Kansas Pharmacists Association // 2025 Annual Meeting & Trade Show August 22-24 // Lawrence, KS

IMMUNE CHECKPOINT INHIBITORS:

THE

E
R
A
S

TOUR

Elizabeth Rybolt

PharmD

Kentucky Pharmacy Education and Research Foundation, Inc. is accredited by ACPE as a provider of continuing pharmacy education.

ACPE UAN0143-9999-25-059-L01-P

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Kansas Pharmacists Association // 2025 Annual Meeting & Trade Show August 22-24 // Lawrence, KS

DISCLOSURES

Faculty

Elizabeth Rybolt, faculty for this activity, have no relevant financial relationship(s) with ineligible companies to disclose.

Planners

None of the planners for this activity have any relevant financial relationships with ineligible companies to disclose.

2

PRE-TEST

1. Which of the following agents works by binding to the cytotoxic T-cell lymphocyte-associated protein on T-cells to prevent binding to the B7-1/2 protein on cancer cells?
   A. Durvalumab B. Atezolizumab C. Pembrolizumab D. Ipilimumab
2. Which is the primary lab value associated with adrenal insufficiency?
   A. Hyponatremia B. Hypokalemia C. Hypernatremia D. Hyperprolactinemia
3. Which of the following ICI-related endocrinopathies is unlikely to be permanent?
   A. Hypothyroidism B. Hypophysitis C. Hyperthyroidism D. Adrenal Insufficiency

3

ABBREVIATIONS USED

ACTH: adrenocorticotropic hormone
ASPS: alveolar soft part sarcoma
CPK: creatinine phosphokinase
CRC: colorectal cancer
CNS: central nervous system
CRH: cortisol release hormone
CTLA-4: cytotoxic T-cell lymphocyte-associated protein 4 inhibitor
dMMR: deficient mismatch repair
FPG: fasting plasma glucose
FSH: follicle stimulating hormone
G1: grade 1
G2: grade 2
G3: grade 3
G4: grade 4
GEJ: gastroesophageal junction
GI: gastrointestinal
GU: genitourinary
HCC: hepatocellular carcinoma
HL: hodgkin lymphoma
HNSCC: head and neck squamous cell carcinoma
IBD: inflammatory bowel disease
ICI: immune checkpoint inhibitor
irAE: immune-related adverse effect
LAG-3: lymphocyte activation gene-3
LDH: lactate dehydrogenase
LH: luteinizing hormone
MG: myasthenia gravis
MHC II: major histocompatibility complex - II
MSI-H: microsatellite instability - high
NSCLC: non-small cell lung cancer
PD-1: programmed death receptor – 1
PD-L1: programmed death ligand - 1
PMBCL: primary mediastinal b-cell lymphoma
PMR: polymyalgia rheumatica
RCC: renal cell carcinoma
SCC: skin cell carcinoma
SCLC: small cell lung cancer
TMB-H: tumor mutational burden – high
TSH: thyroid stimulating hormone
2hPPG: 2-hour post-prandial glucose

4

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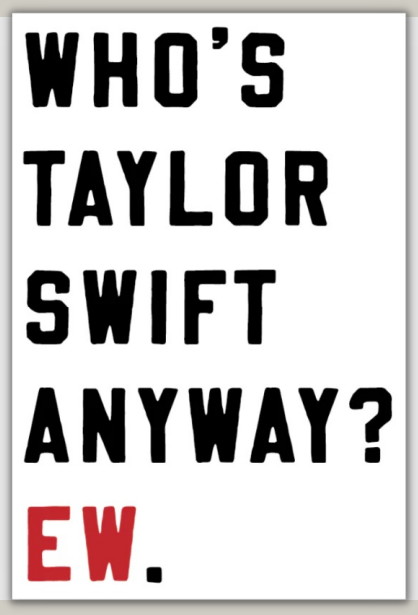
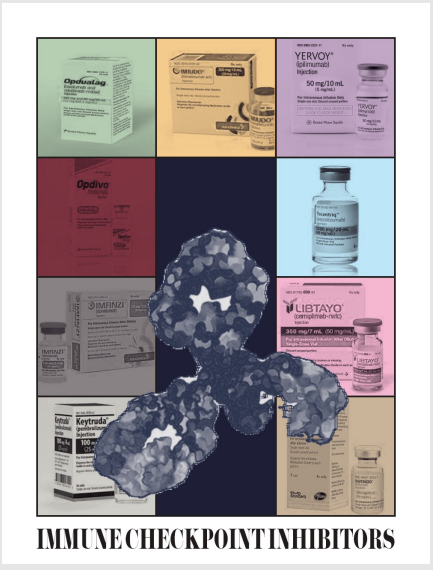
5





6

OBJECTIVES

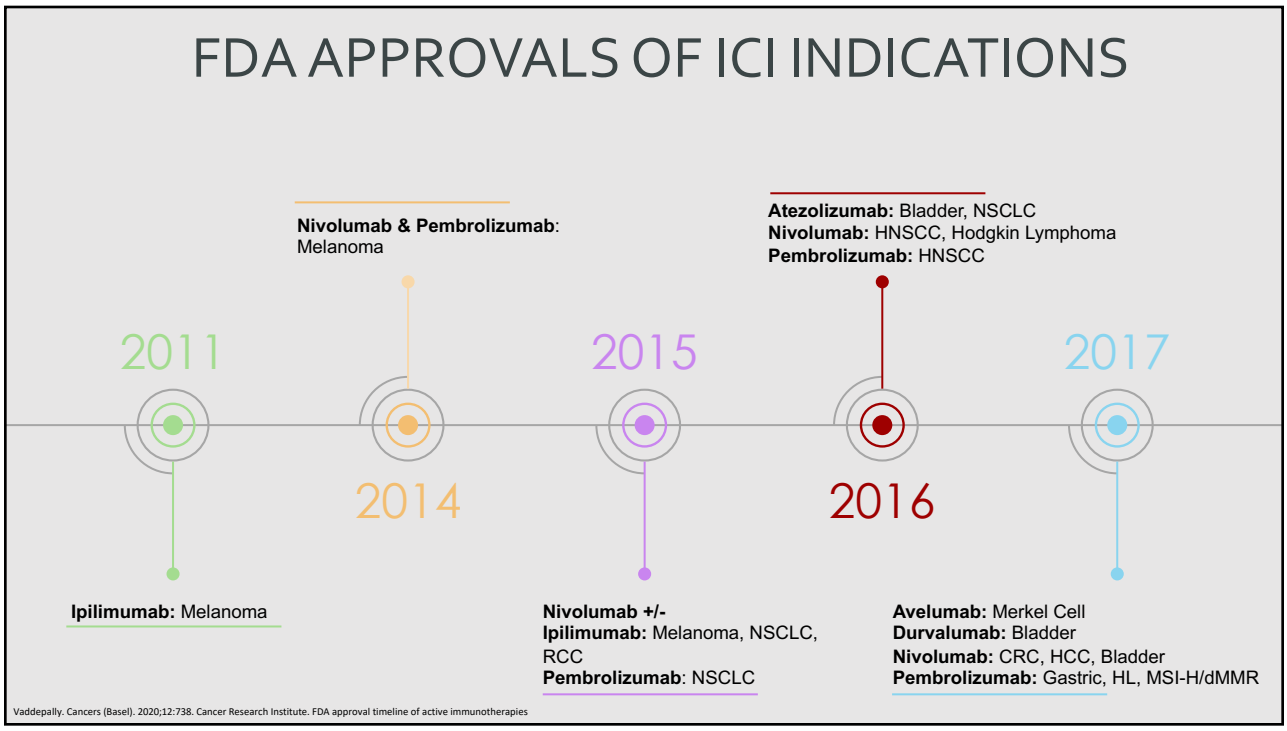
- Explain the different mechanisms of action of immune checkpoint inhibitors (ICI)
- Describe the management of ICI-related endocrinopathies
- Describe the management of ICI-related rheumatologic disorders

7

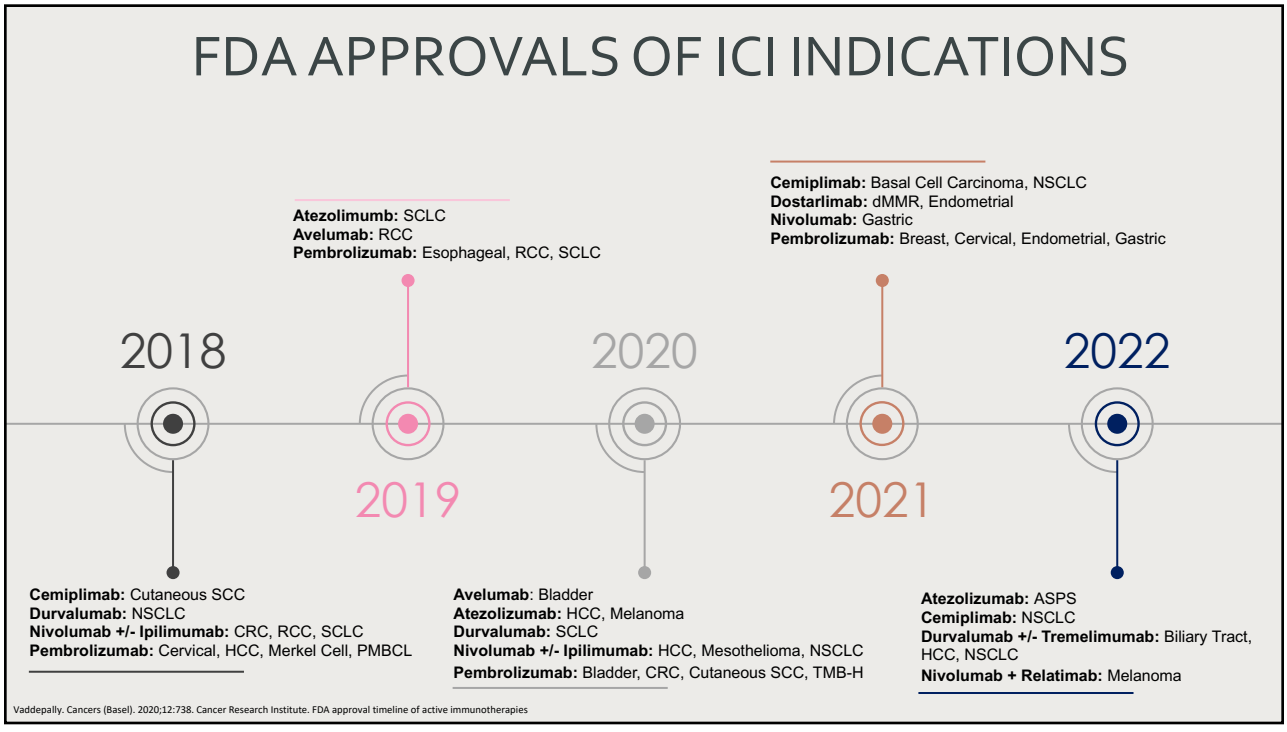
IMMUNE CHECKPOINT INHIBITORS

Indications, mechanism of action, and common adverse effects

8


FDA APPROVALS OF ICI INDICATIONS
2011
Ipilimumab: Melanoma
2014
Nivolumab & Pembrolizumab: Melanoma
2015
Nivolumab +/- Ipilimumab: Melanoma, NSCLC, RCC
Pembrolizumab: NSCLC
2016
Atezolizumab: Bladder, NSCLC
Nivolumab: HNSCC, Hodgkin Lymphoma
Pembrolizumab: HNSCC
2017
Avelumab: Merkel Cell
Durvalumab: Bladder
Nivolumab: CRC, HCC, Bladder
Pembrolizumab: Gastric, HL, MSI-H/dMMR
Vaddepally. Cancers (Basel). 2020;12:738. Cancer Research Institute. FDA approval timeline of active immunotherapies

9


FDA APPROVALS OF ICI INDICATIONS
2018
Cemiplimab: Cutaneous SCC
Durvalumab: NSCLC
Nivolumab +/- Ipilimumab: CRC, RCC, SCLC
Pembrolizumab: Cervical, HCC, Merkel Cell, PMBCL
2019
Atezolimumb: SCLC
Avelumab: RCC
Pembrolizumab: Esophageal, RCC, SCLC
2020
Avelumab: Bladder
Atezolizumab: HCC, Melanoma
Durvalumab: SCLC
Nivolumab +/- Ipilimumab: HCC, Mesothelioma, NSCLC
Pembrolizumab: Bladder, CRC, Cutaneous SCC, TMB-H
2021
Cemiplimab: Basal Cell Carcinoma, NSCLC
Dostarlimab: dMMR, Endometrial
Nivolumab: Gastric
Pembrolizumab: Breast, Cervical, Endometrial, Gastric
2022
Atezolizumab: ASPS
Cemiplimab: NSCLC
Durvalumab +/- Tremelimumab: Biliary Tract, HCC, NSCLC
Nivolumab + Relatimab: Melanoma
Vaddepally. Cancers (Basel). 2020;12:738. Cancer Research Institute. FDA approval timeline of active immunotherapies

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FDA APPROVALS OF ICI INDICATIONS

Cosibelimab: mCSCC
Dostarlimab: Endometrial
Durvalumab: dMMR endometrial
Nivolumab: Bladder
Pembrolizumab: Cervical, Endometrial
Tislelizumab: Esophageal SCC, Mesothelioma

2023

2024

2025

Pembrolizumab: Biliary Tract, GEJ carcinoma
Toripalimab: Nasopharyngeal
Dostarlimab: Endometrial
Retifanlimab-dlwr: Merkel Cell

Nivolumab + hyaluronidase: mCRC, Esophageal, GEJ, HN, HCC, Melanoma, NSCLC, RCC, Urothelial

Vaddepally. Cancers (Basel). 2020;12:738. Cancer Research Institute. FDA approval timeline of active immunotherapies

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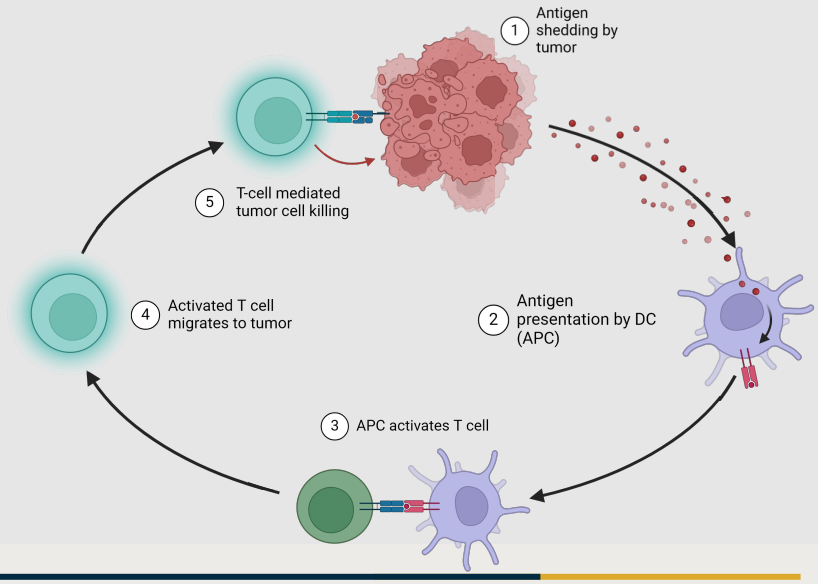
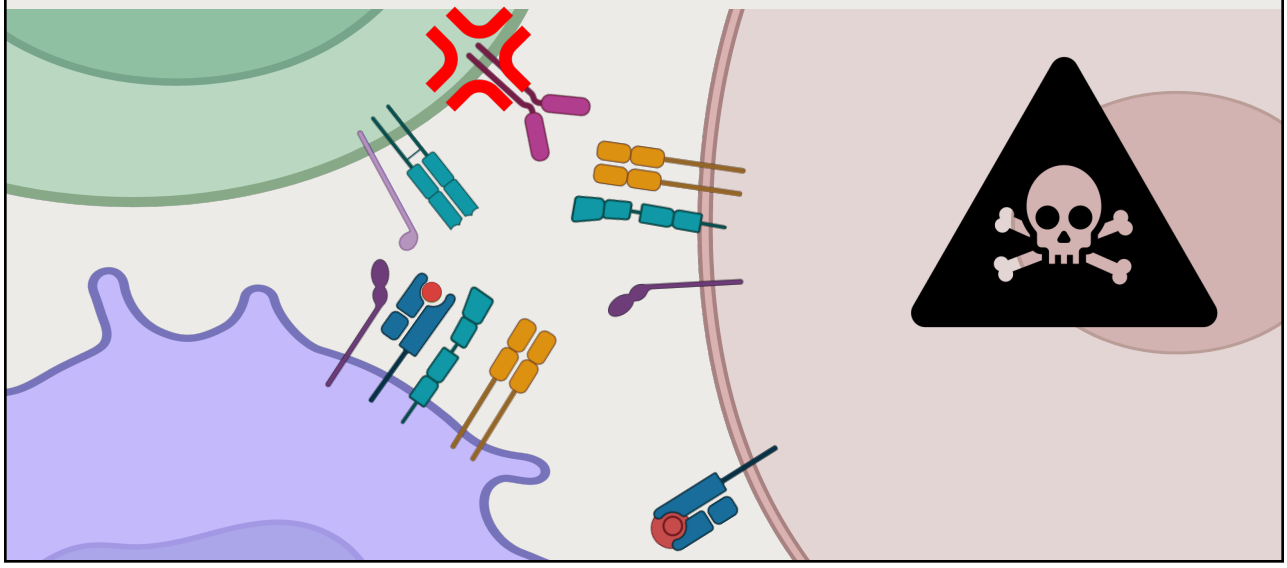
Antigen Presentation in Cancer



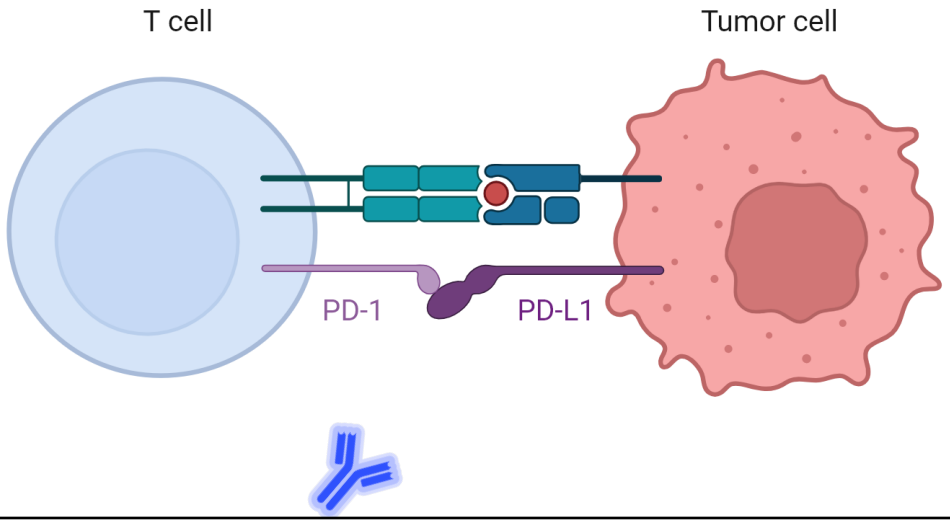
12

TUMOR IMMUNE SUPPRESSION



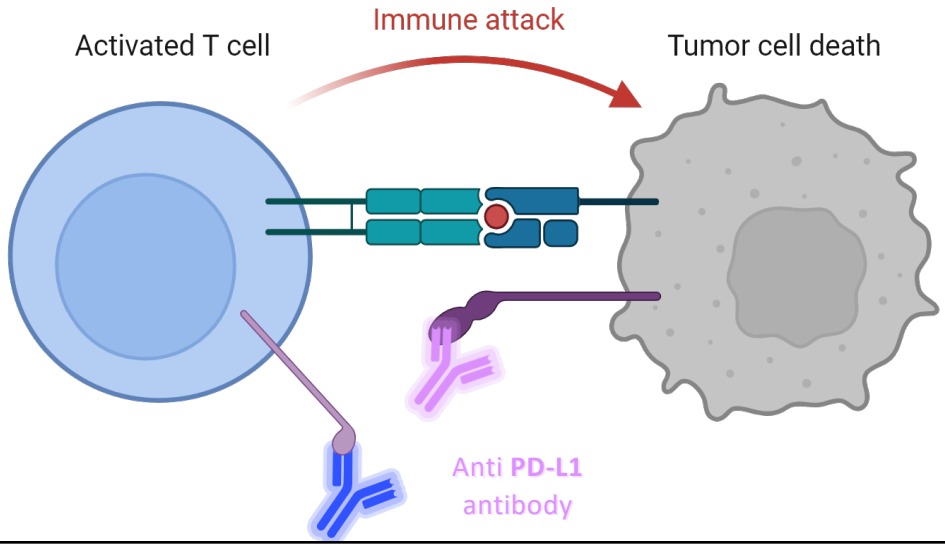
13

Immune checkpoint inhibits T-cell activation



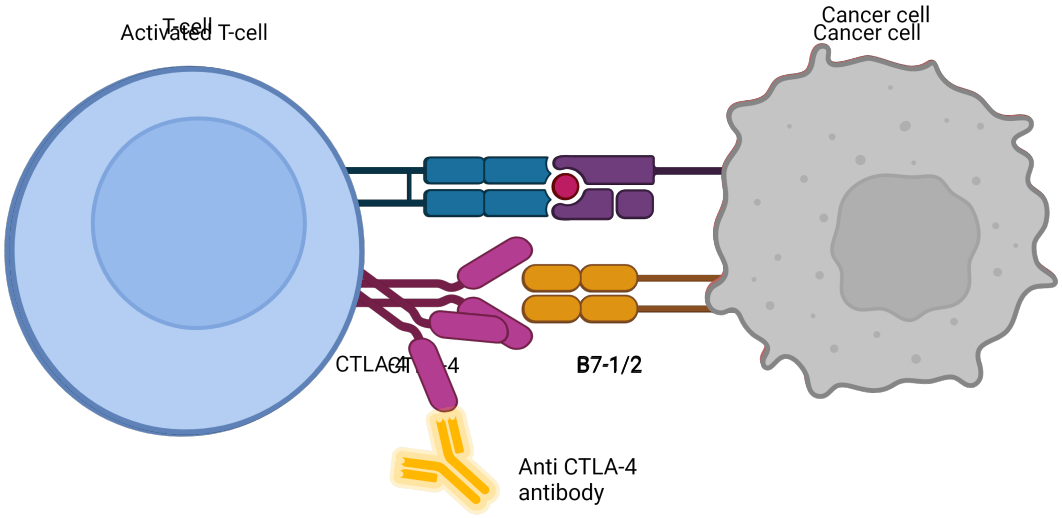
14

Anti-PD-1 antibodies permit T cell activation



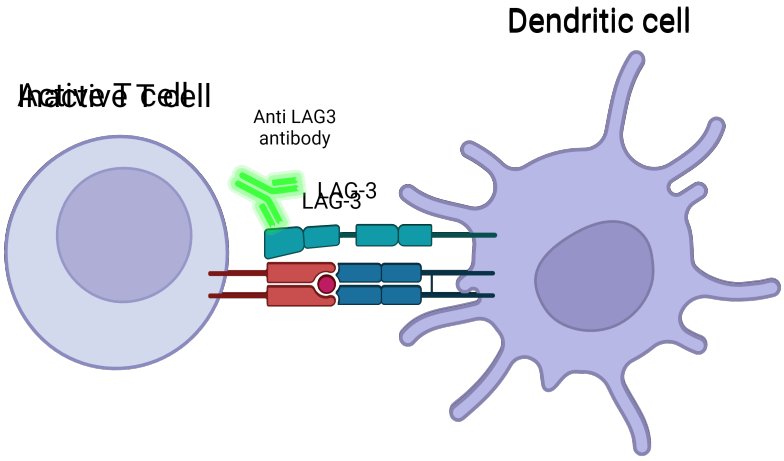
15

Anti CTLA-4 antibodies permits T cell activation



16

Anti LAG3 antibody permits T cell activation



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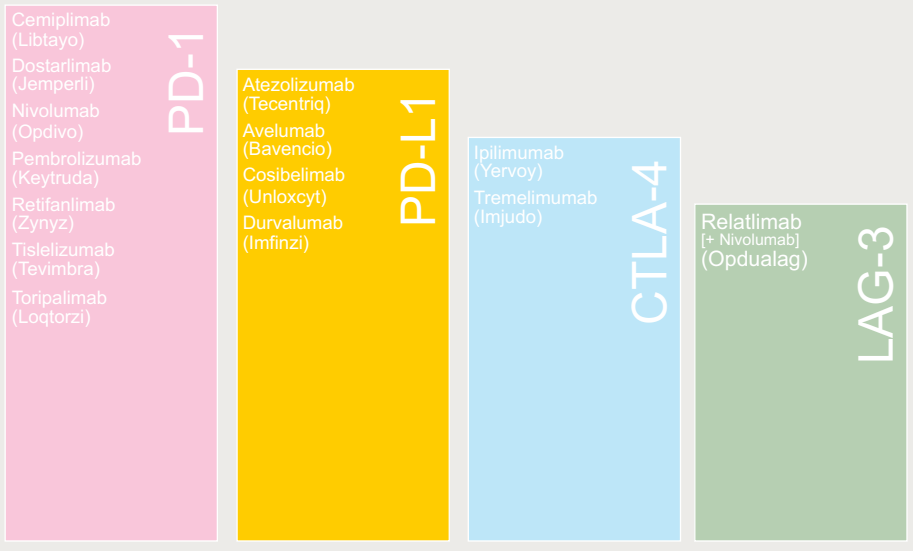

Bavencio (avelumab). Package Insert. Serono Inc. September 2023. Imfinzi (durvalumab). Package Insert. AstraZeneca Pharmaceuticals. April 2023. Imjudo (tremelimumab). Package Insert. AstraZeneca Pharmaceuticals LP. June 2023. Jemperli (dostarlimab). Package Insert. GlaxoSmithKline Inc. January 2023. Keytruda (pembrolizumab). Package Insert. Merck Canada Inc. December 2023. Libtayo (cemiplimab). Package Insert. Regeneron Pharmaceuticals Inc. December 2023. Loqtorzi (toripalimab). Package Insert. Coherus BioSciences Inc. October 2023. Opdualag (nivolumab/relatlimab). Package Insert. Bristol-Myers Squibb Company. March 2022. Opdivo (nivolumab). Package Insert. Bristol-Myers Squibb Company. October 2023.Tecentriq (atezolizumab). Package Insert. Genetech Inc. May 2023. Yervoy (ipilimumab). Package Insert. Bristol-Myers Squibb Company. February 2023. Zynyz (Retifanlimab). Package Insert. Incyte Corporation. March 2023.

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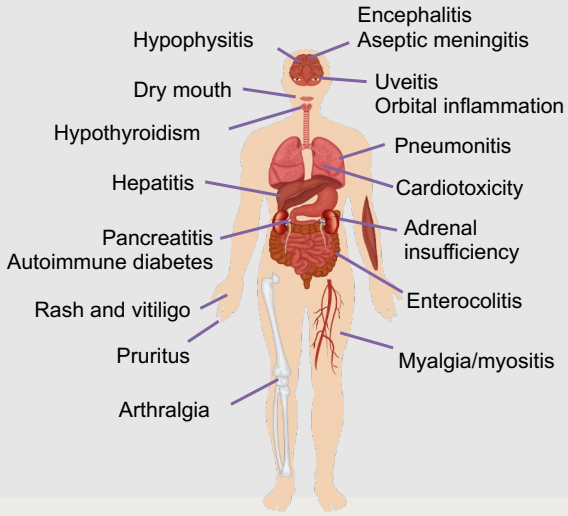
OVERVIEW OF IMMUNE-RELATED ADVERSE EFFECTS

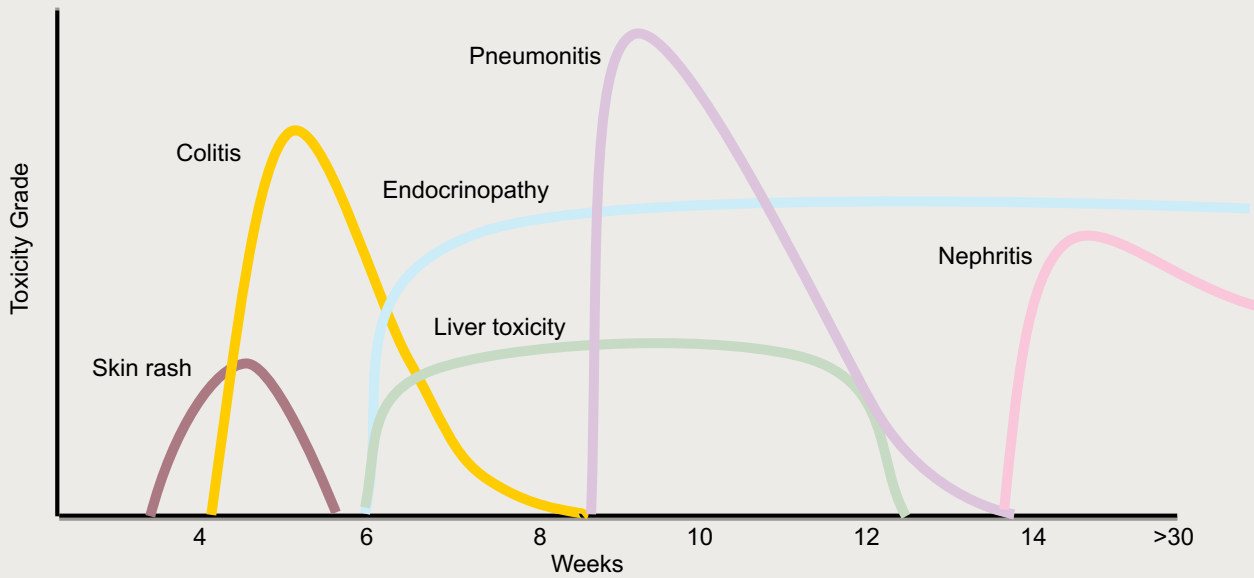


- Due to the nature of the immune system, all organ systems are at risk of irAEs.

Michot. Eur J Cancer. 2016;54:139. Albarrán-Artahona. Diagnostics (Basel). 2022;12:2091. Winer. J Thorac Dis. 2018;10(suppl 3):S480.
Steven. Rheumatology (Oxford). 2019;58(suppl 7):vii29. Robert. ASCO 2017. Education session: checkpoint inhibitor immunotherapy

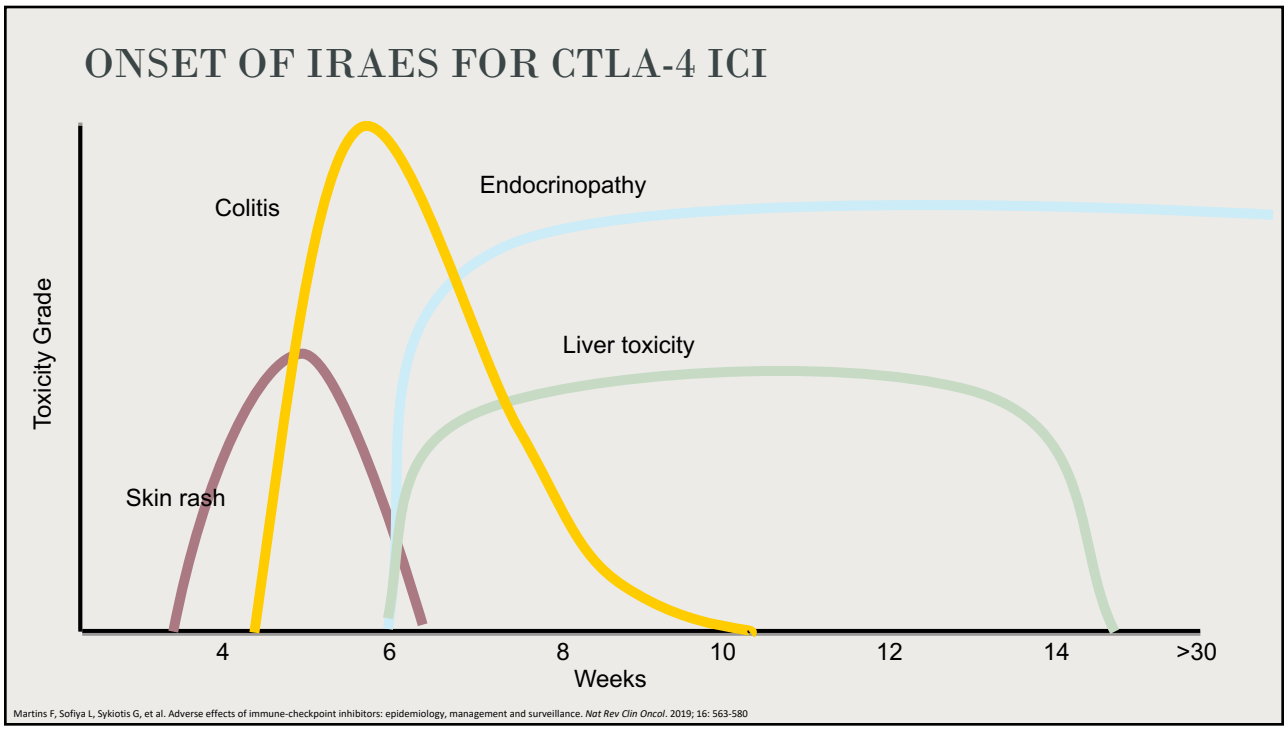
19

ONSET OF IRAES FOR PD-1/PD-L1 ICI

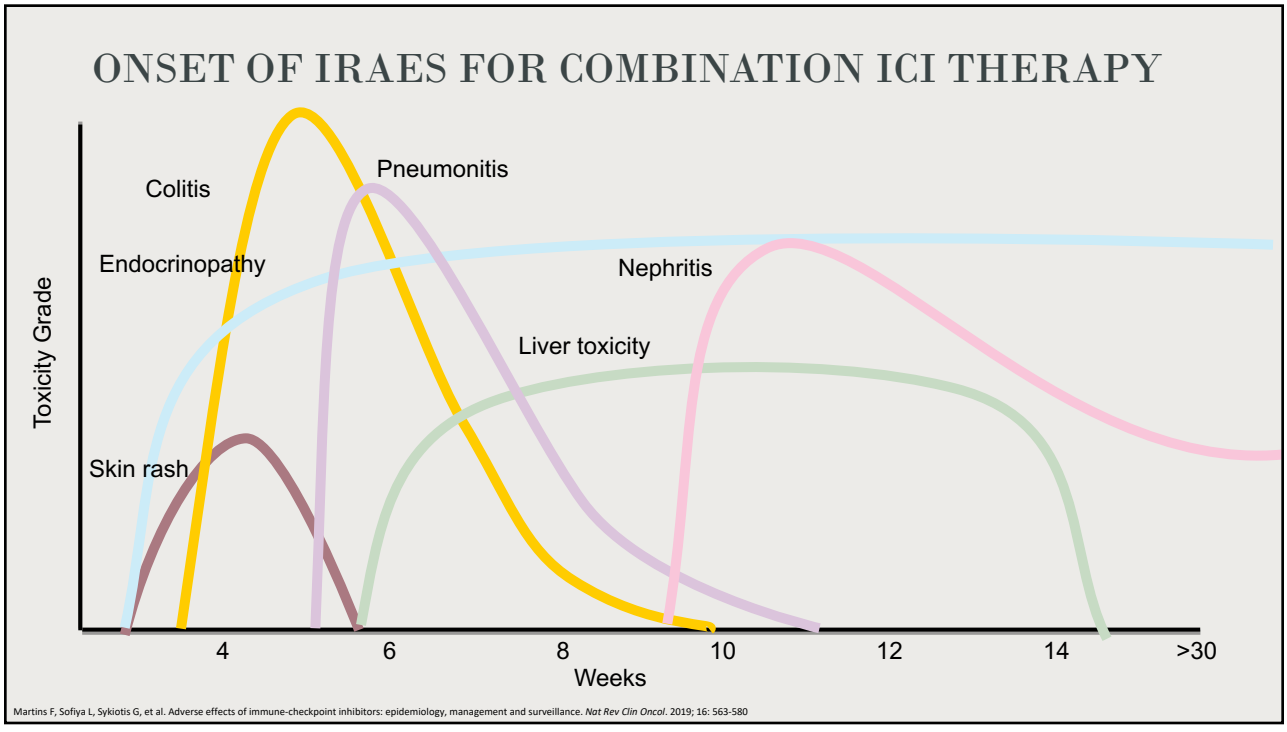


Martins F, Sofiya L, Sykiotis G, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nat Rev Clin Oncol*. 2019; 16: 563-580

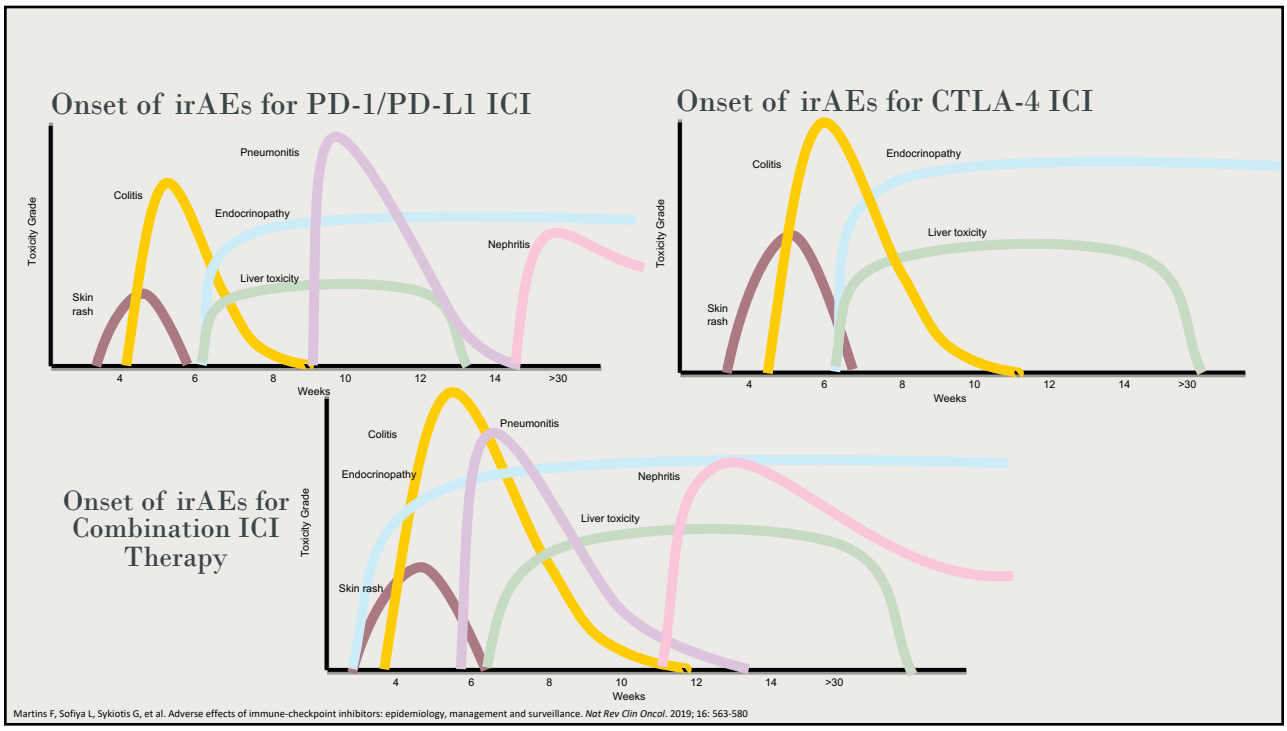
20


ONSET OF IRAES FOR CTLA-4 ICI
Colitis
Endocrinopathy
Liver toxicity
Skin rash
Toxicity Grade
4
6
8
10
12
14
>30
Weeks
Martins F, Sofiya L, Sykiotis G, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev Clin Oncol. 2019; 16: 563-580

21


ONSET OF IRAES FOR COMBINATION ICI THERAPY
Colitis
Pneumonitis
Endocrinopathy
Nephritis
Liver toxicity
Skin rash
Toxicity Grade
4
6
8
10
12
14
>30
Weeks
Martins F, Sofiya L, Sykiotis G, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev Clin Oncol. 2019; 16: 563-580

22



Martins F, Sofiya L, Sykiotis G, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nat Rev Clin Oncol*. 2019; 16: 563-580

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ENDOCRINE EFFECTS

Conditions, incidence, treatment, and monitoring

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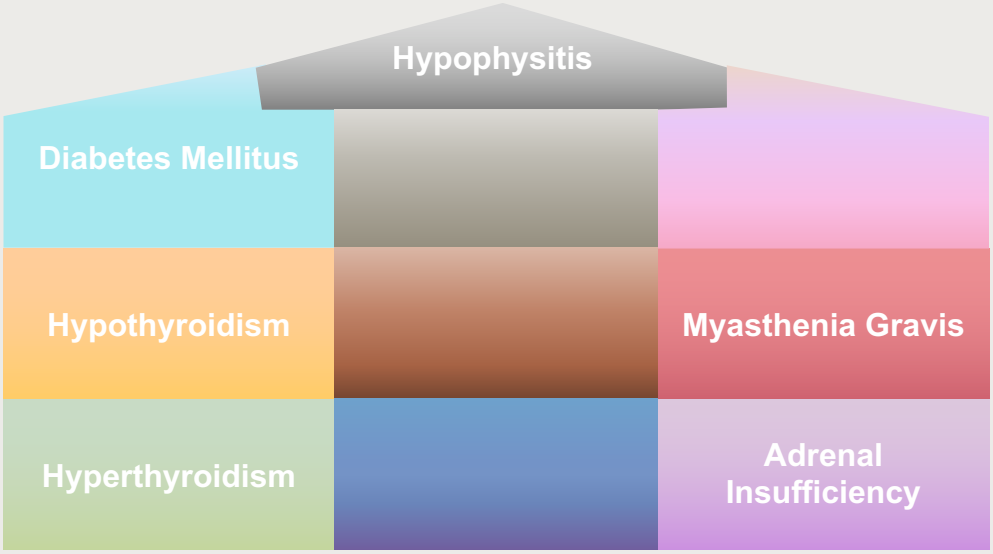
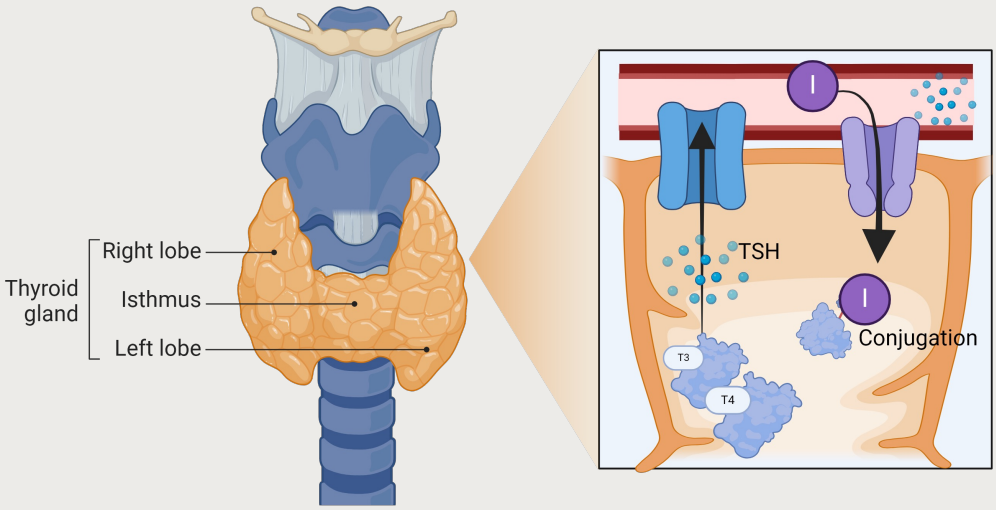
ENDOCRINOPATHIES OF ICI



25

Pathophysiology of Thyroid Hormones



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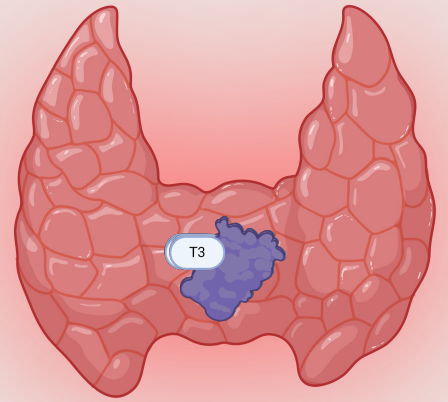
ICI-RELATED HYPERTHYROIDISM



Peiffert M, Cugnet-Anceau C, Dalle St, et al. Grave's disease during immune checkpoint inhibitor therapy (a case series and literature review). *Cancers*. 2021; 13: 1944

27

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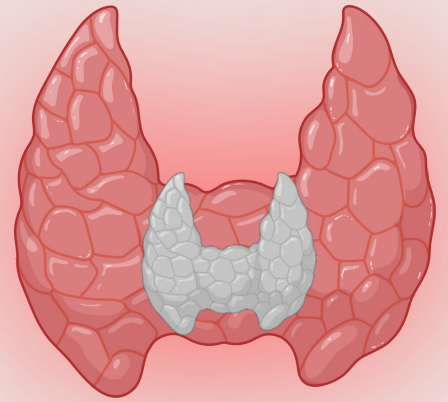

Peiffert M, Cugnet-Anceau C, Dalle St, et al. Grave's disease during immune checkpoint inhibitor therapy (a case series and literature review). *Cancers*. 2021; 13: 1944

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ICI-RELATED HYPOTHYROIDISM

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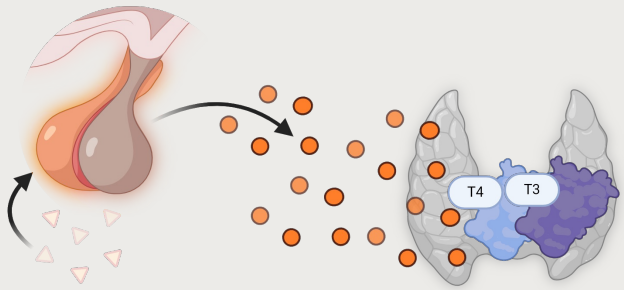
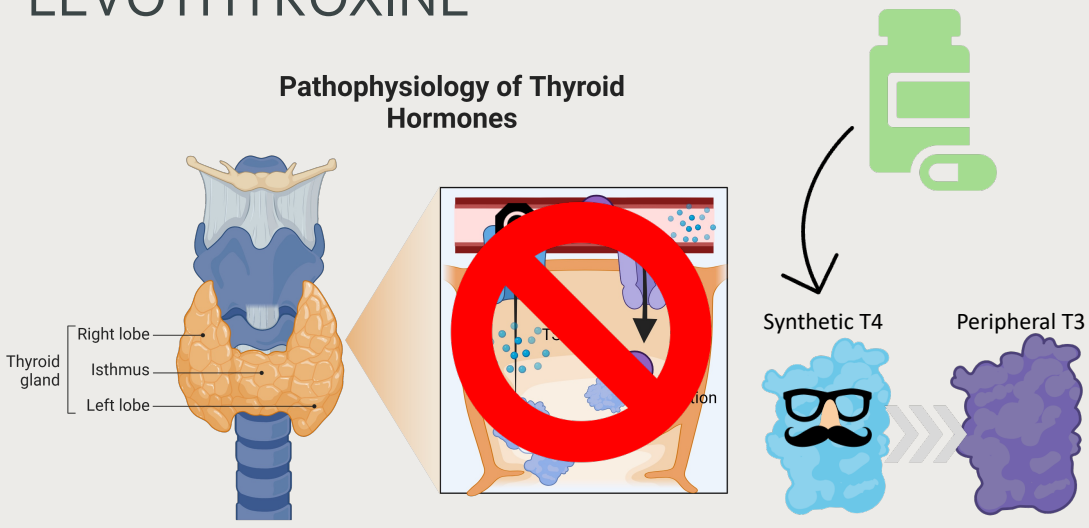


Osorio JC et al. Antibody-mediated thyroid dysfunction during T-cell blockade in patients with non-small-cell-lung cancer. *Ann Oncol*. 2017; 28(3): 583-589.
Chalan P et al. Thyroid dysfunctions secondary to cancer immunotherapy. *J Endocrinol Invest*. 2018; 41(6): 625-638.
Sabbagh RE, Azar NS, Eid AA, Azar ST. Thyroid dysfunctions due to immune checkpoint inhibitors: a review. *International Journal of General Medicine*. 2020; 1003-1009.

29

LEVOTHYROXINE



Synthroid (levothyroxine). Package Insert. AbbVie Inc. October 2022.

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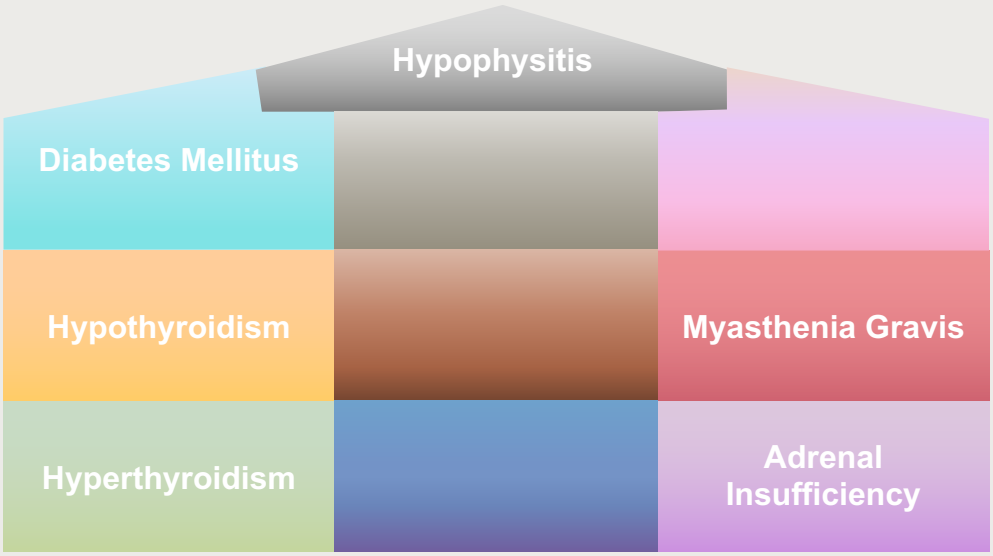
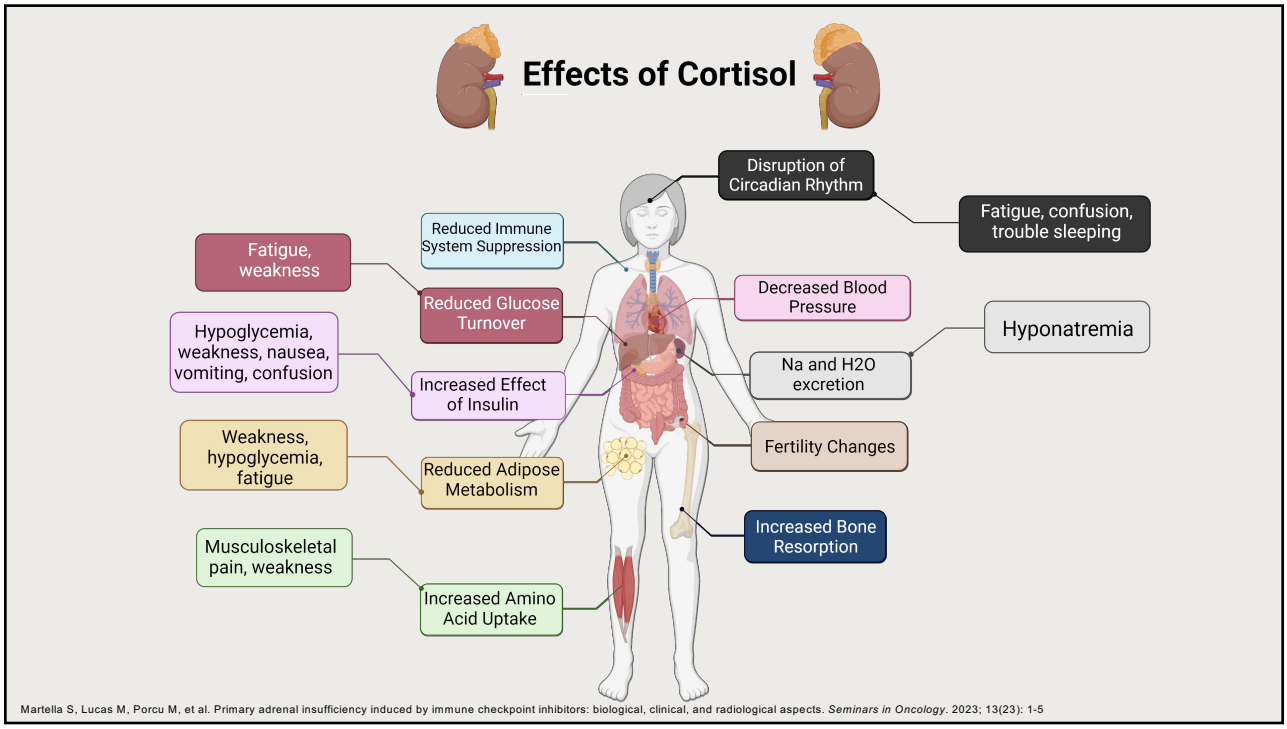
ENDOCRINOPATHIES OF ICI



31



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CORTICOSTEROIDS

Hyperglycemia	Weight Gain	Fluid Retention	Sodium Resorption	Hypertension	Increased Energy	Antiemetic Properties
Hypoglycemia	Weight Loss	Fluid Loss	Hyponatremia	Hypotension	Loss of Energy	Nausea/ Vomiting

ADRENAL INSUFFICIENCY

Martella S, Lucas M, Porcu M, et al. Primary adrenal insufficiency induced by immune checkpoint inhibitors: biological, clinical, and radiological aspects. *Seminars in Oncology*. 2023; 13(23): 1-5

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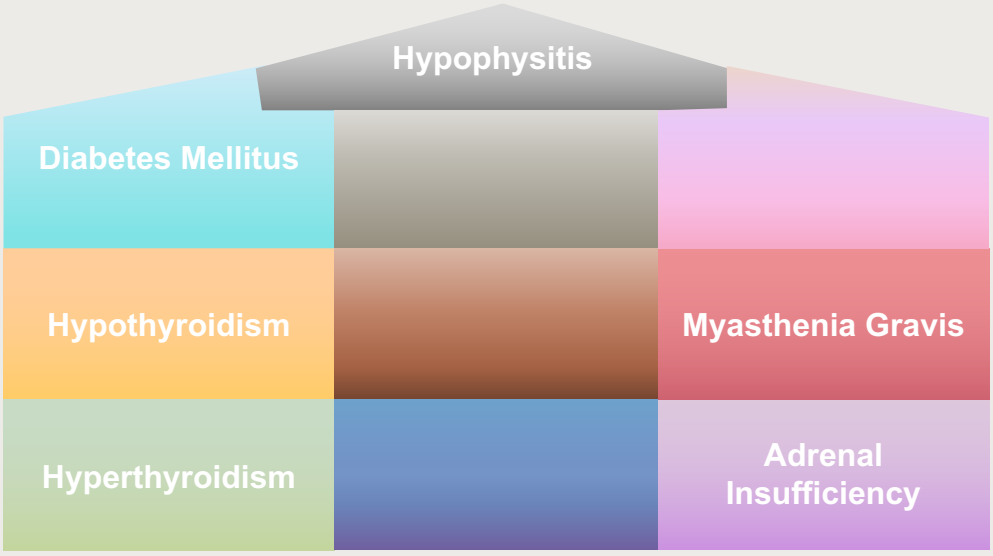
ENDOCRINOPATHIES OF ICI



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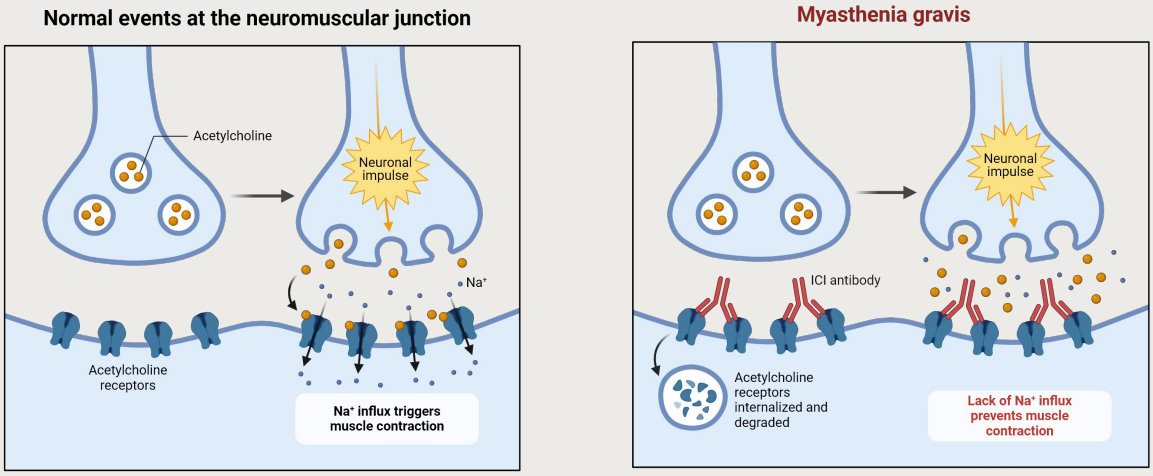
ICI RELATED MYASTHENIA GRAVIS



Huang YT, Chen YP, Lin WC, Su WC, Sun YT. Immune checkpoint inhibitor-induced myasthenia gravis. *Front. Neurol.* 2020; 11 (634): 1-10.
Safa H, Johnson DH, Trinh VA et al. Immune checkpoint inhibitor related myasthenia gravis: single enter experience and systematic review of literature. *J Immunother Cancer.* 2019; 7: 319.

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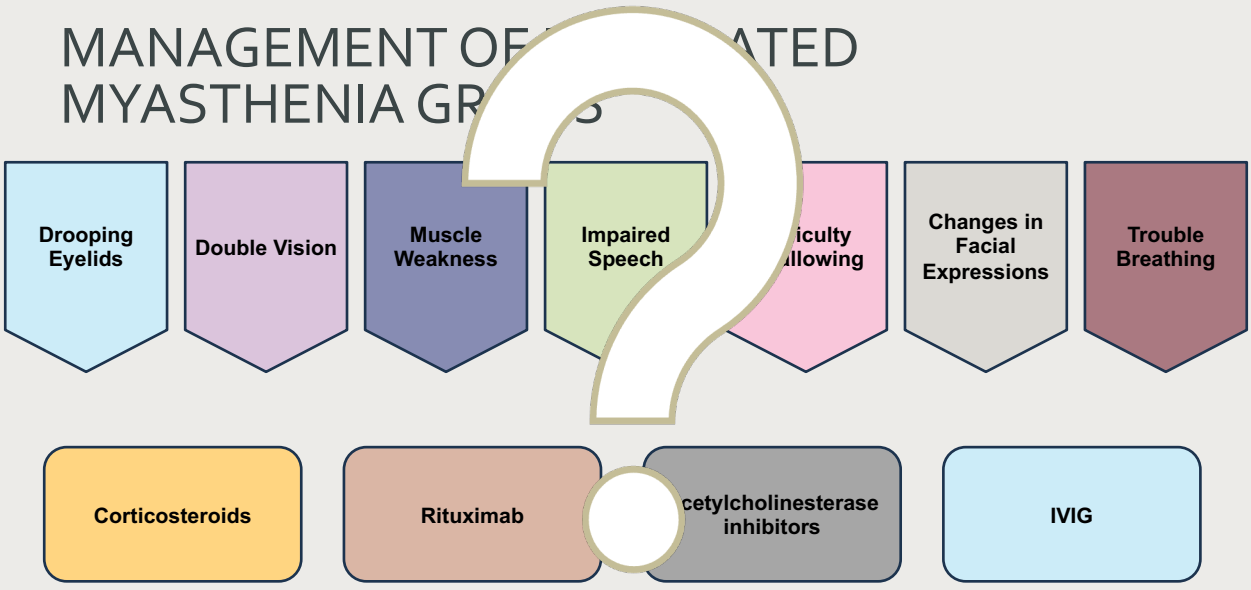
MANAGEMENT OF ATED MYASTHENIA GR S



Huang YT, Chen YP, Lin WC, Su WC, Sun YT. Immune checkpoint inhibitor-induced myasthenia gravis. *Front. Neurol.* 2020; 11 (634): 1-10.
Safa H, Johnson DH, Trinh VA et al. Immune checkpoint inhibitor related myasthenia gravis: single enter experience and systematic review of literature. *J Immunother Cancer.* 2019; 7: 319.

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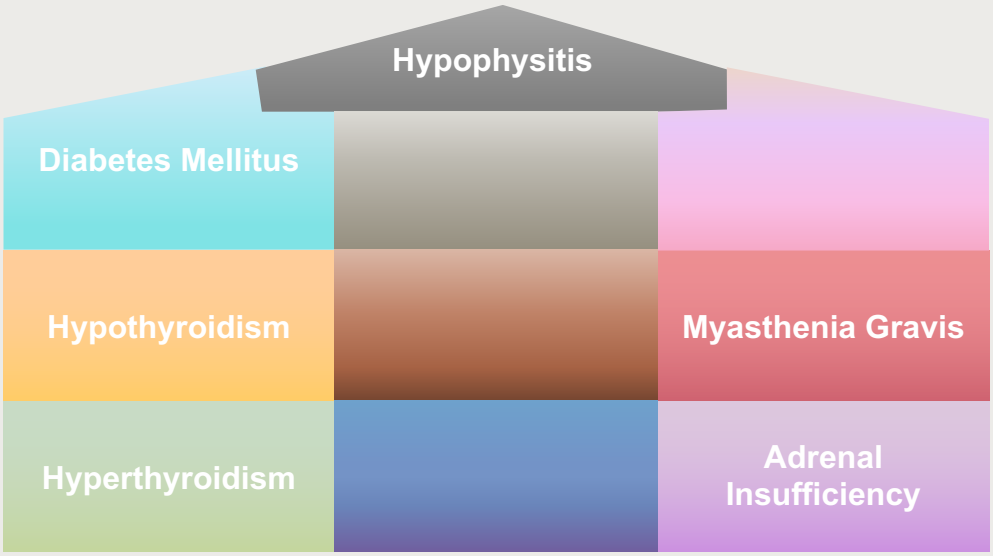
ENDOCRINOPATHIES OF ICI



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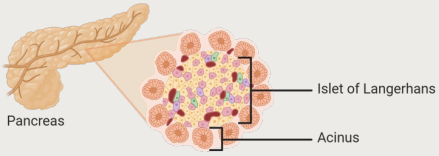
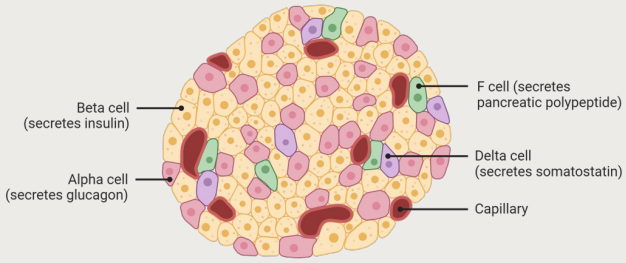
PANCREAS FUNCTION



Islet of Langerhans



Akturk HK, Kahramangil D, Sarwal A, Hoffecker L, Murad MH, Michels AW. Immune checkpoint inhibitor-induced type 1 diabetes: a systematic review and meta-analysis. *Diabet. Med.* 2019; 36: 1075-1081.
Standards of Care in Diabetes-2023. Classification and diagnosis of diabetes. *Diabetes Care*. 2023; 46(1): 19-40.
Mourad D, Azar NS, Eid AA, Azar ST. Immune checkpoint inhibitor-induced diabetes mellitus: potential role of T cells in the underlying mechanism. *Int J Mol Sci.* 2021; 22(4): 2093

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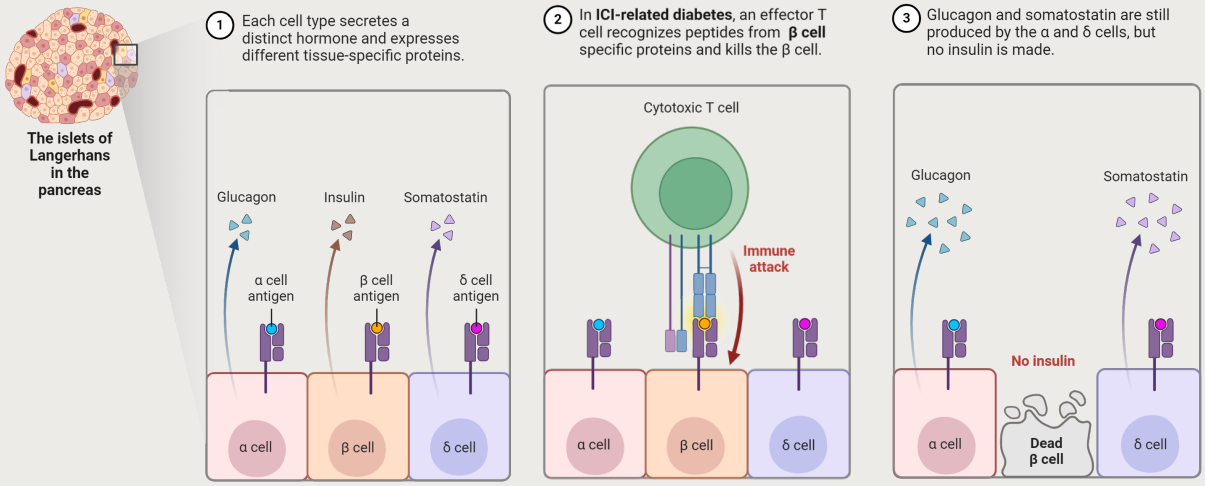
DIABETES MELLITUS



Mourad D, Azar NS, Eid AA, Azar ST. Immune checkpoint inhibitor-induced diabetes mellitus: potential role of T cells in the underlying mechanism. *Int J Mol Sci*. 2021; 22(4): 2093

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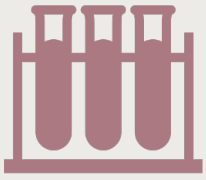
MANAGEMENT OF ICI-RELATED DIABETES MELLITUS

Monitoring:



Treatment:

Continuity of Care:

Stage 1
Normoglycemia
Presymptomatic

Stage 2
Dysglycemia
Presymptomatic

Stage 3
Overt hyperglycemia
Symptomatic

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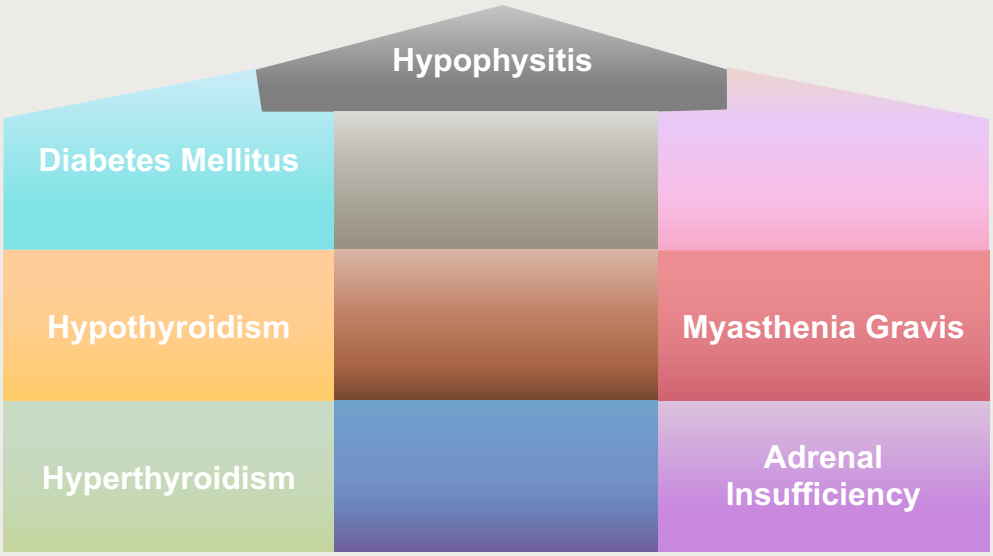
ENDOCRINOPATHIES OF ICI



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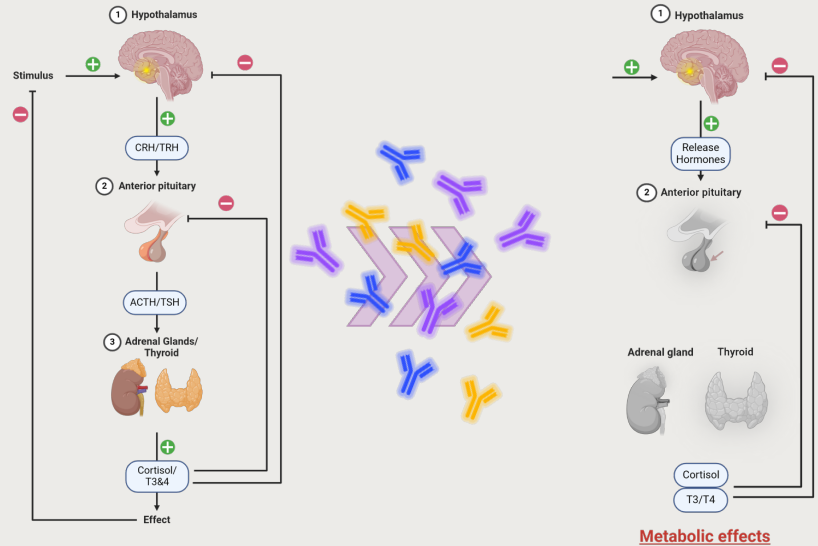
HYPOTHALAMUS PITUITARY ADRENAL-AXIS



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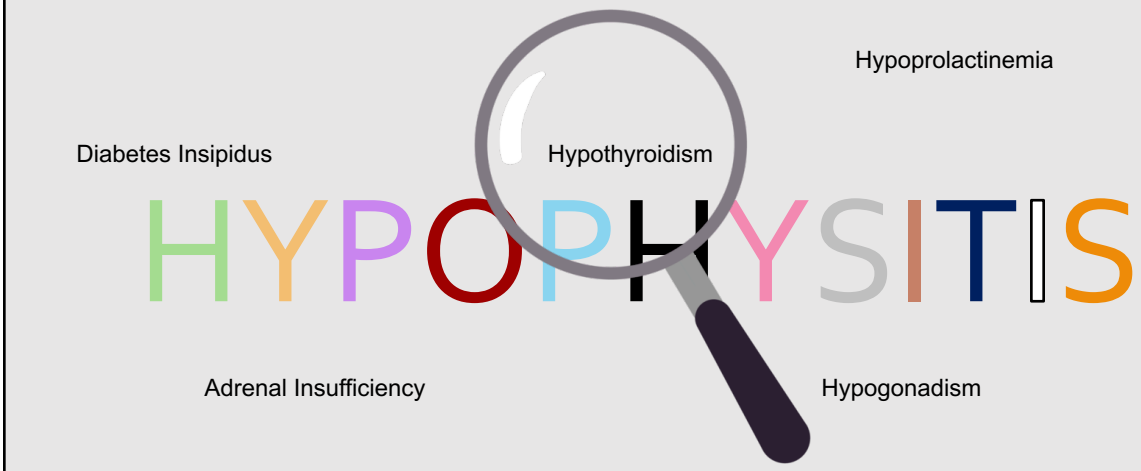
DIFFERENTIAL FOR



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RHEUMATOLOGIC EFFECTS

Incidence, treatment, and monitoring

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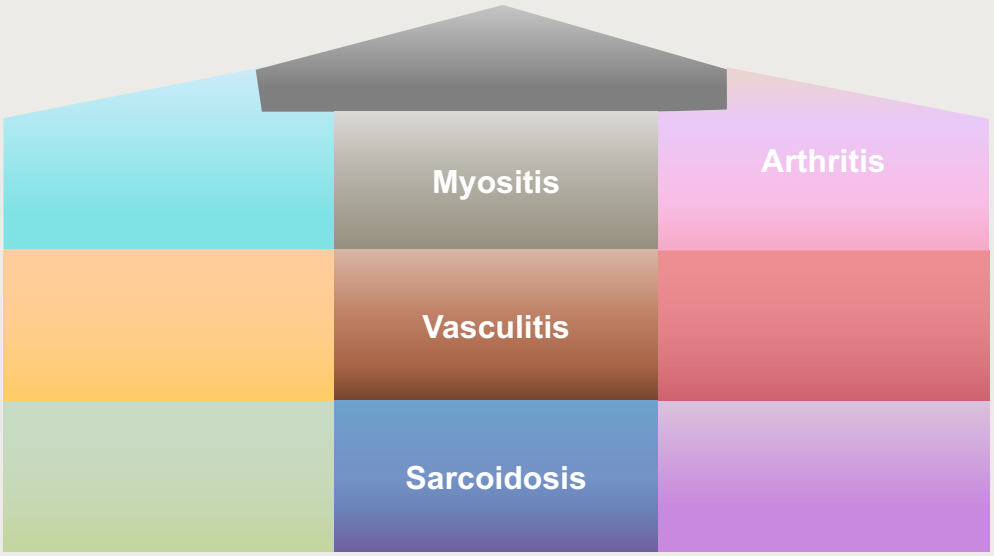
RHEUMATIC EFFECTS OF ICI



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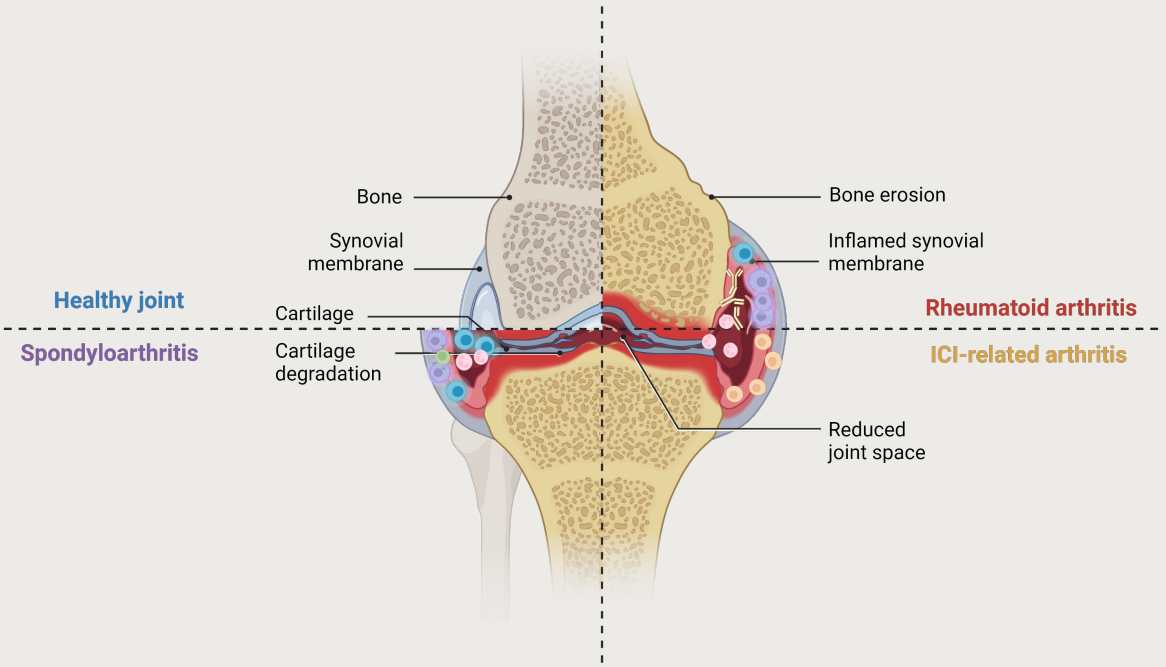

Cappelli LC, Brahmer JR, Forde PM et al. Clinical presentation of immune checkpoint inhibitor-induced inflammatory arthritis differs by immunotherapy regimen. *Seminars in Arthritis and Rheumatism*. 2018; 48: 553-557.
Cappelli LC, Thomas MA, Bingham III CO, et al. Immune checkpoint inhibitor-induced inflammatory arthritis as a model of autoimmune arthritis. *Immunological Reviews*. 2020; 294: 106-123.

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MANAGEMENT OF IMMUNE-RELATED ARTHRITIS

- Most patients will require **systemic corticosteroids**
- If no improvement after three months, additional **immunosuppression** may be necessary

  (TNF inhibitors, methotrexate, etc.)
  - Patients treated with combination therapy are more likely to require additional immunosuppression

Drug/class	Efficacy in Rheumatoid	Efficacy in Spondylo-	Efficacy in ICI related-arthritis
Hydroxychloroquine	Yes	No	Yes
Sulfasalazine	Yes	Yes	Yes
Methotrexate	Yes	Yes	Yes
Leflunomide	Yes	Yes	Yes
Apremilast (PDE4 inhibitor)	No	Yes	Not reported yet
Abatacept (CTLA-4 agonist)	Yes	Yes	Not reported yet
TNF inhibitors	Yes	Yes	Yes
IL-6 inhibitors	Yes	No	Yes
IL-12/23 inhibitors	No	Yes	Not reported yet
IL-17 inhibitors	No	Yes	Not reported yet
JAK inhibitors	Yes	Yes	Not reported yet
Rituximab	Yes	No	Not reported yet

Cappelli LC, Brahmer JR, Forde PM et al. Clinical presentation of immune checkpoint inhibitor-induced inflammatory arthritis differs by immunotherapy regimen. *Seminars in Arthritis and Rheumatism*. 2018; 48: 553-557.
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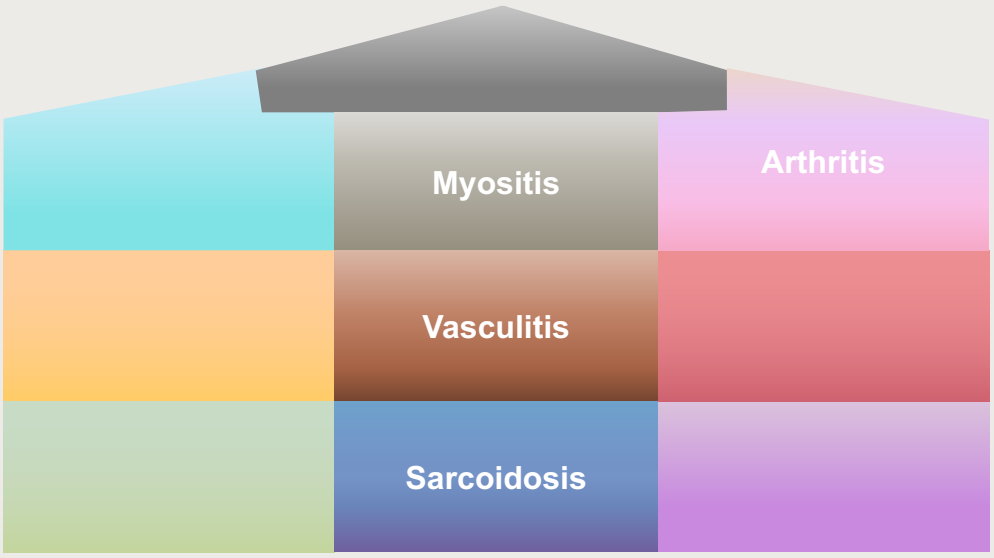
RHEUMATIC EFFECTS OF ICI



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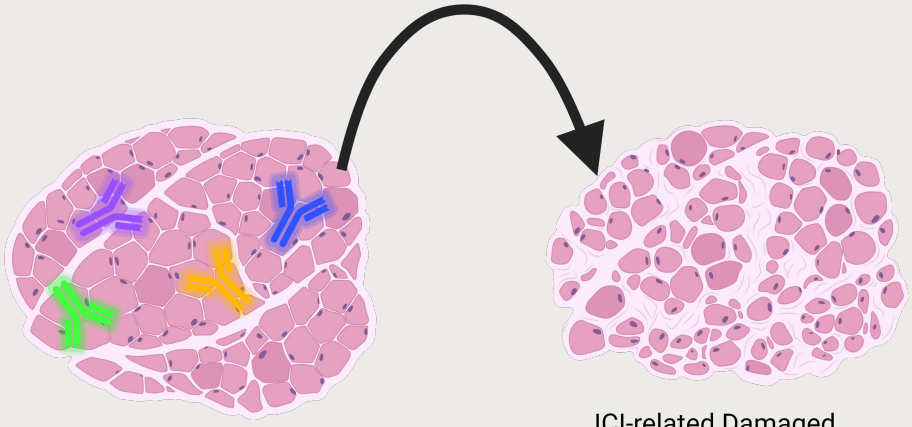
ICI-RELATED MYOSITIS



Aldrich J, Pundole X, Tummala S et al. Inflammatory myositis in cancer patients receiving immune checkpoint inhibitors. *Arthritis & Rheumatology*. 2021; 73(5): 866-874.
Allenback Y, Anquetil C, Manouchehri A, et al. Immune checkpoint inhibitor-induced myositis, the earliest and most lethal complication among rheumatic and musculoskeletal toxicities. *Autoimmunity Reviews*. 2020; 19: 102586.

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MANAGEMENT OF MYOSITIS

Immune-related myositis

Aldrich J, Pundole X, Tummala S et al. Inflammatory myositis in cancer patients receiving immune checkpoint inhibitors. *Arthritis & Rheumatology*. 2021; 73(5): 866-874.
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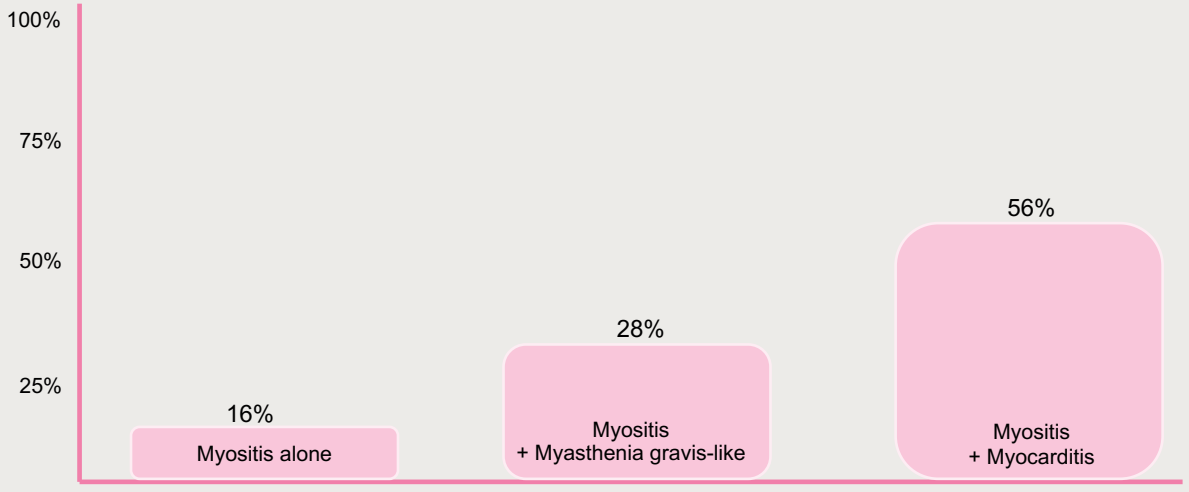
MORTALITY ASSOCIATED WITH ICI-RELATED MYOSITIS



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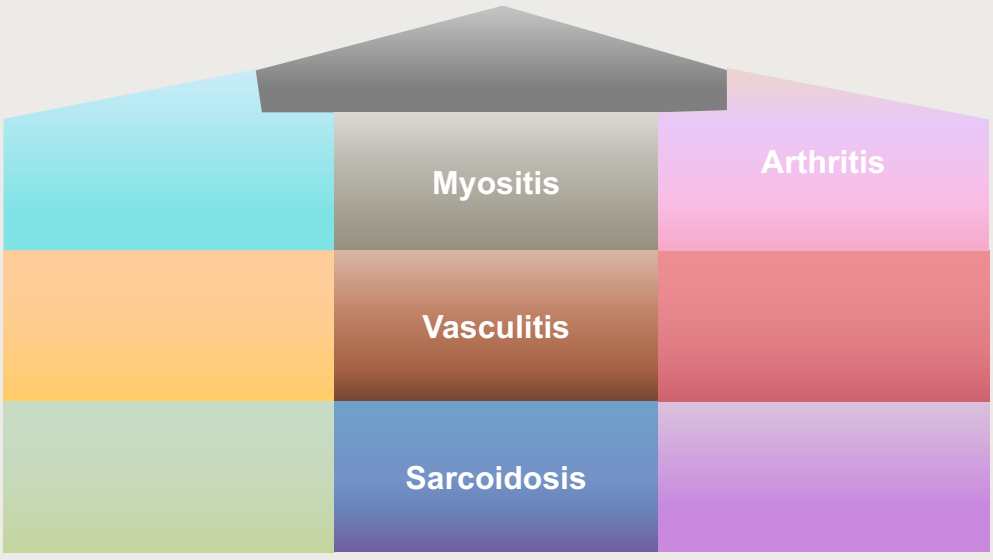

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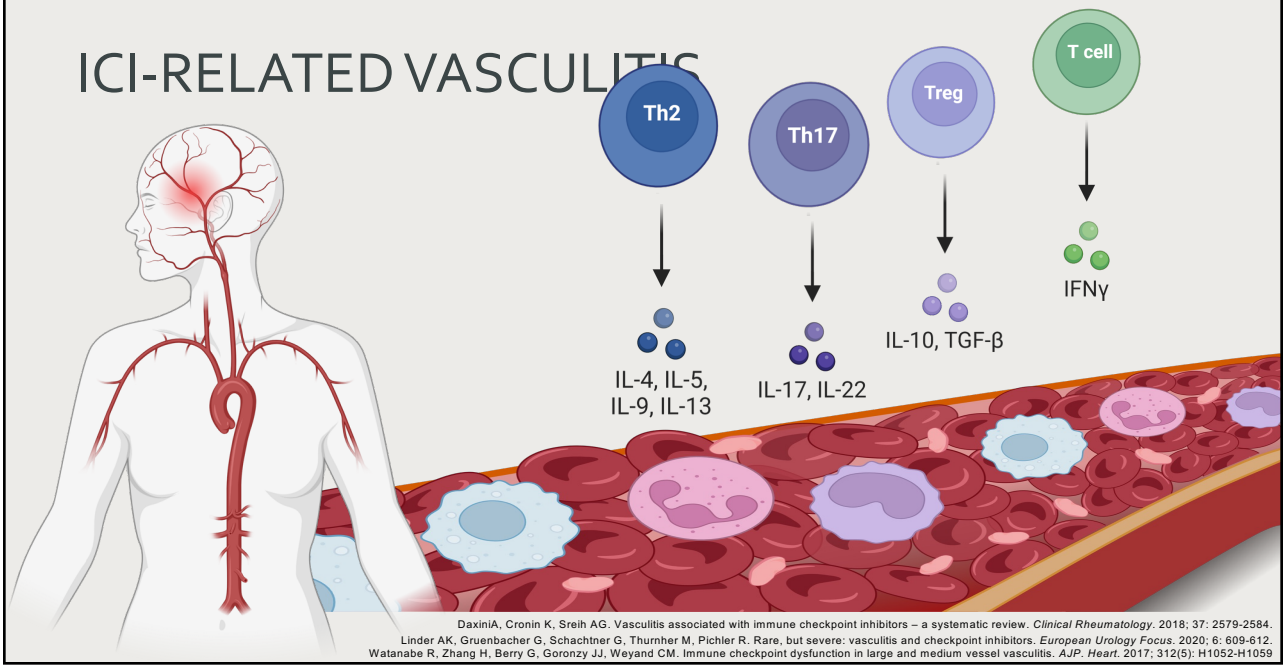
ICI-RELATED VASCULITIS



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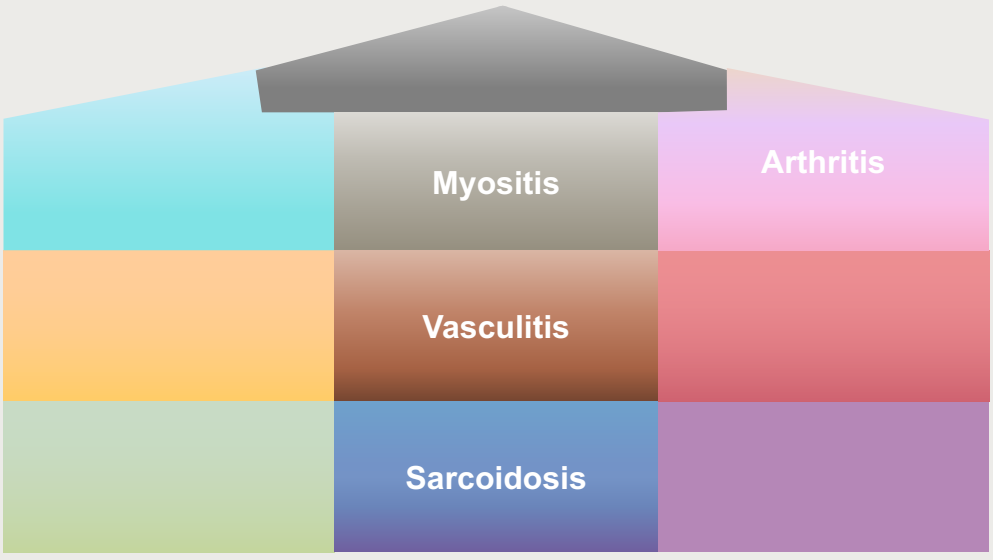
RHEUMATIC EFFECTS OF ICI



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ICI-RELATED SARCOIDOSIS

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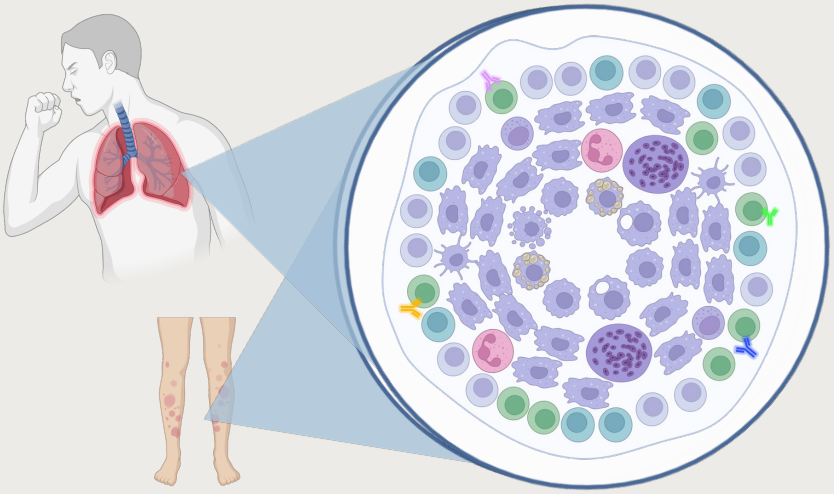

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BEGIN AGAIN

	Hyperthyroidism	Hypothyroidism	Adrenal insufficiency	Myasthenia Gravis	Diabetes	Hypophysitis	Myositis	Vasculitis	Sarcoidosis	Arthritis
Incidence										
Onset*										
Presentation										
Management										
Reversibility										

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KEY TAKEAWAYS

Immune checkpoint inhibitors carry-out treatment with different mechanisms of action that lead to different rates of adverse effects

Endocrinopathies of ICI are typically controlled with replacement of endogenous hormones with exogenous.

Rheumatologic effects of ICI are typically controlled with short, potent steroid regimens

Endocrinopathies discussed are not reversible, whereas some rheumatologic effects may reverse with treatment and time.

Prompt diagnosis, appropriate therapy, and close follow up are all essential to management of adverse effects for patients.

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POST-TEST QUESTION...?

Which of the following agents works by binding to the cytotoxic T-cell lymphocyte-associated protein on T-cells to prevent binding to the B7-1/2 protein on cancer cells?

A. Durvalumab

B. Atezolizumab

C. Pembrolizumab

D. Ipilimumab

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POST-TEST QUESTION...?

Which is the primary lab value associated with adrenal insufficiency?

A. Hyponatremia
B. Hypokalemia
C. Hypernatremia
D. Hyperprolactinemia

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POST-TEST QUESTION...?

Which of the following ICI-related endocrinopathies is unlikely to be permanent?

A. Hypothyroidism
B. Hypophysitis
C. Hyperthyroidism
D. Adrenal Insufficiency

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ACKNOWLEDGEMENTS

Taylor Swift
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Colleen Bohnenkamp
BioRender

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THANK YOU!

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