



Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Emerging Immune Biomarkers

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- I am an inventor on patents held by the University of Washington

Types of Immune Related Cancer Biomarkers

1. Prognostic Biomarkers may identify the likelihood of a clinical event, such as disease progression, disease recurrence, or death, independent of the therapy received

2. Predictive Biomarkers are present at diagnosis and may identify whether individuals are more likely to experience a favorable or unfavorable response to treatment

3. Pharmacodynamic Biomarkers may show that a biologic response has occurred in an individual who has received treatment

- Immune score in colorectal cancer (good prognosis)
- T-regulatory cells in ovarian cancer (poor prognosis)

- MSI^{high} in CRC (response to ICI)
- PD-L1 expression in NSCLC (response to ICI)

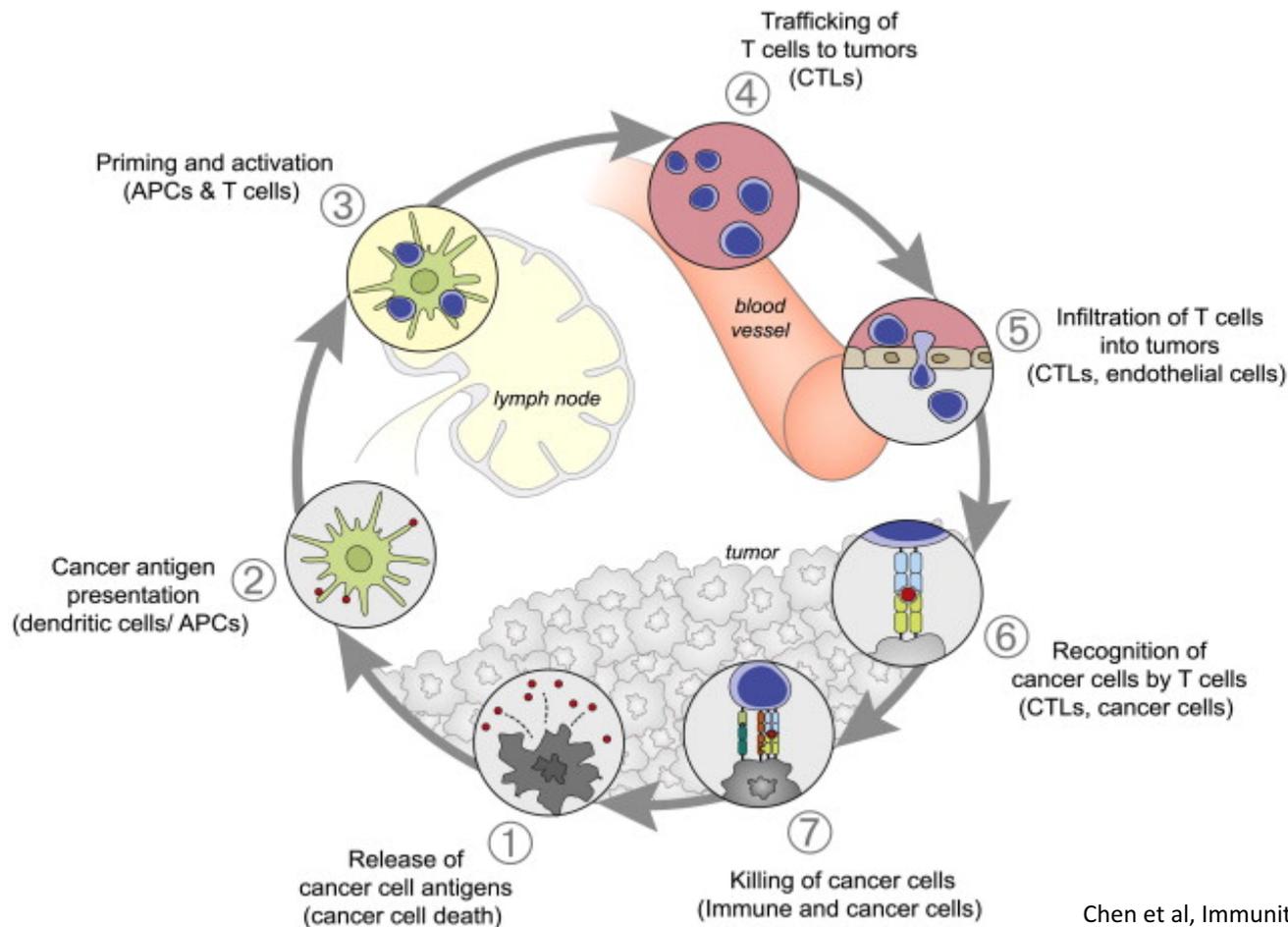
- Level of antigen specific immunity after vaccination
- Immune related adverse event after ICI

Many prognostic biomarkers are also predictive

Effective Anti-Cancer Immunity

Biomarker locations

Blood
Lymph node
Tumor

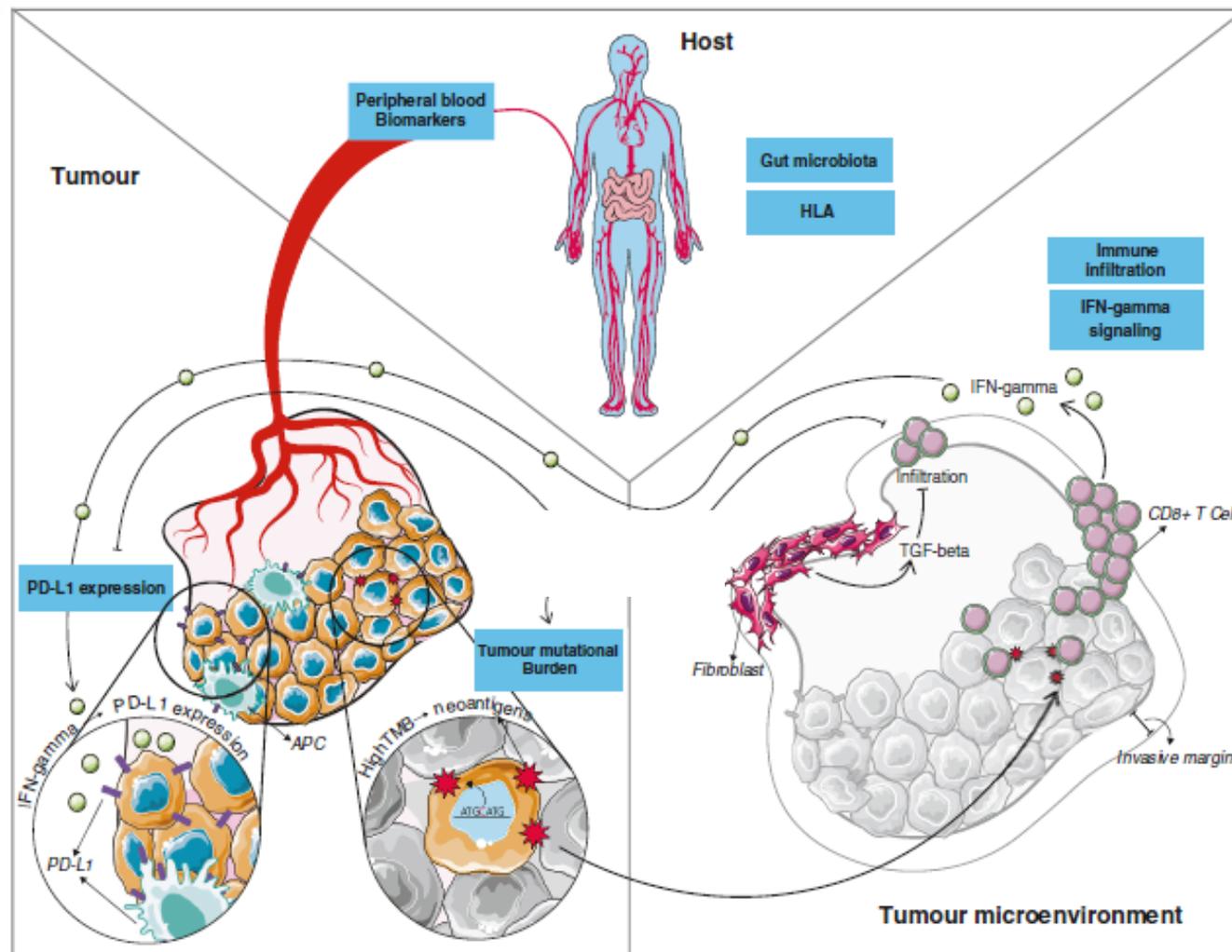


Chen et al, Immunity, 2013

Current Predictive Immune Biomarkers

FDA approved for selection

- PD-L1
- TMB
- dMMR
- MSI^{high}

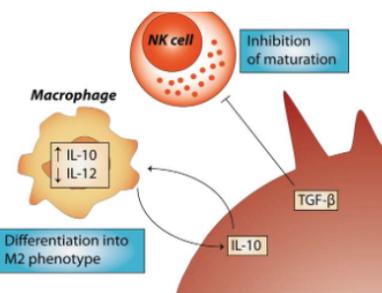


Emerging Immune Biomarkers

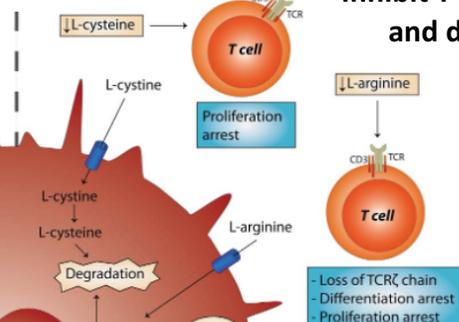
- Systemic review of predictive biomarkers for outcomes of ICI in melanoma
- Melanoma trials of ICI, Phase II/III, biomarkers associated with clinical outcomes: screened 2536 trials, analyzed 177 studies inclusive of 128 biomarkers
- QUIPS risk of bias six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, adjustment for other prognostic factors, and statistical analysis. Most with high or moderate risk of bias.
- **Peripheral blood markers: Myeloid derived suppressor cells, CD8⁺ memory T-cells, T-cell receptor diversity, circulating tumor cells or DNA**
- **Tumor associated markers: TIL, gene expression profiles**
- **Specific species in the gut microbiome**
- **Clinical biomarkers***

MDSC

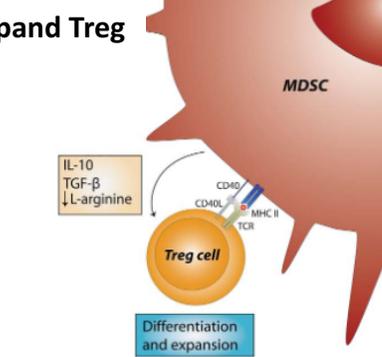
Inhibit innate cells, increase M2



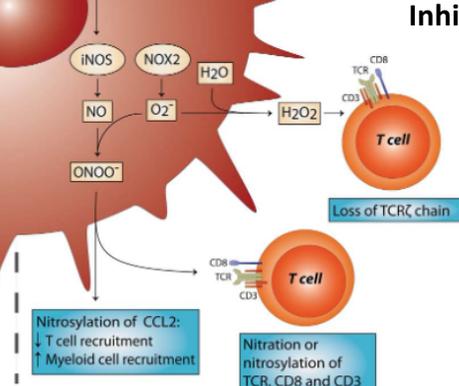
Inhibit T-cell proliferation and differentiation



Expand Treg

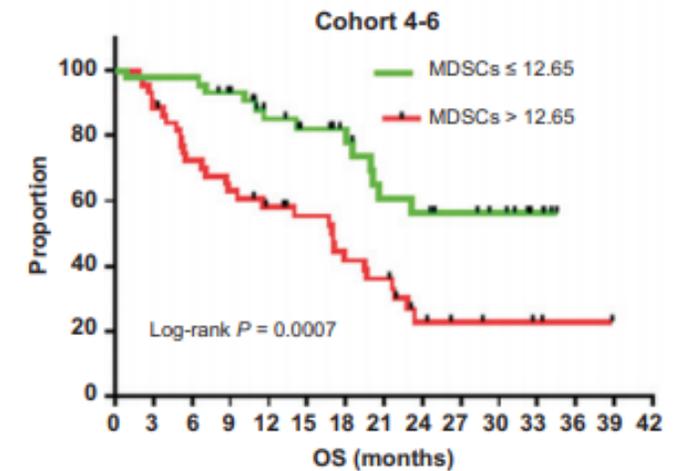
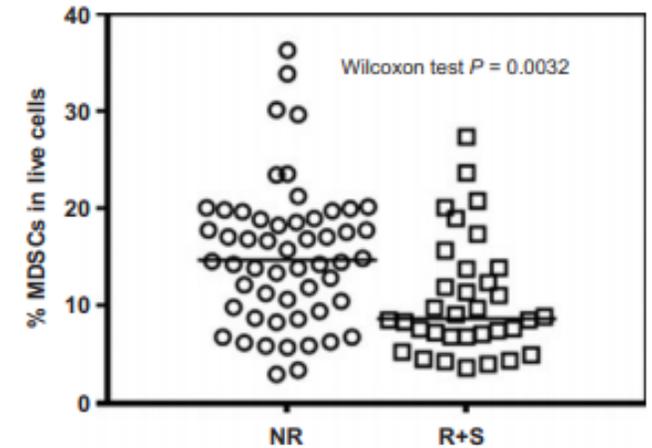


Inhibit T-cell activation



de Koning et al, Oncoimmunology, 2016

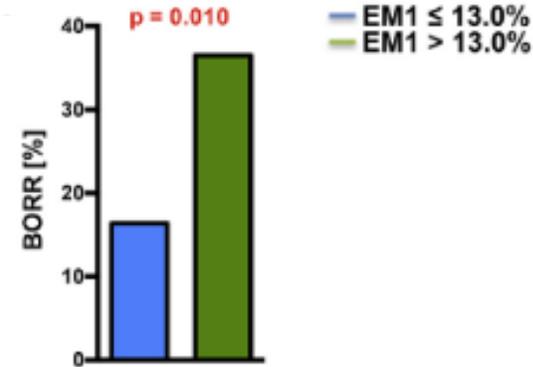
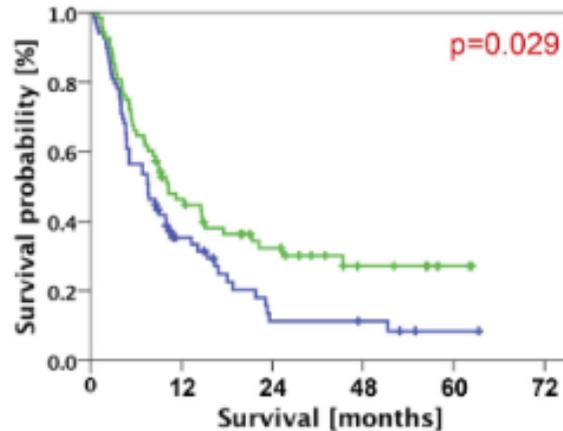
- >90 patients
- Phase I/II trial
- Advanced melanoma
- Ipilimumab refractory
- Treated with nivolumab
- +/- vaccine
- Low baseline MDSC correlated with outcome
- MoMDC stronger inverse predictor of outcome



MDSCs	N	Event	Censored	Median (95% CI)
≤12.65	44	13 (30%)	31(70%)	NA (19.9–NA)
>12.65	44	30 (68%)	14 (32%)	16.9 (8.7–21.7)

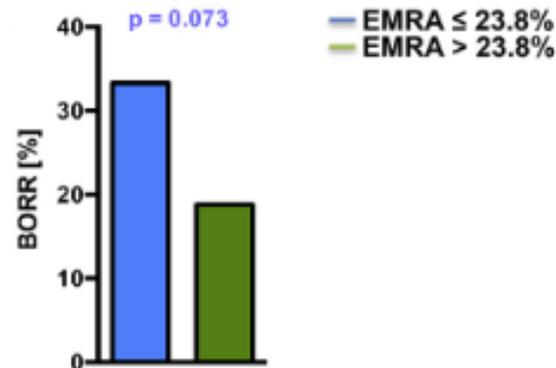
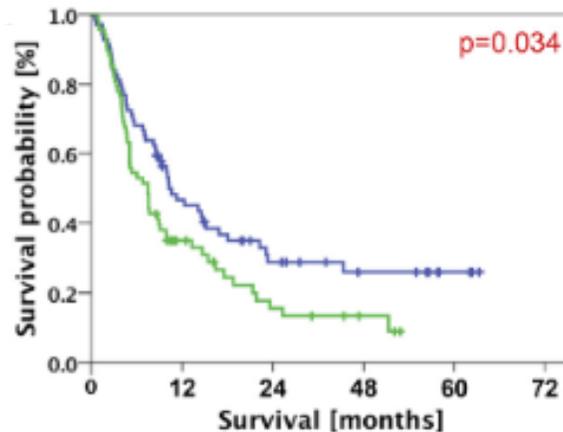
CD8+ Memory T-cells

Effector memory



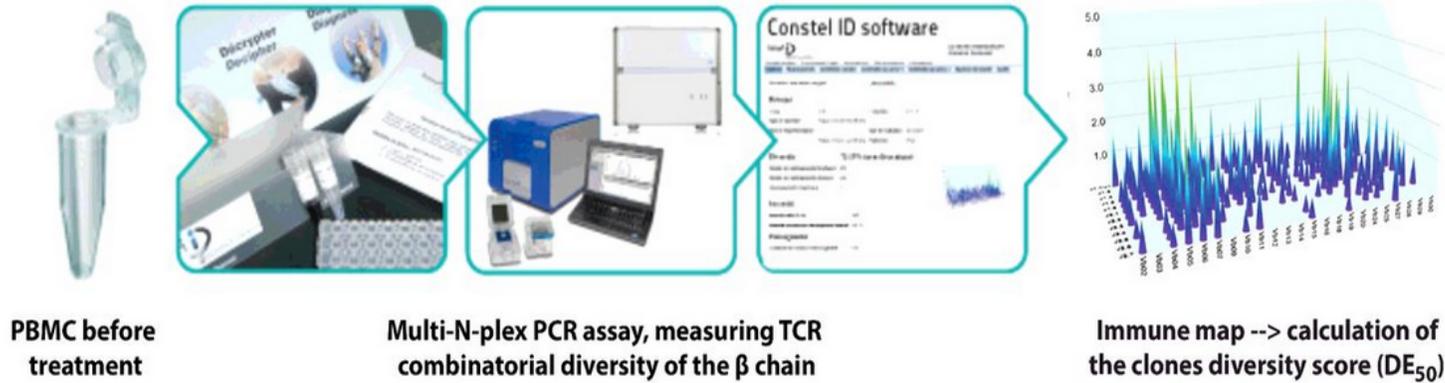
- 137 patients
- Advanced melanoma
- Treated ipilimumab
- Baseline blood
- High effector memory, positive correlation
- High terminally differentiated EM, negative correlation

Terminally differentiated effector memory

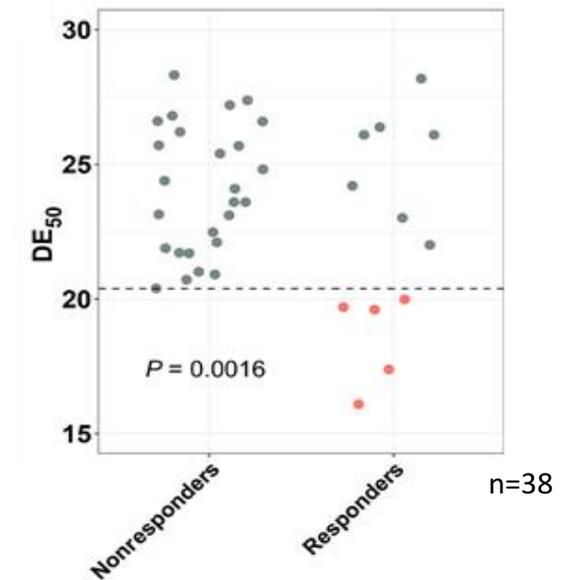


TCR Diversity

T-cell repertoire diversity evenness (DE_{50})

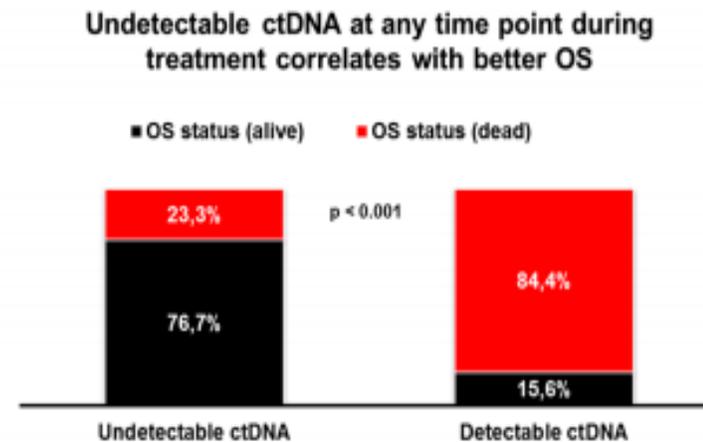
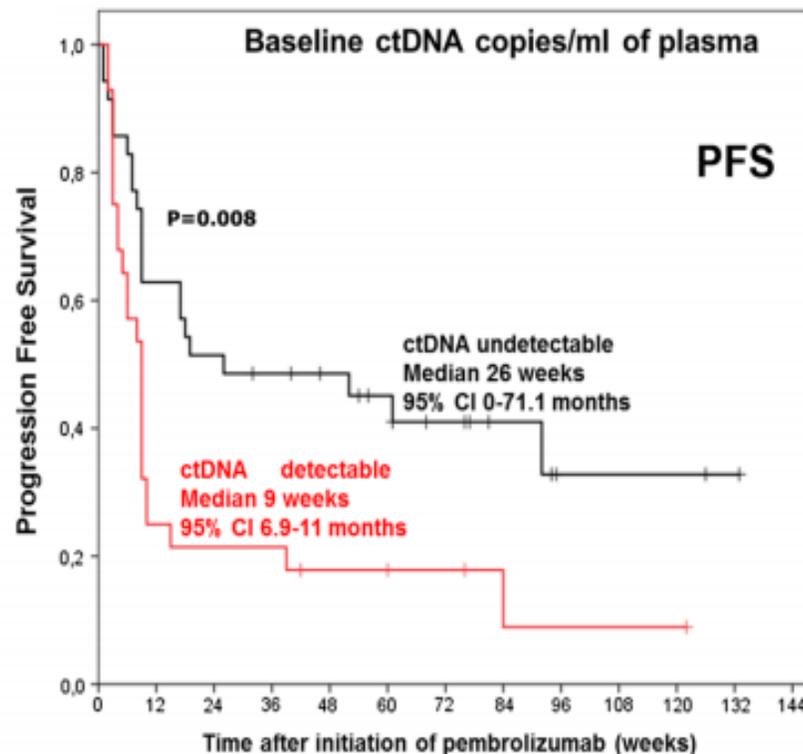
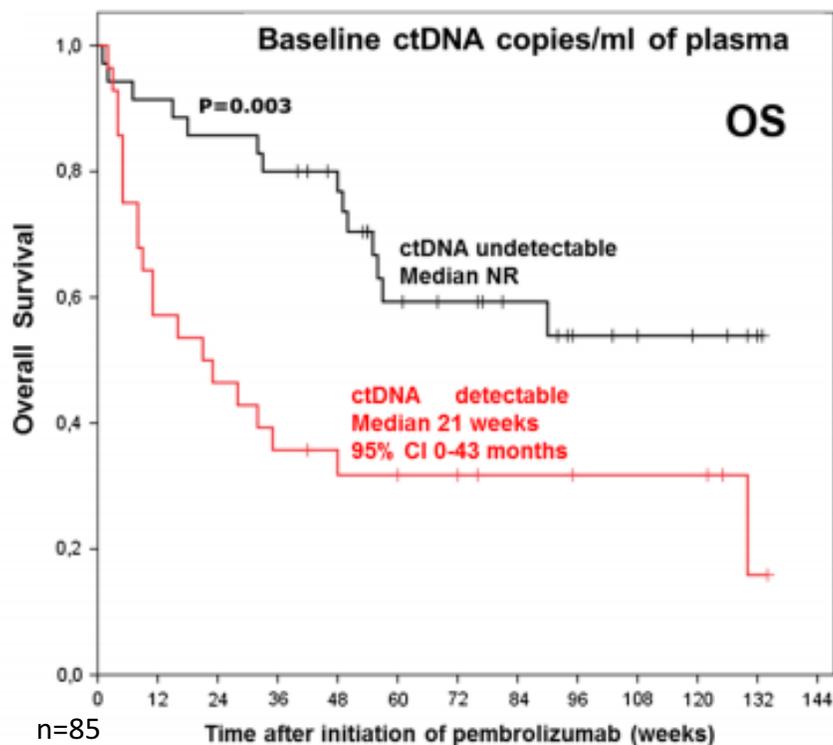


Predictive of response to anti-PD-1



- Advanced melanoma treated with ICI
- Even frequency distribution=low clonality=high DE_{50} score
- Specific frequencies abundant=high clonality=low DE_{50} score
- Low DE_{50} (<20.4) is an independent predictor of increased OS ($p=0.034$)

Circulating Tumor Cells or DNA

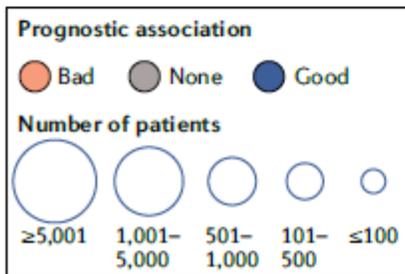
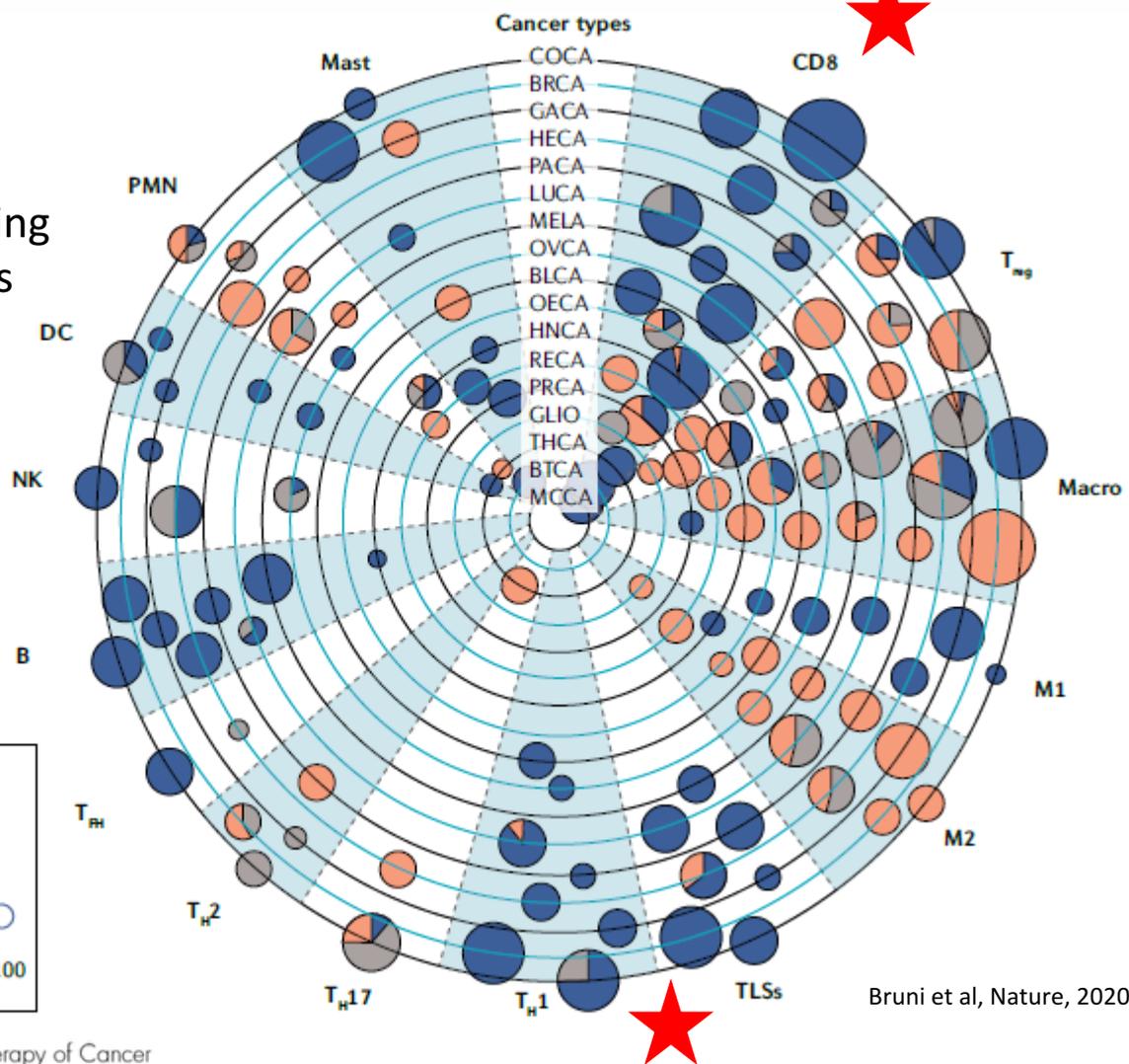


Seremet et al, J Trans Med, 2019

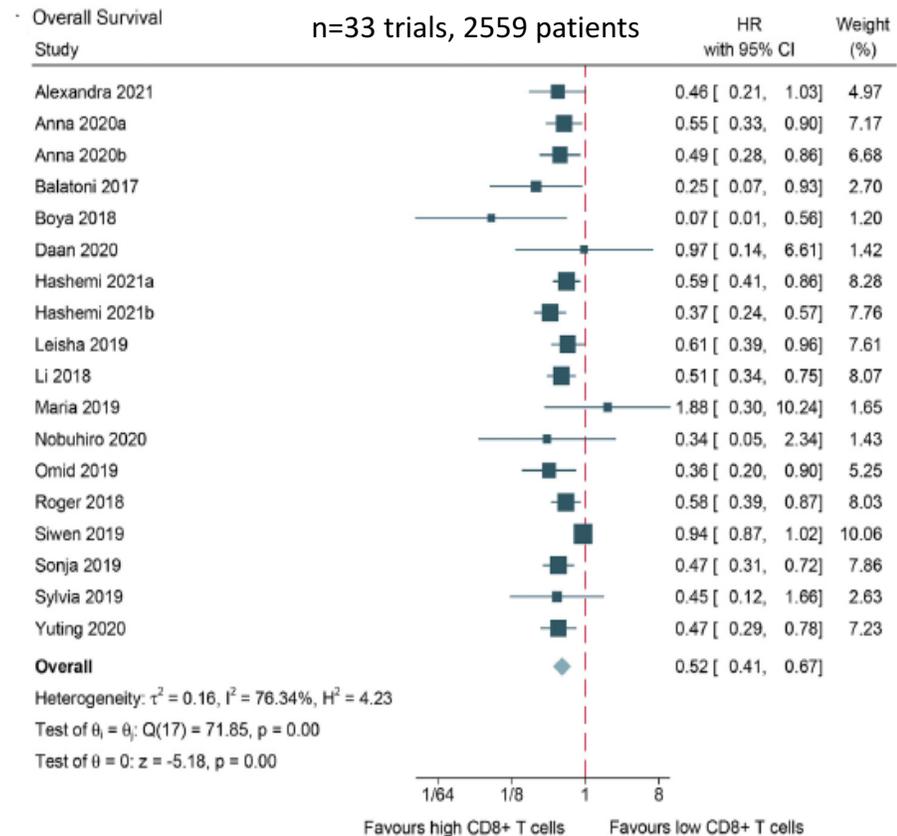
- Advanced melanoma
- Treated with anti-PD-1
- Baselines ctDNA an independent predictor of PFS and OS
- Potential as a pharmacodynamic biomarker

Tumor Infiltrating Lymphocytes

- 300 studies
- 70,000 patients
- 17 cancers
- 15 tumor infiltrating immune cell types



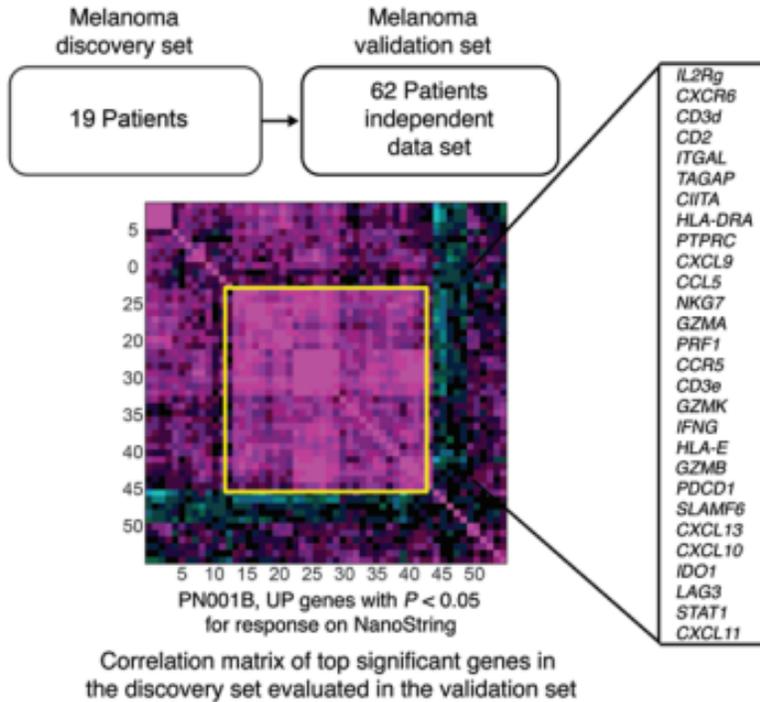
Baseline CD8 TIL and OS after ICI



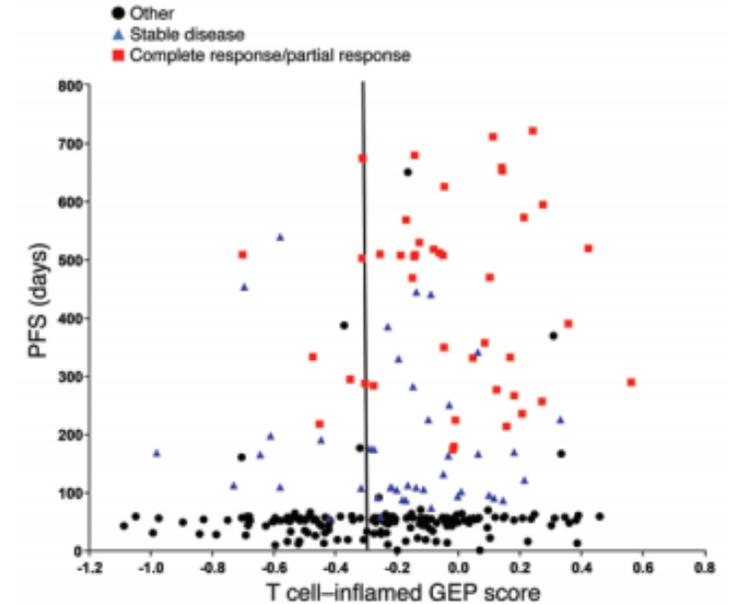
Bruni et al, Nature, 2020

Li et al, eClinical Medicine, 2021

Gene Expression Profiles: T-cell Inflammation



IFN- γ	Expanded immune gene signature	
IDO1	CD3D	IL2RG
CXCL10	IDO1	NKG7
CXCL9	CIITA	HLA-E
HLA-DRA	CD3E	CXCR6
STAT1	CCL5	LAG3
IFNG	GZMK	TAGAP
	CD2	CXCL10
	HLA-DRA	STAT1
	CXCL13	GZMB

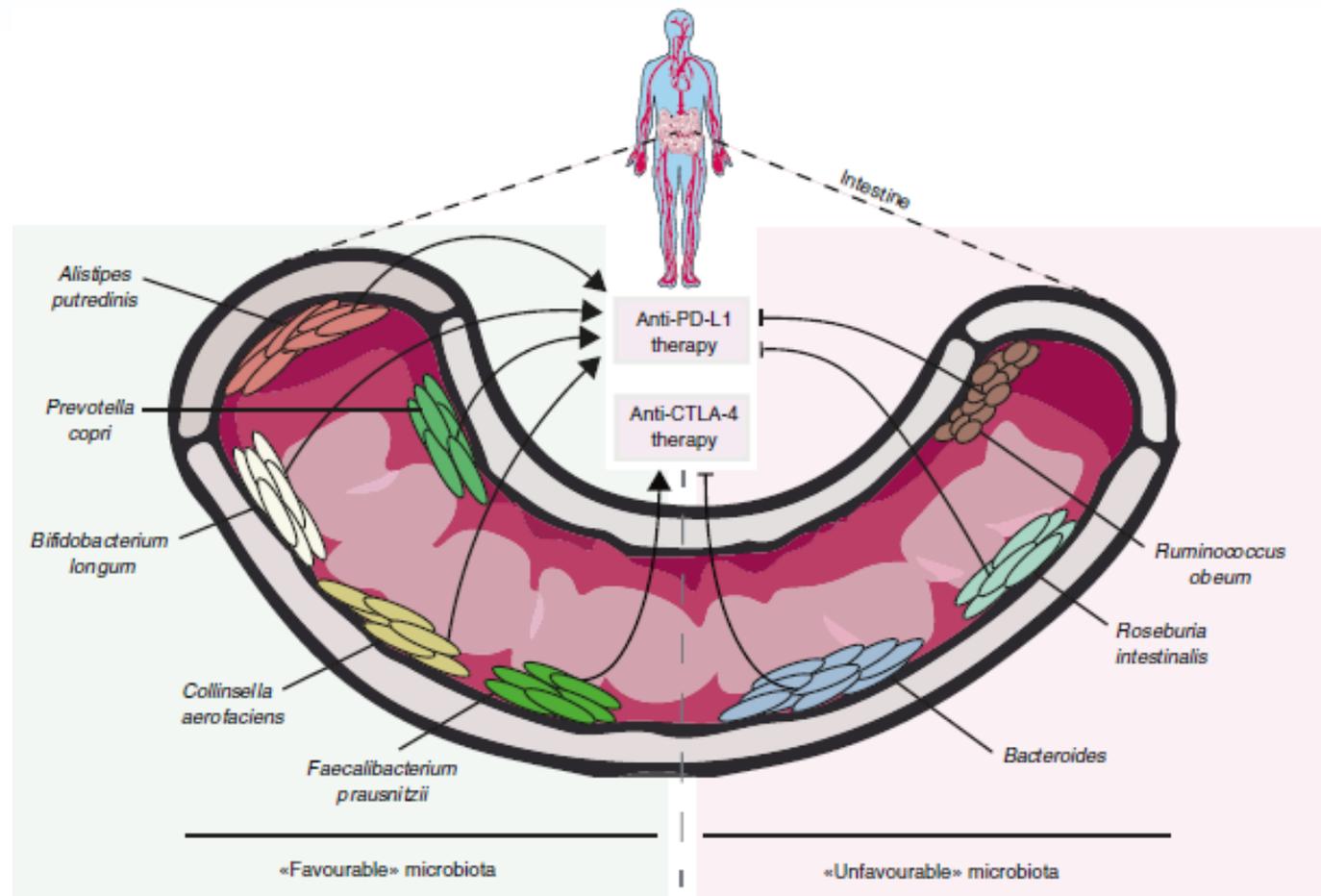


Ayers et al, JCI, 2017

- “T-cell inflamed” GEP has been validated in clinical trials and other retrospective studies
- Most advanced candidate for a predictive biomarker

KEYNOTE 012, 028
9 cancer cohorts

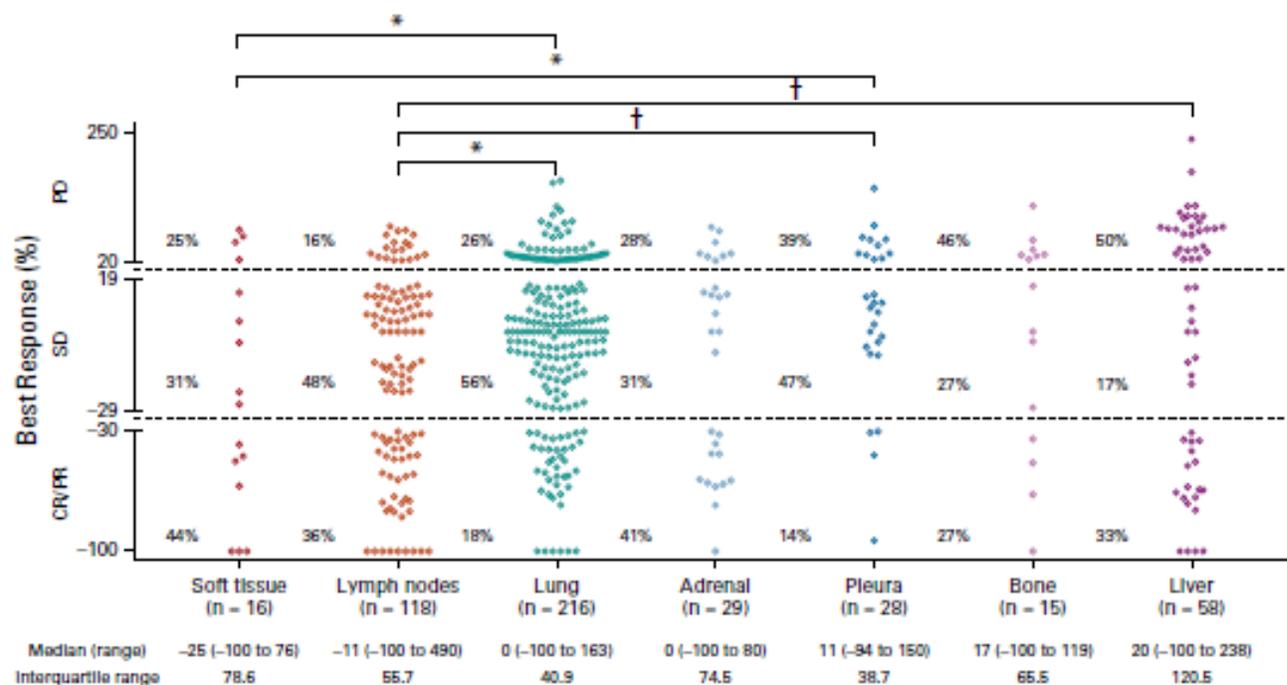
Changes in the Gut Microbiome



Pilard et al, BJC, 2021

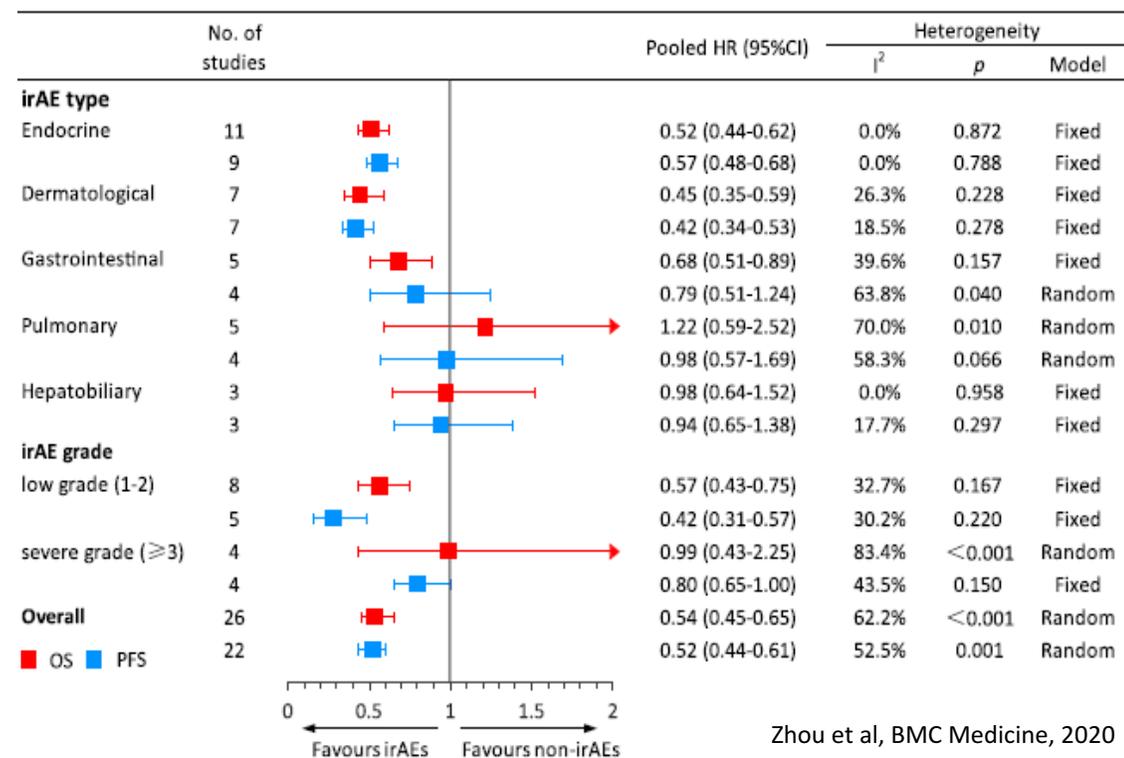
Clinical Biomarkers: Disease Sites/irAE

761 lesions from 214 NSCLC, 290 lesions from 78 MMRD
Best Overall Response



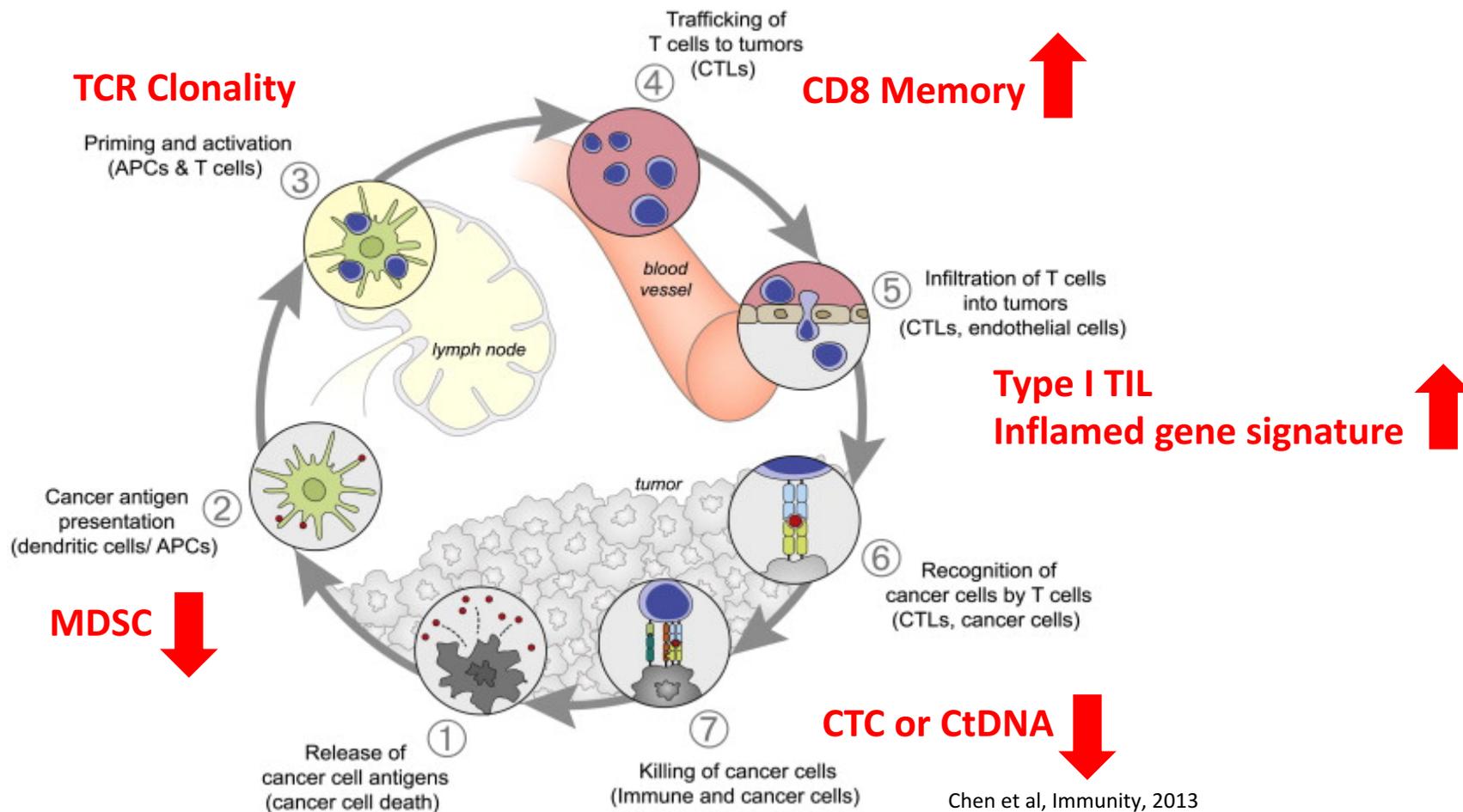
Osorio et al, JCO, 2019

22 studies, multiple tumor types, 3297 patients
Progression Free Survival

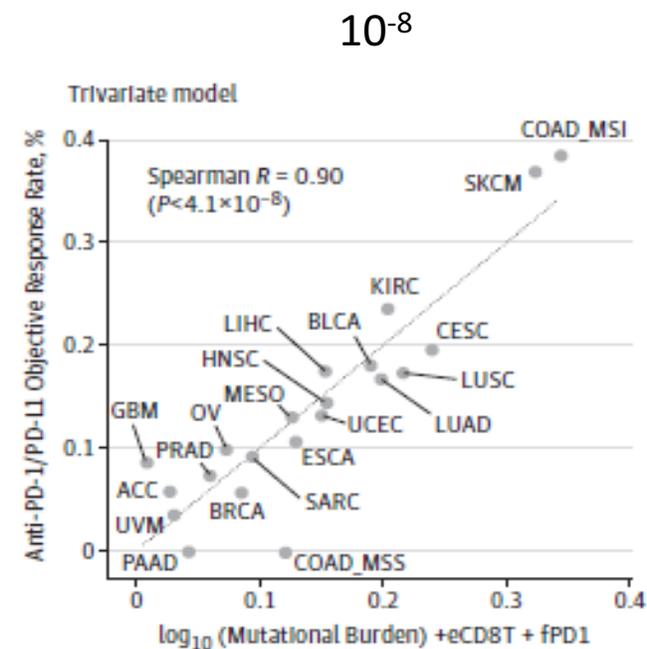
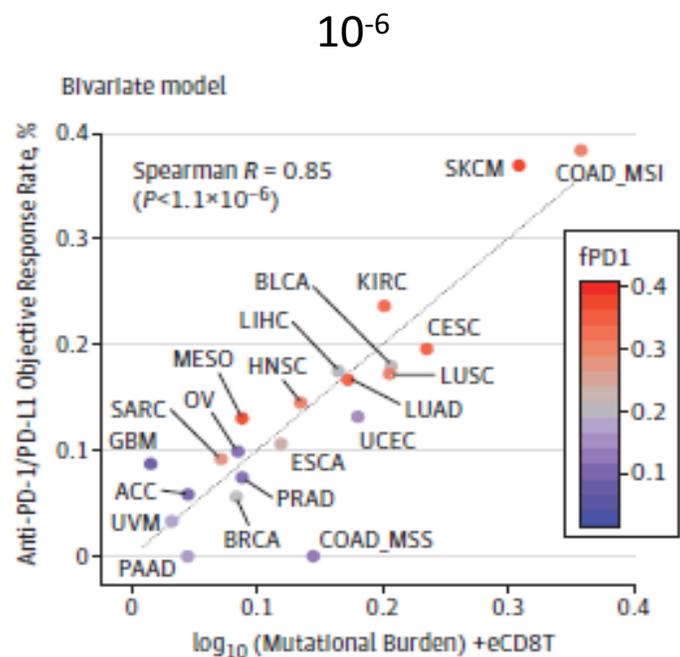
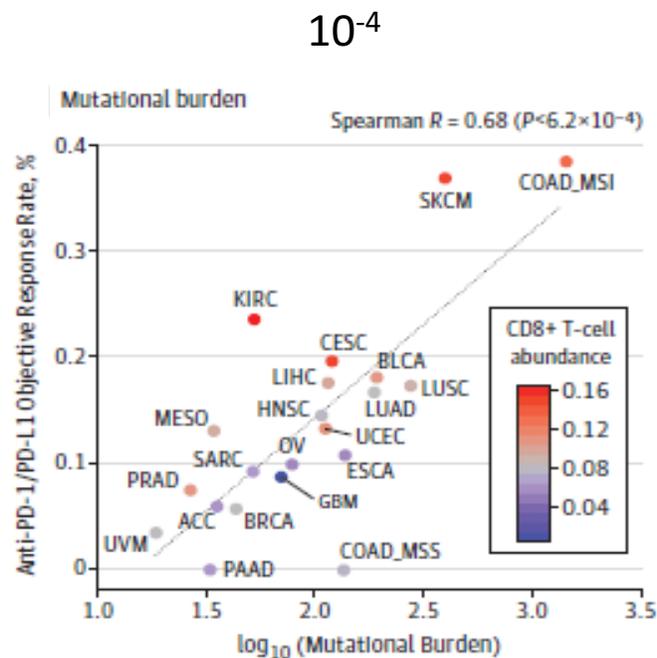


Zhou et al, BMC Medicine, 2020

Effective Anti-Cancer Immunity



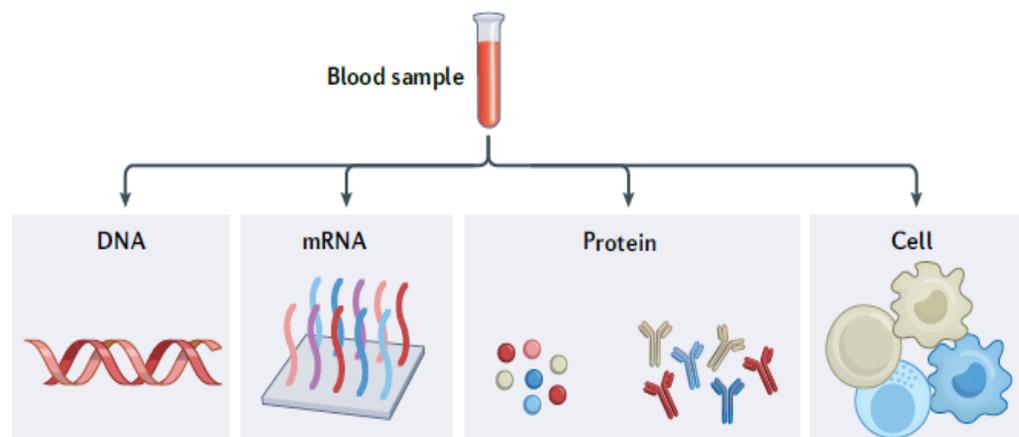
Multiple Markers Needed



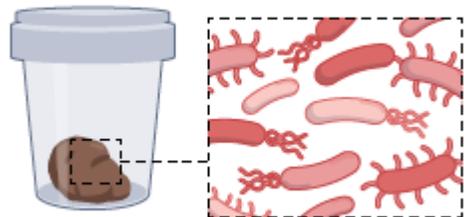
Lee et al, JAMA Oncology, 2019

- TCGA, 7187 patients, 21 cancer types, 36 variables
- Whole exome and RNA sequencing
- Predict objective response to ICI

Systems Approach to Predictive Biomarkers

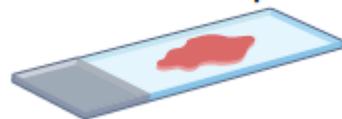


Stool sample

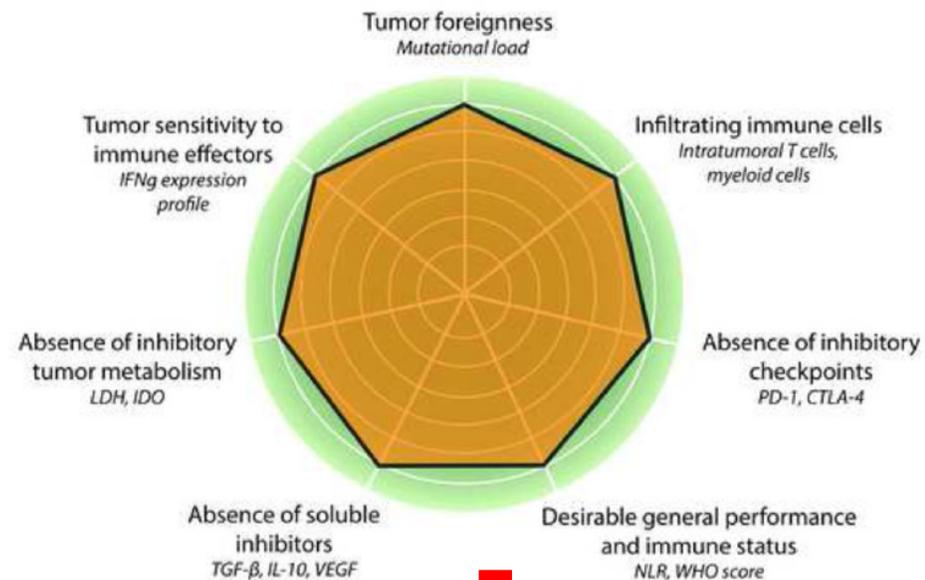


Gut microbiome

Tumour sample



Jing et al, Nat Rev Clin Oncol, 2022



Van Dijk et al, Eur Urol, 2019

