



Management of Complex IO Toxicity

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Society for Immunotherapy of Cancer

#SITC2019

Disclosures

Research Funding:
BMS

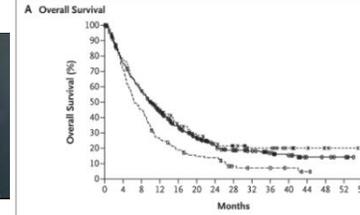
Consulting:
Bristol Myers-Squibb
AstraZeneca
Roche/Genentech
Merck

Honoraria:
Roche/Genentech

The Revolution: Immunotherapy for Cancer

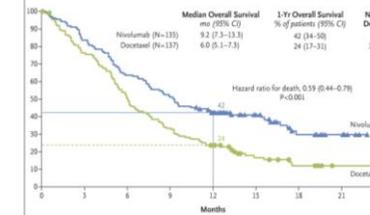


Anti-CTLA-4 in Melanoma



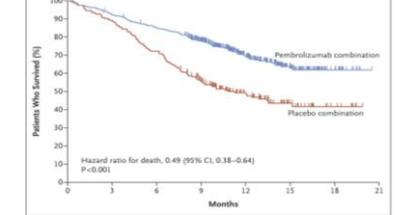
First approval of an immune checkpoint inhibitor for cancer

Anti-PD-1 in NSCLC



First approval of immunotherapy for lung cancer

Anti-PD-1+Chemo in NSCLC



Immunotherapy-based combinations approved

Anti-PD-1 for early stage cancer

William Coley uses live bacteria as immune stimulant to treat cancer

IL-2 is approved as an anti-cancer therapy

First preventive vaccine used for cervix cancer

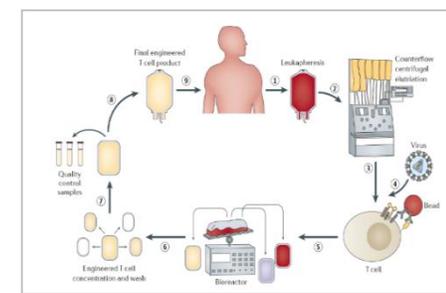
Tumor-specific antigens discovered in mice

First responses seen with anti-cancer vaccine

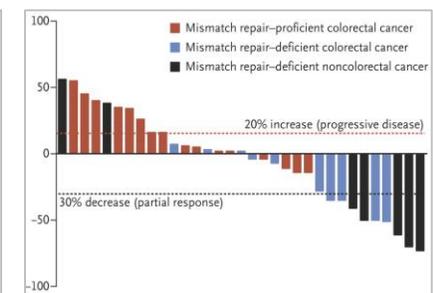
First regulatory approval of an anti-cancer vaccine

First regulatory approval of CAR T-cell therapy

Tumor agnostic approval for Anti-PD-1



CD19-CARs in ALL

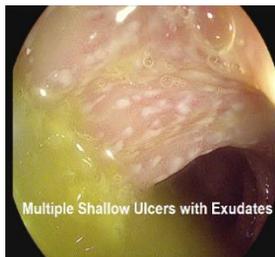


MSI-high tumors

Melero et al, *Nat Rev Clin Oncol* 2014
 Fesnak AF et al, *Nat Rev* 2016
 Maude et al, *NEJM* 2014
 Hodi et al, *NEJM* 2010
 Slide Courtesy of Jarushka Naidoo

Immune-related Adverse Events

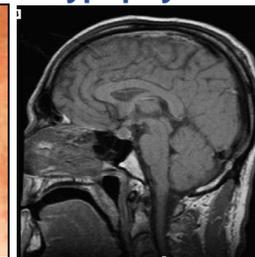
CTLA-4 colitis



Dermatitis



Hypophysitis



Organ-specific irAEs

Pneumonitis	Thyroiditis	Arthritis
Myocarditis	Hepatitis	Nephritis
Encephalitis	Colitis	Type I Diabetes
Uveitis	Pancreatitis	ITP

Coley's Toxin

IL-2

Anti-cancer vaccines

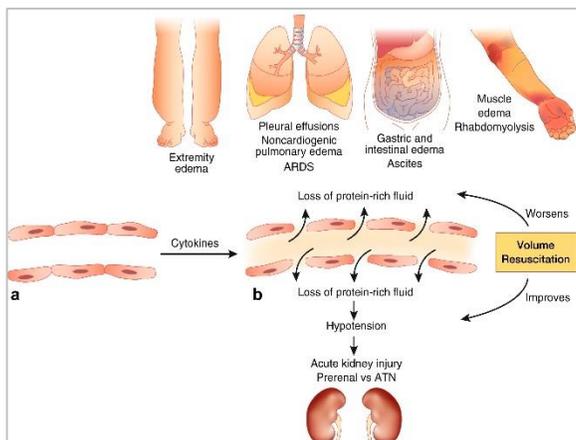
Anti-CTLA-4 Therapy

Anti-PD-1 Therapy

PD-1-based Combinations

1893 1957 1992 1998 2006 2010 2011 2014 2015 2017 2019

Fever
Hyperthermia

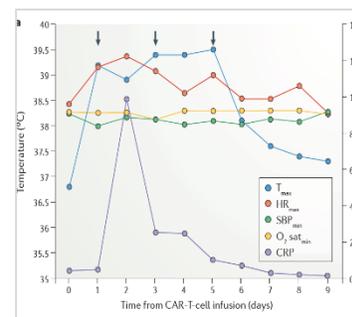


Capillary-Leak Syndrome

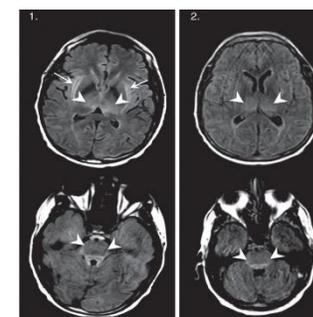
Slide Courtesy of Jarushka Naidoo

Fever
Injection-site reactions

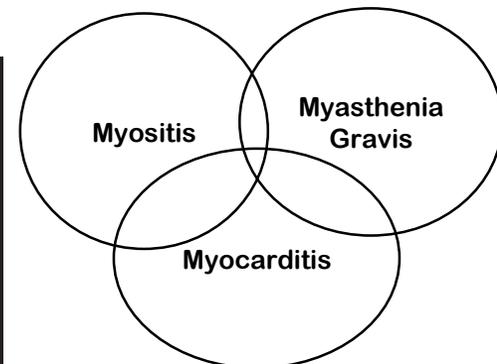
CAR T-cell therapy



Cytokine-Release Syndrome



CAR T Neurotoxicity



Multisystem irAE Syndromes

Immune-Related Toxicity

General Management Principles

- Always suspect an autoimmune toxicity
- Rule out competing diagnoses (?infection ?progression)
- Identify the toxicity (diarrhea vs. colitis)
- Grade the toxicity via CTCAE

Naidoo et al, *Ann Oncol* 2015

Grade 1:

- Supportive care
- Consider drug withhold

Grade 2:

- Withhold drug.
- Low-dose corticosteroids (prednisone 0.5-1mg/kg/day or equivalent).
- Consider re-dose if toxicity resolves to \leq Grade 1.

Grade 3-4:

- Discontinue drug.
- High-dose corticosteroids (prednisone 1-2mg/kg/day or equivalent) tapered over \geq 1 month once toxicity resolves to \leq Grade 1.

Immune-Related Toxicity Guidelines

- **ESMO**
 - Oncology expert consensus
- **SITC**
 - Multidisciplinary expert consensus
 - Panel event
- **ASCO/NCCN**
 - Multidisciplinary expert consensus
 - Cochrane review 204 articles
 - Collaborations with:
 - Oncology Nursing Society
 - SITC
 - Parker Institute
 - Friends of Cancer

Brahmer et al, *J Clin Oncol* 2018

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



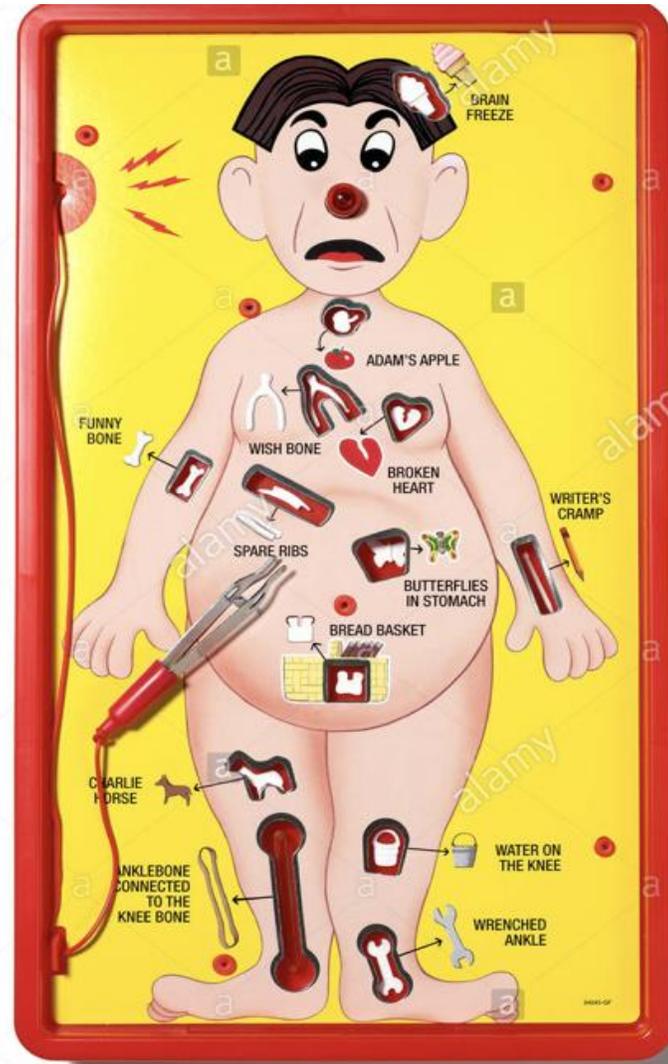
JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

Julie R. Brahmer, Christina Lachetti, Bryan J. Schneider, Michael B. Atkins, Kelly J. Brassil, Jeffrey M. Caterino, Ian Chau, Marc S. Ernstoff, Jennifer M. Gardner, Pamela Ginex, Sigrun Hallmeyer, Jennifer Holter Chakrabarty, Natasha B. Leighl, Jennifer S. Mammen, David F. McDermott, Aung Naing, Loretta J. Nastoupil, Tanyanika Phillips, Laura D. Porter, Igor Puzanov, Cristina A. Reichner, Bianca D. Santomaso, Carole Seigel, Alexander Spira, Maria E. Suarez-Almazor, Yinghong Wang, Jeffrey S. Weber, Jedd D. Wolchok, and John A. Thompson in collaboration with the National Comprehensive Cancer Network

What organ systems are affected by immunotherapy?

“It’s all fair game!”



Dermatologic

- Maculopapular Rash
- Pruritis
- Blistering Disorder

Gastrointestinal

- Diarrhea/Colitis
- Hepatic Toxicity
- Elevation in Amylase/Lipase
- Acute Pancreatitis

Endocrine

- Hyperglycemia/Diabetes Mellitus
- Thyroid
- Adrenal
- Hypophysitis

Pulmonary Toxicity

- Pneumonitis

Renal Toxicity

- Nephritis

Ocular Toxicity

Nervous System

- Myasthenia Gravis
- Guillian-Barre Syndrome
- Peripheral Neuropathy
- Aseptic Meningitis
- Encephalitis
- Transverse Myelitis

Musculoskeletal

- Inflammatory Arthritis
- Myalgias/Myositis

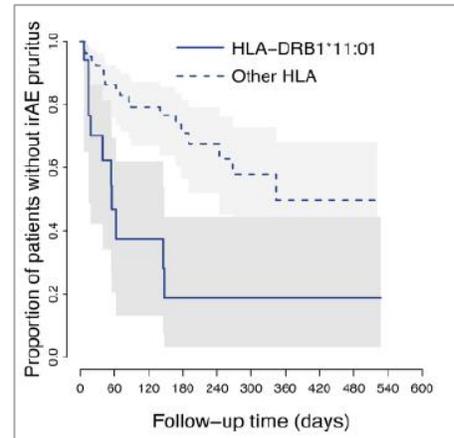
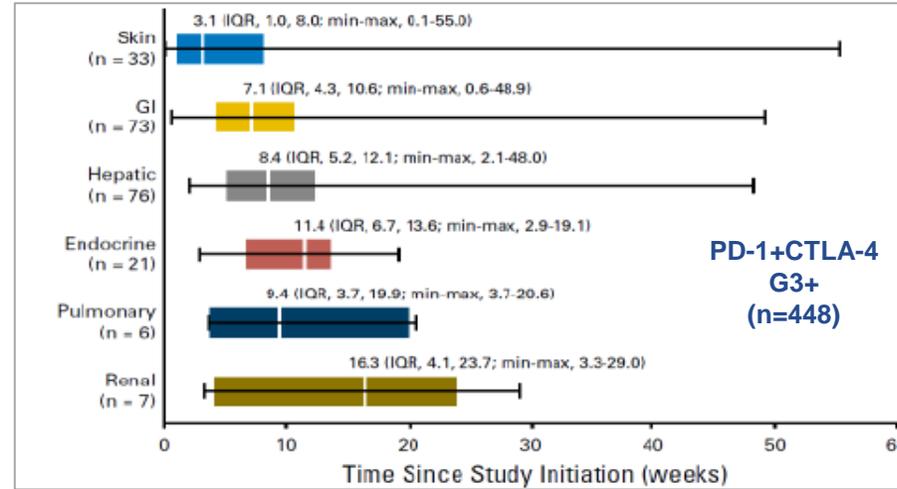
PD-1+/-CTLA4 Skin Toxicities

- First and most frequent irAE
- Phenotypically diverse
- Most common is maculopapular rash
- <5% cases lead to treatment discontinuation
- Grading/severity based in BSA and presence of selected features*

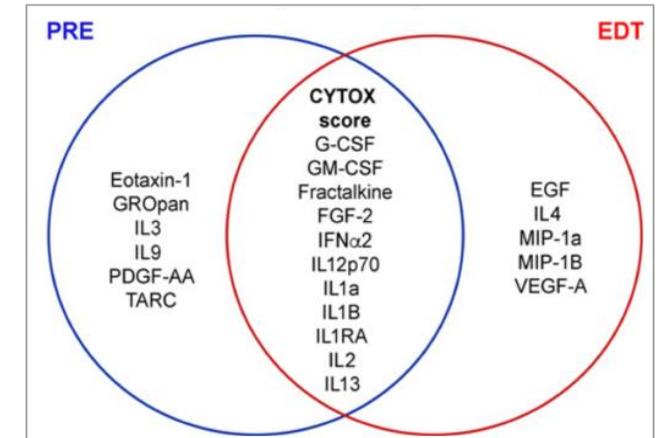
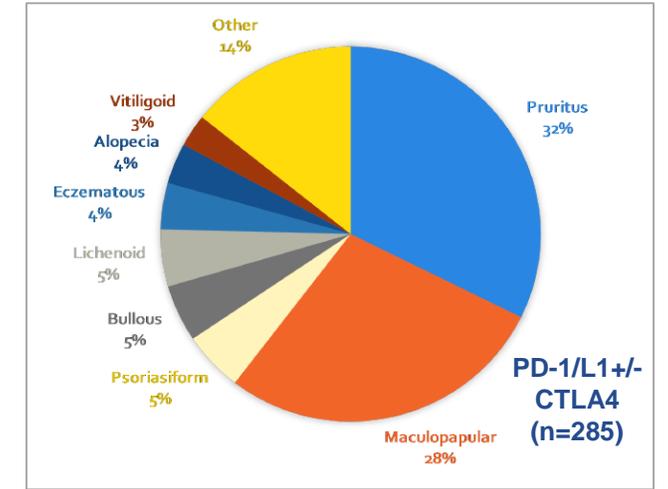
Mechanisms

- HLA subtypes and cytokine panels may predict for cutaneous irAE

Santini, *Cancer Immunol Res* 2018
 Phillips, *J Clin Oncol* 2019
 Lim, *Clin Can Res* 2018
 Ali, *Eur J Cancer* 2019
 Slide Courtesy of J Naidoo



CTLAE or PD-1 (n=102)



G3+ irAE (n=49)

Colitis

Classically due to CTLA-4 Inhibition



Severe inflammation with large deep ulcerated mucosa



Moderate to severe inflammation with diffuse/patchy erythema, superficial ulcers, exudate, LOV



Mild inflammation with mild patchy erythema, aphtha, edema or normal mucosa

Diagnostic Workup

- Rule out alternative diagnosis: C.difficile, other GI infections
- Distinguish between diarrhea and colitis
- Consider invasive testing with colonoscopy particularly if refractory to steroids

Management

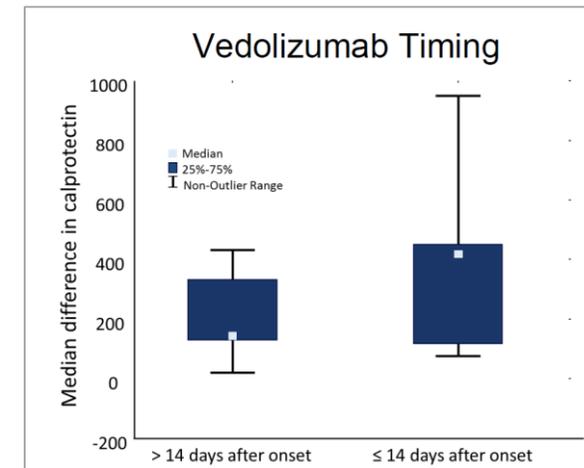
- Low threshold for starting corticosteroids
- No benefit for corticosteroid pre-treatment (budesonide)
- Colitis that is slow to improve/refractory to steroids: treat with anti-TNF
- Infliximab 5mg/kg once or twice q14 days
- Consider Vedolizumab if still refractory

Steroid-Refractory Colitis

Lessons from IBD

- **Stool lactoferrin is a stool biomarker for colitis**
 - 90% concordance with histologic inflammation
 - 70% sensitivity for endoscopic abnormality
- **Stool calprotectin**
 - Associated with presence of ulcers on endoscopy
- **High-risk features on endoscopy**
 - Associated with need for TNF-inhibition, hospitalization
- **Vedolizumab**
 - Anti-integrin $\alpha 4\beta 7$ mAb, used for IBD
 - Responses in steroid-refractory CTLA-4 colitis, follow calprotectin

	Lactoferrin (+) N (%)	Lactoferrin (-) N (%)	Scope Findings	Calprotectin (SD)
Abnormal Scope	42 (70)	4 (36)	Ulcers	465 (363)
Normal Scope	18 (30)	7 (64)	Non-Ulcer Inflammation	213 (184)
Abnormal Histology	54 (90)	3 (27)	Normal	152 (133)
Normal Histology	6 (10)	8 (73)	P	0.006



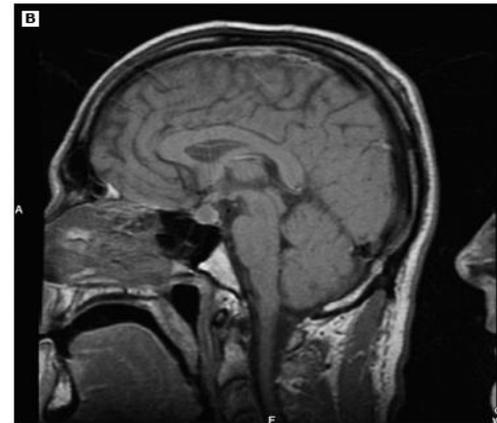
Specific irAEs

Endocrine Toxicities – other than Thyroid disease

- **Other Main Endocrine irAEs**
 - Hypophysitis (CTLA-4 mainly)
 - Type 1 Diabetes Mellitus (important to differentiate from Type II Diabetes Mellitus)
 - Adrenal insufficiency (clear cases few)
 - ?Hypogonadism ?Hypoparathyroidism
- **Diagnostic Workup:**
 - Laboratory monitoring for hormonal function.
 - MRI pituitary for suspected hypophysitis – if headaches or visual changes present
- **Management**
 - Endocrinology consult can help to distinguish primary from secondary effects
 - Hormonal replacement as needed
 - Consider steroids for pituitary dysfunction



06/30/04 - Baseline (4.5 mm)



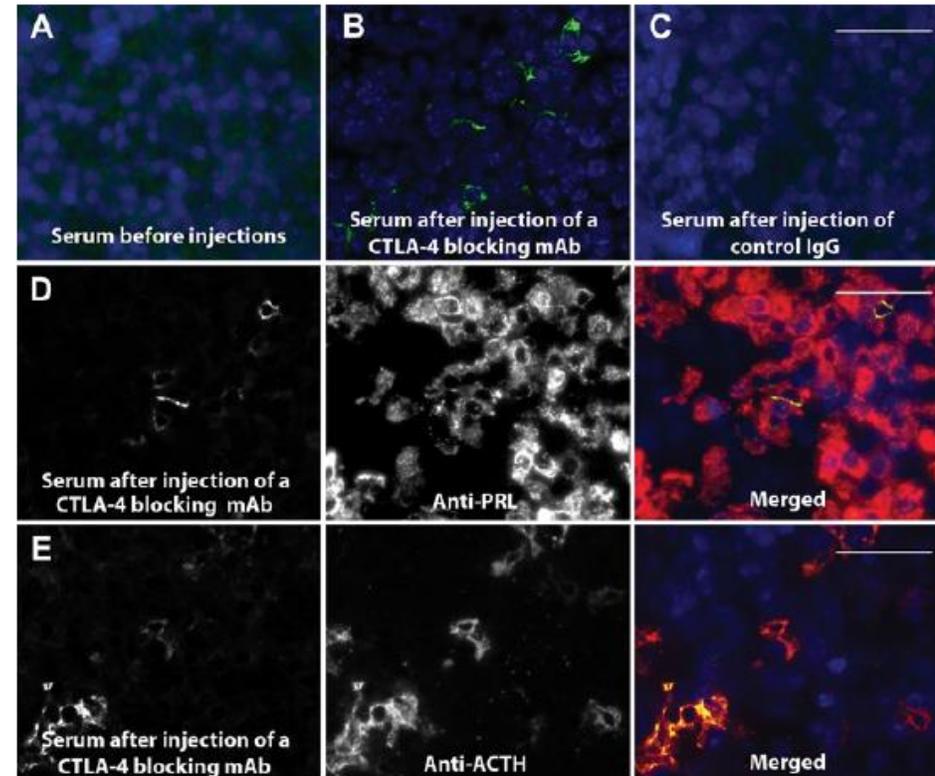
12/03/04 - Headache/fatigue (10.8 mm)

Hypophysitis

- Classic endocrine toxicity of CTLA4 inhibition
- Symptoms: fatigue, weakness, headache, confusion
- 75% abnormal MRI
- 60% abnormal TFTs

Pathobiology

- CTLA-4 expressed in pituitary
- Antibodies bind to pituitary cells after exposure to drug
- Deposition of complement/pathway activation
- Antibody bonding directly to pituitary cells
- Ipilimumab directly activates complement (IgG1)

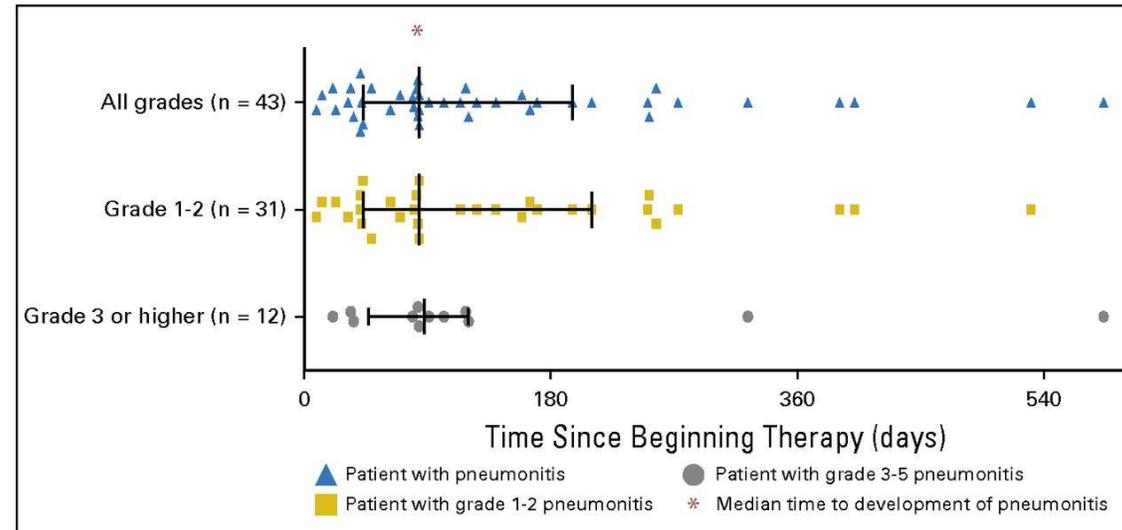


Iwama et al, *Sci Transl Med* 2018
Slide Courtesy of J Naidoo

PD-1/PD-L1 Inhibition Pneumonitis

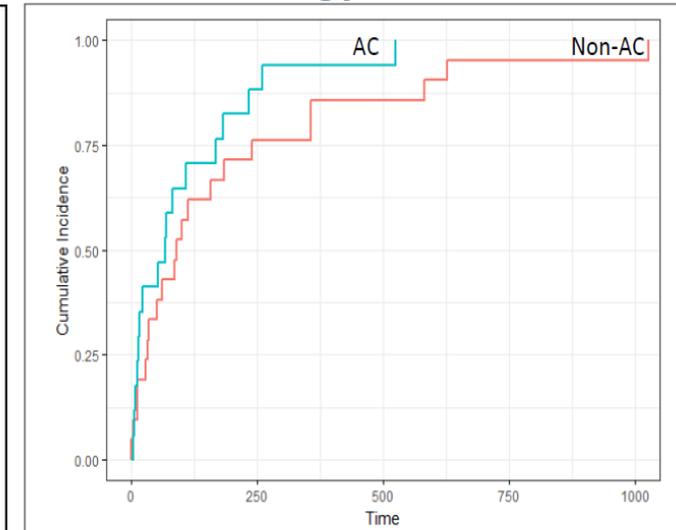
Radiologic Subtypes	Representative Image
Cryptogenic-Organizing Pneumonia-like (COP-like) (n=5, 19%)	
Ground Glass Opacifications (GGO) (n=10, 37%)	
Interstitial Type (n=6, 22%)	
Hypersensitivity Type (n=2, 7%)	
Pneumonitis Not-Otherwise Specified (n=4, 15%)	

Timing is unpredictable



MSKCC/MIA cohorts (n=43/449)

Tumor histology is a risk factor



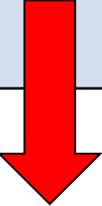
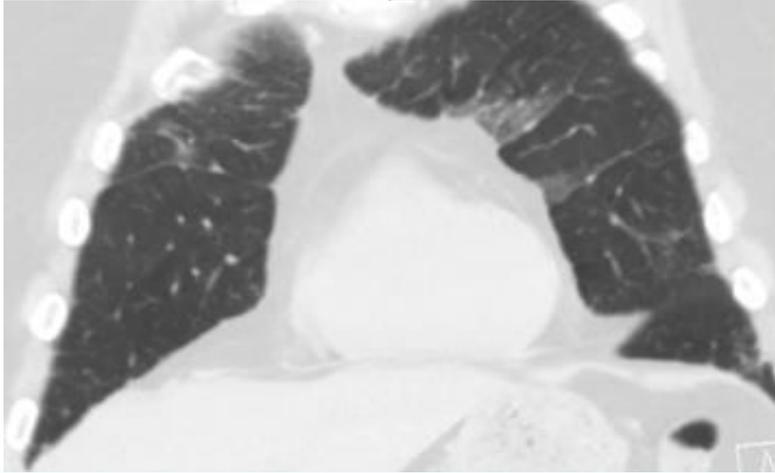
JHU Cohort (n=39/205)

Naidoo et al, *J Clin Oncol* 2016
Suresh, Naidoo et al, *J Thoracic Oncol* 2018



PD-1/PD-L1 Inhibition Pneumonitis

Mild (Gr 1)	Moderate (Gr 2)	Severe (Gr 3-4)
<ul style="list-style-type: none"> Consider holding immunotherapy Reassess in 1-2 weeks Pulse oximetry (resting and with ambulation) Consider CT chest w/ or w/o contrast Repeat CT in 4 weeks or as clinically indicated for worsening symptoms 	<ul style="list-style-type: none"> Hold immunotherapy Consult pulmonary specialist Must r/o infection (nasal swab, sputum, blood culture, urine culture) Bronchoscopy CT chest Empiric abx if infection not r/o Prednisone/methylprednisolone 1-2 mg/kg/day – monitor every 3-7 days 	<ul style="list-style-type: none"> Permanently d/c immunotherapy Inpatient care Infectious workup Bronchoscopy Methylprednisolone 1-2 mg/kg/day – assess response w/in 48 hours and plan to taper over 6 weeks If not improvement after 48 hours THEN

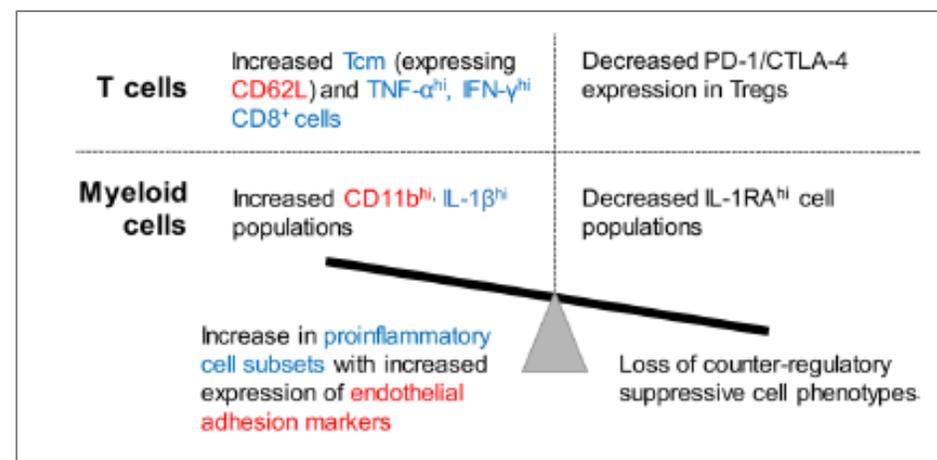
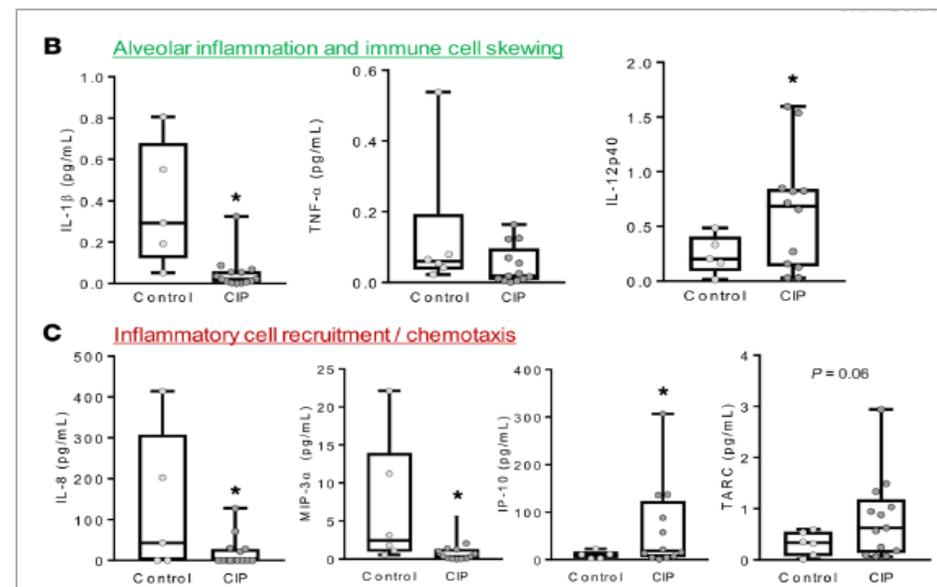
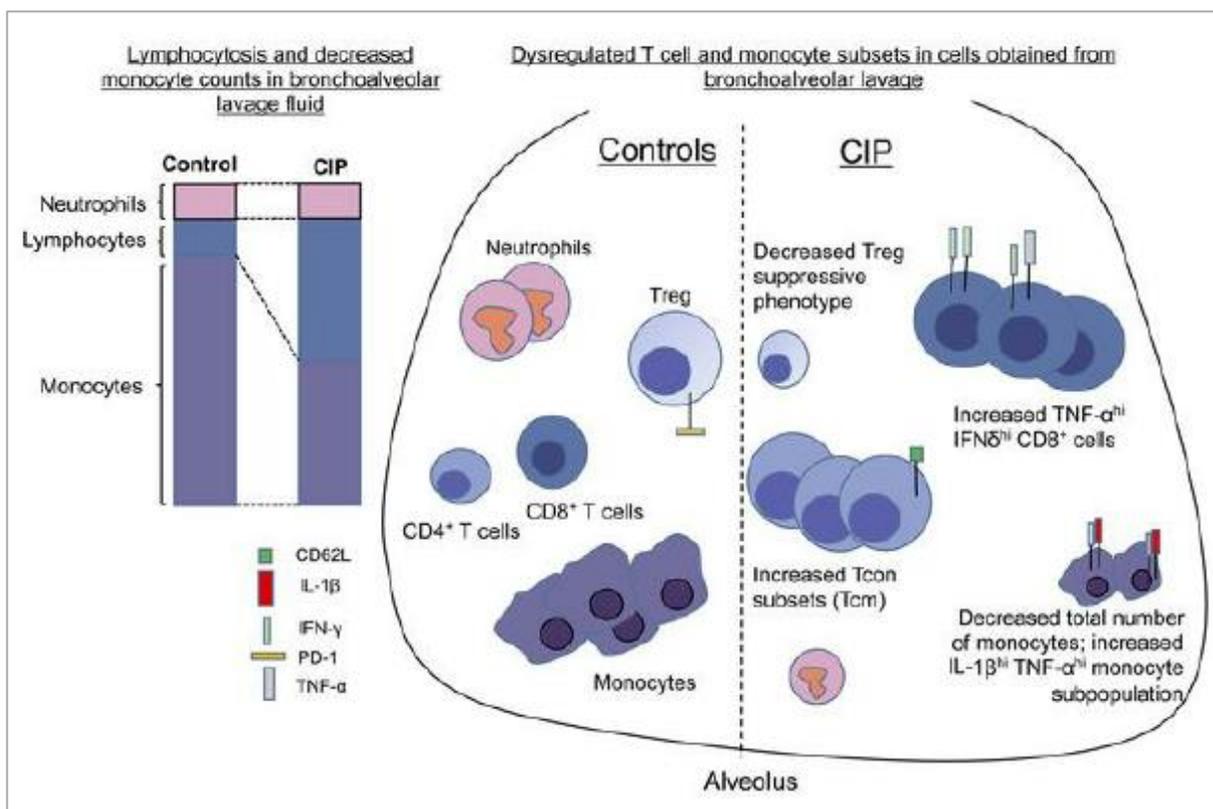


Consider adding:

- Infliximab 5mg/kg/IV, 2nd dose may be repeated 14 days at discretion of tx provider
- IVIg
- Mycophenolate mofetil 1-1.5g BID then taper in consultation w/pulmonary service

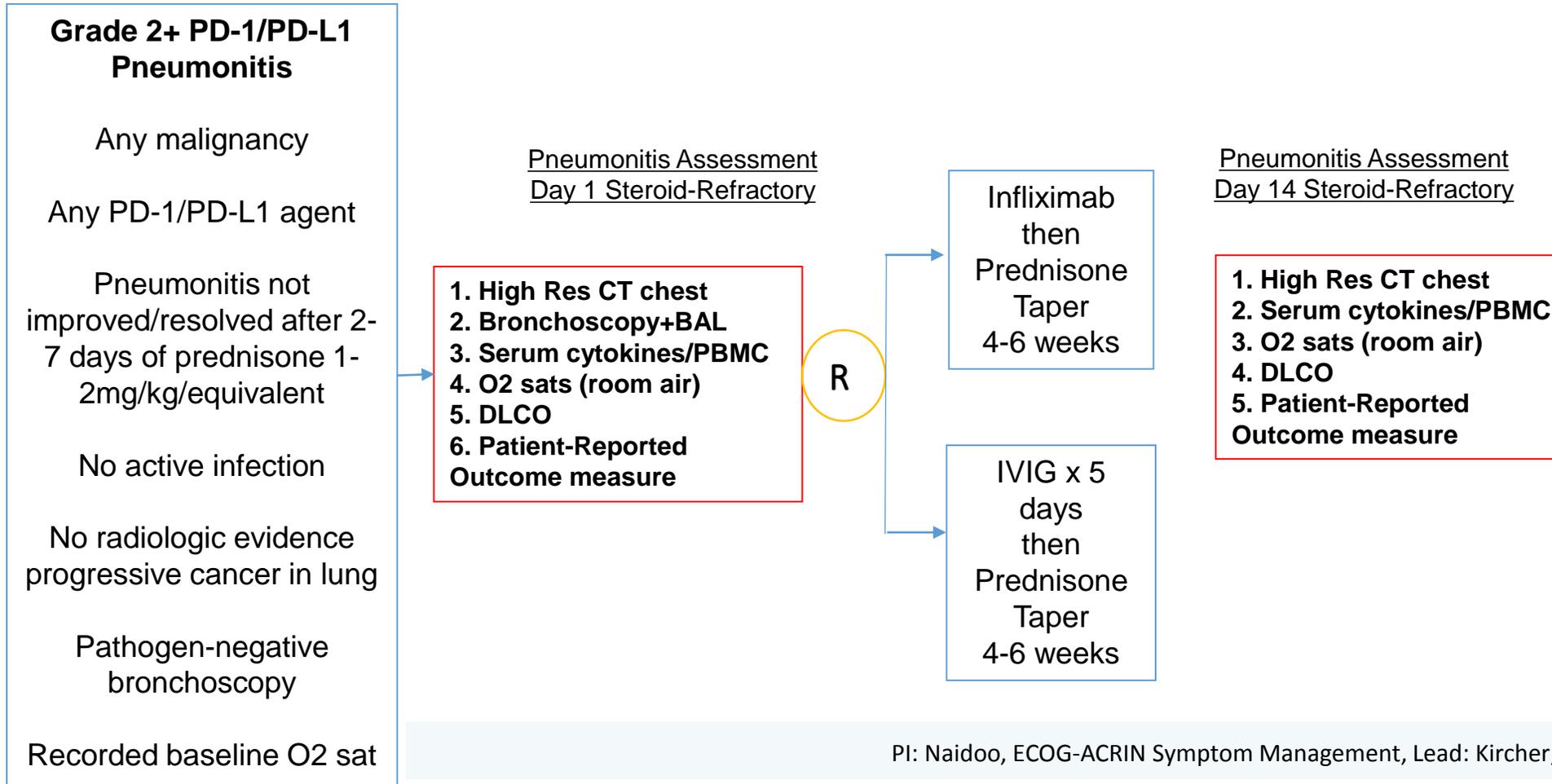
PD-1/PD-L1 Inhibition

Risk factors and T-cell mediated mechanisms for pneumonitis



Suresh, Naidoo et al, *J Clin Invest* 2019

Pneumonitis Future Directions: Prospective Studies for irAEs: Steroid-Refractory Pneumonitis



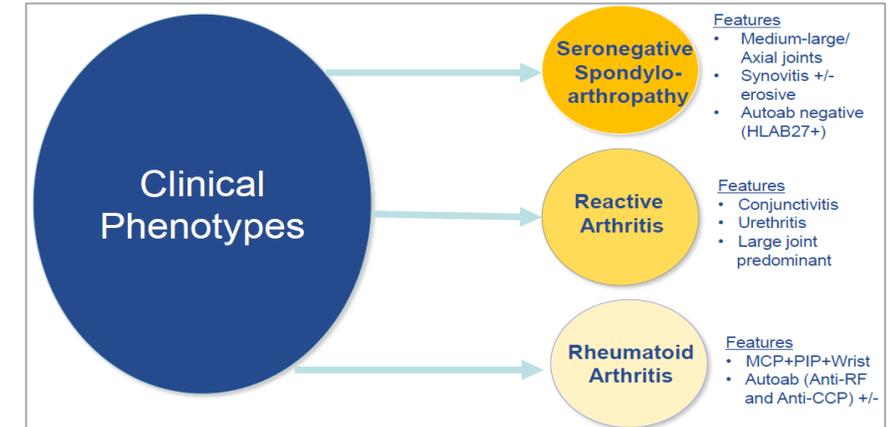
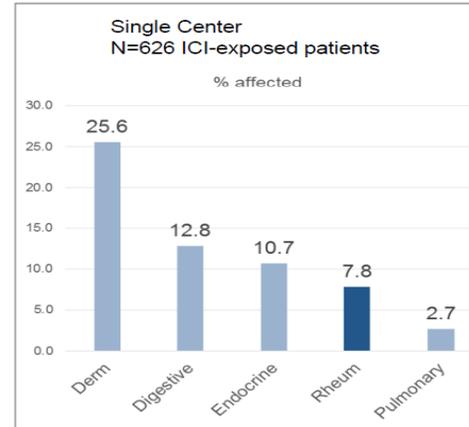
PI: Naidoo, ECOG-ACRIN Symptom Management, Lead: Kircher; Wagner

National Cancer Institute
Division of Cancer Prevention



PD-1/PD-L1 Inhibition Rheumatologic irAEs

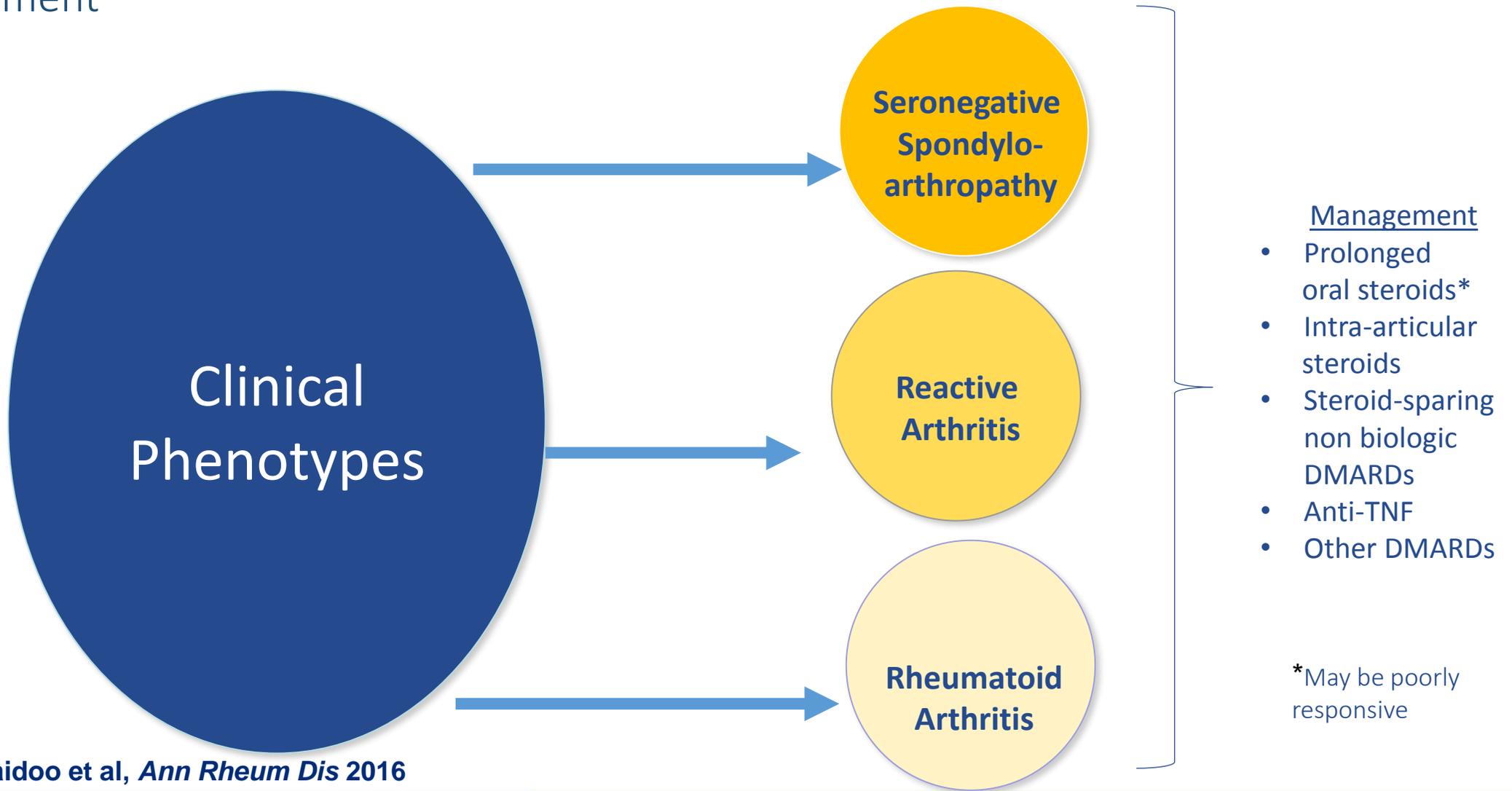
- Poorly recognized from RCTs
- Lack of standardized reporting (arthralgia, arthritis, joint pain, joint effusion-aggregate >20%)
- Spectrum:
 - Sicca syndrome
 - Polymyalgia rheumatica/Giant Cell Arteritis
 - Myositis (dermatomyositis, polymyositis)
 - Single Organ Vasculitis
 - Psoriasis, Psoriatic arthritis
 - Scleroderma, others



HLA allele/s	Odds Ratio (95% CI) ICI-induced IA vs. controls	p-value*
A*03:01	2.2 (0.9, 5.1)	0.07
B*08:01	0.9 (0.3, 2.6)	0.56
B*15:01	2.2 (0.7, 5.9)	0.12
B*27:05	0.6 (0.0, 4.0)	1.00
B*52:01*	5.0 (0.5, 24.1)	0.08
C*06:02	0.9 (0.3, 2.7)	1.00
C*12:02**	5.4 (0.6, 26.8)	0.07
DQB1*03:01	0.4 (0.1, 1.1)	0.06
DRB1*03:01	1.1 (0.4, 2.9)	0.81
DRB1*04:05	8.6 (1.7, 43.4)	0.04
At least 1 Shared epitope allele	2.3 (1.0, 5.1)	0.04

Cappelli et al, *Ann Rheum Dis* 2016
Kostine et al, *Ann Rheum Dis* 2018

Rheumatologic irAEs Management



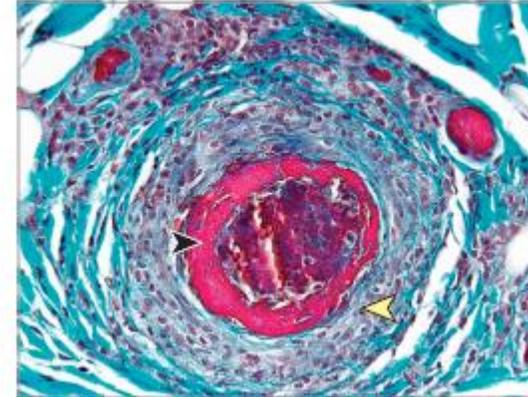
Cappelli, Naidoo et al, *Ann Rheum Dis* 2016

Rare irAEs

- Cardiac Toxicity
 - Myocarditis, Incidence: 1%
- Ocular irAEs
 - Episcleritis, scleritis, blepharitis, conjunctivitis, Incidence: <1%
- Renal
 - Tubulointerstitial nephritis, GN described, Incidence: <1%
- Pancreatic
 - Asymptomatic elevations amylase/lipase in preclinical CTLA-4
 - Rule out pancreatitis (CT, MRCP, ERCP, clinical exam), Incidence: <1%
- Neurologic
 - Myasthenia gravis, aseptic meningitis, encephalitis, neuropathy, GBS, <1%
- Hematologic
 - Aplastic anemia, pernicious anemia, ITP, acquired hemophilia A, MDS, <1%

PD-1/PD-L1/CTLA-4 Inhibition Neurologic irAEs

- Diverse Phenotype
- Neuromuscular phenotype more likely
- Time of onset can be unpredictable
- Rapid onset and life threatening



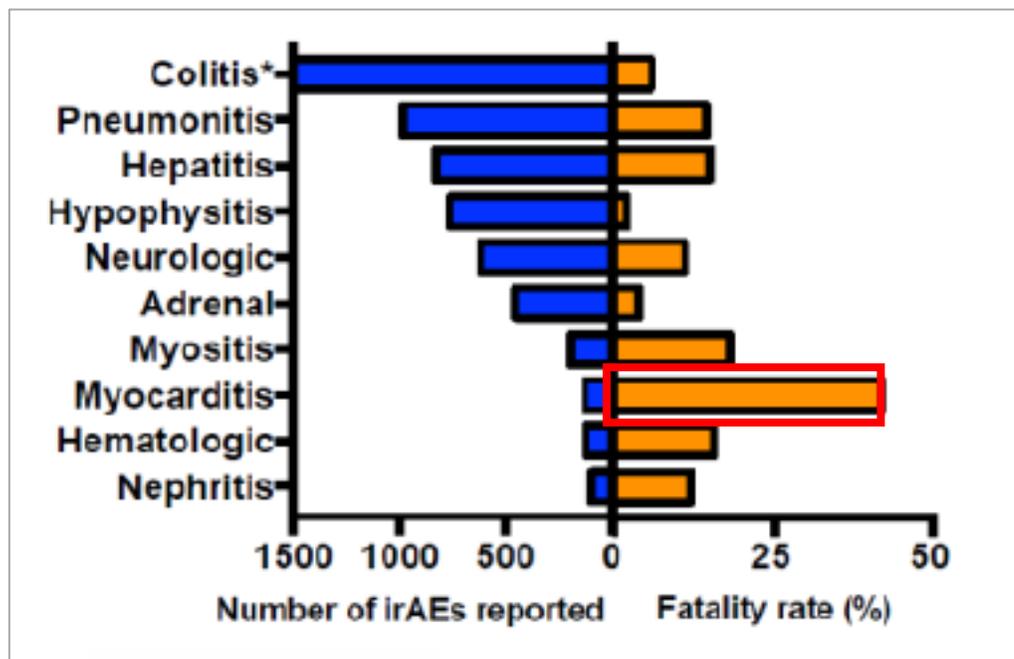
Treatment may include:

- Steroids
- IVIg
- Plasma exchange
- Rituximab

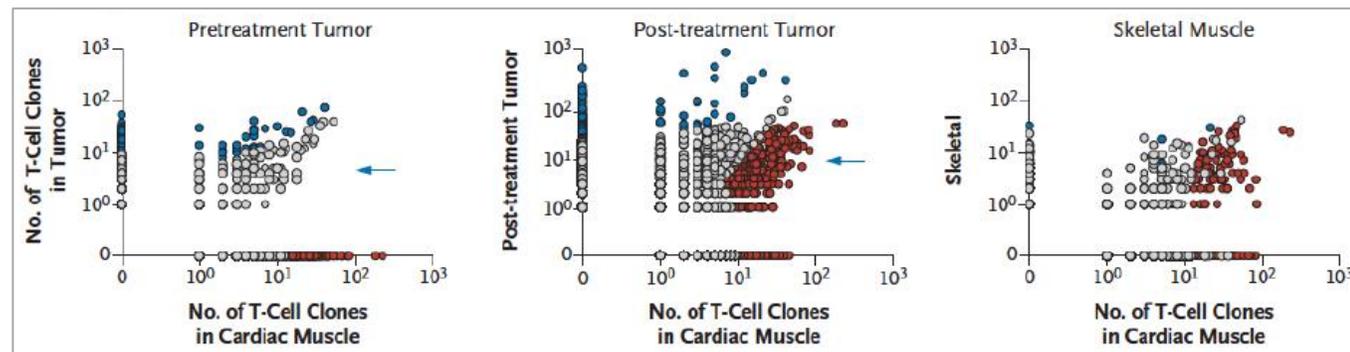
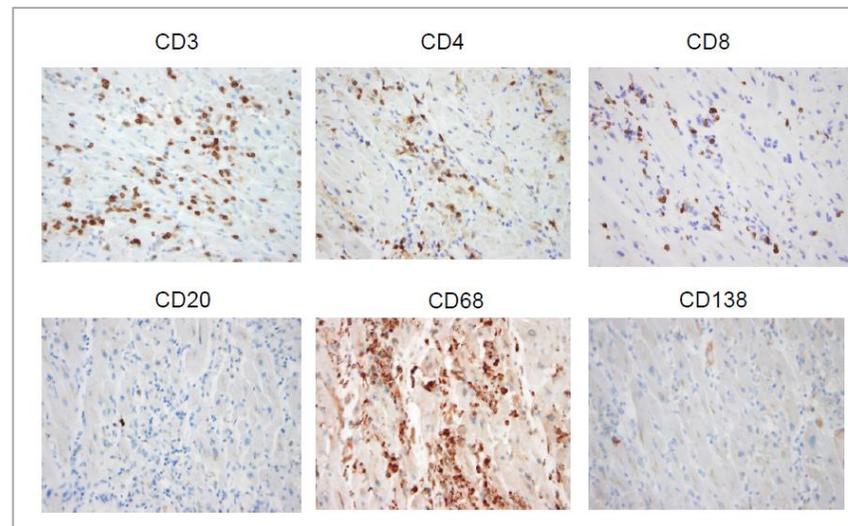
Kao J et al JAMA Neurol 2017

PD-1/CTLA4 Combinations Myocarditis

- Fatal toxicities are rare, 1.2%
- Myocarditis causes highest rate of fatality from combination ICI regimens



T-cell infiltrates in heart and skeletal muscle

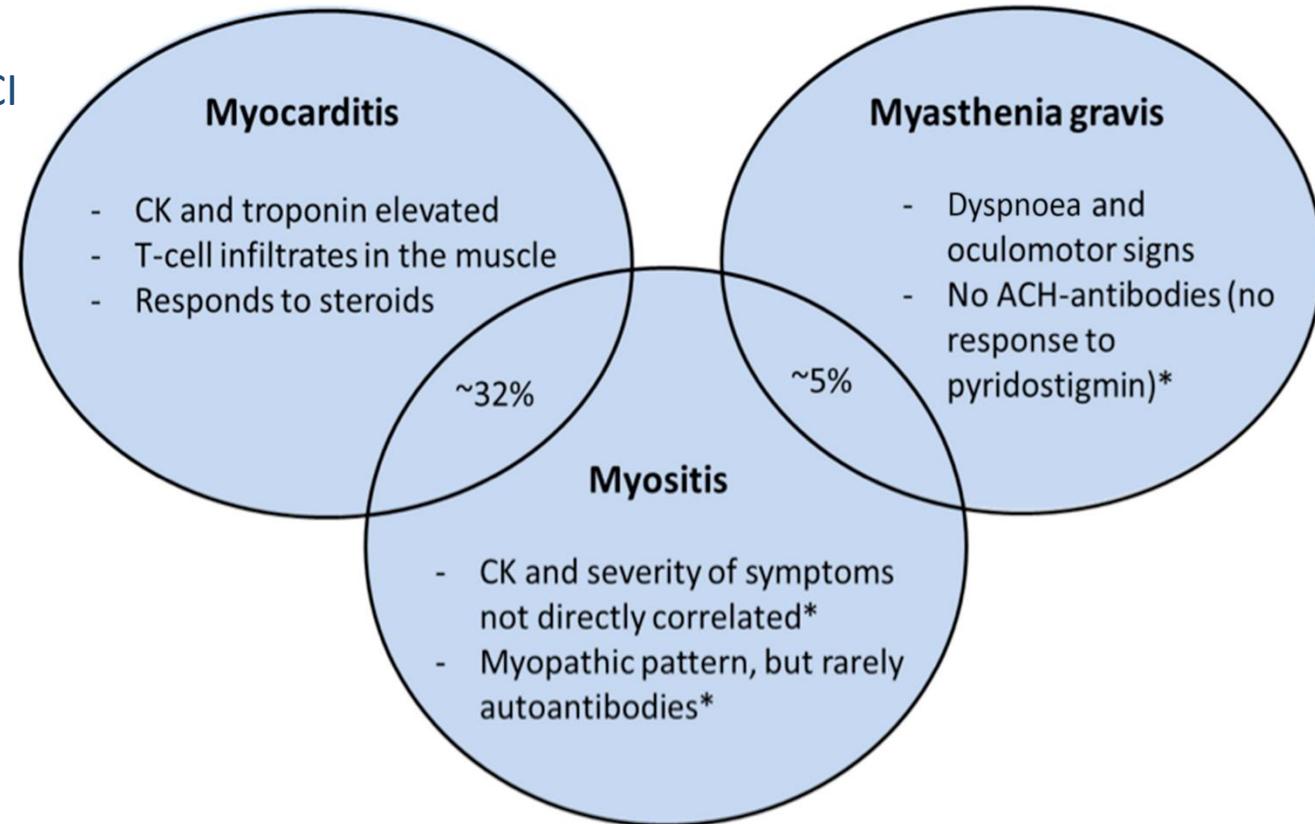


High dose steroids right away and if no improvement can try ATG

PD-1/CTLA4 Combinations

Multisystem irAEs/Overlap syndromes

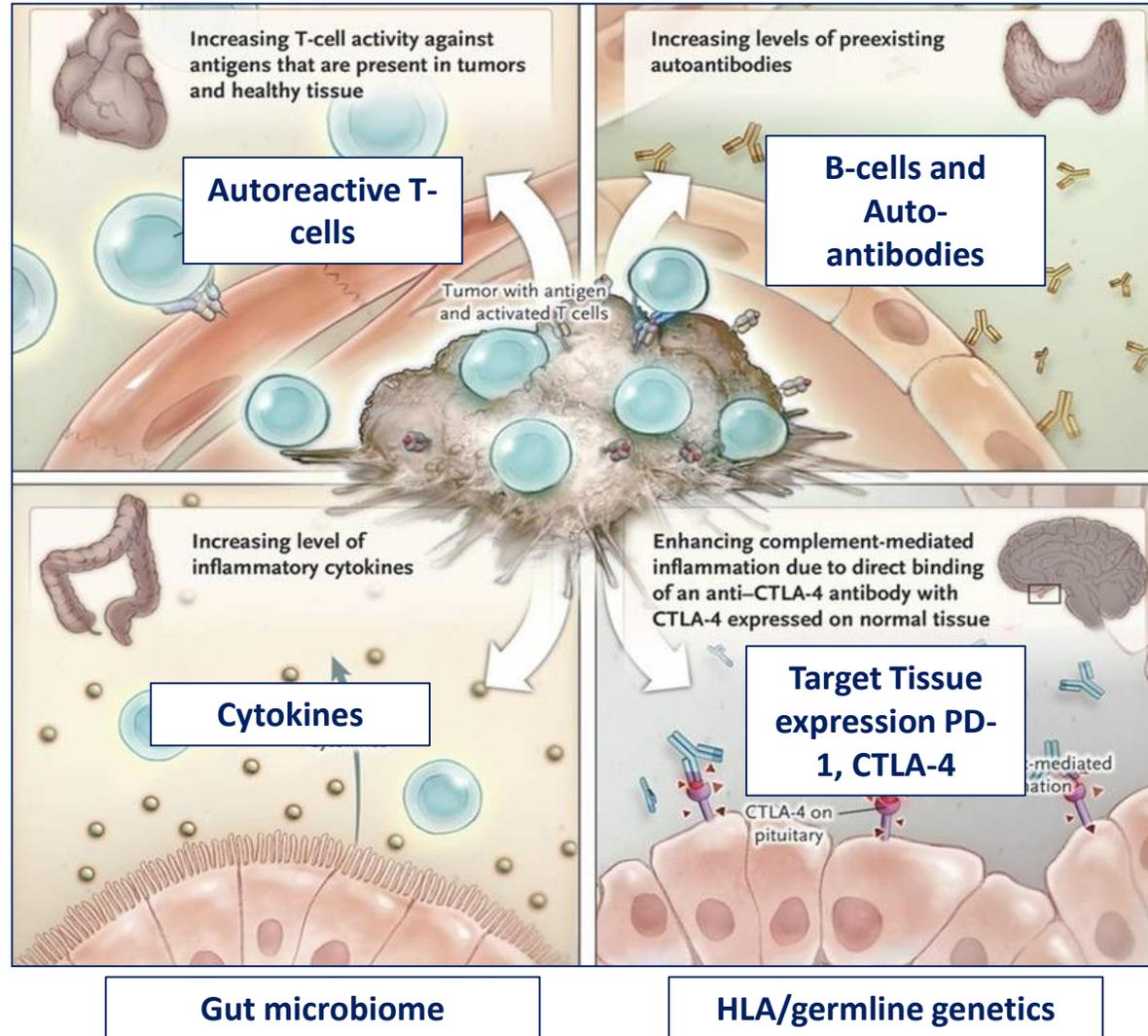
- 38 patients with metastatic skin cancers treated with ICI
- Myositis was the most frequent NM irAE
- 32% concomitant myocarditis.
- Time of onset: 1-115 weeks after the start of therapy.
- 49% G3+
- 2 fatalities
- 50% ongoing
- Role for surveillance CKs, ?troponin?



Moreira et al, *Eur J Cancer* 2018
Slide courtesy of J Naidoo

irAE Mechanisms

Colitis
Myocarditis



Hypophysitis
Thyroiditis
Skin toxicities
Neurologic irAEs

Dermatitis
All irAE
Colitis

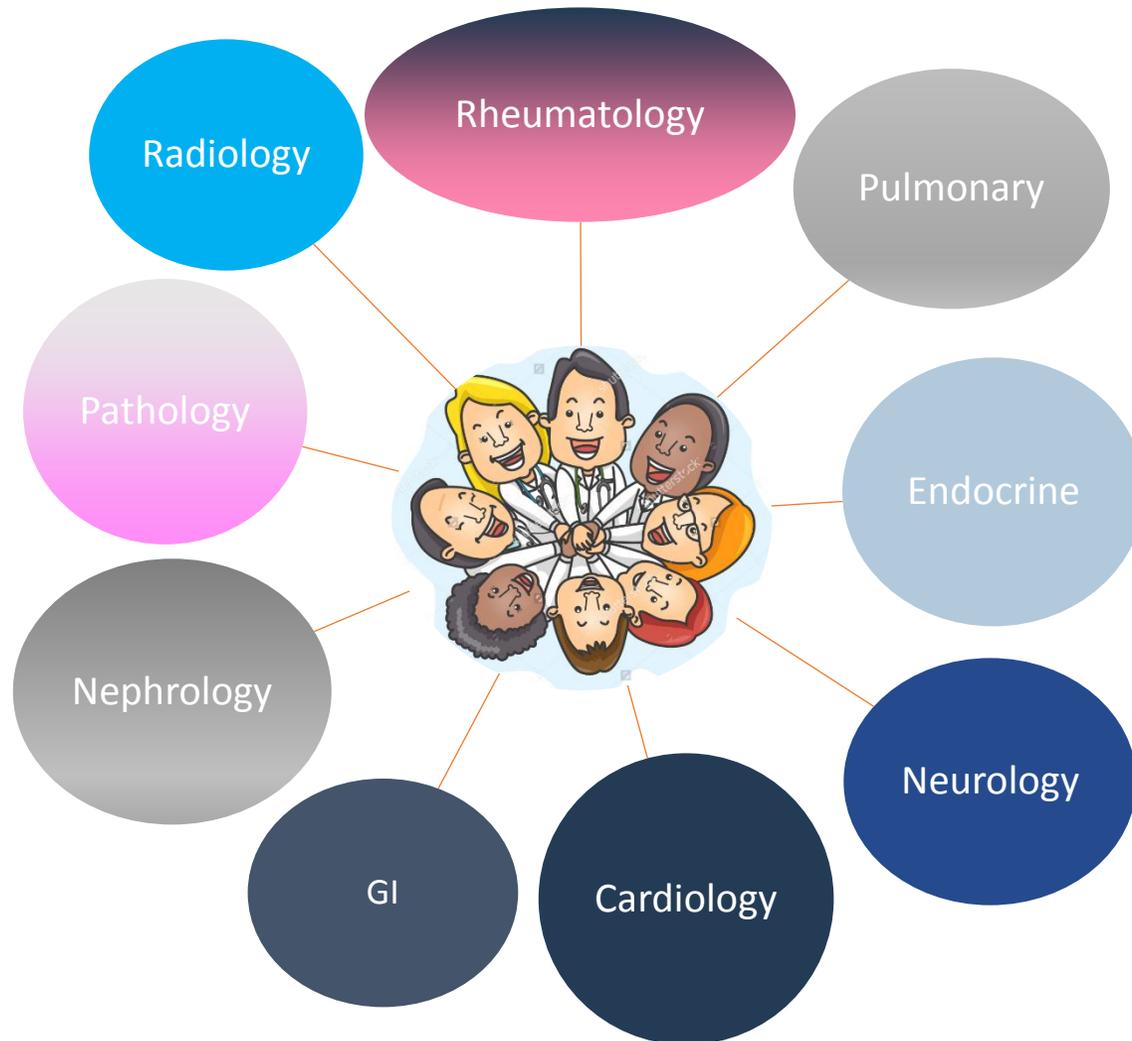
Hypophysitis
Type I DM

Colitis

Type I DM
Arthritis

Postow et al, *NEJM* 2018
Slide Courtesy of J Naidoo

JHH Immune-related Toxicity Teams



Clinical Goals

- Centralize discussion of complex irAE cases
- Discuss and refine guidelines
- Ordersets for irAEs

Translational Goals

- Examine serial biospecimens
- Propose prospective studies

Educational Goals

- Teaching booklets
- Group masterclasses

Co-Directors

Oncology: J Naidoo

Medicine: L Cappelli

Future Directions

Immune-related Toxicity Teams

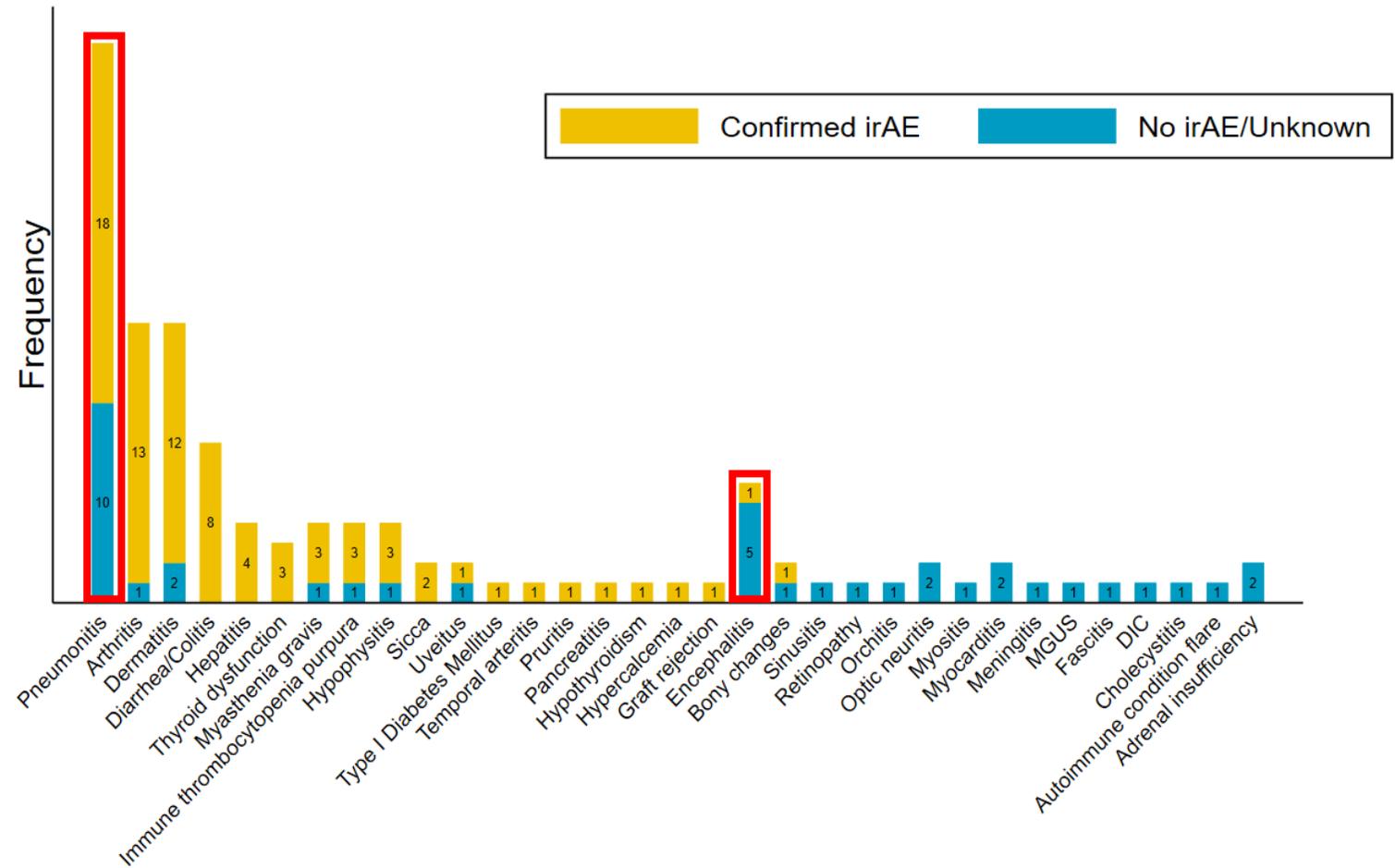
- These data identify the toxicities with the greatest diagnostic dilemmas:

- pneumonitis
- neurologic irAEs

- These data identify the services most needed for this new group of patients

- Pulmonary
- Rheumatology
- Dermatology
- Endocrinology
- Gastroenterology
- neurology

- A new irAE of osteitis was identified



Naidoo et al, *JNCCN* 2019

CPI Toxicity Management: Simplification

- **Mild symptoms** (grade 1): consider delay I-O, frequent re-assessment, & symptomatic treatment.
- **Moderate symptoms** (grade 2): delay I-O, evaluate early and frequently, consider steroids, once symptoms improve steroids are tapered over ≥ 4 weeks.
- **Moderate to severe** (grade 3-4): discontinue I-O, early assessment, corticosteroids, if no improvement within 2-5 days (depending on AE) consider additional immuno-suppressants.

- When on steroids, patient should receive stomach protection & consider prophylactic antibiotics. During steroid taper, patient should be evaluated frequently and for an extended period of time.

Immune-Related Toxicity Guidelines

- **ESMO**
 - Oncology expert consensus
- **SITC**
 - Multidisciplinary expert consensus
 - Panel event
- **ASCO/NCCN**
 - Multidisciplinary expert consensus
 - Cochrane review 204 articles
 - Collaborations with:
 - Oncology Nursing Society
 - SITC
 - Parker Institute
 - Friends of Cancer

Brahmer et al, *J Clin Oncol* 2018





Colleagues and Collaborators

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Kristen Marrone, MD

JHH Melanoma Program

Evan J. Lipson, MD

William Sharfman, MD

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Division of Cardiology

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