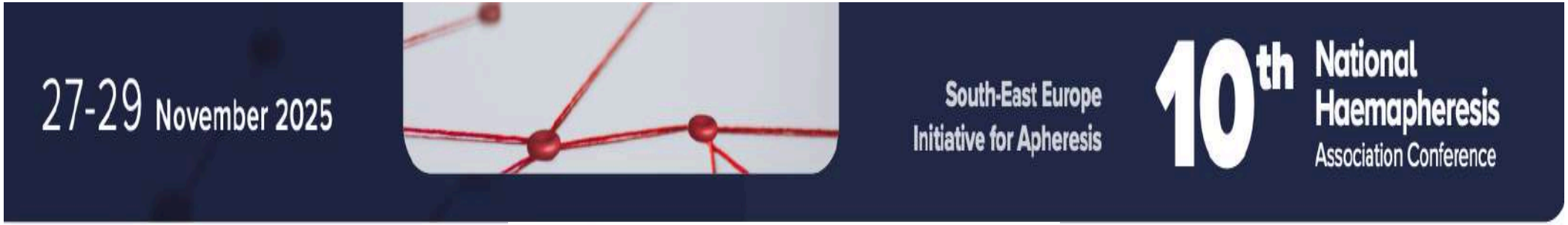

ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ
ΑΙΜΑΦΑΙΡΕΣΗΣ

Immune Checkpoint Inhibitors (ICI) και πλασμαφαίρεση

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Κατευθυντήριες οδηγίες ASFA – 9η επικαιροποίηση

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Journal of Clinical Apheresis ASFA WILEY

Guidelines on the Use of Therapeutic Apheresis in Clinical Practice – Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Ninth Special Issue

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L. Connely-Smith et al, J. of Cl Aph. 2023

Κατευθυντήριες οδηγίες ASFA – 9η επικαιροποίηση

166 graded and categorized indications. This includes seven new fact sheets, nine new indications on existing fact sheets, and eight changes in the category for existing indications. The Ninth Edition of the JCA Special Issue seeks to continue to serve as a key resource that guides the utilization of TA in the treatment of human disease.

L. Connely-Smith et al, J. of Cl Aph. 2023

TABLE 6 Diseases/conditions considered for new fact sheets in 2023.

Incorporated as new fact sheets
Alzheimer's disease
Autoimmune dysautonomia
Idiopathic inflammatory myopathies
Immune checkpoint inhibitors, immune-related adverse events
Paraneoplastic autoimmune retinopathies
Transplantation, intestine
Vaccine-induced immune thrombotic thrombocytopenia
Incorporated into existing fact sheets
Mechanical hemolysis incorporated into acute toxins, venoms and poisons
Methemoglobinemia incorporated into acute toxins, venoms and poisons
Bone marrow necrosis/fat embolism syndrome incorporated into sickle cell disease, acute
Insufficient evidence at time of review
Autoimmune myofasciitis
Autoimmune recurrent pregnancy failure
Hyperbilirubinemia, kidney failure/bile cast nephropathy
Pancreatic transplantation
Platelet refractoriness due to human leukocyte antigen (HLA) antibodies
Transplantation, composite tissue

Κατευθυντήριες οδηγίες ASFA – 9η επικαιροποίηση

Sixteen diseases/conditions were considered for the creation of new fact sheets. To meet criteria for a new fact sheet, the committee required a minimum of 10 cases published in the last decade in peer-reviewed journals, ideally by more than one group. Based on these criteria, there were seven new fact sheets added to this edition (Table 1,

IMMUNE CHECKPOINT INHIBITORS, IMMUNE-RELATED ADVERSE EVENTS

Incidence: 39% to 70% of patients treated with immune checkpoint inhibitors

Indication	**Procedure**		**Category**	**Grade**
	TPE		III*	2C
# Reported patients: 100 to 300	**RCT**	**CT**	**CS**	**CR**
	0	0	9 (46)	75 (75)

*Immune related adverse events due to immune checkpoint inhibitor toxicity include myasthenia gravis, thrombotic thrombocytopenic purpura (see *separate fact sheets*), myocarditis, myositis, and transverse myelitis, among other conditions.

L. Connely-Smith et al, J. of Cl Aph. 2023

Κατευθυντήριες οδηγίες ASFA – 9η επικαιροποίηση

TABLE 1 (Continued)

Disease/condition	Indication	Procedure	Category	Grade	Page
IgA nephropathy	Crescentic	TPE	III	2B	165
	Chronic progressive	TPE	III	2C	
Immune checkpoint inhibitors, immune-related adverse events[a]		TPE	III	2C	167
Immune thrombocytopenia	Refractory	TPE/IA	III	2C	169

III Optimum role of apheresis therapy is not established. Decision-making should be individualized.

Grade 2C	Weak recommendation, low-quality or very low-quality evidence	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

L. Connely-Smith et al, J. of Cl Aph. 2023

27-29 November 2025

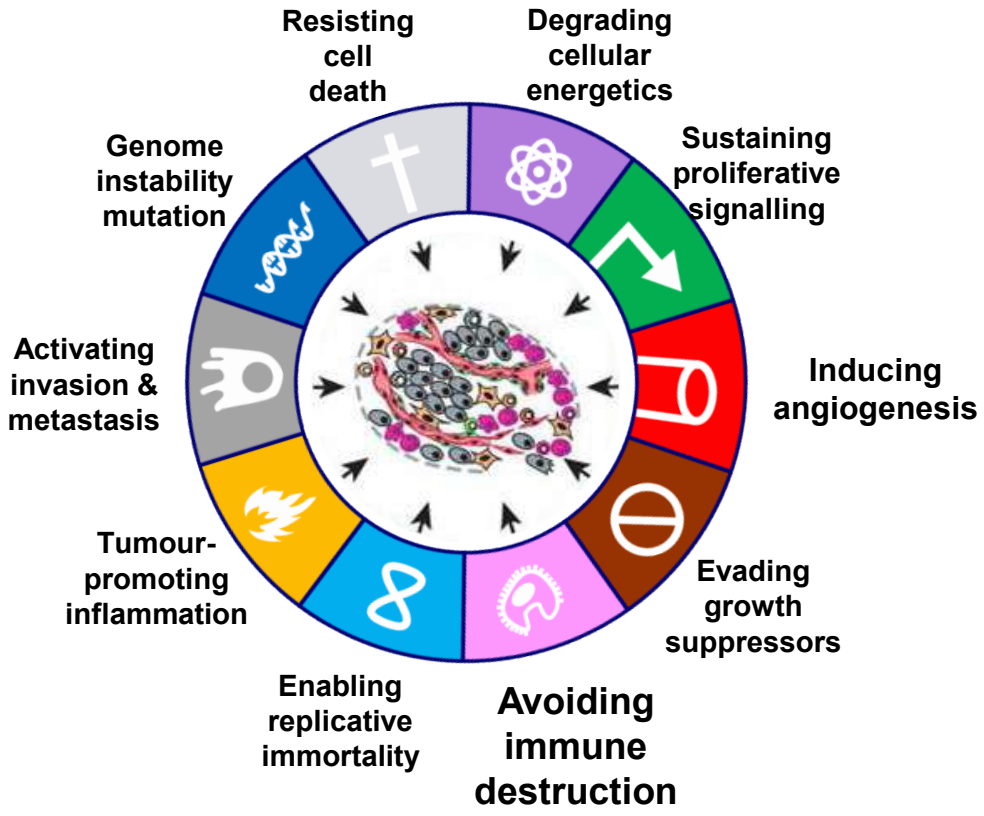
South-East Europe Initiative for Apheresis

10th National Haemapheresis Association Conference

ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΑΙΜΑΦΑΙΡΕΣΗΣ

Immune Checkpoint Inhibitors (ICI)
Αναστολείς σημείων ελέγχου ανοσοποιητικού στην αντιμετώπιση του καρκίνου

Χαρακτηριστικά καρκινικών κυττάρων
Κύκλος DOUGLAS HANAHAN



Hanahan & Weinberg. Cell 2011

Διαφορετικές θεραπευτικές προσεγγίσεις στην αντιμετώπιση του καρκίνου

Surgery can be used to either remove the entire tumour, debulk or alleviate cancer symptoms[1]

Surgery

Radiation

High dose x-rays are used to kill cancer cells or slow their growth by damaging their DNA. Nearby health cells can be affected and become damaged[1]

Chemotherapy works by preventing or inhibiting the growth of cancer cells. Used to either treat cancer or alleviate the symptoms of cancer by shrinking the tumour. Not only kills cancer cells but kills healthy cells that grow and divide rapidly[1]

Chemotherapy / Targeted therapy

Immuno-Oncology

I-O is based on the principle of stimulating the body's own immune system to generate, restore or augment an anti-tumour immune response to control or eradicate cancer cells[2]

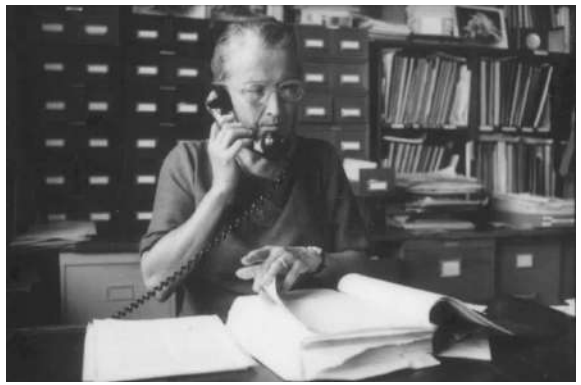
1. NIH National Cancer Institute. Types of cancer treatment. Available at: https://www.cancer.gov/about-cancer/treatment/types [accessed August 2018];
2. Masters GA, et al. J Clin Oncol 2015;33:786–809

2600 π.Χ. Αιγύπτιος φυσικός Ιμχοτέπ – Πάπυρος Έμπερς

William B. Coley, M.D.

1891 μ.Χ. Dr William B. Coley ο »πατέρας της ανοσοθεραπείας»

Τοξίνη του Coley



1953 μ.Χ. Helen Coley Nauts ιδρύει το Ινστιτούτο Έρευνας του Καρκίνου
1ο μη κερδοσκοπικό οργανισμό αφιερωμένο εξολοκλήρου στην ανάπτυξη της ανοσοθεραπείας

Ιστορία ανοσοθεραπείας στον καρκίνο

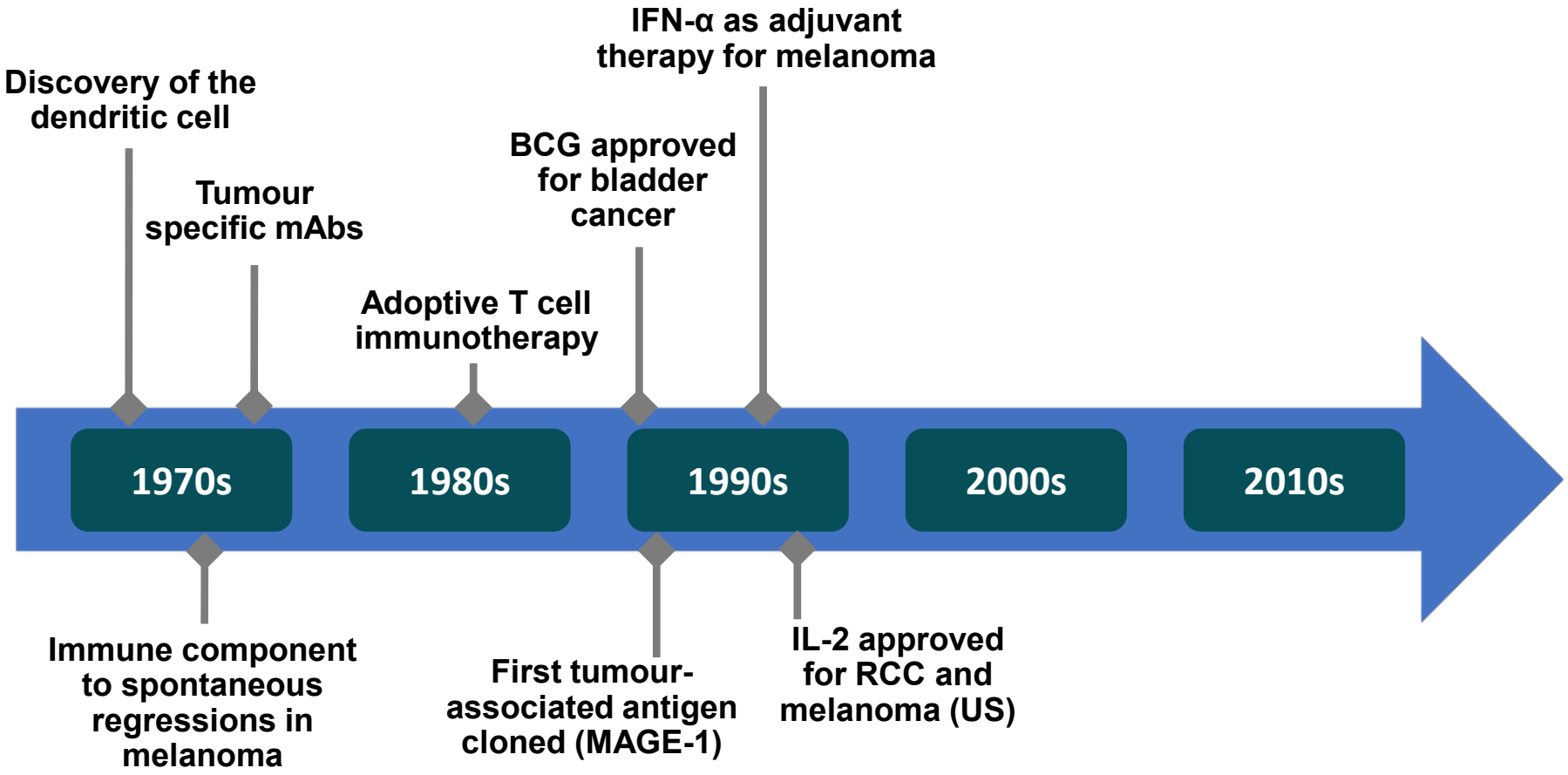


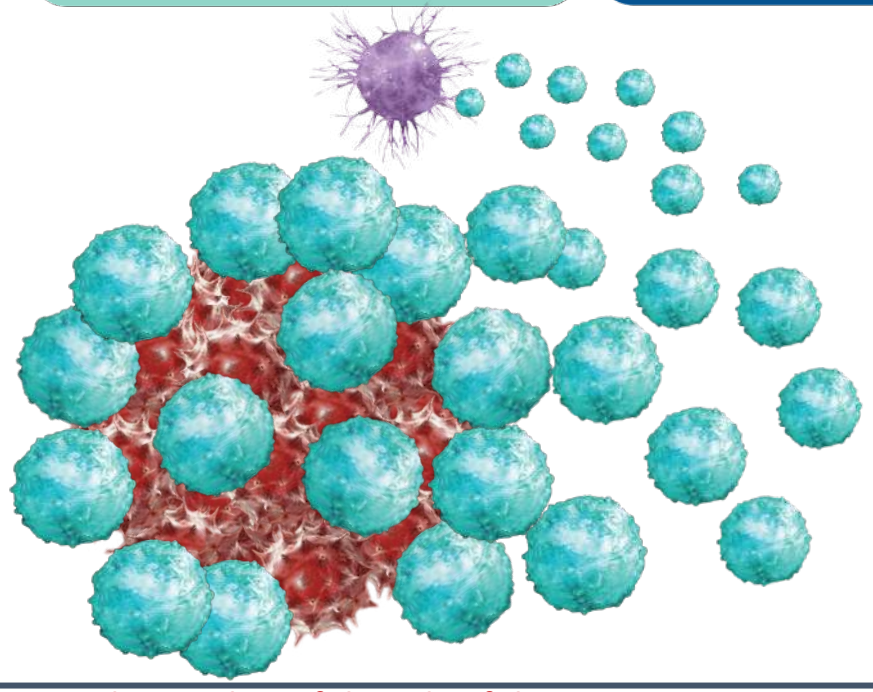
Figure adapted from Kirkwood JM. Ca J Clin 2012;62:309–35, Copyright ©2012 American Cancer Society; George S, et al. JNCCN 2011;9:1011–8; Garbe C, et al. The Oncologist 2011;16:2–24; Rosenberg SA. Sci Transl Med 2012;4:127ps8; Cheever MA, et al. Clin Cancer Res 2011;17:3520–6; Kantoff PW, et al. N Engl J Med 2010;363; Mansh M. Yale J Biol Med 2011;84:381–9; Hodi FS, et al. N Engl J Med 2010;363:711–23

Μηχανισμοί ανοσοθεραπείας κατά του καρκίνου

They enhance the body's immune system, which targets the tumour[1,2]

They enable the immune system to selectively recognise and attack cancer cells[,2]

They may give long-lasting memory to the immune system, providing a durable long-term response to the cancer[1,2]



I-O treatments are built on a better understanding of the role of the immune system in cancer, and the way cancer evades the immune system

1. Pardoll DM. Nat Rev Cancer 2012;12:252–264; 2. Eggermont A, et al. Oncoimmunology 2014;3:e27560.

Ιστορία ανοσοθεραπείας στον καρκίνο

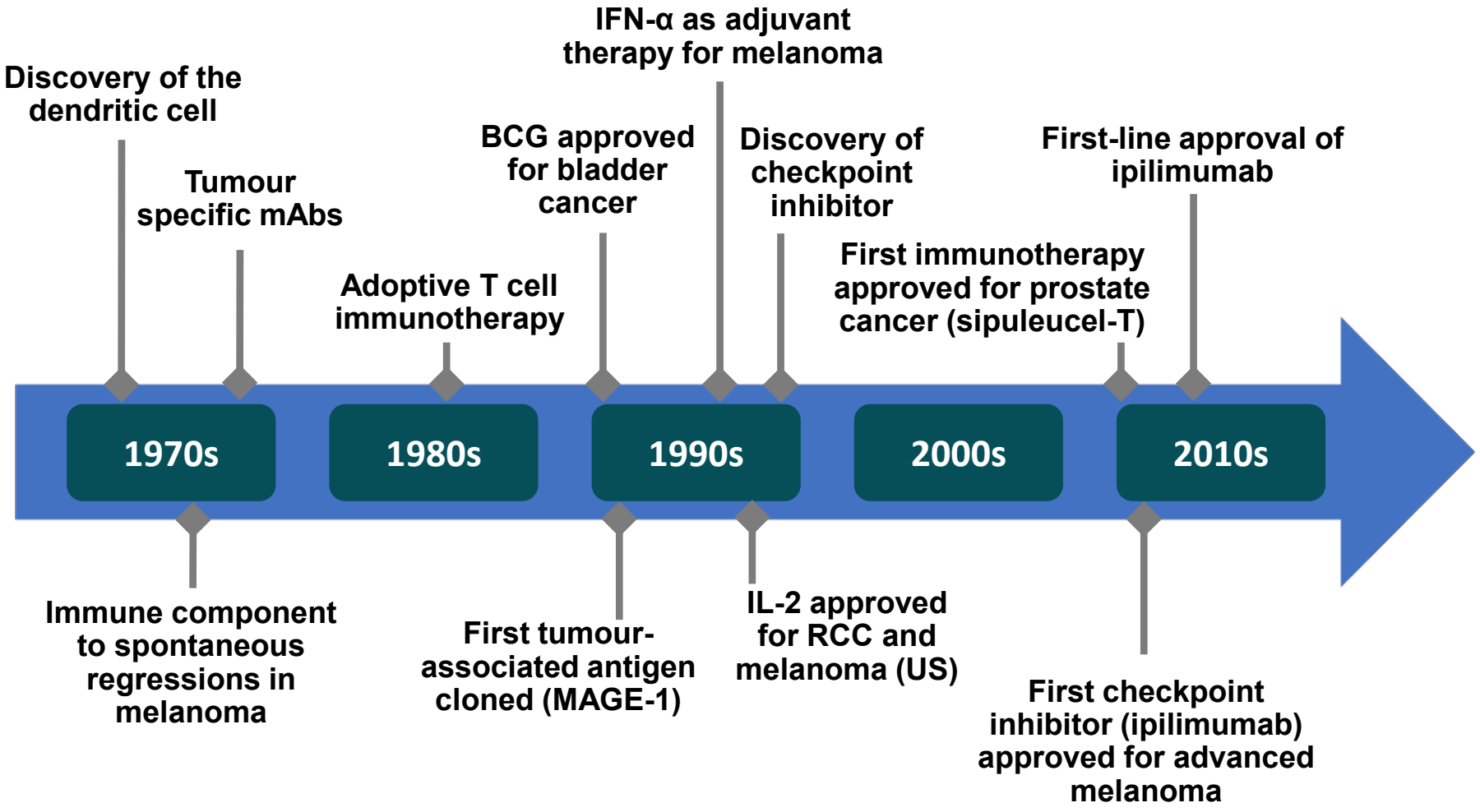
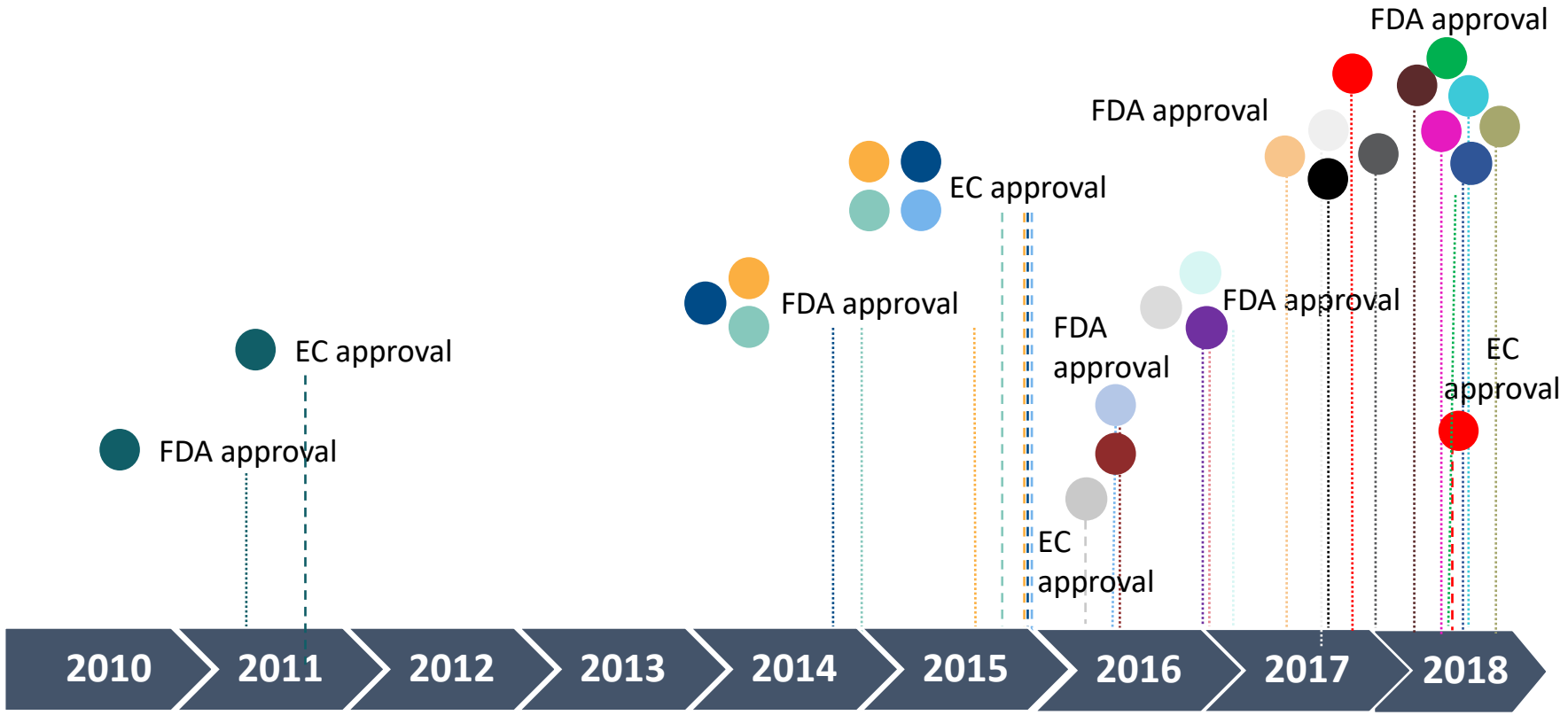


Figure adapted from Kirkwood JM. Ca J Clin 2012;62:309–35, Copyright ©2012 American Cancer Society; George S, et al. JNCCN 2011;9:1011–8; Garbe C, et al. The Oncologist 2011;16:2–24; Rosenberg SA. Sci Transl Med 2012;4:127ps8; Cheever MA, et al. Clin Cancer Res 2011;17:3520–6; Kantoff PW, et al. N Engl J Med 2010;363; Mansh M. Yale J Biol Med 2011;84:381–9; Hodi FS, et al. N Engl J Med 2010;363:711–23

Έγκριση ανοσοθεραπευτικών σκευασμάτων κατά του καρκίνου



*Nivolumab received Japan approval July 2014. ☆ = FDA breakthrough therapy designation. Not applicable to ipilimumab.
EC, European Commission; FDA, Food and Drug Administration; I-O, immuno-oncology.

able at: www.ClinicalTrials.gov; 2. Ipilimumab [summary of product characteristics]. Uxbridge, United Kingdom: Bristol-Myers Squibb Pharma EEIG 2015; 3. Pembrolizumab [prescribing information]. Whitehouse Station, NJ: Merck & Co, Inc 2017; 4. EMA. CHMP summary of positive opinion for 24 April 2015 and 21 May 2015; 5. FDA. Available at: https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm [Last accessed: June 2018]. Please see slide notes for full references.

Ιστορία αναστολέων σημείων ελέγχου ανοσοποιητικού κατά του καρκίνου

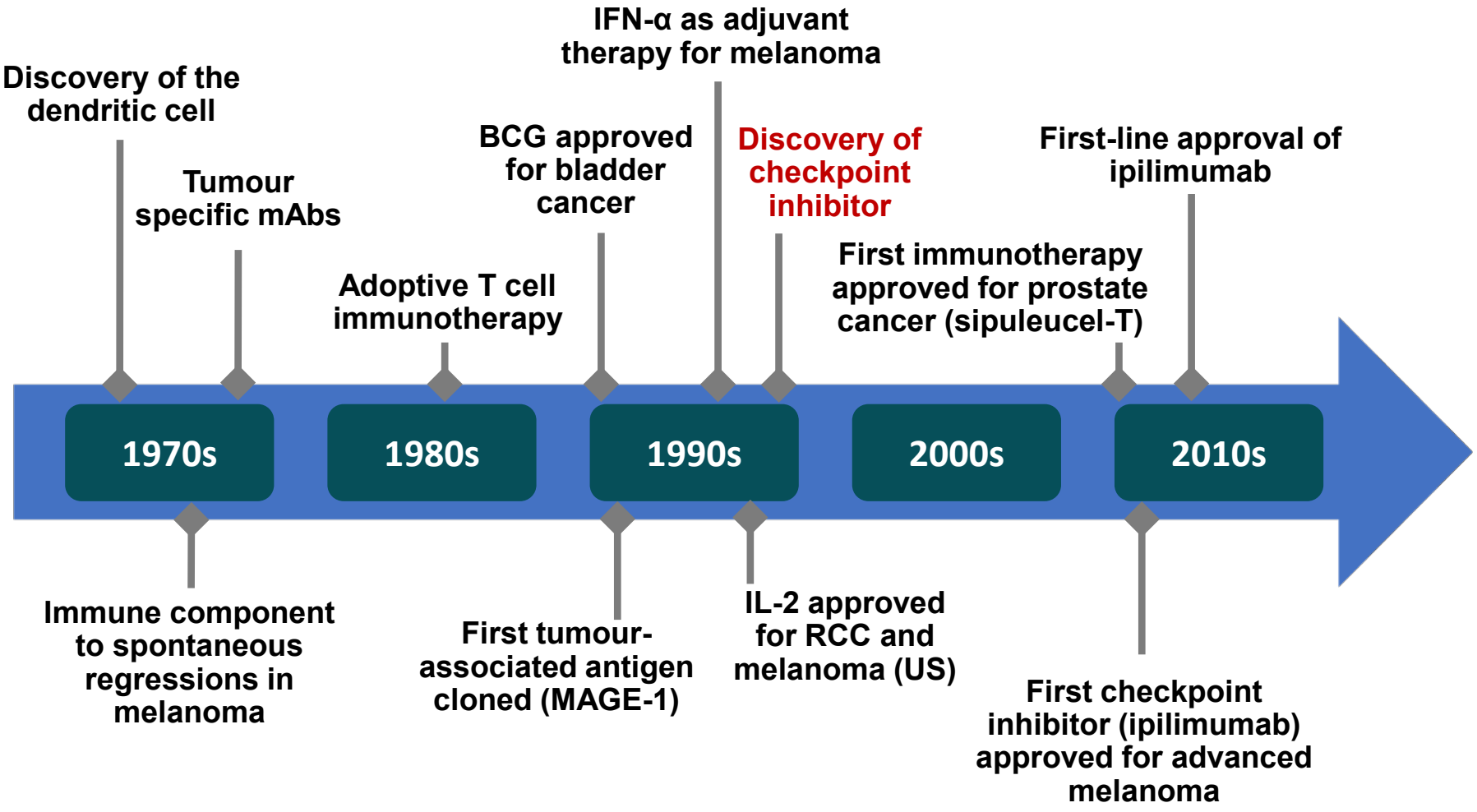


Figure adapted from Kirkwood JM. Ca J Clin 2012;62:309–35, Copyright ©2012 American Cancer Society; George S, et al. JNCCN 2011;9:1011–8; Garbe C, et al. The Oncologist 2011;16:2–24; Rosenberg SA. Sci Transl Med 2012;4:127ps8; Cheever MA, et al. Clin Cancer Res 2011;17:3520–6; Kantoff PW, et al. N Engl J Med 2010;363; Mansh M. Yale J Biol Med 2011;84:381–9; Hodi FS, et al. N Engl J Med 2010;363:711–23

Ιστορία αναστολέων σημείων ελέγχου ανοσοποιητικού κατά του καρκίνου

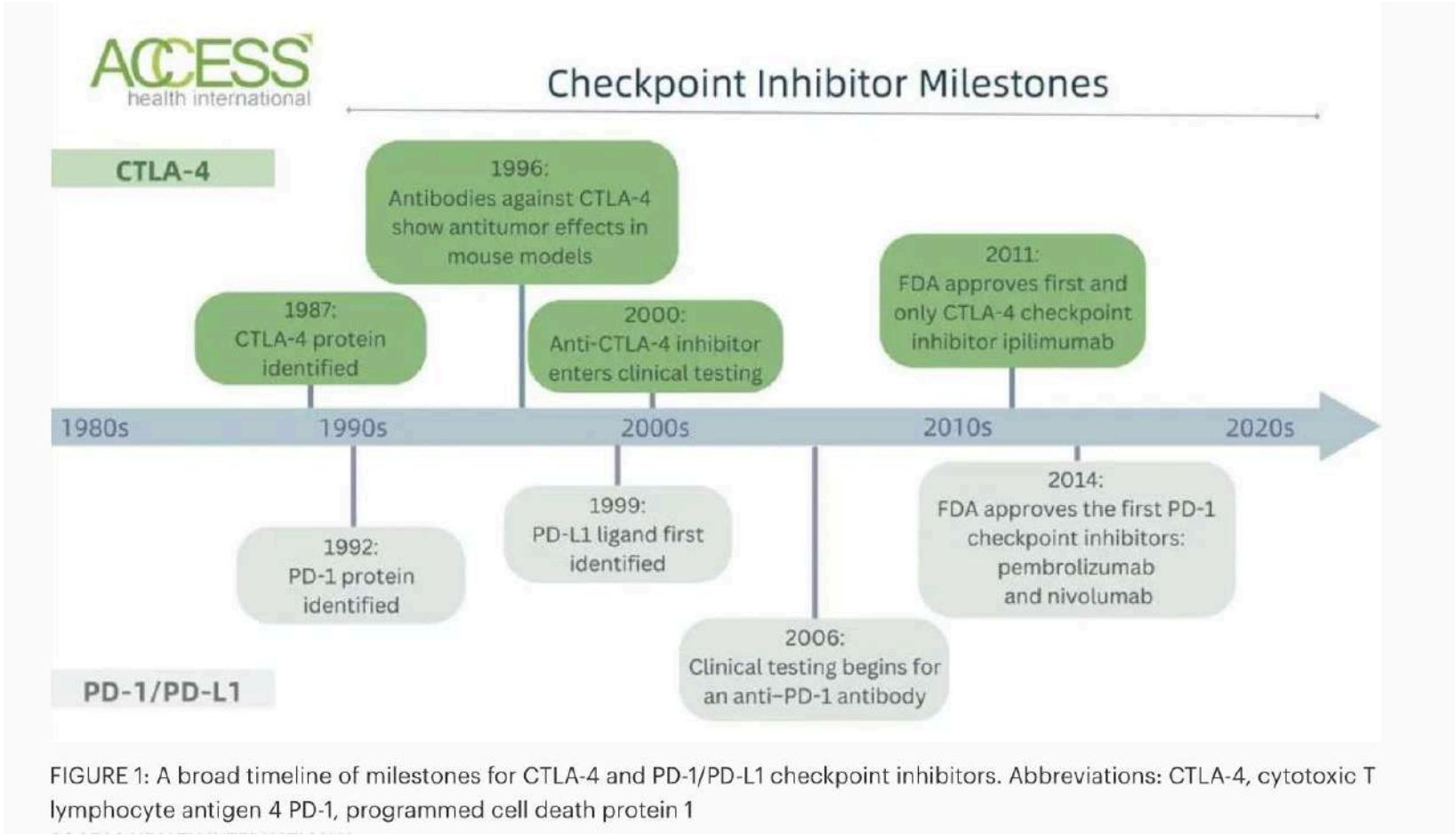
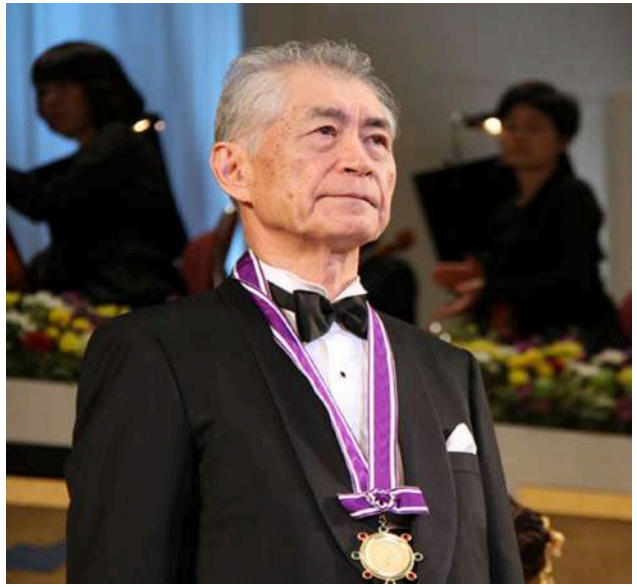


FIGURE 1: A broad timeline of milestones for CTLA-4 and PD-1/PD-L1 checkpoint inhibitors. Abbreviations: CTLA-4, cytotoxic T lymphocyte antigen 4 PD-1, programmed cell death protein 1

Ιστορία αναστολέων σημείων ελέγχου ανοσοποιητικού κατά του καρκίνου

1996 Dr James P. Allison

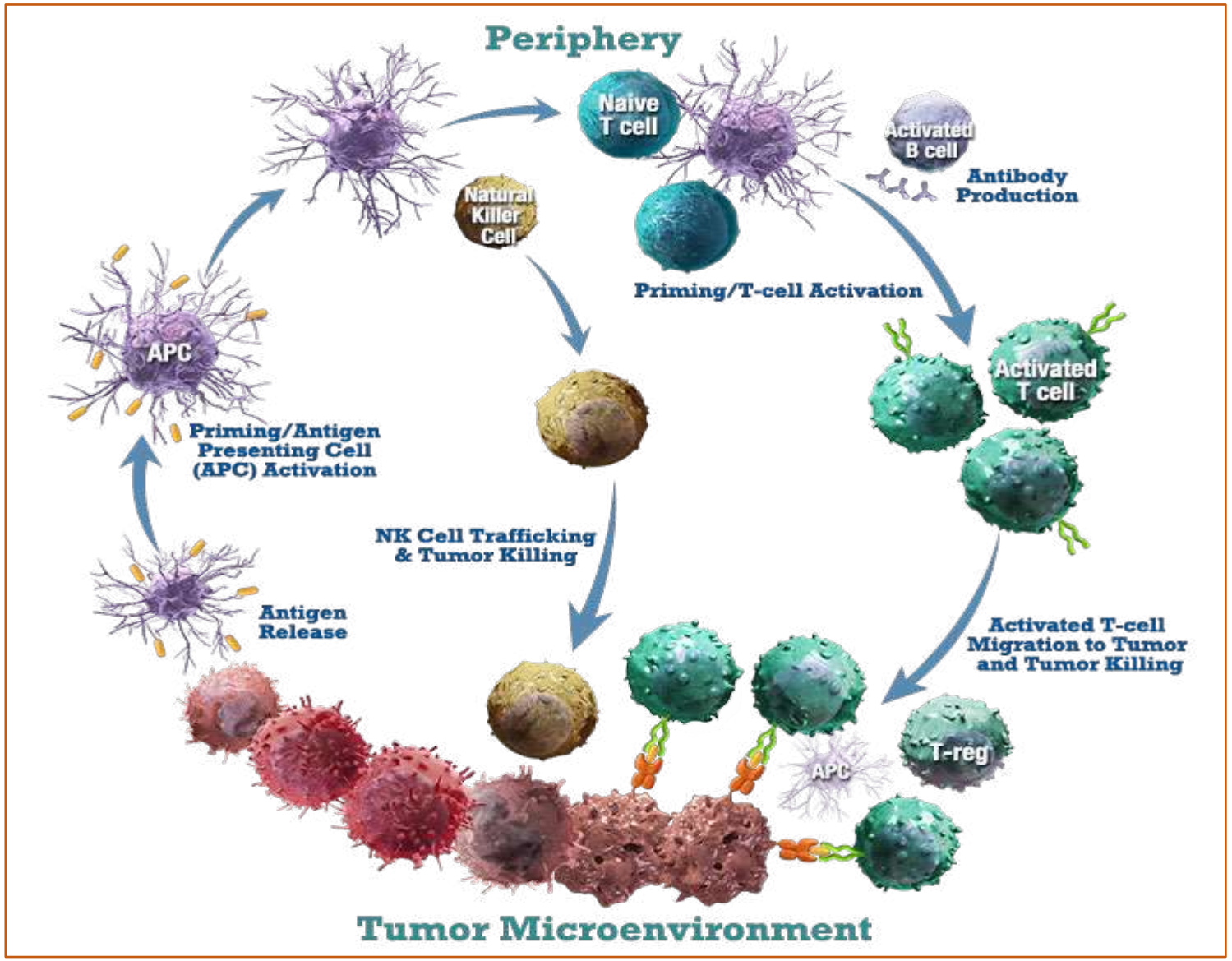
CTLA-4 Cytotoxic T Lymphocyte Antigen -4



1992 Dr Tasuku Honjo

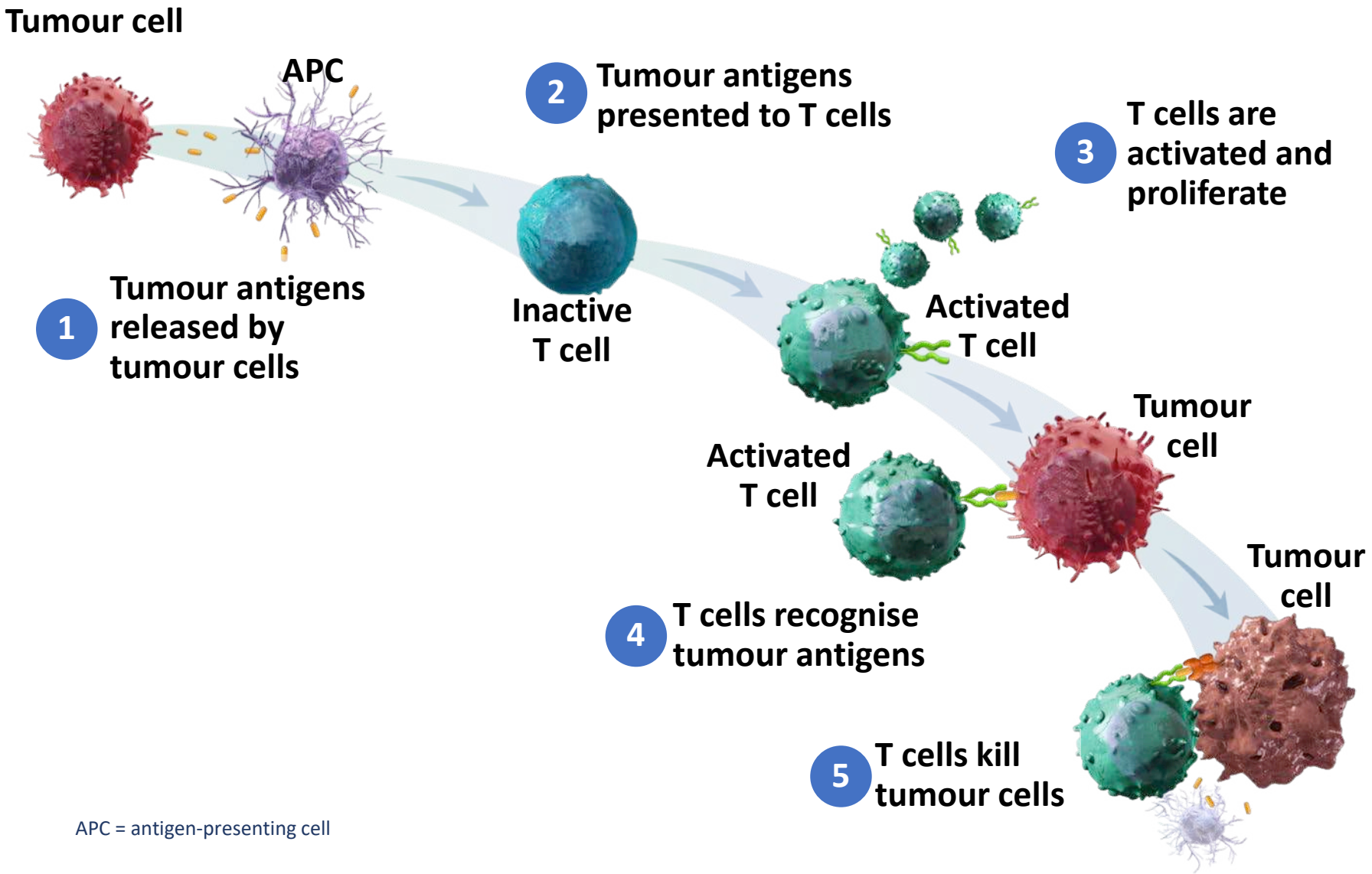
PD-1 Programmed cell Death -1

Μηχανισμοί αναγνώρισης και εξάλειψης των καρκινικών κυττάρων του ανοσοποιητικού συστήματος



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;43:509–19; 3. Kim R, et al. Immunology 2007;121:1–14
4. Vivier E, et al. Science 2011;331:44–9; 5. Dunn GP, et al. Nat Immunol 2002;3:991–8

Μηχανισμοί αναγνώρισης και εξάλειψης των καρκινικών κυττάρων του ανοσοποιητικού συστήματος

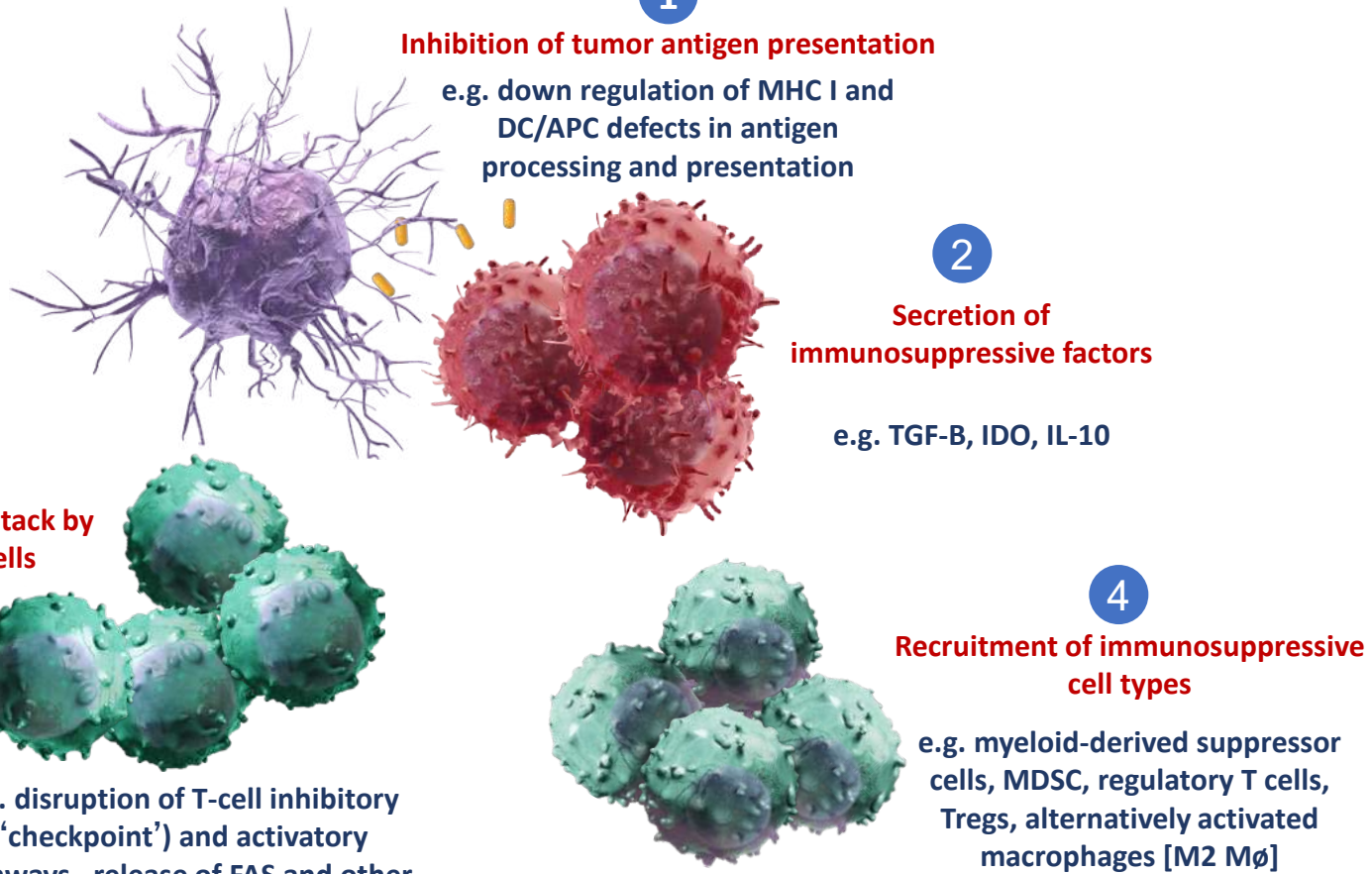


APC = antigen-presenting cell

Andersen MH, et al. J Invest Dermatol 2006;126:32–41; Pardoll DM. Nat Rev Cancer 2012;11:252–64; Mellman I, et al. Nature 2011;480:480–9; Heemskerk B, et al. EMBO J 2013;32:194–203; Boudreau JE, et al. Mol Ther 2011;19:841–53; Janeway CA, et al. Immunobiology: The Immune System in Health and Disease. 6th ed. New York, NY: Garland Science; 2004

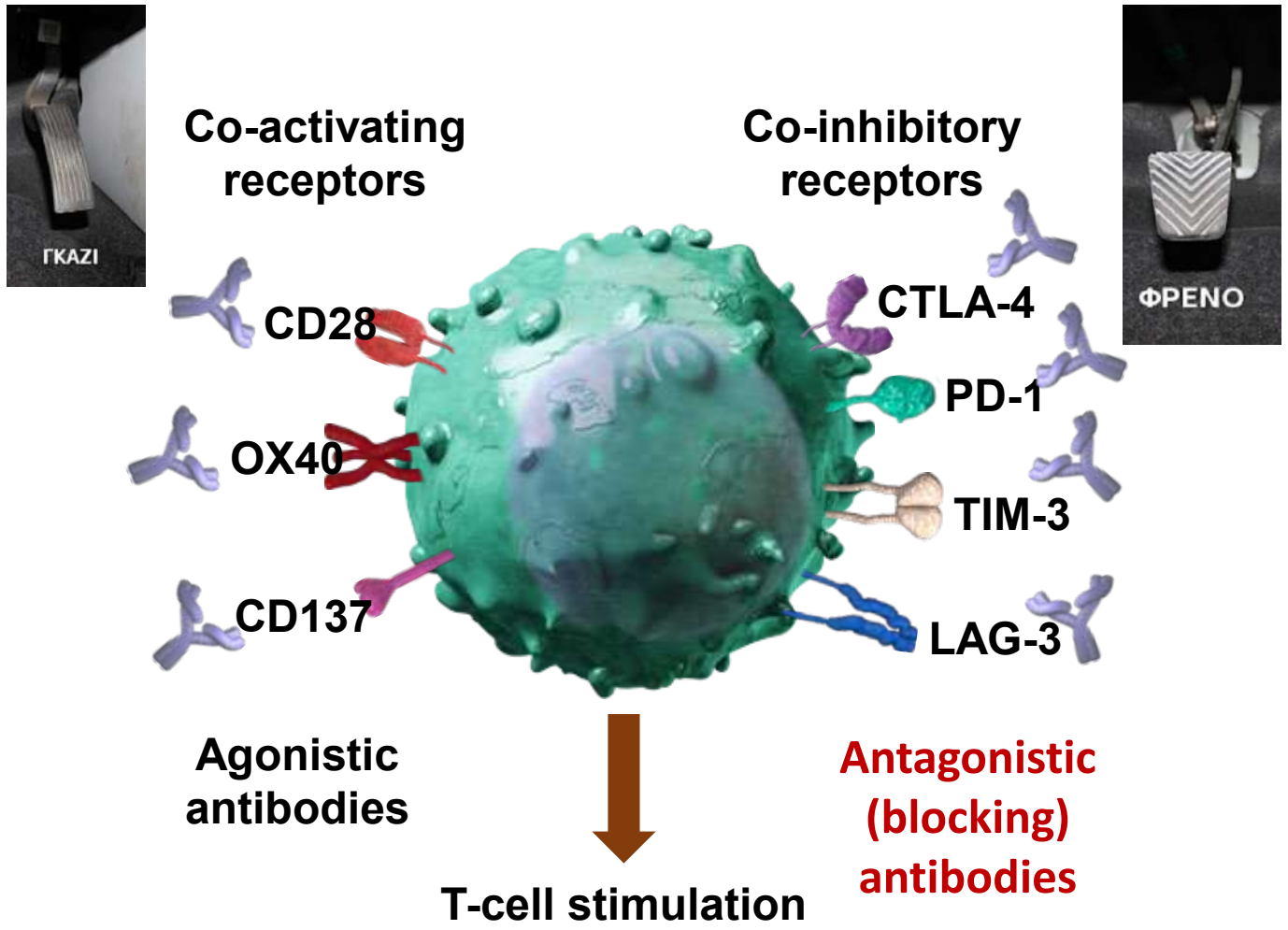
Μηχανισμοί διαφυγής των καρκινικών κυττάρων από την ανοσιακή απάντηση

Ο καρκίνος χρησιμοποιεί σύνθετους, επικαλυπτόμενους μηχανισμούς για να αποφύγει ή/και να καταστέλλει το ανοσοποιητικό σύστημα



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

Ρυθμιστικοί μηχανισμοί – Σημεία ελέγχου ανοσιακής απάντησης



- T-cell responses are regulated through 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 cancer therapy, designed to promote an immune response

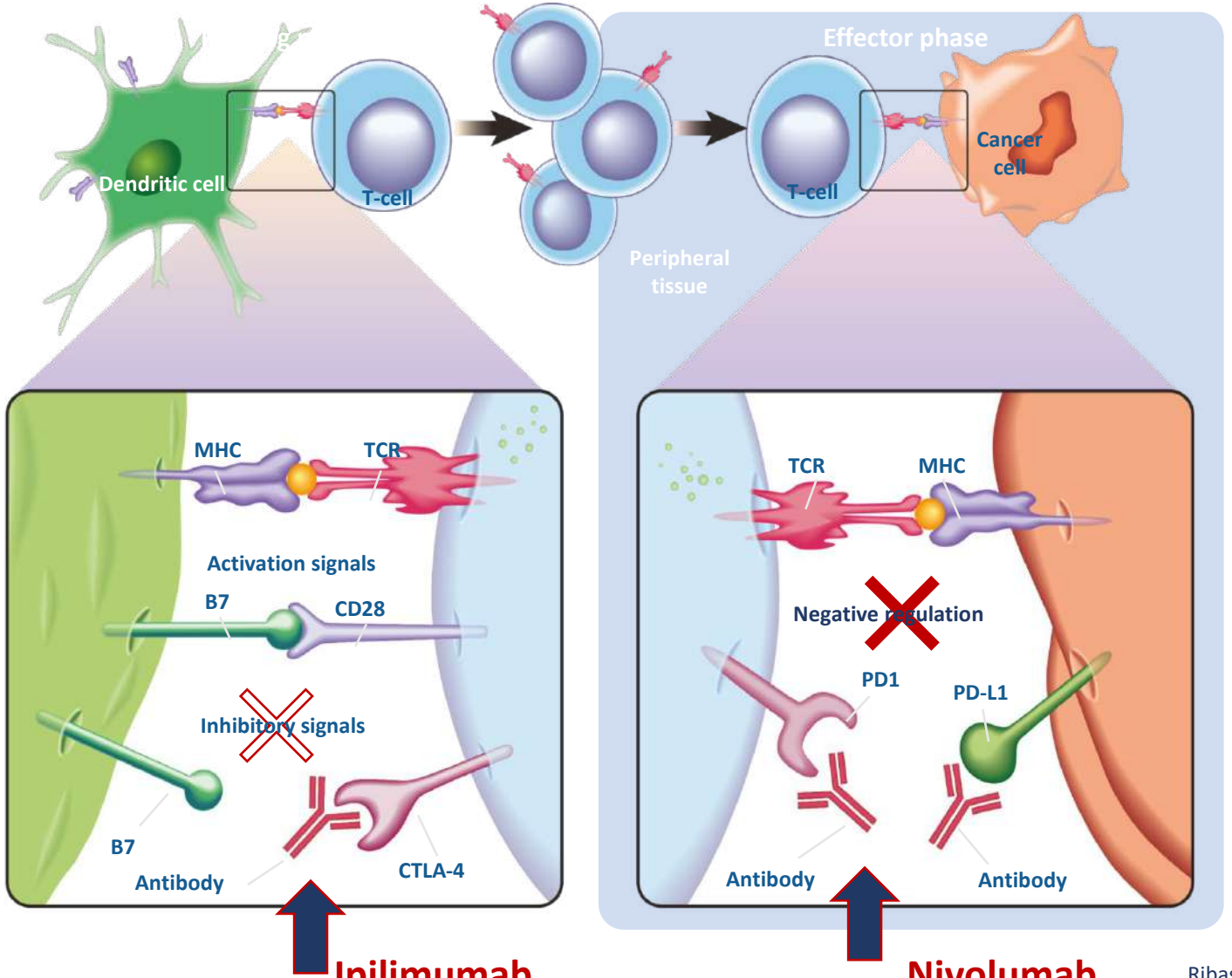
CTLA-4 = cytotoxic T-lymphocyte antigen-4; LAG-3 = lymphocyte-activation gene 3; PD-1 = programmed cell death 1; TIM-3 = T-cell immunoglobulin domain and mucin domain 3.

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

Στοχεύοντας σημεία ελέγχου ανοσιακής απάντησης

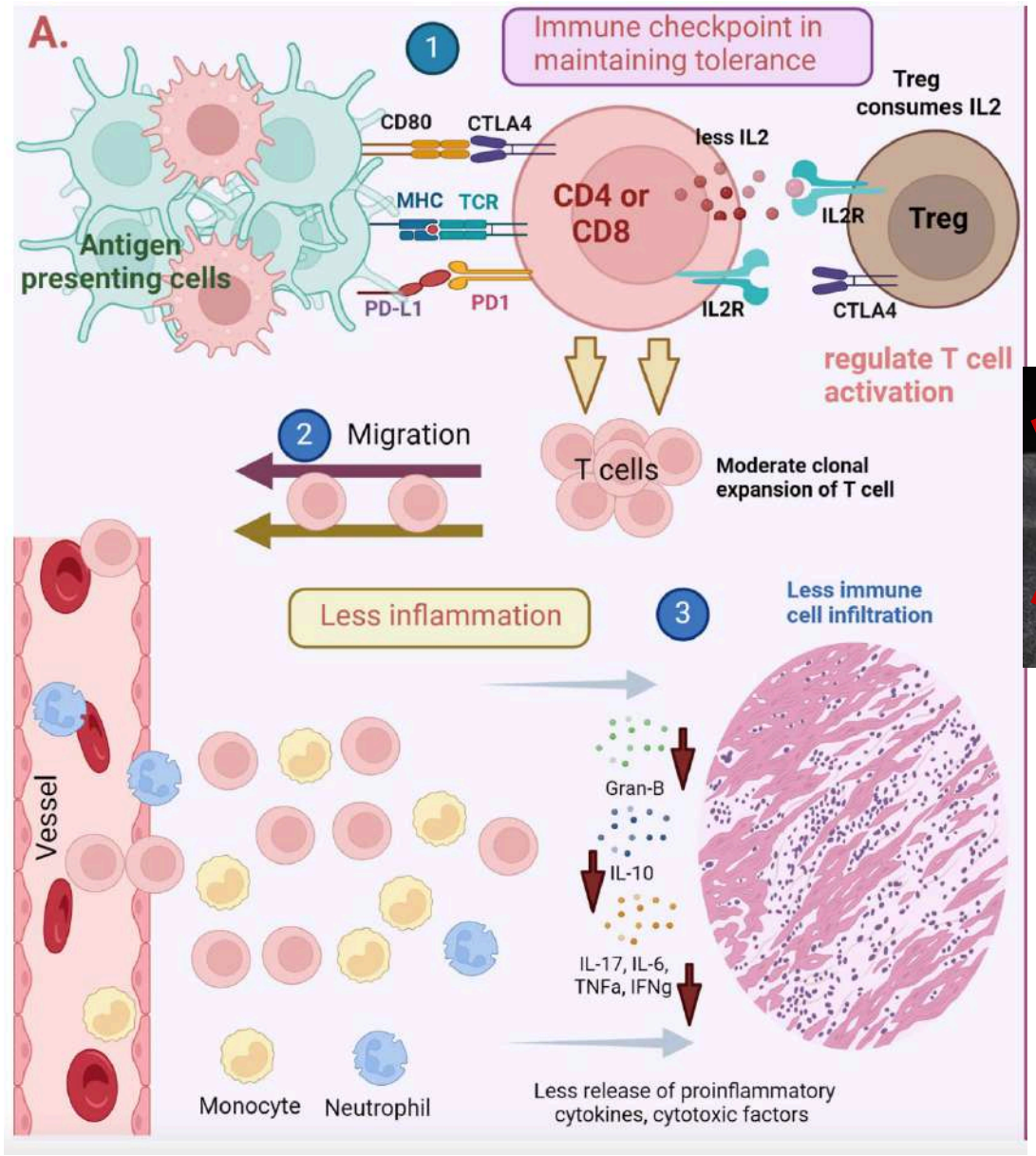
Μονοπάτι CTLA-4

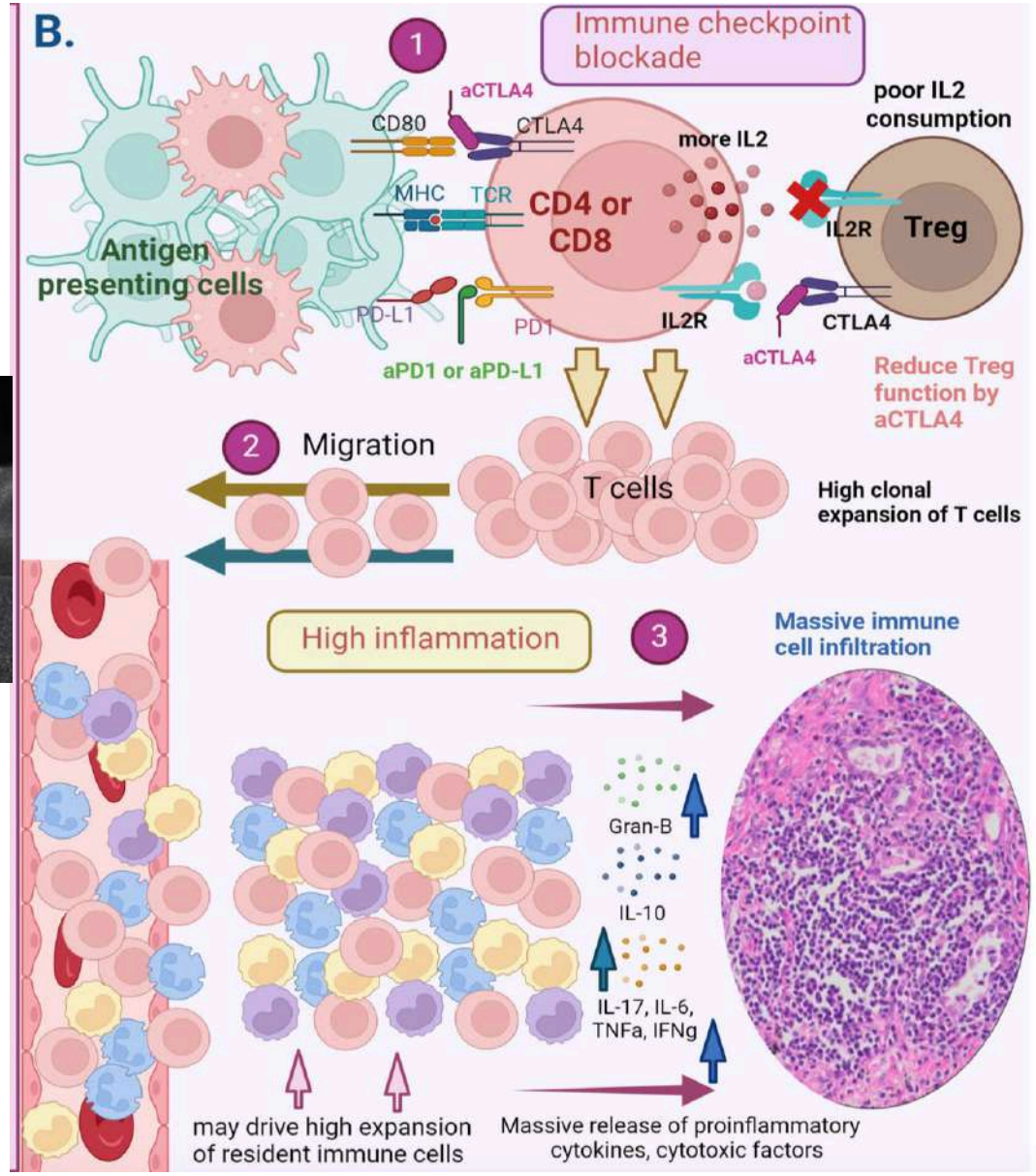
Μονοπάτι PD-1



Ribas A, et al. *N Engl J Med* 2012;366:2517–9

Στοχεύοντας σημεία ελέγχου ανοσιακής απάντησης

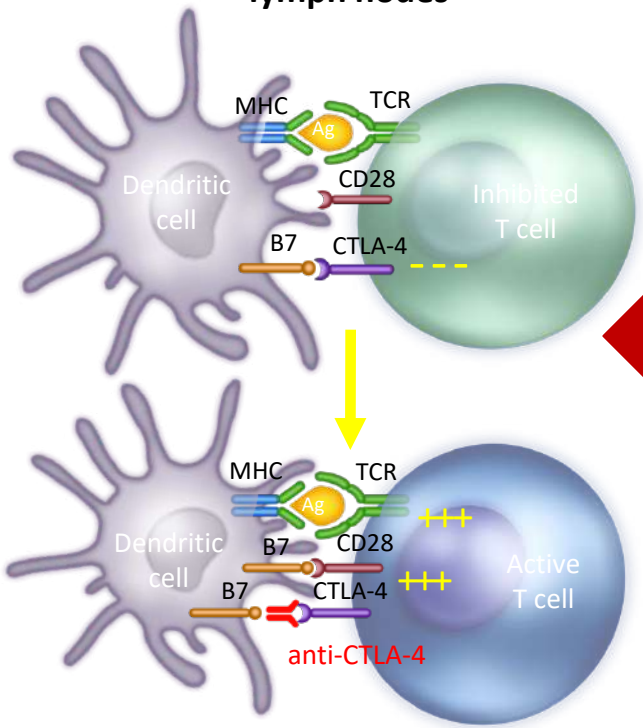




Στοχεύοντας σημεία ελέγχου ανοσιακής απάντησης

Μονοπάτι CTLA-4

CTLA-4:B7 interactions between T cells and antigen presenting cells are postulated to occur primarily in the lymph nodes

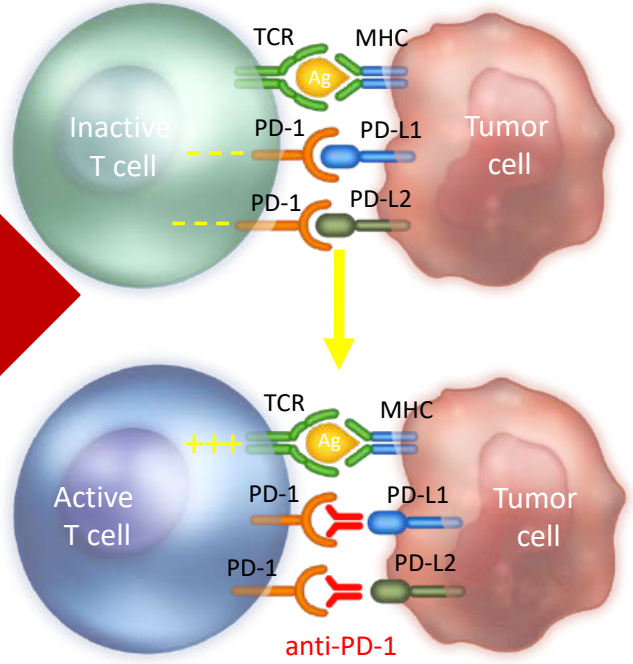


CTLA-4 blockade (ipilimumab)

ΣΥΝΕΡΓΙΚΗ ΔΡΑΣΗ;

Μονοπάτι PD-1

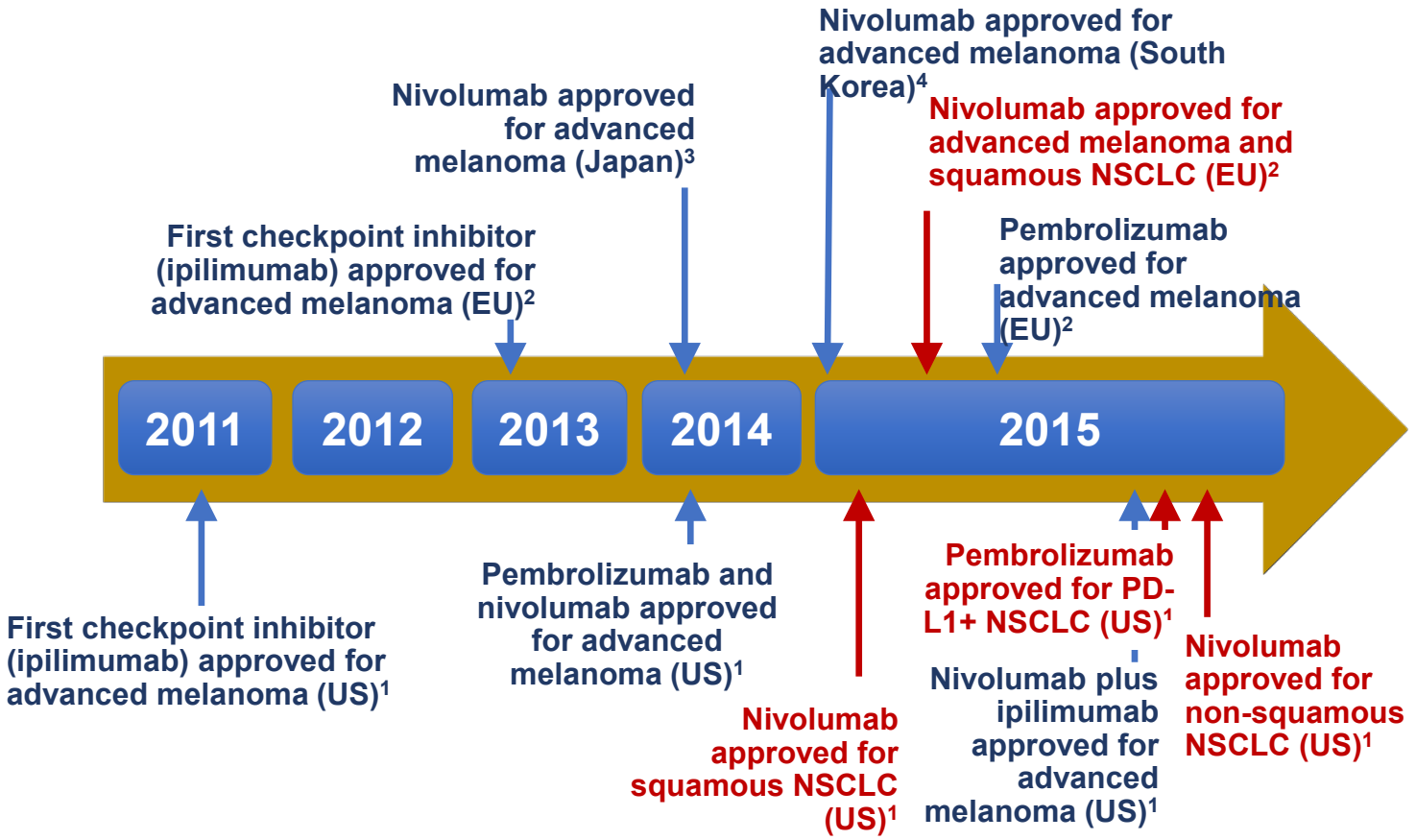
PD-1:PD-L1/2 interactions are suggested to occur specifically within peripheral sites



PD-1 blockade (nivolumab)

1. Topalian, et al. 2012. Curr Opin Imm:24:207-212.
2. Pardoll 2012. Nature Reviews Cancer:12:252-264.

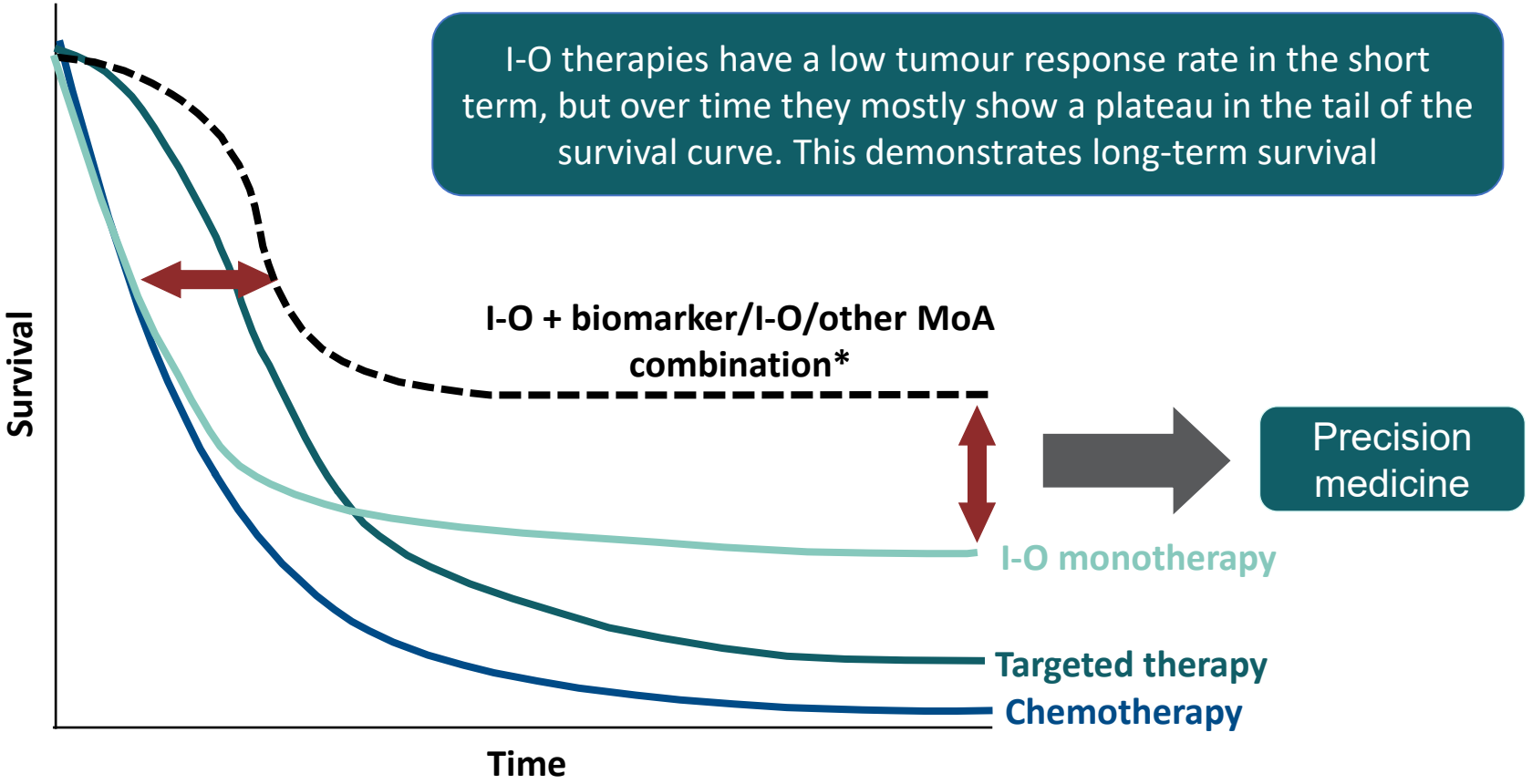
Έγκριση αναστολέων σημείου ελέγχου ανοσοποιητικού κατά του καρκίνου



1. U.S. Food and Drug Administration. Available at: http://www.fda.gov. Accessed October 13, 2015.
2. European Medicines Agency. Available at: http://www.ema.europa.eu/ema/. Accessed October 13, 2015.
3. Medscape. July 9, 2014. Available at: http://www.medscape.com/viewarticle/827893. Accessed October 13, 2015.
4. ONO Pharmaceutical Co., LTD. [press release]. March 23, 2015. Available at: https://www.ono.co.jp/eng/news/pdf/sm_cn150323.pdf. Accessed October 13, 2015.

Καμπύλη επιβίωσης ασθενών με μελάνωμα – Επίδραση διαφόρων θεραπευτικών προσεγγίσεων

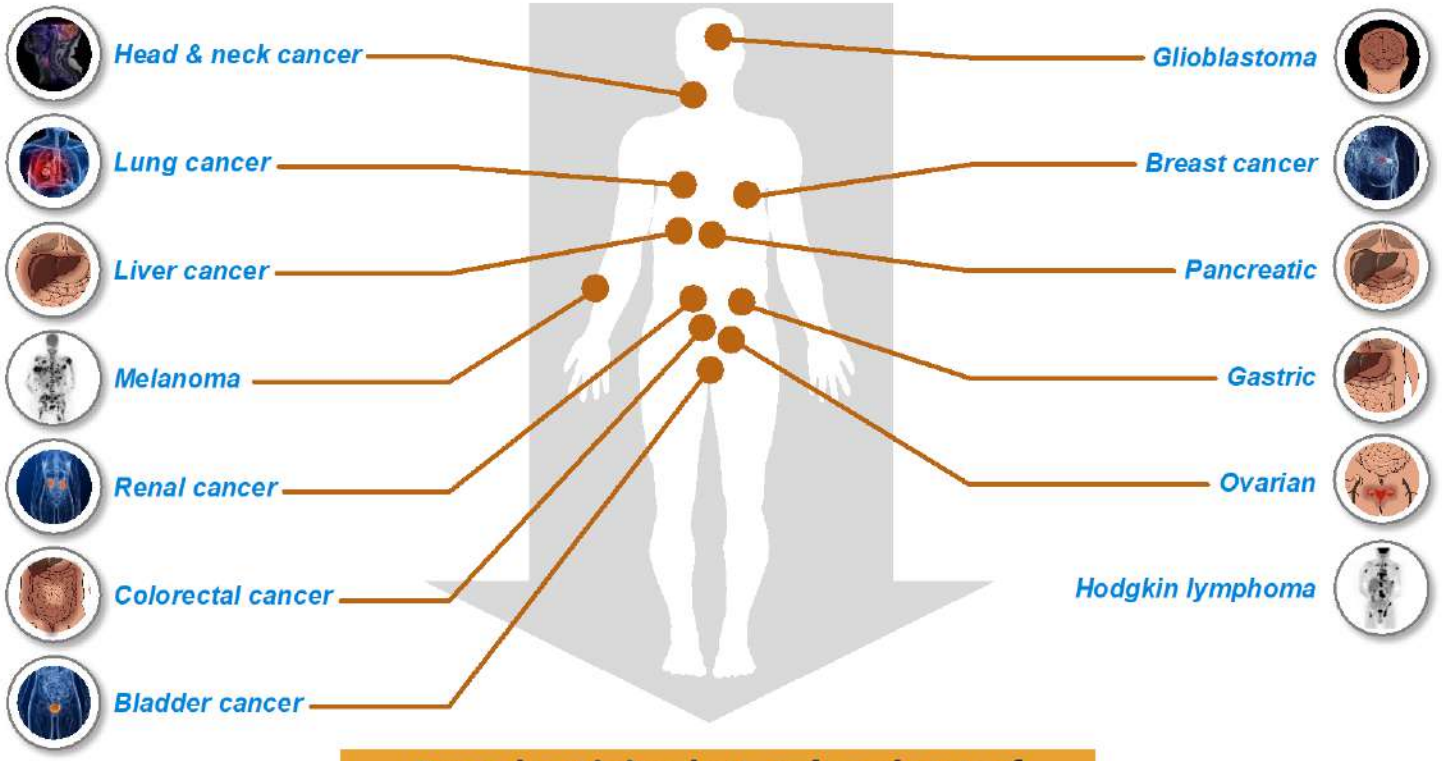
- As cancer therapies evolve, the cancer survival curve continues to change



*I-O, immuno-oncology; MoA; mode of action. *This is a hypothetical curve and does not represent actual observed survival.*

Adapted from: Ribas A, et al. Clin Cancer Res 2012;18:336–341.

Broad activity for anti-PD-L1/PD-1 in human cancer



Broad activity, but only subset of patients benefit: ~10-30%

27-29 November 2025

South-East Europe Initiative for Apheresis

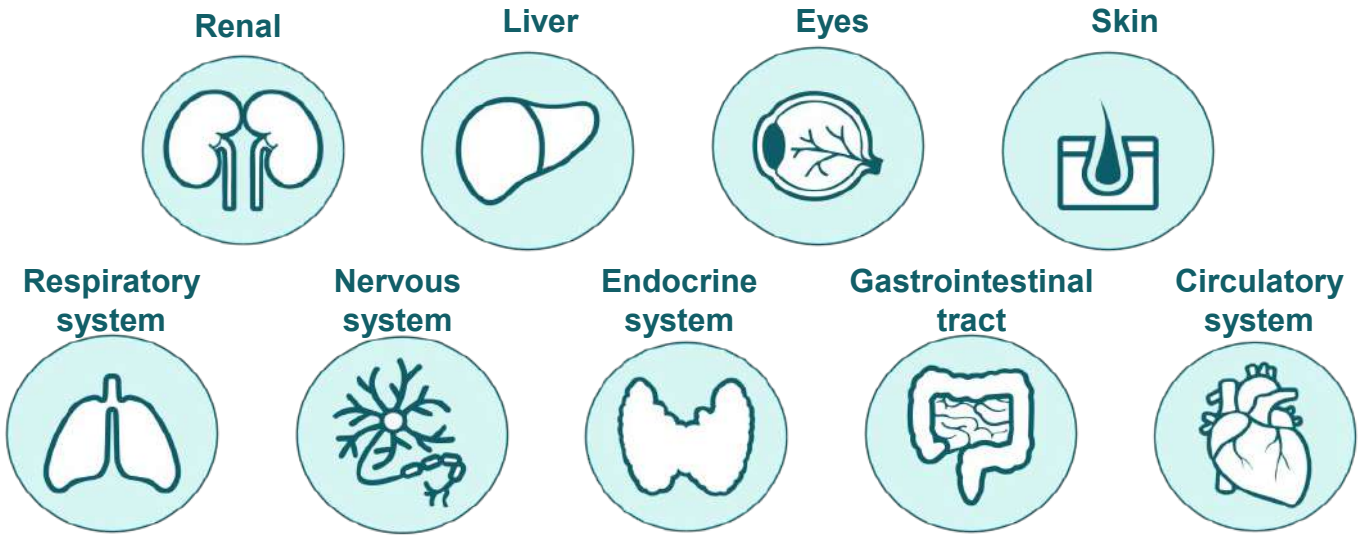
10th National Haemapheresis Association Conference

ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΑΙΜΑΦΑΙΡΕΣΗΣ

Ανεπιθύμητες ενέργειες (ΑΕ) αναστολέων σημείων ελέγχου ανοσοποιητικού

Προφίλ ανεπιθύμητων ενεργειών ανοσοθεραπείας

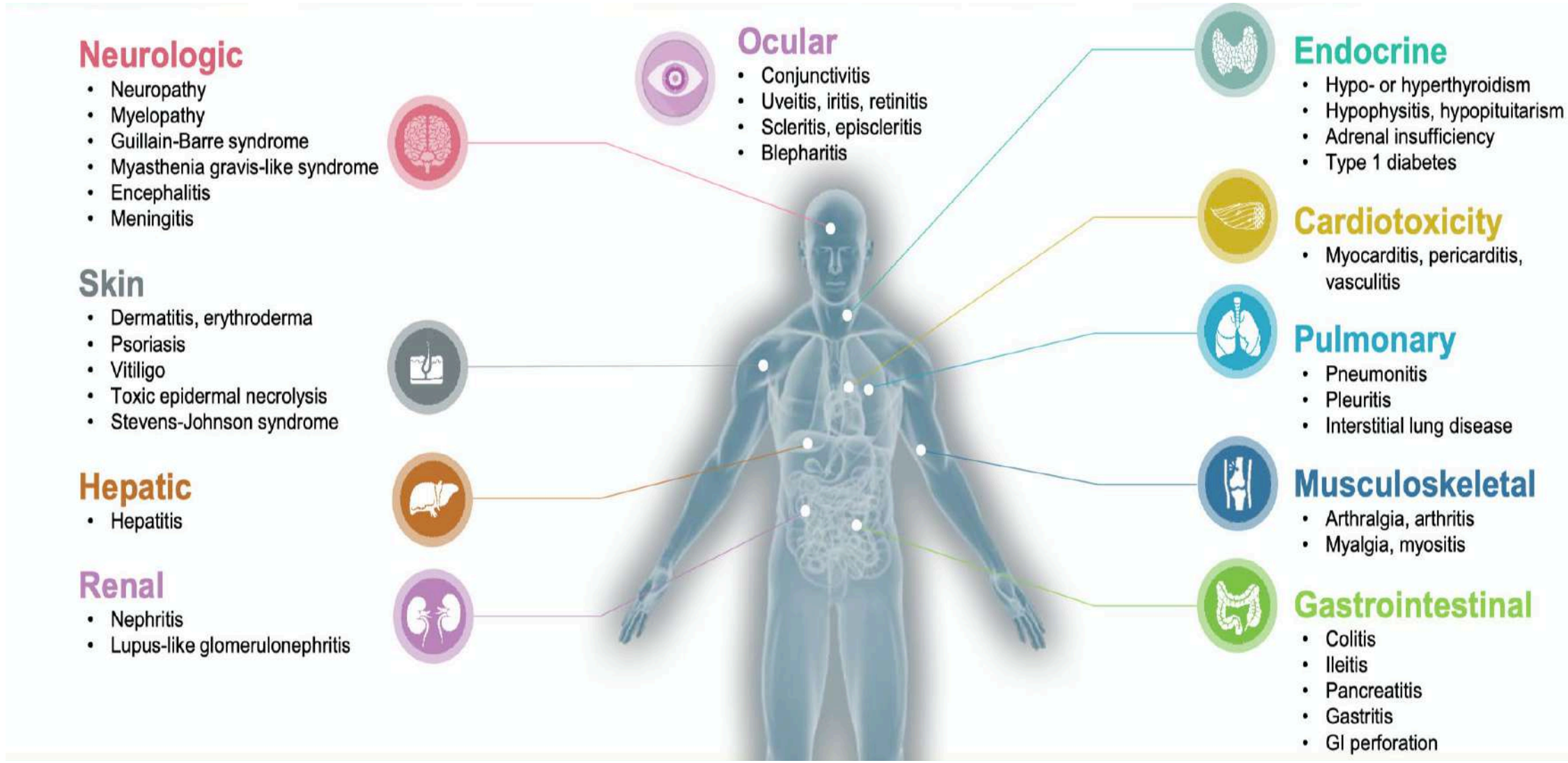
- Anti-tumour immune activity can also affect healthy cells[1]
- This can enable the immune system to attack healthy cells along with tumour cells; these effects are known as immune-mediated adverse reactions[1]
- The activation of certain immune cells has been associated with autoimmunity and may influence the likelihood of an immune-mediated adverse reaction[2,3]



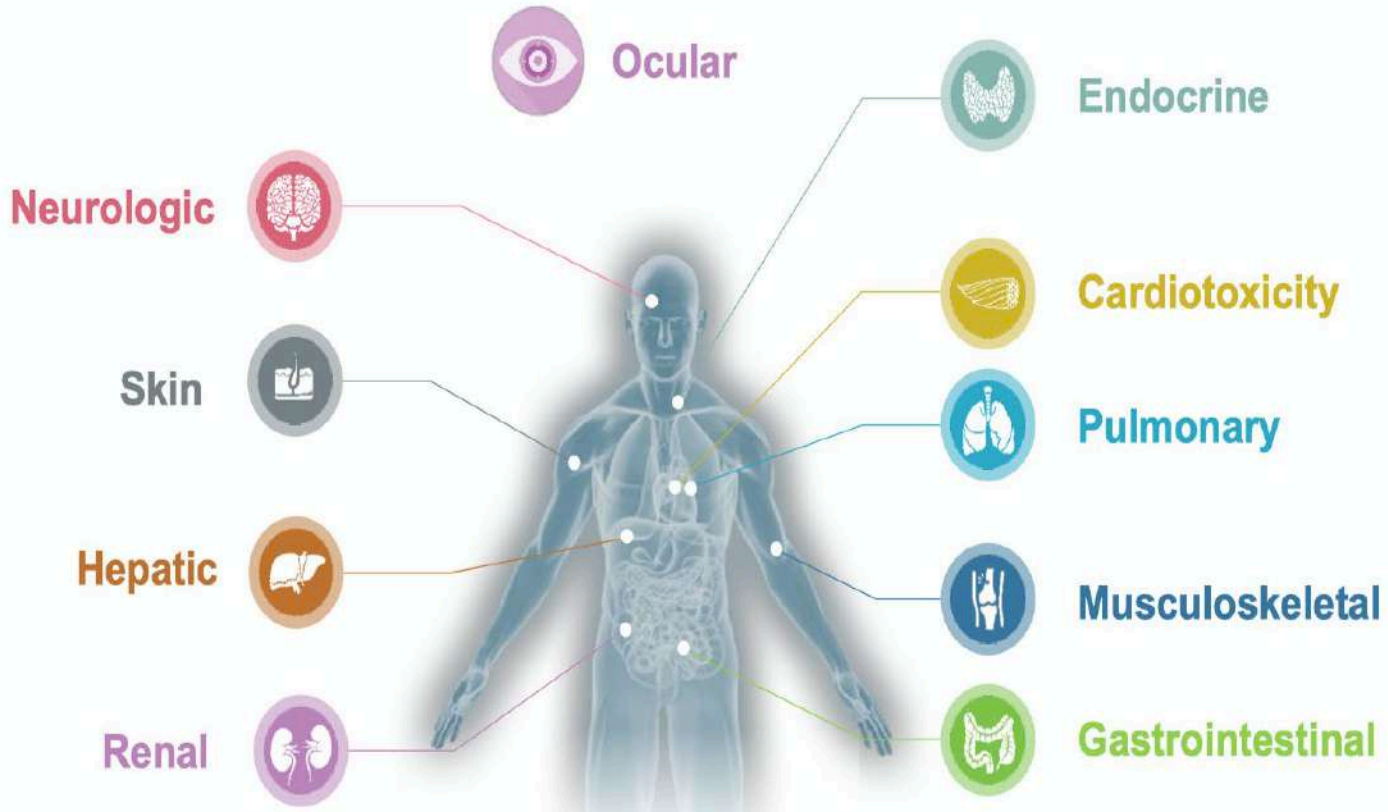
Patients, caregivers, and physicians should be educated to remain vigilant throughout and after I-O treatment to minimize complications, some of which may be life-threatening[1]

Amos SM, et al. Blood 2011;118:499–509; 2. Nishimura H, et al. Science 2001;291:319–322; 3. Mellman I, et al. Nature 2011;480:480–490.

Προφίλ ανεπιθύμητων ενεργειών αναστολέων σημείου ελέγχου ανοσοποιητικού



Προφίλ ανεπιθύμητων ενεργειών αναστολέων σημείου ελέγχου ανοσοποιητικού όταν συνδυάζονται



Anti-PD(L)-1 + Chemo
- e.g. nausea, anaemia, fatigue

Anti-PD(L)-1 + TKI
- e.g. fatigue, diarrhoea

Anti-PD(L)-1 + Anti-CTLA-4
- Diarrhea, colitis, hepatitis, endocrine

I-O + Radiation
- Limited data on concurrent therapy
- No unexpected safety concern reported

Ανεπιθύμητες ενέργειες (ΑΕ) αναστολέων σημείων ελέγχου ανοσοποιητικού

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Toxicity in the era of immune checkpoint inhibitor therapy

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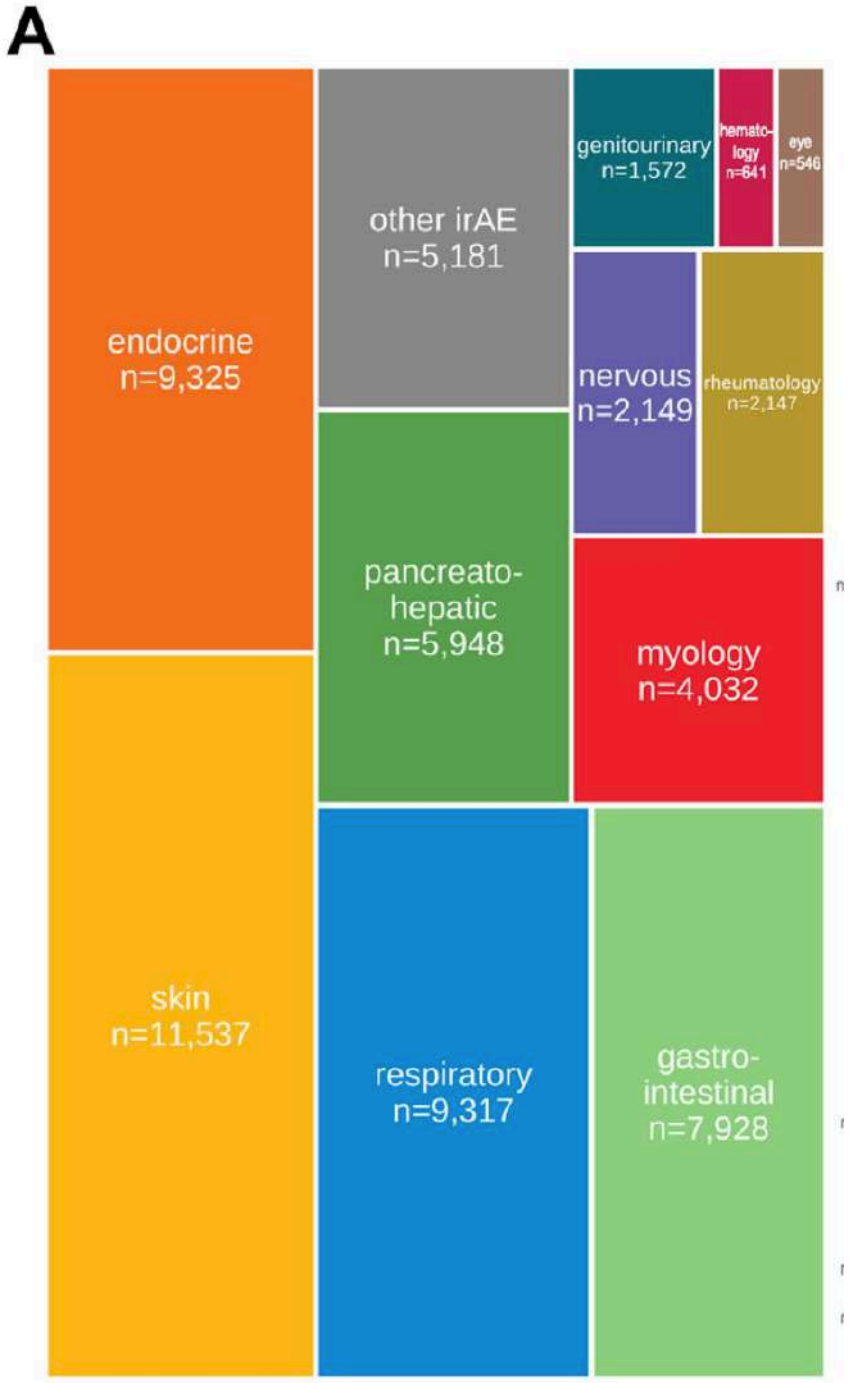
S. Keam et al, Frontiers Vol 15, Aug 2024

TABLE 1 Incidence, associated regimens, and standards of care for common irAEs.

System	Incidence	irAE	Associated Regimen	Standard Therapy	Ref.
Cutaneous	30-60%	Inflammatory dermatoses, bullous dermatoses, SCAR	Anti-CTLA-4, Combo ICIs	Topical or systemic corticosteroids	(77–79)
Gastrointestinal	10-30%	Colitis	Anti-CTLA-4, Combo ICIs	Corticosteroids, Infliximab, Vedolizumab, Ustekinumab, Tofacitinib, FMT	(77, 78)
Hepatic	11-29%	Hepatitis	Combo ICIs	Corticosteroids	(77, 78)
Neurological	1-12%	Meningitis, Encephalitis	Anti-CTLA-4, Combo ICIs	Corticosteroids, Rituximab, Tacrolimus	(77, 78)
		Guillain-Barrè syndrome	Anti-CTLA-4, Combo ICIs	Corticosteroids, Plasmapheresis, IVIG	
		Myositis, Myasthenic syndromes	Anti-PD-1/PD-L1, Combo ICIs	Corticosteroids, Plasmapheresis, IVIG, Tacrolimus, Rituximab	
Endocrine	10%	Hypophysitis	Anti-CTLA-4, Combo ICIs	Corticosteroids, Thyroid hormone replacement, Sex hormone replacement	(77, 78)
		Thyroid dysfunction	Anti-PD-1/PD-L1, Combo ICIs	Thyroid hormone supplementation, Beta-blocker,	
		Diabetes	Anti-PD-1/PD-L1, Combo ICIs	Insulin	
Pulmonary	1-6%	Pneumonitis	Anti-PD-1, Combo ICIs	Corticosteroids, IVIG, Infliximab, Mycophenolate mofetil, Cyclophosphamide	(77, 78)
Renal	1-5%	Nephritis, Acute Kidney Injury	Combo ICIs	Corticosteroids	(77, 78)
Rheumatological	<5%	Arthritis, Arthralgia	Anti-PD-1, Combo ICIs	Corticosteroids, DMARDs, Infliximab, Tocilizumab	(77, 78, 80)
Hematological	3.6%	Autoimmune hemolytic anemia, Immune thrombocytopenia purpura, autoimmune neutropenia, aplastic anemia	Anti-PD-1/PD-L1, Combo ICIs	Corticosteroids, IVIG	(77, 78)
Cardiovascular	1%	Myocarditis, Pericarditis, Arrythmias, Impaired ventricular function with HF, Vasculitis	Combo ICIs	Corticosteroids, Infliximab, antithymocyte globulin, abatacept, alemtuzumab	(77, 78)
Ophthalmic	1%	Ocular myasthenia, Eye inflammation	Anti-PD-1/PD-L1, Combo ICIs	Corticosteroids, Plasmapheresis, IVIG	(77, 78)
		Uveitis	Anti-CTLA-4, Combo ICIs	Topical or systemic corticosteroids	

SCAR, Severe cutaneous adverse reactions; Combo ICIs, Anti-PD-1 + Anti-CTLA-4; FMT, Fecal microbiota transplantation; HF, Heart Failure; DMARDs, Disease modifying anti-rheumatic drugs.

S. Keam et al, Frontiers Vol 15, Aug 2024



Clinical spectrum and evolution of immune-checkpoint inhibitors toxicities over a decade—a worldwide perspective

Paul Gougis,[a,b,c] Floriane Jochum,[a,d] Baptiste Abbar,[b,c,e] Elise Dumas,[a] Kevin Bihan,[c] Bénédicte Lebrun-Vignes,[c,f] Javid Moslehi,[g] Jean-Philippe Spano,[b,c,h] Enora Laas,[i] Judicael Hotton,[j] Fabien Reyal,[a,i,j] Anne-Sophie Hamy,[a,k] and Joe-Elie Salem[c,*]

eClinicalMedicine 2024;70: 102536

nature COMMUNICATIONS

COMMENT

https://doi.org/10.1038/s41467-022-27960-2 OPEN

Immune-related adverse events and the balancing act of immunotherapy

Michael Conroy [1,2,3] & Jarushka Naidoo [1,2,3,4]✉

- Grade 1 – Mild
- Grade 2 – Moderate
- Grade 3 – Severe
- Grade 4 – Life threatening or disabling
- Grade 5 – Death related to AE

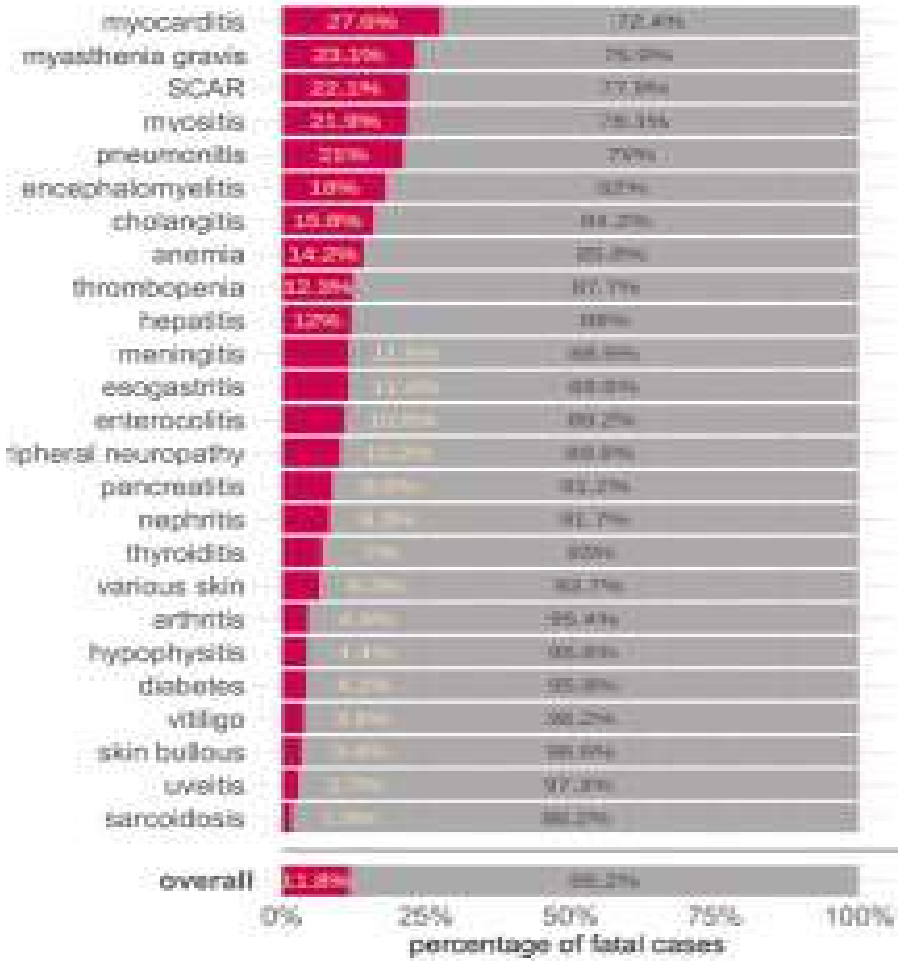
M.Conroy et al, Nat Communication 13: 392, 2022

Table 1 Prevalence of irAEs and high-grade irAEs in major immunotherapy clinical trials.

Selected phase II and III trials	Immune-related adverse events		
	All %	High grade %	Top three most frequent (% of patients)
PEMBROLIZUMAB			
NSCLC			
NCT02142738—Keynote 024	29	10	Hypothyroidism (9), Hyperthyroidism (8), Pneumonitis (6)
NCT01905657—Keynote 010	20	5	Hypothyroidism (8), Hyperthyroidism (5), Pneumonitis (5)
Melanoma			
NCT03142334—Keynote 564	35	9	Hypothyroidism (21), Hyperthyroidism (12), Pneumonitis (2)
NCT01866319—Keynote 006	27	10	Hypothyroidism (11), Hyperthyroidism (5), Colitis (3)
NCT02362594—Keynote 054	37	7	Hypothyroidism (14), Hyperthyroidism (10), Vitiligo (5)
Urothelial			
NCT02256436—Keynote 045	17	5	Hypothyroidism (6), Hyperthyroidism (4), Pneumonitis (4)
NCT02335424—Keynote 052	26	10	Hypothyroidism (11), Pneumonitis (5), Hyperthyroidism (3)
NIVOLUMAB			
Melanoma			
NCT01721746—Checkmate 037	NR	NR	Pruritus (22), Diarrhoea (18), Rash (13)
NCT02388906—Checkmate 238	NR	NR	Diarrhoea (24), Pruritus (23), Rash (20)
NCT01721772—Checkmate 066	60	7	Pruritus (17), Diarrhoea (16), Rash (15)
Urothelial			
NCT02387996—Checkmate 275	NR	NR	Dermatologic (24), Gastrointestinal (13), Hepatic (6)
ATEZOLIZUMAB			
NSCLC			
NCT02409342—Impower 110	40	7	Hepatitis (16), Rash (15), Hypothyroidism (9)
NCT02486718—Impower 010	52	8	Rash (18), Hepatitis (17), Hypothyroidism (17)
Urothelial			
NCT02108652—IMvigor210	12	7	Rash (3), ALT increase (2), Rhabdomyolysis (2)
DURVALUMAB			
NSCLC			
NCT02125461—PACIFIC	24	3	Pneumonitis (11), Hypothyroidism (9), Hyperthyroidism (3)
Urothelial			
NCT02516241—DANUBE	18	6	Diarrhoea (7), Rash (7), Hypothyroidism (6)
IPILIMUMAB			
Melanoma			
NCT00094653—Hodi et al. 2010.	61	15	Diarrhoea (32), Pruritus (24), Rash (20)
NCT01866319—Keynote 006	19	12	Colitis (7), Hyperthyroidism (2), Hypothyroidism (2)
NCT01844505—Checkmate 067	NR	NR	Pruritus (36), Diarrhoea (34), Rash (22)
NIVOLUMAB/IPILIMUMAB			
NSCLC			
NCT02477826—CheckMate 227	NR	NR	Skin (34), Endocrine (24), gastrointestinal (18)
Melanoma			
NCT01844505—CheckMate 067	NR	NR	Diarrhoea (45), Pruritus (36), Rash (30)
Renal cell carcinoma			
NCT02231749—Checkmate 214	79	48	Pruritus (31), Diarrhoea (28), Rash (23)
DURVALUMAB/TREMELIMUMAB			
NSCLC			
NCT02453282—MYSTIC	28	11	Hypothyroidism (8), Pneumonitis (7), Diarrhoea (5)
Urothelial			
NCT02516241—DANUBE	37	17	Diarrhoea (22), Rash (15), Hypothyroidism (7)

NSCLC non-small cell lung cancer, *NR* not reported, *ALT* alanine aminotransferase.

M.Conroy et al, Nat Communication 13: 392, 2022



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eClinicalMedicine 2024;70: 102536

Πρωτόκολλα – Κατευθυντήριες οδηγίες αντιμετώπισης ΑΕ

- Patients and family caregivers should receive timely and up-to-date education about immunotherapies, their mechanism of action, and the clinical profile of possible irAEs before initiating therapy and throughout treatment and survivorship.
- There should be high level of suspicion that new symptoms are treatment related.

- In general, ICPi therapy should be continued with close monitoring for grade 1 toxicities, with the exception of some neurologic, hematologic, and cardiac toxicities.

- Hold ICPis for most grade 2 toxicities and consider resuming when symptoms and/or laboratory values revert to grade ≤ 1. Corticosteroids at an initial dose of 0.5 to 1 mg/kg/d of prednisone or equivalent may be administered.

- Hold ICPis for grade 3 toxicities and initiate high-dose corticosteroids—prednisone 1–2 mg/kg/d or methylprednisolone IV 1 to 2 mg/kg/d. Corticosteroids should be tapered over the course of at least 4 to 6 weeks. If symptoms do not improve with 48 to 72 hours of high-dose corticosteroid, infliximab may be offered for some toxicities.

- When symptoms and/or laboratory values revert to grade ≤ 1, rechallenging with ICPis may be offered; however, caution is advised, especially in those patients with early-onset irAEs. Dose adjustments are not recommended.

- In general, grade 4 toxicities warrant the permanent discontinuation of ICPis, with the exception of endocrinopathies that have been controlled by hormone replacement.

TABLE 1 Incidence, associated regimens, and standards of care for common irAEs.

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Cutaneous	30-60%	Inflammatory dermatoses, bullous dermatoses, SCAR	Anti-CTLA-4, Combo ICIs	Topical or systemic corticosteroids	(77–79)
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		Guillain-Barrè syndrome	Anti-CTLA-4, Combo ICIs	Corticosteroids, Plasmapheresis, IVIG	
		Myositis, Myasthenic syndromes	Anti-PD-1/PD-L1, Combo ICIs	Corticosteroids, Plasmapheresis, IVIG, Tacrolimus, Rituximab	
Endocrine	10%	Hypophysitis	Anti-CTLA-4, Combo ICIs	Corticosteroids, Thyroid hormone replacement, Sex hormone replacement	(77, 78)
		Thyroid dysfunction	Anti-PD-1/PD-L1, Combo ICIs	Thyroid hormone supplementation, Beta-blocker,	
		Diabetes	Anti-PD-1/PD-L1, Combo ICIs	Insulin	
Pulmonary	1-6%	Pneumonitis	Anti-PD-1, Combo ICIs	Corticosteroids, IVIG, Infliximab, Mycophenolate mofetil, Cyclophosphamide	(77, 78)
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SCAR, Severe cutaneous adverse reactions; Combo ICIs, Anti-PD-1 + Anti-CTLA-4; FMT, Fecal microbiota transplantation; HF, Heart Failure; DMARDs, Disease modifying anti-rheumatic drugs.

S. Keam et al, Frontiers Vol 15, Aug 2024

VOLUME 36 · NUMBER 17 · JUNE 10, 2018

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

Julie R. Brahmer, Christina Lacchetti, Bryan J. Schneider, Michael B. Atkins, Kelly J. Brassil, Jeffrey M. Caterino, Ian Chau, Marc S. Ernstoff, Jennifer M. Gardner, Pamela Ginex, Sigrun Hallmeyer, Jennifer Holter Chakrabarty, Natasha B. Leighl, Jennifer S. Mammen, David F. McDermott, Aung Naing, Loretta J. Nastoupil, Tanyanika Phillips, Laura D. Porter, Igor Puzanov, Cristina A. Reichner, Bianca D. Santomasso, Carole Seigel, Alexander Spira, Maria E. Suarez-Almazor, Yinghong Wang, Jeffrey S. Weber, Jedd D. Wolchok, and John A. Thompson in collaboration with the National Comprehensive Cancer Network

GUIDELINE QUESTION

This clinical practice guideline addresses one overarching clinical question: How should clinicians manage irAEs in adult patients with cancer treated with immune checkpoint blockade antibodies?

The PICO criteria for the studies that were included in this review are as follows:

- Population: Adult patients with cancer receiving treatment with immune checkpoint blockade inhibitors alone (not in combination with chemotherapy)
- Intervention: Corticosteroids; immunosuppressive therapy; dose modification or discontinuation of therapy; organ-specific management, including hormone replacement, disease-modifying antirheumatic drugs (DMARDs), plasmapheresis, hospitalization, consultation to subspecialties, and best supportive care
- Comparator: No intervention or best supportive care
- Outcomes: Hospitalization, discontinuations of immunotherapy due to AE, AE-related morbidity or mortality, organ dysfunction based on organ system affected, required treatment due to irAEs, retreatment with immunotherapy, recovery from AEs, and health-related quality of life

JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Consider PCP prophylaxis for patients treated with high dose of corticosteroids for > 12 weeks, as per local guidelines.

5.2 Myositis

Definition: A disorder characterized by muscle inflammation with weakness and elevated muscle enzymes (CK). Muscle pain can be present in severe cases. Can be life threatening if respiratory muscles or myocardium are involved

G3-4: Severe weakness with or without pain, limiting self-care ADL	Hold ICPi until G1 or less while off immune suppression and permanently discontinue if any evidence of myocardial involvement Consider hospitalization for severe weakness Referral to rheumatologist or neurologist Initiate prednisone 1 mg/kg or equivalent. Consider 1-2 mg/kg of methylprednisolone IV or higher-dose bolus if severe compromise (weakness severely limiting mobility, cardiac, respiratory, dysphagia) Consider plasmapheresis Consider IVIG therapy Consider other immunosuppressant therapy, such as methotrexate, azathioprine, or mycophenolate mofetil, if symptoms and CK levels do not improve or worsen after 4-6 weeks; rituximab is used in primary myositis but caution is advised given its long biologic duration
Additional considerations: Caution is advised with rechallenging	

G3-4: Severe weakness with or without pain, limiting self-care ADL	Hold ICPi until G1 or less while off immune suppression and permanently discontinue if any evidence of myocardial involvement Consider hospitalization for severe weakness Referral to rheumatologist or neurologist Initiate prednisone 1 mg/kg or equivalent. Consider 1-2 mg/kg of methylprednisolone IV or higher-dose bolus if severe compromise (weakness severely limiting mobility, cardiac, respiratory, dysphagia) Consider plasmapheresis Consider IVIG therapy Consider other immunosuppressant therapy, such as methotrexate, azathioprine, or mycophenolate mofetil, if symptoms and CK levels do not improve or worsen after 4-6 weeks; rituximab is used in primary myositis but caution is advised given its long biologic duration

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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

7.1 Myasthenia gravis

Definition: Fatigable or fluctuating muscle weakness, generally more proximal than distal. Frequently has ocular and/or bulbar involvement (ptosis, extraocular movement abnormalities resulting in double vision, dysphagia, dysarthria, facial muscle weakness). May have neck and/or respiratory muscle weakness. (Note: May occur with myositis and/or myocarditis. Respiratory symptoms may require evaluation to rule out pneumonitis, myocarditis. Miller Fisher variant of Guillain-Barré syndrome (ophthalmoparesis) and the oculobulbar myositis (ptosis, ophthalmoparesis, dysphagia, neck and respiratory weakness) with ICPi may have overlapping symptoms.

G3-4: Limiting self-care and aids warranted, weakness limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms, or MGFA severity class 3-4 moderate to severe generalized weakness to myasthenic crisis	Permanently discontinue ICPi Admit patient, may need ICU-level monitoring Neurology consult Continue corticosteroids and initiate IVIG 2 g/kg IV over 5 days (0.4 g/kg/d) or plasmapheresis for 5 days Frequent pulmonary function assessment Daily neurologic review

Additional considerations

- Avoid medications that can worsen myasthenia: β-blockers, IV magnesium, fluoroquinolones, aminoglycosides, and macrolides
- Initially a 5-day course of plasmapheresis or a 2 g/kg course of IVIG over 5 days
- 1-2 mg/kg methylprednisolone daily, wean based on symptom improvement
- Pyridostigmine, wean based on improvement
- ICPi-associated myasthenia gravis may be monophasic, and additional corticosteroid-sparing agents may not be required

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JOURNAL OF CLINICAL ONCOLOGY
ASCO SPECIAL ARTICLE

7.2 Guillain-Barré syndrome

Definition: Progressive, most often symmetrical muscle weakness with absent or reduced deep tendon reflexes. Often starts with sensory symptoms/neuropathic pain localized to lower back and thighs. May involve extremities (typically ascending weakness but not always), facial, respiratory, and bulbar and oculomotor nerves. May have dysregulation of autonomic nerves.

G2: Moderate, some interference with ADL, symptoms concerning to patient G3-4: Severe, limiting self-care and aids warranted, weakness limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms	Discontinue ICPi Admission to inpatient unit with capability of rapid transfer to ICU-level monitoring Start IVIG (0.4 g/kg/d for 5 days for a total dose of 2 g/kg) or plasmapheresis. Corticosteroids are usually not recommended for idiopathic Guillain-Barré syndrome; however, in ICPi-related forms, a trial is reasonable (methylprednisolone 2-4 mg/kg/d), followed by slow corticosteroid taper Pulse corticosteroid dosing (methylprednisolone 1 g/d for 5 days) may also be considered for G3-4 along with IVIG or plasmapheresis Frequent neurochecks and pulmonary function monitoring Monitor for concurrent autonomic dysfunction Nonopioid management of neuropathic pain Treatment of constipation/ileus

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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

7.6 Encephalitis

Definition: As for aseptic meningitis, need to exclude infectious causes, especially viral (ie, HSV).
Confusion, altered behavior, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, speech abnormality

Grading	Management
G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate. G2: Moderate, some interference with ADL, symptoms concerning to patient (ie, pain but no weakness or gait limitation) G3-4: Severe, limiting self-care and aids warranted	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits As above for aseptic meningitis, suggest concurrent IV acyclovir until PCR results obtained and negative Trial of methylprednisolone 1-2 mg/kg If severe or progressing symptoms or oligoclonal bands present, consider pulse corticosteroids methylprednisolone 1 g IV daily for 3-5 days plus IVIG 2 g/kg over 5 days If positive for autoimmune encephalopathy antibody and limited or no improvement, consider rituximab or plasmapheresis in consultation with neurology

Πρωτόκολλα – Κατευθυντήριες οδηγίες αντιμετώπισης ΑΕ

- Consensus guidelines offer resources for understanding the management of immune-mediated adverse events:[1–3]*

Immuno-oncology

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) in Partnership With ASCO: Management of Immunotherapy-Related Toxicities (Immune Checkpoint Inhibitor-Related Toxicities)

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

Managing Toxicities Associated With Immune Checkpoint Inhibitors: Consensus Recommendations From the SITC Toxicity Management Working Group

eferenced with permission from: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Management of Immunotherapy-Related cities V.1.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. (Last accessed 10 April 2018).To view the most recent and plete version of the guideline, go online to NCCN.org.; 2. Brahmer JR, et al. J Clin Oncol 2018. doi:10.1200/JCO.2017.77.6385. 3. Puzanov I, et al. J unother Cancer 2017;5:95

NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Management of Immune Checkpoint Inhibitor-Related Toxicities

Version 1.2026 — October 23, 2025

PLEASE NOTE

NERVOUS SYSTEM ADVERSE EVENT(S)	ASSESSMENT/GRADING		MANAGEMENT[e]
Myasthenia gravis/ myasthenia gravis-like syndrome[a]	• Evaluate for concomitant irAEs myocarditis (ICI_CARDIO-1) and myositis (ICI_MS-3) as myasthenia gravis/myasthenia gravis-like syndrome can exist as an overlap syndrome[b] ▸ Cardiac exam and ECG ▸ Troponin, CK, and aldolase ▸ Consider transthoracic echocardiogram (TTE) • Neurology consultation • AChR antibodies, anti–muscle-specific tyrosine kinase antibodies, and anti-striational antibodies in blood (not needed for diagnosis) • Pulmonary function assessment with negative inspiratory force (NIF) and vital capacity (VC) • EMG/nerve conduction study (NCS) with repetitive nerve stimulation and, if available, single-fiber EMG • Consider MRI of the brain with and without contrast to rule out metastasis/ leptomeningeal disease if there is facial/ ocular/bulbar weakness	Moderate (G2)[c] →	• Discontinue immunotherapy[f] • Consider inpatient care (even for initially mild cases, which can progress rapidly with a high mortality rate) • Low-dose oral prednisone 20 mg daily[g] ▸ If no symptom improvement on low dose ◊ Increase every 3–5 days to a target dose of 1 mg/kg/day but not >100 mg daily ◊ Taper steroid based on symptom improvement • Pyridostigmine 30 mg 3 times a day and gradually increase to maximum of 120 mg orally 4 times a day as tolerated and based on symptoms
		Severe (G3–4)[d] →	• Permanently discontinue immunotherapy[f] • Inpatient care (may need ICU-level monitoring) • IV methylprednisolone 1–2 mg/kg/day[g] (steroid taper based on symptom improvement) • Initiate plasmapheresis or IVIG[h] ▸ Consider adding rituximab (375 mg/m² weekly for 4 treatments or 500 mg/m² every 2 weeks for 2 doses) if refractory to plasmapheresis or IVIG • Frequent pulmonary function assessment • Daily neurologic evaluation • Avoid medications that can worsen myasthenia[g,i]

[a] Progressive or fluctuating muscle weakness, generally proximal to distal. May have bulbar involvement (ie, ptosis, extraocular movement abnormalities resulting in double vision, dysphagia, facial muscle weakness) and/or respiratory muscle weakness. May occur with myositis and myocarditis. Respiratory symptoms may require evaluation to rule out pneumonitis. Miller Fisher variant of GBS has overlapping symptoms (ophthalmoplegia and ascending weakness).

[b] Myocarditis symptoms are nonspecific (eg, chest pain, dyspnea, fatigue, palpitations [arrhythmia: heart block or ventricular ectopic beats], syncope, generalized weakness) and may occur as early as days to weeks after 1–2 doses of ICI. Although rare, myocarditis is often severe and associated with myositis/myasthenia gravis/myasthenia gravis-like syndrome (3 M's), and more common with combination therapy. In most fatal cases, conduction abnormalities were the cause of death, and ejection fraction was preserved.

[c] Some symptoms interfering with ADLs. Myasthenia Gravis Foundation of America (MGFA) severity class I (ocular symptoms and findings only) and MGFA severity class II (mild generalized weakness).

[d] Limiting self-care and aids warranted, weakness limiting walking, any dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms or MGFA severity class III–IV moderate to severe generalized weakness to myasthenic crisis.

[e] Principles of Immunosuppression (IMMUNO-A).

[f] Principles of Immunotherapy Rechallenge (IMMUNO-C).

[g] High-dose steroids (≥2 mg/kg/day) may exacerbate symptoms.

[h] IVIG 2 g/kg divided in equal doses given over 2–5 consecutive days. Refer to the FDA-approved package insert for important safety information.

[i] Examples include, but are not limited to, beta-blockers, fluoroquinolones, and IV magnesium.

Note: All recommendations are category 2A unless otherwise indicated.

NERVOUS SYSTEM ADVERSE EVENT(S)	ASSESSMENT/GRADING		MANAGEMENT[e]
Guillain-Barré syndrome (GBS)[j]	• Inpatient care with access to ICU-level monitoring • Neurology consultation • MRI of the spine with and without contrast (rule out compressive lesion) • Serum ganglioside antibody tests for GBS variants (GQ1b for Miller Fisher variant associated with ataxia and ophthalmoplegia) • PFTs (NIF/VC) • EMG/NCS[k] • Lumbar puncture[l] (to exclude leptomeningeal disease, which can mimic GBS)	Moderate (G2)[m] or Severe (G3–4)[n]	• Discontinue immunotherapy[f] • Inpatient care with capability of rapid transfer to ICU-level monitoring • Start IVIG[h] or plasmapheresis in addition to IV methylprednisolone 1 gram daily for 5 days[o] then taper over 4 weeks • Frequent neurologic evaluation and pulmonary function monitoring • Monitor for concurrent autonomic dysfunction • Gabapentin, pregabalin, or duloxetine for pain

[e] Principles of Immunosuppression (IMMUNO-A).
[f] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[h] IVIG 2 g/kg divided in equal doses given over 2–5 consecutive days. Refer to the FDA-approved package insert for important safety information.
[j] Progressive, most often symmetrical muscle weakness with absent or reduced deep tendon reflexes. May involve extremities, facial, respiratory, and bulbar and oculomotor nerves. May have dysregulation of autonomic nerves. Often starts with pain in lower back and thighs.
[k] Early EMG/NCS findings may assess potential severity of GBS (Sejvar JJ, et al. Vaccine 2011;29:599-612; Leonhard SE, et al. Nat Rev Neurol 2019;15:671-683) and rule out sensory ganglionopathy, which may have a different prognosis.
[l] Cerebrospinal fluid (CSF) typically has elevated protein and often elevated white blood cell (WBC) count; while cytology is negative in typical GBS, it is important to send given the risk of leptomeningeal carcinomatosis. Consider ID consult. ID workup: Measure opening pressure and check cell count, protein glucose, Gram stain, culture, PCR for HSV, and other viral PCRs depending on suspicion and cytology. May see normal glucose, normal culture, and Gram stain. May see reactive lymphocytes or histiocytes on cytology.
[m] Some interference with ADLs, symptoms concerning to patient.
[n] Limiting self-care and aids warranted, weakness limiting walking, any dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms.
[o] Steroids are not usually recommended for idiopathic GBS; however, in immunotherapy-related forms, a trial is reasonable in addition to IVIG or plasmapheresis.

Note: All recommendations are category 2A unless otherwise indicated.

NCCN National Comprehensive Cancer Network®

PLEASE NOTE

NERVOUS SYSTEM ADVERSE EVENT(S)	ASSESSMENT	MANAGEMENT[e]
Aseptic meningitis[x]	• MRI of the brain with and without contrast[z] + pituitary protocol • Consider MRI of the spine with and without contrast, especially if abnormal neurologic exam of extremities, or unable to obtain exam • Lumbar puncture (to exclude leptomeningeal disease)[aa] • Consider neurology consultation	• Hold immunotherapy[f] if mild/moderate • Consider discontinuing immunotherapy if severe • Inpatient care (G3–4[cc]) • Consider IV acyclovir[dd] until HSV and varicella zoster virus (VZV) PCR results obtained • Add bacterial coverage until cultures/panel results are back • Rule out bacterial and viral infection, then closely monitor off steroids • Start prednisone 0.5–1 mg/kg/day. For severe symptoms may start IV methylprednisolone 1–2 mg/kg/day[ee]
Encephalitis[y]	• Neurology consultation • MRI of the brain with and without contrast[bb] • Consider MRI of the spine with and without contrast, especially if abnormal neurologic exam of extremities, or unable to obtain exam • Lumbar puncture[aa] • Electroencephalogram (EEG) to evaluate for non-convulsive seizure • ESR, CRP, ANCA (if vasculitic process suspected) • Autoimmune encephalopathy in cerebrospinal fluid (CSF) and serum	• Hold immunotherapy[f] if mild • Discontinue immunotherapy if moderate/severe • Inpatient care (G3–4[cc]) • Consider IV acyclovir[dd] until HSV and VZV PCR results are obtained • Add bacterial coverage until cultures/panel results are back; manage in consultation with ID team • Trial of IV methylprednisolone 1–2 mg/kg/day[ee] • If severe or progressing symptoms over 24 h, strongly consider IV methylprednisolone 1 g daily for 3–5 days plus IVIG[h] or plasmapheresis • If positive for autoimmune encephalopathy antibody or limited or no improvement after 7–14 days, consider rituximab

[e] Principles of Immunosuppression (IMMUNO-A).
[f] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[h] IVIG 2 g/kg divided in equal doses given over 2–5 consecutive days. Refer to the FDA-approved package insert for important safety information.
[x] May present with headache, photophobia, and neck stiffness, often afebrile but may be febrile. There may be nausea/vomiting. Mental status should be normal (distinguishes from encephalitis).
[y] Confusion, altered behavior, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, and speech abnormality.
[z] May reveal leptomeningeal enhancement that can resemble leptomeningeal metastasis. CSF sampling for cytology evaluation is needed to differentiate.
[aa] Measure opening pressure and check cell count, protein glucose, Gram stain, culture, PCR for HSV, VZV, CMV, and other viral PCRs depending on suspicion, cytology, flow cytometry, and oligoclonal bands. If the patient is encephalopathic, check autoimmune encephalopathy panel. May see elevated WBC with normal glucose, normal culture, Gram stain, and elevated protein. May see reactive lymphocytes or histiocytes on cytology.
[bb] May reveal T2/FLAIR changes typical of what is seen in autoimmune encephalopathies or limbic encephalitis or may be normal.
[cc] Limiting self-care and aids warranted.
[dd] 10 mg/kg IV every 8 hours.
[ee] Taper steroids over 4 weeks once symptoms resolve.

Note: All recommendations are category 2A unless otherwise indicated.

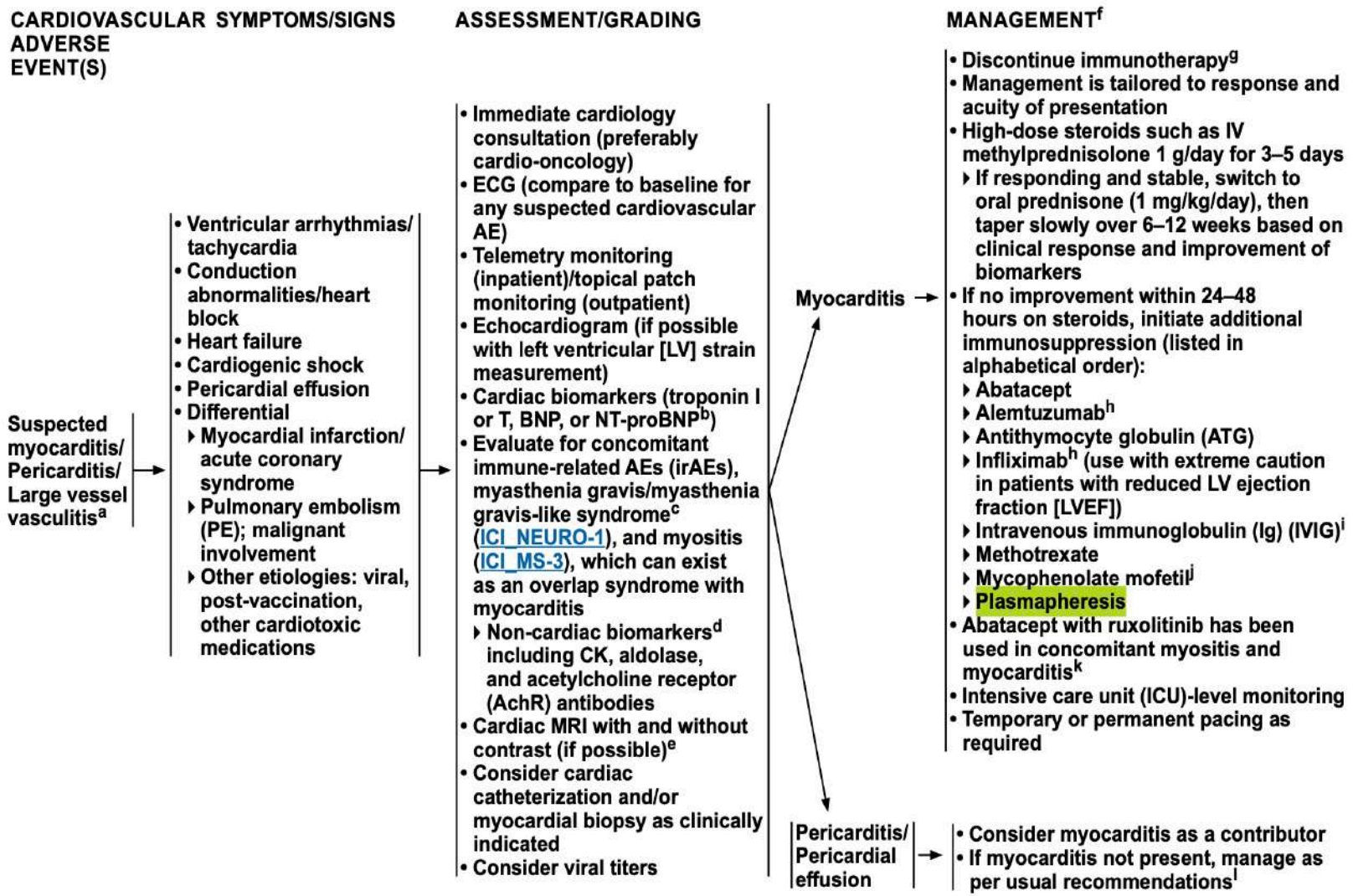
PLEASE NOTE

NERVOUS SYSTEM ADVERSE EVENT(S)	ASSESSMENT	MANAGEMENT[e]
Demyelinating disease[ff] (optic neuritis,[gg] transverse myelitis,[hh] ADEM[ii] [acute demyelinating encephalomyelitis])	• Neurology consultation • MRI of the spine and brain with and without contrast[jj] • Lumbar puncture[kk] • B_{12}, copper, HIV, syphilis serologies, antinuclear antibody (ANA), anti-Ro/La antibodies, aquaporin-4 IgG, myelin oligodendrocyte glycoprotein (MOG) IgG, autoimmune encephalopathy panel, and paraneoplastic panel • Evaluation for constipation and urinary retention with bladder scan	• Discontinue immunotherapy[f] • Inpatient care • IV methylprednisolone 1 g/day[ee] for 3–5 days • If there is no response or worsening after 48 hours on high-dose IV methylprednisolone, consider IVIG[h] or plasmapheresis • For management of optic neuritis, see ICI_OCUL-3

[e] Principles of Immunosuppression (IMMUNO-A).
[f] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[h] IVIG 2 g/kg divided in equal doses given over 2–5 consecutive days. Refer to the FDA-approved package insert for important safety information.
[ee] Taper steroids over 4 weeks once symptoms resolve.
[ff] Guidon AC, et al. J Immunother Cancer 2021;9:e0028890.
[gg] Vision loss, eye pain, decreased visual acuity, visual field loss, dyschromatopsia, relative afferent pupillary defect, optic disc edema.
[hh] Acute or subacute weakness or sensory changes bilaterally, often with bowel/bladder changes and spinal level to pinprick, hyperreflexia, positive Babinski.
[ii] May present with headache, confusion, seizures, depressed level of consciousness, speech abnormality, focal weakness, sensory change (numbness or tingling), ataxia/loss of balance, or vision loss.
[jj] In patients with suspected optic neuritis, MRI of the orbits with and without contrast is recommended.
[kk] Cell count, protein, glucose, oligoclonal bands, viral PCRs, flow cytometry and cytology, and paraneoplastic panel.

Note: All recommendations are category 2A unless otherwise indicated.

National Comprehensive Cancer Network®

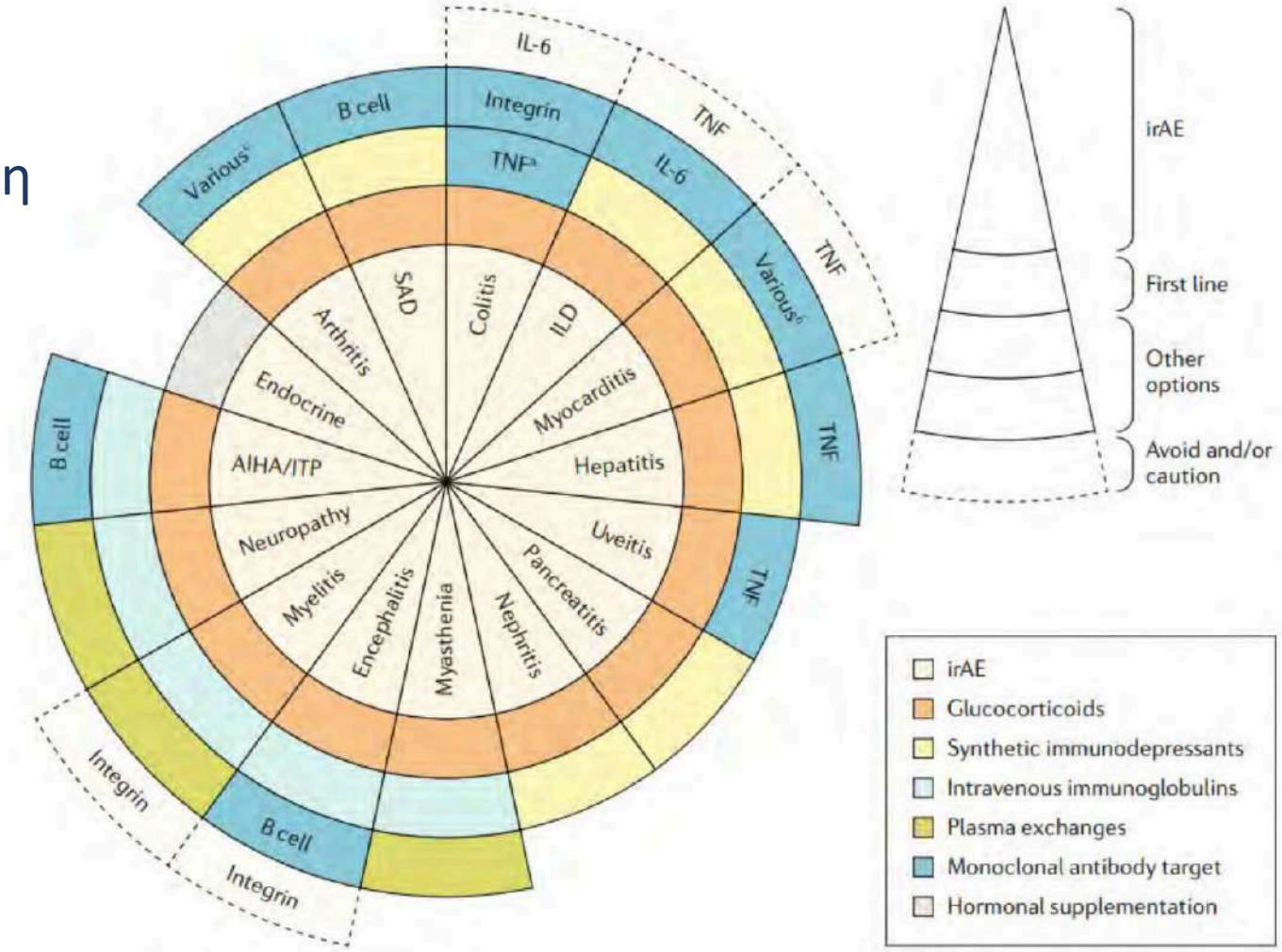


Footnotes on ICI_CARDIO-1A

Note: All recommendations are category 2A unless otherwise indicated.

Επιλογή βέλτιστης αντιμετώπισης AE

1ης ΓΡΑΜΜΗΣ: Κορτικοστεροείδη

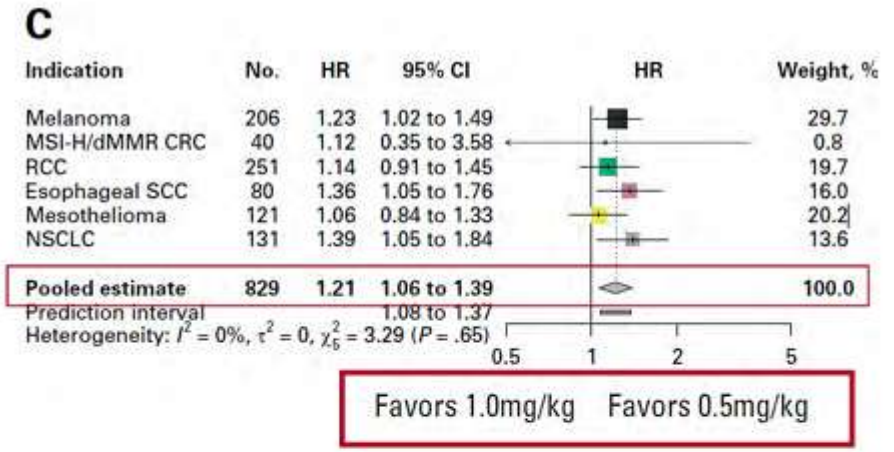


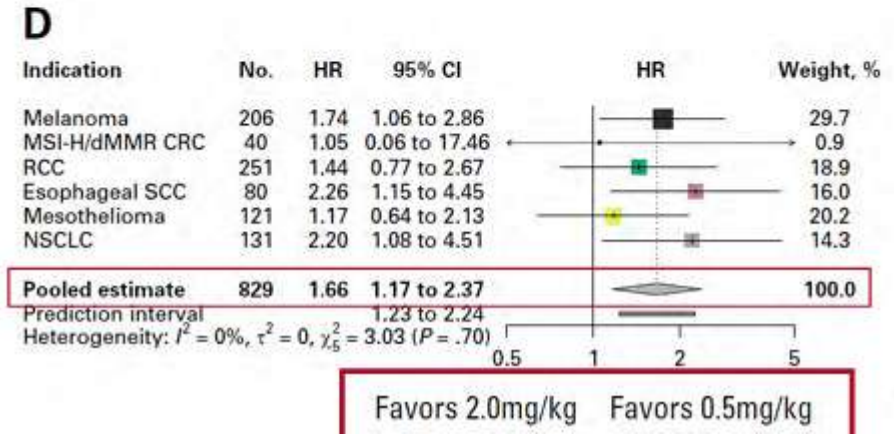
Ramos-Casals et al, Nature Reviews, 2020

Επιλογή βέλτιστης αντιμετώπισης ΑΕ

Υψηλότερες μέγιστες δόσεις κορτικοστεροειδών για τις ΑΕ που σχετίζονται με τους αναστολείς σημείων ελέγχου συνδέονται με μικρότερη επιβίωση σε όλους τους τύπους καρκίνου

- Six ph II/III RCT using ipi/nivo
  - CM-067, CM-142, CM-214, CM-648, CM-743, CM-9LA
- 834 patients with trAEs
- 90% received corticosteroids only
- 9% received corticosteroids plus second-line immunosuppressants
- Association of corticosteroid peak dose with OS (Fig C +D)
  - while cumulative dose was not associated





Συνετή χρήση των κορτικοστεροειδών

Επιλογή βέλτιστης αντιμετώπισης ΑΕ

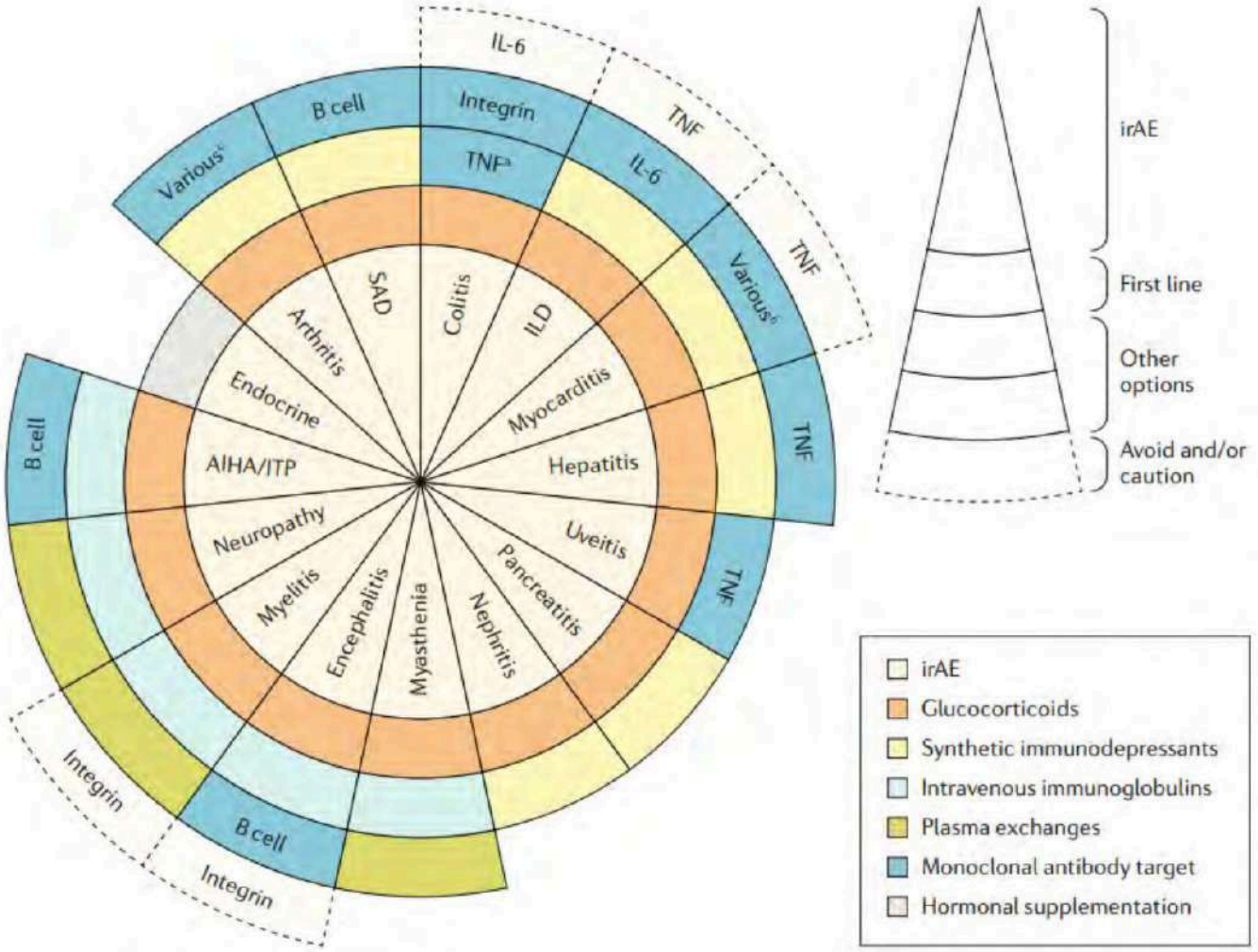
1ης ΓΡΑΜΜΗΣ: Κορτικοστεροείδη

2ης ΓΡΑΜΜΗΣ: Επιλογή ανάλογα:

- Προσβληθέν όργανο
- Πιθανολογούμενο μηχανισμό δράσης

Ο χρόνος μεταξύ 1ης και 2ης γραμμής θεραπεία εξαρτάται:

- μη απάντηση ή αντίσταση στη κορτιζόνη
- Κορτικοεξάρτηση
- Σοβαρότητα και όργανο ΑΕ



Ramos-Casals et al, Nature Reviews, 2020

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

J. Haanen[1†], M. Obeid[2,3,4†], L. Spain[5,6,7], F. Carbonnel[8,9], Y. Wang[10], C. Robert[11,12], A. R. Lyon[13,14], W. Wick[15,16], M. Kostine[17], S. Peters[4], K. Jordan[18,19] & J. Larkin[20], on behalf of the ESMO Guidelines Committee[*]

[1]Division of Medical Oncology, Netherlands Cancer Institute (NKI), Amsterdam, The Netherlands; [2]Immunology and Allergy Service, CHUV, Lausanne; [3]Lausanne Center for Immuno-oncology Toxicities (LCIT), CHUV, Lausanne; [4]Department of Oncology, CHUV, Lausanne, Switzerland; [5]Medical Oncology Department, Peter MacCallum Cancer Centre, Melbourne; [6]Department of Medical Oncology, Eastern Health, Melbourne; [7]Monash University Eastern Health Clinical School, Box Hill, Australia; [8]Gastroenterology Department, Assistance Publique-Hôpitaux de Paris, Hôpital Universitaire Bicêtre, Le Kremlin Bicêtre; [9]Université Paris Saclay 11, Le Kremlin-Bicêtre, France; [10]Department of Gastroenterology, Hepatology & Nutrition, The University of Texas MD Anderson Cancer Center, Houston, USA; [11]Department of Medicine, Gustave Roussy Cancer Centre, Villejuif; [12]Paris-Saclay University, Villejuif, France; [13]Cardio-Oncology Service, Royal Brompton Hospital, London; [14]National Heart and Lung Institute, Imperial College London, London, UK; [15]Neurology Clinic and National Centre for Tumour Diseases, University Hospital Heidelberg, Heidelberg; [16]DKTK and Clinical Cooperation Unit NeuroOncology, DKFZ, Heidelberg, Germany; [17]Department of Rheumatology, Hôpital Pellegrin, CHU de Bordeaux, Bordeaux, France; [18]Department of Haematology, Oncology and Palliative Medicine, Ernst von Bergmann Hospital Potsdam, Potsdam; [19]Department of Haematology, Oncology and Rheumatology, University Hospital Heidelberg, Heidelberg, Germany; [20]Royal Marsden NHS Foundation Trust, London, UK

Available online 18 October 2022

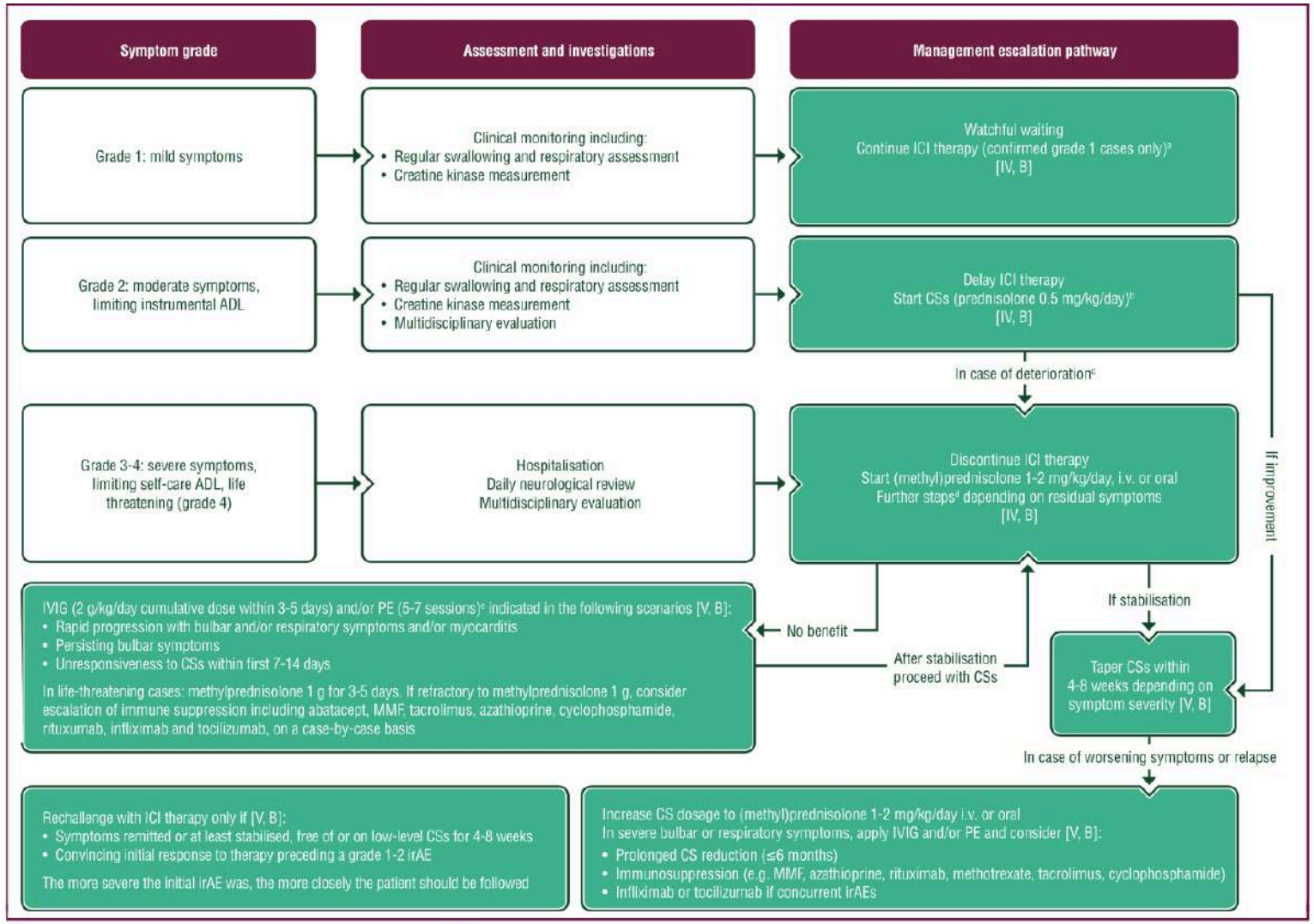


Figure 8. Management of IR-neuro(muscular) toxicity.[115]

Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management. ADL, activities of daily living; CS, corticosteroid; GBS, Guillain–Barré syndrome; ICI, immune checkpoint inhibitor; IR, immune-related; irAE, immune-related adverse event; i.v., intravenous; IVIG, intravenous immunoglobulin; MMF, mycophenolate mofetil; PE, plasma exchange.

[a]Patients presenting with any neurological symptoms should be referred to a neurologist and ICI should be held until the grade of symptoms is confirmed.

[b]In all scenarios, pyridostigmine starting from 3 × 30 mg orally up to 600 mg daily may be used in case of myasthenic symptoms; in i.v. application, 30 mg oral pyridostigmine corresponds to 1 mg i.v. or 0.75 mg neostigmine i.m. In case of intubation, pyridostigmine may be discontinued or withheld.

[c]Timely consultation of a neurologist.

[d]CSs are not usually recommended for idiopathic GBS; in mild ICI-related forms, however, a trial is reasonable (methylprednisolone 2-4 mg/kg/day) followed by slow CS taper. Pulse CS dosing (methylprednisolone 1 g/day for 5 days) may also be considered for grade 3-4 events along with IVIG or plasmapheresis.

[e]For life-threatening symptoms, PE might be the favourable option; consider contraindications: renal failure, hypercoagulable states, sepsis, haemodynamic instability.

IR-CHOLANGITIS

IR-cholangitis is a rare AE which may affect large bile ducts, small ducts or both. Elevations of γ-glutamyltransferase and ALP are more prominent than transaminases. Pathological findings include portal inflammation, bile duct injury or loss, cholestasis and lobular injury. Most patients receive urso-deoxycholic acid and prednisone or budesonide, although other immunosuppressive agents, e.g. MMF, azathioprine, tacrolimus, tocilizumab and plasmapheresis, have also been used. With medical treatment, biliary enzymes decrease in the majority of patients but reach normal values in only a minority of cases after 6-12 weeks.[36]

Table 1. Summary of current oncology treatment guidelines regarding use of PLEX

	NCCN [20]	ASCO [17]	SITC [18]	ESMO [19]
Myasthenia Gravis	**Grade 3-4:** "Initiate plasmapheresis or IVIG if no improvement/ worsening on steroids or severe symptoms"	**Grade 3-4:**"Initiate IVIG 2 g/kg IV over 5 d or plasmapheresis x 5 d"	**Grade 3-4:**"IVIG 2 g/kg over 5 d or plasmapheresis over 5 days may be considered"	"In the case of GBS or myasthenia-like symptoms, consider adding plasmapheresis or IVIG"
Guillain-Barre Syndrome	**Grade 2 or 3-4:** "Start IVIG or plasmapheresis in addition to pulse methylprednisolone 1 g daily x 5 d"	**Grade 2 or 3-4:** "Start IVIG or plasmapheresis."	"Patients with any grade of encephalitis or GBS should receive pulse-dose methylprednisolone at 1000 mg IV daily for 3-5 d and should additionally receive IVIG or PLEX"	"In the case of GBS or myasthenia-like symptoms, consider adding plasmapheresis or IVIG"
Demyelinating diseases including transverse myelitis	"Methylprednisolone pulse dosing 1 g/d for 3-5 days, Strongly consider IVIG or plasmapheresis"	**Grade 3-4:**"Methylprednisolone pulse dosing 1 g/d and consider IVIG or plasmapheresis if no improvement or symptoms worsen after 3 days"		
Myositis		**Grade 3-4:**"Consider plasmapheresis in patients with acute or severe disease as guided by rheumatology or neurology"	**Grade 3:**"For muscle weakness severely limiting mobility, cardiac or respiratory involvement, or dysphagia, 1-2 mg/ kg methylprednisolone IV or higher dose bolus may be considered as well as plasmapheresis or IVIG"	
Encephalitis		**Grade 3-4:**"If severe or progressing symptoms or oligoclonal bands present, consider pulse dose CS plus IVIG 2 g/kg x 5 d or plasmapheresis"	"If ICI-related encephalitis does not respond to pulse-dose corticosteroids, patients may receive IVIG (2 g/kg in divided doses over the course of 5 d), PLEX (one session every other day for 5-7 cycles), or rituximab"	

ASCO: American Society of Clinical Oncology; CS: corticosteroid; ESMO: European Society for Medical Oncology; GBS: Guillain-Barre Syndrome; IVIG; intravenous immunoglobulin; NCCN: National Comprehensive Cancer Network; PLEX: plasma exchange; SITC: Society for Immunotherapy of Cancer.

Επιλογή βέλτιστης αντιμετώπισης ΑΕ

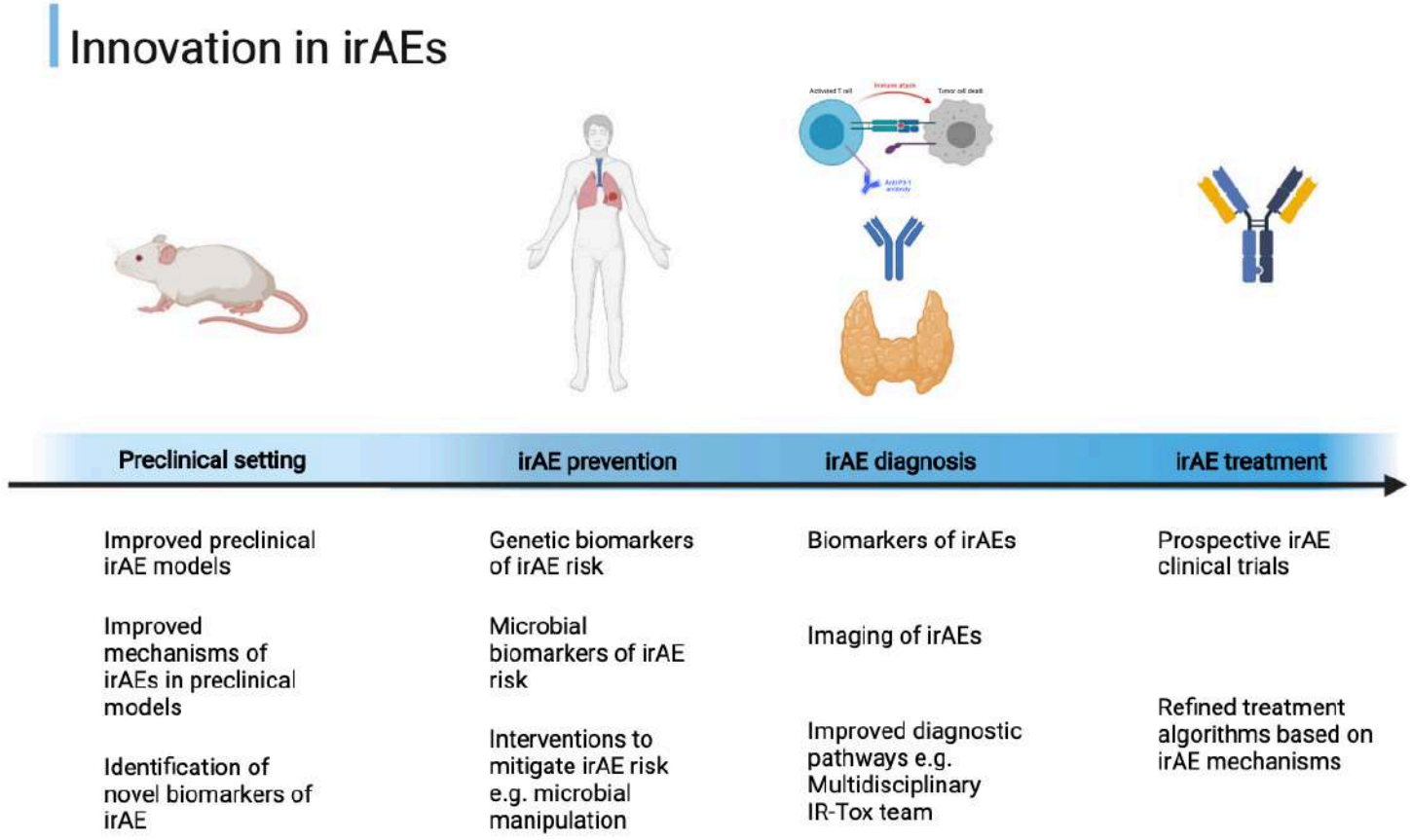
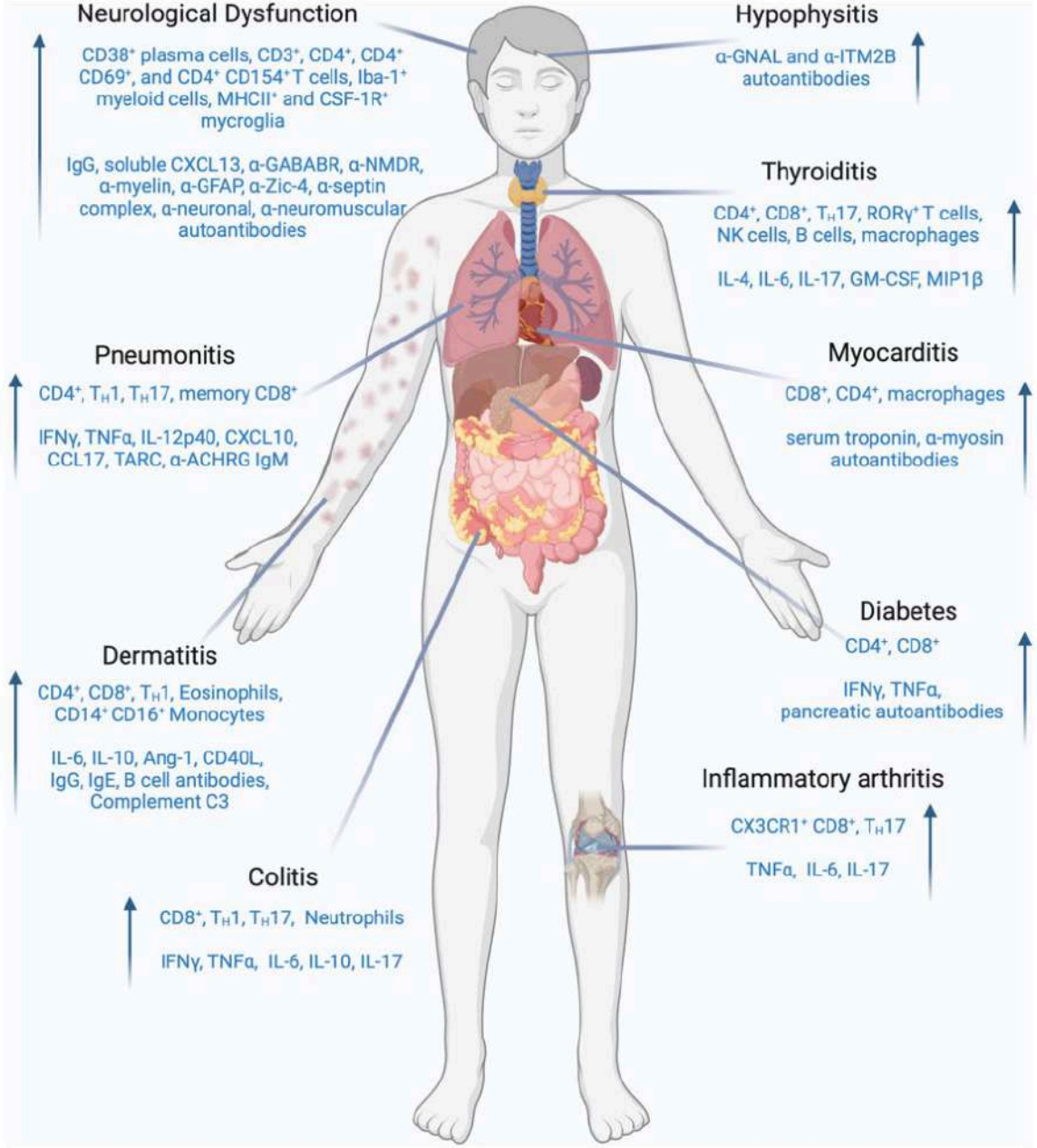


Fig. 1 Innovation in immune-related adverse event research spans the preclinical setting (preclinical models exploring mechanisms and biomarkers), irAE prevention studies (based on genetic or microbial biomarkers and potential interventions), studies that focus on optimizing irAE diagnosis (based on biomarkers or imaging to improve diagnostic pathways), and lastly irAE treatment (prospective irAE trials to inform guidelines).

M.Conroy et al, Nat Communication 13: 392, 2022

Επιλογή βέλτιστης αντιμετώπισης ΑΕ



Κυτταρικοί και μοριακοί παράγοντες που πιθανώς εμπλέκονται στην παθογένεια και βρίσκονται αυξημένοι στις ΑΕ

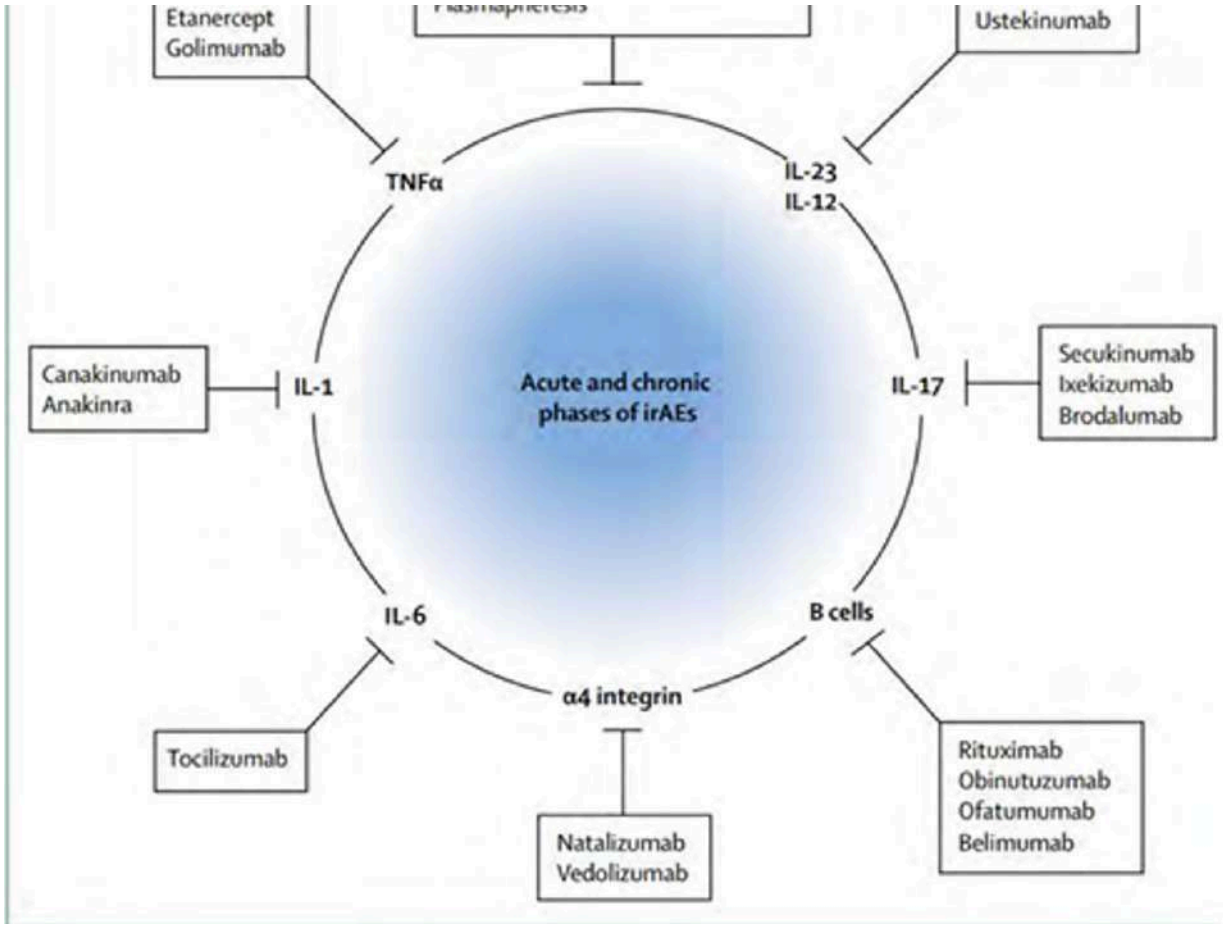
Επιλογή βέλτιστης αντιμετώπισης ΑΕ

ΥΠΟΠΤΟ ΠΑΘΟΓΕΝΕΤΙΚΟ ΜΟΡΙΟ

TNF-alpha
IL-6
IL-1
Alpha-4 Integrin
B-cell mediated
CTLA-4

ΣΤΟΧΕΥΜΕΝΟ ΦΑΡΜΑΚΟ

TNF-alpha	INFLIXIMAB
IL-6	TOCOLIZUMAB
IL-1	ANAKINRA
Alpha-4 Integrin	VEDOLIZUMAB
B-cell mediated	RITUXIMAB
CTLA-4	ABATACEPT



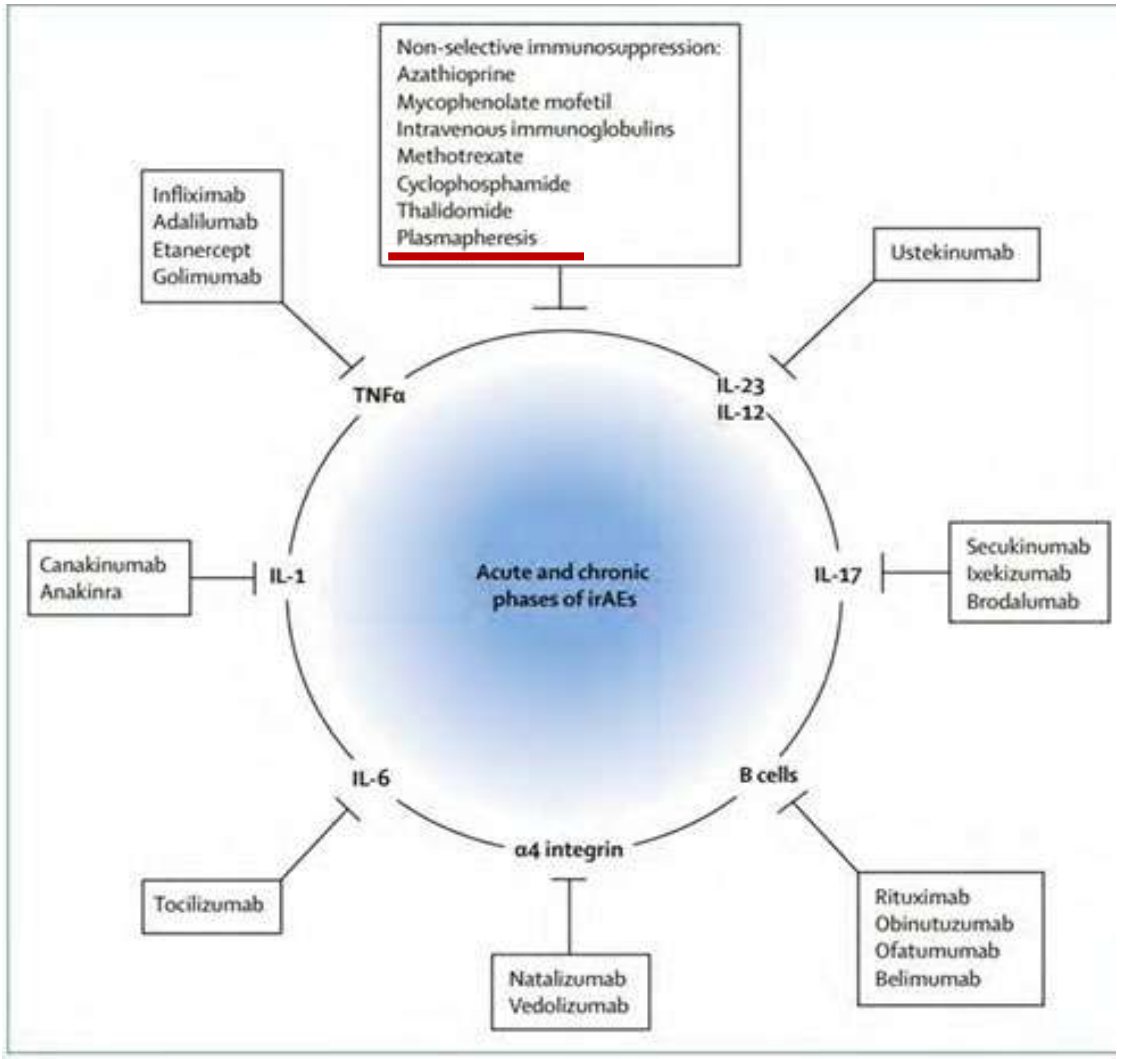
Martins et al, Lancet Oncol, 2019

Επιλογή βέλτιστης αντιμετώπισης ΑΕ

ΑΛΛΕΣ ΜΗ ΕΚΛΕΚΤΙΚΕΣ ΘΕΡΑΠΕΥΤΙΚΕΣ ΕΠΙΛΟΓΕΣ

AZATHIOPRINE
MYCOPHENOLATE MOFETIL
IVIG
METHOTREXATE
CYCLOPHOSPHAMIDE
THALIDOMIDE

PLASMAPHERESIS



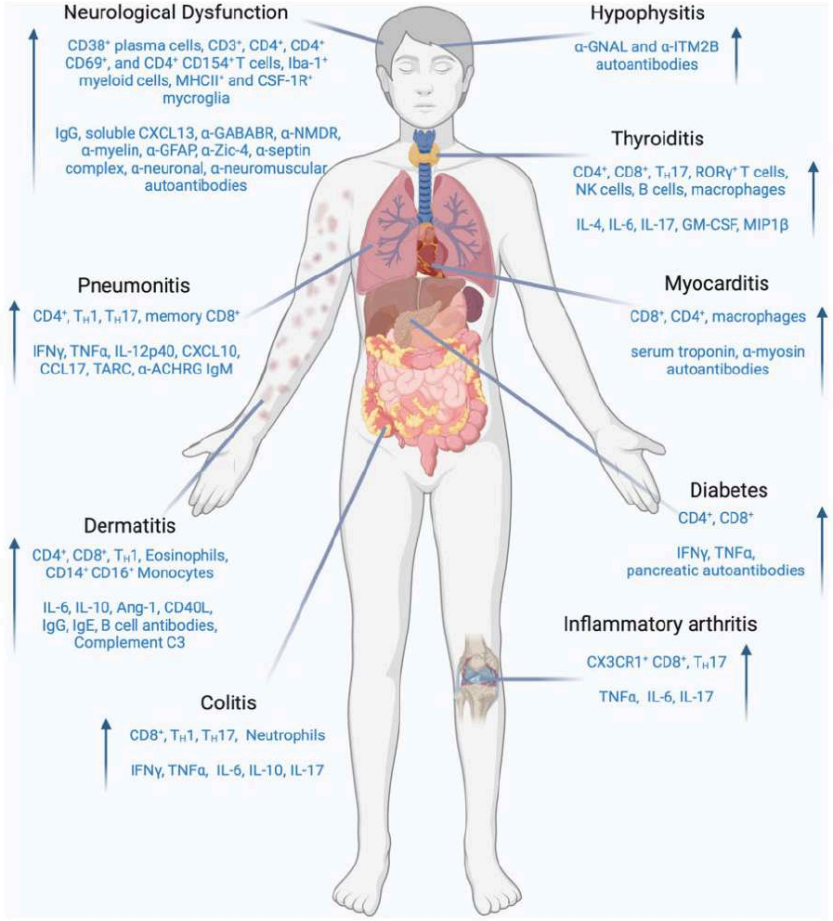
Martins et al, Lancet Oncol, 2019

Κατευθυντήριες οδηγίες ASFA – 9η επικαιροποίηση

Rationale for therapeutic apheresis

directly removed by TPE to decrease systemic effects. TPE is also known to remove autoantibodies that are precipitated by ICIs, including autoantibodies implicated in irAEs such as in MG, transverse myelitis, and TTP. Furthermore, TPE may further act by removing circulating systemic inflammatory cytokines due to ICI-induced cytokine release syndrome.

Κάποια εξέχοντα μόρια που αυξάνονται στις ΑΕ δύναται να απομακρυνθούν άμεσα με πλασμαφαίρεση



Κατευθυντήριες οδηγίες ASFA – 9η επικαιροποίηση

Rationale for therapeutic apheresis

The ICIs are monoclonal IgG antibodies with half-lives ranging from 6 days (avelumab) to 27 days (atezolizumab). These antibodies can be directly removed by TPE to decrease systemic effects.

Βάσει αυτών των χαρακτηριστικών δύναται να απομακρυνθούν άμεσα με πλασμαφαίρεση

Table 2. Pharmacologic characteristics of immune checkpoint inhibitors.

ICI	T 1/2	Vd	IgG subclass	MoA
Nivolumab	25 days	6.8 l	IgG4	anti-PD-1
Pembrolizumab	22 days	6 l	IgG4	anti-PD-1
Cemiplimab	20 days	5.3 l	IgG4	anti-PD-1
Dostarlimab	23.5 days	5.3 l	IgG4	anti-PD-1
Camrelizumab	14 days	5.4 l	IgG4	anti-PD-1
Atezolizumab	27 days	6.9 l	IgG1	anti-PD-L1
Avelumab	6.1 days	4 l	IgG1	anti-PD-L1
Durvalumab	17 days	6.9 l	IgG1	anti-PD-L1
Ipilimumab	15 days	7.2 l	IgG1	anti-CTLA-4

ICI: immune checkpoint inhibitor; T1/2: Half-life; Vd: Volume of distribution; MoA: Mechanism of action; L: Liter; IgG: Immunoglobulin G; anti-PD(L)1: anti-Programmed Cell Death (Ligand)1; anti-CTLA-4: anti-cytotoxic T-lymphocyte-associated protein 4. From reference [43].

Κατευθυντήριες οδηγίες ASFA – 9η επικαιροποίηση

IMMUNE CHECKPOINT INHIBITORS, IMMUNE-RELATED ADVERSE EVENTS

Incidence: 39% to 70% of patients treated with immune checkpoint inhibitors

Indication	**Procedure**		**Category**	**Grade**
	TPE		III*	2C
# Reported patients: 100 to 300	**RCT**	**CT**	**CS**	**CR**
	0	0	9 (46)	75 (75)

*Immune related adverse events due to immune checkpoint inhibitor toxicity include myasthenia gravis, thrombotic thrombocytopenic purpura (see *separate fact sheets*), myocarditis, myositis, and transverse myelitis, among other conditions.

Technical notes

Typically, the replacement fluid is albumin. However, in patients with TTP related to ICI exposure, or in those with bleeding symptoms, plasma is recommended.

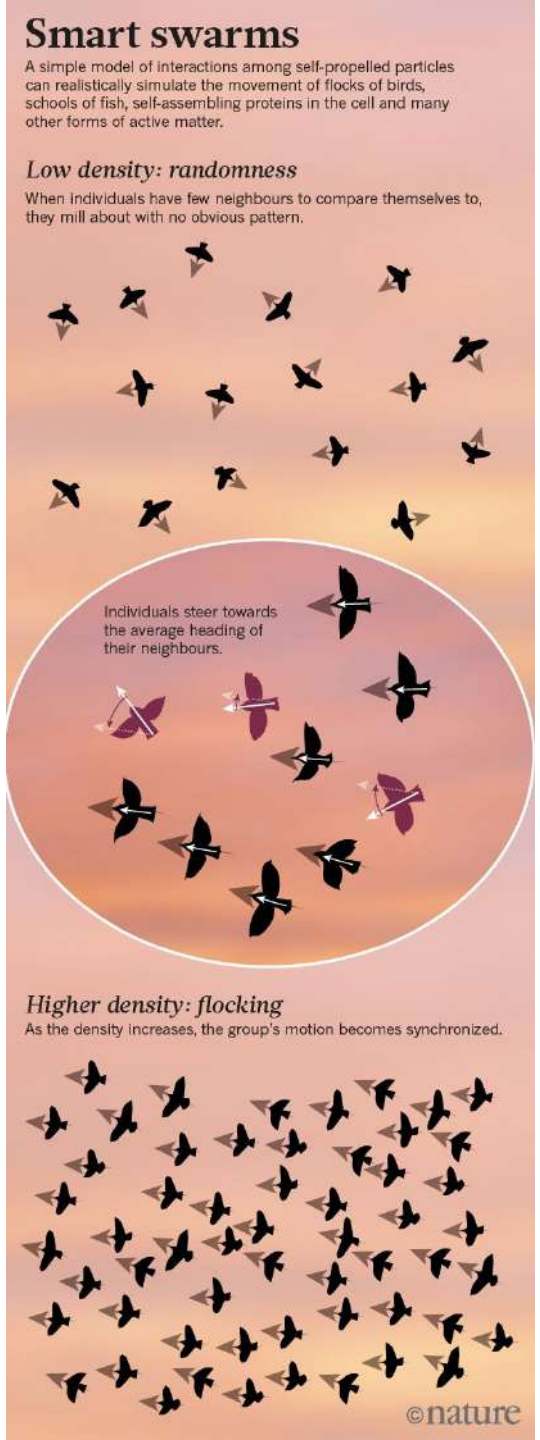
Volume treated: 1.0-1.5 TPV **Frequency:** Daily or every other day

Replacement fluid: Albumin, plasma

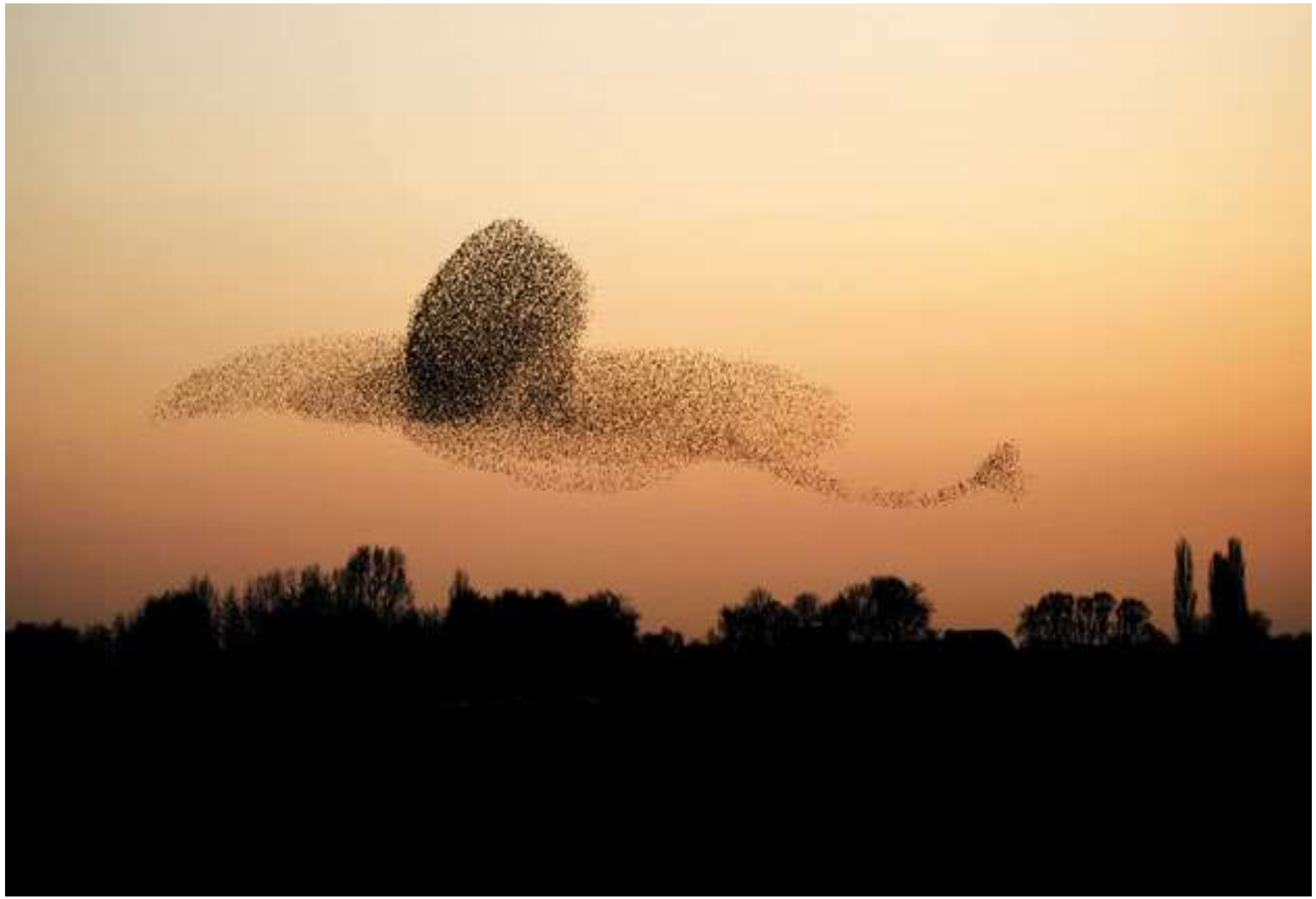
Duration and discontinuation/number of procedures

Duration depends on the underlying irAE. For most irAEs such as MG, myocarditis, or myositis, a minimum of 5 to 7 treatments may be needed to deplete IgG-specific antibodies.

L. Connely-Smith et al, J. of Cl Aph. 2023



From randomness to synchronization in every active matter



Σας ευχαριστώ για την προσοχή σας