Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Microsatellite Instability or Tumor Mutational Burden – High Cancers

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

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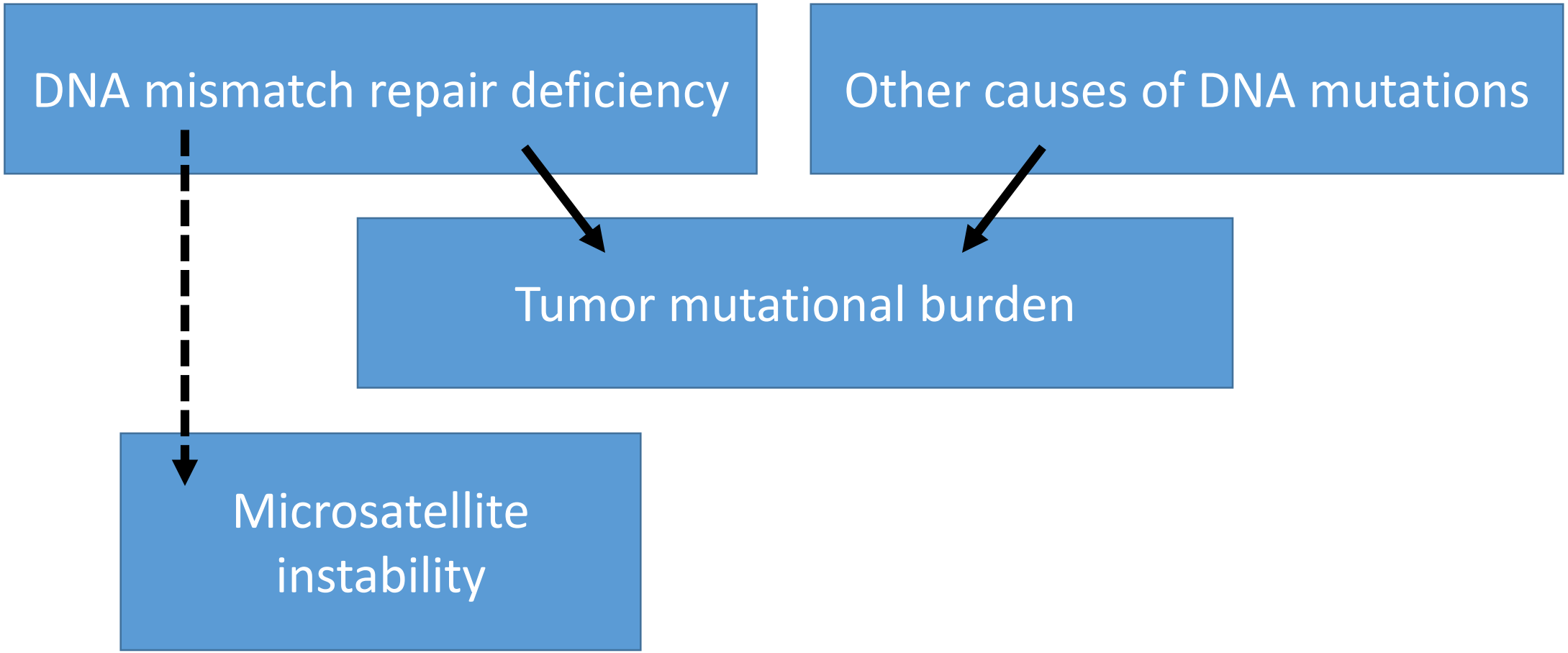
Disclosures

- Consulting Fees: Eisai, AstraZeneca, Agios
- Ownership Interest Less Than 5%: Parthenon Therapeutics
- I will be discussing non-FDA approved indications during my presentation.

A few definitions

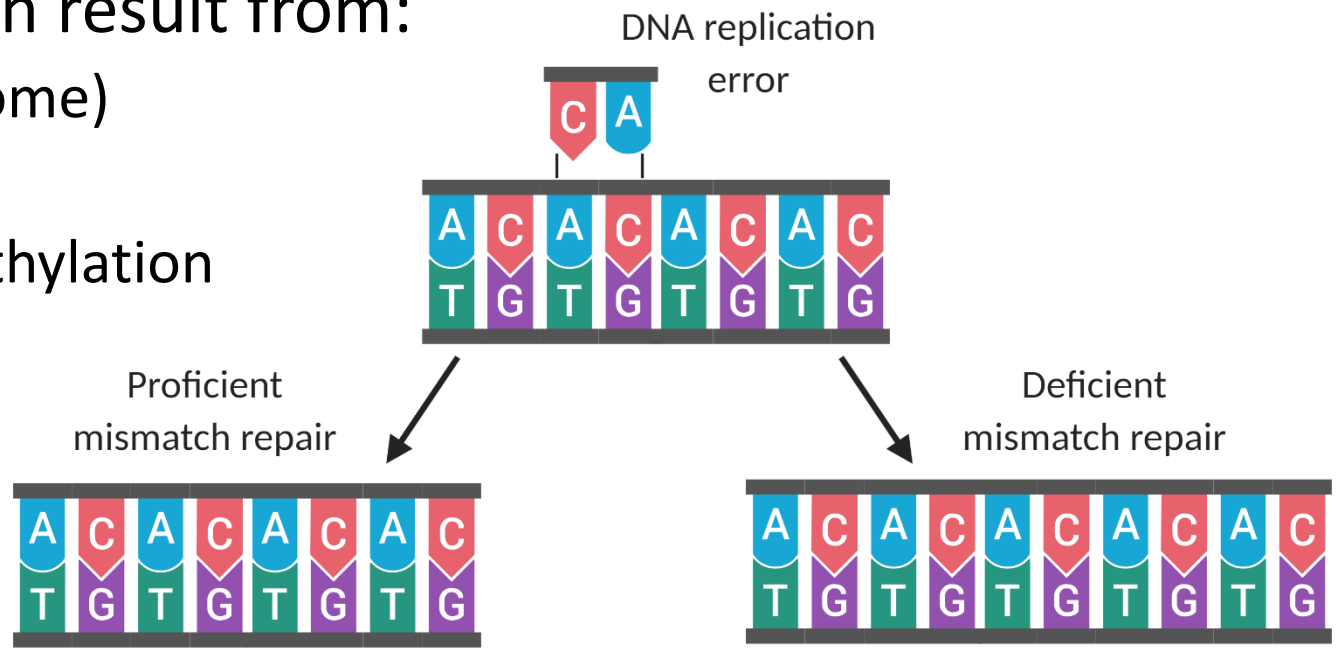
- **DNA mismatch repair deficiency:** Sub-optimal cell machinery for fixing mistakes made during DNA replication.
- **Tumor mutational burden:** The number of mutations in a cancer's genome.
- **Microsatellite instability:** The number of repeated DNA bases in a microsatellite changes during DNA copying. The presence of MSI is phenotypic evidence that DNA mismatch repair is not functioning properly.

A few definitions



DNA mismatch repair

- MMR dysfunction can be caused by mutations in genes that code for MMR proteins (MLH1, MSH2, MSH6, PMS2)
- Mutations in MMR proteins can result from:
  - Hereditary causes (Lynch syndrome)
  - Somatic mutations
  - Silencing through promoter methylation



Somatic mutation: *an alteration in DNA that occurs after birth; can occur in any non-germline cell*

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Microsatellite Instability

Microsatellites are stretches of DNA with a repetitive sequence of nucleotides and are susceptible to acquiring errors when defective MMR genes are present.

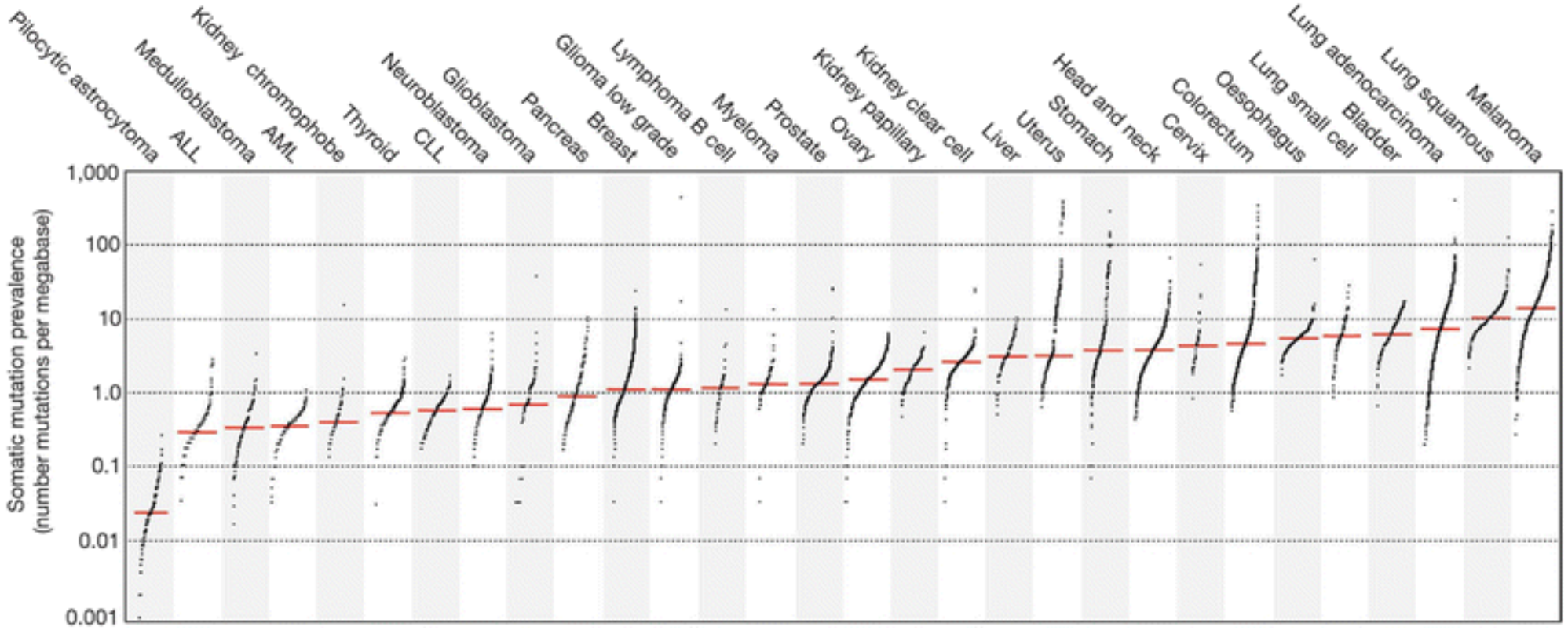
Method to measure MSI/MMR	What is measured?
Polymerase chain reaction (PCR)	5 targeted mononucleotide loci in the cancer DNA
Immunohistochemical staining (IHC)	Presence or absence of MMR proteins in sample
Next-generation sequencing (NGS)	Compares microsatellite sequences to matched normal or consensus sequence

Tumor mutational burden

TMB is a measure of the somatic mutations per area of a tumor's genome, reported in mutations/megabase (mut/Mb).

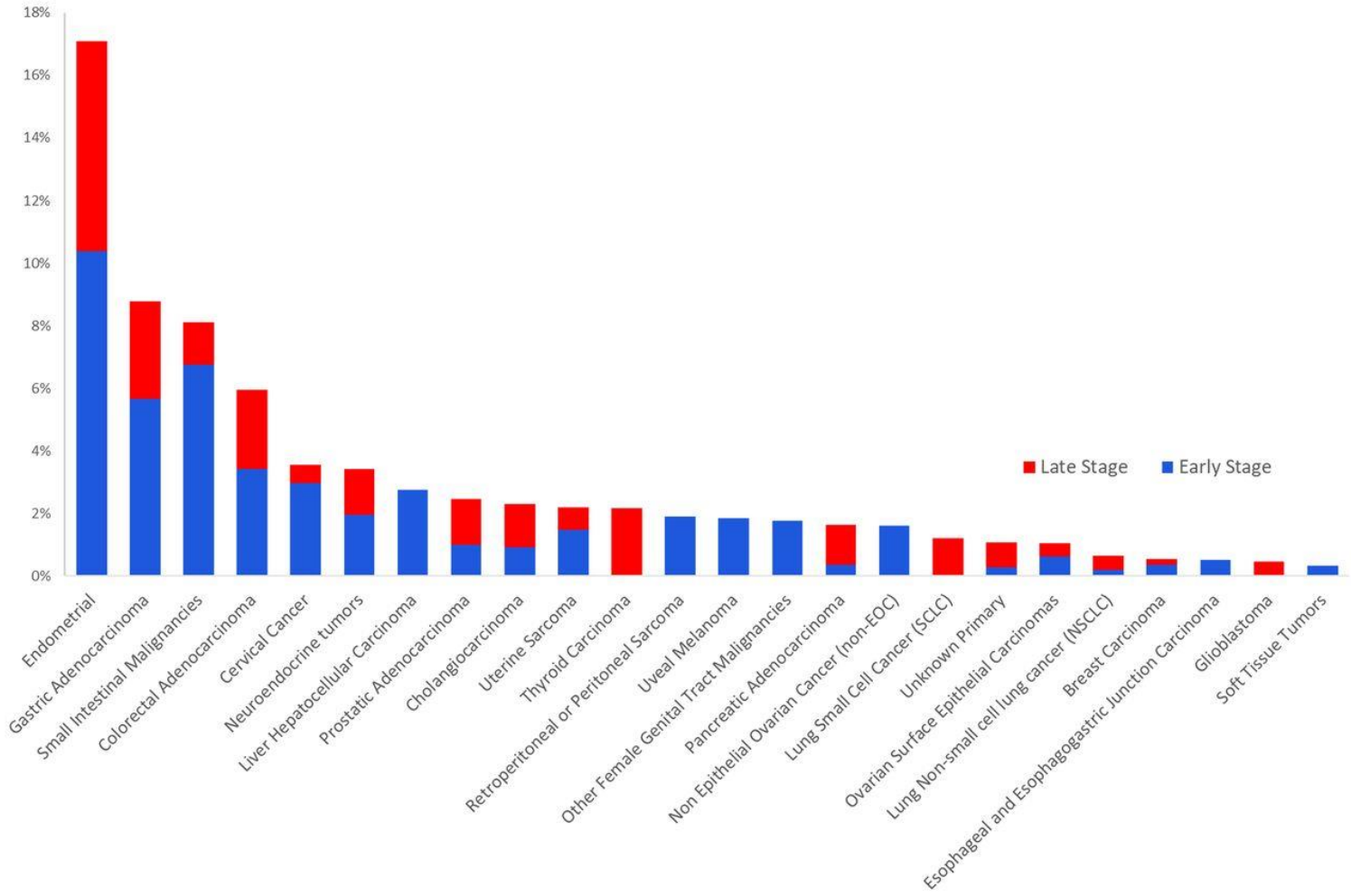
Method to measure TMB	What is measured?
Whole-exome sequencing (WES)	Sequencing all the protein-encoding regions of a tumor's DNA
Targeted panels	Sequencing of smaller portions of tumor's DNA

Somatic mutations by cancer type



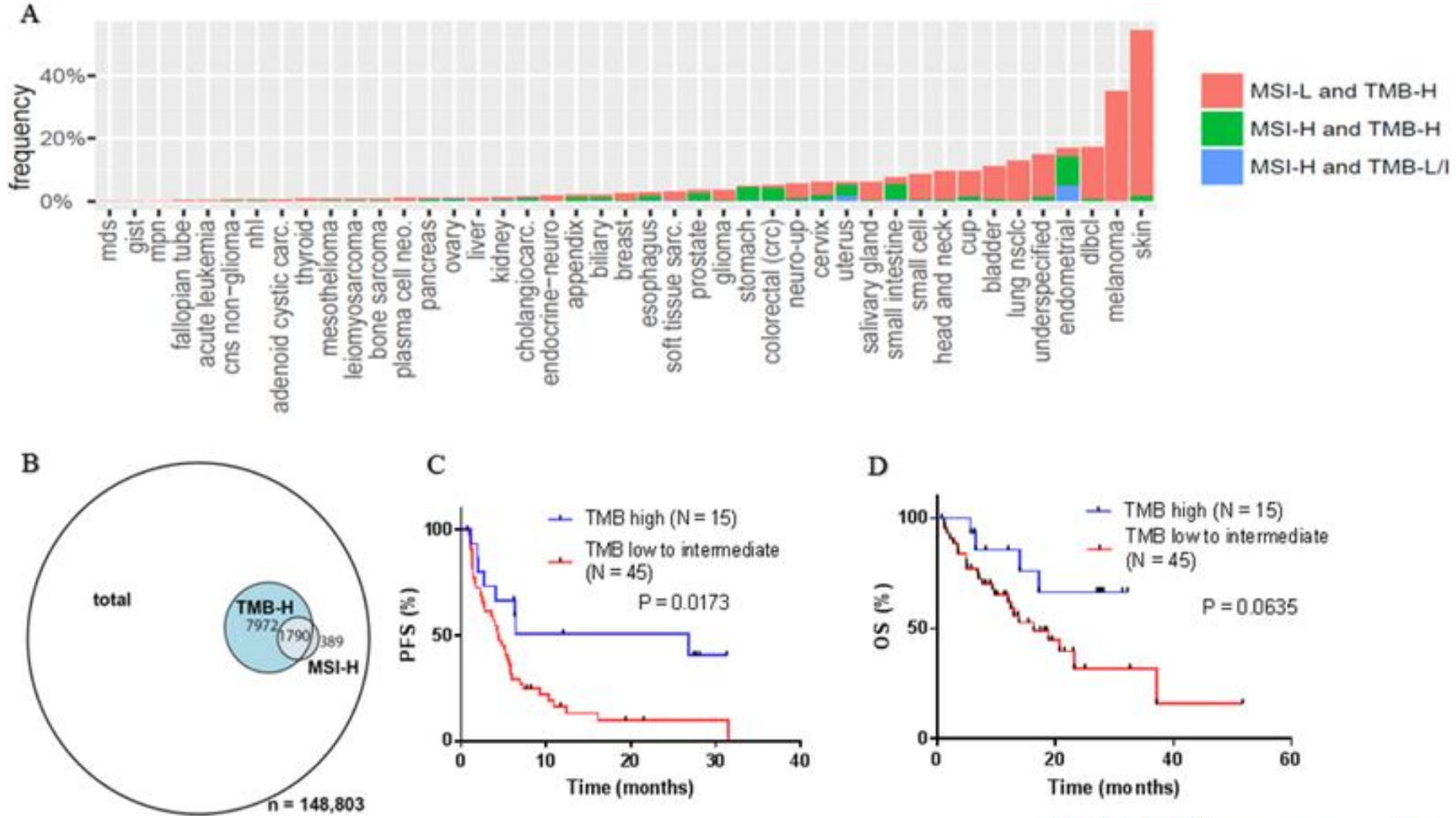
Alexandrov, Nature 2013.

Many tumors are MSI-high or MMR-deficient



Le, Science 2017.

Relationship between TMB and MSI



Goodman, Cancer Immunol Res 2019.

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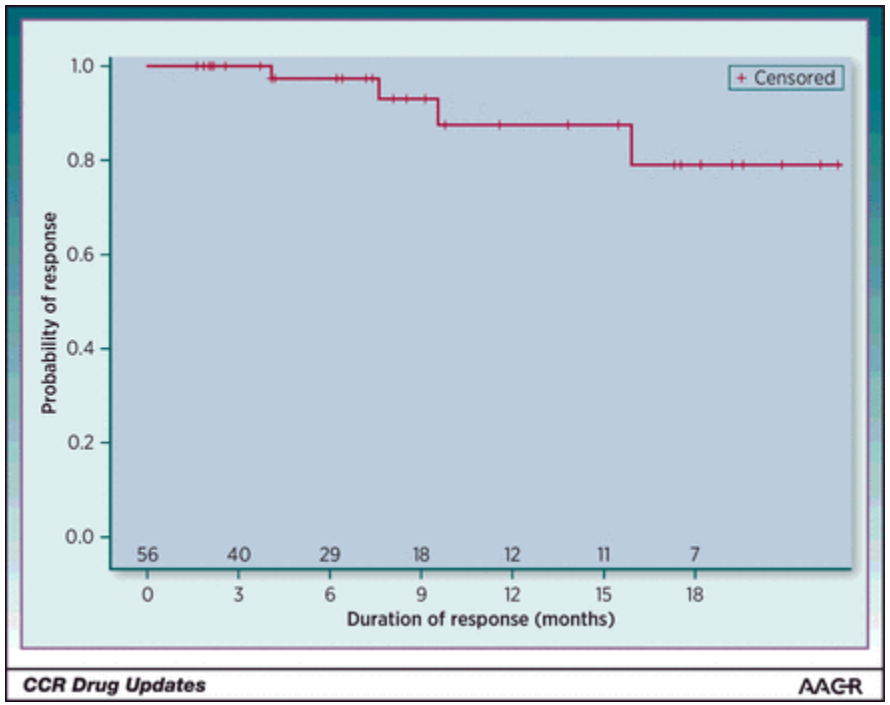
FDA-approved immunotherapies for MSI-high or TMB-high populations

	Drug	Indication	Dose
Tissue-agnostic	Pembrolizumab	Adult/pediatric patients with unresectable/metastatic **MSI-H or dMMR solid tumors** with progression on other treatment	Adults: 200 mg Q3W or 400 mg Q6W Pediatric: 2 mg/kg (up to 200 mg) Q3W
	Pembrolizumab	Adult/pediatric patients with unresectable/metastatic **TMB-high solid tumors** with progression on other treatment	Adults: 200 mg Q3W or 400 mg Q6W Pediatric: 2 mg/kg (up to 200 mg) Q3W
Colorectal cancer	Nivolumab	Patients >12 yr with **MSI-H/dMMR metastatic CRC** with progression after fluoropyrimidine, oxaliplatin, and irinotecan	≥40 kg: 240 mg Q2W or 480 mg Q4W <40 kg: 3 mg/kg Q2W
	Ipilimumab + nivolumab	Patients >12 yr with **MSI-H/dMMR metastatic CRC** with progression after fluoropyrimidine, oxaliplatin, and irinotecan	≥40 kg: 3 mg/kg nivolumab + 1 mg/kg ipilimumab Q3W for 4 doses, Then nivolumab 240 mg Q2W or 480 mg Q4W
	Pembrolizumab	**MSI-H or dMMR colorectal cancer** with progression after fluoropyrimidine, oxaliplatin, and irinotecan Or First-line treatment of **MSI-H or dMMR colorectal cancer**	Adults: 200 mg Q3W or 400 mg Q6W Pediatric: 2 mg/kg (up to 200 mg) Q3W

Pembrolizumab in MSI-high cancers

Trial	Study population
KEYNOTE-016	Colorectal cancer Non-colorectal cancer
KEYNOTE-164	Colorectal cancer
KEYNOTE-012	Retrospectively identified, PD-L1+ cancers
KEYNOTE-028	Retrospectively identified, PD-L1+ cancers
KEYNOTE-158	Non-colorectal cancers

All studies combined:
ORR: 39.6%
CR rate: 7%
78% of responses lasted ≥ 6 mo.

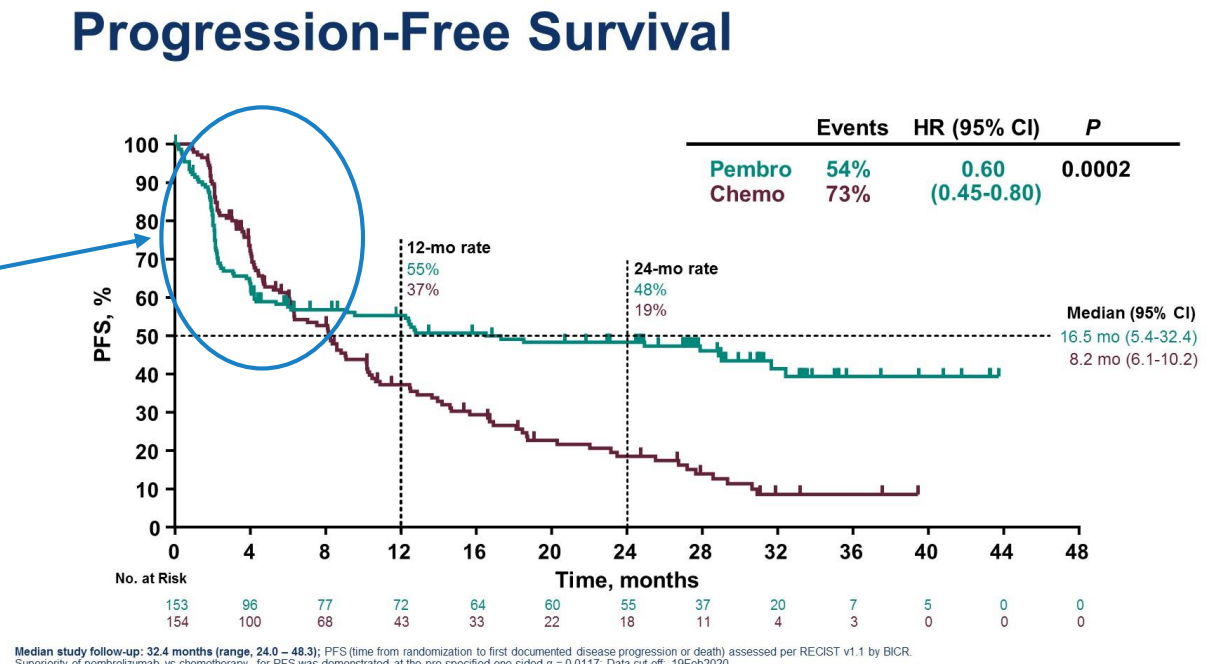


Marcus, Clin Cancer Res 2019.

First-line pembrolizumab for MSI-H/ dMMR CRC – KEYNOTE-177

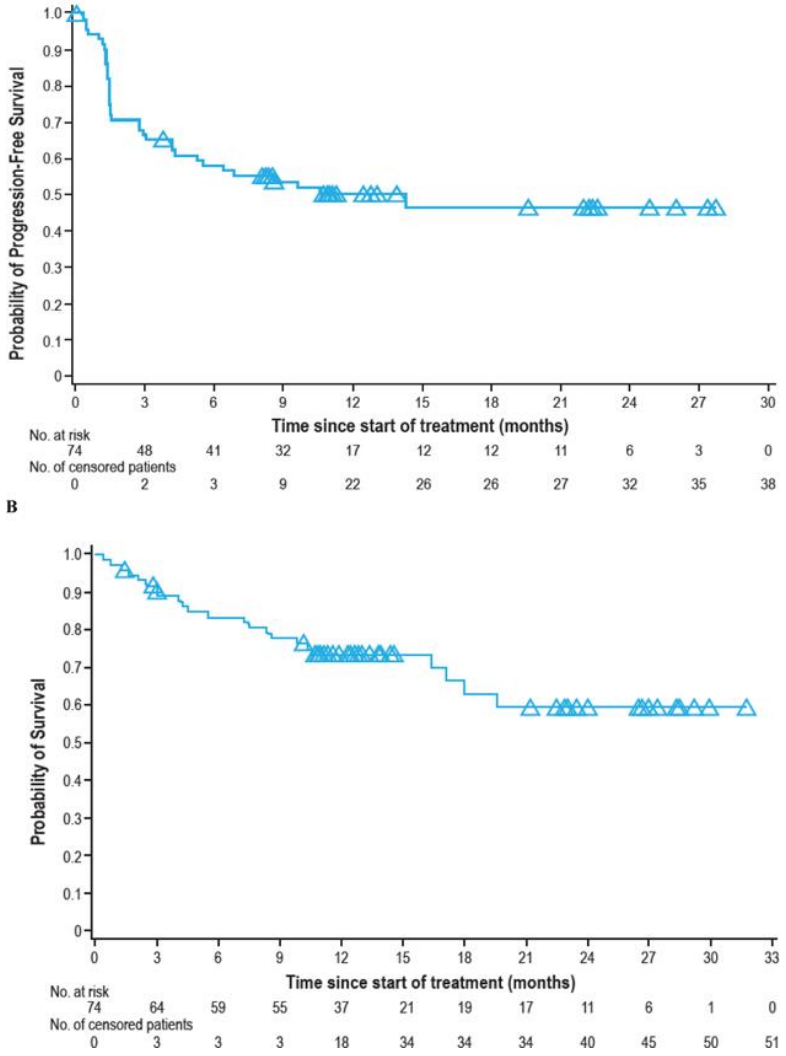
Treatment	N	ORR	CRR
Pembrolizumab	153	43.8%	11.1%
Investigator's choice	154	33.1%	3.9%

Cross-over of curves at early time point



Andre, ASCO 2020.

Nivolumab in MSI-high CRC



- CheckMate 142
- mCRC with MSI-H, progressed after ≥1 therapy
- Nivolumab 3 mg/kg Q2W
- At 12 months: 31% ORR
- 68.9% disease control >12 weeks
- Median DOR not reached

Overman, Lancet Oncol 2017.

First-line nivolumab + ipilimumab in MSI-high CRC

Nivolumab 3 mg/kg q2w + ipilimumab 1 mg/kg Q6W until disease progression

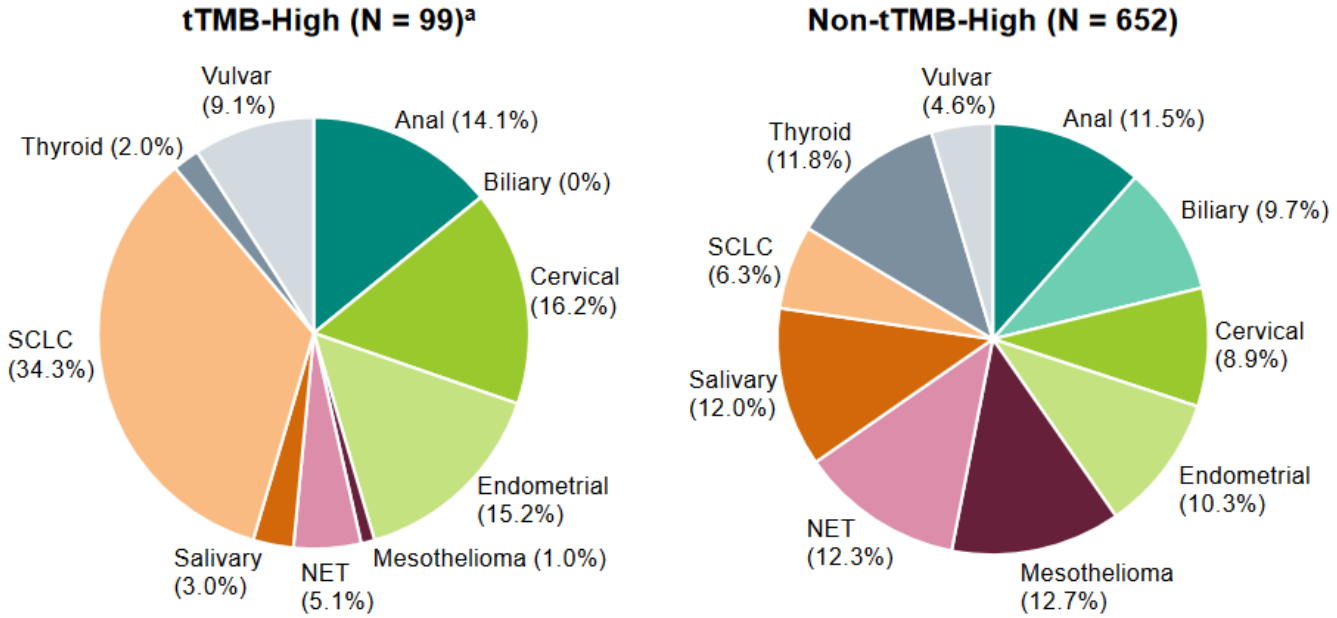
ORR[a,b] in Overall Patients and Subgroups.

			Nivolumab plus low-dose ipilimumab	
			n/N (%)	
ORR (all patients)[c]			27/45 (60)	
Age, years	< 65	≥ 65	14/22 (64)	13/23 (57)
ECOG performance status	0	≥ 1	13/25 (52)	14/20 (70)
Prior adjuvant/neoadjuvant therapy	Yes	No	12/19 (63)	15/26 (58)
Mutation status				
BRAF/KRAS wild type			8/13 (62)	
BRAF mutation[c]			12/17 (71)	
KRAS mutation			5/10 (50)	
Unknown			2/5 (40)	

Lenz, ASCO-GI 2020.

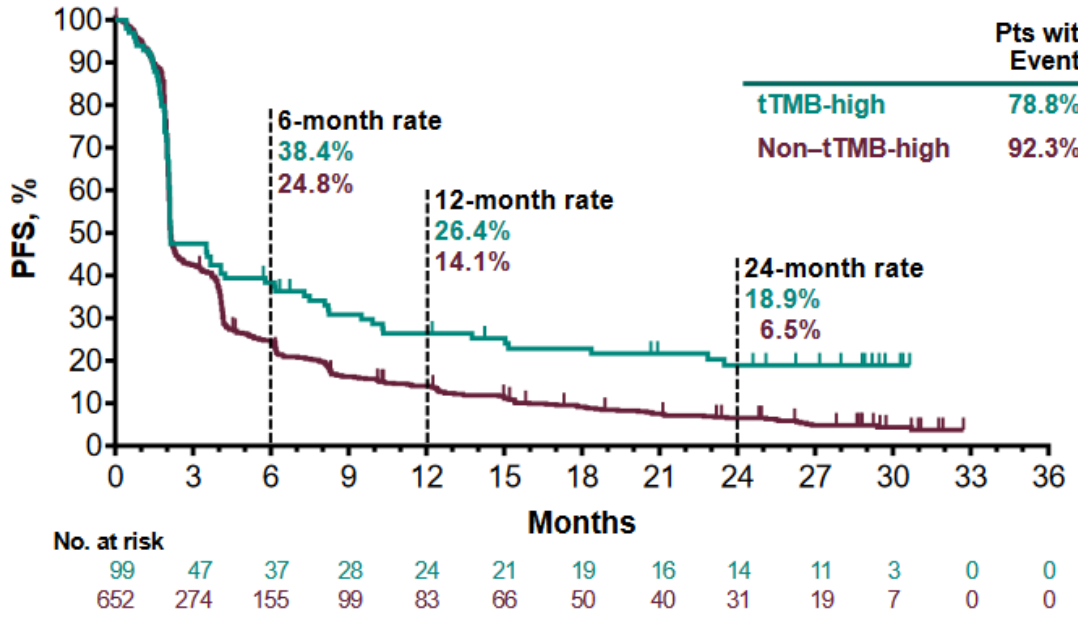
Pembrolizumab in TMB-high tumors

- Retrospective (but planned) analysis of KEYNOTE-158
- 13% of patients on the trial had TMB-high tumors (≥10 mut/Mb)

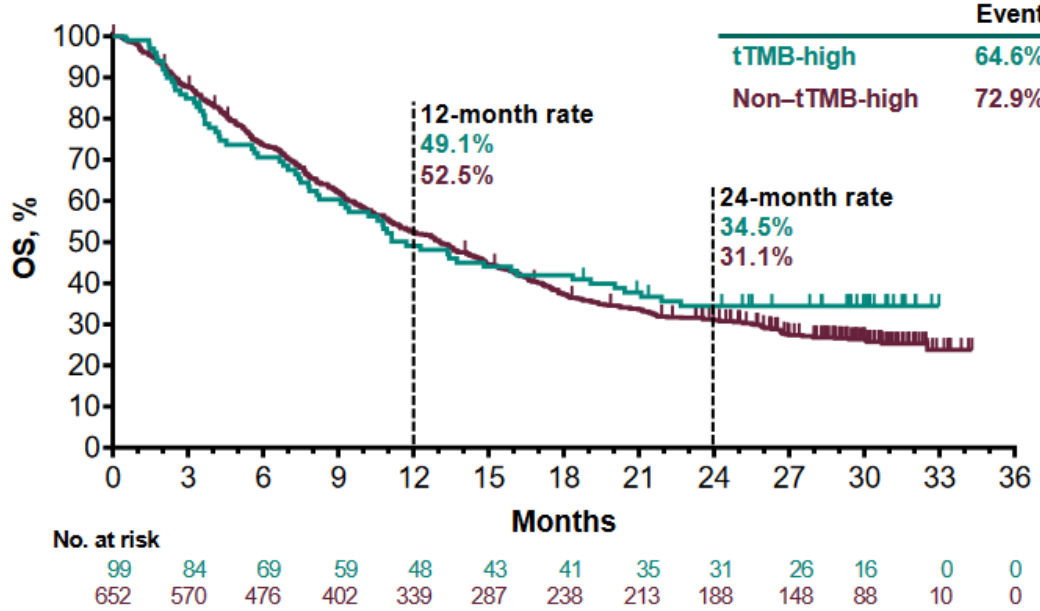


Marabelle, ESMO 2019

Pembrolizumab in TMB-high tumors



	Pts with Event	Median (95% CI), mo
tTMB-high	78.8%	2.1 (2.1-4.1)
Non–tTMB-high	92.3%	2.1 (2.1-2.3)



	Pts with Event	Median (95% CI), mo
tTMB-high	64.6%	11.7 (8.2-19.1)
Non–tTMB-high	72.9%	13.0 (11.5-14.6)

Marabelle, ESMO 2019

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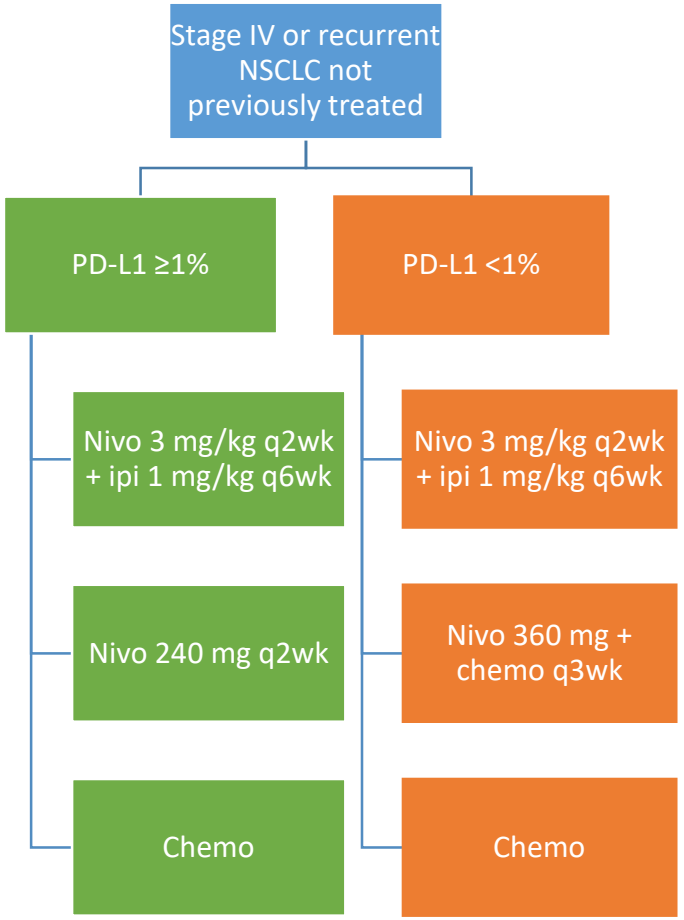
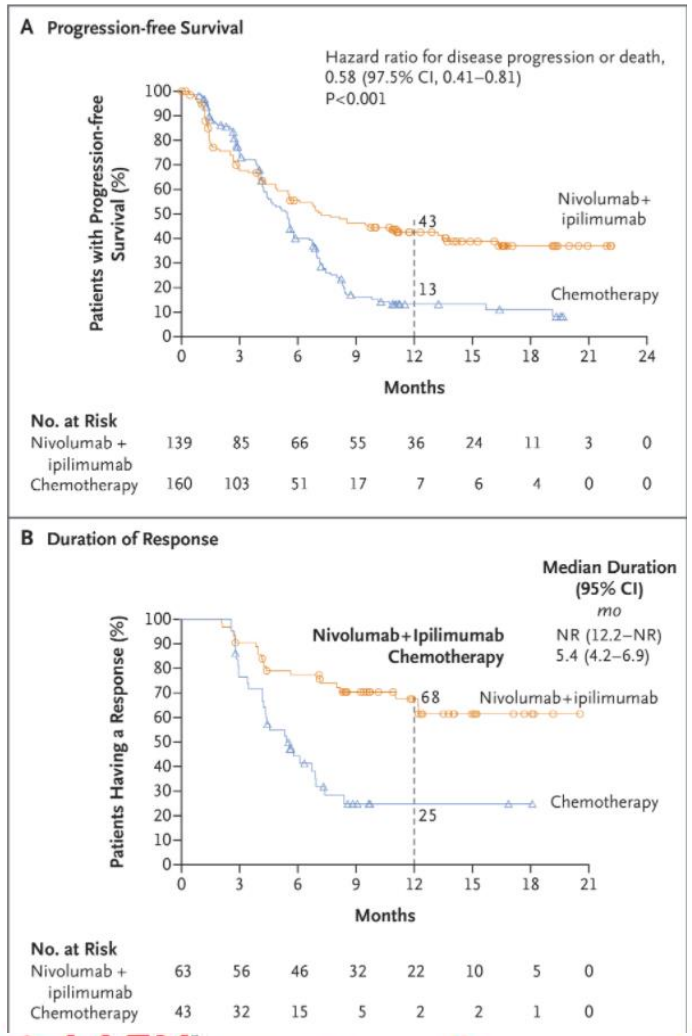
In development: First-line nivolumab + ipilimumab in TMB-high NSCLC

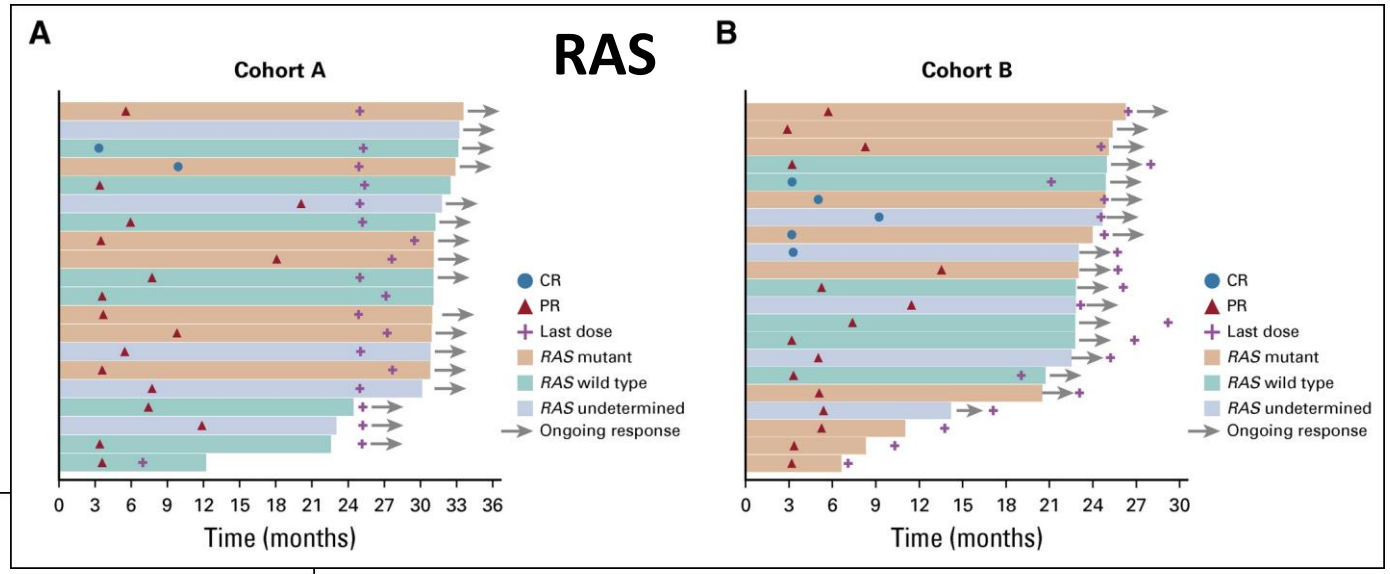


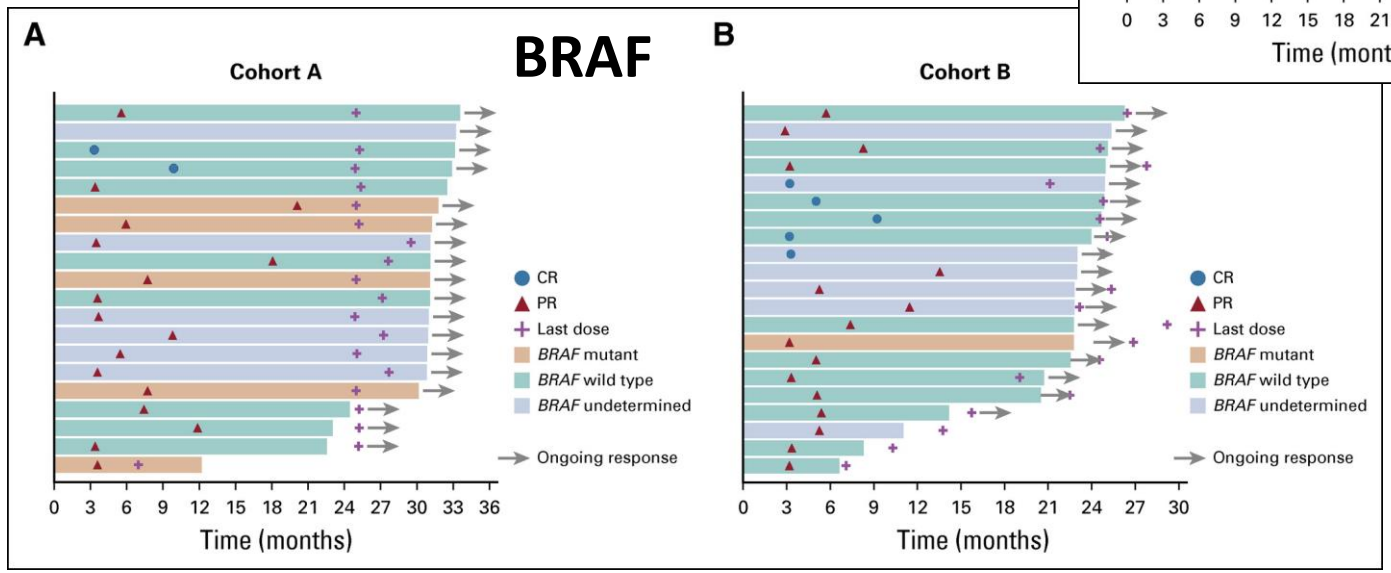
- Part 1 of Checkmate 227: patients with TMB ≥10 mut/mb
- Application for FDA approval based on TMB status <u>withdrawn</u> due to no difference in survival between low and high TMB



Hellmann, N Engl J Med 2018.

Under investigation: Pembrolizumab in MSI-H, BRAF/RAS-mutant CRC





Le, J Clin Oncol 2020.

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Future Directions

- No standard companion diagnostic test for all approvals – subjectivity of interpreting results; lack of consistency
- Not every clinic has access to these resources for measuring MSI/MMR/TMB (PCR, IHC, NGS) – may limit who can use the treatment
- Laid the groundwork for future biomarker-related drug approvals