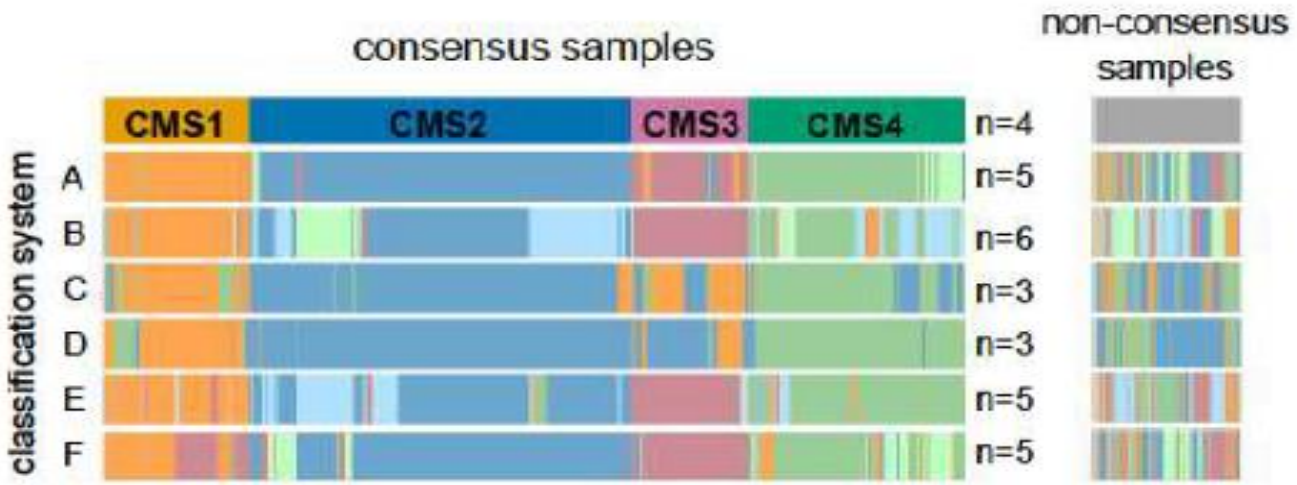
Immunotherapy in MSI-H CRC

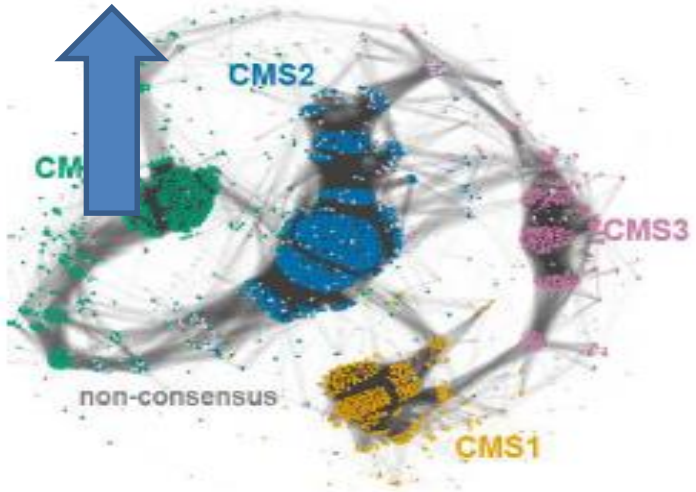
Shereef Elsamany

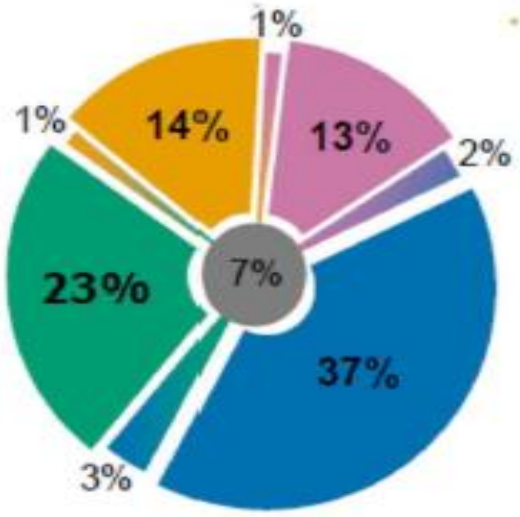
Oncology Centre, KAMC, Makkah

CRC subtyping consortium – 2015

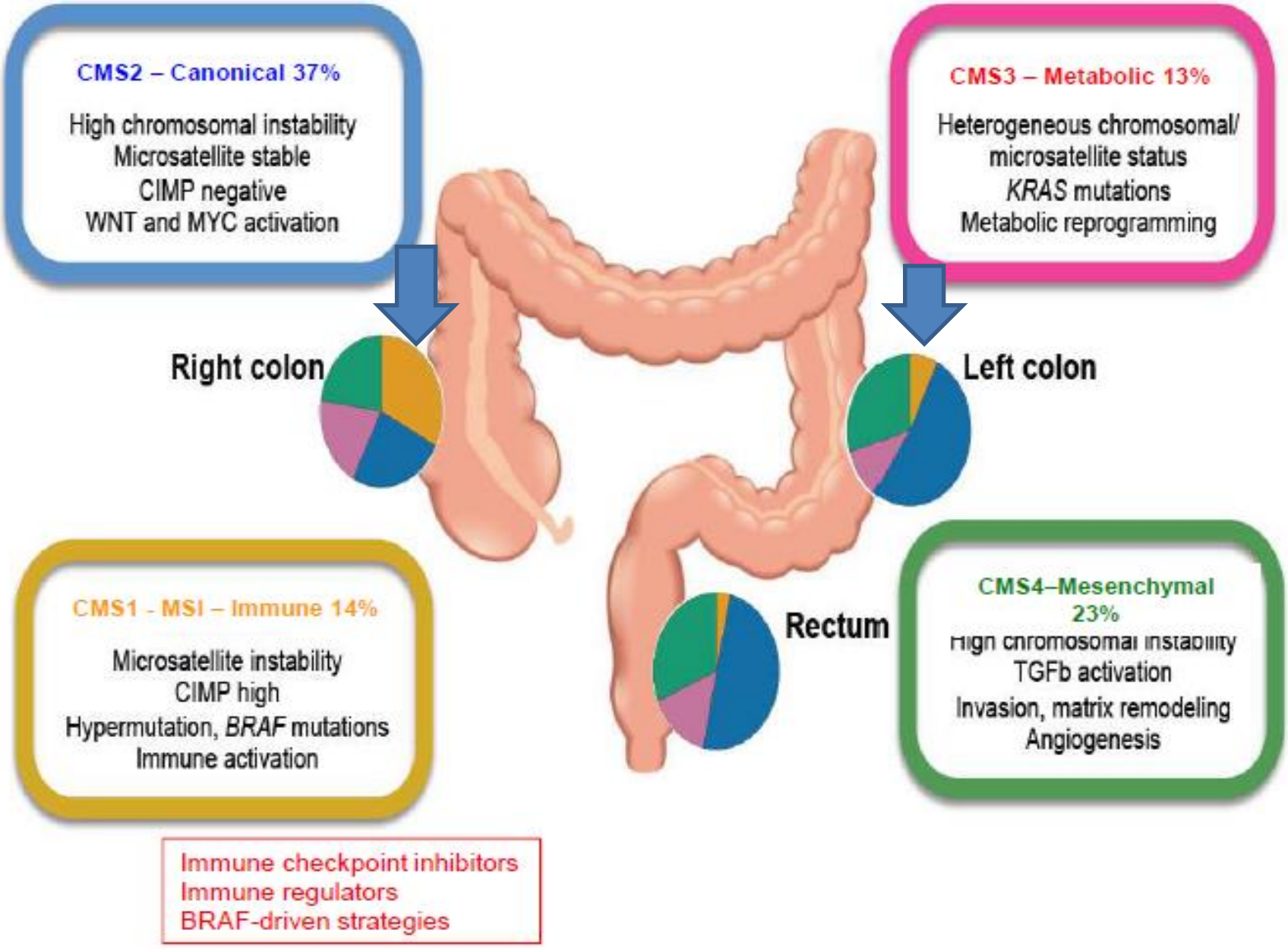


CMS1 MSI Immune | **CMS2** Canonical | **CMS3** Metabolic | **CMS4** Mesenchymal





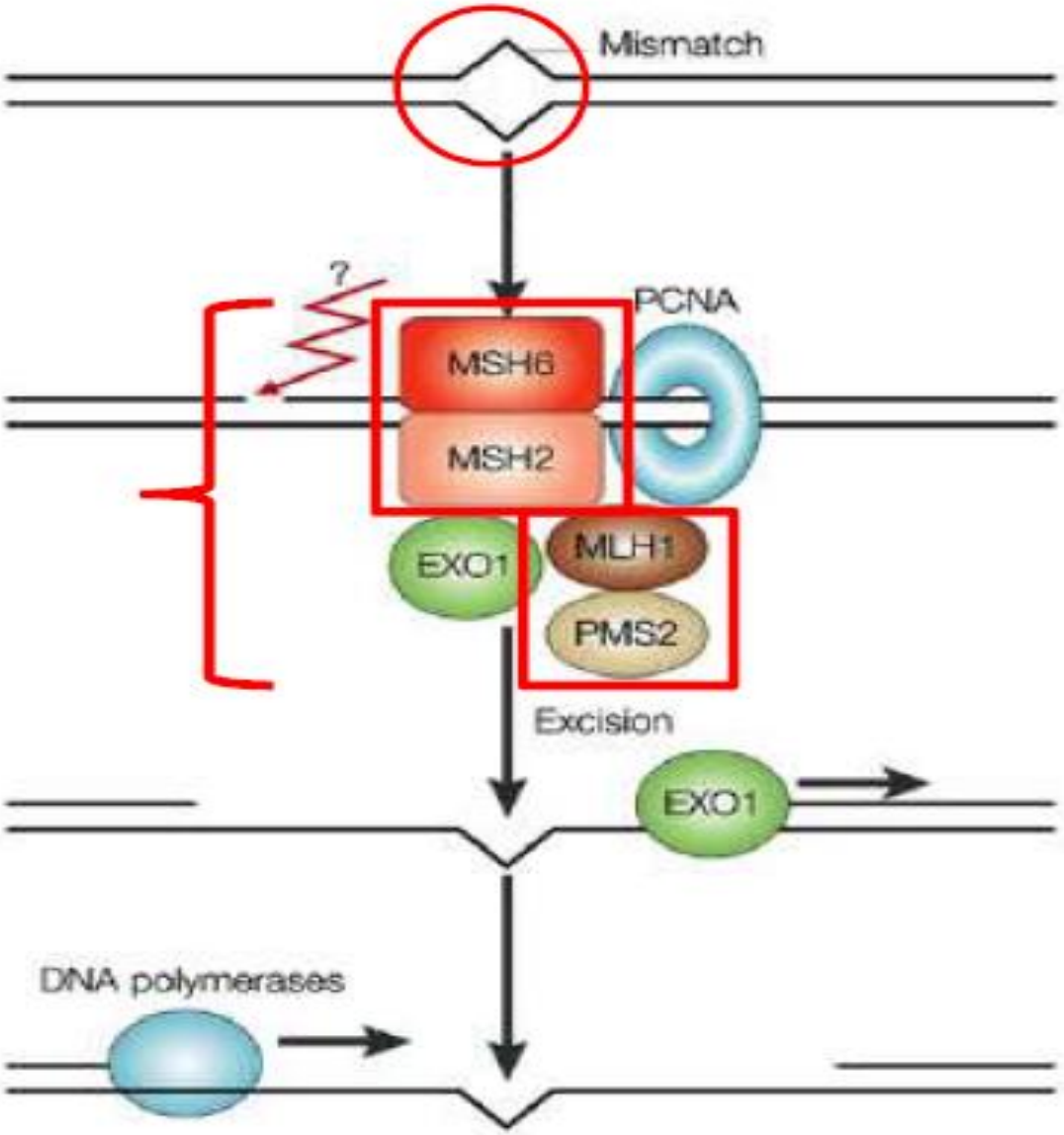
Guinney J, Dienstmann R et al. Nat Med 2015



Guinney J, Dienstmann R et al. Nat Med 2015

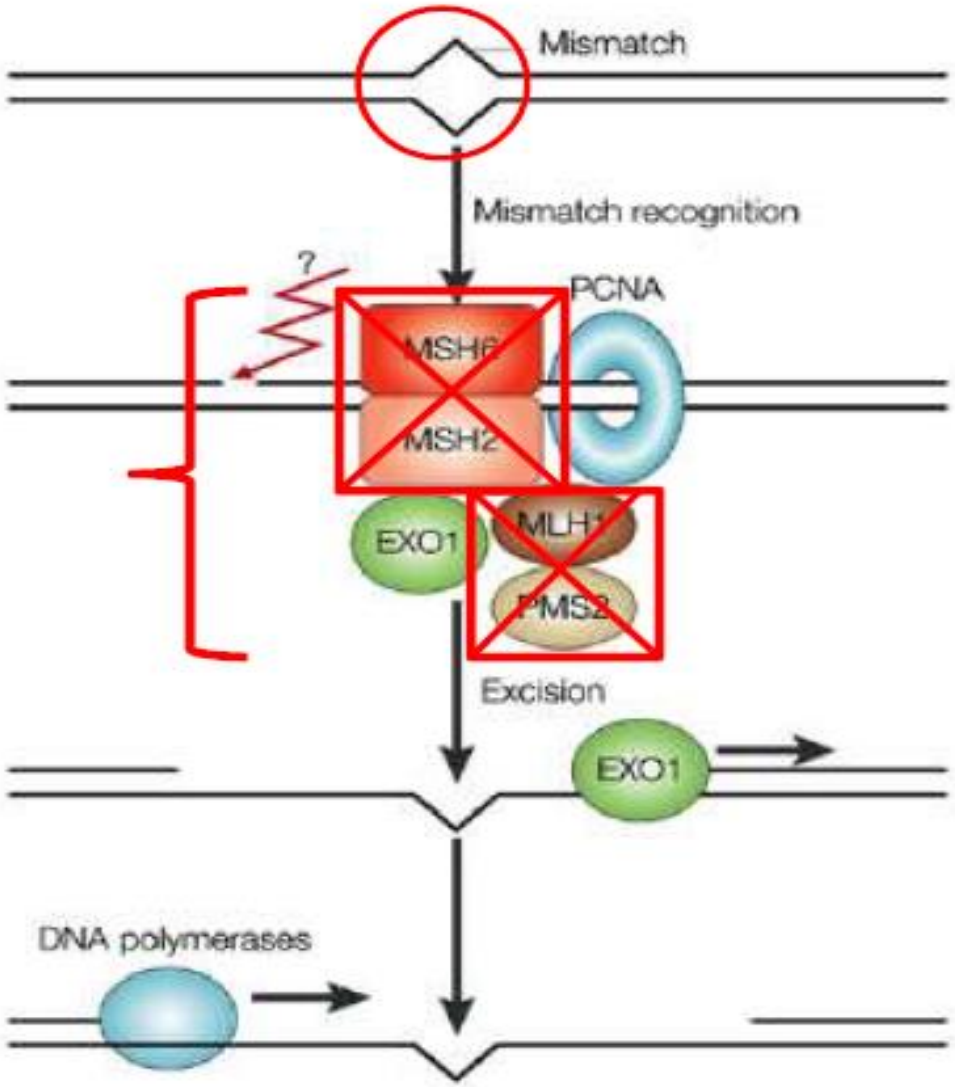
MisMatch Repair system (MMR)

4 proteins for DNA reparation



Deficient MMR system

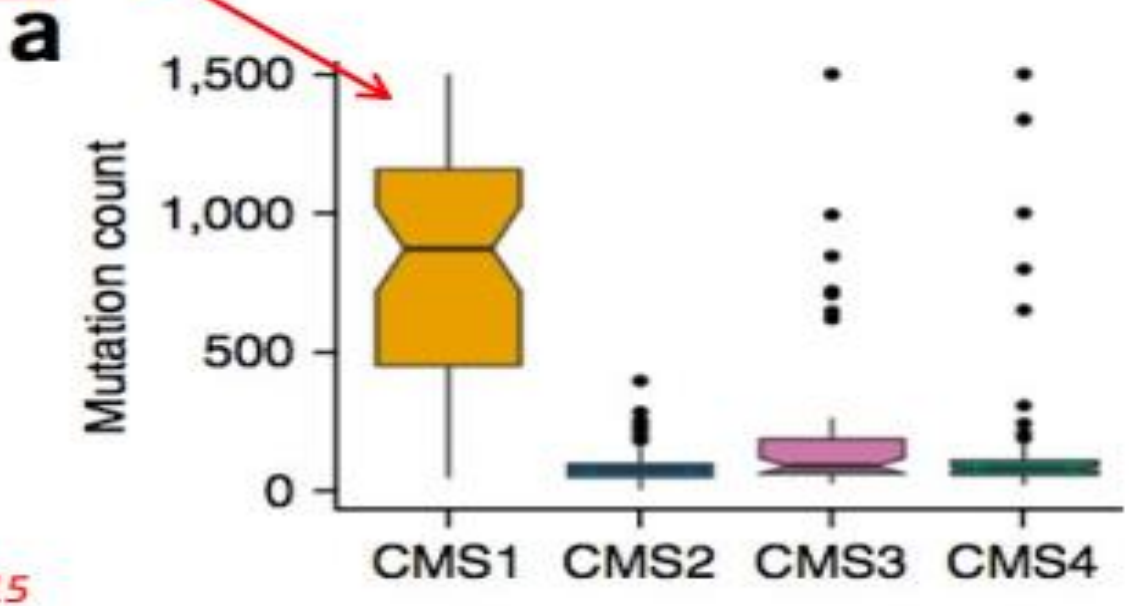
4 proteins for DNA reparation



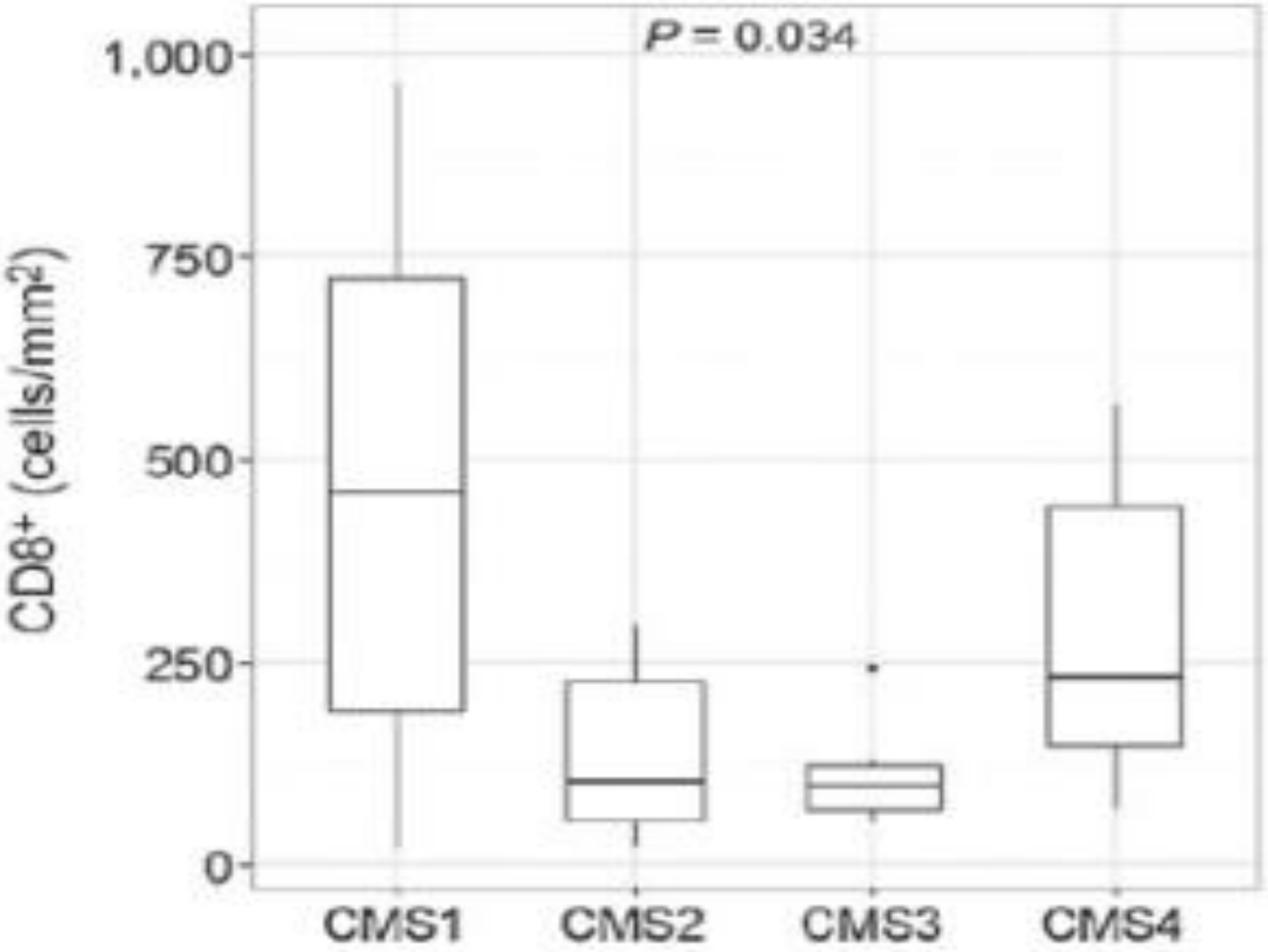
Altered apoptose, cell cycle related gened ⟶ MSI CRC carcinogenesis

CMS1 MSI immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high, hypermutation	SCNA high	Mixed MSI status, SCNA low, CIMP low	SCNA high
BRAF mutations		*KRAS* mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration, TGF-β activation, angiogenesis
Worse survival after relapse			Worse relapse-free and overall survival

"MSI-like"



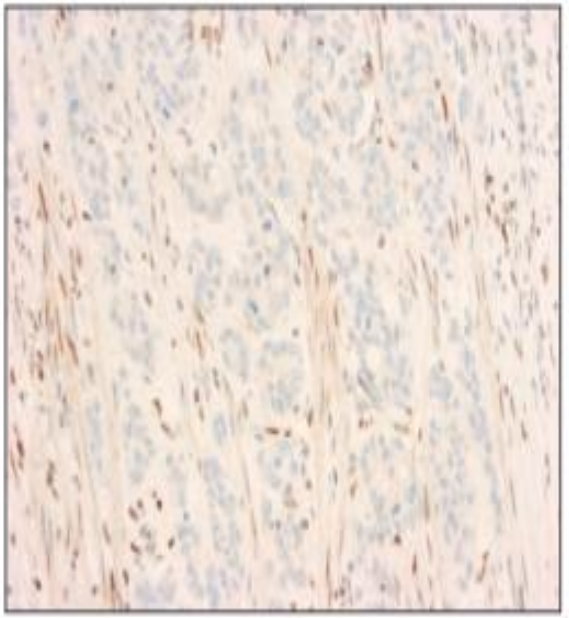
Guinney et al, Nature 2015


P = 0.034
1,000
750
500
250
0
CD8+ (cells/mm2)
CMS1
CMS2
CMS3
CMS4

How to test MSI-status ?

- IHC of MLH1, MSH2, MSH6, PMS2 expression
- Molecular testing
- Both

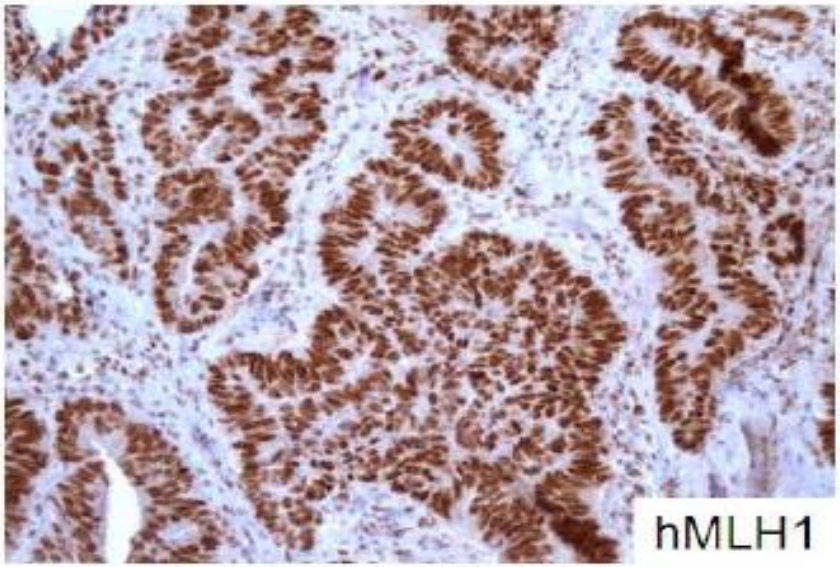
- **Molecular testing:** Genotyping 5 microsatellites allows the characterization of microsatellite tumor instability
  - If at least 2 of the 5 microsatellites are unstable, the tumor phenotype is "**MSI-high**" or **dMMR**
- **Immunohistochemical testing:** Tumor tissue can be checked for expression of DNA mismatch repair protein MLH1, MSH2, MSH6 or PMS1.
  - Loss of expression indicates that the corresponding gene is not being appropriately expressed and suggests the existence of a mutation or epigenetic silencing

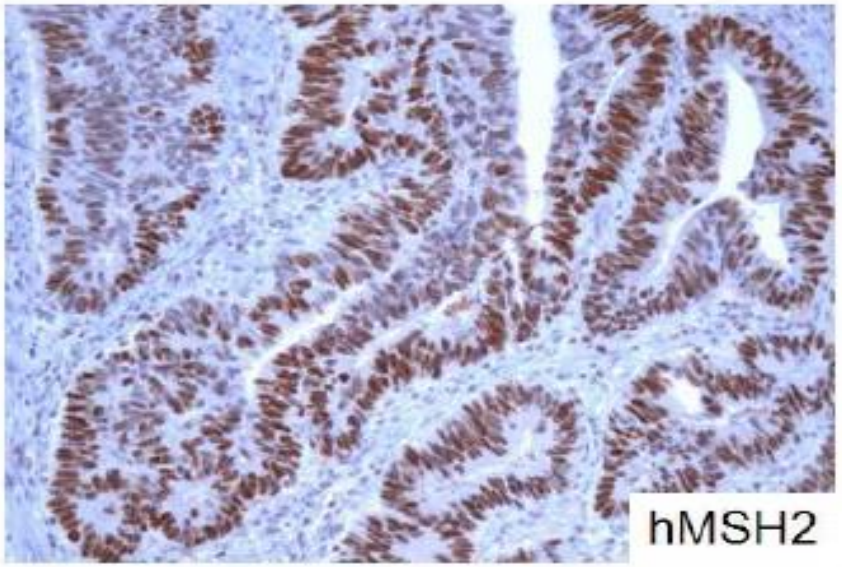


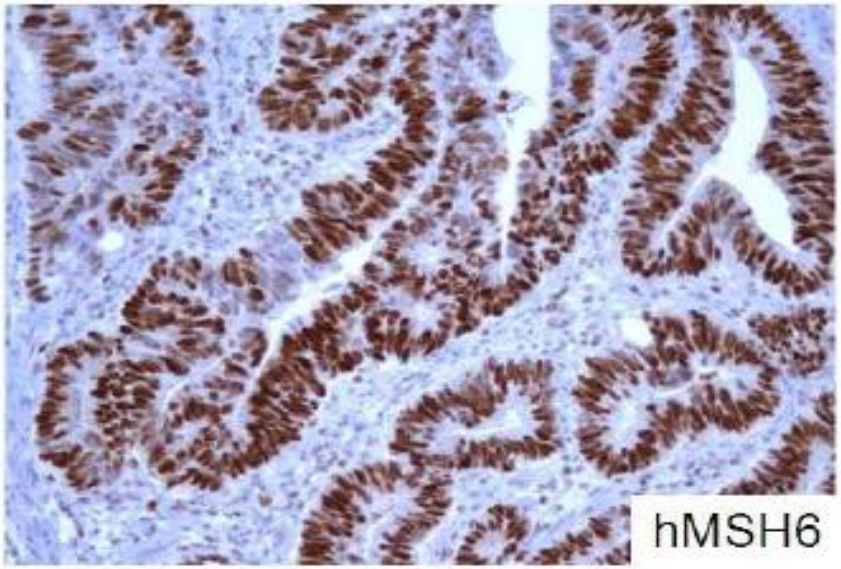
MSI: loss of MLH1 in tumor cells

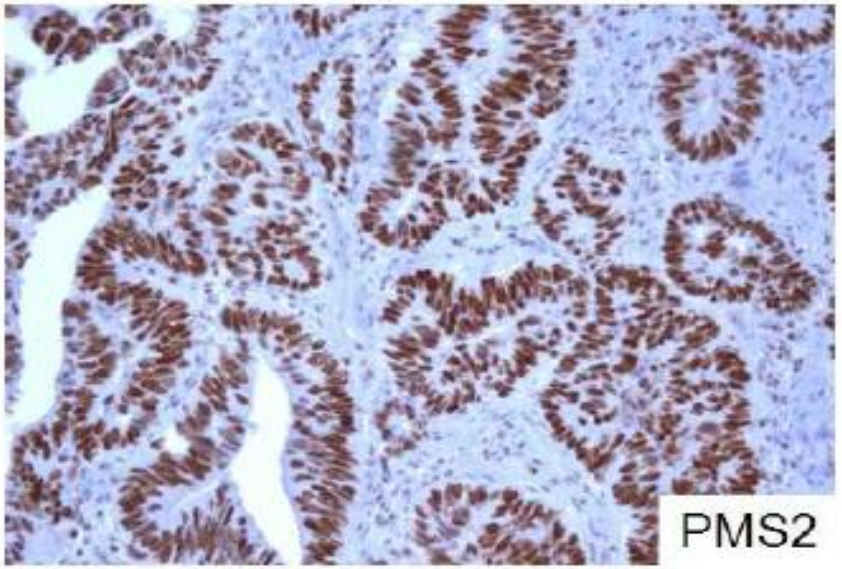
Immunohistochemistry

Stable tumour (MSS): 4 MMR proteins expressed



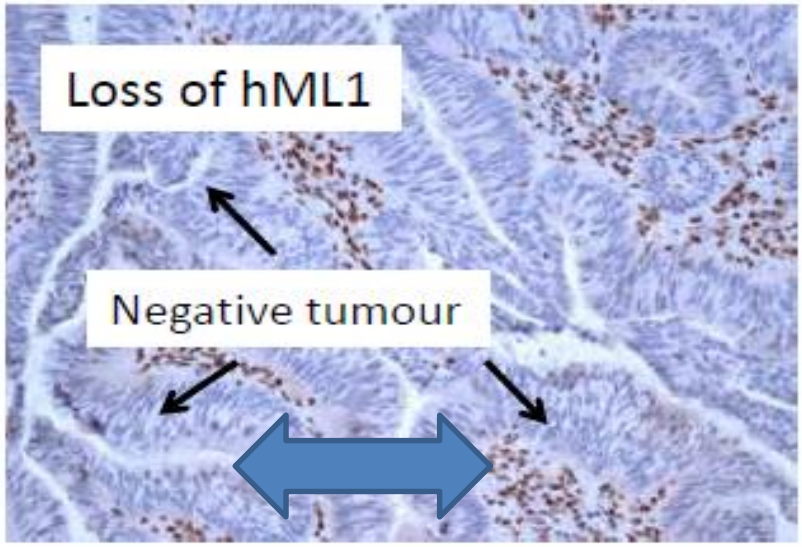


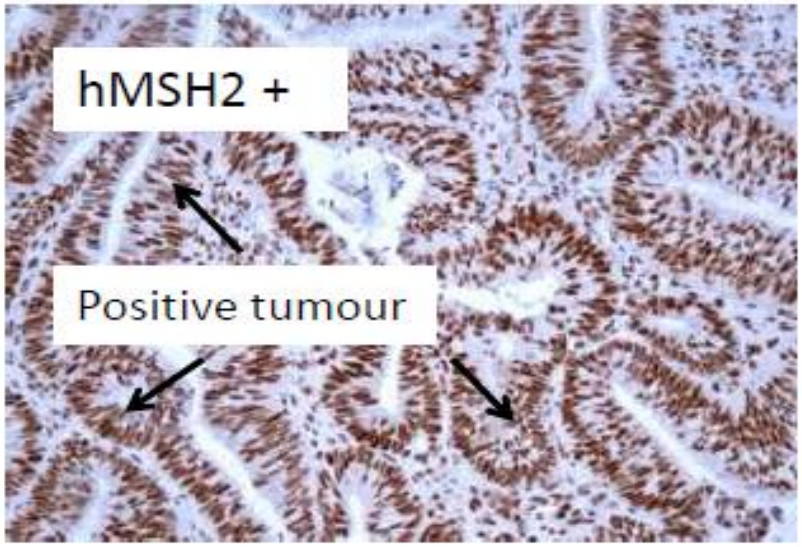


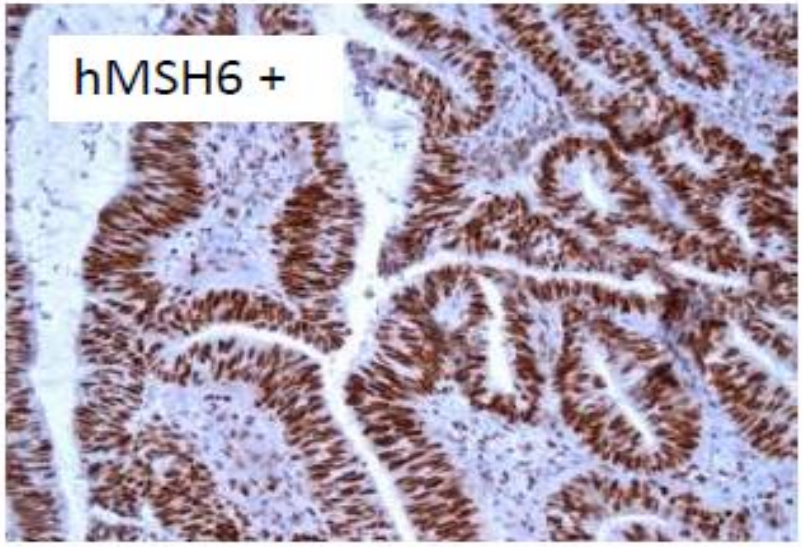


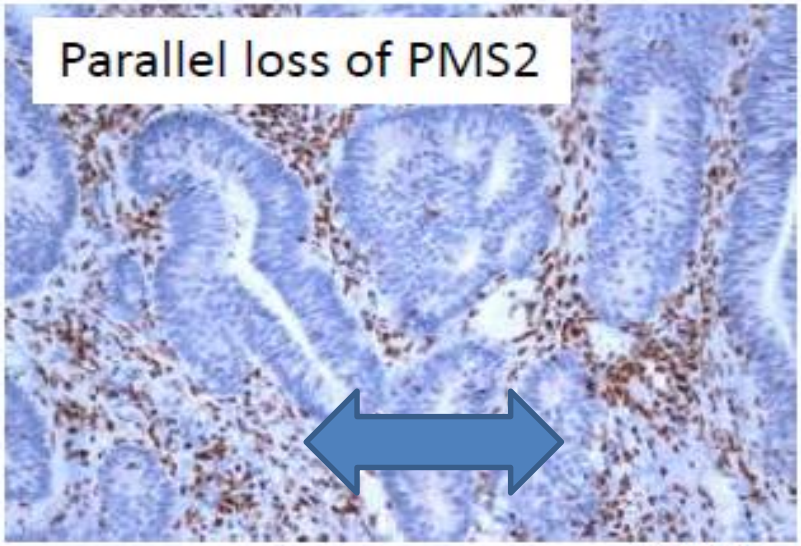
Immunohistochemistry

Instable tumour(MSI): extinction of MMR proteins









personnal casel F. Bibeau

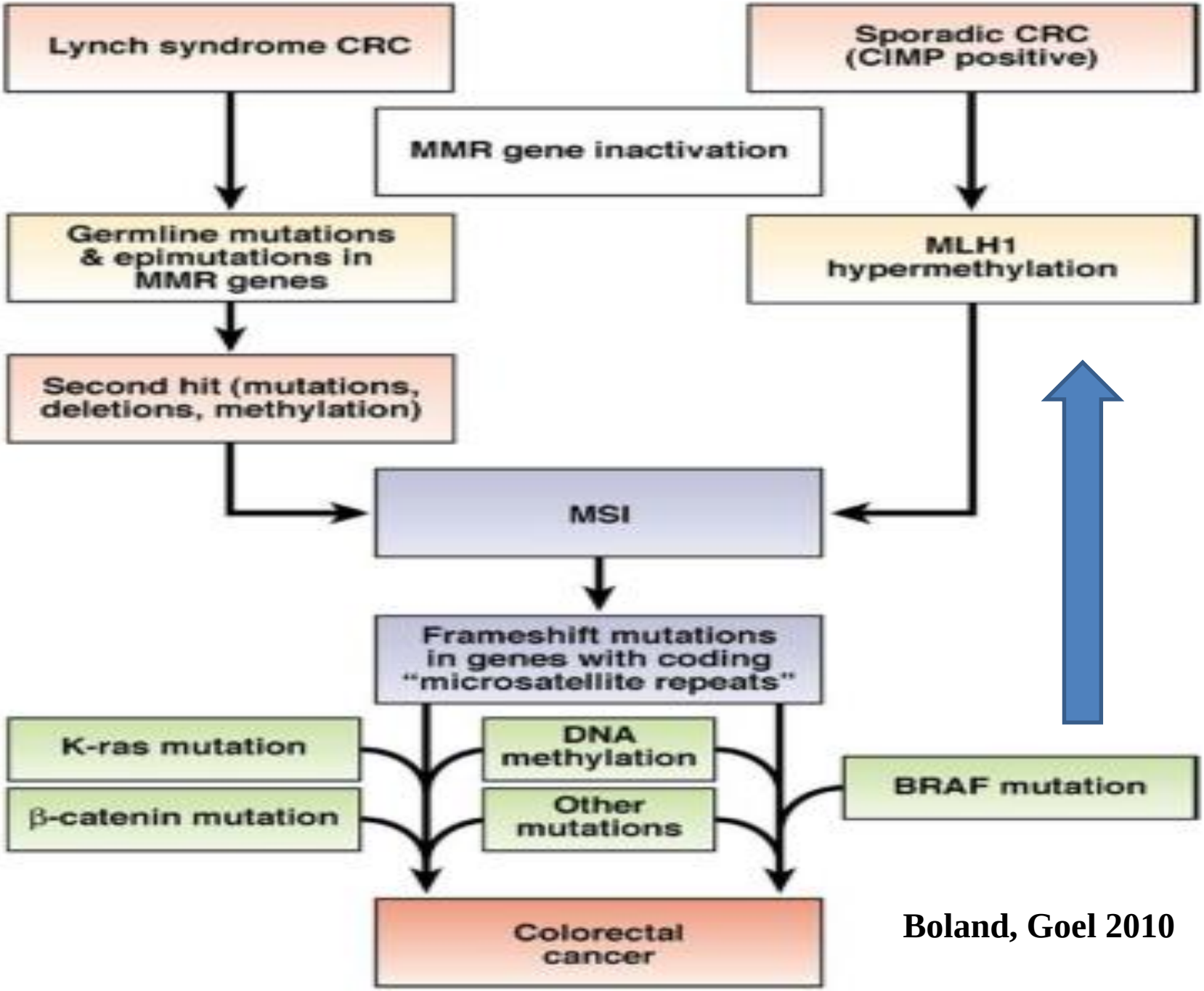
*MisMatch Repair

How to test MSI-status ?

- IHC of MLH1, MSH2, MSH6, PMS2 expression
- Molecular testing of microsatellites mutation
- Both

MSI-H in hereditary tumours only ??

- Yes (Hereditary non-polyposis colorectal cancer)
- No



Boland, Goel 2010

Microsatellite instability context

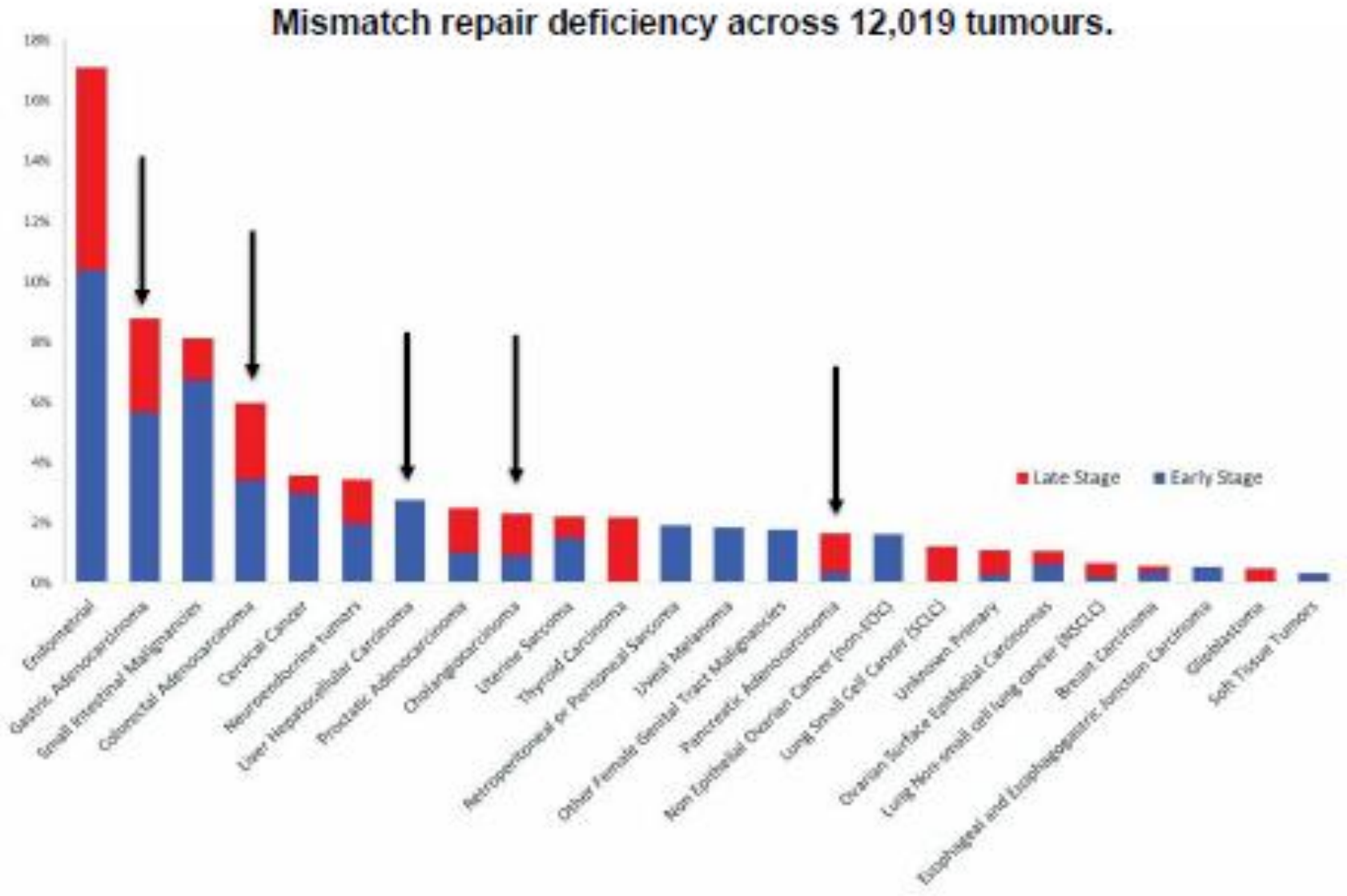
MSI and hMLH1 loss

Sporadic cancer (15%)	Lynch syndrome (2%)
Hypermethylation *MLH1* promotor	Absent
BRAF mutation	Absent
Elderly patient	Young patient

MSI-H in hereditary tumours only ??

- Yes
- No, mostly sporadic cases

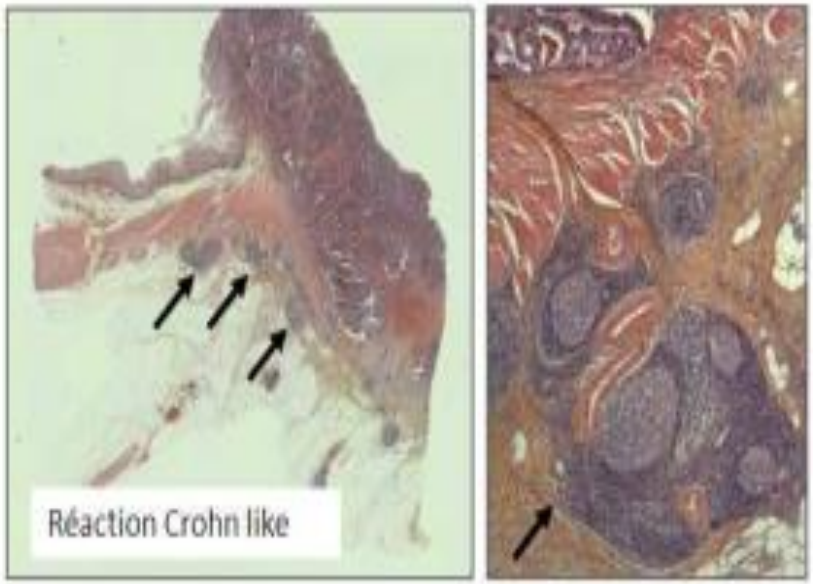
MISMATCH REPAIR DEFICIENCY ACROSS CANCERS

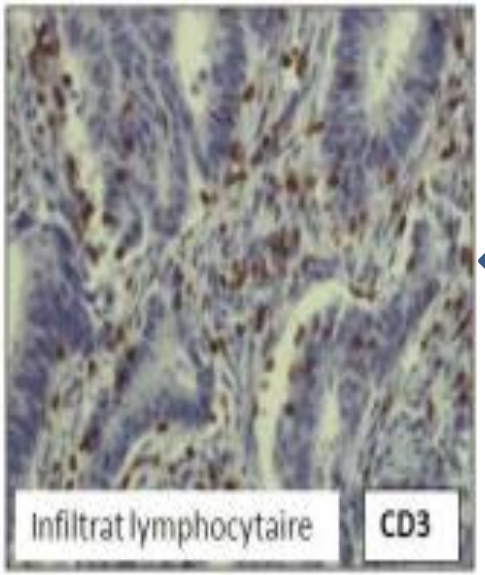


Who should be tested for MSI

- All GI patients
- Selected patients
- At time of diagnosis
- After failure of 1-2 lines

MSI CRC : immunogenic tumour





undifferentiated, signet-ring cell, mucinous carcinomas

Molecular grading (MSI-status)

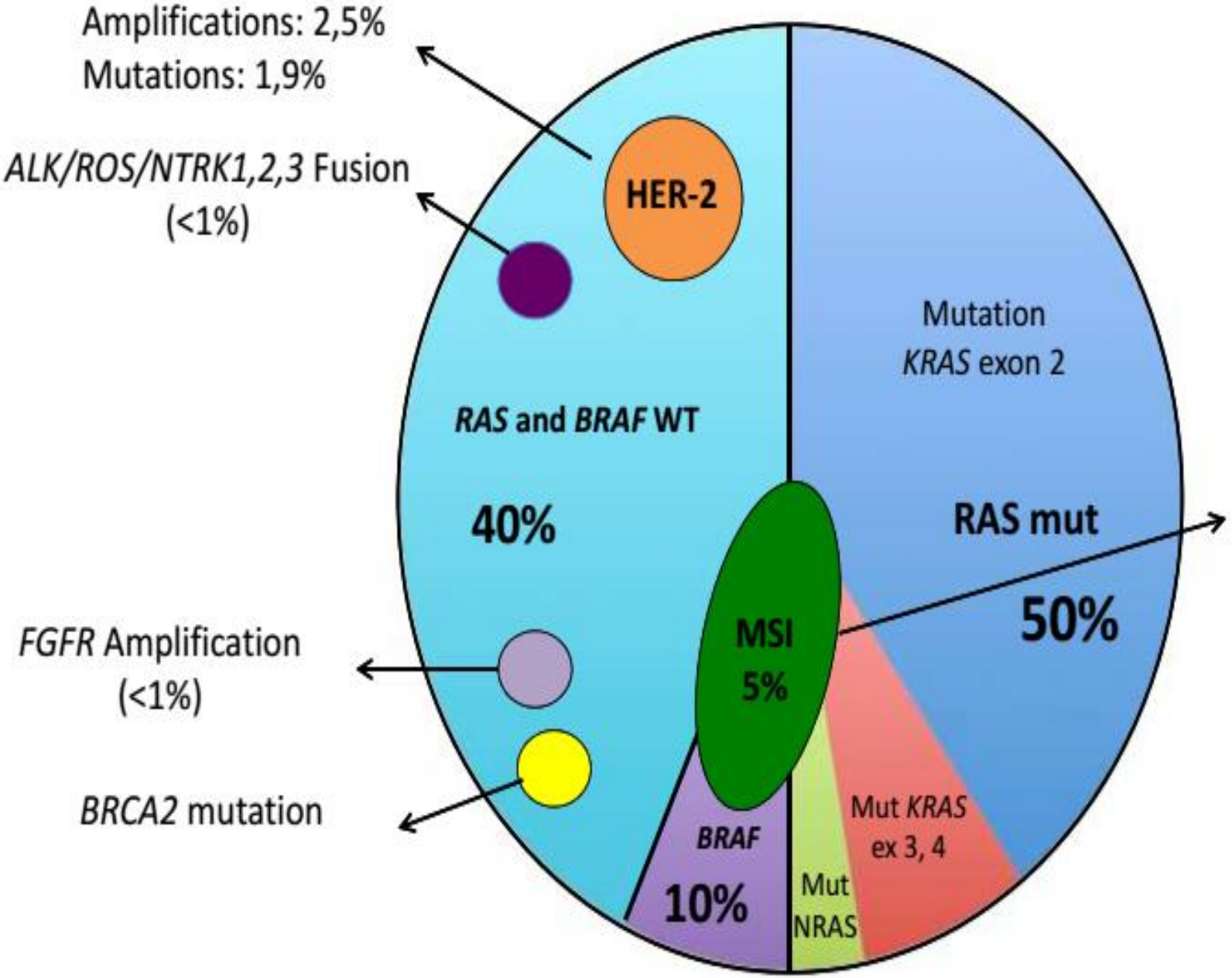
undifferentiated, signet-ring cell, mucinous carcinomas

MSI-H

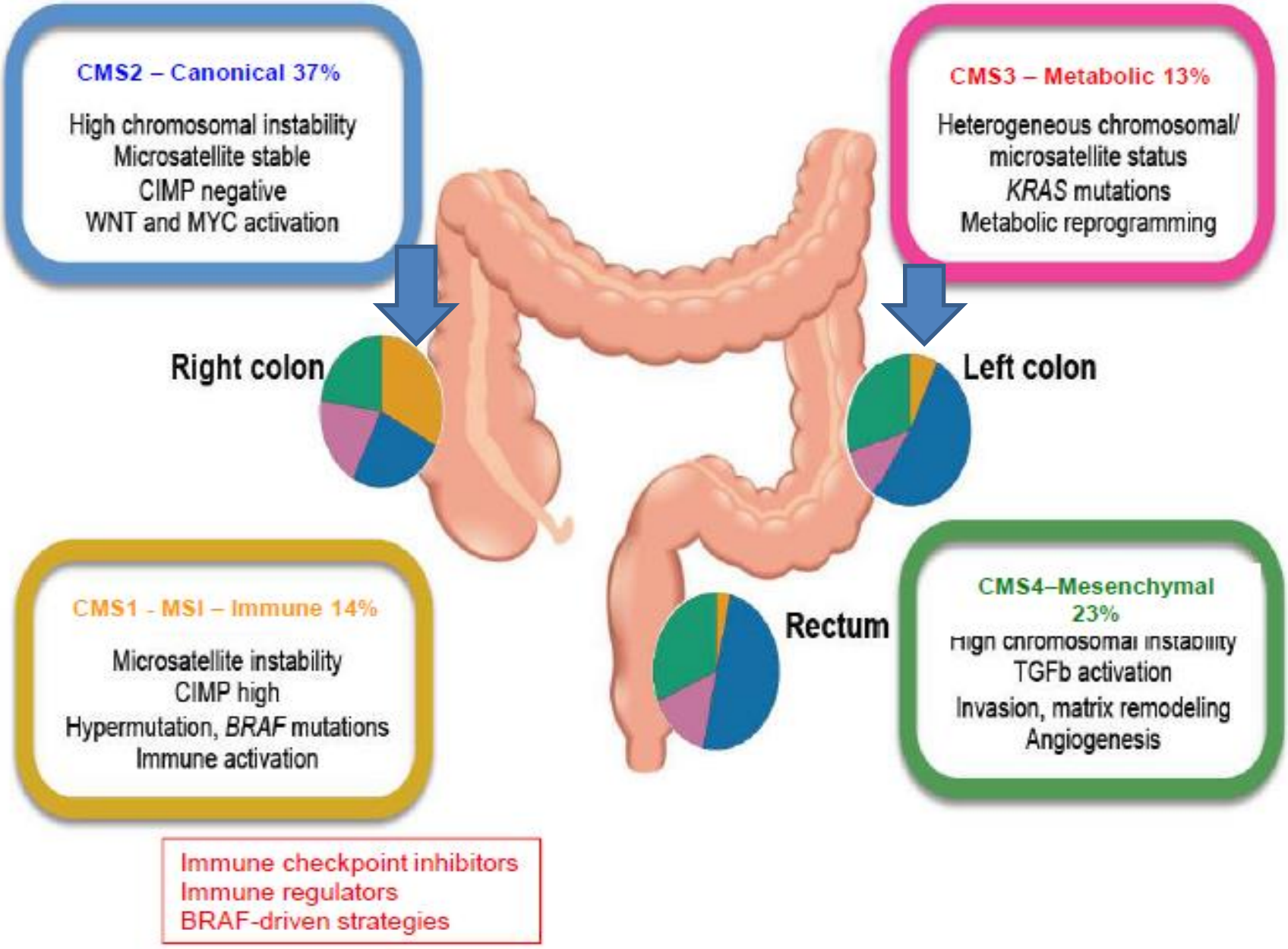
MSS

low grade

high grade



Rankin Oncologist 2016



Guinney J, Dienstmann R et al. Nat Med 2015

Who should be tested for MSI

- All GI patients
- **Selected patients: RT, mucinous, BRAF mut**
- **At time of diagnosis**
- After failure of 1-2 lines

Chemotherapy in MSI-H patients

VOLUME 28 · NUMBER 20 · JULY 10 2010

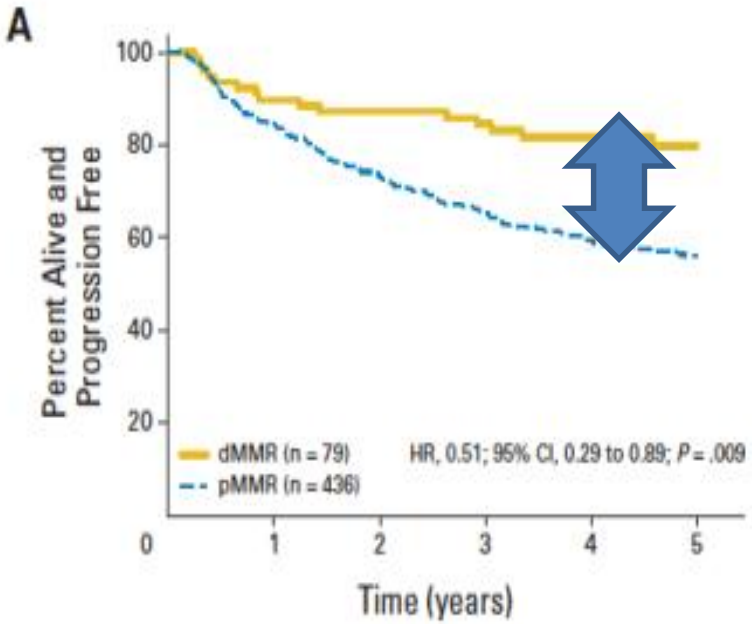
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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

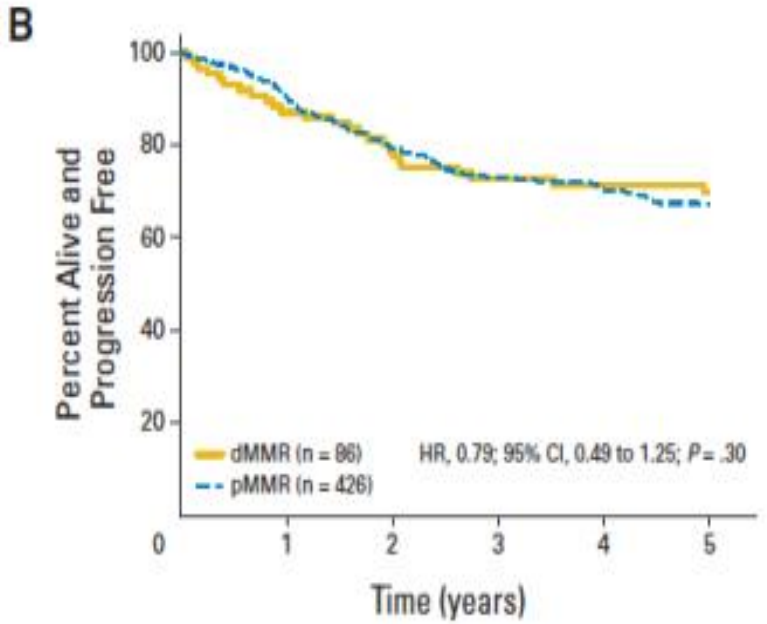
1027 patients included in trials demonstrating the effect of FU in adjuvant settings

MSI + (dMMR) 185 pts (18%)

No chemotherapy



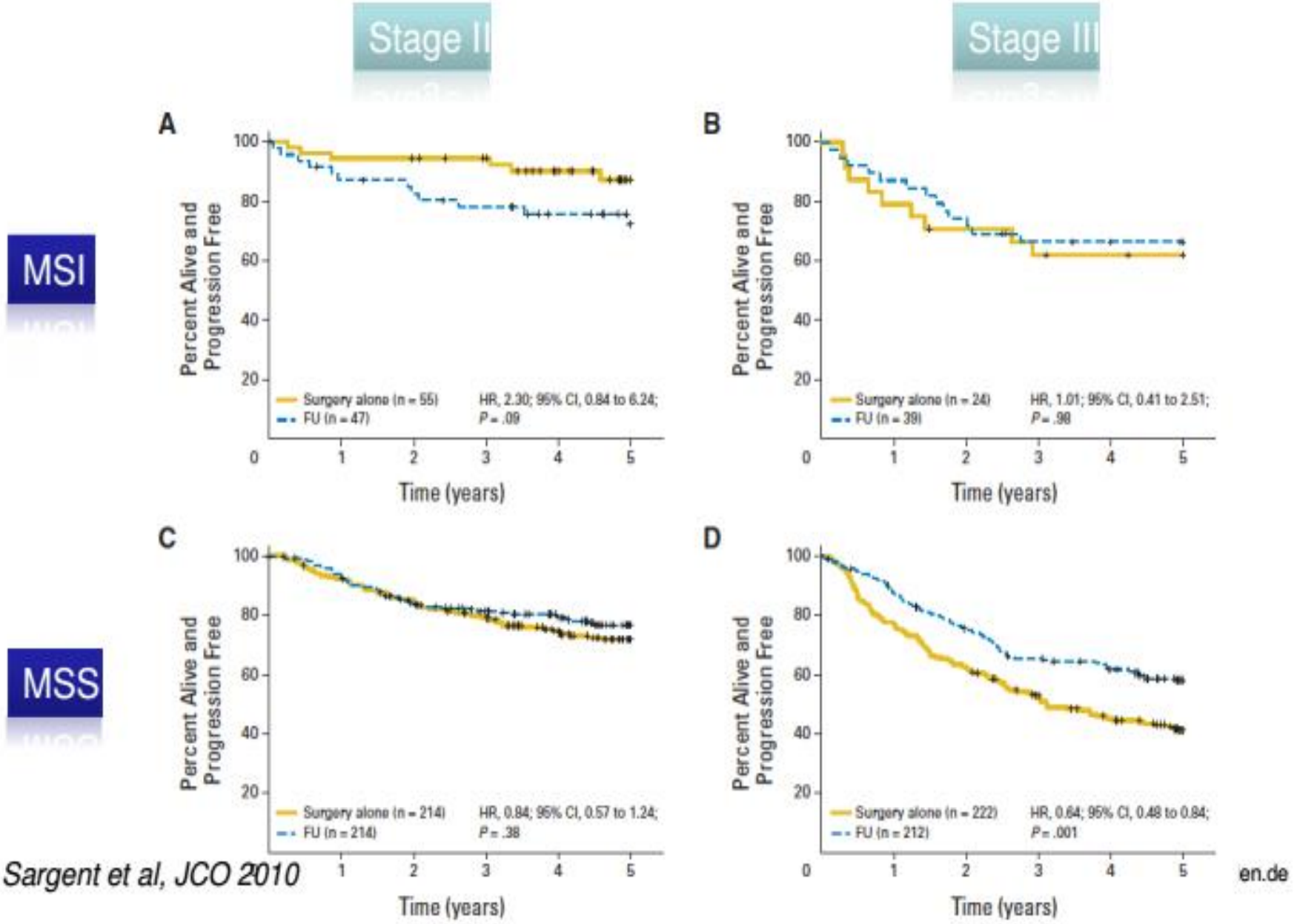
5FU chemotherapy



Dan Sargent et al, JCO 2010

www.pathologie-universitaetsmedizin-dresden.de

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



Dan Sargent et al, JCO 2010

en.de

Pembrolizumab in MSI-H CRC

Anti-PD1 in CRC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

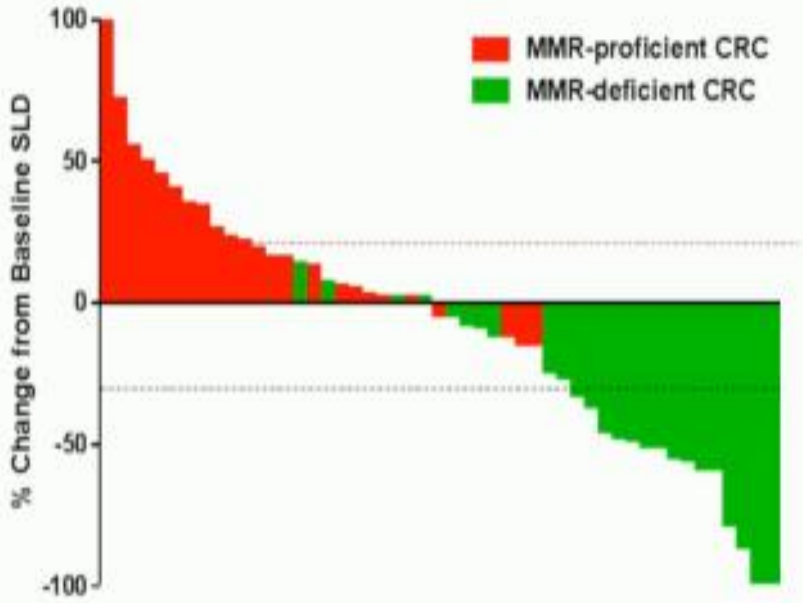
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

Le et al, NEJM 2015

MSI vs MSS

Best Radiographic Response

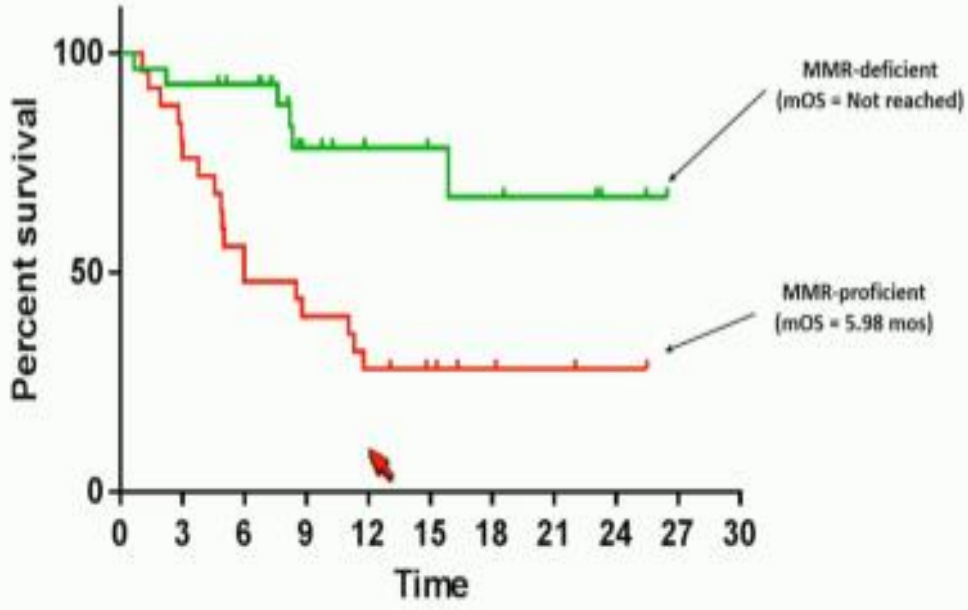


MSS (n=25) vs MSI (n=28)

ORR: 0% vs 57%

OS: 6mo vs NR

Overall Survival



Le et al, ASCO 2016

FDA approval pembrolizumab MSI tumors

FDA News Release

FDA approves first cancer treatment for any solid tumor with a specific genetic feature

FDA Approves Mercks KEYTRUDA (pembrolizumab) for Adult and Pediatric Patients with Unresectable or Metastatic, Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient Cancer

Pembrolizumab Approved for MSI-H or Mismatch Repair Deficient Tumors

Table 23: MSI-H Trials

Study	Design and Patient Population	Number of patients	MSI-H/dMMR testing	Dose	Prior therapy
KEYNOTE-016 NCT01876511	• prospective, investigator-initiated • 6 sites • patients with CRC and other tumors	28 CRC 30 non-CRC	local PCR or IHC	10 mg/kg every 2 weeks	• CRC: ≥ 2 prior regimens • Non-CRC: ≥1 prior regimen
KEYNOTE-164 NCT02460198	• prospective international multi-center • CRC	61	local PCR or IHC	200 mg every 3 weeks	Prior fluoropyrimidine, oxaliplatin, and irinotecan +/- anti-VEGF/EGFR mAb
KEYNOTE-012 NCT01848834	• retrospectively identified patients with PD-L1-positive gastric, bladder, or triple-negative breast cancer	8	central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
KEYNOTE-028 NCT02054806	• retrospectively identified patients with PD-L1-positive esophageal, biliary, breast, endometrial, or CRC	5	central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
KEYNOTE-158 NCT02628067	• prospective international multi-center enrollment of patients with MSI-H/dMMR non-CRC • retrospectively identified patients who were enrolled in specific rare tumor non-CRC cohorts	19	local PCR or IHC (central PCR for patients in rare tumor non-CRC cohorts)	200 mg every 3 weeks	≥1 prior regimen
Total		**149**			

CRC = colorectal cancer
PCR = polymerase chain reaction
IHC = immunohistochemistry

Package insert

Pembrolizumab Approved for MSI-H or Mismatch Repair Deficient Tumors

Table 25: Response by Tumor Type

	N	Objective response rate n (%)	95% CI	DOR range (months)
CRC	90	32 (36%)	(26%, 46%)	(1.6+, 22.7+)
Non-CRC	59	27 (46%)	(33%, 59%)	(1.9+, 22.1+)
Endometrial cancer	14	5 (36%)	(13%, 65%)	(4.2+, 17.3+)
Biliary cancer	11	3 (27%)	(6%, 61%)	(11.6+, 19.6+)
Gastric or GE junction cancer	9	5 (56%)	(21%, 86%)	(5.8+, 22.1+)
Pancreatic cancer	6	5 (83%)	(36%, 100%)	(2.6+, 9.2+)
Small intestinal cancer	8	3 (38%)	(9%, 76%)	(1.9+, 9.1+)
Breast cancer	2	PR, PR		(7.6, 15.9)
Prostate cancer	2	PR, SD		9.8+
Bladder cancer	1	NE		
Esophageal cancer	1	PR		18.2+
Sarcoma	1	PD		
Thyroid cancer	1	NE		
Retroperitoneal adenocarcinoma	1	PR		7.5+
Small cell lung cancer	1	CR		8.9+
Renal cell cancer	1	PD		

CR = complete response
PR = partial response
SD = stable disease
PD = progressive disease
NE = not evaluable

Package Insert

Nivolumab in CRC

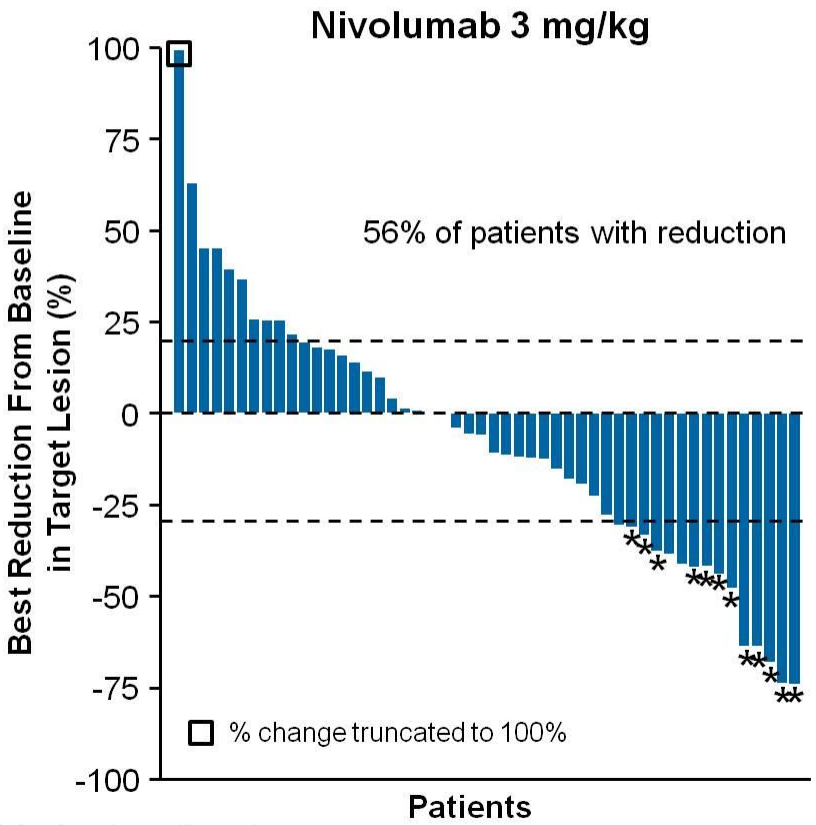
Nivolumab ± Ipilimumab in Treatment of Patients With Metastatic Colorectal Cancer With and Without High Microsatellite Instability: CheckMate 142 Interim Results

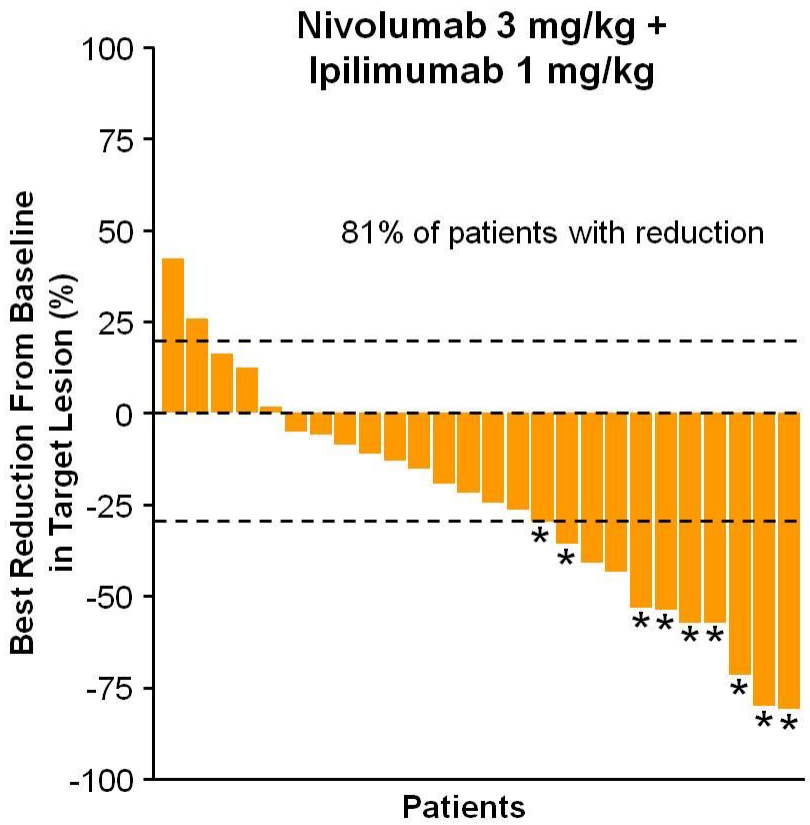
Michael Overman,[1] Scott Kopetz,[1] Ray McDermott,[2] Joseph Leach,[3] Sara Lonardi,[4] Heinz-Josef Lenz,[5] Michael Morse,[6] Jayesh Desai,[7] Andrew Hill,[8] Michael Axelson,[9] Rebecca A. Moss,[9] Chen-Sheng Lin,[9] Monica Goldberg,[9] Thierry Andre[10]

[1]MD Anderson Cancer Center, Houston, TX, USA; [2]St Vincent's University Hospital, Dublin, Ireland; [3]Allina Health System, Minneapolis, MN, USA; [4]Istituto Oncologico Veneto IOV-IRCSS, Padova, Italy; [5]USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [6]Duke University Office of Research Administration, Durham, NC, USA; [7]Royal Melbourne Hospital, Victoria, Australia; [8]Tasman Oncology Research Pty Ltd, Southport, Queensland, Australia; [9]Bristol-Myers Squibb, Princeton, NJ, USA; [10]Hopital Saint Antoine, Paris, France

PRESENTED AT: ASCO ANNUAL MEETING '16

Best Reduction in Target Lesion Size in Patients With MSI-H





*Asterisks denote confirmed responses

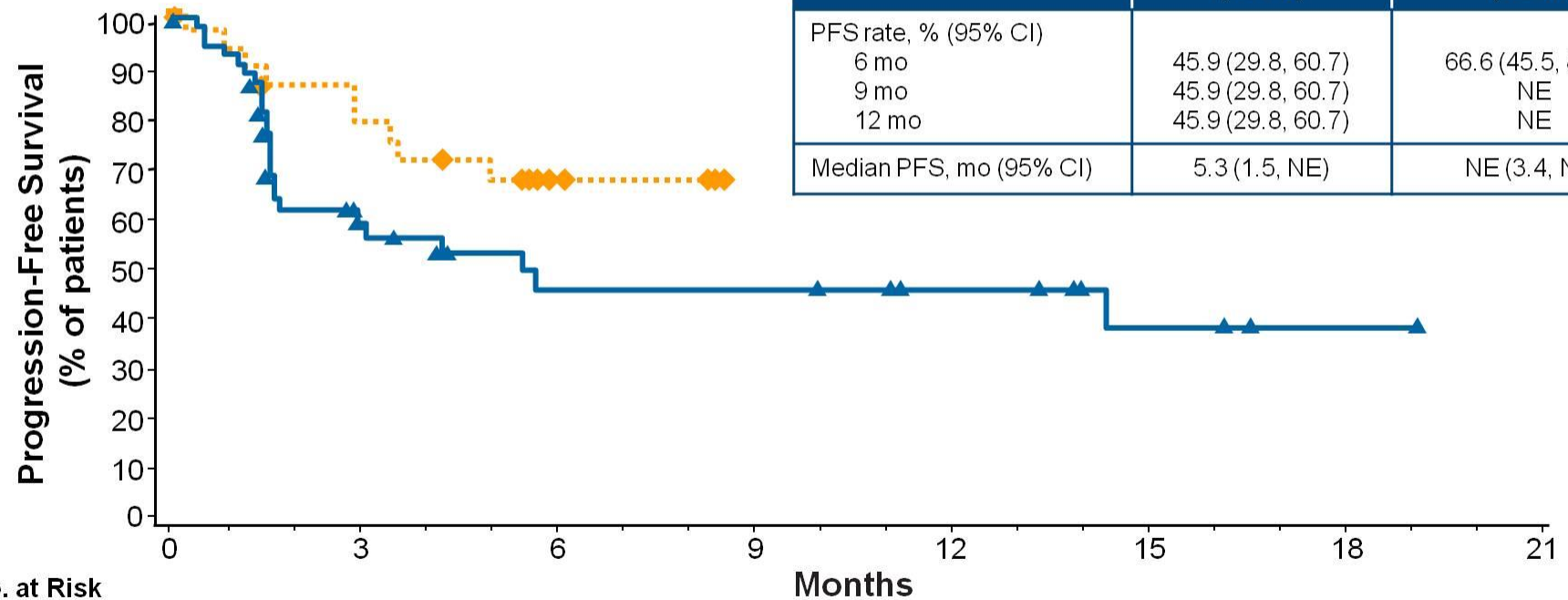
Nivolumab + Ipilimumab
MSI

		N3 (n=70)	N3 + I1 (n=30)
ORR, n (%)[b]		12 (25.5)	9 (33.3)
	CR	0	0
	SD	14 (29.8%)	14 (51.9%)
	PD	17 (36.2%)	3 (11.1%)
	ND/NR	4 (8.5%)	1 (3.7%)

Investigator-Assessed PFS in Patients With MSI-H

Nivolumab ± Ipilimumab in Metastatic CRC

	Nivolumab 3 mg/kg (n = 70)	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg (n = 30)
PFS rate, % (95% CI)		
6 mo	45.9 (29.8, 60.7)	66.6 (45.5, 81.1)
9 mo	45.9 (29.8, 60.7)	NE
12 mo	45.9 (29.8, 60.7)	NE
Median PFS, mo (95% CI)	5.3 (1.5, NE)	NE (3.4, NE)



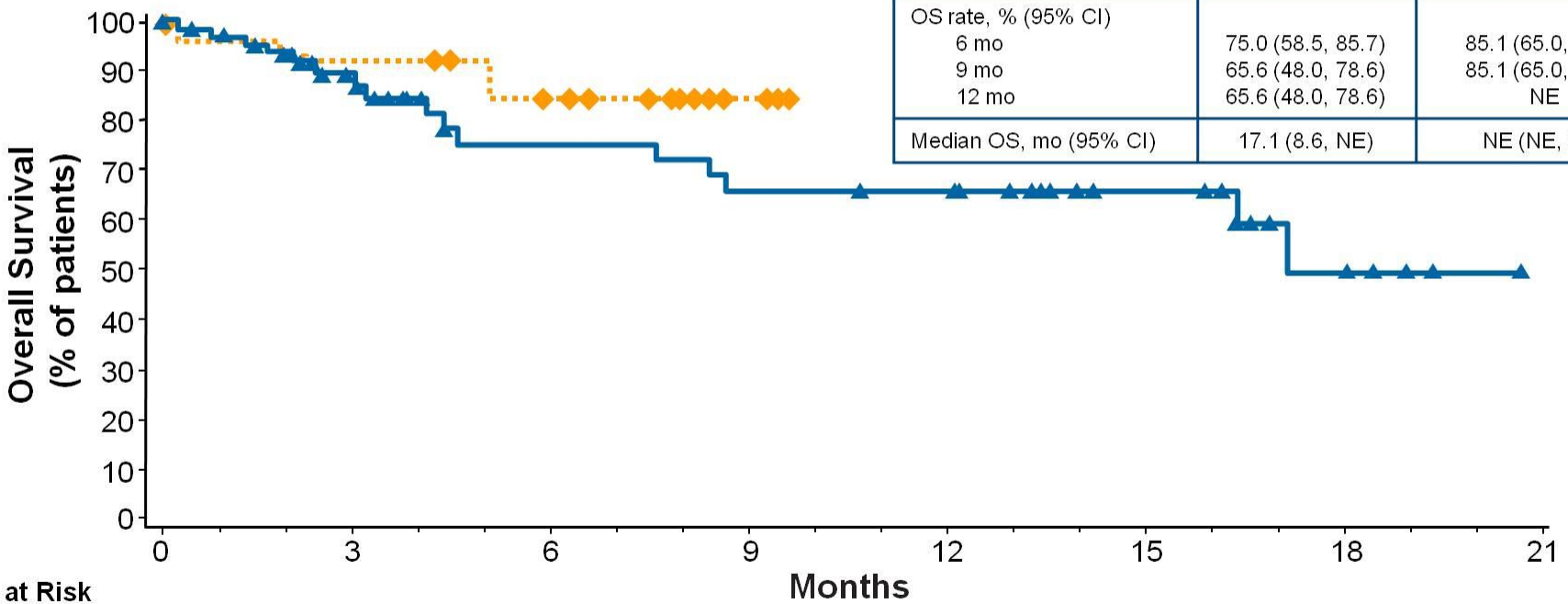
No. at Risk								
Nivolumab	70	19	13	13	9	5	1	0
Nivolumab + Ipilimumab	30	21	7	0	0	0	0	0

NE = not estimable

OS in Patients With MSI-H

Nivolumab ± Ipilimumab in Metastatic CRC

	Nivolumab 3 mg/kg (n = 70)	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg (n = 30)
OS rate, % (95% CI)		
6 mo	75.0 (58.5, 85.7)	85.1 (65.0, 94.2)
9 mo	65.6 (48.0, 78.6)	85.1 (65.0, 94.2)
12 mo	65.6 (48.0, 78.6)	NE
Median OS, mo (95% CI)	17.1 (8.6, NE)	NE (NE, NE)



No. at Risk							
Nivolumab	70	34	24	21	20	12	5	0
Nivolumab + Ipilimumab	30	26	21	4	0	0	0	0

NE = not estimable

Can we use immunetherapy in MSS?

- Yes
- No
- Yes for combination IO.

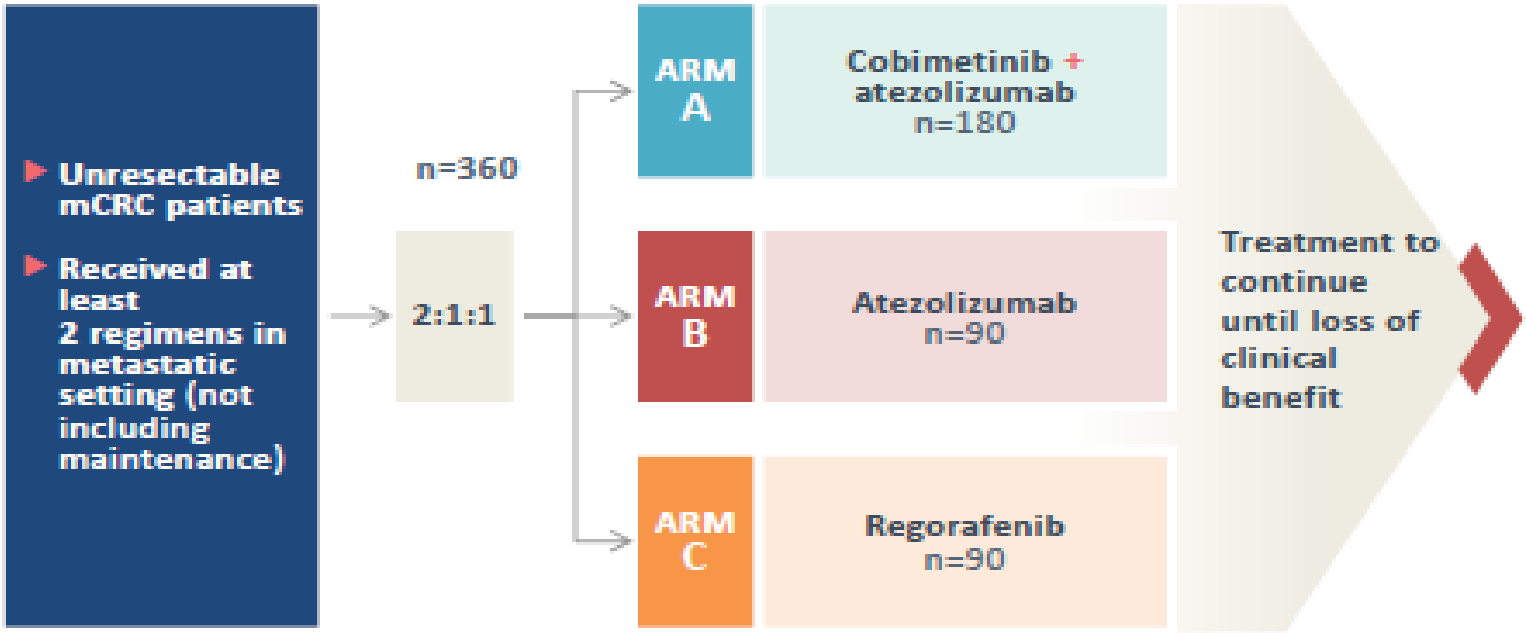
Author		Drug	N	ORR
Le et al	MSS CRC	Pembrolizumab	18	0%
Overman et al	MSS CRC	Nivolumab + ipilimumab	20	5%
Chung et al	Refractory CRC	Tremelimumab	49	2%
Topialan et al	Refractory CRC	Nivolumab	19	0%

Ineffective in MSS tumors

Lee et al, N. Engl. J. Med. 2015;372:2509–2520
Overman et al, J. Clin. Oncol. 2016;34:3501.
Chung et al, J Clin Oncol. 2010 Jul 20; 28(21):3485-90.
Topallan et al, N. Engl. J. Med. 2012;366:2443–2454..

Cobimetinib + Atezolizumab

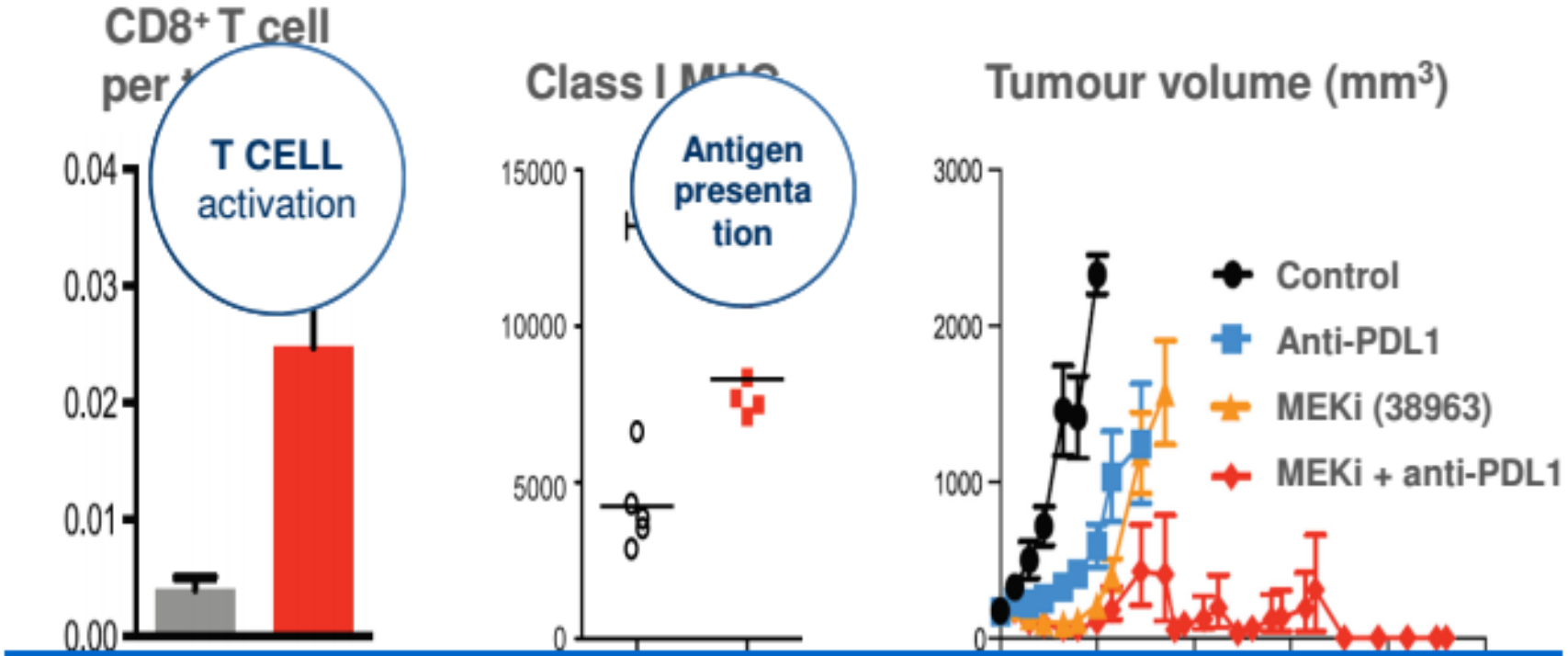
COTEZO TRIAL



- Stratified by tumor extended *RAS* status and time since diagnosis of first metastasis
- MSI-H capped at approximately 5%
- At least 180 patients with extended *RAS*-mutant tumors to be enrolled

Effect of MEK-I on T-cells and TME

- MEKi: **intratumoral T cell accumulation + MHC Class I upregulation**
- MEK inhibition and anti-PDL1 are synergistic in xenograft models

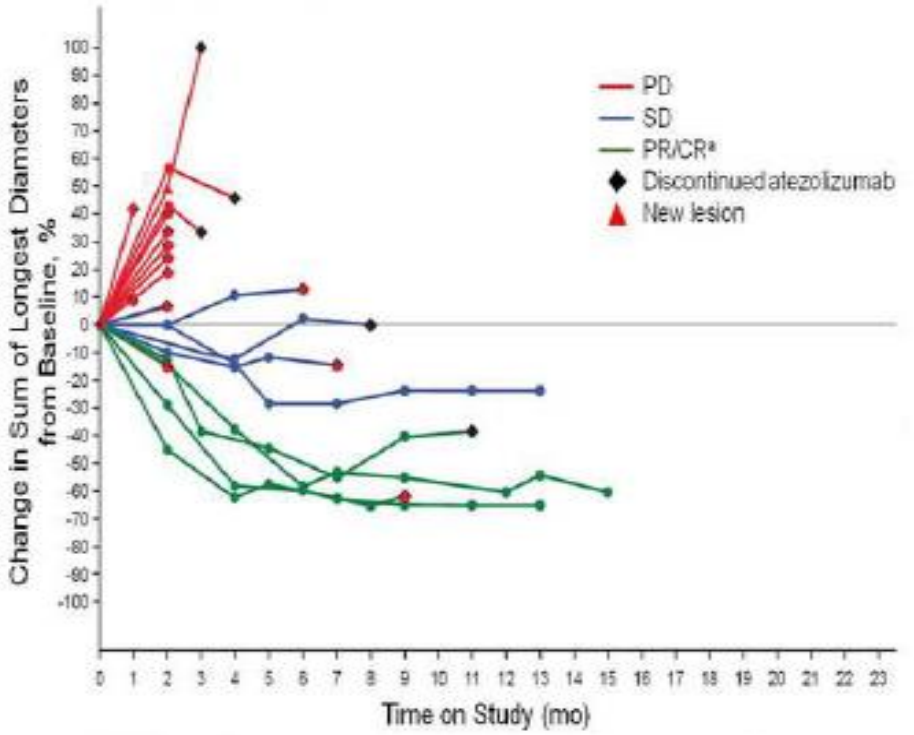


Increased potential for anti-PD(L)1

Bendell et al, ASCO 2016;
Ebert et al. Immunity 2016

Cobimetinib + Atezolizumab

	KRAS MT CRC	All CRC pts
	N=20	N=23
ORR	20%	17%
CR	0	0
PR	20%	17%
SD	20%	22%
PD	50%	52%
NE	10%	9%
mPFS (m)	2.3 (1.8-9.5)	2.3 (1.8-9.5)
mOS (m)	NE (6.5-NE)	NE (6.5-NE)

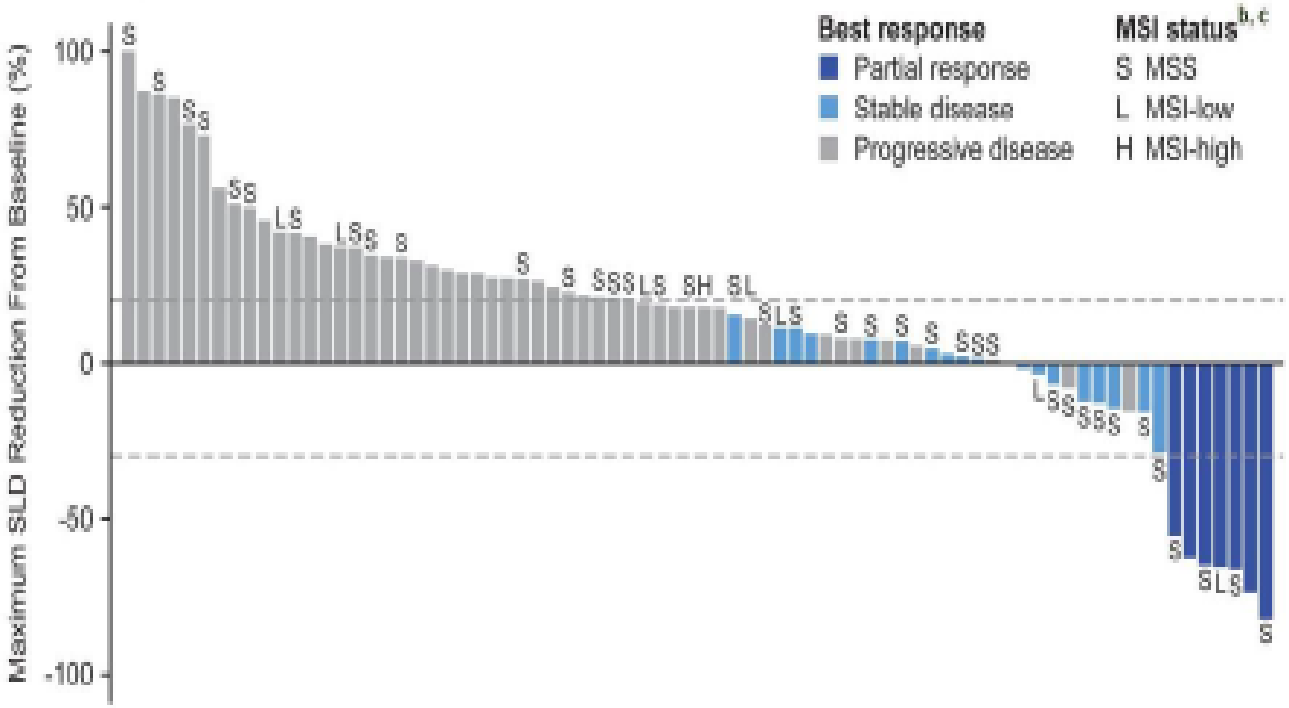


[a]Confirmed per RECIST v1.1. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease. Efficacy-evaluable patients. 2 patients missing or unevaluable are not included. Data cut-off February 12, 2016.

Bendell J et al. Proc ASCO 2016

COBIMETINIB + ATEZOLIZUMAB IN MCRC

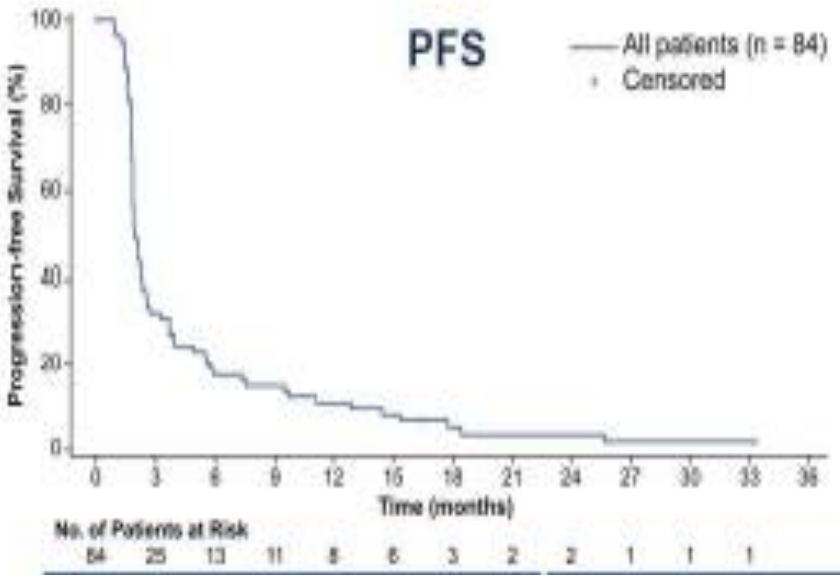
BOR (n = 84)[a]	n (%)
ORR	7 (8%)
CR	0
PR	7 (8%)
SD	19 (23%)
DCR	26 (31%)
PD	51 (61%)

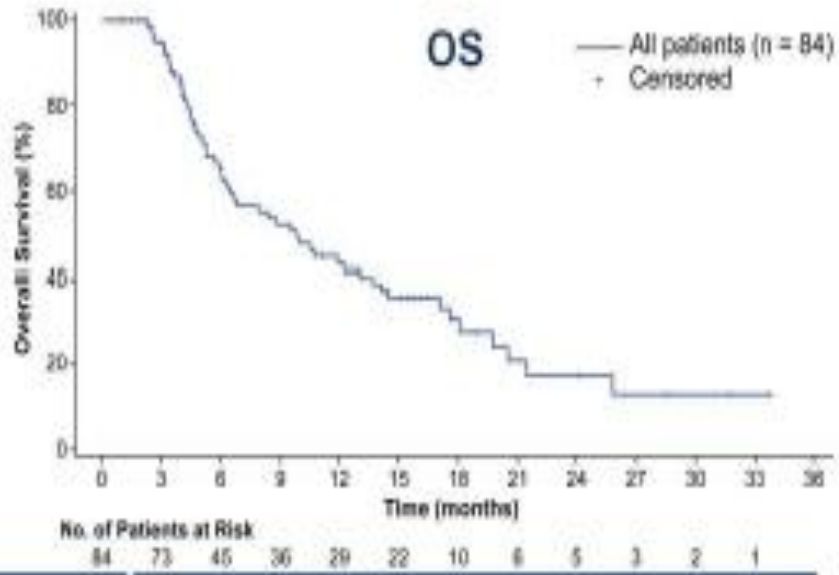


- 7 patients (8% [95% CI: 3, 16]) experienced PR (confirmed per RECIST v1.1)
  - 4 patients had MSS and 1 patient had MSI-low mCRC; the remaining 2 had unknown MSI status[b]
- The DCR was 31% (DCR defined as PR + SD ≥ 6 weeks)

Bendell et al, ASCO GI 2018

COBIMETINIB + ATEZOLIZUMAB IN MCRC





Patients	PFS		OS		
	Median (95% CI)	6-mo	Median (95% CI)	6-mo	12-mo
All (n = 84)	1.9 mo (1.8, 2.3)	18%	9.8 mo (6.2, 14.1)	65%	43%
MSS (n = 42)[a]	2.5 mo (1.8, 3.7)	27%	13.0 mo (6.0, 25.8)	71%	51%
KRAS mutant (n = 57)[b]	2.0 mo (1.8, 2.3)	22%	9.5 mo (6.0, 17.6)	67%	44%
KRAS wild type (n = 25)[b]	1.8 mo (1.8, 2.6)	9%	10.0 mo (4.9, 17.1)	65%	43%

Phase III COTEZO trial – cobimetinib/atezolizumab vs regorafenib vs atezolizumab

Bendell et al, ASCO GI 2018

Can we use immunetherapy in MSS?

- Yes
- **No**
- Yes for combination IO.

Other potential targets

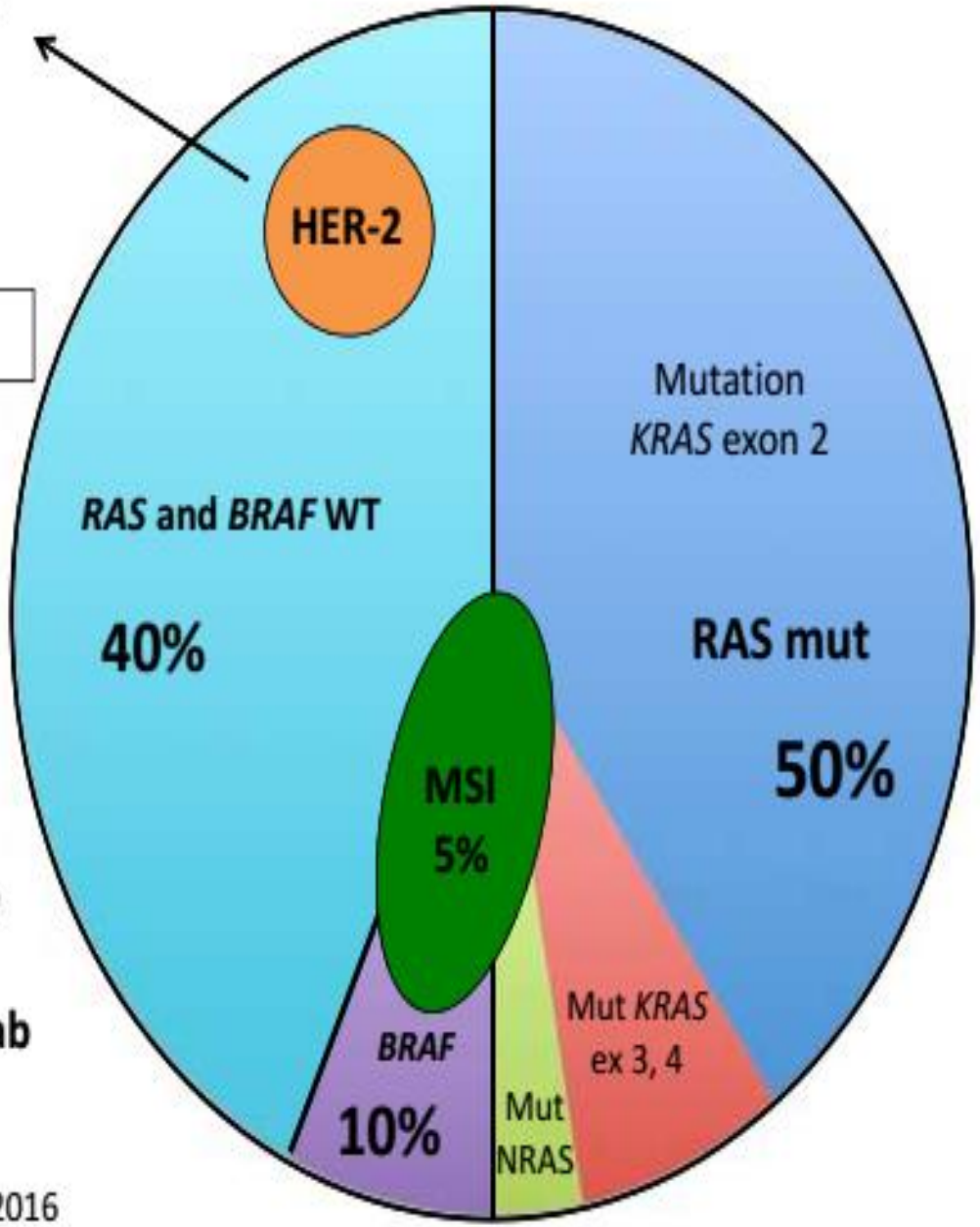
Amplifications: 2,5%
Mutations: 1,9%

anti-EGFR resistance ?

Raghac ASCO 2016

anti-HER2 Targeted therapies ?

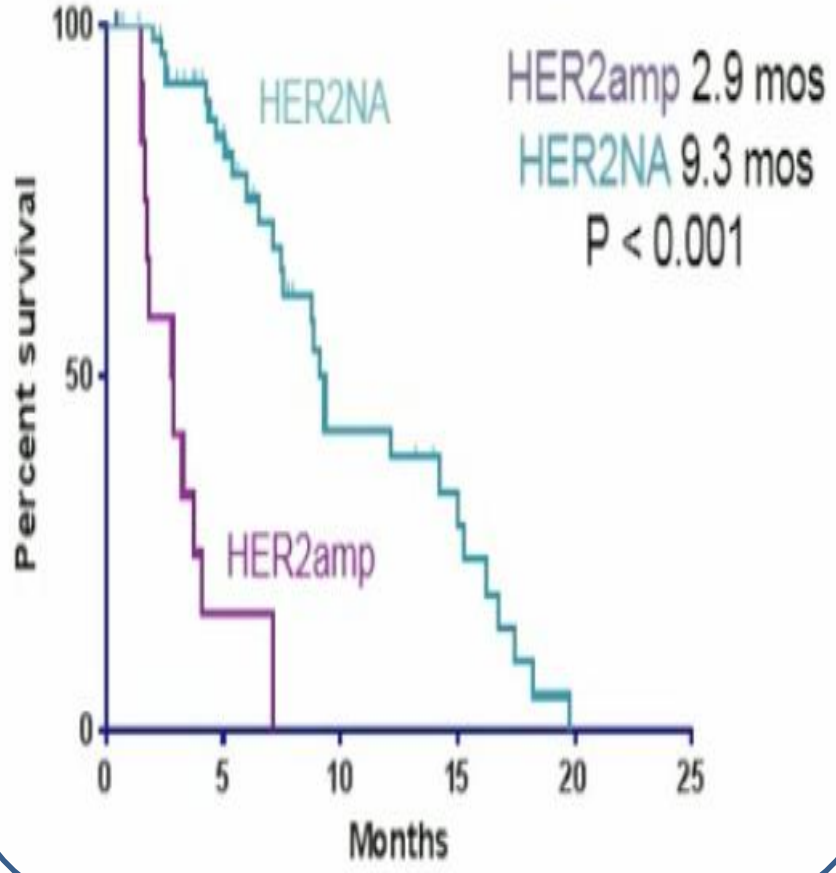
Trastuzumab + lapatinib
(HERACLES)
Trastuzumab + pertuzumab



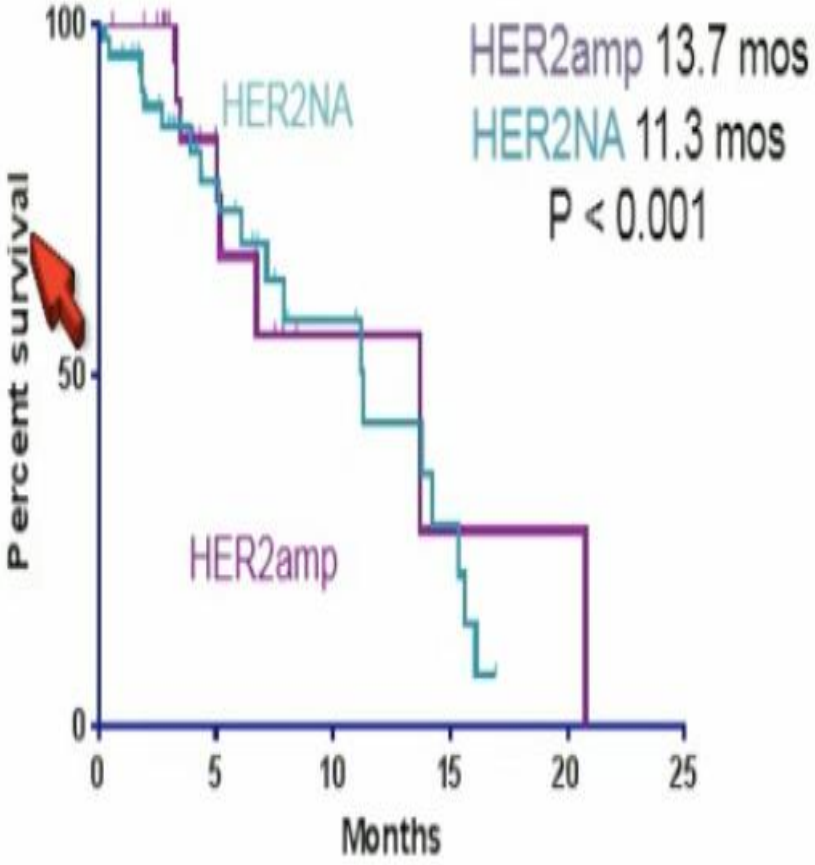
Sartore-Bianchi Lancet Oncol 2016
Hurwitz ASCO GI 2016

SPECTAcolor: Folprecht ESMO 2016, abst 4580

PFS - 2nd/3rd line on *anti-EGFR/based* therapy



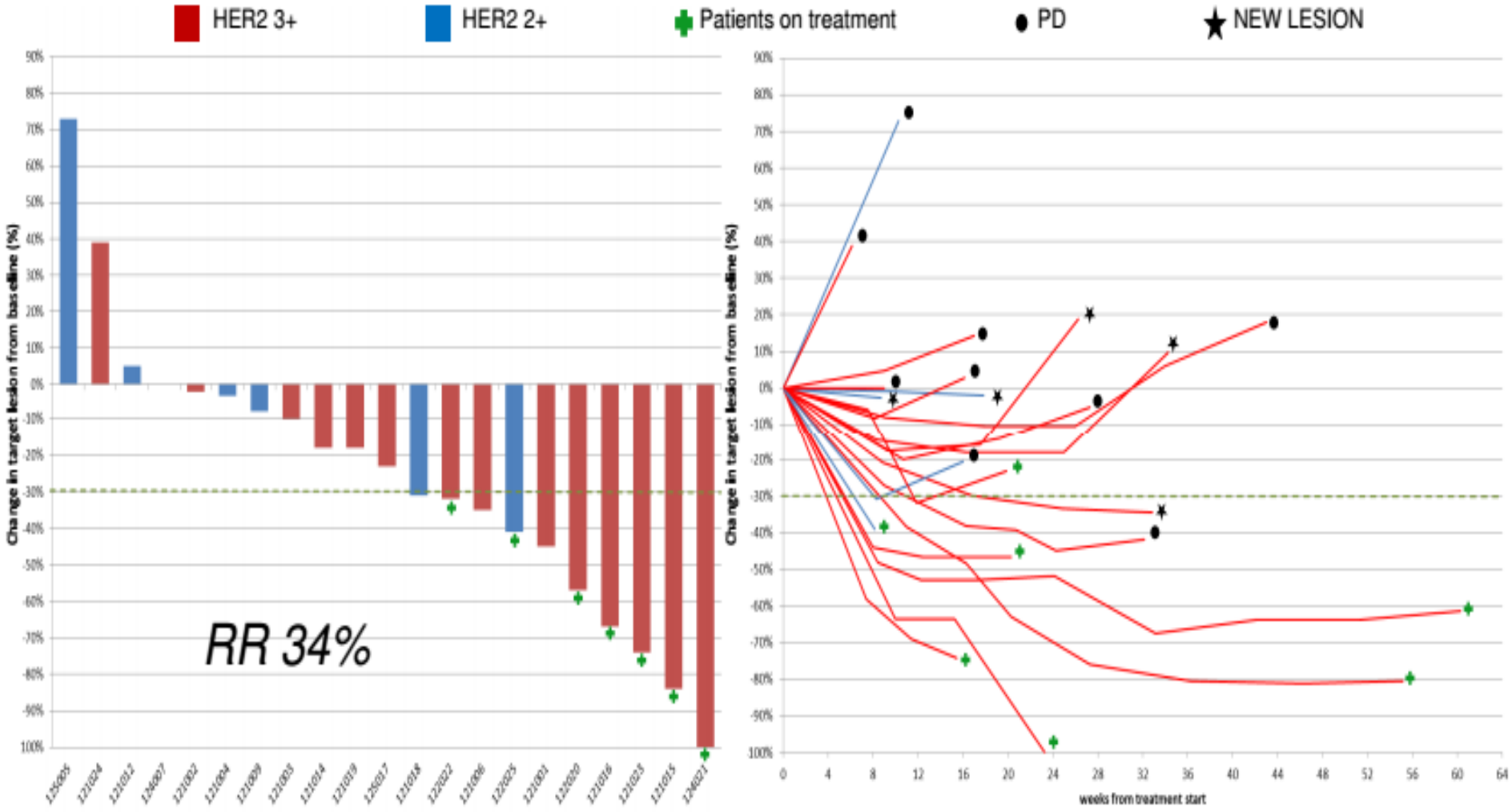
PFS – 1st line on *Non anti-EGFR/based* therapy



Trastuzumab/Lapatinib Responses by HER2 IHC Score

Waterfall plot
(best % tumor shrinkage)

Spaghetti plot
(tumor shrinkage trend)



Conclusion

- Testing for MSI: timing and patient selection should be based on available resources and facilities
- MSI-H CRC: Pembro/nivo in previously treated patients
- MSI-H tumours: Pembro in previously treated patients

Conclusion

- One size does not fit all
- If you pick the target, use the right tool
- Immunotherapy in MSI-H tumours is an example

Thank you