FUNCTIONAL ASSESSMENT OF IMMUNE RESPONSES AND INDENTIFICATION OF NEW ANTIGENS

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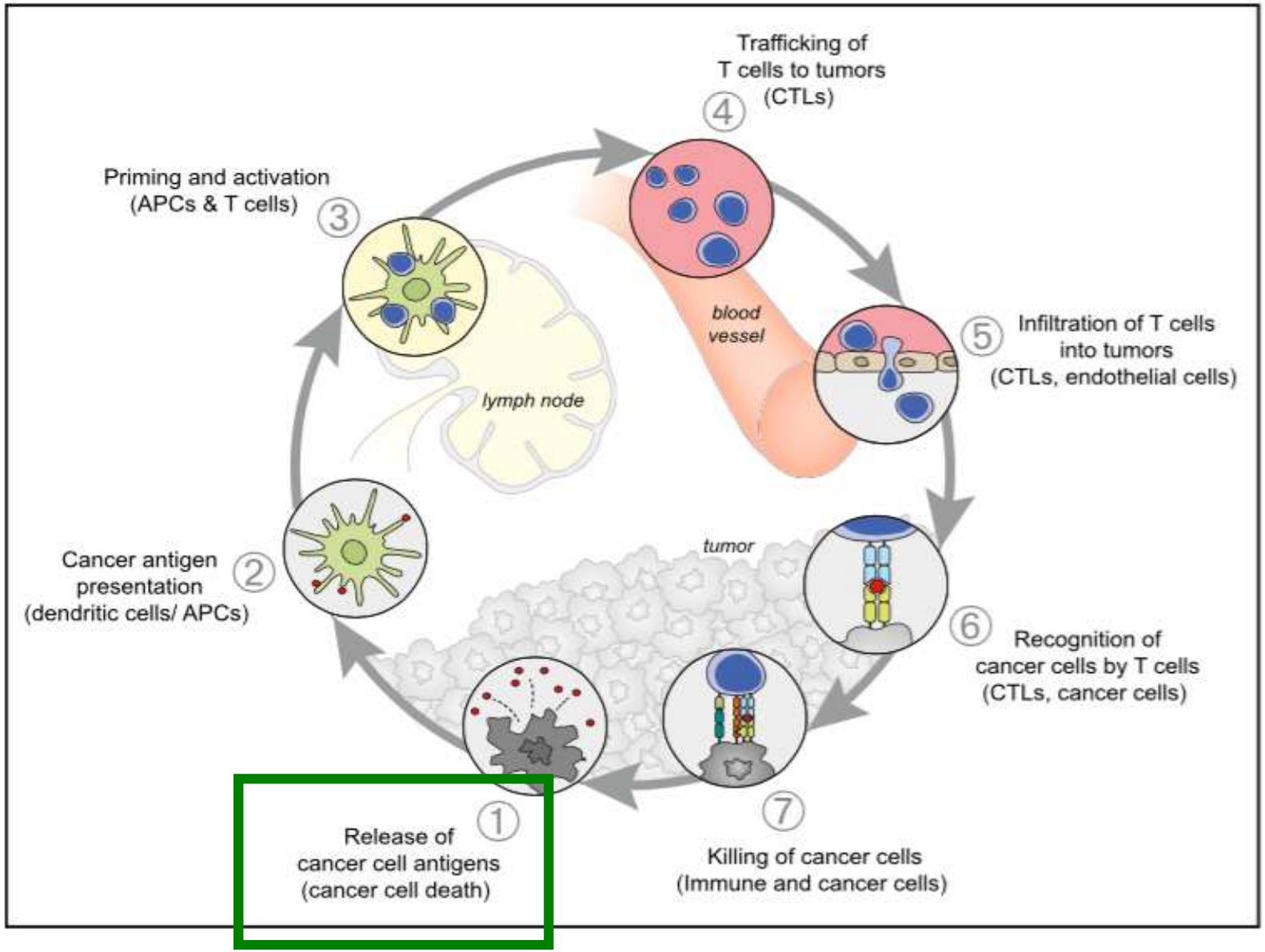
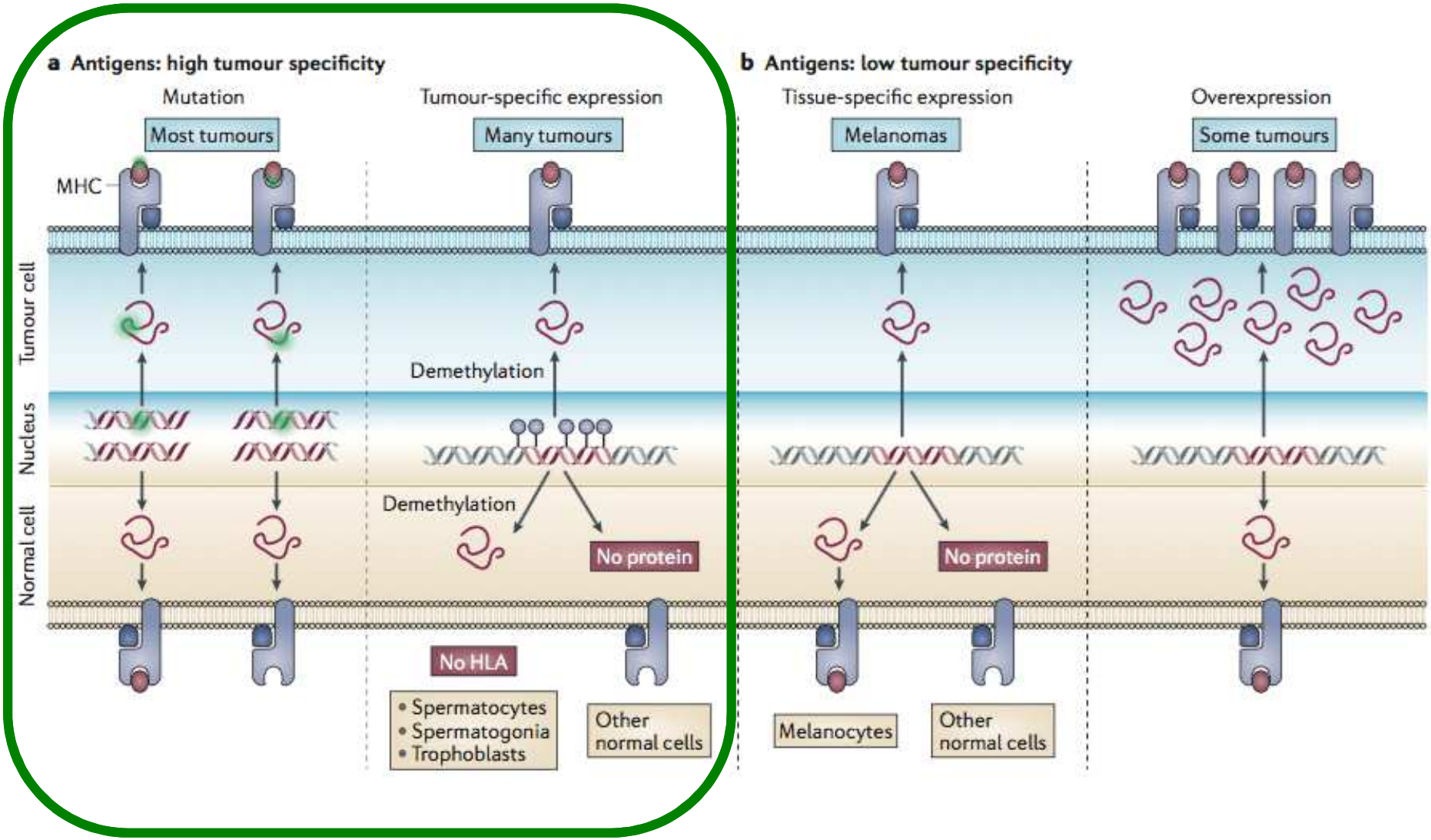
Medical Oncology Department, Thoracic Oncology Unit
Hospital 12 de Octubre, Madrid, Spain

Disclosure slide

- I have no disclosures

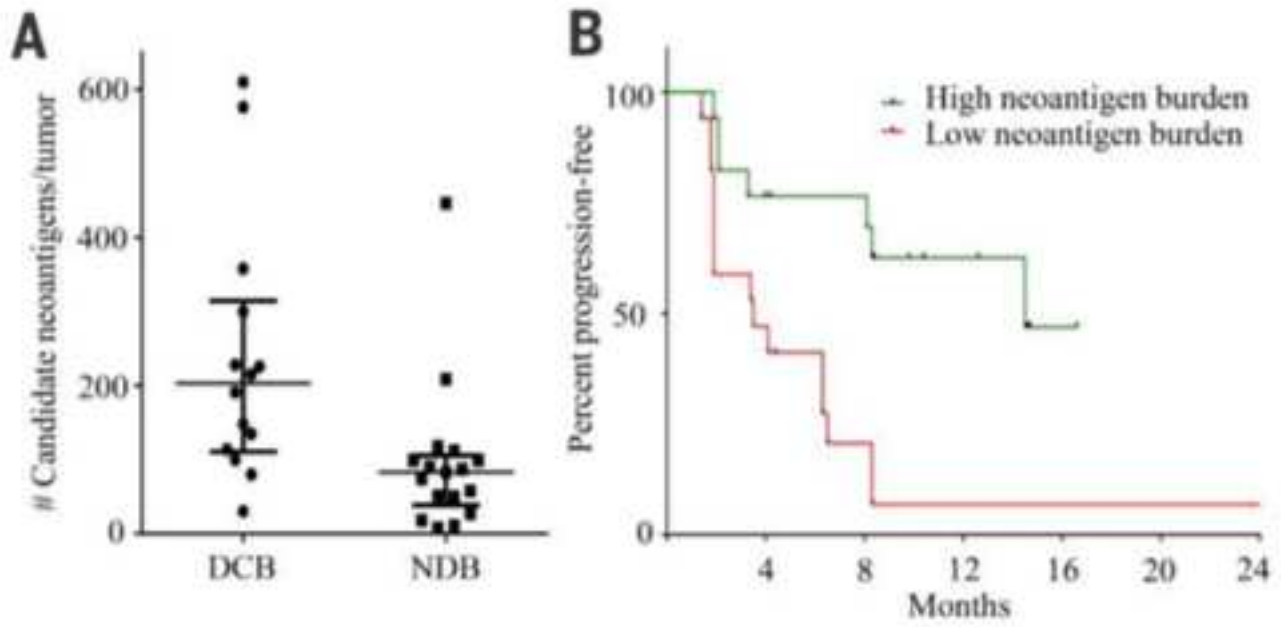


Chen et al. Immunity 2013

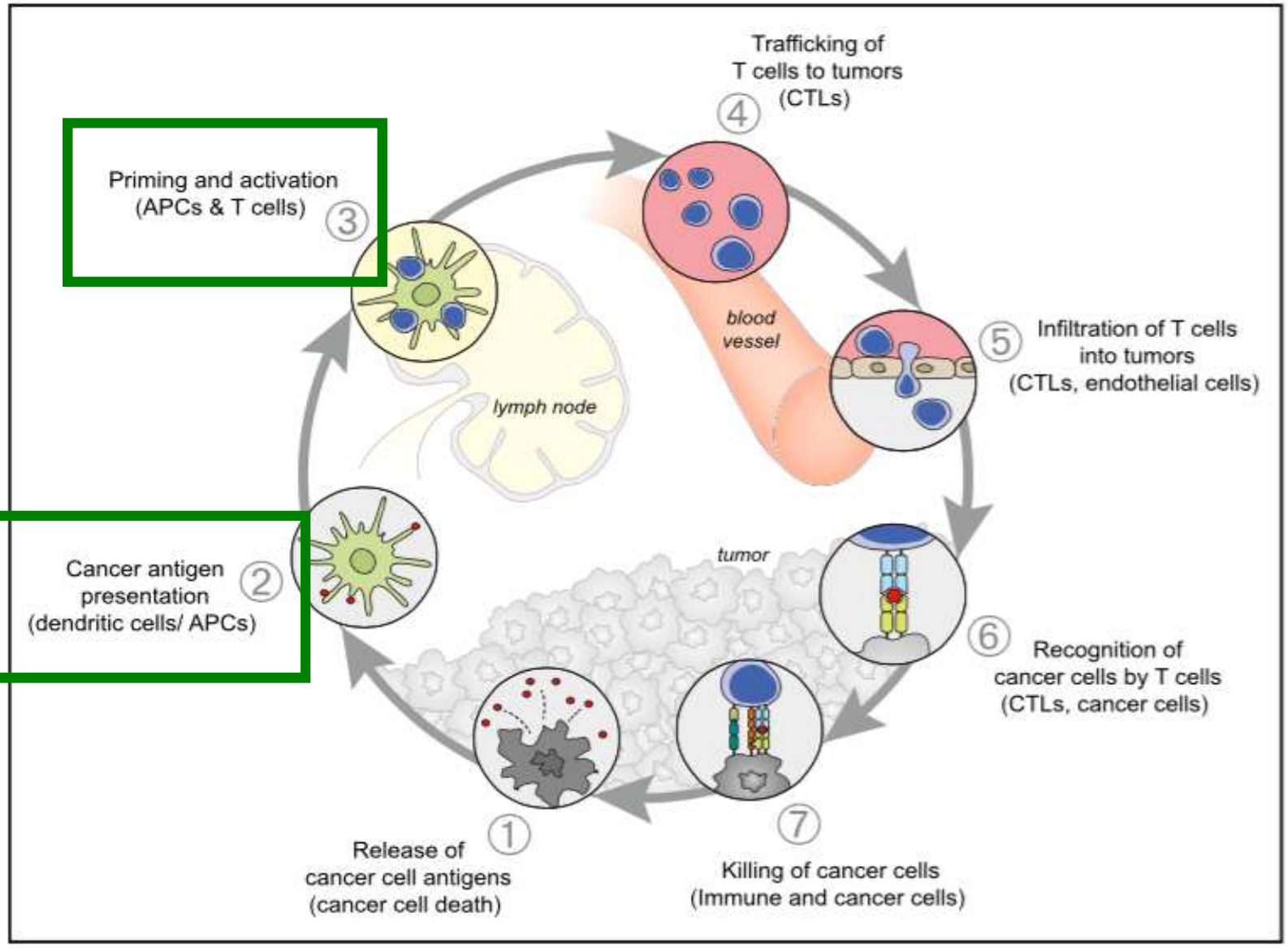


Coulie et al. Nat Rev Cancer 2014

NSCLC cohort treated with pembrolizumab

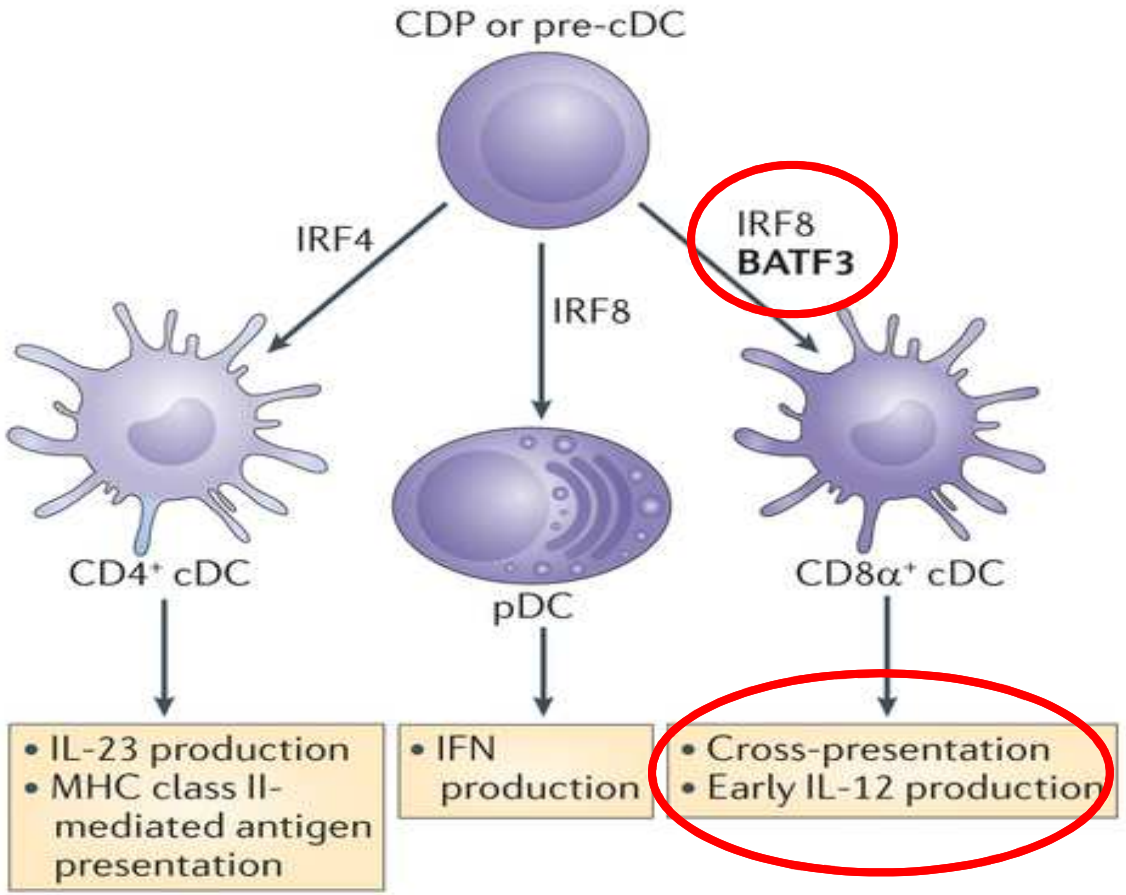


Rizvi et al. Science 2015

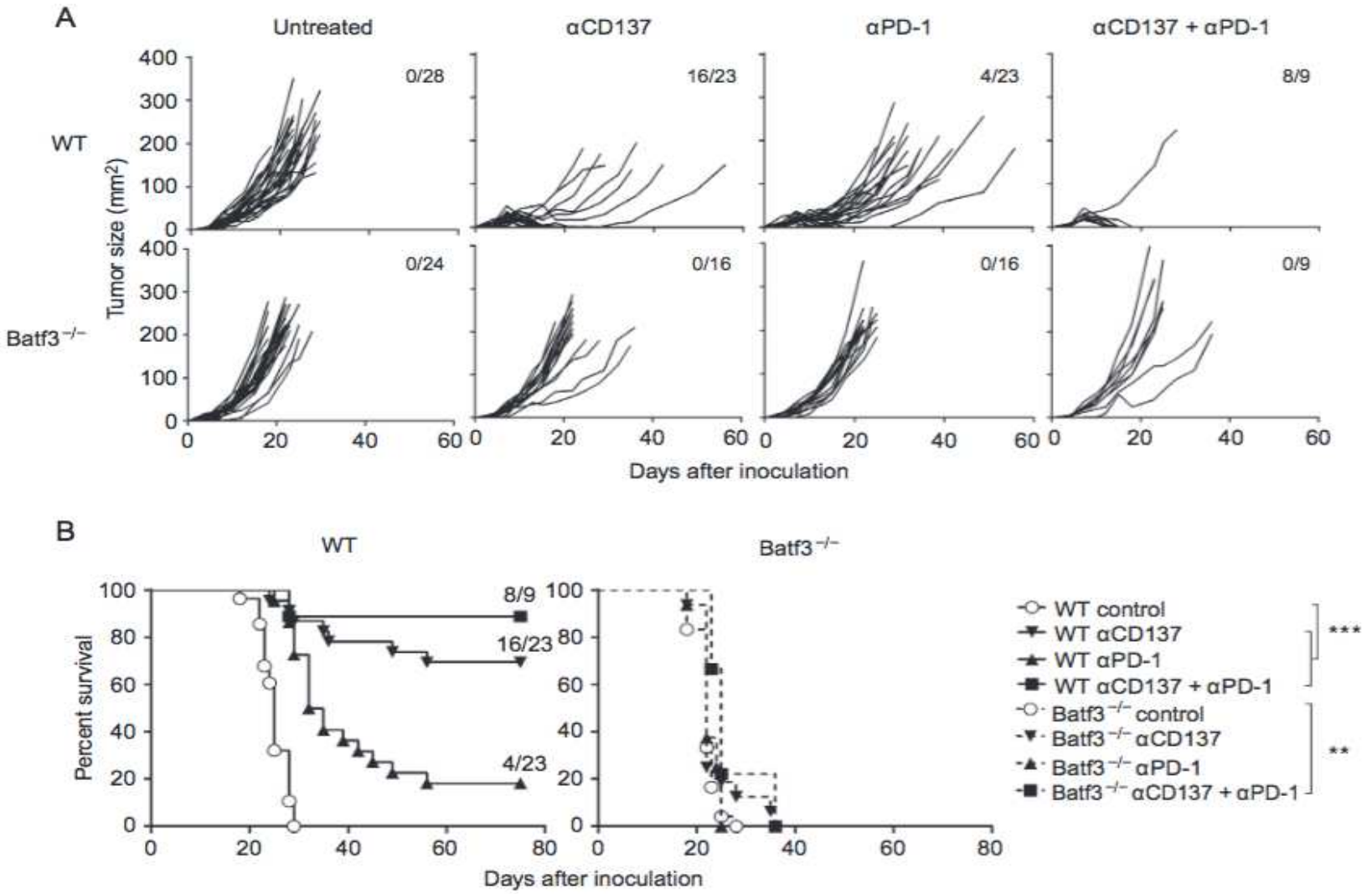


Chen et al. Immunity 2013

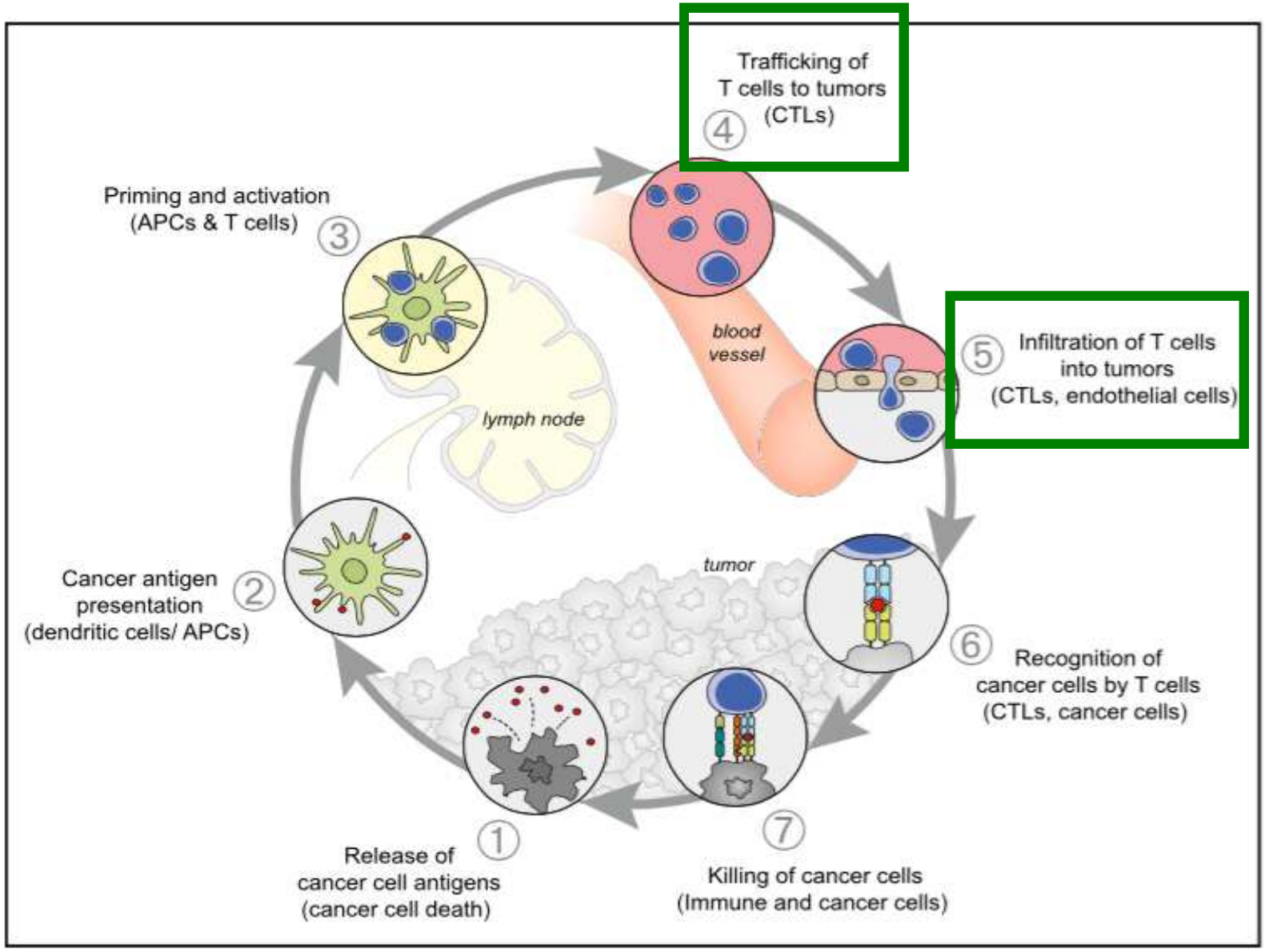
Dendritic cells and cross-presentation of cancer antigens



Murphy et al. Nat Rev Immunol 2013



Sanchez-Paulete et al. Cancer Discov 2016

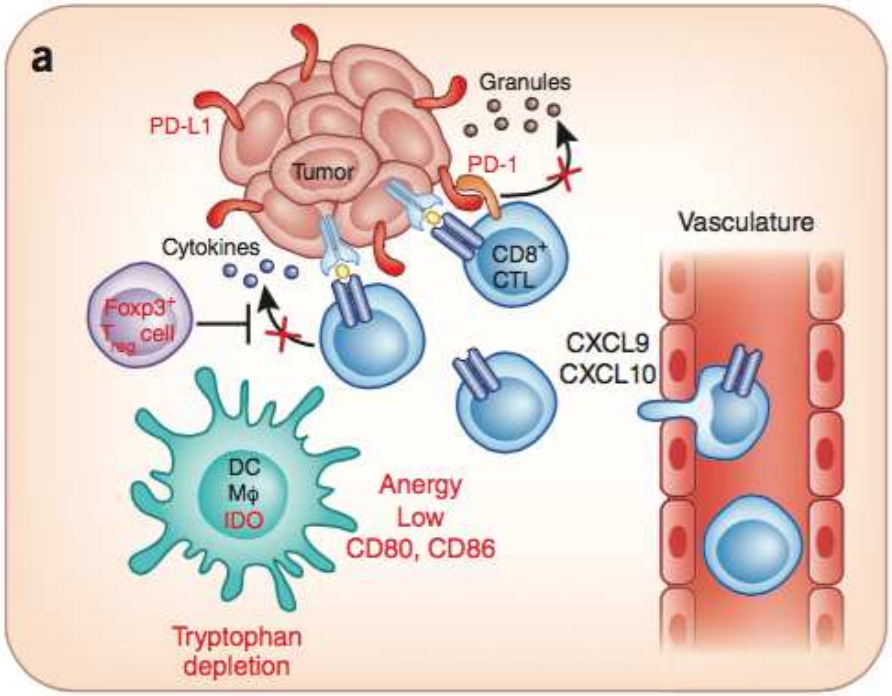


Chen et al. Immunity 2013

Intratumoral T-cell infiltration

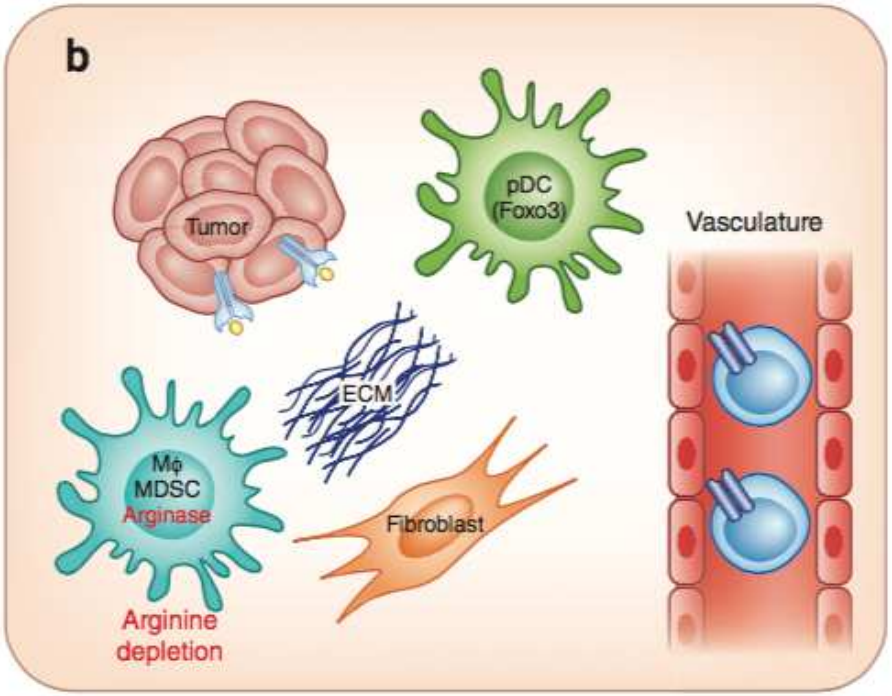
Immunodynamics, biomarkers

T-CELL INFLAMMED



TYPE I/II IFN +

NON T-CELL INFLAMMED

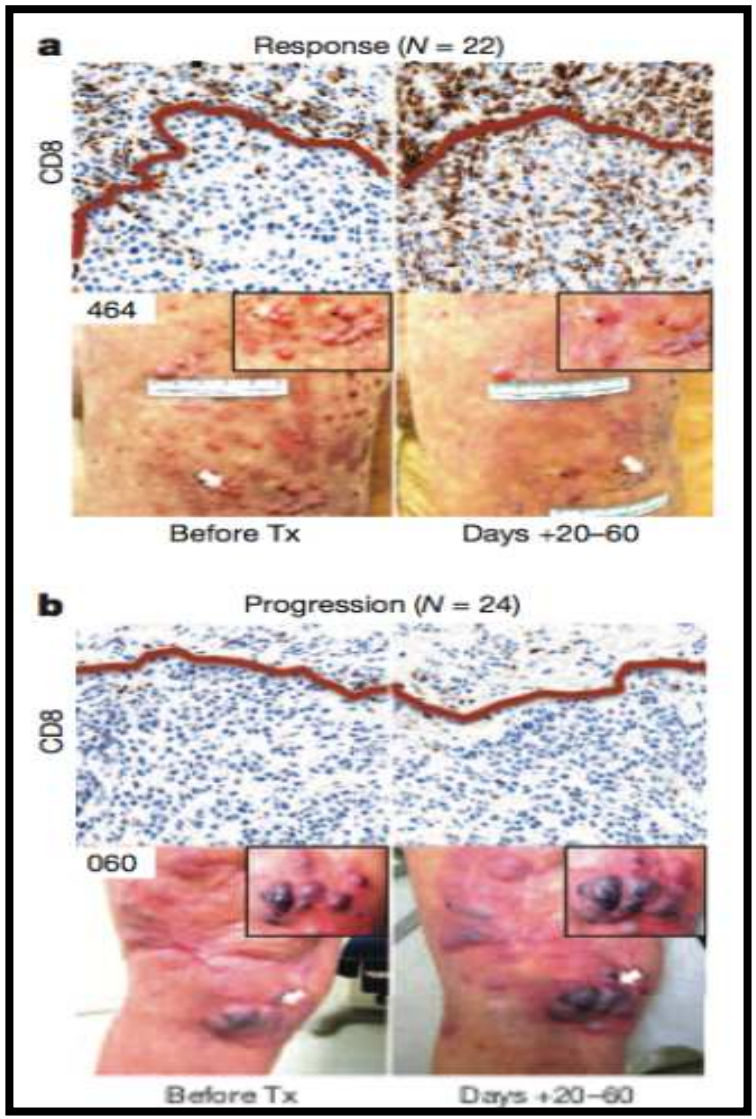


TYPE I/II IFN -

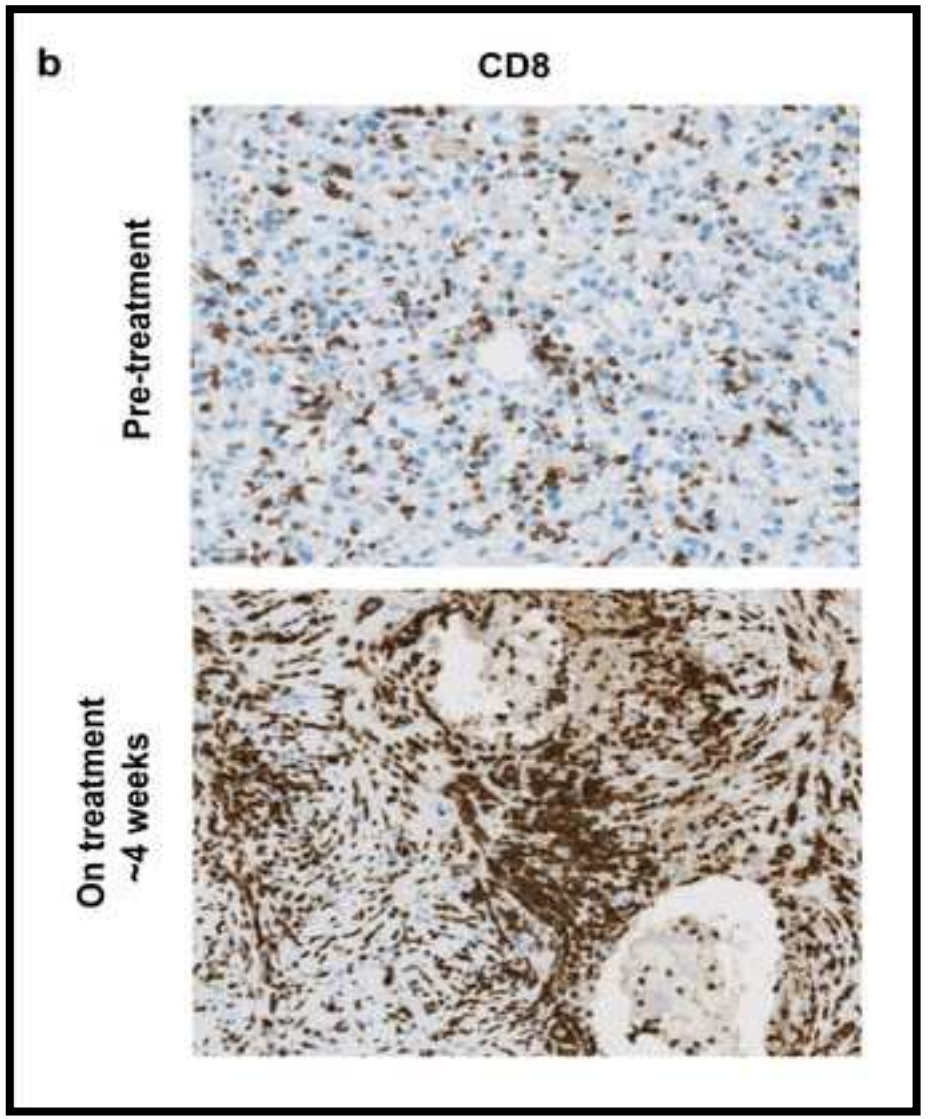
Gajewski et al. Nat Immunol 2013

Intratumoral T-cell infiltration/T-cell inflammed

Immunodynamics, biomarkers (anti-PD-1/L1)



Tumeh et al. Nature 2014



Herbst et al. Nature 2014

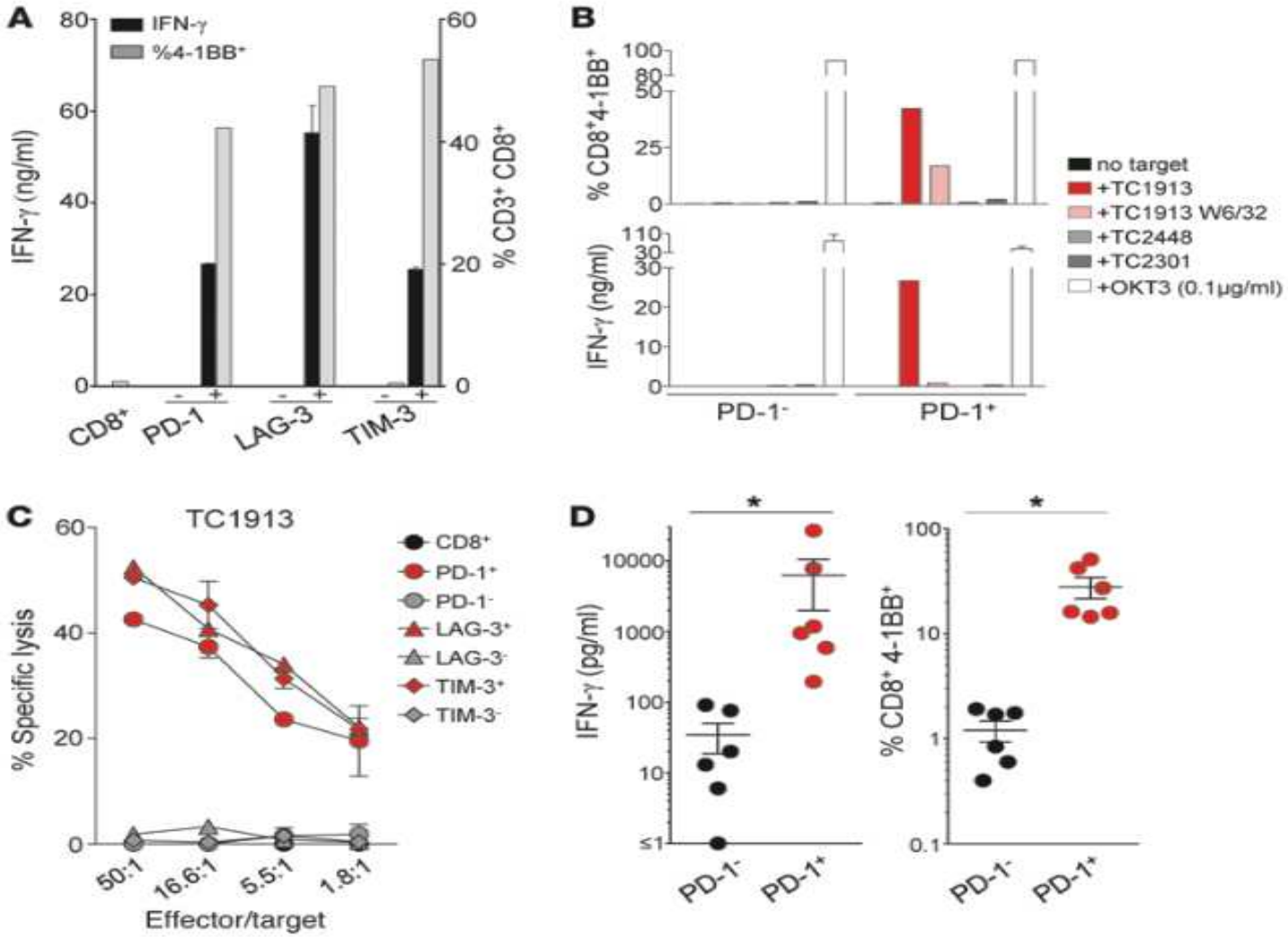
¿How can we predict CD8 T-cell reactivity against cancer antigens?

- Measuring CD8-PD1+ TILs
- Analyzing TCR-CDR3 clonality in TILs
- Detecting neoantigen-specific TILs

Intratumoral T-cell infiltration/T-cell inflammed

Immunodynamics, biomarkers

Tumor reactive TILs: CD8-PD-1+

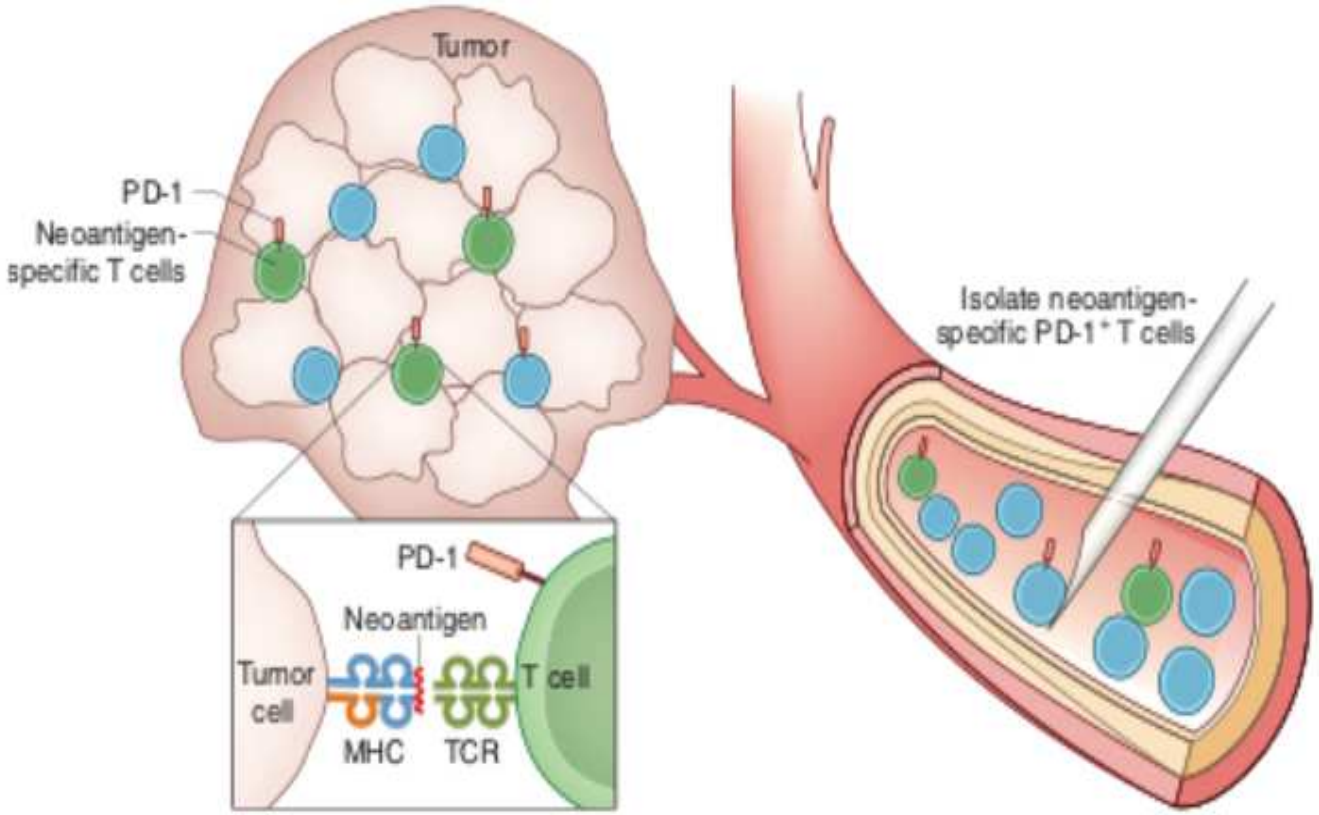


Gros et al. J Clin Invest 2014

Intratumoral T-cell infiltration/T-cell inflammed

Tumor reactive circulating CD8-PD-1+ T cells

Immunodynamics, biomarkers



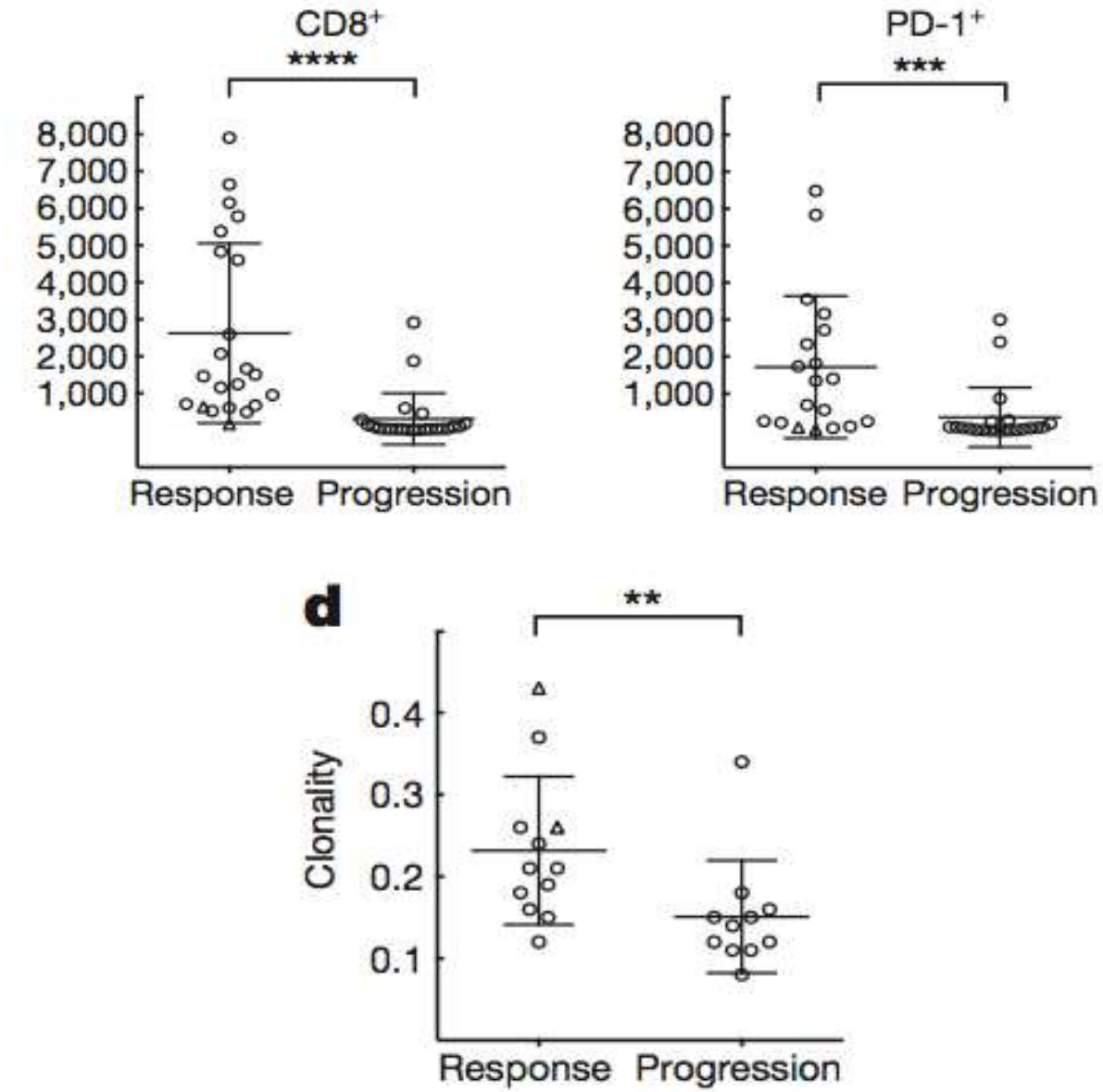
Schumacher et al. Nat Med 2016

(editorial comment on Gros et al. Nat Med 2016)

Intratumoral T-cell infiltration/T-cell inflammed

Tumor reactive TILs: TCR clonatlity

Immunodynamics, biomarkers (anti-PD-1/L1)

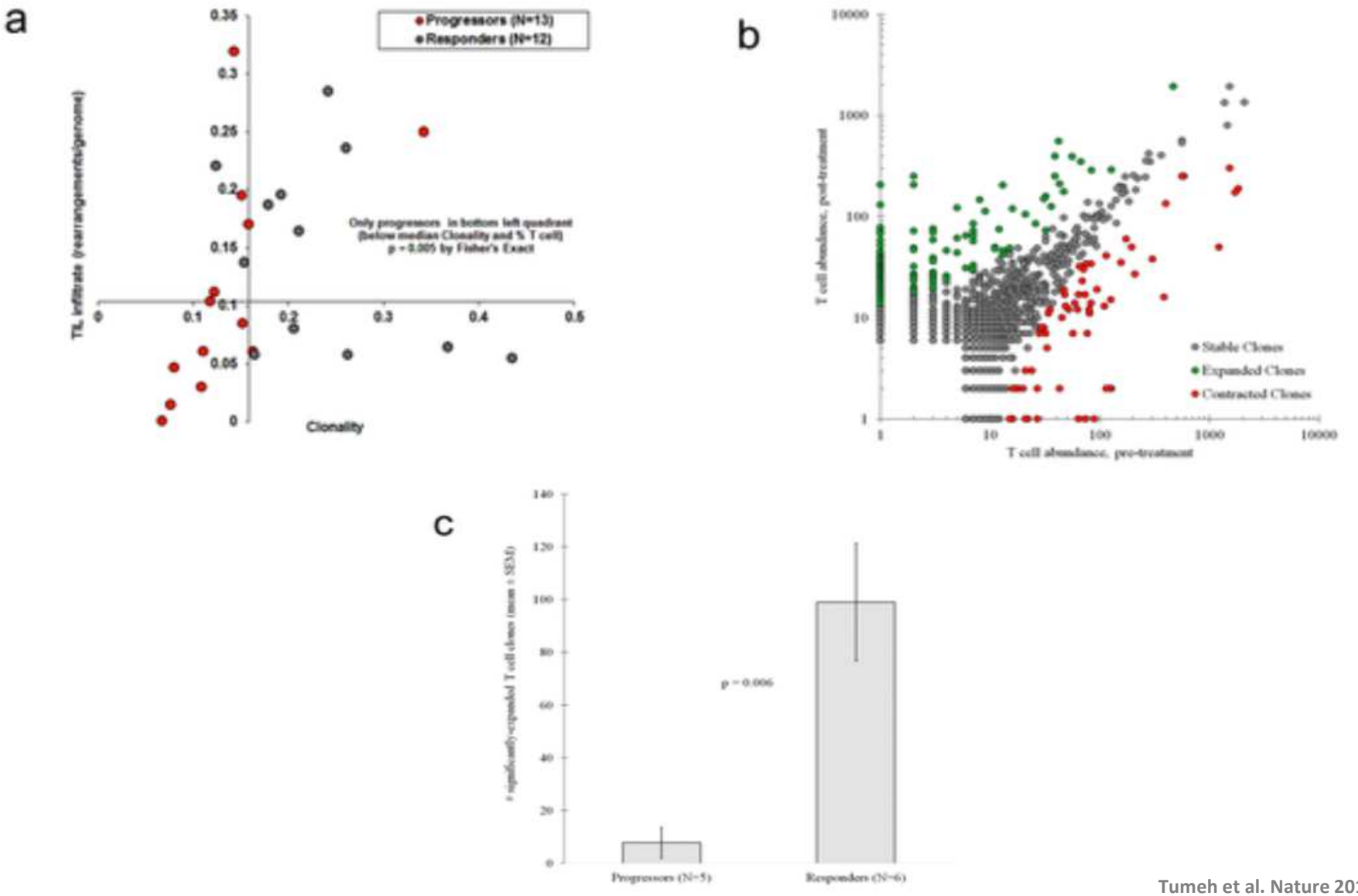


Tumeh et al. Nature 2014

Intratumoral T-cell infiltration/T-cell inflammed

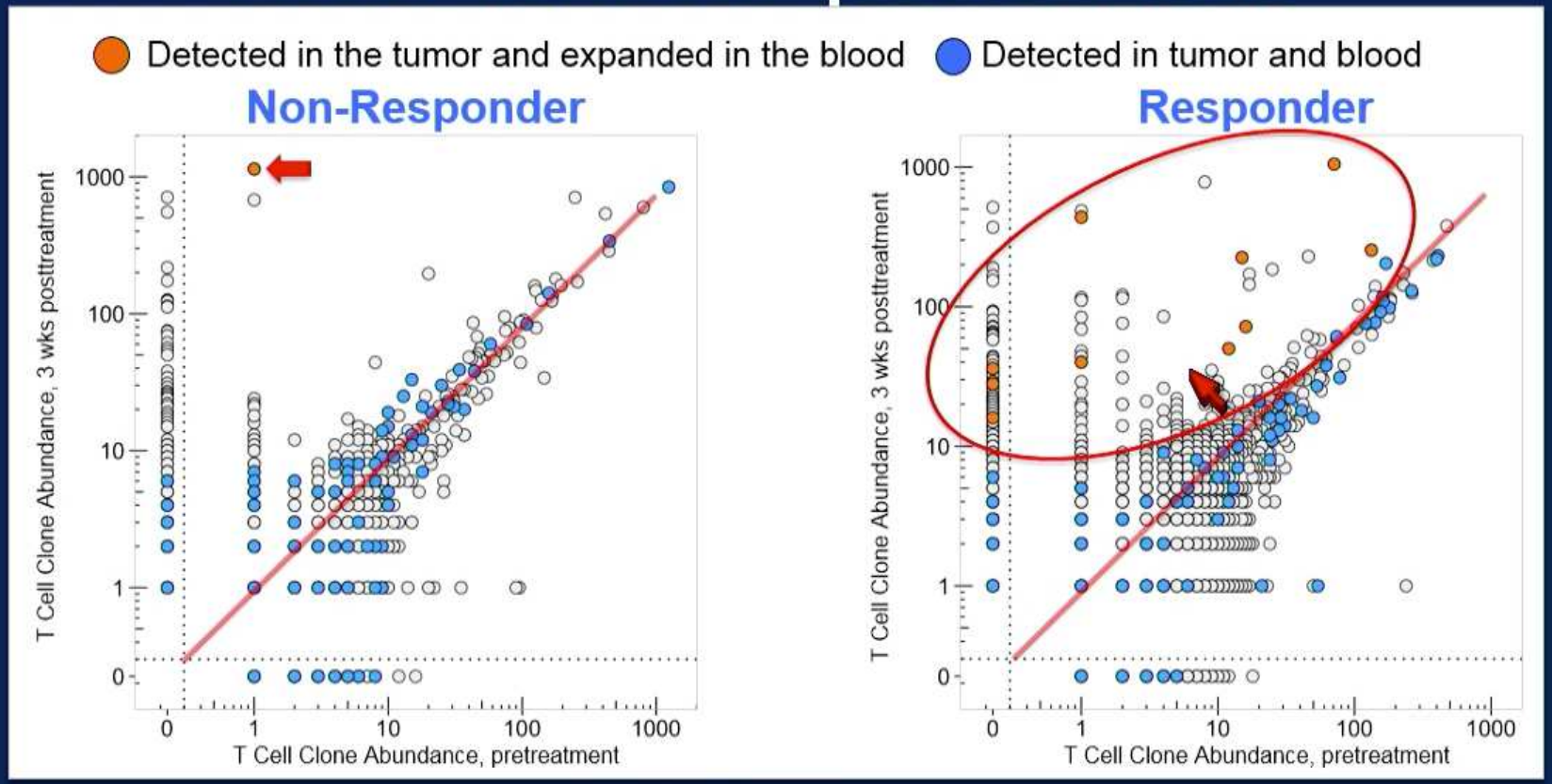
Tumor reactive TILs: TCR clonatlity

Immunodynamics, biomarkers (anti-PD-1/L1)



Tumeh et al. Nature 2014

TIL clones could be detected expanding in the blood at 3 weeks posttreatment



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Is the combination of pre-treatment TIL and blood clonality predictive of clinical benefit? (n=24)

Pre-Treatment Clonality Status*	N	Survival > 1 YR (n,%)
High TIL Clonality AND Low Blood Clonality	6	6 (100%)
EITHER High TIL Clonality OR Low Blood Clonality	12	(33%)
NEITHER High TIL Clonality NOR Low Blood Clonality	6	2 (33%)

*high/low cutoff based on median values

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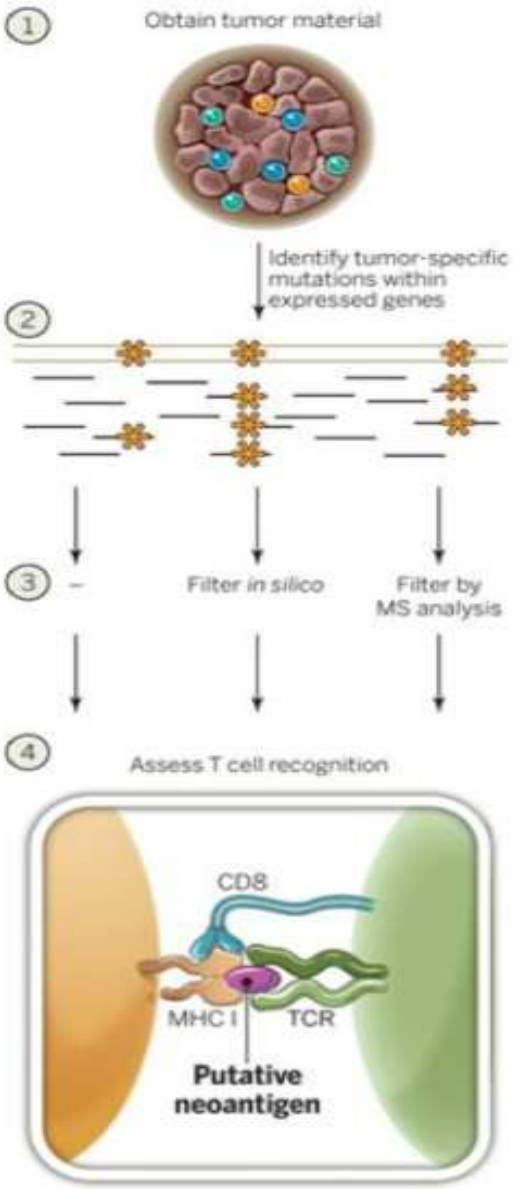
Intratumoral T-cell infiltration/T-cell inflammed

Neoantigen specific TILs

Immunodynamics, biomarkers

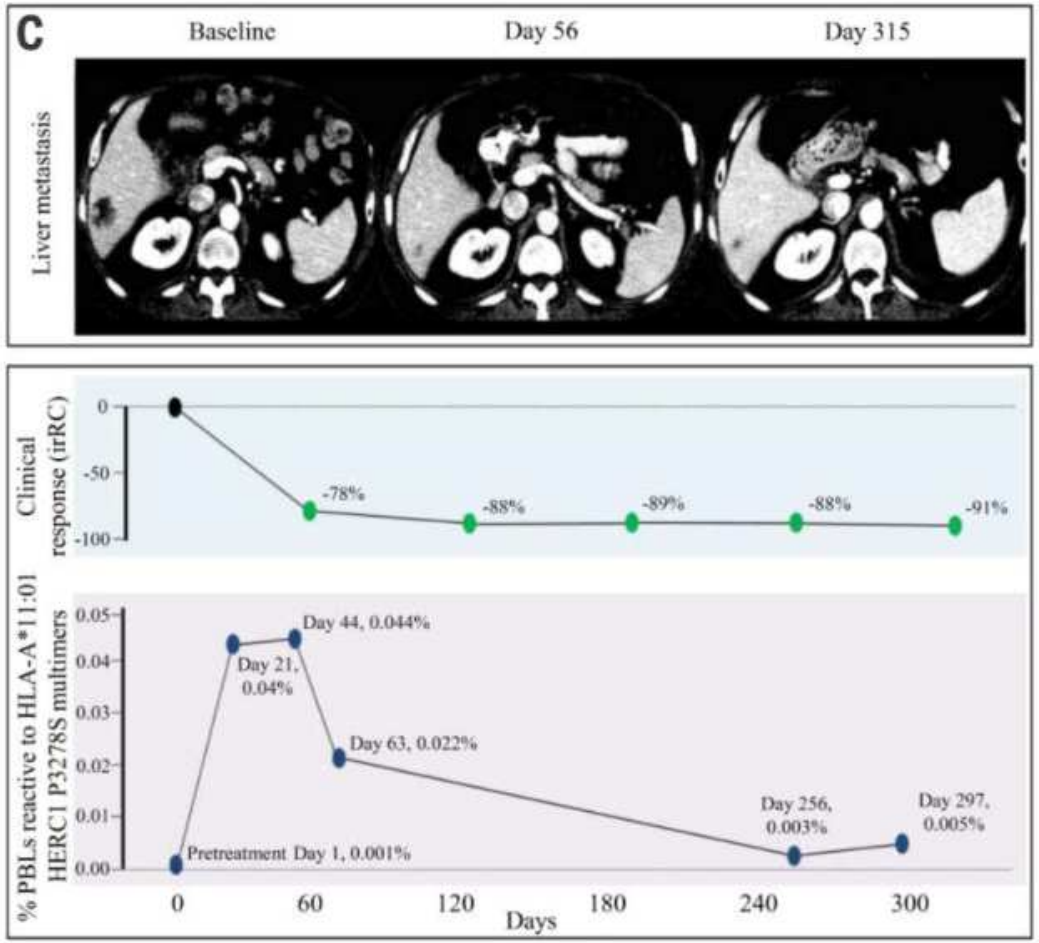


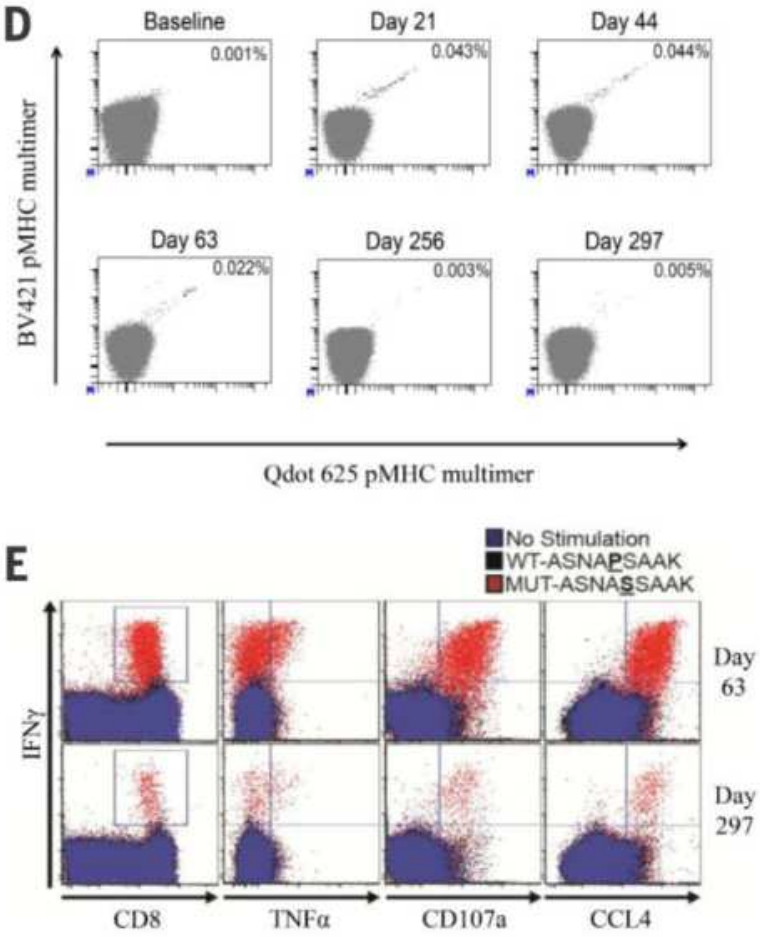
Schumacher et al. Science 2015

Intratumoral T-cell infiltration/T-cell inflammed

Neoantigen specific circulating T-cells

Immunodynamics, biomarkers (anti-PD1/L1)



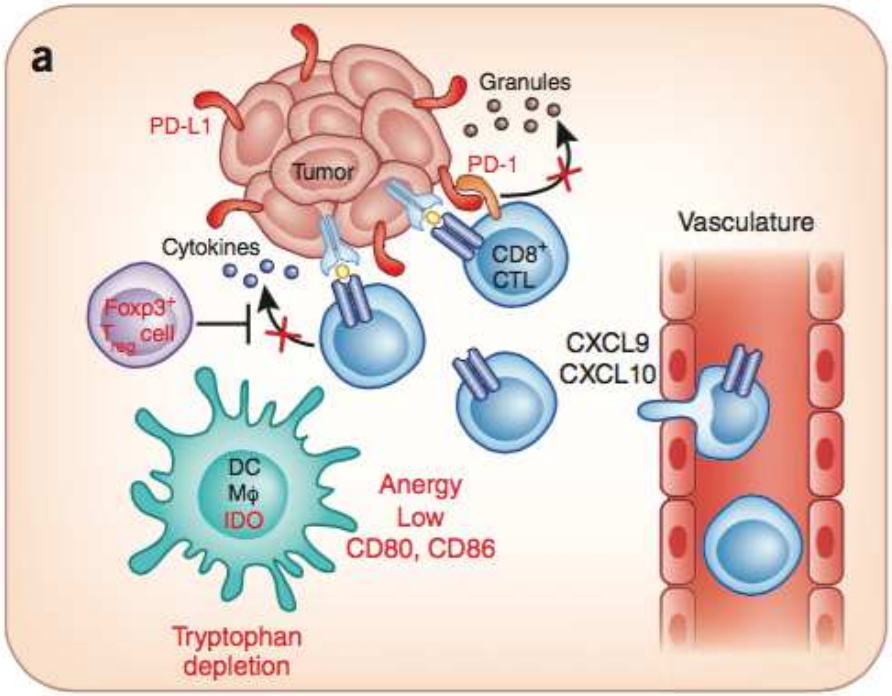


Rizvi et al. Science 2015

Intratumoral T-cell infiltration

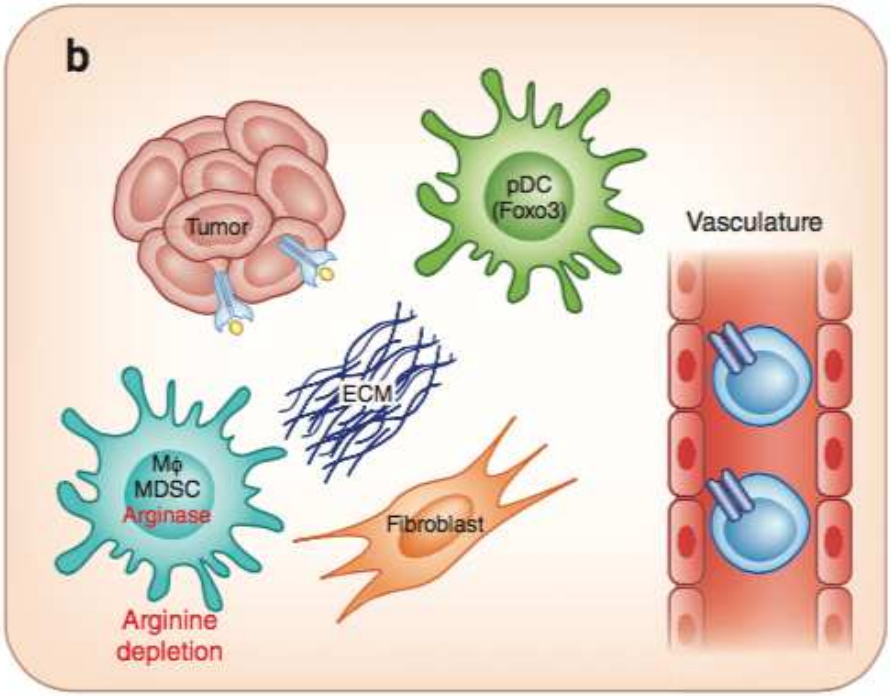
Immunodynamics, biomarkers

T-CELL INFLAMMED



TYPE I/II IFN +

NON T-CELL INFLAMMED



TYPE I/II IFN -

Gajewski et al. Nat Immunol 2013

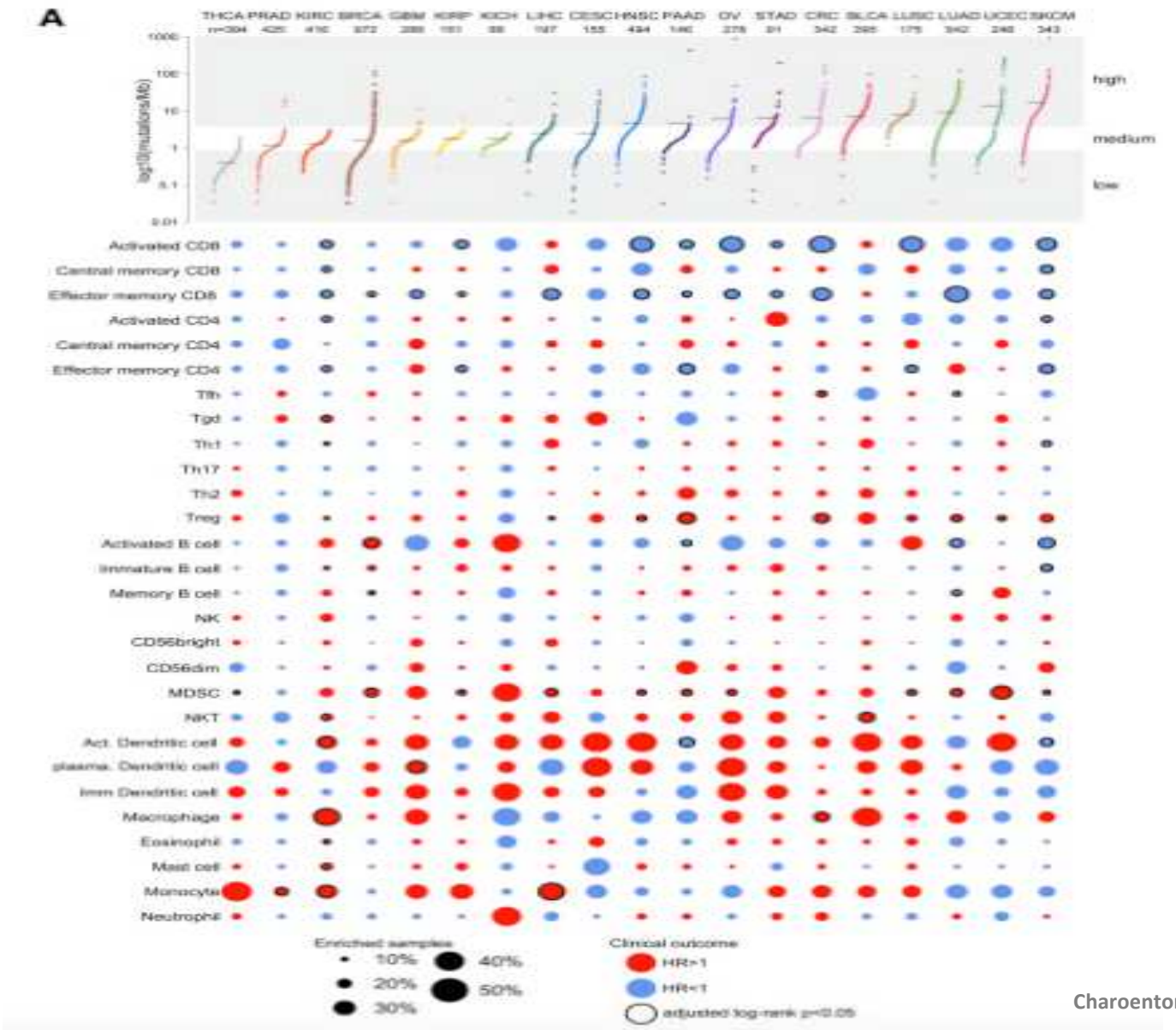
Intratumoral T-cell infiltration/Non T-cell inflammed

¿Which mechanisms drive T-cell exclusion?

- Endothelial barrier
- Neoantigen burden (?)
- Ineffective T-cell priming
- Immunosuppressive molecules (secreted by tumor cells, myeloid-derived cells, Tregs...)

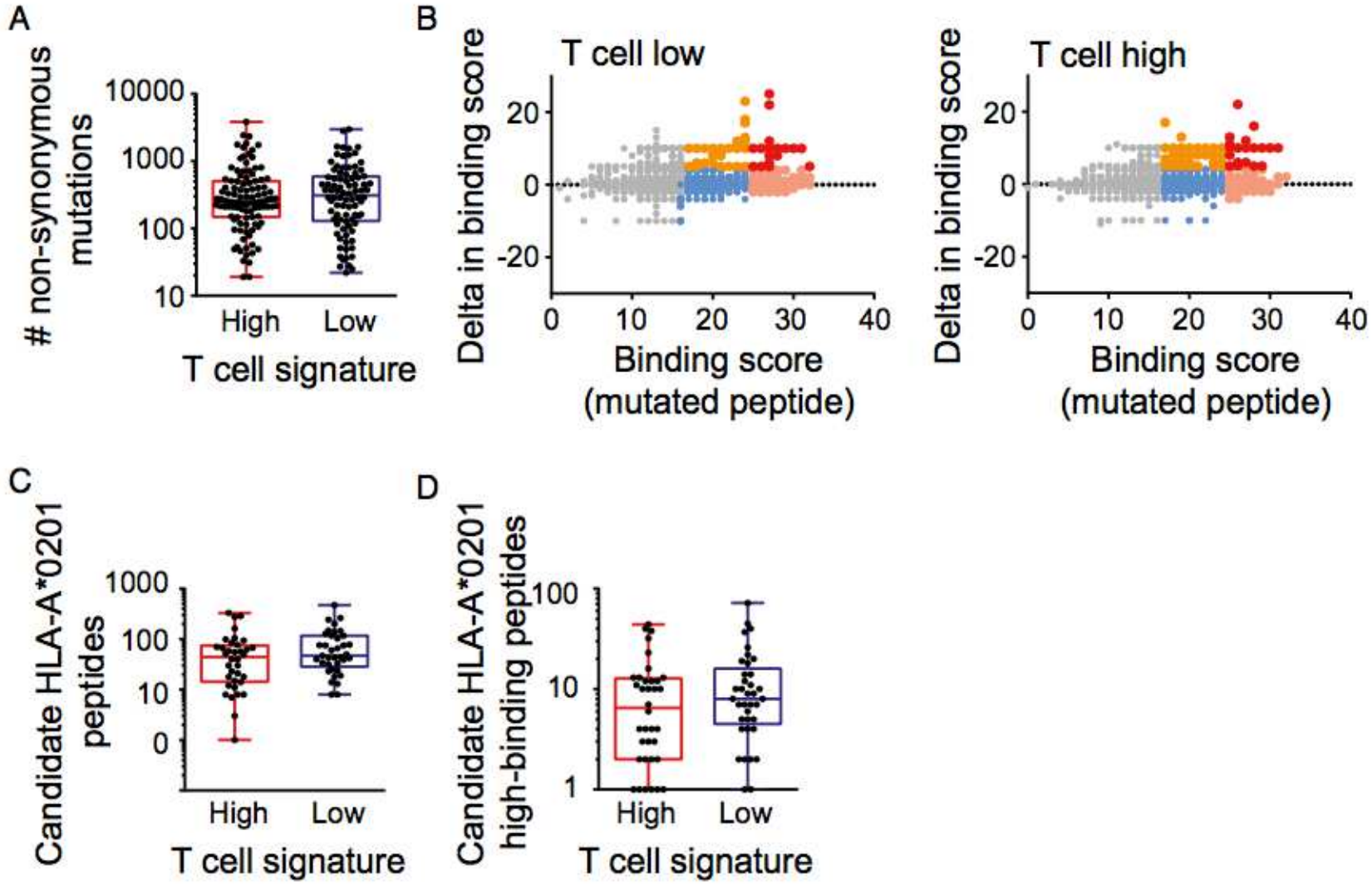
Overlapping mechanisms

b) Neoantigen burden



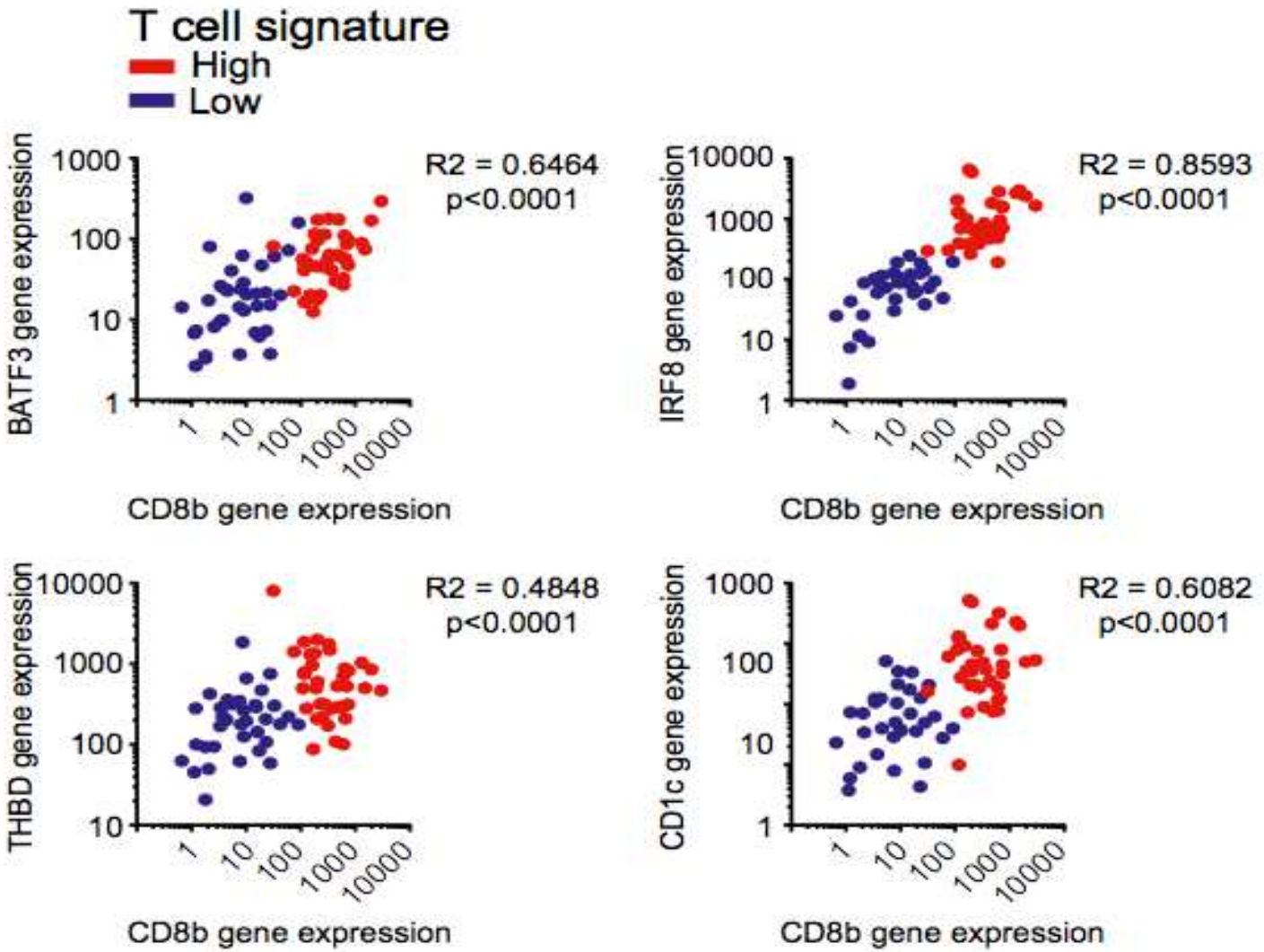
Charoentong et al. Cell Rep 2017

b) Neoantigen burden



Spranger et al. PNAS 2016

c) Priming defects

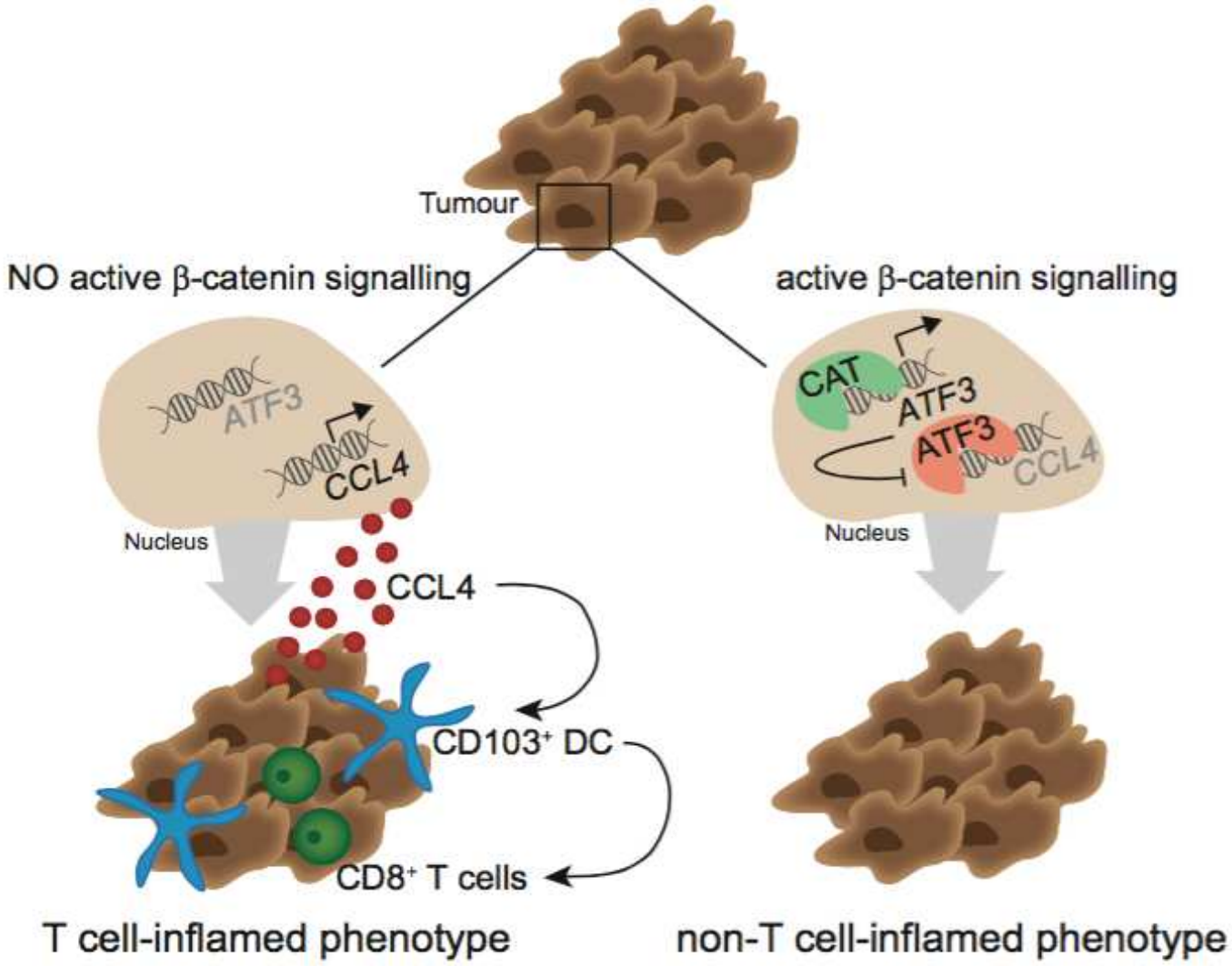


Spranger et al. PNAS 2016

Intratumoral T-cell infiltration/Non T-cell inflammed

Immunodynamics, biomarkers

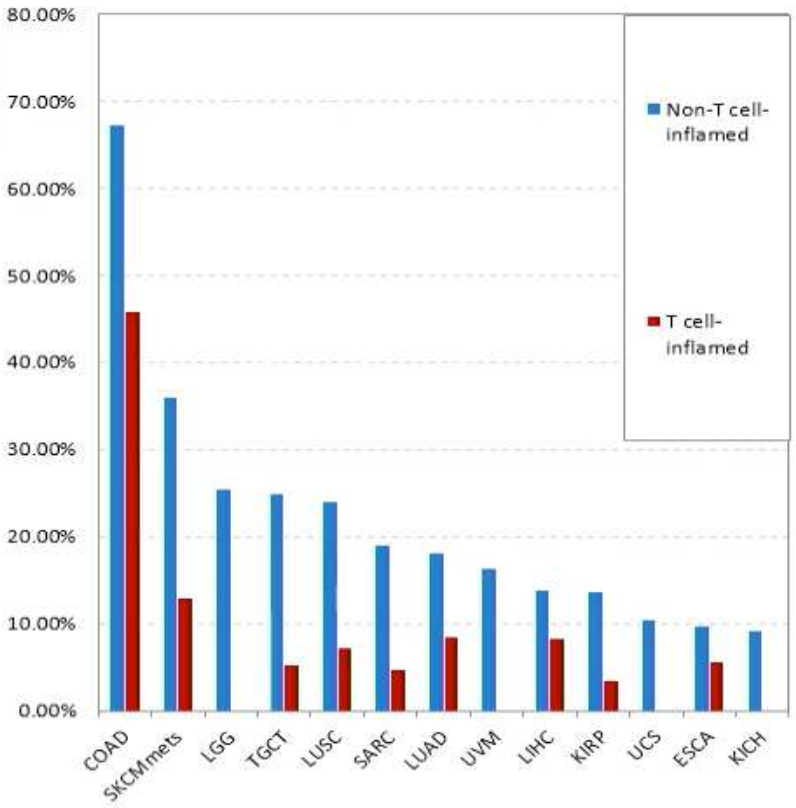
β-catenin and priming defects



Spranger et al. Nature 2015

Tumor types with excess β-catenin pathway activation in the non-T cell-inflamed subset

Cancer Abbrev	Cancer Type	Non-T cell-inflamed	T cell-inflamed
COAD	Colon adenocarcinoma	67.39%	45.83%
SKCMmets	Skin Cutaneous Melanoma (metastatic)	36.11%	12.93%
LGG	Brain Lower Grade Glioma	25.41%	0.00%
TGCT	Testicular Germ Cell Tumors	25.00%	5.19%
LUSC	Lung squamous cell carcinoma	24.00%	7.21%
SARC	Sarcoma	19.12%	4.82%
LUAD	Lung adenocarcinoma	18.18%	8.57%
UVM	Uveal Melanoma	16.36%	0.00%
LIHC	Liver hepatocellular carcinoma	13.79%	8.33%
KIRP	Kidney renal papillary cell carcinoma	13.64%	3.51%
UCS	Uterine Carcinosarcoma	10.53%	0.00%
ESCA	Esophageal carcinoma	9.71%	5.56%
KICH	Kidney Chromophobe	9.30%	0.00%

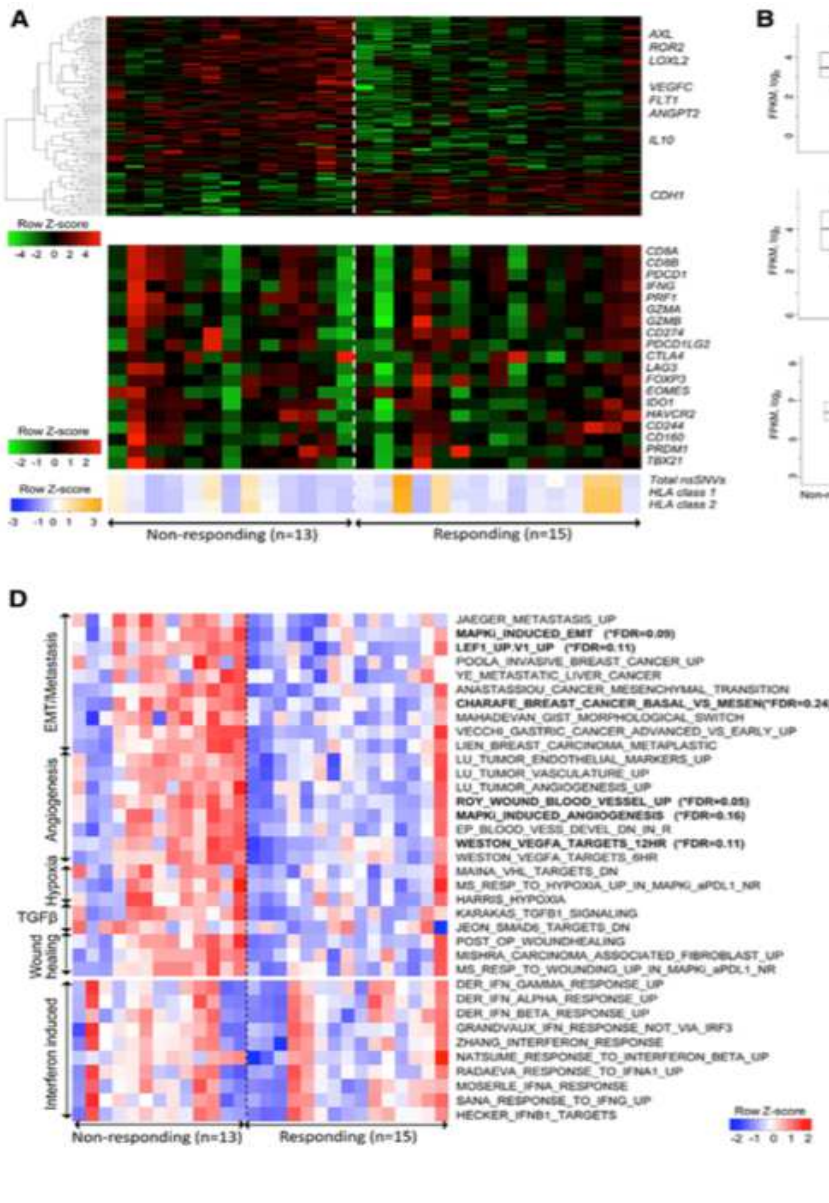


Gajewski et al. ASCO 2016

Intratumoral T-cell infiltration/Non T-cell inflammed

d) Immunosuppressive microenvironment

Immunodynamics, biomarkers (anti-PD-1/L1)

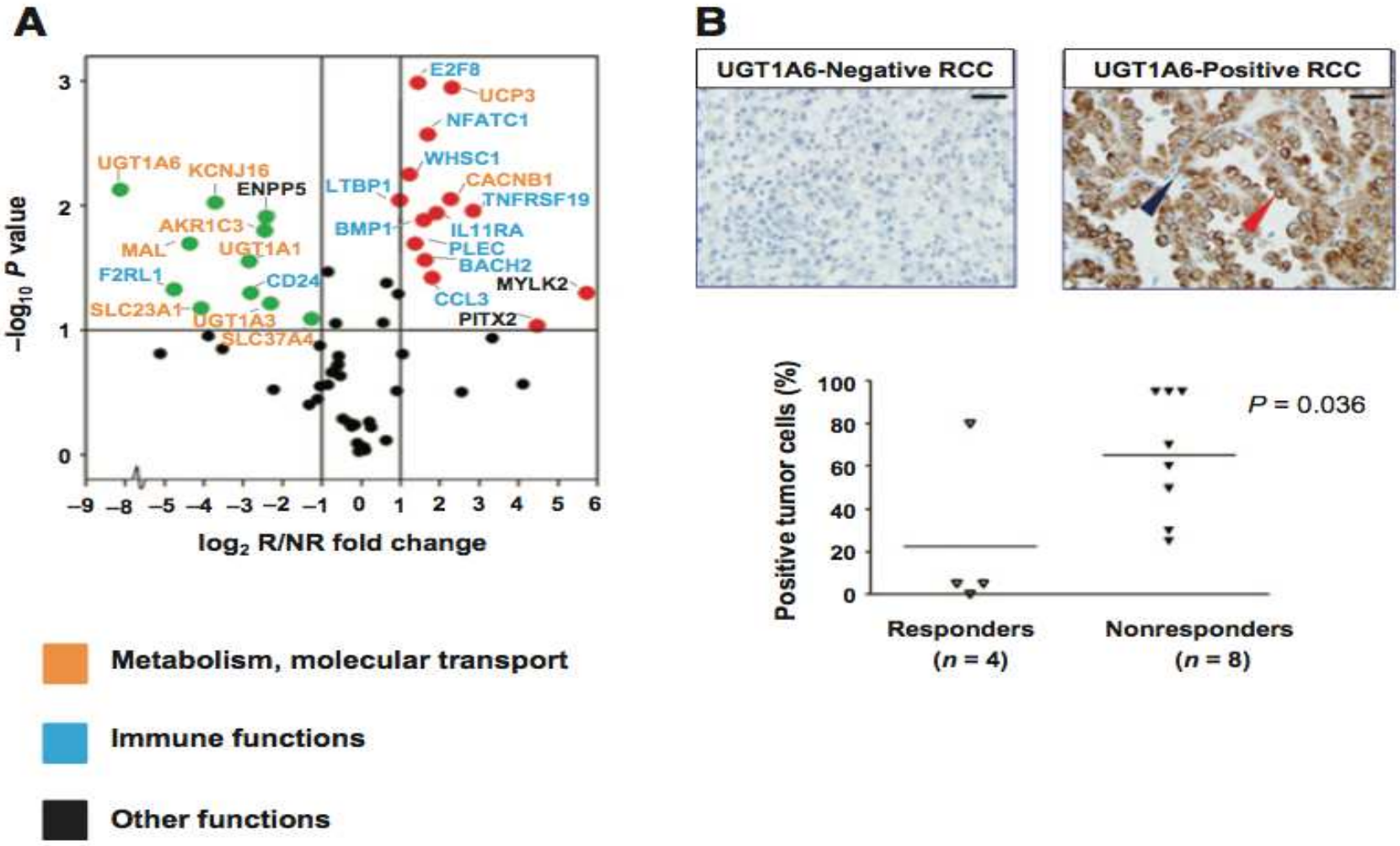


Hugo et al. Cell 2016

Intratumoral T-cell infiltration/Non T-cell inflammed

d) Metabolic reprogramming, antioxidant signature

Immunodynamics, biomarkers (anti-PD1/L1)



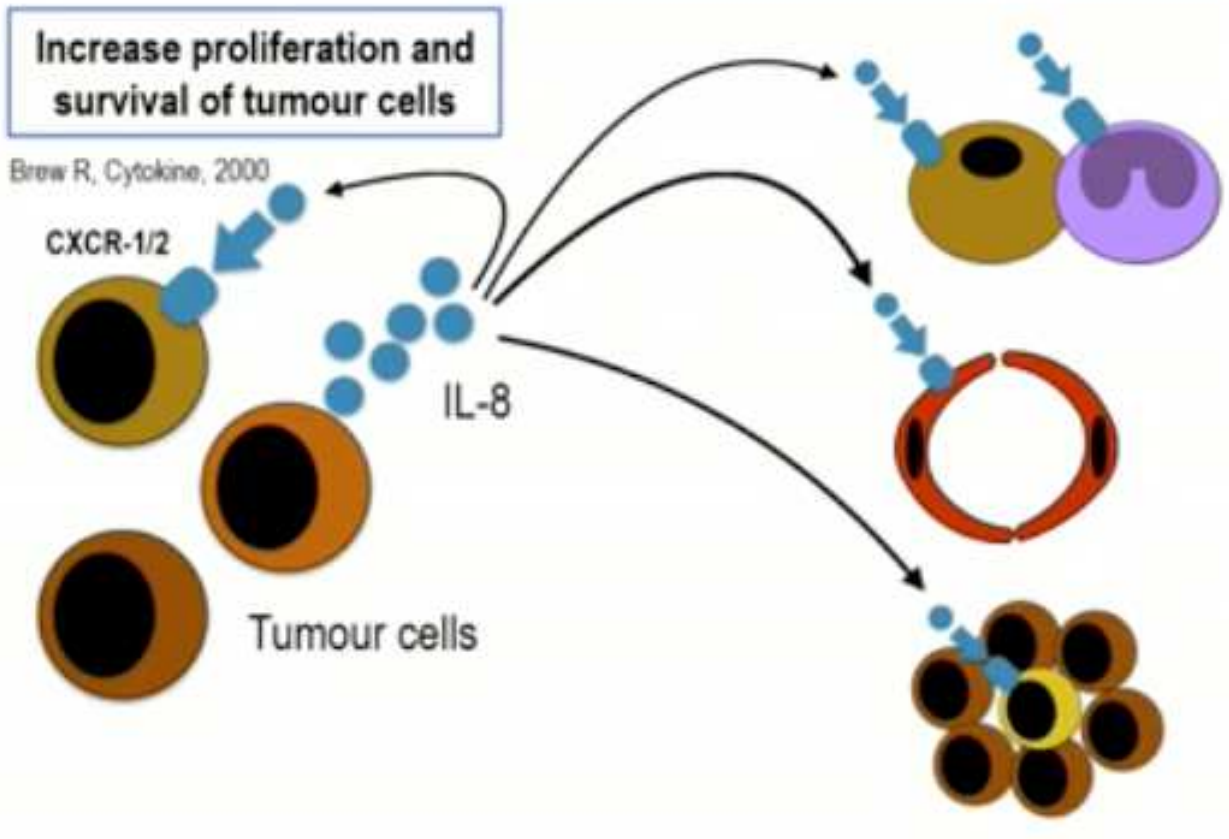
Ascierto et al. Cancer Immunol Res 2016

Some T-cell immunosuppressive molecules (or surrogates of T-cell suppressive states) can be measured in blood and potentially used to monitor or predict outcome of checkpoint inhibitors

- IL-1, IL-6, IL-8, IL-17, CXCL1, VEGF, CRP
- Neutrophil/lymphocyte count
- Myeloid-derived suppressor cell counts
- LDH

Blank et al. Science 2016

IL-8 is a chemokine secreted by malignant cells and has different protumoral actions



Chemoattraction of Myeloid cells

Baggiolini M, J Clin Invest, 1989

Alfaro C, Clin Cancer Res, 2016

Promote angiogenesis

Koch E, Science, 1992

Strieter RM, J Biol Chem, 1995

Favour cancer stem cells

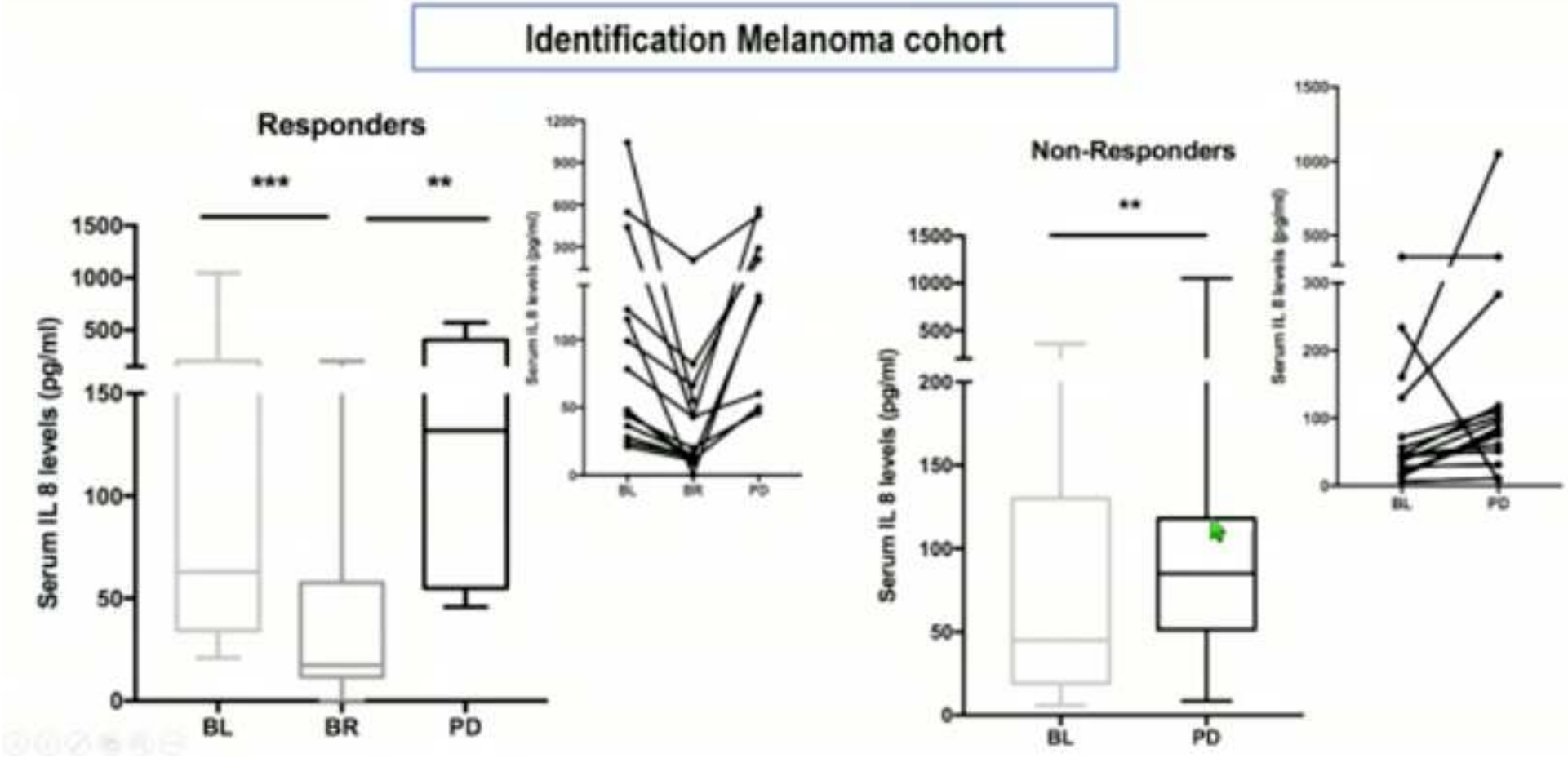
Infanger DW, Cancer Res, 2013

Singh JK, Breast Cancer Res, 2013

ESMO congress

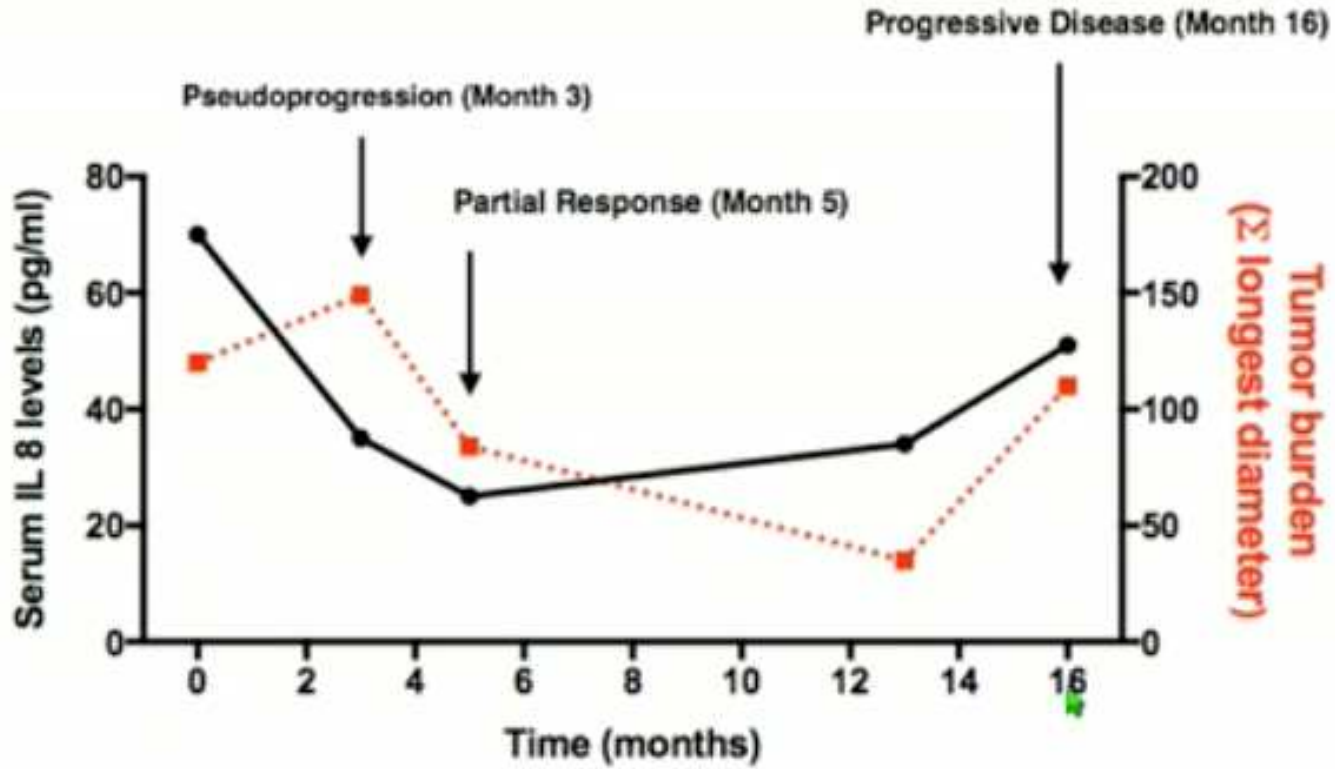
Sanmamed et al. ESMO 2016

Changes in serum IL-8 levels reflect tumor response to anti-PD-1 mAbs in melanoma patients



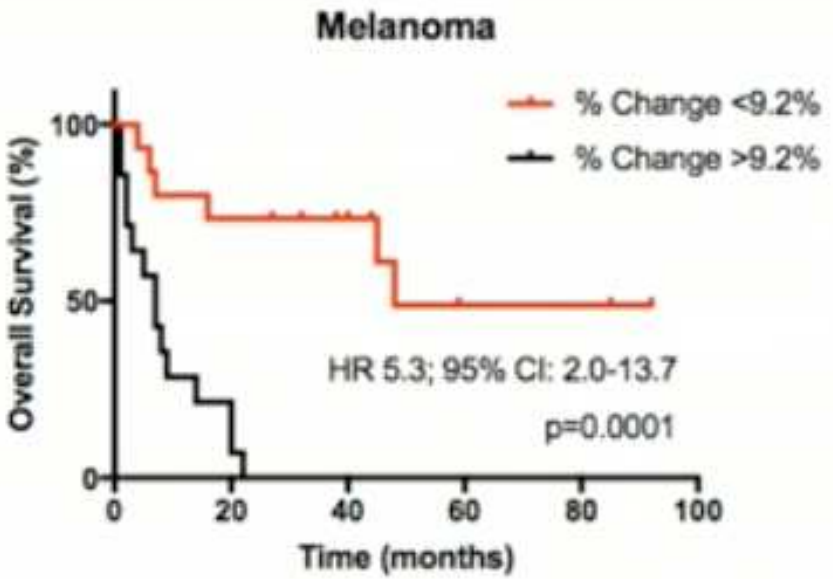
Sanmamed et al. ESMO 2016

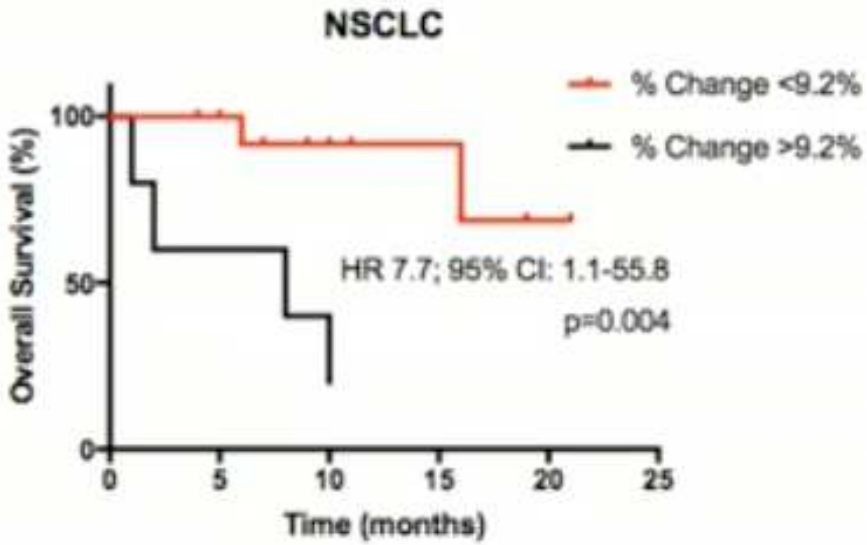
Serum IL8 levels correctly reflected true response in a patient presenting pseudoprogression



Sanmamed et al. ESMO 2016

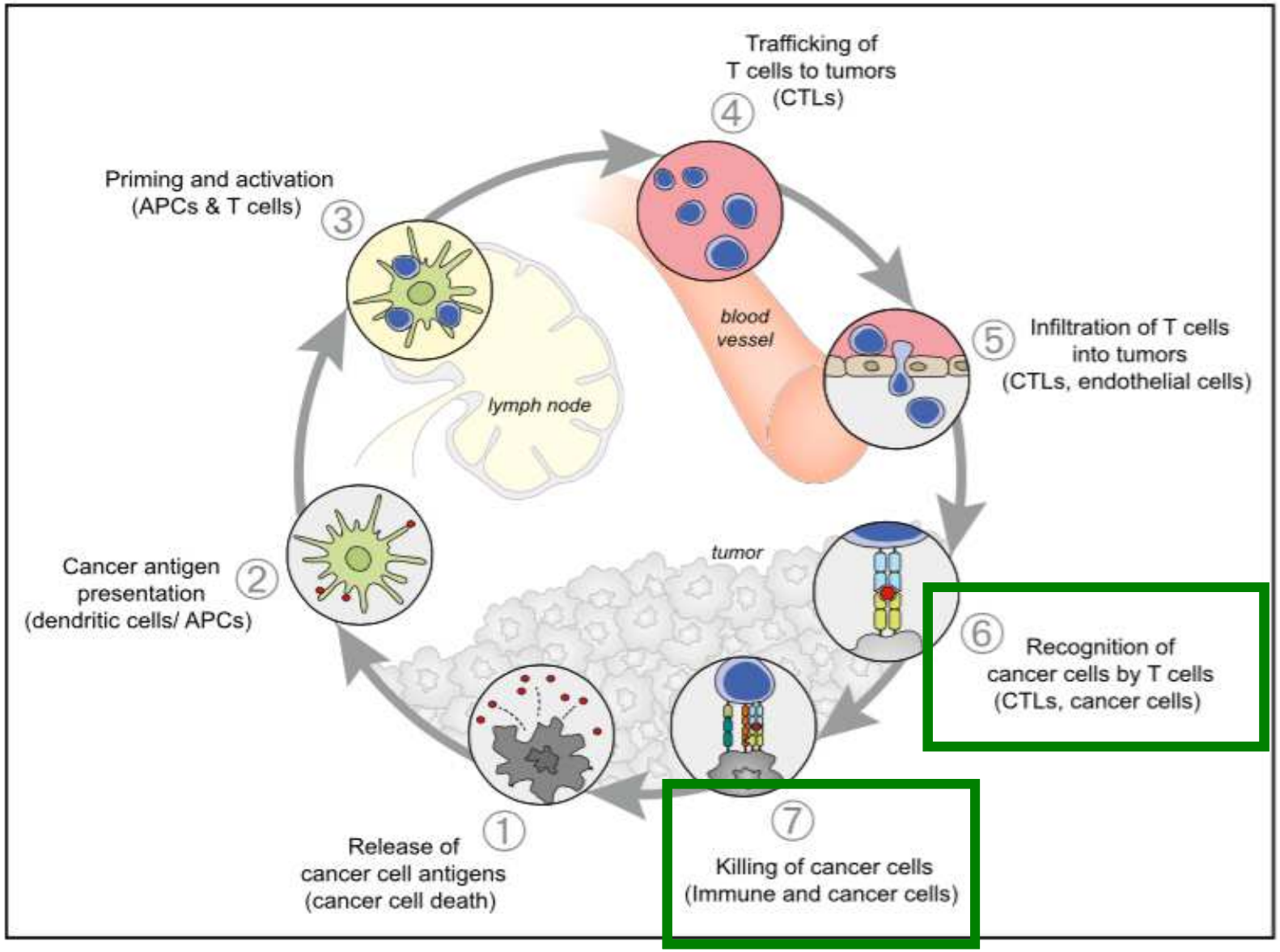
Changes in serum IL-8 levels are associated with OS in cancer patients treated with anti-PD-1 mAbs





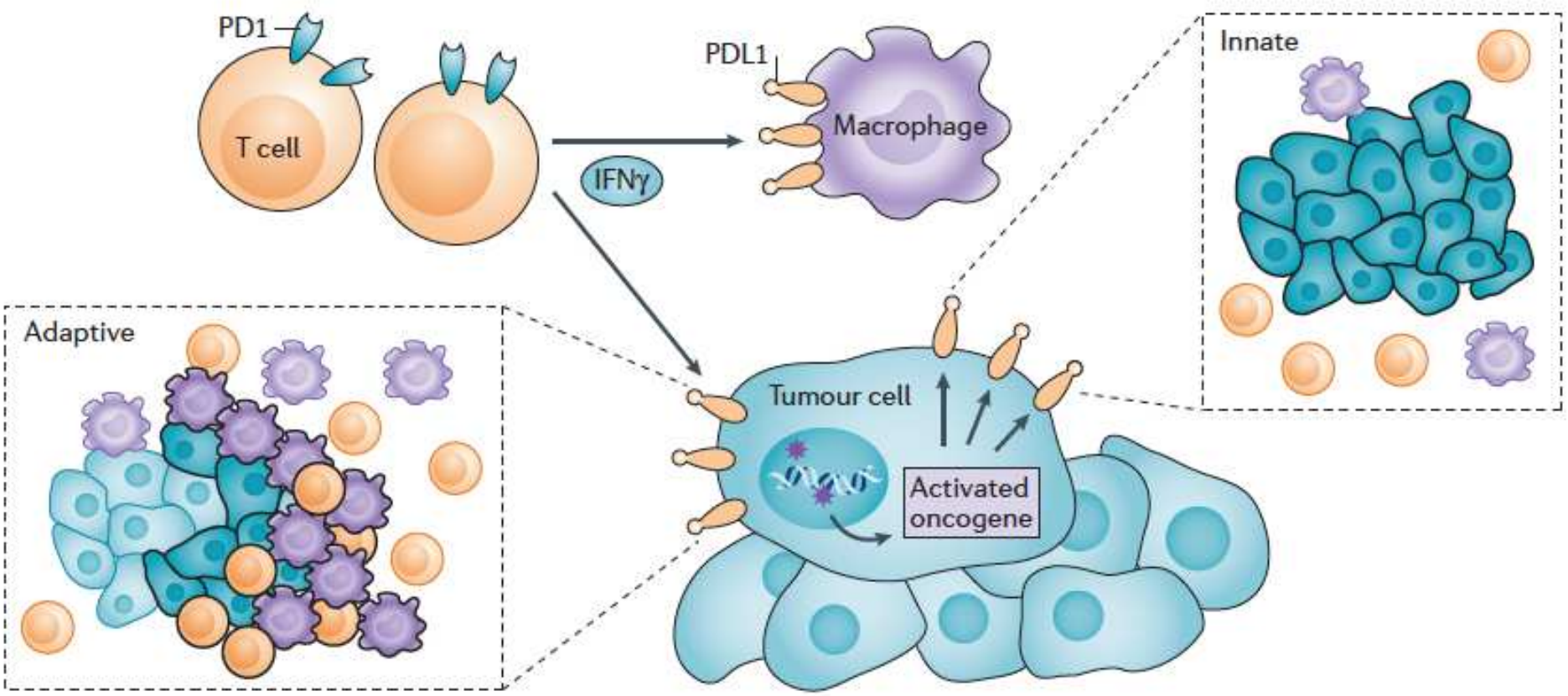
ESMO congress

Sanmamed et al. ESMO 2016



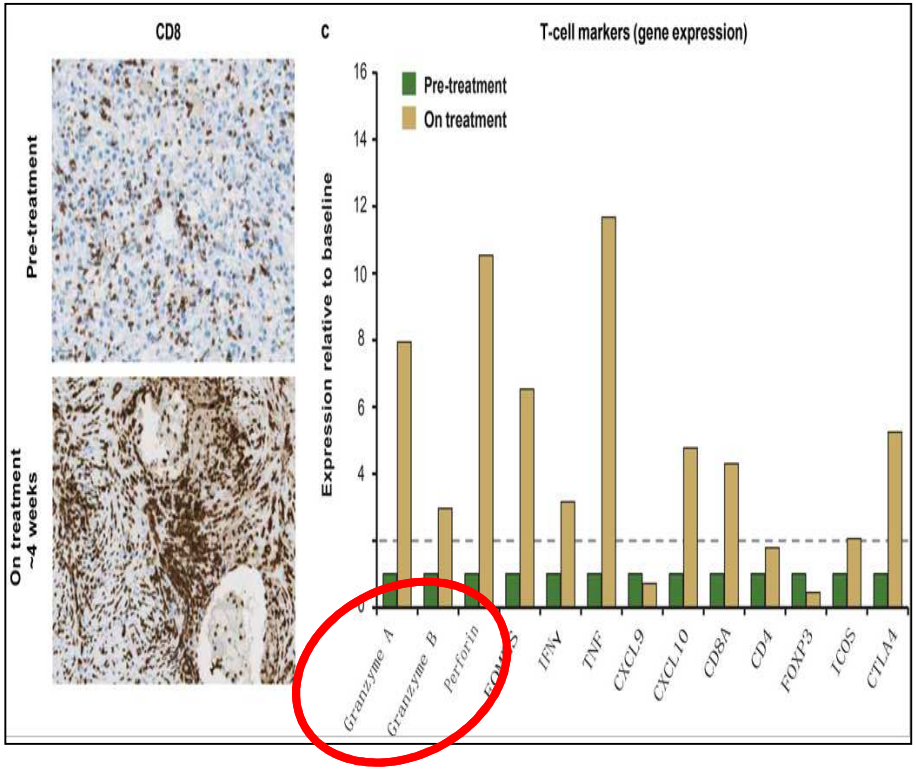
Chen et al. Immunity 2013

Adaptive vs. innate PD-L1 expression

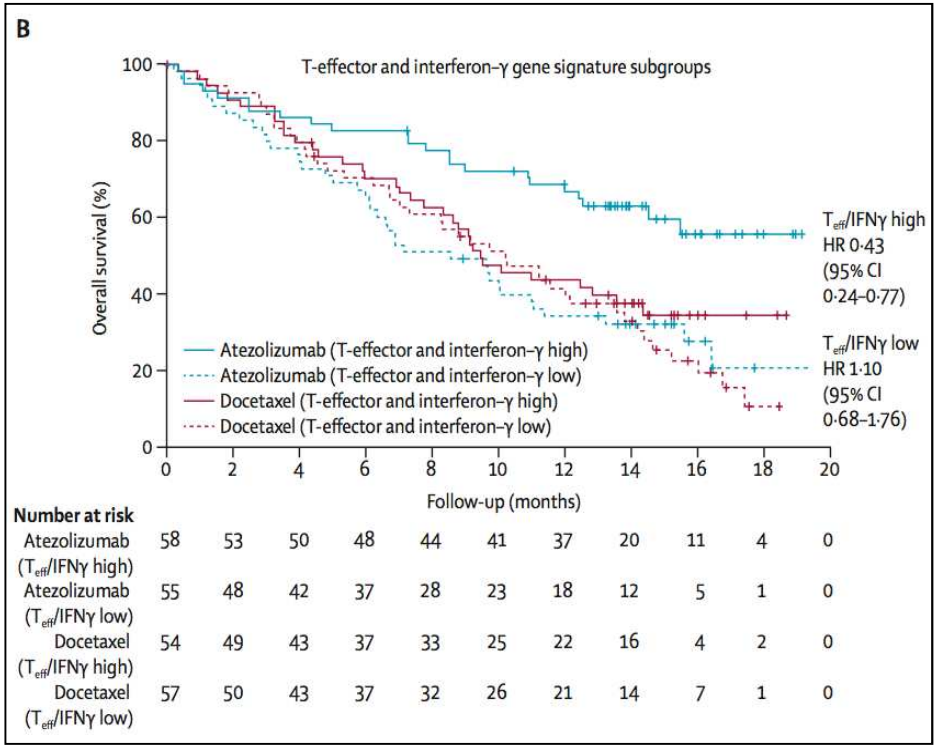


Topalian et al. Nat Rev Cancer 2016

T-cell effector markers

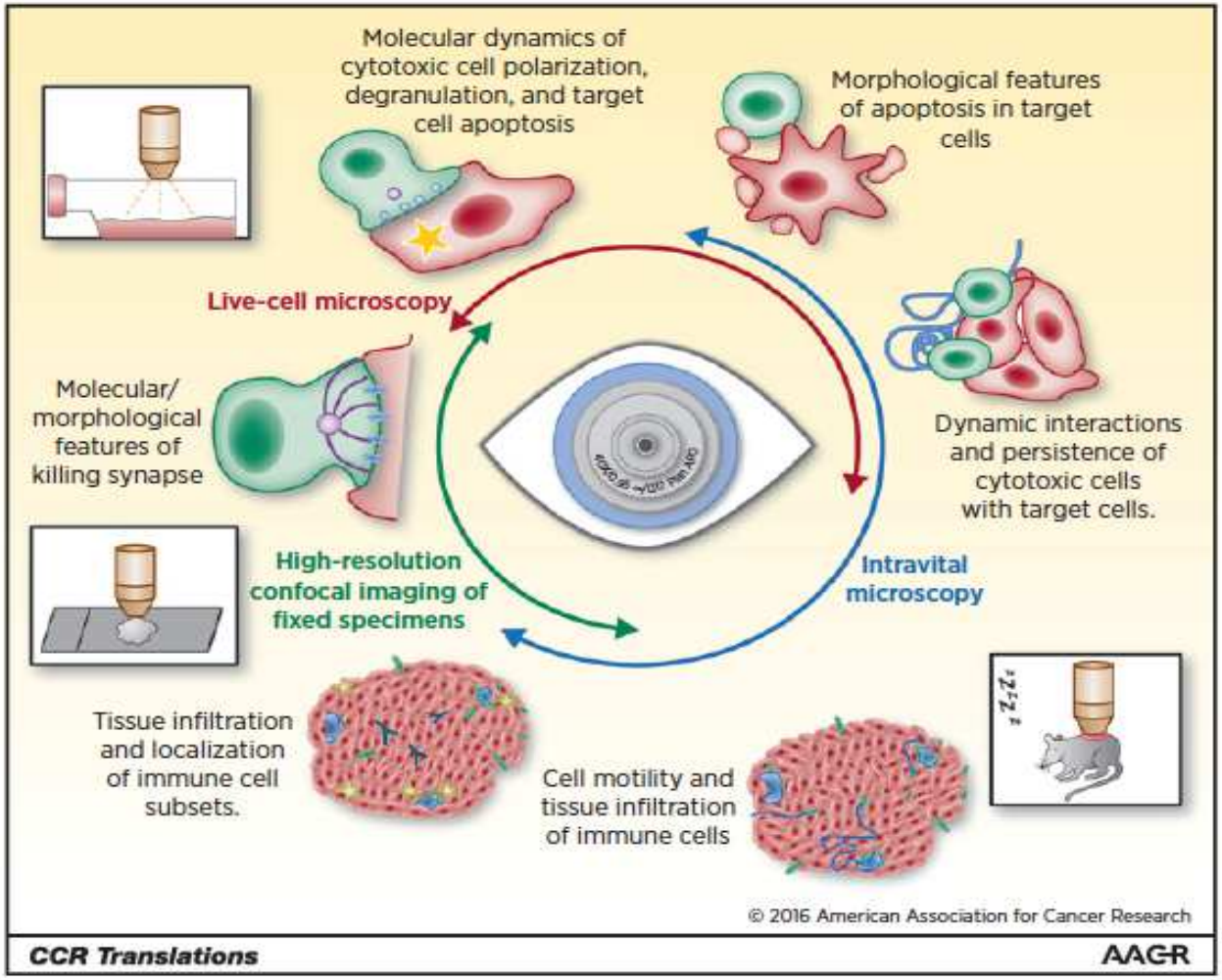


Herbst et al. Nature 2014



Fehrenbacher et al. The Lancet 2016

Advanced microscopy techniques to evaluate cancer immunotherapies



Teijeira et al. Clin Can Res 2016

CONCLUSIONS

- The efficacy of many immune therapies in cancer (particularly anti-PD-1/L1 drugs) relies on pre-existing immunity, in particular on the presence or generation of tumor reactive T-cells.

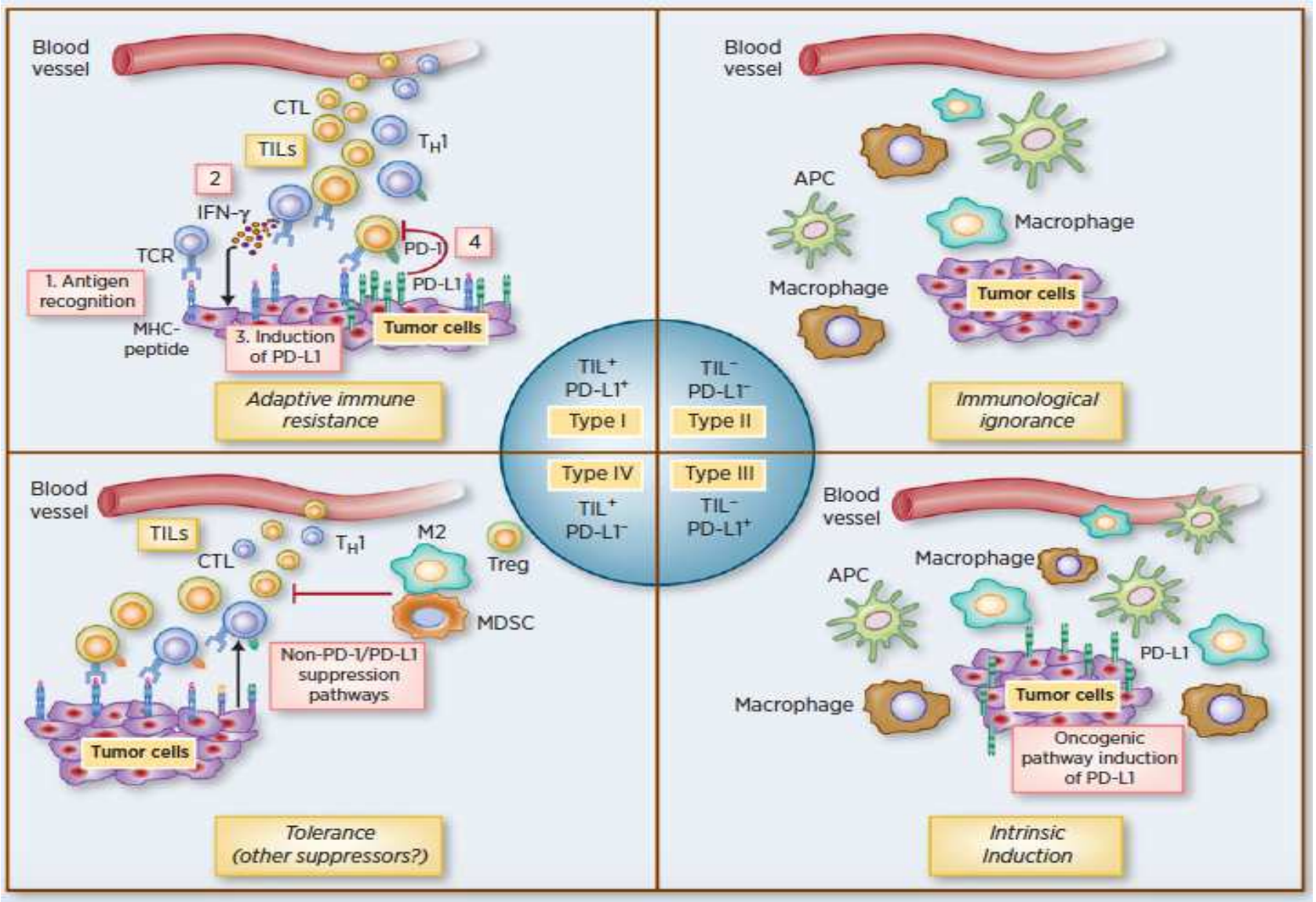
- Surrogate dynamic molecular markers of the presence or absence of adaptive T-cell immune activation (or T-cell immune suppression) can be analyzed in tumor or blood as predictive markers for therapy response or treatment monitoring with anti-PD-1/L1 drugs.

- On the pillar of PD-1 pathway blockade, many combinatorial strategies in clinical development seek to induce T-cell infiltration and/or reverse other immune suppressive mechanisms in the tumor microenvironment.

- Serial pre- and post treatment biopsies and blood collections are paramount in new immune therapy development (early immune-based trials)

- Other tools to measure dynamic changes in the immune and tumor microenvironment might be helpful for translational research

¿Como seleccionar pacientes candidatos a anti-PD-1/L1?

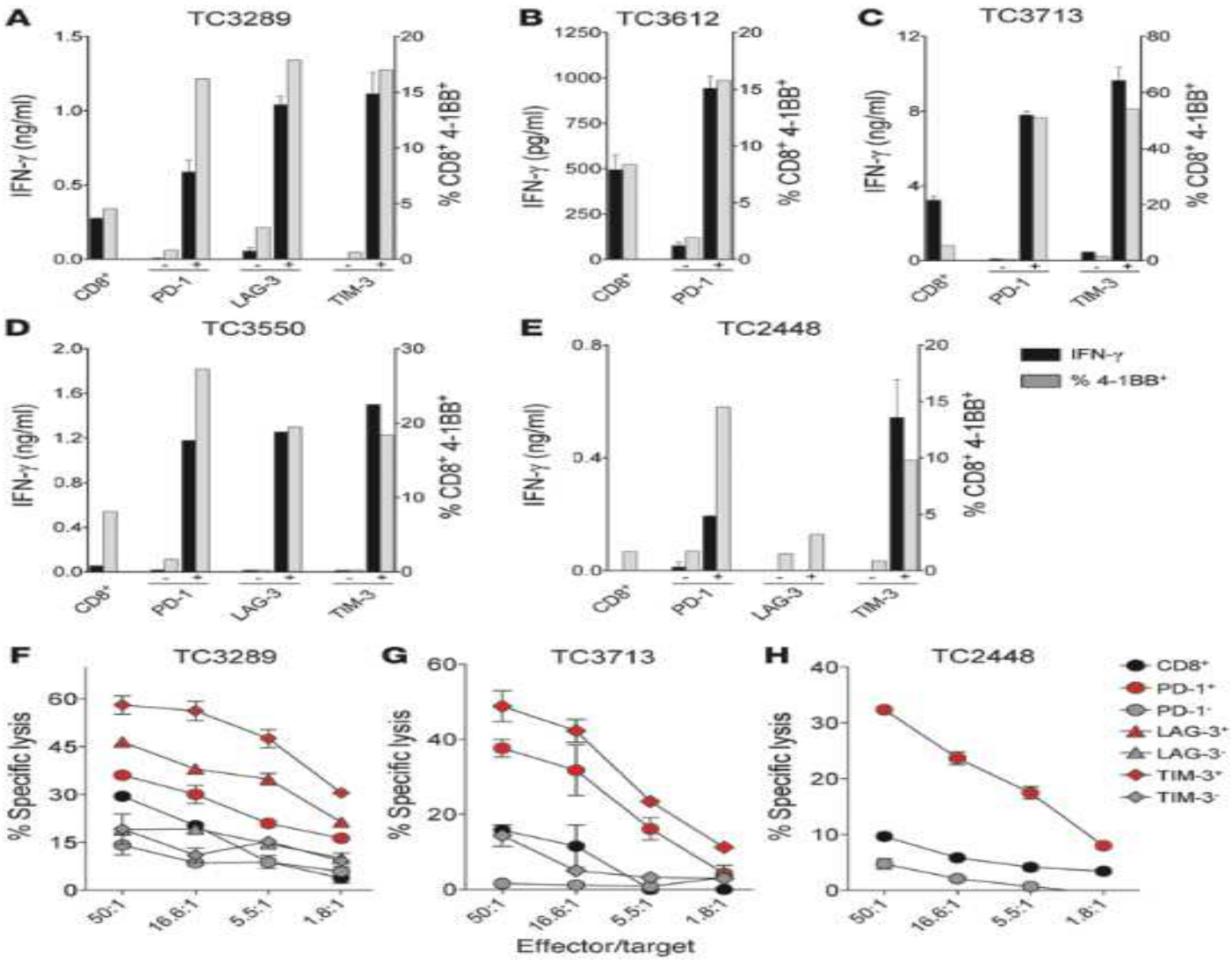


Teng et al. Cancer Res 2015

3. Intratumoral T-cell infiltration

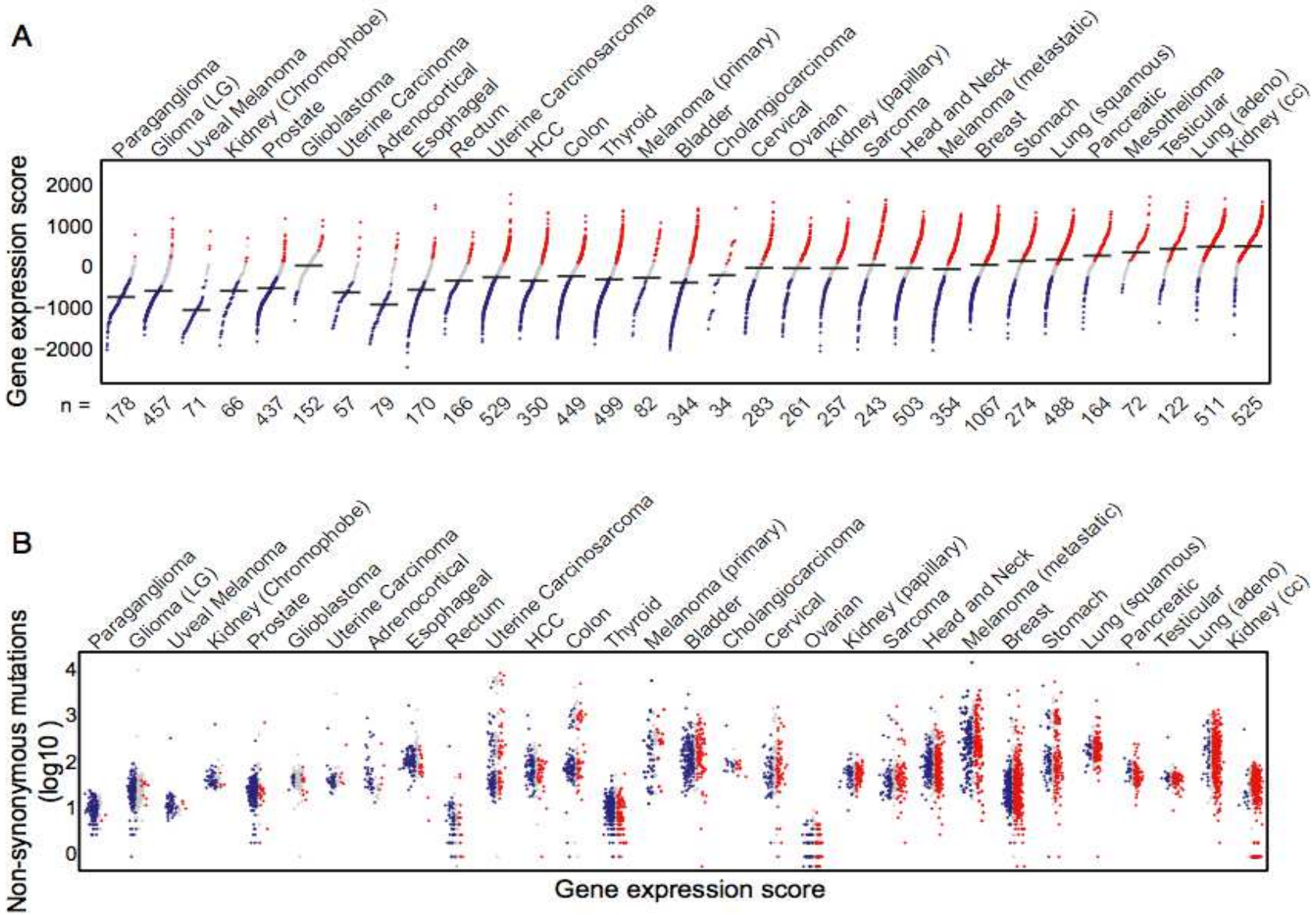
Tumor reactive TILs: CD8-PD-1+

Predictive biomarkers



Gajewski et al. Nat Immunol 2013

b) Neoantigen burden



Spranger et al. PNAS 2016

Kohrt et al. Journal for ImmunoTherapy of Cancer (2016) 4:15
DOI 10.1186/s40425-016-0118-0

Journal for ImmunoTherapy of Cancer

REVIEW Open Access

Immunodynamics: a cancer immunotherapy trials network review of immune monitoring in immuno-oncology clinical trials

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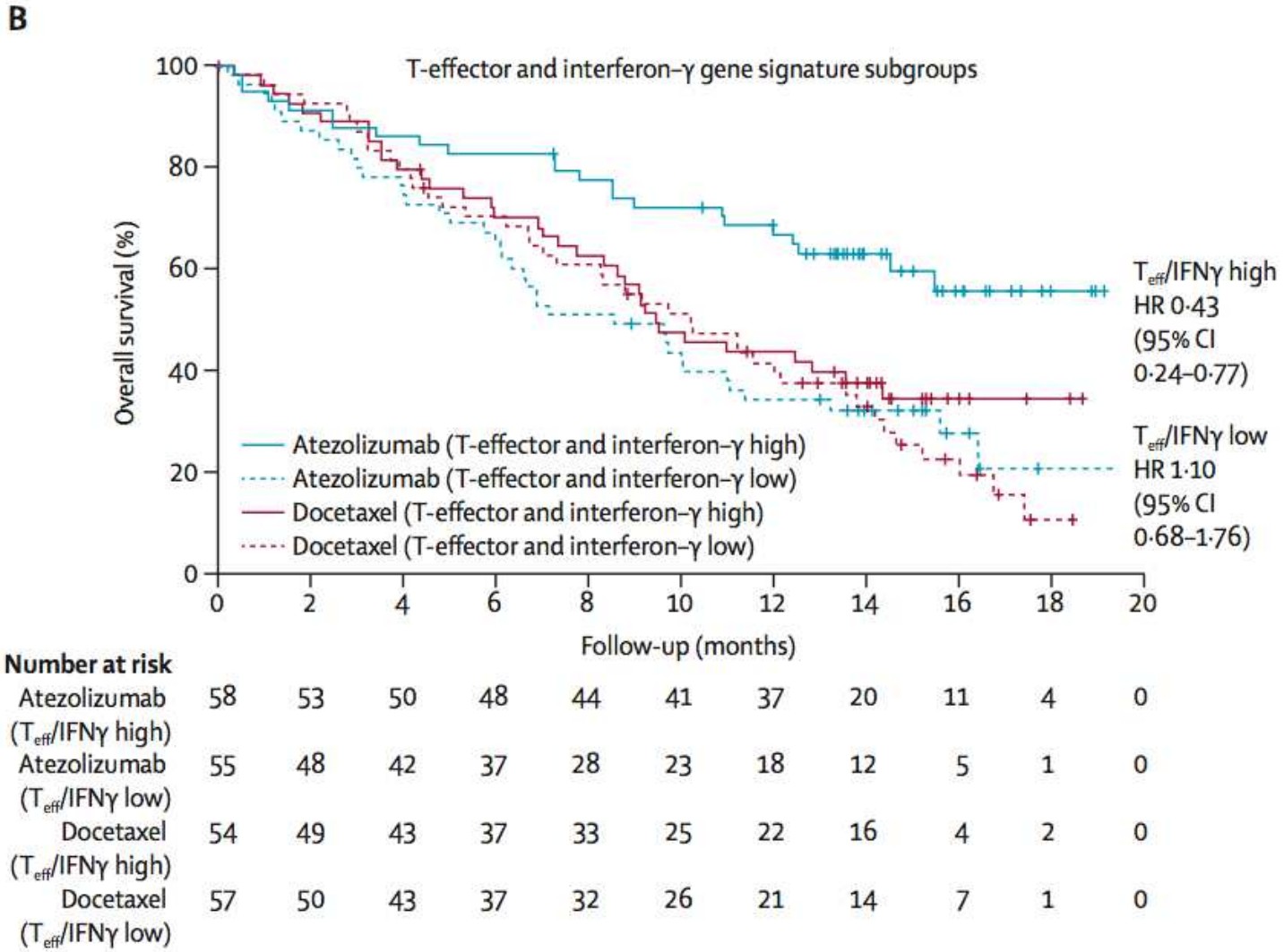
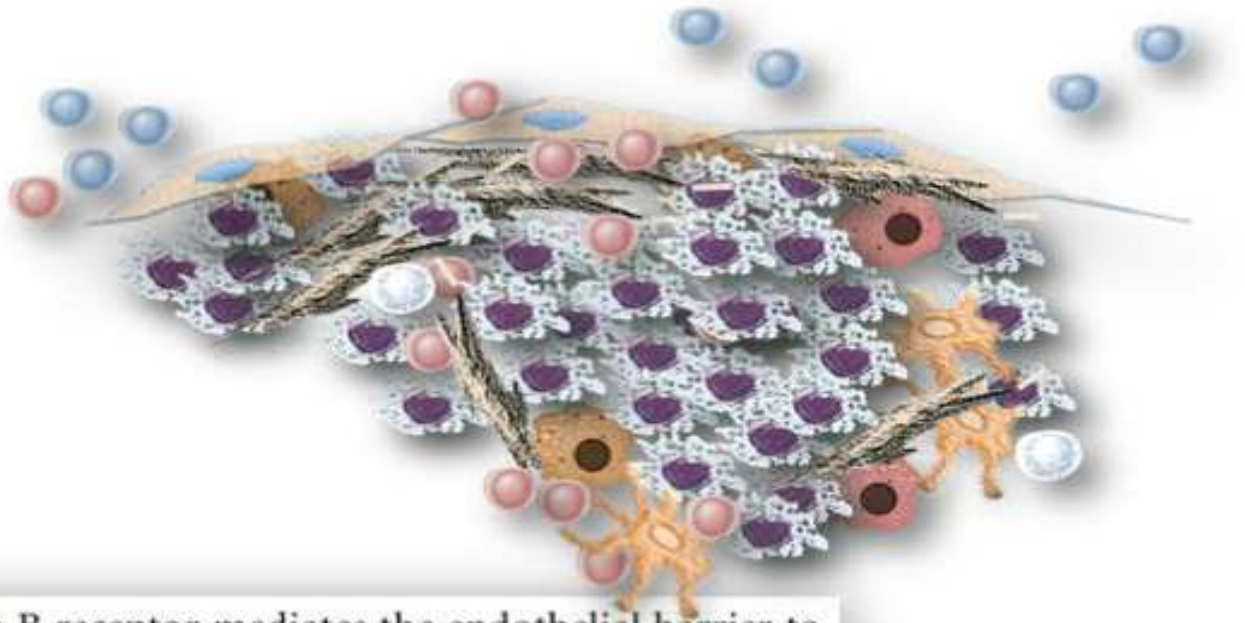


Fehrenbacher et al. The Lancet 2016

Intratumoral T-cell infiltration/Non T-cell inflammed **Immunodynamics, biomarkers**

a) Endothelial barrier

The Endothelial Barrier Hypothesis



Endothelin B receptor mediates the endothelial barrier to T cell homing to tumors and disables immune therapy

Ronald J Buckanovich[1,2,7,8], Andrea Facciabene[1,8], Sarah Kim[1], Fabian Benencia[1,3], Dimitra Sasaroli[1,4], Klara Balint[1], Dionysios Katsaros[6], Anne O'Brien-Jenkins[1], Phyllis A Gimotty[1,5] & George Coukos[1,3]

nature medicine

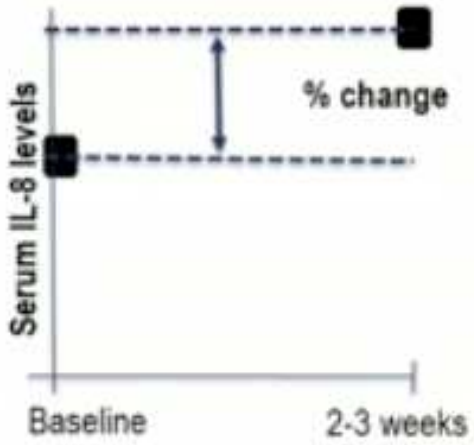
Tumor endothelium FasL establishes a selective immune barrier promoting tolerance in tumors

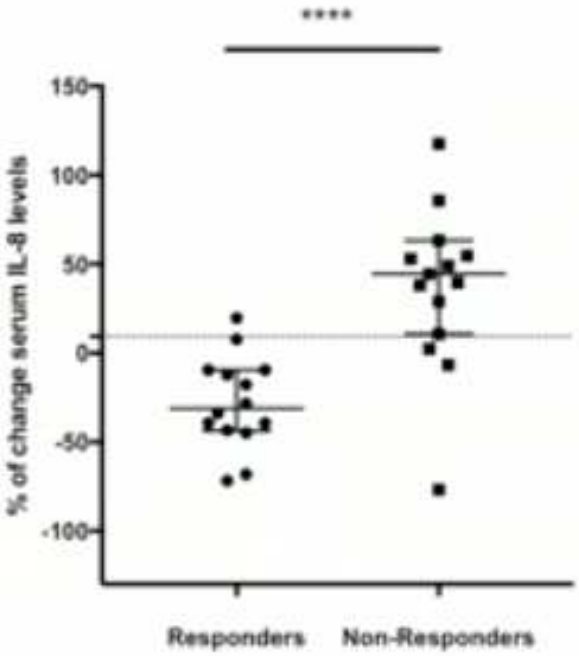
Gregory T Motz[1], Stephen P Santoro[1], Li-Ping Wang[2], Tom Garrabrant[1], Ricardo R Lastra[2], Ian S Hagemann[2], Priti Lal[2], Michael D Feldman[2], Fabian Benencia[1] & George Coukos[1,3]

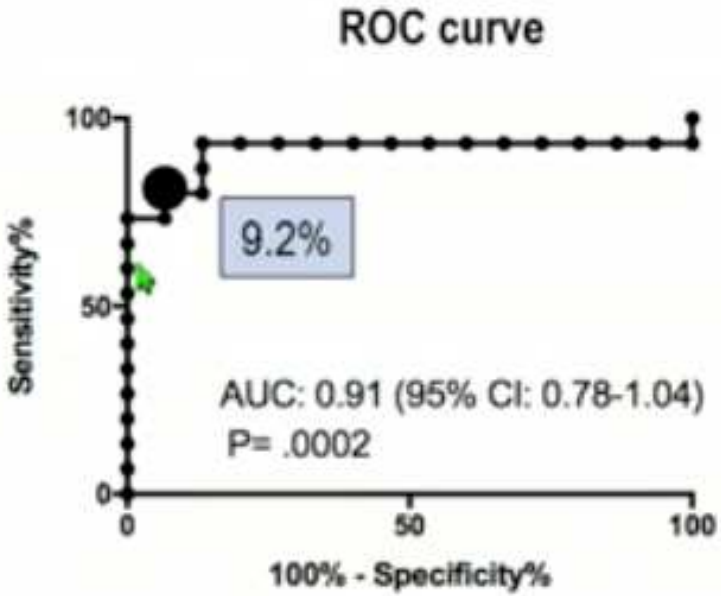
nature medicine

Early changes in serum IL-8 levels predict responses to anti-PD-1 mAbs in melanoma patients

Identification Melanoma cohort

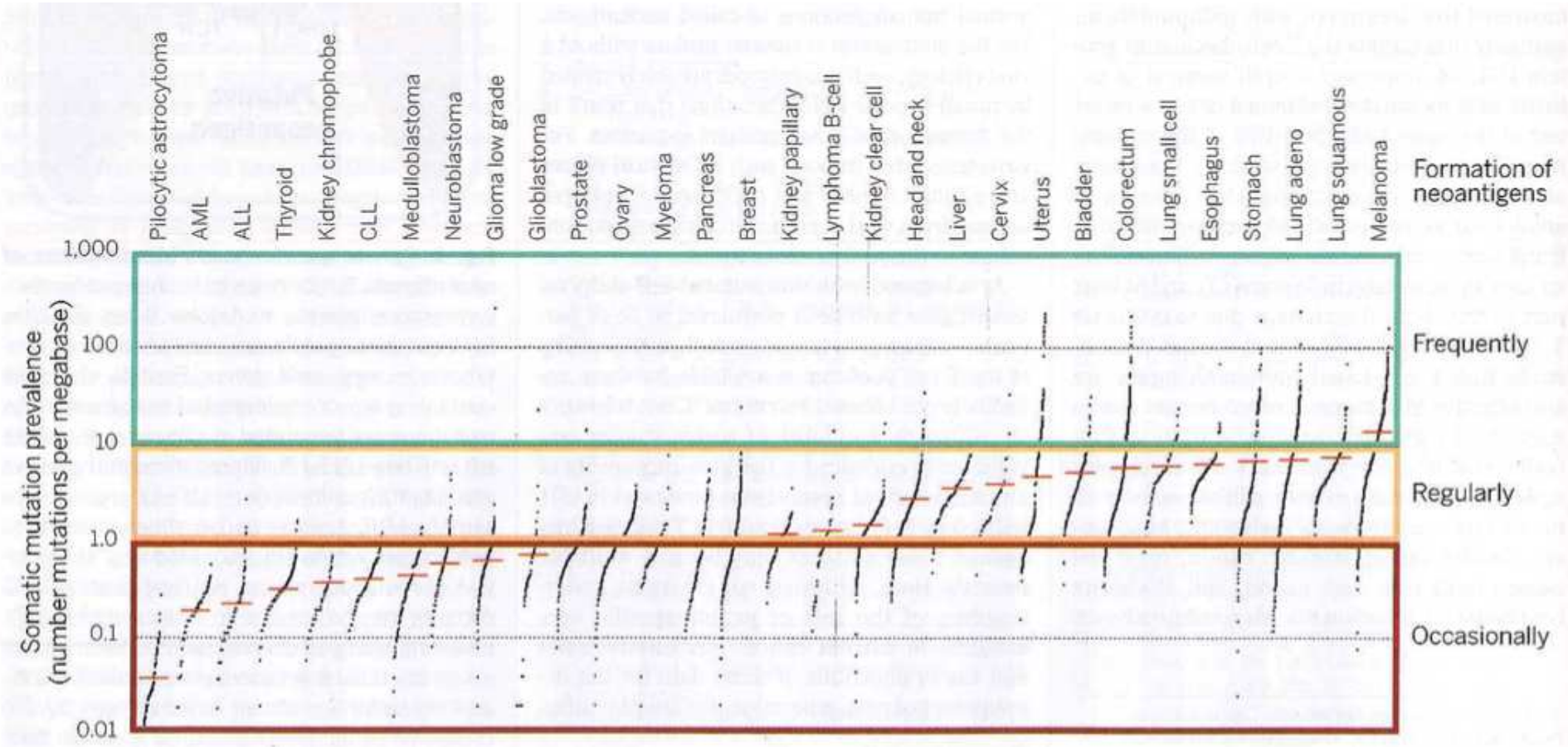






ESMO congress

Sanmamed et al. ESMO 2016



Schumacher et al. Science 2015