



Clinical Considerations of Immune-Related Adverse Events

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Society for Immunotherapy of Cancer

#SITC2019

Disclosures

Research Funding:

Merck

AstraZeneca

Consulting:

Bristol Myers-Squibb

AstraZeneca

Roche/Genentech

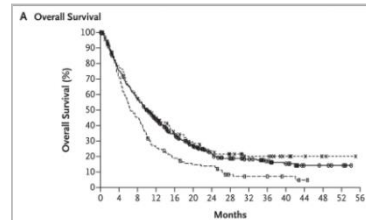
Honoraria:

Bristol Myers-Squibb

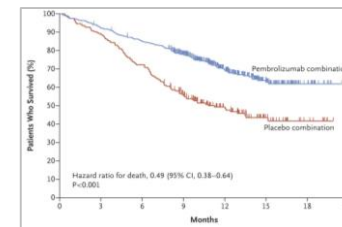
AstraZeneca/MedImmune

Key Milestones Immunotherapy for Cancer

Anti-CTLA-4 in Melanoma



Anti-PD-1+Chemo in NSCLC



Immunotherapy-based combinations approved

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

First regulatory approval of an anti-cancer vaccine

First approval of an immune checkpoint inhibitor for cancer

1893

1992

2006

2010

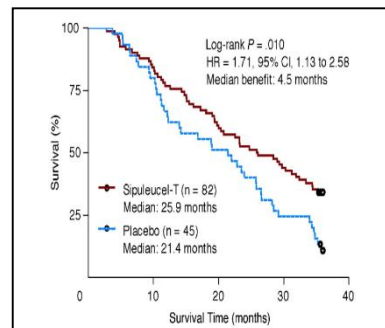
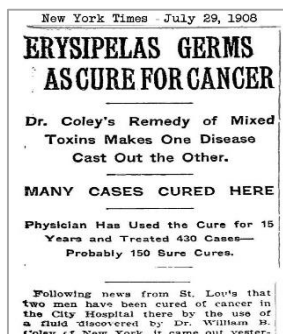
2011

2014

2015

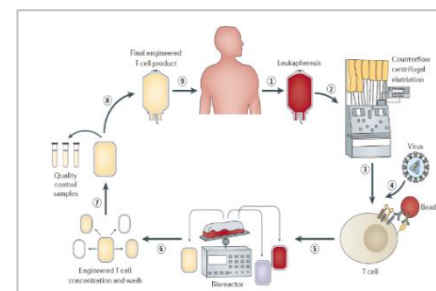
2017

2019



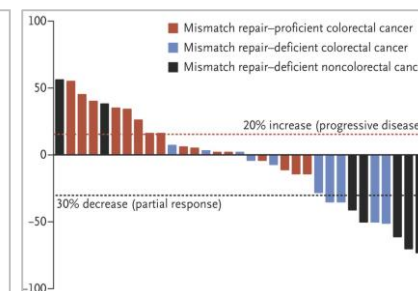
Sipuleucel-T
Prostate Cancer

First regulatory approval of CAR T-cell therapy



CD19-CARs in ALL

Tumor agnostic approval for Anti-PD-1

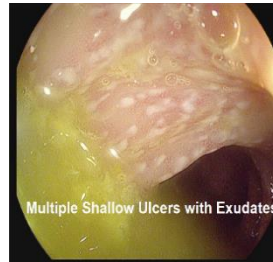


MSI-high tumors

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

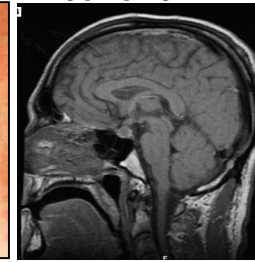
CTLA-4 colitis



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

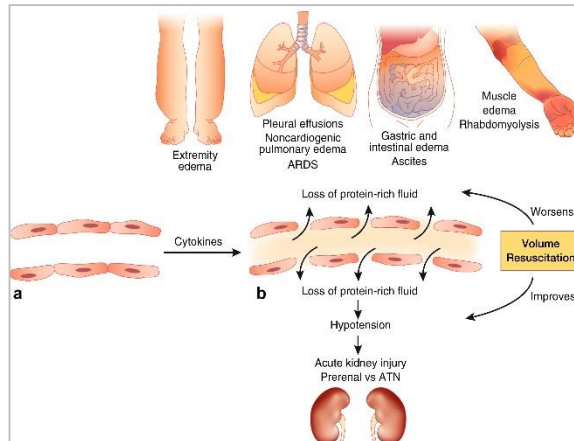
2014

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2017

2019

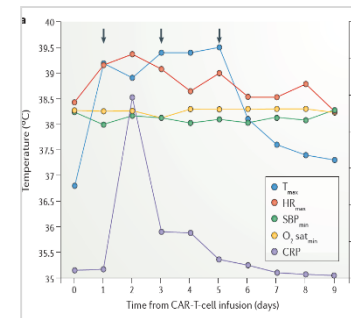
Fever
Hyperthermia



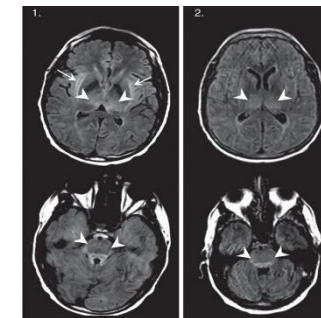
Capillary-Leak Syndrome

Fever
Injection-site
reactions

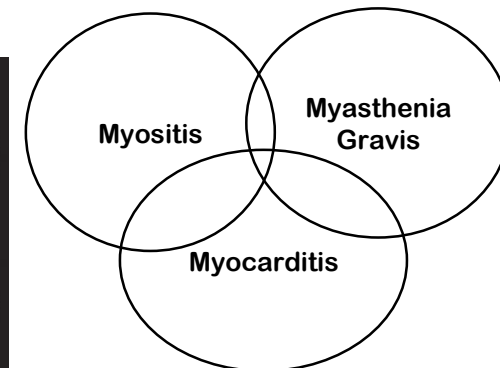
CAR T-cell therapy



Cytokine-Release Syndrome



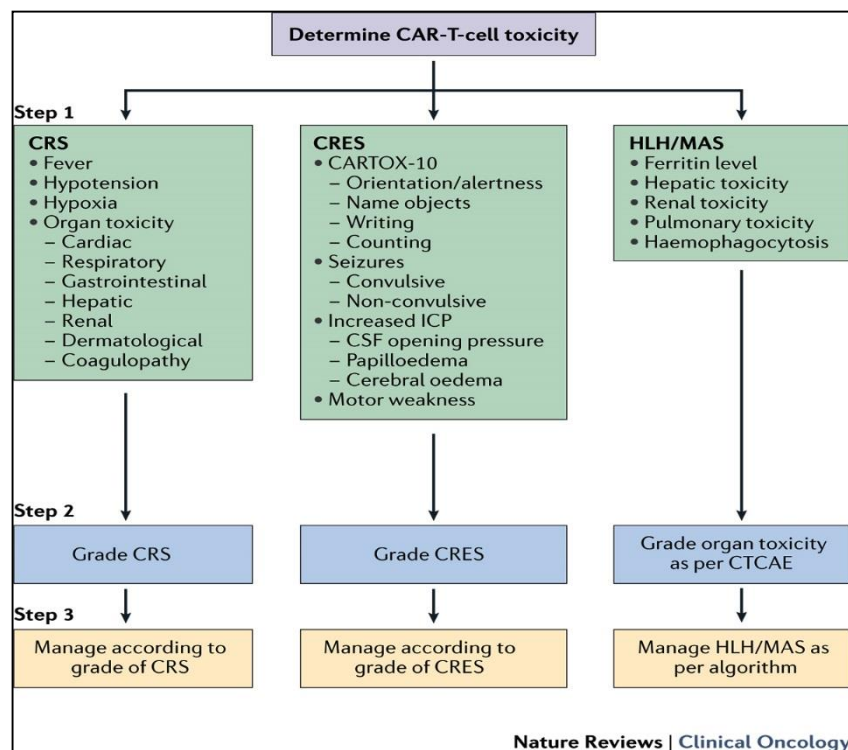
CAR T Neurotoxicity



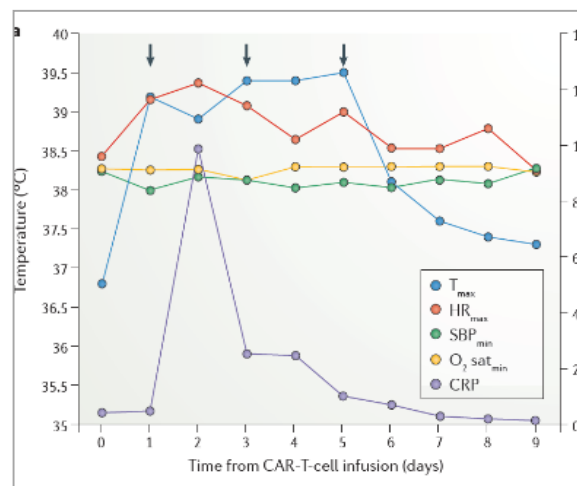
Multisystem irAE Syndromes

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



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.

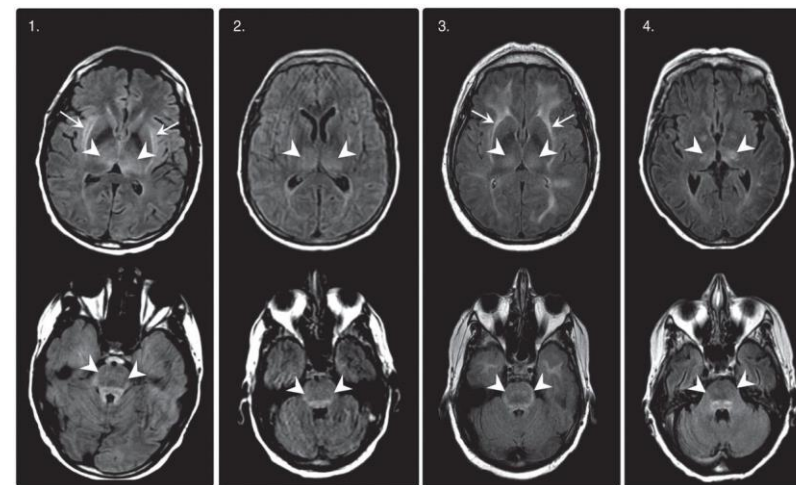
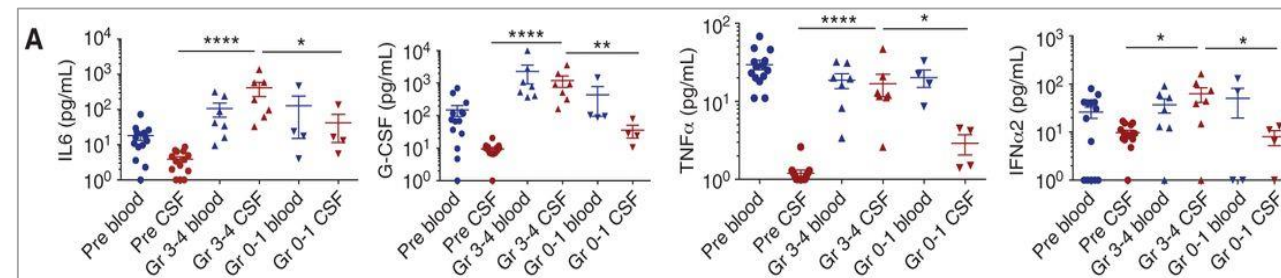
Neelapu et al, *Nat Rev Clin Oncol* 2018
Thompson et al, *JNCCN* 2019, NCCN guidelines
Lee et al, *Biol Blood Marrow Transplant* 2018

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

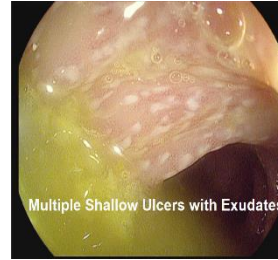


- Severe neurotoxicity in 53 CAR-T B-ALL pts, associated with:
 - high pretreatment disease burden
 - higher peak CAR T-cell expansion in blood
 - early/higher pro-inflammatory cytokines in blood
 - grade and CSF protein levels, IL6, IL8, MCP1, and IP10
 - elevated levels of NMDA receptor agonists in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

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

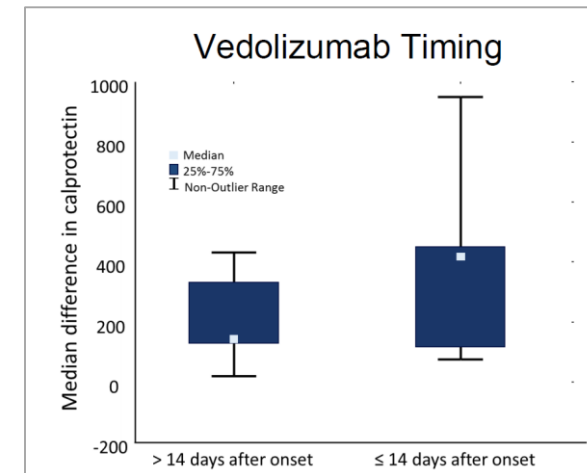
- Low threshold for starting corticosteroids
- No benefit for corticosteroid pre-treatment (budesonide)
- Colitis that is slow to improve/refractory to steroids: treat with anti-TNF
- Infliximab 5mg/kg once or twice q14 days

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

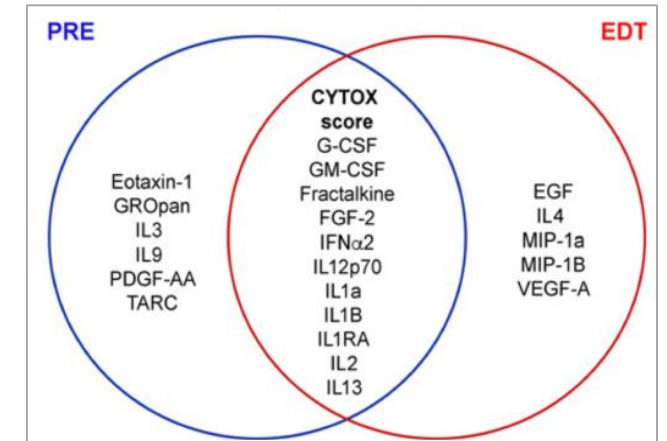
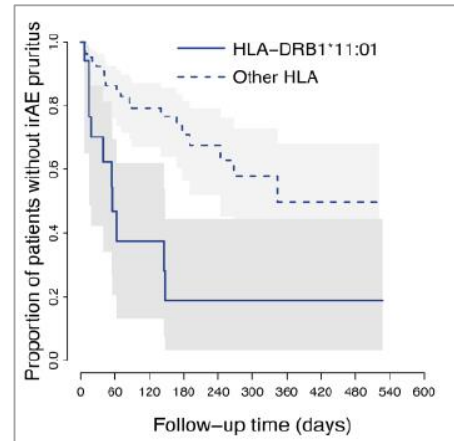
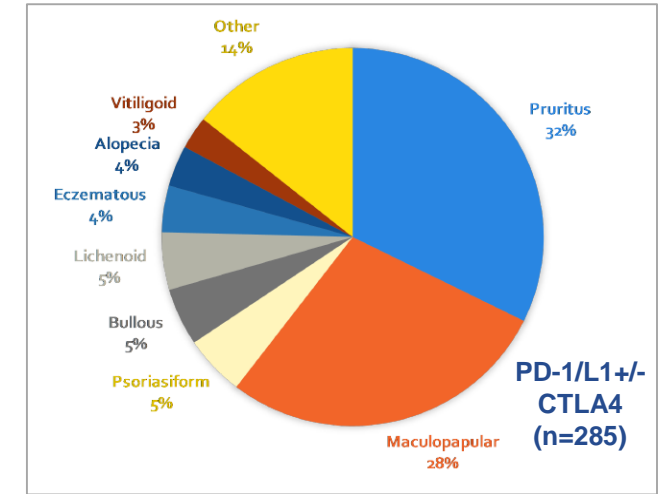
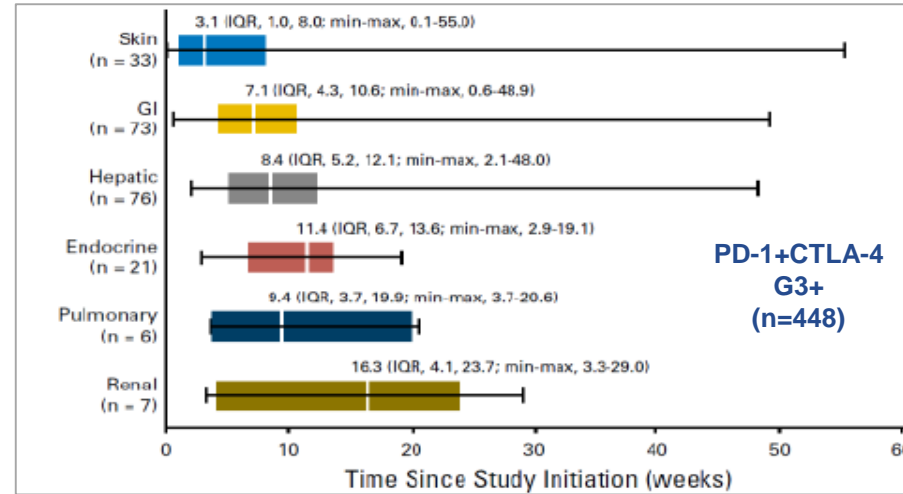


PD-1+/-CTLA4 Skin Toxicities

- 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



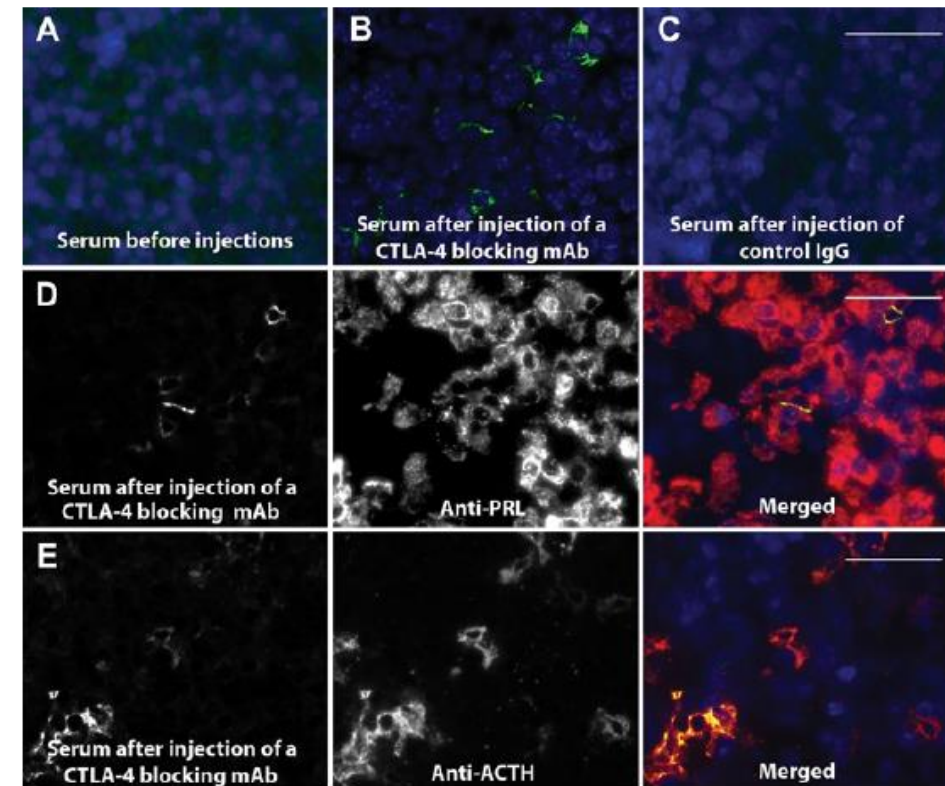
Santini, *Cancer Immunol Res* 2018
 Phillips, *J Clin Oncol* 2019
 Lim, *Clin Can Res* 2018
 Ali, *Eur J Cancer* 2019

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

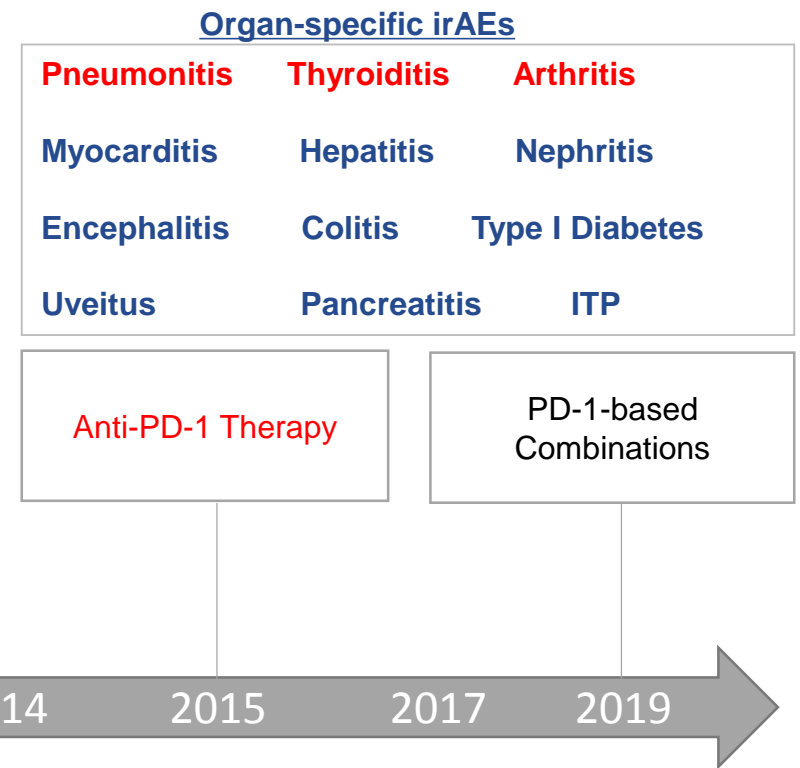
- CTLA-4 expressed in pituitary
- Antibodies bind to pituitary cells after exposure to drug
- Deposition of complement/pathway activation
- Antibody bonding directly to pituitary cells
- Ipilimumab directly activates complement (IgG1)



Iwama et al, *Sci Transl Med* 2018

Key Milestones

Immune-related Adverse Events

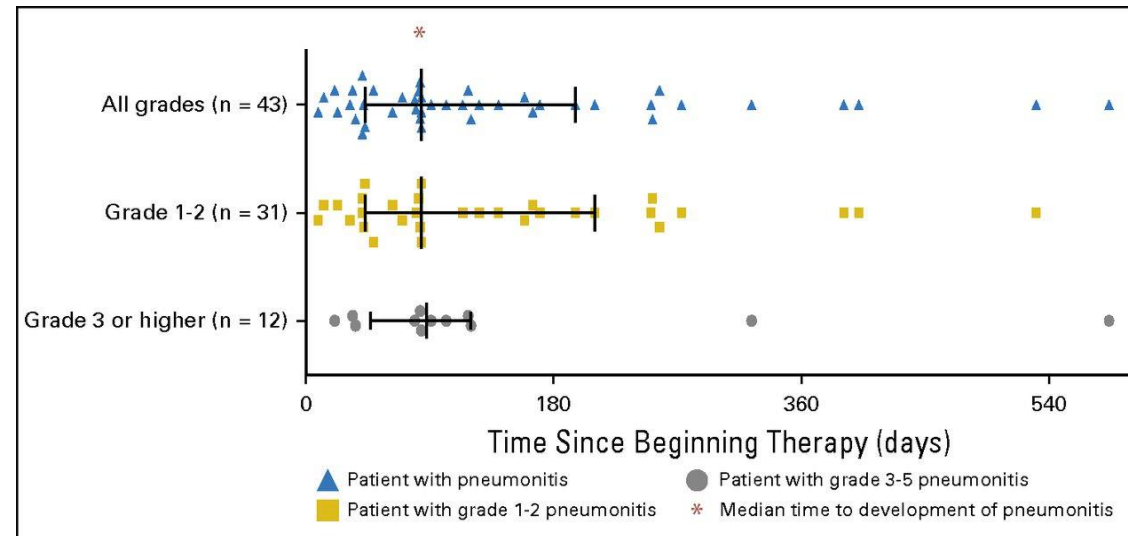


PD-1/PD-L1 Inhibition Pneumonitis

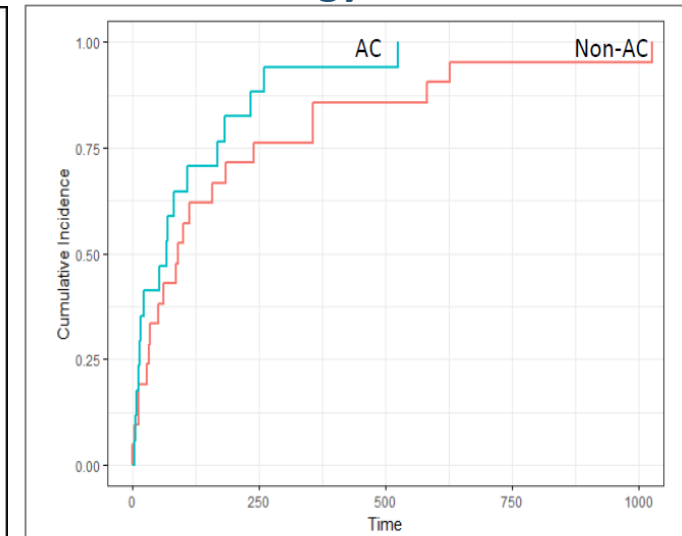


Radiologic Subtypes	Representative Image
Cryptogenic-Organizing Pneumonia-like (COP-like) (n=5, 19%)	
Ground Glass Opacifications (GGO) (n=10, 37%)	
Interstitial Type (n=6, 22%)	
Hypersensitivity Type (n=2, 7%)	
Pneumonitis Not-Otherwise Specified (n=4, 15%)	

Timing is unpredictable



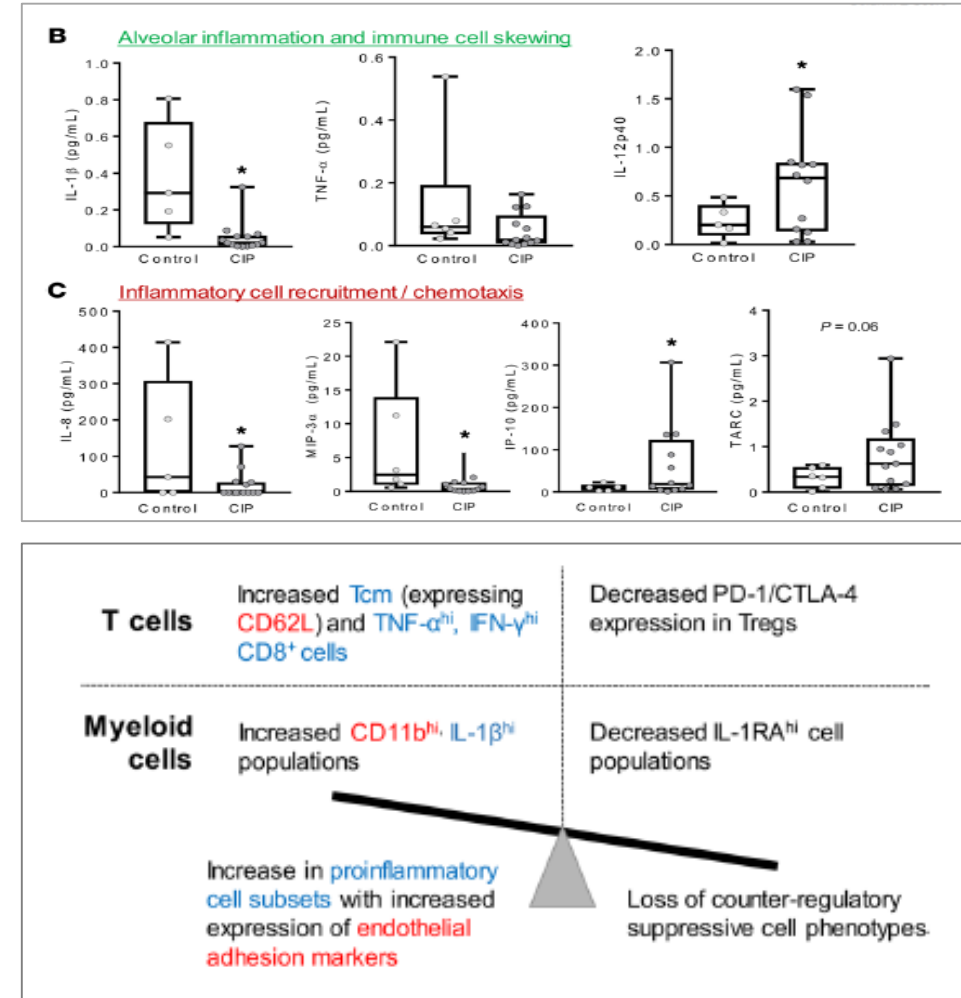
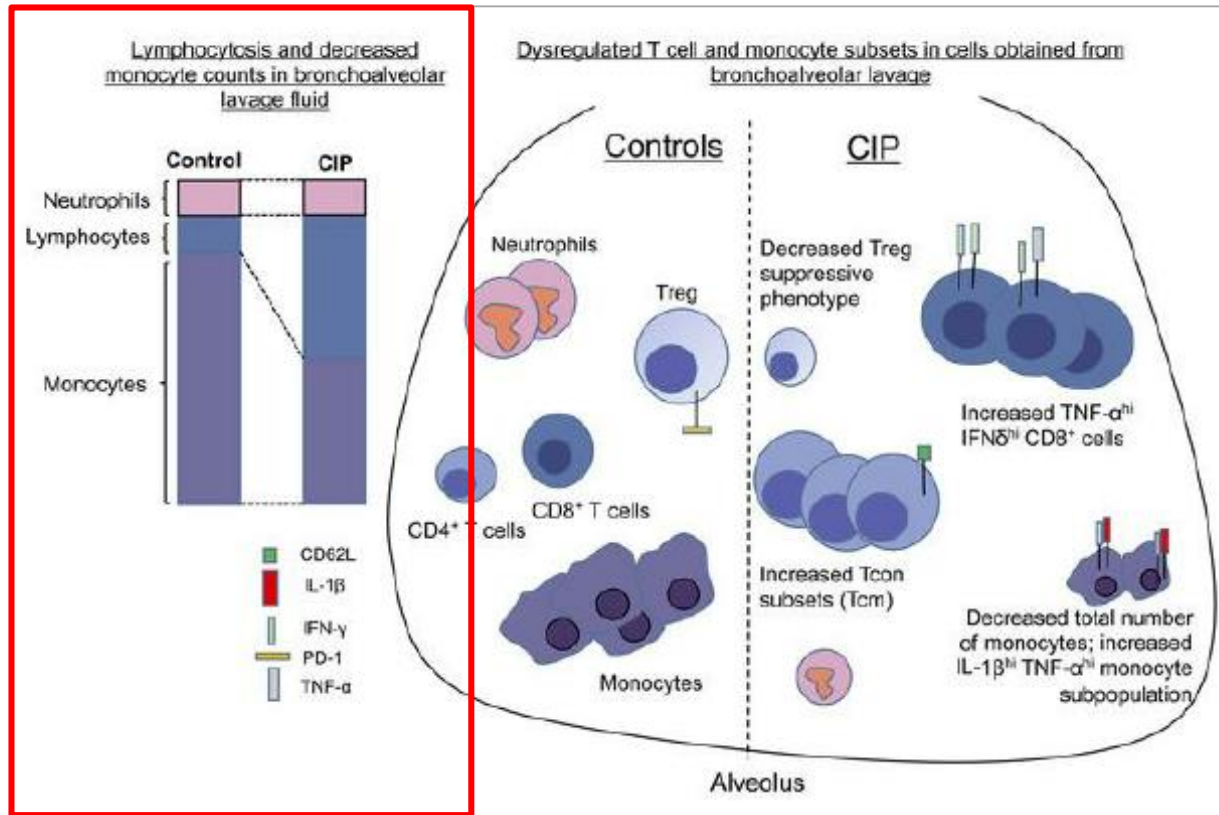
Tumor histology is a risk factor



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



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

PD-1/PD-L1 Inhibition Thyroiditis

Hyperthyroid Phase

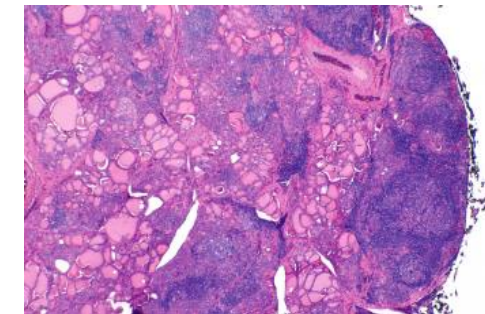
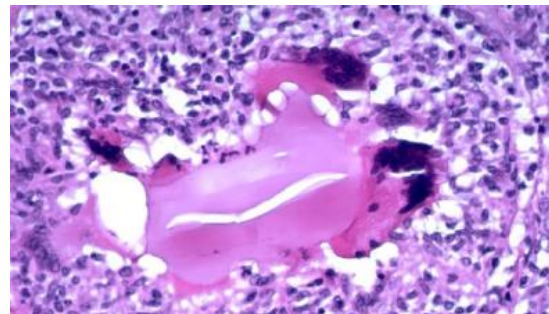
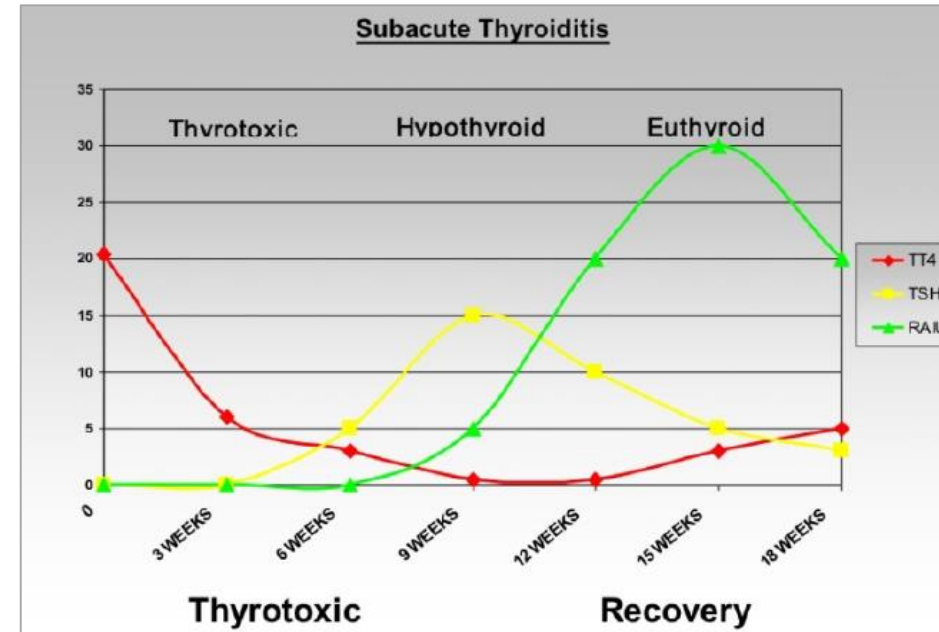
- Leaky thyroid, Variable symptoms
- 2-6 weeks duration

Hypothyroidism Phase

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

Pathobiology

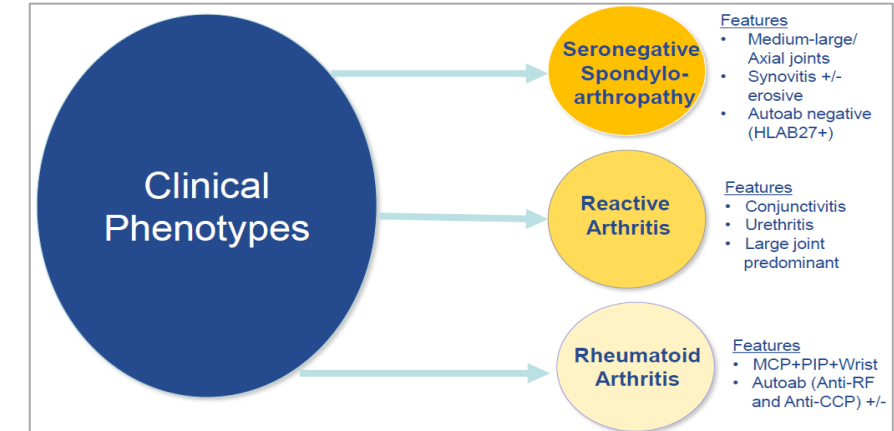
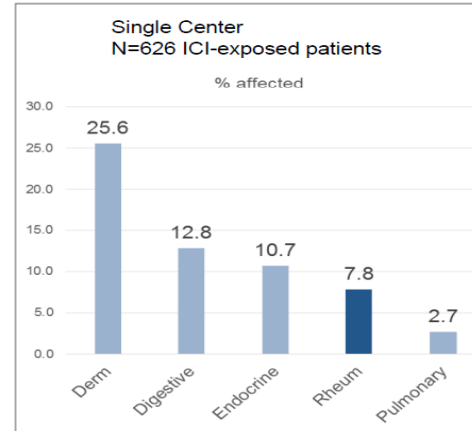
- Lymphocytic infiltration of gland
- T-cell mediated
- Autoantibody mediated (50% of ab+ patients develop thyroiditis with nivolumab).



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
Myocarditis	Hepatitis	Nephritis
Encephalitis	Colitis	Type I Diabetes
Uveitis	Pancreatitis	ITP

Anti-PD-1 Therapy

**PD-1-based
Combinations**

1893

1957

1992

1998

2006

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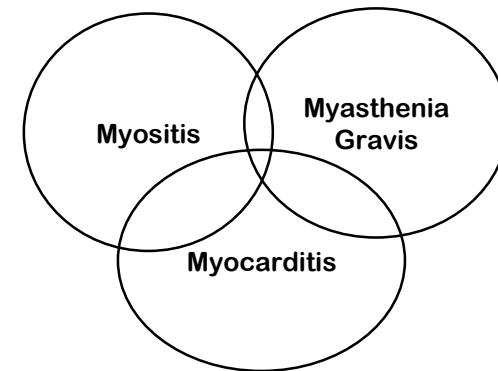
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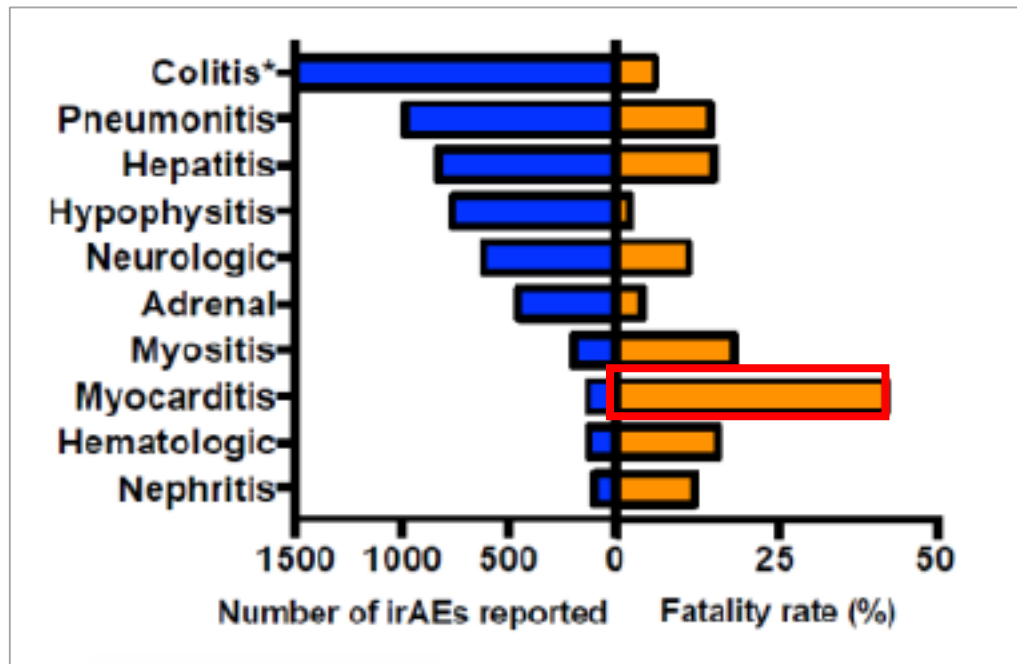


Multisystem irAE Syndromes

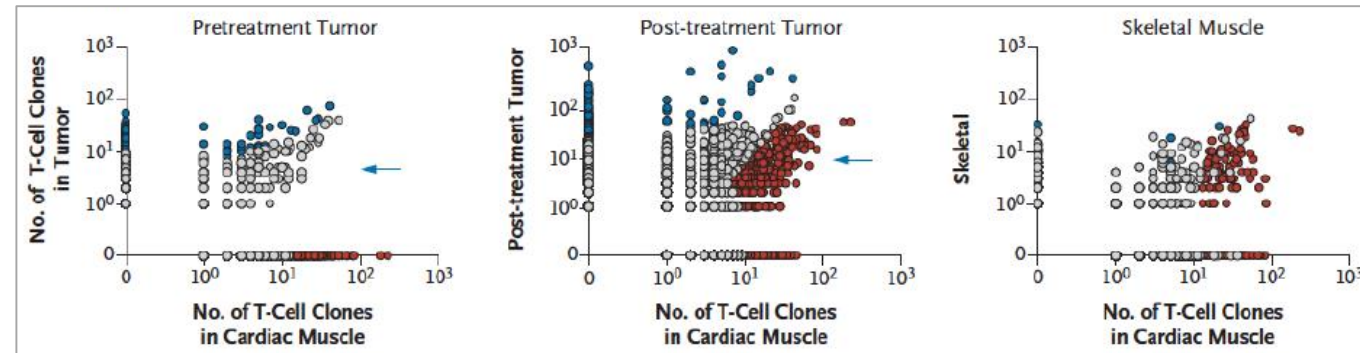
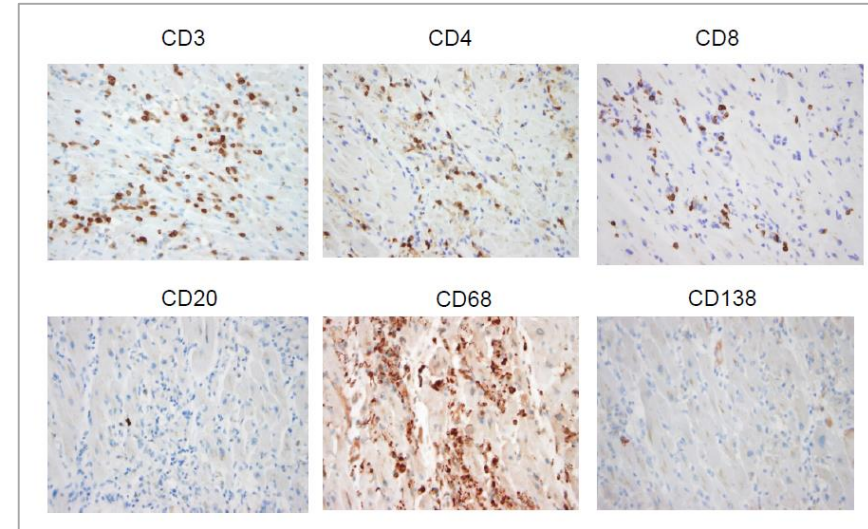
PD-1/CTLA4 Combinations

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

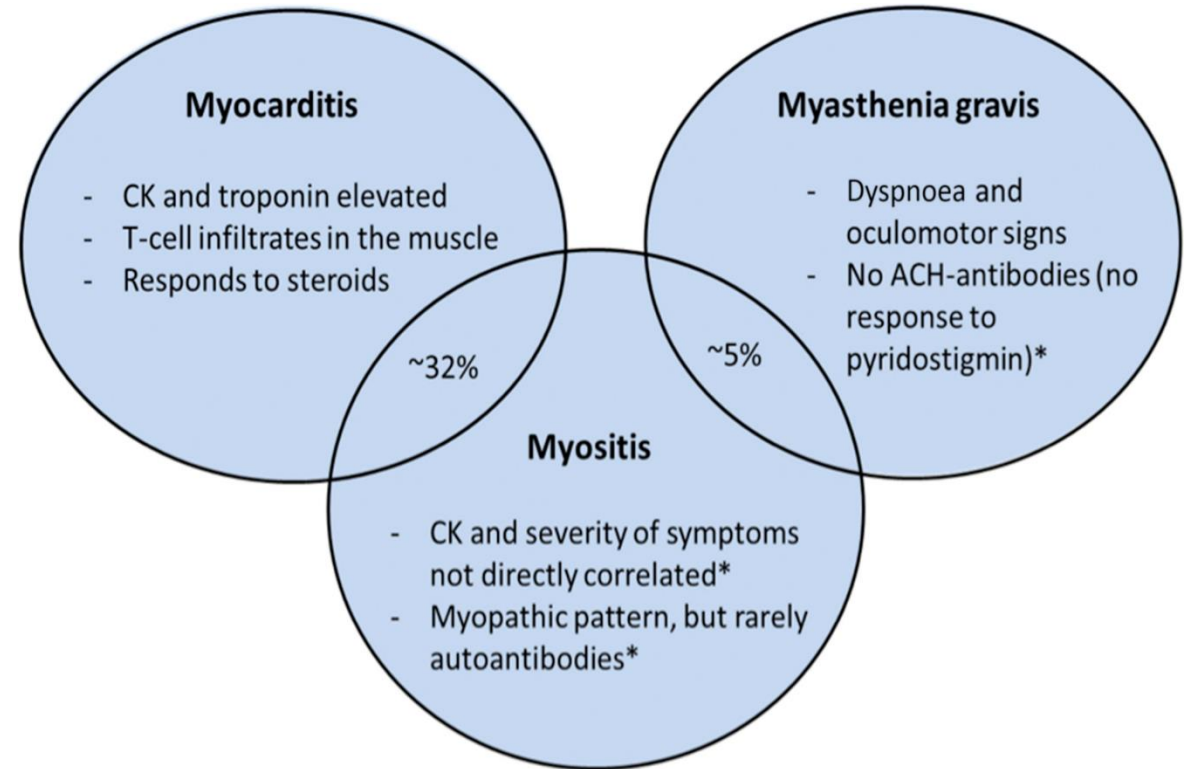


Johnson et al, *NEJM* 2016
Wang et al, *JAMA Oncol* 2018

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



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

Immune-related Toxicity and Response

Metastatic Melanoma

Table 2. Impact of Treatment-Related Select AEs and IM Use on Response to Nivolumab Therapy

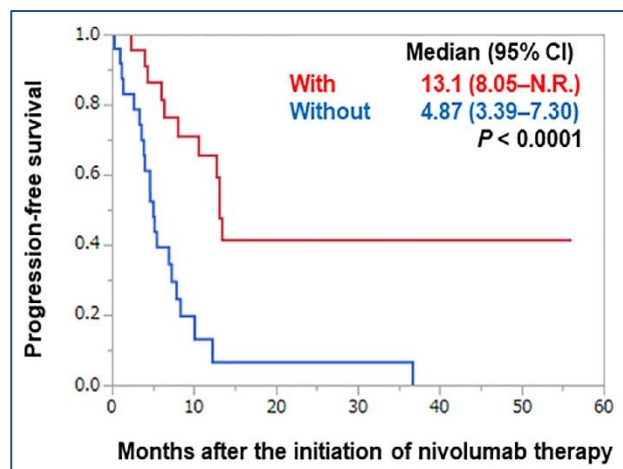
	All Patients (N = 576)	Any-Grade Treatment-Related Select AEs*				Grade 3 to 4 Treatment-Related Select AEs		Patients Receiving Systemic IM	
		Any (n = 255)	None (n = 321)	1-2 (n = 242)	≥ 3 (n = 13)	Yes (n = 18)	No (n = 558)	Yes (n = 114)	No (n = 462)
ORR, No. of patients (%)	181 (31.4)	124 (48.6)	57 (17.8)	113 (46.7)	11 (84.6)	5 (27.8)	176 (31.5)	34 (29.8)	147 (31.8)
95% CI	27.6 to 35.4	42.3 to 54.9	13.7 to 22.4	40.3 to 53.2	54.6 to 98.1	9.7 to 53.5	27.7 to 35.6	21.6 to 39.1	27.6 to 36.3
P			< .001	< .0001†	< .001†		1.00		.736

Abbreviations: AE, adverse event; IM, immune-modulating agent; ORR, objective response rate.

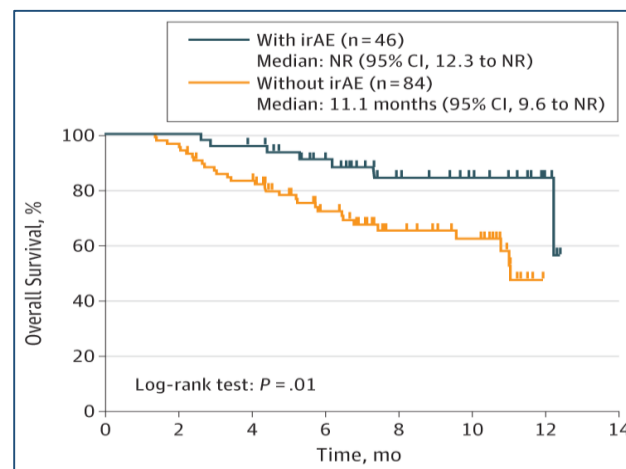
*Data in these columns are for patients with the indicated numbers of any-grade treatment-related select AEs: any AE, no AEs, 1-2 AEs, and ≥ 3 AEs.

†Versus no treatment-related select AEs.

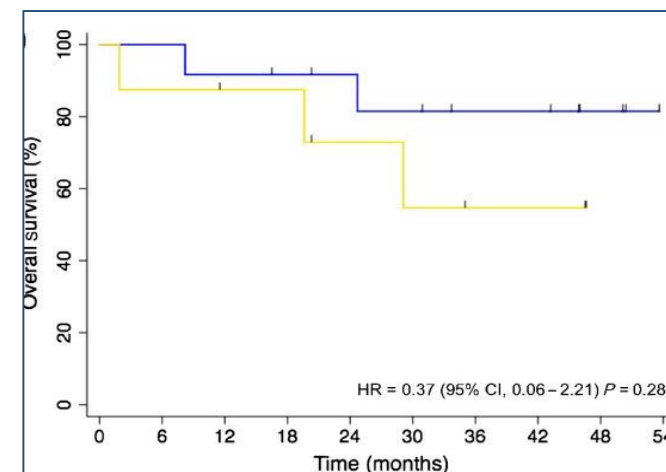
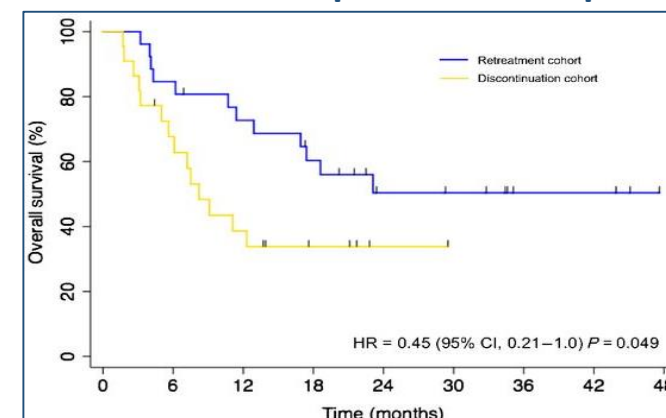
Renal Cell Carcinoma



NSCLC



To retreat or not to retreat post irAE? Response matters



Weber et al, *J Clin Oncol* 2017

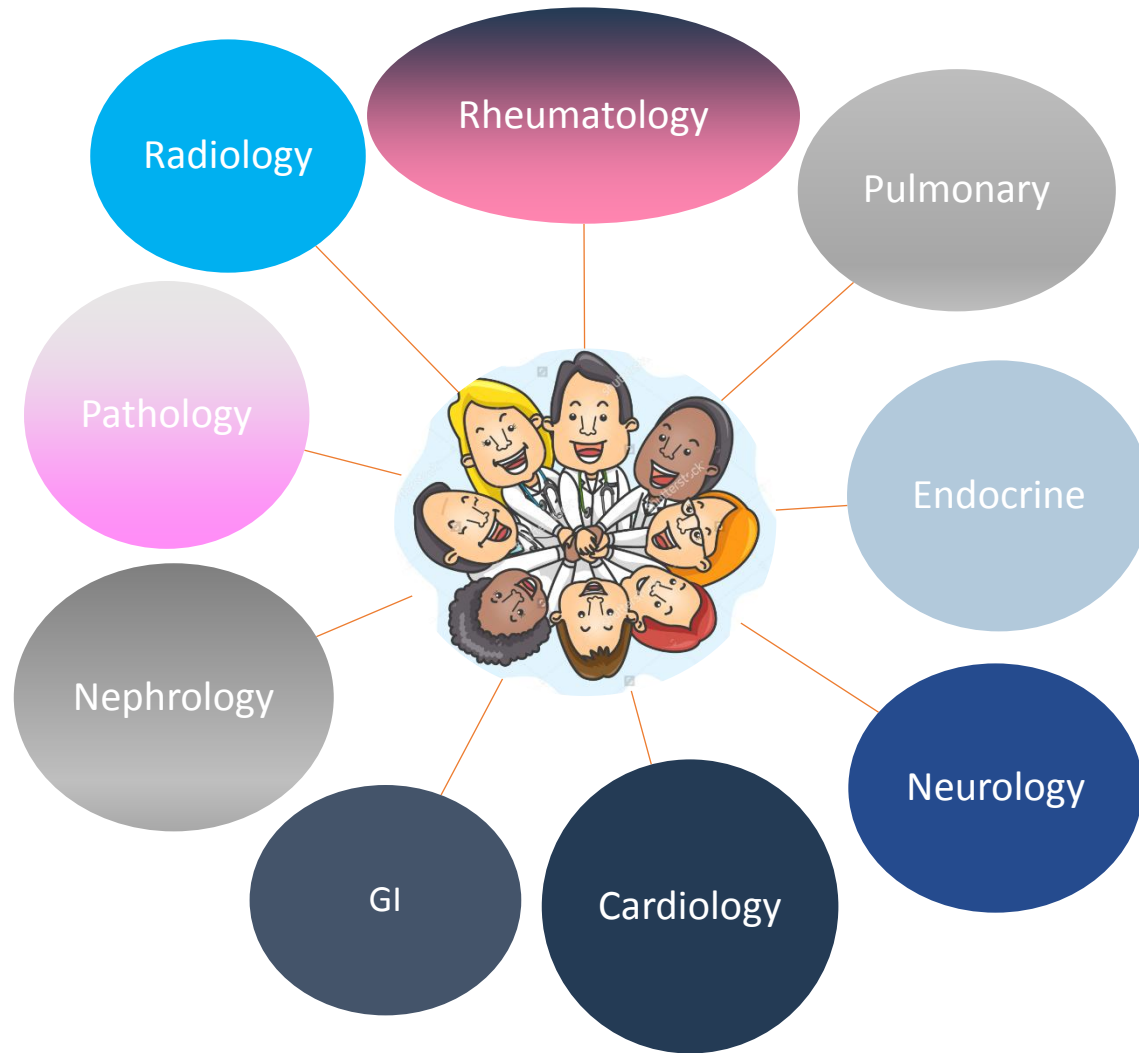
Haratani et al, *JAMA Oncol* 2018

Ishihara et al, *Clin Kidney Cancer* 2019

Santini et al, *Can Immunol Res* 2019

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

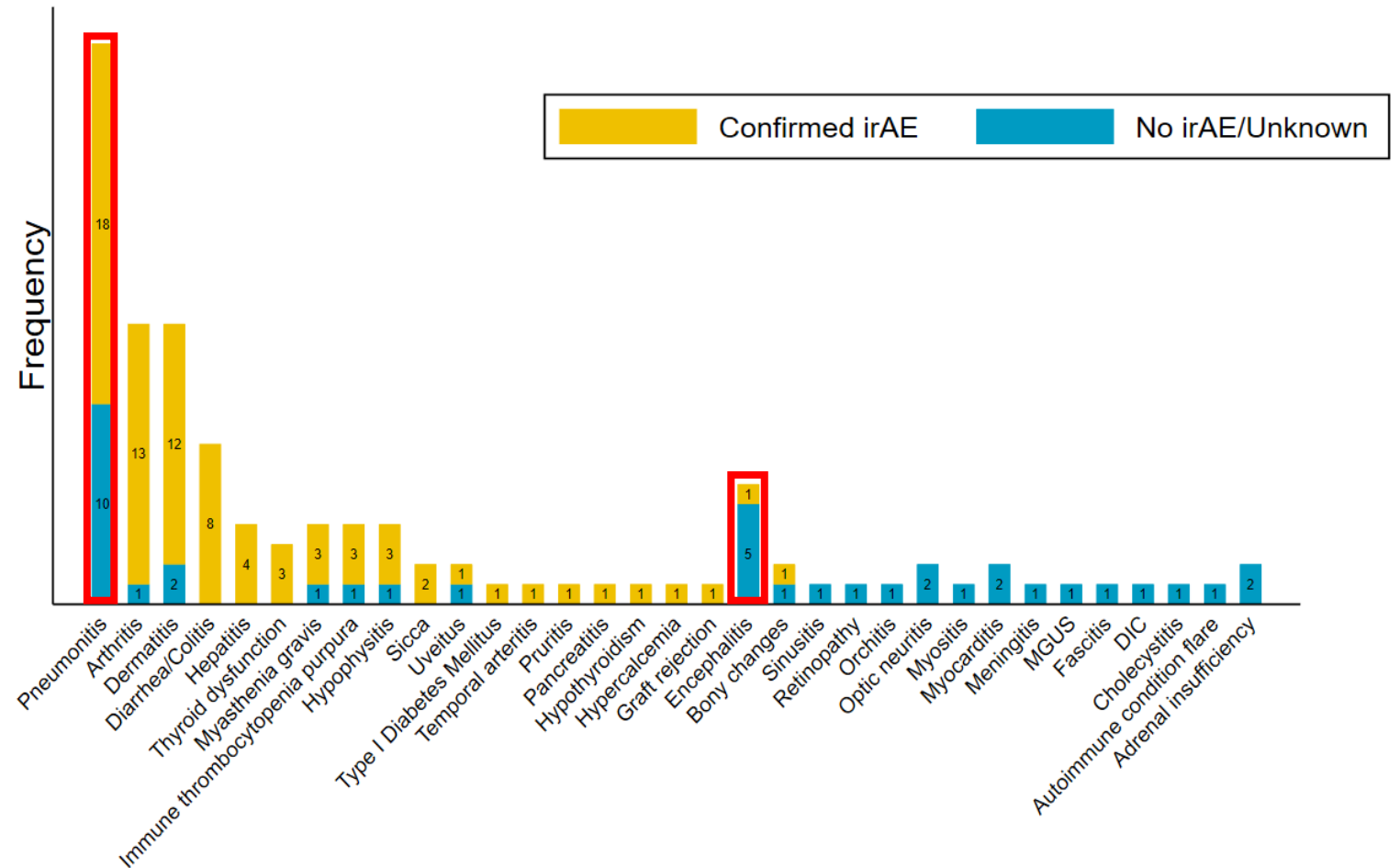
- These data identify the toxicities with the greatest diagnostic dilemmas:

- pneumonitis
- neurologic irAEs

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

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

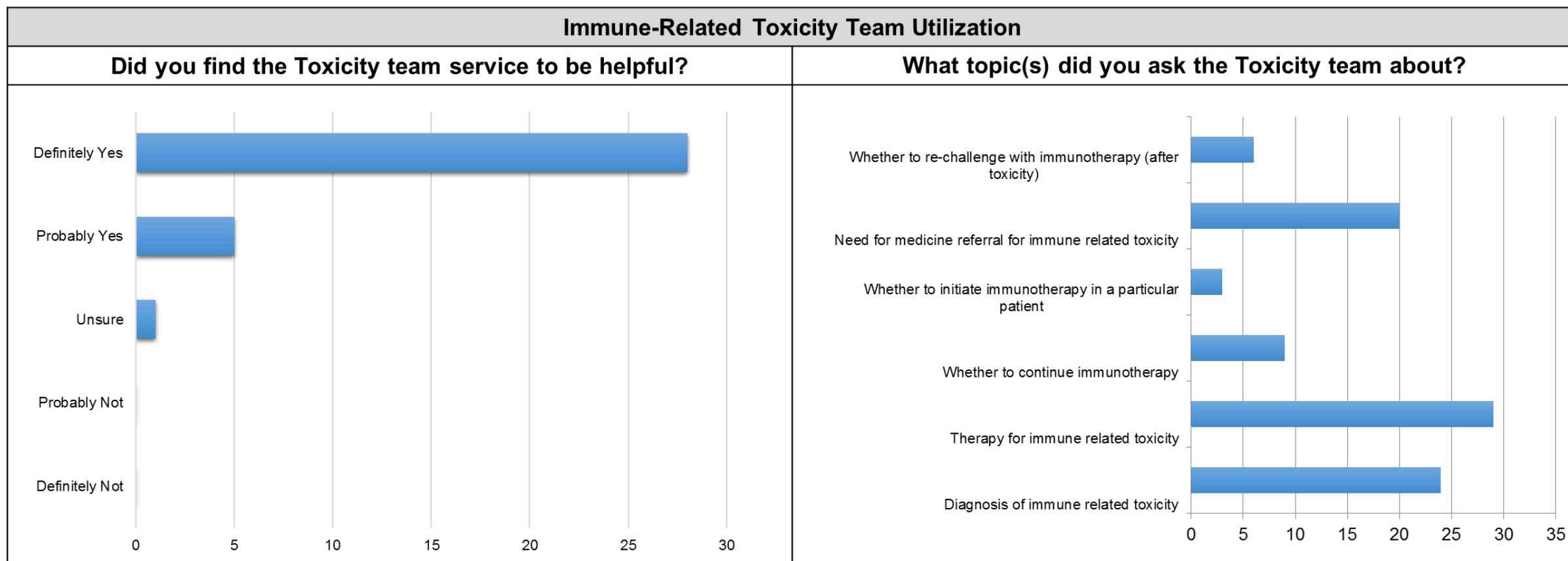
- A new irAE of osteitis was identified



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

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ORIGINAL RESEARCH

A Multidisciplinary Toxicity Team for Cancer Immunotherapy–Related Adverse Events

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CLINICAL MEDICINE

The alveolar immune cell landscape is dysregulated in checkpoint inhibitor pneumonitis

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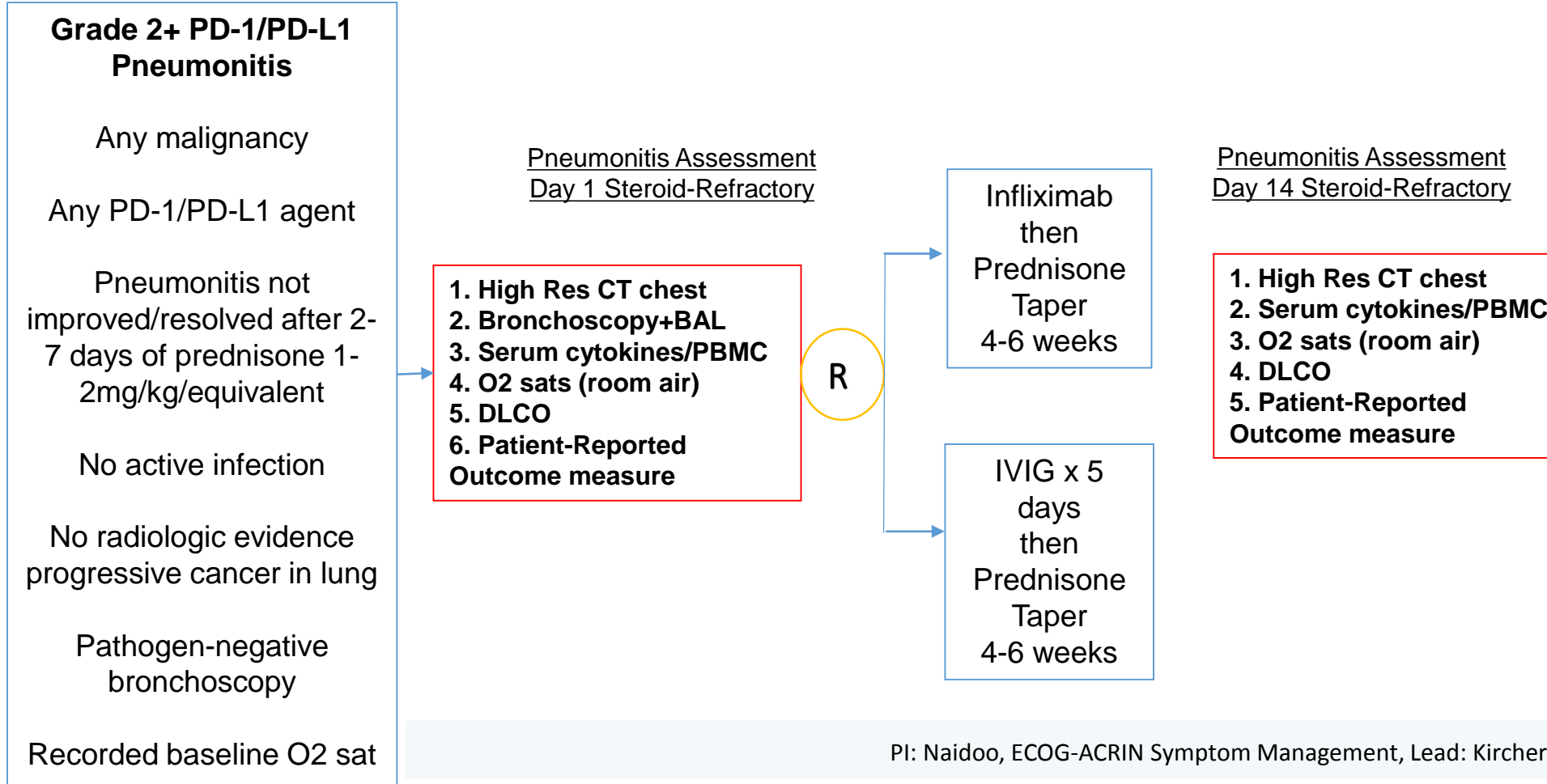
JAMA Neurology | Original Investigation

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

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Future Directions

Prospective Studies for irAEs: Steroid-Refractory Pneumonitis



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