Mutations as Immune Antigens: PD-1 Blockade in Tumors with Mismatch Repair Deficiency

Swim Across America Laboratory
Ludwig Center for Cancer Genetics and Therapeutics

Disclosure Information

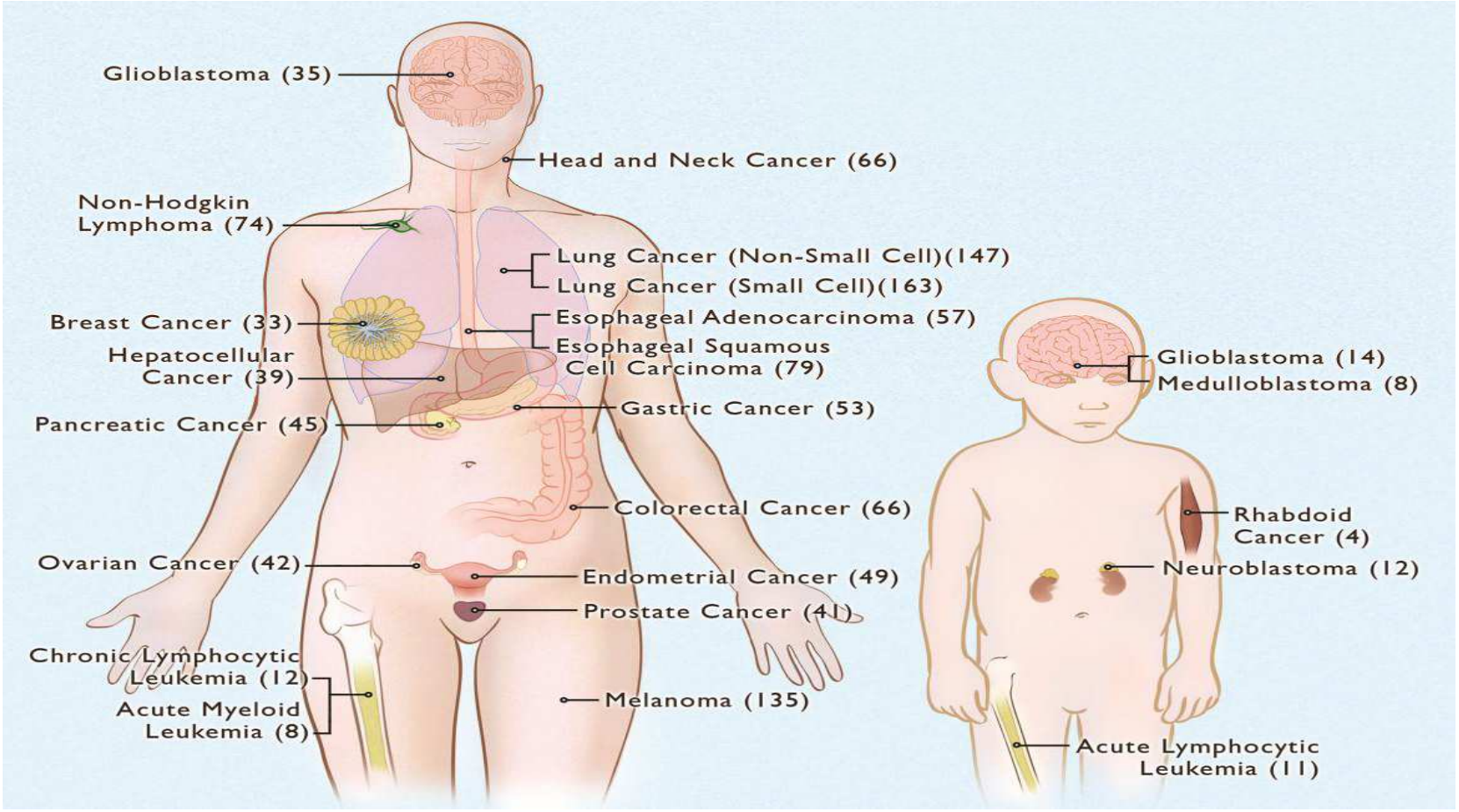
I have the following financial relationships to disclose:

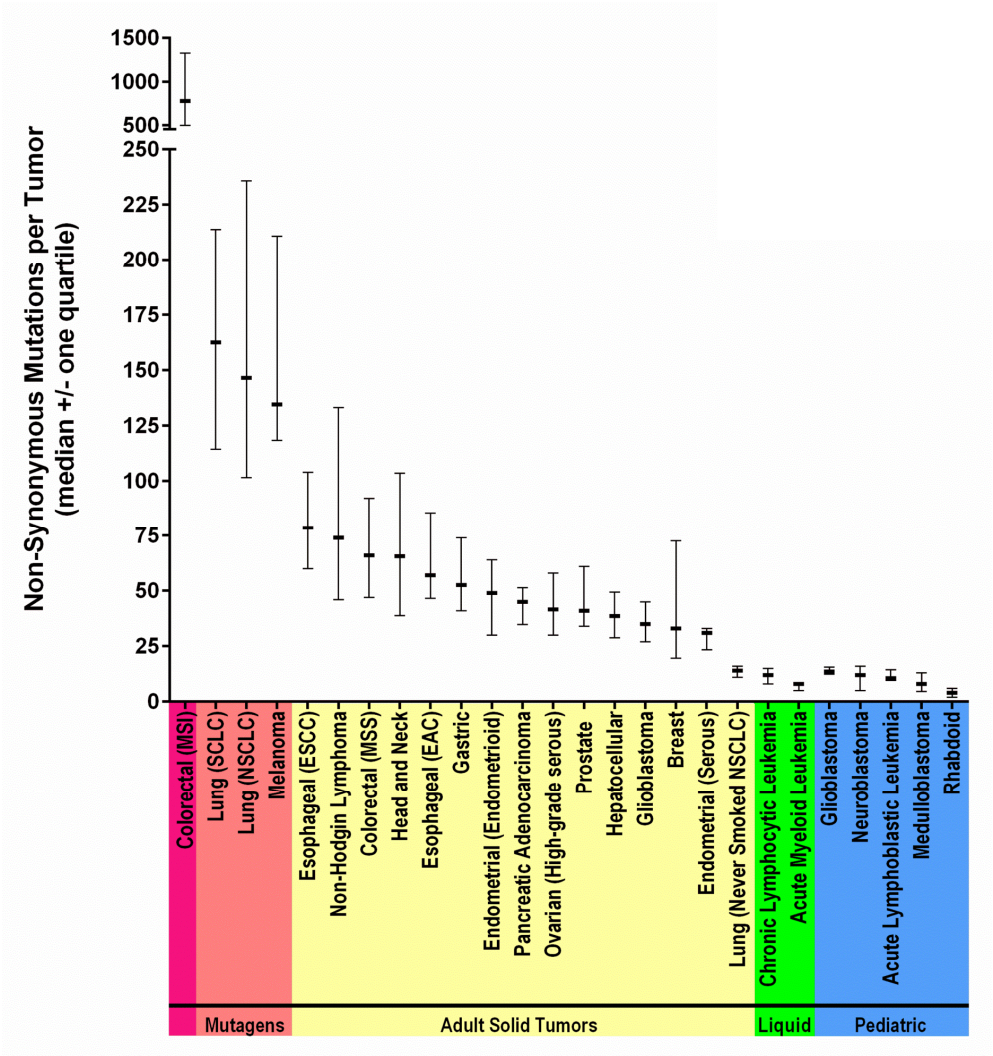
Founder and shareholder in Pagerbox, Papgene, LLC and Personal Genome Diagnostics, Inc.

Consultant for Merck.

Under separate licensing agreements between Inostics, Personal Genome Diagnostics and the Johns Hopkins University, Dr. Diaz is entitled to a share of royalty and milestone payments received by the University on sales of products related to research described in this presentation.

Human Cancer Exomes Sequenced





Non-synonymous Mutations per tumor

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Cancer Mutations

Coding Mutations

1,712,998

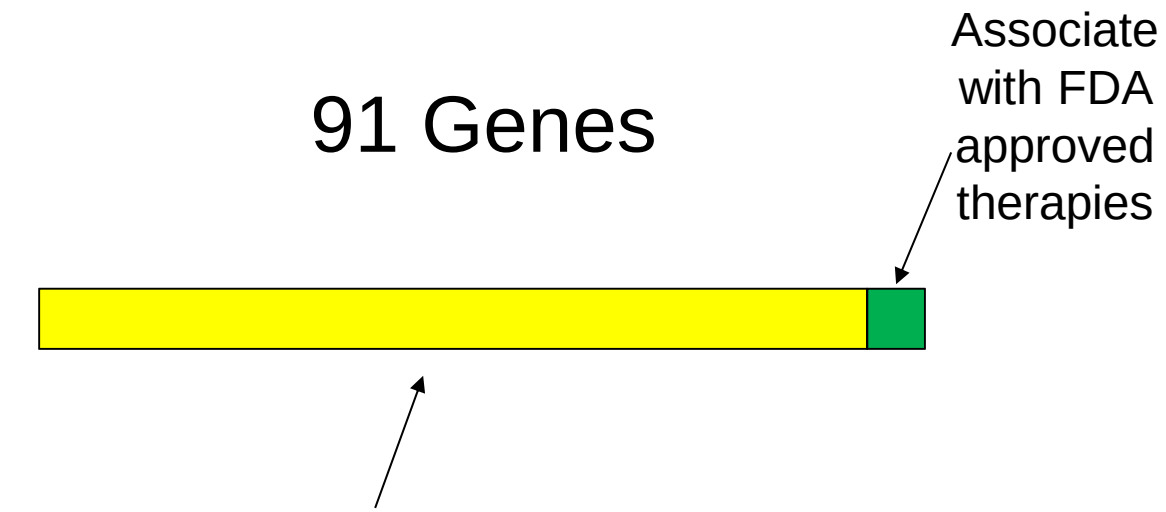
Genes

>20,000

Clinically Meaningful

91 Genes

Cancer Mutations



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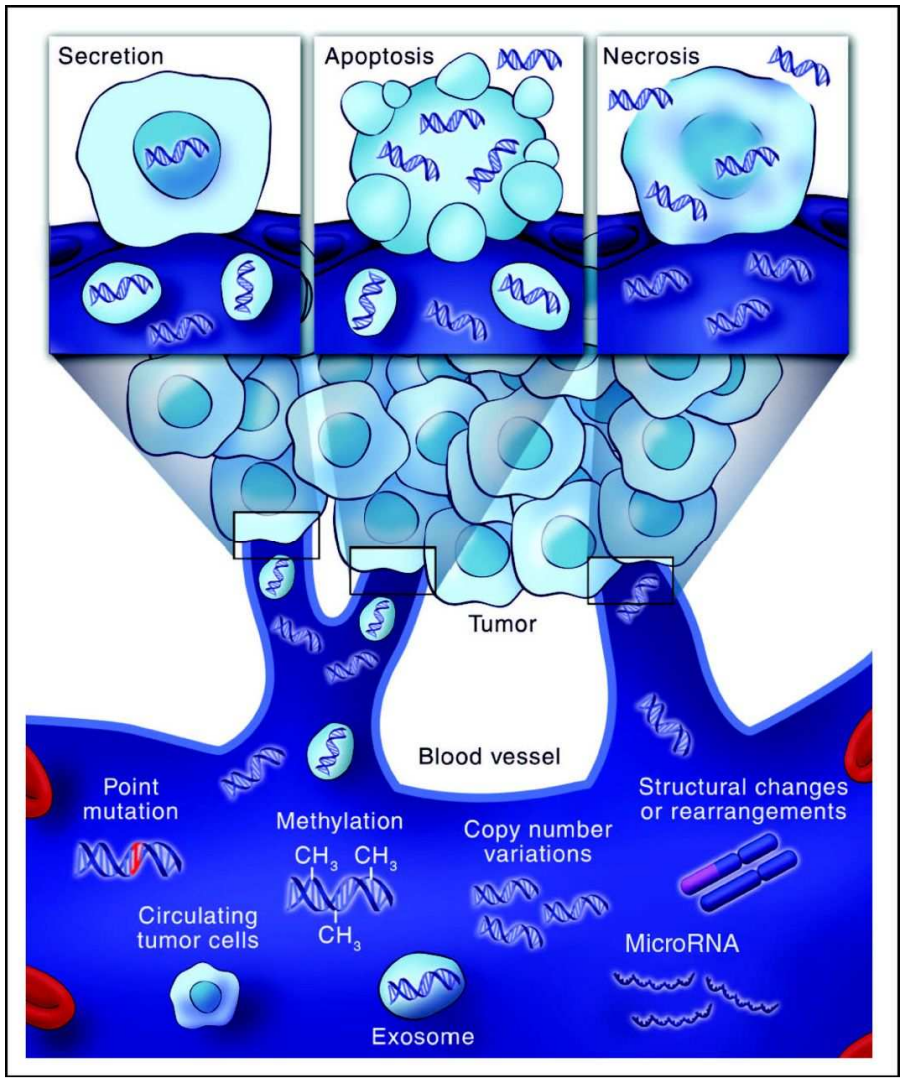
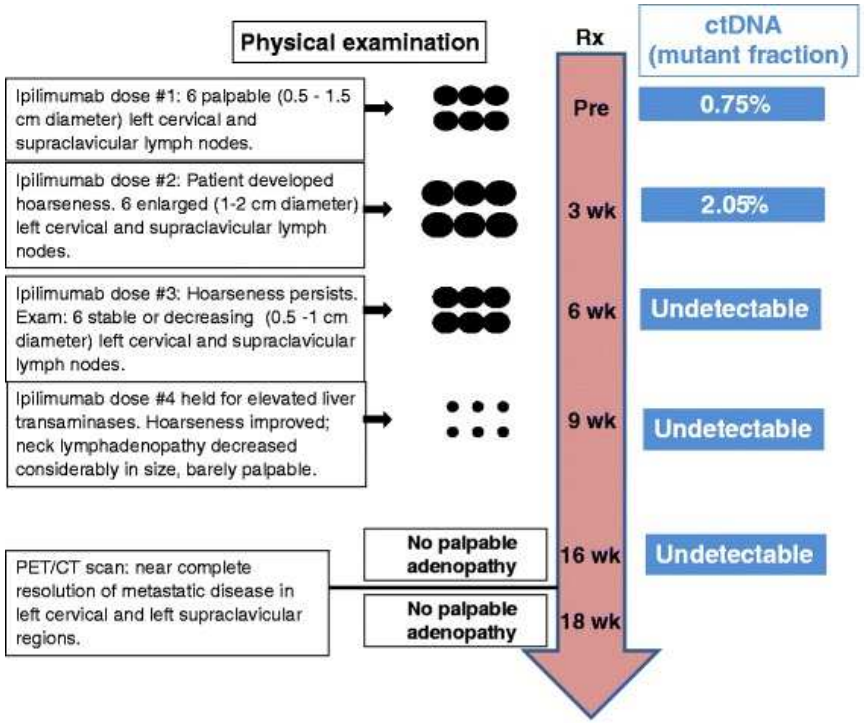


- DNA fragments of 180-200bp with half life of ~2 hours
- Specific to tumor
- Real-time, non-invasive, multi-lesions, potentially cheaper (considering cost of biopsies)
- Often very low amount of ctDNA in the sea of wild type DNA - ”Needle in a farm”

Monitoring response to checkpoint inhibitors using ctDNA



ctDNA levels increased initially as lymphadenopathy progressed by examination, but then became undetectable 3 weeks prior to clinical improvement.

Lipson et al. J. of Immunotherapy 2014.

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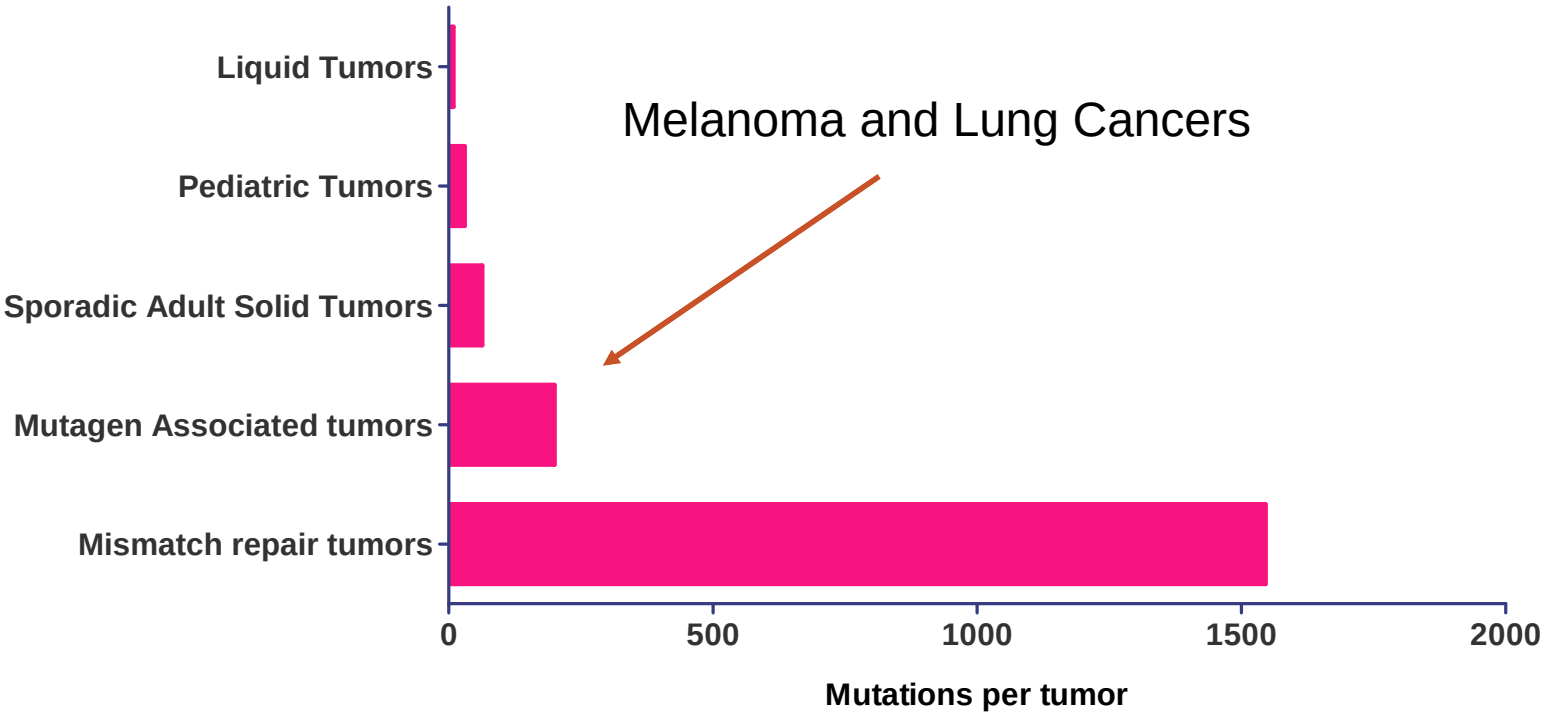
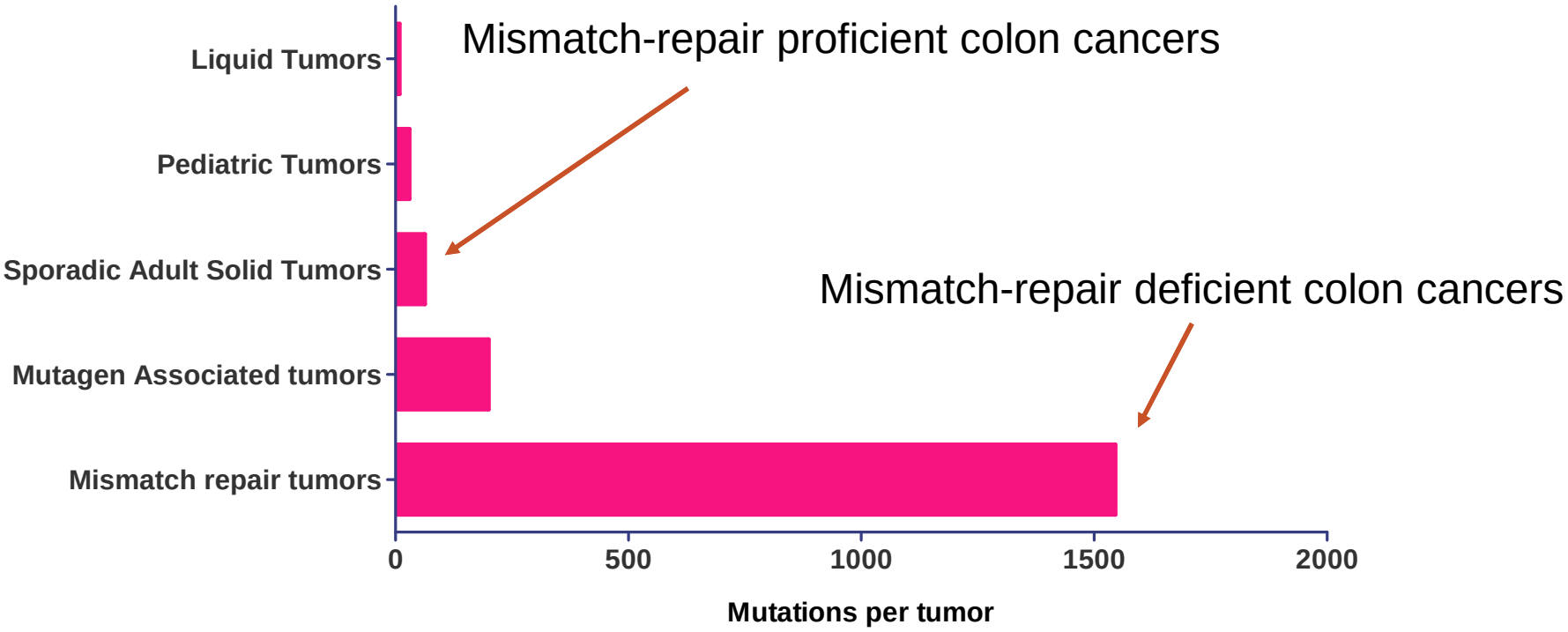
Mutations per tumor



Mutations per tumor



Hypothesis

- Mutations have been shown to encode proteins that can be recognized and targeted by the immune system
- Average tumor has dozens of somatic mutations; Mismatch repair deficient tumors harbor thousands of mutations
- Immune augmentation with PD-1 blockade may be highly effective in mismatch repair deficient tumors

Mismatch Repair Deficiency

Microsatellite instability in tumor cells is due to deficient DNA mismatch repair:

- **germline** (Lynch syndrome) and/or **sporadic** mutations (MLH1, MSH2, MSH6, PMS2, EpCAM)
- **epigenetic silencing** (MLH1 hyper-methylation)

Associated tumor types

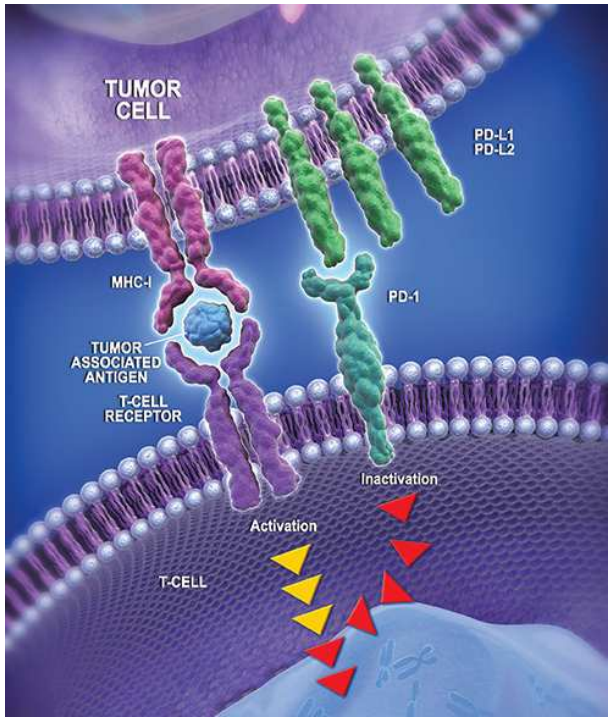
Colorectal cancer

- Associated with hereditary nonpolyposis colorectal carcinoma (HNPCC)
- 15% of sporadic colorectal carcinomas (3-5% of advanced disease)
- stage II CRC: associated with better prognosis, no benefit from 5FU alone
- stage IV CRC: associated with worse prognosis

Other tumor types:

Endometrial, gastric, small bowel, ampullary, cholangiocarcinoma, pancreatic, sarcoma, prostate, gliomas and others at similar frequencies.

PD-1 Pathway and Pembrolizumab



- Binding of PD-1 to its ligands PD-L1 and PD-L2 inhibits effector T-cell function[1]
- PD-L1 expression on tumor cells and macrophages suppresses immune surveillance, permitting neoplastic growth[2]
- Pembrolizumab is a humanized, IgG4 monoclonal antibody that
  - Binds to PD-1 with high affinity, preventing pD-1 from binding to PD-L1 and PD-L2
  - Has demonstrated robust antitumor activity and manageable toxicity in multiple advanced cancers[a]

[a]FDA approved for the treatment of unresectable or metastatic melanoma and disease progression following ipilimumab and, if $BRAF^{V600}$ mutant, a BRAF inhibitor.

1. Keir ME et al. *Annu Rev Immunol*. 2008;26:677-704. 2. Pardoll DM. *Nat Rev Cancer*. 2012;12:252-64.

Study Design

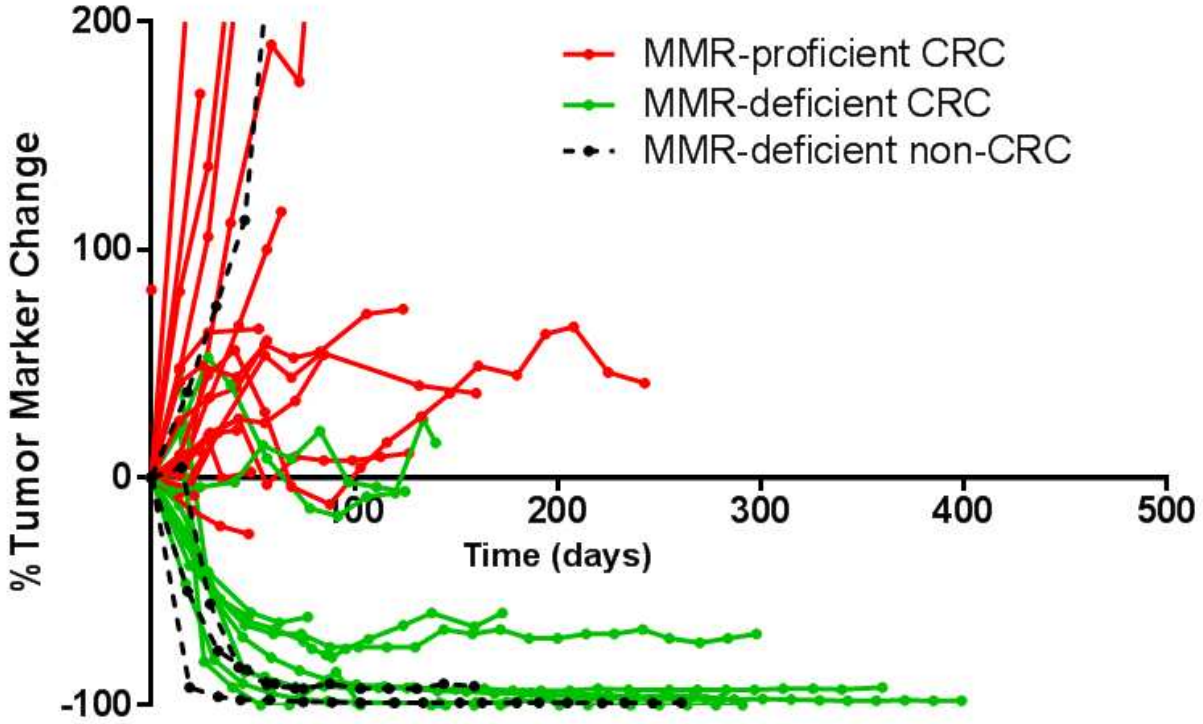
Colorectal Cancers		Non-Colorectal Cancers
Cohort A **Deficient in Mismatch Repair (n=25)**	Cohort B **Proficient in Mismatch Repair (n=25)**	Cohort C **Deficient in Mismatch Repair (n=21)**

- Anti-PD1 (Pembrolizumab) – 10 mg/kg every 2 weeks
- Primary endpoint: immune-related 20-week PFS rate and response rate

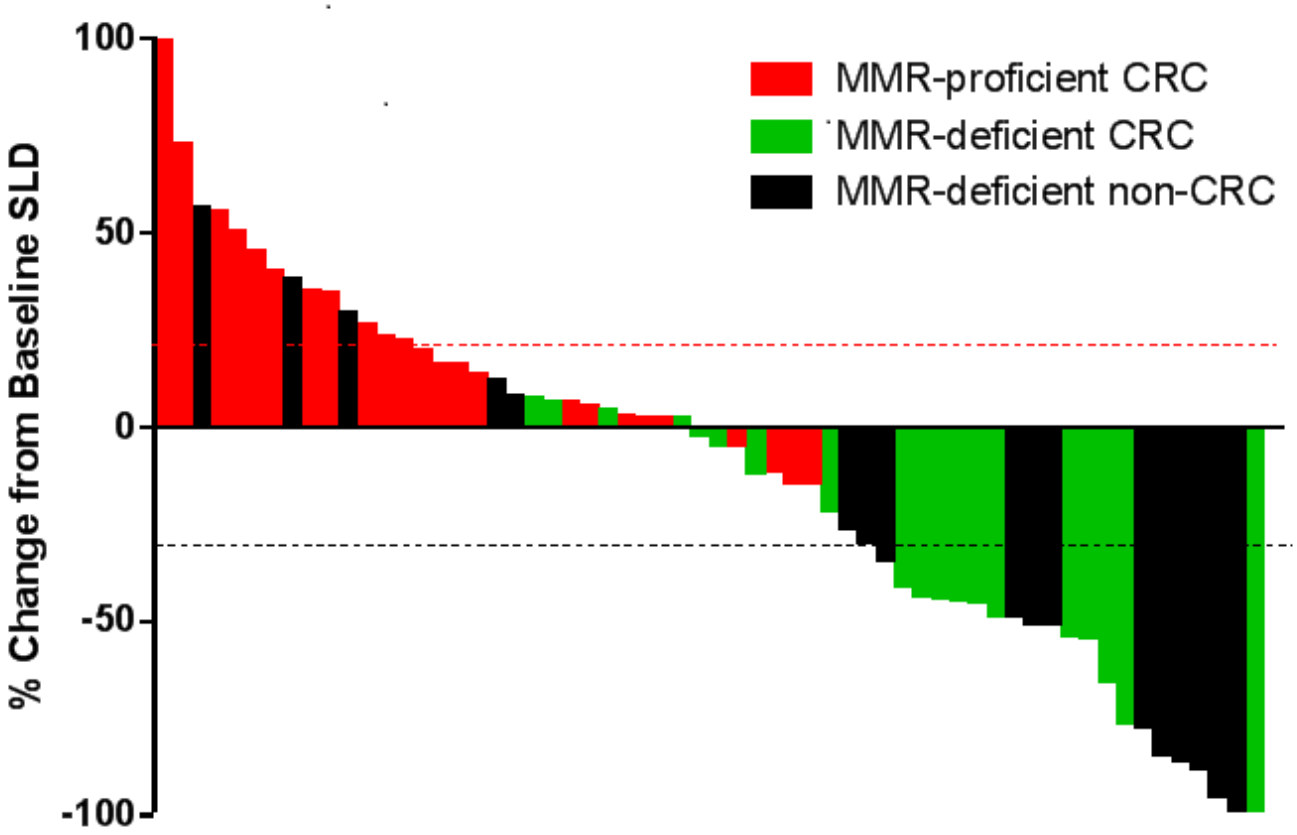
Objective Responses (Sept 2015, N=63)

	MMR-deficient CRC	MMR-proficient CRC	MMR-deficient non-CRC
N	20	25	18
Objective Response Rate	55%	0%	55%
Disease Control Rate	90%	16%	72%

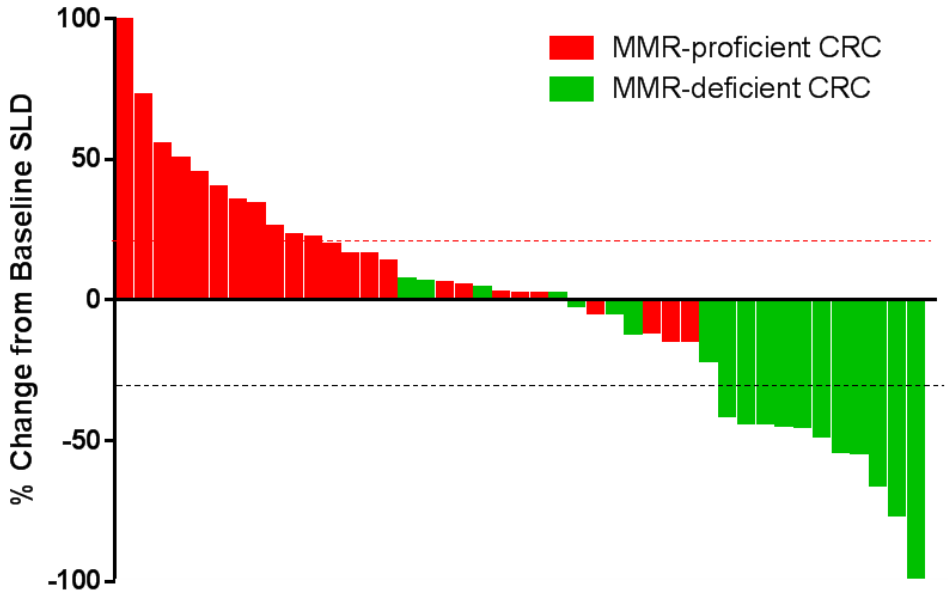
Biochemical Responses



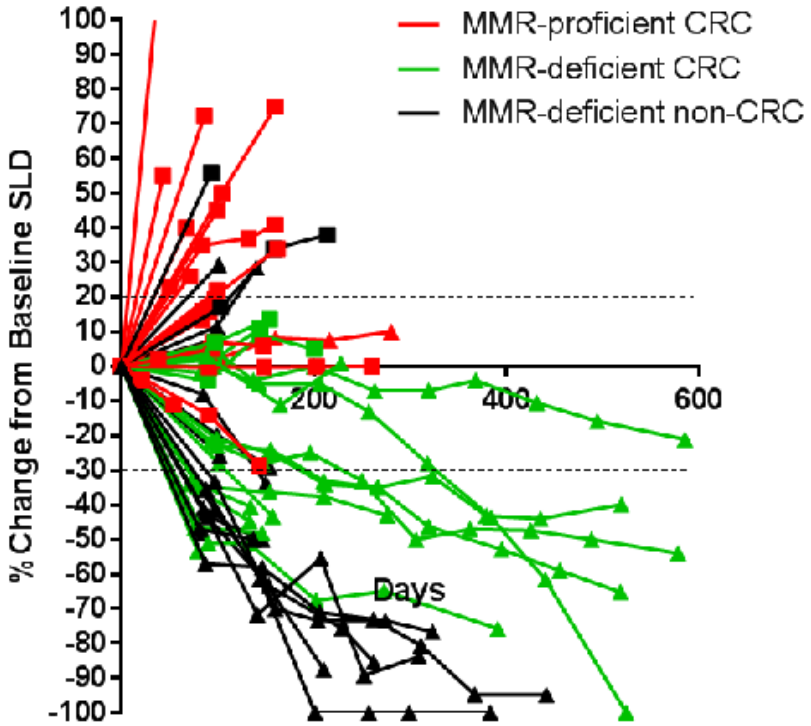
Target Lesions



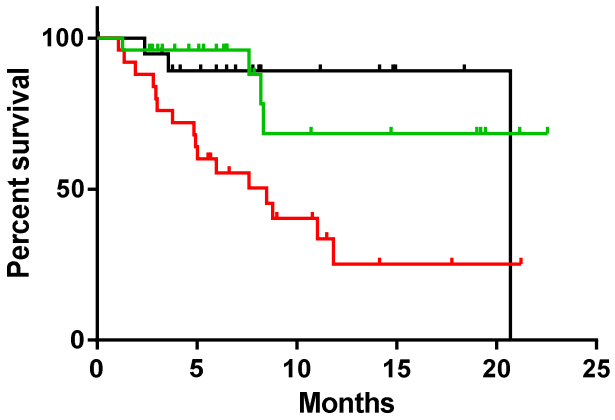
Target Lesions: CRC Cohorts



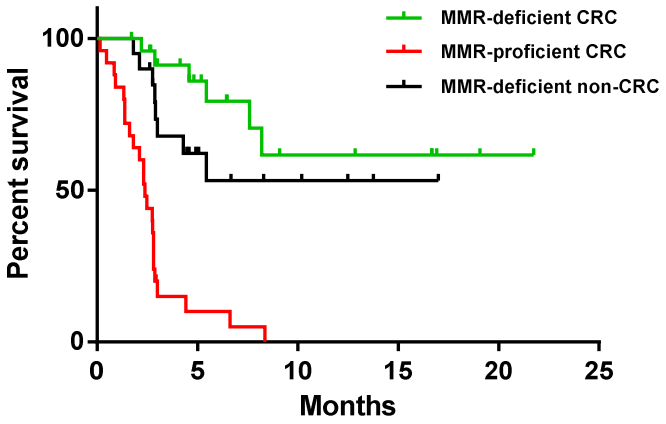
Duration of Response



Surival Curves (October 2015)

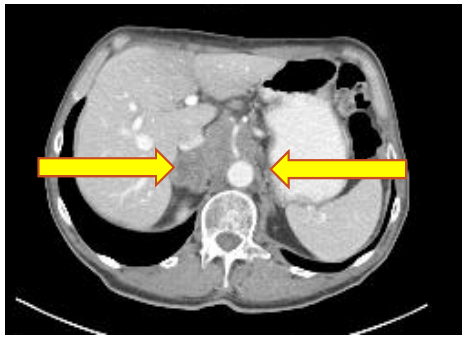


Overall Survival

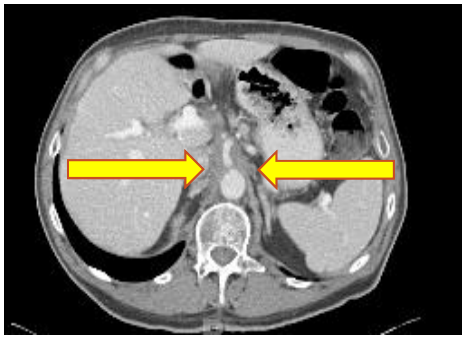


Progression-Free Survival

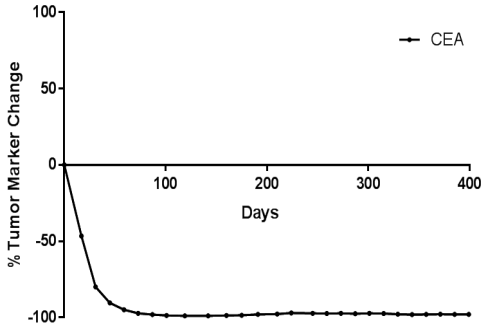
Mismatch repair deficient Colorectal Cancer



Baseline

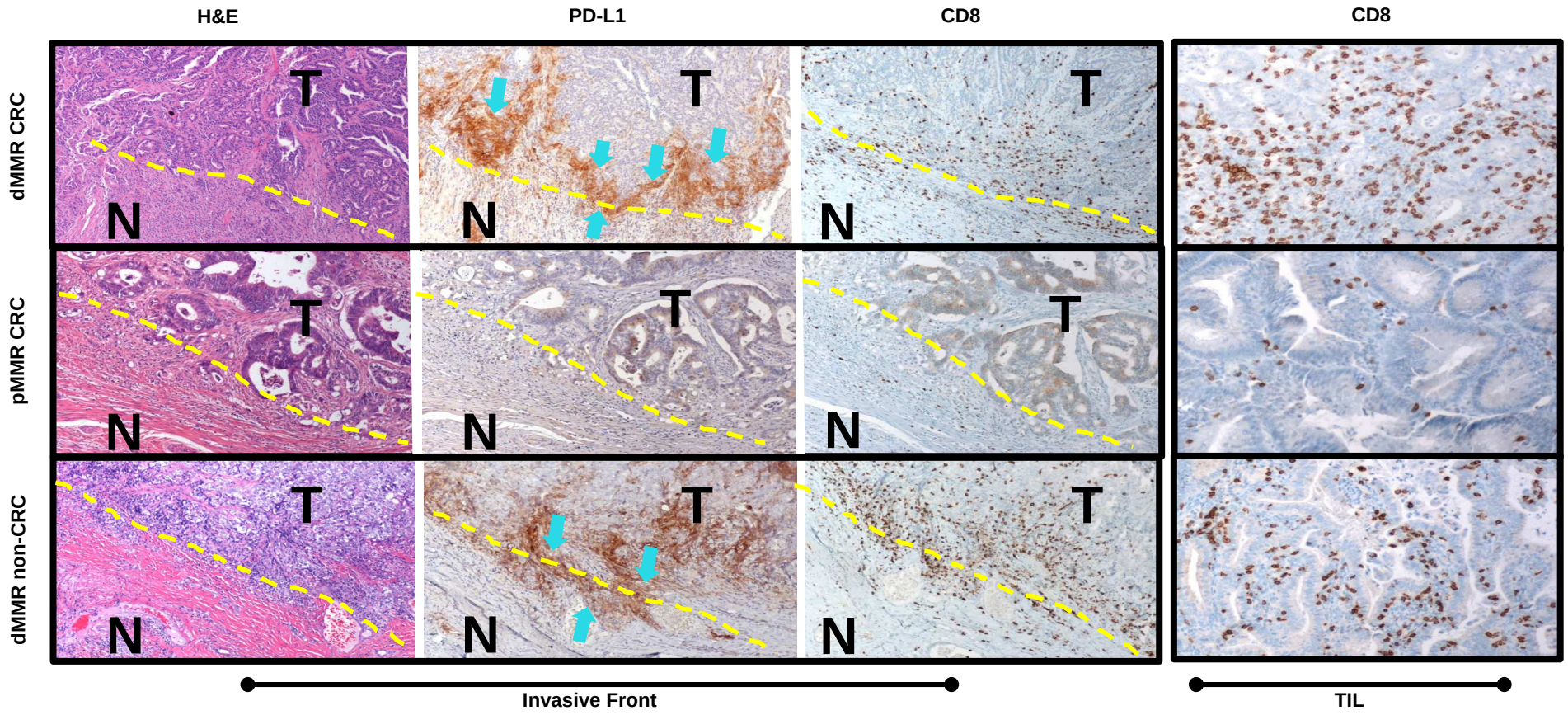


Week 20

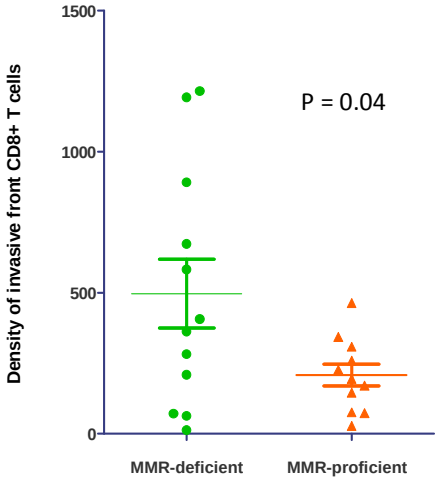


Tumor Markers

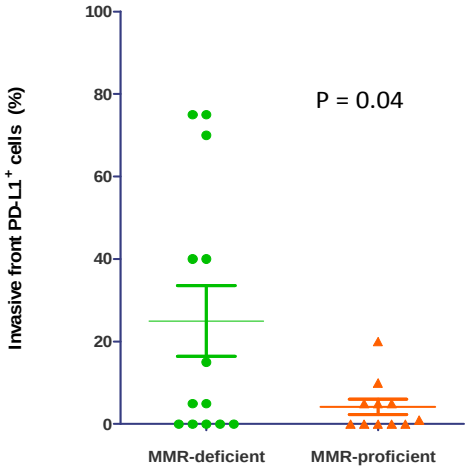
Baseline PD-L1 Expression and CD8 T Cell Infiltration



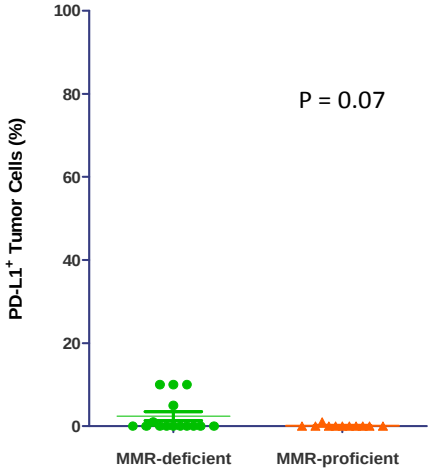
Invasive Front PD-L1 Expression and CD8 T Cell Infiltration



Invasive Front CD8⁺ T cells

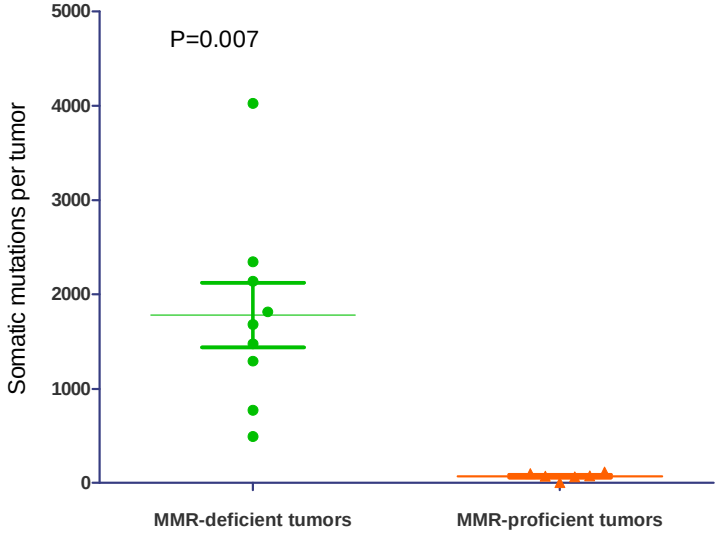


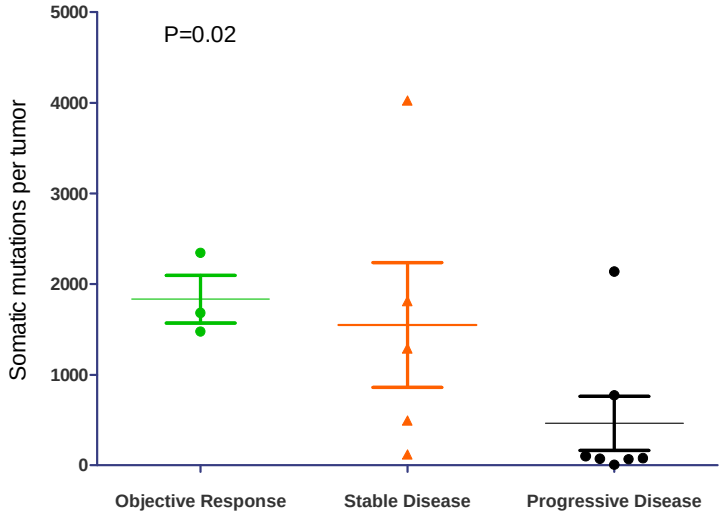
Invasive Front PD-L1 Expression



Tumor Front PD-L1 Expression

Mutation Burden is Associated with Efficacy





Summary

- Radiographic changes may not be tumor progression.
- Patients with mixed responses (e.g. brain mets) may derive benefit.
- Mismatch repair deficiency is easily determined using an existing commercially available test.
- Suggests genomics more influential than histology for mismatch repair deficient tumors treated with anti-PD1

Future Directions

- Primary Resistance

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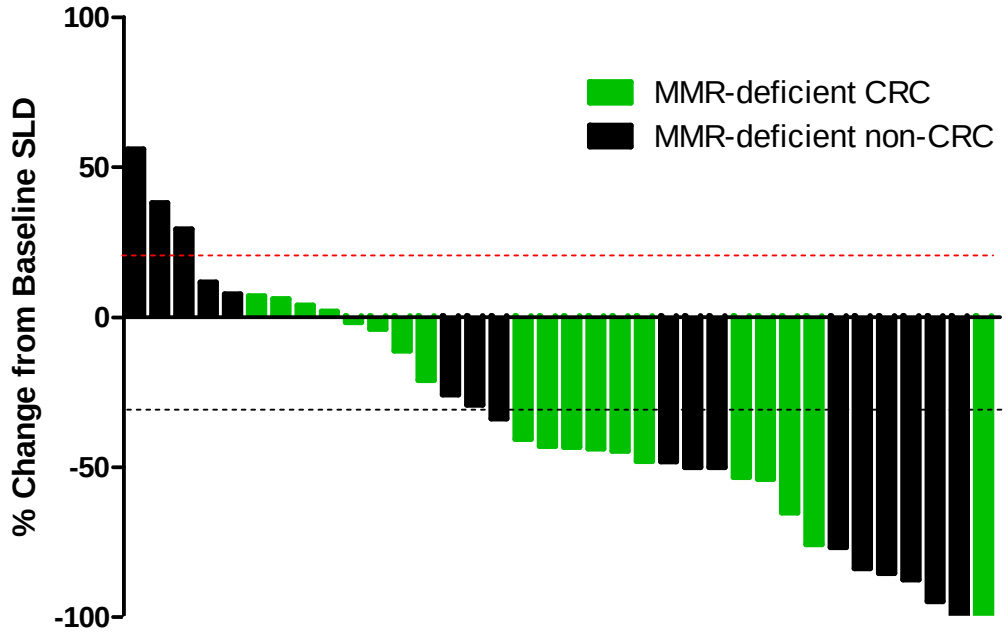
Primary resistance to anti-PD1 in MSI-H tumors



Non-responders with >1500 mutations per genome

No difference in PD-1 expression

Comprehensive evaluation ongoing

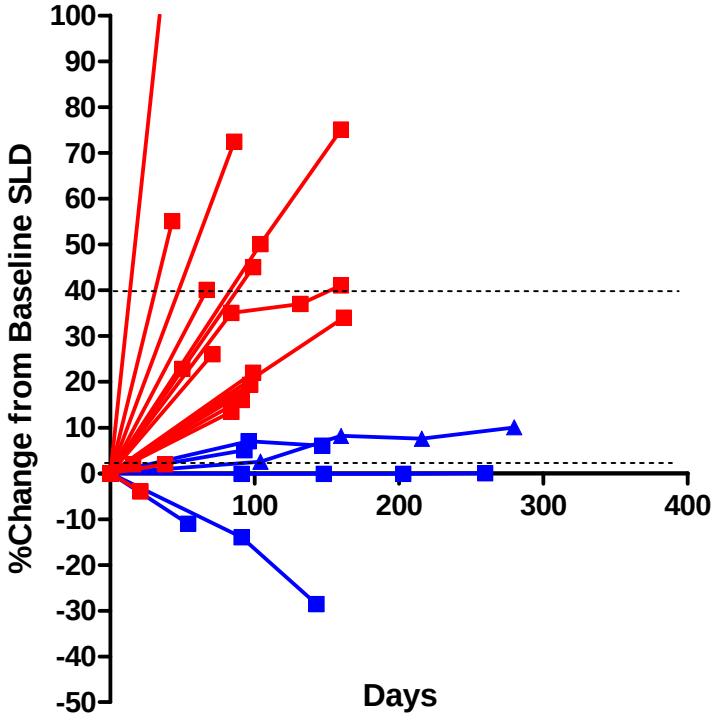
Future Directions

- Primary Resistance
- Secondary Resistance (if any)?

Future Directions

- Primary Resistance
- Secondary Resistance (if any)?
- Subpopulations

Response or Stable Disease in MSS CRC cohort



25 MSS CRC patients

<100 mutations across all 25 tumors

Broad exploration of microenvironment and neoantigens in these tumors

Future Directions

- Primary Resistance
- Secondary Resistance (if any)?
- Subpopulations
- MSI-H in context of other tumor types

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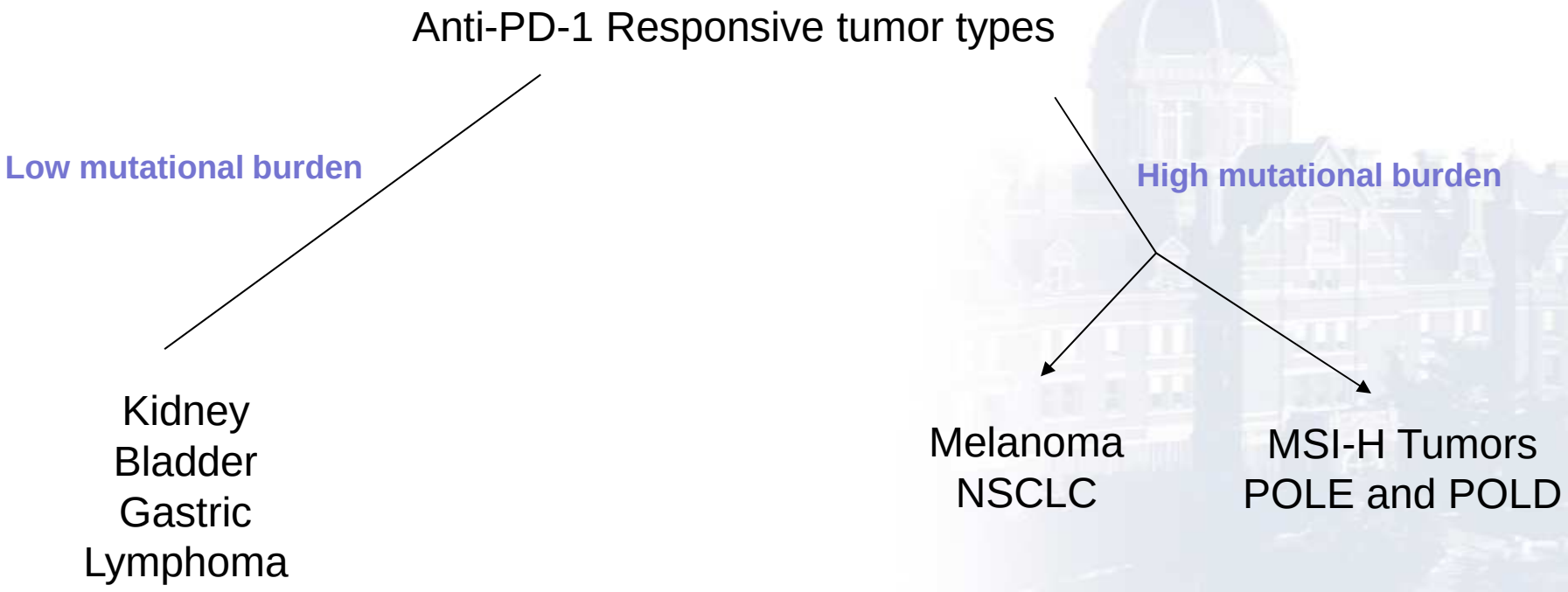
Where do MSI-H tumors fit into the checkpoint inhibition paradigm?



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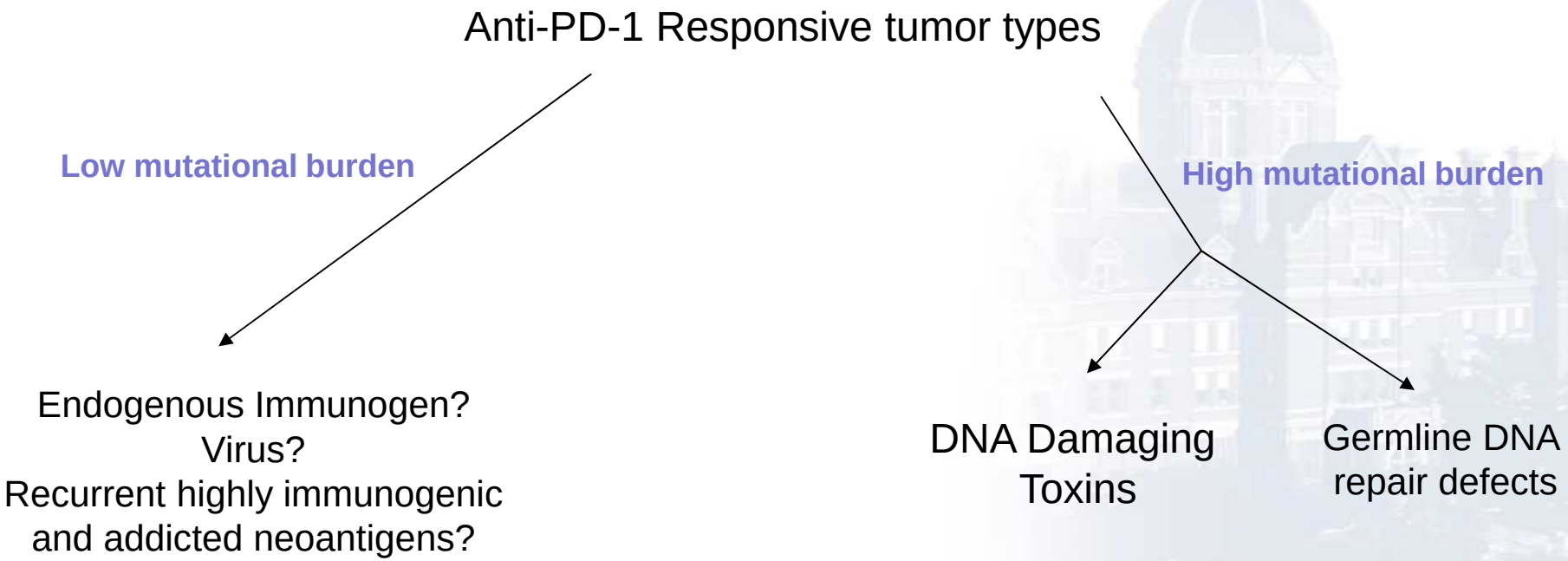
Where do MSI-H tumors fit into the checkpoint inhibition paradigm?



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Clinical Trials

- KEYNOTE – 164: 3rd line MSI-H CRC
- KEYNOTE – 177: 1st line MSI-H CRC
- FDA Breakthrough Therapy Designation

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