Cancer Immunology and Immunotherapy: Colon Cancer

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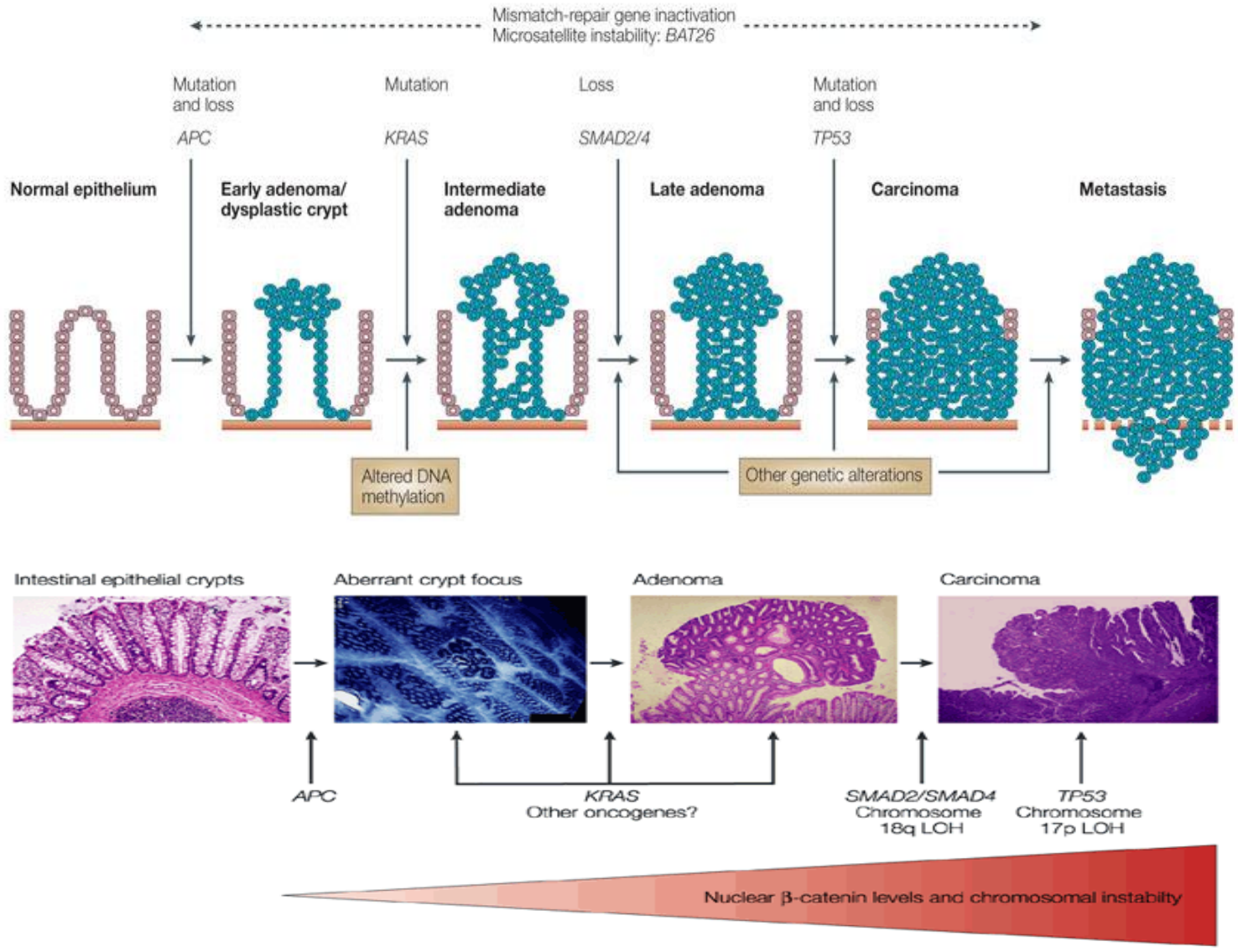
Disclosures

- During the last two years I was either a member of the advisory board/consultant or received speakers´ honoraria from the following companies:
  - BMS, MSD, Amgen, Sanofi, Merck Serono, Pierre Fabre, Servier, CellGene, Ipsen
- Received research funding from
  - Amgen
  - Sanofi
  - Roche
  - Leo

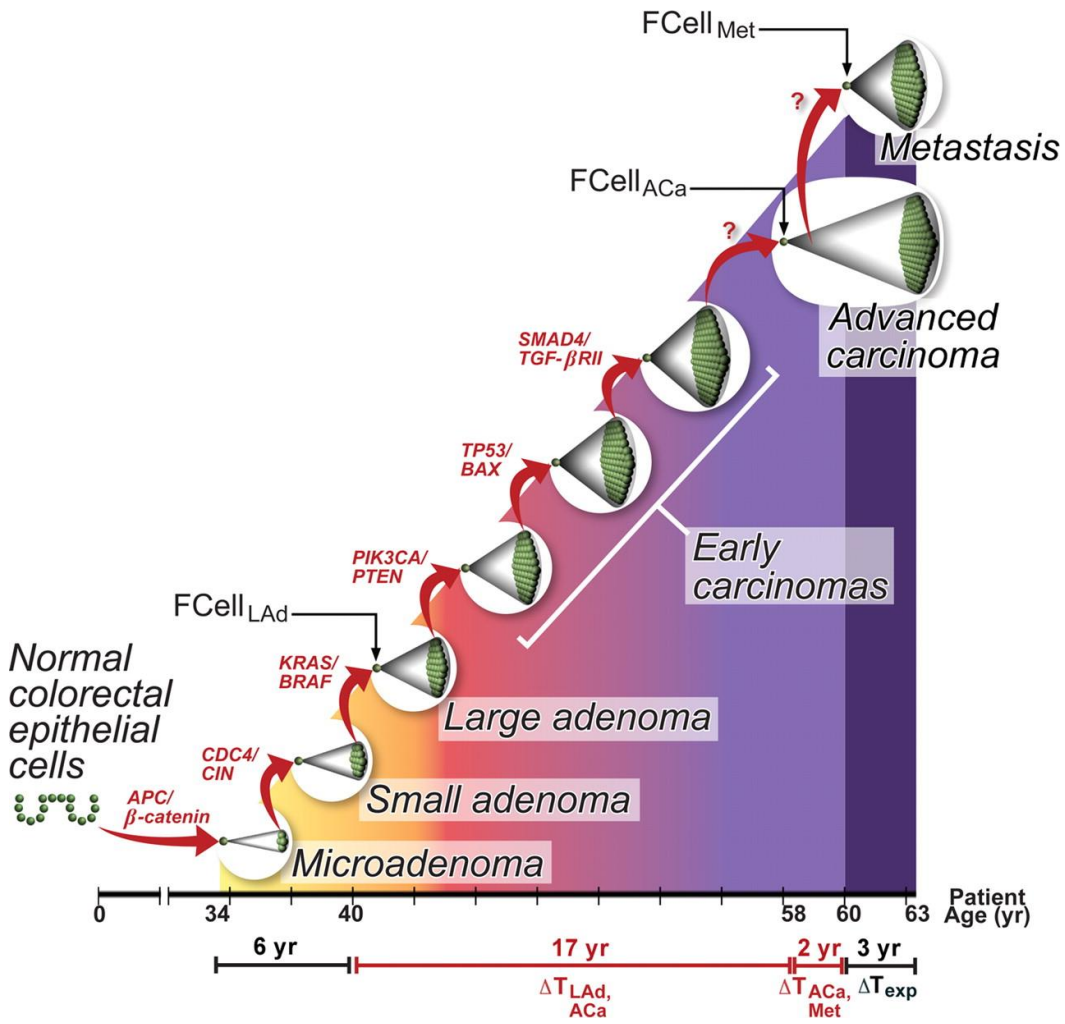
Presentation's Outline

- Introduction
  - Types of colon cancer (CC)
  - CMS classification
- Colonic epithelium, CC and Immune System
- Clinical implications:
  - Prognosis in early stage CC
  - Effect on chemotherapy
  - Immunotherapy in dMMR/MSI-H pMMR/MSS mCRC
- Perspectives & Take-home messages

1979: Fearon-Vogelstein Model

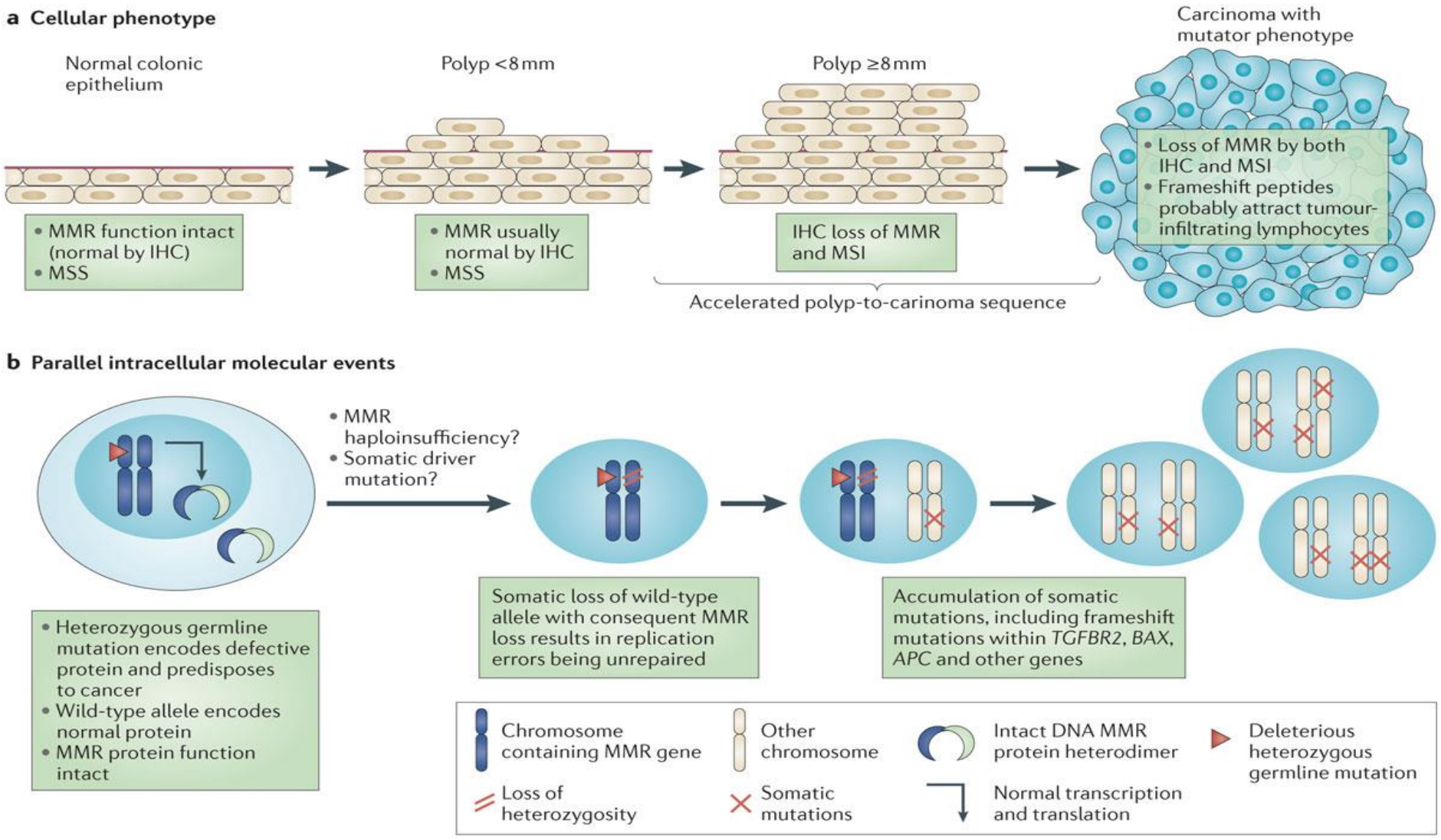


Development of Neoplasia



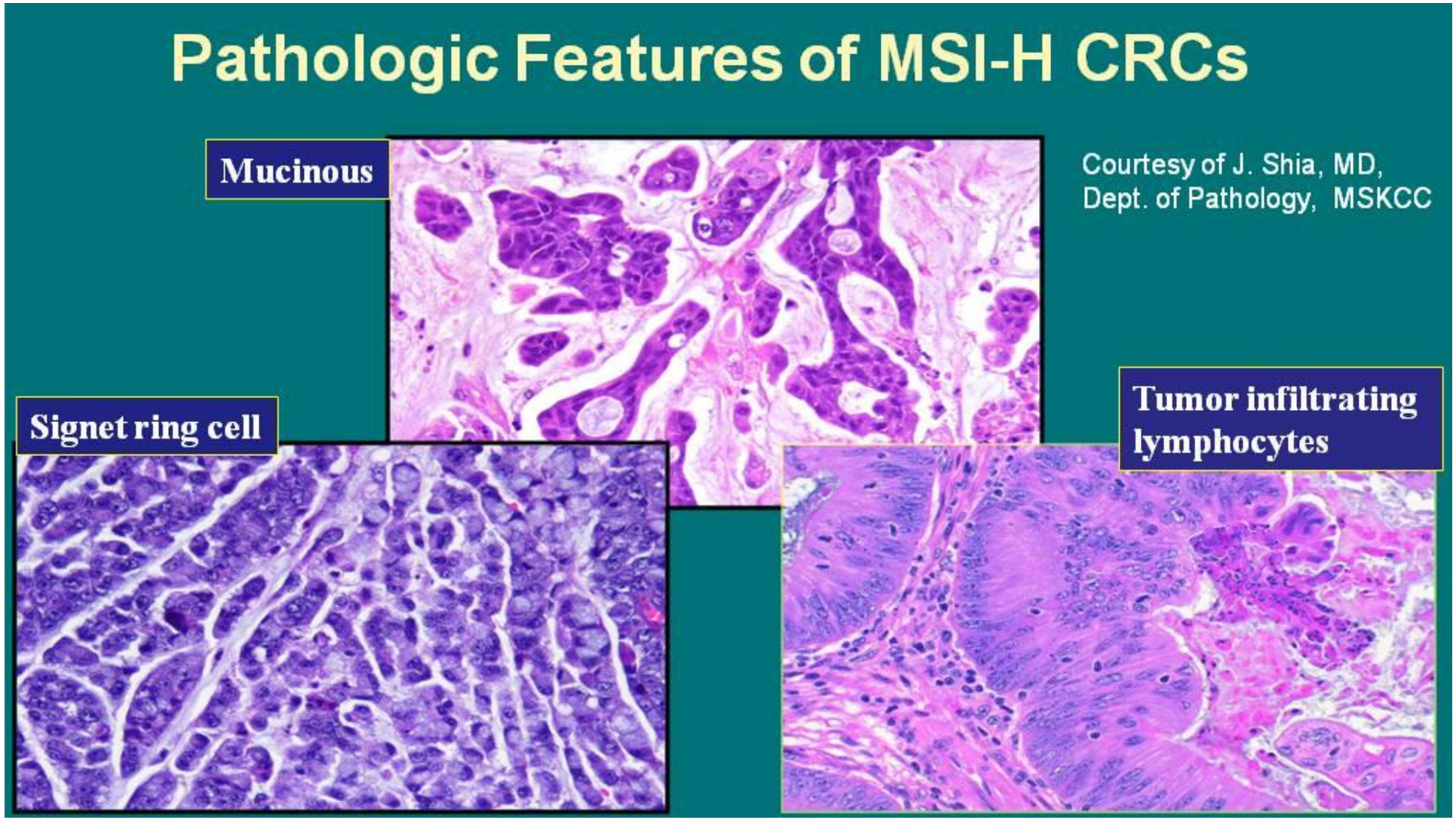
Jones, S et al, 2008 *Proc. Natl. Acad. Sci.* 105, 4283-4288

Mismatch Repair (Lynch) Pathway



Lynch HT et al. Nature Rev Cancer 2015; 15:181-94

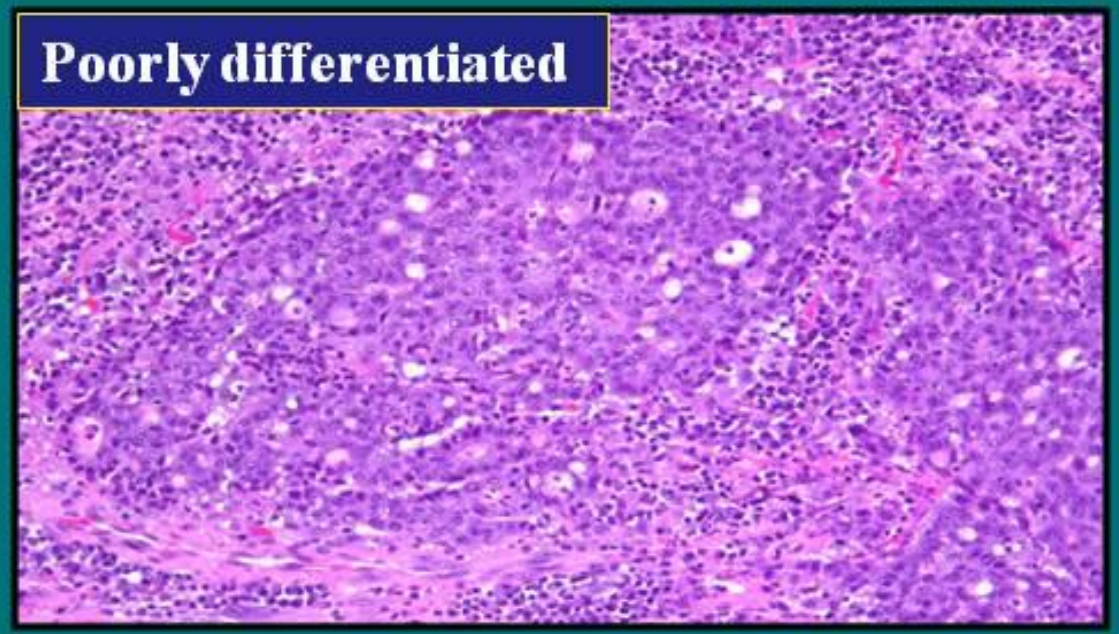
Pathologic Features of MSI-H CRCs

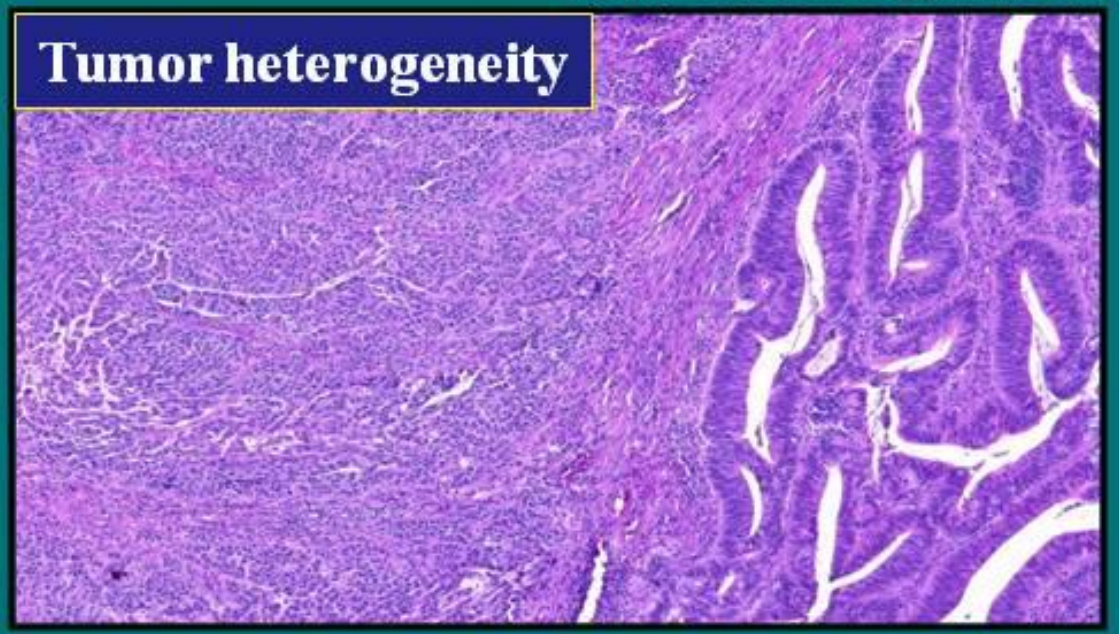


Pathologic Features of MSI-H Colorectal Cancers

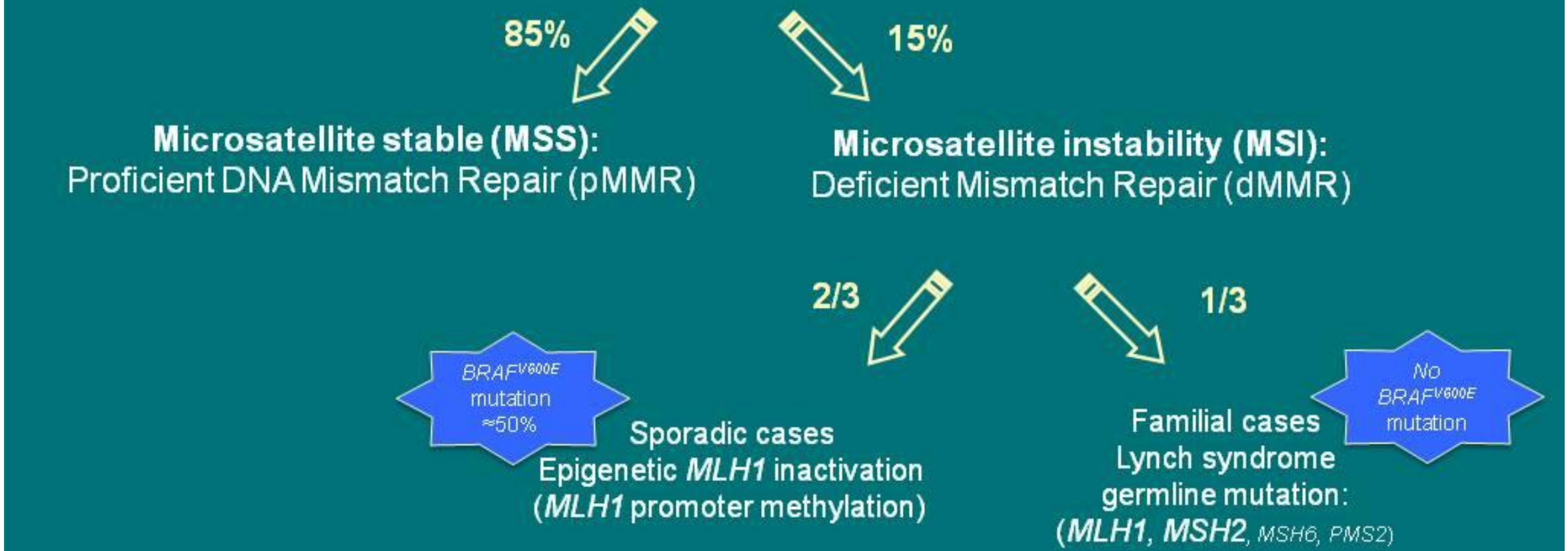
- Poorly-differentiated
- Tumor heterogeneity

Courtesy of J. Shia, MD,
Dept. of Pathology, MSKCC





Two different pathways of carcinogenesis



Sinicrope FA, Nat. Rev. Clin. Oncol. 7:174-177, 2010

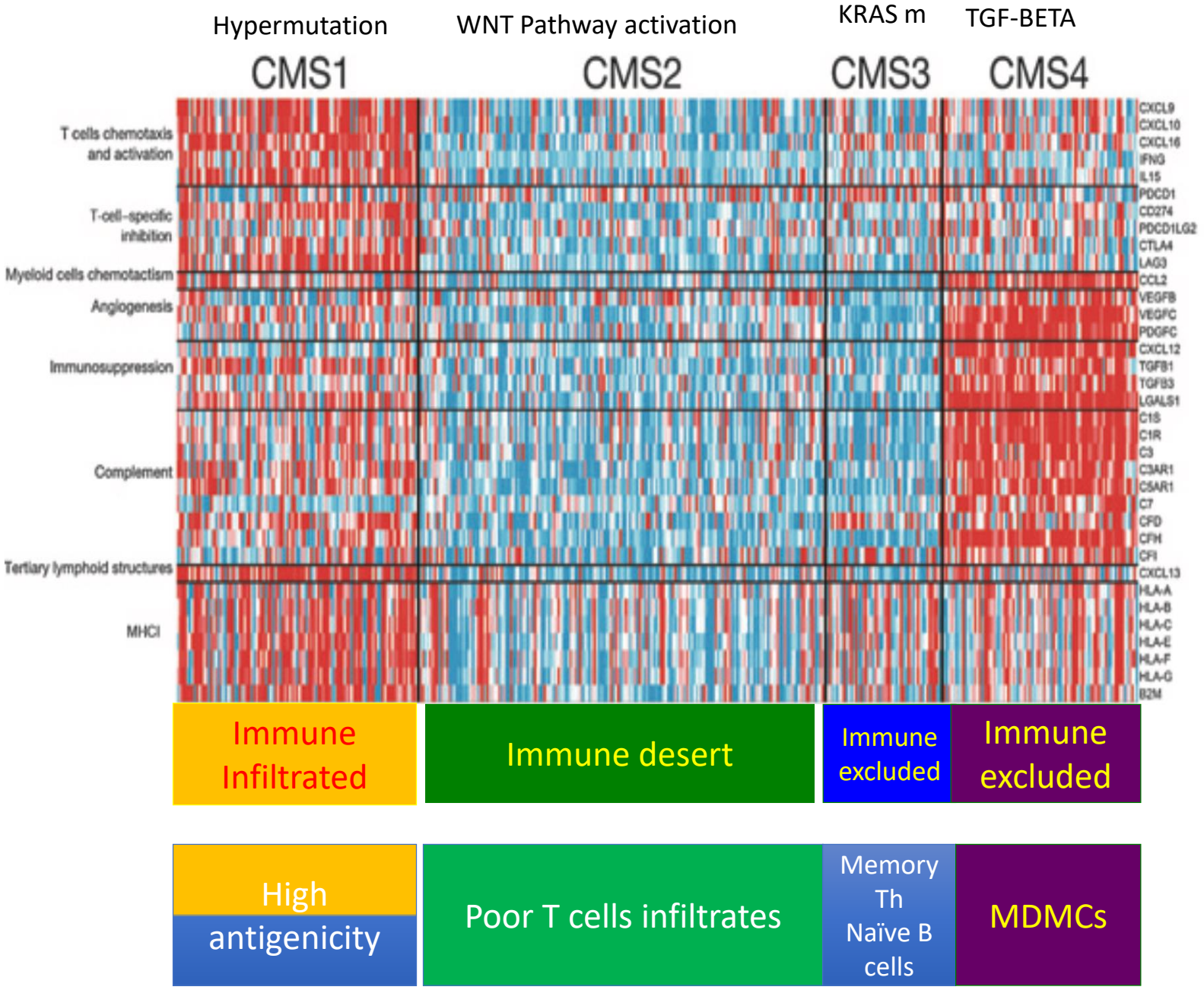
Consensus Molecular Subtypes

76% MSI-H/dMMR

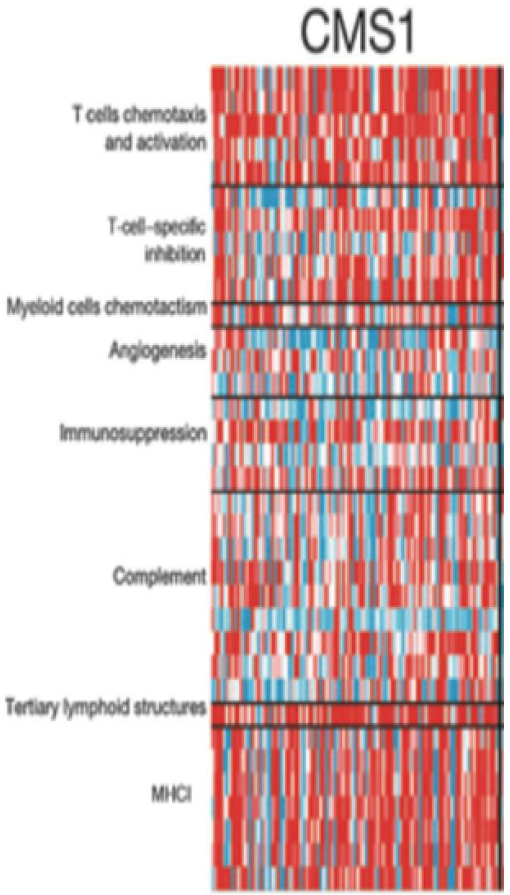
CMS1 MSI Immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high Hypermutation	SCNA high	Mixed MSI status SCNA low, CIMP low	SCN high
BRAF mutations		***KRAS*** mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration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

Guinney J, et al Nat Med 2015

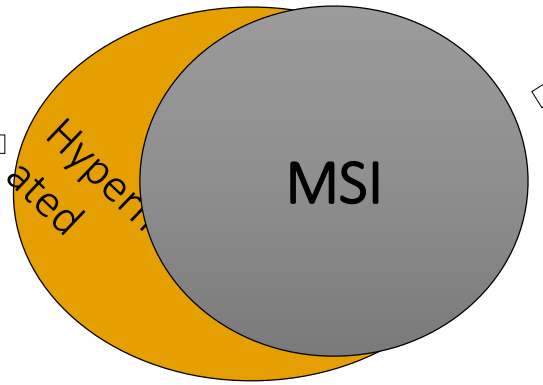
CRC Immune classification at transcriptomic level



Molecular-driven therapeutic hypothesis



Immune CMS1



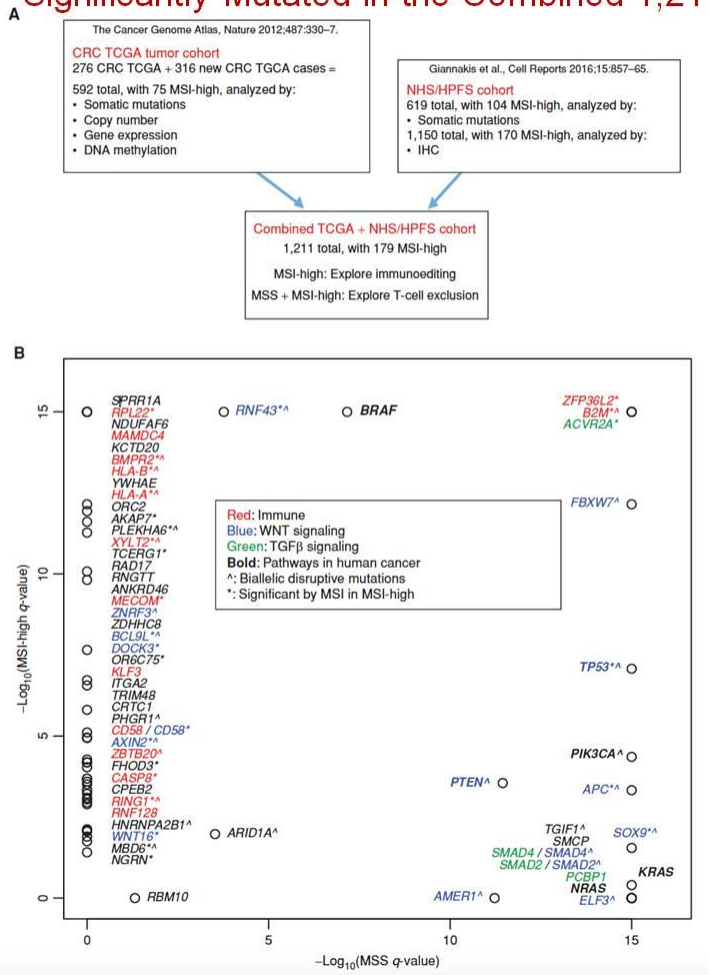
Strategy:
PD1 blockade

PD1 blockade responsive

FDA approval:
Nivolumab
Pembrolizumab

Adapted from Guinney Nat Med 2015 & Becht E Can Cell 2016

WNT Signaling and Immune-Related Genes and Pathways Significantly Mutated in the Combined 1,211 CRC Cases



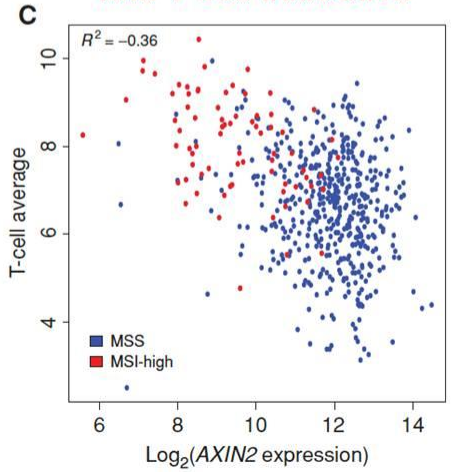
RESEARCH ARTICLE

Genetic Mechanisms of Immune Evasion in Colorectal Cancer

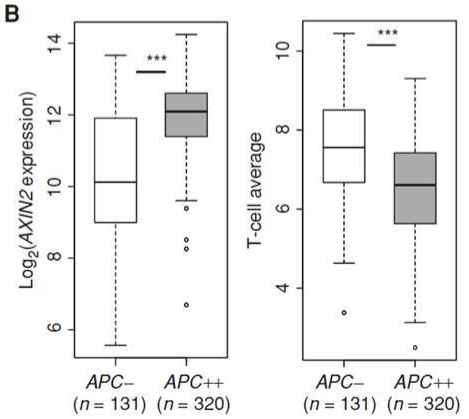
Catherine S. Grasso[1,2], Marios Giannakis[3,4], Daniel K. Wells[2], Tsuyoshi Hamada[5], Xinmeng Jasmine Mu[3,4], Michael Quist[1,6], Jonathan A. Nowak[7], Reiko Nishihara[5,7,8,9,10], Zhi Rong Qian[5], Kentaro Inamura[3], Teppei Morikawa[3], Katsuhiko Nosho[3], Gabriel Abril-Rodriguez[1,2], Charles Connolly[6], Helena Escuin-Ordinas[1,2], Milan S. Geybels[6], William M. Grady[11,12], Li Hsu[6], Siwen Hu-Lieskovan[1,2], Jeroen R. Huyghe[6], Yeon Joo Kim[1,2], Paige Krystofinski[1,2], Mark D.M. Leiserson[13], Dennis J. Montoya[14], Brian B. Nadel[14], Matteo Pellegrini[14], Colin C. Pritchard[15], Cristina Puig-Saus[1,2], Elleanor H. Quist[1,2], Ben J. Raphael[13], Stephen J. Salipante[15], Daniel Sanghoon Shin[1,2], Eve Shinbrot[16], Brian Shirts[15], Sachet Shukla[3,4,17], Janet L. Stanford[6,18], Wei Sun[6], Jennifer Tsoi[19], Alexander Upfill-Brown[1,2], David A. Wheeler[16], Catherine J. Wu[3,4], Ming Yu[11], Syed H. Zaidi[20], Jesse M. Zaretsky[1,2], Stacey B. Gabriel[4], Eric S. Lander[4], Levi A. Garraway[3,4], Thomas J. Hudson[20,21], Charles S. Fuchs[22,23,24,25], Antoni Ribas[1,2], Shuji Ogino[4,5,7,10], and Ulrike Peters[6,26]

Grasso, et all. Cancer Discov. 2018 Jun;8(6):730-749

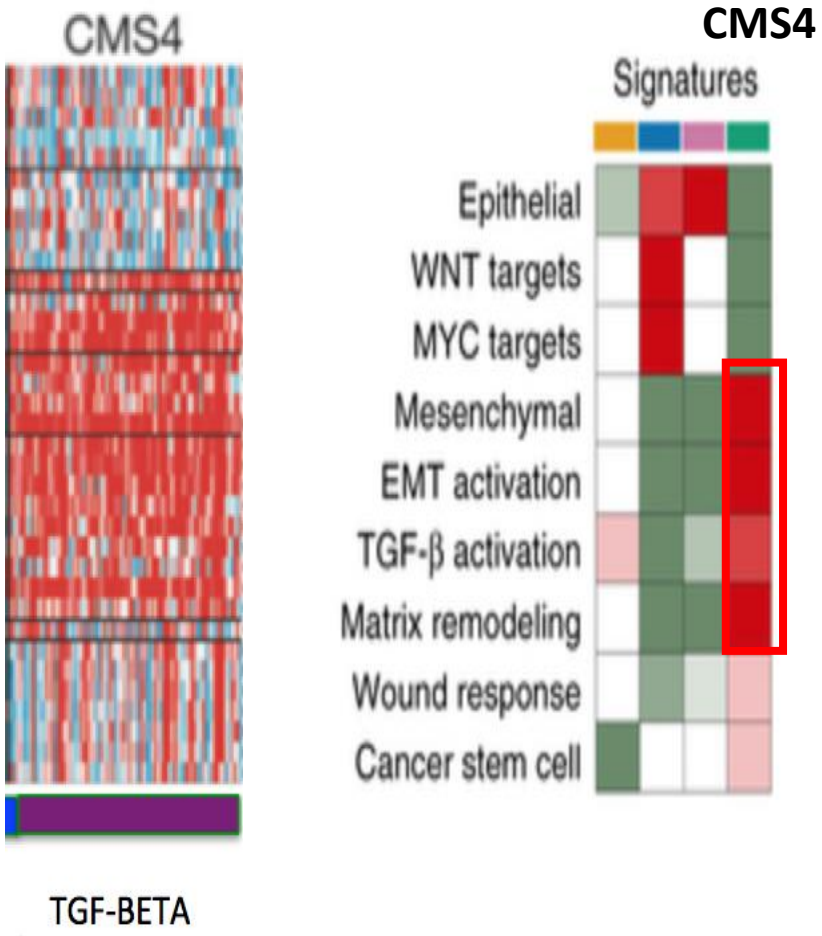
WNT signaling anticorrelated with T-cell infiltration



APC biallelic loss a genomic driver of immunosuppression of TILs by WNT

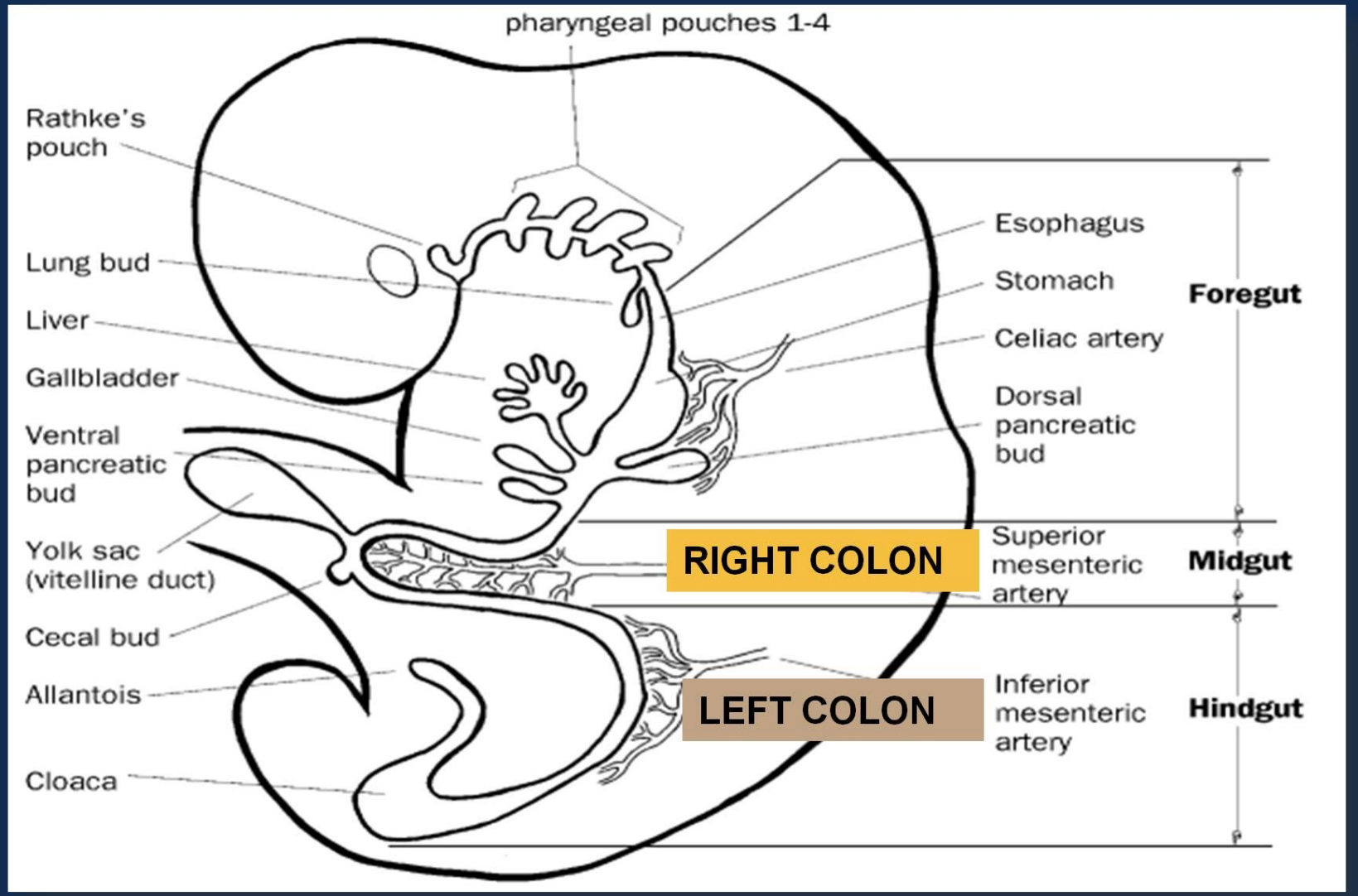


CMS-4 TGF-activation

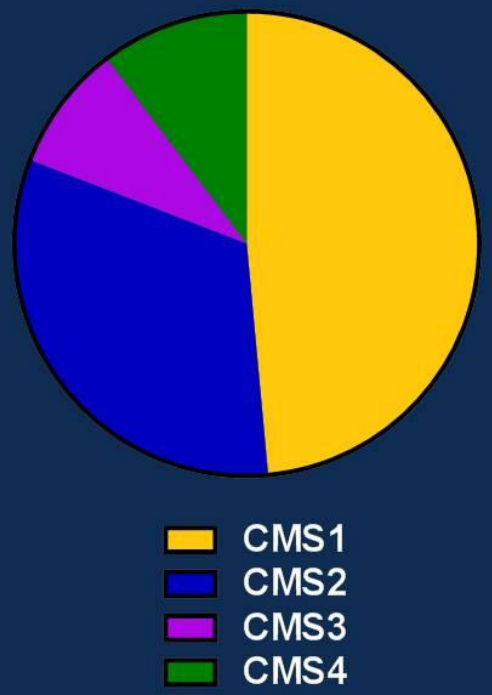


- TGF- activation drives stromal hypertrophy in CMS 4.
- Chemo-resistance
- Immune evasion

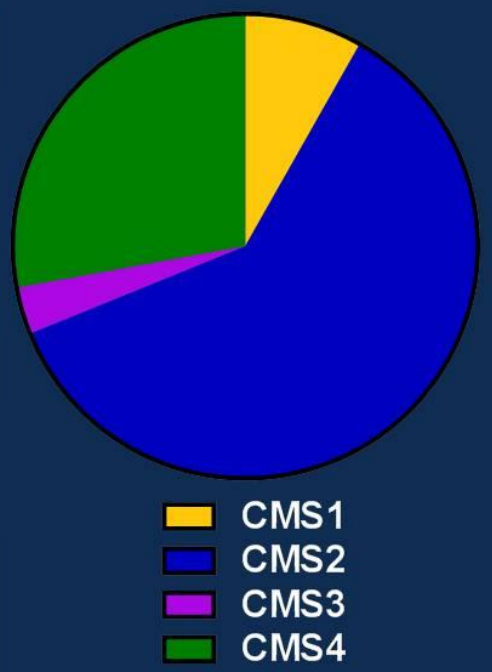
Embryology: The origin of the colon



Right-sided primary is associated with CMS 1 & 3

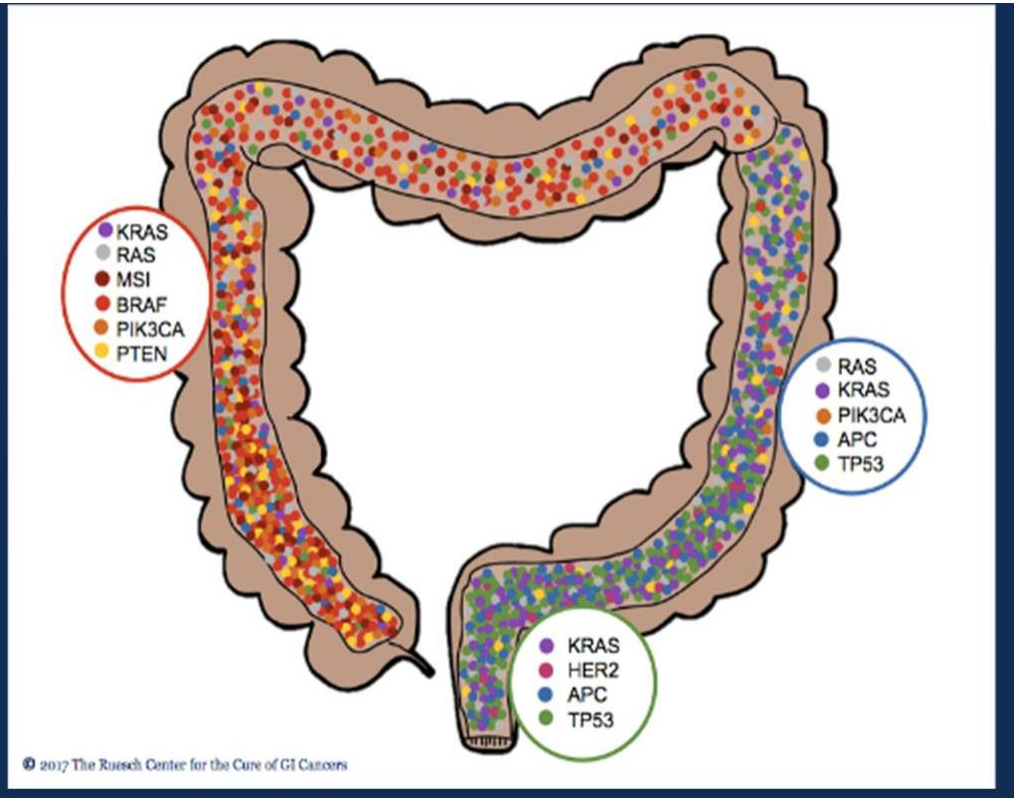


Right-Sided		Left-Sided
33/68 (49%)	CMS 1 Immune	5/61 (8%)
22/68 (32%)	CMS 2 Canonical	37/61 (61%)
6/68 (9%)	CMS 3 Metabolic	2/61 (3%)
7/68 (10%)	CMS 4 Mesenchymal	17/61 (28%)

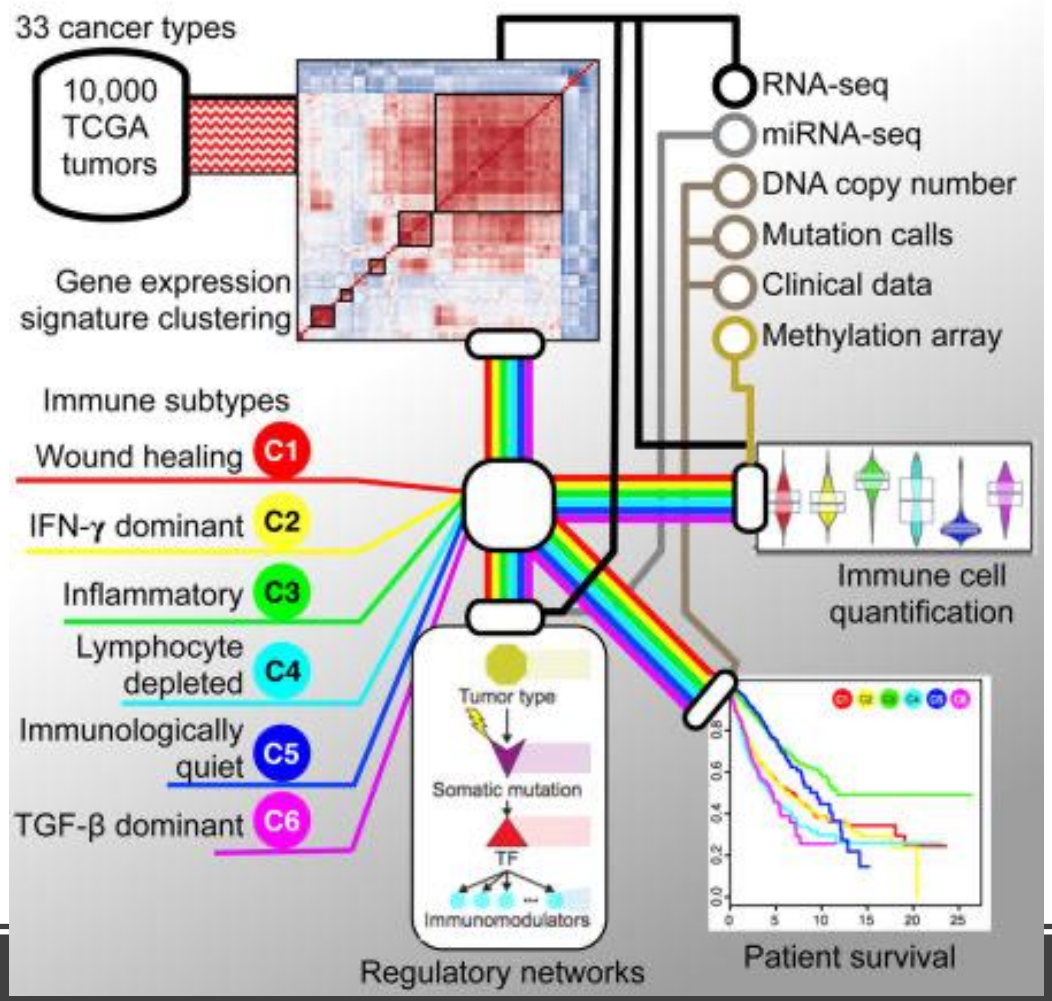


Right vs. Left, is that right?

- CRCs carry a continuum of molecular alterations from right to left, rather than having a sharp, clear-cut distinction



Immunity. 2018 April 17; 48(4): 812–830.e14. doi:10.1016/j.immuni.2018.03.023.



The Immune Landscape of Cancer

- IS 1 would healing (5y OS 65%)
- IS 2 IFN dominant (5y OS 49%)
- Are the most frequent in CC

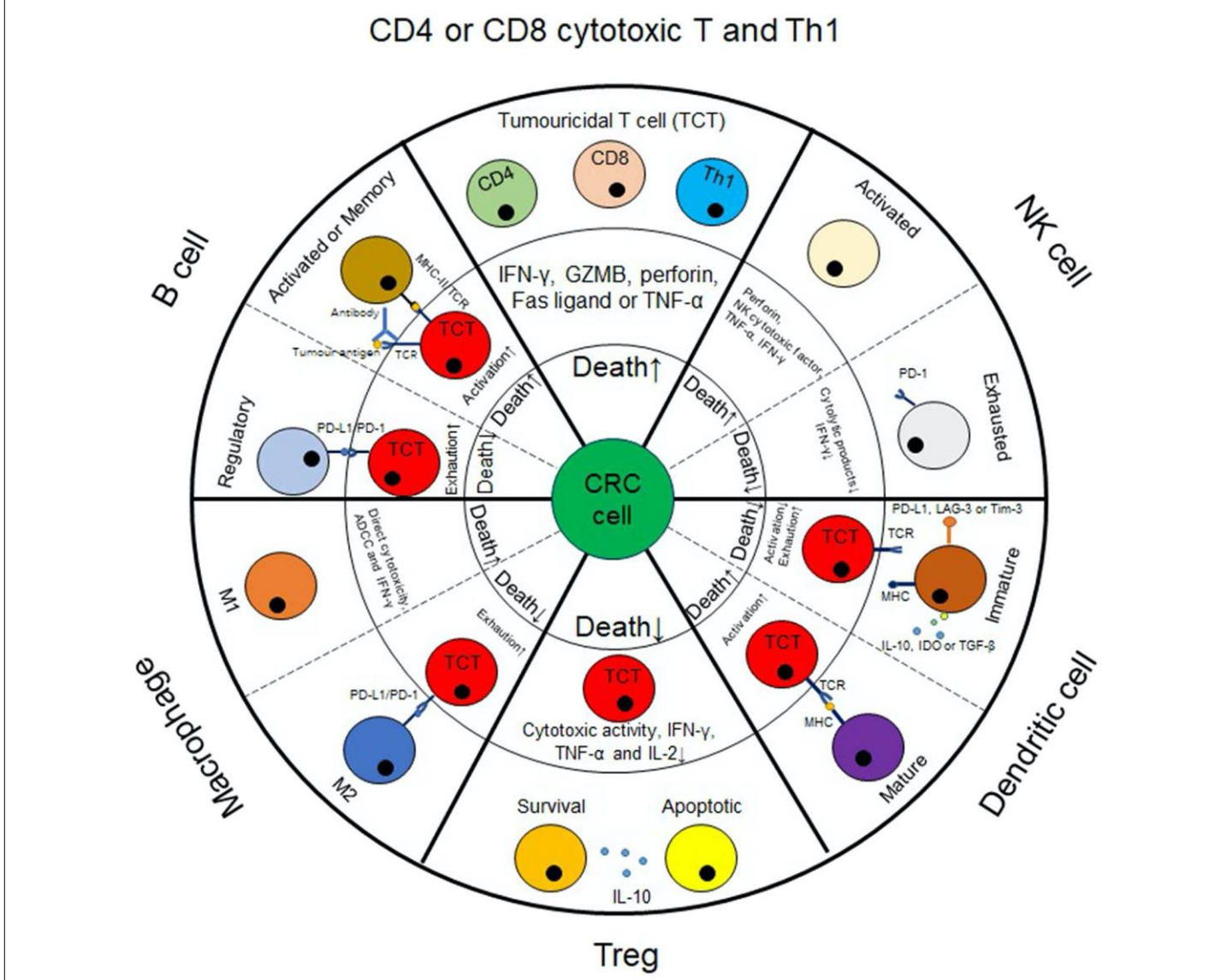
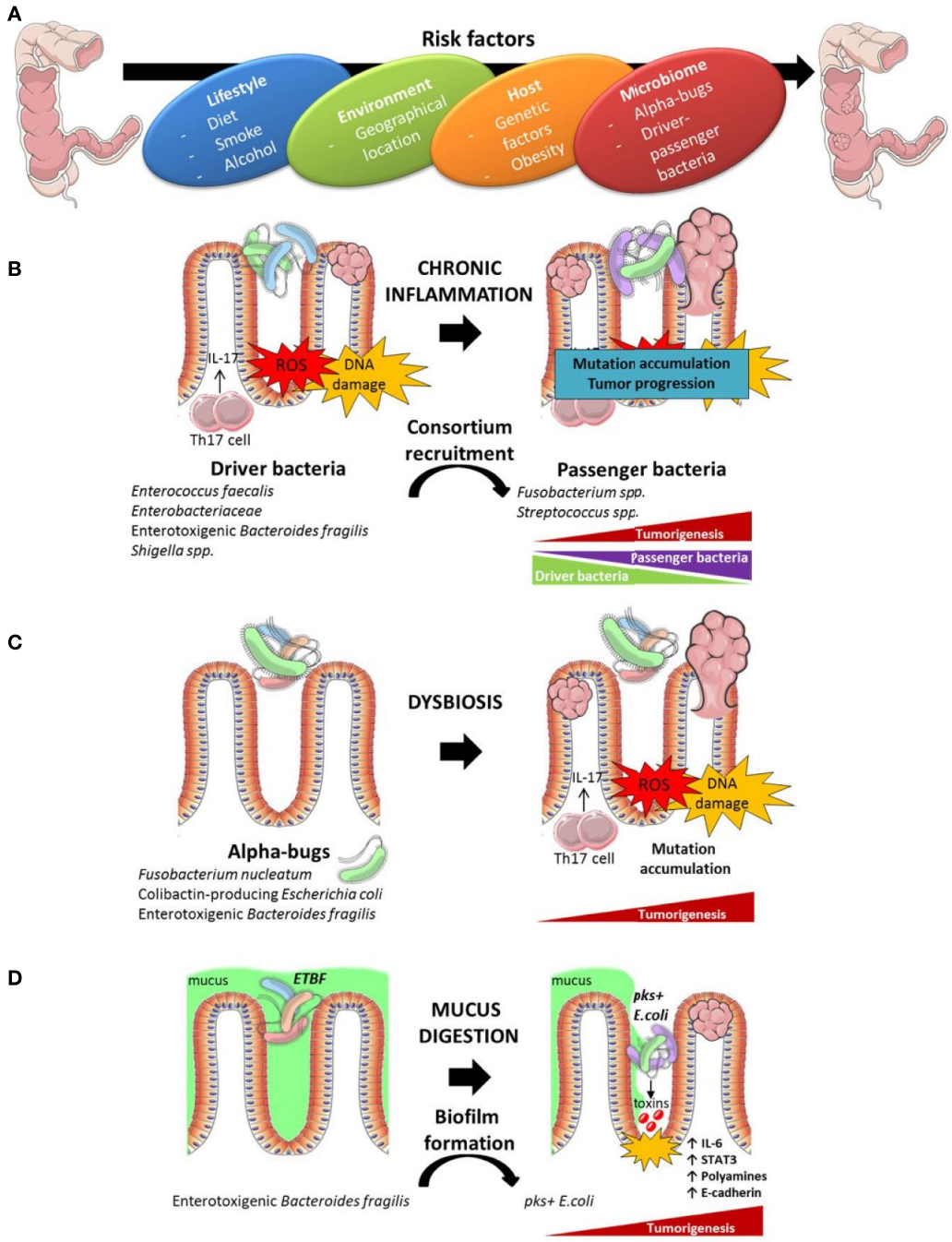
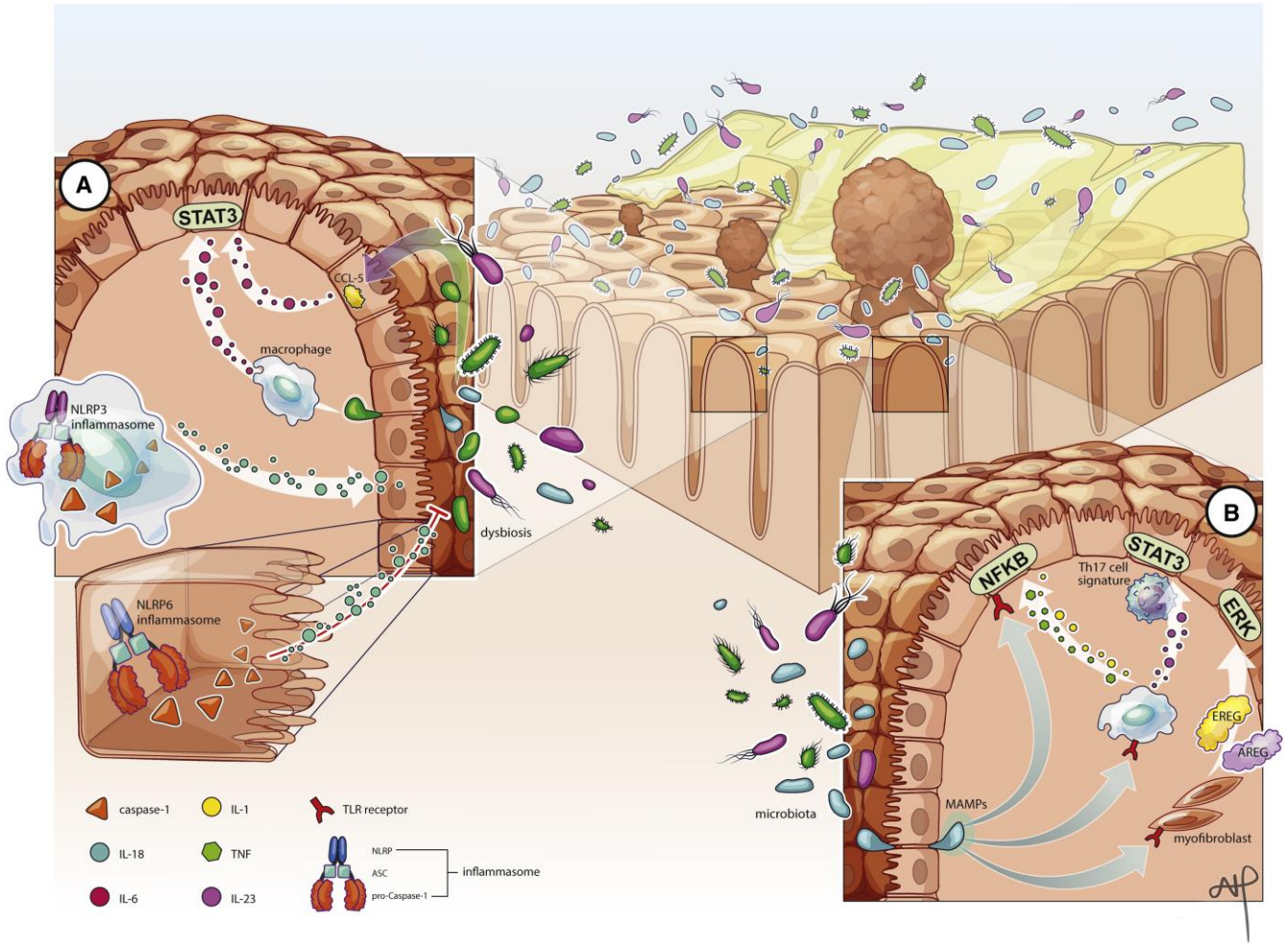


FIGURE 1 | The impact of immune infiltrates on colorectal cancer cell death. In CRC tumors, immune infiltrates can impact CRC cell death, either directly or via tumoricidal T cells (TCT) and consequently affect tumor progression. For example, cytotoxic T cells, M1-like macrophages and NK cells can exert cytolytic effect on CRC cells. For other populations of cells, such as Treg, B cells, dendritic cells or M2-like macrophages, they generally impact CRC cell death by mediating the tumoricidal activity of TCT cells. Herein, Treg, regulatory B cells, immature dendritic cells and M2-like macrophages enable TCT cells to be exhausted, thus causing substantial progression in CRC tumors. By contrast, mature dendritic cells, activated or memory B cells generally induce TCT cell activation, thus causing tumor cell death.


A
Risk factors
Lifestyle
- Diet
- Smoke
- Alcohol
Environment
- Geographical location
Host
- Genetic factors
- Obesity
Microbiome
- Alpha-bugs
- Driver-passenger bacteria
B
CHRONIC INFLAMMATION
IL-17
ROS
DNA damage
Th17 cell
Mutation accumulation
Tumor progression
Consortium recruitment
Driver bacteria
Enterococcus faecalis
Enterobacteriaceae
Enterotoxigenic Bacteroides fragilis
Shigella spp.
Passenger bacteria
Fusobacterium spp.
Streptococcus spp.
Tumorigenesis
Passenger bacteria
Driver bacteria
C
DYSBIOSIS
Alpha-bugs
Fusobacterium nucleatum
Colibactin-producing Escherichia coli
Enterotoxigenic Bacteroides fragilis
IL-17
ROS
DNA damage
Th17 cell
Mutation accumulation
Tumorigenesis
D
mucus
ETBF
MUCUS DIGESTION
Biofilm formation
Enterotoxigenic Bacteroides fragilis
mucus
pks+ E.coli
toxins
↑ IL-6
↑ STAT3
↑ Polyamines
↑ E-cadherin
pks+ E.coli
Tumorigenesis

Role of Dysbiosis and Immune Dysfunctions in Colon Carcinogenesis

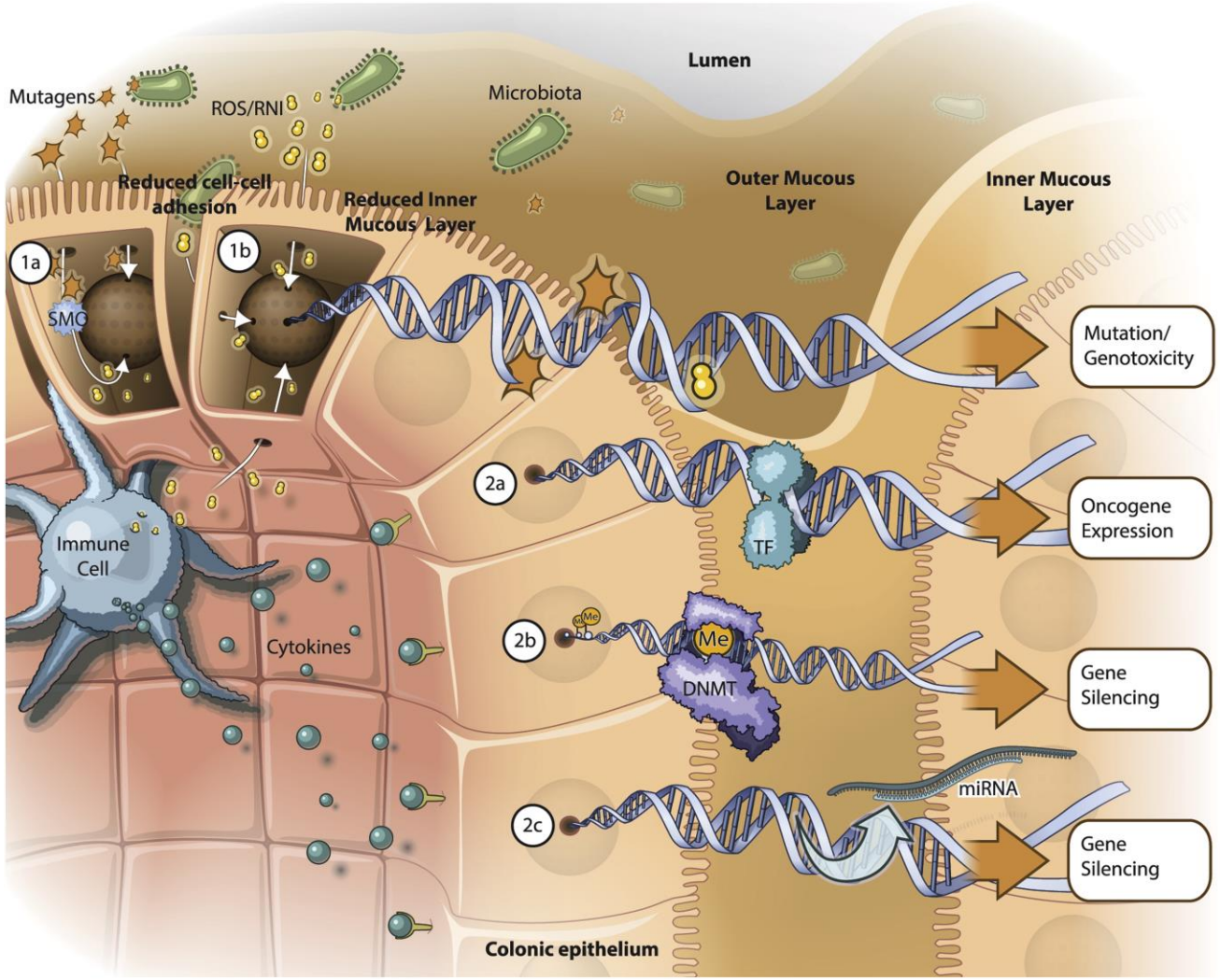


The **inflammasome** is a multiprotein oligomer consisting of caspase 1, PYCARD, NALP and sometimes caspase 5 .

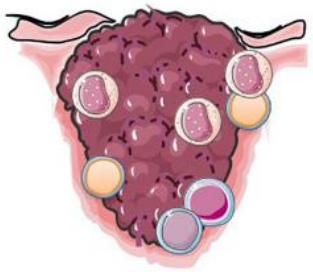
It is expressed in myeloid cells and is a component of the innate immune system.

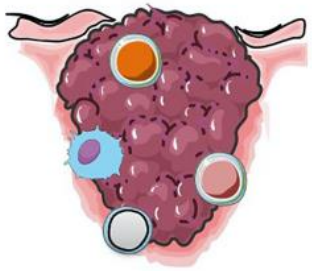
Molecular Cell 2014 54, 309-320DOI: (10.1016/j.molcel.2014.03.039)

The role of microbiota



Immune contexture of CC





Cellular components

CD8 T cell (CD45RO⁺/Cytotoxic)	Th17 cell
Th1 cell	γδT17
Tfh cell	FOXP3^{hi}Treg
B cell (Mainly in TLO)	MDSC

Associated cytokines/chemokines

• CXCL13	• CCL20
• CXCL9/CXCL10	• TGF-β
• IFNγ	• IL-17

Immune checkpoint expression

High (PD-L1, PD-1, CTLA-4, IDO1, LAG3)	Low

Ileal microbiome

B. fragilis, C. ramosum, A. ondordonkii Erysipelotrichaceae Acidaminococcaceae	*P. clara, F. nucleatum Fusobacteriaceae, Prevotellaceae*

Clinical outcome

Good Prolonged survival	Poor High recurrence risk

Clinical implications

“Early Colon Cancer

Overview of adjuvant treatment in stage III Colon Cancer

50% of the patients are cured by surgery alone

Additional 22-24% are cured with FP adjuvant treatment

Additional 4-5% will the addition of Oxaliplatin

20-22% will eventually relapse

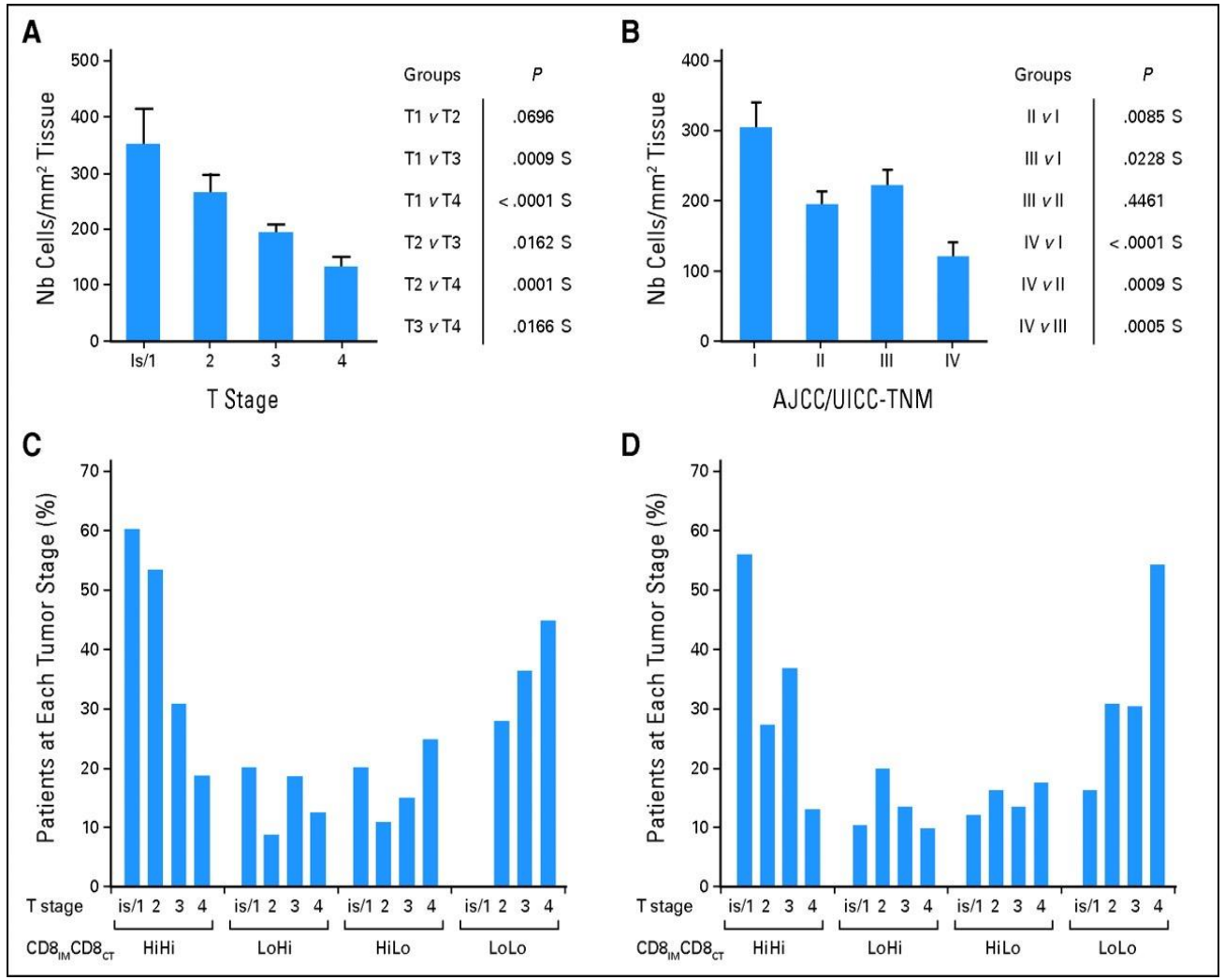
No needed to treat

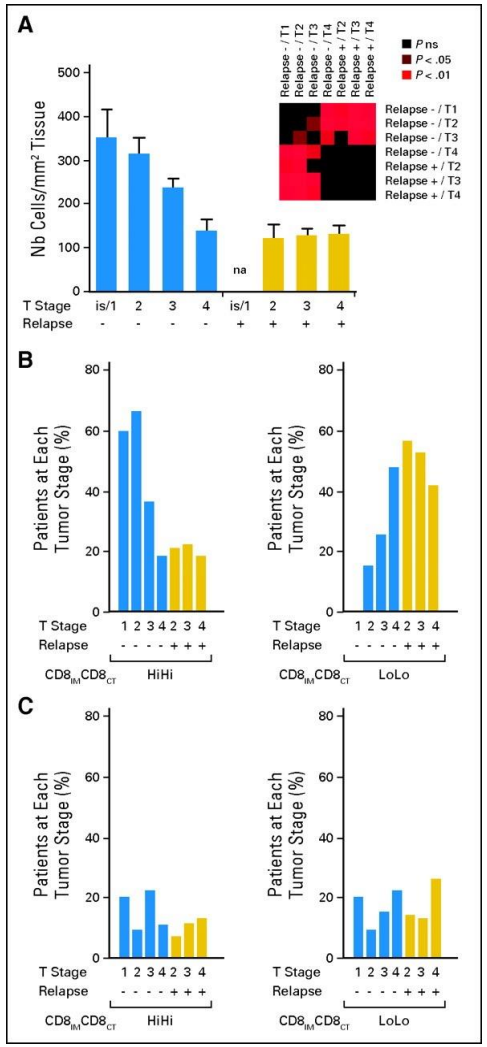
FP 1 out of 4

Oxali 1 out of 25

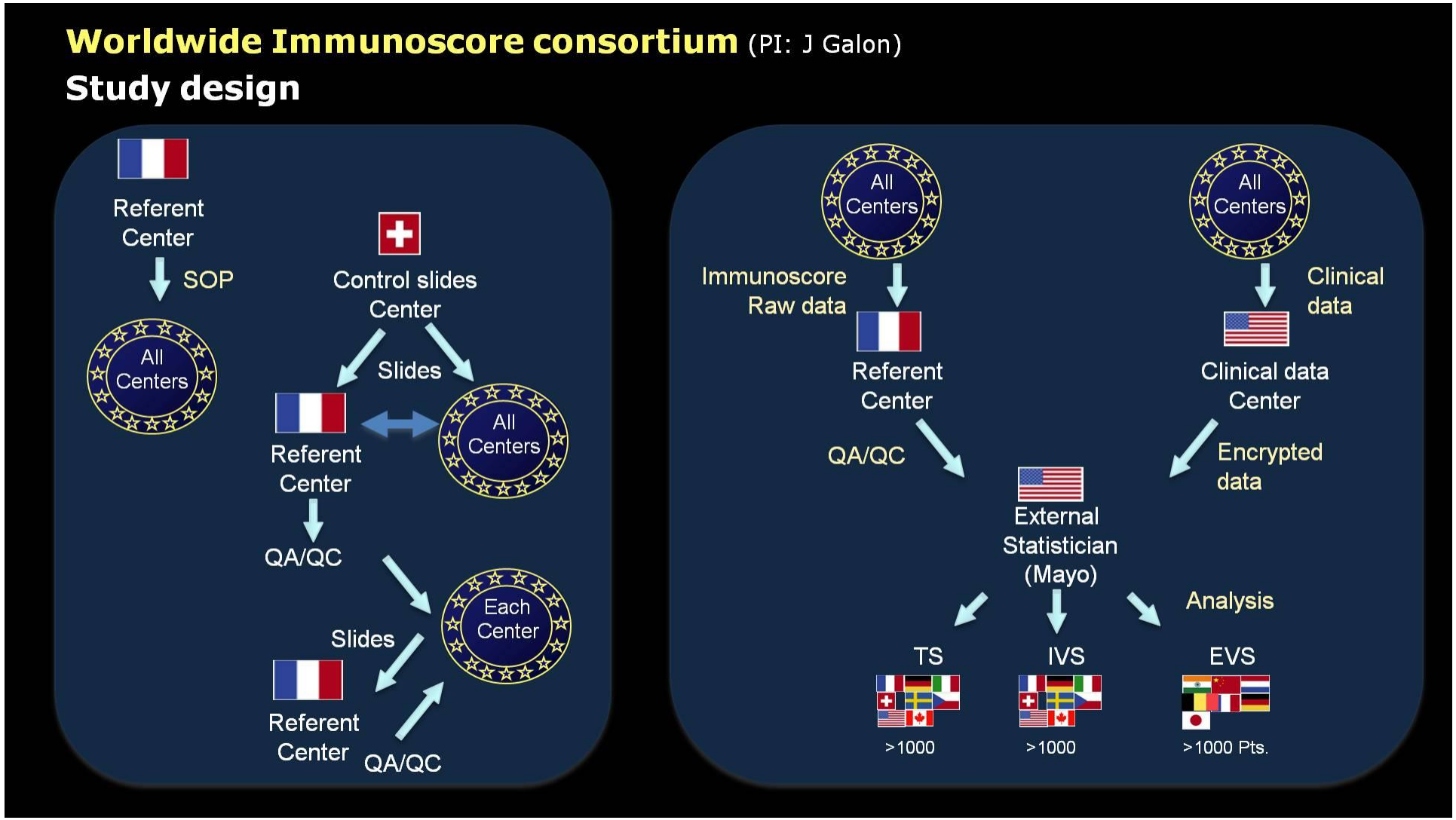
6m 1 out of 110

Local Immune Reaction



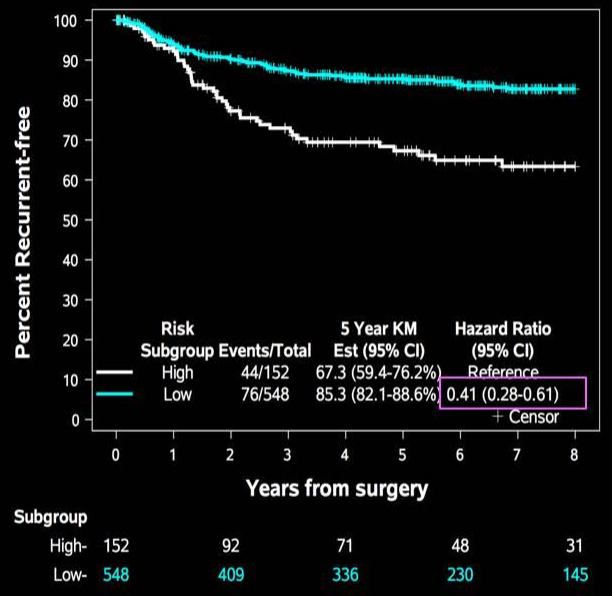


Mlecnik B et al. JCO 2011;29:610-618


Worldwide Immunoscore consortium (PI: J Galon)
Study design
Referent Center
SOP
All Centers
Control slides Center
Slides
Referent Center
All Centers
QA/QC
Each Center
Slides
Referent Center
QA/QC
All Centers
Immunoscore Raw data
Referent Center
QA/QC
All Centers
Clinical data
Clinical data Center
Encrypted data
External Statistician (Mayo)
Analysis
TS
IVS
EVS
>1000
>1000
>1000 Pts.

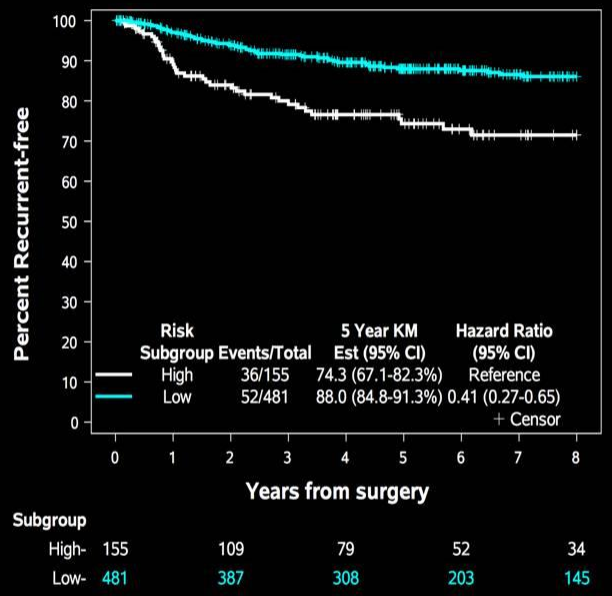
Primary Objective: Time to recurrence (TTR) for Immunoscore (High/Low)

TS



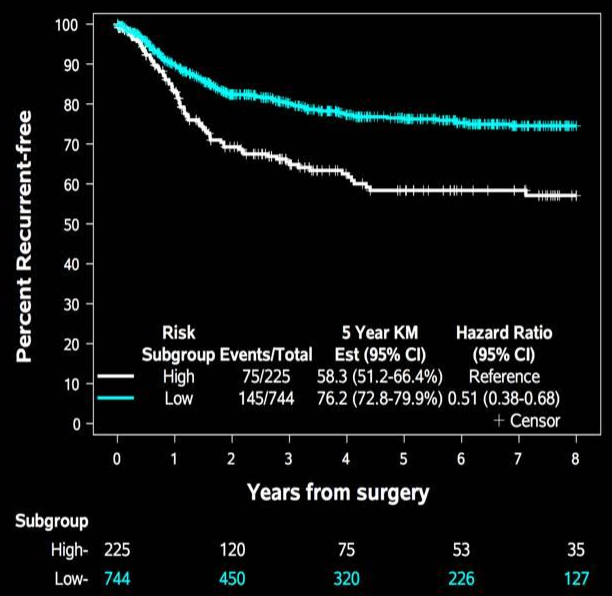
***P*< 0.0001**
HR = 0.41
C-index = 0.60

IVS



***P*< 0.0001**
HR = 0.41
C-index = 0.60

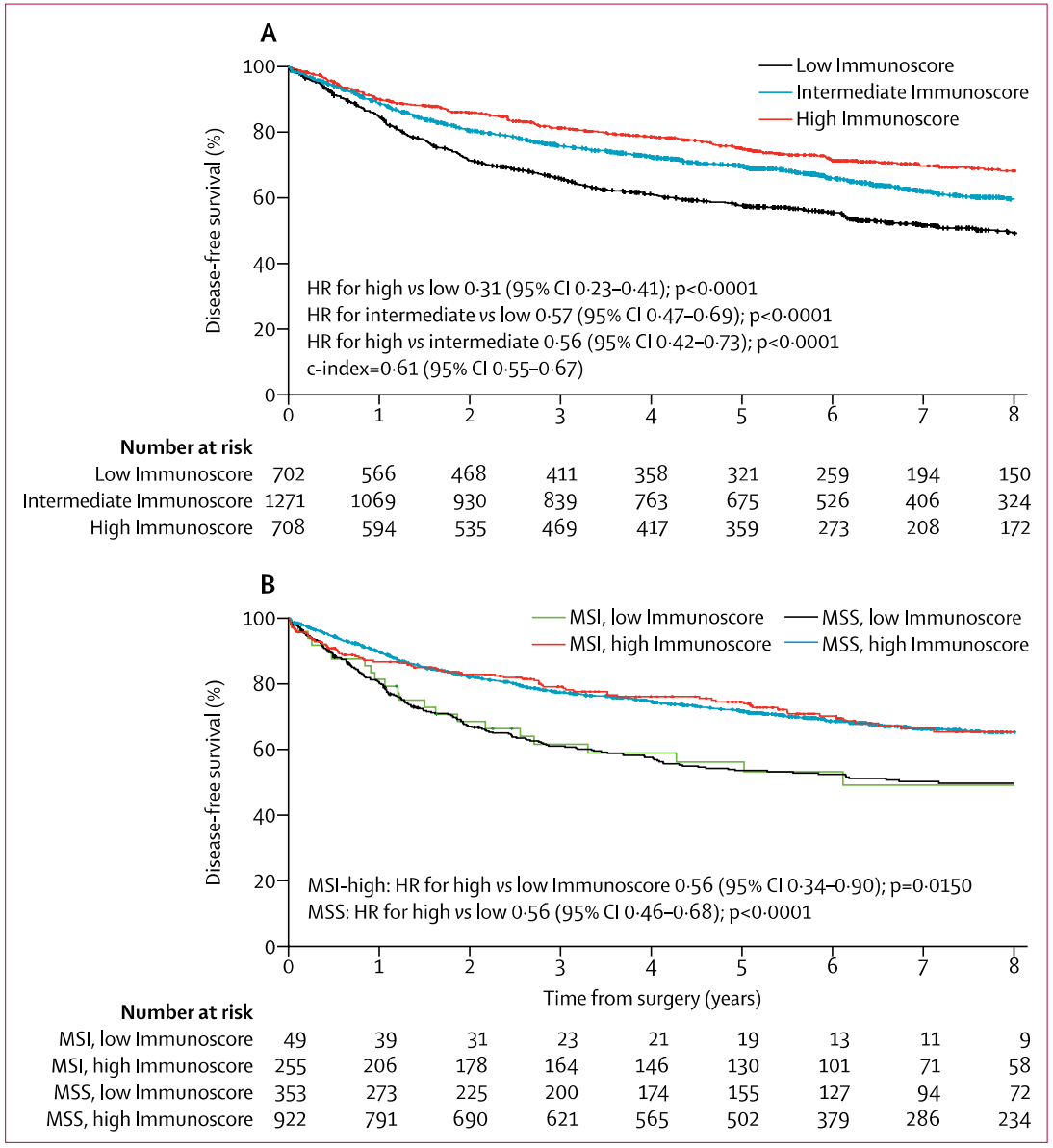
EVS

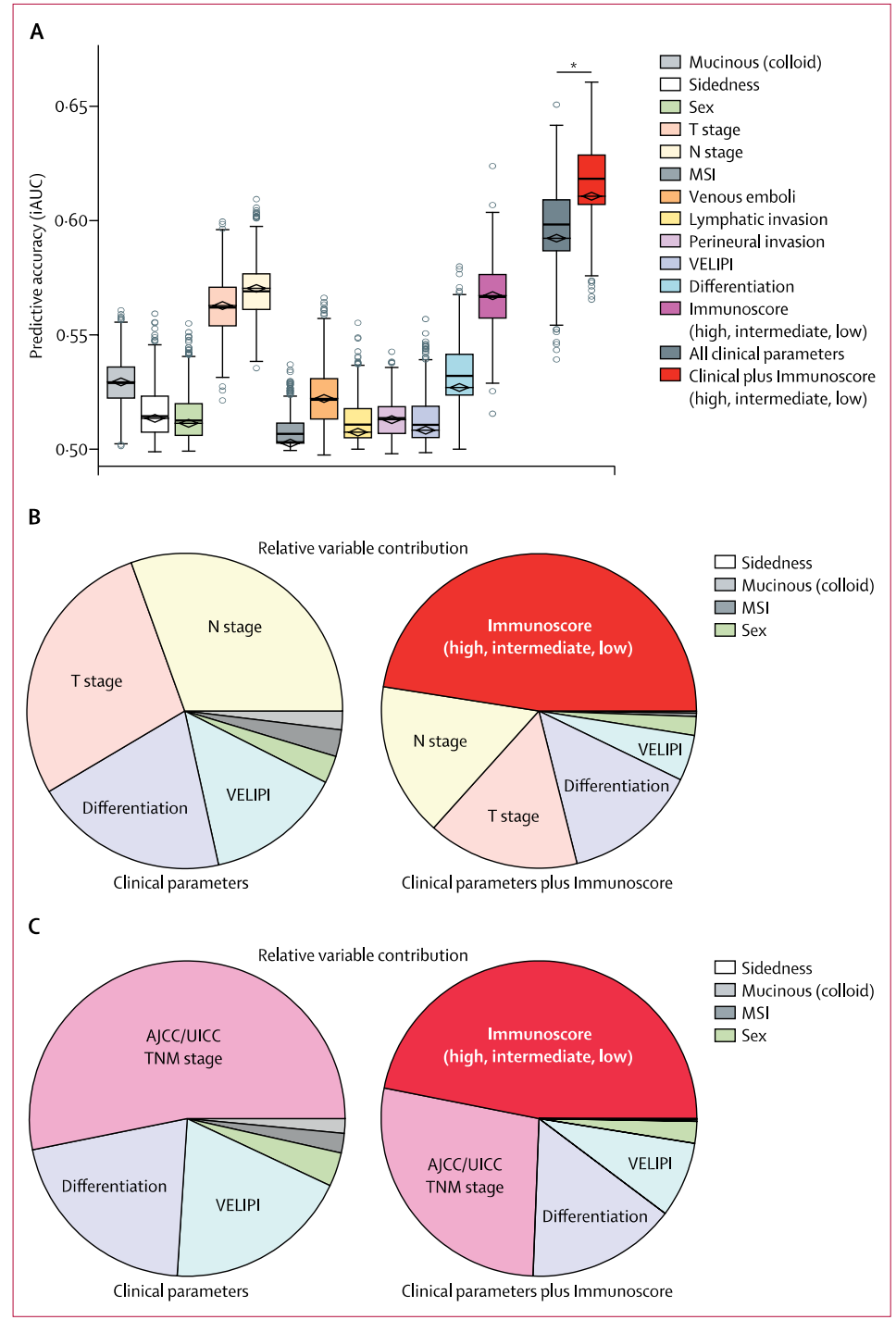


***P*< 0.0001**
HR = 0.51
C-index = 0.56

Primary objective is reached

Immunoscore predicted time to recurrence on Training Set (TS), and on 2 independent validation sets (IVS and EVS), blinded to clinical outcome.


A
Low Immunoscore
Intermediate Immunoscore
High Immunoscore
Disease-free survival (%)
HR for high vs low 0·31 (95% CI 0·23–0·41); p<0·0001
HR for intermediate vs low 0·57 (95% CI 0·47–0·69); p<0·0001
HR for high vs intermediate 0·56 (95% CI 0·42–0·73); p<0·0001
c-index=0·61 (95% CI 0·55–0·67)
Number at risk
Low Immunoscore 702 566 468 411 358 321 259 194 150
Intermediate Immunoscore 1271 1069 930 839 763 675 526 406 324
High Immunoscore 708 594 535 469 417 359 273 208 172
B
MSI, low Immunoscore
MSS, low Immunoscore
MSI, high Immunoscore
MSS, high Immunoscore
Disease-free survival (%)
MSI-high: HR for high vs low Immunoscore 0·56 (95% CI 0·34–0·90); p=0·0150
MSS: HR for high vs low 0·56 (95% CI 0·46–0·68); p<0·0001
Time from surgery (years)
Number at risk
MSI, low Immunoscore 49 39 31 23 21 19 13 11 9
MSI, high Immunoscore 255 206 178 164 146 130 101 71 58
MSS, low Immunoscore 353 273 225 200 174 155 127 94 72
MSS, high Immunoscore 922 791 690 621 565 502 379 286 234


A
Predictive accuracy (iAUC)
Mucinous (colloid)
Sidedness
Sex
T stage
N stage
MSI
Venous emboli
Lymphatic invasion
Perineural invasion
VELIPI
Differentiation
Immunoscore (high, intermediate, low)
All clinical parameters
Clinical plus Immunoscore (high, intermediate, low)
B
Relative variable contribution
T stage
N stage
Differentiation
VELIPI
Clinical parameters
Immunoscore (high, intermediate, low)
N stage
T stage
Differentiation
VELIPI
Clinical parameters plus Immunoscore
Sidedness
Mucinous (colloid)
MSI
Sex
C
Relative variable contribution
AJCC/UICC TNM stage
Differentiation
VELIPI
Clinical parameters
Immunoscore (high, intermediate, low)
AJCC/UICC TNM stage
VELIPI
Differentiation
Clinical parameters plus Immunoscore
Sidedness
Mucinous (colloid)
MSI
Sex

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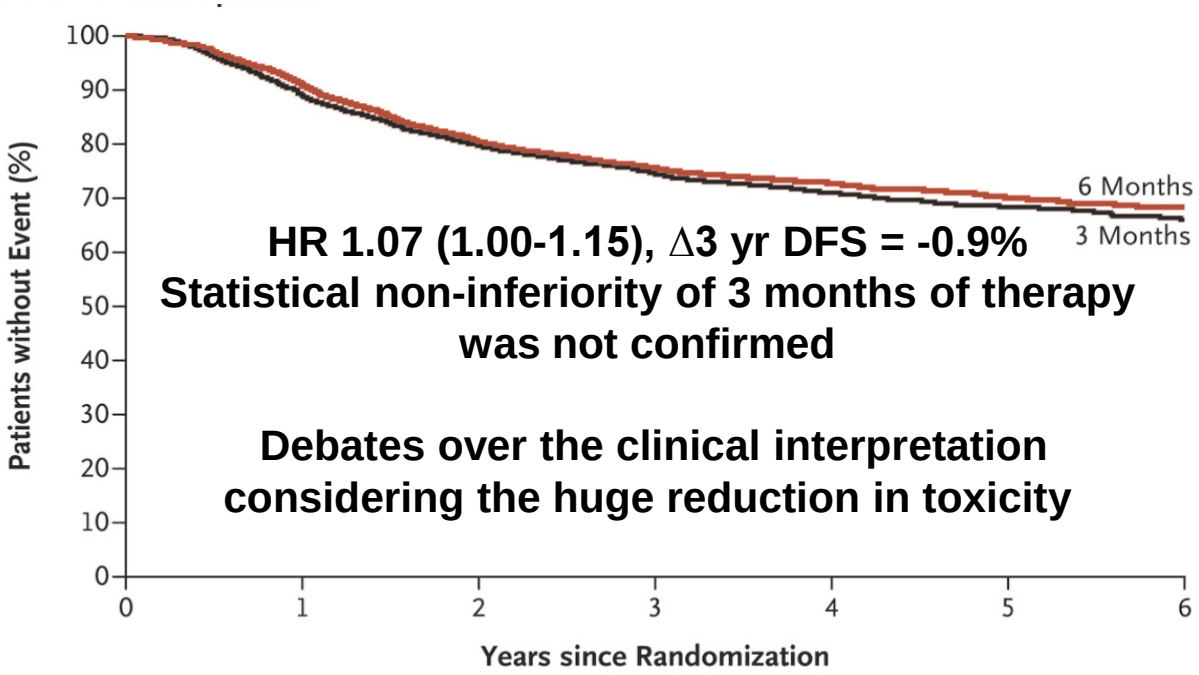
Duration of Adjuvant Chemotherapy for Stage III Colon Cancer

A. Grothey, A.F. Sobrero, A.F. Shields, T. Yoshino, J. Paul, J. Taieb, J. Souglakos, Q. Shi, R. Kerr, R. Labianca, J.A. Meyerhardt, D. Vernerey, T. Yamanaka, I. Boukovinas, J.P. Meyers, L.A. Renfro, D. Niedzwiecki, T. Watanabe,* V. Torri, M. Saunders, D.J. Sargent,* T. Andre, and T. Iveson



HR 1.07 (1.00-1.15), Δ3 yr DFS = -0.9%
Statistical non-inferiority of 3 months of therapy was not confirmed

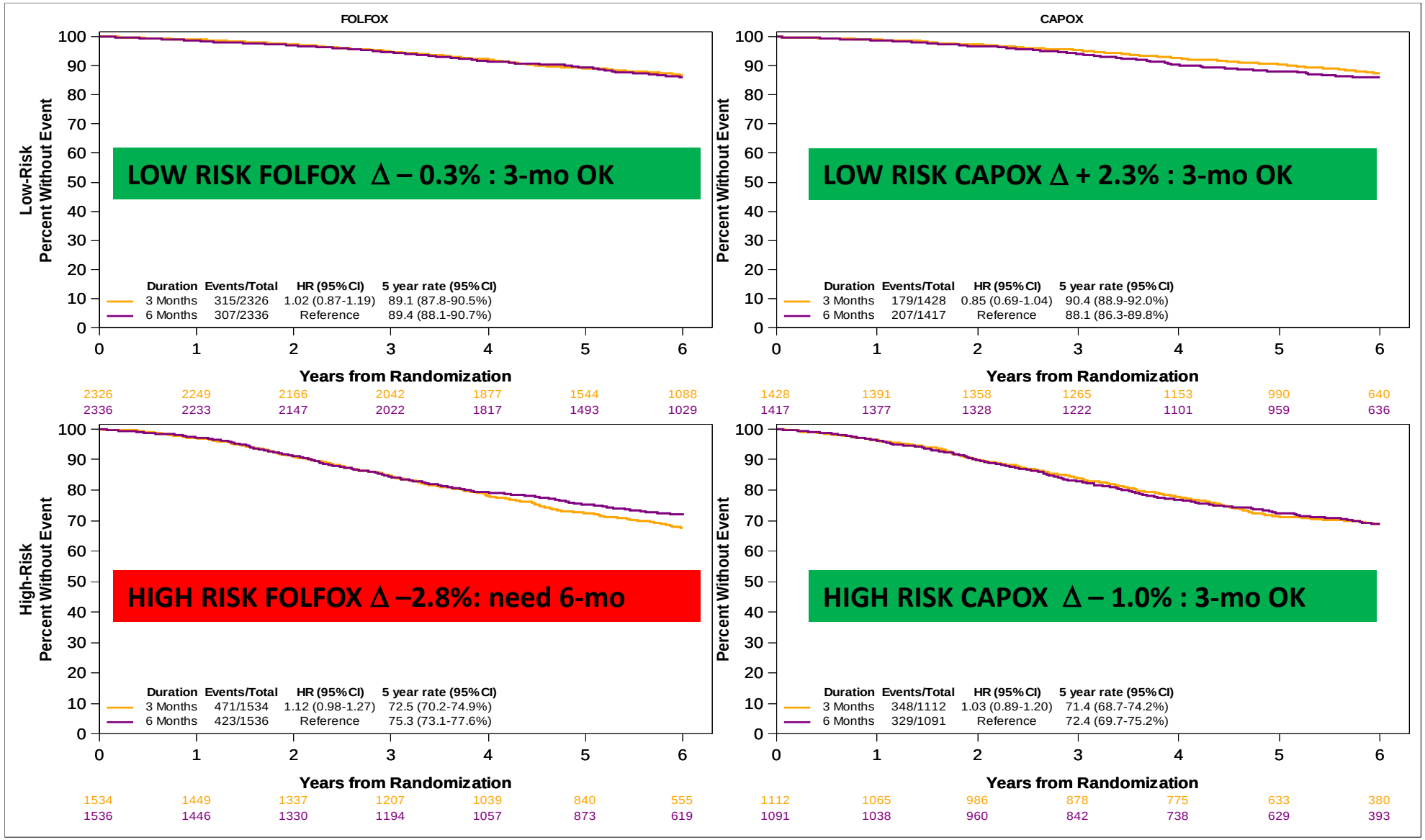
Debates over the clinical interpretation considering the huge reduction in toxicity

No. at Risk							
6 Months	6410	5530	4477	3065	1679	873	334
3 Months	6424	5446	4464	3000	1609	826	321

6 trials, 12,834 pts

- **TOSCA**
- **SCOT**
- **IDEA FRANCE**
- **ACHIEVE**
- **HORG**
- **CALGB/SWOG 80702**

IDEA 5-yr OS by regimen/risk



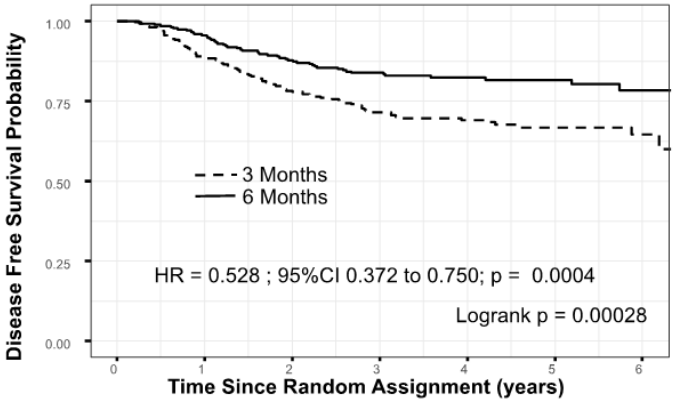
Sobrero et al Lancer Ocology 2021

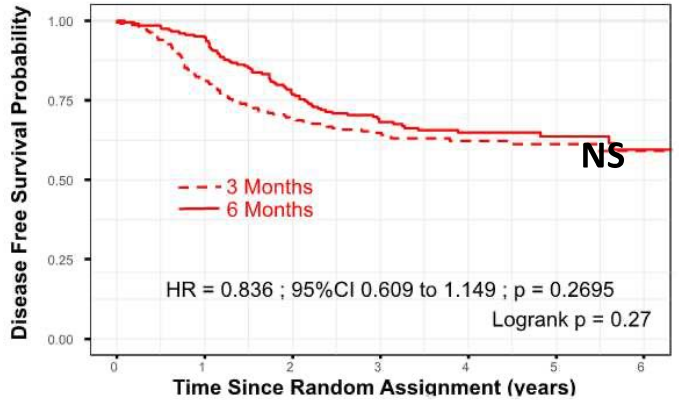
IS in IDEA France

A

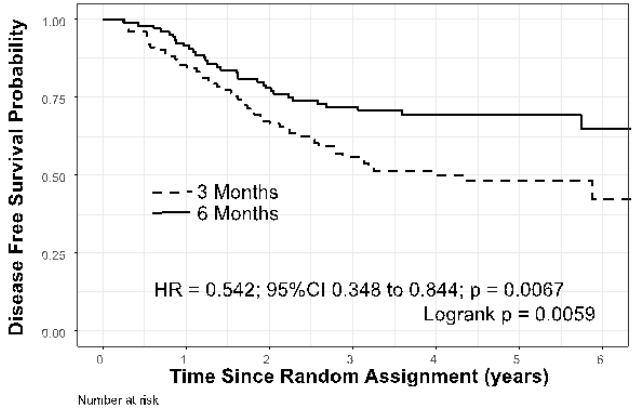
IS Int or High | **IS Low**

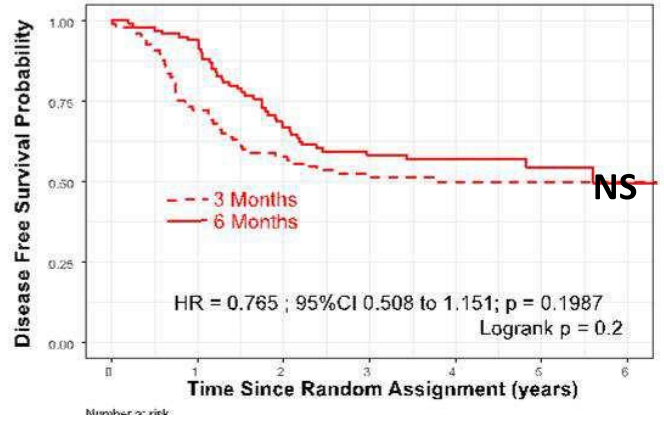
All patients



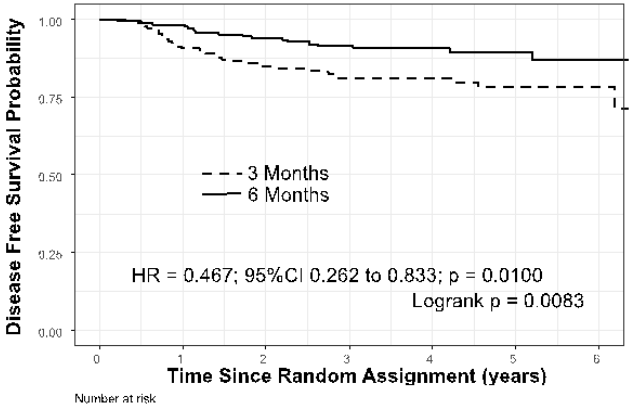


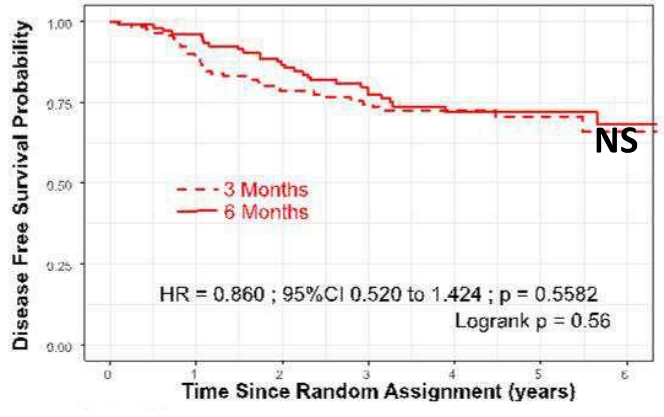
Clinically High-risk (T4 and/or N2)





Clinically Low-risk (T1-T3, N1)





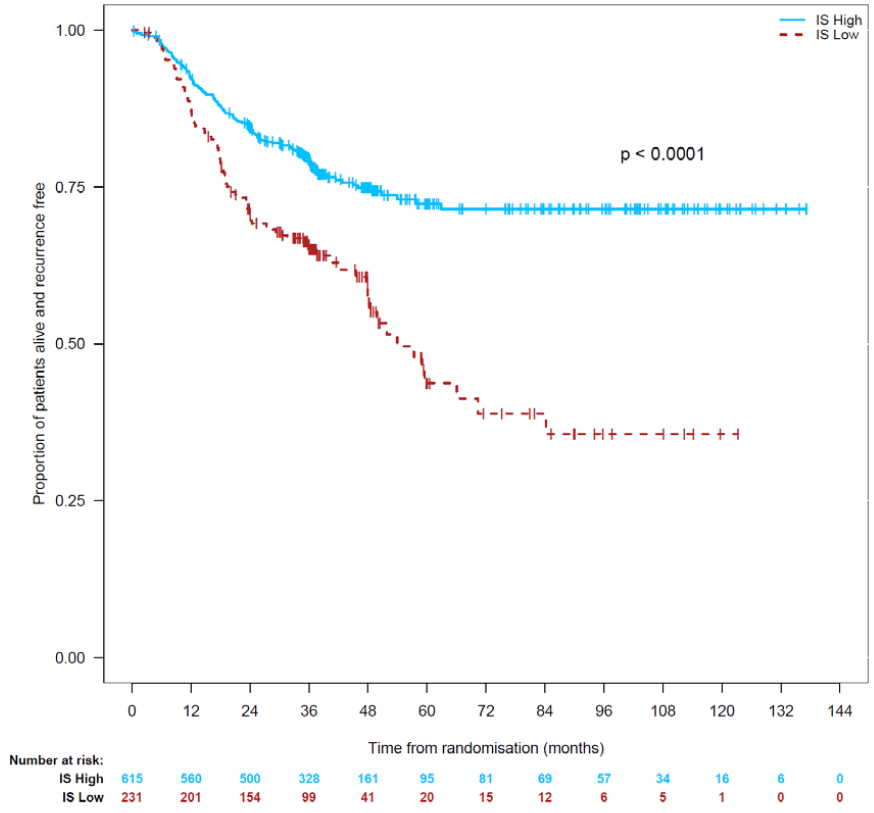
Pages F et all, Ann Oncol 2020

IDEA GREECE - SCOT VALIDATION COHORT

Stage III				Stage III			
All risk strata				All risk strata		FFPE BLOCKS	EVENTS
capox	any duration	1607	414	capox	any duration	332	126
	3mo	801	207		3mo	165	
	6mo	806	207		6mo	167	
folfox	any duration	698	165	folfox	any duration	240	110
	3mo	366	94		3mo	121	
	6mo	332	71		6mo	119	
total		2305	579	total		572	236
lo_risk				lo_risk			
capox	any duration	881	140	capox	any duration	212	66
	3mo	439	63		3mo	107	34
	6mo	442	77		6mo	105	32
folfox	any duration	371	56	folfox	any duration	134	59
	3mo	201	39		3mo	64	30
	6mo	170	17		6mo	70	29
total		1252	196	total		346	125
hi_risk				hi_risk			
capox	any duration	726	274	capox	any duration	120	60
	3mo	362	144		3mo	58	29
	6mo	364	130		6mo	62	31
folfox	any duration	327	109	folfox	any duration	106	51
	3mo	165	55		3mo	57	28
	6mo	162	54		6mo	49	23
total		1053	383	total		226	111

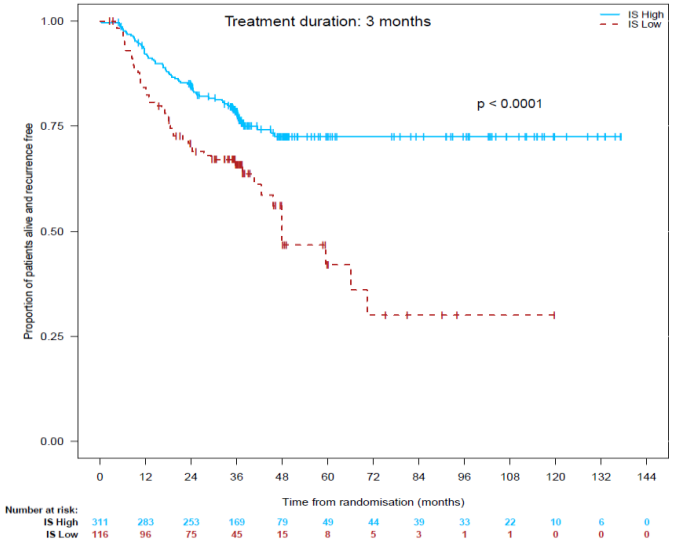
3y Disease Free Survival

overall

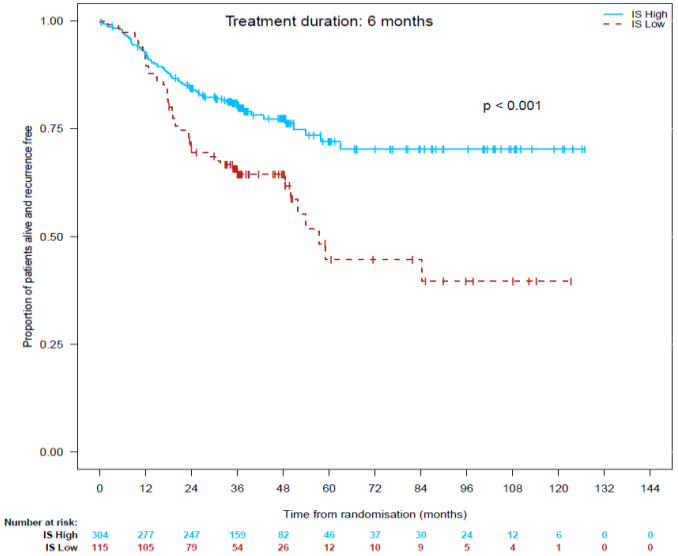


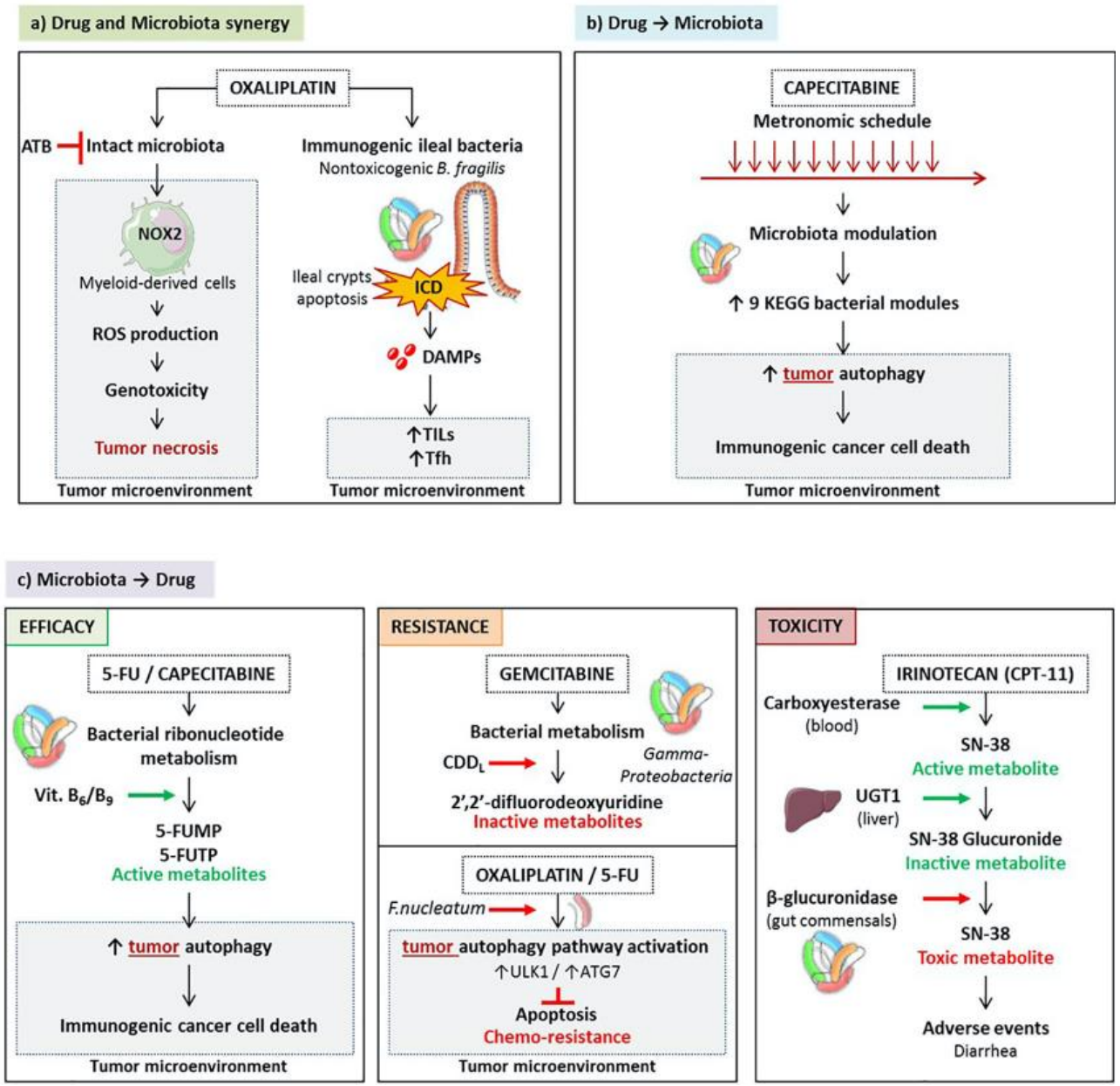
3-year DFS	IS Low	IS High
Treatment duration: 3 months	65.8%, 95% CI (56.1% to 73.9%)	78.5%, 95% CI (73.4% to 82.7%)
Treatment duration: 6 months	64.4%, 95% CI (54.8% to 72.6%)	80.3%, 95% CI (75.3% to 84.5%)

3months treatment

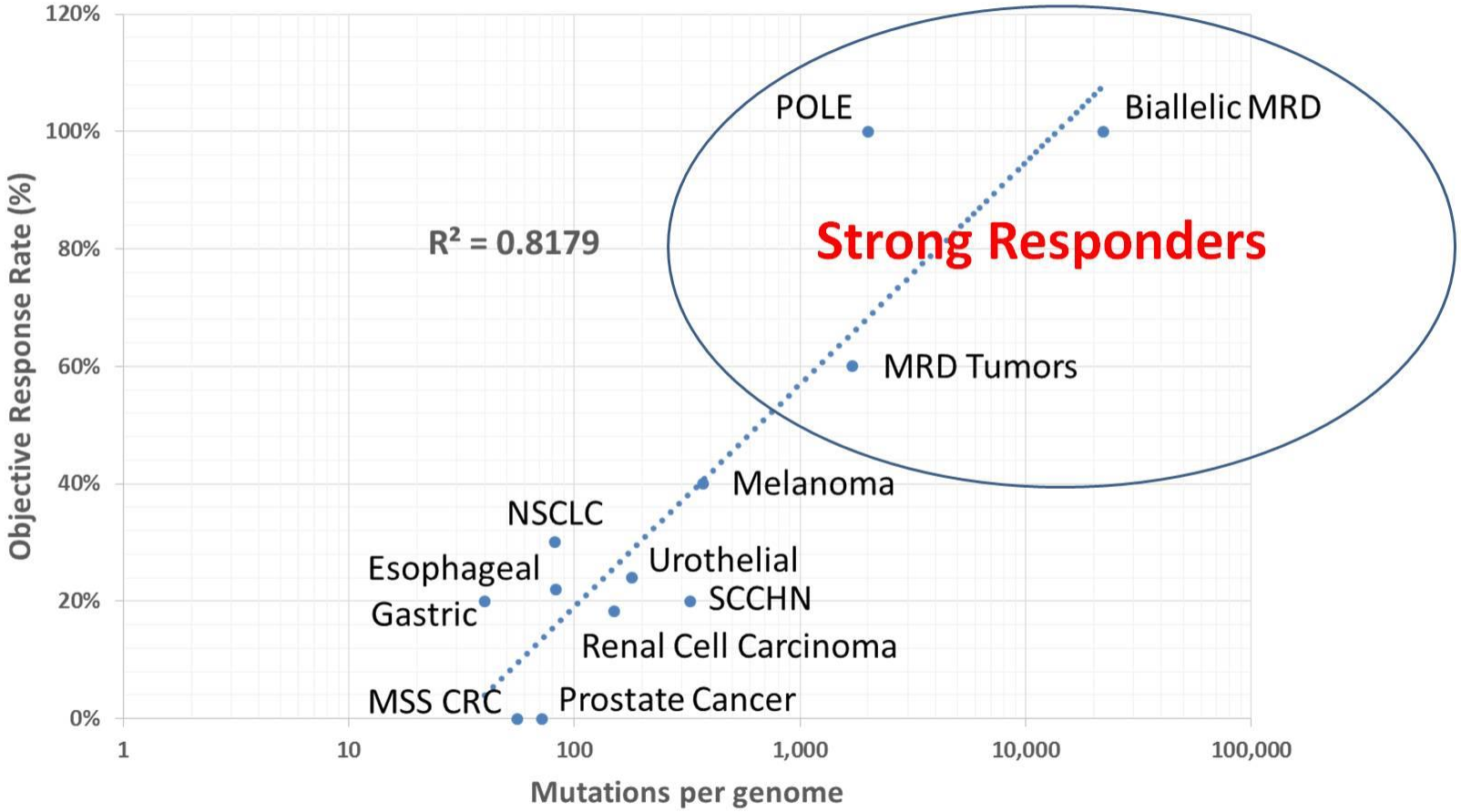


6months treatment



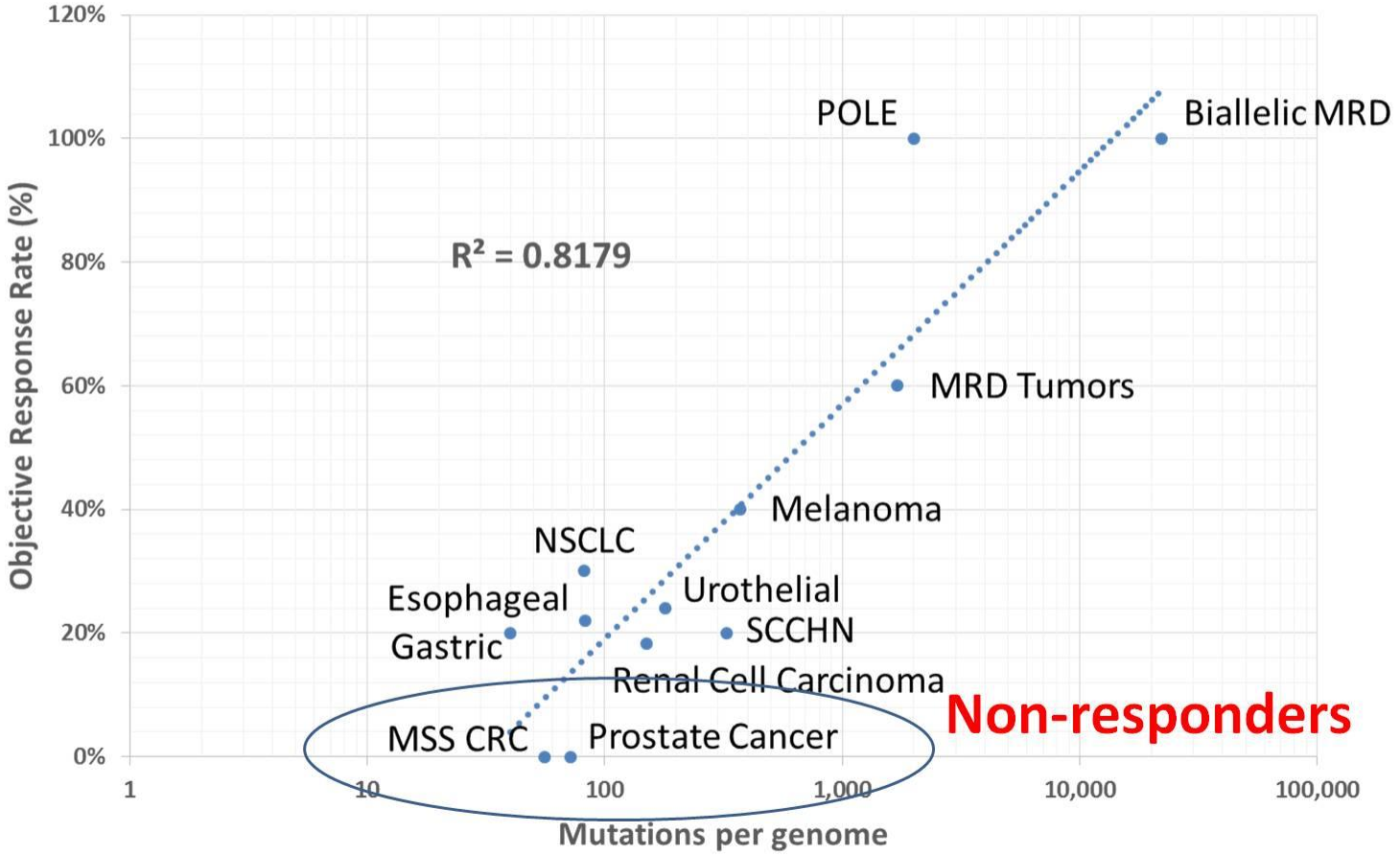

a) Drug and Microbiota synergy
OXALIPLATIN
ATB
Intact microbiota
NOX2
Myeloid-derived cells
ROS production
Genotoxicity
Tumor necrosis
Tumor microenvironment
Immunogenic ileal bacteria
Nontoxicogenic B. fragilis
Ileal crypts apoptosis
ICD
DAMPs
↑TILs
↑Tfh
Tumor microenvironment
b) Drug → Microbiota
CAPECITABINE
Metronomic schedule
Microbiota modulation
↑ 9 KEGG bacterial modules
↑ tumor autophagy
Immunogenic cancer cell death
Tumor microenvironment
c) Microbiota → Drug
EFFICACY
5-FU / CAPECITABINE
Bacterial ribonucleotide metabolism
Vit. B6/B9
5-FUMP
5-FUTP
Active metabolites
↑ tumor autophagy
Immunogenic cancer cell death
Tumor microenvironment
RESISTANCE
GEMCITABINE
Bacterial metabolism
CDDL
Gamma-Proteobacteria
2',2'-difluorodeoxyuridine
Inactive metabolites
OXALIPLATIN / 5-FU
F.nucleatum
tumor autophagy pathway activation
↑ULK1 / ↑ATG7
Apoptosis
Chemo-resistance
Tumor microenvironment
TOXICITY
IRINOTECAN (CPT-11)
Carboxyesterase
(blood)
SN-38
Active metabolite
UGT1
(liver)
SN-38 Glucuronide
Inactive metabolite
β-glucuronidase
(gut commensals)
SN-38
Toxic metabolite
Adverse events
Diarrhea

Mutation Burden vs. Response to PD-1 Blockade



Presented By Luis Diaz at 2017 Gastrointestinal Cancers Symposium

Mutation Burden vs. Response to PD-1 Blockade



Presented By Luis Diaz at 2017 Gastrointestinal Cancers Symposium

Polymerase proofreading-associated polyposis (PPAP)

POLE Mutation

- ✓AD
- ✓Early-onset CRC, multiple or large adenomas with conventional pathology
- ✓Tumours: MSS
- ✓No extracolonic tumours

POLD1 Mutation

- ✓AD
- ✓Early-onset CRC, multiple or large adenomas
- ✓Tumours: MSS
- ✓Presence of early-onset EC; 1 pt with two primary brain tumours
- ✓No mutations identified in 386 early-onset ECs

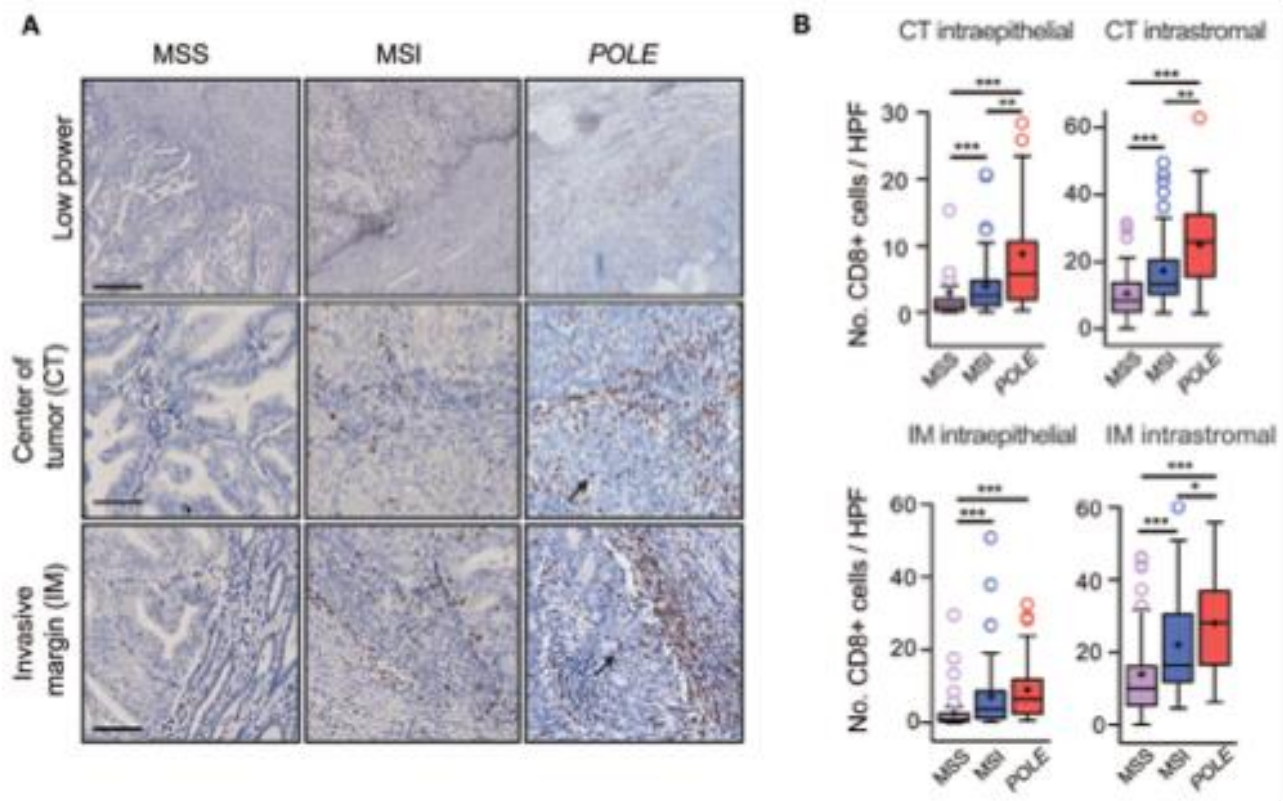
Clinical Cancer Research

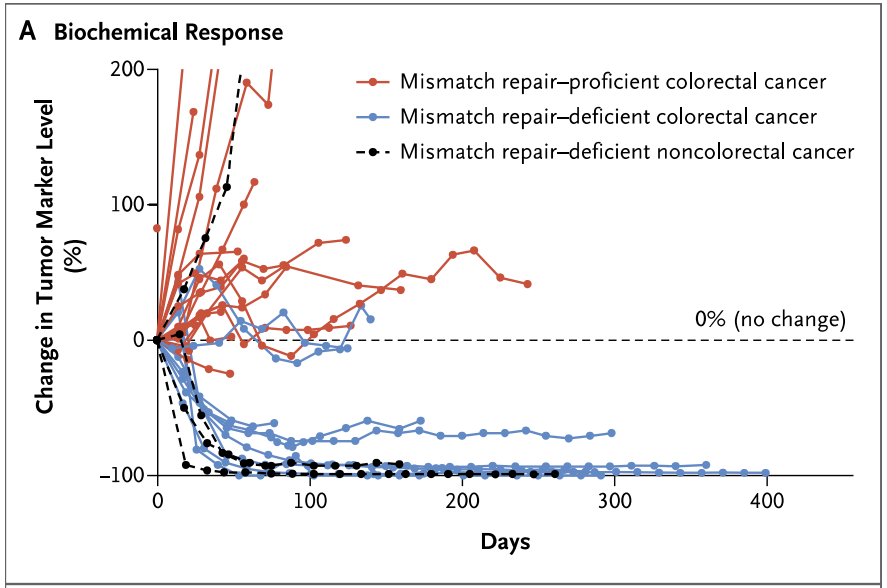
Biology of Human Tumors

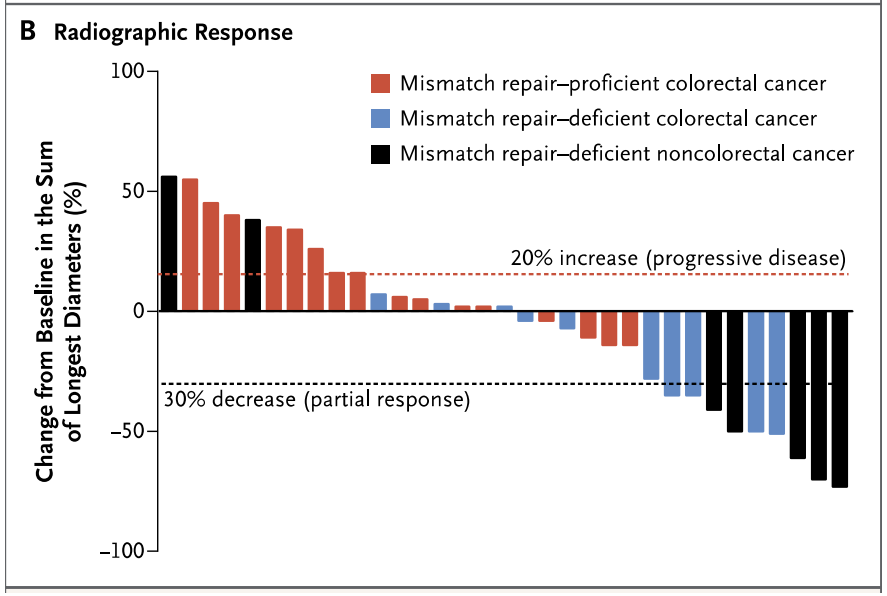
POLE Proofreading Mutations Elicit an Antitumor Immune Response in Endometrial Cancer

Inge C. van Gool, Florine A. Eggink, Luke Freeman-Mills, Ellen Stelloo, Emanuele Marchi, Marco de Bruyn, Claire Palles, Remi A. Nout, Cor D. de Kroon, Elisabeth M. Osse, Paul Klenerman, Carien L. Creutzberg, Ian P.M. Tomlinson, Vincent T.H.B.M. Smit, Hans W. Nijman, Tjalling Bosse, and David N. Church

DOI: 10.1158/1078-0432.CCR-15-0057 Published 15 July 2015







The NEW ENGLAND JOURNAL of MEDICINE

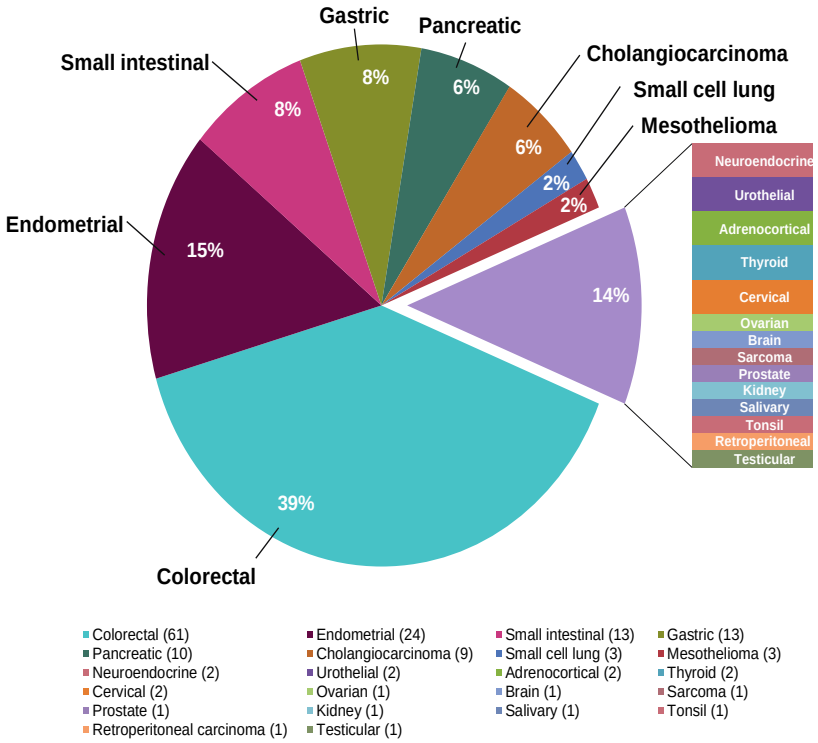
ORIGINAL ARTICLE

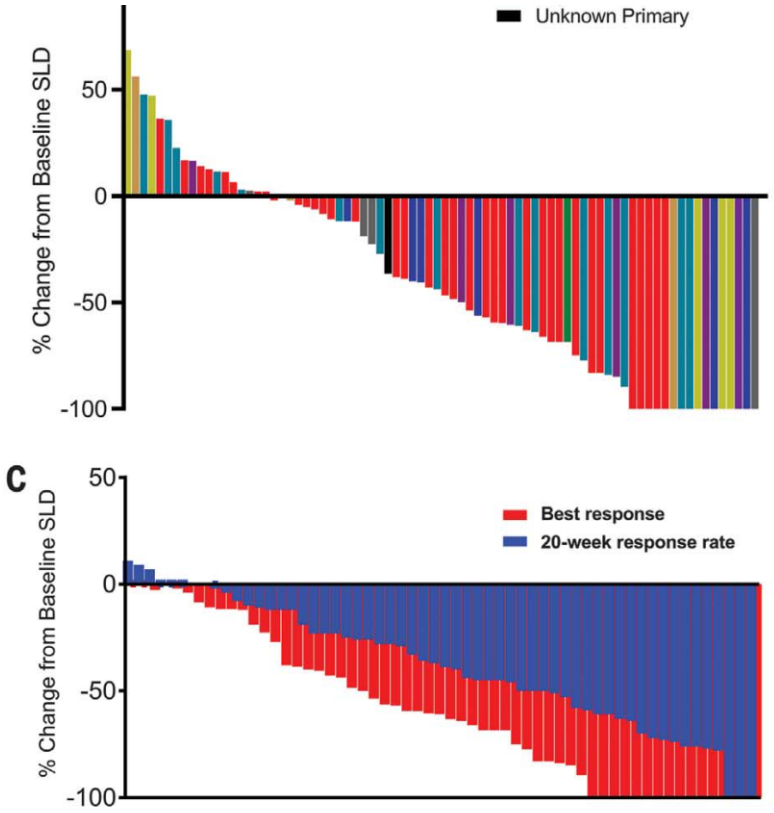
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

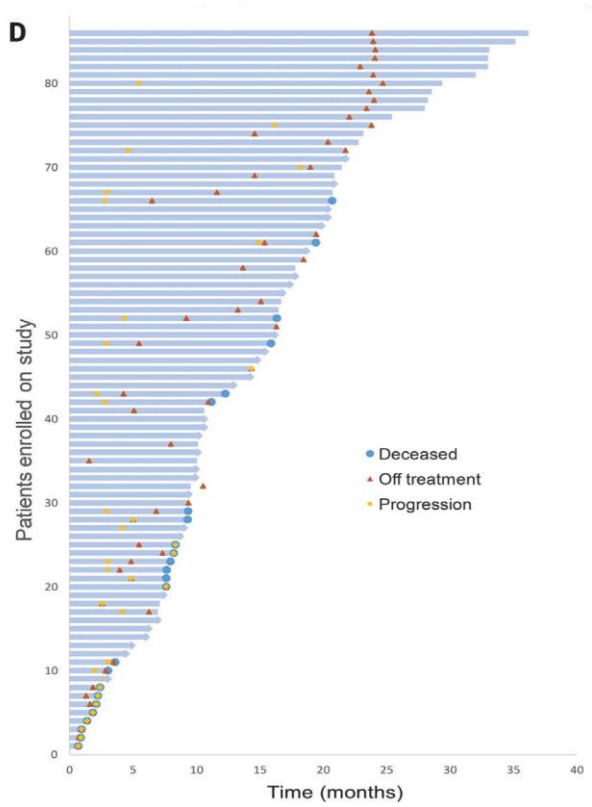
D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, 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.

Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade

Dung T. Le,[1,2,3] Jennifer N. Durham,[1,2,3*] Kellie N. Smith,[1,3*] Hao Wang,[3*]



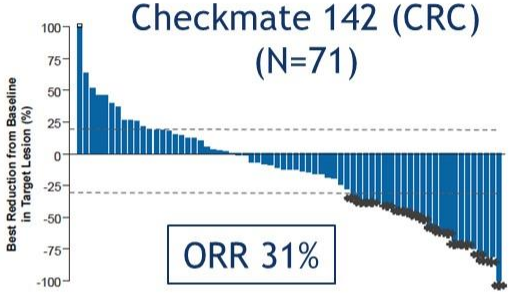




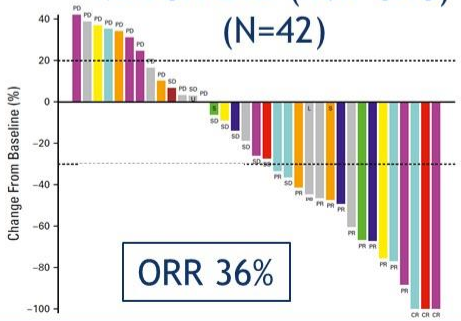
Pembrolizumab and Nivolumab in dMMR/MSI-H Cancers

Nivolumab

Checkmate 142 (CRC)
(N=71)

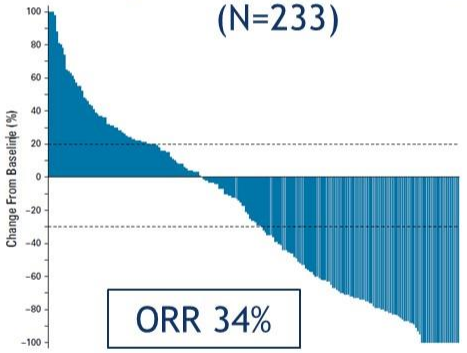


MATCH Z1D (non-CRC)
(N=42)

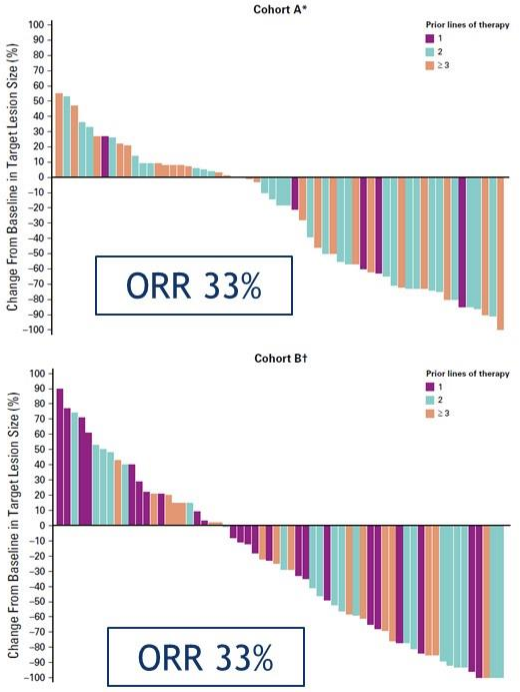


Pembrolizumab

Keynote 158 (non-CRC)
(N=233)

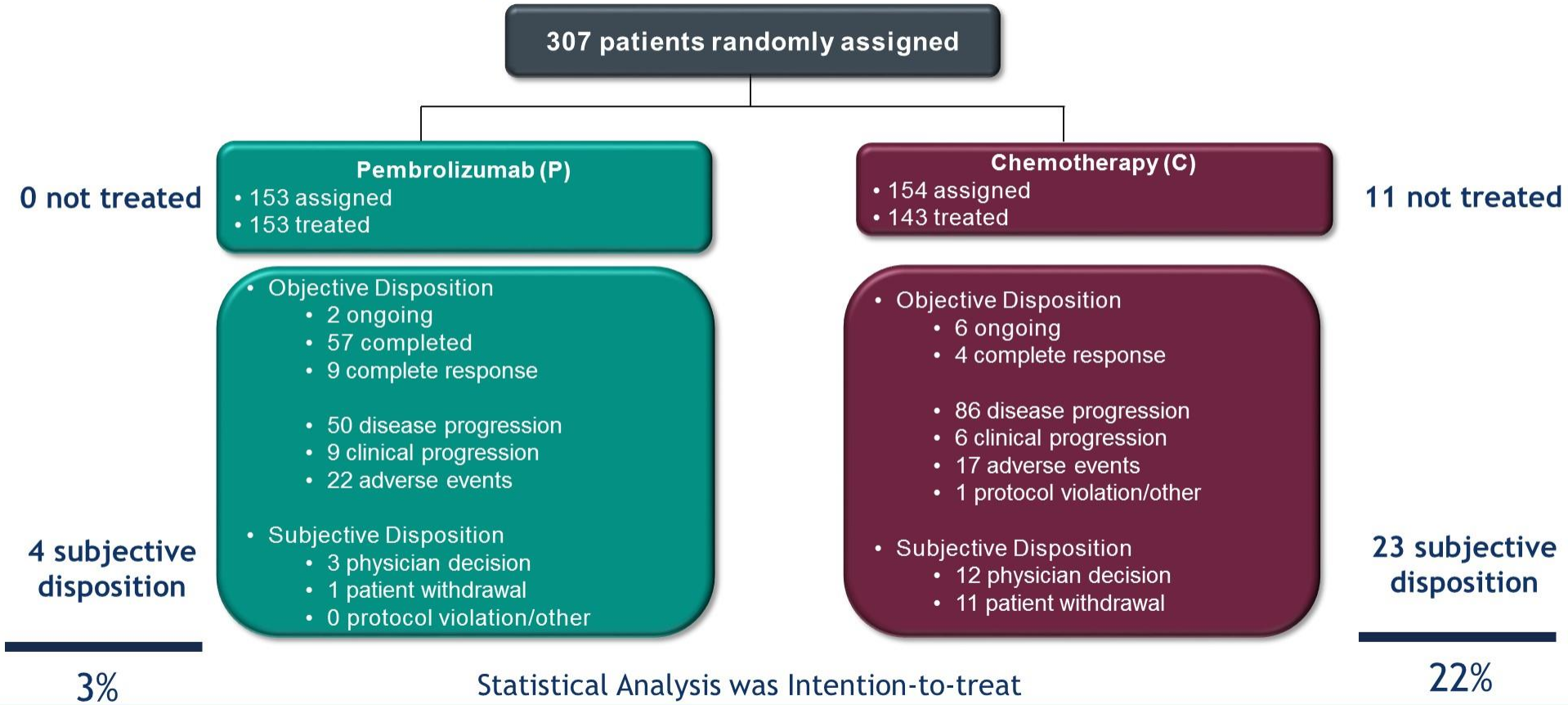


Keynote 164 (CRC)
(N=124)



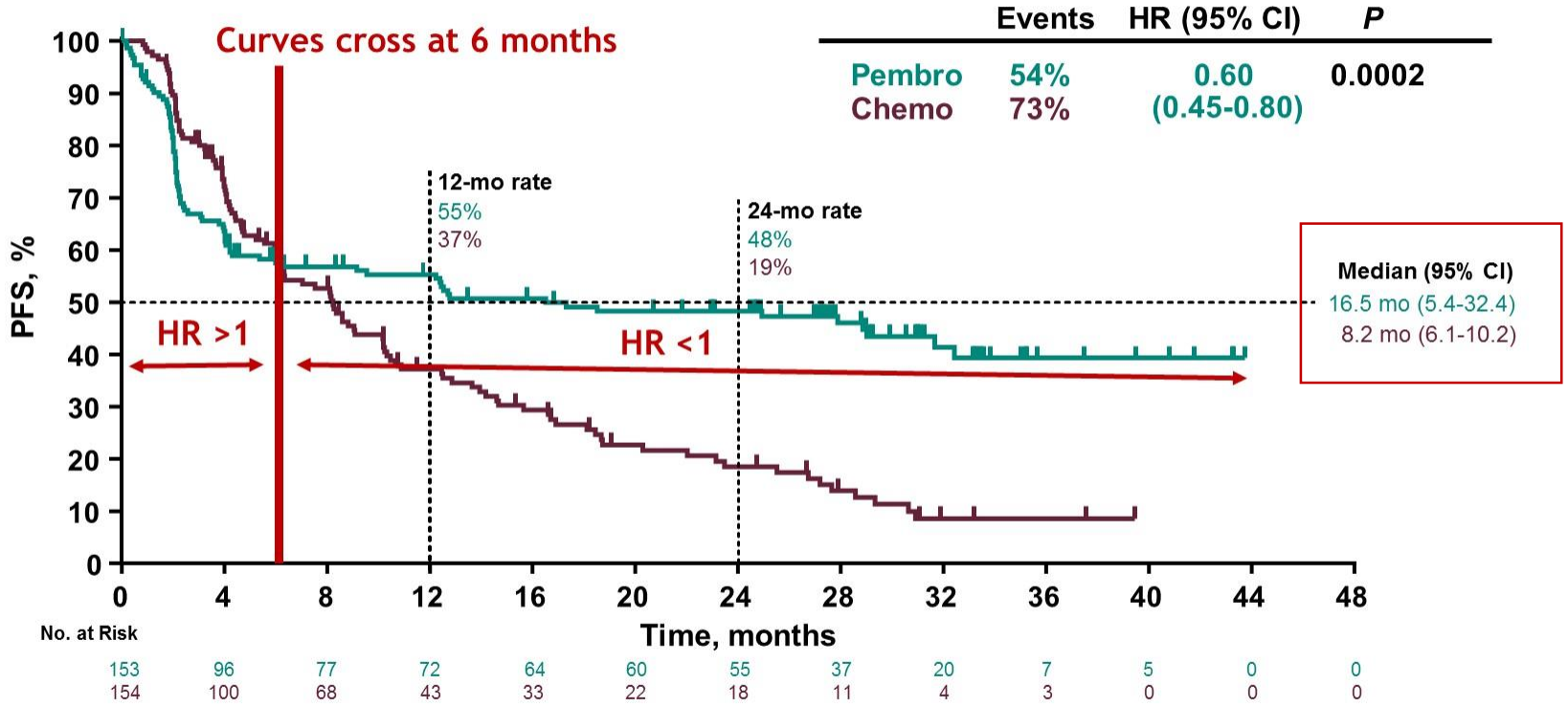
Overman et al. Lancet Onc 2017; Lee et al. JCO 2020, Marabelle JCO 2019, Azad et al. JCO 2019

Treatment Disposition



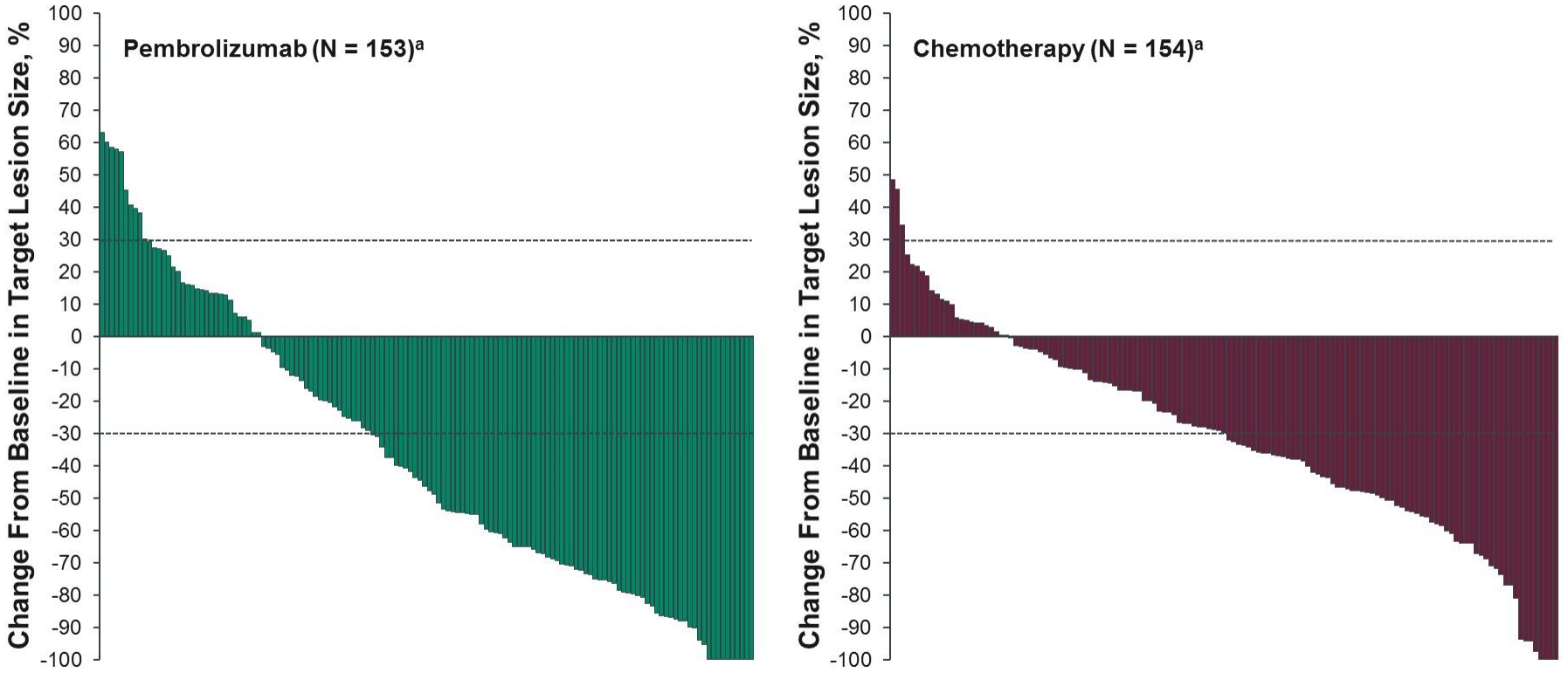
Statistical Analysis was Intention-to-treat

Progression-Free Survival



Median study follow-up: 32.4 months (range, 24.0 – 48.3); PFS (time from randomization to first documented disease progression or death) assessed per RECIST v1.1 by BICR; Superiority of pembrolizumab vs chemotherapy for PFS was demonstrated at the pre-specified one-sided α = 0.0117; Data cut-off: 19Feb2020.

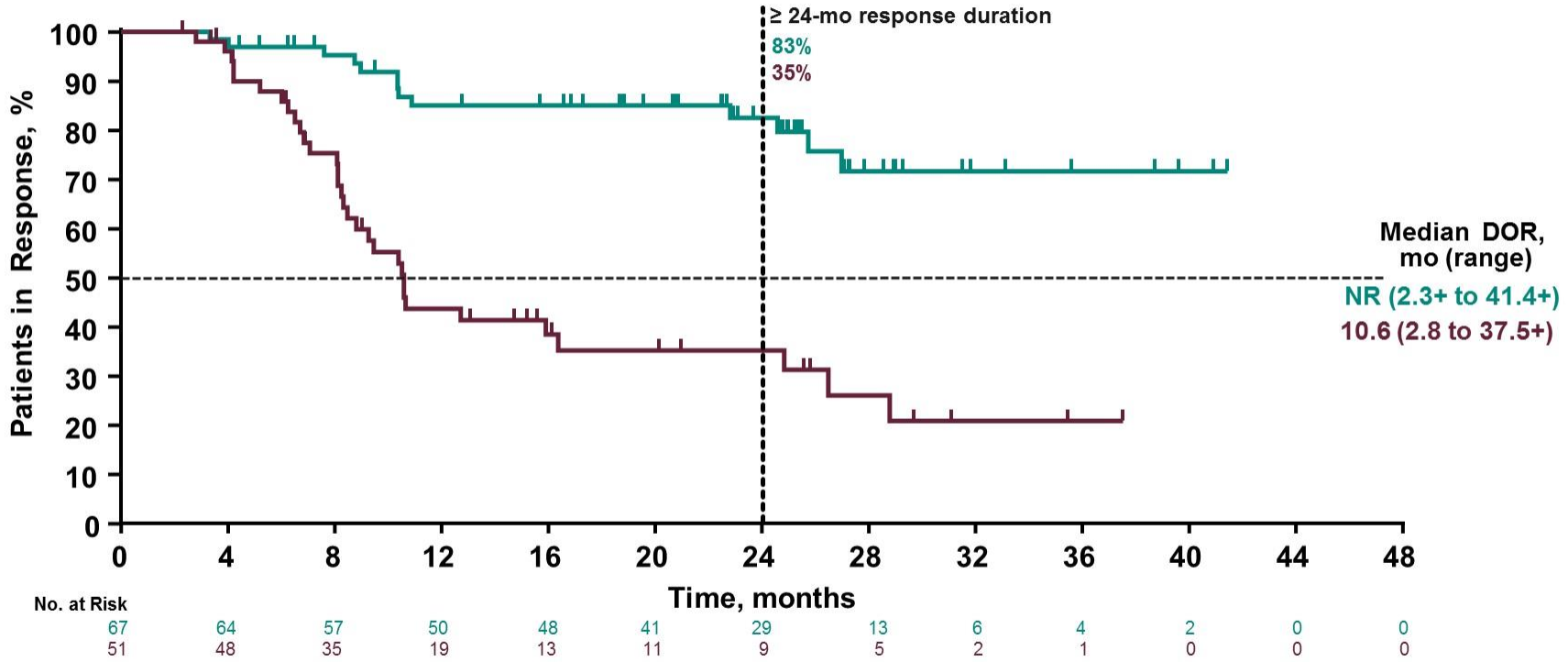
Radiographic Response in Target Lesions



[a]104 of 138 (75%) evaluable patients in the pembrolizumab arm and 111 of 135 (82%) evaluable patients in the chemotherapy arm had a reduction from baseline in target lesion size.
Evaluable patients include those with ≥1 post-baseline target lesion imaging assessment in the intention-to-treat population; Data cut-off: 19Feb2020.

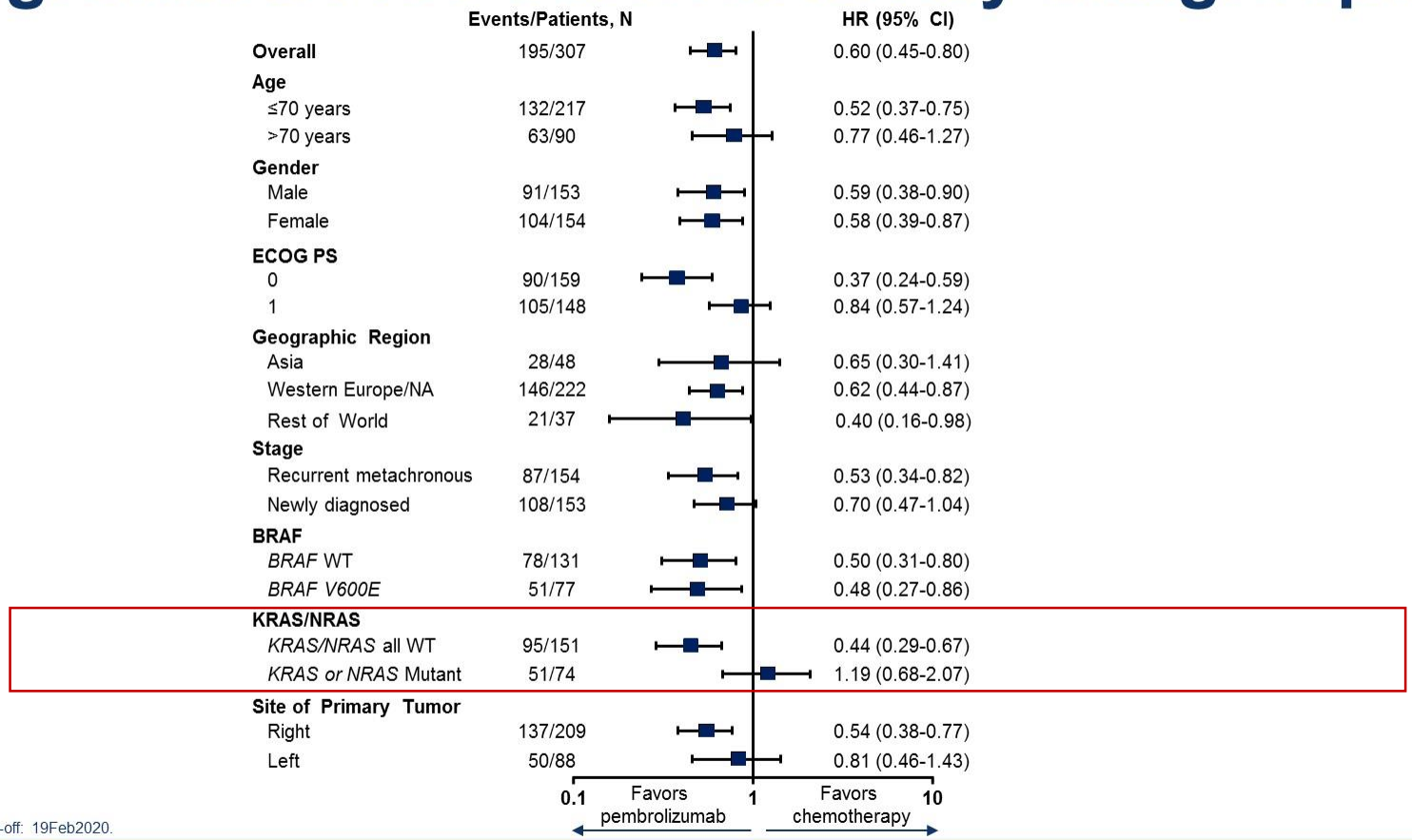
Presented By Thierry Andre at TBD

Duration of Response



Duration of Response assessed per RECIST v1.1 by BICR; Data cut-off: 19Feb2020.

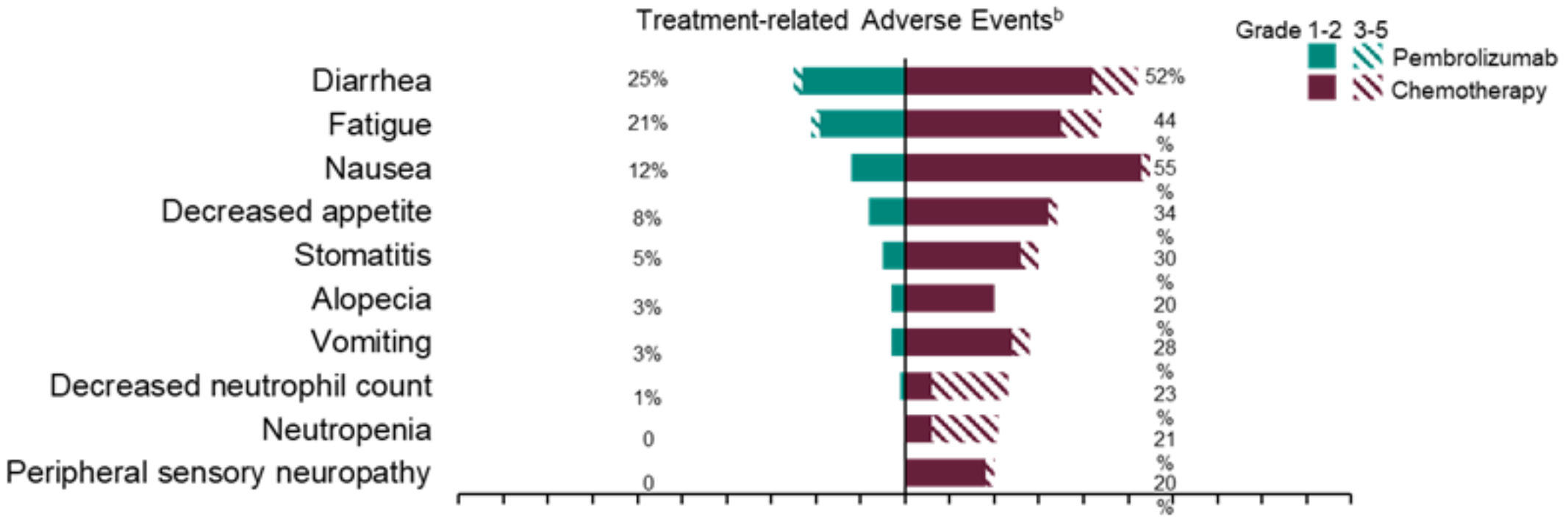
Progression-Free Survival in Key Subgroups



NA, North America; Data cut-off: 19Feb2020.

Adverse Events (AEs) in All Treated Patients

Events	Pembrolizumab N = 153	Chemotherapy N = 143
All AEs	97%	99%
Treatment-related	80%	99%
Grade ≥3	22%	66%
Death	0	1%[a]
Discontinued	10%	6%



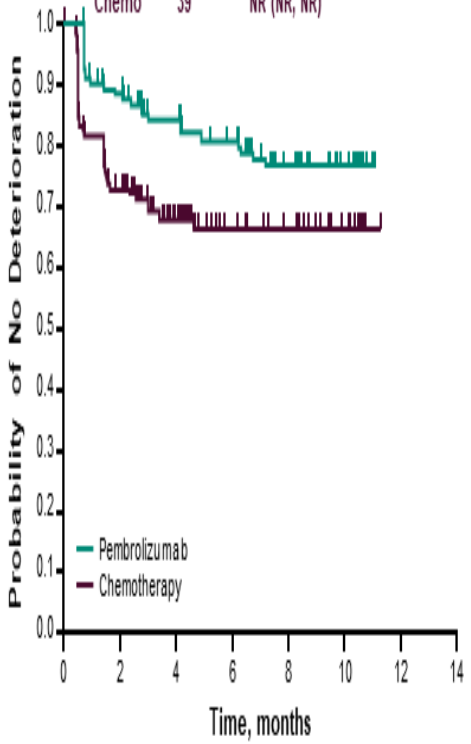
[a]One grade 5 event of intestinal perforation; [b]Incidence ≥20% in any group; Data cut-off: 19Feb2020.

Time to Deterioration

EORTC QLQ-C30 GHS/QoL and Physical Functioning

Social Functioning[a]

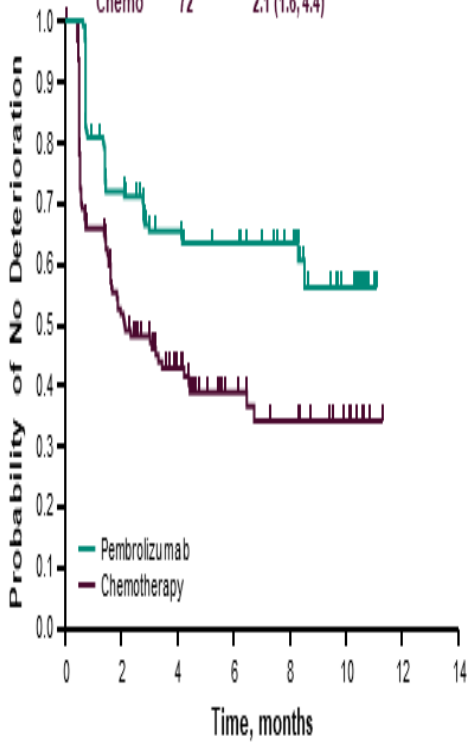
	Events, n	Median (95% CI), mo	HR (95% CI)	*P* Value[b]
Pembro	27	NR (NR, NR)	0.53 (0.32-0.87)	0.0050
Chemo	39	NR (NR, NR)		



No. at risk								
Pembrolizumab	141	108	86	74	58	45	0	0
Chemotherapy	131	83	54	30	24	10	0	0

Fatigue[a]

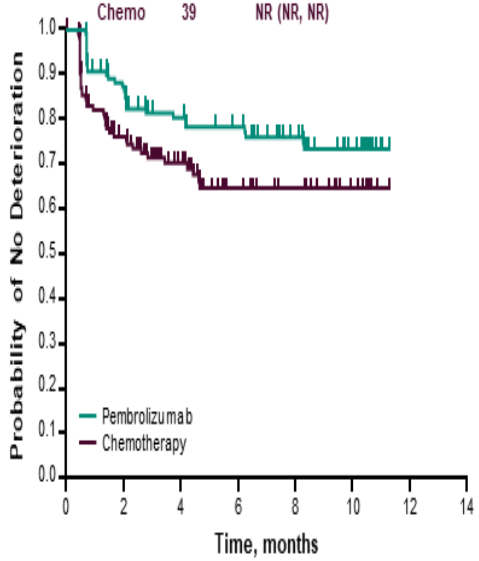
	Events, n	Median (95% CI), mo	HR (95% CI)	*P* Value[b]
Pembro	50	NR (8.5, NR)	0.48 (0.33-0.69)	<0.0001
Chemo	72	2.1 (1.6, 4.4)		



No. at risk								
Pembrolizumab	141	85	65	57	48	31	0	0
Chemotherapy	131	58	35	18	13	7	0	0

GHS/QoL[a]

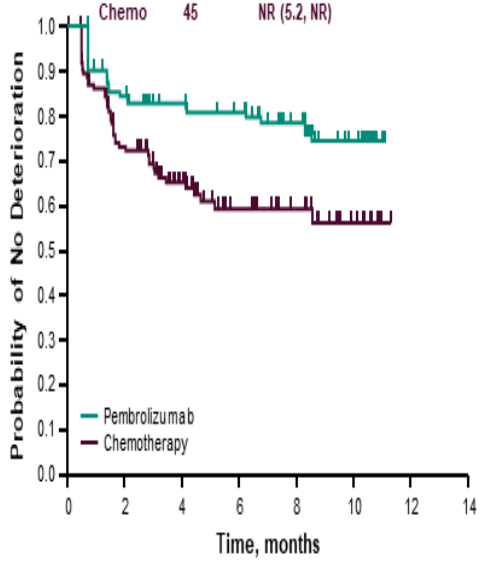
	Events, n	Median (95% CI), mo	HR (95% CI)	*P* Value[b]
Pembro	30	NR (NR, NR)	0.61 (0.38-0.98)	0.0195
Chemo	39	NR (NR, NR)		



No. at risk								
Pembrolizumab	141	104	82	71	58	42	0	0
Chemotherapy	131	85	57	32	25	10	0	0

Physical Functioning[a]

	Events, n	Median (95% CI), mo	HR (95% CI)	*P* Value[b]
Pembro	29	NR (NR, NR)	0.50 (0.32-0.81)	0.0016
Chemo	45	NR (5.2, NR)		

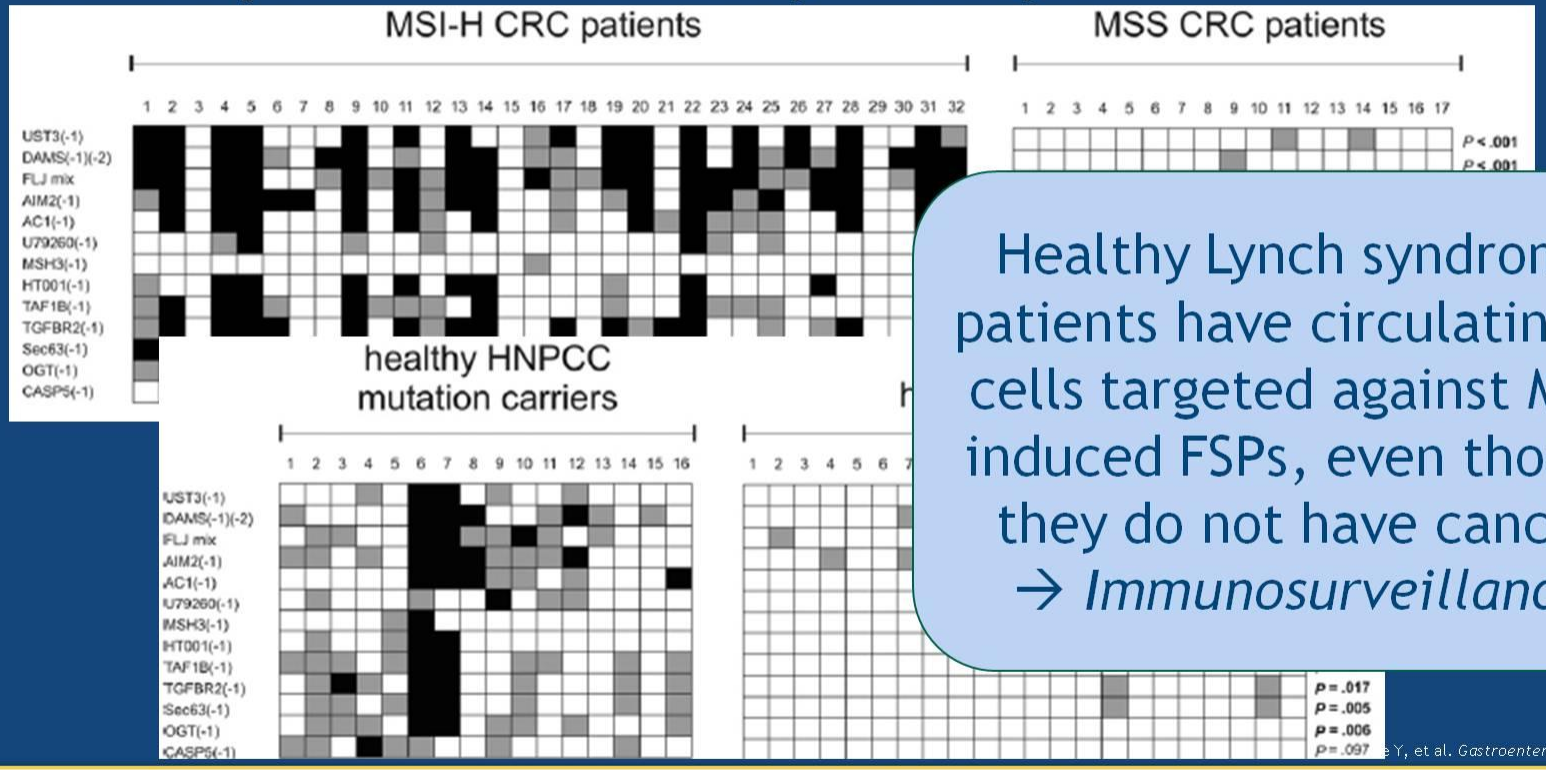


No. at risk								
Pembrolizumab	141	101	84	74	60	43	0	0
Chemotherapy	131	83	54	31	23	10	0	0

[a]Time to deterioration was defined as first onset of a ≥10-point change in score from baseline. [b]*P* values are 1-sided and nominal with no adjustment for multiplicity.

Data cutoff: February 19, 2020.

Immuno*prevention* in Lynch Syndrome?



Healthy Lynch syndrome patients have circulating T-cells targeted against MSI-induced FSPs, even though they do not have cancer
→ *Immunosurveillance*

e Y, et al. *Gastroenterology* 2008;134:988-97.

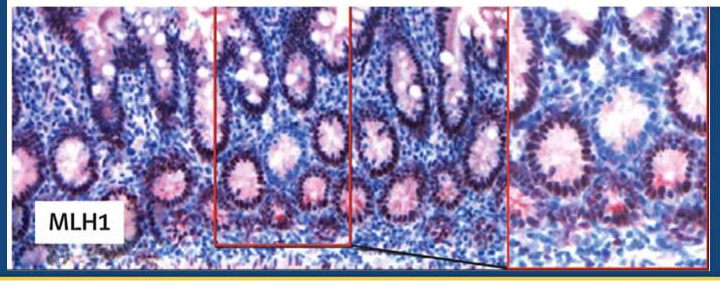
Immuno*surveillance* in Lynch Syndrome

Familial Cancer (2013) 12:307–312
DOI 10.1007/s10689-013-9662-7

ORIGINAL ARTICLE

Towards a vaccine to prevent cancer in Lynch syndrome patients

Magnus von Knebel Doeberitz · Matthias Kloor



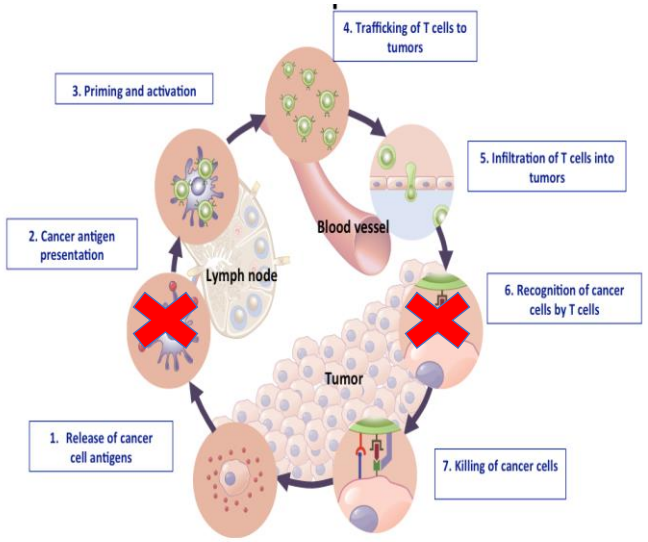
- Source of FSP exposure/immunosurveillance?
- Auto-vaccination against FSPs?

Kloor M, et al. *Lancet Oncol* 2012;13:598-606.

Presented By Matthew Yurgelun at 2018 ASCO Annual Meeting

Immunotherapy in unselected CRC population

Drug	ORR
Ipilimumab	0%
Nivolumab	0%
Pembrolizumab	0%
Atezolizumab	0%



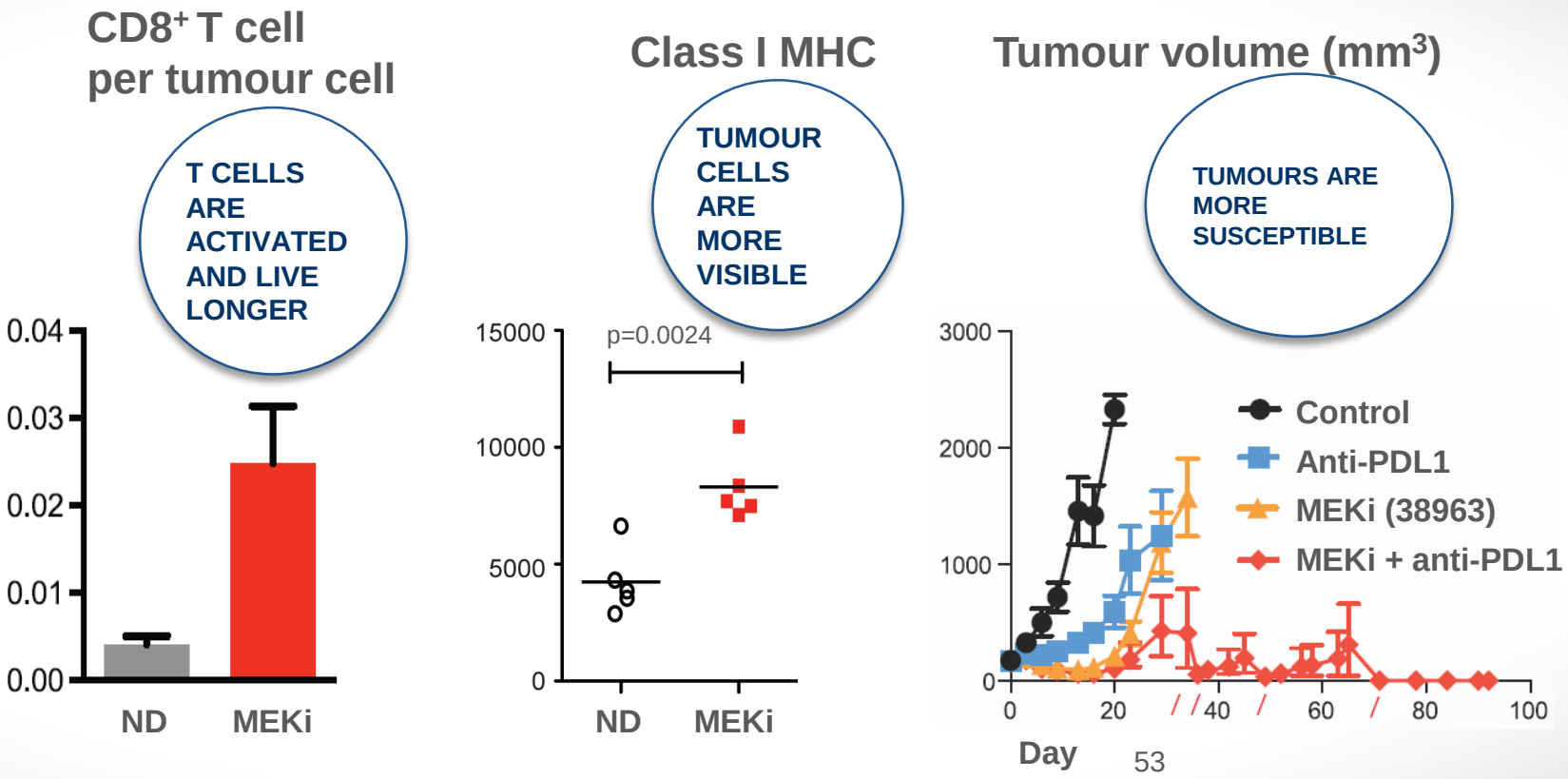
Colorectal tumors have low number of mutations

Colorectal tumor have impaired antigen presentation

Topalian NEJM 2012
Patnaik Clin Can Res 2015
Herbst R ASCO 2013

MEK inhibition has a direct effect on T cells and the tumour microenvironment

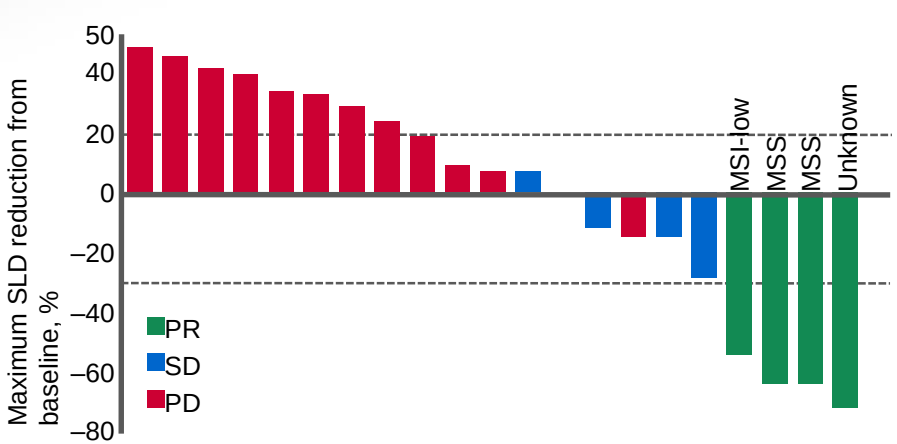
- MEK inhibition alone can result in **intratumoural T cell accumulation** and **MHC Class I upregulation**
- MEK inhibition and anti-PDL1 are synergistic in xenograft models

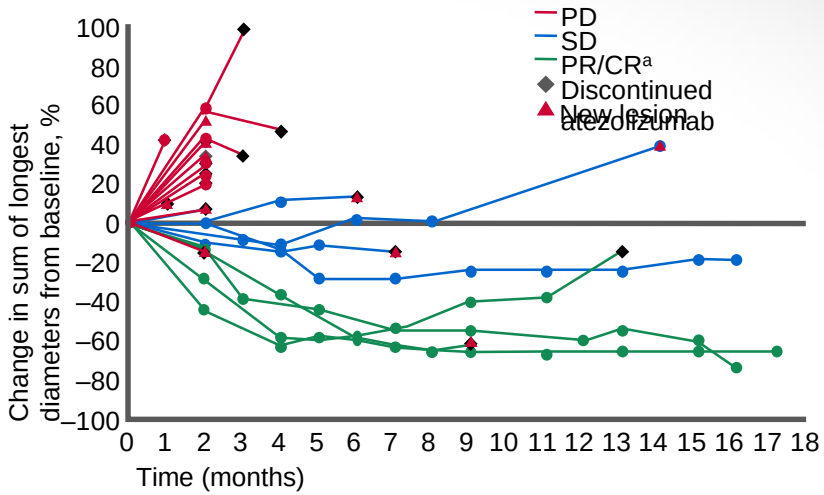


Ebert et al. Immunity 2016

A more favourable tumour microenvironment from MEK inhibition may help to unlock the full anti-tumour potential of PD-L1 inhibition

Cobimetinib + Atezolizumab efficacy: change in tumour burden





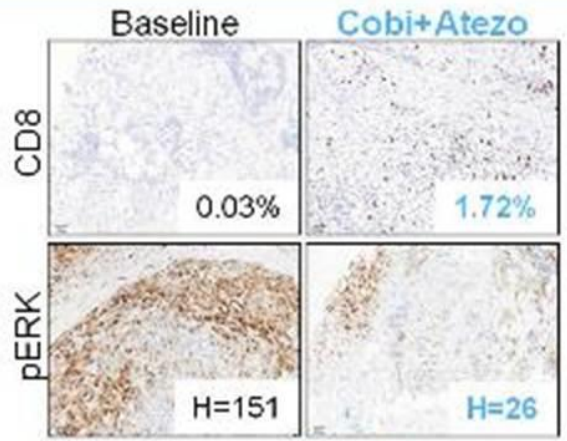
- Four patients had partial responses (confirmed per RECIST v1.1); responses are ongoing in two of these patients
- Median duration of response was not reached (range: 5.4–14.9+ months)
- Tumour volume reduction was not associated with PD-L1 status: TC3 (n=1, PD), TC0 (n=18), NA (n=4)

[a]Confirmed per RECIST v1.1

Bendell et al. ASCO 2016
Desai et al. ESMO 2016

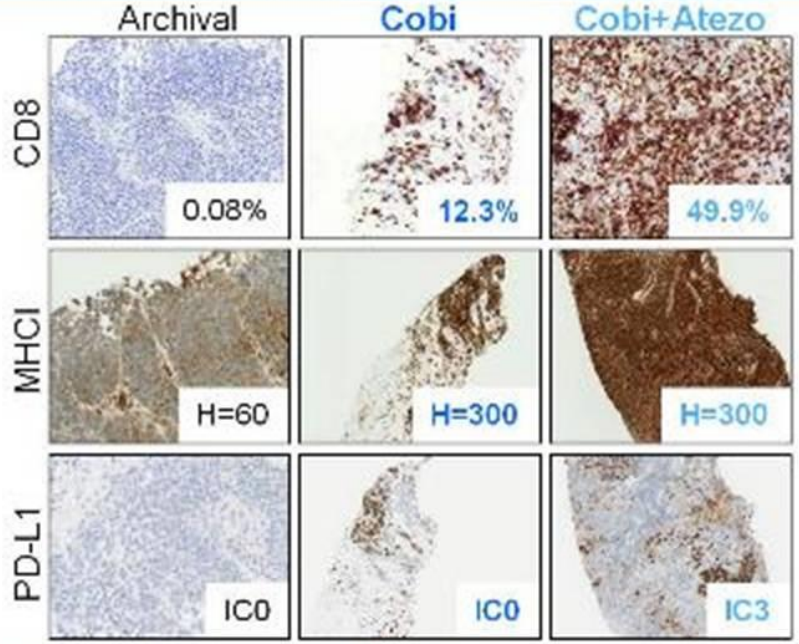
Biomarkers: CD8 T-cell Accumulation and MHC I Expression

KRAS mutant responder[a] (mCRC cohort)



- Increased intratumoral CD8 T-cell infiltration and MHC I expression were observed with cobimetinib alone
- Further enhancement seen with cobimetinib + atezolizumab

Clear cell sarcoma patient[b] (Solid tumors serial biopsy cohort)



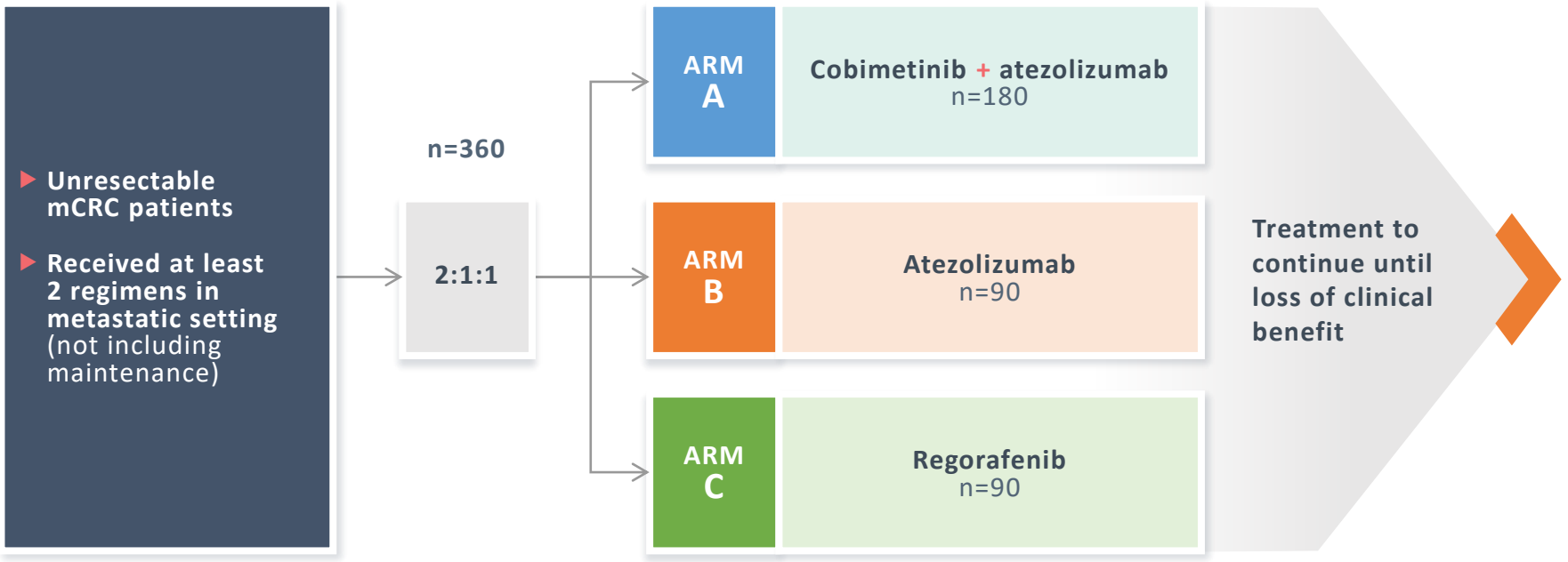
- Similar results were seen in 75% of patients in the biopsy cohort

[a]Sarah Cannon Research Institute/Tennessee Oncology (J. Bendell).
[b]Princess Margaret Cancer Center (J. Levin, L. Siu).

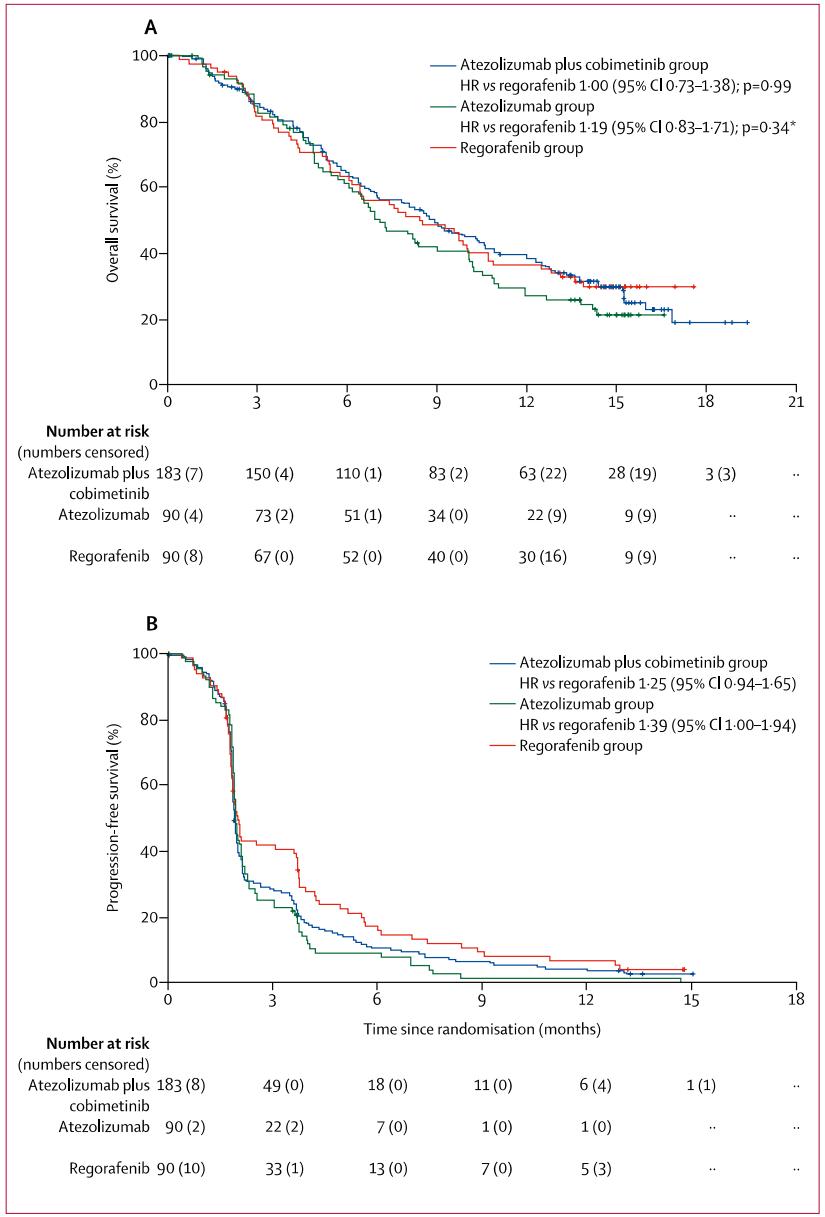
Presented By Johanna Bendell at 2016 ASCO Annual Meeting; Reused with permission

COTEZO (GO30182)

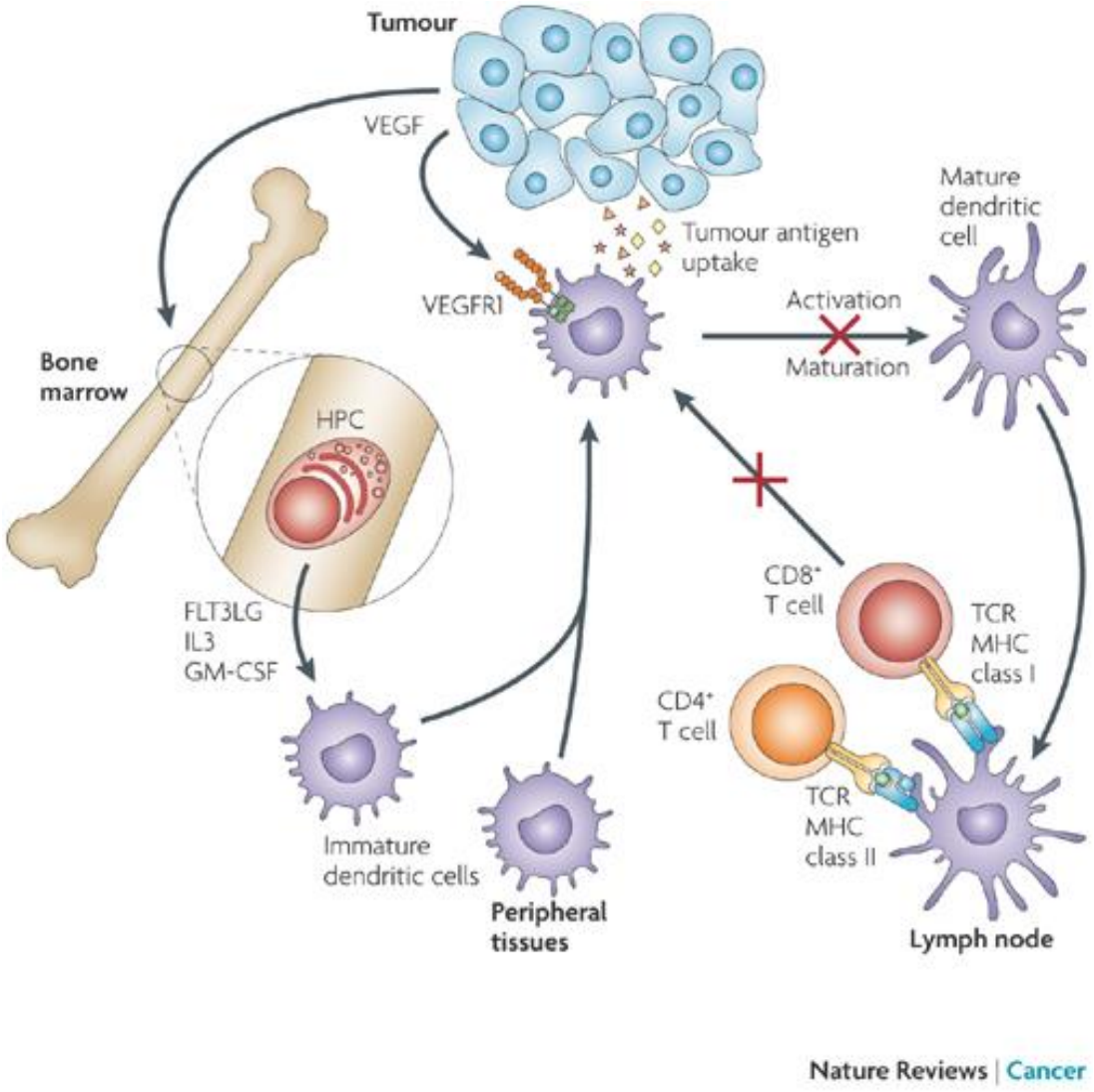
Protocol Design



- 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

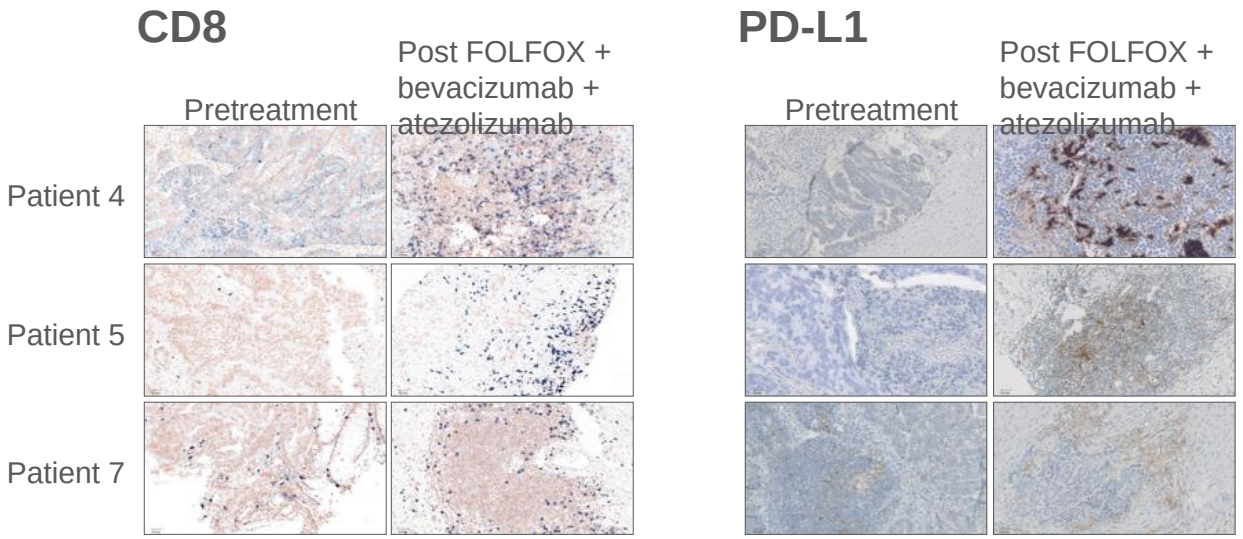

A
Overall survival (%)
Atezolizumab plus cobimetinib group
HR vs regorafenib 1·00 (95% CI 0·73–1·38); p=0·99
Atezolizumab group
HR vs regorafenib 1·19 (95% CI 0·83–1·71); p=0·34*
Regorafenib group
Number at risk
(numbers censored)
Atezolizumab plus cobimetinib 183 (7) 150 (4) 110 (1) 83 (2) 63 (22) 28 (19) 3 (3) ..
Atezolizumab 90 (4) 73 (2) 51 (1) 34 (0) 22 (9) 9 (9) .. ..
Regorafenib 90 (8) 67 (0) 52 (0) 40 (0) 30 (16) 9 (9) .. ..
B
Progression-free survival (%)
Atezolizumab plus cobimetinib group
HR vs regorafenib 1·25 (95% CI 0·94–1·65)
Atezolizumab group
HR vs regorafenib 1·39 (95% CI 1·00–1·94)
Regorafenib group
Time since randomisation (months)
Number at risk
(numbers censored)
Atezolizumab plus cobimetinib 183 (8) 49 (0) 18 (0) 11 (0) 6 (4) 1 (1) ..
Atezolizumab 90 (2) 22 (2) 7 (0) 1 (0) 1 (0) .. ..
Regorafenib 90 (10) 33 (1) 13 (0) 7 (0) 5 (3) .. ..

Tumour-derived VeGF inhibits maturation of dendritic cells (Dcs)



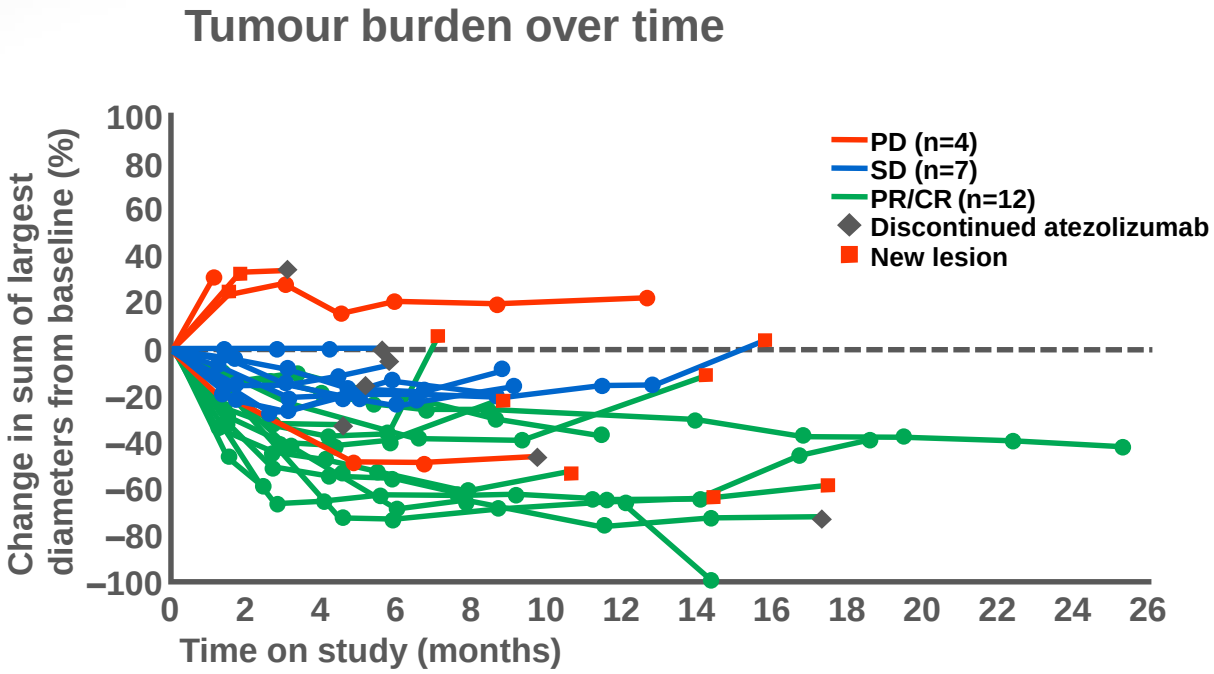
Combined chemotherapy plus Bevacizumab may create a favourable microenvironment for immunotherapy

- Increases in PD-L1 expression on immune cells are observed on-treatment (4/7)
- Baseline PD-L1 levels were not predictive of response



Wallin et al. AACR 2016

Atezolizumab plus Bevacizumab and/or FOLFOX in mCRC: phase Ib

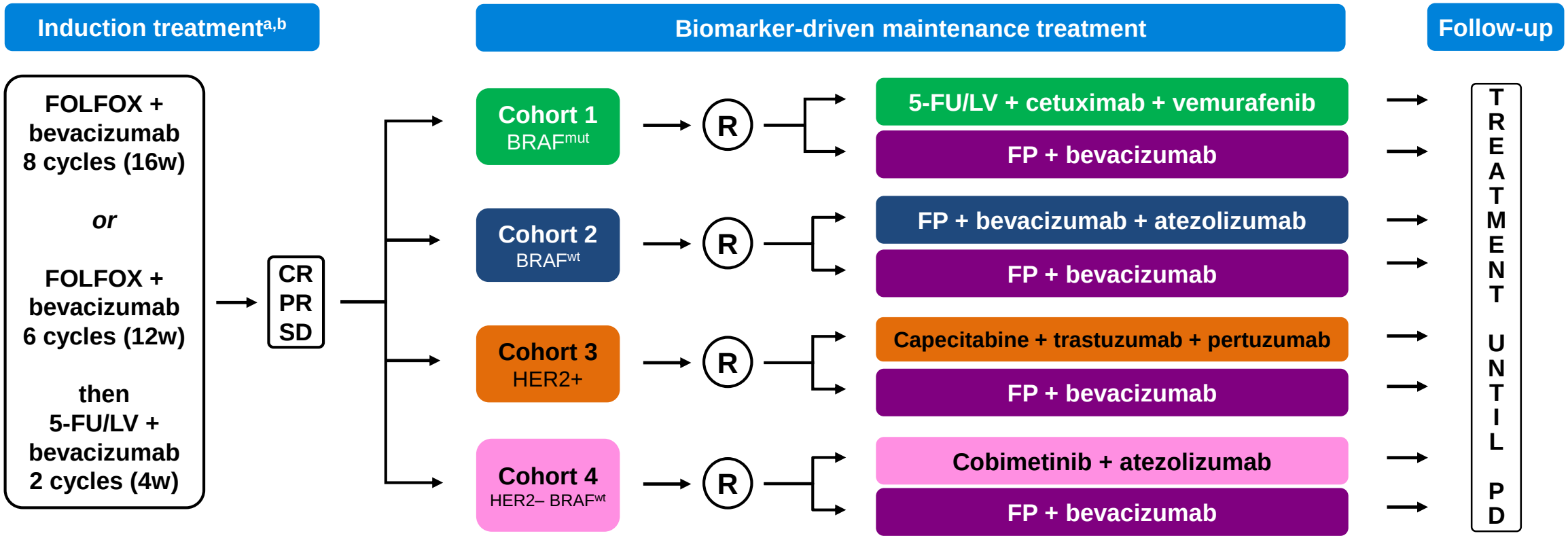


Patient number	ORR	mPFS	DOR
23	52%	14.1 months	11.4 months

- 3/9 patients treated beyond 15 months continue to be on treatment
- No unexpected toxicities were observed

Wallin et al. AACR 2016

MODUL: overall study design



Primary objective: Progression-free survival (PFS; RECIST v1.1) measured from randomization in each maintenance treatment cohort

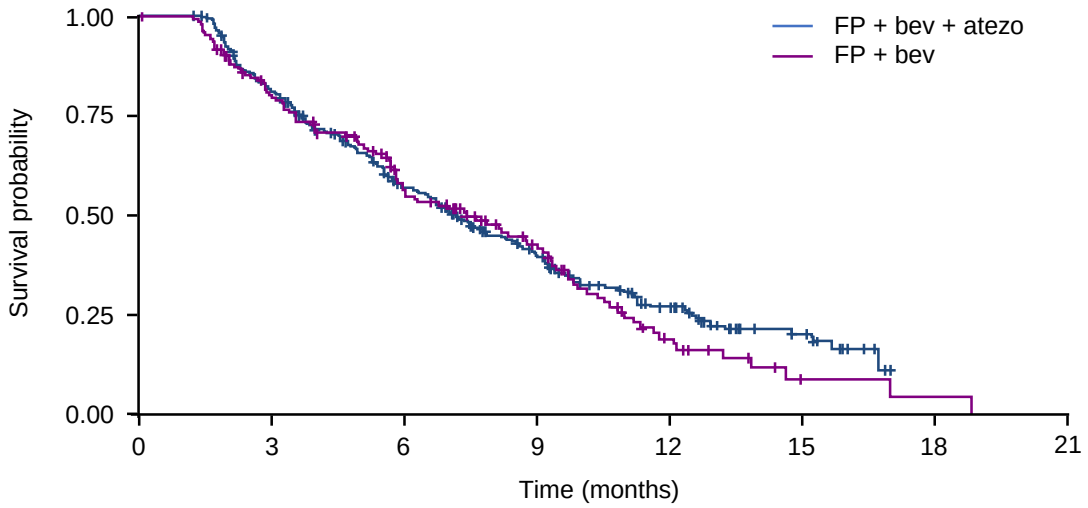
Secondary objectives: Overall survival (OS); overall response rate (ORR); disease control rate (DCR); time to treatment response (TTR); duration of response (DoR); change in ECOG performance status; safety

[a]Key eligibility criteria: histologically confirmed mCRC; measurable, unresectable disease (RECIST 1.1); no prior chemotherapy for mCRC; age ≥18 years; ECOG PS ≤2

[b]Patients with disease progression following Induction treatment can receive further treatment at the discretion of their physician

Primary analysis of PFS: 1L BRAF^{wt} Median follow-up 10.5 months

PFS

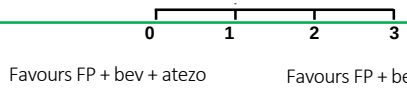


No. at risk								
FP+bev+atezo	297	224	141	83	39	13	0	0
FP+bev	148	109	69	40	13	2	1	0

	FP + bev + atezo	FP + bev
Median PFS, months	7.13	7.39
Stratified HR (95% CI)	0.92 (0.72–1.17) p=0.48	

Subgroup analysis

Subgroup	Level	Hazard ratio (95%CI)
Total	Total (N=445)	0.92 (0.72–1.17)
Age	<65 years (n=254)	0.89 (0.65–1.23)
	≥65 years (n=191)	0.93 (0.64–1.35)
Gender	Male (n=271)	0.77 (0.56–1.04)
	Female (n=174)	1.21 (0.81–1.80)
Region	Europe (n=398)	0.92 (0.71–1.19)
	ROW (n=47)	0.81 (0.38–1.76)
Tumour response at end of ITP	CR/PR (n=275)	0.76 (0.55–1.05)
	SD (n=169)	1.23 (0.85–1.79)
Baseline ECOG status	0 (n=266)	0.74 (0.54–1.01)
	1/2 (n=179)	1.25 (0.85–1.84)
AJCC/UICC stage at diagnosis	Stage I/II/III (n=117)	1.23 (0.75–2.01)
	Stage IV (n=325)	0.83 (0.63–1.11)
Prior systematic adjuvant therapy	Yes (n=60)	1.41 (0.71–2.80)
	No (n=383)	0.85 (0.65–1.10)
No. of metastatic sites at baseline	<2 (n=203)	0.98 (0.68–1.41)
	≥2 (n=242)	0.88 (0.63–1.22)
Liver metastatic sites at baseline	Yes (n=345)	0.91 (0.69–1.20)
	No (n=100)	0.87 (0.52–1.45)
Cancer type	Colon (n=269)	0.91 (0.66–1.26)
	Rectal (n=125)	1.09 (0.70–1.69)
Tumour colon location	Right (n=81)	0.92 (0.51–1.66)
	Left (n=313)	0.97 (0.73–1.30)
Initial diagnosis	Synchronous (n=336)	0.79 (0.60–1.05)
	Metachronous (n=100)	1.57 (0.90–2.74)

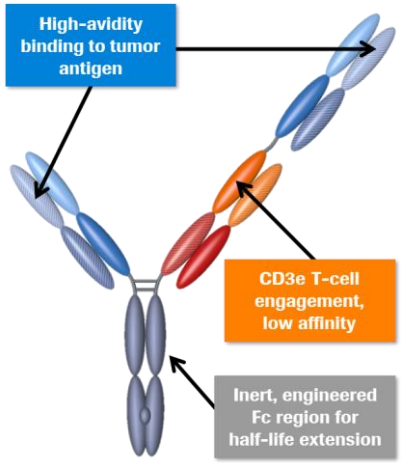


Median duration of induction treatment phase: 4.1 months

One MSI patient in the FP + bev + atezo arm had a complete response during the maintenance treatment phase

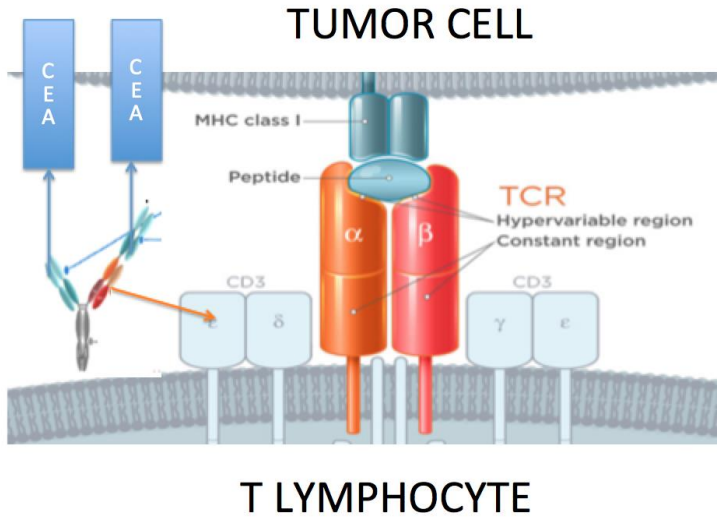
CEA-TCB is the first T-cell bispecific antibody with a novel 2-to-1 format, optimized for efficacy and safety

CEA-TCB structure



- Binds simultaneously with 1 arm to CD3 on T cells and with 2 arms to CEA on tumor cells
- Flexible 2-to-1 format enables high-avidity binding and selective killing of high CEA-expressing tumor cells
- Longer half-life compared with other TCB formats
- Silent Fc results in reduced risk of FcγR-related cytokine release/IRRs

Direct T-cell activation skipping antigen recognition upon binding to CEA protein.

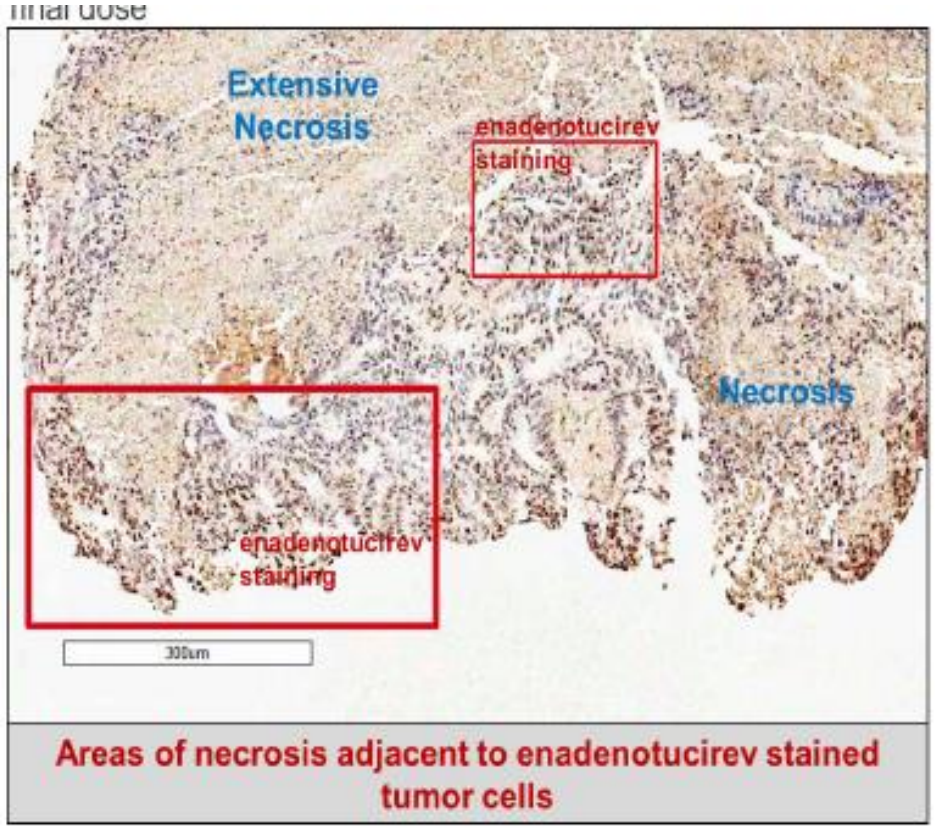


- Simultaneous binding of TCB to tumor (CEA) and T cells (CD3)
- Killing of tumor cells independent of pre-existing immunity
- T-cell proliferation at site of activation

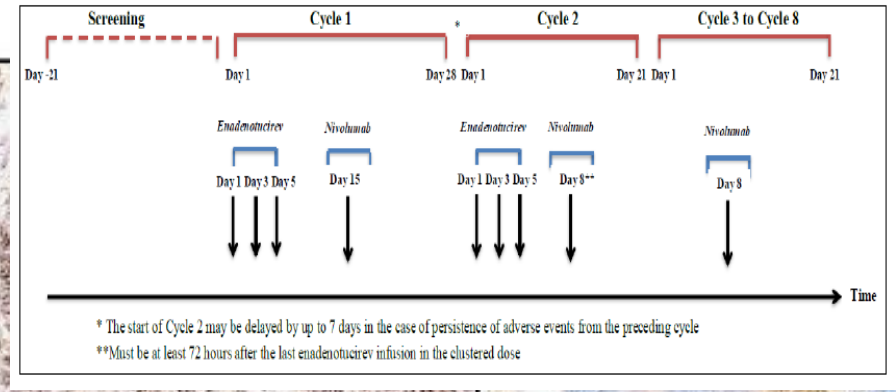
Fab, fragment antigen-binding region; IRR, infusion-related reaction. 1. Bacac M, et al. *Clin Cancer Res*. 2016; 2. Bacac M, et al. *OncoImmunology.* 2016; 3. Figure (right) adapted from: Green J, Ariyan C. *The Scientist*, April 2014.

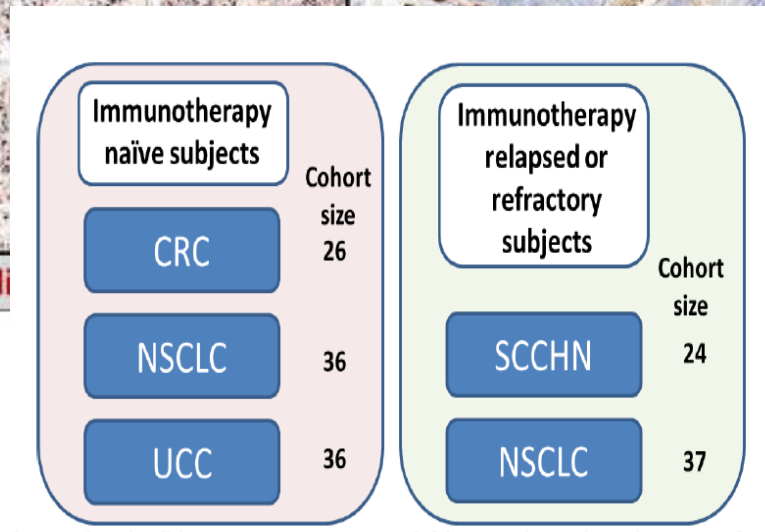
A phase I study of enadenotucirev, an oncolytic Ad11/Ad3 chimeric group B adenovirus, in combination with nivolumab in tumors of epithelial origin.

Wael Harb[1], Lee Rosen[2], Ding Wang[3], Marwan Fakih[4], Daruka Mahadevan[5], Wendy Clemens[6], Giovanni Selvaggi[6], Suzanne Bosque[7], Richard Brown[7], Simon Alvis[7], Brian Champion[7], Hilary McElwaine-Johnn[7]



Areas of necrosis adjacent to enadenotucirev stained tumor cells





Would you swipe your own credit card?

VOLUME 24 · NUMBER 22 · AUGUST 1 2006

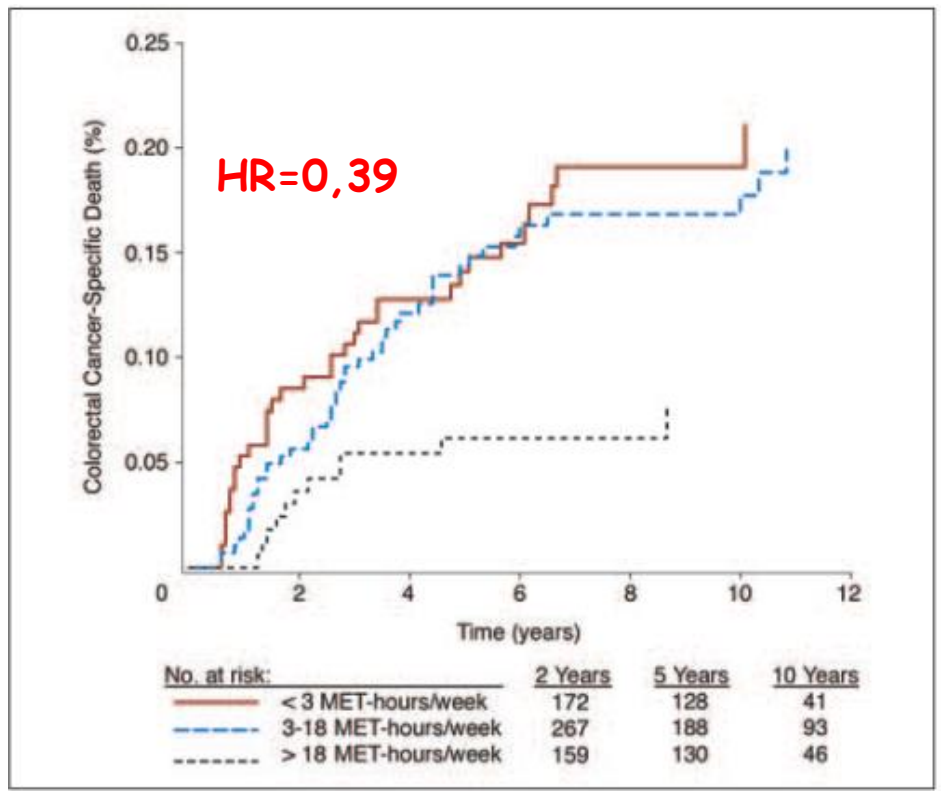
JOURNAL OF CLINICAL ONCOLOGY

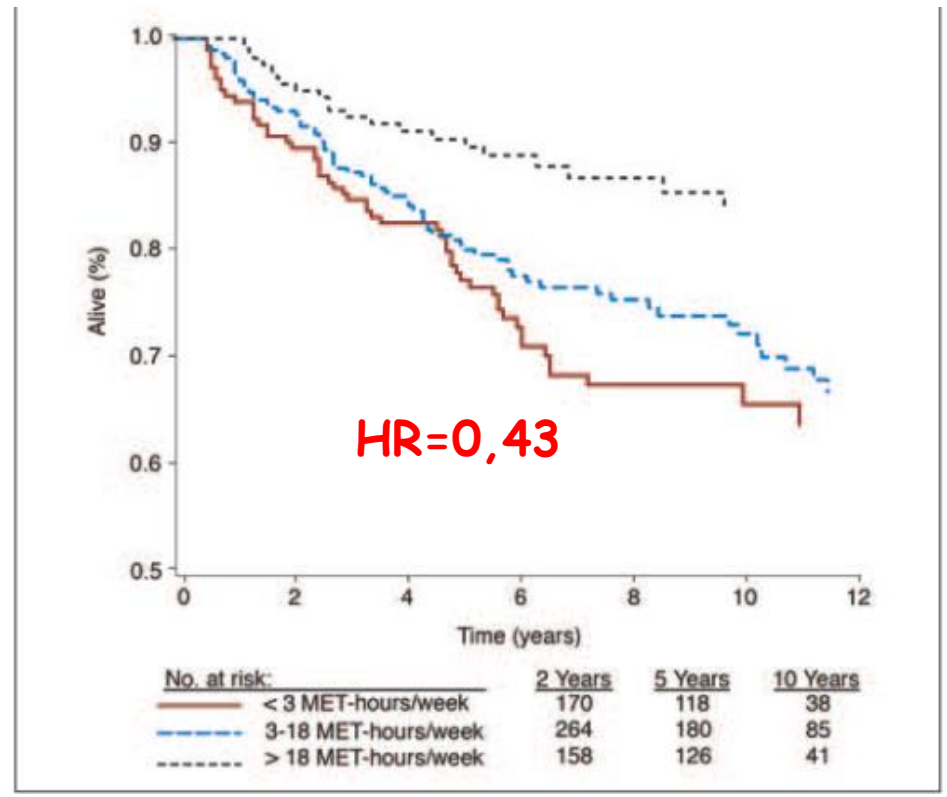
ORIGINAL REPORT

Physical Activity and Survival After Colorectal Cancer Diagnosis

Jeffrey A. Meyerhardt, Edward L. Giovannucci, Michelle D. Holmes, Andrew T. Chan, Jennifer A. Chan, Graham A. Colditz, and Charles S. Fuchs

Harvard, NCI





573 women stage I to III colorectal ca

National Comprehensive Cancer Network®

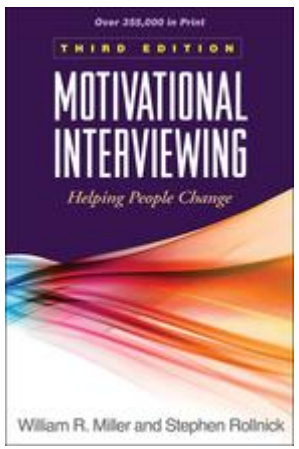
NCCN Guidelines Version 2.2018
Physical Activity

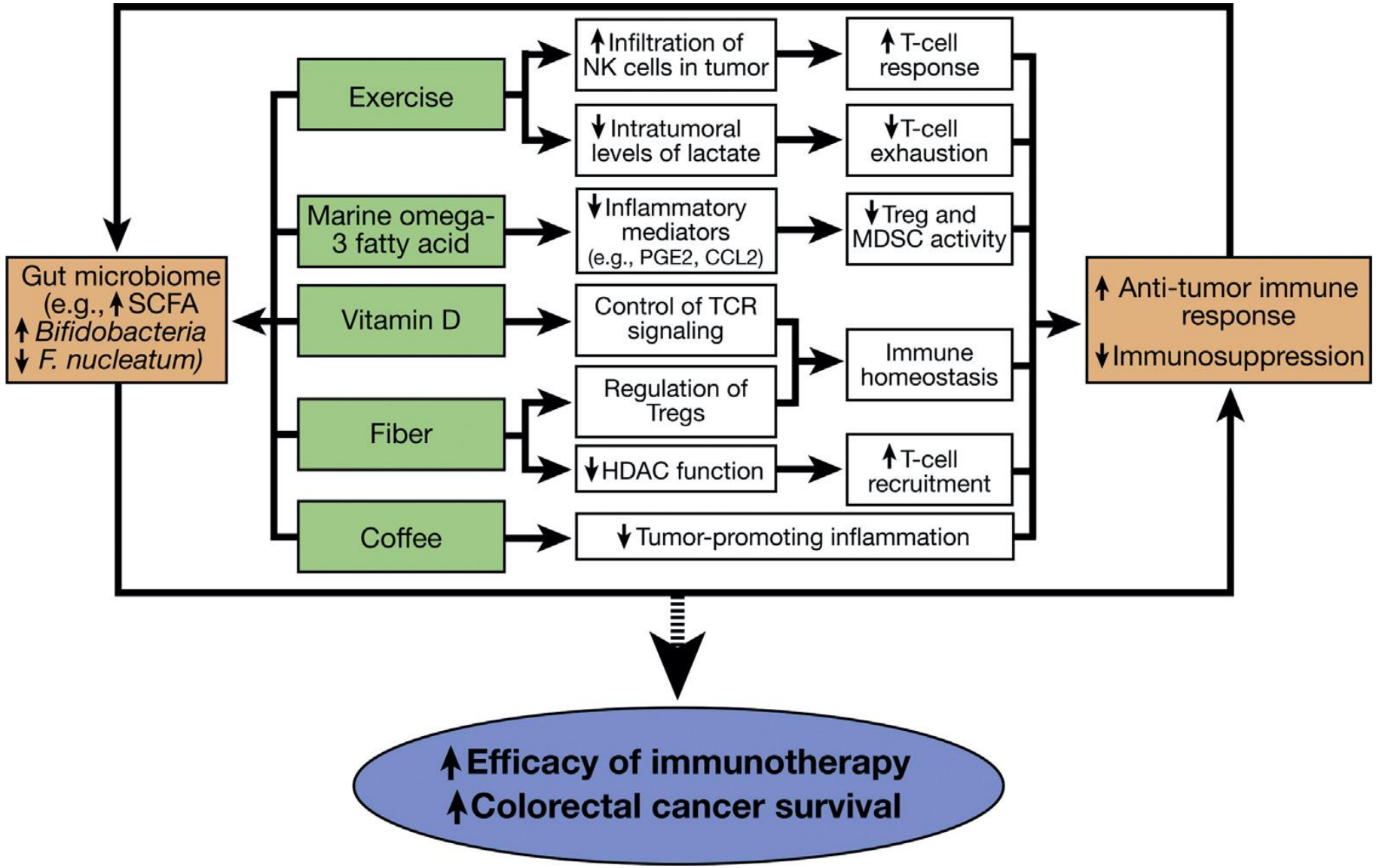
NCCN Guidelines Index
Table of Contents
Discussion

EXAMPLES OF PHYSICAL ACTIVITY		
Light Exercise[1] (No noticeable change in breathing pattern) • Leisurely biking at 5 miles/hour or less • Activity-promoting video game • Light housework (light sweeping, dusting) • Bowling • Playing catch • Slow walking • Child care • Yoga • Tai chi	**Moderate Exercise**[2] (Can talk, but not sing) • Ballroom/line dancing • Biking on level ground or with few hills • General gardening • Baseball, softball, volleyball • Doubles tennis • Using a manual wheelchair • Brisk walking • Water aerobics • Yoga	**Vigorous Exercise**[2] (Can say a few words without stopping to catch a breath) • Aerobic/Fast dancing • Biking faster than 10 miles/hour • Heavy gardening • Hiking uphill • Jumping rope • Martial arts • Race walking, jogging, running • Running sports (basketball, hockey, soccer) • Swimming (fast pace or laps) • Singles tennis • Stair climbing • High-intensity yoga

Motivational Interviewing:
Preparing People to Change Addictive Behavior

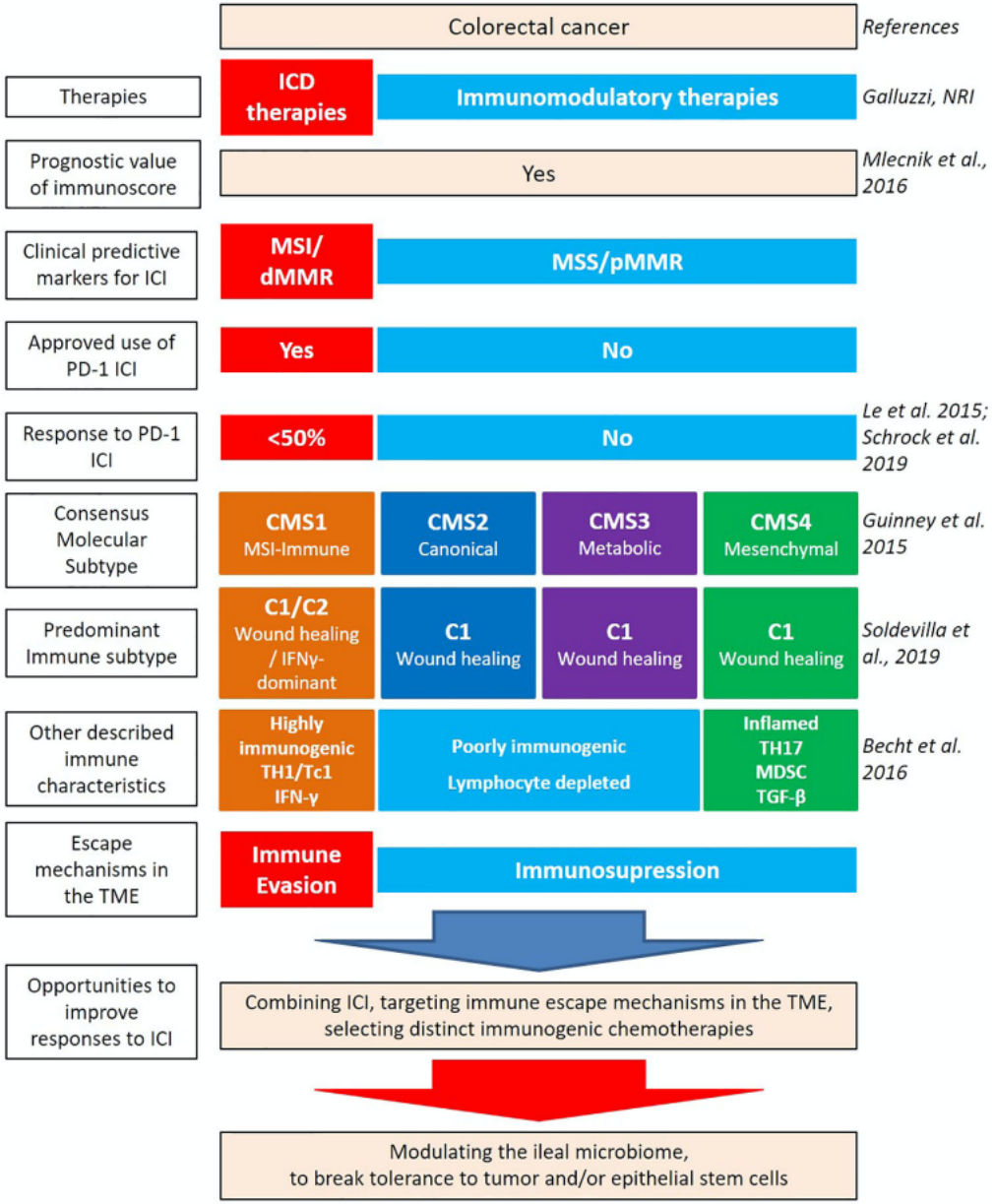
STRATEGIES TO INCREASE PHYSICAL ACTIVITY
• Physician and/or fitness expert recommendation
• Supervised exercise program or classes
• Telephone counseling
• Motivational interviewing[3]
• Evaluate readiness to change, importance of change, self-efficacy
• Cancer survivor-specific print materials (See SURV-B 2 of 2)
• Set short- and long-term goals
• Consider use of pedometer or wearable fitness tracker to monitor activity goals (eg, obtain 10,000 steps per day)
• Encourage social support (exercise buddy, group)





Gastroenterology 2018;155:596–600

CC clasification based on heterogeneity



TAKE HOME MESSAGES:

- Immunotherapy is the new standard of care for the 5% of MSI-H mCRC
- Immunoscore is a strong prognostic biomarkers and could be used for risk stratification in stage II and III Colon Cancer
- The complex interplay between the epithelial barrier, its microbial ecosystem, and the local immune system are key element in understanding of CC immunobiology

thebmj

RAPID RECOMMENDATIONS

Colorectal cancer screening with faecal immunochemical testing, sigmoidoscopy or colonoscopy: a clinical practice guideline

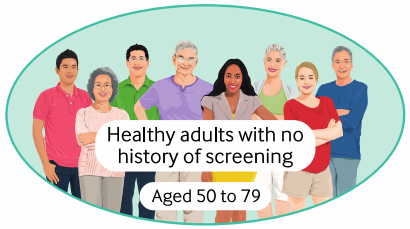
Lise M Helsingen,[1 2 3] Per Olav Vandvik,[4 5] Henriette C Jodal,[1 2 3] Thomas Agoritsas,[6 7] Lyubov Lytvyn,[7] Joseph C Anderson,[8 9 10] Reto Auer,[11 12] Silje Bjerkelund Murphy,[13] Majid Abdulrahman Almadi,[14 15] Douglas A Corley,[16 17] Casey Quinlan,[18 19 20] Jonathan M Fuchs,[21] Annette McKinnon,[22] Amir Qaseem,[23] Anja Fog Heen,[24] Reed A C Siemieniuk,[7] Mette Kalager,[1 2 3] Juliet A Usher-Smith,[25] Iris Lansdorp-Vogelaar,[26] Michael Bretthauer,[1 2 3] Gordon Guyatt[7]

cost per year of survival gain

- CRC screening : $6600
- Mamography: $22000
- Test Pap: $250000

Visual summary of recommendation (1 of 5)

Population



Estimating risk

Understanding a person's risk of cancer can help to determine the benefits and harms of different screening tests for their individual situation.

We suggest using a tool such as the QCancer® calculator to estimate the risk of colorectal cancer for each person in the next 15 years. This calculates risk, based on:

Age | Sex | Ethnicity | BMI | Smoking status | Medical and family history

Link to QCancer® calculator qcancer.org/15yr/colorectal/

Interventions compared

No screening	FIT Every year	FIT Every two years	Sigmoidoscopy Single	Colonoscopy Single
	Faecal testing with a faecal immunochemical test (FIT) every year	Faecal testing with a faecal immunochemical test (FIT) every two years	Endoscopic examination of only the lower part of the colon	Endoscopic examination of the entire colon

Colonoscopy offered if FIT or sigmoidoscopy positive

Recommendations

Favours no screening — Strong — Weak | Weak — Strong — Favours screening

People with an estimated 15 year risk of colorectal cancer **below** 3%

We suggest no screening

Favours no screening — Strong — Weak | Weak — Strong — Favours screening

People with an estimated 15 year risk of colorectal cancer **above** 3%

We suggest screening with one of the four screening options