Immuno-Oncology:

New breakthrough of cancer treatment

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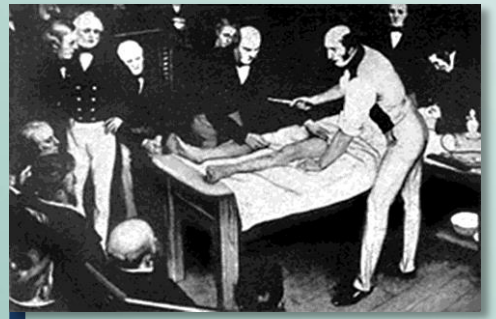
Overview

- **Despite developments to the core therapeutic modalities of surgery, radiotherapy, and chemo/targeted therapy, there remains room for improving survival, particularly for patients with advanced cancer[1–3]**
- **The immune system has a natural response to cancer, recognizing and eliminating tumor cells from the body throughout life[4]**
- **The ability to evade immune destruction is a defining characteristic of most cancers[5]**
- **I-O is an evolving treatment modality encompassing agents designed to harness the patient's own immune system to fight cancer, countering tumor immune escape mechanisms[6,7]**
- **I-O is being studied for its potential to provide long-term survival and become a new modality of treatment for multiple tumor types[7–9]**

I-O = immuno-oncology.

1. DeVita VT Jr, et al. *N Engl J Med*. 2012;366:2207–2214; 2. Kirkwood JM, et al. *CA Cancer J Clin*. 2012;62:309–335; 3. Surveillance, Epidemiology and End Results (SEER) Program. http://seer.cancer.gov; 4. Vesely MD, et al. *Annu Rev Immunol*. 2011;29:235–271; 5. Hanahan D, et al. *Cell*. 2011;144:646–674; 6. Finn OJ. *Ann Oncol*. 2012;23(suppl 8):viii6–viii9; 7. Eggermont AM. *Ann Oncol*. 2012;23(suppl 8):viii53–viii57; 8. Hodi FS, et al. *N Engl J Med.* 2010;363:711–723; 9. Kantoff PW, et al. *N Engl J Med*. 2010;363:411–422.

Evolution of Cancer Therapy: Core Treatment Modalities[1–3]

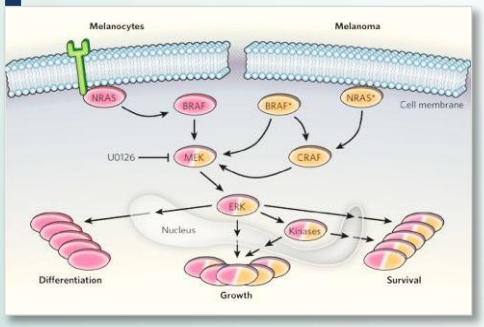


Surgery
1846

Chemotherapy
1946

Radiation Therapy
1901

Targeted Therapy
1997

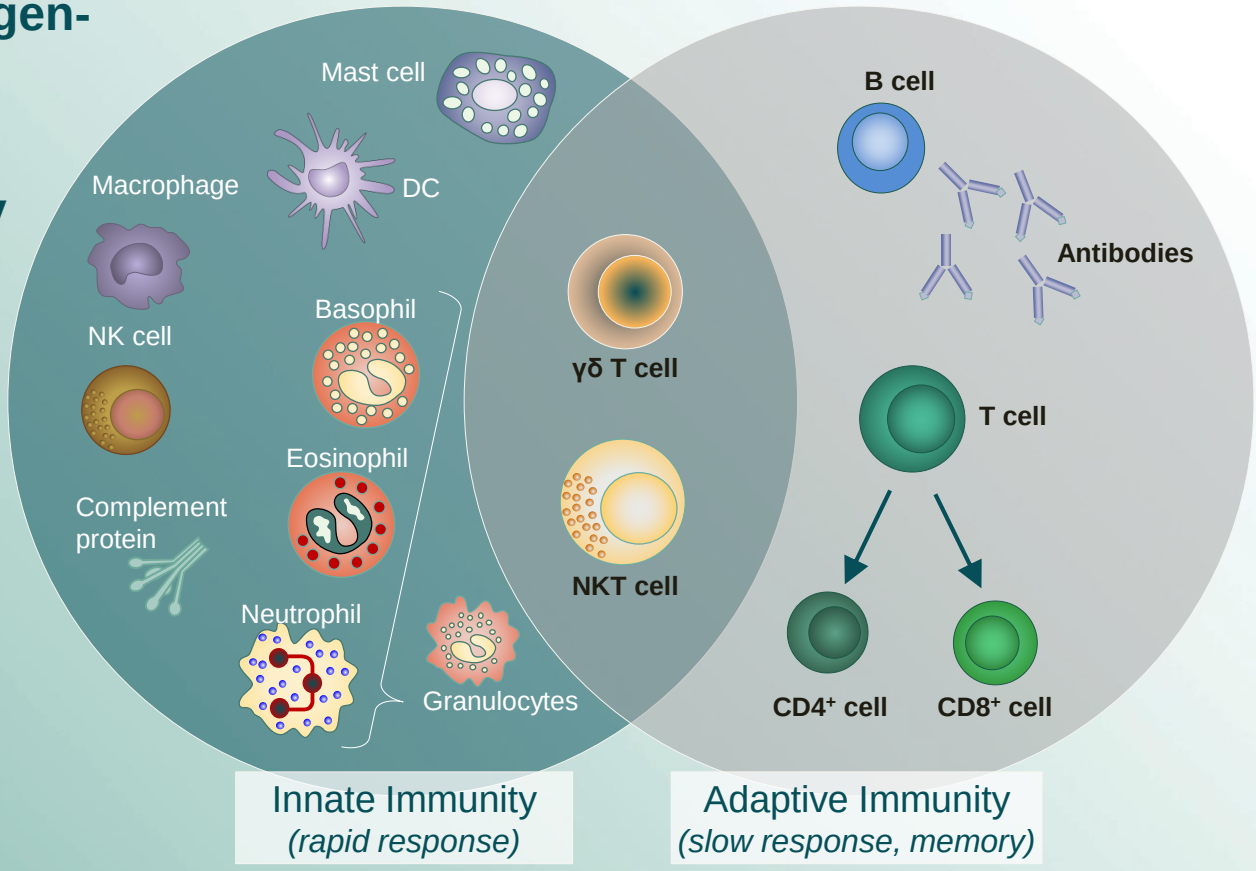


1. DeVita VT Jr, et al. *Cancer Res*. 2008;68:8643–8653; 2. American Cancer Society. http://www.cancer.org/cancer/cancerbasics/thehistoryofcancer/; 3. Ross JS, et al. *Am J Clin Pathol*. 2004;122:598–609.

The Immune System and Cancer

Cells of the Immune System

- **Innate immune system: involving proteins (chemokines and cytokines) and cells, is considered to be the first line of immune defense and does not generate an antigen-specific response[1,2]**
- **Adaptive immune system: mediated by B and T cells is highly specific and capable of generating an antigen-specific response[1,2]**
  - Induction requires presentation of antigens by cells of the innate immune system

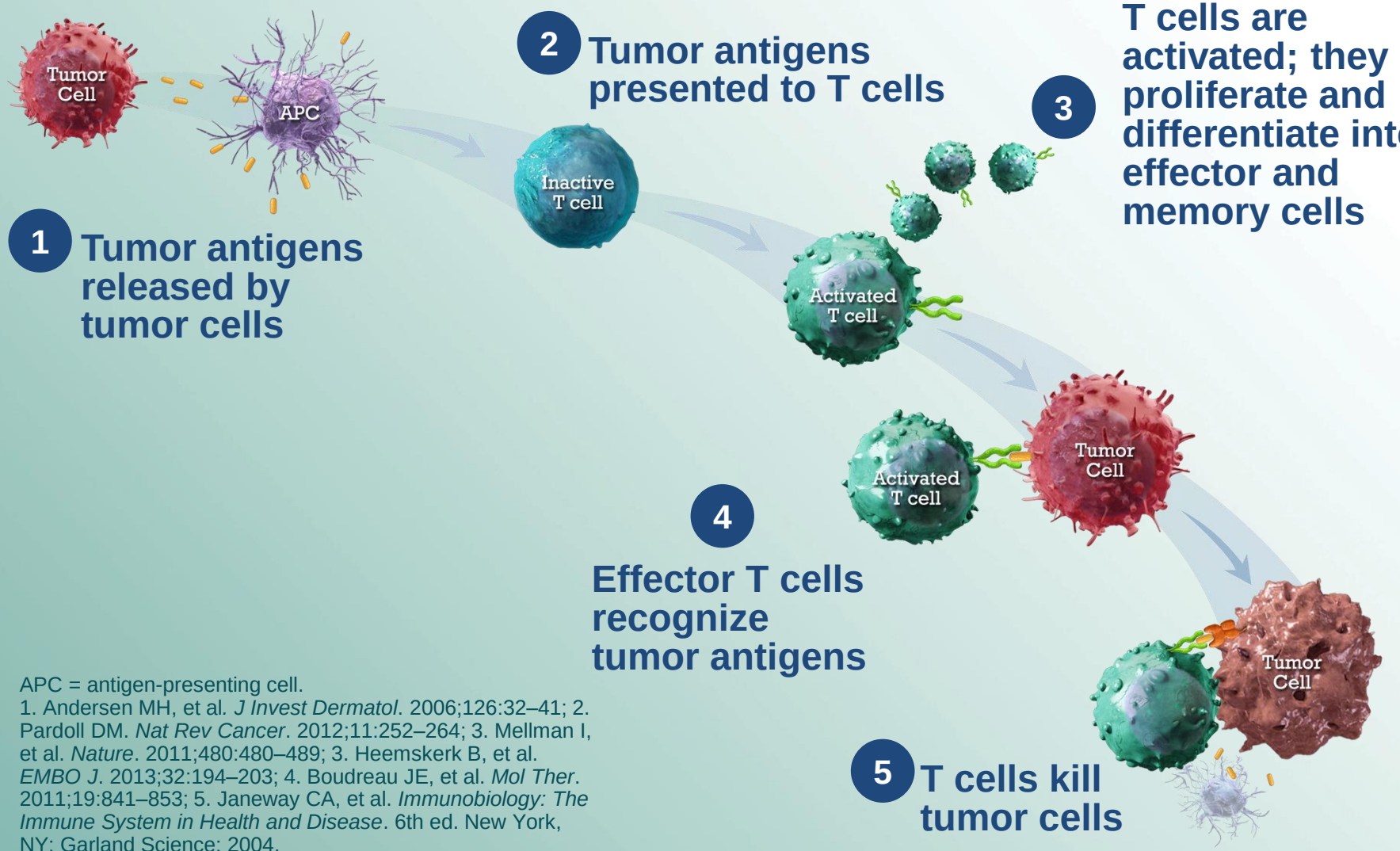


DC = dendritic cell; NK = natural killer.

1. Dranoff G. *Nat Rev Cancer*. 2004;4:11–22; 2. Janeway CA, et al. *Immunobiology: The Immune System in Health and Disease*. 6th ed. New York, NY: Garland Science; 2004.

Adapted from Dranoff G.[1]

The T-Cell Antitumor Response[1–6]

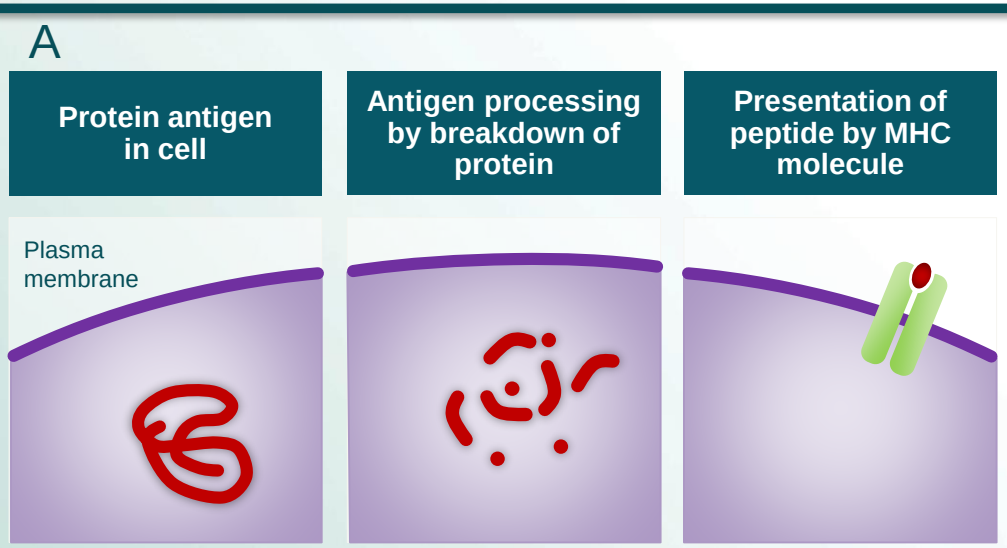


APC = antigen-presenting cell.

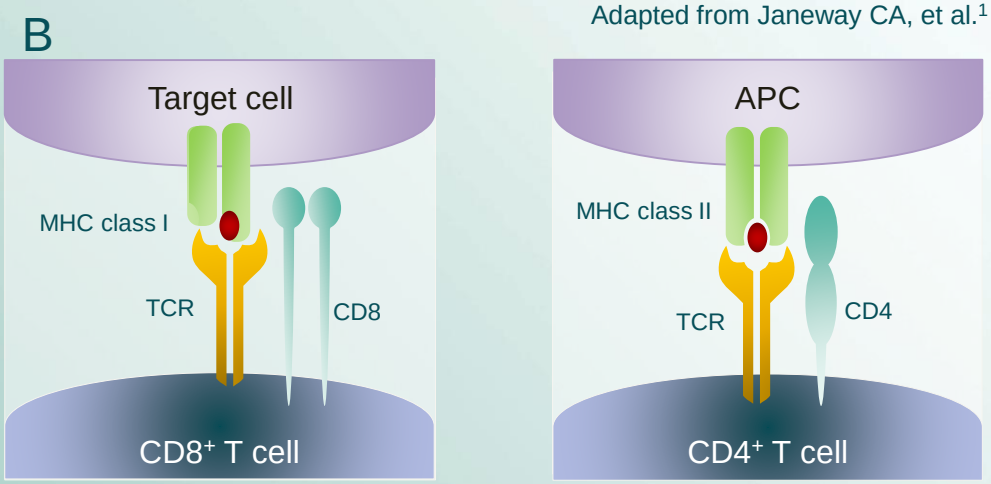
1. Andersen MH, et al. *J Invest Dermatol*. 2006;126:32–41; 2. Pardoll DM. *Nat Rev Cancer*. 2012;11:252–264; 3. Mellman I, et al. *Nature*. 2011;480:480–489; 3. Heemskerk B, et al. *EMBO J*. 2013;32:194–203; 4. Boudreau JE, et al. *Mol Ther*. 2011;19:841–853; 5. Janeway CA, et al. *Immunobiology: The Immune System in Health and Disease*. 6th ed. New York, NY: Garland Science; 2004.

Tumor Antigen Presentation to T cells

- **DCs, macrophages, and B cells are the most common "professional" APCs[1,2]**
- **T cells can only recognize an antigen when it is "presented" to them by an APC[1,2] (Figs A and B)**
  - Antigens are presented as peptide fragments in MHC[1] (Fig A)
  - Tumor cells that downregulate MHC may evade detection by the immune system and escape immune attack[2]
- **Antigen presentation is not required for antibody activity or initiating innate immunity[1,2]**



Adapted from Janeway CA, et al.[1]

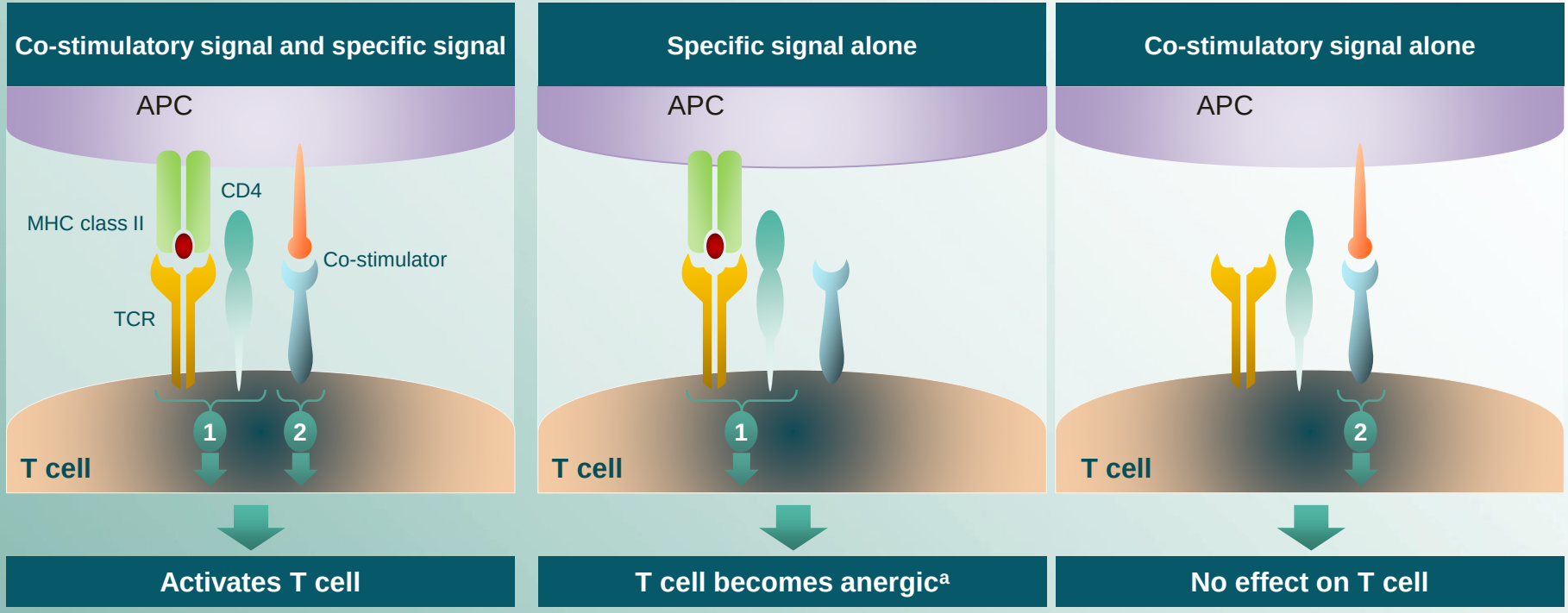


Adapted from Janeway CA, et al.[1]

1. Janeway CA, et al. *Immunobiology*. 2008; 2. Vesely MD, et al. *Ann Rev Immunol.* 2011;29:235–271.

Activation of Naïve T Cells

- T cells require multiple signals to become fully activated[1]
- In addition to antigen stimulation in the context of MHC molecules, positive co-stimulation is required[1]
- Co-stimulatory or activating receptors include CD28, CD137, CD40, and OX-40[2]

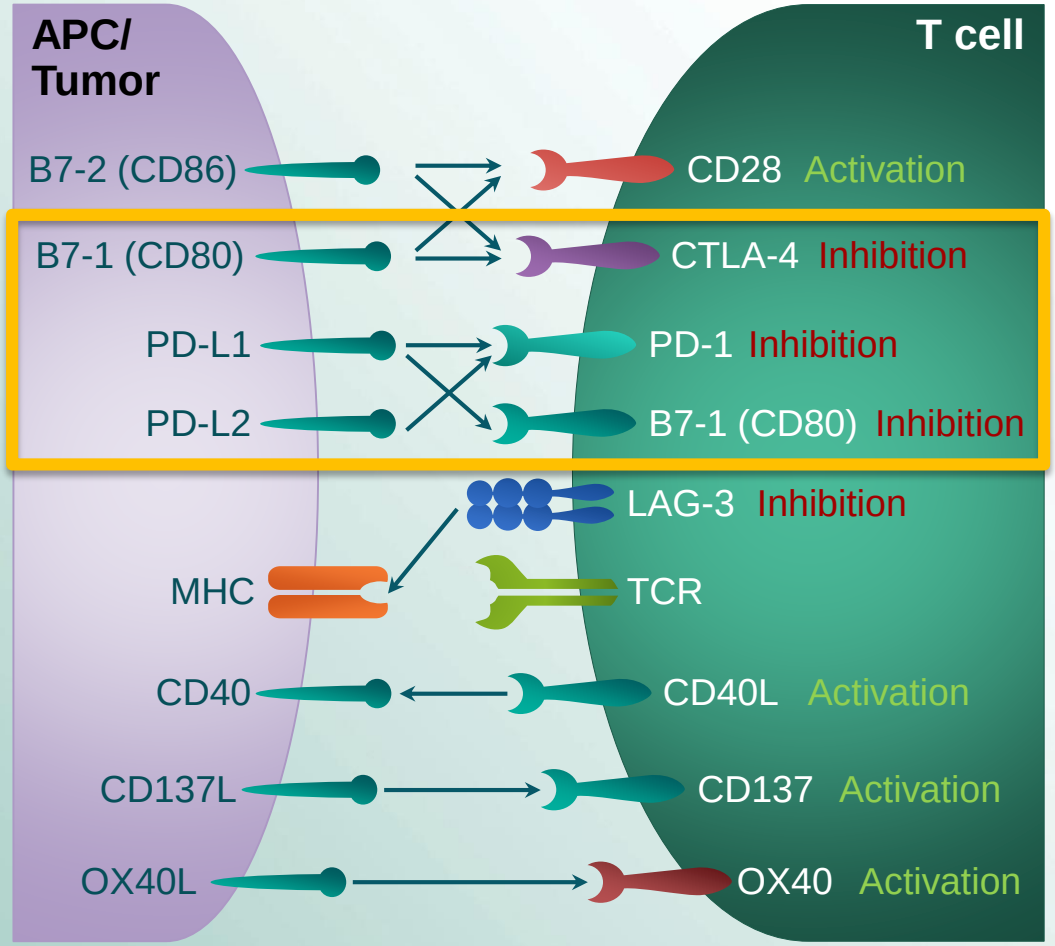


[a]Anergy describes a state of functional inactivation.

1. Janeway CA, et al. *Immunobiology*. 2008; 2. Pardoll DM. *Nat Rev Cancer.* 2012;12:252–264.

Regulation of T-Cell Activation: Balancing Activating and Inhibitory Signals

- **Immune checkpoints limit, or "check," an ongoing immune response**
- **Prevents damage to the body's healthy tissues**
  - Negative co-stimulation, also called "co-inhibition," helps shut down immune responses
  - PD-1, CTLA-4, and LAG-3 are examples of co-inhibitory "checkpoint" molecules
- **Amplitude and quality of a T-cell response is regulated by a balance of activating and inhibitory signals**



CTLA-4 = cytotoxic T-lymphocyte antigen-4; LAG-3 = lymphocyte activation gene-3; PD-1 = programmed death-1; PD-L1 = programmed death-ligand 1.

Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264.

Evidence of an Antitumor Immune Response in Many Types of Cancer

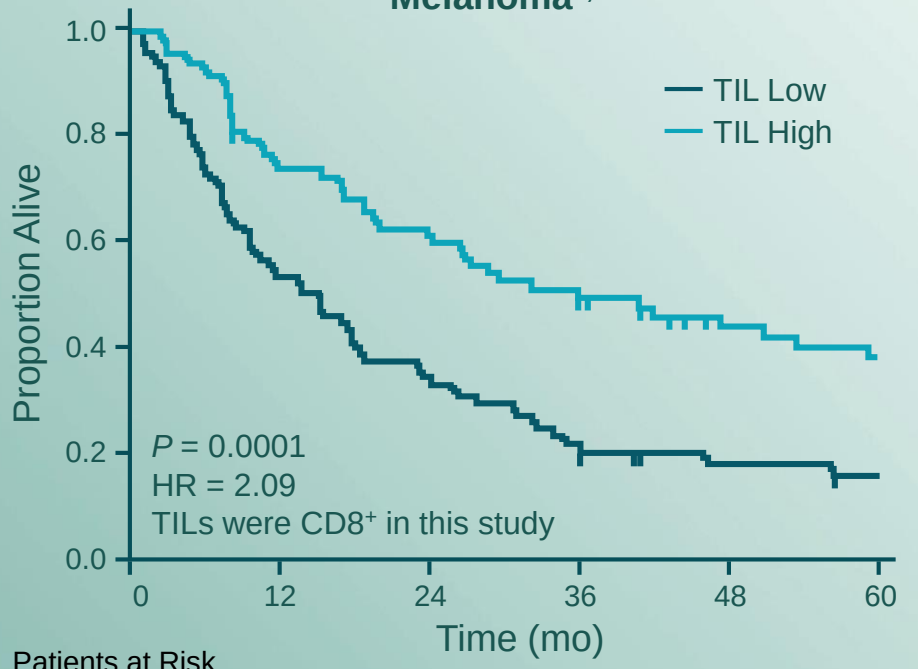
- **In the presence of cancer, there is evidence that the immune system has responded to the tumor:[1,2]**
  - Antibodies against tumor antigens[3]
  - Tumor-specific T cells[4]
  - TILs[5]
- **In some tumors, the infiltration of $CD8^+$ effector T cells correlates with improved prognosis and therapy outcome[6,7]**
- **Occasional reports of spontaneous regression of metastatic tumors proposed to be at least partly immune mediated[5,8]**

TILs = tumor-infiltrating lymphocytes.

1. Vesely MD, et al. *Annu Rev Immunol*. 2011;29:235–271; 2. Finn OJ. *Ann Oncol*. 2012;23(suppl 8):viii6–viii9; 3. Reuschenback M, et al. *Cancer Immunol Immunother.* 2009;58:1535–1544; 4. Godet Y, et al. *Clin Can Res.* 2012;18:2943–2953; 5. Mlecnik B, et al. *Cancer Metastasis Rev*. 2011;30:5–12; 6. Jochems C, et al. *Exp Biol Med* (Maywood). 2011;236:567–579; 7. Galon J, et al. *Science*. 2006;313:1960–1964; 8. Kalialis LV, et al. *Melanoma Res.* 2009;19:275–282.

Data Suggesting Tumor Infiltration of Cytotoxic (CD8$^+$) T Cells is Associated With Favorable Prognosis

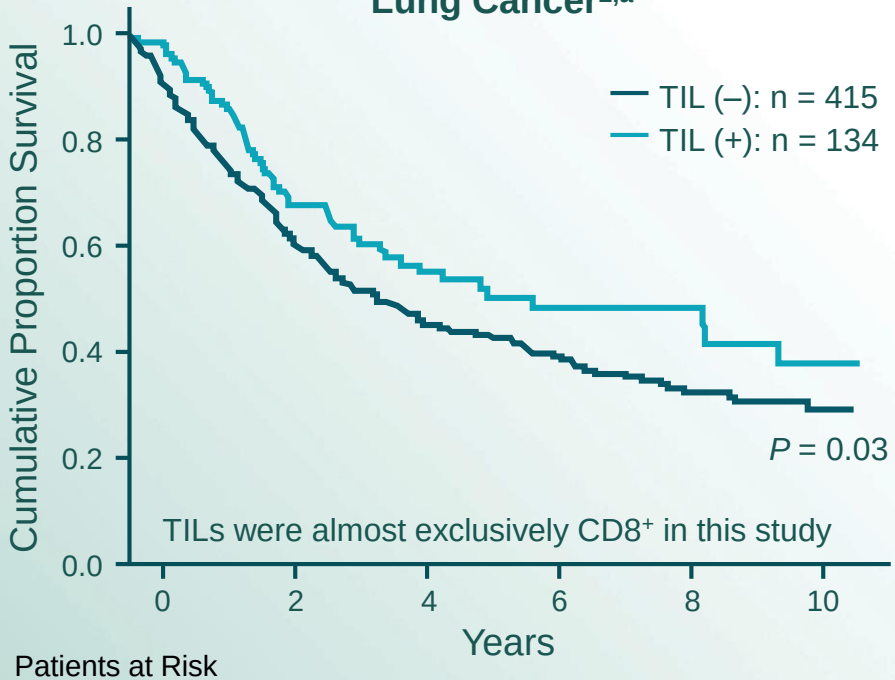
Survival in Metastatic Melanoma[1,a]



Patients at Risk

TIL (L)	72	53	43	32	23	20
TIL (H)	73	39	25	14	11	8

Survival in Squamous Cell Lung Cancer[2,a]



Patients at Risk

TIL (-)	415	228	150	77	49	31
TIL (+)	134	81	51	23	17	12

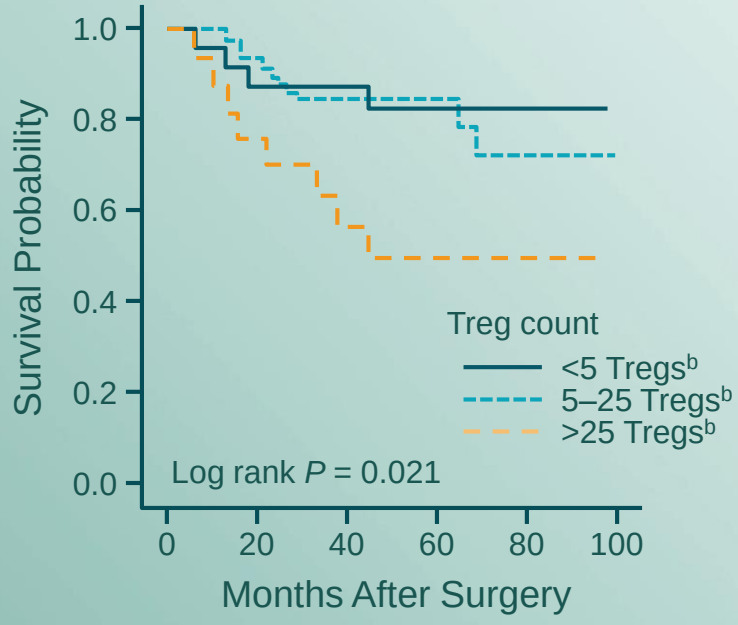
L = Low (lower than the median) numbers of CD8$^+$ cells
H = High (greater than the median) numbers of CD8$^+$ cells

[a]Analysis conducted using surgical specimens.

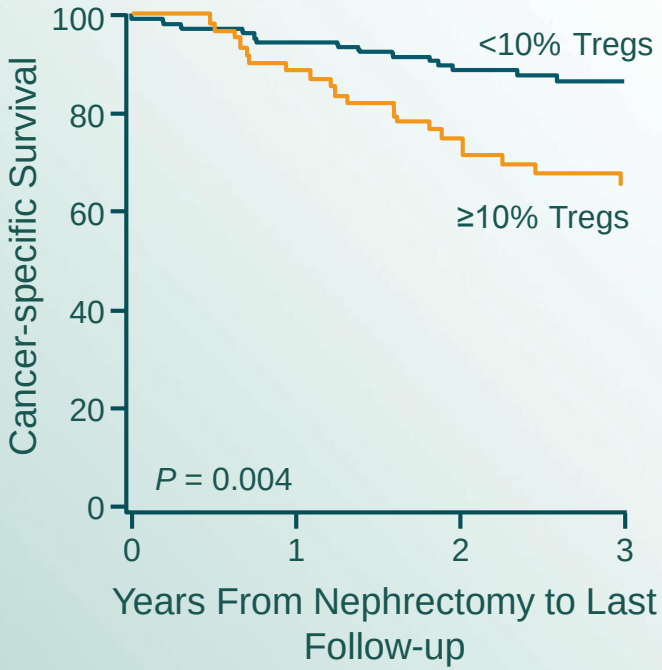
1. Erdag G, et al. *Cancer Res*. 2012;72:1070–1080; 2. Ruffini E, et al. *Ann Thorac Surg*. 2009;87:356–372.

Data Suggesting Tumor Infiltration of Regulatory T Cells is Associated With Unfavorable Prognosis

Survival in Early-Stage Non-Small Cell Lung Cancer[1,a]



Survival in Renal Cell Carcinoma[2,a]

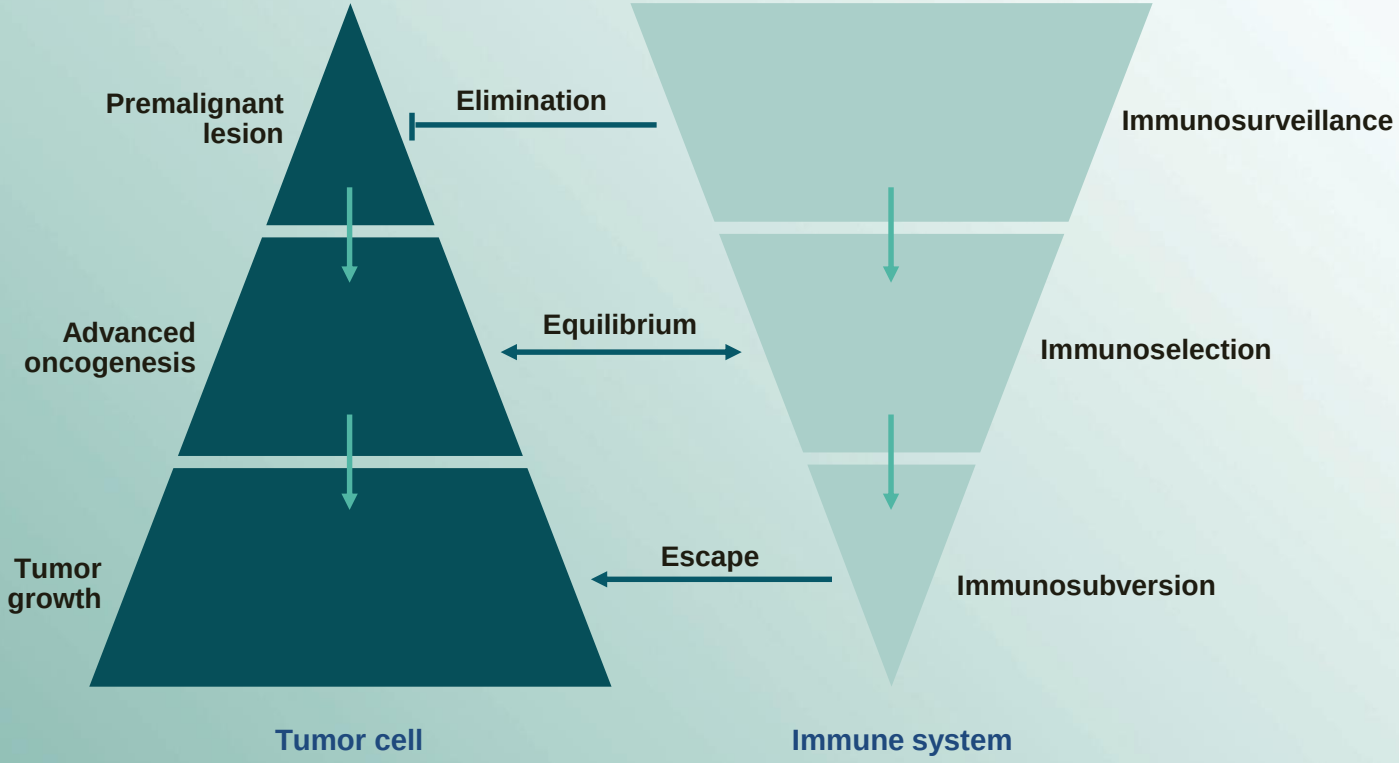


[a]Analysis conducted using surgical specimens.
[b]FOXP3+ cells.
Tregs = regulatory T cells.

1. Tao H, et al. *Lung Cancer.* 2012;75:95–101; 2. Siddiqui SA, et al. *Clin Cancer Res*. 2007;13:2075–2081.

How Tumors Escape the Immune System

- Numerous innate and adaptive cells and molecules participate in the recognition and destruction of cancer cells
- Tumor cells can avoid destruction through the outgrowth of cells not recognized by the immune system and/or adept at evading the immune response



Adapted from Zitvogel L, et al. *Nat Rev Immunol*. 2006;6:715–727.

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Immunoediting: The Role of the Immune System in Cancer Development and Progression

- **The three E's of cancer immunoediting describe the immune system's roles in protecting against tumor development and promoting tumor growth**

Elimination
Cancer Immunosurveillance

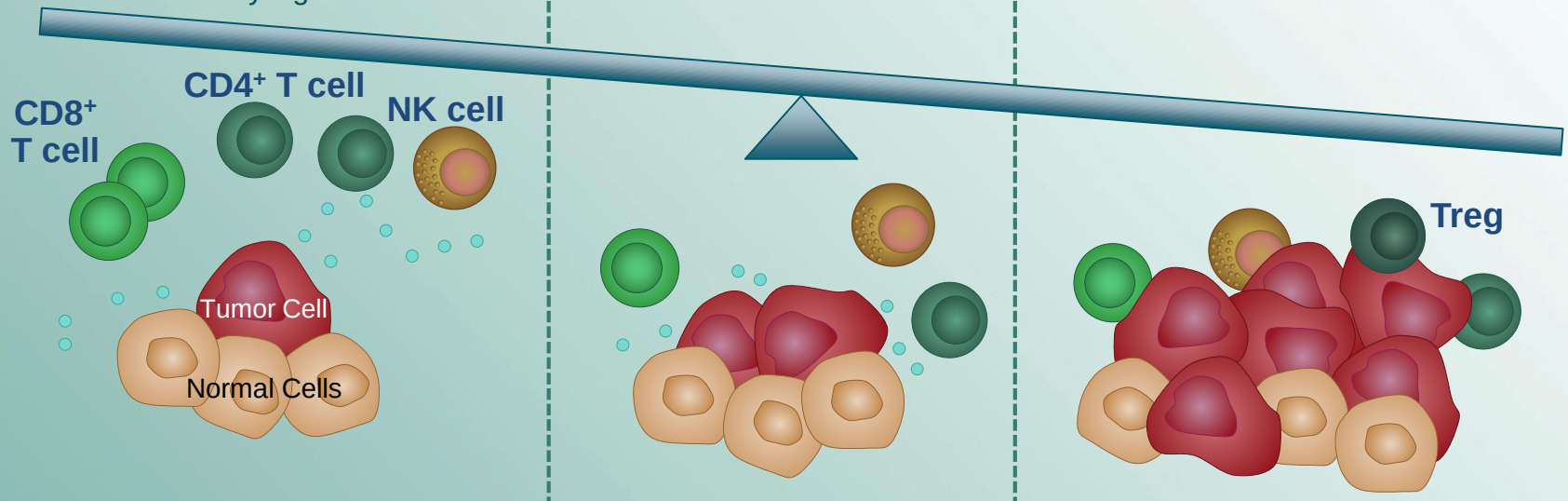
- Effective antigen processing/presentation
- Effective activation and function of effector cells
  - eg, T-cell activation without co-inhibitory signals

Equilibrium
Cancer Dormancy

- Genetic instability
- Tumor heterogeneity
- Immune selection

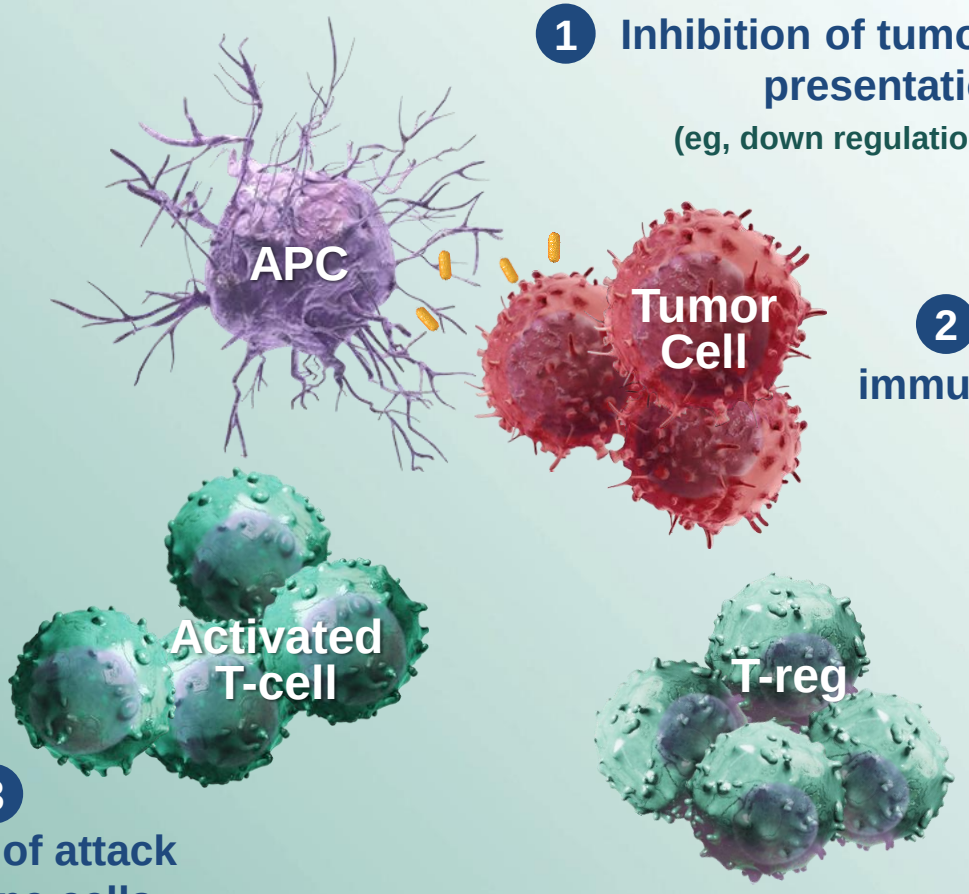
Escape
Cancer Progression

- Tumors may avoid elimination by the immune system through outgrowth tumor cells that can suppress, disrupt, or "escape" the immune system



Vesely MD, et al. *Ann Rev Immunol*. 2011;29:235–271.

Tumors Use Complex, Overlapping Mechanisms to Evade and Suppress the Immune System



1 **Inhibition of tumor antigen presentation**

(eg, down regulation of MHC I)

2 **Secretion of immunosuppressive factors**

(eg, TGF-B)

3 **Inhibition of attack by immune cells**

(eg, disruption of T-cell checkpoint pathways)

4 **Recruitment of immunosuppressive cell types**

(eg, Tregs)

1. Drake CG, et al. *Adv Immunol*. 2006;90:51–81; 2. Vesely MD, et al. *Annu Rev Immunol*. 2011;29:235–271.

Targeting the Immune System for Cancer Therapy

Advantages

- Acts throughout the body[1,2]
- Adapts to changing tumor characteristics[3,4]
- Potential to provide long-term memory and durable tumor control[1,2,4,5]
- Potential for activity in multiple tumor types[3]

Disadvantages

- Selective pressure from the immune system can result in tumors capable of evading the immune system[1]
- Tumors may use multiple mechanisms to evade the immune system[6]
- Potential for inflammatory reactions in normal tissue[7]

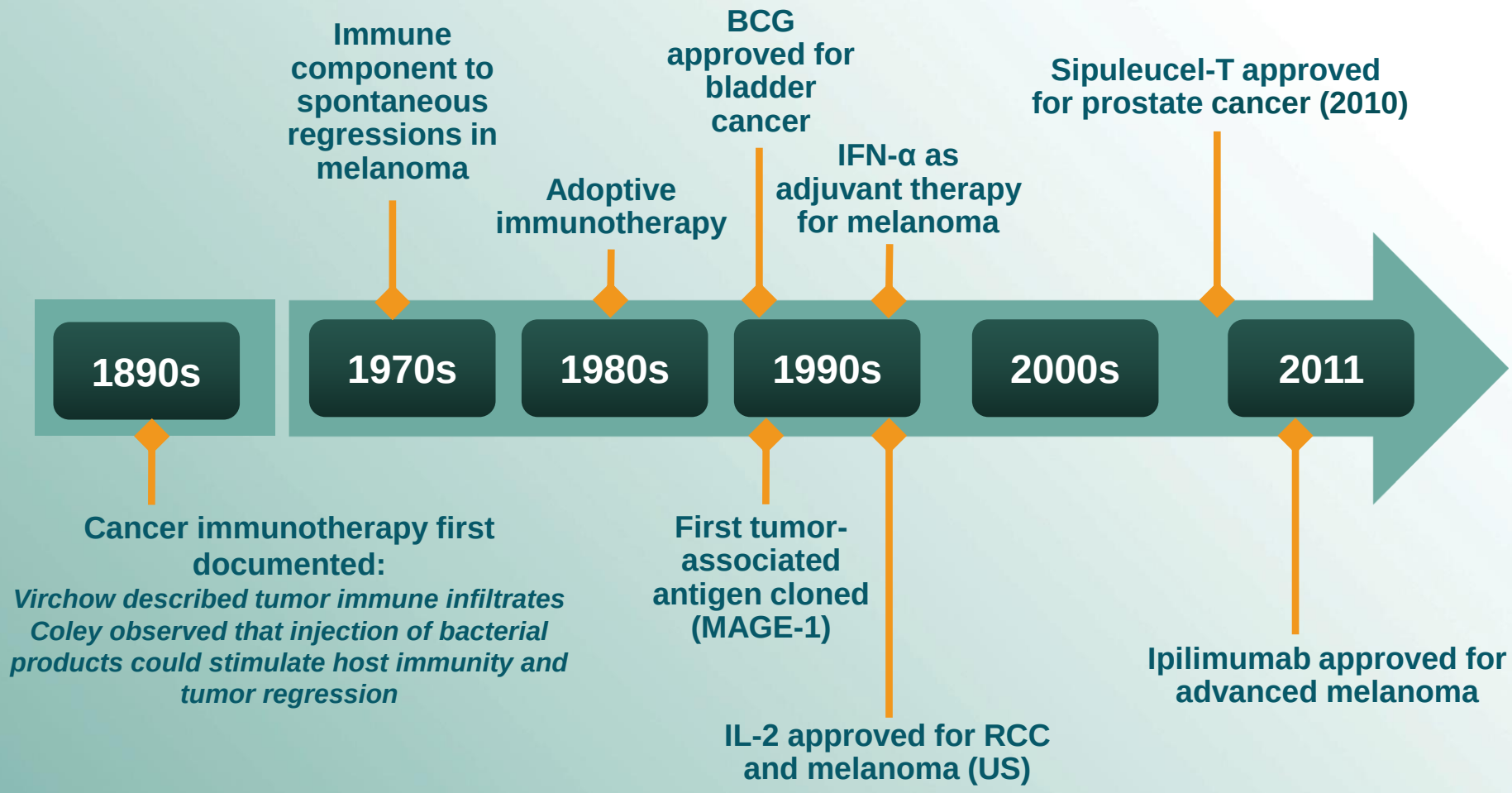
Harnessing the body's own natural defense/surveillance mechanisms may enable tumor control[4]

1. Vesely MD, et al. *Annu Rev Immunol*. 2011;29:235–271; 2. Janeway CA, et al. *Immunobiology: The Immune System in Health and Disease.* 5th ed. New York, NY: Garland Science; 2004; 3. Eggermont AM. *Ann Oncol*. 2012;23(suppl 8):viii53–viii57; 4. Finn OJ. *Ann Oncol*. 2012;23(suppl 8):viii6–viii9; 5. Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264; 6. Drake CG, et al. *Adv Immunol*. 2006;90:51–81; 7. Corsello SM, et al. *J Clin Endocrinol Metab*. 2013;98:1361–1375.

Immuno-Oncology

An Evolving Approach to Cancer Therapy

The History of Cancer Immunotherapy



BCG = Bacillus Calmette-Guérin; MAGE = melanoma-associated antigen.

1. Adapted from Kirkwood JM, et al. *Ca J Clin.* 2012;62:309–335; 2. George S, et al. *JNCCN.* 2011;9:1011–1018; 3. Garbe C, et al. *The Oncologist.* 2011;16:2–24; 4. Cheever MA, et al. *Clin Cancer Res.* 2011;17:3520–3526; 5. Kantoff PW, et al. *N Engl J Med.* 2010;363:411–422; 6. Mansh M. *Yale J Biol Med.* 2011;84:381–389; 7. Hodi FS, et al. *N Engl J Med.* 2010;363:711–723; 8. Aldousari S, et al. *CUAJ*. 2010;4:56–64.

Immuno-Oncology: An Evolving Approach to Cancer Therapy

- **Improved understanding of the immune system in cancer and how tumors can evade it has led to the identification of a range of novel therapeutic targets[1,2]**
- **I-O is an evolving treatment modality that includes active immunotherapies that are designed to target and harness the patient's own immune system directly to fight cancer[1,2]**
  - Designed to leverage the unique properties of the immune system (specificity, adaptability, and memory)
  - Distinct from surgery, radiotherapy, and cytotoxic/targeted therapeutic modalities which target the tumor or tumor blood supply
  - Goal is to shift the balance in favor of an immune response against the tumor, allowing tumor eradication or long-term suppression of tumor growth, and the generation of immunological memory
- **Investigational I-O agents are being studied for their potential to provide durable, long-term survival for patients with various solid or hematologic malignancies[1,2]**

1. Finn OJ, et al. *Ann Oncol*. 2012;23(suppl 8):viii6–viii9; 2. Eggermont A, et al. *Ann Oncol*. 2012;23(suppl 8):viii53–viii57.

Numerous Potential Strategies Could Be Explored to Overcome Tumor Immune Evasion Mechanisms[1–5]

Examples include:

Reversing the Inhibition of Adaptive Immunity (blocking T-cell checkpoint pathways)

- Inhibiting the CTLA-4 checkpoint molecule[a]
- Inhibiting the interaction between PD-1 checkpoint and its ligands[a]
- Inhibiting the LAG-3 checkpoint molecule

Switching on Adaptive Immunity (promoting T-cell activation pathways)

- Promoting CD137 signaling
- Enhancing OX-40 signaling
- CD40 activation
- Systemic recombinant IL-21 administration (range of effects including enhancing activation and cytolytic activity of NK and $CD8^+$ T cells)

Improving the Function of Innate Immune Cells

- Manipulating the activation of KIRs
- Stimulating NK cells to increase ADCC against antibody-coated tumor cell

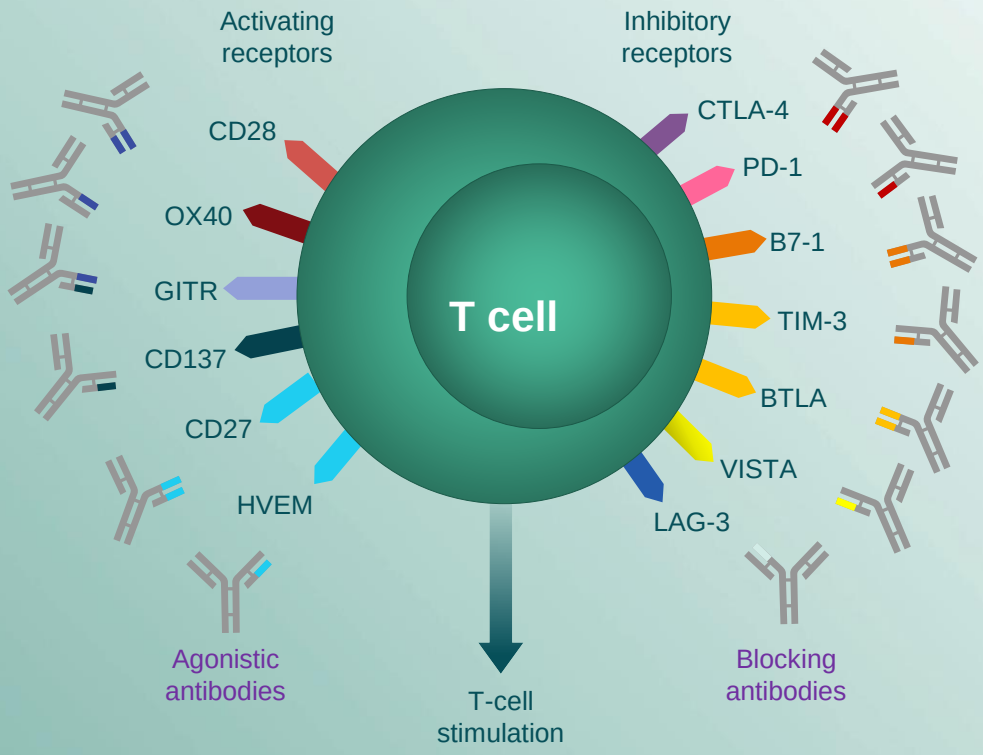
Switching on the Immune System (potentiating immune-cell effector function)

- IDO inhibition
- Systemic recombinant IL-21 administration (range of effects including enhancing activation and cytolytic activity of NK and $CD8^+$ T cells)
- Systemic IL-2 or IFN-α administration[a]

[a]Approaches where there are approved compounds or investigational compounds being studied in phase III trials.

1. Mellman I, et al. *Nature.* 2011:480;481–489; 2. Pardoll DM. *Nat Rev Cancer.* 2012;12:252–264; 3. Kirkwood JM, et al. *Cancer J Clin*. 2012;62:309–335; 4. Houot R, et al. *Oncoimmunology.* 2012;1:957–958; 5. Waggie KS, et al. *Int J Toxicol.* 2012;31:303–316.

Selected T-Cell Checkpoints: Targets for Active Immunotherapy[1,2,a]



- T-cell responses are regulated though a complex balance of inhibitory ("checkpoint") and activating signals
- Tumors can dysregulate checkpoint and activating pathways, and consequently, the immune response
- Targeting checkpoint and activating pathways is an evolving approach to active immunotherapy, designed to promote an immune response

[a]The image shows only a selection of the receptors/pathways involved.

1. Adapted from Mellman I, et al. *Nature*. 2011:480;481–489; 2. Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264.

Active Immunotherapies in Development Designed to Target T-Cell Inhibitory Checkpoint Pathways[a]

Pathway	Name	Approach	Company	Highest Development Phase/Tumor Type
CTLA-4	Ipilimumab	Anti-CTLA-4 mAb	Bristol-Myers Squibb	Approved[b]/melanoma
	Tremelimumab	Anti-CTLA-4 mAb	Medimmune/AstraZeneca; Pfizer	Phase II/malignant mesothelioma
PD-1	Nivolumab	Anti-PD-1 mAb	Bristol-Myers Squibb	Phase III/melanoma, NSCLC, RCC
	Pembrolizumab (MK-3475)	Anti-PD-1 mAb	Merck & Co	Phase III/NSCLC, melanoma
	MPDL3280A (RG7446)	Anti-PD-L1 mAb	Genentech/Roche	Phase III/NSCLC
	Pidilizumab (CT-011)	Anti-PD-1 mAb	CureTech	Phase II/FL, prostate, pancreatic
	AMP-224	Recombinant PD-L2-Fc fusion protein	GlaxoSmithKline	Phase I/solid tumors
	rHIgM12B7	Anti-PD-L2 mAb	Mayo Clinic	Phase I/melanoma
LAG-3	IMP321	Soluble recombinant -3 protein	Immuntep SA	Phase II/melanoma
	BMS-986016	Anti-LAG-3 mAb	Bristol-Myers Squibb	Phase I/solid tumors

[a]Selected agents under evaluation in clinical trials for solid tumors are shown.
[b]Unresectable or metastatic melanoma.
FL = follicular lymphoma.
www.clinicaltrials.gov accessed 14 November 2013.

Active Immunotherapies in Development Designed to Target T-Cell Activating Pathways[a]

Pathway	Name	Approach	Company	Highest Development Phase/Tumor Type
CD137	Urelumab	Agonist anti-CD137 mAb	Bristol-Myers Squibb	Phase I/solid tumors, B-cell NHL, CLL
	PF-05082566	Agonist anti-CD137 mAb	Pfizer	Phase I/NHL
OX-40	Anti-OX-40	Agonist anti-OX-40 mAb	AgonOx	Phase II/breast, prostate, solid tumors
GITR	TRX518	Anti-GITR mAb	GITR Inc.	Phase I/solid tumors
CD40	CP-870-893	Agonist anti-CD40 mAb	Pfizer	Phase I/melanoma, pancreatic
	ChiLob 7/4	Agonist anti-CD40 mAb	Cancer Research UK	Phase I/advanced malignancies
CD27	CDX-1127	Agonist anti-CD27 mAb	Celldex Therapeutics	Phase I/advanced malignancies

[a]Selected agents under evaluation in clinical trials for solid tumors are shown.
CLL = chronic lymphocytic leukemia; NHL = non-Hodgkin's lymphoma.
www.clinicaltrials.gov accessed 14 November 2013.

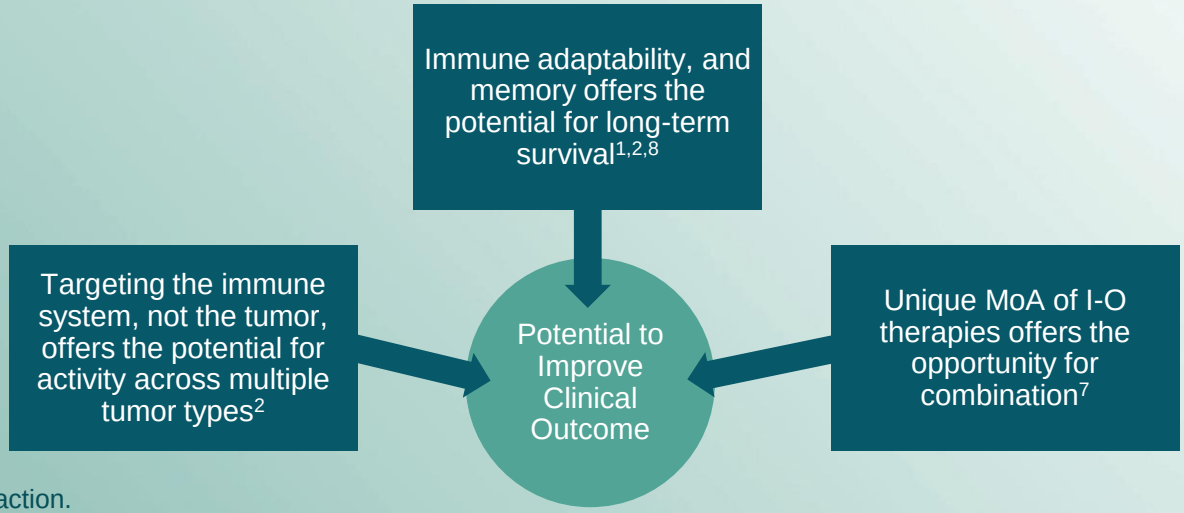
Active Immunotherapies in Development Designed to Enhance Immune Cell Function[a]

Pathway/ Target	Name	Approach	Company	Highest Development Phase/Tumor Type
IL-21	Denenicokin	Recombinant human IL-21	Bristol-Myers Squibb	Phase II/melanoma
IL-15	rhIL-15	Recombinant human IL-15	National Cancer Institute	Phase I/advanced malignancies
NK cells	Lirilumab	Anti-KIR mAb	Bristol-Myers Squibb	Phase II/solid tumors
IDO	INCB024360	IDO inhibitor	Incyte	Phase II/melanoma, EOC, PPC, FTC
	Indoximod	IDO inhibitor	NewLink Genetics Corporation	Phase II/breast, prostate

[a]Selected agents under evaluation in clinical trials for solid tumors are shown; note does not include vaccine approaches.
EOC = epithelial ovarian cancer; FT = fallopian tube cancer; PPC = primary peritoneal cancer.
www.clinicaltrials.gov accessed 14 November 2013..

The Potential of Immuno-Oncology Therapies

- **Based on the natural capabilities of the immune system, I-O therapies are being investigated for their potential to provide long-term survival in patients with various solid or hematologic malignancies[1–4]**
  - Data from clinical trials with I-O therapies in solid tumors, particularly ipilimumab in advanced melanoma, provide supportive data[3,5,6]
- **Combining I-O therapies with different MOA, or with current/future standards of care, could potentially lead to enhanced efficacy[7]**

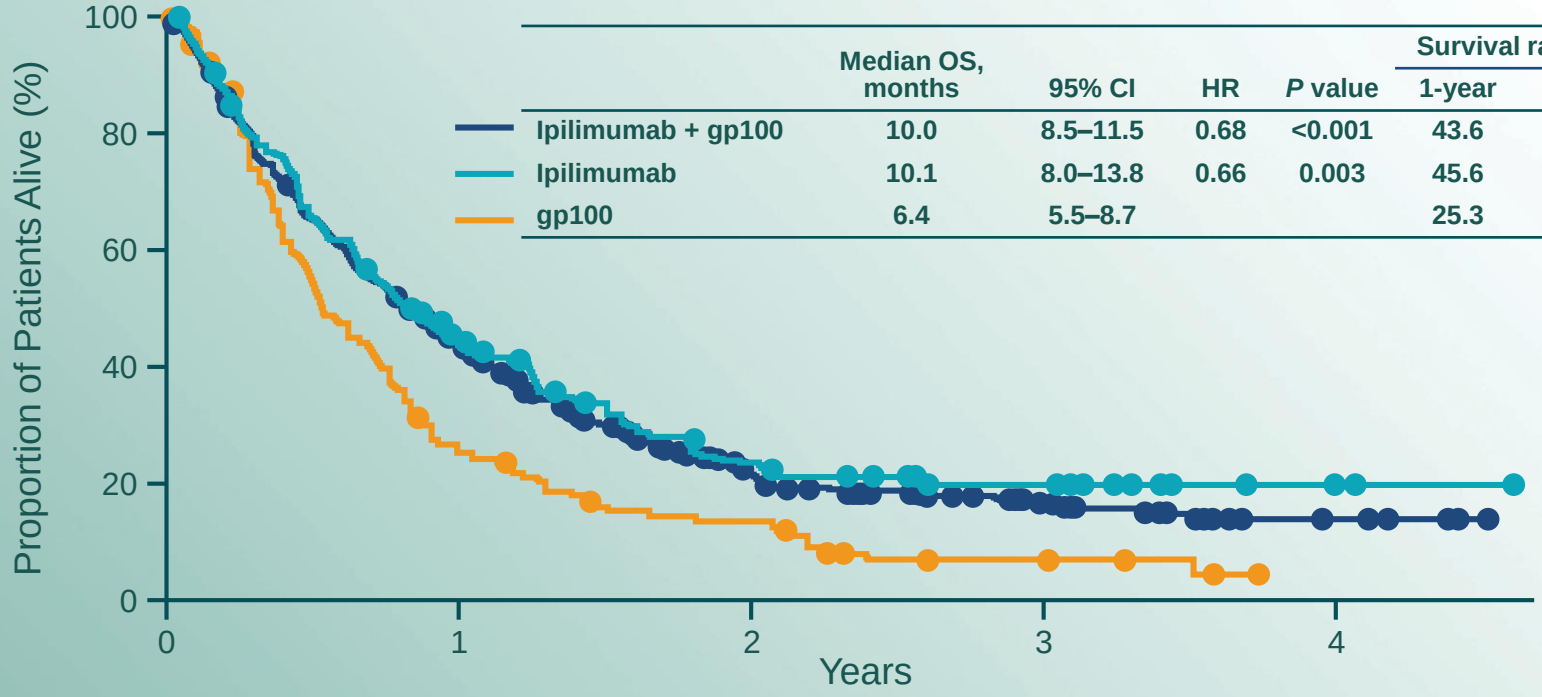


MOA = mechanism of action.

1. Finn OJ. *Ann Oncol*. 2012;23(suppl 8):viii6–viii9; 2. Eggermont AM. *Ann Oncol*. 2012;23(suppl 8):viii53–viii57; 3. Hodi FS, et al. *N Engl J Med.* 2010;363:711–723; 4. Kantoff PW, et al. *N Engl J Med*. 2010;363:411–422; 5. Brahmer JR, et al. IASCL 15th WCLC 2013;abstract MO18.03; 6. Hamid O, et al. *N Eng J Med* 2013;369:134–144; 7. Drake CG. *Ann Oncol*. 2012;23(suppl 8):viii41–viii46; 8. Janeway CA, et al. *Immunobiology*. 2008.

T-Cell Checkpoint Pathway Inhibition Using Ipilimumab in Patients With Melanoma

- **Ipilimumab was the first therapy for unresectable or metastatic melanoma to improve OS in a phase III trial[1]**



	Median OS, months	95% CI	HR	*P* value	Survival rate (%) 1-year	2-year
Ipilimumab + gp100	10.0	8.5–11.5	0.68	<0.001	43.6	21.6
Ipilimumab	10.1	8.0–13.8	0.66	0.003	45.6	23.5
gp100	6.4	5.5–8.7			25.3	13.7

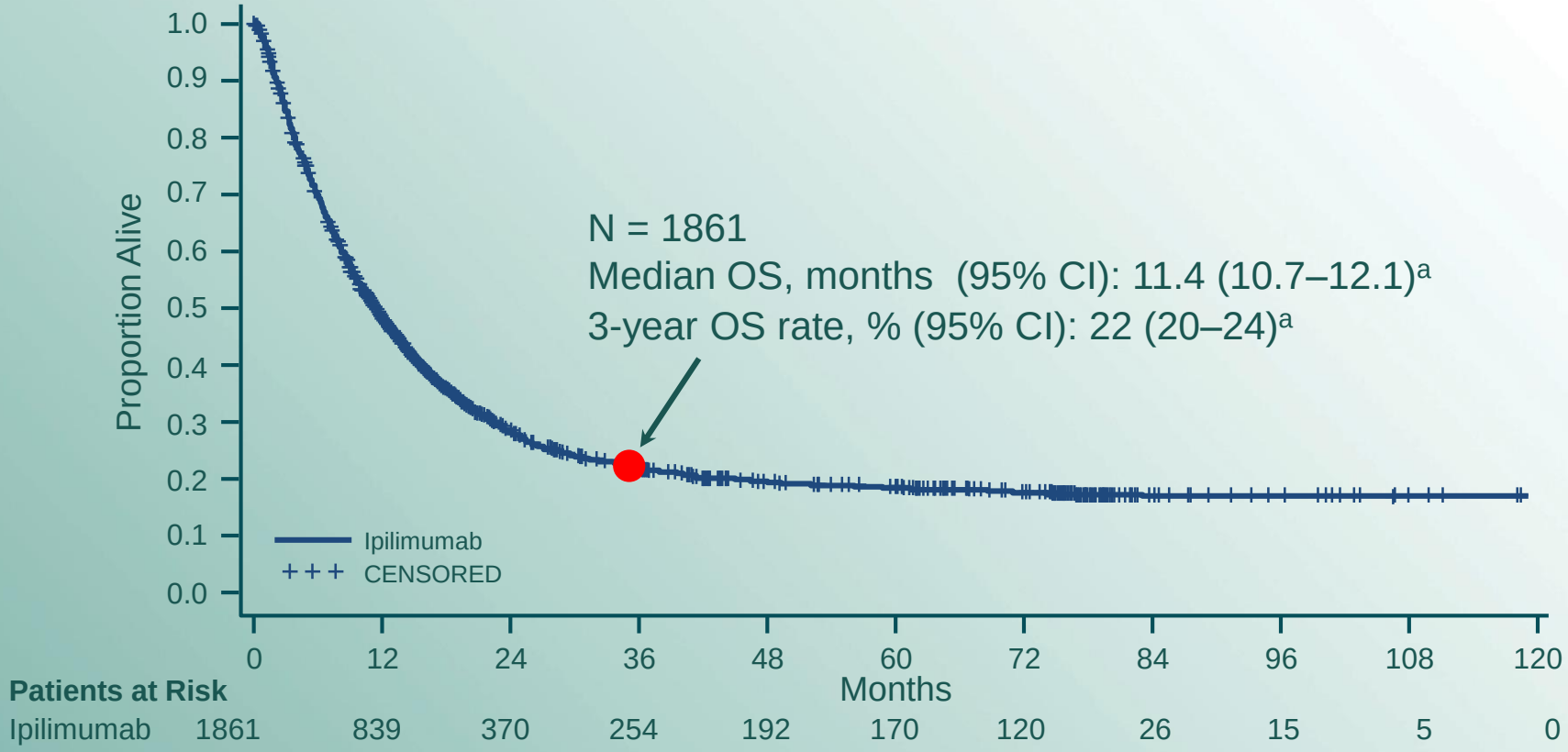
- **In clinical trials, most AEs associated with ipilimumab were immune related and were managed using ipilimumab-specific treatment algorithms[2]**
- **The most frequently reported irAEs associated with ipilimumab monotherapy (≥10%, all grades) in a phase III trial were: diarrhea (28%), pruritus (24%), and rash (19%)[1]**

AEs = adverse events; irAEs = immune-related adverse events. .

1. Adapted from Hodi FS, et al. *N Engl J Med.* 2010;363:711–723; 2. Data on file; Bristol-Myers-Squibb Company, Princeton, NJ.

T-Cell Checkpoint Pathway Inhibition Using Ipilimumab: Pooled OS Data From Melanoma Patients

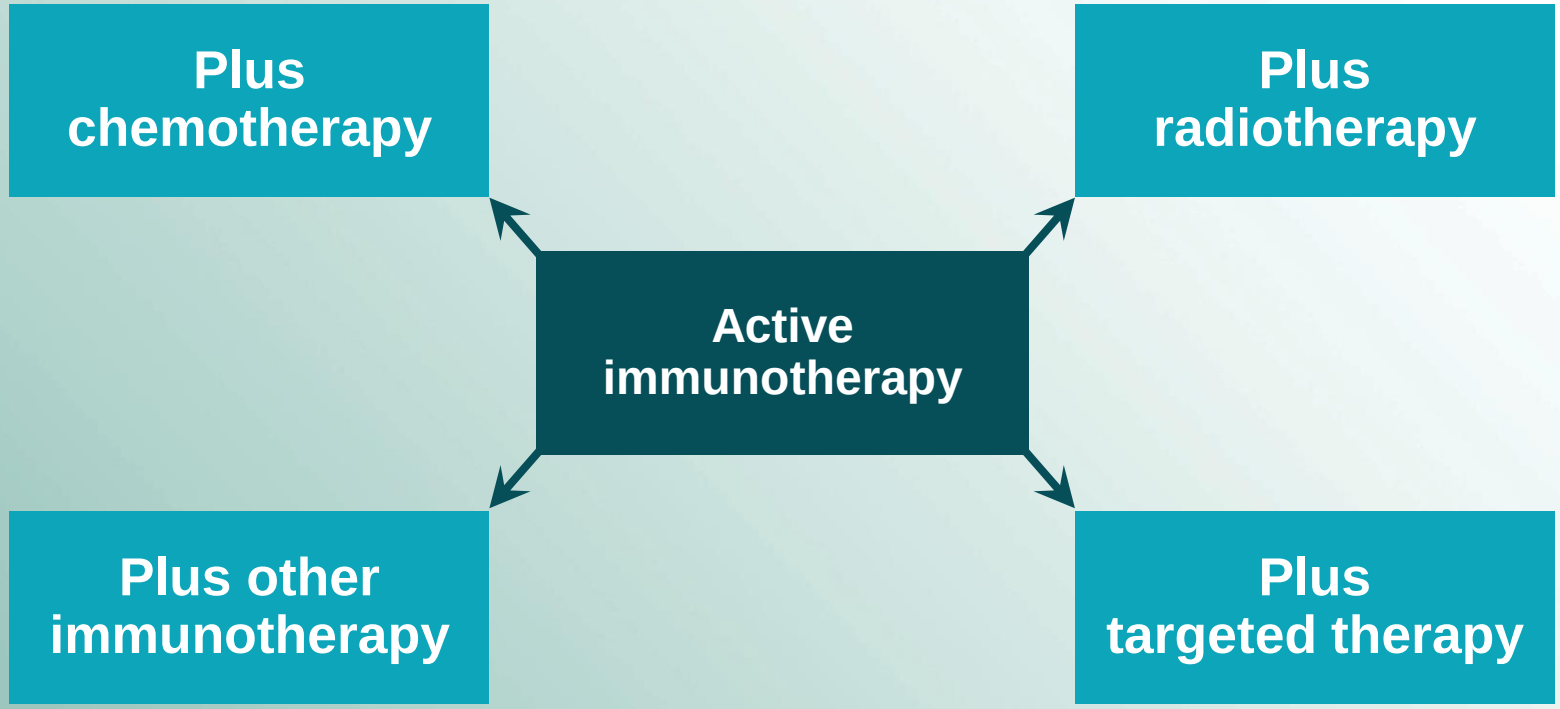
- **In a pooled analysis of 12 studies, an OS plateau starts at approximately 3 years with follow-up of up to 10 years in some patients**



[a]Ipilimumab was given at different doses and lines of therapy, and using different schedules across the 12 studies.

Schadendorf D, et al. ECC Congress. 2013 Abs 24LBA.

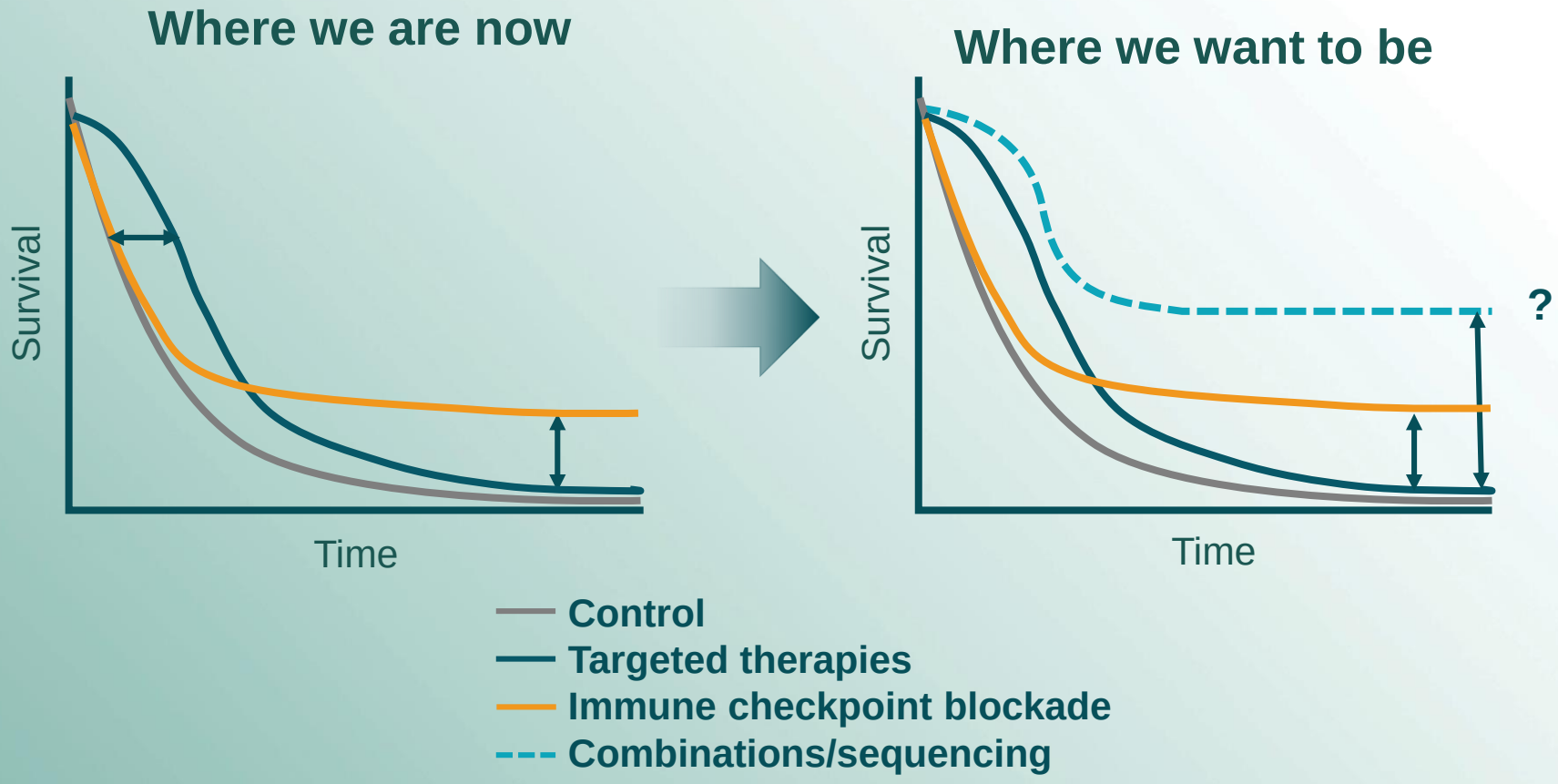
Experimental Approaches to Build on Active Immunotherapies to Maximize Clinical Benefit



- **Research and development will continue to inform future strategies, including new targets and rational drug combinations and sequencing**

1. Drake CG. *Ann Oncol*. 2012;23(suppl 8):viii41–viii46; 2. Hannani D, et al. *Cancer J.* 2011;17:351–358; 3. Ménard C, et al. *Cancer Immunol Immunother*. 2008;57:1579–1587; 4. Ribas A, et al. *Curr Opin Immunol*. 2013:25:291–296.

Hypothetical Effect of Targeting Distinct and Potentially Complementary Immune Evasion Pathways: Advanced Melanoma

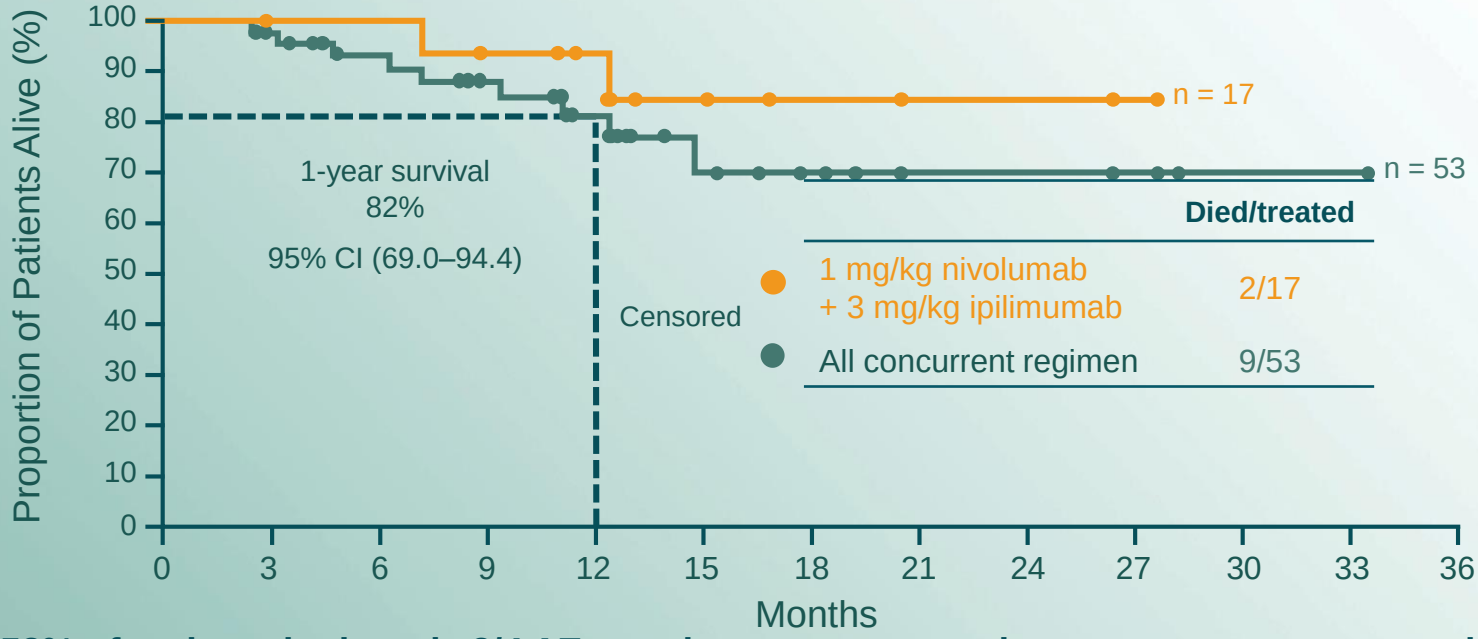


Hypothetical slide illustrating a scientific concept, and is beyond data available to date. These charts are not intended to predict what may actually be observed in clinical studies.

1. Adapted from Ribas A, presented at WCM, 2013; 2. Ribas A, et al. *Clin Cancer Res.* 2012;18:336–341; 3. Drake CG. *Ann Oncol*. 2012;23(suppl 8):viii41–viii46.

Studying the Clinical Effect of Targeting Distinct and Potentially Complementary Immune Evasion Pathways: Anti-PD-1 + Anti-CTLA-4

- **Clinical activity of nivolumab[a] plus ipilimumab on a concurrent or sequenced regimen in a phase I trial in patients with advanced melanoma[1]**



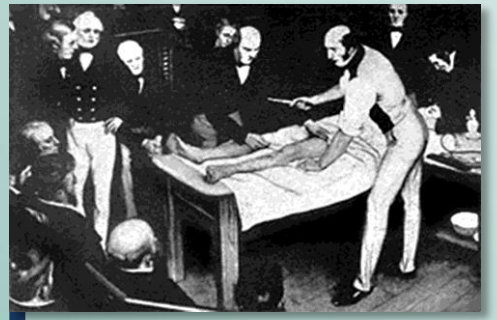
- **53% of patients had grade 3/4 AEs on the concurrent regimen; most were manageable using standard protocols[1]**
- **With ~13 months of follow-up, 90% of patients continue to respond[1]**
- **Historical 1-year survival rates with ipilimumab and nivolumab monotherapy in patients with advanced melanoma are 45.6% (phase III)[2] and 62% (phase I), respectively[3,b]**

[a]Investigational compound.

[b]Data from separate, non-comparative trials; use cross-trial comparisons with caution in the absence data from a randomized, comparative trial.

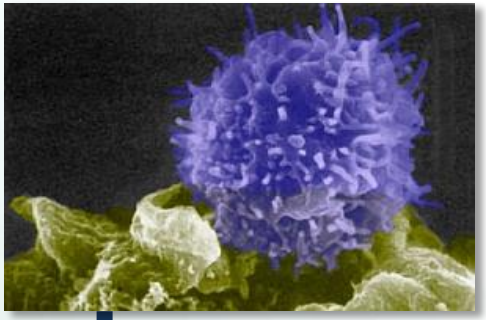
1. Adapted from Wolchok J, et al. Presented at ASCO 2013:oral presentation 9012; 2. Hodi FS, et al. *N Engl J Med.* 2010;363:711–723; 3. Sznol M, et al. Presented at ASCO 2013:oral presentation CRA9006.

Immuno-Oncology is Being Studied for its Potential to Become a New Treatment Modality for Cancer



Surgery
1846

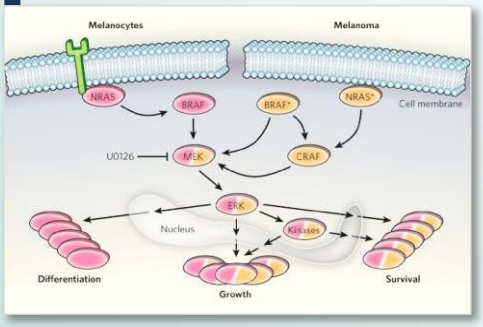
Chemotherapy
1946



Immuno-Oncology
2011

Radiation Therapy
1901

Targeted Therapy
1997



1. DeVita VT Jr, et al. *Cancer Res*. 2008;68:8643–8653; 2. American Cancer Society. http://www.cancer.org/cancer/cancerbasics/thehistoryofcancer/; 3. Hodi FS, et al. *N Engl J Med.* 2010;363:711–723; 4. Sznol M, et al. Presented at ASCO 2013: oral presentation; 5. Kantoff PW, et al. *N Engl J Med*. 2010;363:411–422; 6. Finn OJ. *Ann Oncol*. 2012;23(suppl 8):viii6–viii9.

Clinical Considerations and Future Directions

Tolerability Considerations With I-O Therapy

- **Therapies designed to enhance the patient's immune response against the tumor can result in a novel spectrum of AEs arising from the activation of the immune system[1]**
  - Termed immune-mediated adverse reactions
- **Immune-mediated adverse reactions may be unfamiliar to clinicians[1,2]**
- **Immune-mediated adverse reactions can be serious and potentially fatal[1,2]**
- **Require prompt recognition and treatment[1]**
- **Require education of the patient and healthcare team[3]**

1. Postow M, et al. *Cancer J.* 2012;18:152–159; 2. Amos SM, et al. *Blood.* 2011;118:499–509; 3. Ledezma B, et al. *Cancer Manag Res*. 2014;6:5–14.

Tolerability of Oncology Therapies

Chemotherapy
Target: rapidly dividing tumor and normal cells
AEs: diverse due to non-specific nature of therapy

Targeted therapies
Target: specific molecules involved in tumor growth and progression
AEs: reflect targeted nature

I-O therapies
Target: immune system
AEs: unique events can occur as a result of immune-system activity

Different spectrum of AEs with each modality

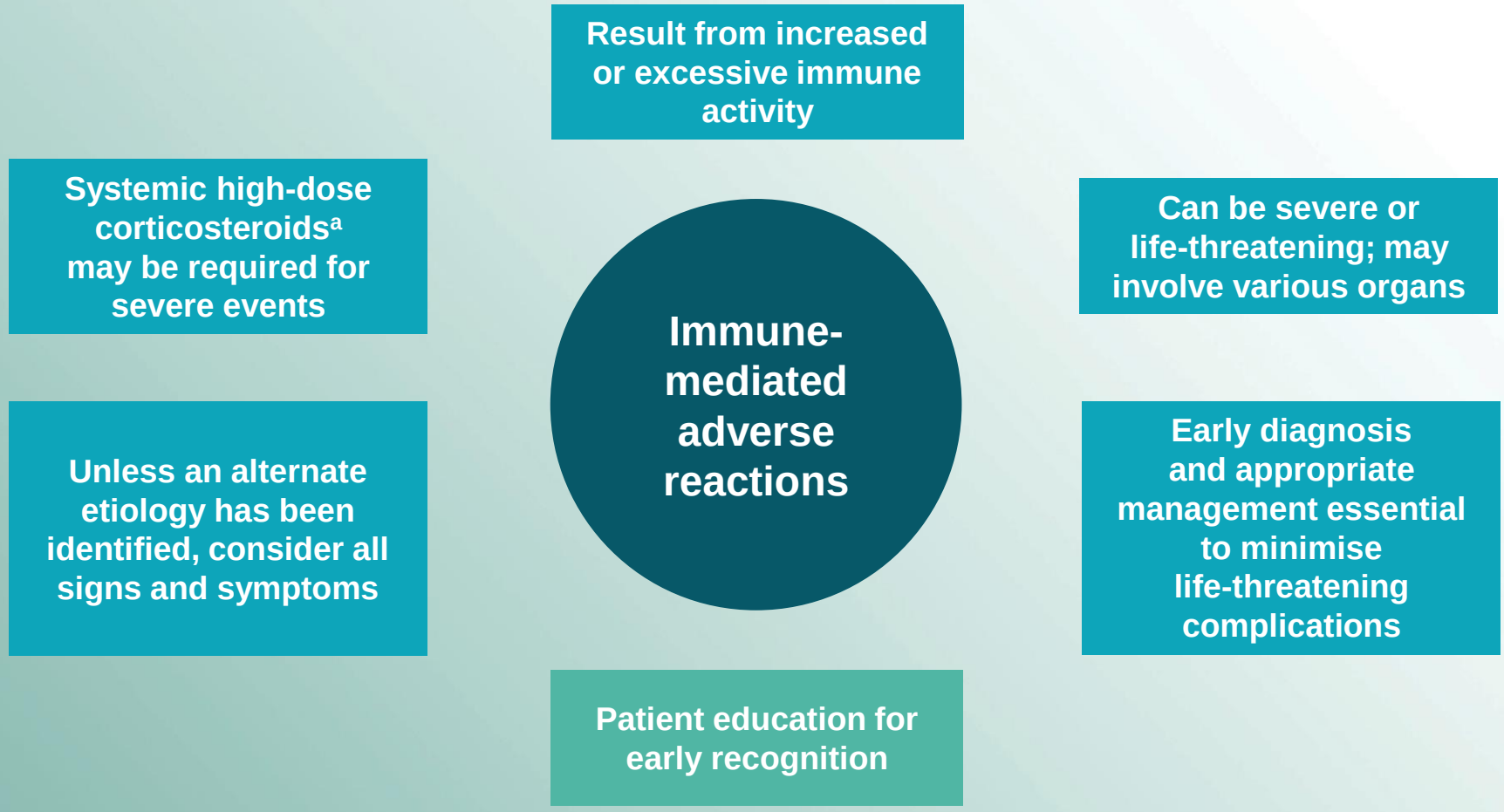
Some AEs with I-O may present like those with other therapies

BUT – AEs may have different etiologies
(eg, diarrhea/colitis, fatigue, rash/pruritus, endocrinopathies)

Require different management strategies

1. American Cancer Society. Treatment types. http://www.cancer.org/; 2. Topalian SL, et al. *N Eng J Med.* 2012;366:2443–2454 and oral presentation at ASCO 2013: *J Clin Oncol.* 2013;31(15 suppl):abstract 3002; 3. Hamid O, et al. *N Eng J Med.* 2013;369:134–144; 4. Dendreon. PROVENGE® prescribing information; 5. YERVOY (ipilimumab) REMS and prescribing information. http://www.yervoy.com.

Treatment Algorithms/Experience Aid Early Diagnosis and Management of Immune-Mediated Adverse Reactions



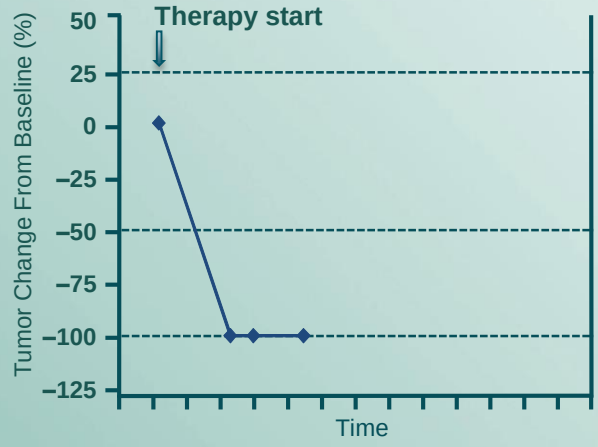
[a]With or without additional immunosuppressive therapy.

YERVOY (ipilimumab) REMS and prescribing information. http://www.yervoy.com.

Mercury No: ONCHQ14NP02639-01

Potential Tumor Response Patterns to Immuno-Oncology Therapy

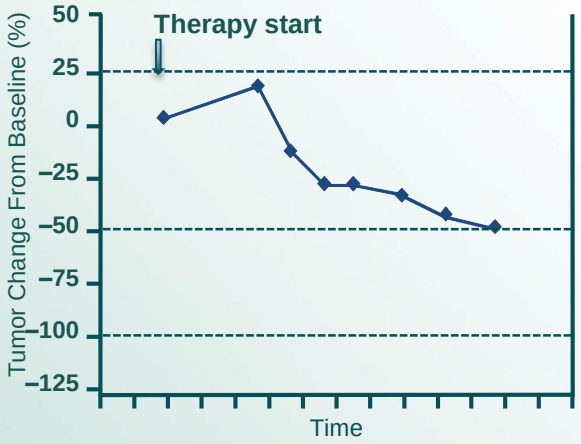
A patient with response in baseline lesions Seen with chemotherapy, but also I-O therapies Captured by existing RECIST and WHO criteria



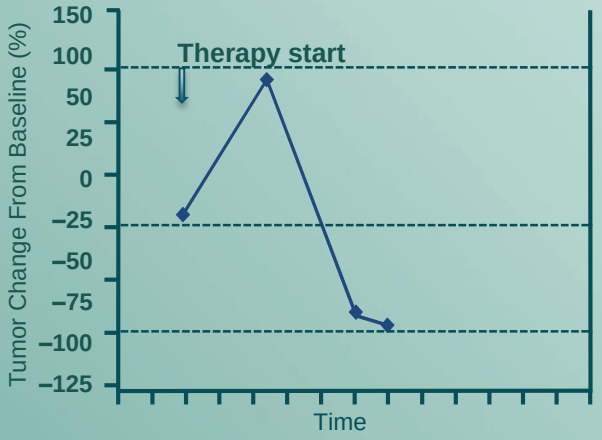
----- Thresholds for response or progressive disease (RECIST)

Graphs for illustrative purposes showing responses to ipilimumab in individual patients with advanced melanoma

A patient with "stable disease": Slow, steady decline in tumor volume seen with chemotherapy, targeted and I-O therapies. Captured by existing RECIST and WHO criteria

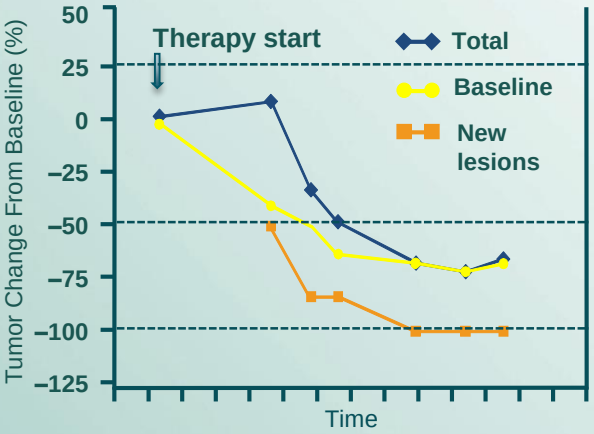


A patient with response after initial increase in tumor volume. Novel and specific to I-O therapy RECIST or WHO criteria may not be optimal



Some vaccines may not have response patterns like other I-O therapies

A patient with reduction in tumor burden after appearance of new lesions; novel and specific to I-O therapy RECIST or WHO criteria may not be optimal

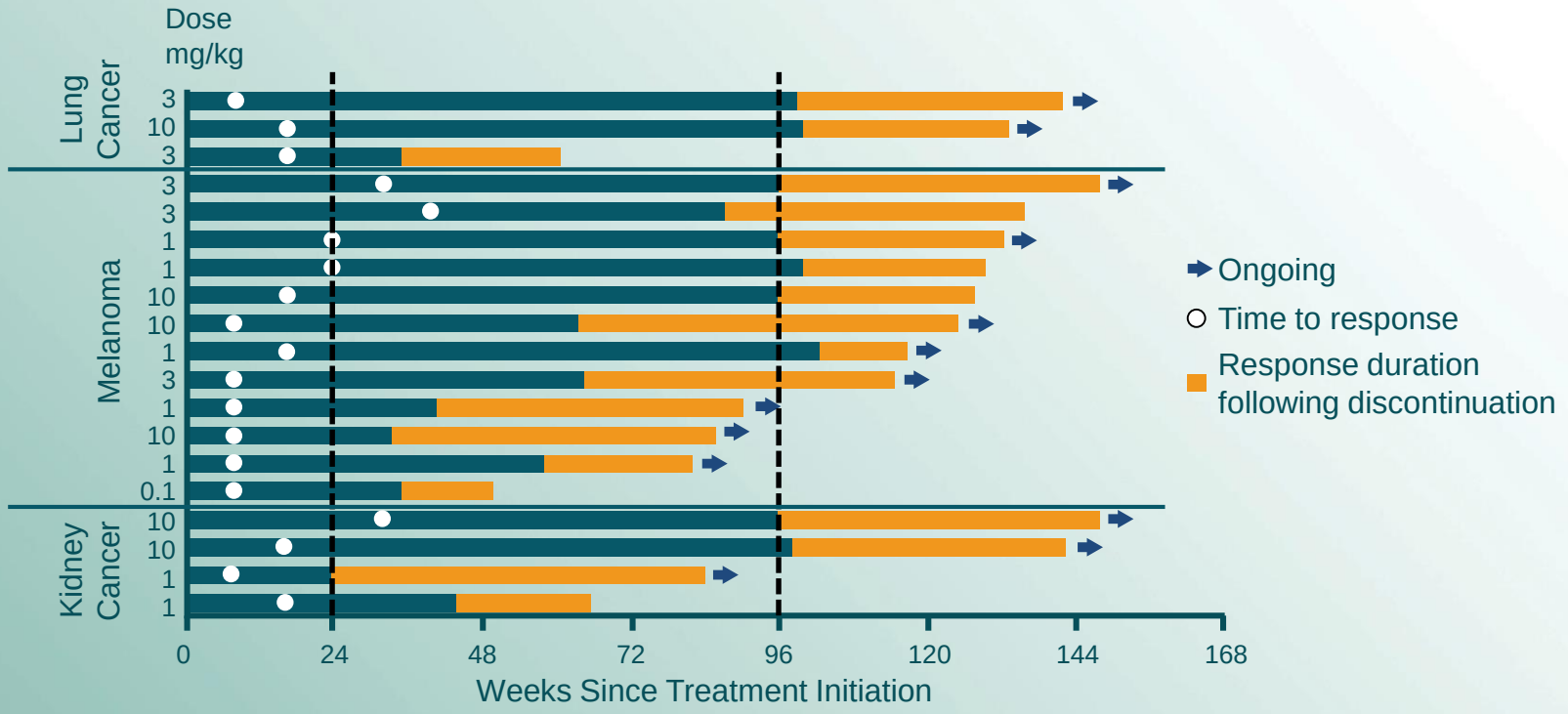


1. Adapted from Wolchok JD, et al. *Clin Cancer Res.* 2009;15:7412–7420; 2. Hoos A, et al. *Ann Oncol.* 2012;23(suppl 8):viii47–viii52.

Mercury No: ONCHQ14NP02639-01

Response Duration with an Investigational Immuno-Oncology Therapy in a Phase I Trial: Nivolumab Example

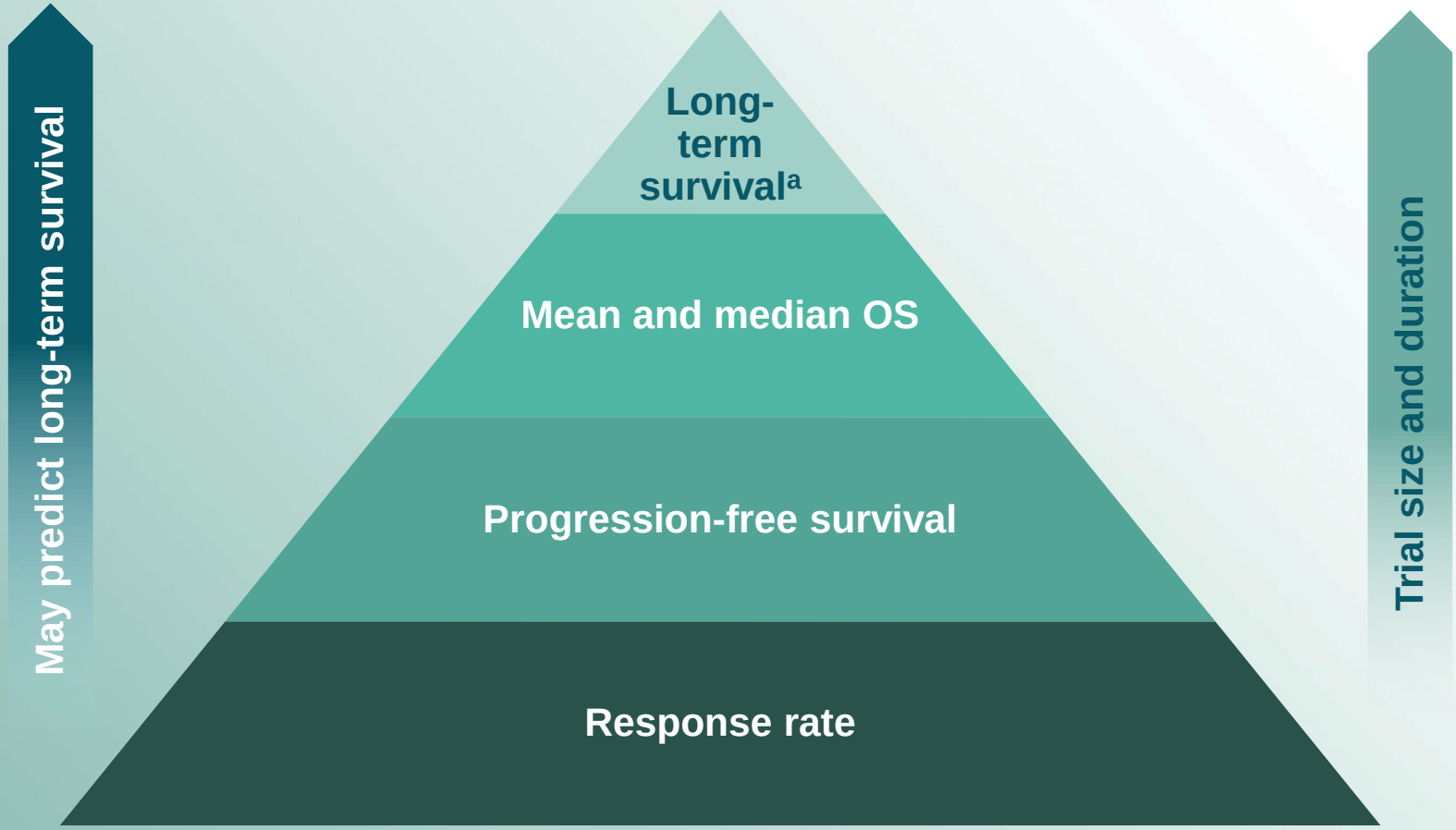
- **Investigational nivolumab was evaluated in a phase I trial in patients with previously treated, advanced solid tumors**



- **Responses may occur early or late, and may continue after discontinuation (patients could be treated for up to 96 weeks)**
- **27 responders discontinued treatment for reasons other than progressive disease**
- **Responses were durable for many patients: 19/27 (70%) maintained response off treatment for 16–59 weeks; 14/19 responses were ongoing at time of analysis**

1. Adapted from Topalian SL, et al. Oral presentation at ASCO 2013. *J Clin Oncol.* 2013;31(15 suppl):abstract 3002; 2. Hodi FS, et al. Poster presentation at ECC. 2013:abstract 880.

Potential Treatment Outcomes Influence the Choice of Metrics[1–3]



[a]Long-term survival can be measured by cure fraction or survival rate at landmarks (eg, 1 year, 2 year, 5 year).

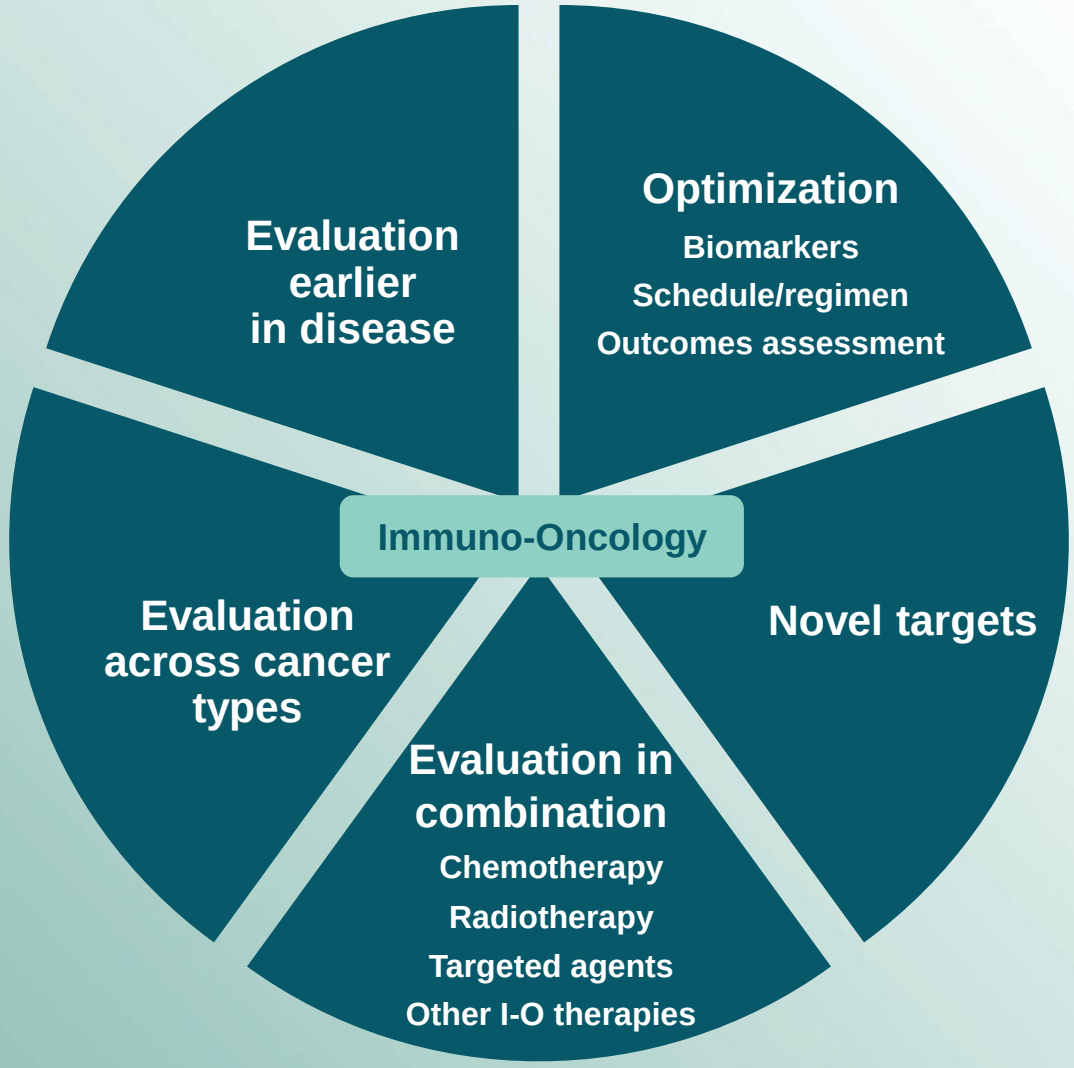
1. Eggermont A, et al. *Eur J Cancer.* 2013;49:2965–2967; 2. Ribas A, et al. *Clin Cancer Res.* 2012;18:336–341; 3. Davies A, et al. *Health Outcomes Res Med.* 2012;3:e25–e36.

Summary

- Understanding of the immune system's role in cancer and how tumors evade recognition and attack has evolved[1]
- This has led to the identification of a range of novel therapeutic targets and approaches for research[1]
- I-O is an evolving treatment modality that includes active immunotherapies designed to harness the patient's own immune system to fight cancer, countering tumor escape mechanisms[1]
- A goal of I-O research is to evaluate long-term survival for patients with advanced cancer[1–3]

1. Finn OJ. *Ann Oncol.* 2012;23(suppl 8):viii6–viii9; 2. Hodi FS, et al. *N Engl J Med.* 2010;363:711–7233; 3. Kantoff PW, et al. *N Engl J Med.* 2010;363:411–422.

What may the Future Hold?[1–4]



1. Drake CG. *Ann Oncol*. 2012;23(suppl 8):viii41–viii46; 2. Eggermont AM. *Ann Oncol*. 2012;23(suppl 8):viii53–viii57; 3. Eggermont AM, et al. *Eur J Cancer.* 2013;49:2965–2967; 4. Mellman I, et al. *Nature*. 2011;480:480–489.