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Toxicity Management

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

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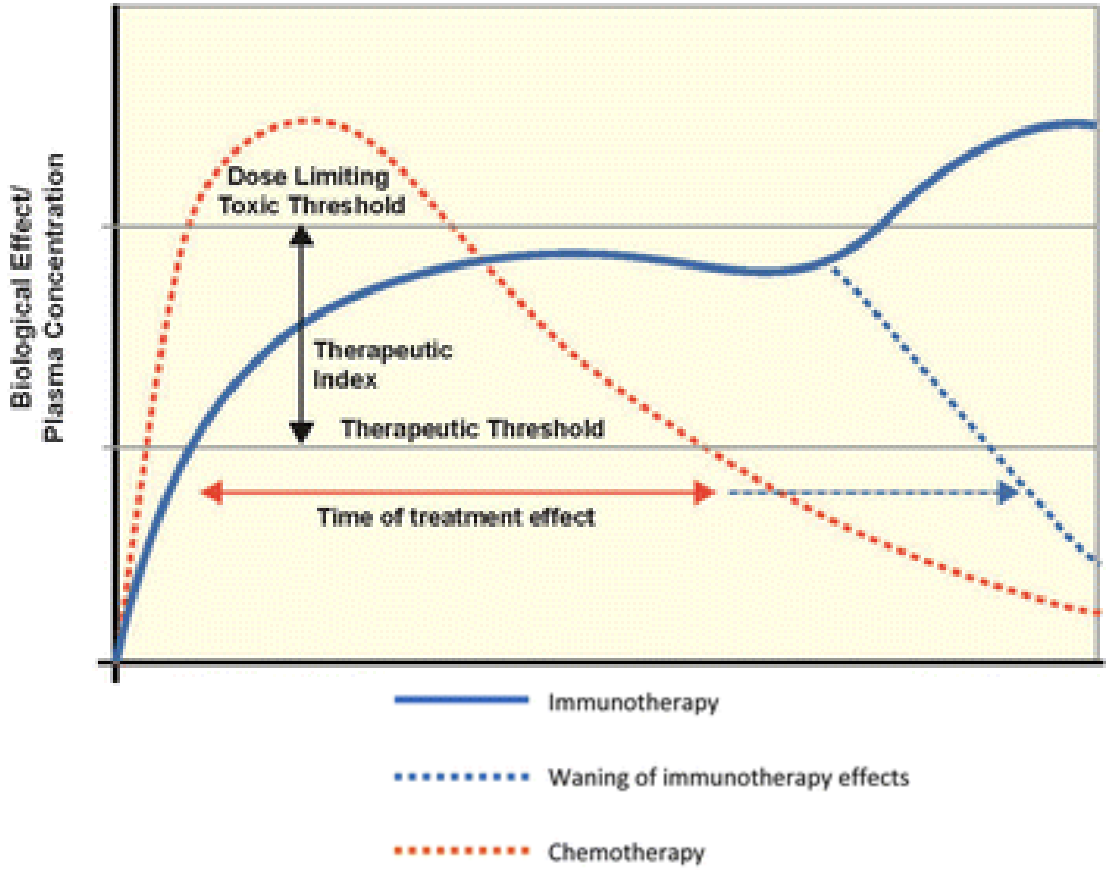
Disclosures

- I have no disclosures.
- I will be discussing non-FDA approved indications during my presentation.

Immune-related adverse events (irAEs)

- Immune checkpoint inhibitor (ICI) toxicities often have delayed onset and prolonged duration relative to chemotherapy toxicity
- Toxicities result from non-specific activation of the immune system and can mimic a number of other medical conditions



Puzanov and Diab, JITC 2017

Incidence of irAEs

- Overall incidence of all-grade irAEs with single-agent ICI reported as 15-90% in studies
- Anti-CTLA-4 inhibitor (ipilimumab): dose-dependent toxicities
  - Any grade toxicity ≤ 75% (**Grade 3+: ≤ 43%**)
- PD-1/PD-L1 inhibitors: toxicities less dose-dependent
  - Any grade toxicity ≤ 30% (**Grade 3+: ≤ 20%**)
- Life-threatening irAEs are rare but treatment-related deaths reported in up to 2% of clinical trial patients

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

Common irAEs with ICIs

- Dermatologic: maculopapular rash, dermatitis, pruritis
- Gastrointestinal: diarrhea, colitis, hepatitis, gastritis
- Rheumatologic: arthralgias, myositis, sicca symptoms
- Pulmonary: pneumonitis, sarcoidosis
- Endocrine: thyroid dysfunction, hypophysitis

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

Uncommon irAEs with ICIs

Cardiovascular:

Myocarditis, pericarditis, arrhythmias

Renal:

Interstitial nephritis, granulomatous nephritis

Endocrine:

Adrenal insufficiency, pancreatitis, type 1 diabetes mellitus

Hematologic:

Hemolytic anemia, red cell aplasia, neutropenia, thrombocytopenia

Neurologic:

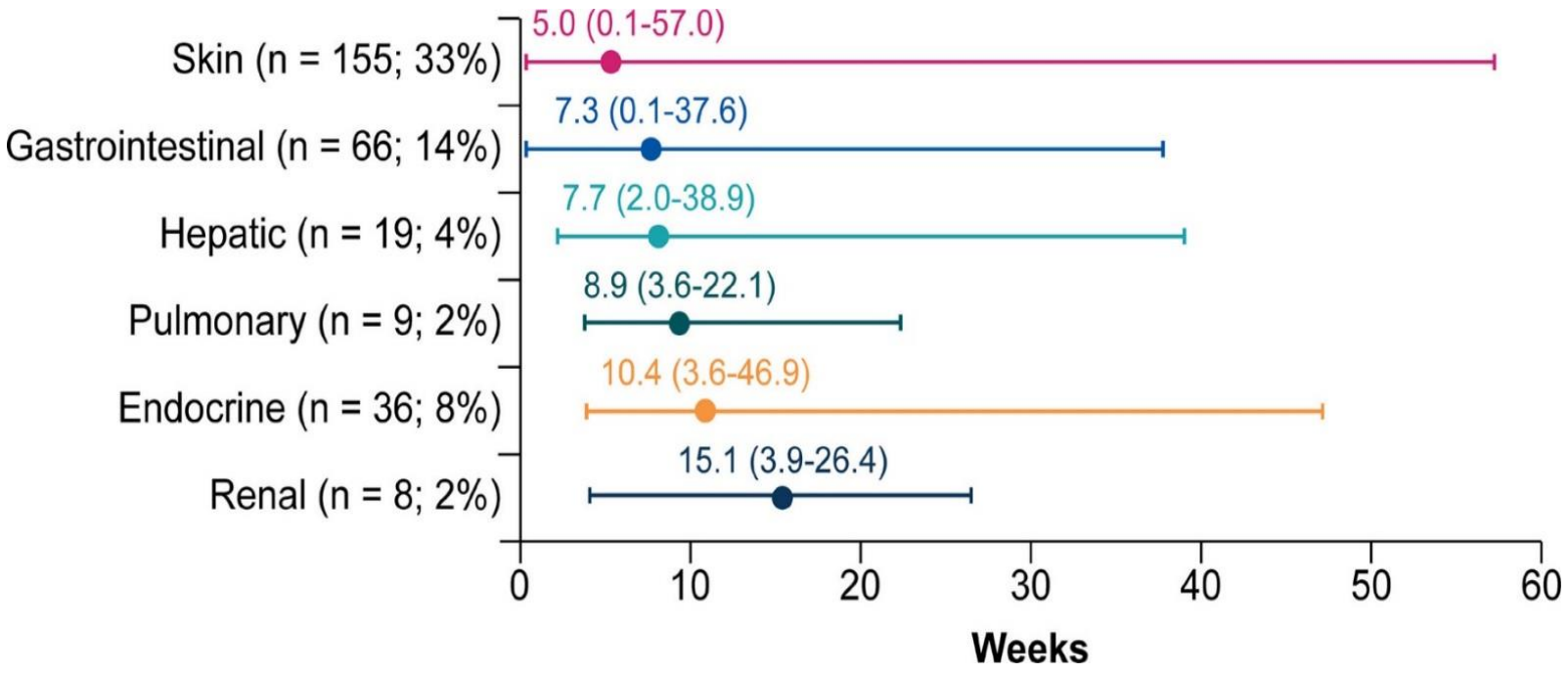
Myasthenia gravis, Guillain-Barré syndrome, peripheral neuropathies

Ophthalmologic:

Uveitis, episcleritis, conjunctivitis

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

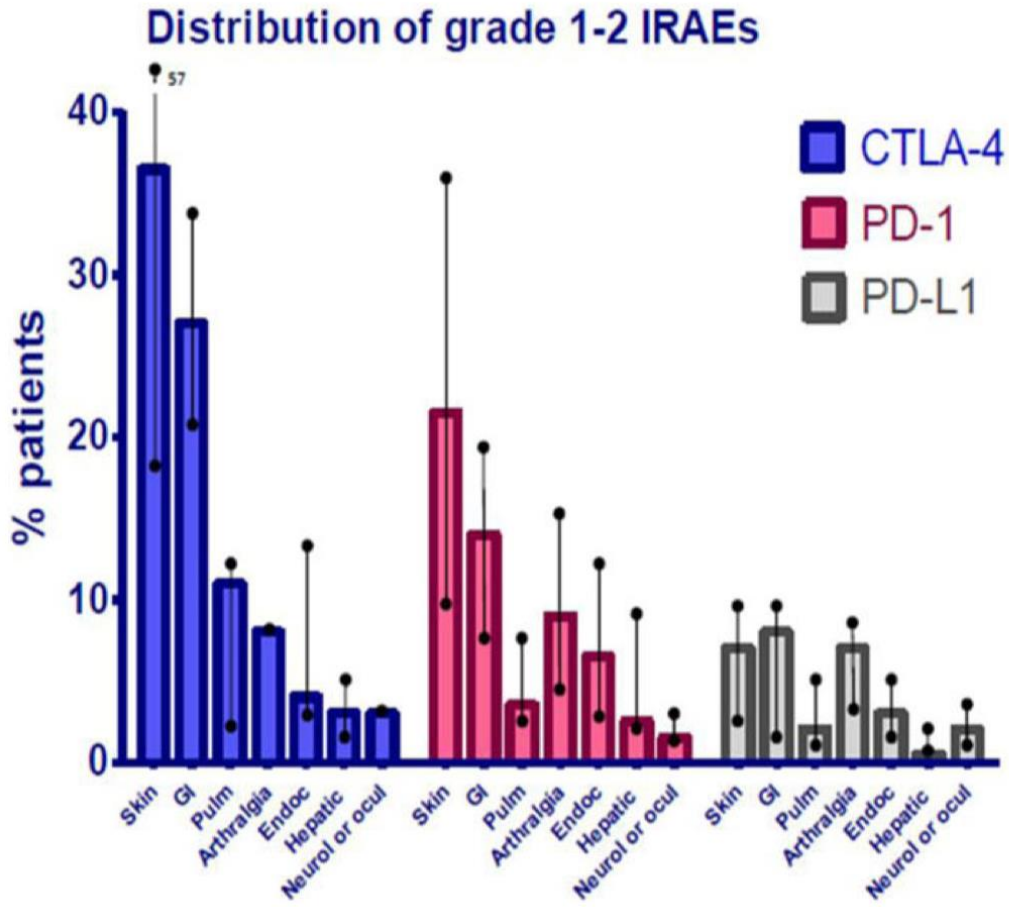
Onset of irAEs

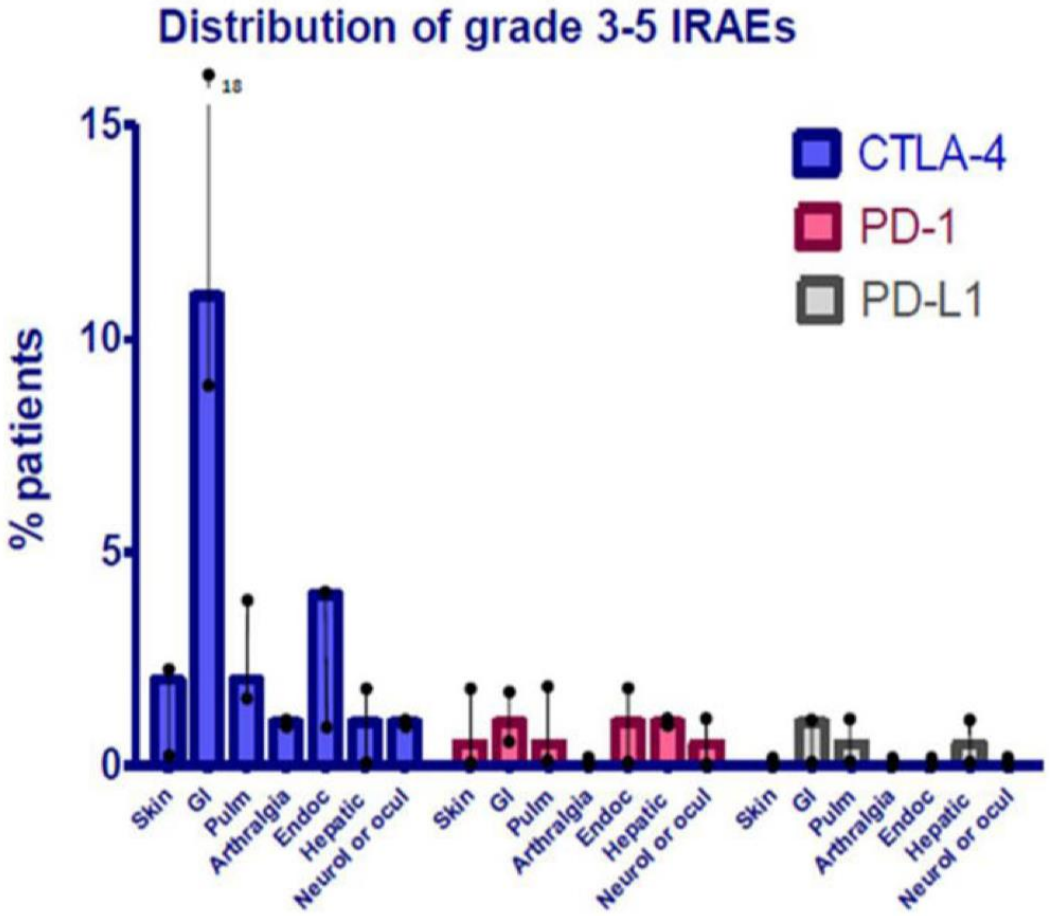


- Can be days to months after therapy initiation
- May occur even after treatment is discontinued
- Important to identify patients who are currently **OR** previously on ICI treatment!

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

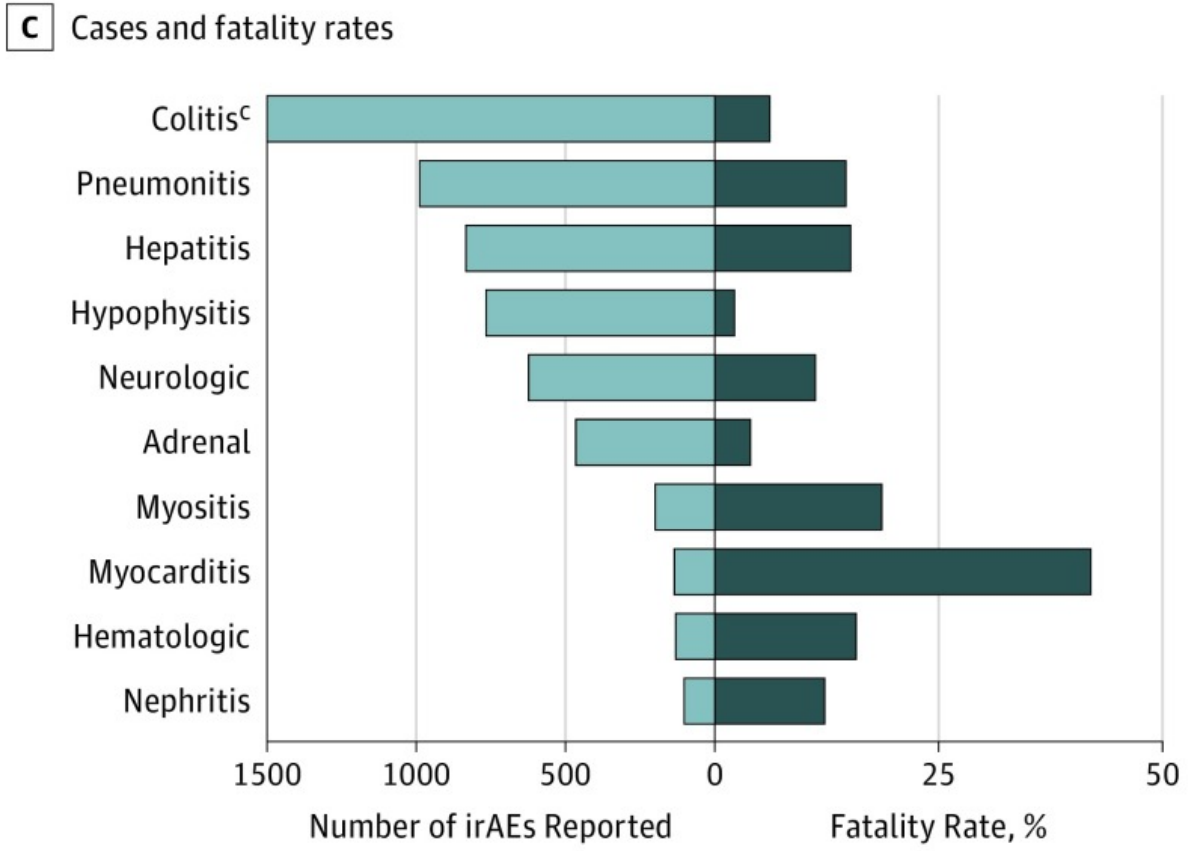
Severity of irAEs by ICI

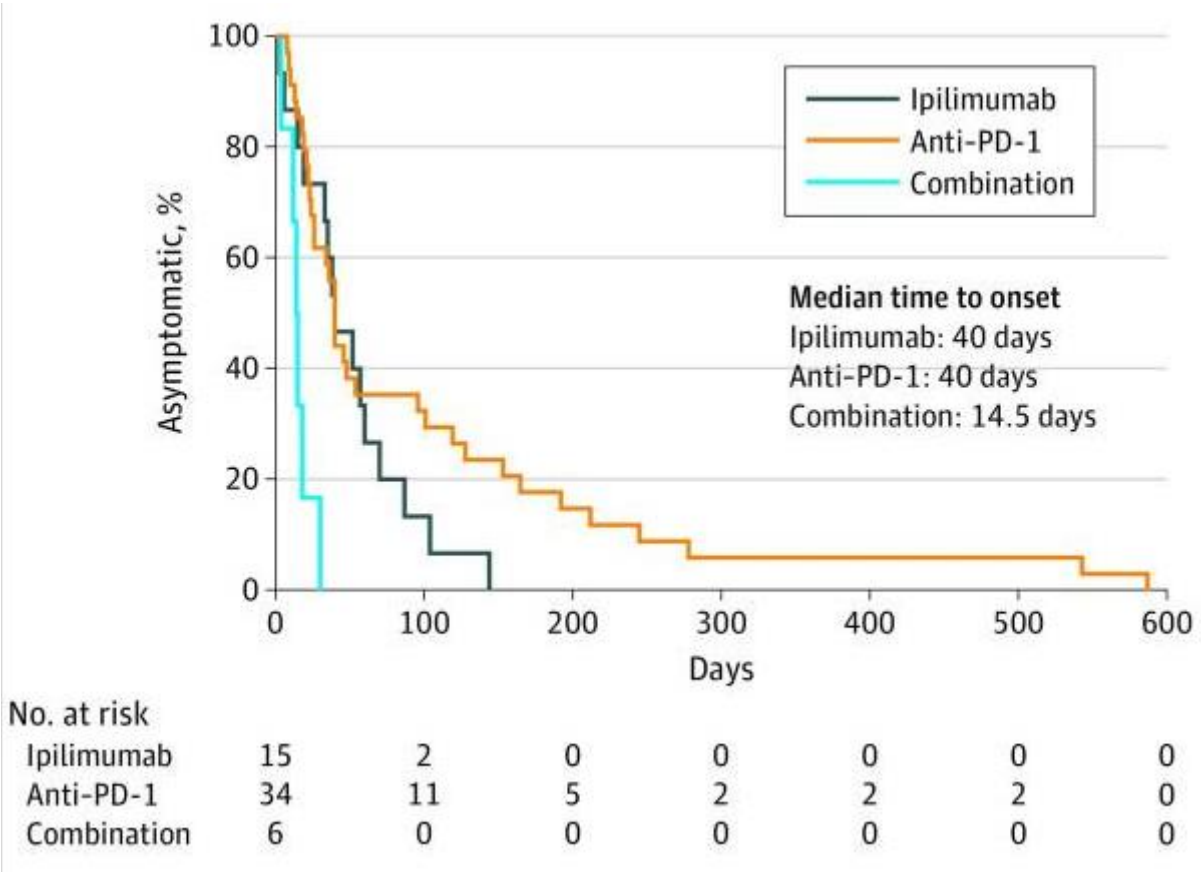




Puzanov and Diab, JITC 2017

Fatal Events with ICIs





Wang et al, JAMA Oncol 2018.

Incidence of specific irAEs by ICI

Drug	Dermatitis	Colitis	Hepatitis	Endocrinopathies	Pneumonitis
	All grades [%] (grade 3-4)				
Ipilimumab	14.5 (12)	10 (7)	5 (2)	10 (3)	<1
Ipilimumab/Nivolumab	30 (3)	26 (16)	13 (6)	35 (4)	6 (2.2)
Nivolumab	28 (1.5)	2.9 (0.7)	1.8 (0.7)	12 (0)	3.1 (1.1)
Pembrolizumab	20 (0.5)	1.7 (1.1)	0.7 (0.4)	12.5 (0.3)	3.4 (1.3)
Atezolizumab	17 (0.8)	1 (<1)	1.3 (<1)	5.9 (<1)	2.6 (<1)
Avelumab	15 (0.4)	1.5 (0.4)	0.9 (0.7)	6.5 (0.3)	1.2 (0.5)
Durvalumab	11 (1)	1.3 (0.3)	1.1 (0.6)	16.2 (0.1)	2.3 (0.5)

Puzanov and Diab, JITC 2017

Pre-treatment screening

- 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.

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** irAE's 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

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 symptoms do not improve in 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)

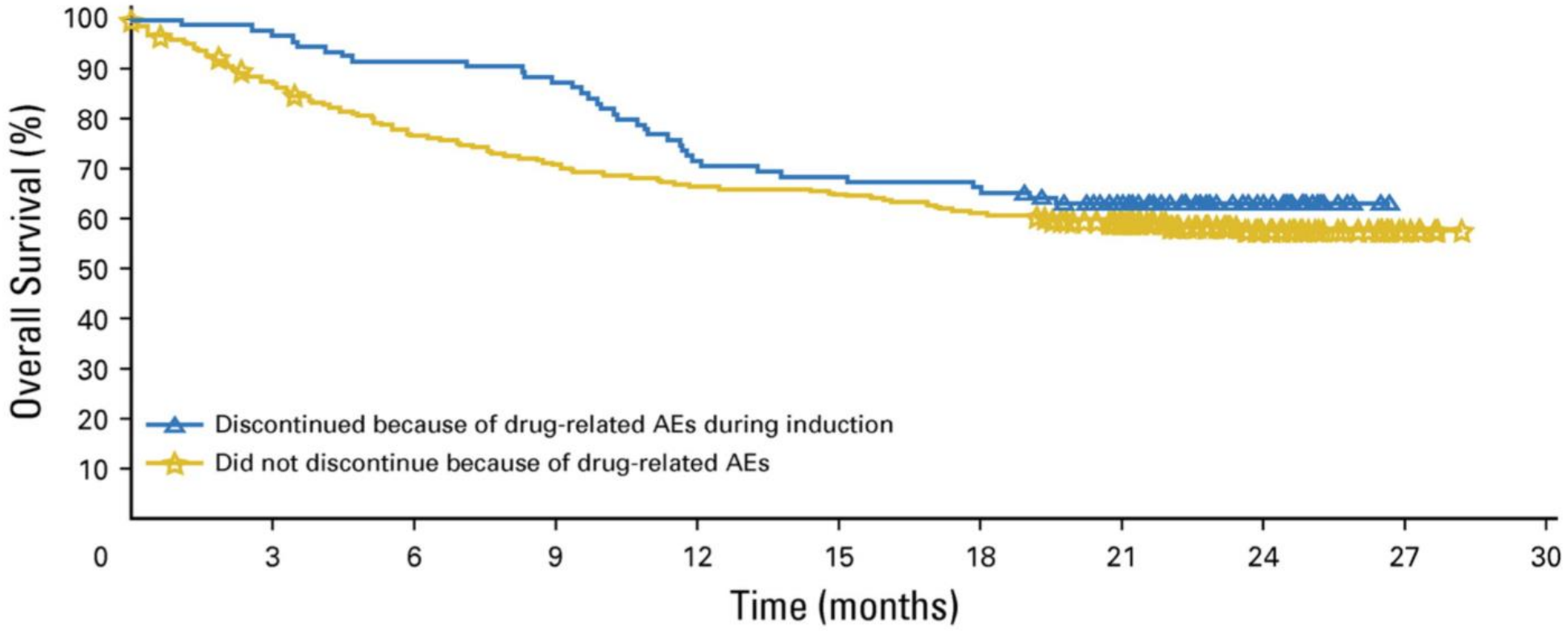
Pazanov & Diab, JITC 2017.

Additional immunosuppressives

- Infliximab: anti-TNF-α mAb
  - Hepatotoxic so should NOT be used for immune-mediated hepatitis
  - Risk for hepatitis B and tuberculosis activation; obtain hepatitis serologies and TB testing prior to initiation
  - Dose: 5 mg/kg; 2nd dose may be administered after 2 weeks
- Vedolizumab: α4β7 integrin mAb
  - **Selective GI immunosuppression** → inhibits migration of T cells across endothelium into inflamed GI tissues
  - Dose: 300 mg; repeat dose at 2 and 6 weeks
- Others: mycophenolate, IVIG, tacrolimus

Abu-Sbeih H. JITC. 2018 Dec 5;6(1):142.
NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

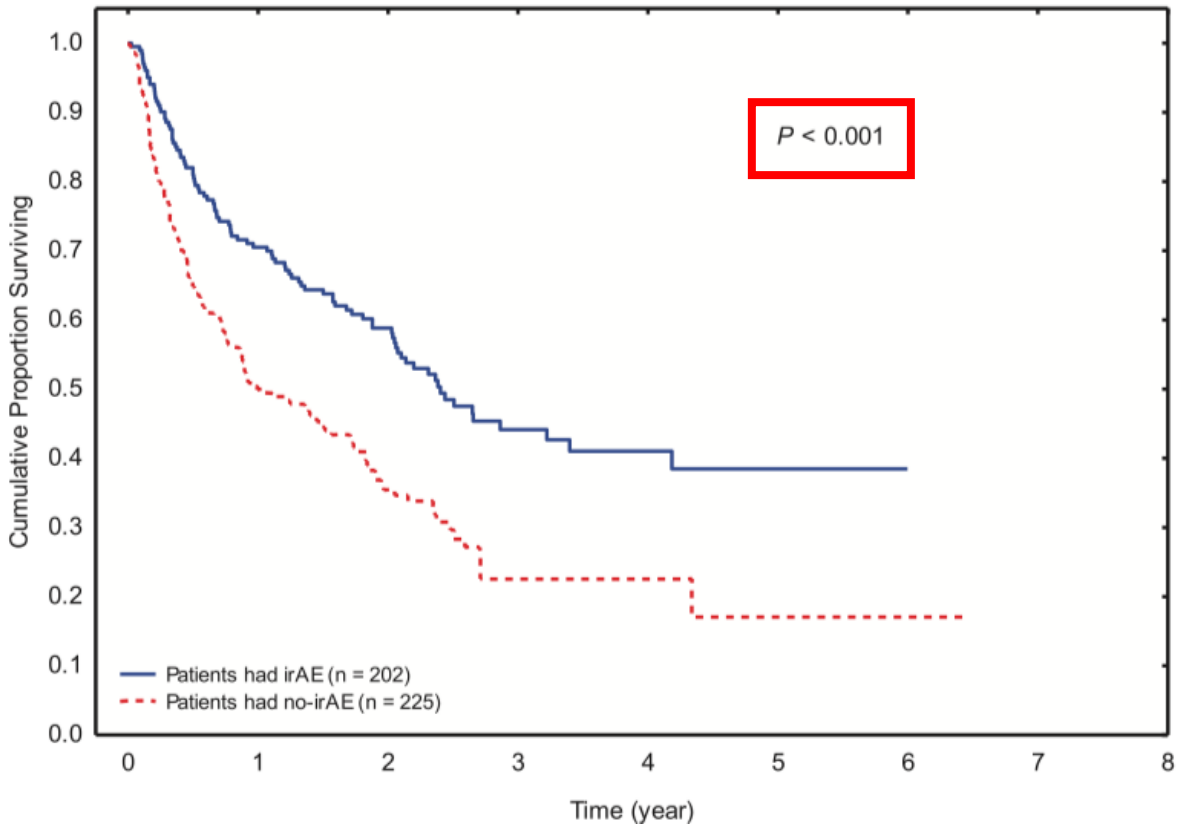
Effect of irAEs on patient outcomes

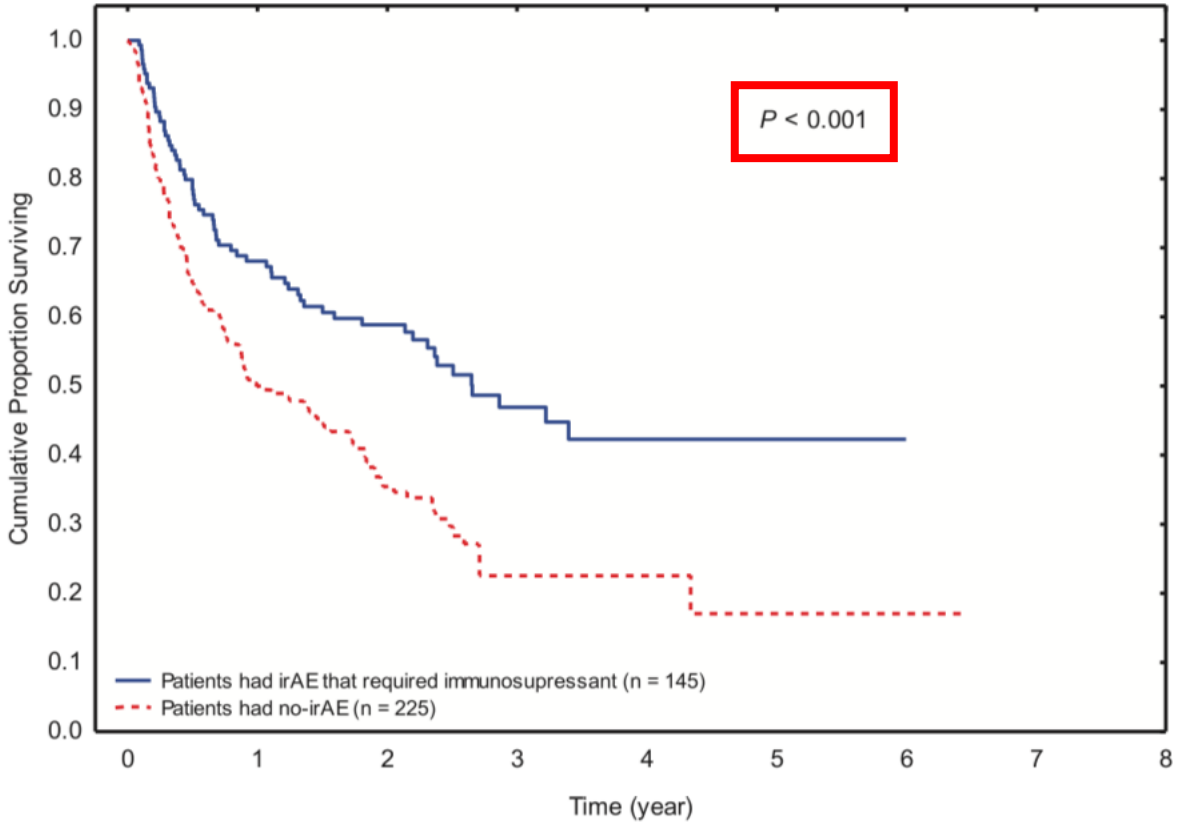


No significant difference in survival in melanoma patients who discontinued ipilimumab + nivolumab due to irAEs versus those who did not discontinue treatment

Schadendorf D. J Clin Oncol 2017 Dec; 35(35):3807-3814.

Autoimmunity as prognostic marker?

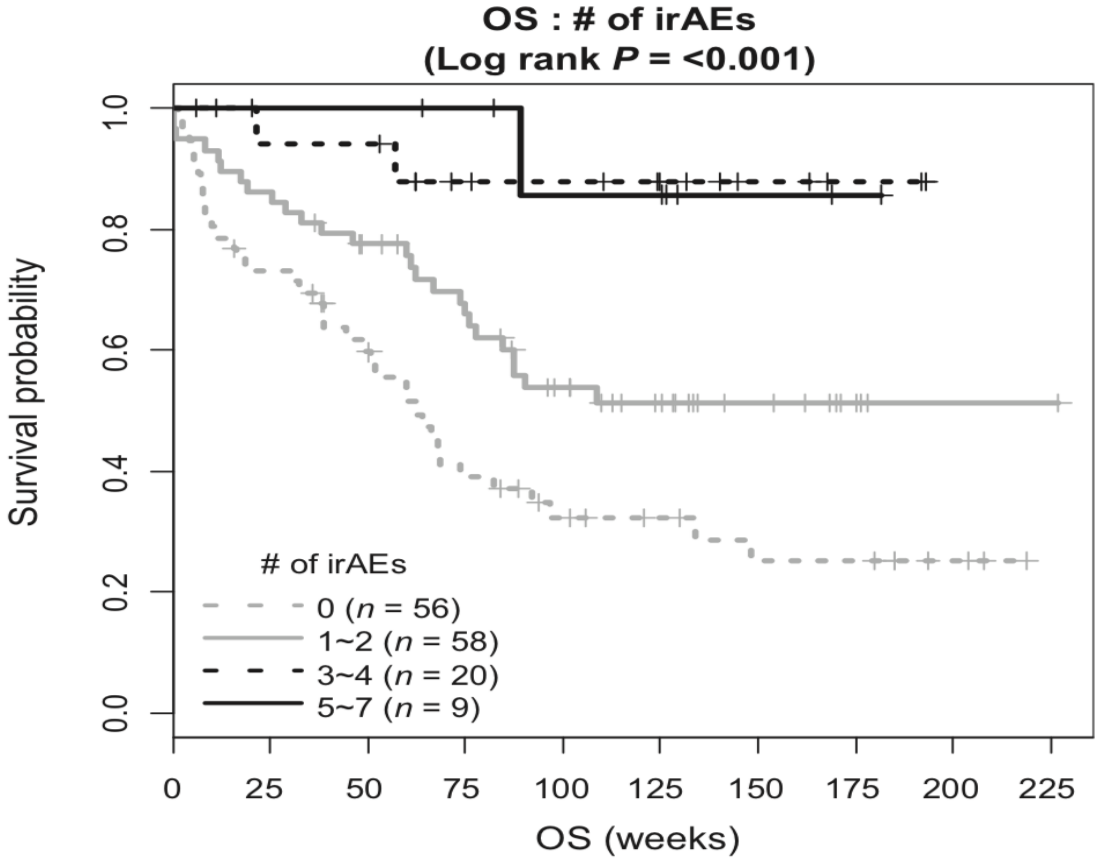




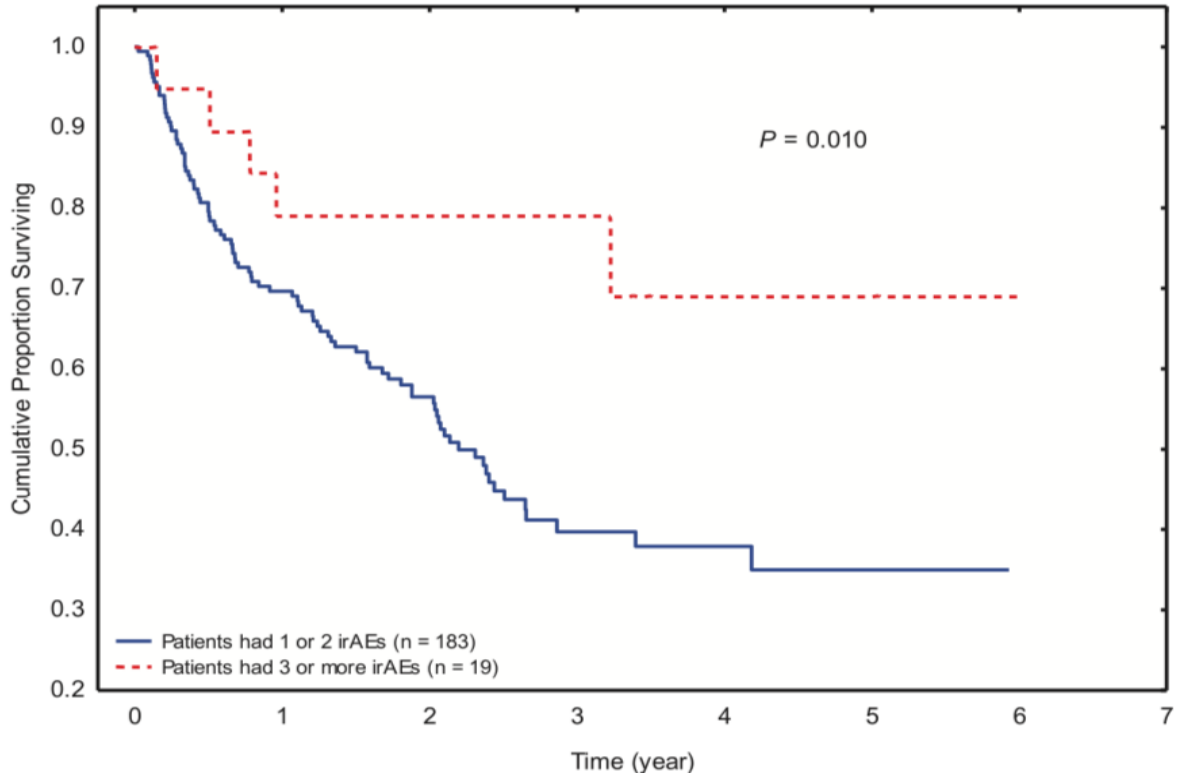
Based on **retrospective** data, patients who experience irAEs (regardless of needing treatment) may have better outcomes compared to patients who do not experience irAEs

Abu-Sbeih, J Immunoth Prec Oncol 2018.

Number of irAEs on patient outcomes



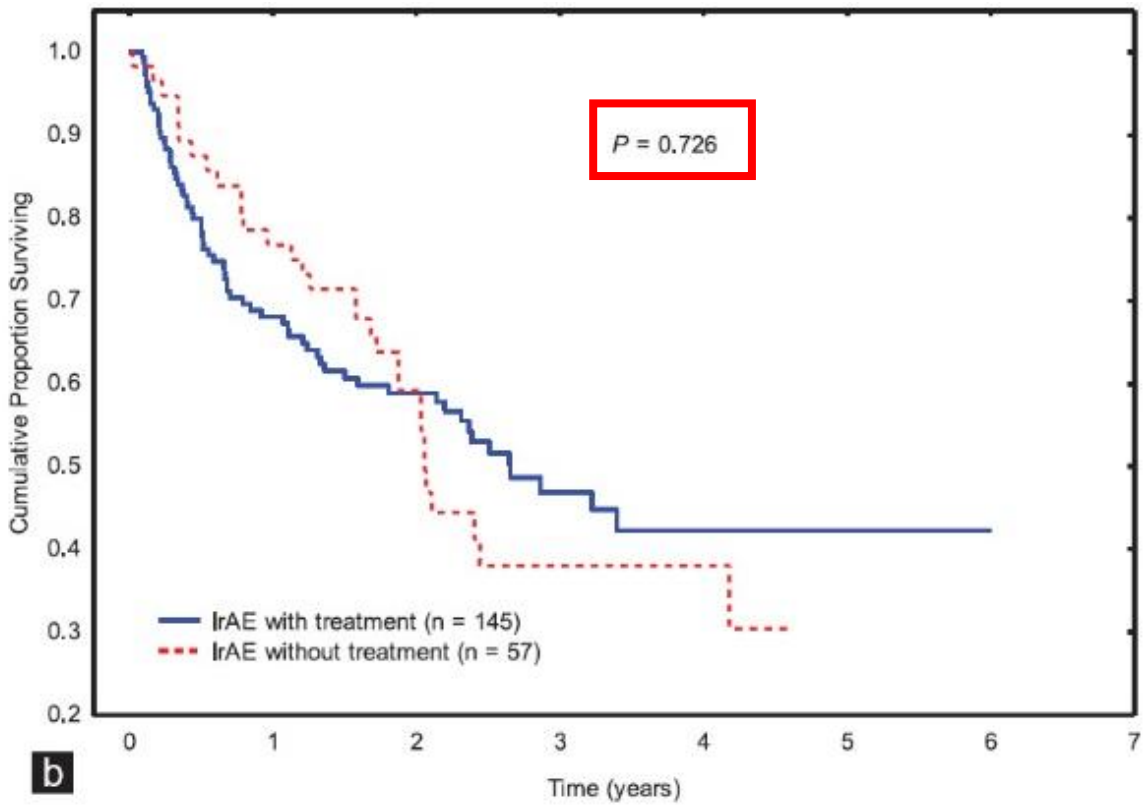
Nivolumab in metastatic melanoma: greater OS in patients with 3+ irAEs versus ≤ 1 irAE

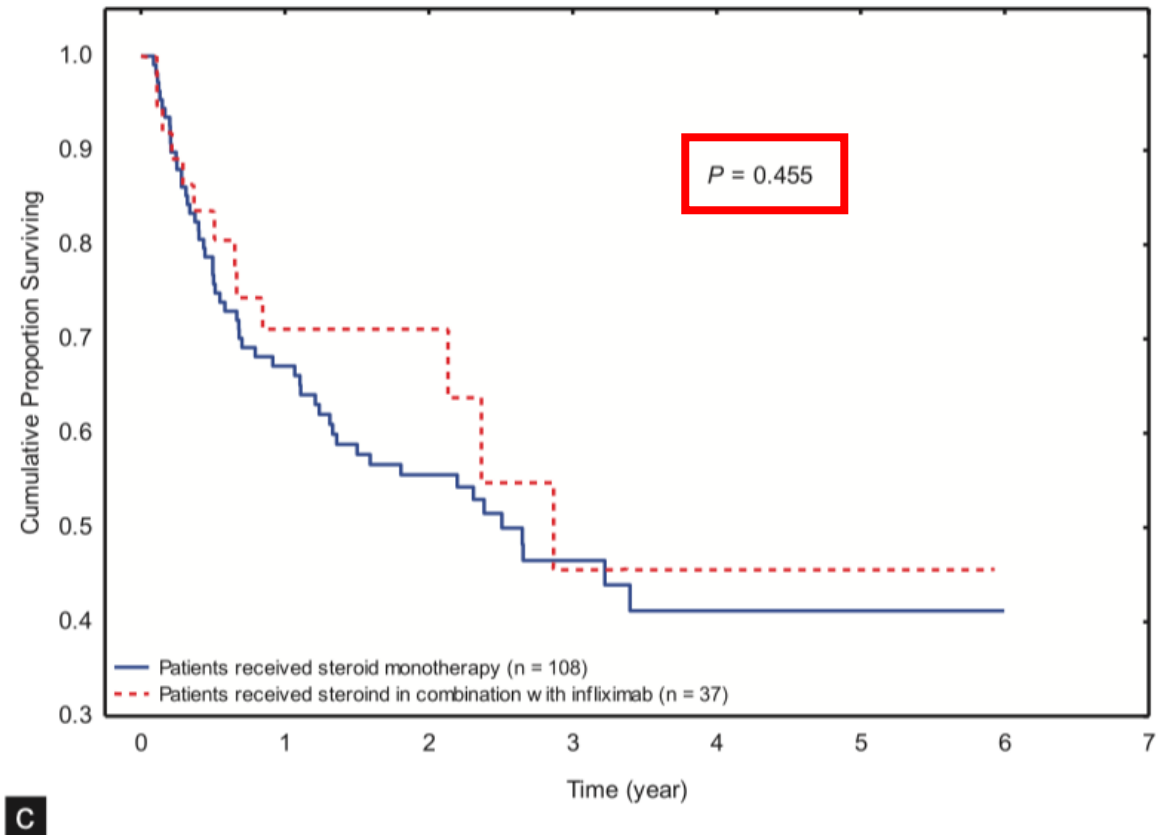


Patients receiving ICI's for various malignancies: greater OS in those with 3+ irAEs versus ≤ 2 irAEs

Freeman-Keller, Clin Can Res 2016.
Abu-Sbeih, J Immunoth Prec Oncol 2018.

Impact of toxicity management on patient outcomes



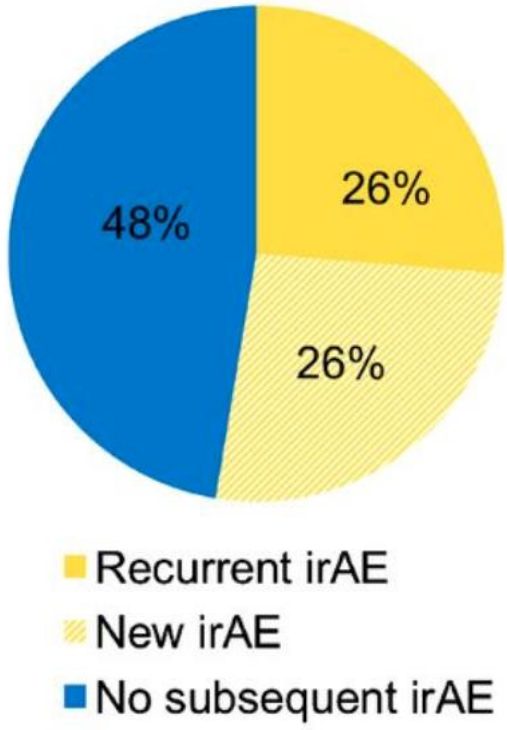


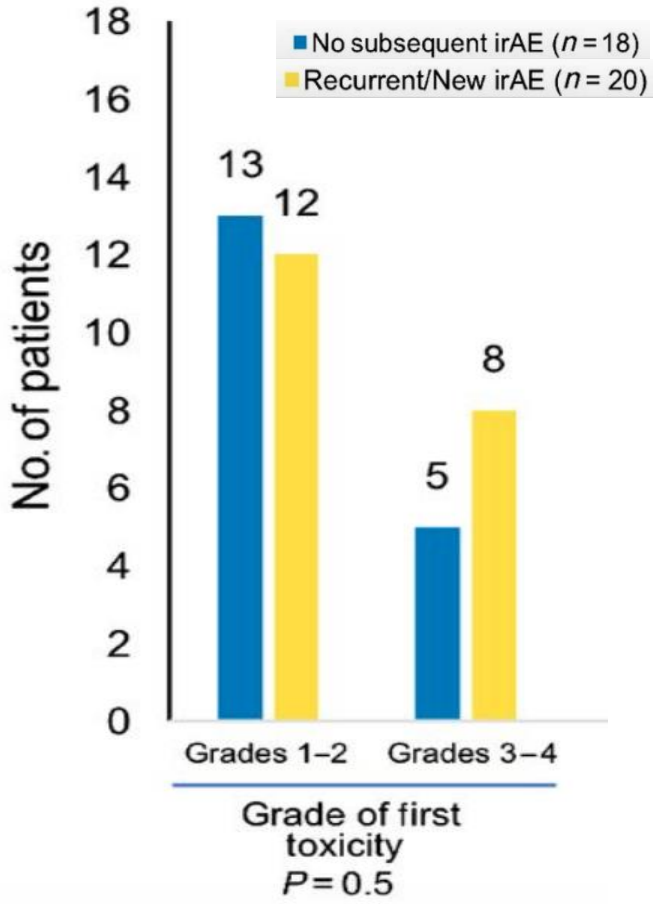
While still under debate, the administration of immunosuppressive treatments NOR the type of immunosuppressant used for irAE management does not seem to impact cancer control

Abu-Sbeih, J Immunoth Prec Oncol 2018.

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 ± 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.

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

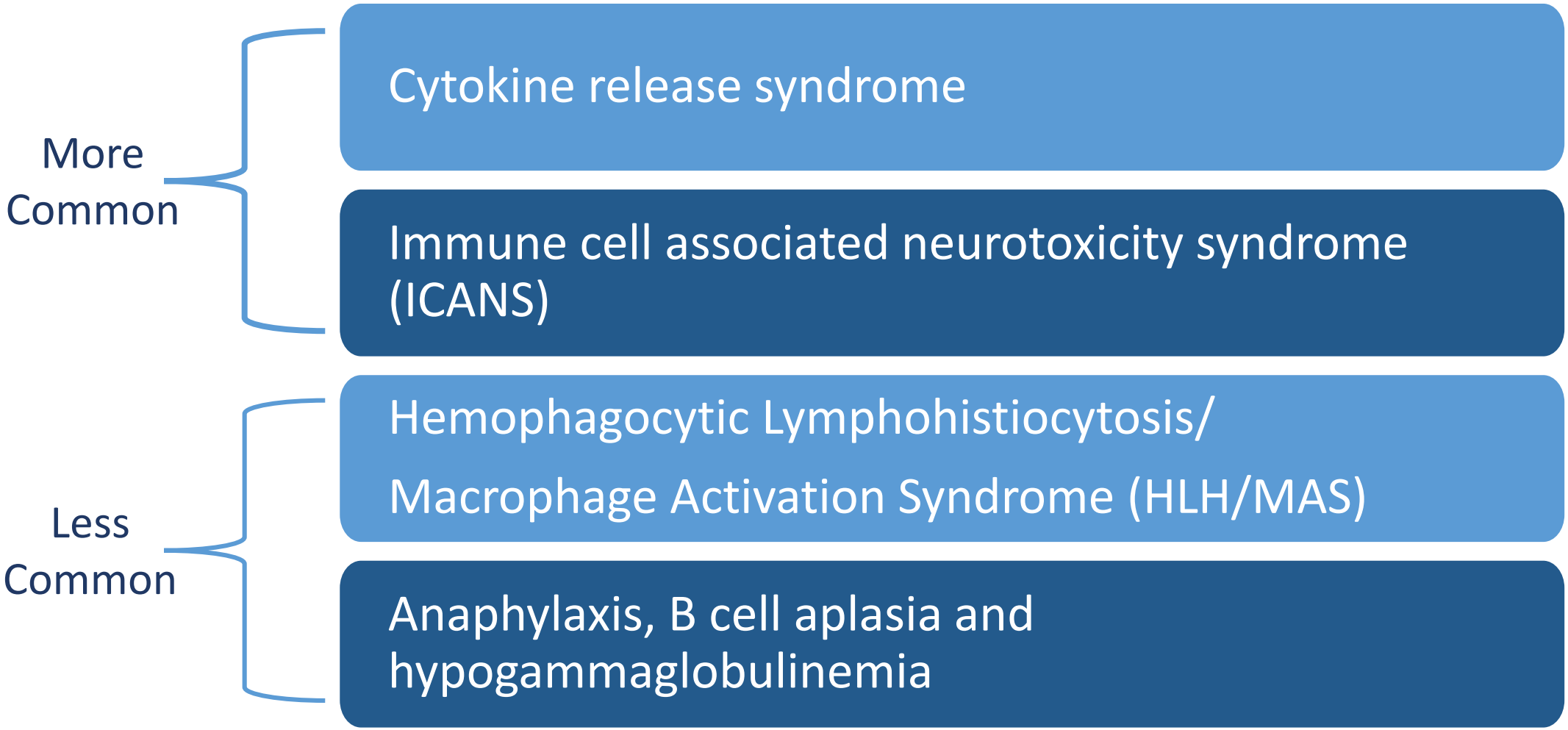
Kahler KC. Cancer Immunol Immunother. 2018.

ICI use in SOT or SCT

- 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.

CAR T-cell related toxicities



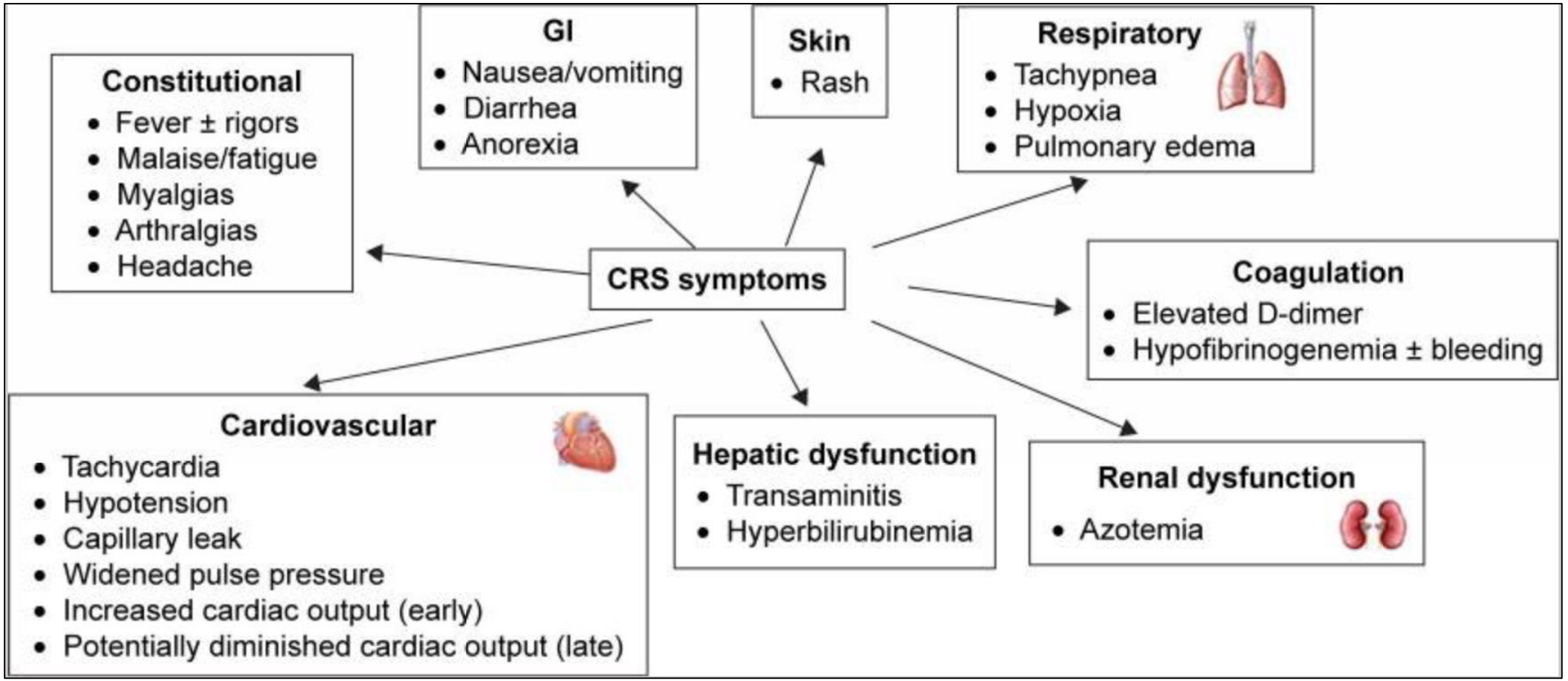
NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

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



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
- Tocilizumab approved for CRS treatment (blocks IL-6R)
  - Dose for patients >30 kg: 8 mg/kg (up to 800 mg/dose)
  - May be repeated every 8 hours up to 4 doses
- Consider adding dexamethasone 10 mg q6h for grade 3-4 CRS and/or refractory to tocilizumab

Lee DW. BBMT 2019.
NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

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
- Common symptoms include encephalopathy, headache, delirium, anxiety, tremor, aphasia
  - Severe neurotoxicity: seizures, cerebral edema, hemi/paraparesis
- Diagnosis usually based on clinical symptoms
  - MRI/CT often negative although ~30% will have abnormal MRI (poorer outcome)
- Also has multiple grading systems which guide treatment
  - Usually includes early use of high-dose steroids (dexamethasone 10 mg IV q6h)

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.

The importance of patient education

- Many immune-related adverse events can present in similar ways to other disease states, but the treatment of them is very different.
- Patients may not go back to their oncologist for treatment of irAEs and need to identify themselves as immunotherapy recipients
  - Emergency room & general practitioners need to understand the proper identification and management of irAEs
- 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

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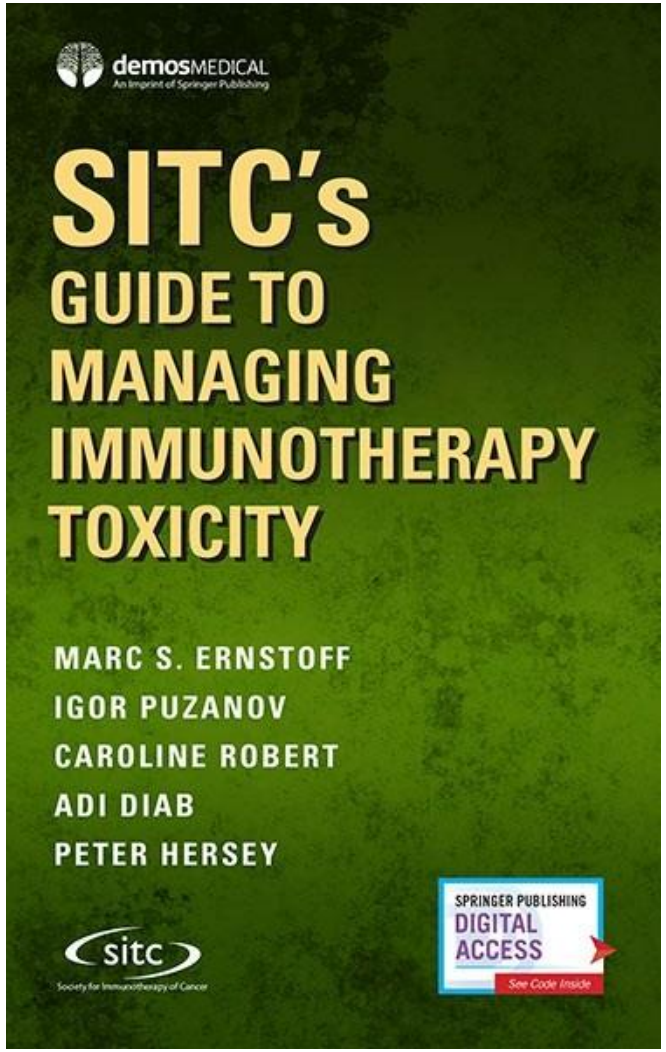
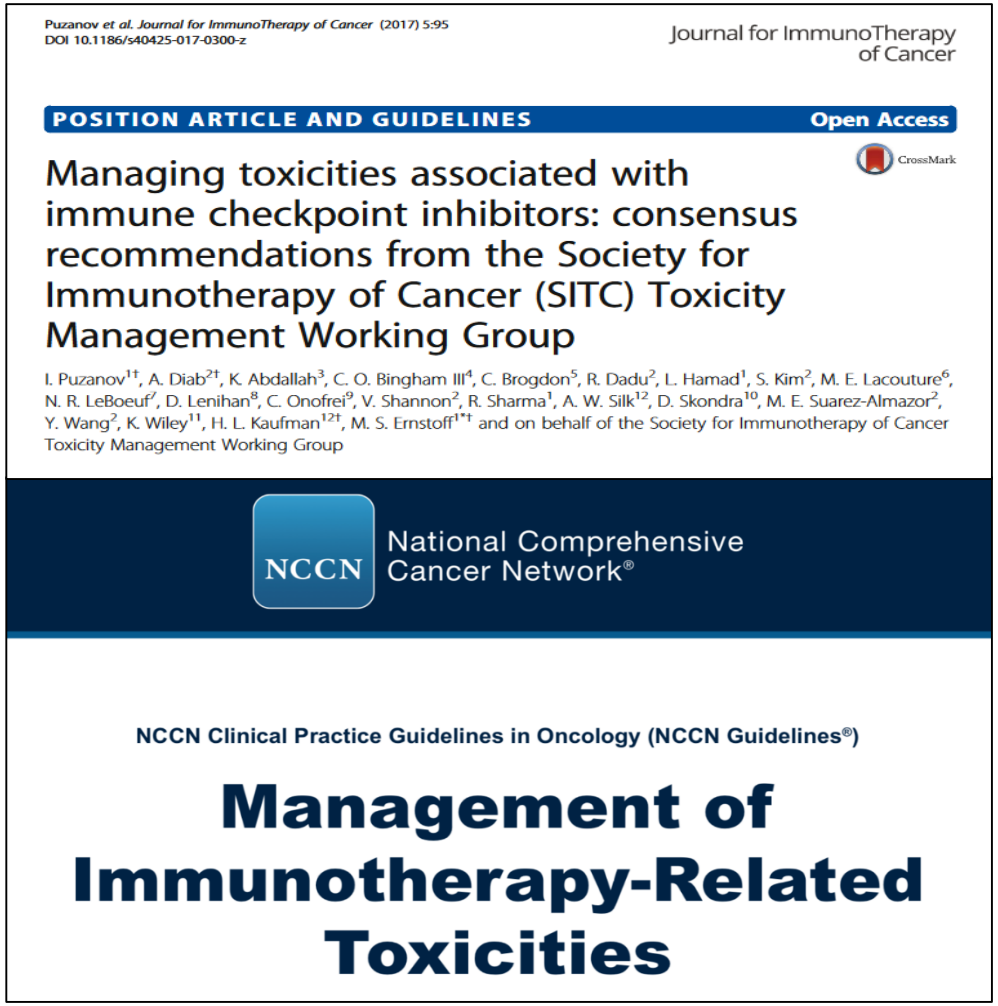
Additional Resources





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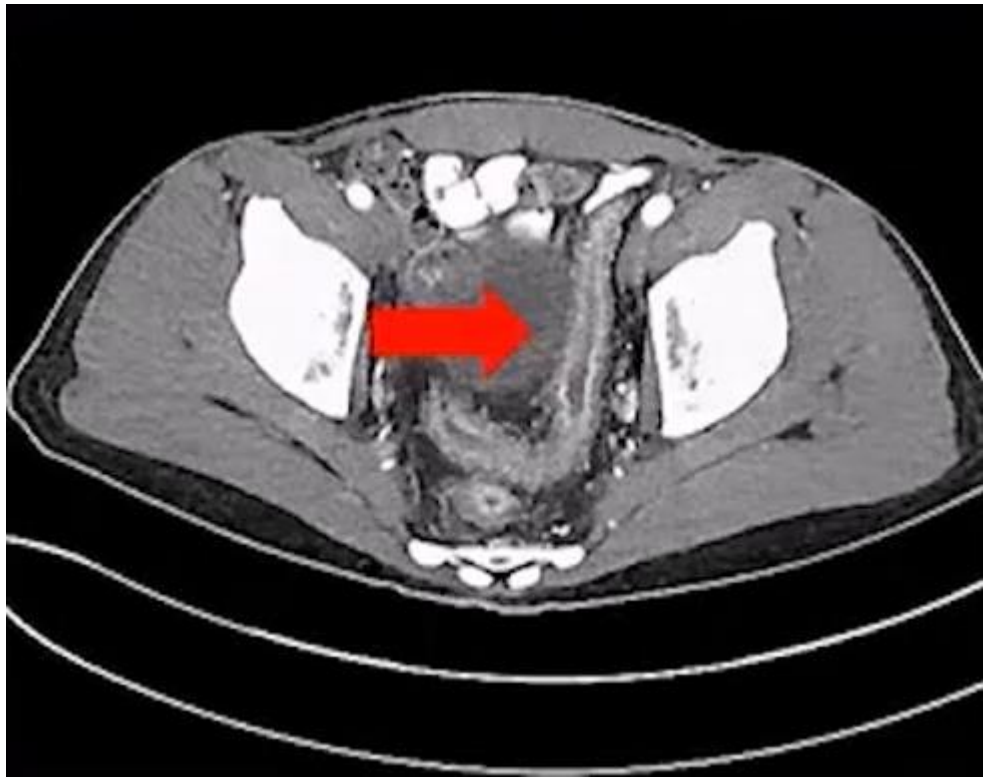
Case Study 1 – Brief Summary

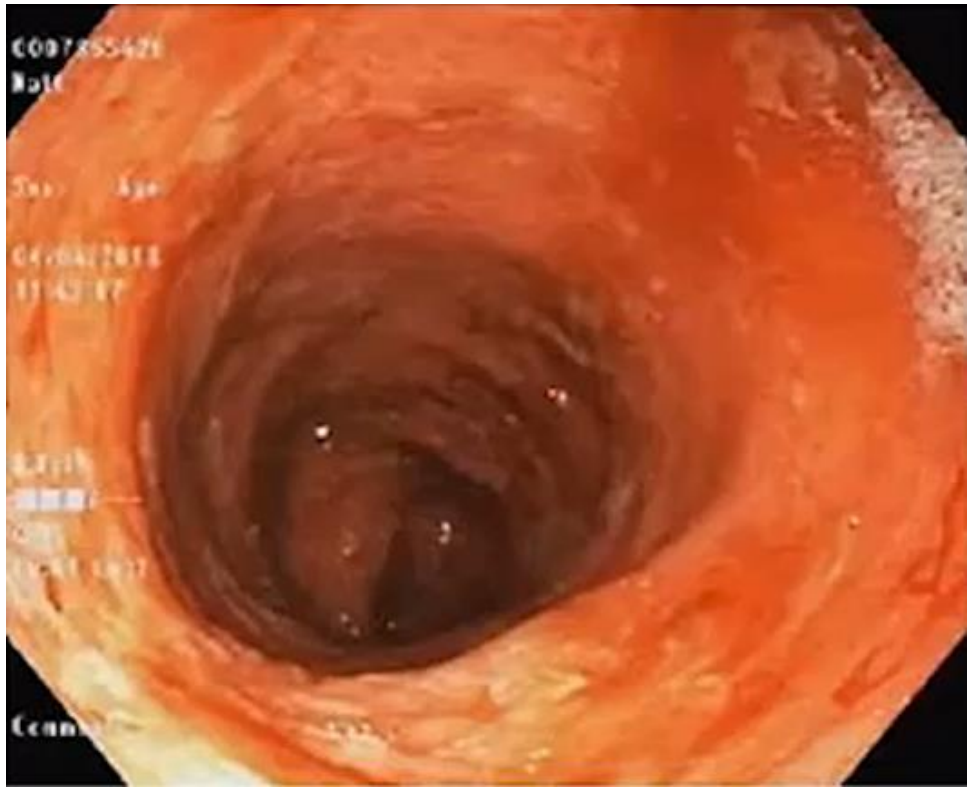
- 60-year-old man with stage IV malignant melanoma
- 12/2015: Underwent wide local excision and sentinel lymph node mapping for malignant melanoma of the left shoulder. Pathologic stage: pT1b pN0.
- 01/09/2018: Presented with abdominal pain to his local ED where a CT scan of the abdomen and pelvis showed a right-sided mesenteric mass that measured 4.2 x 2.8 x 3.1 cm and two small hypodense lesions were noted in the liver.
- 01/11/2018: PET CT scan showed a left axillary nodule with increased metabolic activity. Lobular mass noted in the anterior mesentery of the mid abdomen with increased uptake consistent with a metastatic deposit.
- 02/01/2018: Underwent a biopsy of the mesenteric mass that confirmed metastatic malignant melanoma.

Case Study 1 – Brief Summary

- 2/2018: Initial consultation with Medical Oncology.
- 02/21/2018: Initiated treatment with combination immunotherapy with ipilimumab plus nivolumab.
- 03/02/2018: Presented to clinic with grade 1 watery diarrhea. Initiated on bland diet and monitoring of symptoms.
- 03/08/2018: Presented with escalation of his diarrhea to grade 3.

Case Study 1





Case Study 1

- What is the preferred diagnostic test for immunotherapy induced colitis?
  - A. Stool studies
  - B. Flexible sigmoidoscopy with biopsy
  - C. Colonoscopy
  - D. CT abdomen and pelvis with contrast

Case Study 1 – Brief Summary

- 03/09/2018: Underwent a flexible sigmoidoscopy with pathology consistent with autoimmune colitis.
- He was started on IV high dose steroids.
- Symptoms worsen despite steroids.

Case Study 1

- What biologic agent is the preferred choice for steroid refractory autoimmune colitis?
  - A. Tocilizumab
  - B. Infliximab
  - C. Vedolizumab
  - D. Mycophenolate

Case Study 1 – Brief Summary

- He is given one dose of infliximab 5 mg/kg.
- GI symptoms improve and he placed on a slow steroid taper.
- Late March 2018: Diarrhea worsens and prednisone dose is increased. Diarrhea persists and he receives a second dose of infliximab 5 mg/kg.
- 04/02/2018 – 04/23/2018: Admitted for ongoing non-bloody diarrhea with fecal incontinence and weight loss. He received a third dose of infliximab. He underwent repeat endoscopy that demonstrated severe left sided colitis. Stool was negative for C diffcile toxin. Despite bowel rest, diarrhea persists and he receives 1 dose of vedolizumab with brief initial improvement then worsening of symptoms with bloody diarrhea and low grade fever.
- 05/02/2018: Underwent total colectomy. Pathology demonstrated moderate to severely active chronic pancolitis.

Case Study 2 – Brief Summary

- 75 year old woman with Stage IV malignant melanoma.
- 2005: Patient was treated for a right upper extremity malignant melanoma with wide local excision and sentinel lymph node biopsy with re-excision of the primary malignant melanoma to obtain adequate negative margins.
- July 2018: Established care with a new PCP after recently moving to NC. She reported a persistent cough with clear mucus production and underwent a chest x-ray with a lingular infiltrate for which she was treated with azithromycin.
- 08/20/2018: Given lack of clinical improvement in her symptoms, she underwent a repeat chest x-ray with persistent opacity noted.
- 09/10/2018: CT chest - Lingular bronchi appear obstructed. Postoperative consolidation within the lingula is present. Subcarinal and left hilar adenopathy are present. Subcarinal node measures 3.1 x 3.3 cm. Left hilar node measures 1.9 x 2.7 cm. Right posterior pleural lesion, 0.6 x 1.8 cm.

Case Study 2 – Brief Summary

- 09/20/2018: Underwent EBUS with FNA biopsy of the left upper lobe which revealed necrotic cellular debris. Lymph node biopsy of region 7 was positive for malignant cells consistent with malignant melanoma.
- 09/24/2018: PET/CT - Hypermetabolic thick bandlike consolidation extending from the left hilum into the lingula measuring 28 x 62 mm with a max SUV of 12.3. This appears to represent a combination of central lung and perihilar obstructive atelectasis and inflammation. In addition, there is a large hypermetabolic subcarinal mass measuring 30 x 33 mm with a max SUV of 49.1. There is a focal uptake involving the spinous process of L2 to vertebral body which appears sclerotic on CT with a max SUV of 3.6.
- 09/28/2018: Initial medical oncology consultation for her diagnosis of stage IV malignant melanoma. Combination immunotherapy with ipilimumab 3 mg/kg IV and Nivolumab 1 mg/kg IV every 3 weeks for 4 doses followed by maintenance Nivolumab was recommended. BRAF mutation not detected.

Case Study 2 – Brief Summary

- She received 2 infusions of Ipilimumab and nivolumab.
- 11/15/2018: Acute follow up visit. She was experiencing severe fatigue, right eye ptosis, and dyspnea with exertion and at rest over the last 2 days. She reported weakness and was present in a wheelchair. Her extraocular movements were intact. She denied any fevers, headaches, dysphasia, facial nerve deficits, or dysphagia. She did have mild to moderate arthralgias and myalgias. She did have a persistent dry cough.
- Patient was admitted directly to the hospital directly from clinic due to concern for a neurologic immune related adverse event and concern for respiratory status. She did experience acute respiratory failure requiring intubation. She went into sustained ventricular tachycardia requiring cardioversion on 3 occasions.

Case Study 2

- What diagnostic test is most commonly abnormal with checkpoint inhibitor induced myocarditis?
  - A. ECG
  - B. Echocardiogram
  - C. BNP
  - D. Troponin

Case Study 2

- What is the best way to monitor a patient with myasthenia gravis for respiratory failure?
  - A. FVC
  - B. Single breath count test
  - C. O2 saturation
  - D. A and B

Case Study 2 – Brief Summary

- She was diagnosed with immunotherapy induced myasthenia gravis for which she ultimately required plasmapheresis, treatment with pyridostigmine, high-dose steroids and IVIG. She did require intubation. Antibody testing confirmed myasthenia gravis.
- Patient was diagnosed with myocarditis and myositis. She underwent a TTE which revealed a left ventricular ejection fraction of 50% with right ventricle moderately dilated with moderate pulmonary hypertension noted. She had elevated troponins and CPK levels during her hospitalization. She did require cardioversion for sustained ventricular tachycardia.
- CT imaging during the hospitalization revealed interval response to therapy with decreased tumor burden.
- In light of her multiple immune related toxicities and declining performance status despite aggressive supportive care, the patient and family chose to proceed with comfort care and enrollment in hospice.