Charting the Course: The Pharmacist's Role in Safeguarding Patients from Immune-Related Adverse Events

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Faculty and Staff Disclosures

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DIRECTIONS IN Oncology Pharmacy

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Educational Objectives

After completion of this activity, participants will be able to:

- Apply knowledge of immune-related adverse event (irAE) characteristics, risk factors for development, and appropriate monitoring requirements to promptly identify toxicities of checkpoint inhibitor treatment
- Manage steroid tapers for individual patients, considering the type and severity of irAEs and patient characteristics
- Implement strategies for identification and management of immune-mediated endocrinopathies
- Provide comprehensive patient education on irAEs, stressing early recognition and reporting

Pretest Questions

Pretest Question 1

When compared to chemotherapy adverse effects (AEs), which statement is accurate regarding immune-related adverse events (irAEs)?

A. Timeline of irAEs is unpredictable.
B. Endocrine irAEs are rarely permanent.
C. irAEs are due to immune suppression.
D. Nausea and vomiting are common irAEs.

Pretest Question 2

RC is a 68-year-old man receiving immune checkpoint inhibitor (ICI) therapy. He was diagnosed with grade 2 colitis 3 weeks ago and is currently taking prednisone 1 mg/kg/day. Today in clinic, he reports no symptoms of colitis. What recommendation is most appropriate at this time for RC?

A. Initiate taper of prednisone over 1 week.
B. Initiate taper of prednisone over 4 weeks.
C. Continue prednisone 1 mg/kg/day to complete 6 weeks.
D. Initiate atovaquone for *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis.

Pretest Question 3

NA is a 49-year-old patient who presents for C3 of pembrolizumab, reporting new-onset severe fatigue. TSH is 96 mU/L (high) and free T4 is 0.6 ng/dL (low). Which irAE is NA likely experiencing?

A. Hypogonadism
B. Hypophysitis
C. Hyperthyroidism
D. Hypothyroidism

Pretest Question 4

Which strategy should be used when providing education to patients receiving ICIs?

A. Avoid comparison with traditional chemotherapy
B. Review steroid taper plan prior to starting ICI therapy
C. Emphasize the general timeline of irAE symptom onset
D. Focus irAE self-monitoring on grade 3-4 thresholds

Pretest Question 5

Before participating in this activity, how confident are you in managing immune-related adverse events?

A. Not at all
B. Somewhat
C. Moderately
D. Very
E. Extremely

Optimizing Early Recognition of Immune-Related Adverse Events

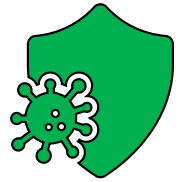
Immune Checkpoint Inhibitors (ICIs)

- **"Foot off the brake(s)" → ICI results in non-specific T cell overactivation**
  - Anticancer activity against cancers with high somatic mutation burden
- **13 FDA-approved ICI agents**
  - Driven significant OS benefit in cancers
  - >90 indications (September 2024)
  - >1 in 3 pts with cancer eligible for ICI
- **Immune-related adverse events (irAEs) imitate autoimmune diseases**

CTLA-4	Ipilimumab Tremelimumab NEW
PD-1	Cemiplimab Dostarlimab Pembrolizumab Nivolumab Tislelizumab NEW Retifanlimab NEW Toripalimab NEW
PD-L1	Atezolizumab Avelumab Durvalumab
LAG-3	Relatlimab NEW

Haslam A et al. *JAMA Netw Open*. 2020;3(3):e200423; Paul J et al. *J Clin Oncol*. 2024;42(16_suppl):11057; Tevimbra. Prescribing information. BeiGene USA; March 2024; FDA approves Opdualag for unresectable or metastatic melanoma. March 21, 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-opdualag-unresectable-or-metastatic-melanoma. NIH National Cancer Institute. Immune Checkpoint Inhibitors. Accessed September 19, 2024. https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/checkpoint-inhibitors

Chemotherapy versus Immunotherapy



- **Direct** anticancer effect
- **Usually shorter** response
- **Predictable** AE timeline
- Immune system **suppressed**
- **Anticancer effect stops** after drug is discontinued
- Nausea/vomiting **common**
- **Rarely** AEs permanent

- **Indirect** anticancer effect
- **Durable** response possible
- **Unpredictable** AE timeline
- Immune system **activated**
- **Immune activation persists** after drug is discontinued
- Nausea/vomiting **rare**
- **Endocrine** irAEs permanent

Ramos-Casals M et al. *Nat Rev Dis Primer*. 2020;6(1):38; Wolchok JD et al. *J Clin Oncol*. 2022;40(2):127-137; Tawbi HA et al. *N Engl J Med*. 2022;386(1):24-34; NCCN Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related Toxicities, v1.2024.

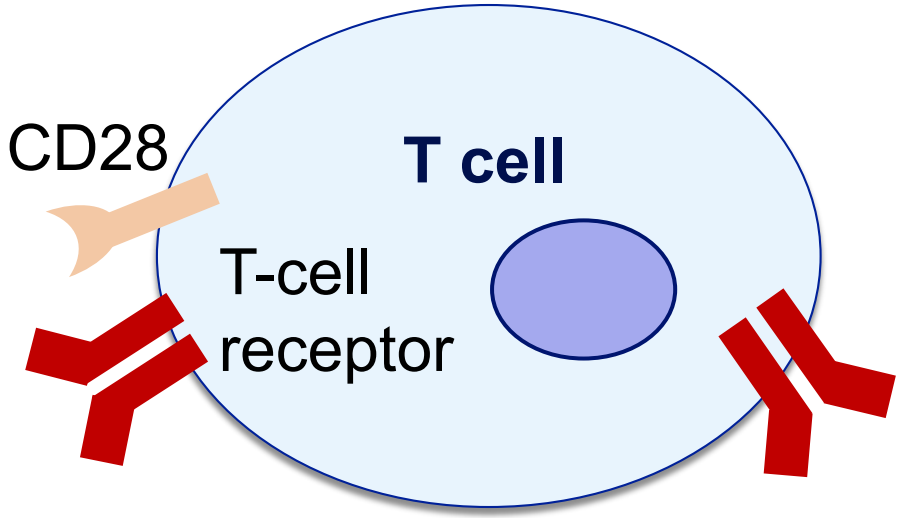
Approved ICI Combination Therapies

- **Atezolizumab** + bevacizumab
- **Atezolizumab** + chemotherapy ± bevacizumab
- **Avelumab** + axitinib
- **Durvalumab** + chemotherapy
- **Durvalumab** + **tremelimumab**
- **Nivolumab** + cabozantinib
- **Nivolumab** + **ipilimumab** (±) limited chemotherapy
- **Nivolumab** + **relatlimab**
- **Pembrolizumab** + chemotherapy
- **Pembrolizumab** + axitinib
- **Pembrolizumab** + lenvatinib
- **Dostarlimab** + chemotherapy

Toxicity identification / management challenging

See respective package inserts.

ICI Mechanism of Action

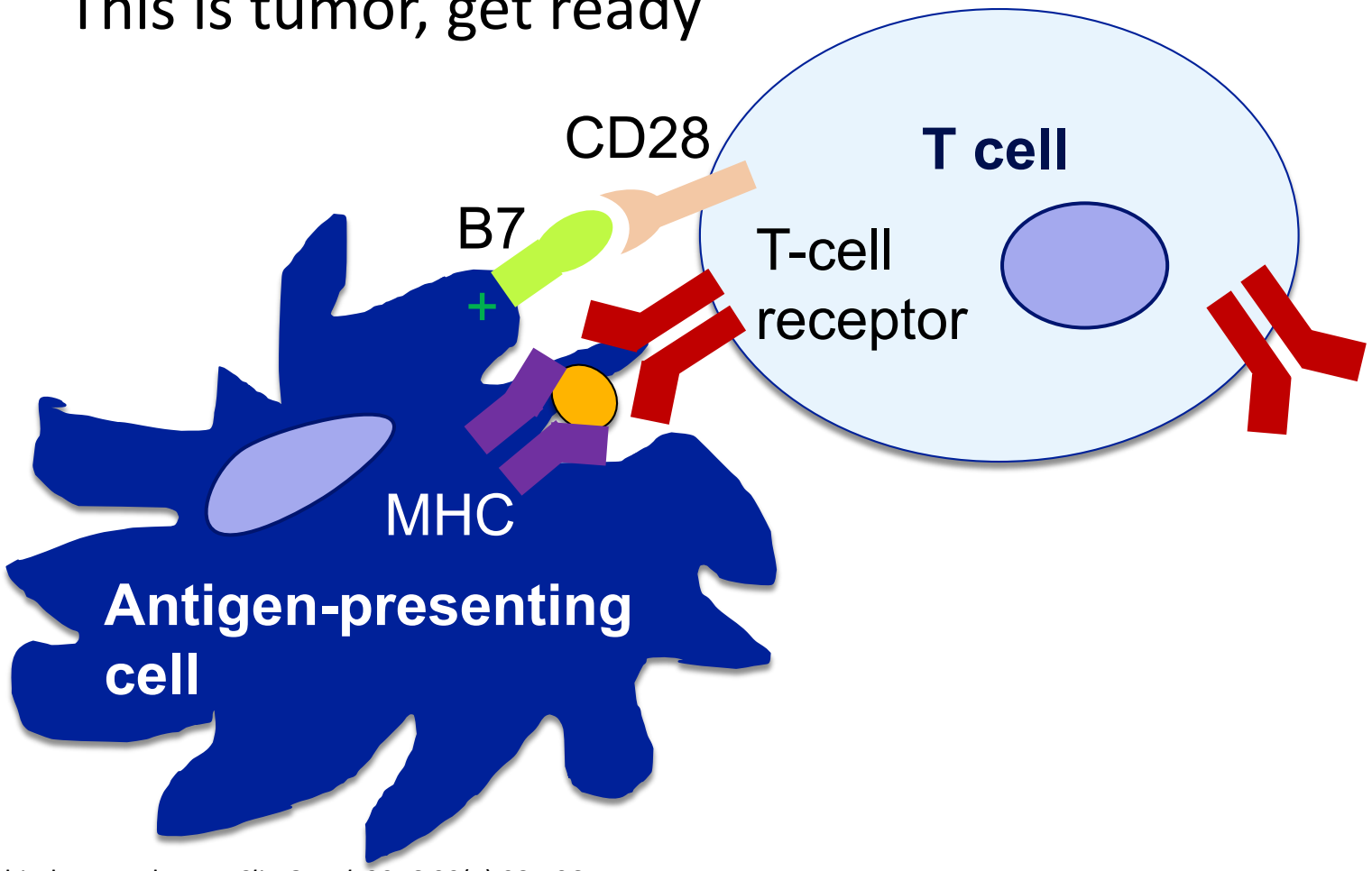


Buchbinder E et al. *Am J Clin Oncol*. 2016;39(1):98-106.

ICI Mechanism of Action

Priming Phase

"This is tumor, get ready"



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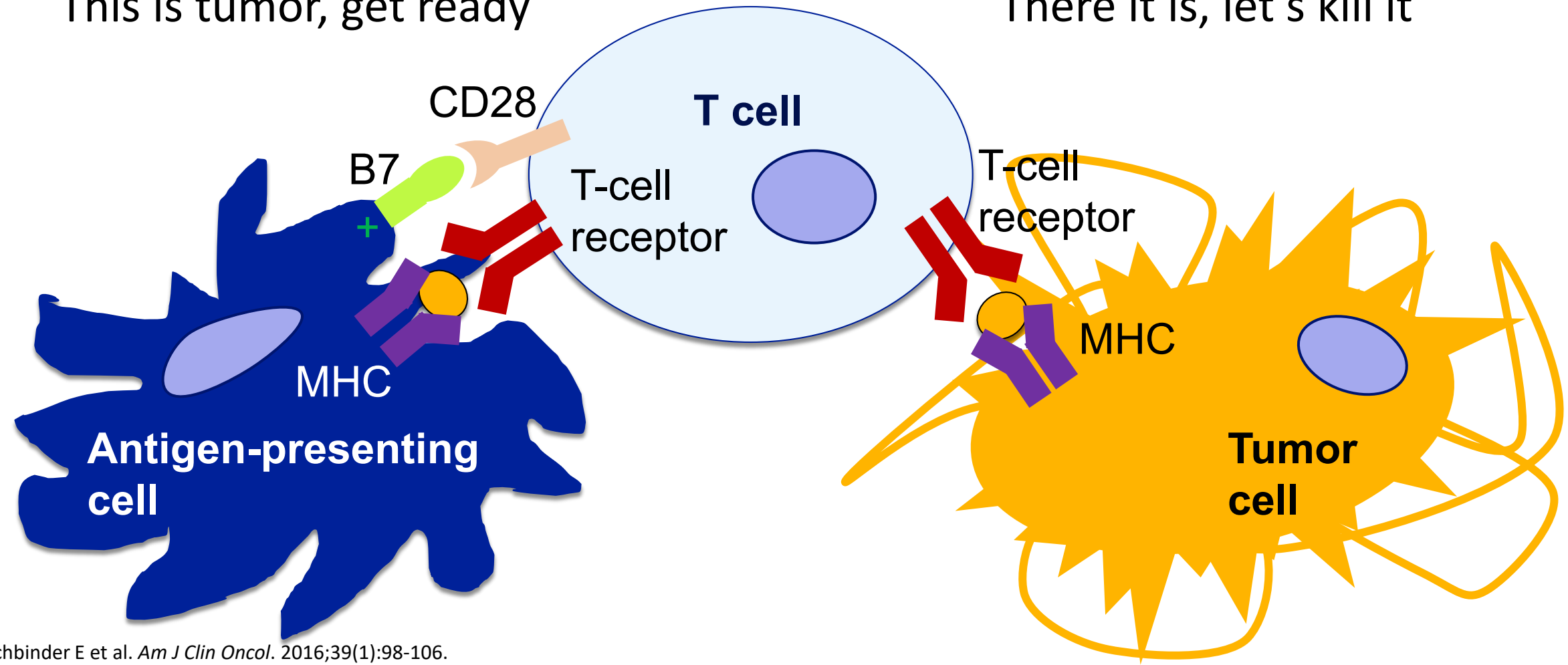
ICI Mechanism of Action

Priming Phase

"This is tumor, get ready"

Effector Phase

"There it is, let's kill it"



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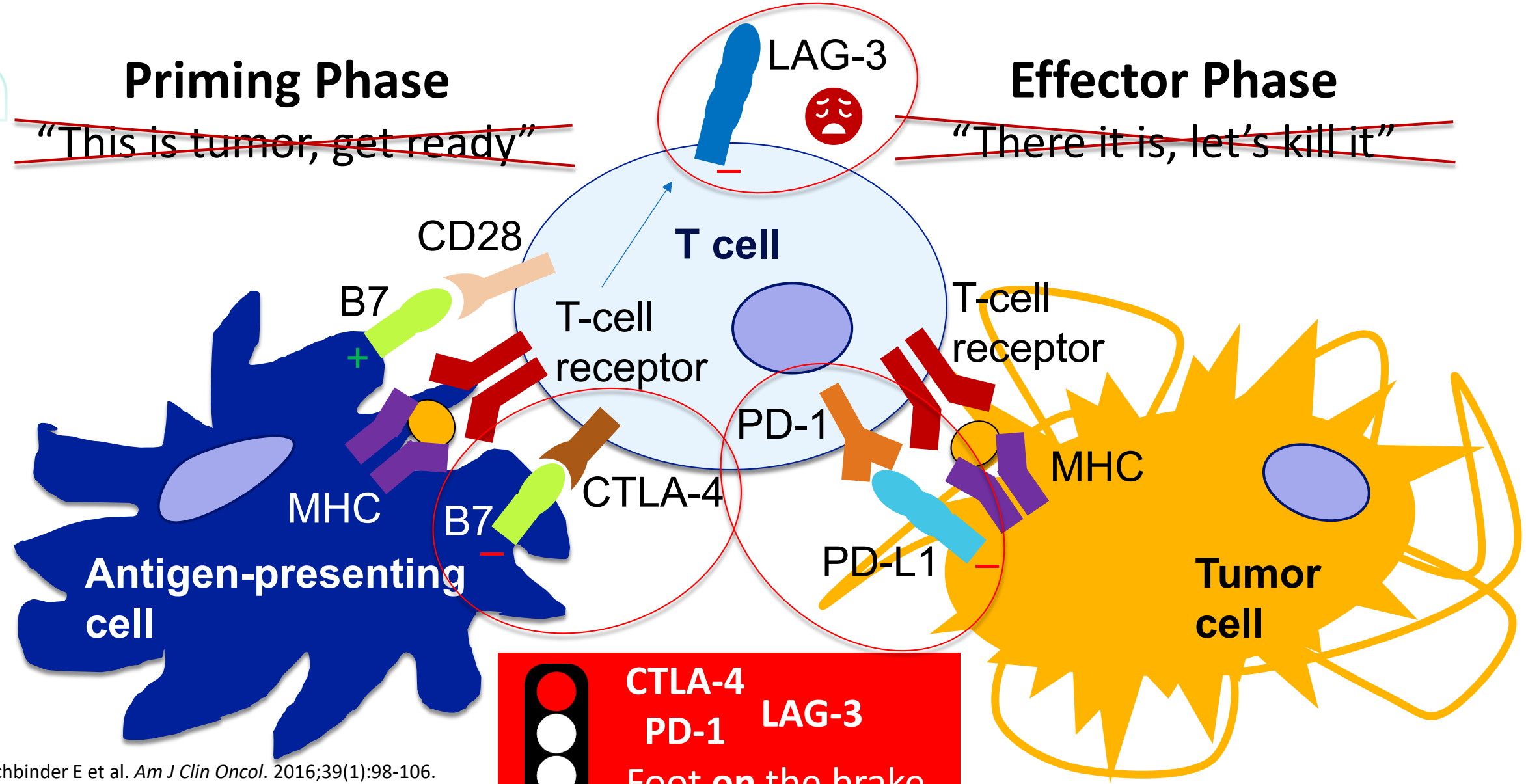
ICI Mechanism of Action



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ICI Mechanism of Action

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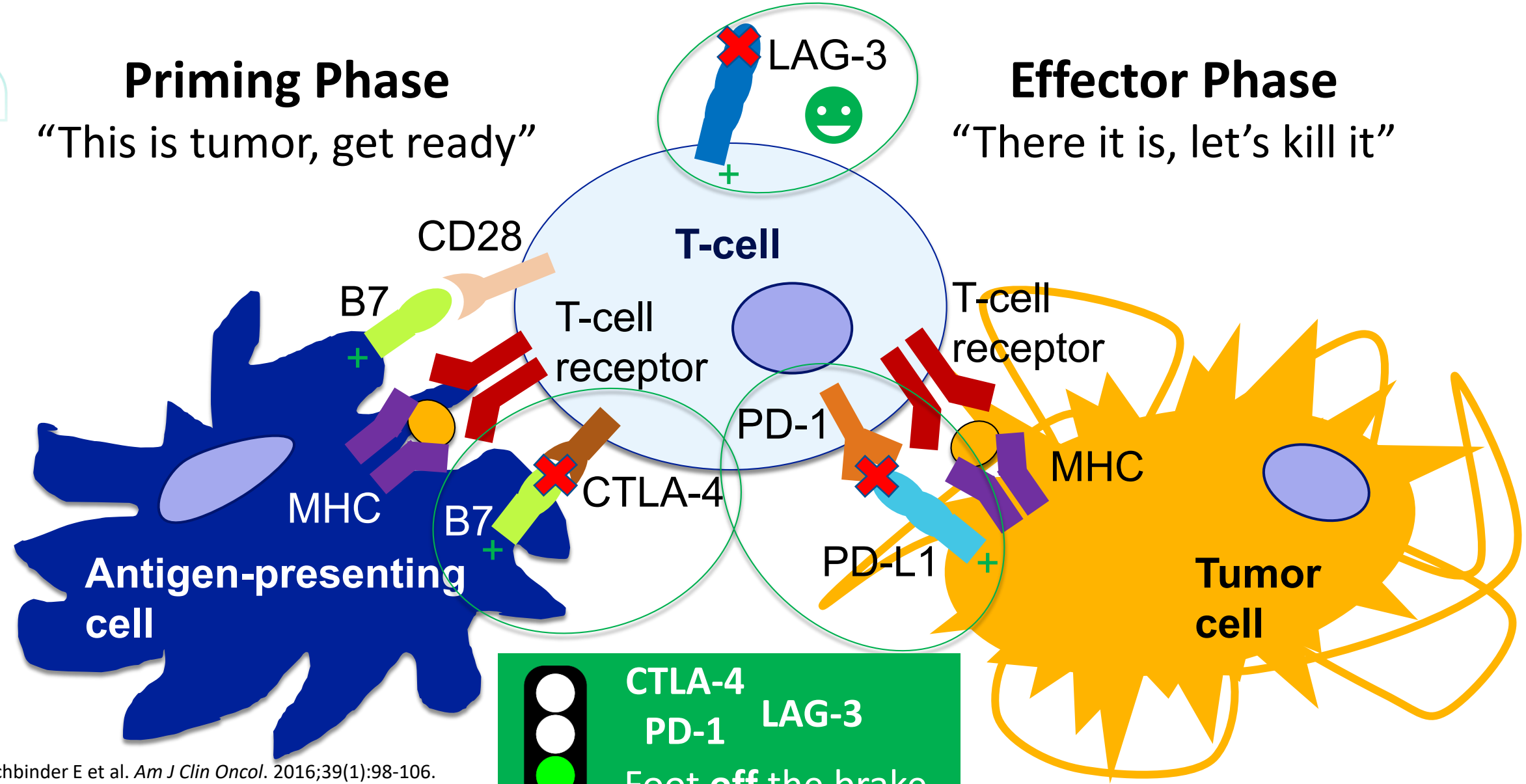


Buchbinder E et al. *Am J Clin Oncol*. 2016;39(1):98-106.

Immune-Related Adverse Events (irAEs)

Dermatologic	Rheumatologic	Nervous System
Blistering disorder	Arthritis	Aseptic meningitis
Maculopapular rash	Myositis	Encephalitis
Pruritus	Polymyalgia rheumatica	Guillain-Barré syndrome
Mucositis	Sicca syndrome	Myasthenia gravis
Lichen planus		Peripheral neuropathy
Oral dysesthesia		Transverse myelitis
Endocrine	**Ocular**	
Hypophysitis	Episcleritis	**Cardiovascular**
Thyroiditis	Scleritis	Myocarditis
Type 1 diabetes	Uveitis	
Gastrointestinal	**Pulmonary**	**Hematologic**
Colitis	Pneumonitis	Hemolytic anemia
Hepatitis	**Renal**	HLH
Pancreatitis	Nephritis	ITP

Any organ can be inflamed by the immune system

Vigilance is essential; pharmacists can help team with irAE identification, management

HLH, hemophagocytic lymphohistiocytosis; ITP, immune thrombocytopenic purpura.

NCCN Clinical Practice Guidelines in Oncology®, Management of Immunotherapy-Related Toxicities, v1.2024.

Possible Risk Factors for Common irAEs

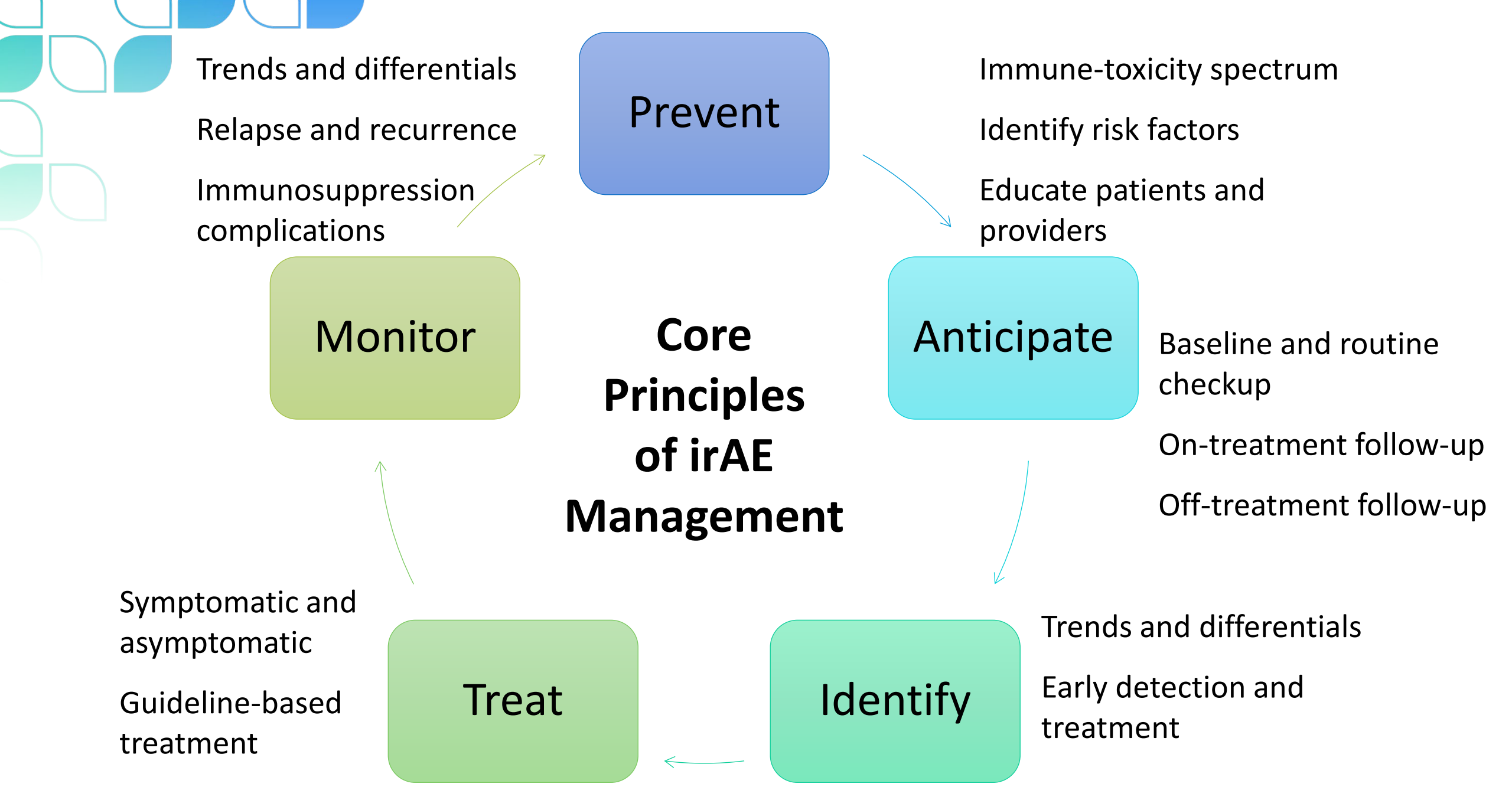
Thyroiditis	Rash/Pruritus	Colitis	Pneumonitis
• Female sex • Elevated body mass index • Advanced age • Presence of thyroid autoantibodies	• Diagnosis of melanoma	• Diagnosis of melanoma	• Age ≤ 60 years • ECOG PS ≥2 • Autoimmune disease • Pulmonary comorbidity*
Anti-PD1 + anti-CTLA4	Anti-CTLA4	Regimens containing ipilimumab	Anti-PD-1 or Anti PD-1 + anti-CTLA-4

*Interstitial lung disease (ILD), chronic obstructive pulmonary disease (COPD), thoracic radiation, asthma, pulmonary fibrosis.

ECOG PS, Eastern Cooperative Oncology Group performance status.

Chennamadhavuni A et al. *Front Immunol*. 2022;13:779691; Barroso-Sousa R et al. *JAMA Oncol*. 2018;4(2):173-182; Kennedy R et al. *Cleve Clin J Med.* 2023;90(5):307-317; Okada N et al. *Br J Cancer.* 2020;122:771-777.

Core Principles of irAE Management



irAE-lly Need to Know the Basics

- **Timing + incidence unpredictable; identification/workup challenging**
  - irAEs most common a few months after start of ICI
  - Cover all potential differential diagnoses until ruled out
  - Results of workup should not delay empiric treatment for severe irAE

Suspect irAE for anyone on ICI

- **Management dictated by grade of presumed irAE toxicity**
- **Early treatment may prevent transition to more severe grade of irAE**
  - Grade 3 or 4 irAEs can be life-threatening and may require inpatient care
- **Mainstay of therapy = high-dose corticosteroids, then taper**
  - Oral prednisone/IV methylprednisolone 0.5-1 mg/kg/d; 2 mg/kg/d if very severe
- **Subspecialist consult if higher grade/steroid-unresponsive/rare irAE**

Ramos-Casals M et al. *Nat Rev Dis Primer*. 2020;6(1):38; NCCN Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related Toxicities, v1.2024. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

irAE Grading and Management Strategies

Grade 1	Grade 2	Grade 3	Grade 4
• Asymptomatic; clinical or diagnostic observations only; intervention not indicated	• Symptomatic; limiting instrumental ADLs	• Severe symptoms; limiting self-care ADLs; hospitalization indicated	• Life-threatening consequences; urgent intervention indicated

Grade 1/2

- **Supportive care, topical steroids if able**; outpatient; consider early oral steroids (esp. grade 2) to prevent higher grade irAE
  - Generally hold ICI starting at grade 2 or higher (some exceptions: derm, SS)
  - Patient education on early irAE identification/treatment is key

Grade 3/4

- **Oral/IV steroids with PJP/GI/insomnia prophylaxis**; inpatient
  - Involve subspecialists, consider secondary immunosuppressants if needed
  - When improves to grade 1: Make clear steroid taper and monitoring plan

After irAE

- **Consider rechallenge**: 30%-40% risk of recurrent/new irAE

ADLs, activities of daily living; GI, gastrointestinal; IV, intravenous; PJP, *Pneumocystis jirovecii* pneumonia; SS, Sicca syndrome.

CTCAE v.5; NCCN Clinical Practice Guidelines in Oncology, Management of Immunotherapy-Related Toxicities, v1.2024.

The ~~Science~~ Art of the Steroid Taper

- **Important to avoid long-term AEs**
- **Start taper once irAE grade 1 or less**
  - **Goal:** 4-6 weeks
  - 10-20 mg every 5-7 days common
  - Rapid tapers are **NOT** advised
- **Extended taper/chronic duration**
  - Hepatitis, pneumonitis, neurologic irAEs: ≥6-8 week tapers common
  - Pneumonitis, arthritis: May require chronic treatment
- **Each team member plays role in ensuring adherence**
  - Steroid taper care plans are complex and change over time
  - Supportive care needs easily missed
- **Patient education and monitoring plans are vital**
  - Success depends on clear communication and understanding
  - Checklists can help with consistency

Ramos-Casals M et al. *Nat Rev Dis Primer*. 2020;6(1):38; Medina P et al. *J Pharm Pract*. 2020;33(3):338-349; NCCN Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related Toxicities, v1.2024. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Steroid Taper Examples

Prednisone Taper Calendar for ***

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
31-Oct	1-Nov	2-Nov	3-Nov	4-Nov **prednisone 70 mg (7 tablets)**	5-Nov prednisone 70 mg	6-Nov prednisone 70 mg
7-Nov prednisone 70 mg	8-Nov prednisone 70 mg	9-Nov **DOSE CHANGE prednisone 60 mg (6 tablets)**	10-Nov prednisone 60 mg	11-Nov prednisone 60 mg	12-Nov prednisone 60 mg	13-Nov prednisone 60 mg
14-Nov **DOSE CHANGE prednisone 50 mg (5 tablets)**	15-Nov prednisone 50 mg	16-Nov prednisone 50 mg	17-Nov prednisone 50 mg	18-Nov prednisone 50 mg	19-Nov **DOSE CHANGE prednisone 40 mg**	20-Nov prednisone 40 mg

Dates	Drug (Prednisone 10 mg tablet)
12/9 - 12/15	Prednisone 80 mg (8 tablets) in the morning for 7 days
12/16 - 12/22	Prednisone 50 mg (5 tablets) in the morning for 7 days
12/23 - 12/29	Prednisone 30 mg (3 tablets) in the morning for 7 days
12/30 - 1/5	Prednisone 10 mg (1 tablet) in the morning for 7 days

These example screenshots were shared with *Pharmacy Times* Continuing Education™ by faculty for use by this audience.

Supportive Care With High-Dose Steroids

	Medications / Strategies	Notes
***Pneumocystis jirovecii* pneumonia (PJP) prophylaxis**	**Sulfamethoxazole/trimethoprim** Pentamidine IV/inhaled (Avoid dapsone: hemolytic anemia) (Avoid atovaquone: diarrhea)	**Indication:** prednisone dose equivalent ≥20 mg/day for ≥4 weeks
Gastrointestinal prophylaxis	**Histamine H_2 receptor antagonists (H_2RAs)** Proton pump inhibitors (PPIs; may lower ICI efficacy and increase nephritis, colitis risk)	**Indication:** concomitant NSAID, anticoagulation; improved GI comfort
Insomnia	Trazodone; earlier steroid administration	Commonly needed
Bone prophylaxis	Calcium and vitamin D	Longer steroid use/tapers
Hyperglycemia	Insulin lispro Insulin aspart	Sliding scale common during taper with concomitant type 2 diabetes
Fungal prophylaxis	N/A	Invasive fungal infections rare

Thompson JA et al. *J Natl Compr Canc Netw*. 2020;18(3):230-241; NCCN Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related Toxicities, v1.2024. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf; Lopes S et al. *Front Immunol.* 2023;14:1070076.

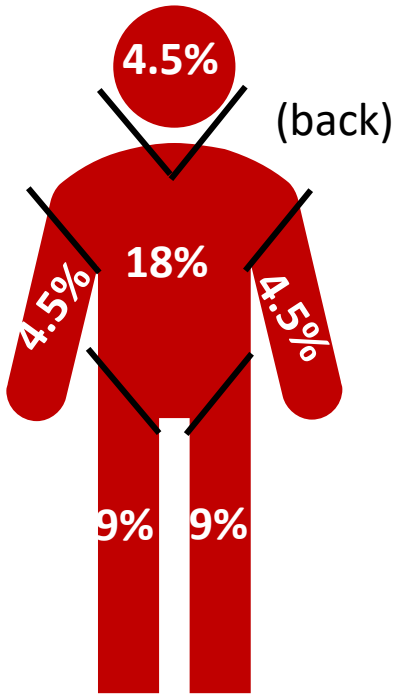
Management of Reversible vs Irreversible irAEs

Free irAE Consensus Guidelines: Use Them!

- **National Comprehensive Cancer Network** Guidelines for Management of Immunotherapy-Related Toxicities
- **Society for Immunotherapy of Cancer (SITC)** Clinical Practice Guideline on Immune Checkpoint Inhibitor-Related Adverse Events
- Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: **American Society of Clinical Oncology** Clinical Practice Guideline
- Management of Toxicities From Immunotherapy: **ESMO** Clinical Practice Guidelines

Thompson JA et al. *J Natl Compr Canc Netw*. 2020;18(3):230-241; Brahmer JR et al. *J Immunother Cancer*. 2021;9(6):e002435; Schneider BJ et al. *J Clin Oncol*. 2021;39(36):4073-4126; Haanen J et al. *Ann Oncol*. 2022;33(12):1217-1238.

Rash and Pruritus: Inflamed Skin



Rule of Nines

Grading

- **Rash:** % body surface area (BSA) involved
  - 10%-30% BSA = grade 2; >30% BSA = grade 3
- **Pruritus:** Tolerability, quality of life (eg, inability to sleep), ADLs

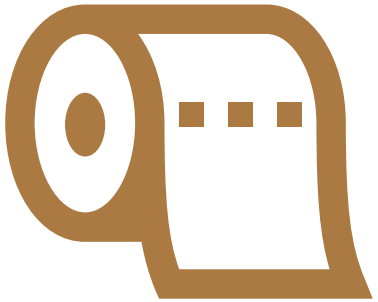
Treatment

- **Grade 1/2:** Moderate (triamcinolone 0.1%) to high (clobetasol 0.05%) potency topical corticosteroids + non-fragranced emollient preferable when possible; continue ICI
- **Grade 3/4:** High-dose corticosteroids + topical interventions; hold/discontinue ICI

Moore RA et al. Rule of Nines. In: StatPearls. Treasure Island (FL): StatPearls Publishing; February 12, 2024; NCCN Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related Toxicities, v1.2024. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Colitis: Inflamed Colon

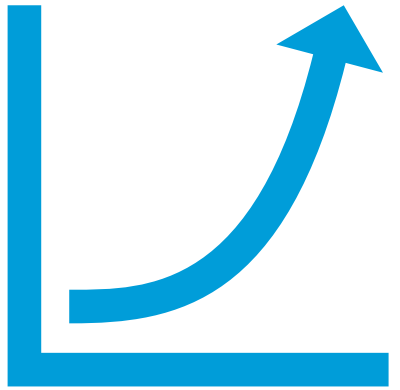
- **Highest risk in regimens containing ipilimumab**
  - Can be life-threatening
- **Presentation: increased # of loose stools daily**
  - ≥4 loose stools in 24 hours = grade 2
- **Fecal calprotectin + lactoferrin; *C diff***
  - Electrolyte / hydration assessment also important
- **High-dose steroids early (grade 2)**
  - Loperamide may mask immune-related diarrhea; avoid use
  - Steroids after stool studies obtained, before lab results received



NCCN Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related Toxicities, v1.2024.
https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Hepatitis: Inflamed Liver

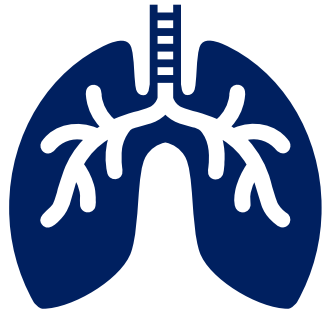
- **Manifests as isolated, acute increase in transaminases**
  - Grade 2 = AST or ALT >3-5x ULN
  - Occasionally T bilirubin or alkaline phosphatase may be elevated
    - May indicate more severe case, or alternate etiology
  - Otherwise asymptomatic
- **Rule out other causes (alcohol, meds, etc)**
  - If grade 1-2, consider repeating LFTs in 3-5 days
- **SLOW recovery with high-dose steroids**
  - 6-8 week steroid tapers common
  - Mycophenolate often required as steroid-sparing secondary agent



NCCN Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related Toxicities, v1.2024.

Pneumonitis: Inflamed Lungs

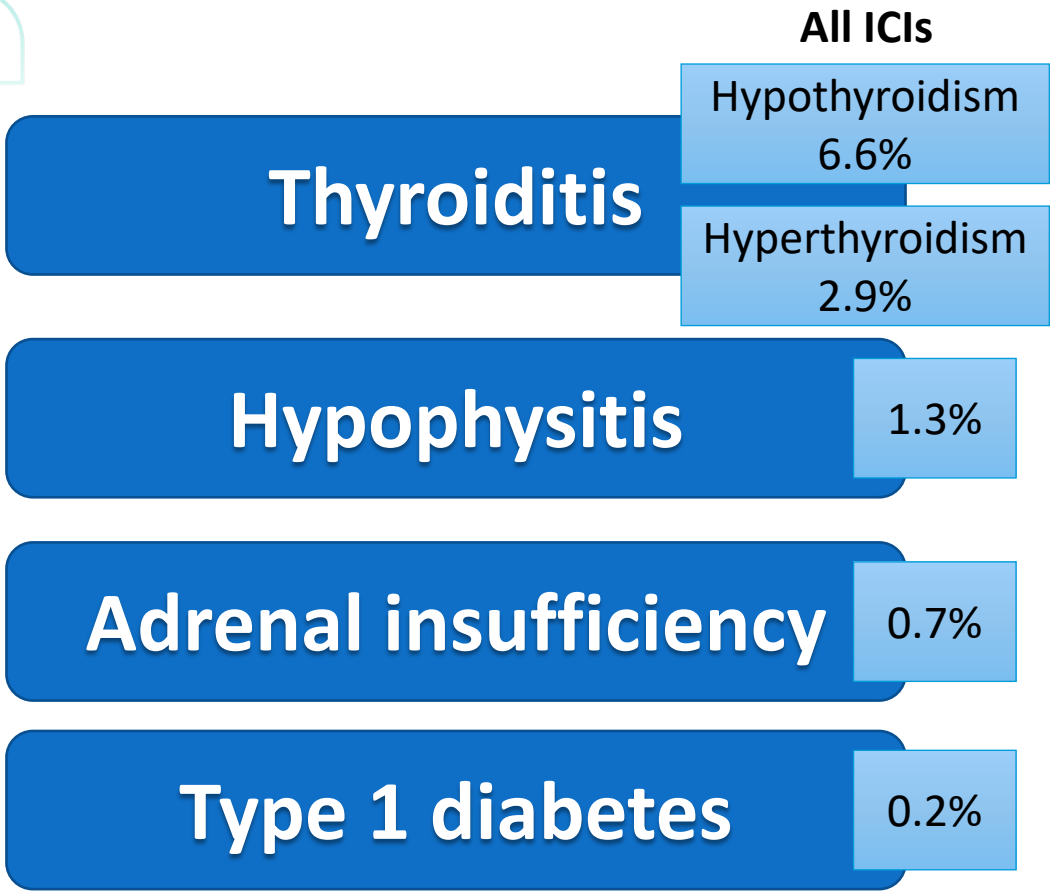
- **One of most common irAEs**
  - **Incidence:** 3%-5% (lung: 7%-13%)
  - **↑ risk:** PD-1, PD-1 + CTLA-4 ICI
- **Most frequent cause of death among irAEs**
  - Mortality risk: 10%-17%
- **Workup challenging**
  - Dry cough, SOB, ↓ activity tolerance, new O2 requirement
  - CT chest (ground glass opacities 37%)
- **Often extended 6-8+ wk steroid tapers**
  - May become chronic irAE (low-dose steroid)



Admit, use high-dose steroids

Wang H et al. *Thorac Cancer*. 2020;11(1):191-197; Zhai X et al. *Cancer Biol Med*. 2020;17(3):599-611; NCCN Guidelines. Management of Immunotherapy-Related Toxicities, v1.2024. www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf; Naidoo J et al. *J Clin Oncol.* 2017;35:709-717.

Endocrine irAEs: Inflamed Glands



- **>1 in 10** of all ICI-treated pts
- Severe endocrine irAEs = **Rare**
  - Diagnosis **challenging** due to non-specific signs/symptoms
  - Can require **urgent** management
- **Treatable,** but often **permanent**
  - After stabilized, continue ICI
- **Hormone replacement**

Focus on thyroiditis and hypophysitis today

Barroso-Sousa R et al. *JAMA Oncol*. 2017;4(2):173-182; Delivanis DA et al. *J Clin Endocrinol Metab*. 2017;102(8):2770-2780; Akturk HK et al. *Diabet Med*. 2019;36(9):1075-1081.

Thyroiditis: Inflamed Thyroid

Hyperthyroidism/ Thyrotoxicosis	Subclinical Hypothyroidism (*Transition phase*)	Primary (Overt) Hypothyroidism
TSH low, FT4 high	TSH 4-10 mIU/L, FT4 normal/low	TSH >10 mIU/L, FT4 low

Ramos-Casals M et al. *Nat Rev Dis Primer*. 2020;6(1):38; Kennedy R et al. *Cleve Clin J Med*. 2023;90(5):307-317; Kotwal A et al. *JCO Oncol Pract*. 2023;19:395-402; Schneider BJ et al. *J Clin Oncol*. 2021;39(36):4073-4126; NCCN Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related Toxicities, v1.2024.

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Hyperthyroidism/ Thyrotoxicosis	Subclinical Hypothyroidism (*Transition phase*)	Primary (Overt) Hypothyroidism
TSH low, FT4 high	TSH 4-10 mIU/L, FT4 normal/low	TSH >10 mIU/L, FT4 low

6-8 week duration

- Often incidental finding on routine TSH/FT4 monitoring every 4-6 weeks

Usually transient + asymptomatic

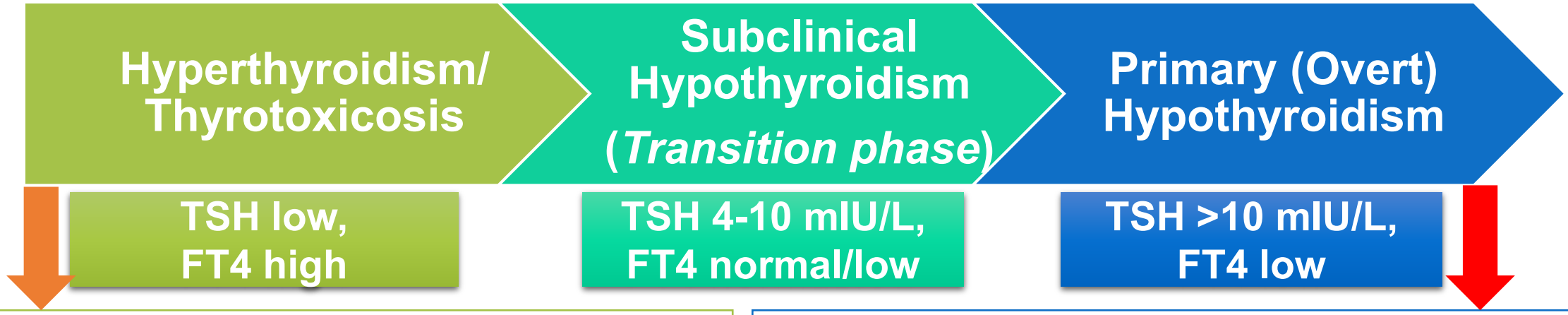
- **If symptomatic** (tachycardia, tremor, anxiety, restless): beta blocker

If T4 low, TSH inappropriately normal/low

→ Hypophysitis?

Ramos-Casals M et al. *Nat Rev Dis Primer*. 2020;6(1):38; Kennedy R et al. *Cleve Clin J Med*. 2023;90(5):307-317; Kotwal A et al. *JCO Oncol Pract*. 2023;19:395-402; Schneider BJ et al. *J Clin Oncol*. 2021;39(36):4073-4126; NCCN Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related Toxicities, v1.2024.

Thyroiditis: Inflamed Thyroid



6-8 week duration

- Often incidental finding on routine TSH/FT4 monitoring every 4-6 weeks

Usually transient + asymptomatic

- **If symptomatic** (tachycardia, tremor, anxiety, restless): beta blocker

If T4 low, TSH inappropriately normal/low

→ Hypophysitis?

4-6 weeks after hyperthyroidism

- 80%+ convert to hypothyroid state

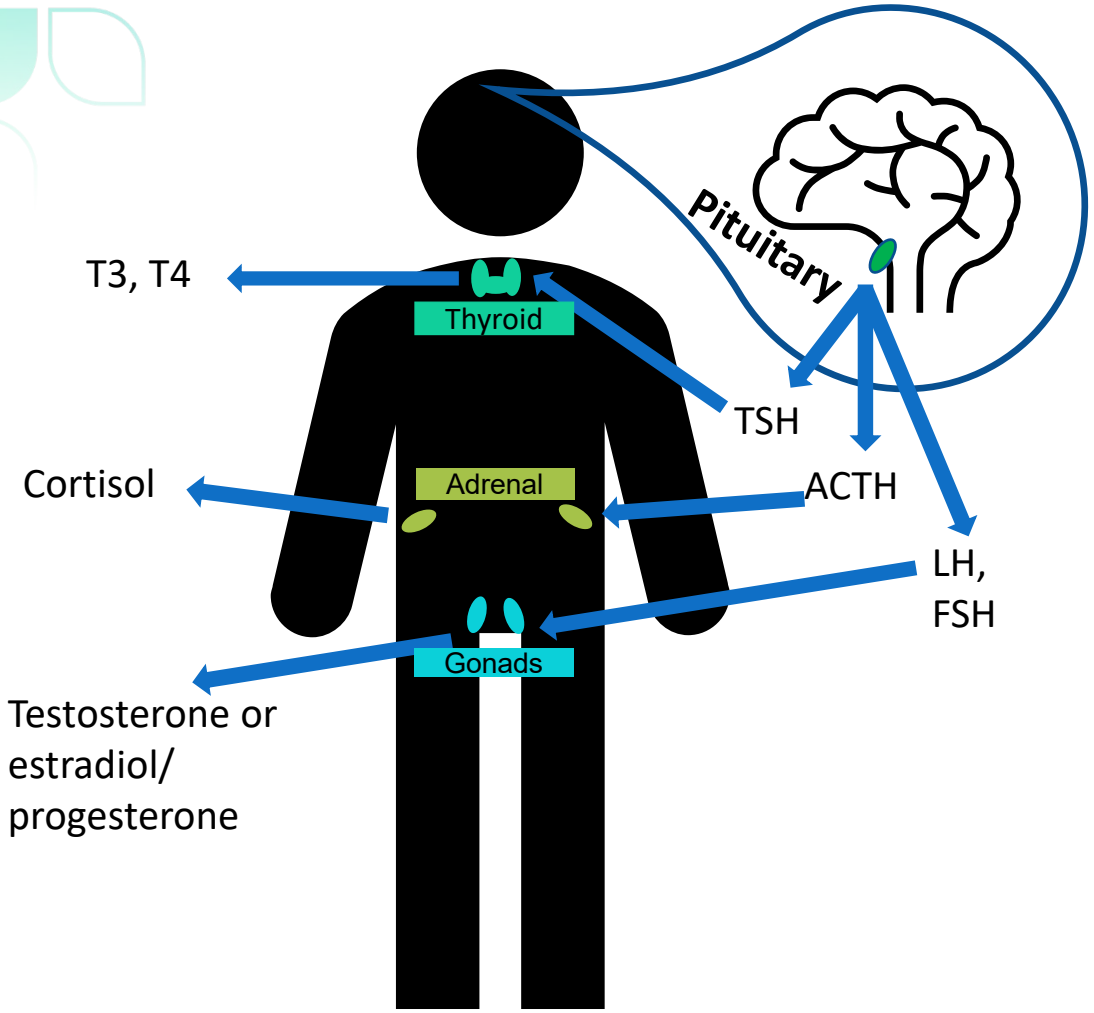
Fatigue/lethargy/cold/GI/taste

Lifelong thyroid replacement

- Levothyroxine 1.2-1.4 mcg/kg/day
- Monitor TSH every 6-8 weeks (titration)
- Elderly/comorbidities: 25%-50% ↓ dose?

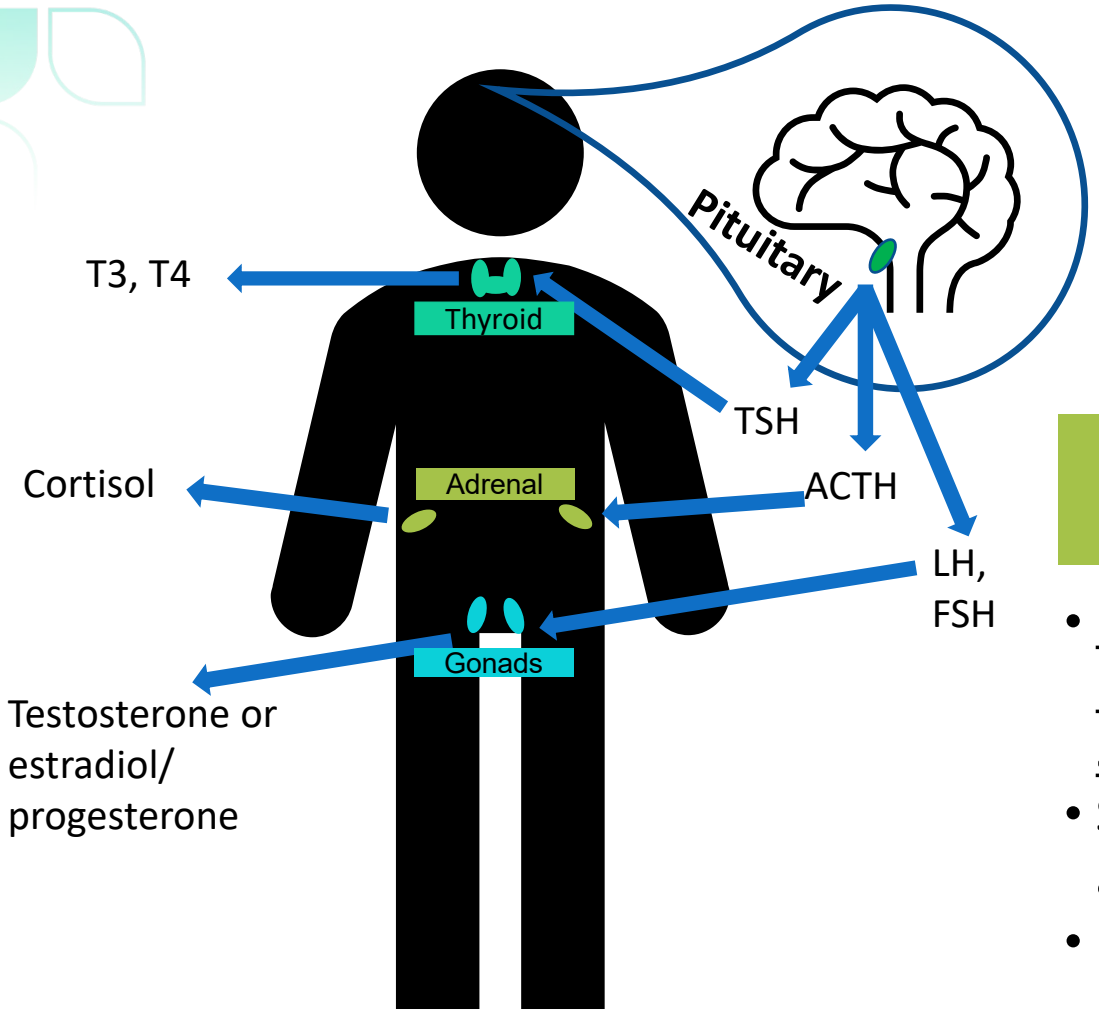
Ramos-Casals M et al. *Nat Rev Dis Primer*. 2020;6(1):38; Kennedy R et al. *Cleve Clin J Med*. 2023;90(5):307-317; Kotwal A et al. *JCO Oncol Pract*. 2023;19:395-402; Schneider BJ et al. *J Clin Oncol*. 2021;39(36):4073-4126; NCCN Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related Toxicities, v1.2024.

Hypophysitis: Inflamed Pituitary



Barroso-Sousa R et al. *Cancer.* 2018;124(6):1111-1121; Brahmer JR et al. *J Clin Oncol*. 2018;36(17):1714-1768; NCCN Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related Toxicities, v1.2024. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Hypophysitis: Inflamed Pituitary



Mass Effect

Headache, nausea, vomiting, dizziness, lightheadedness, visual

Secondary Effects: Unpredictable

Fatigue, hyponatremia, electrolyte disturbance, sexual dysfunction; shock, fever, confusion

Adrenal Insufficiency	Hypothyroidism	Hypogonadism
• **Hydrocortisone 10-20 mg in AM, 5-10 mg in PM** • Stress dosing to avoid crisis • Permanent	• **Levothyroxine replacement** • Treat adrenal insufficiency first (adrenal crisis risk) • May recover	• **Testosterone/ estrogen replacement** (if deficient and as appropriate) • May recover

Barroso-Sousa R et al. *Cancer.* 2018;124(6):1111-1121; Brahmer JR et al. *J Clin Oncol*. 2018;36(17):1714-1768; Kotwal A et al. *JCO Oncol Pract*. 2023;19(7):395-402; NCCN Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related Toxicities, v1.2024.

What Caused What? Sorting Through the Overlap of Toxicities With ICI + VEGF Inhibitor Combinations

Approved Combinations

VEGF Tyrosine Kinase Inhibitor

- Pembrolizumab + lenvatinib (renal cell carcinoma [RCC], endometrial)
- Pembrolizumab + axitinib (RCC)
- Nivolumab + cabozantinib (RCC)
- Avelumab + axitinib (RCC)

Anti-VEGF Antibodies

- Atezolizumab + bevacizumab (hepatocellular carcinoma)
- Atezolizumab + bevacizumab + chemotherapy (non-small cell lung cancer)

Overlapping

- Fatigue/thyroid issues
- Diarrhea (colitis)
- Hepatic (hepatitis)
- Cardiac (myocarditis)
- Rash (dermatitis)
- Proteinuria (nephritis)

VEGF Only

- Hypertension
- Hand-foot syndrome
- Mucositis/stomatitis
- Dysgeusia
- Delayed healing

ICI Only

- Other inflammatory conditions in organ systems

McGregor B et al. *Cancer Treat Rev*. 2022;103:102333; Keytruda. Prescribing information. Merck Sharp & Dohme; September 2024; Opdivo. Prescribing information. Bristol Myers Squibb; March 2024; Bavencio. Prescribing information. EMD Serono; March 2024; Tecentriq. Prescribing information. Genentech; April 2024.

General Thought Process for Identification and Management of AEs During ICI + VEGF TKI Combination Therapy

Does AE match potential toxicity from both?

- **If yes:** Must consider trend and timeline, with possibility of AE from either agent
- **If no:** Pursue agent-specific AE management

When did the AE occur, and what was the timeline?

- **Delayed onset with acute worsening** (and later, delayed resolution) → ICI more likely, but still likely hold TKI during treatment
- **Early onset or mild/gradual worsening** → TKI more likely, but should still pursue irAE workup

What happens with AE status after holding of the VEGF TKI?

- **AE improves within days to wk** → TKI more likely
- **AE same/worse in days to wk** → ICI more likely

How should I approach resuming therapy after an AE?

Depends on toxicity type, grade, resolution

- **ICI:** irAE may recur with rechallenge
- **TKI:** Dose reduction may be needed

Grünwald V et al. *Br J Cancer*. 2020;123:898; McGregor B et al. *Cancer Treat Rev*. 2022;103:102333.

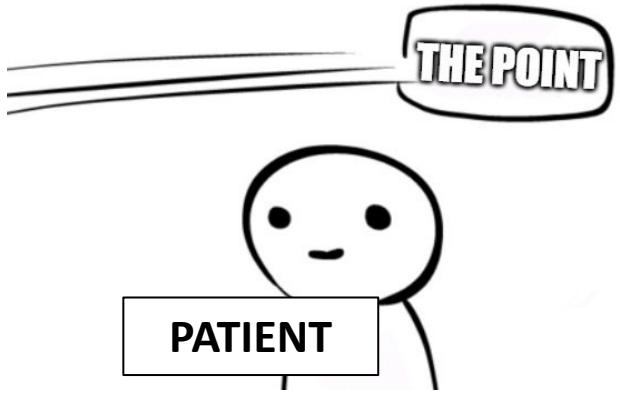
Pharmacists as the Link to Patient Knowledge on irAEs

Be a Health Literacy Advocate and irAE Educator

- **Health literacy (HL) matters**
  - Healthy People 2030 initiative
  - Improving HL empowers patients

Organizational health literacy: "The degree to which **organizations equitably enable** individuals to find, understand, and use information and services to inform health-related decisions and actions for themselves and others."

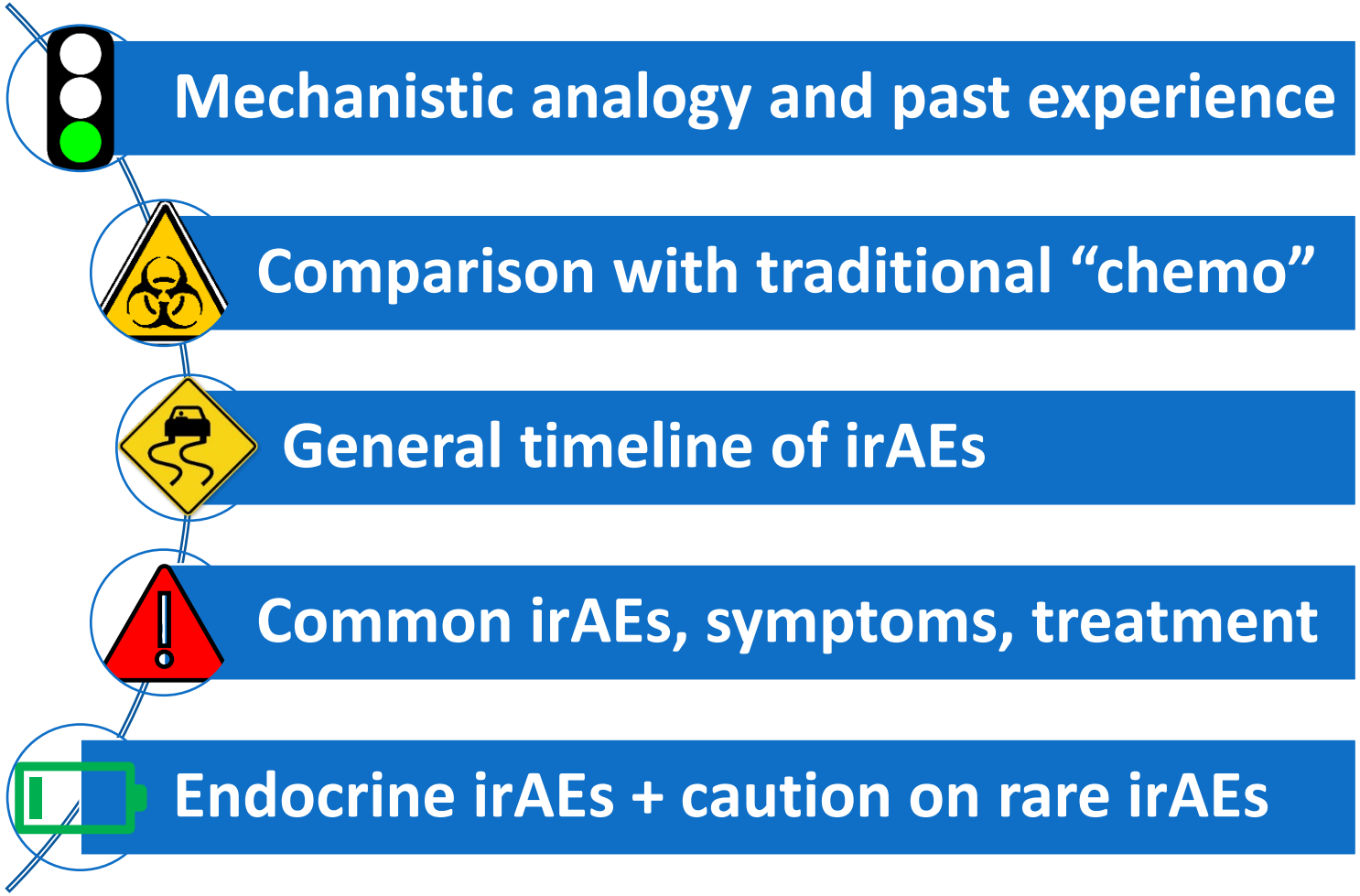
- **Prioritize simplicity without loss of meaning**
  - Educate patients as you would a parent, not a colleague



- **Materials: Maximize readability**
  - Flesch-Kincaid: 6th-8th grade (can assess in MS Word)
  - **Tip:** Short words, sentences
- **Focus irAE self-monitoring on grade 2 thresholds**
  - "Red alert zones" to trigger action

Ngoh LN. *J Am Pharm Assoc (2003).* 2009;49(5):e132-e149; Santana S et al. *J Public Health Manag Pract*. 2021;27(suppl 6):S258-S264; Best A. Can Health Literacy Improve Cancer-Related Outcomes and Mitigate Disparities in Care? *ASCO Daily News*. November 25, 2020; Bakerjian D. Personal Health Literacy. PSNet [internet]. Rockville (MD): Agency for Healthcare Research and Quality, US Department of Health and Human Services. 2023.

Essentials of ICI and irAE Education



Would Mom Understand?

Bad: “Immunotherapy may cause pneumonitis in the lungs. This can result in nonproductive cough, dyspnea, or breathlessness after activity. This may require us to temporarily discontinue immune checkpoint inhibition and start corticosteroids.”

Good: “Your immune system may inflame your lungs. This can cause dry cough, make breathing harder, or make you easily winded. We may have to stop immune therapy for a time and start steroids.”

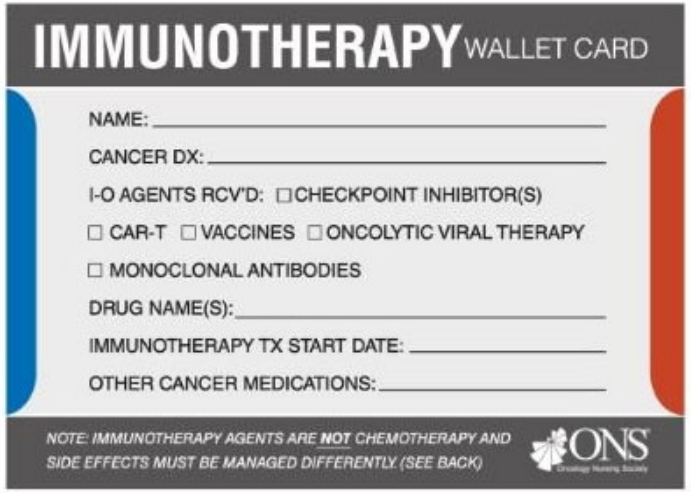
Would Mom Understand?

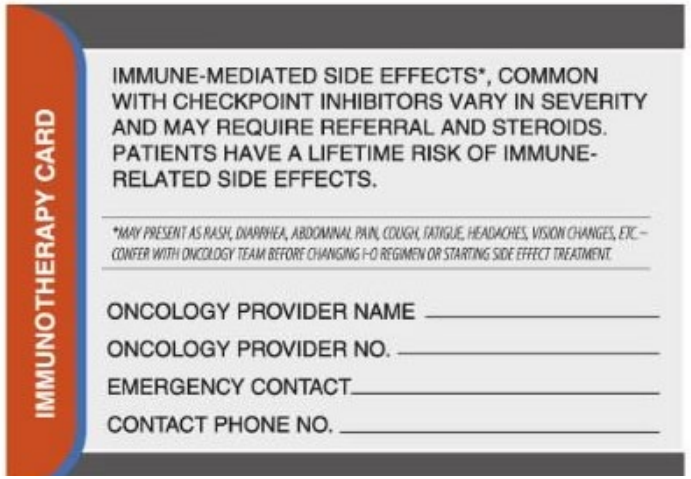
Bad: “Irreversible endocrinopathies may occur due to autoimmune attack on the thyroid or pituitary glands. Patients may need to initiate supplementation that will continue for the rest of their lives.”

Good: “Your immune system may burn out glands that release hormones. These side effects may be permanent and require lifelong treatment to replace the hormone your body needs.”

Training Patients & Caregivers to Self-Advocate

- **Lack of awareness is bad medicine**
  - Care in both rural and urban areas
- **Patients are own best advocates**
  - Infrequent oncology clinic follow-up
  - Lack of recognition in some settings
  - Self-monitoring for symptoms of irAEs
- **Wallet cards and irAE education**
  - Basic ICI agent information
  - Contact info for oncology clinic
  - Awareness and empowerment





Brahmer JR et al. J Clin Oncol. 2018 Jun 10; 36(17):1714-1768.

Conclusion

- **Treatment of cancer with ICIs continues to expand**
  - irAEs more likely to be identified across spectrum of care
- **Pharmacists in varied care settings can take active role in identification, management, monitoring of irAEs**
  - Listen to patients, consider irAEs as possible reason for symptoms, utilize national guidelines to ensure adherence to best management
- **Ensure ICI and irAE education is simple, focused to optimize patient ownership in recognizing immune toxicity**
  - Take effort to improve both personal and organizational health literacy; educate patients like you would your parents

Additional Resources

Resource
Schneider BJ, Naidoo J, Santomasso BD, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update [published correction appears in *J Clin Oncol*. 2022;40(3):315. doi:10.1200/JCO.21.02786]. *J Clin Oncol*. 2021;39(36):4073-4126.
Kotwal A, Perlman JE, Goldner WS, Marr A, Mammen JS. Endocrine dysfunction from immune checkpoint inhibitors: pearls and pitfalls in evaluation and management. *JCO Oncol Pract*. 2023;19(7):395-402. doi:10.1200/OP.23.00023
Martins F, Sofiya L, Sykiotis GP, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nat Rev Clin Oncol*. 2019;16(9):563-580. doi:10.1038/s41571-019-0218-0

Posttest Questions

Posttest Question 1

When compared to chemotherapy adverse effects (AEs), which statement is accurate regarding immune-related adverse events (irAEs)?

A. Timeline of irAEs is unpredictable.
B. Endocrine irAEs are rarely permanent.
C. irAEs are due to immune suppression.
D. Nausea and vomiting are common irAEs.

Posttest Question 2

RC is a 68-year-old man receiving immune checkpoint inhibitor (ICI) therapy. He was diagnosed with grade 2 colitis 3 weeks ago and is currently taking prednisone 1 mg/kg/day. Today in clinic, he reports no symptoms of colitis. What recommendation is most appropriate at this time for RC?

A. Initiate taper of prednisone over 1 week.
B. Initiate taper of prednisone over 4 weeks.
C. Continue prednisone 1 mg/kg/day to complete 6 weeks.
D. Initiate atovaquone for *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis.

Posttest Question 3

NA is a 49-year-old patient who presents for C3 of pembrolizumab, reporting new-onset severe fatigue. TSH is 96 mU/L (high) and free T4 is 0.6 ng/dL (low). Which irAE is NA likely experiencing?

A. Hypogonadism
B. Hypophysitis
C. Hyperthyroidism
D. Hypothyroidism

Posttest Question 4

Which strategy should be used when providing education to patients receiving ICIs?

A. Avoid comparison with traditional chemotherapy
B. Review steroid taper plan prior to starting ICI therapy
C. Emphasize the general timeline of irAE symptom onset
D. Focus irAE self-monitoring on grade 3-4 thresholds

Posttest Question 5

After participating in this activity, how confident are you in managing immune-related adverse events?

A. Not at all
B. Somewhat
C. Moderately
D. Very
E. Extremely

Thank you!