Recognition and Management of Immunotherapy Toxicity

Colton Zwart PharmD, BCOP
Mark Wagner PharmD, BCOP

Disclosures

- Mark
  - Speaker for Merck on Keytruda
  - Speaker for AstraZeneca on Calquence
  - Speaker for Sanofi on Sarclisa

Objectives

- Describe Immunotherapies mechanism of action
- Distinguish and grade Immunotherapy toxicities
- Evaluate steroid management techniques
- Assess resources related to patient population and equity

Abbreviation

- Immune checkpoint inhibitors (ICIs)
- Cytotoxic T-lymphocyte-associated-4 (CTLA-4)
- Programmed cell death protein (PD-1)
- Programmed cell death protein ligan (PD-L1)
- Immune-related adverse effect (irAE)
- Common Terminology Criteria for Adverse Events (CTCAE)
- Lymphocyte-Activation-Gene-3 (LAG-3)
- Hypothalamic-pituitary-adrenal (HPA)
- National Comprehensive Cancer Network (NCCN)
- American Society of Clinical Oncology (ASCO)
- Society for Immunotherapy of Cancer (SITC)

History

1970s | 1980s | 1990s | 2000s | 2010s | 2020s

1976: Spontaneous regression in melanoma believed to be secondary to immune component

1986: Interferon-α approved in cancer immunotherapy

1992: Interleukin-2 approved for cancer immunotherapy

2001-07: PD-1/PD-L1 discovered and T-cell activation and inhibition

2011: Ipilimumab approved for advanced melanoma

2014: Prembrolizumab and nivolumab approved for advanced melanoma

2016: Atezolizumab is FDA approved

2017: Avelumab and Durvalumab FDA approved

2018: Cemiplimab approved for squamous cell carcinoma

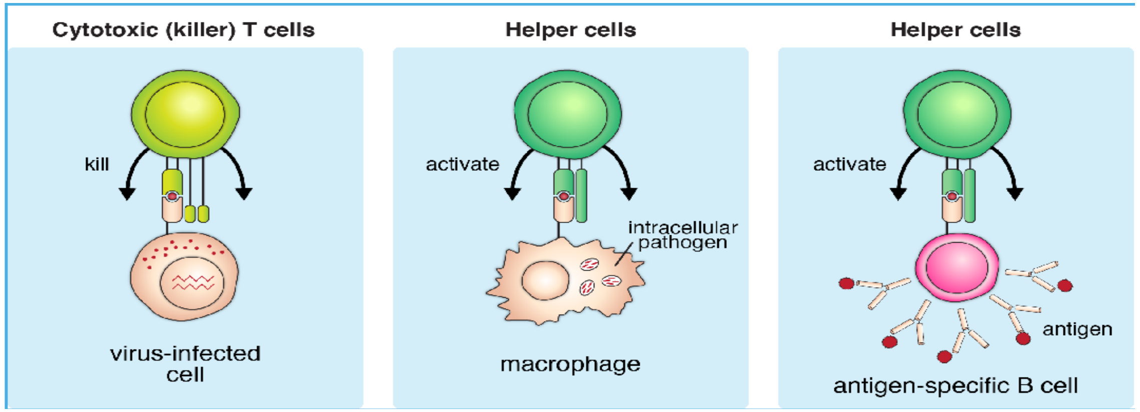
2021: Dostarlimab endometrial cancer

2022: Nivolumab and Relatlimab approved for Melanoma

2023: Toripaliomab approved for nasopharyngeal

The Immune System

- Innate Immunity
  - Non-specific
    - Skin and mucous membranes
    - Phagocytes, macrophages, dendritic cells and natural killer cell
  - Short-lived
  - No immunological memory

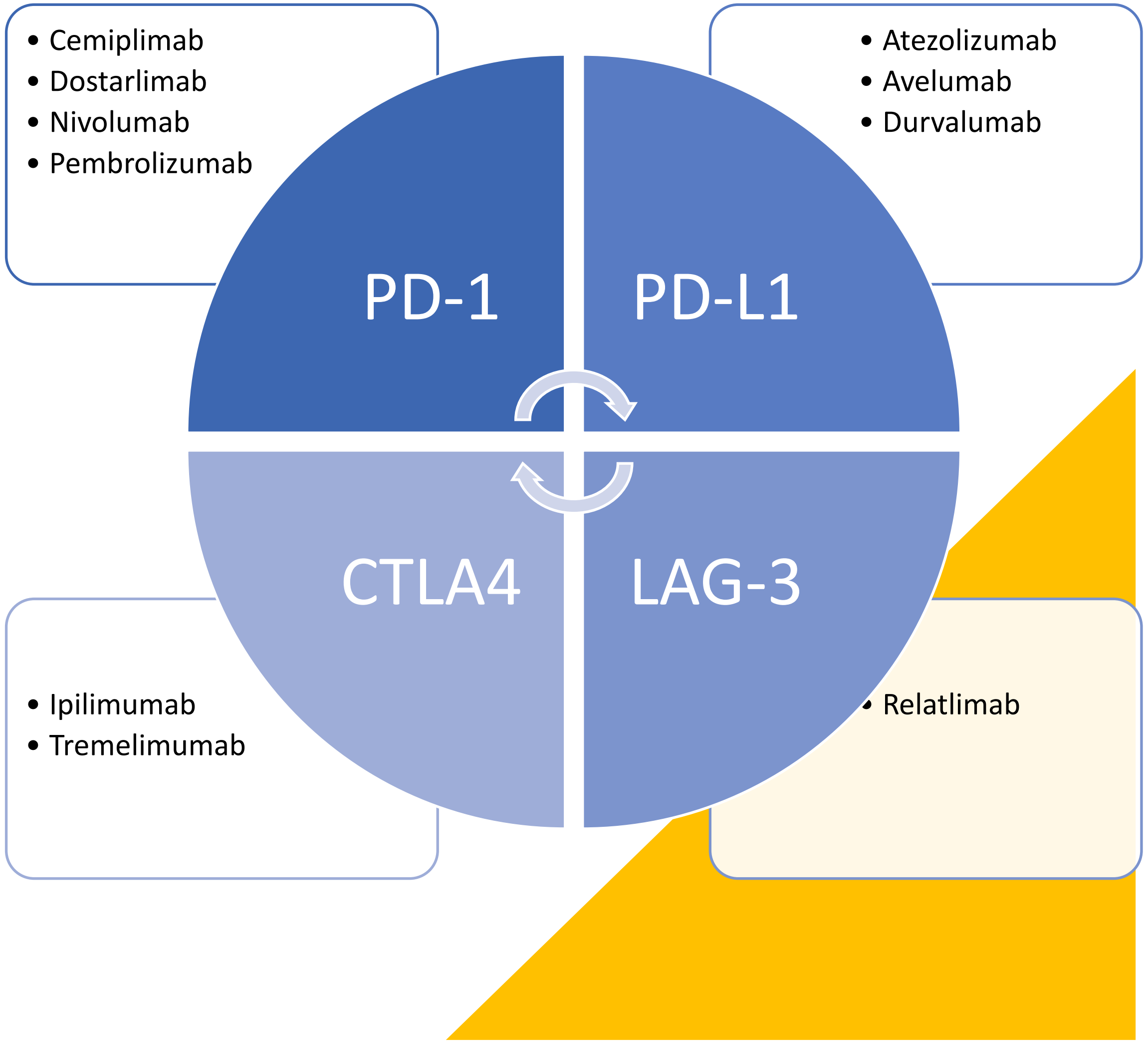


- Adaptive Immunity
  - Specific
    - Humoral response
      - B Lymphocytes
      - Antibodies
    - Cell-medicated response
      - T Lymphocytes
        - CD4 Helper T cells
        - CD8 cytotoxic T lymphocytes
      - Immunological memory
  - Self-tolerance mechanism
    - Central and peripheral domains

Blanc V et al. *Clin Cancer Res*. 2011

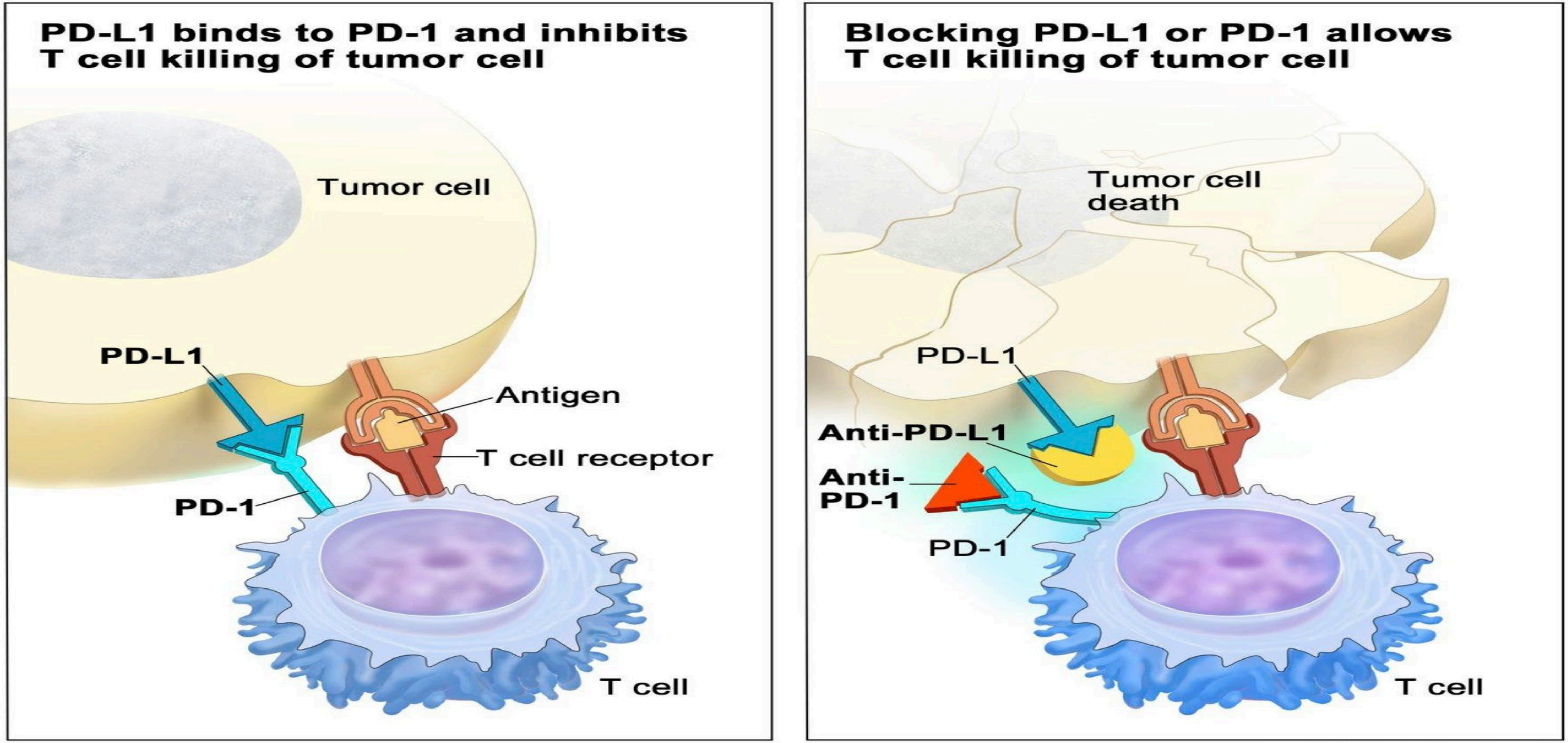
Mechanism of Action

- CTLA4
  - Important regulator of T cell priming and activation
- PD1 and PD-L1
  - Regulate immune activation within the peripheral tissues or tumors
- LAG-3
  - Induces T cell exhaustion
  - Alter T cell function and cytokine release



Sullivan R and Weber J. Nat Rev Clin Oncol. 2022

Example



Terese Winslow LLC U.S. Govt. 2015

Timeline and Identification irAE

Risk Factors

Demographics	Medical History	Medication History
• Age < 60 years • High body mass index • Chronic smokers • Women on CTLA4 • Men on PD-1/PD-L1 • Poor performance status	• Chronic kidney disease • Cardiac or lung disease • Allergies • Hypertension • Pre-existing autoimmune disease	• Previous chemotherapy • Diuretics • Proton Pump inhibitors • Anti-inflammatory agents

POEM

Chennamadhavuni A, et al. Front Immunol. 2022

Pathogenesis of irAE

Precise mechanism remains unknown

- Innate tolerance mechanism (Self vs Non-self)
  - Physiologic brake system on cytotoxic T-cell activation and effector function

Proposed mechanism

- Increased levels of inflammatory cytokines from T-cell activate inflammation
- Direct checkpoint blockade of targets in health complement-medicated inflammation
- Unintended increase of preexisting autoreactive antibodies

POEM

Sullivan R and Weber J. Nat Rev Clin Oncol. 2022

Immunotherapy Toxicity

- Dermatologic
  - Rash
  - Pruritus
- Gastrointestinal
  - Colitis
  - Hepatitis
  - Pancreatitis
- Endocrine
  - Thyroiditis
  - Hypophysis
  - Type 1 diabetes
  - Adrenal insufficiency

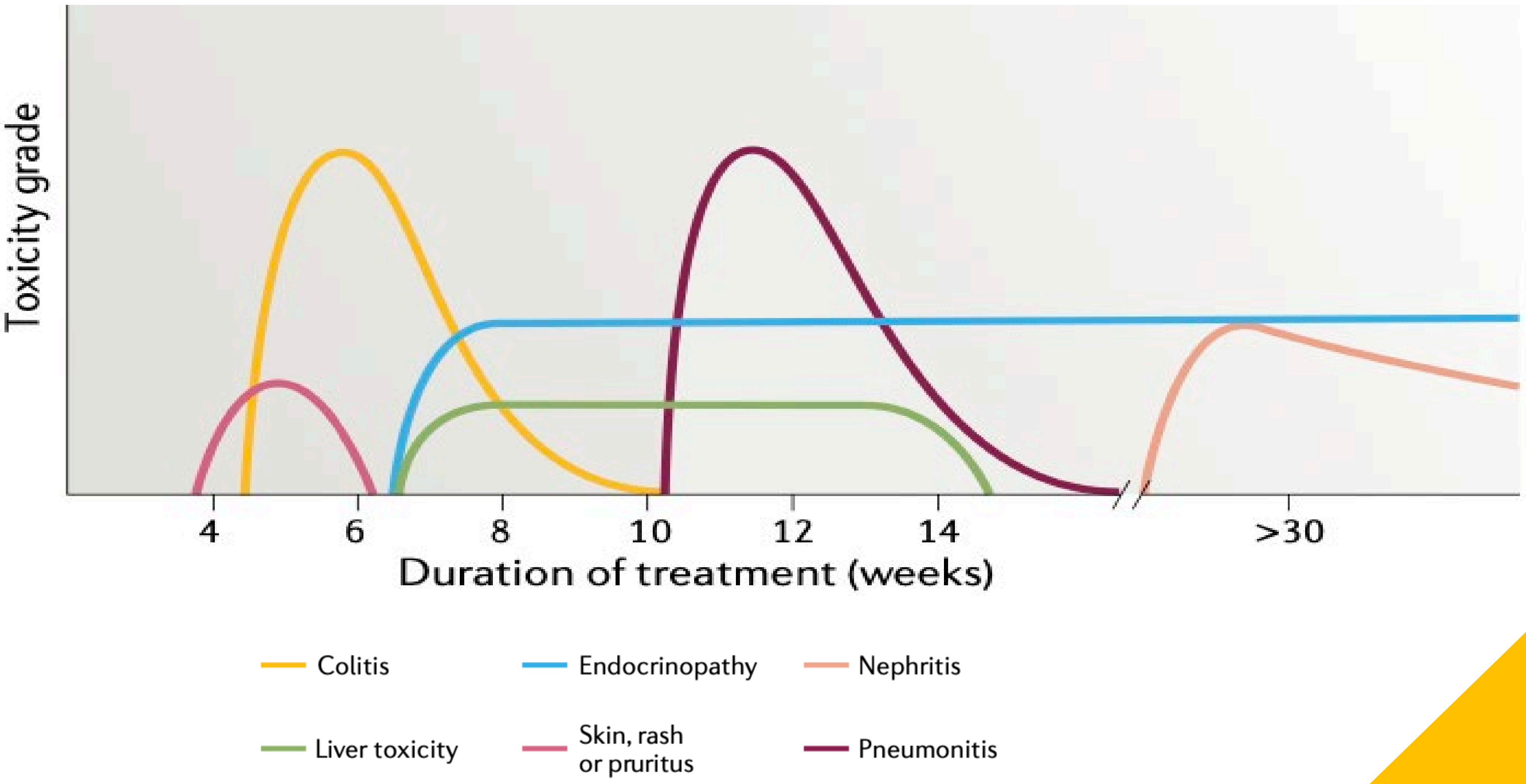
- Pulmonary
  - Pneumonitis
- Renal
  - Nephritis
- Musculoskeletal
  - Arthritis
  - Myositis
  - Polymyalgia rheumatica
- Ocular
- Cardiovascular
- Hematologic
  - Hemolytic anemia

- Central Nervous System
  - Myasthenia gravis
  - Guillain-Barre syndrome
  - Peripheral neuropathy
  - Meningitis
  - Encephalitis
  - Transverse myelitis

POEM

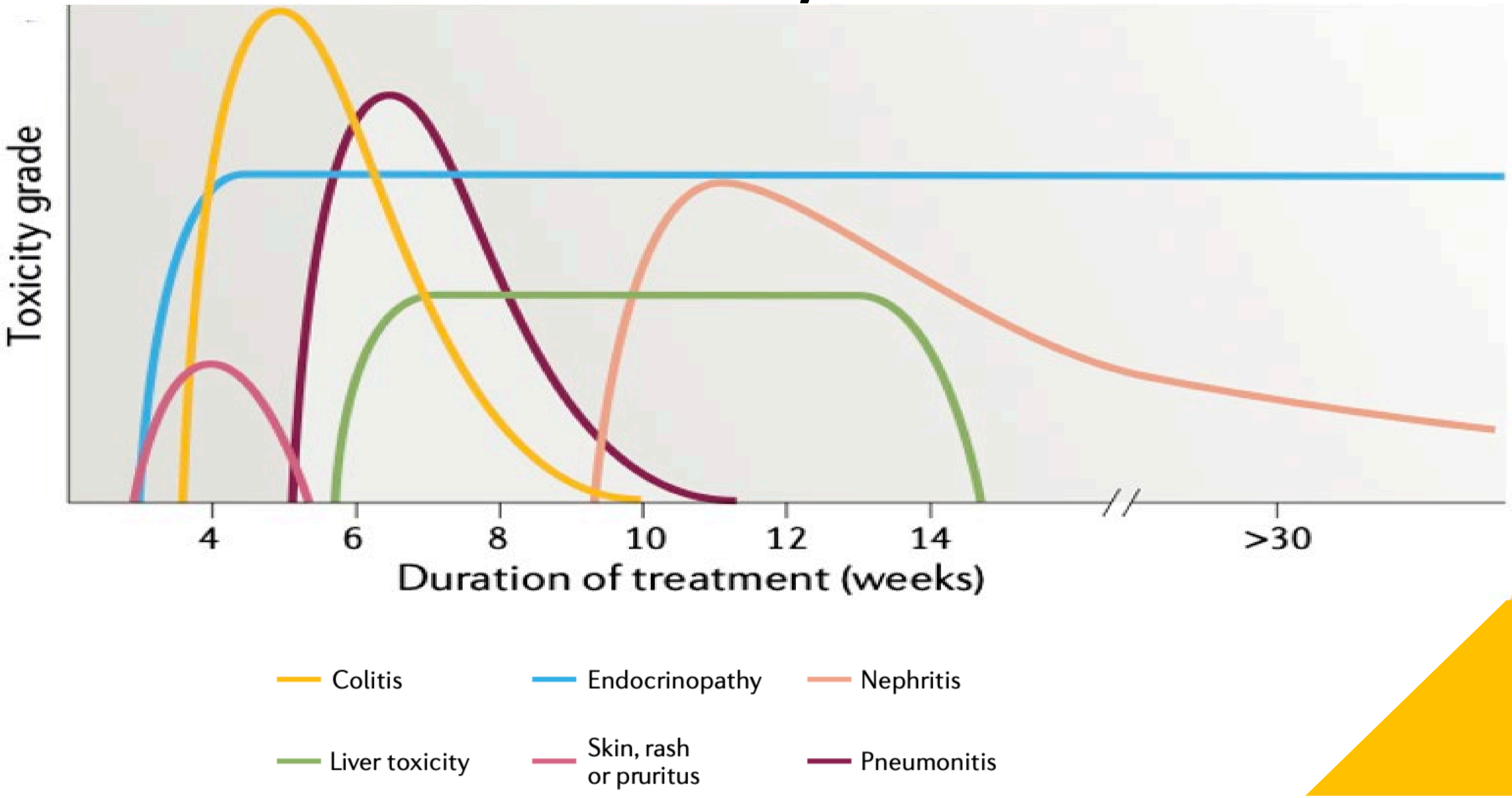
Aldea M, et al. Eur J Cancer. 2020

PD-L1 and PD-1 Inhibitors



Martins F, et al. Nat Rev Clin Oncol. 2019

Combination PD-1/CTLA-4 Blockade



Martins F, et al. Nat Rev Clin Oncol. 2019

Common Terminology Criteria for Adverse Events (CTCAE)

Grade	Action
1	• Asymptomatic or mild symptoms • Clinical or diagnostic observations only • Intervention not indicated
2	• minimal, local or noninvasive intervention indicated • Limiting age-appropriate instrumental ADL
3	• Severe or medically significant but not immediately life-threatening • Hospitalization or prolongation of hospitalization indicated • Disabling • Limiting self care ADL
4	• Life-threatening consequences • Urgent intervention indicated
5	• Death related to AE

POEM

Dermatologic

- Incidence varies by type of IRAE
  - 33-50% overall
- Assessment
  - Total body skin exam, including mucosa
  - History of prior inflammatory dermatologic diseases
  - Consider biopsy if unusual features
  - Eosinophil count, peripheral blood smear, and liver function tests (LFTs)

Maculopapular rash	Pruritus	Bullous dermatitis
SJS/TEN	Lichen planus/ Lichenoid diseases	Psoriasis/ Psoriasiform diseases
Oral mucosa inflammation	Dry mouth	Oral dysesthesia

POEM

Maculopapular Rash Management

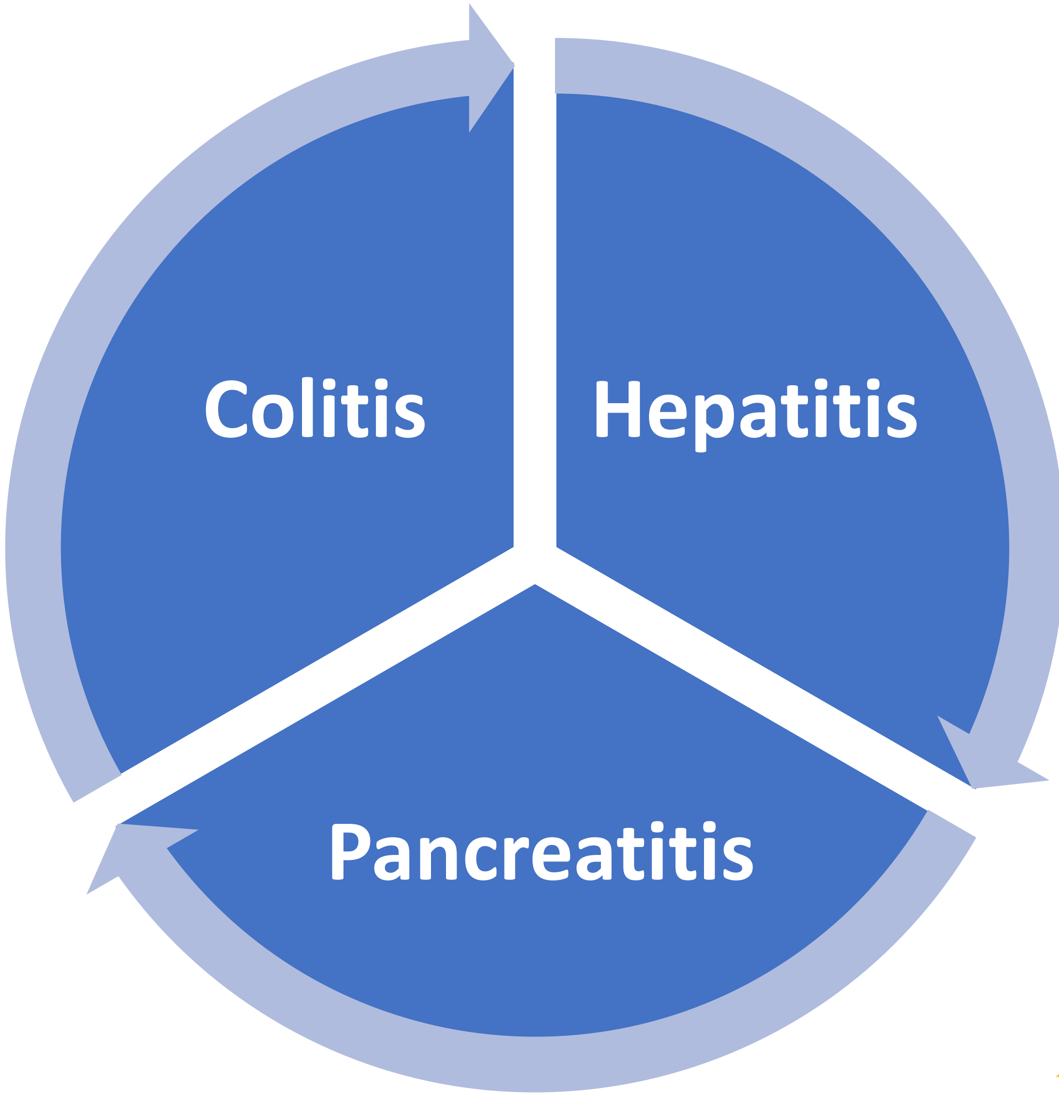
- Mild (G1)
  - Topical emollient and moderate potency topical steroid
  - Consider oral antihistamine if pruritus present
- Moderate (G2)
  - Topical emollient and moderate to high potency topical steroid
  - If no response after 1 week consider prednisone 0.5 mg/kg/day
  - Consider oral antihistamine if pruritus present
  - Consider dermatology consult
- Severe (G3)
  - Hold immunotherapy
  - High potency topical steroids
  - Prednisone/IV methylprednisolone 0.5-1 mg/kg/day (increase to 2 mg/kg/day if no response
  - Urgent dermatology consult, consider biopsy and inpatient care

Pruritus Management

- Grade 1-3
  - Oral antihistamines
  - Whole body moisturization with non-fragranced moisturizer
- Mild (G1)
  - Treatment with moderate potency topical steroids to affected areas for localized pruritus
  - Consider over-the-counter topical anesthetic/antiitch creams
- Moderate (G2)
  - Hold immunotherapy, if symptoms improve with intensified antipruritic therapy, resume immunotherapy
  - Consider gabapentinoids (gabapentin, pregabalin)
  - Treatment with high potency topical steroids to affected areas
  - Consider narrow-band UVB phototherapy for refractory cases
  - Dermatology consultation
- Severe (G3)
  - Hold immunotherapy
  - Prednisone/IV methylprednisolone 0.5–1 mg/kg/day
  - Consider gabapentinoids (gabapentin, pregabalin) If no response in 1 month, consider dupilumab, omalizumab, or narrow-band UVB phototherapy
  - Urgent dermatology consultation

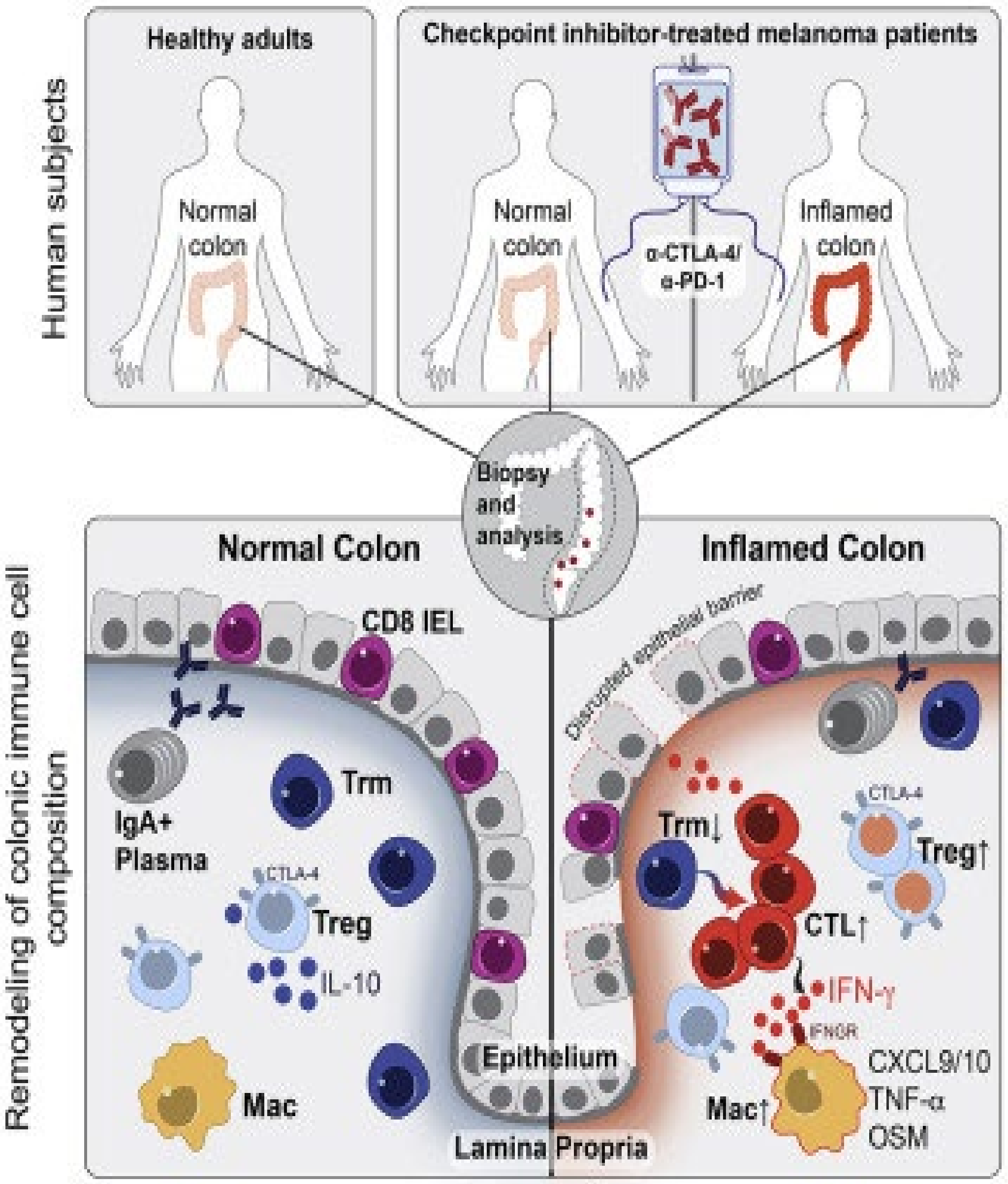
POEM

Gastrointestinal



Colitis Management

- Incidence
  - Diarrhea ~20%
  - Colitis 1-2%
- Assessment
  - Consider stool evaluation to rule out infectious etiology
  - Based on institutional availability, consider fecal lactoferrin/calprotectin
  - Consider abdominal/pelvic CT with contrast
  - Consider GI consultation Colonoscopy or flexible sigmoidoscopy ± esophagogastroduodenoscopy (EGD) with biopsy (recommend for G3-4)



Colitis Management (cont.)

- Mild (G1)
  - Consider holding immunotherapy
  - Consider loperamide or diphenoxylate/atropine for 2–3 days as an adjunct for symptom relief
    - Infectious workup if no improvement
    - Discontinue antidiarrheals if diarrhea persists, to assess response to immunosuppressive therapy
  - Hydration
  - Close monitoring
  - If persistent or progressive symptoms, check lactoferrin/calprotectin
    - If positive, treat as G2
    - If negative and no infection, continue G1 management and consider adding mesalamine and/or cholestyramine as needed
  - Dietary modifications
- Moderate (G2)
  - Hold immunotherapy
  - For pathologically confirmed microscopic colitis, consider budesonide 9 mg daily prior to systemic steroids
  - Prednisone/IV methylprednisolone (1–2 mg/kg/day)
  - If no response to oral steroids after 3 days, consider IV steroids, consider adding infliximab or vedolizumab,
    - Consider tofacitinib or ustekinumab for infliximab and/or vedolizumab-refractory colitis

Colitis Management (cont.)

- Severe (G3-4)
  - G3: If using combination IO therapy, discontinue current therapy; consider resuming anti-PD-1/PD-L1 monotherapy after resolution of toxicity
  - G4: Discontinue immunotherapy agent responsible for toxicity
  - Consider inpatient care for provision of supportive care
  - IV methylprednisolone (1–2 mg/kg/day)
    - If no response in 1–2 days or unable to transition to oral steroids, additional immunosuppression required. Continue steroids and strongly consider adding infliximab or vedolizumab
      - Consider tofacitinib or ustekinumab for infliximab and/or vedolizumab-refractory colitis

POEM

Hepatitis

- Incidence
  - 1-17% various by immunotherapy regimen
- Assessment
  - Elevated AST/ALT/Tbili
  - Rule out viral etiology, disease-related hepatic dysfunction, other drug-induced ALT/AST elevations
  - Consider abdominal ultrasound
    - Contrast-enhanced CT/MRI may be considered if no response to treatment or if there is a cholestatic pattern of liver tests
  - Rule out alternative causes of drug induced liver injury
    - Limit/discontinue hepatotoxic medications (assess acetaminophen, dietary supplement, and alcohol use)

POEM

Hepatitis Management (Elevated AST/ALT) G1 or G2

- G1 (<3x ULN)
  - Consider holding immunotherapy for concerning lab value trend
  - Perform liver tests with increased frequency
- G2 (3-5x ULN)
  - Hold immunotherapy
  - Perform liver tests every 3–5 days
  - Monitor PT/INR periodically
  - Consider prednisone 0.5–1 mg/kg/day
    - If liver tests suggest worsening or no improvement after 3–7 days, treat as G3
  - Check creatinine phosphokinase (CPK) and aldolase to rule out myositis

Hepatitis Management G3 or G4

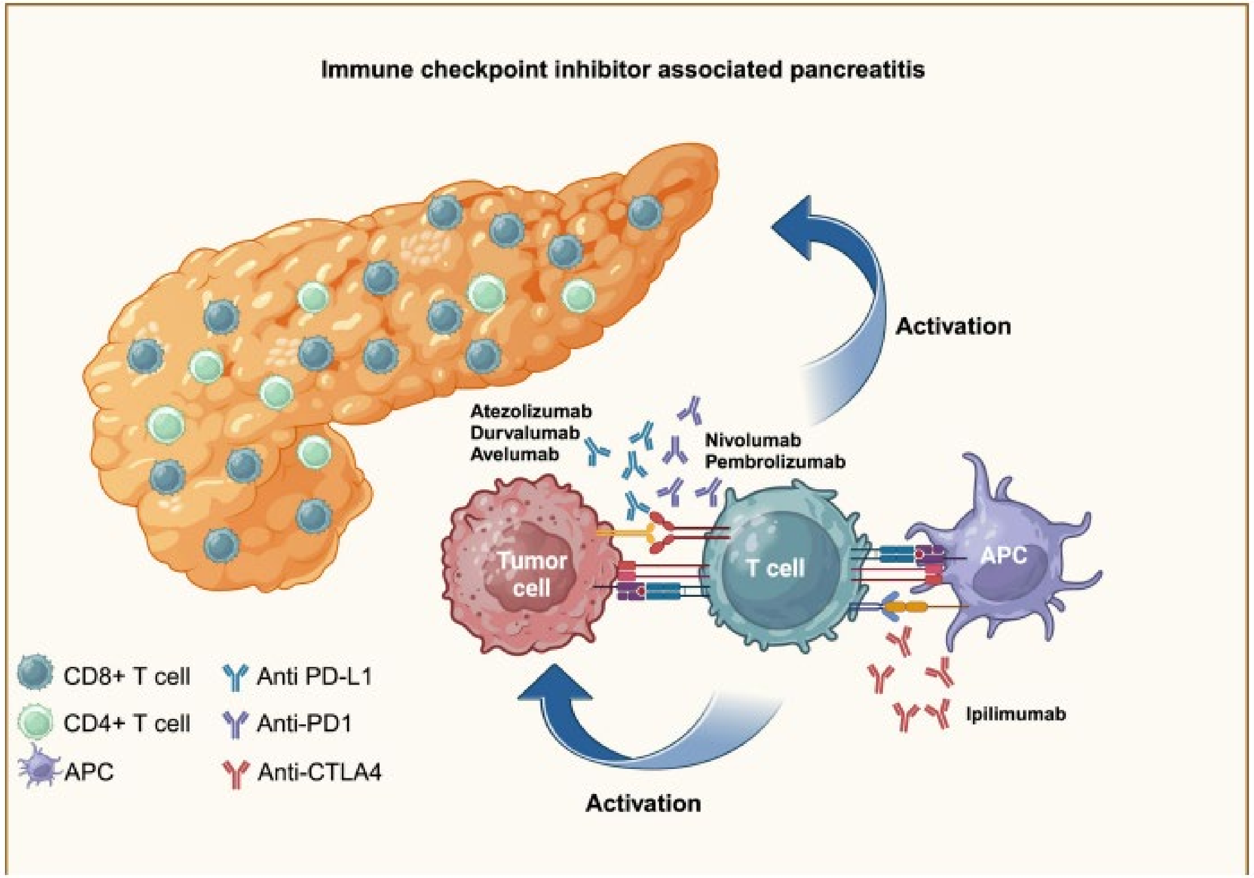
- G3 and G4
  - Recommend GI/hepatology evaluation
  - Synthetic LFTs PT/INR, bilirubin, and serum albumin levels
  - Consider diagnostic parenchymal liver biopsy if no contraindications
    - Reserve for atypical (cholestatic) clinical/biochemical presentation or when there is no response to standard therapy
  - Monitor PT/INR periodically

- G3 (>5-20x ULN)
  - hold immunotherapyh
  - Initiate prednisone/IV methylprednisolone 1 mg/kg/day
    - If no improvement after 1–2 days, consider adding steroid-sparing immunosuppressive therapy
  - Consider inpatient care, particularly if synthetic hepatic dysfunction is observed
  - Perform liver tests every 1–5 days depending on magnitude and rate of change
- G4 (>20x ULN)
  - Discontinue immunotherapy
  - Initiate prednisone/IV methylprednisolone 1 mg/kg/day
    - If no improvement after 1–2 days, consider adding steroid-sparing immunosuppressive therapy
  - Inpatient care, particularly if synthetic hepatic dysfunction is observed
  - Perform liver tests every 1–3 days

POEM

Pancreatitis

- Incidence
  - Less than 2%
- Assessment
  - Assess for signs/symptoms of pancreatitis
  - Abdominal CT with contrast
  - Consider MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT
  - Assess for other causes (ie, alcohol use, biliary)



Pancreatitis Management

- Mild (G2)
  - Consider holding immunotherapy
  - Consider gastroenterology referral
  - Consider IV hydration
  - Manage as per elevation in amylase/lipase (asymptomatic)
- Moderate (G3)
  - Hold immunotherapy
  - Gastroenterology referral
  - IV hydration
  - Prednisone/IV methylprednisolone 0.5–1 mg/kg/day
- Severe (G4)
  - Permanently discontinue immunotherapy
  - Gastroenterology referral
  - IV hydration
  - Prednisone/IV methylprednisolone 1–2 mg/kg/day

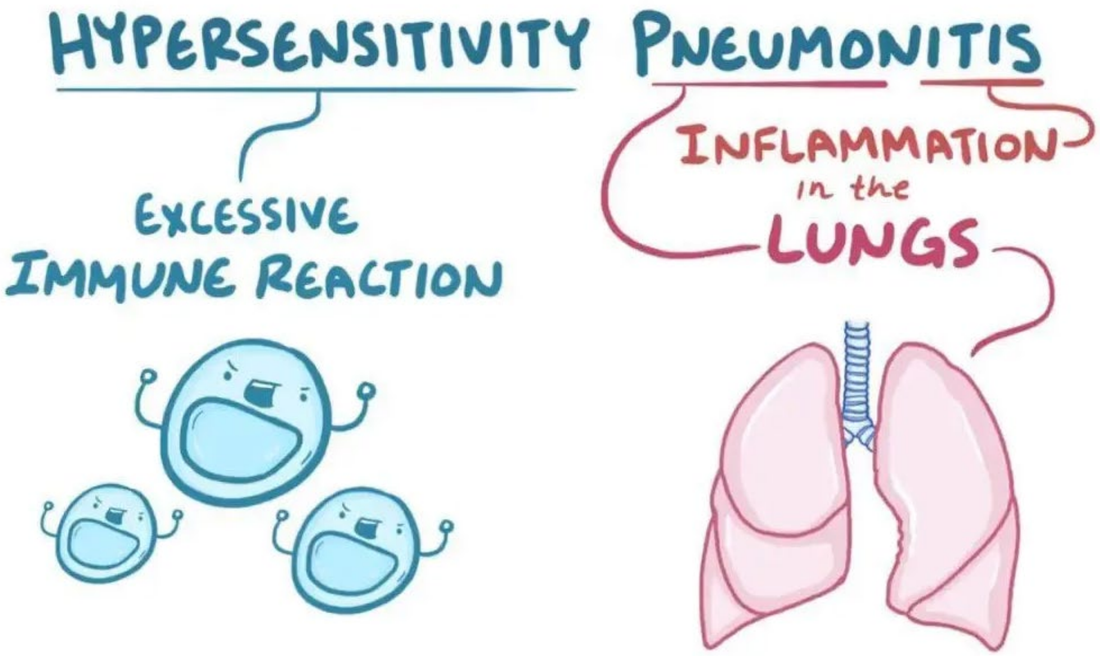
POEM

Pneumonitis

- Incidence
  - 2.5-4%
  - More frequent if prior radiation therapy in patients with NSCLC
- Assessment
  - Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging)
  - Symptoms may include dry cough, shortness of breath, fever, chest pain, and increased oxygen requirement
  - The imaging features of pneumonitis are known to be variable and may include ground-glass opacities, organizing pneumonia, hypersensitivity, reticulonodular changes, or a mixture of all these appearances.

Pneumonitis Management

- Mild (G1)
  - Consider holding immunotherapy
  - Reassess in 1–2 weeks
    - H&P
    - Pulse oximetry (resting and with ambulation)
  - Consider chest CT with contrast
    - Consider repeat chest CT in 4–6 weeks or as clinically indicated if patient develops symptoms



Pneumonitis Management

- Moderate (G2)
    - Hold immunotherapy
    - Consider pulmonary consultation
    - Minimally invasive evaluation
        - Consider infectious workup
            - Nasal swab for potential viral pathogens
            - Sputum culture (including bacterial, fungal, and acid-fast bacilli [AFB]), blood culture, and urine antigen test (pneumococcus, legionella)
        - Chest CT with contrast and repeat chest CT in 3–4 weeks
    - Invasive evaluation
        - Consider bronchoscopy with BAL (send for institutional immunocompromised panel) and consider transbronchial lung biopsy if clinically feasible to rule out progressive malignancy or fungal infections
    - Consider empiric broad-spectrum antibiotics (including coverage for atypical pathogens) if infection has not yet been fully excluded
    - Prednisone/IV methylprednisolone 1–2 mg/kg/day
    - Monitor every 3–7 days with
        - H&P and Pulse oximetry (resting and with ambulation)
    - If no improvement after 48–72 hours of steroids, treat as grade 3

Pneumonitis Management

- Severe (G3-4)
  - Discontinue immunotherapy
  - Inpatient care
  - Pulmonary and infectious disease consultation
  - Minimally invasive evaluation Infectious workup:
    - Consider that the patient may be immunocompromised
      - Nasal swab for potential viral pathogens
      - Sputum culture (including bacterial, fungal, and AFB), blood culture, and urine antigen test (pneumococcus, legionella)
      - Consider cardiac evaluation to exclude cardiac causes for clinical presentation
  - Invasive evaluation
    - Bronchoscopy with BAL (send for institutional immunocompromised panel) if feasible to rule out infection and malignant lung infiltration and consider transbronchial lung biopsy if feasible and clinically indicated
  - Consider empiric broad-spectrum antibiotics (including coverage for atypical pathogens) if infection has not yet been fully excluded
  - IV methylprednisolone 1–2 mg/kg/day. Assess response within 48 hours and plan taper over ≥6 weeks
  - Consider adding any of the following if no improvement after 48 hours:
    - IV infliximab 5 mg/kg, a second dose may be repeated 14 days later at the discretion of the treating provider
    - IVIG
    - Mycophenolate mofetil 1–1.5 g BID then taper in consultation with pulmonary service

Endocrinopathies

Incidence can vary

- Approximately 10% of all ICI-treated patient have clinically relevant endocrine irAE

Endocrine irAE Evaluation

- Comprehensive metabolic panel
- Thyroid stimulation hormone (TSH)
- Free thyroxine (FT4)
- 8 AM cortisol and ACTH
- Thyroid-specific autoantibodies
- Thyroid peroxidase (TPOAb) and Thyroglobulin (TgAb)
- Hemoglobin A1C

More commonly presents as a biphasic

Thyroiditis	Hypophysitis
Adrenal Insufficiency	Type 1 Diabetes

Wright J, et al. Nat Rev Clin Oncol. 2021

Endocrinopathies Progression

Endocrine Management

- Treatable, but often irreversible
- Focus on replacement of deficiency – Hormone replacement
- Can require urgent management – Adrenal crisis and diabetic ketoacidosis

Chronic management

- Collaboration with endocrinologists
- Diagnosis challenging due to often nonspecific signs and symptoms
- Continuation of ICI if able

POEM

Wright J, et al. Nat Rev Clin Oncol. 2021

Endocrinopathy Management

Initial

- Continue ICI if symptomatic utilize B-blocker
  - Propranolol and atenolol

Persistent Thyrotoxicosis

- Thyroid Hormone replacement
  - Young/Healthy: Levothyroxine 1.1-1.6 mcg/kg/day
  - Special populations (Elderly/comorbidities): 25 to 50 mcg daily
- Monitoring
  - TSH every 6-8 weeks and titrate to euthyroid and monitor FT4

POEM

Wright J, et al. Nat Rev Clin Oncol. 2021

Rare IRAE

Type 1 Diabetes

- 1%

Myocarditis

- 0.04-1.14%

Ocular toxicities

- 2.8-4.3%

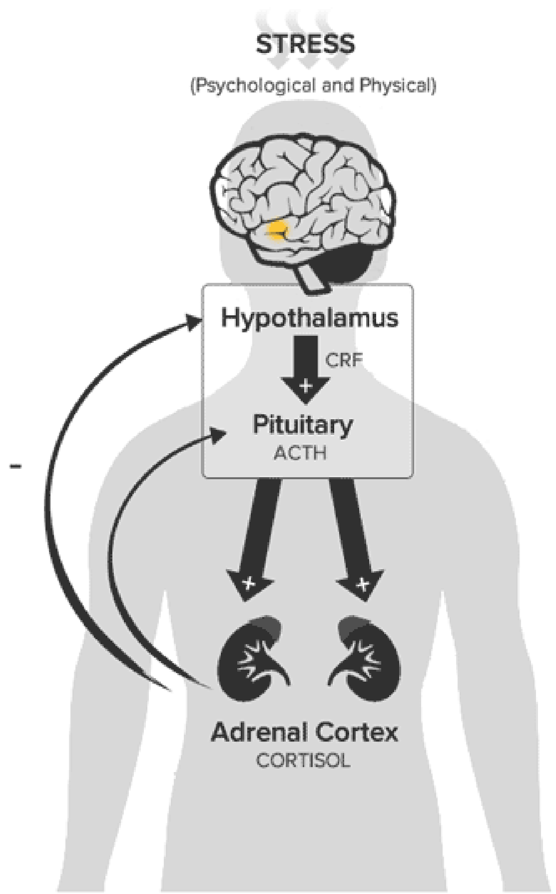
Take Away Points

- Majority mild, but can be severe or fatal
- Any organ(s) or tissue(s)
- Anytime during or after treatment completion
- Early identification and management is crucial

irAE Supportive Care

Steroids

- Corticosteroids
  - Immunomodulatory agents
  - Alteration of HPA axis
  - Tapering to prevent adrenal insufficiency
- Guidelines
  - Treatment until symptoms improve to grade ≤ 1
  - Then taper steroids over 4-6 weeks
    - Can differ based on irAE



Aldea M, et al. Eur J Cancer. 2020

Supportive Care

- Prevention of infectious diseases
  - Confirm no active infectious process
    - Bacterial, viral, fungal, or parasitic infection
  - Prolonged treatment might necessitate the use of Bactrim or Acyclovir
- Change in electrolytes
  - Increase renal potassium excretion
    - Monitor for hypokalemia and supplement with potassium as needed
- Blood glucose monitoring
  - Evaluate baseline blood glucose
  - Coordinate with primary care provider in those with active diabetes

POEM

Aldea M, et al. Eur J Cancer. 2020

Supportive Care Conc.

- Mood Disorders
  - Psychostimulatory effects leading to irritability and depression
- Adrenal Insufficiency
  - Inhibition of endogenous hormonal secretion
    - Monitor for symptoms of fatigue, low blood pressure, abdominal pain, ion disorders
- Skeletal, Muscle and others Miscellaneous events
  - Screening for patients at risk for osteoporosis
    - Those on long terms steroids
  - Muscle weakness
  - Stress ulcers
    - Proton Pump inhibitor

POEM

Aldea M, et al. Eur J Cancer. 2020

Steroid Tapering

- Classification and physiologic effects of steroids
  - Potency
  - Mineralocorticoid activity
  - Duration of action
- Taper dose in 10 mg increments every 3 to 4 day based on total taper duration
  - Once 20 mg/day is reach reassess patient for symptoms and appropriate response
    - Complete taper in 2.5 to 5 mg increments

Drug	Biological half-life (hours)	Anti-inflammatory potency[1]	Equivalent potency[1]	Mineral corticosteroid activity
Hydrocortisone	8–12	1	20 mg	1
Prednisone	12–36	4	5 mg	0.8
Prednisolone	12–36	4	5 mg	0.8
Methylprednisolone	12–36	5	4 mg	0.5
Betamethasone	36–54	25–30	0.75 mg	0
Dexamethasone	36–54	25–30	0.75 mg	0

Aldea M, et al. Eur J Cancer. 2020

Patient Follow-up

- Implementation of a pharmacy driven education and monitoring service
  - Pharmacist lead education for all patient starting immunotherapy
  - Follow-up phone calls in between each treatment to evaluate toxicity
  - Weekly follow-up calls during steroid initiation and tapering
    - Allowed for collaboration between providers and early recognition of irAE
  - The pharmacist group saw less hospitalizations (24% vs 41%, p=0.009) less ED visits (28% vs 46%, p=0.005)
    - Within the first 6 months of therapy for cancer or treatment related toxicity

Take Away Points

- irAE should begin to improve within 2-3 days after starting high-dose steroids
- Evaluate supportive care needs based on steroid dose and duration
- Coordinate appropriate patient follow-up and prompt escalation of care

POEM

Patient Resources and Equity of Care

Disparities in Access and Outcomes

- Gap within health care prevail across the cancer care continuum

Prevention → Incidence → Diagnosis → Staging → Treatment

  - Socioeconomic characteristics and individual demographic have historically been the focus, but are not readily modifiable

- Interventions within the providers, organizations, and social policies are often most impactful

Osarogiagbon R, et al. Am Soc Clin Oncol Educ Book. 2021

Patient Level

Lack of data on minority groups in clinical trials

- Educate patients, caregivers, and their influencing network on the value of clinical trials

Language barriers

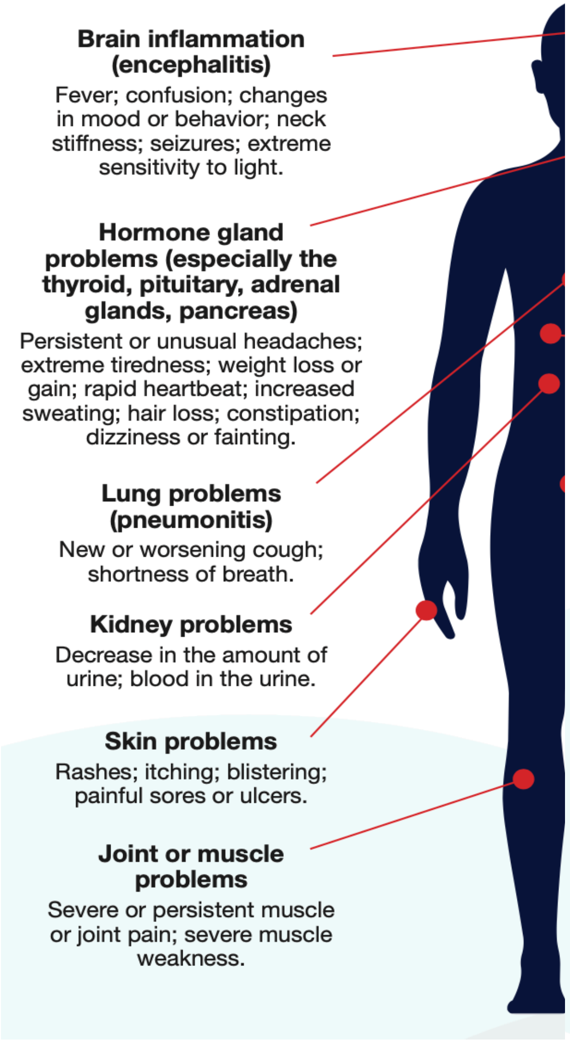
- Provider interpreter services and education materials in multiple languages

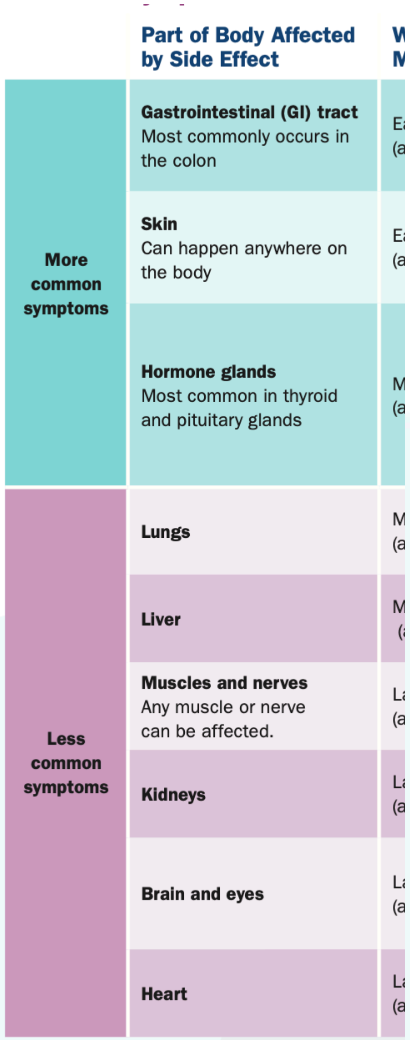
Lack of adequate health coverage

- Safety nets for low-income groups

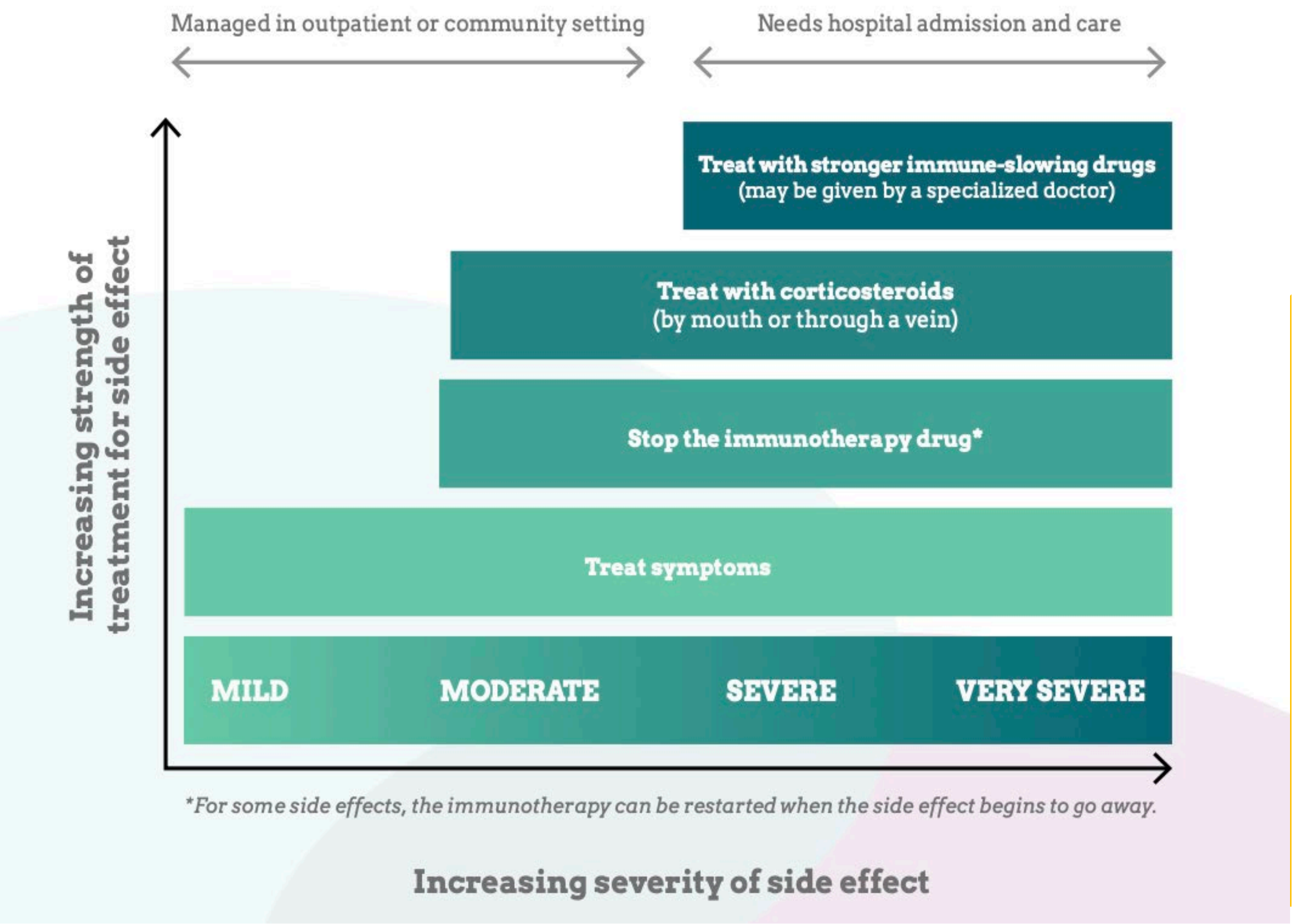
POEM

Patient Level Resources





	Part of Body Affected by Side Effect	W M
More common symptoms	**Gastrointestinal (GI) tract** Most commonly occurs in the colon	Ea (a
	Skin Can happen anywhere on the body	Ea (a
	Hormone glands Most common in thyroid and pituitary glands	M (a
Less common symptoms	**Lungs**	M (a
	Liver	M (a
	Muscles and nerves Any muscle or nerve can be affected.	La (a
	Kidneys	La (a
	Brain and eyes	La (a
	Heart	La (a



Provider Level

Restraints on new technology for diagnostic

- Effect education opportunities and medical literacy focused on the care of the minority

Implicit bias

- Educational program and bias avoidance

Disinclination

- Incentivize providers related to opportunities

Health Care System-Level

Unfavorable geographic location

- Facilitate transportation and expand resources to rural areas

Absence of infrastructure

- Multidisciplinary team

Societal/Policy Level

High cost of immunotherapy

- Facilitate patient support programs
- Lower cost of drugs
- Policy changes at levels of legislatures and executive branches

Unemployed and underemployed

- Expansion of government-sponsored covered
- Programs to help patient navigate insurance

Summary

- IO reinvigorate antitumor immune responses
- Wide range of toxicities that vary based on CTCAE
- Steroids tapered over an extended period can lead to multiple supportive care needs
- Multiple disparities within oncology leading to poor outcomes

POEM

POEM

Recognition and Management of Immunotherapy Toxicity

Colton Zwart PharmD, BCOP
Mark Wagner PharmD, BCOP