ESMO
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

EMERGING BIOMARKERS OF IMMUNE CHECKPOINT INHIBITORS

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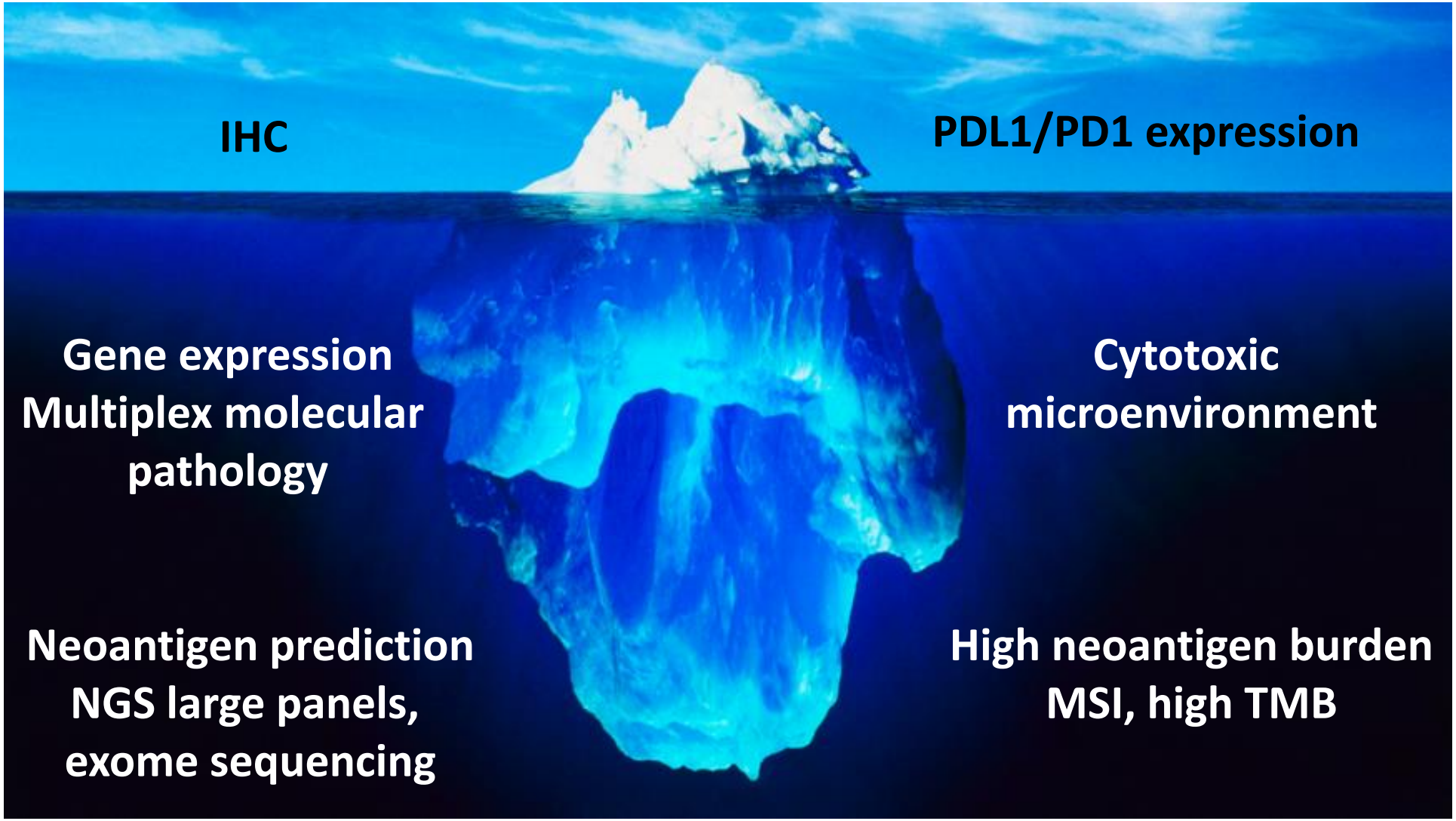
VHIO
VALL D'HEBRON
Institute of Oncology

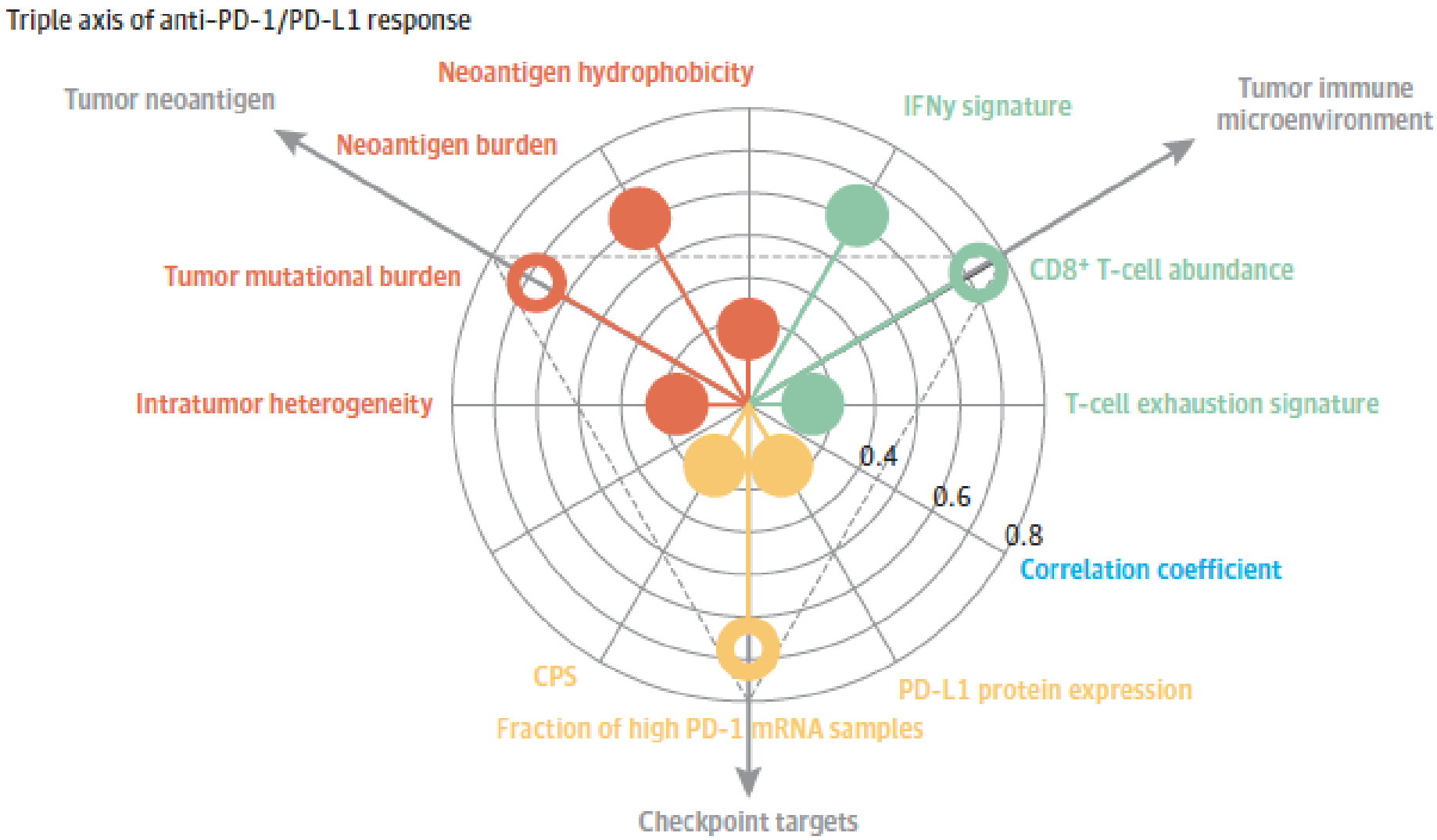
(PERSONAL) CONFLICTS OF INTEREST

Advisory role:	Roche, Foundation Medicine Boehringer-Ingelheim
Speaker's fee:	Roche Amgen Ipsen Servier Sanofi MSD
Research grant:	Merck Pierre Fabre BMS

INTEGRATED BIOMARKER ANALYSIS



MULTI-OMICS PREDICTIVE MARKERS



Lee & Ruppin, JAMA Oncol 2019

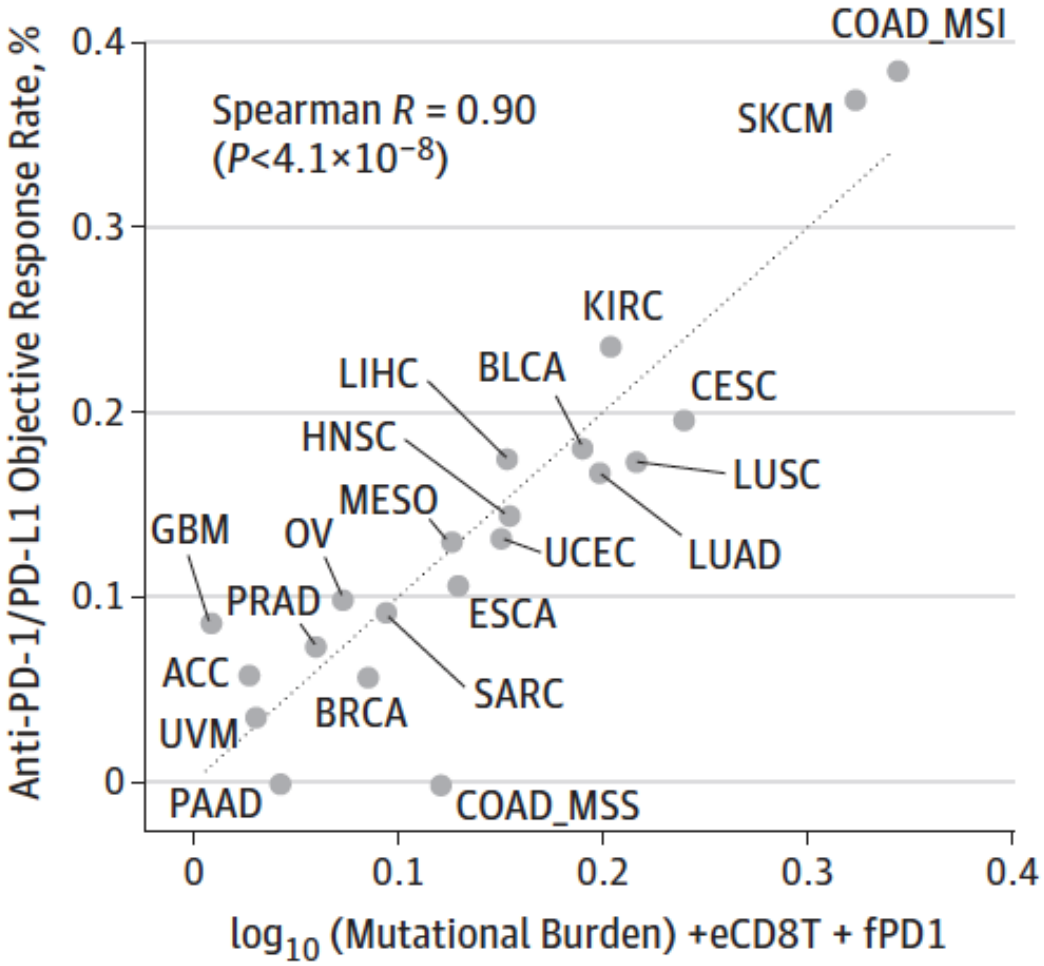
MULTI-OMICS PREDICTIVE MARKERS

In-silico analysis

TCGA data vs. results clinical trials

Spearman *R* = 0.9

Model with **PDL1 + CD8 + TMB**
explains **80%** of **ORR** across tumor types



Lee & Ruppin, JAMA Oncol 2019

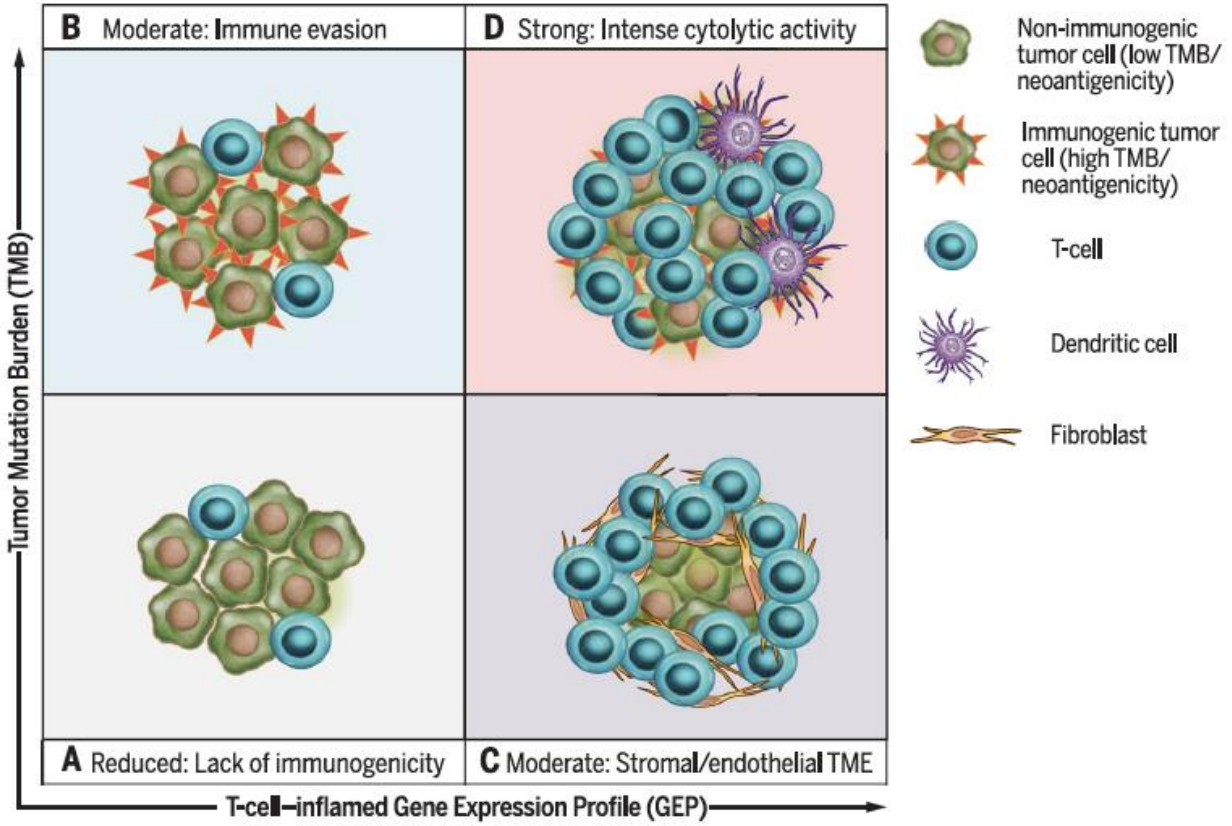
MULTI-OMICS PREDICTIVE MARKERS

Metanalysis KEYNOTE trials

300 patients, 22 tumors

TMB

GEP cytotoxicity signature (18 genes)



Cristescu et al, Science 2018

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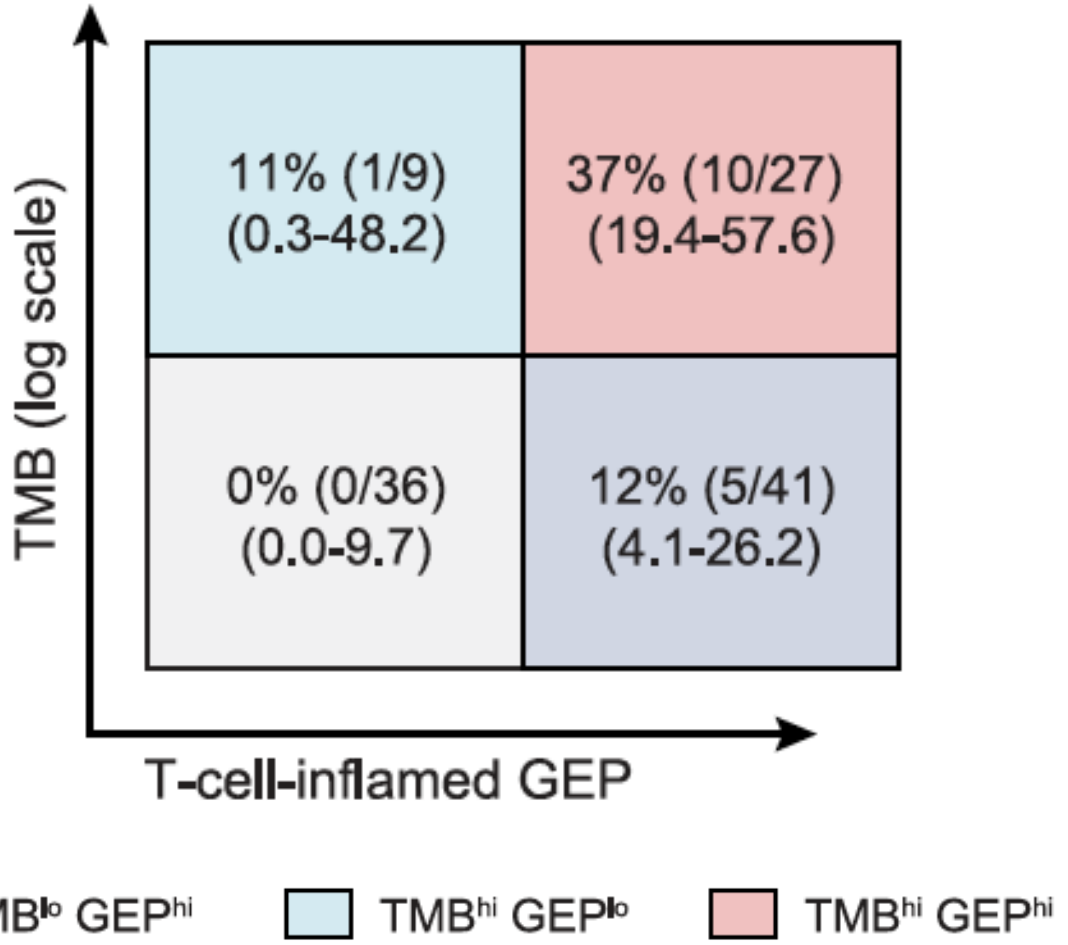

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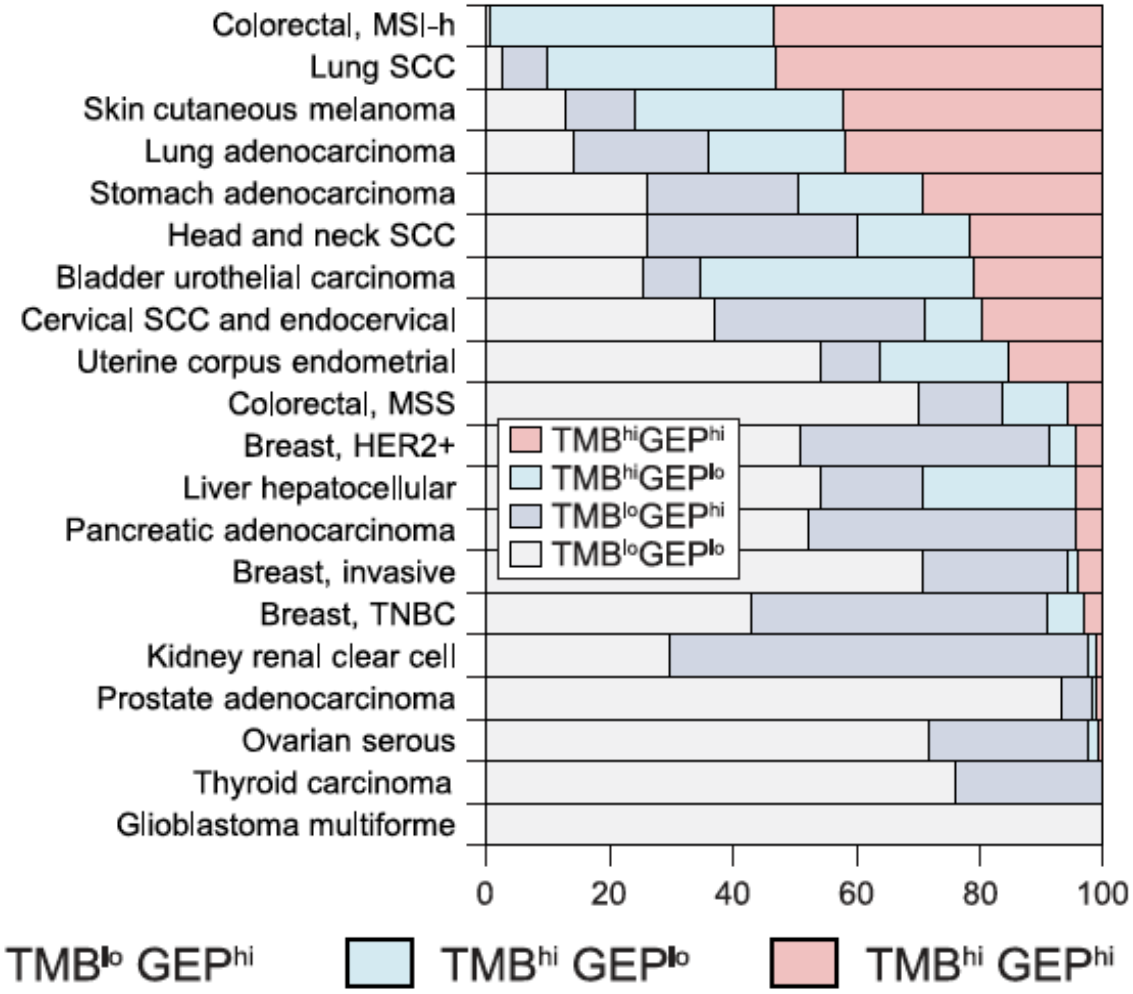


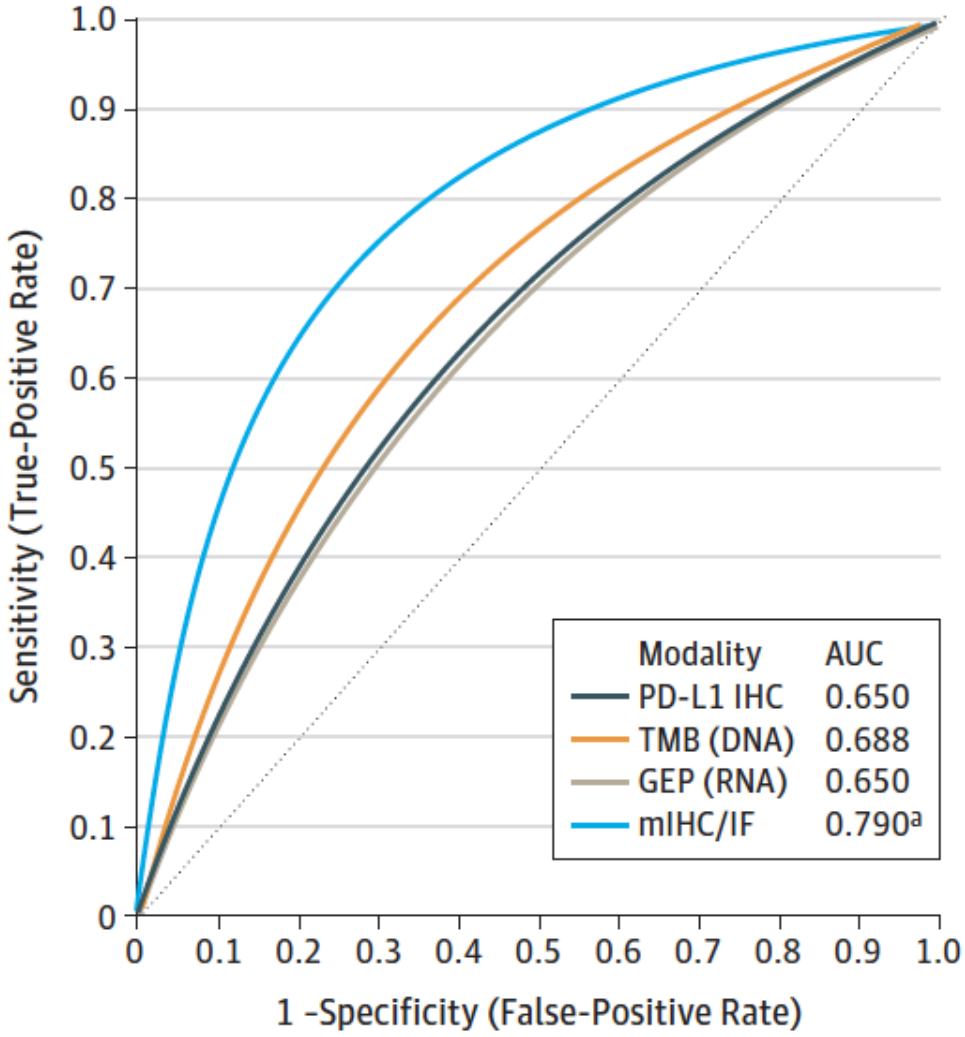
Cristescu et al, Science 2018

MULTI-OMICS PREDICTIVE MARKERS

Systematic review and metanalysis

45 clinical trials

PD-L1 IHC
TMB
GEP cytotoxicity signature
Multiplex IHC/IF: quantitative CD8/PD-L1



Lu et al, JAMA Oncol 2019

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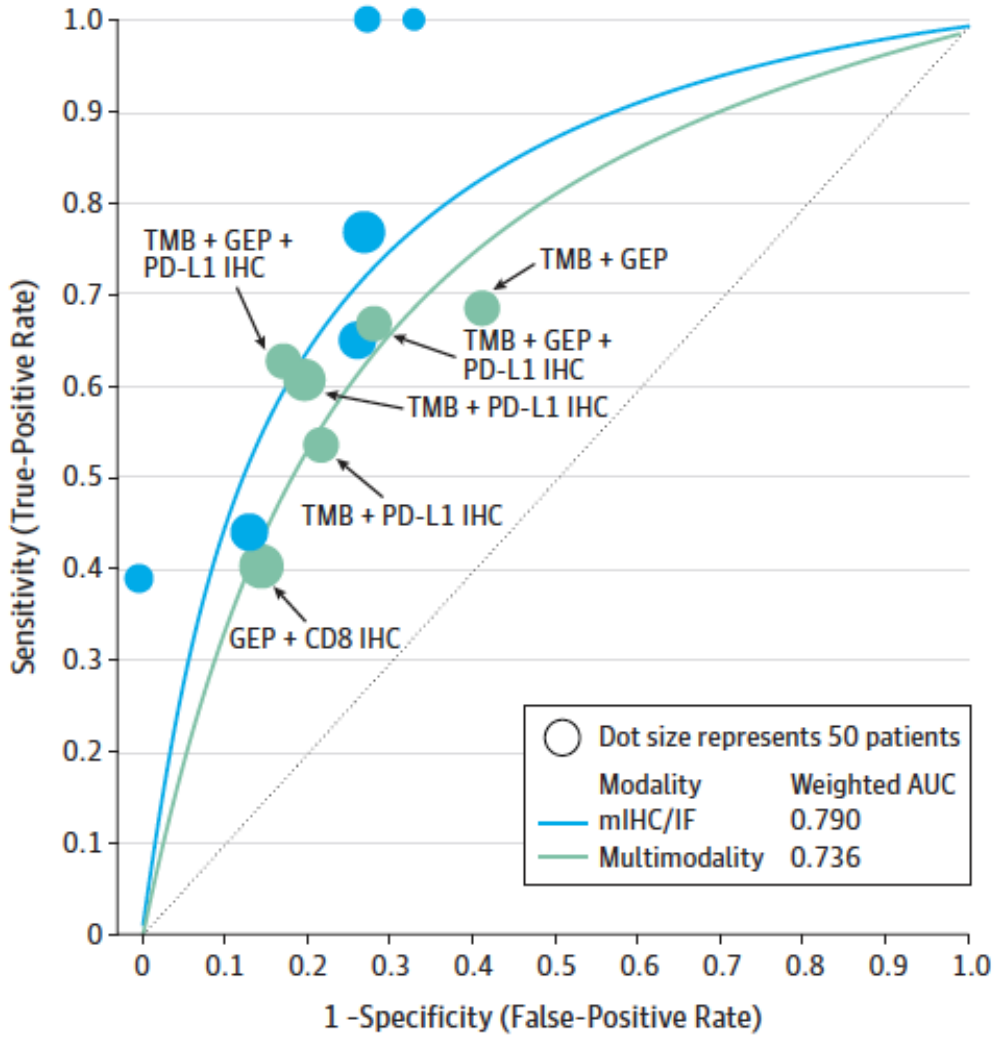


Lu et al, JAMA Oncol 2019

GENOMIC MARKERS

Response

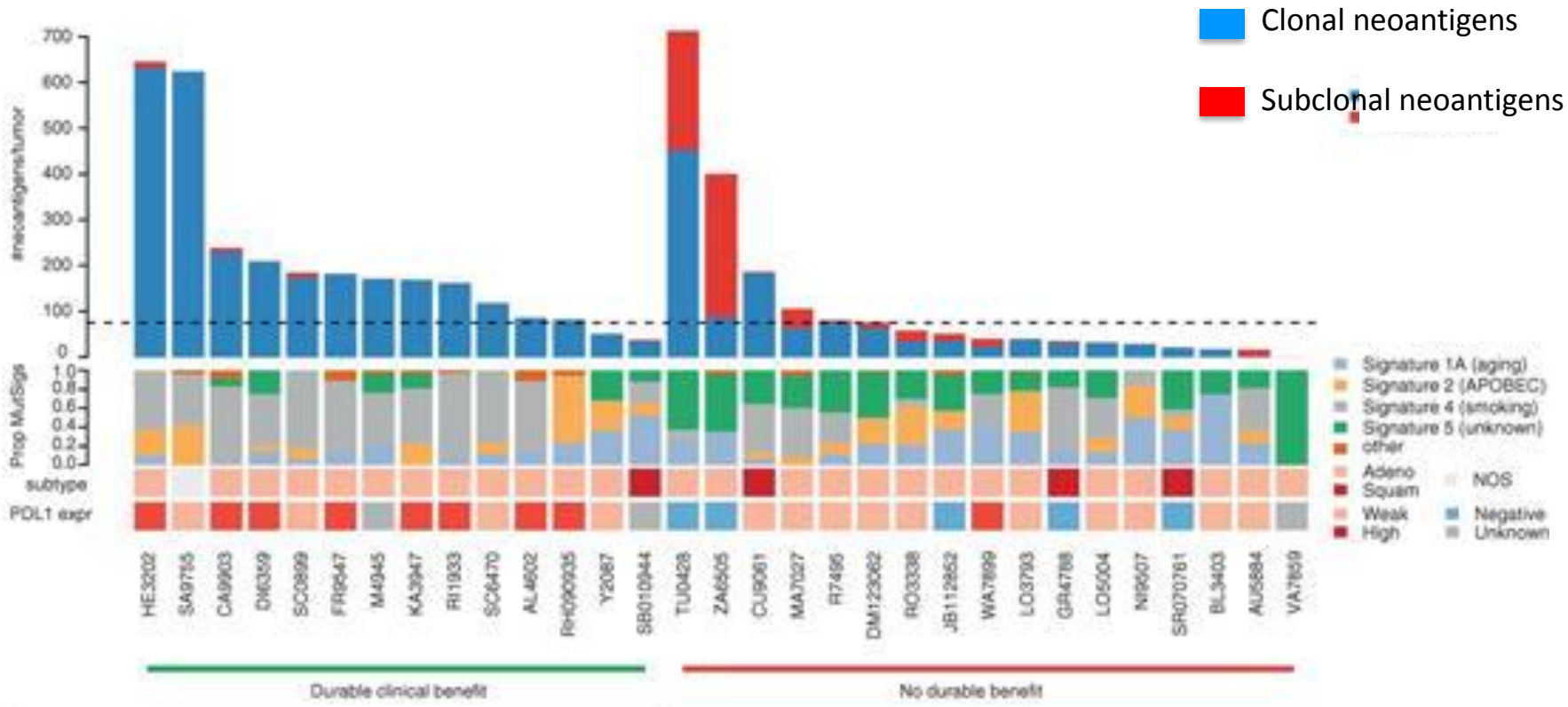
- Clonal mutations, viral neoantigens
- Hypermutation – MSI, *POLE* mut, high TMB, DDR alt
- Upregulation of *PDL1* (ampl)
- Epigenetic events (*PBMR1*, *SMARCA4*, *ARID1A*, *ARID2*...)

Resistance

- Single gene alterations – *STK11* mut, *PTEN* loss, *CDK4*/*CCND1* ampl
- High levels of copy number loss
- Alterations in Interferon and antigen presentation signaling

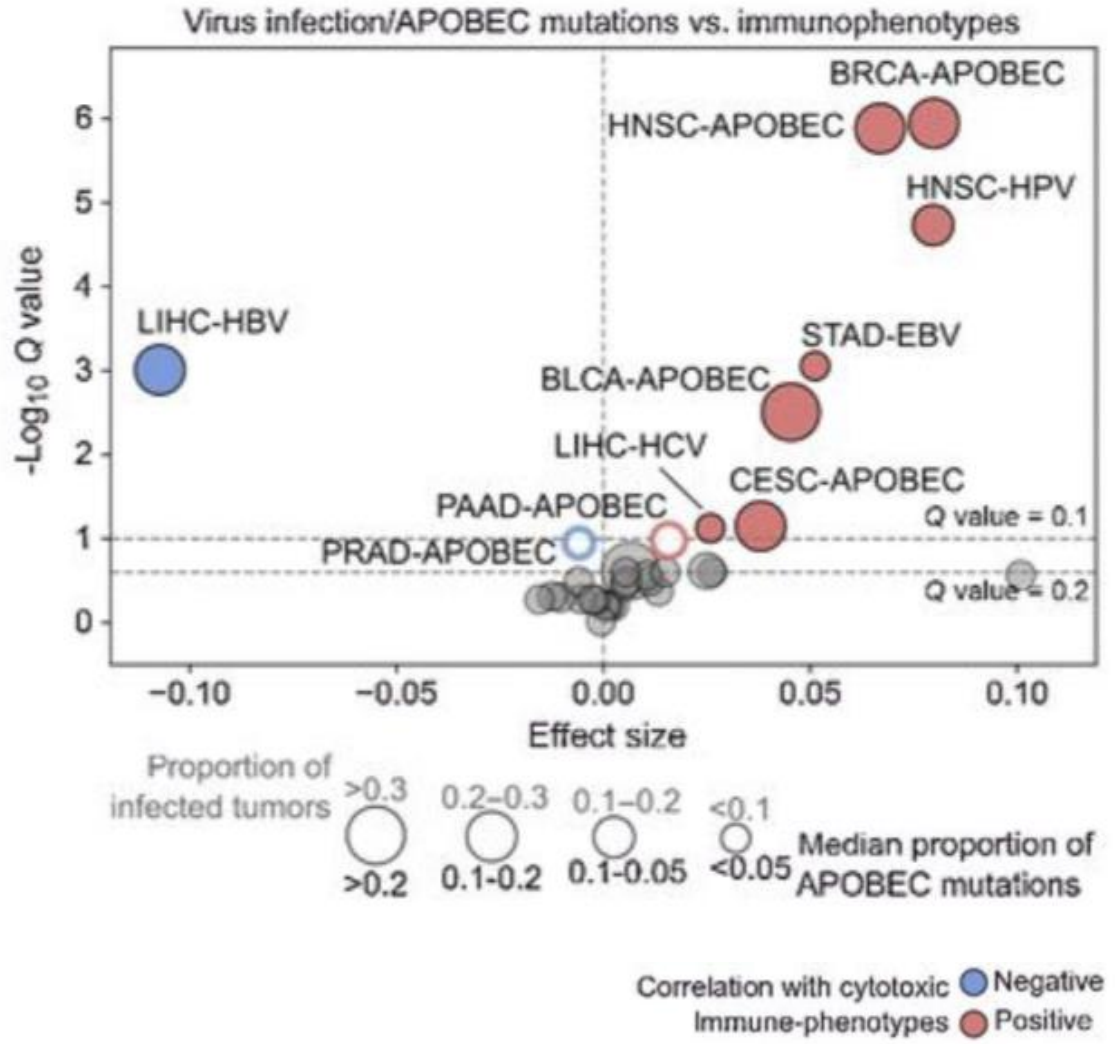
Adapted from Gatalica et al, Mod Pathol 2019

CLONAL NEOANTIGENS IN LUNG CANCER



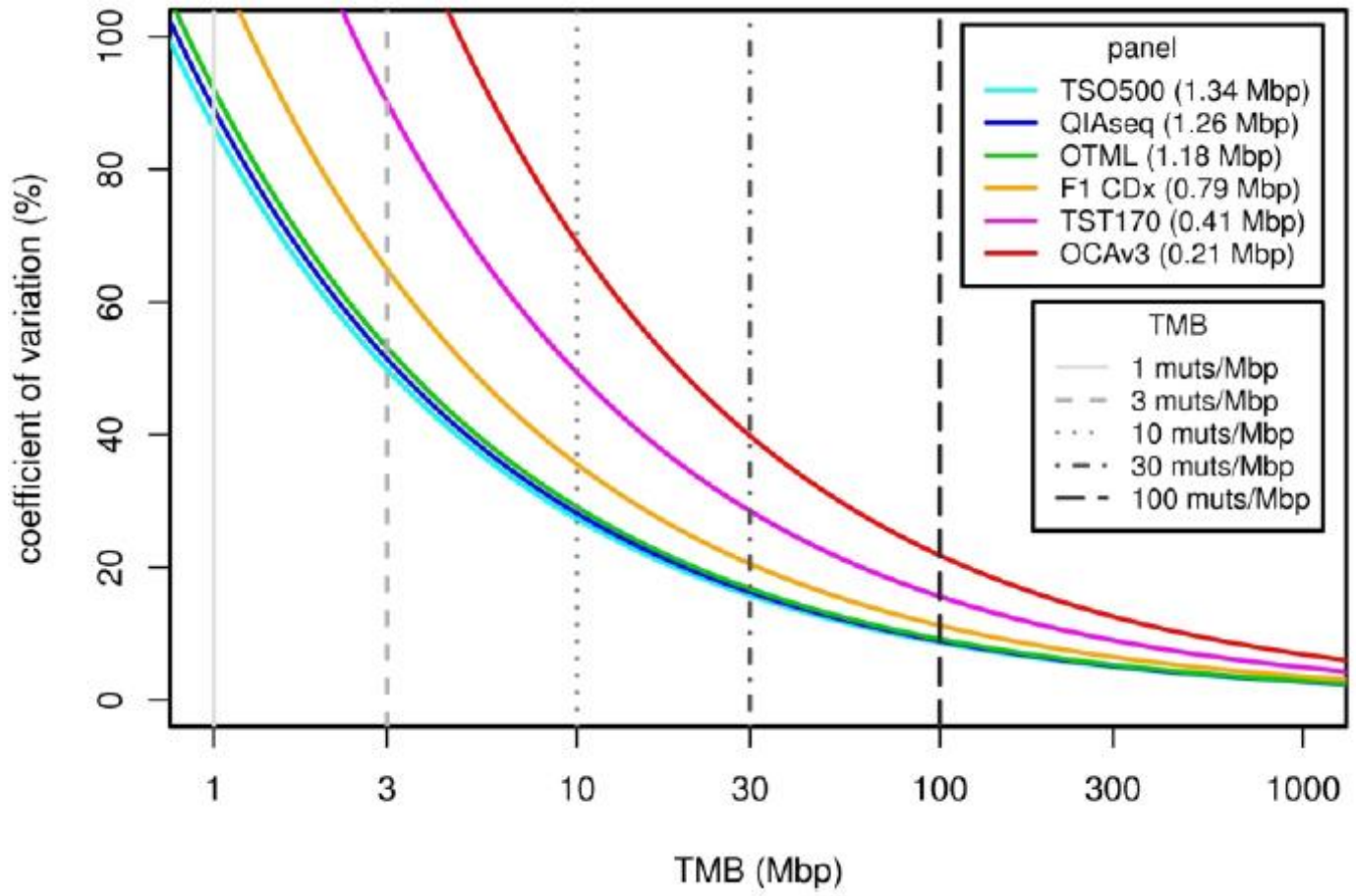
McGranahan et al, Science 2016

VIRAL NEOANTIGENS AND APOBEC MUTATION SIGNATURE



Tamborero et al, Clin Cancer Res 2018

OPTIMIZING PANEL-BASED TMB MEASUREMENT



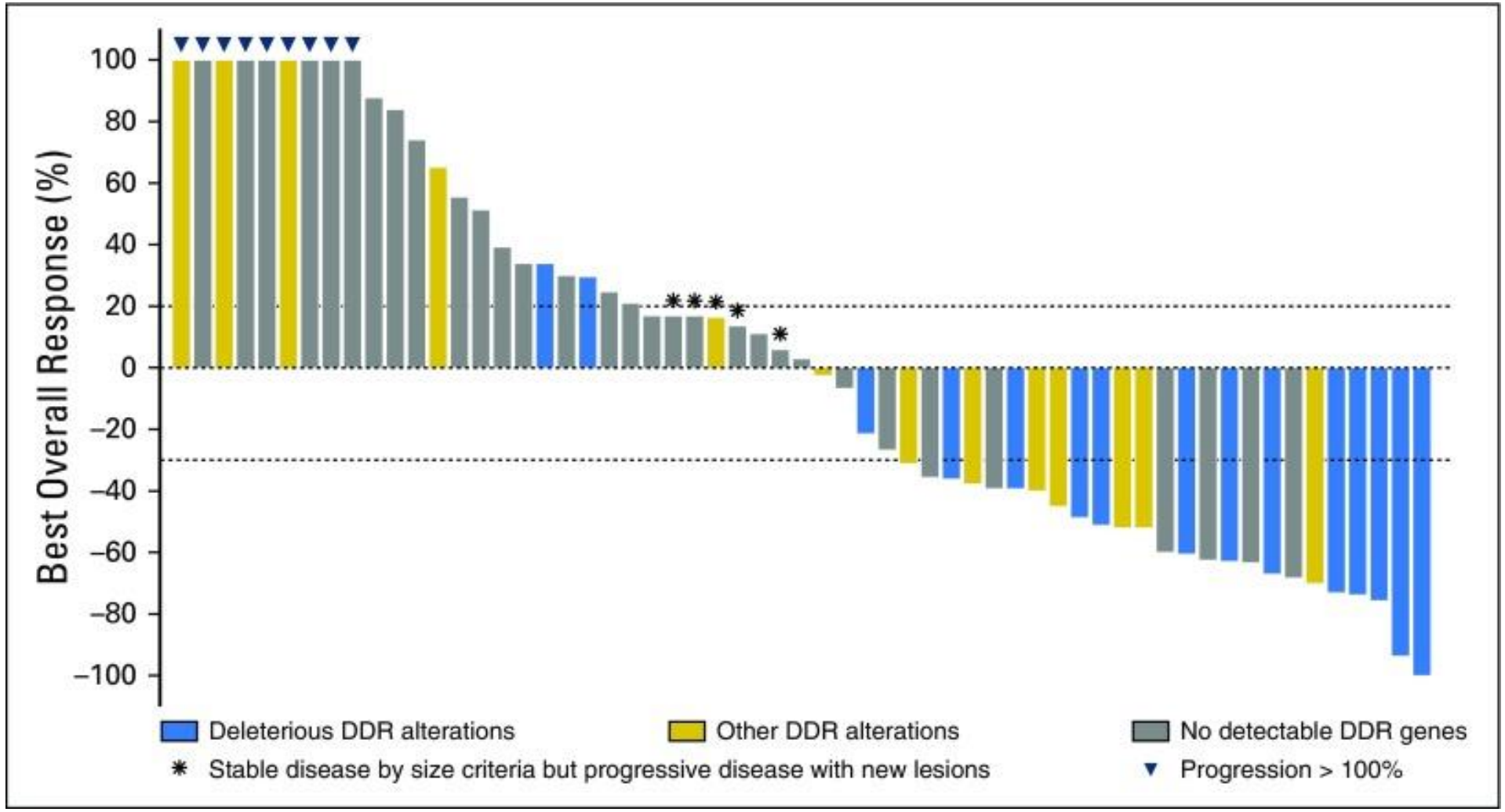
~ 33% misclassification rate across commercial panels

Important aspects:

- Cut-offs (tumor type/ setting)
- Source (tissue, ctDNA)
- Harmonization
- Prognostic vs. predictive (OS gain)

Budczies et al, Ann Oncol 2019

DNA DAMAGE REPAIR ALTERATIONS



Teo et al, J Clin Oncol 2018

PD-L1 UPREGULATION

Hodgkin's lymphoma – 9p24.1 gain

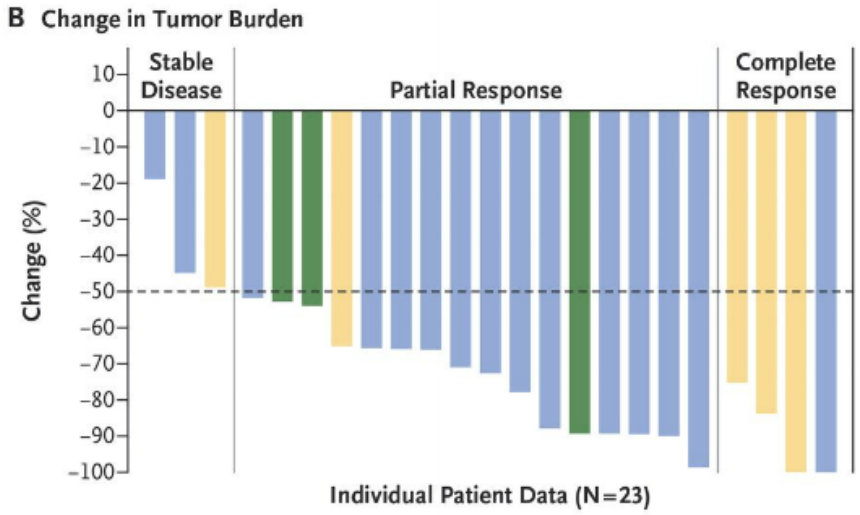
ORR 70%

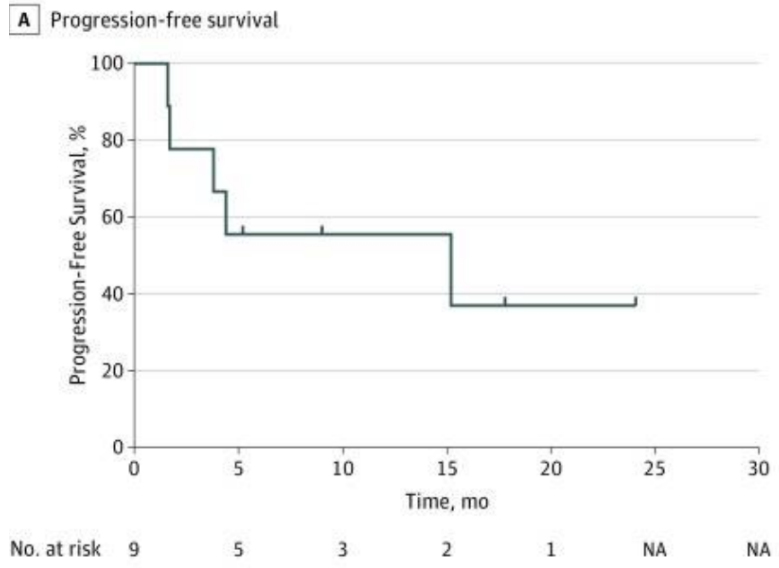
Ansell et al, NEJM 2015

PDL1 amplification in solid tumors

ORR 67%

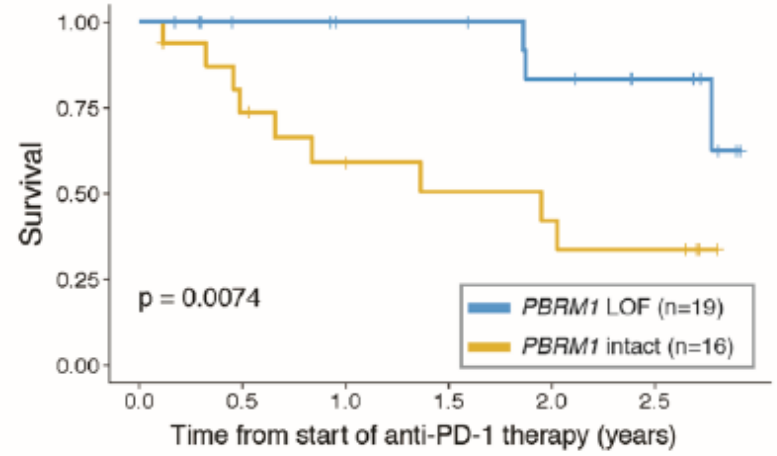
Goodman et al, JAMA Oncol 2018

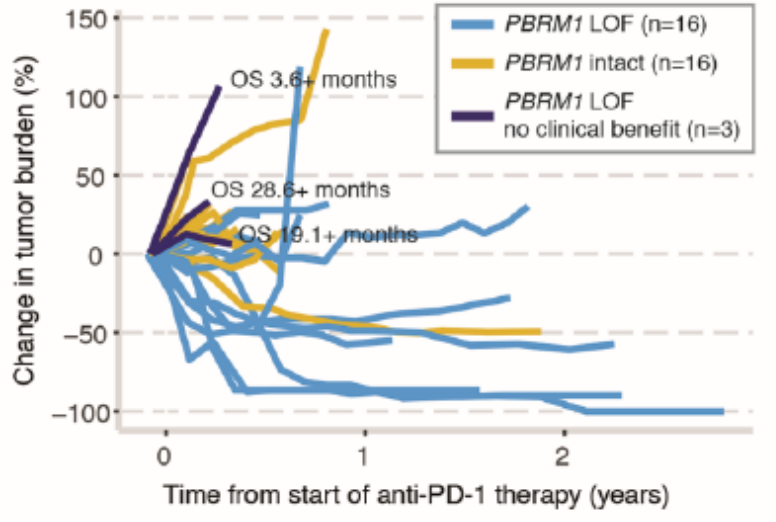


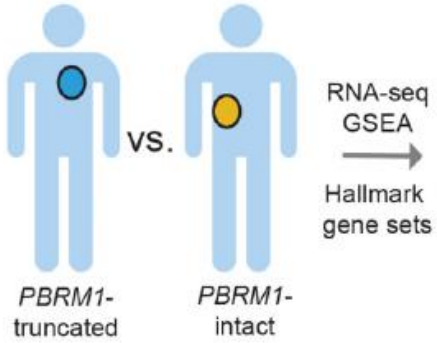


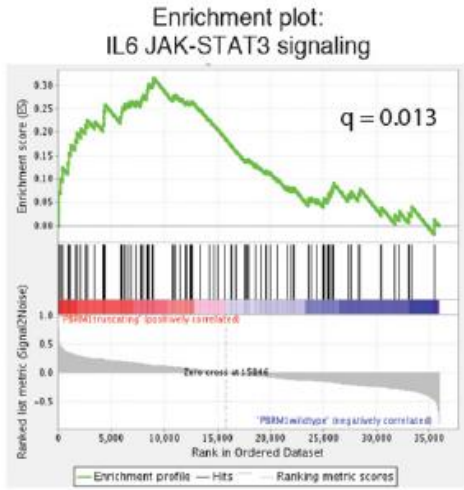
EPIGENETIC ALTERATIONS IN RENAL CANCER

SWI/SNF alterations: *PBMR1* mut









Miao et al, Science 2018

EPIGENETIC ALTERATIONS ACROSS TUMORS

ARID1A deficiency promotes mutability and potentiates therapeutic antitumor immunity unleashed by immune checkpoint blockade

***ARID1A* mut** — Nature Medicine 2018

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

***PBMR1* mut, *ARID2* mut** — Science 2018

Immune-Active Microenvironment in Small Cell Carcinoma of the Ovary, Hypercalcemic Type: Rationale for Immune Checkpoint Blockade

***SMARCA4* mut** — JNCI 2018

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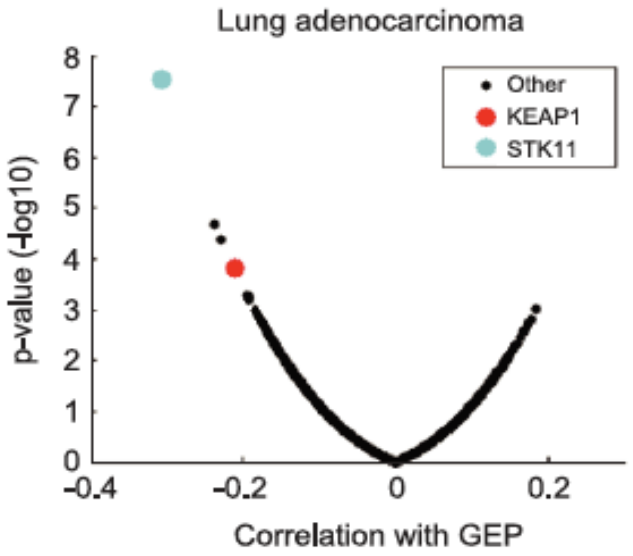
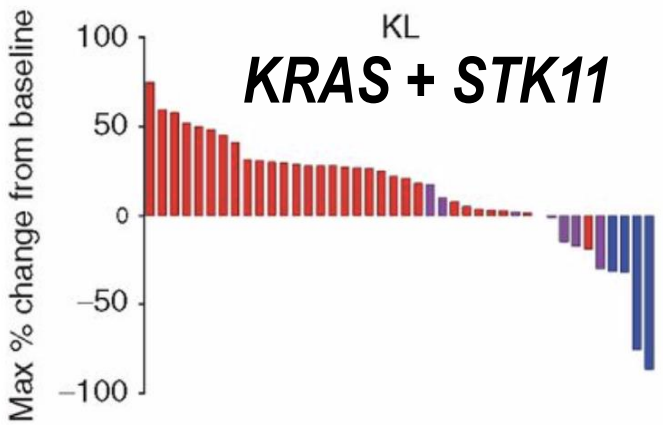
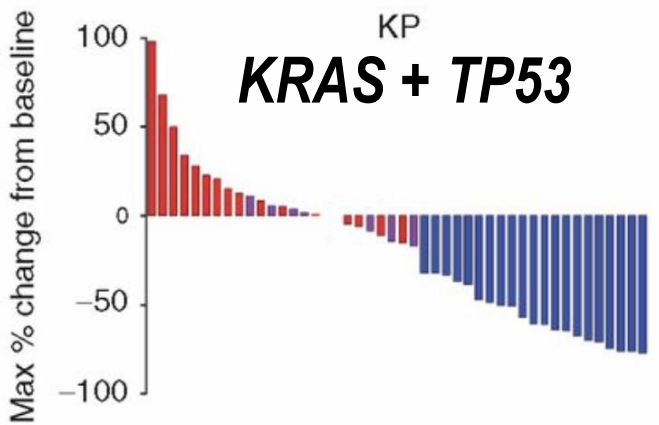
Adapted from Gatalica et al, Mod Pathol 2019

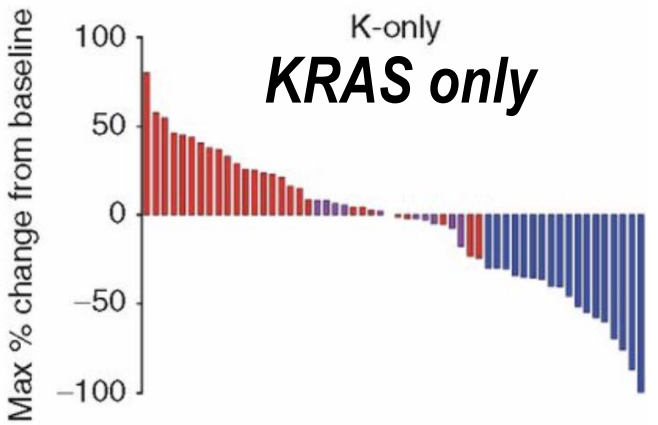
STK11 MUTATIONS IN LUNG CANCER



Cristescu et al, Science 2018



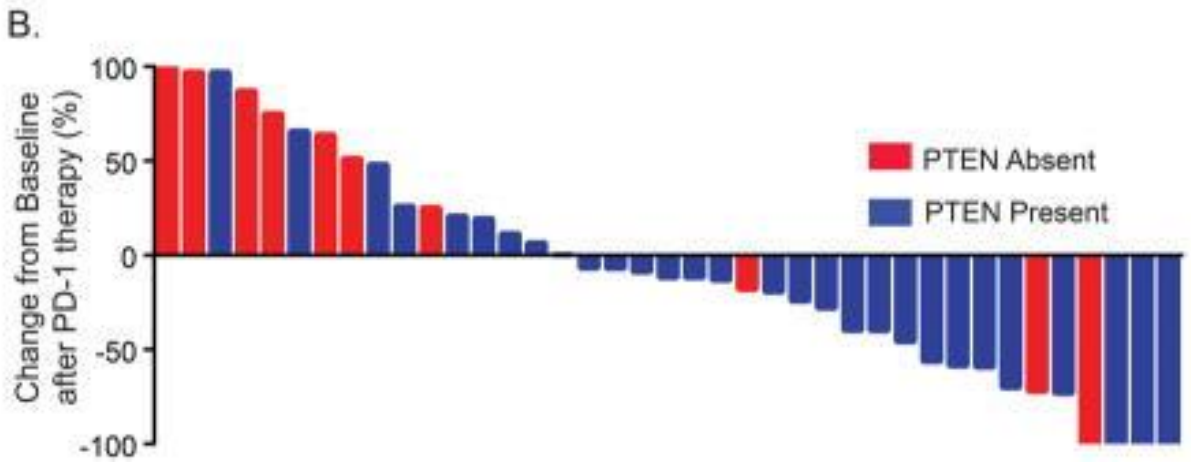




Skoulidis et al, Cancer Discov 2018

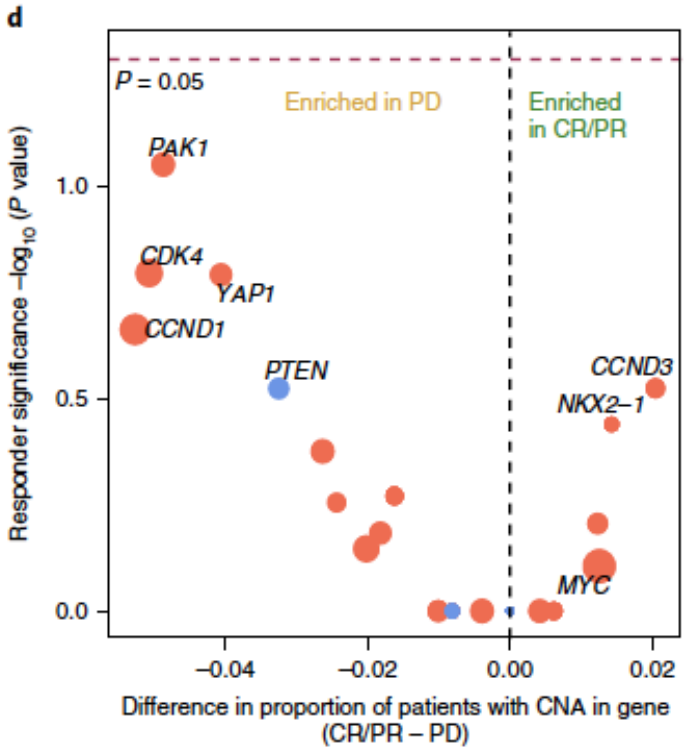
PTEN LOSS AND *CDK4/CCND1* AMPL

Melanoma



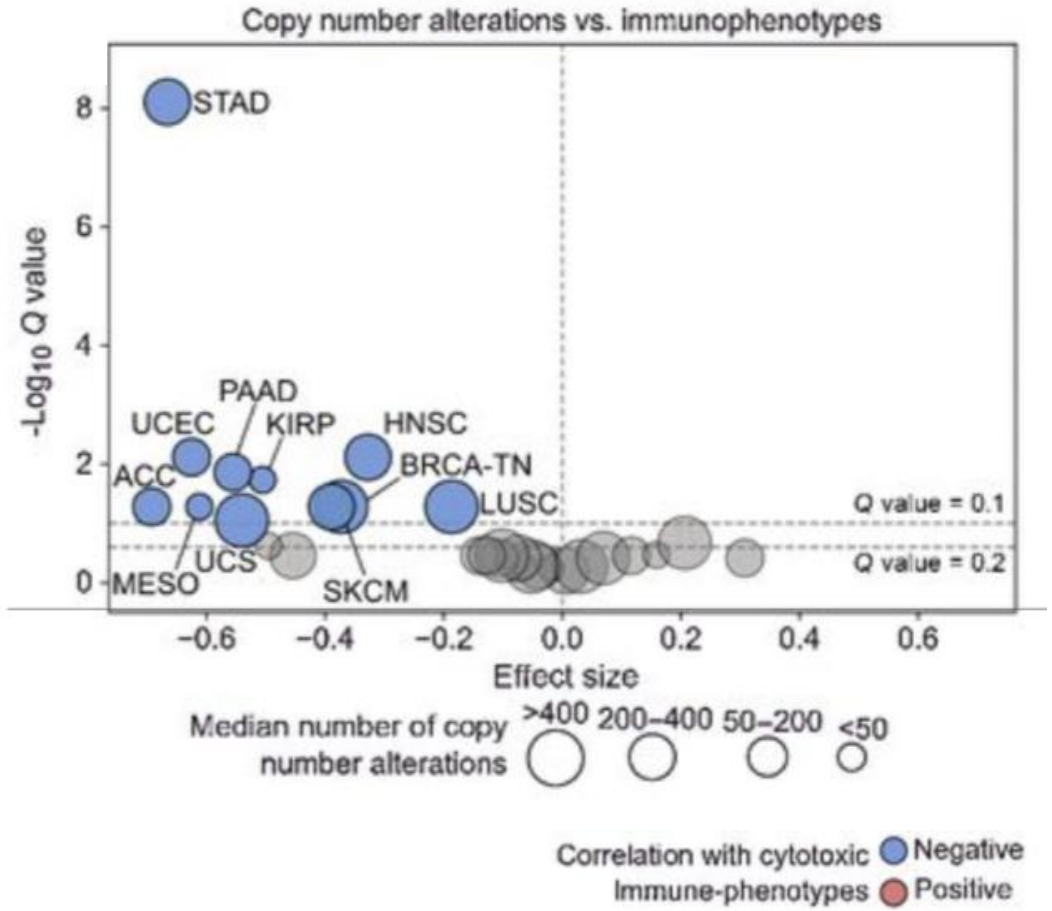
Peng et al, Cancer Discov 2016

Pan-tumor



Miao et al, Nat Genet 2018

HIGH COPY NUMBER ALTERATIONS ACROSS TUMORS

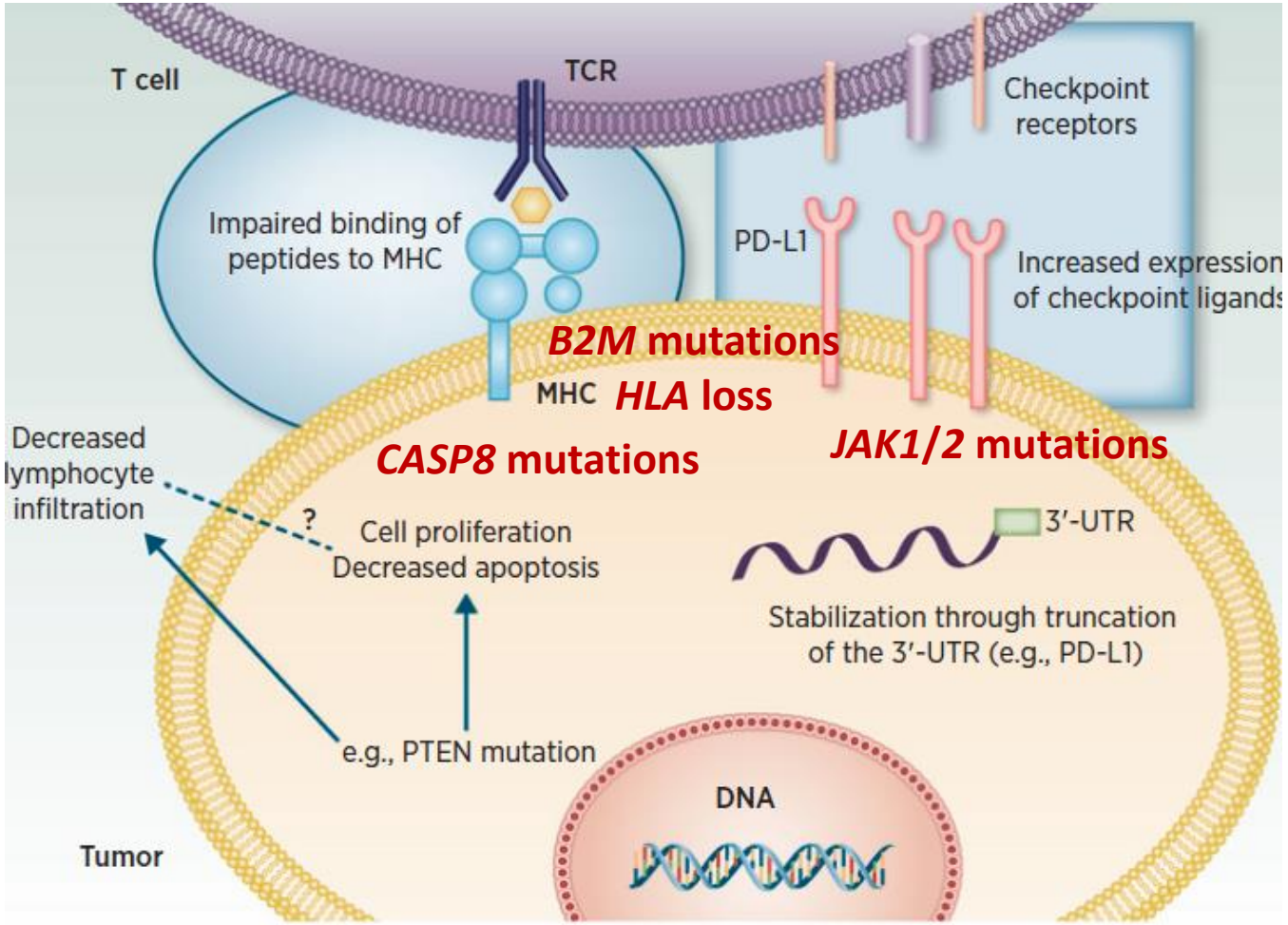


Tamborero et al, Clin Cancer Rer 2018

INTERFERON PATHWAY MUTATIONS IN MELANOMA AND MSI COLON CANCER

Shin et al, Cancer Discov 2017

ACQUIRED ANTIGEN PRESENTATION PATHWAY ALTERATIONS



Clin Cancer Res 2016

TRANSCRIPTOMIC MARKERS

Response

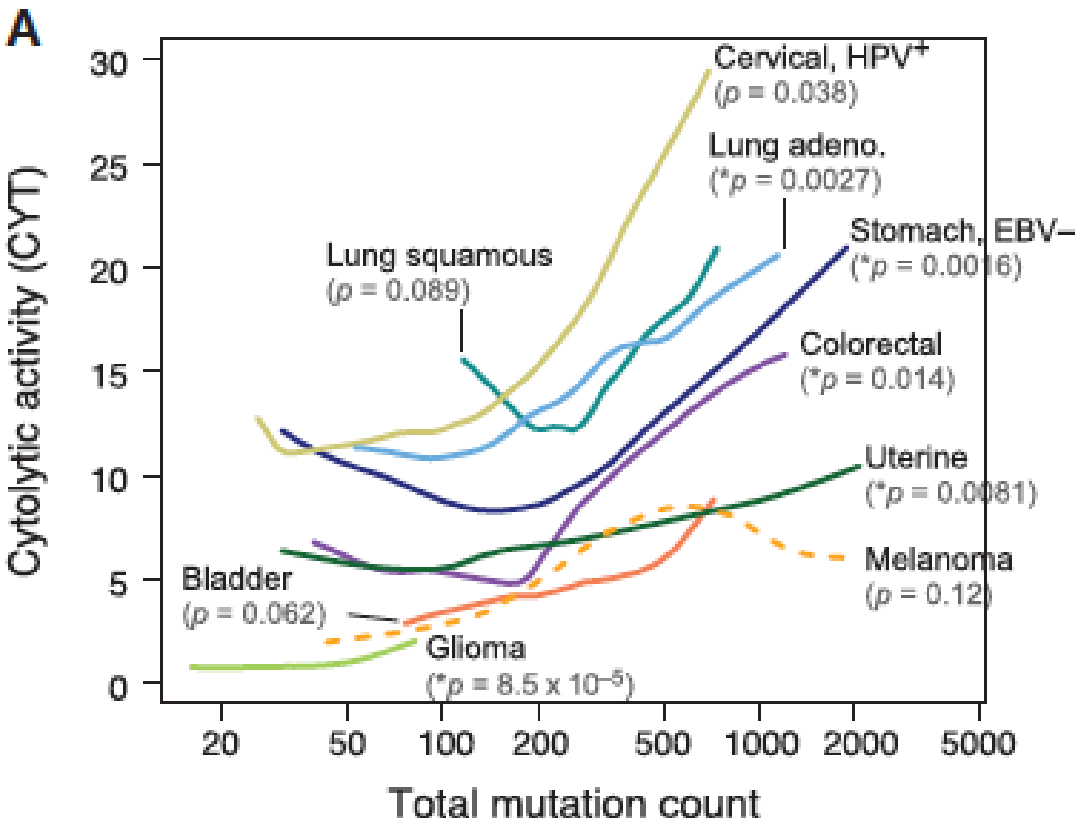
Cytotoxic (CD8 T cell inflammation) microenvironment signatures

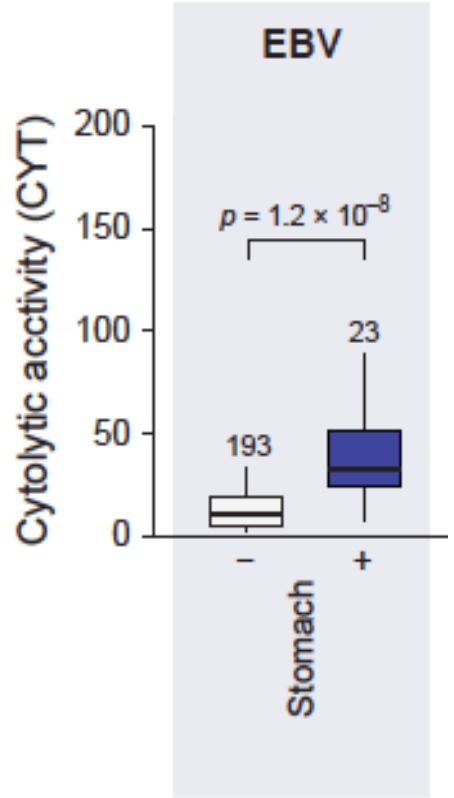
Resistance

Pathway alterations – WNT high, TGFB high

CYTOTOXIC SIGNATURES

granzyme A (*GZMA*) and perforin (PRF1)





Cell 2015

CYTOTOXIC SIGNATURES

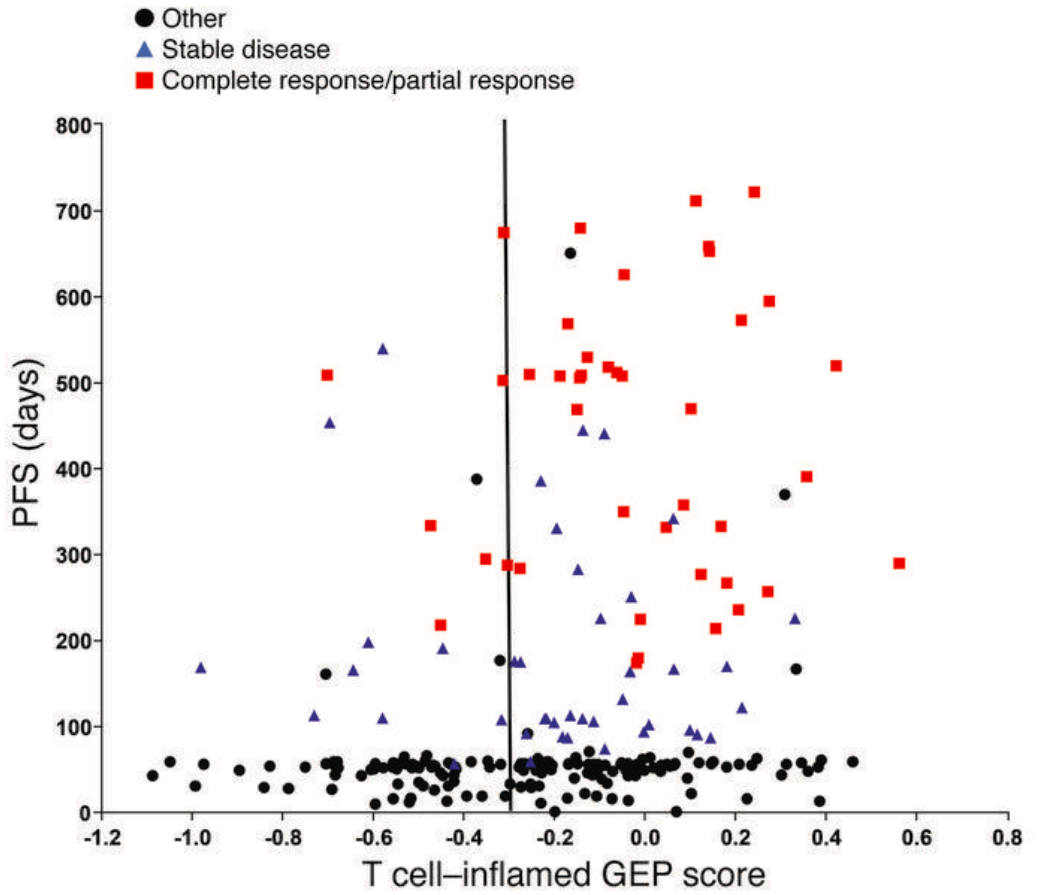
Metanalysis

Melanoma, HNSCC, gastric

Pembrolizumab

GEP cytotoxicity signature (10 genes)

Nanostring nCounter



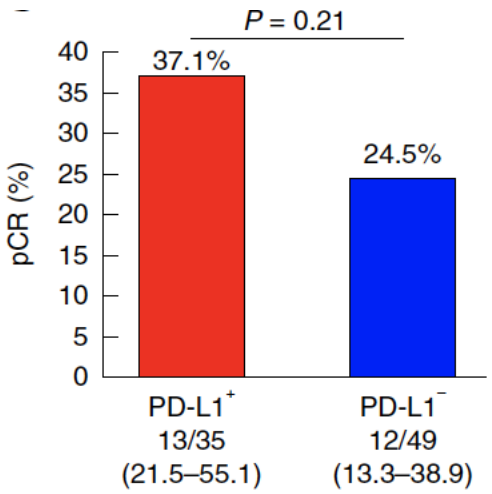
J Clin Invest 2017, 127:2930-40

CYTOTOXIC SIGNATURES

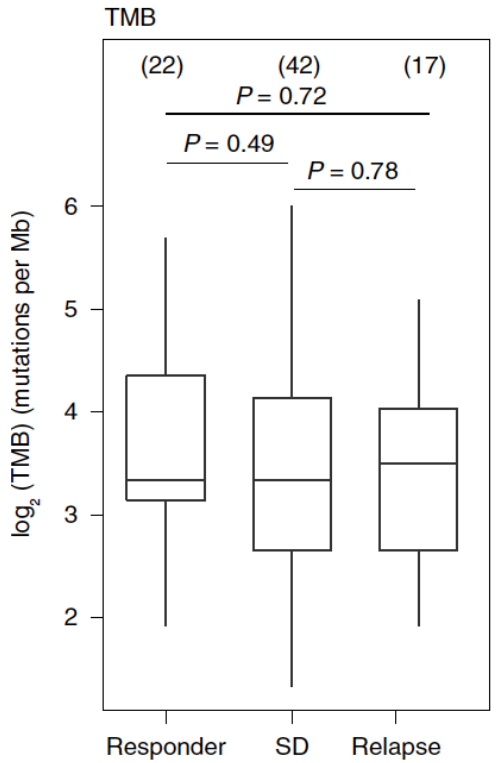
ABACUS trial Bladder Cancer

Atezolizumab neoadjuvant

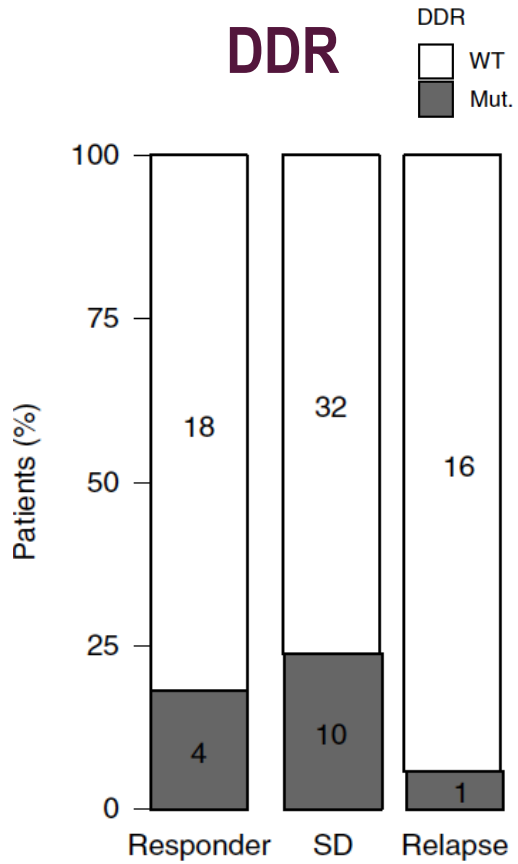
PD-L1



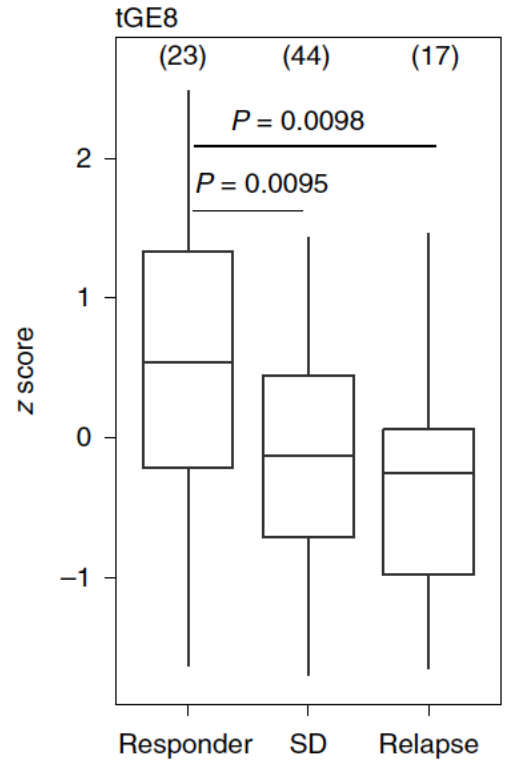
TMB



DDR



GEP (CD8)



Keenan et al, Nat Med 2018

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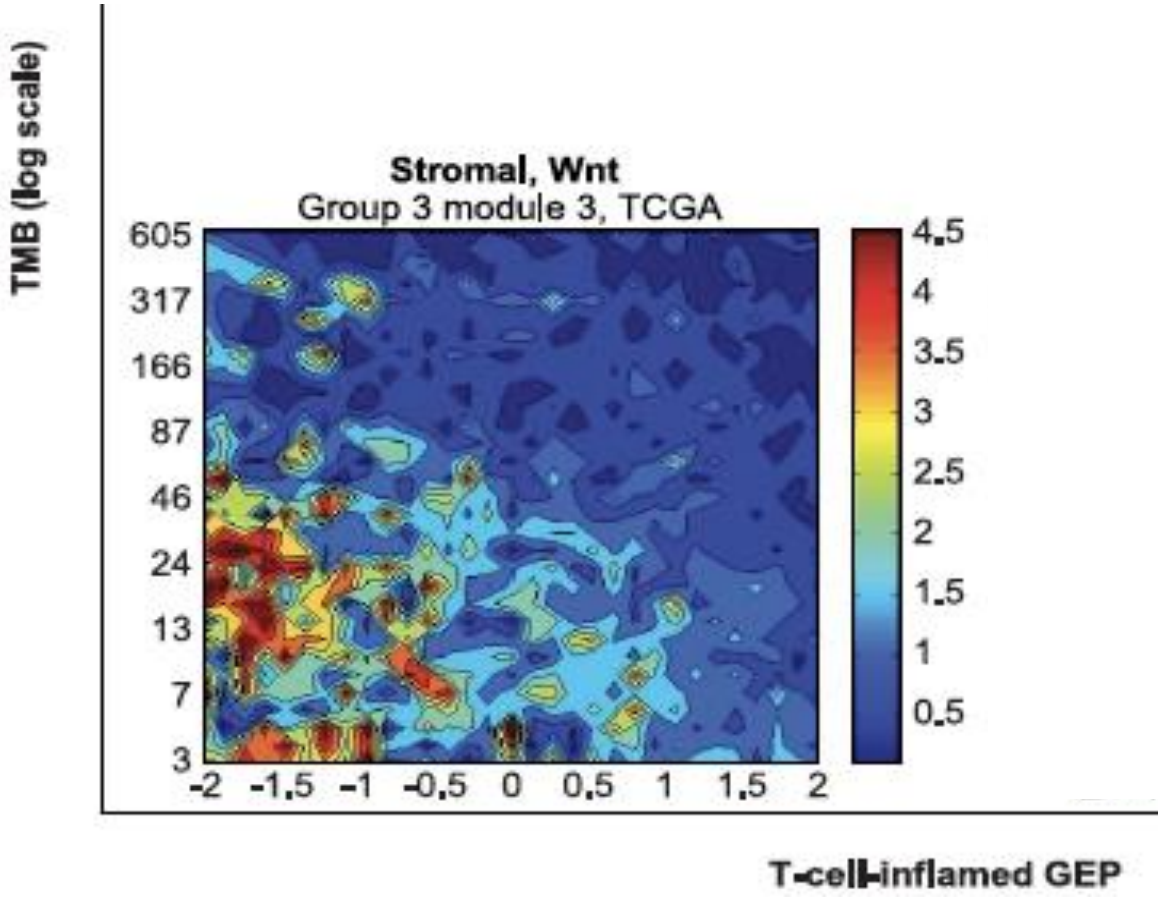
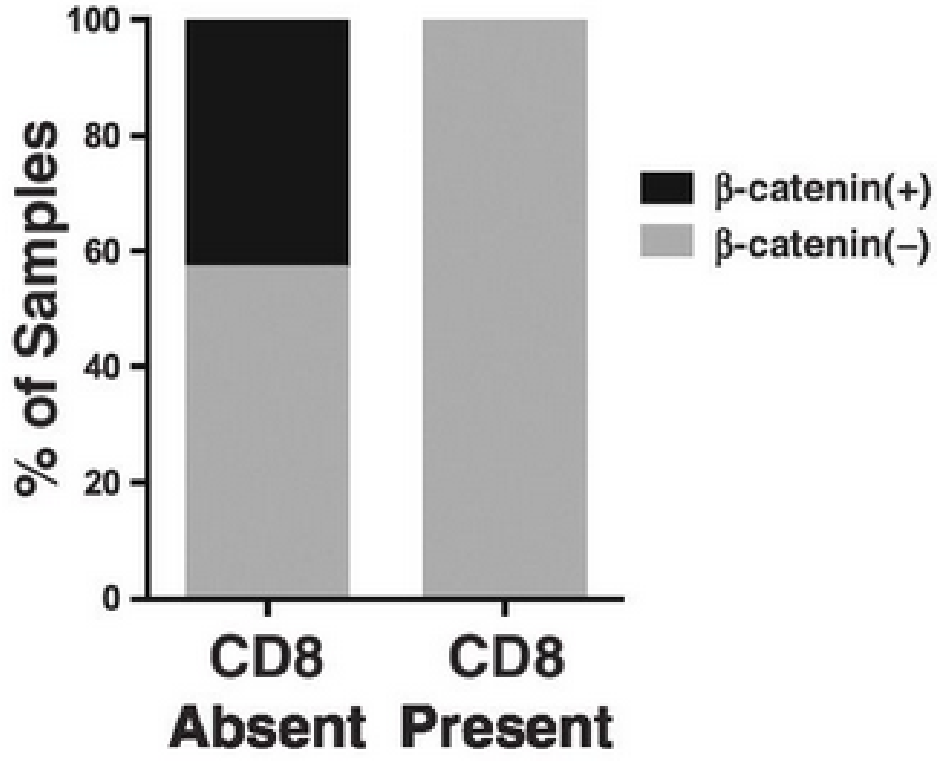
WNT AND TGFB HIGH SIGNATURES



Cristescu et al, Science 2018

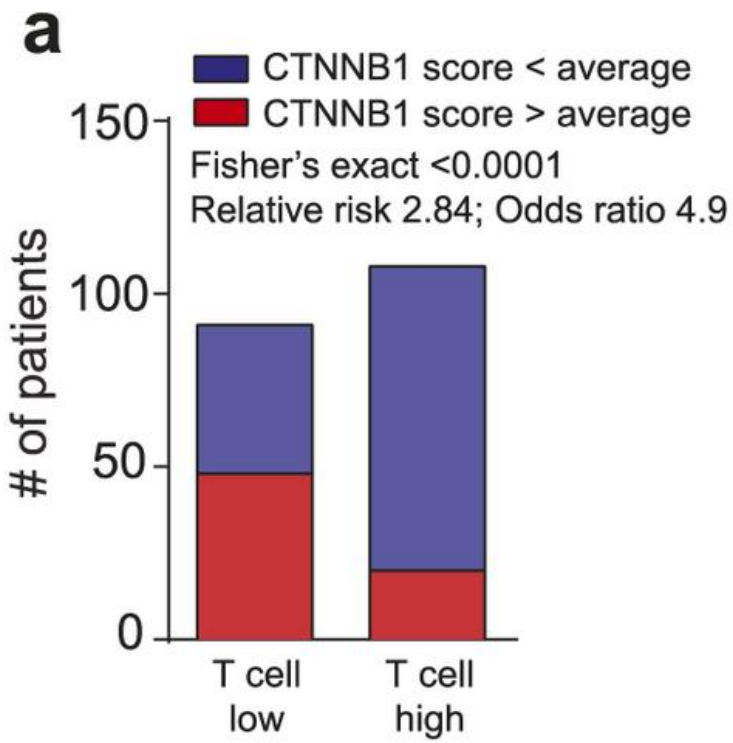
B CATENIN POSITIVE/HIGH

Bladder



Sweis et al, Cancer Immunol Res. 2016

Melanoma



Spranger et al, Nature 2015

CONCLUSIONS

- Response to immune checkpoint inhibitors is multi-factorial

- PD-L1, TMB and CD8 signatures (and combinations) have highest potential
  - ➢ Tumor type and disease setting matter

- There is room for further biomarker development (digital pathology, radiomics, patient genetics/phenomics)

- Design clinical trials with power for retrospective correlative analysis (not only “exploratory analysis”) in homogeneous populations.

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TIME TO MOVE TO NEGATIVE PREDICTIVE MARKERS?

ARE THERE UNIVERSAL RESISTANCE MARKERS?