Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Basic Immunology and Immune Microenvironment

Tanguy Seiwert, MD

Johns Hopkins University

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Disclosures

Personal financial interests (last 12 months):

Advisory role: Nanobiotix, MSD/Merck, Regeneron, Innate Pharma, Bristol-Myers (BMS), Sanofi, Surface Oncology, Vir Biotechnology

Steering Committee Member: BioNTech, Nektar, Astra-Zeneca

Institutional financial interests:

Research funding (PI): MSD/Merck; Astra-Zeneca; BMS
Trial funding (PI): Bristol-Myers (BMS); Astra-Zeneca; Nanobiotix, MSD/Merck, Cue Therapeutics, Roche-Genentech, Regeneron

- I will NOT be discussing any non-FDA approved indications during my presentation.

FDA News Re

FDA ap
cell lun

First drug appr

"The field of immunother
exploded in the last decad
more and more patients a
benefiting" — *Steven O'Day AS*

FDA Approves Pembro
Advanced Melanoma

Thursday, 4 Sep 2014 | 5:07 PM ET

ORIGINAL ARTICLE

Nivolumab versus Docetaxel in A
Nonsquamous Non–Small-Cell Lung Cancer

H. Borghaei, L. Paz-Ares, L. Horn, D.R. Spigel, M. Steins, N.E. Ready, L.Q. Chow, E.E. Vokes, E. Felip, E. Holgado, F. Barlesi, M. Kohlhäufl, O. Arrieta, M.A. Burgio, J. Fayette, H. Lena, E. Poddubskaya, D.E. Gerber, S.N. Gettinger, C.M. Rudin, N. Rizvi, L. Crinò, G.R. Blumenschein, Jr., S.J. Antonia, C. Dorange, C.T. Harbison, F. Graf Finckenstein, and J.R. Brahmer

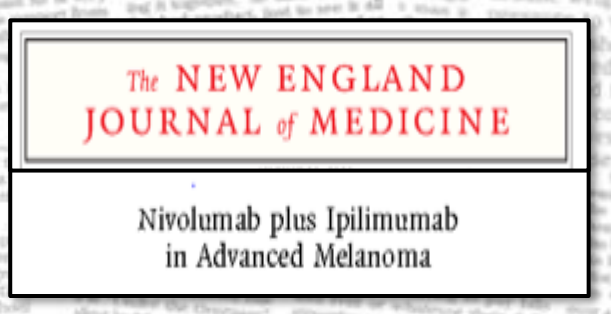
Anti-PD-1 cancer s
first regulatory app

July 7, 2014 | By John Carroll

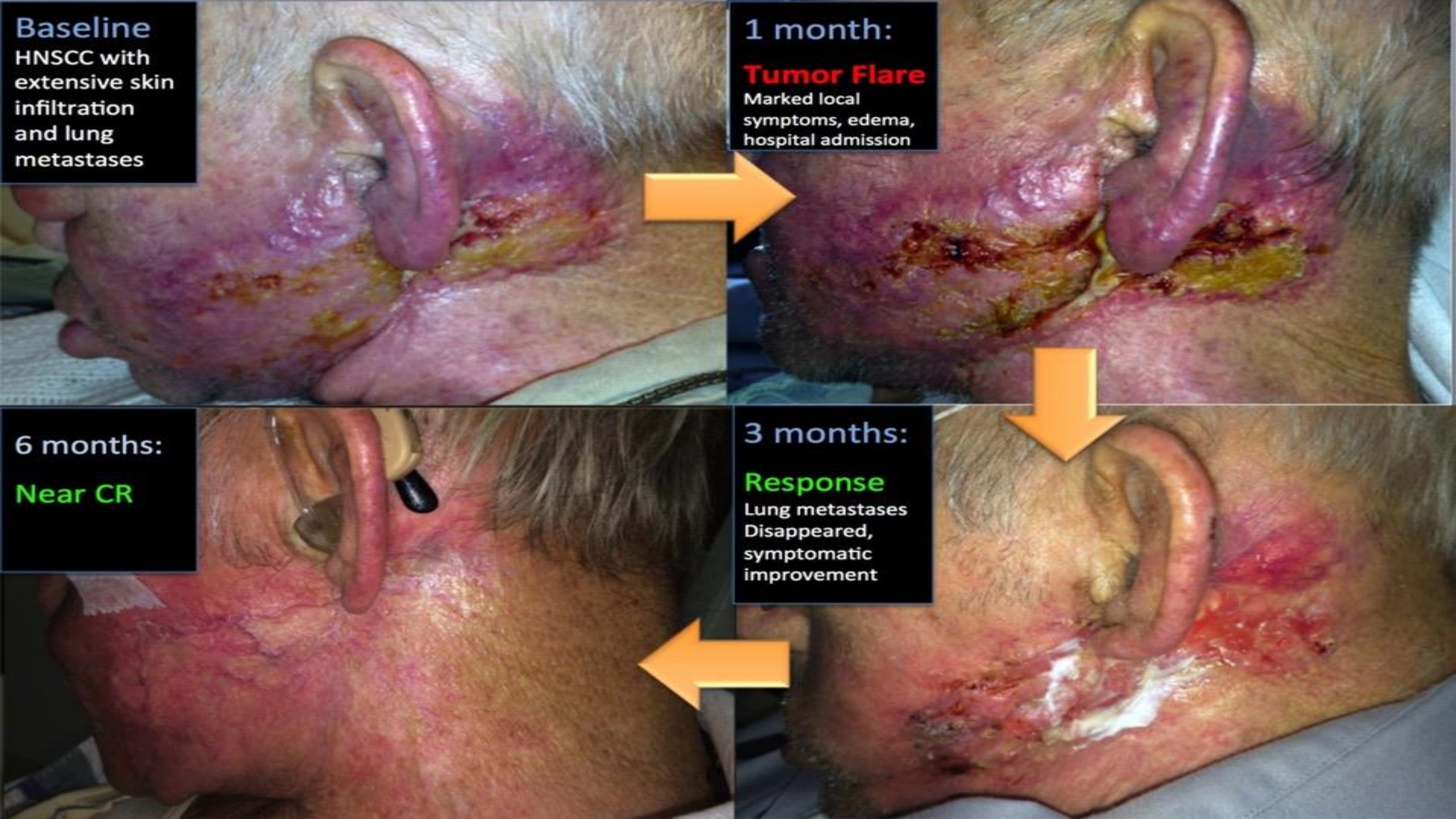
es Marketing Authorisation for First-Line Treatment of
lelanoma in Europe

o treat advanced form of

ates of response to the anti-PD-L1
3280A in cancer patients



Modified from Steven O'Day


Baseline
HNSCC with extensive skin infiltration and lung metastases
1 month:
Tumor Flare
Marked local symptoms, edema, hospital admission
3 months:
Response
Lung metastases Disappeared, symptomatic improvement
6 months:
Near CR

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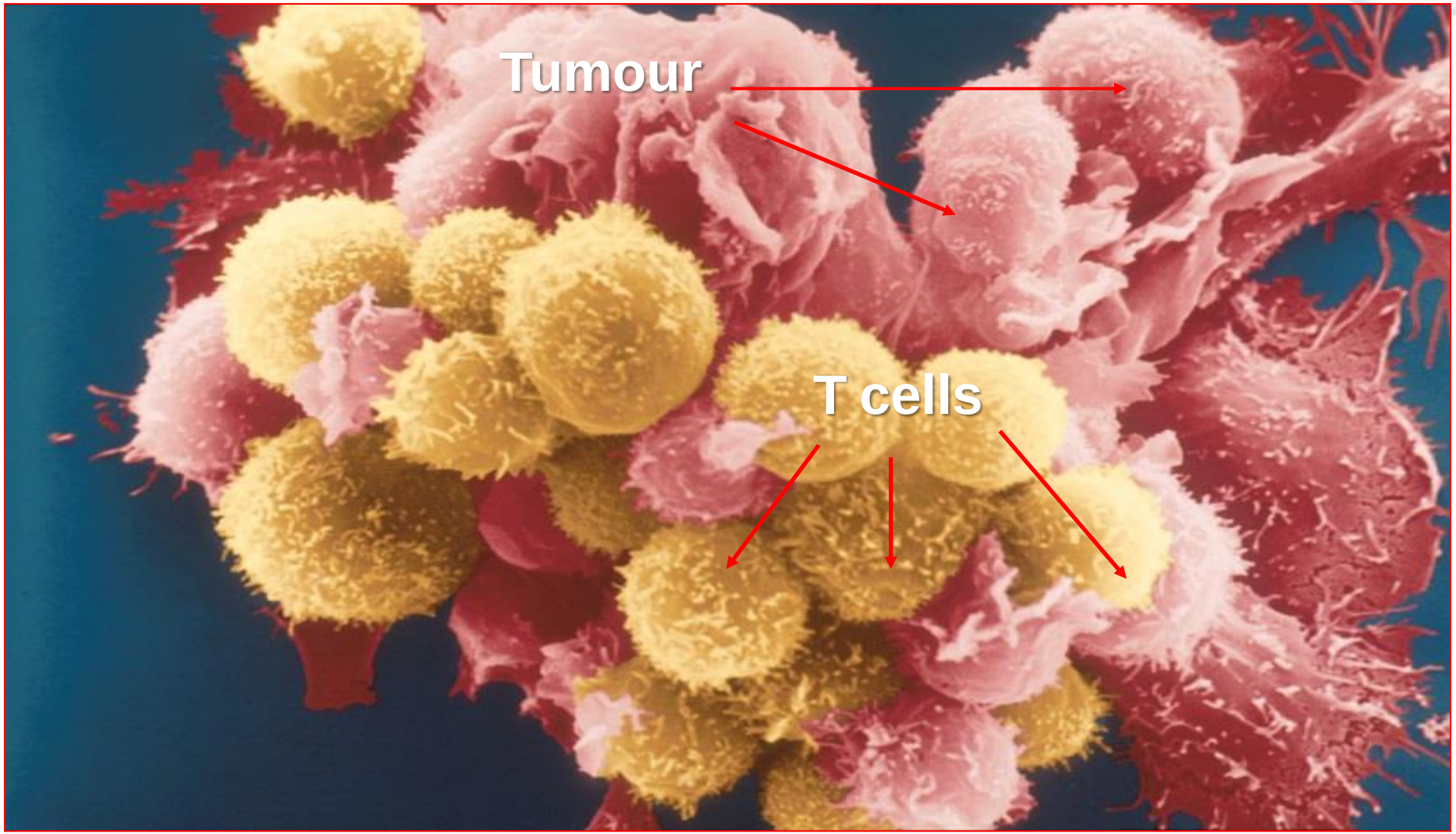
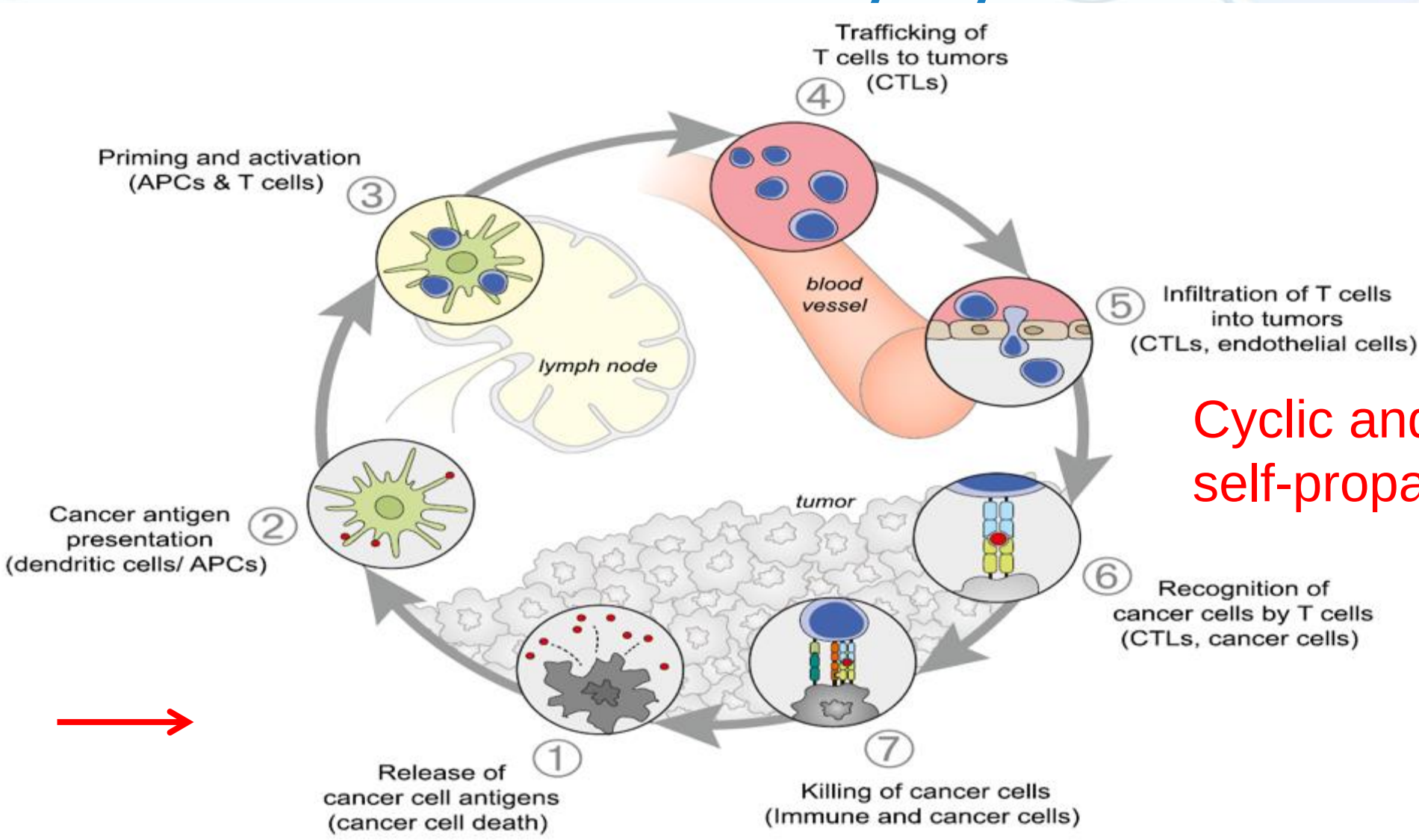
1. Tumor Immunology

By definition: Cancers are ~invisible to the immune system



The Cancer Immunity Cycle



Cyclic and self-propagating

START ⟶

Chen, Melman Nature

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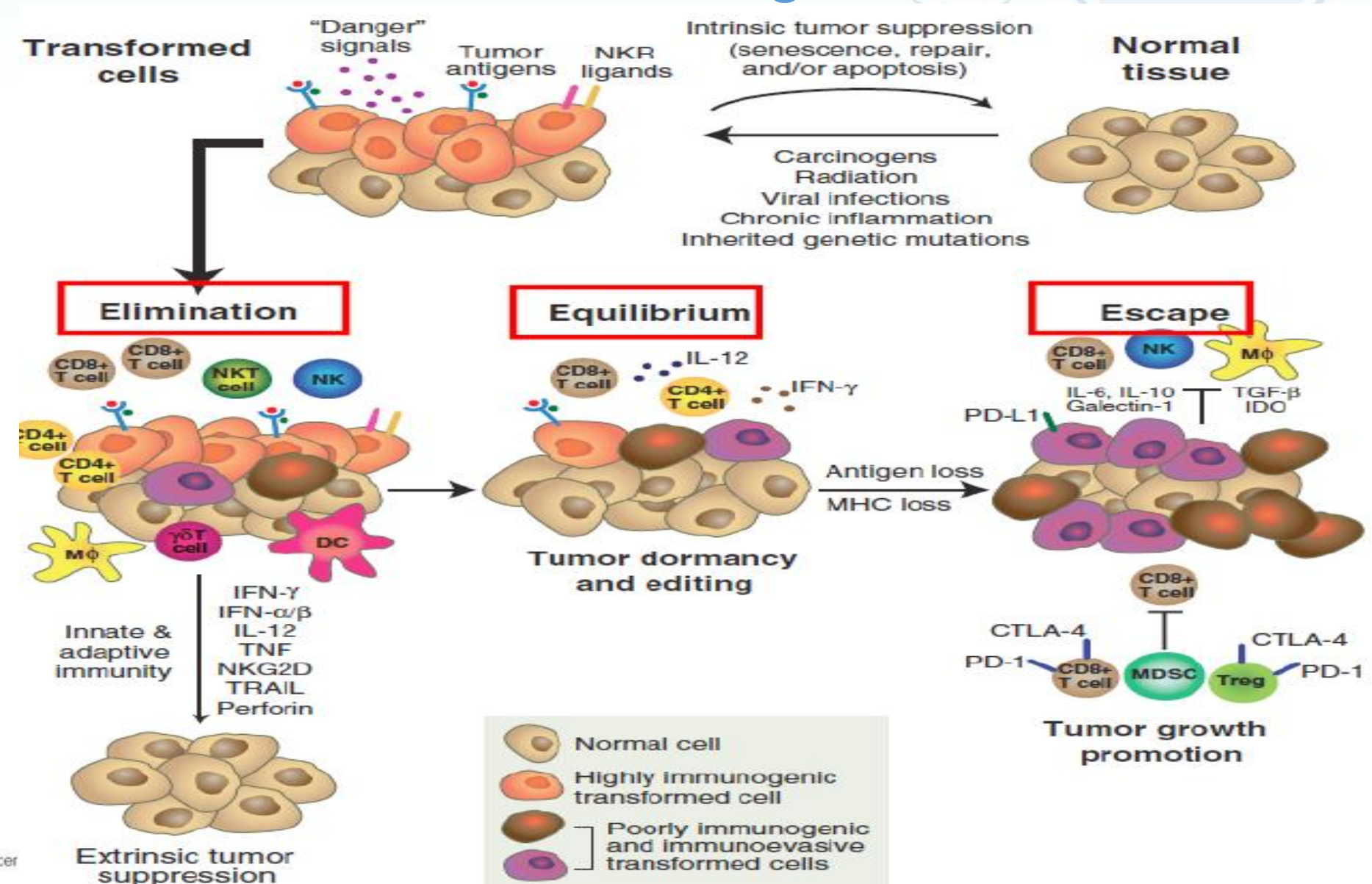
Tumor Editing



Schreiber R et al. Science 2001

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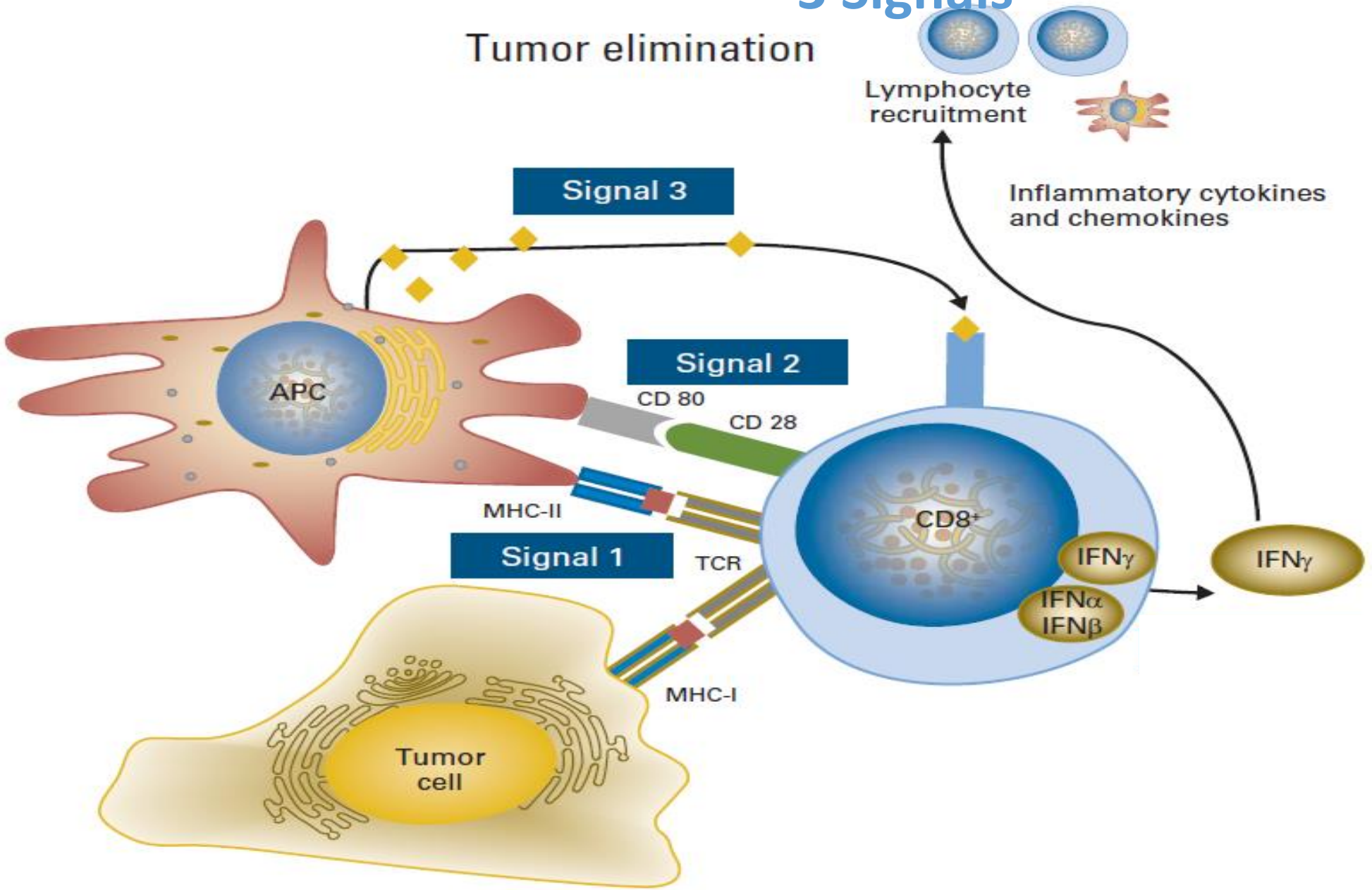
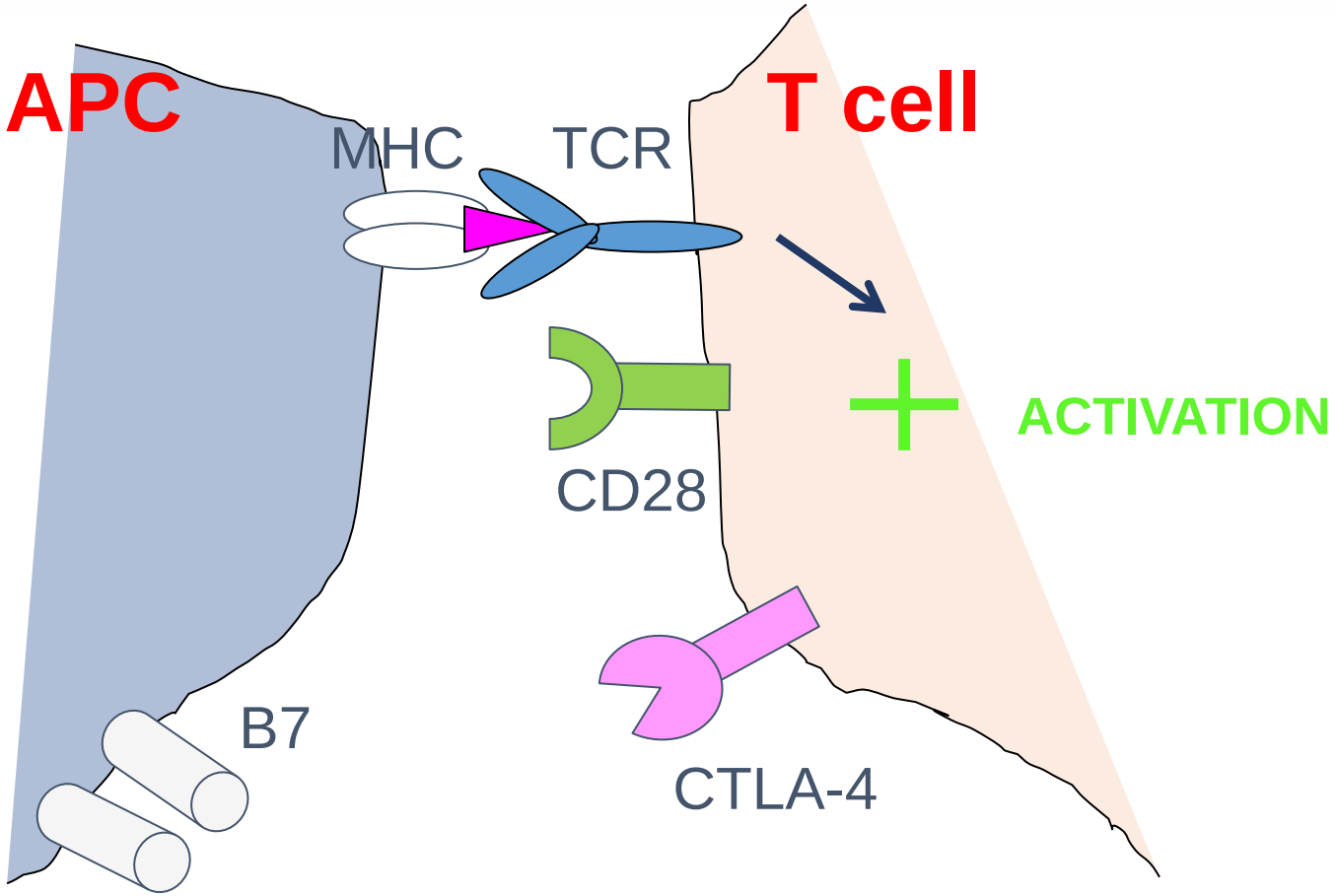
Signalling at the Immune Synapse

3 Signals



Ferris R. JCO 2015

Activation Phase (1)

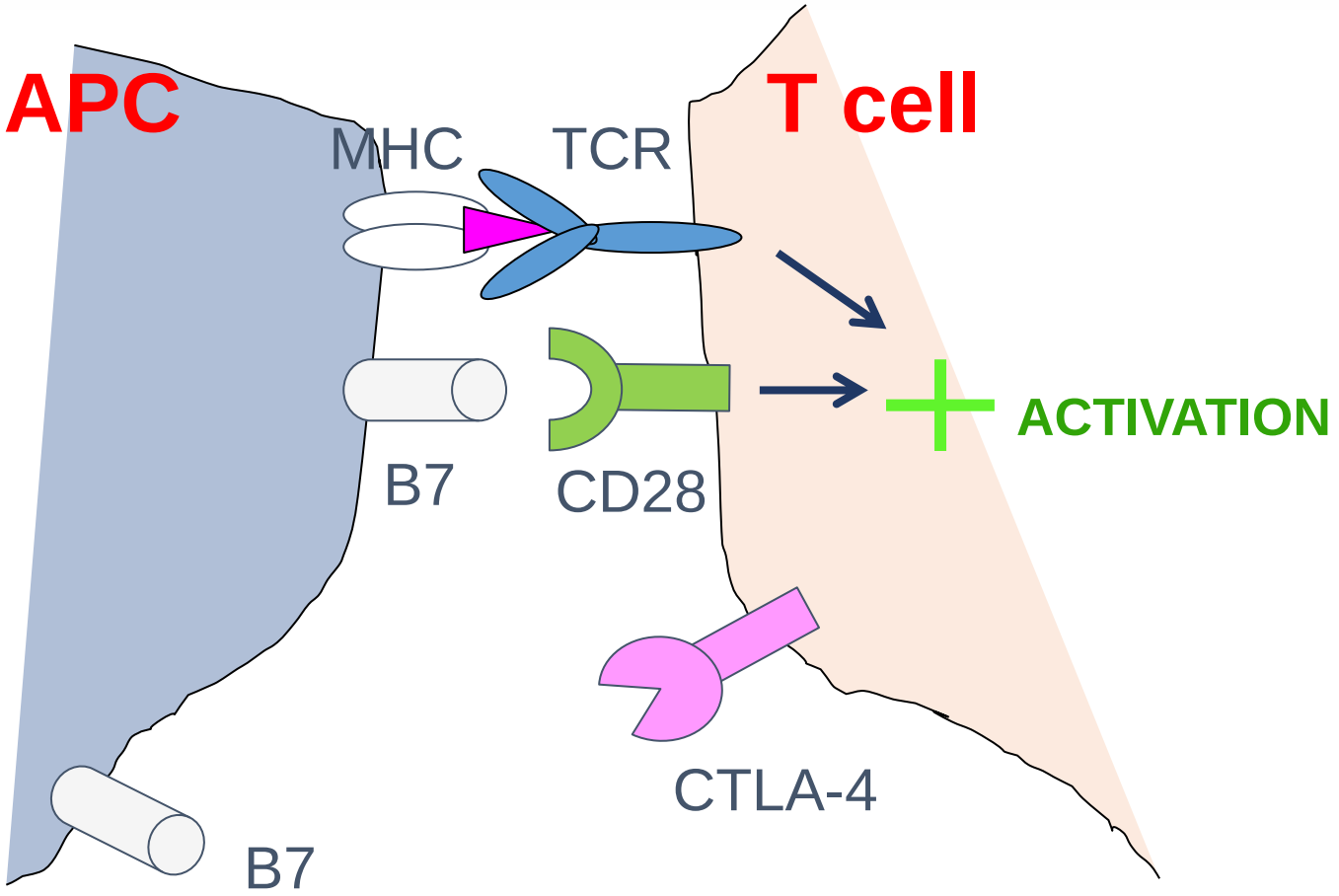


Signal 1:
MHC Class I – CD8 TCR
MHC Class II – CD4 TCR

Provides specificity at level of TCR recognition of specific antigen in the correct MHC context

Slide courtesy
Kevin Harrington

Activation Phase (2)

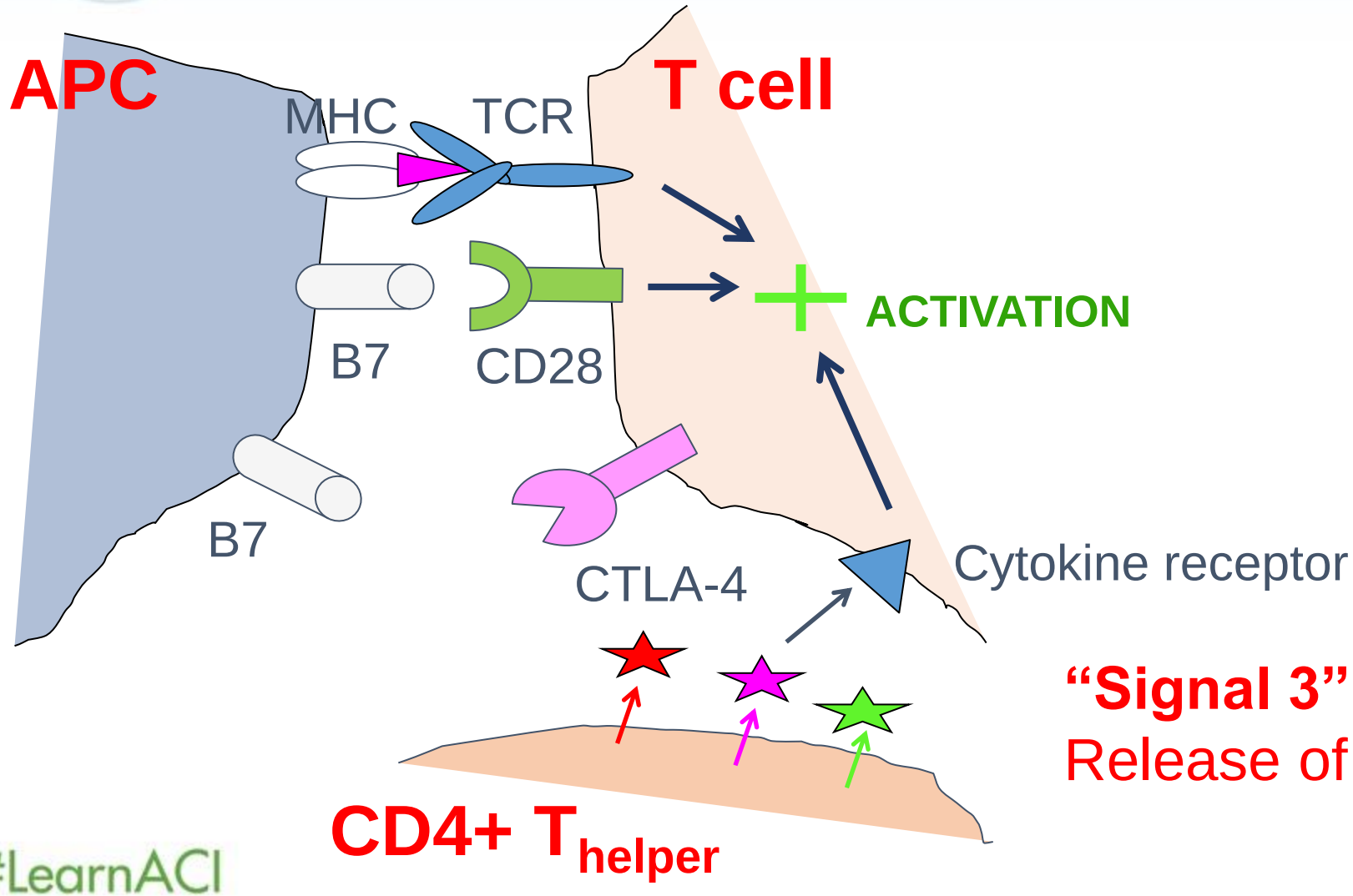


Positive Signal 2:
Co-stimulation

CD28 molecules on T cell must receive an additional +ve signal by binding B7 in order to reinforce Signal 1

Slide courtesy
Kevin Harrington

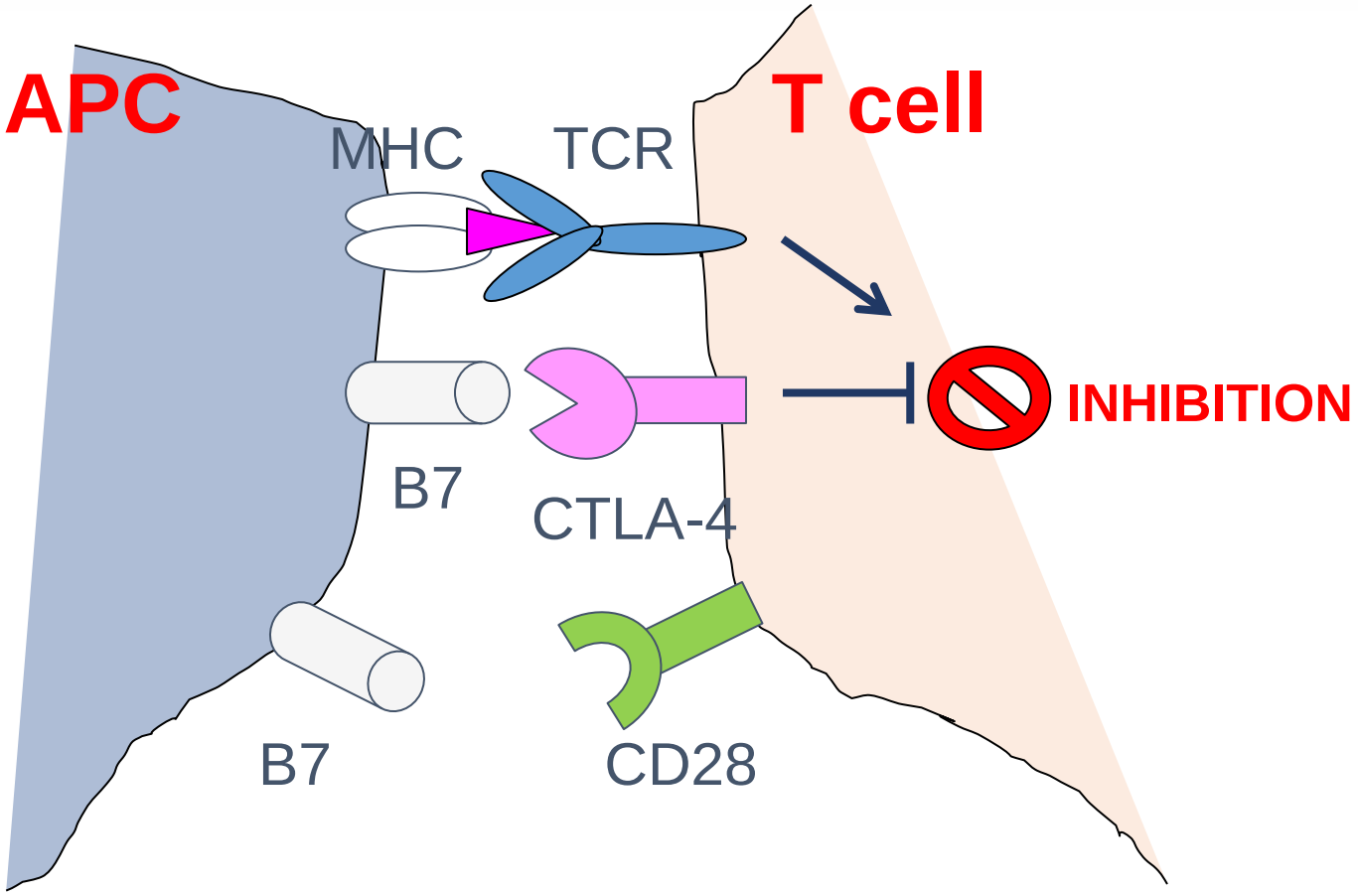
Activation Phase (3)



"Signal 3"
Release of stimulatory cytokines

Slide courtesy
Kevin Harrington

Activation Phase (4) (= INHIBITION)

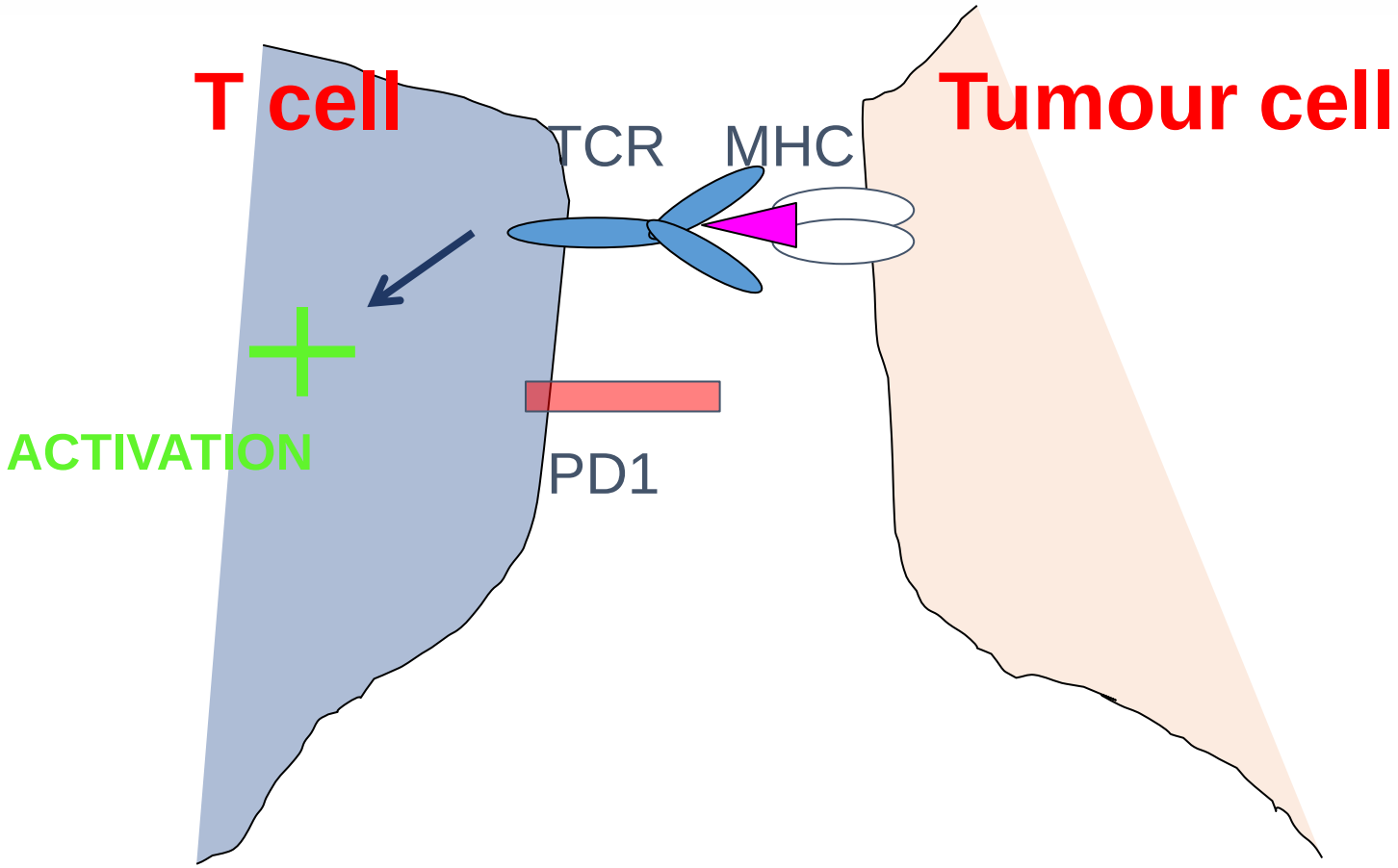


Negative Signal 2:
Inhibition

B7 molecules on APC are bound to CTLA4 receptor on T cells. T cell does not receive Signal 2 and is inhibited

Slide courtesy
Kevin Harrington

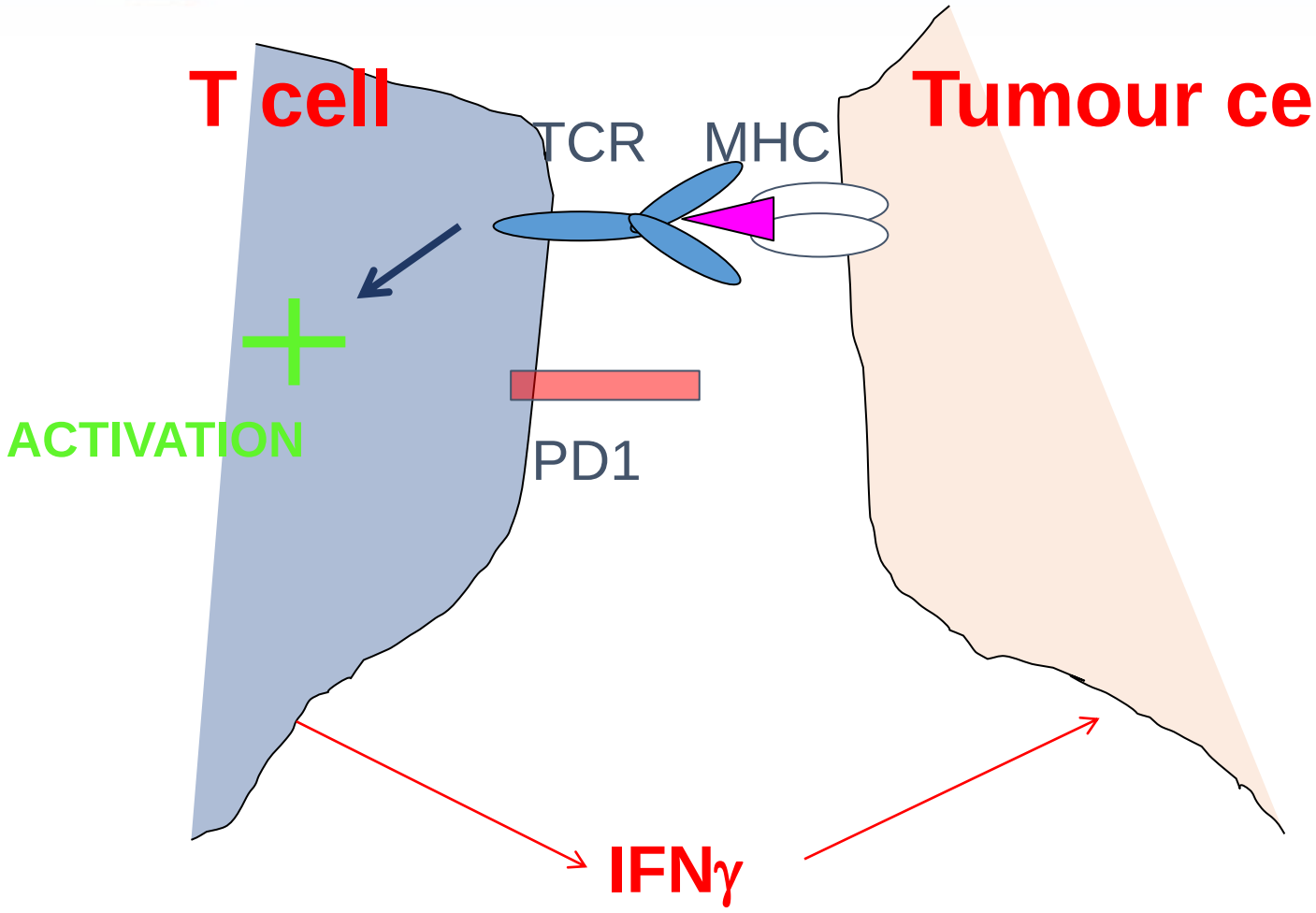
Effector Phase (1)



T cell activation:
Tumour cell does not express PD-L1.
TCR recognition of antigen results in T cell activation against target
SIGNAL 1 = POSITIVE

Slide courtesy
Kevin Harrington

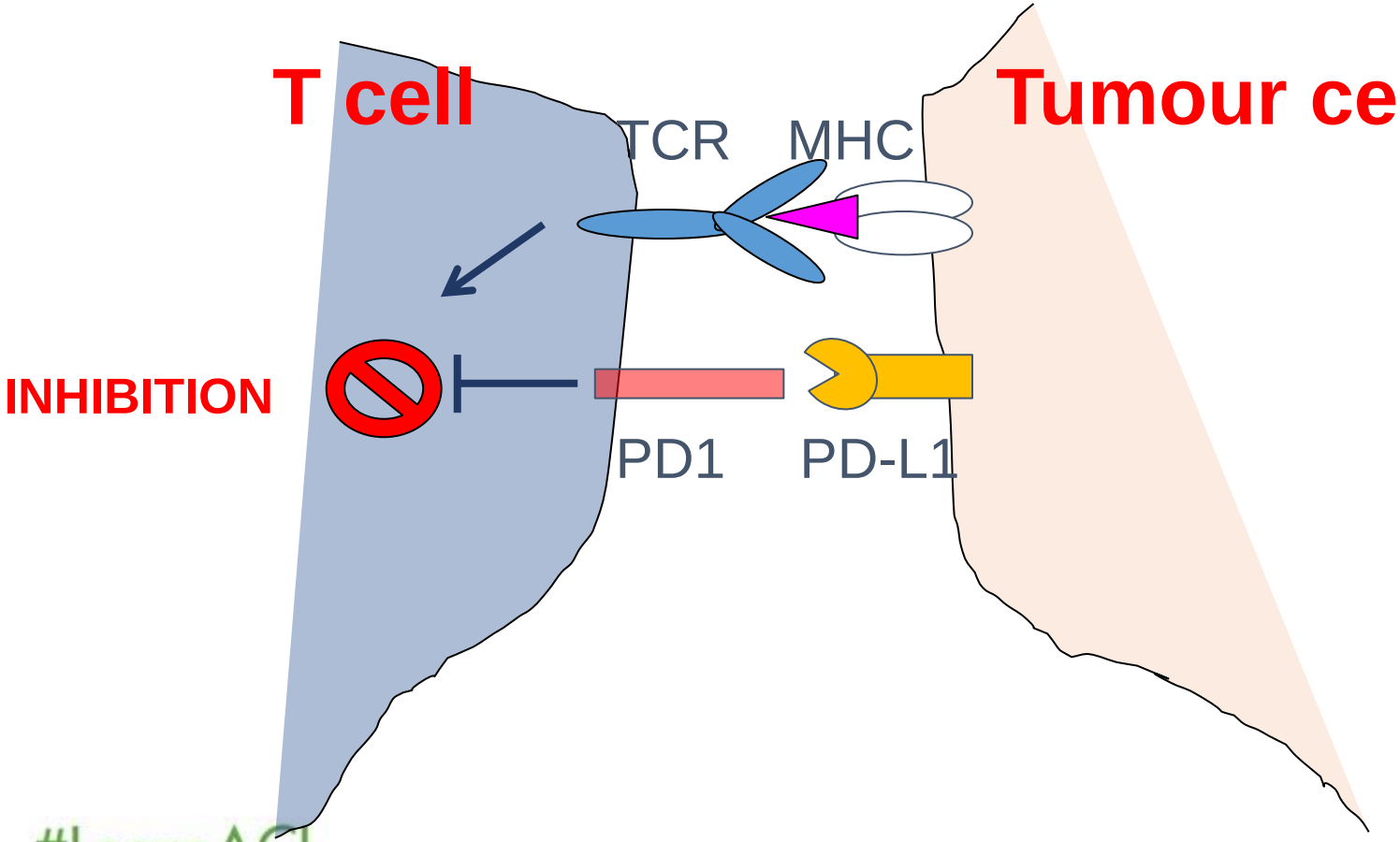
Effector Phase (2)



T cell activation:
T cell secretes IFNg (and other cytokines) which upregulates expression of PD-L1 on tumour cells

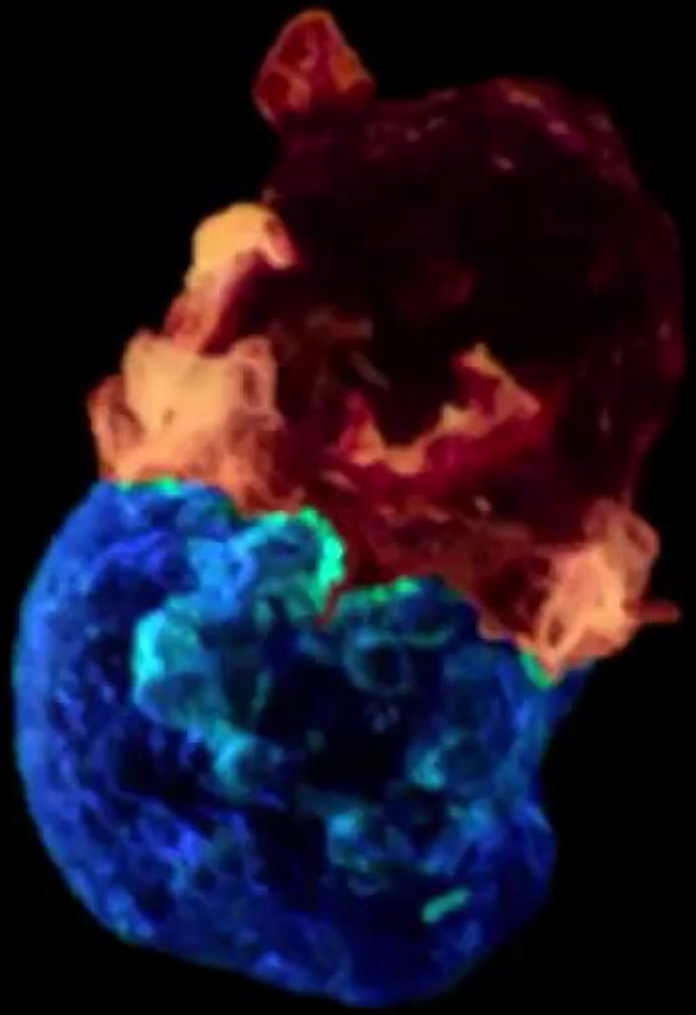
Slide courtesy
Kevin Harrington

Effector Phase (3)



T cell inactivation:
Inhibition of T cell activity by binding of an inhibitory ligand (PD-L1) to the programmed death-1 receptor
SIGNAL 2 IS NEGATIVE

Slide courtesy
Kevin Harrington



Source: PhRMA TV Commercial, 'Go Boldly: Cells'
Full video at: https://www.ispot.tv/ad/d5CO/phrma-go-boldly-cells

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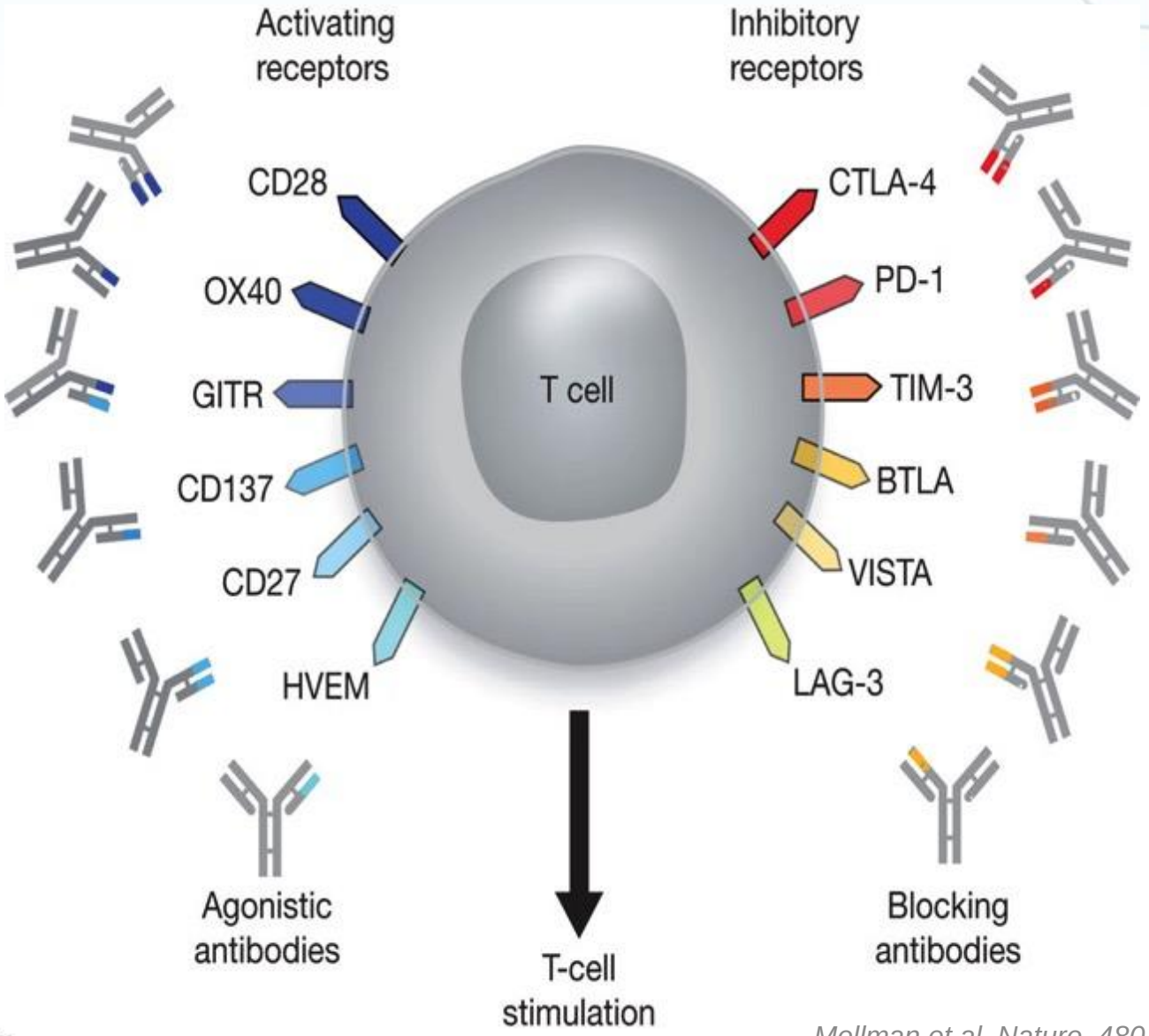
2. Immune Checkpoints & T-cells

Activating & Inhibitory Receptors:

Many Potential Targets!



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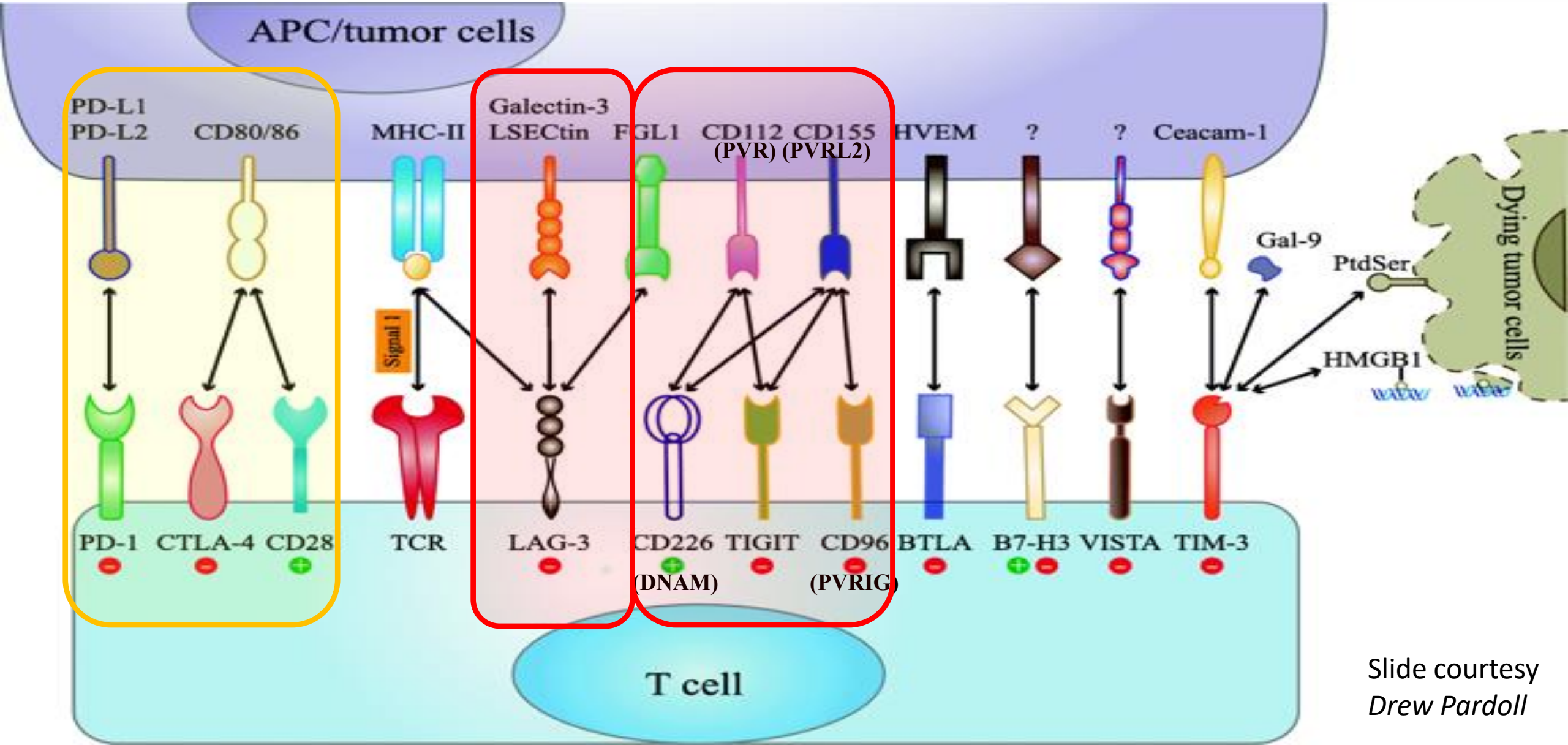
Mellman et al. Nature. 480, 480-489 (2011) doi:10.1038/nature10673

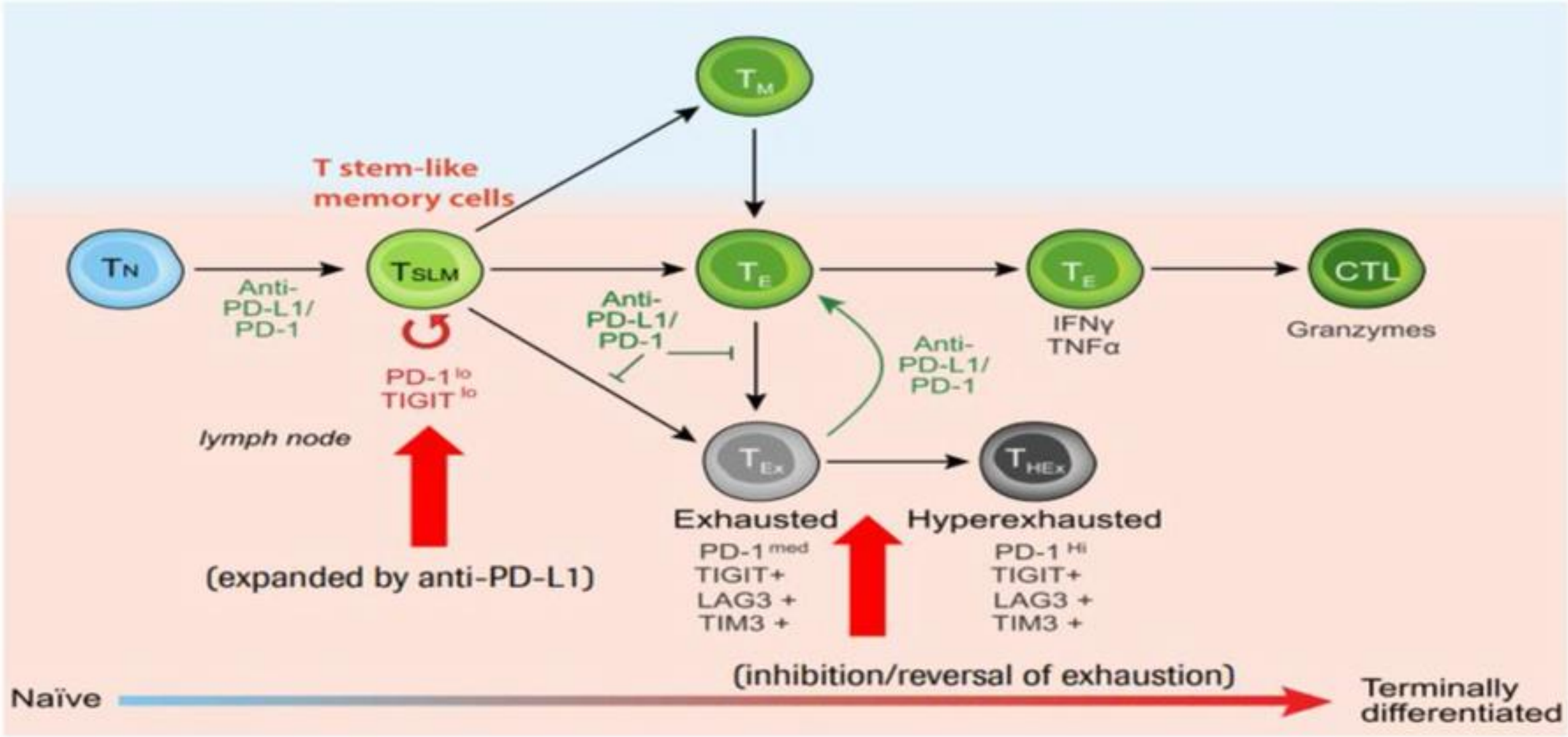
Blockade of multiple "secondary" checkpoints (i.e. beyond PD-1) being tested clinically, almost all in combination with anti-PD-1/L1



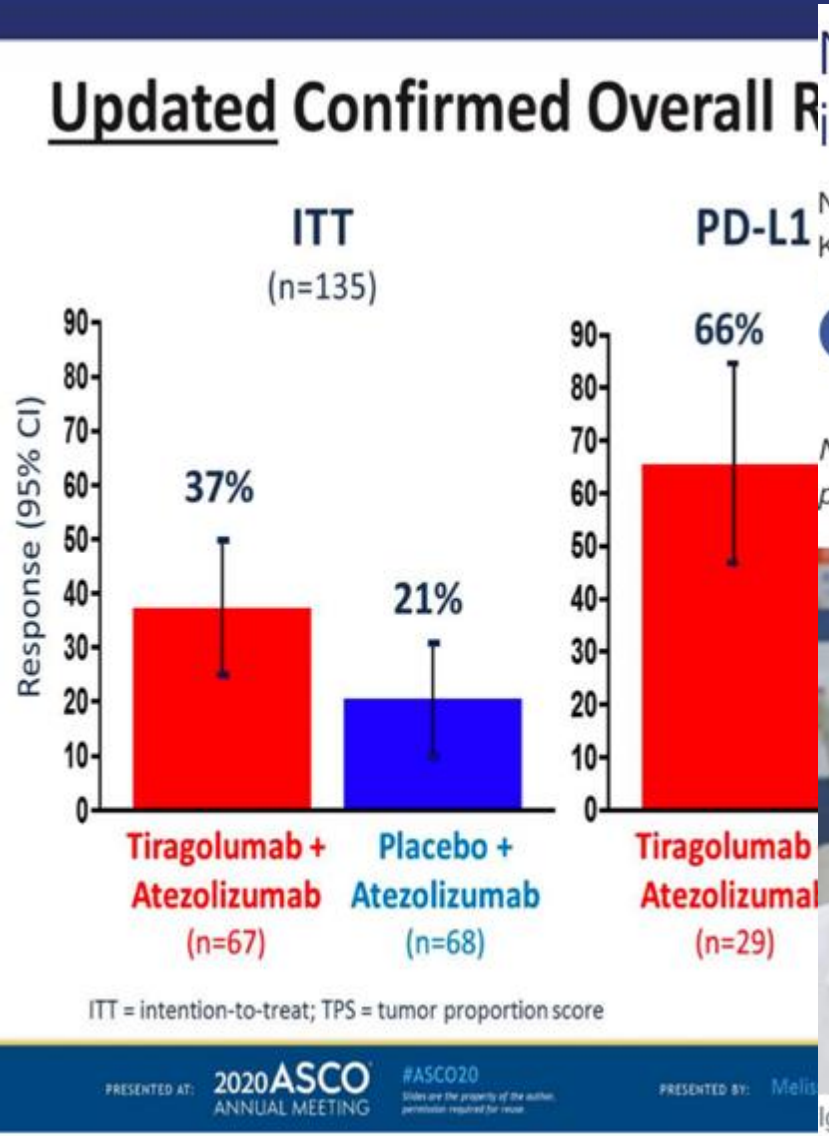
Slide courtesy
Drew Pardoll

T I G I T

Anti-PD-L1 expands a key population of PD-1-positive T stem-like cells, which also express TIGIT but no other negative regulator



d from Chen and Mellman Nature 2017

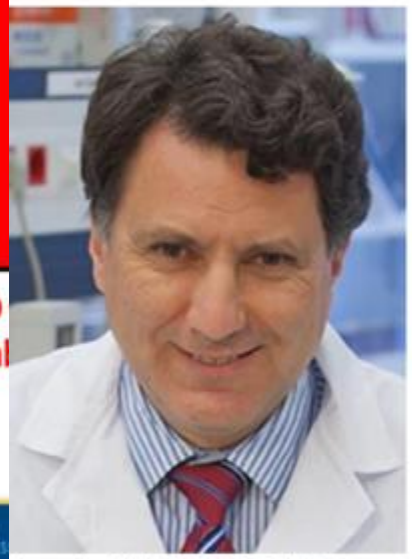


Next-Generation Bispecific Antibody Shows Early Clinical Activity in Advanced Solid Tumors

November 12, 2020
Kristi Rosa

sitc
Society for Immunotherapy of Cancer

November 12, 2020 - The first-in-class, next-generation, DuoBody-PD-L1×4-1BB bispecific antibody GEN1046 demonstrated promising early activity and an acceptable safety profile in in patients with advanced solid tumors.


Ignacio Melero, MD, PhD

The first-in-class, next-generation, DuoBody-PD-L1×4-1BB bispecific antibody GEN1046 demonstrated promising early activity and an acceptable safety profile in in patients with advanced solid tumors, according to data from a first-in-human phase 1/2a trial (NCT03917381) presented during the virtual 2020 SITC Annual Meeting.[1]

Results showed that the agent had clinical benefit across different dosing levels, including in patients who had developed resistance to prior immunotherapy and those who had disease that was less sensitive to immune checkpoint inhibitors. Specifically, GEN1046 led to a disease control rate of 65.6%, with partial responses (PRs) observed in 1 patient with triple-negative breast cancer (TNBC), 1 patient with ovarian cancer, and 2 patients with non–small cell lung cancer (NSCLC) who had received prior immune checkpoint inhibitors.

"GEN1046 is a…bispecific antibody with an acceptable safety profile and encouraging early clinical activity, potentially addressing key limitations of the existing 4-1BB agonists," lead study author Ignacio Melero, MD,

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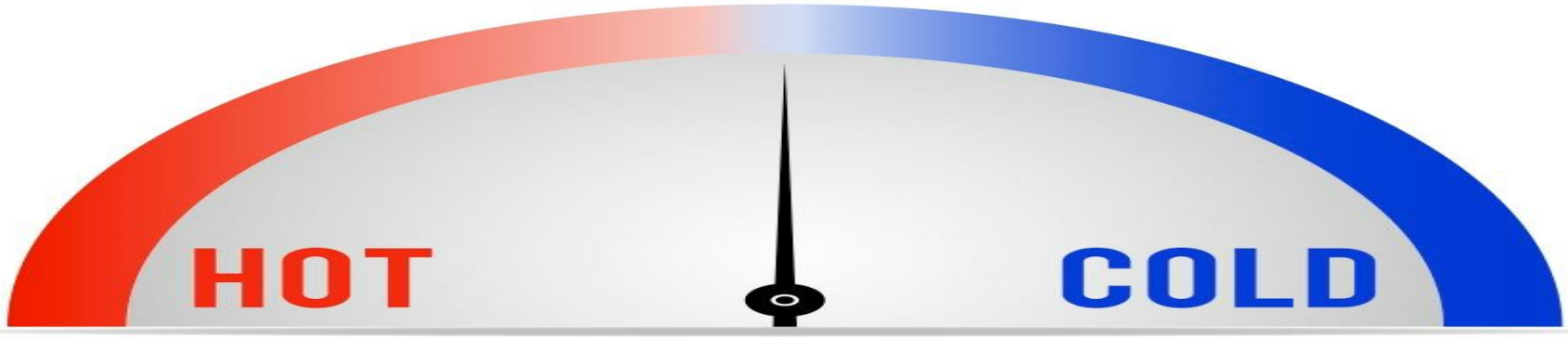
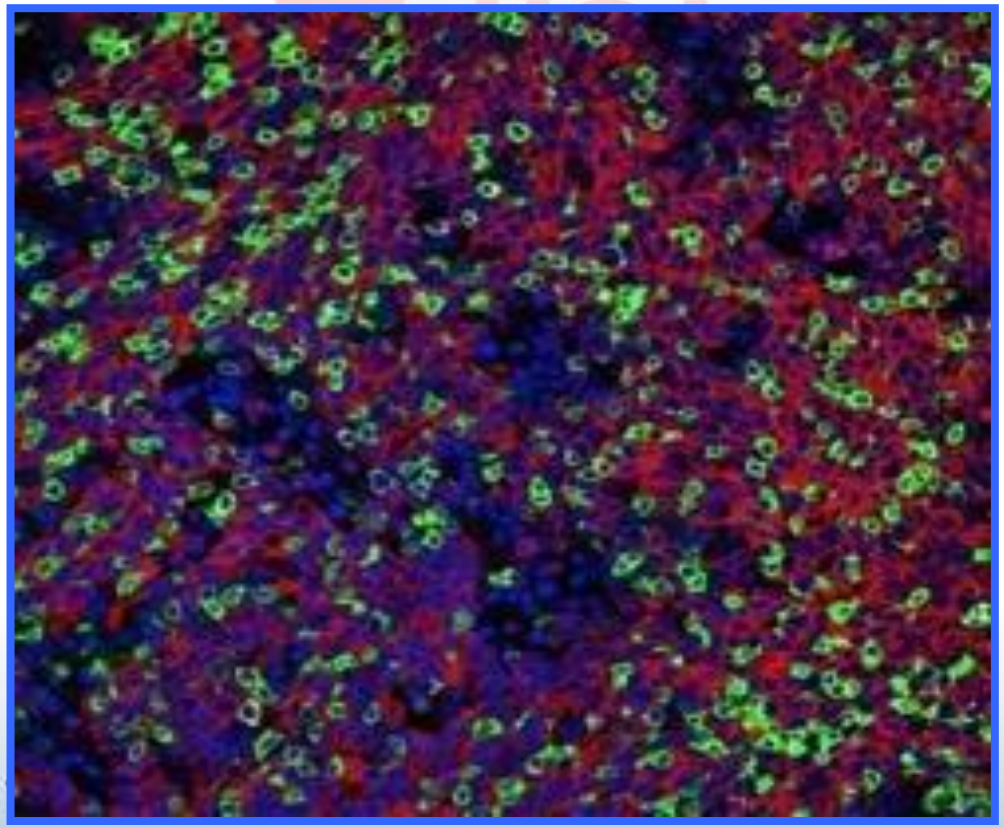
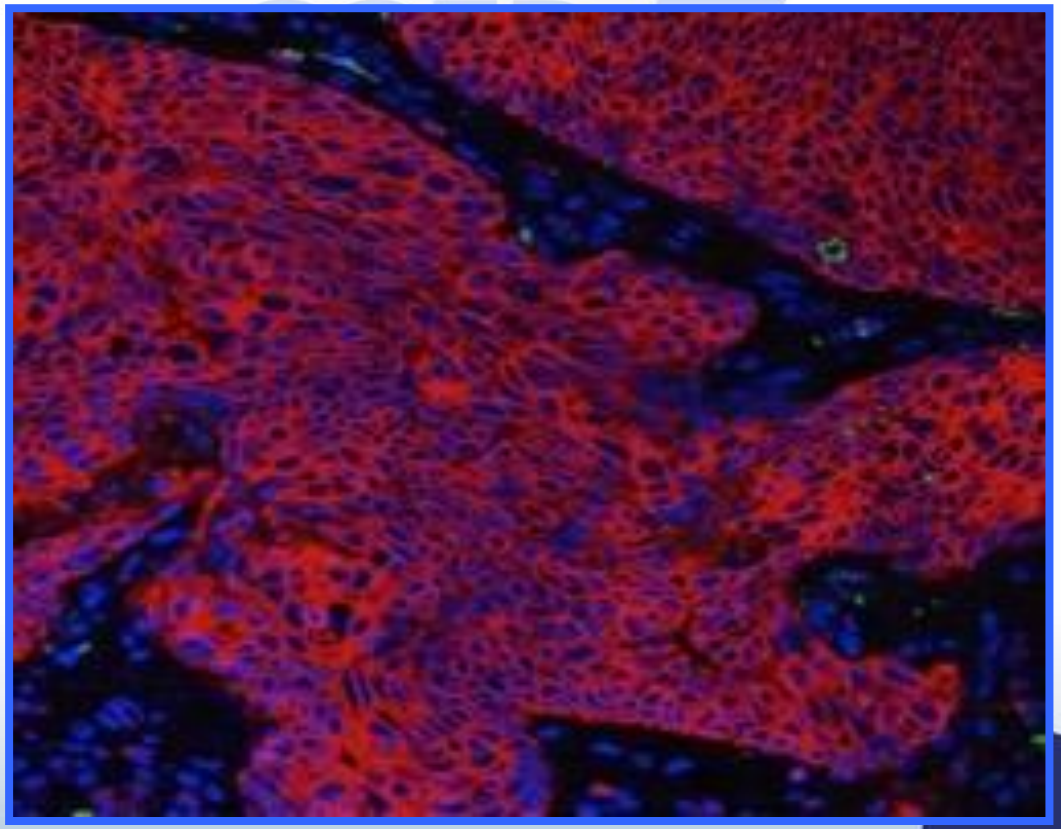
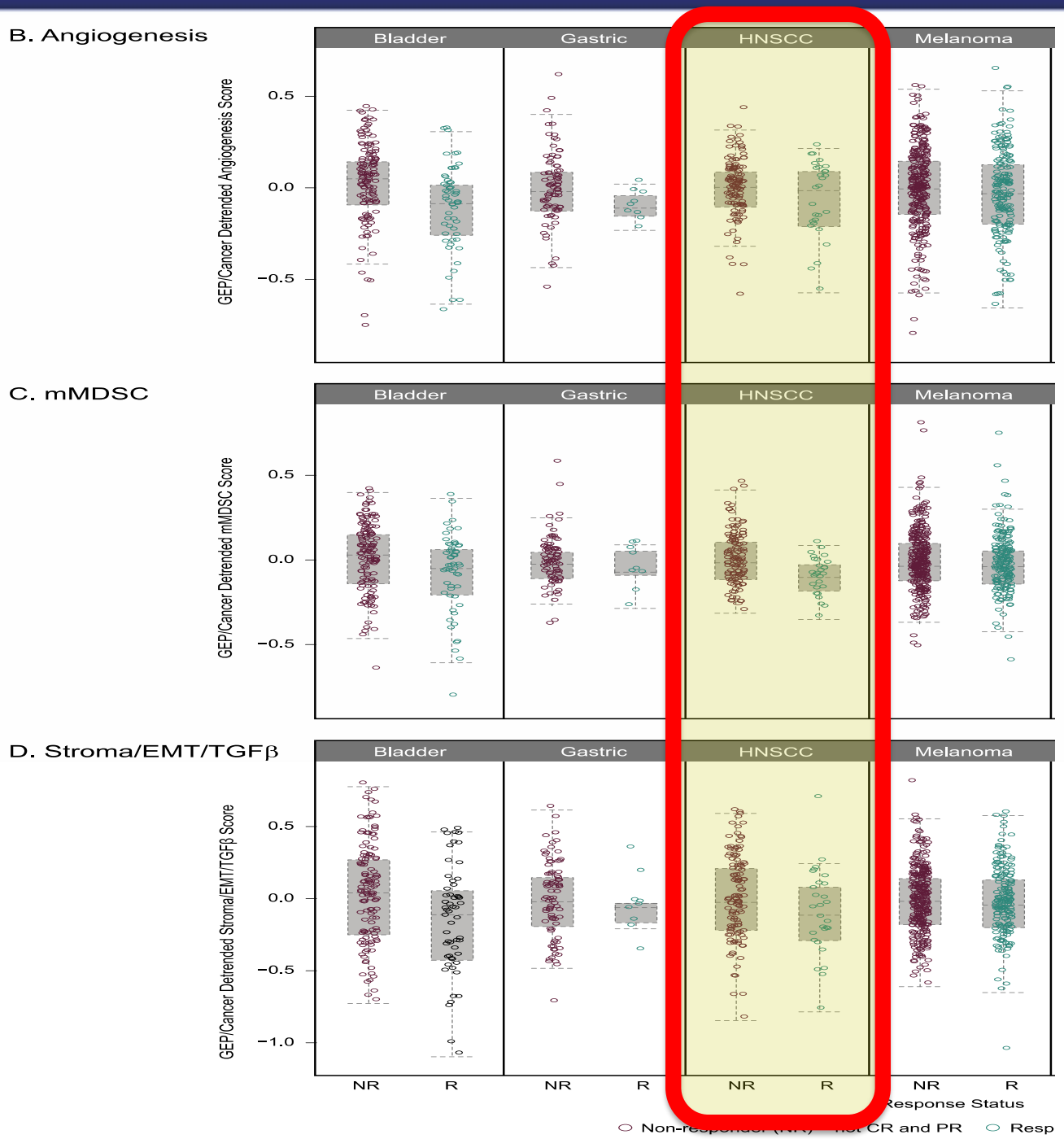
3. Immune/Tumor Microenvironment

HOT and COLD tumors









3 Henchmen of Immune Escape after PD-1:

a) TGF-beta / Stromal-CAFs

b) Suppressive myeloid cells (M2 and MDSCs)

c) Metabolic environment (Angiogenesis/Hypoxia)

Cristescu SITC 2019

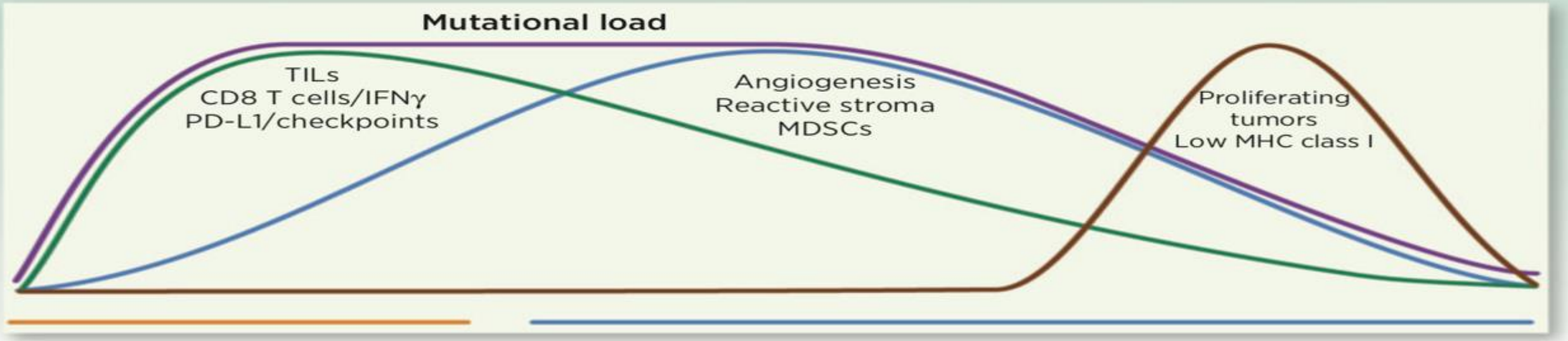
Inflamed

Noninflamed

Preexisting immunity

Excluded infiltrate

Immunologically ignorant



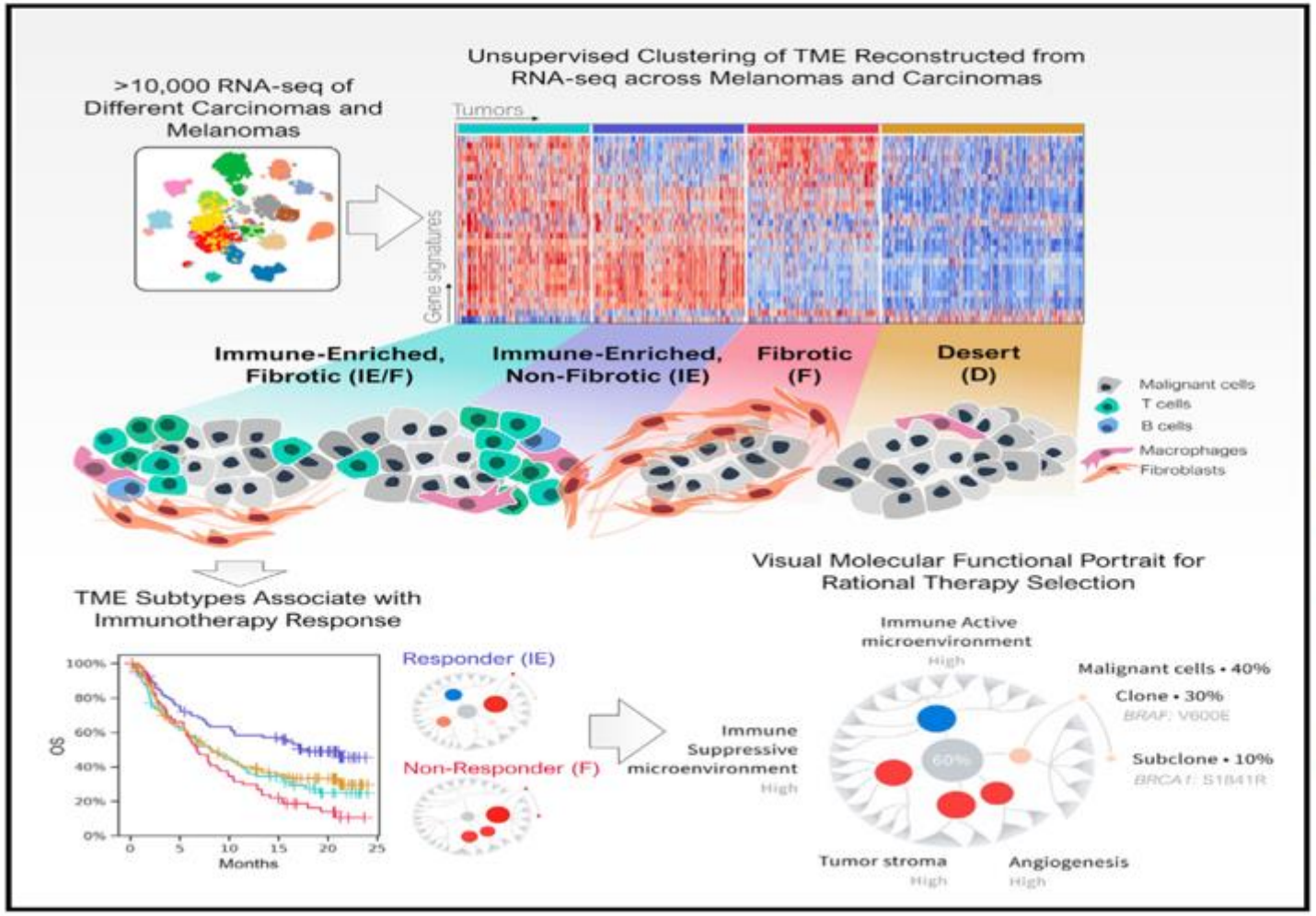
Respond favorably to checkpoint inhibition

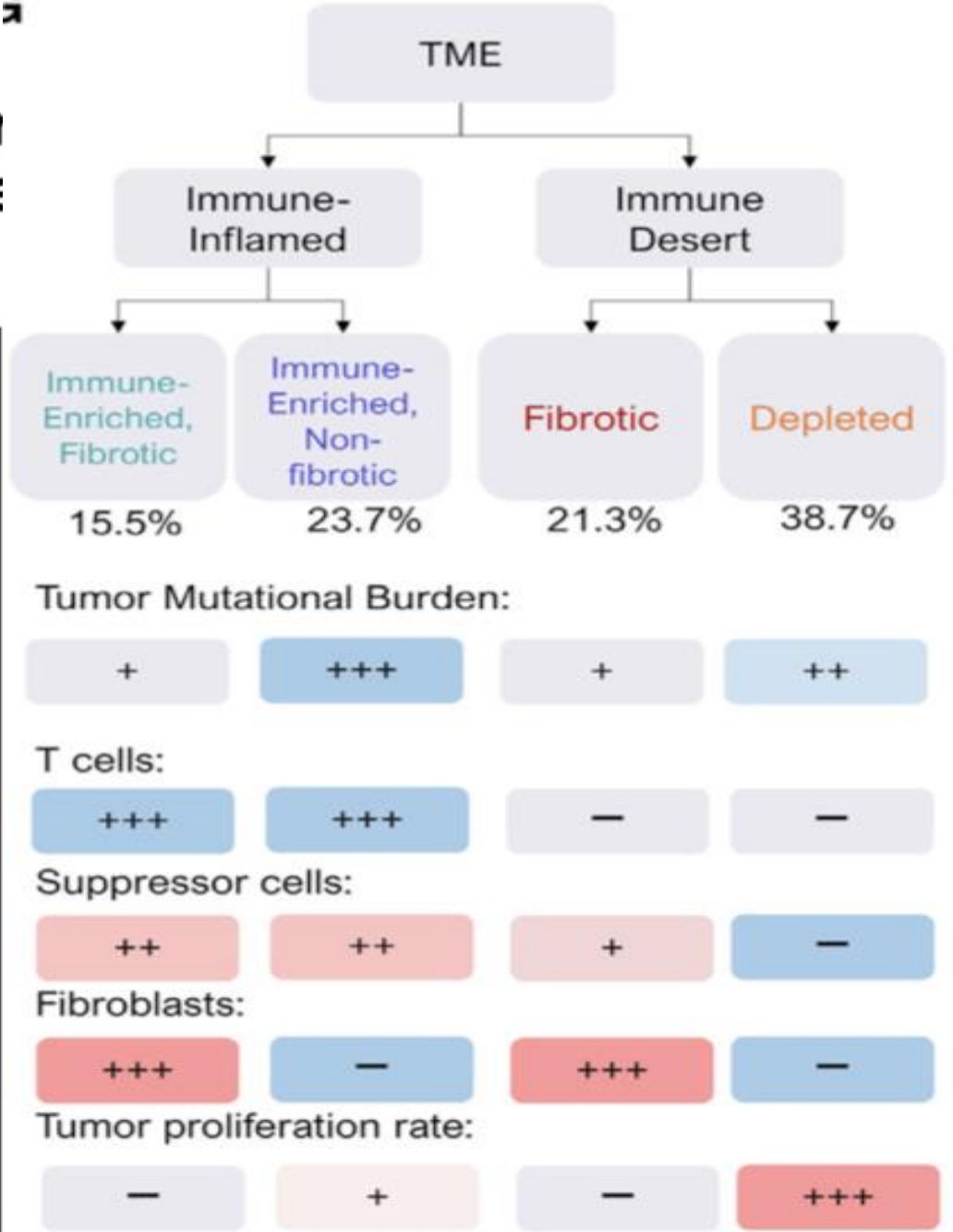
Convert to inflamed phenotype with combinations

Cancer Cell

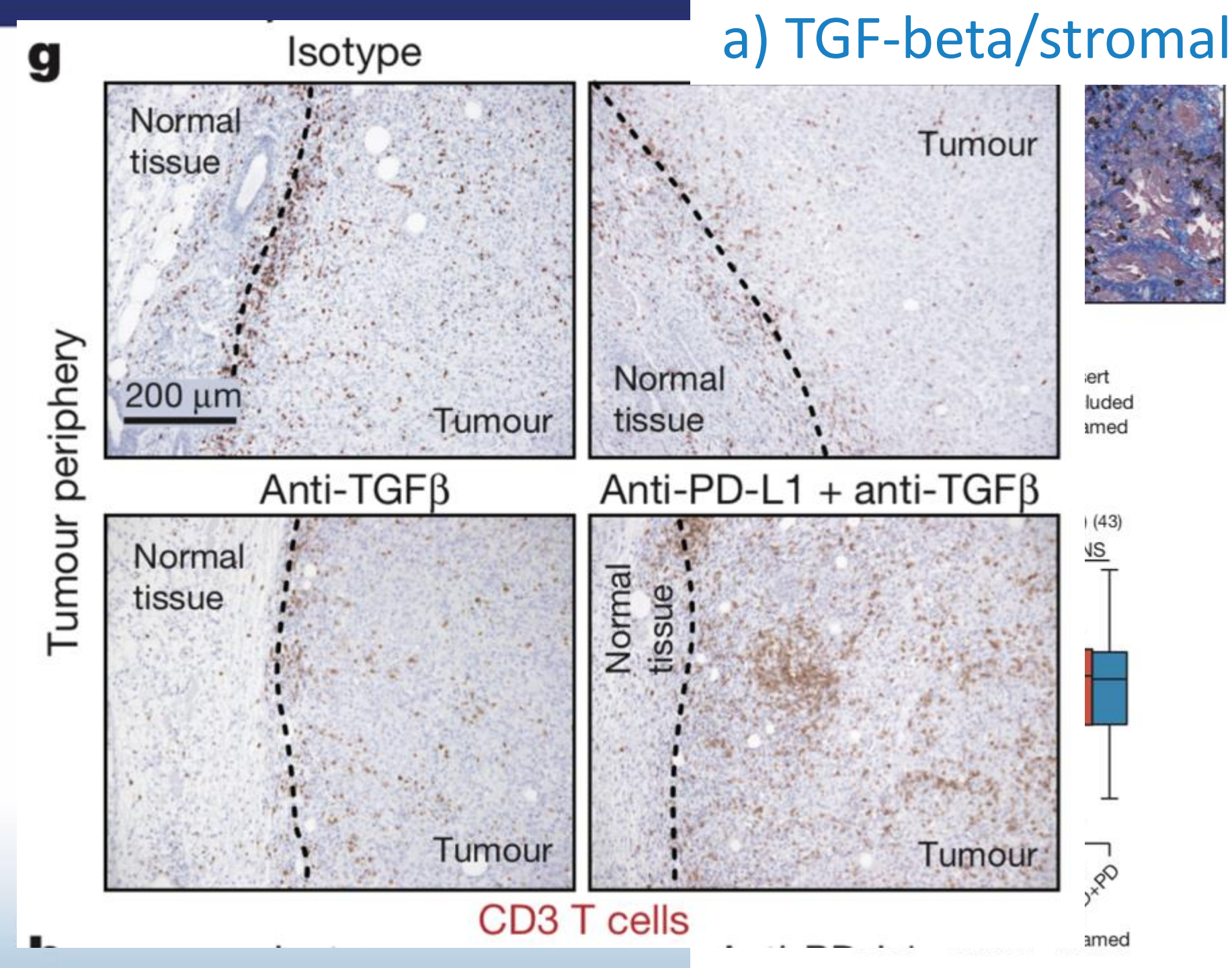
Conserved pan-cancer microen
predict response to immunothe

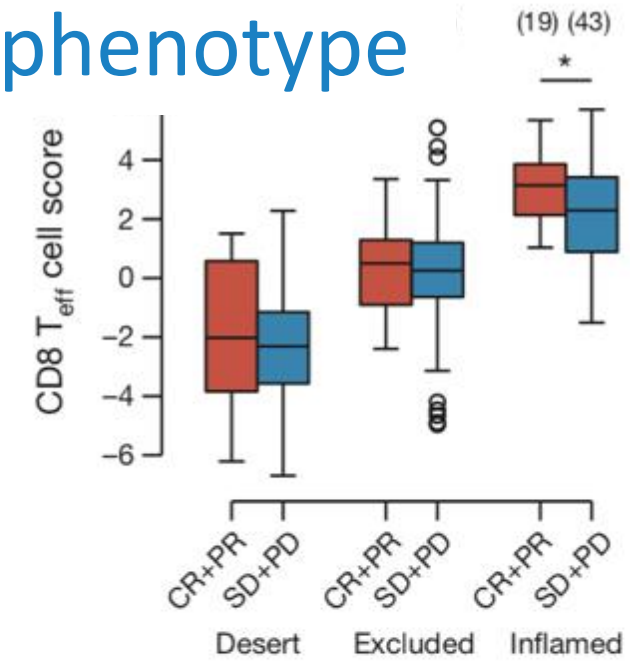
Graphical abstract

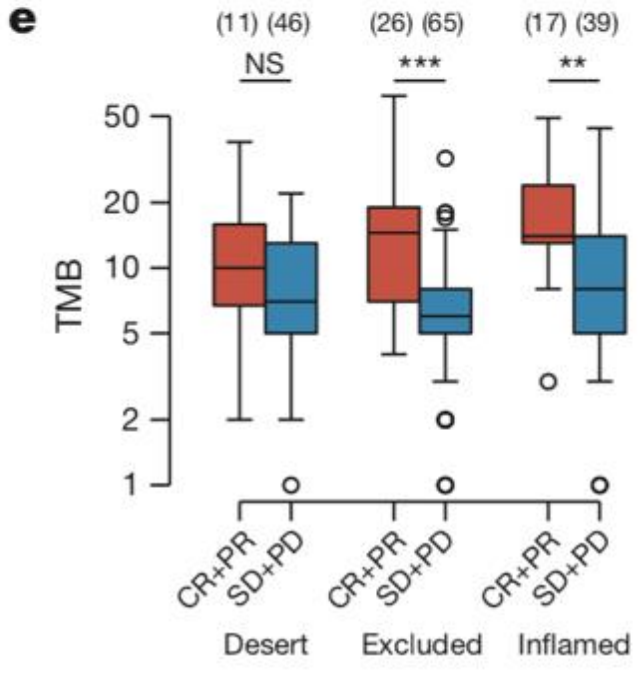




a) TGF-beta/stromal phenotype



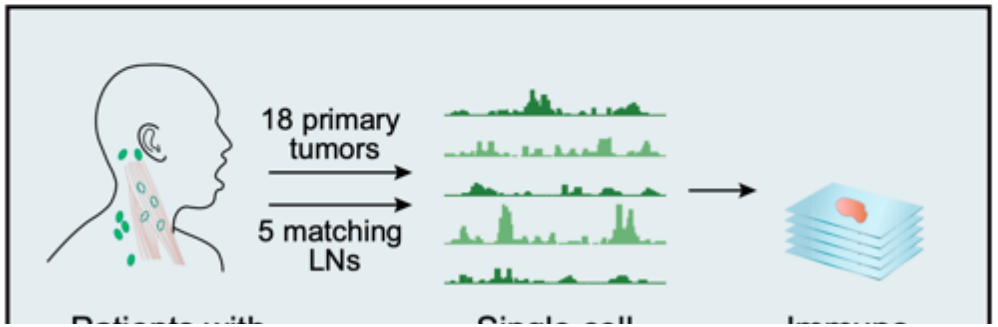


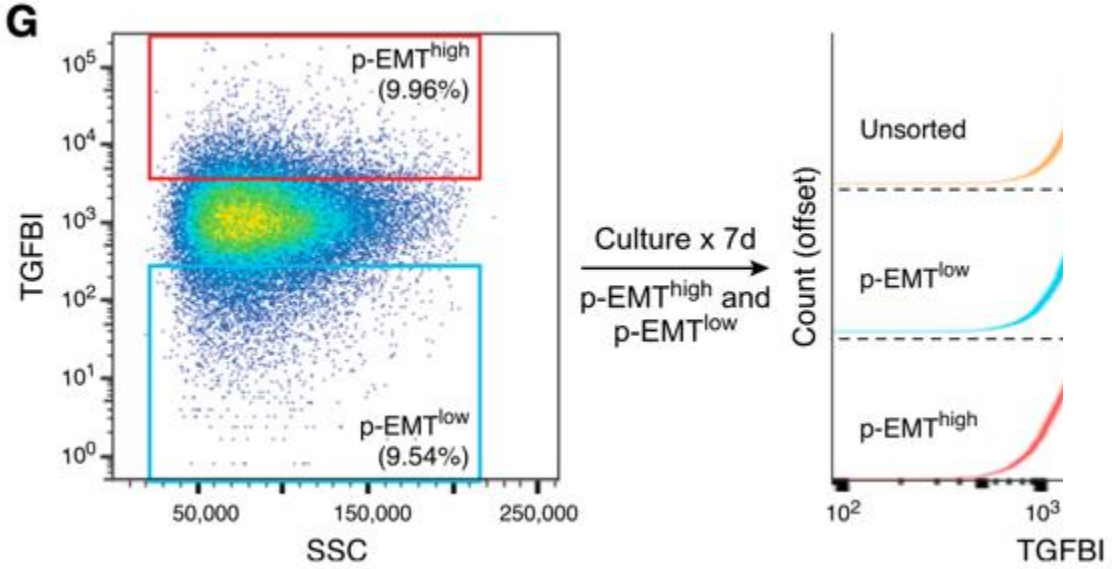


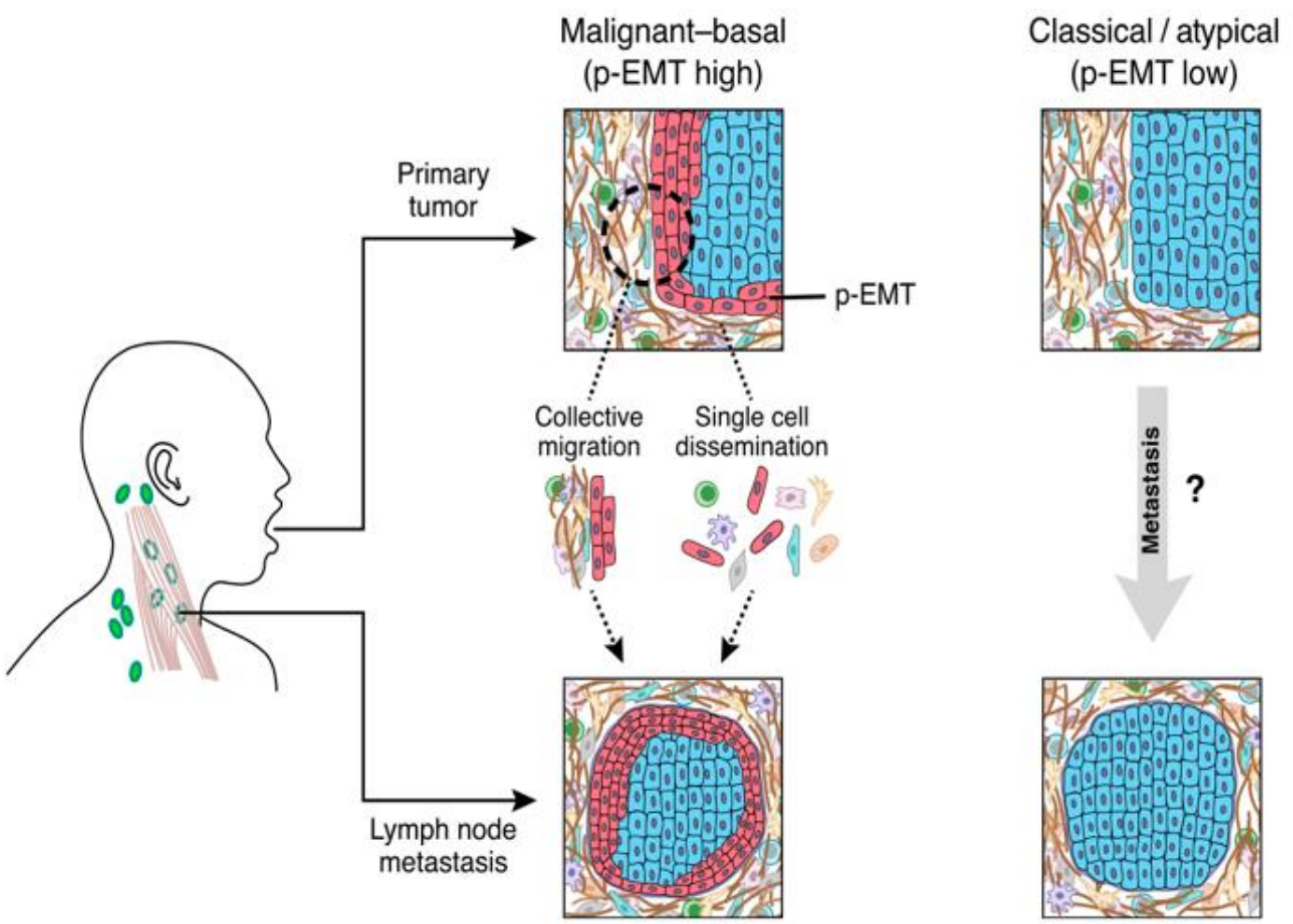
Cell

Single-Cell Transcriptomic Analysis of Primary and Metastatic Tumor Ecosystems in Head and Neck Cancer

Graphical Abstract







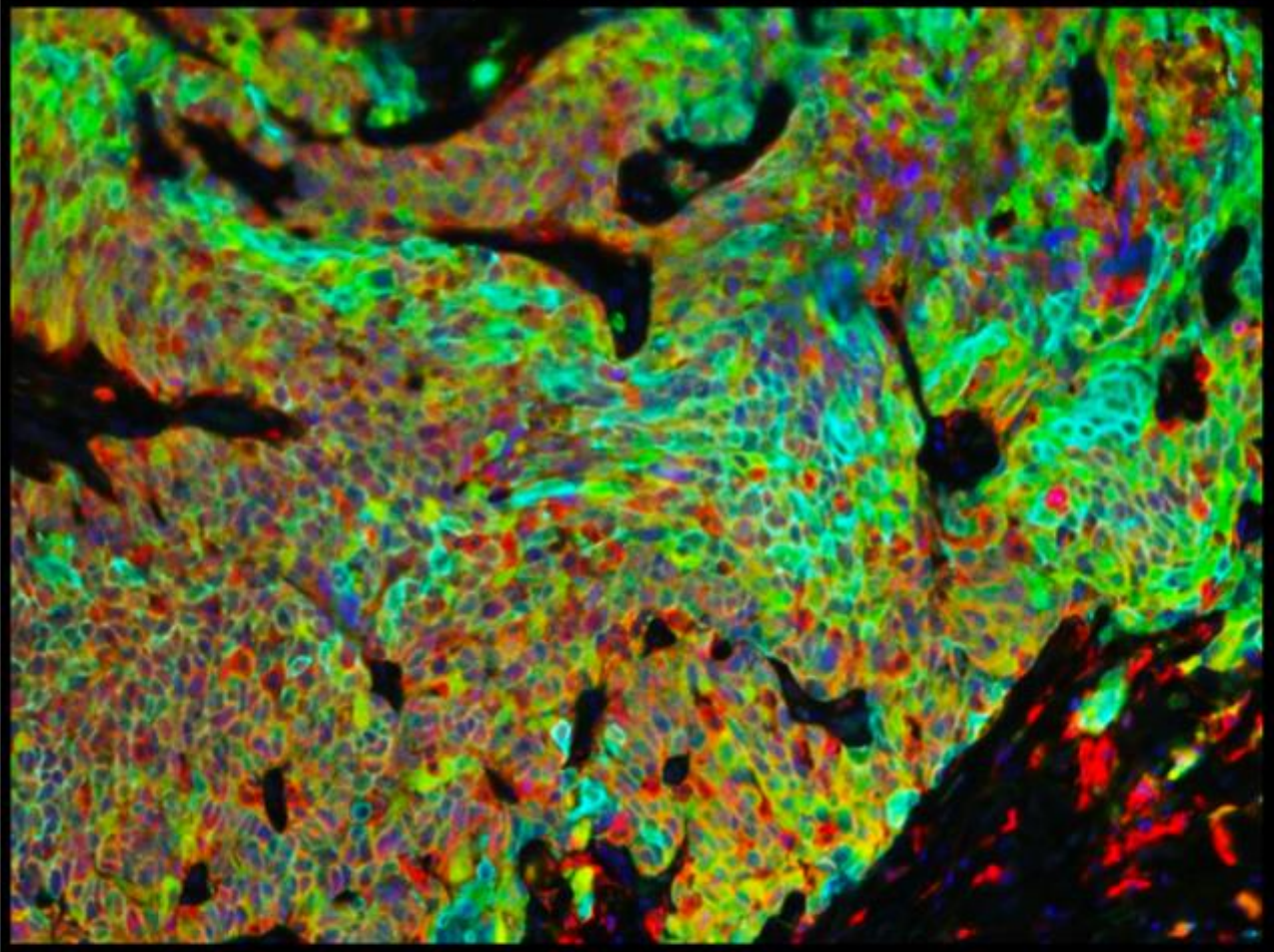
b) Suppressive Myeloid Cells

- Immature myeloid cell populations (iMC, i.e. neutrophils/grMDSCs) as well as tumor associated macrophages (TAM) are implicated in constitutive resistance to anti-PD-1 and poor outcomes.
- Myeloid cells are highly represented in HNSCC based on our multicolor IF imaging HNC cohort [*Seiwert et al SITC 2018*].
- Furthermore, in our cohort of PD-1 treated HNC patients, elevated IL8/CXCL8 levels associate with poor response (~ neutrophil/grMDSC infiltration)
- Presence of certain macrophage sub-populations associate with poor survival [*Seiwert et al ASCO 2017*].
- Similar findings have been seen measuring IL8/CXCL8 in peripheral blood in several tumors [*Sanmamed, MF et al. Ann Oncol. 2017;28:1988-1995, Yuen et al, AACR 2019, and I-ION 2019 meeting/BMS*].

However, the precise mechanisms and contribution of myeloid cells remains unknown, especially at a single cell level → M2 TAM versus grMDSCs

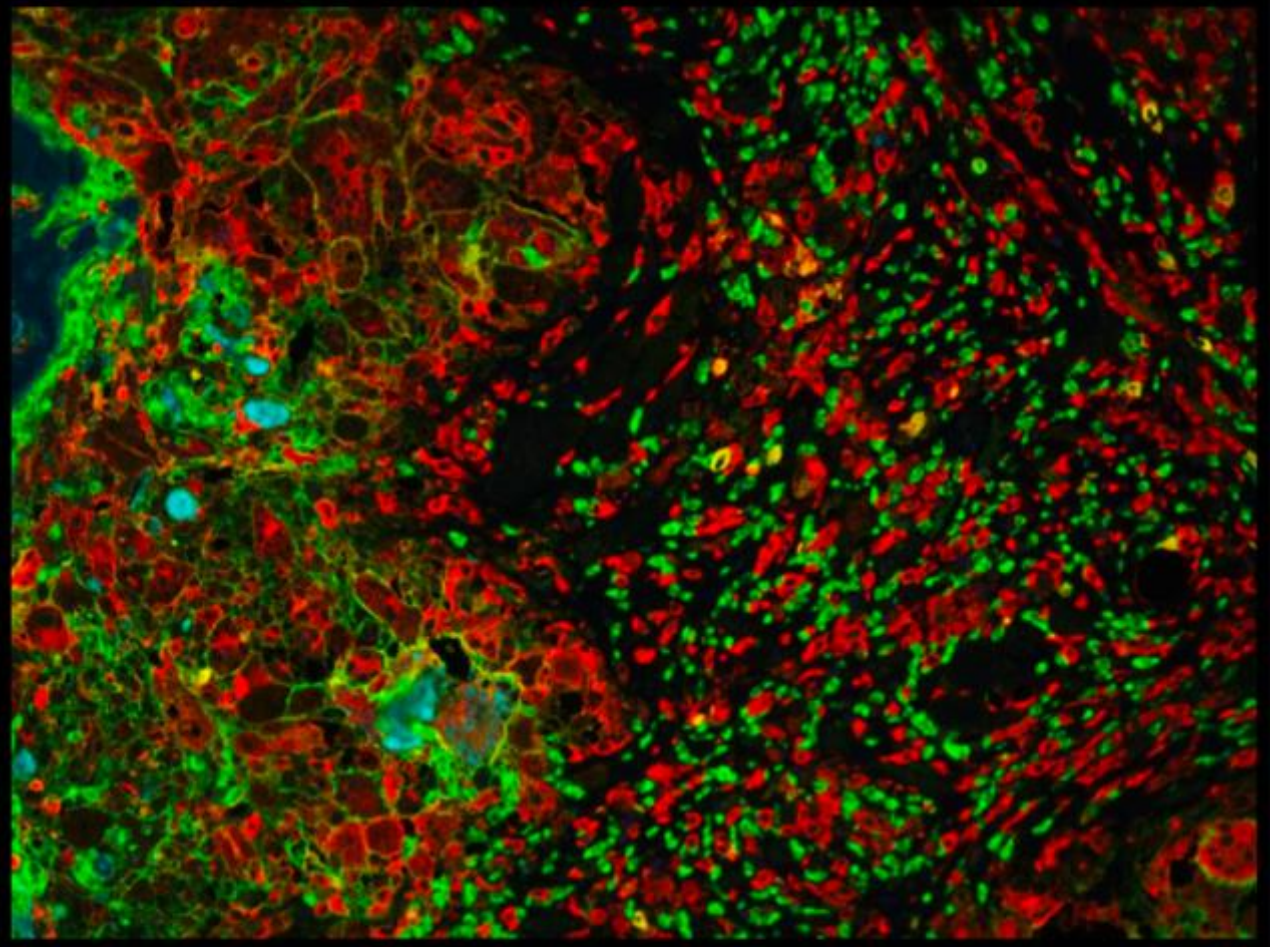
DAPI CK HLADR IDO1 CD11b

High (S16-20385)

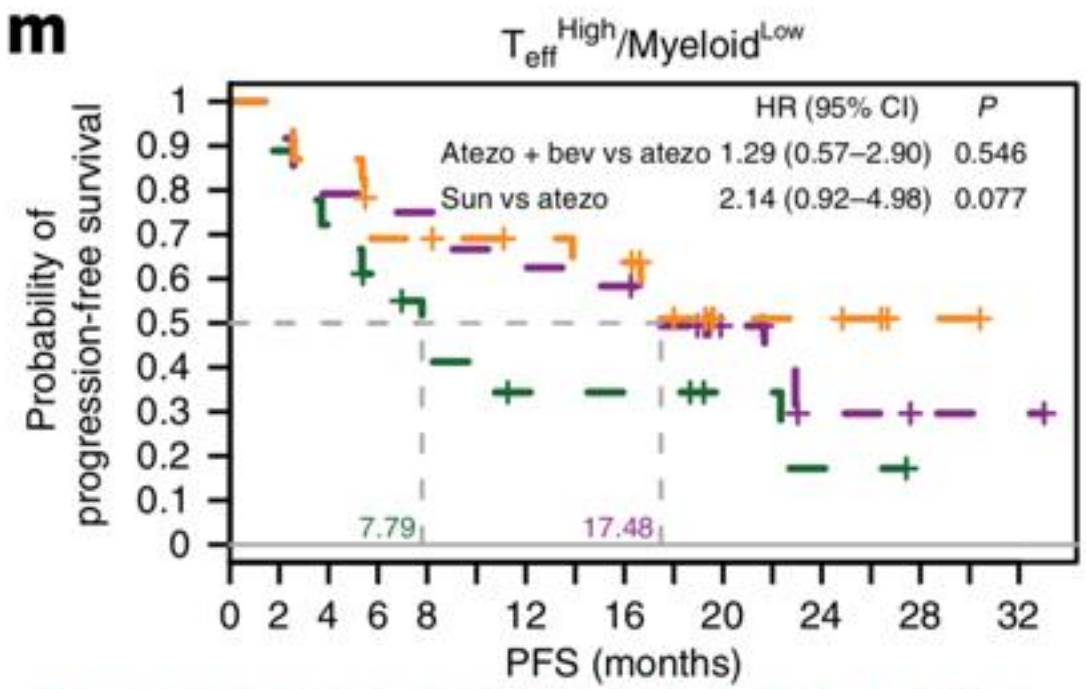


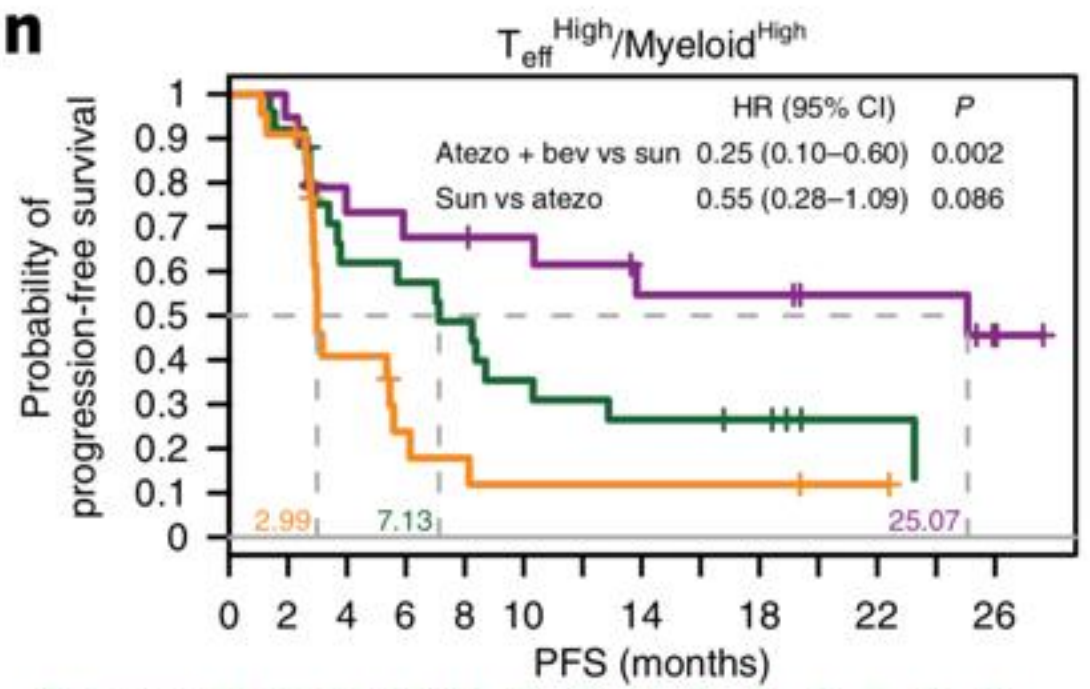
CD11b	HLADR	IDO1	TAM	MDSC	IDO1 (HLADR)	TumorIDO1 (HLADR)	NontumorIDO1 (HLADR)	IDO1 (CD11b)
18%	78%	62%	74%	3%	75%	64%	19%	77%

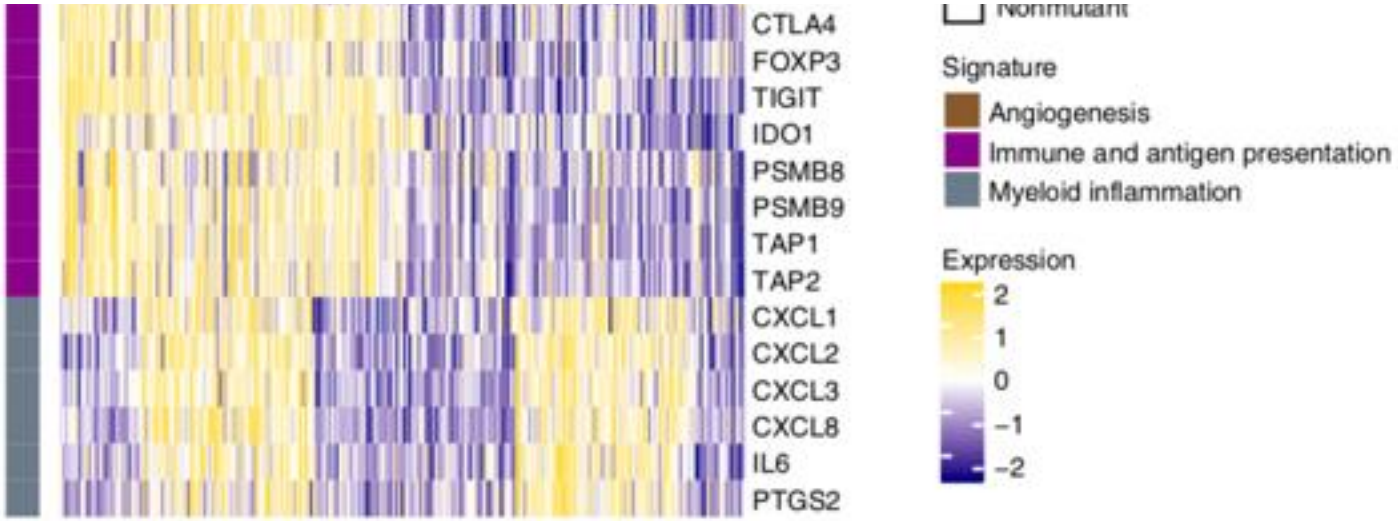
Low (IS14-6443)

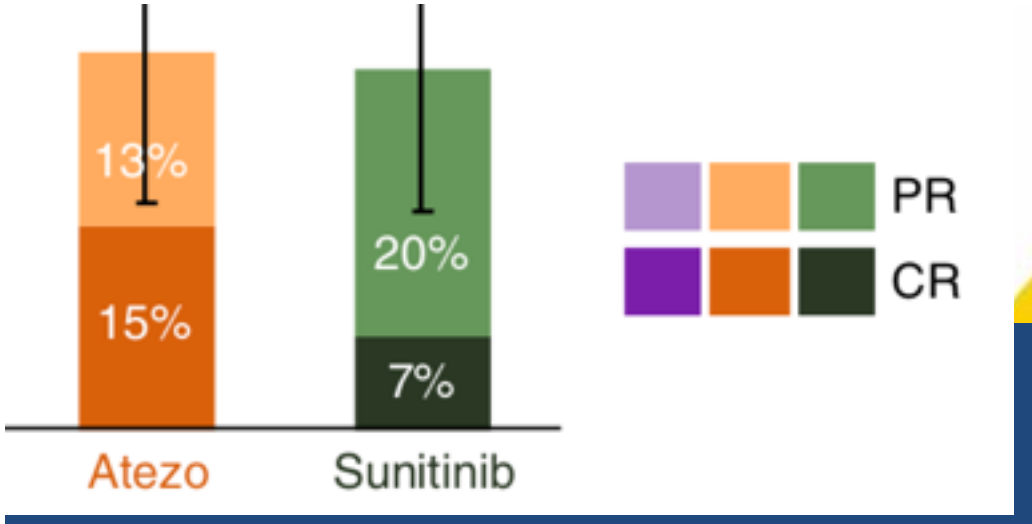


CD11b	HLADR	IDO1	TAM	MDSC	IDO1 (HLADR)	TumorIDO1 (HLADR)	NontumorIDO1 (HLADR)	IDO1 (CD11b)
14%	29%	7%	14%	5%	18%	5%	73%	19%

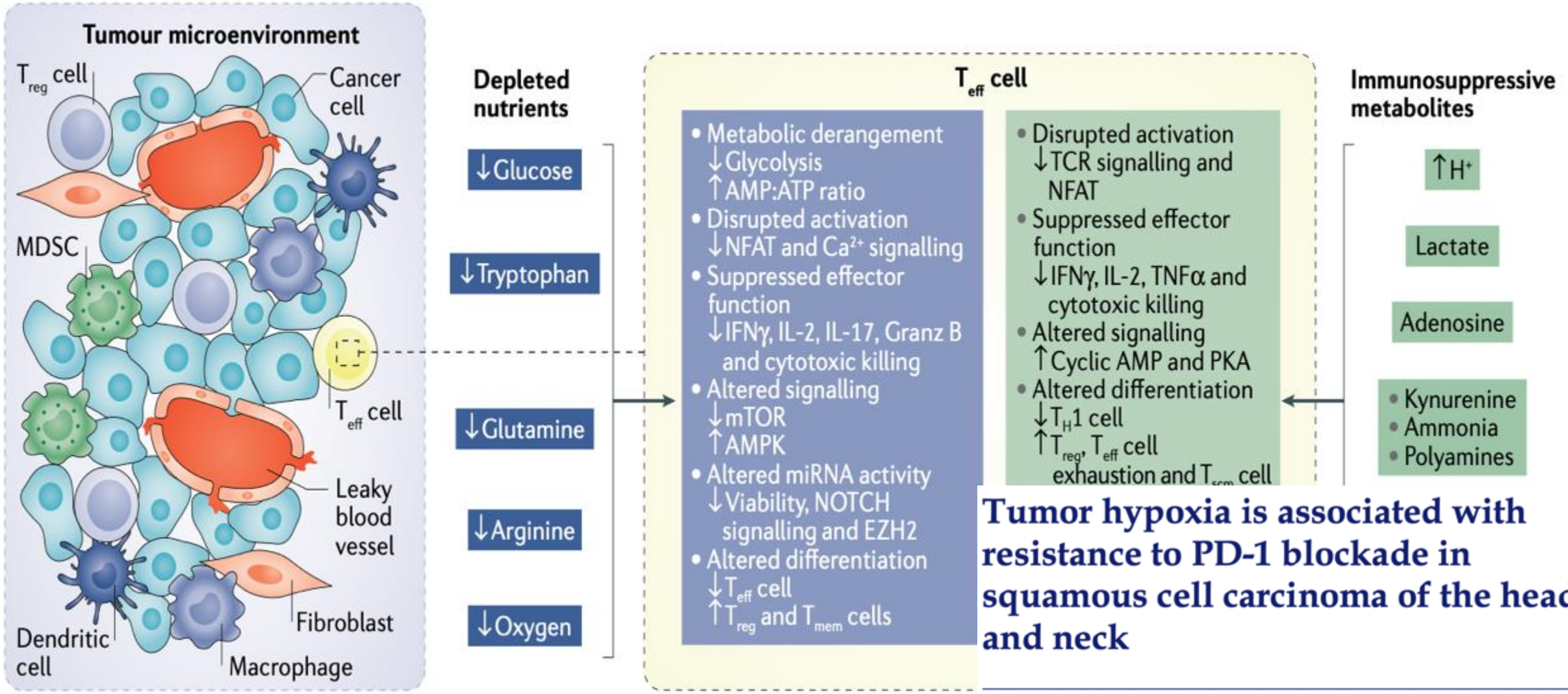

m
T_{eff}^{High}/$Myeloid^{Low}$
HR (95% CI) P
Atezo + bev vs atezo 1.29 (0.57–2.90) 0.546
Sun vs atezo 2.14 (0.92–4.98) 0.077
Probability of progression-free survival
7.79
17.48
PFS (months)
Sunitinib 18 16 13 9 7 6 4 4 4 4 2 2 1 1 0 0 0
Atezo + bev 24 22 19 18 18 16 15 15 14 11 6 4 2 2 1 1 1
Atezo 24 23 20 15 15 14 13 12 12 8 4 4 4 3 1 1 0


n
T_{eff}^{High}/$Myeloid^{High}$
HR (95% CI) P
Atezo + bev vs sun 0.25 (0.10–0.60) 0.002
Sun vs atezo 0.55 (0.28–1.09) 0.086
Probability of progression-free survival
2.99
7.13
25.07
PFS (months)
Sunitinib 25 23 14 13 11 8 7 6 6 5 2 2 0 0
Atezo + bev 19 18 13 12 12 11 10 8 8 8 6 6 6 3
Atezo 22 20 8 4 3 2 2 2 2 2 1 1 0 0


CTLA4
FOXP3
TIGIT
IDO1
PSMB8
PSMB9
TAP1
TAP2
CXCL1
CXCL2
CXCL3
CXCL8
IL6
PTGS2
Signature
Angiogenesis
Immune and antigen presentation
Myeloid inflammation
Expression
2
1
0
−1
−2


13%
15%
20%
7%
Atezo
Sunitinib
PR
CR

c) Tumor Metabolism Checkpoint



Tumor hypoxia is associated with resistance to PD-1 blockade in squamous cell carcinoma of the head and neck

Dan P Zandberg,[1] Ashley V Menk,[2] Maria Velez,[1] Daniel Normolle,[1] Kristin DePeaux,[2,3] Angen Liu,[1] Robert L Ferris,[1,2] Greg M Delgoffe [2,3]

Leone/Powell Nature Rev 2020

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sitc Society for Immunotherapy of Cancer Advances in Cancer Immunotherapy™

c) Tumor Metabolism Checkpoint

Anti-tumor 'inflammation'

Cell type	Function	Metabolic phenotype
Immune activation or inflammatory		
NK cell 	MHC-independent cytotoxicity: Perforin, granzymes FASL, TRAIL IFNγ, TNF	Glycolysis and OXPHOS
Inflammatory TAM 	MHC-independent cytotoxicity: TNF, IL-1β Oxidative burst Antigen presentation	Glycolysis and PPP
DC 	DAMP processing T_{eff} cell activation Antigen presentation	Glycolysis
T_{eff} cell 	Antigen-specific cytotoxicity: Perforin, granzymes FASL IFNγ, TNF	Highly glycolytic and OXPHOS Amino acid metabolism (arginine, tryptophan, serine, leucine, glutamine, cysteine) PPP
T_{mem} cell 	Maintain long-lived response	OXPHOS

Pro-tumor 'inflammation'

Immunosuppression		
MDSC 	IL-10, TGFβ Amino acid depletion Polyamines, kynurenine	Glycolysis and OXPHOS
Immunosuppressive TAM 	IL-10 Amino acid depletion Polyamines, kynurenine VEGF	OXPHOS, HBP
T_{reg} cell 	IL-2 sequestration: Dampen APC co-stimulation IL-10, TGFβ Adenosine	OXPHOS

Conclusions

1. Tumor Immunology
   a) *Three Signals of the Immune Synapse*
   b) Priming and effector phase

2. Novel Immune Checkpoints are emerging
   a) *TIGIT/LAG3 with proof of principle clinical activity*
   b) *Costimulatory targets with Bispecific format also show activity (SITC 2021)*

3. Tumor Microenvironment factors associate with PD-1 resistance
   a) *TGF-beta/ stromal phenotype*
   b) *Suppressive Myeloid Cells*
   c) *Tumor Metabolism*