Basic Principals of Tumor Immunotherapy

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Disclosures

- **Consulting:** Novartis
  AstraZeneca
  Aura Biosciences
  Rgenix
- **Scientific Advisory Board:** Aura Biosciences
- **Clinical Advisory Board:** Rgenix

Learning Objectives

1. To understand the tumor-immune system interface and the role immuno-oncology in cancer therapy

2. To review the various ways the immune system can be modulated for the treatment of cancer

3. To be aware of challenges associated with effectively using immunotherapy for cancer care

Tumor Immunotherapy

Tumor immunotherapy is the use of substances to stimulate the immune system to fight cancer

Adaptable
- Designed to adapt the response beyond the initially targeted antigen

Specific
- Trains the body to recognize and target only tumor cells

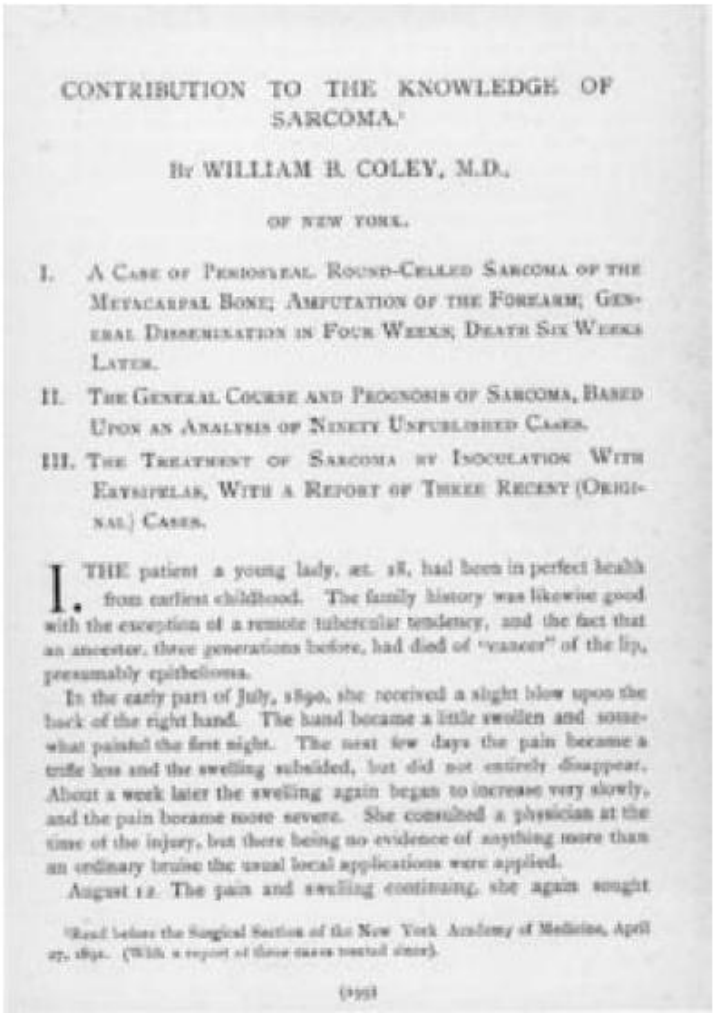
Long Lasting
- Capacity for memory results in durability of response

Universal
- Applicable to nearly all cancers

Coley's Toxin: The First Immunotherapy

William B. Coley
(1862 – 1936)

Chief, Bone Sarcoma Unit
Memorial Hospital
New York, New York



CONTRIBUTION TO THE KNOWLEDGE OF SARCOMA.[1]

By WILLIAM B. COLEY, M.D.,

OF NEW YORK.

I. A Case of Periosteal Round-Celled Sarcoma of the Metacarpal Bone; Amputation of the Forearm; General Dissemination in Four Weeks; Death Six Weeks Later.

II. The General Course and Prognosis of Sarcoma, Based Upon an Analysis of Ninety Unpublished Cases.

III. The Treatment of Sarcoma by Inoculation With Erysipelas, With a Report of Three Recent (Original) Cases.

I. THE patient a young lady, æt. 18, had been in perfect health from earliest childhood. The family history was likewise good with the exception of a remote tubercular tendency, and the fact that an ancestor, three generations before, had died of "cancer" of the lip, presumably epithelioma.

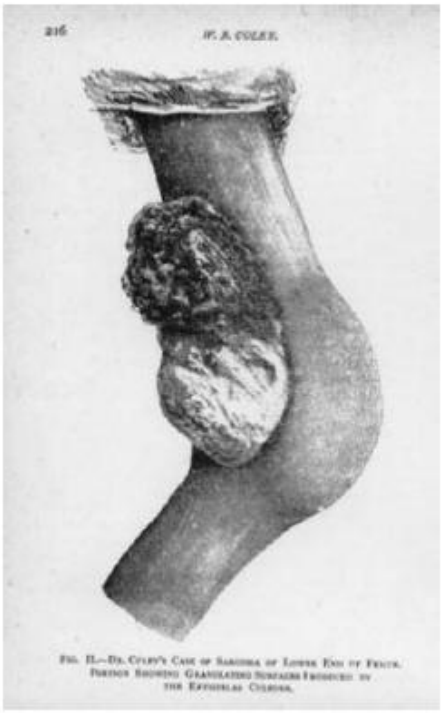
In the early part of July, 1890, she received a slight blow upon the back of the right hand. The hand became a little swollen and somewhat painful the first night. The next few days the pain became a trifle less and the swelling subsided, but did not entirely disappear. About a week later the swelling again began to increase very slowly, and the pain became more severe. She consulted a physician at the time of the injury, but there being no evidence of anything more than an ordinary bruise the usual local applications were applied.

August 12. The pain and swelling continuing, she again sought

[1]Read before the Surgical Section of the New York Academy of Medicine, April 27, 1891. (With a report of three cases treated since).

(193)

Coley WB. Annals of Surgery 1891;14:199–200



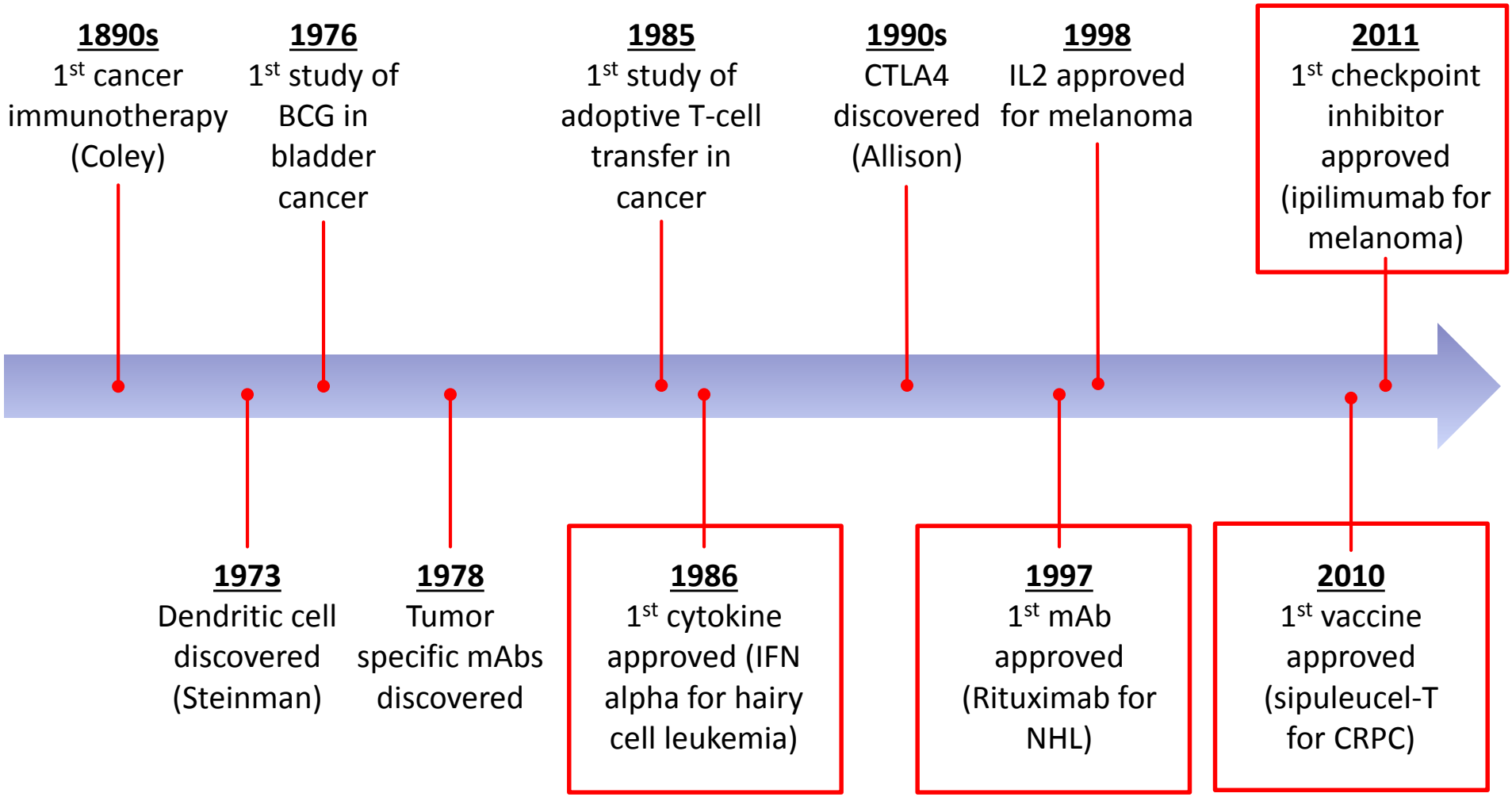
216 W. B. COLEY.

FIG. II.—DR. COLEY'S CASE OF SARCOMA OF LOWER END OF FEMUR. PATIENT SHOWING GRANULATING SURFACES PRODUCED BY THE ERYSIPELAS CULTURE.

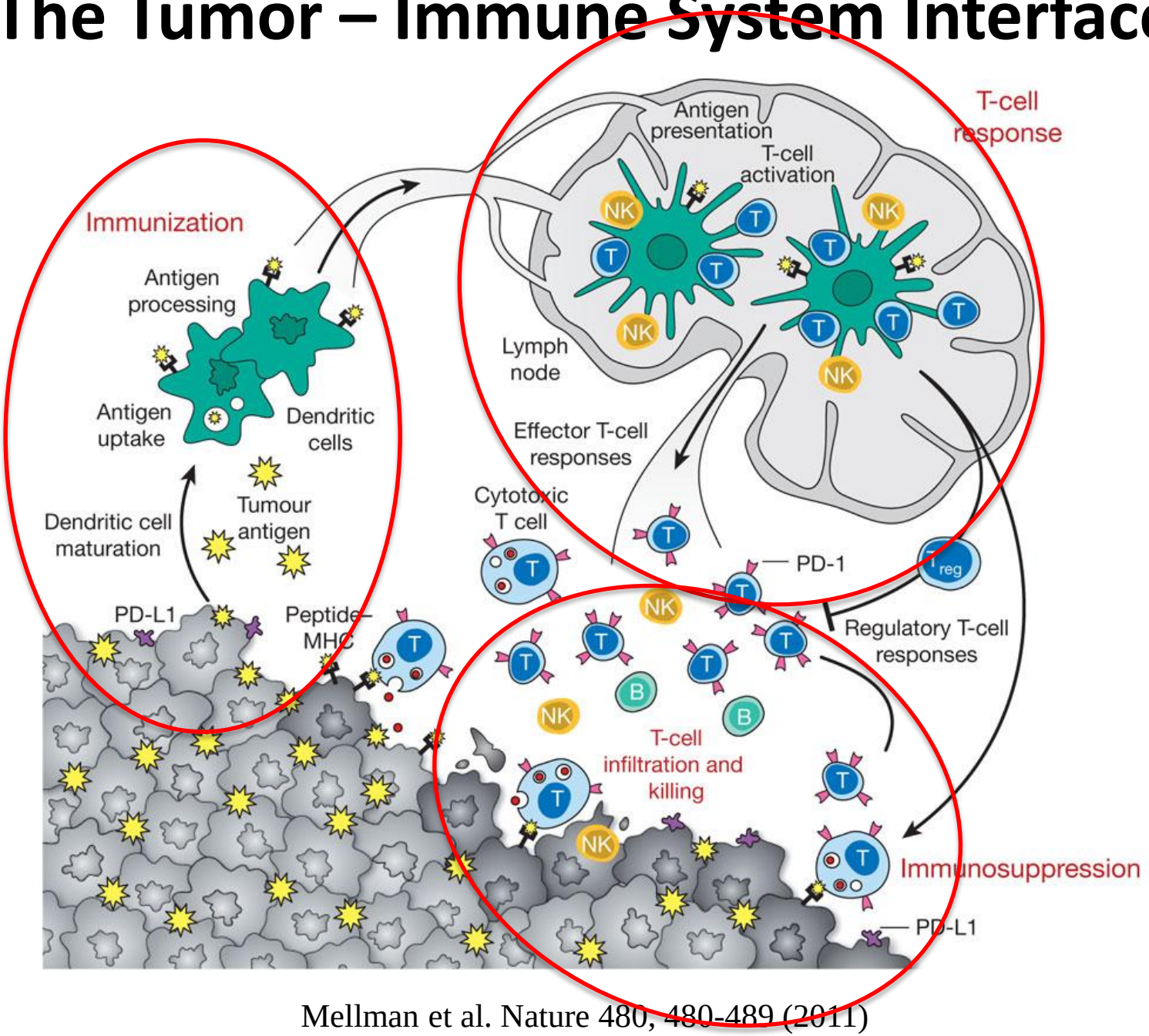
Coley's First Bone Sarcoma Case

McCarthy EF. IOWA Orthop J, 2006.

Timeline of Immuno-Oncology



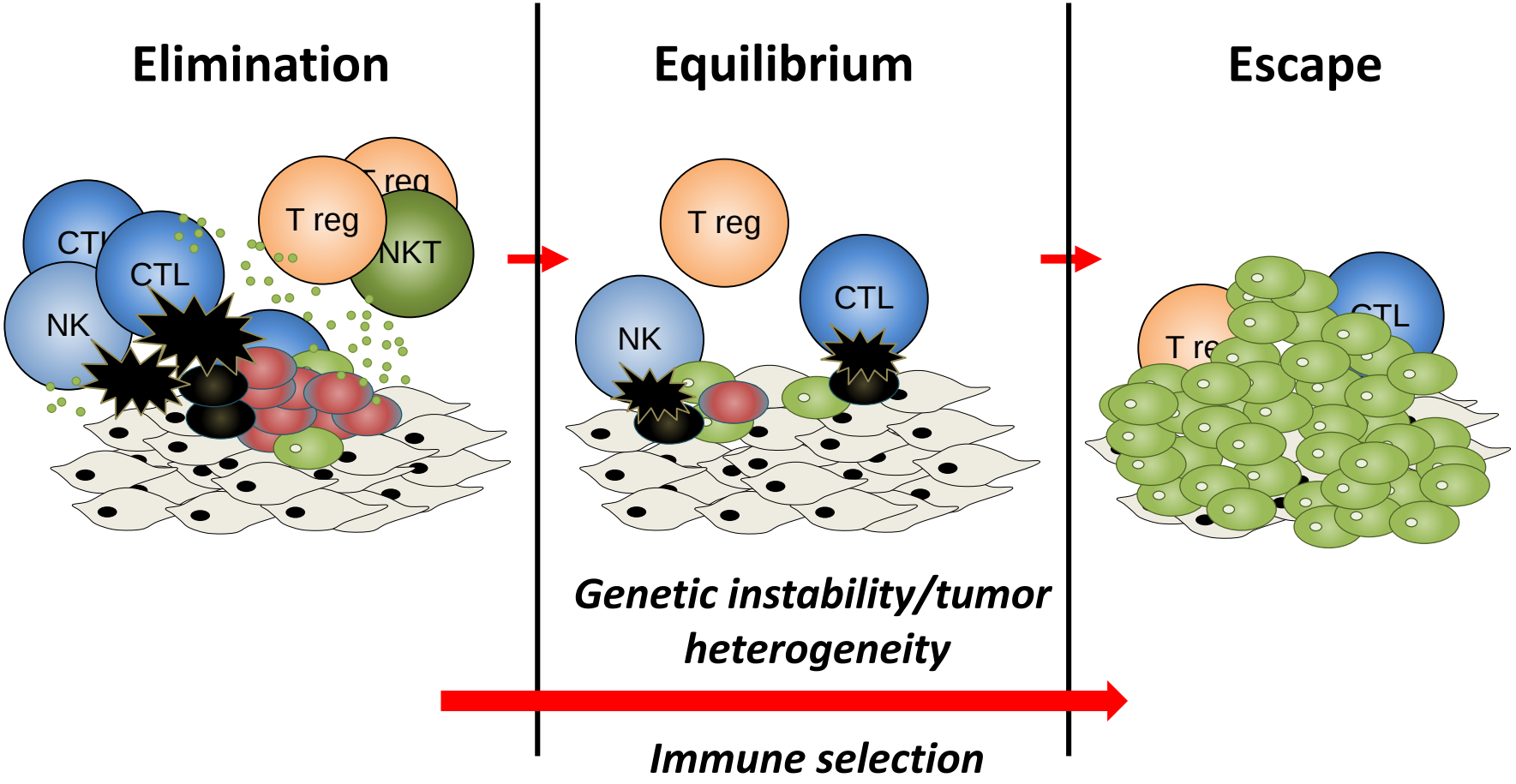
The Tumor – Immune System Interface



Mellman et al. Nature 480, 480-489 (2011)

The Three ‘E’s of Immunoediting

The immune system controls tumor quantity
as well as tumor quality



Dunn GP, et al. Nat Immuno. 2002;3:991-998. Schreiber R, et al. Science. 2011;331:1565-1570.
Mittal D, et al. Curr Opin Immunol. 2014;27:16-25.

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Categories of Immunotherapy

	Active	Passive
Tumor Specific	Vaccines	Monoclonal Antibodies
Tumor Non-Specific	Immunologic Checkpoint Inhibitors	Cytokines

- **Active Immunotherapy**: Dependent upon the patient's own immune system for antitumor effects
- **Passive Immunotherapy:** Administration of antibodies or pretreated immune cells

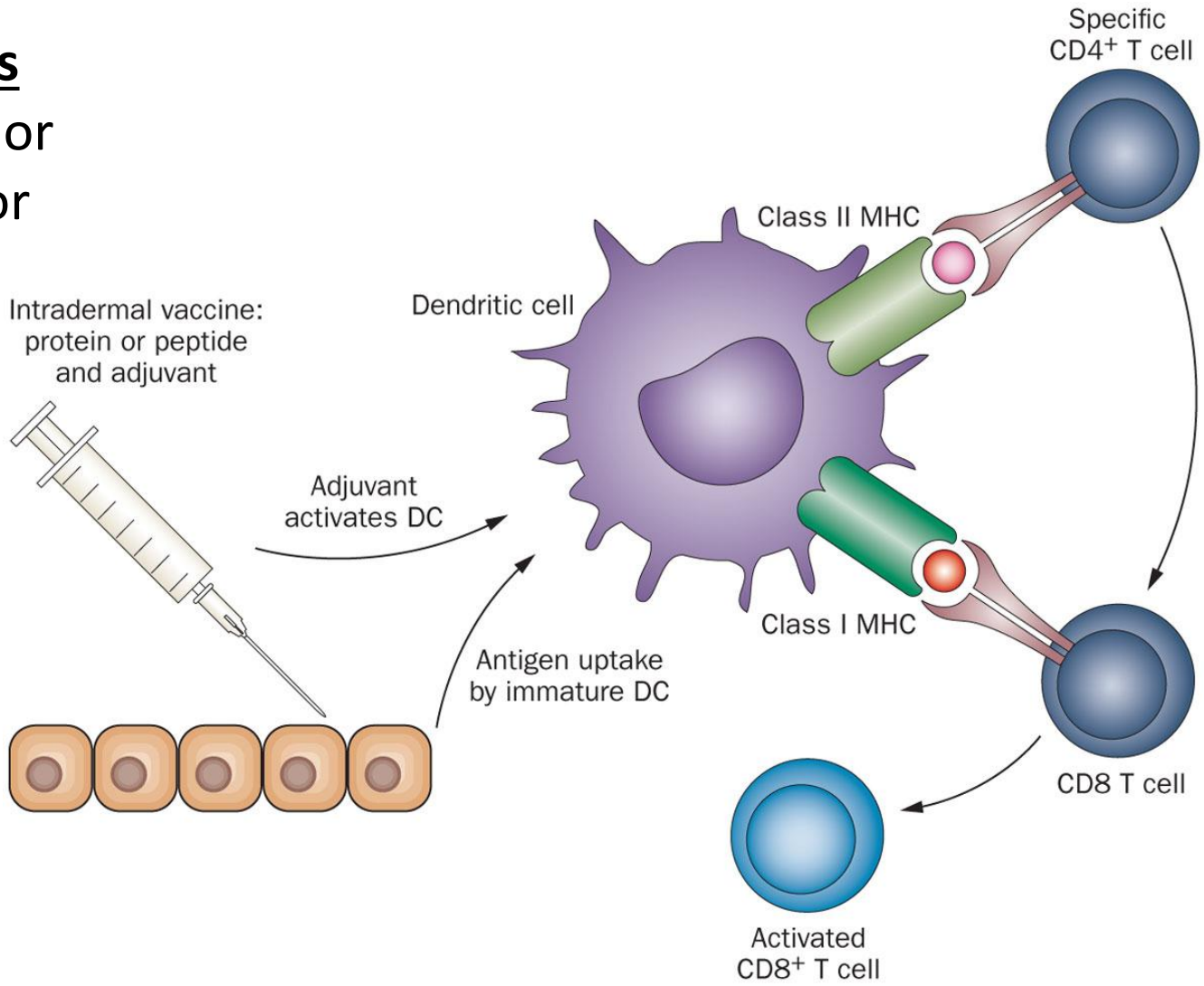
Major Approaches to Tumor Immunotherapy

Approach		Examples
I. Vaccines	**Preventative**	HPV, HBV
	Therapeutic	Sipuleucel-T
II. Antibodies	**Naked**	Alemtuzumab, Trastuzumab
	Conjugated	Ado-trastuzumab emtansine
	Bispecific	Blinatumomab
	Checkpoint Inhibitors	Ipilimumab, Pembrolizumab, Nivolumab
	Co-Stimulatory Activators	GITR, OX40, CD27
III. Cytokines		IL2, Interferon, GM-CSF
IV. Oncolytic Viruses		TVEC
V. Cellular Therapy	Adoptive T Cell Therapy	
	Chimeric Antigen Receptor T Cell Therapy	

Vaccine Therapy: Mechanism of Action

Types of Vaccines

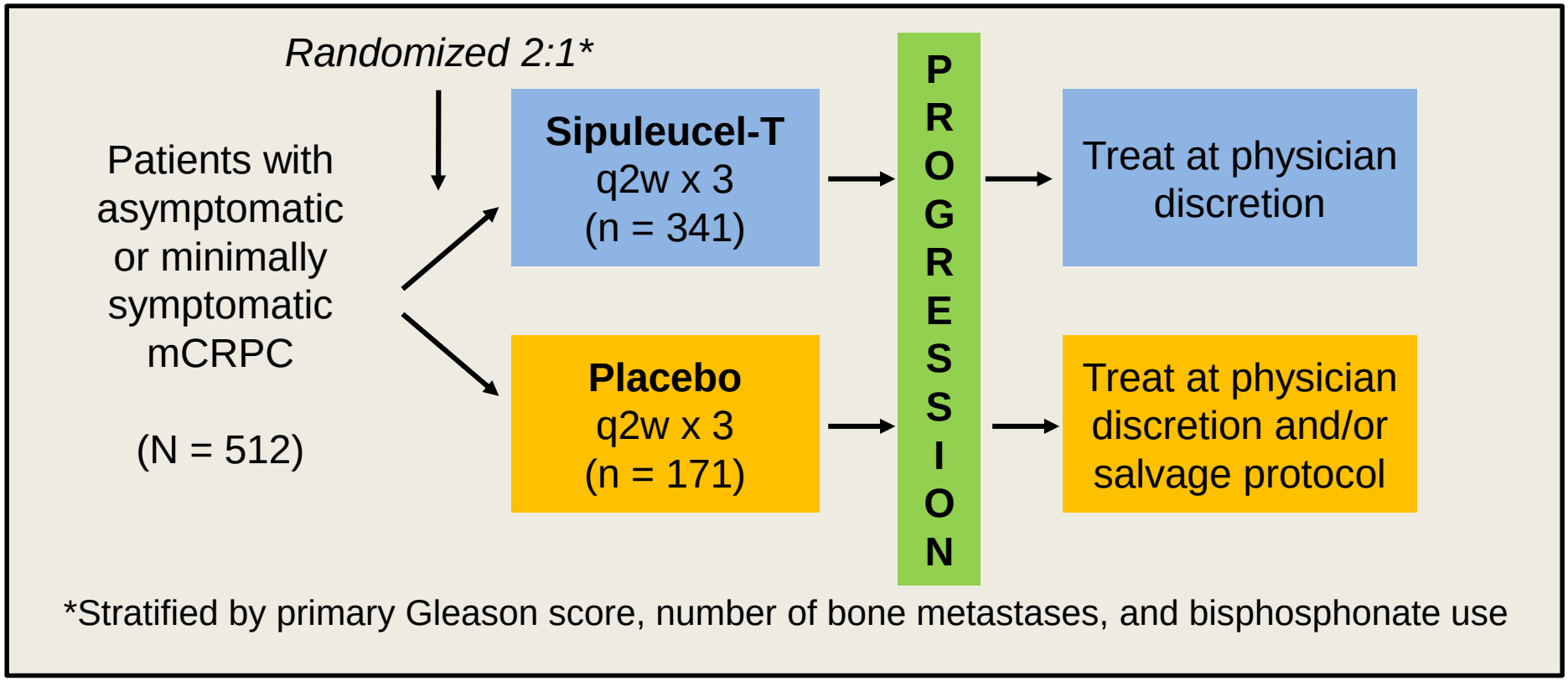
- Autologous Tumor
- Allogeneic Tumor
- Peptide
- Dendritic Cell
- Viral Based



Drake, C. G. *et al.* (2013) Breathing new life into immunotherapy: review of melanoma, lung and kidney cancer *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2013.208

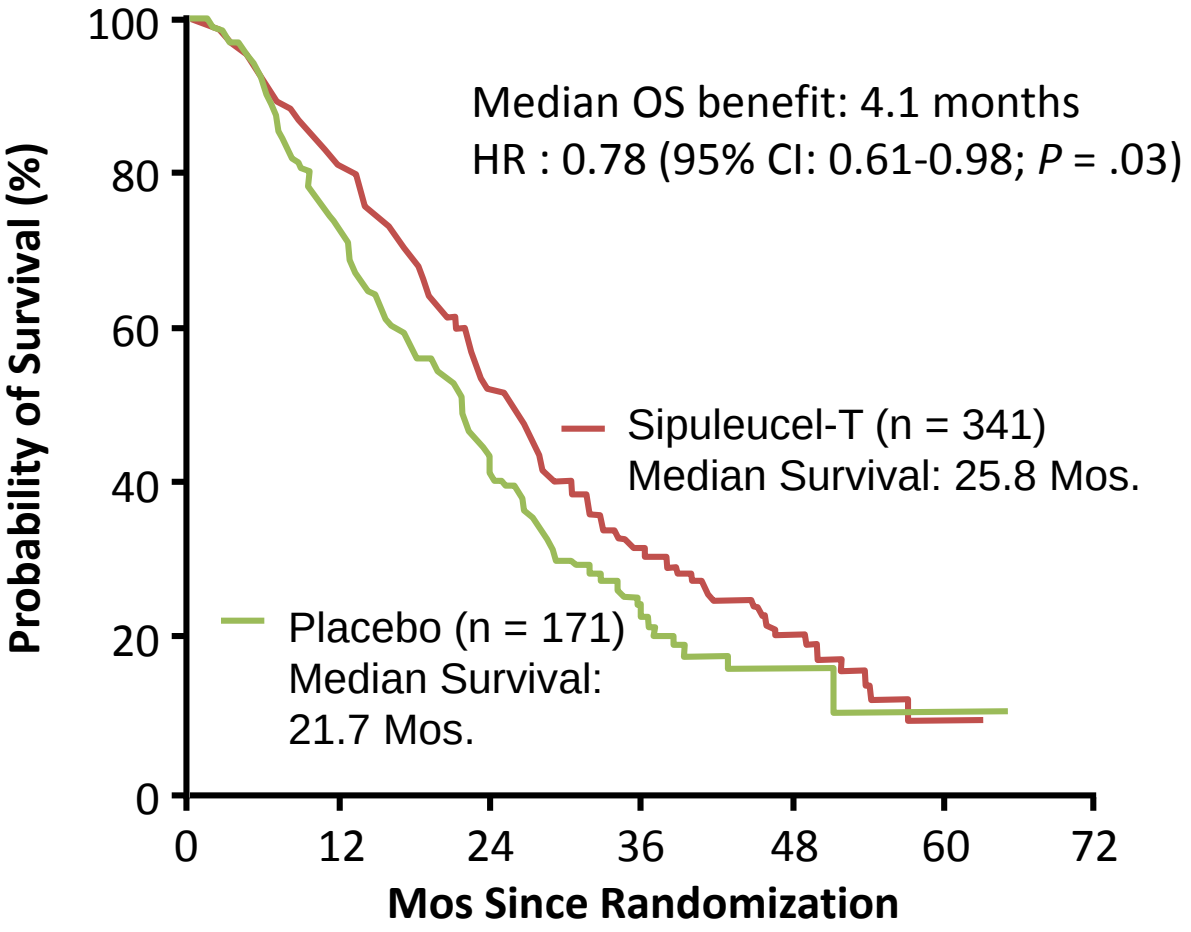
Phase III IMPACT Study: Sipuleucel-T in mCRPC

- **Sipuleucel-T:** Cellular active immunotherapy produced by exposing a patient's leukapheresed cells to recombinant fusion protein consisting of prostatic acid phosphatase (PAP) antigen and GM-CSF
- **Primary endpoint:** OS



Kantoff P, et al. New Engl J Med. 2010;363:411-422.

Phase III Trial of Sipuleucel-T Immunotherapy in mCRPC (IMPACT): OS



Kantoff PW, et al. N Engl J Med. 2010;363:411-422.

Therapeutic Cancer Vaccines: Challenges

Despite many promising phase II studies with positive results when compared with historical controls, all but one vaccine have failed to show an OS benefit in phase III trials

- Vaccines successfully induce immune reactions against the vaccine, but not the tumor
- The immune system mainly recognizes “neo-antigens” from “passenger” mutations rather than shared antigens
  - Target antigens are different for each tumor
- Although most immune-responsive tumors “autovaccinate,” an effective anti-tumor response is not achieved
  - Immunosuppressed tumor microenvironment
  - Activation of immunologic checkpoints

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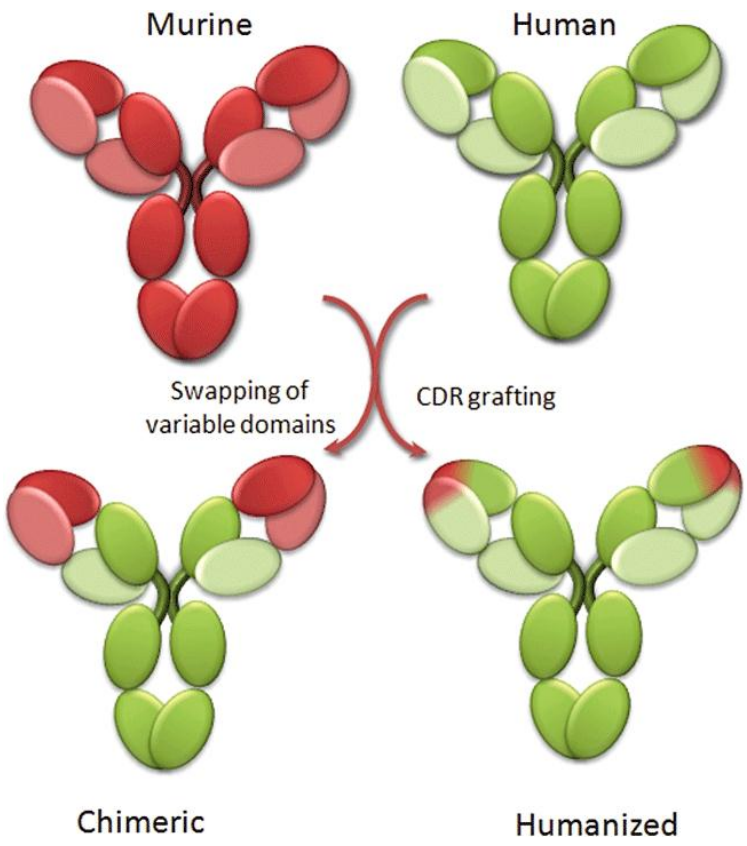
V. Cellular Therapy	Adoptive T Cell Therapy	
	Chimeric Antigen Receptor T Cell Therapy	

Monoclonal Antibodies

- mAb's are a single type of antibody directed against a specific antigenic determinant (epitope)
- Can be:
  - Naked antibodies
  - Conjugated antibodies
  - Bispecific antibodies



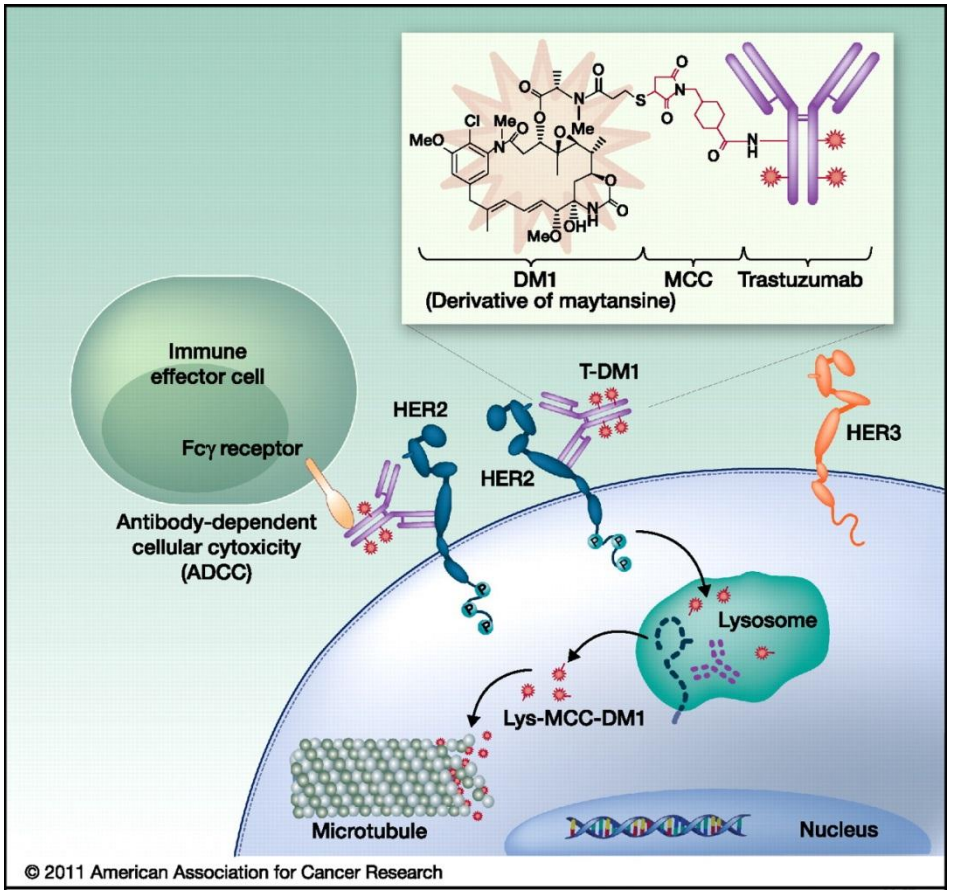
	Murine mAb	Chimeric mAb	Humanized mAb	Human mAb
Suffix	-omab	-ximab	-zumab	-umab
Example	Tositumomab (CD20)	Cetuximab (EGFR)	Bevacizumab (VEGF)	Panitumumab (EGFR)

Chames et al. Br J Pharmacol. 2009 May; 157(2): 220–233

Conjugated Monoclonal Antibodies

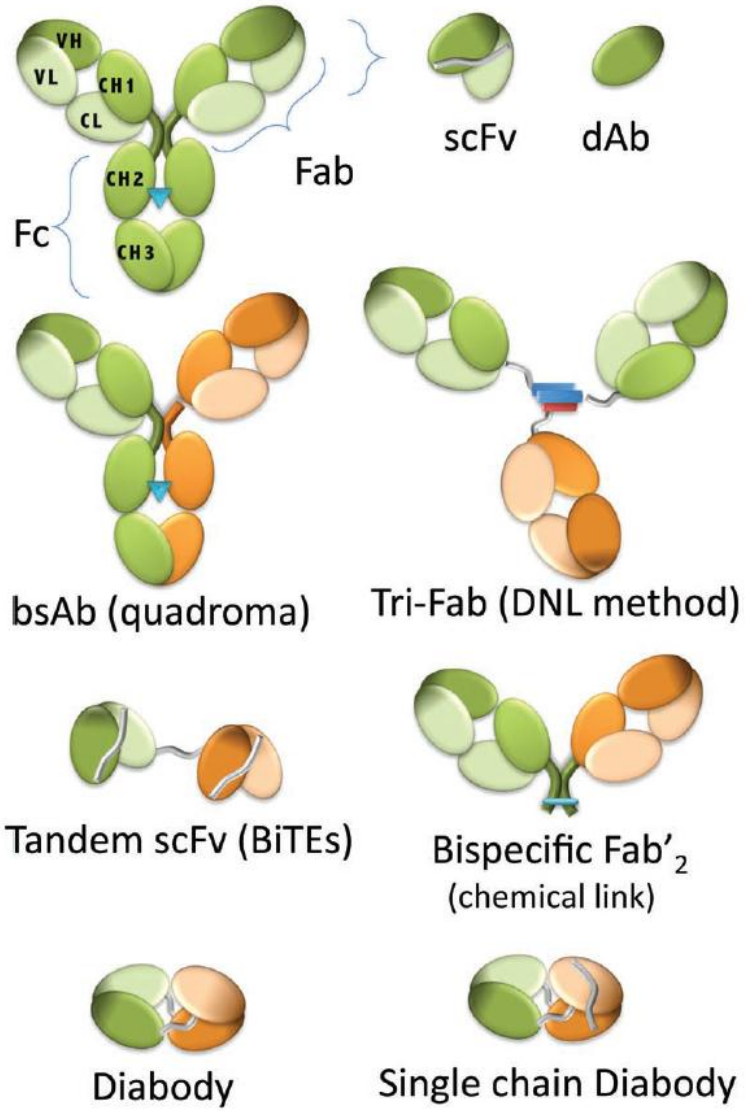
- Antibodies conjugated to chemotherapy, radioactive particles, or other poisons

Drug	Target	Toxin
Ibrutumomab tiuxetan	CD20	RT
Brentuximab	CD30	MMAE
Ado-trastuzumab emtansine	HER2	DM1



LoRusso P M et al. Clin Cancer Res 2011;17:6437-6447

Bispecific Monoclonal Antibodies



- Bispecific antibodies are made up of parts of 2 different mAbs
- Allows for the attachment to 2 different proteins at the same time

Drug	Target 1	Target 2
Blinatumomab (ALL)	CD19	CD3

Chames et al. MAbs. 2009

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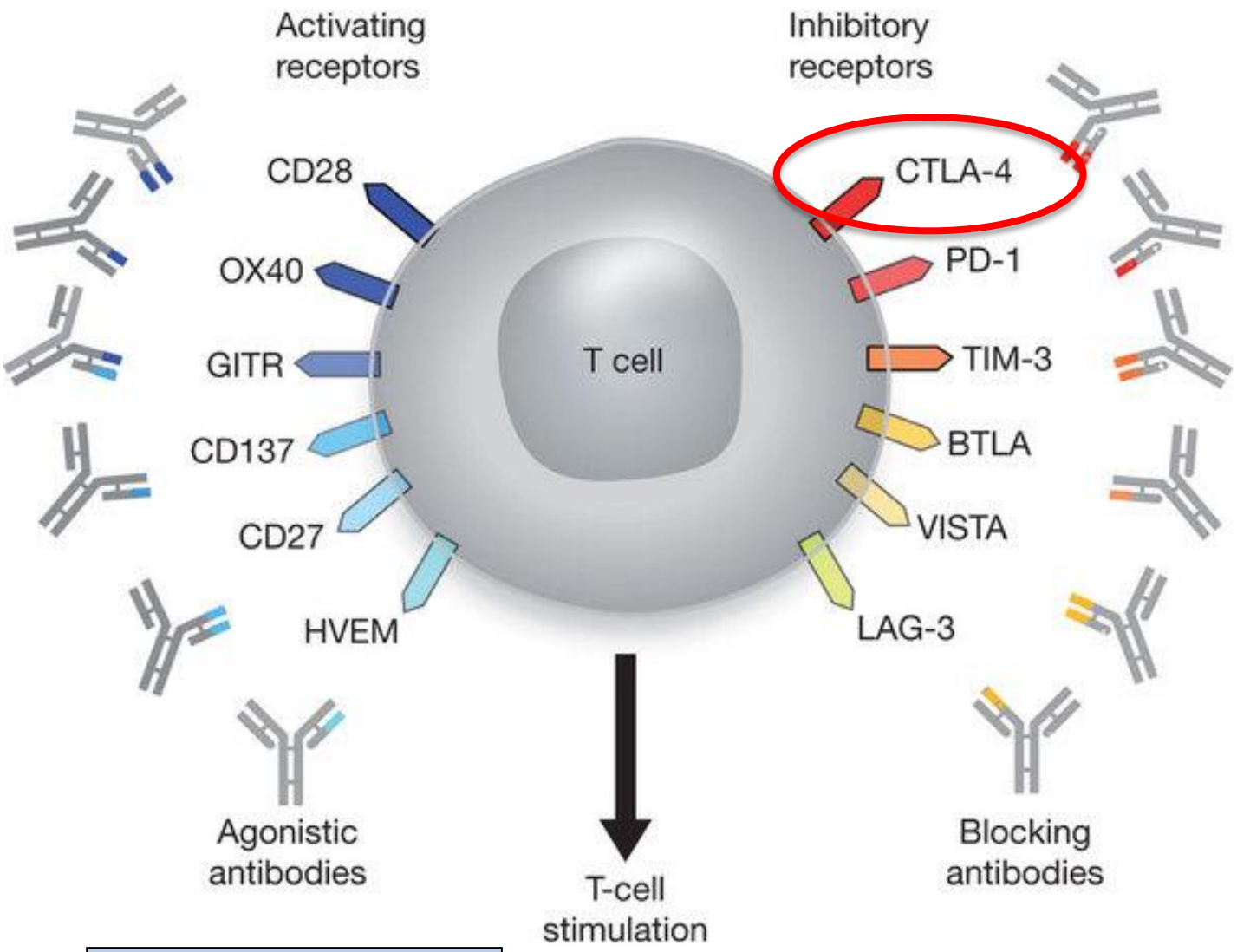
Immunological Checkpoint Receptors

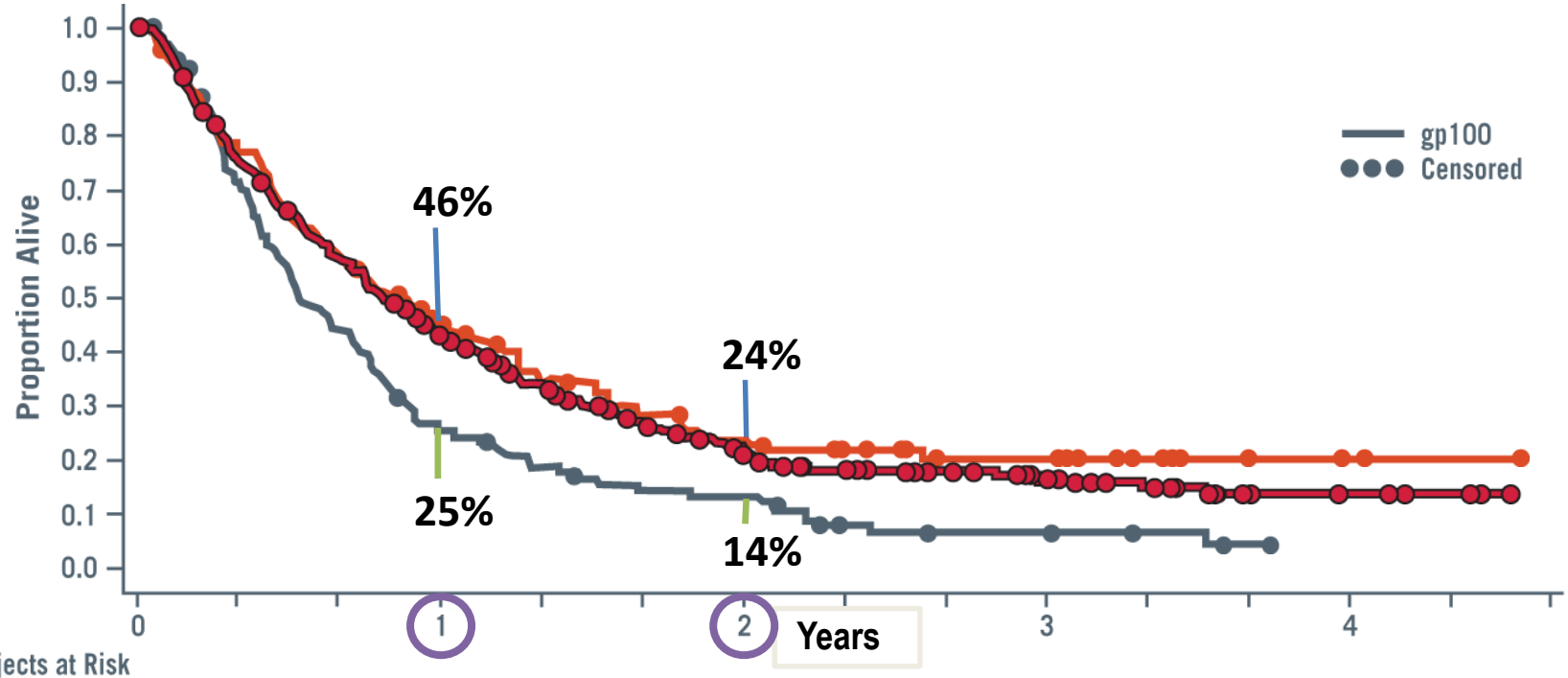


Activating

Inhibiting

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.



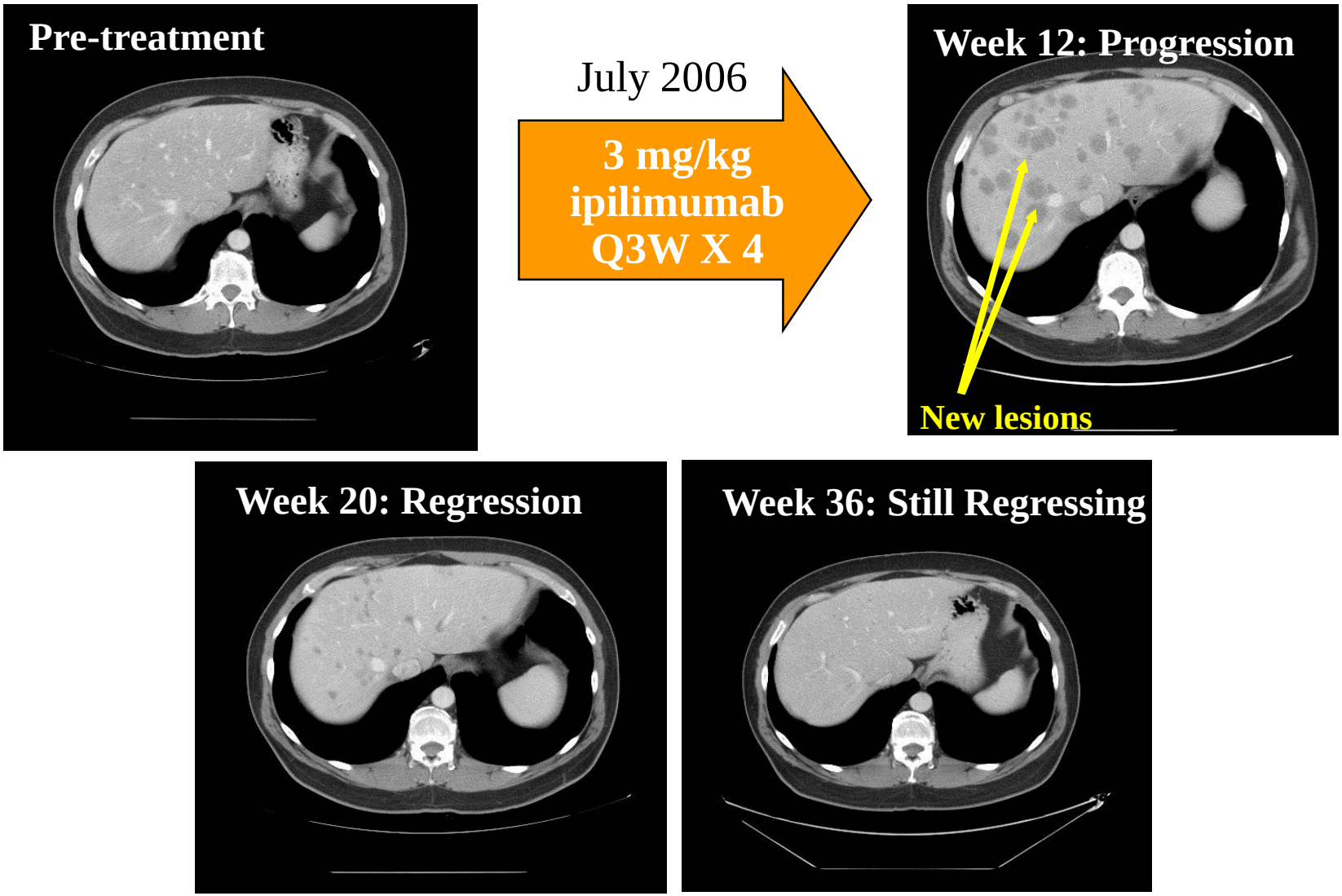
Subjects at Risk

YERVOY + gp100	403	297	223	163	115	81	54	42	33	24	17	7	6	4	0
YERVOY	137	106	79	56	38	30	24	18	13	13	8	5	2	1	0
gp100	136	93	58	32	23	17	16	7	5	5	3	1	0	0	0

NEJM, August 2010

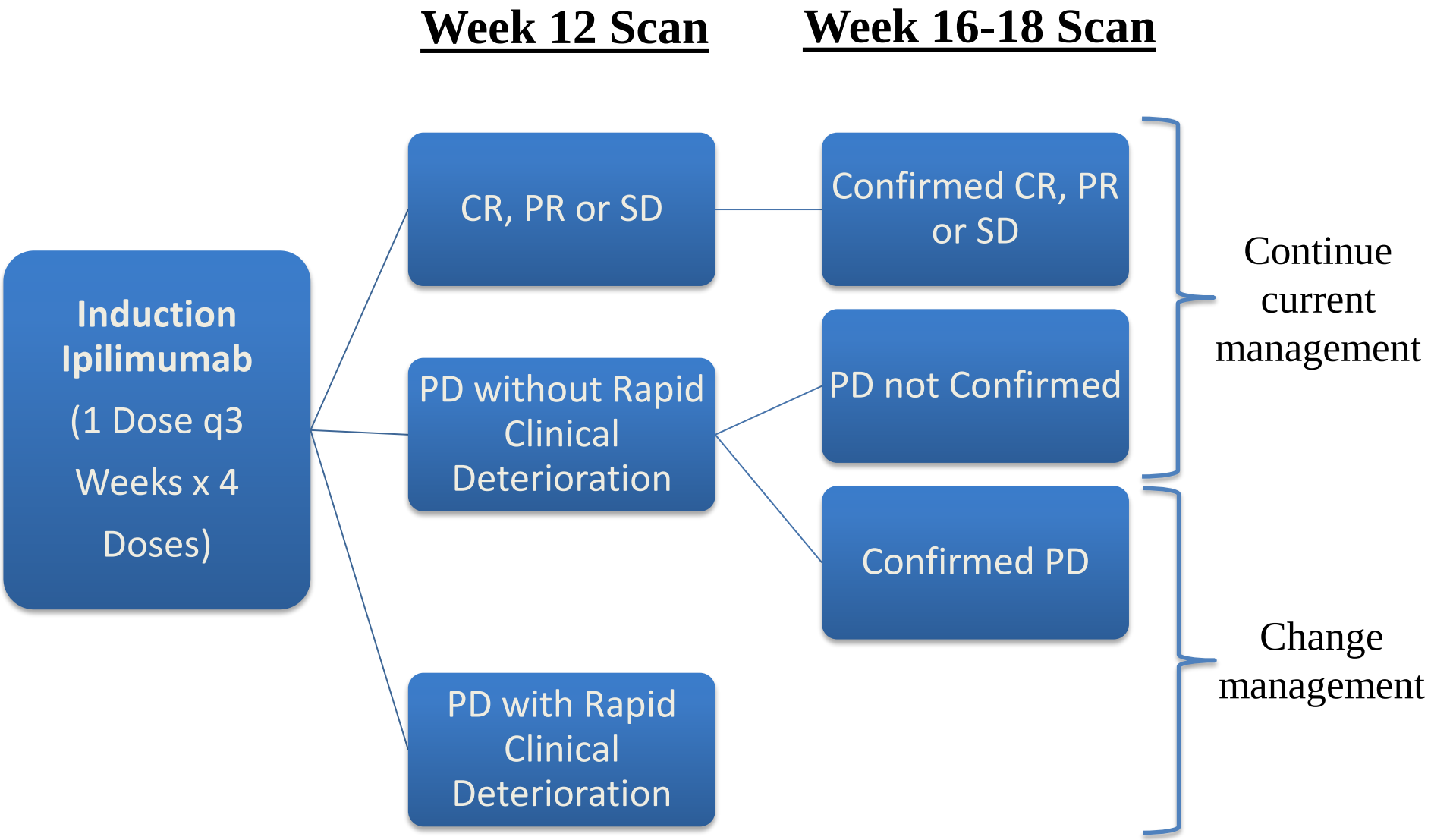
Immunological Pattern of Response:

Initial Appearance and Subsequent Disappearance of New Lesions



Saenger and Wolchok. Cancer Immun. 2008.

Treatment Strategy for Ipilimumab Using irRC



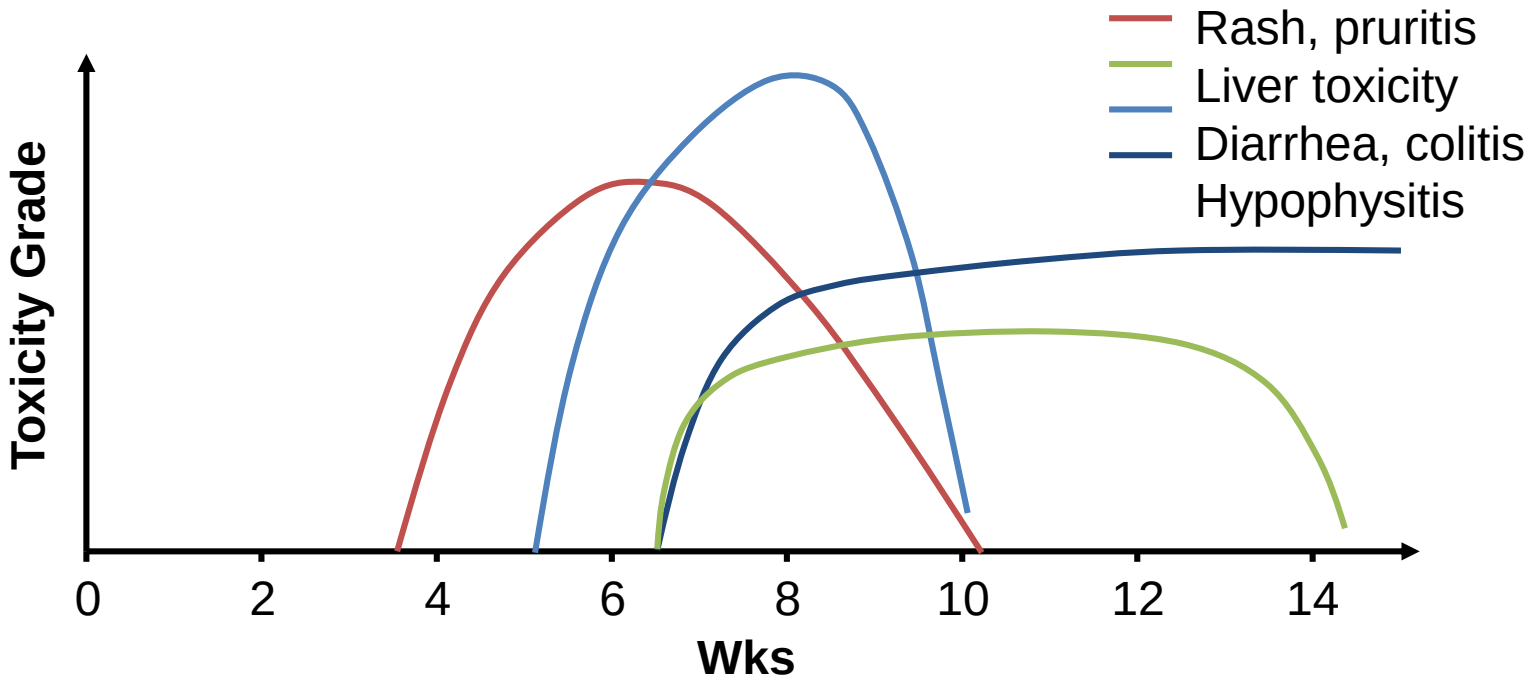
Immune-Related Adverse Events

- Toxicities arising from autoimmunity induced by immune-activating agents

- Broadly categorized as toxicities affecting the:
    1. Skin (pruritis, rash)
    2. Gastrointestinal tract (diarrhea, colitis)
    3. Liver (transaminitis)
    4. Endocrine organs (hypophysitis, thyroiditis, adrenal insufficiency)
    5. Neurological system (peripheral sensory and motor neuropathies)
    6. Eyes (uveitis, episceritis)
    7. Pancreas (pancreatitis)

Kinetics of Grade 3/4 irAEs with Ipilumumab

Toxicity	Ipi 3 mg/kg + gp100 (n = 380)	Ipi 3 mg/kg + Placebo (n = 131)	gp100 + Placebo (n = 132)
Any	9.7% Gr 3; 0.5% Gr 4	12.2% Gr 3; 2.3% Gr 4	3.0% Gr 3; 0% Gr 4
Dermatologic	2.1% Gr 3/0.3% Gr 4	1.5% Gr 3/0% Gr 4	0% Gr 3;0% Gr 4
GI	5.3% Gr 3/0.5% Gr 4	7.6% Gr 3;0% Gr 4	0.8% GR 3/0% Gr 4
Endocrine	1.1% Gr 3/0% Gr 4	2.3% Gr 3/1.5% Gr 4	0% Gr 3/0% Gr 4
Hepatic	1.1% Gr 3/0% Gr 4	0% Gr 3/0% Gr 4	2.3% Gr 3/0% Gr 4



Hodi et al. N Engl J Med. 2010 Aug 19;363(8):711-23; Weber JS, et al. J Clin Oncol. 2012;30:2691-2697.

Approach to Potential irAEs

- Always include drug induced autoimmune toxicity in differential diagnosis
- Can affect any organ system
- Rule out other etiologies (e.g., infection, other drugs, neoplasm, etc.)
- Early recognition, evaluation and treatment are critical for patient safety
- **Management strategy for drug induced colitis:**

Grade	Management
Grade 1 (< 4 BMs over baseline)	• Initiate bland diet and oral hydration • Increase monitoring (phone call f/u 1-2 times/week)
Grade 2 (4 - 6 BMs over baseline)	• Hold drug • Rule out infection (Clostridium difficile, stool cx) • Consider oral budesonide 9 mg daily or other antidiarrheals • Initiate corticosteroids 0.5 – 1 mg/kg/day
Grade 3 - 4 (7+ BMs over baseline)	• Hold drug • Administer IV corticosteroids (methylprednisolone 125 mg qd) until symptoms improved and then begin taper of oral steroids 1 – 2 mg/kg/day over 30+ days • Consider infliximab IV 5 mg/kg

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Lessons and Take Home Messages

- The tumor – immune system interface is complex and dynamic
- Immunotherapy can produce durable antitumor responses in some patients with cancer
- Challenges associated with treatment of patients with immunotherapy differ than those faced with conventional therapies
  - Identify unconventional responses to immune checkpoint inhibitors
  - Understand and manage immune-related adverse events
- Further work is required to overcome tumor anti-immunity and optimize the efficacy of immunotherapy for the treatment of cancer

Question #1

A 66-year-old woman presents with BRAF wild-type metastatic melanoma is treated with four doses of ipilimumab 3 mg/kg. Two weeks following her last dose of therapy, she feels well; however, a CT scan shows what appears to be tumor growth. Reasonable management options include:

1. Re-initiating an induction course of ipilimumab

2. Beginning therapy with dabrafeninib and trametinib

3. Closely monitoring the patient and repeating the CT scan in 4 – 8 weeks to assess for pseudo-progression

4. Administering a course of systemic steroids to reduce tumor inflammation

Question #2

An example of tumor-specific active immunotherapy includes:

1. Interleukin 2
2. Sipuleucel-T
3. Pembrolizumab
4. Ado-trastuzumab emtansine