Immunotherapy 101 for the Non-Immunologist

Yvonne Saenger MD
Director Melanoma Immunotherapy
Faculty Co-Director, Human Immune Monitoring Core
Assistant Professor, Medicine
Columbia University

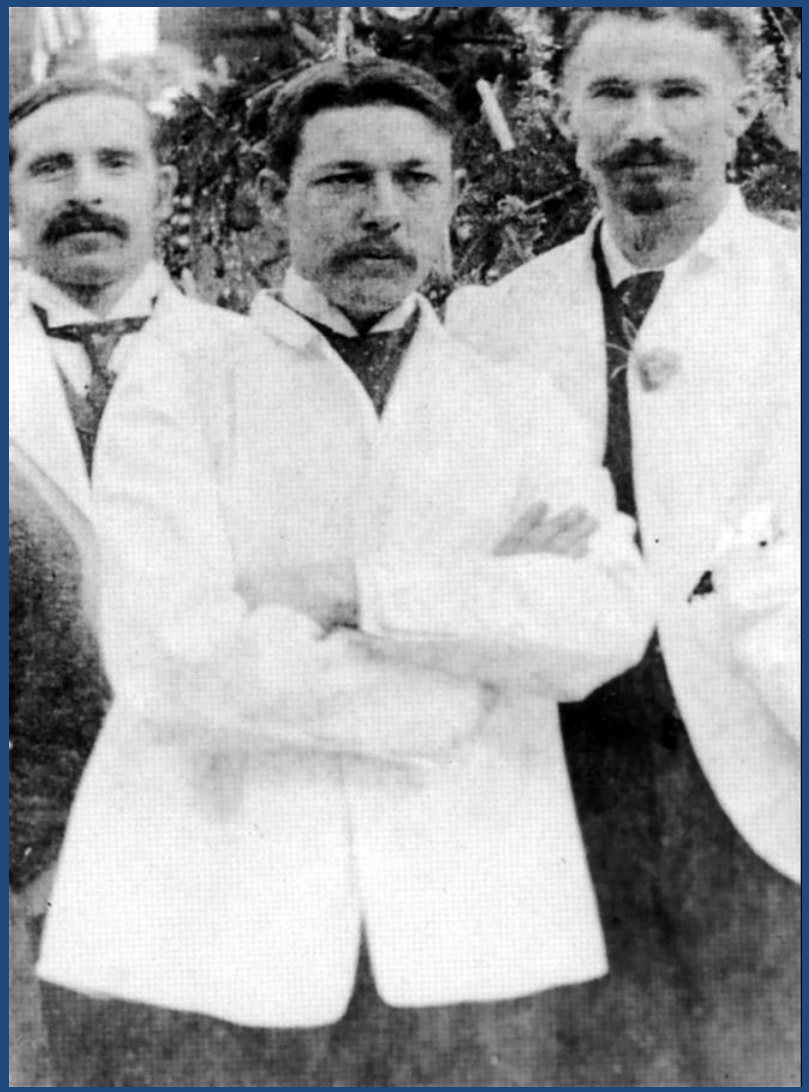
Disclosures

- Advisory Boards for Amgen and BMS
- Investigator Initiated Trials funded by Merck and Amgen
- Research funding from Amgen
- Non-FDA approved agents will not be reviewed

Talk Outline

- General Concepts in Cancer Immunotherapy
- Review of FDA Approved Immunotherapy Agents
- Clinical Implications of Immunology Principles on Immunotherapy
- Future Directions in Immunotherapy

The long history of cancer immunotherapy



New York Times - July 29, 1908

ERYSIPELAS GERMS AS CURE FOR CANCER

Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

MANY CASES CURED HERE

Physician Has Used the Cure for 15 Years and Treated 430 Cases— Probably 150 Sure Cures.

Following news from St. Louis that two men have been cured of cancer in the City Hospital there by the use of a fluid discovered by Dr. William B. Coley of New York, it came out yester-

Chemotherapy- “20th century medicine” in melanoma

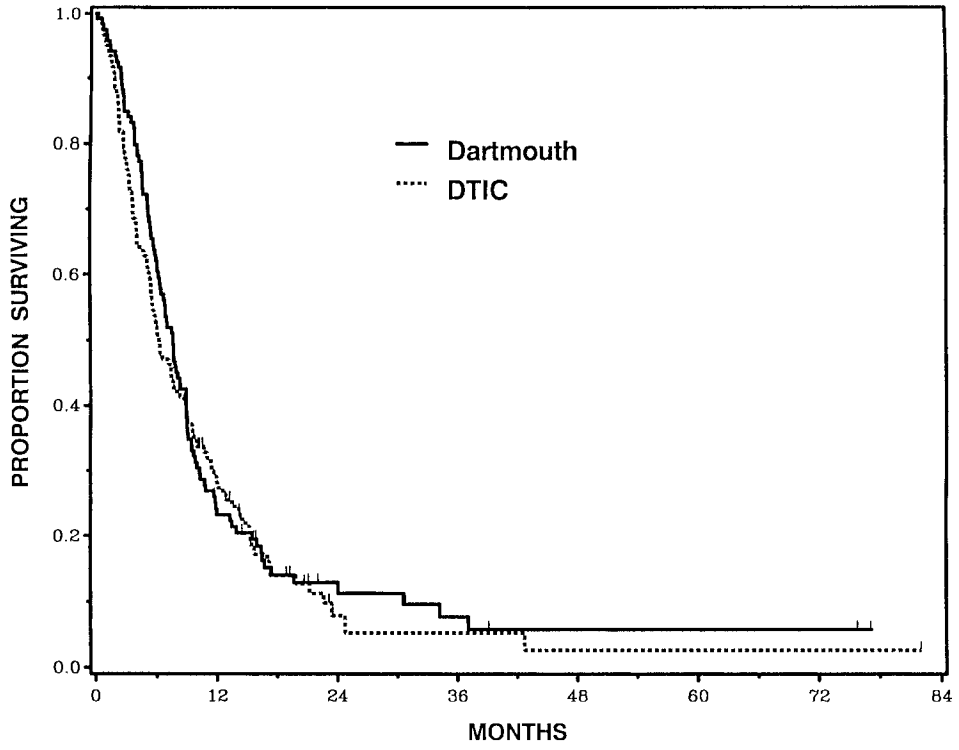


Fig 1. Kaplan-Meier survival plot of all 240 patients randomized based on intent to treat. Median survival time on Dartmouth regimen was 7.7 months (95% CI, 6.3 to 8.9 months) versus 6.3 months (95% CI, 5.4 to 8.7 months) on dacarbazine ($P = .52$). Tick marks represent censored patients.

Chapman et al, “Phase III multicenter randomized trial of the Dartmouth regimen versus dacarbazine in metastatic melanoma,” *Journal of Clinical Oncology,* 1999.

The JAMA Network

From: **Association of Pembrolizumab With Tumor Response and Survival Among Patients With Advanced Melanoma**

JAMA. 2016;315(15):1600-1609. doi:10.1001/jama.2016.4059

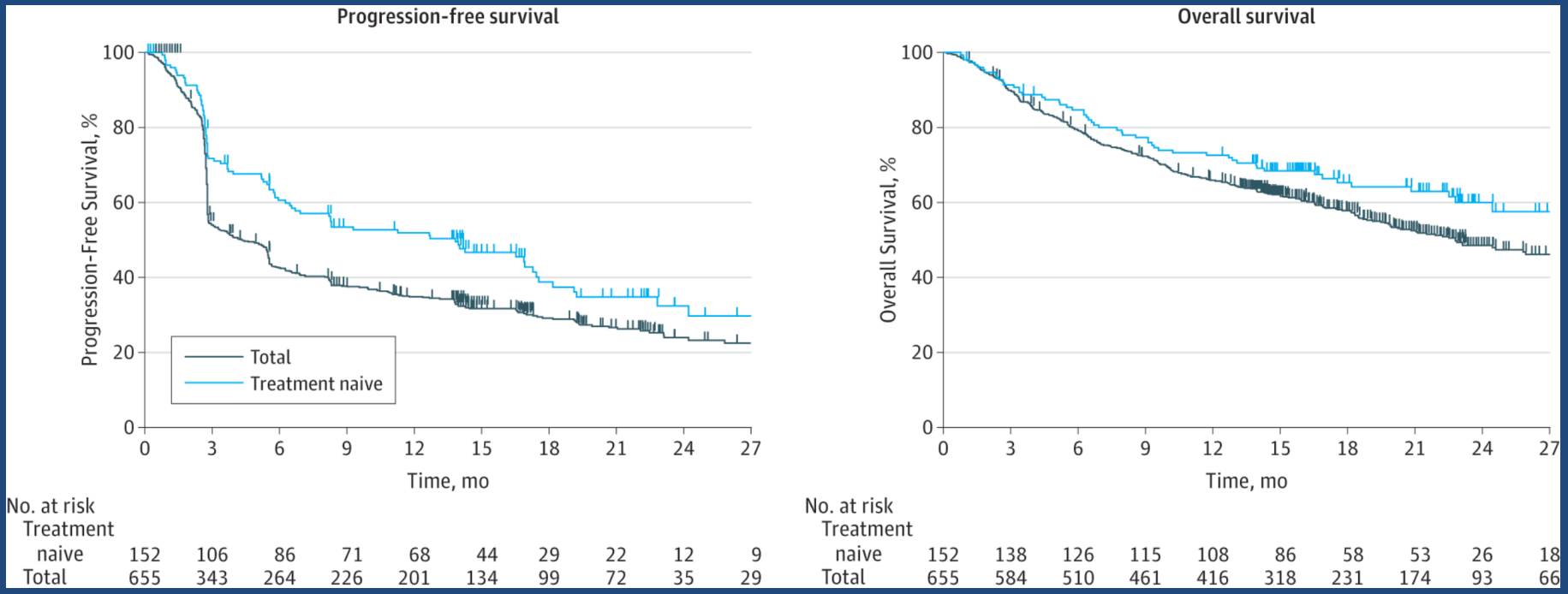


Figure Legend:

Progression-Free and Overall Survival in Patients Treated With Pembrolizumab in Total and Treatment-Naive PopulationsThe small vertical tick marks represent patients who were censored at that specific time in the survival analysis. Tick marks appear to be floating when multiple events occurred at the same time. Data were assessed by independent central review using RECIST v1.1.

Date of download: 6/30/2016

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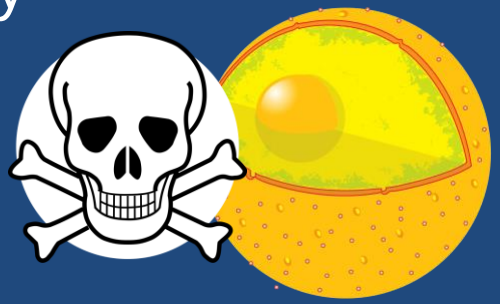
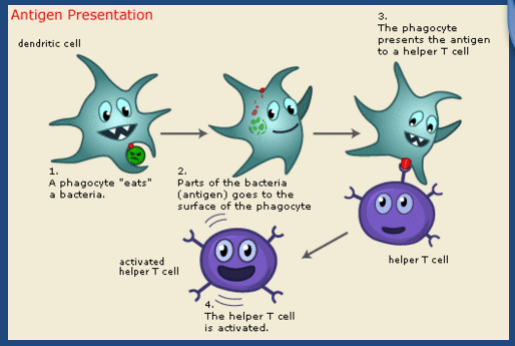
Chemotherapy is a poison. Purpose is to kill cancer cells more quickly than normal cells.

Comparison of Mechanisms of Cancer Chemotherapy and Cancer Immunotherapy

Chemotherapy

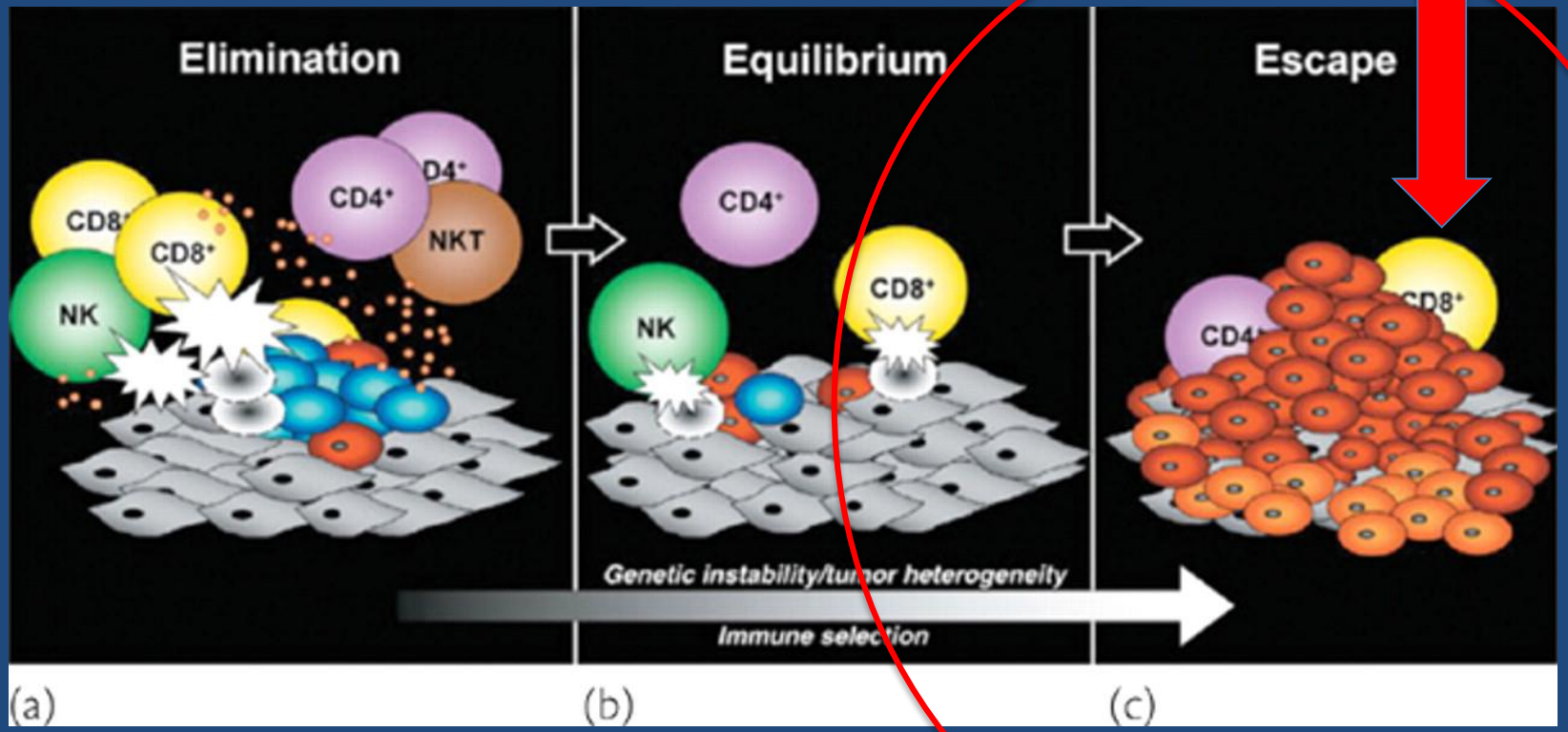


Immunotherapy



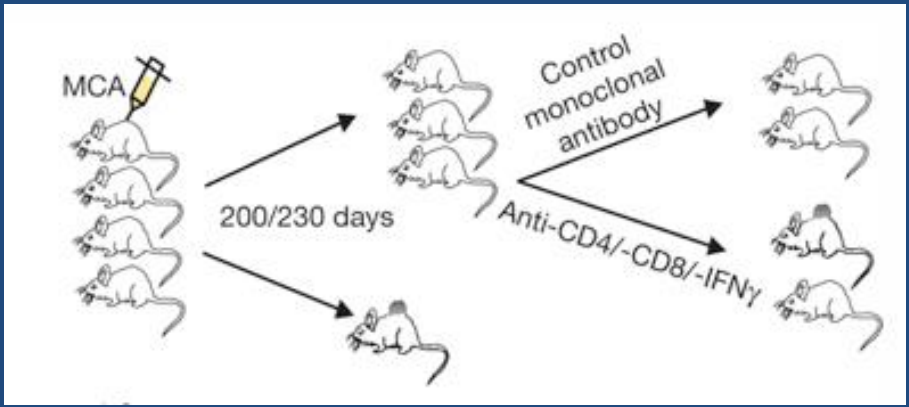
WAKE UP!

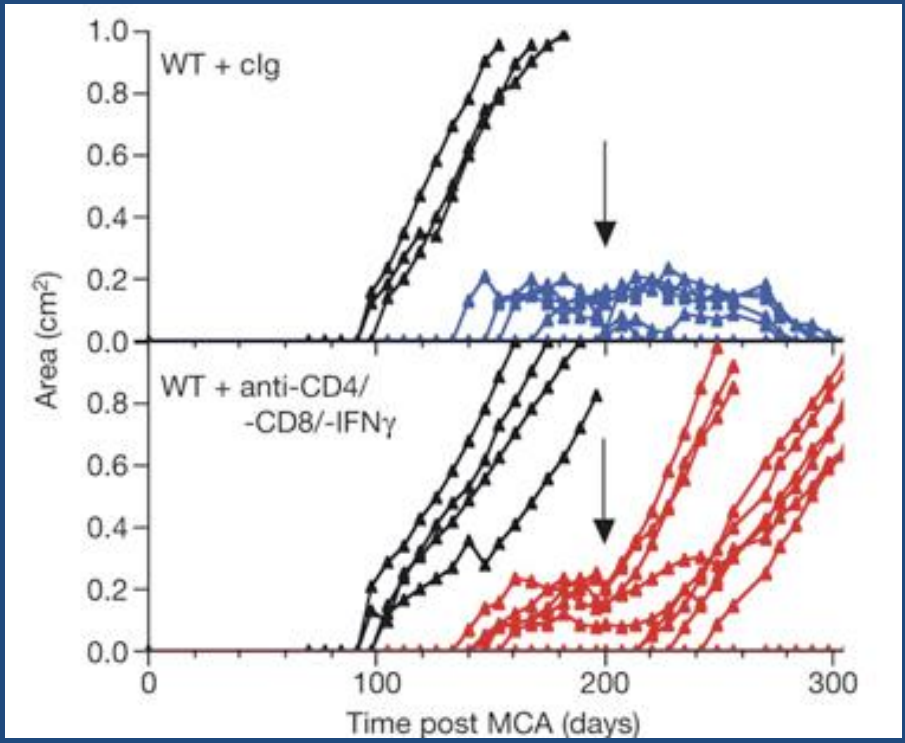
Immunosurveillance



Dunn et al,,"Cancer immunoediting: from immunosurveillance to tumor escape" *Nature Immunology* 2002.

Immune surveillance controls dormant tumors

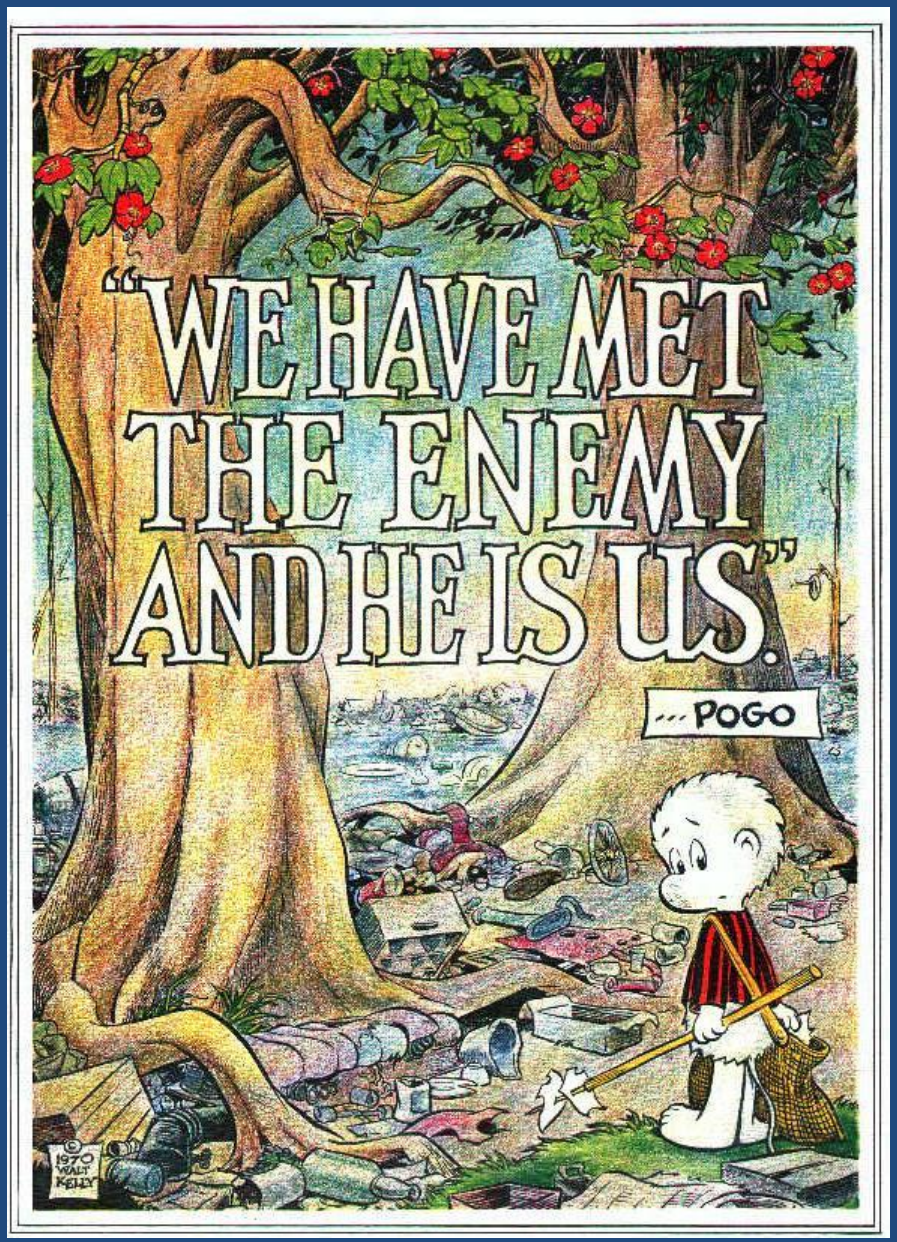




Koebel et al. Nature;450:903, 2007

Why does the immune system eventually fail to control cancer in some patients?

Problem #1- The tumor looks like normal tissue



Mutational profiles of tumor types- in general tumors with more mutations look less like “self”

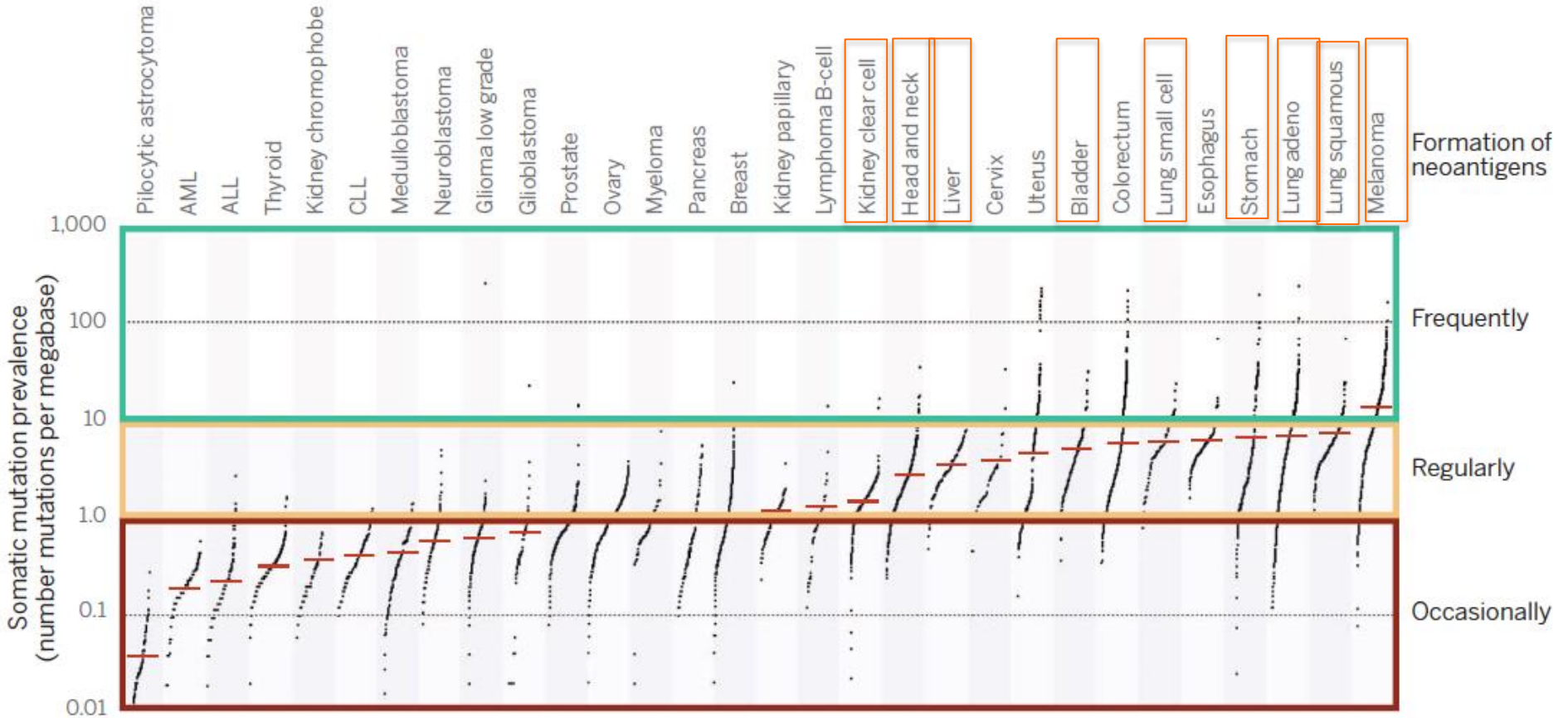
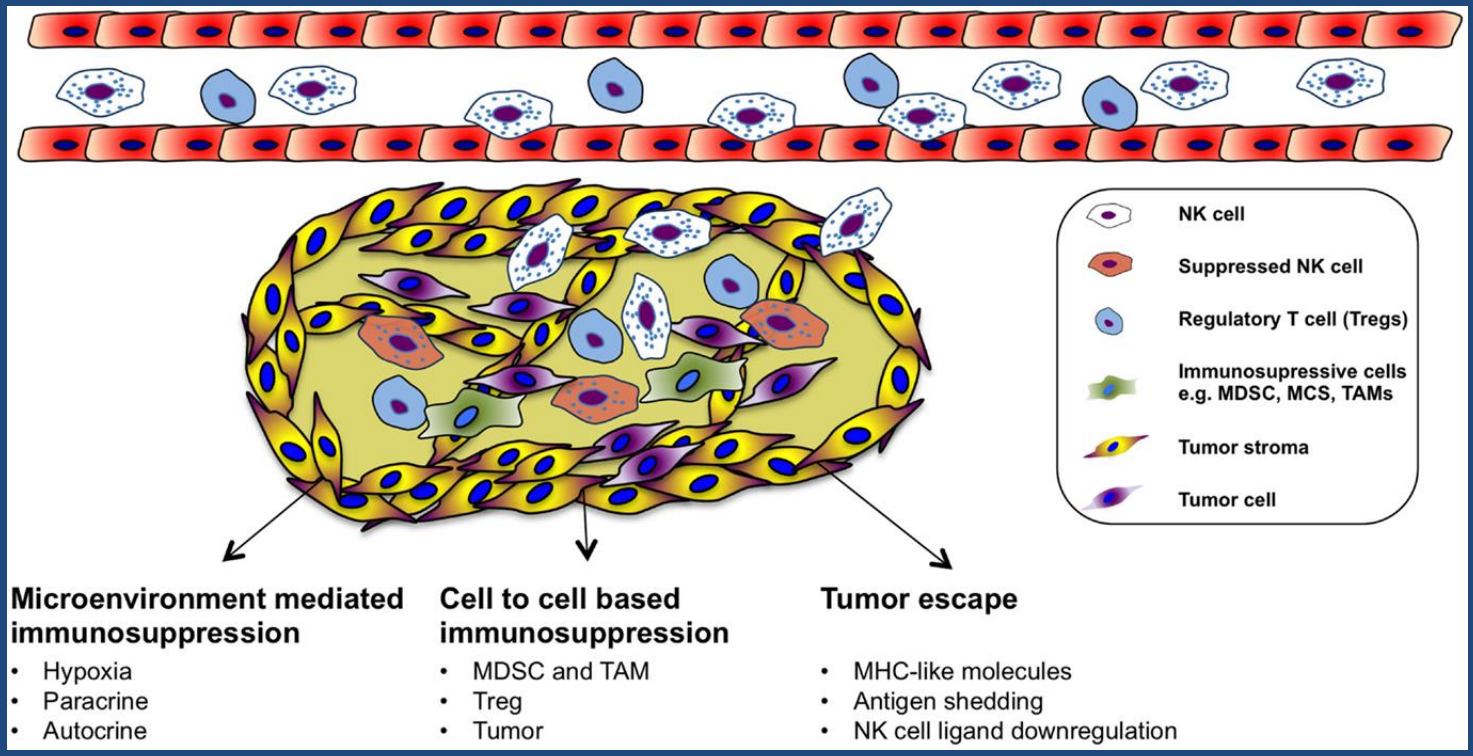
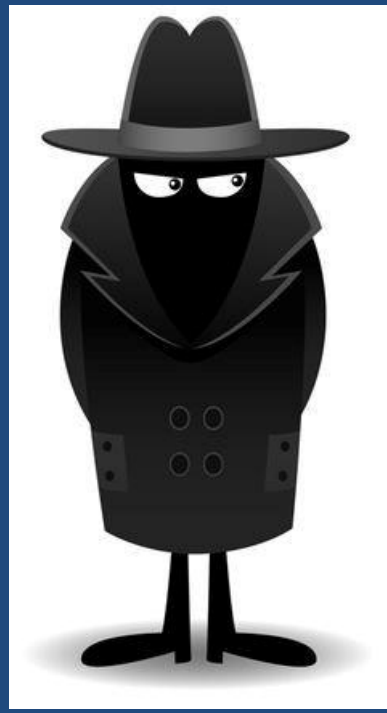


Fig. 2. Estimate of the neoantigen repertoire in human cancer. Data depict the number of somatic mutations in individual tumors. Categories on the right indicate current estimates of the likelihood of neoantigen formation in different tumor types. Adapted from (*50*). It is possible that the immune system in melanoma patients picks up on only a fraction of the available neoantigen repertoire, in which case the current analysis will be an underestimate. A value of 10 somatic mutations per Mb of coding DNA corresponds to ~150 nonsynonymous mutations within expressed genes.

Schumacher et al *Science* 2015.

Problem #2- Tumors turn off the immune system

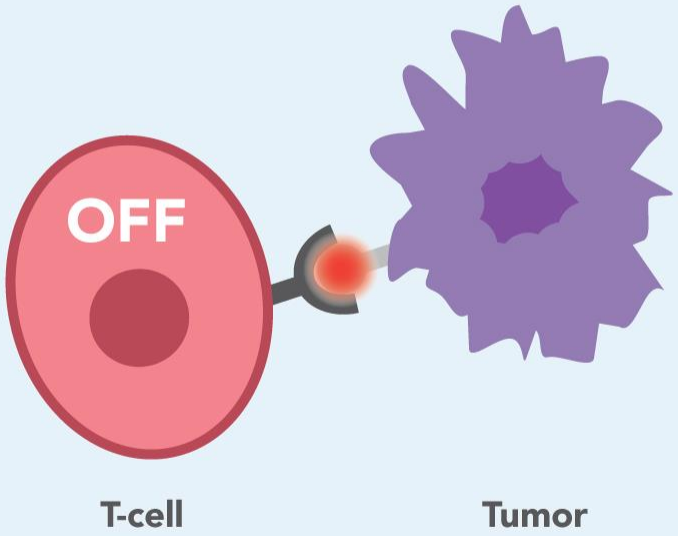




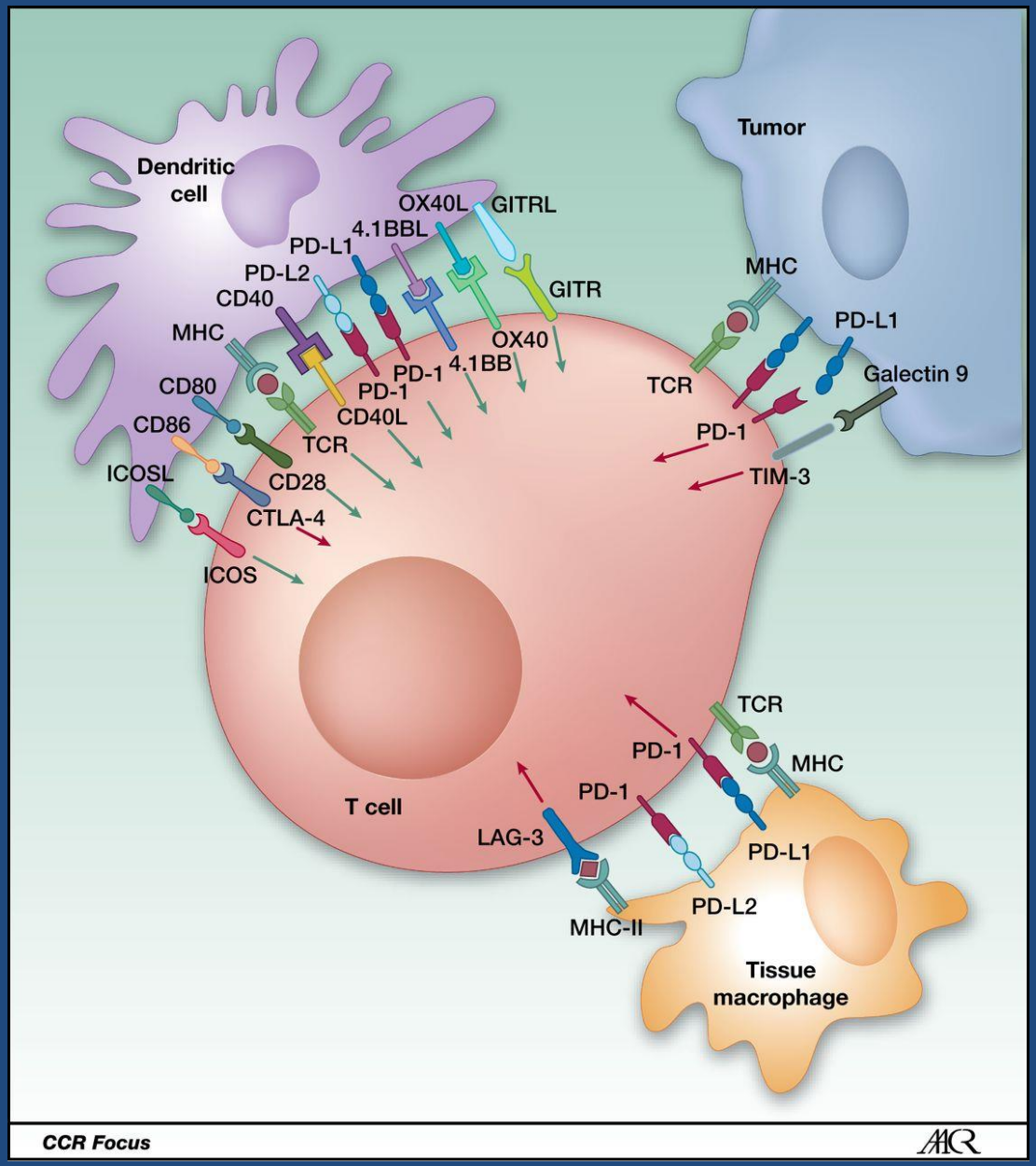
Dshlbertg et al, *Fronteirs in Immunology* 2015

How Does Immunotherapy Work?

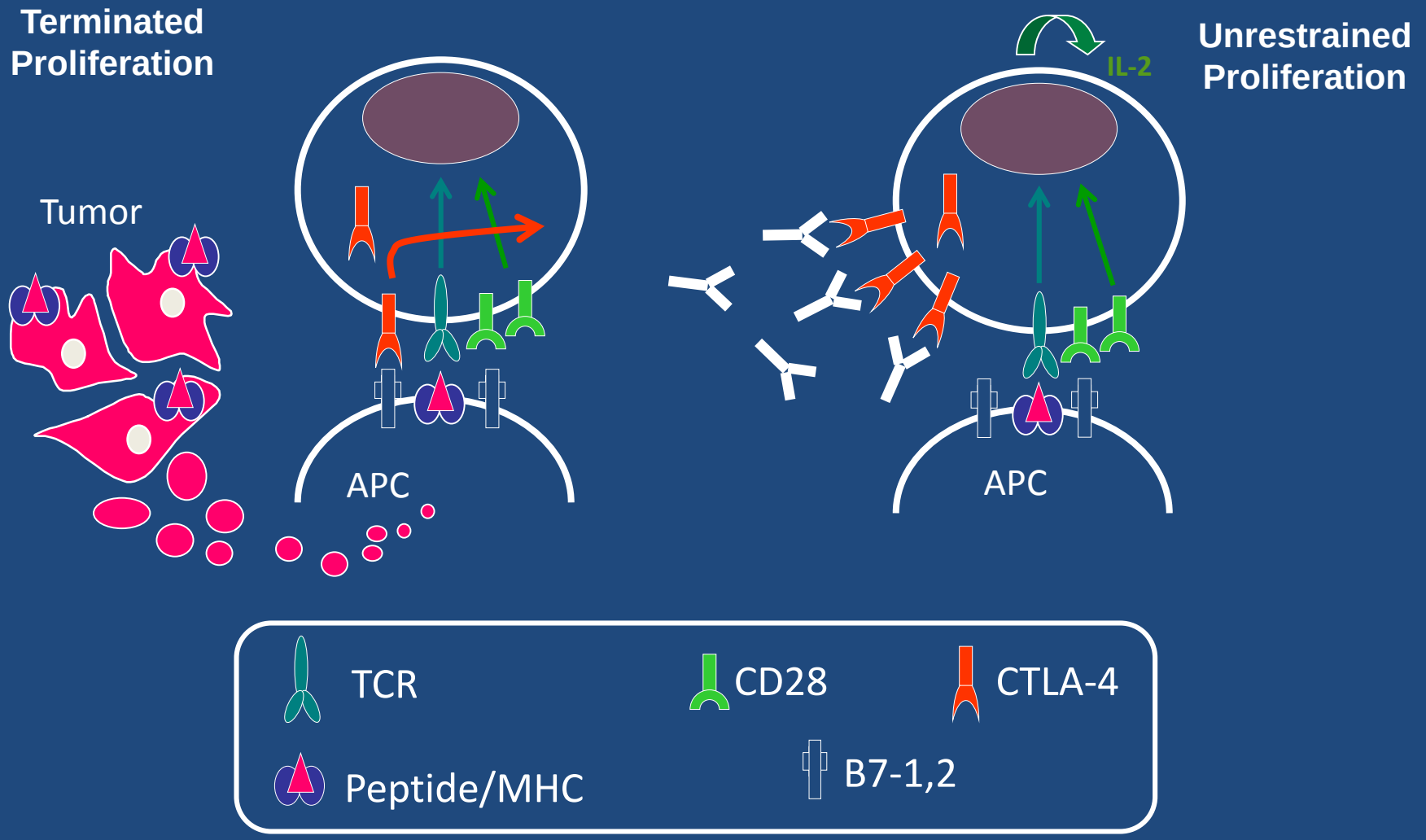
Tumor cells bind to T-cells
to deactivate them



Multiple ways to wake up T cells



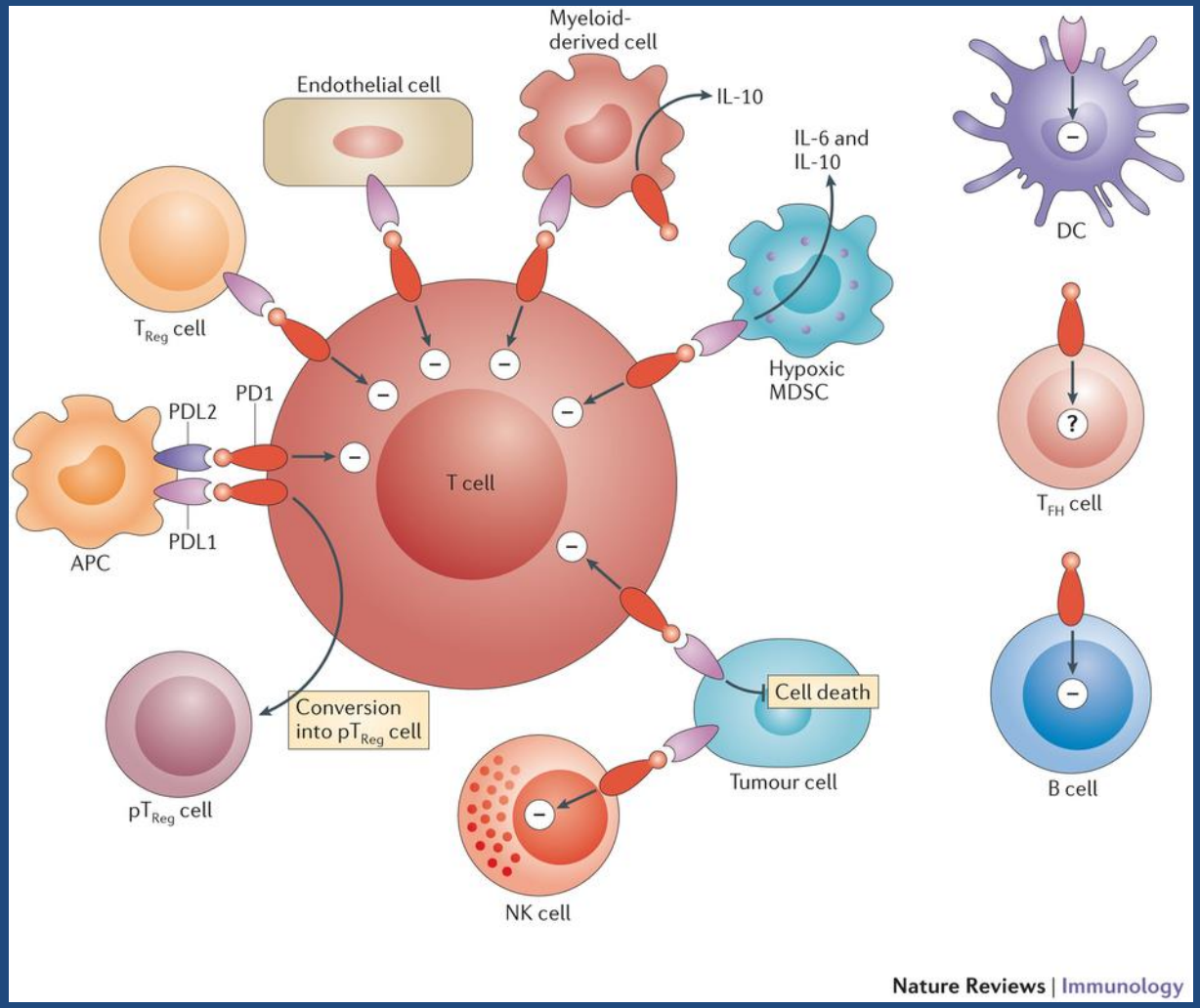
CTLA-4 Blockade Enhances Tumor-Specific Immune Responses by Releasing "Brakes" on T cells (*the "Jedd Wolchok" slide*)



Cytotoxic T Lymphocyte Antigen 4 (CTLA4

- Ipilimumab
  - Melanoma 2011

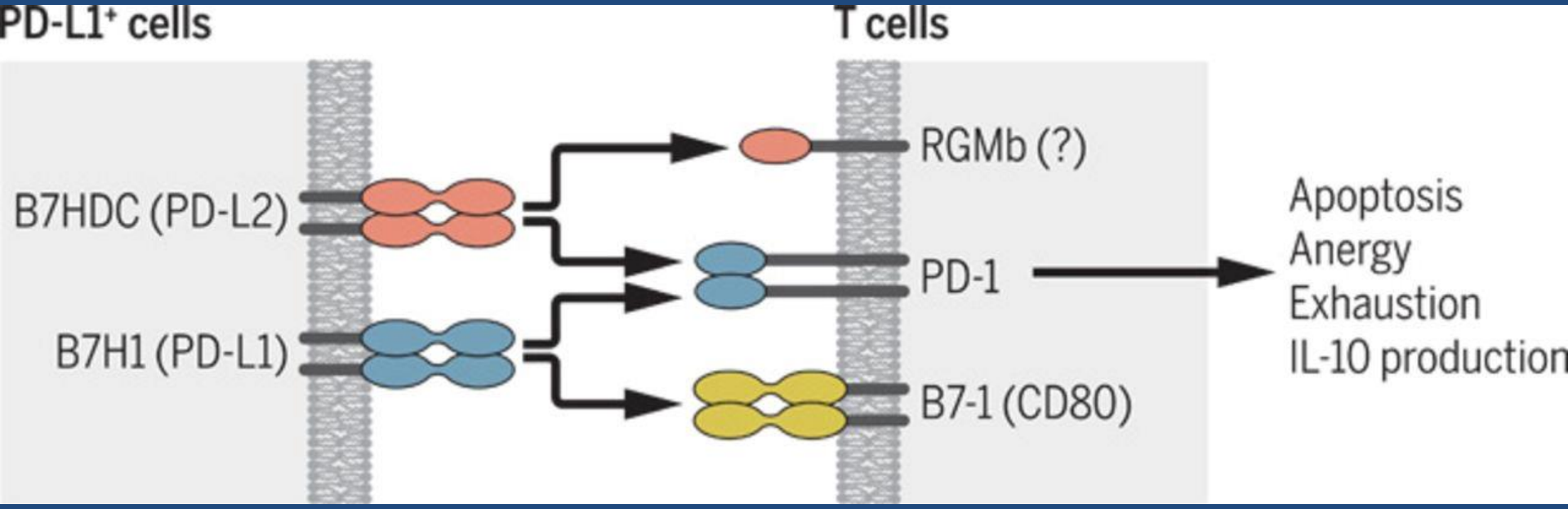
PD-1 is used by viruses, tumor and normal tissues to quiet down the immune system



Programmed Death 1 (PD-1)

- Nivolumab
  - Melanoma
  - Non-small cell lung cancer
  - Head and neck squamous cancer
  - Urothelial cancer
  - Renal call cancer
  - Hodgkin’s Lymphoma
  - MSI-high cancers (colon cancer and others)
  - Hepatocellular carcinoma
- Pembrolizumab
  - Melanoma
  - Non-small cell lung cancer
  - Head and neck squamous cancer
  - Urothelial cancer
  - MSI-high cancers (colon cancer and others)
  - Hodgkin’s Lymphoma

PD-L1 is a promiscuous ligand for PD1



Zou et al, Science Translational Medicine 2016

Programmed Death Ligand 1 (PD-L1)

- Atezolizumab
  - Lung cancer
  - Urothelial cancer
- Avelumab
  - Merkle cell cancer
  - Urothelial cancer

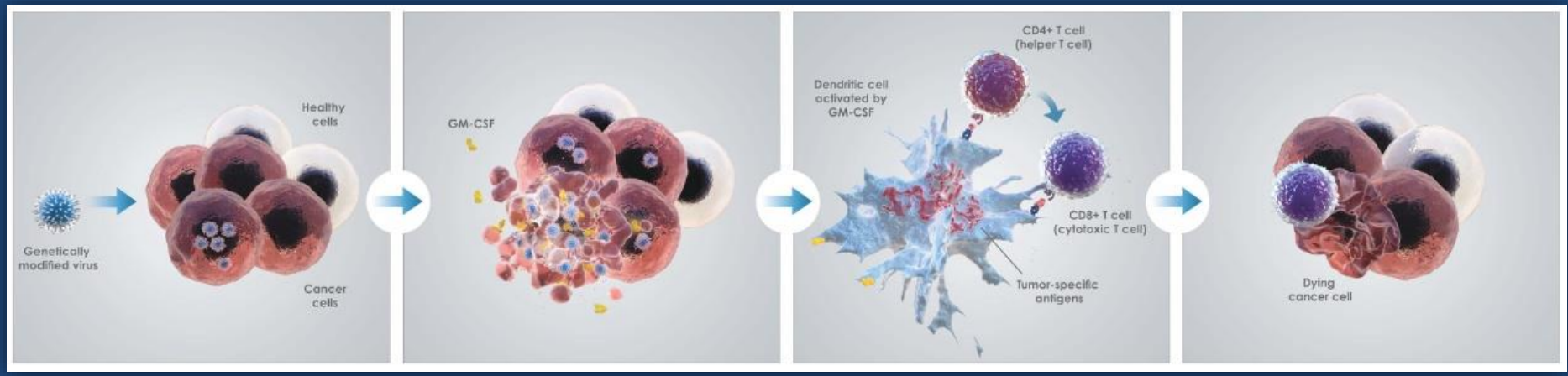
In situ vaccination

Selective viral replication in tumor tissue

Tumor cells rupture for an oncolytic effect

Systemic tumor-specific immune response

Death of distant cancer cells

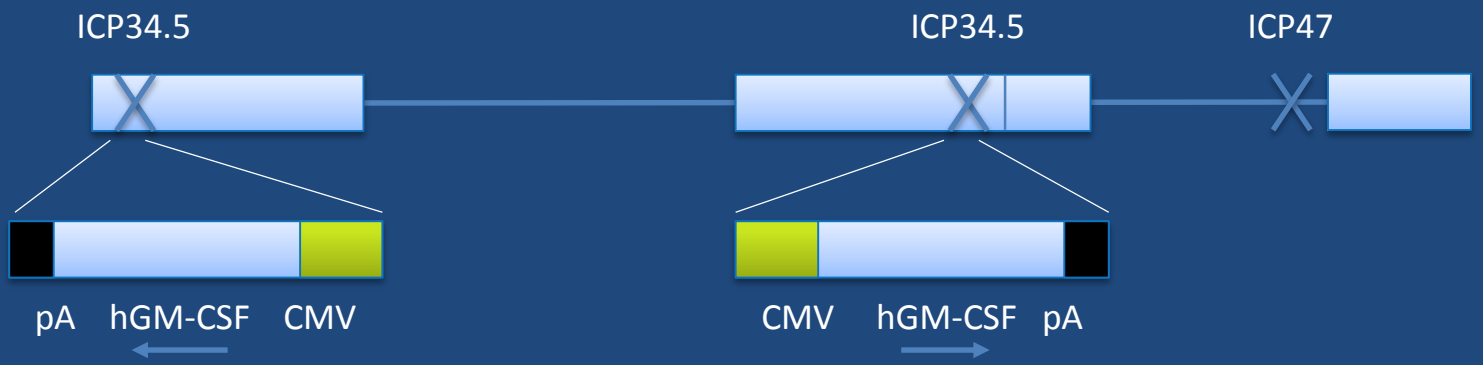


Local Effect: Tumor Cell Lysis

Systemic Effect: Tumor-Specific Immune Response

1. Varghese S, et al. *Cancer Gene Ther*. 2002;9:967-978. 2. Hawkins LK, et al. *Lancet Oncol*. 2002;3:17-26. 3. Fukuhara H, et al. *Curr Cancer Drug Targets*. 2007;7:149-155. 4. Sobl PT, et al. . *Mol Ther*. 2011;19:335-344. 5. Liu BL, et al. *Gene Ther*. 2003;10:292-303. 6. Melcher A, et al. *Mol Ther*. 2011;19:1008-1016. 7. Fagoaga OR In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods, 22nd ed. Philadelphia, PA: Elsevier; 2011:933-953. 8. Dranoff G. *Oncogene*. 2003;22:3188-3192.

Talimogene laherparepvec (TVEC)



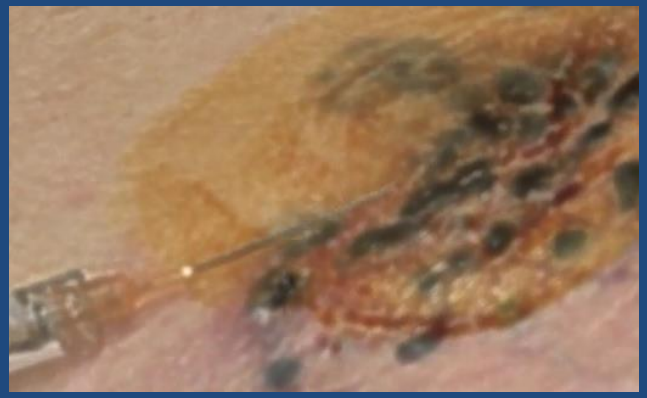
Talimogene laherparepvec (JS1/ICP34.5-/ICP47-/hGM-CSF)

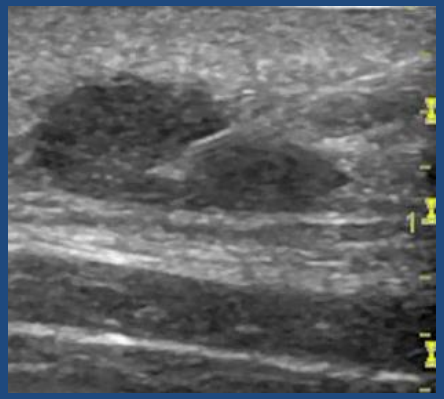
HSV: Herpes simplex virus; ICP: Infected cell protein; CMV: Cytomegalovirus promoter

- Derived from HSV-1 (cultured from human cold sores)
- Genetically modified to eliminate neurotropism and enhance oncolysis
  - Elimination of neurovirulance factor ICP34.5
  - Elimination of antigen-presentation blocker ICP47
  - Insertion of hGM-CSF (cytokine that recruits immune cells, specifically antigen presenting cells)

[1] Liu BL, et al. *Gene Therapy.* 2003;10:292-303.

Method of Administration





Lesion size (diameter)	T-VEC injection volume
> 5.0 cm	≤ 4.0 mL
> 2.5 cm to 5.0 cm	≤ 2.0 mL
> 1.5 cm to 2.5 cm	≤ 1.0 mL
> 0.5 cm to 1.5 cm	≤ 0.5 mL
≤ 0.5 cm	≤ 0.1 mL
This total dose administered in any one treatment session should not exceed 4.0 mL	

Andtbacka RHJ et al. *J Clin Oncol* 2013;31(suppl; abstr LBA9008) and oral presentation at ASCO 2013 Annual Meeting, May 31 – June 4, Chicago, IL

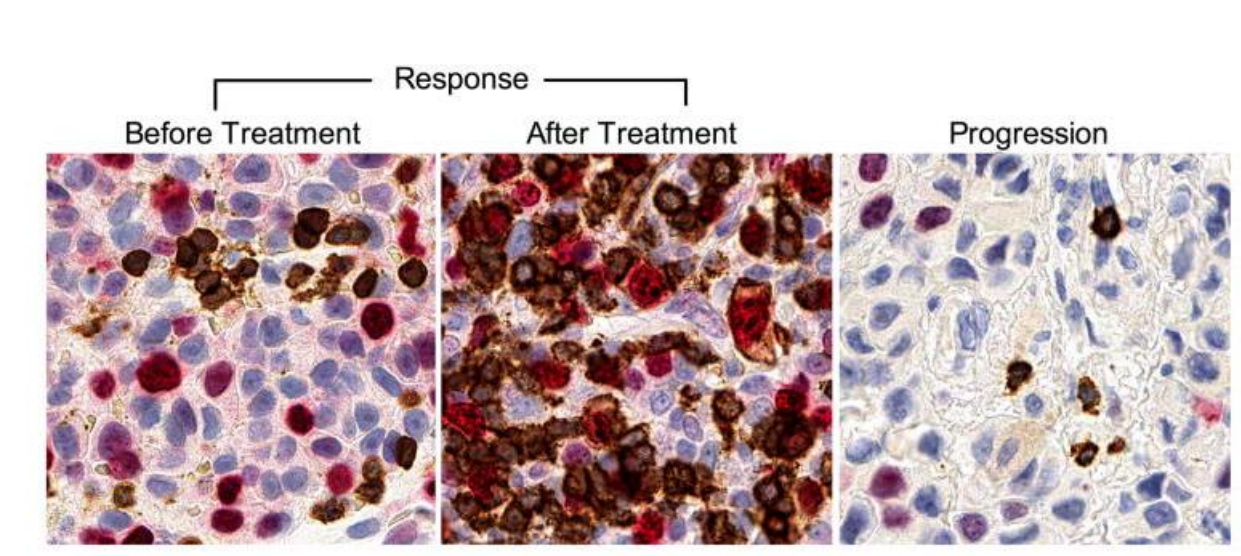
T-VEC Responses in Injected And Uninjected Lesions

Cycle 1

Cycle 13

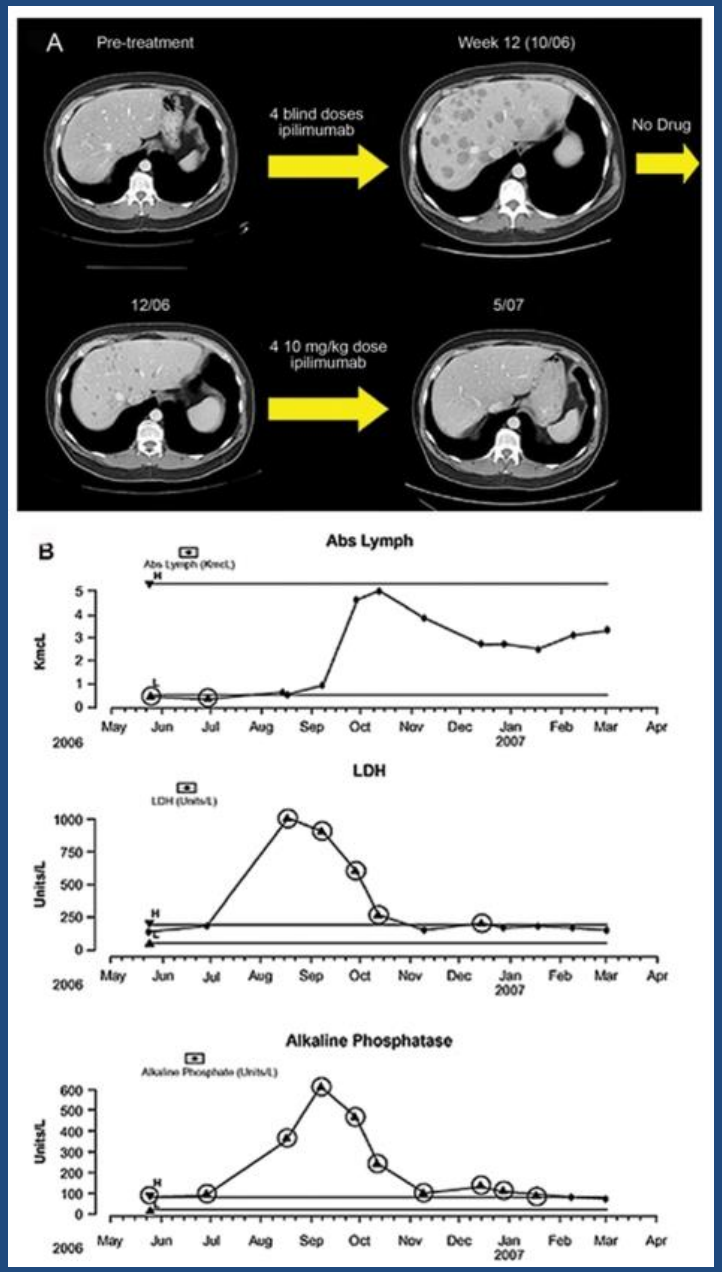
Andtbacka RHJ et al. *J Clin Oncol* 2013;31(suppl; abstr LBA9008) and oral presentation at ASCO 2013 Annual Meeting, May 31 – June 4, Chicago, IL

Immunotherapy causes infiltration of T cells into tumors



Tumwen et al, “PD-1 blockade induces responses by inhibitng adaptive immune resistance,” *Nature* 2014.

Responding tumors can grow before they shrink



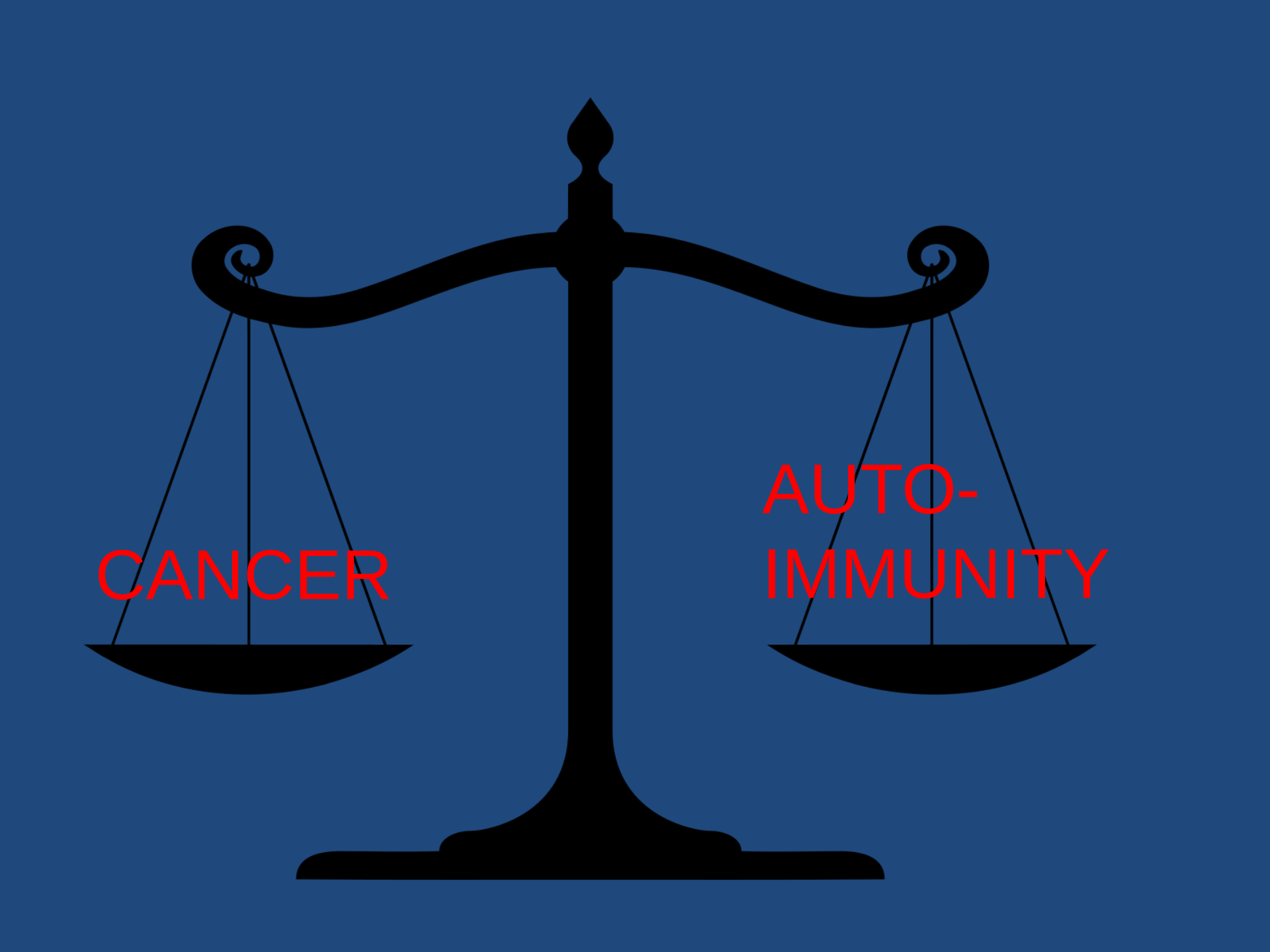
Saenger and Wolchok, “The heterogeneity of the kinetics of response to ipilimumab in metastatic melanoma: patient cases, “ *Cancer Immunity* 2008

Kinetics of response may be unpredictable- Immune Related Response Criteria

Table 1. Comparison between WHO criteria and the irRC

	WHO	irRC
New, measurable lesions (i.e., ≥5 × 5 mm)	Always represent PD	Incorporated into tumor burden
New, nonmeasurable lesions (i.e., <5 × 5 mm)	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining BOR of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in two consecutive observations not less than 4 wk apart	Disappearance of all lesions in two consecutive observations not less than 4 wk apart
PR	≥50% decrease in SPD of all index lesions compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions	≥50% decrease in tumor burden compared with baseline in two observations at least 4 wk apart
SD	50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
PD	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart

Wolchok et al, “Guidelines for the Evaluation of Immune Tharapy Activity in Solid Tumors: Immune-Related Responnse Criteria. *Clinical Cancer Research* 2009


CANCER
AUTO-
IMMUNITY

Autoimmune toxicities are common

Table 3. Adverse Events.*

Event	Nivolumab (N=313)		Nivolumab plus Ipilimumab (N=313)		Ipilimumab (N=311)	
	Any	Grade 3 or 4	Any	Grade 3 or 4	Any	Grade 3 or 4
	number of patients with event (percent)					
Any adverse event	311 (99.4)	136 (43.5)	312 (99.7)	215 (68.7)	308 (99.0)	173 (55.6)
Treatment-related adverse event†	257 (82.1)	51 (16.3)	299 (95.5)	172 (55.0)	268 (86.2)	85 (27.3)
Diarrhea	60 (19.2)	7 (2.2)	138 (44.1)	29 (9.3)	103 (33.1)	19 (6.1)
Fatigue	107 (34.2)	4 (1.3)	110 (35.1)	13 (4.2)	87 (28.0)	3 (1.0)
Pruritus	59 (18.8)	0	104 (33.2)	6 (1.9)	110 (35.4)	1 (0.3)
Rash	81 (25.9)	2 (0.6)	126 (40.3)	15 (4.8)	102 (32.8)	6 (1.9)
Nausea	41 (13.1)	0	81 (25.9)	7 (2.2)	50 (16.1)	2 (0.6)
Pyrexia	18 (5.8)	0	58 (18.5)	2 (0.6)	21 (6.8)	1 (0.3)
Decreased appetite	34 (10.9)	0	56 (17.9)	4 (1.3)	39 (12.5)	1 (0.3)
Increase in alanine aminotransferase level	12 (3.8)	4 (1.3)	55 (17.6)	26 (8.3)	12 (3.9)	5 (1.6)
Vomiting	20 (6.4)	1 (0.3)	48 (15.3)	8 (2.6)	23 (7.4)	1 (0.3)
Increase in aspartate aminotransferase level	12 (3.8)	3 (1.0)	48 (15.3)	19 (6.1)	11 (3.5)	2 (0.6)
Hypothyroidism	27 (8.6)	0	47 (15.0)	1 (0.3)	13 (4.2)	0
Colitis	4 (1.3)	2 (0.6)	37 (11.8)	24 (7.7)	36 (11.6)	27 (8.7)
Arthralgia	24 (7.7)	0	33 (10.5)	1 (0.3)	19 (6.1)	0
Headache	23 (7.3)	0	32 (10.2)	1 (0.3)	24 (7.7)	1 (0.3)
Dyspnea	14 (4.5)	1 (0.3)	32 (10.2)	2 (0.6)	13 (4.2)	0
Treatment-related adverse event leading to discontinuation	24 (7.7)	16 (5.1)	114 (36.4)	92 (29.4)	46 (14.8)	41 (13.2)

* The safety population included all the patients who received at least one dose of study drug. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
† The treatment-related adverse events listed here were those reported in at least 10% of the patients in any of the three study groups.

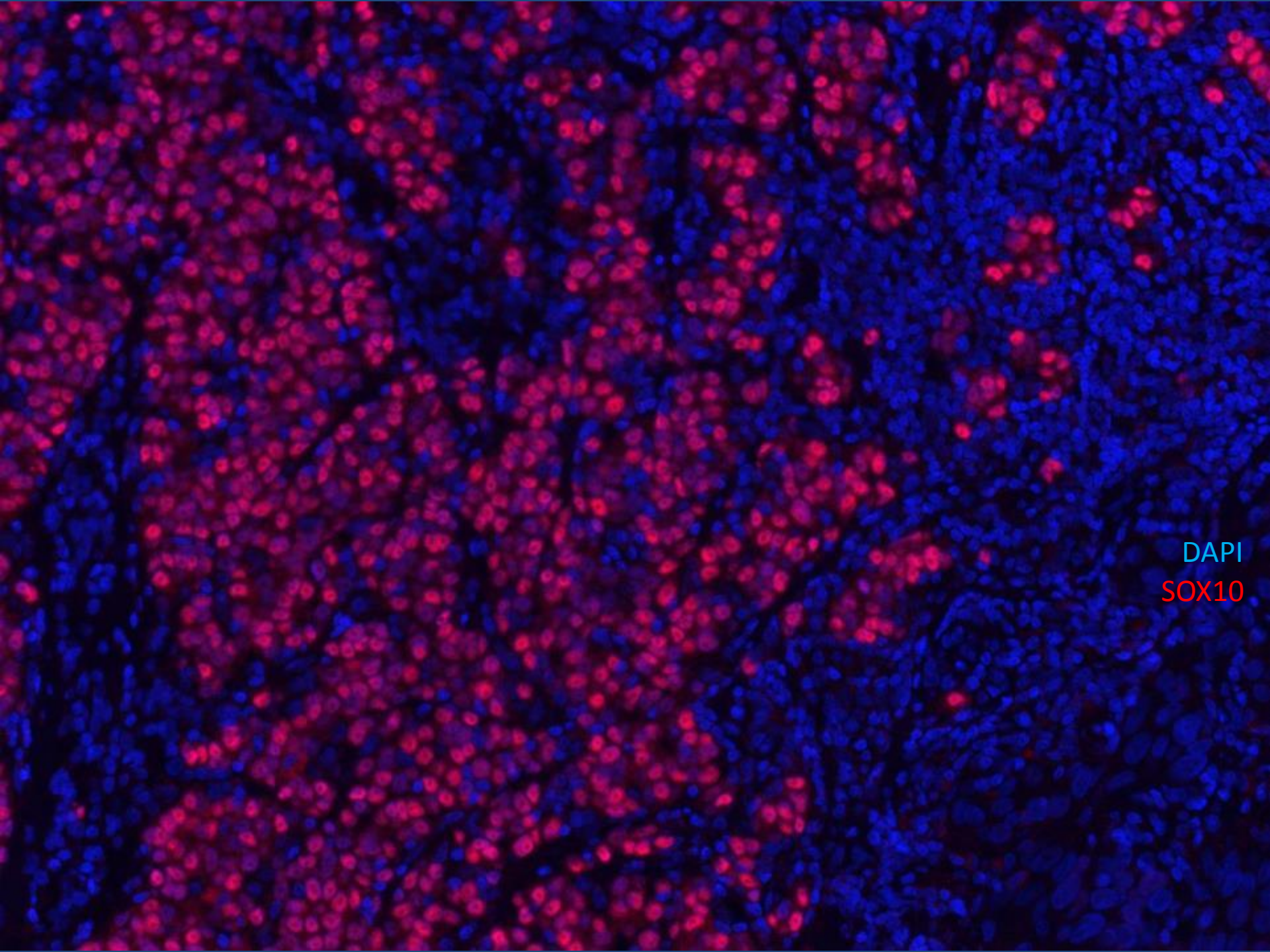
Larkin et al, "Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma, " *NEJM* 2015

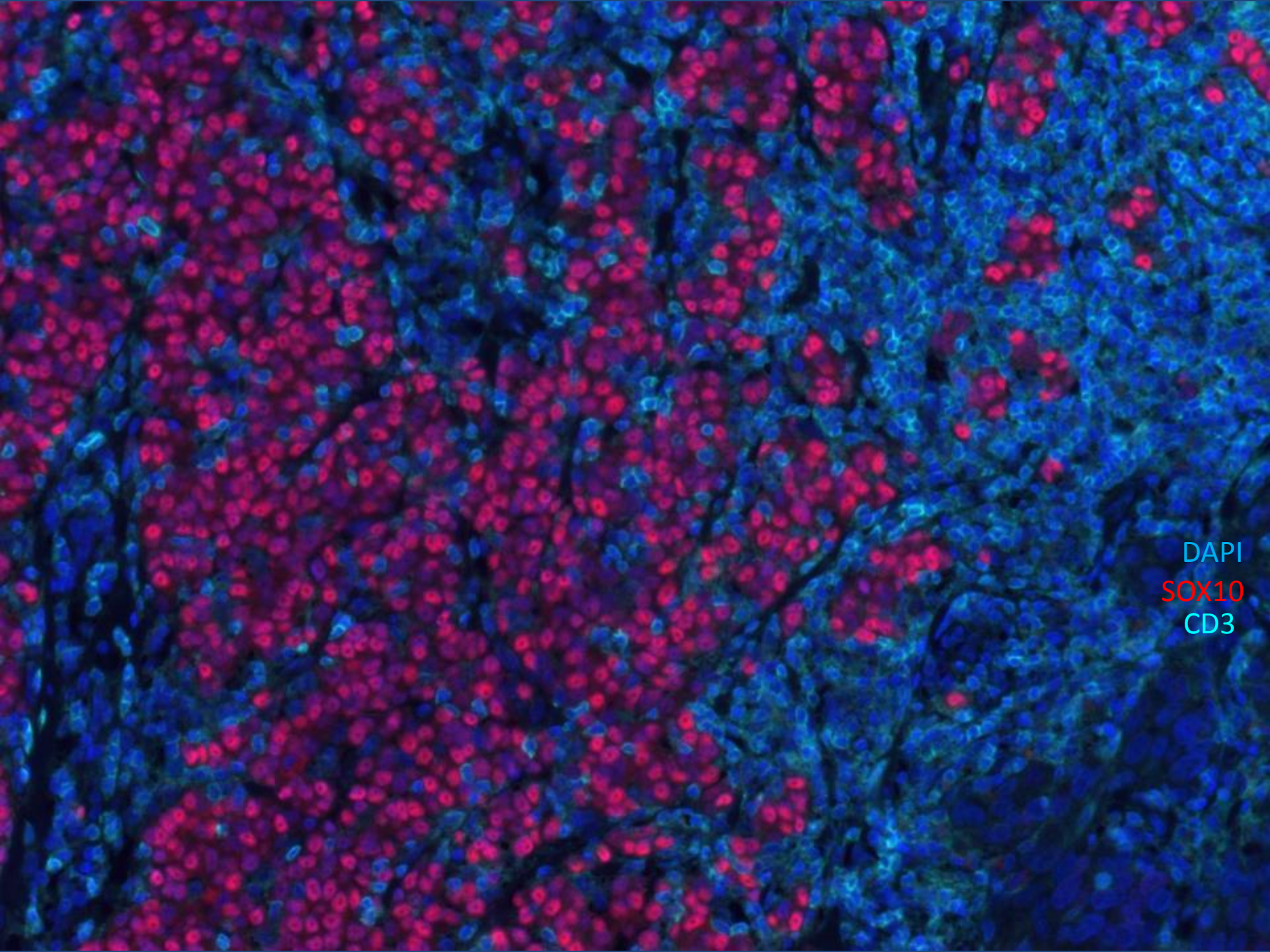
Kinetics of toxicities are unpredictable- Auto-immune vitiligo appearing in injected area in patient 1 year following completion of therapy with anti-CTLA4 combined with T-vec

Why doesn’t immunotherapy always work?

The immune system has traitors in its midst.

Tumor associated macrophage- cells that can prevent T cells from entering tumors.


DAPI
SOX10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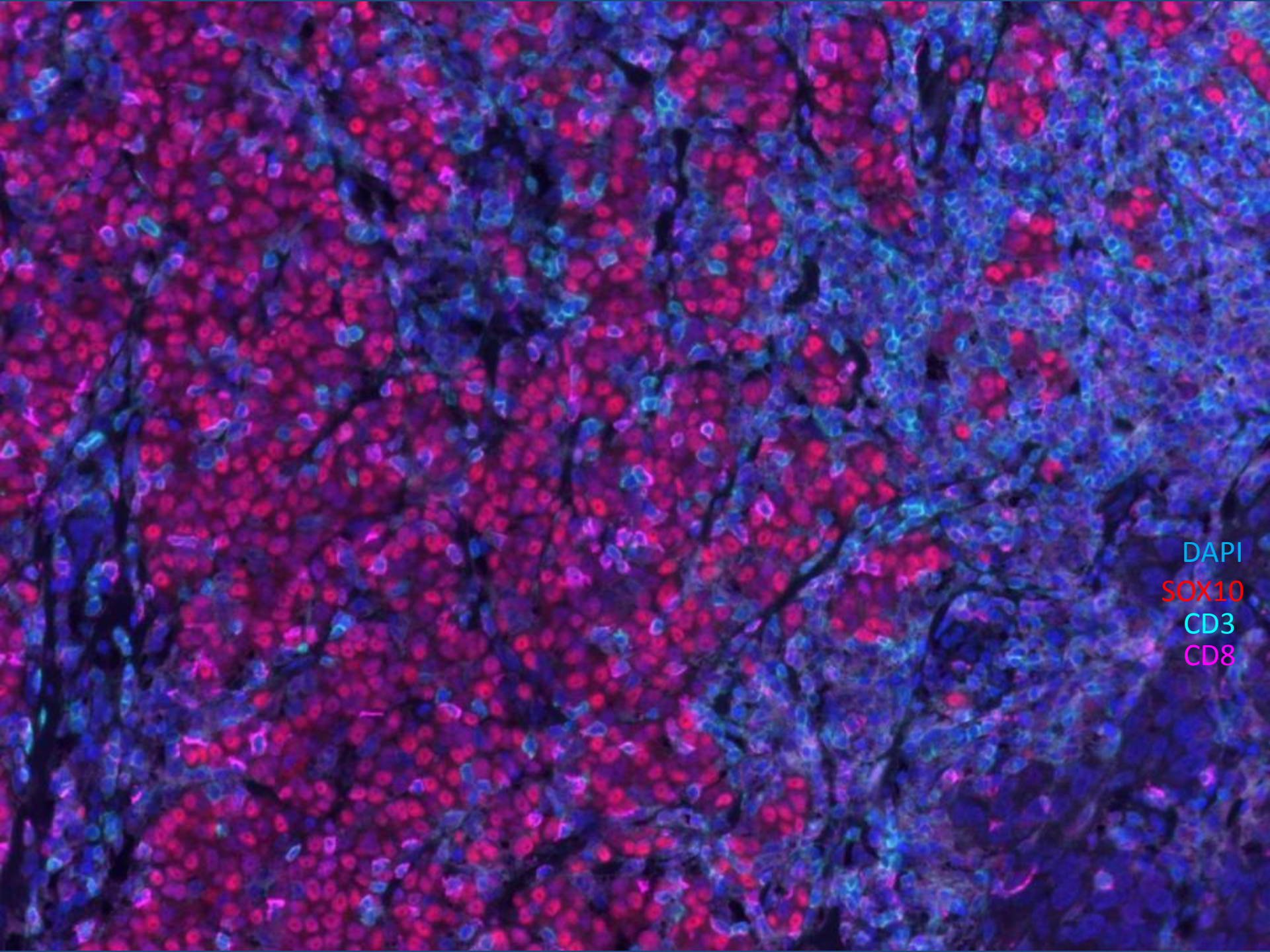
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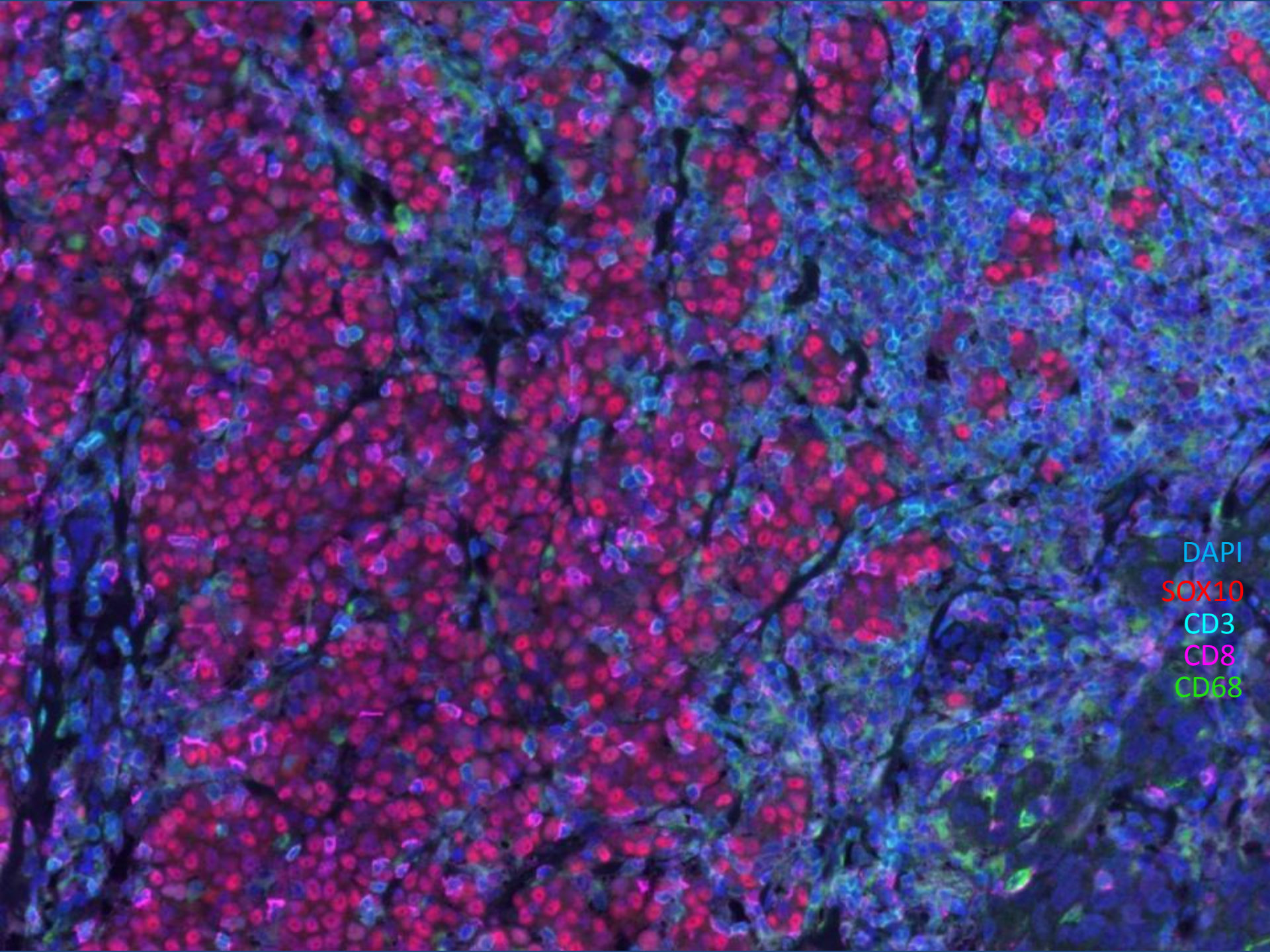
SOX10
CD3
CD8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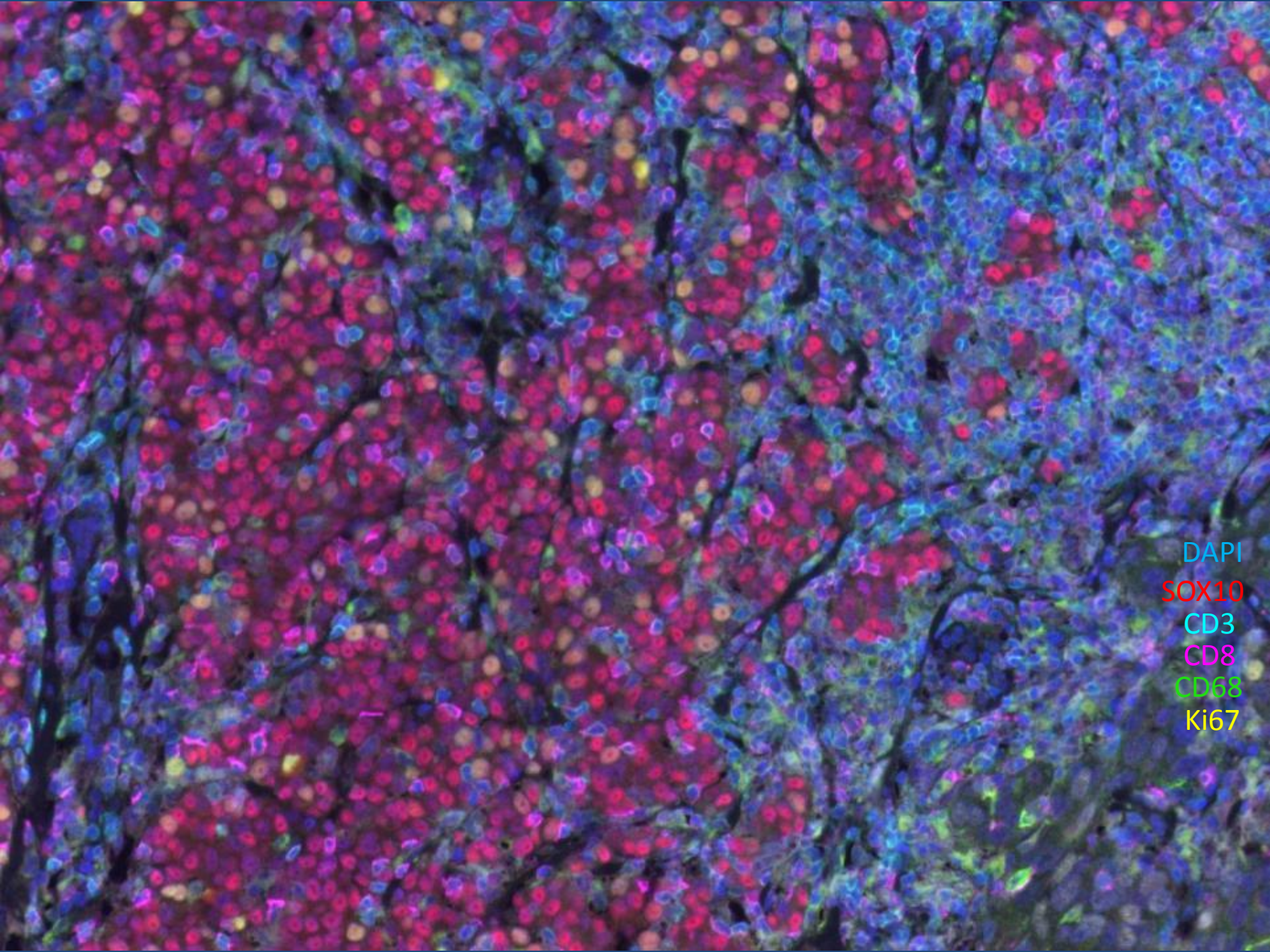
CD68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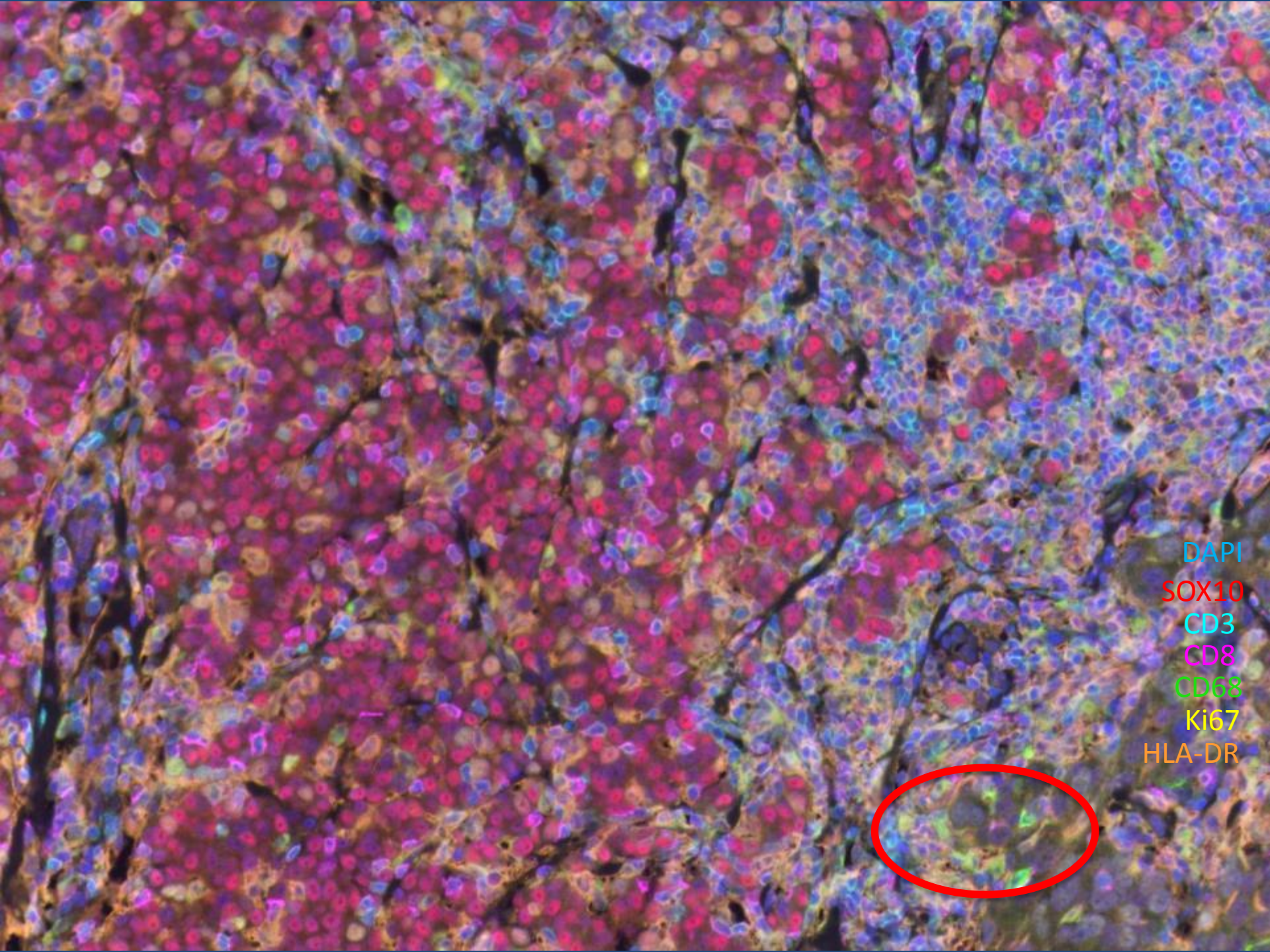
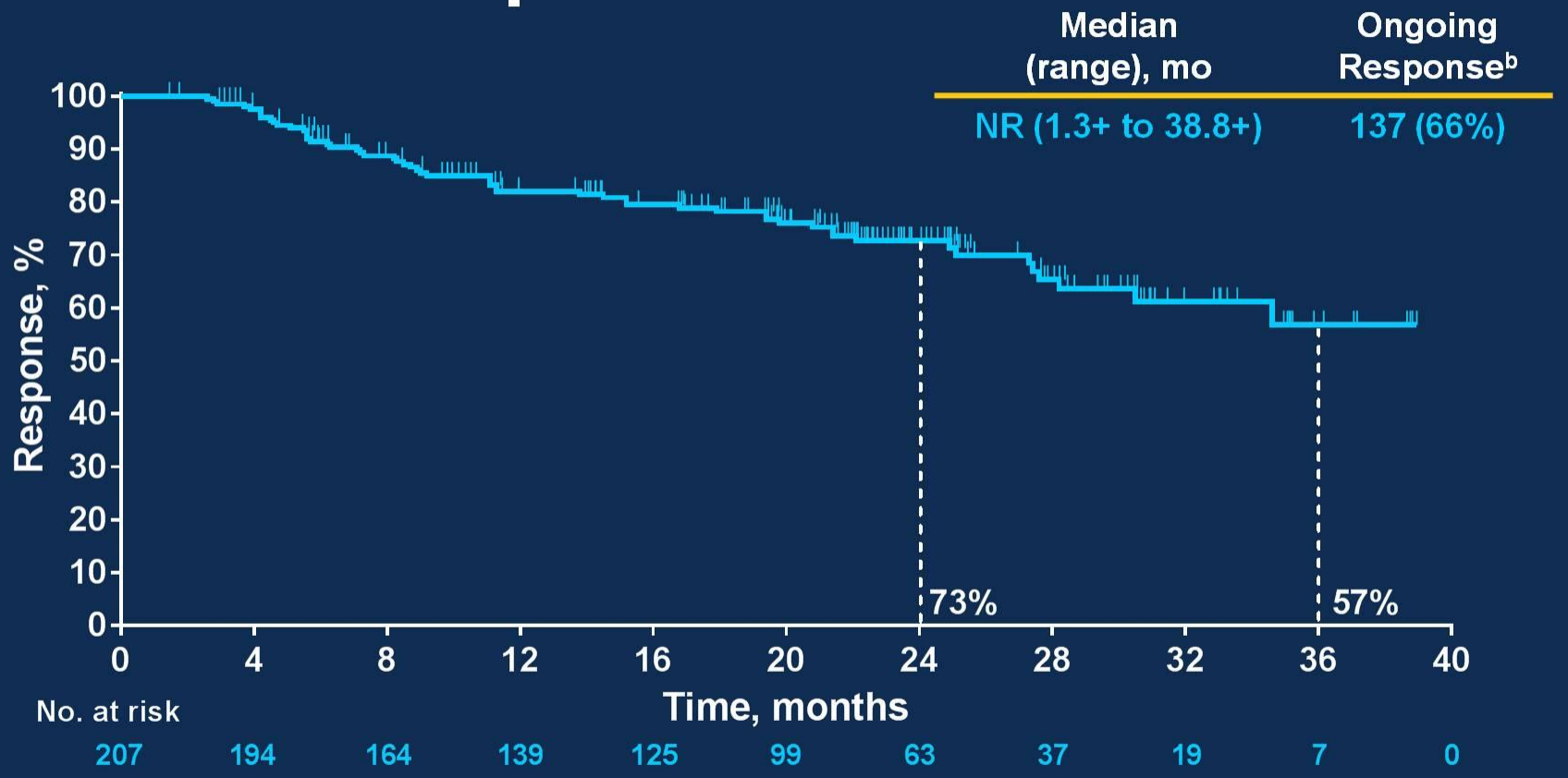
Ki67


DAPI
SOX10
CD3
CD8
CD68
Ki67
HLA-DR

What to expect with immunotherapy

- Little if any toxicity of the infusion itself. Patients receiving T-vec may develop rigors or mild inflammatory symptoms.
- Auto-immune disease may develop over weeks to months to years
- Immunotherapy can take a little longer to work

Duration of Response[a]



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[a]Assessed per RECIST v1.1 by independent central review in patients with response, regardless of centrally evaluable disease at baseline. [b]Responders who were alive without disease progression or new anticancer therapy. Analysis cutoff date: Sep 18, 2015.

SUMMARY: KEY GENERAL PRINCIPLES

- We all have innate immune responses against cancer
- Some cancers are able to hide from the immune system in part because cancer cells are so similar to normal cells
- Immunotherapy “wakes up” T cells against the cancer
- It can also “wake up” T cells against normal tissues causing autoimmune disease
- Anti-PD1 is the most effective immunotherapy and it acts by taking the breaks of T cells
- The first oncolytic virus was recently approved in cancer
- Many new treatments are showing great promise and will be approved soon particularly treatments targetting macrophages

SUMMARY: KEY CLINICAL IMPLICATIONS

- Immunotherapy does not cause the “poison” effects of chemotherapy
- Immunotherapy does cause autoimmune disease and this can be life threatening
- Immunotherapy generally produces more durable benefit than chemotherapy when it works
- Immunotherapy cures a minority of patients even in melanoma
- Immunotherapy can take longer to work and there can be a period of disease growth before response is seen, possibly due to inflammation
- Patients who have received immunotherapy may develop auto-immunity after treatment is completed