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ADVANCES IN Cancer IMMUNOTHERAPY™

Toxicity Management

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Disclosures

- Consulting Fees:
  - Apricity Health, LLC
- I will be discussing non-FDA approved indications during my presentation.

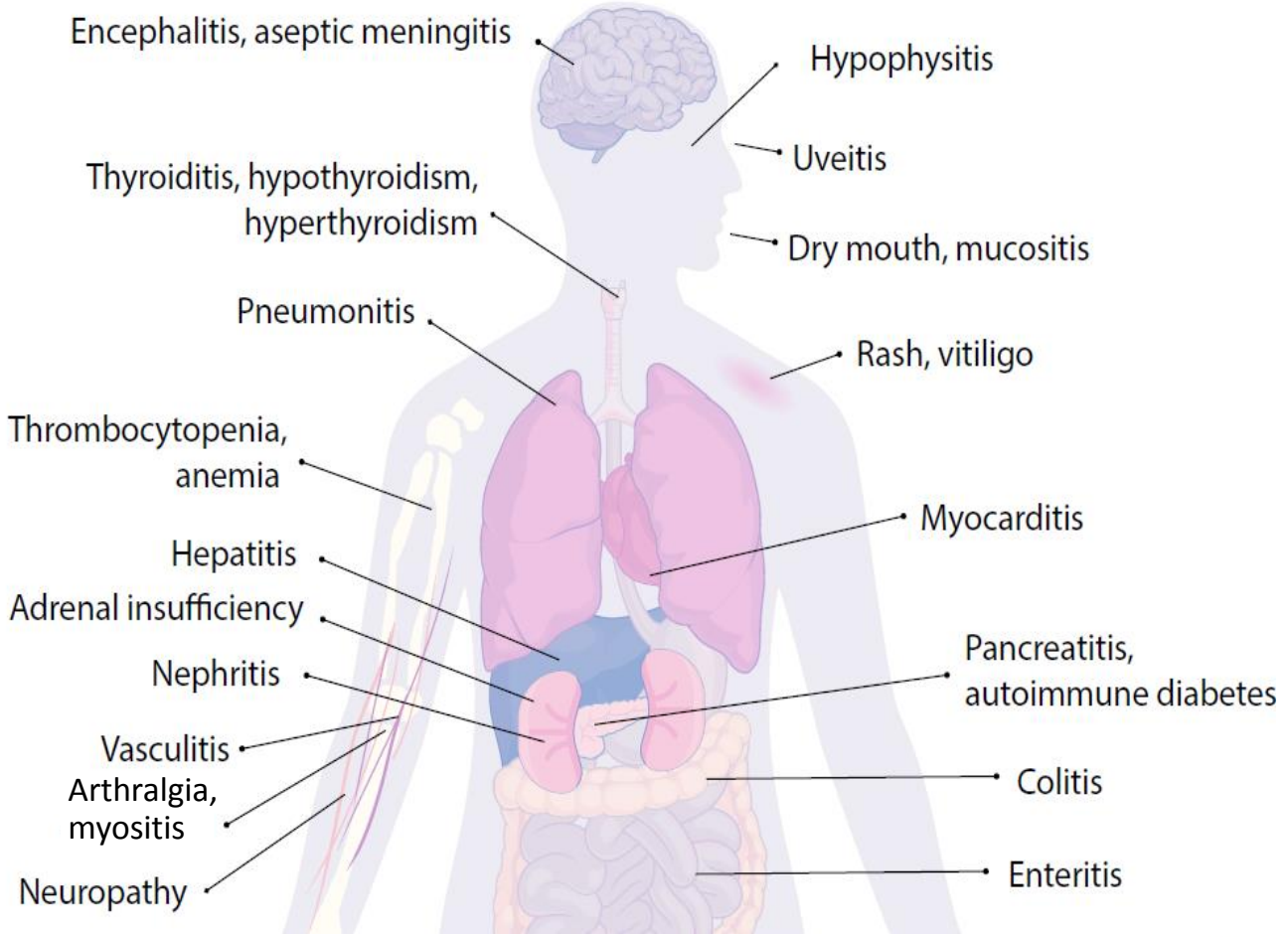
Immune-related adverse events

- Patient outcomes improve with good toxicity management
- Prompt recognition and treatment is critical
- May affect any organ system
- High suspicion if patient develops new symptoms while on ICI's
- Communication b/t patient and oncology team is key

The Spectrum of Immune-Related Adverse Events (irAEs)

1. ***"Taking the brakes off" of the immune system can help the body fight cancer, but it can also lead to toxicity from a supercharged immune system***

2. ***Any organ system can be affected***



1. Postow MA et al. *N Engl J Med*. 2018;378:158-168. 2. Brahmer JR et al. *J Clin Oncol*. 2018;36:1714-1768.

Common irAEs with ICI's

- 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 ICI's

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

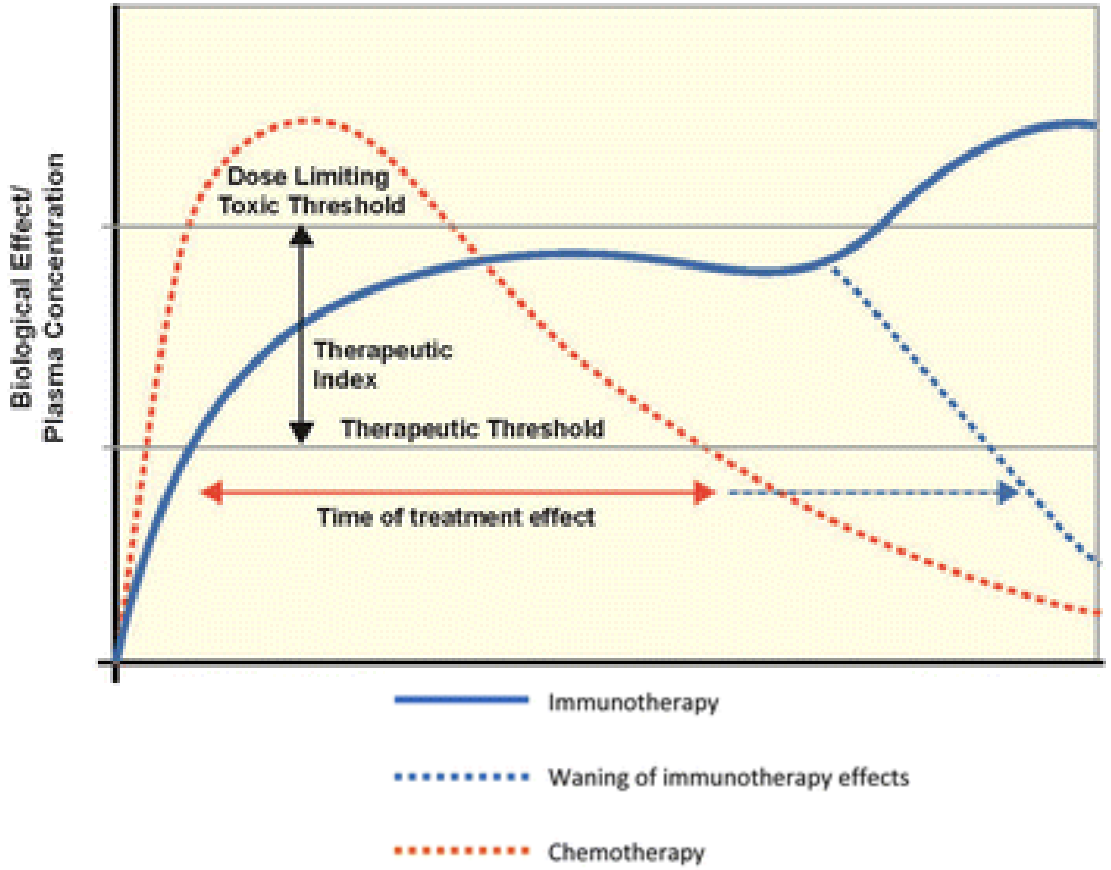
Ophthalmologic:

Uveitis, episcleritis, conjunctivitis

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

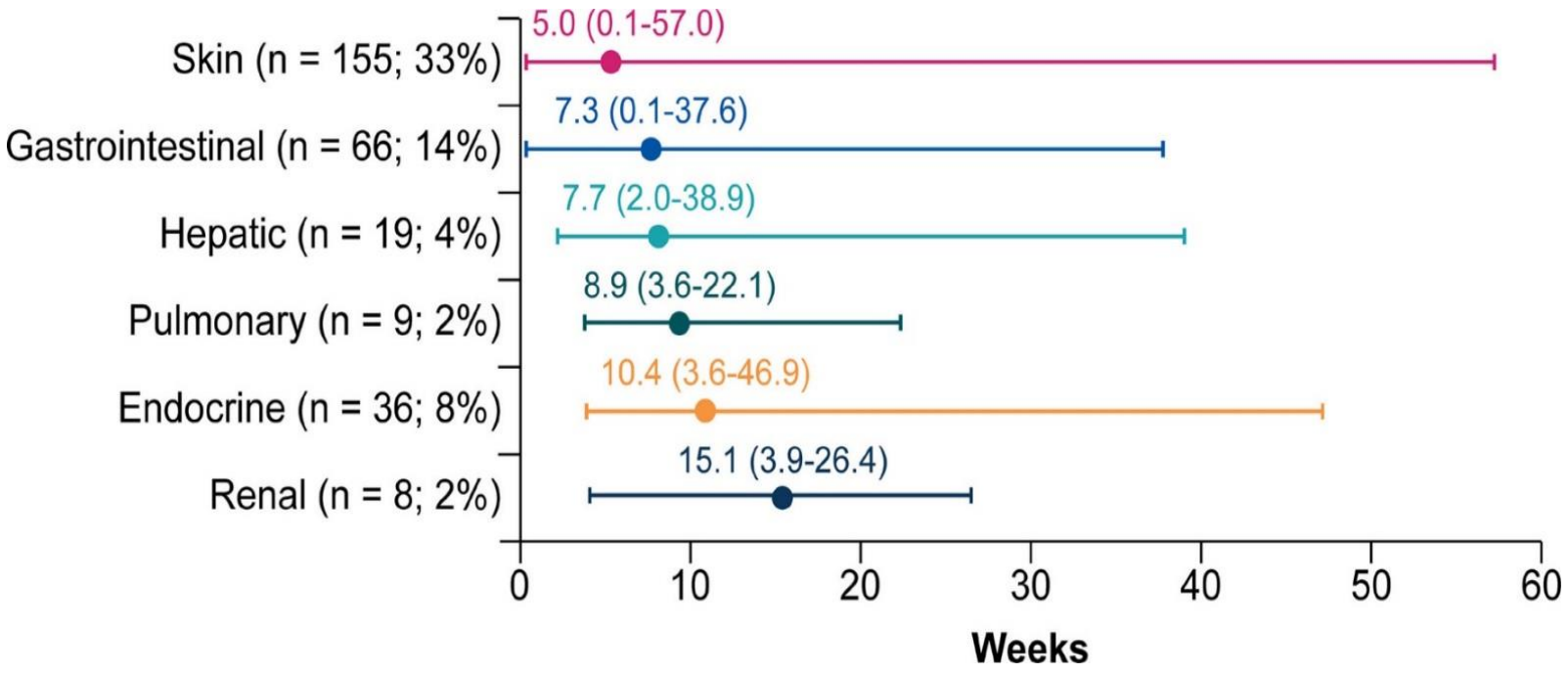
Immune-related adverse events (irAEs)

- 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

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

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

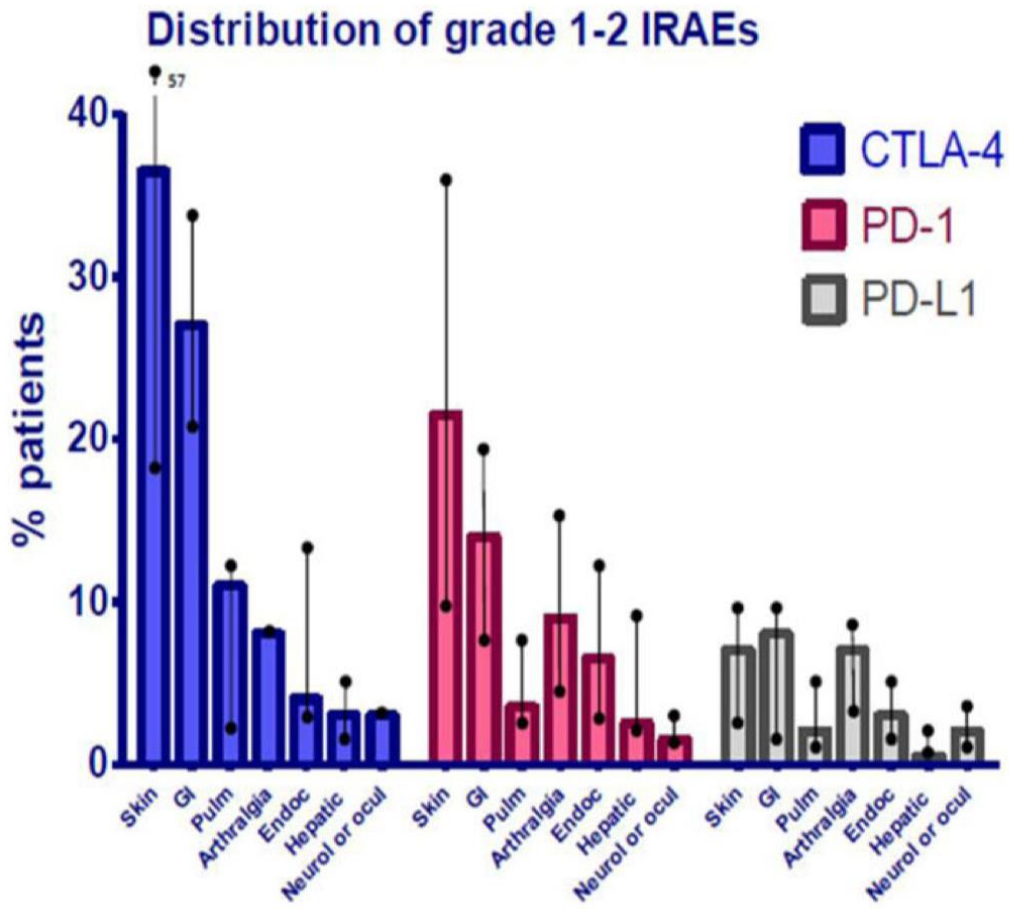
Puzanov and Diab, JITC 2017.
NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

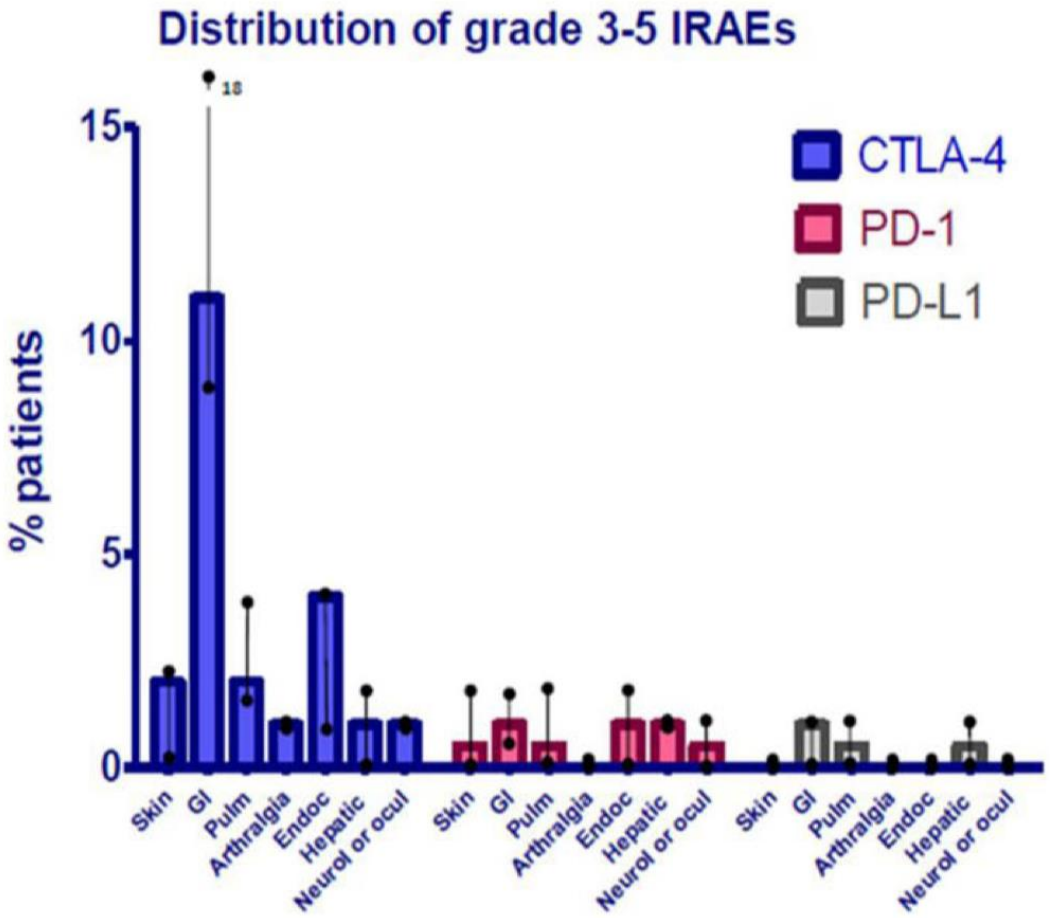
Incidence of specific irAEs by ICI

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

Severity of irAEs by ICI





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

CTCAE adverse event grading

- Grade 1 Mild
- Grade 2 Moderate
- Grade 3 Severe, but not life-threatening
- Grade 4 Life-threatening
- Grade 5 Death related to AE

Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03 June 14, 2010) U.S. Dept. of Health and Human Services; National Institutes of Health; NCI

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)

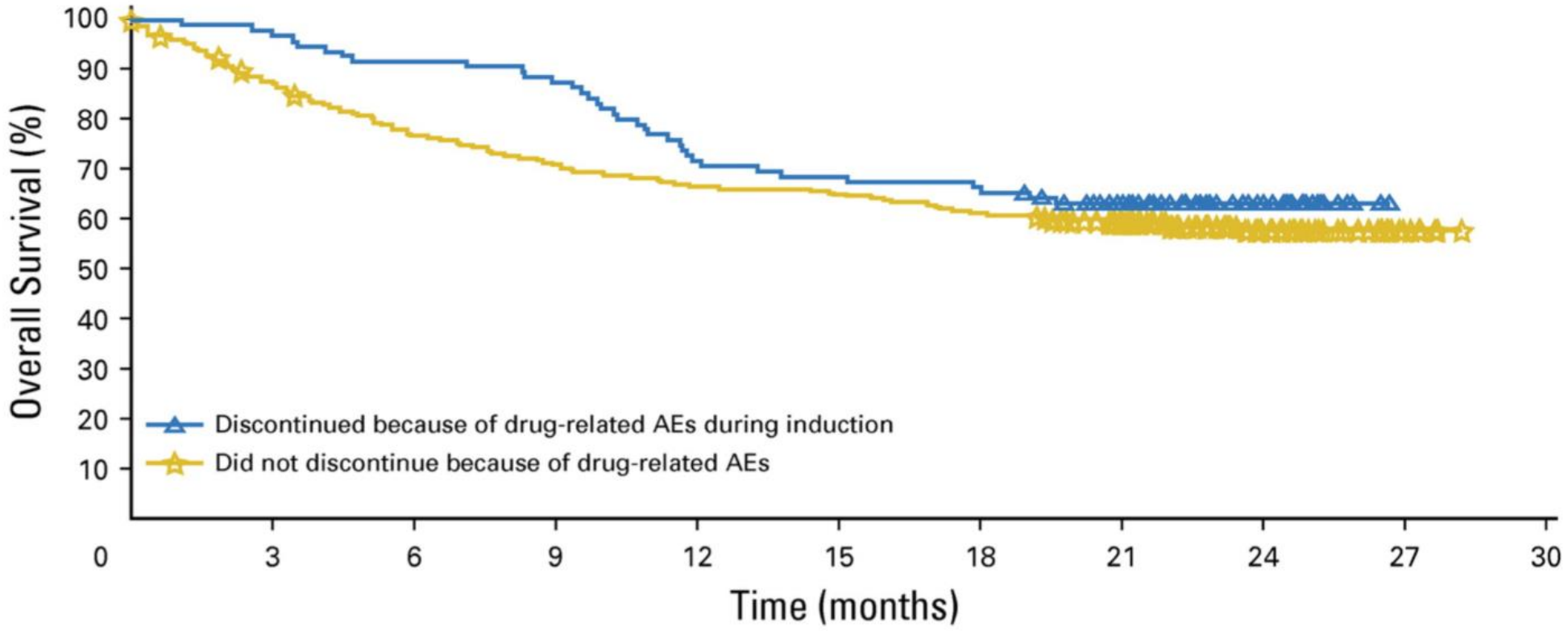
Pazanov & Diab, JITC 2017.

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.

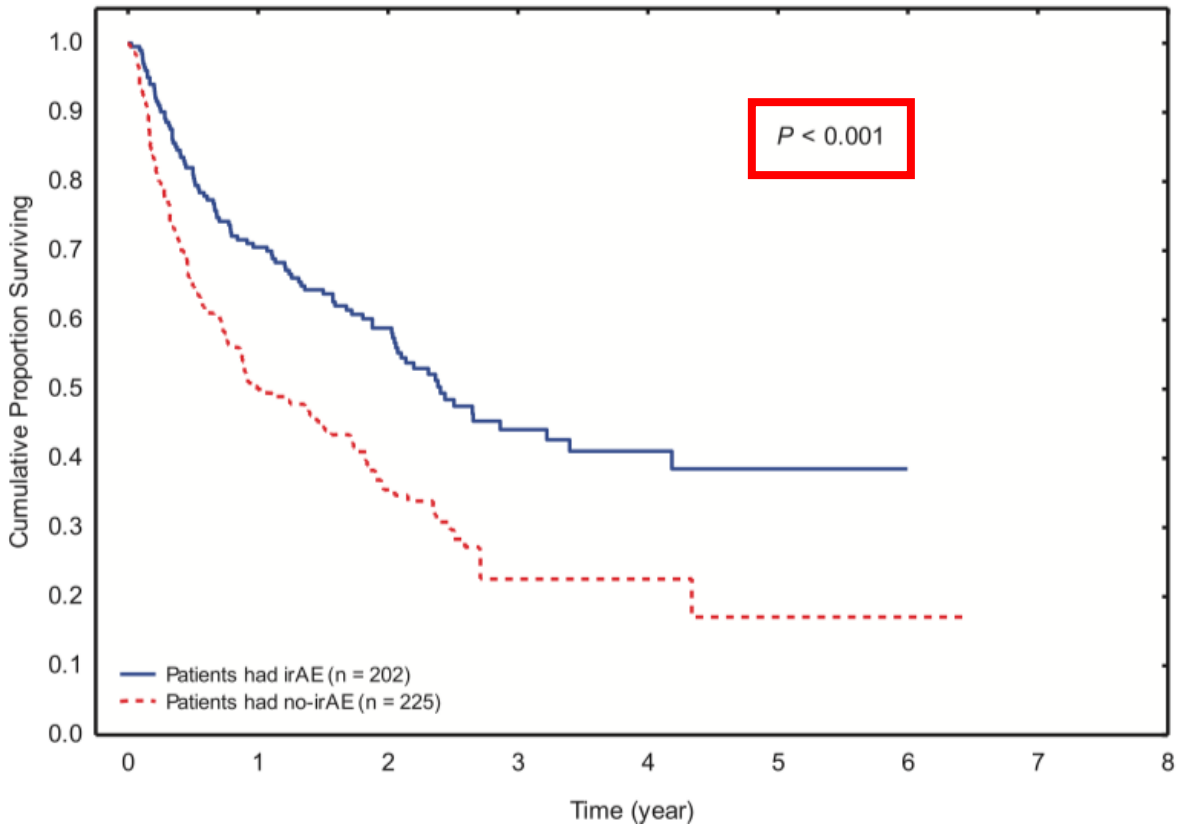
Effect of irAEs on patient outcomes

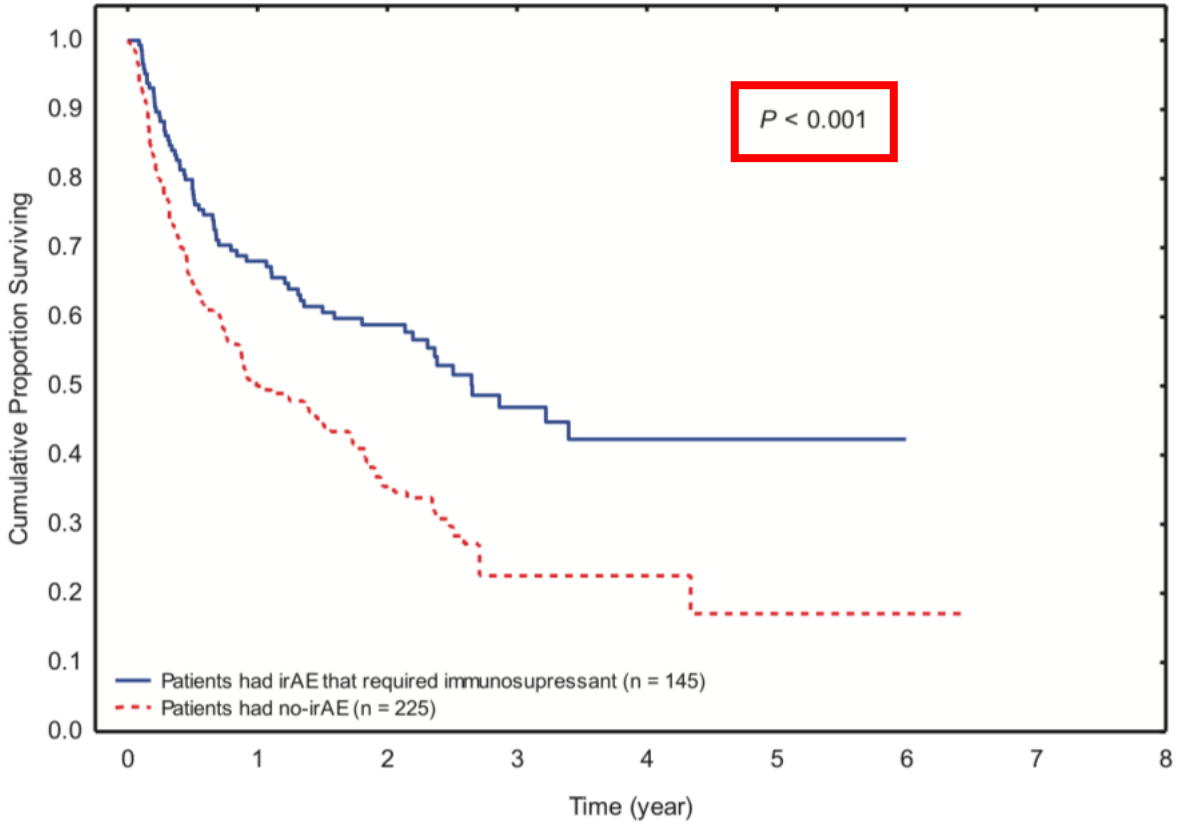


No significant difference in survival in melanoma patients who discontinued ipilimumab + nivolumab due to irAEs versus those who did not discontinue treatment

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

Autoimmunity as prognostic marker?

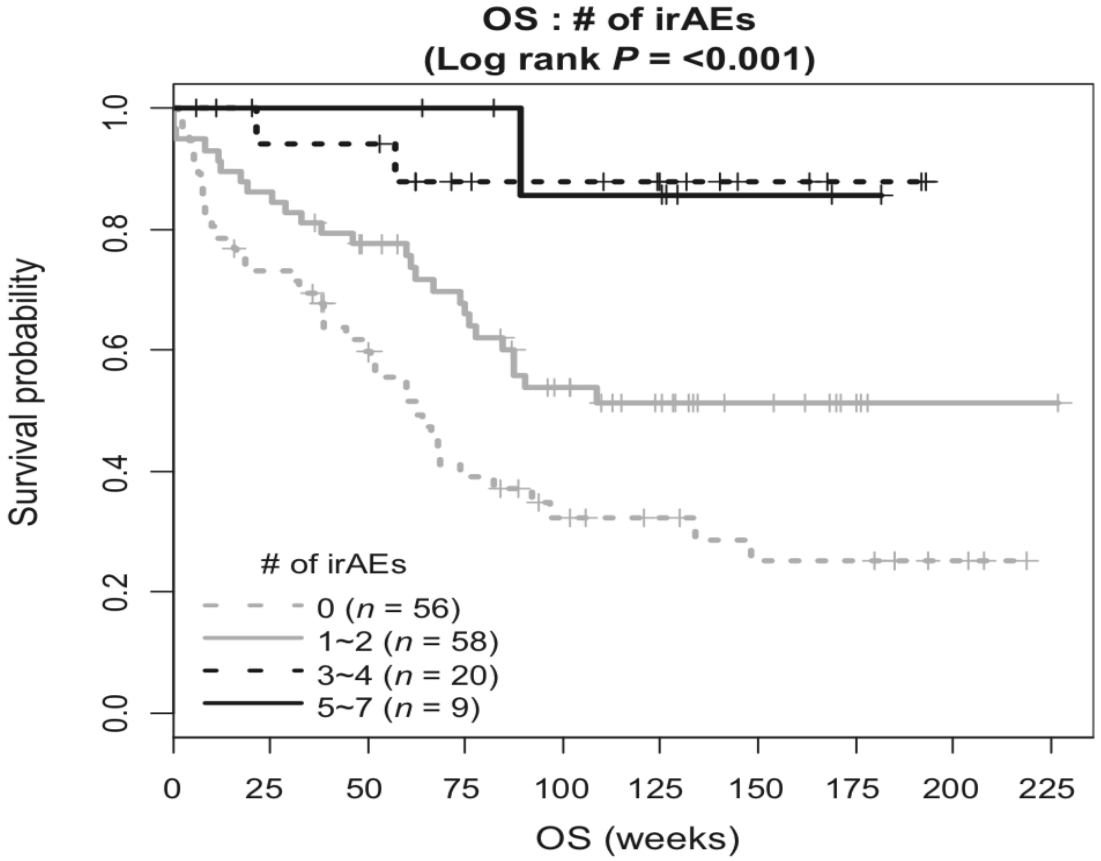




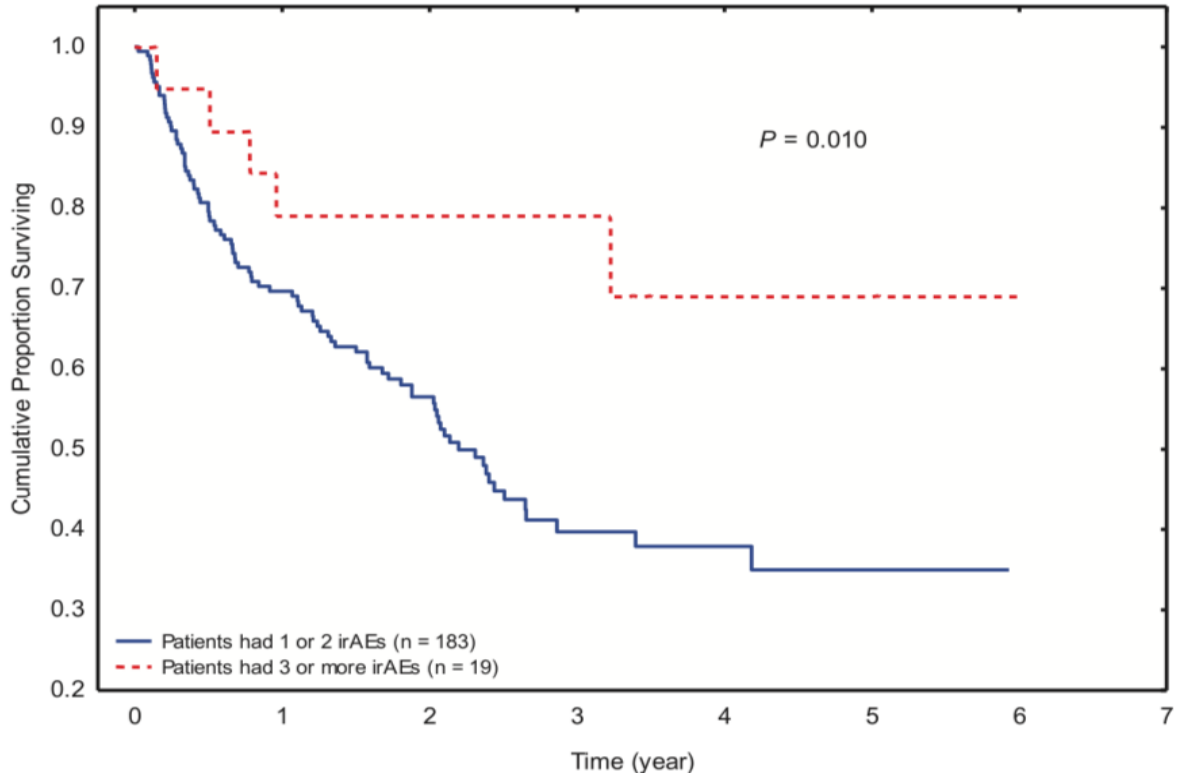
Based on **retrospective** data, patients who experience irAEs (regardless of needing treatment) may have better outcomes compared to patients who do not experience irAEs

Abu-Sbeih, J Immunoth Prec Oncol 2018.

Number of irAEs on patient outcomes



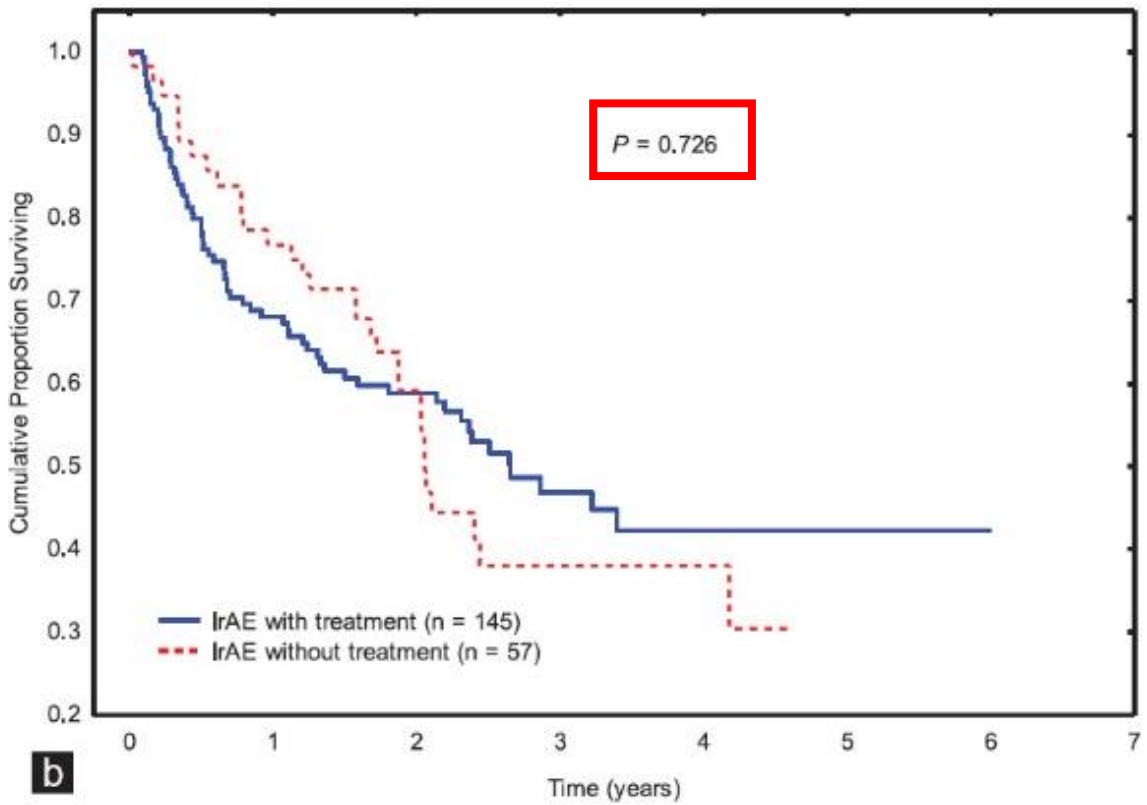
Nivolumab in metastatic melanoma: greater OS in patients with 3+ irAEs versus ≤ 1 irAE

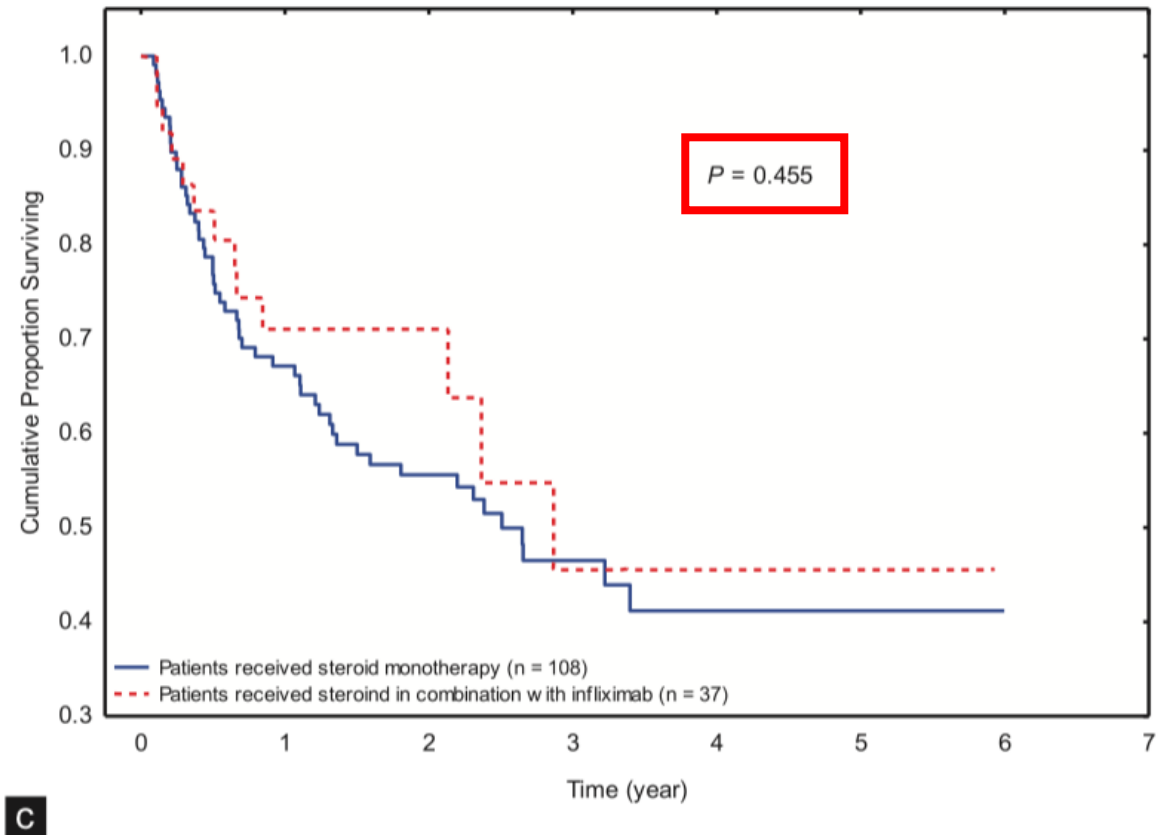


Patients receiving ICI's for various malignancies: greater OS in those with 3+ irAEs versus ≤ 2 irAEs

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

Impact of toxicity management on patient outcomes



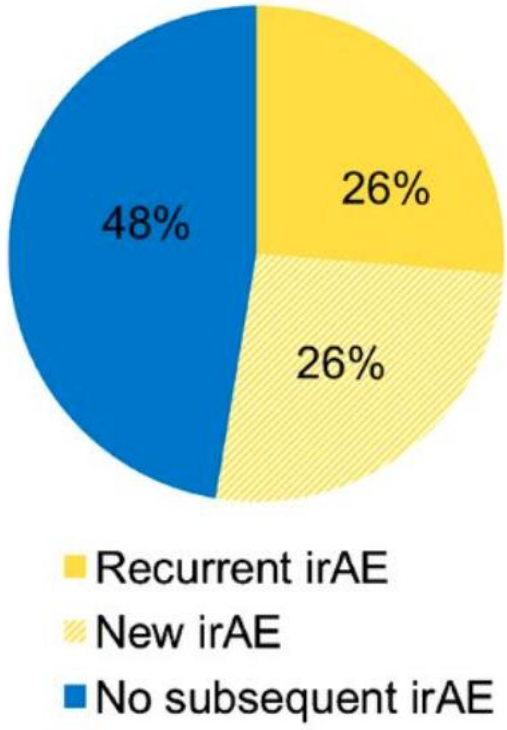


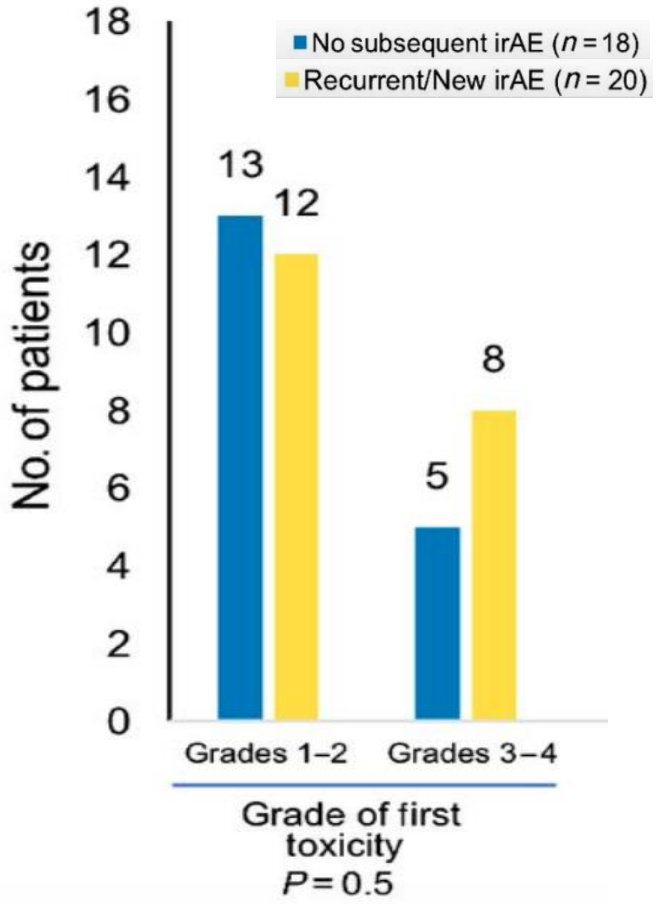
While still under debate, the administration of immunosuppressive treatments NOR the type of immunosuppressant used for irAE management does not seem to impact cancer control

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

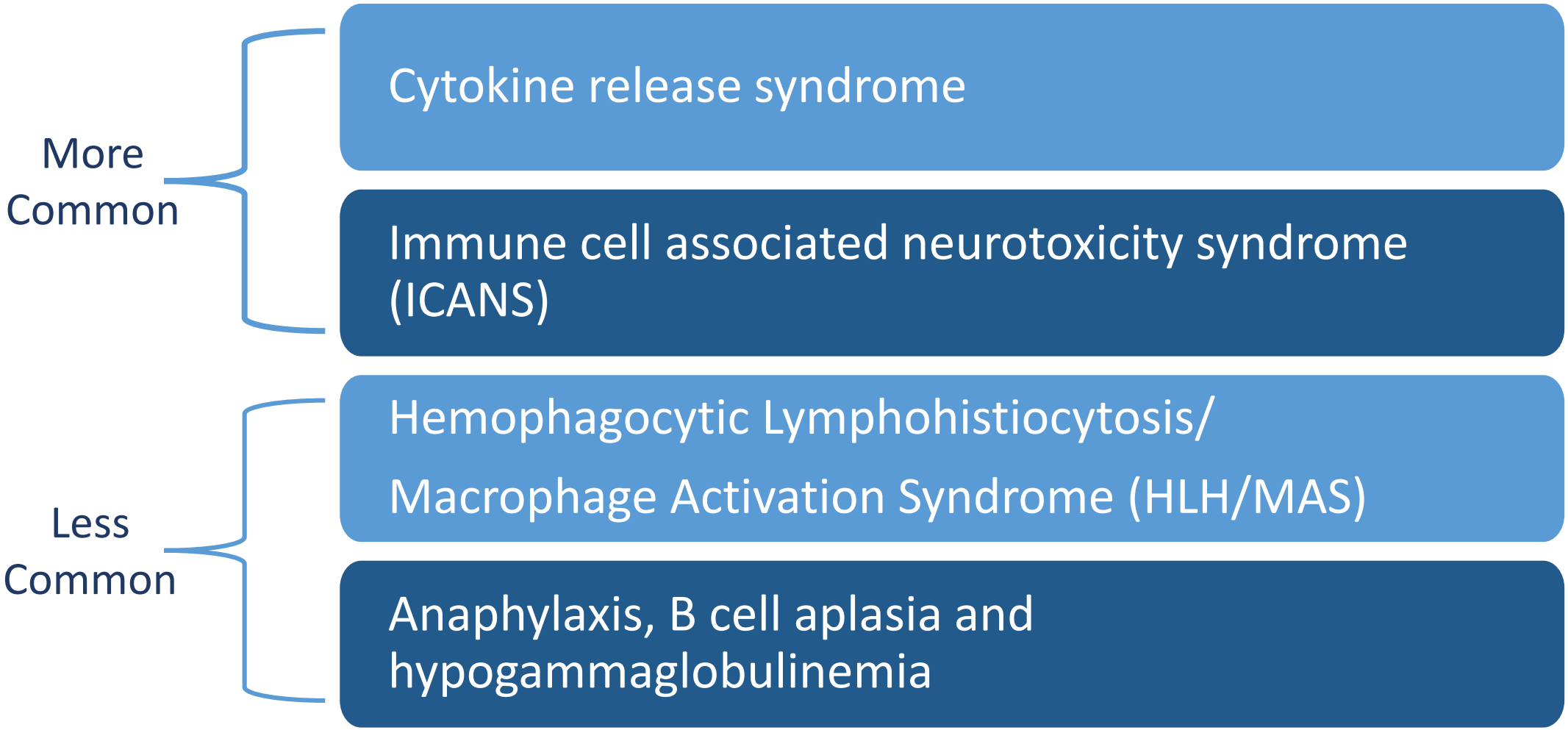
Kahler KC. Cancer Immunol Immunother. 2018.

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 allograft rejection in 41%
  - Of those with rejection, 81% had graft loss and 46% died
  - Rapid time to rejection with median onset of 21 days
- PD-1 pathway appears to be more critical in allograft immune tolerance and rejection compared to CTLA-4 pathway

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

CAR T-cell related toxicities



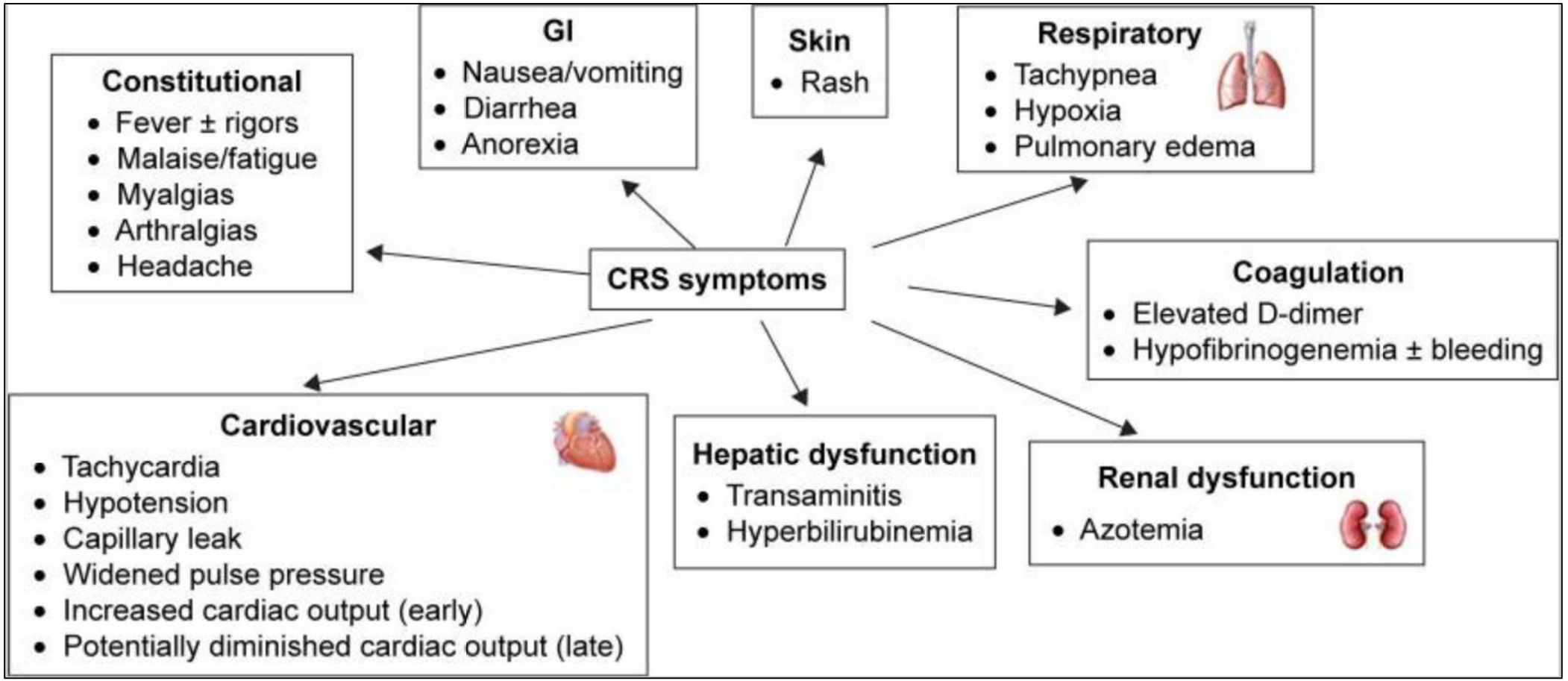
NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

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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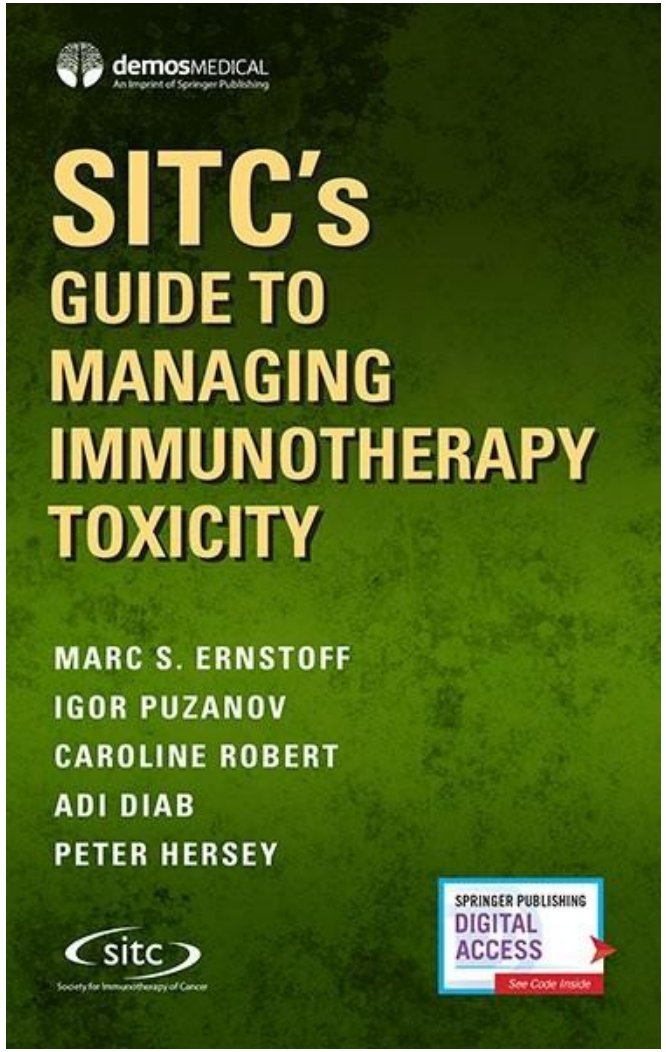
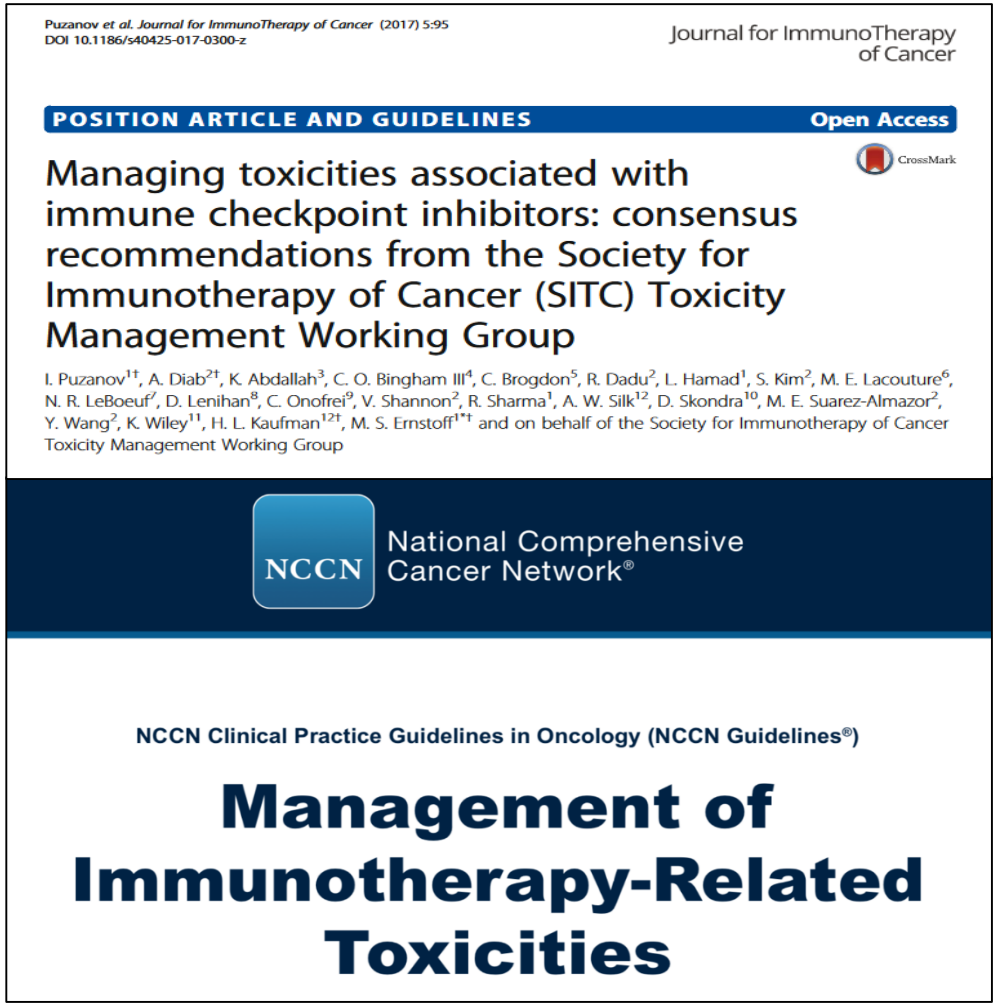
Additional Resources





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Case Study 1

- Mr. L is a 71 y.o. male with Stage IV melanoma with widely metastatic disease, including CNS metastases
- Received 2 doses of combination ipilimumab and nivolumab
- Presented with abdominal pain of unclear etiology; CT scan shows clear disease regression. Ipi/nivo held
- 10 days later, he developed recurrent abdominal pain, nausea, vomiting and loose stools

Case Study 1

- What would be your plan?

A. Admit the patient for supportive care and further GI workup

B. Hydrate the patient and send him home with VNA and antiemetics/antidiarrheals with clinic visit in 3 days

C. Set up a GI consult and start steroids

D. Administer a 3rd dose of ipilimumab/nivolumab after IV hydration and antiemetics

Case Study 1

- He was admitted and underwent CT showing small bowel enteritis
- Began IV solumedrol
- Had EGD c/w enteritis clinically with biopsy confirmation
- GI symptoms and pain improved; he was DC'ed to home with IV solumedrol
- Transitioned to oral prednisone 100 mg (2 mg/kg) one week later with continued improvement
- Prednisone tapered to 80 mg daily after one week
- Reported recurrent diarrhea with urgency and incontinence

Case Study 1

- What would be your next management step?
  - A. Set up an infliximab infusion, continue antidiarrheals
  - B. Admit the patient, restart IV fluids, resume IV steroids, obtain GI consult for infliximab
  - C. Continue the steroid taper and BRAT diet while giving antidiarrheals
  - D. Set up outpatient IV fluids, IV steroids and GI consult

Case Study 1

- He was admitted for IV hydration and IV solumedrol with improvement
- GI consult done with recommendation for infliximab
- DC’ed to home with PICC line in place
- Received one dose of infliximab as outpatient 6 days later
- Transitioned to oral steroids 2 weeks later
- Slow taper of oral prednisone which he tolerated well
- Serial torso CT's show stable regressed melanoma, including brain

Case Study 2

- Ms. S. is a 76 y.o. female with Stage IIIC melanoma of the RLE
- She started pembrolizumab when her disease was deemed unresectable
- Increased SQ nodules noted along RLE c/w disease progression after 5 cycles of pembro
- TVEC (modified herpes virus given by intra-tumoral injection) added
- PET shows FDG avid lung nodules – biopsy done c/w sarcoid felt r/t immunotherapy
- Evidence of disease regression on RLE with decreased size of nodules and no new sites of disease
- 13 months into pembro, noted to have grade 2 transaminitis (ALT 121, AST 92)
- What would be your approach?

Case Study 2

- A. Continue immunotherapy and ask her to call with new GI symptoms
- B. Hold pembrolizumab and refer to hepatology
- C. Assess for symptoms of hepatitis, review meds for hepatotoxins, ask about ETOH use, hold pembrolizumab
- D. Continue immunotherapy and have labs repeated in one week

Case Study 2

- Assess for symptoms of hepatitis – she had no N/V, anorexia, RUQ pain
- Look for other hepatotoxic agents – atorvastatin held, acetaminophen and alcohol reduced
- Pembrolizumab held
- TVEC continued
- Returned 3 weeks later – transaminases down to grade 1
- Pembro restarted
- 3 weeks later, transaminases back to grade 2 (ALT 150, AST 113, Tbili 0.4)
- What would your approach be here?

Case Study 2

- A. Continue pembrolizumab and watch LFT's closely
- B. Hold pembrolizumab and watch LFT's closely
- C. Continue pembrolizumab, refer to hepatology
- D. Permanently discontinue pembrolizumab

Case Study 2

- Pembro held
- Repeat labs showed grade 3 LFT's (ALT 208, AST 170, Tbili 0.6)
- Remains asymptomatic
- Management?
  - A. Continue pembrolizumab, hold hepatotoxins and avoid ETOH, hepatology consult
  - B. Hold pembrolizumab and check LFT's weekly
  - C. Hold pembrolizumab and obtain hepatology consult
  - D. Continue pembrolizumab and check LFT's weekly

Case Study 2

- Pembro held
- Hepatitis screen checked and negative
- Urgent hepatology consult
- LFT's worsening (ALT 357, AST 329, Tbili 0.7)
- Autoimmune markers sent (IgG, IgM, ANA, ASMA, AMA) – ANA positive
- Liver MRI shows fibrosis
- Liver biopsy done showing plasma cell predominant hepatitis and significant necrosis c/w moderate to severe autoimmune hepatitis
- Remains asymptomatic

Case Study 2

- How would you manage this patient?
  - A. Begin prednisone 1-2 mg/kg/day, monitor LFT's every 2 days, close hepatology follow up, consider permanent discontinuation of pembro
  - B. Begin prednisone 0.5 mg/kg/day to start, monitor LFT's every 3 days, close hepatology follow up, consider permanent discontinuation of pembro
  - C. Admit to the hospital, begin IV methylprednisolone, daily LFT's, inpatient hepatology consult
  - D. Begin prednisone 0.5 mg/kg/day, monitor LFT's weekly, restart pembro when LFT's return to grade 1

Case Study 2

- Placed on prednisone 1.5 mg/kg daily
- PPI and PCP prophylaxis started
- LFT's returned to grade 1 within 3 days of starting steroids
- LFT's returned to normal within 3 weeks
- Slow steroid taper over 3-4 months
- Statin restarted
- PET scan shows no evidence of disease and pembro remains on hold