Overcoming T Cell Exhaustion

Brian S Henick, MD
Interim Director, Experimental Therapeutics
Director, Translational Research, Upper-Aerodigestive Malignancies, Medical Oncology
Assistant Professor of Medicine at CUIMC
Herbert Irving Comprehensive Cancer Center

Keith Allison, Kinston, USA

Derick E. Hingle-USA TODAY Sports


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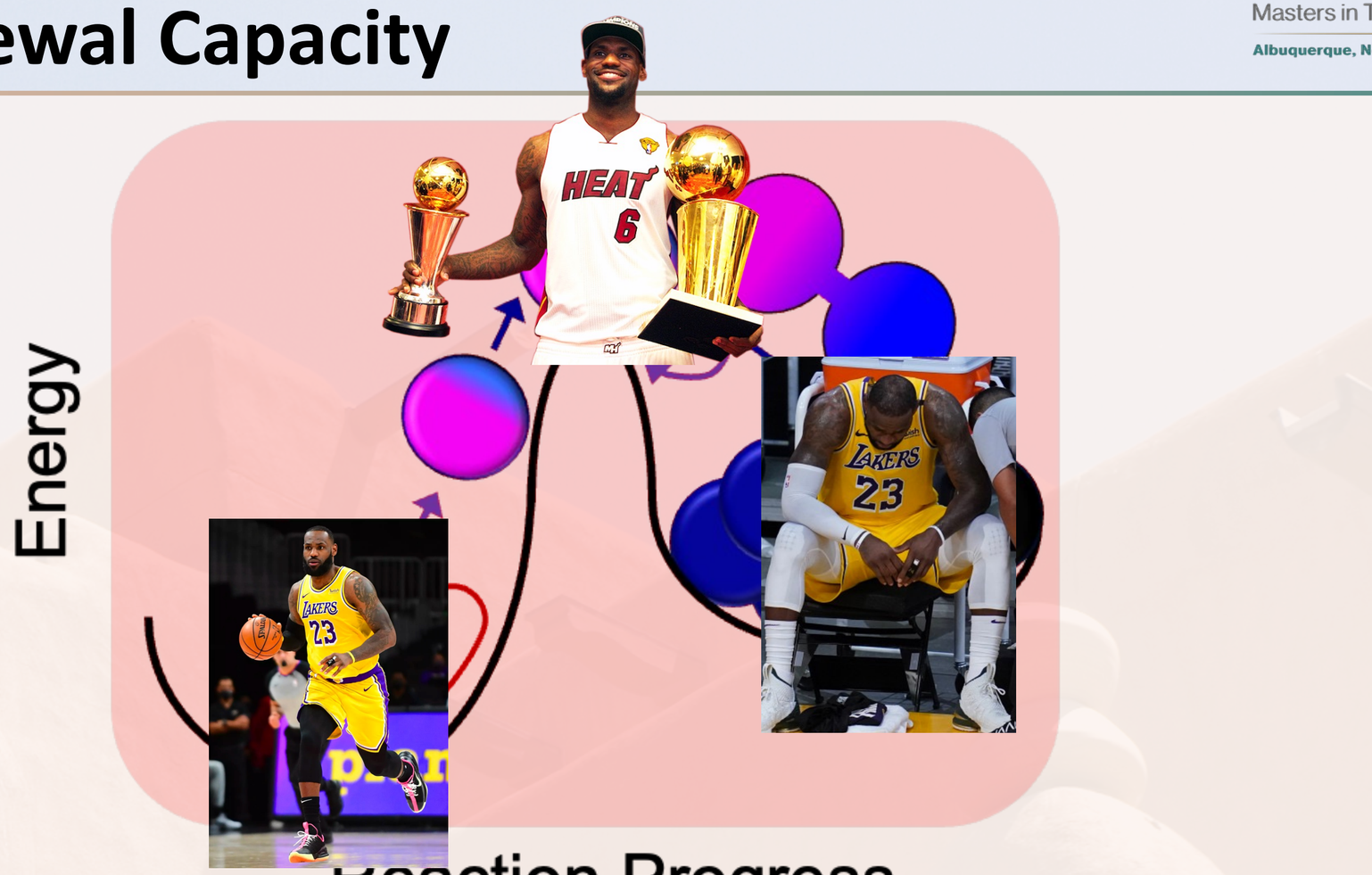
What Is T-Cell Exhaustion?
Immunologist's Perspective

- NP Restifo, RC Lynn: 'T cell exhaustion' is a basket term that describes various distinct epigenetic and metabolic states of post-thymic T cells
- A Kallies, D Zehn: effector T cells with a reduced capacity to secrete cytokines and increased expression of inhibitory receptors
- WN Haning, A Sharpe: T cell exhaustion does not involve the complete absence of function: exhausted T cells can proliferate in vivo, produce effector molecules, including inflammatory cytokines and granzymes, and exert some control over pathogens or tumours
- EJ Wherry: T cell exhaustion is an evolutionarily conserved adaptation to chronic antigen stimulation that is probably important to limit immunopathology or autoreactivity; thus, exhausted T cells are not inherently good or bad
- M Philip, A Schietinger: Exhausted T cells express inhibitory receptors but can retain some antipathogen effector function, resulting in a pathogen–host 'stalemate'

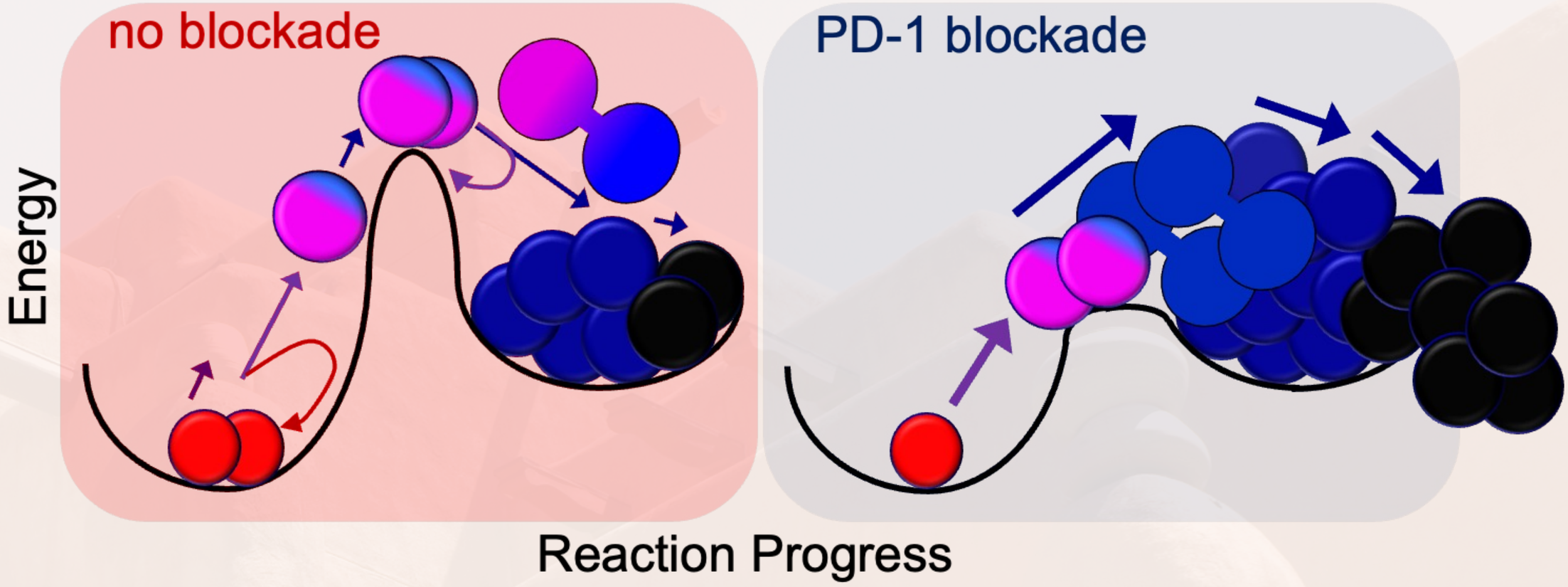
Blank, *Nat Rev Immunol* 2019

Anti-Tumor T-Cells Must Balance Differentiation with Self-Renewal Capacity



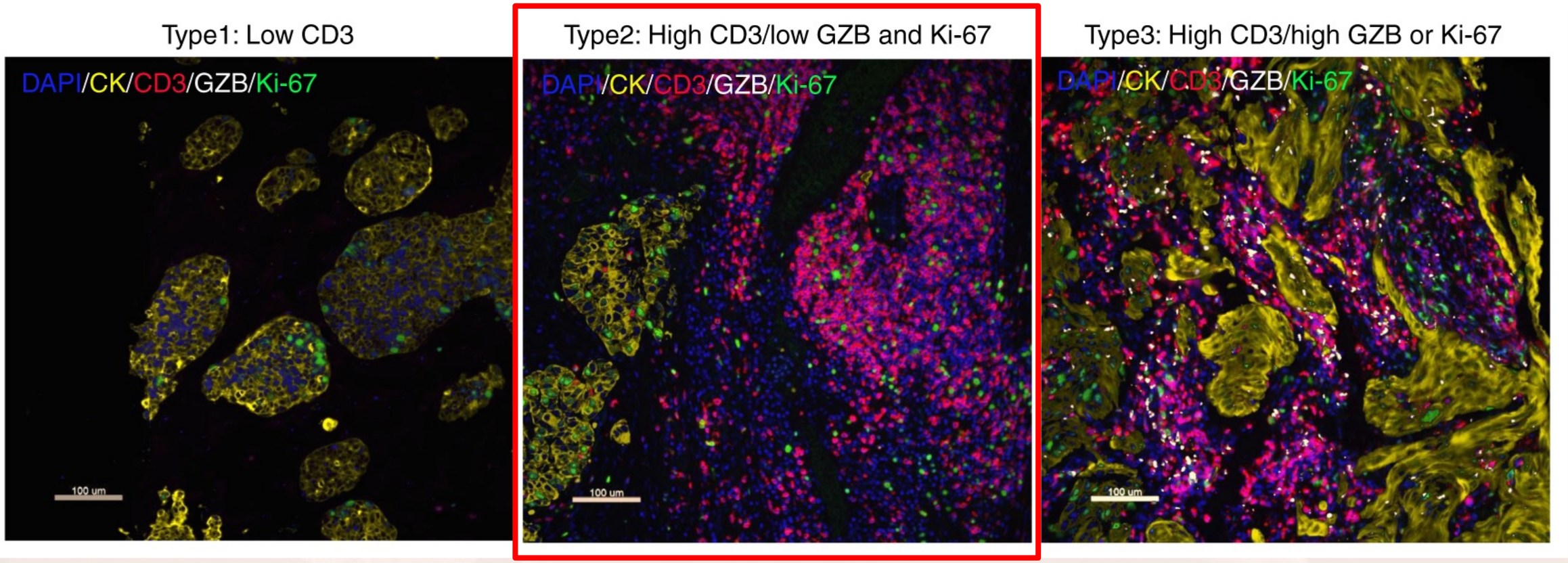
c/o Steven Reiner

PD-1 Blockade Promotes T-Cell Differentiation



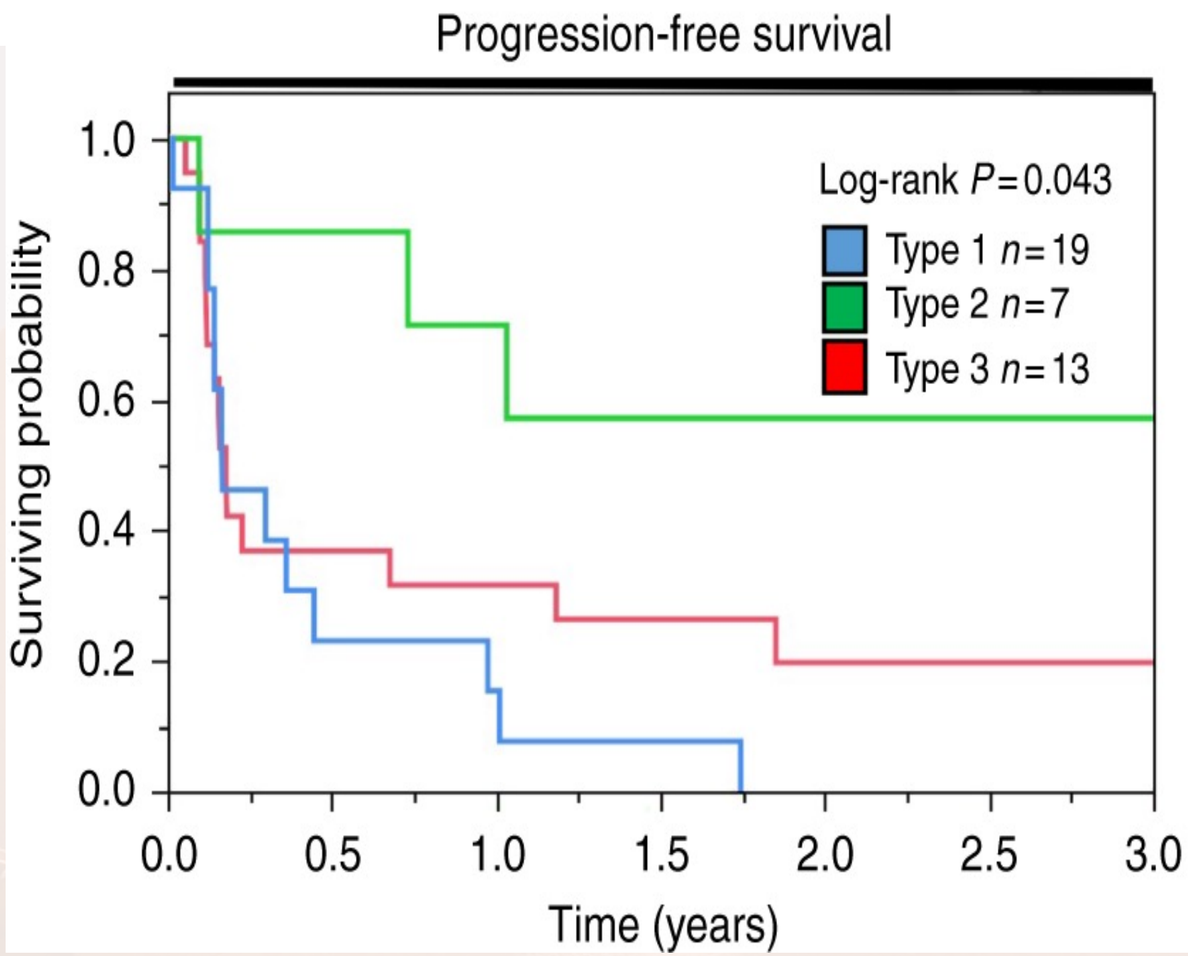
c/o Steven Reiner

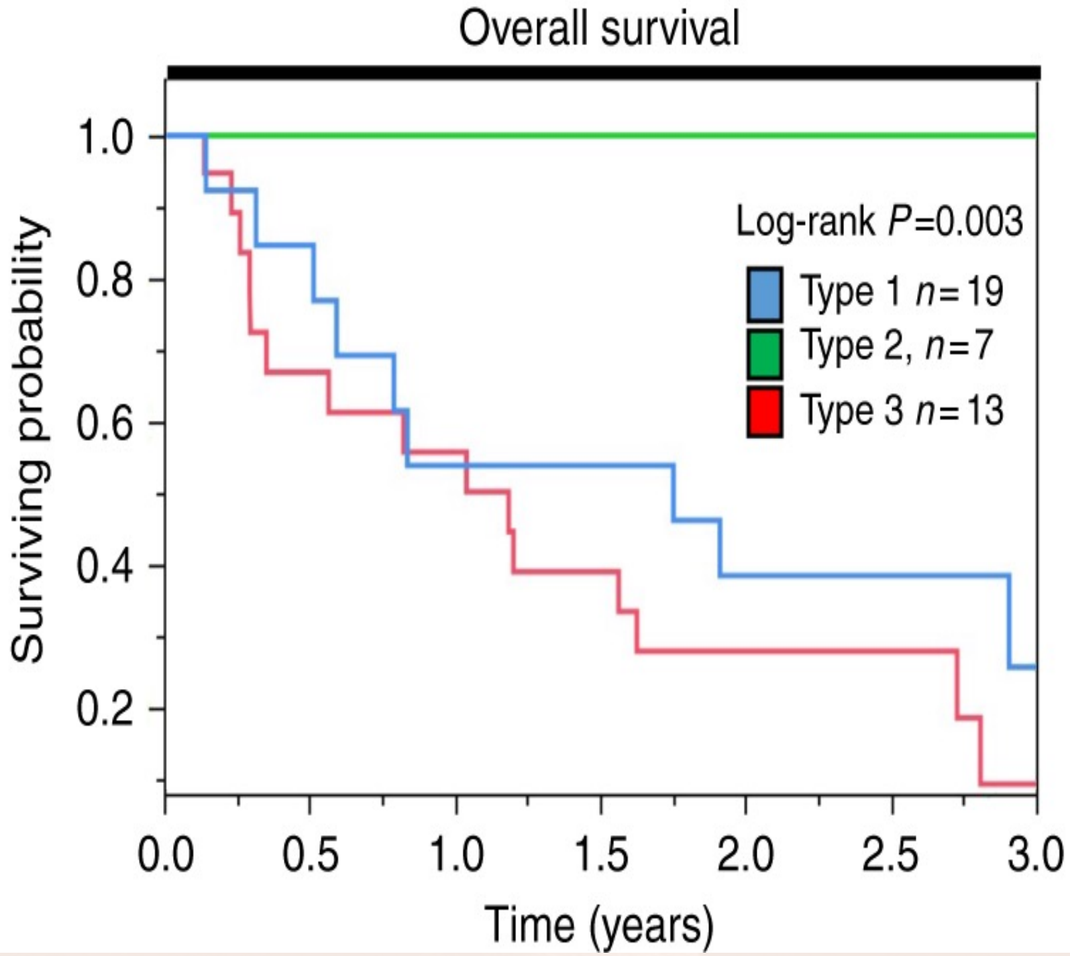
Activated T Cells Are Measurable in NSCLC



Gettinger, *Nat Comm* 2018

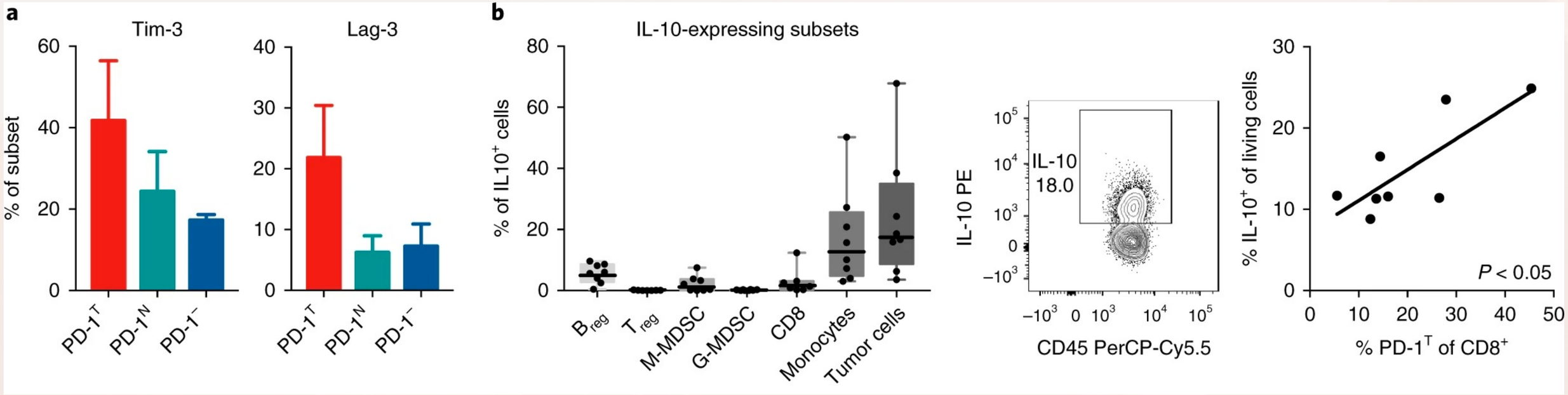
Activated T Cells Are Prognostic in NSCLC





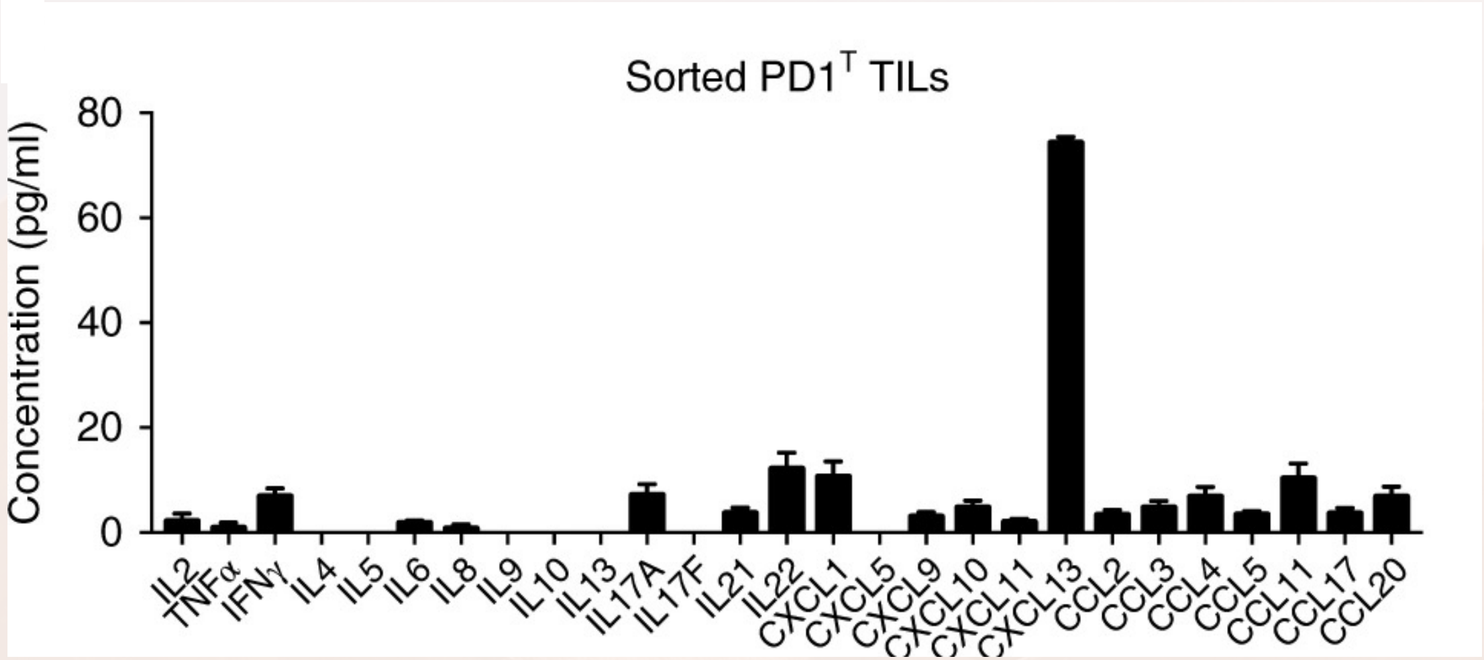
Gettinger, *Nat Comm* 2018

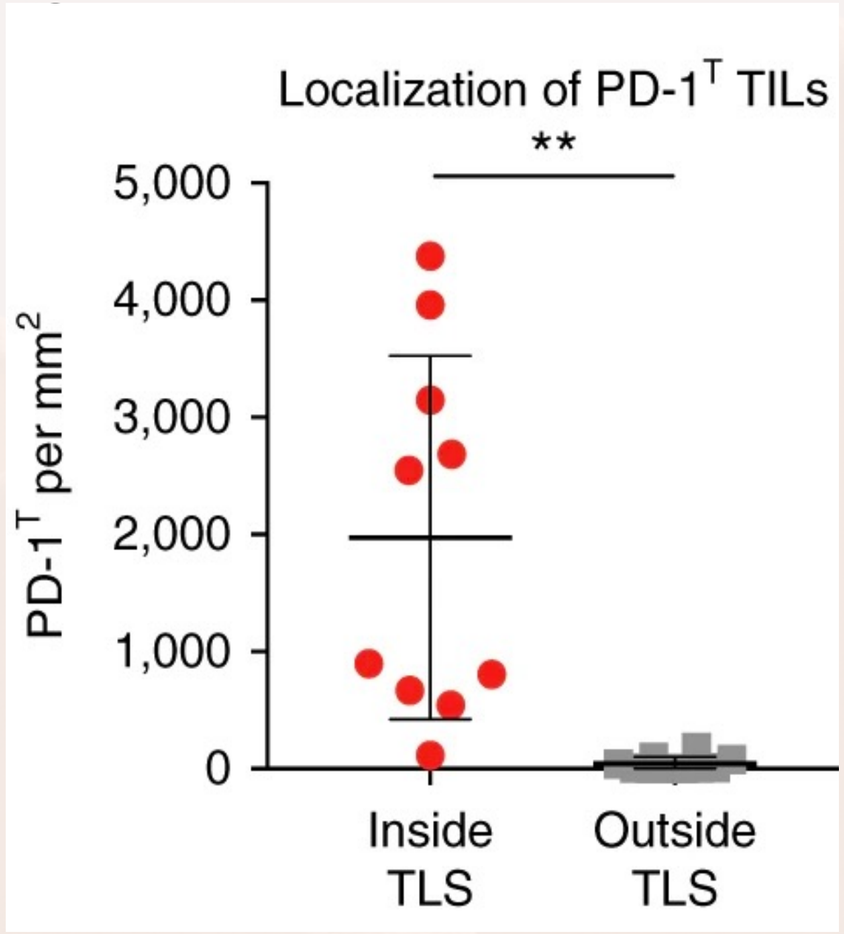
PD-1^{T} TILs in Lung Cancer Express Inhibitory Markers Suggestive of Dysfunction



Thommen, *Nat Med* 2018

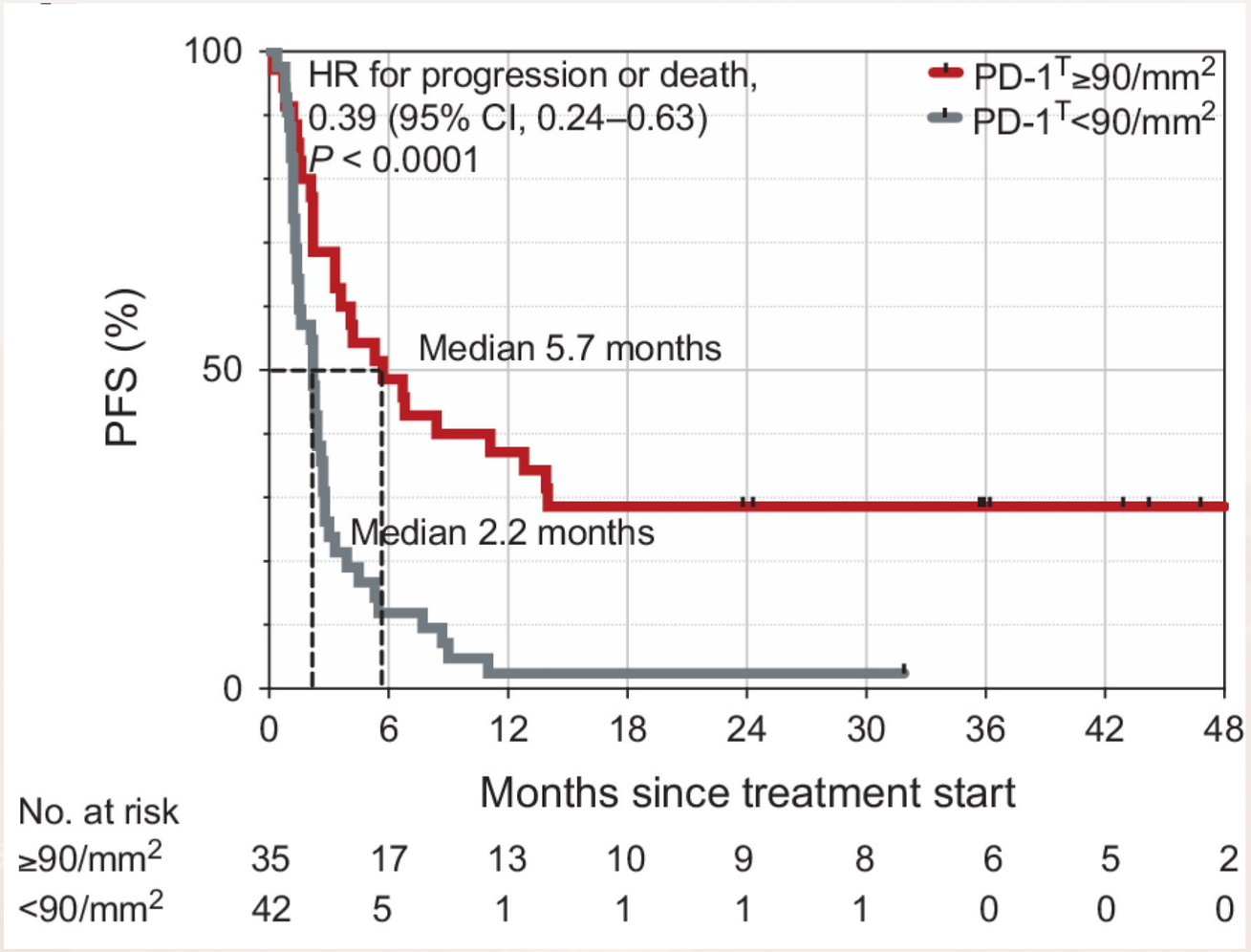
…But Can Promote CXCL13-Mediated Organization of Tertiary Lymphoid Structures…

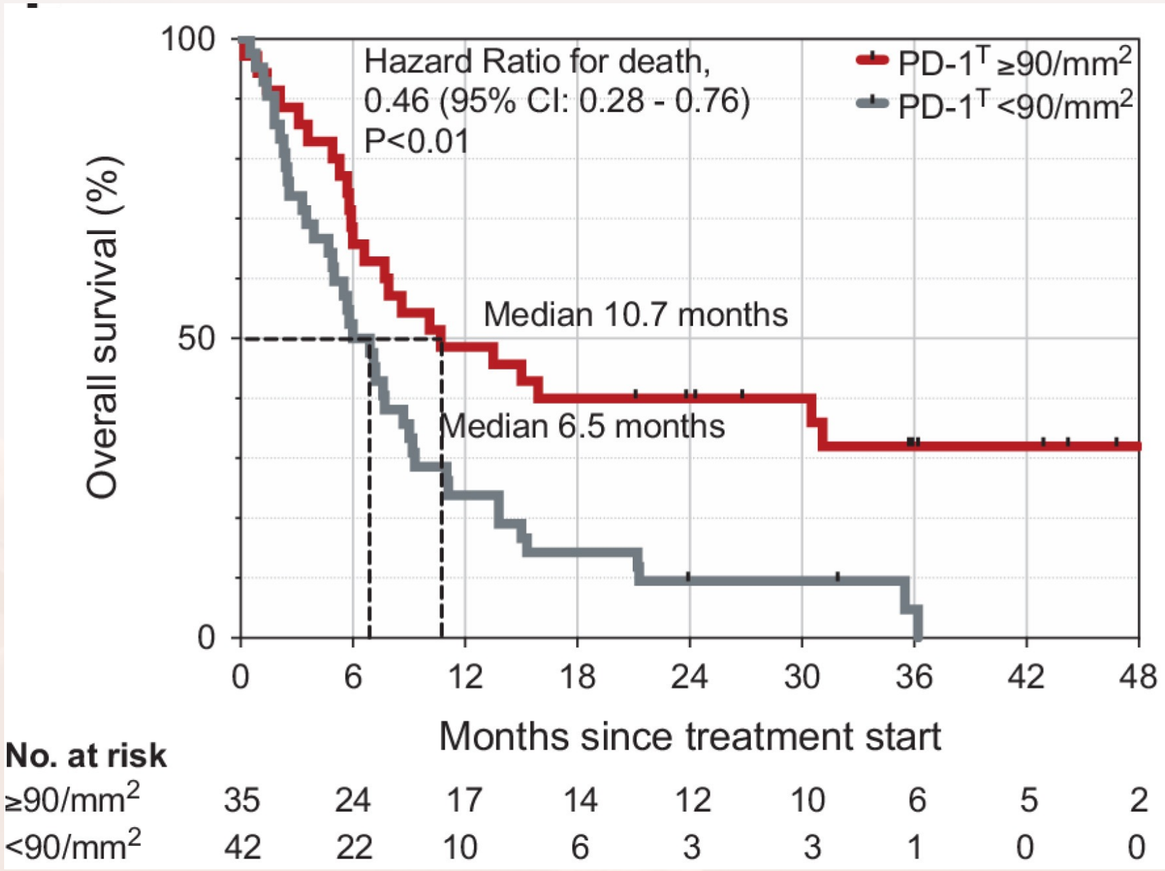




Thommen, *Nat Med* 2018

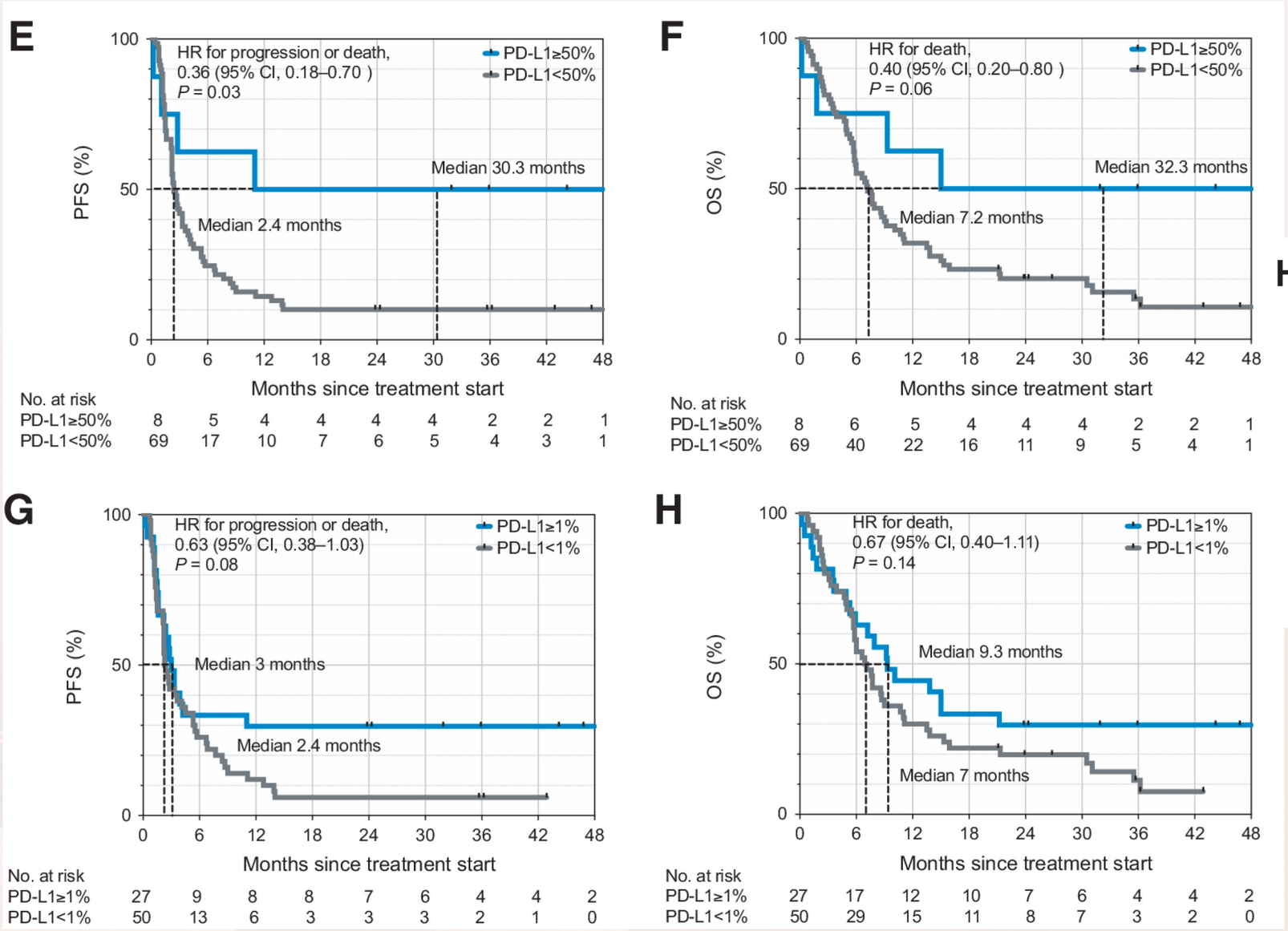
…And Can Predict Benefit from Immunotherapy in NSCLC…

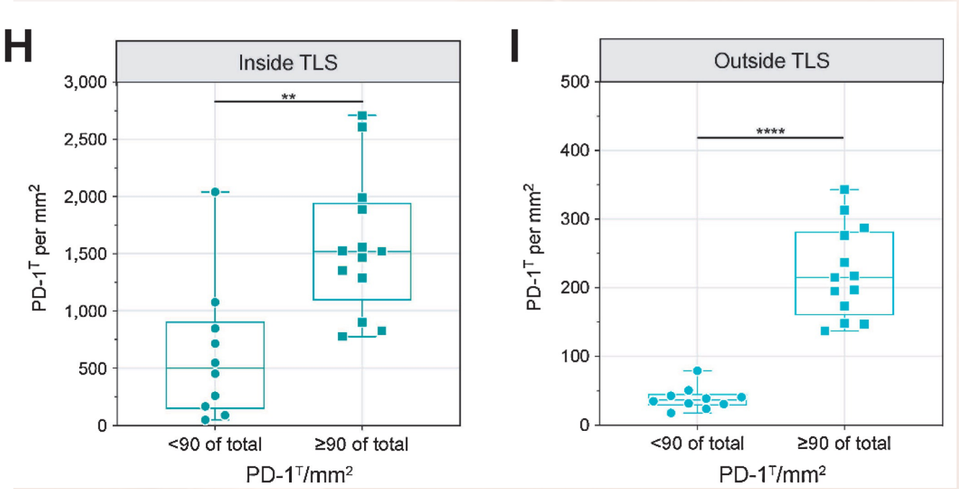




Hummelink, *Clin Cancer Res* 2022

…Independent of PD-L1 TPS Level and TLS…





Hummelink, *Clin Cancer Res* 2022

T-Cells Driving IO-Response Can Be Measured by TCF1 Expression in the Tumor

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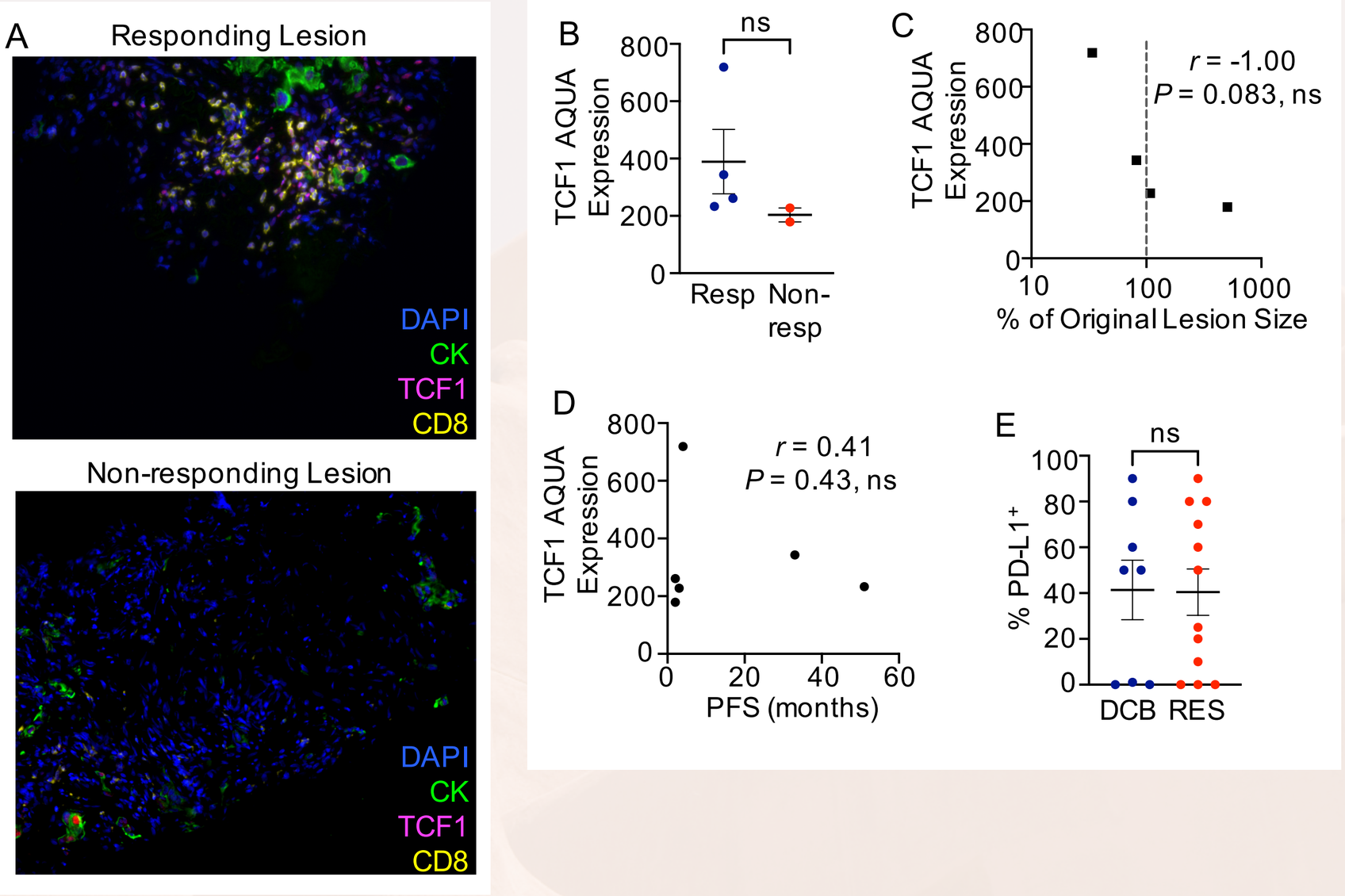

Maniar, *Clin Immunol Res* 2022

T-Cells Driving IO-Response Can Be Measured by TCF1 Expression in the Tumor and Periphery

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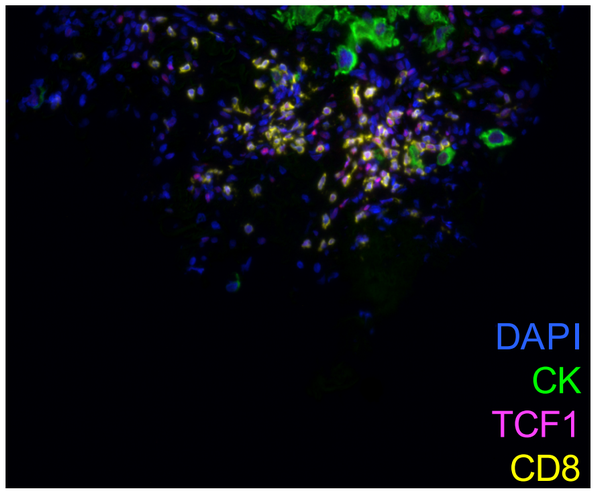
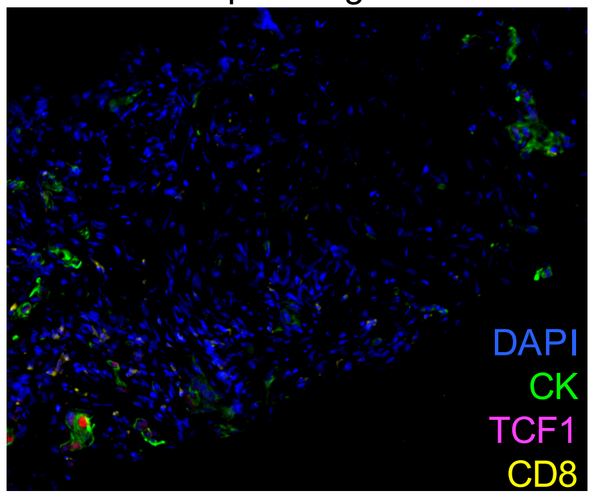
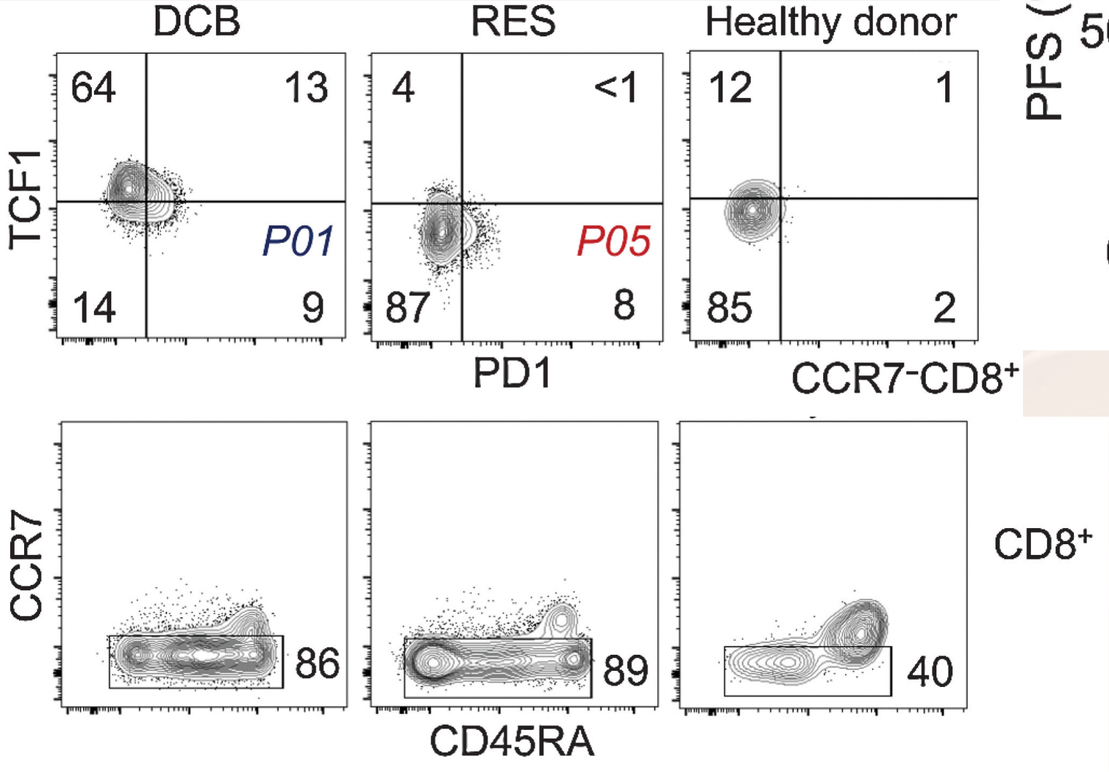
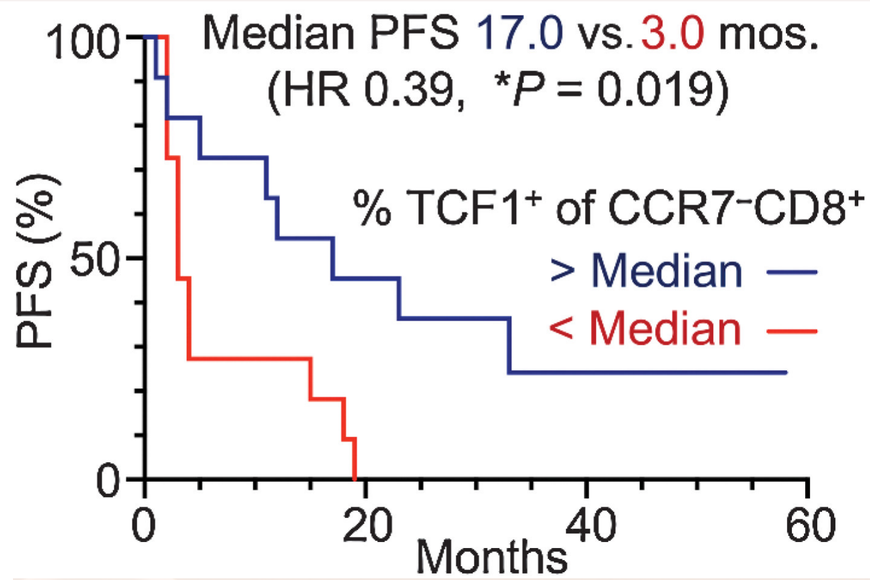


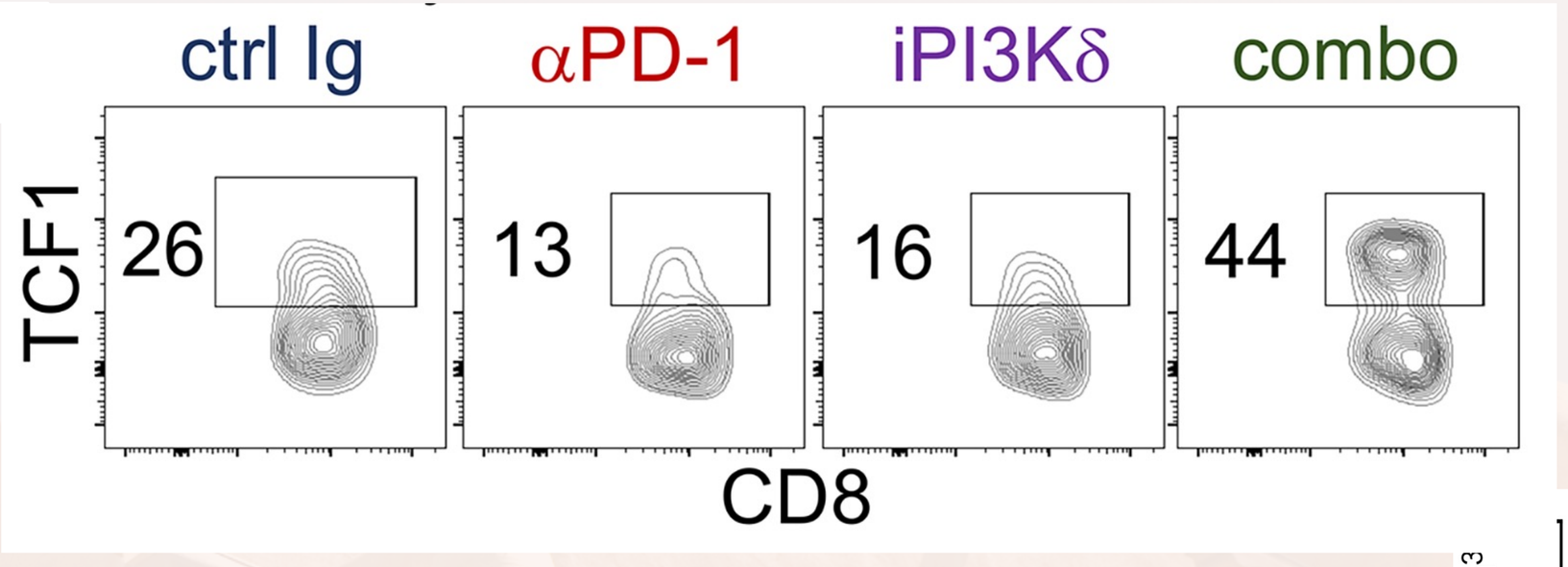


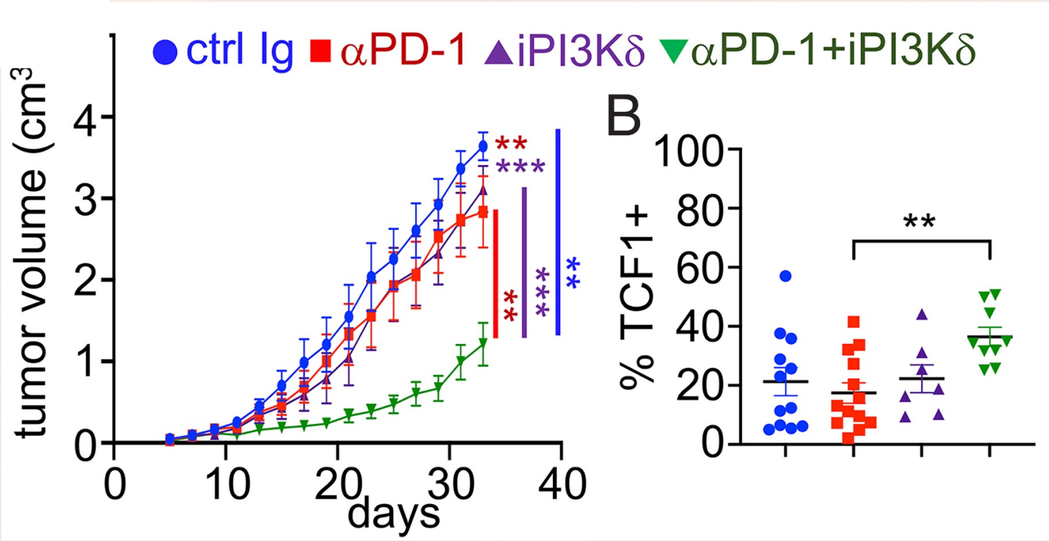




Maniar, *Clin Immunol Res* 2022

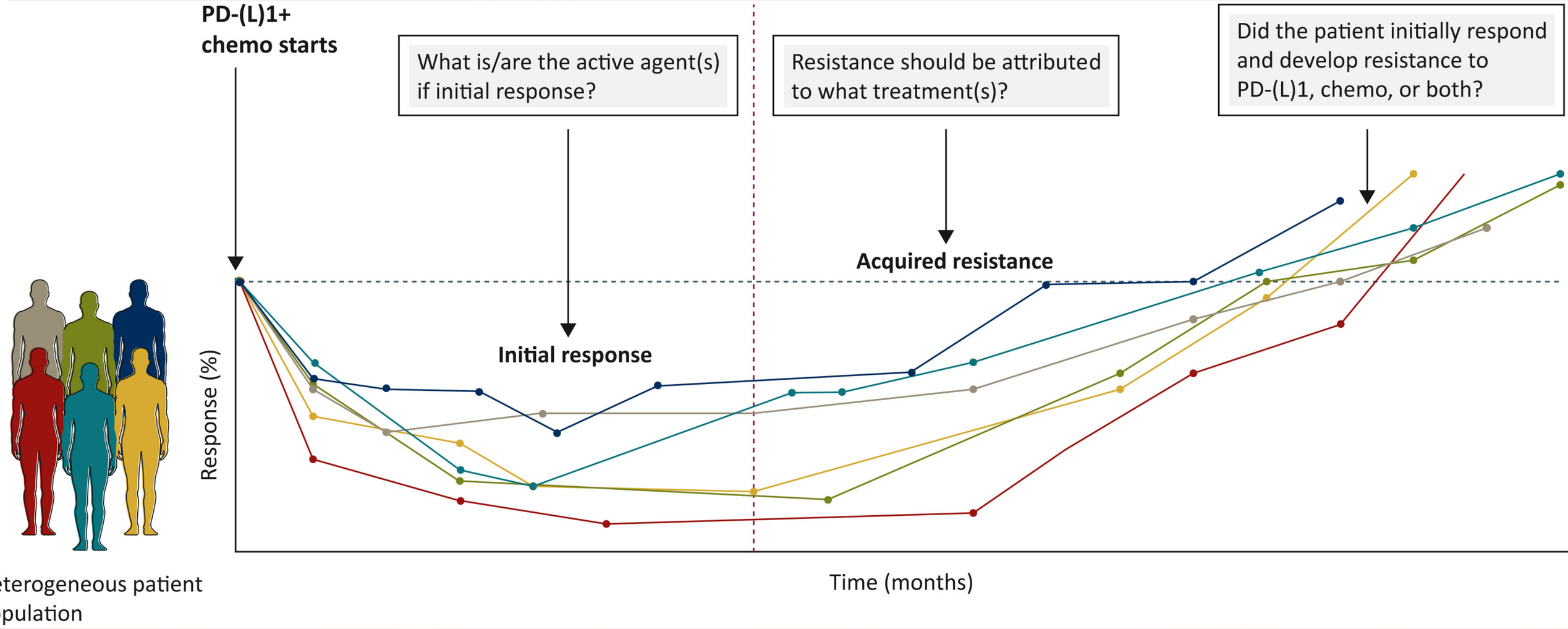
…and Could Be Repopulated with Metabolic Manipulation





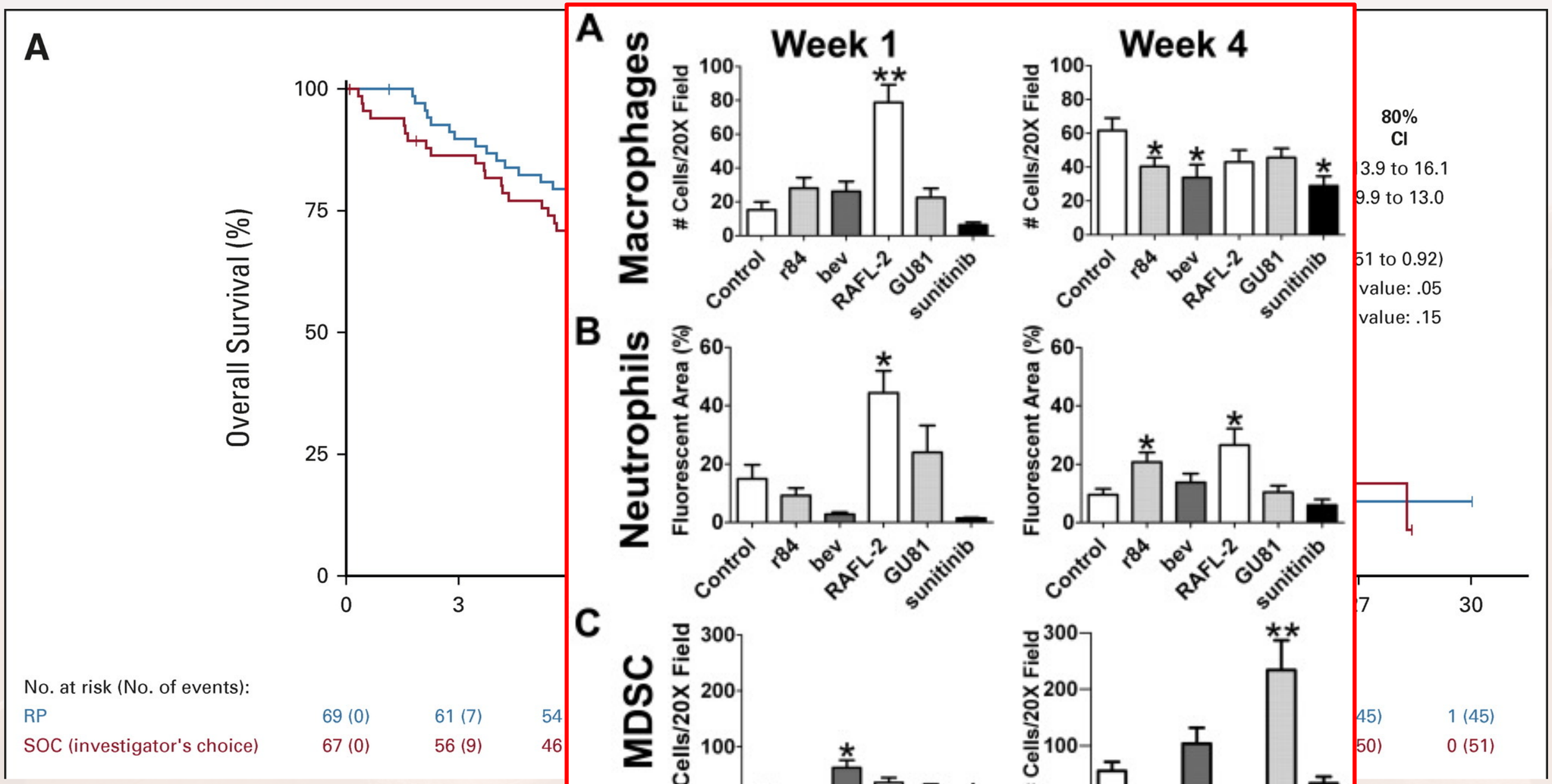
Wang, *J Immunol Res* 2022

What Else Is Impacting T Cell Exhaustion States?



Schoenfeld, *Ann Oncol* 2021

Clinical Hints: VEGF?



Reckamp, *JCO* 2022
Roland, *PloS One* 2009

Clinical Hints: CTLA4?

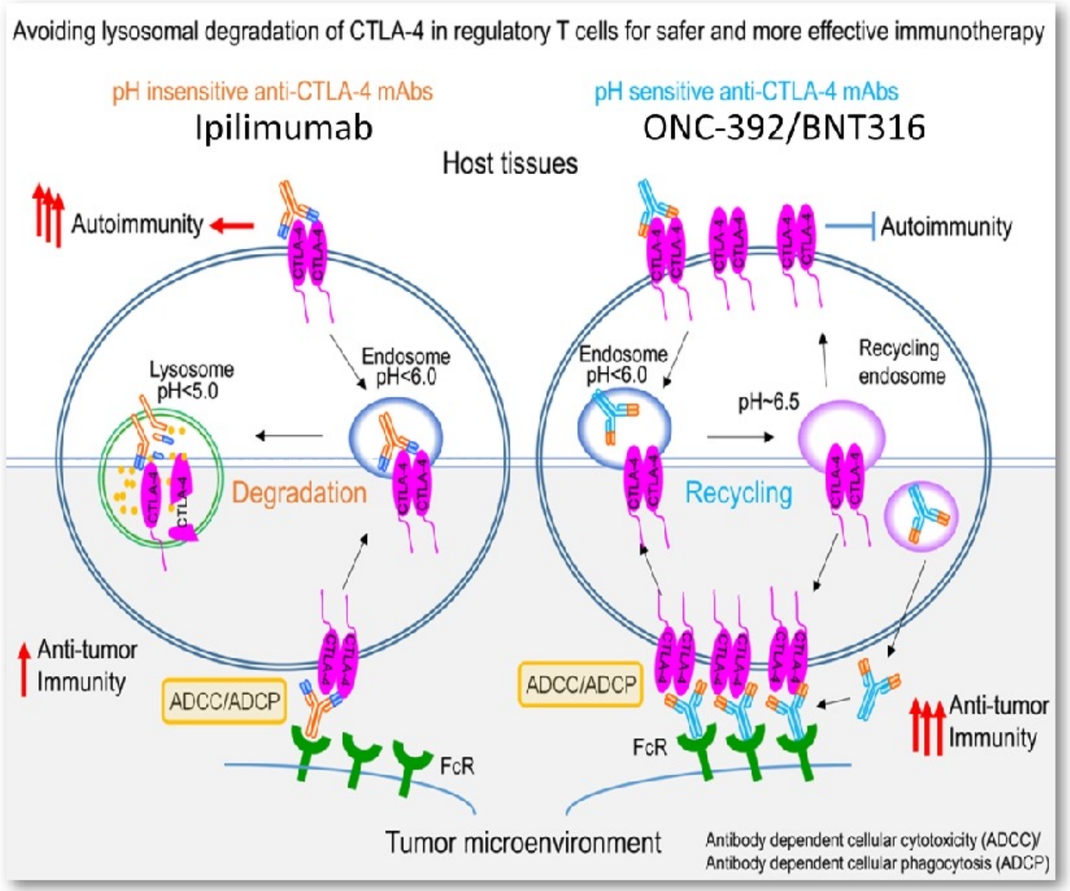
Schema

Patients with Acquired Resistance to Prior IO (Cohort 2) and Durable Clinical Benefit (DCB) with Nivolumab/ Ipilimumab

Pt	Histo	Mutation	Prior Lines	[1]Prior IO, PFS (months, m)	Prior IO to 1st Trial Tx	[2]Trial Best Response-Δ*Target Lesion*, PFS	Time from 1st to last Tx	Reason for Tx d/c	OS
01	Adeno	KRAS G12F	2	Atezolizumab, 41.5	*12.5 m	CR, 27.9 m[3]	1.8 m (40.5 m)[3]	Diabetes[3]	50.9+ m
									6+ m
									8 m
									5 m
									9 m

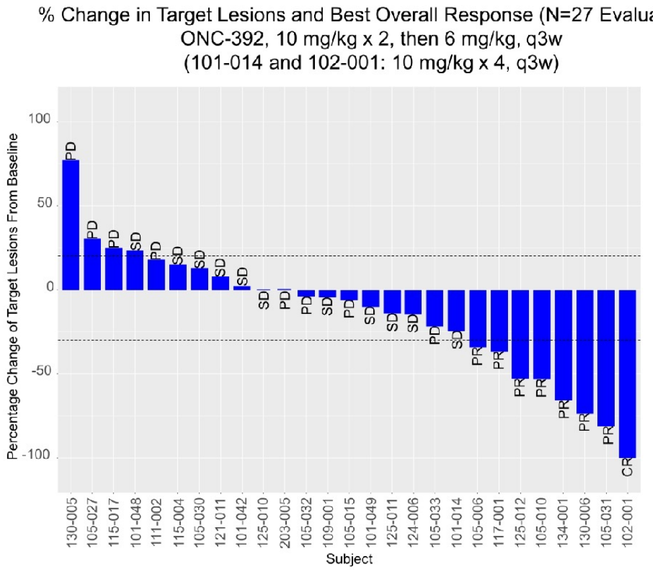
Gettinger, ASCO 2023; Garon, *JTO* 2023

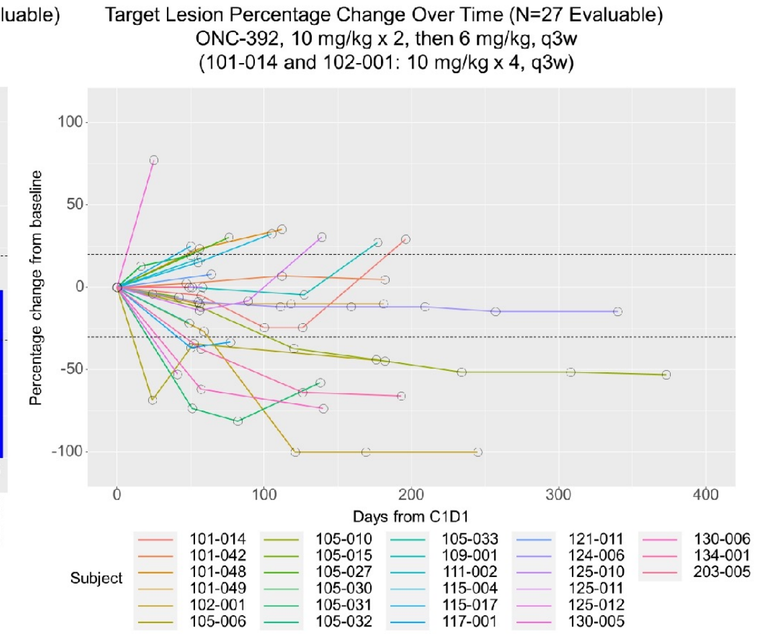
Novel CTLA4i?



Liu Y, Zheng P. Preserving the CTLA-4 Checkpoint for Safer and More Effective Cancer Immunotherapy. *Trends Pharmacol Sci*. 2020;41(1):4-12. doi:10.1016/j.tips.2019.11.003

Clinical Activity in PD-(L)1 Inhibitor Resistant NSCLC





He, ASCO 2023

Key Remaining Questions

- How and when should we optimally measure T cell exhaustion to predict for ICI benefit or resistance?
- What manipulation strategies are best for what patients?
  - Metabolic?
  - Other checkpoints?
  - Perturb other immune cell populations?
  - Which patients need this the most – ICI resistant or refractory?
- Do we need novel antigen-specific T cell products that are “evergreen”?

Blank, *Nat Rev Immunol* 2019