Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Toxicity Management

Mateya Trinkaus MD FRCPC

Markham Stouffville Hospital

AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

sitc Society for Immunotherapy of Cancer

Disclosures

- Consulting Fees: Bayer, AMGEN, Aztra-Zeneca, BMS, Merck, Novartis
- I will be discussing non-FDA approved indications during my presentation.
- Thank you to the SITC committee for providing many slides and for this invitation.

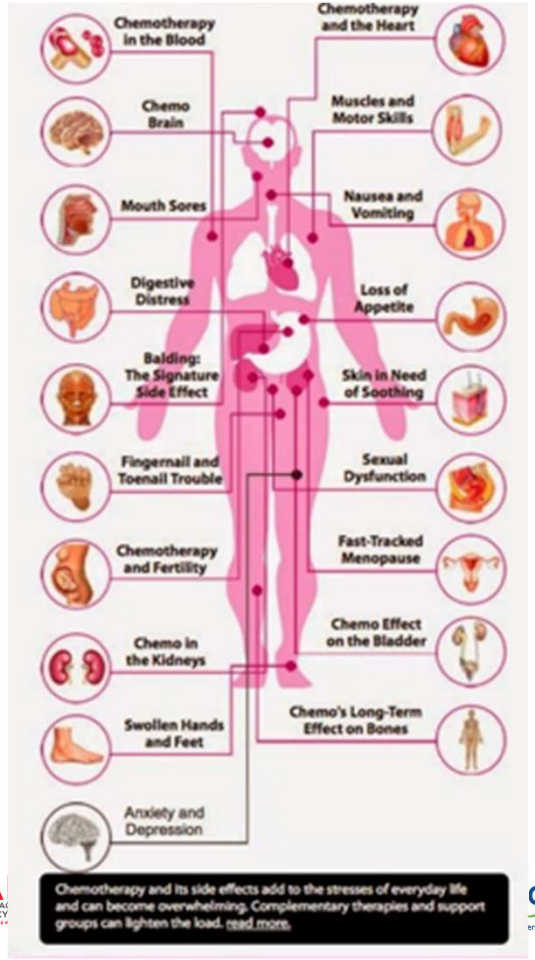
Why is Immune Checkpoint Inhibitor (ICI) toxicity a fundamental topic?

- ICI use is exponentially growing
- ICI combinations (ICI + chemo; ICI + radiation; ICI + targeted drugs) are now being approved and are now standards of care
- Treatment is potentially very toxic
- ICI therapy costs a lot of money and leads to more hospital service utilization[1]
- ICIs often result in better survival – toxicity must therefore be monitored for longer
- The toxicity profile is different from chemotherapy toxicities

1 - Smith, DA et al, ASCO 2019

Chemotherapy side effects

- Myelosuppression with risk of febrile neutropenia
  - GCSF (filgrastim or pegfilgrastim)
  - IV ferritin, Epo
- Hair Loss (cooling caps)
- GI: Nausea/vomiting, dysguisia, mucositis, diarrhea/constipation
- Fatigue
- Neuropathy
- Rashes
- Menopause (additional complications), Infertility
- “Chemo Brain”
- Leukemia (0.1 to 1%), Heart Disease (<u>leading cause death in early stage Br Ca</u>)



sitc Society for Immunotherapy of Cancer
ADVANCES IN Cancer IMMUNOTHERAPY™

The New York Times

HEALTH

Immune System, Unleashed by Cancer Therapies, Can Attack Organs

By MATT RICHTEL DEC. 3, 2016

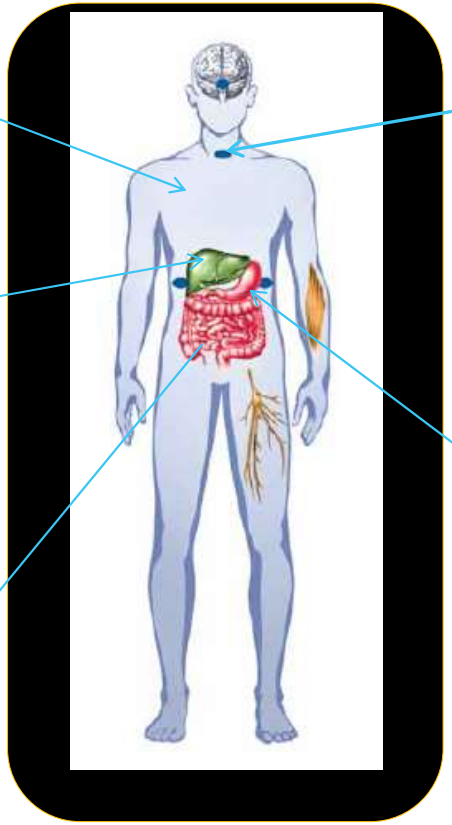
Chuck Peal, 61, at home in Southbury, Conn. He developed acute-onset diabetes, as did other patients who received immunotherapy at Yale. Ángel Franco/The New York Times

IMMUNE RELATED Observed EVENTS with Novel Immuno-oncology Therapy

Skin
- Skin rash or pruritus

Hepatic
- Abnormal LFTs (eg, AST, ALT, total bilirubin)

Gastrointestinal (GI)
- Diarrhea
- Stomach pain
- Nausea/vomiting/pain
- Blood in stool
- Constipation



Endocrine
- Headache
- Visual changes
- Fever
- Fatigue/weakness
- Confusion

Neurologic
- Sensory or motor neuropathy
- Muscle weakness
- Fatigue
- Difficulty waking up

Autoimmune complications for virtually any organ system

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
  - Renal, liver, LDH, full electrolytes
  - 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.

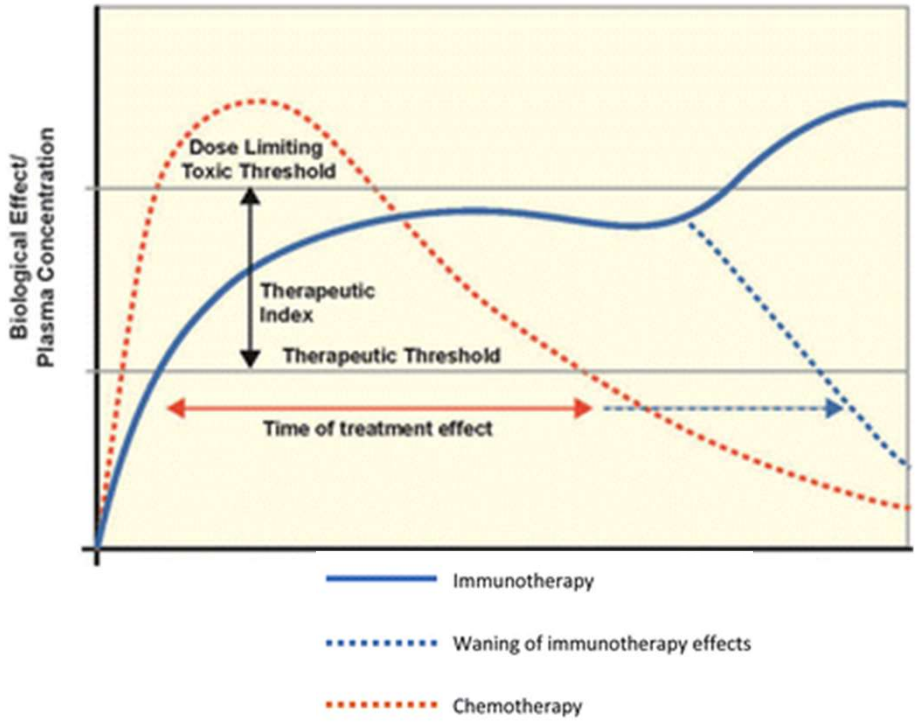
Additional screening for high-risk patients

- 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.

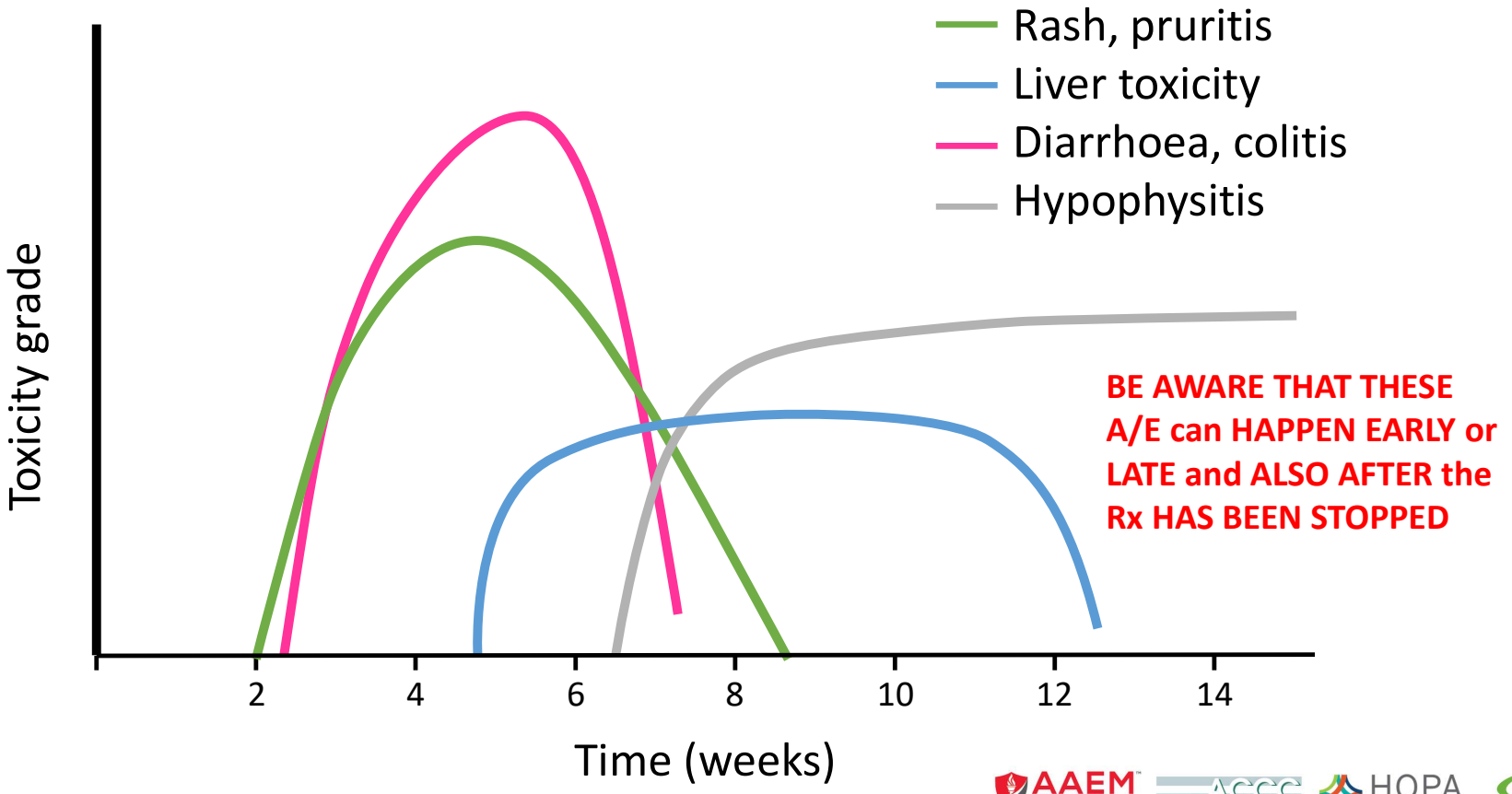
Immune-related adverse events (irAEs)

- 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



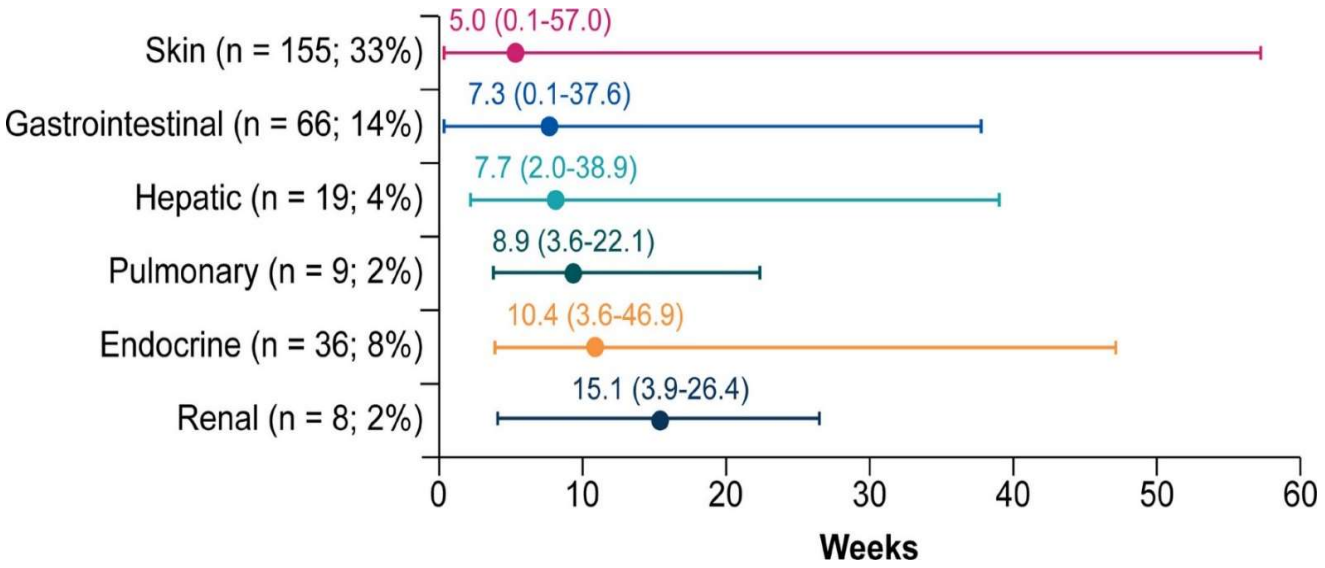
Puzanov and Diab, JITC 2017

Kinetics of irAEs



BE AWARE THAT THESE A/E can HAPPEN EARLY or LATE and ALSO AFTER the Rx HAS BEEN STOPPED

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

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:

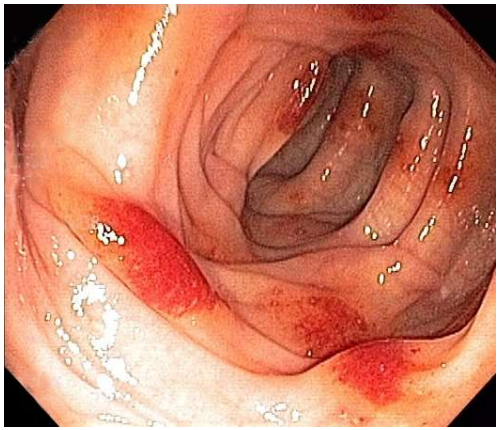
Uveitis, episcleritis, conjunctivitis

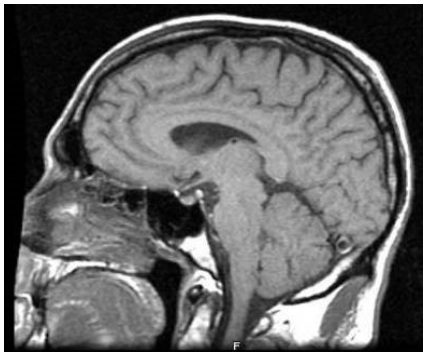
Puzanov and Diab, JITC 2017.
NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

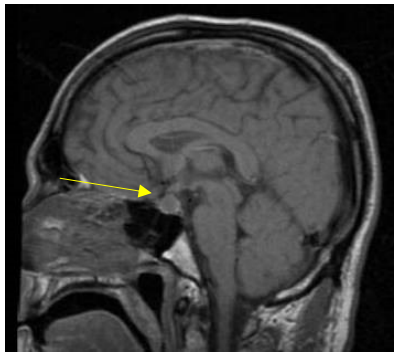
Immunotherapy AEs Requiring Immediate Treatment

Immune-mediated side effects that should be addressed immediately:

- Diarrhea, blood in stool, constipation, fever
- Headache, visual-field defects, fatigue/weakness, coma
- Dyspnea, cough, drop Sp02
- Elevations in liver function tests (LFTs) (eg, AST, ALT, total bilirubin) in the absence of clinical symptoms
- Diffuse rash + systemically unwell
- Changes in visual acuity







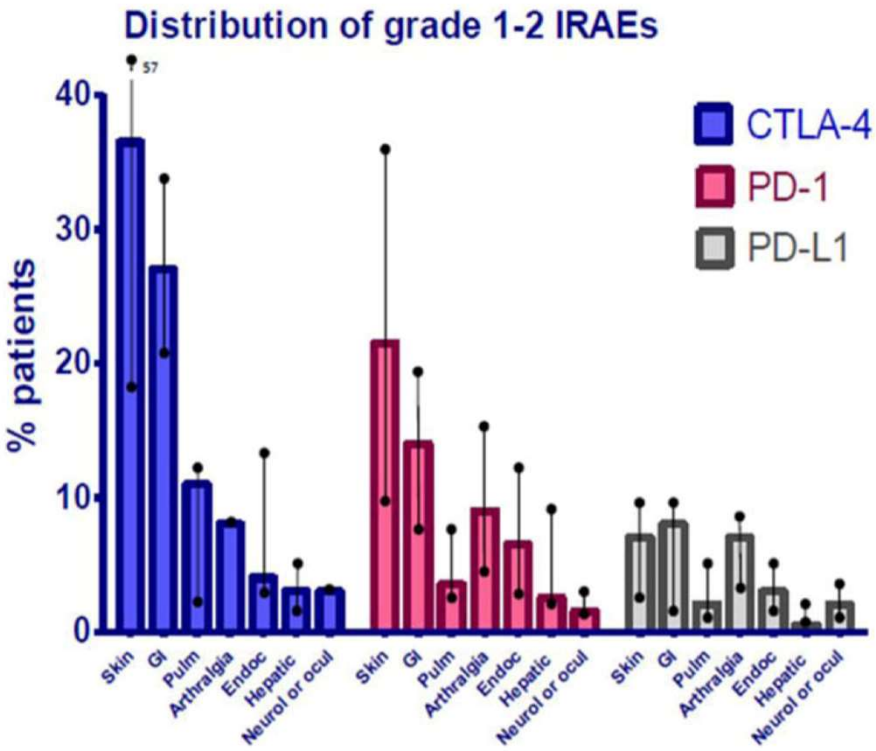
imAE: immune-mediated side effect, ALT = alanine aminotransferase, AST = aspartate aminotransferase, GI = gastrointestinal, LFTs = liver function tests

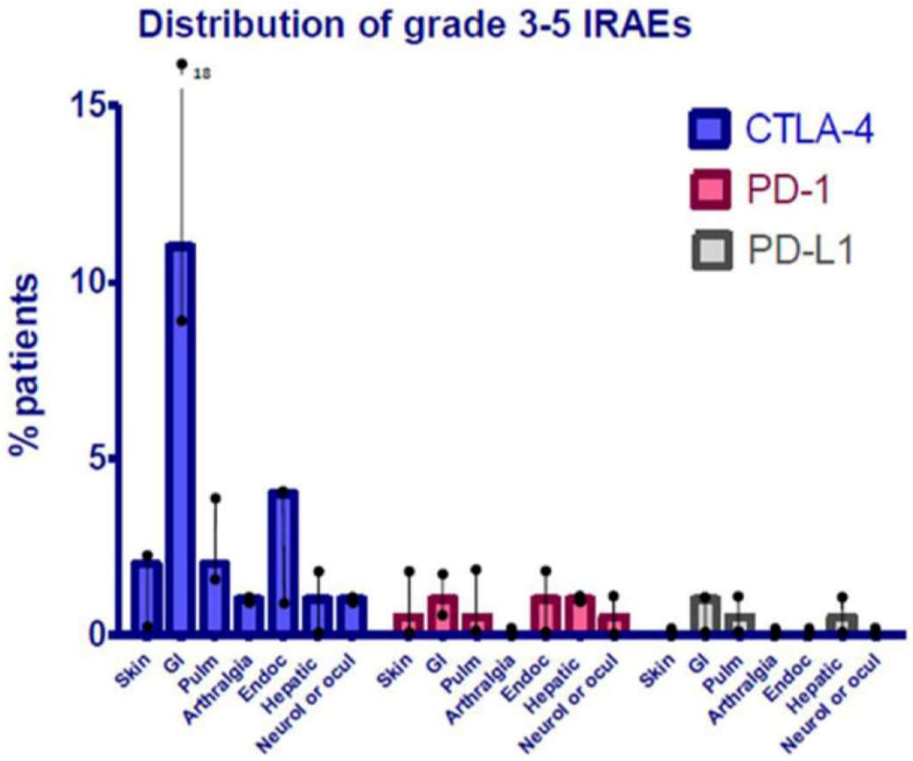
Incidence of irAEs

- 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.

Severity of irAEs by ICI (single agent)





Puzanov and Diab, JITC 2017

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

Dual ICI combinations (Ipi/Nivo)

Disease site	Regimen	Grade > 3 toxicities (%)
Melanoma (Larkin NEJM 2019) Checkmate 067 N=945	Nivo 1 mg/kg + Ipi 3 mg/kg Nivo 3 mg/kg Ipi 3 mg/ig	59 23 18
Lung (Hellman NEJM 2019) N=550	Nivo 3 mg/kg + ipi 1 mg/kg Nivo 3 mg/kg + chemotherapy Chemotherapy	33 PDL1 < 1% = 55% 36
Renal (Motzer NEJM 2018)	Nivo 3 mg/kg + Ipi 1 mg/kg Sunitinib	46 63

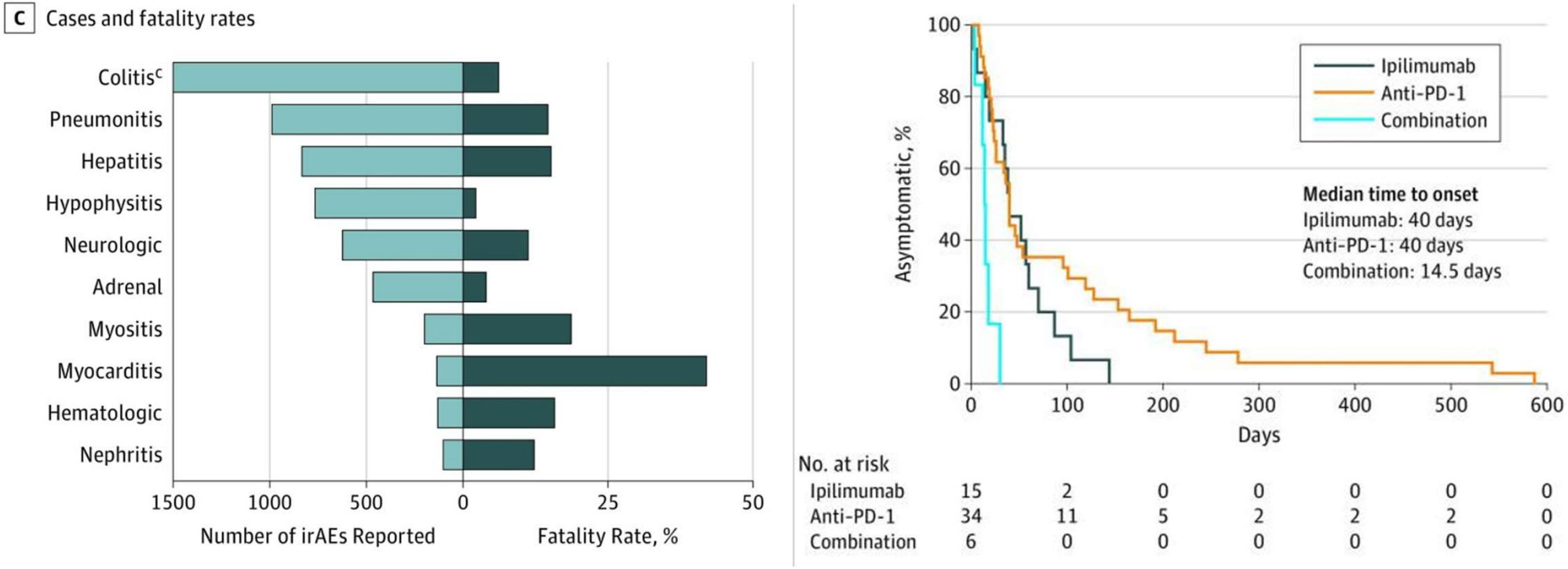
- Dual ICI – More toxic than single ICI
- Variation in dosing between melanoma and renal/lung cancer treatment – melanoma dosing for ipi/nivo is more toxic

ICI and targeted drugs
ICI and chemotherapy

Disease Site, N	Regimen	Grade ¾ Toxicities
Lung (Gandhi NEJM 2018) N=616	Platinum/Pemetrexed + Pembro followed by Pembro/Pemetrexed maintenance Chemo alone	67% 66%
Renal (Rini NEJM 2019) N=861	Pembro + Axitinib Sunitinib	76% 71%
Breast (Schmid NEJM 2018) N=902	Atezolizumab + Abraxane Abraxane	49% 42%

Toxicity rate with addition of chemotherapy or targeted Rx to ICI – comparable to the standard of care

Fatal Events with ICIs



Wang et al, JAMA Oncol 2018.

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.

sitc Society for Immunotherapy of Cancer
ADVANCES IN Cancer IMMUNOTHERAPY™

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.

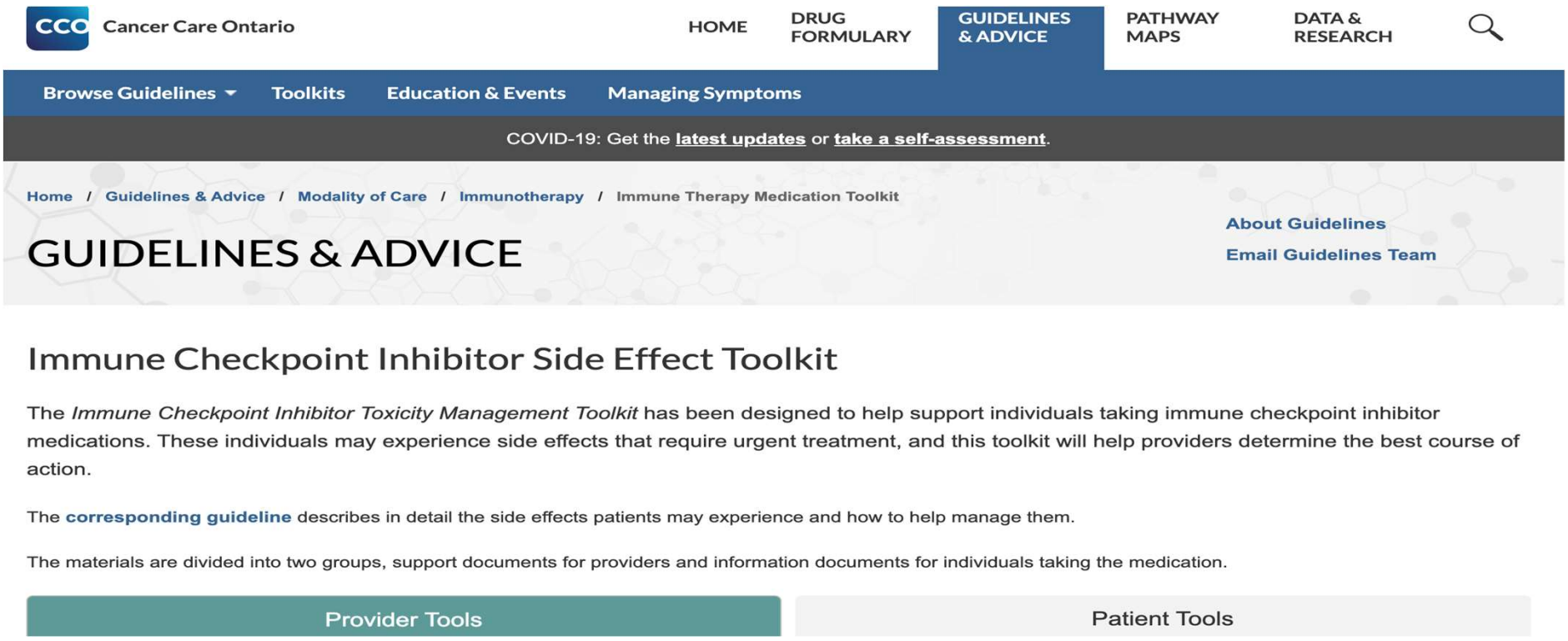
AAEM American Academy of Emergency Medicine · ACCC Association of Community Cancer Centers · HOPA Hematology/Oncology Pharmacy Association · sitc Society for Immunotherapy of Cancer

Additional immunosuppressives

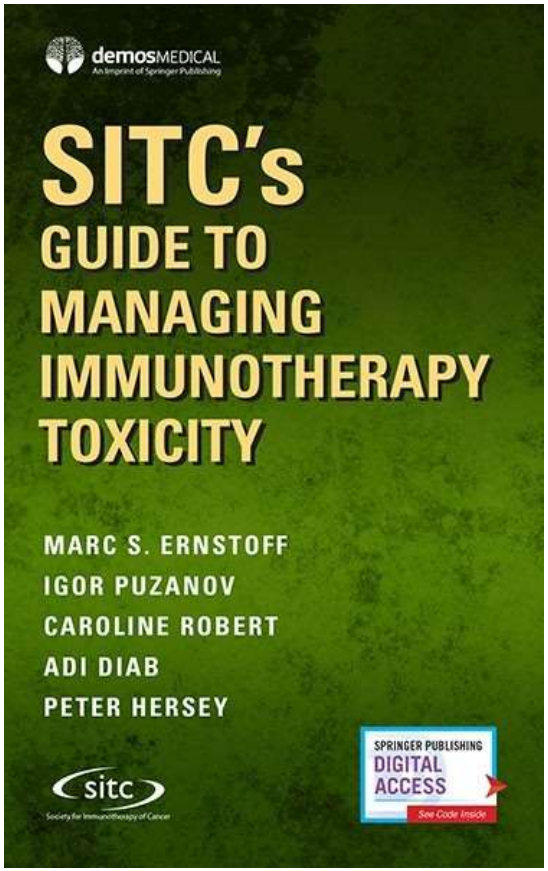
- Infliximab: anti-TNF-α mAb
  - Hepatotoxic so should NOT be used for immune-mediated hepatitis
  - Risk for hepatitis B and tuberculosis activation; obtain hepatitis serologies and TB testing prior to initiation
  - Dose: 5 mg/kg; 2nd dose may be administered after 2 weeks
- Vedolizumab: α4β7 integrin mAb (primarily used in refractory IBD)
  - **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

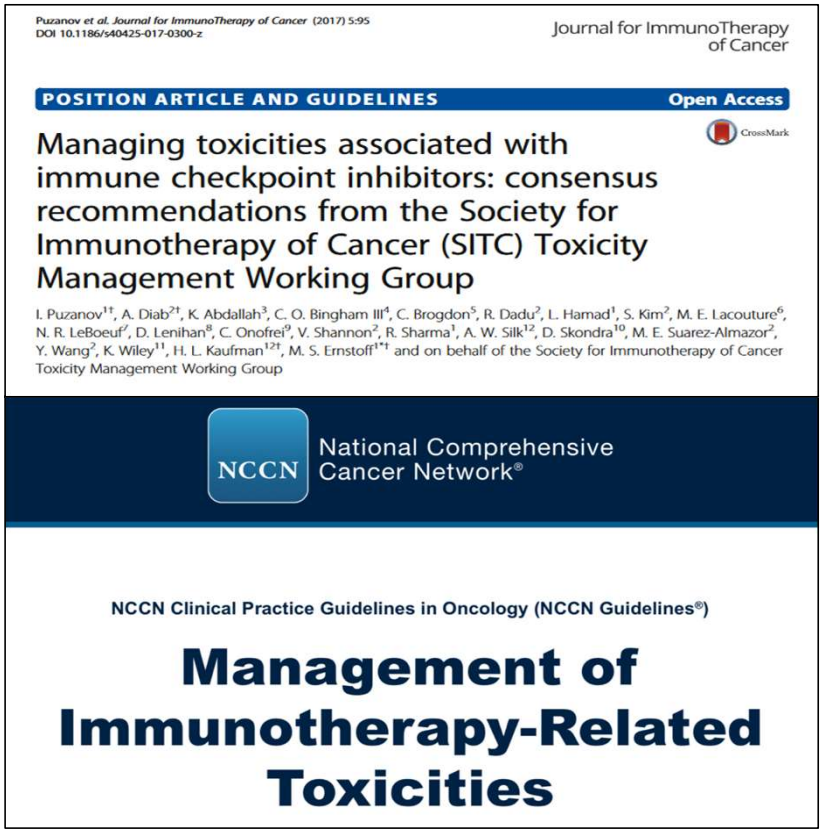
Abu-Sbeih H. JITC. 2018 Dec 5;6(1):142.
NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

CCO Tools/Guidelines



Additional Resources





Mrs. KC – Case Study 1

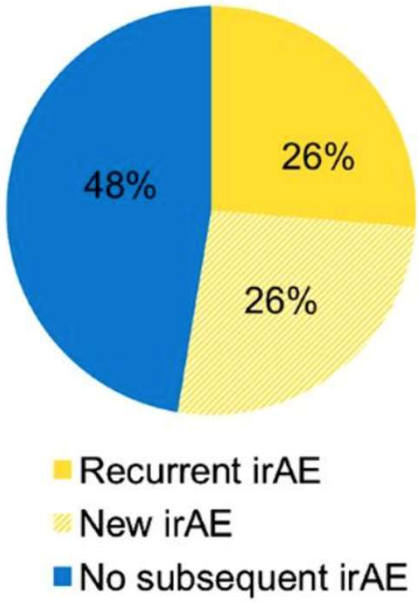
- 54F metastatic melanoma, Braf V600E positive
- Initial diagnosis 2017 (stage 2B) – recurrence in April 2020 – inguinal nodes, satellite lesions, possible bone metastases, possible metastases near spleen
- ECOG 0; no comorbidities
- Ipilimumab + nivolumab given early May 2020
- Presented prior to Cycle #2 with HR 130s, PB 117/90, afebrile, sense of palpitations and irritability, otherwise "I feel okay"; clinically complete response re: nodal and satellite lesions but grade 1 skin rash diffusely
- What may be occurring?

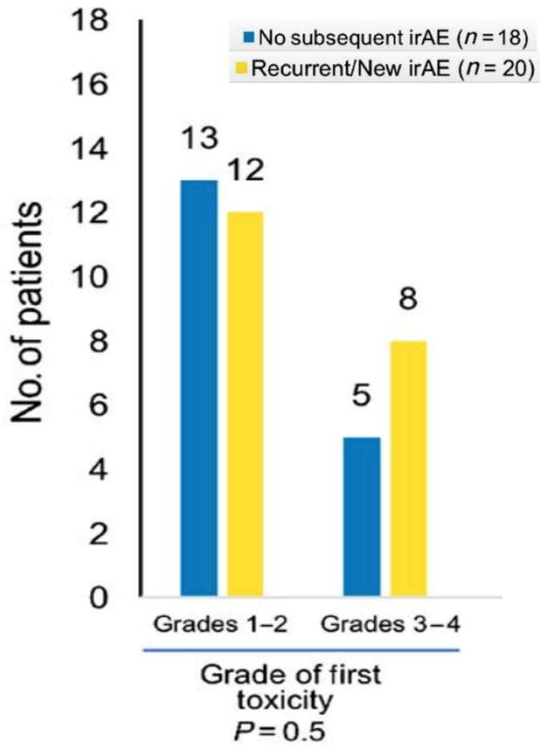
Mrs. KC – Case Study 1

- Labs showed TSH < 0.1 mU/L; fT4 71 pmol/L
- Called my endocrinology “champion” at my site
- Atenolol 50 mg started
- Thyroid scan suggestive of thyroiditis
- Total antimicrosomal antibodies and TSH receptor antibodies negative
- fT4 improved in 2 weeks to 19, reduced in the summer to 5.7, more recently 10
- No L-thyroxine Rx needed thus far – continues under endocrine surveillance
- Can she be re-challenged with Ipilimumab and Nivolumab?

Rechallenging with ICI after irAEs

- Patients should not be rechallenged until irAE resolved to grade ≤1 (prednisone dose < 10 mg/day)
- 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.

Mrs. KC – Case Study 1

- Cycle #2 ipilimumab/Nivolumab given early June 2020
- Week-end – developed 7-10 watery stools, nausea, abdominal pain, cramping
- Called “after hours number” – conservative recommendations provided + immodium (8/day)
- The patient knew to contact our clinic on Monday morning and was directed to the ER for further assessment
- Electrolyte panel; K+ 3.1, Mg 0.68, HCO 17, Cr 53; hemodynamically stable but 3 kg weight loss in 4 days, feeling weak, unable to sleep due to overnight diarrhea
- What would be your approach?

Mrs. KC – Grade 3 diarrhea

Option 1: Start oral steroids 1 mg/kg, continue Imodium, IVF, electrolyte resuscitation, stool cultures, consult GI

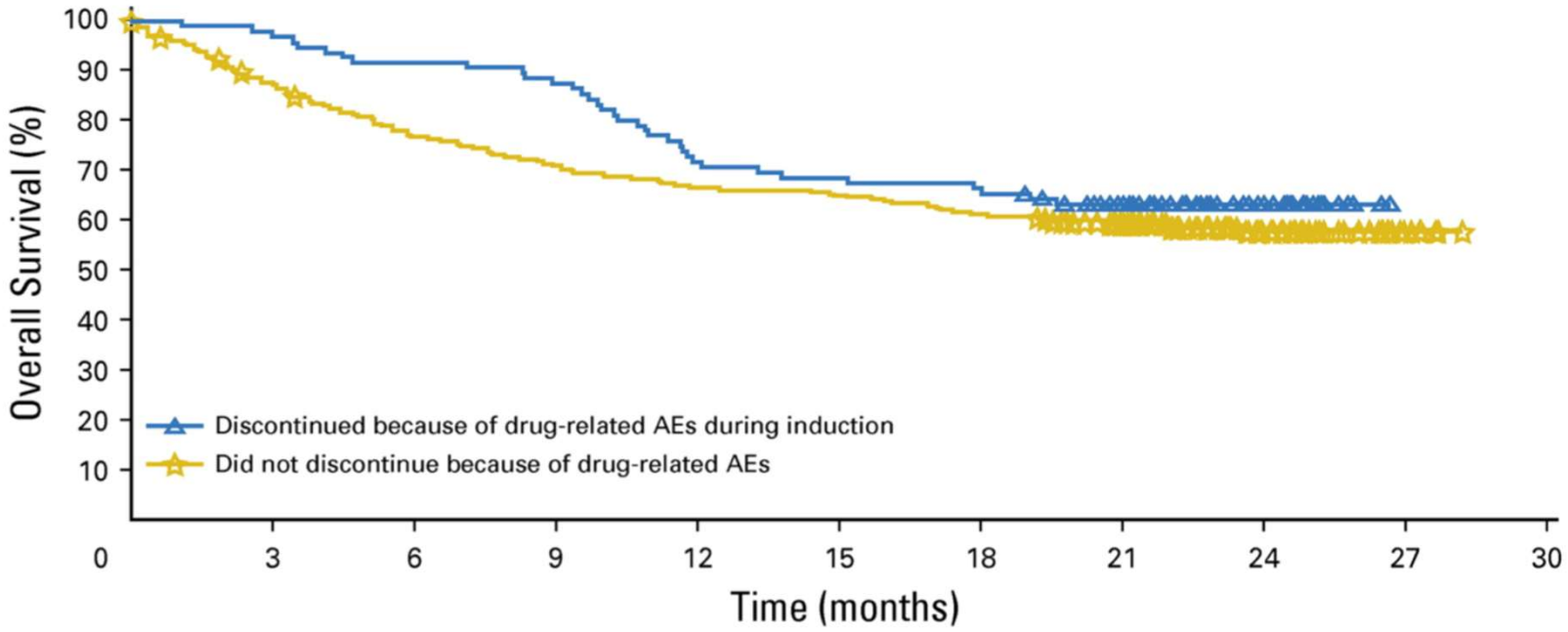
Option 2: Start IV steroids 1 mg/kg, continue Imodium, IVF, electrolyte resuscitation, stool cultures, GI consult

Options 3: Start IV steroids and offer Infliximab at this time, IVF, electrolyte resuscitation, stool cultures, GI consult

Mrs. KC – Case Study 1

- Admission to hospital; diagnosis = autoimmune colitis
- Volume resuscitation, Prednisone 1.5 mg/kg started orally
- Stool cultures, C diff sent off, GI consult
- Not improved after < 24 hours; IV prednisone 2mg/kg tried
- Not improved < 24 hours; endoscopy suggested colitis, urgent TB skin test
- Infliximab 5 mg/kg started – symptoms responded in 4 hours
- Steroids taper – remained well thereafter
- ICI put on hold … "What is my prognosis?"

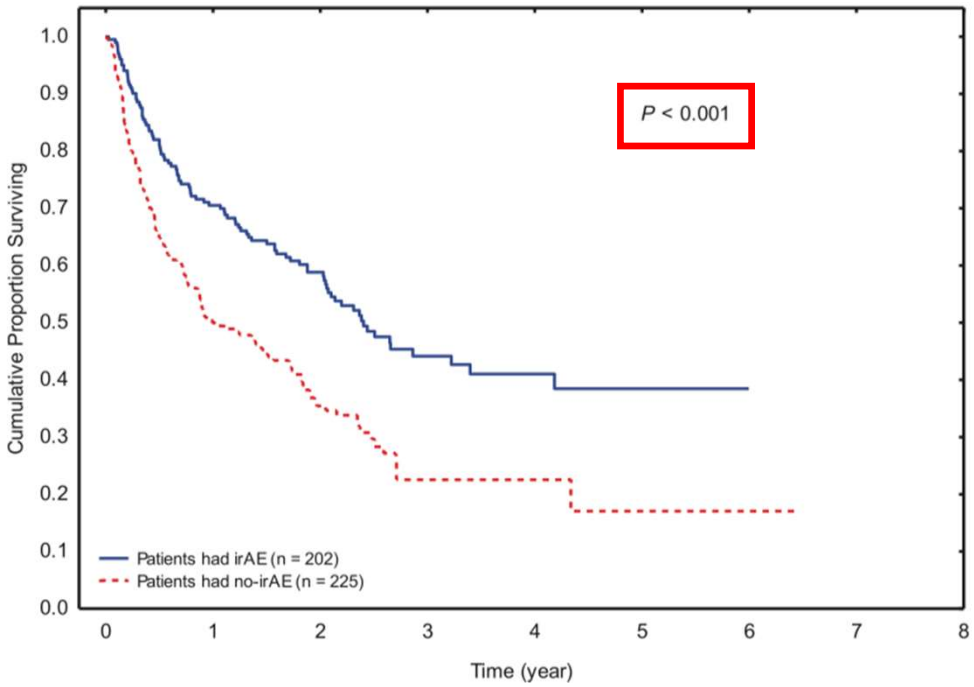
Effect of irAEs on patient outcomes

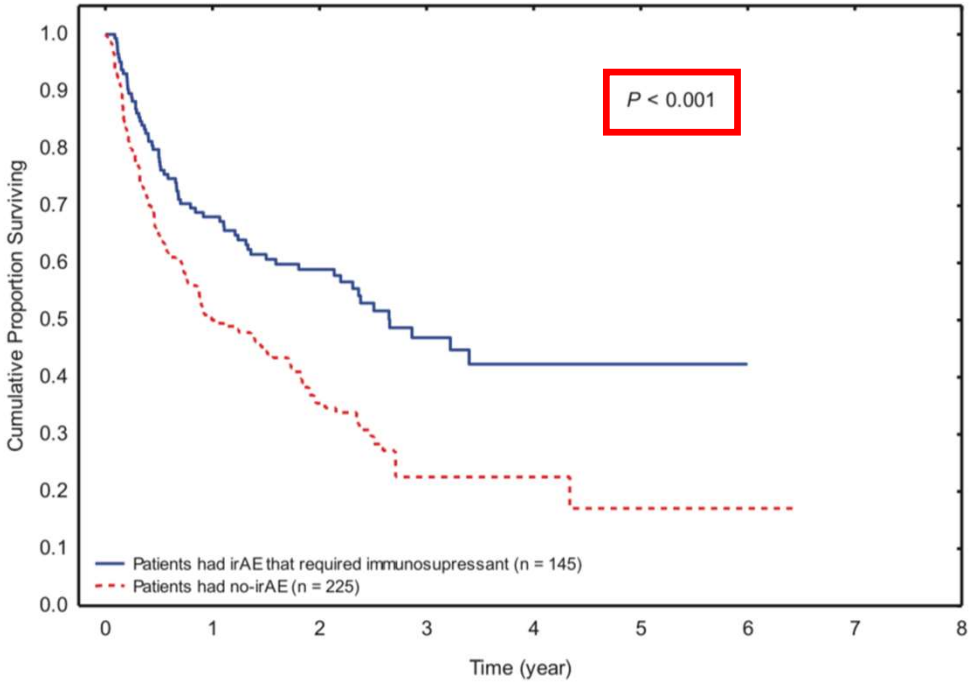


No significant difference in survival in melanoma patients who discontinued ipilimumab + nivolumab due to irAEs versus those who did not discontinue treatment

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

Autoimmunity as prognostic marker?

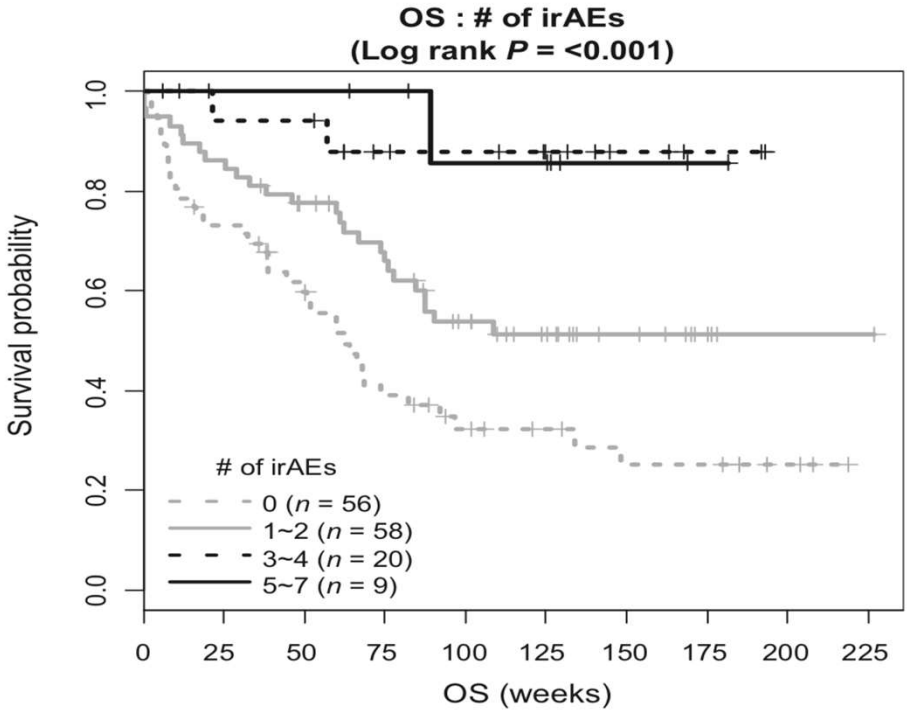




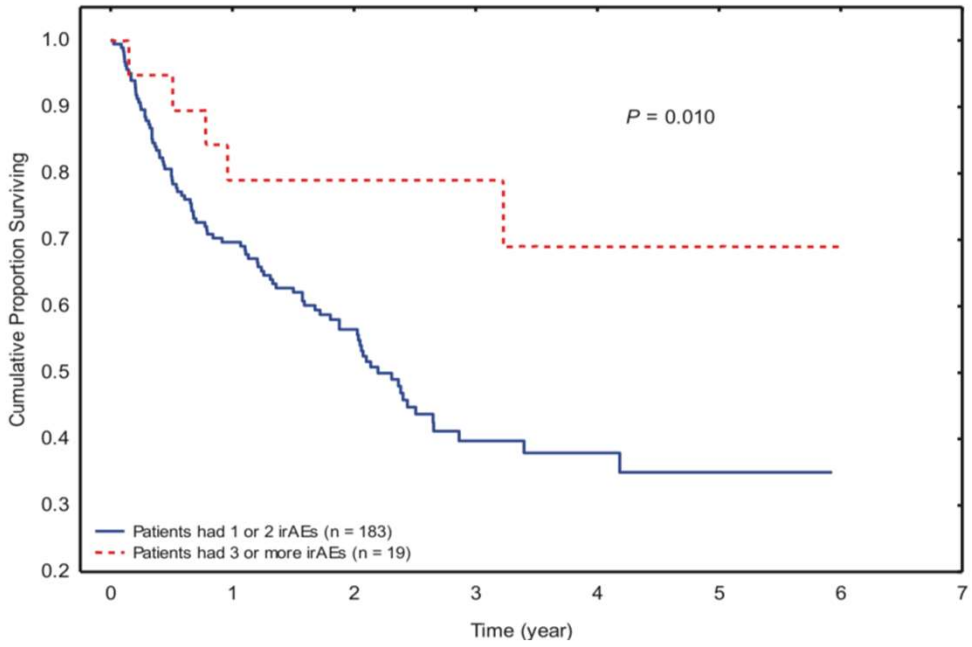
Based on **retrospective** data, patients who experience irAEs (regardless of needing treatment) may have better outcomes compared to patients who do not experience irAEs

Abu-Sbeih, J Immunoth Prec Oncol 2018.

Number of irAEs on patient outcomes



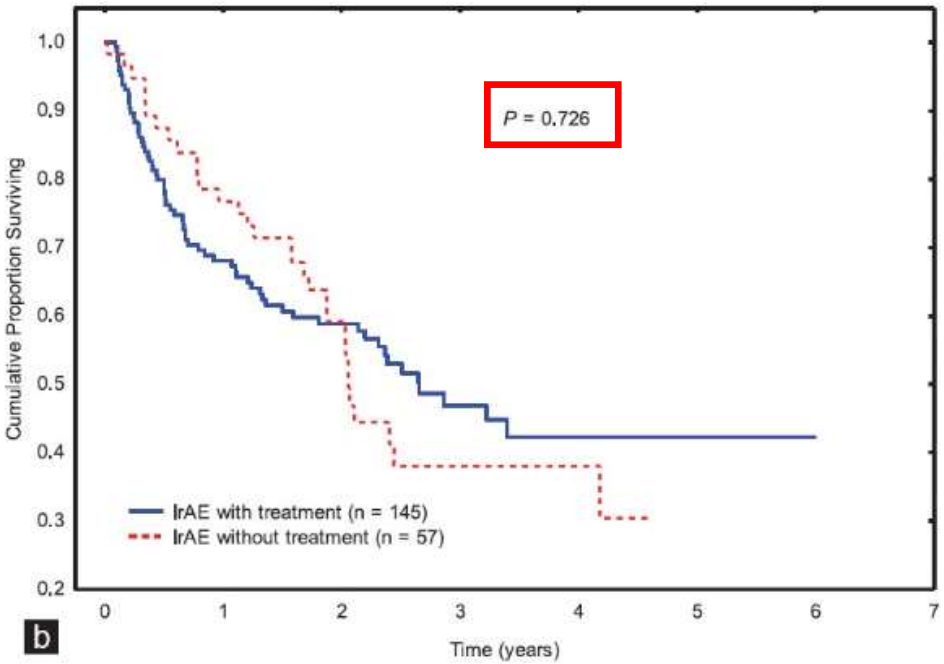
Nivolumab in metastatic melanoma: greater OS in patients with 3+ irAEs versus ≤ 1 irAE

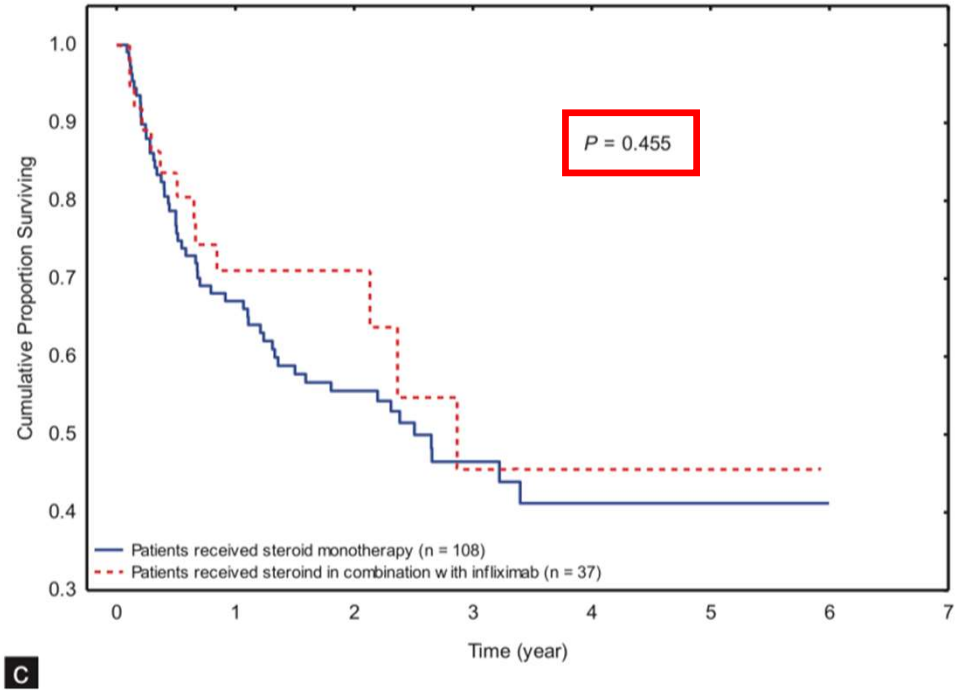


Patients receiving ICI's for various malignancies: greater OS in those with 3+ irAEs versus ≤ 2 irAEs

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.

Case Study 2 – Mr. DA

- 68M metastatic melanoma
- baseline CLL with history of autoimmune hemolytic anemia -
- baseline on prednisone 10 mg daily x years. Previously requiring IVIG, high dose steroids
- Now developed metastatic melanoma with pulmonary metastases, LDH normal.
- Braf wild type
- ECOG 1

Mr. DA – Should he receive treatment?

- 1) Yes but only PD1 agent (not with CTLA4) given history of autoimmune issues
- 2) Yes with informed consent ensuring he is aware of the risk for auto-immune reactivation of AIHA and other autoimmune AEs
- 3) Yes with close collaboration with his hematologist
- 4) Yes with consideration for trying to reduce his basal prednisone dose to the lowest dosing possible
- 5) All of the above

Patients with autoimmune disorders – Risk for re-activation

- 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.

Mr. DA

- Patient received Nivolumab – initially Q2weekly, and then transitioned to Q4weekly x 3 years – partial response
- Developed brain metastases – treated SRS
- Oligometastatic progression treated with radiation with ongoing nivolumab
- Further disease progression May 2020 – opted for trial of ipilimumab
- Admitted in June and July with recurrent neutropenic sepsis – responded to steroids, added lapelga July. Radiologic partial response.
- November 2020 – disease progression – retreat?

Reducing the Risk with treating and re-challenging with ICIs

- Patient education and informed consent
- Being well versed with potential side effects and management
- Developing and maintaining a safe ICI program

CARE DELIVERY AND PRACTICE MANAGEMENT

Managing Immuno-Oncology Toxicity: Top 10 Innovative Institutional Solutions

Suzanne Cole, MD[1]; Matthew Zibelman, MD[2]; Erin Bertino, MD[3]; Filiz Yucebay, PharmD[3]; and Kerry Reynolds, MD[4]

ASCO Educational Handbook 2019

- Educate patients about IO and IO toxicity
- Identify patients who have received immunotherapy
- Optimize the use of IO nurse navigators
- Identify physicians who are champions in IO toxicity
- Create pharmacy guidelines and order sets for IO toxicity
- Form pharmacy guidelines and pathways for corticosteroid IO refractory toxicity
- Use telehealth for patient monitoring

Summary

- Most irAEs occur in first 12 weeks of therapy
- Patient Education is most important in preventing morbidity re: irAE and ensuring recovery
- Steroids can be used to manage almost all irAEs; Prolonged steroid tapering may be required
- irAEs can wax and wane, particularly colitis; Late irAEs can occur
- Toxicity rate is higher with IO combinations
- Rechallenging is possible with these agents
- Some data suggests better long term outcomes with irAE
- Reassure patients – most irAEs resolve except endocrinopathies
- Guidelines exist; create a champion RN/specialists at your site

sitc Society for Immunotherapy of Cancer
ADVANCES IN Cancer IMMUNOTHERAPY™

- Thank you for your attention.

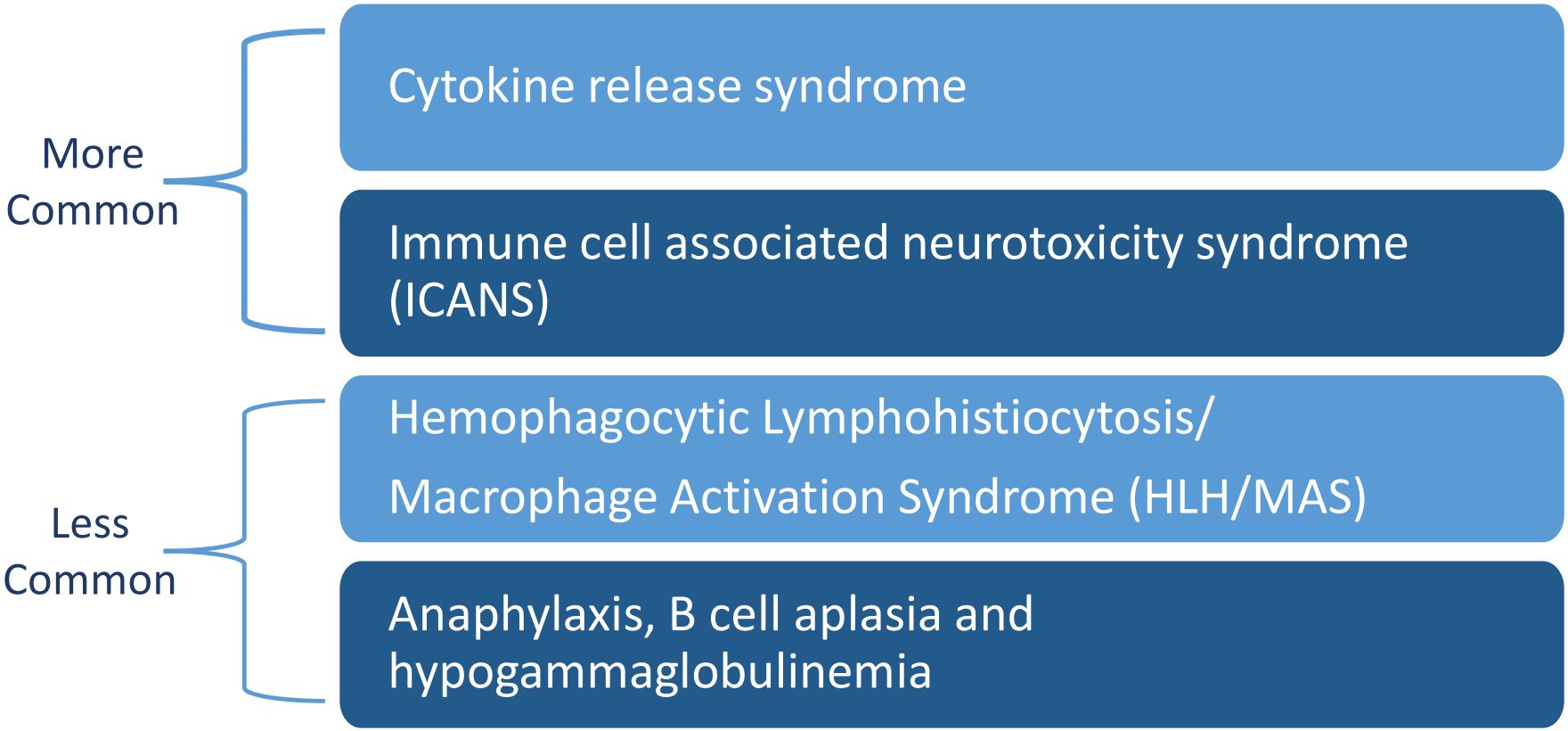
- Questions?

Society for Immunotherapy of Cancer
ADVANCES IN Cancer IMMUNOTHERAPY™

Additional Slides

sitc Society for Immunotherapy of Cancer
ADVANCES IN Cancer IMMUNOTHERAPY™

CAR T-cell related toxicities



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

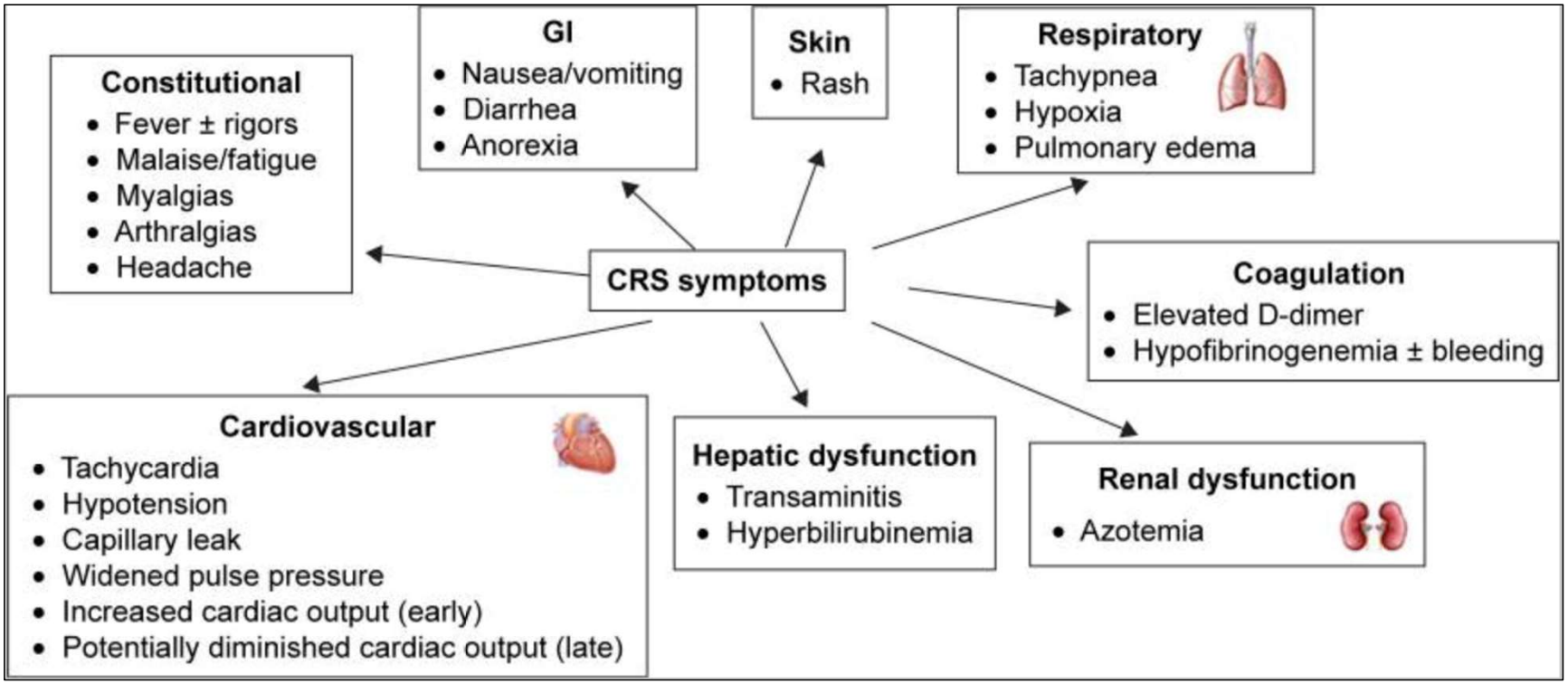
AAEM American Academy of Emergency Medicine · ACCC Association of Community Cancer Centers · HOPA Hematology/Oncology Pharmacy Association · sitc Society for Immunotherapy of Cancer

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.

sitc Society for Immunotherapy of Cancer
ADVANCES IN Cancer IMMUNOTHERAPY™

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.

AAEM American Academy of Emergency Medicine · ACCC Association of Community Cancer Centers · HOPA Hematology/Oncology Pharmacy Association · sitc Society for Immunotherapy of Cancer

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

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.