

# Basic Mechanisms of Cancer Immunotherapy

Yvonne Saenger MD  
Director Melanoma Immunotherapy  
Assistant Professor, Medicine  
Columbia University  
Society for the Immunotherapy of Cancer

# Disclosures

- Advisory Boards for Amgen and BMS
- Investigator Initiated Trials funded by Merck and Amgen
- Research funding from Amgen
- Non-FDA approved therapies will not be discussed in this talk.

# Immunotherapy is the future

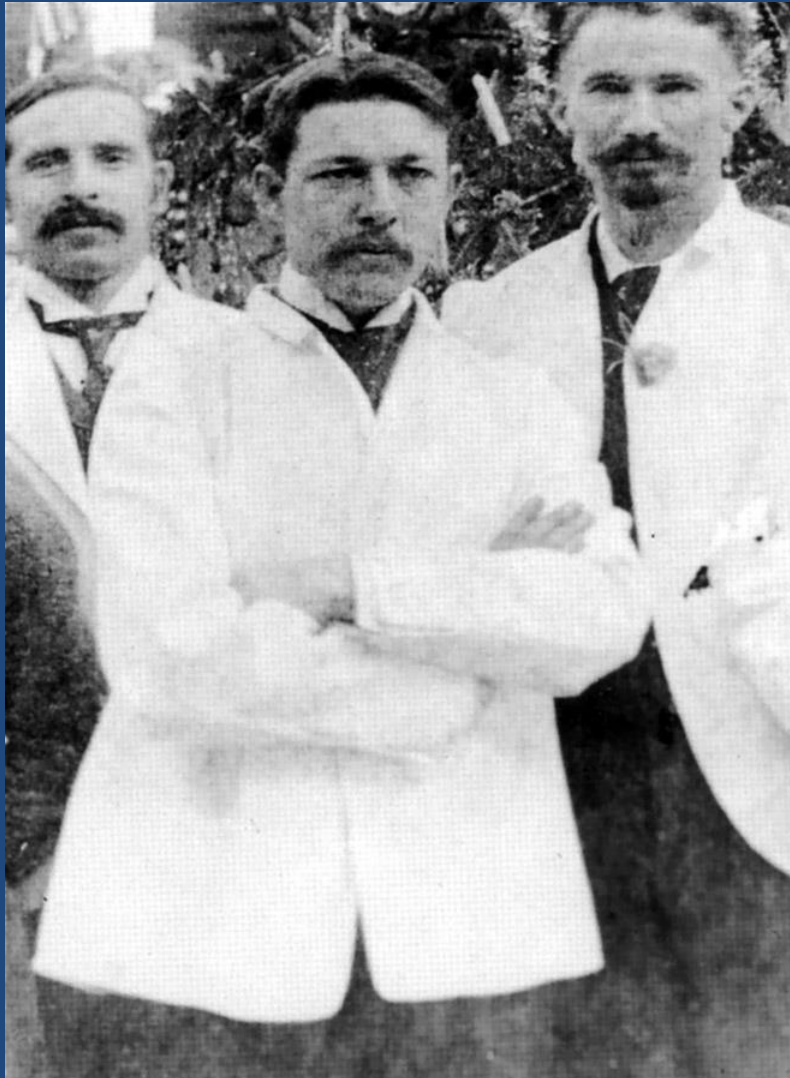


- Interleukin 2
- Interferon alpha2b



- Anti-CTLA4)
- Anti-PD1
- T-Vec
  - PDL1
  - Lag3
  - IDO
  - Tim3
  - GITR
  - CD27
  - CD40
  - FLT3L
  - IL15
  - And many more....

# 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- the way of the past in melanoma

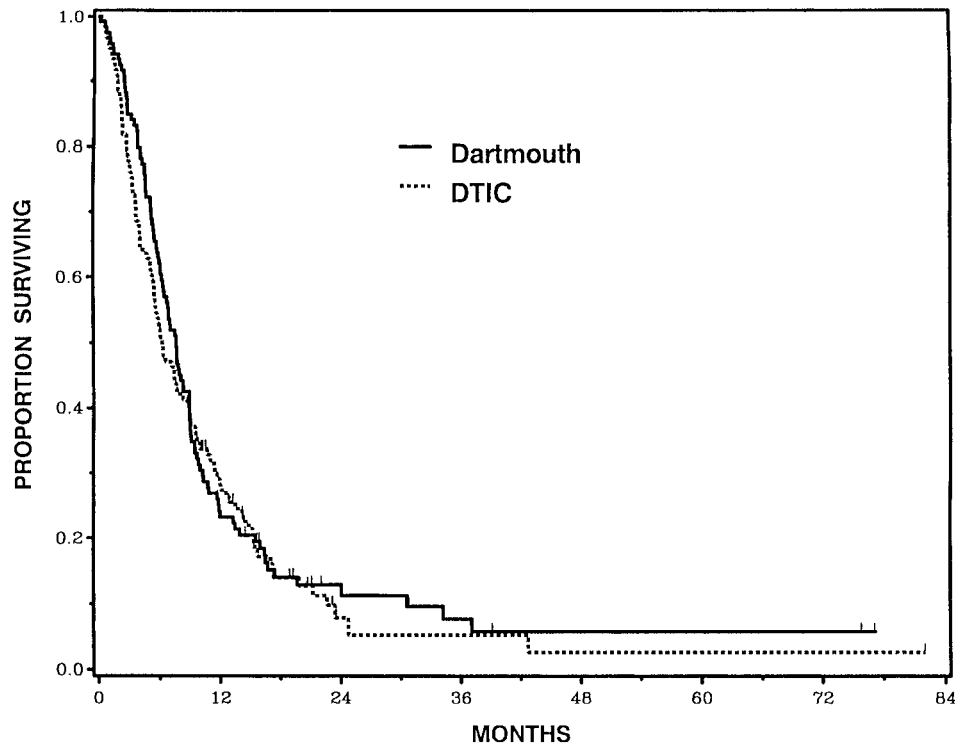
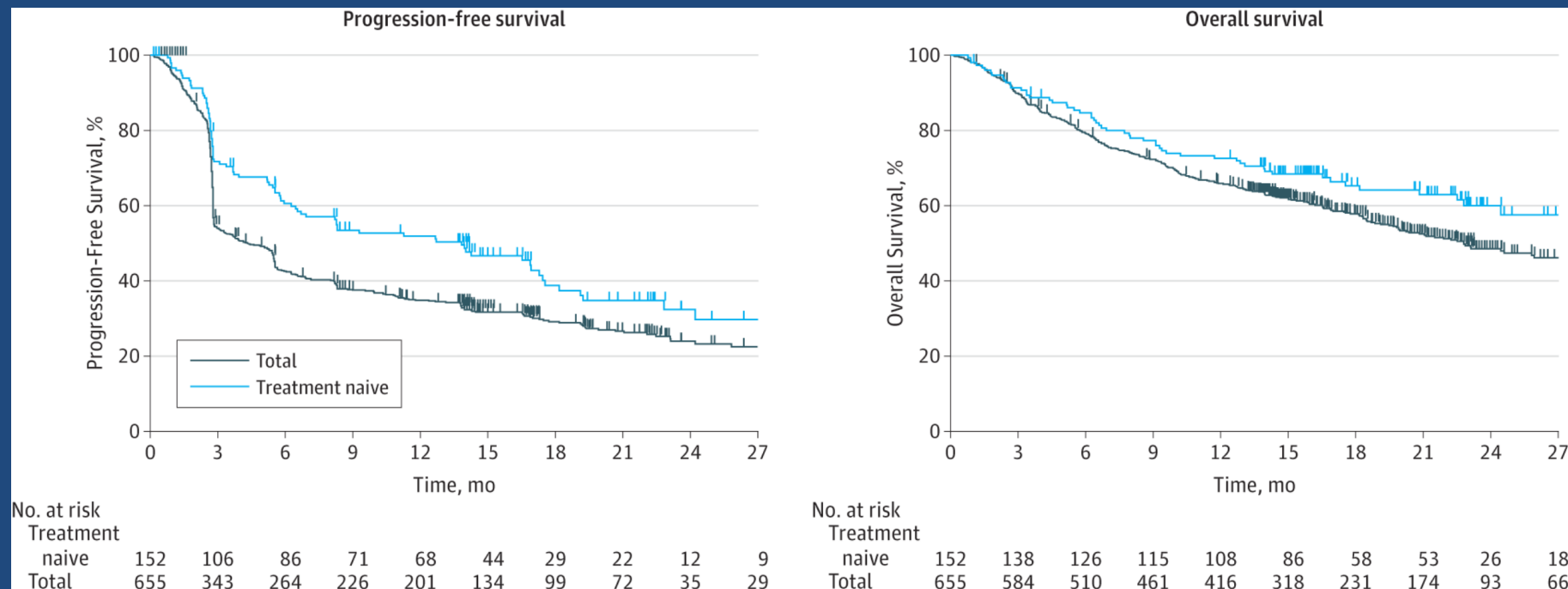


Fig 1. Kaplan-Meier survival plot of all 240 patients randomized based on intent to treat. Median survival time on Dartmouth regimen was 7.7 months (95% CI, 6.3 to 8.9 months) versus 6.3 months (95% CI, 5.4 to 8.7 months) on dacarbazine ( $P = .52$ ). Tick marks represent censored patients.

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

# 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:

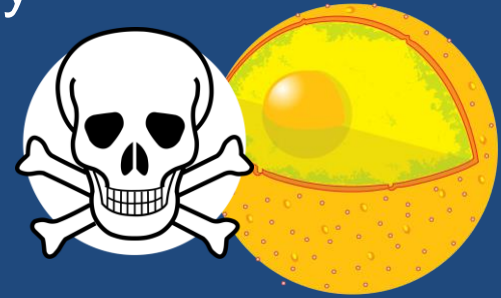
Progression-Free and Overall Survival in Patients Treated With Pembrolizumab in Total and Treatment-Naive Populations The small vertical tick marks represent patients who were censored at that specific time in the survival analysis. Tick marks appear to be floating when multiple events occurred at the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

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

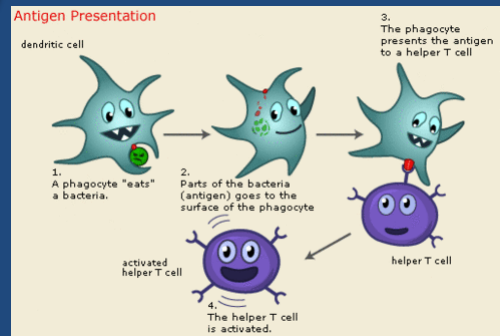


# Comparison of Mechanisms of Cancer Chemotherapy and Cancer Immunotherapy

Chemotherapy

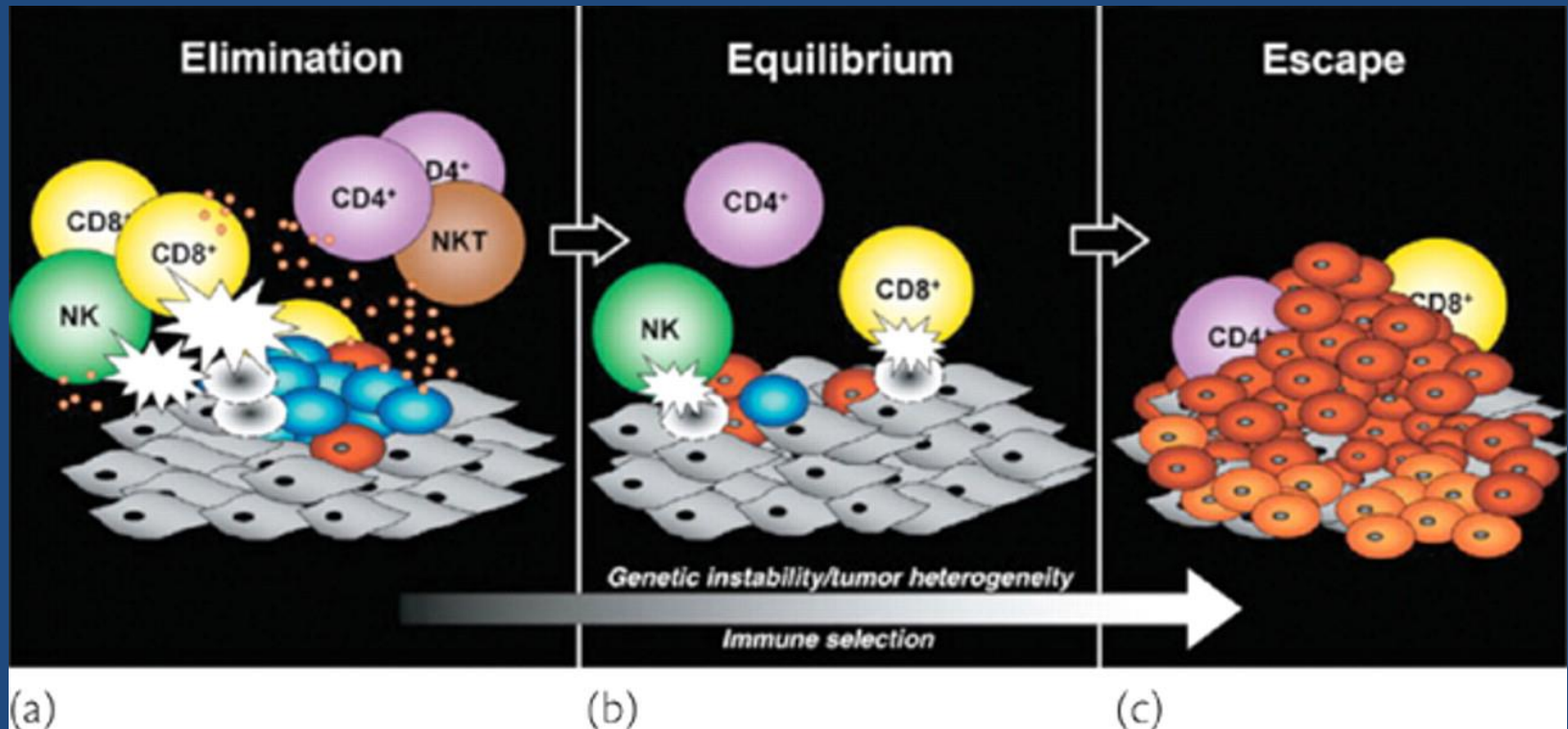


Immunotherapy



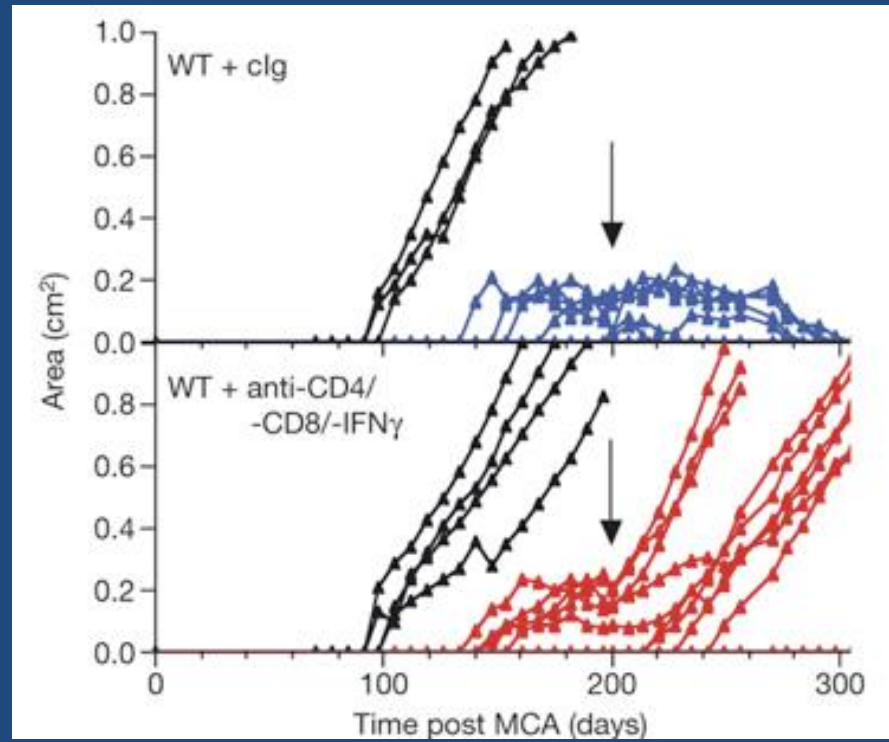
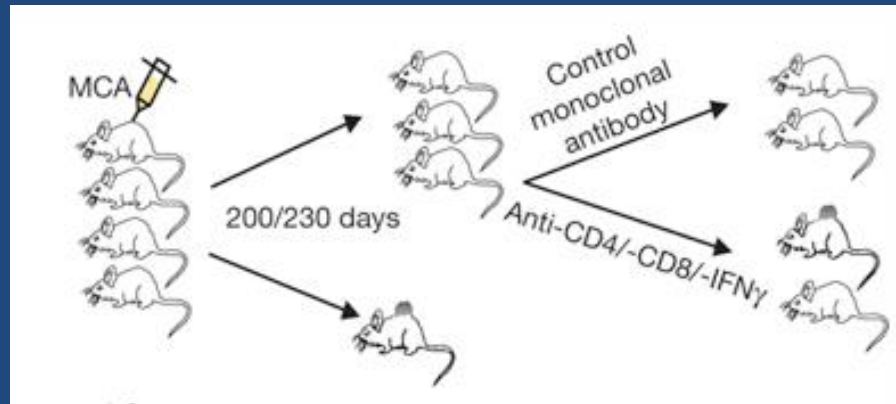


# Immunosurveillance



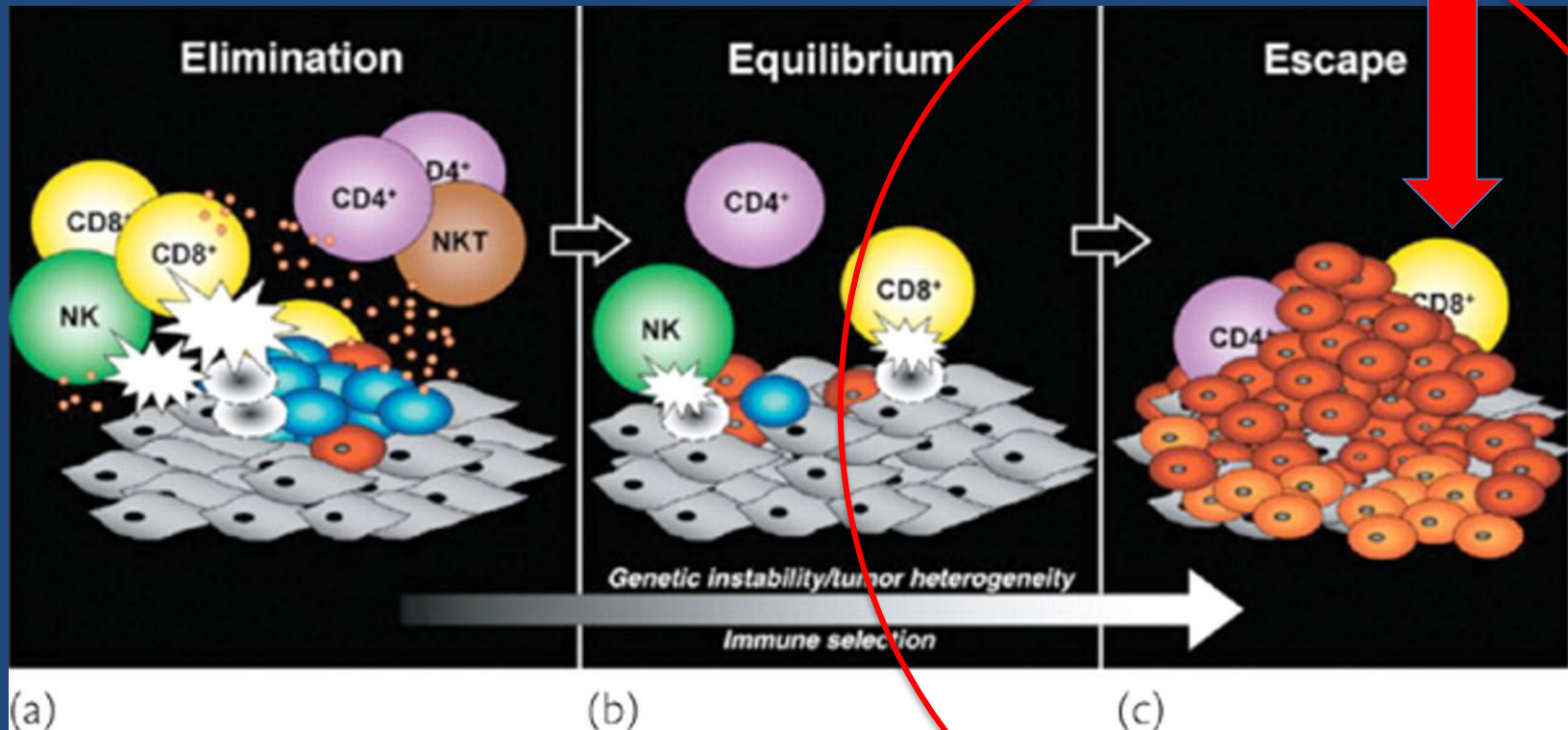
Dunn et al., "Cancer immunoediting: from immunosurveillance to tumor escape"  
*Nature Immunology* 2002.

# Immune surveillance controls dormant tumors



# Immunosurveillance

**WAKE UP!**

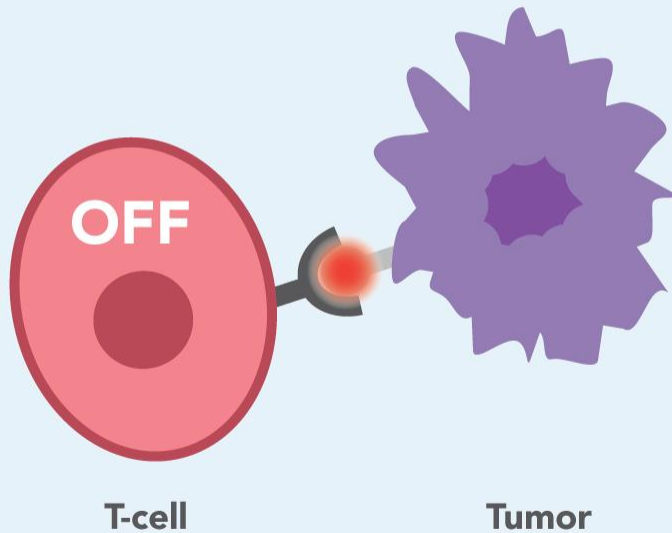


Dunn et al., "Cancer immunoediting: from immunosurveillance to tumor escape"  
*Nature Immunology* 2002.

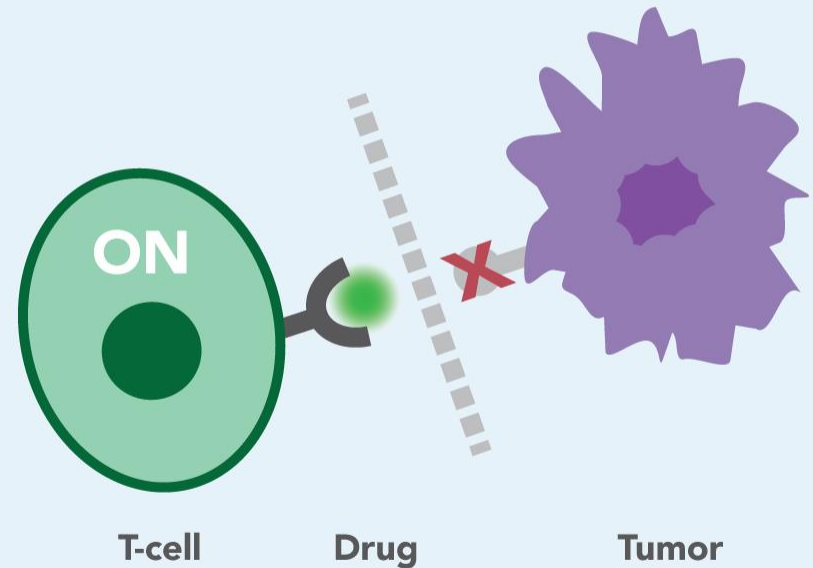
# How Does Immunotherapy Work?

(T cell centered view)

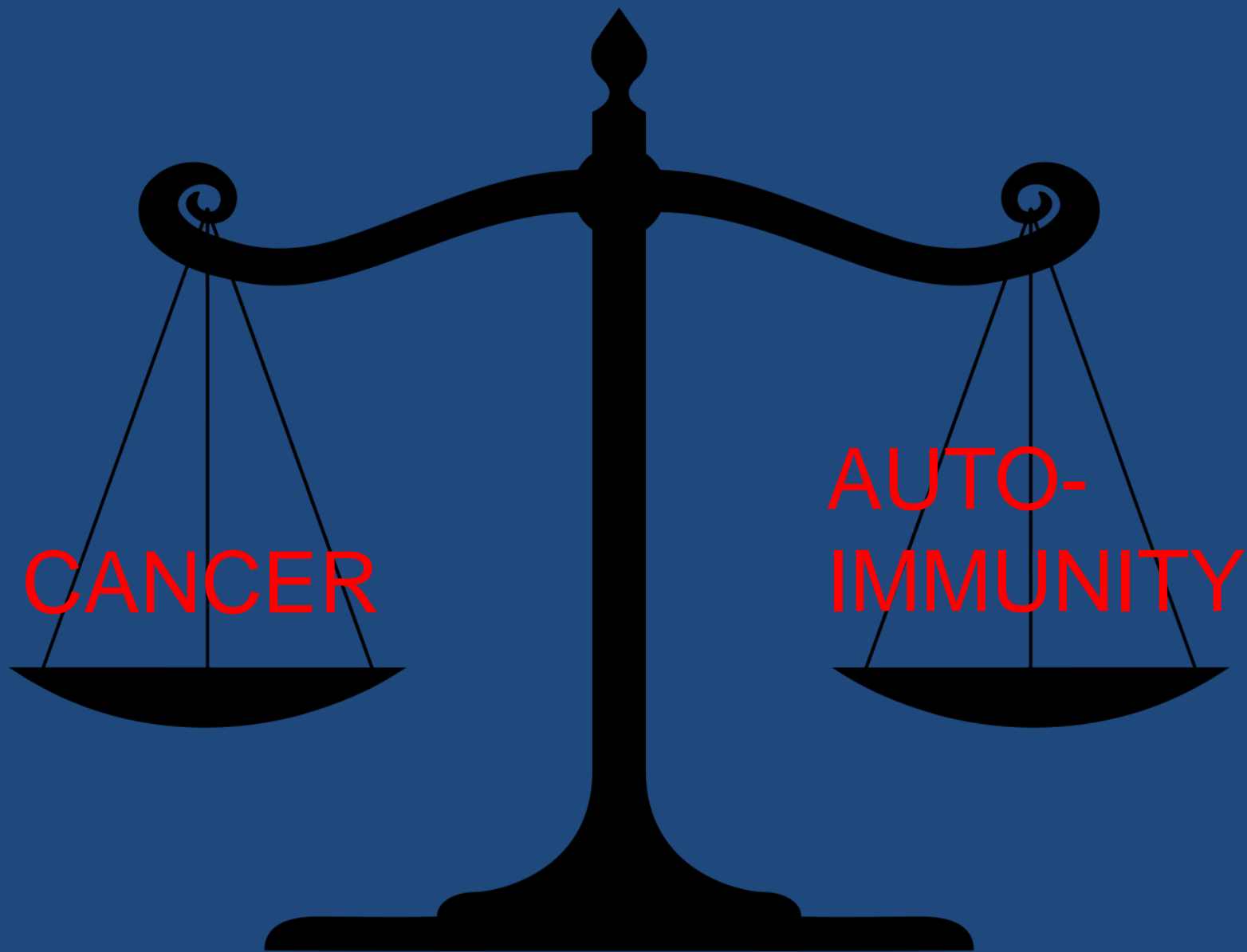
Tumor cells bind to T-cells  
to deactivate them



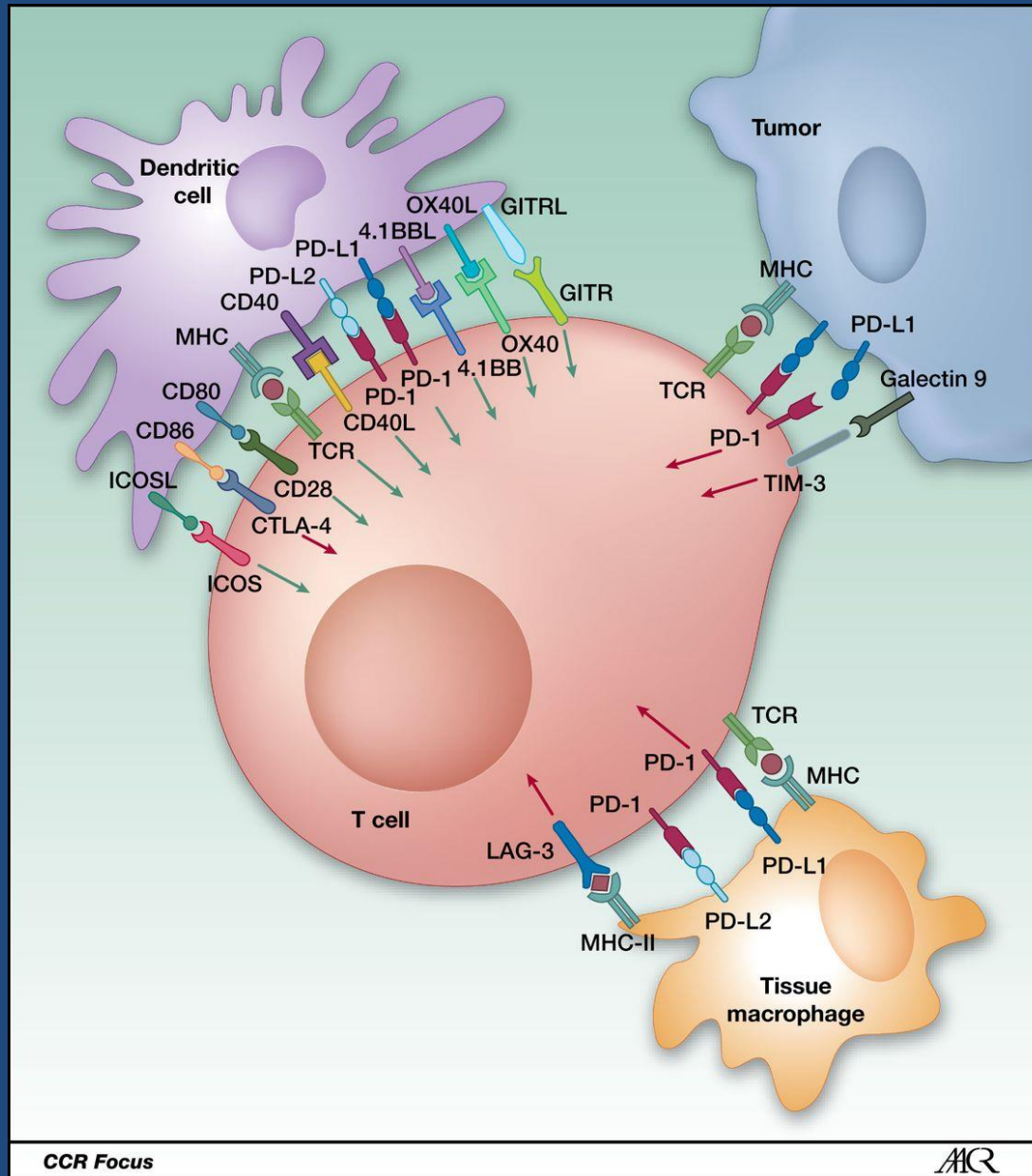
Immunotherapy drugs can block  
tumor cells from deactivating T-cells



COLUMBIA UNIVERSITY  
MEDICAL CENTER



# Multiple ways to wake up T cells (or put them to sleep)

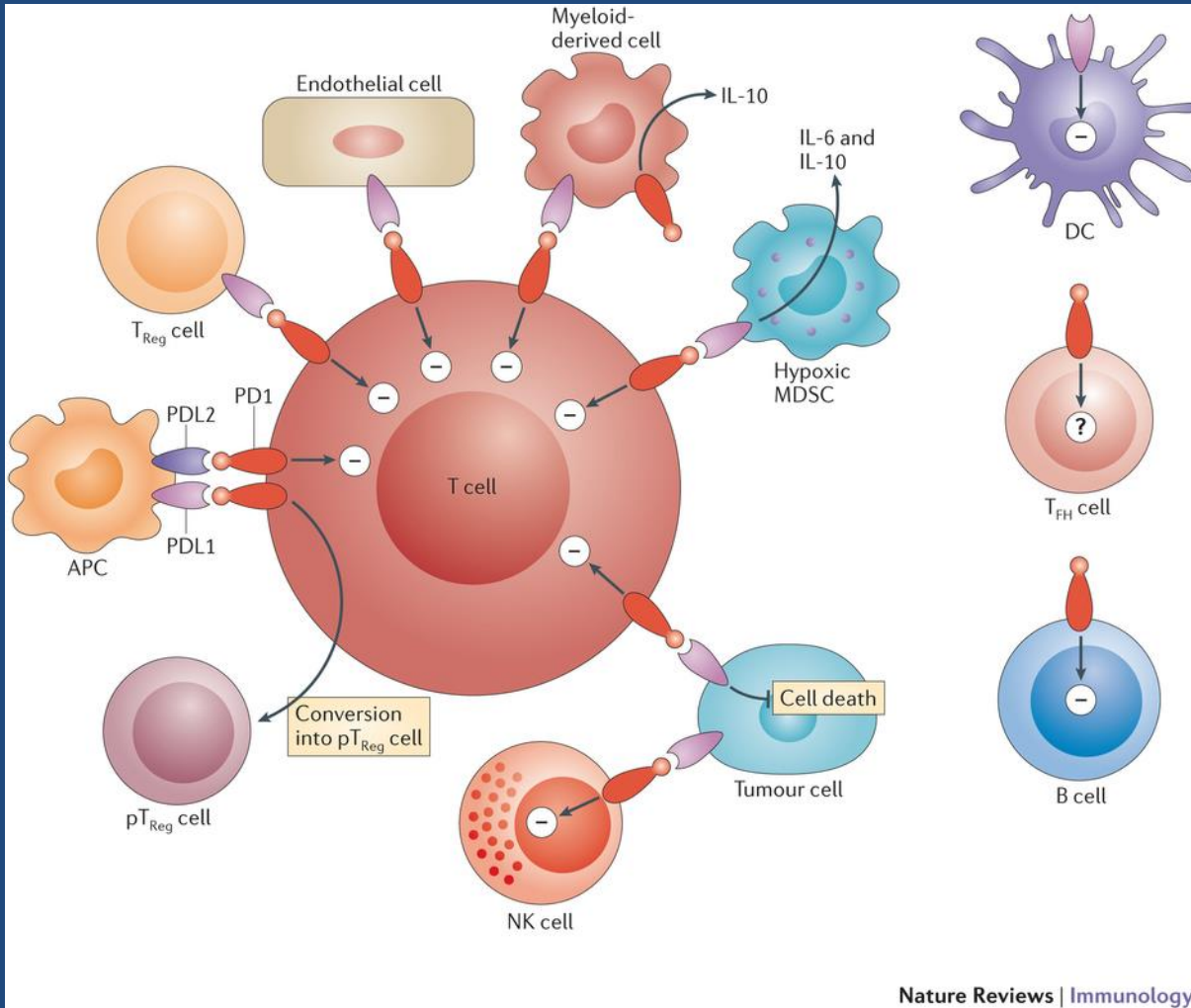


# Programmed Death 1 (PD-1)

- Nivolumab
  - Melanoma
  - Non-small cell lung Cancer
  - Renal cell cancer
- Pembrolizumab
  - Melanoma
  - Non-small cell lung cancer



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



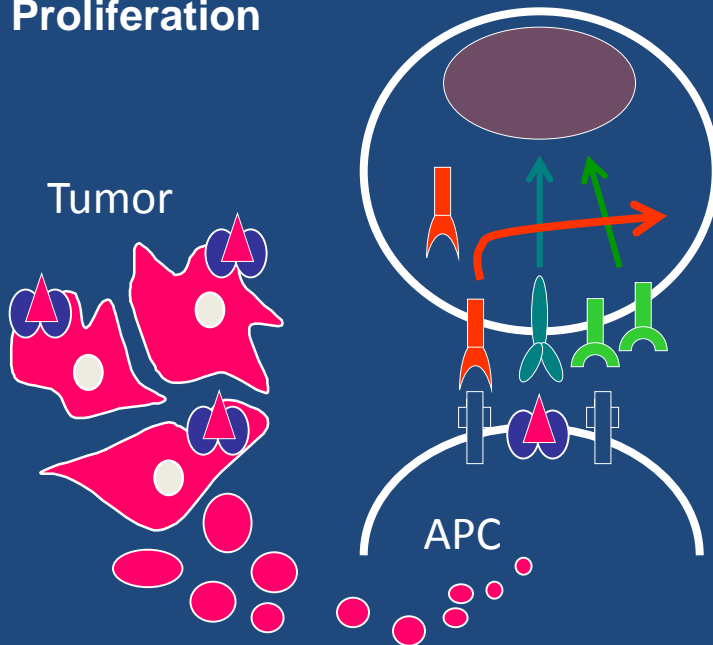


# Cytotoxic T Lymphocyte Antigen 4 (CTLA4)

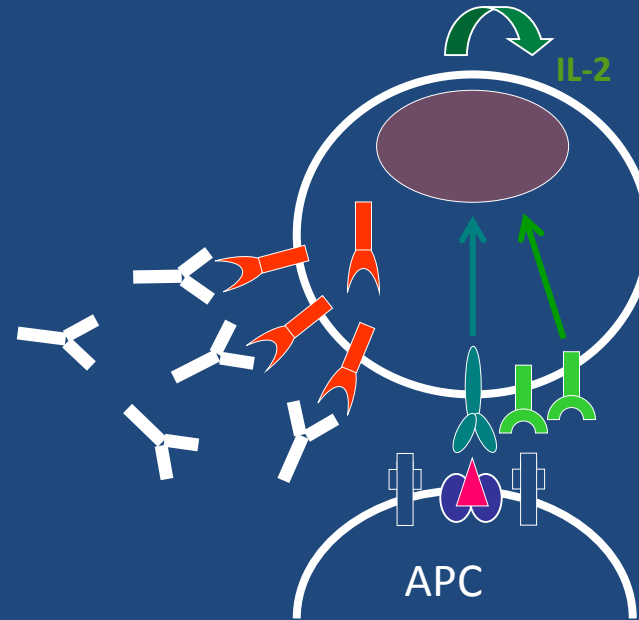
- Ipilimumab
  - Melanoma
- Ipilimumab + Nivolumab
  - Melanoma

# CTLA-4 Blockade Enhances Tumor-Specific Immune Responses by Releasing “Brakes” on T cells

**Terminated Proliferation**



**Unrestrained Proliferation**



Take home point:  
Interaction is between T cell and APC (less specific to tumor and more toxic)



TCR



CD28



CTLA-4

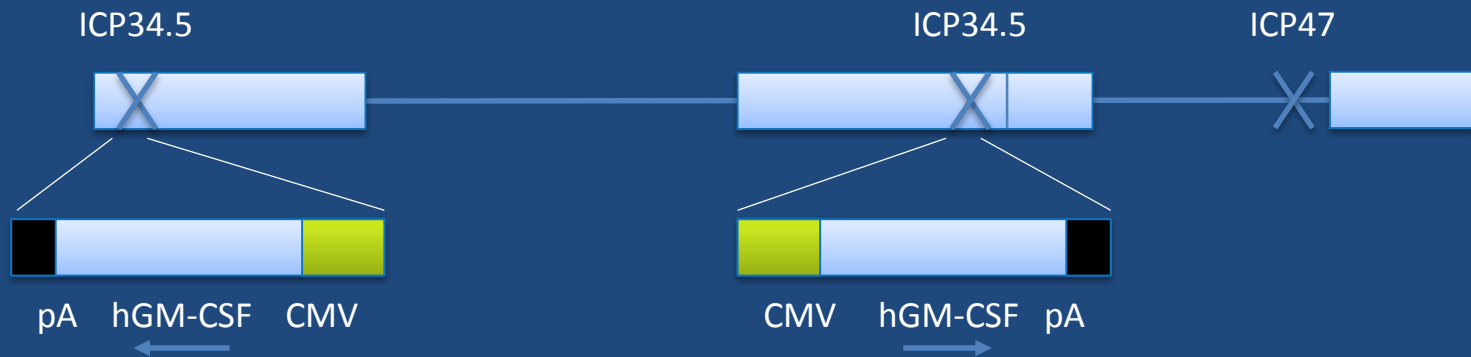


Peptide/MHC



B7-1,2

# Talimogene laherparepvec (TVEC)



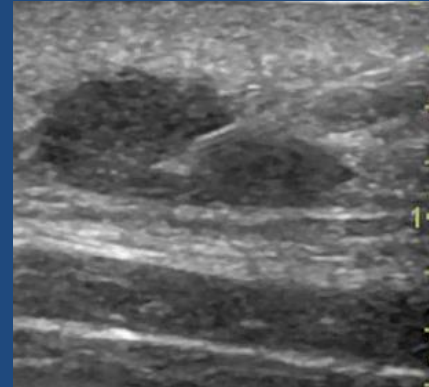
Talimogene laherparepvec (JS1/ICP34.5-/ICP47-/hGM-CSF)

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 neurovirulence factor ICP34.5
  - Elimination of antigen-presentation blocker ICP47
  - Insertion of hGM-CSF (cytokine that recruits immune cells, specifically antigen presenting cells)

<sup>1</sup> 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	

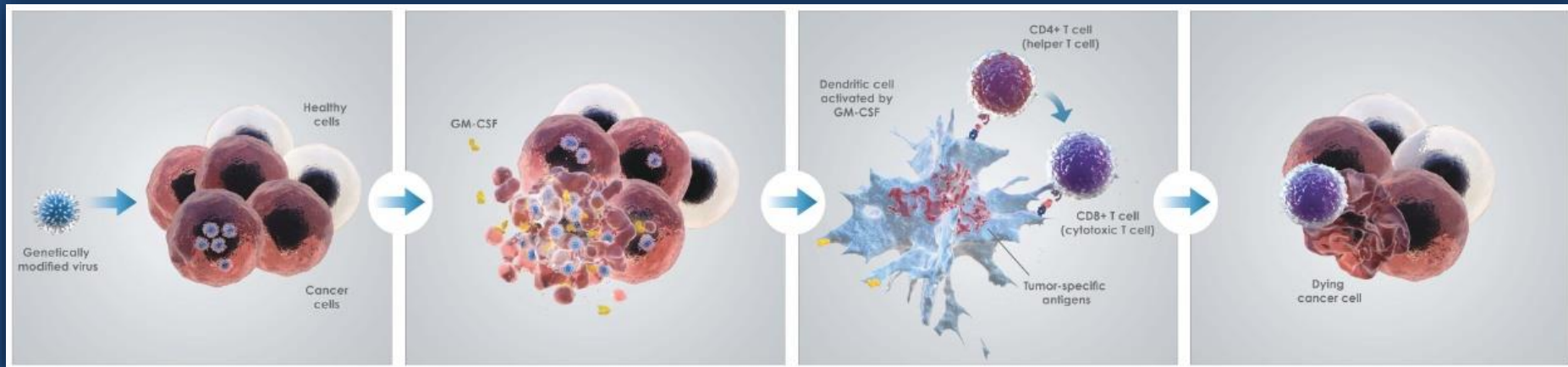
# In situ vaccination

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.

# T-VEC Responses in Injected And Uninjected Lesions

## Cycle 1



## Cycle 13





# Lymphoid Aggregates form in tumors

DAPI

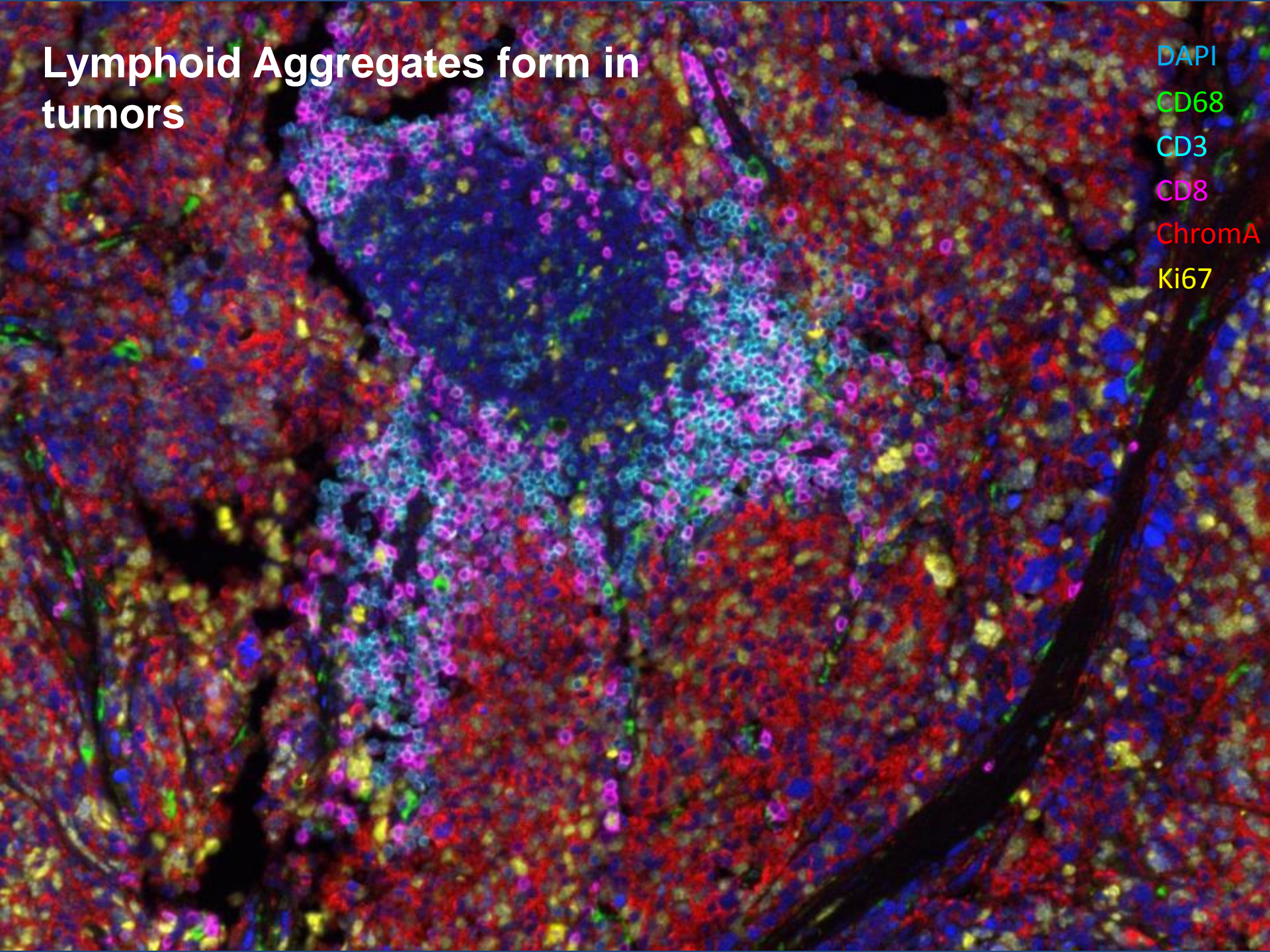
CD68

CD3

CD8

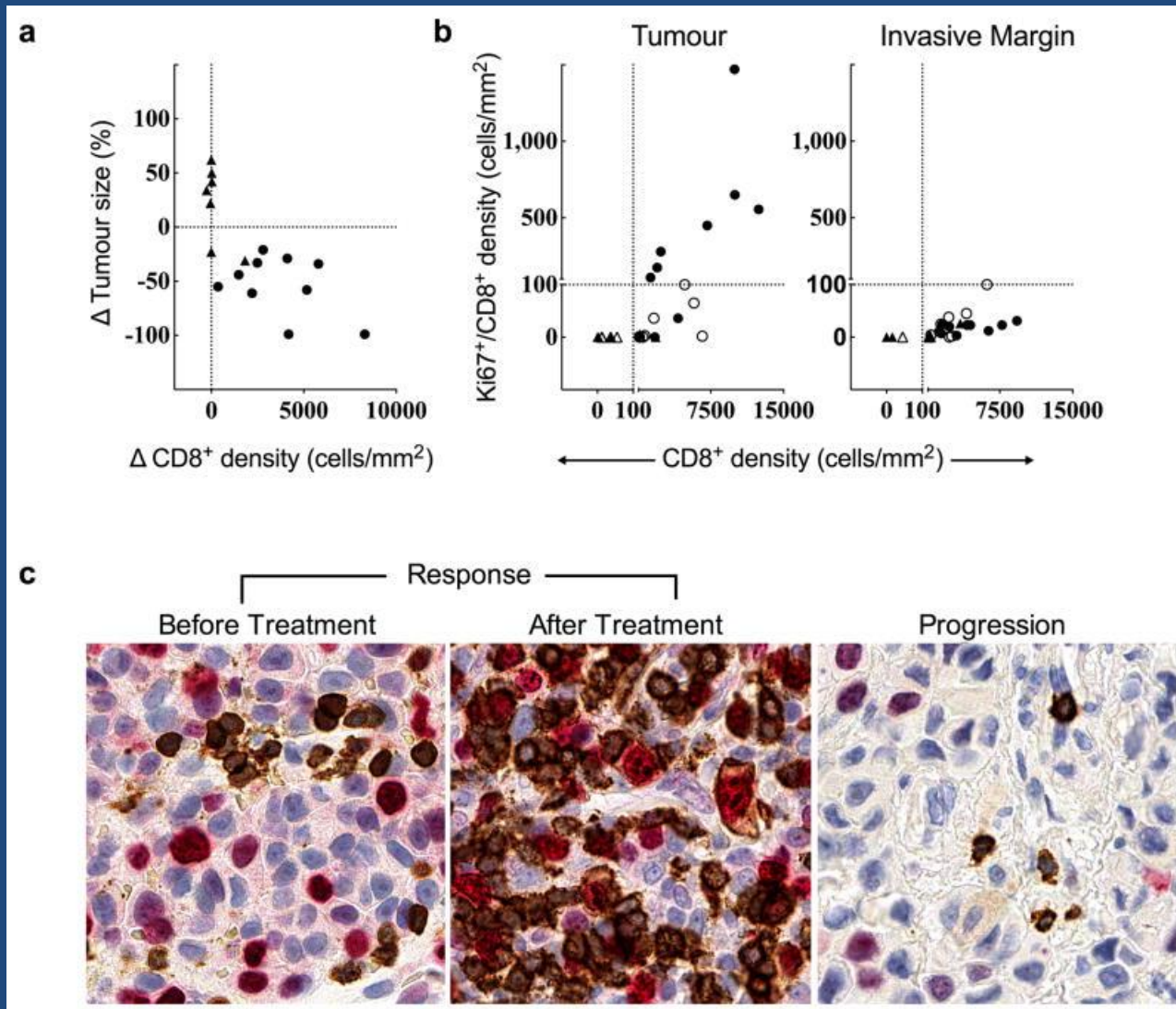
ChromA

Ki67





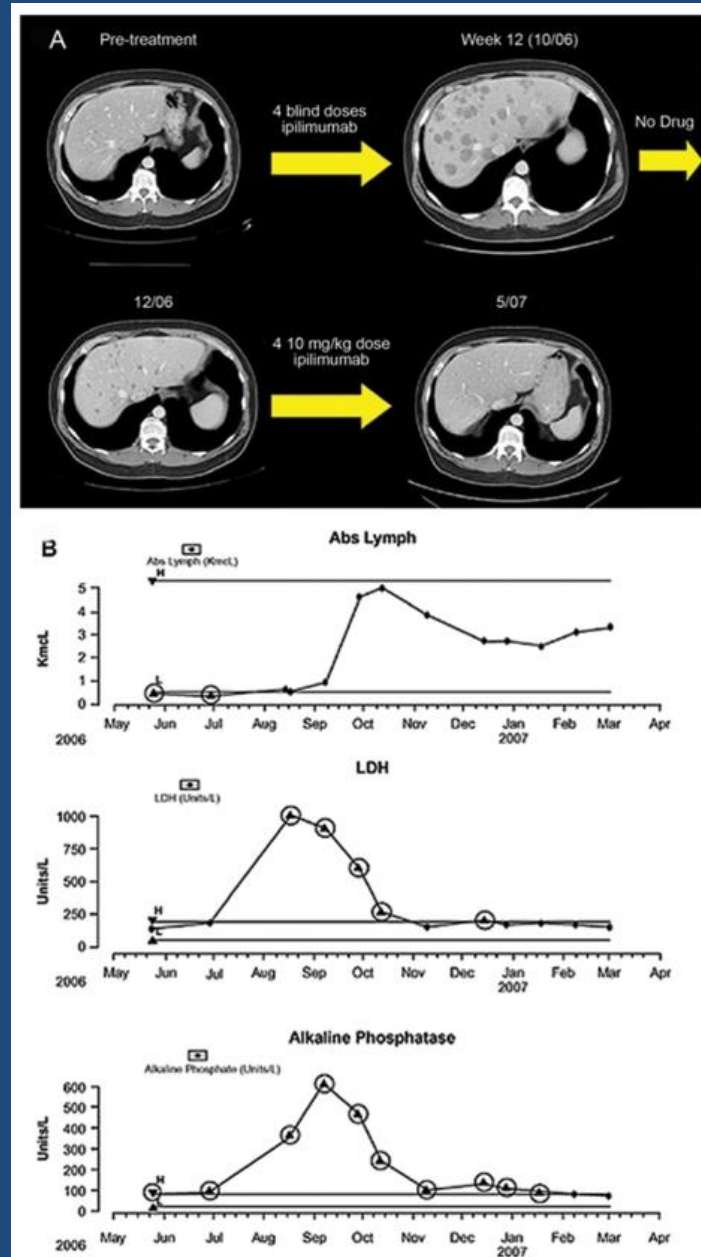
# Immunotherapy causes infiltration of T cells into tumors



Tumwien et al, "PD-1 blockade induces responses by inhibiting 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., $\geq 5 \times 5$ mm)	Always represent PD	Incorporated into tumor burden
New, nonmeasurable lesions (i.e., $< 5 \times 5$ 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	$\geq 50\%$ 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	$\geq 50\%$ 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

# Kinetics of toxicities may also be unpredictable

**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
	<i>number of patients with event (percent)</i>					
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 amino- transferase 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 amino- transferase 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

# 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



# Immunotherapy is the future

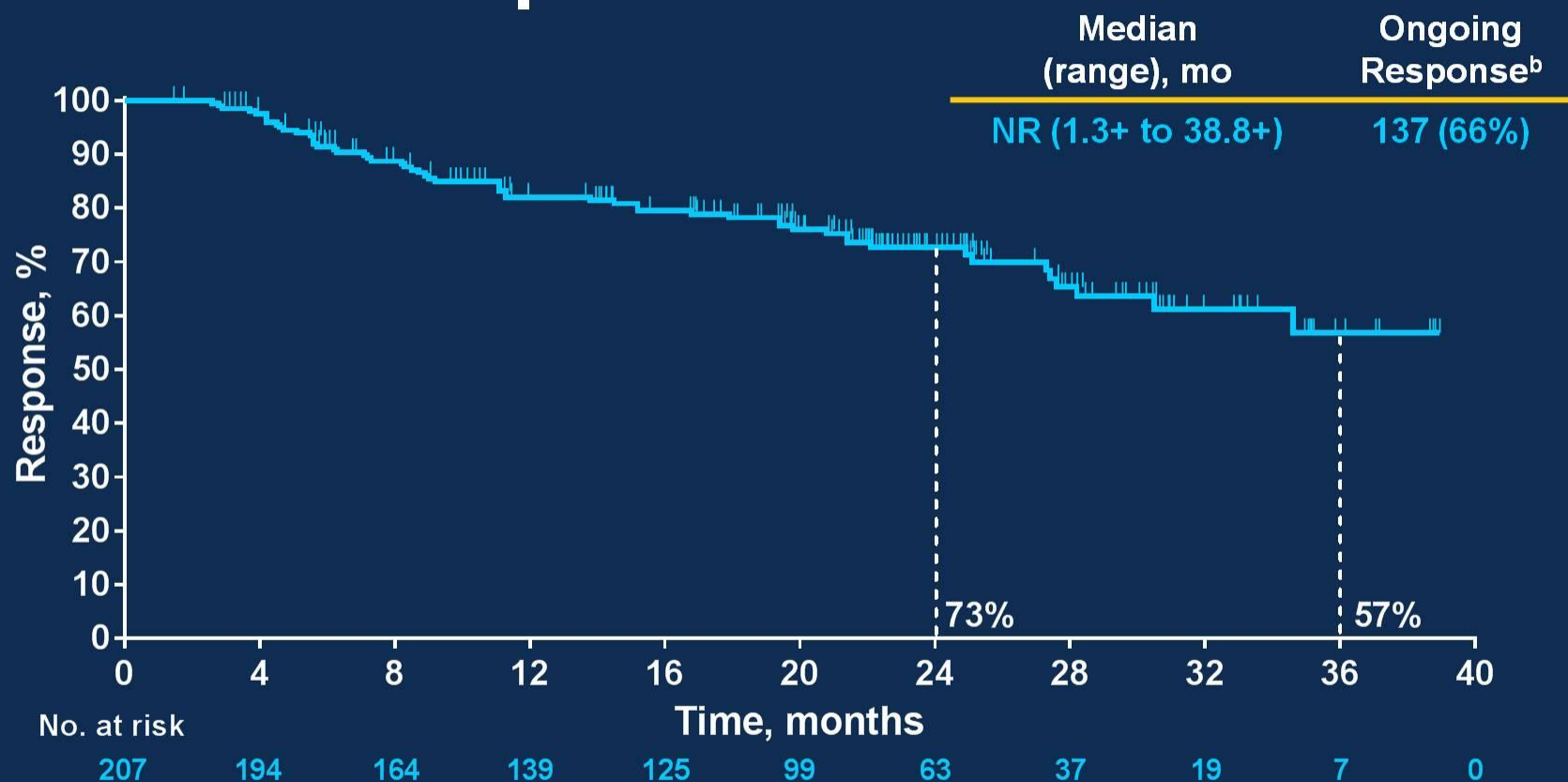


- Interleukin 2
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- Anti-CTLA4)
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  - CD27
  - CD40
  - FLT3L
  - IL15
  - And many more....

# Duration of Response<sup>a</sup>



PRESENTED AT: **ASCO ANNUAL MEETING '16**

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<sup>a</sup>Assessed per RECIST v1.1 by independent central review in patients with response, regardless of centrally evaluable disease at baseline. <sup>b</sup>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
- Anti-CTLA-4 has a similar mechanism of action but can cause more toxicity
- The first oncolytic virus was recently approved in cancer
- Many new treatments are showing great promise and will be approved soon



## 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