Diagnosis and management issues in colorectal cancer

- What can molecular pathology offer for optimal decision making?

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Disclosure slide

- Member of advisory board for AMGEN
- Speaker honoraria from FALK Pharma, GmbH and ROCHE
- Third party funds from MERCK for immunohistochemistry in a clinical trial

What can (molecular) pathology offer?

Better understanding of the disease

Prognostic markers

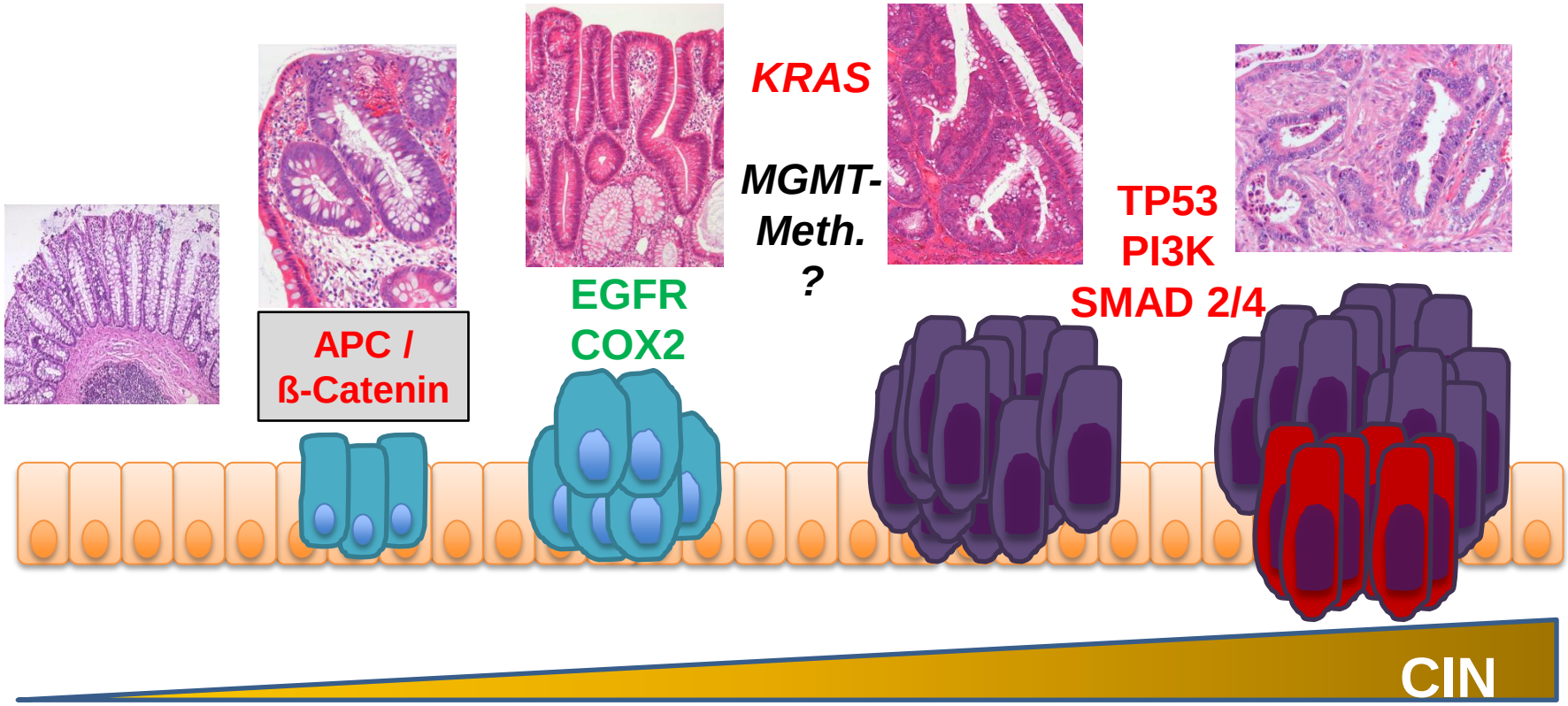
Predictive markers

Different pathways of colorectal carcinogenesis

- Adenoma-Carcinoma-Sequence (FAP)
- HNPCC, Lynch-Syndrom
- Serrated Pathway
- Alternate Pathway

Classical Adenoma-Carcinoma-Sequence (sporadic and FAP)

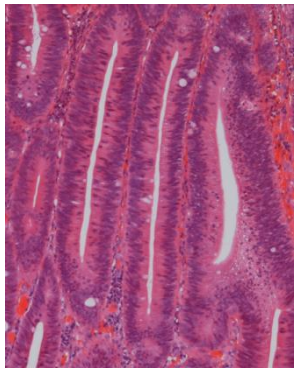
60-70%

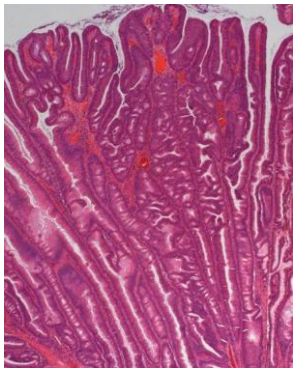


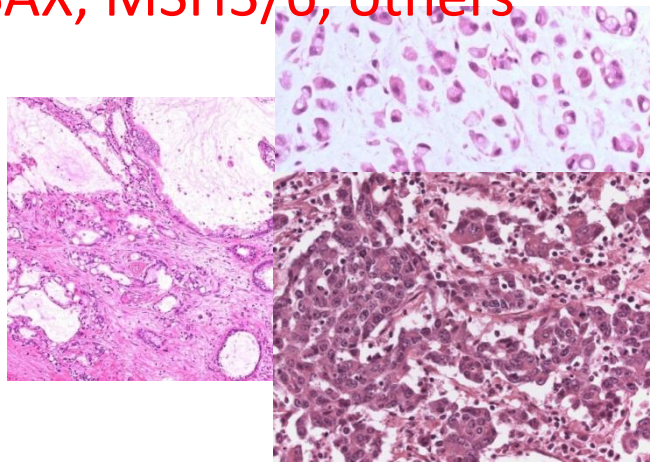
HNPCC, Lynch-Syndrom
~2-3%

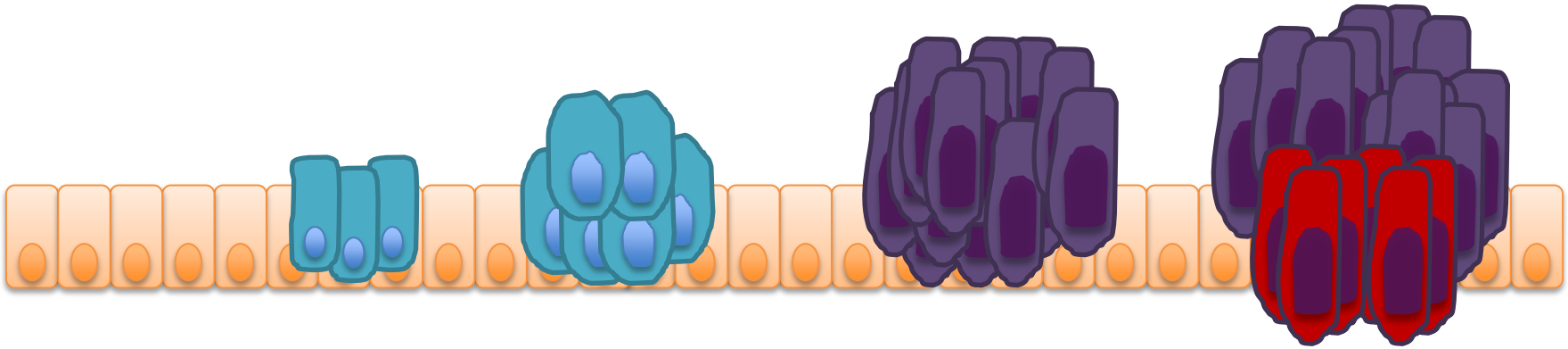
TGFßIIR, IGF2R, Caspase 5, BAX, MSH3/6, others

germline-mutation MMR-Gene (MSH2, MLH1) gatekeeper





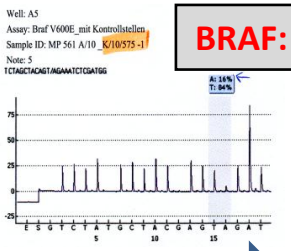




MSI

Serrated Pathway of colorectal carcinogenesis

~15-20%



BRAF: V600E

p16INK4a-Expr.↑ und IGFBP7-Sekr. ↑ (oncogene-induced senescence)

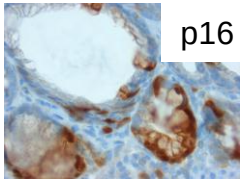
Normal colorectal epithelium

Proliferation boost to ACF (serr.)

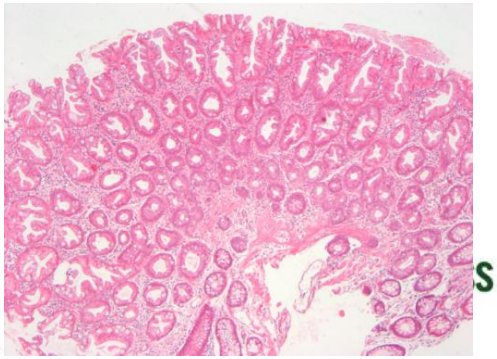
CIMP
p16INK4a, IGFBP7 methylation

Alteration of Wnt-pathway: aberrant ß-Catenin via MCC-methylation

Hyperplastic polyp (MVHP): senescence via p16, IGFBP7 etc..

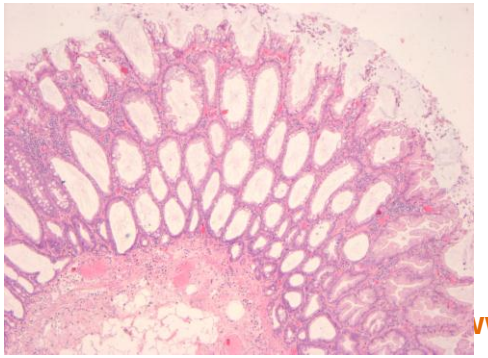


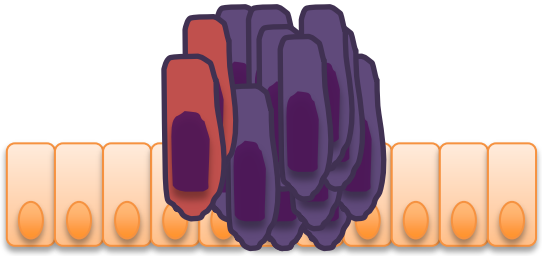
progression to SSA w/o dysplasia

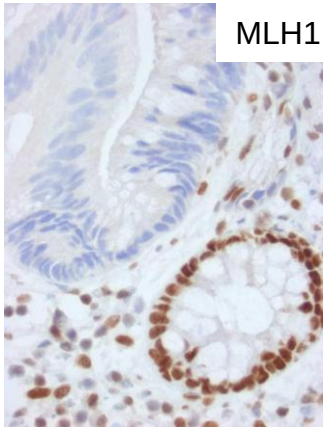


STOP

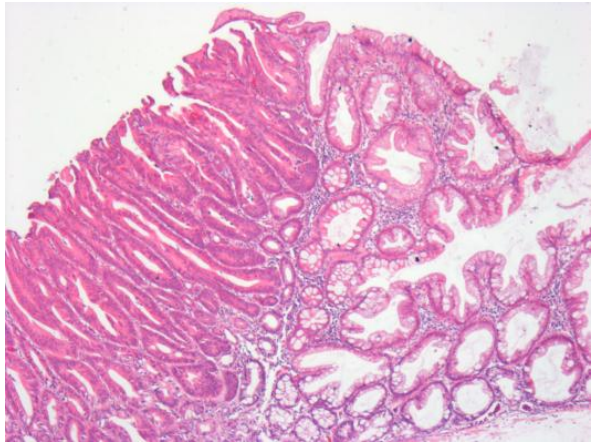
senescent lesion, no progression





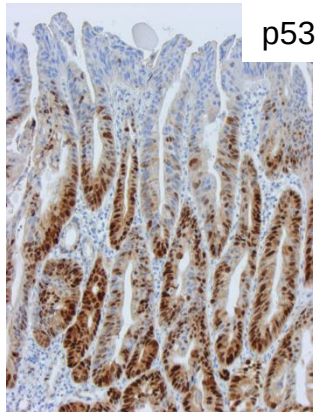


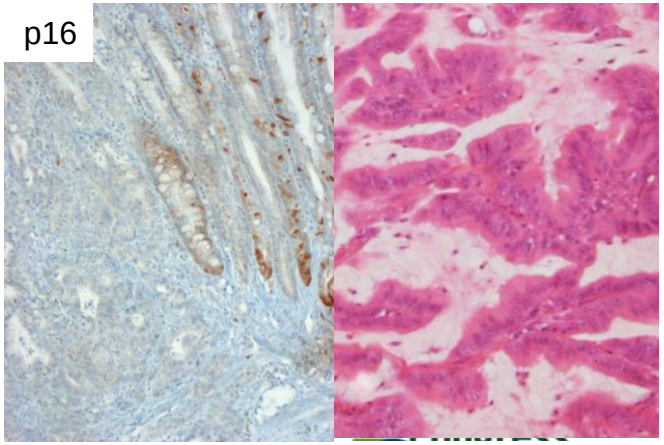
MLH1-loss
in dysplastic
epithelium;
MSI;
TGFßRII-Mut.



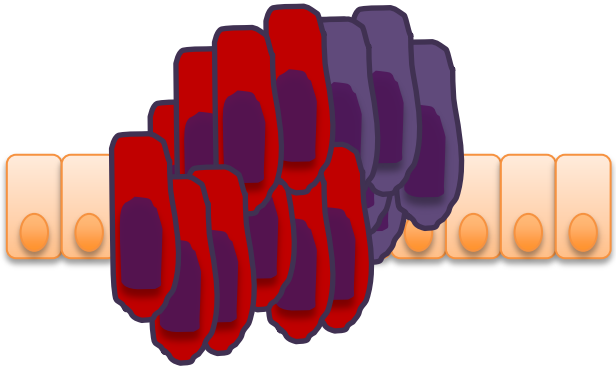
Progression to SSA
/w dysplasia

Other
CIMP-Targets
Wnt-pathway?
18q LOH?
p53-Mutation?

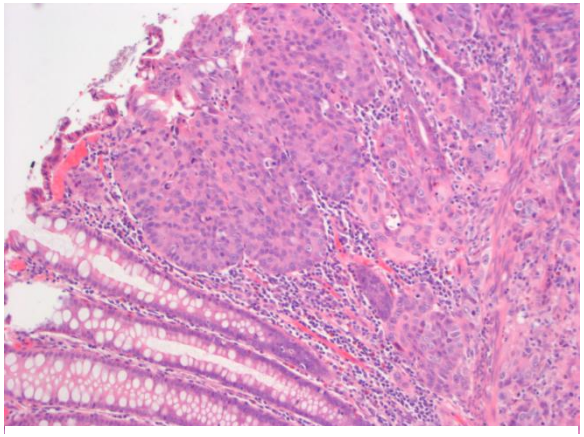




Progression to MSI carcinoma
CIMP-H, BRAF mut.



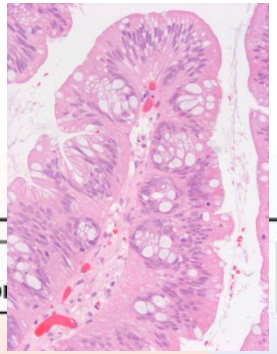
Progression to carcinoma

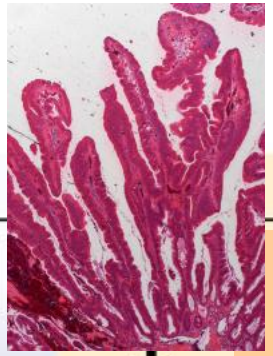


Progression to MSS carcinoma
CIMP-H, BRAF mut.

Alternate Pathway of colorectal carcinogenesis

~15-20%





Leggett B & Whitehall V, 2010

Different pathways of sporadic colorectal carcinogenesis

	Adenoma-Carcinoma-Sequence	Alternate (mixed type) pathway	Serrated pathway
Precursor lesion	Adenoma	Villous adenoma or traditional serrated adenoma	Sessile serrated adenoma
Key mutation	APC	KRAS	BRAF
Secondary genetic alterations	Mutations in KRAS, p53	CIMP low, mutations of APC, p53	CIMP high (silencing of hMLH1, MGMT and/or p16)
MSI status	MSS	MSS or MSI-L	MSI-H
Frequency	60 %	15-20%	15-20%
Localisation	Left > right	Left > right	Right > left

Different pathways of colorectal carcinogenesis

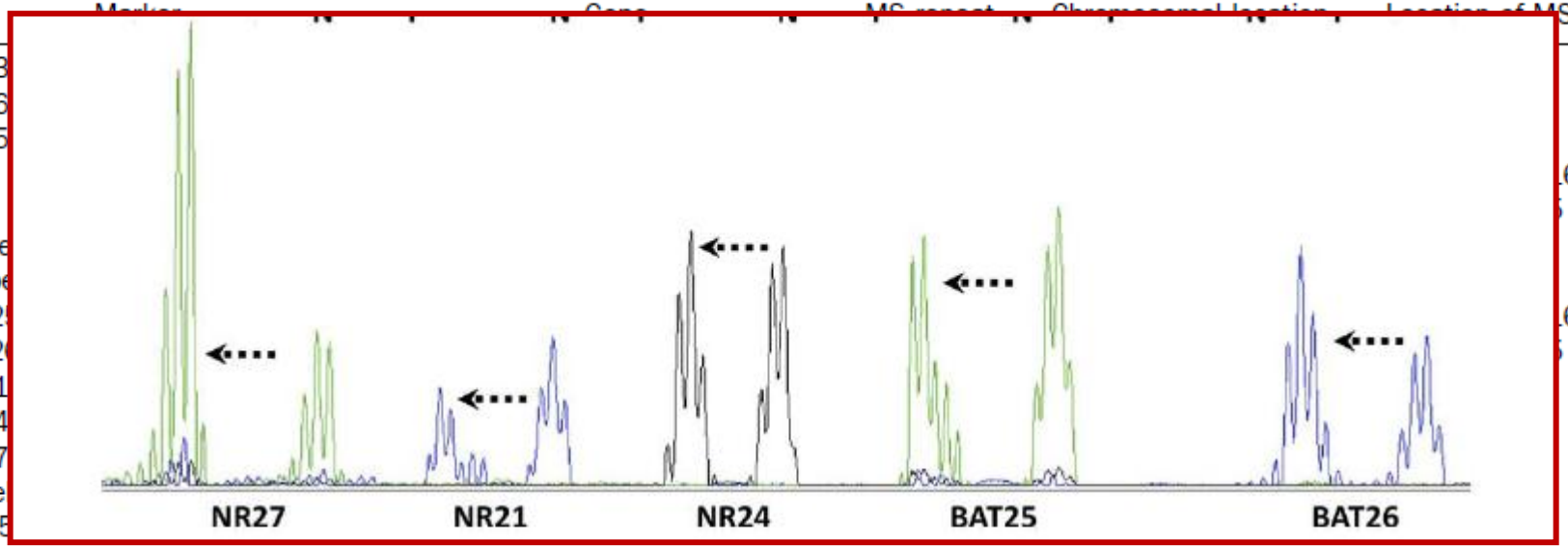
- Colorectal cancer is not one disease, it consists of different subentities, developed through different pathways of carcinogenesis
- Certain mutations may be present as either drivers or passengers and thus may have different prognostic value in different pathways

Prognostic markers in colorectal cancer

- pTNM
- Microsatellite instability
- BRAF
- Conflicting data: p53, loss of 18q, 17p, gain of 20q13, KRAS, etc.

Microsatellite instability (MSI): definition

Table 2. Microsatellite Markers Used in Diagnosis of Microsatellite Instability in Colorectal Cancer



MS, microsatellite; NCI, National Cancer Institute.

Boland & Goel, Gastroenterology 2010

- **2/5 panel-markers instable or > 30% of tested markers instable** } **MSI-H**
- **1/5 panel-markern instable or < 30% of tested markers instable** } **MSI-L**
- **All markers stable** } **MSS**

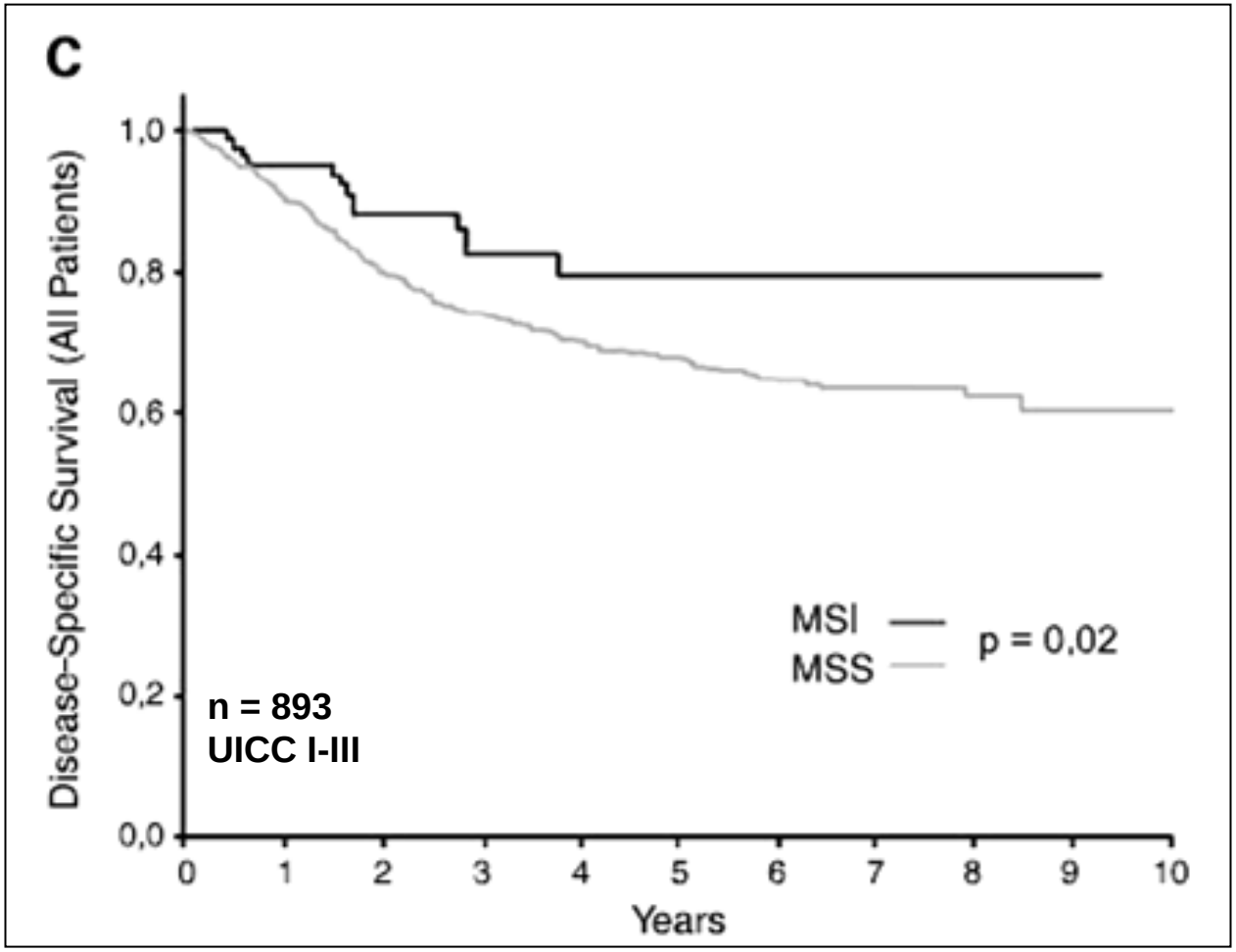
MSI-H frequency in CRC

Author and journal	year	n	method	frequency
Watanabe et al., NEJM	2001	229	MSI/IHC	20%
Samowitz et al., Cancer Epid Prev	2001	1986	MSI	12%
Barratt et al., Lancet	2001	368	MSI/IHC	24%
Ribic et al., NEJM	2003	570	MSI/IHC	17%
Westra et al., J Clin Oncol	2005	273	MSI	16%
Sinicrope et al., Gastroenterology	2006	528	IHC	18%
Malesci et al., Clin Cancer Res	2007	893	MSI	10%
Deschoolmeester et al., EJC	2008	241	MSI	12%
Nehls et al., IJCD	2009	344	MSI	15%
Kim et al., Cancer ChemoPrev	2010	134	MSI	9%
Qui tal., CancGenProt	2011	803	MSI	10%
Lin et al., IJCD	2011	709	MSI	9%
Yoon et al., JournalGastroHepatol	2011	2028	IHC	10%
		8914		**10%**

MSI-H as a favorable prognostic marker in CRC

Source	Stage / Treatment	Endpoint	MMR-D vs MMR-P HR (95% CI); p-value
Ribic et al[1]	II/III Surgery alone	Overall survival	0.31 (0.14-0.72) p=0.004
Sargent et al[2]	II/III Surgery alone	Disease-free survival Overall survival	0.46 (0.22-0.95); p=0.03 0.51 (0.24-1.10); p=0.06
Gray et al[3] (QUASAR)	II Surgery alone	Recurrence-free interval	0.31 (0.15-0.63) p<0.001
Roth et al[4] (PETACC-3)	II 5FU ± irinotecan	Relapse-free survival	0.30 p=0.004

MSI-H as a favorable prognostic marker in CRC



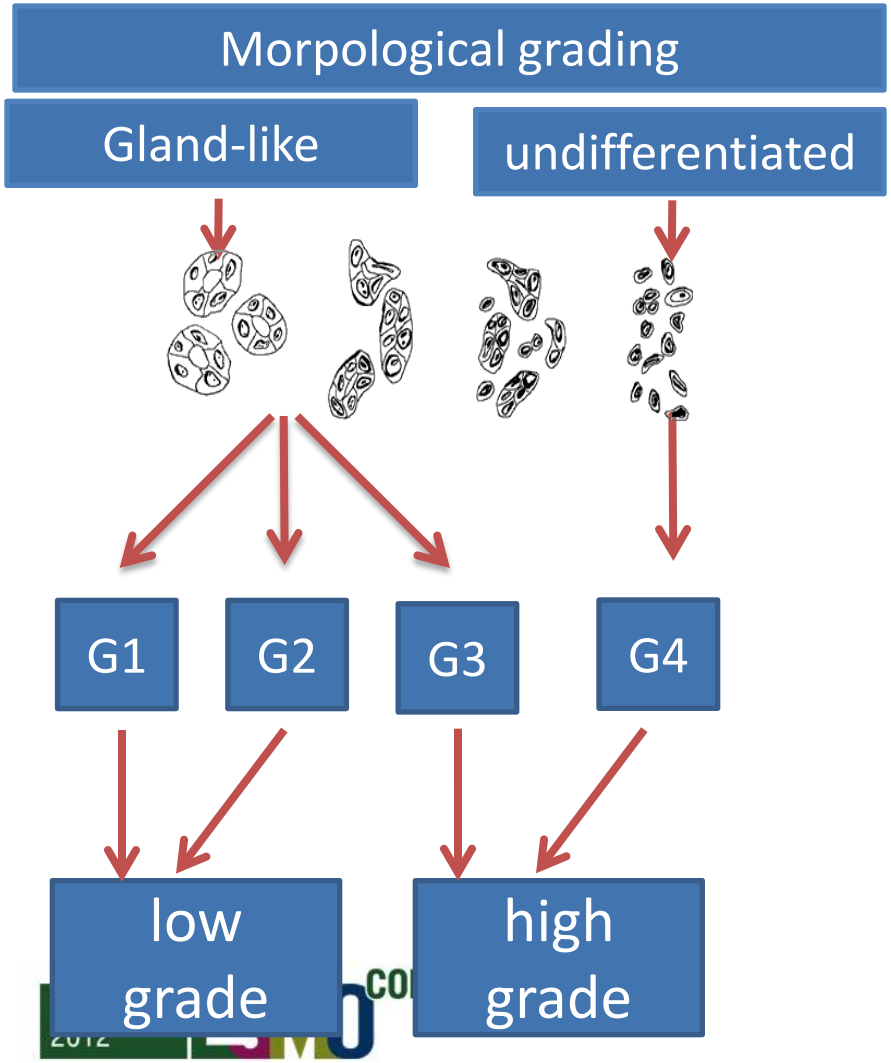
Malesci A et al. (2007) Clin Cancer Res 13:3831-3839

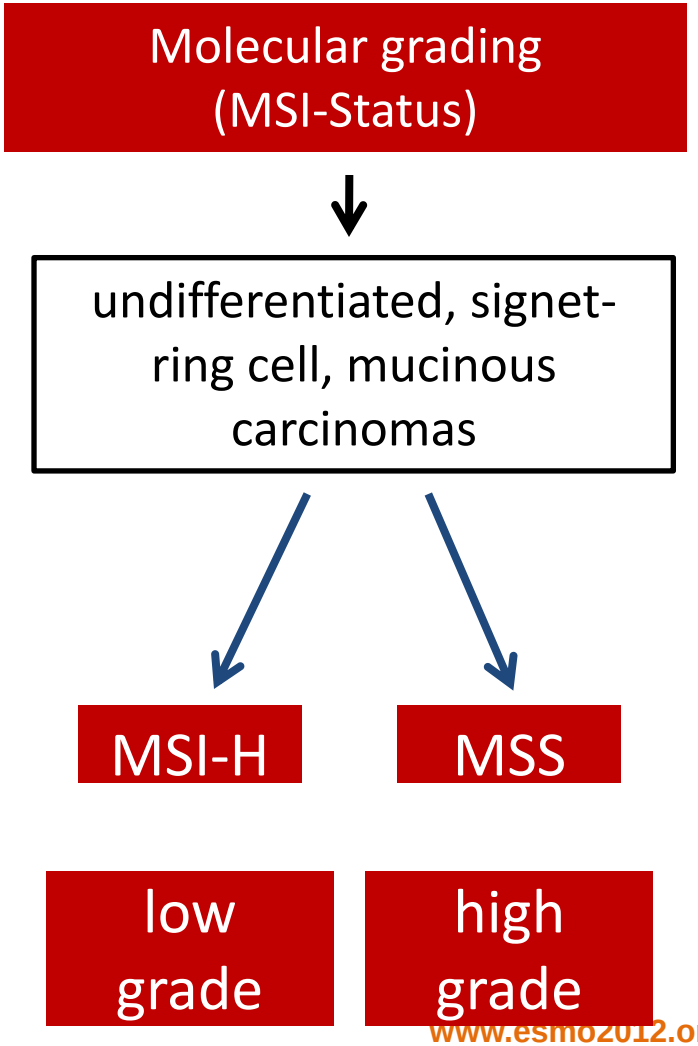
MSI-H tumors have less metastases

		MSS n (%)	MSI-H n (%)	p-value
UICC stage	I	146 (18,2)	13 (14,6)	<0,001
	II	204 (25,4)	42 (47,2)	
	III	237 (29,4)	27 (30,3)	
	IV	217 (27,9)	**7 (7,9)**	
lymphnode metastases				
yes		423 (52,6)	33 (37,1)	<0,001
no		381 (47,4)	56 (62,9)	
distant Metastases				
yes		217 (27,0)	7 (7,9)	<0,001
no		587 (73,0)	**82 (92,1)**	

Malesci A et al. (2007) Clin Cancer Res 13: 3831-3839

Molecular grading according to MSI (WHO 2010)





MSI-H: prognostic value in association with CIMP-phenotype

Table 3. Crude and relative survival at 5 y in MSS and MSI groups according to methylation status

		Crude	95% CI	Relative	95% CI
MSS	No-CIMP	53.1	46.8–59.0	64.0	56.4–70.7
	CIMP-Low	40.8	33.5–47.9	50.6	41.6–59.0
	CIMP-High	27.9	14.5–43.0	37.7	18.9–56.6
MSI-H	No-CIMP	54.3	19.1–79.8	61.2	18.5–86.7
	CIMP-Low	52.9	23.8–75.4	74.3	18.6–94.9
	CIMP-High	57.7	43.8–69.4	72.5	53.8–84.7

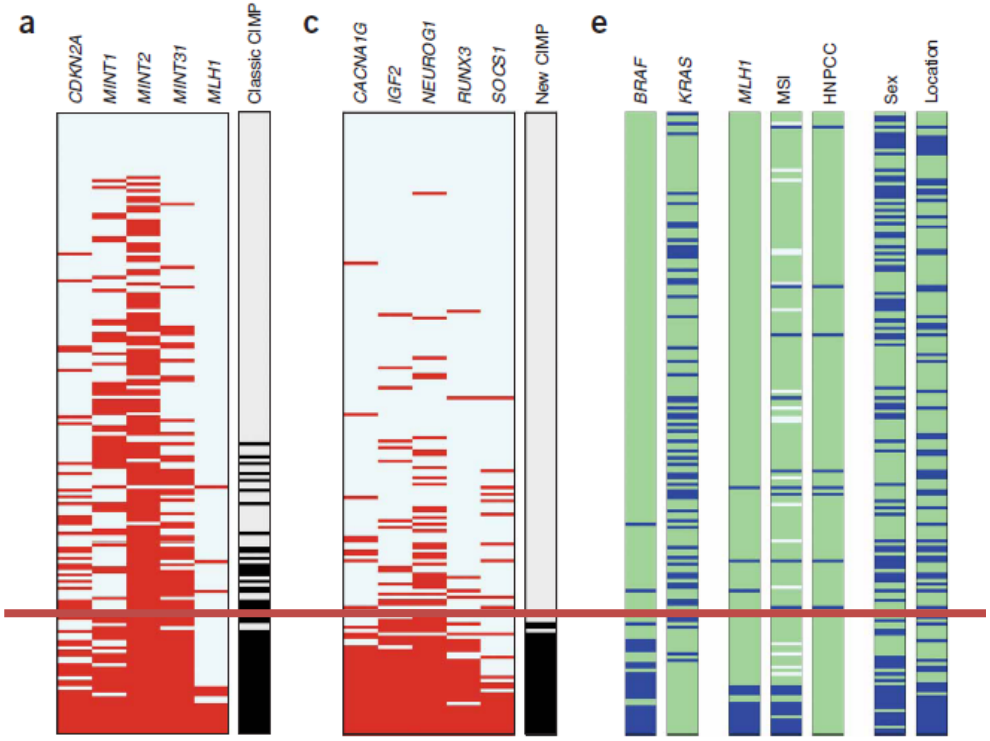
populationsbased study, UICC-stage I-IV, n=582

Barault, Cancer Res 2008

CpG-Island-Methylator-Phenotype (CIMP)

- Definition CIMP+: Methylation of ≥ 3 loci

- CIMP-H: 4-5 loci
- CIMP-L: 1-3 loci
- No CIMP: 0 loci



Weisenberger, Nature Genetics 2006
Barault, Cancer Res 2008

BRAF-Mutation

- Wild-type BRAF is required for response to Panitumumab or Cetuximab in metastatic CRC*

→ predictive marker??

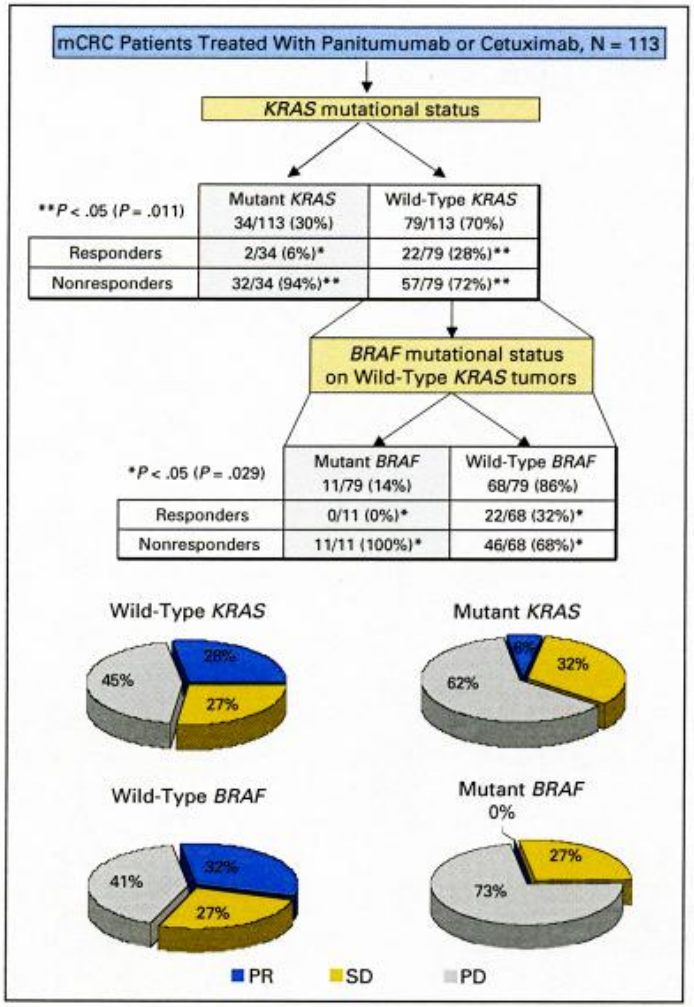
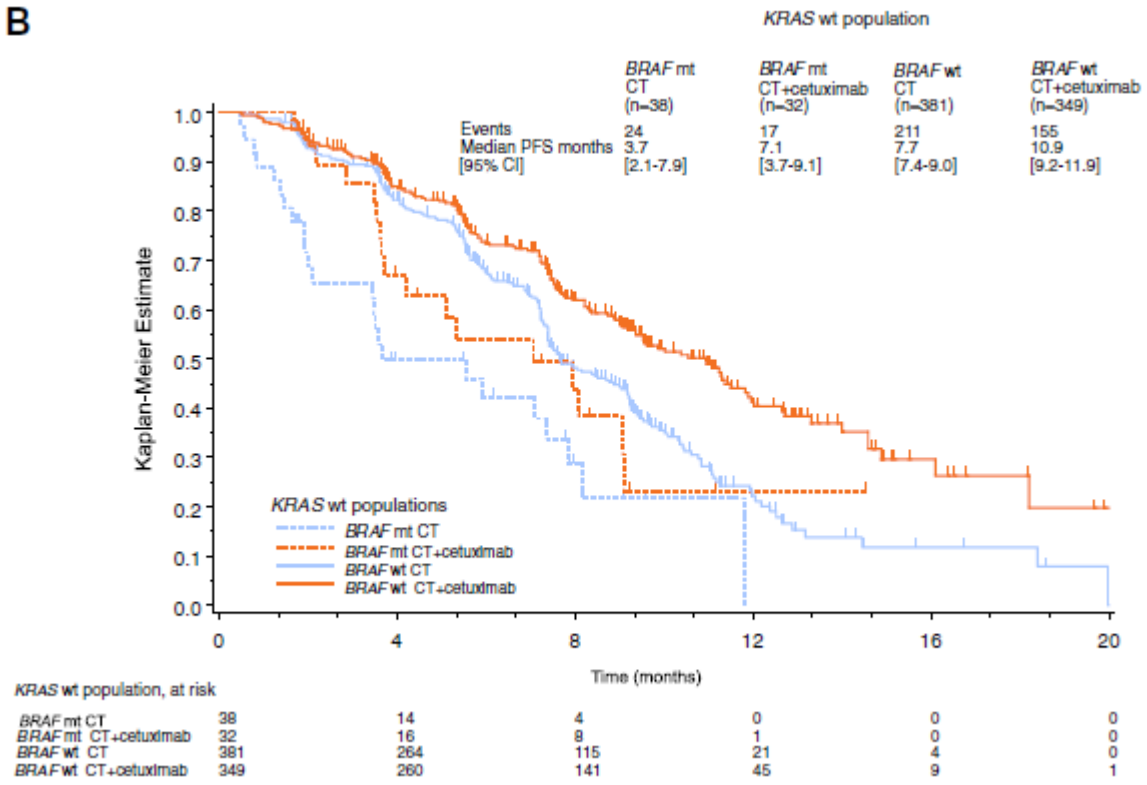


Fig 1. *KRAS* and *BRAF* mutations correlate with lack of response to treatment with monoclonal antibodies targeting epidermal growth factor receptor. The number of responders and nonresponders (stable disease [SD] + progressive disease [PD]) is indicated according to *KRAS* or *BRAF* mutational status. The percentage of patients displaying partial response (PR), SD, or PD is shown in the pie charts. mCRC, metastatic colorectal cancer.

*Di Nicolantonio F et al., 2008

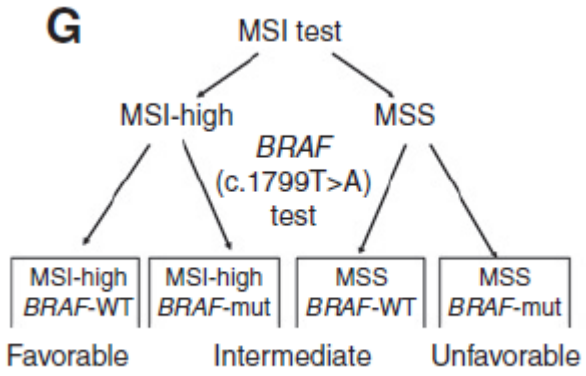
BRAF as a prognostic marker



Bokemeyer, EJC 2012
CRYSTAL- and OPUS-trials
n = 1535
UICC stage IV

No significant difference between treatment arms

Prognostic value of BRAF is dependent on MSI-Status



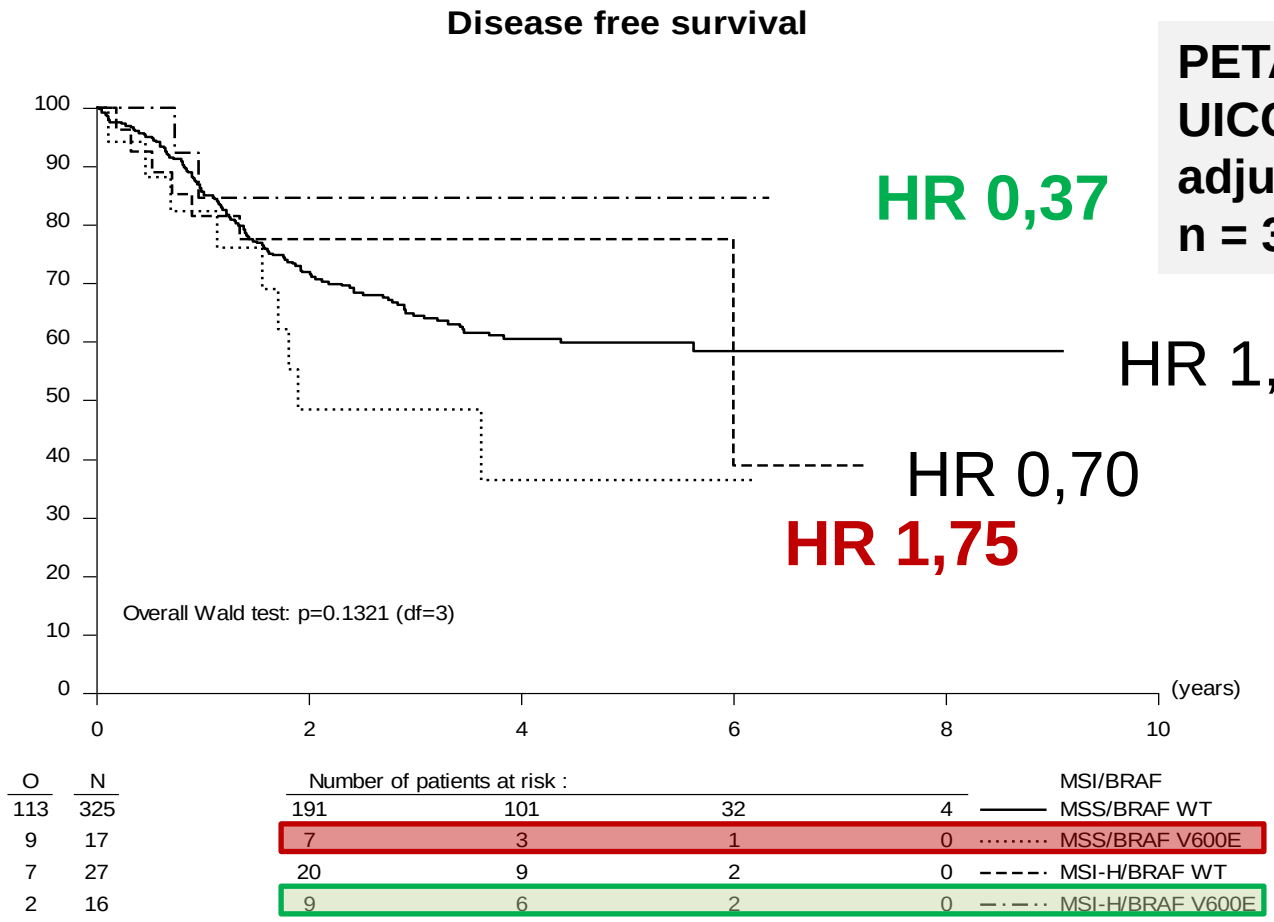
CALGB-Study
adjuvant therapy 5-FU vs. Irinotecan
UICC Stage III
n=506

Table 3. Combined *BRAF* mutation and MSI status and clinical outcome in stage III colon cancer

BRAF mutation and MSI status	No.	RFS		DFS		OS	
		Five-year survival probability	Multivariate HR (95% CI)	Five-year survival probability	Multivariate HR (95% CI)	Five-year survival probability	Multivariate HR (95% CI)
BRAF wild-type MSS	387	0.65	1 (referent)	0.63	1 (referent)	0.75	1 (referent)
BRAF wild-type MSI-high	43	0.74	0.57 (0.31–1.07)	0.74	0.51 (0.27–0.95)	0.79	0.54 (0.27–1.08)
BRAF-mutant MSS	41	0.48	1.38 (0.84–2.26)	0.45	1.38 (0.85–2.25)	0.61	1.61 (0.96–2.69)
BRAF-mutant MSI-high	34	0.74	0.63 (0.32–1.28)	0.67	0.81 (0.44–1.51)	0.66	1.02 (0.54–1.93)

Ogino, Clin Cancer Res 2012

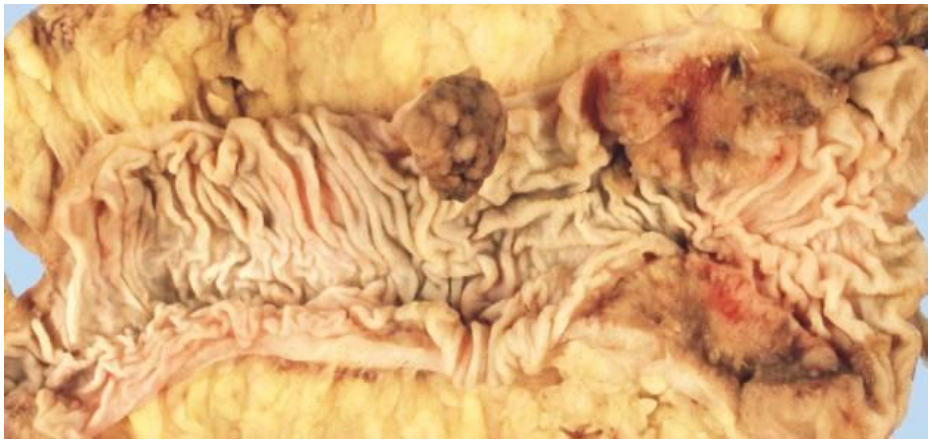
Prognostic value of BRAF is dependent on MSI-Status



PETACC2
UICC stage III
adjuvant 5-FU
n = 385

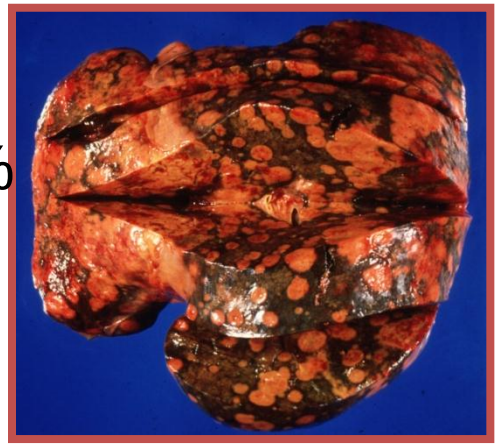
Prognostic value of BRAF is dependent on MSI-Status

BRAF-Mutation



12%

5%



UICC stage I stage II/III stage IV

BRAF V600E + MSI

BRAF V600E + MSS

MSI-H and BRAF : Prognostic Relevance for CRC with CIMP

Good prognosis:

CIMP +
MLH1-Methylation
MSI-H

± *BRAF*-Mutation

proximal colon
elderly women

mucinous or medullary cancers
tumor infiltrating lympho-cytes

ca. 50%

CIMP +
MSS/MSI-L

proximal colon
old age

mucinous carcinomas
advanced pT

ca. 50%

Bad prognosis:

CIMP-H +
MSS

+ *BRAF*-Mutation
3,19fold higher risk for tumor-associated †

Summary prognostic markers

- MSI and BRAF are prognostic markers (for the serrated pathway)
- MSI-H is a strong prognostic indicator in stage II and may lead to a better risk stratification
- MSI-status must be tested for molecular grading in mucinous, undifferentiated and signet ring cell cancers (WHO 2010)
- MSI-status should be tested for its prognostic value and for detection of patients with Lynch-Syndrom
- Prognostic impact of BRAF depends on MSI-status
- For the adenoma-carcinoma-sequence and the alternate pathway, there is abundant but conflicting data on various markers (p53, 18q, 17p-, EGFR, KRAS, etc.)

Predictive markers

- MSI for 5-FU, irinotecan ?
- TS, TP, DPD for 5-FU-therapy
- ERCC1 for oxaliplatin
- KRAS for anti-EGFR-therapy
-
-

MSI-H: Predictive value for 5-FU

Table 3. Chemotherapy in Colorectal Cancer with Microsatellite Instability

First author	Year	Study design	Adjuvant chemotherapy regimen	No. of patients (MSI/MSS)	Benefit of chemotherapy in patients with MSI
Elsaleh[135]	2000	Consecutive patients	5-FU	63/669	Yes
Ribic[141]	2003	Randomized controlled study	5-FU	95/475	No
Carethers[94]	2004	Consecutive patients	5-FU	36/168	No
de Vos tot Nederveen Cappel[143]	2004	Lynch syndrome patients	5-FU	28/0	No
Storojeva[136]	2005	Randomized controlled study	5-FU/mitomycin	21/139	No
Benatti[142]	2005	Consecutive patients	5-FU	256/1007	No
Popat[51]	2005	Pooled data from multiple studies	5-FU	1277/6365	No
Lanza[137]	2006	Consecutive patients	5-FU	75/288	No
Jover[138]	2006	Consecutive patients	5-FU	66/688	No
Kim[126]	2007	Prospective study	5-FU/leuocovorin	98/444	No
Des Guetz[139]	2009	Meta-analysis	—	454/2871	No
Bertagnolli[140]	2009	Randomized controlled study	5-FU/irinotecan/leucovorin	106/677	No

5-FU, 5-fluorouracil; MSS, microsatellite stable.

Boland & Goel, Gastroenterology 2010

MSI-H: negative predictive value for 5-FU therapy?

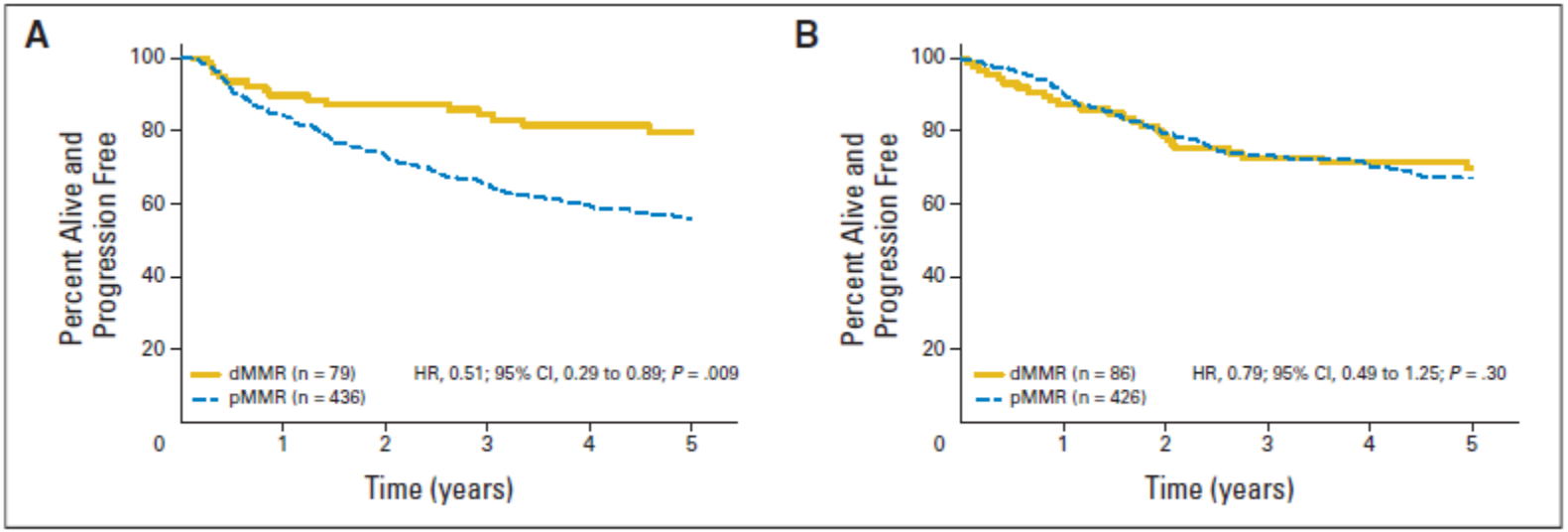


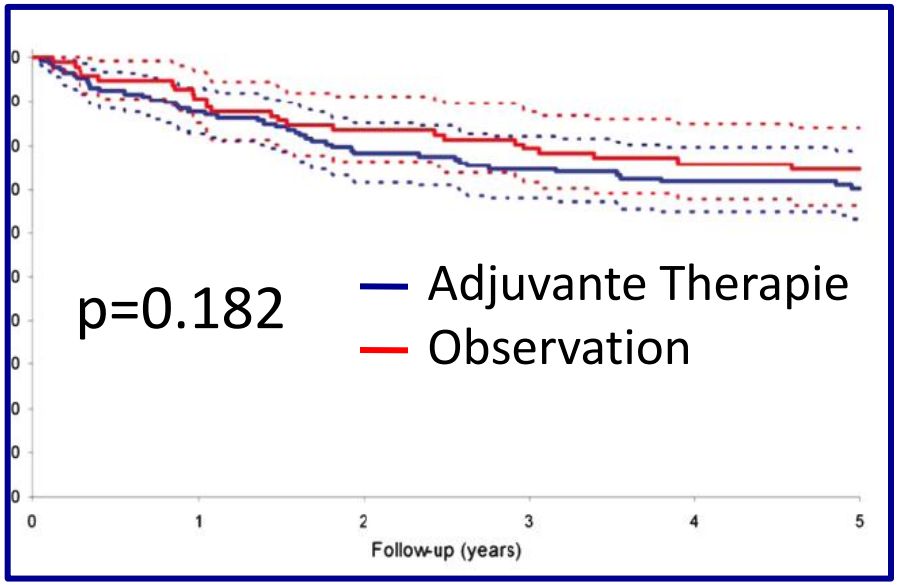
Fig 1. (A) Disease-free survival (DFS) in untreated patients by DNA mismatch repair (MMR) status. (B) DFS in treated patients by MMR. dMMR, defective DNA mismatch repair; pMMR, proficient DNA mismatch repair.

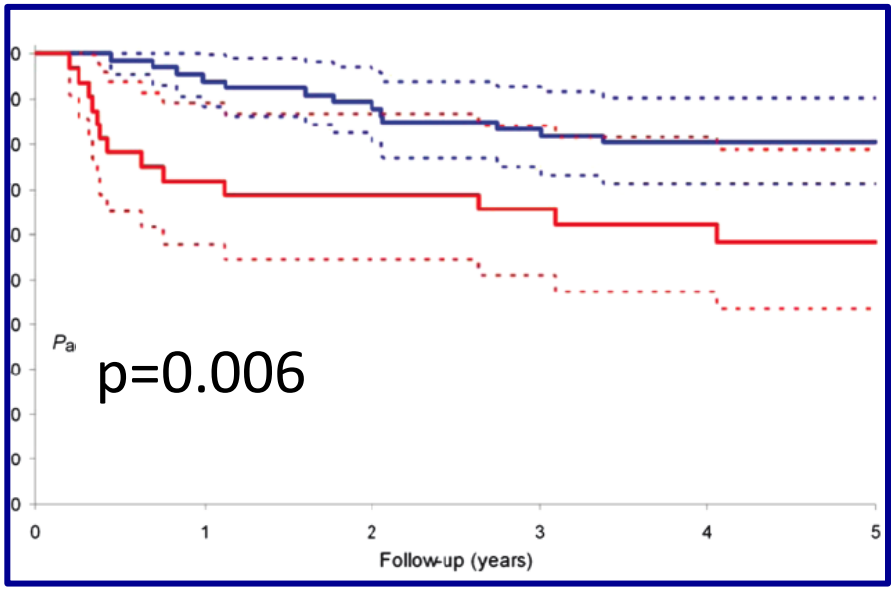
Sargent, JCO 2008
N= 1027
UICC stage II and III

Predictive value of MSI-H dependent on background?

Sporadic MSI

„Hereditary“ MSI
(BRAF-WT, <55y, MSH-2)



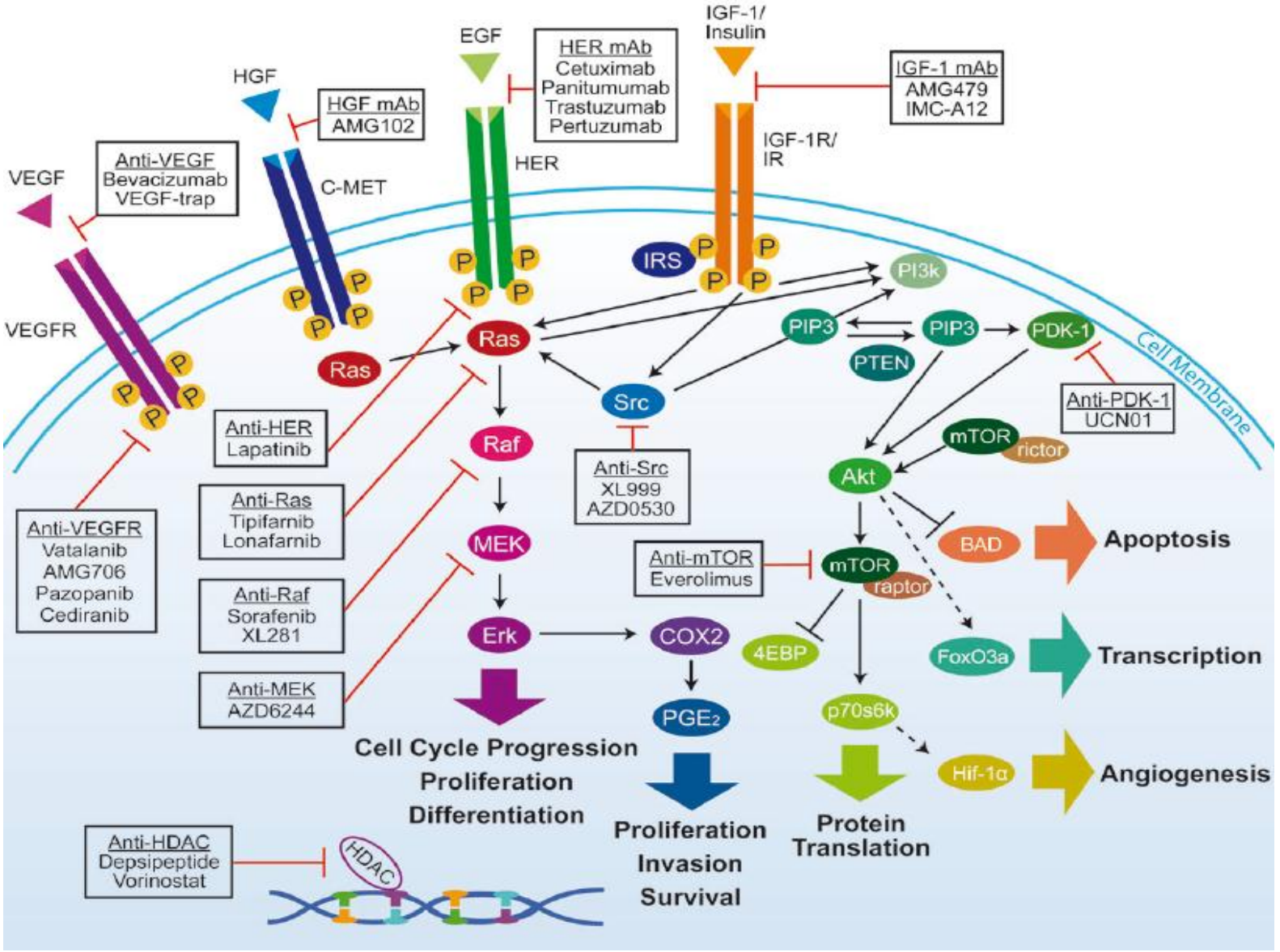


>> no benefit from 5-FU

Benefit from 5-FU ?
Sinicrope, J Natl Cancer Inst 2011
n = 778 UICC stage 2

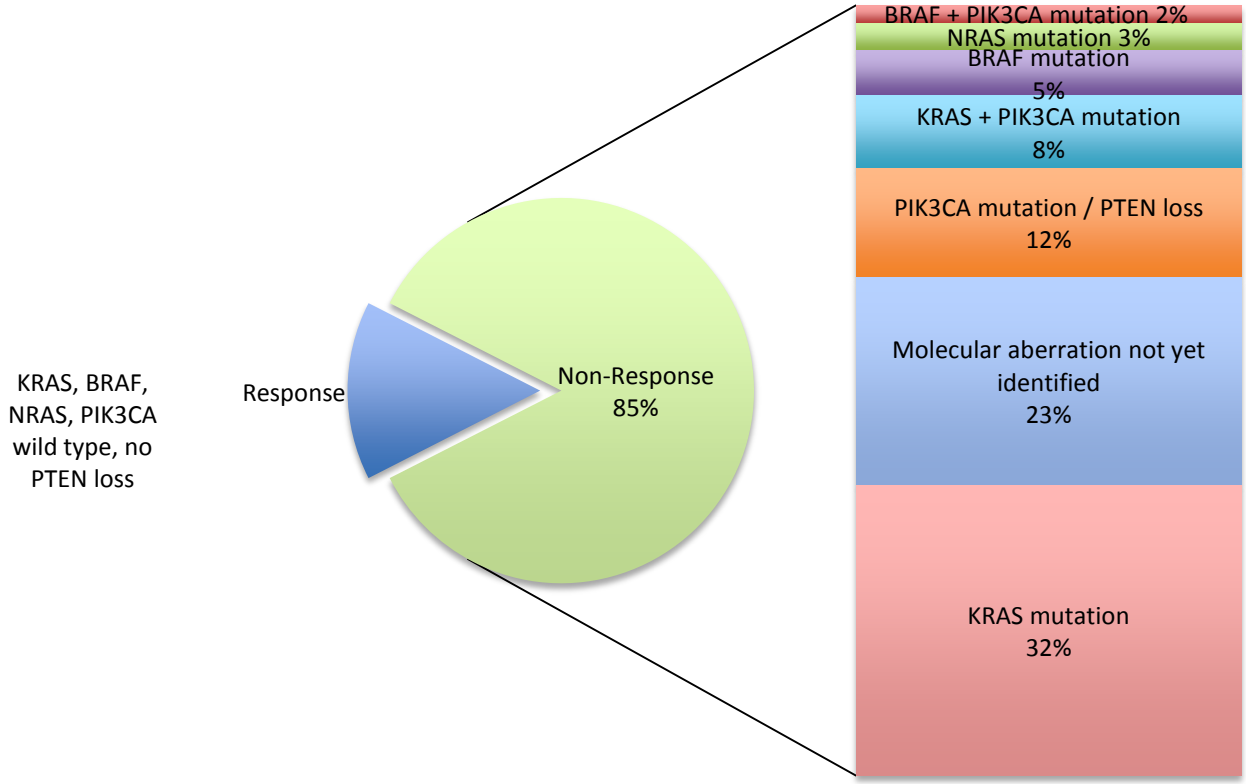
Summary MSI-H

- The predictive value of MSI-H is questionable and may depend on background (hereditary vs. sporadic)



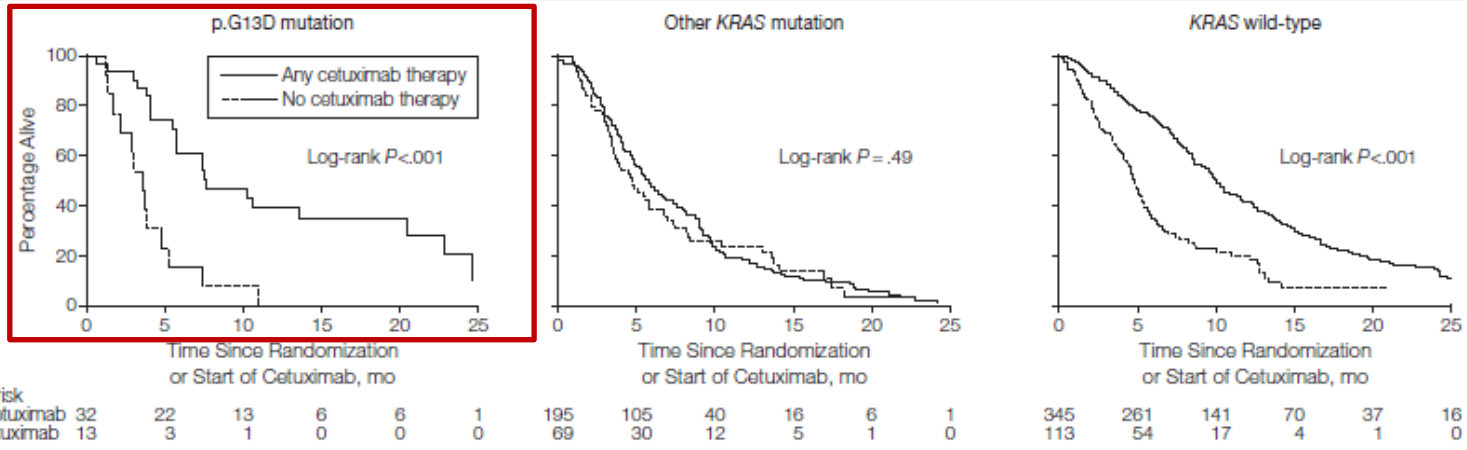
RAS-/RAF-pathway

KRAS-mutation as a negative predictor for anti-EGFR-treatment



Association of *KRAS* p.G13D Mutation With Outcome in Patients With Chemotherapy-Refractory Metastatic Colorectal Cancer Treated With Cetuximab

Figure 1. Overall Survival: Predictive Analysis by *KRAS* Status for Patients Receiving Any Cetuximab-Based Therapy vs No Cetuximab



The no cetuximab group for all patients from the pooled data set is the best supportive care group from the CO.17 trial.

De Roock W et al., JAMA 2010

Summary KRAS and EGFR

- KRAS-Mutation is a negative predictor of response to anti-EGFR-therapy, but
- Other members of the pathway may also contribute to non-response: PI3K, PTEN, NRAS, EGFR, etc.
- Different KRAS-mutations may have varying predictive impact
- Amphiregulin and epiregulin may prove to be the first positive predictive markers for anti-EGFR-treatment

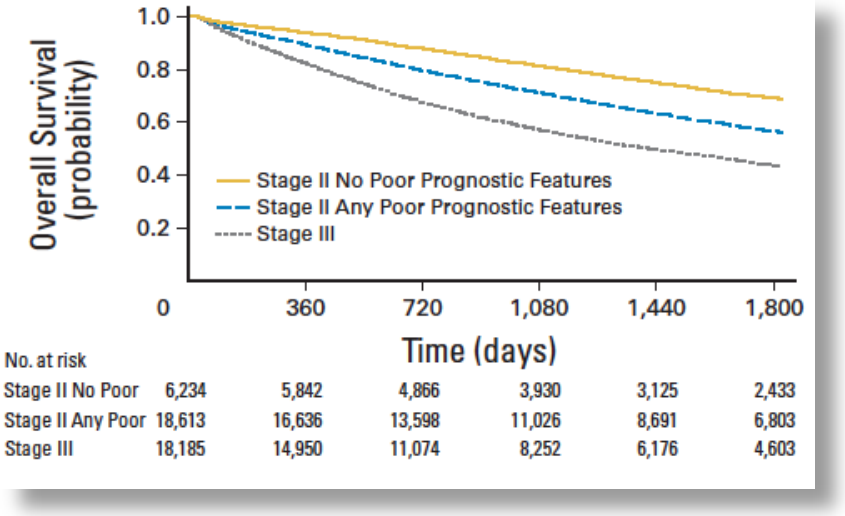
Molecular signatures in CRC – do we need them?

YES

- To select stage II patients who are at risk of recurrence (~15%)
- To select stage III patients who are at low risk of recurrence (~50%)
- To select stage II and III patients who will benefit from adjuvant chemotherapy

UICC Stage II and Stage III prognosis

- Inside each tumour stage the risk of recurrence is depending of various risk factors
- For UICC stage II : obstruction/perforation, emergent admission, T4 stage, high-grade, less than 12 LN are indicative of poor prognosis
- For stage III the number of positive lymph-nodes are associated with the risk of recurrence
- The only validated prognostic biomarker is the MSI status in stage II patients



O'Connor J Clin Oncol 2011;29:3381-88
Weisser J Clin Oncol 2011; 29:4796-802
Roth J Cin Oncol 2009; 28:466-74

The different signatures for UICC stage II

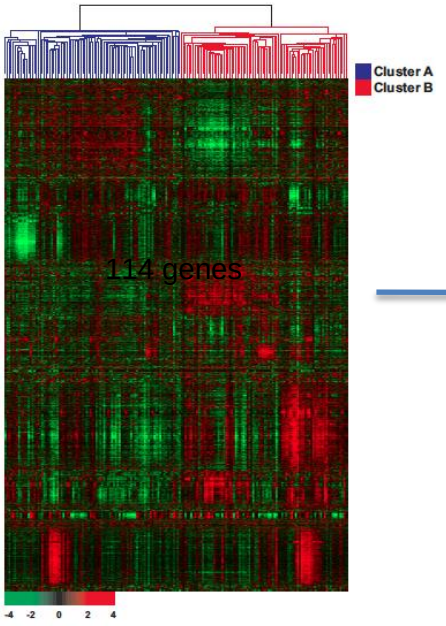
- 114 genes → MD Anderson
- 12 genes → Recurrence score™ Genomic Health
- 18 genes → Coloprint Agendia
- 634 genes → Colorectal DSA Almac
- 13 genes → ColoGuideEX

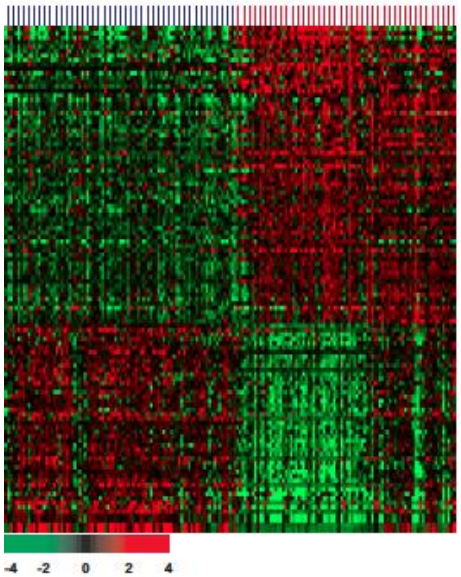
114 genes signatures Fresh frozen tissues (MD Anderson)

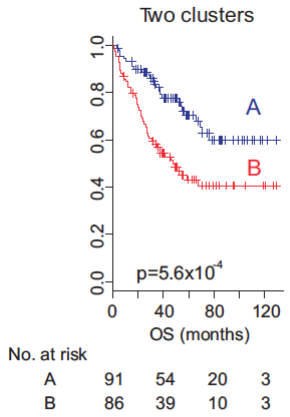
Method : unsupervised signature
National Center for Biotechnology Information Gene Expression Omnibus database

One set of training Moffit cancer Center (n=177)

Two cohorts of validation
Vanderbilt and Max Planck Institute (VMP) cohort (117)
Melbourne hospital cohort (96)







Oh et al. Gut 2011 on line

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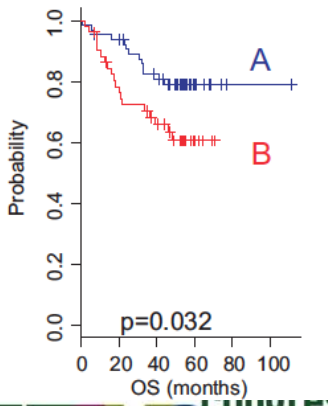
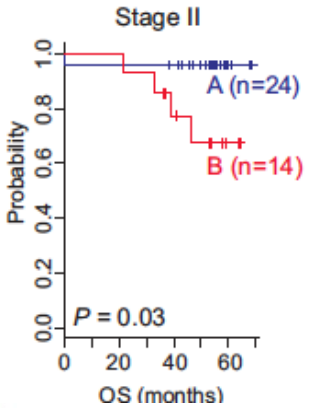
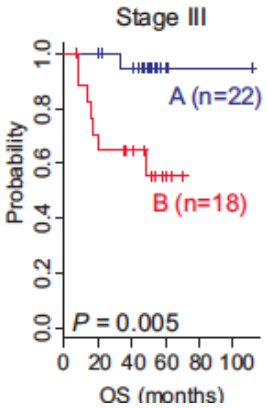
Validation cohorts

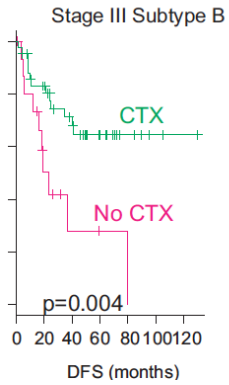


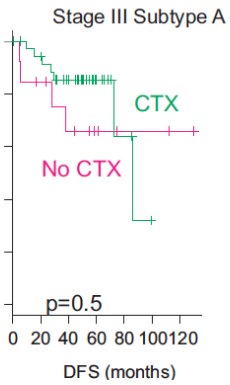
Stage II & III





Impact of chemotherapy stage III





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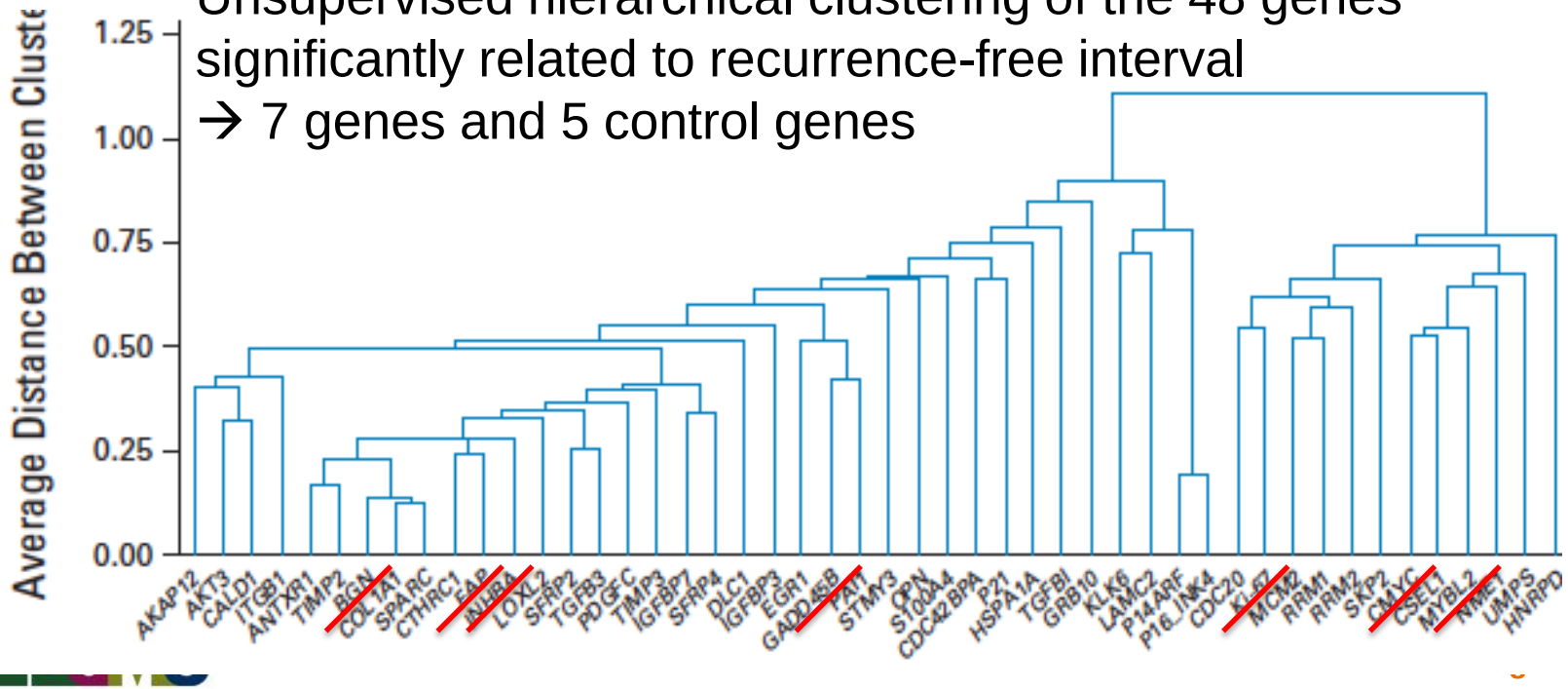
Oh et al. Gut 2011 on line

12 genes signature FFPE tissues: Recurrence score ™

Method : Supervised signature
RT-PCR from FFPE

Development : 1,851 patients with stage II and stage III colon cancer in four independent studies: (NSABP C-01/C-02 (n = 270), Cleveland Clinic (n = 765), NSABP C-04 (n = 308), NSABP C-06 (n = 508)

Unsupervised hierarchical clustering of the 48 genes significantly related to recurrence-free interval
→ 7 genes and 5 control genes



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O'connell J Clin Oncol 2010;28:3937-44

12 genes signature FFPE tissues: Recurrence score™

Three cohorts of validation
Stage II Colon Cancer QUASAR (n = 1436)
Stage II Colon Cancer CALGB 9581 (n = 690)
Stage II/III Colon Cancer 5FU vs 5FU+Oxaliplatin NSABP C-07 (n = 892)

- Validated in stage II patients included in QUASAR and CALBG 9581
- Significant association between the recurrence score™ and the risk of recurrence HR per interquartile range, 1.38; $CI_{95\%}$ [1.1- to 1.7]; p=*0.004*
- Remains significant in multivariate analysis

Gray J Clin Oncol 2011;29:4611-19;
Venook ASCO 2011 abst 3818

12 genes signature FFPE tissues: Recurrence score™

Three cohorts of validation
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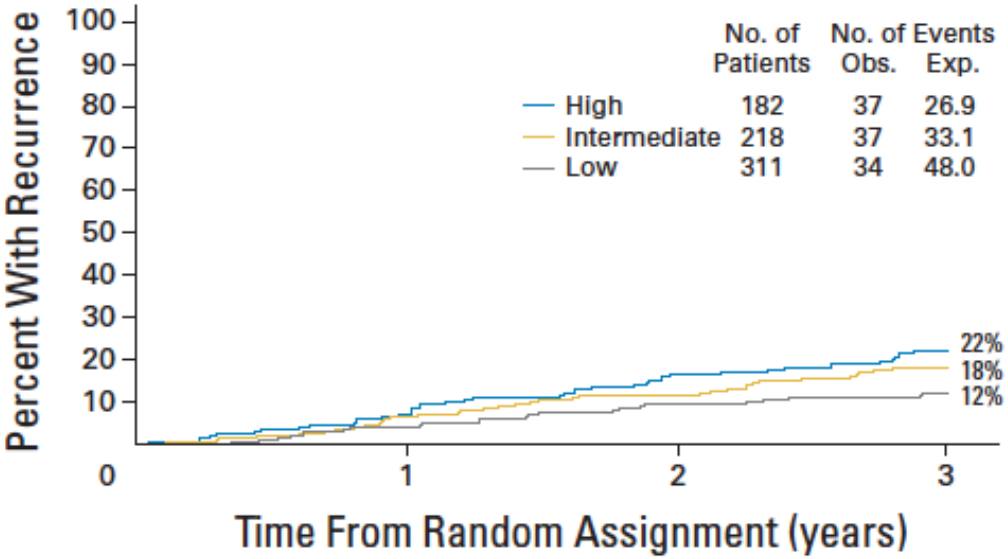


Gray J Clin Oncol 2011;29:4611-19;
Venook ASCO 2011 Abstract 3518

Contribution of Recurrence Score® Result Beyond Clinical and Pathologic Covariates
Pre-specified Multivariate Analysis (n=892)

Variable	Value	HR	HR 95% CI	P value
Stage (by nodal status)	Stage III A/B vs II Stage III C vs II	0.97 2.07	(0.55,1.71) (1.16,3.68)	<0.001
Treatment	5FU+Ox vs 5FU	0.82	(0.64,1.06)	0.12
MMR	MMR-D vs MMR-P	0.27	(0.12,0.62)	<0.001
T-stage	T4 st II & T3-T4 st III vs T3 st II & T1-T2 st III	3.04	(1.84,5.02)	<0.001
Nodes examined	<12 vs ≥12	1.51	(1.17,1.95)	0.002
Tumor grade	High vs Low	1.36	(1.02,1.82)	0.041
RS	**per 25 units**	**1.57**	**(1.19,2.08)**	**0.001**

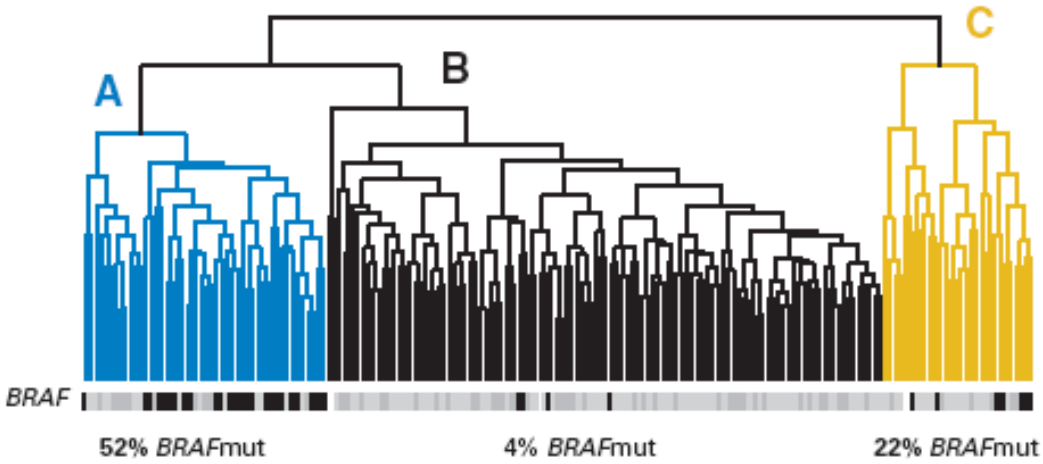
- The Recurrence Score value is significantly associated with risk of recurrence after controlling for effects of T and N stage, MMR status, number of nodes examined, grade and treatment.

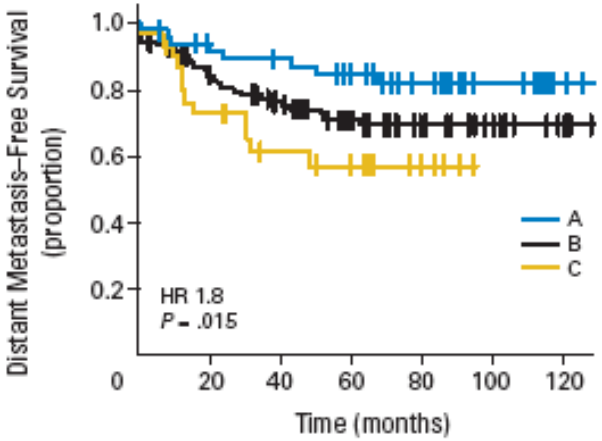
18 genes signature Fresh Frozen Tissues: Coloprint

Method : Unsupervised selection
RT-PCR from Fresh frozen tissues

Development : Training Set (stage I-IV) (n=188)
Netherlands Cancer Institute, Leiden Medical Center, Slotervaart
Clinical Validation Study 1 (stage I-III) Institute Catala d'Oncologia Barcelona
In-silico Validation Study (stage I-III) public datasets (n=322)

Whole Genome Array 44K Agilent → defined three groups of tumors





Salazar J Clin Oncol 2011;29:17-24

Selection of 18 genes

18 genes signatures fresh frozen tissues

Method : Unsupervised selection
RT-PCR from Fresh frozen tissues

Development : Training Set (stage I-IV) (n=188)
Netherlands Cancer Institute, Leiden Medical Center, Slotervaart
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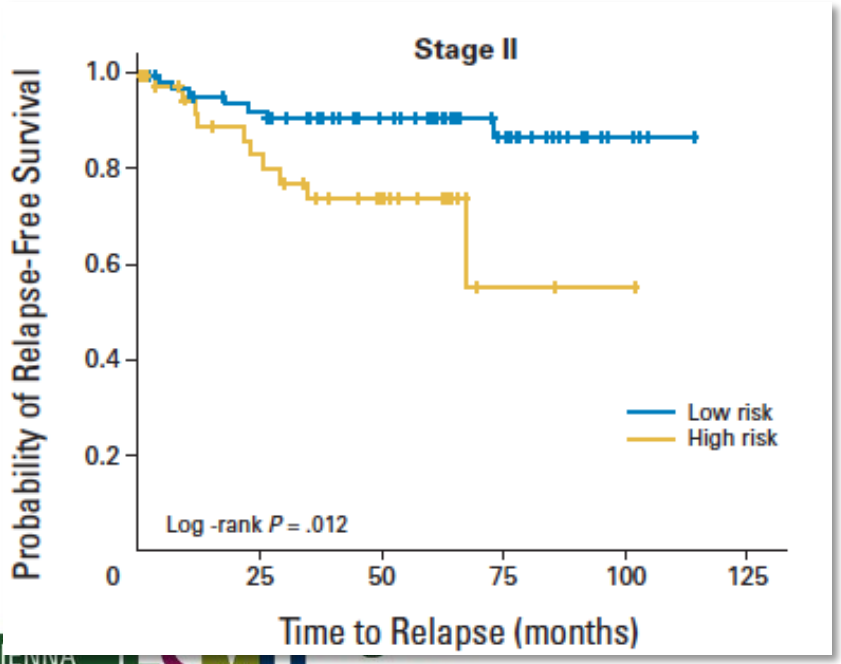


Table 4. Multivariate Analysis for Relapse-Free Survival in Validation Set

Variable	*P*	HR	95% CI
All stages, N = 206			
ColoPrint, high *v* low	.003	2.69	1.41 to 5.14
pT			
T2	.000		
T3 *v* T2	.038	0.19	0.04 to 0.91
T4 *v* T2	.960	1.05	0.19 to 5.88
Stage, continuous	.021	0.05	0.00 to 0.063
pN			
No positive LNs	.000		
1-3 positive LNs *v* no positive LNs	.327	1.52	0.66 to 3.52
> 3 positive LNs *v* no positive LNs	.000	5.97	2.62 to 13.63
No. of LNs assessed, continuous	.059		
Lymphatic, venous, or perineural invasion, any	.491		
Stage II only, n = 114			
ColoPrint, high *v* low	.018	3.29	1.24 to 8.83
pT, T4 *v* T3	.051	3.06	0.99 to 9.44

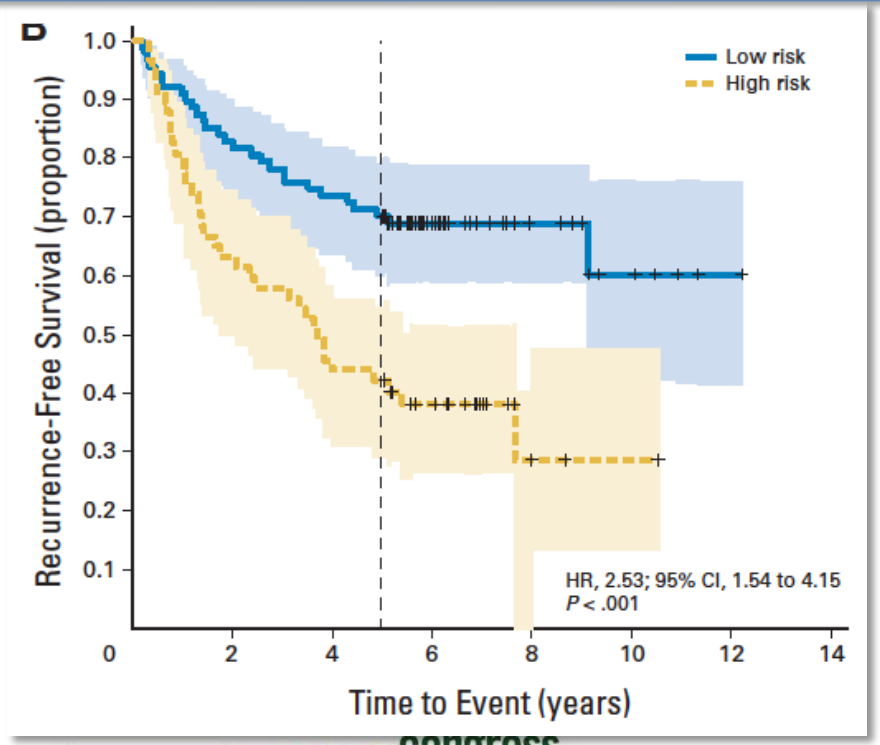
NOTE. Multivariate analysis includes only variables that were significant ($P < .05$) in the univariate analysis.
Abbreviations: HR, hazard ratio; LN, lymph node.

Salazar J Clin Oncol 2011;29:17-24

Colorectal DSA Almac
634 transcript signature from FFPE

Method : Supervised selection
Microarray Colorectal Cancer DSA from fresh frozen tissues

Development : Training Set stage II (n=215)
Validation stage II (n=144)



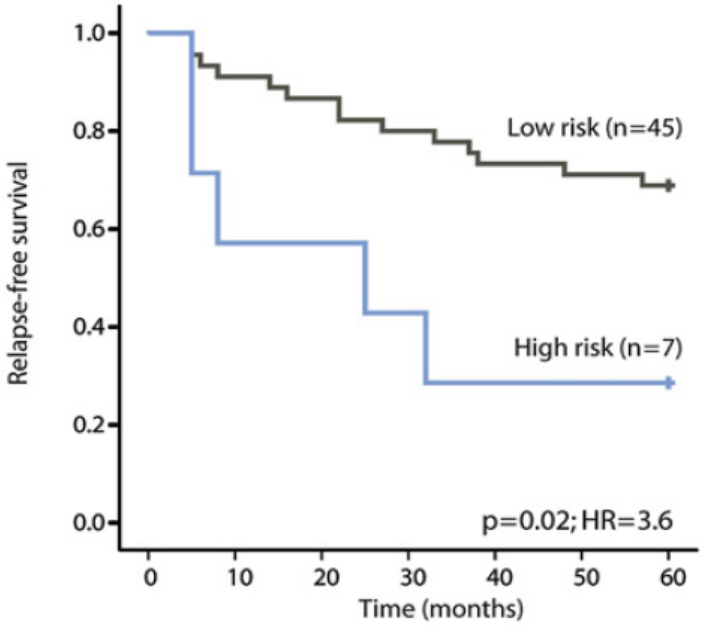
Kennedy J Clin Oncol 2011;35:4620

ColoGuideEX
13 genes signature fresh frozen tissues

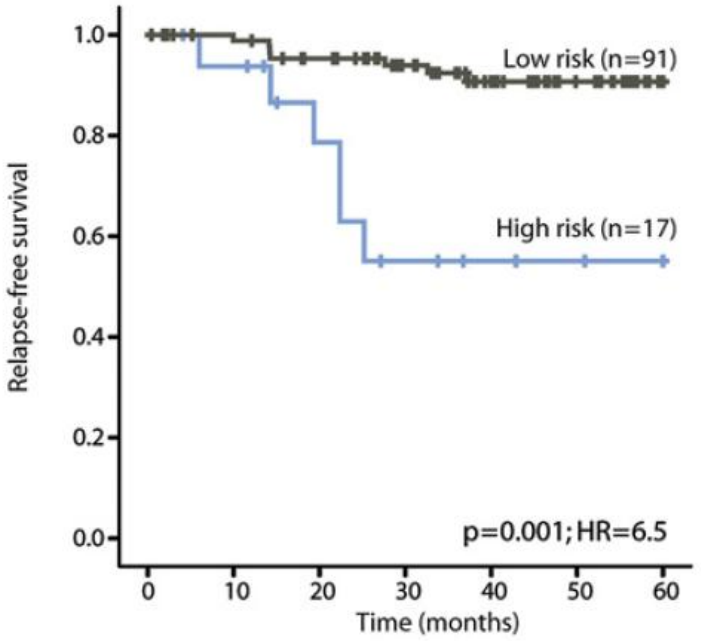
Method : Supervised selection
Affymetrix array from fresh frozen tissues

207 training set (stage I-IV)
53 and 108 validation sets (stage II)

Validation series I, 53 stage II CRC



Validation series II, 108 stage II CRC, external dataset



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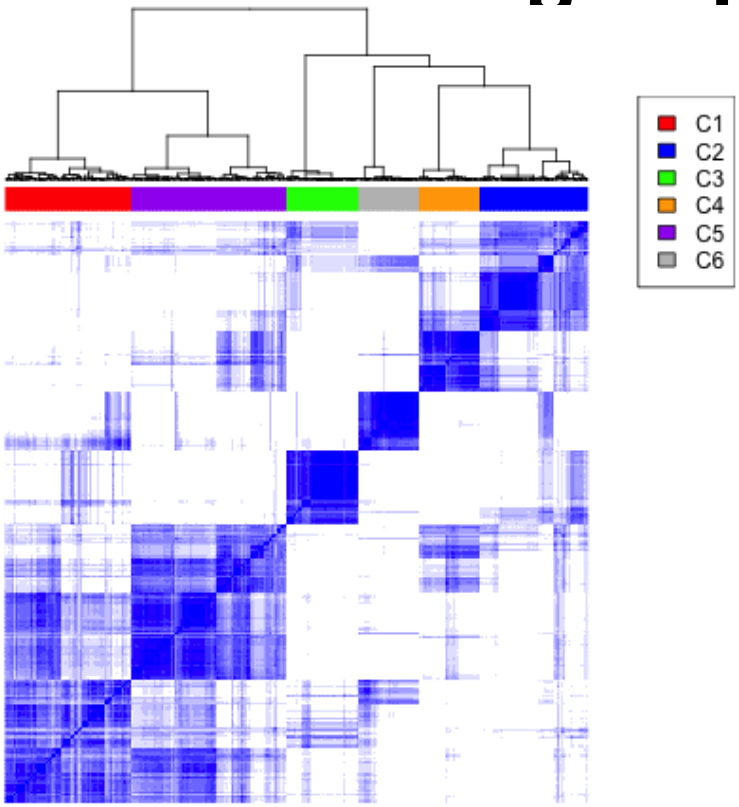
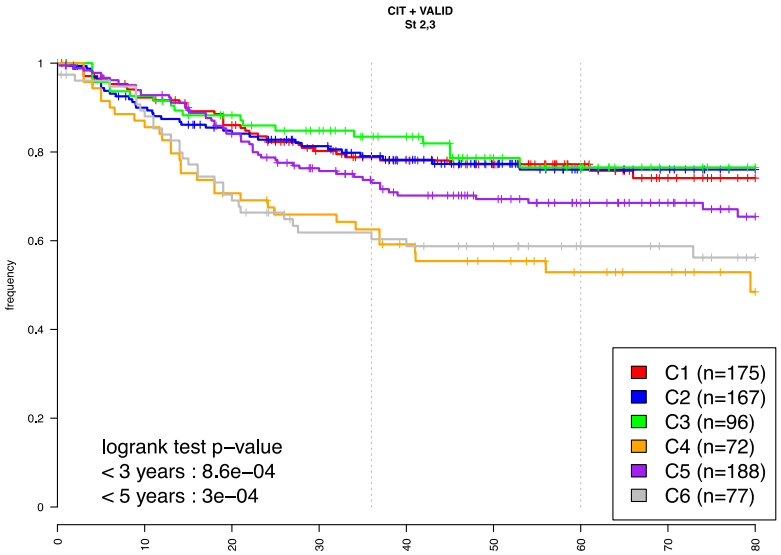
Summary Signatures in CRC II

- There are multiple prognostic signatures
  - for stage II and sometimes for stage III
- All signatures seem to be validated
  - The level of "validation" is different
- The overlap between these different signatures is weak
- None of these signatures is able to predict the benefit of adjuvant chemotherapy
- They all make the hypothesis that colon cancer is an homogenous cancer → which is clearly not the case

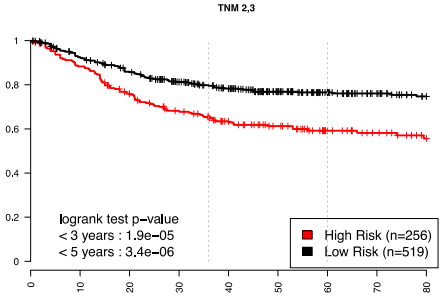
Different groups of colorectal cancer



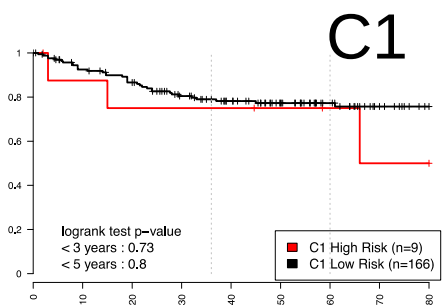


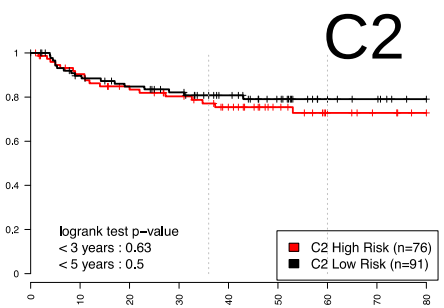
CIT CCMST		C2 (n=83)	C4 (n=46)	C3 (n=56)	C6 (n=45)	C5 (n=118)	C1 (n=95)
MSI	2.1e-42	68%	12%	7%	0%	1%	1%
CIMP+	1.1e-23	59%	34%	18%	3%	3%	4%
CIN+	1.7e-15	44%	73%	65%	83%	95%	95%
BRAF mut	4.1e-19	40%	22%	6%	0%	1%	0%
KRAS mut	1.1e-12	28%	50%	87%	28%	27%	42%
TP53 mut	7.3e-03	41%	45%	35%	59%	71%	59%
Proximal Location	5e-17	72%	57%	59%	16%	21%	26%

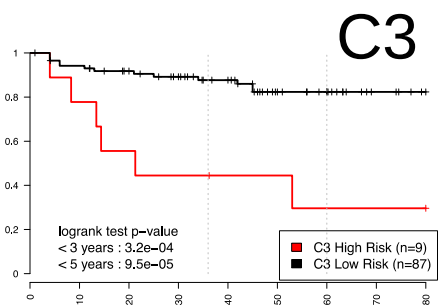
Oncotype signature versus the different groups of CRC

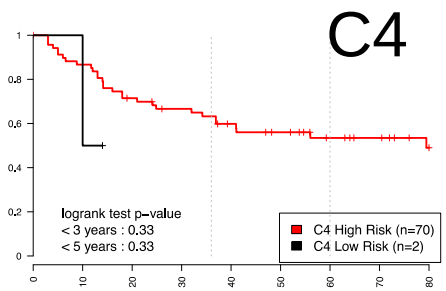


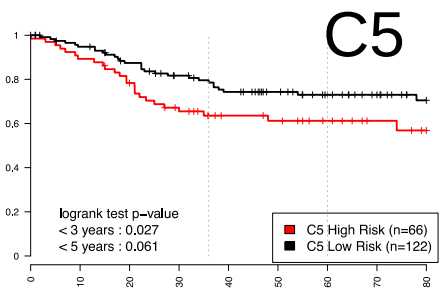
Stage II and III
775 patients

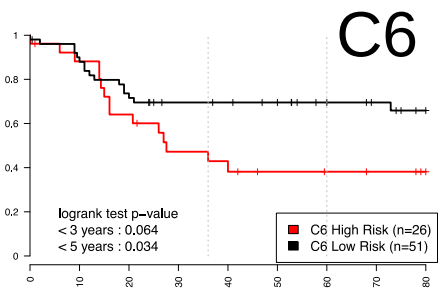












Summary Conclusion I

- CRC is a comlex disease with several subentities derived through different pathways
- MSI-H is a prognostic indicator in stage II
- The prognostic impact of BRAF is dependent on MSI-status
- KRAS is still the only validated predictive marker for anti-EGFR treatment
- The role of different KRAS-mutations needs to be verified in large prospective trials
- Signatures need to be developed for the different subentities, rather than „one size fits all“

Summary Conclusion II

- The division of CRC in various subentities generates the necessity of multicenter trials, since subgroups will be small
- FFPE-material should be collected in these trials and investigated for potential prognostic and predictive markers
- The gold standard of risk-stratification is still correct pTNM-staging and thorough histopathological workup
- The addition of molecular data will – hopefully – allow the development of a more personalized treatment of CRC