# Immune-related Adverse Events and Toxicities

**Jarushka Naidoo, MB BCH MHS**

Consultant Medical Oncologist

Beaumont RCSI Cancer Centre, Dublin Ireland

Adj Assistant Professor of Oncology, Johns Hopkins University

@DrJNaidoo

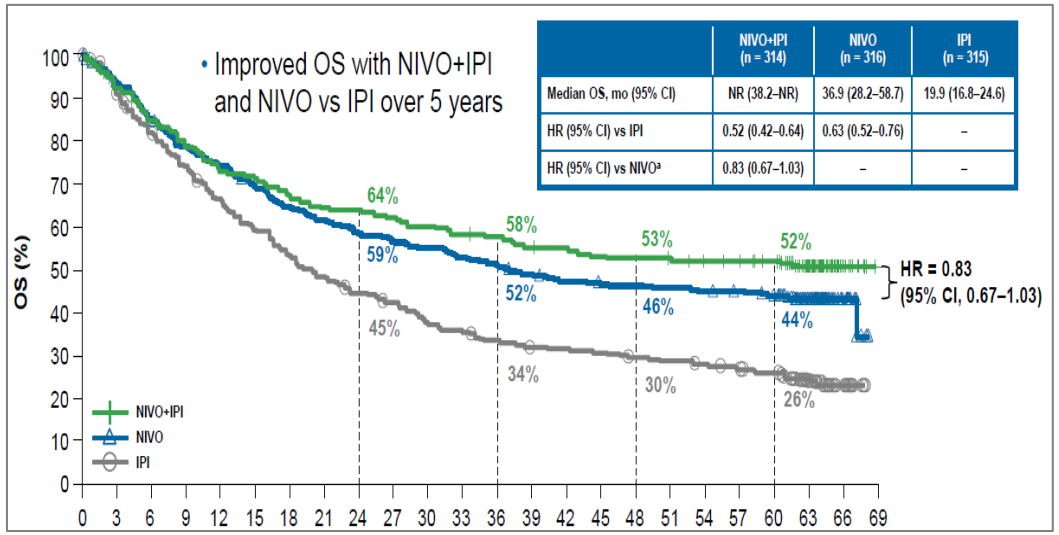
# Disclosures

Consulting Fees: AstraZeneca, Bristol Myers-Squibb, Roche/Genentech, Takeda, Pfizer, Daiichi Sankyo, Kaleido Biosciences, Merck

Contracted Research: AstraZeneza, Merck, Bristol myers Squibb, Mirati

Other (Data Safety Monitoring Board): Daiichi Sankyo

# Immune Checkpoint Inhibitors
## More patients 'surviving' from immunotherapy




| | NIVO+IPI (n = 314) | NIVO (n = 316) | IPI (n = 315) |
|---|---|---|---|
| Median OS, mo (95% CI) | NR (38.2–NR) | 36.9 (28.2–58.7) | 19.9 (16.8–24.6) |
| HR (95% CI) vs IPI | 0.52 (0.42–0.64) | 0.63 (0.52–0.76) | – |
| HR (95% CI) vs NIVO[a] | 0.83 (0.67–1.03) | – | – |

| | NIVO+IPI (n = 313) | | NIVO (n = 313) | | IPI (n = 311) | |
|---|---|---|---|---|---|---|
| | Any grade | Grade 3/4 | Any grade | Grade 3/4 | Any grade | Grade 3/4 |
| TRAE, % | 96 | 59 | 87 | 23 | 86 | 28 |
| TRAE leading to discontinuation, % | 42 | 31 | 13 | 8 | 15 | 14 |
| TRAE-death, n (%) | 2 (1) | | 1 (< 1) | | 1 (< 1) | |

**Early recognition affects outcomes**

| Immune-related Colitis | | | |
|---|---|---|---|
| | >30 days post onset | <30 days post onset | p |
| Steroid duration | 87 days | 53 days | 0.02 |
| Hospitalization | 27 (67.5) | 105 (73.9) | 0.43 |
| ICU admission | 4 (10) | 3 (2.1) | 0.07 |
| Recurrent colitis | 20 (50) | 31 (21.8) | 0.01 |

Larkin et al, ESMO 2019
Wang et al, *JITC* 2018

# Immune-Related Toxicity
## Diversity of Presentations and Mechanisms

### Selected Adverse Events

Hypophysitis

Thyroiditis

Adrenal Insufficiency

Enterocolitis

Dermatitis

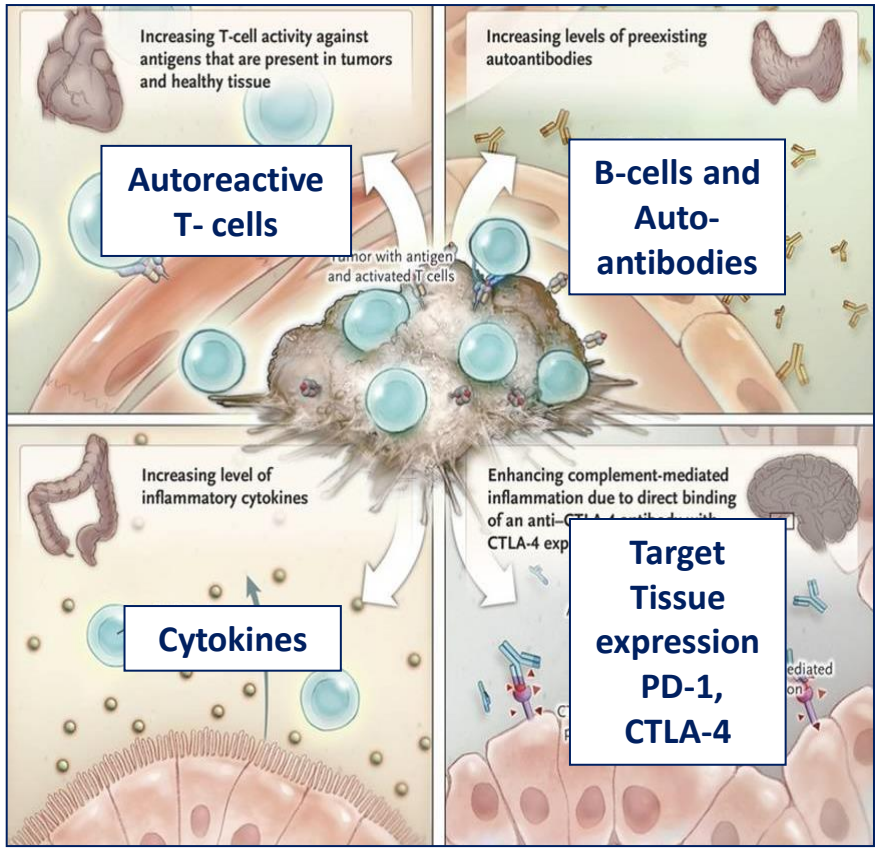
Pneumonitis

Hepatitis
Pancreatitis

Neuropathy

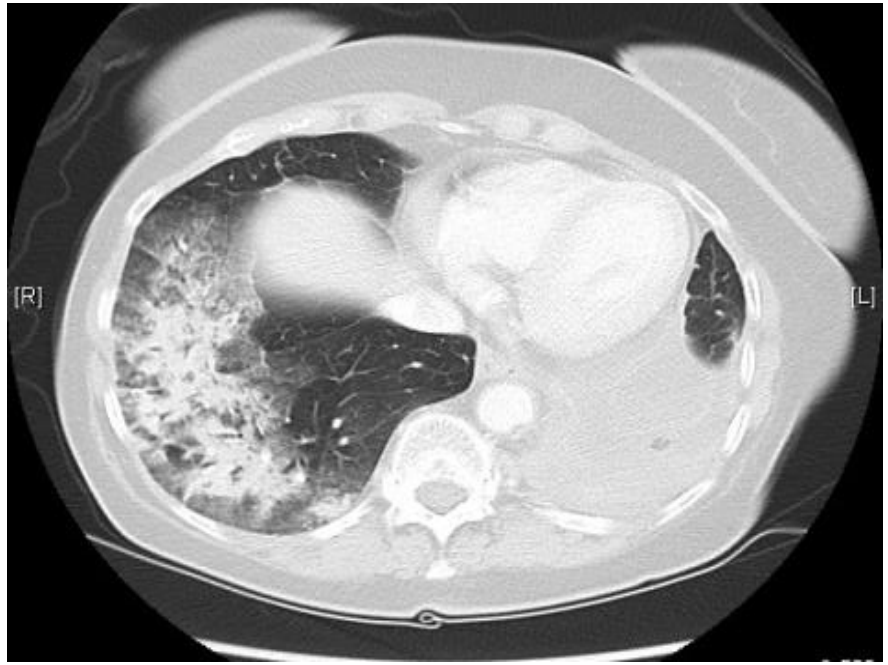
Arthritis

### Mechanisms of irAEs

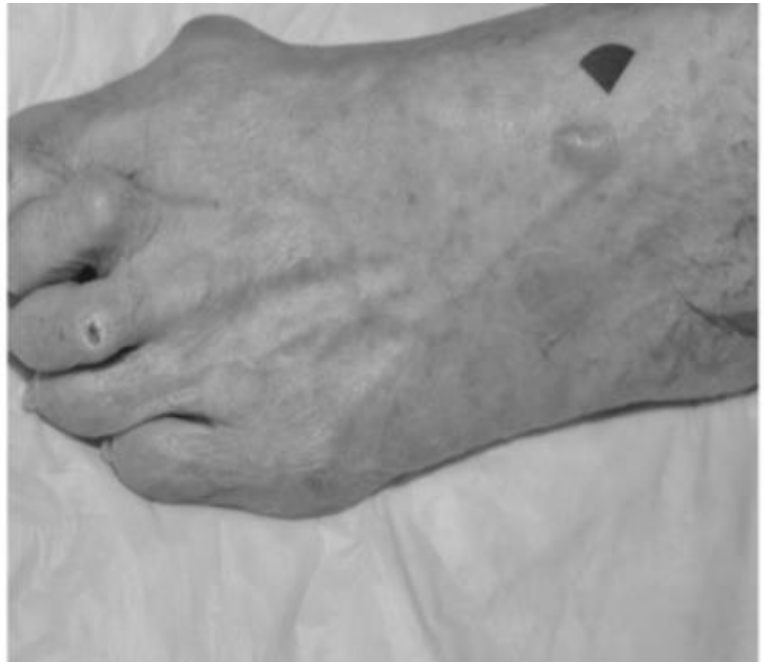



Postow et al, *NEJM* 2019

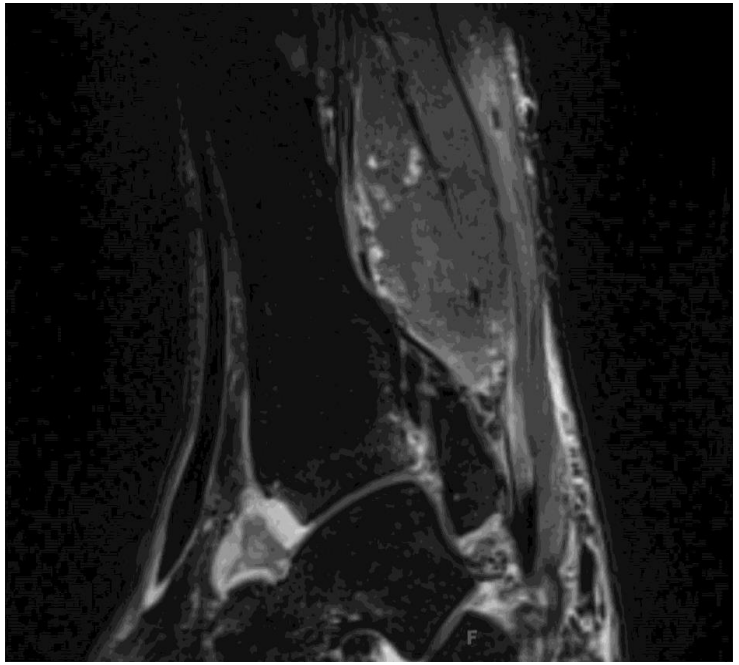
# Immunotherapy Toxicities
## Week #1 in Clinic




PD-1 Pneumonitis



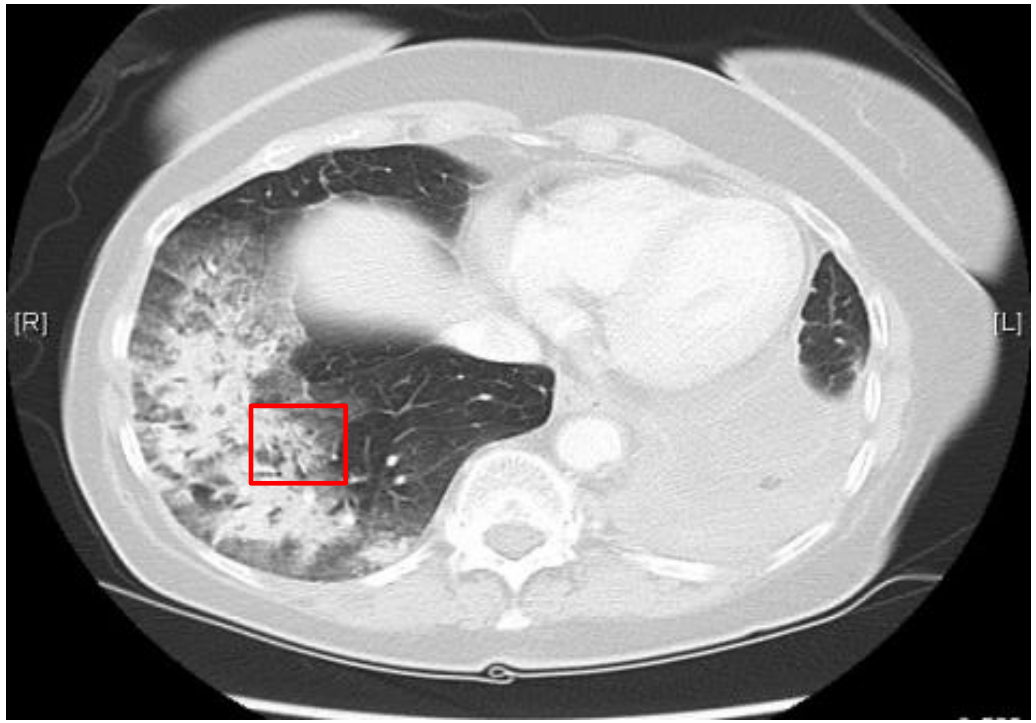
Bullous Pemphigoid



Inflammatory Arthritis

**Naidoo et al, *Cancer Immol Res* 2015**
**Naidoo et al, *J Clin Oncol* 2016**
**Cappelli et al, *Ann Rheum Dis* 2016**

# Pulmonary Toxicities
## Pneumonitis




- CT chest (CTPA if ruling out PE)
- Standard infectious evaluation
- Bronchoscopy +/- BAL

- Corticosteroid, Infliximab based on colitis

## Open Questions

1. Incidence

1. Risk Factors

2. Natural History

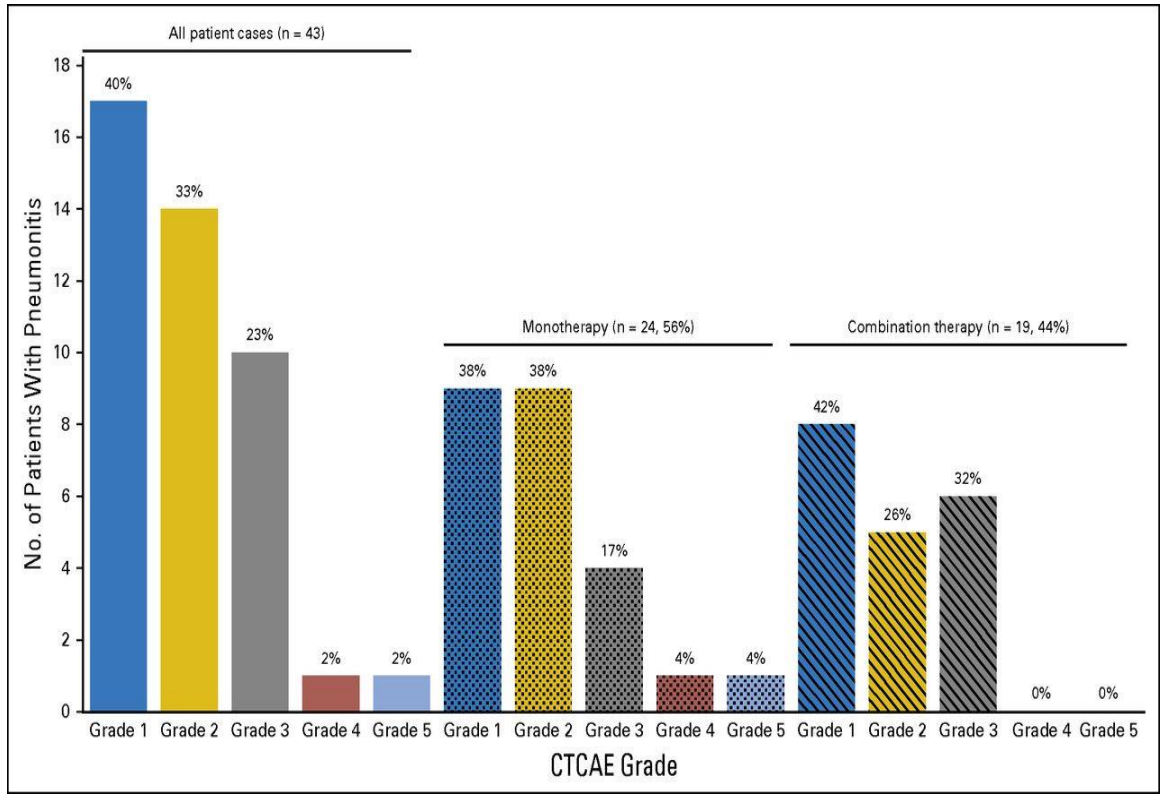
3. Clinical Manifestations

4. Mechanisms

5. Optimal Treatments

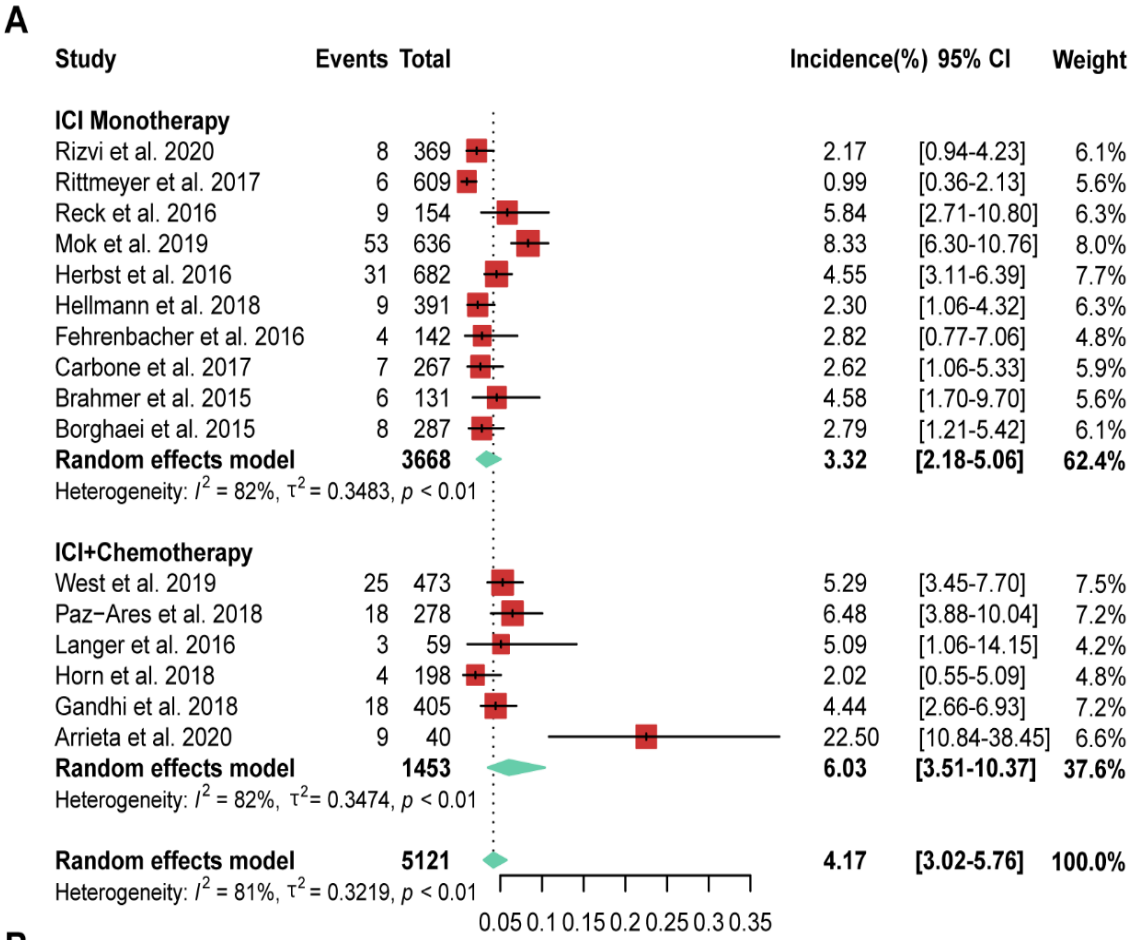
# Incidence
## Pneumonitis

**Initial reports: 5-10%**




**Real-world data: up to 19%**

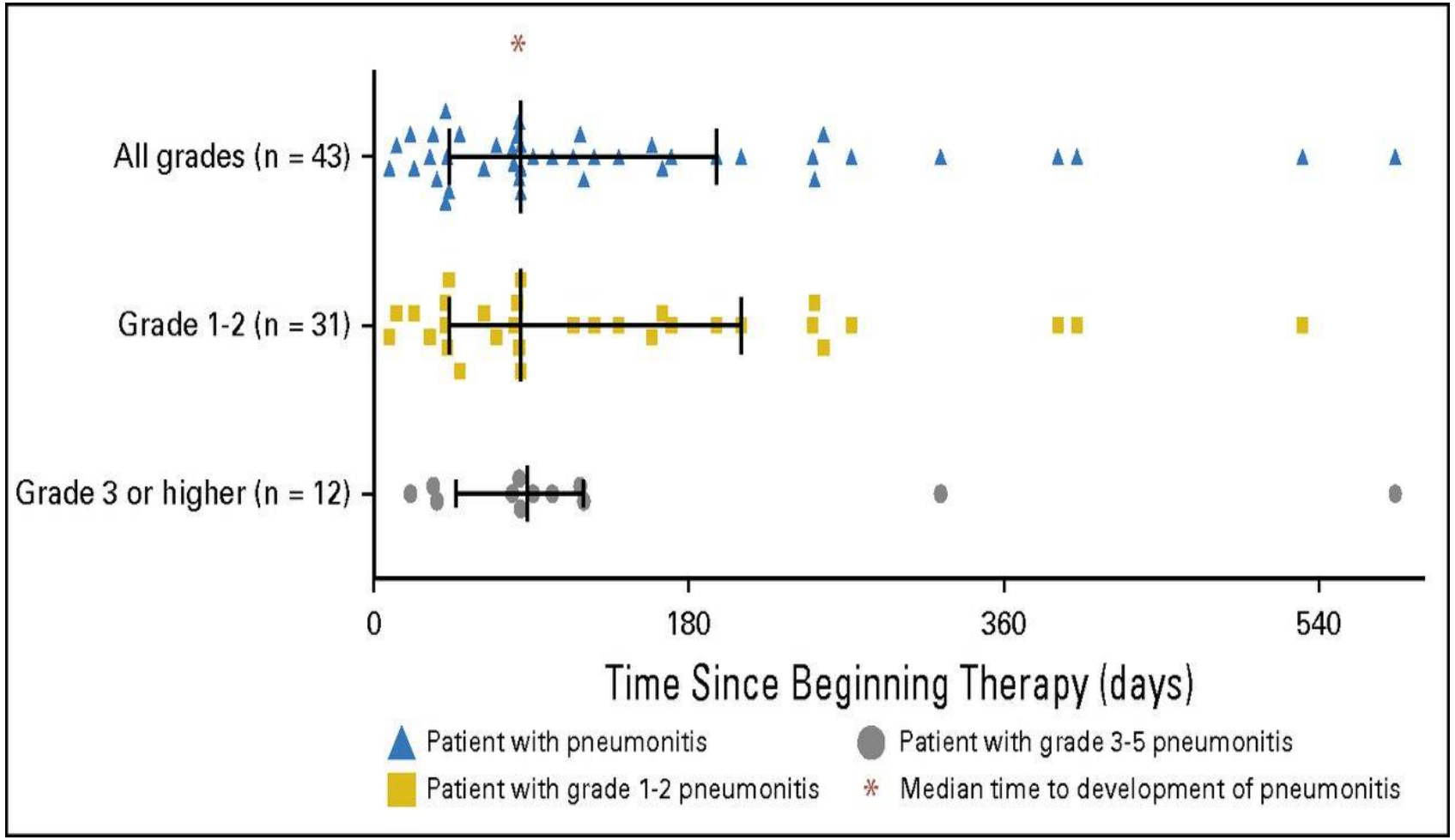
**Meta-analysis (NSCLC): 3%** ICI; **6%** ICI+chemo
↑risk all-grade & high-grade pneumonitis with ICIs vs. chemo





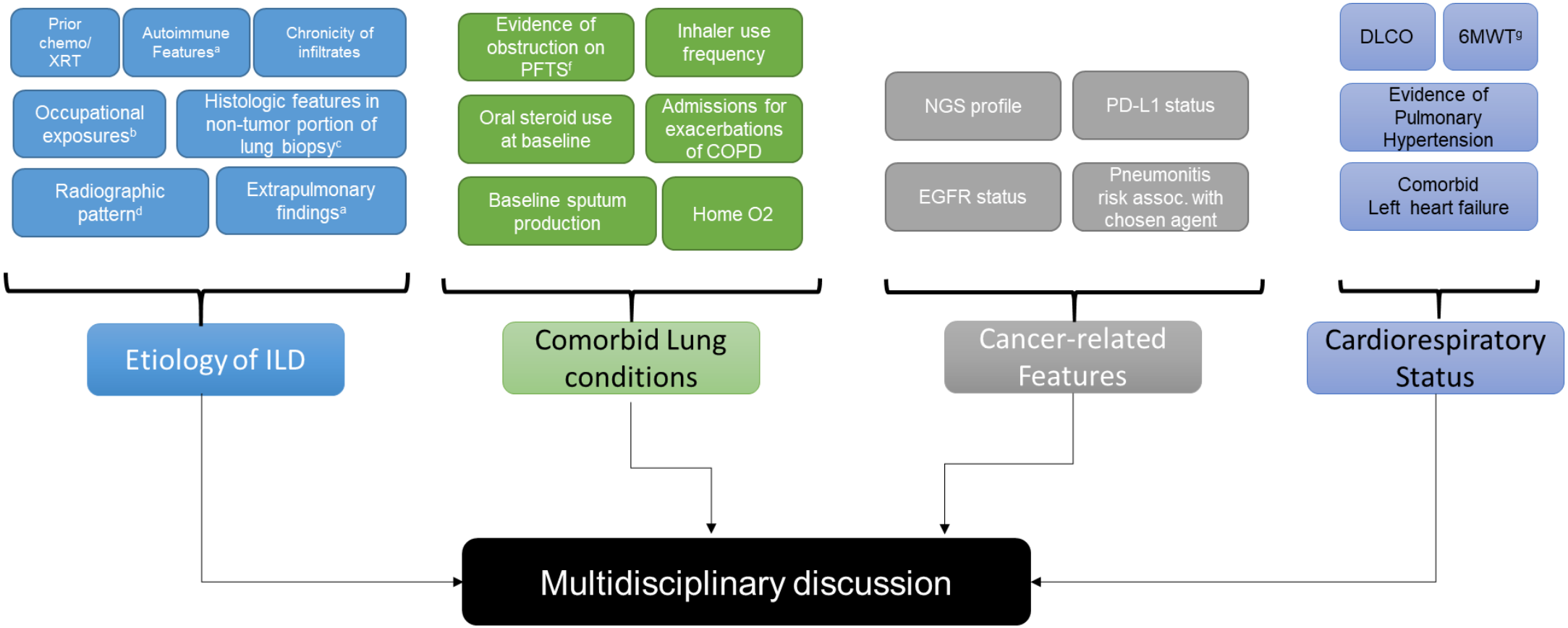
Naidoo et al, *J Clin Oncol 2016*
Suresh et al, *JTO 2018*
Lin et al, *Int immunopharm 2021*

# Pneumonitis
## Variable Timing of Onset




Naidoo et al, *J Clin Oncol 2016*

# PD-1/PD-L1 Inhibition
## Pneumonitis

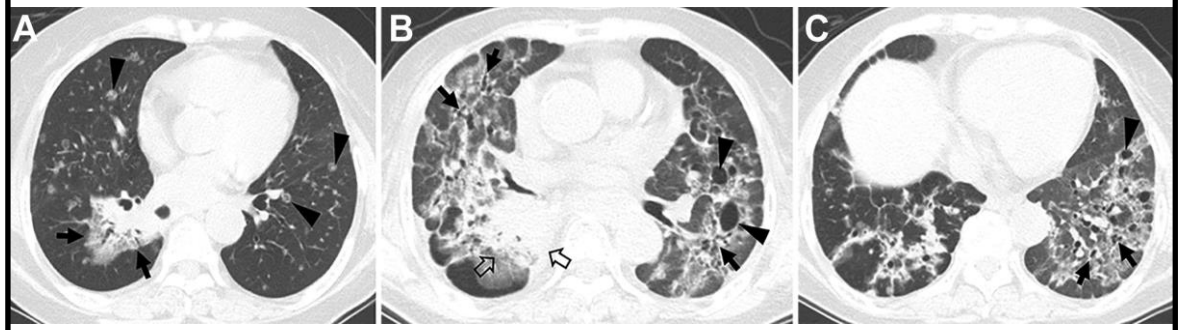



[a] Rashes (Gottron's papules, Heliotrope rash), evidence of synovitis, family history of RA/SLE, history of dry eyes/mouth, Raynaud's phenomenon
[b] Steelworkers, farmers, exposures to heavy metals, organic fumes, dusts, birds, etc. [c] such as poorly-formed granulomas, lymphocytic aggregates
[d] NSIP vs UIP-pattern, evidence of air-trapping, lobar dominance. [f] may present as complex obstruction (TLCpp – FVCpp > 15).

**Naidoo, Suresh, *Oncologist 2020*.**

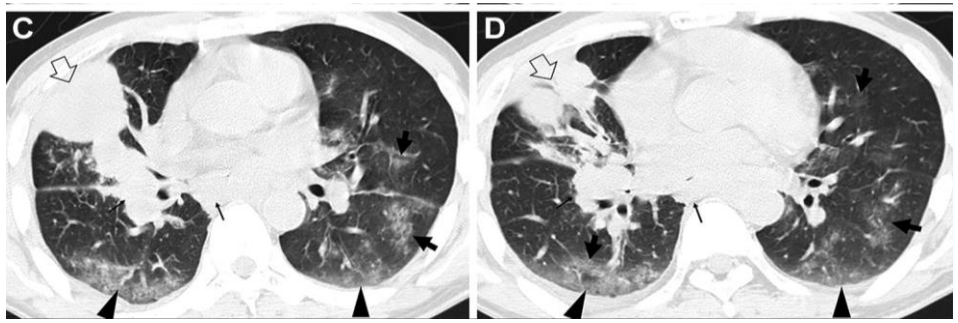
# Pneumonitis
## Fleishner Radiographic Subtypes

### NSIP Type



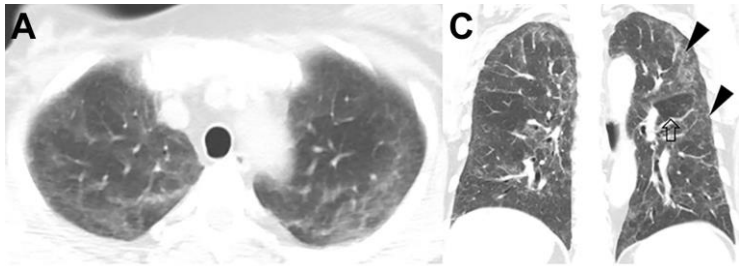

- Patchy areas of GGO +/- consolidation;
- Bilateral, symmetric; lower-lung involvement

### Organizing Pneumonia Type



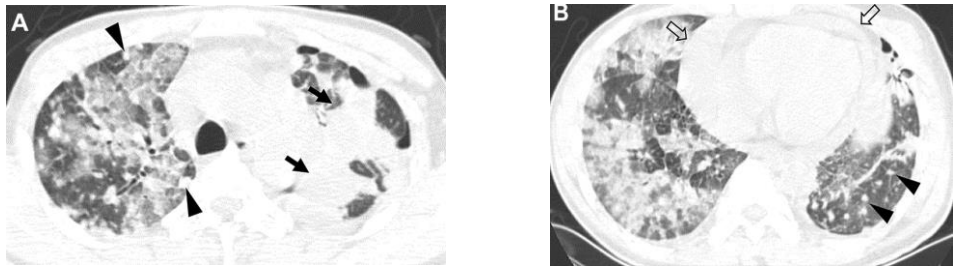

- Multifocal patchy alveolar opacities
- Peribronchovascular +/- peripheral

### Hypersensitivity Pneumonia




- Small centrilobular nodules; bilateral GGO
- Areas of decreased attenuation/ vascularity

### Diffuse Alveolar Damage

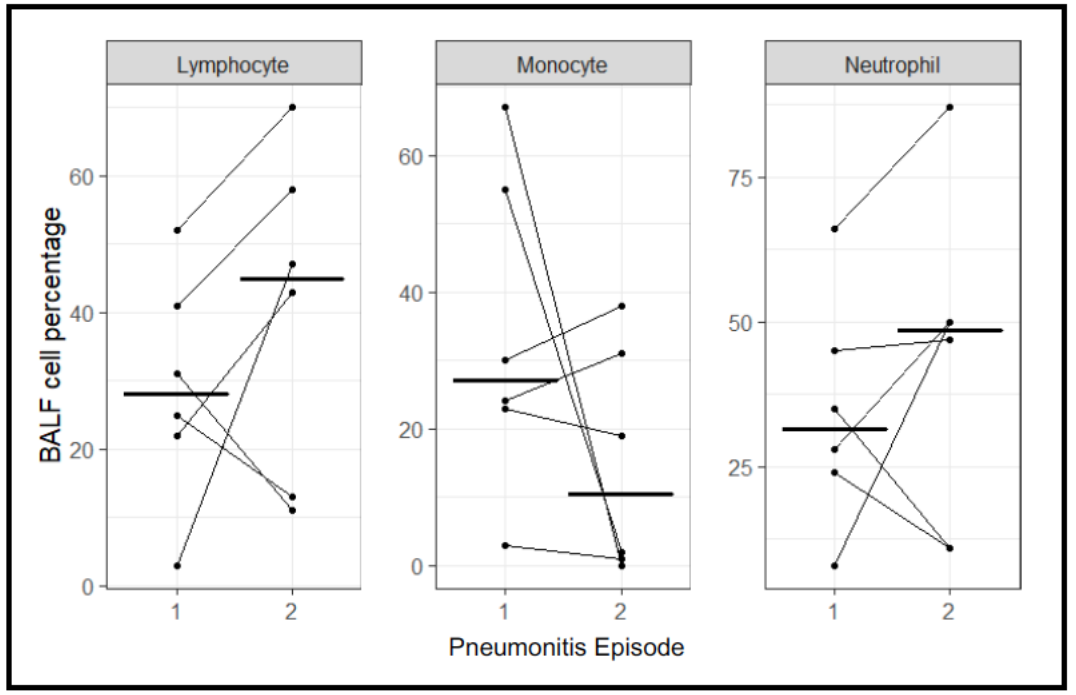


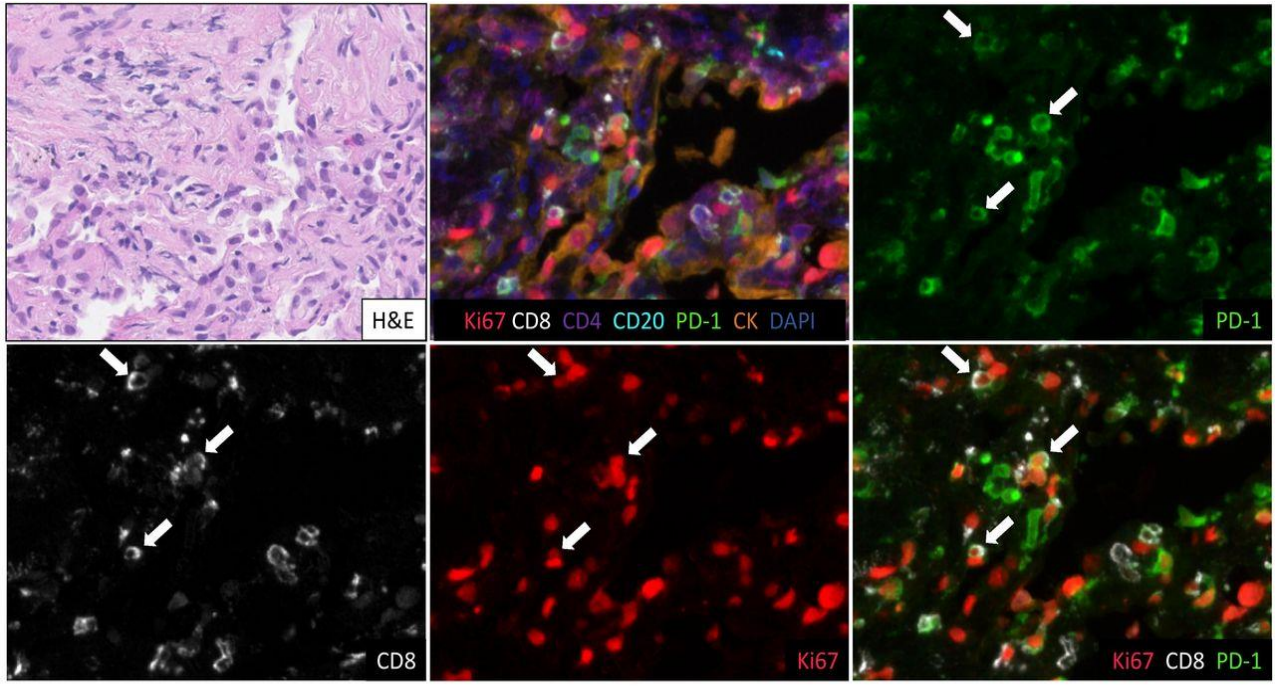

- Airspace consolidation (exudative phase)
- organizing and fibrotic phases

Johkoh et al, Chest 2021

# PD-1/PD-L1 Pneumonitis
## Chronic Pneumonitis

- Pneumonitis that lasts >= 12 weeks post ICI stop
- Patients who require long-term immunosuppression >= 12 weeks
- 2% of NSCLC and melanoma patients treated with anti-PD-1/PD-L1
- Persistent BAL lymphocytosis despite steroids
- Histopathologic BOOP, with infiltration of CD8+ T-cells in pneumonitis tissue




Naidoo, Suresh, *J Immunother Cancer* 2020

# PD-1/PD-L1 Pneumonitis

## Mechanisms: T-cell mediated; autoantibody mediated (anti-CD74)

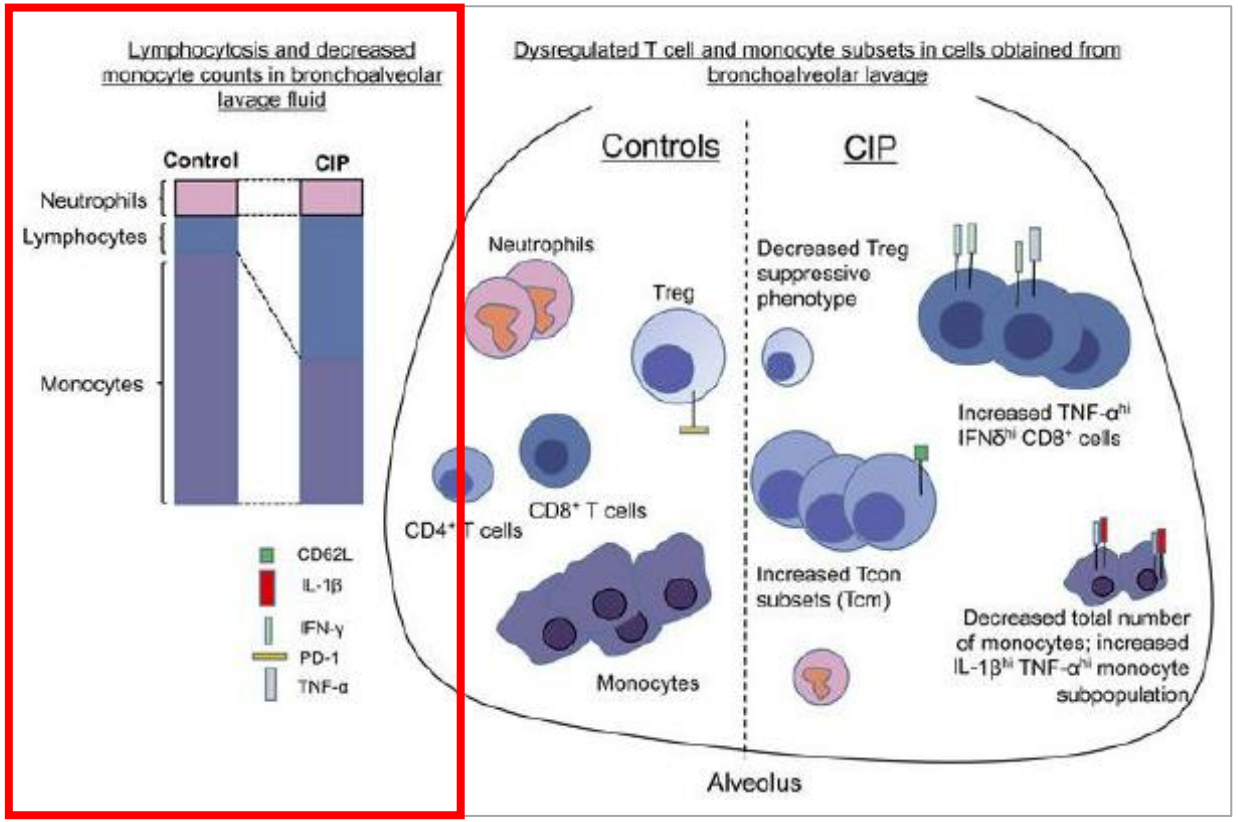
BAL fluid from pneumonitis p (n=12) v. controls (n=6):

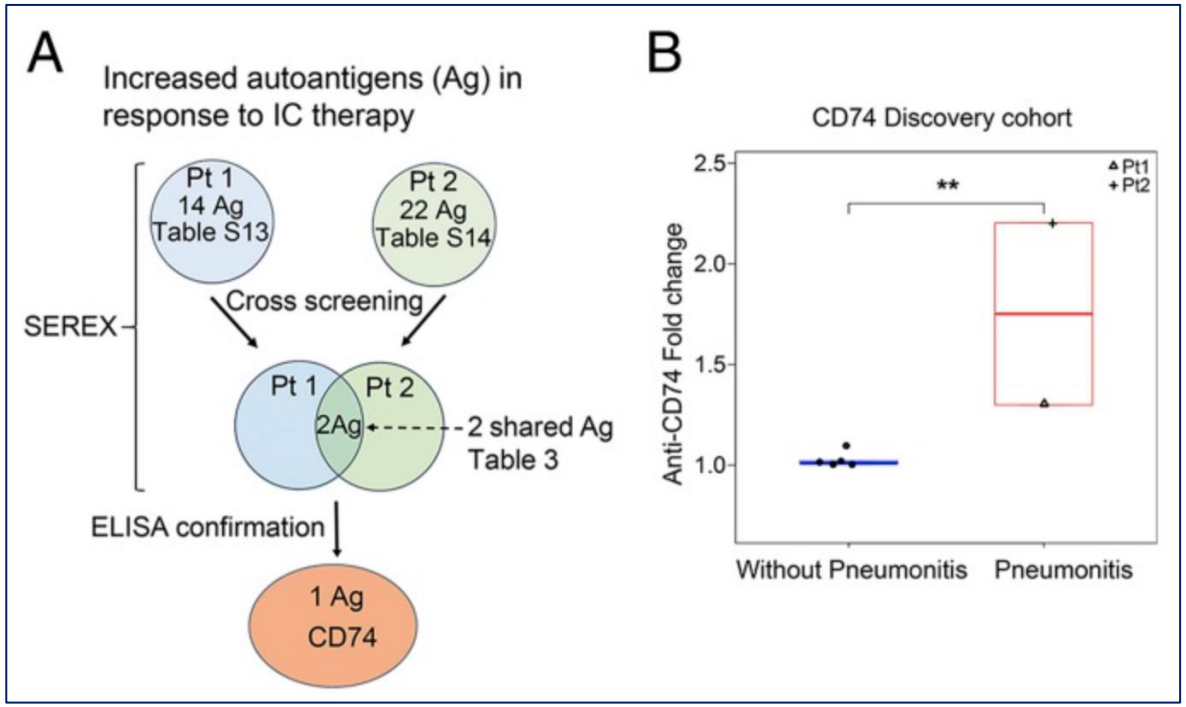
BAL cell differential; flow cytometry; cytokine analysis

**CD74:** cell-surface receptor for MIF

MHC class II chaperone, lung inflammation

autoimmune disease



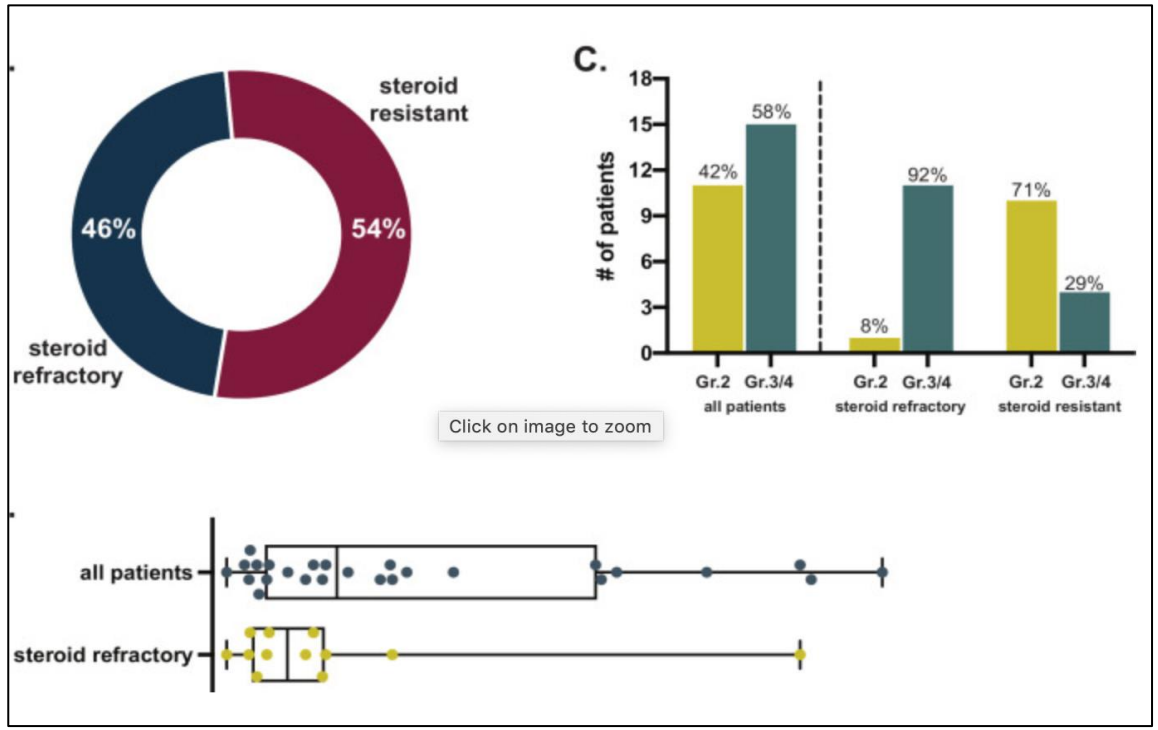



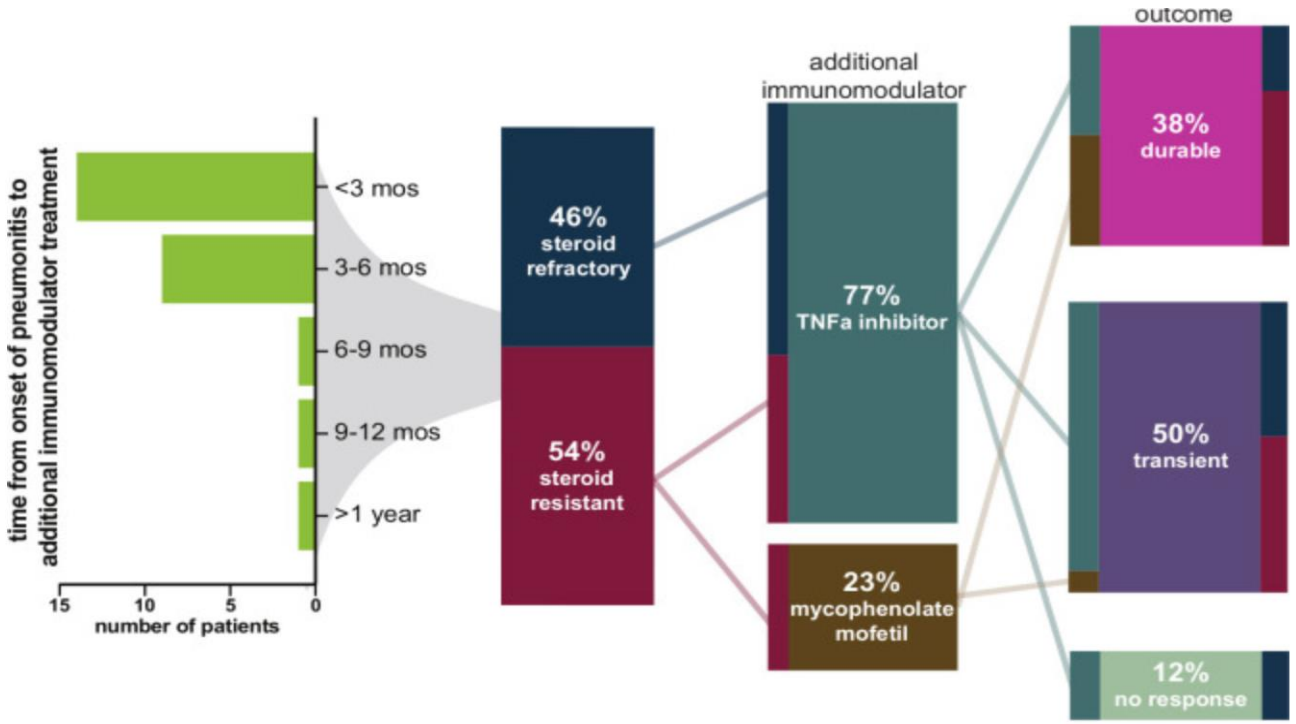

**Suresh, Naidoo et al, *J Clin Invest 2019***

# Treatment
## Steroid-refractory vs. Steroid-resistant Pneumonitis

- 26 pts with pneumonitis requiring immunosuppression beyond steroids

- ‘Steroid-refractory’ : no improvement with steroids
- ‘Steroid-resistant’ : transient improvement

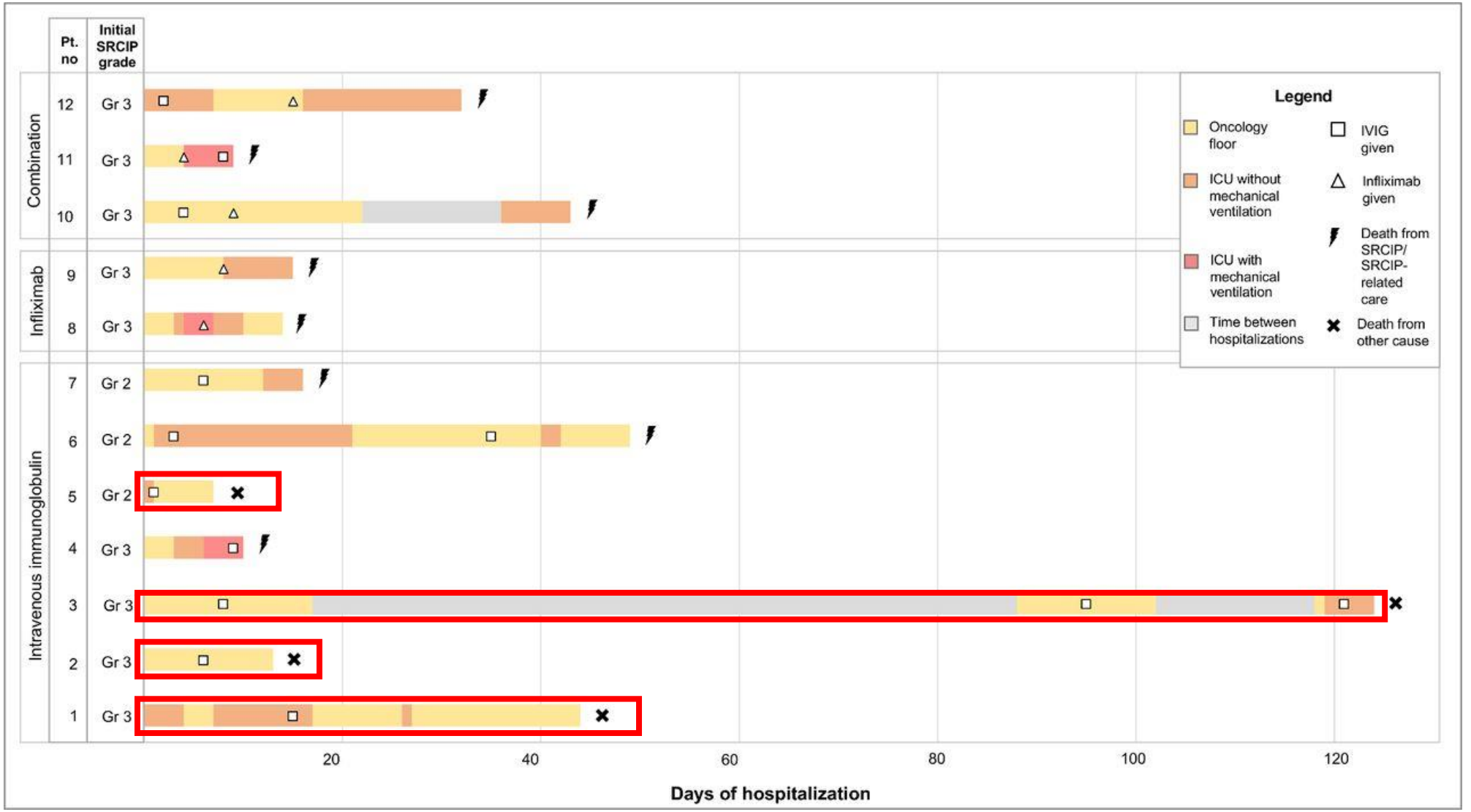



10/26 (38%) had durable response
- Infliximab
- Mycophenolate mofetil

**Beattie et al, *J Immunother Cancer 2021***

# Steroid-Refractory Pneumonitis
## Selected patients improve with IVIG




Balaji et al, *J Immunother Cancer 2021*

# Pneumonitis Trials
## EAQ172: ECOG Steroid-Refractory PD-1/PD-L1 Pneumonitis

**Patient with Grade 2+ PD-1/PD-L1 Pneumonitis**

Any solid/hematologic malignancy

Any PD-1/PD-L1 agent

Pneumonitis that has not improved to CTCAE grade 1 or less, after 2-10 days prednisone 1-2mg/kg/equivalent

No active infection

No radiologic evidence progressive cancer in lung

Pathogen-negative bronchoscopy

Pneumonitis Assessment Day 1 Steroid-Refractory

1. **Hb saturation (PaO2/FiO2 on ABG)**
2. **PFTs**
3. **High Res CT chest**
4. **Blood (correlatives)**
5. **Bronchoscopy +BAL (+/- biopsy)**
6. **Patient Reported Outcomes**

**R**

Infliximab then Prednisone Taper 4-6 weeks

IVIG x 5 days then Prednisone Taper 4-6 weeks

Pneumonitis Assessment Day 14 Steroid-Refractory

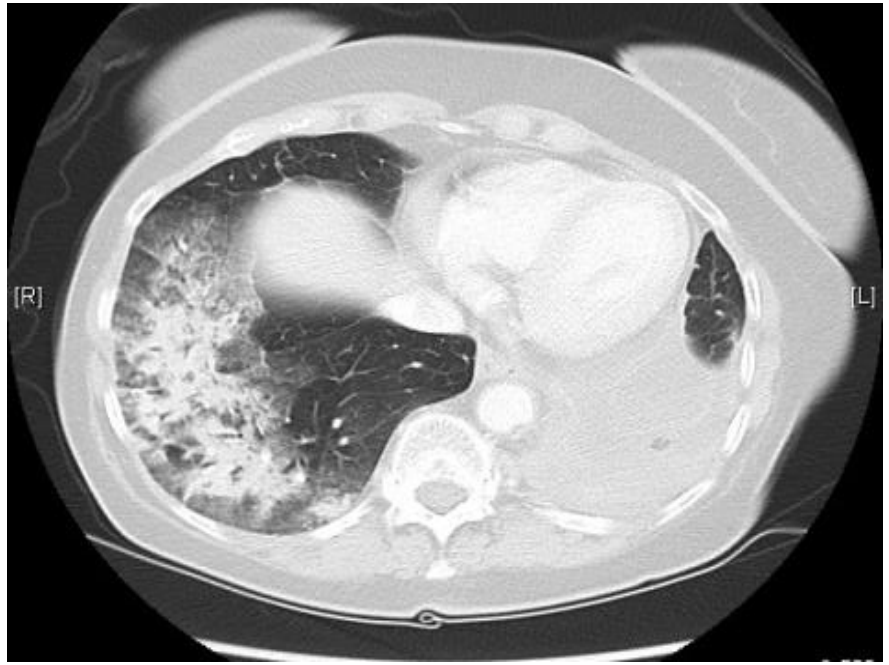
1. **Hb saturation (PaO2/FiO2 on ABG)**
2. **PFTs**
3. **High Res CT chest**
4. **Blood (correlatives)**
5. **Bronchoscopy +BAL (+/- biopsy)**
6. **Patient Reported Outcomes**

Pneumonitis Response Day 28
Any improvement in P/F Ratio on ABG

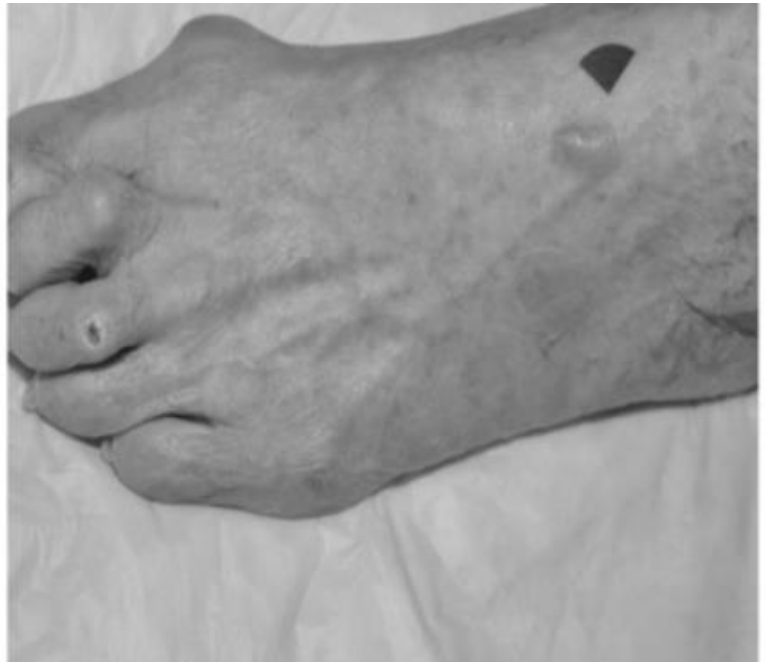
*Primary Endpoint:
- Improvement in PAO2/FiO2 on ABG from day 1, at 28-days

ECOG-ACRIN PI: Naidoo,

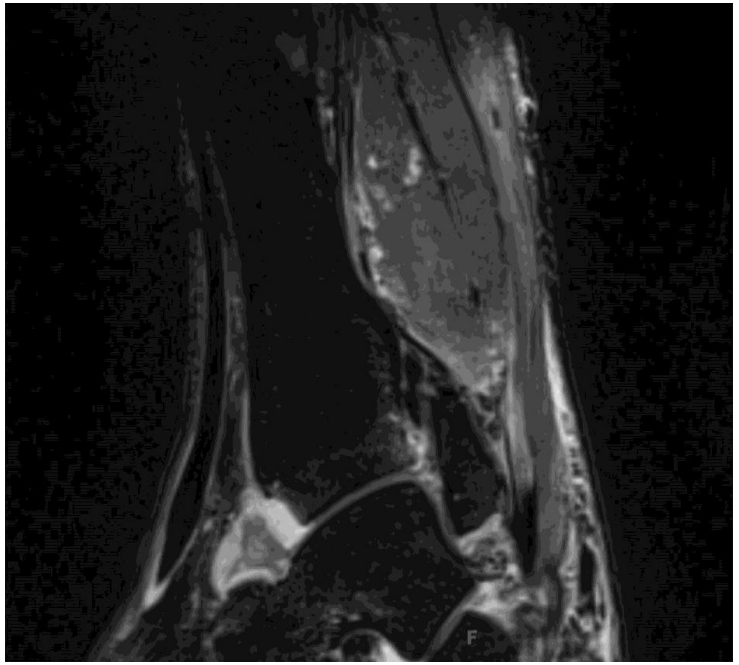
# Immunotherapy Toxicities
## Week #1 in Clinic




PD-1 Pneumonitis



Bullous Pemphigoid



Inflammatory Arthritis

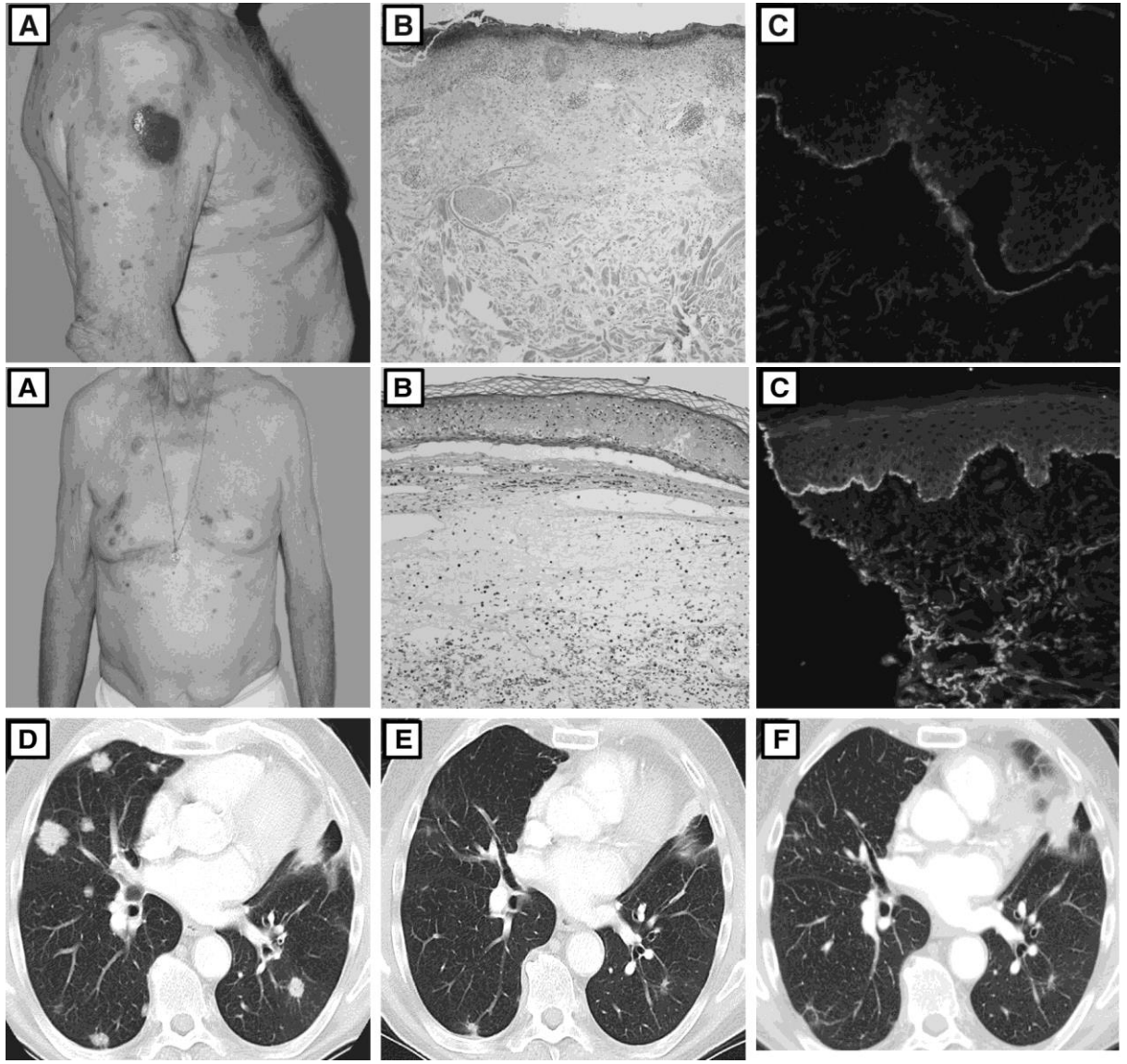
Naidoo et al, *Cancer Immol Res* 2015
Naidoo et al, *J Clin Oncol* 2016
Cappelli et al, *Ann Rheum Dis* 2016

# Skin Toxicities
## Bullous Pemphigoid

- **Blistering Disorders**
- TEN and SJS case reports only

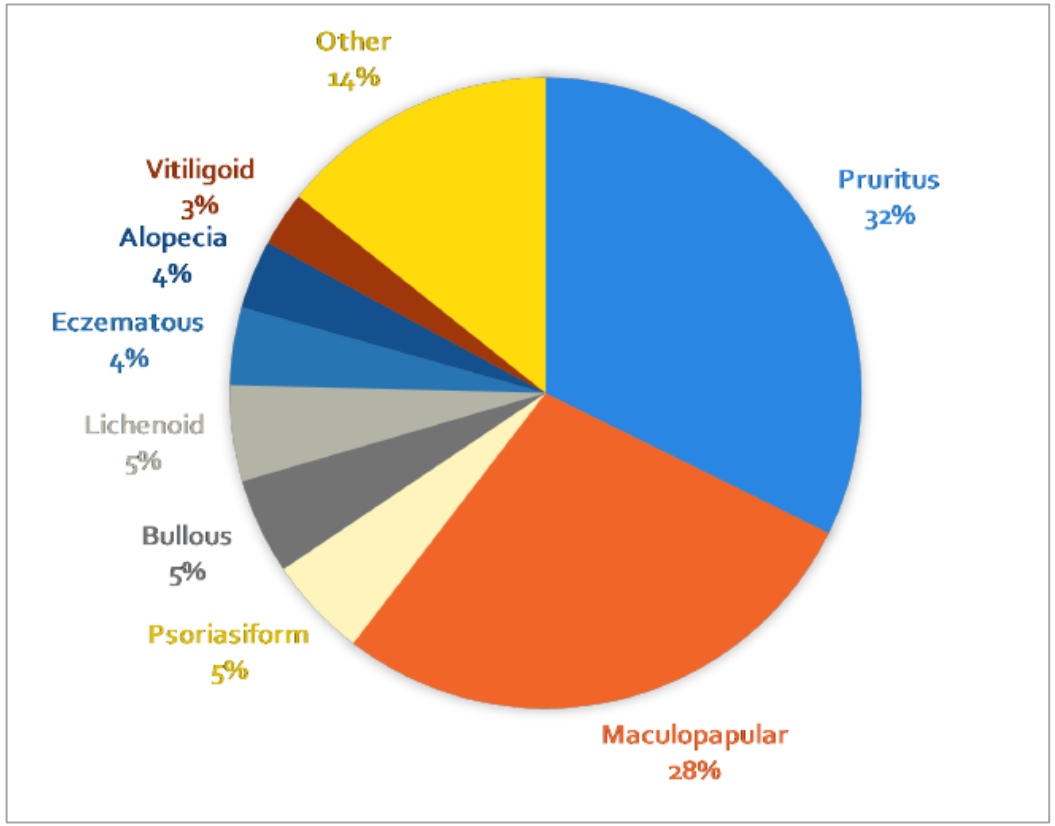
- **Bullous Pemphigoid**
- Skin biopsy: H&E, DIF and IIF
- IgG + C3 deposits at blister roof
- + BP180 +BP230 antibodies

- First described cases BP from anti-PD-1/PD-L1
- Responders to immunotherapy
- Antibody-mediated toxicity, B-cell mediated

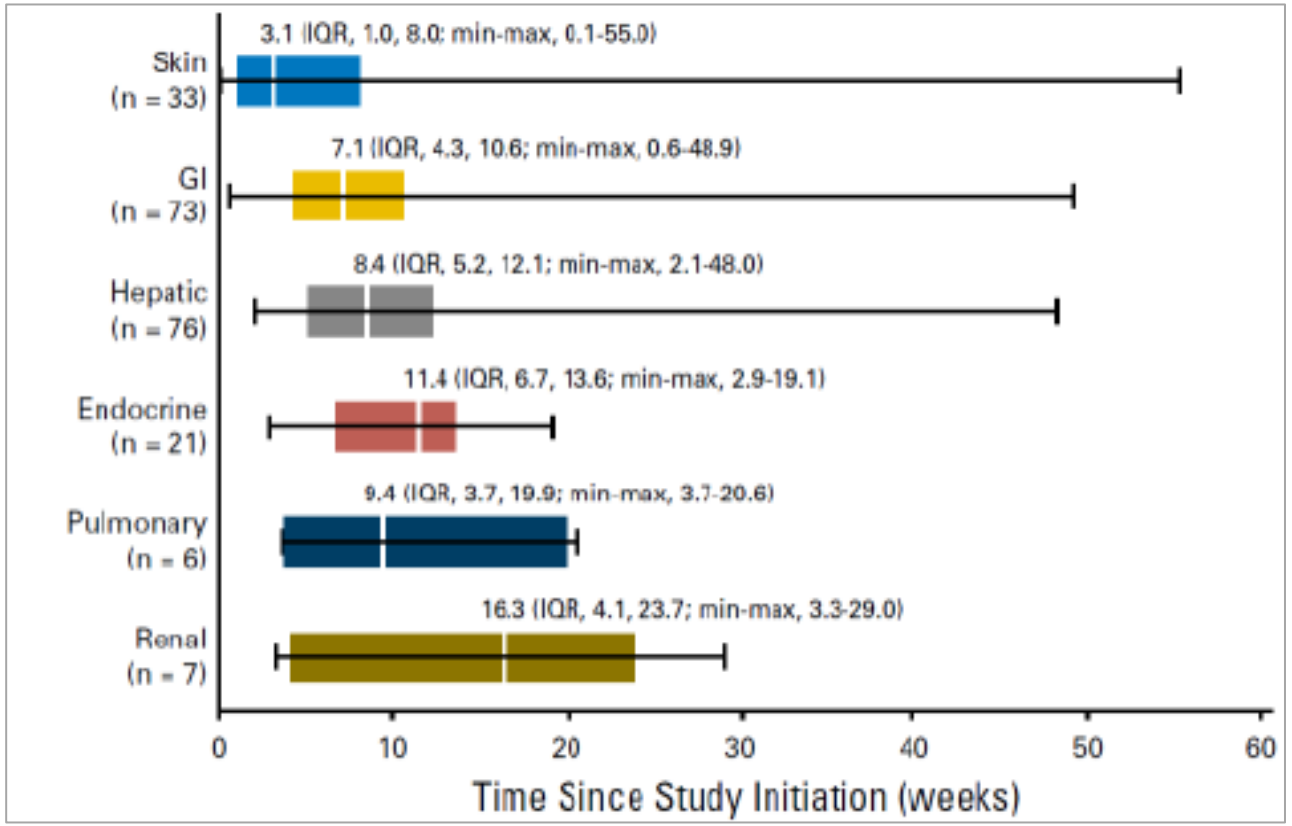



Naidoo et al, *Cancer Immunol Res* 2016

# Skin Toxicities
## Diagnosis




**PD-1/L1+/-CTLA4, All Solid Tumours (n=285)**



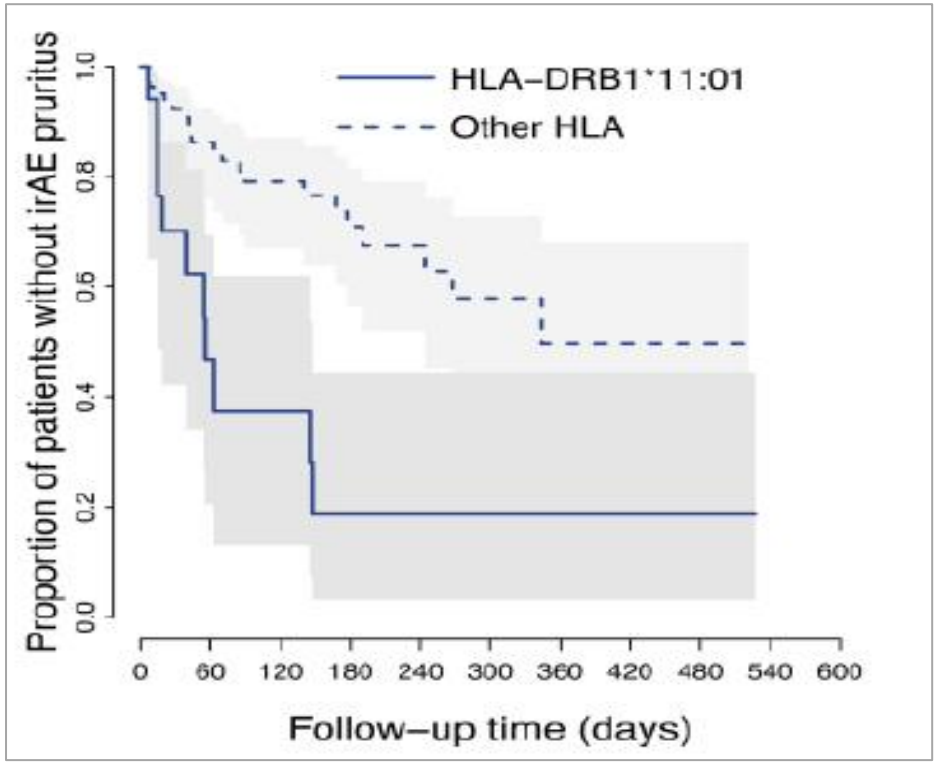

**PD-1+CTLA-4 G3+, Melanoma (n=448)**

Sznol, *J Clin Oncoll* 2017
Phillips, *J Clin Oncol* 2019

# Skin Toxicities
## Spectrum and Mechanisms

- Anti-PD-1 treated patients had a higher risk of mucositis, xerostomia, pruritus, lichenoid dermatitis
- HLA subtypes may predict for skin irAEs (melanoma patients)

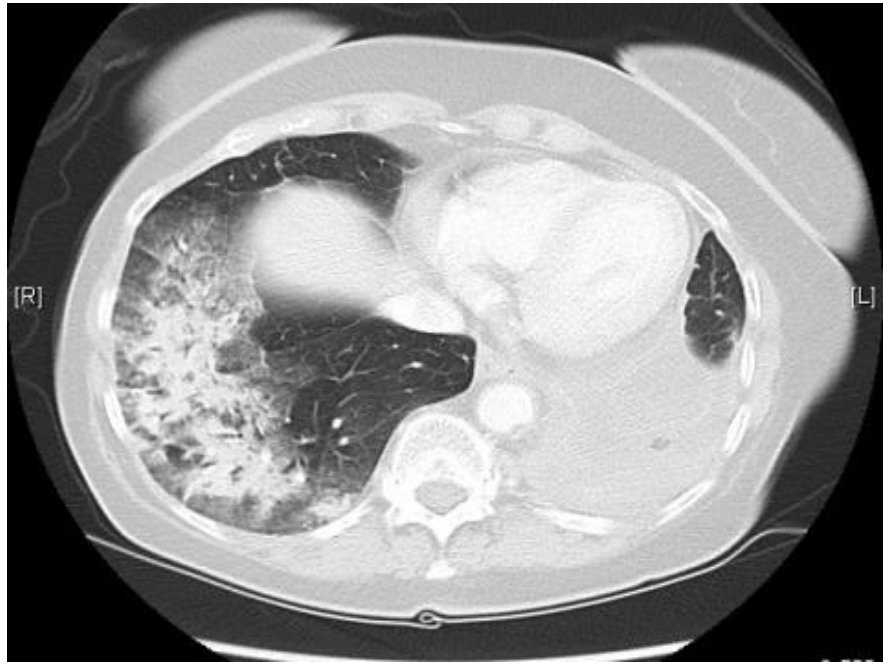
| Cutaneous AEs | General population | PD-1, n (%) | OR (95% CI) | P-value |
|---|---|---|---|---|
| Pruritus | 17132 (0.4) | 21 (3.8) | 11.3 (8.9-14.3) | <0.005 |
| Mucositis | 425 (0.009) | 10 (0.5) | 65.7 (35-123.3) | <0.005 |
| Xerostomia | 7396 (0.2) | 33 (1.8) | 11.9 (8.4-16.8) | <0.005 |
| Lichenoid dermatitis | 2217 (0.05) | 9 (0.5) | 10.7 (5.5-10.7) | <0.005 |
| Scleroderma | 1689 (0.003) | 6 (0.3) | 9.3 (4.2-20.9) | <0.005) |



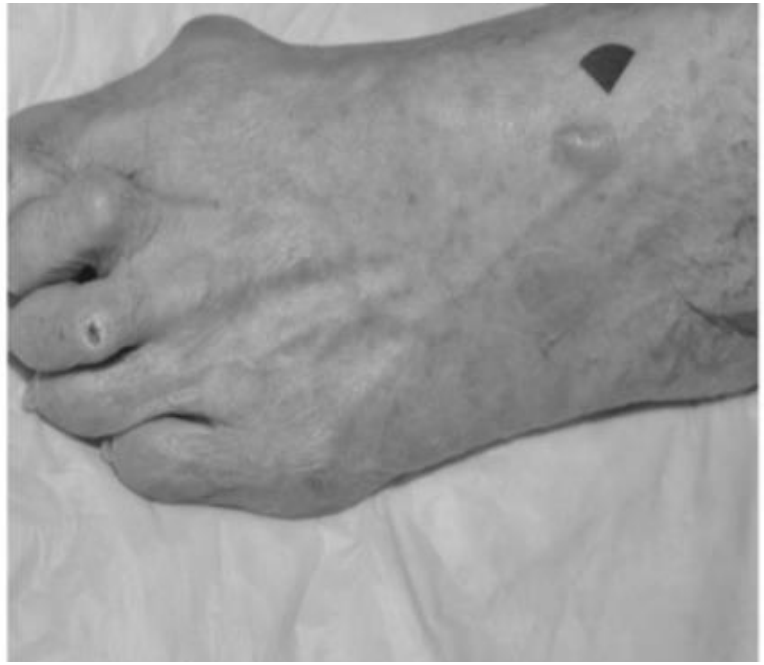

**CTLAE or PD-1, NSCLC or Melanoma (n=102)**


Le, Semenov, Naidoo, Kwatra et al, *J Dermatol Treat* 2021
Ali, *Eur J Cancer* 2019

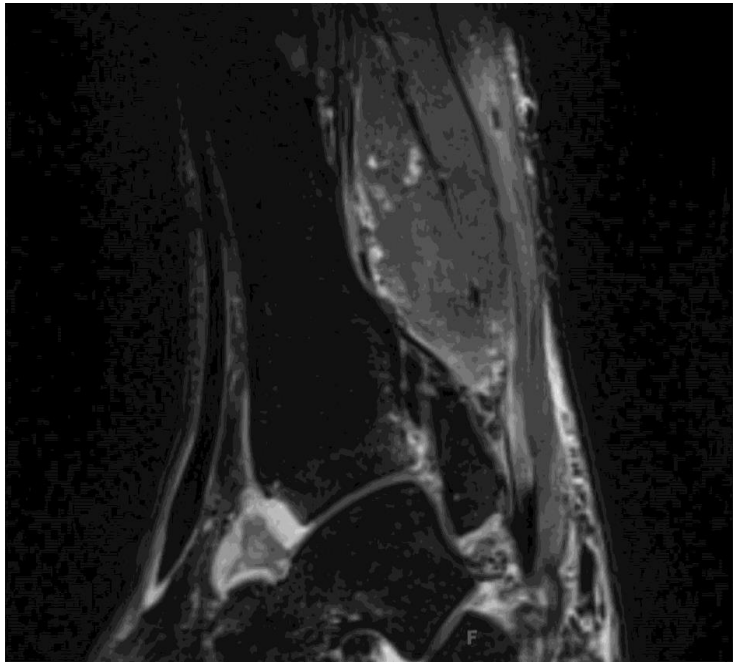
# Immunotherapy Toxicities
## Week #1 in Clinic




PD-1 Pneumonitis



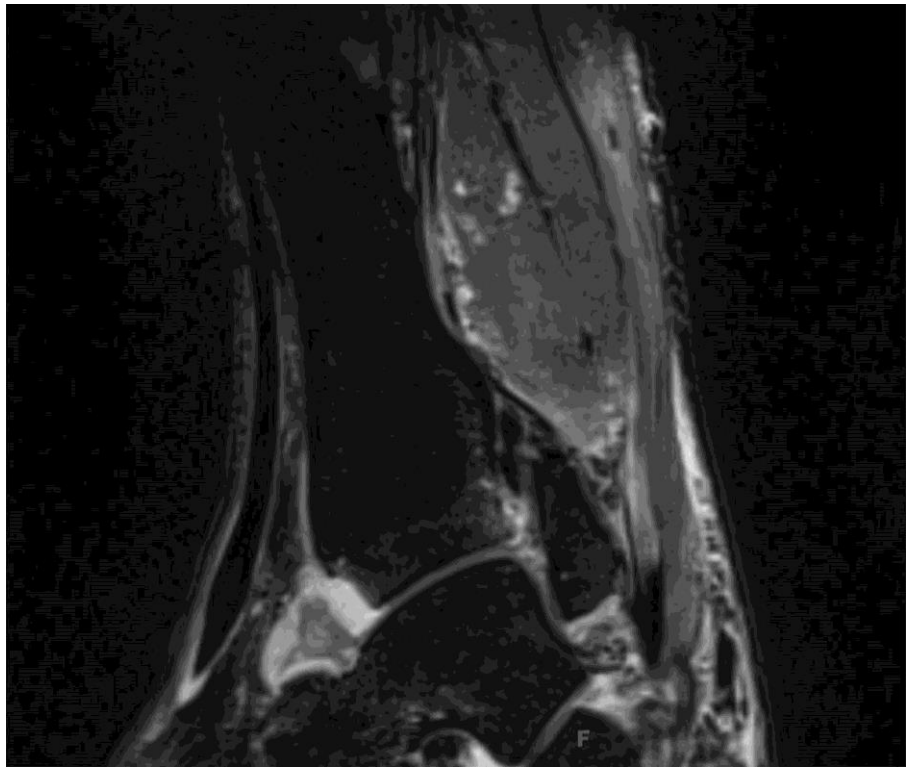
Bullous Pemphigoid



Inflammatory Arthritis

**Naidoo et al, *Cancer Immol Res* 2015**
**Naidoo et al, *J Clin Oncol* 2016**
**Cappelli et al, *Ann Rheum Dis* 2016**

# Rheumatologic irAEs
## Inflammatory Arthritis



- Immune-related synovitis
- Optimal evaluation: US, MRI
- Management:
  - Corticosteroid, Methotrexate

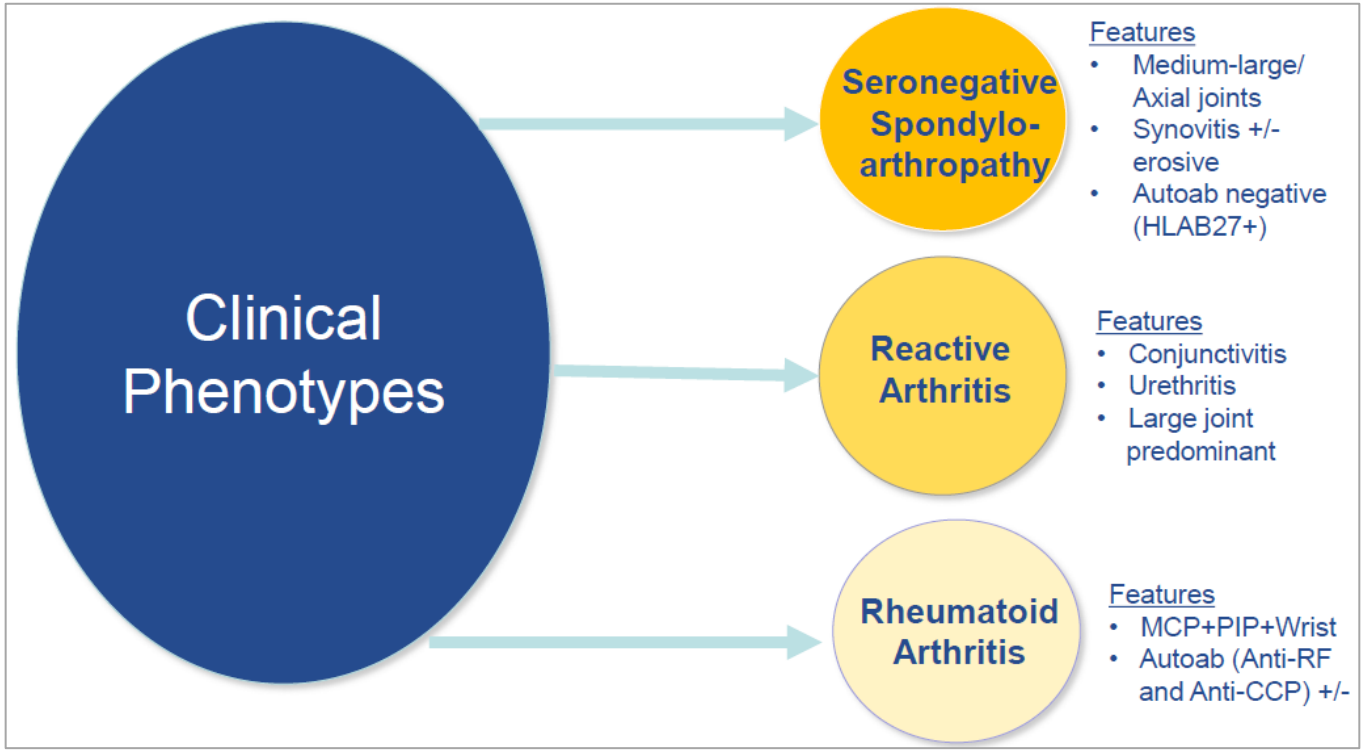
**Cappelli et al, *Ann Rheum Dis* 2016**
**Kostine et al, *Ann Rheum Dis* 2018**

### Open Questions

1. Risk Factors
2. Natural History
3. Clinical Manifestations
4. Mechanisms
5. Optimal Treatments

# PD-1/PD-L1 Inhibition
## Inflammatory Arthritis

- **Inflammatory arthritis**
- Distinct phenotypes by ICI regimen
- Combination ICIs:
  - Associated with RA-subtype
  - Knee involvement first
  - Higher baseline CRP
- 10% develop chronic arthritis (> 6 months)




- **Management**
- Lower doses of corticosteroids (prednisone 10-20-mg for grade 2+)
- Low threshold for immunosuppression

**Cappelli et al, Semin Arth Rheu 2018**
**Naidoo et al, *Oncologist* 2017**
**Braaten et al, *Ann Rheum Dis* 2019**

# Inflammatory Arthritis
## Mechanisms

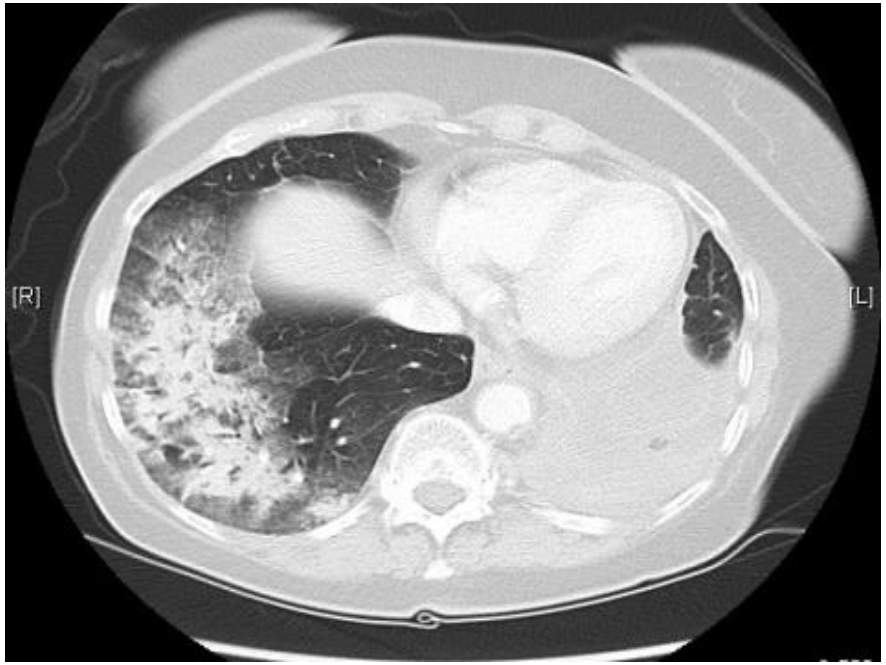
- ICI-arthritis tends to be autoantibody negative
- Patients with ICI-arthritis had a greater odds of shared alleles
- Specific alleles enriched in ICI arthritis (DRB1*04:05)
- HLA genotypes may be implicated in who develops ICI-arthritis

| | ICI inflammatory arthritis *n* = 26 (%) | RA *n* = 220 (%) | *P* value* |
|---|---|---|---|
| Positive for SE (at least 1) | 16 (61.5%) | 145 (65.9%) | 0.66 |
| Number of SE alleles | Two alleles: 2 (7.7%) | Two alleles: 52 (23.6%) | 0.15 |
| | One allele: 14 (53.8%) | One allele: 93 (42.3%) | |
| | Zero allele: 10 (38.5%) | Zero allele: 75 (34%) | |
| CCP positive | 2 (7.7%) | 142 (64.6%) | **<0.01** |
| RF positive | 2 (7.7%) | 122/215 (56.7%) | **<0.01** |
| RF and CCP positive | 0 (0%) | 106/215 (49.3%) | **<0.01** |

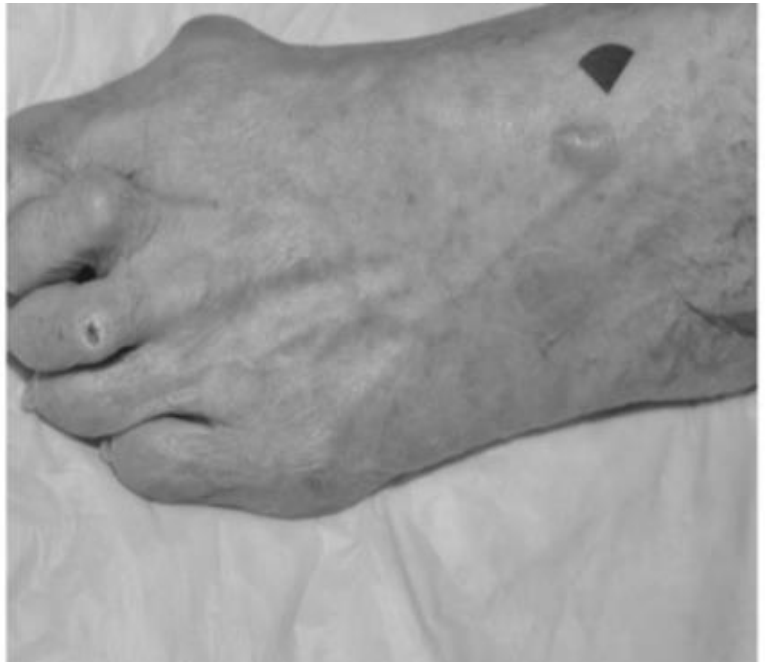
| HLA allele/s | OR(95% CI) ICI inflammatory arthritis *vs* controls | *P* value |
|---|---|---|
| A*03: 01 | 2.2 (0.9, 5.1) | 0.07 |
| C*12: 02 | 5.4 (0.6, 26.8) | 0.07 |
| DQB1*03: 01 | 0.4 (0.1, 1.1) | 0.06 |
| DRB1*03: 01 | 1.1 (0.4, 2.9) | 0.81 |
| DRB1*04: 05 | 8.6 (1.7, 43.4) | **0.04** |
| At least 1 SE allele | 2.3 (1.0, 5.1) | **0.04** |

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

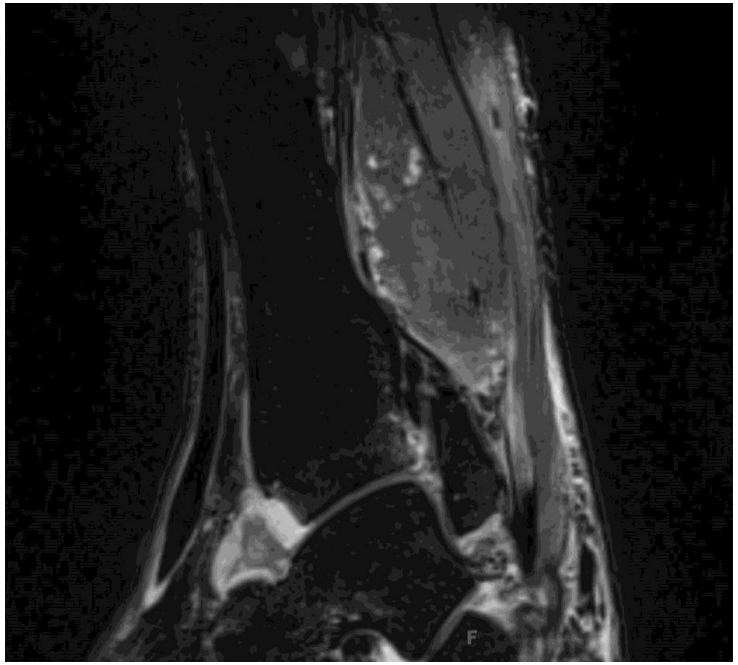
# Immunotherapy Toxicities
## Year #5 in Clinic




PD-1 Pneumonitis



Bullous Pemphigoid



Inflammatory Arthritis

**Naidoo et al, *Cancer Immol Res* 2015**
**Naidoo et al, *J Clin Oncol* 2016**
**Cappelli et al, *Ann Rheum Dis* 2016**

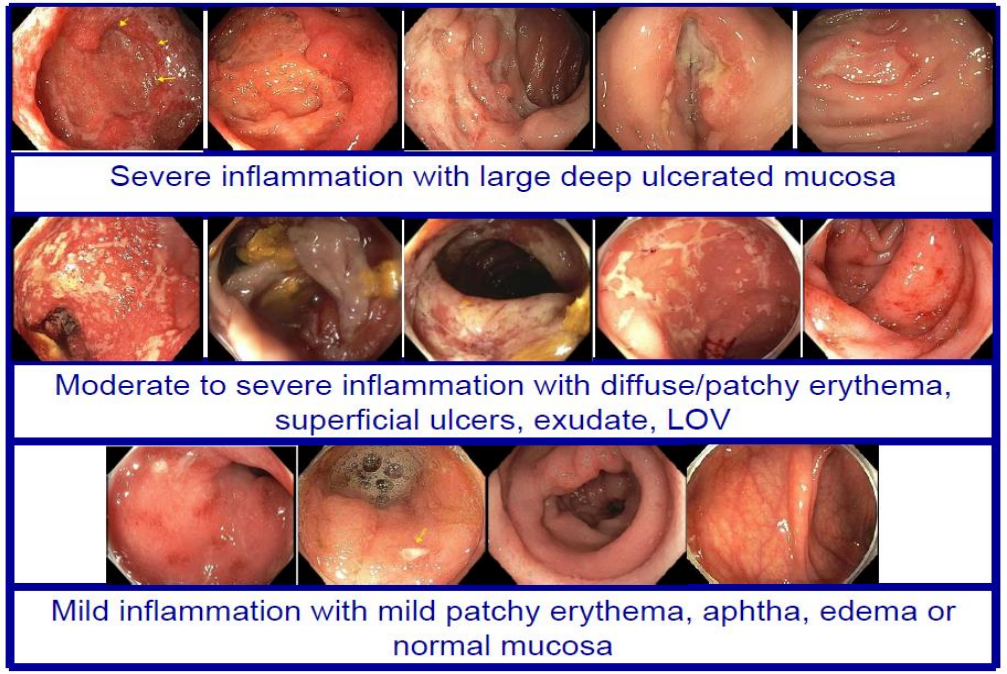
# Colitis
## Diagnosis

- **Fecal lactoferrin**
- 90% concordance with histologic inflammation
- 70% sensitivity for endoscopic abnormality

- **Fecal calprotectin**
- Associated with presence of ulcers on endoscopy

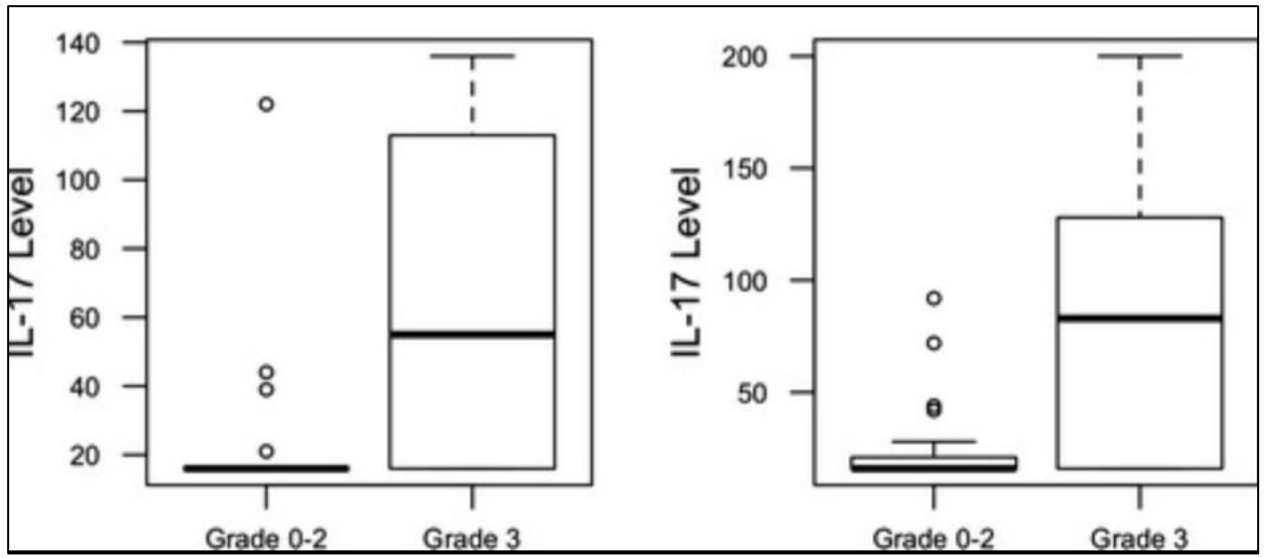
- **Endoscopic features to risk stratify**
- Associated with need for TNF-inhibition
- Associated with need for hospitalization

| | 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 |

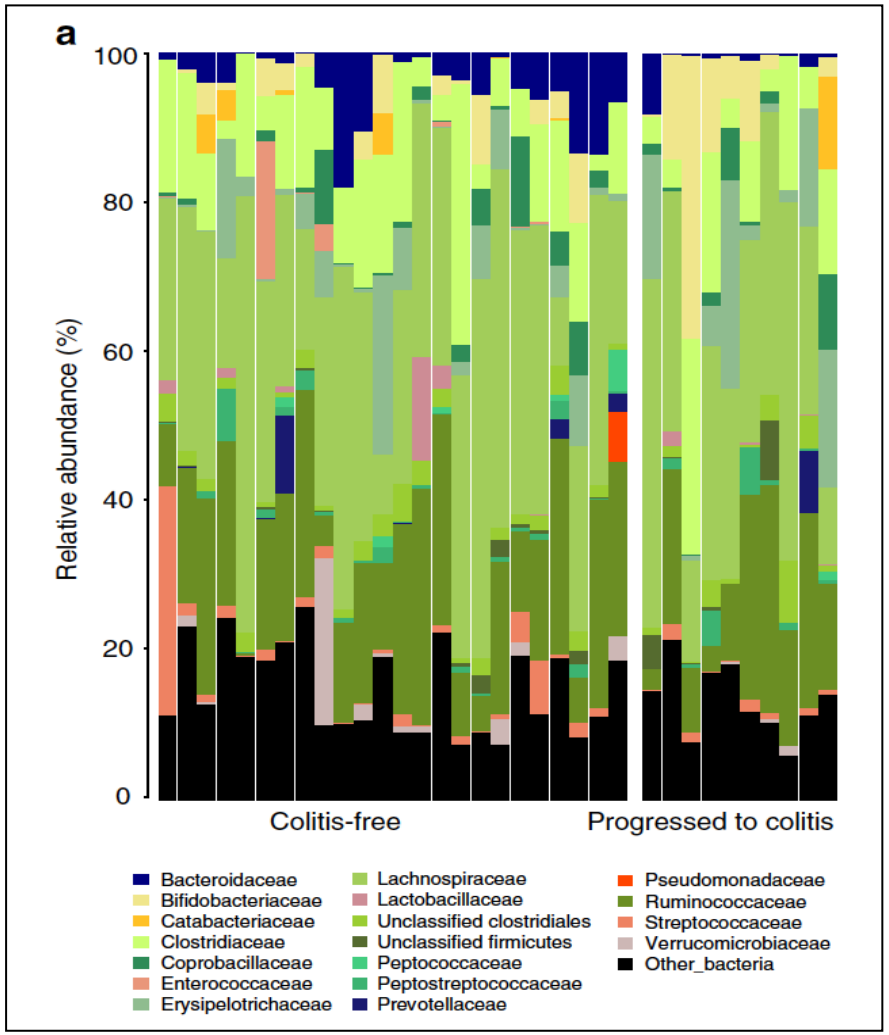



Wang et al, *JITC* 2018

# **Colitis**
Mechanisms




**Neoadjuvant Melanoma treated with ipilimumab**




**Metastatic Melanoma treated with ipilimumab**

Tarhini et al, *JITC* 2017
Dubin et al, *Nat Commun* 2016

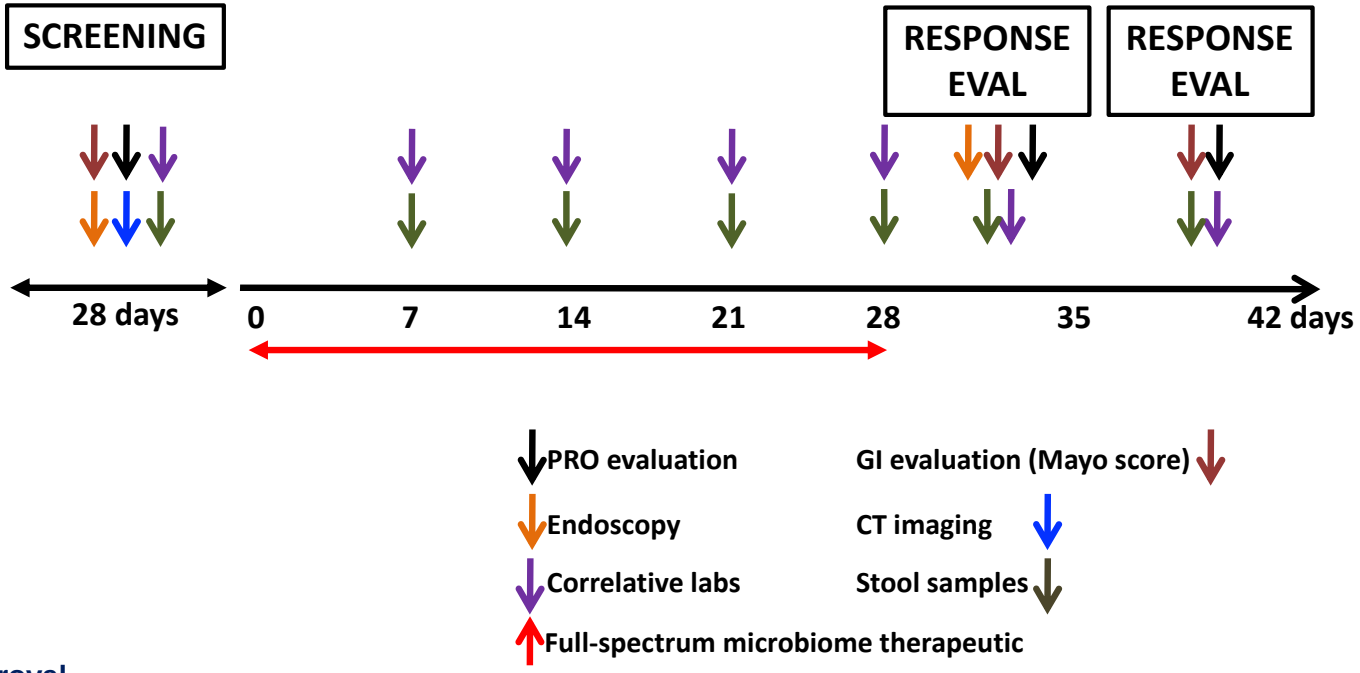
# irAE ELIMINATE
## Ph II Study of microbiome therapeutic for Steroid-refractory ICI colitis

- Steroid and biologic relapsed/refractory colitis
- Intervention:
  - Orally bioavailable full-spectrum microbiome therapeutic (MTP-101-C) for 28 days
  - Rapid steroid taper (over 7-14 days).
- Endpoints:
  - Primary: Full/complete Mayo score at 28 days
  - Secondary: Partial Mayo score at 42 days; PRO' corticosteroid-free remission

- Inclusion Criteria
  - Steroid-refractory colitis as defined in the protocol.
  - Willingness to comply with MTP-101-C administration
- Exclusion Criteria:
  - Any prior diagnosis of diarrhea-predominant IBS
  - Contra-indication to CP101 administration.

**Steroid-refractory irAE** secondary to anti-PD-(L)1 singly or in combination

- **I/E criteria as above**

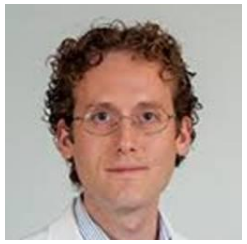



**EAQ concept**
**Funding: NCI DCP**
**Stage: Funding secured, pending EA committee approval**

# irAE ELIMINATE

## Study Team

### Study PI and co-PI

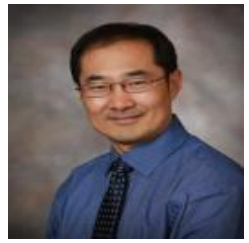



Diwakar Davar (Med Onc, HCC); Michael Dougan (GI, DF/HCC)

### Patient Co-Chair

Seamus Cotter (Ireland)

### Community Co-Chair



Xin Yao (Med Onc, ThedaCare)

### Study Statistician

Ju-Whei Lee (Biostatistics, EA and DF/HCC)

### Study Sponsors

FINCH

Alexander Khoruts (Institute of Functional Medicine, U Minn); Finch

### Study Leadership

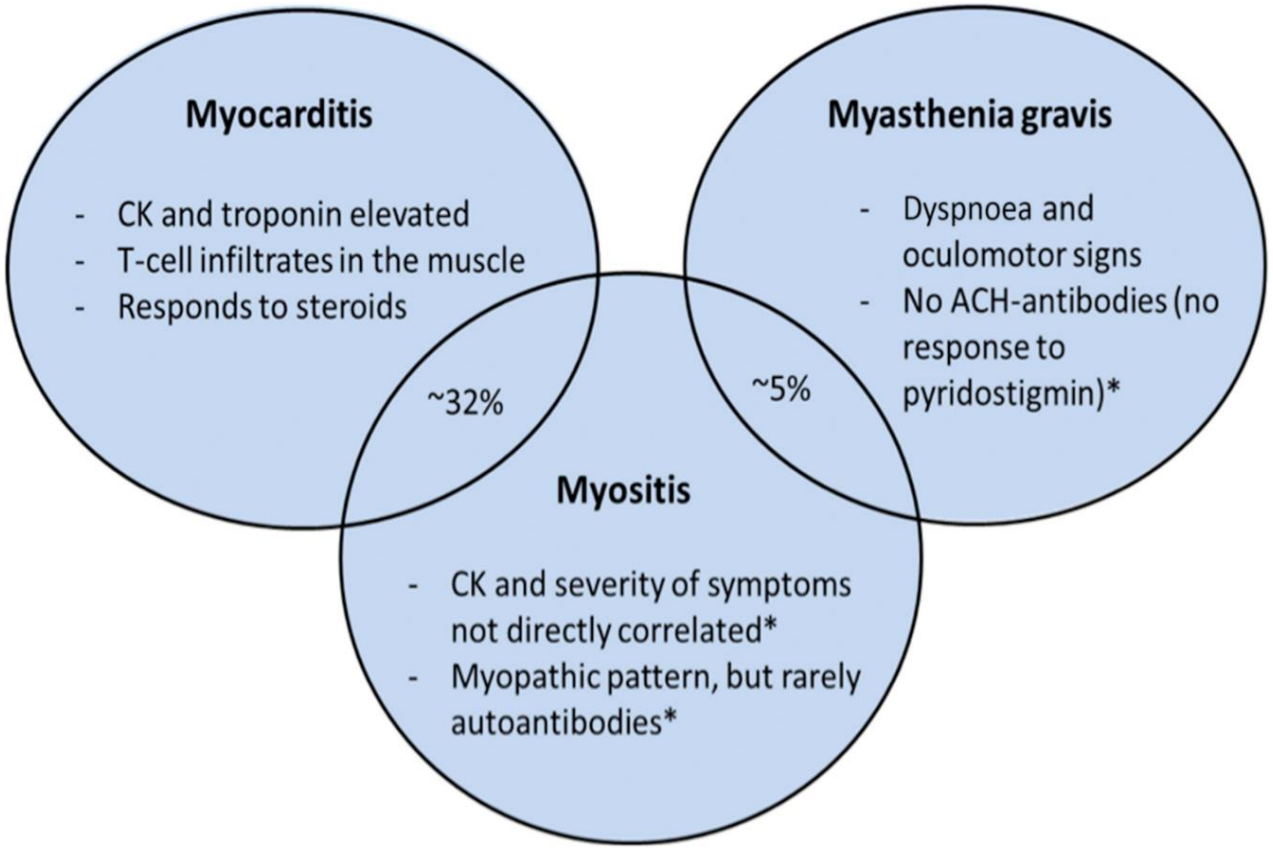

Lynne Wagner; Sheetal Kircher (ECOG ACRIN)

# PD-1/CTLA4 Combinations
## Multisystem irAEs/Overlap syndromes

- 38 patients with metastatic skin cancers treated with ICI
- Myositis was the most frequent NM irAE

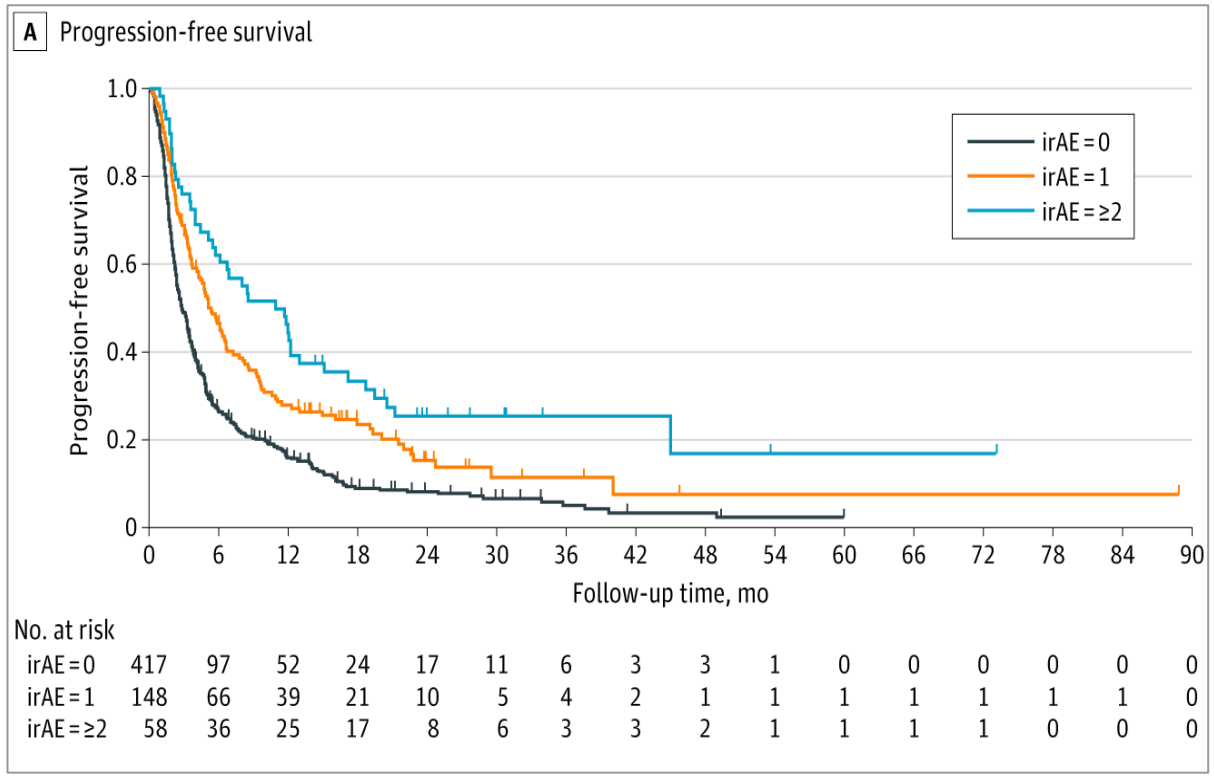
- 32% concomitant myocarditis.
- 49% G3+
- 2 fatalities
- 50% ongoing
- Role for surveillance CKs

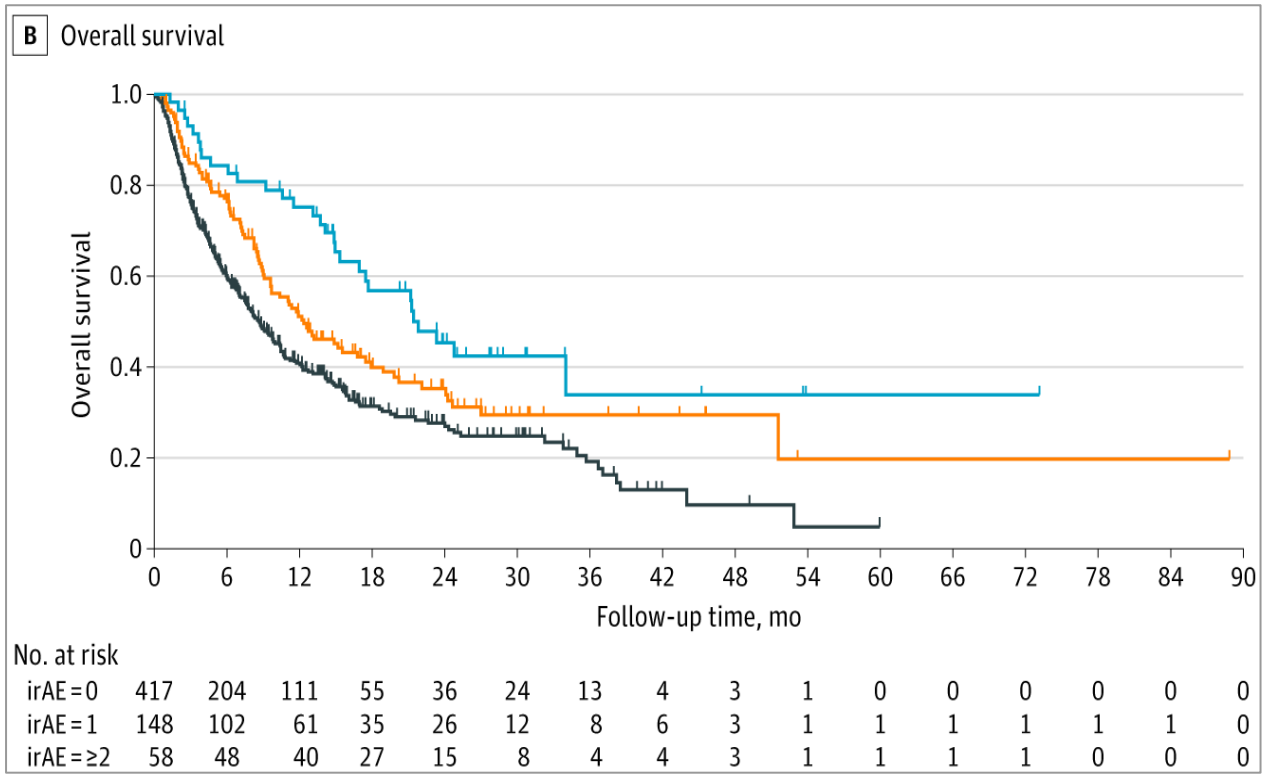
- Multidisciplinary IR- toxicity teams
- may facilitate identification
- 15% referred patients had multisystem irAEs




Moreira et al, *Eur J Cancer* 2018

# Multisystem-irAEs
## Incremental Benefit in PFS and OS




1 irAE: HR 0.67, **p=0.001**
≥2 irAEs: HR 0.38, **p<0.0001**

1 irAE: HR 0.86, P = 0.253
≥2 irAEs: HR 0.56, **P=0.005**

**Shankar, Naidoo et al, *JAMA Oncol* 2020**

# Immune-related Adverse Events
## Emerging Terminology, Need for Definitions

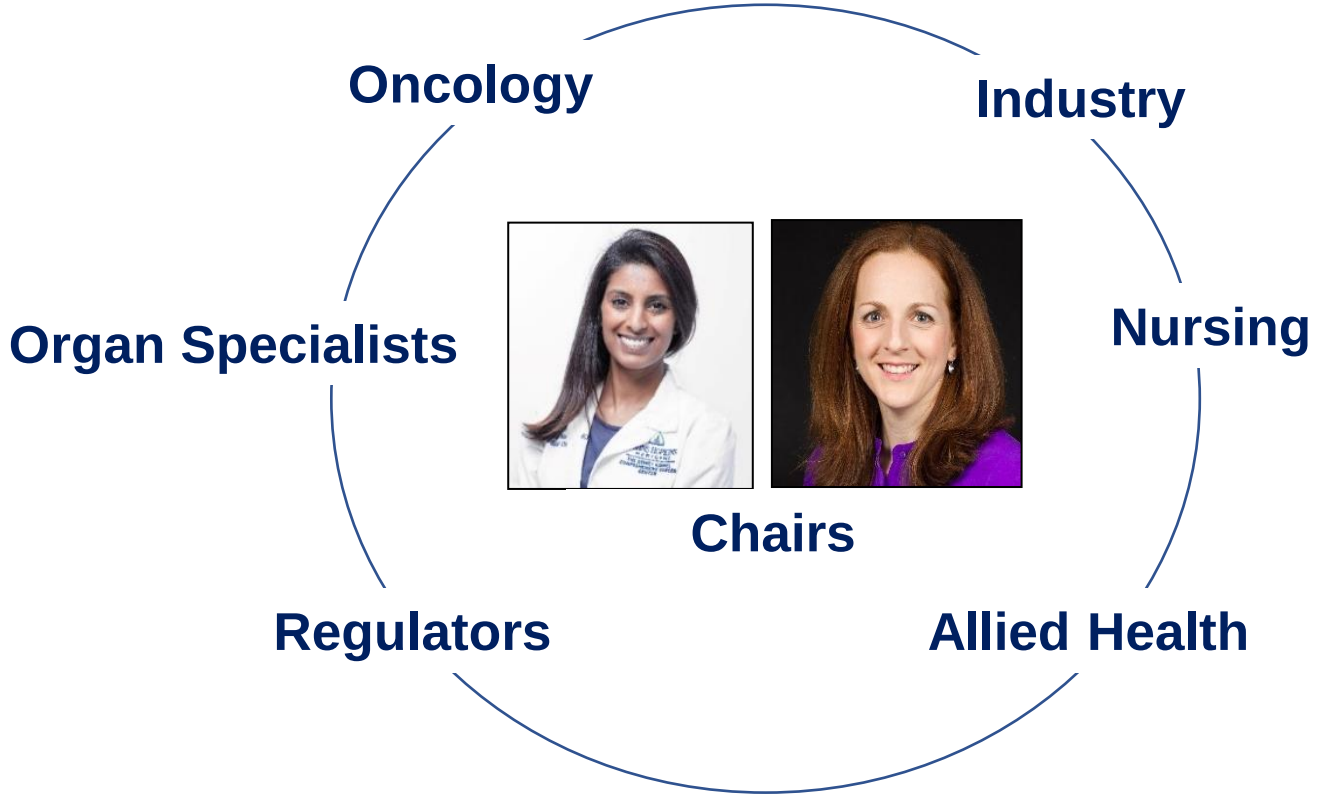
Natural history/Timing of irAEs:

- Recurrent irAEs
- Chronic/Long-term Toxicity
- Delayed/Late Onset

Treatment of irAEs:

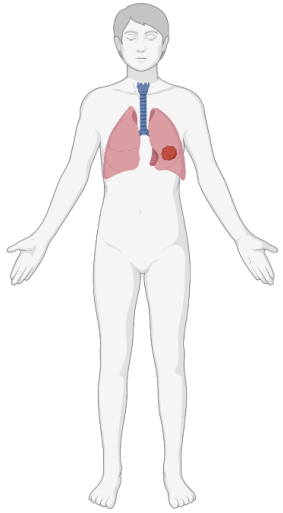
- Steroid-refractory
- Steroid-resistant/relapsed
- Steroid-dependent

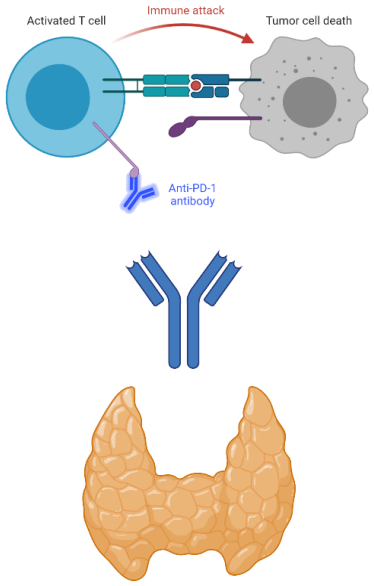
**SITC irAE Definitions Working Group**

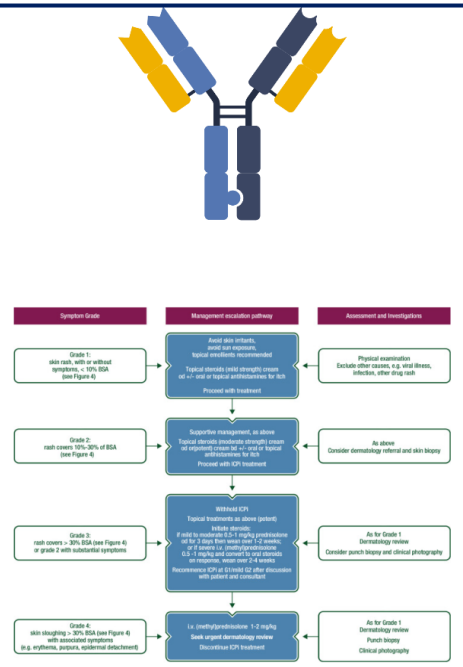



Naidoo, Murphy, Cappelli et al, *IASLC WCLC 2020*

# Immune-related Adverse Events
## Future Directions





**Preclinical Setting**

irAE Mouse models

Mechanistic insights

**Risk Factors**

Genetic features

Microbial features

Interventions to mitigate risk

**irAE Diagnosis**

Biomarkers/Imaging

IR-Tox Teams

**irAE Treatment**

Prospective irAE trials

Refined treatment algorithms

**Conroy, Naidoo, *Nature Comms 2022***

# Colleagues and Collaborators

**Johns Hopkins IR-Tox Team**
Laura Cappelli, MD
Clifton O. Bingham, MD
Ami A. Shah, MD
Julie R. Brahmer, MD
Elizabeth Jaffee, MD

**MSKCC**
Jedd D. Wolchok, MD PhD
Naiyer Rizvi, MD
Matthew Hellmann, MD
David B. Page, MD

Medical Oncology, Beaumont Hospital
Liam Grogan, MD
Oscar S. Breathnach, MD
Patrick Morris, MD
Bryan Hennessy, MD

Royal College of Surgeons of Ireland
Gerry McElvaney, MD
Arnie Hill, MD
Leonie Young, PhD
Ger Curley, MD
Fergal O'Brien, PhD

Cancer Trials Ireland
Linda Coate, MD
Eibhlin Mulroe
Ausra Tierskiene
Seamus Cotter
Eileen O'Sullivan

ETOP
Rolf Stahel, MD
Solange Peters, MD PhD

EORTC
Benjamin Besse, MD PhD
Jordi Remon, MD

ECOG-ACRIN
Sheetal Kircher, MD
Lynne Wagner, MD
Hossein Borghaei, MD PhD

JHH Thoracic Oncology Program
Julie R. Brahmer, MD
Patrick M. Forde, MD
Valsamo Anagnostou

JHH Bloomberg Kimmel Institute of Cancer Immunotherapy
Drew Pardoll, MD PhD
Cynthia Sears, MD PhD
Jiajia Zhang, MD MHS
Laura Cappelli, MD MHS

Funding Sources
NIH KL2
Lung Cancer Foundation of America
IASLC
Johns Hopkins University Seed Grants