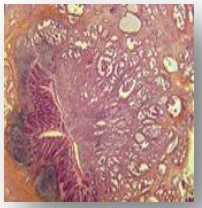
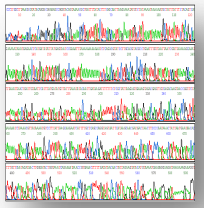
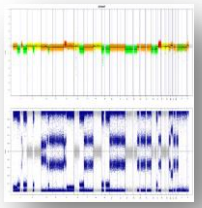
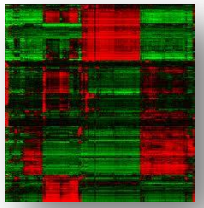
CARPEM
CANCER RESEARCH FOR PERSONALIZED MEDICINE

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

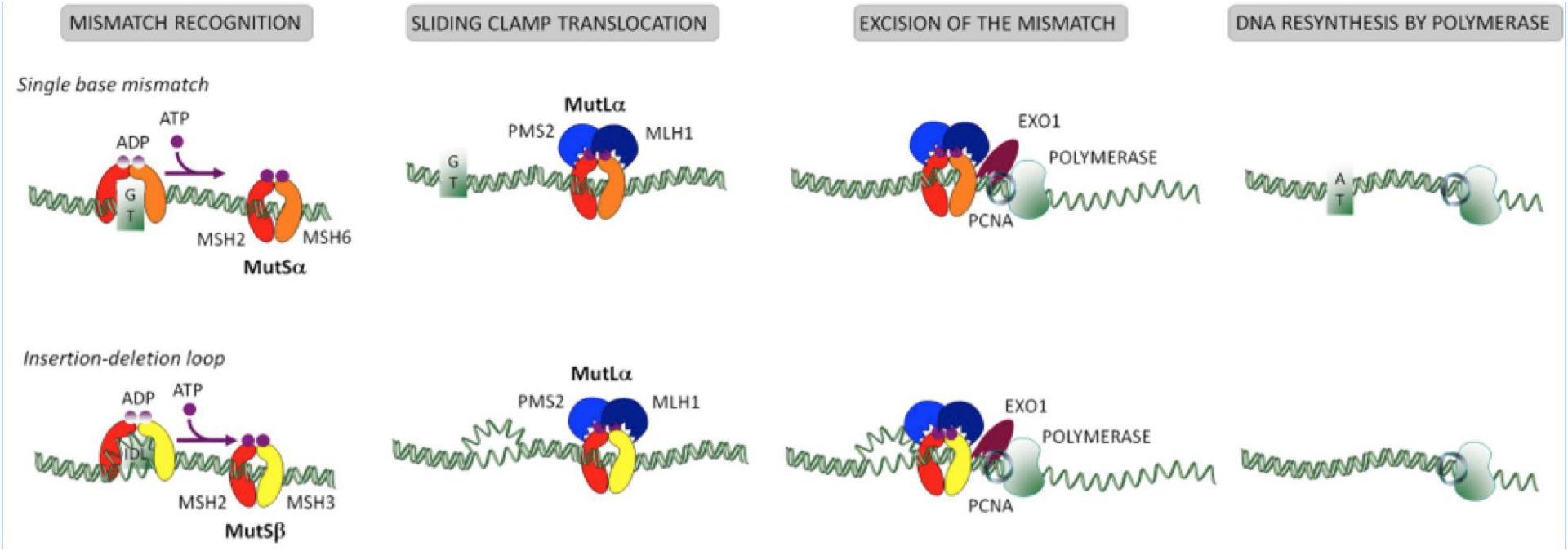
Microsatellite instability: where do we stand ? How useful is it

Pierre Laurent-Puig
Hôpital G. Pompidou
UMR-S1147
INSERM Paris Descartes

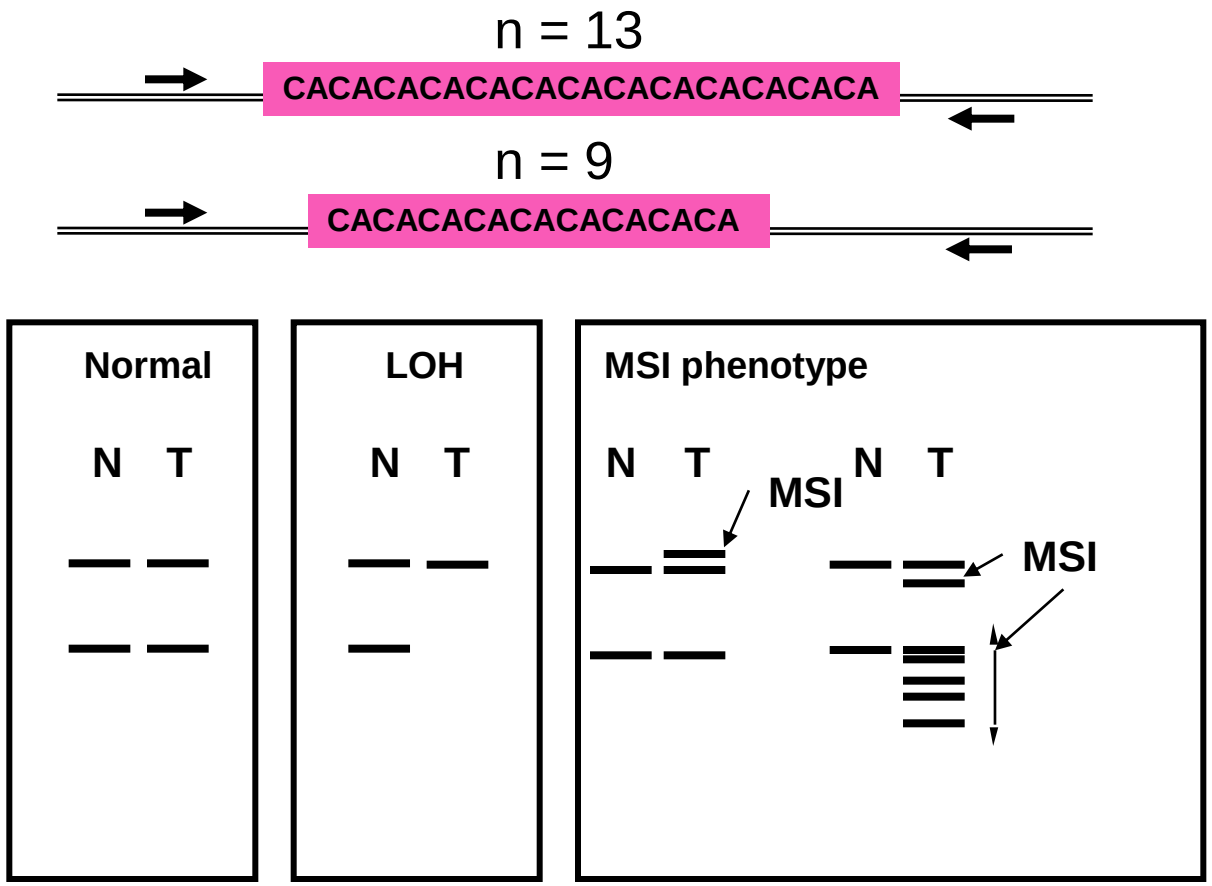
Cancer Inserm

UNIVERSITÉ PARIS DESCARTES

Mismatch repair system

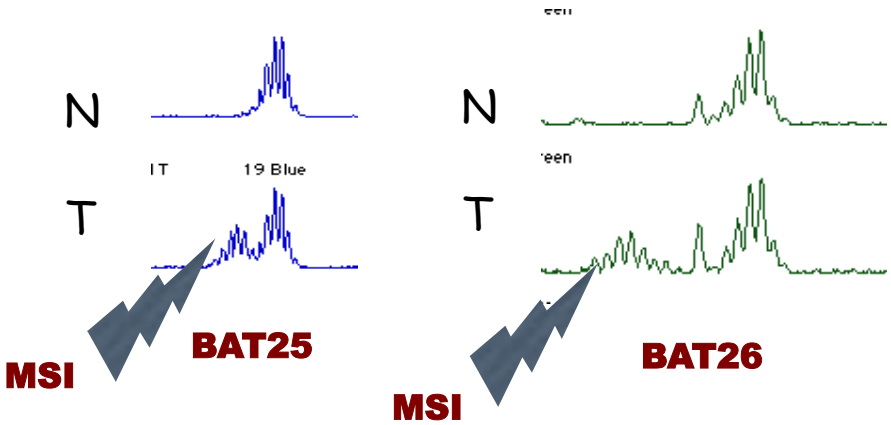


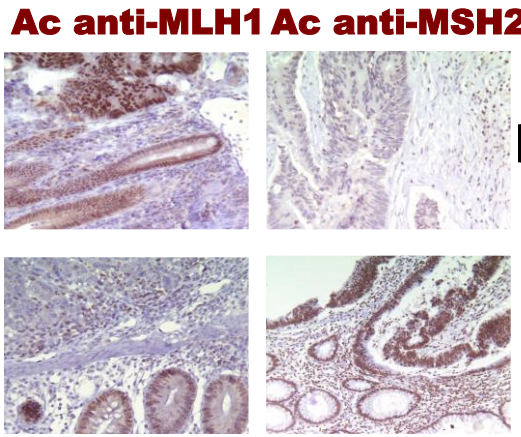
Microsatellite locus

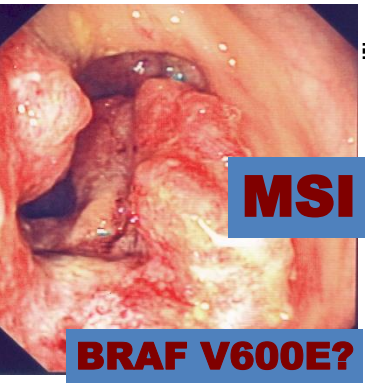


Microsatellite instability Phenotype

- **Molecular biological testing**: Genotyping 5 microsatellites allows the characterization of microsatellite tumor instability
- If at least 2 of the 5 microsatellites are unstable, the tumor phenotype is "**MSI-high**" or **dMMR**
- **Immunohistochemical testing**: Tumor tissue can be immunostained to detect the presence of one or more of the DNA mismatch repair protein Mlh1, Msh2, Msh6 or Pms2.
- Failure of the tumor to stain indicates that the corresponding gene is not being appropriately expressed and suggests the existence of a deleterious mutation







Somatic Alterations

Germline mutation

MSI ?

MSS

STOP

MSI-H

IHC

MSH2/MSH6 neg

MSH2 screening
MSH6 screening

MLH1 neg

BRAF V600E?

No familial history
& proximal cancer

STOP

Familial history
&/or distal cancer

MLH1 screening

BRAF V600E

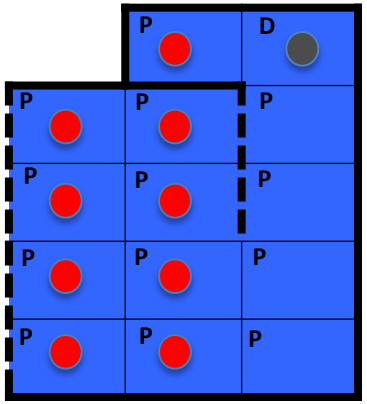
Yes

No

STOP

From Olschwang et al. Bull Cancer 2004;91:303-15 and Gastroenterol Clin Biol 2007;31:136-40

The different phenotypes



MSI +
(12%-15%)

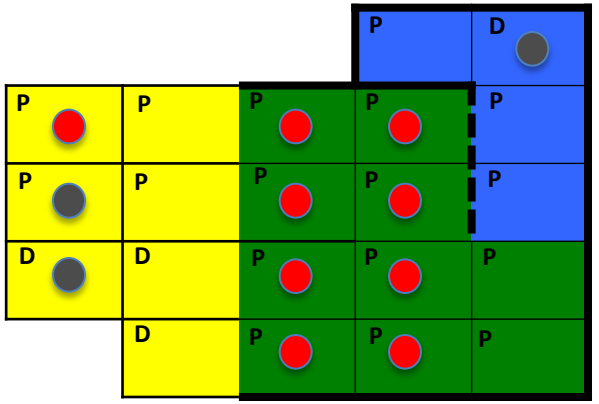
D distal colon

P proximal colon

- BRAF mutation V600E
- KRAS mutation 12-13

Barault et al. Cancer Res 2008;68:8541-46, Barault al. Int J cancer 2008;122:2255-59; & consortium colon CIT2

The different phenotypes



D distal colon

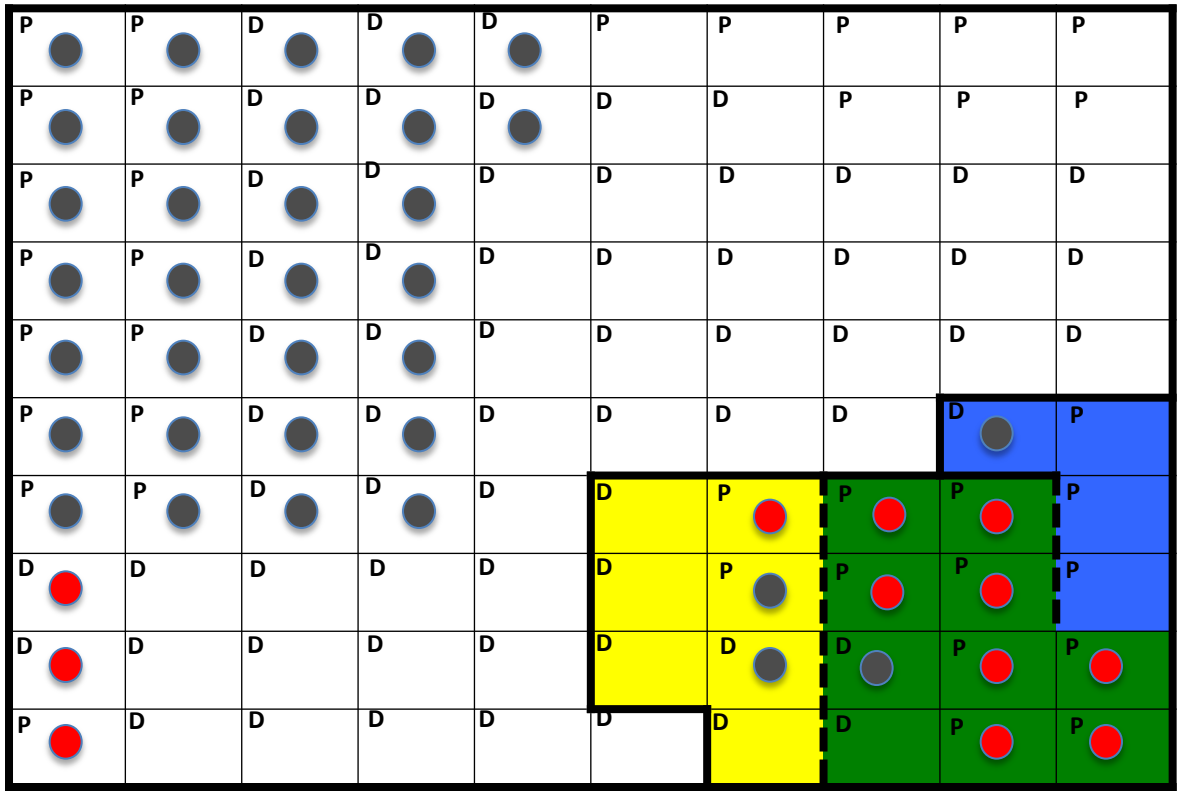
P proximal colon

- BRAF mutation V600E
- KRAS mutation 12-13

Barault et al. Cancer Res 2008;68:8541-46, Barault al. Int J cancer 2008;122:2255-59; & consortium colon CIT2

The different phenotypes

CIN +



MSI +
(12%-15%)

D distal colon

P proximal colon

CIMP+

MSI + / CIMP+

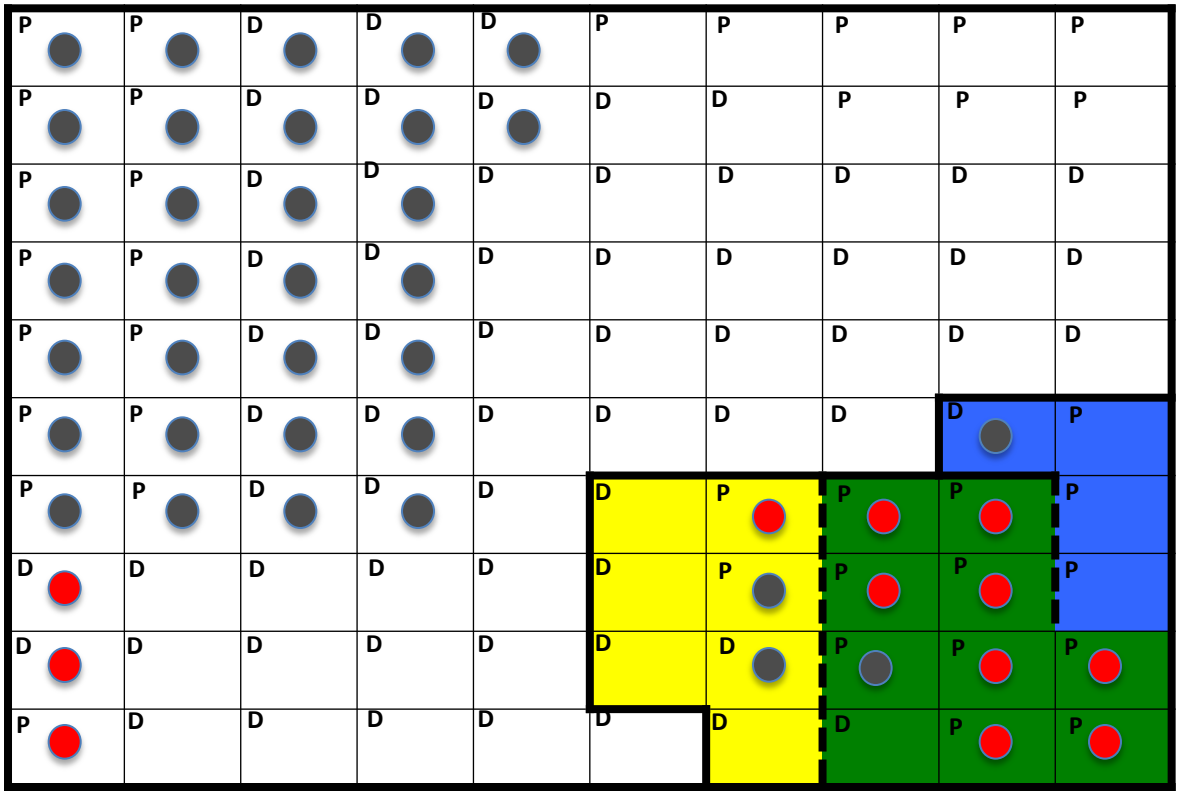
18%

- BRAF mutation V600E
- KRAS mutation 12-13

Barault et al. Cancer Res 2008;68:8541-46, Barault al. Int J cancer 2008;122:2255-59; & consortium colon CIT2

The different phenotypes

CIN +



HNPCC

D distal colon

P proximal colon

CIMP+ SPORADIC MSI

18%

- BRAF mutation V600E
- KRAS mutation 12-13

Barault et al. Cancer Res 2008;68:8541-46, Barault al. Int J cancer 2008;122:2255-59; & consortium colon CIT2

Anticancer agents and MSI phenotype

Drugs	Resistance	Sensitivity	Hypersensitivity
Antimetabolites	**5FU** 6Thioguanine		
Alkylating Agents	Procarbazine Temzolomide MNU	Melphalan Perfosfamide BCNU	CCNU Mitomycin
Platinum compounds	Cisplatin Carboplatin	**Oxaliplatin** Transplatin	
Topoisomerase inhibitor			Camptothecin **CPT11** Etoposide
Radiation sensitizer			Gemcitabine
Antimitotics		Docetaxel	

d' après Valentini AM et al. Cancer Treatment Review 2006;32:607-18

VOLUME 28 · NUMBER 20 · JULY 10 2010
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

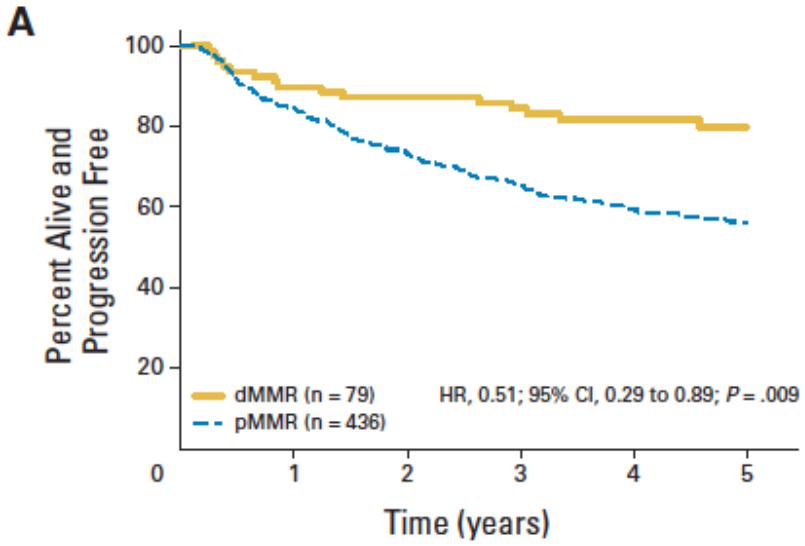
Dan Sargent et al.

Defective Mismatch Repair As a Predictive Marker for Lack of Efficacy of Fluorouracil-Based Adjuvant Therapy in Colon Cancer

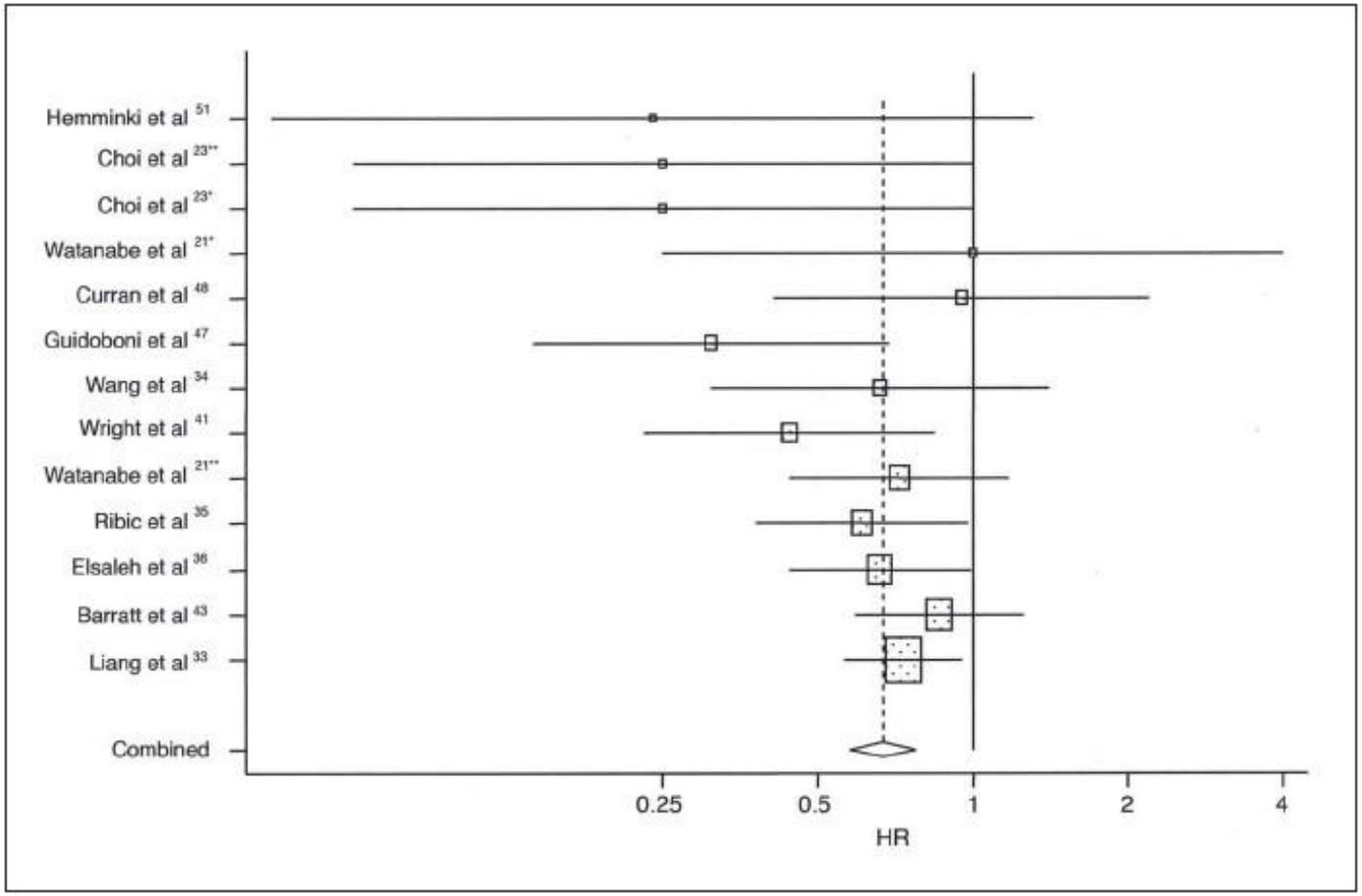
1027 patients included in trials demonstrating the effect of FU in adjuvant settings

MSI + (dMMR) 185 pts (18%)

No chemotherapy



Hazard ratio of overall survival in studies of all stage II-III colorectal cancer associated with microsatellite instability



Popat et al J Clin Oncol 2005;23:609-18

Interaction with 5FU

- Several studies showed the absence of benefit for adjuvant chemotherapy in MSI + patients
  - Ribic et al. N Engl J Med 2003
    - 570 cancers, 95 (16,7 %) with MSI +(MSI-H).
    - Interaction chemotherapy*MSI status p=0.009
  - Jover et al. Gut 2006
    - 505 patients stage II-III 125 stages II (42.2%) 135 stages III (64.5%) with adjuvant chemotherapy
    - Interaction chemotherapy*MSI status p=0.007

VOLUME 28 · NUMBER 20 · JULY 10 2010
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

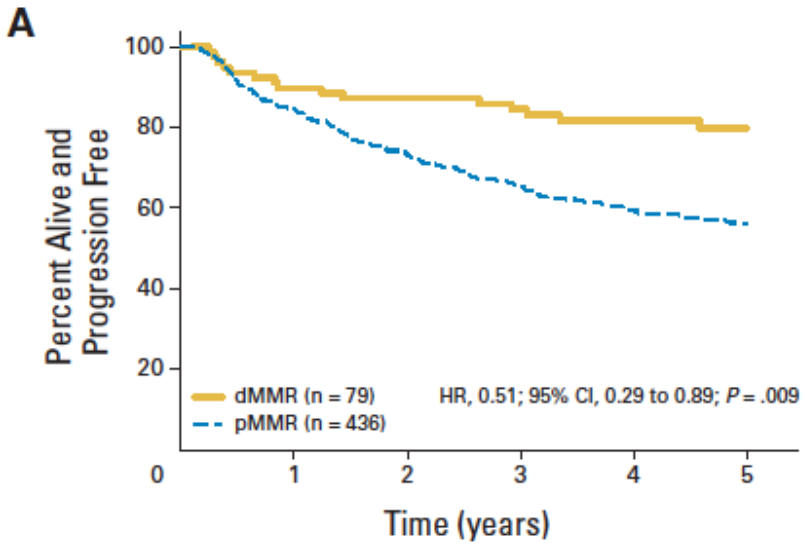
Dan Sargent et al.

Defective Mismatch Repair As a Predictive Marker for Lack of Efficacy of Fluorouracil-Based Adjuvant Therapy in Colon Cancer

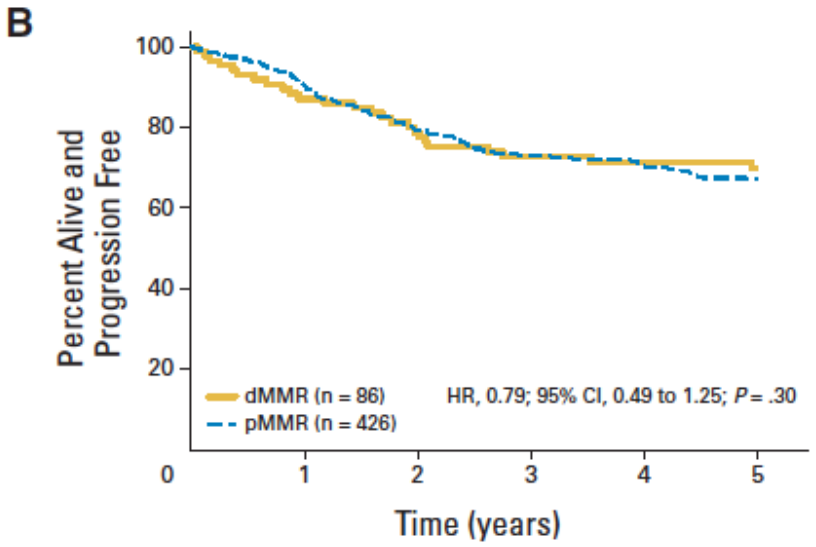
1027 patients included in trials demonstrating the effect of FU in adjuvant settings

MSI + (dMMR) 185 pts (18%)

No chemotherapy



5FU chemotherapy



VOLUME 28 · NUMBER 20 · JULY 10 2010
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Dan Sargent et al.

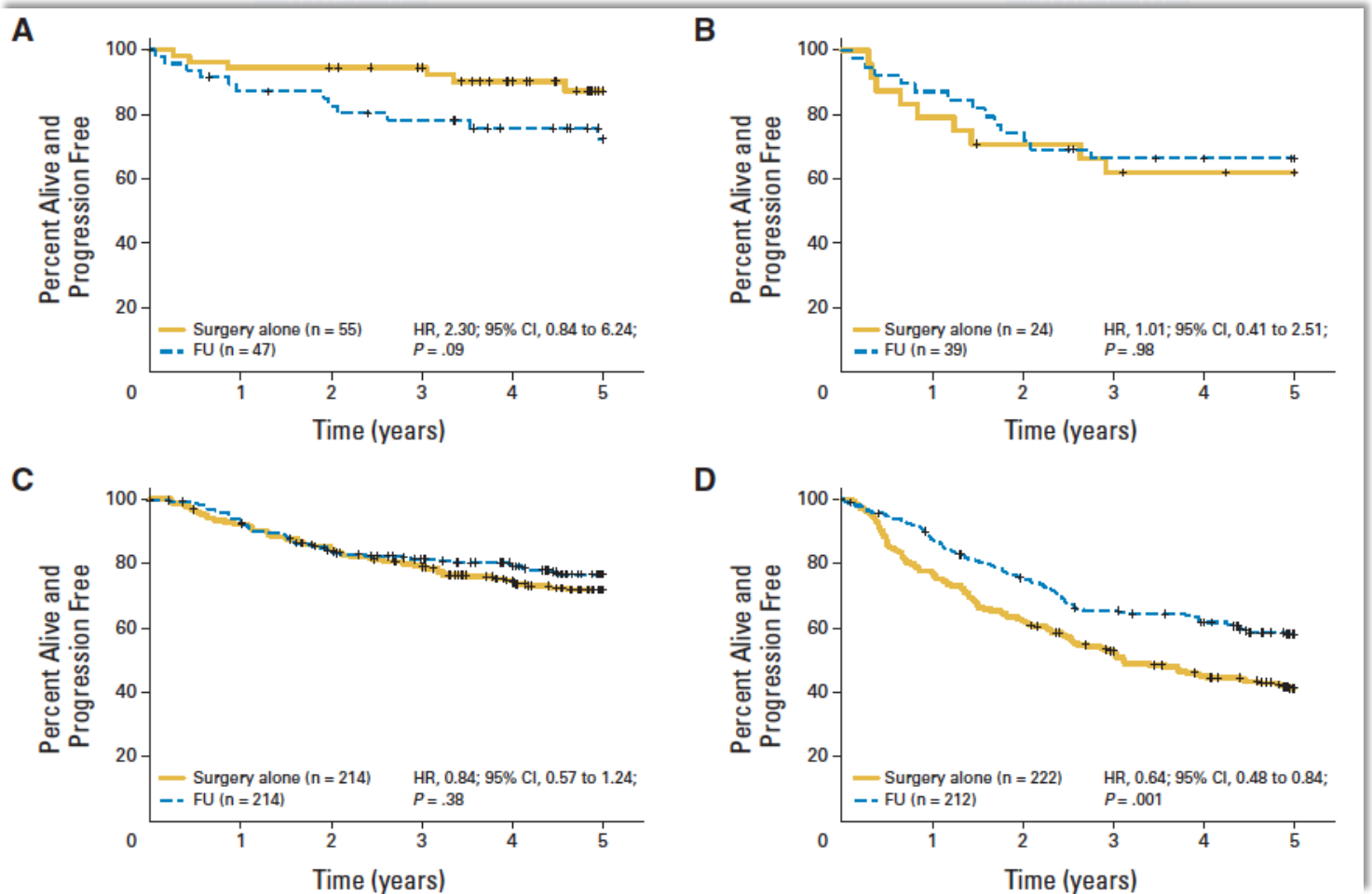
Defective Mismatch Repair As a Predictive Marker for Lack of Efficacy of Fluorouracil-Based Adjuvant Therapy in Colon Cancer

Stage II

Stage III

MSI

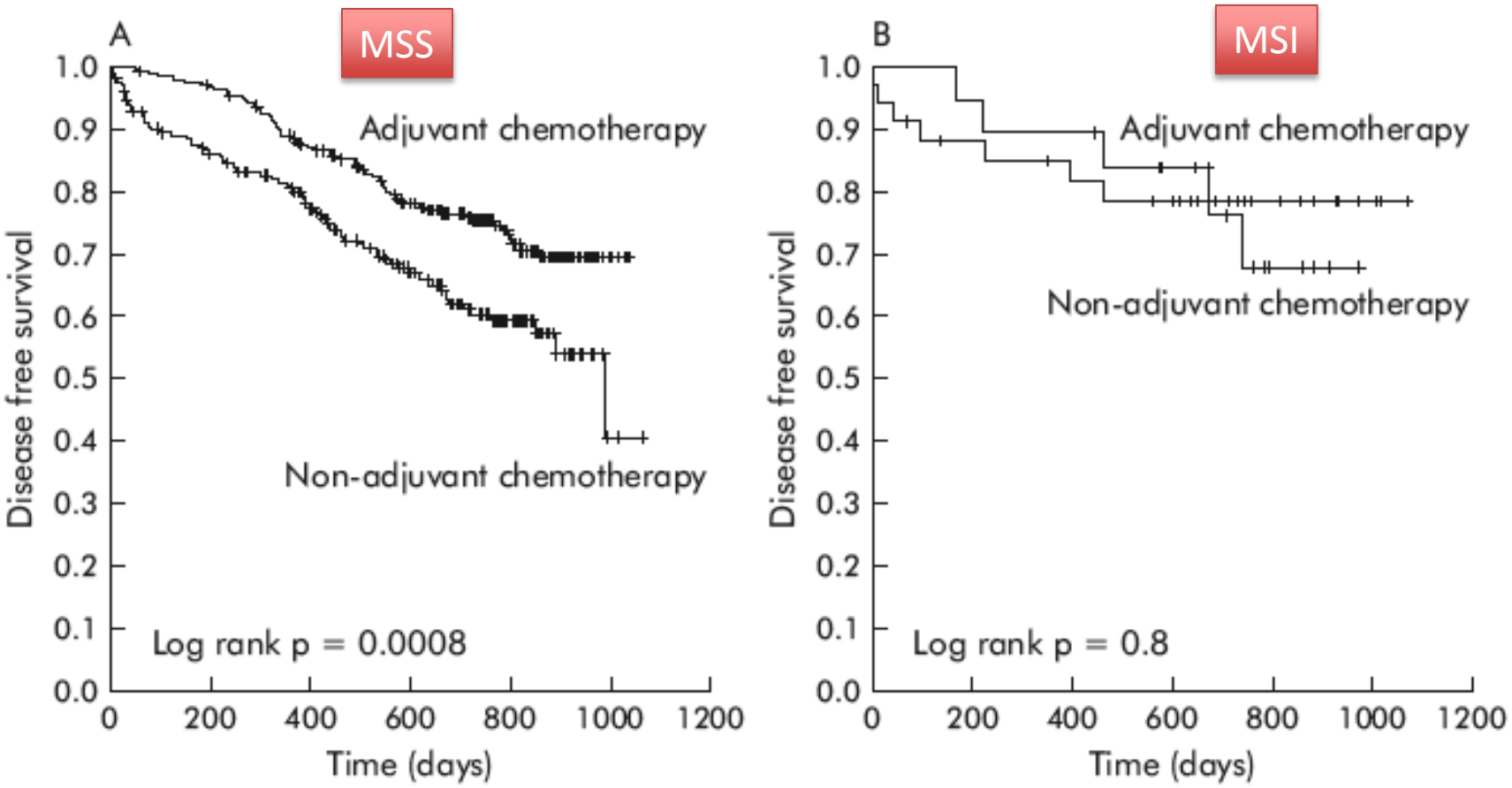
MSS



Jover R et al. Gut 2006

- 505 stage II-III patients
  - 125 patients of stage II with chemotherapy (42.2%)
  - 135 patients of stag e III (64.5%)

DFS according to pMMR or dMMR



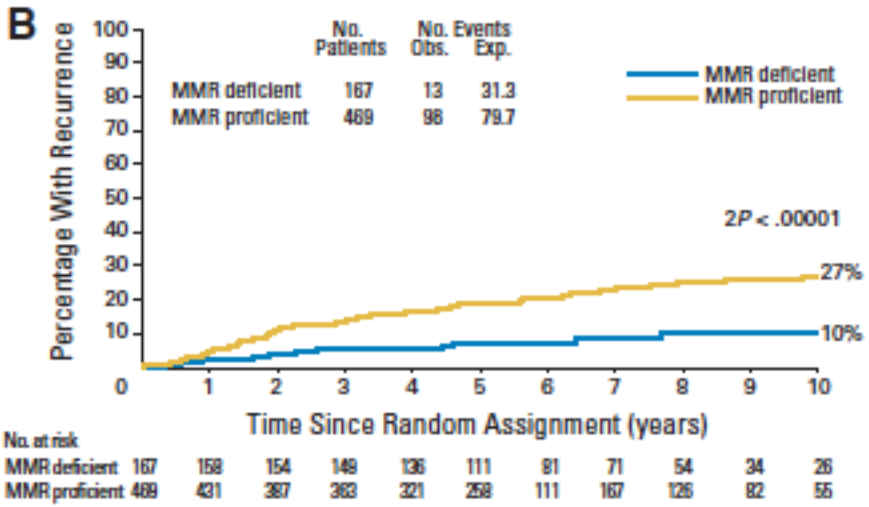
VOLUME 29 · NUMBER 10 · APRIL 1 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

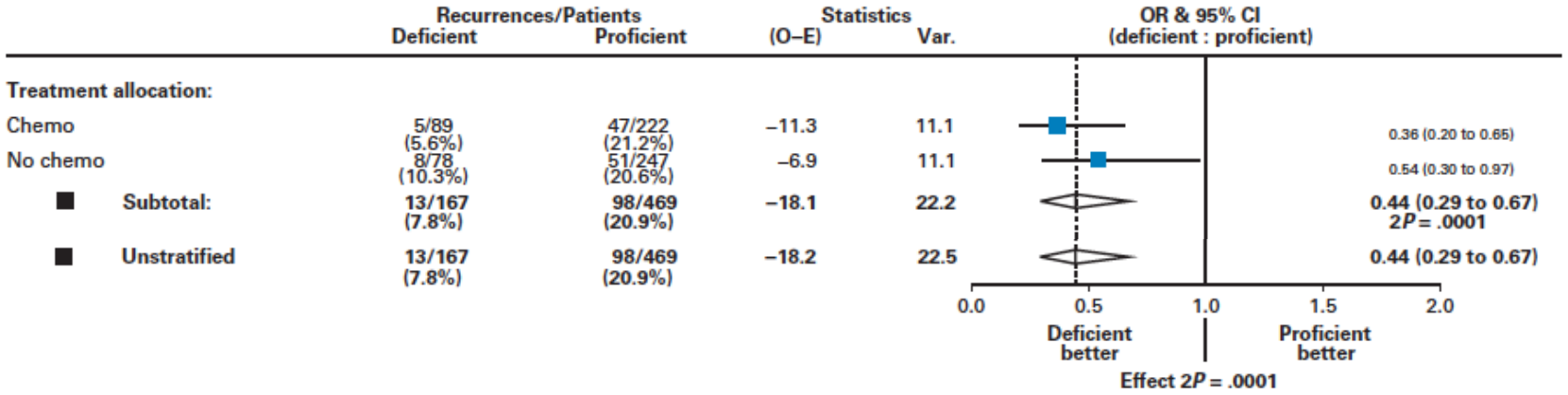
Value of Mismatch Repair, *KRAS*, and *BRAF* Mutations in Predicting Recurrence and Benefits From Chemotherapy in Colorectal Cancer

Gordon Hutchins, Katie Southward, Kelly Handley, Laura Magill, Claire Beaumont, Jens Stahlschmidt, Susan Richman, Philip Chambers, Matthew Seymour, David Kerr, Richard Gray, and Philip Quirke



Patients included in the QUASAR study

Stage II Colon

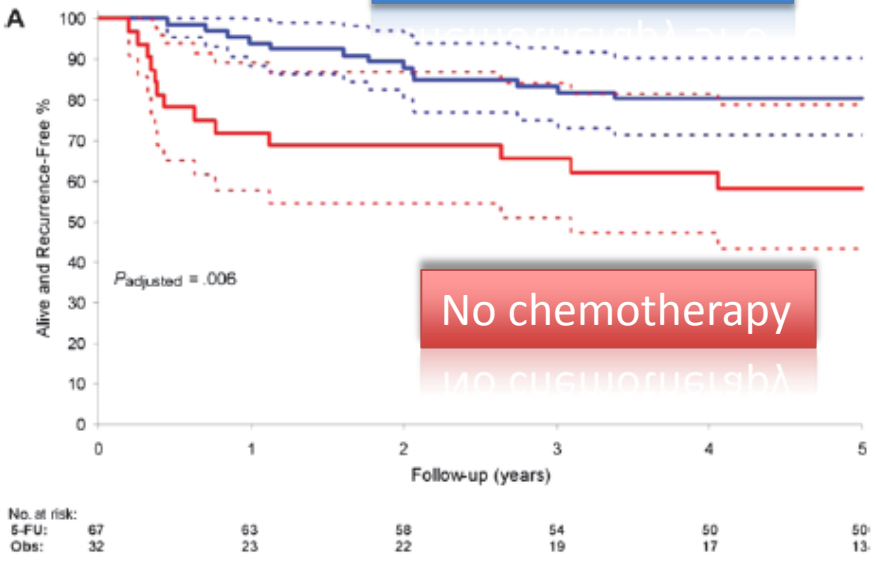


DNA Mismatch Repair Status and Colon Cancer Recurrence and Survival in Clinical Trials of 5-Fluorouracil-Based Adjuvant Therapy

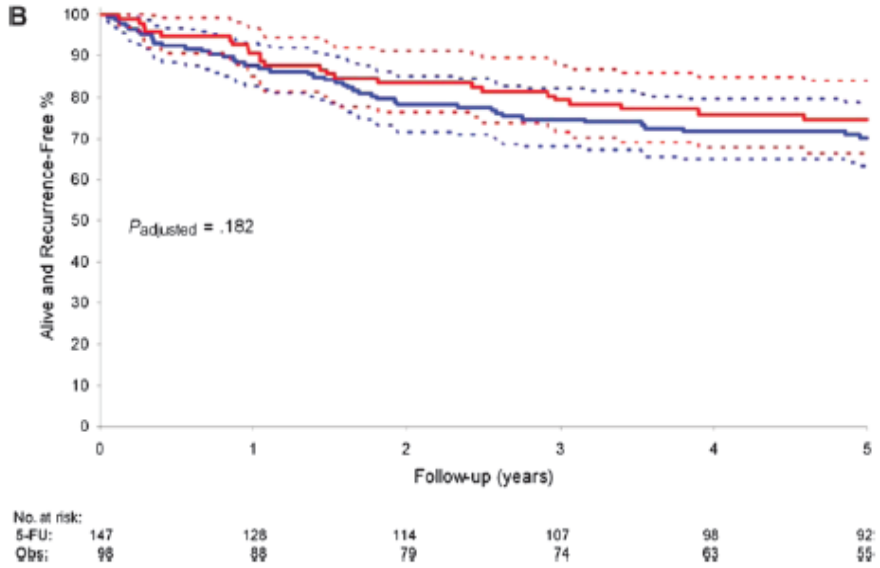
J Natl Cancer Inst 2011;103:863–875

Frank A. Sinicrope, Nathan R. Foster, Stephen N. Thibodeau, Silvia Marsoni, Genevieve Monges, Roberto Labianca, Greg Yothers, Carmen Allegra, Malcolm J. Moore, Steven Gallinger, Daniel J. Sargent

Chemotherapy 5FU



No chemotherapy



Lynch syndrome

Sporadic MSI

2141 patients, 344 MSI + (16%) ; positive effect limited to the group of lynch syndrome

To summarize shortly a very long story…… (1 Fluorouracile)

From A. Zaanan

References	Type of study	Number of patients	Number of MSI tumours (%)	Tumour stage	Number of patients receiving adjuvant CT	Stratification	Survival analysis criteria	Survival results for MSI patients
5-fluorouracil-based adjuvant chemotherapy								
Elsaleh et al, 2000 [19]	R	656	56 (8.5)	III	272	MMR	5 yr-OS	Longer survival
Hemminki et al, 2000 [20]	P / NR	95	11 (12)	III	95	MMR	3 yr-RFS	Longer survival
Ribic et al, 2003 [30]	R from RCT	570	95 (16.7)	II + III	283	MMR and CT	5 yr-DFS 5 yr-OS	No benefit or detrimental[a]
Carethers et al, 2004 [22]	R	204	36 (17.6)	II + III	66	CT	OS	No benefit
de Vos Tot Nederveen Cappel et al, 2004 [23]	R	92	92 (100)[b]	III	28	CT	5 yr-OS	No benefit
Benatti et al, 2005 [24]	R	1263	256 (20.3)	All stages	304	CT	5 yr-OS	No benefit
Westra et al, 2005 [21]	R from RCT	273	44 (16)	III	273	MMR	5 yr-DFS	Longer survival [c]
Jover et al, 2006 [25]	P / NR	754	66 (8.8)	All stages	260	CT	OS	No benefit
Lanza et al, 2006 [26]	R	718	114 (15.9)	II + III	193	MMR and CT	6 yr-OS	No benefit
Kim et al, 2007 [27]	R from RCT	542	98 (18)	II + III	369	MMR	5 yr-RFS/OS	No significant difference[d]
Lamberti et al, 2007 [28]	P / NR	416	52 (13)	All stages	89[e]	MMR	OS	No significant difference
Sargent et al, 2010 [31]	R from RCT	457	70 (15)	II + III	229	MMR and CT	5 yr-DFS 5 yr-OS	No benefit
		1027[f]	165 (16)	II + III	512			No benefit or detrimental
Hutchins et al, 2011 [29]	R from RCT	1913	218 (11.4)	II (90%)	924	MMR and CT	2 yr-RFS	No benefit

JOURNAL OF CLINICAL ONCOLOGY

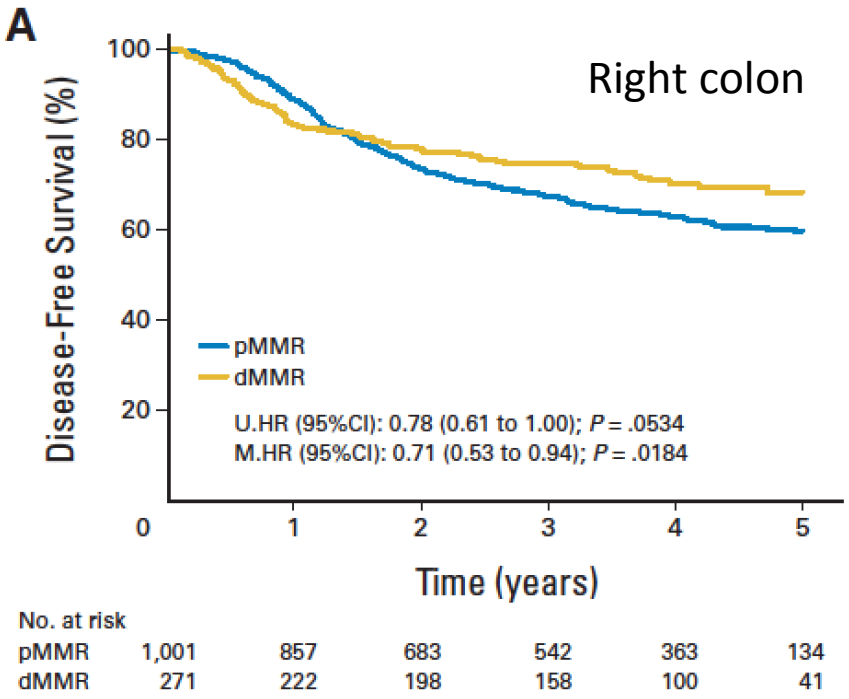
ORIGINAL REPORT

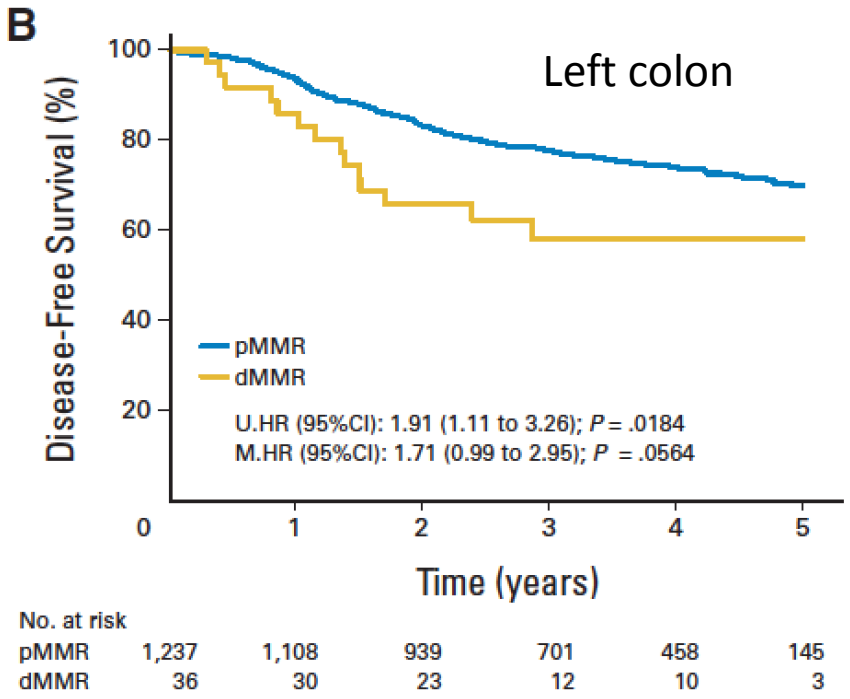
Prognostic Impact of Deficient DNA Mismatch Repair in Patients With Stage III Colon Cancer From a Randomized Trial of FOLFOX-Based Adjuvant Chemotherapy

J Clin Oncol 31:3664-3672.

Frank A. Sinicrope, Michelle R. Mahoney, Thomas C. Smyrk, Stephen N. Thibodeau, Robert S. Warren, Monica M. Bertagnolli, Garth D. Nelson, Richard M. Goldberg, Daniel J. Sargent, and Steven R. Alberts

NO-147



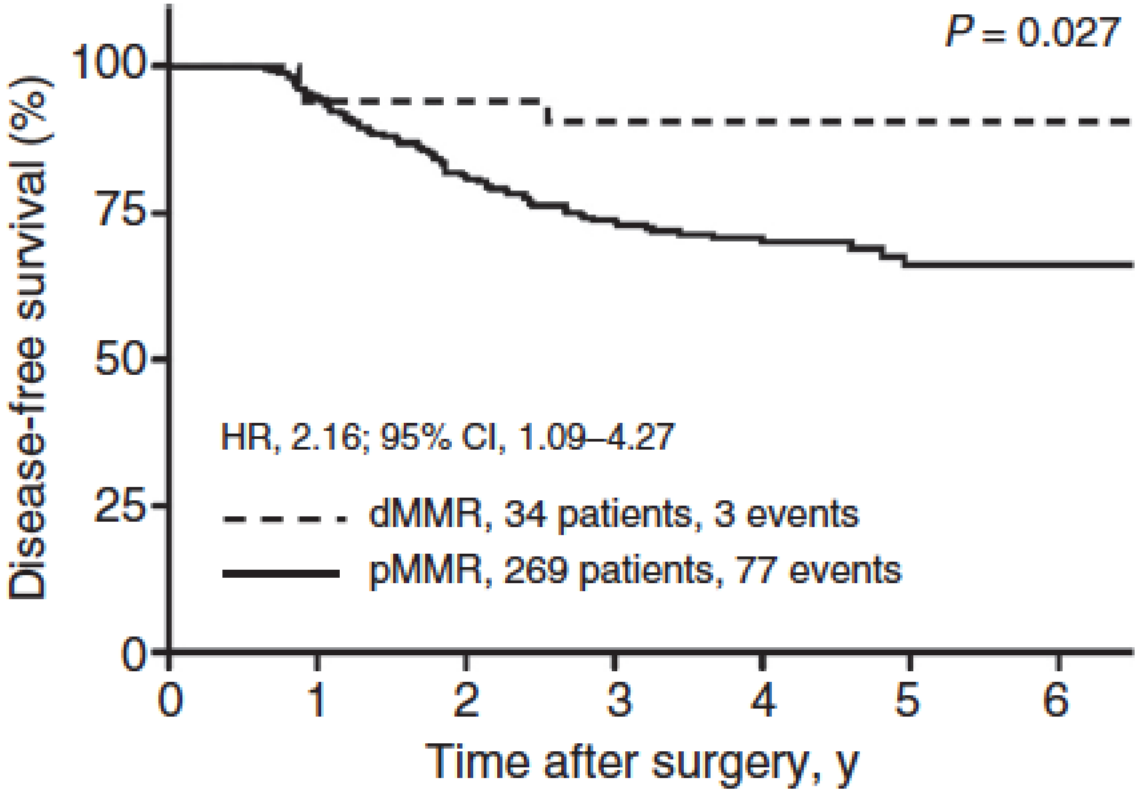


The prognostic impact of MMR depended on tumor site . The interaction is highly significant p=0.009. Validated on CALGB 88903

Clin Cancer Res; 17(23) December 1, 2011

Defective Mismatch Repair Status as a Prognostic Biomarker of Disease-Free Survival in Stage III Colon Cancer Patients Treated with Adjuvant FOLFOX Chemotherapy

Aziz Zaanan[1,2,3], Jean-François Fléjou[2,3,4], Jean-François Emile[9,10], Gaëtan Des Guetz[11], Peggy Cuilliere-Dartigues[12], David Malka[13], Cédric Lecaille[14], Pierre Validire[6], Christophe Louvet[7], Philippe Rougier[1,10], Aimery de Gramont[5], Franck Bonnetain[15], Françoise Praz[2,3], and Julien Taïeb[1,8]



Number at risk

dMMR	34	31	28	23	13	7	3
pMMR	269	247	208	166	95	39	14

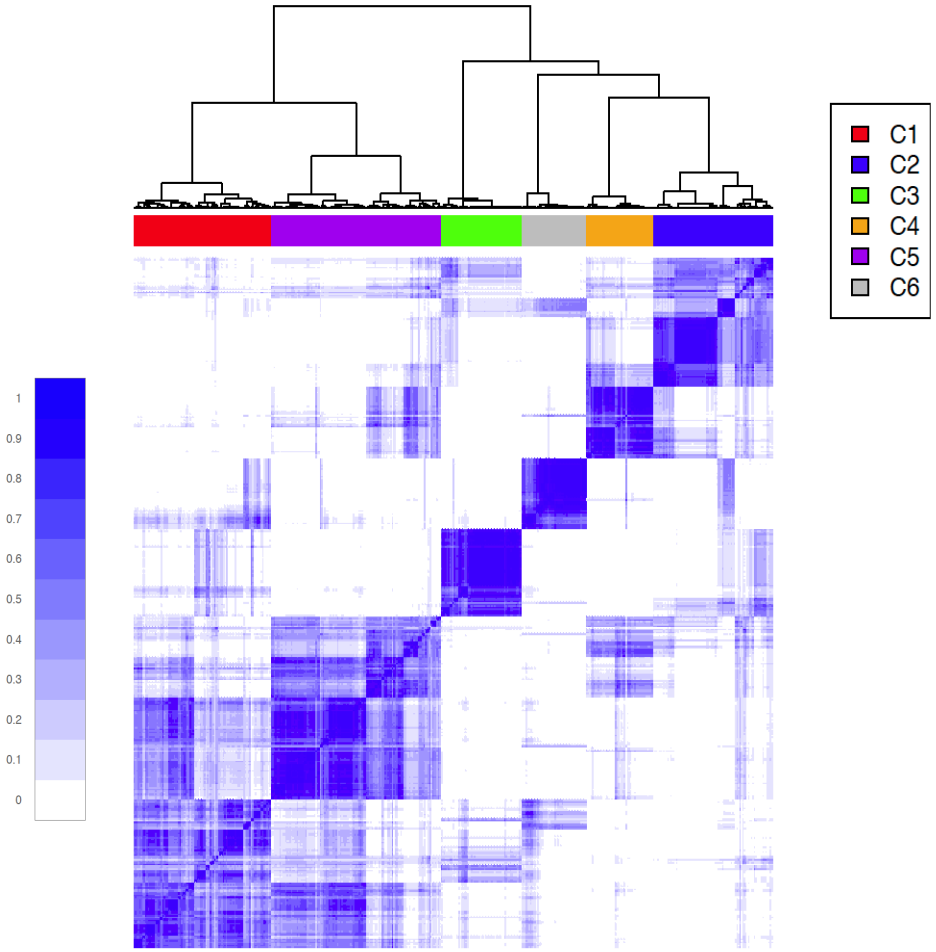
From A. Zaanan

To summarize shortly a very long story…… (2 oxaliplatin and irinotecan)

References	Type of study	Number of patients	Number of MSI tumours (%)	Tumour stage	Number of patients receiving adjuvant CT	Stratification	Survival analysis criteria	Survival results for MSI patients
Oxaliplatin-containing adjuvant chemotherapy								
Kim et al, 2010 [38]	R	135	12 (8.8)	All stages	FOLFOX, n=121	MMR	3 yr-DFS 3 yr-OS	No significant difference
Des Guetz et al, 2010 [39]	R	105	19 (18)	II + III	FOLFOX, n=105	MMR	DFS	Longer survival
Zaanan et al, 2010 [40]	R	233	32 (14)	III	5FU, n=124 FOLFOX, n=109	CT	3 yr-DFS	Longer survival with FOLFOX
Zaanan et al, 2011 [41]	R	303	34 (11.2)	III	FOLFOX, n=303	MMR	3 yr-DFS	Longer survival
Irinotecan-containing adjuvant chemotherapy								
Bertagnolli et al, 2009 [44]	R from RCT	702	96 (13)	III	5FU, n=348 5FU + IRI, n=354	MMR and CT	5 yr-DFS	Longer survival with IRI
Tejpar et al, 2009 [45]	R from RCT	1254	188 (15)	II + III	5FU, n=633 5FU + IRI, n=621	MMR and CT	RFS OS	No significant difference

Unsupervised gene expression analysis of the discovery set (n = 1459 probe sets)

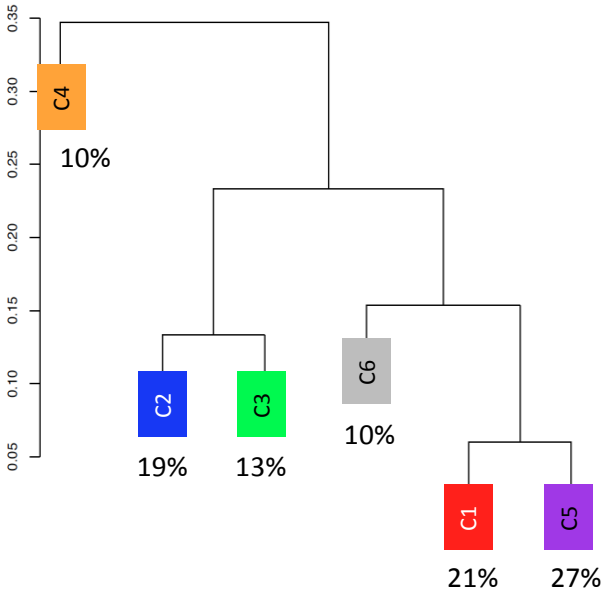
Consensus Matrix K=6



Parameters : *nb probe sets used = 1459 (CVr>0.15)*
proportion of probesets and tumors resampling = 0.9
n iterations = 1000

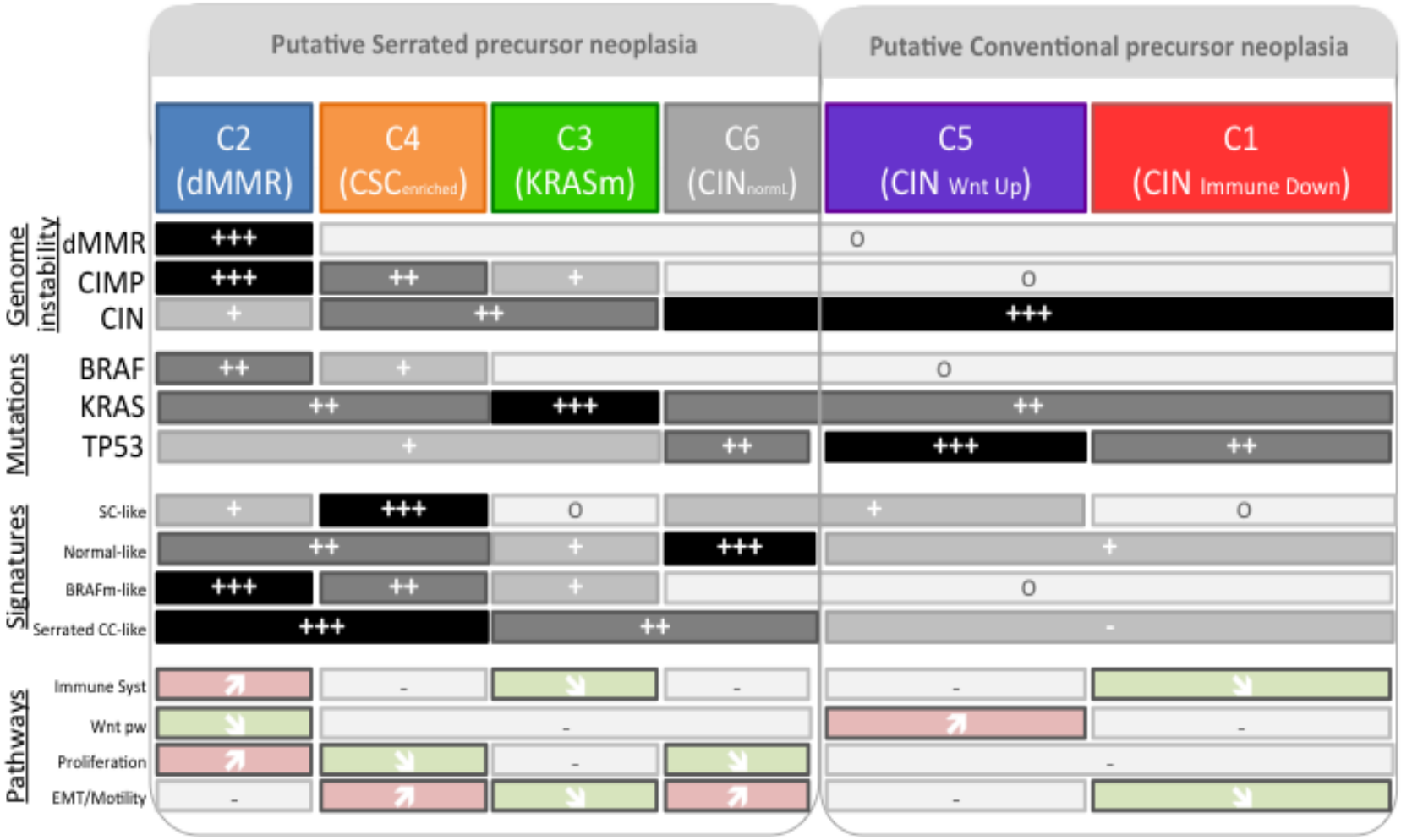
Reference : Matt Wilkerson (2011).

Distance between Group



- C4 (n=46, 10%): the most distinct cluster
- C2 (n=83, 19%), C3 (n=56, 13%), C6 (n=45, 10%): well individualized clusters
- More overlap between GEP of C1 (n=95, 21%) and C5 (n=118, 27%)

Summary of the six-subtype classification according to their main characteristics (DNA alterations/associated signatures/deregulated pathways)



International Colorectal Cancer Subtyping Consortium ICCSC Bionetwork Sage initiative (Justin Guinney Steven Friend)

Association of different group to provide a common classification of colorectal cancer

OPEN ACCESS Freely available online

PLOS | MEDICINE

Gene Expression Classification of Colon Cancer into Molecular Subtypes: Characterization, Validation, and Prognostic Value

Laetitia Marisa[1], Aurélien de Reyniès[1], Alex Duval[2,3], Janick Selves[4], Marie Pierre Gaub[5,6], Laure Vescovo[1], Marie-Christine Etienne-Grimaldi[7], Renaud Schiappa[1], Dominique Guenot[5], Mira Ayadi[1], Sylvain Kirzin[4], Maurice Chazal[8], Jean-François Fléjou[2,3,9], Daniel Benchimol[10], Anne Berger[11], Arnaud Lagarde[12], Erwan Pencreach[5,6,13], Françoise Piard[14], Dominique Elias[15], Yann Parc[3,16], Sylviane Olschwang[12,17,18,19], Gérard Milano[7], Pierre Laurent-Puig[20]*[¶], Valérie Boige[15,20¶]

Journal of Pathology
J Pathol 2013; **231**: 63–76
Published online 8 July 2013 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/path.4212

ORIGINAL PAPER

Gene expression patterns unveil a new level of molecular heterogeneity in colorectal cancer

Eva Budinska,[1,2]* Vlad Popovici,[1,2] Sabine Tejpar,[3] Giovanni D'Ario,[1] Nicolas Lapique,[1] Katarzyna Otylia Sikora,[1] Antonio Fabio Di Narzo,[1] Pu Yan,[4] John Graeme Hodgson,[5] Scott Weinrich,[5] Fred Bosman,[5] Arnaud Roth[6,7] and Mauro Delorenzi[1,8]

LETTERS

nature medicine

Poor-prognosis colon cancer is defined by a molecularly distinct subtype and develops from serrated precursor lesions

Felipe De Sousa E Melo[1,7], Xin Wang[2,7], Marnix Jansen[3], Evelyn Fessler[1], Anne Trinh[2], Laura P M H de Rooij[1], Joan H de Jong[1], Onno J de Boer[3], Ronald van Leersum[1], Maarten F Bijlsma[1], Hans Rodermond[1], Maartje van der Heijden[1,4], Carel J M van Noesel[3], Jurriaan B Tuynman[5], Evelien Dekker[6], Florian Markowetz[2], Jan Paul Medema[1,7] & Louis Vermeulen[1,4,7]

LETTERS

nature medicine

A colorectal cancer classification system that associates cellular phenotype and responses to therapy

Anguraj Sadanandam[1,2], Costas A Lyssiotis[3,4,14,15], Krisztian Homicsko[2,5,15], Eric A Collisson[6], William J Gibb[7], Stephan Wullschleger[2], Liliane C Gonzalez Ostos[2], William A Lannon[3,14], Carsten Grotzinger[8], Maguy Del Rio[9], Benoit Lhermitte[10], Adam B Olshen[11,12], Bertram Wiedenmann[8], Lewis C Cantley[3,4,14], Joe W Gray[13] & Douglas Hanahan[2]

UICC

IJC International Journal of Cancer

Colorectal cancer intrinsic subtypes predict chemotherapy benefit, deficient mismatch repair and epithelial-to-mesenchymal transition

Paul Roepman[1], Andreas Schlicker[2], Josep Tabernero[3], Ian Majewski[2], Sun Tian[1], Victor Moreno[4,5], Mireille H Snel[1], Christine M Chresta[6], Robert Rosenberg[7], Ulrich Nitsche[7], Teresa Macarulla[3], Gabriel Capella[5], Ramon Salazar[5], George Orphanides[6], Lodewyk FA Wessels[2,8], Rene Bernards[1,2] and Iris M Simon[1]

Schlicker *et al. BMC Medical Genomics* 2012, **5**:66
http://www.biomedcentral.com/1755-8794/5/66

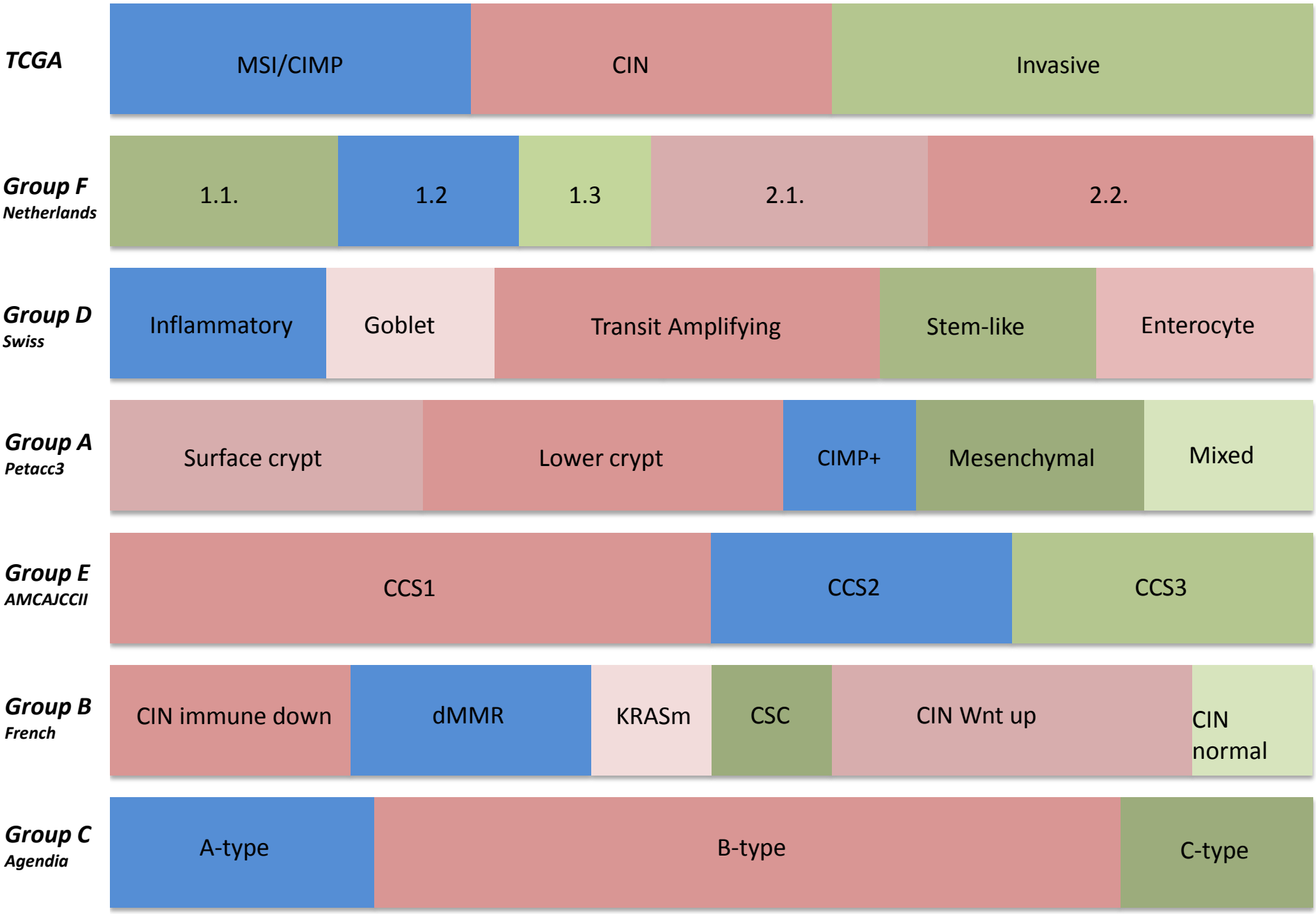
BMC Medical Genomics

RESEARCH ARTICLE Open Access

Subtypes of primary colorectal tumors correlate with response to targeted treatment in colorectal cell lines

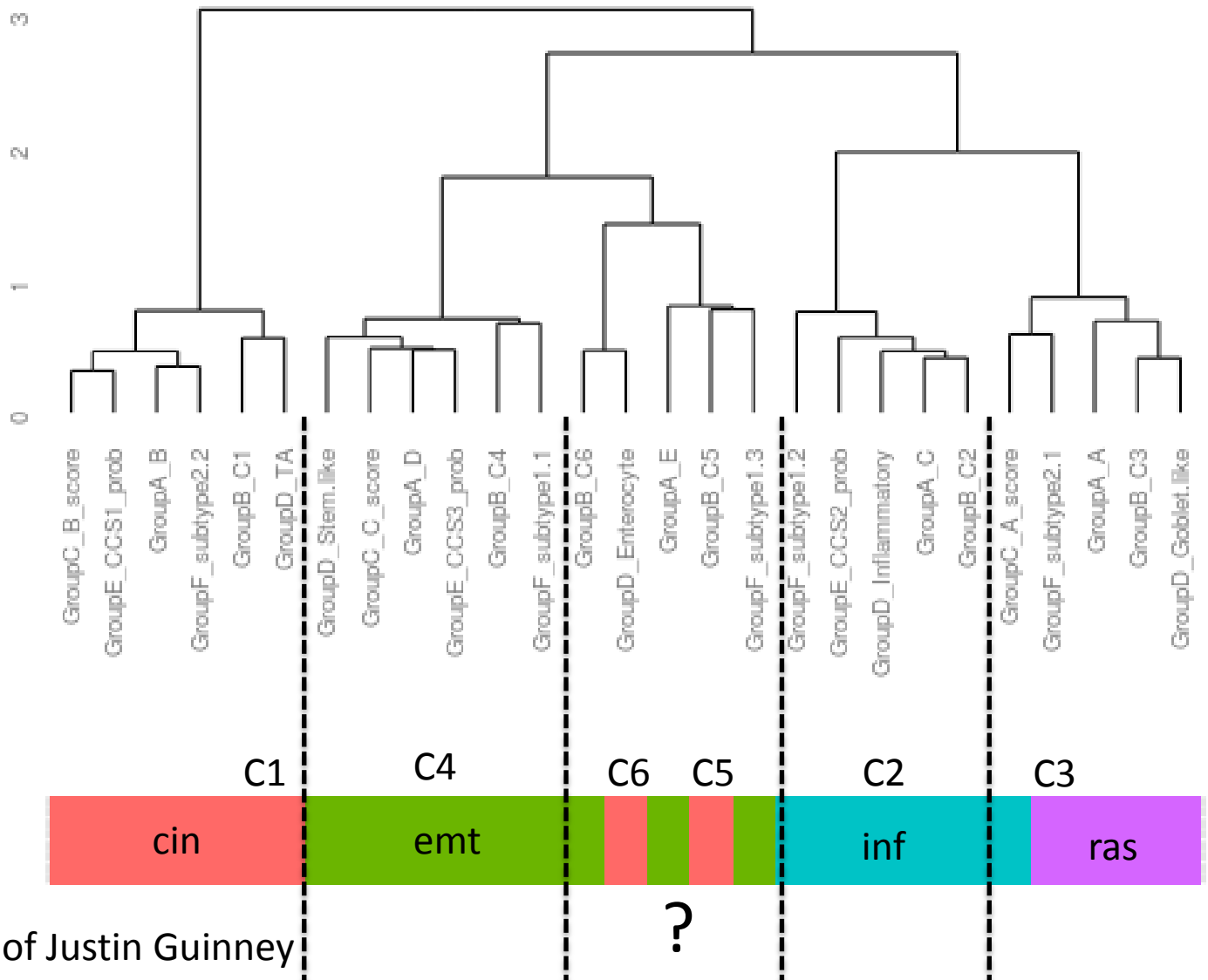
Andreas Schlicker[1], Garry Beran[3], Christine M Chresta[3], Gael McWalter[4], Alison Pritchard[3], Susie Weston[4], Sarah Runswick[4], Sara Davenport[3], Kerry Heathcote[3], Denis Alferez Castro[3], George Orphanides[3], Tim French[4]* and Lodewyk FA Wessels[1,2,5]*

+TCGA COLON DATA + AGENDIA Unpublished

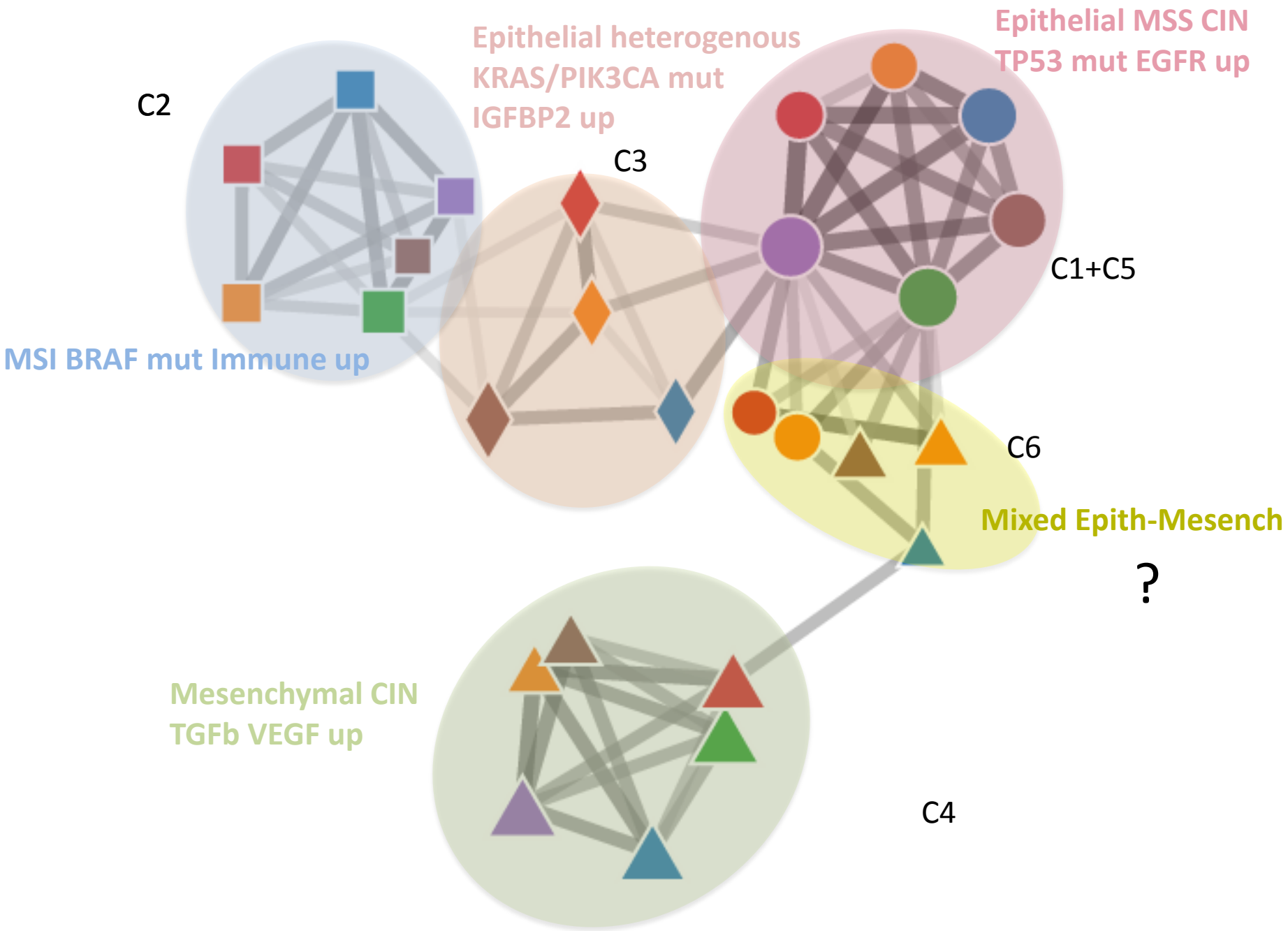


Rodrigo Dienstmann (version 3, Jan 3rd 2013)

1. Jaccard distance between subtypes (n=3400+)
2. Agglomerative clustering (ward)



Courtesy of Justin Guinney


C2
Epithelial heterogenous
KRAS/PIK3CA mut
IGFBP2 up
C3
Epithelial MSS CIN
TP53 mut EGFR up
C1+C5
MSI BRAF mut Immune up
C6
Mixed Epith-Mesench
?
Mesenchymal CIN
TGFb VEGF up
C4

Conclusions

- dMMR colon tumors are clearly a sub group of colon cancer with specific behaviors
- dMMR phenotype should be characterized
  - For recognition of Lynch syndrome
  - For the prognosis determination
  - For the determination of chemotherapy