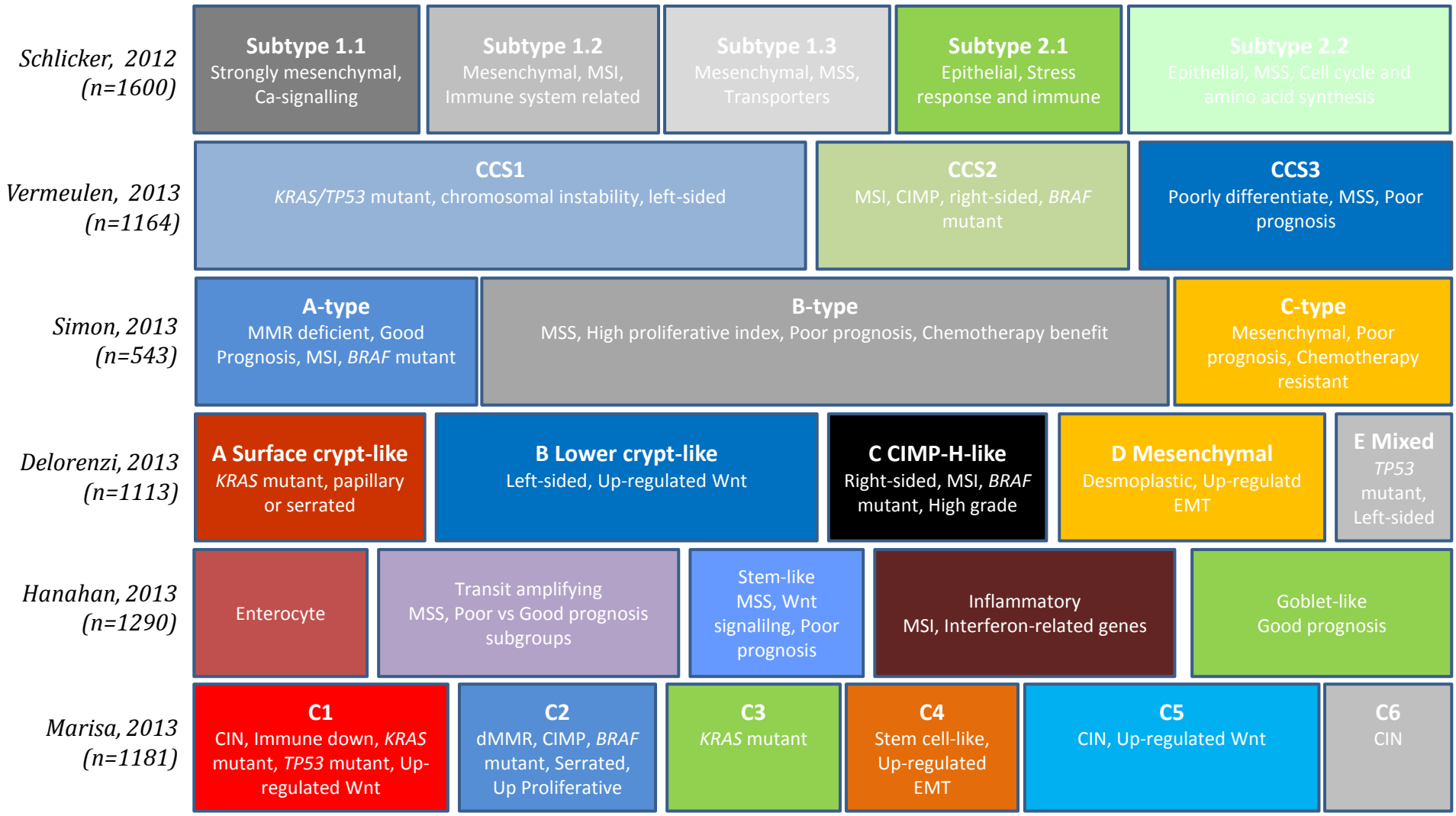
Genomic Profile	Strategy	Clinical Development
KRAS wt anti-EGFR naive	Novel anti-EGFR/HER3 mAbs	Phase II
	MEHD7945A + FOLFIRI versus cetuximab FOLFIRI	NCT01652482
	Anti-EGFR mAbs + irreversible ERBB TKIs	Phase II
	Cetuximab + afatinib versus cetuximab	NCT01919879
	PI3K pathway inhibitors	Phase II
	Cetuximab + irinotecan versus PF-05212384 + irinotecan	NCT01925274
KRAS wt progressing to anti-EGFR mAbs	Novel anti-EGFR mAbs with potent ADCC	Phase I/II
	SYM004	NCT01117428
	Anti-EGFR mAbs + MEK inhibitors	Phase II
	Panitumumab + MEK162	NCT01927341
KRAS wt HER2 amplified progressing to anti-EGFR mAbs	Dual anti-HER2 therapy	Phase II
	Trastuzumab + pertuzumab or lapatinib	Heracles trial
KRAS wt MET high progressing to anti-EGFR mAbs	Anti-EGFR mAbs + MET inhibitors	Phase II
	Cetuximab + AR0197	NCT01892527
Quadruple negative (KRAS, NRAS, BRAF, PIK3CA) progressing to anti-EGFR mAbs	Anti-EGFR mAbs + irreversible ERBB TKIs	Phase II
	Cetuximab + neratinib	NCT01960023
KRAS mut	Anti-EGFR mAbs + MEK inhibitors	Phase I/II
	Panitumumab + MEK162	NCT01927341
	Novel anti-EGFR/HER3 mAbs + MEK inhibitors	Phase I/II
	MEHD7945A + cobimetinib	NCT01986166
	Anti-IGF1R mAbs + MEK inhibitors	Phase I/II
	AMG-479 + MEK162	NCT01562899
KRAS G13D	Anti-EGFR mAbs	Phase II
	Cetuximab	ICECREAM
KRAS mut FcγRIIa genotype (CD32)	Anti-EGFR mAbs	Phase II
	Cetuximab	NCT01450319
BRAF mut (V600) anti-EGFR naive/refractory	BRAF TKIs + anti-EGFR mAbs ± PI3K pathway inhibitors	Phase I/II
	LGX818 + cetuximab ± BYL719	NCT01719380
	BRAF TKIs + anti-EGFR mAbs ± MEK inhibitors	Phase I/II
	Dabrafenib + panitumumab ± trametinib	NCT01750918
NRAS mut	MEK inhibitors ± PI3K pathway inhibitors	Phase I/II
	MEK162 + BKM120	NCT01363232
PIK3CA mut	PI3K pathway inhibitors	Phase I/II
	PF-05212384 ± irinotecan	NCT01347866
MSI	Anti-PD1 mAb	Phase II
	MK-3475	NCT01876511

Abbreviations: ADCC, antibody-dependent cell mediated cytotoxicity; mAb, monoclonal antibody; MSI, microsatellite instability; mut, mutated; TKI, tyrosine kinase inhibitor; wt, wild-type.

Am Soc Clin Oncol Educ Book. 2014:91-9. doi: 10.14694

wellcome trust sanger institute

…and more stratification



wellcome trust sanger institute

A Consensus Molecular Classification

Background:

Recently, a number of independent groups reported novel molecular subtypes in colorectal cancer (CRC).
A formal comparison across these classifiers is needed to reconcile findings and accelerate clinical translation.

Methods:

6 groups (15+ institutions) that analyzed more than 30 patient cohorts with gene expression data, spanning multiple platforms and sample preparation methods,
Each of the 6 classifiers (with 3-6 subtypes) was applied to the collection of public and proprietary datasets,
Encompassing over 4,000 samples, mostly stage II-III CRC.

Results:

Subtype concordance analysis readily yielded a clear consensus on 4 CRC molecular subtypes (CMS1-4) in 84% of samples

Conclusions:

This is the first example of a large-scale, community based comparison of cancer subtypes,
Within the largest collection of CRC samples we identified recurrent signals of 4 biologically distinct subtype classes enriched for key clinical, pathway and molecular traits.

J Clin Oncol 32:5s, 2014 (suppl; abstr 3511) Colorectal Cancer Subtyping Consortium

A Consensus Molecular Classification

J Clin Oncol 32:5s, 2014 (suppl; abstr 3511) Colorectal Cancer Subtyping Consortium

wellcome trust sanger institute

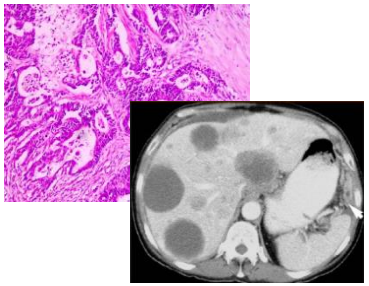
A Consensus Molecular Classification

CMS1	**13%**	Females, older age, right colon, MSI, hypermutation, *BRAF* mut, immune activation	Better RFS, intermediate OS, worse SaR
CMS2	**35%**	Left colon, epithelial, MSS, high CIN, *TP53* mut, WNT/MYC pathway activation	Intermediate RFS, better OS, better SaR
CMS3	**11%**	Epithelial, CIN/MSI, *KRAS* mut, *MYC* ampl, IGFBP2 overexpression	Intermediate RFS, OS and SaR
CMS4	**20%**	Younger age, stage III/IV, mesenchymal, CIN/MSI, TGFβ/VEGF activation, NOTCH3 overexpression	Worse RFS, worse OS Intermediate SaR
Unclassified	**21%**	Mixed subtype with variable epithelial-mesenchymal activation?	Intermediate RFS, OS and SaR

J Clin Oncol 32:5s, 2014 (suppl; abstr 3511) Colorectal Cancer Subtyping Consortium

wellcome trust sanger institute

Tomorrow's stratification of colon cancer?



KRAS/NRAS/BRAF wild-type	EGFR inhibitors
BRAF mutant	BRAF/MEK/EGFR inhibitors
KRAS mutant	EGFR/MEK inhibitors IGF1R/MEK inhibitors
Microsatellite instability	Anti-PD-1 or PD-L1 mAb

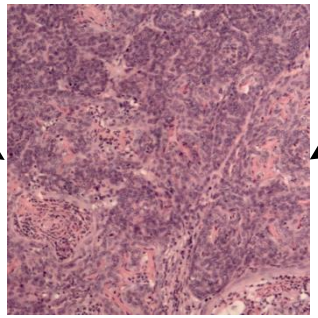
CMS1	13%	Females, older age, right colon, MSI, hypermutation, *BRAF* mut, immune activation	Better RFS, intermediate OS, worse SaR
CMS2	35%	Left colon, epithelial, MSS, high CIN, *TP53* mut, WNT/MYC pathway activation	Intermediate RFS, better OS, better SaR
CMS3	11%	Epithelial, CIN/MSI, *KRAS* mut, *MYC* ampl, IGFBP2 overexpression	Intermediate RFS, OS and SaR
CMS4	20%	Younger age, stage III/IV, mesenchymal, CIN/MSI, TGFβ/VEGF activation, NOTCH3 overexpression	Worse RFS, worse OS Intermediate SaR
Unclassified	21%	Mixed subtype with variable epithelial-mesenchymal activation?	Intermediate RFS, OS and SaR

wellcome trust sanger institute

Cancer diagnostics: now and then

Zacharias and Hans Jansen
(ca 1595)

Modern microscope
(ca 2010)



The light microscope remains the central cancer diagnostic tool for 400 years

wellcome trust sanger institute

Cancer diagnostics: now and then

Next-generation sequencing

Genome
Transcriptome
Epigenome

Cellular origin
Morphology
Differentiation/grading

Unified
Classification?

wellcome trust sanger institute

Conclusions

- Molecular subtypes in colorectal cancer that predict for drug response
- A subset of MSI tumours may respond to PD-1 / PD-L1 inhibitors
- The Sage consensus clusters provide additional stratification ? clinical significance
- Expect these clusters to be built into many future clinical trials
- Many clinical trials now appearing that stratify colorectal cancers for treatment