



# Immune-Related Adverse Events from Cancer Immunotherapy

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Society for Immunotherapy of Cancer

#SITC2019

# Disclosures

## **Research Funding:**

Merck

AstraZeneca

## **Consulting:**

Bristol Myers-Squibb

AstraZeneca

Roche/Genentech

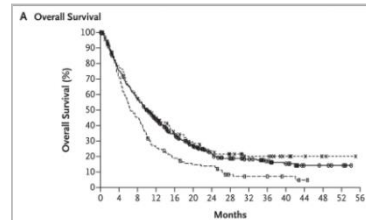
## **Honoraria:**

Bristol Myers-Squibb

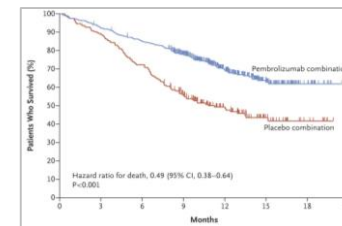
AstraZeneca/MedImmune

# Key Milestones Immunotherapy for Cancer

## Anti-CTLA-4 in Melanoma



## Anti-PD-1+Chemo in NSCLC



Immunotherapy-based combinations approved

Anti-PD-1 for early stage cancer

First approval of an immune checkpoint inhibitor for cancer

First regulatory approval of an anti-cancer vaccine

First preventive vaccine used for cervix cancer

IL-2 is approved as an anti-cancer therapy

William Coley uses live bacteria as immune stimulant to treat cancer

1893

1992

2006

2010

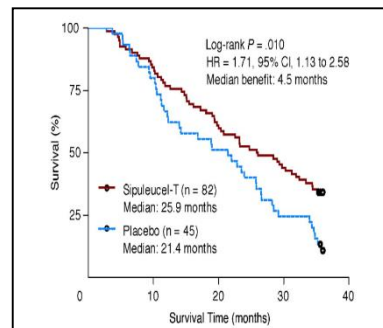
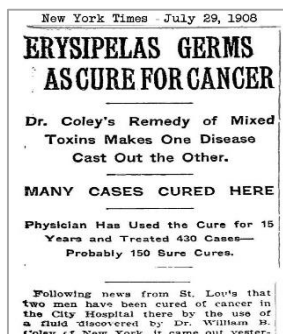
2011

2014

2015

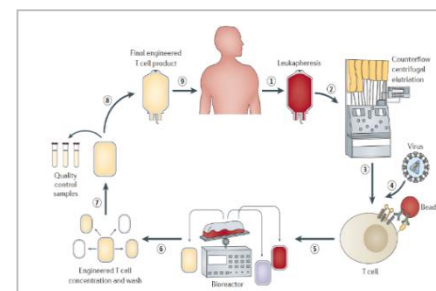
2017

2019



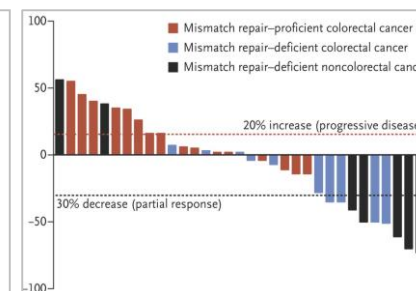
Sipuleucel-T  
Prostate Cancer

First regulatory approval of CAR T-cell therapy



CD19-CARs in ALL

Tumor agnostic approval for Anti-PD-1

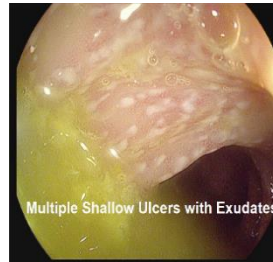


MSI-high tumors

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

# Key Milestones Immune-related Adverse Events

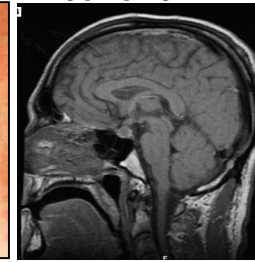
CTLA-4 colitis



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

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2011

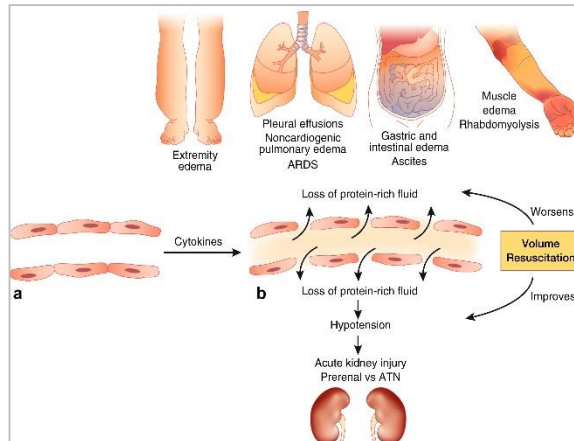
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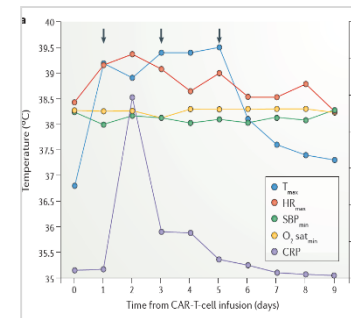
Fever  
Hyperthermia



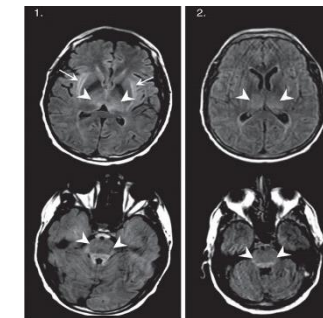
Capillary-Leak Syndrome

Fever  
Injection-site  
reactions

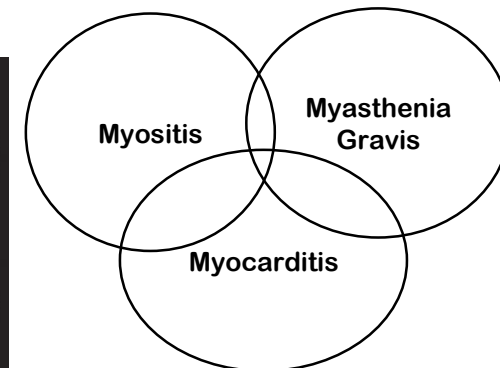
CAR T-cell therapy



Cytokine-Release Syndrome



CAR T Neurotoxicity



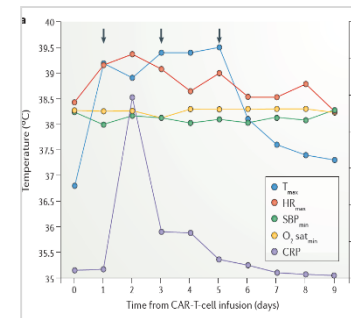
Multisystem irAE Syndromes

# Key Milestones

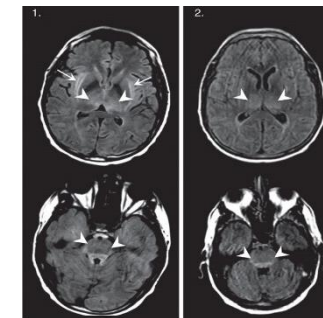
## Immune-related Adverse Events

1893      1957      1992      1998      2006      2010      2011      2014      2015      2017      2019

CAR T-cell therapy



Cytokine-Release Syndrome

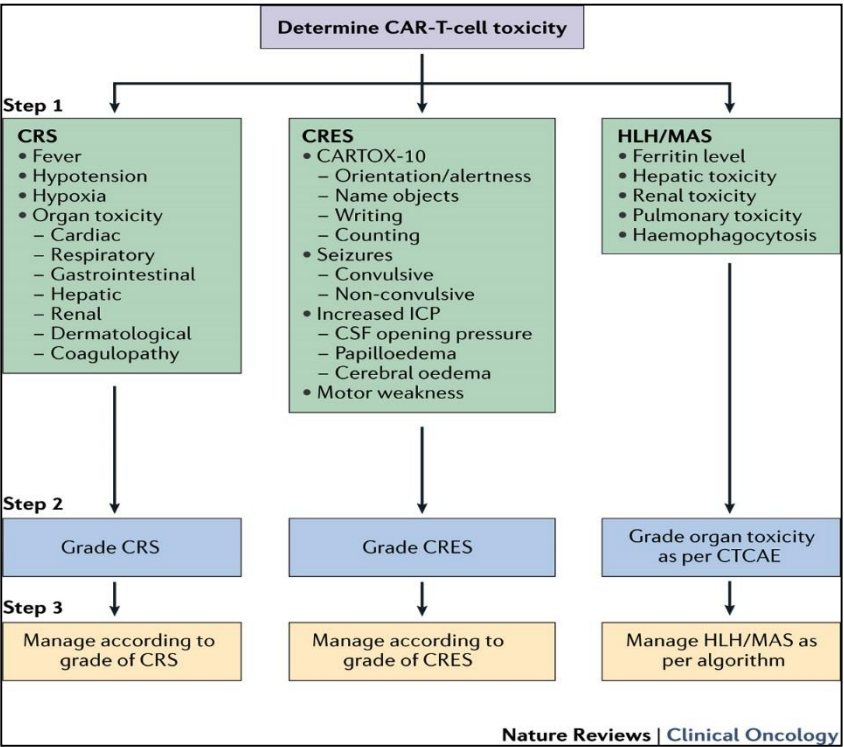


CAR T Neurotoxicity

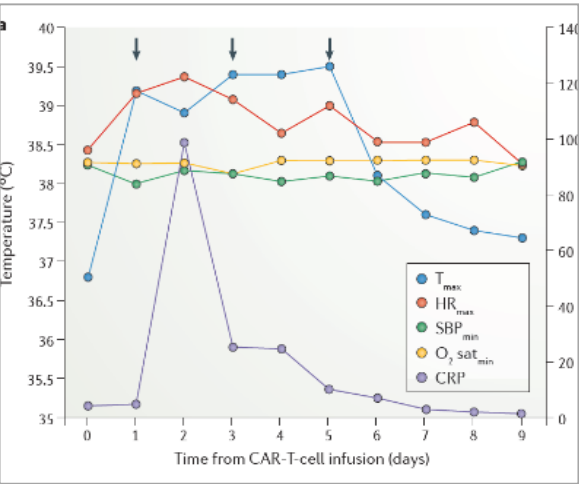
# CAR T-cell Therapy

## Cytokine Release Syndrome

- Most common CAR-T Toxicity
- severe CRS can evolve into fulminant haemophagocytic lymphohistiocytosis (HLH)



CRS Grade	Anti-IL-6	Steroids	Supportive Care
Grade 1 (fever > 38°C)	CRS > 3 days	N/A	<ul style="list-style-type: none"> <li>• Antibiotics</li> <li>• GCSF if neutropenic</li> </ul>
Grade 2 (fever/hypotension)	Tocilizumab 8mg/kg (4 doses max)	refractory hypotension Dex 10mg q6	<ul style="list-style-type: none"> <li>• IV fluids, pressors</li> <li>• Manage as G3 is no improvement in 24hr</li> </ul>
Grade 3 (+pressors)	Tocilizumab 8mg/kg (4 doses max)	Dex 10mg q6	<ul style="list-style-type: none"> <li>• IV fluids, pressors,</li> <li>• Echocardiogram</li> <li>• ICU, oxygen</li> </ul>
Grade 4 (+ventilatory support)	Tocilizumab 8mg/kg (4 doses max)	Dex 10mg q6 Methylpred 1g/day if refractory	<ul style="list-style-type: none"> <li>• ICU care</li> <li>• Mechanical ventilation</li> <li>• Organ toxicity management</li> </ul>



Day 4, MMSE 29/30  
I love Shawnee, KS.

Day 5, MMSE 27/30  
Shawnee, KS.

Day 6, MMSE 29/30  
I miss my kids.

Neelapu et al, *Nat Rev Clin Oncol* 2018  
 Thompson et al, *JNCCN* 2019, NCCN guidelines  
 Lee et al, *Biol Blood Marrow Transplant* 2018

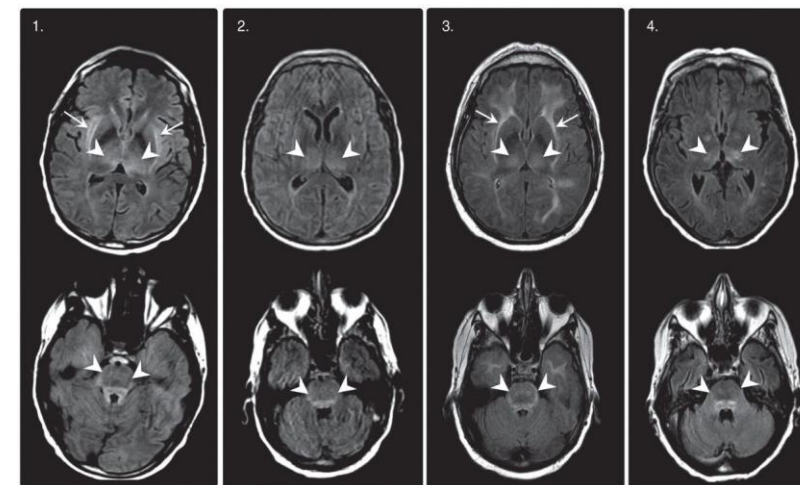
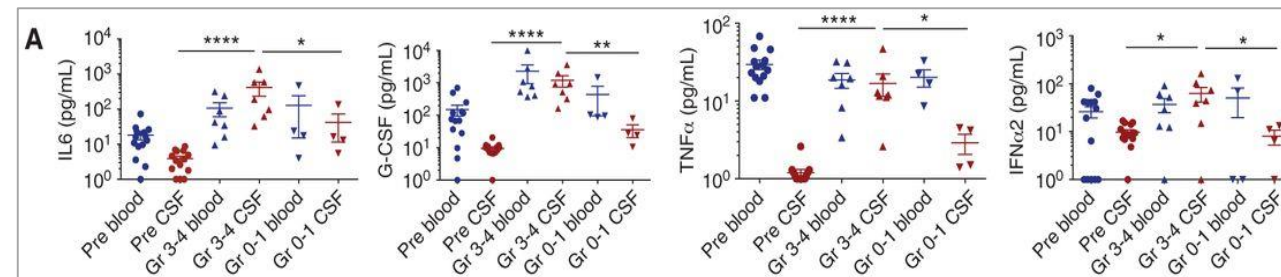


# CAR T-cell Therapy

## CAR T Neurotoxicity

- 'Immune effector cell Encephalopathy' (ICE score, 0-9)
- Orientation, naming, follow commands, writing, attention
- Rare cases of rapid-onset and lethal diffuse cerebral edema
- Can occur alone or with CRS

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7-9	3-6	0-2	0
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens to tactile stimulus	Unroutable
Seizure	N/A	N/A	Any clinical seizure/on EEG	Prolonged/life-threatening seizure
Motor Findings	N/A	N/A	N/A	Hemi or paraparesis, deep focal motor weakness
Raised ICP/cerebral edema	N/A	N/A	Focal edema on imaging	Diffuse cerebral edema on imaging, cranial N palsy, Cushing's triad, Decorticate posture

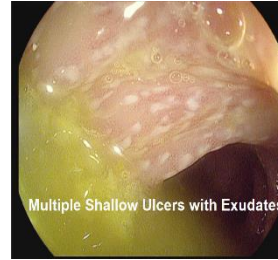


- Severe neurotoxicity in 53 CAR-T B-ALL pts, associated with:
  - high pretreatment disease burden
  - higher peak CAR T-cell expansion in blood
  - early/higher pro-inflammatory cytokines in blood
  - grade and CSF protein levels, IL6, IL8, MCP1, and IP10
  - elevated levels of NMDA receptor agonists in CSF

Neelapu et al, *Nat Rev Clin Oncol* 2018  
 Thompson et al, *JNCCN* 2019, NCCN guidelines  
 Lee et al, *Biol Blood Marrow Transplant* 2018

# Key Milestones Immune-related Adverse Events

CTLA-4 colitis



Dermatitis



Hypophysitis



Anti-CTLA-4 Therapy

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# Immune-Related Toxicity

## General Management Principles

- Suspect an autoimmune toxicity
- Monitor for endocrine toxicities (TSH)
- Rule out competing diagnoses  
(?infection ?progression ? co-morbidity)
- Identify/Grade the toxicity  
(diarrhea vs. colitis; CTCAE grade)
- Consult an organ-specialist if needed

Adapted from 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/equivalent).
- Consider re-dose if resolves  $\leq$  Grade 1.

### **Grade 3-4:**

- Discontinue drug.
- High-dose corticosteroids  
(prednisone 1-2mg/kg/day/equivalent) taper over  $\geq$  4-6 weeks  
until  $\leq$  Grade 1.
- Consider additional immunosuppression  
\*antiviral/fungal prophylaxis

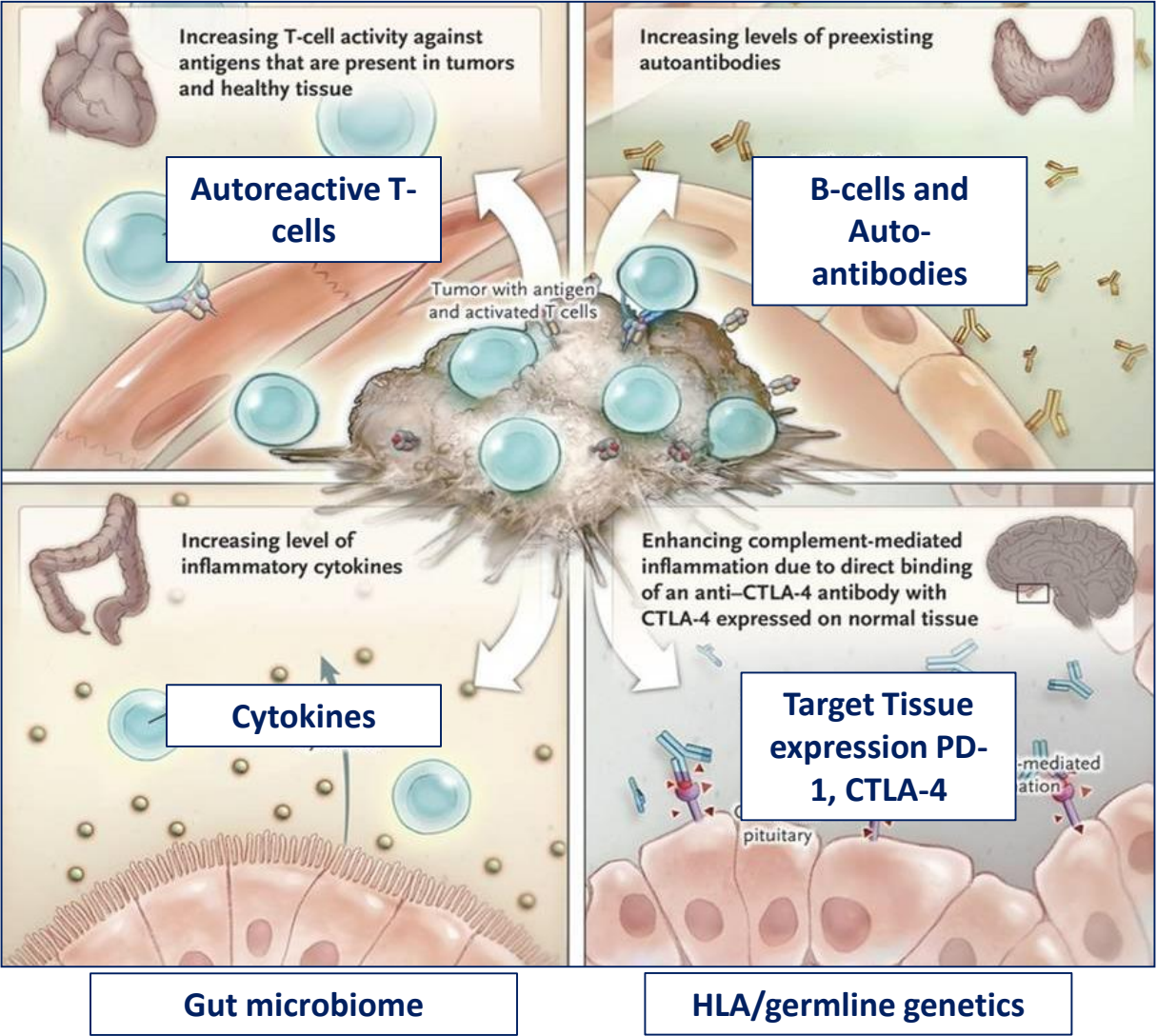
# irAE Mechanisms

## Translational Research

Colitis  
Myocarditis

All irAE  
Colitis  
Dermatitis

Colitis



Hypophysitis  
Thyroiditis  
Skin toxicities  
Neurologic irAEs

Severity and  
Timing irAEs

Type I DM  
Hypophysitis

Type I DM  
Arthritis

Postow et al, *NEJM* 2018

# CTLA-4 Inhibition Colitis



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

## Management

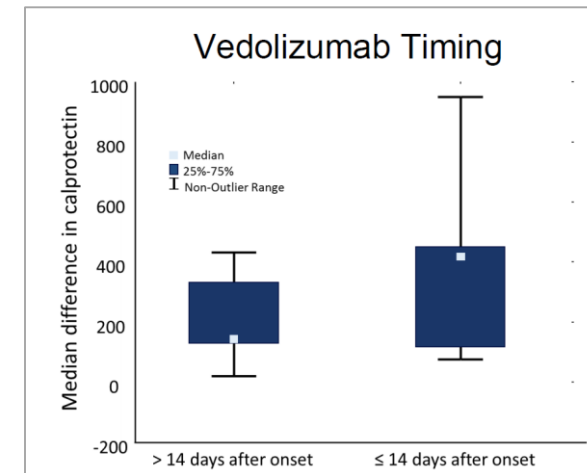
- Low threshold for starting corticosteroids
- No benefit for corticosteroid pre-treatment (budesonide)
- Colitis that is slow to improve/refractory to steroids: treat with anti-TNF
- Infliximab 5mg/kg once or twice q14 days

# Steroid-Refractory CTLA-4 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



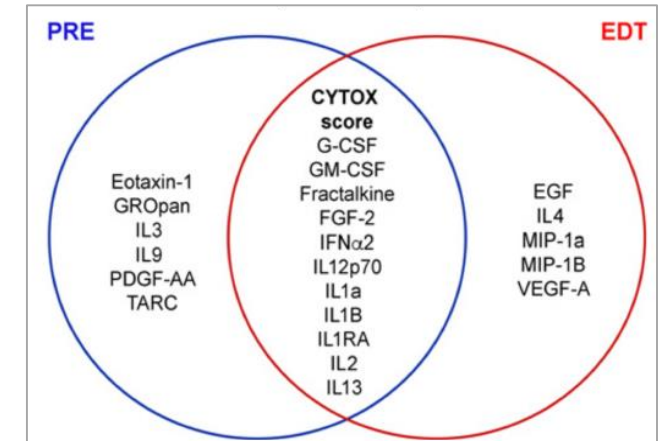
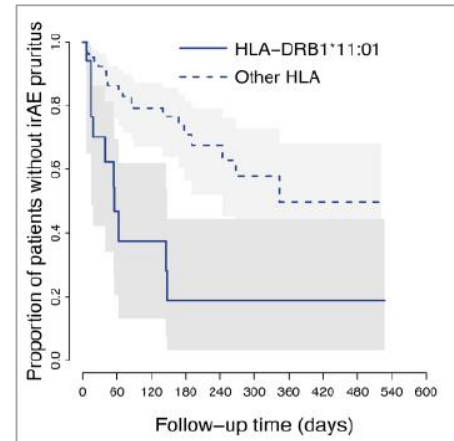
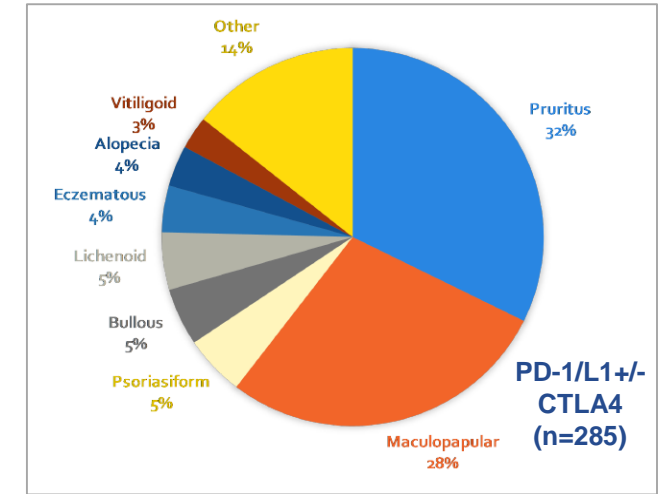
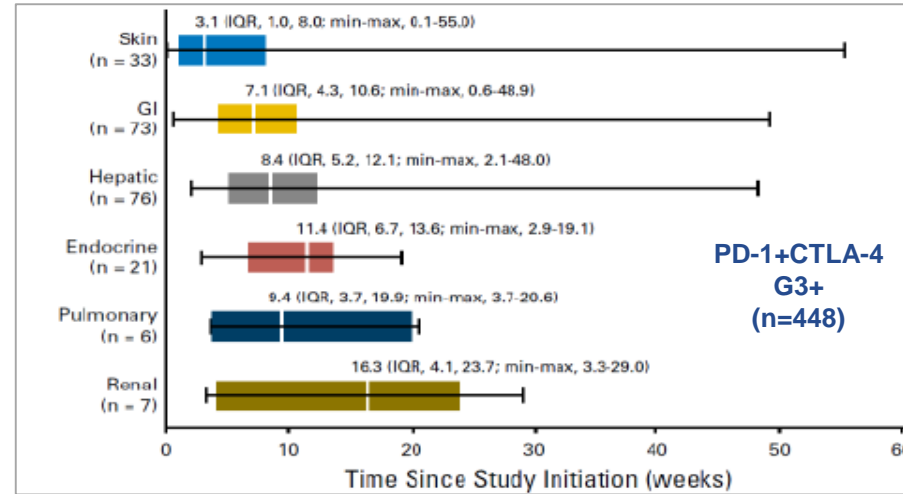


# PD-1+/-CTLA4 Skin Toxicities

- First and most frequent irAE
- Phenotypically diverse
- <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



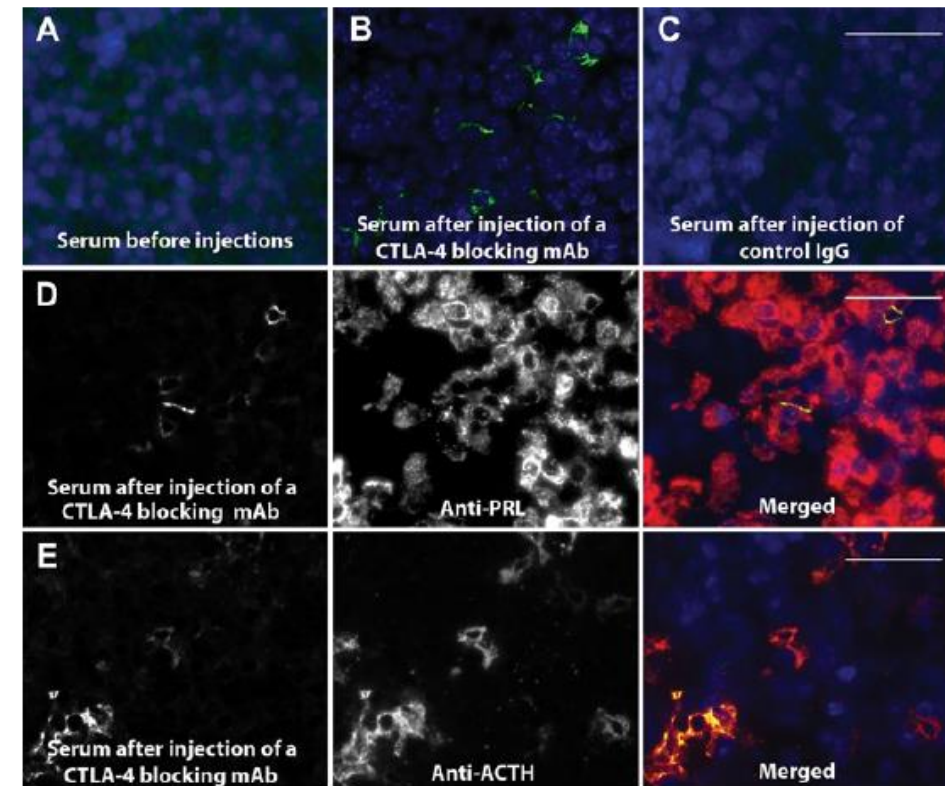
Santini, *Cancer Immunol Res* 2018  
 Phillips, *J Clin Oncol* 2019  
 Lim, *Clin Can Res* 2018  
 Ali, *Eur J Cancer* 2019

# CTLA-4 Inhibition Hypophysitis

- Classic endocrine toxicity of ipilimumab
- Symptoms: fatigue, weakness, headache, confusion
- Develops 4 months from first cycle of finding low cortisol
- 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)

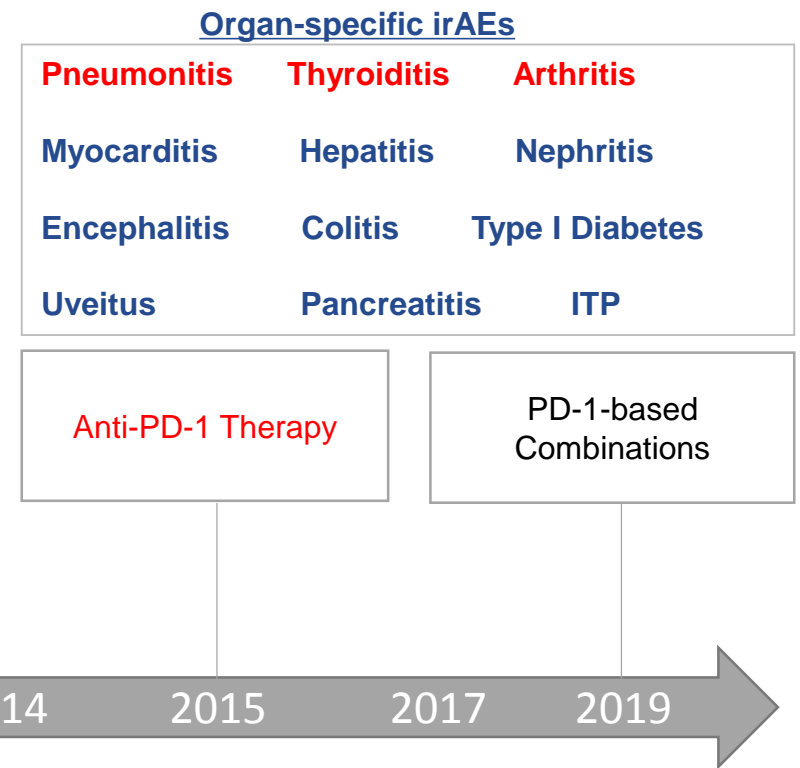


Iwama et al, *Sci Transl Med* 2018



# Key Milestones

## Immune-related Adverse Events

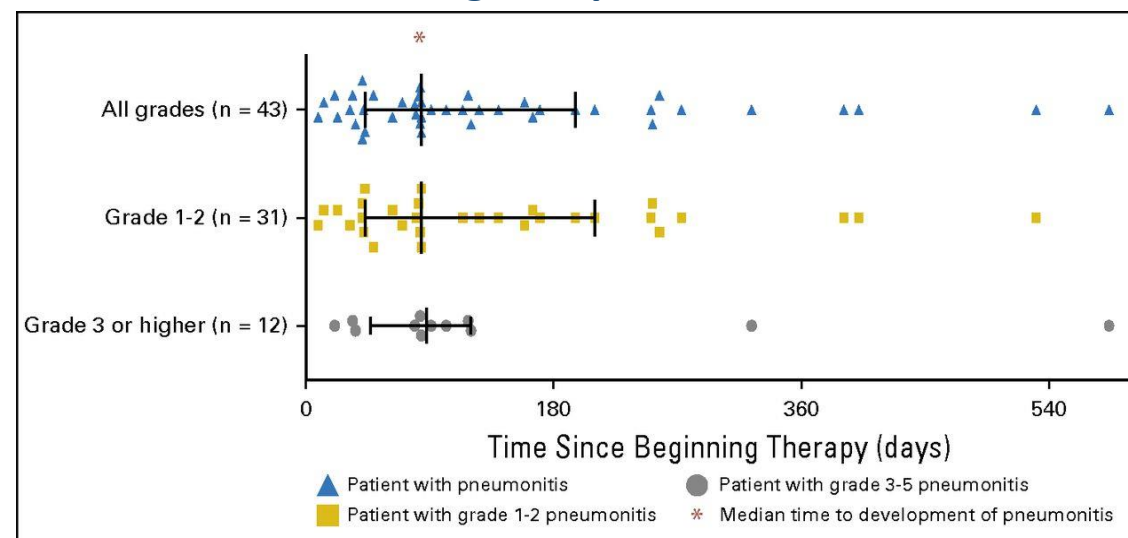


# PD-1/PD-L1 Inhibition Pneumonitis

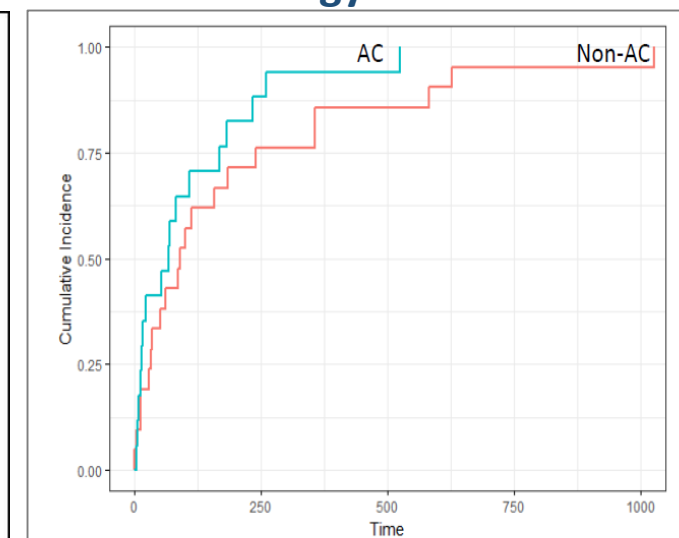


Radiologic Subtypes	Representative Image
<b>Cryptogenic-Organizing Pneumonia-like (COP-like)</b> (n=5, 19%)	
<b>Ground Glass Opacifications (GGO)</b> (n=10, 37%)	
<b>Interstitial Type</b> (n=6, 22%)	
<b>Hypersensitivity Type</b> (n=2, 7%)	
<b>Pneumonitis Not-Otherwise Specified</b> (n=4, 15%)	

## Timing is unpredictable



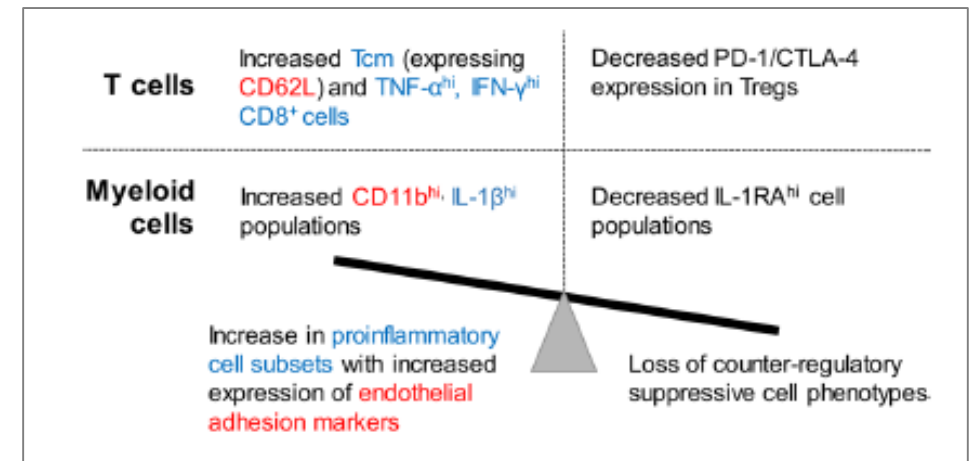
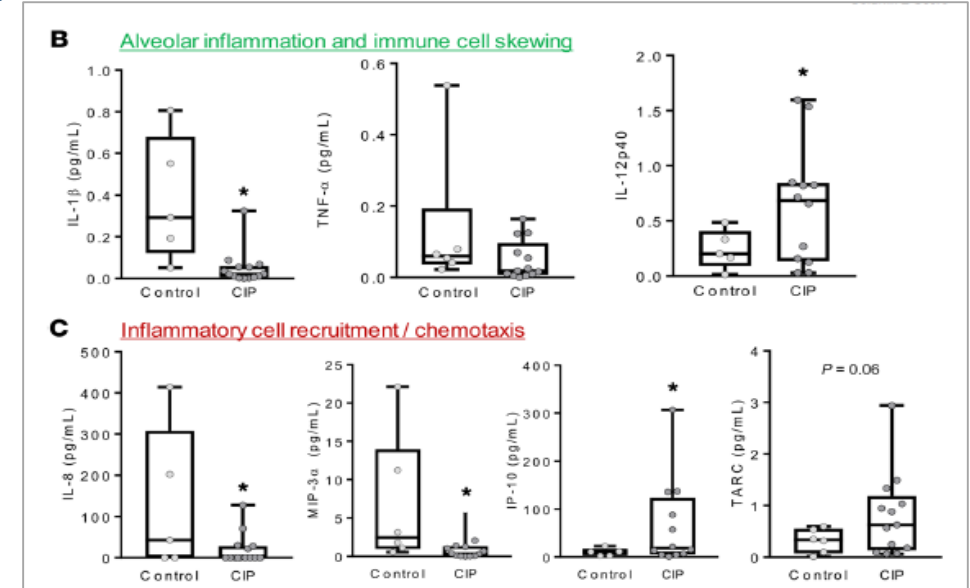
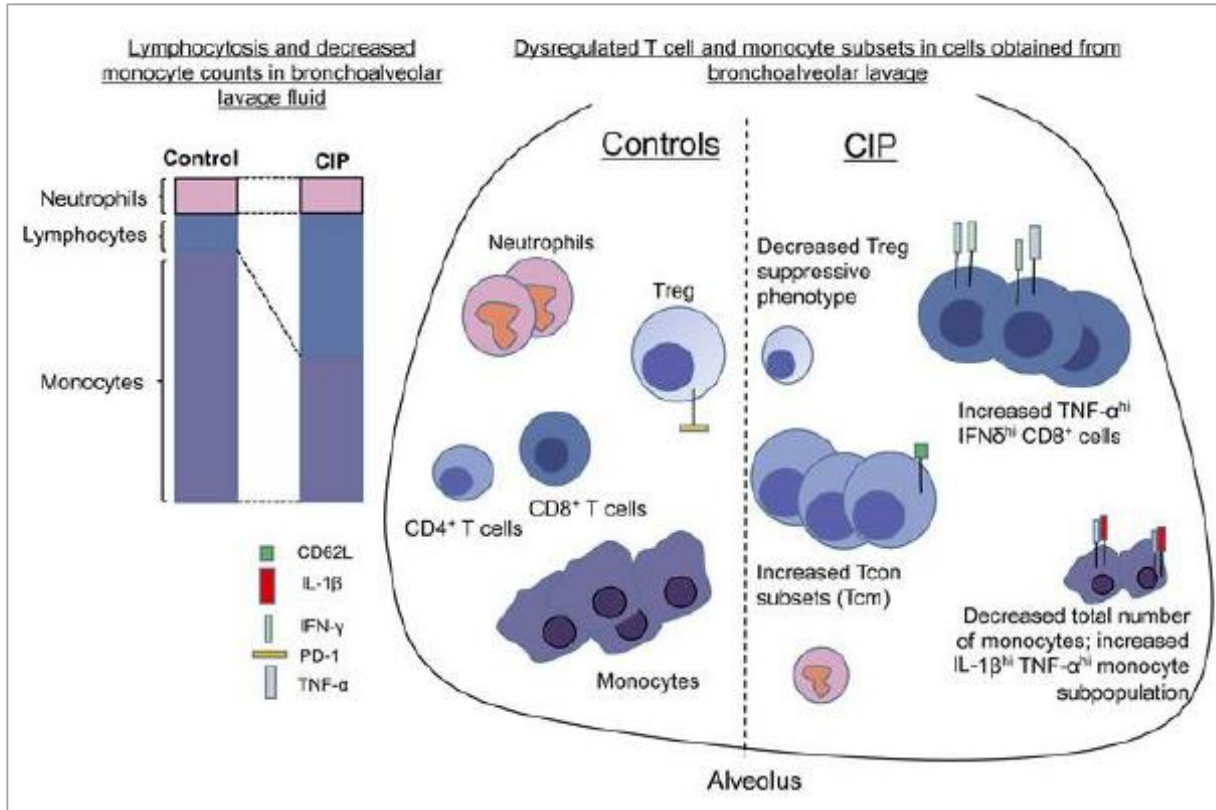
## Tumor histology is a risk factor



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

# PD-1/PD-L1 Inhibition

## Risk factors and T-cell mediated mechanisms



# PD-1/PD-L1 Inhibition Thyroiditis

## Hyperthyroid Phase

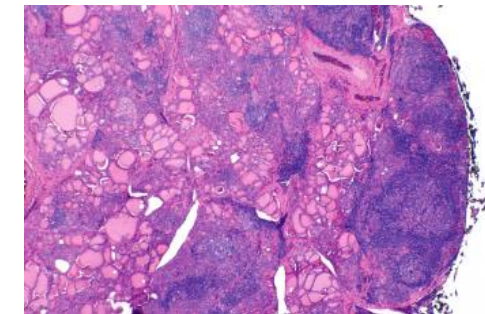
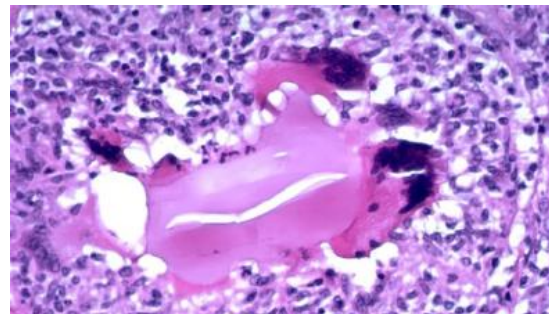
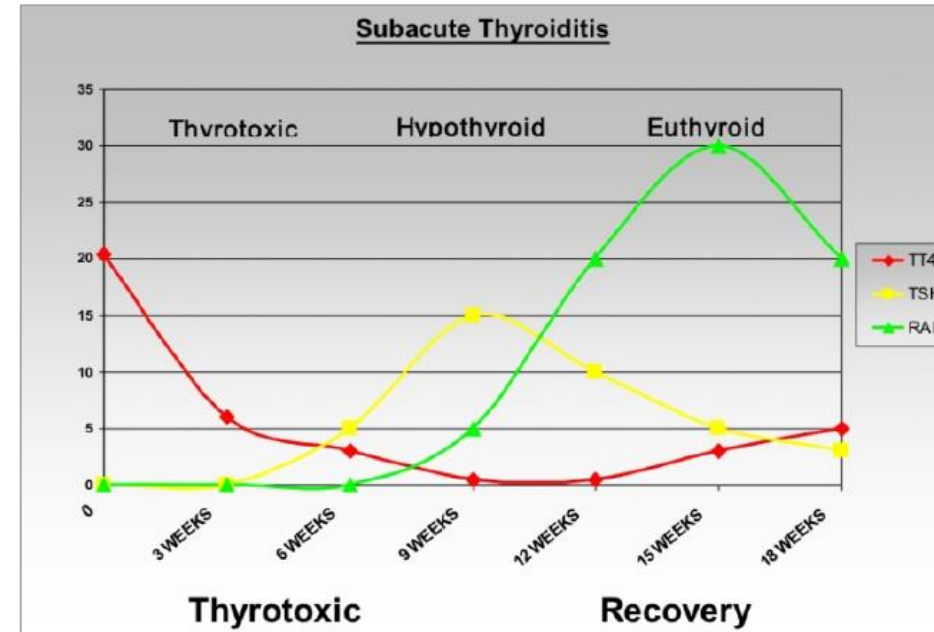
- Leaky thyroid, Variable symptoms
- 2-6 weeks duration

## Hypothyroidism Phase

- Recovery of depleted gland
- Symptoms: fatigue, hair and skin changes, fluid retention, constipation
- Transient or permanent

## Pathobiology

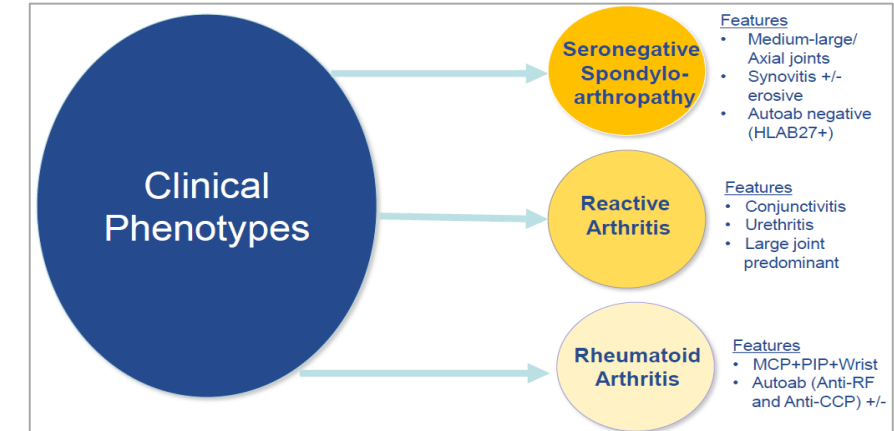
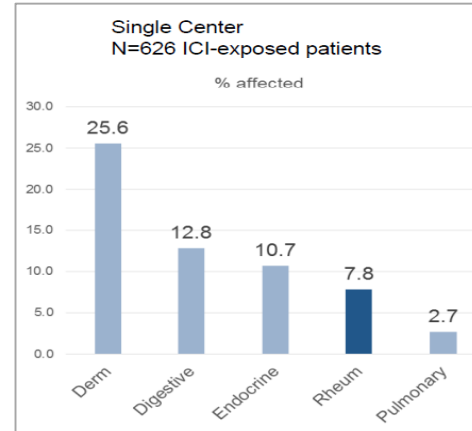
- Lymphocytic infiltration of gland
- T-cell mediated
- Autoantibody mediated (50% of ab+ patients develop thyroiditis with nivolumab).



Kobayashi et al, *J Endoc Soc* 2018

# 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

# Key Milestones

## Immune-related Adverse Events

### Organ-specific irAEs

Pneumonitis	Thyroiditis	Arthritis
<b>Myocarditis</b>	Hepatitis	Nephritis
Encephalitis	Colitis	Type I Diabetes
Uveitis	Pancreatitis	ITP

Anti-PD-1 Therapy

**PD-1-based  
Combinations**

1893

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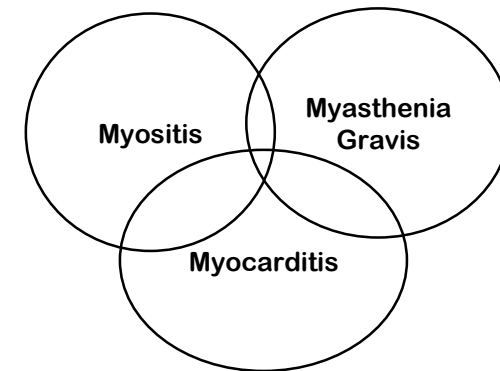
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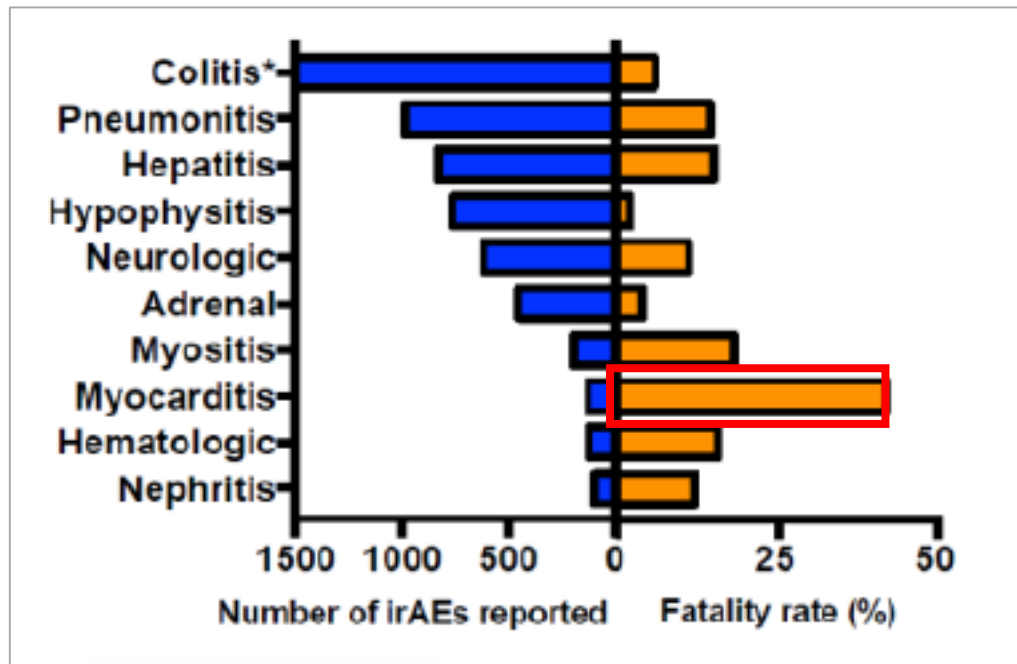




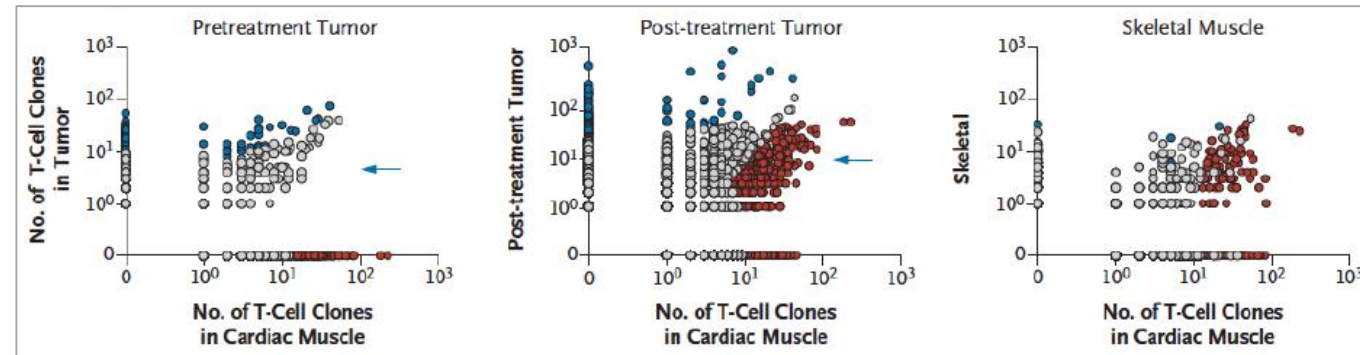
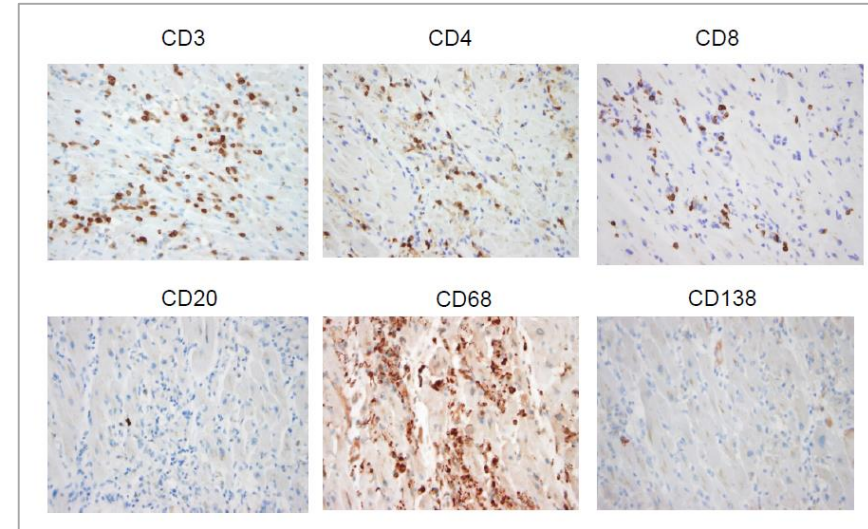
# PD-1/CTLA4 Combinations

## 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



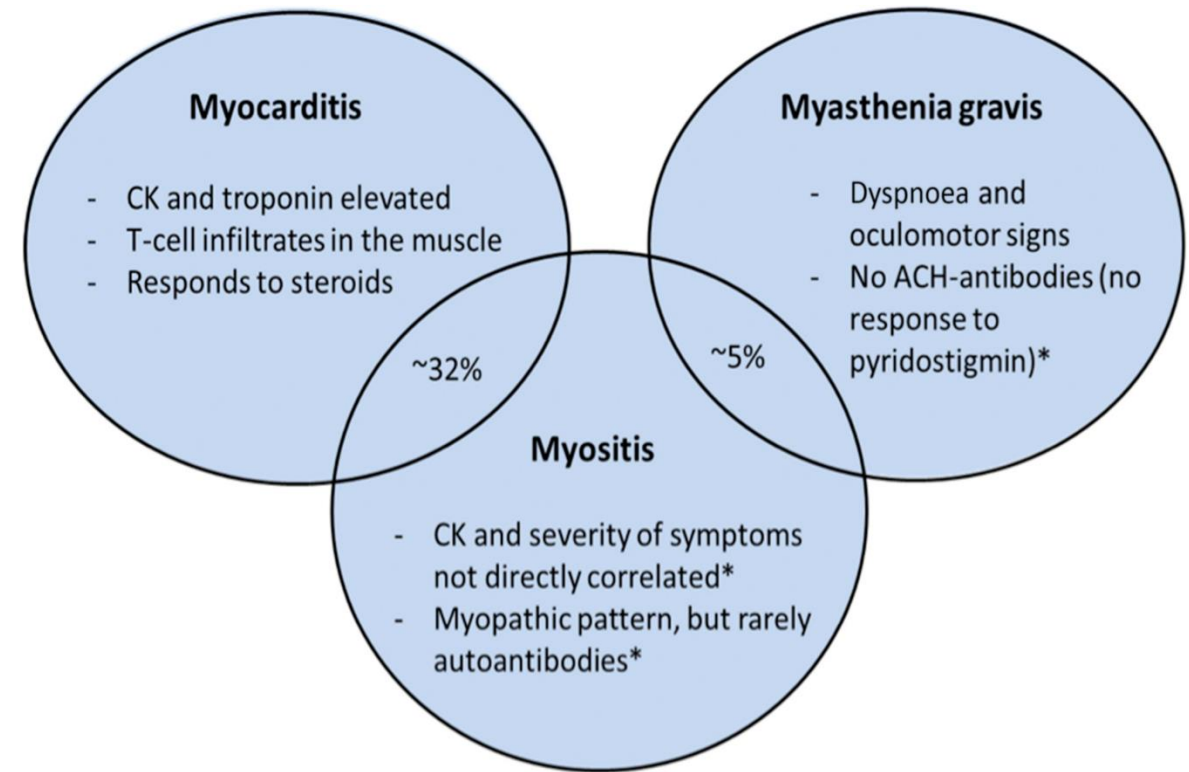
Johnson et al, *NEJM* 2016  
Wang et al, *JAMA Oncol* 2018

# 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
- 
- Multidisciplinary IR- toxicity teams may facilitate identification
    - 15% referred patients had multisystem irAEs

Moreira et al, *Eur J Cancer* 2018  
Naidoo et al, *JNCCN* 2019

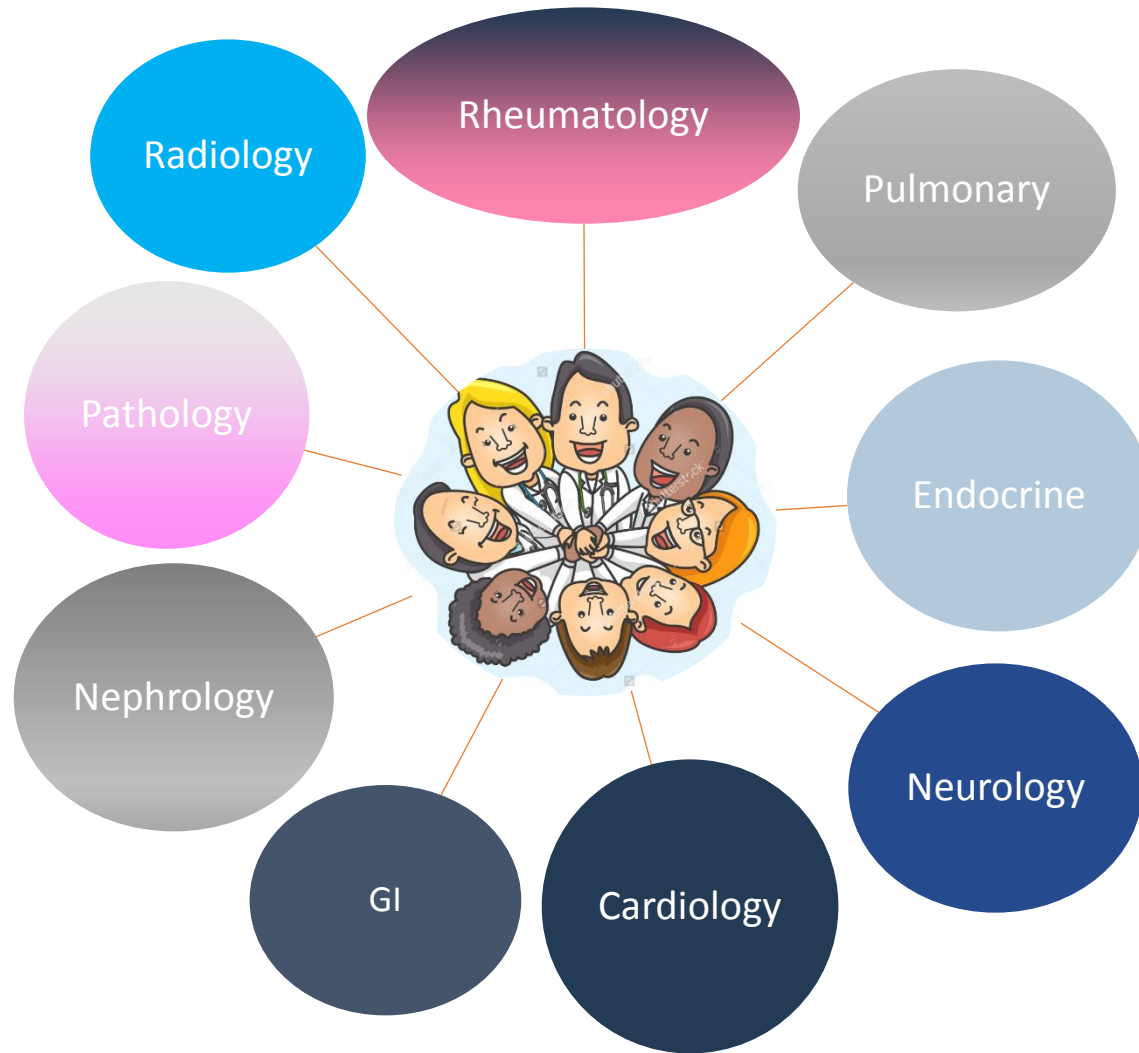


### A Multidisciplinary Toxicity Team for Cancer Immunotherapy–Related Adverse Events

Jarushka Naidoo, MBBCh<sup>a</sup>; Jiajia Zhang, MD, PhD<sup>a</sup>; Evan J. Lipson, MD<sup>a</sup>; Patrick M. Forde, MBBCh<sup>a</sup>; Karthik Suresh, MD<sup>b</sup>; Kendall F. Moseley, MD<sup>c</sup>; Seema Mehta, MD<sup>d</sup>; Shawn G. Kwatra, MD<sup>e</sup>; Alyssa M. Parian, MD<sup>f</sup>; Amy K. Kim, MD<sup>f</sup>; John C. Probasco, MD, PhD<sup>g</sup>; Rosanne Rouf, MD<sup>h</sup>; Jennifer E. Thorne, MD, PhD<sup>ij</sup>; Satish Shanbhag, MD<sup>a</sup>; Joanne Riemer, RN, BSN<sup>a</sup>; Ami A. Shah, MD<sup>k</sup>; Drew M. Pardoll, MD, PhD<sup>a</sup>; Clifton O. Bingham III, MD<sup>k</sup>; Julie R. Brahmer, MD, MHS<sup>a</sup>; and Laura C. Cappelli, MD, MHS<sup>k</sup>

# Future Directions

## 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

# Future Directions

## Immune-related Toxicity Teams

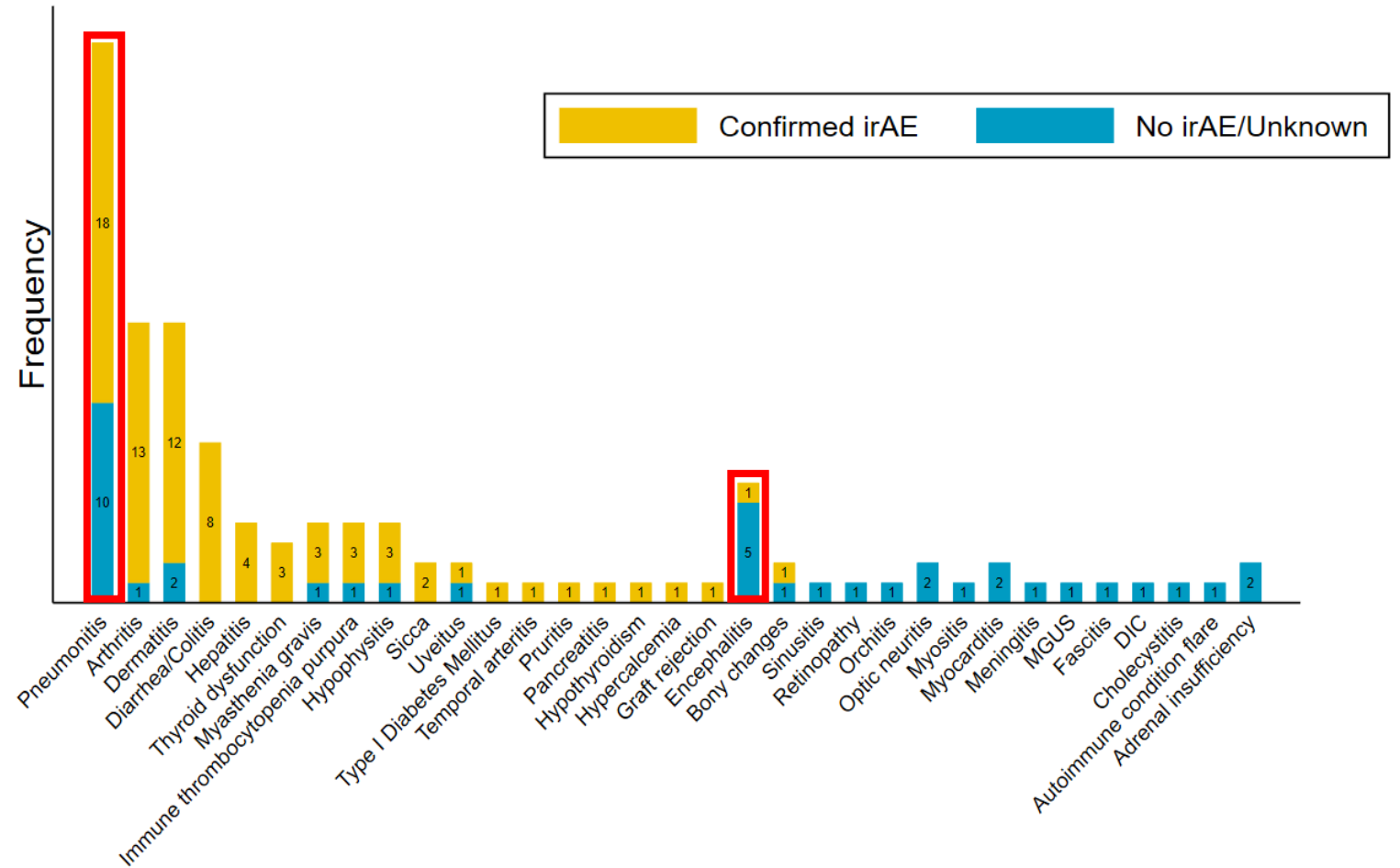
- These data identify the toxicities with the greatest diagnostic dilemmas:

- pneumonitis
- neurologic irAEs

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

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

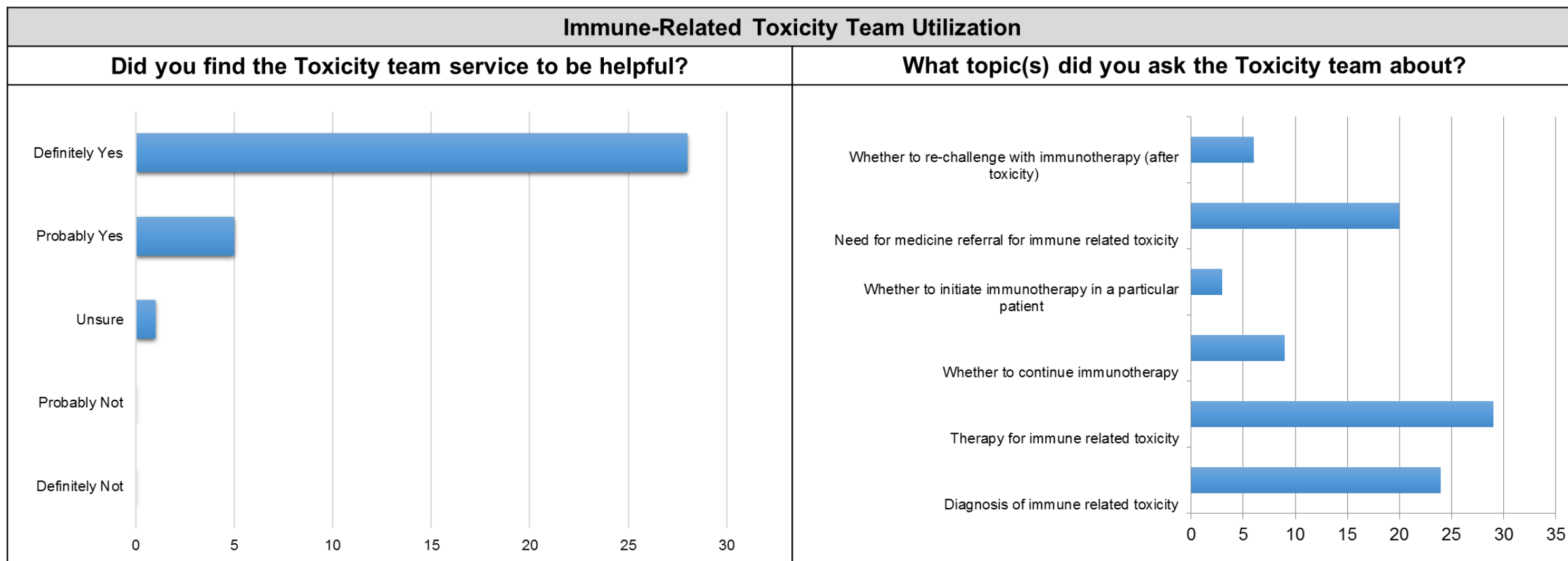
- A new irAE of osteitis was identified



Naidoo et al, JNCCN 2019

# Future Directions

## Immune-related Toxicity Teams



- 97% of respondents (58/60) deferred to team recommendations  
MD= 35, NP/PA=7, RN=15, Other=4

Naidoo et al, *JNCCN* 2019



# Future Directions

## Immune-related Toxicity Teams

- **18 publications**
- Pulmonary/Oncology (6)
- Rheumatology/Oncology (5)
- Endocrine/Oncology (1)
- Dermatology/Oncology (1)
- Gastroenterology/Oncology (3)
- Neurology/Oncology (1)
- Multidisciplinary Team (1)

### CLINICAL SCIENCE

## Immune checkpoint inhibitor-induced inflammatory arthritis persists after immunotherapy cessation

Tawnie J Braaten,<sup>1</sup> Julie R Brahmer,<sup>2</sup> Patrick M Forde,<sup>2</sup> Dung Le,<sup>2</sup> Evan J Lipson,<sup>2</sup> Jarushka Naidoo,<sup>2</sup> Megan Schollenberger,<sup>2</sup> Lei Zheng,<sup>2</sup> Clifton O Bingham III,<sup>1</sup> Ami A Shah,<sup>1</sup> Laura C Cappelli<sup>1</sup>

### ORIGINAL RESEARCH

## A Multidisciplinary Toxicity Team for Cancer Immunotherapy–Related Adverse Events

Jarushka Naidoo, MBBCh<sup>a</sup>; Jiajia Zhang, MD, PhD<sup>a</sup>; Evan J. Lipson, MD<sup>a</sup>; Patrick M. Forde, MBBCh<sup>a</sup>; Karthik Suresh, MD<sup>b</sup>; Kendall F. Moseley, MD<sup>c</sup>; Seema Mehta, MD<sup>d</sup>; Shawn G. Kwatra, MD<sup>e</sup>; Alyssa M. Parian, MD<sup>f</sup>; Amy K. Kim, MD<sup>f</sup>; John C. Probasco, MD, PhD<sup>g</sup>; Rosanne Rouf, MD<sup>h</sup>; Jennifer E. Thorne, MD, PhD<sup>i,j</sup>; Satish Shanbhag, MD<sup>a</sup>; Joanne Riemer, RN, BSN<sup>a</sup>; Ami A. Shah, MD<sup>k</sup>; Drew M. Pardoll, MD, PhD<sup>a</sup>; Clifton O. Bingham III, MD<sup>k</sup>; Julie R. Brahmer, MD, MHS<sup>a</sup>; and Laura C. Cappelli, MD, MHS<sup>k</sup>

The Journal of Clinical Investigation

CLINICAL MEDICINE

## The alveolar immune cell landscape is dysregulated in checkpoint inhibitor pneumonitis

Karthik Suresh,<sup>1</sup> Jarushka Naidoo,<sup>2,3</sup> Qiong Zhong,<sup>1</sup> Ye Xiong,<sup>1</sup> Jennifer Mammen,<sup>4</sup> Marcia Villegas de Flores,<sup>5</sup> Laura Cappelli,<sup>5</sup> Aanika Balaji,<sup>2</sup> Tsvi Palmer,<sup>1</sup> Patrick M. Forde,<sup>2,3</sup> Valsamo Anagnostou,<sup>2,3</sup> David S. Ettinger,<sup>2</sup> Kristen A. Marrone,<sup>2,3</sup> Ronan J. Kelly,<sup>2,3</sup> Christine L. Hann,<sup>2,3</sup> Benjamin Levy,<sup>2,3</sup> Josephine L. Feliciano,<sup>2,3</sup> Cheng-Ting Lin,<sup>6</sup> David Feller-Kopman,<sup>1</sup> Andrew D. Lerner,<sup>1</sup> Hans Lee,<sup>1</sup> Majid Shafiq,<sup>1</sup> Lonny Yarmus,<sup>1</sup> Evan J. Lipson,<sup>3,4</sup> Mark Soloski,<sup>5</sup> Julie R. Brahmer,<sup>2,3</sup> Sonye K. Danoff,<sup>1</sup> and Franco D'Alessio<sup>1</sup>

### JAMA Neurology | Original Investigation

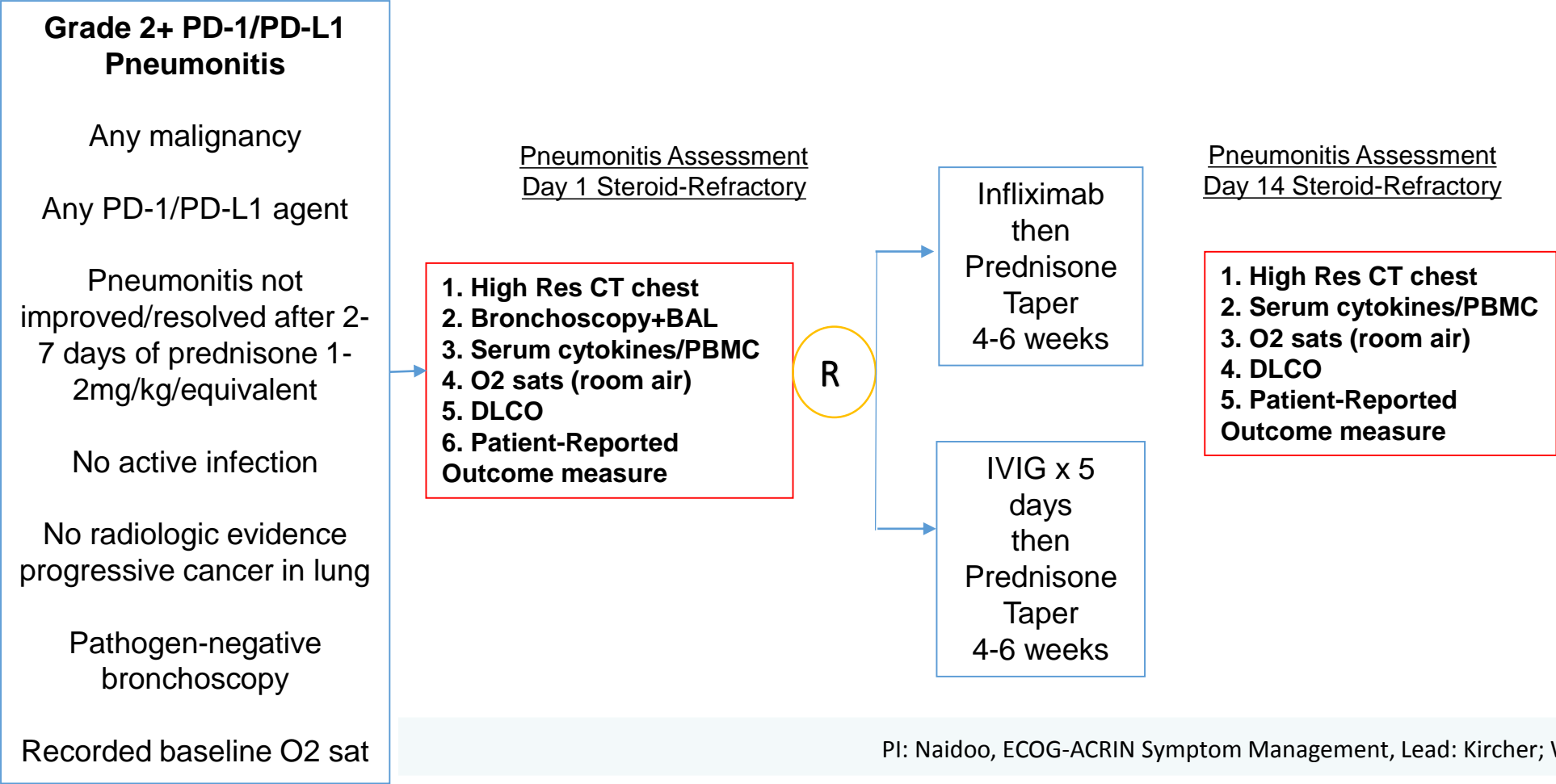
## Association of Autoimmune Encephalitis With Combined Immune Checkpoint Inhibitor Treatment for Metastatic Cancer

Tanya J. Williams, MD, PhD; David R. Benavides, MD, PhD; Kelly-Ann Patrice, MBBS; Josep O. Dalmau, MD, PhD; Alexandre Leon Ribeiro de Ávila, MD, PhD; Dung T. Le, MD; Evan J. Lipson, MD; John C. Probasco, MD; Ellen M. Mowry, MD, MCR



# 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



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for Cancer  
Immunotherapy

