Advances in Cancer Immunotherapy™

Immunotherapy for the Treatment of Microsatellite Instability or Tumor Mutational Burden – High Cancers: Biology Deep Dive

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Disclosures

- No relevant financial relationships to disclose
- I will not 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.

- **Neoantigen:** A mutated, immunogenic peptide

A Few Definitions

DNA mismatch repair deficiency

Other causes of DNA mutations

Tumor mutational burden

Microsatellite instability
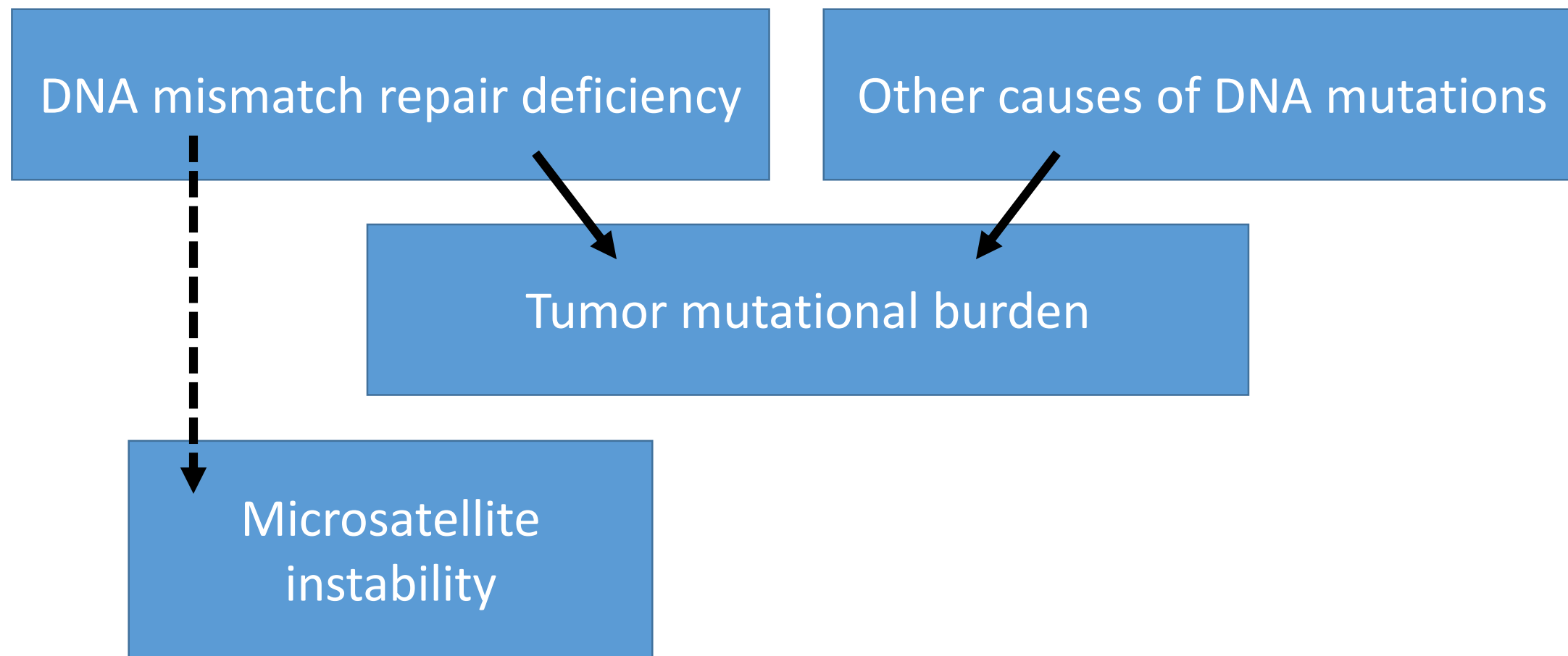
DNA Mismatch Repair

- 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

DNA replication error

Proficient mismatch repair

Deficient mismatch repair
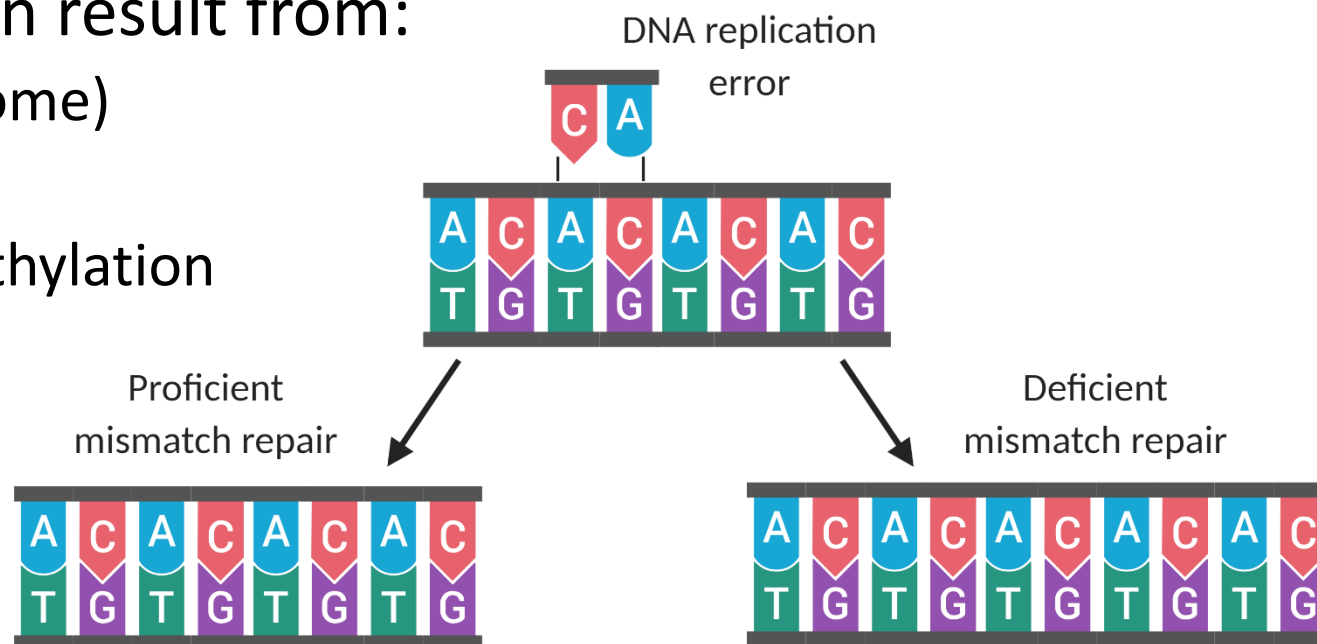
Microsatellite Instability

Microsatellites are stretches of DNA with a repetitive sequence of nucleotides and are susceptible to acquiring errors when defective MMR genes are present.
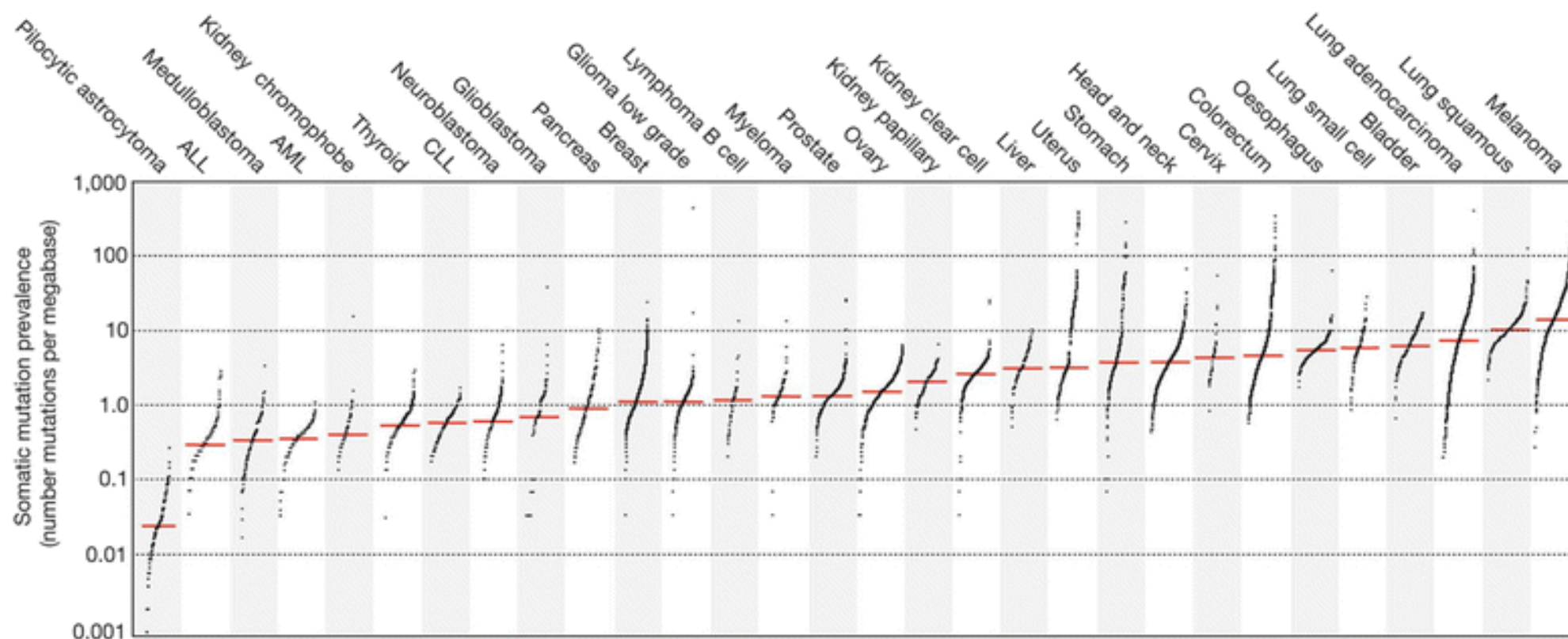
Method to measure MSI/MMR	What is measured?
Polymerase chain reaction (PCR)	5 targeted mononucleotide loci in the cancer DNA
Immunohistochemical staining (IHC)	Presence or absence of MMR proteins in sample
Next-generation sequencing (NGS)	Compares microsatellite sequences to matched normal or consensus 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).

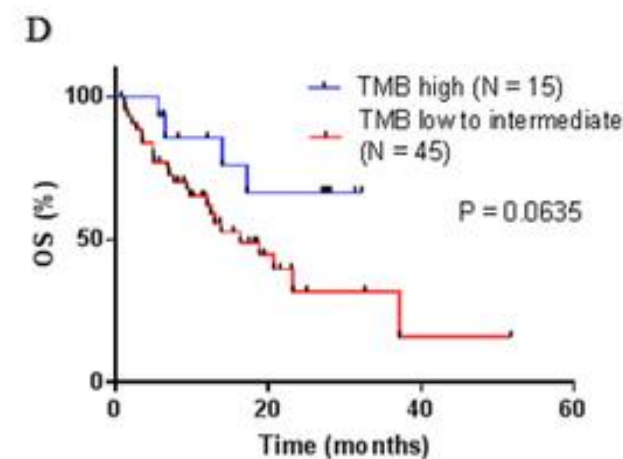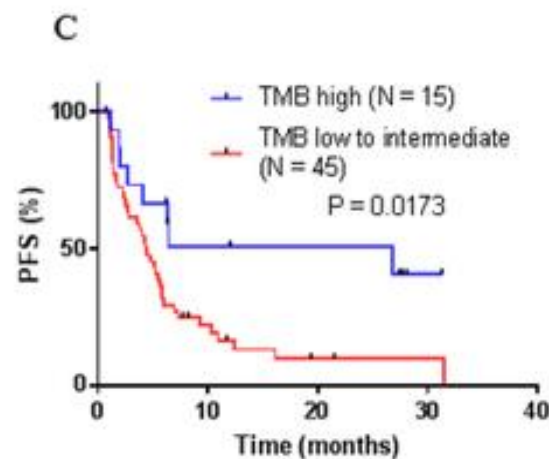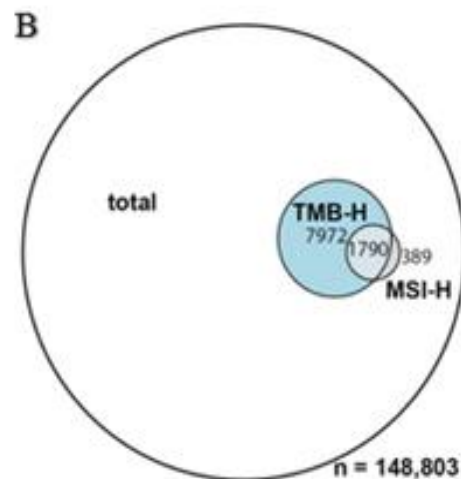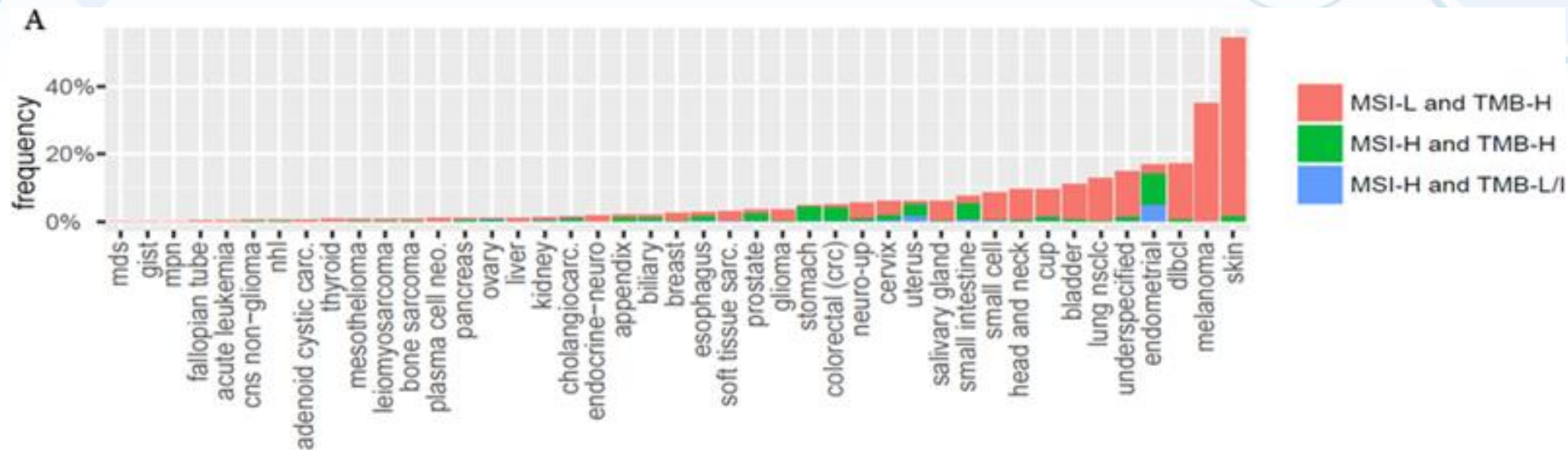| Method to measure TMB	What is measured?
Whole-exome sequencing (WES)	Sequencing all the protein-encoding regions of a tumor's DNA
Targeted panels	Sequencing of smaller portions of tumor's DNA

Somatic mutations by cancer type

Alexandrov, Nature 2013.

Many tumors are MSI-high or MMR-deficient

Le, Science 2017.
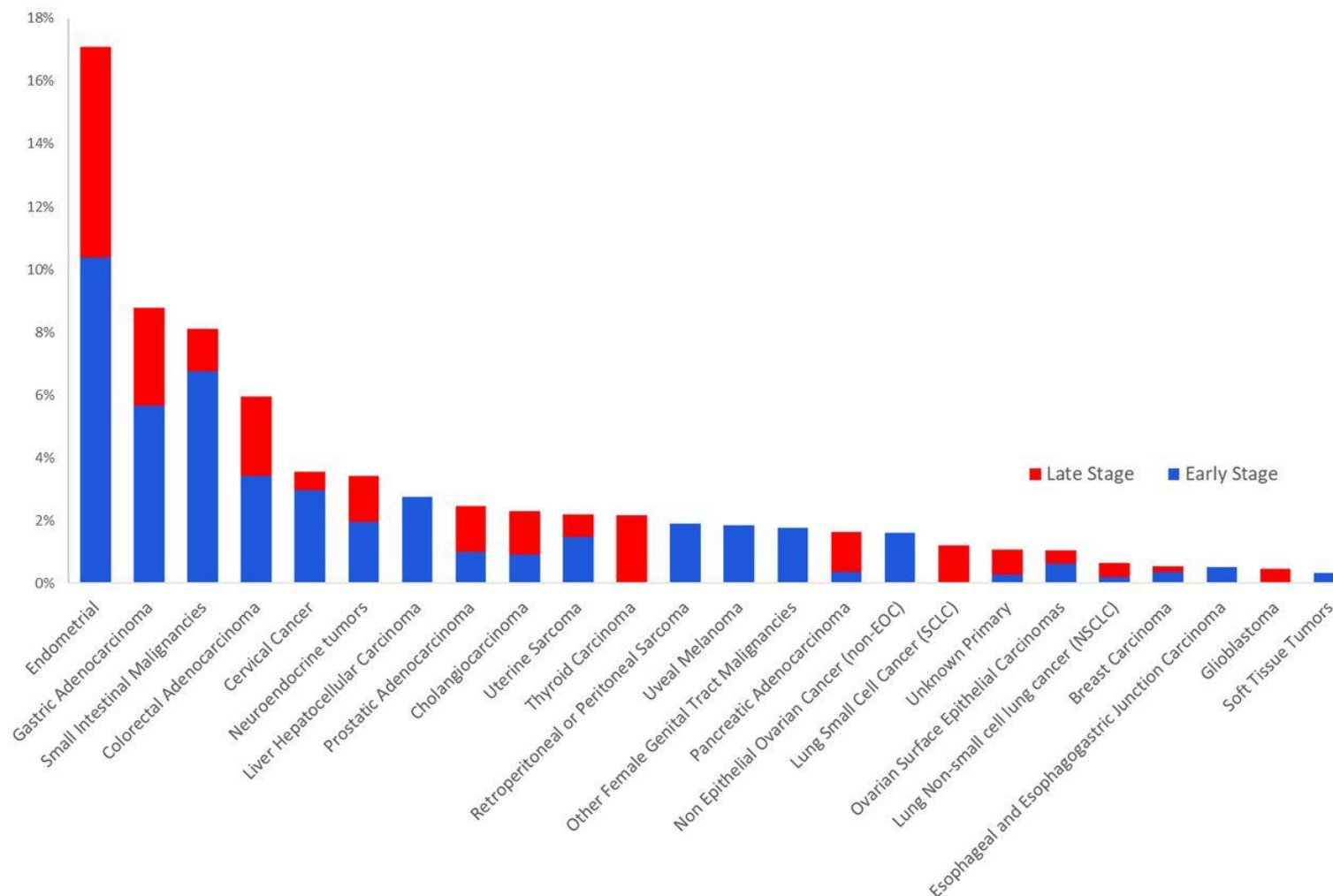
Relationship between TMB and MSI

Rationale for Immunotherapy

Higher mutational burden = More Neoantigens → **Recognition by Antigen Presenting Cells** → **T-cell receptor recognition and expansion, T-cell killing** ↔ **Interferon gamma production at the tumor site and tumor elimination** → **Tumor Immune Escape via PD-1:PD-L1**

Tumor Volume

Rationale for Immunotherapy

Antigen Recognition → T-cell killing → IFNγ
→ PD-L1 upregulation

Sahin, BJC 2019.
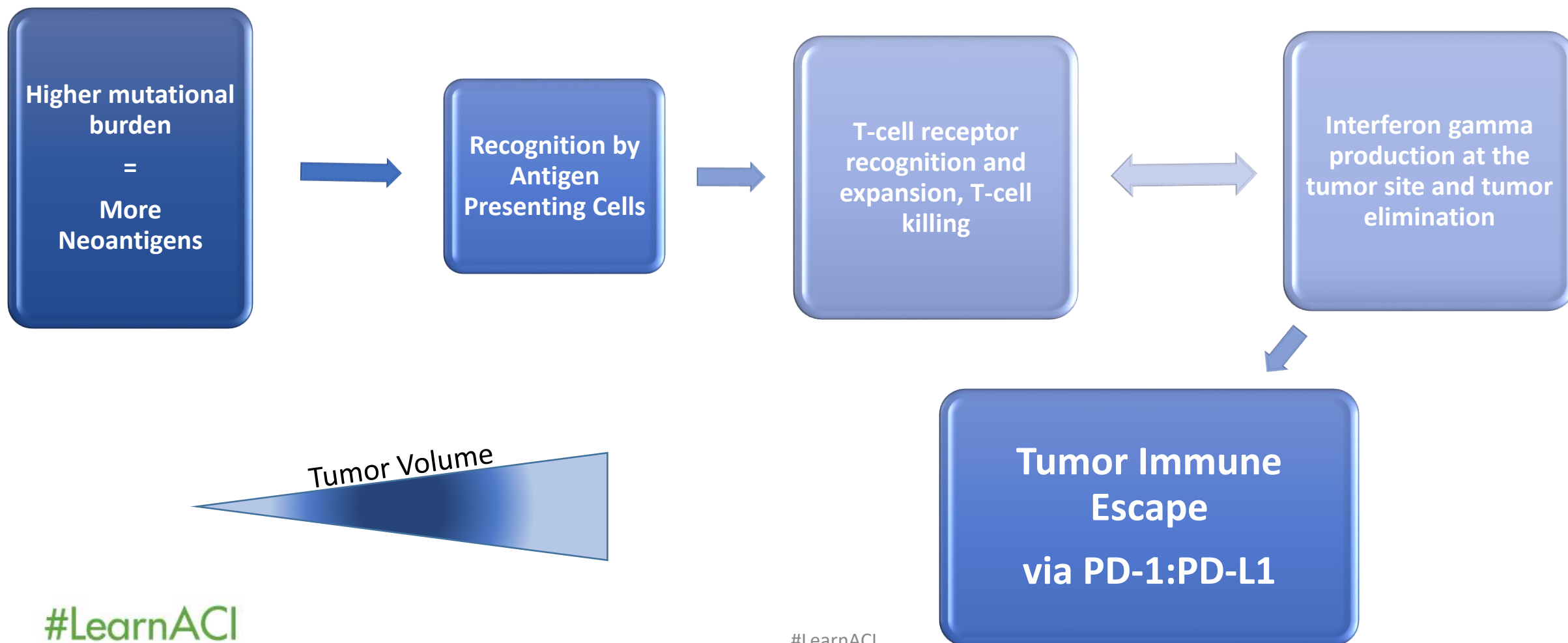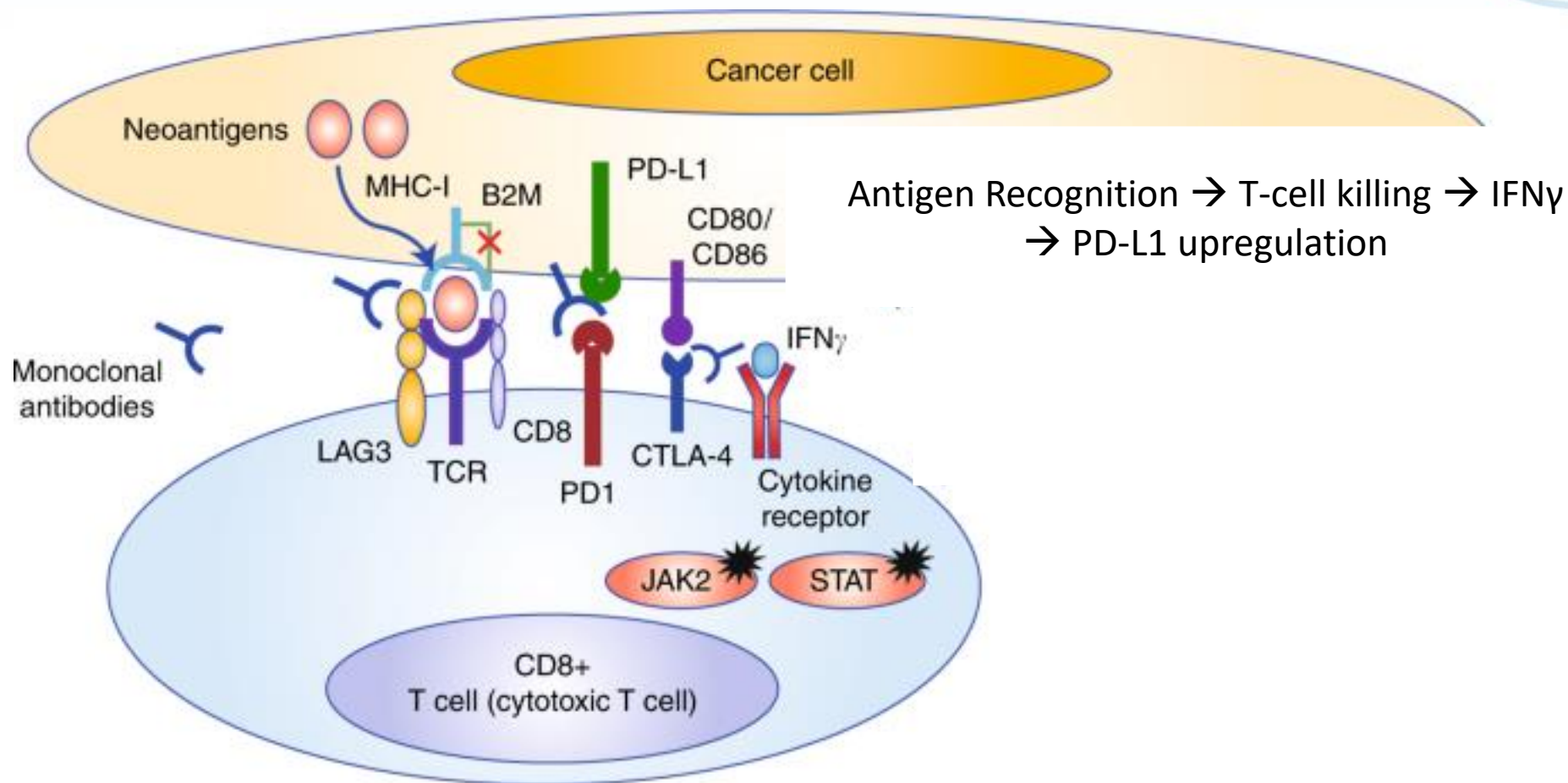
First-line pembrolizumab for MSI-H/ dMMR CRC – KEYNOTE-177

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

Innate Resistance to Immunotherapy

Can we improve MSI (and perhaps TMB) Interpretation to better predict who will respond?

Progression-Free Survival

	Events	HR (95% CI)	P
Pembro	54%	0.60	0.0002
Chemo	73%	(0.45-0.80)	

12-mo rate
55%
37%

24-mo rate
48%
19%

Median (95% CI)
16.5 mo (5.4-32.4)
8.2 mo (6.1-10.2)

PFS, %

Time, months

No. at Risk
153 96 77 72 64 60 55 37 20 7 5 0 0
154 100 68 43 33 22 18 4 3 1 0 0 0
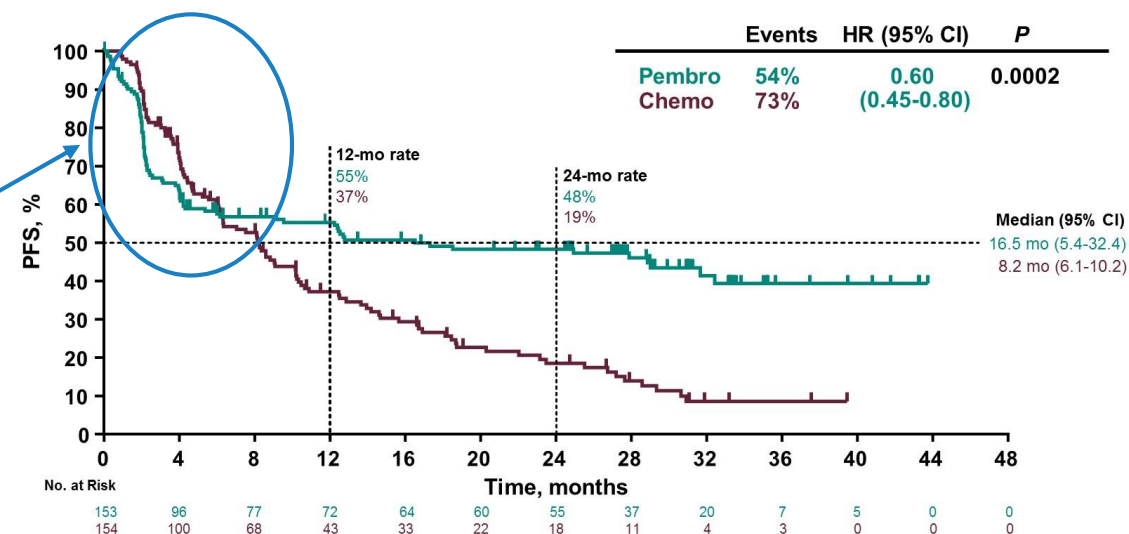
Median study follow-up: 32.4 months (range, 24.0 – 48.3); PFS (time from randomization to first documented disease progression or death) assessed per RECIST v1.1 by BICR.
Superiority of pembrolizumab vs chemotherapy for PFS was demonstrated at the pre-specified one-sided α = 0.0117; Data cut off: 19Feb2020.

Andre, ASCO 2020.

Degree of MSI and Quality of Neoantigens
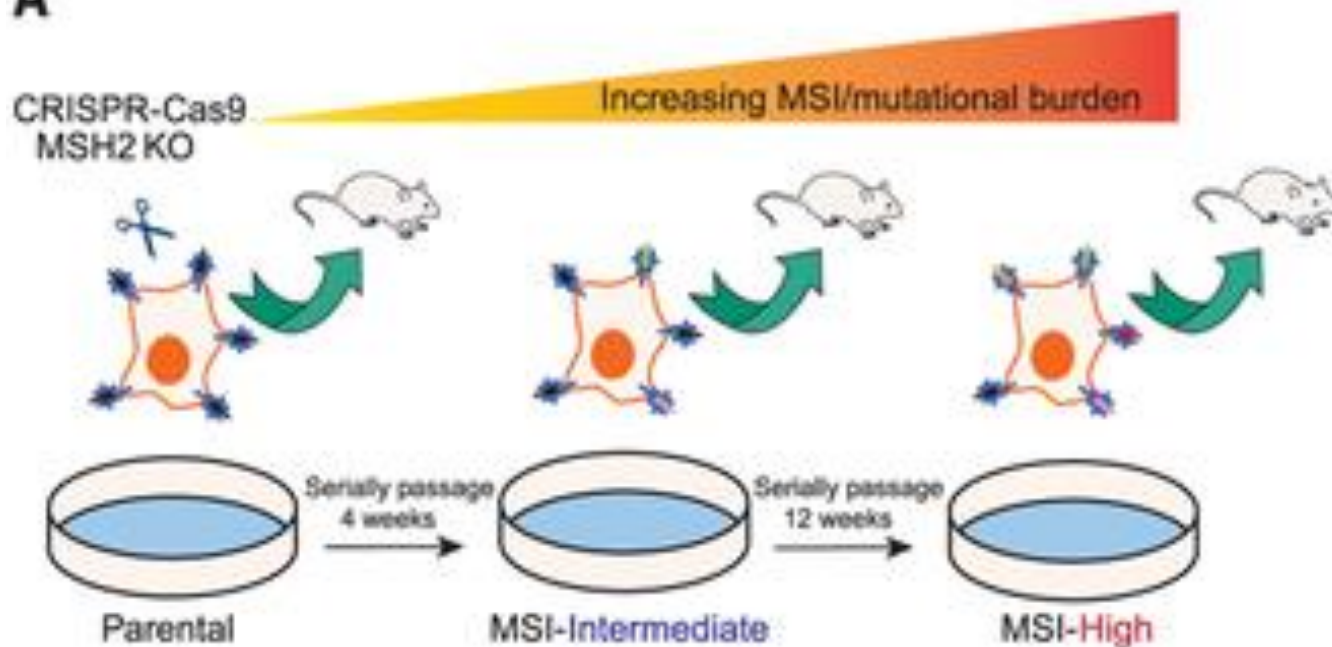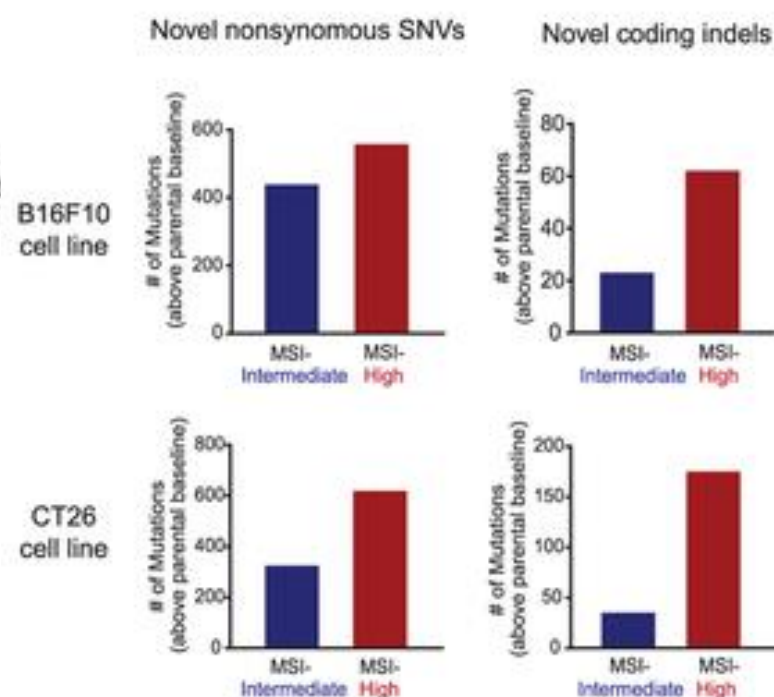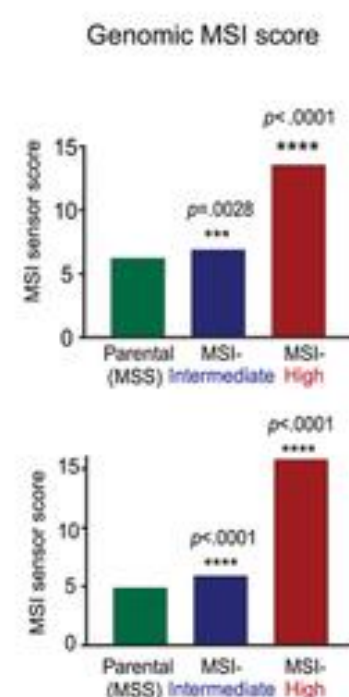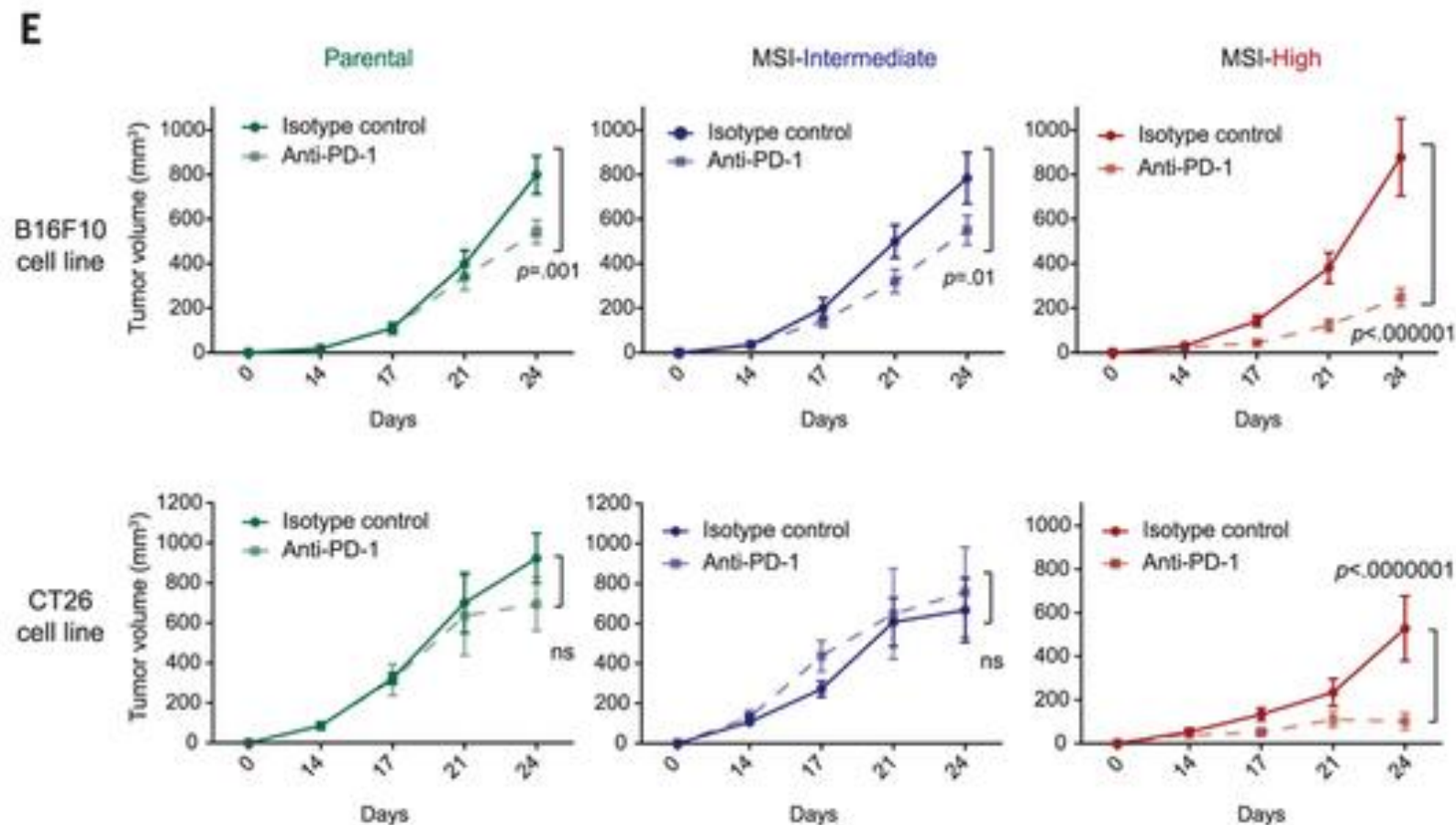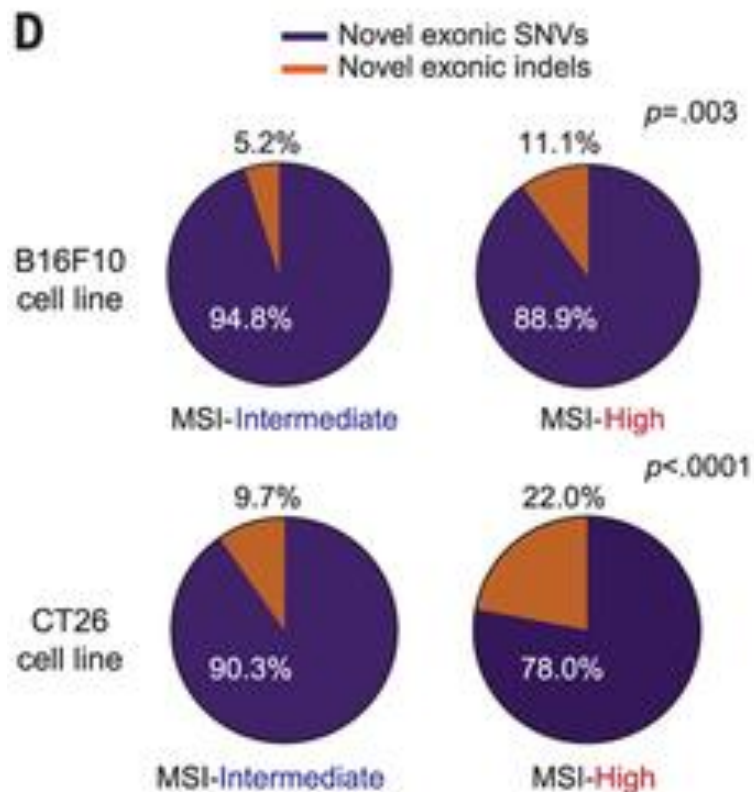
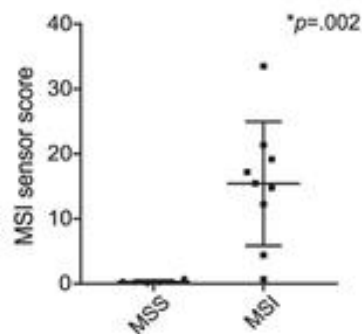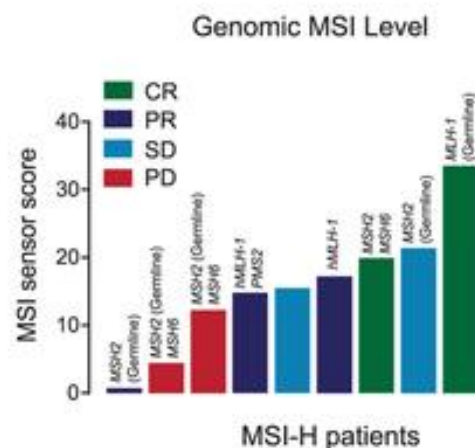# Degree of MSI and Quality of Neoantigens
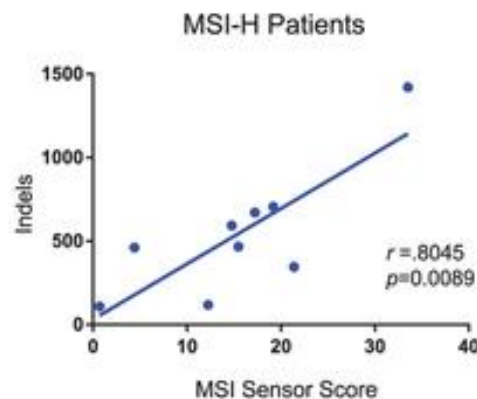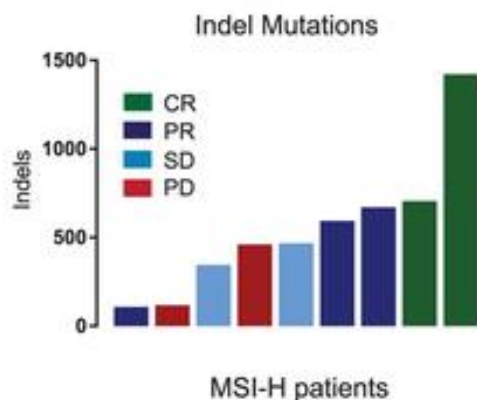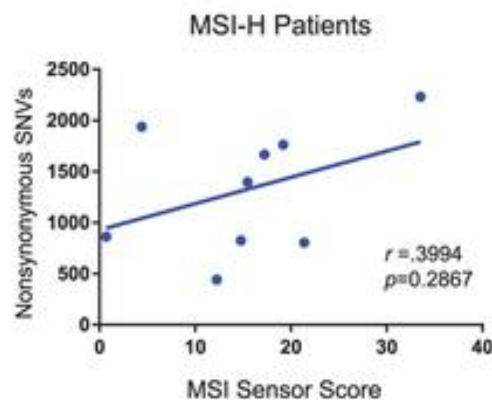
Degree of MSI and Quality of Neoantigens
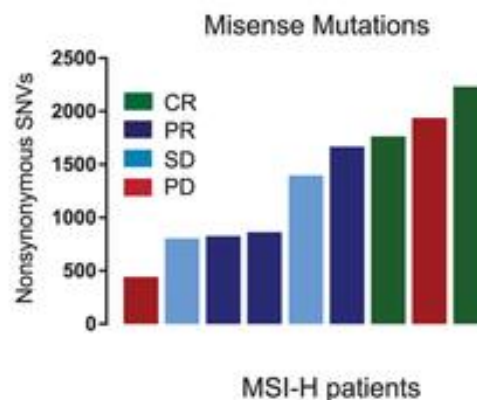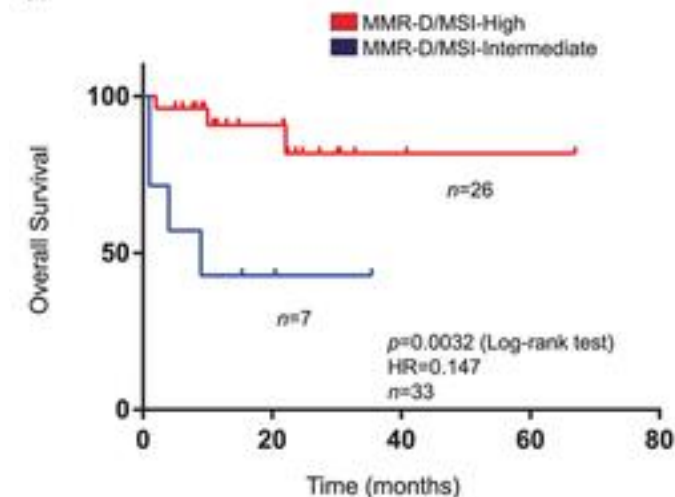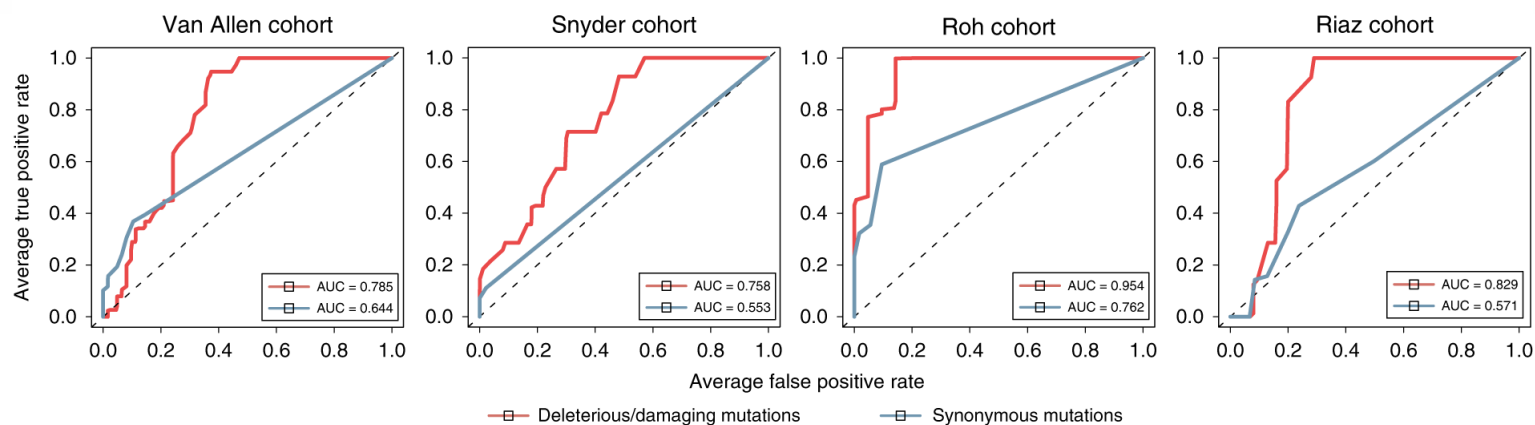
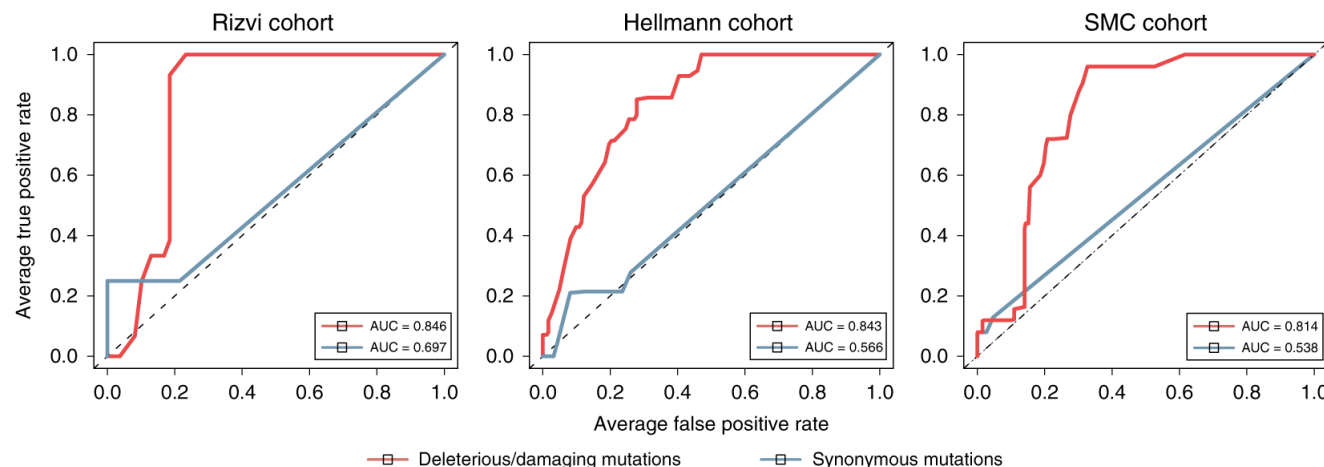# TMB and Quality of Neoantigens

Summary and Future Directions

- TMB-H and MSI-H tumors harbor neoantigens that are recognized as non-self by the immune system; resulting in T-cell killing, IFNγ production, and PD-1:PD-L1 interactions leading to eventual immune escape
  - Rendering many of these tumors sensitive to immune checkpoint inhibitor-based immunotherapy

- TMB-H and MSI-H tumors differ in the quality and quantity of mutations, and a binary approach to these biomarkers may diminish their predictive ability

- Neoantigen prediction, distinguishing indels v. SNVs (ideally using WES), MSI-H scoring, and TCR clonality represent opportunities to improve immunotherapy outcomes and possibly develop new treatments
  - These will need to be widely available in the community

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Questions