Immune Biomarkers to Guide Clinical Care

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Disclosures

- Founder of Wasaba Technologies
- Research Funding from Regeneron and Amgen

- Predictive Biomarkers- How do we predict if the immunotherapy will work?
- Prognostic Biomarkers- How do we know if the patient needs immunotherapy?

Predictive Biomarkers- Comparison of Mechanisms of Cancer Chemotherapy and Cancer Immunotherapy

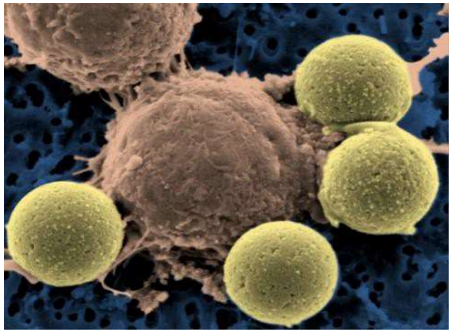
Chemotherapy

DIRECT KILL

CANCER CELLS DIE IF SUSCEPTIBLE TO CHEMICAL DAMAGE

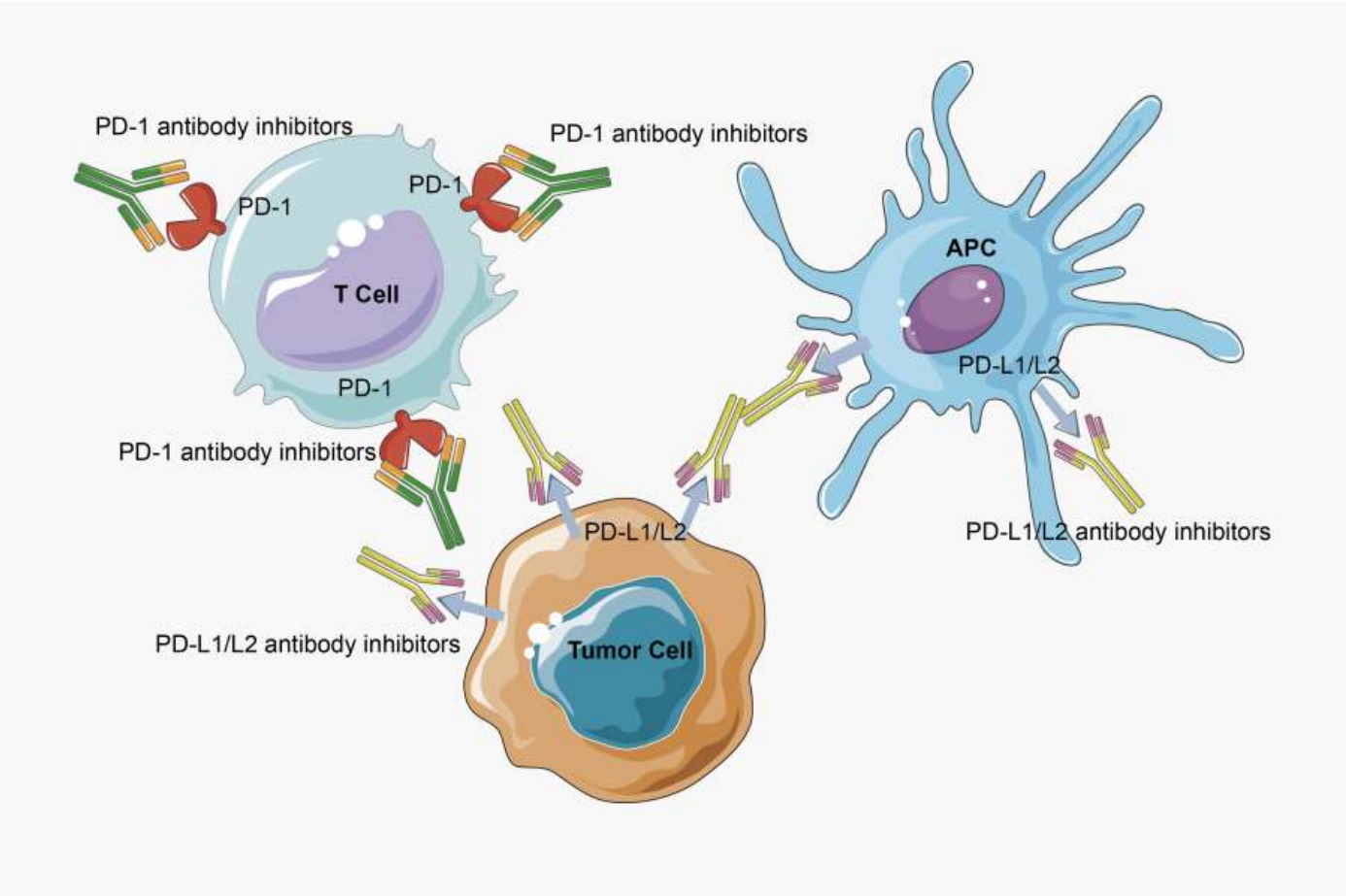
Immunotherapy

IMMUNE CELLS DO SOMETHING



CANCER CELLS DIE IF IMMUNE CELLS KILL THEM

PD-1 Blockade- THE GOLD STANDARD

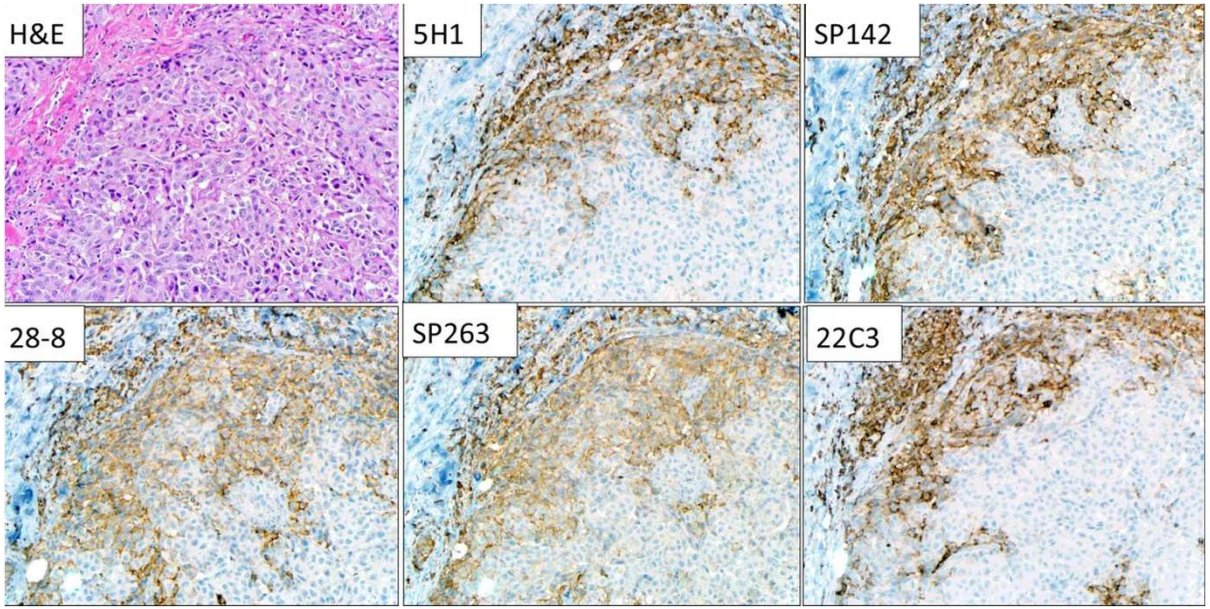


APPROVALS-

- Melanoma
- Small cell and non-small cell lung cancer
- Renal cell cancer
- Hodgkin's lymphoma
- Head and neck cancer
- Urothelial cancer,
- Colorectal cancer
- Esophageal cancer
- Mesothelioma
- Gastric cancer,
- Endometrial cancer
- Cervical cancer
- Hepatocellular cancer
- Squamous cell cancer
- Merkel cell cancer
- And more…

https://www.clipartkey.com

Standard PDL-1 Immuno-histochemistry- Sometimes required



<u>Requirement</u> for Pembrolizumab treatment for

- Lung cancer
- Head and neck cancer
- Urothelial cancer
- Gastric cancer
- Esophageal cancer
- Cervical cancer

<u>Requirement</u> for Atezolizumab (anti-PDL1)

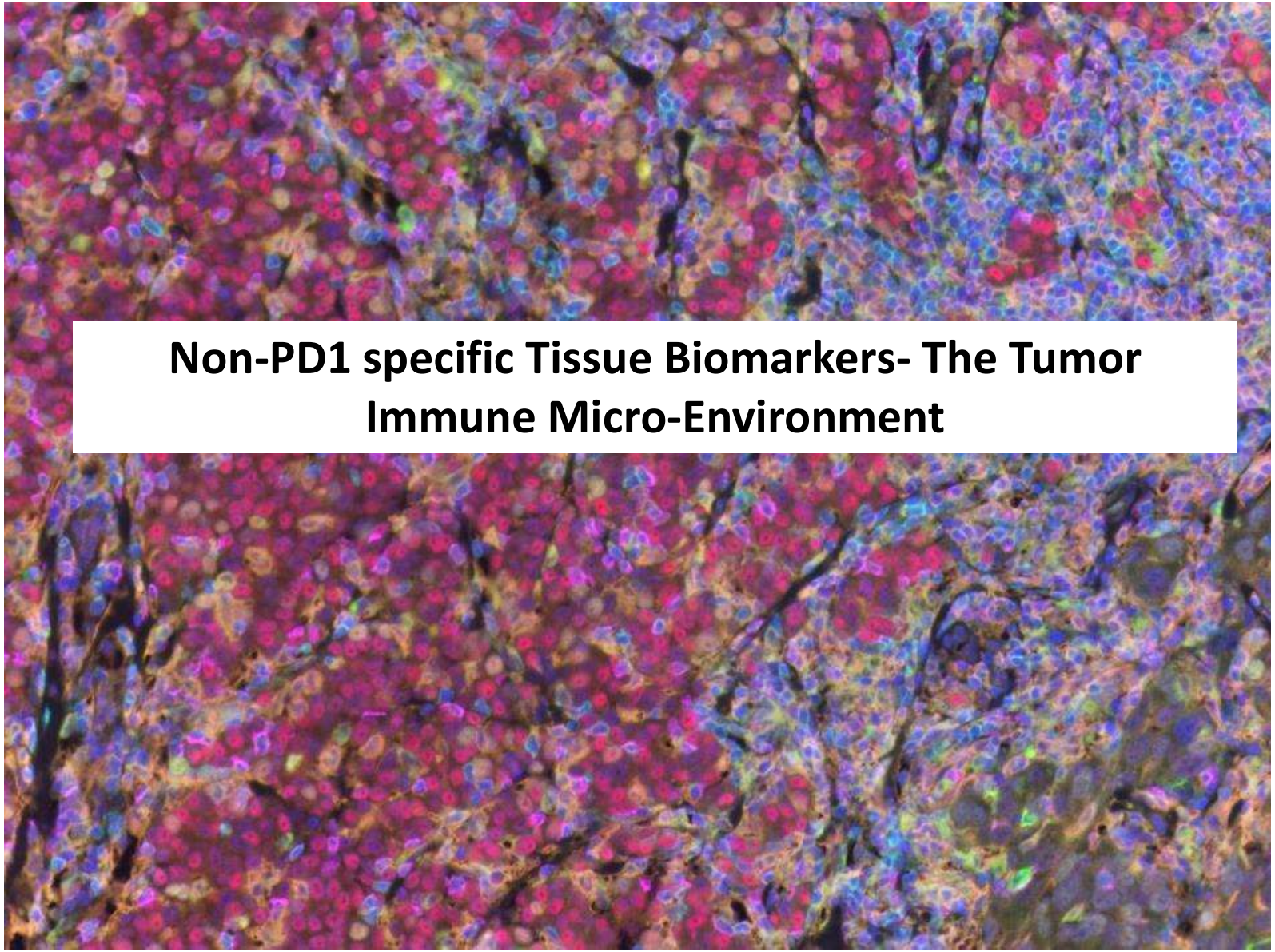
- Triple negative breast cancer
- Urothelial cancer

Sunshine…Taube et al, Clinical Cancer Research 2017

Standard PDL-1 Immuno-histochemistry- Not always an indicator of response

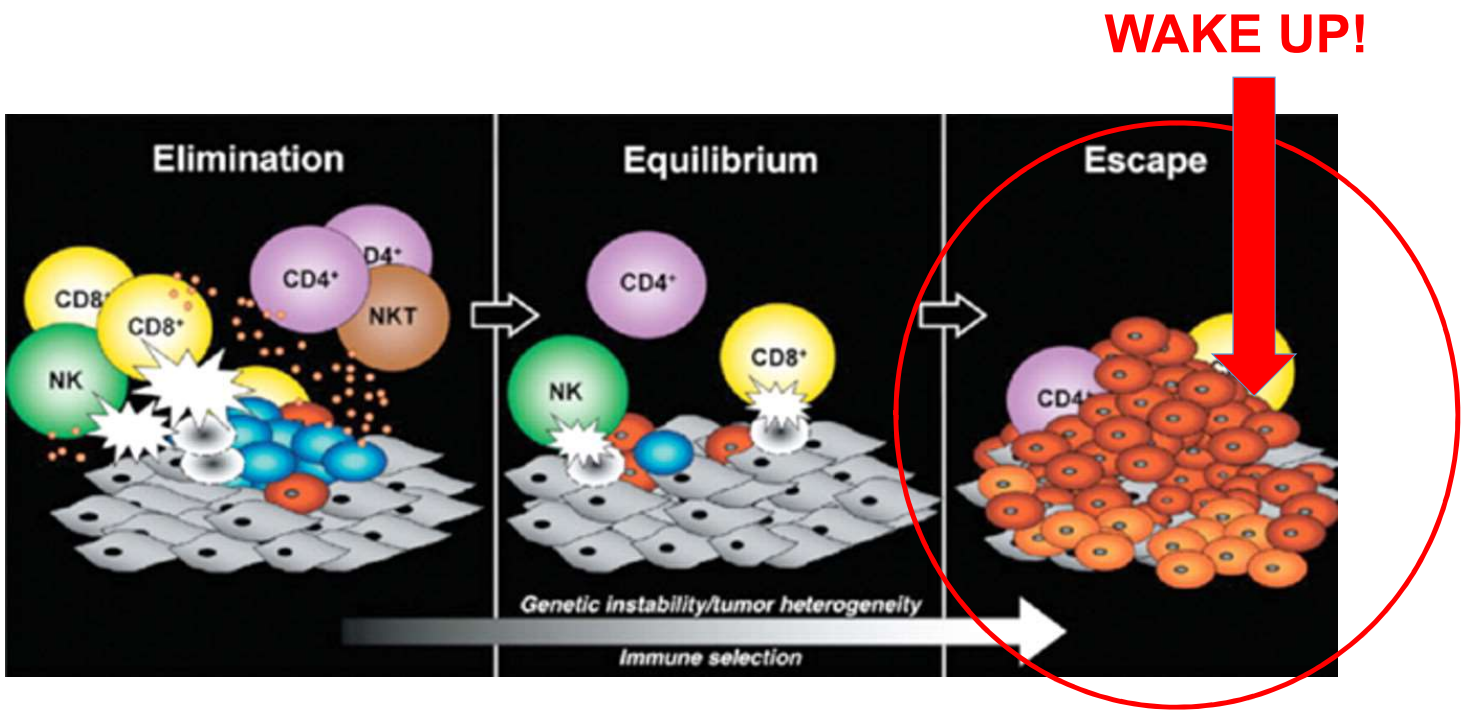
- Variability between antibody clones used for staining can lead to ambiguous results
- Depending on the malignancy, patients documented as negative based on established thresholds may still respond to therapy
- Not all positive patients will respond
- Very useful in specific contexts but overall meta-analysis Rimm, Taube and colleagues AUC 0.65 without very high specificity or sensitivity)…

Just OK



Non-PD1 specific Tissue Biomarkers- The Tumor Immune Micro-Environment

Immuno-surveillance-Assessing Quality of Local Immune response



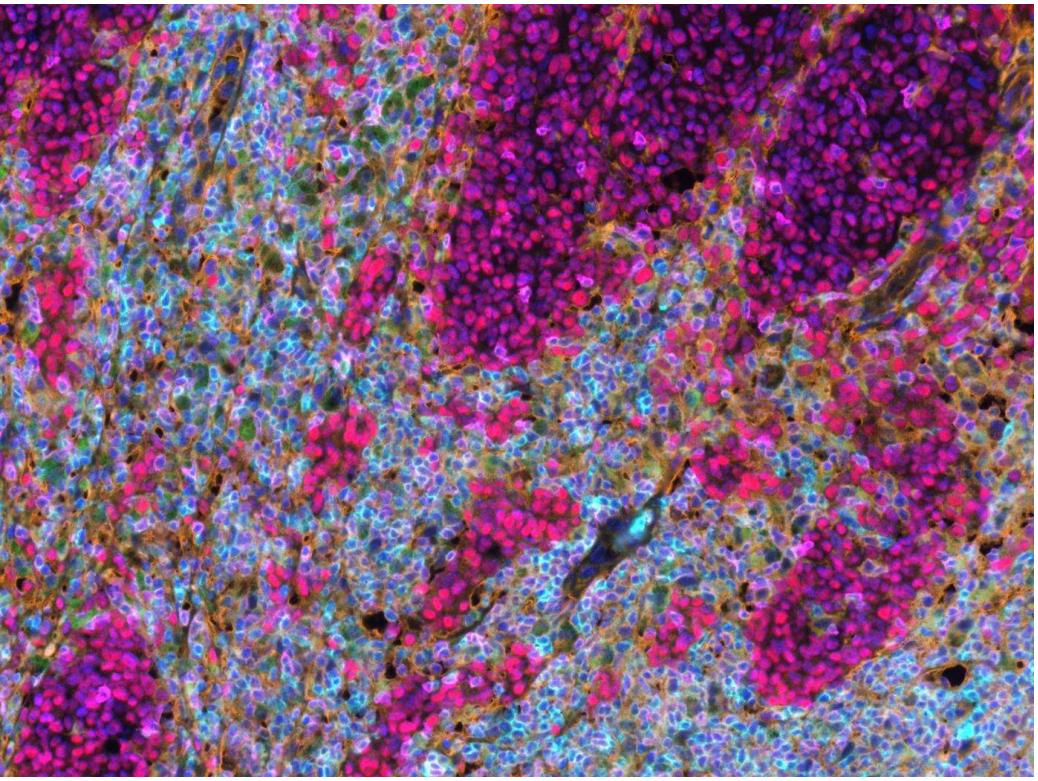
Three Flavors-

- Morphology based- characterization of Immune Infiltrate
- Tumor mutational Burden
- Interferon Signatures

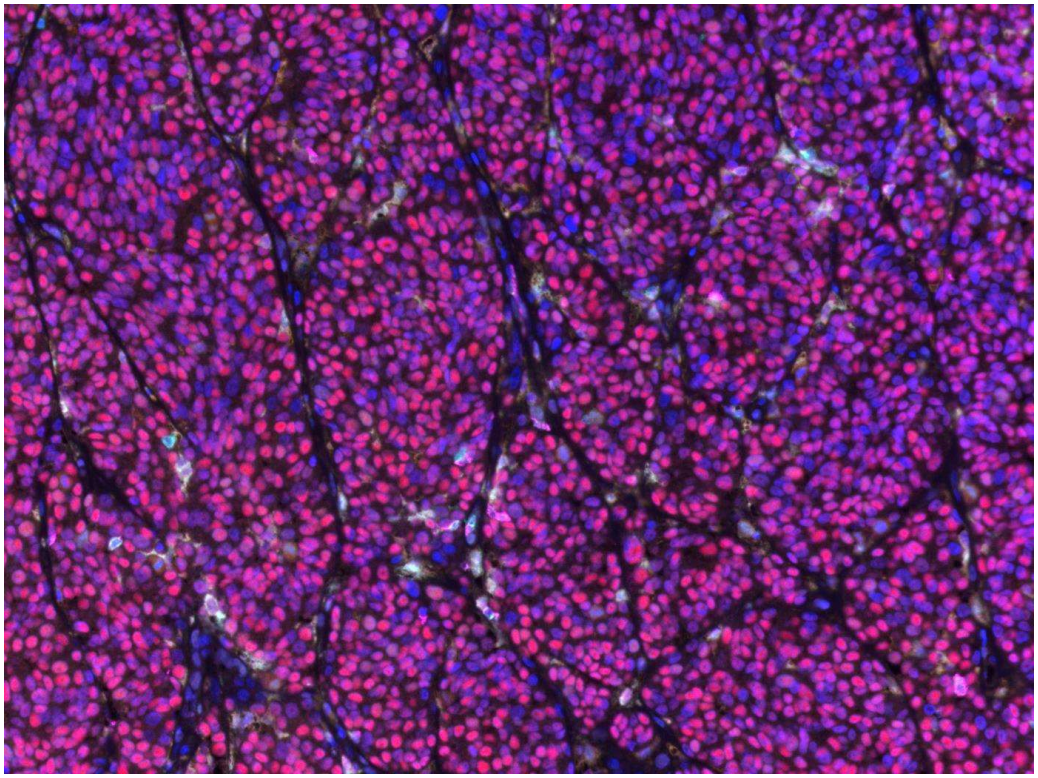
Dunn et al, "Nature Immunology 2002.

Differing Morphologies-Two Very Different Melanomas

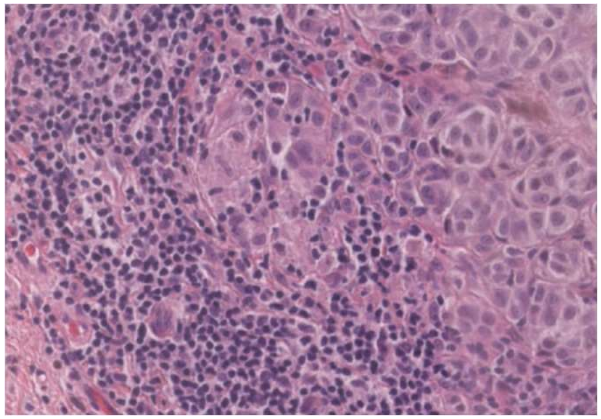
T cell infiltrated Melanoma



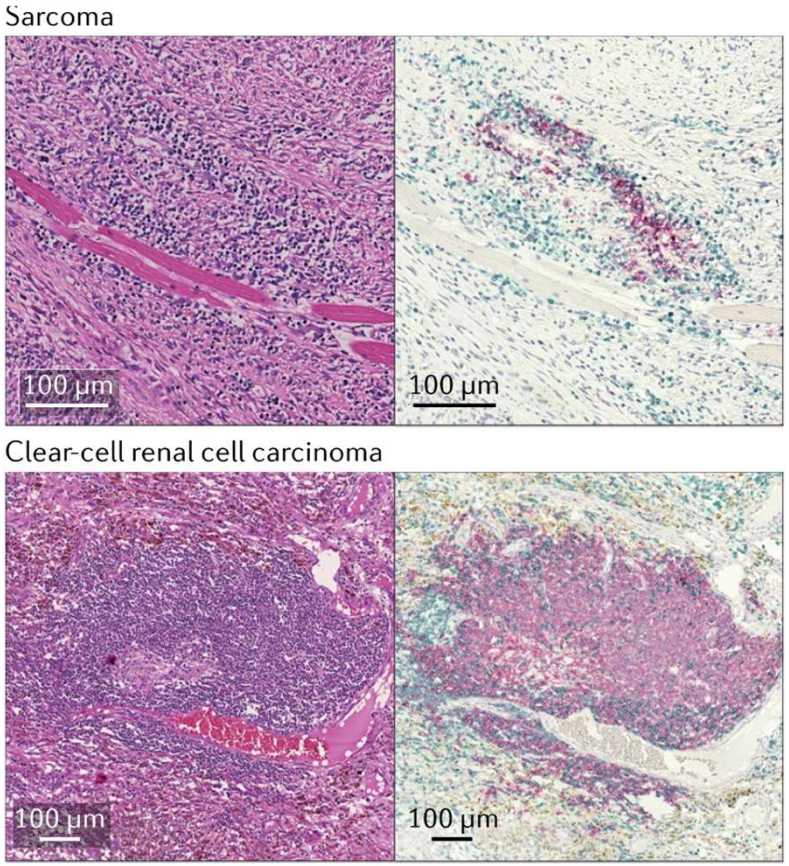
Non- T cell infiltrated Melanoma



Morphology- TILs (Tumor infiltrating Lymphocytes) and TLSs (Tertiary Lymphoid Structures)



Acs, Rimm et al. Nature Communications 2019

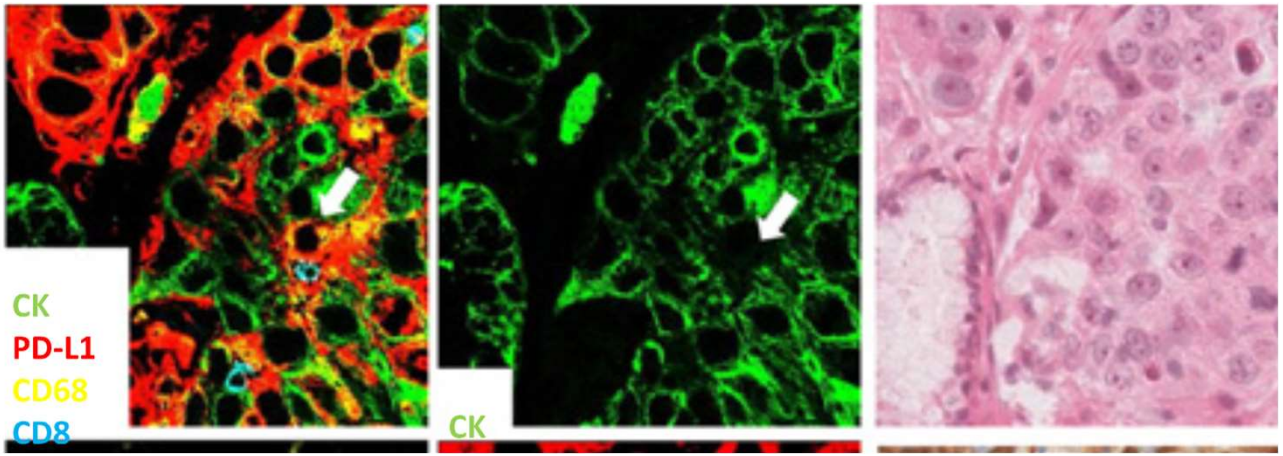


Fridman et al, Nature Reviews Cancer 2019

- Accumulating evidence for predictive value in multiple contexts
- No widely accepted method to reproducibly quantify TILs and TLSs
- Artificial Intelligence methods proposed

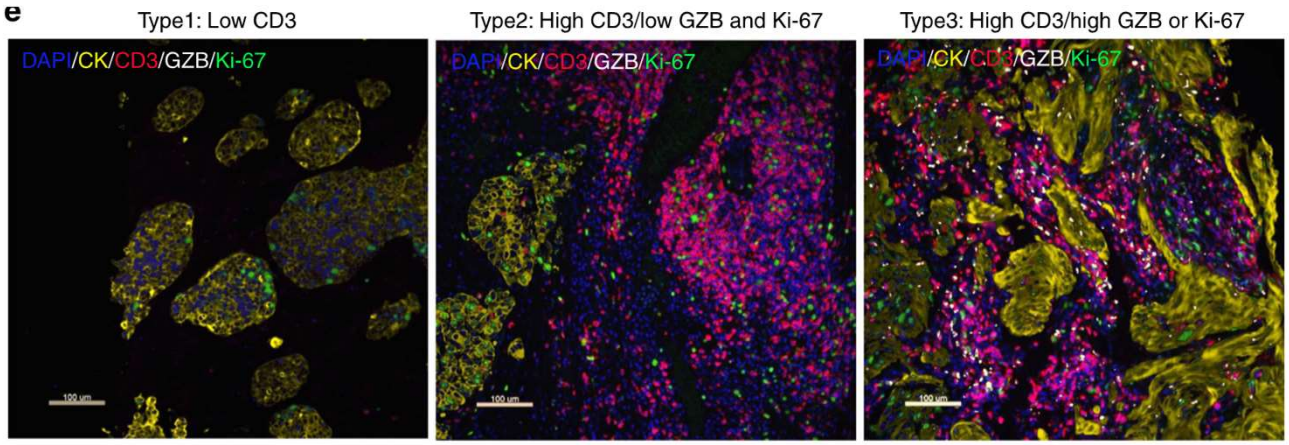
Multi-plex Immuno-fluorescence Phenotyping of the Tumor Immune Micro-Environment

Precise location of PDL1 on macrophages



Liu… Rimm et al, Clinical Cancer Research 2020

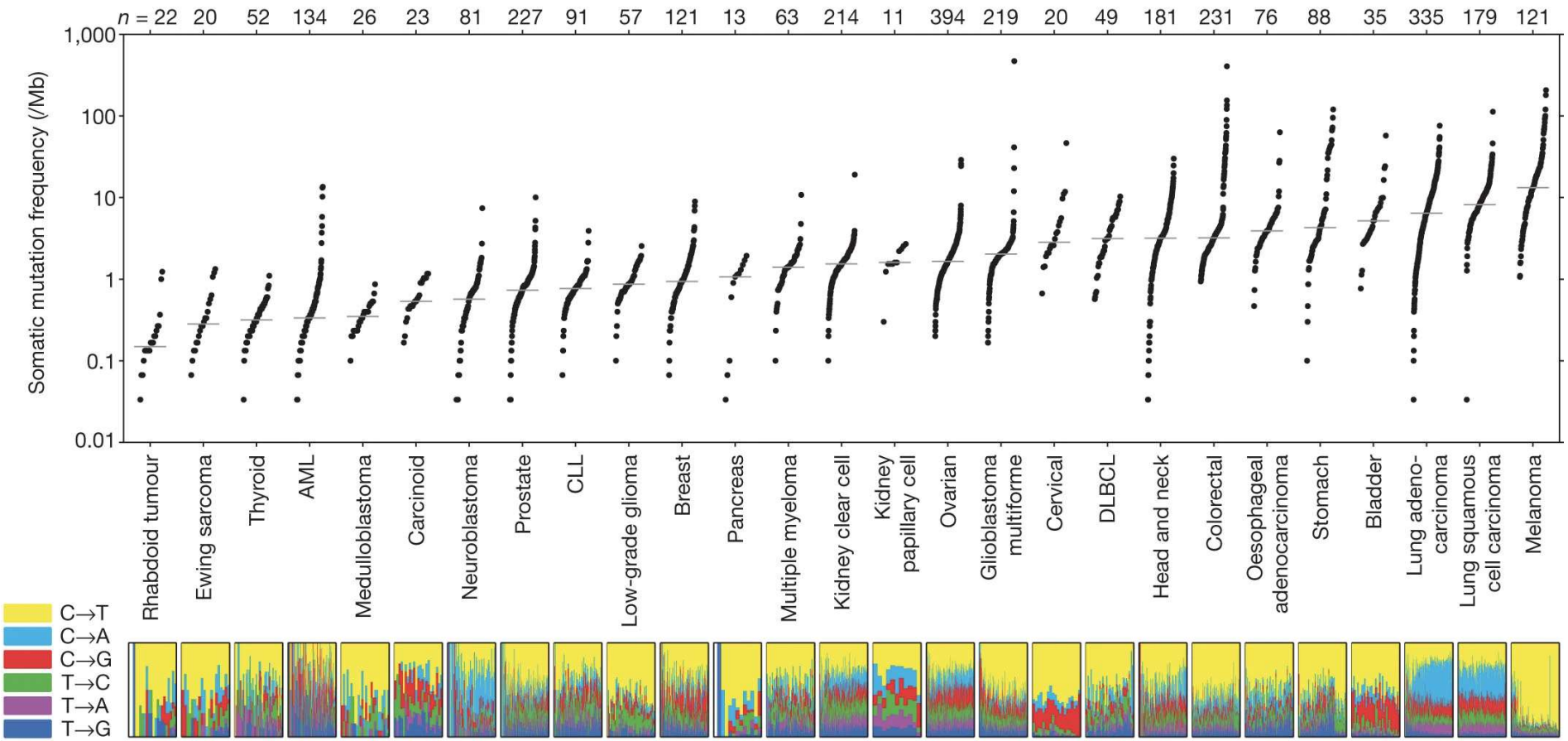
Phenotyping the TIME by subsetting T cells



Gettinger… Schalperet al, Nature Com-munications 2018

Challenge is to mass produce these assays on larger populations for clinical application

Tumor Mutational Burden



Challenge is to account for the immunogenicity of divergent mutations across genetically diverse populations.

Lawrence et al.
Nature 2013

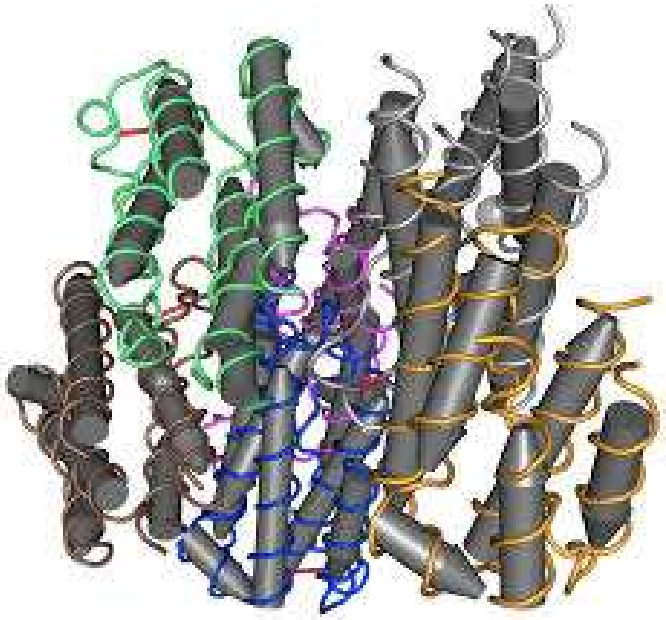
Micro-Satellite Instability

Tumor Type	No.	CR, No.	PR, No.	ORR, % (95% CI)	Median PFS, Months (95% CI)	Median OS, Months (95% CI)	Median DOR, Months (range)
Endometrial	49	8	20	57.1 (42.2 to 71.2)	25.7 (4.9 to NR)	NR (27.2 to NR)	NR (2.9 to 27.0+)
Gastric	24	4	7	45.8 (25.6 to 67.2)	11.0 (2.1 to NR)	NR (7.2 to NR)	NR (6.3 to 28.4+)
Cholangiocarcinoma	22	2	7	40.9 (20.7 to 63.6)	4.2 (2.1 to NR)	24.3 (6.5 to NR)	NR (4.1+ to 24.9+)
Pancreatic	22	1	3	18.2 (5.2 to 40.3)	2.1 (1.9 to 3.4)	4.0 (2.1 to 9.8)	13.4 (8.1 to 16.0+)
Small intestine	19	3	5	42.1 (20.3 to 66.5)	9.2 (2.3 to NR)	NR (10.6 to NR)	NR (4.3+ to 31.3+)
Ovarian	15	3	2	33.3 (11.8 to 61.6)	2.3 (1.9 to 6.2)	NR (3.8 to NR)	NR (4.2 to 20.7+)
Brain	13	0	0	0.0 (0.0 to 24.7)	1.1 (0.7 to 2.1)	5.6 (1.5 to 16.2)	–

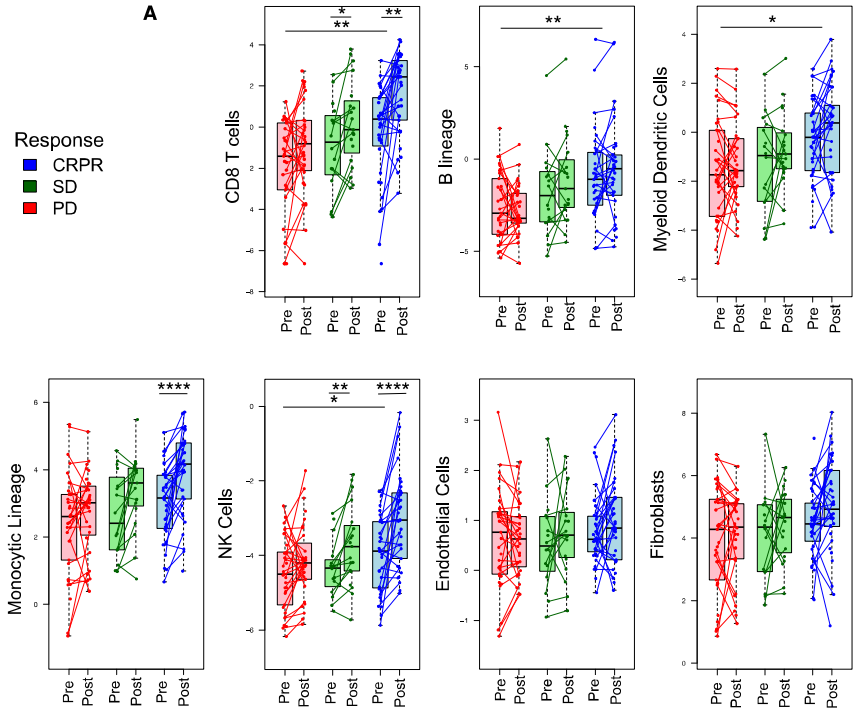
NOTE. Efficacy analyses included all patients who received at least one dose of pembrolizumab. Only confirmed responses are included. Response was assessed per RECIST version 1.1 by independent central radiologic review.

Marabelle et al, Journal of Clinical Oncology 2020

Immune RNA Signatures



Interferon



Interferon signatures have been proposed for multiple solid tumor types

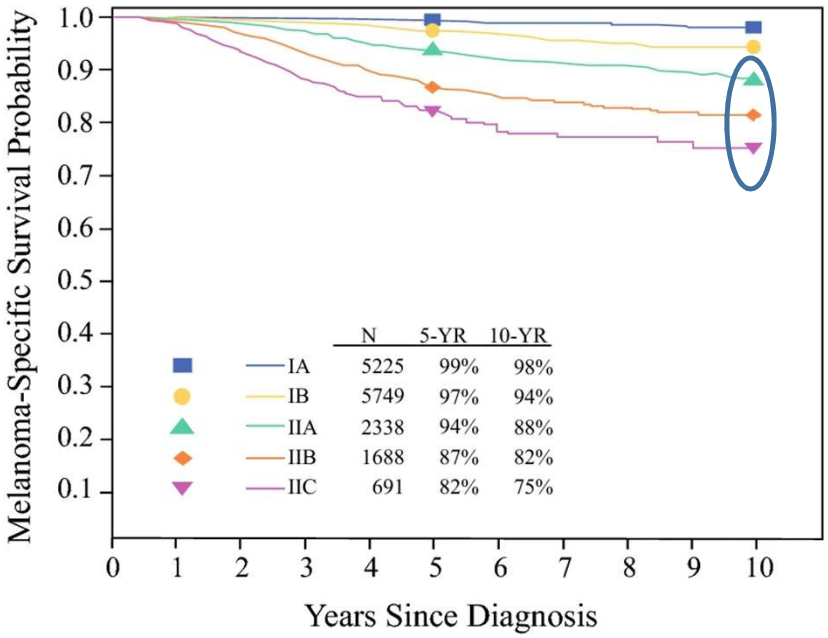
Grasso… Ribas et al. Cancer Cell 2020

Summary of Predictive Immune Tissue Biomarkers

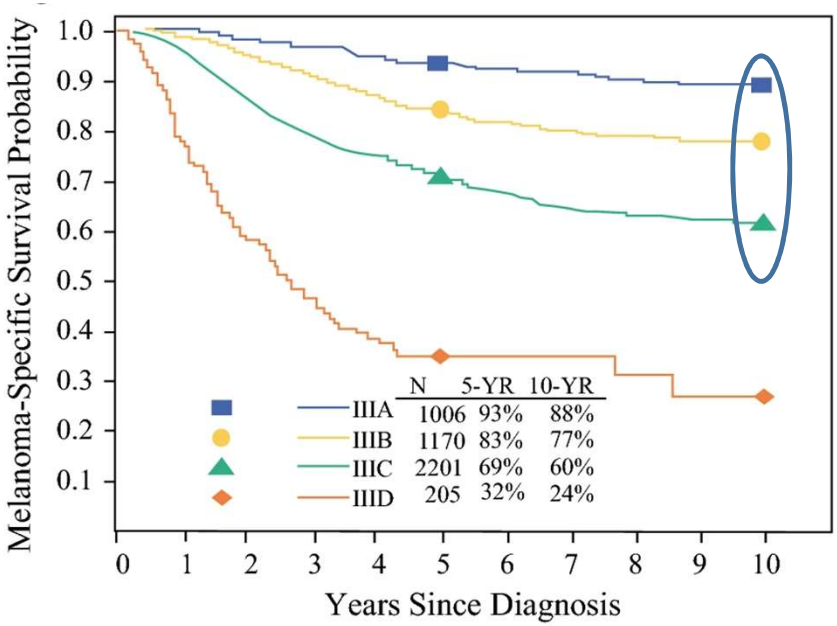
- PDL1 staining is used to select patients for therapy in specific situations but is not highly reliable
- Microsatellite unstable patients have reproducibly high rates of response to immunotherapy
- A ”favorable” T infiltrated, interferon-rich, tumor immune micro-environment (TIME) associates with response.
- Markers of favorable TIME may be genetic, genomic, morphologic or antibody based
- **Clinical Questions- What are our alternatives? Chemotherapy is toxic and almost never curative…**

Prognostic Immune Biomarkers- Who should we treat in adjuvant setting? Who will benefit?

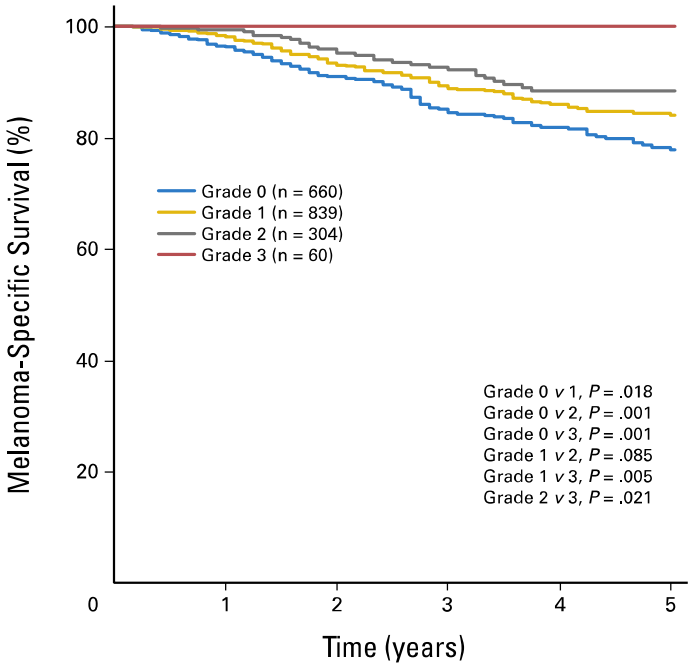
Stage II Melanoma

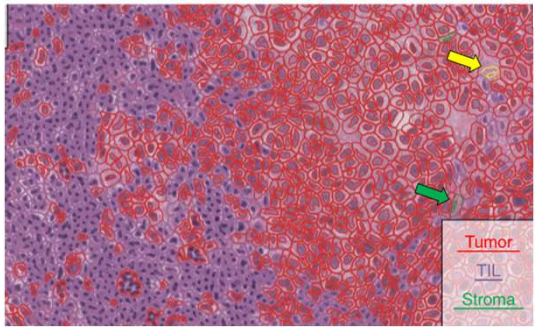


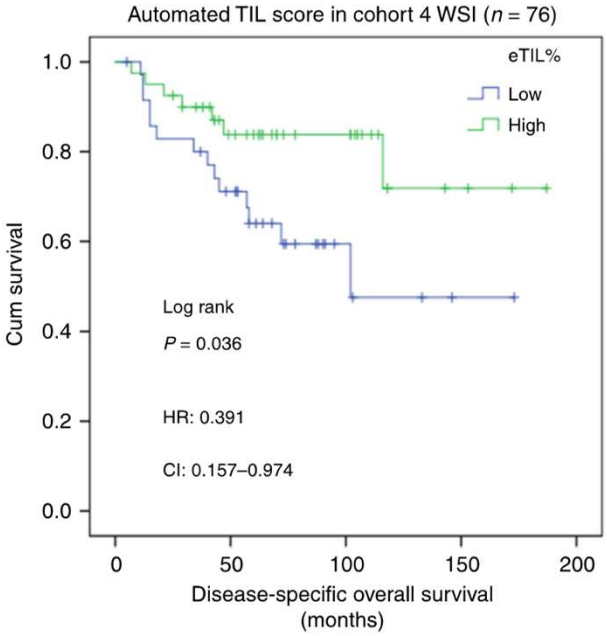
Stage III Melanoma



Prognostic Value of TILs and eTILs

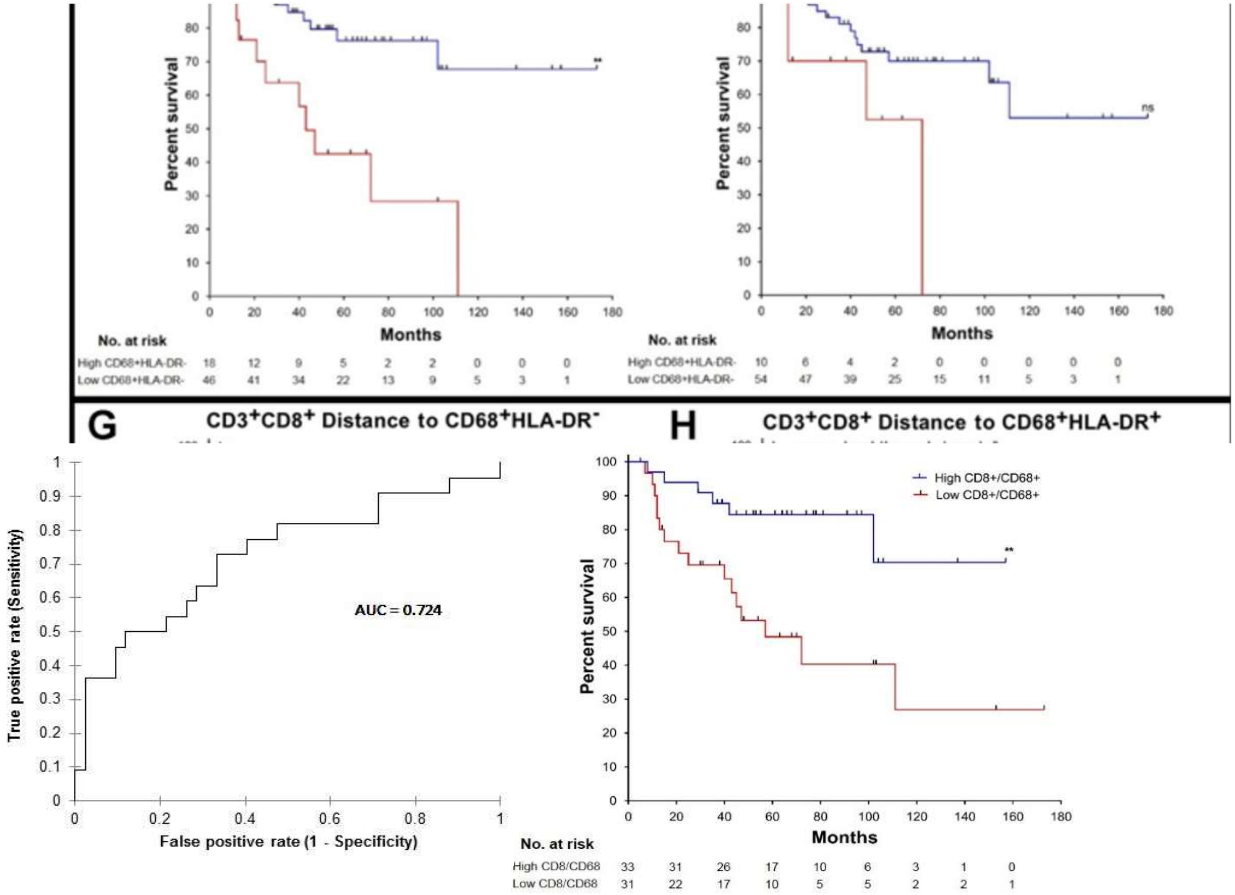






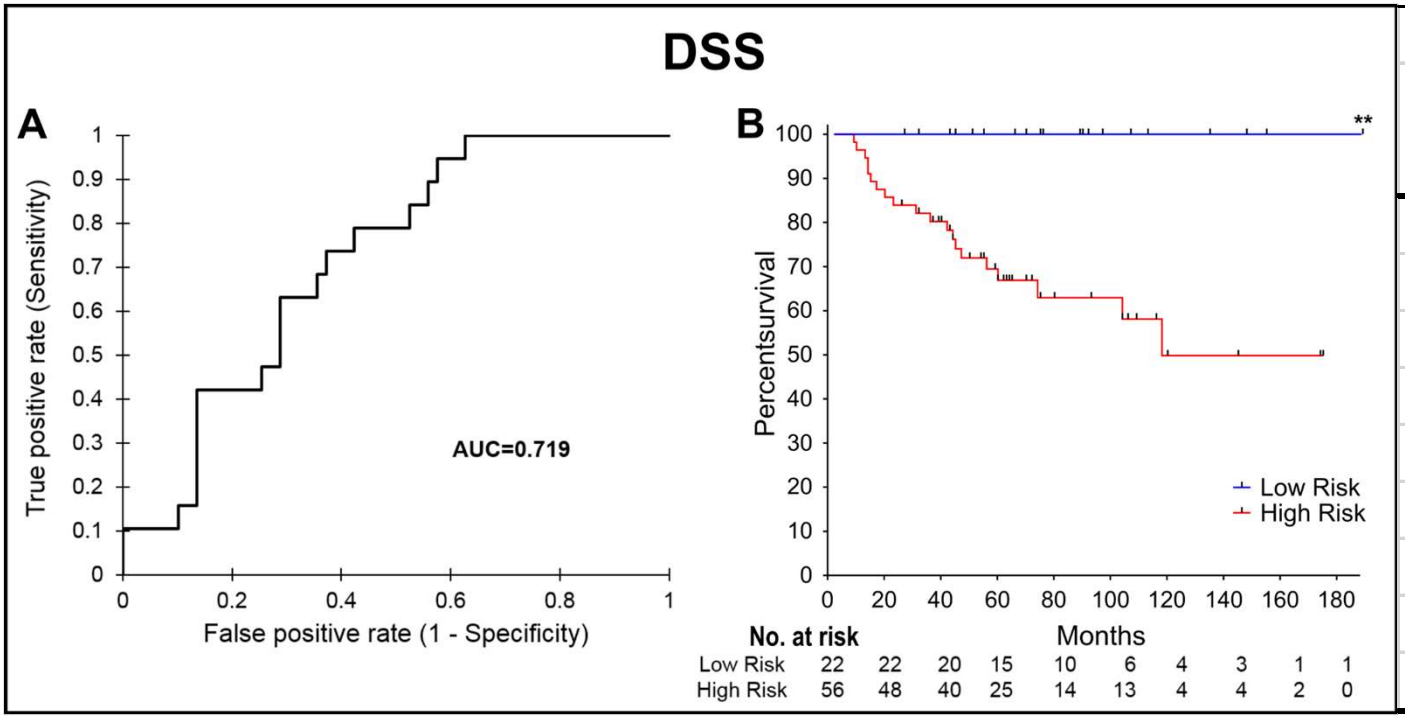
Adapted from Azimi et al Journal of Clinical Oncology 2012 and Acs…Rimm et al Nature Communications. 2019

Multi-plexed Immuno-Fluorescence- CD8/CD68 Ratio



Adapted from Gartrell…Saenger Cancer Immunology Research 2018

Melanoma Immune Panel- Interferon Gene Signature



	Differential expression	
Gene	Fold Change	BH p value
PTPRC	1.07	0.0399
CCL5	1.19	0.0399
CD2	1.05	0.0399
CD27	1.21	0.04
CXCL9	1.56	0.0459
CD8A	1.26	0.0459
CXCR3	1.11	0.0459
CXCL11	1.39	0.0459
LCK	1.14	0.0459

Adapted from Gartrell…Saenger Clinical Cancer Research 2019

Conclusions

- The only immune biomarker currently used in routine clinical practice is PD-L1 IHC which is target based. It predicts response to PD1 pathway signaling blockade in certain contexts.
- Characterization of the tumor immune micro-environment will yield clinically applicable predictive and prognostic biomarkers in the near future
- Immune biomarkers can identify target populations more likely to benefit from immune therapy.

Thank you for your attention!