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Does immunotherapy make sense in gynecologic cancers?

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"Jenner". Giulio Monteverde, 1873

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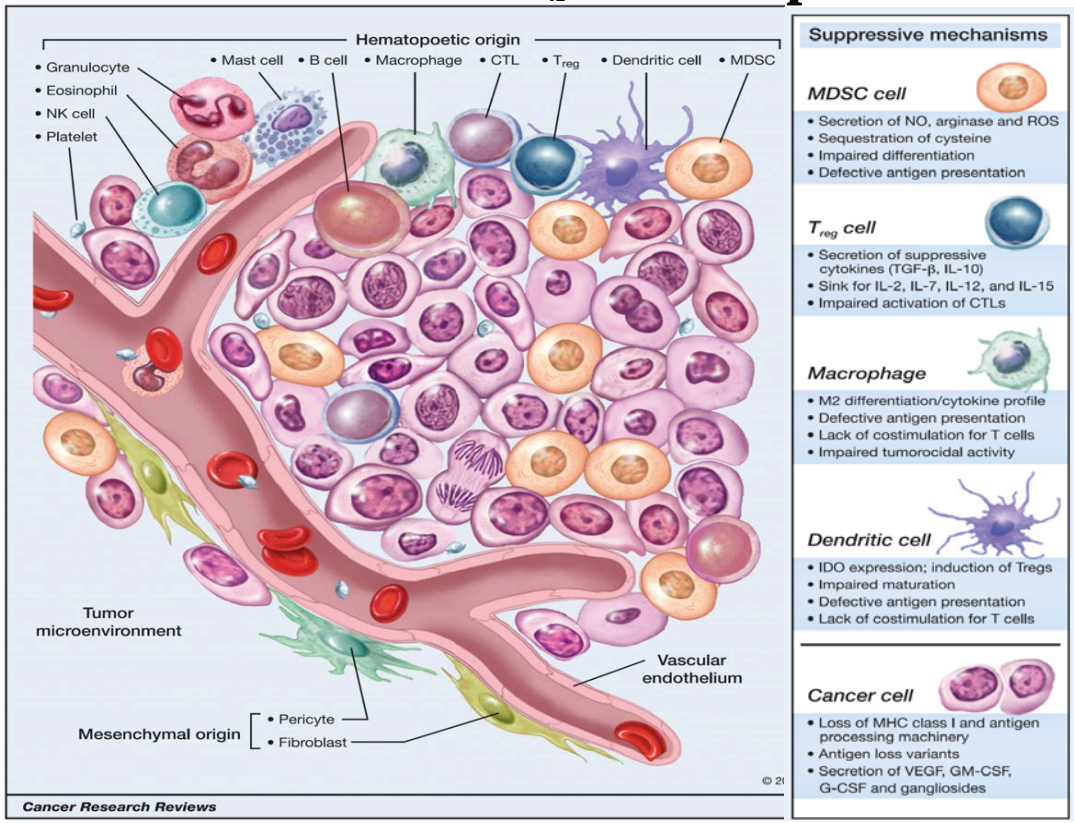
Disclosures

Merck
-Research support, consulting

Biomed Valley Discoveries
-Consulting

Established tumors are not just composed of cancer cells



Kerkar SP , Restifo NP Cancer Res 2012;72:3125-3130

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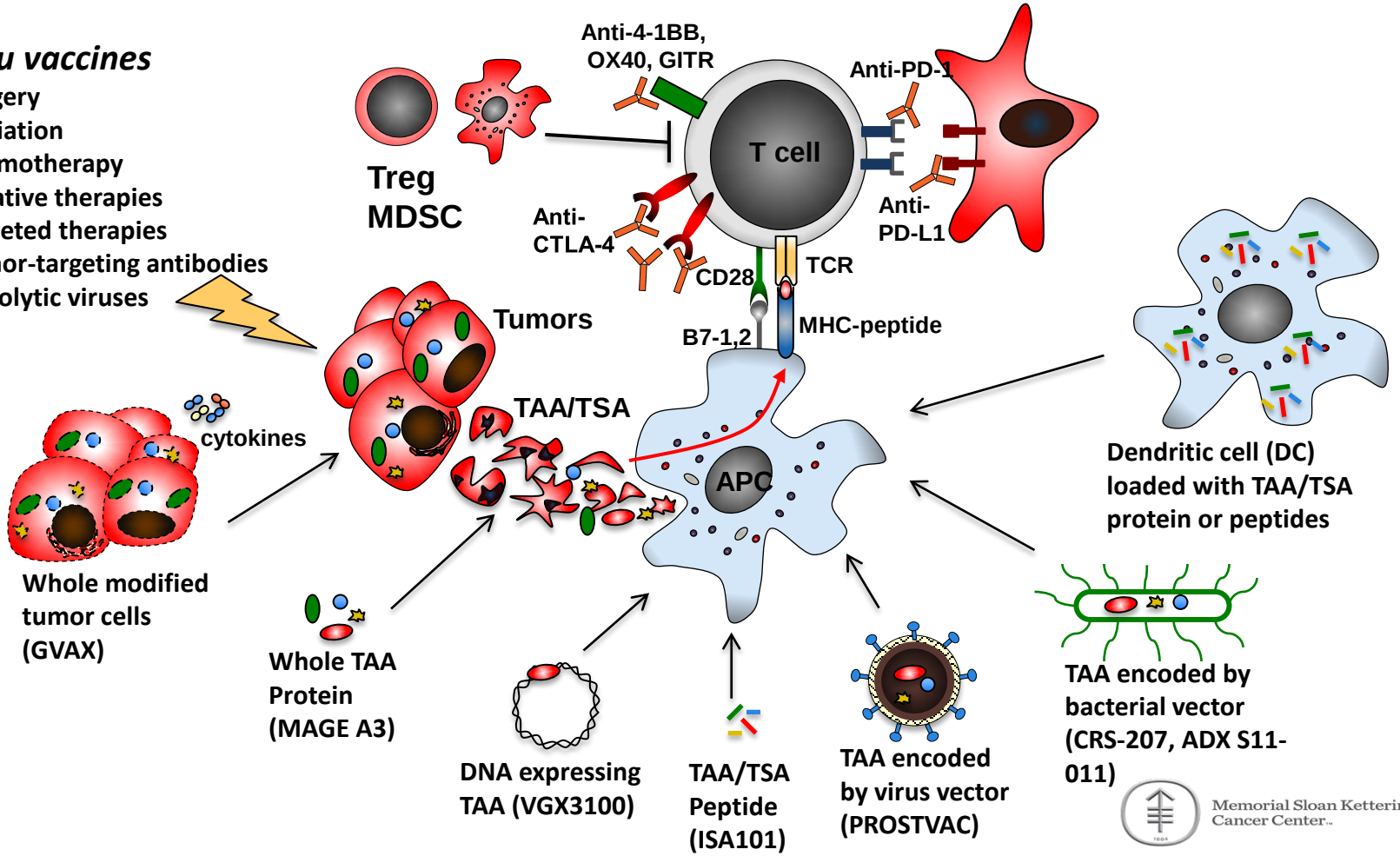
Tumor immunology and immunotherapy in 1 slide

In situ vaccines

- Surgery
- Radiation
- Chemotherapy
- Ablative therapies
- Targeted therapies
- Tumor-targeting antibodies
- Oncolytic viruses



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Biomarkers explored in immunotherapy (response/resistance)

- **Tumor microenvironment**
- TILs (high vs. low)
- immunosuppressive molecules (IDO, PD-L1) (high vs. low)
- immunosuppressive populations (Treg, MDSC) (high vs. low)
- TCR clonality (high vs. low)
- IFNg signature (high vs. low)

- **Tumor cells**
- mutational/neoantigen load (high vs. low)
- -endogenous retroviruses (high vs. low)
- -Type I IFN signaling pathways (high vs. low)

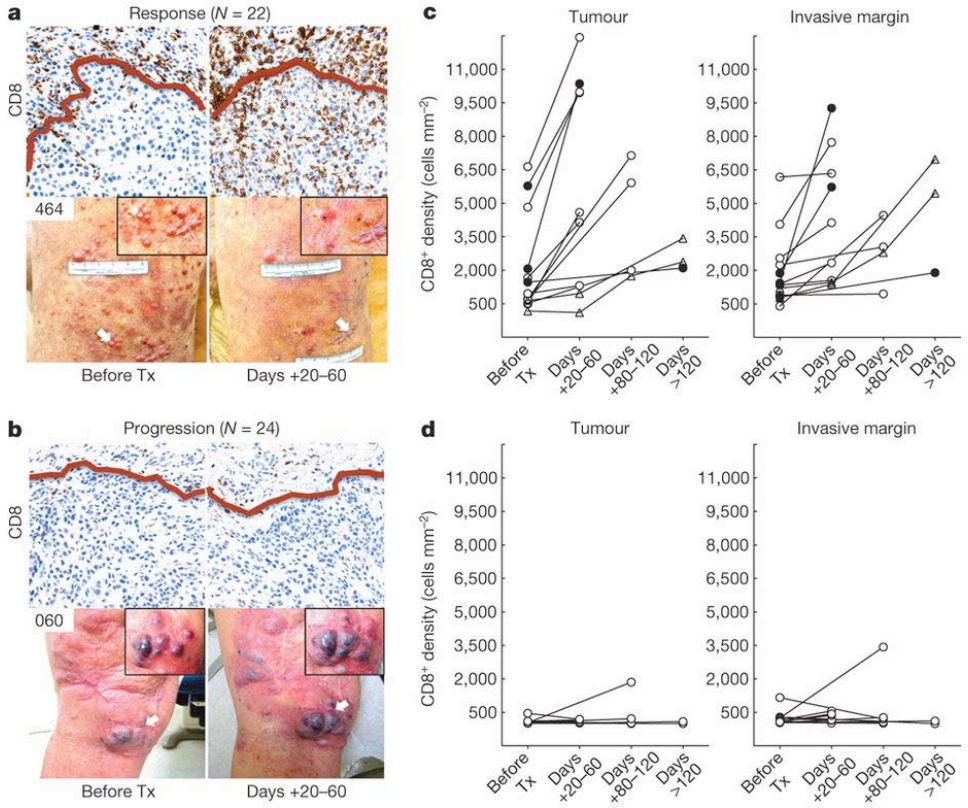
- **Blood**
- PBMC:
- Lymphocyte proliferation and activation markers (Ki-67, ICOS) (high vs. low)
- MDSC percentages (high vs. low)
- RNA/DNA:
- TCR clonality (pre and on-treatment)
- Gene expression
- Serum
- Cytokines
- serologic responses to CT antigens

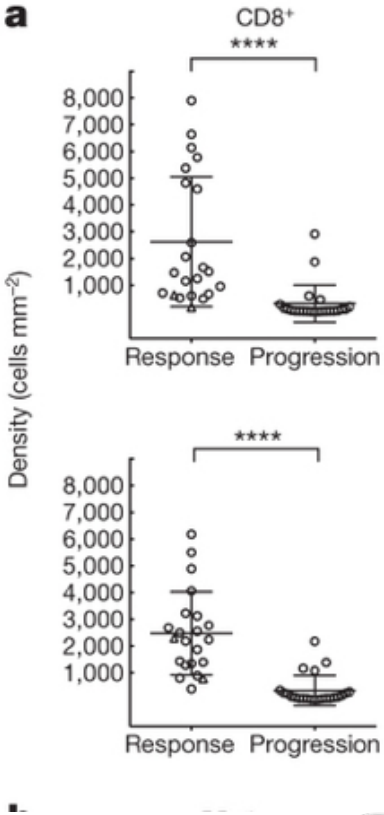
- **Host**
- genetic polymorphisms in immune genes
- gut microbiome

Existing biomarkers: Rationale for immunotherapy in gynecologic cancers

- **Ovarian cancer**
  - Patients with high number of TILs at diagnosis have superior outcomes
  - Patients with immunoreactive TCGA gene expression phenotype have superior outcomes
- **Cervical cancer (and other HPV-driven cancers)**
  - Presence of foreign HPV epitopes should promote tumor immune recognition
- **Endometrial cancer**
  - Neoepitope abundance in MMR-deficient tumors promotes tumor immune recognition

Tumor microenvironment: infiltration with CD8+ lymphocytes in melanoma predicts response to PD-1 blockade





Tumeh et al., Nature 2014

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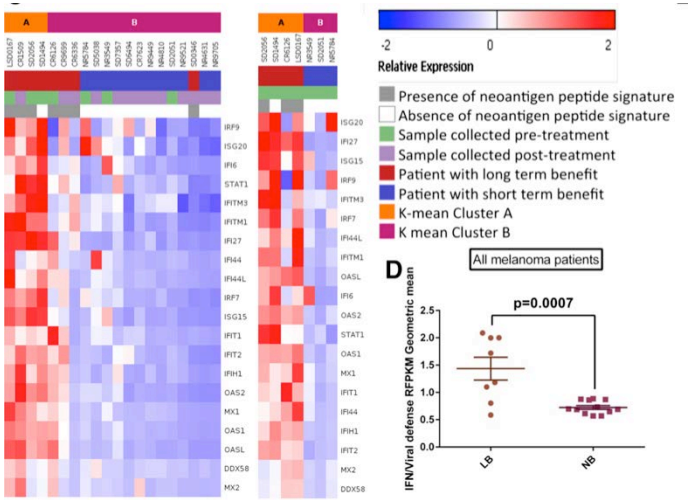
Tumor microenvironment: inflammatory gene expression signatures



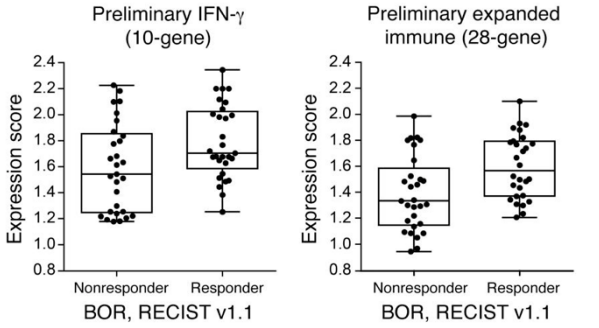


Table 2. IFN-γ and expanded immune gene signatures

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*

Type I IFN signature is associated with clinical benefit from CTLA-4 blockade in melanoma
Chiappinelli et al., Cell 2015

IFNγ signature in pre-treatment tumors is associated with response in different cancers
Ayers et al., JCI 2017

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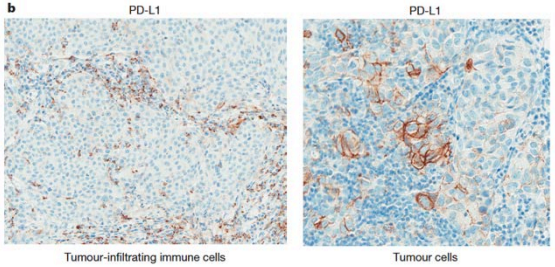
Tumor microenvironment: PD-L1 expression in tumor cells and immune cells enriches for responders, but not in all tumor types

a

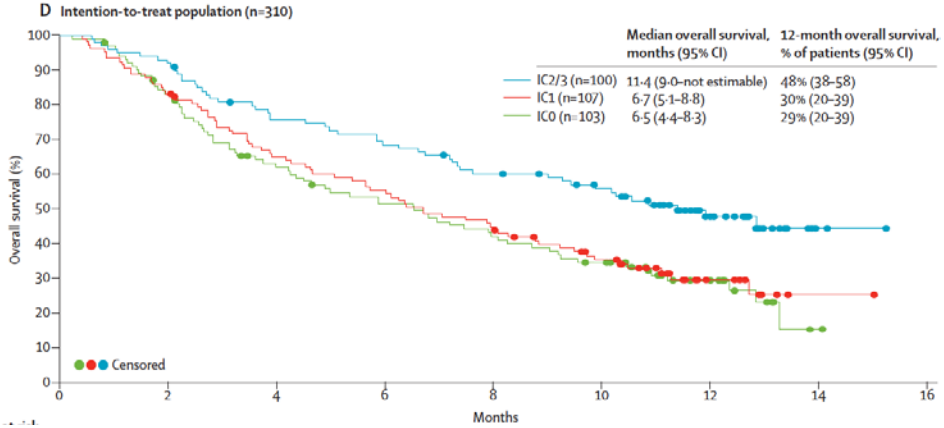
PD-L1 prevalence in UBC tumours by IHC

n = 205	PD-L1-positive tumour-infiltrating immune cells (no. of specimens (%))	PD-L1-positive tumour cells (no. of specimens (%))
IHC 3	18 (9)	14 (7)
IHC 2	37 (18)	8 (4)
IHC 1	89 (43)	37 (18)
IHC 0	61 (30)	146 (71)

b

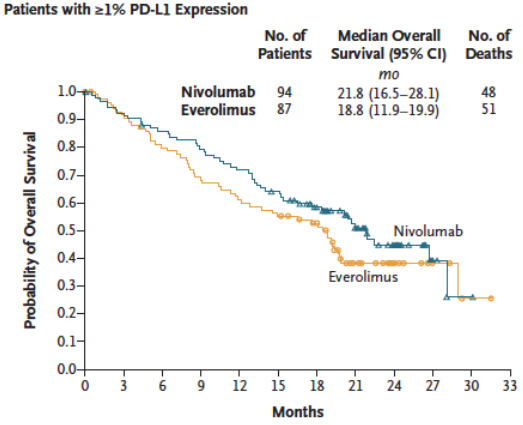


D Intention-to-treat population (n=310)

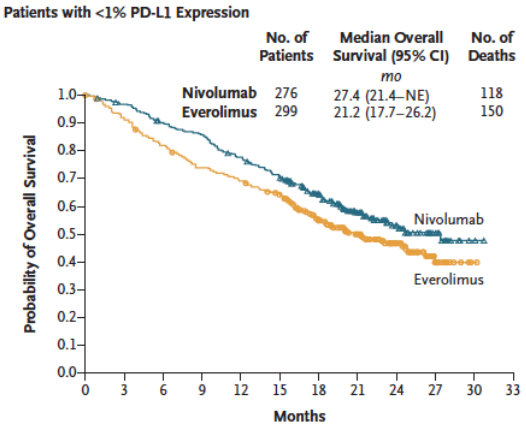


Bladder CA

A Patients with ≥1% PD-L1 Expression



B Patients with <1% PD-L1 Expression



RCC

Motzer et al. Nature 2015, Rosenberg JE, et. al, Lancet 2016

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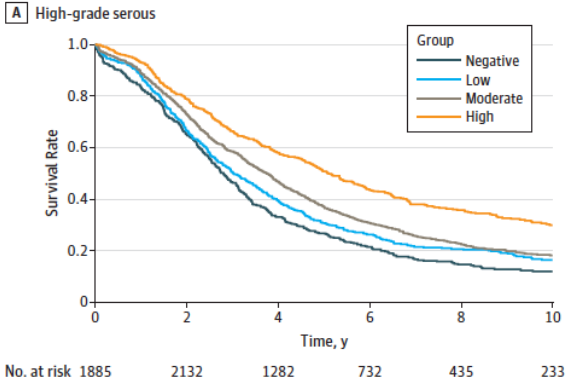
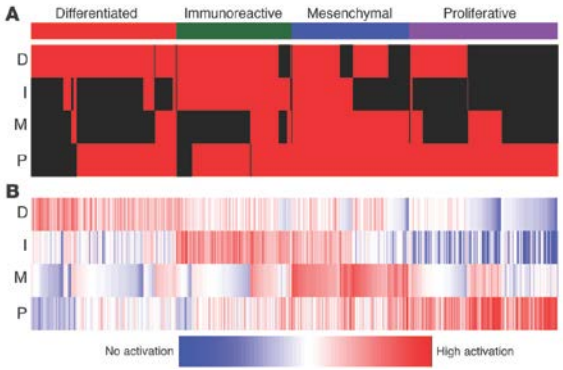
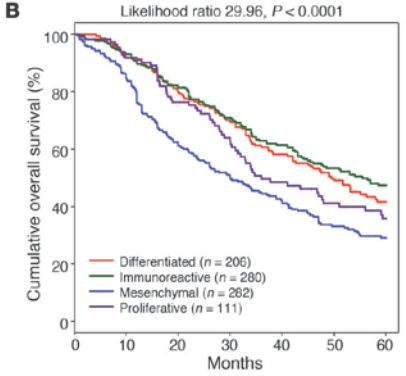
Presence of TILs and immune gene expression signatures are prognostic in ovarian cancer (hence immunotherapy makes sense)

TIL counts per HPF
Negative (17%)
Low: 1-2 (17%)
Moderate: 3-19 (44%)
High: >20 (22%)



JAMA Oncology 2017





Verhaak et al., JCI 2013

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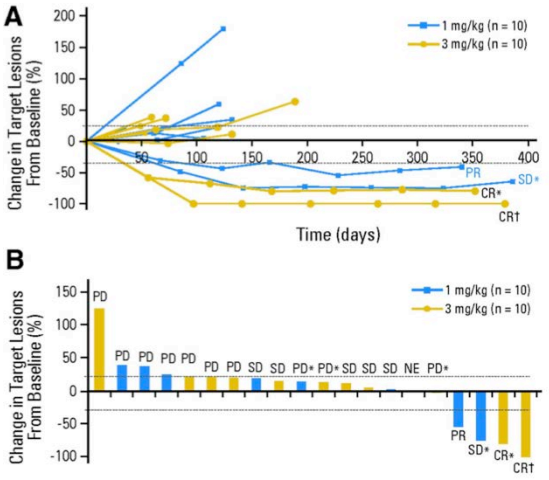
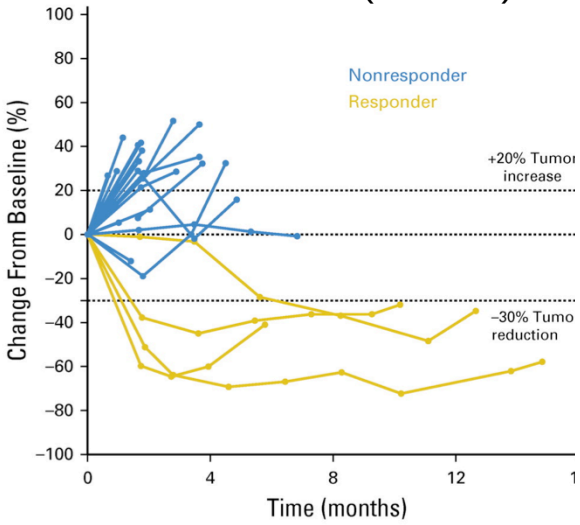
PD-1 blockade has limited activity in GYN cancers

Ovarian



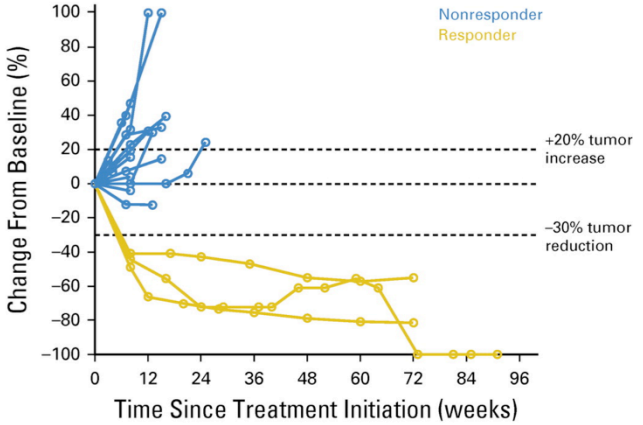
ORR 15%

Cervical (PD-L1+)



ORR 17%

Endometrial (PD-L1+)



ORR 13%

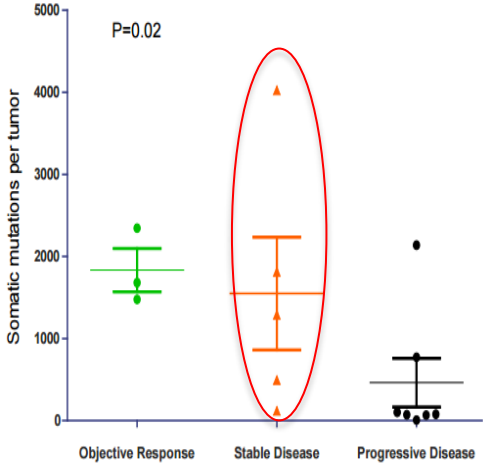
Hamanishi et al., JCO 2015, Frenel et al., JCO 2017; Ott et al., JCO 2017

1. Single-agent immunotherapies are not sufficient for most GYN patients

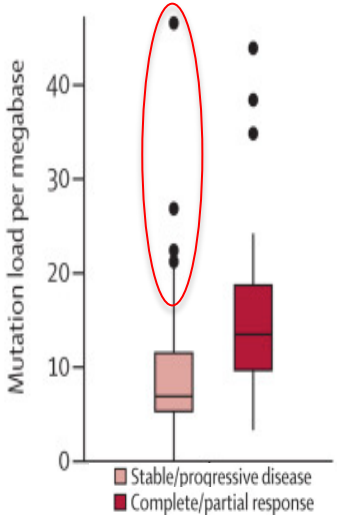
2. Existing biomarkers are not sufficient in guiding GYN patient selection for immunotherapy

Tumor cells: mutational load and neoantigens as predictors of clinical benefit

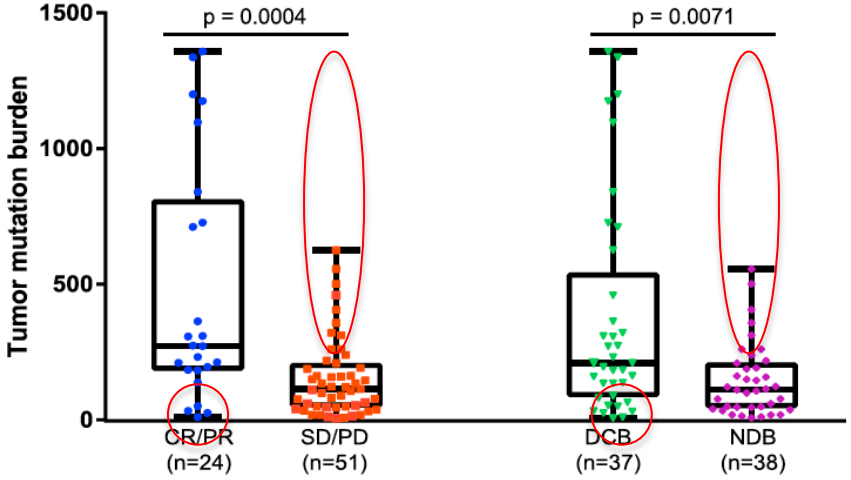
MMR-D CRC/anti-PD-1



Bladder/anti-PD-L1

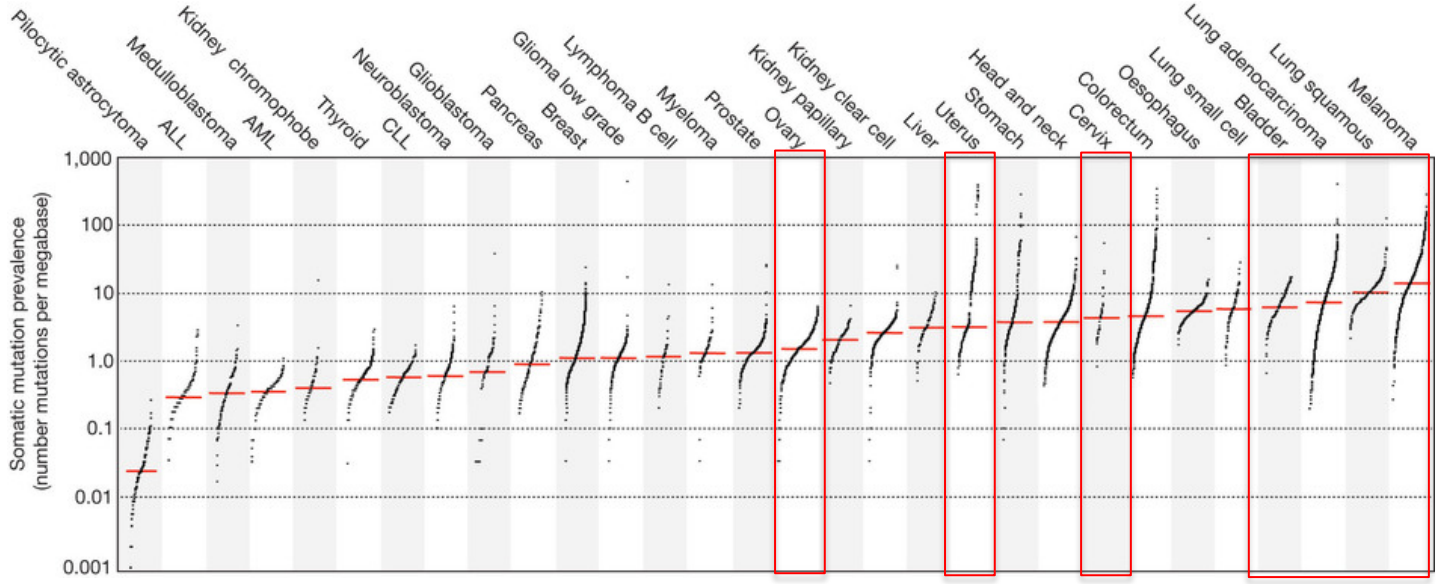


NSCLC/anti-PD-1+anti-CTLA-4



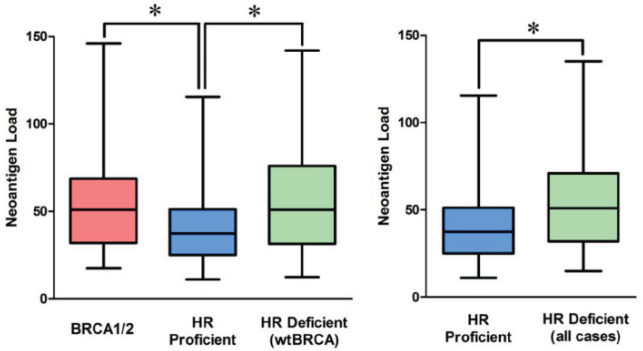
Le et al NEJM 2015, Hellmann et al Cancer Cell 2018, Rosenberg et al Lancet Oncol 2016

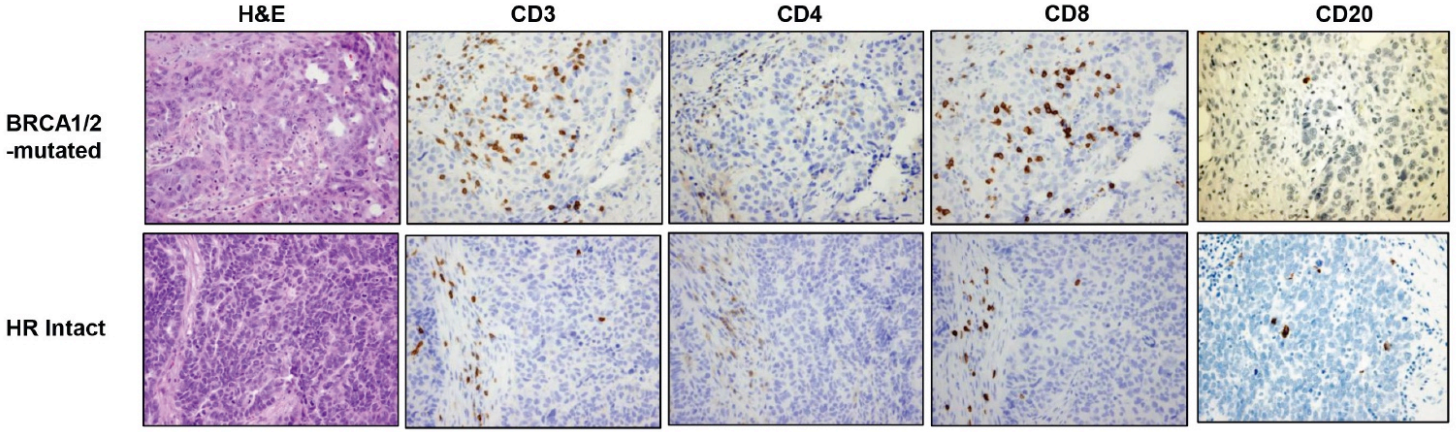
Most GYN cancers exhibit low mutational burden



Alexandrov et al., Nature 2013

BRCA mutation is associated with TIL infiltration and increased neoantigen load in HGSOC





Strickland et al, Oncotarget 2016

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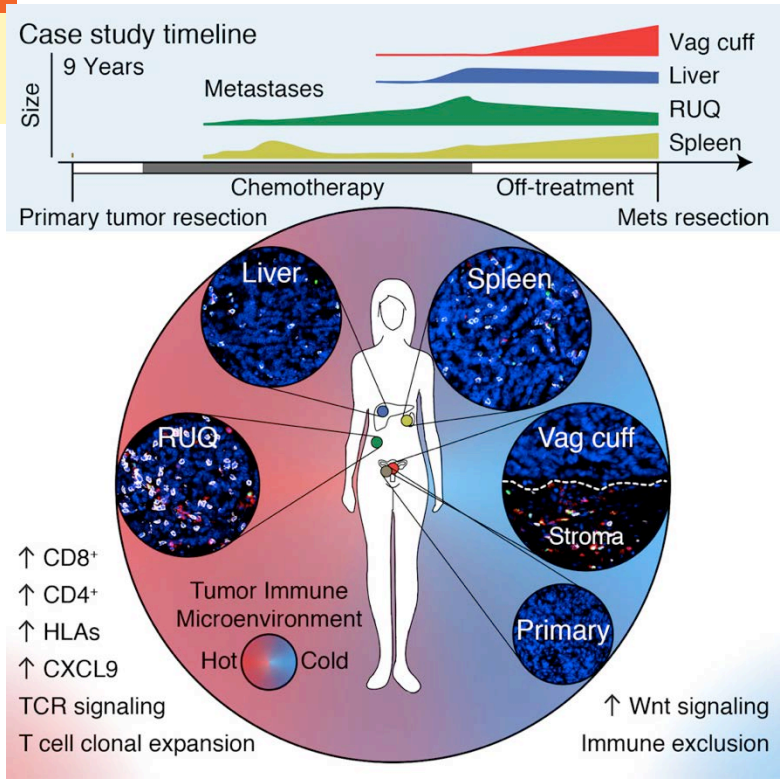
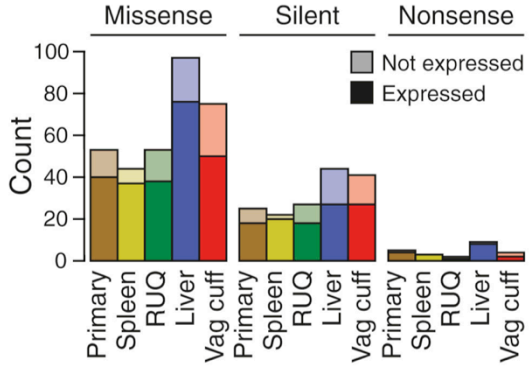
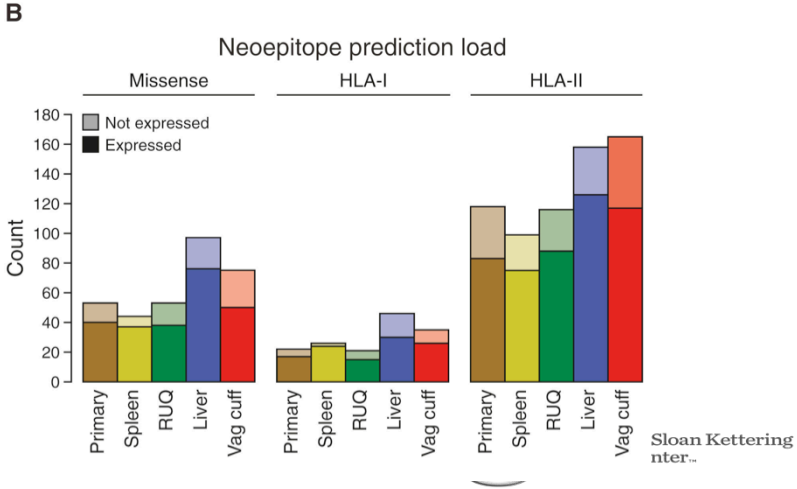
Neoepitope load does not always predict the immune phenotype and fate of ovarian tumor lesions







Jimenez-Sanchez et al., Cell 2017

The New York Times

HEALTH

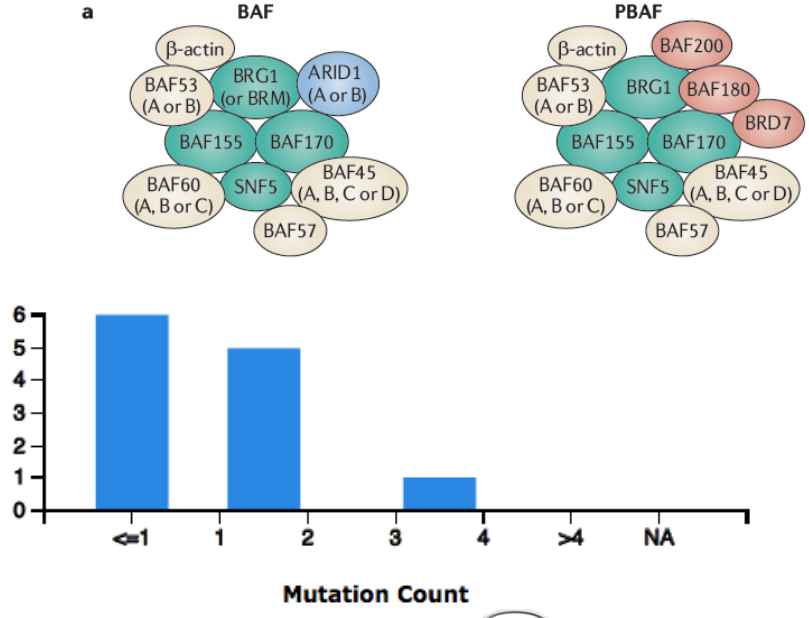
Doctors Said Immunotherapy Would Not Cure Her Cancer. They Were Wrong.

Leer en español

By GINA KOLATA FEB. 19, 2018

Oriana Sousa, 28, who lives in Marinha Grande, Portugal, had a rare, aggressive form of ovarian cancer. Traditional treatments failed, but with immunotherapy her tumors shrank so much that there is no evidence of disease. Daniel Rodrigues for The New York Times

Small cell carcinoma of the ovary hypercalcemic type (SCCOHT): a monogenic disease driven by loss of BRG1 (SMARCA4)



Jelinic et al., Nat Genetics 2014; Witkowsky et al., Nat Genetics 2014; Ramos et al., Nat Genetics 2014

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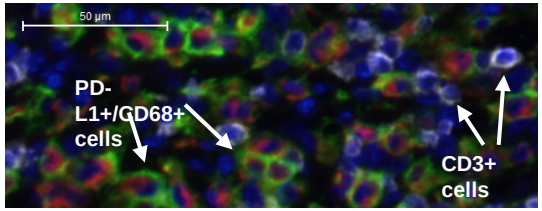
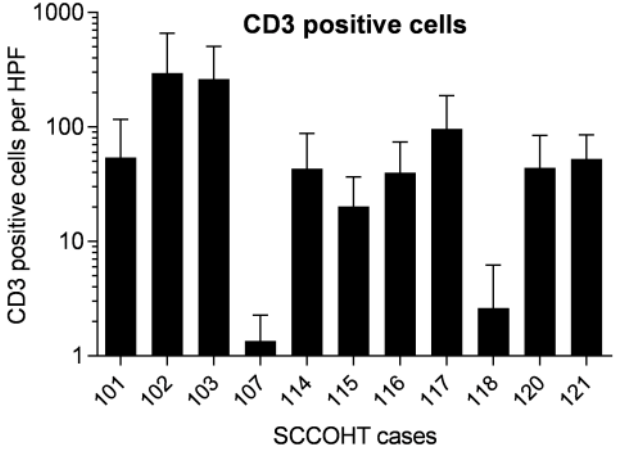
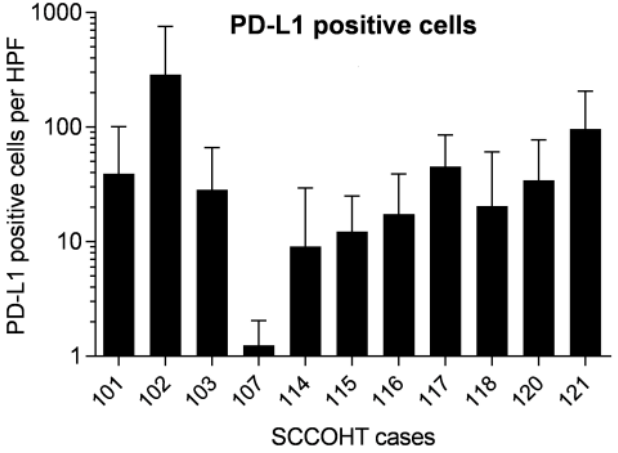
Despite low tumor mutational burden SCCOHTs exhibit immune-active tumor microenvironment.







Jelinic, Ricca, Merghoub, Levine, and Zamarin, JNCI: 2018

Mutations in SWI/SNF component PBRM1 predict response to immunotherapy in kidney cancer

Science

REPORTS

Cite as: D. Miao *et al.*, *Science*
10.1126/science.aan5951 (2018).

Genomic correlates of response to immune checkpoint therapies in clear cell renal cell carcinoma

Diana Miao,[1,2] Claire A. Margolis,[1,2] Wenhua Gao,[1] Martin H. Voss,[3,4] Wei Li,[5] Dylan J. Martini,[1] Craig Norton,[1] Dominick Bossé,[1] Stephanie M. Wankowicz,[1,2] Dana Cullen,[6] Christine Horak,[6] Megan Wind-Rotolo,[6] Adam Tracy,[2] Marios Giannakis,[1,2] Frank Stephen Hodi,[1] Charles G. Drake,[7] Mark W. Ball,[8] Mohamad E. Allaf,[8] Alexandra Snyder,[3]* Matthew D. Hellmann,[3,4] Thai Ho,[9] Robert J. Motzer,[3,4] Sabina Signoretti,[1] William G. Kaelin Jr.,[1,10] Toni K. Choueiri,[1]†‡ Eliezer M. Van Allen[1,2]†‡

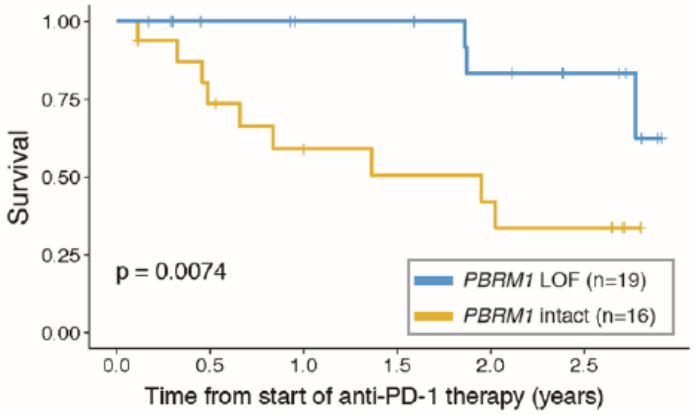
Science

RESEARCH ARTICLES

Cite as: D. Pan *et al.*, *Science*
10.1126/science.aao1710 (2018).

A major chromatin regulator determines resistance of tumor cells to T cell–mediated killing

Deng Pan,[1]* Aya Kobayashi,[1]* Peng Jiang,[2]* Lucas Ferrari de Andrade,[1] Rong En Tay,[1] Adrienne Luoma,[1] Daphne Tsoucas,[2] Xintao Qiu,[3] Klothilda Lim,[3] Prakash Rao,[3]† Henry W. Long,[3] Guo-Cheng Yuan,[2] John Doench,[4] Myles Brown,[3] Shirley Liu,[2]‡ Kai W. Wucherpfennig[1,5]‡



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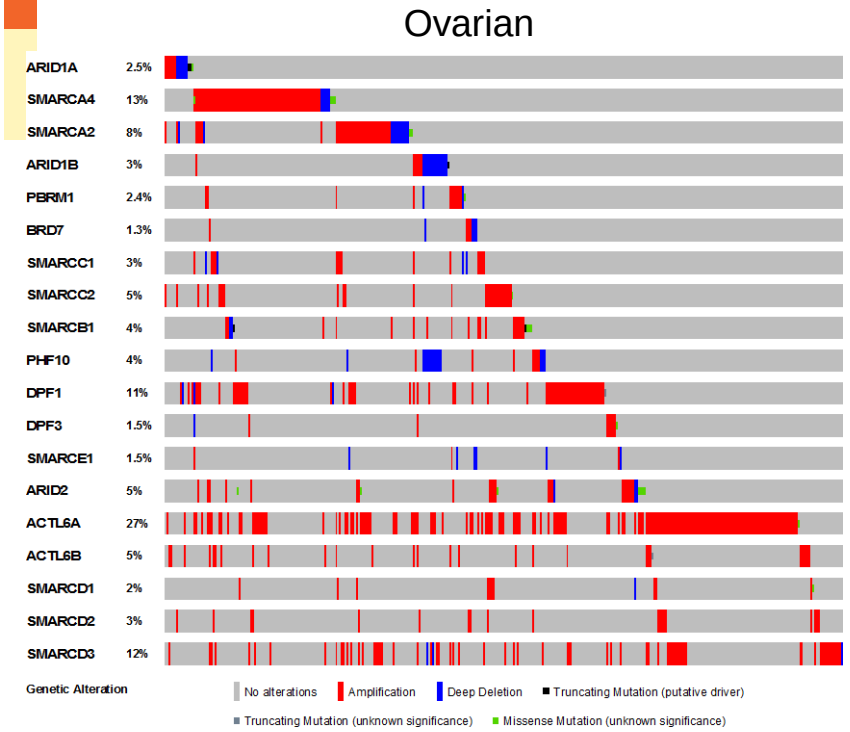
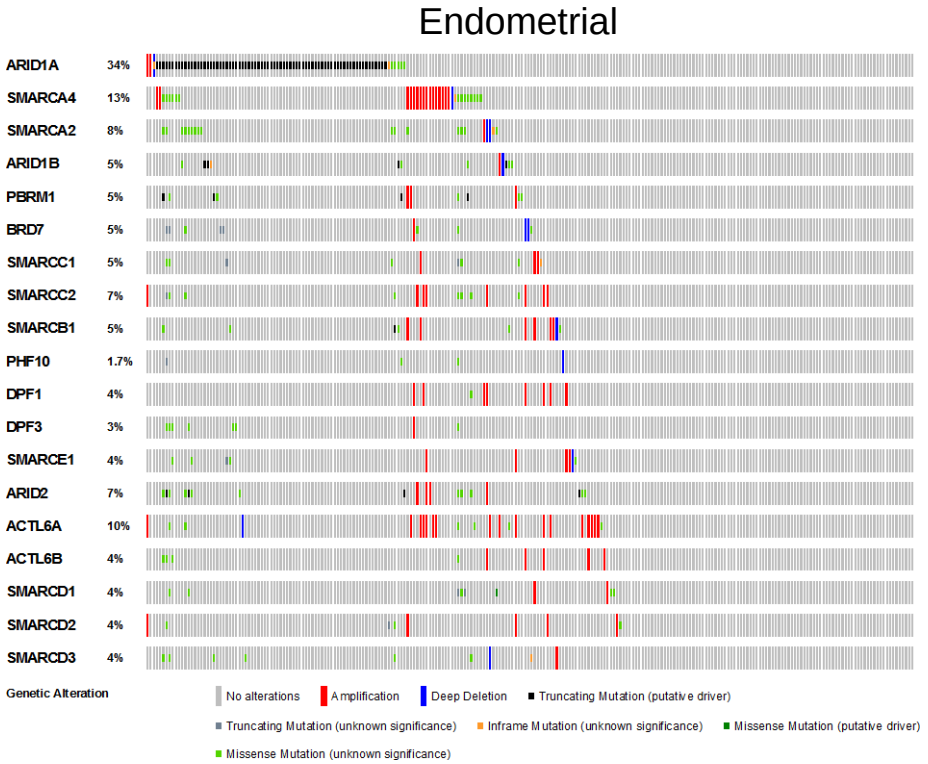
Ovarian and endometrial cancers exhibit recurrent alterations in chromatin remodeling complex components





Altered in 60% of all ovarian and 62% of endometrial cancers

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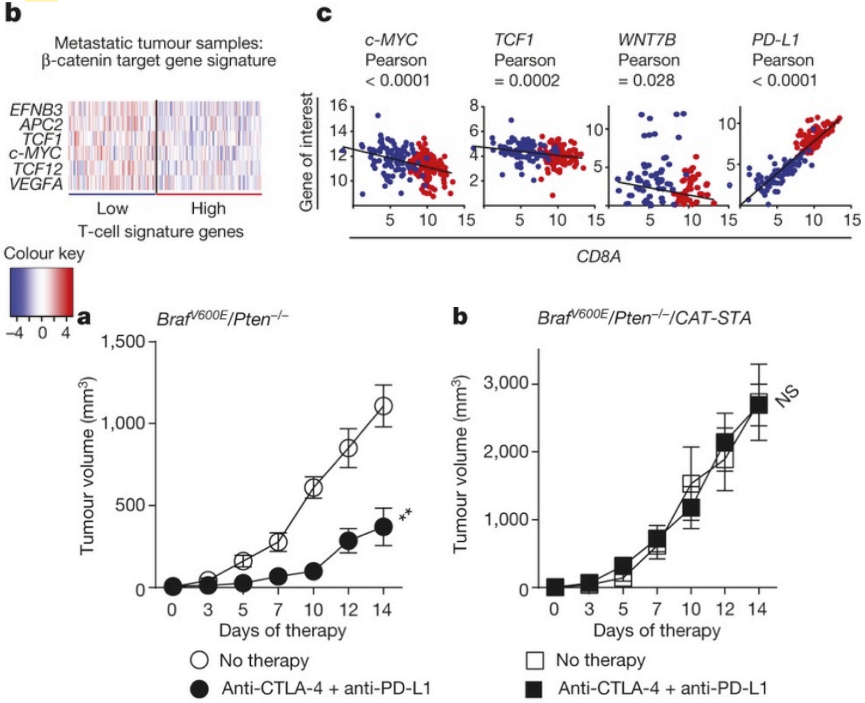
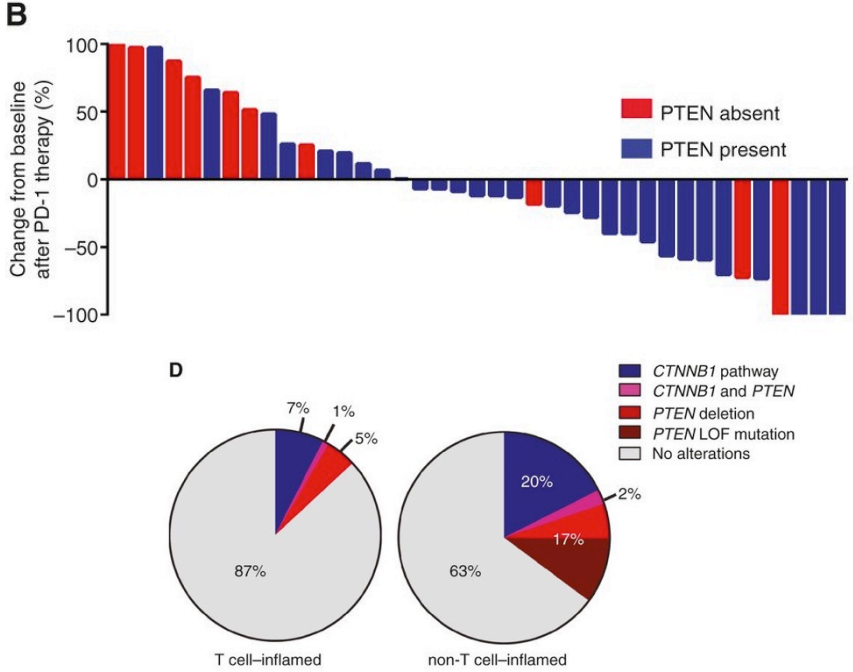
Alterations in some driver pathways can predict resistance to immunotherapy

Beta-catenin pathway in melanoma



Spranger et al., Nature 2015

PTEN pathway in melanoma



Peng, et al., Cancer Discovery 2016

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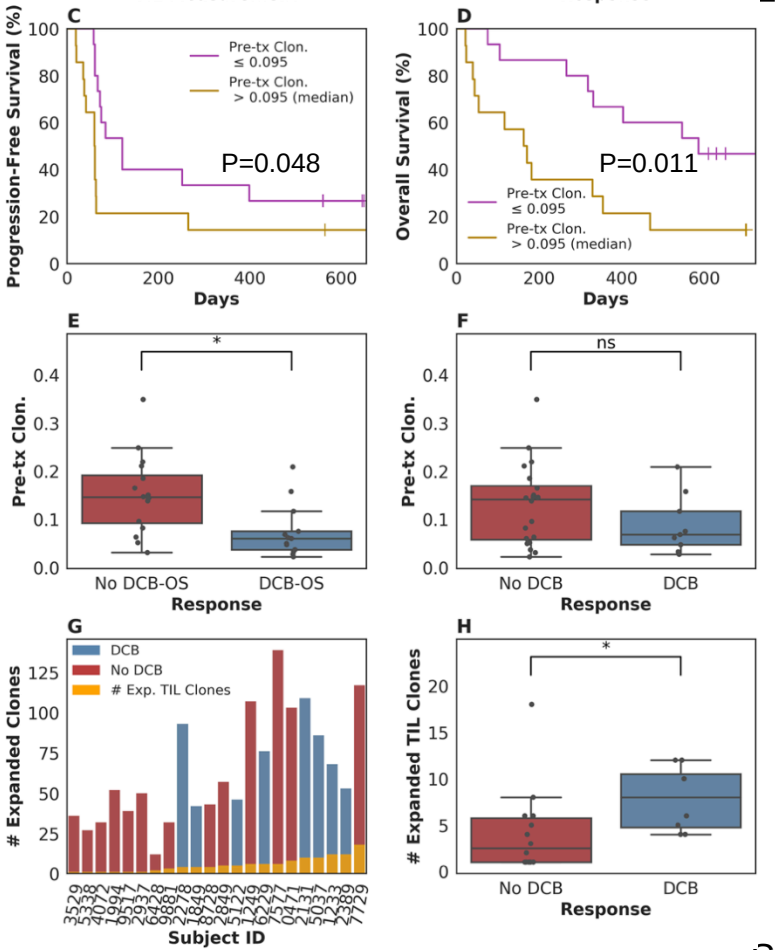
Changes in peripheral blood biomarkers can enrich for responders to immunotherapy

- **Absolute lymphocyte count (ALC)**
  - On treatment ALC increase is associated with survival in melanoma patients treated with ipilimumab (Ku G., et al., Cancer 2010)
- **ICOS+CD4+ lymphocytes**
  - On treatment sustained increase in ICOS+ CD4+ lymphocytes is associated with survival in melanoma patients treated with ipilimumab (Carthon, et al., CCR 2010)
- **CD8+PD-1+Ki67+ lymphocytes/tumor burden**
  - 3-6 week CD8+PD-1+Ki67+/tumor burden ratio predictive of clinical benefit (Huang A., et al., Nature, 2017)
- **Serum autoantibodies**
  - Upregulation of serum autoantibodies predicts response to CTLA-4 blockade in prostate cancer (Kwek et al, J Immunol 2012)

Peripheral blood: T cell receptor (TCR) clonality



Low pre-treatment TCR clonality in blood has prognostic value.
Possibly predictive value?

DCB is associated with increased peripheral expansion of intratumoral TCR clones

Snyder A et al. PLoS Medicine 2017

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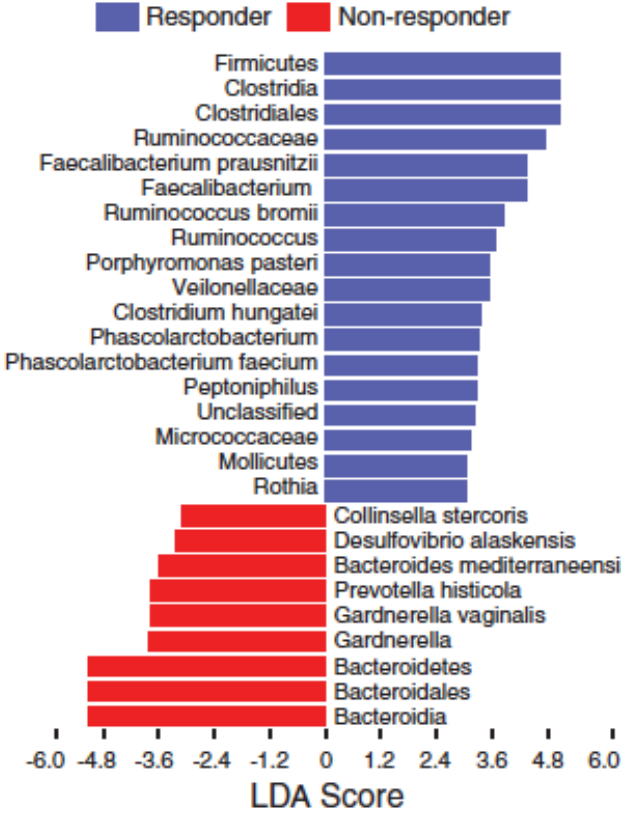
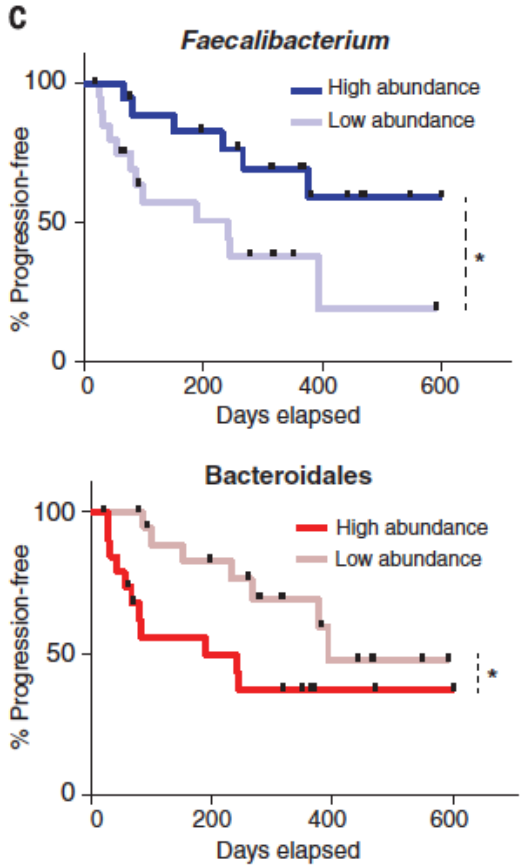
Host: stool microbiota signatures





Gopalakrishnan et al., Science 2018

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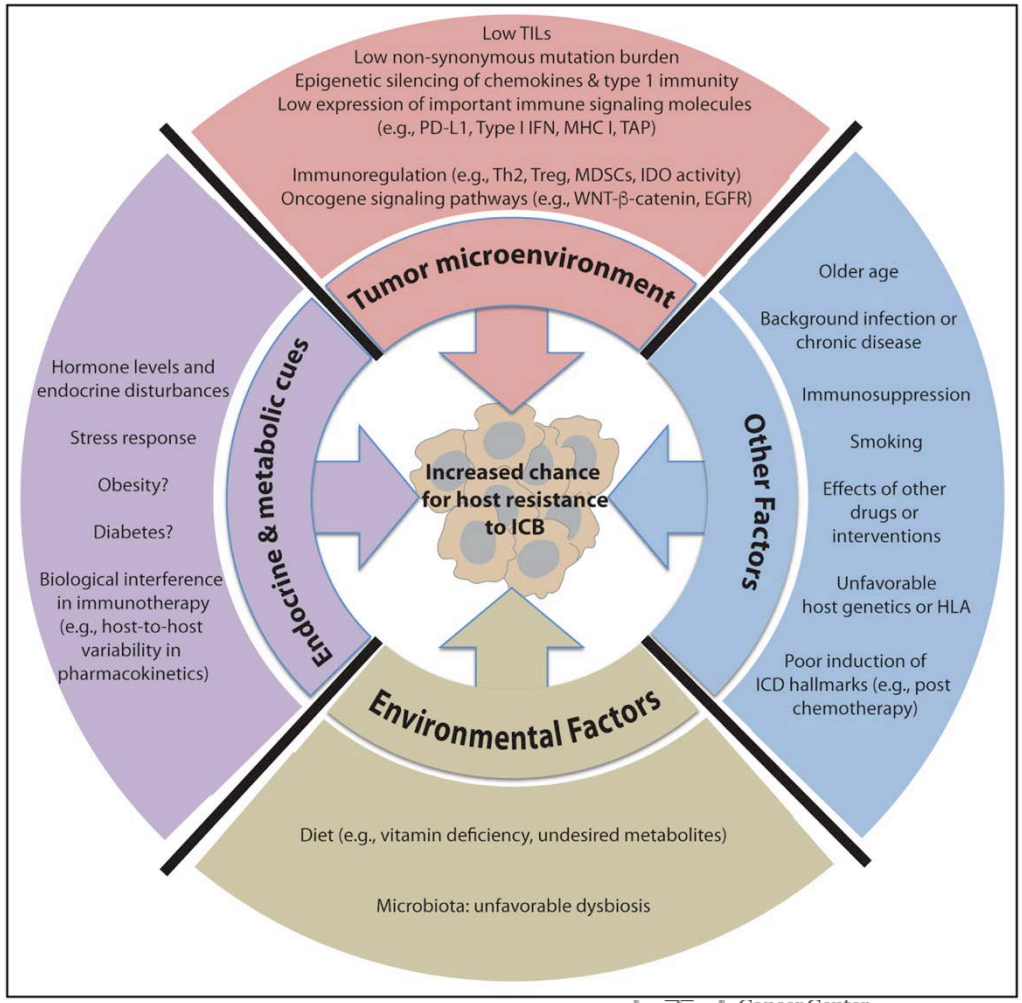
Summary

- Immunotherapy in GYN cancers makes sense, but will likely require combinations in most patients

- There is no single biomarker: optimal patient selection will depend on integration of tumor, blood, host, and environmental factors and these should be analyzed within the context of all trials



Pitt et al., Immunity 2016