Emerging Role of Immunotherapy in Gastrointestinal Cancers: Mutation and Neoantigen Burden as Predictors of Response

MSI mCRC

- 38 year old woman presented with 2 months of diarrhea, was also found to be anemic by her PCP
- Colonoscopy showed a right-sided mass in the colon
- R colectomy
  - 6x5x3 cm cecal poorly differentiated adenocarcinoma with lymphocytic infiltrate, T3NoMo, 0/18 LN positive, MSI, RAS and BRAF WT
  - Lynch positive
- No adjuvant therapy given
- Two years later CT scan showed 2 liver masses, 5.9 x 5.4 cm and 3.3 x 3.3 cm, and abdominal lymphadenopathy

MSI mCRC

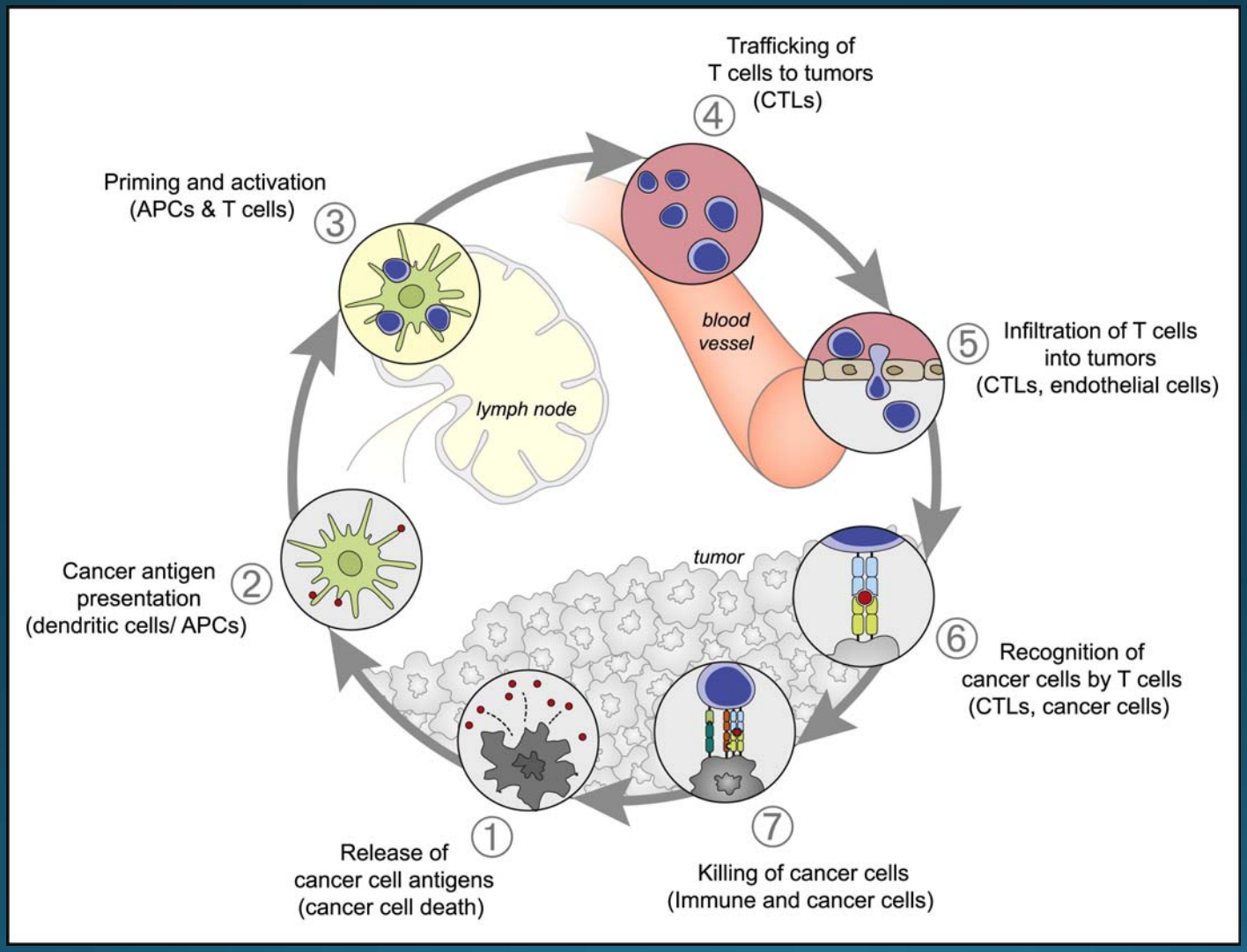
- Biopsy of liver mass confirmed recurrent adenocarcinoma
- Initiated nivolumab
- Partial response seen on first restaging scan (2 months)
- Continues in PR now 2 years
  - Course has been complicated by hypothyroidism

Emerging Role of Immunotherapy in Gastrointestinal Cancers: Mutation and Neoantigen Burden as Predictors of Response

Disclosures

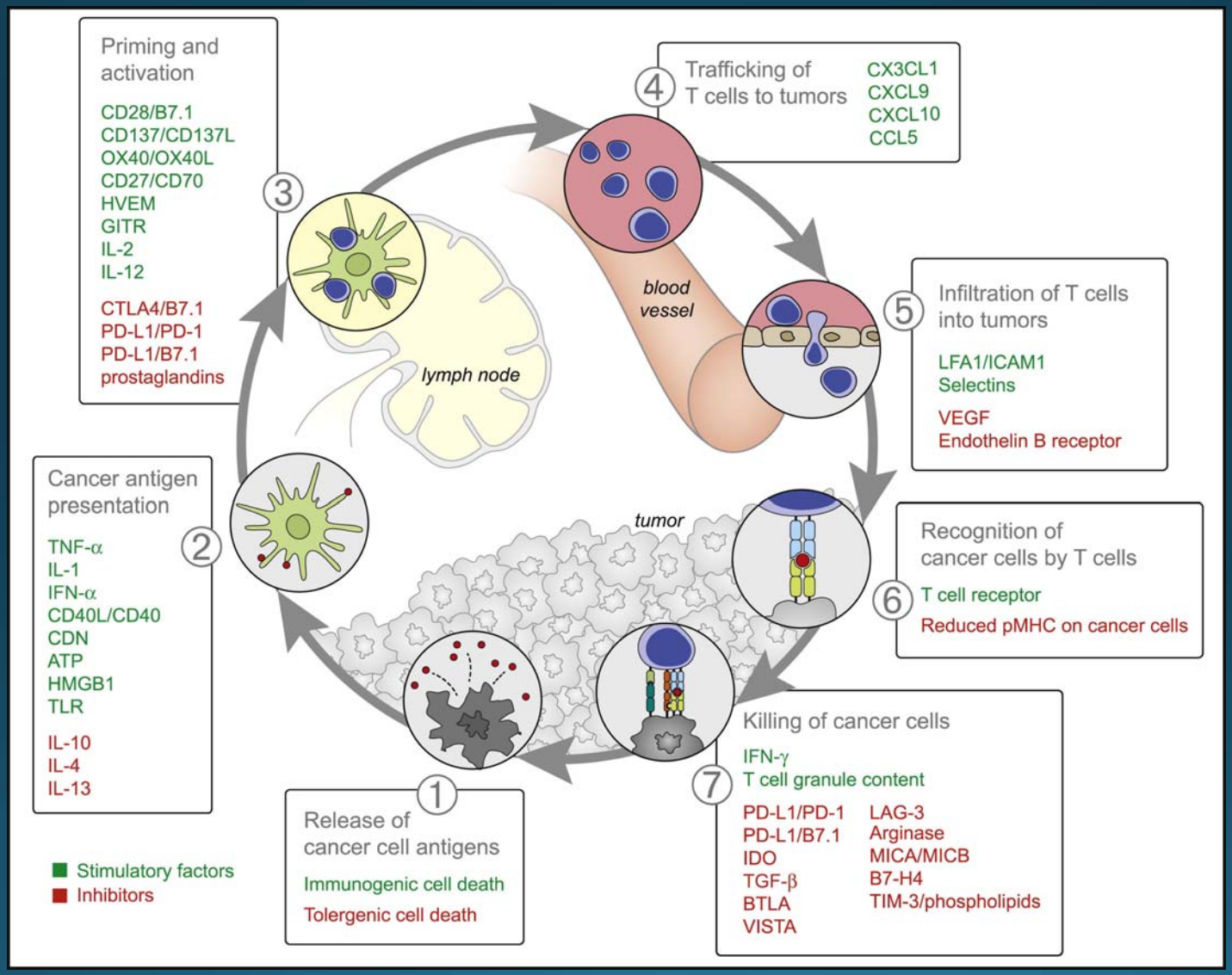
Contracted Research	Abbott Laboratories, AbbVie Inc, Apexigen, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Daiichi Sankyo Inc, Eisai Inc, EMD Serono Inc, Five Prime Therapeutics Inc, Forty Seven Inc, Genentech BioOncology, Gilead Sciences Inc, GlaxoSmithKline, Incyte Corporation, Kolltan Pharmaceuticals Inc, Leap Therapeutics Inc, Lilly, MacroGenics Inc, MedImmune Inc, Merck, Novartis Pharmaceuticals Corporation, OncoMed Pharmaceuticals Inc, Onyx Pharmaceuticals, an Amgen subsidiary, Pfizer Inc, Roche Laboratories Inc, Sanofi Genzyme, Stemcentrx, Taiho Oncology Inc, Takeda Oncology, TG Therapeutics Inc

Cancer-immunity cycle



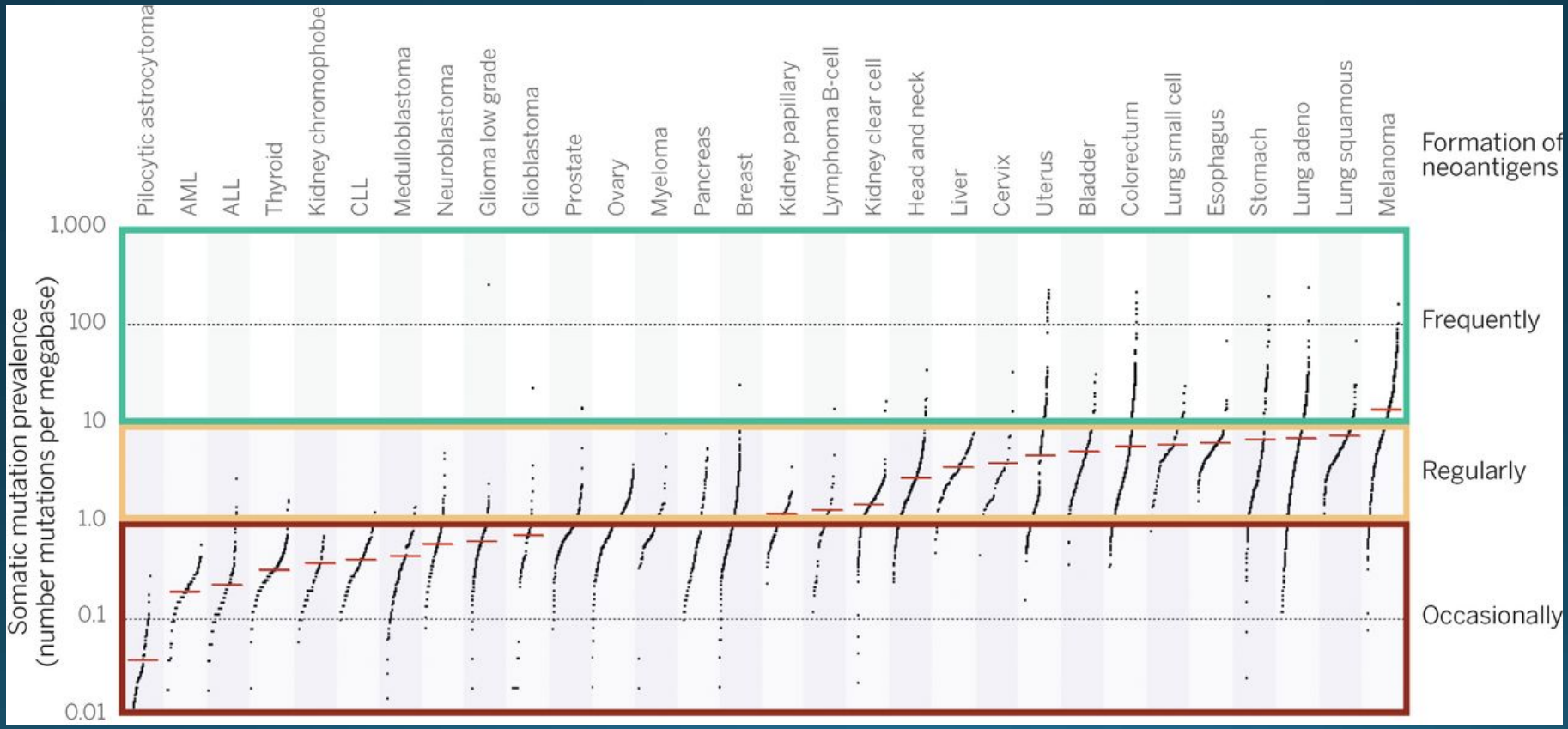
Chen Immunity 2013

Cancer-immunity cycle



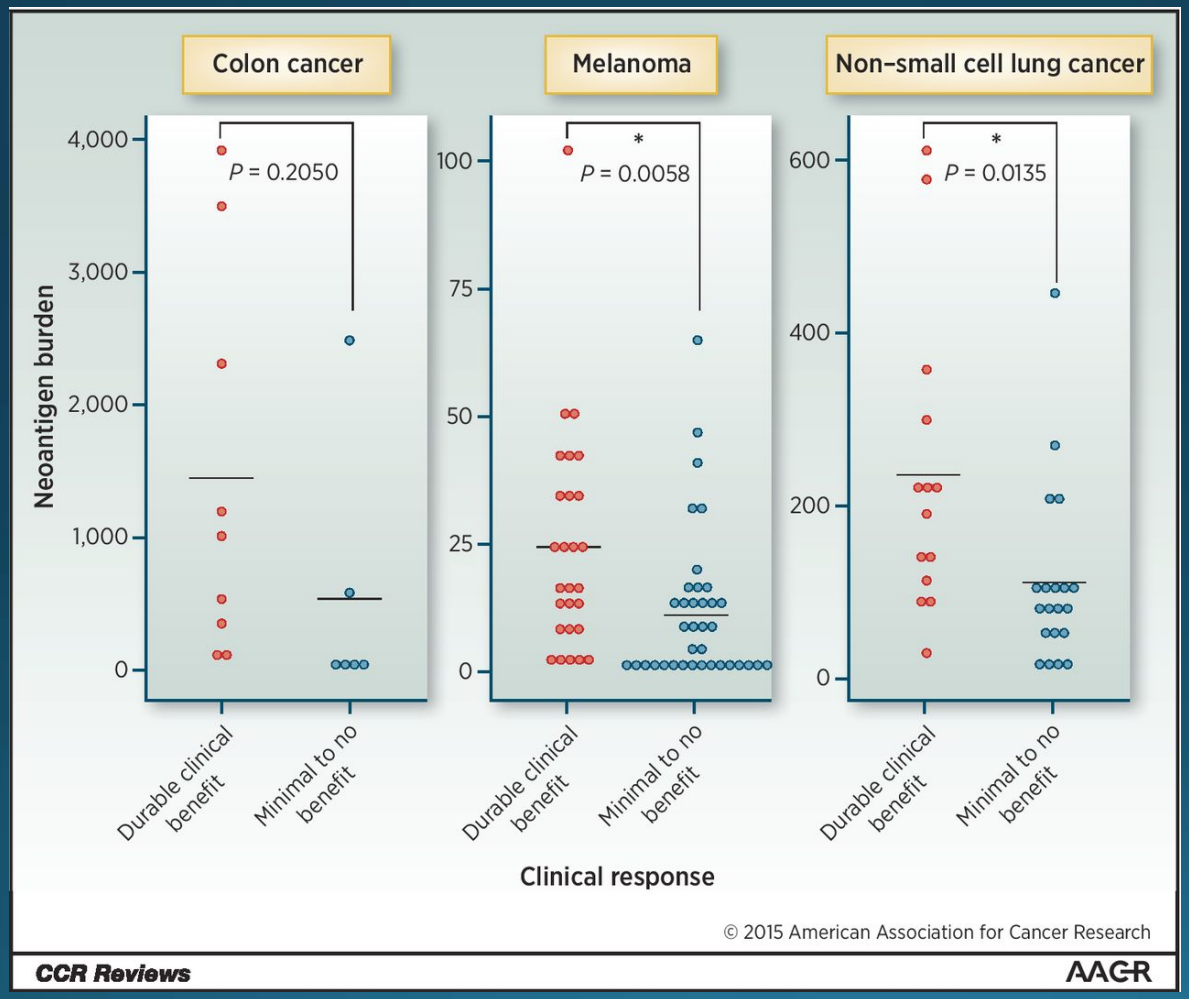
Chen Immunity 2013

Mutational load/neoantigen formation



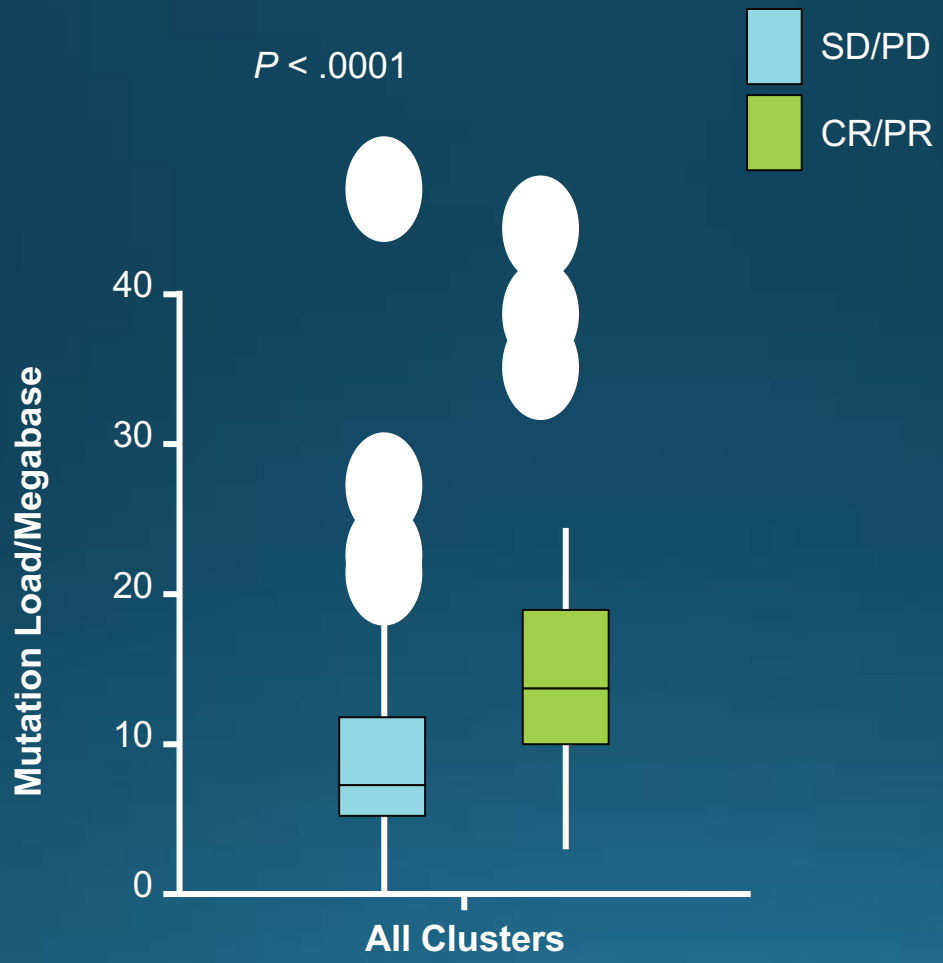
Schumacher Science 2015

Mutational burden and efficacy of checkpoint inhibitors



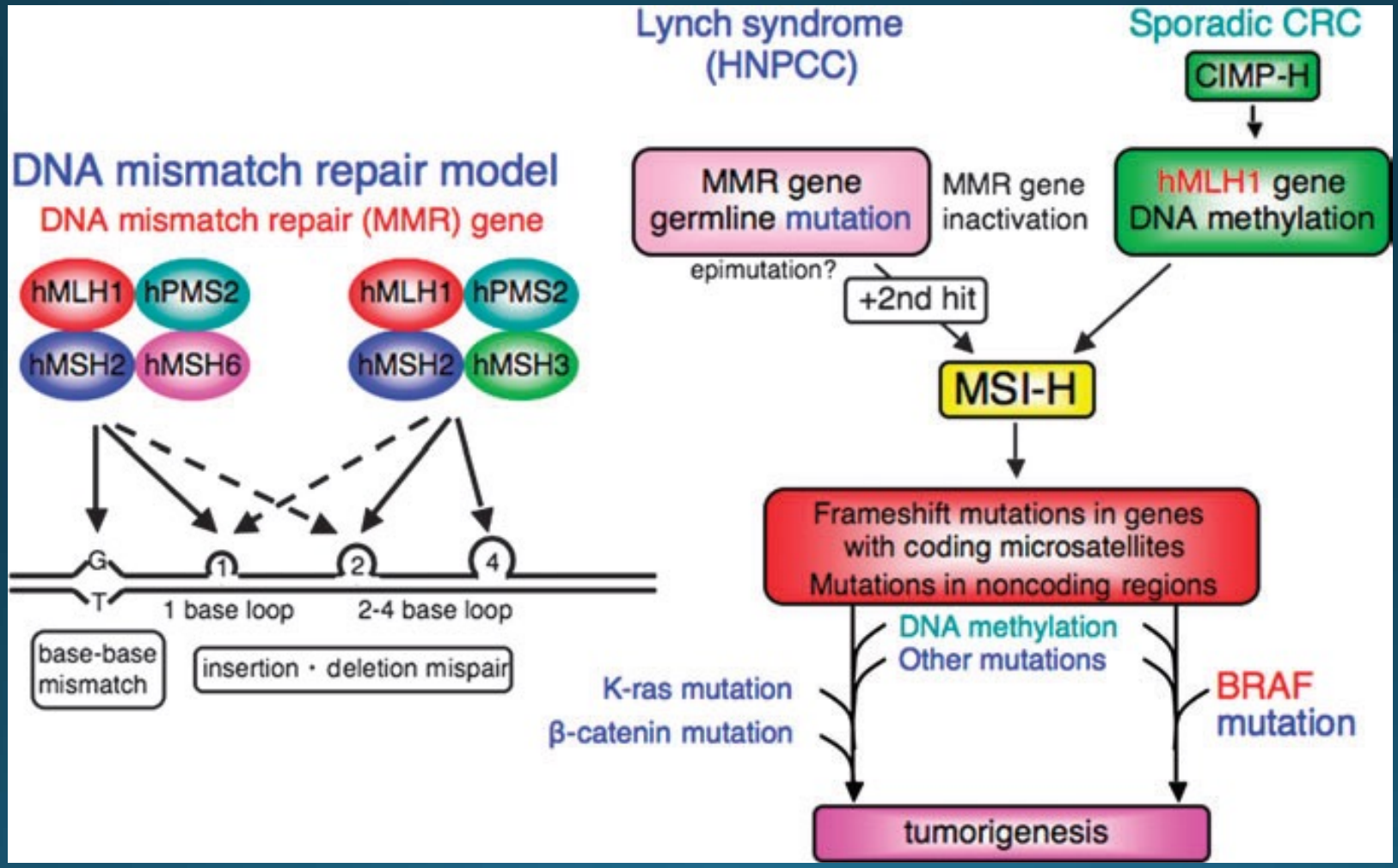
Desrichard CCR 2016
Le NEJM 2015
Snyder NEJM 2014
Rizvi Science 2015

IMvigor210: Mutation Load Associated With Objective Responses

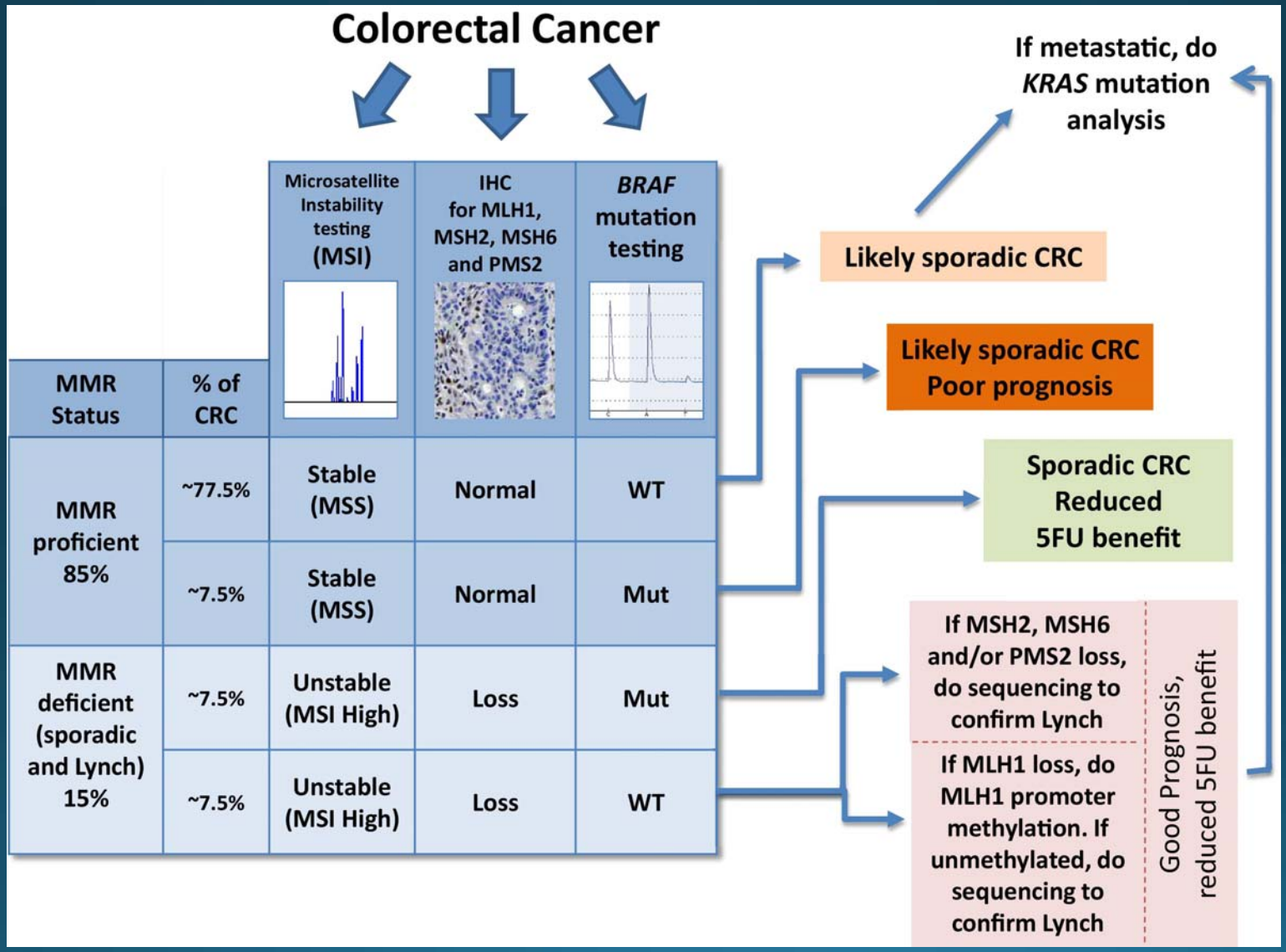


Rosenberg JE, et al. Lancet. 2016;387:1909-1920.

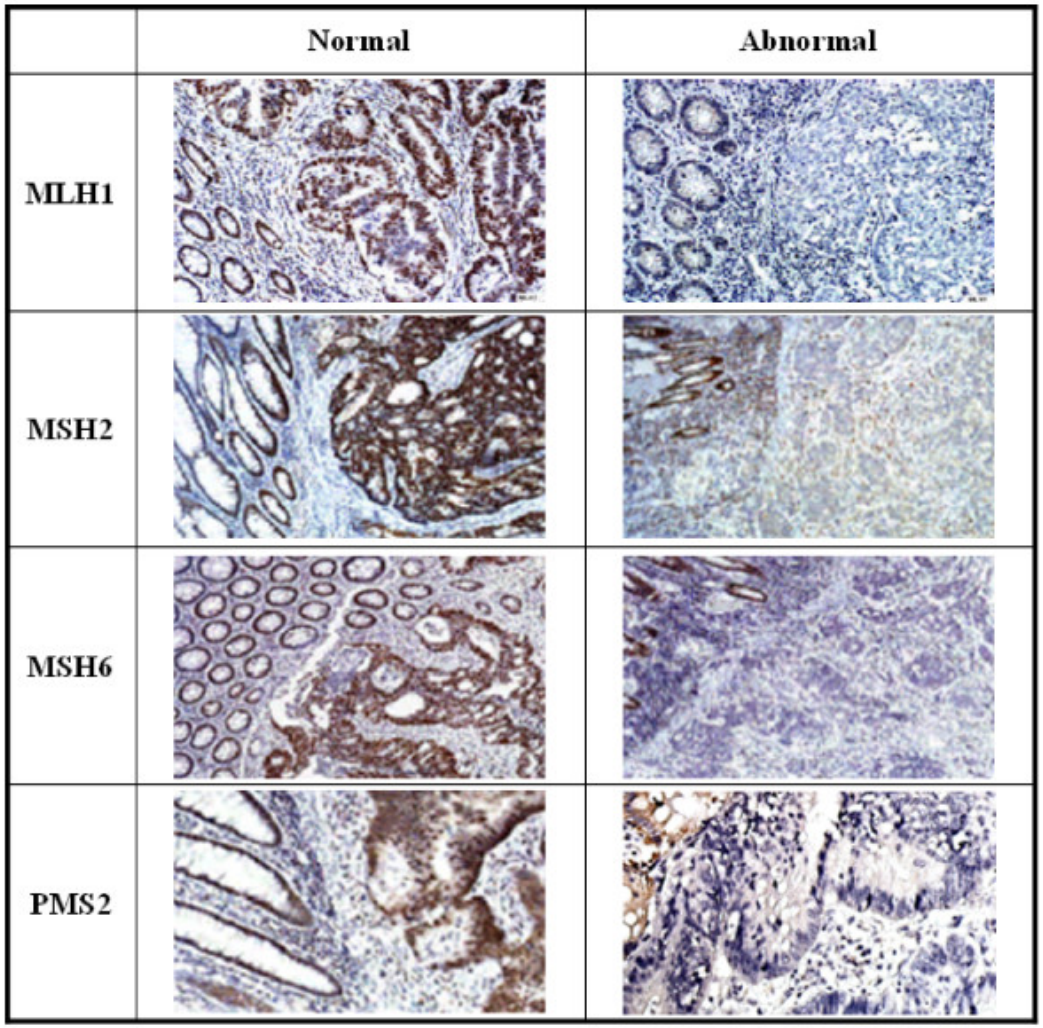
Microsatellite instability



Microsatellite instability



IHC STAINS FOR MLH1, MSH2, MSH6 AND PMS2 PROTEINS

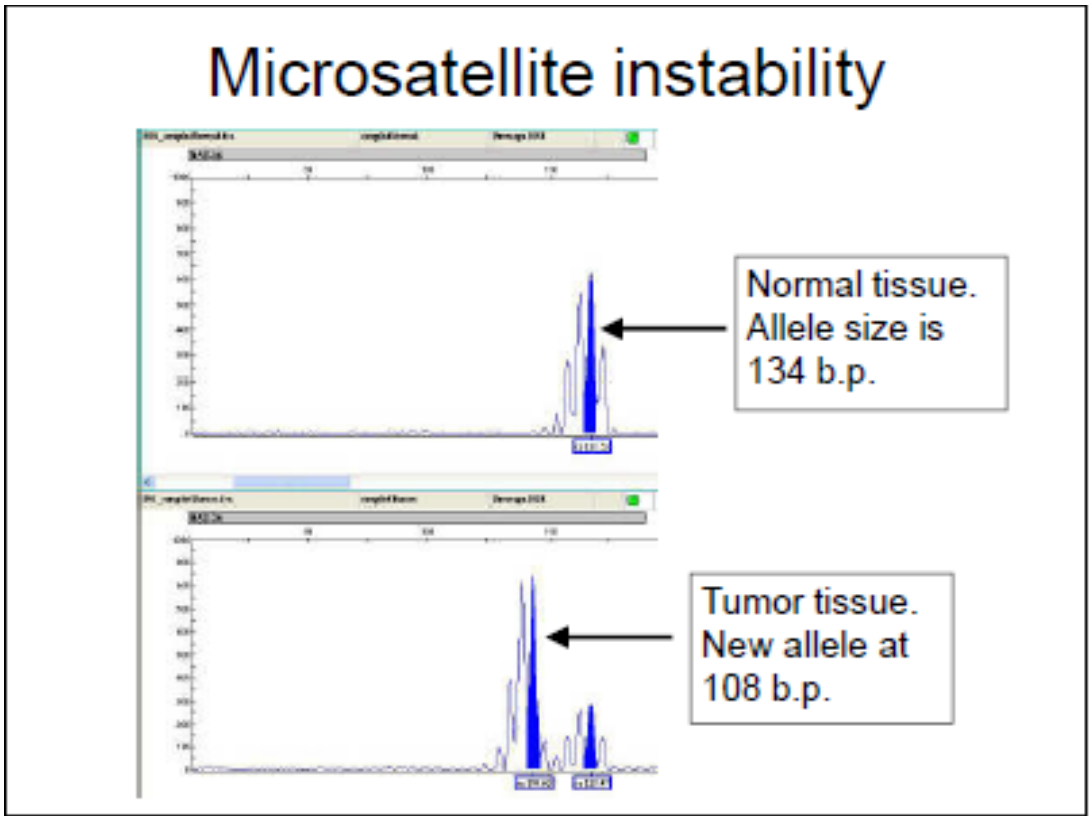


- These proteins are located in the nucleus.
- *It is normal for these proteins to be present, therefore:* Loss of staining is abnormal.

Lin et al.Journal of Biomedical Science 2011, 18:36 http://www.jbiomedsci.com/content/18/1/36

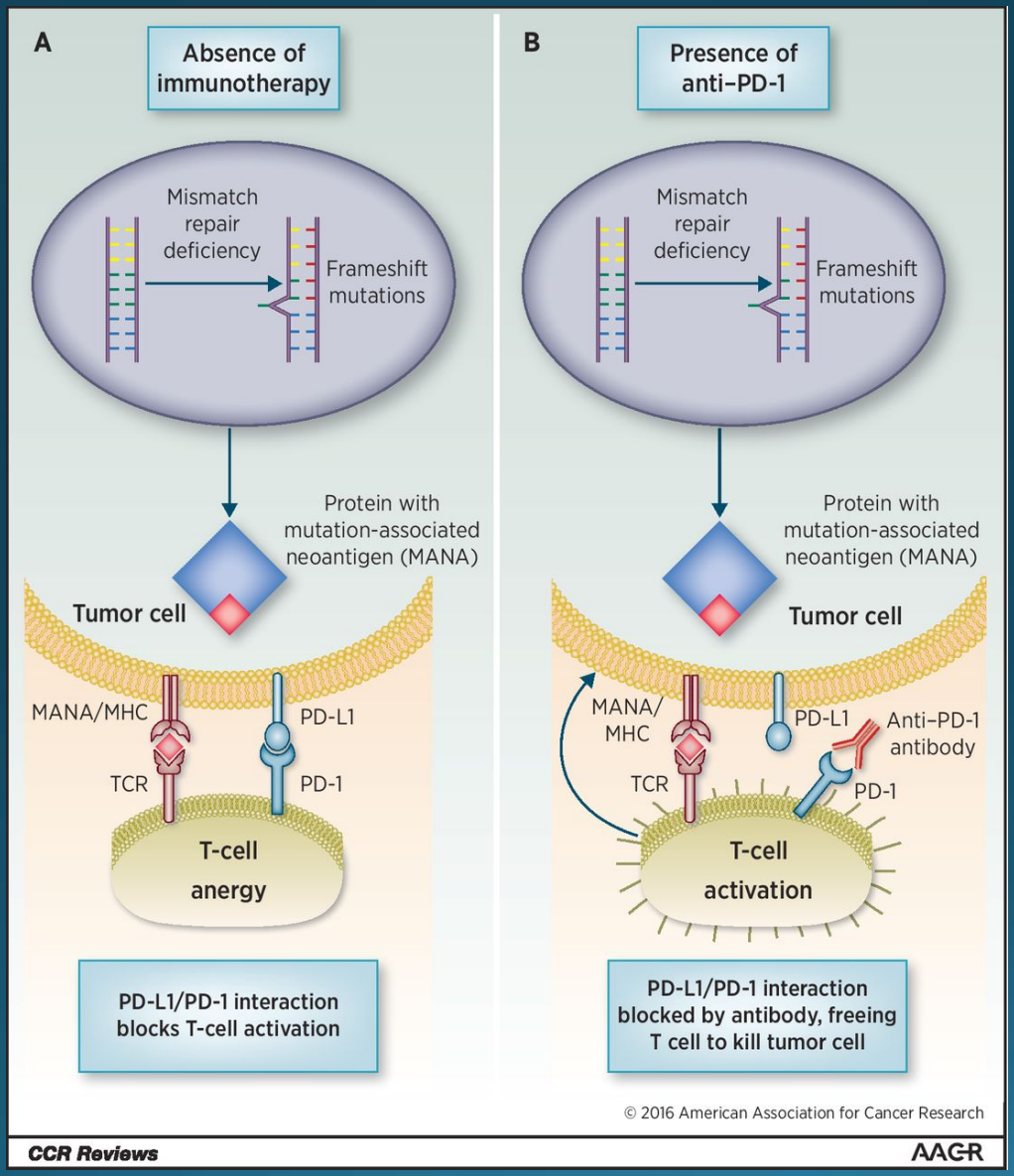
MSI TESTING BY PCR

- A PCR test is used to look for a change in microsatellite size in the tumor compared to the patient's non-tumor tissue.
- Microsatellite repeats amplified from tumor and normal tissue.
- Amplified DNA separated by size using electrophoresis.
- Commercial kit available



UCSF Website: http://www.ucsfcme.com/2009/slides/MAP0901A/0GrenertMSIBasicsForPathologists%20.pdf

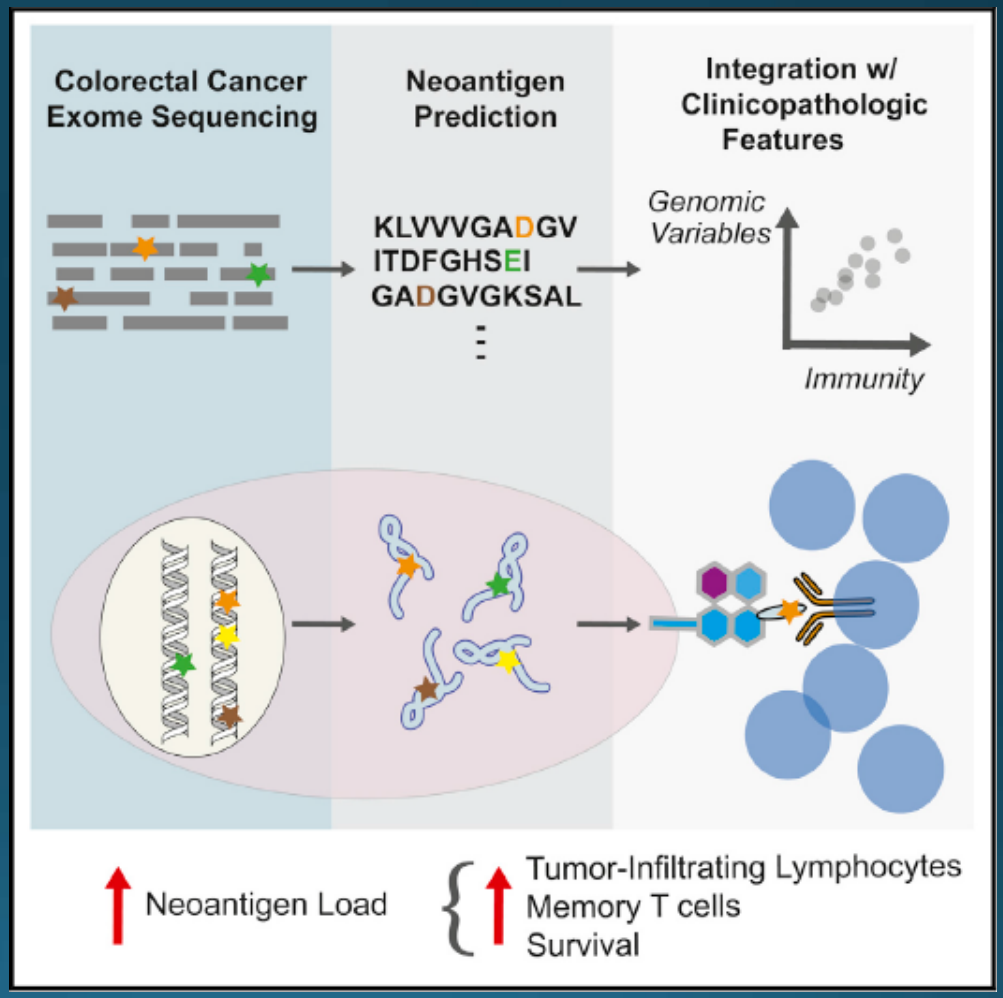
Mismatch repair and mutations



Dudley CCR 2016

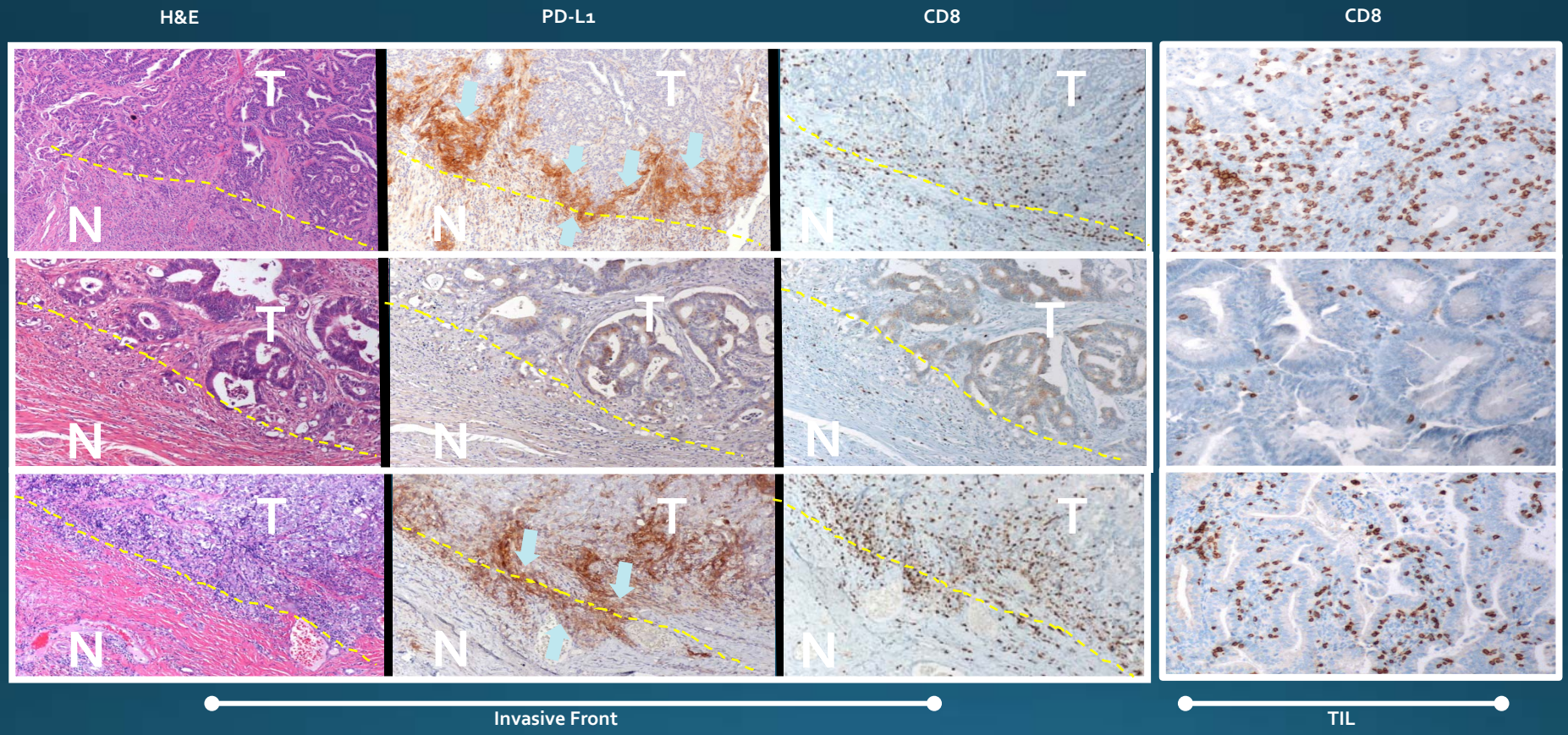
Hypermutation and Immuno-Oncology

- In CRC, MSI-H is associated with increases in immune infiltration and expression of immune checkpoint regulators[1,2]
- MSI-H is also associated with increased number of mutations per tumor
- Tumor mutations produce tumor-specific neoantigens, which when expressed on the tumor cell surface, are a target for T cells
- May improve response to immunotherapy
- Elevated neoantigen load in CRC is associated with improved survival[2]



1. Llosa NJ, et al. *Cancer Discov*. 2015;5:43–51.
2. Giannakis M, et al. *Cell Reports*. 2016;15:857–865.

Baseline PD-L1 Expression and CD8 T Cell Infiltration



Le ASCO 2015

MSI in more than CRC

Cancer Type	General population risk	Lynch syndrome (MLH1 and MSH2 heterozygotes)	
		Risk	Mean age of onset
Colon	5.5%	52-82%	44-61 years
Endometrium	2.7%	25-60%	48-62 years
Stomach	< 1%	6-13%	56 years
Ovary	1.6%	4-12%	42.5 years
Hepatobiliary tract	< 1%	1.4-4%%	Not reported
Urinary tract	< 1%	1-4%	~55 years
Small bowel	< 1%	3-6%	49 years
Brain/central nervous system	< 1%	1-3%	~50 years
Sebaceous neoplasms	< 1%	1-9%	Not reported

Study Design

Colorectal Cancers

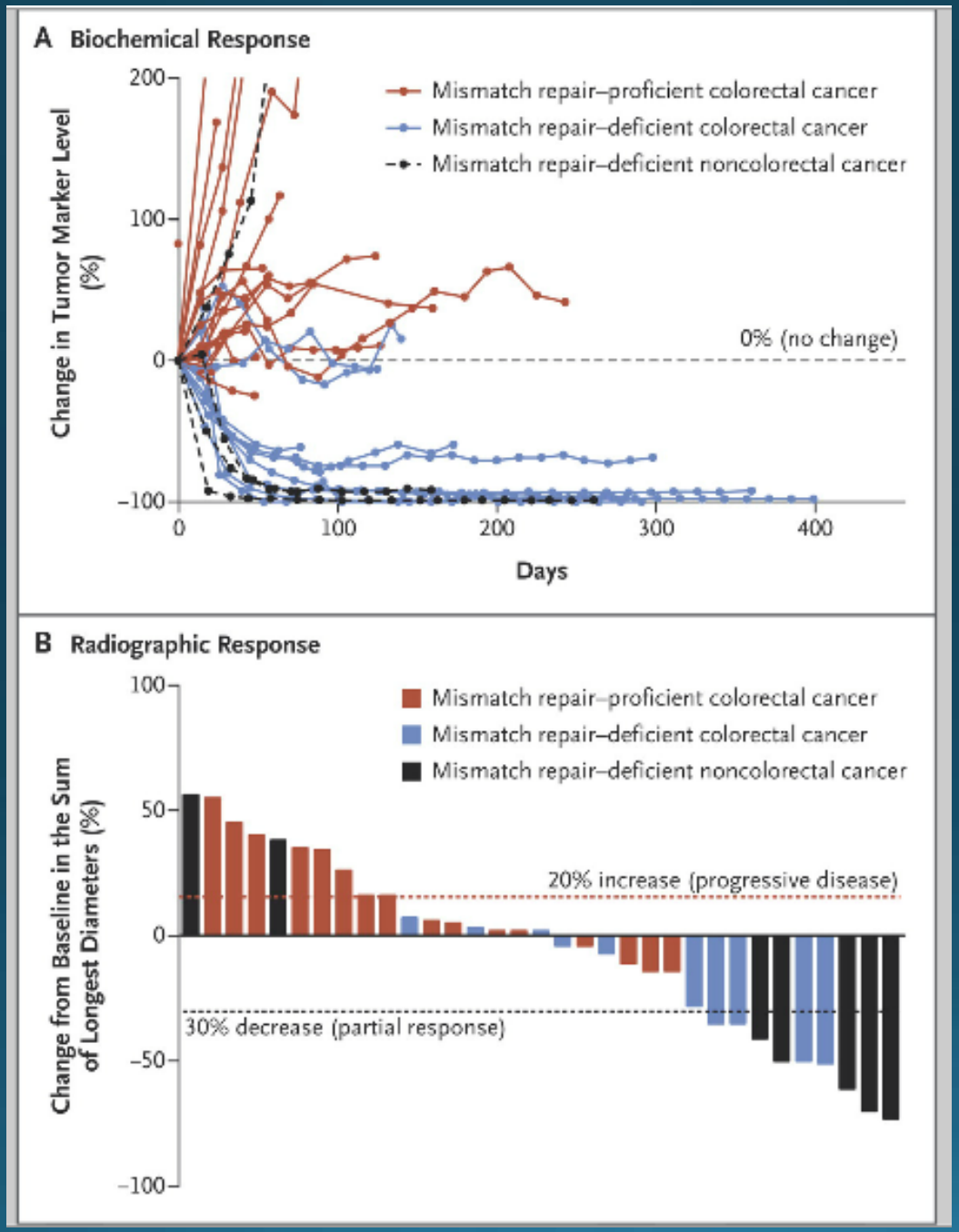
Cohort A
Deficient in Mismatch Repair (n=25)

Cohort B
Proficient in Mismatch Repair (n=25)

Non-Colorectal Cancers

Cohort C
Deficient in Mismatch Repair (n=21)

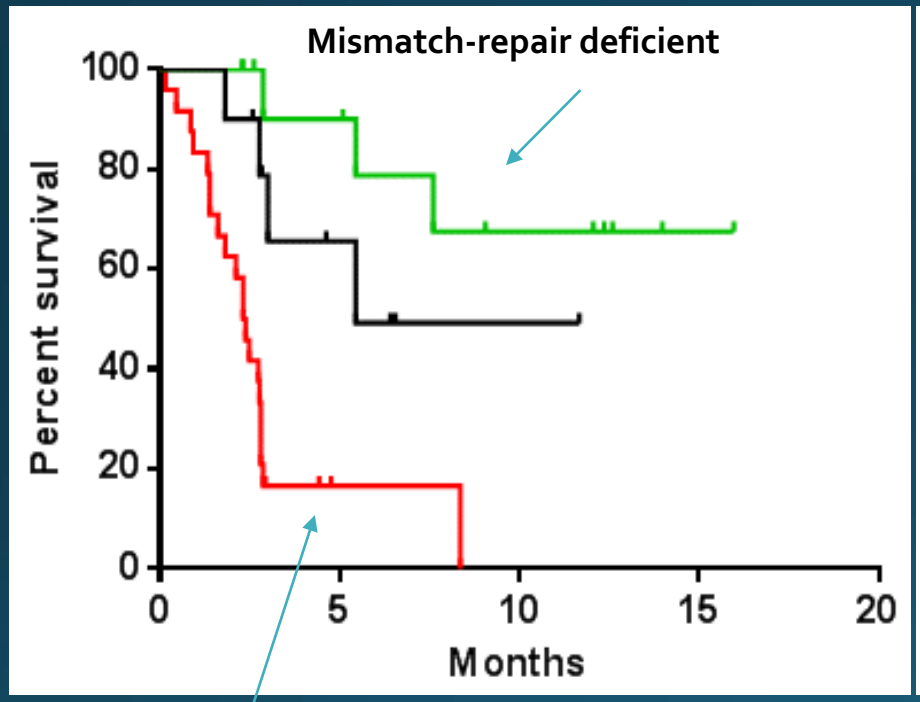
- Anti-PD1 (Pembrolizumab) – 10 mg/kg every 2 weeks
- Primary endpoint: immune-related 20-week PFS rate and response rate
- Mismatch repair testing using standard PCR-based test for detection of microsatellite instability


A Biochemical Response
Change in Tumor Marker Level (%)
200
100
0
−100
0
100
200
300
400
Days
Mismatch repair–proficient colorectal cancer
Mismatch repair–deficient colorectal cancer
Mismatch repair–deficient noncolorectal cancer
0% (no change)
B Radiographic Response
Change from Baseline in the Sum of Longest Diameters (%)
100
50
0
−50
−100
Mismatch repair–proficient colorectal cancer
Mismatch repair–deficient colorectal cancer
Mismatch repair–deficient noncolorectal cancer
20% increase (progressive disease)
30% decrease (partial response)

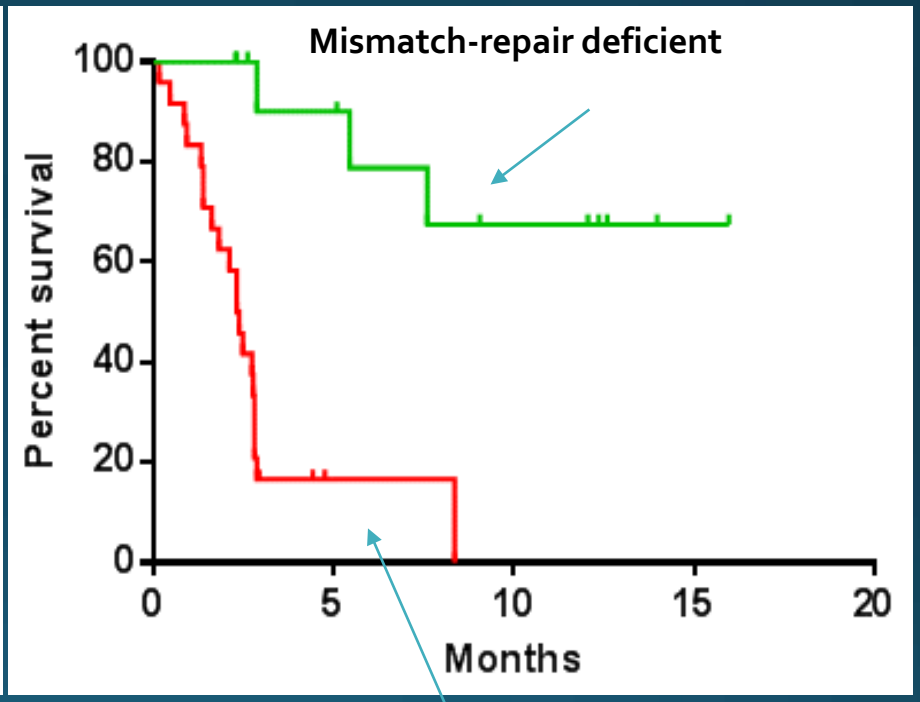
Le, NEJM 2015

Progression-Free Survival

All Cohorts



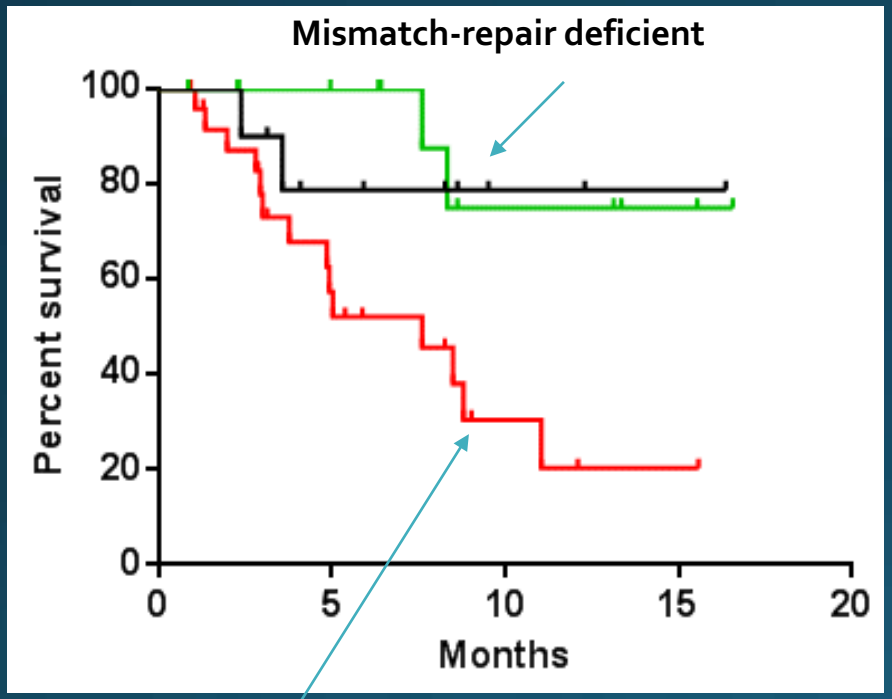
CRC Cohorts



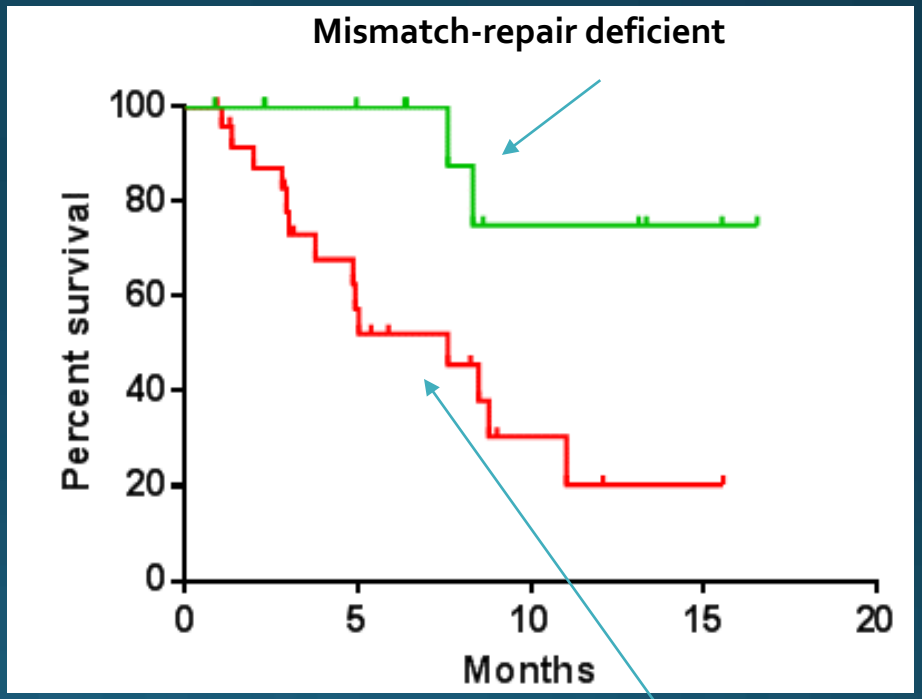
Le ASCO 2015

Overall Survival

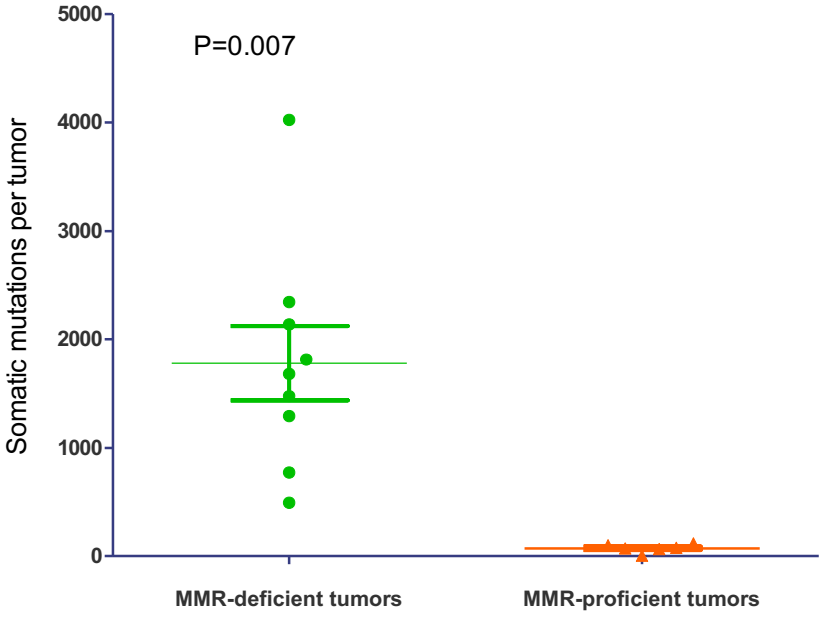
All Cohorts

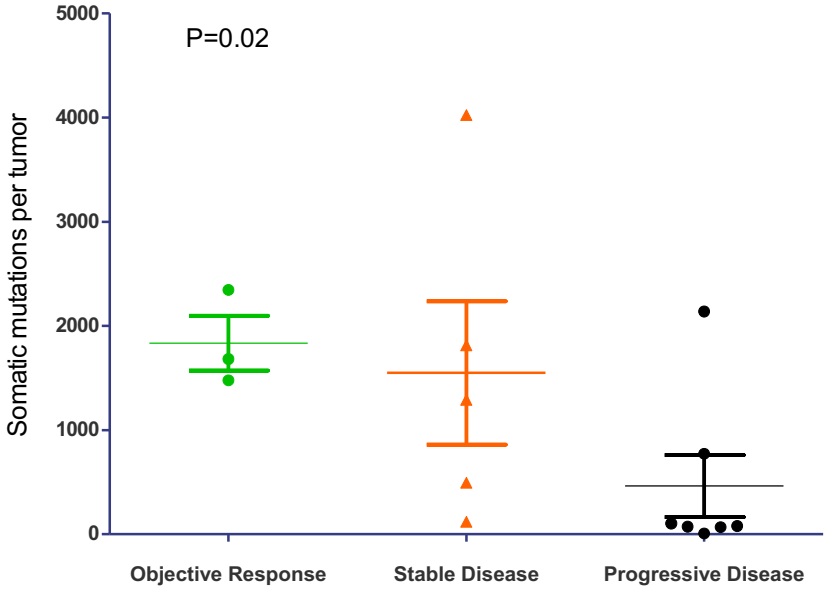


CRC Cohorts



Mutation Burden is Associated with Efficacy



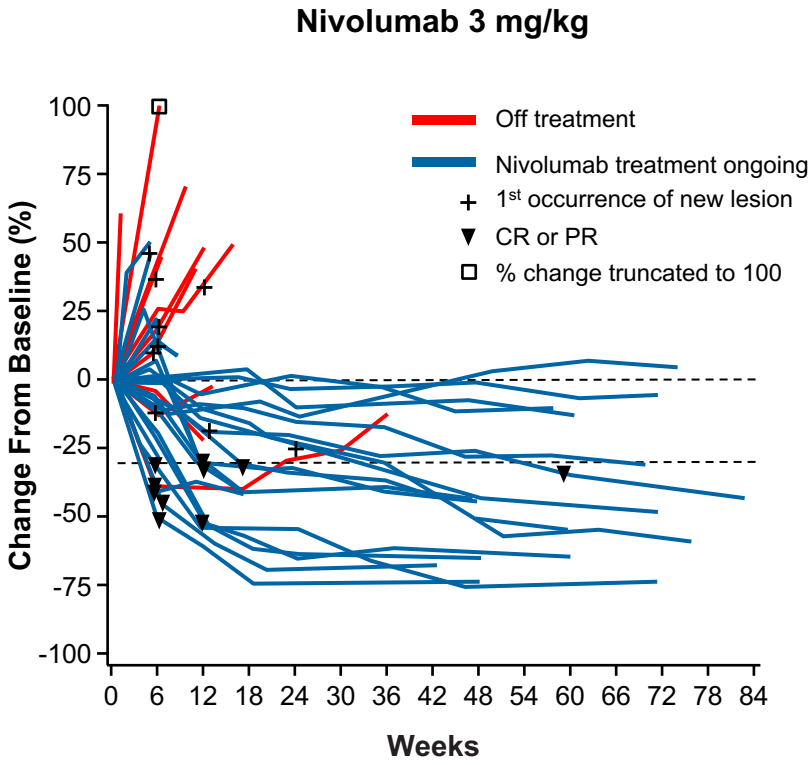


Le ASCO 2015

Investigator-Assessed Best Overall Response in Patients With MSI-H Receiving Nivolumab Monotherapy

	Nivolumab 3 mg/kg (n = 47)[a]
ORR, n (%) (95% exact CI)	12 (25.5) (15.4, 38.1)
Complete response	0
Partial response	12 (25.5)
Stable disease	14 (29.8)
Progressive disease	17 (36.2)
Unable to determine	4 (8.5)
Median time to response, mo (range)	2.12 (1.3–13.6)
Median duration of response, mo (range)	NE (0.0[b]–15.2[b])

[a]Patients with ≥ 12 weeks of follow-up
[b]Includes censored observations
CR = complete response; NE = not estimable; PR = partial response



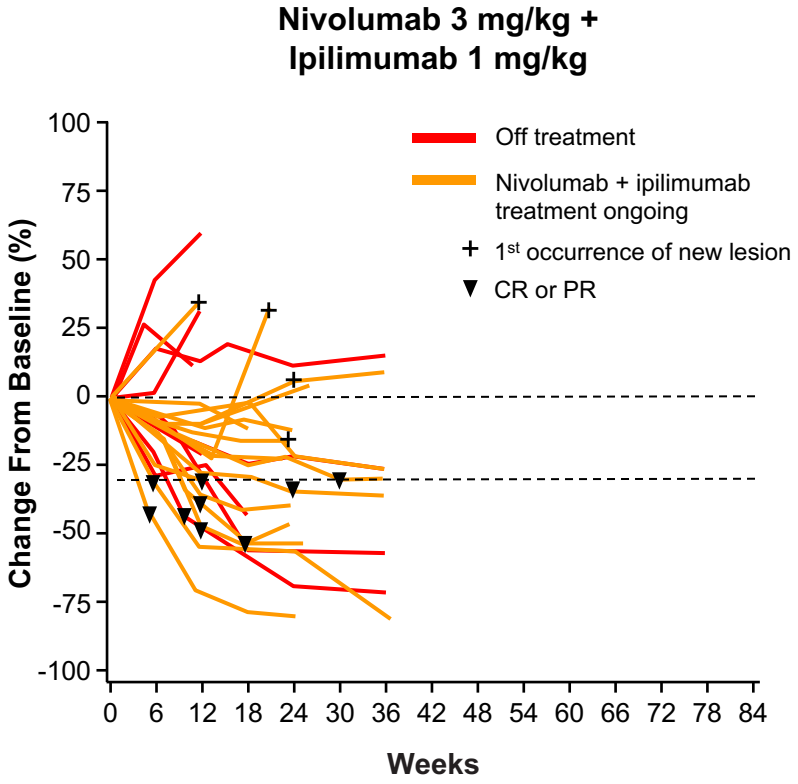
Horizontal reference line indicates 30% reduction

Overman ASCO 2016

Investigator-Assessed Best Overall Response in Patients With MSI-H Receiving Nivolumab + Ipilimumab

	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg (n = 27)[a]
ORR, n (%) (95% exact CI)	9 (33.3) (18.6, 50.9)
Complete response	0
Partial response	9 (33.3)
Stable disease	14 (51.9)
Progressive disease	3 (11.1)
Unable to determine	0
Median time to response, mo (range)	2.73 (1.2–6.9)
Median duration of response, mo (range)	NE (NE–NE)

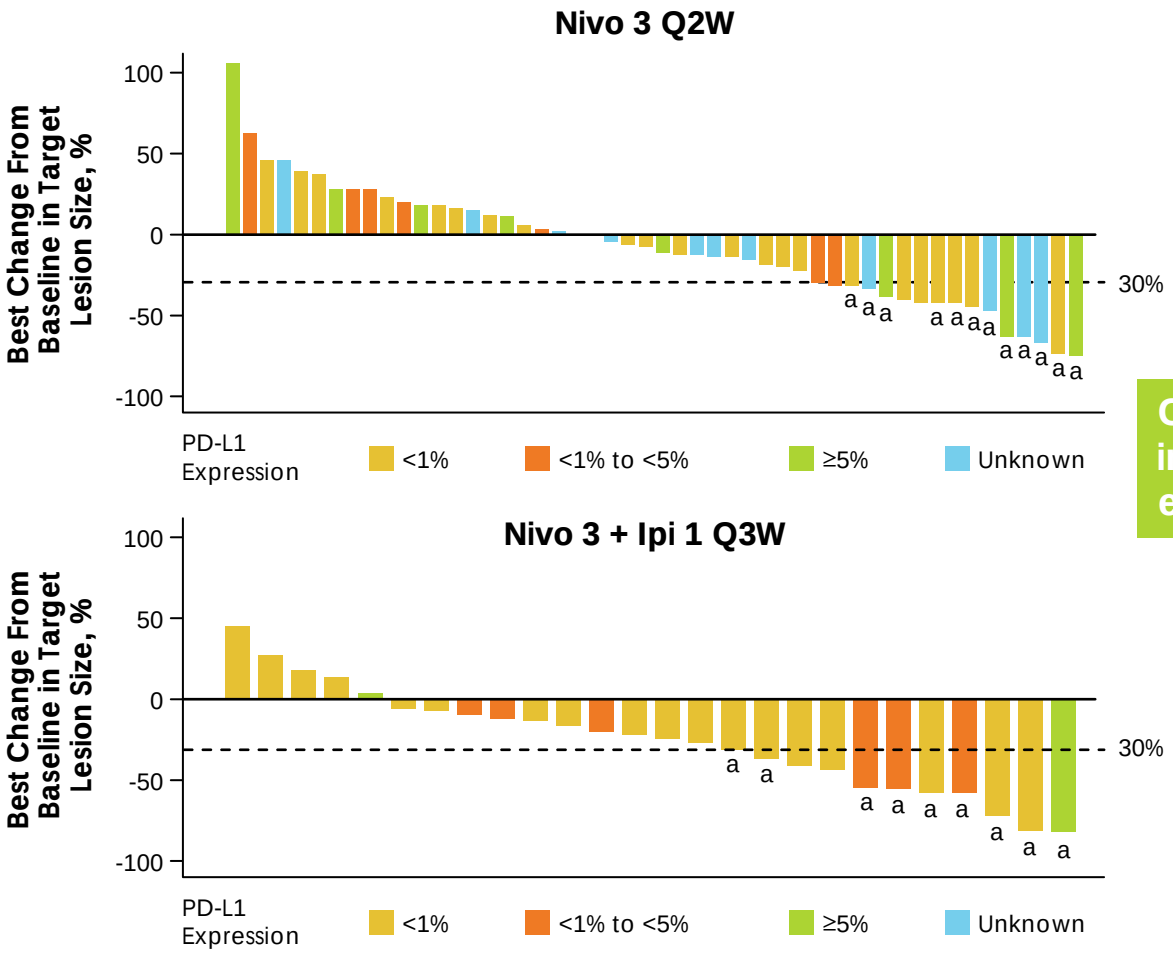
[a]Patients with ≥ 12 weeks of follow-up
[b]Includes censored observations
CR = complete response; NE = not estimable; PR = partial response



Horizontal reference line indicates 30% reduction

Overman ASCO 2016

Nivolumab ± Ipilimumab: CheckMate 142
Response by pd-l1 Status

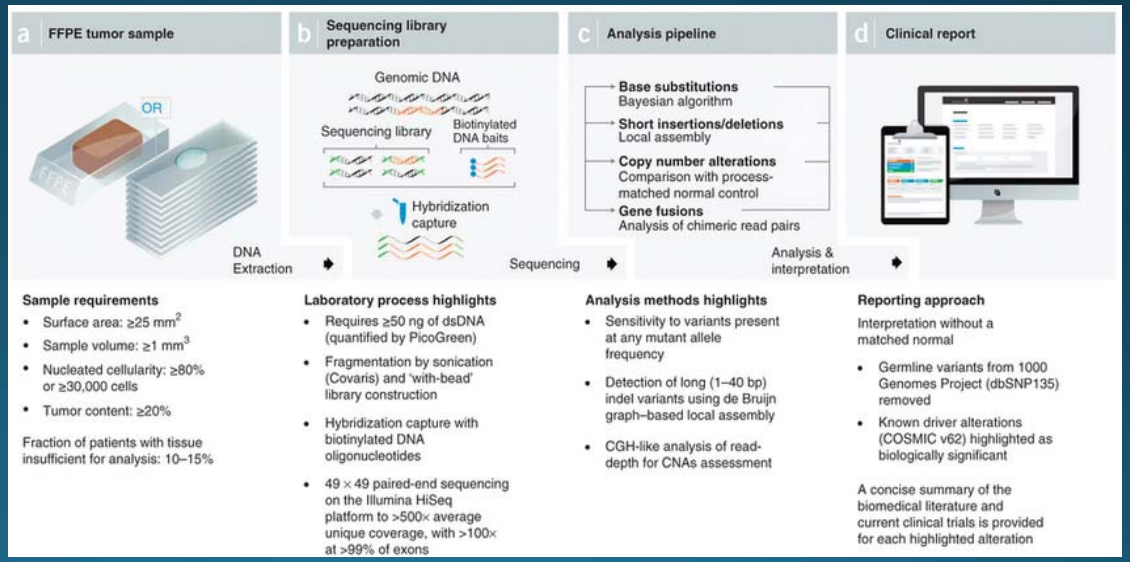


Clinical activity was observed in patients regardless of PD-L1 expression level

Overman M et al. Poster presentation at ESMO 2016. 479P.
Database lock: April 2016.

Testing of tumor mutational burden (TMB)

- Next generation sequencing
- Number of single nucleotide somatic mutations is counted
- This number is divided by the total number of megabases to calculate the average number of mutations/megabase (Mb) which is extrapolated to the whole genome
- In general >10 mutations/Mb designates frequent neoantigen formation
- FMI and Caris
  - TMB high ≥20 mutations/Mb
  - TMB intermediate = 6-19 mutations/Mb
  - TMB low ≤ 5 mutations/Mb



Emerging Role of Immunotherapy in Gastrointestinal Cancers: Mutation and Neoantigen Burden as Predictors of Response

HER2 negative gastric cancer

- 45 year old man with a history of HTN, type I DM, hypothyroidism, and allergic rhinitis presented with a 4 month history of severe reflux refractory to PPI
- Endoscopy performed showing a GE junctional mass from the distal esophagus to proximal stomach. Biopsy showed moderately differentiated adenocarcinoma, HER2 negative.
- PET scan showed hypermetabolic uptake in the gastric cardia mass and periceliac nodes
- He received neoadjuvant chemoradiation with 5FU and oxaliplatin
- He underwent resection with pathology showing minimal residual disease, but 4/21 LN were positive

HER2 negative gastric cancer

- 4 months after surgery surveillance PET scan showed 2 new liver lesions
- He was started on docetaxel but had progressive disease in 3 months
- He was then started on clinical trial with pembrolizumab
- He had an almost partial response and remains on therapy 14 months into treatment