sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Toxicity Management

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

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Disclosures

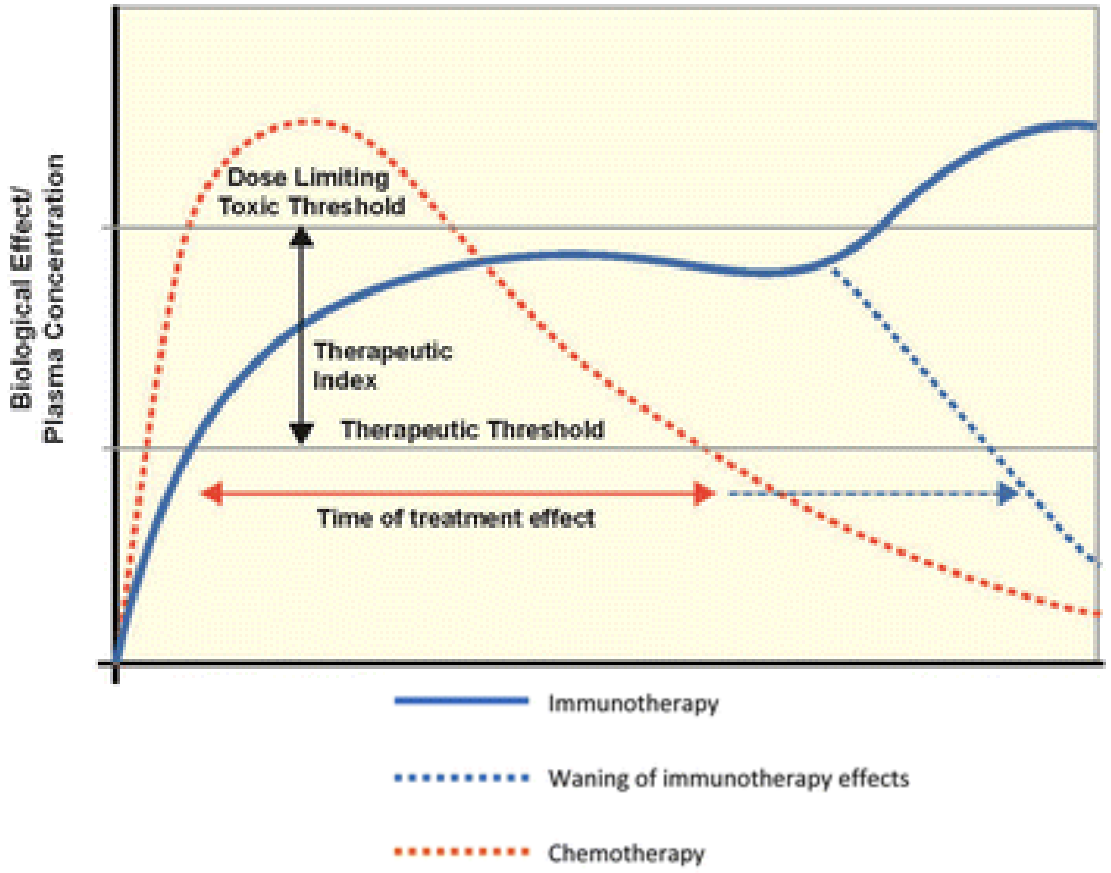
- Speaker Bureaus: Genentech, Merck, BMS and AstraZeneca; All have been discontinued as of November 2019
- I will be discussing non-FDA approved indications during my presentation.

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



Puzanov and Diab, JITC 2017

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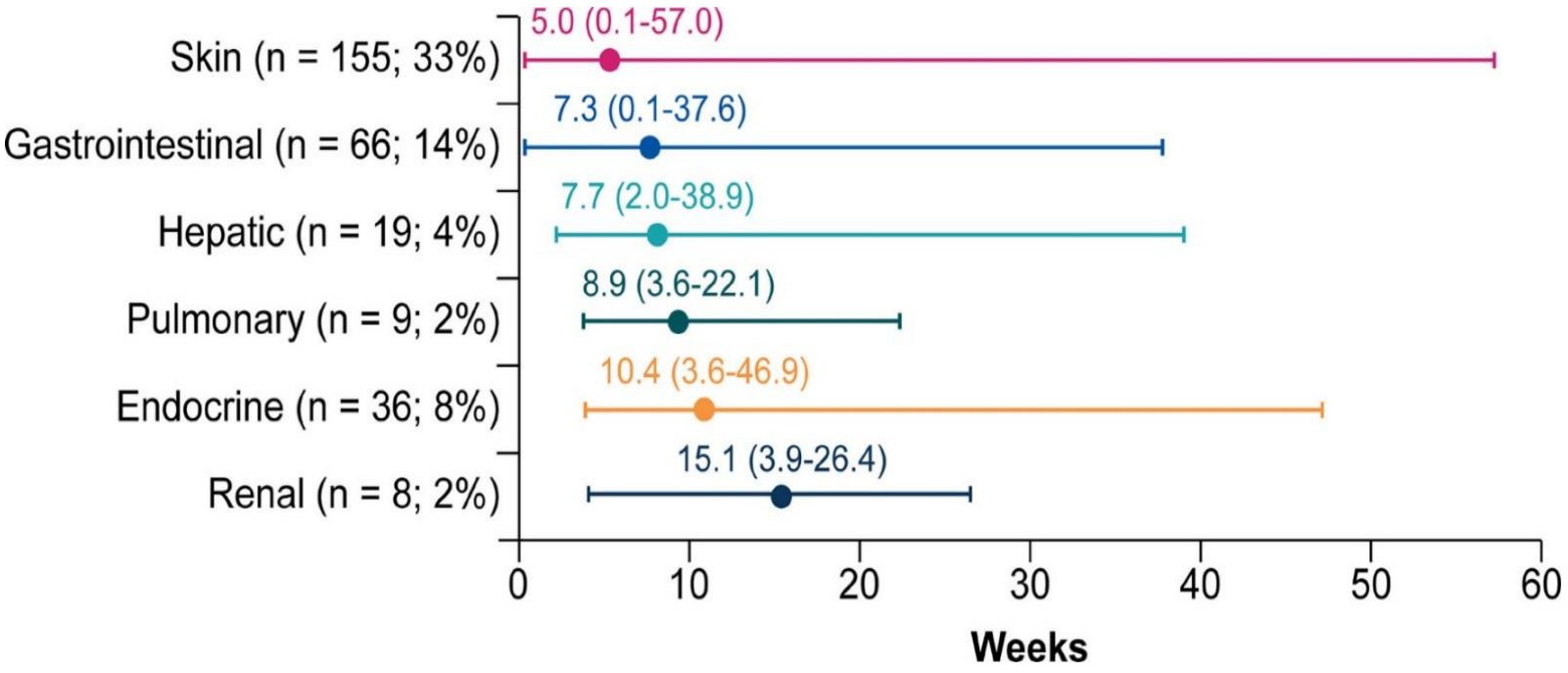
Onset of irAEs



- 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!

Pallin, Acad Emerg Med 2018
Puzanov and Diab, JITC 2017

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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

US Dept of HHS, 2017.

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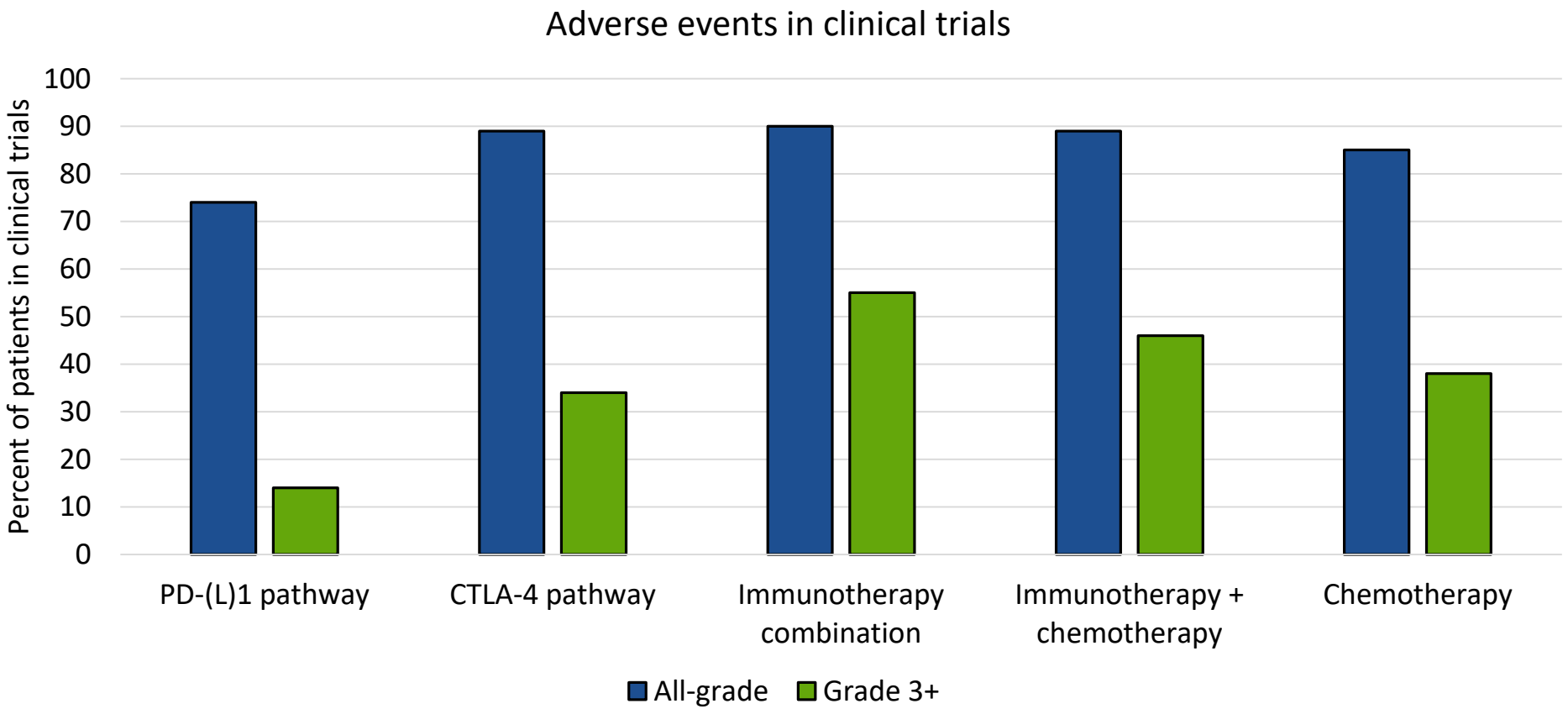
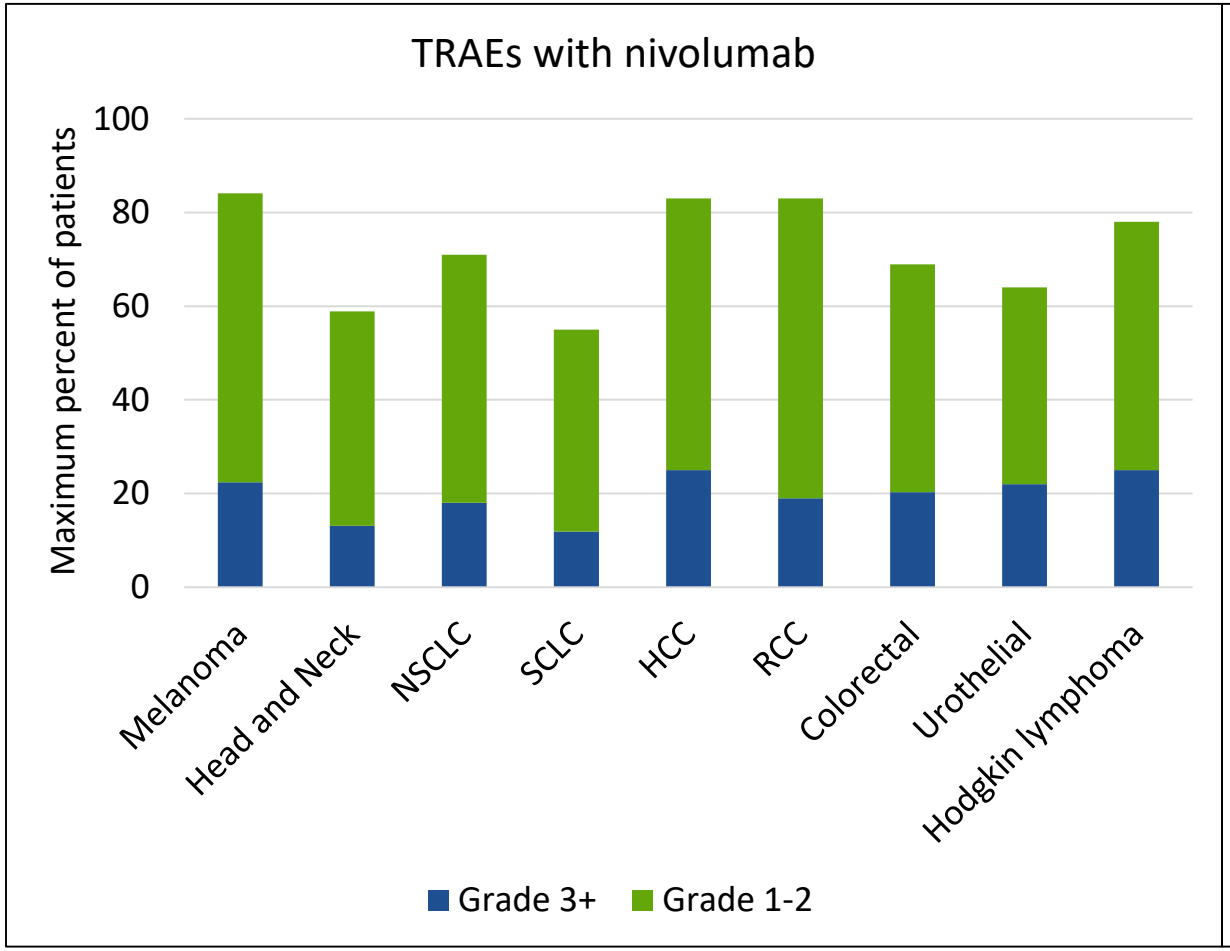
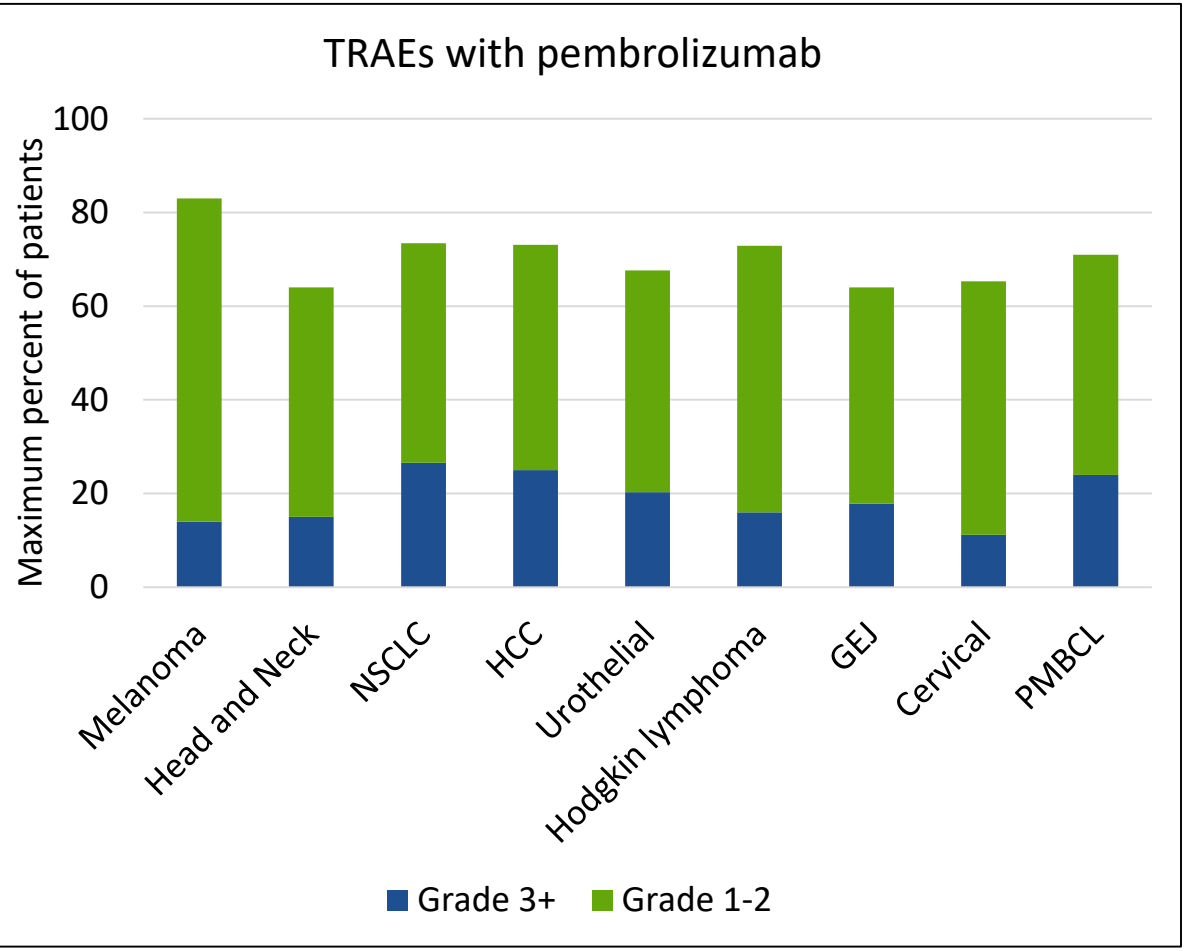
Toxicity with immune checkpoint inhibitors



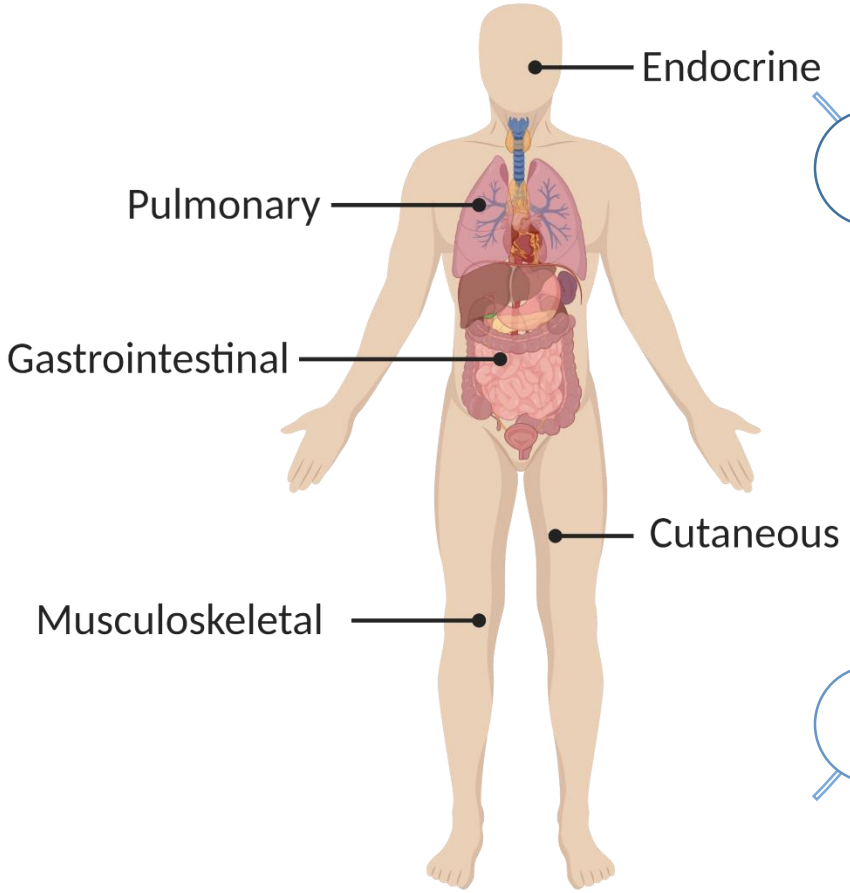
Arnaud-Coffin, Int J Cancer 2019

Toxicity with immune checkpoint inhibitors





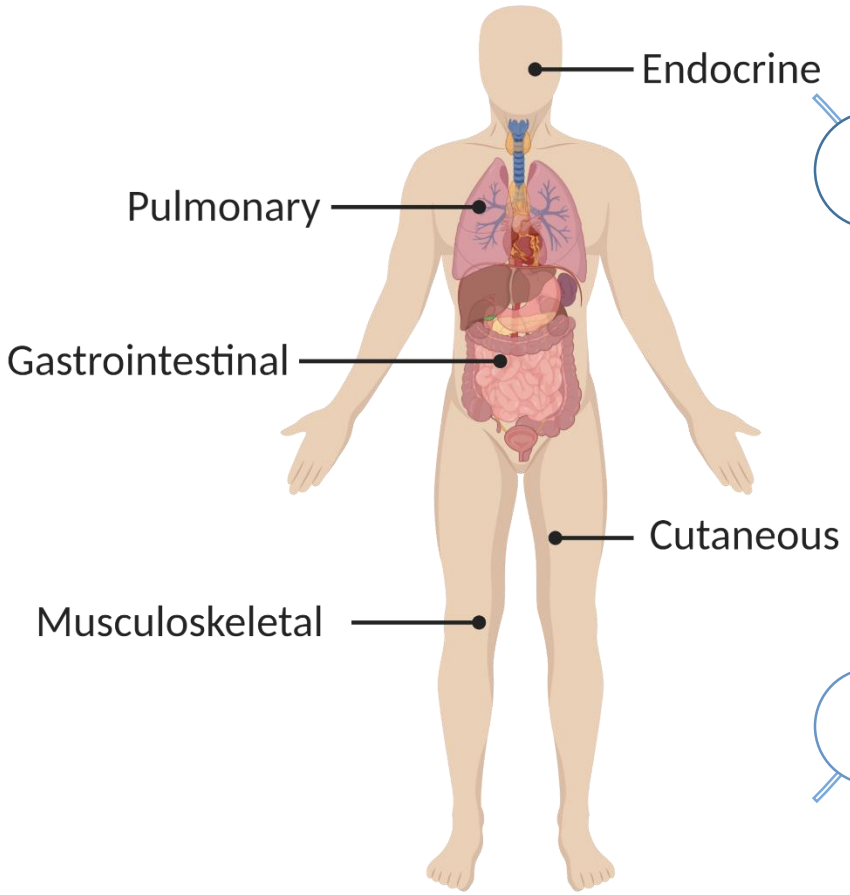
Common irAEs with ICIs



- Cutaneous: dermatitis (maculopapular, lichenoid), pruritis
- Gastrointestinal: diarrhea, colitis, hepatitis, gastritis
- Musculoskeletal: inflammatory arthritis, myositis, sicca syndrome
- Pulmonary: pneumonitis, sarcoidosis
- Endocrine: thyroid dysfunction, hypophysitis, Type 1 diabetes

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

Common irAEs with ICIs



- Cutaneous: dermatitis (maculopapular, lichenoid), pruritis
- Gastrointestinal: diarrhea, **colitis**, **hepatitis**, gastritis
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- Pulmonary: **pneumonitis**, sarcoidosis
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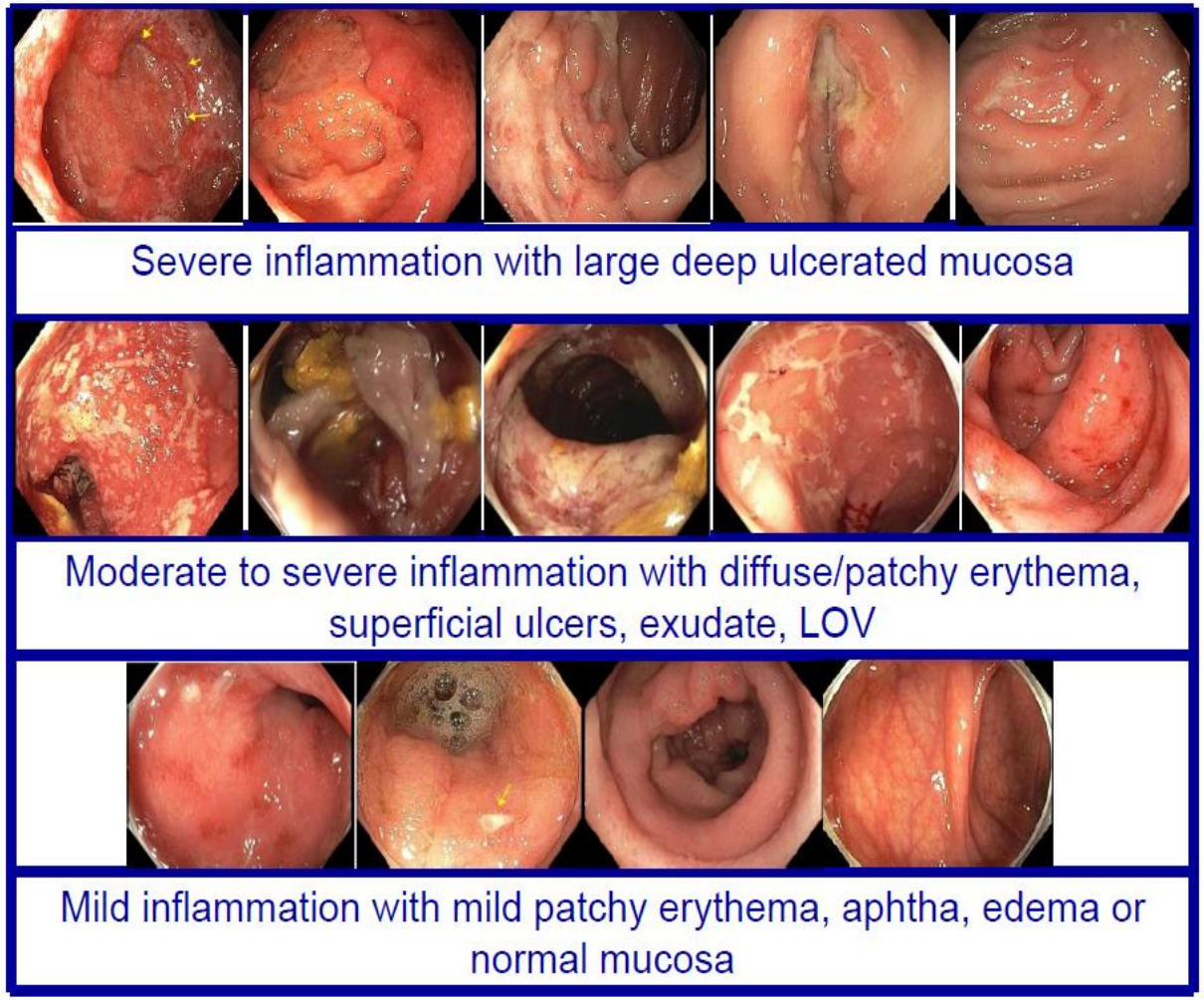
Puzanov and Diab, JITC 2017.
NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

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)



Wang et al, *JITC* 2018

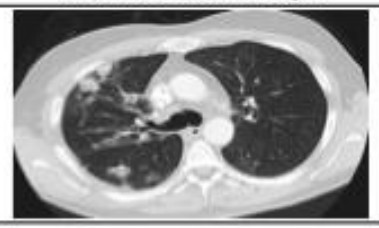
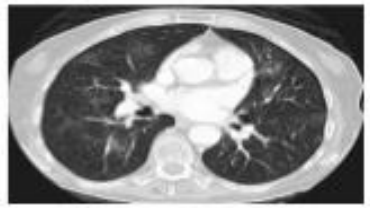
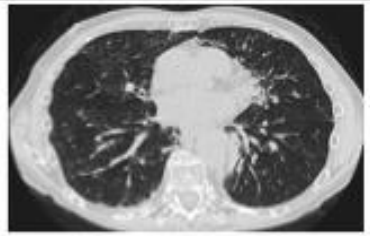
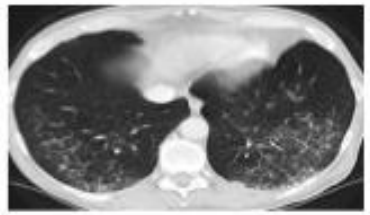
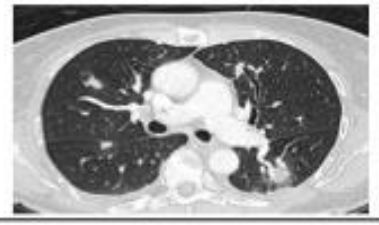
Hepatitis

- 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
• Liver function tests weekly	• Liver function tests weekly • Corticosteroids 0.5 mg/kg/day	• Liver function tests every 1-2 days • Withhold ICIs • Corticosteroids 1-2 mg/kg/day	• Liver function tests every 1-2 days • Discontinue ICIs • Corticosteroids 1-2 mg/kg/day
	• Diagnostic testing includes iron studies, autoimmune hepatitis panel and viral hepatitis panel • Taper steroids over 4-6 weeks once LFTs revert to grade $\leq$ 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		

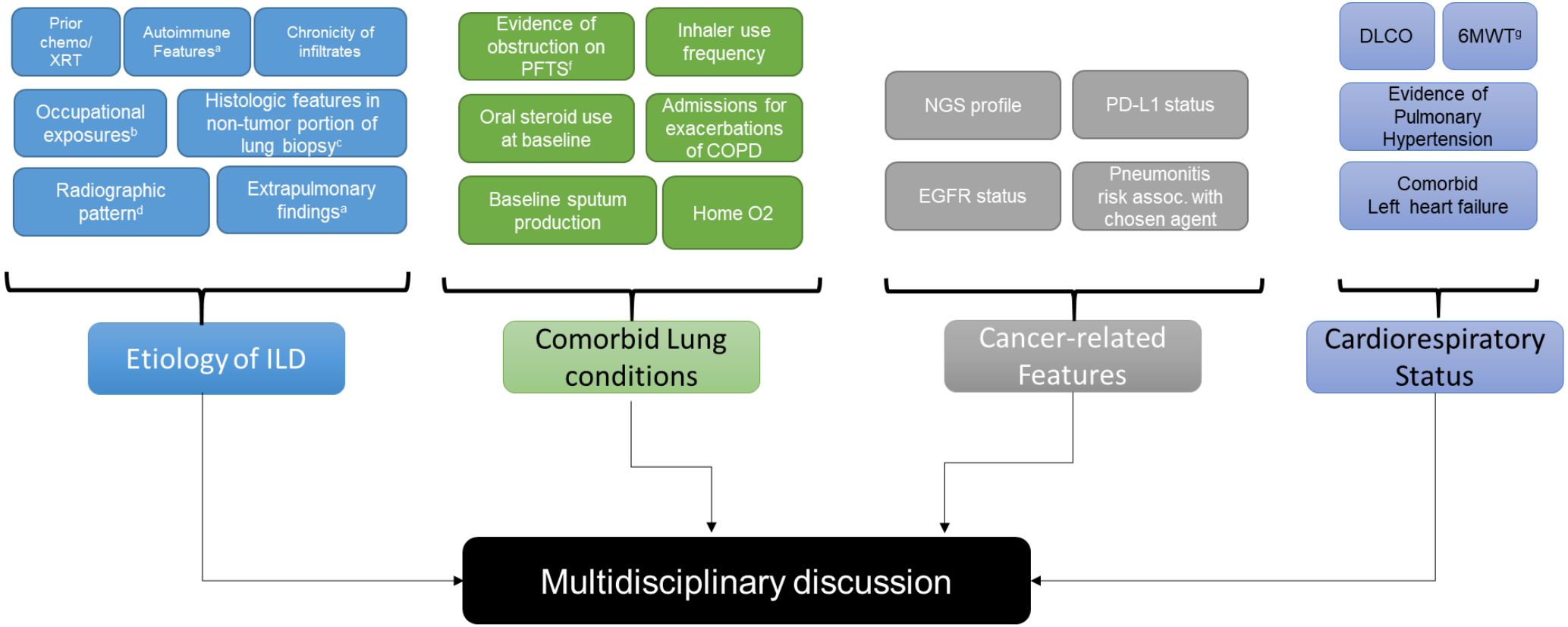
Pneumonitis

- 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%)	

Naidoo et al, *J Clin Oncol* 2016
Suresh, Naidoo et al, *J Thoracic Oncol* 2018

Discerning pneumonitis from other diagnoses

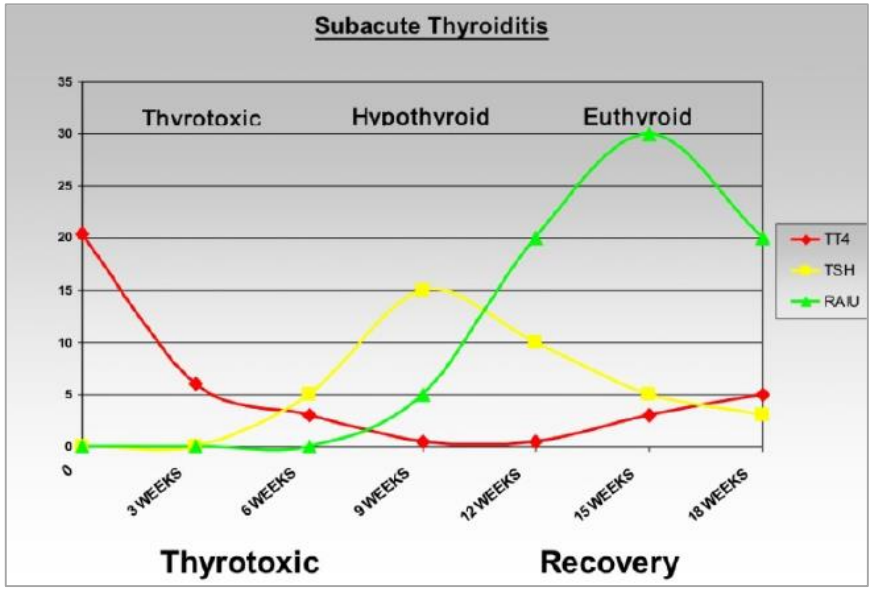


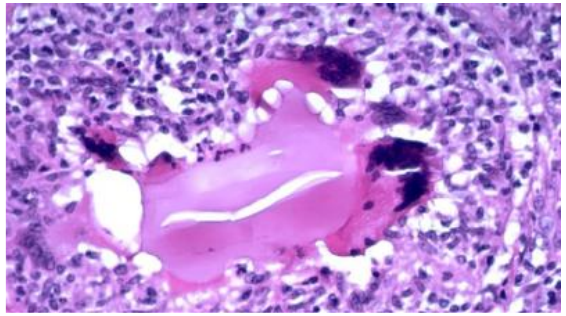
[a] Rashes (Gottron's papules, Heliotrope rash), evidence of synovitis, family history of RA/SLE, history of dry eyes/mouth, Raynaud's phenomenon
[b] Steelworkers, farmers, exposures to heavy metals, organic fumes, dusts, birds, etc. [c] such as poorly-formed granulomas, lymphocytic aggregates
[d] NSIP vs UIP-pattern, evidence of air-trapping, lobar dominance. [f] may present as complex obstruction (TLCpp – FVCpp > 15).

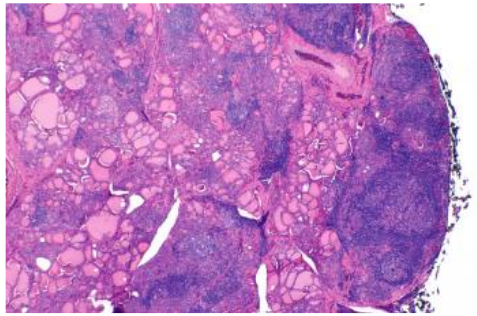
Naidoo, Suresh, The Oncologist 2020.

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



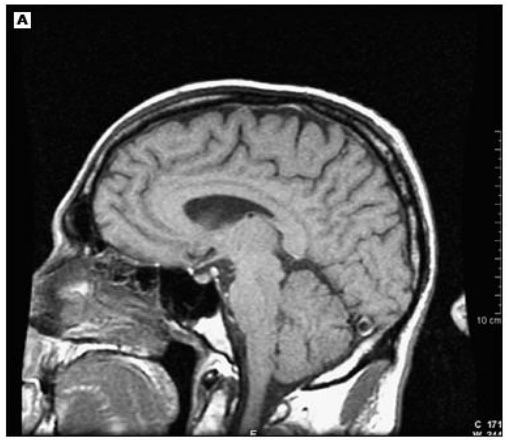




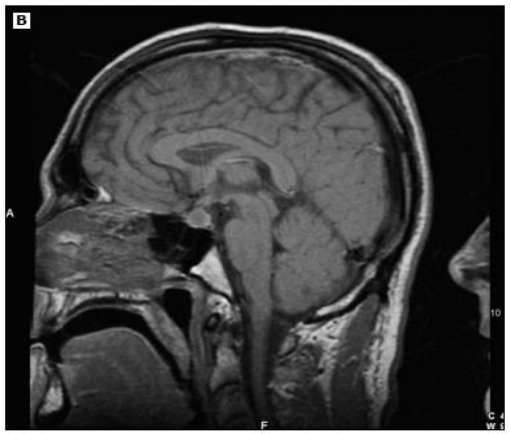
Kobayashi et al, *J Endoc Soc* 2018

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)

Ryder et al, Endocr Relat Cancer 2014

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 O_2 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)

Pazanov & Diab, JITC 2017.

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

Pazanov & Diab, JITC 2017.

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	• 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**	• **Hold immunotherapy** during corticosteroid use • **Continue immunotherapy** once resolved to ≤grade 1 and off corticosteroids • Start proton pump inhibitor for GI prophylaxis

Pazanov & Diab, JITC 2017.

General corticosteroid management

Grade of irAE	Corticosteroid Management	Additional Notes
3	• 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 ≤ grade 1, start **4–6-week steroid taper**	• **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		• **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)

Pazanov & Diab, JITC 2017.

Additional immunosuppressives for specific toxicities

Colitis

Infliximab
anti-TNF-α antibody
Dose: 5 mg/kg; 2nd dose may be administered after 2 weeks

Vedolizumab
A4β7 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 phemphigoid: rituximab
Eczema: dupilumab
Lichenoid rash: infliximab
Urticaria: omalizumab

Abu-Sbeih H. JITC. 2018.
NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

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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

Puzanov and Diab, JITC 2017.
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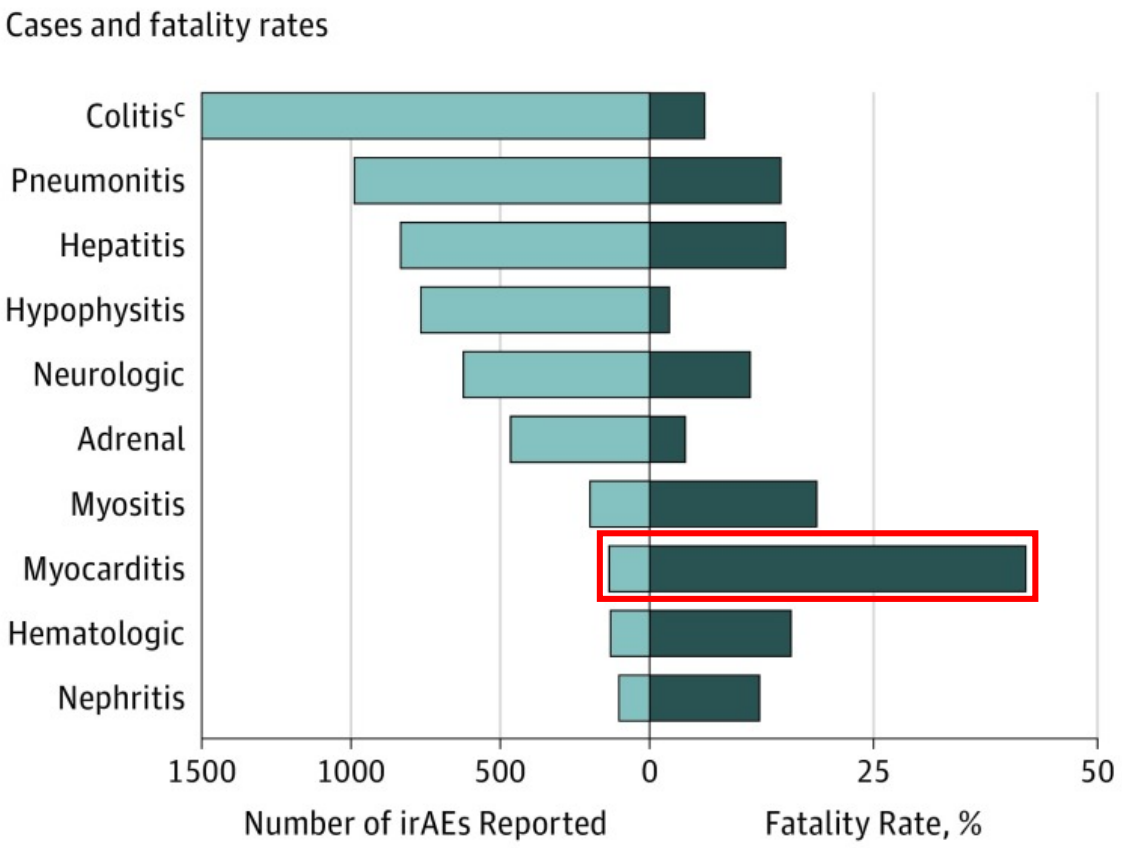
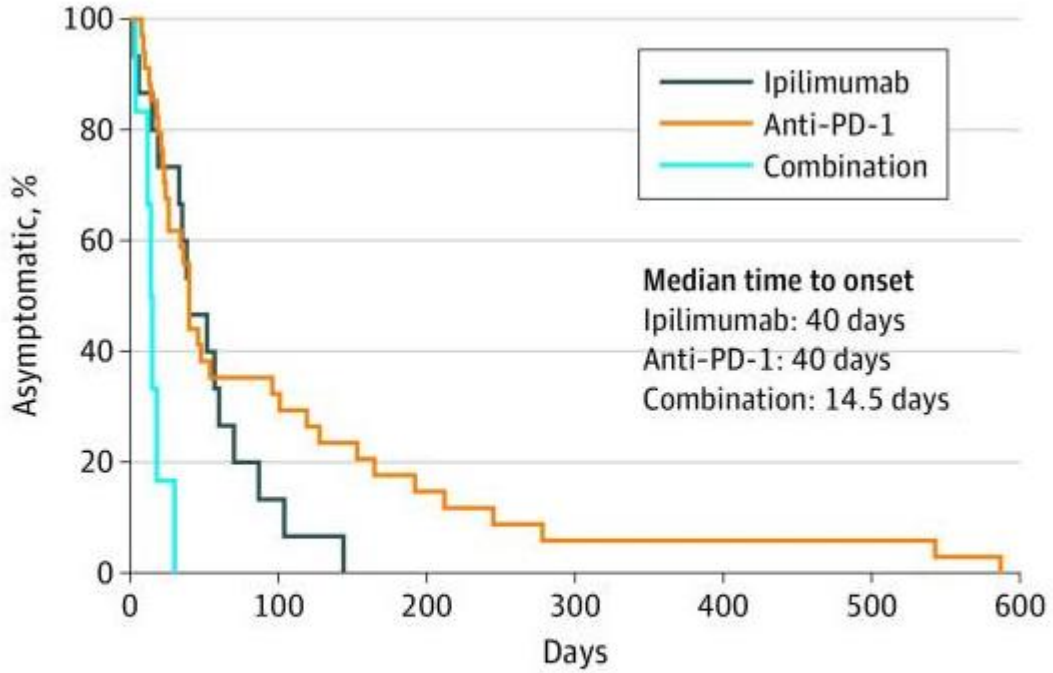
Fatal Events with ICIs



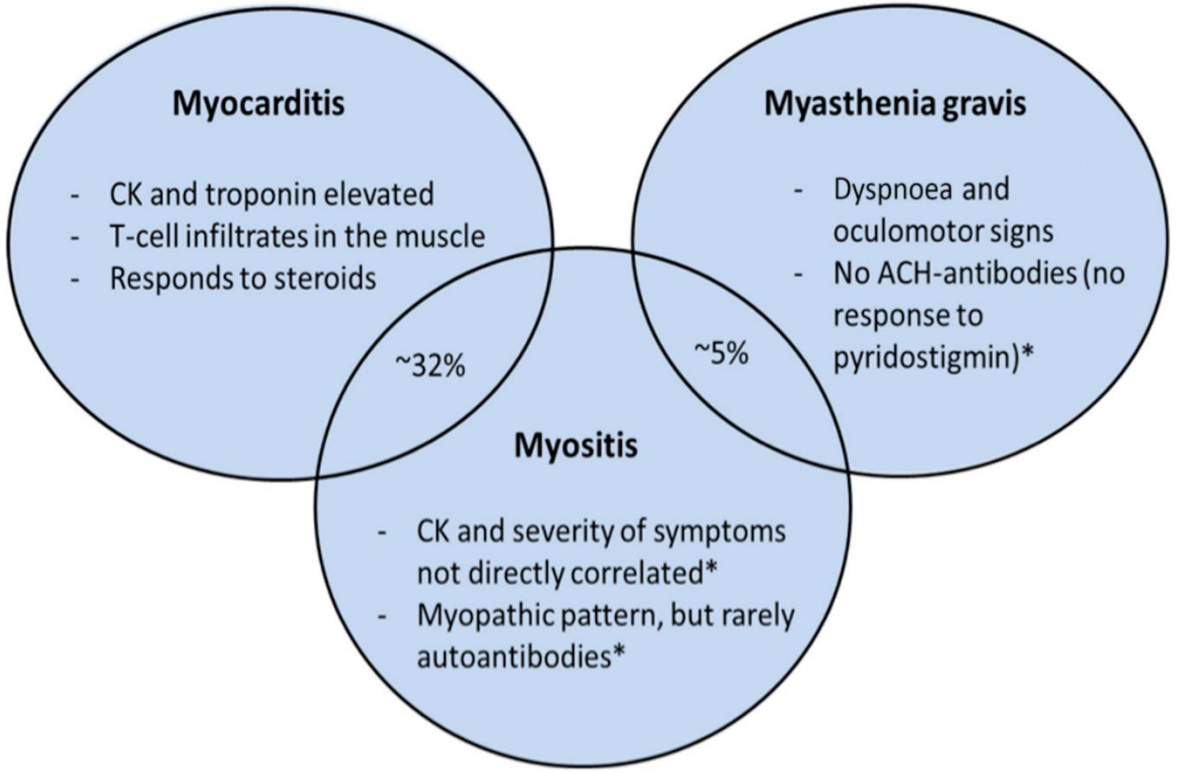


No. at risk							
Ipilimumab	15	2	0	0	0	0	0
Anti-PD-1	34	11	5	2	2	2	0
Combination	6	0	0	0	0	0	0

Wang et al, JAMA Oncol 2018.

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



Moreira et al, *Eur J Cancer* 2018
Naidoo et al, *JNCCN 2019*

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

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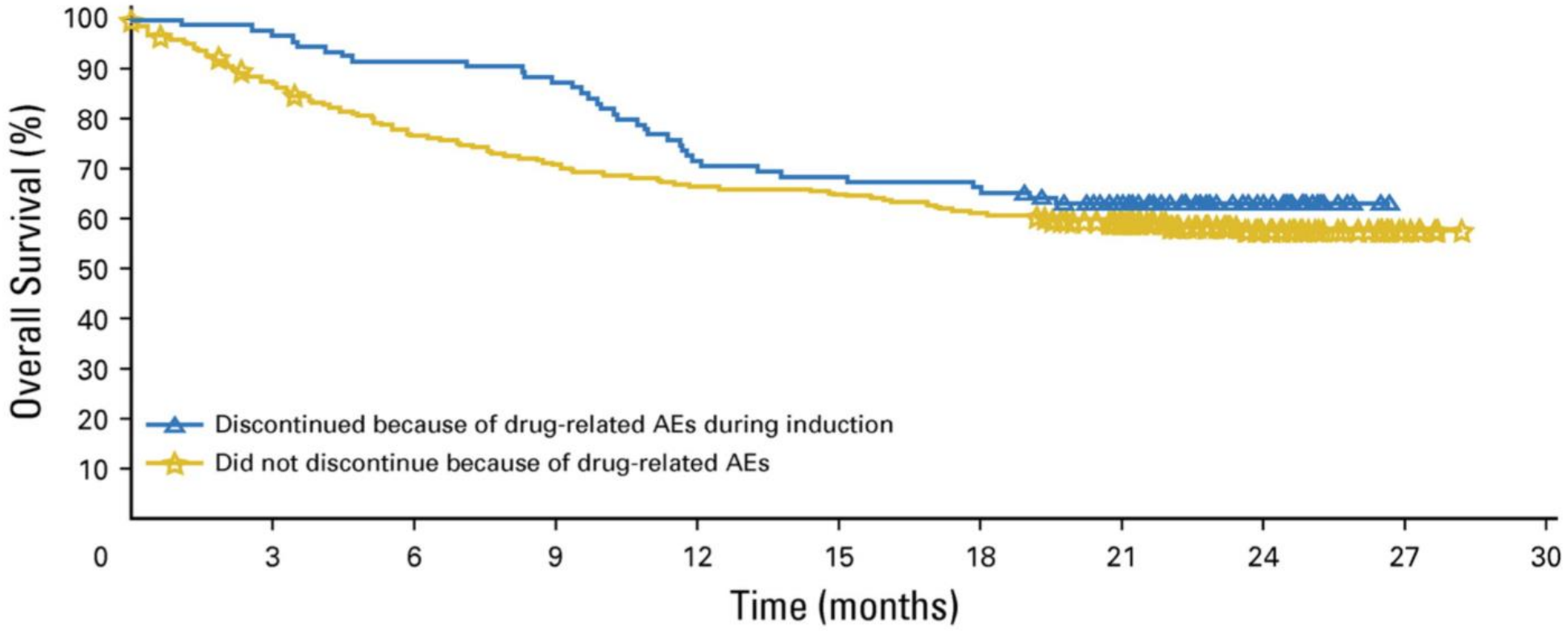
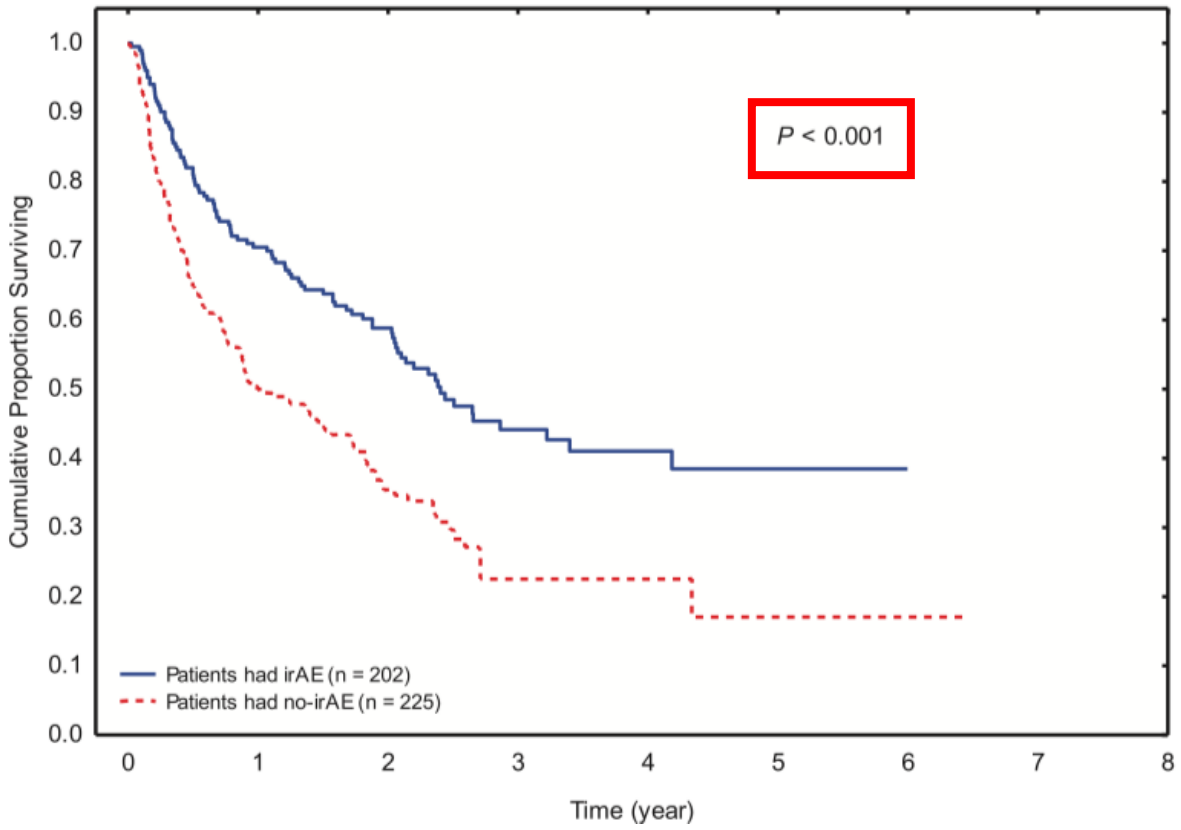
Effect of irAEs on patient outcomes

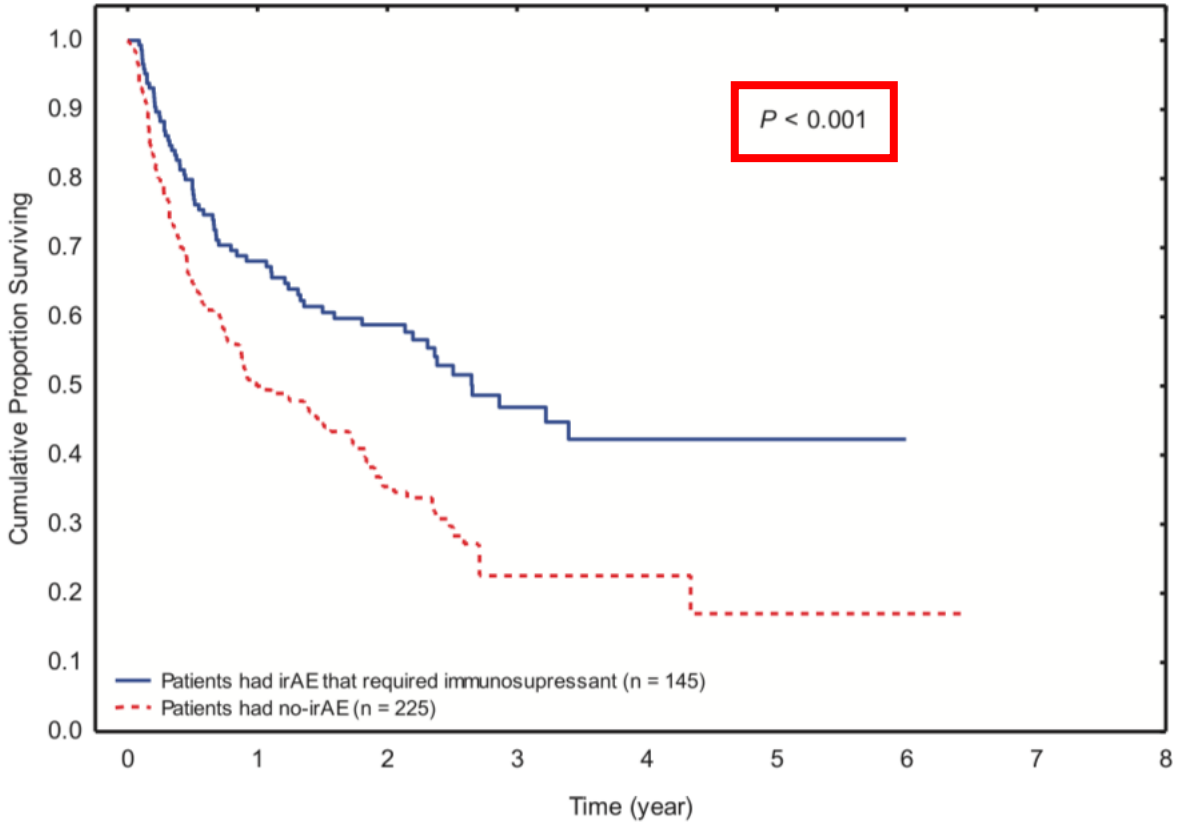


No significant difference in survival in melanoma patients who discontinued ipilimumab + nivolumab due to irAEs versus those who did not discontinue treatment

Schadendorf D. J Clin Oncol 2017

Autoimmunity as a prognostic marker?

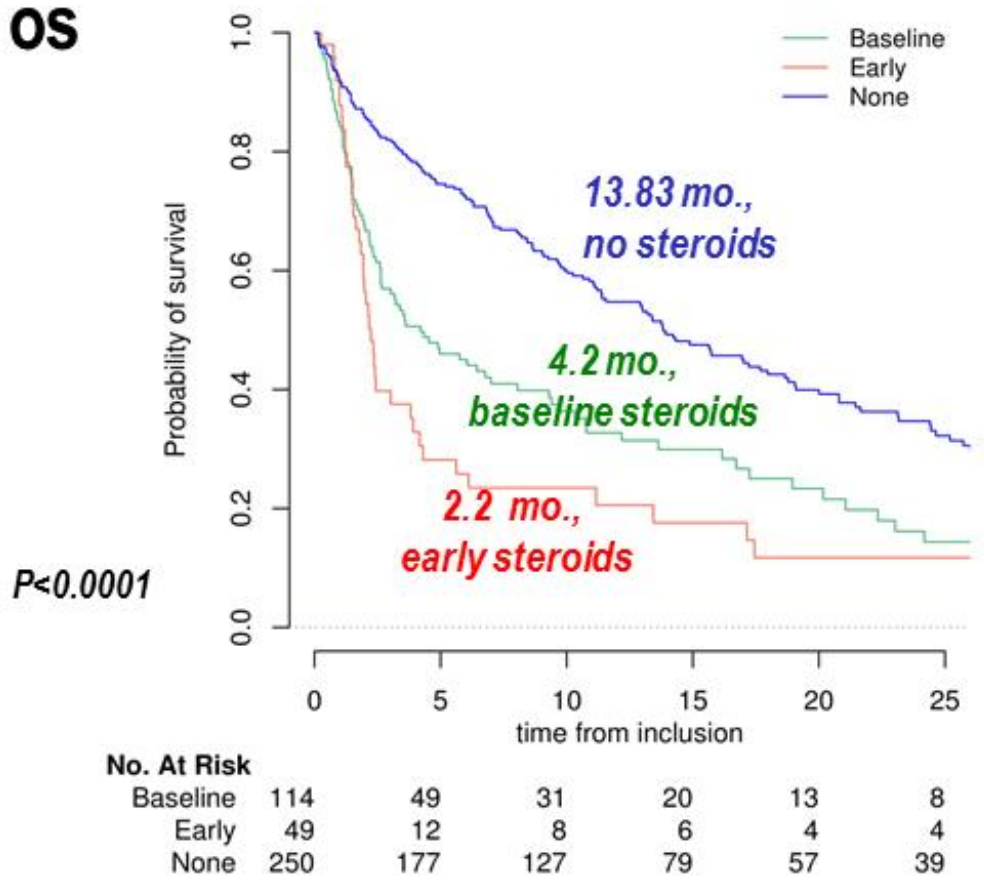


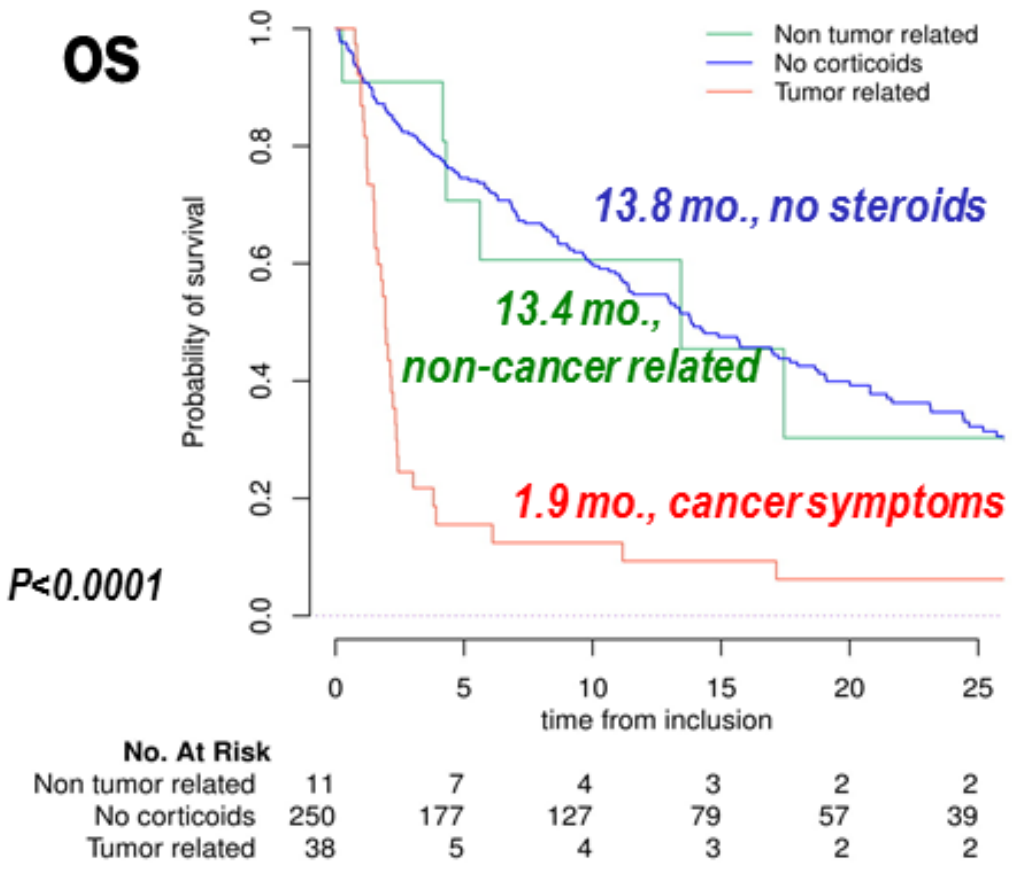


Based on **retrospective** data, patients who experience irAEs (regardless of needing treatment) may have better outcomes compared to patients who do not experience irAEs

Abu-Sbeih, J Immunoth Prec Oncol 2018.

Impact of steroid management on patient outcomes





De Giglio, Mezquita et al, ESMO-IO 2020.

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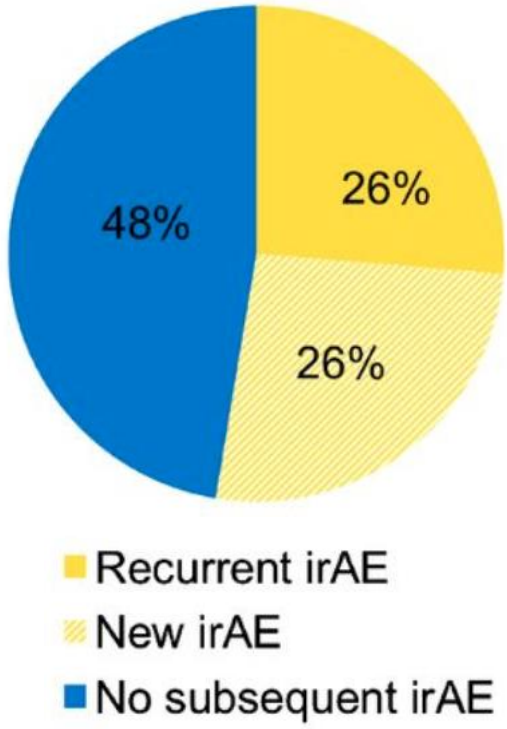
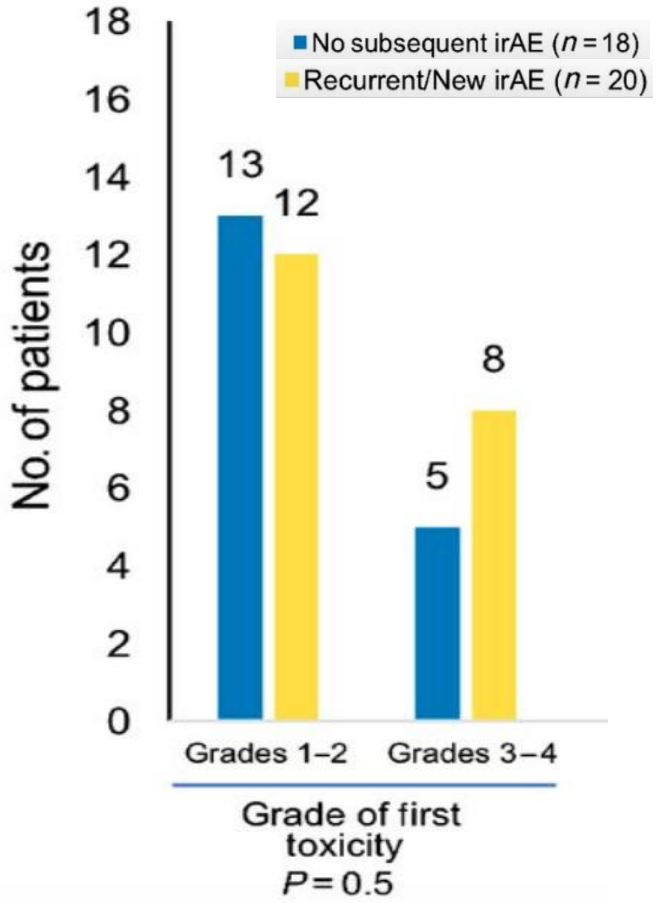
Rechallenging with ICIs after irAEs

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





Santini FC. Cancer Immunol Res 2018.

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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

NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

CRS and Neurotoxicity

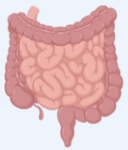
- Should not be viewed as two unrelated adverse events
  - Overlapping toxicities from excessive immune activation
  - May occur together or exclusive of one another
  - However, they do have distinct timing and responses to treatment
- Risk factors for both include:
  - High disease burden
  - Higher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

Santomasso BD. Cancer Discov 2018.
Wang Z. Biomark Res. 2018.

Cytokine release syndrome

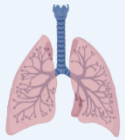
Cytokine Release Syndrome symptoms

Gastrointestinal
- Nausea/vomiting
- Diarrhea
- Anorexia



Skin
- Rash

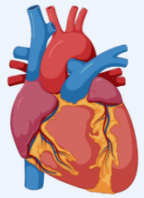
Respiratory
- Tachypnea
- Hypoxia
- Pulmonary edema



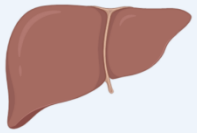
Constitutional
- Fever +/- rigors
- Malaise/fatigue
- Myalgias
- Arthralgias
- Headache

Coagulation
- Elevated D-dimer
- Hypofibrinogenemia +/- bleeding

Cardiovascular
- Tachycardia
- Hypotension
- Capillary leak
- Widened pulse presssure
- Increased cardiac output (early)
- Potentially diminished cardiac output (late)



Hepatic dysfunction
- Transaminitis
- Hyperbilirubinemia



Renal function
- Azotemia

Riegler LL. Ther Clin Risk Manag 2019.

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	• Antibiotics • GCSF if neutropenic
Grade 2 (fever/hypotension)	Tocilizumab 8mg/kg (4 doses max)	refractory hypotension Dex 10mg q6	• IV fluids, pressors • Manage as G3 is no improvement in 24hr
Grade 3 (+pressors)	Tocilizumab 8mg/kg (4 doses max)	Dex 10mg q6	• IV fluids, pressors, • Echocardiogram • ICU, oxygen
Grade 4 (+ventilatory support)	Tocilizumab 8mg/kg (4 doses max)	Dex 10mg q6 Methylpred 1g/day if refractory	• ICU care • Mechanical ventilation • Organ toxicity management

Neelapu et al, *Nat Rev Clin Oncol* 2018
Thompson et al, *JNCCN* 2019, NCCN guidelines
Lee et al, *Biol Blood Marrow Transplant 2018*

Neurotoxicity

- Also called CAR-T Related Encephalopathy Syndrome (CRES) or iIEC-associated neurologic syndrome (ICANS)
- Occurs in 20-64% of patients, ≥ 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	Unrousable
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

Wang Z. Biomark Res. 2018
Hunter BD. J Natl Cancer Inst. 2019

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/m^2
  - 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

Titov A. Cell Death Dis. 2018.
Neelapu SS. Nat Rev Clin Oncol. 2018.

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

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

Kahler KC. Cancer Immunol Immunother. 2018.

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

Davids MS. NEJM 2016
Haverkos BM. Blood 2017
Abdel-Wahab. JITC 2019

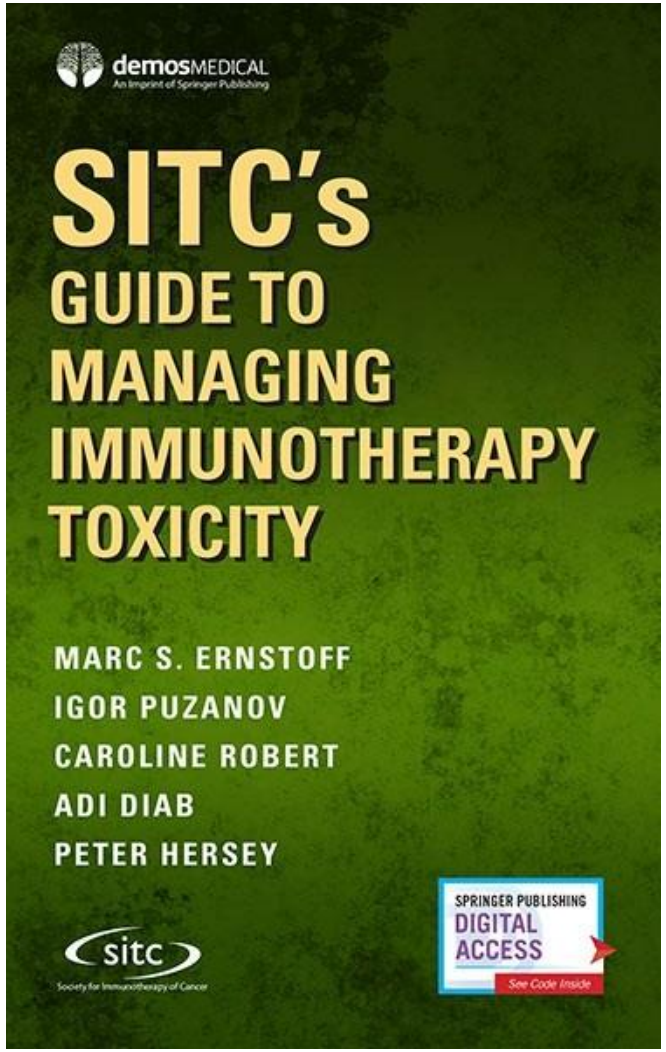
The importance of patient education

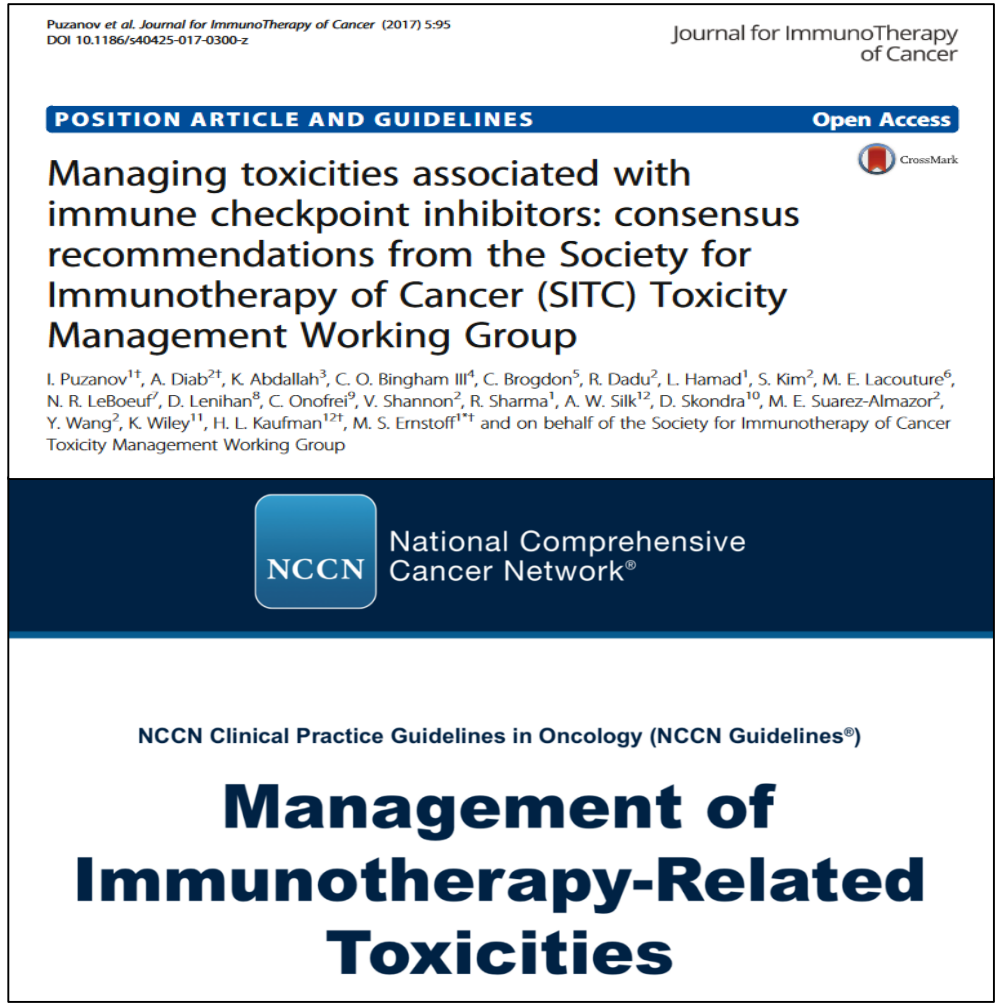
- Many immune-related adverse events can present in similar ways to other diseases, but the treatment of them is very different.
- Patients need to be able to identify themselves as immunotherapy recipients
- Reassure patients that irAEs will likely resolve over time (except endocrinopathies)

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





#LearnACI

Case Study 1

AP is a 32 yo female with metastatic melanoma (pulmonary, liver, and soft tissue metastases). She has received 4 cycles of combination ipilimumab 3mg/kg with nivolumab 1mg/kg and presents following her 4th dose with a 4 day history of diarrhea. She was recently on a 5 day course of antibiotics for sinusitis. She reports that her stools became loose and that the frequency increased over the 4 days to her current 8 BM with some tenesmus, but without blood. She additionally reports nausea and decreased intake of food.

<u>What is the first step in her management?</u>

A. Initiate steroids at 2mg/kg/day, without further workup

B. Initiate steroids at 1mg/kg/day, without further workup

C. Give IV fluids for dehydration; loperimide, and observe

D. Admit patient to hospital for infection workup, colonoscopy, and IV methylprednisolone at 1-2mg/kg/day

Case Study 1

What is the first step in her management?

- A. Initiate steroids without further workup
  - We must first rule out alternative causes for diarrhea: including infection *(c. Diff, ova and parasites or other bacteria), CMV* and colonoscopy to exclude underlying disease.
- B. Consult infectious disease to treat for *C. Diff* given her recent antibiotic use
  - While she was on antibiotics, a 5 day course is unlikely to cause c. diff colitis; however, a complete workup should be performed with stool cultures as well as colonoscopy given her treatment with ipilimumab/nivolumab.
- C. Give IV fluids for dehydration; loperimide, and observe
  - Treating conservatively would miss the underlying cause of the diarrhea, which is immune-mediated colitis. Additionally, Loperimide has been known to increase risk of bowel perforation.
- D. Admit patient to hospital for infection workup, colonoscopy, and IV methylprednisolone at 1-2mg/kg/day

Case Study 1

The patient was admitted, GI was consulted and a colonoscopy and stool cultures for *c.diff, ova & parasites,* and CMV were performed. CT scan of the abdomen and pelvis was negative for disease, but did show stranding around the descending colon. Cultures of the stool were negative for bacteria, ova, parasites; *c. difficile* was negative, and the colonoscopy revealed severe colitis in the descending colon and ileum. Patient was started on methylprednisolone at 2mg/kg/day due to severity. Diarrhea was not resolved after 72 hours.

What is the next step in management of this patient?

A. Continue current dose of steroids

B. Give infliximab or vedolizumab

Case Study 1

What is the next step in management of this patient?

- A. Continue current dose of steroids
- B. Give infliximab or vedolizumab

The patient was given a dose of infliximab at standard dose and her diarrhea improved over the next 36 hours to formed, with nausea and tenesmus improved after just 24 hours. She did was discharged home on 1mg/kg/day oral equivalent of prednisone with a taper over 6 weeks.

Do you dose this patient with nivolumab following recovery of toxicity and taper of steroids?

Case Study 2

- Mr. M. is a 74 y.o. male with Stage IIIC melanoma of the LLE, s/p resection of local recurrence and split thickness skin graft (STSG)
- Began adjuvant nivolumab therapy
- 3 weeks later, noted diplopia. Brain MRI showed no CNS lesions
- Seen by local ophthalmologist without abnormalities noted
- Seen by neuro ophthalmology with limited abduction of both eyes noted, raising concern for myositis or myasthenic syndrome. Neuro consult arranged.

Case Study 2

- Seen in clinic with weakness/trouble swallowing/ DOE
- Labs revealed CK 4986, MB 111, MBI 2.2, troponin 0.58, ALT 220, AST 317 c/w myositis/myocarditis/hepatitis.
- EKG without acute changes
- Admitted and echo showed new LV regional systolic dysfunction from presumed myocarditis
- Treated with IV Solu-Medrol with improvement in cardiac enzymes
- No ventricular arrhythmias

Case Study 2

- Neuro sx's c/w myasthenia gravis/myositis
- Acetylcholine receptor binding antibody positive
- Developed worsening inspiratory capacity; transferred to the ICU
- Treated with 5 days of IVIG and BiPAP with improved inspiratory capacity
- Transaminitis improved on steroids
- DC'ed home 10 days after admission on very slow steroid taper – still very deconditioned/weak

Case Study 2

- Slow improvement in strength and respiratory mechanics
- Presented 6 weeks after D/C with abdominal pain, nausea and vomiting
- Admitted with presumed cholecystitis; US guided percutaneous cholecystostomy placed
- Had worsening inspiratory capacity, transferred to ICU
- s/p IVIG x 5 days w/ improvement in pulmonary mechanics
- DC'ed after two weeks on slow steroid taper
- PET scan showed new FDG avidity in left medial thigh and mid tibial nodules, s/p surgical resection (and ccy)

Case Study 2

- This case study demonstrates the difficulty of severe irAE's, especially when they occur in the adjuvant setting
- Potential for negative outcomes as immunotherapy use becomes more widespread
- Will this type of case impact the application of adjuvant therapy in melanoma?

Acknowledgements

- Some figures created using Biorender.com