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Biomarkers in Imunotherapy: RNA Signatures as predictive biomarker

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Vall d'Hebron University Hospital

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Outline

- Introduction
- Molecular characterization in melanoma
- Molecular characterization in colorectal
- Molecular characterization in bladder
- Molecular characterization in renal
- Conclusions

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Outline

- Introduction

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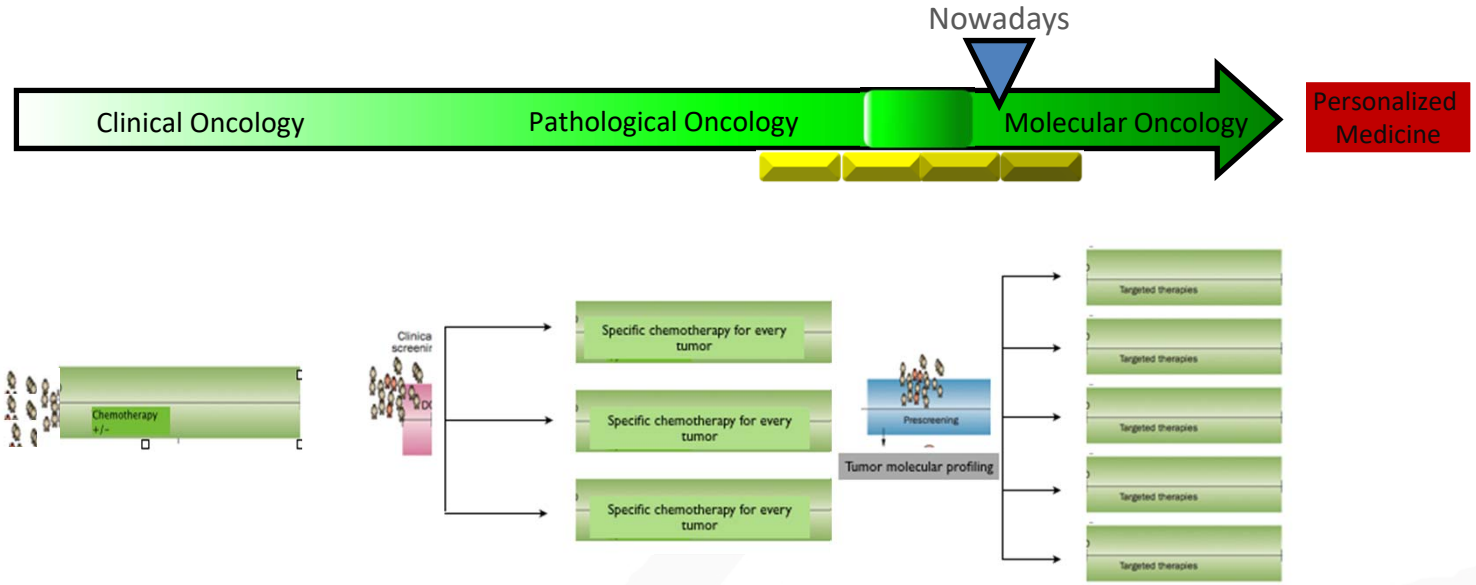
Conceptual evolution of Cancer treatment



Few therapeutic options combined to treat tumors:
-Surgery
-Radiotherapy
-Few chemotherapies

Increase on therapeutic options allowed specific treatments for different tumor types:
-Combined chemo-radiation
-Specific protocols (NCCN guidelines)

Targeted agents that work in specific molecular alterations:
-Broad knowledge of molecular tumor biology
- Development of molecular analysis and targeted therapies

Disease guided approach → Pathological guided approach → Molecular approach

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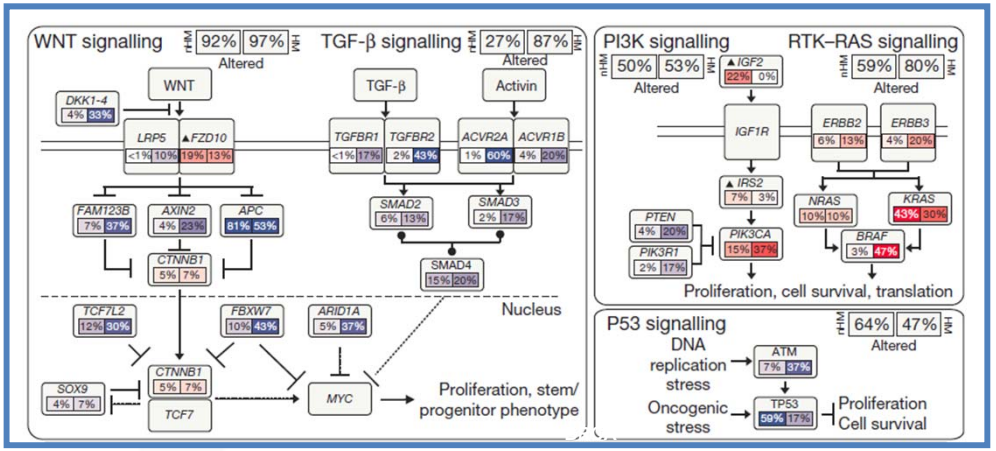
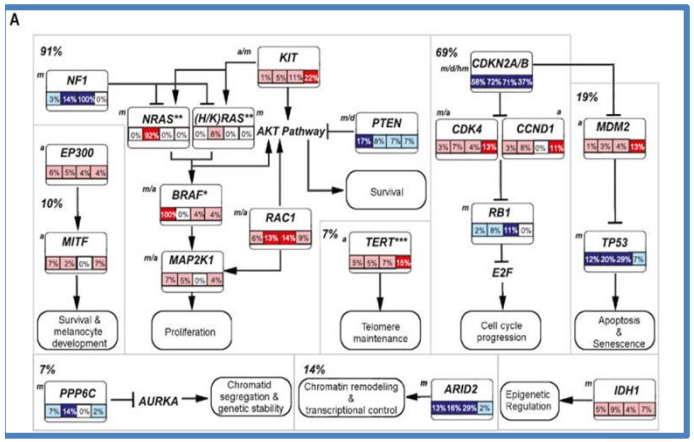
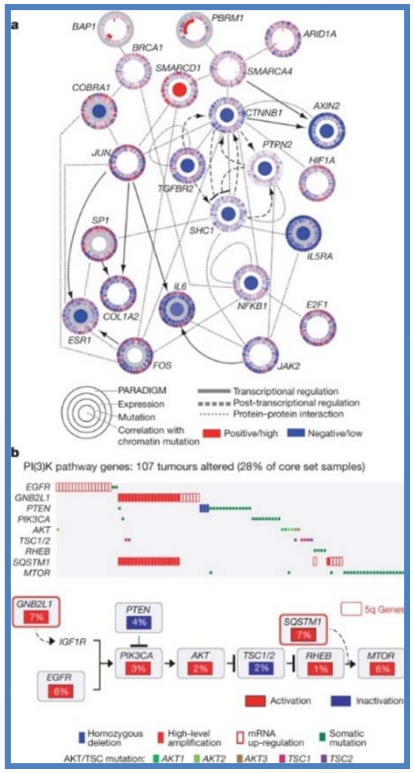
THE CANCER GENOME ATLAS



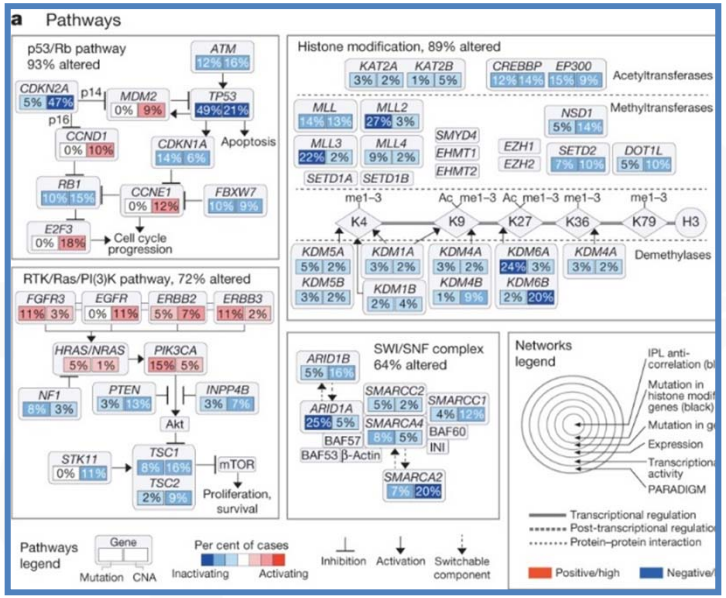
Colorectal



Melanoma



Clear Cell Carcinoma



Bladder

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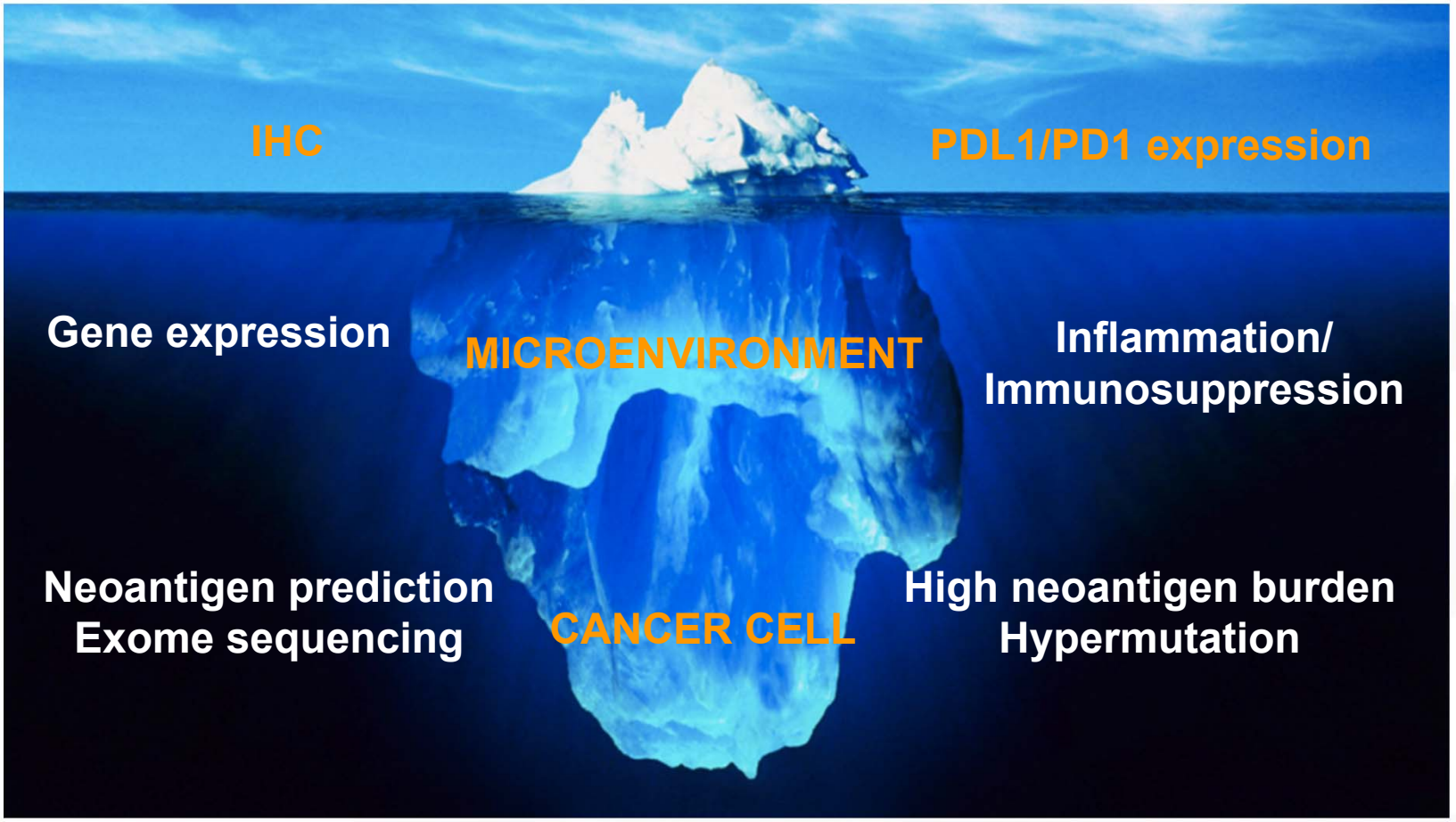
Biomarkers of response to Immunocheckpoints inhibitors



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Outline

- Molecular characterization in melanoma

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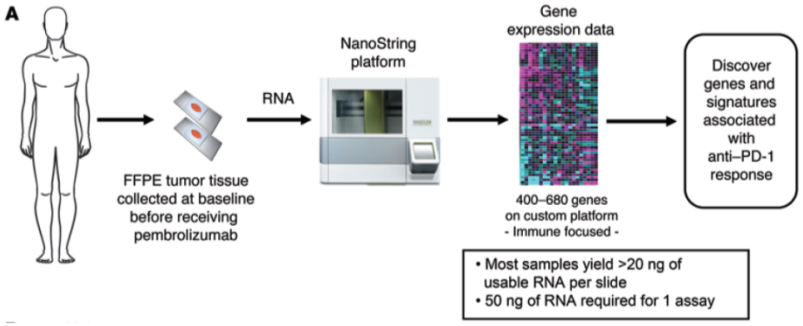
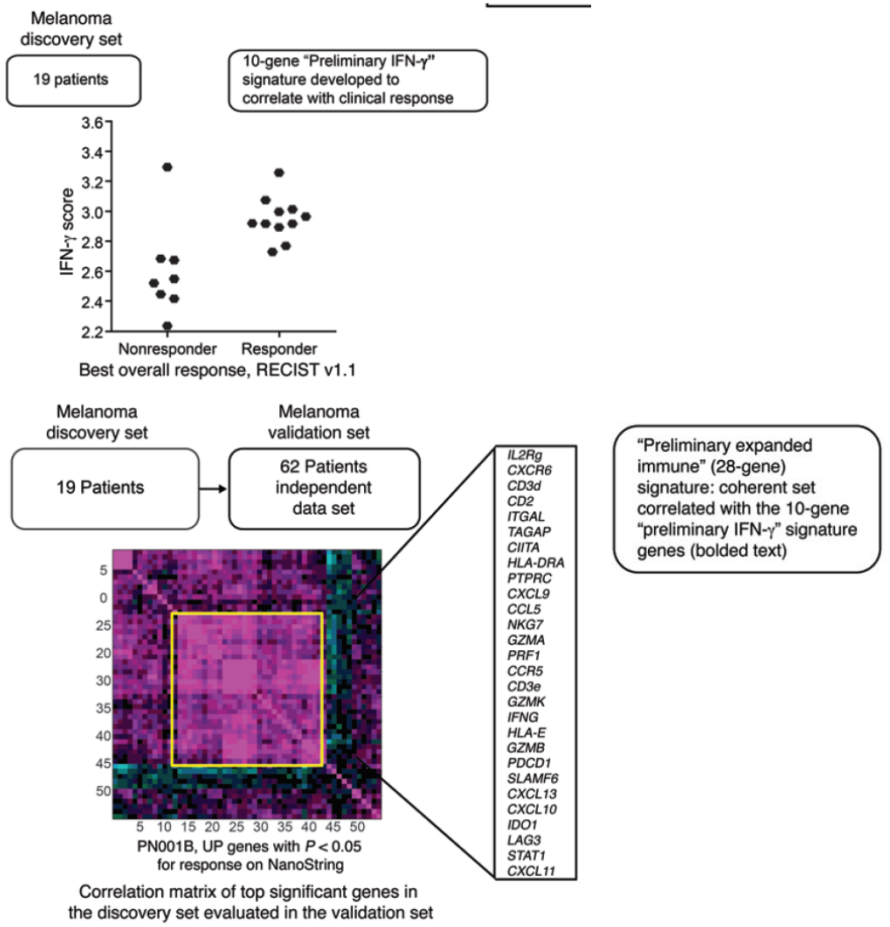
How to use a signature to improve sensitivity to anti IO





Ayers et al.JCI. 2017

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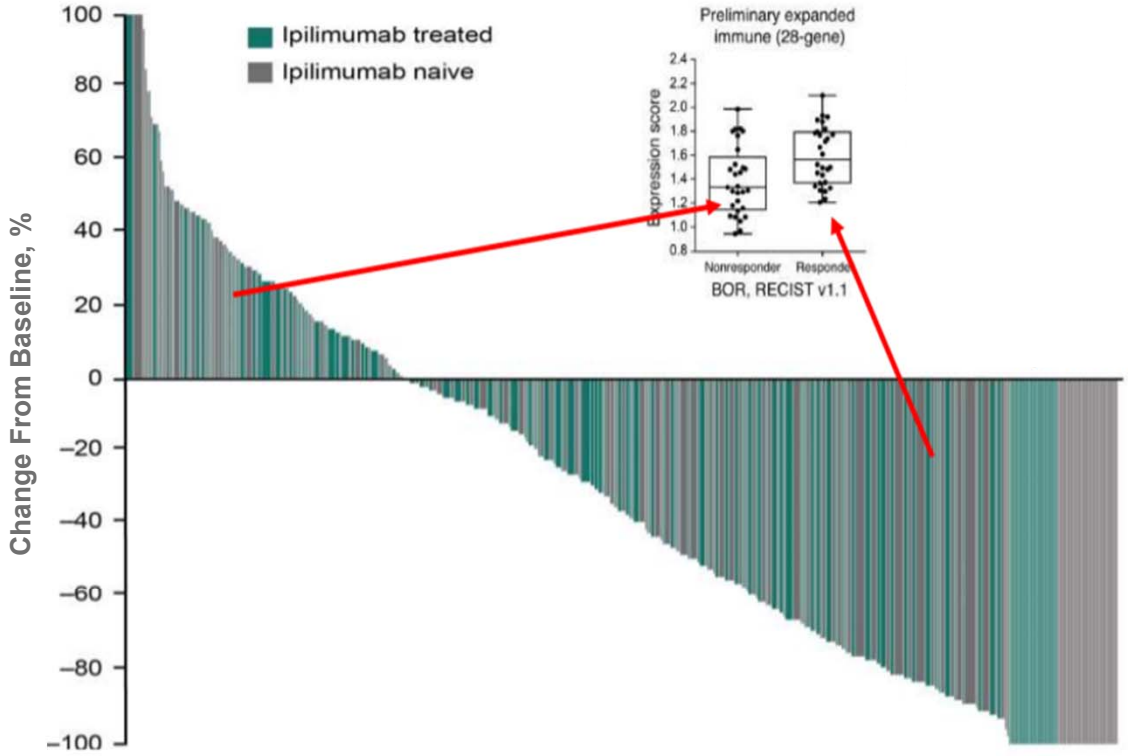
What differentiates Anti PD-1 responsive from non responding melanomas?



Ribas et al. JAMA 2016
Pembrolizumab KEYNOTE-001 trial. Central radiology review by RECIST v1.1

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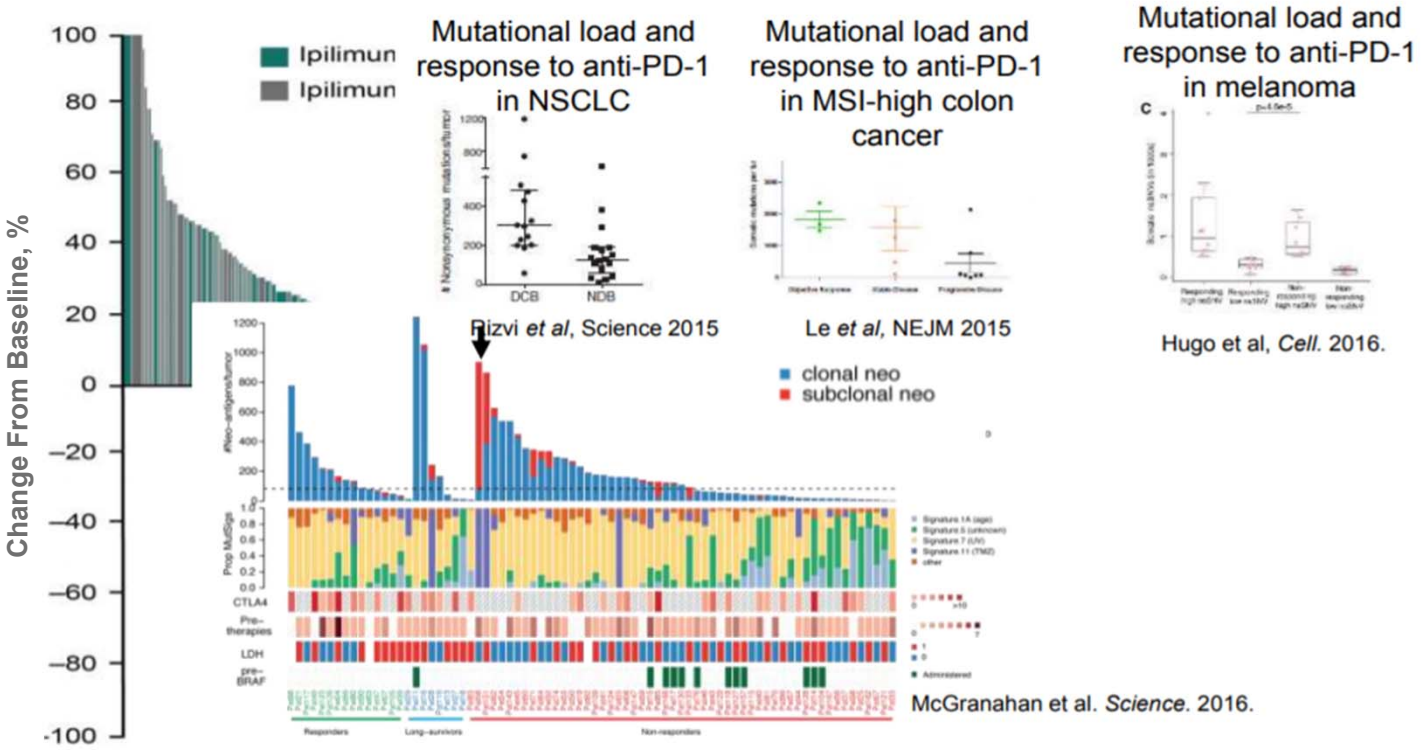
What differentiates Anti PD-1 responsive from non responding melanomas?



Ribas et al. JAMA 2016
Pembrolizumab KEYNOTE-001 trial. Central radiology review by RECIST v1.1 MSI, microsatellite instability; NSCLC, non-small carcinoma.

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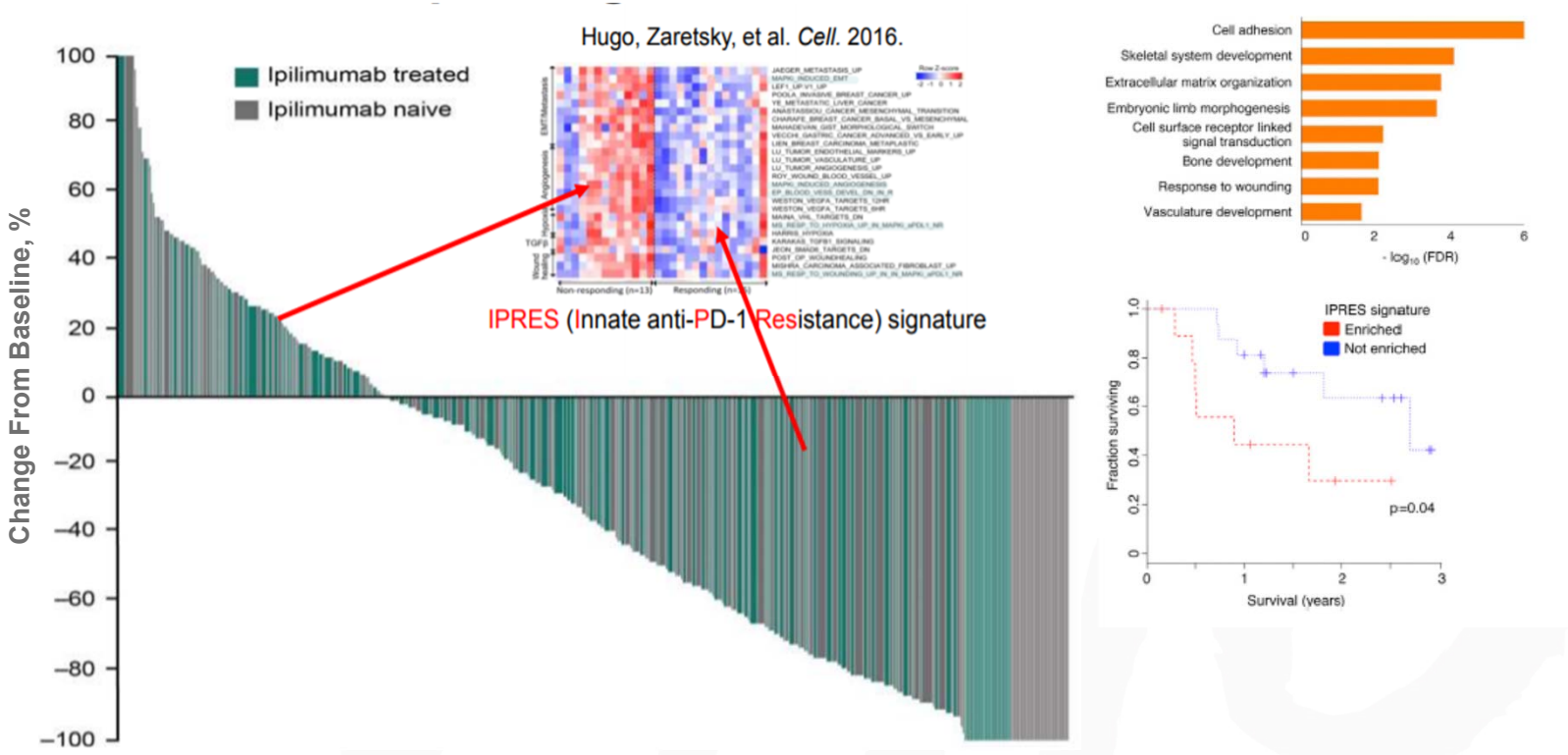
What differentiates Anti PD-1 responsive from non responding melanomas?



Ribas et al. JAMA 2016
Pembrolizumab KEYNOTE-001 trial. Central radiology review by RECIST v1.1

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RESEARCH ARTICLE

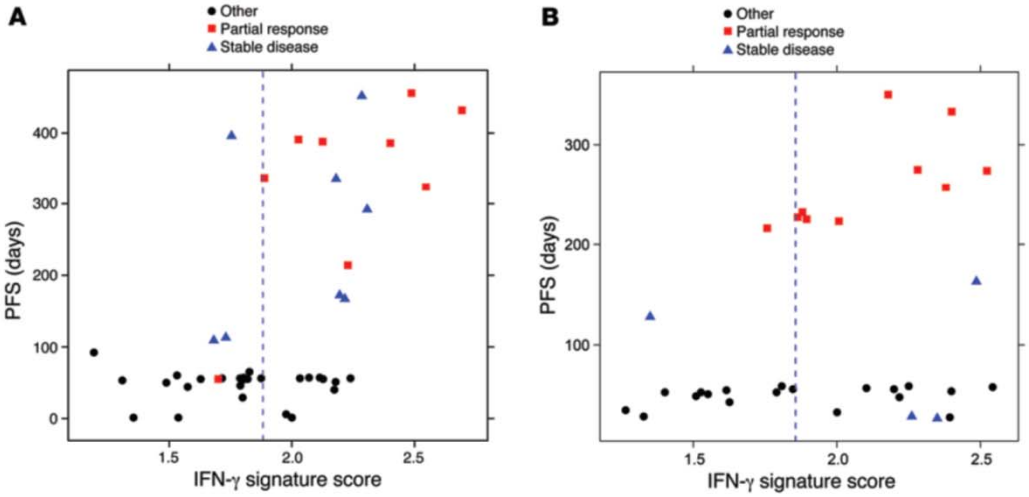
The Journal of Clinical Investigation

IFN-γ–related mRNA profile predicts clinical response to PD-1 blockade

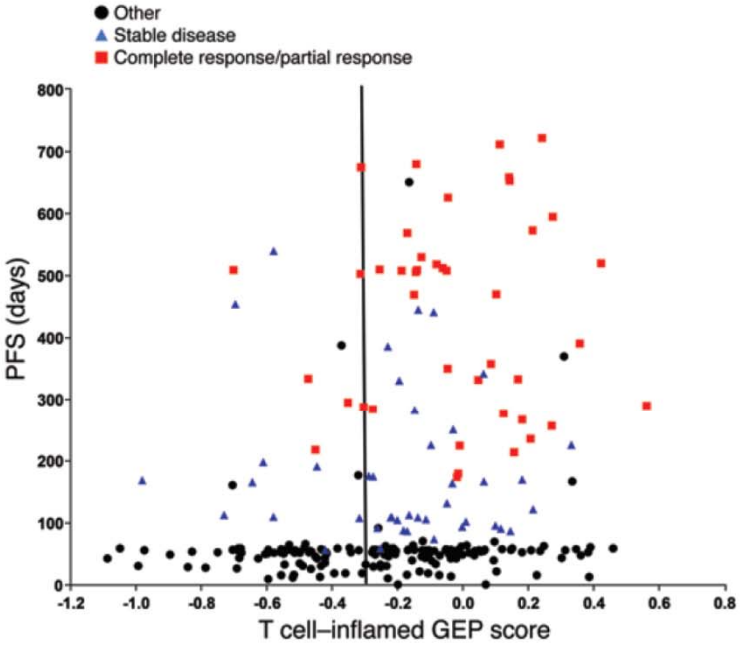
Table 2. IFN-γ and expanded immune gene signatures

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*

HNSCC & Gastric Cancer



244 pts from 9 different tumours



Ayers et al.JCI. 2017

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Outline

- Molecular characterization in colorectal

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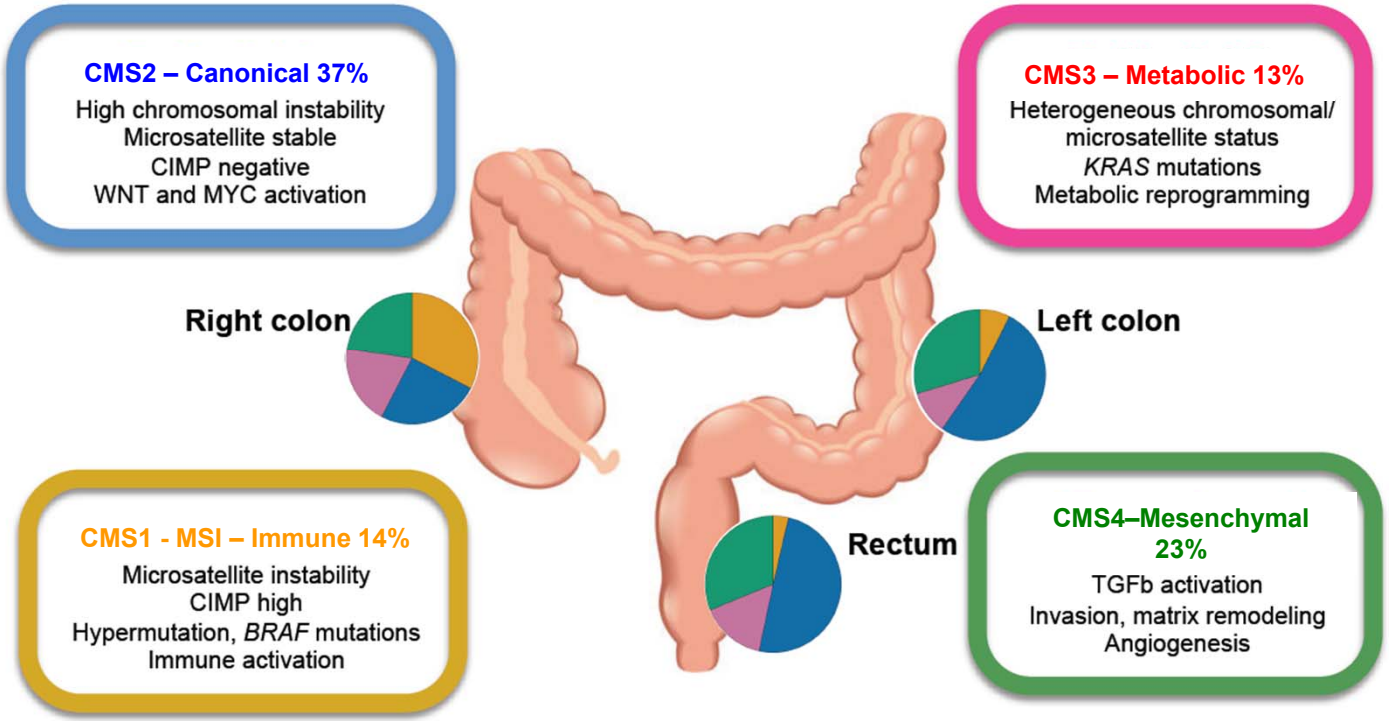
CMS subtypes – clinical and molecular correlates



Guinney J, Dienstmann R et al. Nat Med 2015

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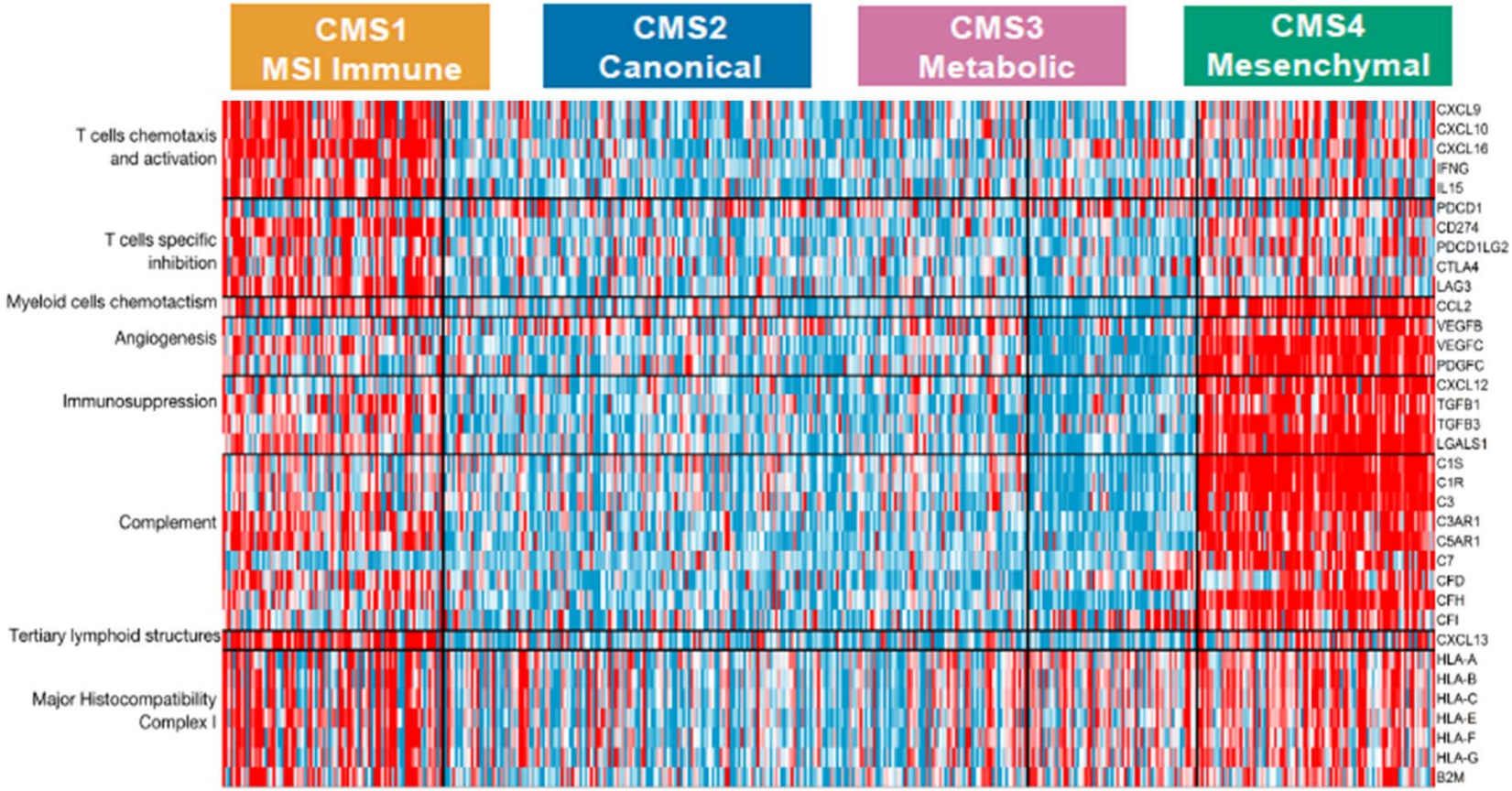
Immune vs Transcriptomic subtypes of CRC

Supervised immune infiltration analysis



Becht E et al, Clin Cancer Res 2016

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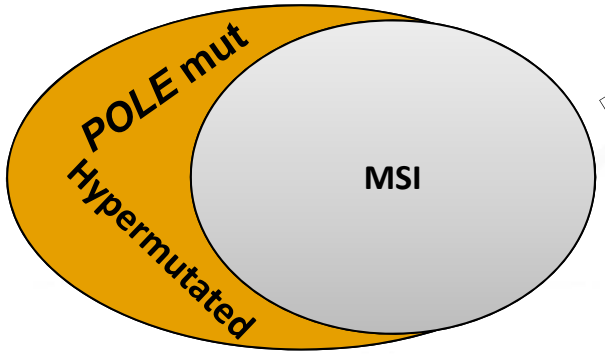
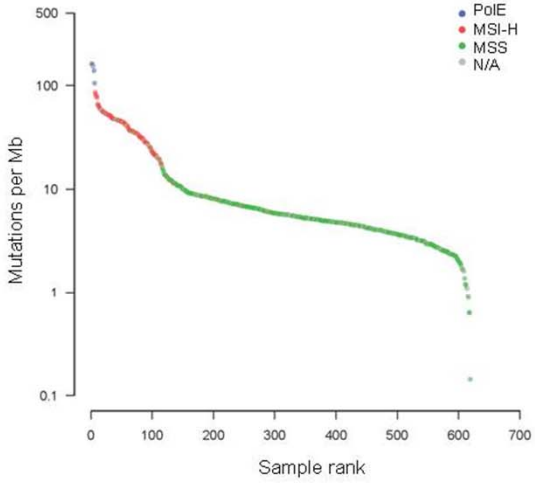
Molecular-driven therapeutic hypothesis

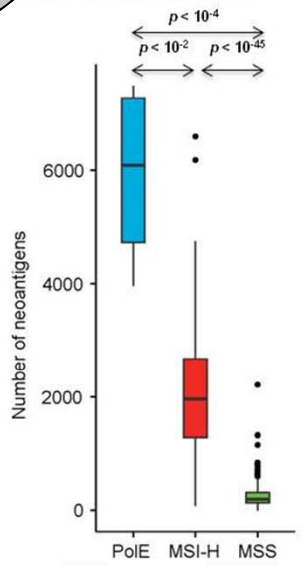
Immune
CMS1



PD1 blockade responsive

Strategy:
PD1 blockade





Giannakis M et al. Cell Reports 2016

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Outline

- Molecular characterization in bladder

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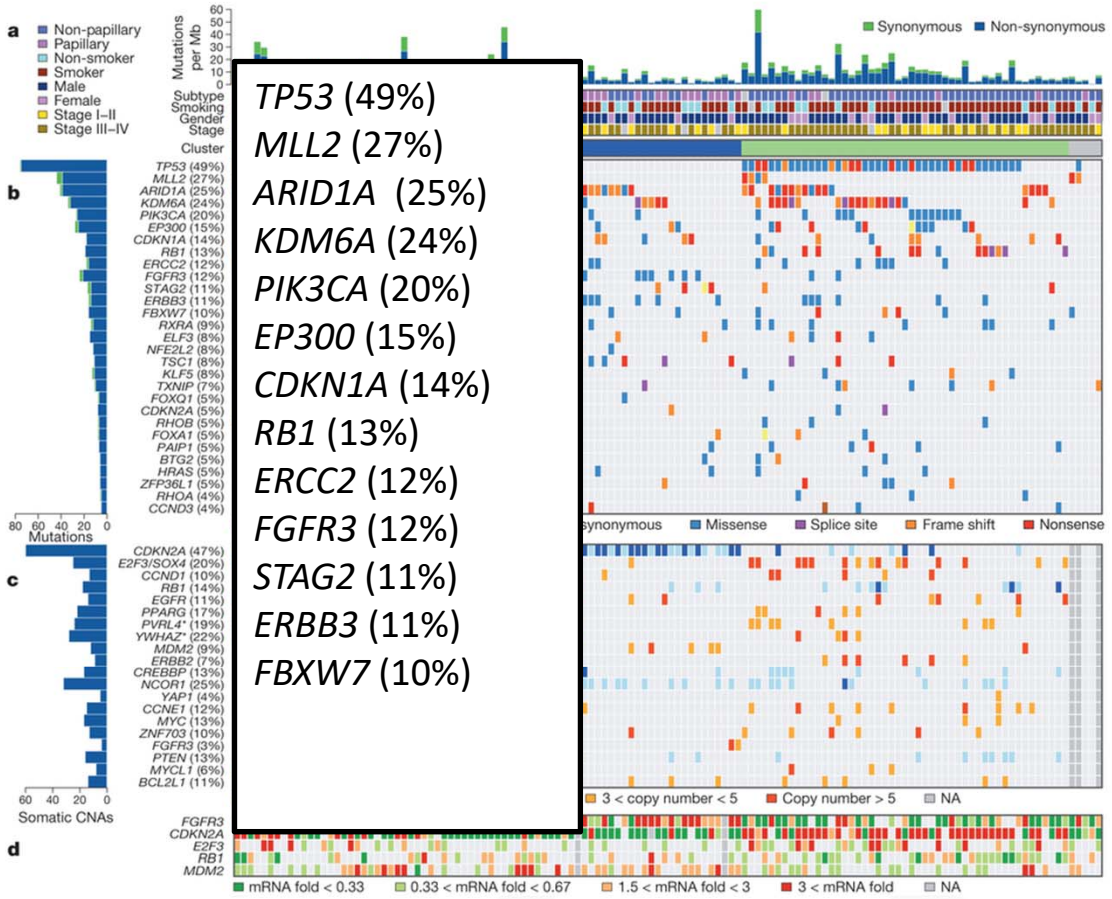
Bladder Cancer is a molecularly heterogeneous disease



TP53 (49%)
MLL2 (27%)
ARID1A (25%)
KDM6A (24%)
PIK3CA (20%)
EP300 (15%)
CDKN1A (14%)
RB1 (13%)
ERCC2 (12%)
FGFR3 (12%)
STAG2 (11%)
ERBB3 (11%)
FBXW7 (10%)

TCGA, Nature, 2014

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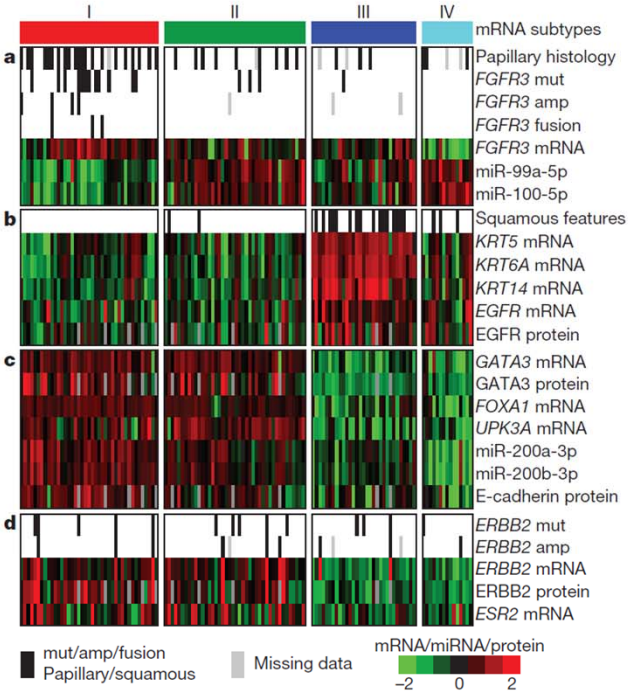
Identification of subtypes of muscle invasive bladder tumors



Cluster I "Papillary-like"
Papillary morphology
FGFR3 mutations and elevated *FGFR3* expression
FGFR-TACC3

Cluster III "basal/squamous like"
Squamous morphology
KRT14 y KRT5

Uroplakins: Cluster I and II

ERBB2 mutation/oestrogen receptor beta: cluster I and II

Cancer Genome Atlas Research Network. Comprehensive molecular characterization of urothelial bladder carcinoma. Nature 2014; 507:315-22.

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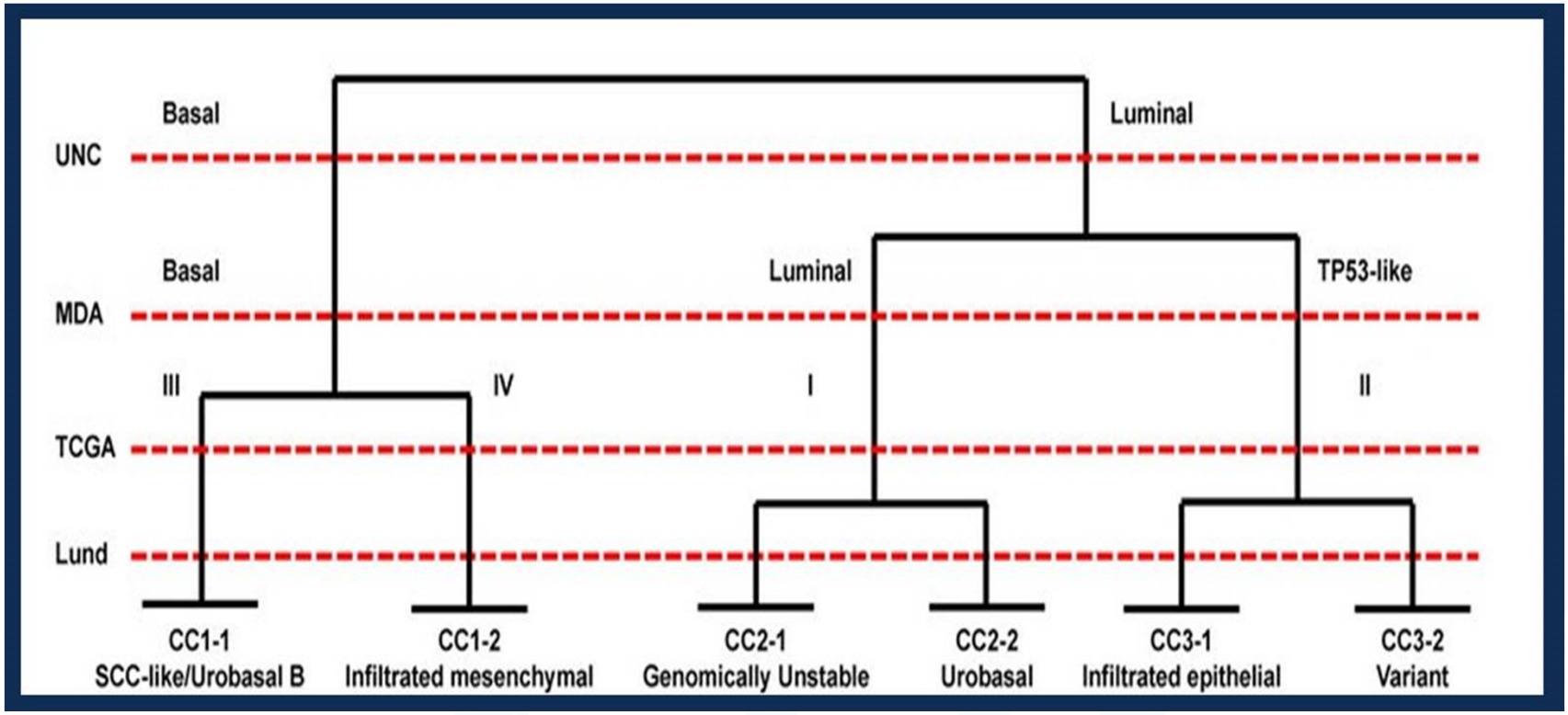
Major overlap between subtypes identified by different groups



Aine et al. Biological determiants of bladder cancer gene expression subtypes. Scientific Reports, 2015

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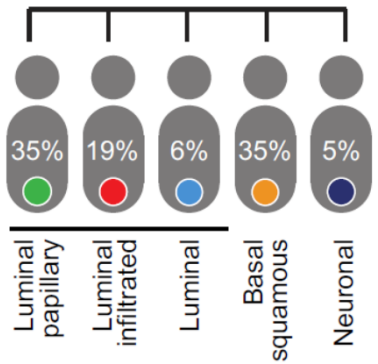

Molecular Characterization

TCGA (n=412)

Luminal
KRT20+, GATA3+, FOXA1+

- **Luminal-papillary**
  - FGFR3 mut, fusion, amp
    Papillary histology
    SHH+
    Low CIS
  - Low risk
    NAC*
    FGFR3 inhibitors
  - * Low likelihood of response based on preliminary data (Seiler *et al.* 2017)
- **Luminal-infiltrated**
  - Low purity
    EMT markers (TWIST1, ZEB1)
    miR-200 family
    Medium CD274 (PD-L1), CTLA-4
    Myofibroblast markers
    'p53-like'
  - Anti-PD-L1, PD-1, CTLA-4
    Cisplatin-based NAC**
  - ** Low response rate
- **Luminal**
  - UPKs
    KRT20
    SNX31
  - Targeted therapy?

Basal/Squamous
KRT5,6,14+, GATA3-, FOXA1-

- **Basal/Squamous**
  - Female
    Squamous differentiation
    Basal keratin markers
    High CD274 (PD-L1), CTLA4
    Immune infiltrates
  - Anti-PD-L1, PD-1, CTLA-4
    Cisplatin-based NAC
- **Neuronal**
  - SOX2
    DLX6
    MSI1
    PLEKHG4B
    E2F3/SOX4 amp
    High cell cycle
  - Etoposide/Cisplatin NAC

Robertson et al. Cell. 2017.

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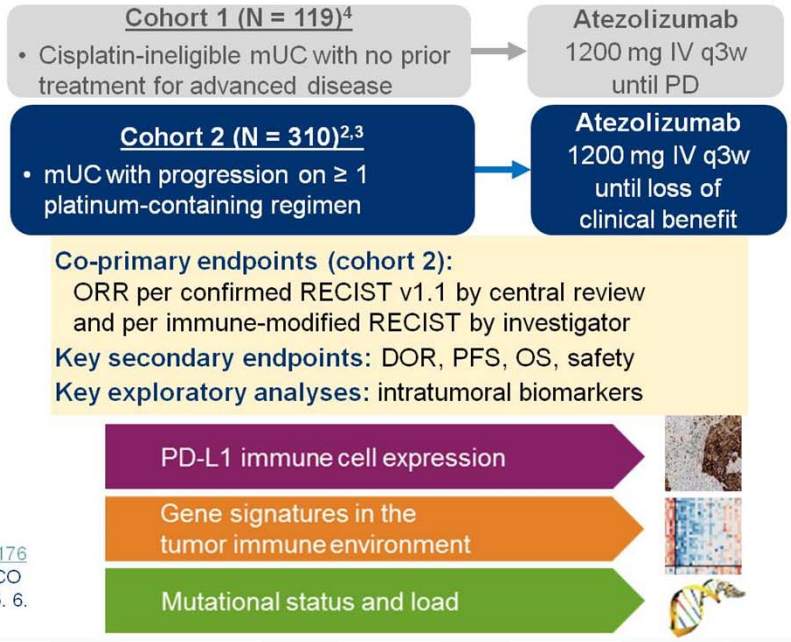
IMvigor210 and biomarkers of Atezolizumab in mUC

- Atezolizumab (anti-PDL1), the first FDA-approved PD-L1 inhibitor,[1] has demonstrated efficacy in mUC,[2,3] a disease with high unmet need
- Clinical benefit with cancer immunotherapy may be associated with biomarkers such as T_{eff} genes and mutation load[4-6]
- Key exploratory objectives of this Phase II study included tumor-associated biomarkers of clinical outcomes



Effector T cell, T_{eff}; PD-L1, programmed death-ligand 1. 1. Press release: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm501762.htm. Trial ID: NCT02108652. 2. Rosenberg *Lancet* 2016. 3. Dreicer ASCO [abstract 4515]. 4. Balar ASCO [abstract LBA4500]. 5. Rizvi *Science* 2015. 6. Van Allen *Science* 2015. 7. Peng *Nature* 2015.

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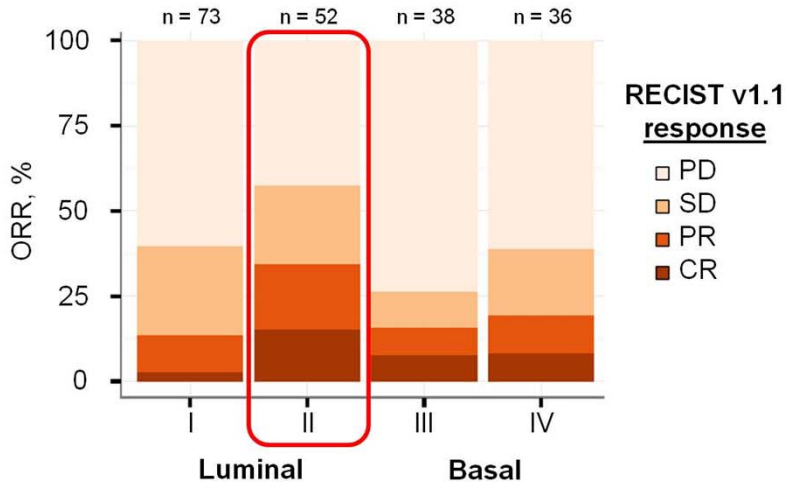
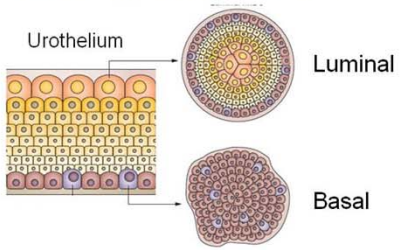
TCGA Subtype II Is Associated With Higher ORR



- Gene expression data used to classify IMvigor210 tumor samples recapitulated TCGA subtypes[1,2]
- Responses occurred in all subtypes, but ORR was significantly higher in luminal II vs other subtypes ($P = 0.0072$)



TCGA, The Cancer Genome Atlas. Data cutoff: March 14, 2016.
1. Cancer Genome Atlas Research Network *Nature* 2014. 2. Rosenberg *Lancet* 2016.

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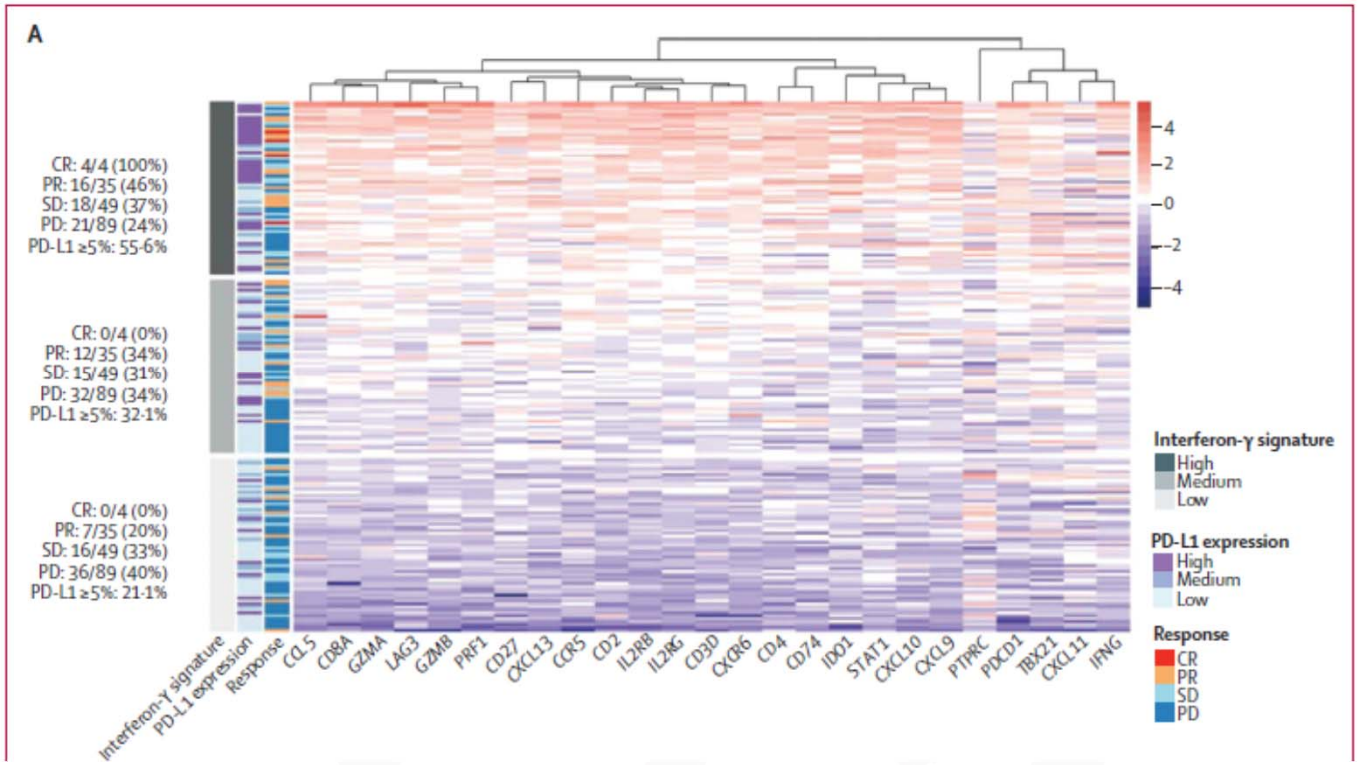
Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial

Padmanee Sharma, Margitta Retz, Arlene Siefker-Radtke, Ari Baron, Andrea Necchi, Jens Bedke, Elizabeth R Plimack, Daniel Vaena, Marc-Oliver Grimm, Sergio Bracarda, José Ángel Arranz, Sumanta Pal, Chikara Ohyama, Abdel Saci, Xiaotao Qu, Alexandre Lambert, Suba Krishnan, Alex Azrilevich, Matthew D Galsky



Higher values of the 25-gene interferon-γ signature were associated with a greater proportion of responders to nivolumab and higher PD-L1 expression

http://dx.doi.org/10.1016/S1470-2045(17)30065-7

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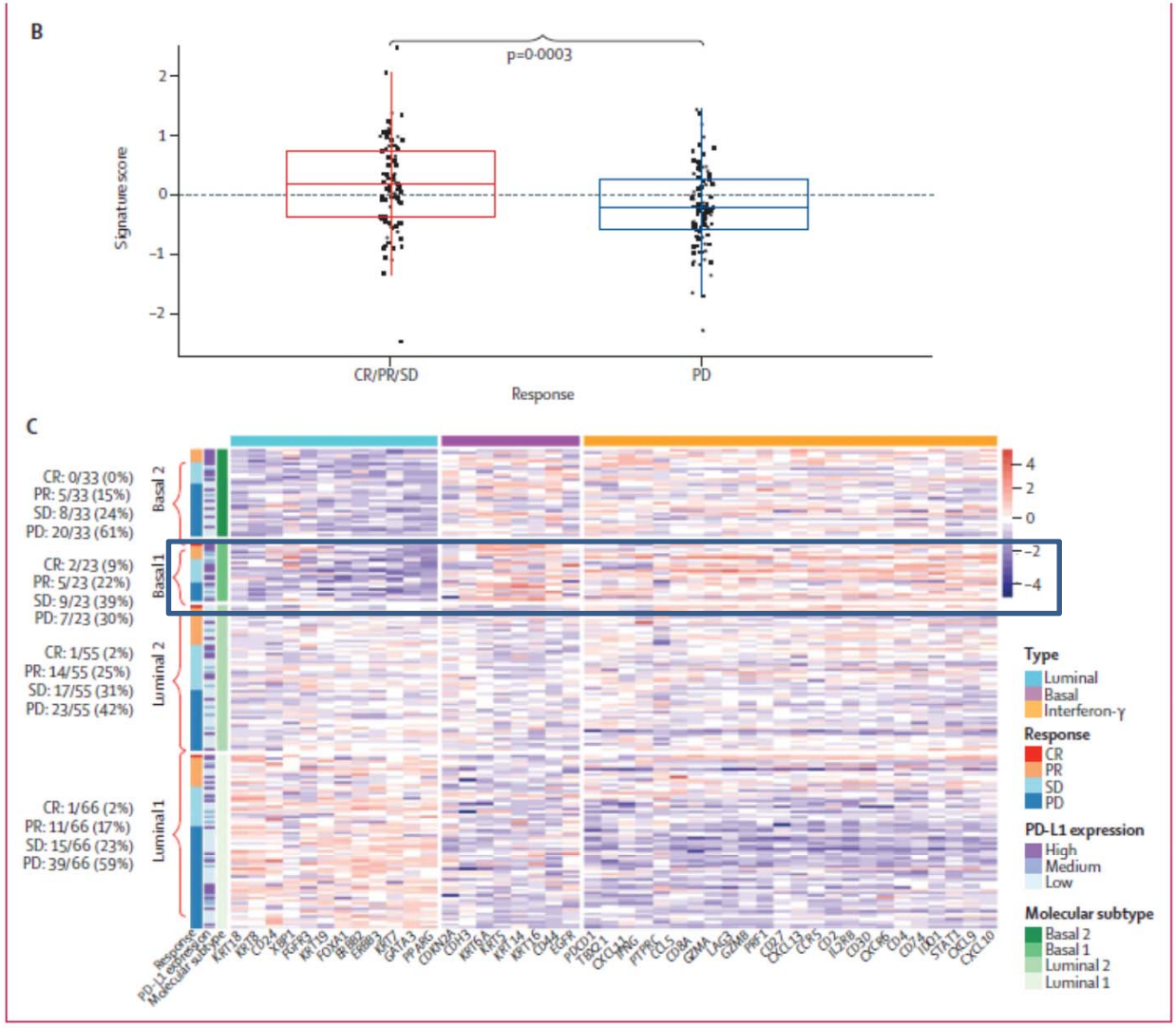

http://dx.doi.org/10.1016/S1470-2045(17)30065-7

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Outline

- Molecular characterization in renal

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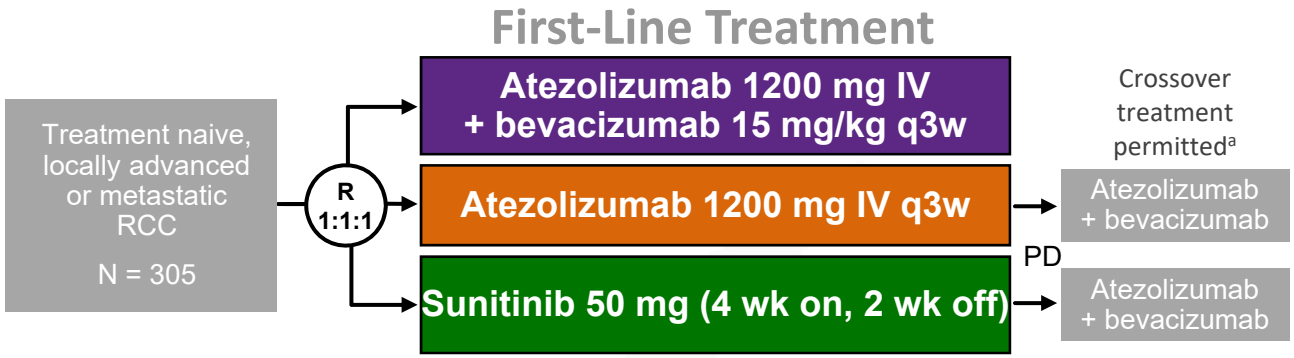
IMmotion150 (Phase II) Trial Design



- **IMmotion150 was designed to be hypothesis generating and inform the Phase III study IMmotion151**
- **Coprimary endpoints were PFS (RECIST v1.1 by IRF) in ITT patients and patients with ≥ 1% of IC expressing PD-L1**
- **Exploratory endpoints included interrogation of the association between outcome and TME gene signatures**

IC, tumor-infiltrating immune cells; IRF, independent review facility; ITT, intention-to-treat; TME, tumor microenvironment.
[a] Crossover from atezolizumab monotherapy not allowed in Europe.
McDermott, *JCO* 2016; McDermott, ASCO GU 2017.

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

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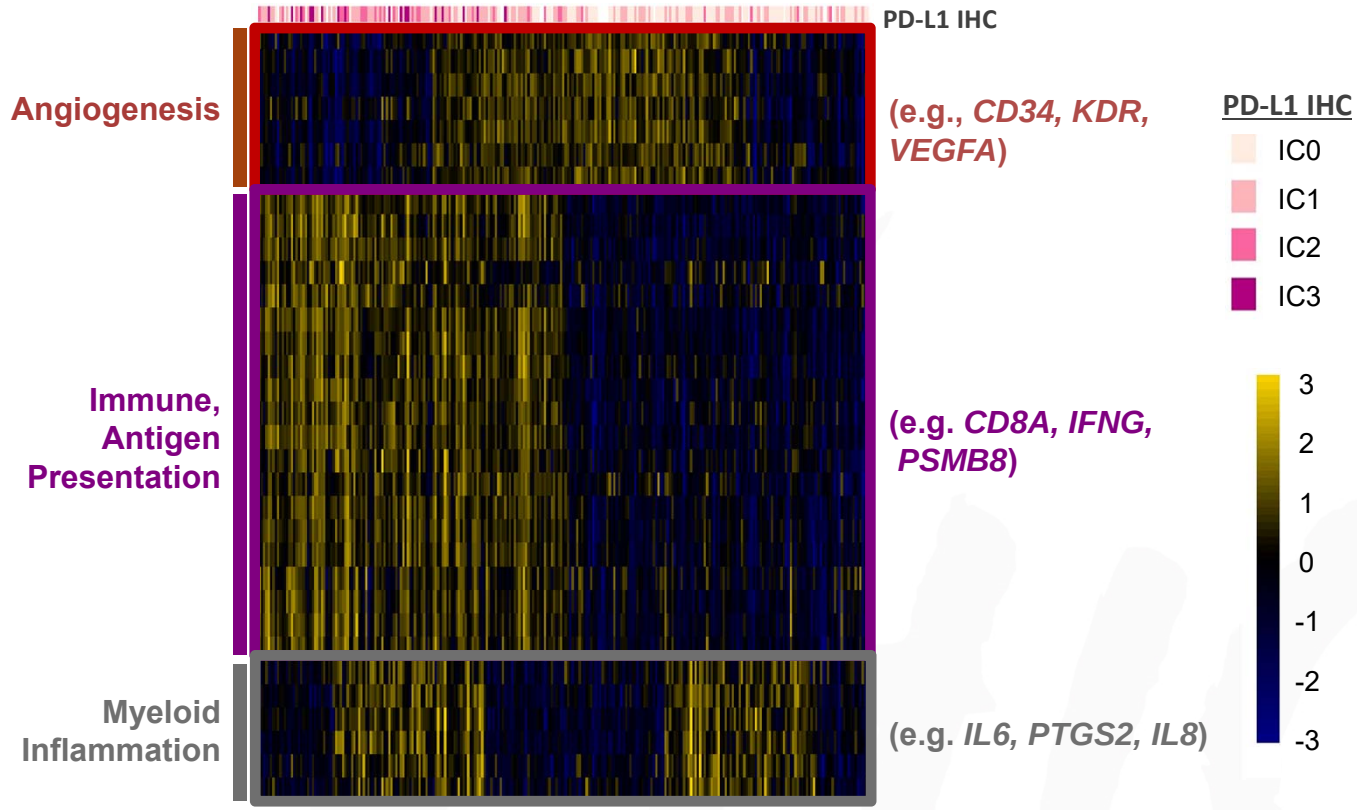
Transcriptome Map of Angiogenesis and Immune-Associated Genes in RCC Tumors



Brauer, Clin Cancer Res. 2012; Herbst, Nature 2014; Powles, SITC 2015; Fehrenbacher, Lancet 2016.

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

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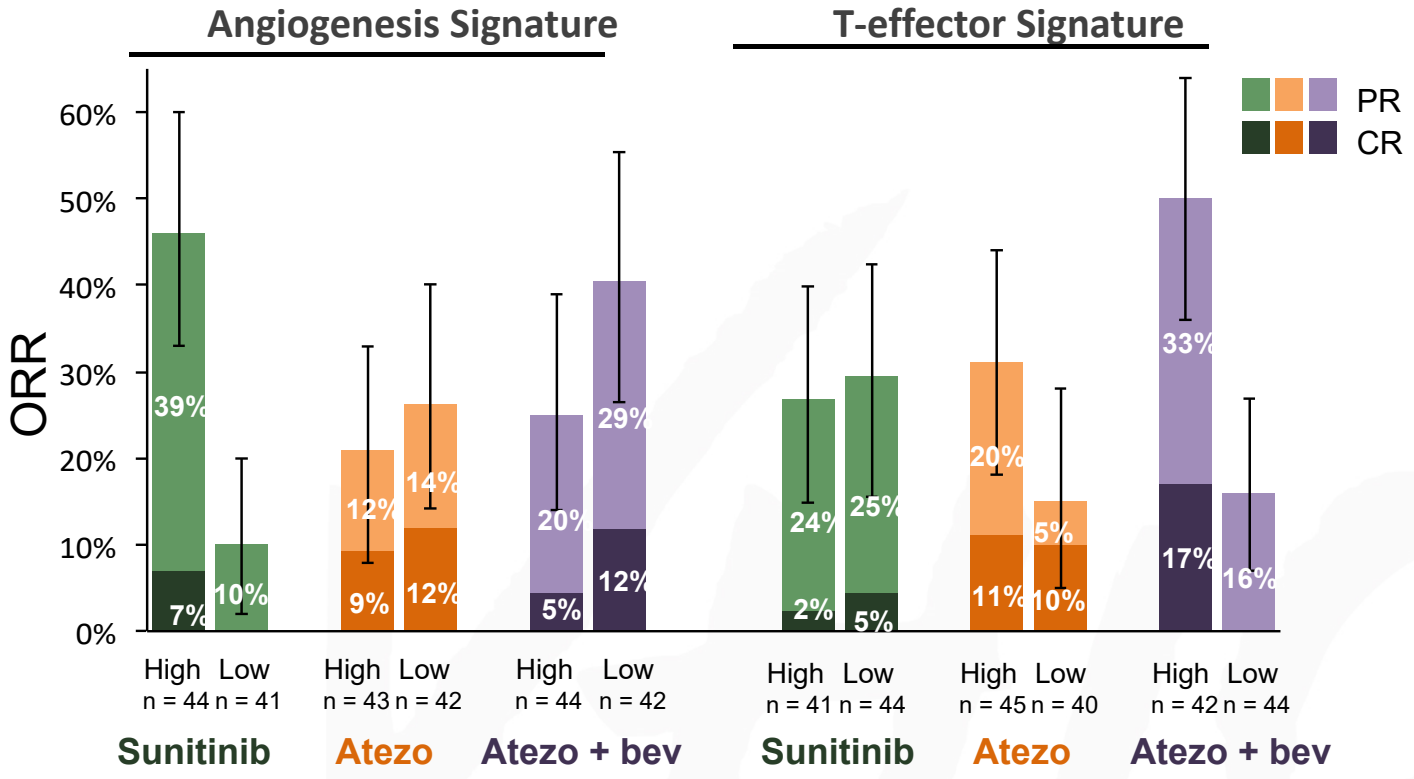
ORR Correlates With PFS in Gene Expression Subgroups



Confirmed IRF-assessed ORR.

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

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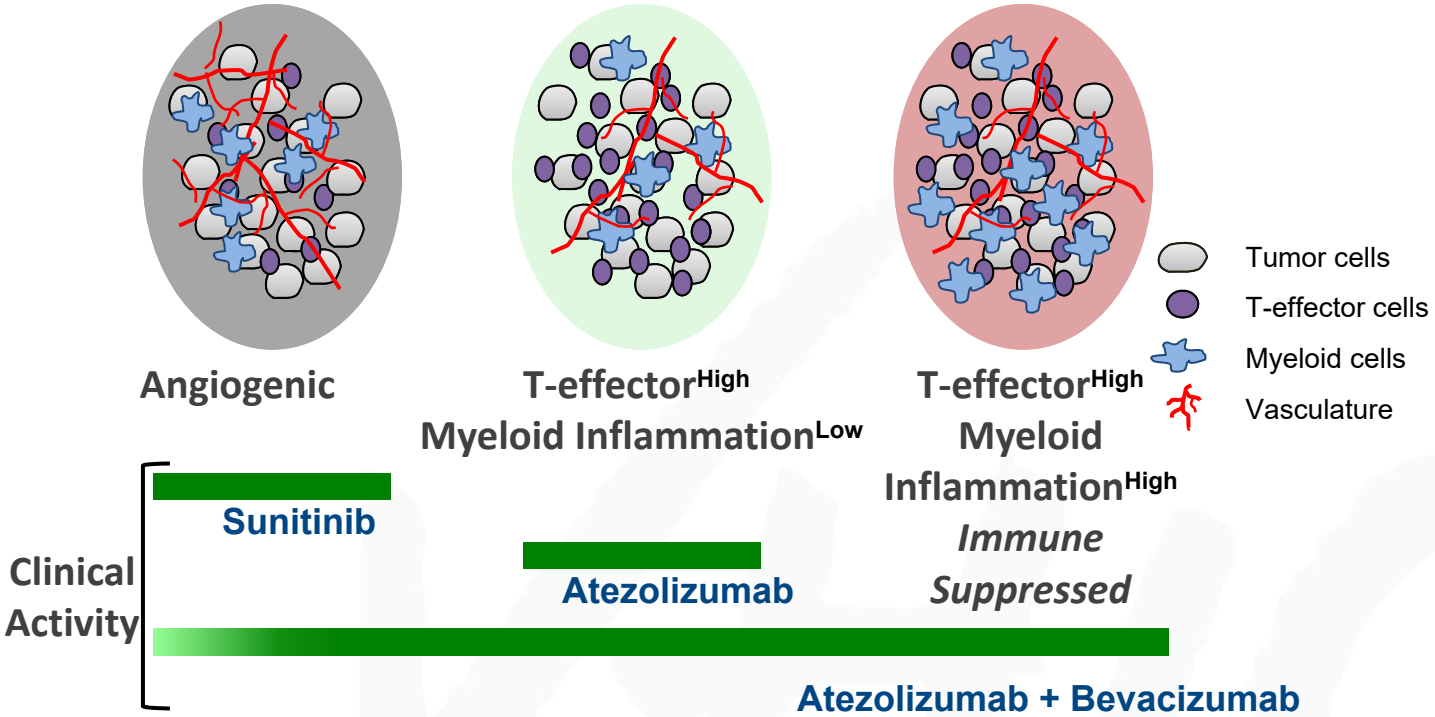
Molecular Correlates of Differential Response to Atezolizumab ± Bevacizumab vs Sunitinib in mRCC



McDermott D, et al. IMmotion150 biomarkers: AACR 2017

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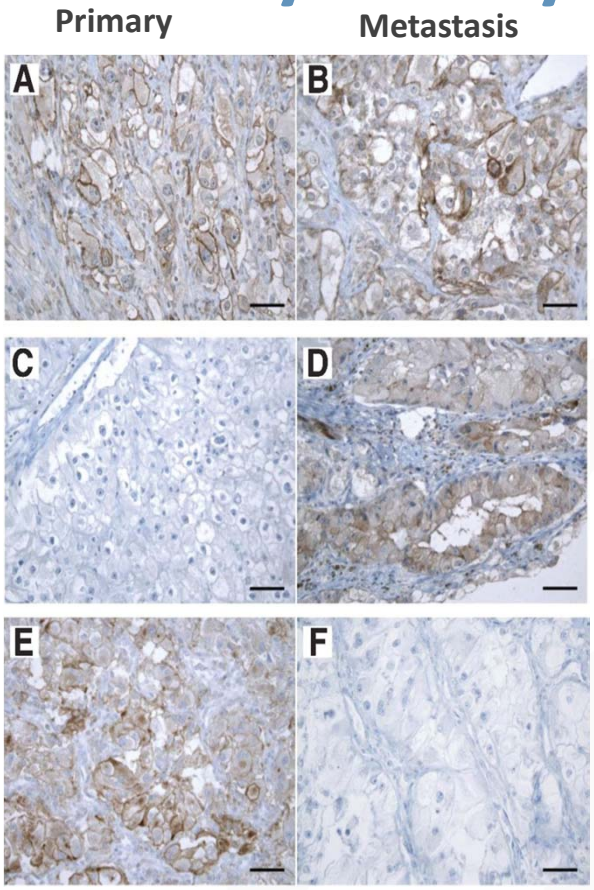
Discordant Tumor Cell PD-L1 Expression Between Primary Kidney Cancer and Mets



- **Discordance** in 21% of cases
- PD-L1 positivity was **heterogeneous** and almost exclusively detected in high nuclear grade areas (*P* <0.001)
- Assessment as a predictive biomarker for PD-1 blockade may require analysis of **metastatic lesions**
- Pathologists should select **high grade tumor areas** for PD-L1 IHC analysis to avoid false negatives

Callea M et al. Cancer Immunol Res. 2015;3:1158-1164.

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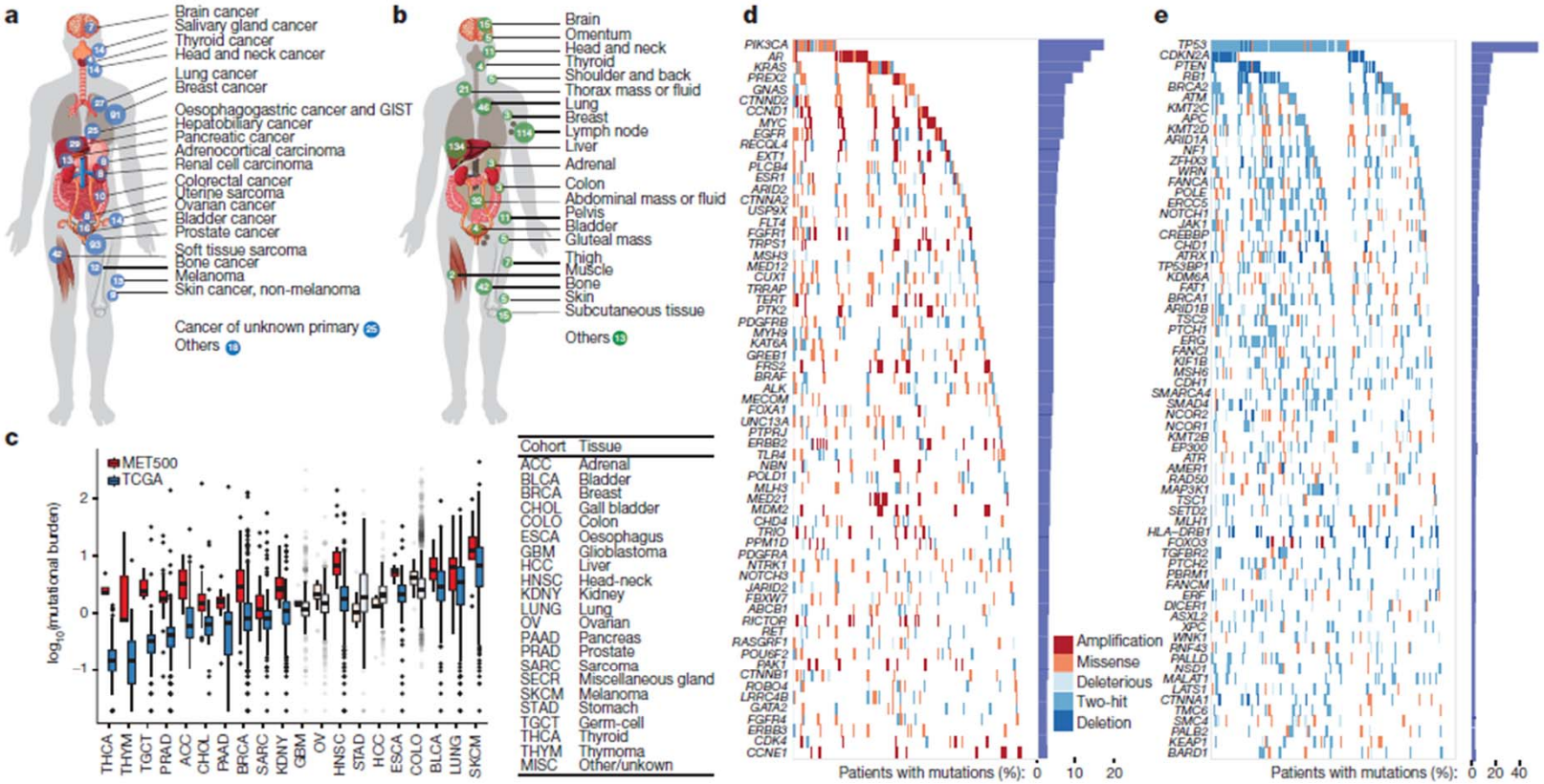
Integrative clinical genomics of metastatic cancer



Robinson et al. Nature 2017;548:297

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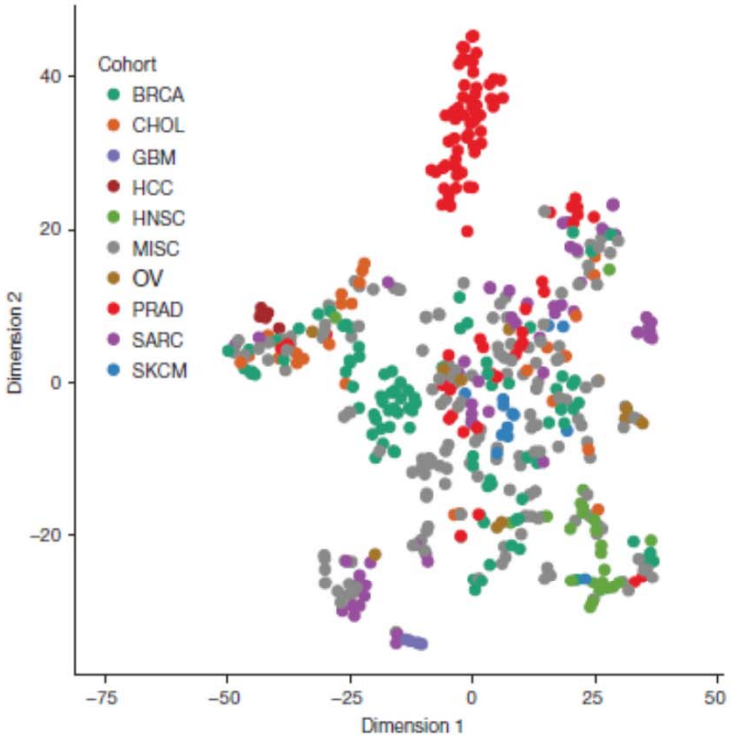
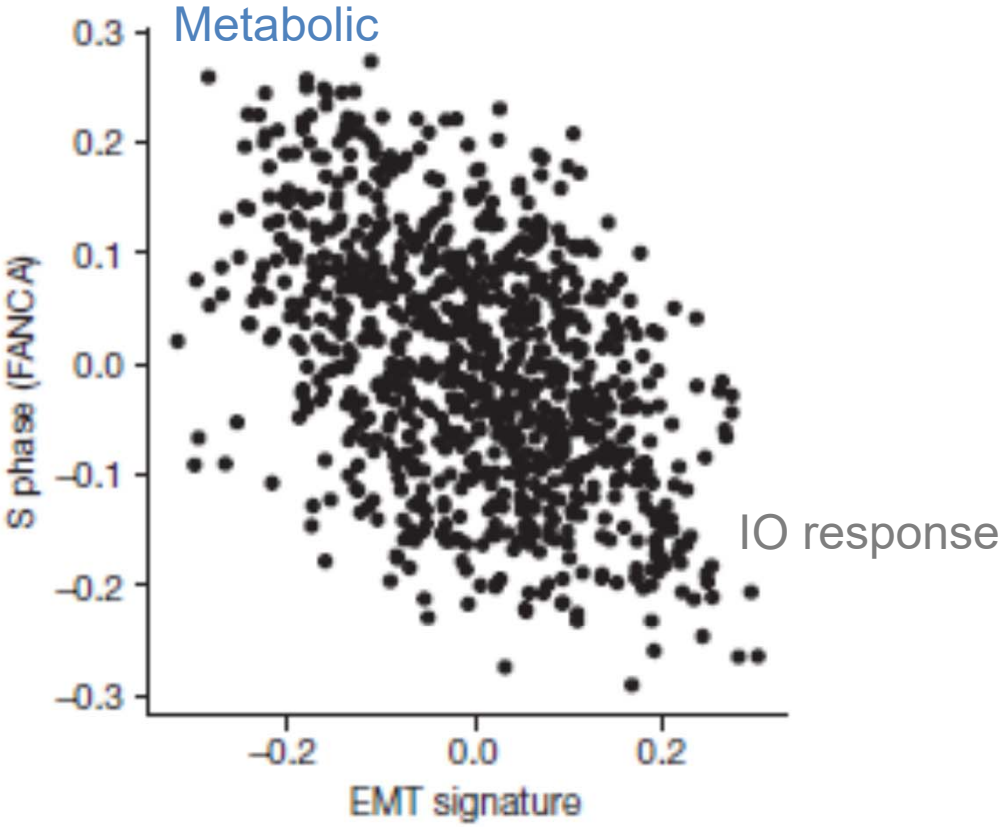
Integrative clinical genomics of metastatic cancer





Robinson et al. Nature 2017;548:297

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Conclusions

- Interrogation of disease biology by whole transcriptome profiling showed distinct biological associations with PFS and OS benefit and may potentially identify patient populations that derive benefit from Immunotherapy
- Data from metastatic cancer expands our understanding of the biology of immune response to different cancers
- We need to develop a signature that could work in most of the tumors to identify those patients who will respond to IO therapy.
- It is important to know which non-genomic features (patient immune system) also contribute to response IO therapy

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Thank you