A Teaching Affiliate of Harvard Medical School

"A Review of Cancer Immunotherapy Toxicity in Practice & Clinical Trials"

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Financial Disclosures

No relevant financial relationships to disclose

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Learning Objectives

- Review the terminology of grading toxicities for Immune Related Adverse Events (irAEs)
- Provide an overview of the evaluation of the oncology patient who may have an irAE related to immunotherapy treatment
- Review the steps in management of patients with irAEs that are hospitalized (e.g. myocarditis, pneumonitis)

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Questions to Contemplate

- How many patients are expected to have a serious immune-related adverse event (irAE) this year in the US alone? (300, 3,000, 10,000, well over 30,000)
- If a patient has one irAE, are they at risk for another? Y/N
- Are all irAE's treated with steroids? Y/N
- Do some irAE's require different doses of steroids? Y/N
- What is the most common organ system involved?
- What are the two most fatal toxicities?

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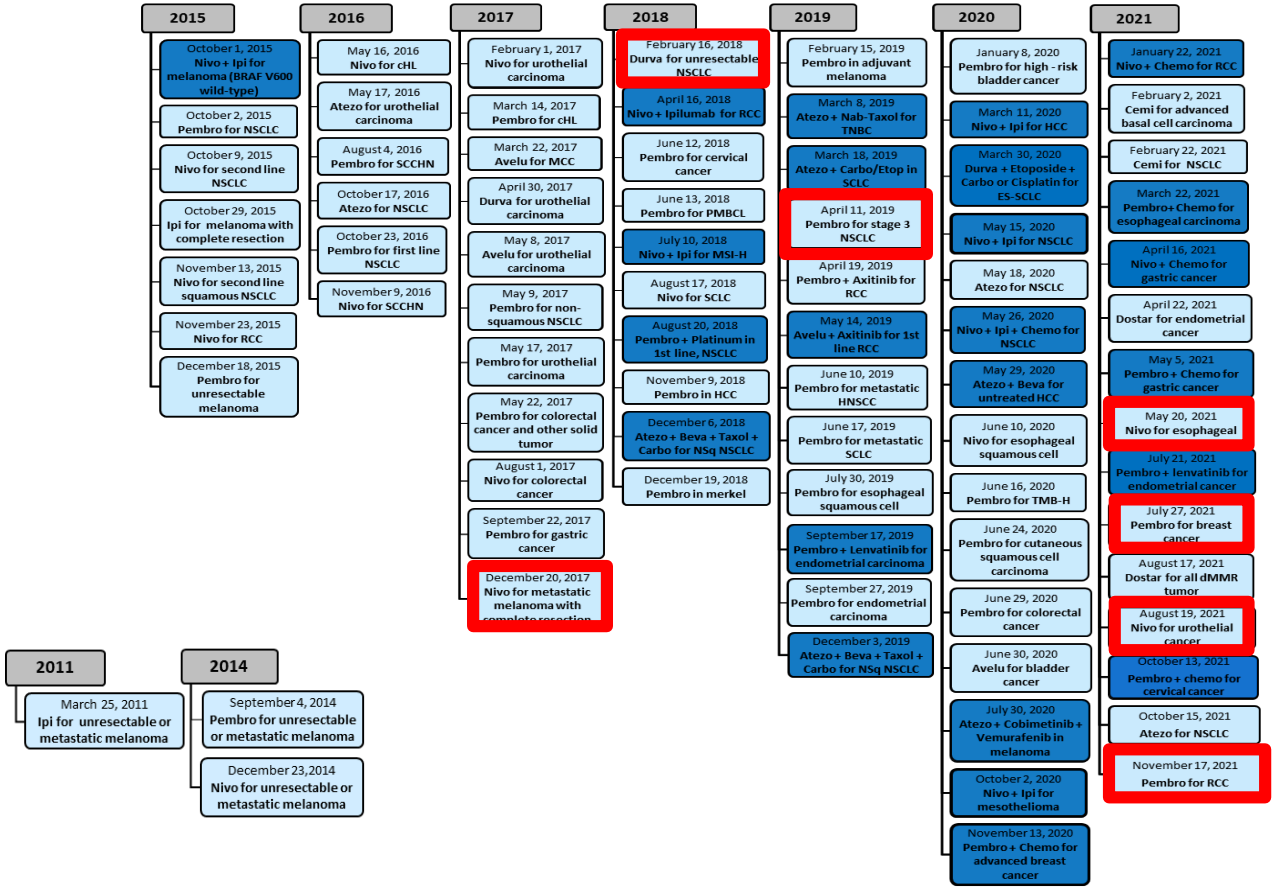
FDA Approvals for Immune Checkpoint Inhibitors



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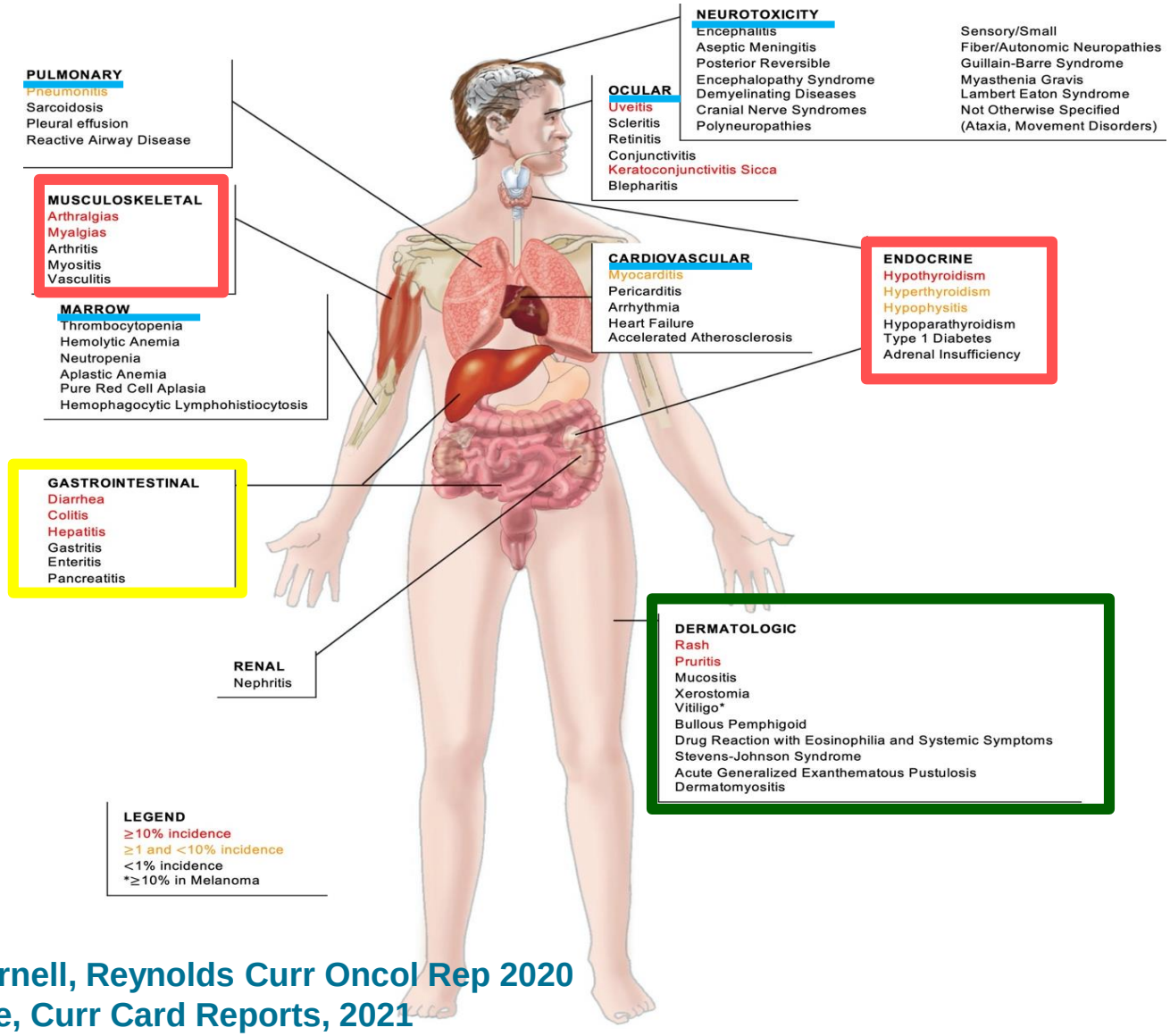
Immune-Related AEs (irAEs)



Darnell, Reynolds Curr Oncol Rep 2020
Lee, Curr Card Reports, 2021

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Grading Criteria for Adverse Events

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Gastrointestinal Toxicity					
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening	Death

Common Terminology Criteria for Adverse Events (CTCAE)

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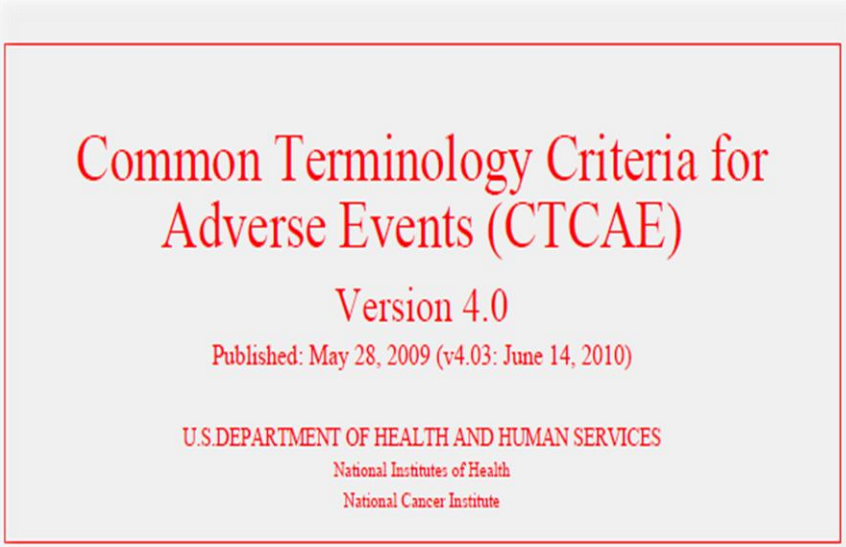
Grading Toxicity



- Grade 1: Mild, asymptomatic, no intervention required
- Grade 2: Moderate, local or non-invasive intervention required
- Grade 3: Severe or medically significant, but not life-threatening.
- Grade 4: Life-threatening consequences; urgent intervention required
- Grade 5: Death related to AE

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Adverse Events Frequency

	ANY TOXICITY	SEVERE G3-4	STOPPED Tx	DEATH
PD-1	74%	14%	6%	.6%
CTLA-4	89%	34%	21%	1.3%
COMBO ICI+ICI	90%	55%	38%	1.23%
COMBO ICI+CHEMO	89%	46%	13%	1.1%

Arnaud-Coffin, IJC, 2019

Wang, JAMA Onc, 2020

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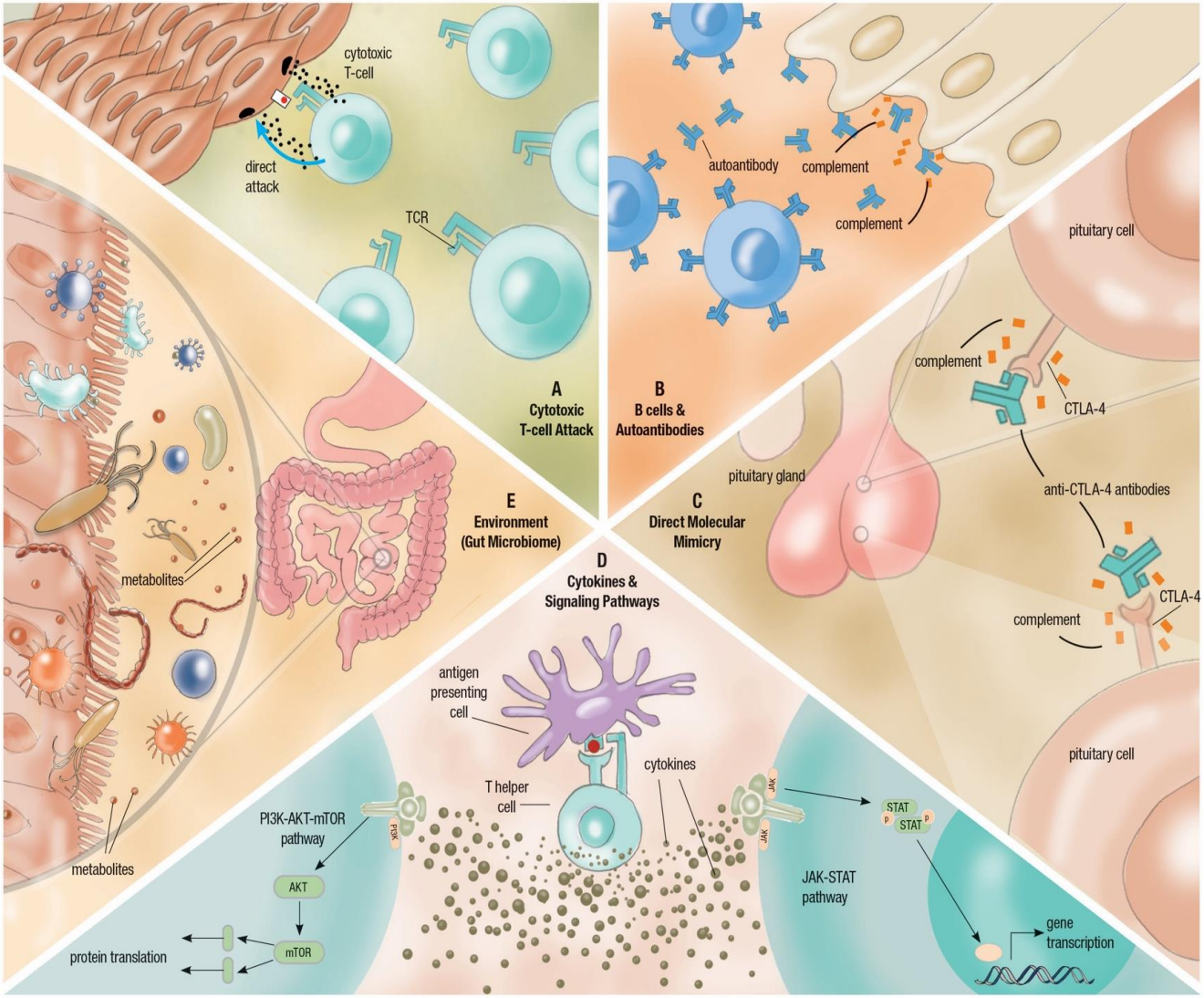
Proposed Mechanisms



Lee, Curr Card Reports, 2021, In Press

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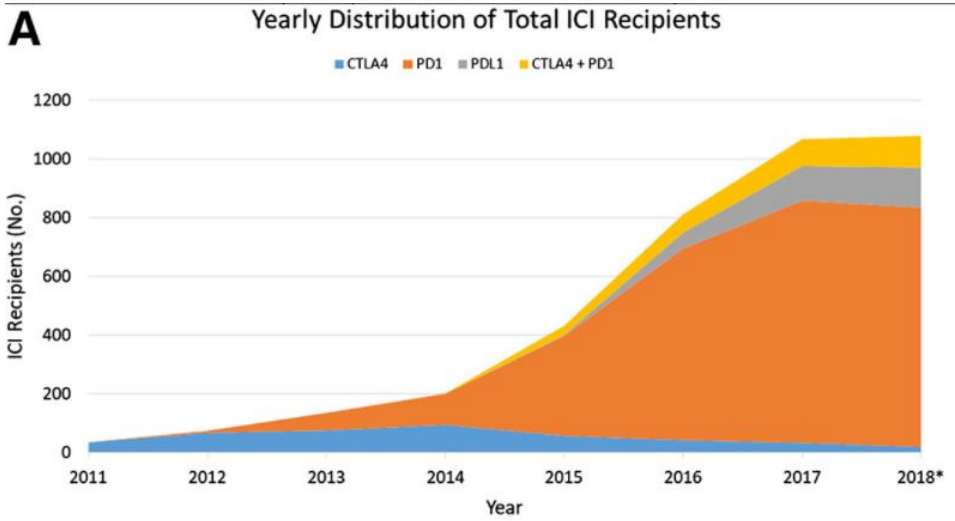
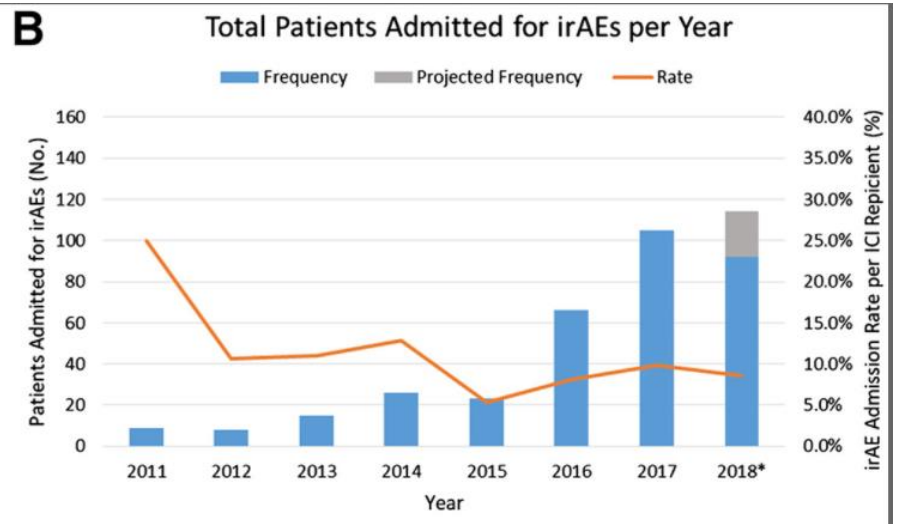
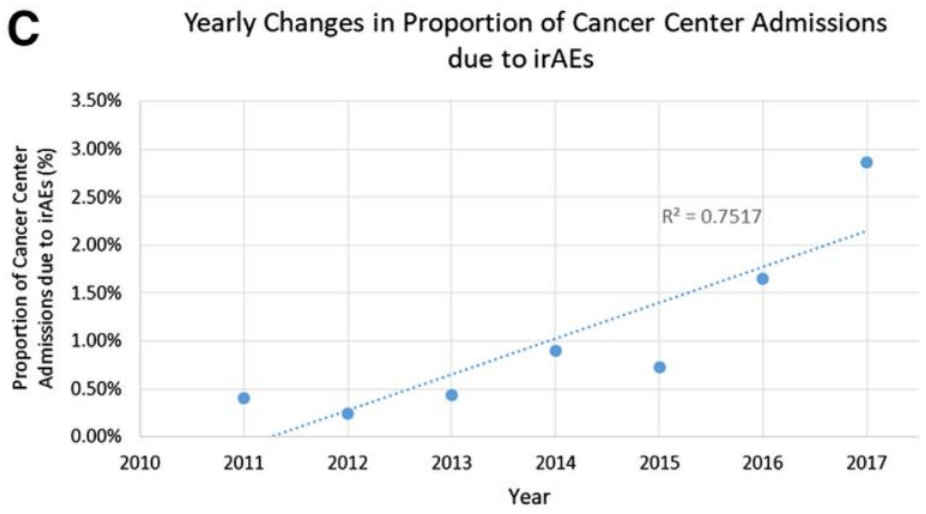
Massachusetts General Hospital







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Molina, Zubiri, et al, Oncologist, 2020

GYN ICI Patients at MGH

GYN								
ICI REGI	2015	2016	2017	2018	2019	2020	2021	TOTALS
ipilimum	0	0	0	0	0	0	0	0
nivoluma	0	12	32	20	11	11	10	96
ipilimum	0	1	2	2	6	6	5	22
pembroli:	2	16	27	22	34	55	48	204
atezolizu	0	3	1	1	1	1	1	8
avelumab	0	5	17	12	7	6	3	50
durvalum	0	0	0	0	0	9	1	10
nivoluma	0	0	0	0	0	0	0	0
TOTALS	2	37	79	57	59	88	68	390

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SUMMARY OF INTRO SLIDES

- Immune Checkpoint Inhibitors Are Now Standard of Care
- Success of Single Agent ICI Led To Combination Approvals
- Subset of Patients Experience Durable, Long Term Response
- Be Aware Of The Unique “Autoimmune” Toxicity Profile
- irAEs Often Within First 3-6 Months
  - Unlike chemotherapy they can last for weeks/months
  - Can occur after ICI discontinuation
- Mechanism is Not Well Understood
- irAEs are Typically Grade 1/2 but Severe irAEs Can Be Fatal
- Multi-disciplinary Care Team Implementation is Key

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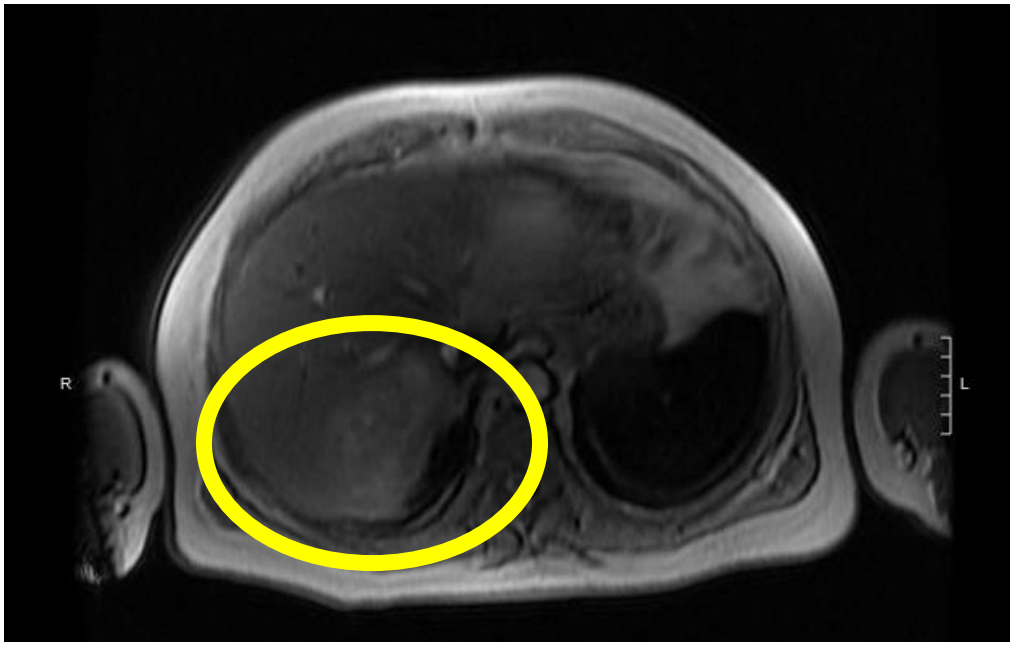
Case, 47 Year Old Man



- 4/2016: Dx: Liver biopsy returned with malignant cells consistent with cholangiocarcinoma.
- 5/2016: Gemcitabine/Cisplatin
- 11/2016: Progressive disease, changed to Nivolumab + TAK-659
- 1/2017: Hypoxia/infiltrates/EF 45%, Myocarditis related to Nivolumab
- 2/2017: Slight decrease in liver lesion
- 3/2017: EF 68%, New Dx: Hepatitis related to Nivolumab
- 6/2017: Anemia/thrombocytopenia
- 2017: Extensive compression fractures due to osteoporosis from chronic high dose steroids, needed Kyphoplasty
- Pass away – Refractory Toxicity from Immune Checkpoint Inhibitors

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Many Questions, Few Answers

*Can we define these events and develop **best practices** to manage the atypical presentations of toxicity?*

*Can we uncover **predictors** for the development of severe toxicity?*

*Or **biomarkers** to indicate if a pt will have an uncomplicated course or one like this patient?*

*What is the **underlying pathophysiology** of these new disease? How can that inform clinical trials for **treatment** of toxicity.*

*Can this be a **window into understanding** early mechanisms of immune regulation (irAE/autoimmune disease)*

*Can we **uncover novel drug targets** that have immunosuppressive potential but preserve tumor*

Guidelines – ASCO, NCCN

NCCN Guidelines, May, 2021
Brahmer, SITC Guidelines, JITC, June 25, 2021
Haanen, Annals of Oncology, 2017 (ESMO)
Brahmer, Journal of Clinical Oncology, February, 2018

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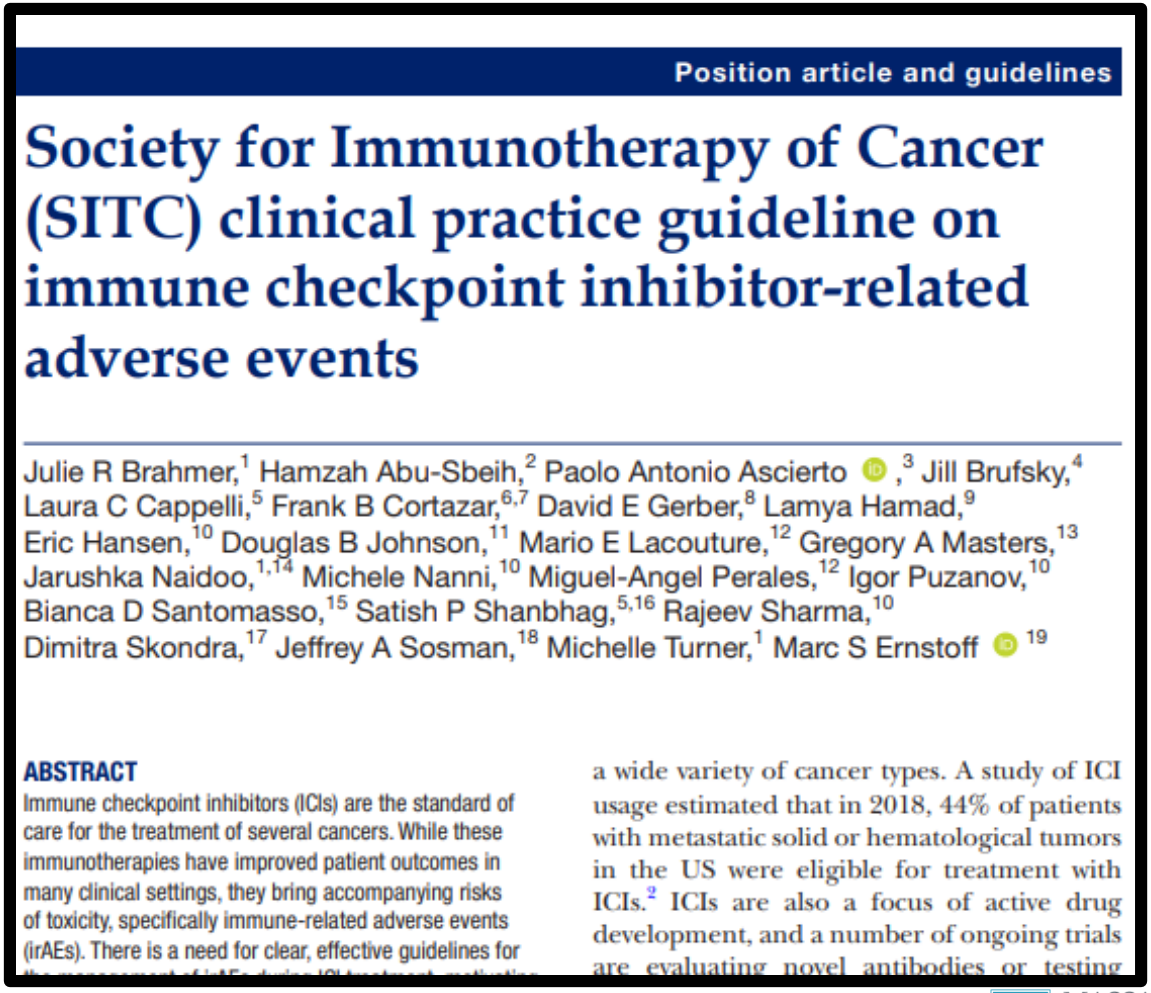
Focus on SITC Guidelines



Position article and guidelines

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events

Julie R Brahmer,[1] Hamzah Abu-Sbeih,[2] Paolo Antonio Ascierto ,[3] Jill Brufsky,[4] Laura C Cappelli,[5] Frank B Cortazar,[6,7] David E Gerber,[8] Lamya Hamad,[9] Eric Hansen,[10] Douglas B Johnson,[11] Mario E Lacouture,[12] Gregory A Masters,[13] Jarushka Naidoo,[1,14] Michele Nanni,[10] Miguel-Angel Perales,[12] Igor Puzanov,[10] Bianca D Santomasso,[15] Satish P Shanbhag,[5,16] Rajeev Sharma,[10] Dimitra Skondra,[17] Jeffrey A Sosman,[18] Michelle Turner,[1] Marc S Ernstoff [19]

ABSTRACT

Immune checkpoint inhibitors (ICIs) are the standard of care for the treatment of several cancers. While these immunotherapies have improved patient outcomes in many clinical settings, they bring accompanying risks of toxicity, specifically immune-related adverse events (irAEs). There is a need for clear, effective guidelines for

a wide variety of cancer types. A study of ICI usage estimated that in 2018, 44% of patients with metastatic solid or hematological tumors in the US were eligible for treatment with ICIs.[2] ICIs are also a focus of active drug development, and a number of ongoing trials are evaluating novel antibodies or testing

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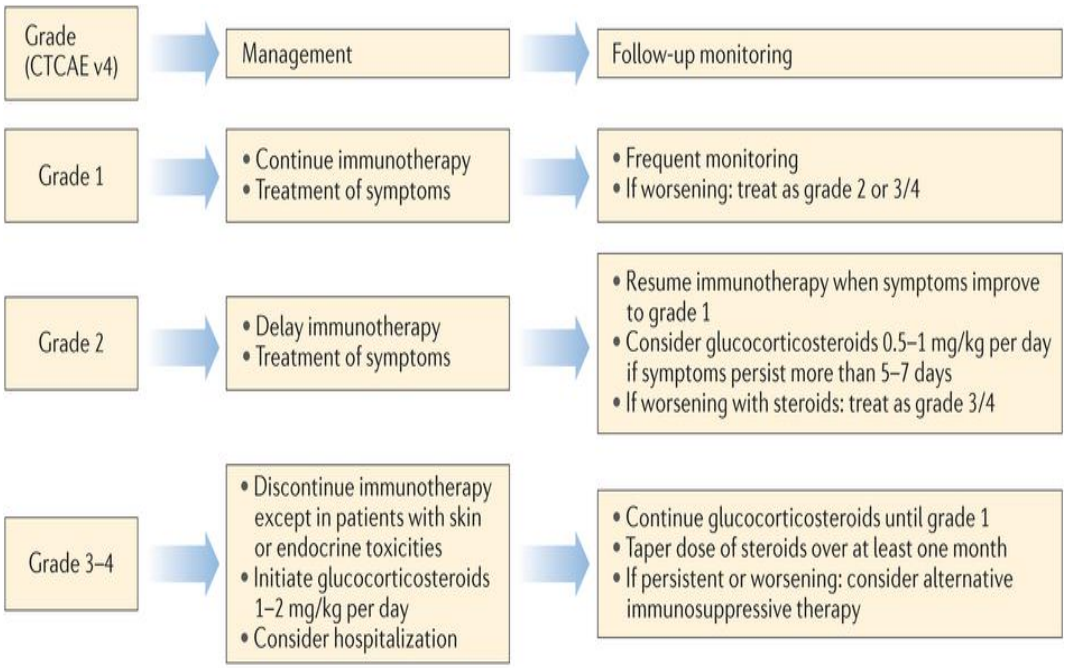
Basic Toxicity Management Summary

- MILD: Treat symptomatically
- PERSISTENT MILD or MODERATE: Oral corticosteroids (i.e. prednisone 1mg/kg/qd)
- PROGRESSIVE, SEVERE, OR LIFE-THREATENING:
  - Hospitalize & begin high dose IV steroids (i.e. methylprednisolone 1 mg/kg qd or bid)
  - If steroid refractory, consider starting immunosuppressive meds (such as mycophenolate mofetil in the case of hepatitis or infliximab in the case of colitis)



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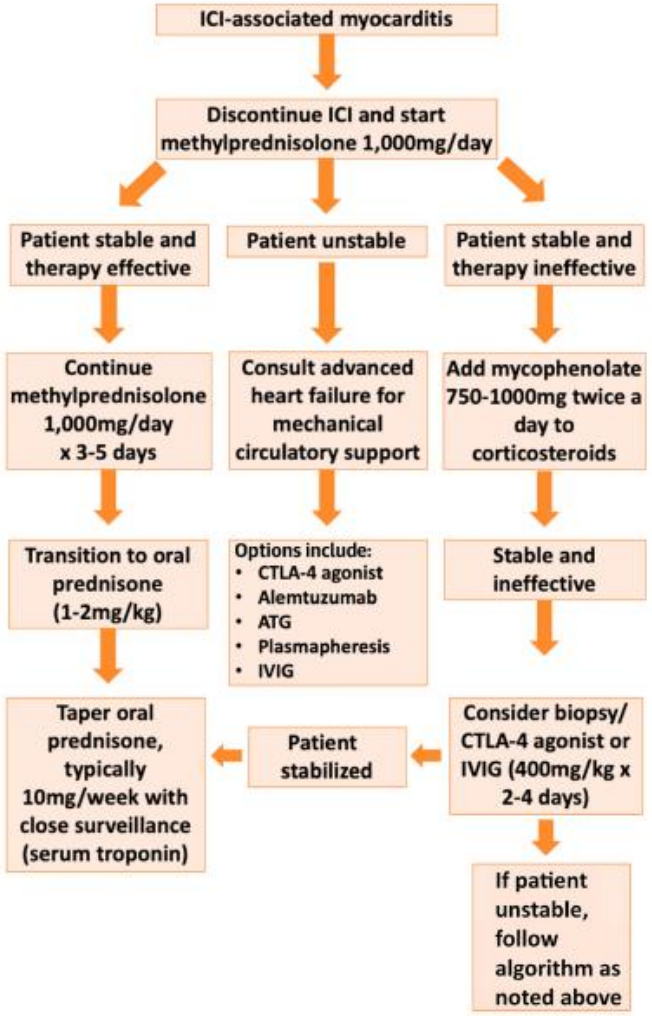
Managing Refractory Cases



Zhang, JACC, Cardiooncology, 2021
Frayberg, Curr Onc Reports, 2021

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Hepatitis

- Hold immunotherapy > grade 2 (3-5X ULN) transaminases
  - Stop any hepatotoxic medications (Tylenol, herbal supplements, alcohol)
  - Rule out viral (Hep A/B/C/E, CMV, EBV, HSV, VZV, HIV) etiology
  - Rule out (other) drug-induced process
  - Look for evidence of disease/alternative diagnosis
    - Imaging – US, consider CT/liver MRI depending on clinical scenario
    - Consider ceruloplasmin, alpha-1-antitrypsin, ferritin, ANA titer, mitochondrial Ab M2, smooth muscule Ab, LKM type 1, tissue transglutaminase IgA and IgG, TSH, iron, transferrin
- - Management:
  - Grade 2 –prednisone .5-1 mg/kg/day
  - Grade 3 - prednisone 1-2 mg/kg/day
  - If no improvement after 3 days, add Cellcept

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Generalists/Specialists are All Critical

- Cardiac – Immediate **Cardiology** consultation
- Grade 1 pancreatitis – Consider **GI referral**
- Grade 2 colitis – Consider **GI consultation**
- Mild eye changes – Refer to **Ophthalmology**
- Myasthenia Gravis, GBS – Refer to **Neurology**
- Grade 2 – **Nephrology** consultation
- Grade 2 pneumonitis – **Pulmonary** consultation
- Moderate myositis – **Rheumatology or neurology** consultation
- Hyperglycemia < 200 – Consider **Endocrine** consultation, > 200 – endocrine consultation
- Primary AI – **Endocrine** consultation
- Hypophysitis – Consider **Endocrine** consultation
- Grade 3 LFTs – **Hepatology** consultation
- Grade 3,4 Rash – **Dermatology** consultation, SJS/TENS – dermatology, urology, ophthalmology

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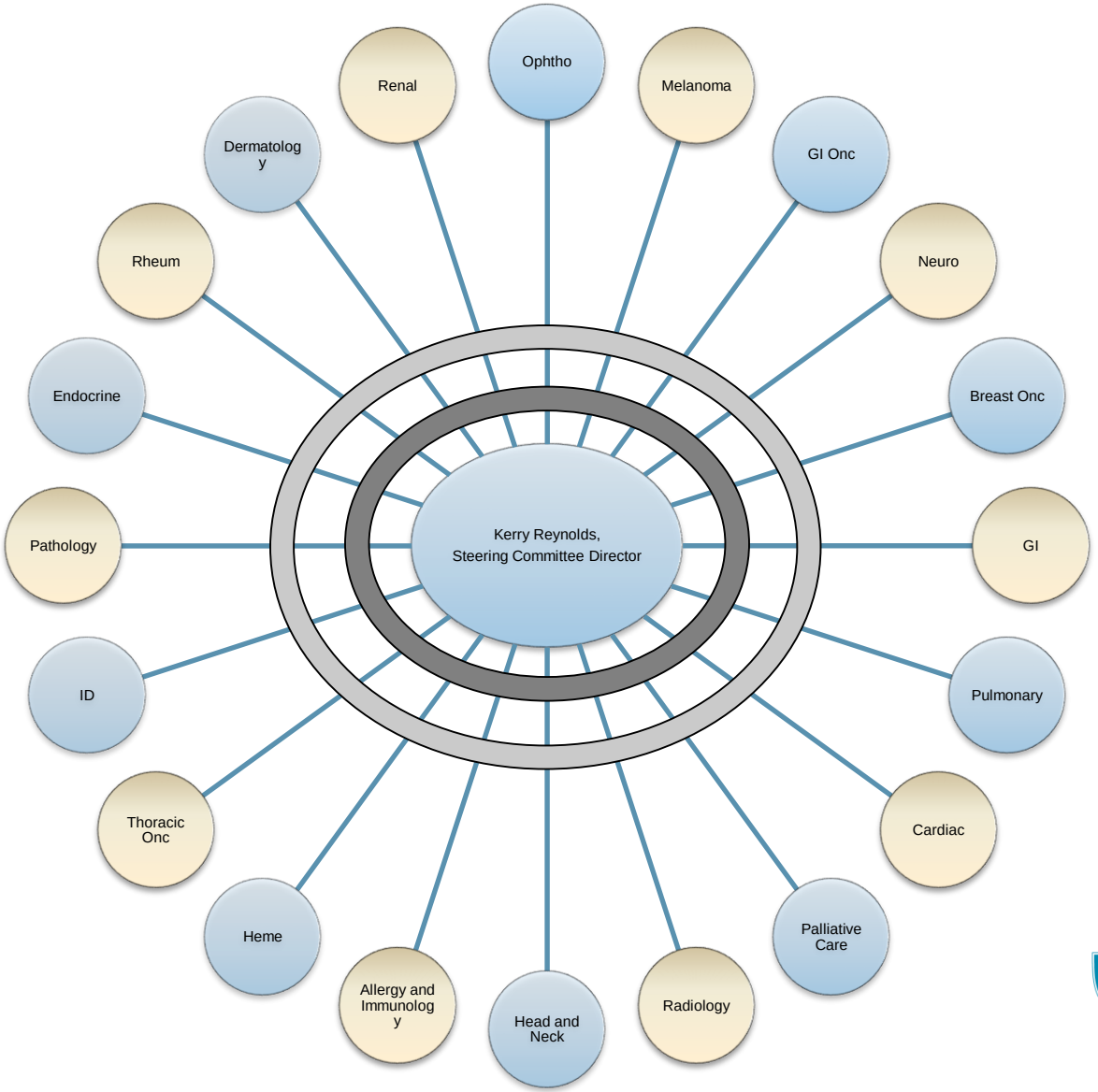
Immunotherapy Toxicity Service



For more information:
https://www.massgeneral.org/cancer-center/treatments-and-services/severe-immunotherapy-complications/

Represents Clinical Research

Represents Translational Research

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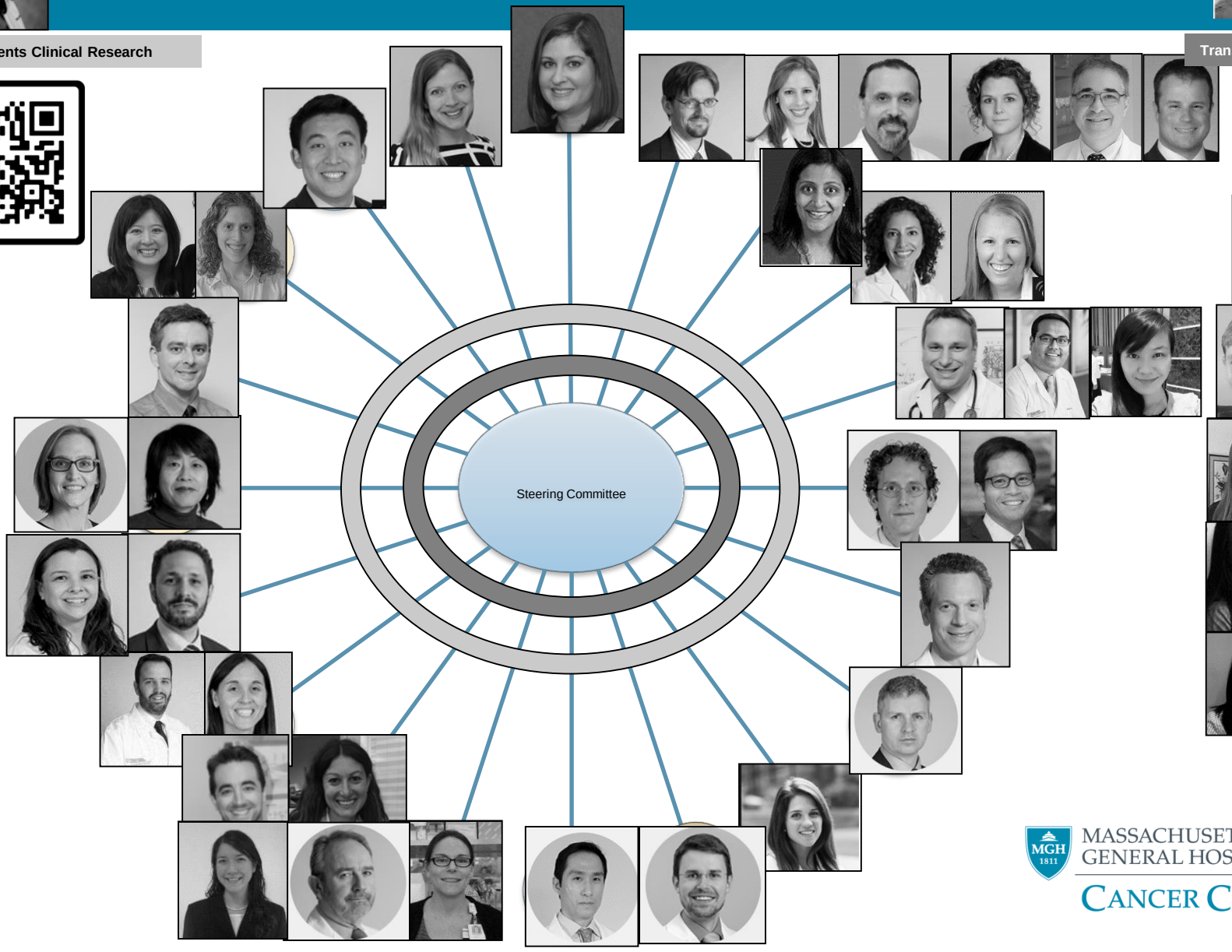
Immunotherapy Toxicity Service

Represents Clinical Research

Translational Research



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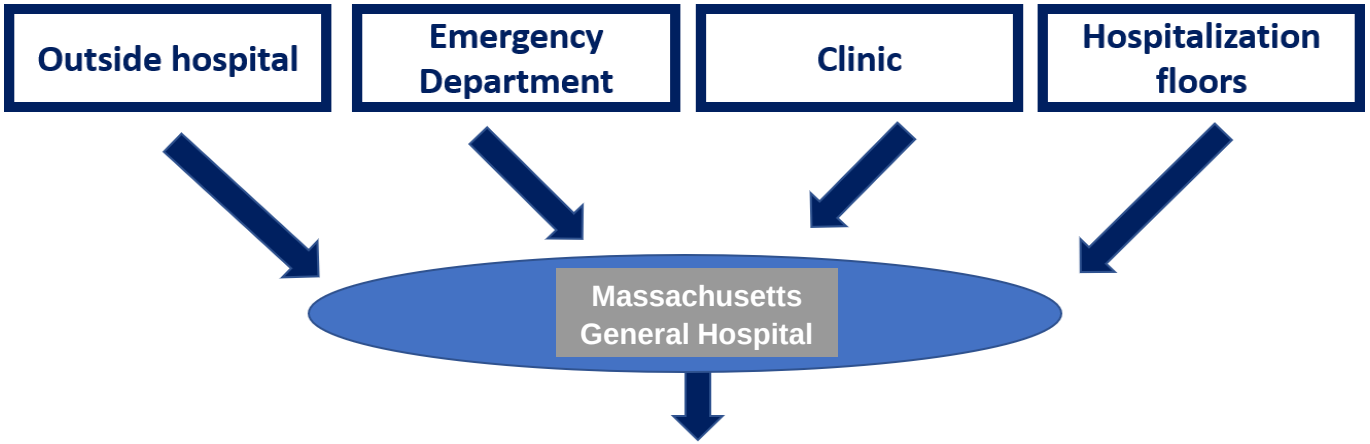
SIC Service



1- Electronic report created by cross reference of patients treated with ICI in our system and inpatient admissions

2- Census runner reviews the electronic report

3- Nurse practitioner screens for patients with iAEs

4- Screened irAE are added to the patients list

5- Patients are seen by Oncology on rounds

6- Coordination between oncology and the different specialists

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SIC Service Implementation

Table 1. Characteristics of Patients Admitted for irAE Before and After SIC Service Implementation

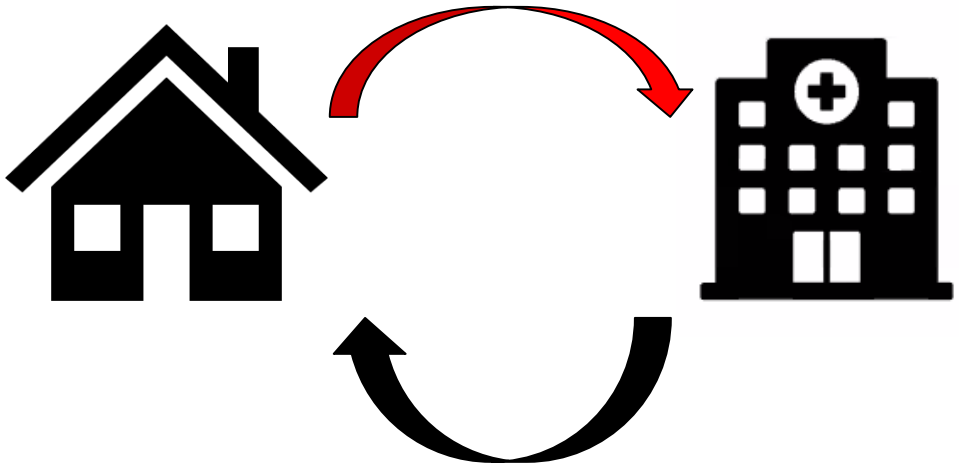
Characteristic	Pre-SIC[a] (*n* = 127 patients)	Post-SIC[b] (*n* = 122 patients)	*P* Value[c]
Age, mean (SD), y	62.6 (13.9)	64.6 (11.1)	0.216
Female Sex	44 (34.7%)	55 (45.1%)	0.093
Cancer Type			
Melanoma	48 (37.8%)	31 (25.4%)	0.156
Thoracic	35 (27.6%)	38 (31.2%)	
Gastrointestinal	14 (11.0%)	26. (21.3%)	
Genitourinary	8 (6.3%)	9 (7.4%)	
Hematologic	3 (2.4%)	7 (5.7%)	
Gynecologic	5 (3.9%)	3 (2.5%)	
Head and Neck	5 (3.9%)	2 (1.6%)	
Neurologic	3 (2.4%)	4 (3.3%)	
Breast	5 (3.9%)	2 (1.6%)	
Sarcoma	1 (0.8%)	0	
ICI Type			
CTLA4	9 (7.1%)	3 (2.5%)	0.147
PD1	84 (66.1%)	92 (75.4%)	
PDL1	8 (6.3%)	10 (8.2%)	
CTLA4 + PD1	26 (20.5%)	17 (13.9%)	
irAE Type			
Allergy	3 (2.4%)	1 (0.8%)	0.311
Cardiac	9 (7.1%)	11 (9.0%)	
Dermatologic	9 (7.1%)	3 (2.5%)	
Endocrine	15 (11.8%)	13 (10.7%)	
Gastrointestinal	28 (22.1%)	20 (16.4%)	
Hepatic	20 (15.8%)	23 (18.9%)	
Hematologic	4 (3.2%)	2 (1.6%)	
Neurologic	10 (7.9%)	14 (11.5%)	
Pulmonary	26 (20.5%)	26 (21.3%)	
Renal	1 (0.8%)	7 (5.7%)	
Rheumatologic	2 (1.6%)	2 (1.6%)	

Zubiri, JITC, 2021, In Press

Decreased Readmission Rates

Table 2. Impact of SIC Service Implementation on Key Outcomes – Logistic Regressions

Outcome	Pre-SIC[a] (*n* = 166 admits)	Post-SIC[b] (*n* = 149 admits)	Coefficient / OR (95% CI)[c]	*P* Value
Length of stay, median (IQR), days	5.5 (3-11)	5 (3-9)	-1.7 (-3.56-0.19)[d]	0.078
Discharged on corticosteroids[e]	121 (75.6%)	96 (69.1%)	0.60 (0.33-1.10)[f]	0.101
Use of non-steroidal immunosuppression	24 (14.5%)	18 (12.1%)	0.87 (0.43-1.77)[f]	0.702
ICI discontinuation for irAE[g]	74 (66.1%)	61 (67.0%)	1.04 (0.55-1.98)[f]	0.897
Died during irAE admission	11 (6.6%)	13 (8.7%)	1.46 (0.60-3.55)[f]	0.398
IrAE readmission	43 (25.9)	22 (14.8)	0.46 (0.22-0.95)[h]	**0.036**
Length of stay of irAE readmission, median (IQR), days	7 (3-16)	6 (3-10)	-8.08 (-16.03, -0.14)[d]	**0.046**



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SUMMARY SLIDE FOR SECTION 2

- Serious irAE can involve a wide range of organ systems
- There is recognition that all generalists and disease-specific subspecialists are essential in the management of irAEs
- It is important to develop expertise to recognize irAEs and to educate all types of providers (MDs, NPs, RNs, residents, patients)
- Steroids are the mainstay of treatment but:
  - Higher doses are required in myocarditis, encephalitis
  - Steroids are not required for endocrinopathies

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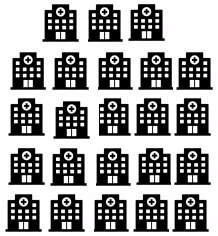
Treatment – How Much? When?



23 Sites

16.7%

Low dose < 60 mg/d methylpred

43.7%

Intermediate dose < 60-500 mg/d

39.6%

High dose < 501-1000 mg/d

34.1%

< 24 Hrs

27.8%

24-72 Hrs

38.1%

> 72 Hrs

High Dose Steroids for the Win

Early Steroids for the Win

MACE: Major adverse cardiac events: CV death, cardiac arrest/shock, or sig heart block requiring pacemaker

- High Dose Steroid Group – 22% MACE
- Int Dose Steroid Group – 54.6% MACE
- Low Dose Steroid Group 61.9% MACE

Zhang, Circulation, 2020

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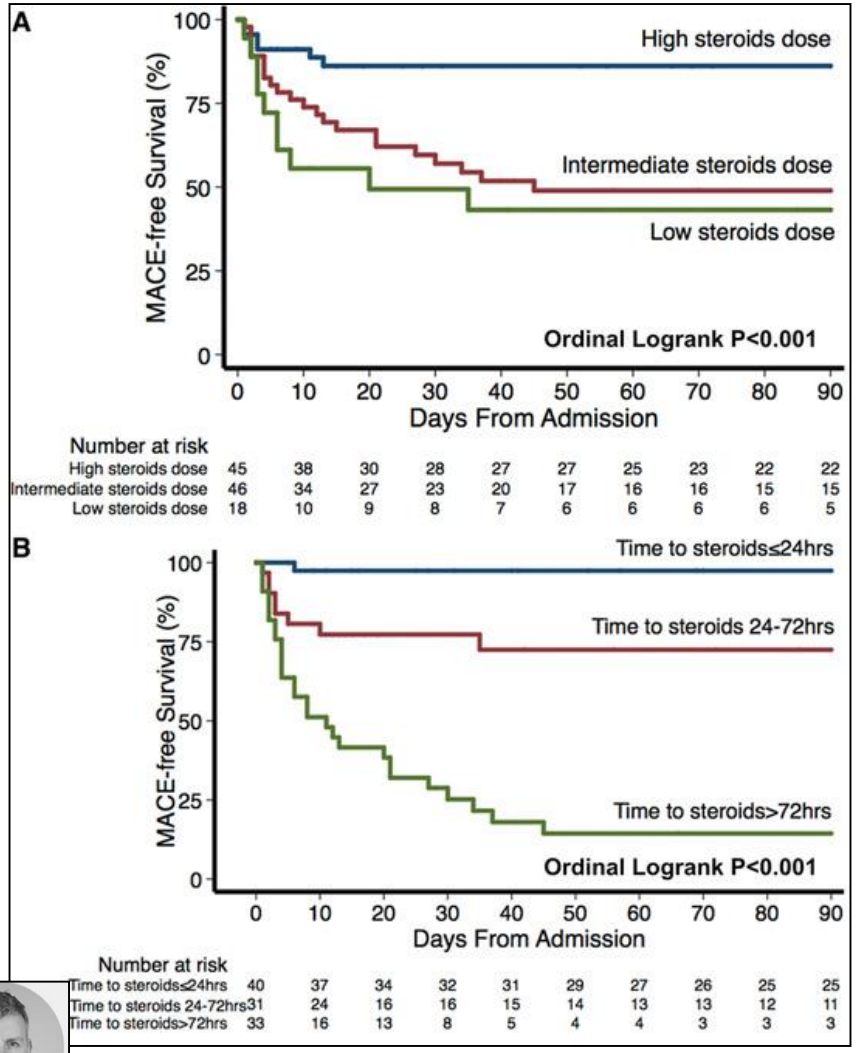
Informing Treatment Guidelines



Clearly an inverse relationship between initial dose of corticosteroids and MACE
- High dose was associated with a 73% lower risk of MACE (HR .27)

Earlier the better! (HR for < 24 hrs, 0.03, HR for 24-72 0.3)

Zhang, Circulation, 2020

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Case – Too Much?

- 51 yo male with stage IIIB melanoma on adjuvant nivolumab (cycle 21 completed 7/16/18) presenting with AKI
  - 7/20/18: developed increasing fatigue, chills and night sweats
  - 7/27/18 clinic visit: creatinine 1.69 from baseline 1
    - Given 2L NS in office with no change in creatinine on re-check later that day
    - Sent home with follow-up in 4 days
  - 7/31/18 clinic visit: creatinine 2.90
    - Admitted to hospital

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Oncologic History

- Stage IIIB melanoma
  - 02/2013: melanoma in situ on right neck, resected
  - 05/2017: left thigh melanoma; wide excision with sentinel lymph node biopsy performed, SLN positive; PET-CT demonstrated left inguinal LN FDG uptake proximal to the surgical site
  - 07/17/17: completion dissection performed, 2/11 LNs positive, NED afterwards (stage IIIA or IIIB)
  - 10/6/17: started adjuvant nivolumab 240 mg (3mg/kg) q2wk as part of clinical trial
  - Serial scans afterwards show no evidence of disease
  - Underwent 21 cycles of nivolumab from 10/2017 to 07/2018
    - No IrAEs with treatment

Other medical history

- Medical history
  - DVT: diagnosed in 07/2017 following lymph node dissection, previously on Eliquis; discontinued iso no evidence of disease
  - GERD
- Home medications:
  - **Omeprazole** 20 mg daily
  - No prior steroid or other immunosuppressant use
  - No recent antibiotic use, minimal NSAID use (one dose in last week)
- Allergies
  - NKDA

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Physical Exam – Unremarkable, Labs:

BMP	
Na	137
K	3.9
Cl	95
Bicarb	25
BUN	▲ **34**
Cr	▲ **2.83**
Gluc	106

LFTs	
ALT	17
AST	17
Alk phos	65
Tbili	0.4
Alb	4.0
Prot	7.6

Extended labs	
Ca	9.2
LDH	▲ **215**
Sosm	293
TSH	1.91

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Diagnostics

CBC

WBC 9.8

- 74% NP
- 7% lymph
- 11.7% monos
- 6.3% Eos
- 0.3% basos

Hgb ▼ 12.4

Hct ▼ 37.8

Plt 322

Immunologic studies

- C3 160
- C4 45
- ANA neg
- dsDNA neg
- ANCA neg

U/A negative

Mild increase in protein

Micro

- HBV serologies neg
- HCV neg
- HIV neg
- BCx x 2 neg
- UCx neg

CT Abdomen/Pelvis (7/31/18):

"The kidneys are edematous with apparent enlargement relative to prior CT with new perinephric edema. No hydronephrosis, stones, or solid mass lesions"

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Diagnostics

Core biopsy (performed 8/1/18, HD 2):

- Severe acute tubulointerstitial nephritis:
  - "Interstitium contains a **severe inflammatory infiltrate** composed mainly of lymphocytes with admixed eosinophils and few plasma cells and neutrophils, involving approximately 70% of the cortical area and associated with moderate to severe tubulitis (more than 10 cells per tubular cross section)."
- No significant fibrosis or irreversible damage
- No glomerular pathology

Treatment

- **Omeprazole** discontinued, ranitidine started
- 8/2: Solumedrol 500 mg x 1 given
- 8/2: prednisone taper started (59 days, 8/2 – 10/2)
  - 7 days prednisone 60 daily (8/2 – 8/8)
  - 7 days prednisone 40 daily (8/9 – 8/15)
  - 7 days prednisone 30 daily (8/16 – 8/22)
  - 7 days prednisone 20 daily (8/23 – 8/29)
  - 14 days prednisone 15 daily (8/30 – 9/12)
  - 14 days prednisone 10 daily (9/13 – 9/26)
  - 5 mg prednisone daily indefinitely (9/27 – 10/2)
- Total steroid duration: 60 days
  - 1 day IV steroids (500 mg IV solumedrol x 1)
  - 59 days PO steroids

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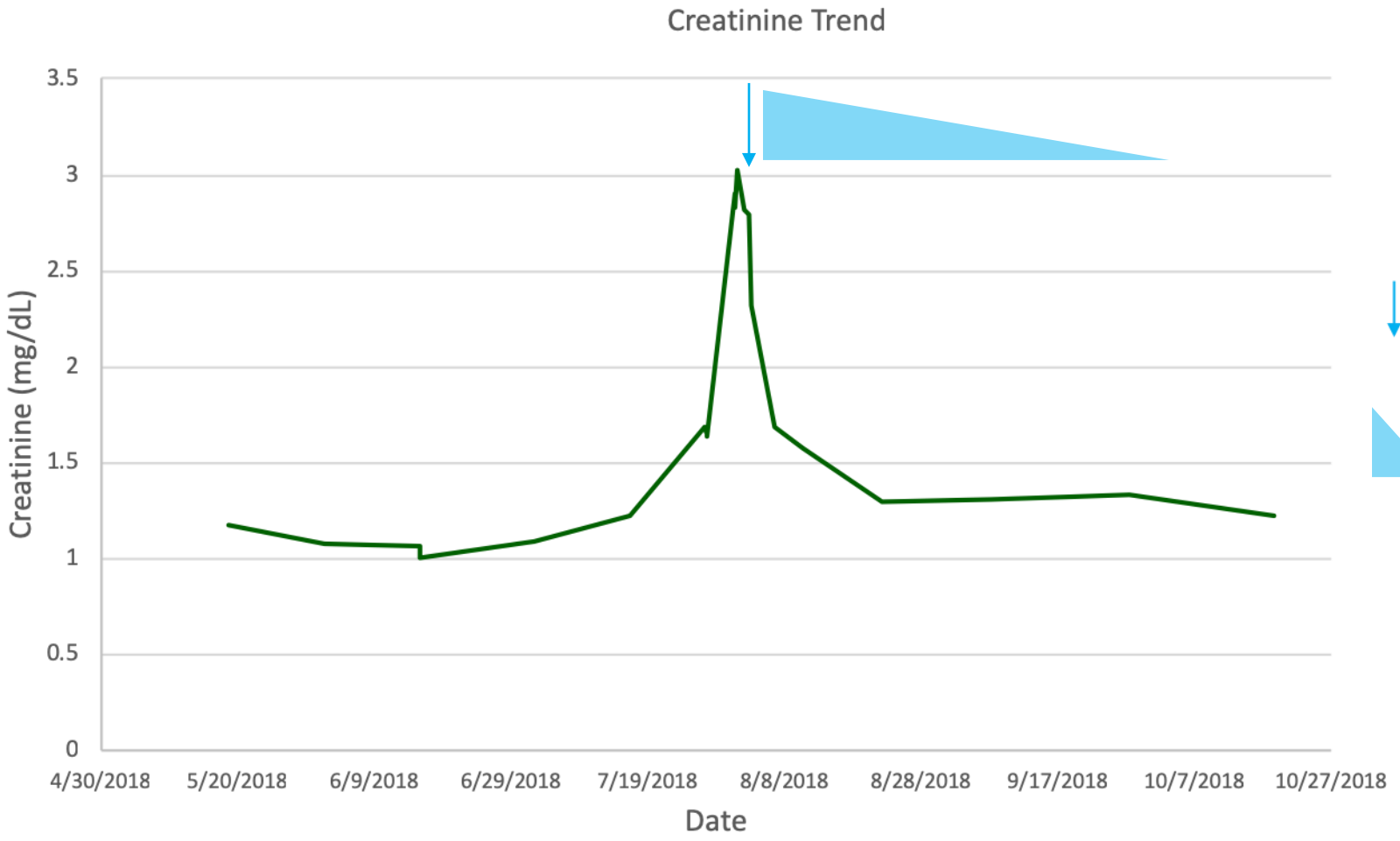
AKI Trend



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AKI outcomes

- Improved to baseline within 1 month
  - Rapid improvement in AKI after steroid initiation
  - Creatinine halved by day 9 of treatment
  - Creatinine returned to baseline at day 20 of treatment
- Discharged home on hospital day 4

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Nephrology

What is the frequency & etiology of AKI and what are its risk factors in patients on checkpoint inhibitors?

CJASN
Clinical Journal of American Society of Nephrology

Cohort

1016 patients

61% male

Mean eGFR 82 mL/min

Follow-up 12 months

Acute kidney injury 17%

Sustained AKI (≥ 3 days) 8%

Checkpoint inhibitor related AKI 3%

Proton Pump Inhibitors → Hazard ratio

Sustained AKI (≥ 3 days)	Checkpoint inhibitor related AKI
2.85	2.24
95%CI 1.34-6.08	95%CI 0.96-5.21

Conclusions: AKI is common in patients receiving checkpoint inhibitors, and the causes are heterogeneous. Proton pump inhibitor therapy is a risk factor for sustained AKI.

Harish Seethapathy, Sophia Zhao, Donald Chute, Leyre Zubiri, et al. ***The Incidence, Causes, and Risk Factors of Acute Kidney Injury in Patients Receiving Immune Checkpoint Inhibitors.*** CJASN doi: 10.2215/CJN.00990119. **Visual Abstract by Pablo Garcia, MD**

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL
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Seethapathy et al, CJASN, 2019

Do we need a long taper of steroids?

- Permanently discontinue AIN-associated medications (PPI, allopurinol, NSAIDS, antibiotics).
- Temporarily hold ICI.
- Begin prednisone 1mg/kg/day In hospitalized patients, consider 1-3 days of intravenous methylprednisolone. Repeat creatinine in 5-7 days provided creatinine is improving by ≥25%.
- Continue rapid taper Rapid corticosteroid taper: 40mg x 3 days, 30mg x 3 days, 20mg x 3 days, 10mg daily.
- Repeat creatinine every 7 days and continue taper as long as creatinine continues to decline.
- If creatinine rises, restart 60mg day and taper over 4-6 weeks.

Lee, JITC, 2020

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Clinical Outcomes

Table 2 Clinical outcomes

	Rapid taper n=13	Standard of care n=14
Corticosteroid treatment, count (%) or median (IQR)		
Received intravenous pulse methylprednisolone	3 (23%)	6 (43%)
Grams of methylprednisolone	0.75 (0.2–1.0)	0.65 (0.13–1)
Initial daily oral prednisone dose, mg	60 (60–60)	60 (6–60)
Median days at initial oral prednisone dose*	7 (3–7)	7 (6–8)
Median days until≤10 mg of prednisone	20 (15–25)	38 (30–58)
Received second-line immunosuppression	0	0
Renal recovery (defined by creatinine<1.5 fold baseline)		
Renal recovery within 30 days	11 (85%)	6 (46%)
Best creatinine (mg/dL) within 30 days, median (IQR)	1.31 (1.13–1.45)	1.49 (1.29–1.62)
Renal recovery within 60 days	11 (85%)	9 (64%)
Best creatinine within 60 days	1.18 (1.02–1.34)	1.35 (1.29–1.49)
Corticosteroid refractory nephritis† at 90 days	1 (8%)	4 (29%)
Steroid re-initiated or re-escalated prior to ICI-rechallenge	2 (15%)	2 (14%)
Median time to renal recovery, days (IQR)	11 (7–18)	36 (20–100)
Rechallenge with ICI		
Rechallenged with ICI	7 (54%)	8 (57%)
Median days until rechallenge (IQR)	26 (15–182)	135 (53–290)
Relapse of ICI-induced nephritis after ICI rechallenge	1 (14%)	1 (13%)
Relapse within another severe irAE after rechallenge‡	2 (29%)	3 (38%)
Receiving prednisone at rechallenge	6 (86%)	7 (88%)
Median dose of oral prednisone at rechallenge	10 (3.8–10)	7.5 (3.8–10)
Experienced clinical benefit from ICI rechallenge	4 (57%)	4 (50%)

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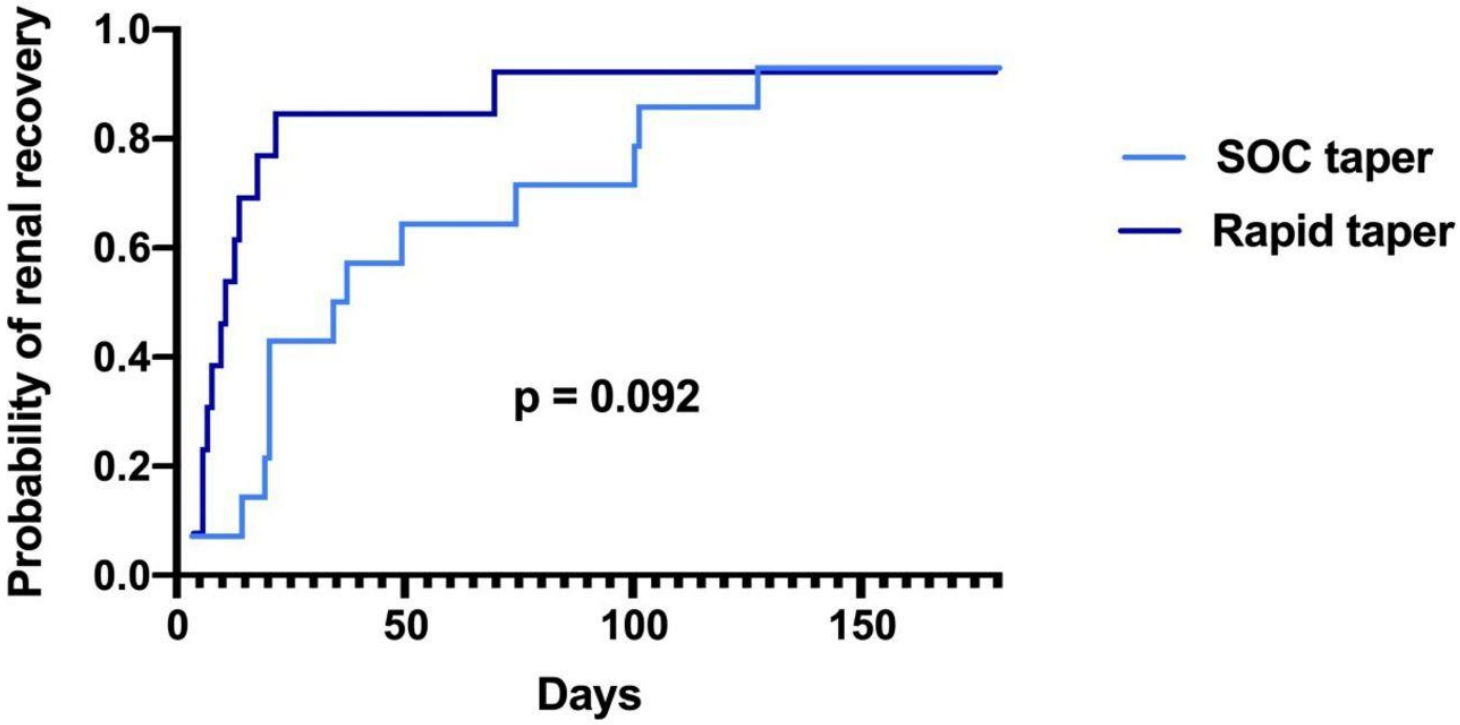
Patients on Rapid Taper Did Well



Lee, JITC, 2020

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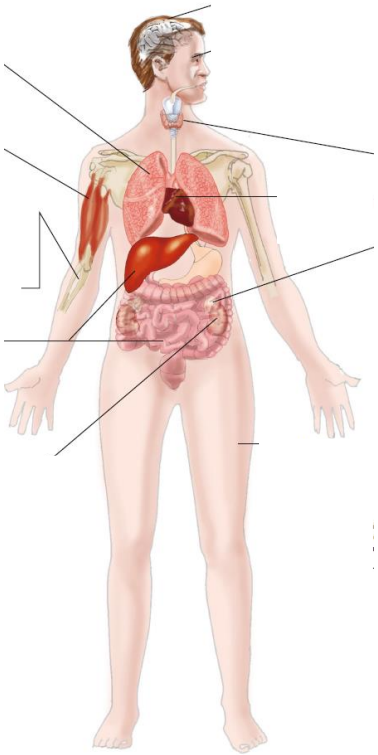
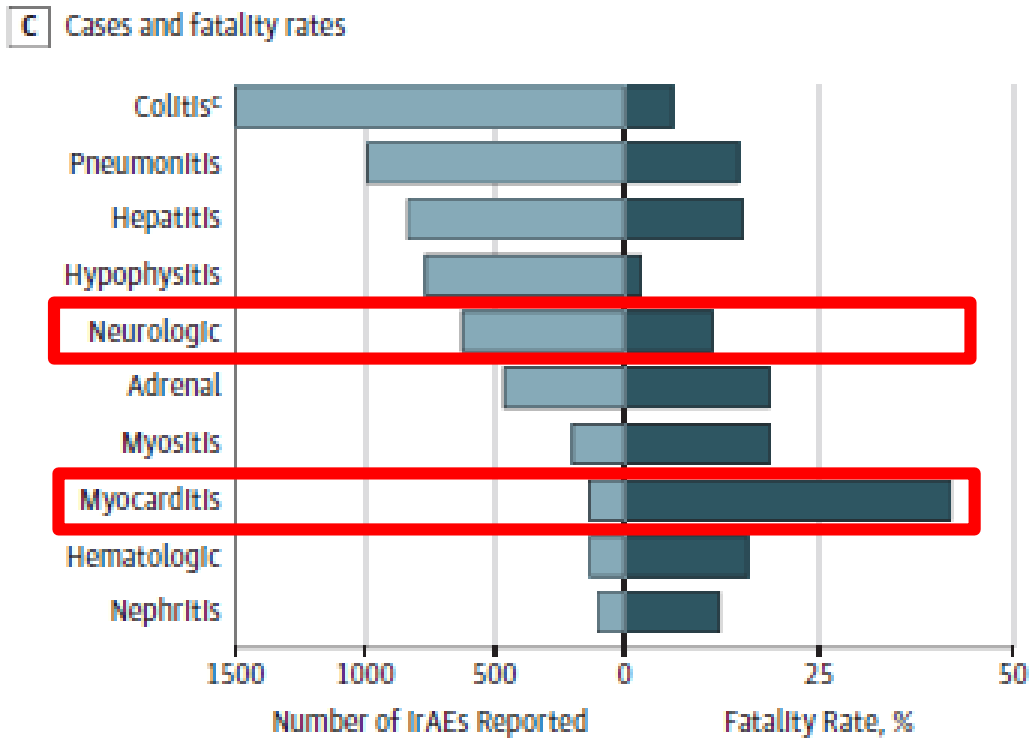
Cases

Fatigue (21-36% of pts on ICI)



Possible Causes:	Work Up:	Next Steps:
Hypophysitis (1-11%) (N/V, weak, H/A, loss of libido, glucose) **Hypothyroidism** **New Onset Type 1 DM (1%)** **Primary AI (RARE!)**	Morning Cortisol, ACTH, FSH, LH Cortisol Stimulation Test, consider brain MRI (pituitary protocol) if abnormal TSH/free T4 Glucose, AG, pH, urine/serum ketones, beta-hydroxybutyrate, c-peptide, consider anti-GAD, anti-islet cell	Determine hypophysitis vs primary AI Steroid replacement Levothyroxine Insulin
Insomnia/depression/anxiety		Exercise, CBT, nutrition

Fatality Rates



Wang, Jama Onc, 2018

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Further Research

- Patient: "*What you are doing is going to benefit so many, I will be happy and honored to help in any way possible, to make this journey easier for others, that will make mine even more worthy*"
- His Wife: *I feel exactly the same, if our journey helps someone elses' be less painful, then it will be even more worthy, if awareness was created then what we endured has more meaning, this is how science advances, this is how we learn, this is how medicine writes the new chapters. I hope God gives me enough years to witness the progresses that I am sure MGH team will achieve. He will remain alive in that progress and one day my kids will have one more reason to be even more proud of their Daddy*.

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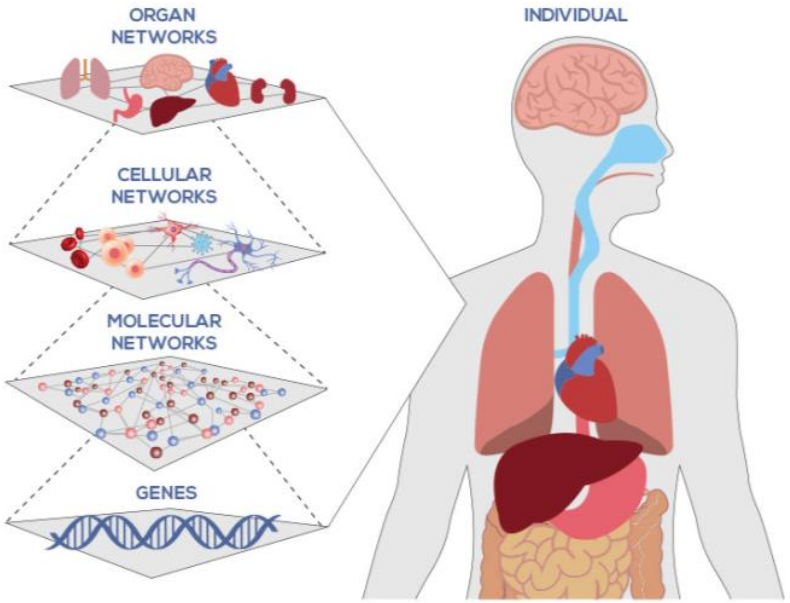
Short Term - Systems Approaches Applied at Unprecedented Resolution

Building Knowledge Network

Different scales



Time: 0 — 1 — 2 — 3

At Diagnosis (pre-steroid)
- Blood, serum, plasma, stools
- Relevant body fluids
- Biopsy affected tissue(s)

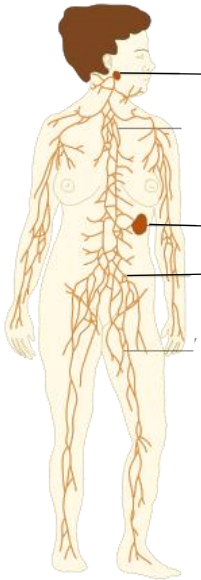
Post-Steroids; collection until recovery
- Blood, serum, plasma, stools
- Body fluids (e.g., urine, CSF, SF)

Collect if patient relapse or develop other irAEs

Next-Generation Microscope: Single Cell Genomics Strategies

Tissues to be profiled

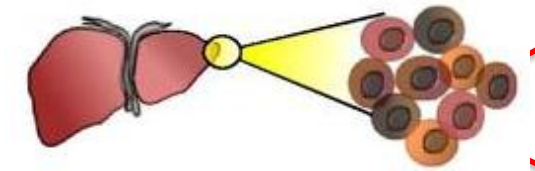
Lymphoid Organs



Non-Lymphoid "Barrier" Organs

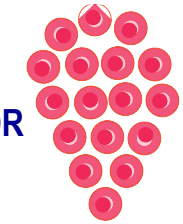
Blood Skin Lung Gut

Sample dissociation,



Solid Tissue Dissociated Tissue

OR



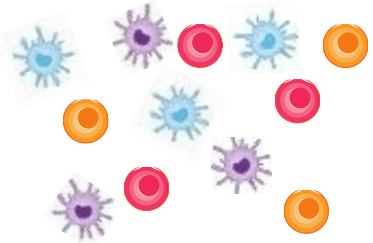
Single cell isolation

Extract every cell genomic information

Single cell RNA-Sequencing

Expression profile clustering

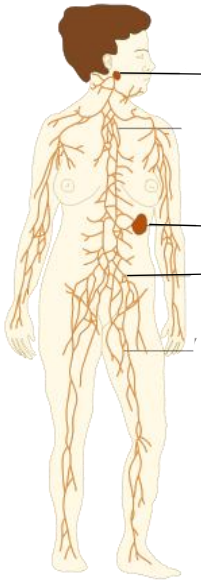
Cell subsets map



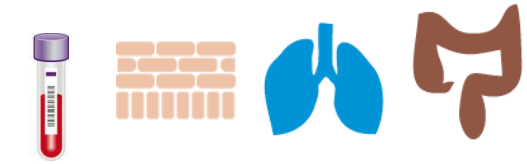
Next-Generation Microscope: Single Cell Genomics Strategies

Tissues to be profiled

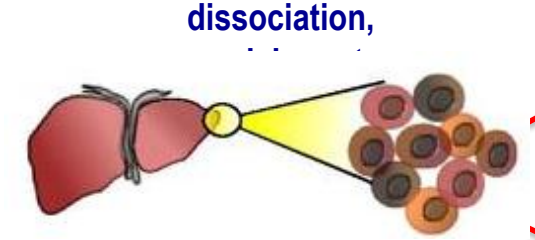
Lymphoid Organs



Non-Lymphoid "Barrier" Organs



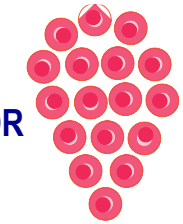
Sample dissociation,



Solid Tissue

Dissociated Tissue

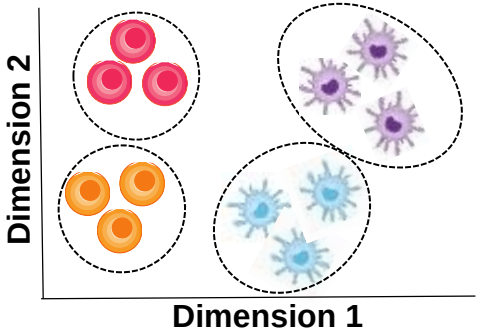
OR



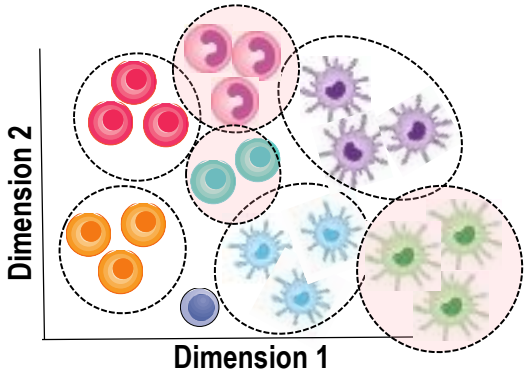
Single cell isolation

Single cell
RNA-Sequencing & analysis

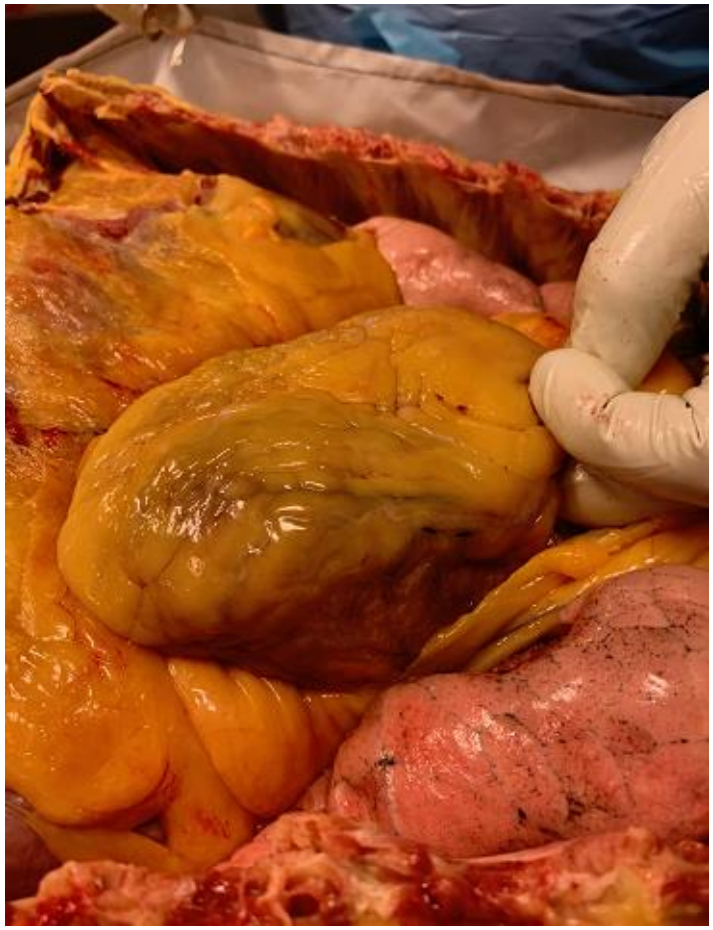
"Healthy" State



Disease State



Rapid Autopsy



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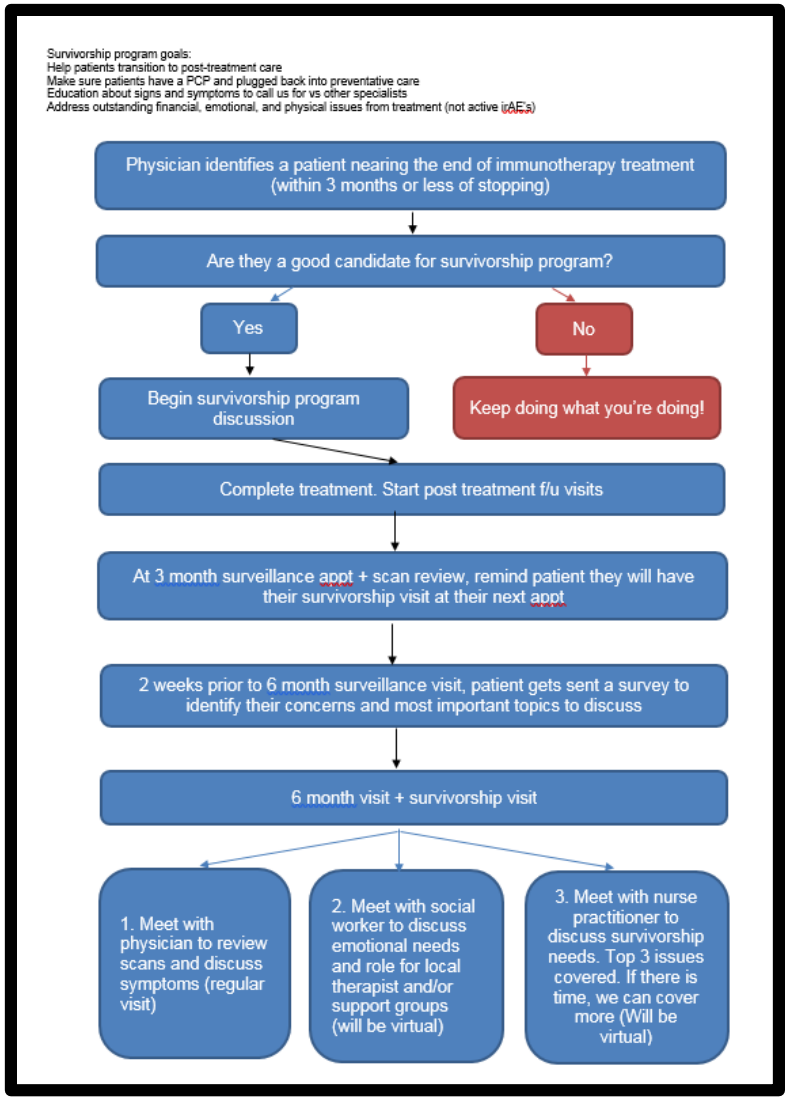
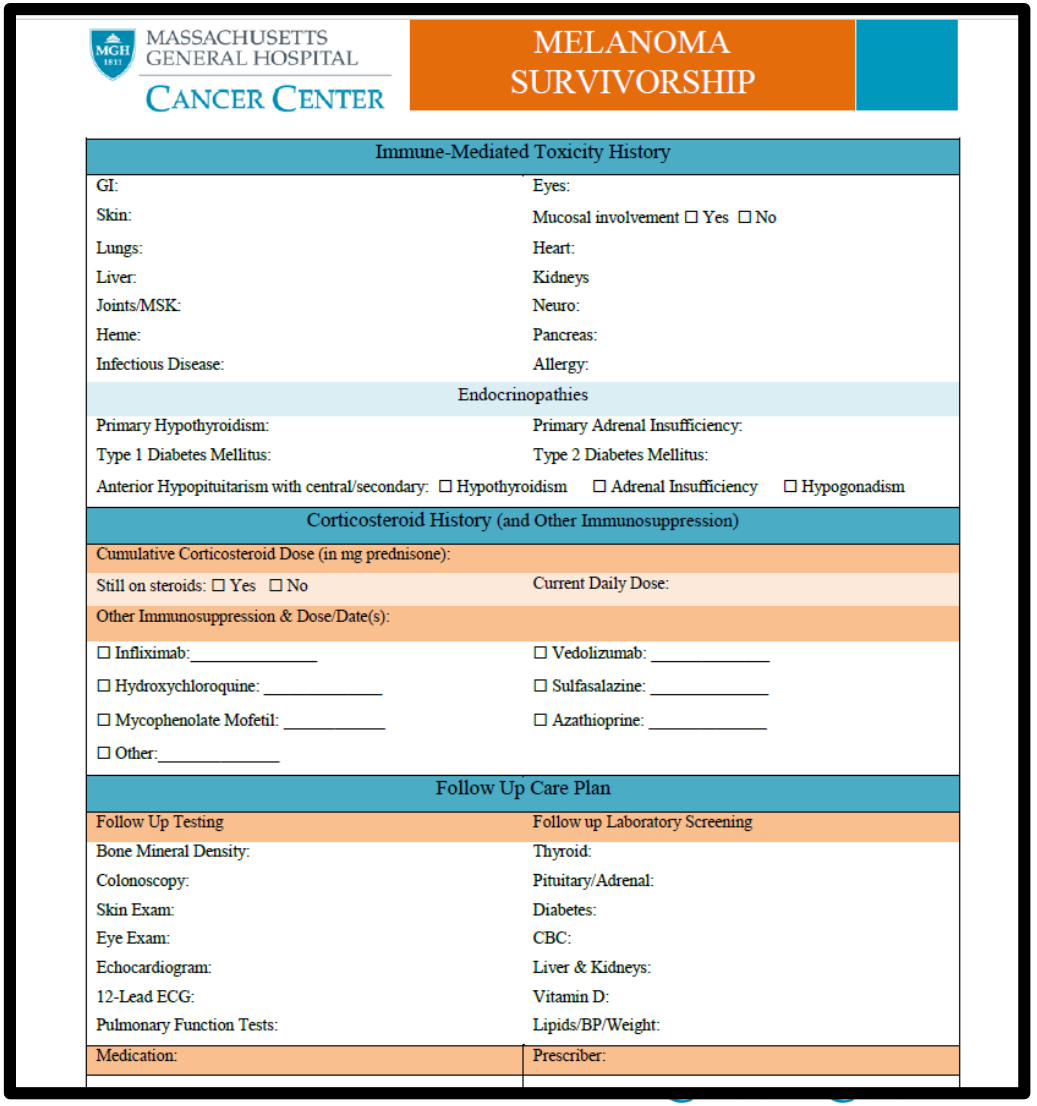
Long term - Survivorship! (Fadden, NP)





Let's Answer Our Questions

- How many patients are expected to have a serious immune-related adverse event (irAE) this year in the US alone? (300, 3,000, 10,000, well over 30,000)
- If a patient has one irAE, are they at risk for another? Y/N
- Are all irAE's treated with steroids? Y/N
- Do some irAE's require different doses of steroids? Y/N
- What is the most common organ system involved?
- What are the two most fatal toxicities?

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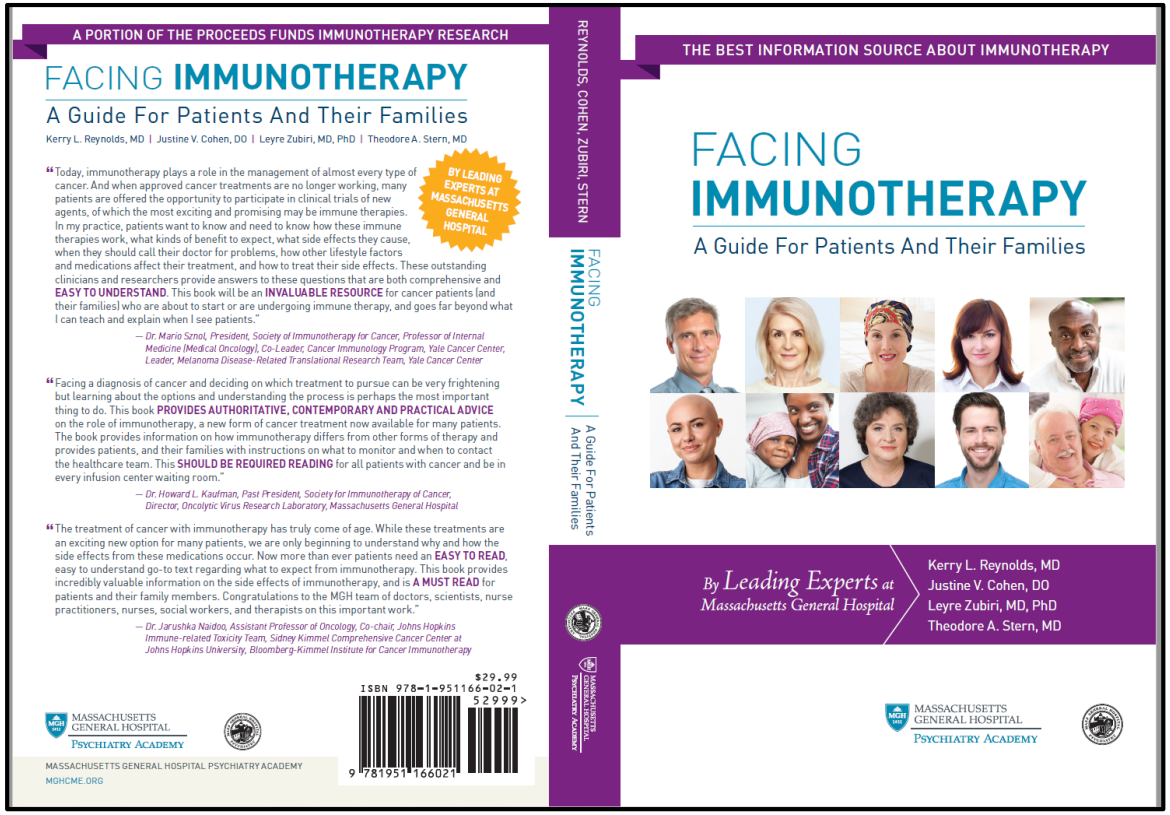
Next Best Steps

Download the FREE management guidelines

- Haanen, Annals of Oncology, 2017
- Puzanov, Journal of ImmuoTherapy of Cancer, 2017
- Brahmer, Journal of Clinical Oncology, February, 2018
- **NCCN Guidelines, May, 2021**



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Thank You

Patients and Families
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Dr. Meghan Mooradian, Thoracic Oncology, MGH
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Mike Podolfi, Informatics, Partners ECare
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QUESTIONS

A Teaching Affiliate of Harvard Medical School

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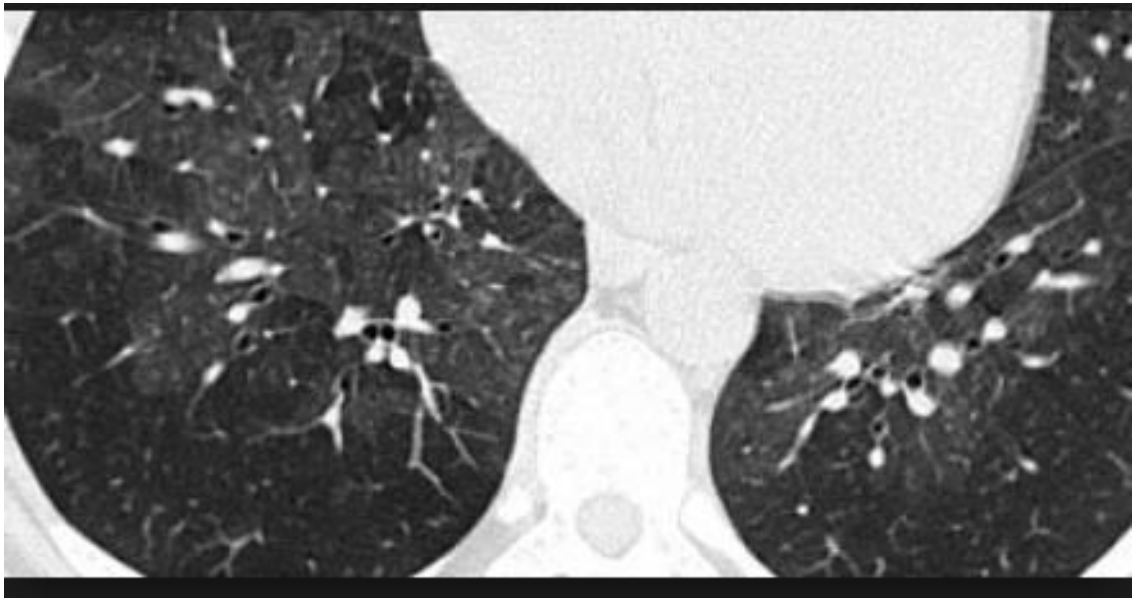
Case 2

Case #2

- ID: 65 y/o M with metastatic **melanoma**
- PMH: prostate cancer (in remission), depression, HL
- Prior treatments: High dose IL-2 and adoptive cell transfer therapy at the NCI. **Radiation** to brain and spine
  - Treatment Course
    - June 1st: C1D1 on a clinical trial. Combination **nivolumab** and **ipilimumab**
    - July 31st: C2D1 reported 2 weeks of **non-productive cough, DOE, pleuritic pain**, night sweats and increased fatigue
    - Chest CT: “New diffuse bilateral centrilobular **groundglass opacity** with superimposed areas of peribronchiolar consolidation within the right middle lobe, and peripheral areas of consolidation with central lucency ("reverse halo") concerning for hypersensitivity pneumonitis with organizing pneumonia secondary to drug reaction.”

Clinical Presentation

53% Dyspnea
35% Cough
12% Fever
7% Chest pain
33% Asymptomatic



Incidence

- PD1/PDL1 – 3%
- CTLA4 + PD1 – 10%
- Real World – 19%

Naidoo, JCO, 2016
Delauney, Eur Respir J, 2017
Suresh, J Thorac Oncol, 2018

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Differential Diagnosis

- Infection/pneumonia
- Disease - lymphangitic carcinomatosis, pseudoprogression
- Pulmonary edema
- COPD/bronchioloitis
- Alveolar hemorrhage
- Pleural and pericardial effusions
- And consider……

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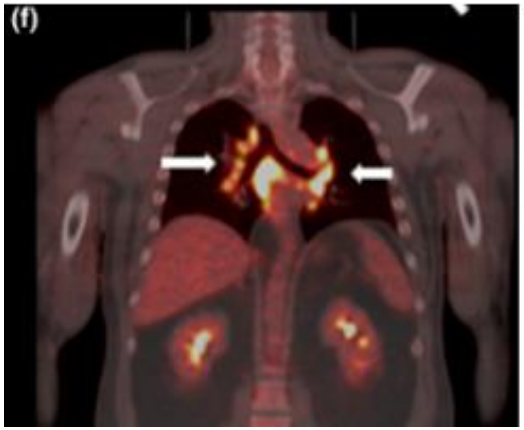
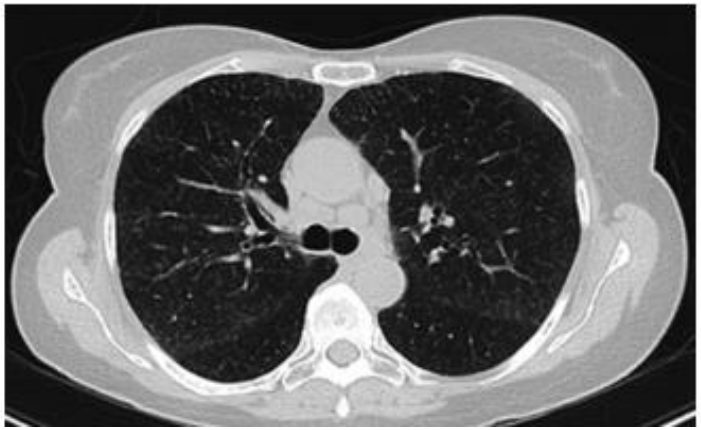
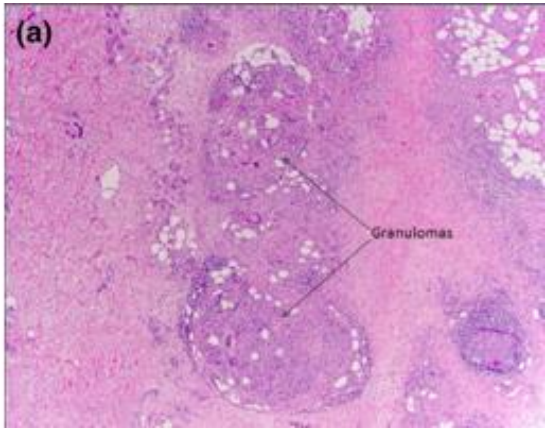
Sarcoidosis







Lomax, Int J Rheum Dis, 2017

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Pneumonitis

Work-Up

- It is a diagnosis of exclusion. Need to rule out active infection, worsening metastatic disease, medication induced ILD/IPF, hypersensitivity pneumonitis, CHF.
- Sputum/induced, viral panel, chest CT, bronchoscopy depending on level of suspicion. Decision to bronch is individualized.
- Chest CT, review with experienced radiologist
  - Ground-glass opacities (37%), Cryptogenic-organizing penumonia-like (COP-like) (19%), Hypersensitivity type (22%), Interstitial type (7%), Pneumonitis – not otherwise specified (15%)

Naidoo, JCO, 2016

Management

Grade	Naidoo 2017 (N = 43)	Delaunay 2017 (N = 64)	Definition	Management
1	40%	15%	Asymptomatic, confined to one lobe or 25% of lung parenchyma	Hold drug, repeat chest CT in 4 weeks, if resolved restart drug
2	33%	39%	Symptomatic, involves more than 1 lob or 25-50% of parenchyma	Pred 1 mg/kg, monitor closely, hold drug
3	23%	26%	Severe, involves all lung lobes or > 50% lung parenchyma	Hospitalize, IV antibiotics, IV steroids, consider bronch, if no improvement in 48 hours, escalate to grade 4
4	2%	9%		
5	2%	9%		

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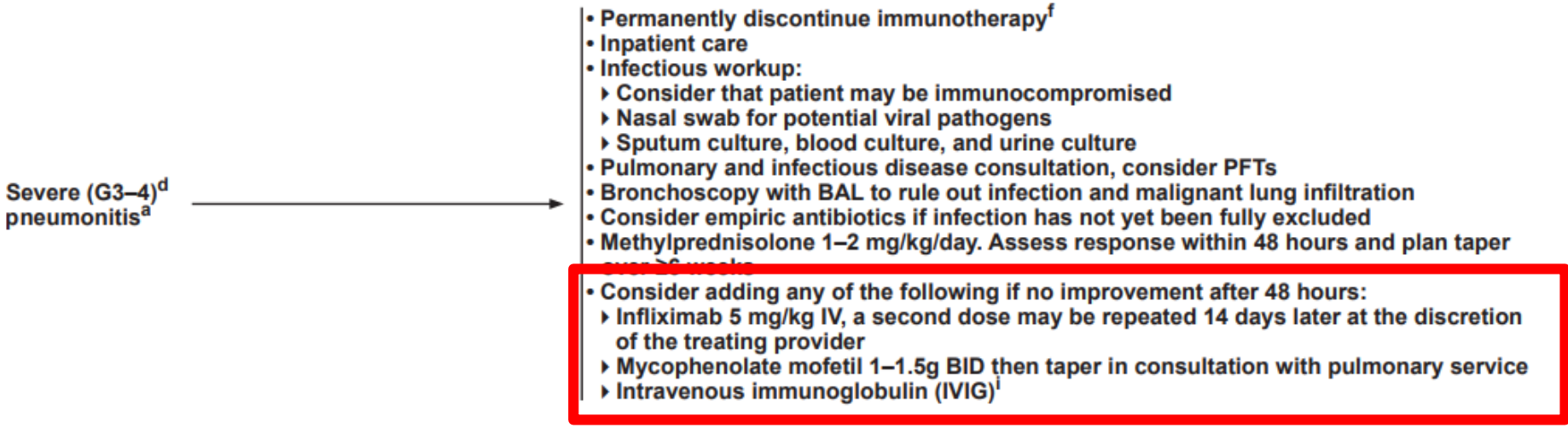
Steroid Refractory Disease

Lack of Evidence Regarding Choice of 2nd Line Immunosuppression



- Ongoing Clinical Trial – PI: Naidoo

Nishino, Clin Cancer Res, 2016
Chipman, J Oncol Pharm Pract, 2017

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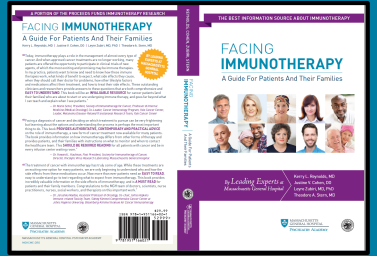
Key Points



- Immune Checkpoint Inhibitors Are Now Standard of Care (> 50 indications, in over 15 types of Cancer)
- Success of Single Agent ICI Led To Combination Approvals
- Be Aware Of The Unique “Autoimmune” Toxicity Profile
- irAEs are Typically Grade 1/2 but Severe irAEs Can Be Fatal
- Steroids are a Mainstay of Treatment
- Beware of “fatigue” and “shortness of breath”

Amazon.com, Facing Immunotherapy

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