Αρχές ανοσοθεραπείας του καρκίνου και ανοσολογικές ανεπιθύμητες ενέργειες

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Περιεχόμενα

Εισαγωγή

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]

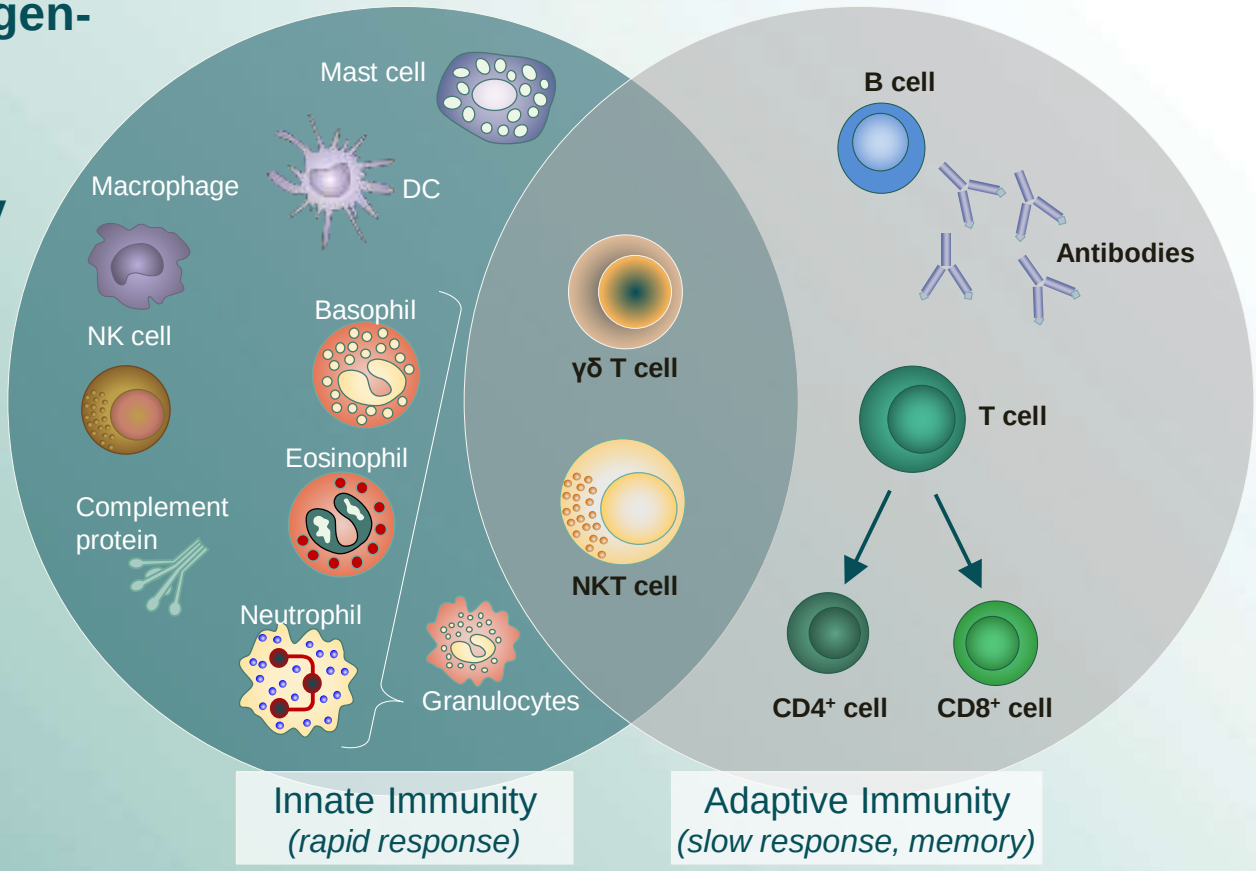
I-O = immuno-oncology.

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.

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

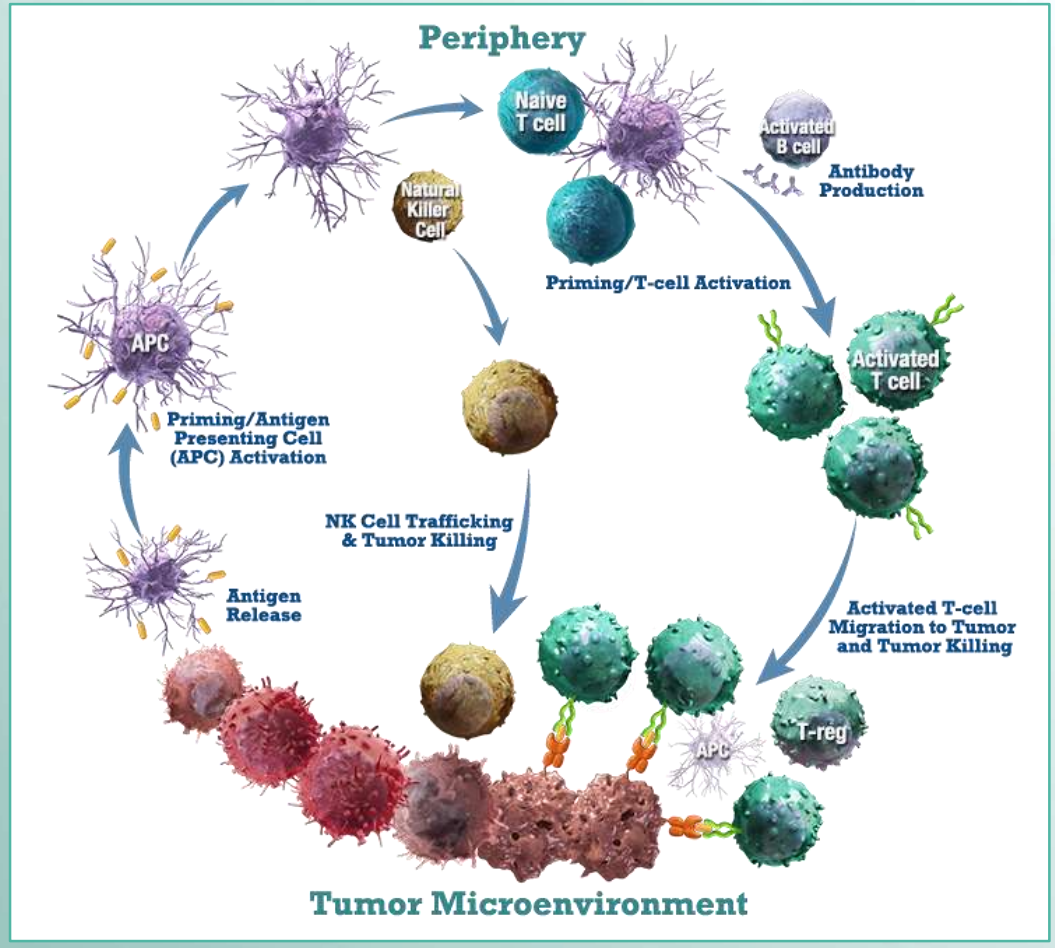


DC = dendritic cell; NK = natural killer.

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]

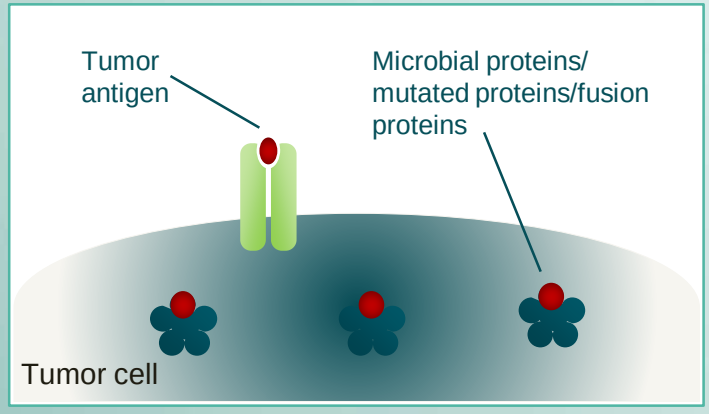
The Immune System Recognizes and Eliminates Cancer Via Multiple, Complex Mechanisms



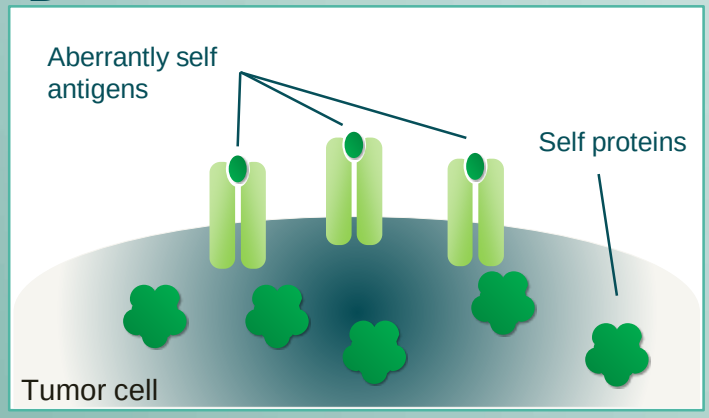
1. Janeway CA, et al. *Immunobiology: The Immune System in Health and Disease*. 6th ed. New York, NY: Garland Science; 2004; 2. Padmanabhan RR, et al. *J Leuk Biol*. 1988;43:509–519; 3. Kim R, et al. *Immunology*. 2007;121:1–14; 4. Vivier E, et al. *Science*. 2011;331:44–49; 5. Dunn GP, et al. *Nat Immunol*. 2002;3:991–998.

Tumor Recognition by the Immune System

A



B



Adapted from Janeway CA, et al.[1]

- **The immune system protects the body against disease; to do this it must distinguish a variety of pathogens/abnormal cells from the body's own healthy tissue[1]**
- **The immune system can identify and eliminate tumor cells based on their expression of tumor-specific antigens via a process termed immunosurveillance (A)[1,2]**
  - Tumors can express microbial proteins, mutated proteins, and fusion proteins
- **The immune system can also recognize aberrantly expressed self proteins[a] (B)[1,2]**

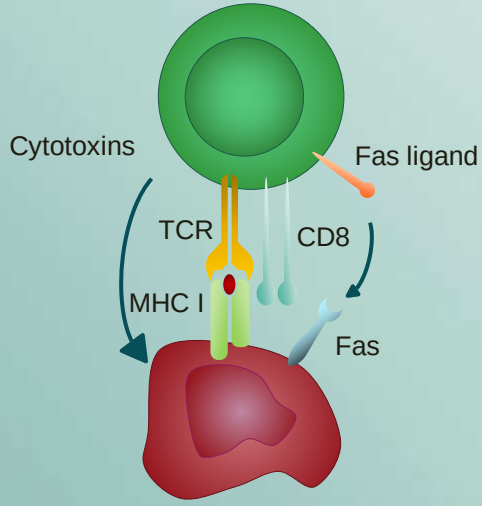
[a]Self proteins are proteins normally produced by the body's healthy cells.

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

Key Effector Cells Involved in an Antitumor Immune Response

$CD8^+$ Effector T cells[1]

Destroy tumor cells

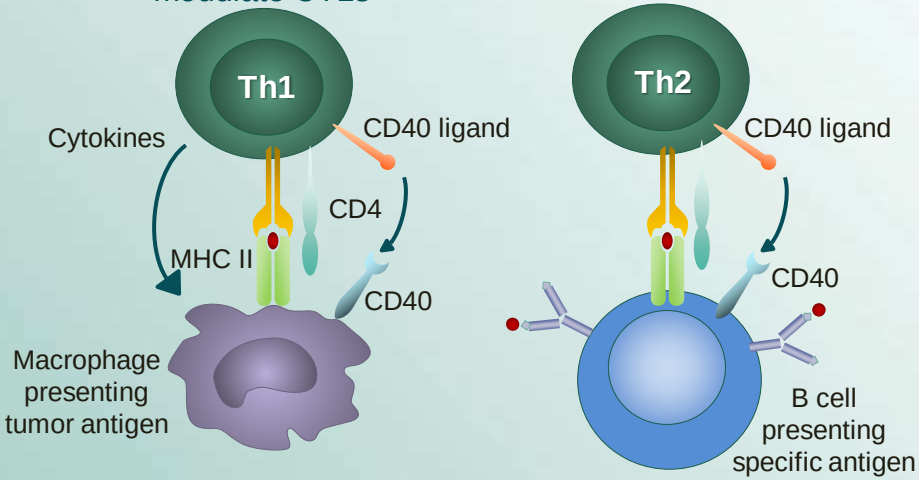


Key cytotoxic effector molecules
Perforin Granzymes Granulysin Fas ligand

Th1 $CD4^+$ Helper T cells[1,2]

Produce cytokines that mediate inflammatory and effector responses; modulate CTLs

Help B cells make antibody; modulate CTLs

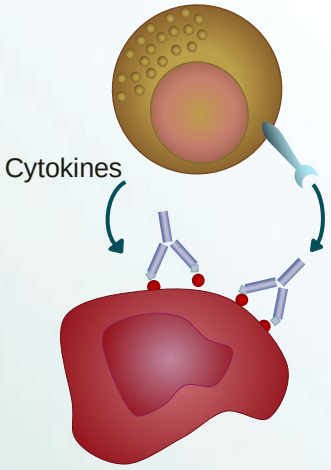


Key effector molecules
IFN-γ GM-CSF TNF-α CD40 ligand Fas ligand

Key effector molecules
IL-4 IL-5 IL-15 CD40 ligand

NK cells[3]

Destroy antibody-coated tumor cells or tumor cells lacking MHC I

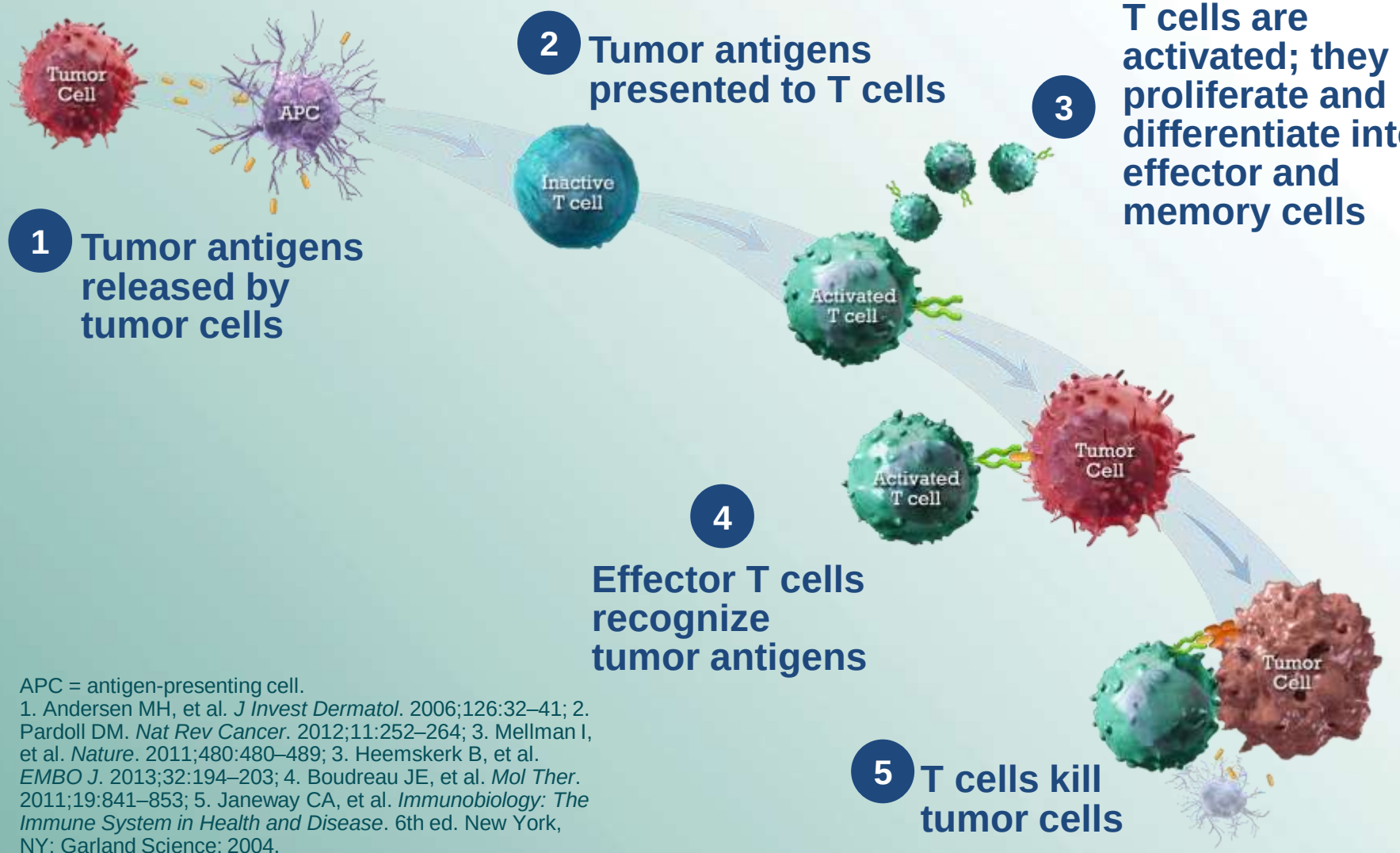


Key effector molecules
IFN-γ TNF-α

CTL = cytotoxic T lymphocyte; GM-CSF = granulocyte macrophage-colony stimulating factor; IFN = interferon; IL = interleukin; MHC = major histocompatibility complex; TCR = T cell receptor; Th = T helper cell; TNF = tumor necrosis factor.

1. Janeway CA, et al. *Immunobiology*. 2008; 2. Pardoll D. *Nat Rev Cancer*. 2012;12:252–264; 3. Vivier E, et al. *Nat Immunol.* 2008;9:503–510.

The T-Cell Antitumor Response[1–6]

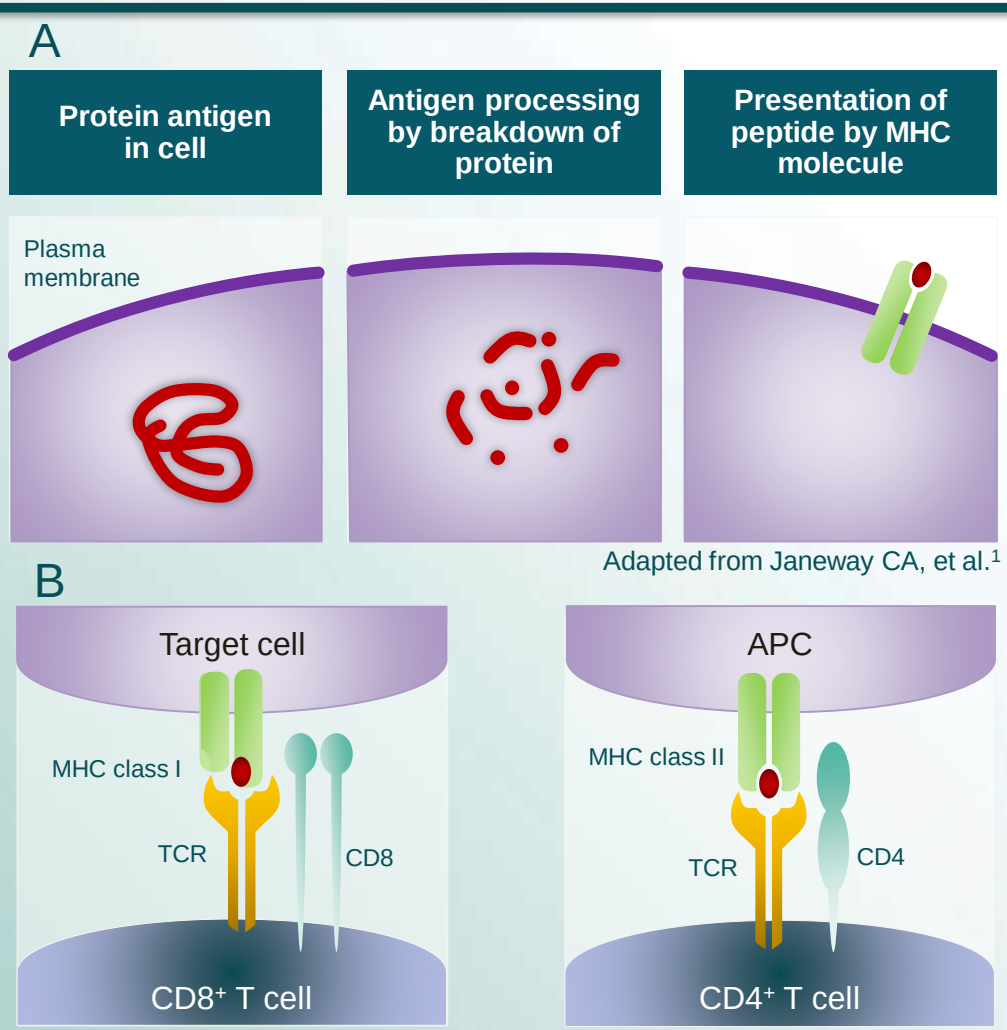


APC = antigen-presenting cell.

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]

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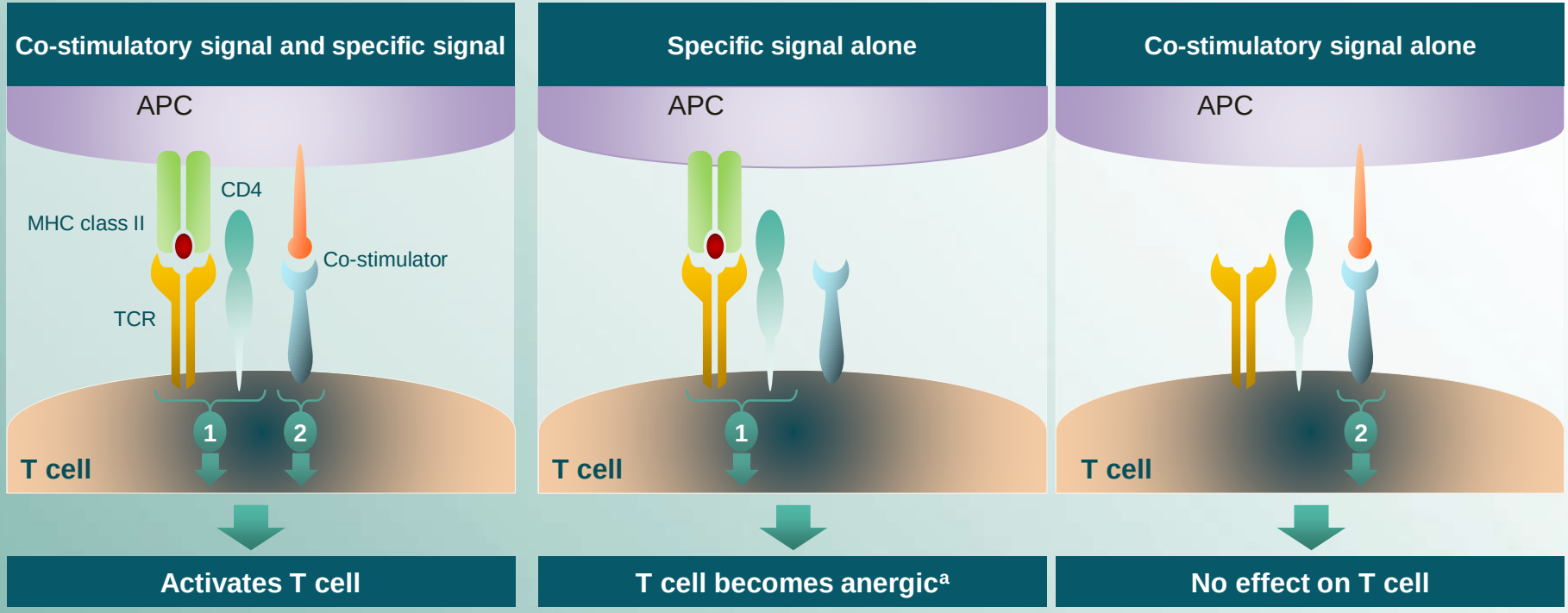
1. Janeway CA, et al. *Immunobiology*. 2008; 2. Vesely MD, et al. *Ann Rev Immunol.* 2011;29:235–271.

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]

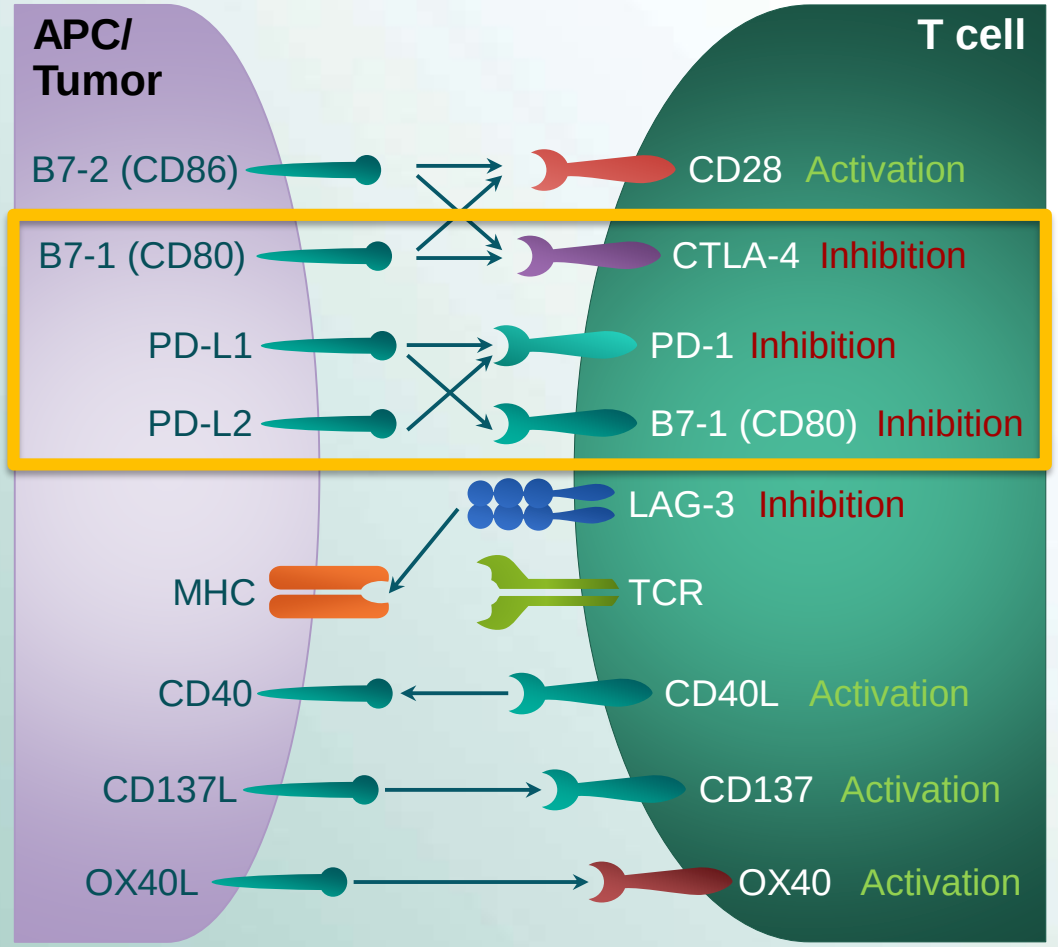


[a]Anergy describes a state of functional inactivation.

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

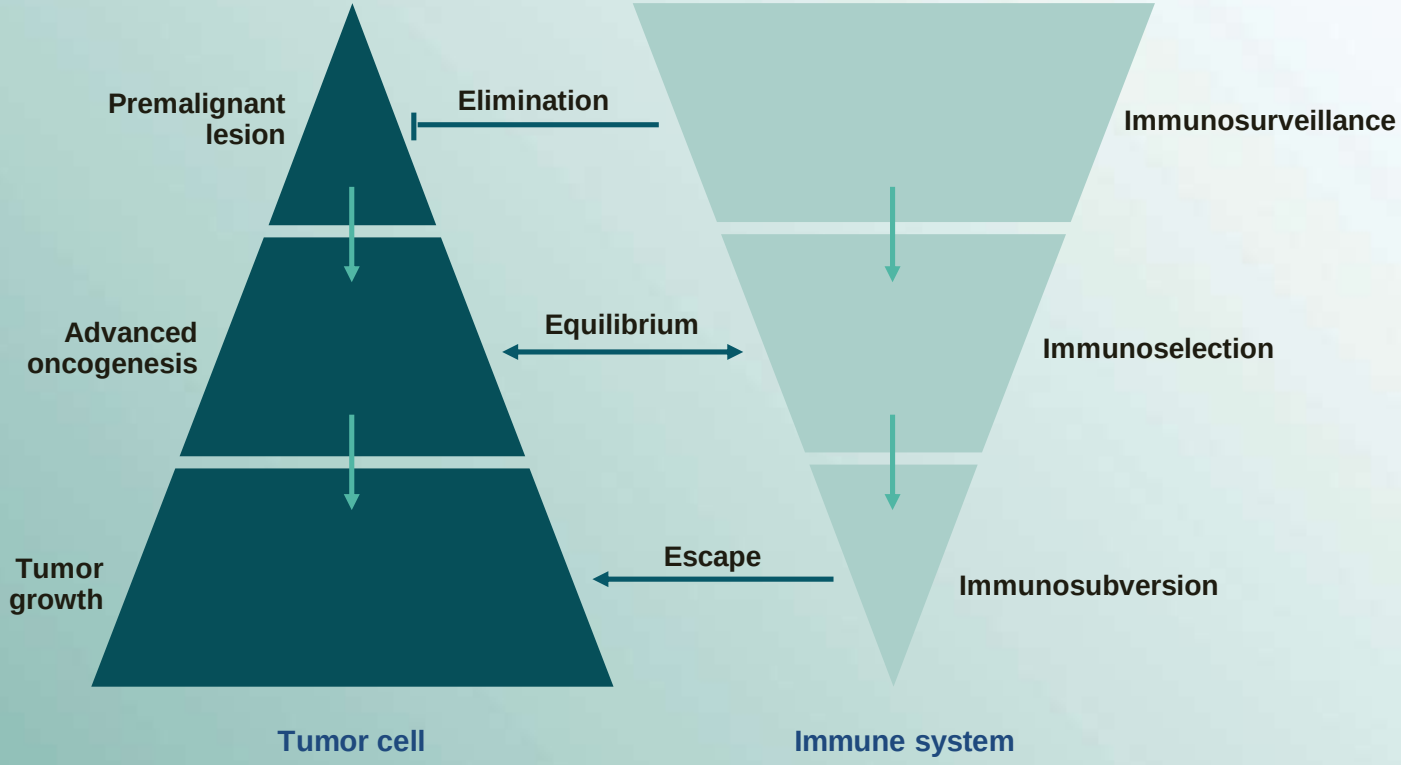
- **In the presence of cancer, there is evidence that the immune system has responded to the tumor:[1,2]**
  - Antibodies against tumor antigens[3]
  - Tumor-specific T cells[4]
  - TILs[5]
- **In some tumors, the infiltration of $CD8^+$ effector T cells correlates with improved prognosis and therapy 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.

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.

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

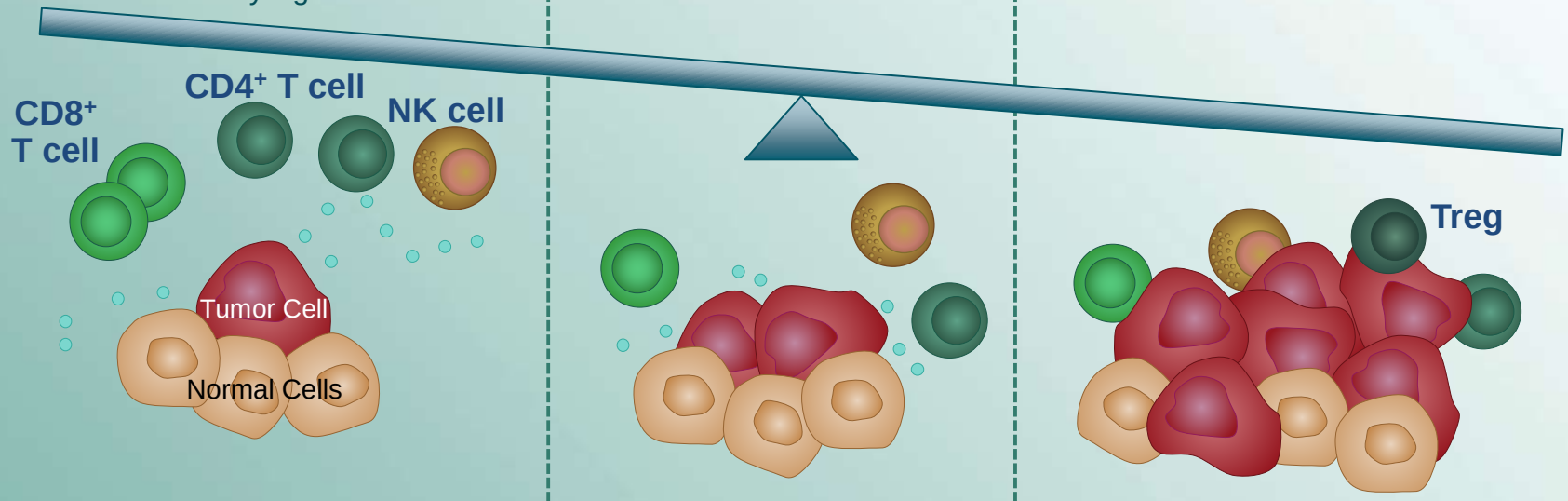
- Effective antigen processing/presentation
- Effective activation and function of effector cells
  - eg, T-cell activation without co-inhibitory signals

Equilibrium
Cancer Dormancy

- Genetic instability
- Tumor heterogeneity
- Immune selection

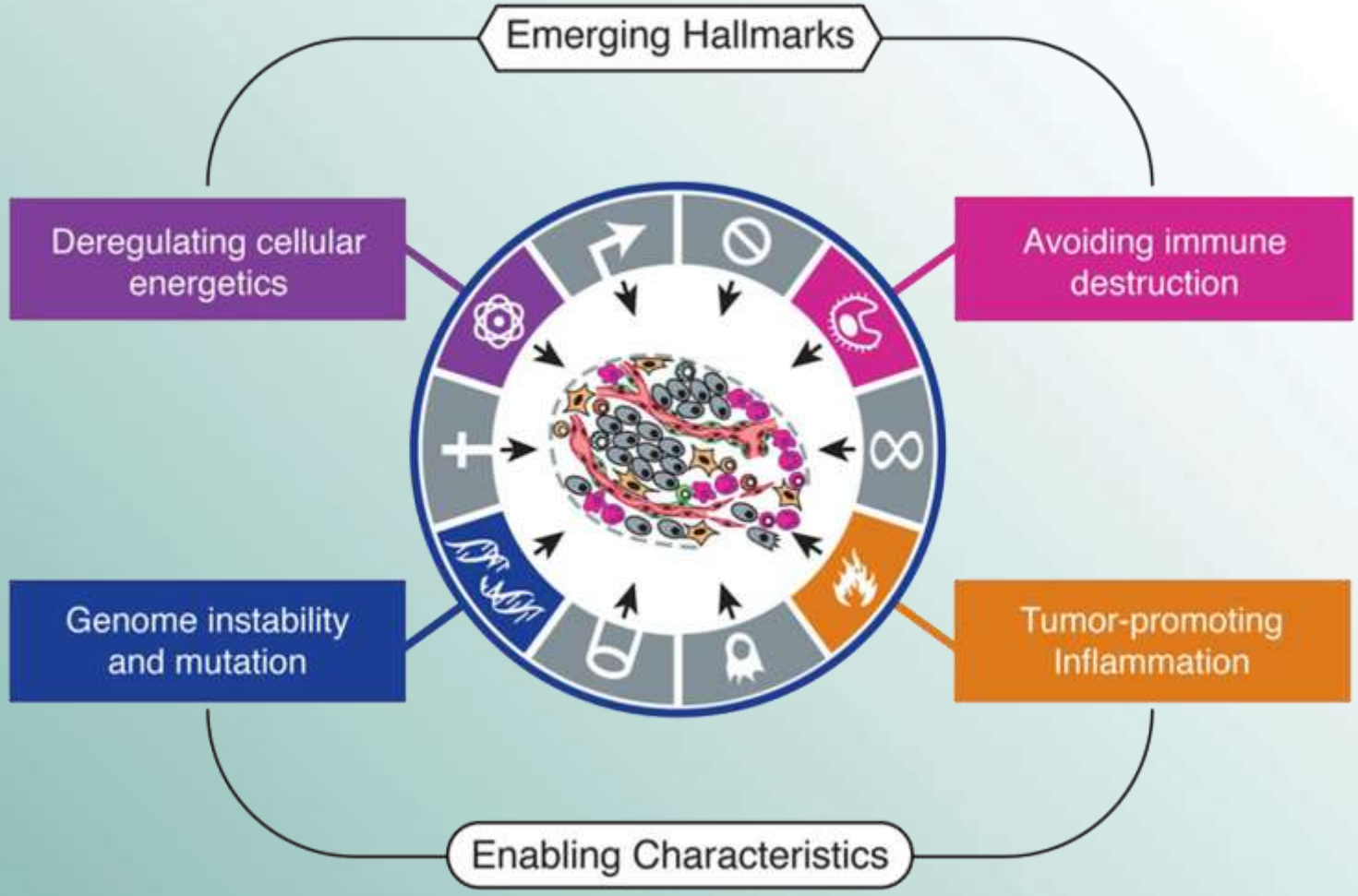
Escape
Cancer Progression

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



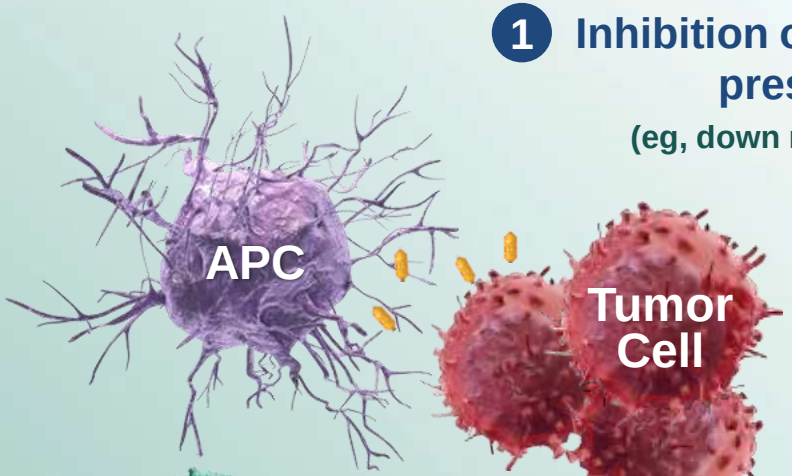
Vesely MD, et al. *Ann Rev Immunol*. 2011;29:235–271.

Emerging Hallmarks of Cancer: Avoiding Immune Destruction



Adapted from Hanahan, et al. *Cell*. 2011;144:646–674.

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

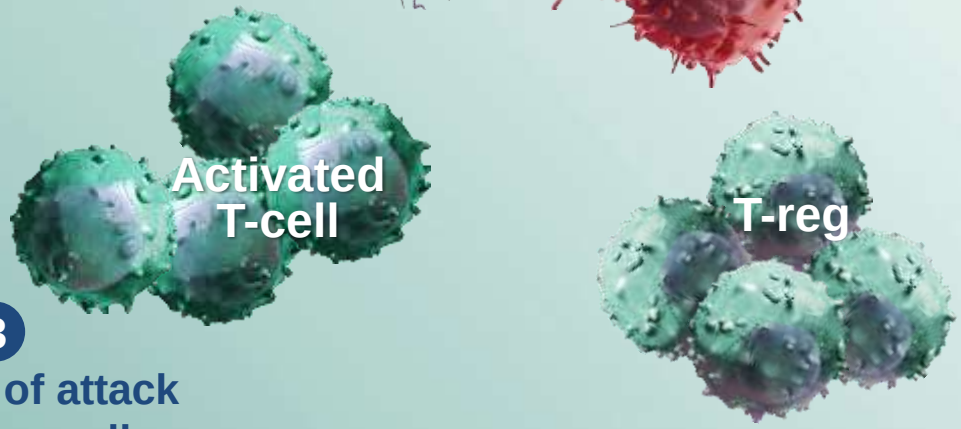


1 **Inhibition of tumor antigen presentation**

(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.

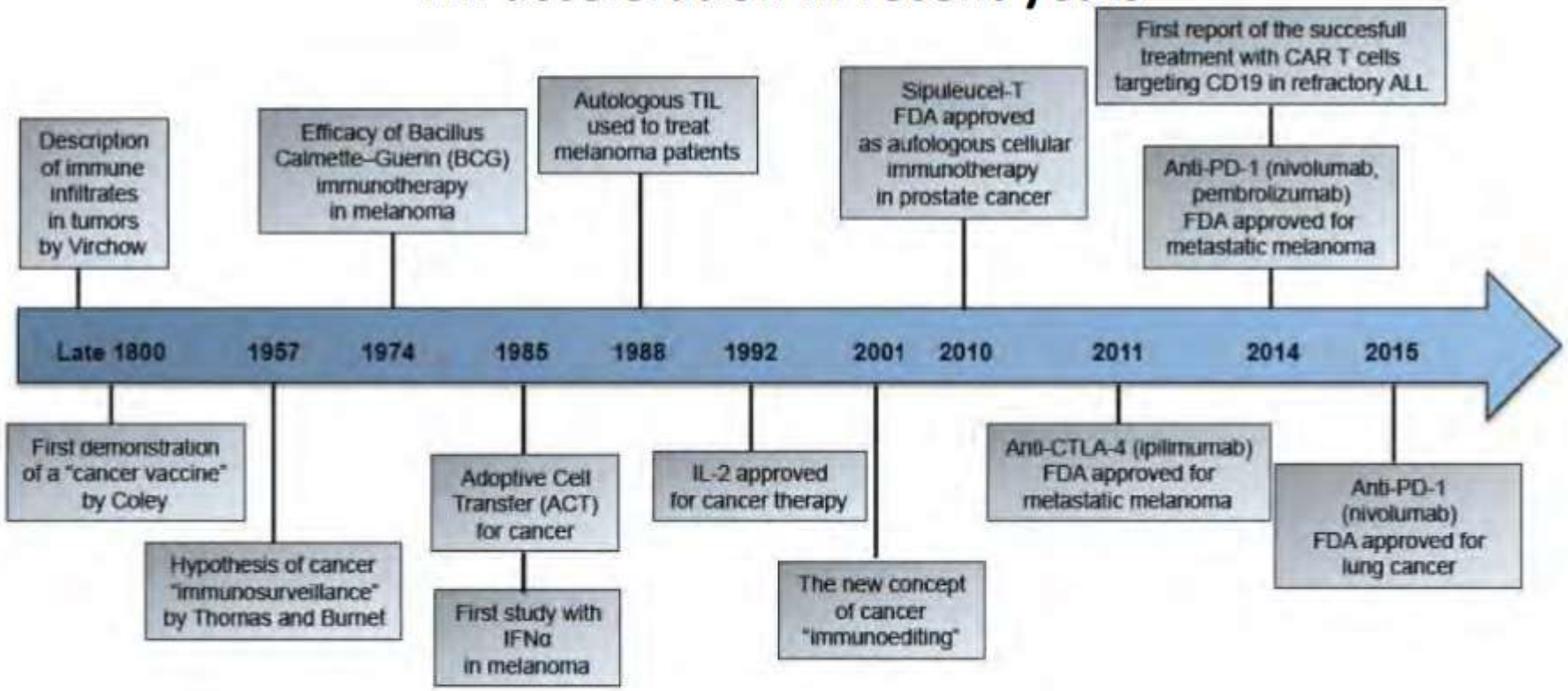
Ανοσο-ογκολογία

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]**

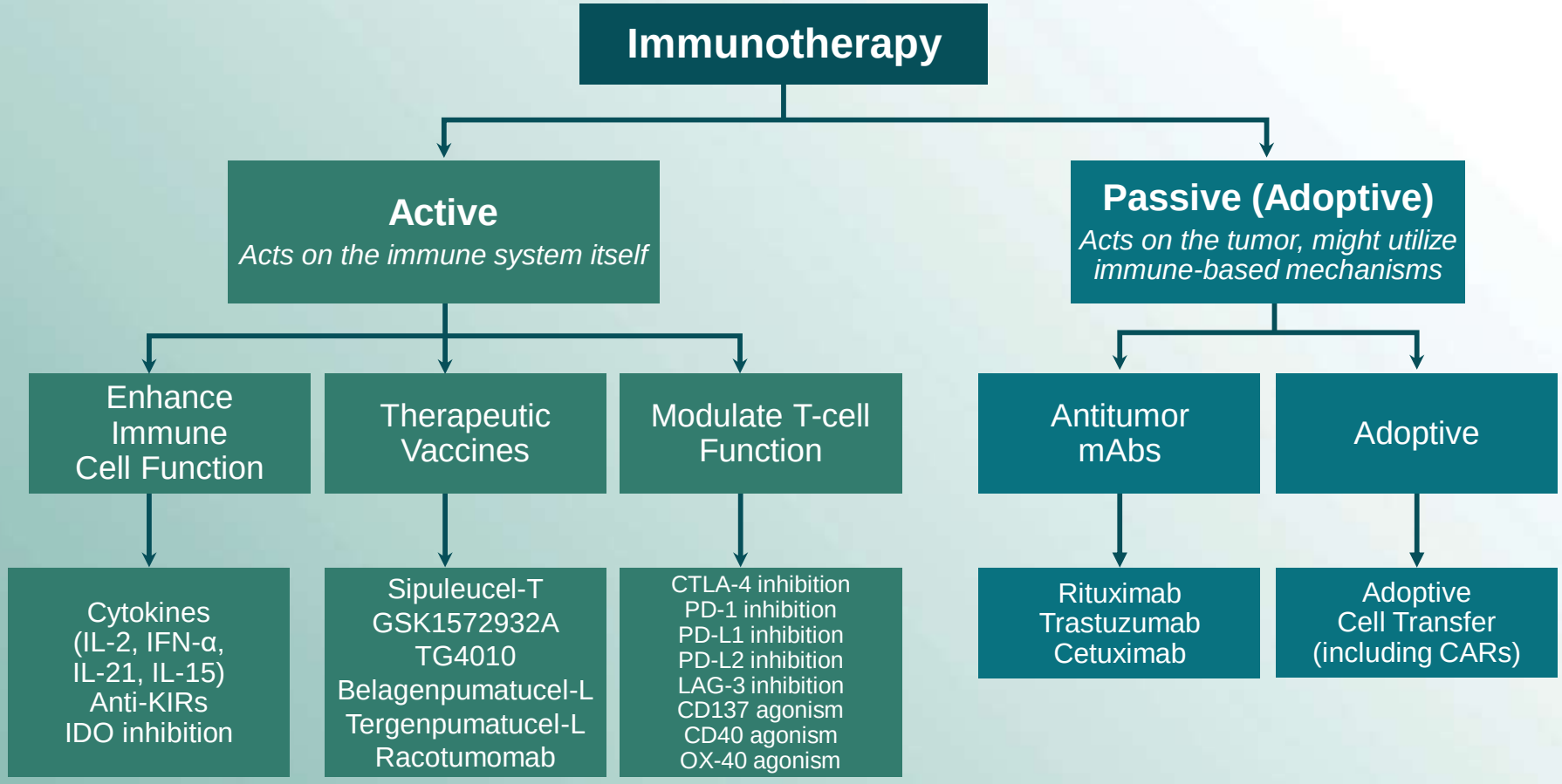
1. Finn OJ, et al. *Ann Oncol*. 2012;23(suppl 8):viii6–viii9; 2. Eggermont A, et al. *Ann Oncol*. 2012;23(suppl 8):viii53–viii57.

Development of immunotherapy
An acceleration in recent years



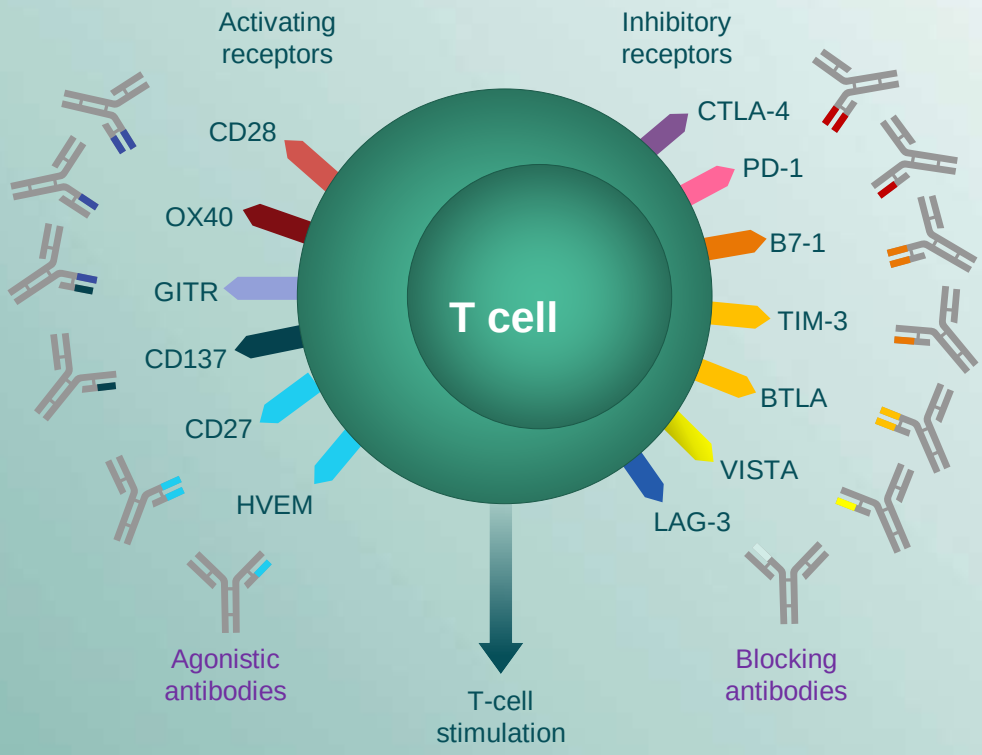
Voena et al., Advances in Cancer Immunology and Cancer Immunotherapy, Discovery Medicine 2016

Selected Immunotherapeutic Approaches for Cancer[a]



[a]Selected examples of approved immunotherapies or immunotherapies under evaluation for cancer. www.clinicaltrials.gov.

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



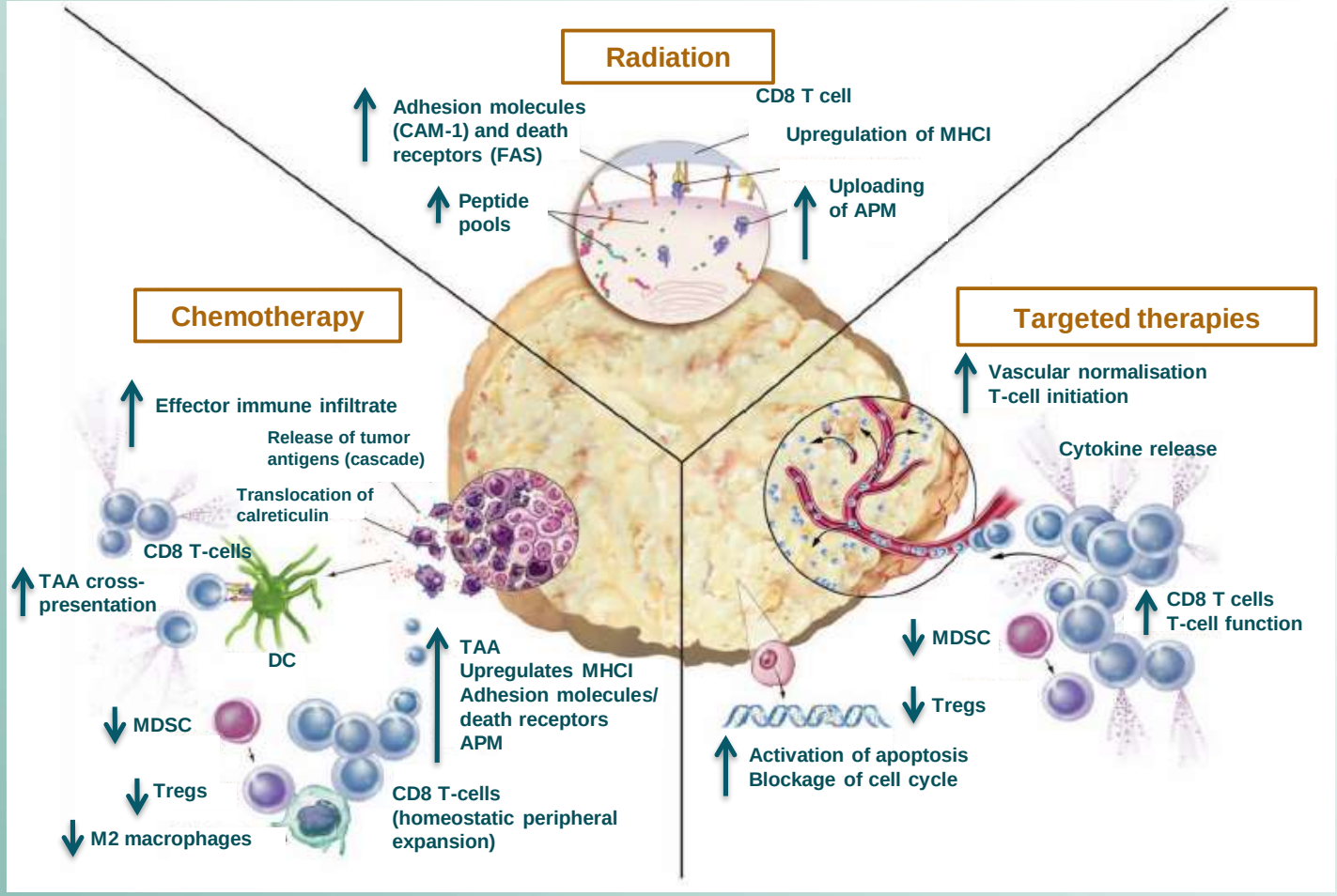
- T-cell responses are regulated though a complex balance of inhibitory ("checkpoint") and activating signals
- Tumors can dysregulate checkpoint and activating pathways, and consequently, the immune response
- Targeting checkpoint and activating pathways is an evolving approach to active immunotherapy,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

Rationale for Investigating Opportunities to Combine Immunotherapy With Other Therapeutic Modalities

Multiple mechanisms of potential synergy between the different treatment modalities



APM = antigen processing machinery; TAA = tumor-associated antigen.

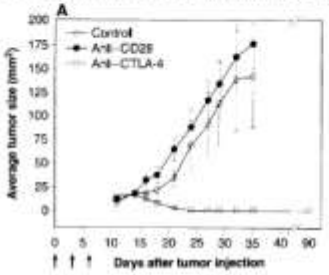
1. Adapted from Hodge JW. *Semin Oncol.* 2012;39:323–339; 2. Drake CG. *Ann Oncol.* 2012;23(suppl 8):viii41–viii46; 3. Ménard C, et al. *Cancer Immunol Immunother.* 2008;57:1579–1587; 4. Hannani D, et al. *Cancer J.* 2011;17:351–358; 5. Ribas A at al. *Curr Opin Immunol.* 2013:25:291–296.

Discovery of immune checkpoints

SCIENCE • VOL. 271 • 22 MARCH 1996

Enhancement of Antitumor Immunity by CTLA-4 Blockade

Dana R. Leach. Matthew F. Krummel. James P. Allison*



The EMBO Journal vol.11 no.11 pp.3887 – 3895, 1992

Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death

Yasumasa Ishida, Yasutoshi Agata, Kaiichi Shibahara and Tasuku Honjo

Nobel Prize in Medicine 2018

James Allison
University of California, Berkeley

Tasuku Honjo
Kyoto University

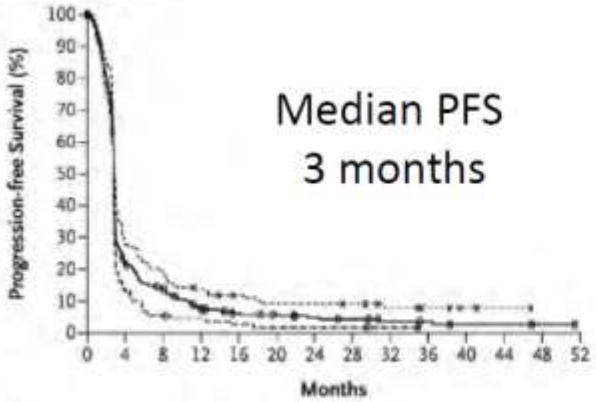
The NEW ENGLAND JOURNAL of MEDICINE

AUGUST 19, 2010

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

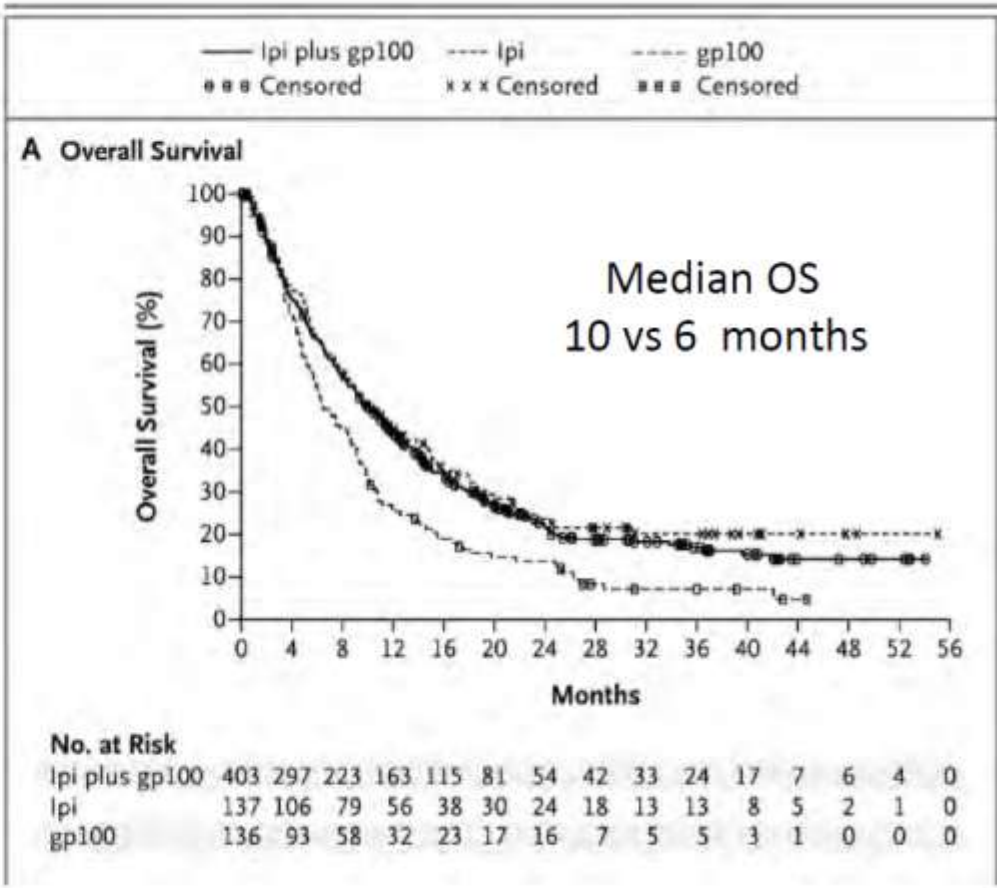
F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wollane Akerley, M.D., Albiris J.M. van den Eertwegh, M.D., 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.

B Progression-free Survival



Median PFS
3 months

No. at Risk														
Ipi plus gp100	403	85	52	27	17	14	10	8	5	4	2	2	1	0
Ipi	137	37	26	17	13	10	10	9	6	4	2	1	0	0
gp100	136	18	7	5	3	2	2	2	1	0	0	0	0	0



Median OS
10 vs 6 months

No. at Risk															
Ipi plus gp100	403	297	223	163	115	81	54	42	33	24	17	7	6	4	0
Ipi	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

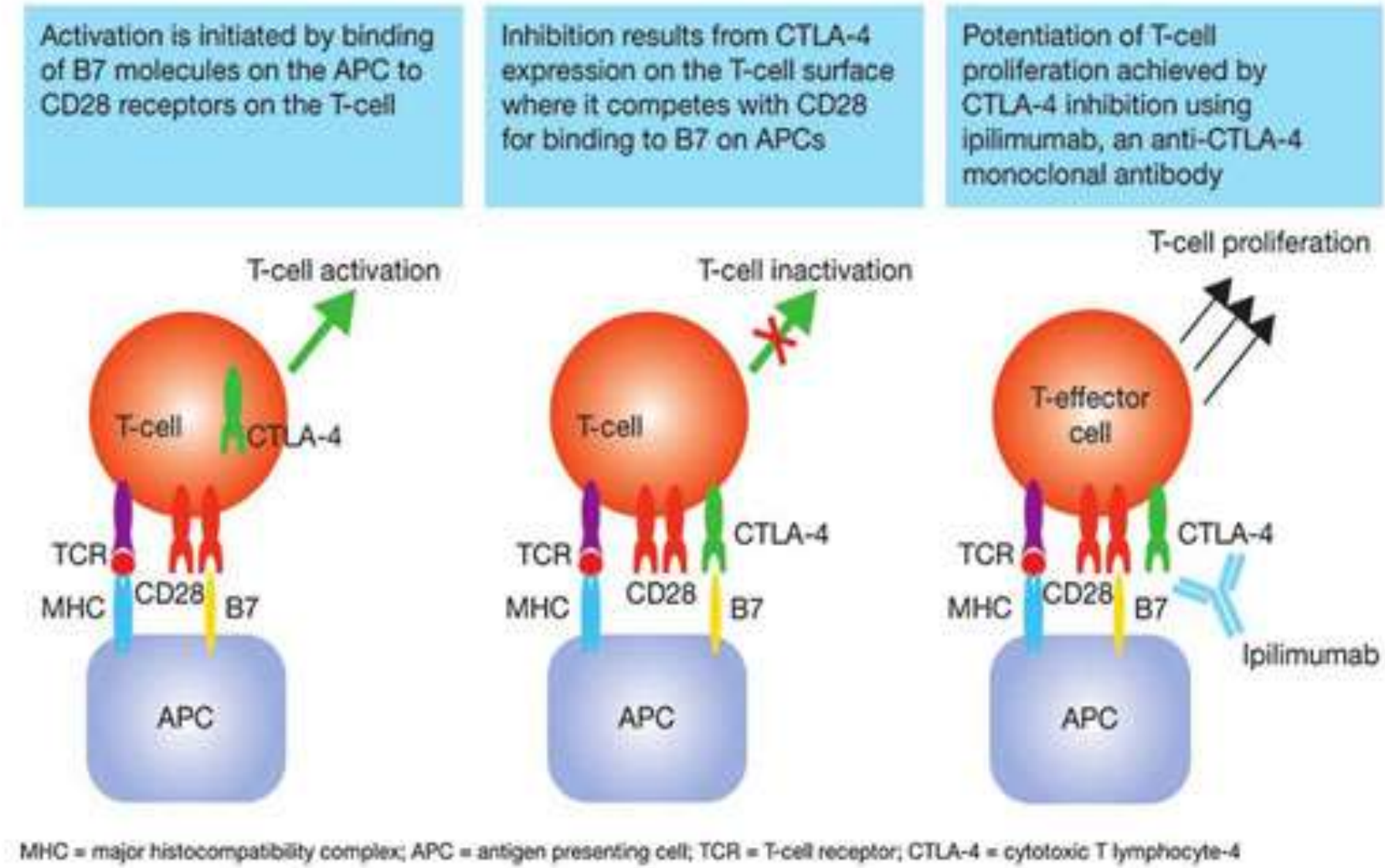
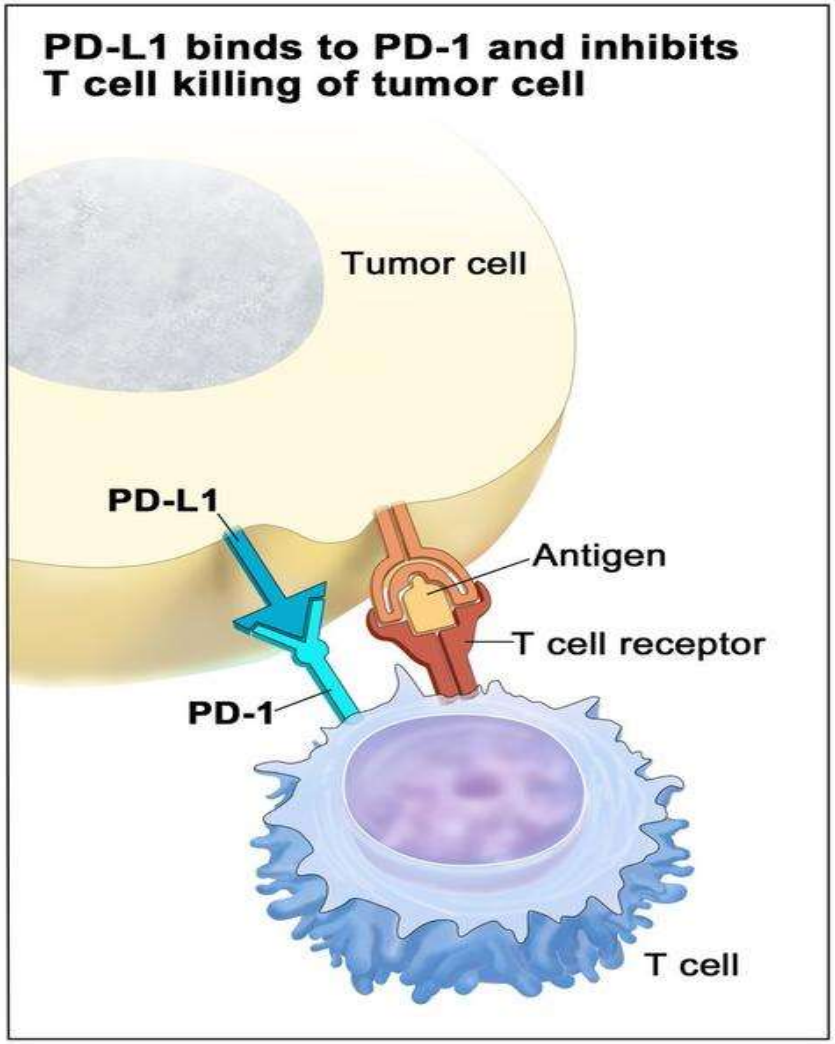
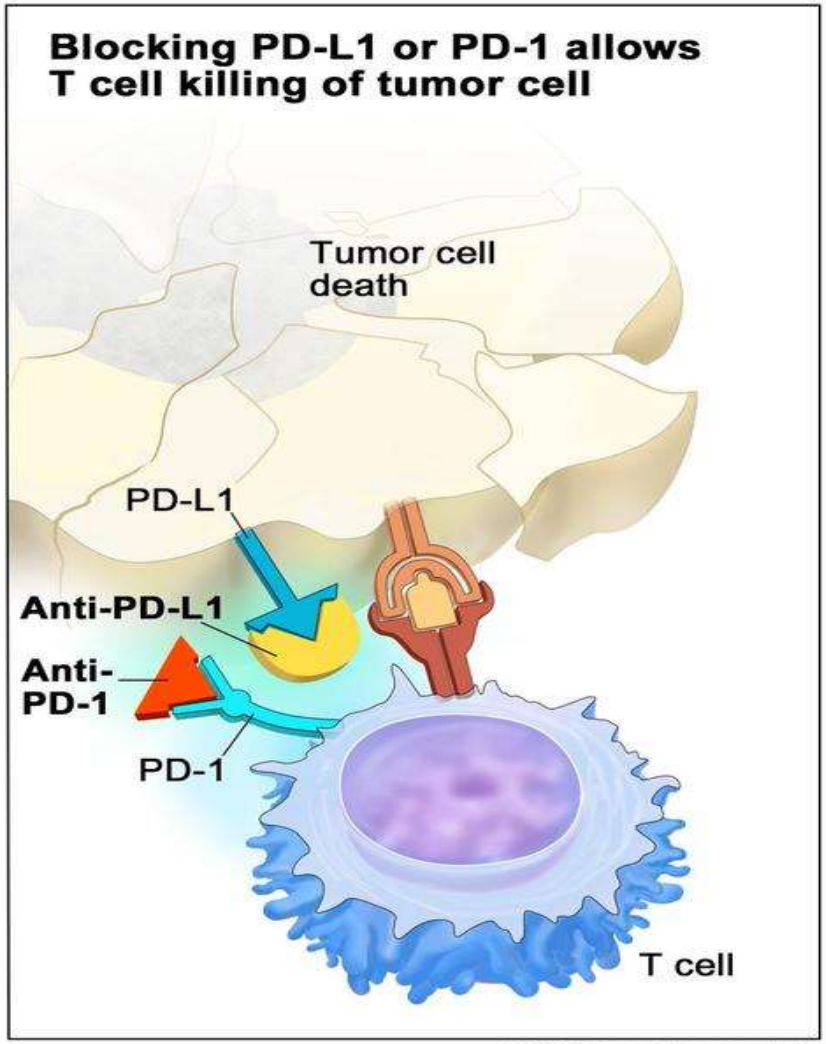


FIG. 1. T-cell activation and mechanism of action of ipilimumab (adapted with permission from Weber[51]). APC, antigen presenting cell; CTLA-4, cytotoxic T lymphocyte antigen-4; TCR, T-cell receptor; MHC, major histocompatibility complex.

Anti-PD-1/ Anti-PD-L1





Anti-CTLA4 mAbs **Ipilimumab**	Stage III and Metastatic melanoma
Anti-PD-L1 mAbs **Atezolizumab**	2nd line regiment for metastatic nonsmall-cell lung cancer Advanced or metastatic urothelial carcinoma
Avelumab	Advanced or metastatic urothelial carcinoma Metastatic Merkel cell carcinoma
Durvalumab	Advanced or metastatic urothelial carcinoma
Anti-PD-1 mAbs **Nivolumab**	Metastatic melanoma 2nd line metastatic regiment of nonsmall-cell lung cancer 2nd line regiment of metastatic renal cell carcinoma Refractory classical Hodgkin lymphoma Recurrent or metastatic squamous cell carcinoma of the head and neck Advanced or metastatic urothelial carcinoma
Pembrolizumab	Metastatic melanoma 1st and 2nd line regiment for metastatic nonsmall-cell lung cancer Advanced or metastatic renal cell carcinoma Refractory classical Hodgkin lymphoma MSI-high or MMR-deficient metastatic solid tumors Advanced or metastatic urothelial carcinoma

Ανταπόκριση στους immune checkpoint inhibitors

Why Immune Targeted Therapies provide Survival Benefits?

Adaptive anti-tumor immunity is polyclonal:

➔ *better control of tumor heterogeneity*

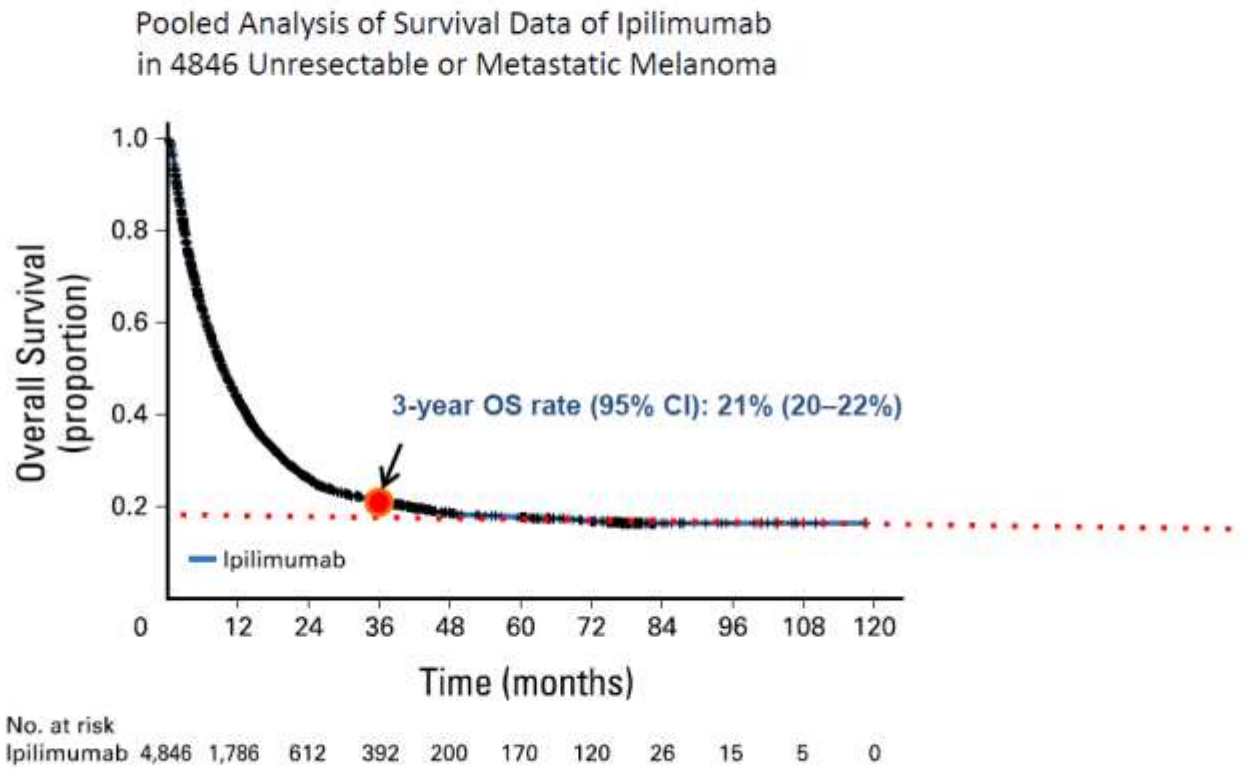
Adaptive anti-tumor immunity has memory:

➔ *durable remissions*

And immune cells can cross the BBB

(whereas most drugs can't)

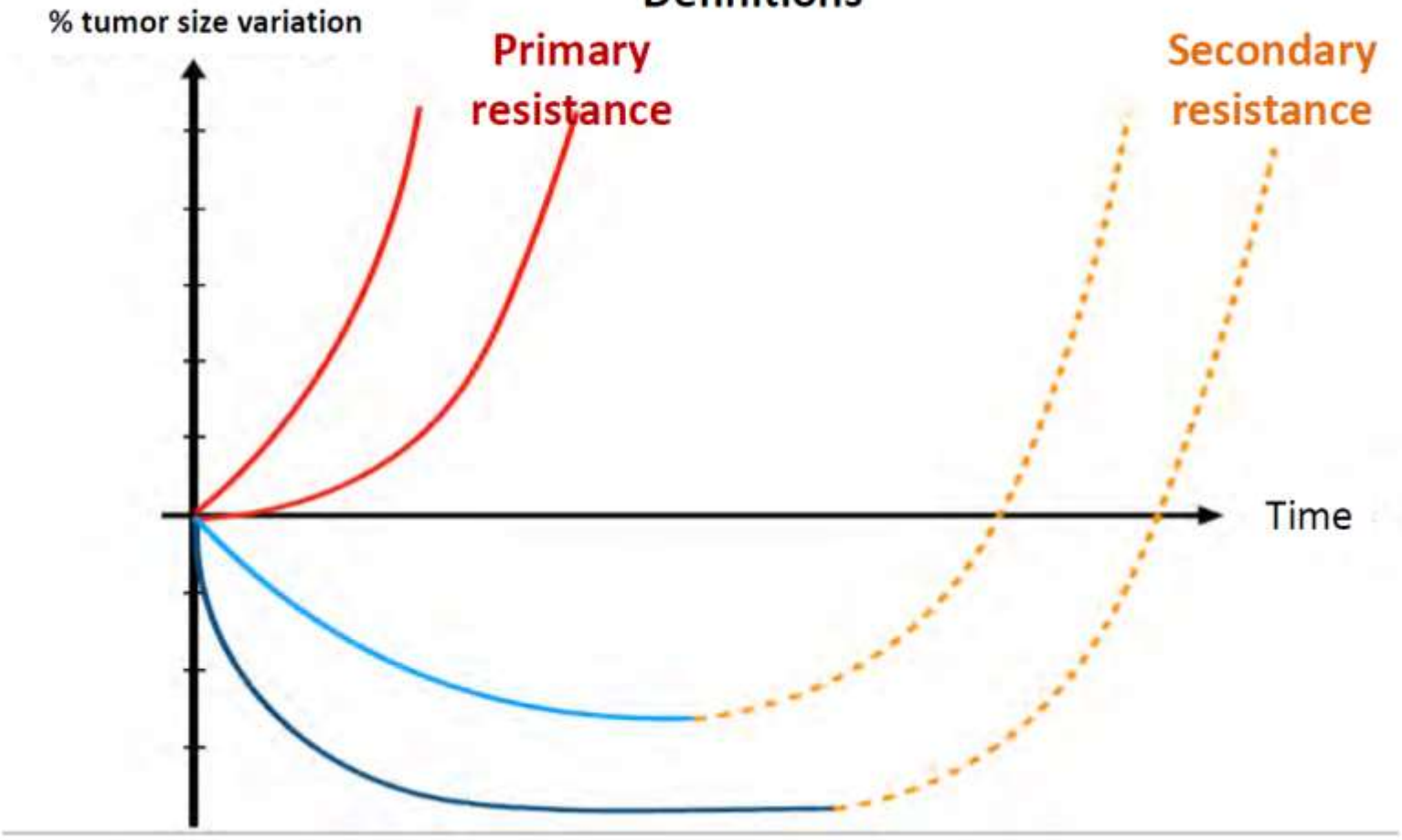
Hope for a cure



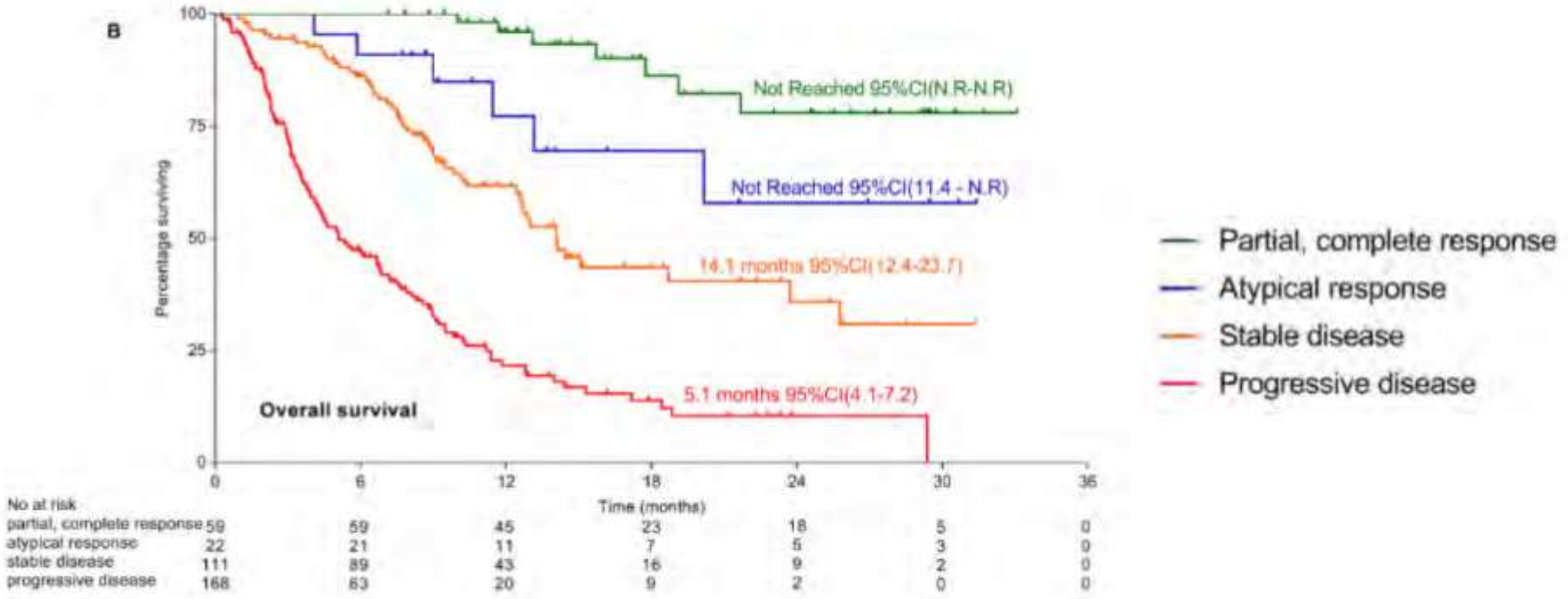
Schadendorf D, J Clin Oncol 2015.

Primary and secondary resistance to anti-PD1 and anti-PD-L1

Definitions



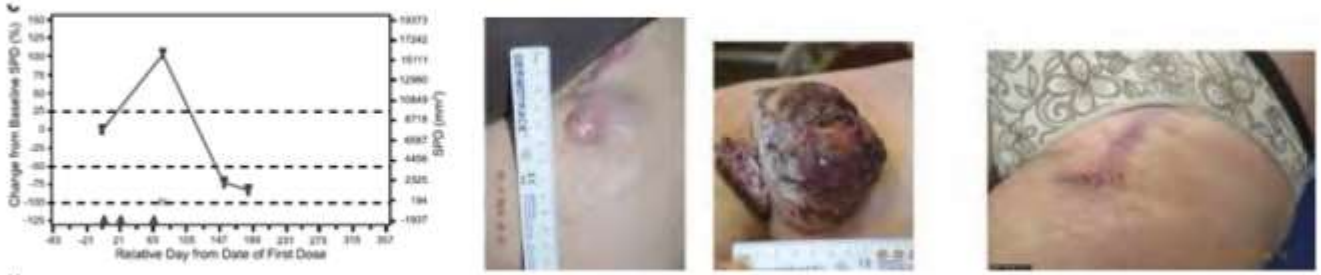
Patterns of progression in patients treated for IO antibodies combination
Survivals according to radiological assessment



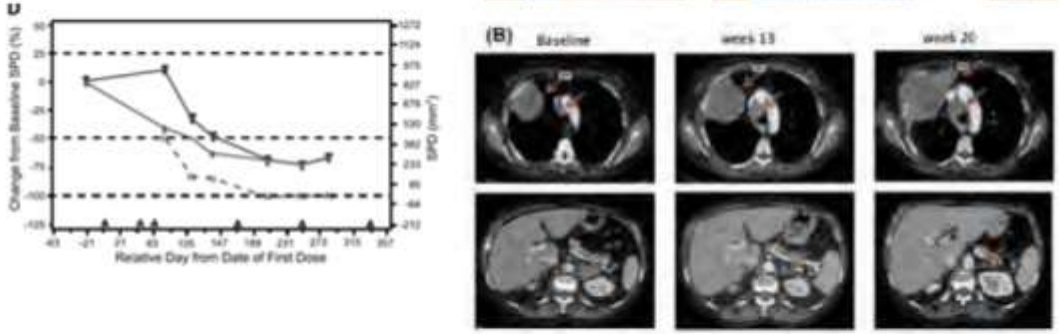
Bernard-Tessier, A. *et al.*
Cancer Immunol Immunother 2020

~~Atypical response~~ **Atypical resistance**

Pseudo progression

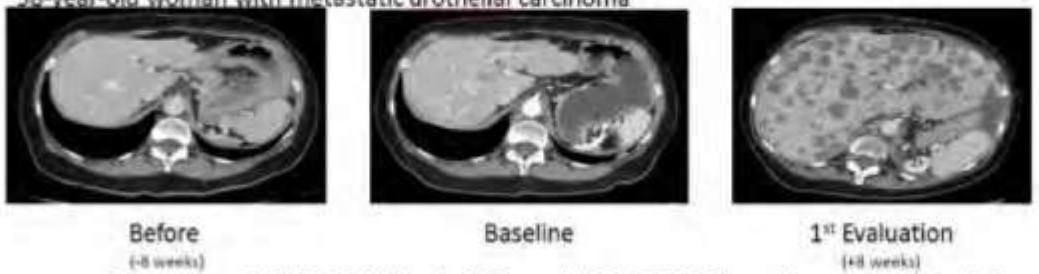


Dissociated response



Hyperprogressive disease

58-year-old woman with metastatic urothelial carcinoma



Tazdait et al. EJC 2018, Hodi, F. S. *et al.* JCO 2016, Champiat et al. Clinical Cancer Research 2017

Ανεπιθύμητες ενέργειες (immune-related adverse events

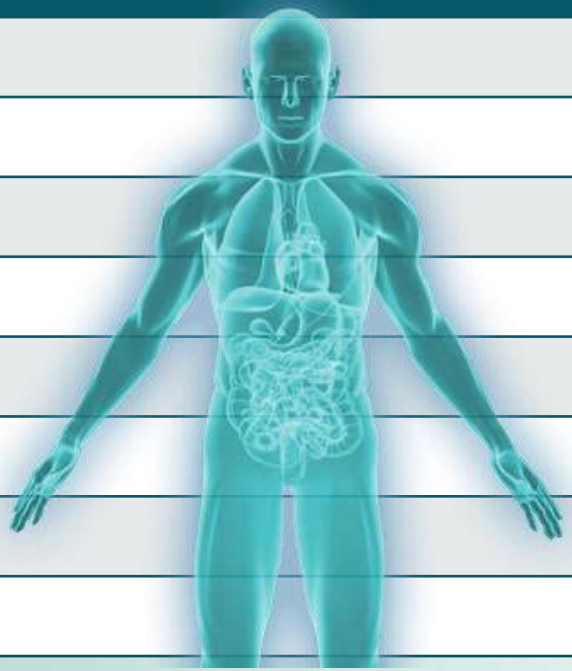
Tolerability Considerations With I-O Therapy

- **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.

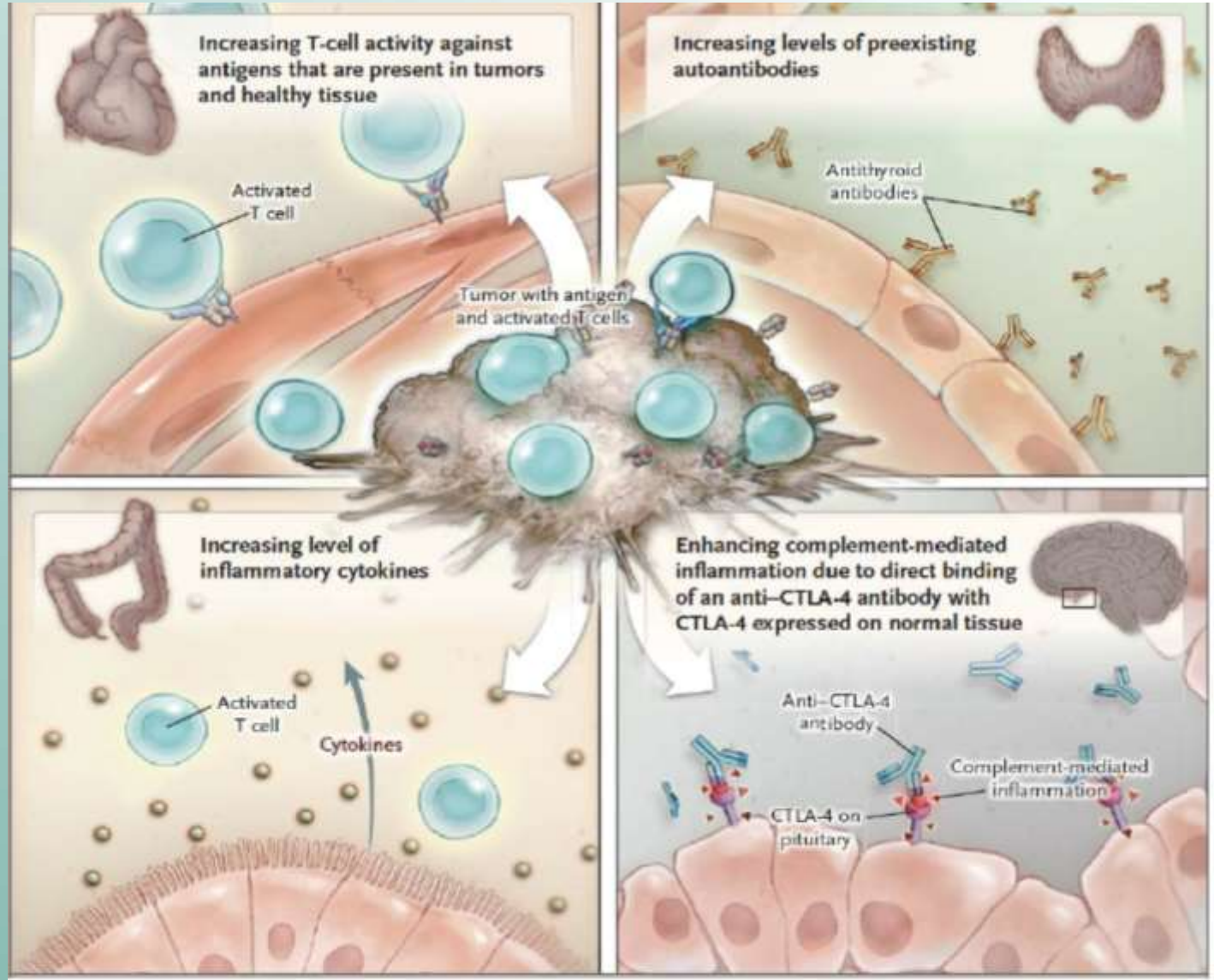
Organs Systems Often Affected by I-O Therapy-Related AEs

I-O therapy-associated AEs target certain organ systems[1]
Skin[1–6]
Endocrine system[2,4,6,7–10]
Liver[2,6,11–12]
Gastrointestinal tract[2,6,9,13]
Nervous system[6,10,14,15]
Eyes[1,4,16–18]
Respiratory system[1,5,6,10,15,19]
Hematopoietic cells[6,9,12,20–22]



1. Amos SM, et al. *Blood.* 2011;118:499–509; 2. Phan GQ, et al. *PNAS.* 2003;100:8372–8377; 3. Rosenberg SA. *J Immunother Emphasis Tumor Immunol.* 1996;19:81–84; 4. Chianese-Bullock KA, et al. *J Immunother.* 2005;28:412–419; 5. Harris J, et al. *Med Pediatr Oncol.* 1994;22:103–106; 6. Chow LQ. *Am Soc Clin Oncol Educ Book*. 2013:280–285; 7. Bendle GM, et al. *Nat Med.* 2010;16:565–570; 8. Soni N, et al. *Cancer Immunol Immunother.* 1996;43:59–62; 9. Ronnblom LE, et al. *Ann Intern Med.* 1991;115:178–183; 10. Fraenkel PG, et al. *J Immunother.* 2002;25:373–378; 11. Lamers CH, et al. *J Clin Oncol.* 2006;24:e20–e22; 12. Roskrow MA, et al. *Leuk Res.* 1999;23:549–557; 13. Parkhurst MR, et al. *Mol Ther.* 2011;19:620–626; 14. Pellkofer H, et al. *Brain.* 2004;127:1822–1830; 15. Smalley RV, et al. *Blood.* 1991;78:3133–3141; 16. Dudley ME, et al. *J Clin Oncol.* 2008;26:5233–5239; 17. Yeh S, et al. *Ophthalmology*. 2009;116:981–989; 18. Robinson MR, et al. *J Immunother*. 2004;27:478–479; 19. Morgan RA, et al. *Mol Ther.* 2010;18:843–851; 20. Kochenderfer JN, et al. *Blood.* 2010;116:4099–4102; 21. Lin TS, et al. *J Clin Oncol.* 2010;28:4500–4506; 22. Herishanu Y, et al. *Leuk Lymphoma.* 2003;44:2103–2108.

Potential mechanisms by which irAes develop

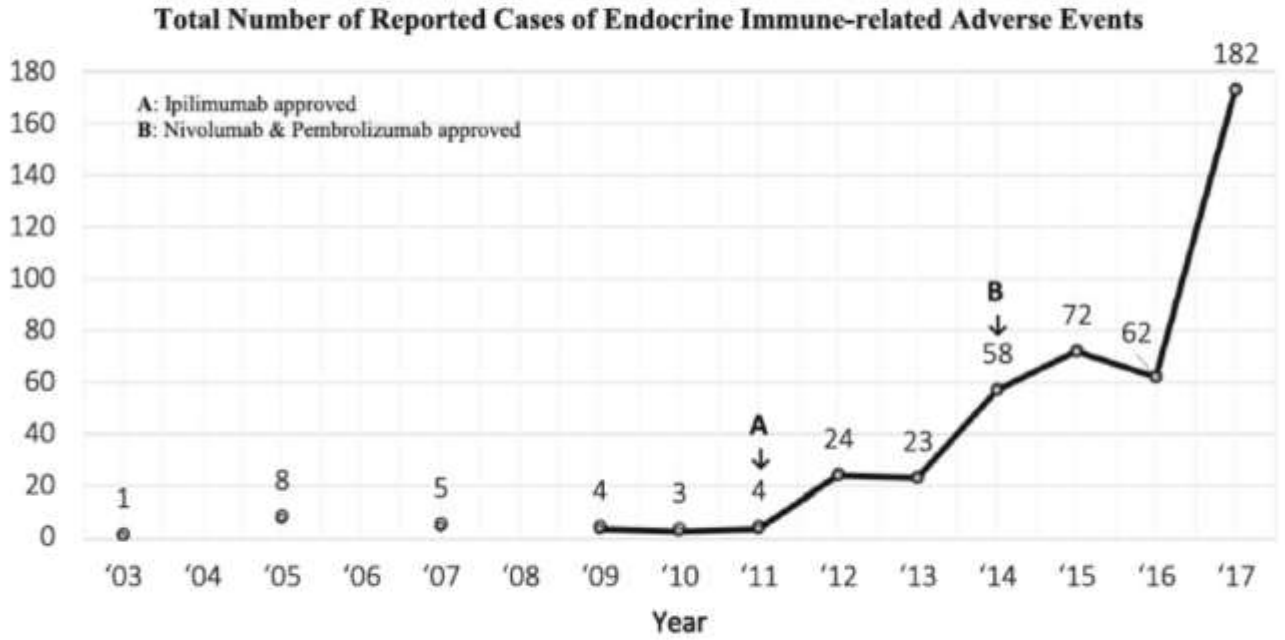


Correlation between irAE and efficacy in NSCLC treated with anti-PD-(L)1

Study	ICI	n	Grade ≥ 3 irAEs, %	RR, %		PFS, mo		OS, mo		Cycles, n	
				irAEs	No irAEs	irAE's	No irAEs	irAEs	No irAEs	irAEs	No irAEs
Ricciuti et al.[12]	Nivolumab	195	7.6	43.5	10.0	5.7	2.0	17.8	4.0	13	2.5
Moor et al.[13]	Nivolumab	196	13.2	NR	NR	5.9	2.5	23.8	6.4	NR	NR
Toi et al.[14]	Nivolumab	70	NR	57	12	12	3.6	NR	NR	12	7[a]
Haratani et al.[15]	Nivolumab	134	9	52	28	9.2	4.8	Not R	11.1	NR	NR
Teraoka et al.[16,b]	Nivolumab	43	0	37	17	6.4	1.5	NR	NR	NR	NR
Sato et al.[17]	Nivolumab	38	NR	64	7.4	Not R	1.6	NR	NR	NR	NR
Lisberg et al.[c]	Pembrolizumab	97	3.1	39.5	8.9	8.2	2	16.4	4.8	NR[d]	NR
Von Pawel et al.[19,b]	Atezolizumab	823	6.0	22.3	9.9	5.4	2.3	20.7	10.6	NR	NR
Kfoury et al.[20]	Anti-PD-1/PD-L1	618[e]	Grade ≥2 28.3%[e]	NR	NR	14.2	13.4	23.7	16.2	NR	NR
Toi et al.[21]	Anti-PD-1	137	NR[f]	52	13	10.3	3.4	Not R	11.4	NR	NR
Shafqat et al.[22]	Anti-PD-1/PD-L1	157[g]	11.4	NR	NR	24.4	4.2	NR	NR	NR	NR

Remon et al., J Thor Oncol 2019; Cortellini et al., Clin Lung Cancer 2019

Increase in frequency of reported of ir-endocrinopathies by ICI over the past 15 years



Tan et al., Clin Diab Endocrinol 2019

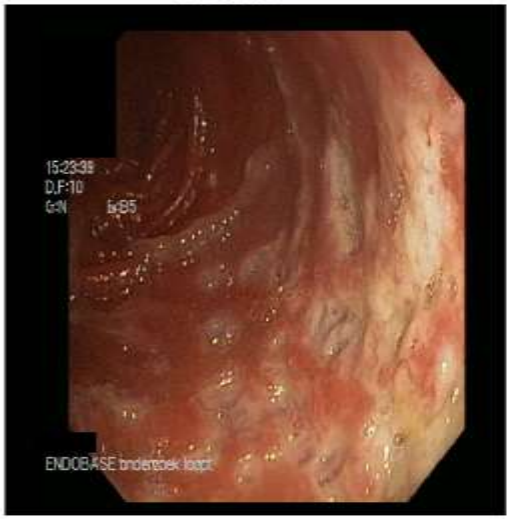
irAEs Can Occur After Discontinuation of ICIs

- **Retrospective review of 64 patients with advanced/unresectable melanoma treated with nivolumab + ipilimumab at a single center (Dec 2014 to Jan 2016)**
  - 31 patients stopped nivolumab + ipilimumab early due to toxicity
    - 4/31 (13%) experienced a clinically significant irAE > 16 wks after discontinuation (range: 22-33 wks post dose)

Shoushtari. JAMA Oncol. 2018;4:98.

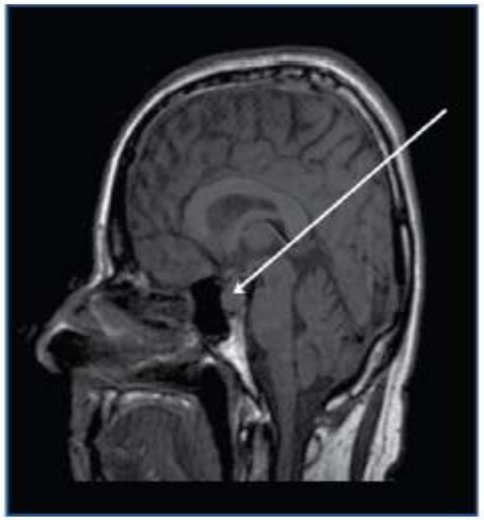
Immune related Adverse Events associated with anti-CTLA4

colitis



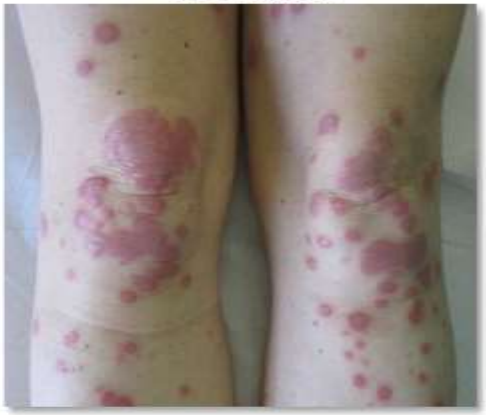
Thyroiditis
Hepatitis
Pneumonitis
Nephritis
Meningitis
etc.

hypophysitis



vitiligo

dermatitis



Haanen, unpublished, with patient consent

PD-1 & PD-L1 antibodies

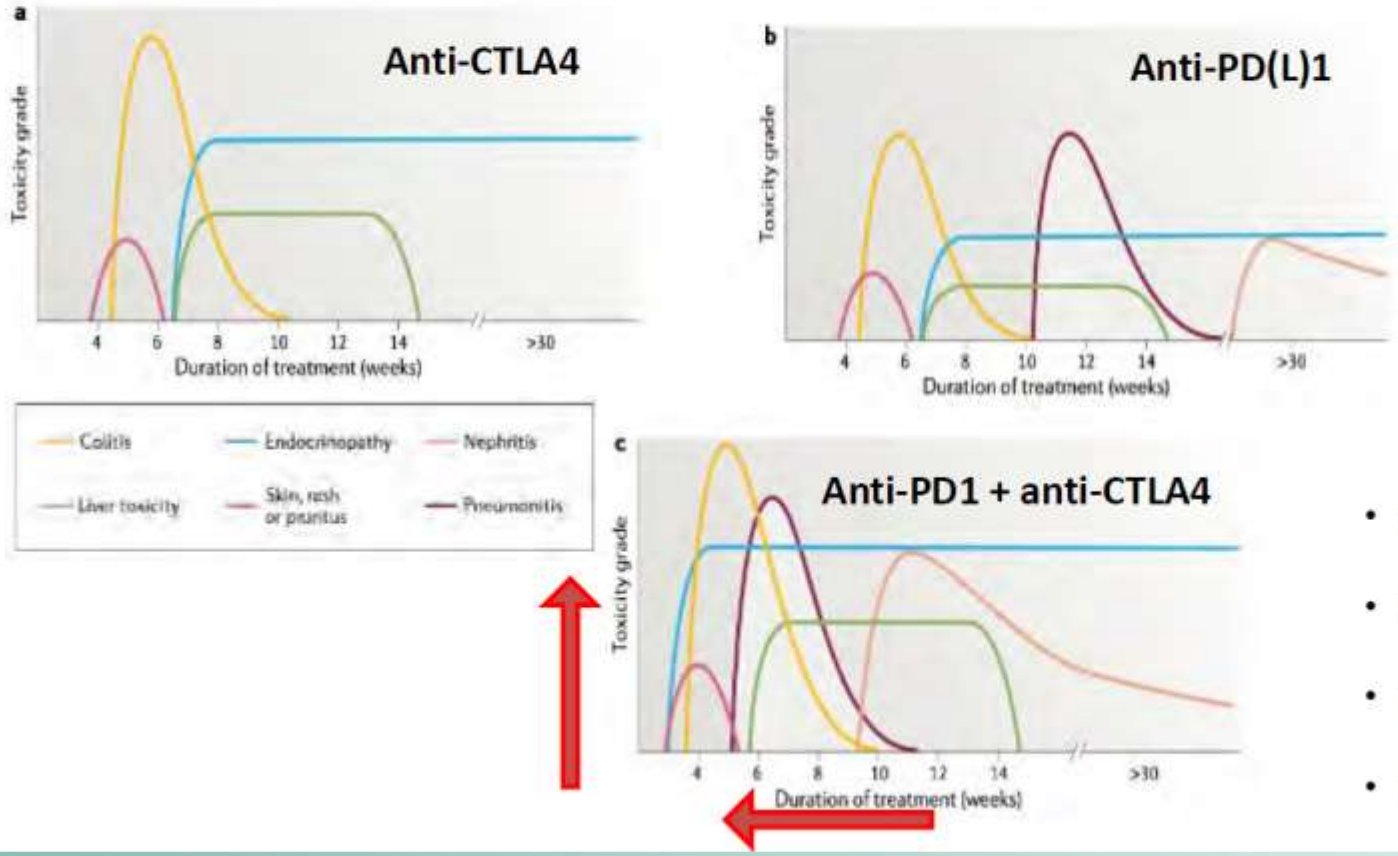
- **Different toxicity profiles from CTLA-4 antibodies [less severe & less frequent]**
- **High grade toxicities: 14% [24%]**
- **Thyroiditis: 9.5% [1.8%]**
- **Pneumonitis: 3% [<1%]**
- **Similar treatment**

Time of occurrence

- **Skin toxicity: 3 weeks**
- **Colitis: 5-10 weeks**
- **Hepatitis: 6-14 weeks**
- **Endocrinopathies: 7 weeks**
- **~Even several months after the last dose**

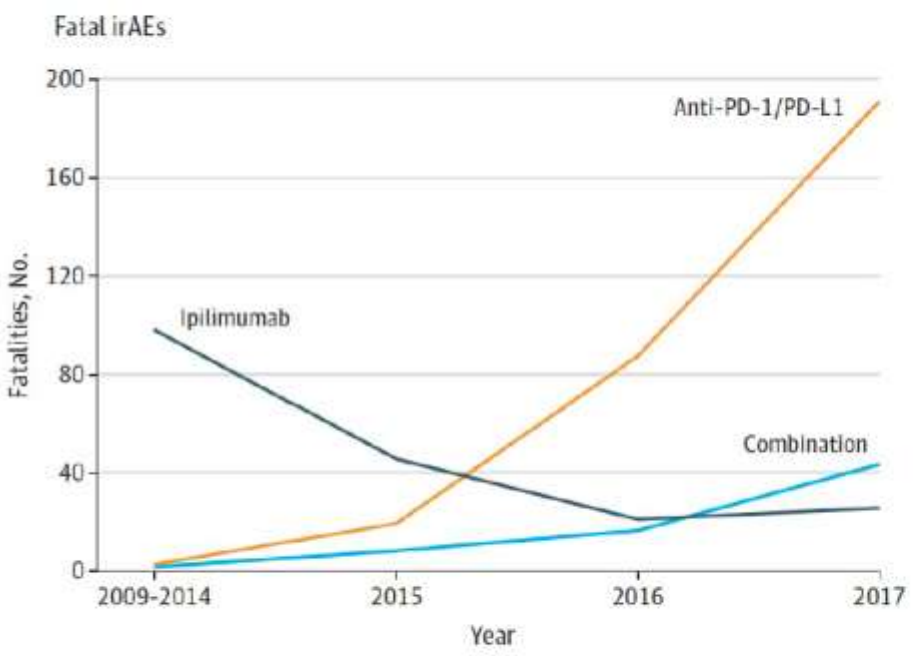
Kinetics of occurrence of side effects

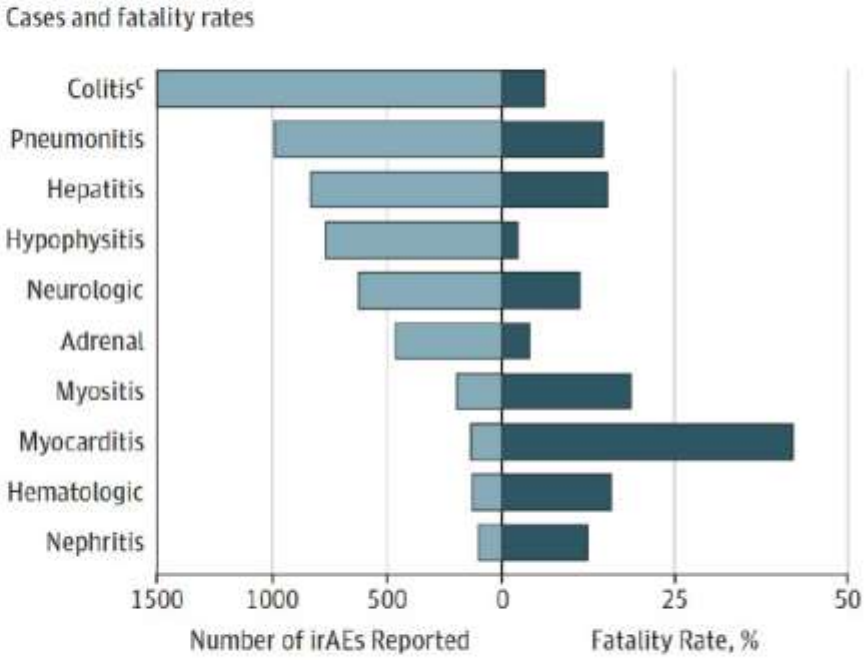
Martins et al. NRCO 2019



- Same toxicity spectrum
- More frequent toxicities
- More severe toxicities
- Earlier onset

Incidence of fatal irAE and fatality rates





Fatal irAE occur following ICI at a rate of 0.3 to 1.3%

Wang et al., JAMA Oncol 2018

Management of Immune-related Adverse Events

- Patient Education
- Clear Notification Pathway for Patients
- Infrastructure and Sub-specialty Consultants

1. Identify Toxicity Early
2. Treat Early and Aggressively → Algorithms
   - Start with corticosteroids
3. Oncologist-led Management

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AVEROM VAN LEEUWENHOEK

General Principles

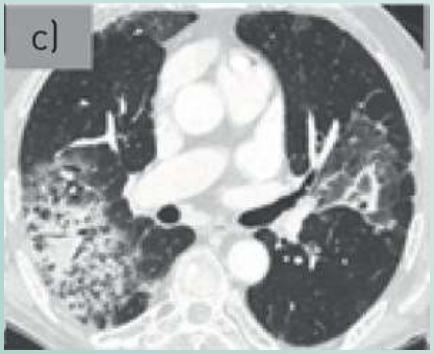
- Low Grade
  - Monitor closely (grade 1 and 2)
  - Delay therapy (grade 2)

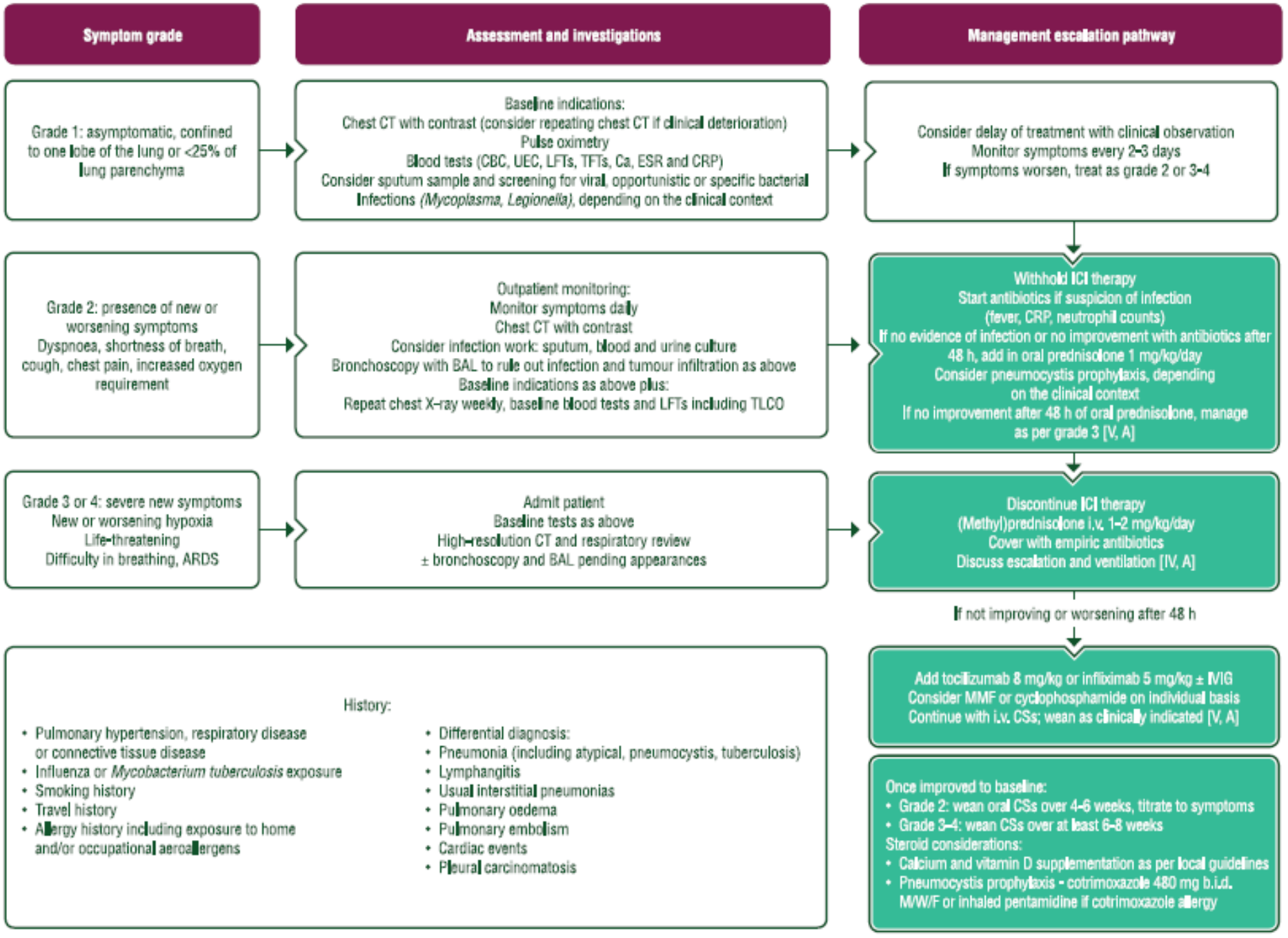
Moderate Grade ?

- High Grade → Immunosuppression
  - **Cease checkpoint inhibitor, consult sub-specialty and consider hospitalisation**
  - Systemic corticosteroids
  - Infliximab (anti-TNFa)
  - Mycophenolate mofetil
  - Tacrolimus
  - Other → plasmapheresis, anti-thymocyte globulin, IVIG

Case 3: Patient With Pulmonary Metastatic Melanoma and Acute Dyspnea

- **An 82-yr-old man presents to the emergency department with acute dyspnea, cough, and sputum production with bilateral basal crackles**
  - His daughter reports that he is receiving pembrolizumab for pulmonary metastatic melanoma, which was diagnosed 2 yrs ago
- **CT shows bilateral areas of consolidations and ground-glass infiltrates**




Symptom grade
Assessment and investigations
Management escalation pathway
Grade 1: asymptomatic, confined to one lobe of the lung or <25% of lung parenchyma
Baseline indications:
Chest CT with contrast (consider repeating chest CT if clinical deterioration)
Pulse oximetry
Blood tests (CBC, UEC, LFTs, TFTs, Ca, ESR and CRP)
Consider sputum sample and screening for viral, opportunistic or specific bacterial infections (Mycoplasma, Legionella), depending on the clinical context
Consider delay of treatment with clinical observation
Monitor symptoms every 2–3 days
If symptoms worsen, treat as grade 2 or 3–4
Grade 2: presence of new or worsening symptoms
Dyspnoea, shortness of breath, cough, chest pain, increased oxygen requirement
Outpatient monitoring:
Monitor symptoms daily
Chest CT with contrast
Consider infection work: sputum, blood and urine culture
Bronchoscopy with BAL to rule out infection and tumour infiltration as above
Baseline indications as above plus:
Repeat chest X-ray weekly, baseline blood tests and LFTs including TLCO
Withhold ICI therapy
Start antibiotics if suspicion of infection (fever, CRP, neutrophil counts)
If no evidence of infection or no improvement with antibiotics after 48 h, add in oral prednisolone 1 mg/kg/day
Consider pneumocystis prophylaxis, depending on the clinical context
If no improvement after 48 h of oral prednisolone, manage as per grade 3 [V, A]
Grade 3 or 4: severe new symptoms
New or worsening hypoxia
Life-threatening
Difficulty in breathing, ARDS
Admit patient
Baseline tests as above
High-resolution CT and respiratory review
± bronchoscopy and BAL pending appearances
Discontinue ICI therapy
(Methyl)prednisolone i.v. 1–2 mg/kg/day
Cover with empiric antibiotics
Discuss escalation and ventilation [IV, A]
If not improving or worsening after 48 h
Add tocilizumab 8 mg/kg or infliximab 5 mg/kg ± IVIG
Consider MMF or cyclophosphamide on individual basis
Continue with i.v. CSs; wean as clinically indicated [V, A]
History:
• Pulmonary hypertension, respiratory disease or connective tissue disease
• Influenza or Mycobacterium tuberculosis exposure
• Smoking history
• Travel history
• Allergy history including exposure to home and/or occupational aeroallergens
• Differential diagnosis:
• Pneumonia (including atypical, pneumocystis, tuberculosis)
• Lymphangitis
• Usual interstitial pneumonias
• Pulmonary oedema
• Pulmonary embolism
• Cardiac events
• Pleural carcinomatosis
Once improved to baseline:
• Grade 2: wean oral CSs over 4–6 weeks, titrate to symptoms
• Grade 3–4: wean CSs over at least 6–8 weeks
Steroid considerations:
• Calcium and vitamin D supplementation as per local guidelines
• Pneumocystis prophylaxis - cotrimoxazole 480 mg b.i.d. M/W/F or inhaled pentamidine if cotrimoxazole allergy

Ρευματολογική τοξικότητα

Epidemiology

- ✓ **Incidence of rheumatic irAEs is less well characterized**

-Oncology clinical trial adverse event reporting uses several mutually exclusive codes for musculoskeletal symptoms (For example, arthritis can be coded as arthralgia, arthritis, swelling in joint or pain in extremity).

-Most rheumatic irAEs do not lead to death or hospitalization and thus may not be reported.

-Grading of rheumatological irAEs might partially explain the low severity of rheumatic irAEs reported. The CTCAE grading system used by oncologists requires events to be disabling or leading to hospitalization to be a grade 3 or higher event, which is not a reasonable metric for grading the severity of many rheumatic complications, especially inflammatory arthritis.

-Finally, rheumatic irAEs can be late adverse events occurring up to 2 years after patients have started CPI

- ✓ **Inflammatory arthritis 5.1%**
- ✓ **Myositis 0.8%**

Calabrese et al , Nat Rev Rheumatol 2018

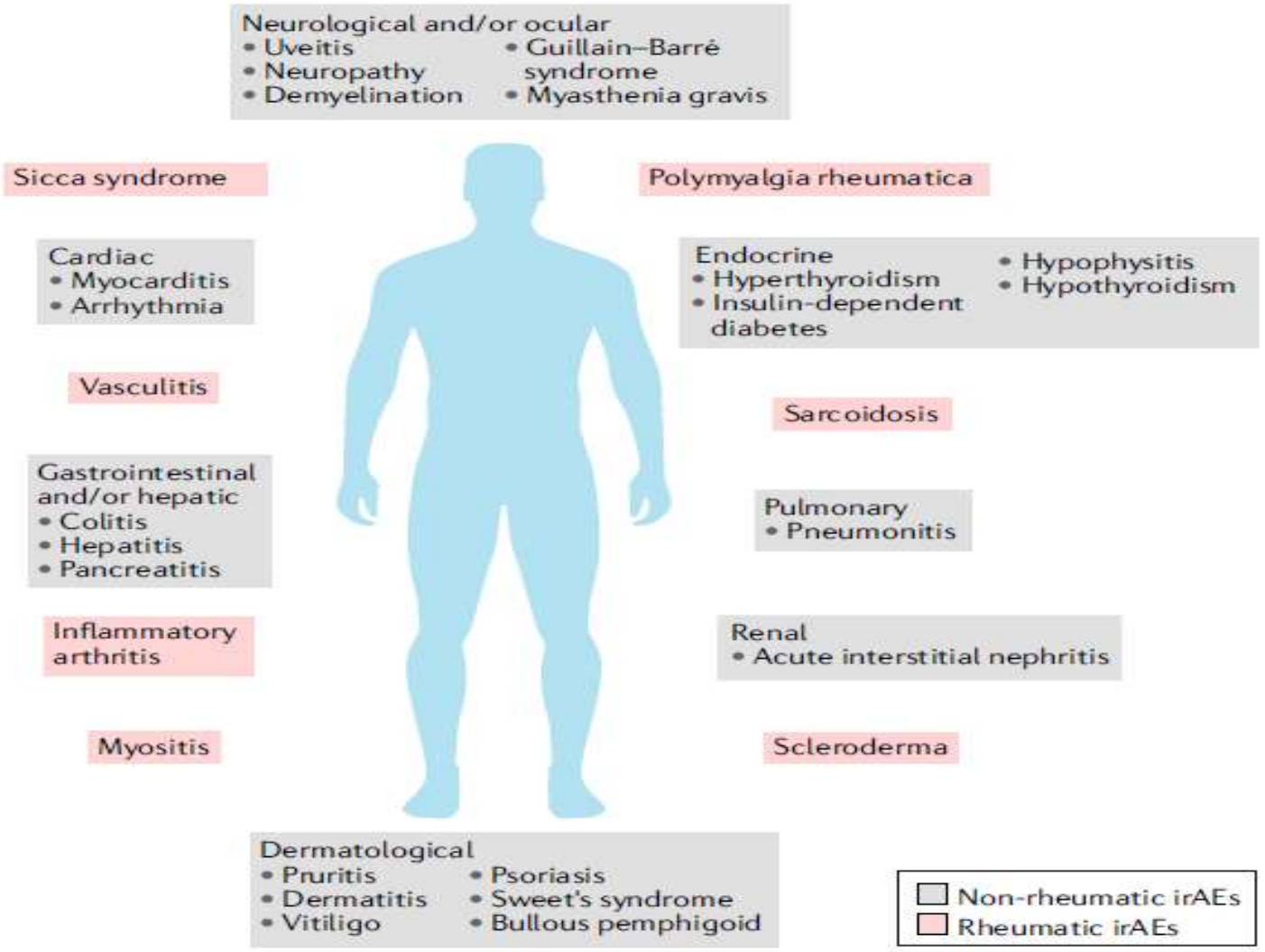


Fig. 1 | **irAEs can affect most organ systems.** Although dermatological, gastrointestinal and endocrine immune-related adverse events (irAEs) are the most frequently reported irAEs, irAEs can affect nearly every organ system and can range from mild and self-limiting to severe and life threatening. Many of these irAEs mirror rheumatic diseases.

Calabrese et al , Nat Rev Rheumatol 2018

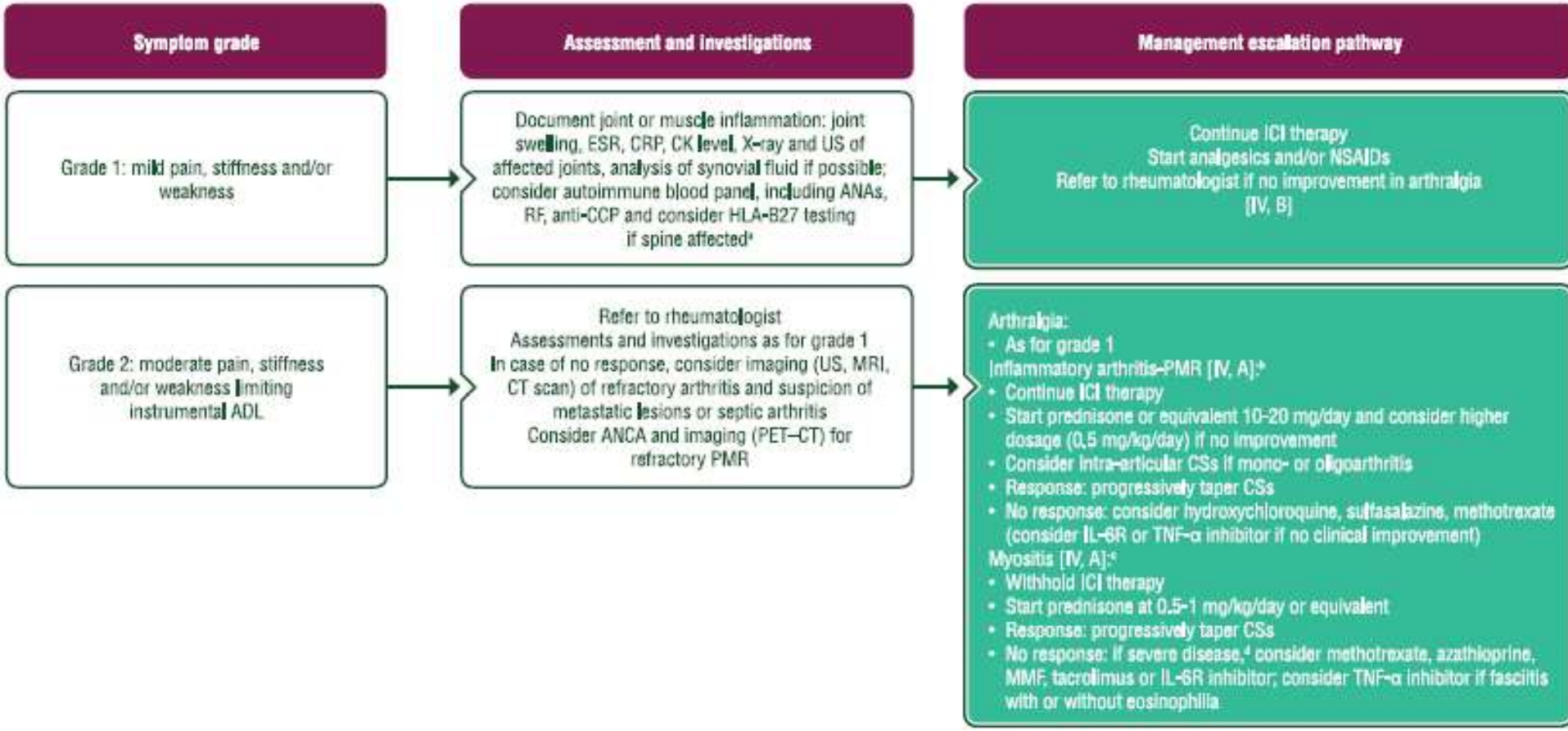
Table 2 | **Comparison of major rheumatic irAEs with corresponding rheumatic diseases**

Rheumatic irAE	Rheumatic disease comparator	Similarities to rheumatic disease	Differences from rheumatic disease
Inflammatory arthritis	RA	• Can cause erosive disease • Many patients with similar joint distribution (MCPs, PIJs, wrists and knees)	• Tendon involvement more prominent early in course of disease • Early erosions • RF and CCP often negative • Not female-predominant
	SpA and PsA	• SpA features such as inflammatory back pain, enthesitis and dactylitis • Sterile urethritis and conjunctivitis with oligoarthritis (reactive arthritis-like)	• Concomitant psoriasis rarely reported • HLA-B27-positivity not reported • Early erosions
Polymyalgia rheumatica and/or GCA	Polymyalgia rheumatica and/or GCA	• Biopsy findings in GCA-like irAEs similar to the rheumatic disease comparator • Patients aged >50 years	• Patients with polymyalgia rheumatica-like disease do not always have elevated inflammatory markers • Some patients with polymyalgia rheumatica-like disease not responsive to low-dose prednisone
Inflammatory myopathy	Dermatomyositis, polymyositis and immune-mediated necrotizing myopathy	• Range of creatine kinase is 10–100 IU/l (upper limit of normal) • Biopsy results are consistent with dermatomyositis, polymyositis or immune-mediated necrotizing myopathy • Can have myasthenia with myositis	• Classic dermatomyositis rash rare • Response to intravenous immunoglobulin may be less effective in irAE
Sicca syndrome	Sjogren syndrome	• Dry mouth responds to treatment with sialagogues • Dry mouth and eyes common	• anti-Ro and anti-La antibodies rare • Rare parotitis

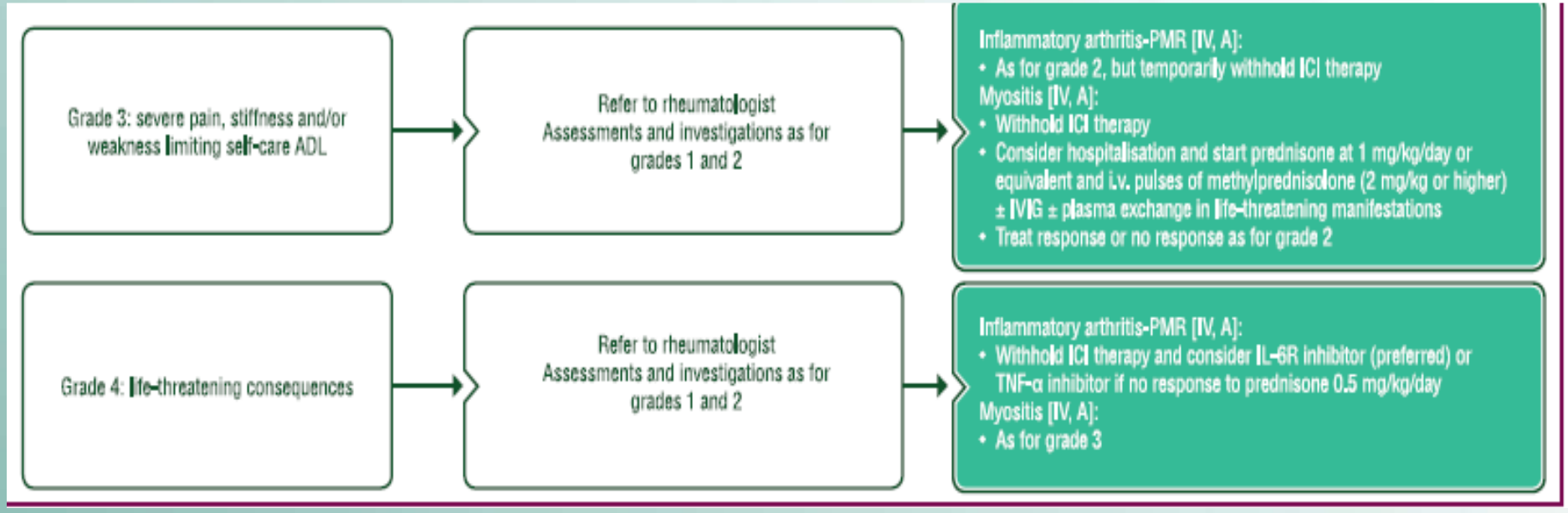
CCP, cyclic citrullinated peptide; GCA, giant cell arteritis; irAE, immune-related adverse event; IU, international units; MCP, metacarpophalangeal joint; PIJ, proximal interphalangeal joint; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RF, rheumatoid factor; SpA, spondyloarthritis.

Calabrese et al , Nat Rev Rheumatol 2018

Rheumatological toxicity-ESMO guidelines



Rheumatological toxicity



Box 3 | **Treatment considerations for rheumatic irAEs**

1) How severe is the irAE?
Severity of disease can affect treatment options. For patients with the immune-related adverse events (irAEs) of mild arthritis or arthritis with only one joint involved, management with NSAIDs and intra-articular steroids is an option[19,33], whereas for patients with severe arthritis and existing erosions, high-dose prednisone (>40 mg/day) and early DMARDs might be more appropriate.

2) Will the patient continue CPI therapy, and what is the future oncology treatment plan?
If the patient has a partial tumour response to immunotherapy and has been on the medication for a limited time, the oncologist might want to continue immunotherapy as long as is feasible. Such a therapeutic extension can mean two things: first, that the irAE can be potentiated by the therapy and, second, that the rheumatologist treatment options might be limited by theoretical concerns that immunosuppressive drugs selected to treat irAEs might inhibit the antitumoural effect of the checkpoint inhibitor (CPI), as well as patient and oncologist preferences regarding immunosuppressive drug selection. This scenario can be a difficult situation clinically, but understanding the long-term plan and goals for cancer therapy helps the rheumatologist explain treatment limitations to the patient.

3) Is the patient in a clinical trial, and if so, what are limitations according to the protocol?
Many clinical trials do not allow DMARDs or >10 mg daily doses of corticosteroid (prednisone equivalent) concurrently with CPI treatment.

4) What are the comorbidities, including other irAEs?
TNF inhibition might treat irAEs in patients with colitis or inflammatory arthritis[107]. Similarly, a patient with myositis and immune-mediated thrombocytopenia might benefit from intravenous immunoglobulin administration[108].

5) What are the patient and oncologist preferences?
As there are limited data presently about the safety of long-term immunosuppression for the treatment of irAEs and effects on tumour response, some variation is to be expected. Data regarding melanoma have shown no difference in tumour response with short-term TNF inhibition for the treatment of irAEs[109], but similar data have not been published in other tumour types. Given the lack of evidence-based guidelines, consensus-based treatment decisions are often reasonable.

6) Are non-immunosuppressive therapies to address symptoms available?
Sicca symptoms can often be addressed with topical, oral or ocular therapies or sialagogues, all of which would not be expected to have any effect on tumour response.

7) What is the plan for longitudinal follow-up?
Additional irAEs might occur long after initiation or even after cessation of CPI therapy. Serial monitoring by the rheumatologist and oncologist regarding this problem, or regarding loss of CPI efficacy, is critical.

Προϋπάρχουσες αυτοάνοσες παθήσεις

Selected exclusion criteria in Empower-Lung 01

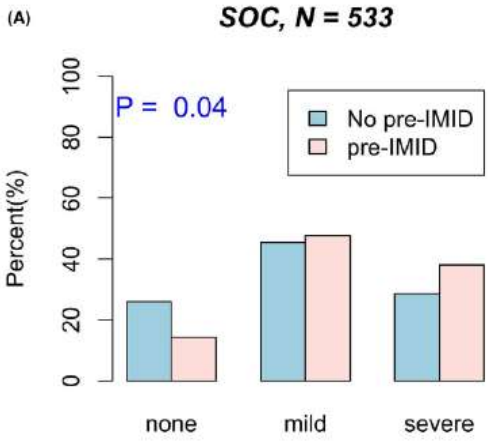
Patients were ineligible if they had ...

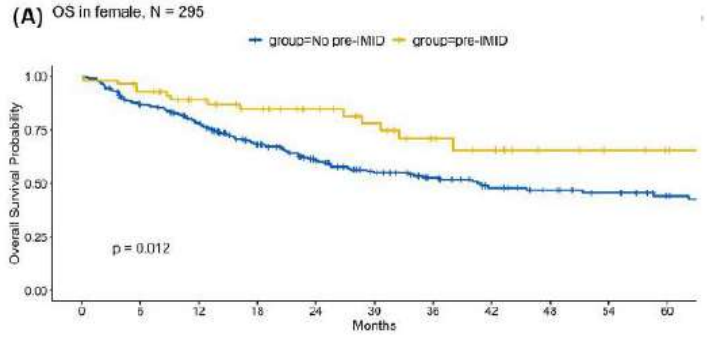
- Active, known, or suspected autoimmune disease that required systemic treatment during the previous 2 years
- Patients with a condition requiring corticosteroid therapy (>10 mg prednisone/day or equivalent) within 14 days of randomization.
- Active infection, e.g tuberculosis
- Uncontrolled infection with hepatitis B or C or HIV.
- Recipients of organ transplants
- ECOG performance status of ≤1
- Unstable brain metastases

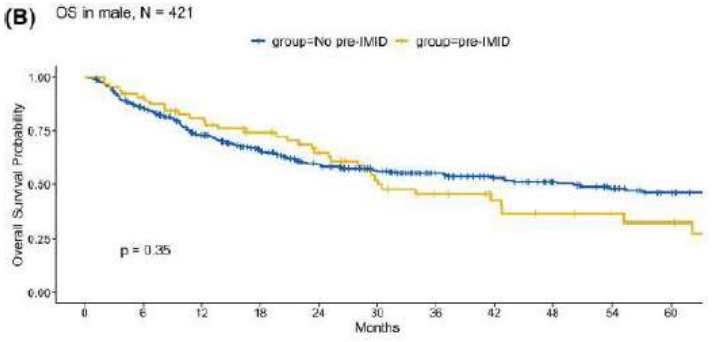
Sezer et al, Lancet 2021

Melanoma: Preexisting immune-mediated inflammatory disease

Immune-mediated inflammatory disease	Number of patients	Females	Males
Asthma	42	22	20
Inflammatory bowel disease (Crohn's disease plus ulcerative colitis)	10	4	6
Psoriasis (including Psoriatic arthritis)	9	2	7
Rheumatoid arthritis	8	5	3
Eczema	6	2	4
Polymyalgia rheumatica	3	1	2
Celiac disease	1	1	0
Sarcoidosis	1	1	0
Scleroderma	1	0	1
Lupus	1	1	0
Graves' disease	1	1	0







Pre-IMID is associated with improved OS in female but not in male melanoma patients treated with ICI.

Gulati et al, Cancer Medicine. 2021;10:7457–7465

Pre-Existing Autoimmune Disease

matched pair control study

- 17 497 patients with preexisting autoimmune diagnoses prior to treatment with anti –PD(L)1 therapy
- 17 497 matched controls through the TriNetX Diamond network of more than 200 million patients across the United States and Europe.

Baseline characteristic	ICI with baseline autoimmunity	ICI without baseline autoimmunity
Total No. of patients	17 497	17 497
Cancer type, mean No. (%)		
Digestive organs	3378 (19.3)	3402 (19.4)
Bronchus and lung	11 079 (63.3)	11 118 (63.5)
Melanoma of skin	3948 (22.6)	3903 (22.3)
Urinary tract	3307 (18.9)	3235 (18.5)
Ill-defined, other secondary, and unspecified sites[c]	13 524 (77.3)	13 617 (77.8)

Tang et al, J Natl Cancer Inst (2022) 114(8): djac046

Pre-Existing Autoimmune Disease

Baseline autoimmune disease does not statistically significantly worsen clinical outcomes in cancer patients treated with ICI

- rheumatoid arthritis
- inflammatory bowel disease
- mucositis

diseases that tend to be more severe, often requiring systemic immunosuppression, which may be responsible for increased association with mortality in subgroup analyses.

Autoimmune diagnosis	No.	Hazard ratio (95% CI)[a]	P[b]
Myasthenia gravis	108	1.31 (0.85 to 2.02)	.21
Morphea	205	1.29 (0.93 to 1.79)	.13
Vasculitis	494	1.18 (0.97 to 1.44)	.09
Scleroderma	128	1.12 (0.77 to 1.63)	.55
Type 1 diabetes	3960	1.11 (1.03 to 1.19)	.002
Psoriasis	1827	1.07 (0.96 to 1.19)	.24
Mucositis	3181	1.04 (0.97 to 1.12)	.30
Inflammatory bowel disease	10 415	1.03 (0.99 to 1.08)	.17
Ankylosing spondylitis	164	1.02 (0.72 to 1.46)	.90
Rheumatoid arthritis	3176	1.01 (0.93 to 1.09)	.80
Autoimmune hepatitis	109	1.00 (0.64 to 1.57)	.99
Graves disease	416	0.96 (0.76 to 1.20)	.68
Multiple sclerosis	281	0.93 (0.70 to 1.23)	.60
Dermatomyositis	79	0.93 (0.55 to 1.55)	.77
Atopic dermatitis	1057	0.89 (0.77 to 1.03)	.12
Systemic lupus erythematosus	541	0.89 (0.74 to 1.06)	.19
Addison disease	920	0.88 (0.76 to 1.01)	.08
Bullous pemphigoid	59	0.86 (0.46 to 1.60)	.64
Hashimoto disease	655	0.75 (0.62 to 0.90)	.002
Celiac disease	241	0.74 (0.57 to 0.97)	.03
Lichen planus	292	0.70 (0.53 to 0.93)	.01
Alopecia areata	94	0.61 (0.39 to 0.97)	.04
Vitiligo	161	0.52 (0.34 to 0.81)	.003
Any cutaneous diagnosis	17 497	1.03 (1.00 to 1.07)	.05

[a]Hazard ratio of the impact of preexisting autoimmune disease on overall survival when compared with patients without preexisting autoimmune disease. Anti-PD-1 = antiprogrammed cell death receptor-1; Anti-PD-L1 = antiprogrammed cell death ligand-1; CI = confidence interval.
[b]Benjamini-Hochberg P value of statistical significance at ≤.006. Log-rank test was used to calculate P values, 2-sided.

Tang et al, J Natl Cancer Inst (2022) 114(8): djac046

Preexisting autoimmune Diseases and Immunotherapy

Table 2 Clinical studies reporting efficacy/safety outcomes in CPI-treated advanced NSCLC patients with preexisting autoimmune diseases

Author	Type of study	Patients, n	Tumor type	CPI type	Line of treatment	Preexisting AIDs	AIDs flare	irAEs	ORR
Danlos *et al.* (58)	Prospective	397 (AID 45; no AID 352)	Melanoma (80%); NSCLC (13%); others (7%)	PD-1/PD-L1	Median of 1 previous line of treatment	Vitiligo 32%; Ps/PsA 22%; TD 13%; pSS 7.5%; RA 3.8%; MS 3.8	24.4%	AID 44.4%; no AID 23.8%	AID 38%; no AID 28%
Cortellini *et al.* (59)	Multicenter retrospective observational	751 (AID 85; no AID 666)	NSCLC (65.5%); melanoma (21.2%); renal cell (12.5%); others (0.8%)	PD-1	1st line 83.3%; 2nd line 51.4%; 3rd line 18%; >3rd line 7.3%	Thyroid disorders (60%); dermatologic (16.4%); rheumatologic (11.8%); others (7.1%); multiple site (4.7%)	47.1%	AID 65.9%; no AID 39.9%	Active AID (50%); inactive AID (38.1%); no AID (35.3%)
Leonardi *et al.* (60)	Retrospective	56 AID	NSCLC	PD-1/PD-L1	NA	Ps/PsA (25%); IBD (20%); RA (19.5%); TD (16%) PMR (9%); SS (3.8%); MS (3.8%); others (5.4%)	23%	38%	22%
Tison *et al.* (61)	Retrospective cohort study	112	Melanoma (59%); NSCLC (35%); other (6%)	PD-1/PD-L1 (84%); CTLA-4 (13%); combination (3%)	1st line 44%; 2nd line 32%; >2nd line 23%	Psoriasis/PsA (28%); RA (18%); IBD (13%); SpA (4.5%); lupus (6.3%); PMR/GCA (6.3%); others (25%)	42%	38%	Melanoma 48%; NSCLC 54%
Abu-Sbeih *et al.* (62)	Multicenter retrospective	102	Melanoma (44%); lung (23%); GI (17%); GU (7%); others (10%)	PD-1/PD-L1 (83%); CTLA-4 (7%); combination (10%)	NA	Crohn's disease (48%); ulcerative colitis (48%); unclassified (4%)	NA	41%	48%

AID, autoimmune disease; GCA, giant cell arteritis; GI, gastrointestinal; GU, genitourinary; IBD, inflammatory bowel diseases; ICI, immune checkpoint inhibitor; irAEs, immunotherapy-related adverse events; MS, multiple sclerosis; NA, not available; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PMR, polymyalgia rheumatica; pSS, primary Sjögren syndrome; Ps, psoriasis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, spondylosis arthropathy; SS, scleroderma; TD, thyroiditis.

- 14-25% of lung cancer pts have Autoimmun-disease (AID)
- Association of Rheumatoid Arthritis and Lung Cancer (up 1.77 fold risk)
- Outcomes from obervational studies:
  - Ir AEs 24-41%
  - AID FLARE 23-47%

Passiglia et al, Transl Lung Cancer Res 2021;10(6):2876-2889; Zhang et al, Front. Immunol. 13:1050876

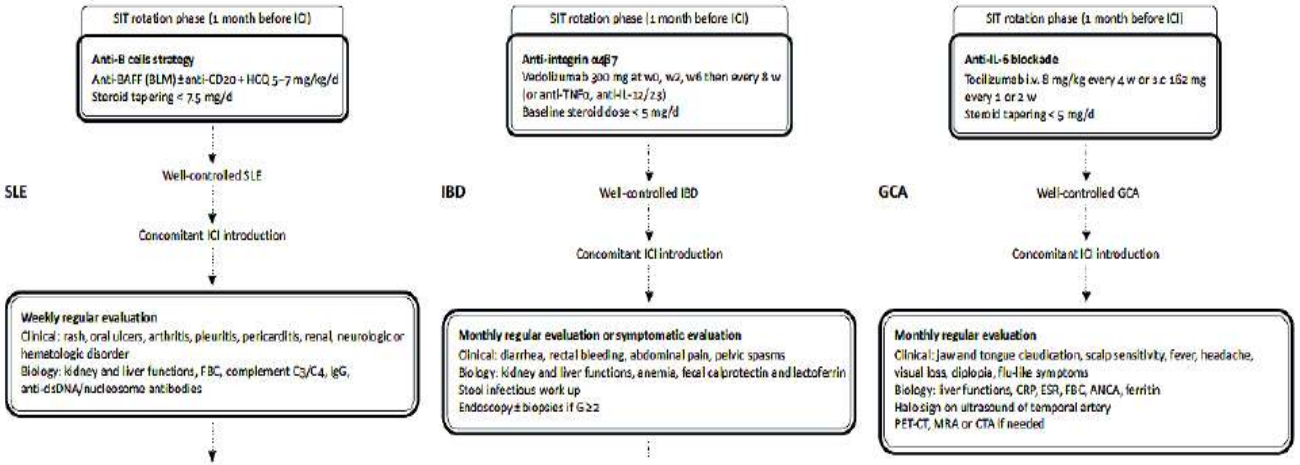
Recommendations for Pre-existing AD

international panel of experts from the International Association for the Study of Lung Cancer (IASLC)

Current evidence indicates that ICI could be offered to patients with NSCLC with non–life-threatening and quiescent AIDs. Nevertheless, close monitoring is highly recommended. Available evidence cannot be extrapolated to cases with more severe AID or in patients with specific AID subtypes.

depending on autoimmune pathology, 2-step approach:

- first phase lasting 1 month: control the autoimmune pathology
- second phase: immunotherapeutic drug may be introduced
- Monitoring, Multidisciplinary Team



Remon_Journal of Thoracic Oncology Vol. 15 No. 6: 914-947; Haanen et al, Ann Oncol 2020 Jun;31(6):724-744

Conclusions

- 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

- Immune checkpoint inhibitors (ICIs) against CTLA-4 and PD-1/PD-L1 are very commonly used in everyday practice and produce durable responses
- Therapy with ICIs can result in a novel spectrum of AEs arising from the activation of the immune system and require prompt recognition and treatment
- Incidence of rheumatic irAEs is less well characterized
- ESMO guidelines suggest refer to a rheumatologist for ≥ 2 events
- I-O can be offered in patients with pre-existing autoimmune diseases