

# Toxicity Management

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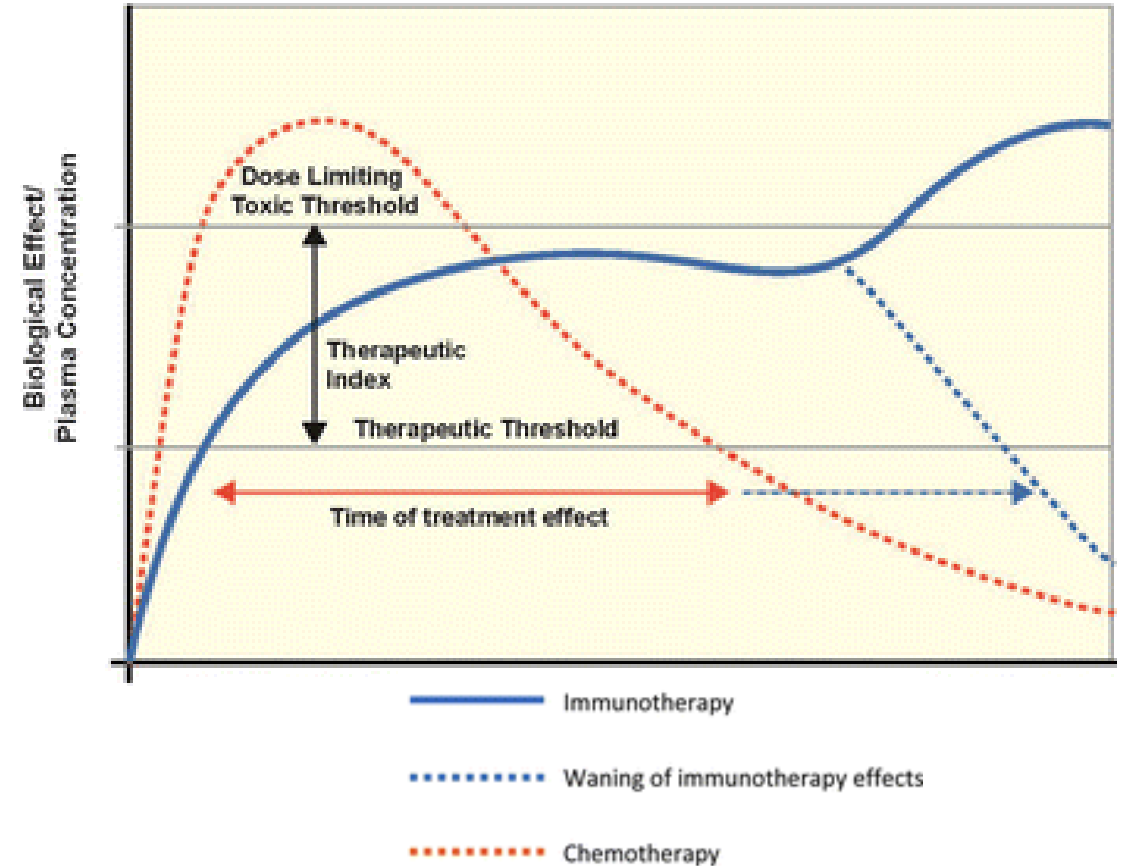
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# Disclosures

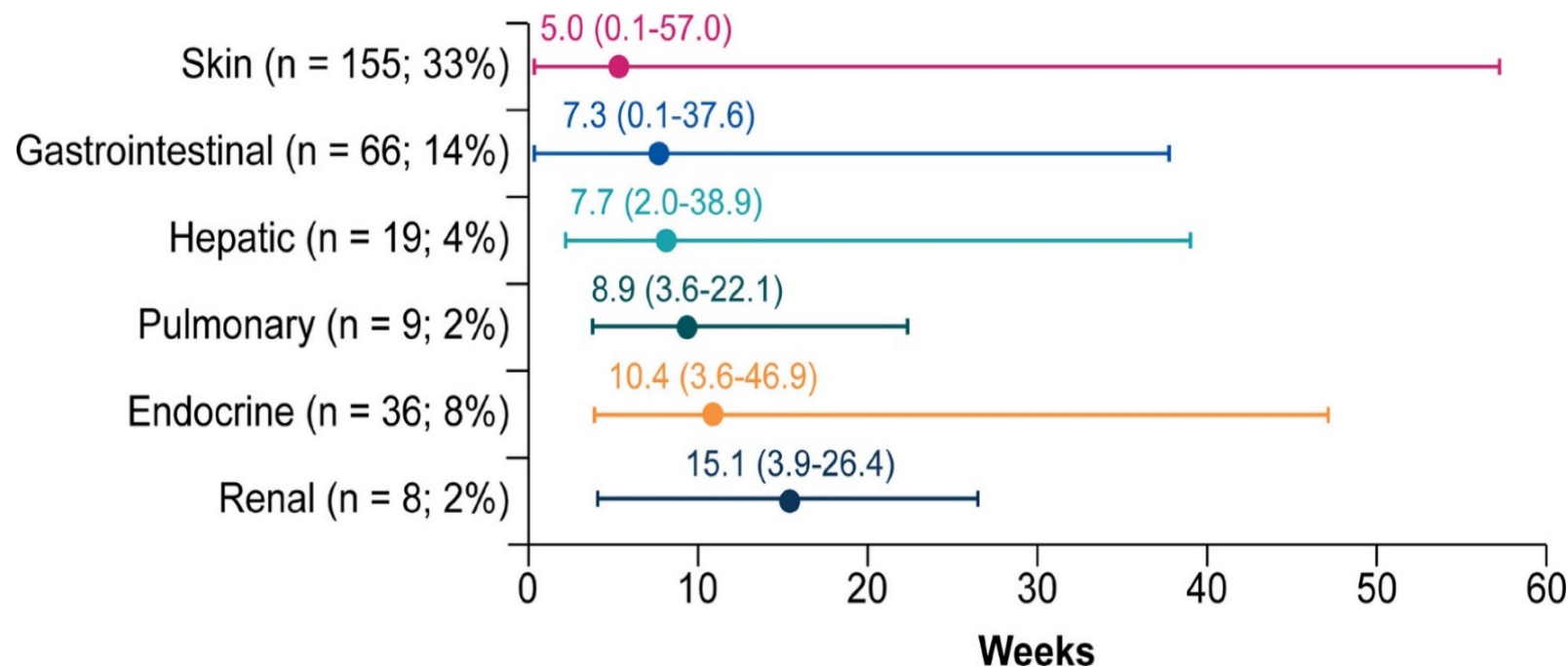
- Consultant: Apricity Health, Exelixis
- I will be discussing non-FDA approved indications during my presentation.

# 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



# 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!

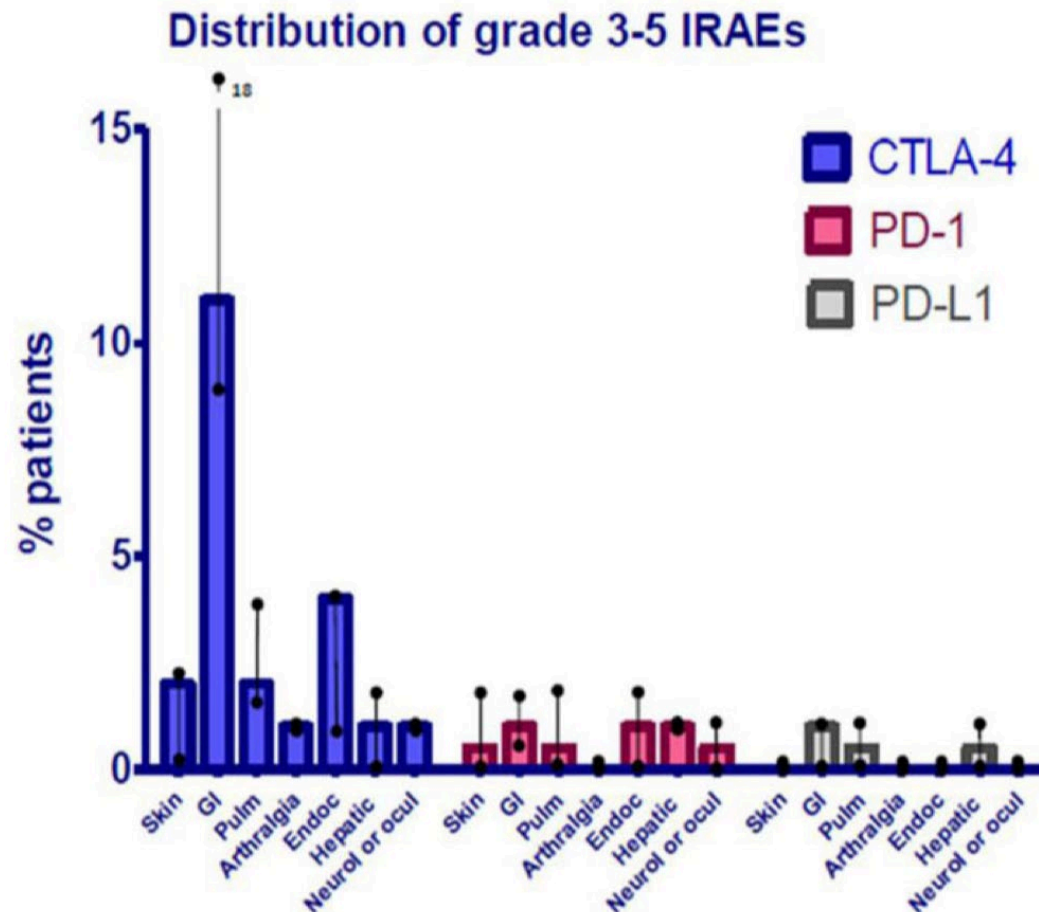
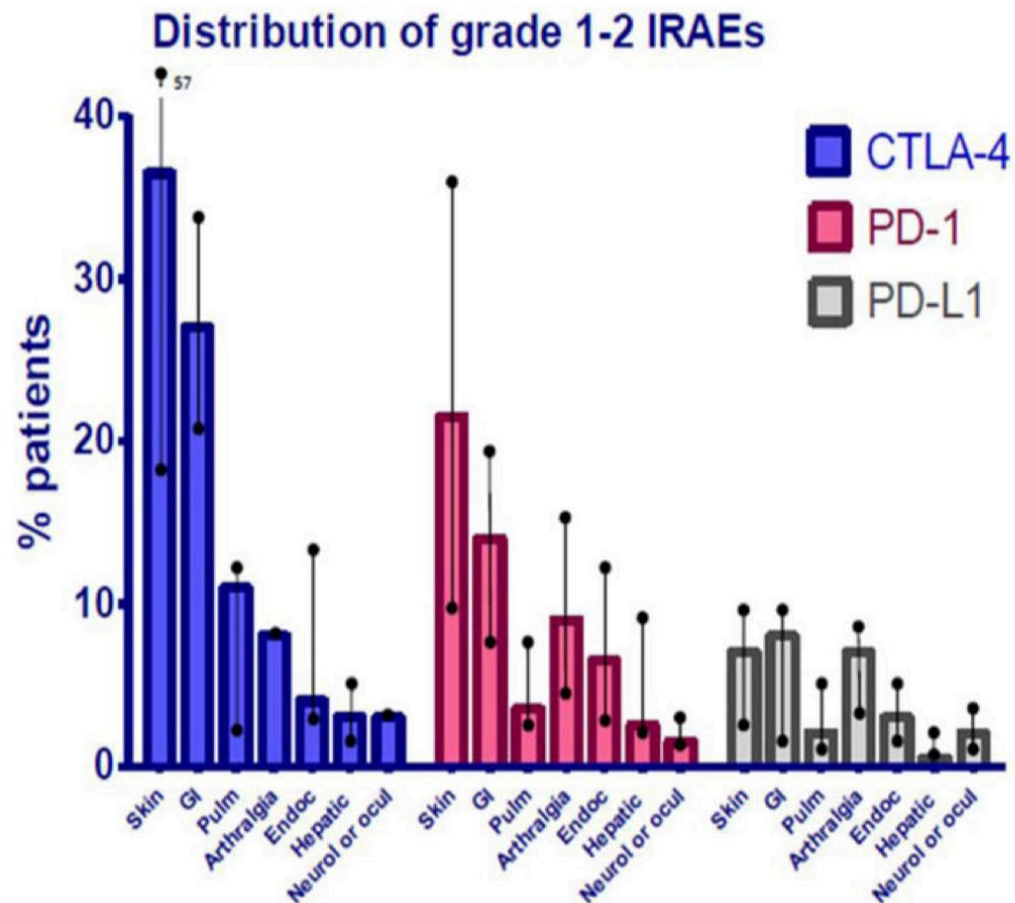
# Incidence of irAEs

- 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  $\leq$  75% (**Grade 3+:  $\leq$  43%**)
- PD-1/PD-L1 inhibitors: toxicities less dose-dependent
  - Any grade toxicity  $\leq$  30% (**Grade 3+:  $\leq$  20%**)
- Life-threatening irAEs are rare but treatment-related deaths reported in up to 2% of clinical trial patients

# Incidence of specific irAEs by ICI

Drug	Dermatitis	Colitis	Hepatitis	Endocrinopathies	Pneumonitis
	<b>All grades (grade 3-4)</b>				
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)

# Severity of irAEs by ICI





# Common irAEs with ICI's

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



# 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

# Pre-treatment screening

- Patient History
  - Autoimmune, infectious, endocrine, organ-specific diseases
  - Baseline bowel habits
- Dermatologic
  - Full skin and mucosal exam
- Pulmonary
  - Baseline O<sub>2</sub> 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)

# Additional screening for high-risk patients

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

# Approach to Treatment

- Treatment approach is guided by grading of specific toxicity
- Resources for grading:
  - SITC Toxicity Management Working Group
  - Common Terminology Criteria for Adverse Events
  - National Comprehensive Cancer Network
- 1<sup>st</sup> 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
<b>1</b>	Usually not indicated	Continue immunotherapy
<b>2</b>	<ul style="list-style-type: none"> <li>Start <b>prednisone 0.5-1 mg/kg/day</b> (or equivalent dose of IV methylprednisolone)</li> <li>If no improvement in 2-3 days, <b>increase dose</b> to 2 mg/kg/day</li> <li>Once improved to ≤grade 1, start <b>4-6 week steroid taper</b></li> </ul>	<ul style="list-style-type: none"> <li><b>Hold immunotherapy</b> during corticosteroid use</li> <li><b>Continue immunotherapy</b> once resolved to ≤grade 1 and off corticosteroids</li> <li>Start proton pump inhibitor for GI prophylaxis</li> </ul>

# General corticosteroid management

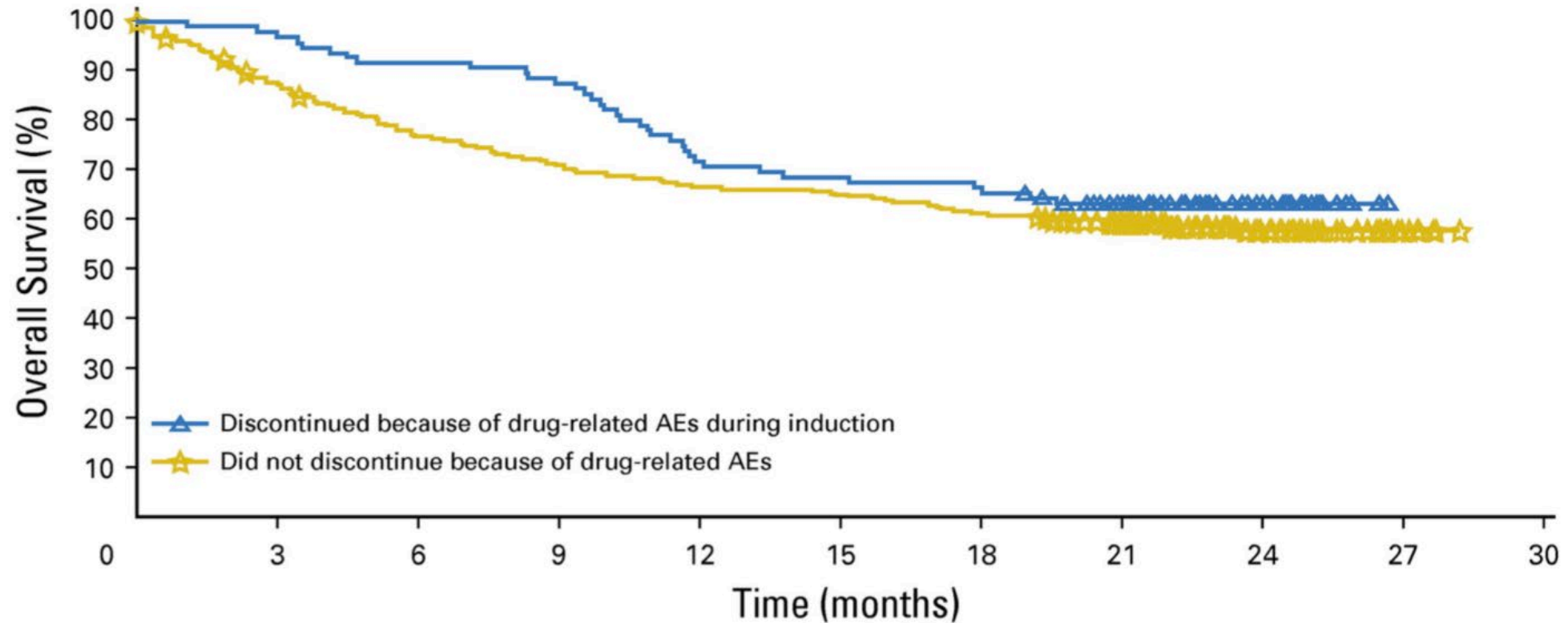
Grade of irAE	Corticosteroid Management	Additional Notes
3	<ul style="list-style-type: none"> <li>Start <b>prednisone 1-2 mg/kg/day</b> (or equivalent dose of IV methylprednisolone)</li> <li>If no improvement in 2–3 days, <b>ADD additional</b> immunosuppressant</li> <li>Once improved to <math>\leq</math> grade 1, start <b>4–6-week steroid taper</b></li> </ul>	<ul style="list-style-type: none"> <li><b>Hold immunotherapy</b>; if symptoms do not improve in 4–6 weeks, <b>discontinue immunotherapy</b></li> <li>Start proton pump inhibitor for GI prophylaxis</li> <li>Add PJP prophylaxis if more than 3 weeks of immunosuppression expected (<math>&gt;30</math> mg prednisone or equivalent/day)</li> </ul>
4		<ul style="list-style-type: none"> <li><b>Discontinue immunotherapy</b></li> <li>Start proton pump inhibitor for GI prophylaxis</li> <li>Add PJP prophylaxis if more than 3 weeks of immunosuppression expected (<math>&gt;30</math> mg prednisone or equivalent/day)</li> </ul>

# Additional immunosuppressives

- **Infliximab: anti-TNF- $\alpha$  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; 2<sup>nd</sup> dose may be administered after 2 weeks
- **Vedolizumab:  $\alpha 4\beta 7$  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**

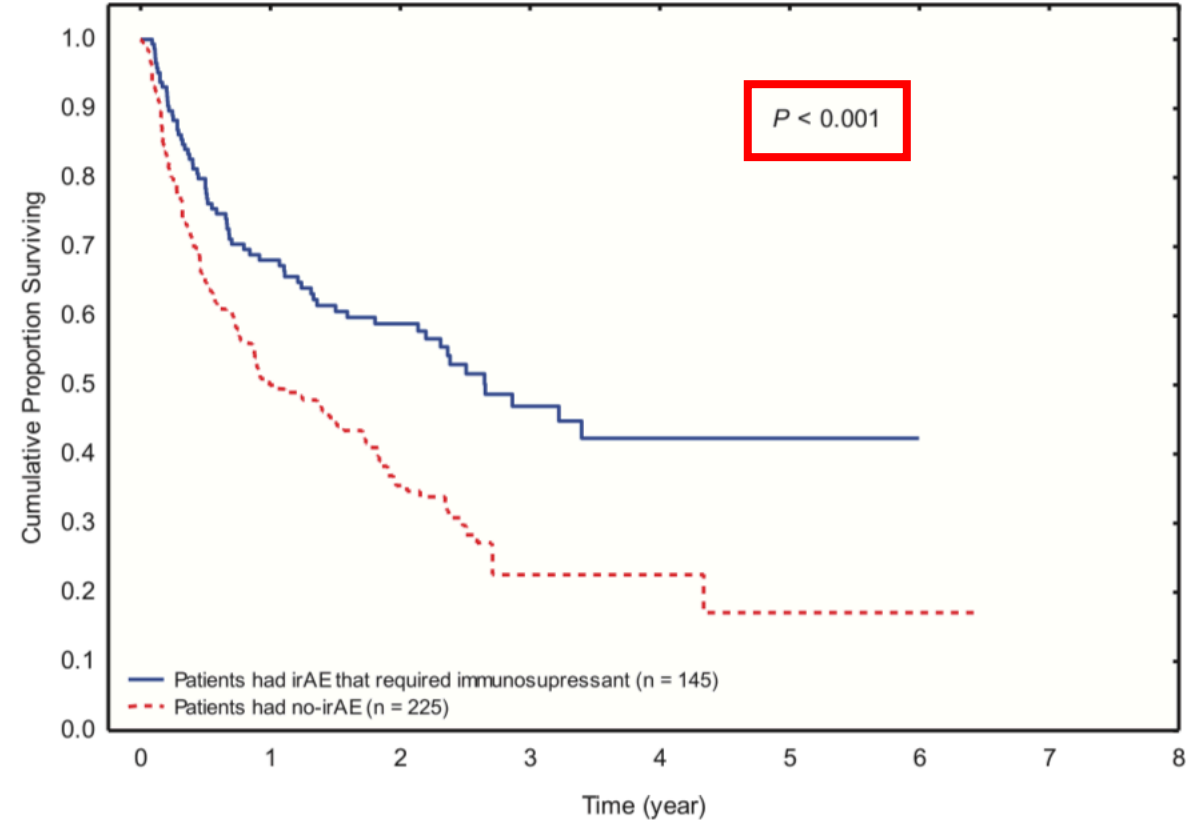
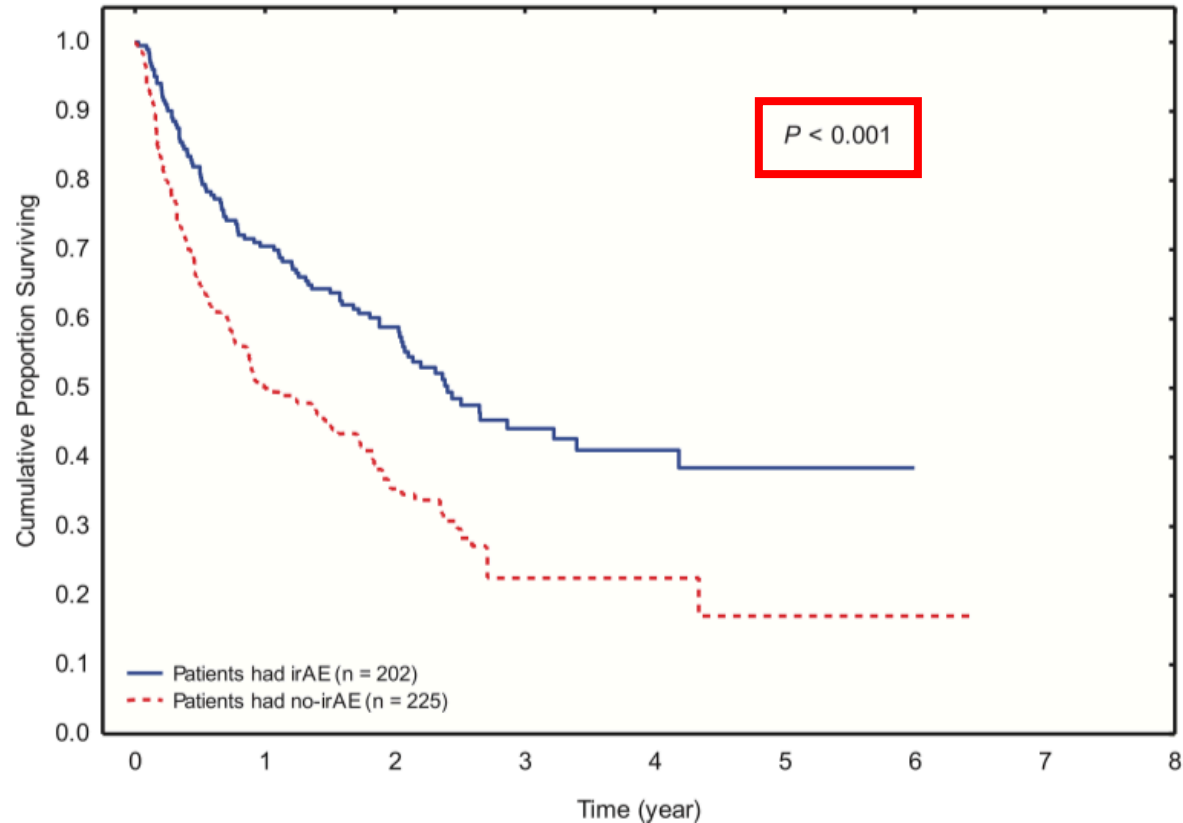


# Effect of irAEs on patient outcomes



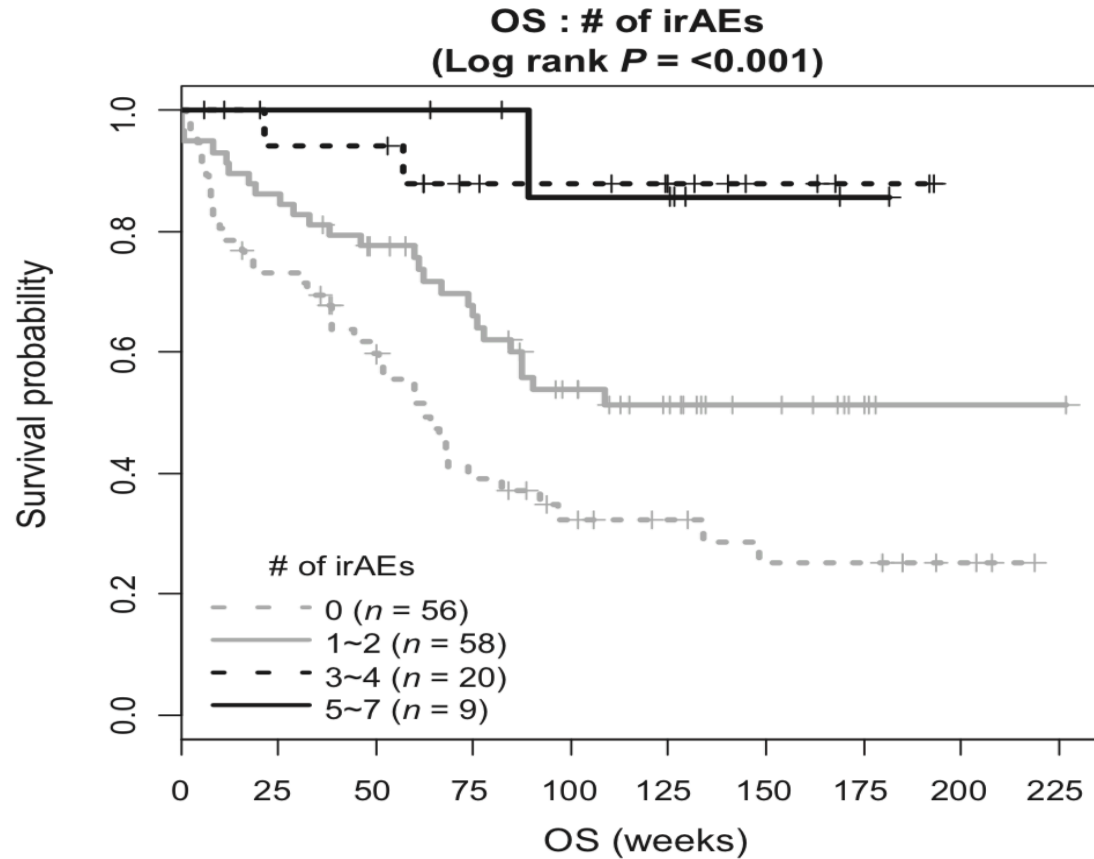
No significant difference in survival in melanoma patients who discontinued ipilimumab + nivolumab due to irAEs versus those who did not discontinue treatment

# Autoimmunity as prognostic marker?

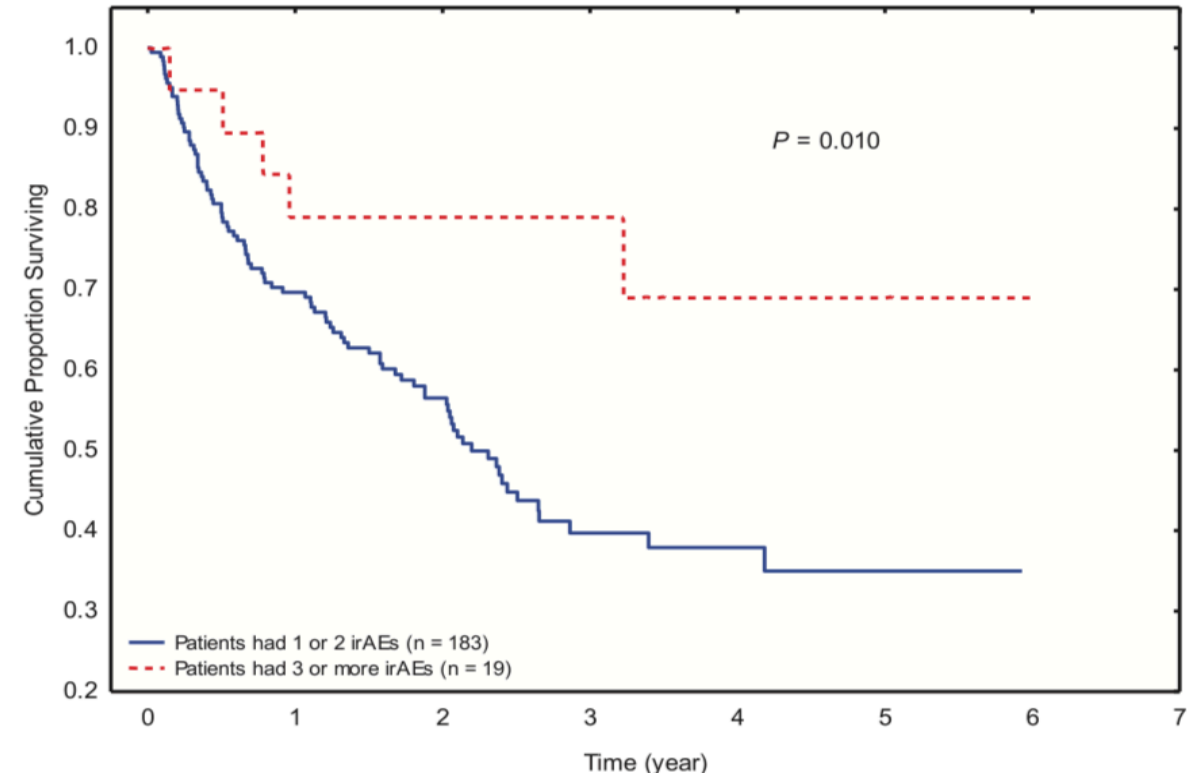


Based on **retrospective** data, patients who experience irAEs (regardless of needing treatment) may have better outcomes compared to patients who do not experience irAEs

# Number of irAEs on patient outcomes

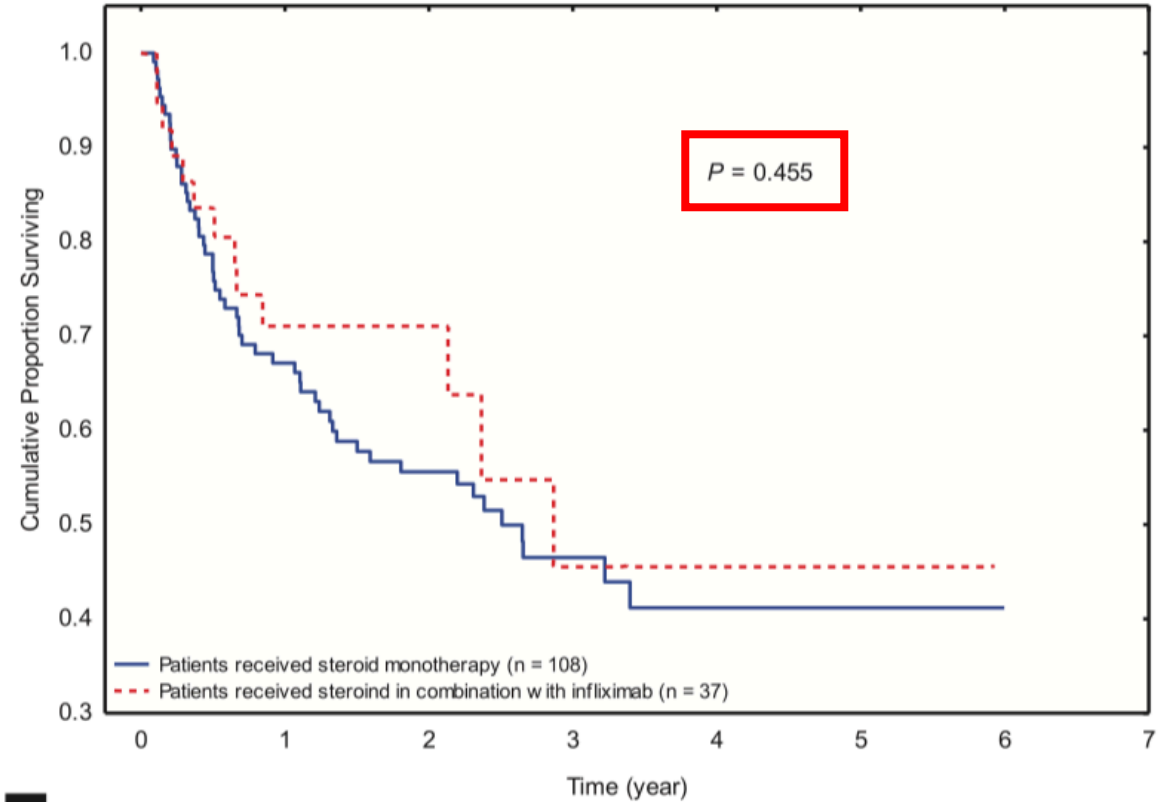
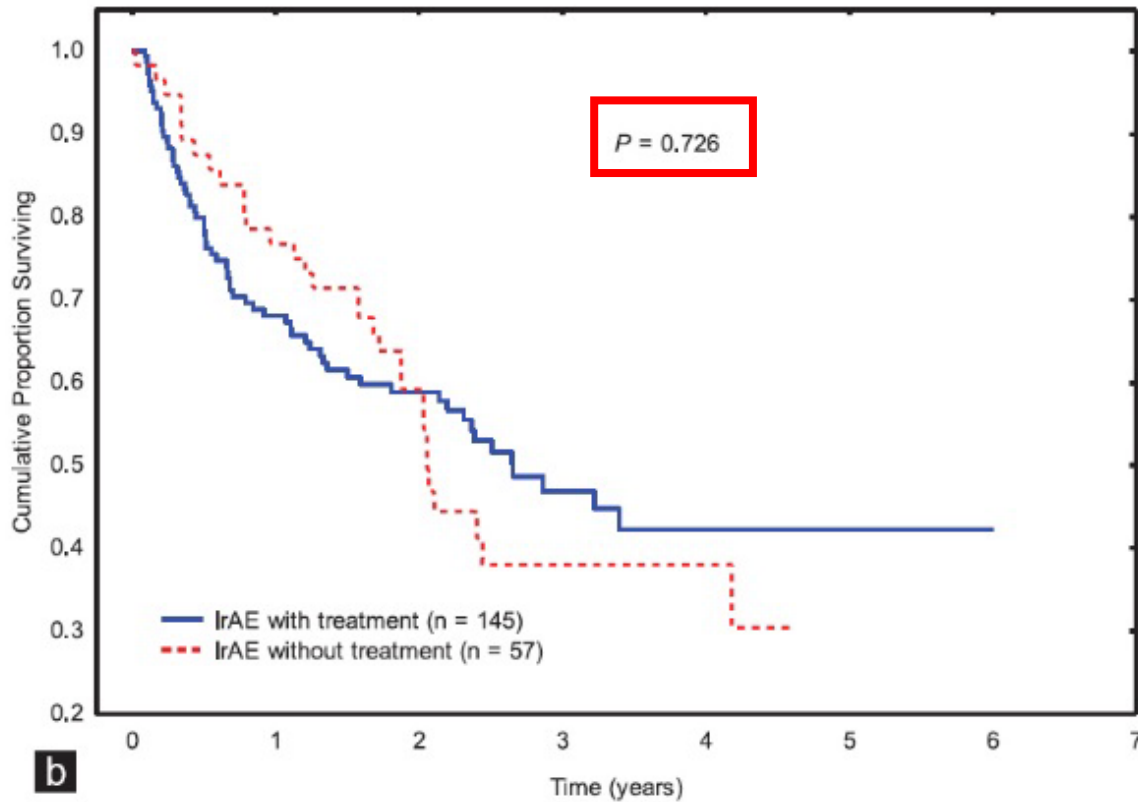


Nivolumab in metastatic melanoma: greater OS  
 in patients with 3+ irAEs versus  $\leq 1$  irAE



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

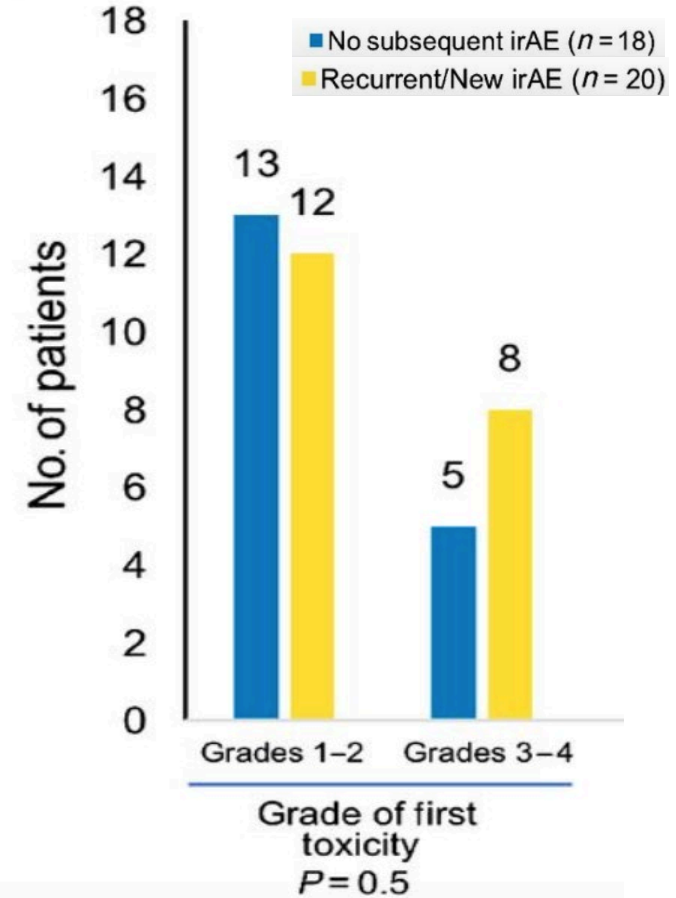
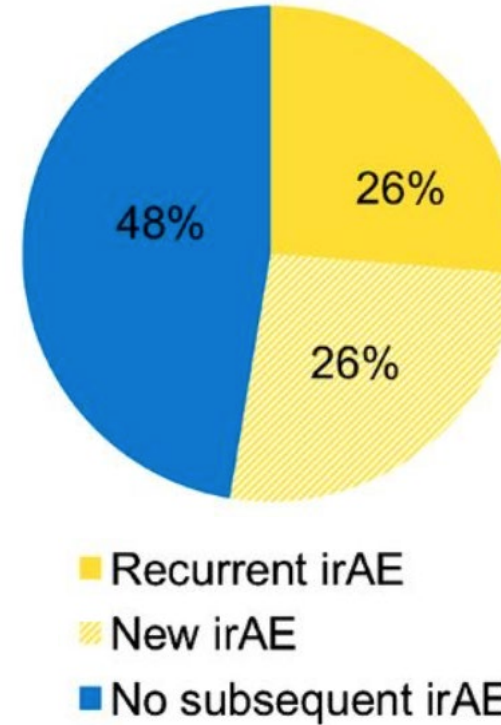
# Impact of toxicity management on patient outcomes



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

# Rechallenging with ICI after irAEs

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



# 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.  
Menzies AM, Johnson DB, Ramanujam S, et al. Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. Ann Oncol. 2017 Feb; 28(2):368-76.

# 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



# CAR T-cell related toxicities

More  
Common

Cytokine release syndrome

Immune cell associated neurotoxicity syndrome (ICANS)

Less  
Common

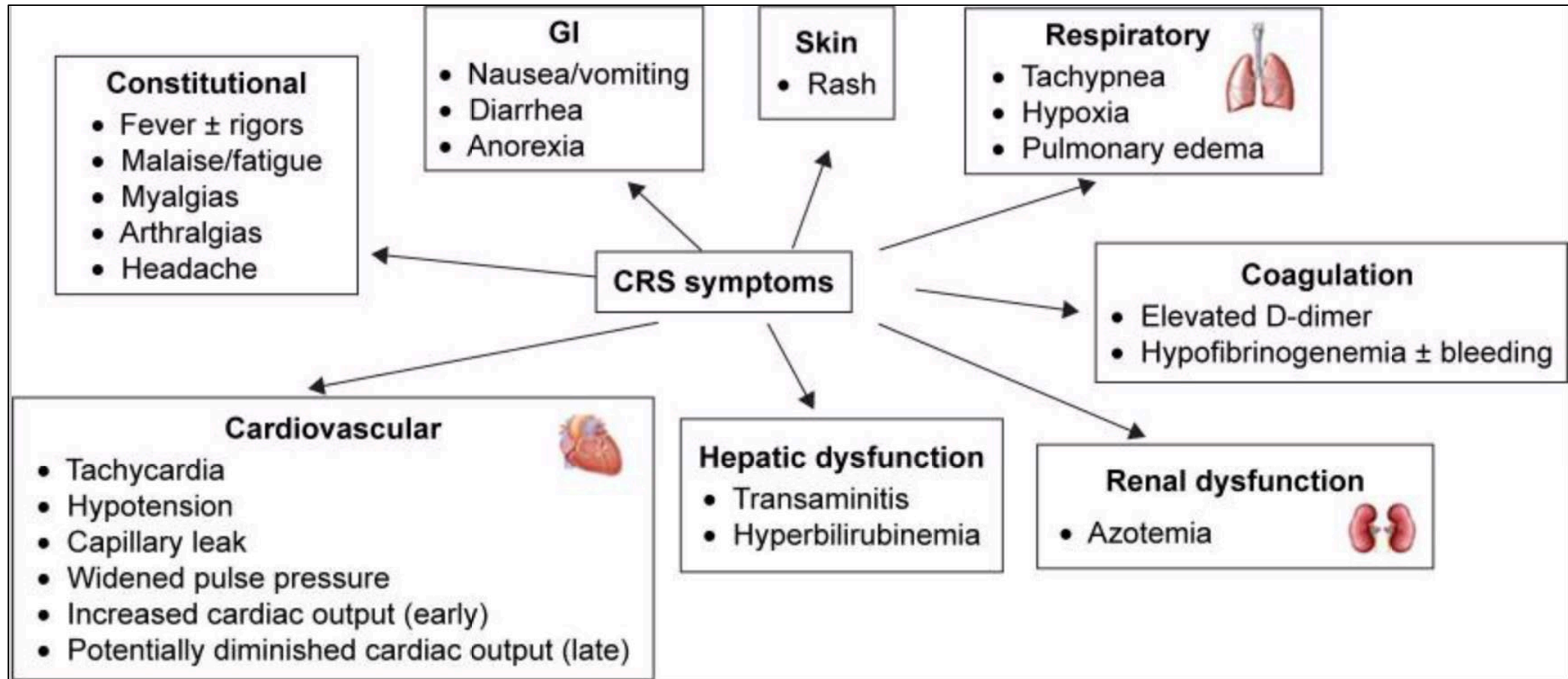
Hemophagocytic Lymphohistiocytosis/  
Macrophage Activation Syndrome (HLH/MAS)

Anaphylaxis, B cell aplasia and  
hypogammaglobulinemia

# CRS and Neurotoxicity

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

# Cytokine release syndrome



# Cytokine release syndrome

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

# Neurotoxicity

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

# 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<sup>2</sup>
  - 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



# The importance of patient education

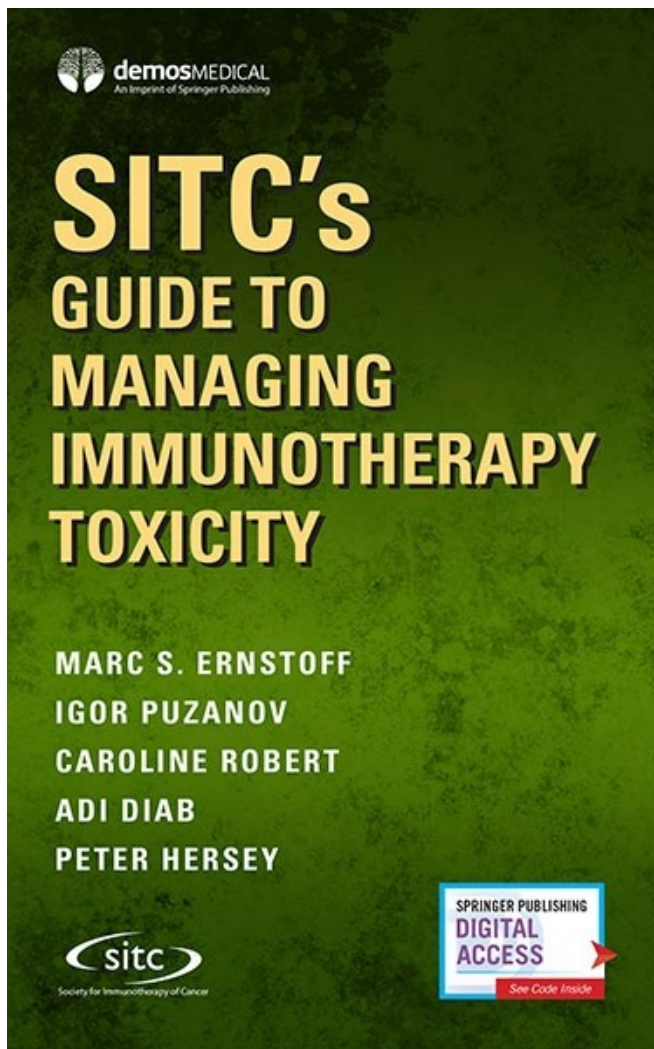
- Many immune-related adverse events can present in similar ways to other disease states, but the treatment of them is very different.
- Patients may not go back to their oncologist for treatment of irAEs and need to identify themselves as immunotherapy recipients
  - Emergency room & general practitioners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


# Additional Resources



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

Journal for Immunotherapy of Cancer

**POSITION ARTICLE AND GUIDELINES** **Open Access**



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

I. Puzanov<sup>1†</sup>, A. Diab<sup>2†</sup>, K. Abdallah<sup>3</sup>, C. O. Bingham III<sup>4</sup>, C. Brogdon<sup>5</sup>, R. Dadu<sup>2</sup>, L. Hamad<sup>1</sup>, S. Kim<sup>2</sup>, M. E. Lacouture<sup>6</sup>, N. R. LeBoeuf<sup>7</sup>, D. Lenihan<sup>8</sup>, C. Onofrei<sup>9</sup>, V. Shannon<sup>2</sup>, R. Sharma<sup>1</sup>, A. W. Silk<sup>12</sup>, D. Skondra<sup>10</sup>, M. E. Suarez-Almazor<sup>2</sup>, Y. Wang<sup>2</sup>, K. Wiley<sup>11</sup>, H. L. Kaufman<sup>12†</sup>, M. S. Ernstoff<sup>1††</sup> and on behalf of the Society for Immunotherapy of Cancer Toxicity Management Working Group

 National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

**Management of Immunotherapy-Related Toxicities**

# Case Study 1

- Mr. M. is a 74 y.o. male with Stage IIIC melanoma of the LLE, s/p resection of local recurrence and 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 1

- 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 1

- 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 1

- 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 1

- 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?



## Case Study 2

- 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 2

- 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 3<sup>rd</sup> dose of ipilimumab/nivolumab after IV hydration and antiemetics

## Case Study 2

- 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 2

- 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 2

- 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