

Toxicity Management

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Disclosures

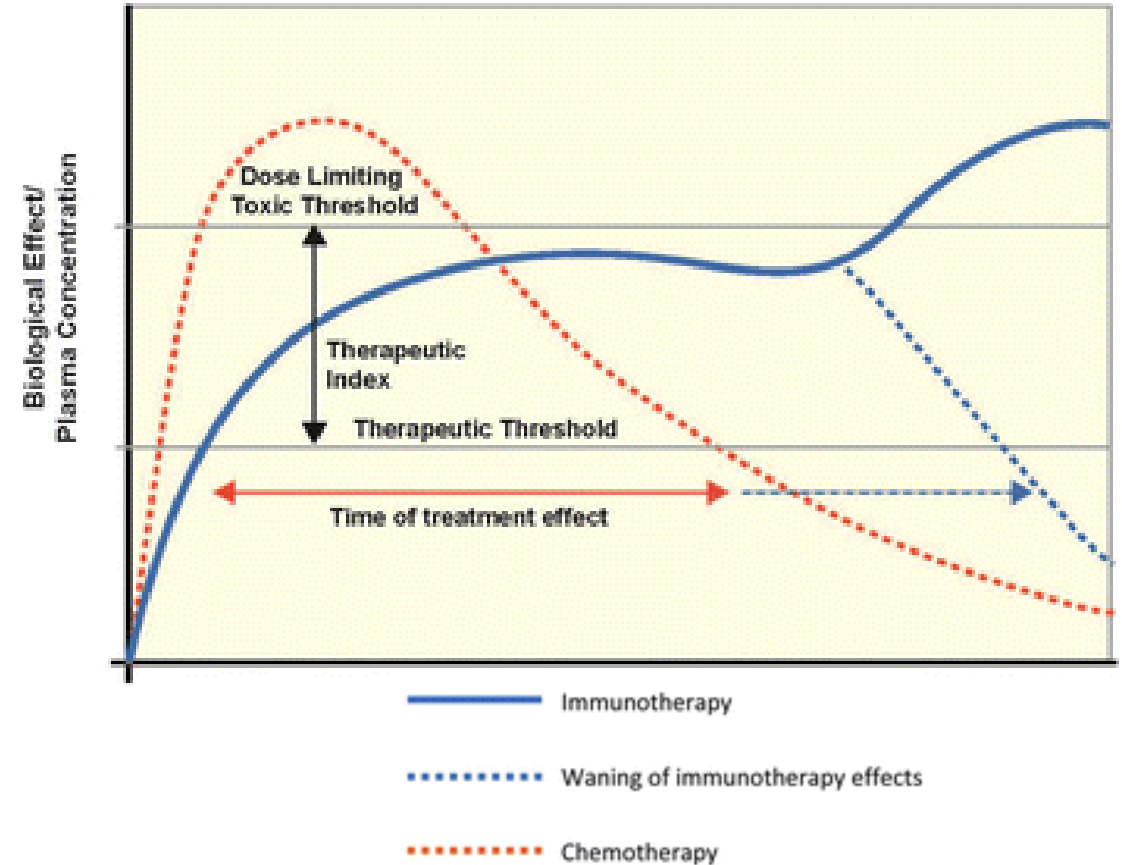
- Consulting Fees: BMS, Merck, Array, Regeneron, Novartis
- I will be discussing non-FDA approved indications during my presentation.

Outline

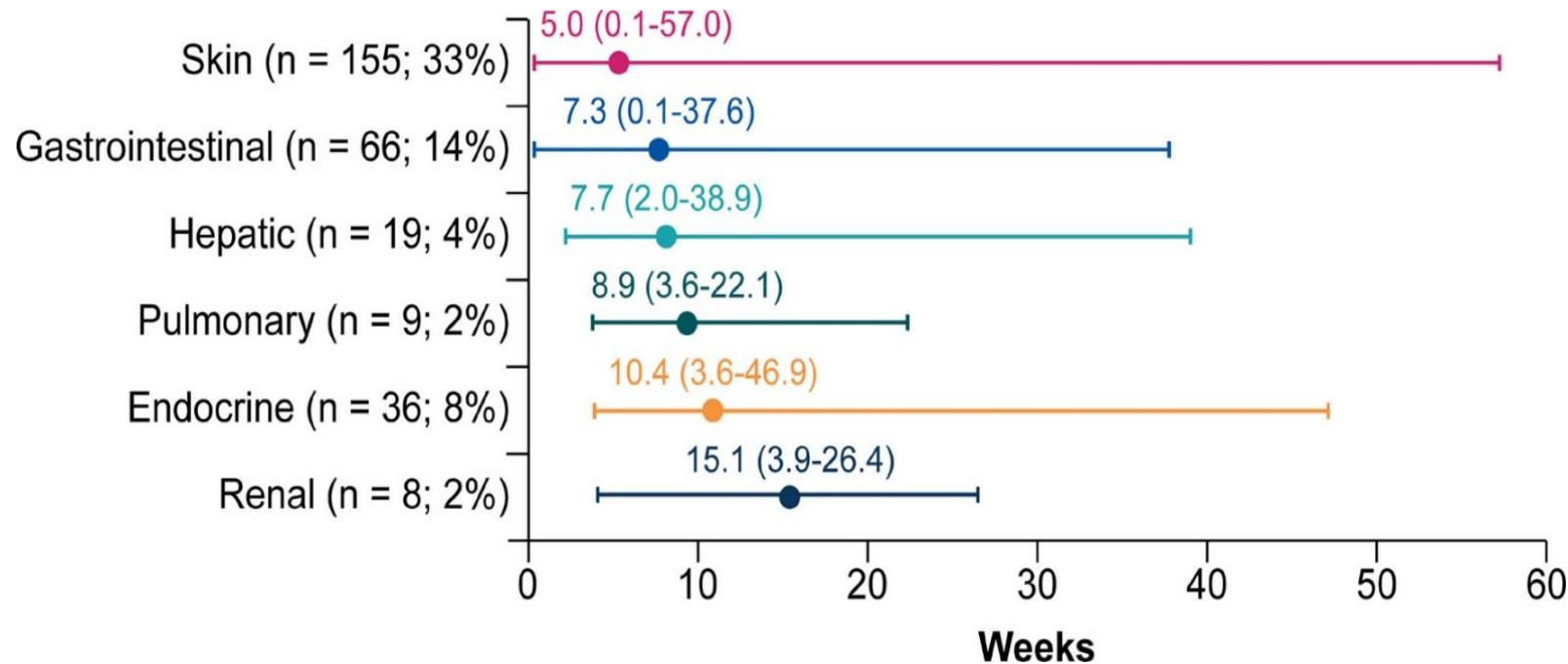
- Incidence, onset and severity grading
- Immune checkpoint inhibitors
 - Common adverse events
 - Rare but serious adverse events
 - Impact of irAEs on cancer outcomes
- Cellular therapies
 - Adverse events and management
- Immunotherapy in special patient populations
- Case studies

Immune-related adverse events (irAEs)

- Immune checkpoint inhibitor (ICI) toxicities often have delayed onset and prolonged duration relative to cytotoxic chemotherapy
- Toxicities result from activation of the immune response, and can mimic a number of autoimmune medical conditions



Onset of irAEs



- Can be days to months after therapy initiation
- May occur even after treatment is discontinued
- Onset may be earlier with combination treatments
- Important to identify patients who are currently **OR** previously on ICI treatment!

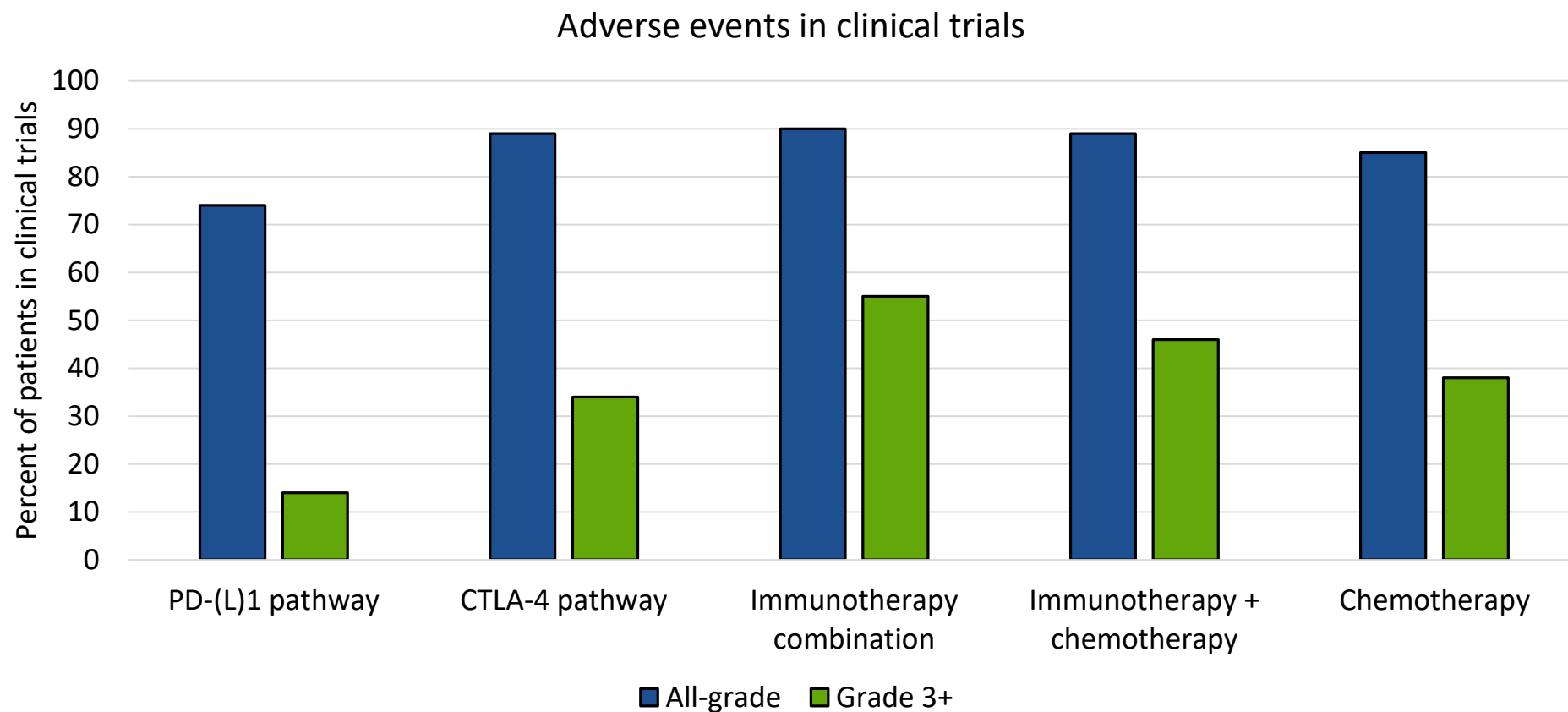
Common terminology criteria for adverse events

CTCAE Grade	Clinical description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; 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 adverse event

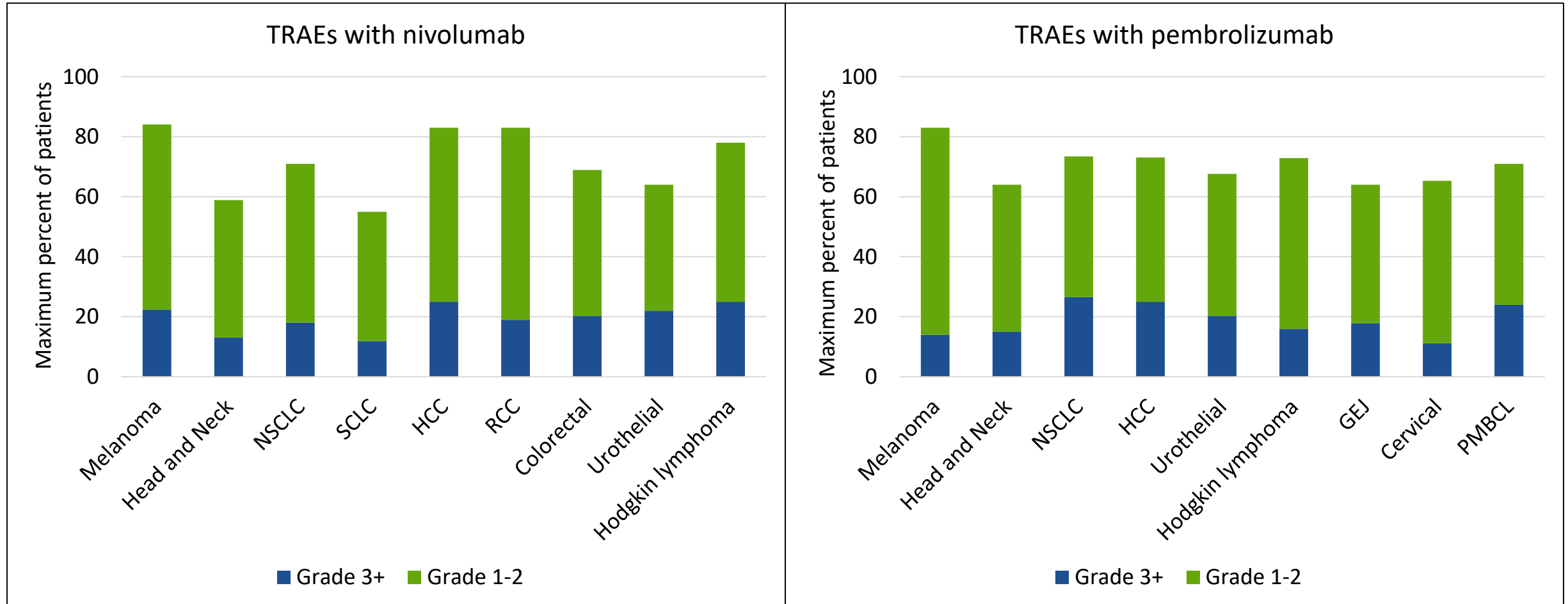
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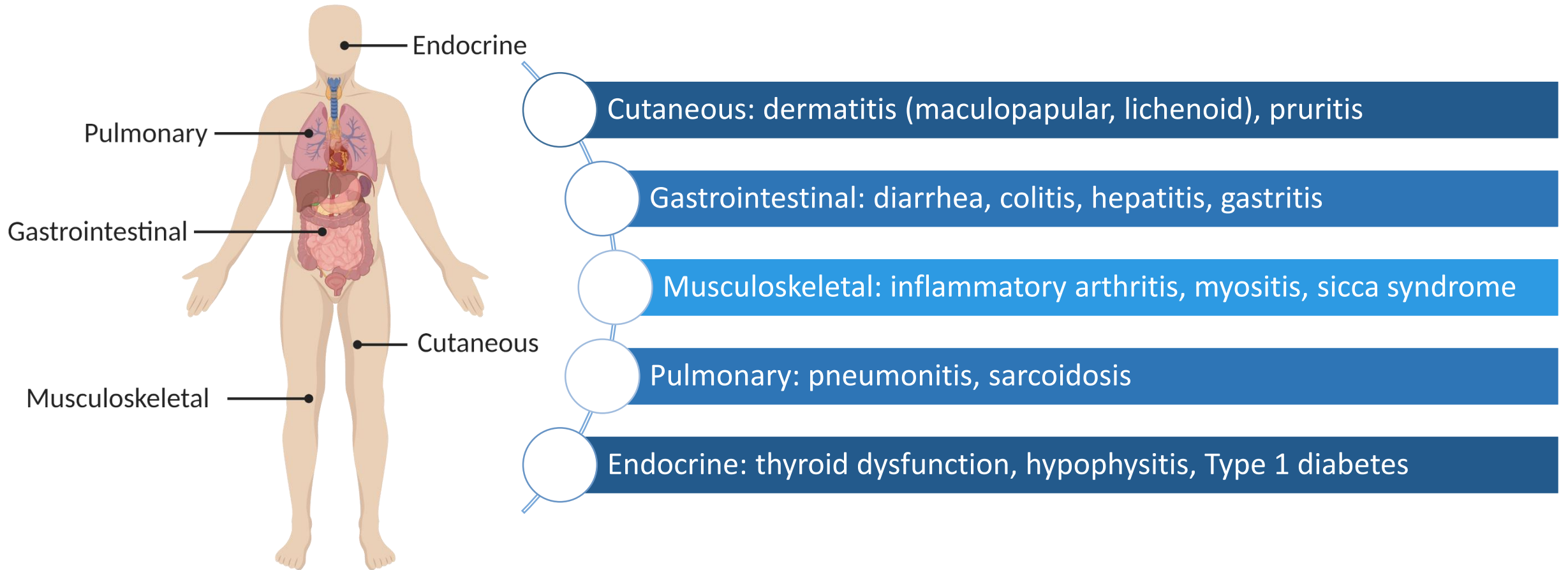
Toxicity with immune checkpoint inhibitors



Toxicity with immune checkpoint inhibitors

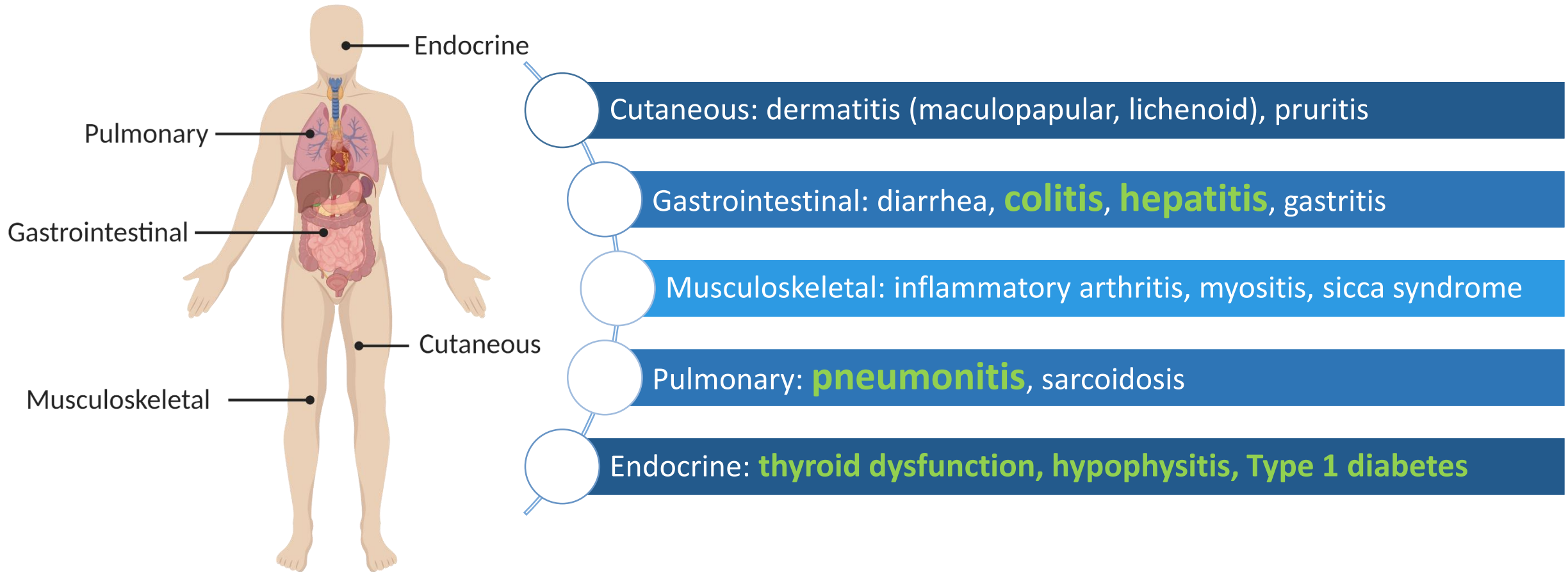


Common irAEs with ICIs



Puzanov and Diab, JITC 2017.
 NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

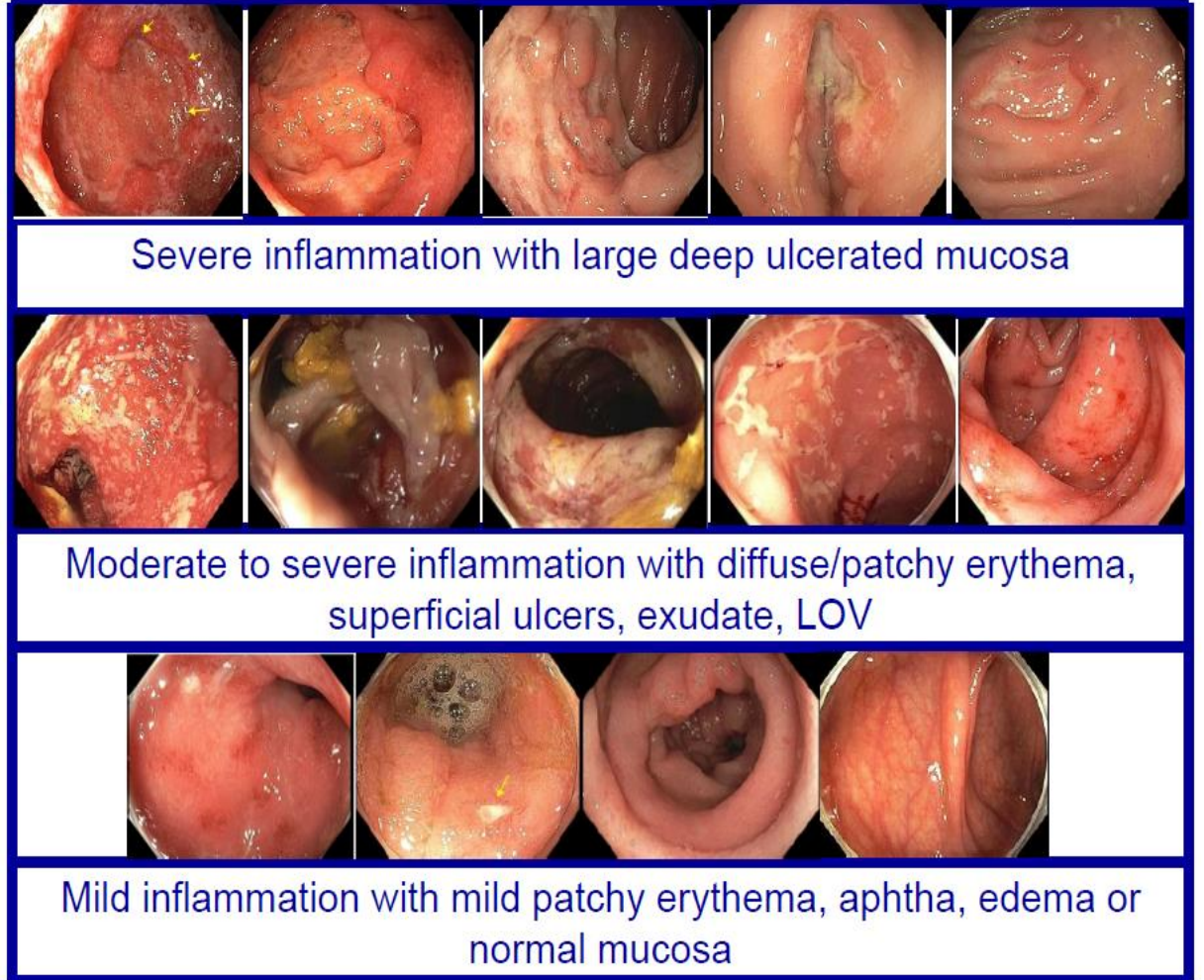
Common irAEs with ICIs



Puzanov and Diab, JITC 2017.
 NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

Diarrhea/Colitis

- Diagnostic evaluation
 - Rule out alternative diagnosis: C.difficile, other GI infections
 - Diarrhea while on ICIs should prompt suspicion of immune-mediated colitis
 - Consider testing with colonoscopy
- Management
 - Low threshold for starting corticosteroids given risk for bowel perforation; typical dose is prednisone 1-2 mg/kg/day (or equivalent)
 - No benefit for corticosteroid pre-treatment (budesonide)
 - Colitis that is slow to improve/refractory to steroids: treat with anti-TNF
 - Infliximab 5mg/kg q14 days (1-3 doses typically required)






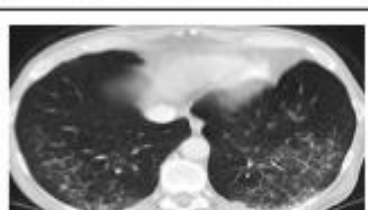

Hepatitis

- Hepatitis is often asymptomatic, but can lead to treatment discontinuation
- Elevations in AST and/or ALT
- Typically 6-14 weeks after treatment

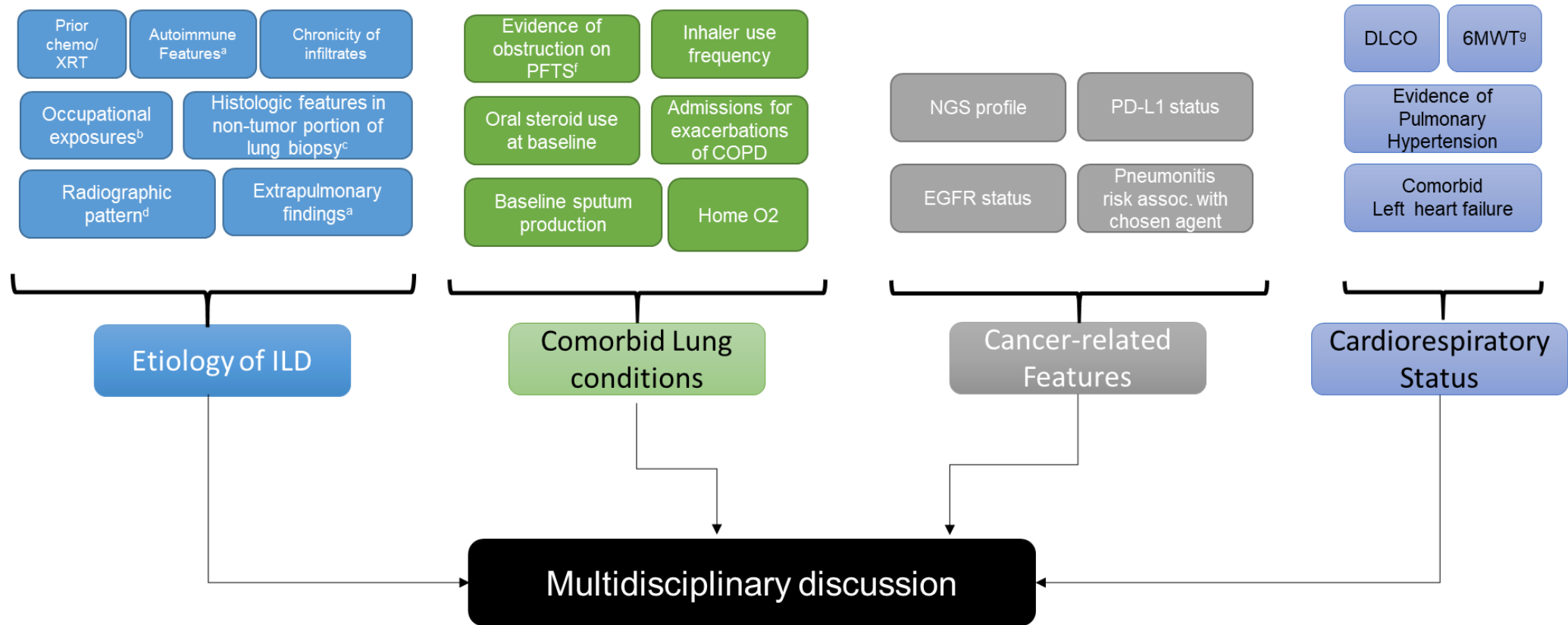
Grade 1	Grade 2	Grade 3	Grade 4
<ul style="list-style-type: none"> • Liver function tests weekly 	<ul style="list-style-type: none"> • Liver function tests weekly • Corticosteroids 0.5 mg/kg/day 	<ul style="list-style-type: none"> • Liver function tests every 1-2 days • Withhold ICIs • Corticosteroids 1-2 mg/kg/day 	<ul style="list-style-type: none"> • Liver function tests every 1-2 days • Discontinue ICIs • Corticosteroids 1-2 mg/kg/day
<ul style="list-style-type: none"> • Diagnostic testing includes iron studies, autoimmune hepatitis panel and viral hepatitis panel • Taper steroids over 4-6 weeks once LFTs revert to grade ≤ 1 • If LFTs do not improve or recur after taper, may administer azathioprine or mycophenolate mofetil • Infliximab should not be used, given risk for hepatotoxicity 			

Pneumonitis

- Diagnostic evaluation
 - Symptoms: persistent dry cough, dyspnea on exertion
 - Rule out alternative diagnosis: infection, malignancy
 - Computed tomography
- Management
 - Can escalate quickly, so prompt symptom reporting is important
 - Withhold drug for low-grade
 - Corticosteroids with close follow-up
 - Additional immunosuppression may be needed

Radiologic Subtypes	Representative Image
Cryptogenic-Organizing Pneumonia-like (COP-like) (n=5, 19%)	
Ground Glass Opacifications (GGO) (n=10, 37%)	
Interstitial Type (n=6, 22%)	
Hypersensitivity Type (n=2, 7%)	
Pneumonitis Not-Otherwise Specified (n=4, 15%)	

Discerning pneumonitis from other diagnoses



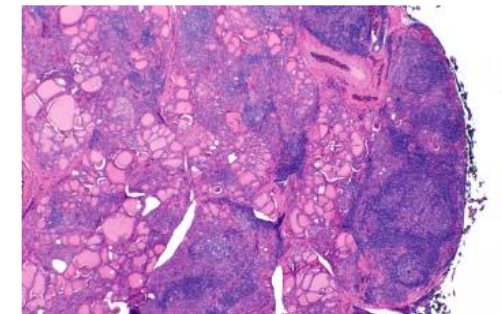
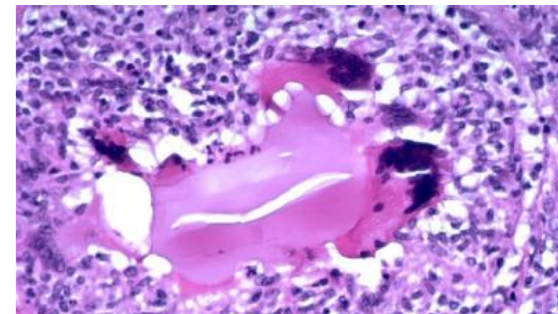
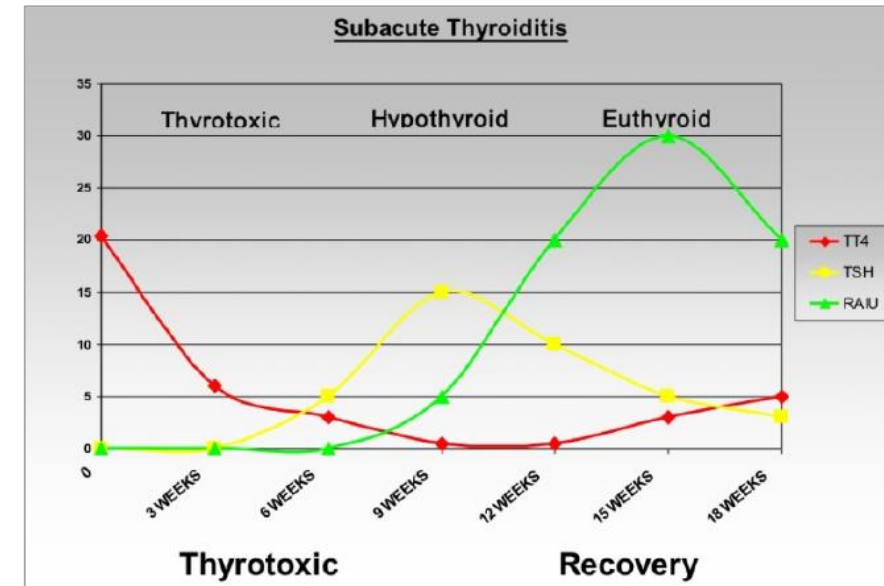
^a Rashes (Gottron's papules, Heliotrope rash), evidence of synovitis, family history of RA/SLE, history of dry eyes/mouth, Raynaud's phenomenon

^b Steelworkers, farmers, exposures to heavy metals, organic fumes, dusts, birds, etc. ^c such as poorly-formed granulomas, lymphocytic aggregates

^d NSIP vs UIP-pattern, evidence of air-trapping, lobar dominance. ^f may present as complex obstruction (TLCpp – FVCpp > 15).

Thyroid dysfunction

- Hyperthyroid Phase
 - Leaky thyroid, variable symptoms
 - 2-6 weeks duration
- Hypothyroidism Phase
 - Recovery of depleted gland
 - Symptoms: fatigue, hair and skin changes, fluid retention, constipation
 - Transient or permanent
- Management
 - Hormone replacement
 - Endocrinology consultation
 - ICI does not need to be held if this is the only irAE

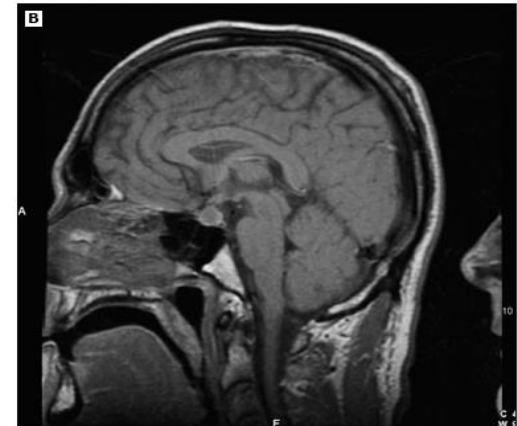


Hypophysitis

- Diagnostic workup
 - Symptoms:
 - Due to increased intracranial pressure: headache, nausea, blurry vision
 - Due to hormonal deficit: fatigue, weakness, hypotension
 - Lab tests: ACTH, TSH, FSH, LH, GH, prolactin
 - Differentiate from primary adrenal insufficiency and hypothyroidism by lab results
 - Enhancement/swelling of pituitary on imaging
- Management
 - Hormone supplementation



06/30/04 - Baseline (4.5 mm)



12/03/04 - Headache/fatigue (10.8 mm)

Pre-treatment screening recommended by SITC

- Patient History
 - Autoimmune, infectious, endocrine, organ-specific diseases
 - Baseline bowel habits
- Dermatologic
 - Full skin and mucosal exam
- Pulmonary
 - Baseline O₂ saturation
- Cardiovascular
 - ECG
 - Troponin I or T
- Blood tests
 - CBC with diff
 - CMP
 - TSH and free T4
 - HbA1c
 - Total CK
 - Fasting lipid profile
 - Infectious disease screen:
 - Hepatitis serologies
 - CMV antibody
 - HIV antibody and antigen (p24)
 - TB testing (T-spot, quantiferon gold)

Potential additional screening for high-risk patients

- Endocrine tests
 - 8 am cortisol and ACTH
- Cardiac tests
 - Brain natriuretic peptide (BNP) or N-terminal pro B-type natriuretic peptide (NT pro-BNP)
- Pulmonary tests
 - PFTs
 - 6MWT

Approach to Treatment

- Treatment approach is guided by grading of specific toxicity
- Resources for grading:
 - SITC Toxicity Management Working Group
 - Common Terminology Criteria for Adverse Events
 - National Comprehensive Cancer Network
- 1st line for **MOST** irAEs is systemic high-dose corticosteroids
 - Endocrine toxicities managed with hormone replacement
 - Some grade 1-2 irAEs may respond to topical steroids (dermatologic, ophthalmologic)
- OTC drugs may not be appropriate for managing symptoms
 - i.e. loperamide for colitis may result in bowel perforation and mask underlying symptoms

General corticosteroid management

Grade of irAE	Corticosteroid Management	Additional Notes
1	Usually not indicated	Continue immunotherapy
2	<ul style="list-style-type: none"> Start prednisone 0.5-1 mg/kg/day (or equivalent dose of IV methylprednisolone) If no improvement in 2-3 days, increase dose to 2 mg/kg/day Once improved to ≤grade 1, start 4-6 week steroid taper 	<ul style="list-style-type: none"> Hold immunotherapy during corticosteroid use Continue immunotherapy once resolved to ≤grade 1 and off corticosteroids Start proton pump inhibitor for GI prophylaxis

General corticosteroid management

Grade of irAE	Corticosteroid Management	Additional Notes
3	<ul style="list-style-type: none"> Start prednisone 1-2 mg/kg/day (or equivalent dose of IV methylprednisolone) If no improvement in 2–3 days, ADD additional immunosuppressant Once improved to \leq grade 1, start 4–6-week steroid taper 	<ul style="list-style-type: none"> Hold immunotherapy; if unable to taper steroids over 4-6 weeks, discontinue immunotherapy Start proton pump inhibitor for GI prophylaxis Add PJP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)
4		<ul style="list-style-type: none"> Discontinue immunotherapy Start proton pump inhibitor for GI prophylaxis Add PJP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)

Additional immunosuppressives for specific toxicities

Colitis

Infliximab

anti-TNF- α antibody

Dose: 5 mg/kg; 2nd dose may be administered after 2 weeks

Vedolizumab

A4 β 7 inhibition; gut-selective

Dose: 300 mg; repeat dose at 2 and 6 weeks

Pneumonitis

Mycophenolate mofetil

Inhibits T and B cell proliferation

Dose: 1 g twice per day

High dose intravenous immunoglobulin (hdIVIG)

Cutaneous

Topical tacrolimus

Calcineurin inhibitor

Indication-specific treatments

Pemphigus or bullous pemphigoid: rituximab

Eczema: dupilumab

Lichenoid rash: infliximab

Urticaria: omalizumab

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Uncommon irAEs with ICIs

Cardiovascular:

Myocarditis, pericarditis,
arrhythmias

Renal:

Interstitial nephritis,
granulomatous nephritis

Endocrine:

Adrenal insufficiency,
pancreatic insufficiency,
type 1 diabetes mellitus

Hematologic:

Hemolytic anemia, red
cell aplasia, neutropenia,
thrombocytopenia

Neurologic:

Myasthenia gravis,
Guillain-Barré syndrome,
peripheral neuropathies

Ophthalmologic:

Uveitis, episcleritis,
conjunctivitis

Uncommon irAEs with ICIs

Cardiovascular:

Myocarditis,
pericarditis, arrhythmias

Renal:

Interstitial nephritis,
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Endocrine:

Adrenal insufficiency,
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Neurologic:

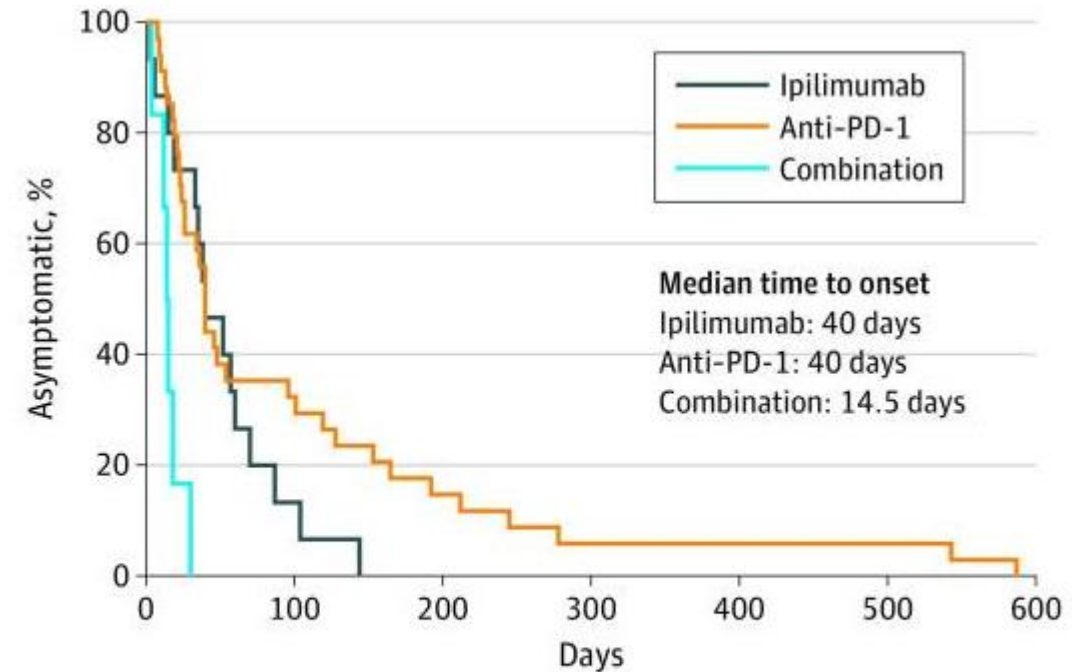
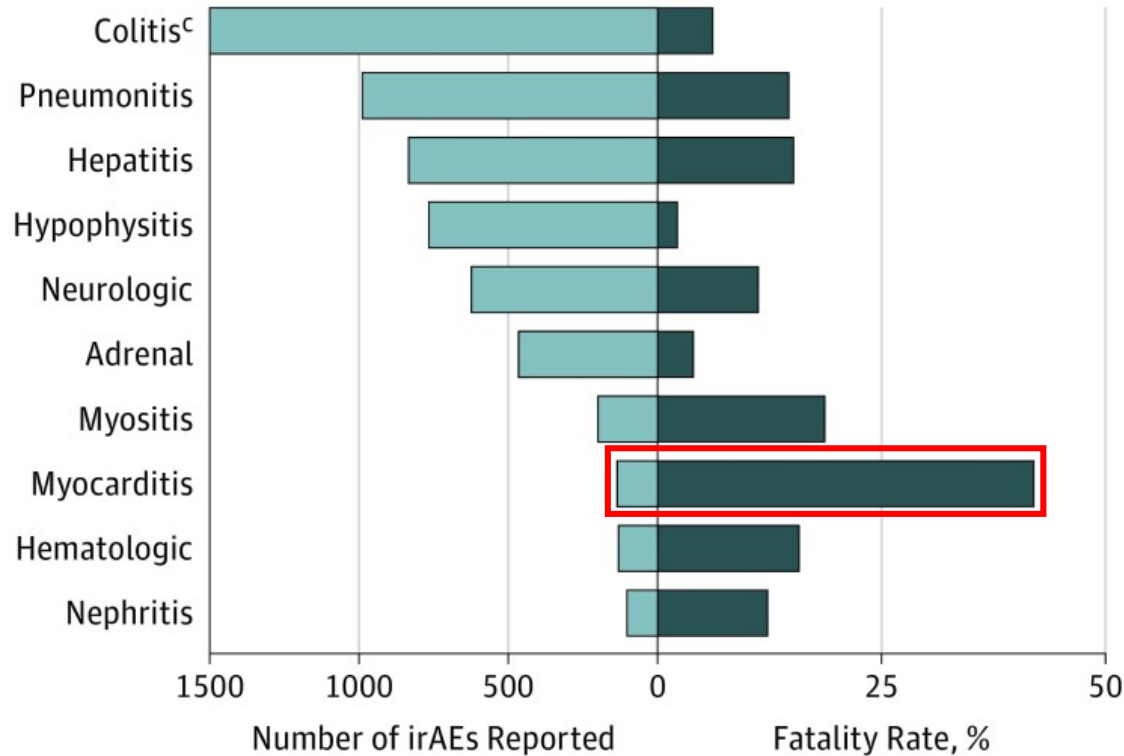
Myasthenia gravis,
Guillain-Barré syndrome,
peripheral neuropathies

Ophthalmologic:

Uveitis, episcleritis,
conjunctivitis

Fatal Events with ICI

Cases and fatality rates

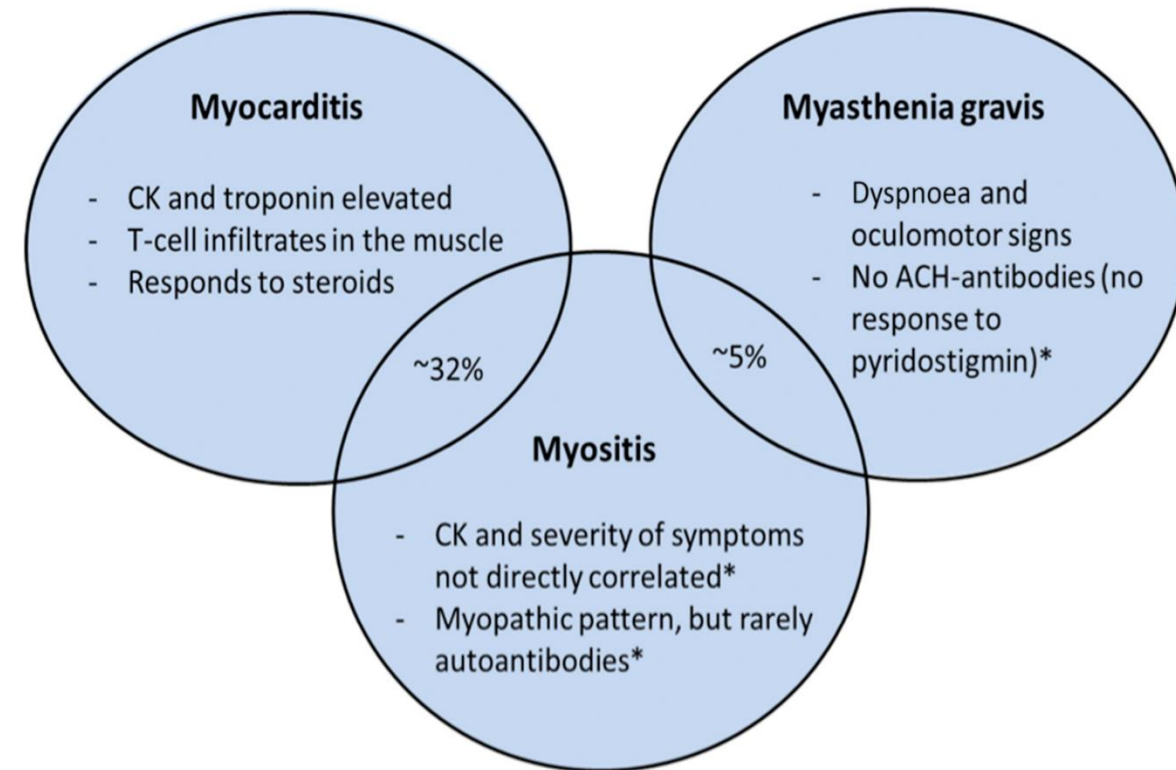


No. at risk

Ipilimumab	15	2	0	0	0	0	0
Anti-PD-1	34	11	5	2	2	2	0
Combination	6	0	0	0	0	0	0

Myocarditis

- More common with anti-CTLA-4 than anti-PD-1, but highest with combination
- Symptoms: dyspnea, chest pain, fatigue, myalgia, palpitations, syncope, dizziness
- Imaging findings usually normal
- Increased serum troponin in almost all patients – high suspicion of ICI-associated myocarditis!
- Management includes:
 - Withholding immunotherapy
 - Immunosuppressives based on grade of myocarditis
 - Heart failure support
- Often overlaps with other irAEs



Type 1 diabetes

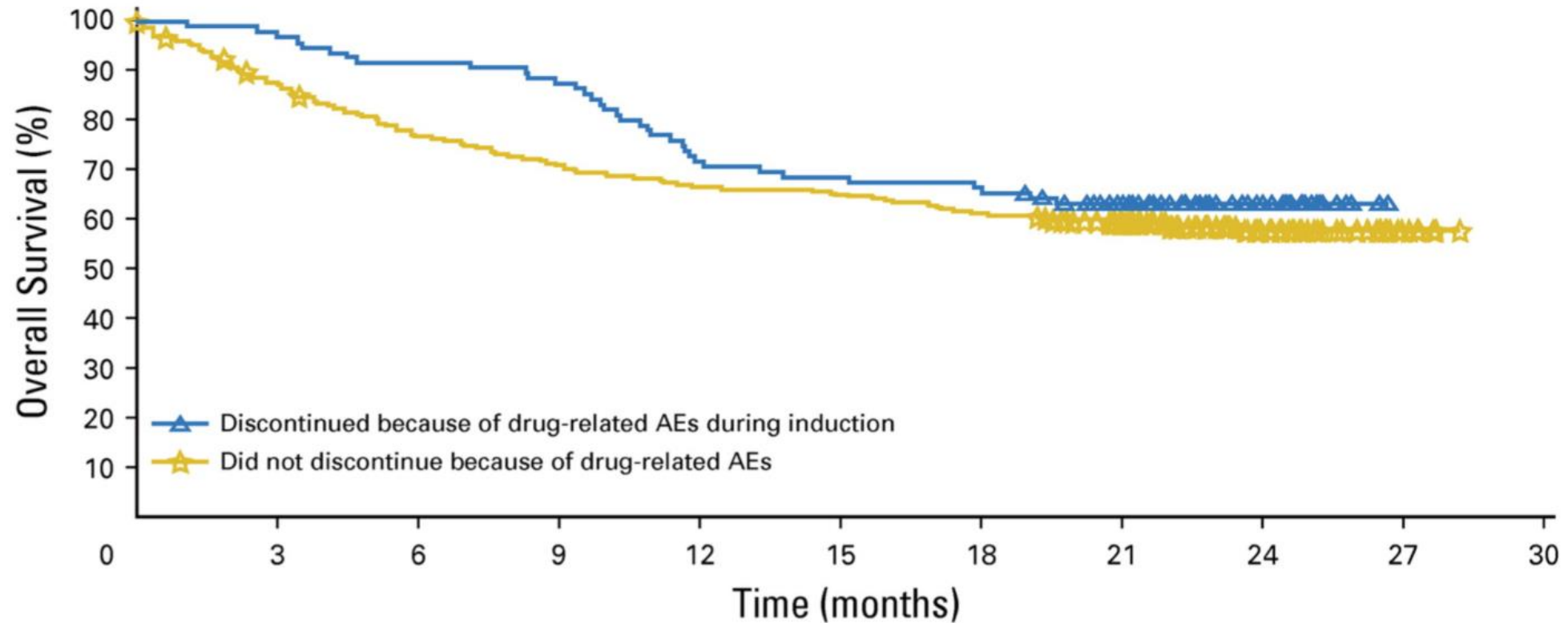
- Diagnostic workup
 - Most common with PD-1 pathway inhibitors
 - Symptoms: severe and sudden onset of hyperglycemia, diabetic ketoacidosis
 - Monitor glucose levels at each dose of immunotherapy
- Management
 - Typically do not respond to immunosuppressives
 - Requires insulin therapy



Outline

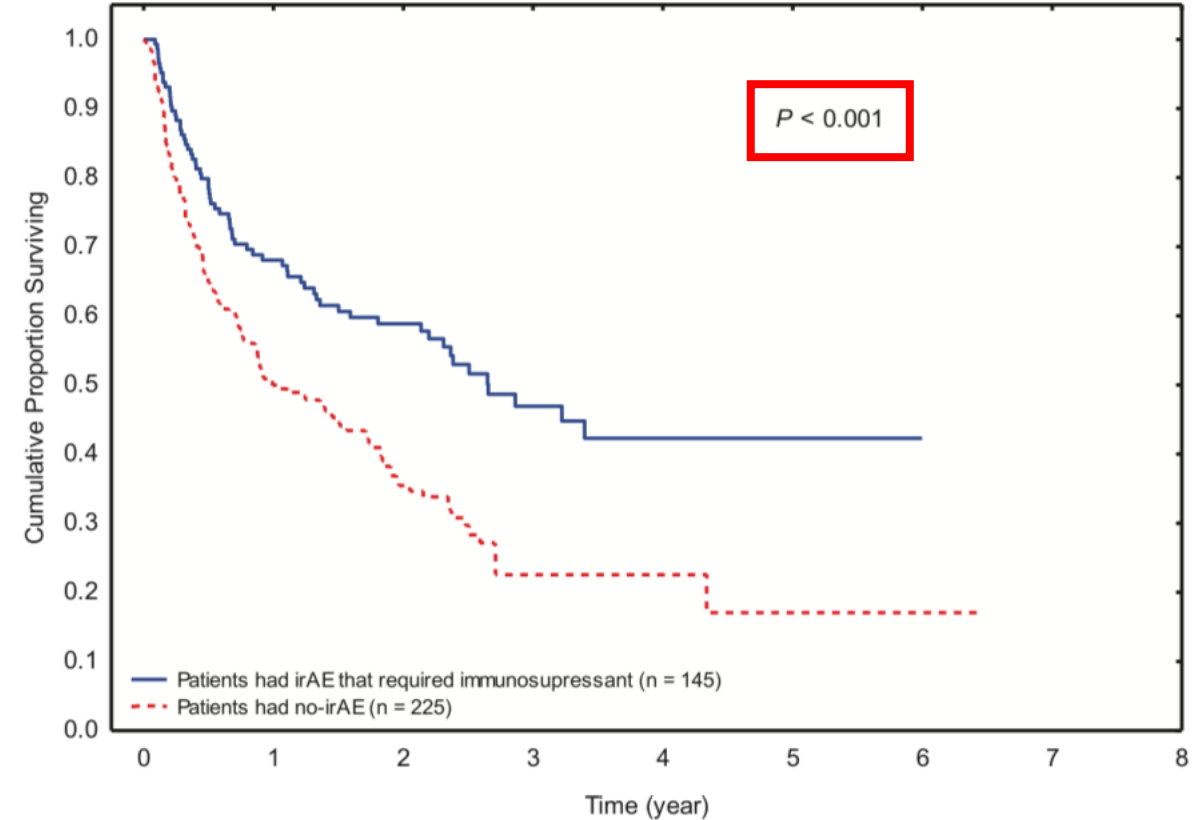
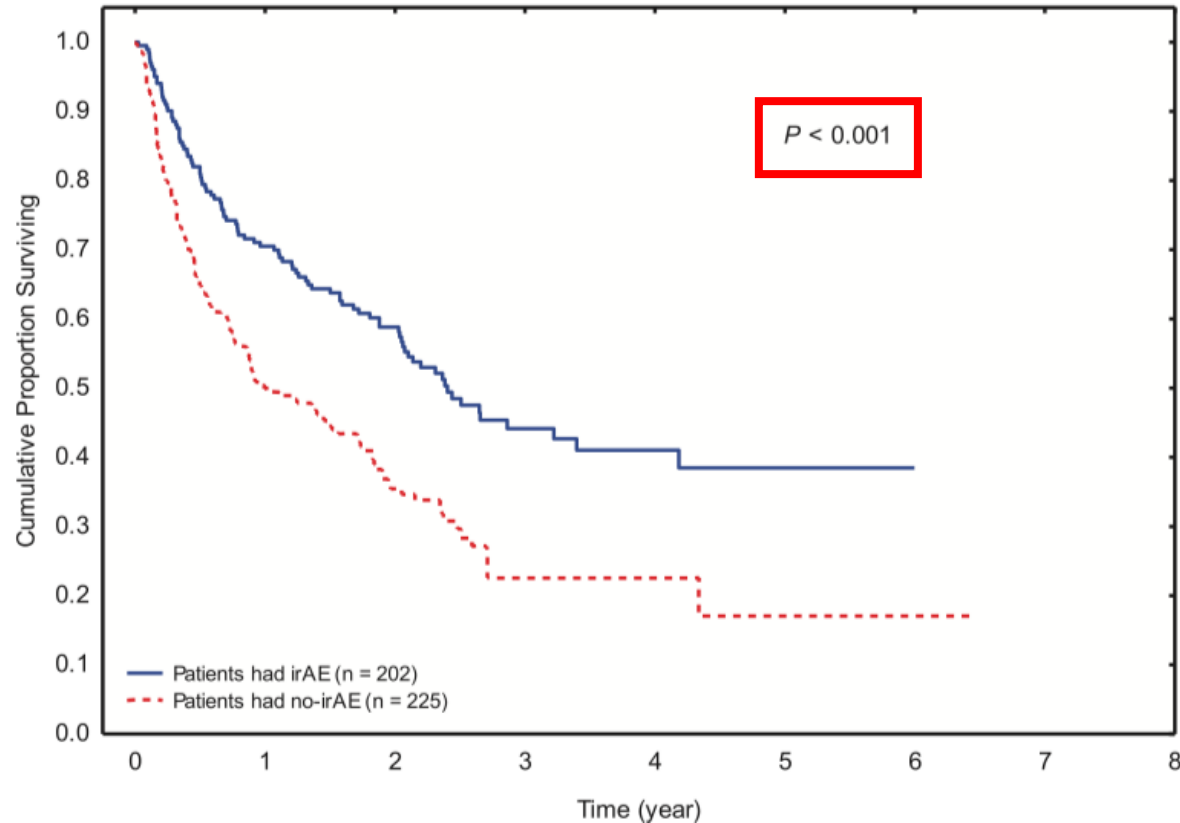
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Effect of irAEs on patient outcomes



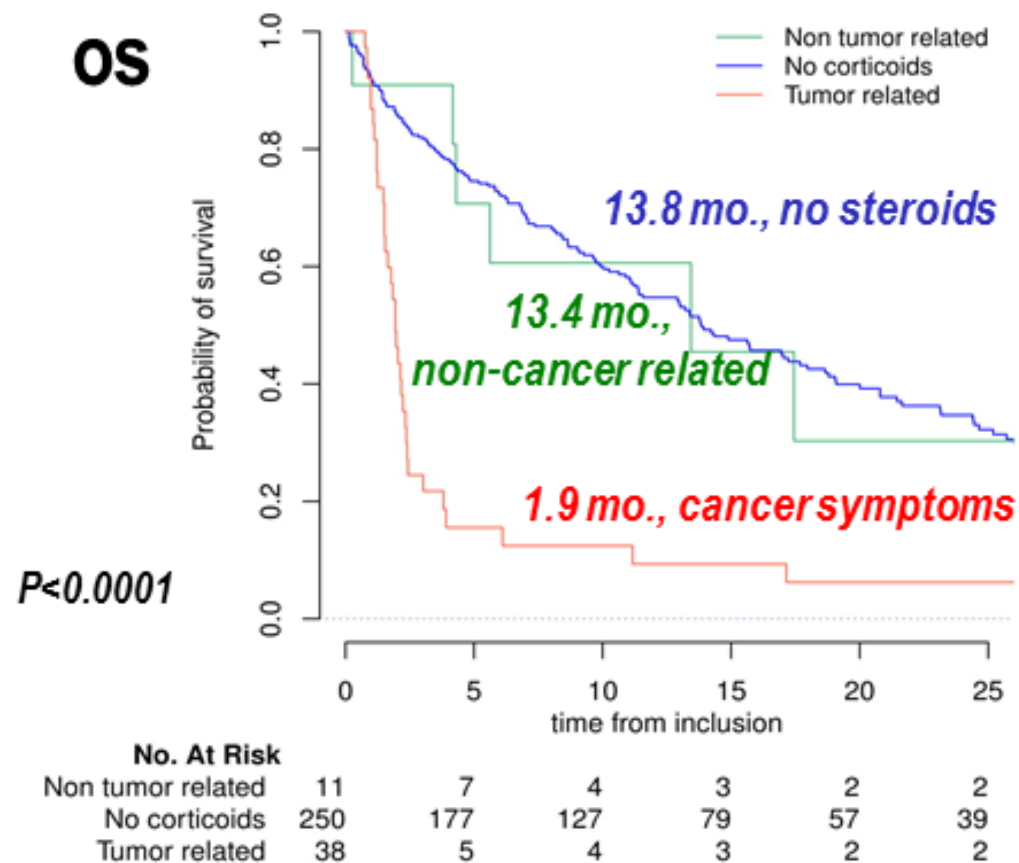
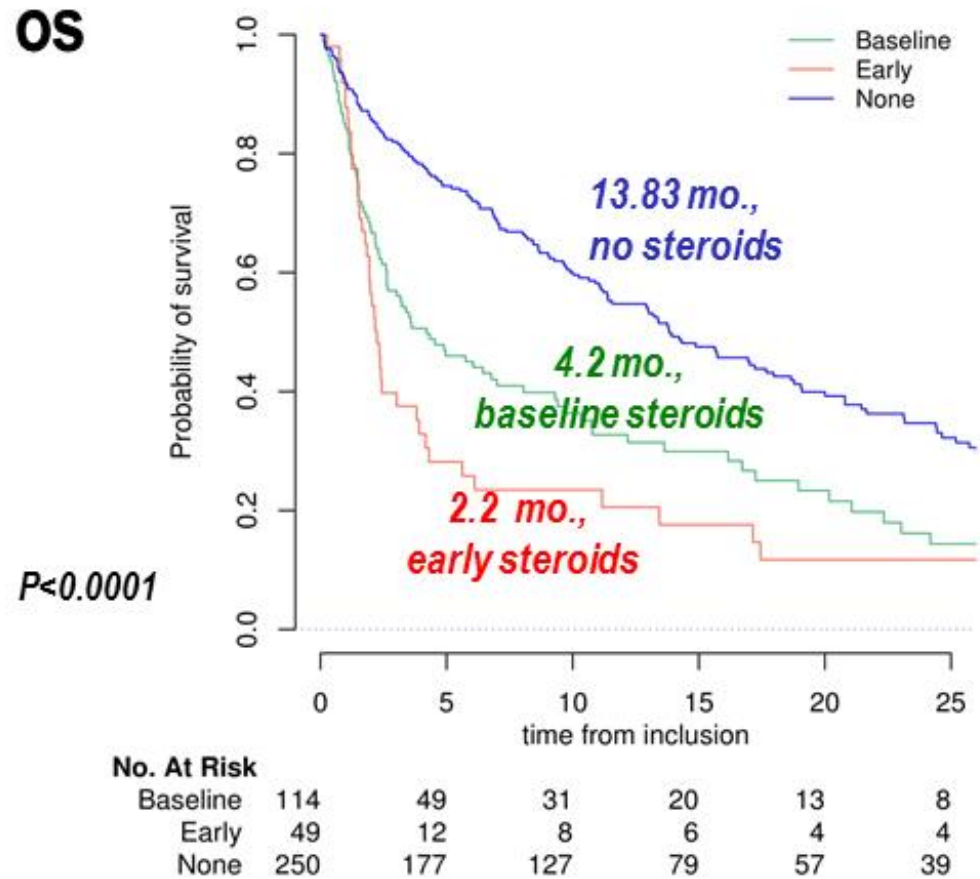
No significant difference in survival in melanoma patients who discontinued ipilimumab + nivolumab due to irAEs versus those who did not discontinue treatment

Autoimmunity as a prognostic marker?



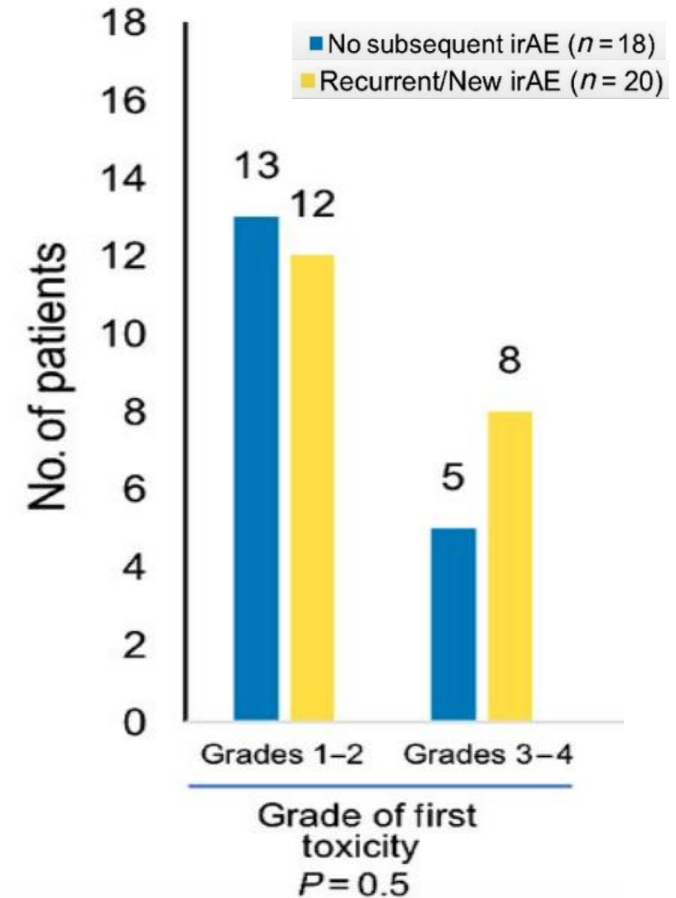
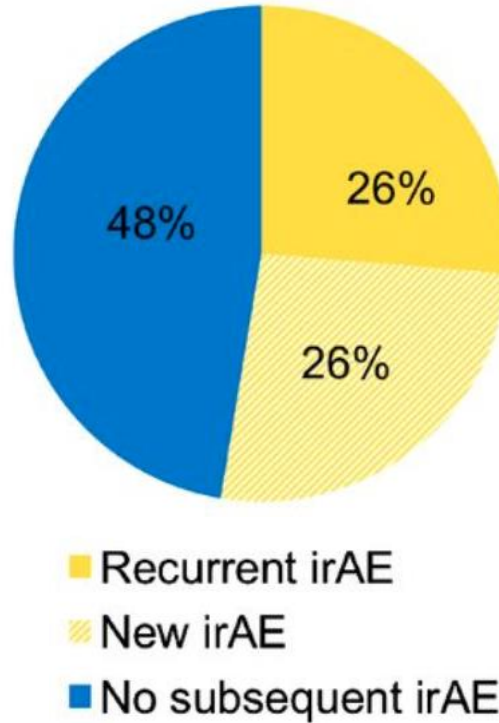
Based on **retrospective** data, patients who experience irAEs (regardless of needing treatment) may have better outcomes compared to patients who do not experience irAEs

Impact of steroid management on patient outcomes



Rechallenging with ICI after irAEs

- Patients should not be rechallenged until irAE resolved to grade ≤ 1
- Re-challenge with anti-PD-1/L1 after anti-CTLA-4 \pm anti-PD-1 likely safe
- Caution in re-challenging with same ICI in patients who previously had grade 3-4 irAEs



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CAR T-cell related toxicities

More
Common

Cytokine release syndrome

Immune cell associated neurotoxicity syndrome (ICANS)

Less
Common

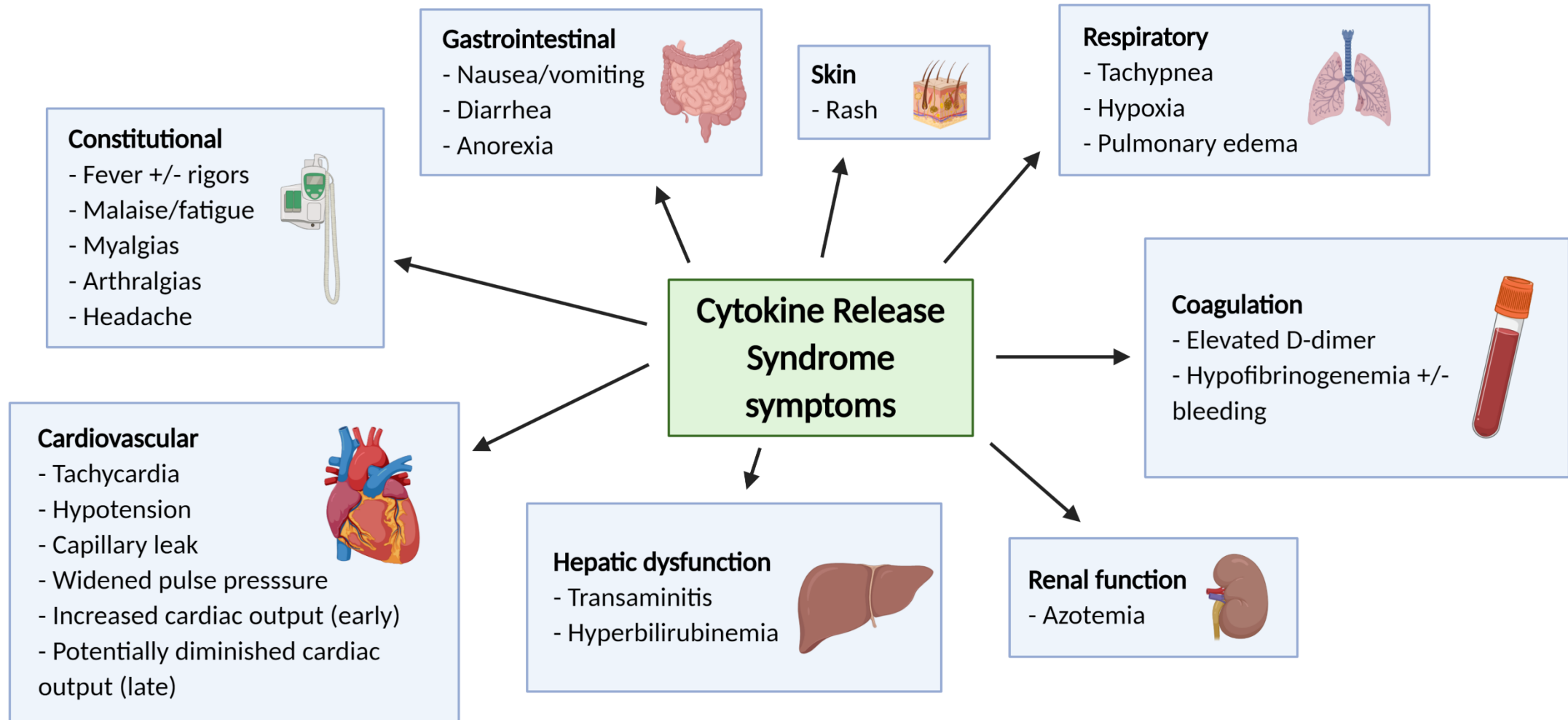
Hemophagocytic Lymphohistiocytosis/
Macrophage Activation Syndrome (HLH/MAS)

Anaphylaxis, B cell aplasia and
hypogammaglobulinemia

CRS and Neurotoxicity

- Should not be viewed as two unrelated adverse events
 - Overlapping toxicities from excessive immune activation
 - May occur together or exclusive of one another
 - However, they do have distinct timing and responses to treatment
- Risk factors for both include:
 - High disease burden
 - Higher infused CAR-T cell dose
 - High intensity lymphodepletion regimen
 - Pre-existing endothelial activation
 - Severe thrombocytopenia

Cytokine release syndrome



Cytokine release syndrome

- Occurs in ~70% of patients; severe = 12-47%
 - Median onset 2-3 days after infusion, typical duration 7-8 days
- Multiple grading systems exist (MSKCC, CarTox, ASTCT)
 - Hypotension and hypoxia are main drivers of CRS severity

CRS Grade	Anti-IL-6	Steroids	Supportive Care
Grade 1 (fever > 38°C)	CRS > 3 days	N/A	<ul style="list-style-type: none"> • Antibiotics • GCSF if neutropenic
Grade 2 (fever/hypotension)	Tocilizumab 8mg/kg (4 doses max)	refractory hypotension Dex 10mg q6	<ul style="list-style-type: none"> • IV fluids, pressors • Manage as G3 is no improvement in 24hr
Grade 3 (+pressors)	Tocilizumab 8mg/kg (4 doses max)	Dex 10mg q6	<ul style="list-style-type: none"> • IV fluids, pressors, • Echocardiogram • ICU, oxygen
Grade 4 (+ventilatory support)	Tocilizumab 8mg/kg (4 doses max)	Dex 10mg q6 Methylpred 1g/day if refractory	<ul style="list-style-type: none"> • ICU care • Mechanical ventilation • Organ toxicity management

Day 4, MMSE 29/30
 I love Shawnee, KS.

Day 5, MMSE 27/30
 Shawnee is a ~~great~~ *great* area.

Day 6, MMSE 29/30
 I miss my kids.

Neurotoxicity

- Also called CAR-T Related Encephalopathy Syndrome (CRES) or iIEC-associated neurologic syndrome (ICANS)
- Occurs in 20-64% of patients, \geq grade 3 in 11-42%
 - Onset 4-5 days after infusion, typical duration 5-12 days

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7-9	3-6	0-2	0
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens to tactile stimulus	Unroutable
Seizure	N/A	N/A	Any clinical seizure/on EEG	Prolonged/life-threatening seizure
Motor Findings	N/A	N/A	N/A	Hemi or paraparesis, deep focal motor weakness
Raised ICP/ cerebral edema	N/A	N/A	Focal edema on imaging	Diffuse cerebral edema on imaging, cranial N palsy, Cushing's triad, Decorticate posture

HLH/MAS

- Inflammatory syndrome caused by hyperactivation of macrophages and lymphocytes
- Rare; frequency reported to be as low as ~1%
- Should be managed with anti-IL-6 and corticosteroid therapy
- If no improvement after 48 hours, consider adding etoposide for additional immunosuppression
 - Dose: 75-100 mg/m²
 - May be repeated after 4-7 days

Box 5 | Diagnostic criteria for CAR-T-cell-related HLH/MAS

A patient might have HLH/MAS if he/she had a peak serum ferritin level of >10,000 ng/ml during the cytokine-release syndrome phase of CAR-T-cell therapy (typically the first 5 days after cell infusion) and subsequently developed any two of the following:

- Grade ≥3 increase in serum bilirubin, aspartate aminotransferase, or alanine aminotransferase levels*
- Grade ≥3 oliguria or increase in serum creatinine levels*
- Grade ≥3 pulmonary oedema*
- Presence of haemophagocytosis in bone marrow or organs based on histopathological assessment of cell morphology and/or CD68 immunohistochemistry

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Patients with autoimmune disorders

- Ipilimumab in melanoma patients
 - 29% experienced flare of pre-existing disorder; 29% experienced new irAEs
 - 56% experienced no flare OR additional irAEs
- PD-1 in melanoma patients
 - 38% experienced flare; 29% experienced new irAEs
 - Lower response rates in patients who remained on immunosuppressive treatment (15% vs 44%)
- Efficacy appears similar for patients with autoimmune disorders compared to those without

ICI use in patients with solid organ or stem cell transplants

- Patients who relapse after allogeneic SCT:
 - Ipilimumab: 32% response (10 mg/kg); 14% GVHD; 21% irAEs
 - Anti-PD-1: 77% response; 26% died due to new-onset GVHD
- Solid organ data is limited; most is in renal SOT patients
 - One retrospective study (n=39) reported graft loss in 81% and death in 46%
 - Also reported rapid time to rejection with median onset of 21 days
- PD-1 pathway appears to be more critical in allograft immune tolerance compared to CTLA-4 pathway

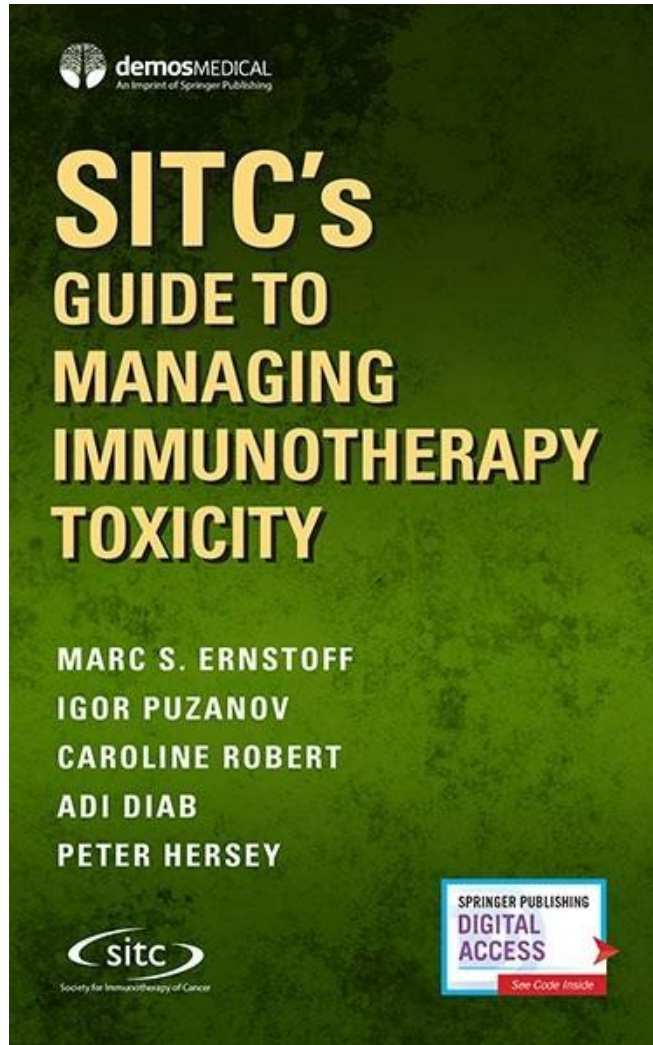
The importance of patient education

- Many immune-related adverse events can present in similar ways to other diseases, but the treatment of them is very different.
- Patients need to be able to identify themselves as immunotherapy recipients
- Reassure patients that irAEs will likely resolve over time (except endocrinopathies)

Education along the healthcare continuum

- Patients may not go back to their original clinic for adverse event management
- Emergency departments and primary care physicians need to recognize and know how to manage irAEs
- For example, the most common irAE in emergency departments is diarrhea – recognize immune-related symptoms versus other causes (including chemotherapy related diarrhea)

Additional Resources



Puzanov et al. *Journal for Immunotherapy of Cancer* (2017) 5:95
 DOI 10.1186/s40425-017-0300-z

Journal for Immunotherapy
 of Cancer

POSITION ARTICLE AND GUIDELINES **Open Access**

CrossMark

Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group

I. Puzanov^{1†}, A. Diab^{2†}, K. Abdallah³, C. O. Bingham III⁴, C. Brogdon⁵, R. Dadu², L. Hamad¹, S. Kim², M. E. Lacouture⁶, N. R. LeBoeuf⁷, D. Lenihan⁸, C. Onofrei⁹, V. Shannon², R. Sharma¹, A. W. Silk¹², D. Skondra¹⁰, M. E. Suarez-Almazor², Y. Wang², K. Wiley¹¹, H. L. Kaufman^{12†}, M. S. Ernstoff^{1††} and on behalf of the Society for Immunotherapy of Cancer Toxicity Management Working Group

National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Management of Immunotherapy-Related Toxicities

Case Study 1

45 year old Caucasian female presents for evaluation for cycle 4 of treatment on adjuvant nivolumab.

She had a 3.1 mm ulcerated melanoma on her right lower leg that was treated with wide local excision and sentinel node biopsy. Wide excision specimen had no residual melanoma and SNL biopsy showed 1/1 lymph node positive for metastatic melanoma, measuring 5 mm in greatest dimension. Tumor was *BRAF* wildtype.

She was start on adjuvant nivolumab 2 months after surgery and has been on 480mg IV q4weeks and has completed 3 without complication.

She also reports her watch shows her Heart Rate at baseline in the 90s. She is an avid runner and knows at baseline she is typically in the 60s. She otherwise feels well and has no other complaints and physical exam is unremarkable.

Case Study 1

- Question 1: What work up would you include at this point if any?
- Question 2: Would you treat this patient with nivolumab today?
- Question 3: How would you counsel the patient regarding the natural history of this immune related adverse event?

Case Study 2

55 year old Indian male presents for evaluation for cycle 3 of ipilimumab 3mg/kg + nivolumab 1mg/kg for Stage IV rectal melanoma.

The patient originally presented with a bleeding rectal mass that was thought to be hemorrhoids. At resection it was noted to be a 1 cm melanoma. Imaging was performed and noted to have multiple liver lesions and pelvic adenopathy. Biopsy of the liver lesion demonstrated metastatic melanoma. 26-gene panel showed no actionable alterations. He was initiated on ipilimumab 3mg/kg + nivolumab 1mg/kg. He tolerated the first two doses well - he noted mild rash and pruritus on his trunk. He also noted areas of depigmentation on his face.

Today he reports 8-10 watery bowel movements per day. They are non-bloody and occasionally incontinent of stool. He is able to hydrate and keep food down but states his appetite is low. He has mild cramping abdominal pain.

Physical exam shows hyperactive bowel sounds and mild abd pain without guarding. He appears hydrated and vitals are stable. Labs show a potassium of 3.3 and Mg of 1.6.

Case Study 2

- Question 1: What are the best next steps in management?
 - Stool studies
 - Hydration with electrolyte replacement
 - 1 mg/kg of steroids
- Question 2: After one week of steroids though the patient has improved he is still having 5-6 watery bowel movements per day – what's the best next step?
 - Infliximab 5mg/kg
- Question 3: True or False – Once the patient has recovered and is off steroids, retreatment with ipilimumab and nivolumab is recommended
 - False