Immunotherapy for MSI-H cancers and Hepatocellular Carcinoma

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Disclosures

- No disclosures

Outline

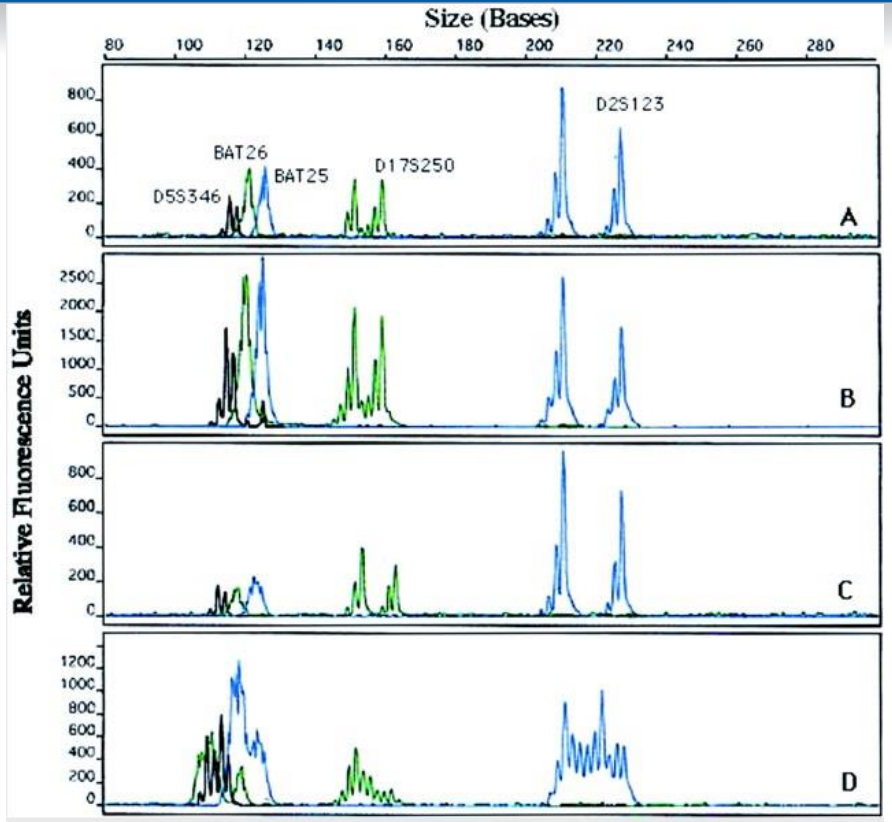
- Immunotherapy for mismatch repair (MMR) deficient cancers
- Immunotherapy for hepatocellular carcinoma (HCC)

IMMUNOTHERAPY FOR MMR DEFICIENT CANCERS

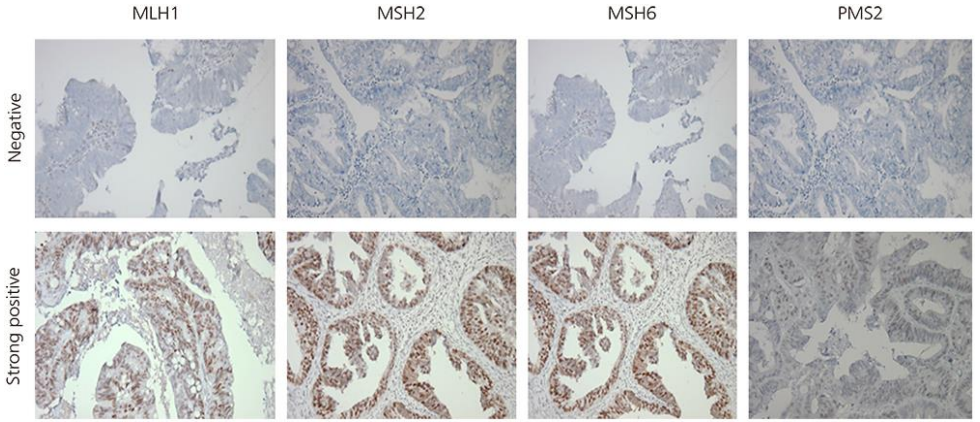
Definition

- Microsatellite (MS) instability: expansion or reduction in the length of repetitive DNA sequences compared to normal DNA (PCR)
  - Bethesda Panel: 2 mono- (BAT25 and BAT26) and 3 dinucleotide (D2S123, D5S346 and D17S250) markers
  - MS-high: Instability in 2 or more out of 5 MS loci
  - MS-low: Instability in 1 out of 5 MS loci
  - MS-stable: No instability detected
- Loss of MLH1, MSH2, MSH6 or PMS2 (IHC)

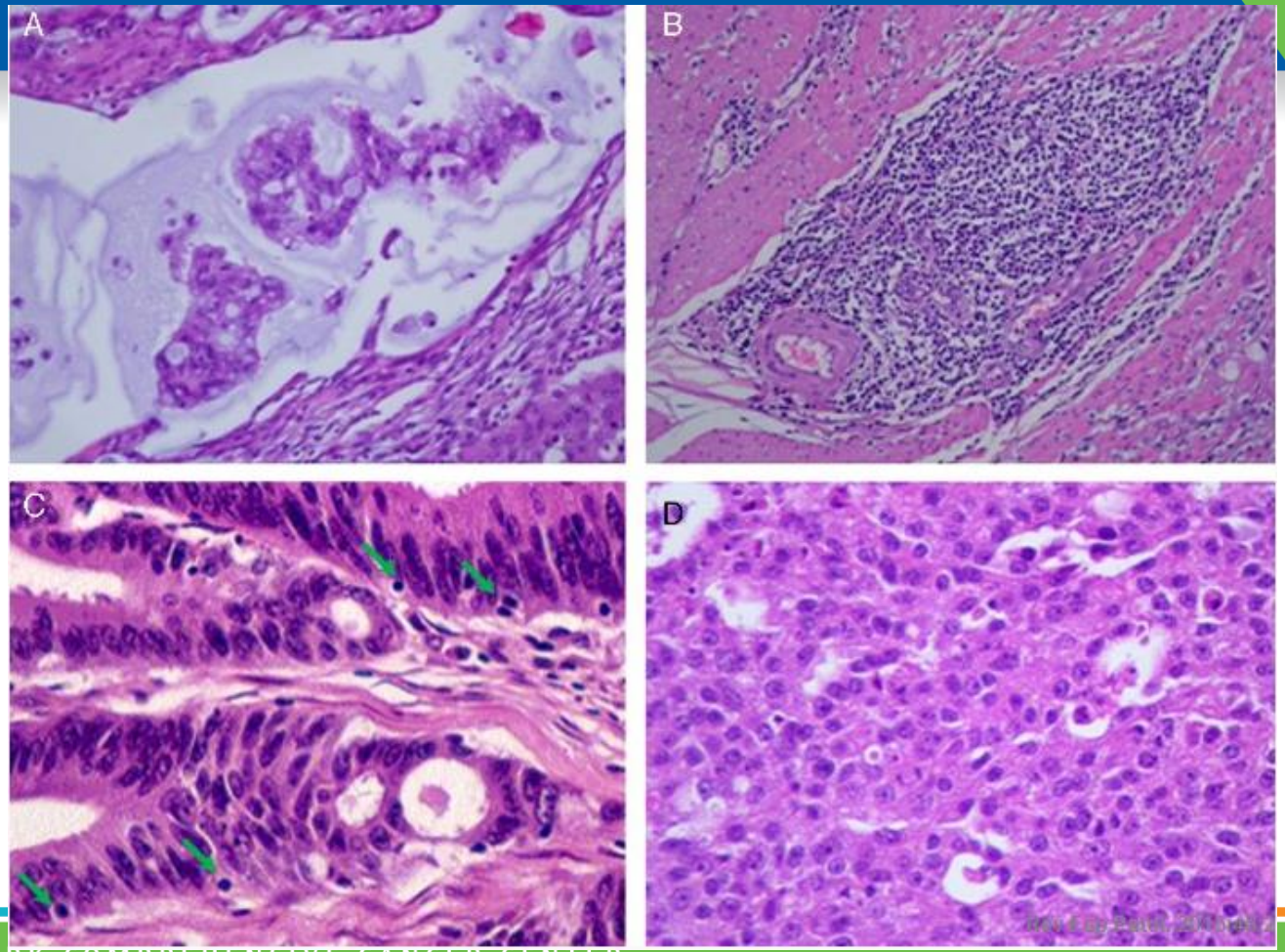
MSI-H = MMR-D



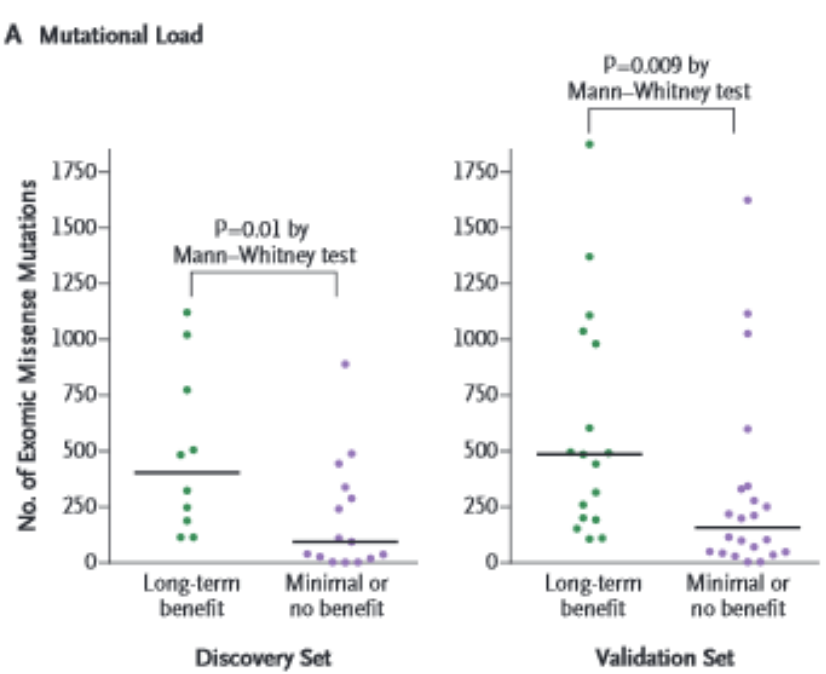
High concordance, 5-10% of MSI-H may retain antigenicity for MMR protein. IHC will not detect other genes associated with MSI i.e. *POLE*

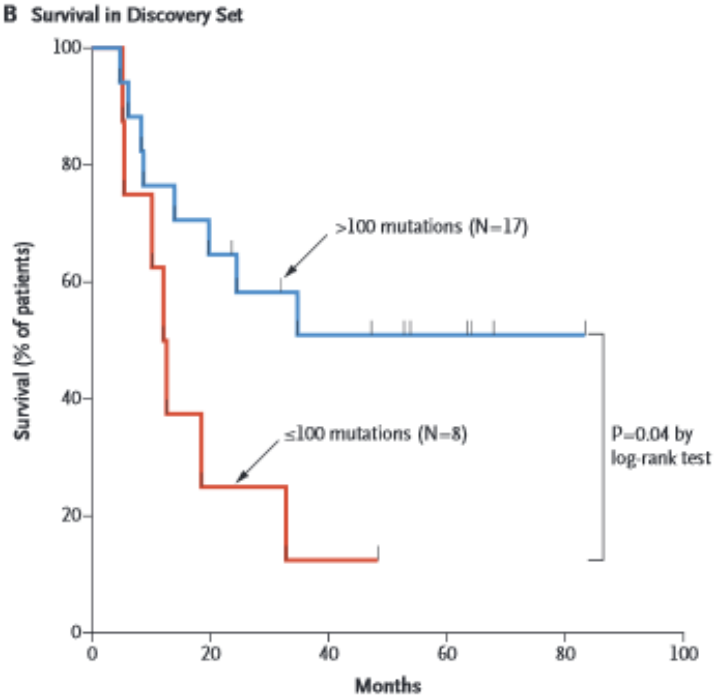


NGS? High concordance rate with PCR (>95%) but MLH1 hypermethylation might be missed if the assay tests only for MMR genes and not for multiple MS foci


A
B
C
D

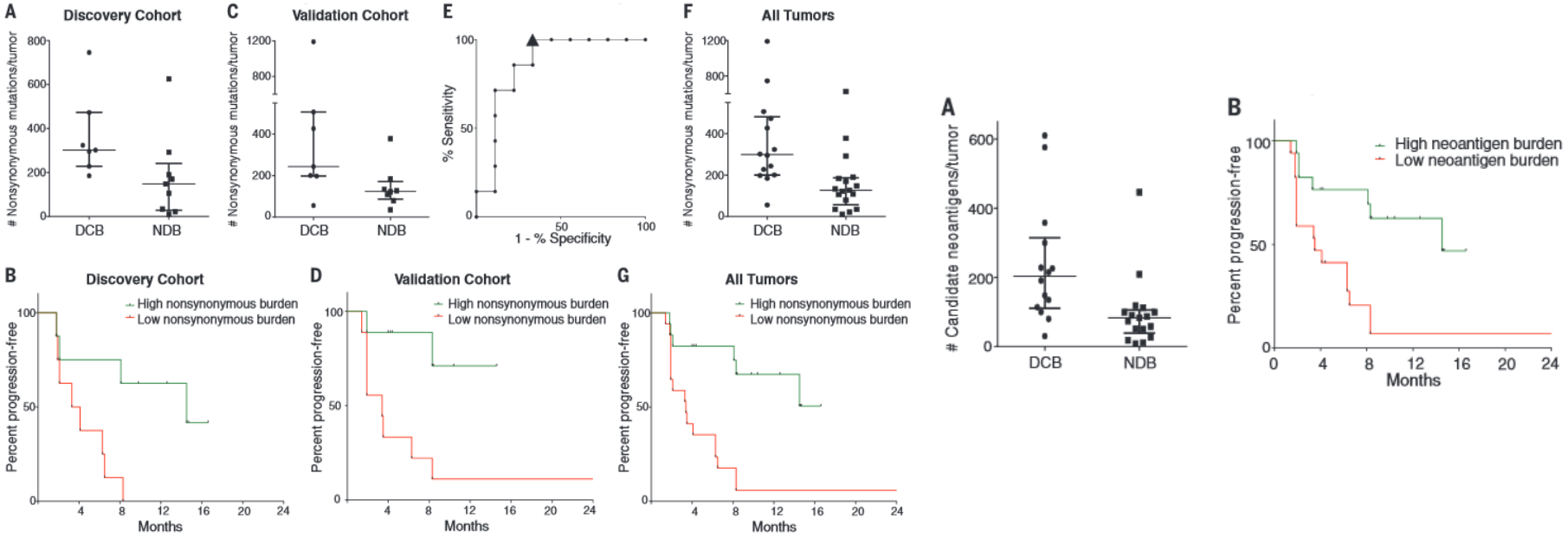
Ipilimumab and Mutation Burden in Melanoma





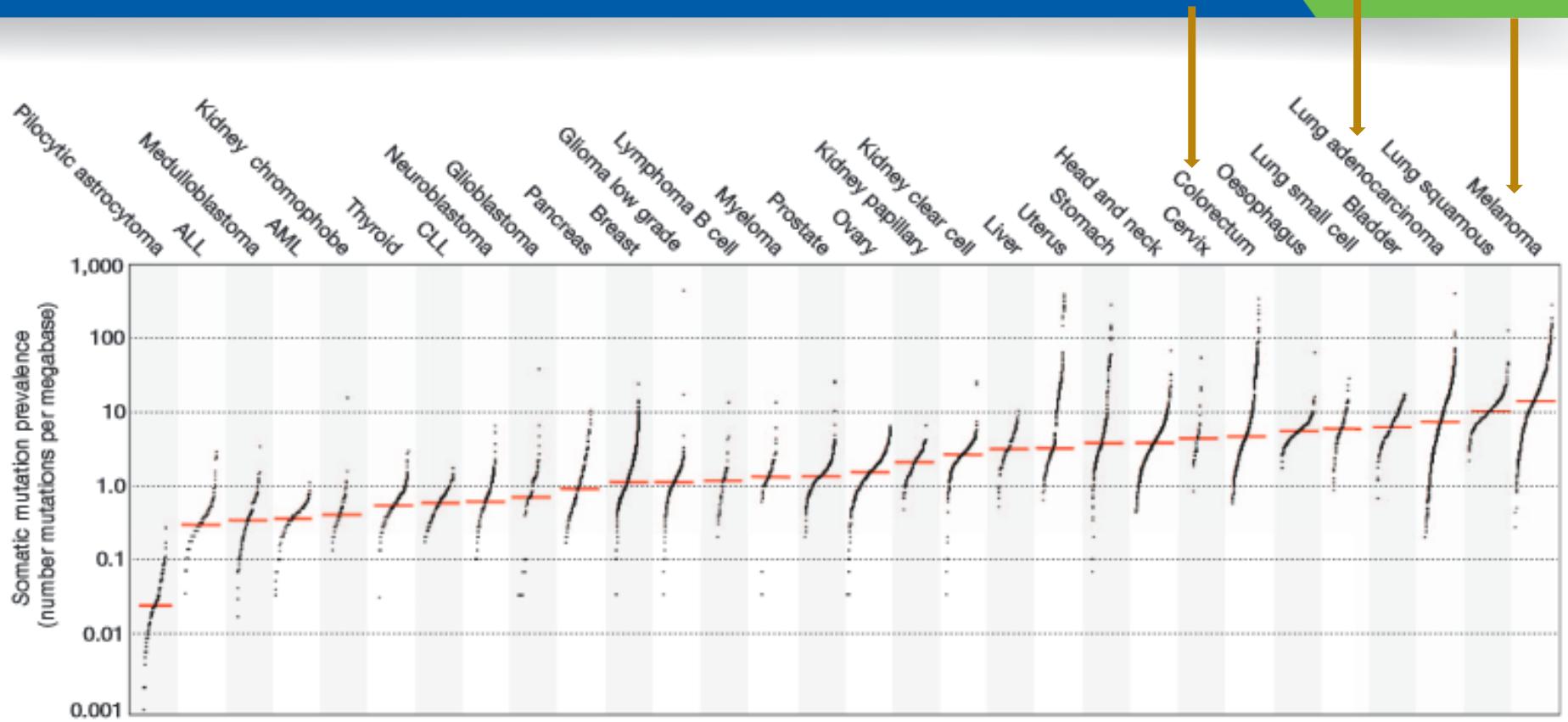
Snyder et al, NEJM 2014

Nivolumab and Mutation Burden in NSCLC



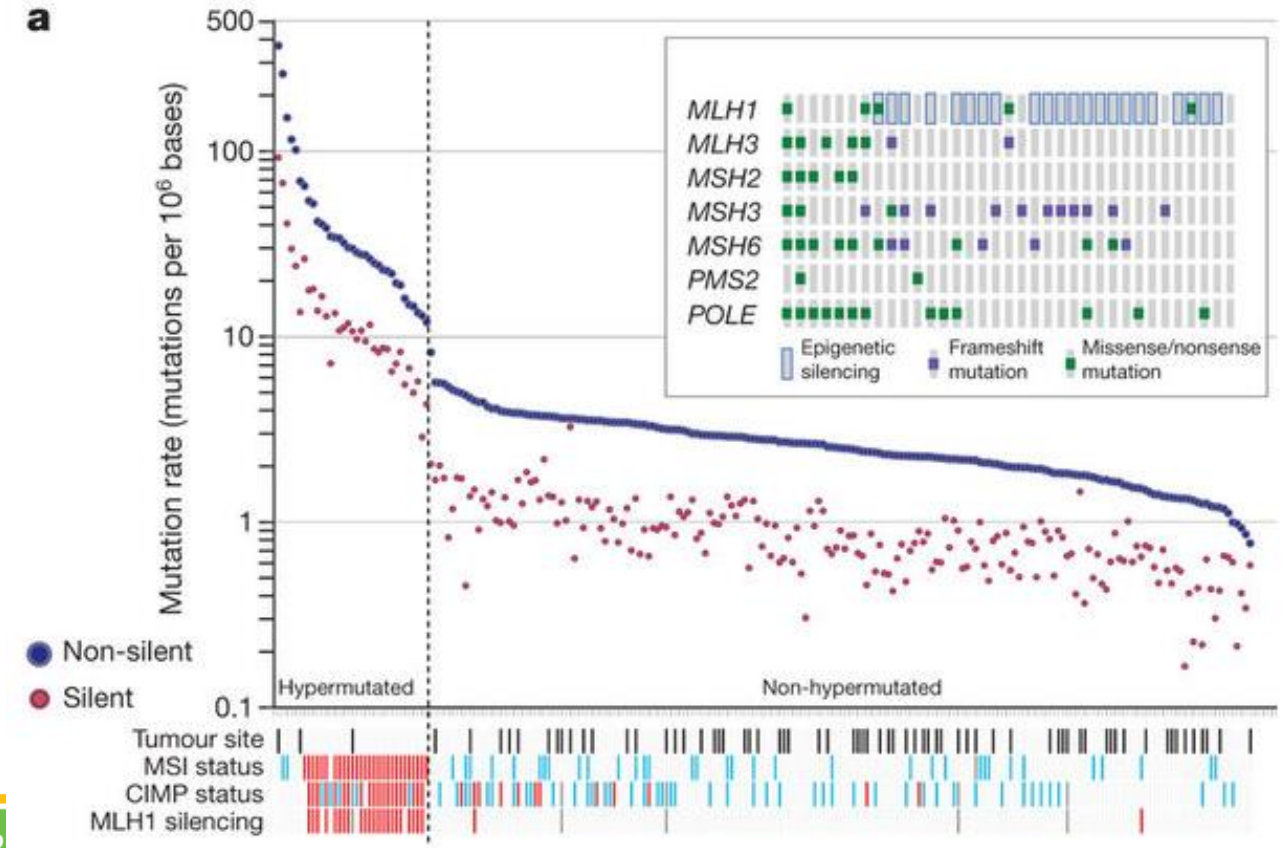
Rizni et al, Science 2015

Mutational Burden of Cancer



Nature 2013 (doi:10.1038/nature12477)

Mutational Landscape in MMR-D

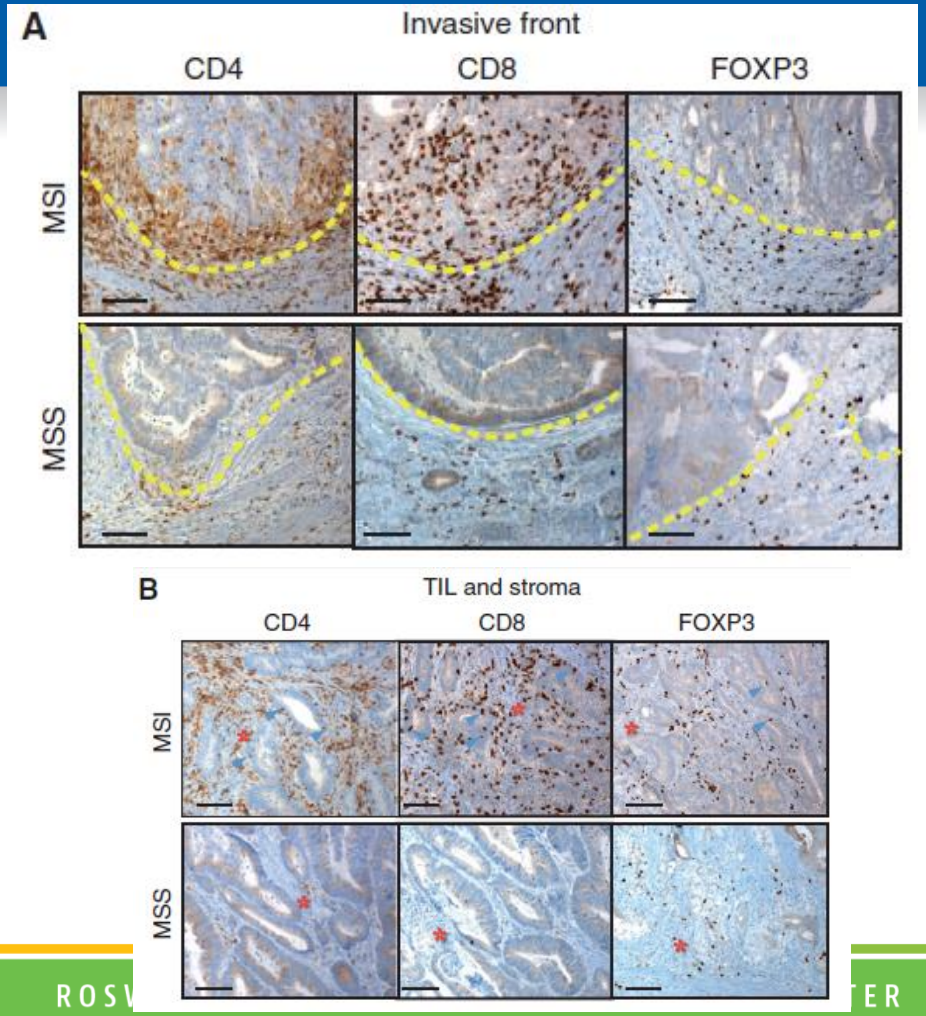


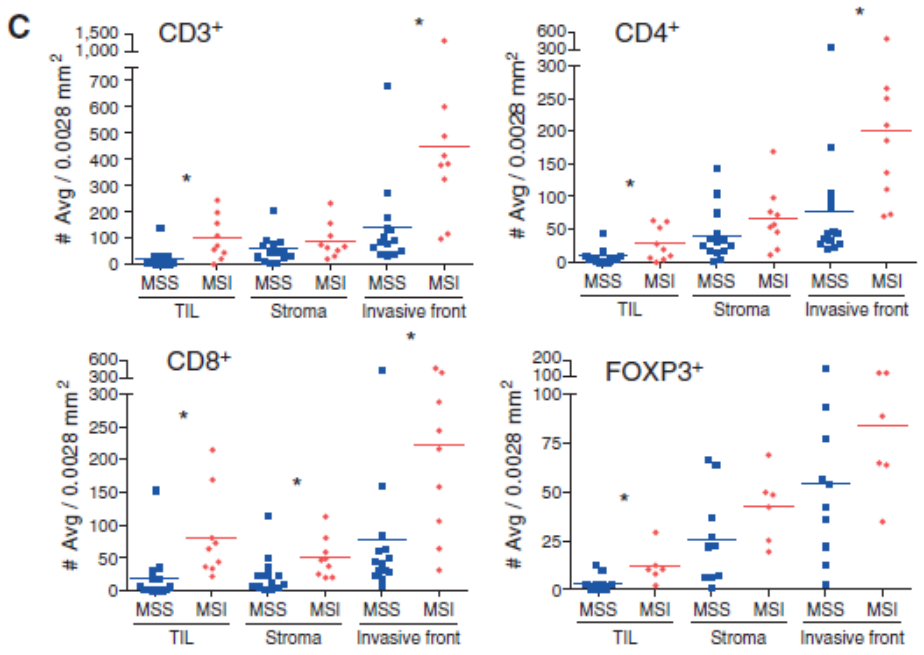
TCGA, Nature 2012

RESEARCH BRIEF

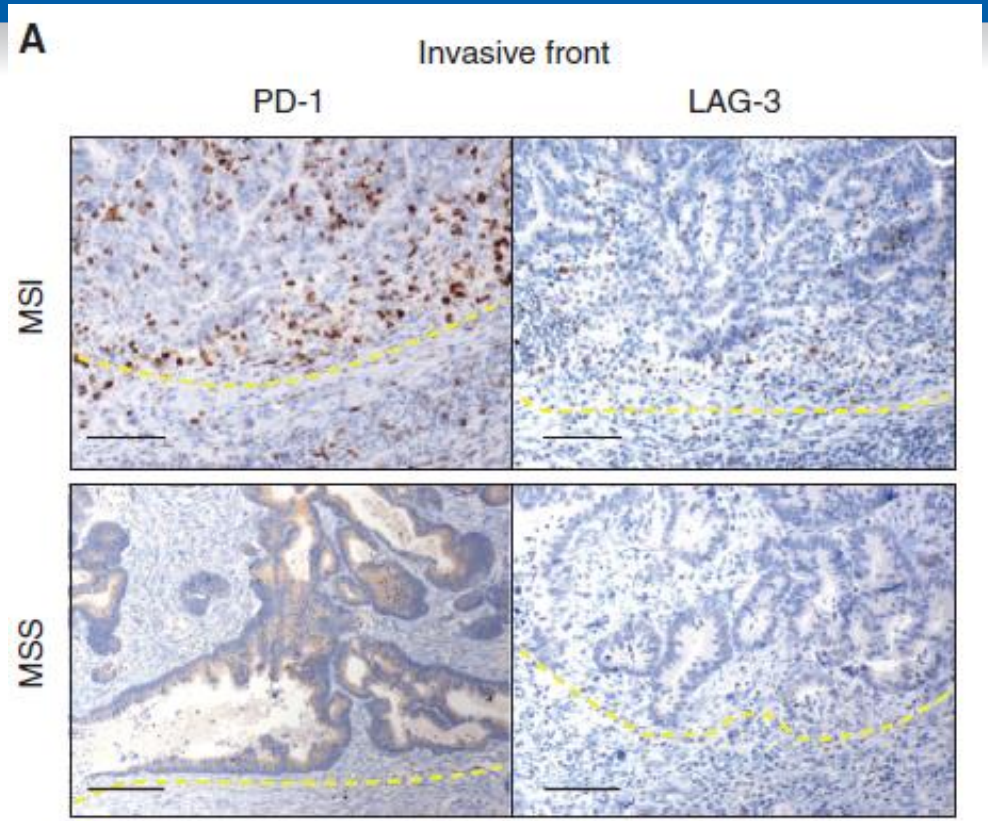
The Vigorous Immune Microenvironment of Microsatellite Instable Colon Cancer Is Balanced by Multiple Counter-Inhibitory Checkpoints

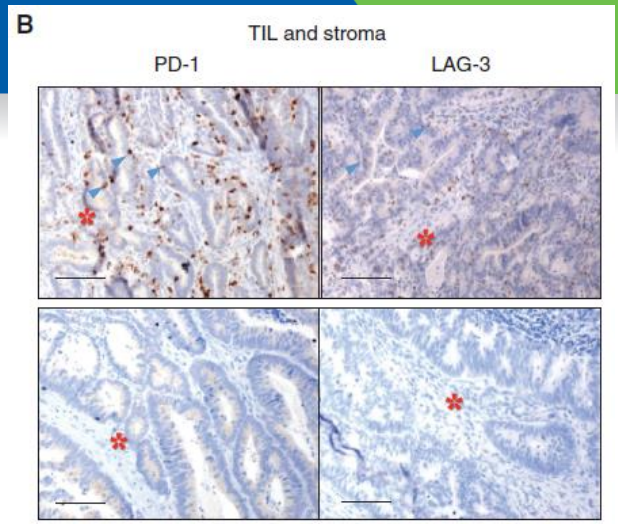
Nicolas J. Llosa[1], Michael Cruise[2], Ada Tam[3], Elizabeth C. Wicks[4], Elizabeth M. Hechenbleikner[4], Janis M. Taube[2], Richard L. Blosser[3], Hongni Fan[1], Hao Wang[5], Brandon S. Luber[5], Ming Zhang[6], Nickolas Papadopoulos[6], Kenneth W. Kinzler[6], Bert Vogelstein[6], Cynthia L. Sears[1,7], Robert A. Anders[2], Drew M. Pardoll[1,2,7,8], and Franck Housseau[1]





Llosa et al, Cancer Discov 2014

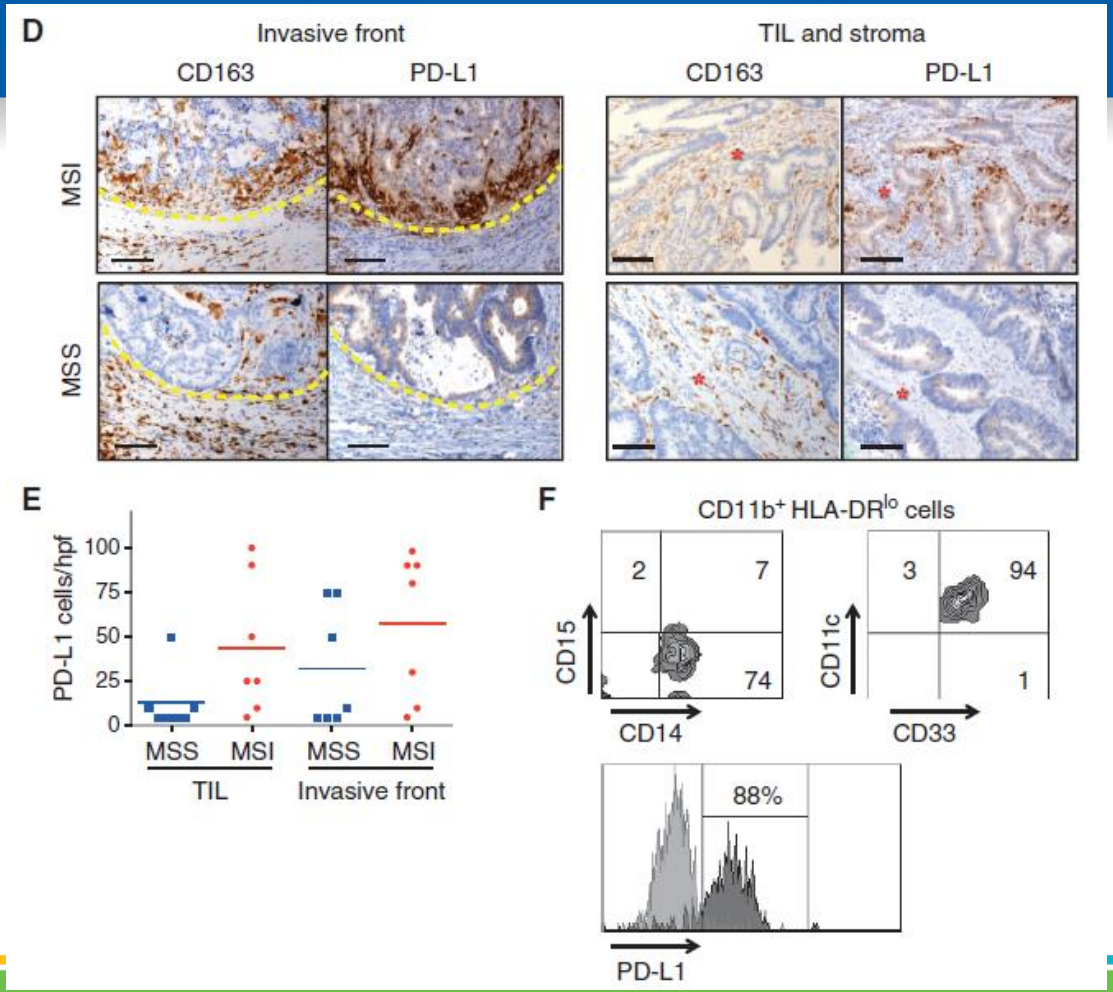




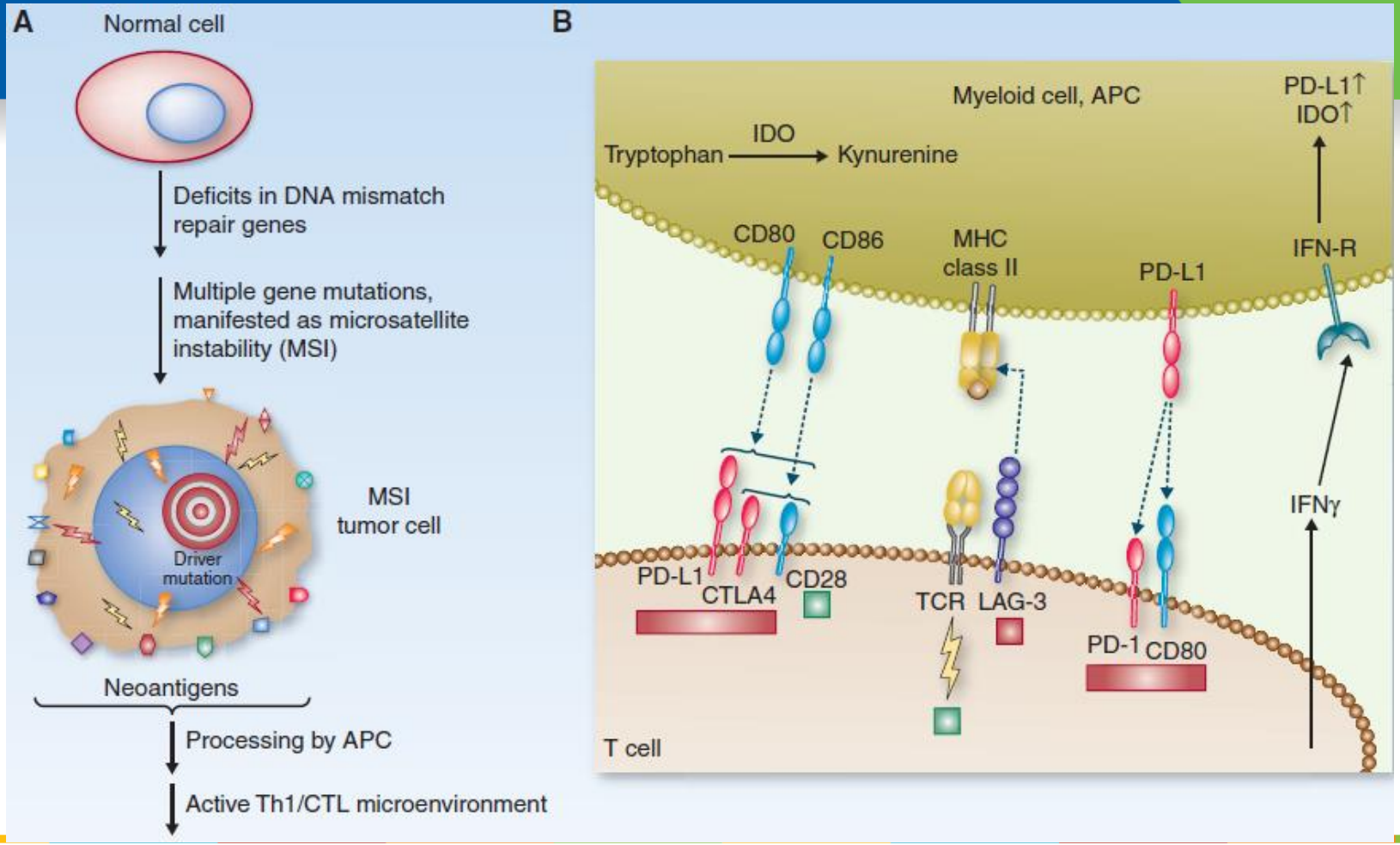
Gene group comparison between MSS and MSI CRC

Gene group	Wilcoxon permutation test *p* value		
	TIL	Stroma	Invasive front
Th1/Tc1	0.035*	0.069	0.030*
CTL	0.001*	0.006*	0.093
Th17	0.525	0.497	0.436
Treg	0.026*	0.273	0.432
Checkpoints	0.010*	0.019*	0.014*

Llosa et al, Cancer Discov 2014



Llosa et al, Cancer Discov 2014



Xiao, Cancer Discovery, 2015

PD-1 Inhibition and Colorectal Cancer

- Early clinical development: Only one responder (Topalian NEJM 2012 and Brahmer JCO 2010).
- This patient had a MMR deficient tumor (Lipson CCR 2013)

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.

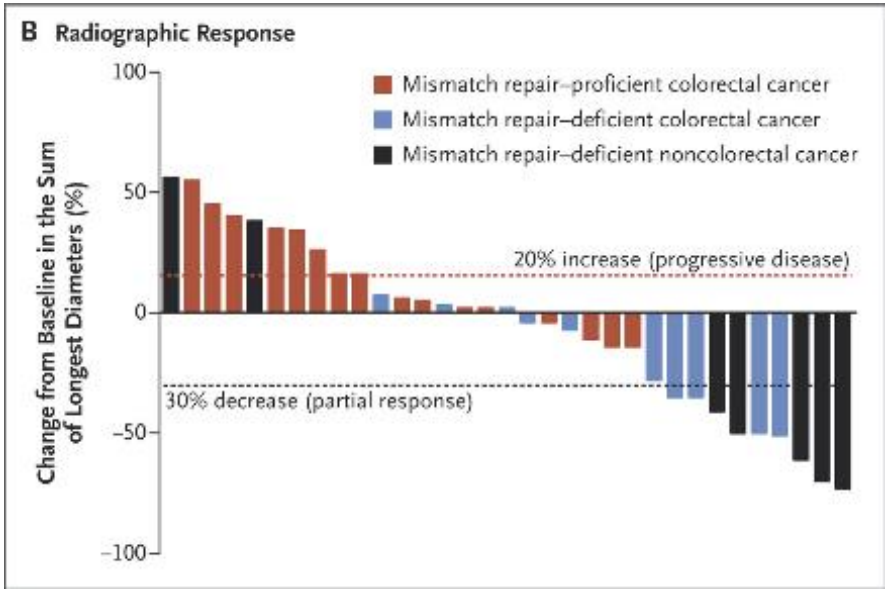
Le NEJM 2015

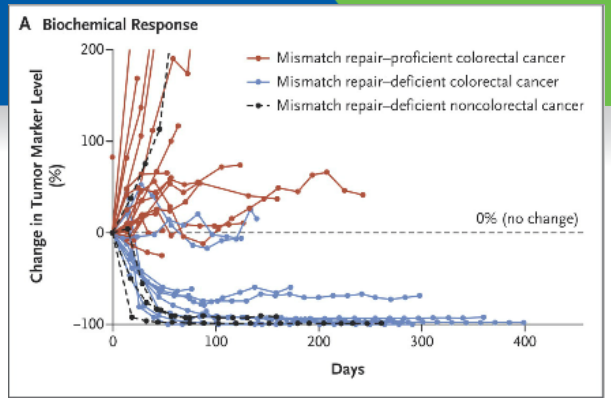
Immune-related Response and iPFS

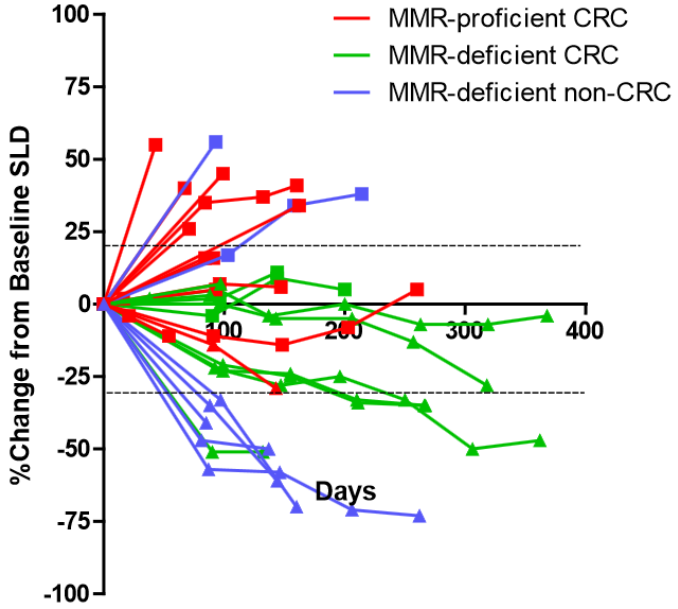
Type of immune-related responses-no (%)	MMR-deficient CRC n=10	MMR-proficient CRC n=18	MMR-deficient non-CRC n=7
Complete Response	0 (0)	0 (0)	1 (14)[1]
Partial Response	4 (40)	0 (0)	4 (57)[2]
Stable Disease (Week 12)	5 (50)	2 (11)	0 (0)
Progressive Disease	1 (10)	11 (61)	2 (29)
Not Evaluable[3]	0 (0)	5 (28)	0 (0)
Immune-related objective response rate (%)	40	0	71
95% CI	12-74	0-19	29-96
Immune-related disease control rate (%)[4]	90	11	71
95% CI	55-100	1-35	29-96
Immune-related PFS at 20 weeks (%)	78	11	67
95% CI	40-97	1-35	22-96

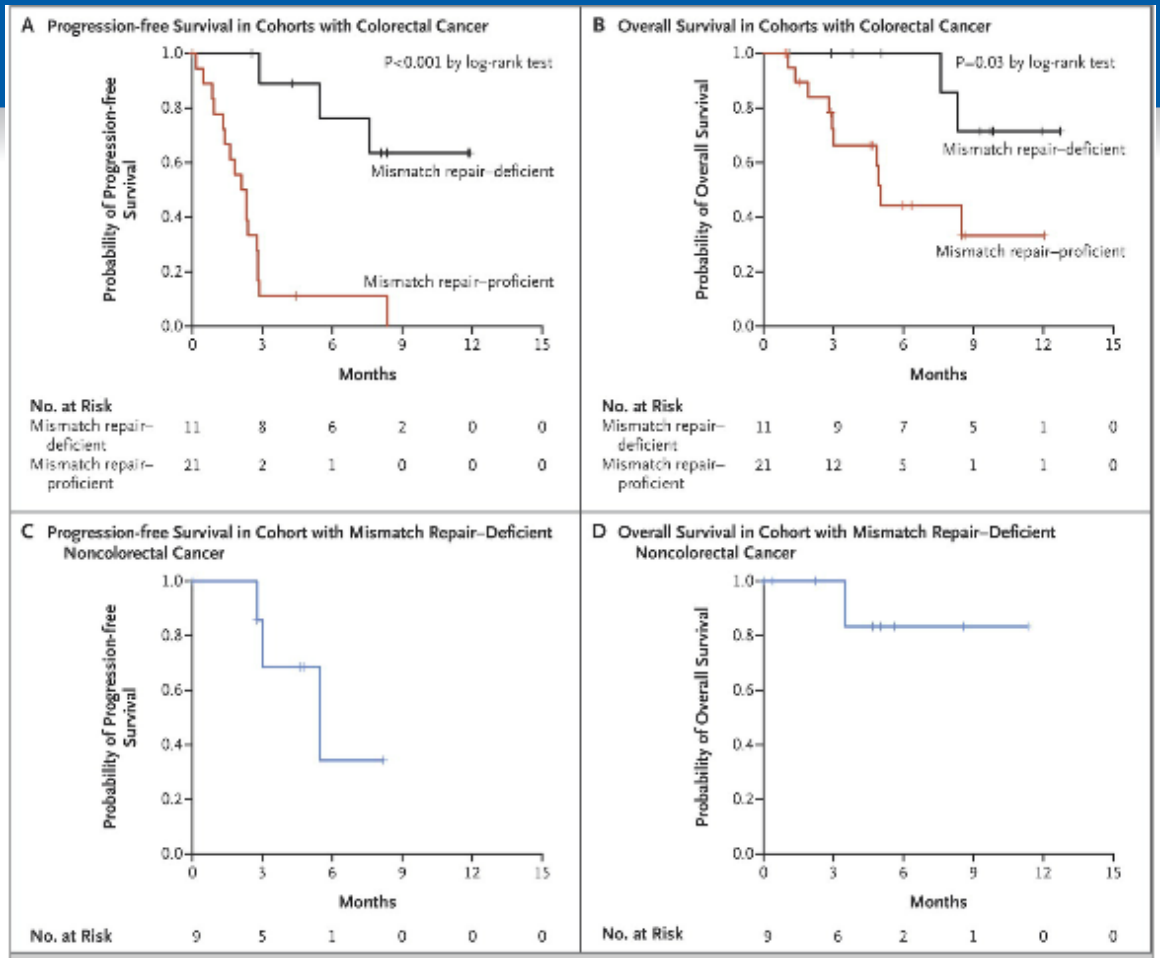
Response by RECIST

Type of Response	Mismatch Repair–Deficient Colorectal Cancer (N=10)	Mismatch Repair–Proficient Colorectal Cancer (N=18)	Mismatch Repair–Deficient Noncolorectal Cancer (N=7)
Complete response — no. (%)	0	0	1 (14)*
Partial response — no. (%)	4 (40)	0	4 (57)†
Stable disease at week 12 — no. (%)	5 (50)	2 (11)	0
Progressive disease — no. (%)	1 (10)	11 (61)	2 (29)
Could not be evaluated — no. (%)‡	0	5 (28)	0
Objective response rate (95% CI) — %	40 (12–74)	0 (0–19)	71 (29–96)
Disease control rate (95% CI) — %§	90 (55–100)	11 (1–35)	71 (29–96)
Median duration of response — wk	Not reached	NA¶	Not reached
Median time to response (range) — wk	28 (13–35)	NA¶	12 (10–13)


B Radiographic Response
Mismatch repair–proficient colorectal cancer
Mismatch repair–deficient colorectal cancer
Mismatch repair–deficient noncolorectal cancer
Change from Baseline in the Sum of Longest Diameters (%)
100
50
0
−50
−100
20% increase (progressive disease)
30% decrease (partial response)


A Biochemical Response
Mismatch repair–proficient colorectal cancer
Mismatch repair–deficient colorectal cancer
Mismatch repair–deficient noncolorectal cancer
Change in Tumor Marker Level (%)
200
100
0
−100
0% (no change)
0
100
200
300
400
Days


MMR-proficient CRC
MMR-deficient CRC
MMR-deficient non-CRC
%Change from Baseline SLD
100
75
50
25
0
-25
-50
-75
-100
100
200
300
400
Days

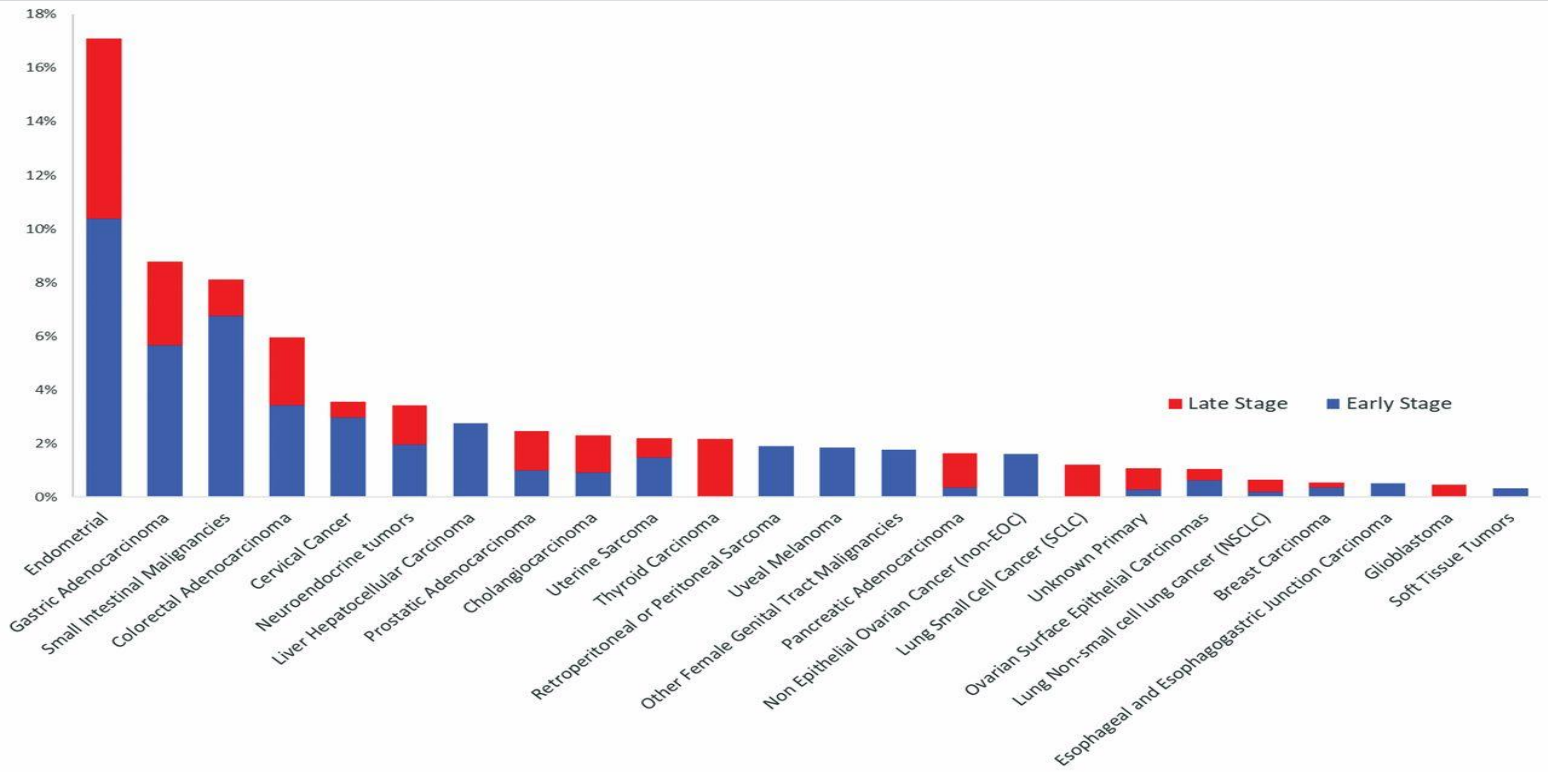

A Progression-free Survival in Cohorts with Colorectal Cancer
P<0.001 by log-rank test
Mismatch repair–deficient
Mismatch repair–proficient
Probability of Progression-free Survival
Months
No. at Risk
Mismatch repair–deficient 11 8 6 2 0 0
Mismatch repair–proficient 21 2 1 0 0 0
B Overall Survival in Cohorts with Colorectal Cancer
P=0.03 by log-rank test
Mismatch repair–deficient
Mismatch repair–proficient
Probability of Overall Survival
Months
No. at Risk
Mismatch repair–deficient 11 9 7 5 1 0
Mismatch repair–proficient 21 12 5 1 1 0
C Progression-free Survival in Cohort with Mismatch Repair–Deficient Noncolorectal Cancer
Probability of Progression-free Survival
Months
No. at Risk 9 5 1 0 0 0
D Overall Survival in Cohort with Mismatch Repair–Deficient Noncolorectal Cancer
Probability of Overall Survival
Months
No. at Risk 9 6 2 1 0 0

Correlative studies

- MMR-D:
  - higher CD8 infiltration
  - Higher PD-L1+ → in TAMs
- High numbers of mutations/neoantigens were associated with:
  - longer PFS
  - Trend toward OR
- The expression of CD8 and PD-L1 was not significantly associated with PFS/OS.

	MMR-D	MMR-P
Mutations	1782	73
Neoantigens/tumor	578	21
Neoantigens/mutations	32%	29%

Frequency of mismatch repair deficiency across different tumor types



Dung T. Le et al. Science 2017;357:409-413

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Science AAAS

CANCER BIOMARKERS

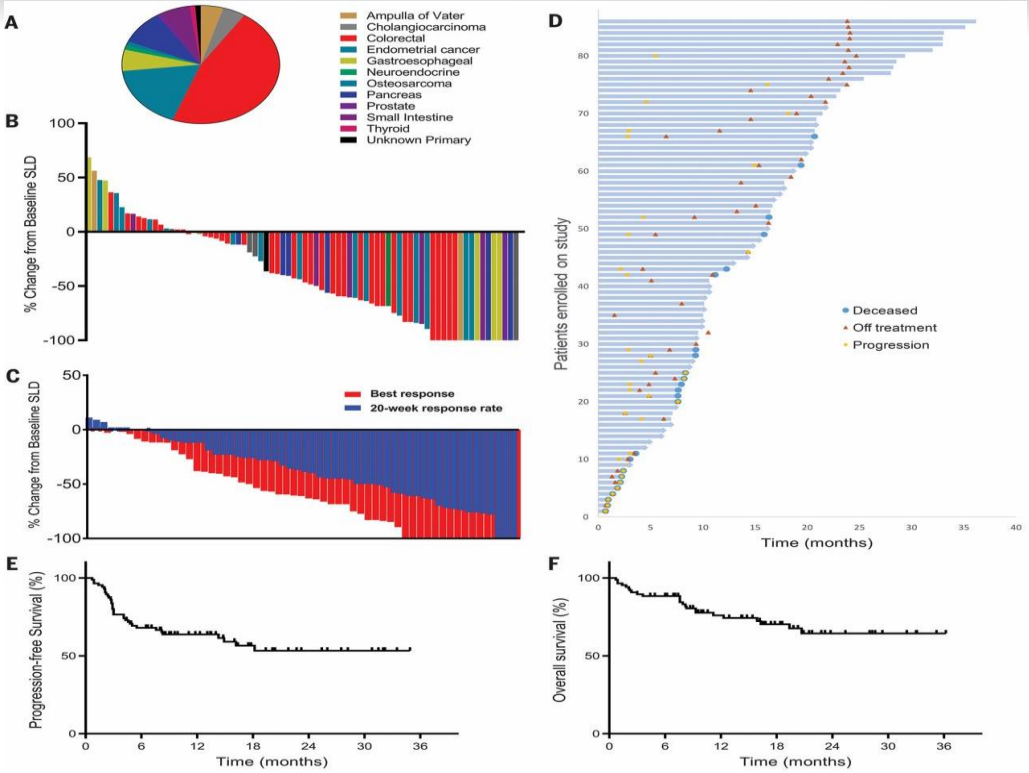
Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade

Dung T. Le,[1,2,3] Jennifer N. Durham,[1,2,3*] Kellie N. Smith,[1,3*] Hao Wang,[3*] Bjarne R. Bartlett,[2,4*] Laveet K. Aulakh,[2,4] Steve Lu,[2,4] Holly Kemberling,[3] Cara Wilt,[3] Brandon S. Luber,[3] Fay Wong,[2,4] Nilofer S. Azad,[1,3] Agnieszka A. Rucki,[1,3] Dan Laheru,[3] Ross Donehower,[3] Atif Zaheer,[5] George A. Fisher,[6] Todd S. Crocenzi,[7] James J. Lee,[8] Tim F. Greten,[9] Austin G. Duffy,[9] Kristen K. Ciombor,[10] Aleksandra D. Eyring,[11] Bao H. Lam,[11] Andrew Joe,[11] S. Peter Kang,[11] Matthias Holdhoff,[3] Ludmila Danilova,[1,3] Leslie Cope,[1,3] Christian Meyer,[3] Shibin Zhou,[1,3,4] Richard M. Goldberg,[12] Deborah K. Armstrong,[3] Katherine M. Bever,[3] Amanda N. Fader,[13] Janis Taube,[1,3] Franck Housseau,[1,3] David Spetzler,[14] Nianqing Xiao,[14] Drew M. Pardoll,[1,3] Nickolas Papadopoulos,[3,4] Kenneth W. Kinzler,[3,4] James R. Eshleman,[15] Bert Vogelstein,[1,3,4] Robert A. Anders,[1,3,15] Luis A. Diaz Jr.[1,2,3†‡]

Le Science 2017

Patient survival and clinical response to pembrolizumab across 12 different tumor types with MMR

Evidence of T-cell expansion – clones against mutation specific neoantigens (frameshift)



Dung T. Le et al. Science 2017;357:409-413

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Science AAAS

Dual Checkpoint Inhibition

VOLUME 36 · NUMBER 8 · MARCH 10, 2018

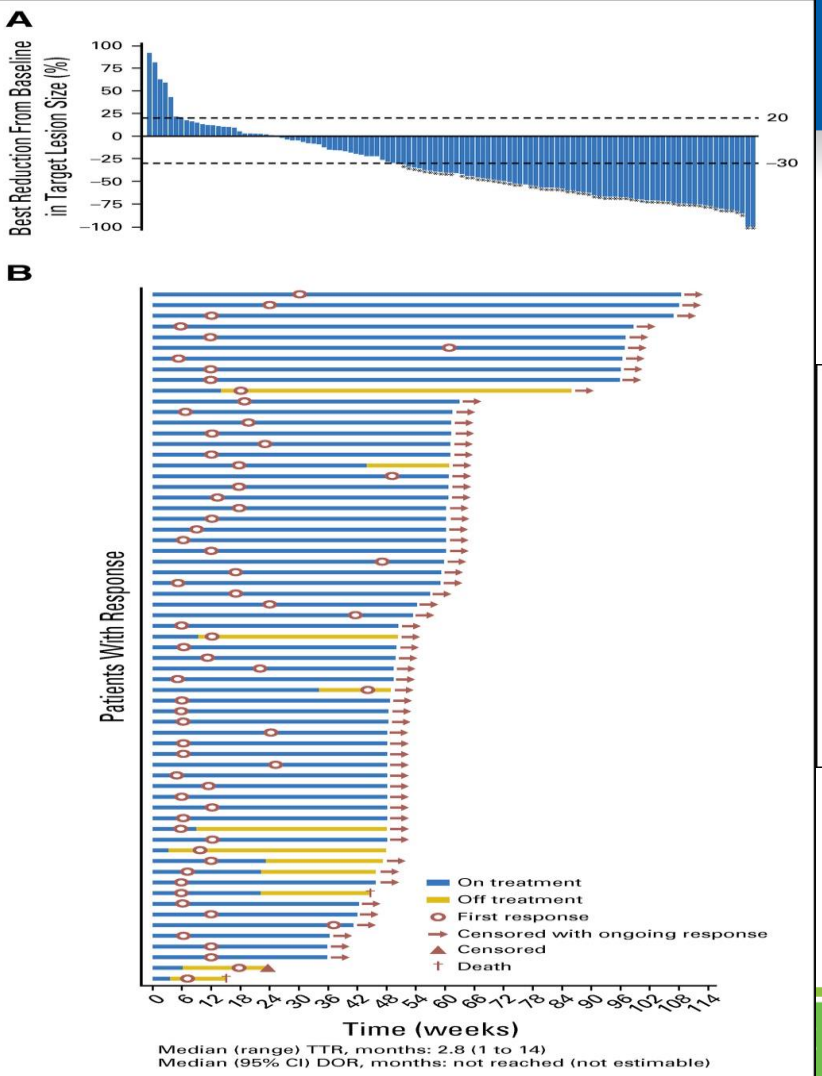
JOURNAL OF CLINICAL ONCOLOGY

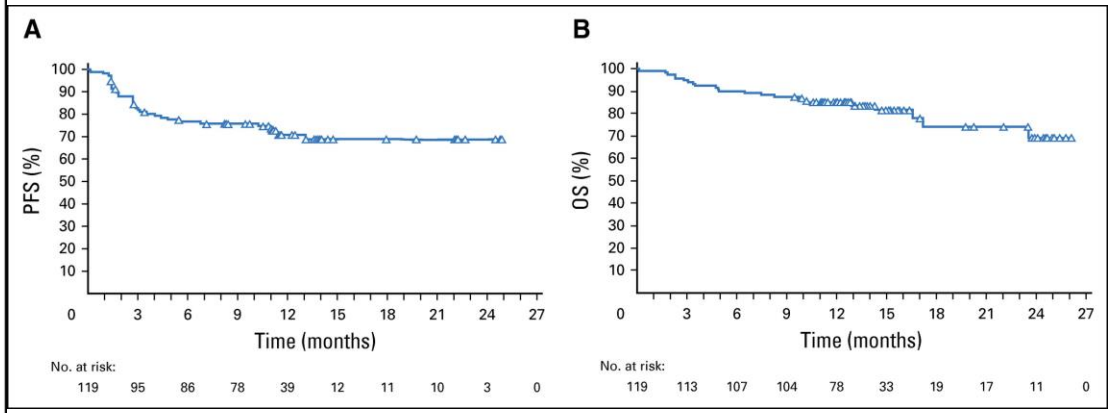
ORIGINAL REPORT

Low dose IPI/Nivo 3

Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair–Deficient/Microsatellite Instability–High Metastatic Colorectal Cancer

Michael J. Overman, Sara Lonardi, Ka Yeung Mark Wong, Heinz-Josef Lenz, Fabio Gelsomino, Massimo Aglietta, Michael A. Morse, Eric Van Cutsem, Ray McDermott, Andrew Hill, Michael B. Sawyer, Alain Hendlisz, Bart Neyns, Magali Svrcek, Rebecca A. Moss, Jean-Marie Ledeine, Z. Alexander Cao, Shital Kamble, Scott Kopetz, and Thierry André


A
Best Reduction From Baseline in Target Lesion Size (%)
100
75
50
25
0
−25
−50
−75
−100
20
−30
B
Patients With Response
On treatment
Off treatment
First response
Censored with ongoing response
Censored
Death
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96 102 108 114
Time (weeks)
Median (range) TTR, months: 2.8 (1 to 14)
Median (95% CI) DOR, months: not reached (not estimable)


A
PFS (%)
100
90
80
70
60
50
40
30
20
10
0 3 6 9 12 15 18 21 24 27
Time (months)
No. at risk:
119 95 86 78 39 12 11 10 3 0
B
OS (%)
100
90
80
70
60
50
40
30
20
10
0 3 6 9 12 15 18 21 24 27
Time (months)
No. at risk:
119 113 107 104 78 33 19 17 11 0

NTER

SCIENTIFIC REPORTS

OPEN

A cancer vaccine approach for personalized treatment of Lynch Syndrome

Received: 17 April 2018
Accepted: 30 July 2018
Published online: 14 August 2018

Snigdha Majumder[1], Rakshit Shah[2], Jisha Elias[1,2], Malini Manoharan[1], Priyanka Shah[1], Anjali Kumari[1], Papia Chakraborty[3], Vasumathi Kode[3], Yogesh Mistry[2], Karunakaran Coral[1], Bharti Mittal[1], Sakthivel Murugan SM[1], Lakshmi Mahadevan[1], Ravi Gupta[1], Amitabha Chaudhuri[1,3] & Arati Khanna-Gupta[1]

The Future for MSI-H cancers

- Vaccines
  - MMR→ frameshift mutations→ highly immunogenic neoantigens
  - Peptide cocktails from MS containing genes
  - Examples: NOUS-209, MicOryx
  - NOUS-209 plus pembrolizumab study for PD(L)1 naïve CRC/EGC to open at RPCI soon
- Anti-VEGF?
  - Atezolizumab/Bevacizumab: ORR 30% (Hochster ASCO GI 2017)

Case

- 82 yo woman with Lynch syndrome and diagnosis of advanced PDAC
- Consideration for gemcitabine but concern for poor tolerance
- Initiation of immune checkpoint inhibitor (PD1) standard of care

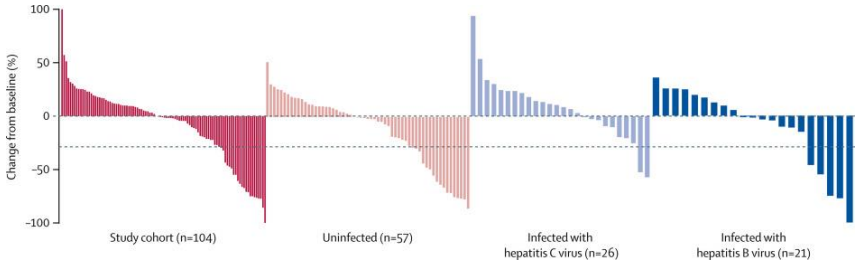
Case continued

- Radiographic and biochemical response
- 15 months on anti-PD1 with ongoing response
- Options upon progression beyond gemcitabine?
  - Dual checkpoint inhibition? No data
  - IDO/PD1 study or another PD(L)1 plus study
  - MSI vaccine study

HEPATOCELLULAR CARCINOMA

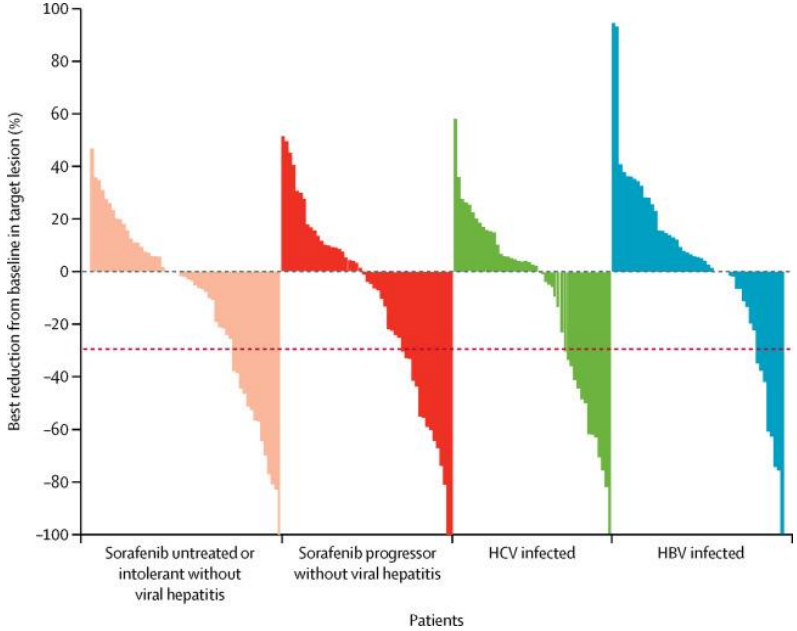
Immune Checkpoint Inhibitors in 2nd line

Keynote 224 (Zhu Lancet Oncololy 2018)



ORR: 17%, DCR: 62%, DOR: NR

CheckMate 040 (El Khoueiri Lancet 2017)



ORR: 20%, DCR: 64%, DOR: 9.9 months

Results of KEYNOTE-240: Phase 3 Study of Pembrolizumab vs Best Supportive Care for Second-Line Therapy in Advanced Hepatocellular Carcinoma

Richard S. Finn,[1] Baek-Yeol Ryoo,[2] Philippe Merle,[3] Masatoshi Kudo,[4] Mohamed Bouattour,[5] Ho-Yeong Lim,[6] Valeriy Breder,[7] Julien Edeline,[8] Yee Chao,[9] Sadahisa Ogasawara,[10] Thomas Yau,[11] Marcelo Garrido,[12] Stephen L. Chan,[13] Jennifer Knox,[14] Bruno Daniele,[15] Scot W. Ebbinghaus,[16] Erluo Chen,[16] Abby B. Siegel,[16] Andrew X. Zhu,[17] Ann-Lii Cheng,[18] for the KEYNOTE-240 Investigators

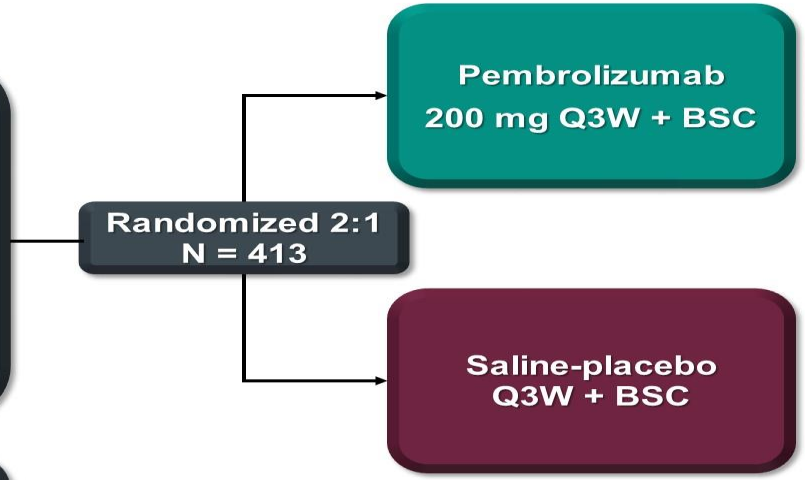
[1]University of California, Los Angeles, Los Angeles, CA, USA; [2]Asan Medical Center University of Ulsan College of Medicine, Seoul, Republic of Korea; [3]Lyon North Hospital, Hepatology Unit, Lyon, France; [4]Kindai University Faculty of Medicine, Osaka, Japan; [5]Beaujon University Hospital, APHP, Clichy, France; [6]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [7]NN Blokhin National Medical Research Center of Oncology *of MoH*, Moscow, Russian Federation; [8]Centre Eugène Marquis, Rennes, France; [9]Taipei Veterans General Hospital, Taipai, Taiwan; [10]Chiba University Graduate School of Medicine, Chiba, Japan; [11]The University at Hong Kong, Hong Kong, China; [12]Pontificia Universidad Catolica de Chile, Santiago, Chile; [13]State Key Laboratory of Translation Oncology, Sir YK Pao Centre for Cancer, The Chinese University of Hong Kong, Shatin, Hong Kong, China; [14]Princess Margaret Cancer Centre and University of Toronto, Toronto, Canada; [15]Ospedale del Mare, Napoli, Italy; [16]Merck & Co., Inc., Kenilworth, NJ, USA; [17]Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA; [18]National Taiwan University Hospital and National Taiwan University Cancer Center, Taipei, Taiwan

Presented By Richard Finn at 2019 ASCO Annual Meeting

KEYNOTE-240 Study Design

Key Eligibility Criteria
- Pathologically/radiographically confirmed HCC
- Progression on/intolerance to sorafenib
- Child Pugh class A
- BCLC stage B/C
- ECOG PS 0-1
- Measurable disease per RECIST v1.1
- Main portal vein invasion was excluded

Stratification Factors
- Geographic region (Asia w/o Japan vs non-Asia w/Japan)
- Macrovascular invasion (Y vs N)
- AFP level (≥200 vs <200 ng/mL)



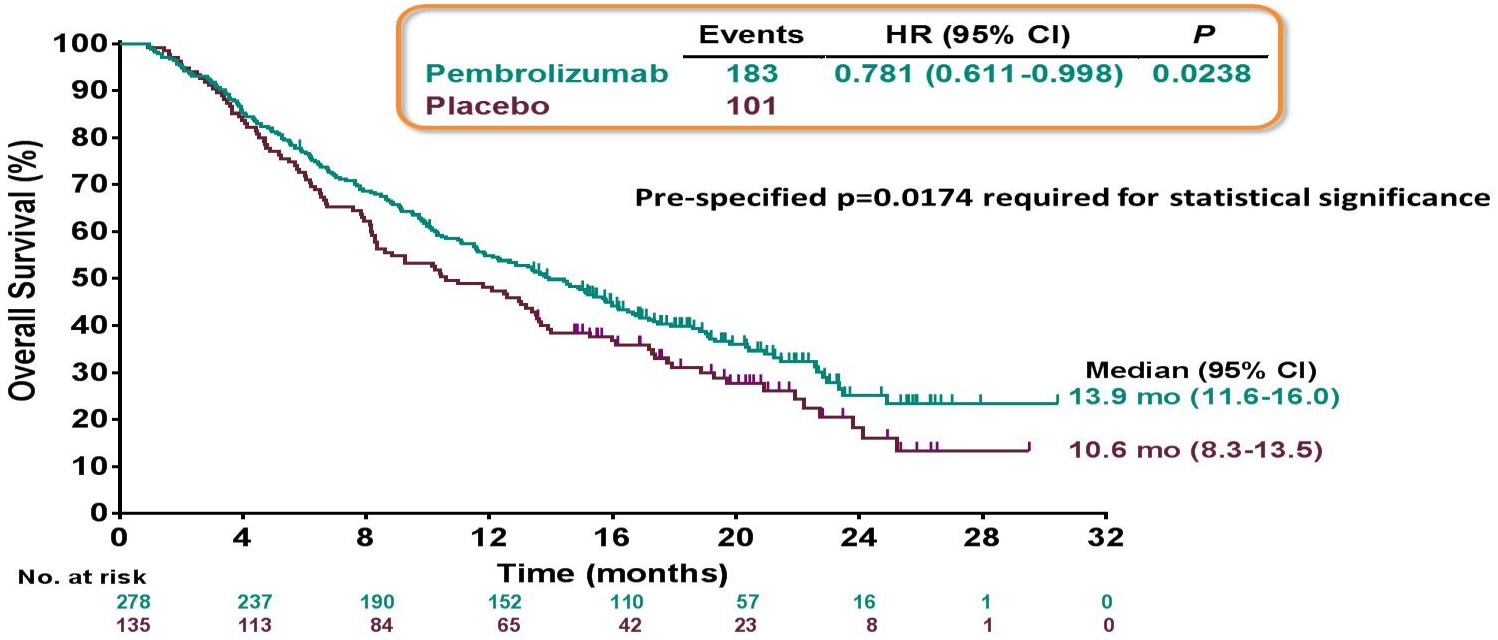
- **Enrollment May 31, 2016 – November 23, 2017**

Statistical Considerations

- Overall Type I error (α)=0.025 controlled across testing of PFS, OS and ORR[1]
  - Initial α allocation
    - PFS α=0.002; OS α=0.023
    - ORR α=0.0 (tested only if OS or PFS criteria met)
  - α re-allocated per multiplicity strategy specified in the protocol
- OS testing by group sequential design
  - α controlled over 2 interim and final efficacy analyses (O'Brien-Fleming spending function[2])
  - Primary analysis of PFS and ORR at 1st interim cut-off
- Efficacy boundaries
  - p=0.0174 for OS (final analysis cutoff, Jan 2, 2019, based on 284 observed events)
  - p=0.0020 for PFS (at 1st interim cutoff, Mar 26, 2018)
- Study power
  - 92% for OS with 273 deaths at α=2.3%, HR=0.65
  - 94% for PFS with 331 PFS events at α=0.2%, HR=0.60

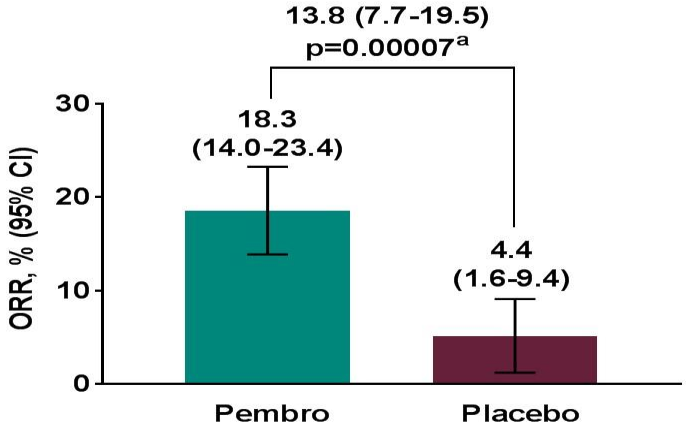
1. Maurer W, Bretz F. *Stat Biopharm Res* 2013; 5(4): 311-20. 2. Lan KKG, Demets DL. *Biometrika* 1983; 70(3): 659-63.

Overall Survival



Data Cutoff: Jan 2, 2019.

Objective Response Rate at Final Analysis
(RECIST 1.1, BICR)



Response n (%)	Pembrolizumab N=278	Placebo N=135
Best Overall Response		
CR	6 (2.2)	0 (0.0)
PR	45 (16.2)	6 (4.4)
SD	122 (43.9)	66 (48.9)
SD ≥23 wks	37 (18.3)	20 (14.8)
Progressive Disease	90 (32.4)	57 (42.2)
Disease Control Rate (CR+PR+SD)	173 (62.2)	72 (53.3)

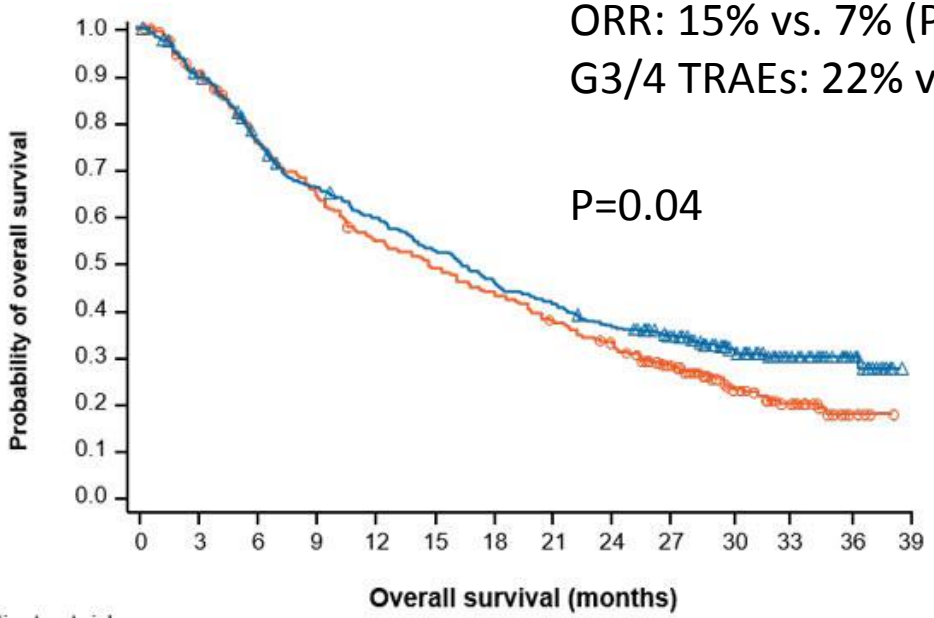
Duration of response, median (range)[b,c]:
- Pembrolizumab: 13.8 mo (1.5+ mo − 23.6+ mo)
- Placebo: not reached (2.8 mo−20.4+ mo)

[a]Nominal one-sided P-value based on the Miettinen and Nurminen method stratified by randomization factors. [b]From product-limit (Kaplan-Meier) method for censored data. [c]"+" indicates no PD by the time of last disease assessment. Data cutoff: Jan 2, 2019.

First Line? CheckMate 459

PFS: 3.7 vs. 3.8 months
ORR: 15% vs. 7% (PD-L1>1=28%)
G3/4 TRAEs: 22% vs. 49%

P=0.04



Yau ESMO 2019

The Future: VEGF + PD1 inhibition

- Sorafenib (in vivo and in vitro preclinical model)
  - Low dose sorafenib has immune activating effects
  - High dose sorafenib has immunosuppressive effects
- Sorafenib (prospective biomarker study in HCC)
  - High baseline T_{eff}/T_{reg} ratio and $CD8^+$ T-cells → better outcomes
  - Sorafenib therapy can decrease T_{reg} and MDSCs

Iyer Cancers (Basel) 2019, Kalathil JCI Insight 2019

Atezolizumab+Bevacizumab Ph1

- Treatment-naïve
- ORR: 65%, DCR: 96%
- 6-month PFS/OS: 65%/86%

Lenvatinib+ Pembrolizumab

- ORR: 37%
- DCR: 90%

Ikeda AACR 2019

Ongoing studies

- Sorafenib/Pembrolizumab (RPCI)
- Tivozanib/Durvalumab (RPCI-to be activated soon)
- Lenvatinib/Pembrolizumab (LEAP-002)

Case

- 60 yo man, NASH cirrhosis, CP B(7)
- 4 cm liver seg 4 HCC
- Not transplant/resection candidate→ SBRT
- Progression with multifocal disease after 8 months, encephalopathy
- Started lenvatinib with poor tolerance (encephalopathy, high bilirubin) and eventually PD on imaging
- Started anti-PD1 therapy

Case continued

- Radiographic (size and enhancement response) and biochemical response
- No major toxicity
- Options upon progression?
  - Hospice

Questions

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