

Methods to assess and discover biomarkers

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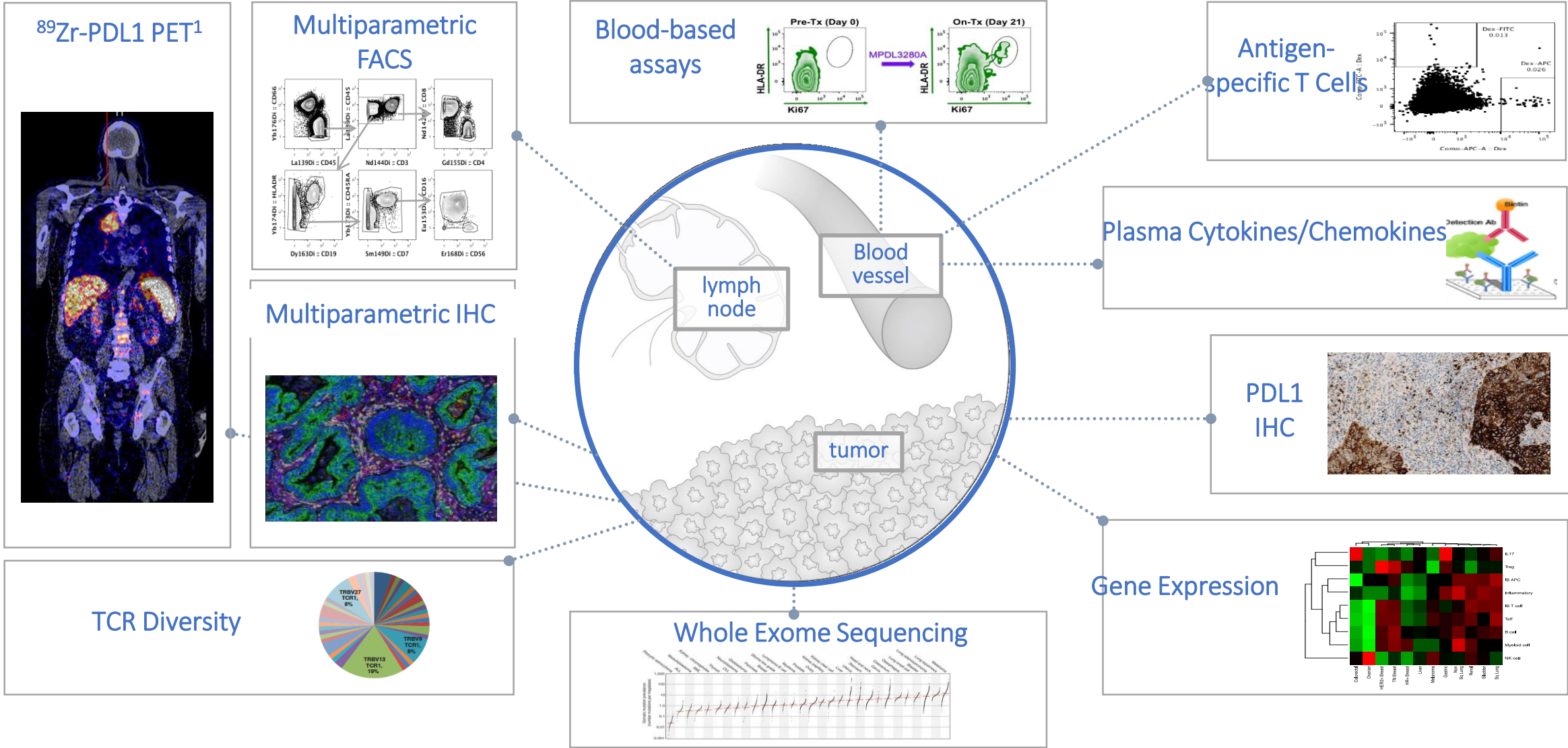
Genentech

SITC Cancer Immunotherapy Winter School

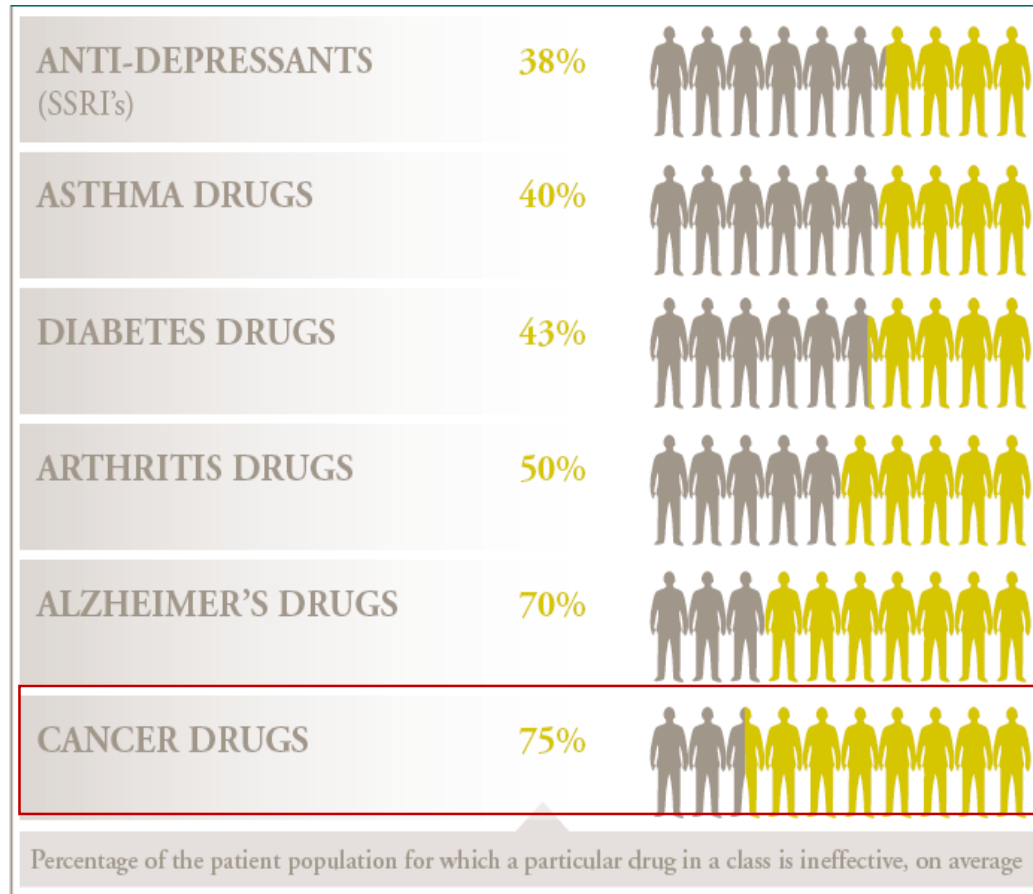
Phoenix, AZ

Feb 18 2019

Comprehensive CIT Biomarker Platform

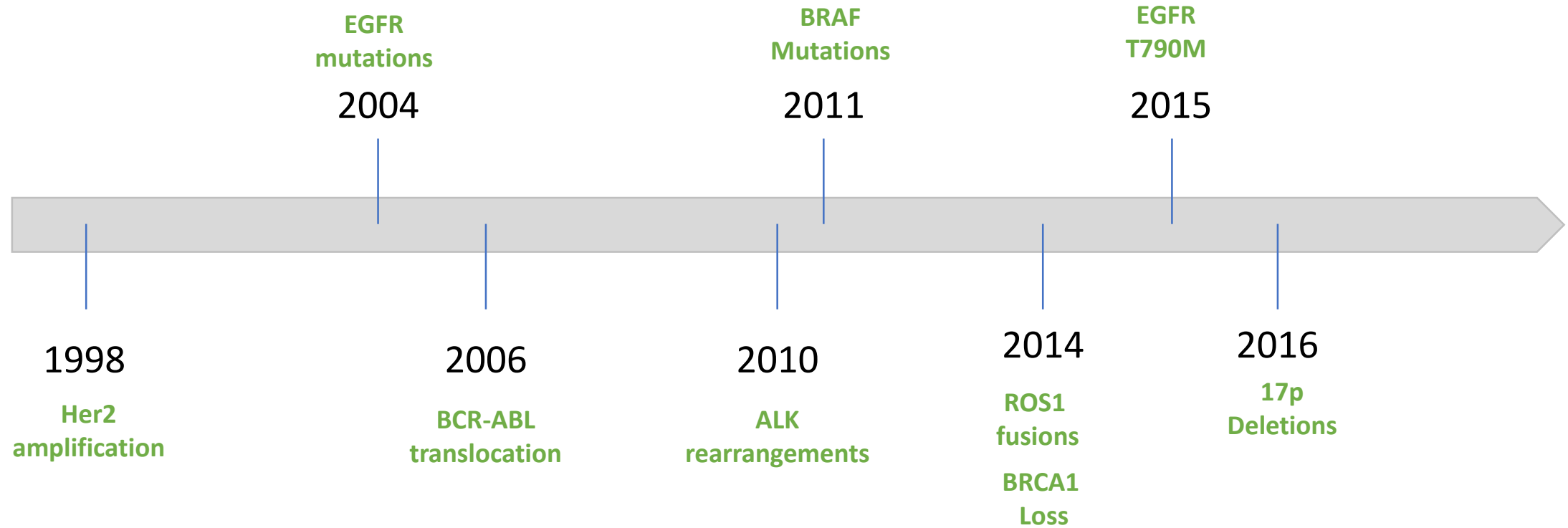


Why are biomarkers important in drug development?



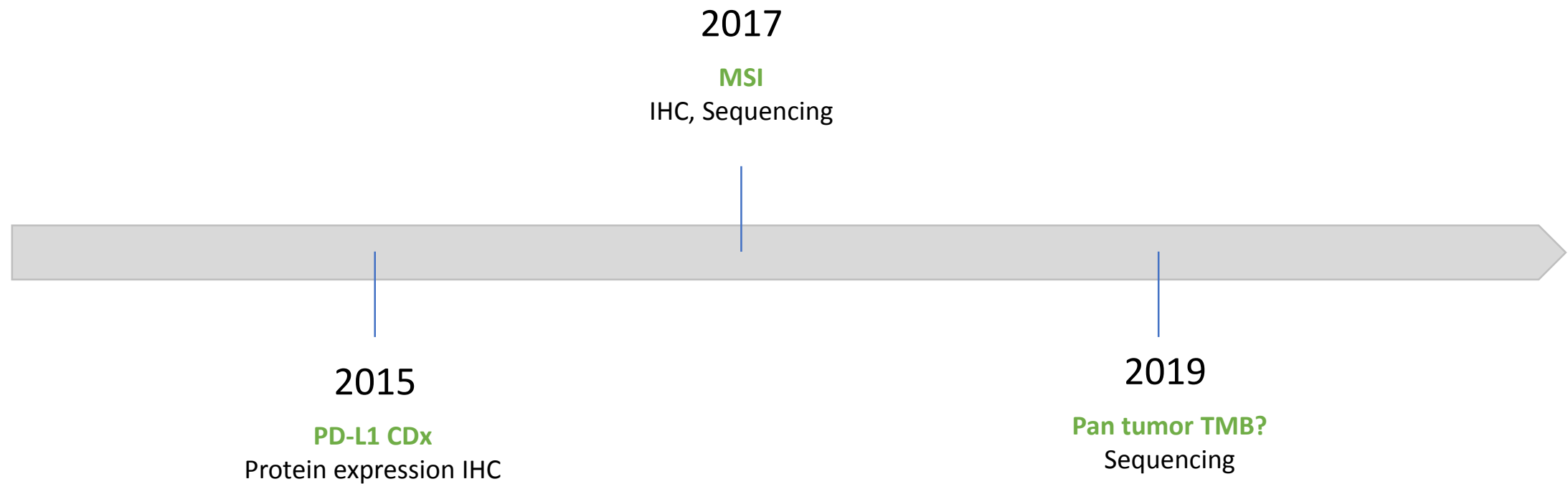
**Cancer patients carry
the highest risk to
undergo an inefficient
treatment**

Most widely used biomarkers in Oncology have been genetic alterations



- These are often driver defects
- Direct measures of the target/pathway
- Simpler to measure (yes/no) and
- Simple to communicate to the practicing community.

Biomarkers in CIT- The issue of the continuous variable



- Often not driver mutations, definitions can differ between drug developer A and B
- May not be direct measures of the target
- Need to interrogate multiple cutoffs before defining the dx
- Not simple to communicate to the practicing community (many predictors for the same drug/s).

Clinically Useful Biomarkers

What Defines a ‘Clinically Useful’ Biomarker?

Robust

Magnitude of effect is sufficiently large that clinical decisions based on the data result in favorable outcomes

Greater chance for benefit

Smaller or similar toxicity risk

Validated

Results are validated in a prospective clinical study

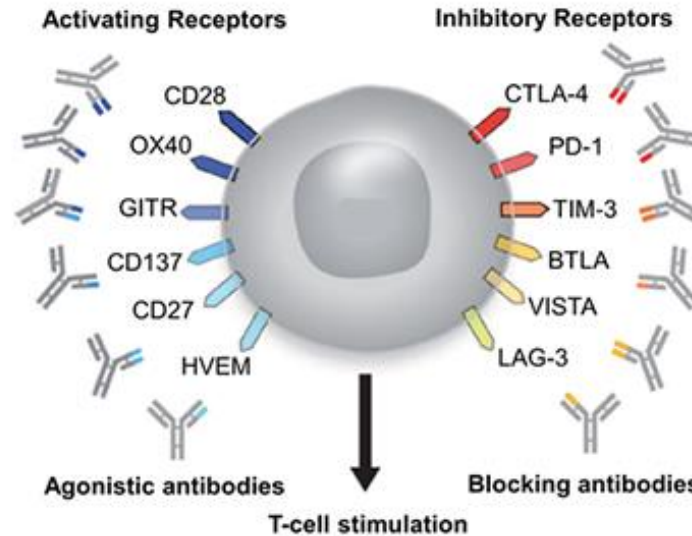
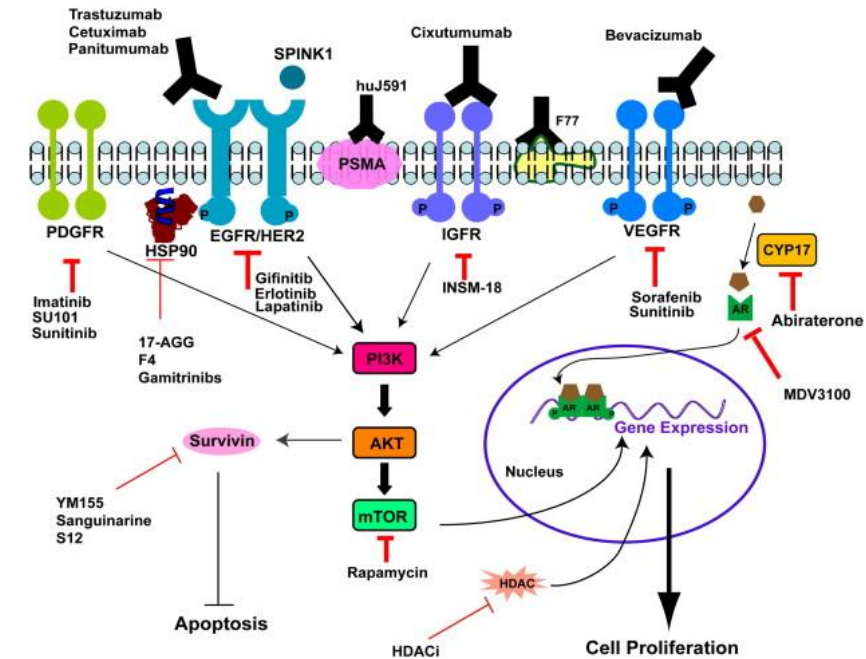
Reliable

Assay results are reproducible

Assay can be run at external labs, hospitals or physicians

Discovery Process

- Most Oncology NMEs are Targeted Agents



Mellman I et al., Nature 2011

- Primary Hypothesis for Target
 - Target Expression
 - Known Mutations

Important considerations in testing a biomarker hypothesis in the clinic

Biomarker prevalence

Dictates size of the trial/speed of enrollment

Biomarker stability

Between archival and pre-tx timepoint

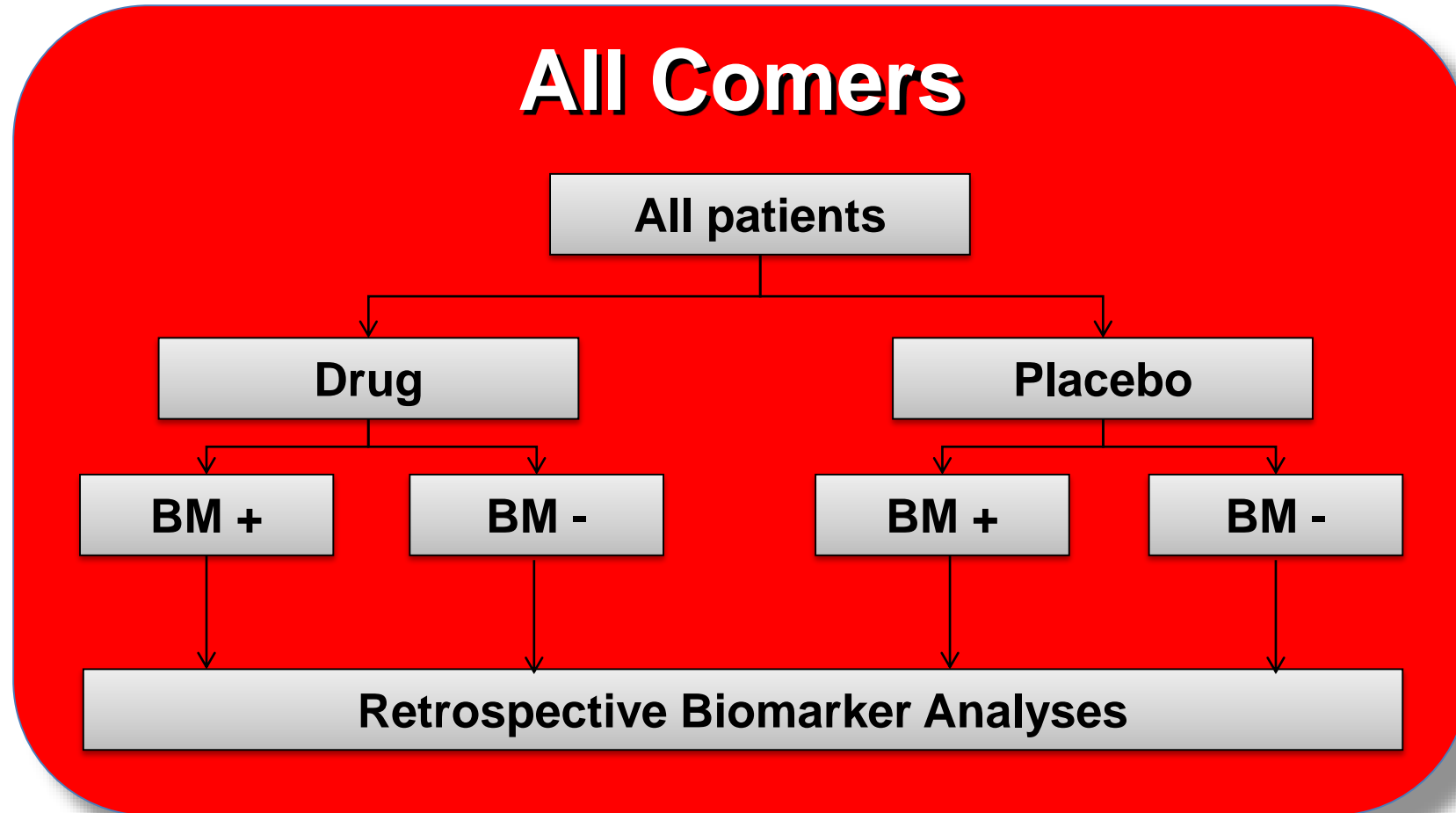
Prognostic association

Is it good prognostic? (impacts statistical considerations of trial)

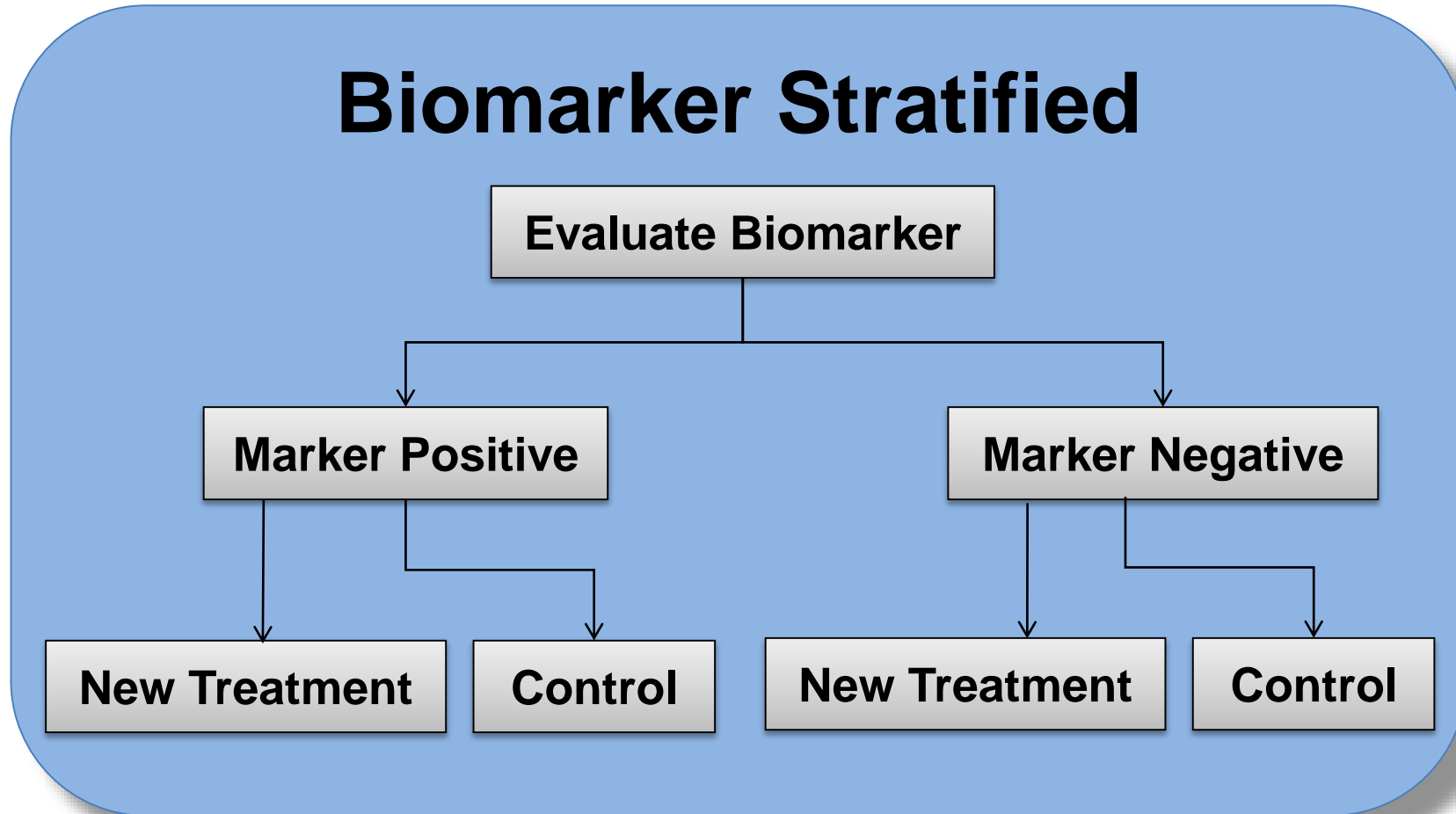
Is it poor prognostic? (events may come in earlier)

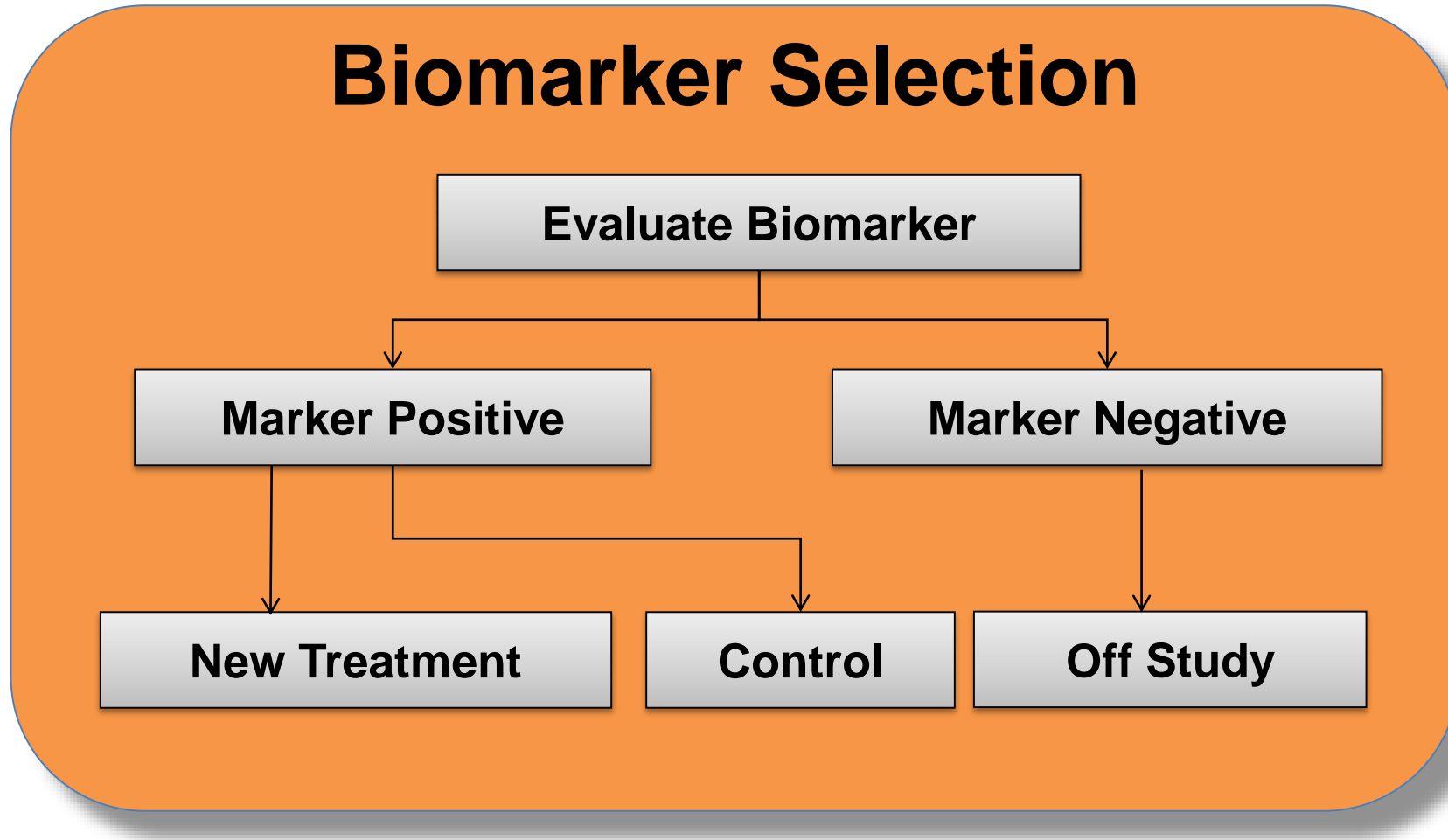
PD-L1 Expression Cut-off	Prevalence
IC \geq 1%	~50%
IC \geq 5%	19-43%
IC \geq 10%*	9-30%

Biomarker Trial Designs



Trial Designs – Biomarker Stratified





Methods to assess Pharmacodynamic Biomarkers



Murine syngeneic models

Well suited to understand general MoA

Confirm if target expression in preclinical model is similar to human disease

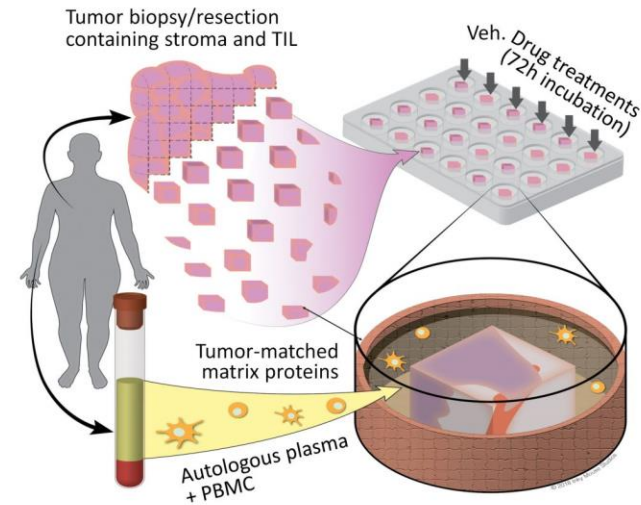
Confirm if cell type being explored is similarly translatable to human disease

Human tumor explant models

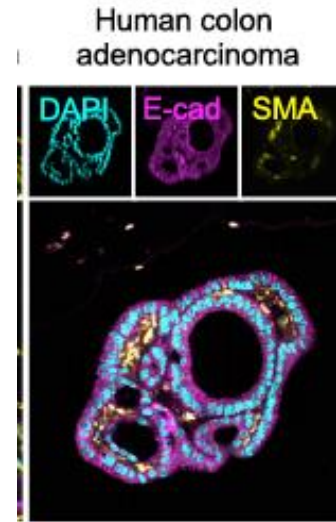
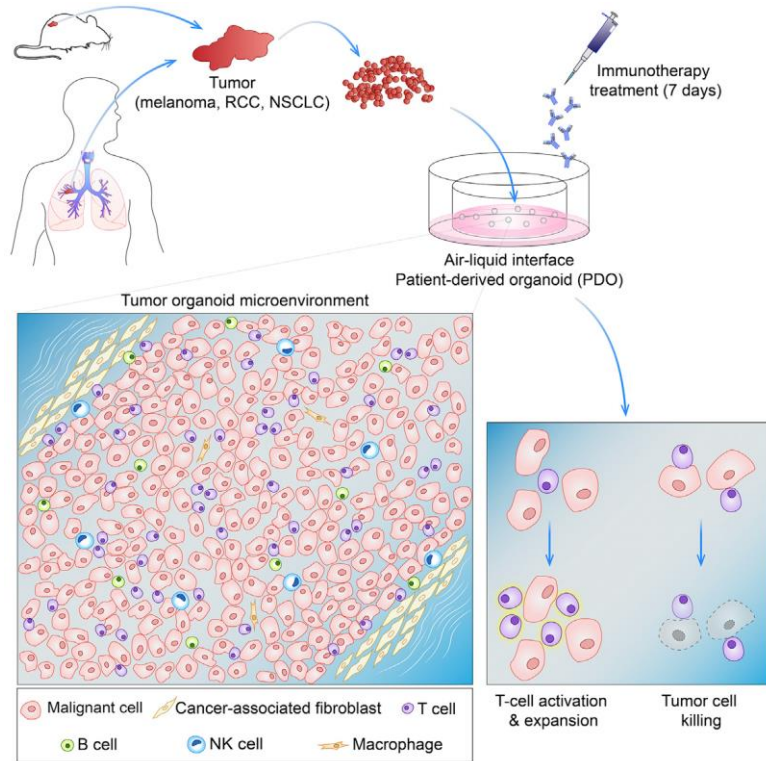
Well suited to study MoA

TME similar to human disease

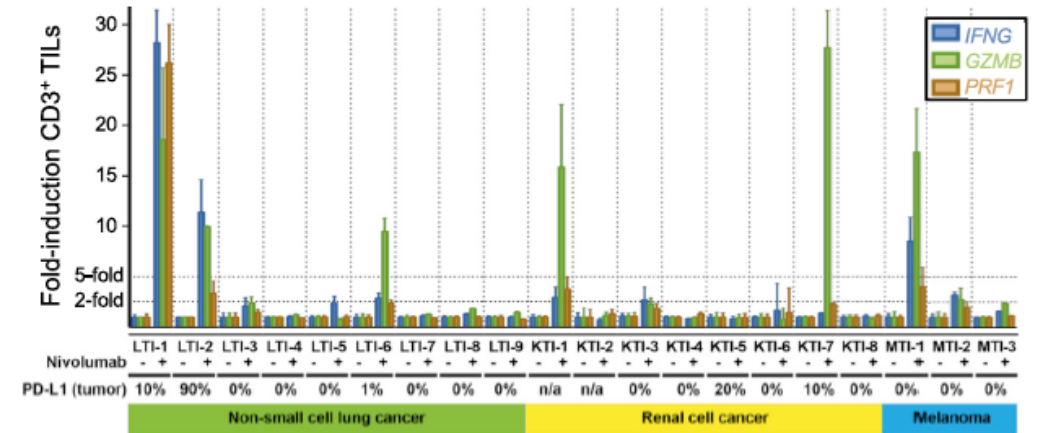
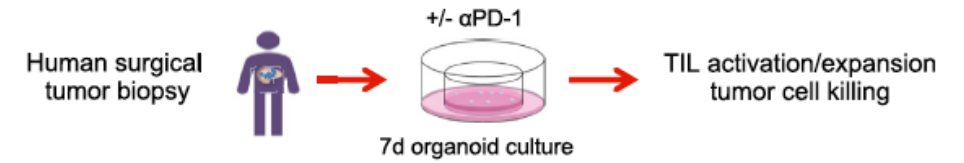
Ability to immunophenotype cells upon treatment



Human tumor organoid models



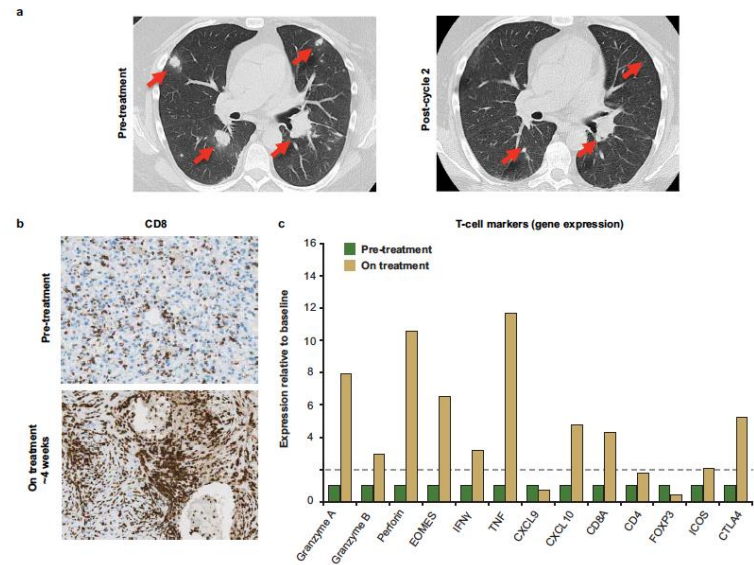
Method preserves diversity of cell types/general architecture



TILs functionally exhibit activation, expansion and cytotoxic response to PD-1/PD-L1 inhibition

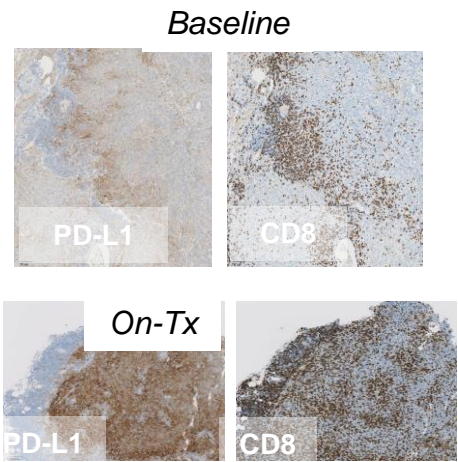
Assessment of human tumor microenvironment upon checkpoint inhibition

Increased infiltration of activated intra-tumoral T-cells In biopsies upon treatment with a CPI



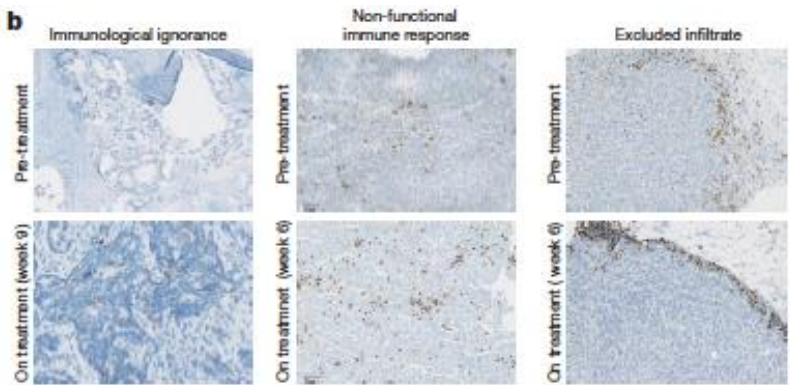
Herbst R et al., Nature 2014

Infiltration of T-cells, IFN γ sig, adaptive increase in PD-L1



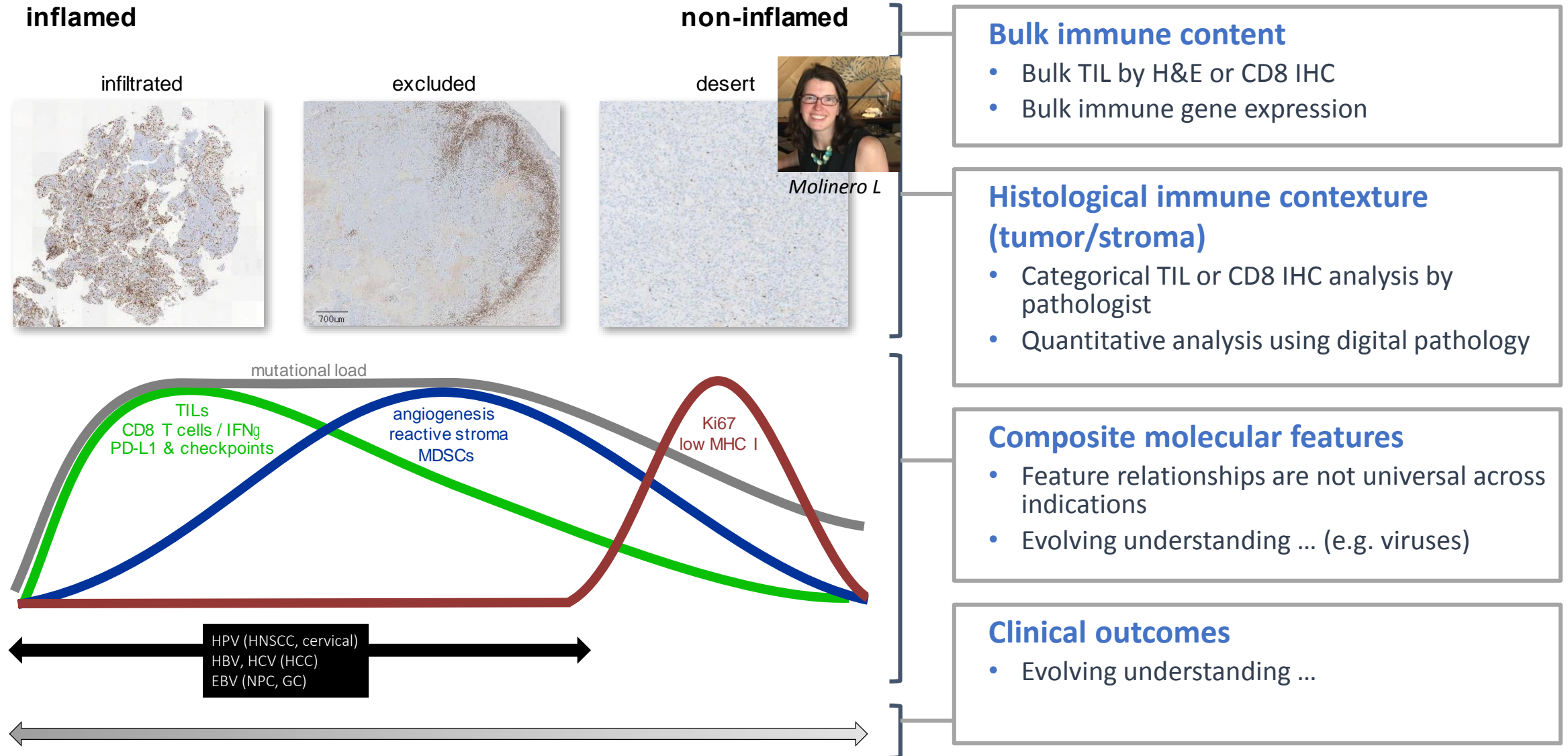
Powderly et al. MPDL3280A Anti-PDL1 Phase I ASCO 2013

Three distinct patterns of T-cell infiltrates in tumors

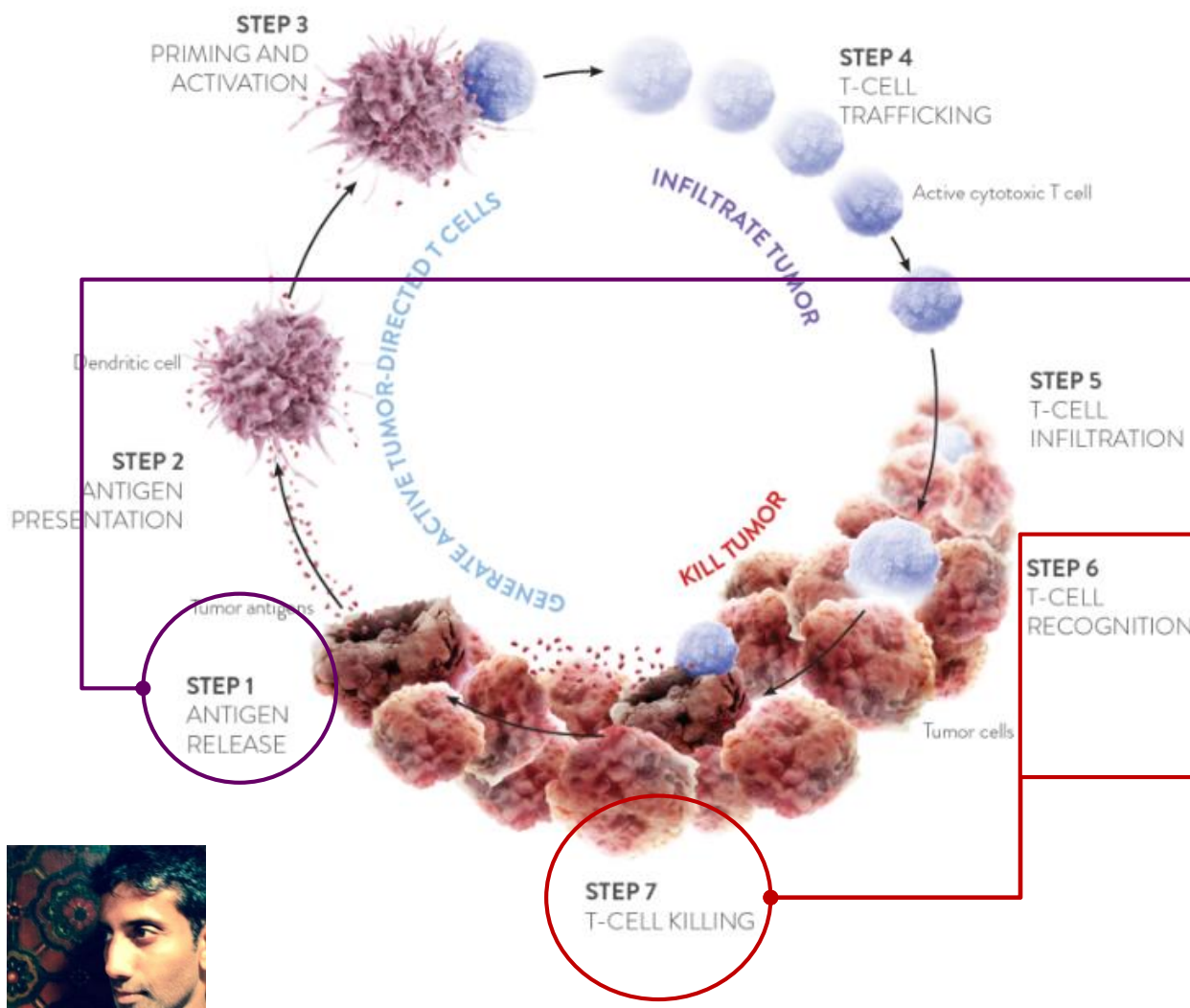


What defines a tumor immune phenotype?

Complexity of underlying biology means answer has multiple layers




An integrated pre-treatment tumor biomarker analysis to determine drivers of efficacy and resistance to atezolizumab in mUC



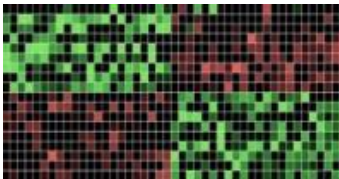
Integrated tumor biomarker analysis

IMvigor210 (Phase 2 trial): samples n = 326 for one or more of these assays

DNA alternations, Mutational Burden (FMOne)




RNA expression




gene signatures

PD-L1 IHC

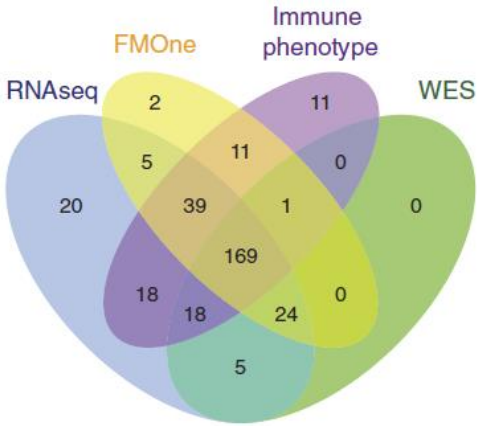


CD8 IHC: CIT phenotypes

Inflamed Excluded infiltrate Immune desert



Anti-CD8

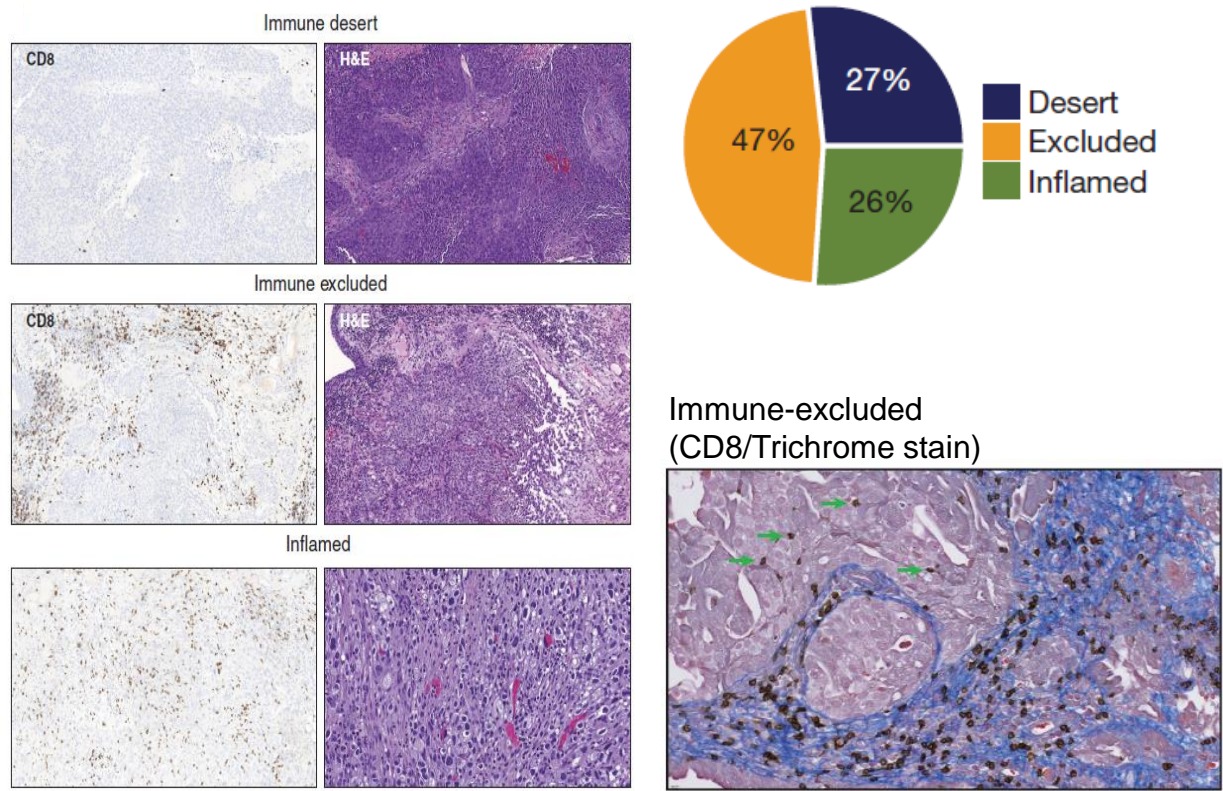


Mariathasan et al, 2018 *Nature*

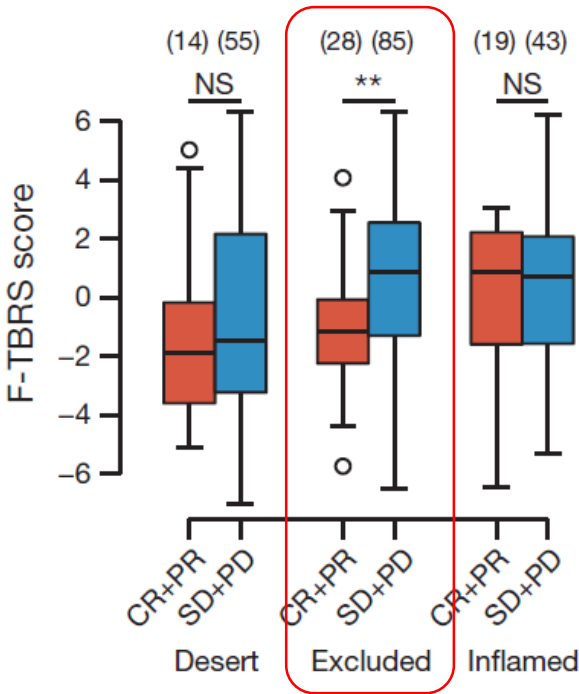


Sanj M.

Bladder cancers are enriched for “immune excluded” tumors where extent of TGFβ signaling influences responses to atezolizumab

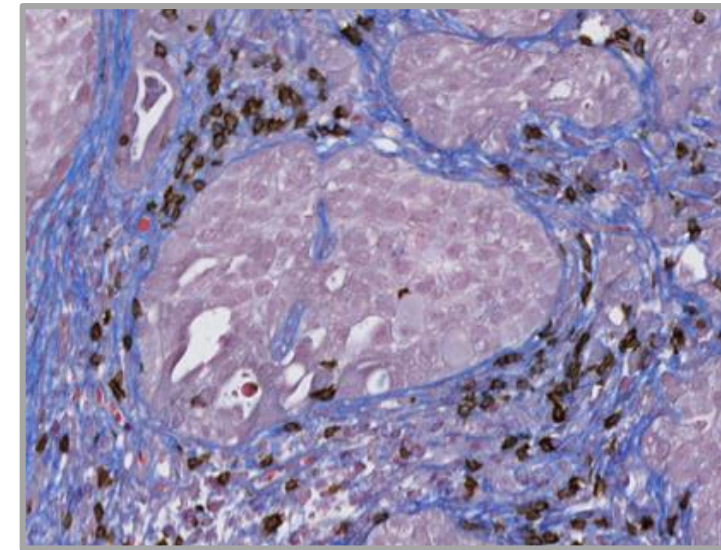
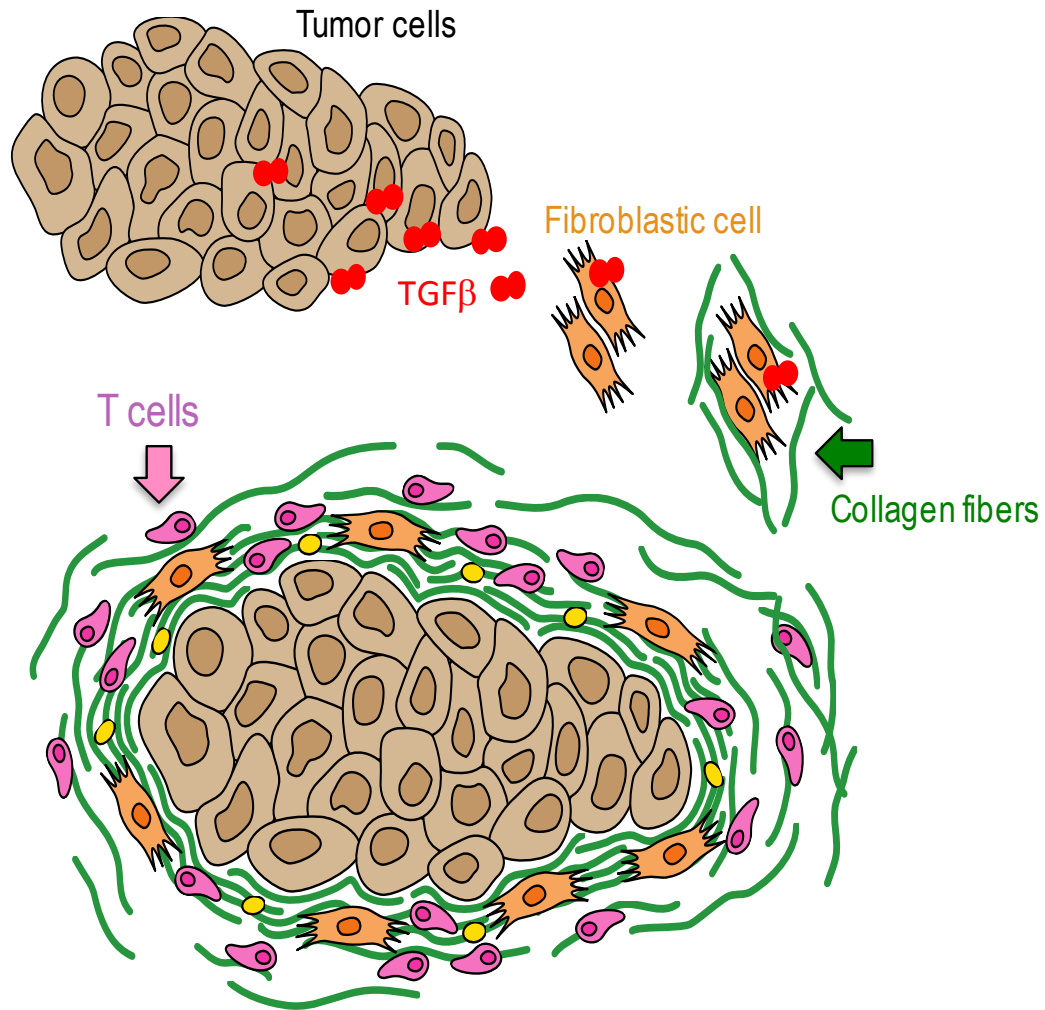


TGF- β pathway associated with PD in excluded tumors



19 gene Pan-fibroblast TGFβ response signature

One of TGF β 's functions is to trigger the formation of collagen fibers that can trap T cells

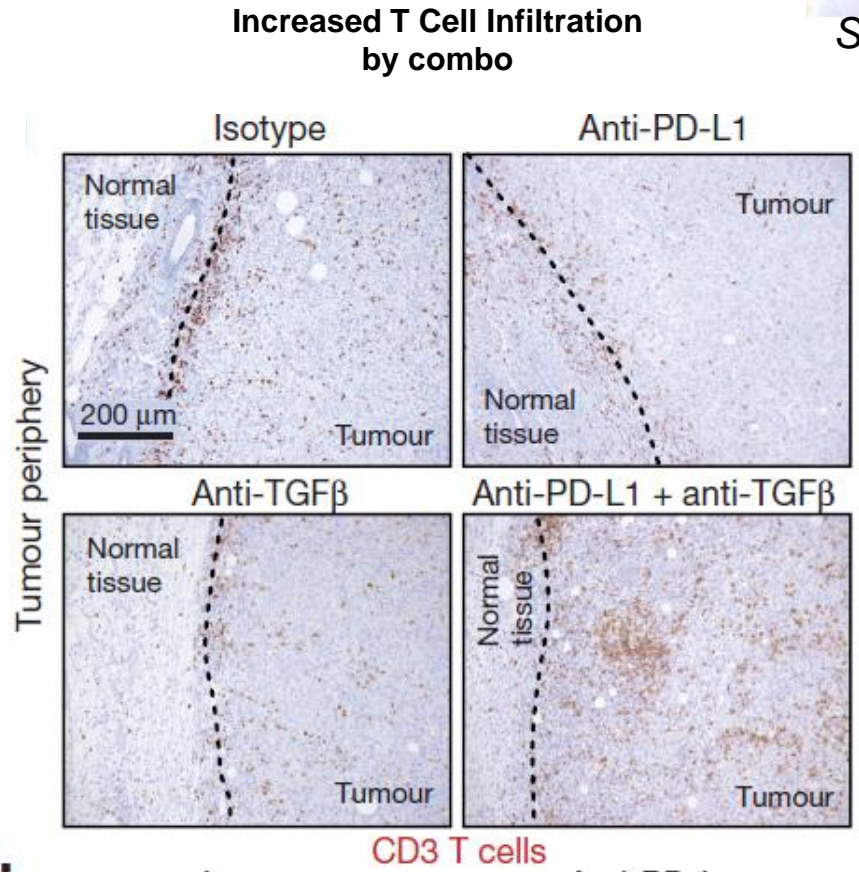
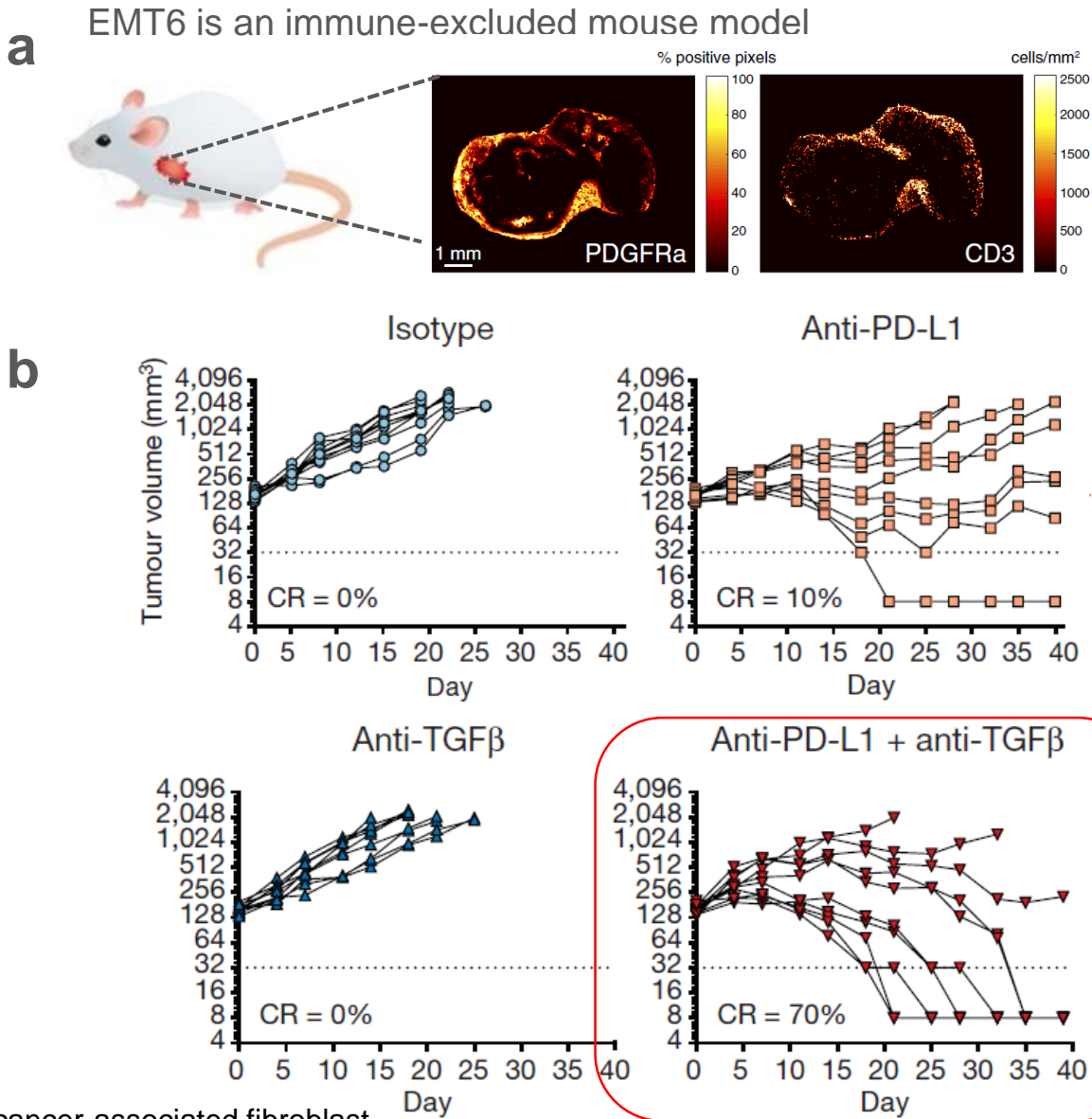


Bladder “excluded” phenotype: CD8/Collagen

Therapeutic administration of anti-TGFβ with anti-PD-L1 promotes T cell infiltration, CAF remodeling leading to complete responses in mice

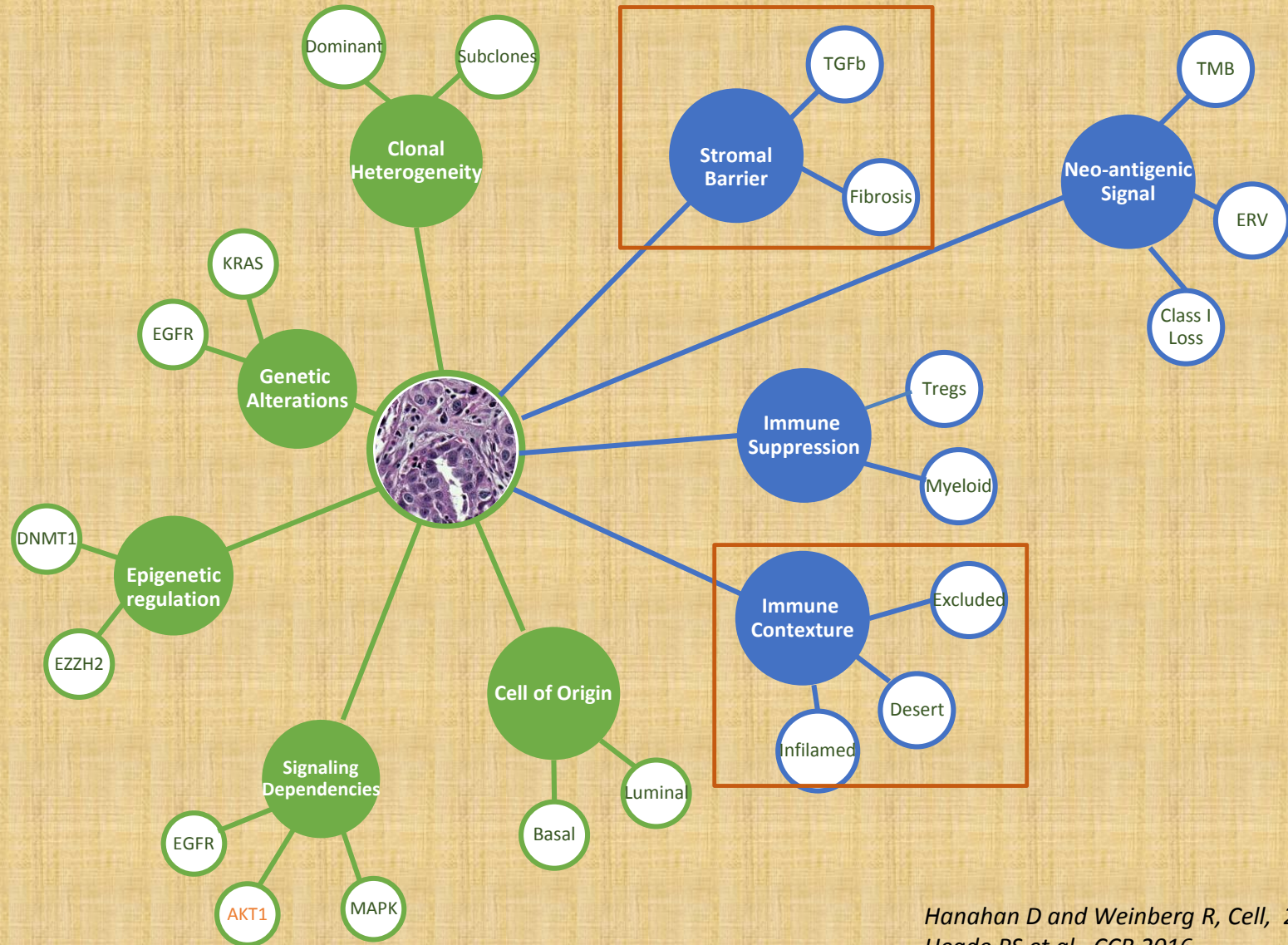


Shannon T.



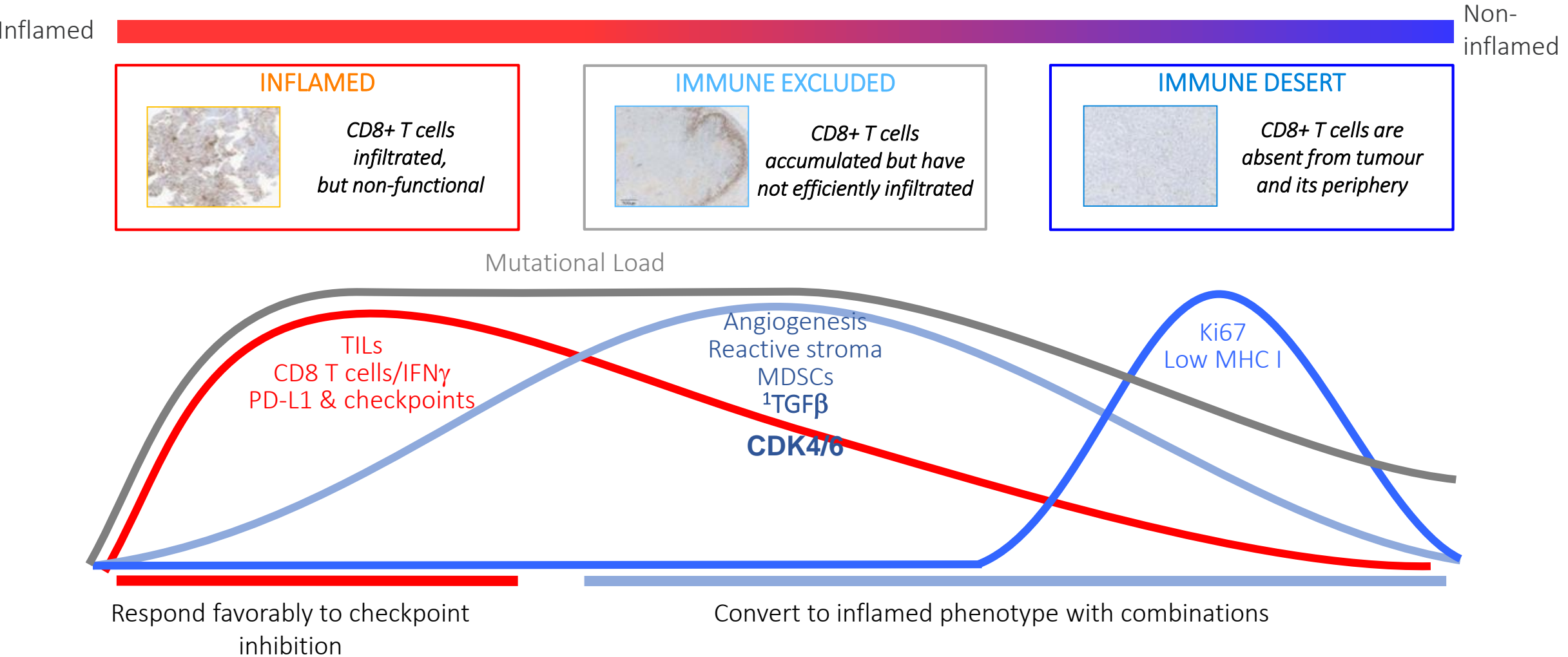
Cancer is a heterogenous disease

Treatment options need to account for heterogeneity



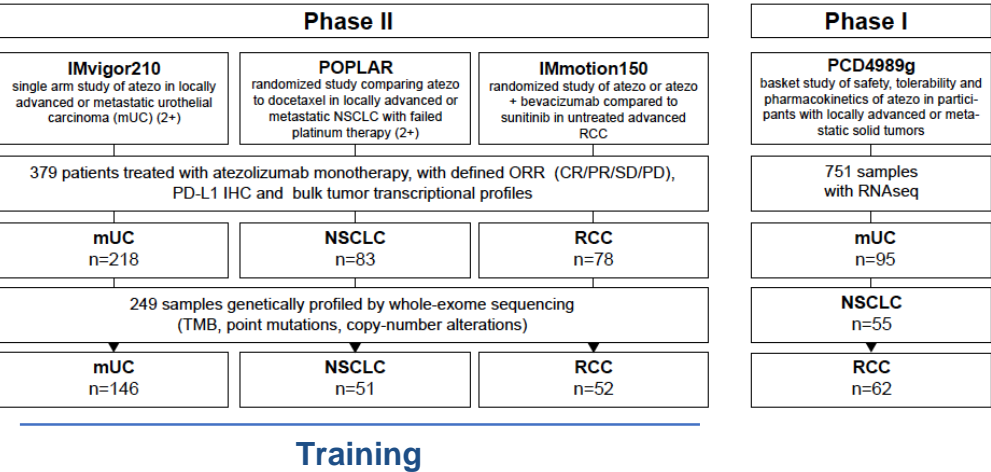
Hanahan D and Weinberg R, *Cell*, 2011
Hegde PS et al., *CCR* 2016
Chen D and Mellman I, *Nature* 2017

CDK4/6 contributes to immune escape

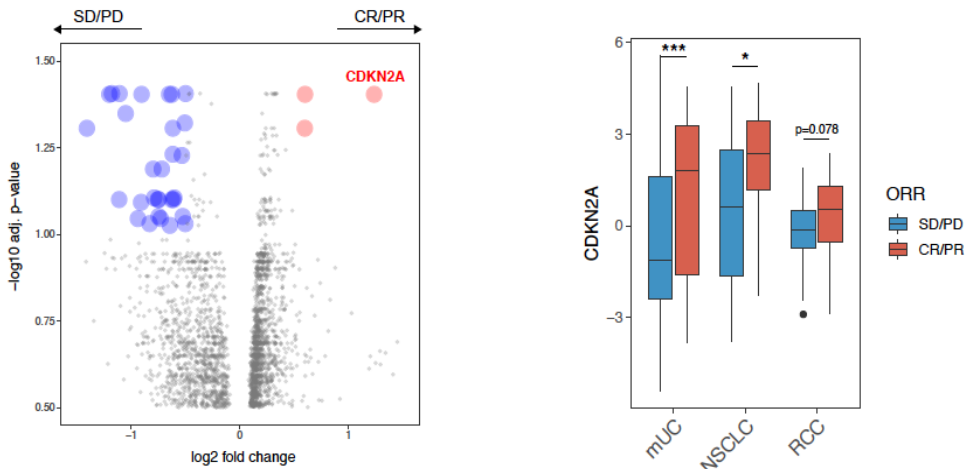


CDKN2A a marker of response to CPI

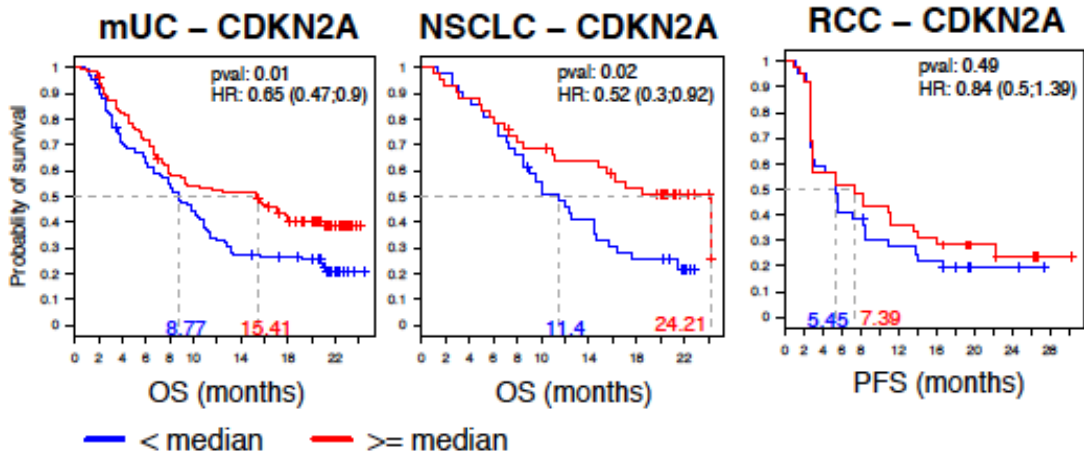
Pan tumor markers of response to Atezolizumab
(WES, RNAseq, CD8 IHC, PD-L1 IHC) N>400 patients



CDKN2A transcript strongly correlates with response to CPI



A trend toward increased efficacy in patients with no deletions in CDKN2A



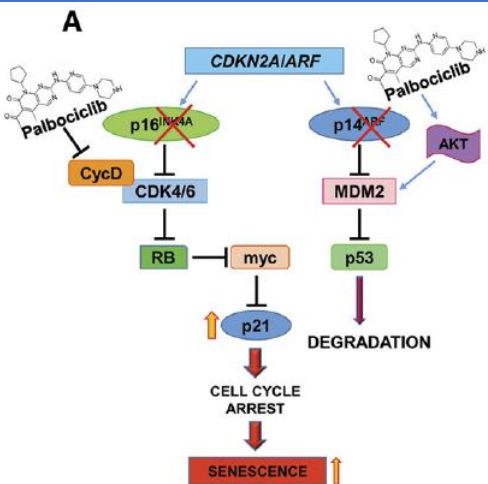
Romain B



Sanj M

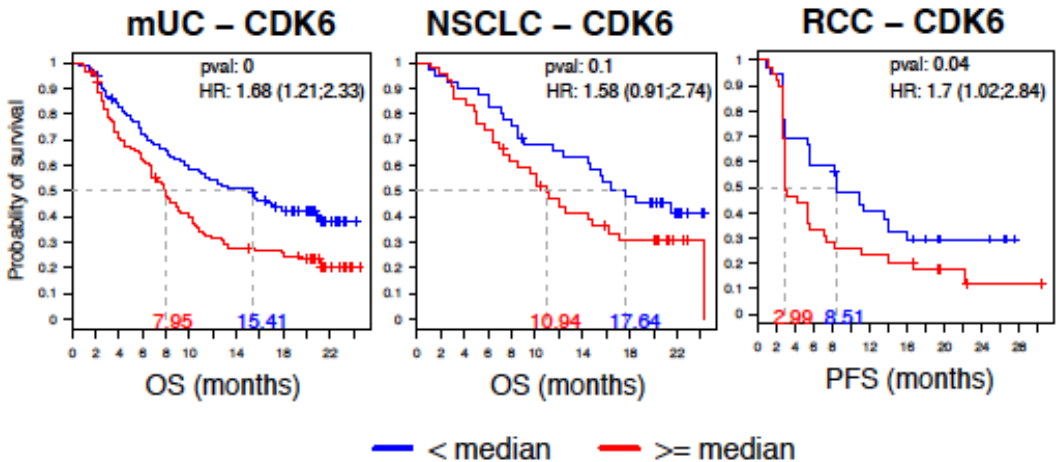
CDK4/6- a potential mechanism of escape

CDKN2A blocks CDK4/6 complexes

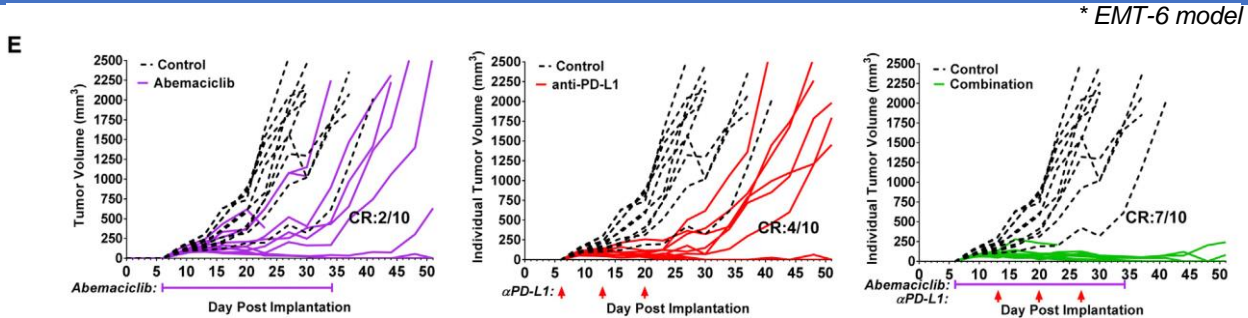


Boneli M et al., Neoplasia, 2017

High expression of CDK6 is associated with poor OS to atezolizumab



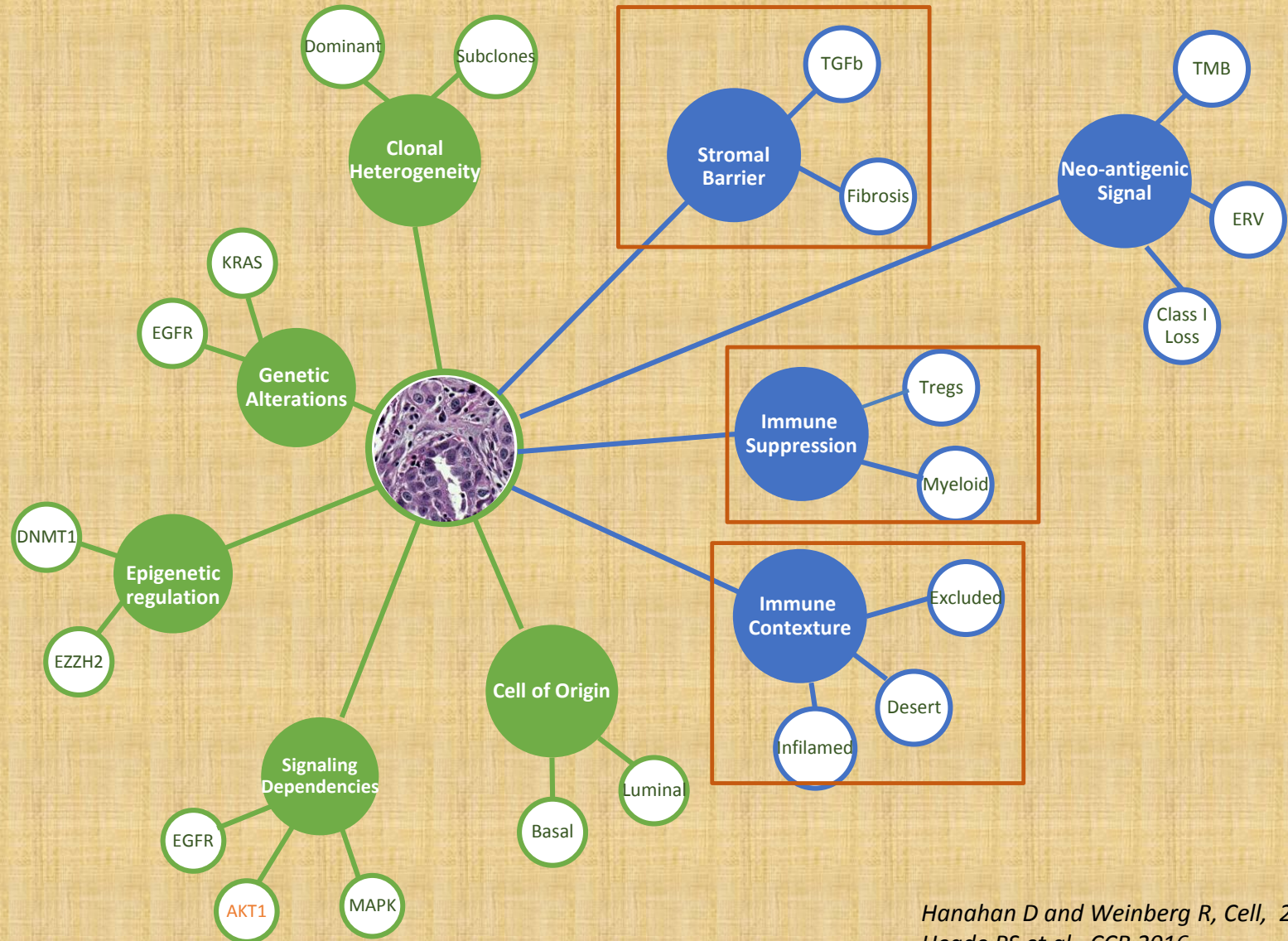
Continuous administration of Abemaciclib during phased treatment with aPD-L1



Schaer DA, et al., Cell Reports 2018

Cancer is a heterogenous disease

Treatment options need to account for heterogeneity



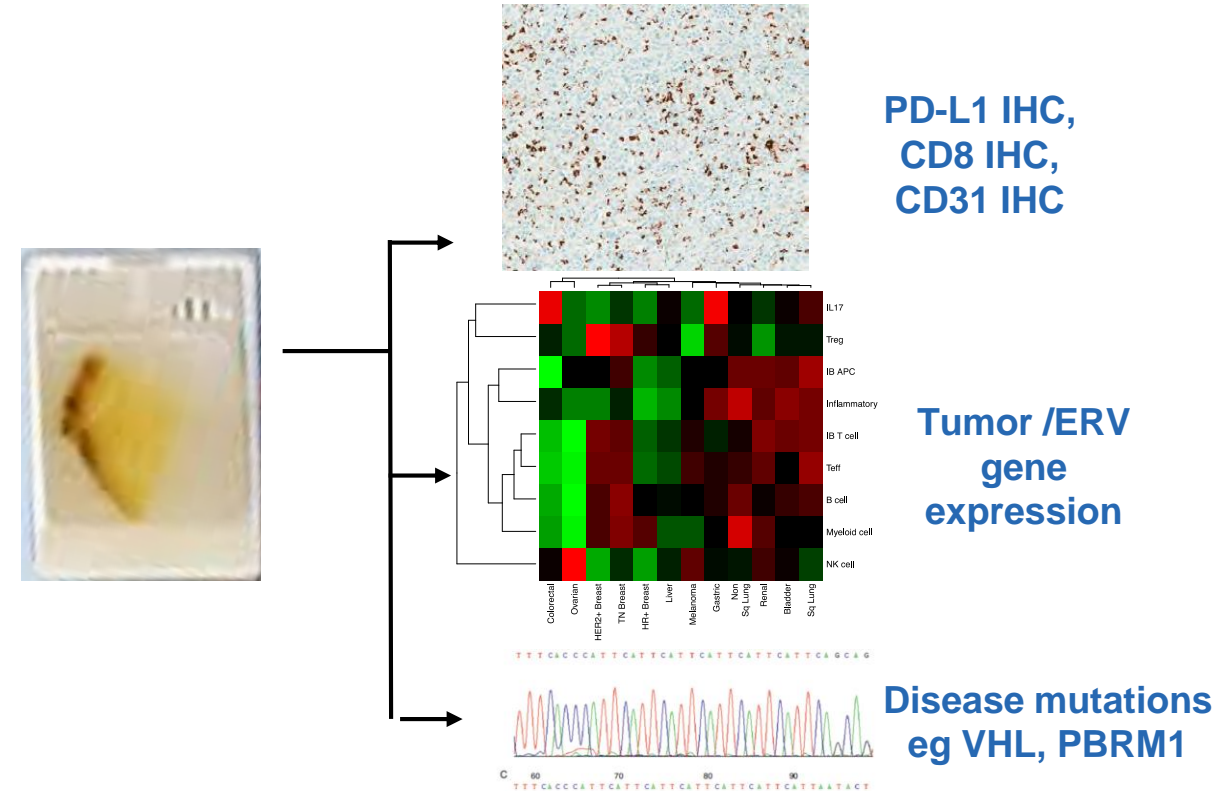
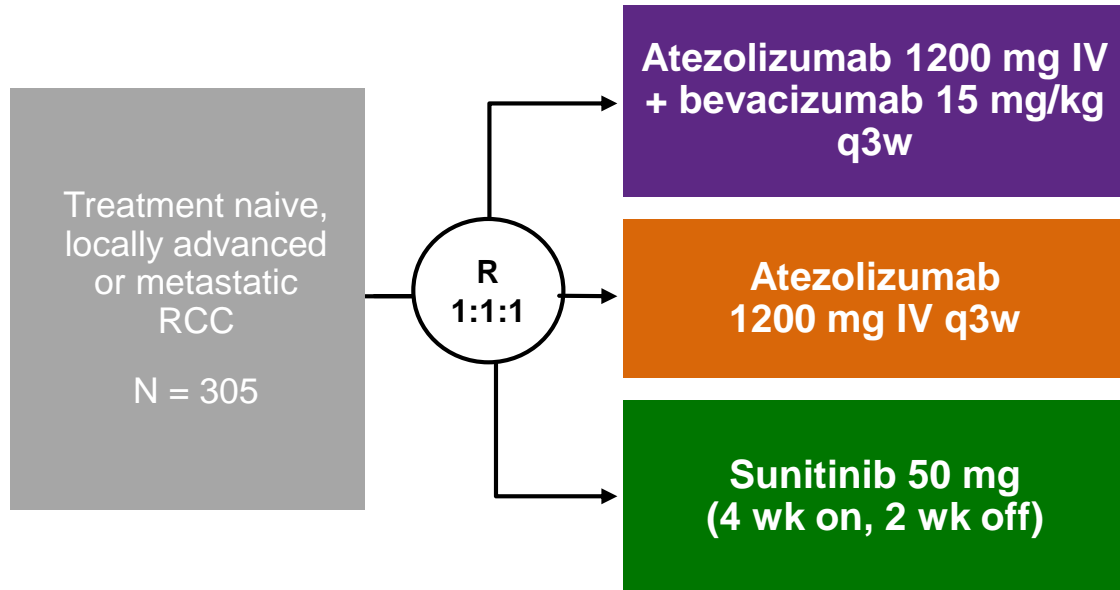
Hanahan D and Weinberg R, Cell, 2011

Hegde PS et al., CCR 2016

Chen D and Mellman I, Nature 2017

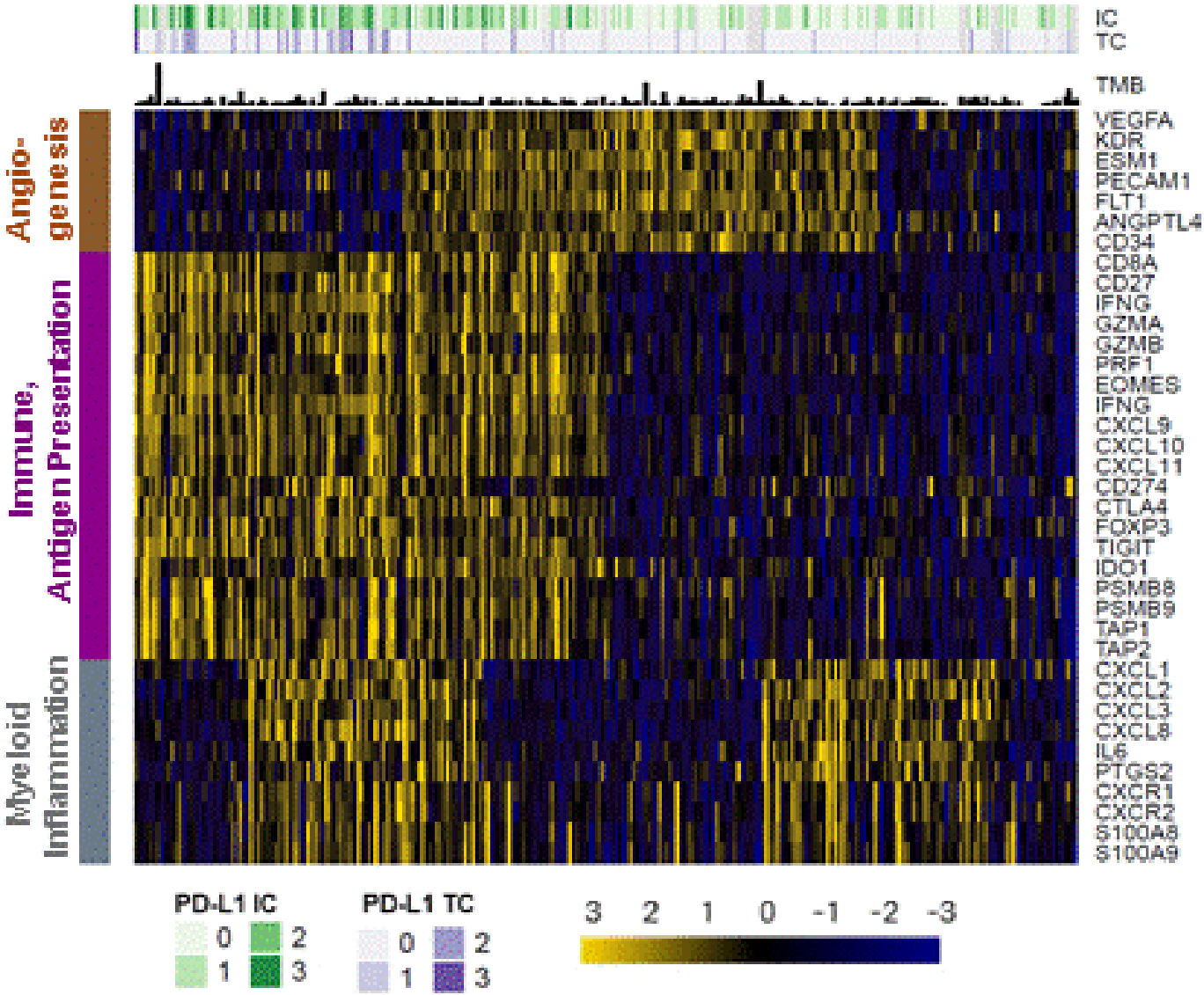
Myeloid inflammation is associated with escape in RCC

IMmotion 150 Phase II RCC



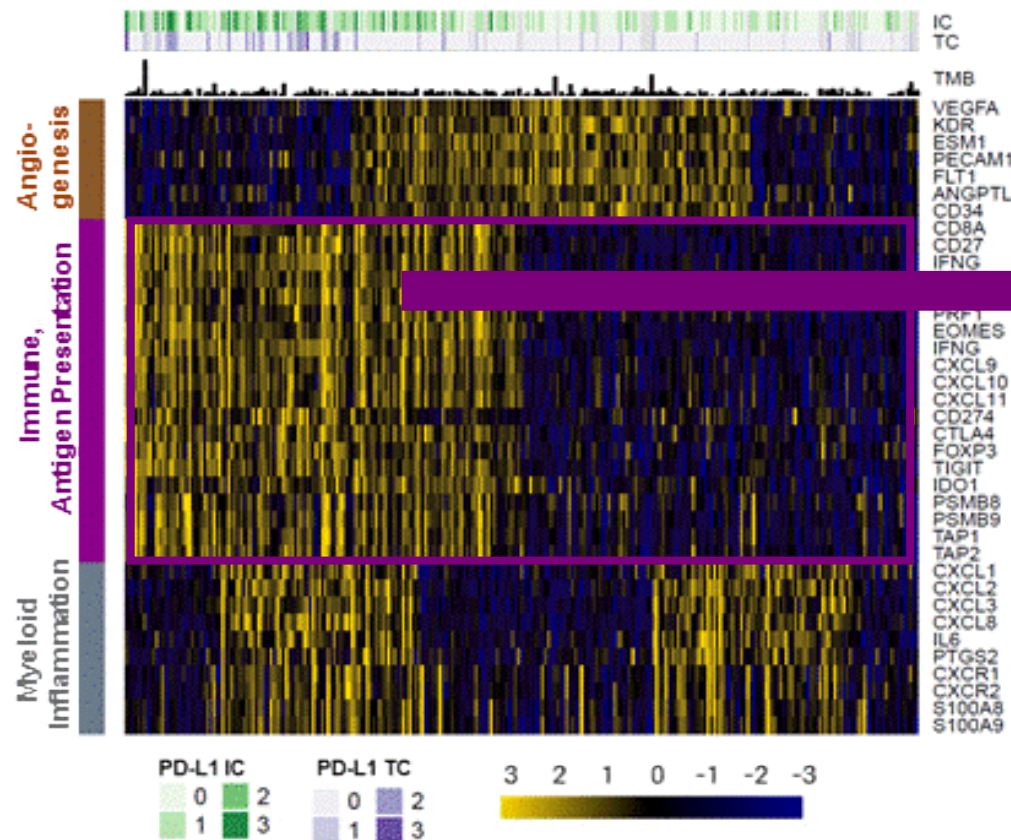
- IMmotion150 was designed to be hypothesis generating and inform the Phase III study IMmotion151
- Co-primary endpoints were PFS (RECIST v1.1 by IRF) in ITT patients and patients with $\geq 1\%$ of IC expressing PD-L1
- Exploratory endpoints included interrogation of the association between outcome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

Tumor microenvironment in RCC



Mahrukh H.

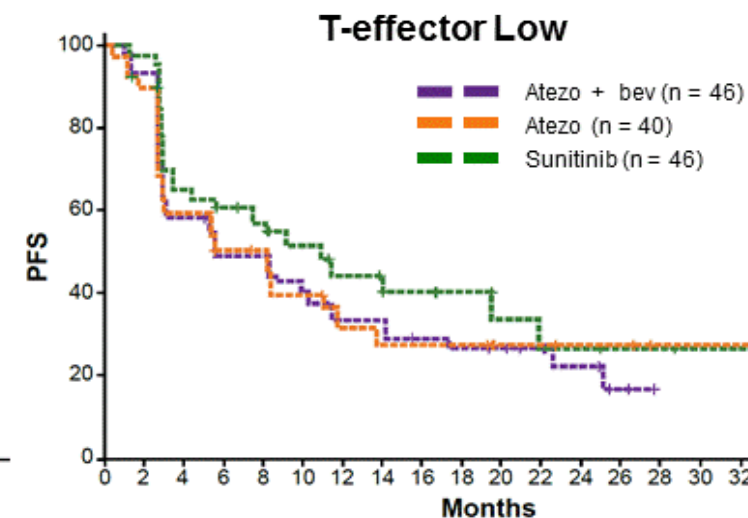
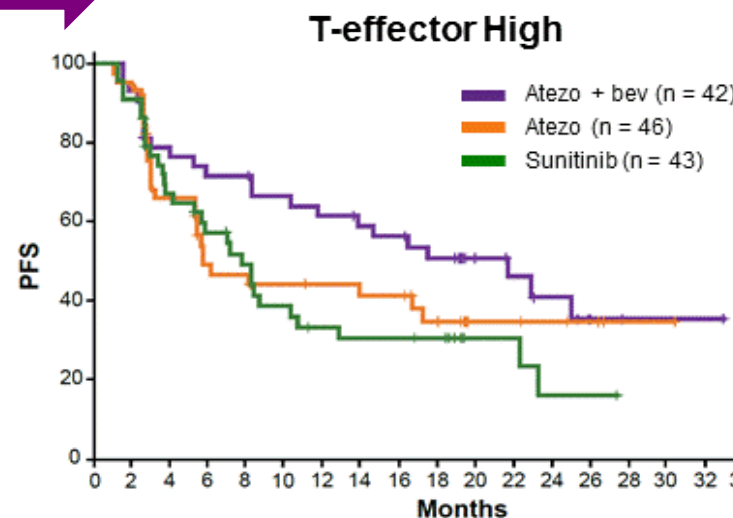
Atezolizumab and Bevacizumab Demonstrated Improved PFS vs Sunitinib in the T-Effector^{High} Subset



Mahrukh H.

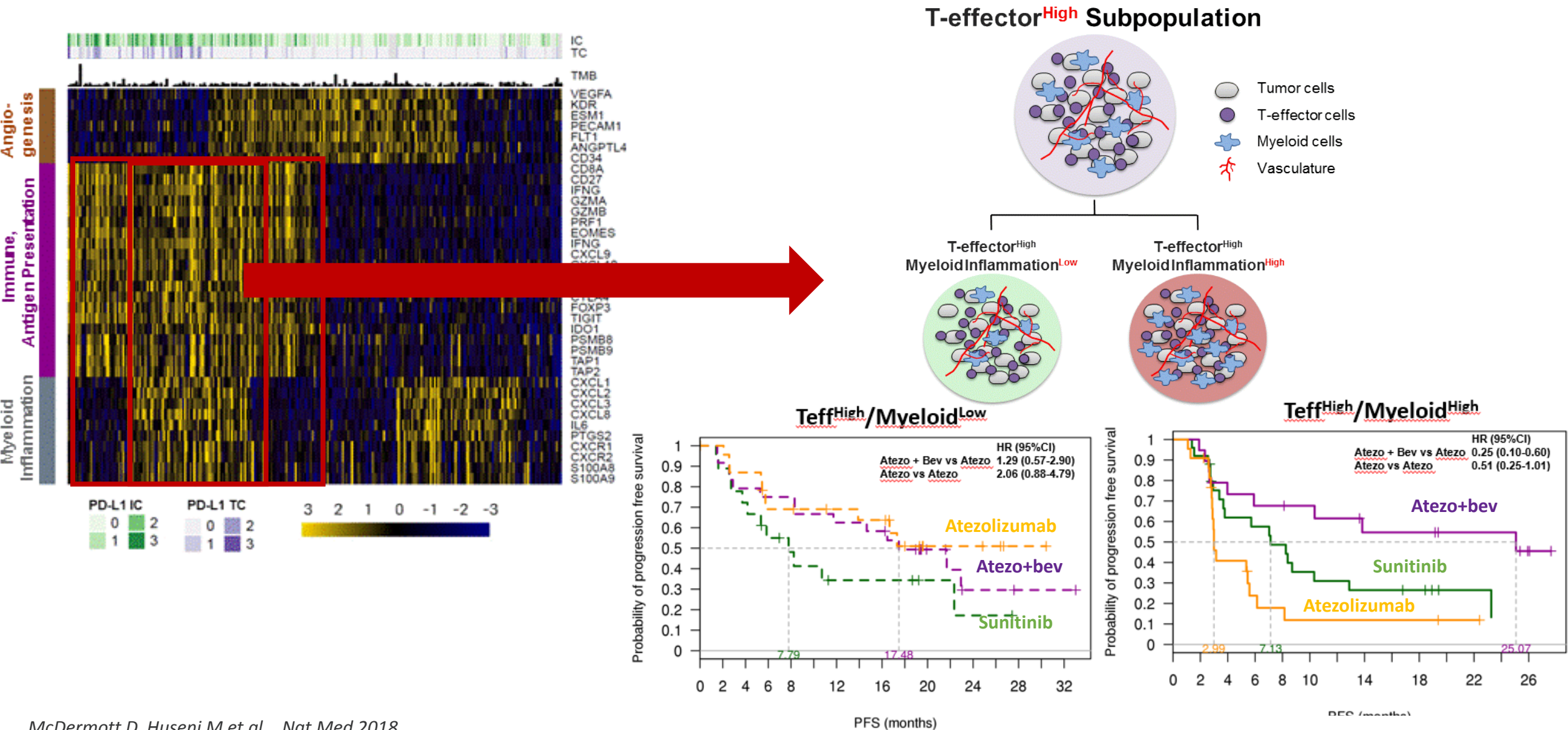


Doro D.



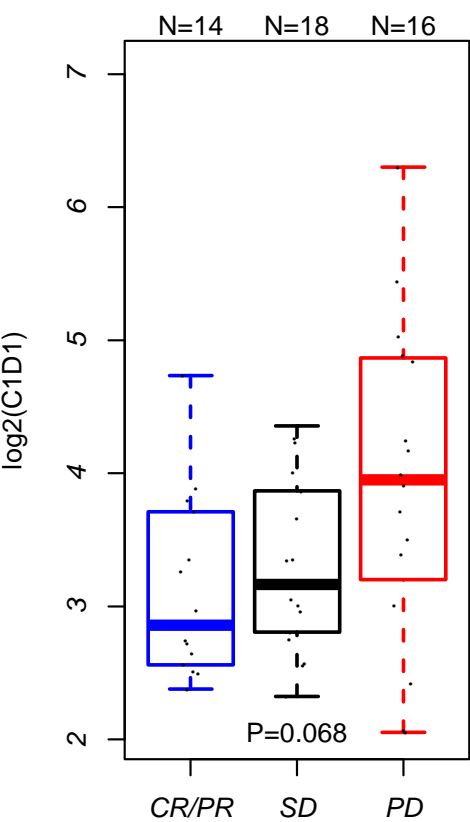
	HR (95% CI)	
	T-effector High	T-effector Low
Atezo + bev vs sunitinib	0.55 (0.32, 0.95)	1.41 (0.84, 2.36)
Atezo vs sunitinib	0.85 (0.50, 1.43)	1.33 (0.76, 2.33)

Myeloid inflammation may be associated with lack of clinical benefit to CPI - α VEGF may overcome this escape mechanism

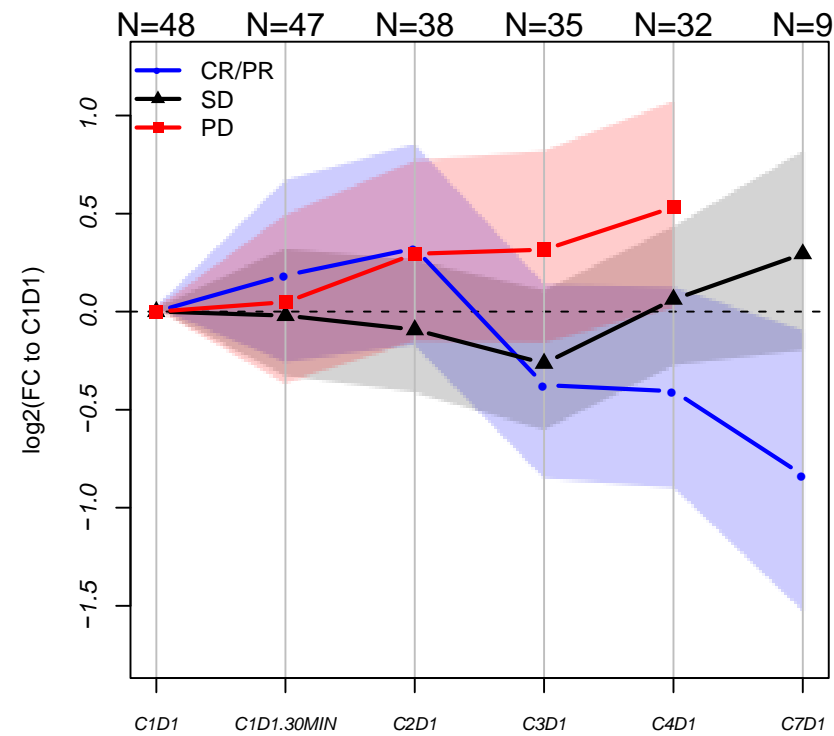


Baseline plasma IL-8 is associated with disease progression to CPI in Bladder Cancer

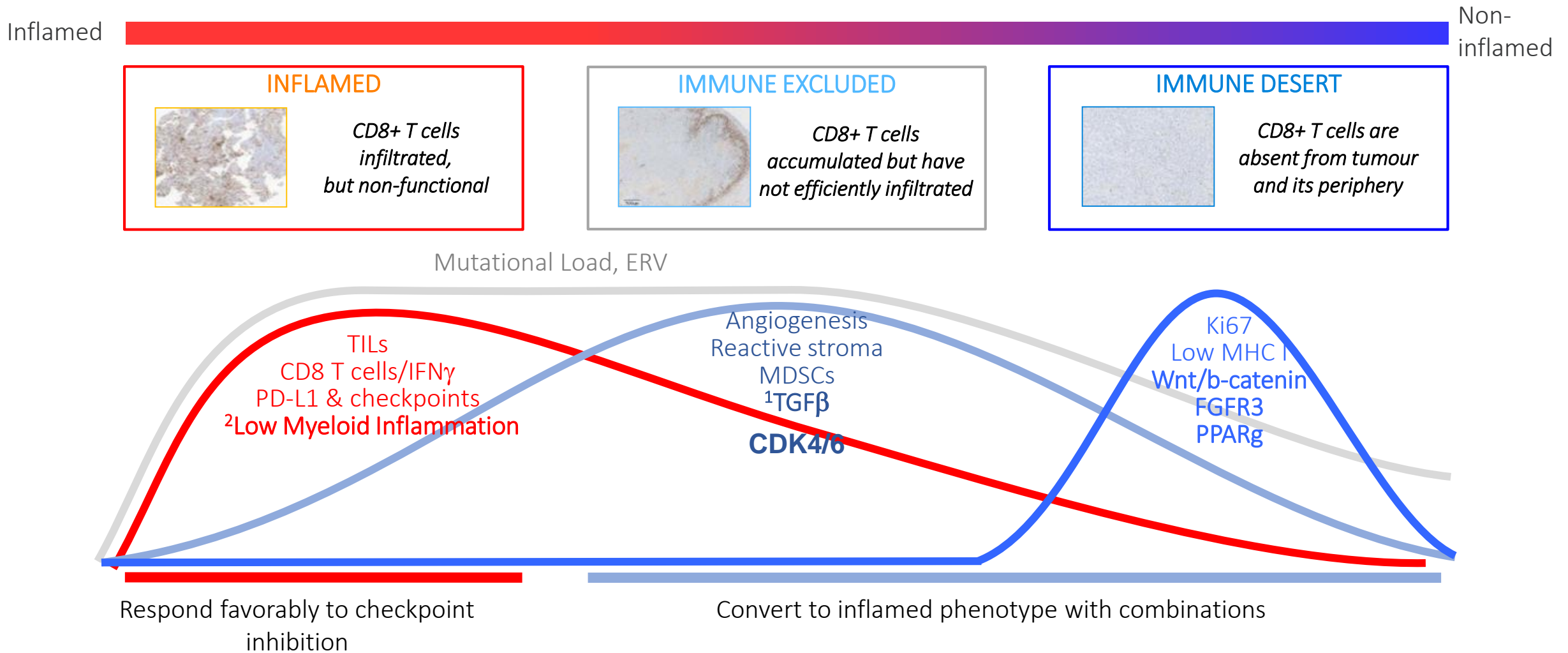
Baseline plasma IL8 levels
higher in patients who
progress on MPDL3280A



Pharmacodynamic decrease in
plasma IL8 observed in patients with
CR/PR compared to PD with
atezolizumab



Tumor immunity continuum- a framework for combinations



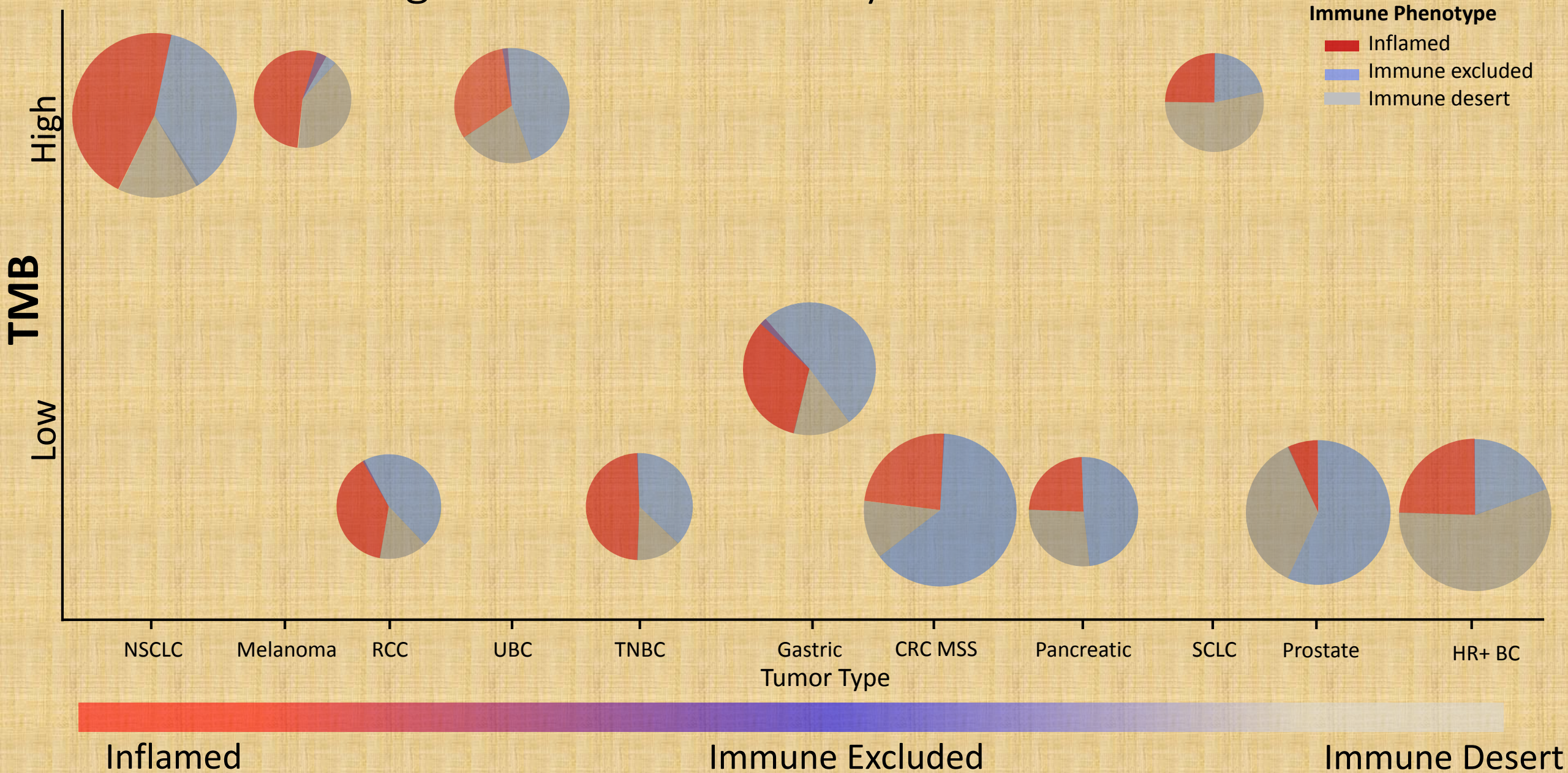
Hegde PS SITC 2018

Modified from Hegde PS et al., Clin Canc Res 2016

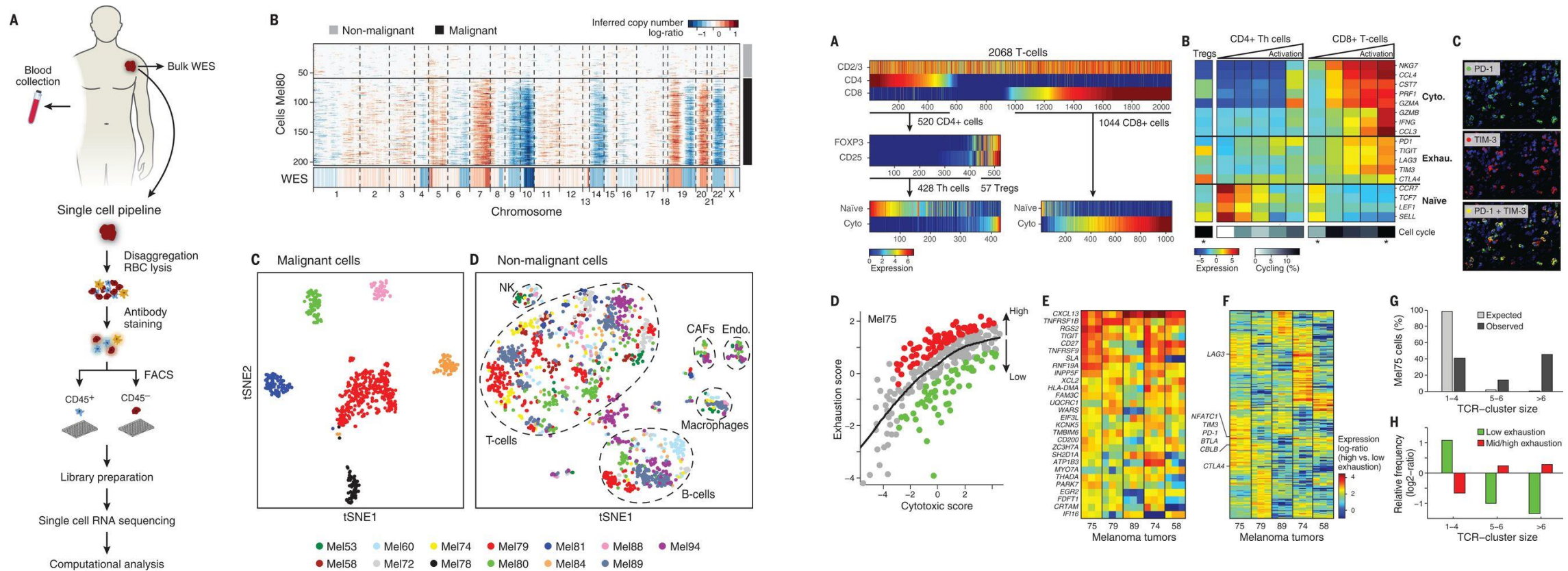
¹ Mariathasan S, Turley S et al., Nature 2018; Jiang P et al., Nat Med 2018

² McDermott D, Huseni M et al., Nat Med 2018

Diseases along the tumor immunity continuum



Methods to assess biomarkers in research



At a single cell level, better able to characterize cells, identify novel markers of functional states

The learning loop to drive scientific innovation

Reverse Translation

