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

Society for Immunotherapy of Cancer

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Disclosures

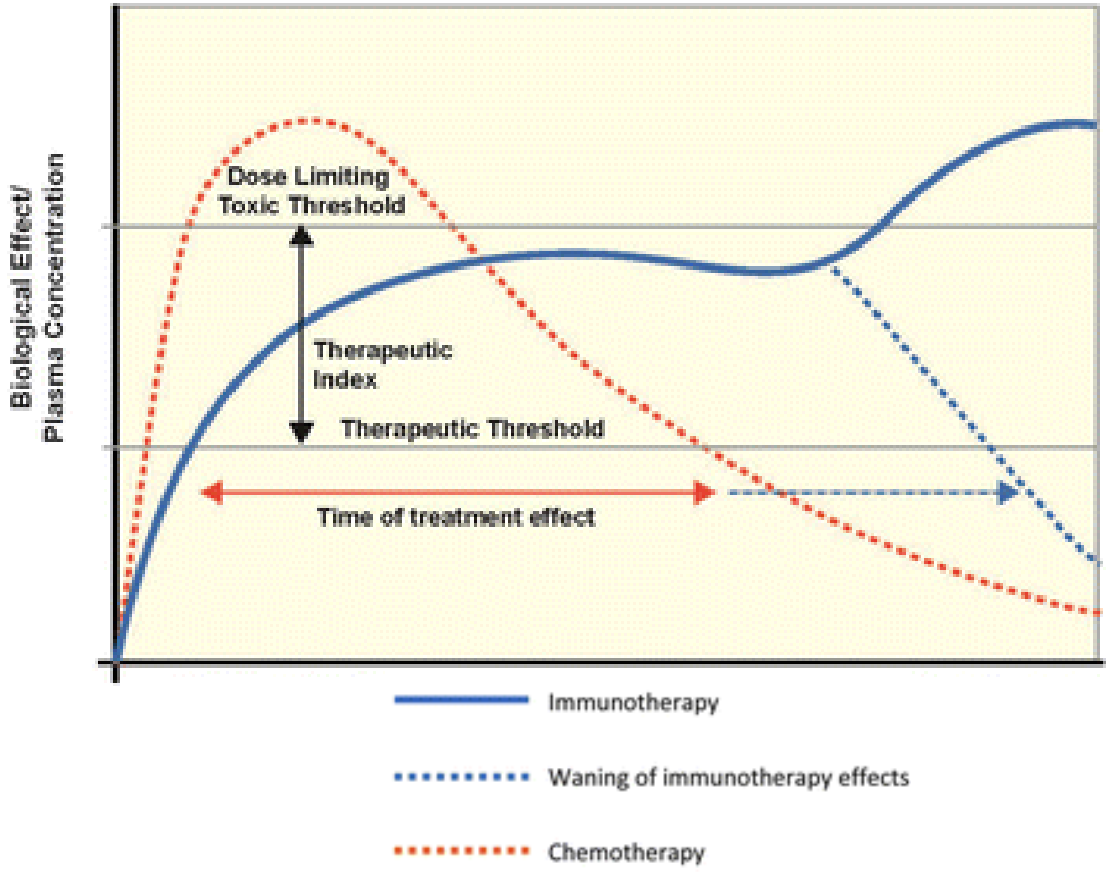
- Consulting Fees: Eisai
- I will be discussing non-FDA approved indications during my presentation.

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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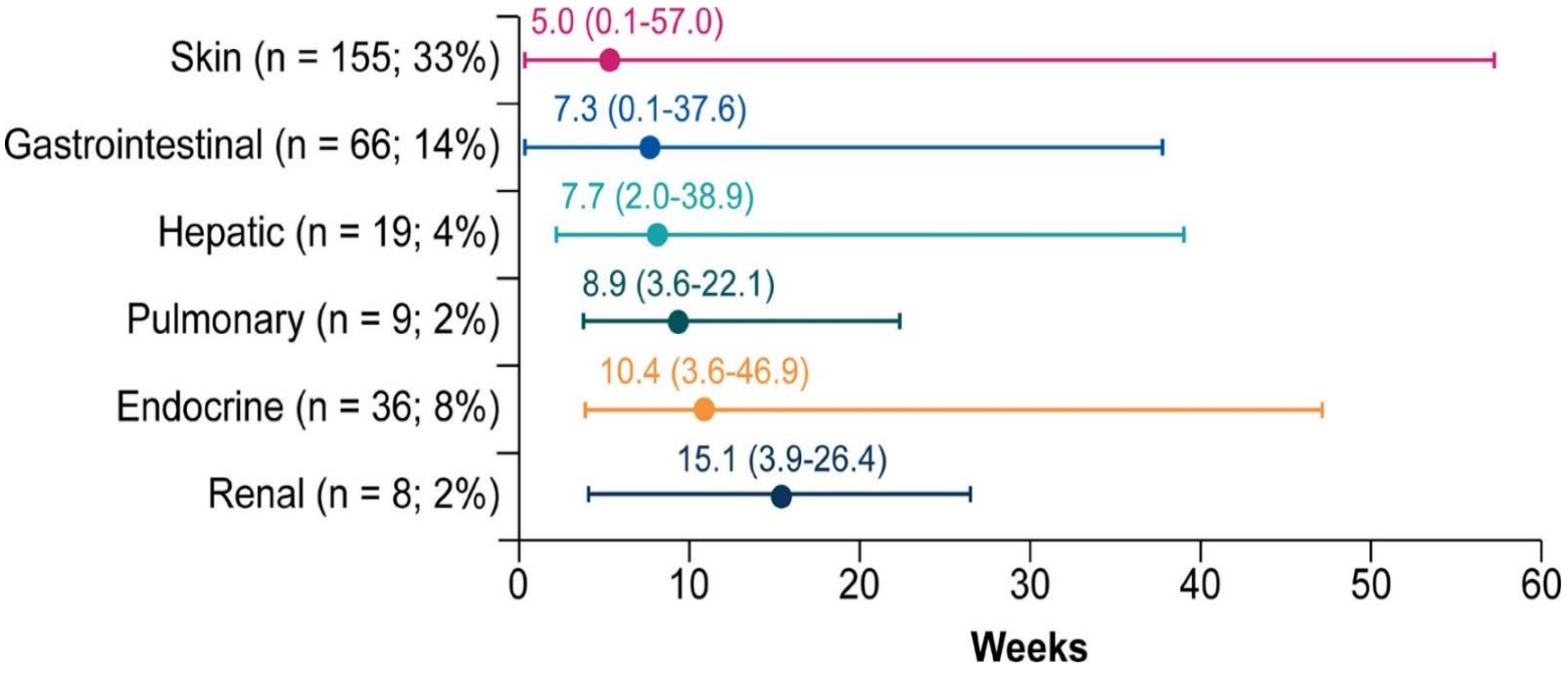
Onset of irAEs



- 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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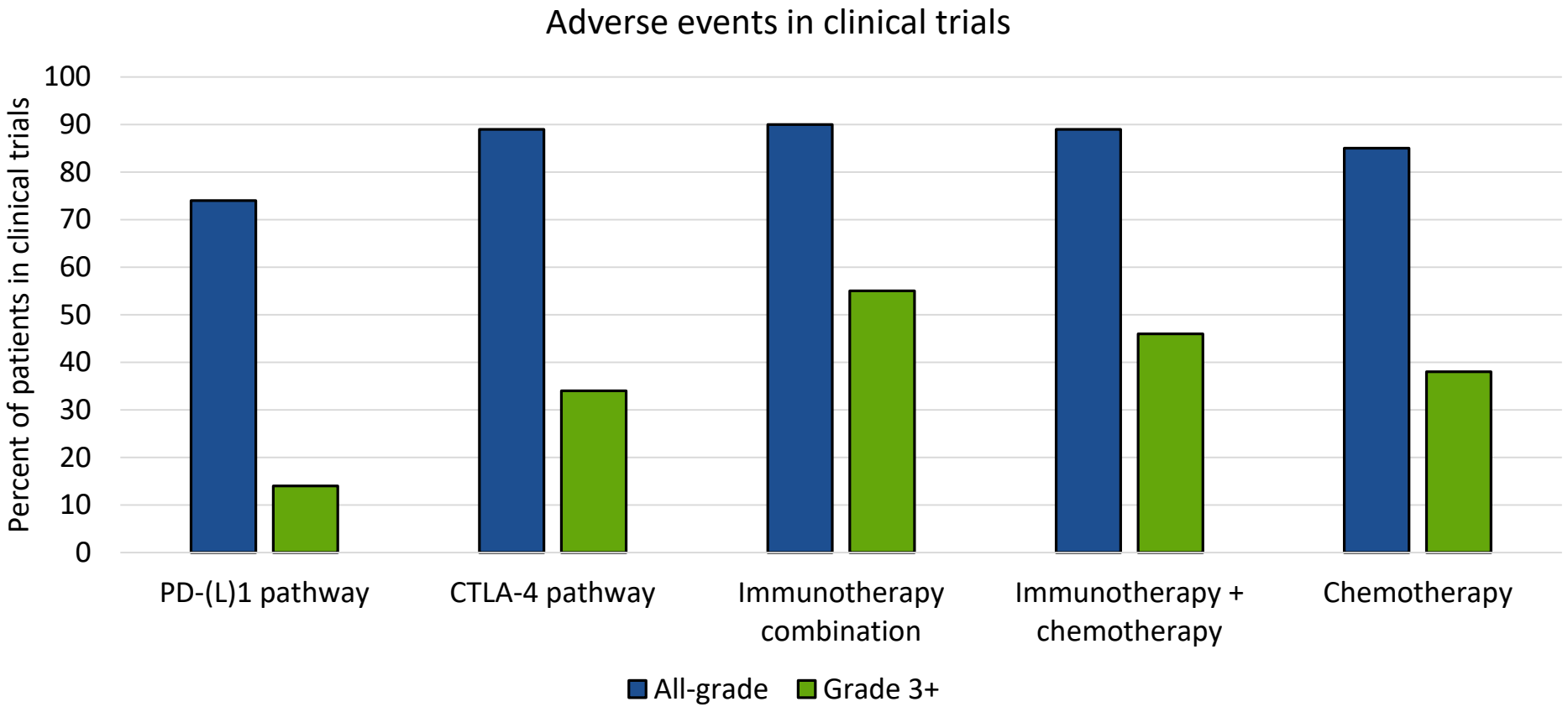
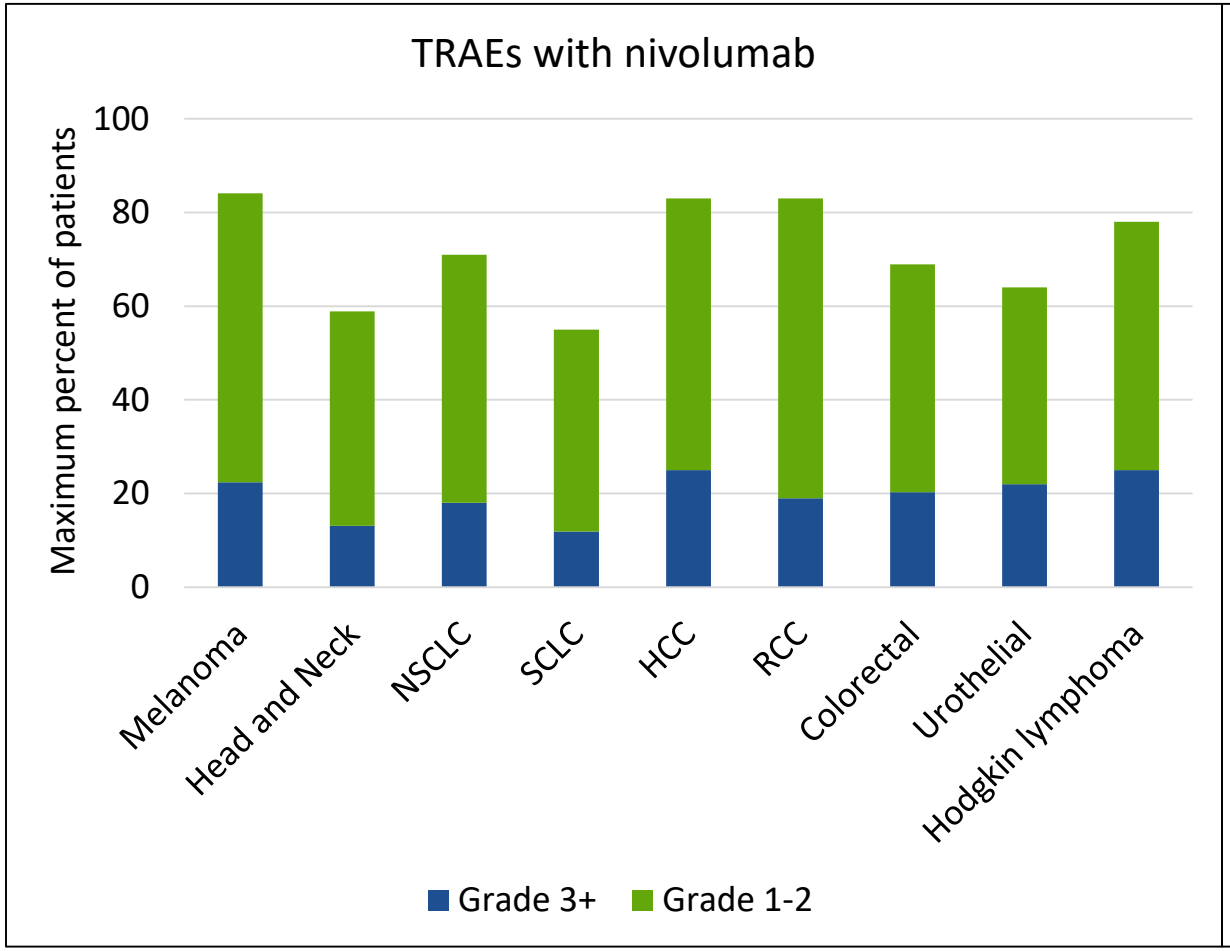
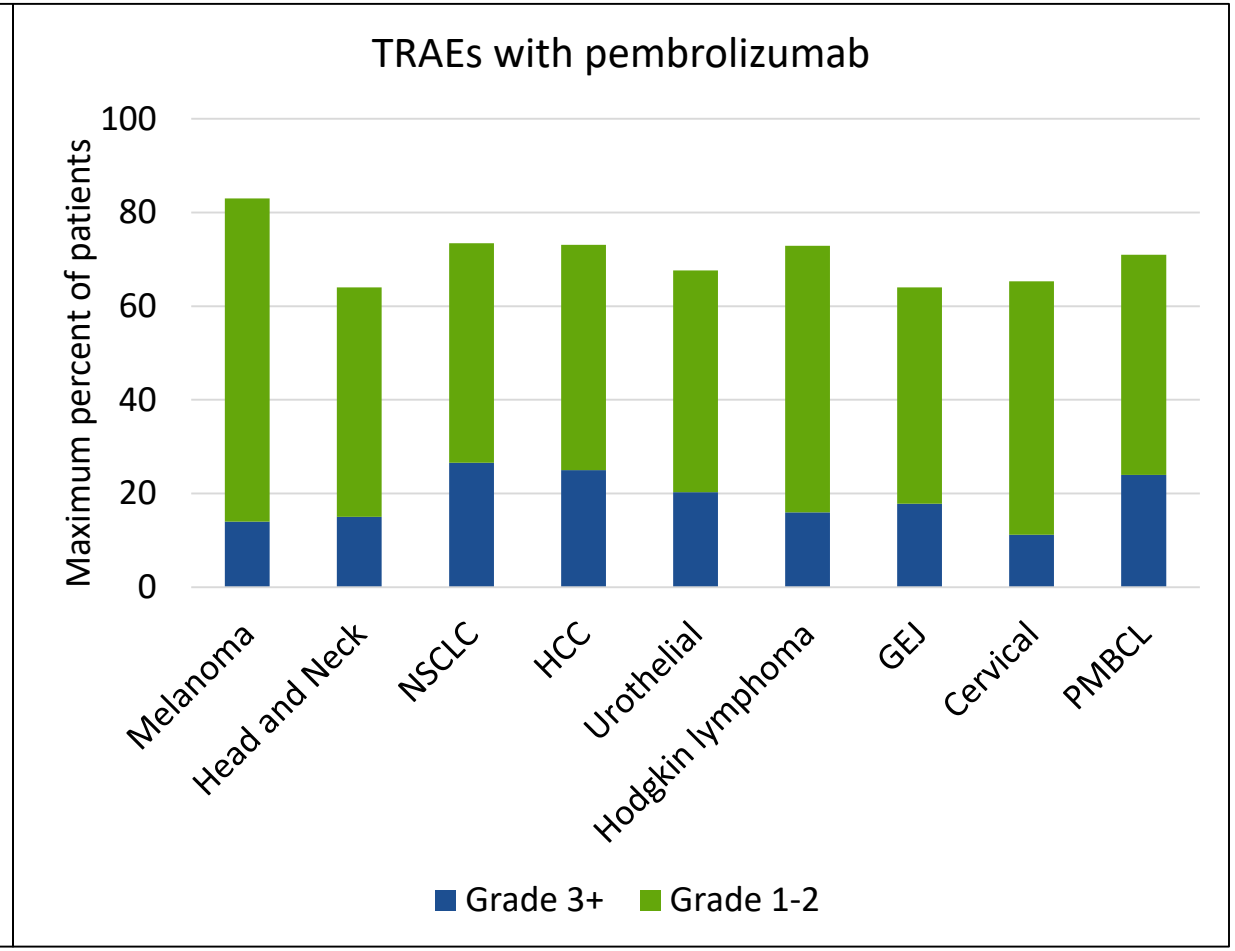
Toxicity with immune checkpoint inhibitors



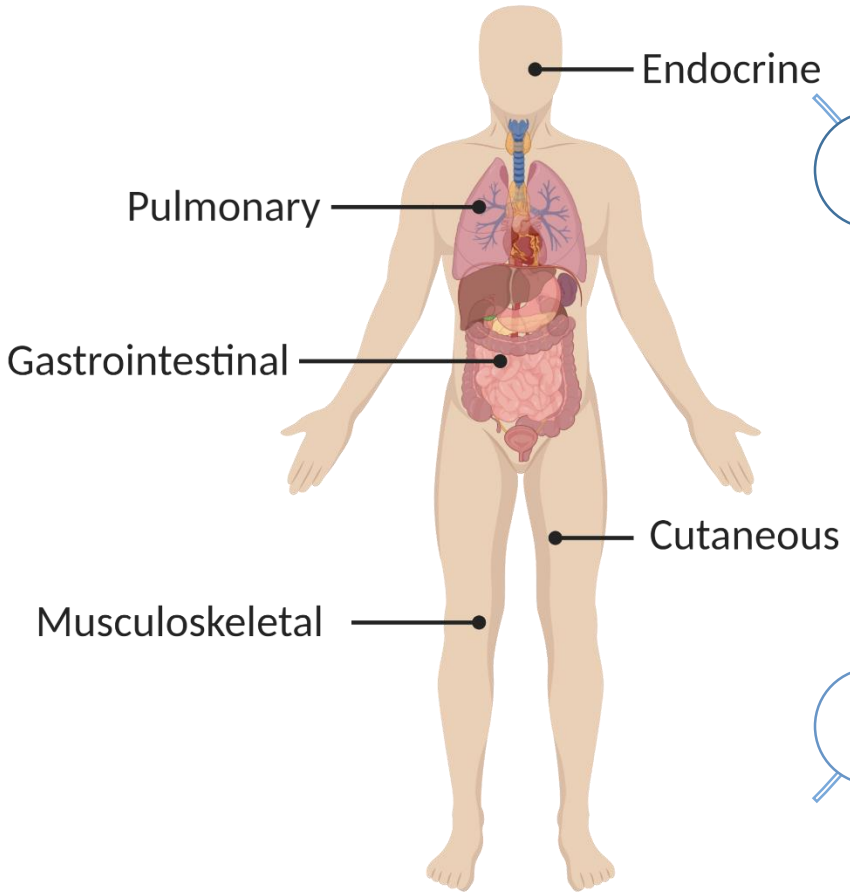
Arnaud-Coffin, Int J Cancer 2019

Toxicity with immune checkpoint inhibitors





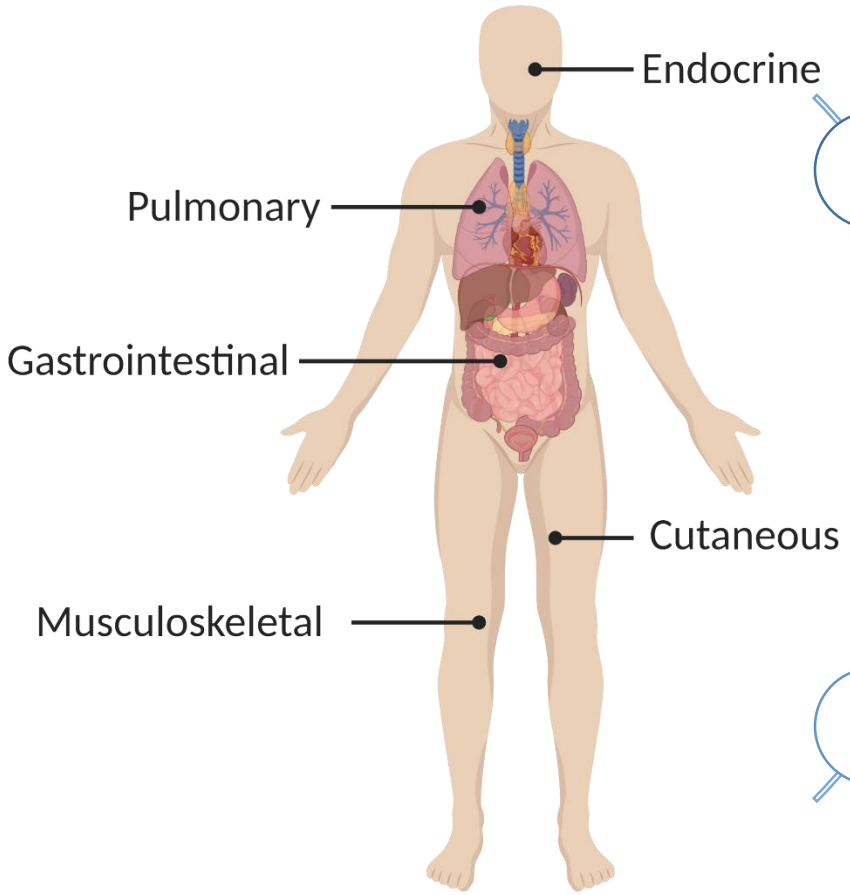
Common irAEs with ICIs



- 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



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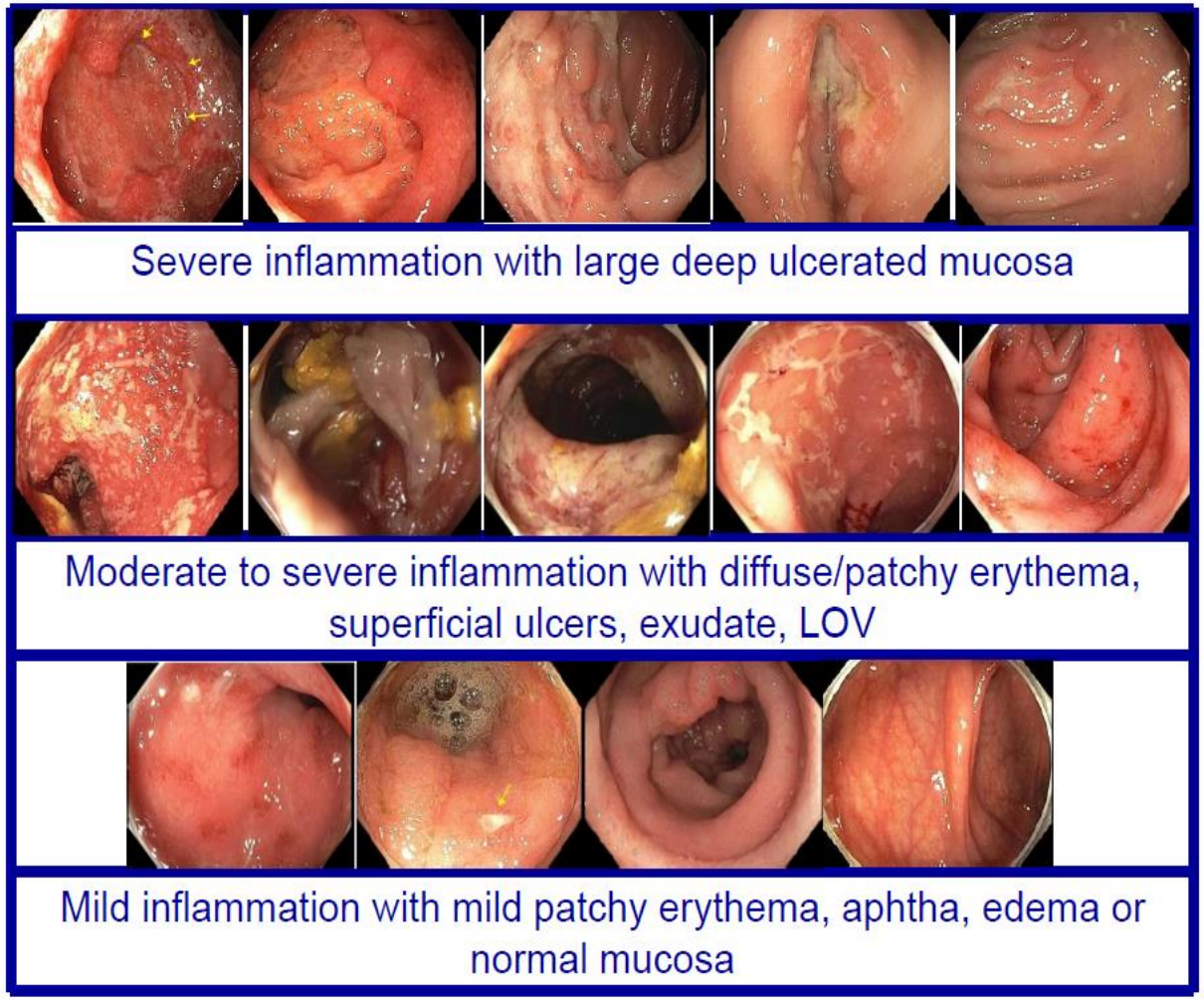
- Gastrointestinal: diarrhea, **colitis**, **hepatitis**, gastritis
- Musculoskeletal: inflammatory arthritis, myositis, sicca syndrome
- Pulmonary: **pneumonitis**, sarcoidosis
- Endocrine: **thyroid dysfunction, hypophysitis, Type 1 diabetes**

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

Diarrhea/Colitis

- Diagnostic evaluation
  - Rule out alternative diagnosis: C.difficile, other GI infections
  - Diarrhea while on ICIs should prompt suspicion of immune-mediated colitis
  - Labs: Stool lactoferrin (colitis) /calprotectin (ulcers)
  - 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

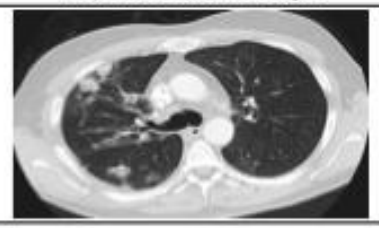
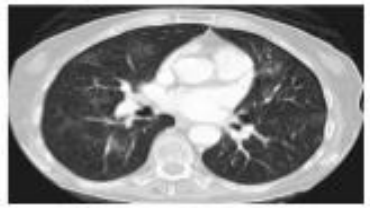
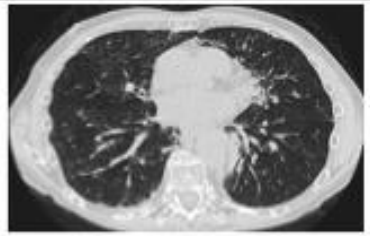
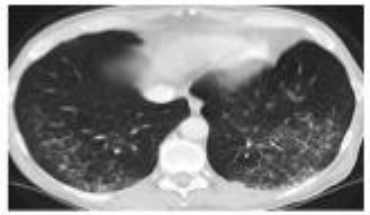
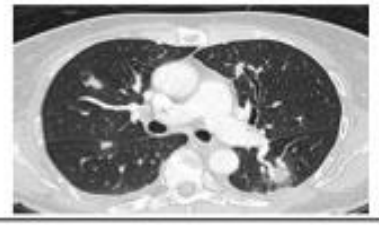
Hepatitis

- 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		

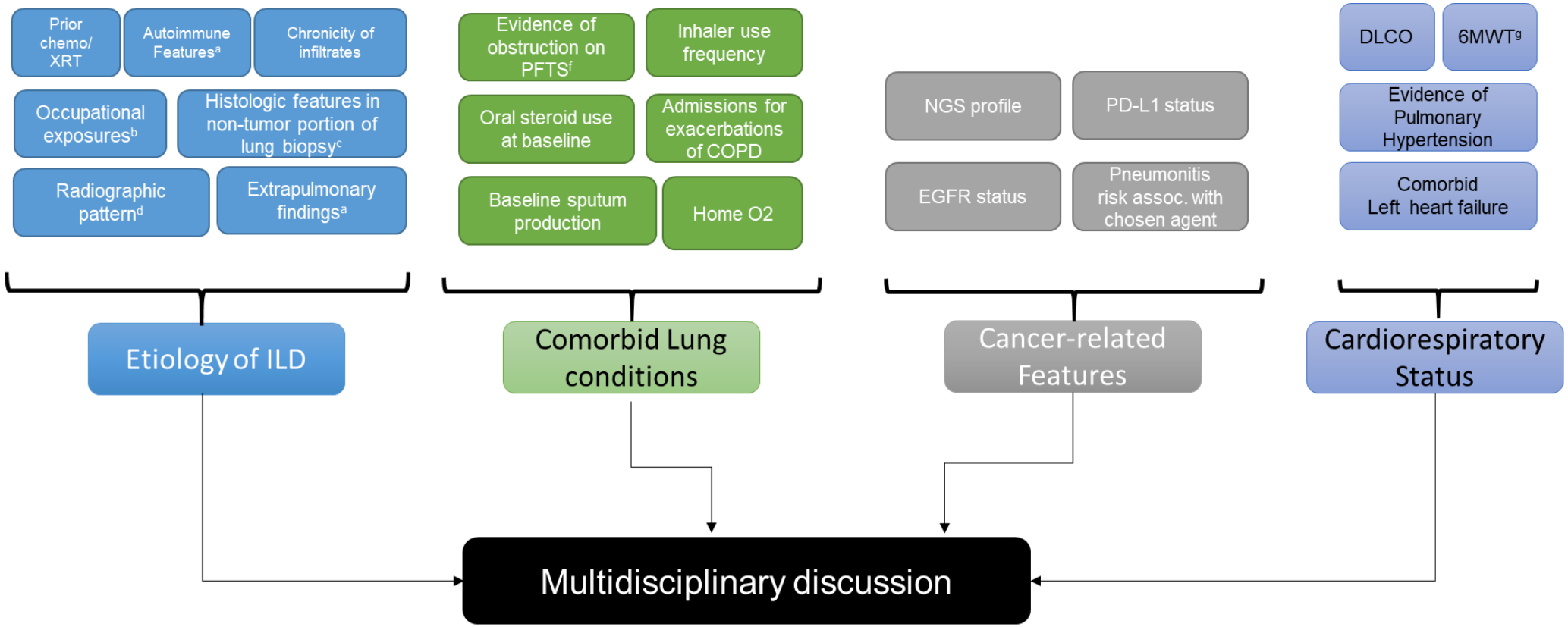
Pneumonitis

- 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

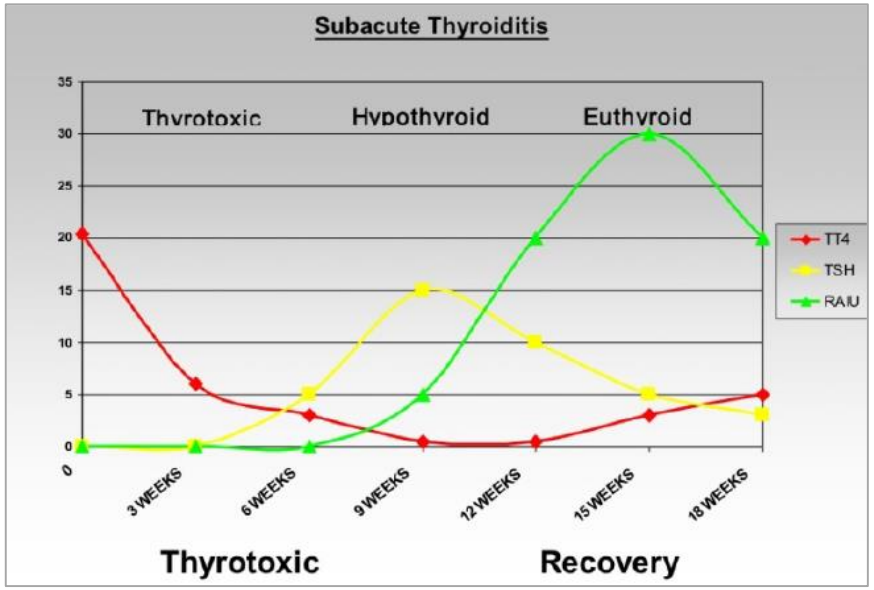


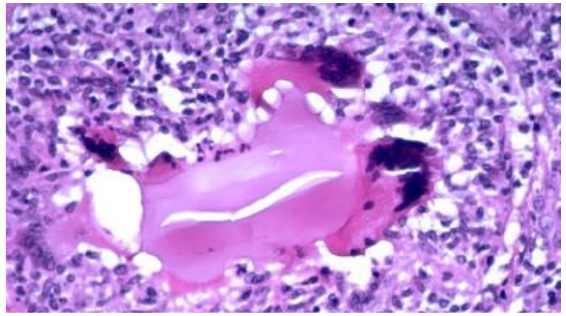
[a] Rashes (Gottron's papules, Heliotrope rash), evidence of synovitis, family history of RA/SLE, history of dry eyes/mouth, Raynaud's phenomenon
[b] Steelworkers, farmers, exposures to heavy metals, organic fumes, dusts, birds, etc. [c] such as poorly-formed granulomas, lymphocytic aggregates
[d] NSIP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

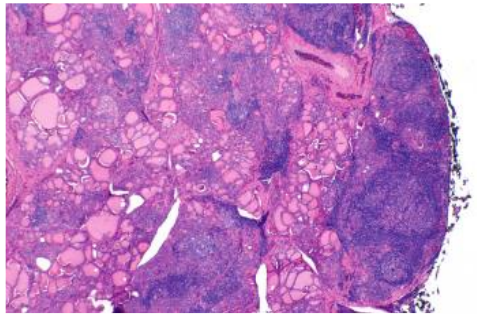
Naidoo, Suresh, The Oncologist 2020.

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

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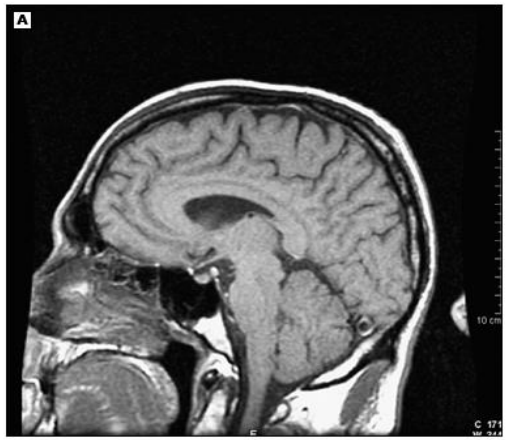
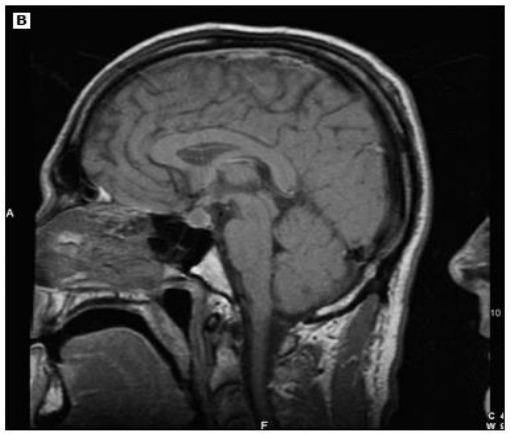
Hypophysitis

- 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
  - 6 minute walk test

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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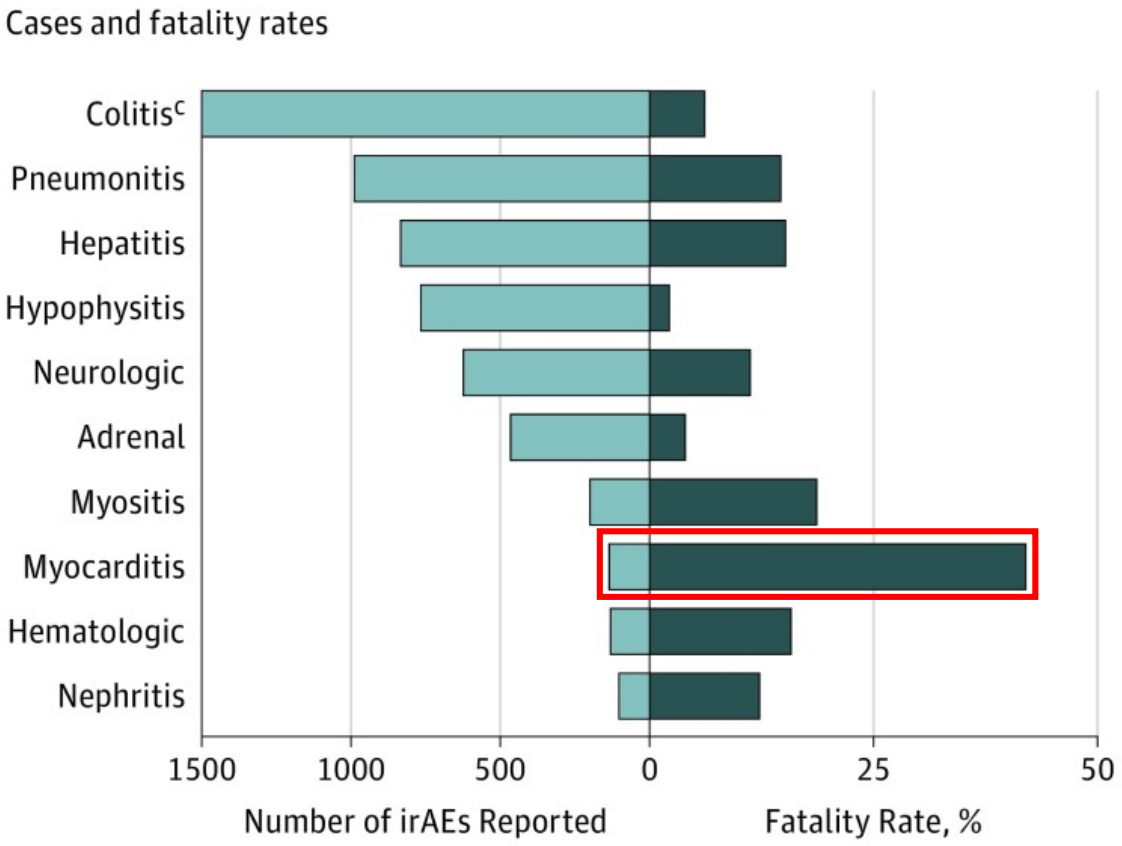
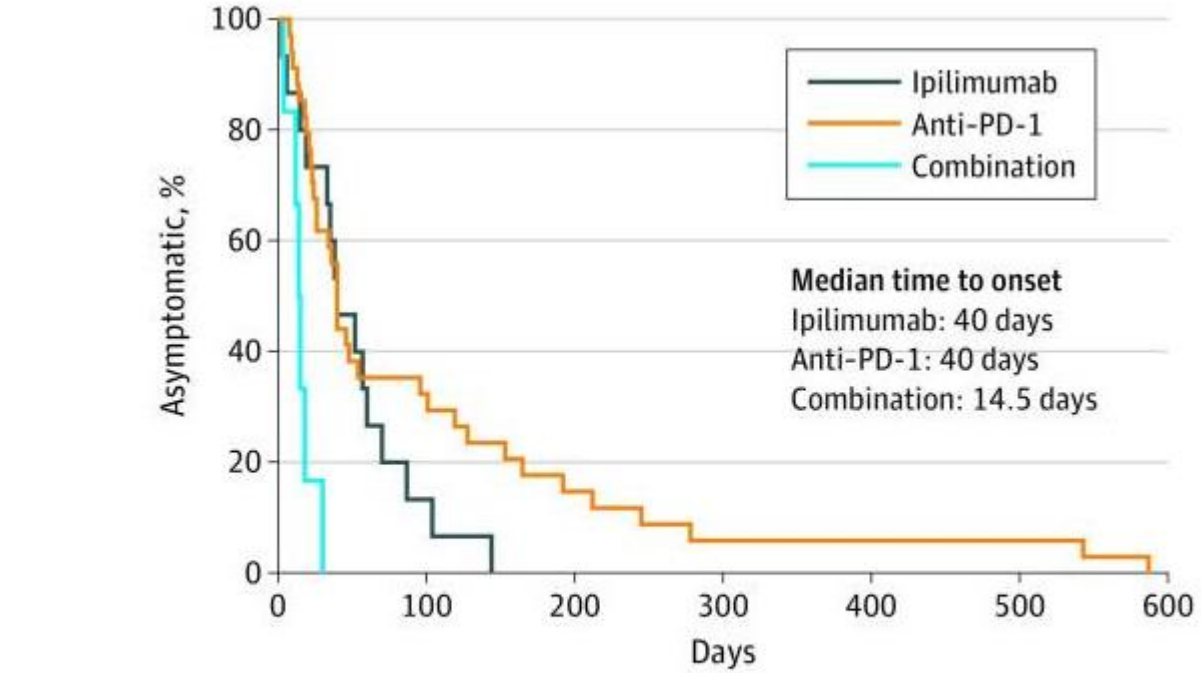
Fatal Events with ICIs



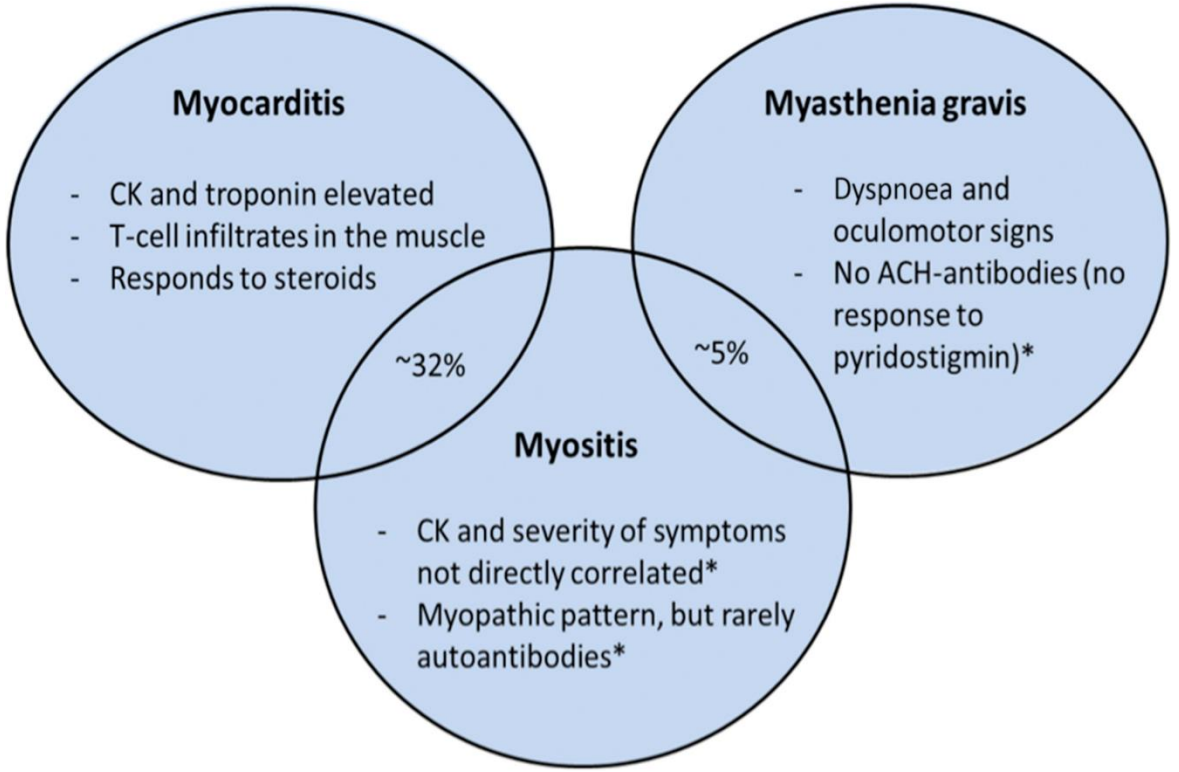


No. at risk							
Ipilimumab	15	2	0	0	0	0	0
Anti-PD-1	34	11	5	2	2	2	0
Combination	6	0	0	0	0	0	0

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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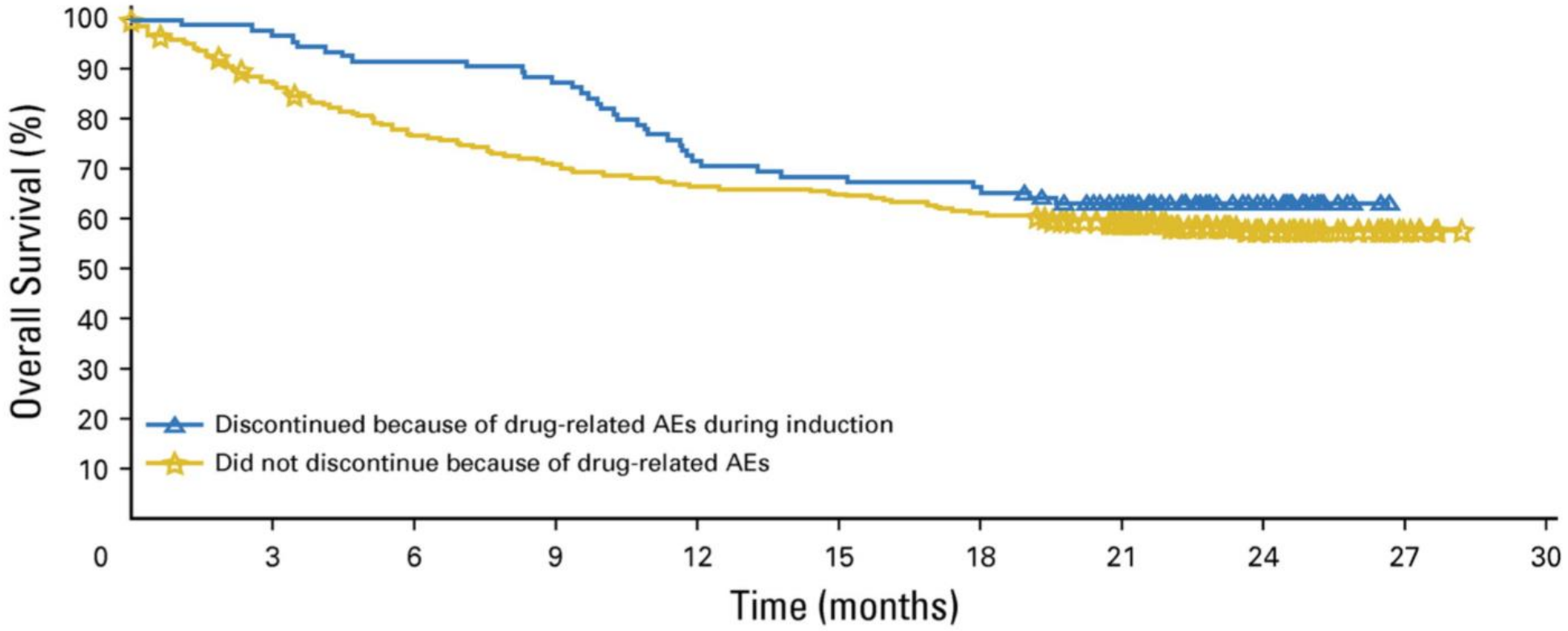
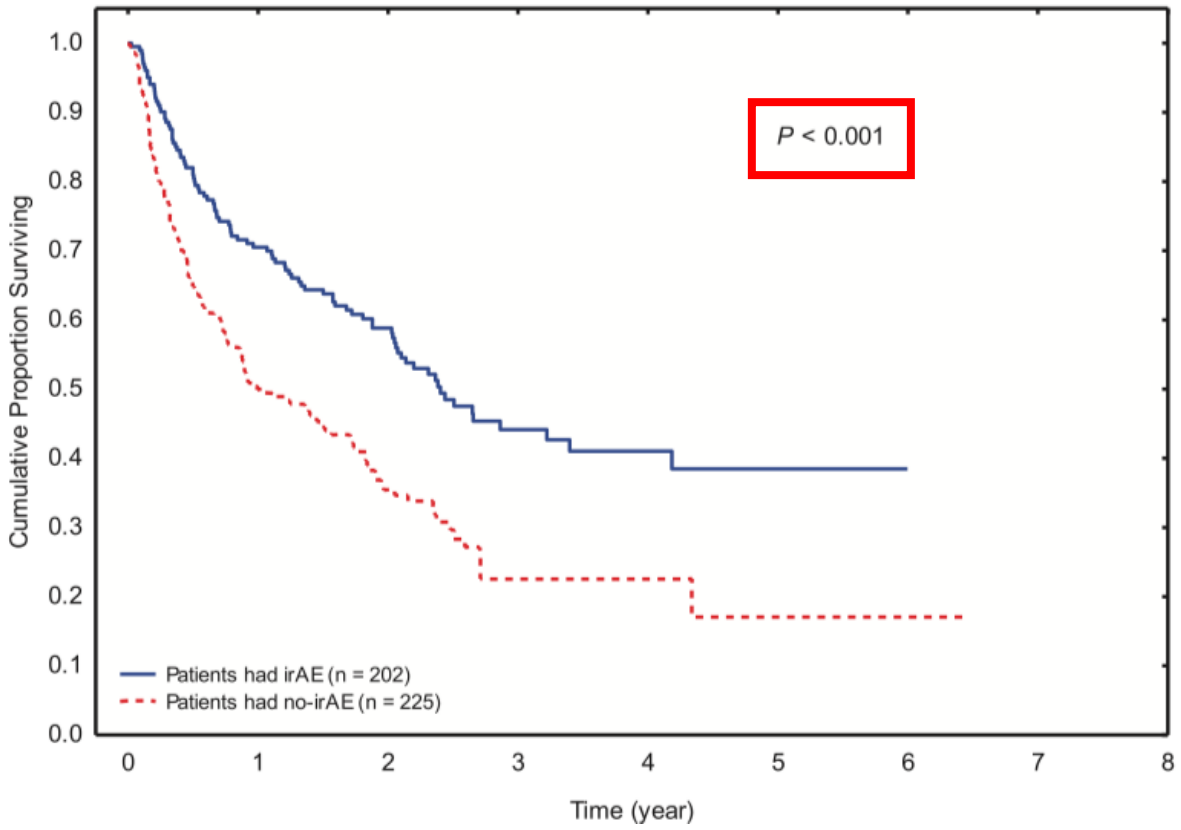
Effect of irAEs on patient outcomes

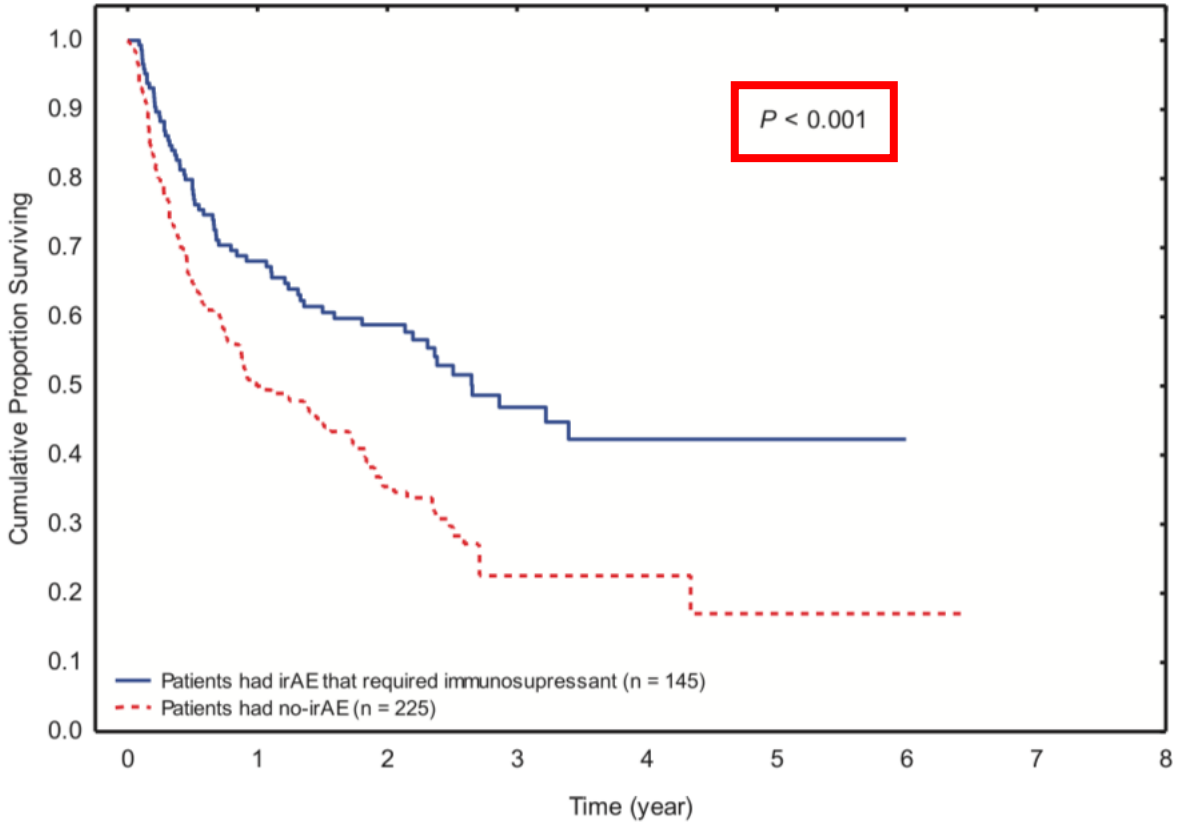


No significant difference in survival in melanoma patients who discontinued ipilimumab + nivolumab due to irAEs versus those who did not discontinue treatment

Schadendorf D. J Clin Oncol 2017

Autoimmunity as a prognostic marker?

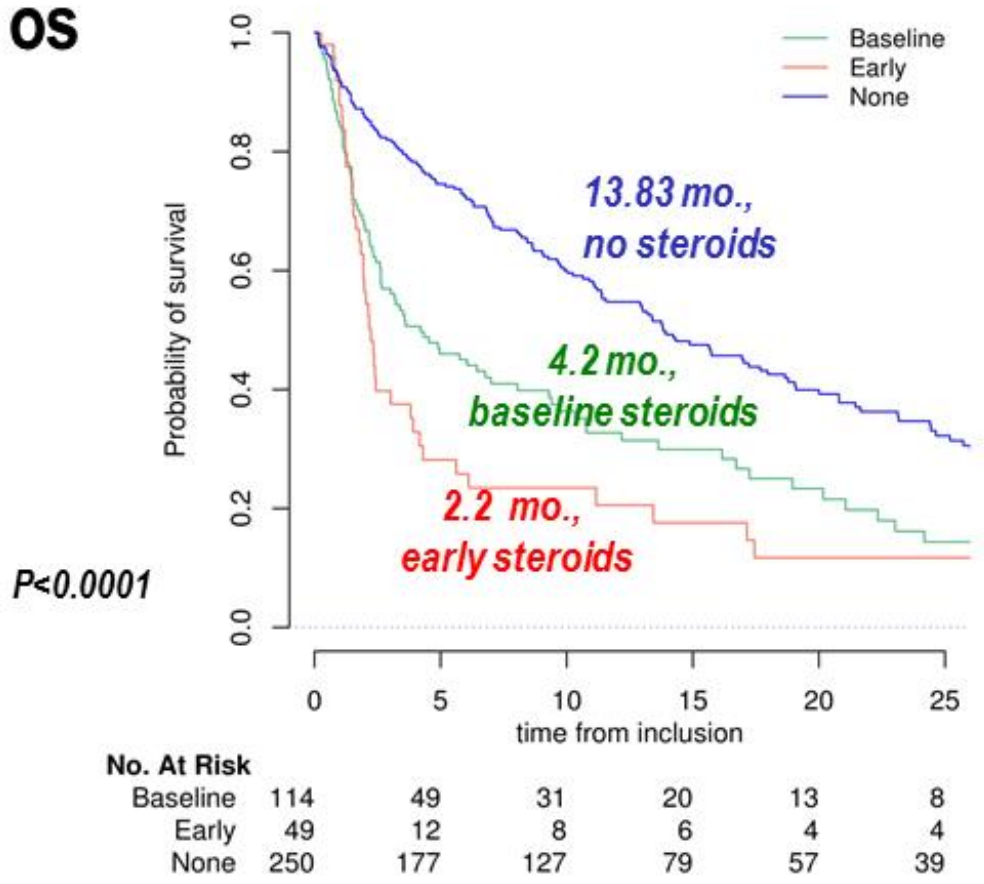


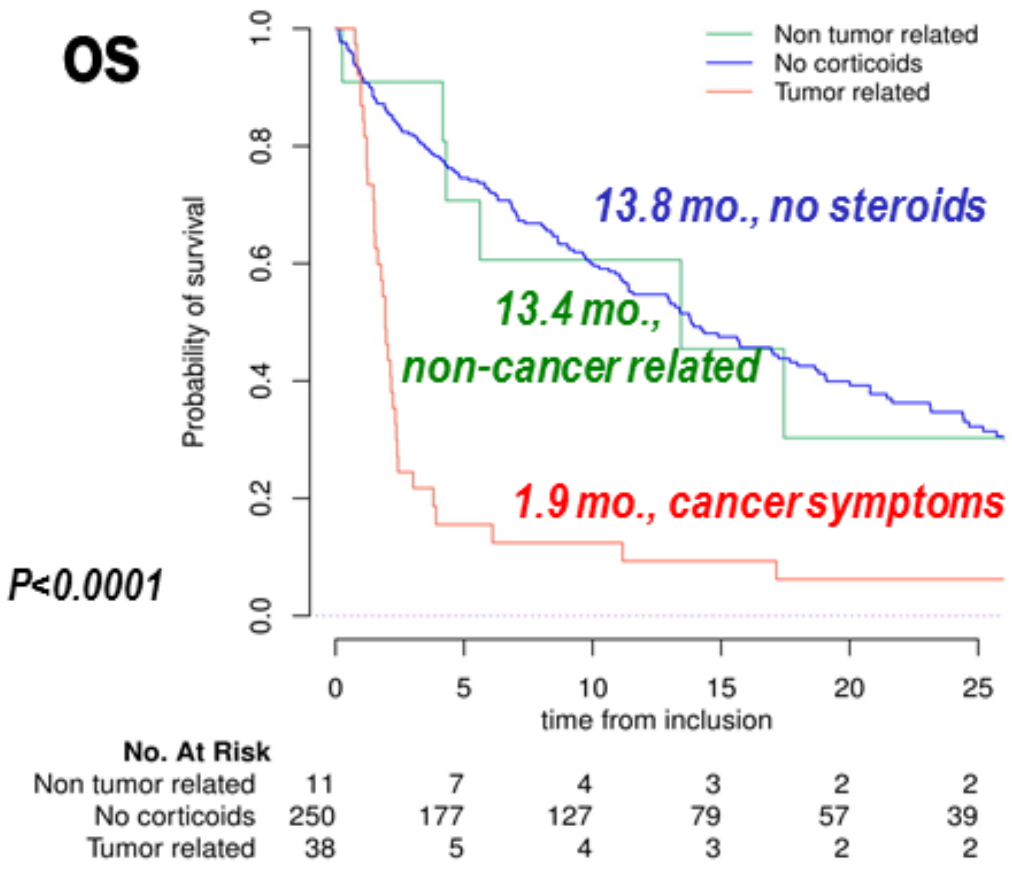


Based on **retrospective** data, patients who experience irAEs (regardless of needing treatment) may have better outcomes compared to patients who do not experience irAEs

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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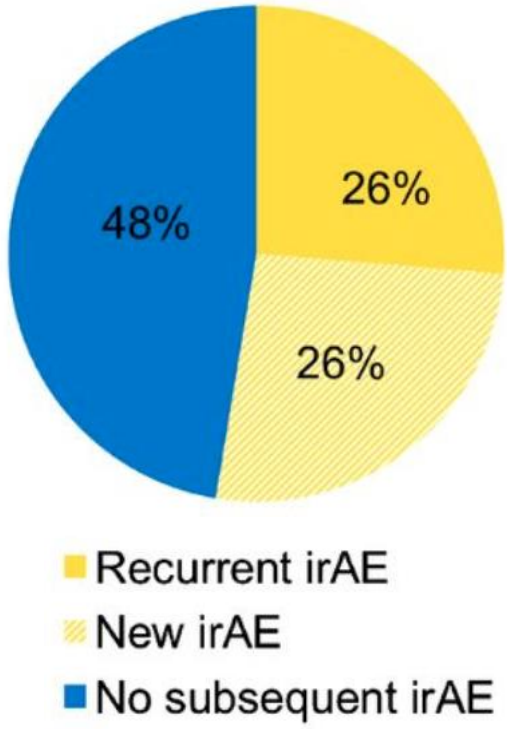
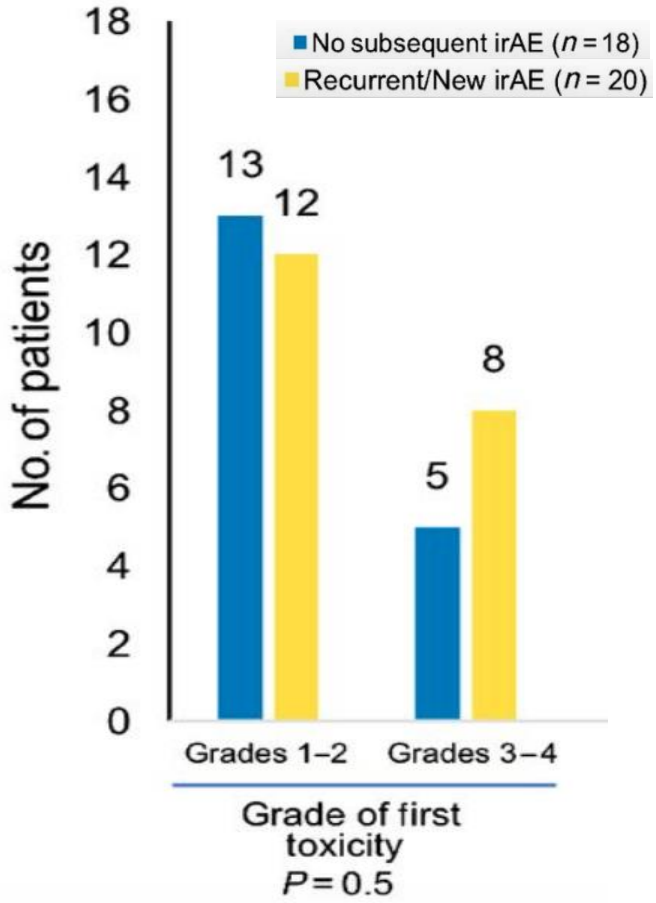
Rechallenging with ICIs after irAEs

- 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

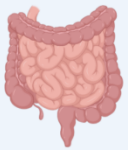
- Should not be viewed as two unrelated adverse events
  - Overlapping toxicities from excessive immune activation
  - May occur together or exclusive of one another
  - However, they do have distinct timing and responses to treatment
- Risk factors for both include:
  - High disease burden
  - Higher 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.

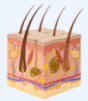
Cytokine release syndrome

Cytokine Release Syndrome symptoms

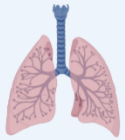
Gastrointestinal
- Nausea/vomiting
- Diarrhea
- Anorexia



Skin
- Rash



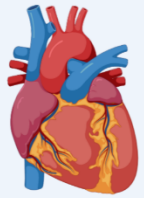
Respiratory
- Tachypnea
- Hypoxia
- Pulmonary edema



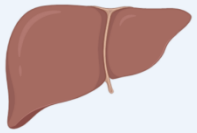
Constitutional
- Fever +/- rigors
- Malaise/fatigue
- Myalgias
- Arthralgias
- Headache

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

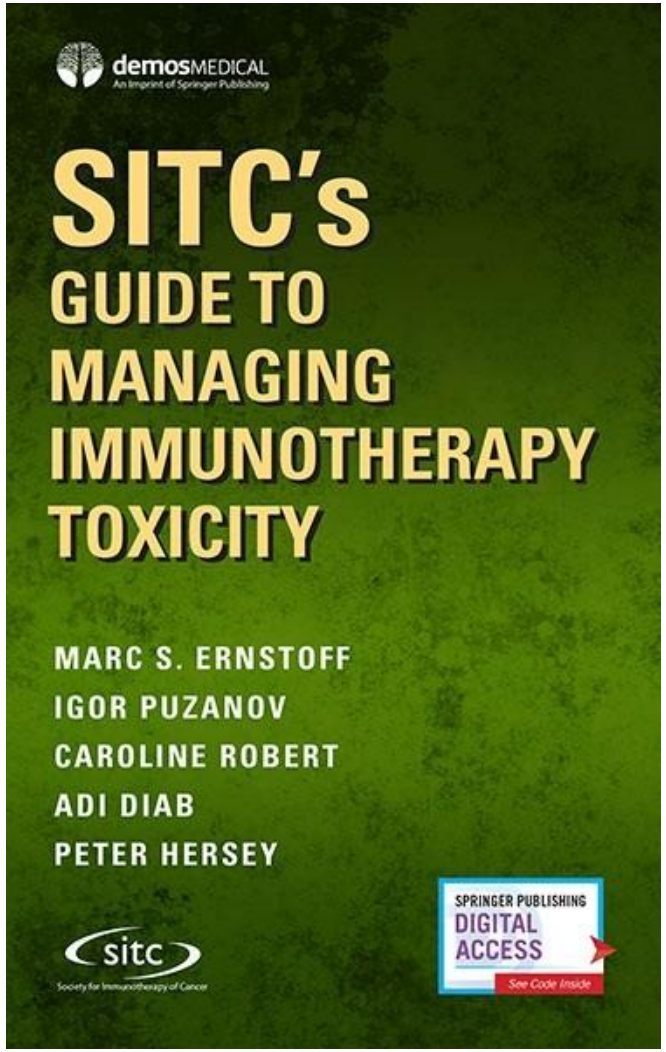
The importance of patient education

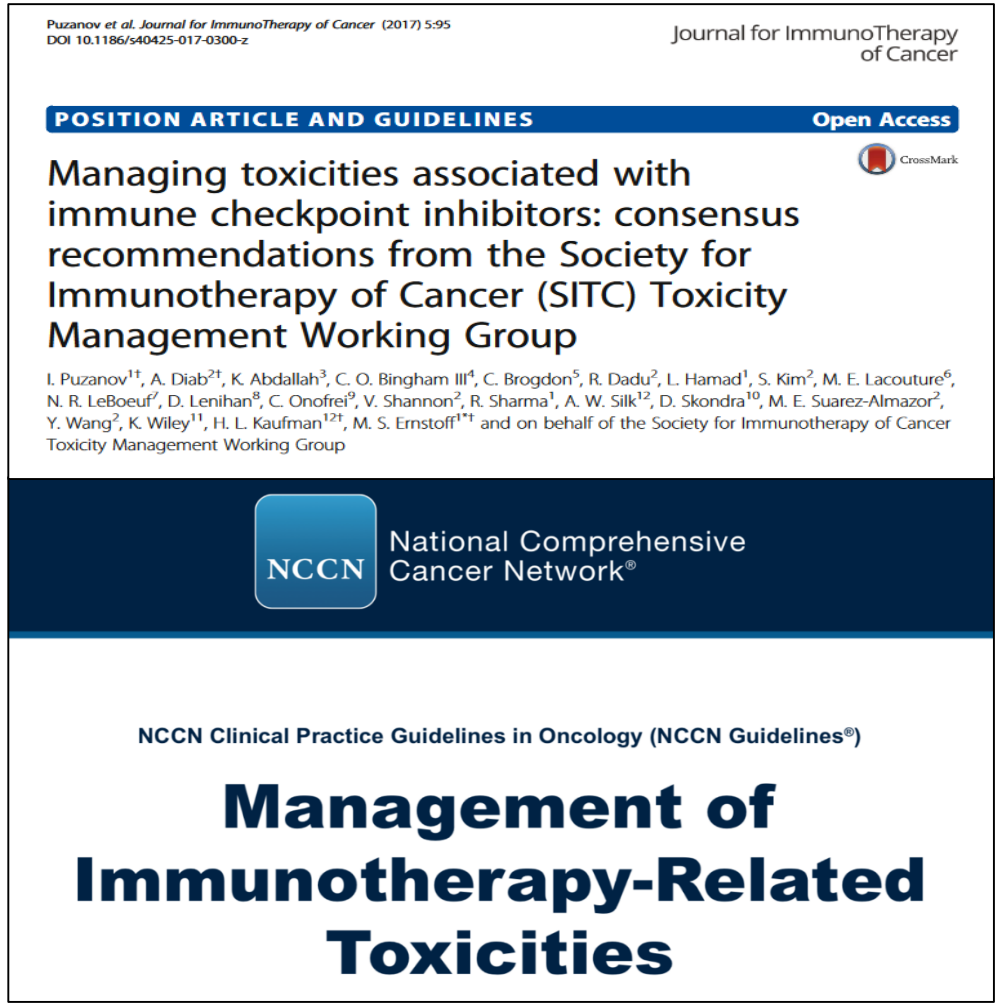
- Many immune-related adverse events can present in similar ways to other diseases, but the treatment of them is very different.
- Patients need to be able to identify themselves as immunotherapy recipients
- Reassure patients that irAEs will likely resolve over time (except endocrinopathies)

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





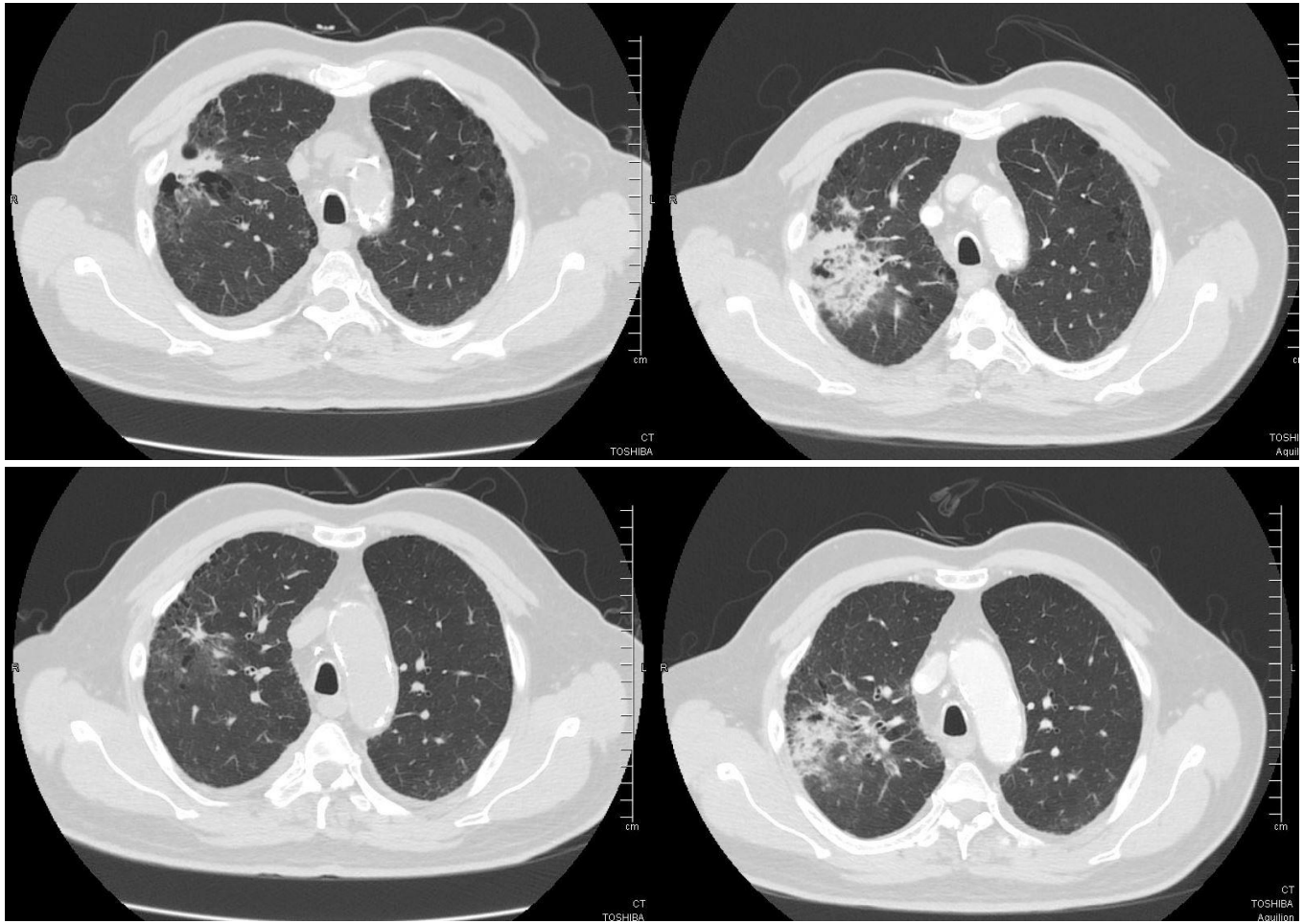
#LearnACI

Case Study 1

- 65 yo male
  - DIAGNOSIS: Adenocarcinoma, Non Small Cell Lung Cancer; No Genomic alterations
  - STAGING: IV : with Brain and adrenal metastasis
  - PRIOR THERAPIES:
    - Gamma Knife surgery for brain mets
    - Pemetrexed with Carboplatin and Bevacizumab x 4 cycles January – May 2017 tolerated with weight loss and poor taste
  - Diagnosed with adrenal insufficiency and symptoms improved with treatment of adrenal insufficiency
- With POD, started with second line Pembrolizumab 10/2017 –
- On routine scan at 3 and 6 months: Asymptomatic

Case Study 1

- January 2018



- April 2018

Case Study 1

1. What is the likely cause of the lung CT finding?

- A) Worsening Cancer
- B) Infection
- C) Inflammation (pneumonitis) due to immunotherapy
- D) All of the above

Case Study 1

1. What is the likely cause of the lung CT finding?

- A) Worsening Cancer
- B) Infection
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- **D) All of the above**

Case Study 1

2. What is the next step?

- A) Start Antibiotics
- B) Start Steroids
- C) Observe

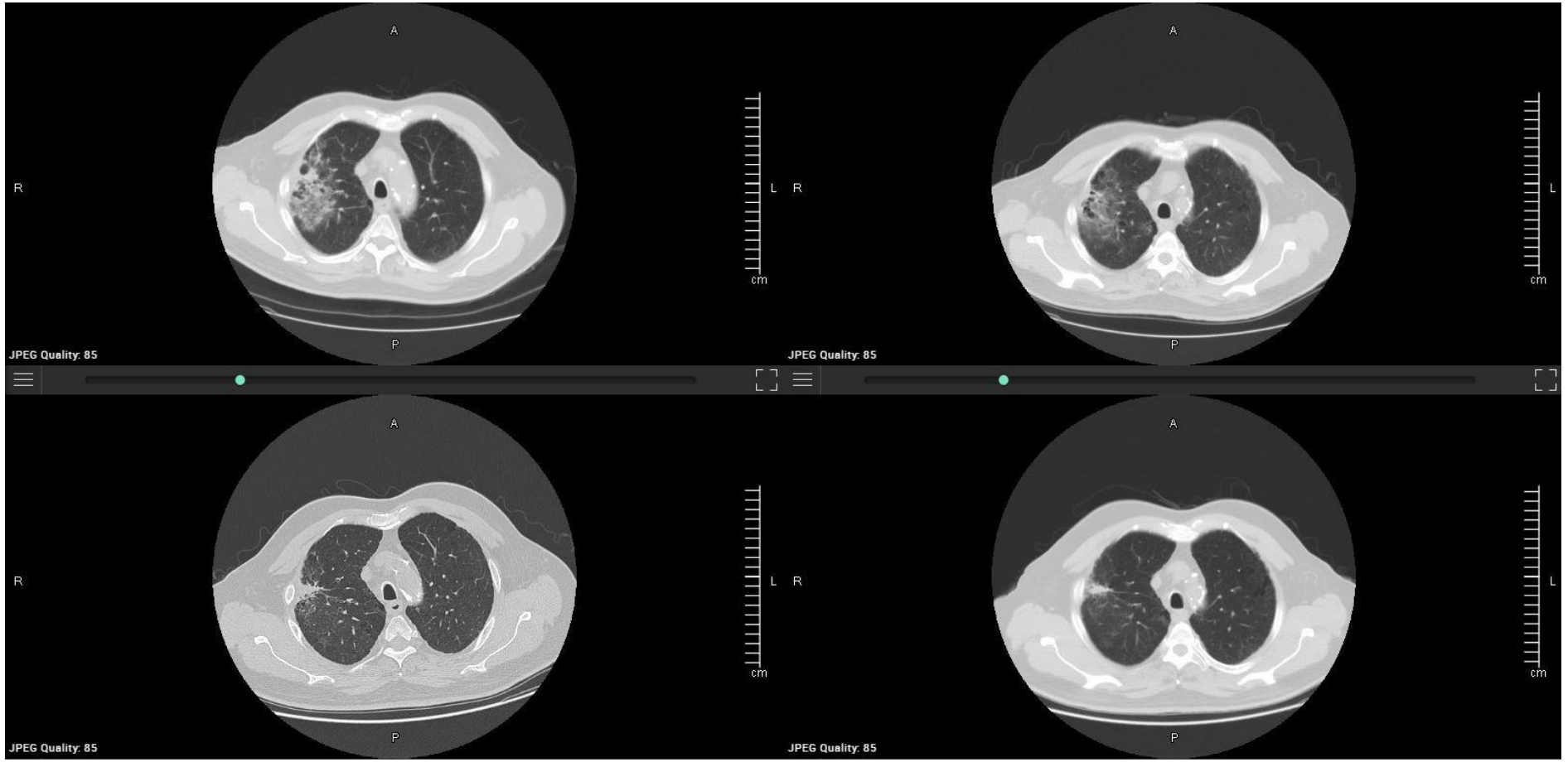
Case Study 1

2. What is the next step?

- A) Start Antibiotics
- **B) Start Steroids**
- C) Observe

May 2018

June 2018



Dec 2018

March 2021

#LearnACI

Case Study 2

- 68 yo male with non muscle invasive bladder cancer s/p multiple TURBT and 2 courses of BCG – does not wish cystectomy
- Started on Pembrolizumab Q3 weeks x 3 cycles
- Tried Pembrolizumab Q6 week dose
- Presents with increased diarrhea ~ 6/day; liquid (4-5 more than routine)
- Has taken OTC meds

Case Study 2

- What is your next step in evaluation for diarrhea
- A) Check history of antibiotic use
- B) Check stool studies including cultures and C. Diff
- C) Check Lactoferrin and Calprolectin
- D) All of the above

Case Study 2

- What is your next step in evaluation for diarrhea
- A) Check history of antibiotic use **– None**
- B) Check stool studies including cultures and C. Diff **– NEGATIVE**
- C) Check Lactoferrin and Calprolectin – Normal (< 1 ug/mL and 25 ug/g respectively)
- **D) All of the above**

Case Study 2

- How do you manage diarrhea? (choose that apply)
- A) Institute Loperamide
- B) Institute Steroids regimen
- C) Continue Pembrolizumab at 400 mg dose
- D) Continue Pembrolizumab at 200 mg dose

Case Study 2

- How do you manage diarrhea? (choose that apply)
- *A) Institute Loperamide*
- B) **Institute Steroids regimen**
- C) Continue Pembrolizumab at 400 mg dose
- D) Continue Pembrolizumab at 200 mg dose

Acknowledgements

- Some figures created using Biorender.com