

Toxicity Management

Rajeev Sharma, MD, FACE

Endocrinologist

Assistant Professor of Oncology

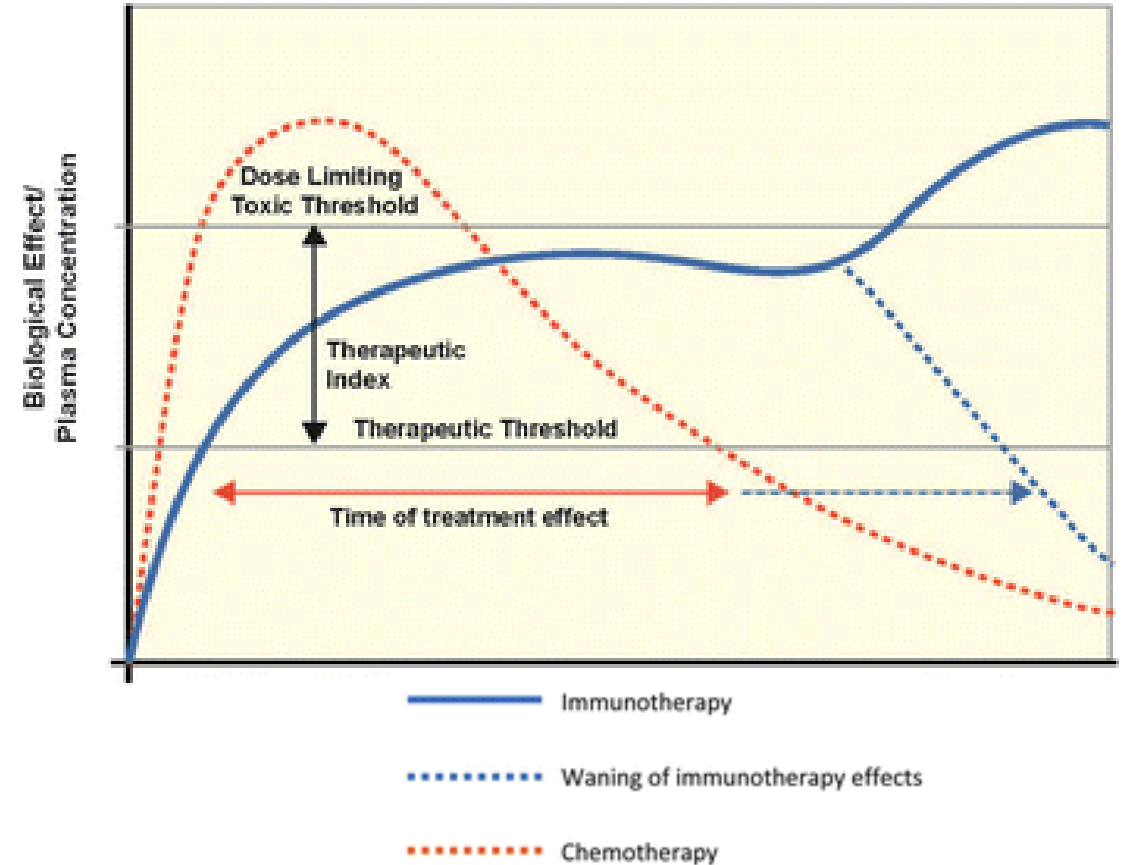
Roswell Park Comprehensive Cancer Center

Disclosures

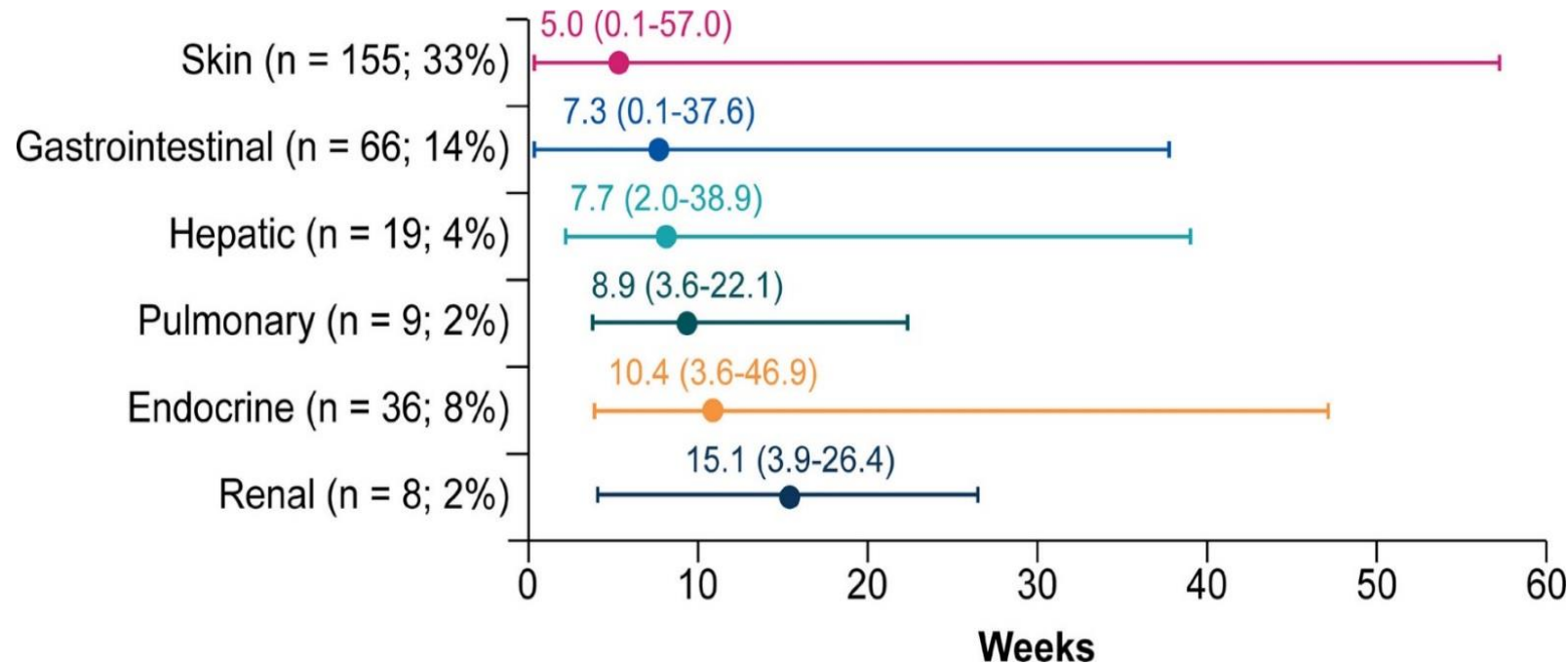
- Nothing to disclose
- I will be discussing non-FDA approved indications during my presentation.

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!

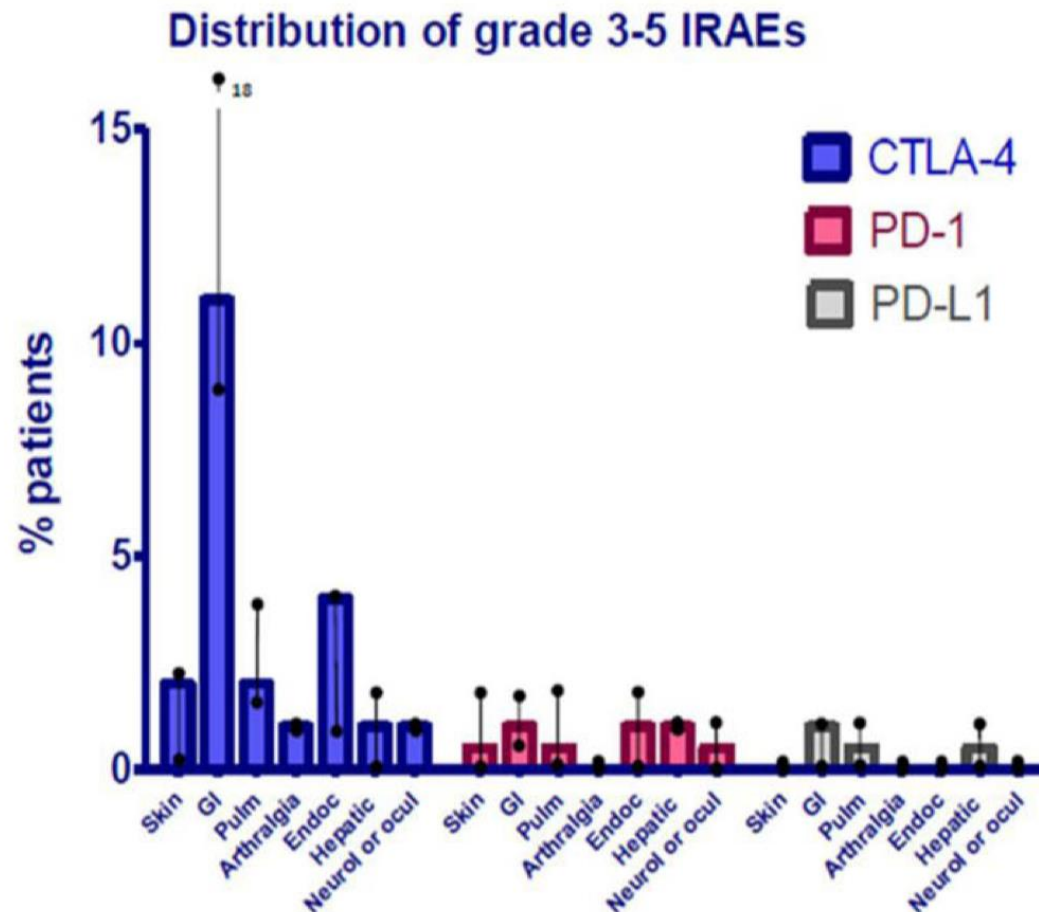
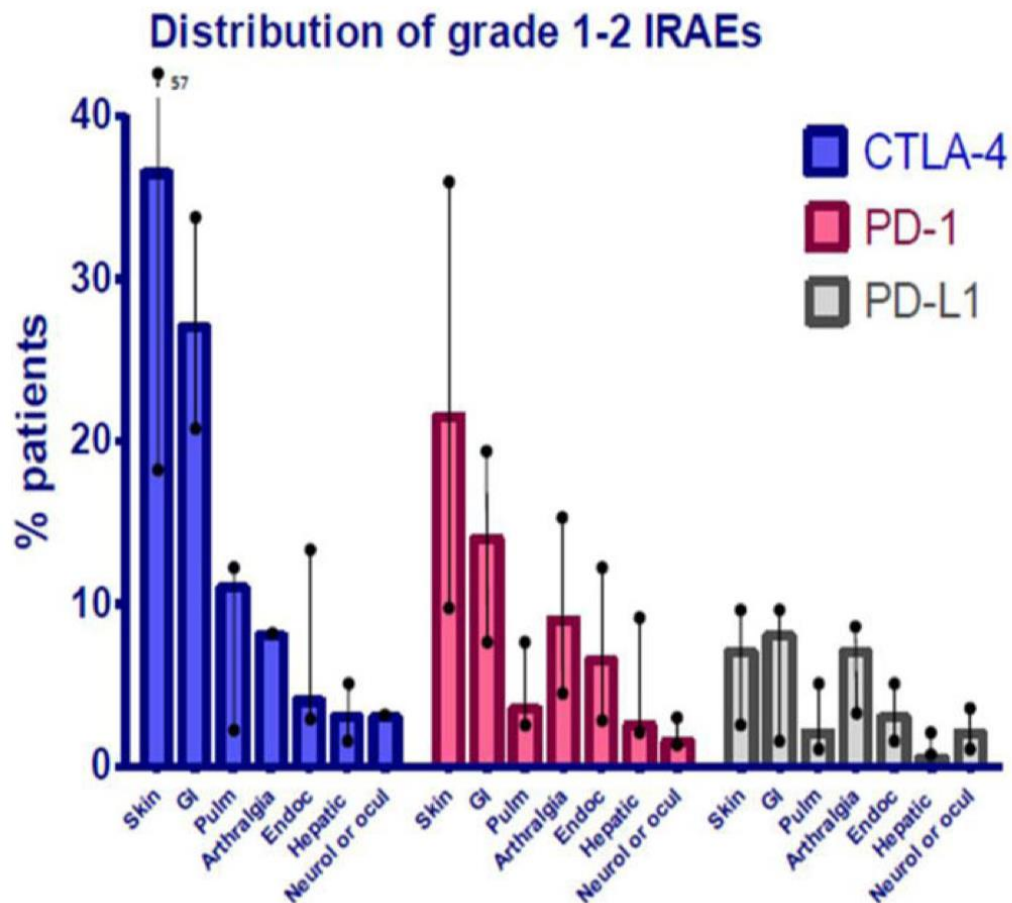
Incidence of irAEs

- 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
	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)

Severity of irAEs by ICI



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

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 O₂ 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
- 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	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Hold immunotherapy during corticosteroid use Continue immunotherapy once resolved to ≤grade 1 and off corticosteroids Start proton pump inhibitor for GI prophylaxis

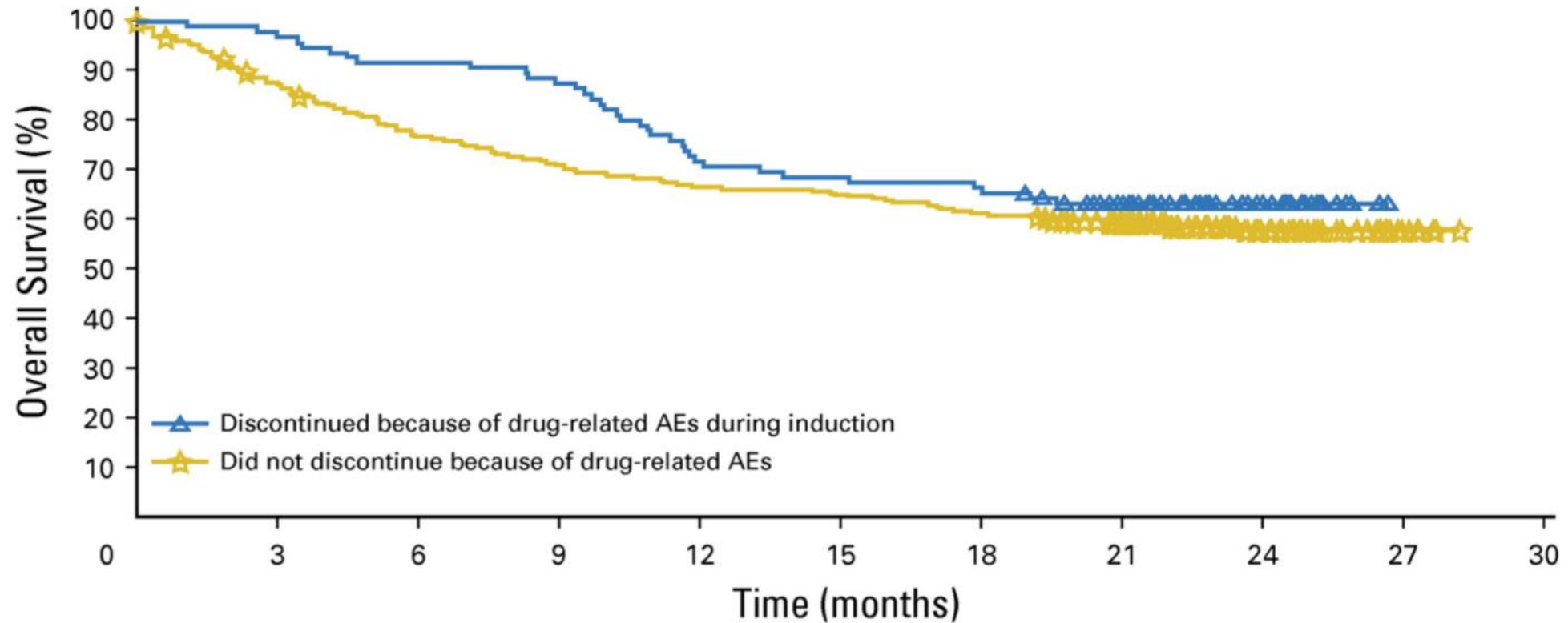
General corticosteroid management

Grade of irAE	Corticosteroid Management	Additional Notes
3	<ul style="list-style-type: none"> 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 \leq grade 1, start 4–6-week steroid taper 	<ul style="list-style-type: none"> 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		<ul style="list-style-type: none"> 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)

Additional immunosuppressives

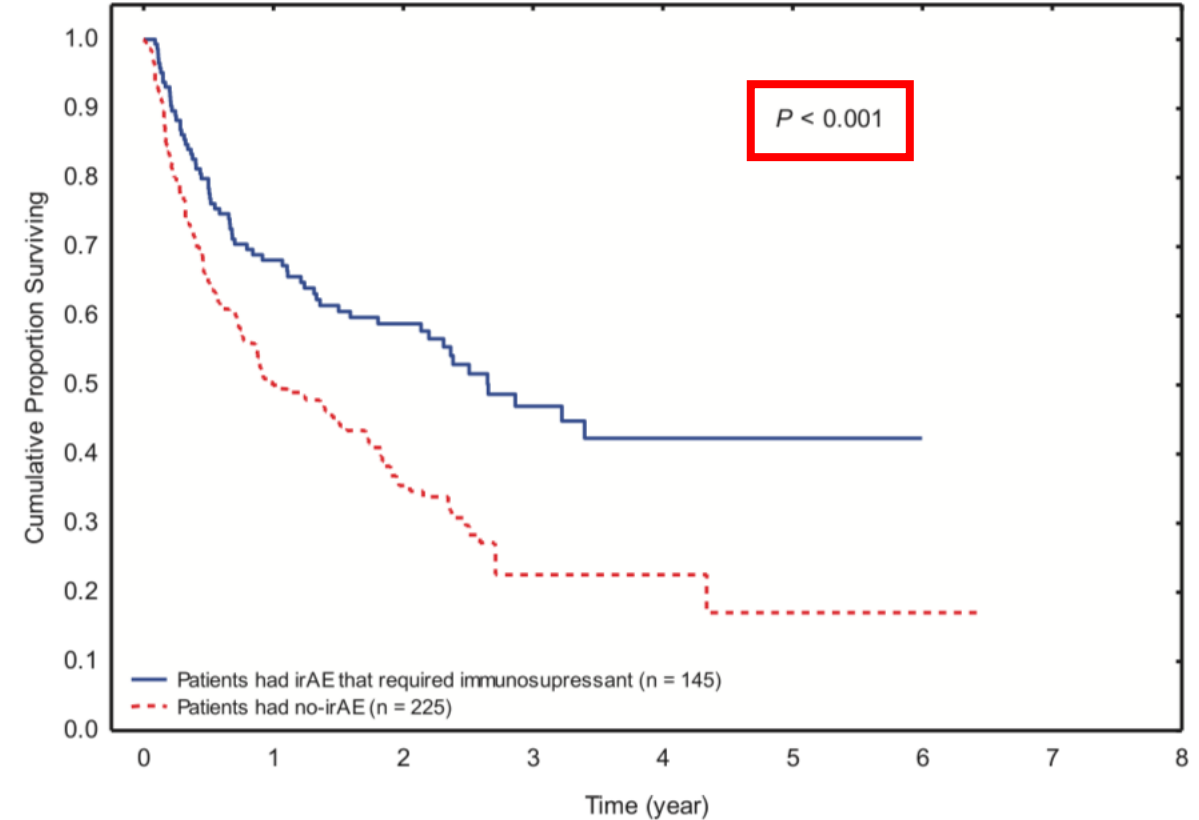
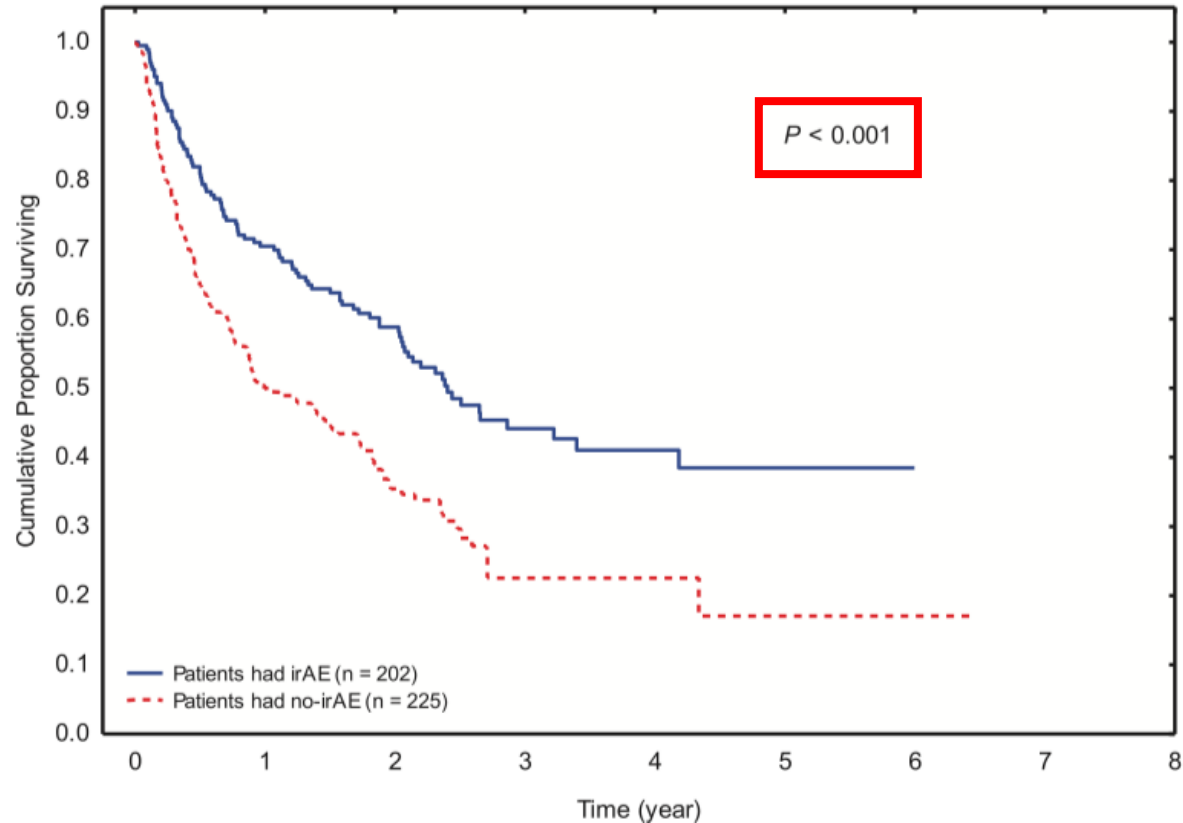
- Infliximab: anti-TNF- α mAb
 - Hepatotoxic so should NOT be used for immune-mediated hepatitis
 - Risk for hepatitis B and tuberculosis activation; obtain hepatitis serologies and TB testing prior to initiation
 - Dose: 5 mg/kg; 2nd dose may be administered after 2 weeks
- Vedolizumab: $\alpha 4\beta 7$ 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



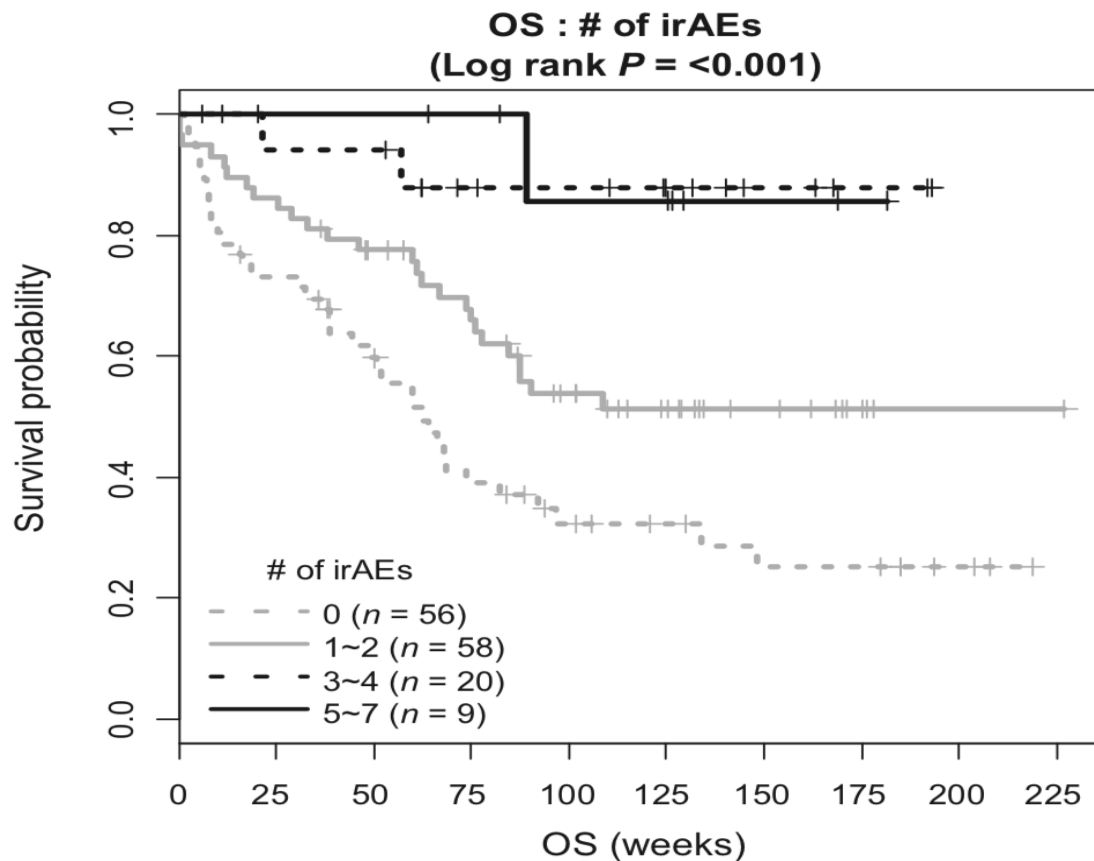
No significant difference in survival in melanoma patients who discontinued ipilimumab + nivolumab due to irAEs versus those who did not discontinue treatment

Autoimmunity as prognostic marker?

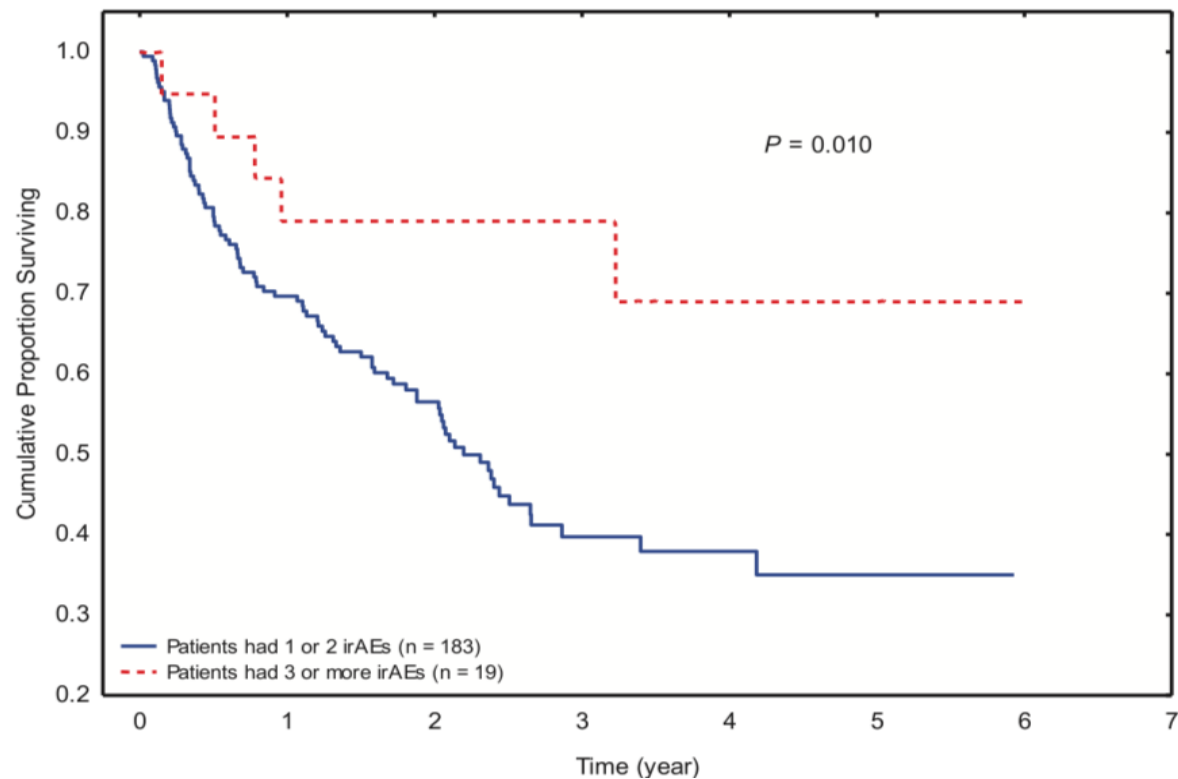


Based on **retrospective** data, patients who experience irAEs (regardless of needing treatment) may have better outcomes compared to patients who do not experience irAEs

Number of irAEs on patient outcomes

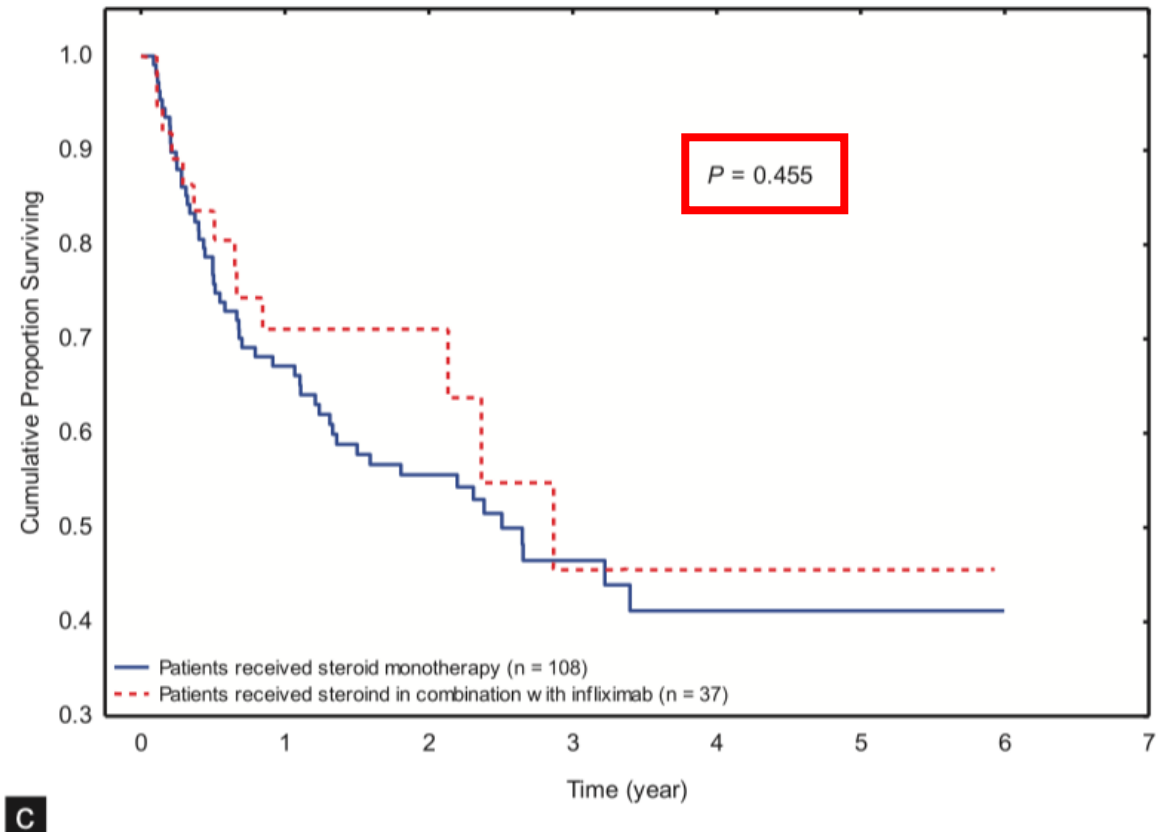
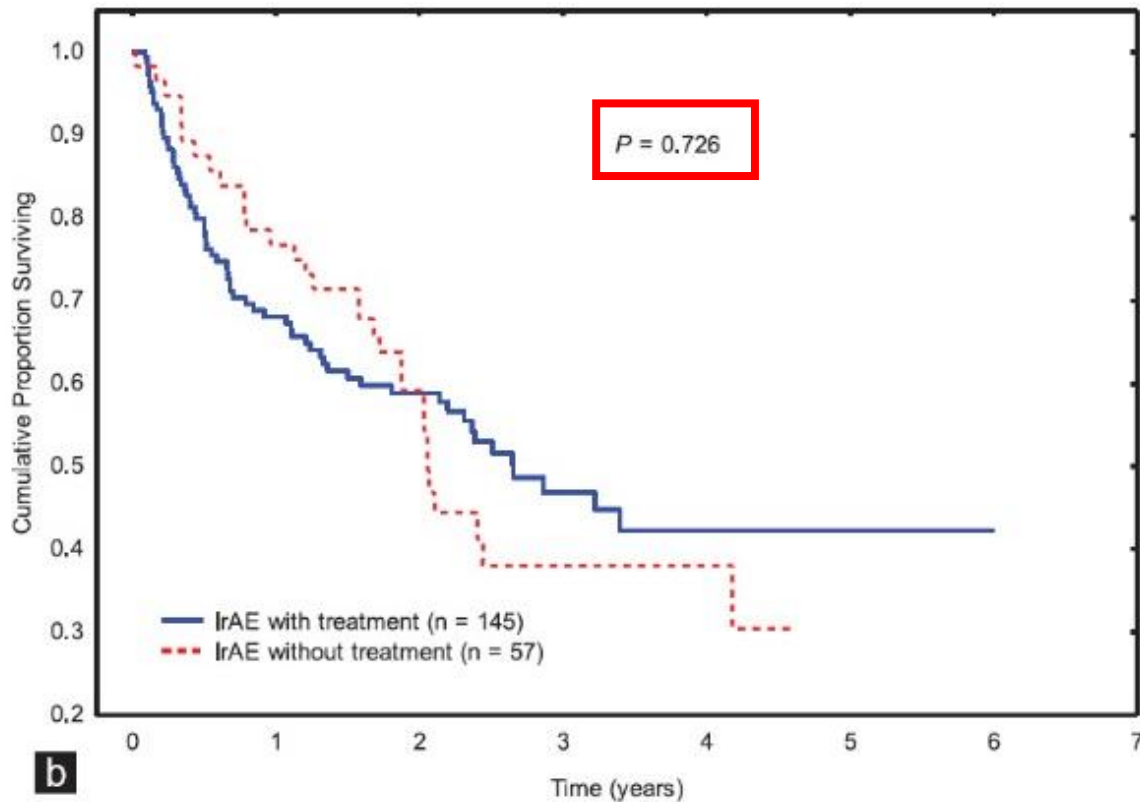


Nivolumab in metastatic melanoma: greater OS
in patients with 3+ irAEs versus ≤ 1 irAE



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

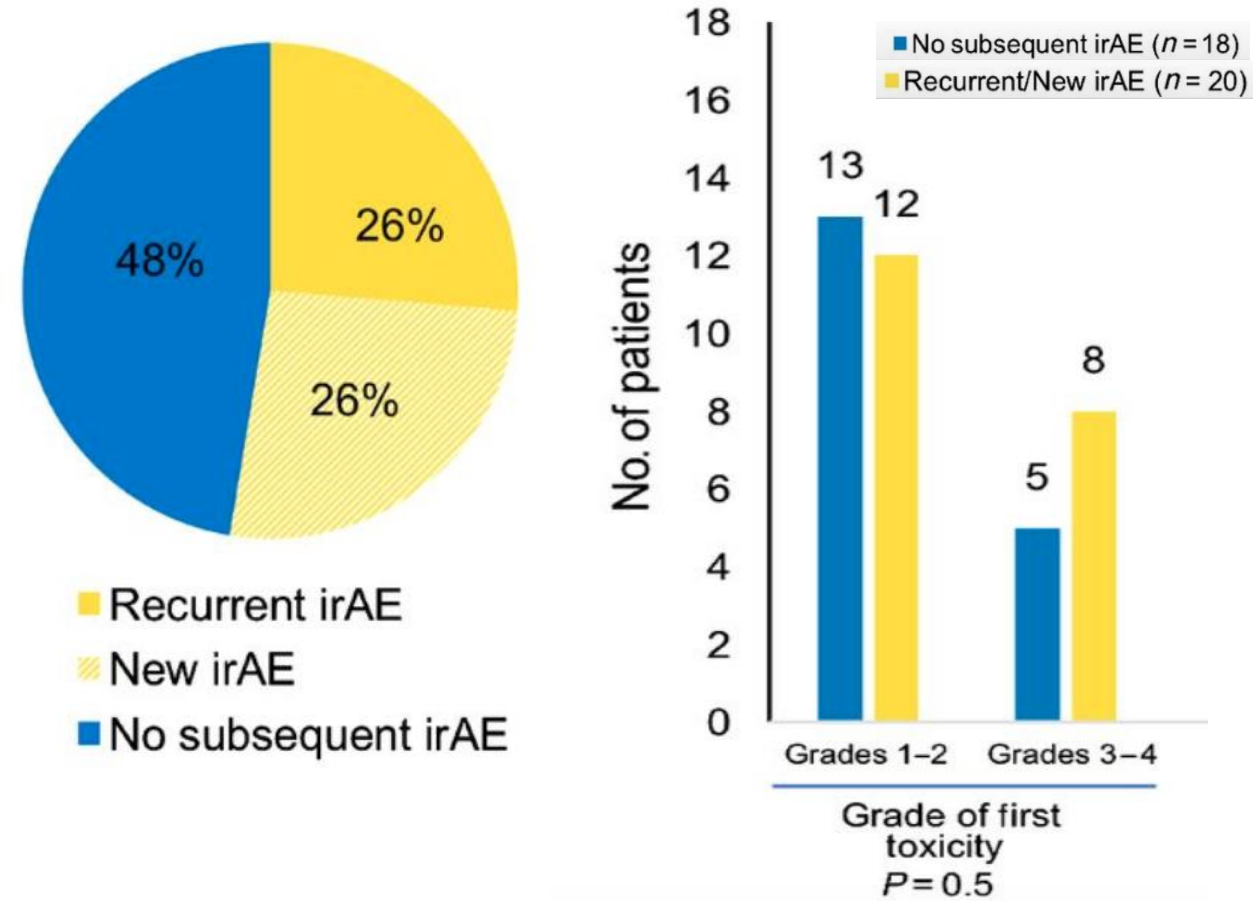
Impact of toxicity management on patient outcomes



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 ≤ 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

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

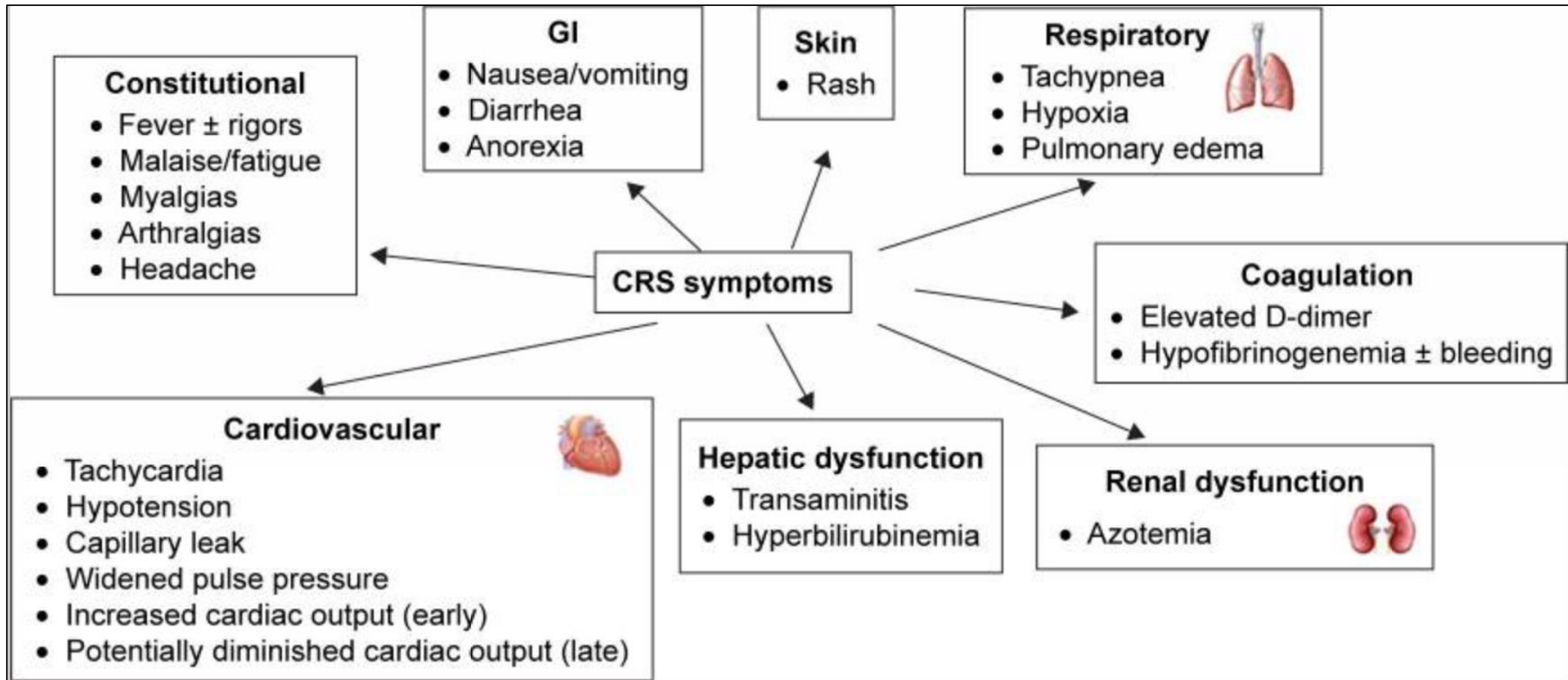
Hemophagocytic Lymphohistiocytosis/
Macrophage Activation Syndrome (HLH/MAS)

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/m²
 - 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

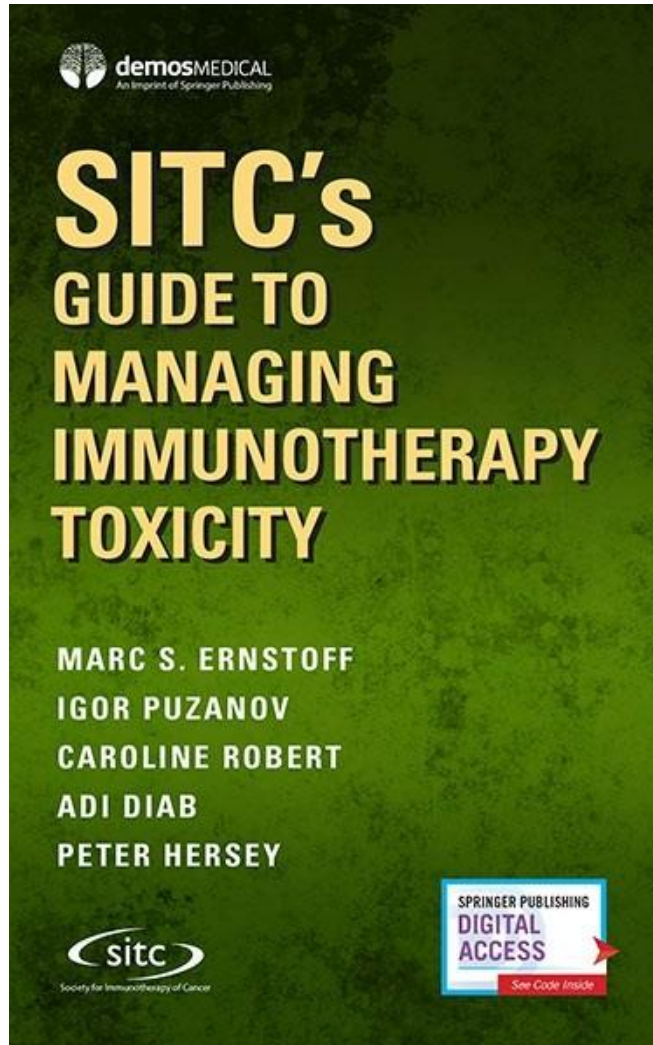
The importance of patient education

- 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
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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^{1†}, A. Diab^{2†}, K. Abdallah³, C. O. Bingham III⁴, C. Brogdon⁵, R. Dadu², L. Hamad¹, S. Kim², M. E. Lacouture⁶,
 N. R. LeBoeuf⁷, D. Lenihan⁸, C. Onofrei⁹, V. Shannon², R. Sharma¹, A. W. Silk¹², D. Skondra¹⁰, M. E. Suarez-Almazor²,
 Y. Wang², K. Wiley¹¹, H. L. Kaufman^{12†}, M. S. Ernstoff^{1††} and on behalf of the Society for Immunotherapy of Cancer
 Toxicity Management Working Group

NCCN

National Comprehensive
 Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Management of Immunotherapy-Related Toxicities

Case study 1

Toxicity

Case 1

- 57 yo woman is admitted to hospital with complaints of fatigue, headache, nausea, decreased appetite and generalized weakness
- History of metastatic melanoma diagnosed in 8/2016. Started on CTLA-4 inhibitor ipilimumab on 1/25/2019
- Developed above symptoms 3-4 weeks after starting immunotherapy

- Melanoma clinic visit evaluation on 3/8/2017. Blood work shows low ACTH/cortisol and low TSH/T4 s/o pituitary dysfunction.
- MRI Brain showed diffusely enlarged pituitary gland with findings suspicious for acute hypophysitis
- She was started on IV fluids and hydrocortisone 100 mg q 8 hrs. Endocrine service consulted.

- Baseline tests (ACTH/cortisol/TSH/T4) normal prior to immunotherapy
- Discharged on oral hydrocortisone 20 mg in morning and 10 mg in afternoon along with levothyroxine 50 mcg daily
- Seen in endocrine clinic 4 weeks after discharge with improved symptoms

- No recovery in ACTH-cortisol axis seen on subsequent visits
- Thyroid tests improved and maintained on levothyroxine 25 mcg daily
- Stable from melanoma point of view (on observation now)

Case study 2

Toxicity

Case 2

- 54 yo man with metastatic Renal cell carcinoma diagnosed on 4/15/2019
- Started on immunotherapy with combination CTLA- 4 inhibitor ipilimumab and PD-1 inhibitor nivolumab on 5/22/19
- Baseline TSH 1.28, T4 5.1 (normal), normal ACTH and cortisol

- Patient reported fatigue and palpitation on his second infusion on 6/11/2019. Mild tachycardia on exam. No hypotension.
- What is the next step?
 - A) Do nothing
 - B) Check cortisol and thyroid tests
 - C) Start steroids immediately

- Answer is option B

Check cortisol and thyroid tests

- Lab showed suppressed TSH (0.036) with elevated T4 (14.6) and total T3 (210). Cortisol is normal.
- What is the diagnosis?
 - A) Grave's disease
 - B) Acute Thyroiditis
 - C) Primary hypothyroidism

- Answer is option B

Acute Thyroiditis

- Lab showed neg marker for Grave's disease (normal TSI)
- What is the next step?
 - A) Start high dose steroids
 - B) Start methimazole
 - C) Start beta blocker

- Answer is option C

Start beta blocker

Ipilimumab held and he is continued on Nivolumab by GU team

- 6 weeks after thyroiditis diagnosis, patient thyroid tests were as below.
 - TSH 161 (high), Total T4- 3.4 (Low), Total T3- 29 (low)
- What is the diagnosis?
 - A) Primary hyperthyroidism
 - B) Primary hypothyroidism
 - C) None of the above

- Answer is option B

Primary Hypothyroidism

- Patient started on levothyroxine
- 6 weeks later TSH trended down to 10.3
- Dose of levothyroxine increased, patient feels better