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Immune Checkpoint Inhibitor Pneumonitis: Diagnosis and Treatment

Society for Immunotherapy of Cancer (SITC) Advances in Cancer Immunotherapy™ (ACI)

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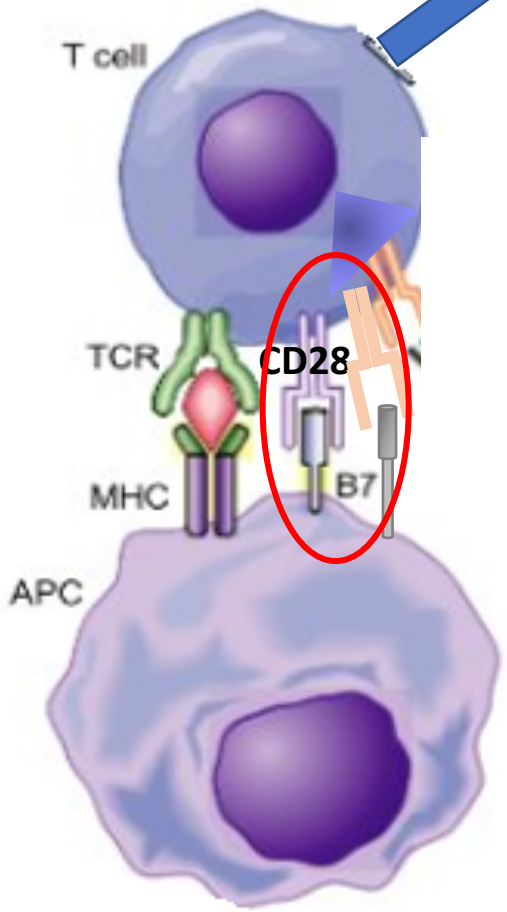
Immune Checkpoint Inhibitor Pneumonitis: Diagnosis and Treatment

I have no financial disclosures

CTLA-4 Blockade Augments T cell Activities

T cell activation involves a 2-step process:

- MCH-antigen complex on Antigen presenting cells (APC) binds with TCR
- Costimulatory binding of CD28 to B7



T cell activation, tumor killing

Block B7-CTLA-4 binding

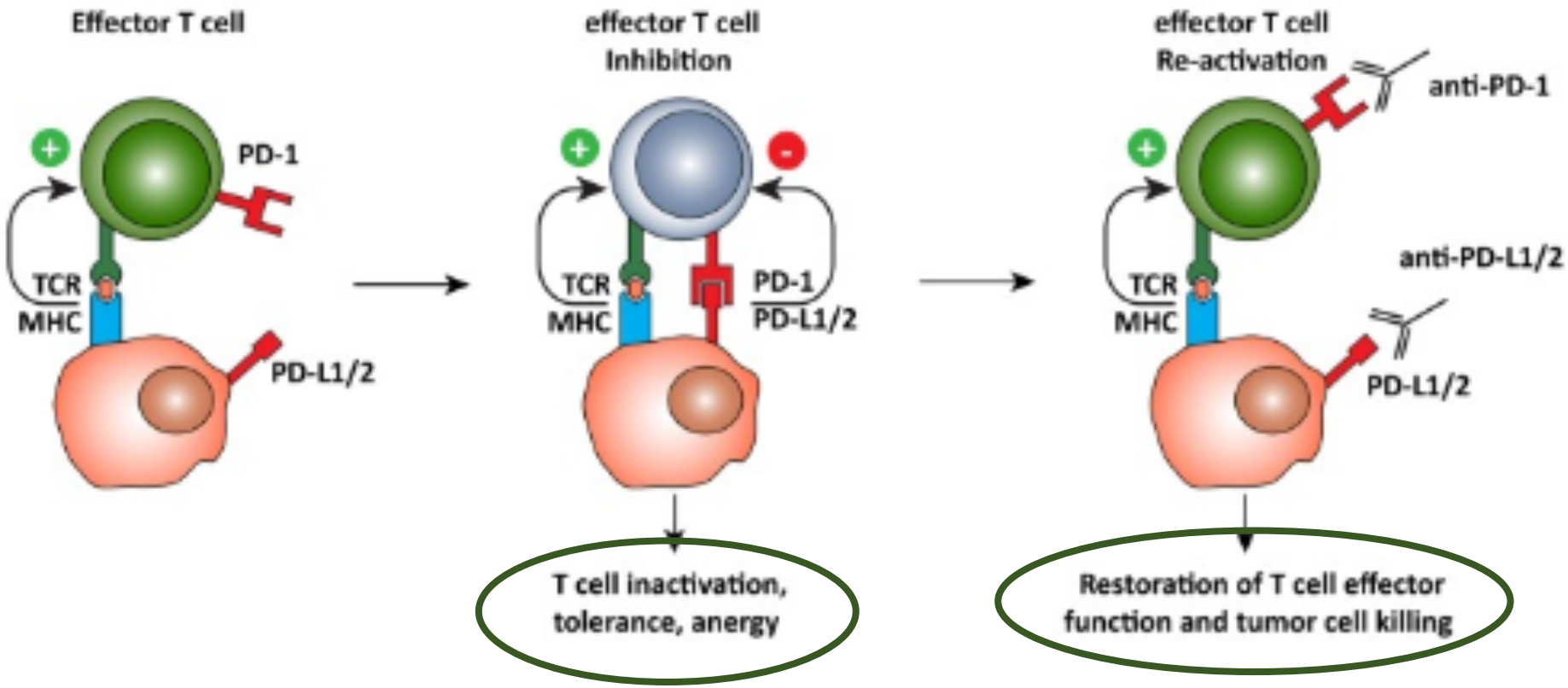
B7 free to bind CD28 co-stimulator

Increased CD4/8 T cell activation

Tumor apoptosis

Co-inhibitory protein, CTLA-4 outcompetes CD28 for B7, resulting in downregulation of T cell activities

PD-1-mediated inhibition of effector T cells



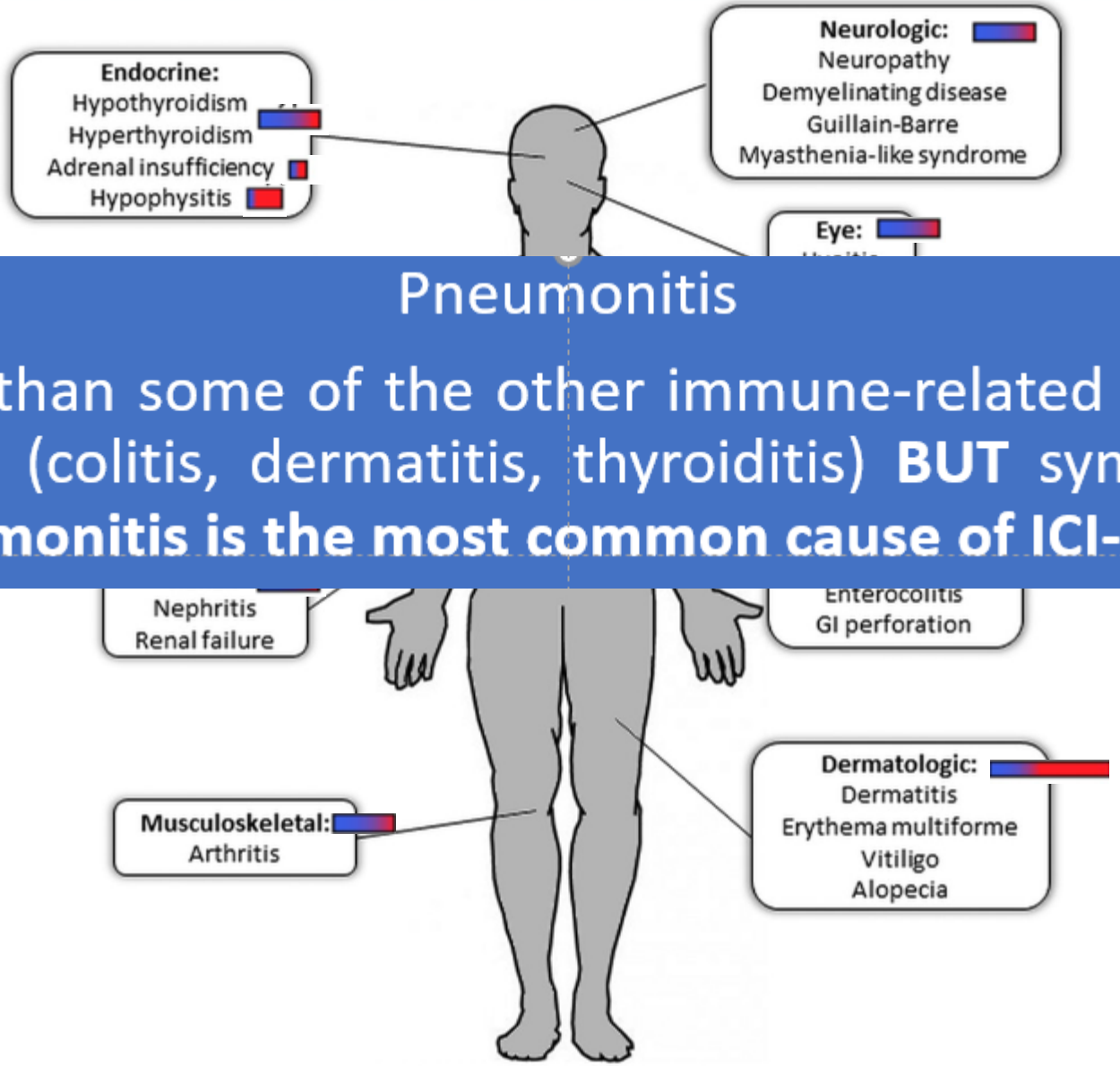
Nivolumab
Pembrolizumab
Cemiplimab
Dostarlimab

Atezalizumab
Durvalumab
Avelumab

Francisco LM et al ***Immunol Rev.*** 2010

Target	Drug	FDA-approved
CTLA-4 (CD152) **(Cytotoxic T-lymphocyte-associated antigen-4)**	**Ipilimumab (Yervoy)**	Unresectable metastatic melanoma Renal cell carcinoma (with nivolumab)
PD-1 (CD279) **(Programmed cell death protein-1)**	**Pembrolizumab (Keytruda)**	Unresectable metastatic melanoma NSCLC-Stage V Merkel cell carcinoma Hepatocellular carcinoma Gastric carcinoma GE junction carcinoma Cervical cancer Urothelial carcinoma Hodgkin lymphoma
	Nivolumab (Opdivo)	Unresectable metastatic melanoma NSCLC-St. V SCLC Hepatocellular carcinoma Renal cell carcinoma (with ipilimumab)
	Cemiplimab (Libtayo)	SCCA – skin
	Dostarlimab (Jemperli)	Endometrial carcinoma
PD-L1 (CD274, B7 homolog) **(Programmed cell death –ligand 1)**	**Atezolizumab (Tecentriq)**	NSCLC-St. V SCLC Breast carcinoma (triple negative)
	Avelumab (Bavencio)	Merkel cell carcinoma
	Durvalumab (Imfinzi)	Urothelial cancer

Immune-related Adverse events (irAE): Class-specific organ toxicities



Pneumonitis

Less common than some of the other immune-related adverse effects (irAEs) of ICIs, (colitis, dermatitis, thyroiditis) **BUT** symptoms can be severe - **pneumonitis is the most common cause of ICI-related fatality**

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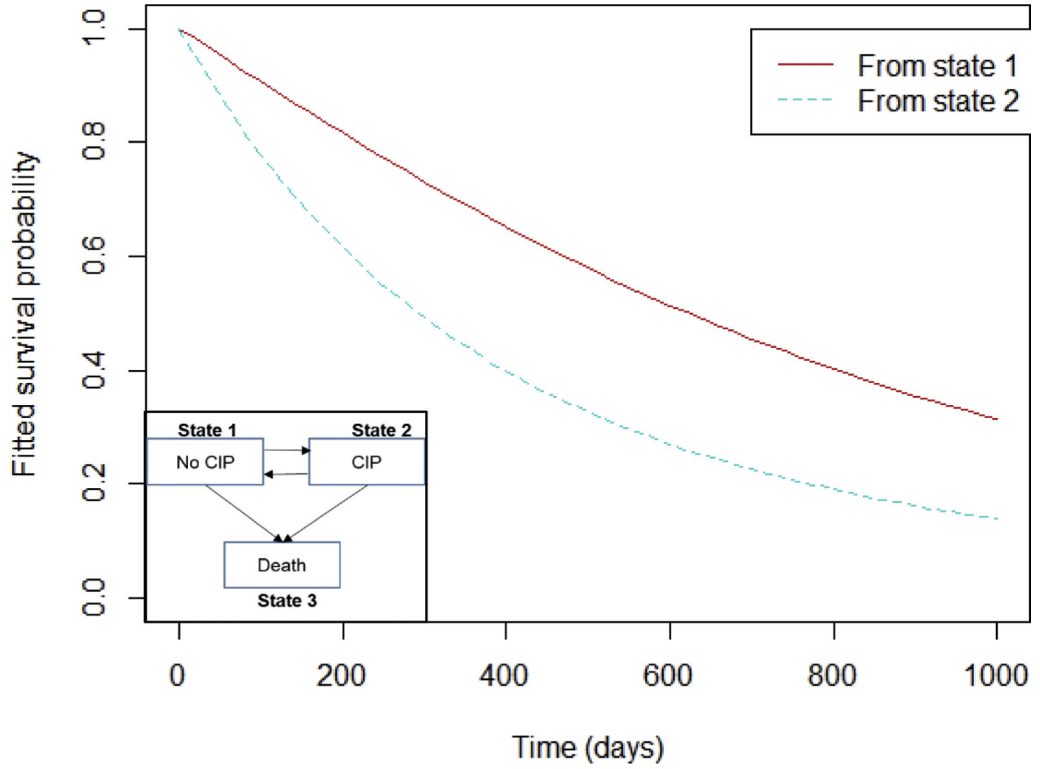
Pneumonitis is Common in the Real World – and Deadly

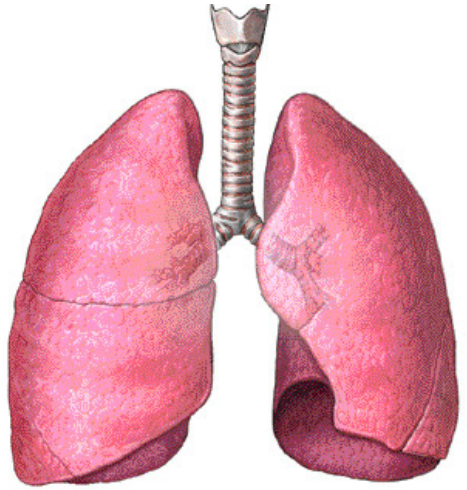
- In 205 NSCLC patients treated with ICI on trial (~60%) or standard of care (40%), the incidence of pneumonitis was 19% at a median of 82 days
  - Only noted risk factor was squamous histology
  - HR for death was 2.7 in patients who developed pneumonitis
- Most common cause of treatment-related mortality

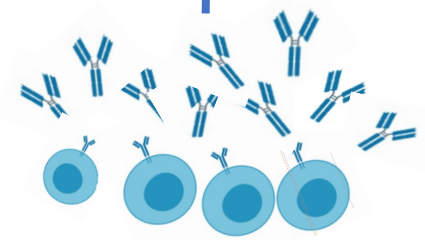


Suresh J Thorac Oncol 2018
Suresh J Thorac Oncol 2019

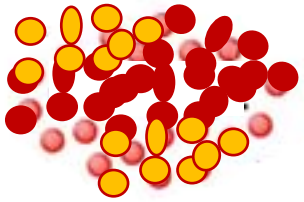
ICI-related pneumonitis: mechanism of action

Increased reactive T cell activity





Increased autoantibodies

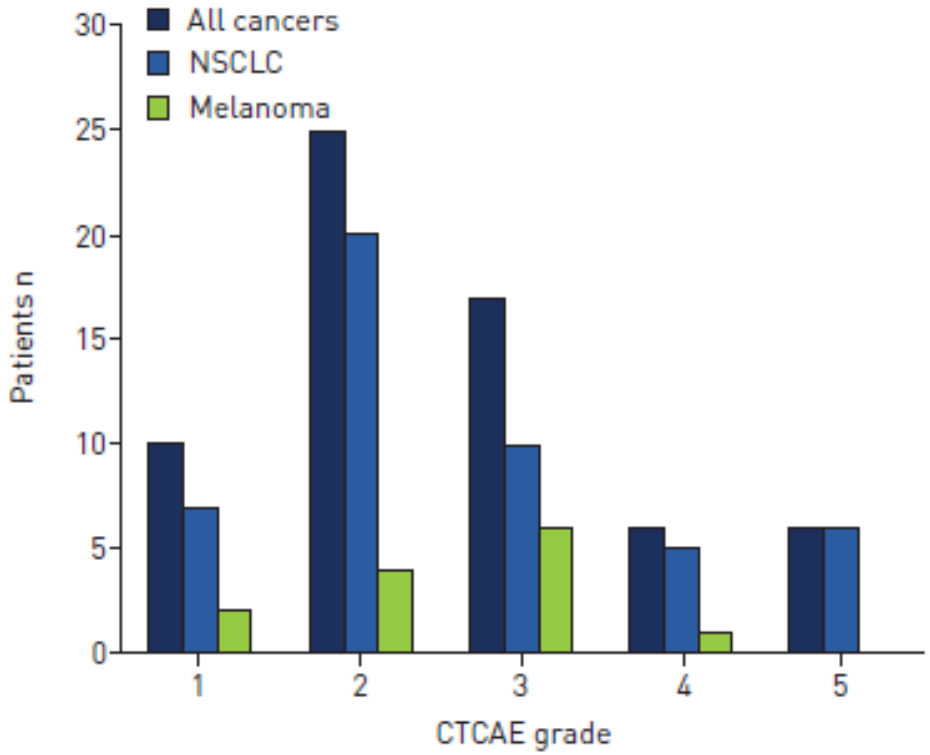


Increased inflammatory cytokines

Incidence and Risk factors for Pneumonitis	Reference
ICI class/Regimen	
Monotherapy: PD-1 (2.7-5.3%) PD-L1 (1-3%) CTLA-4 (1%) **Dual therapy:** PD-1/PD-L1 plus CTLA-4 vs PD-1/PD-L1 monotherapy (6.6 - 10% vs. 2.7%)	Khoja L. *Ann Oncol* 2017 Khunger M. *Chest*. 2017 Su *Front. Immunol*. 2019
Combination therapy (NSCLC): **TATTON trial:** PD-L1 (Durvalumab) plus osimertinib vs. osimertinib alone (38% vs. 2.9%) ICIP highest when EGFR therapies given after ICI therapy; highest using osimertinib vs. other EGFR therapies	Hellmann M. (Checkmate227) *NEJM* 2018 Ahn MJ. *J Thor Oncol* 2016 Schoenfeld AJ. *Ann Oncol* 2019
Combination therapy (melanoma): Ipilimumab alone 1%; Ipilimumab plus vemurafenib and cobimetinib - 10% KEYNOTE 022 trial: Pembrolizumab/dabrafenib/trametinib vs. placebo/dabrafenib/trametinib 17% vs. 3% Ipilimumab alone (1%) vs. Ipilimumab plus PD-1 inhibitor (10%)	Nishino M. *JAMA Oncol* 2016 Ascierto PA *Immunother Cancer* 2020 Ferrucci PF. *Cancer* 2020 Huynh S. *Cancer* 2020

Incidence and Risk factors for Pneumonitis	Reference
Cancer histology Highest among NSCLC (5 -19%) and RCCA (4-5%) Highest among NSCLC with squamous histology Hematologic malignancies (10 - 12%)	Nishino, *JAMA Oncol*. 2016 Ma K. *Front Pharmacol* 2018 Daver N. *Blood* 2016
Preexisting interstitial lung disease (ILD) NSCLC patients with/without prior ILD: 31% vs. 12%	Yamaguchi T. *Lung Cancer* 2018 Kanai O Thorac Cancer 2018 Shimoji JAMA network 2020
Prior lung irradiation Keynote 001 trial: Thoracic XRT followed by anti PD-1 vs. no anti-PD-1 in NSCLC (13% vs. 1%) DETERRED trial: Concurrent Atezolizumab plus XRT in NSCLC: No significant difference in ICIP rates	Shaverdian N. *Lancet Oncol* 2017 Bradley JD *J Clin Oncol* 2019 Lin SH. *J Clin Oncol* 2019 Voog KR. *Clinic Lung Cancer* 2019
Other suspected risk factors: Tobacco use? COPD/asthma? abnormal baseline PFTs? Age >70 years?	Nishino M, *JAMA* 2016 Suresh K *Thor Oncol* 2018 Voong KR *Thor Oncol* 2017

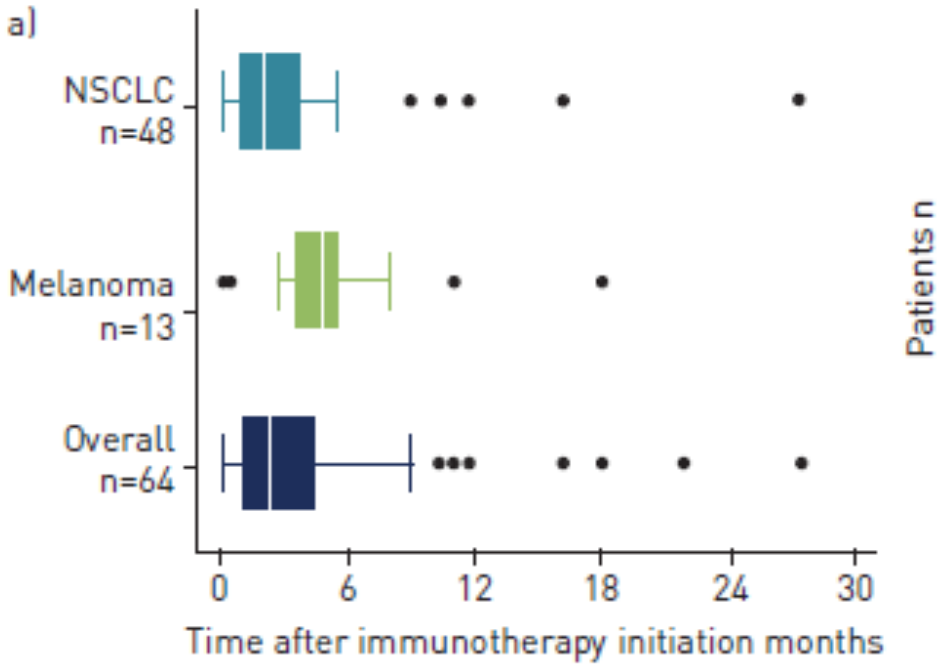
ILD stratified according to Common Terminology Criteria for Adverse Events (CTCAE)



More frequent and severe ILD among patients with NSCLC vs. Melanoma

Time to onset of ILD stratified by cancer type

Data presented as median quartile



- **Overall interval** : 2.3 months (range 0.2-27.4 months)
- Earlier presentation for NSCLC (2.1 months) vs. 5.2 months for melanoma

Delaunay et al. ***Eur Resp J*** 2017

ICI-Pneumonitis: Clinical Evaluation

- Symptoms:
  - 1/3 asymptomatic (CTCAE grade 1)
  - Most common presenting symptoms: dyspnea (50-60%), cough (35-50%), fever (10-15%), chest pain (5-7%)
- Median onset: 2.5 - 6 months post initiation of ICI agent (range 9 days – 19 months); varies broadly with risk factors
- Concomitant/prior immune related toxicity (58%), including rash, vitiligo, colitis, hypophysitis, thyroiditis, arthritis, hepatitis, esophagitis, nephritis, myositis
- Not dose-related (PD-1, PD-L1)

Naidoo, *J Clin Oncol* 2017
Su, Front. Immunol. 2019
Khunger, Chest 2017
Fukihara, Clin. Lung Ca 2019

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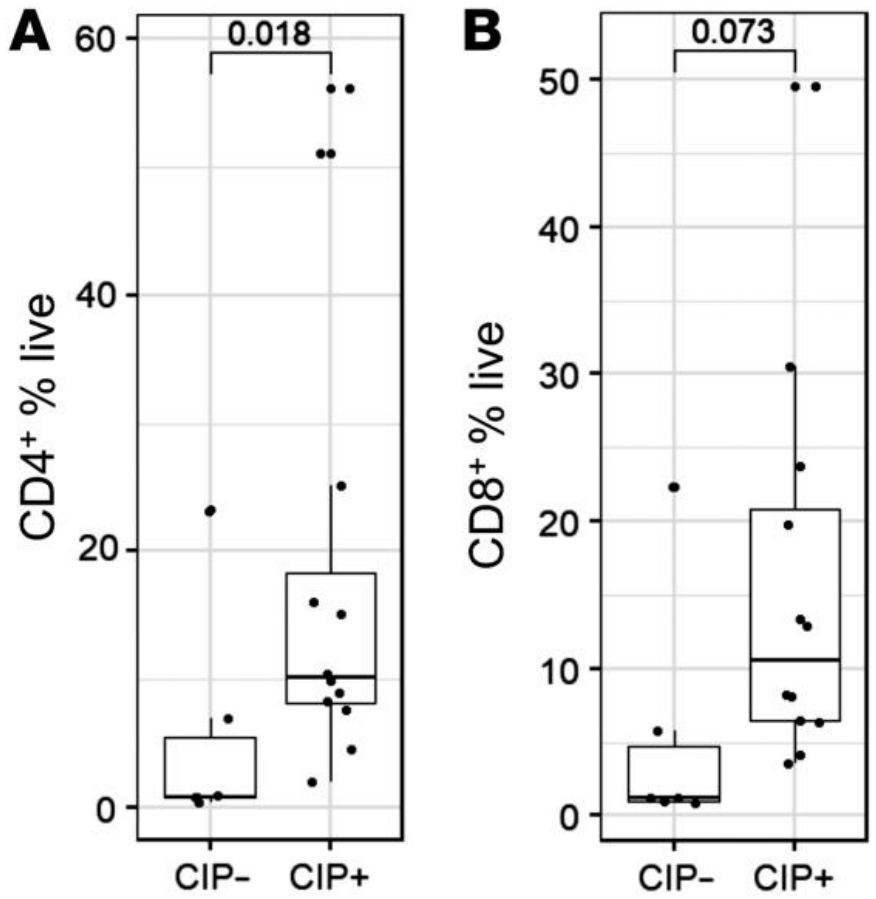
ICI Pneumonitis: Diagnosis

- **Diagnosis of exclusion**
- Initial workup:
  - Clinical evaluation
  - Non-contrast chest CT
- **Pulmonary consultation** for worsening symptoms that cannot be attributed to disease progression
  - Exclude competing diagnoses (infection, alveolar hemorrhage, cancer progression/pseudoprogression, pulmonary edema)
  - Exclude respiratory symptoms caused by other irAEs (thyroiditis, myocarditis, myopathy, myasthenia gravis)
- **Bronchoscopy with BAL**
  - Recommended in pneumonitis grade 2 or higher
  - Lung biopsies (surgical, transbronchial, cryobiopsies, FNA) may be considered to exclude cancer progression and identify histologic phenotypes of pneumonitis
  - May permit identification of biomarkers for ICI pneumonitis
- **Pulmonary function testing and 6MWT**
- **Cardiology consult and echocardiogram** for acute volume overload to evaluate for ICI-related myocarditis

Naidoo, *J Clin Oncol* 2017
Su, *Front. Immunol*. 2019
Khunger, *Chest* 2017
Fukihara, *Clin. Lung Ca* 2019
Kim ST *Front Immunol* 2021

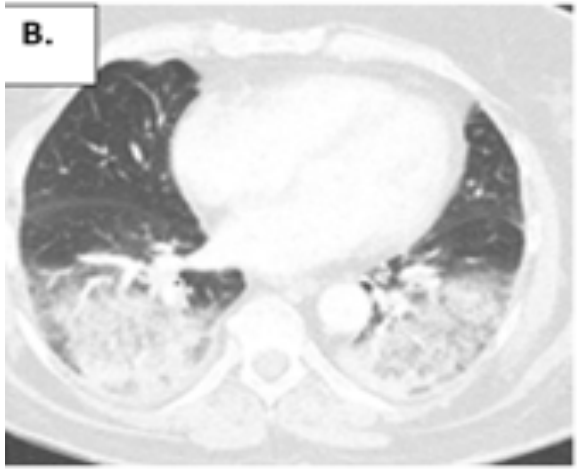
The role of bronchoscopy and lung biopsy

- The primary goal of bronchoscopy is to rule out pulmonary infections
- Lymphocytosis may help to differentiate pneumonitis from pneumonia, but needs validation



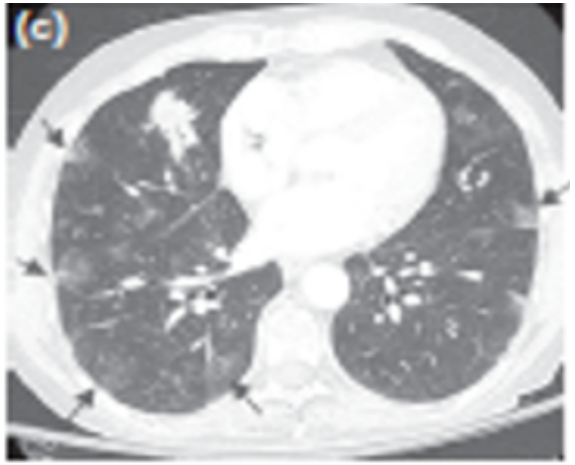
Suresh *JCI* 2019

The many faces of CPI Pneumonitis



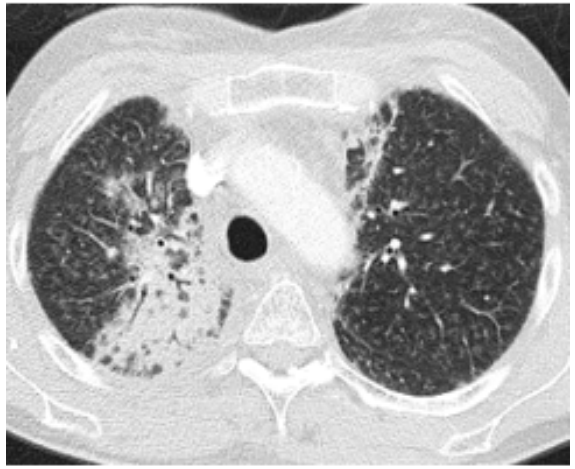
Organizing Pneumonia

- Most common- up to 65% of patients
- Consolidative, ground glass opacities with peripheral peribronchovascular predominance within mid-to lower lung fields; reverse halo (atoll) sign



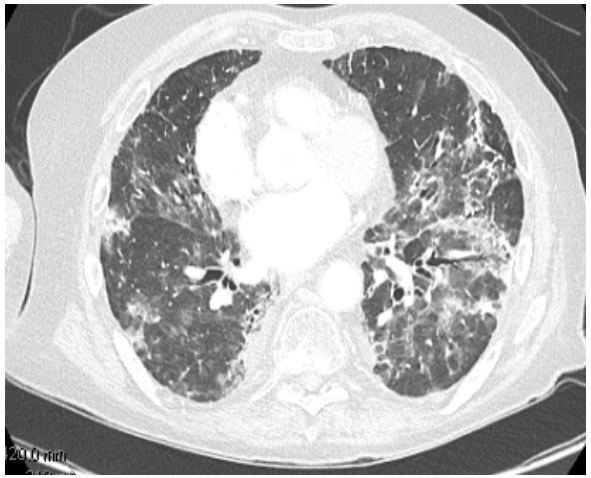
Nonspecific interstitial Pneumonitis (NSIP)

- 2nd most common – (15%)
- Ground glass/reticular opacities with lower lobe predominance; subpleural sparing
- May progress to architectural distortion



Hypersensitivity Pneumonia (HP)

- Innumerable bilateral centrilobular ground glass nodules, mosaic attenuation
- Usually steroid-responsive

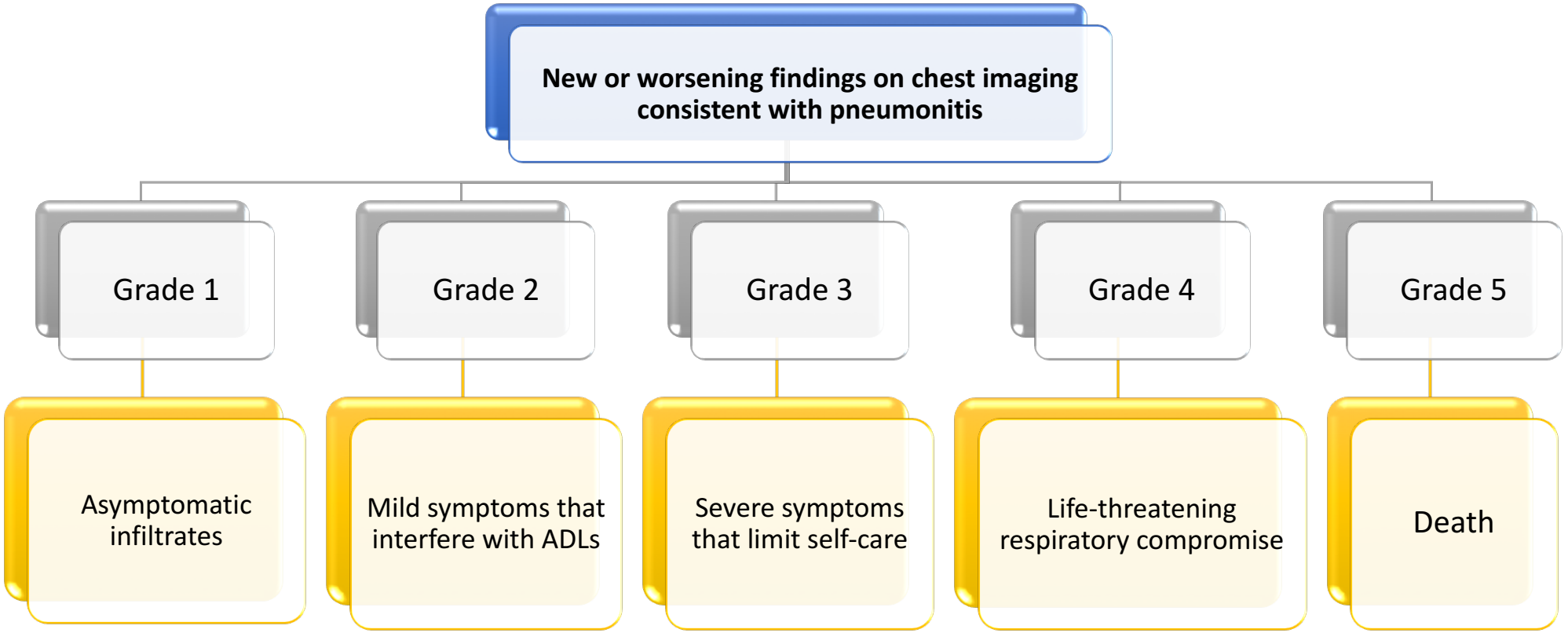


Diffuse Alveolar Damage/Acute Respiratory Distress Syndrome (DAD/ARDS)

- Up to 10% of patients
- Patchy or diffuse ground-glass and consolidative opacities involving the majority or entire lung
- Extensive inflammatory injury vs. late-stage ICIP??

National Cancer Institute CTCAE* Pneumonitis Grading System (version 5.0)

- **Pneumonitis Definition**
- **Pneumonitis Grade**
- **Definition**



CTCAE = Common Terminology Criteria for Adverse Events

US Health and Human Services, November 2017

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Immune-related pneumonitis: Checkpoint inhibitor management guidelines

Grade of Pneumonitis	Grade 1	Grade 2	Grade 3	Grade 4
FOB/BAL	No	Yes	Yes, if stable	Yes, when stable
Treatment	Consider holding drug	Hold drug Usually treated as outpatient Prednisone 1 mg/kg/day PO Consider antibiotics	Discontinue drug Hospitalize High dose IV: 1-2 mg/kg/day methylprednisolone Add antibiotics	
Follow-up	Reassess after 3 weeks: if completely resolved or non-drug-related continue ICI treatment. If worsens treat as grade 2 or 3/4 PFTs/6MWT upon reassessment	Reassess every 1-3 days Symptoms improving after 48-72 hours: slowly taper steroids; Symptoms worsening after 48-72 hours: treat as grade 3/4 Add PJP prophylaxis PFTs/6MWT upon reassessment	Reassess daily Check T-spot No symptom improvement or symptoms worsening after 48-72 hours - add additional immunosuppressive therapy: Infliximab 5 mg/kg IV (avoid in liver disease) Mycophenolate mofetil 1 gm BID Tocilizumab: 4 mg/kg IV given over 1 hour IVIG: 2 mg/kg Cyclophosphamide Add PJP prophylaxis PFTs/6MWT upon outpatient reassessment	
RX duration	N/A	4-6 weeks	6-8 weeks	
ICI rechallenge?	Yes	May be considered if symptoms resolve to grade 1	No	

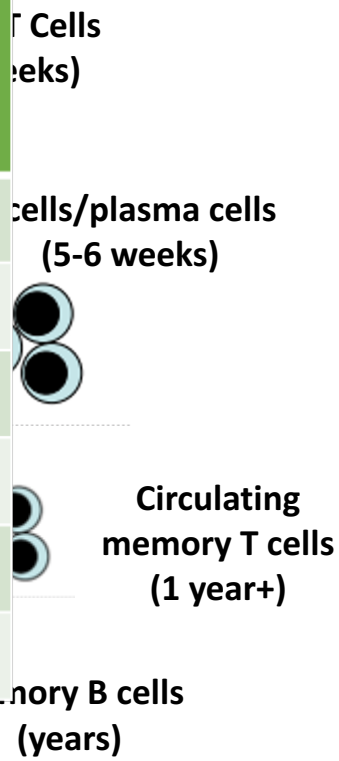
RX = treatment; IVIG = intravenous immune globulin

Shannon VR ***Curr Op Pul Med*** 2017

Checkpoint inhibitors: lasting effects – beware of pneumonitis flares

- ❑ **Checkpoi**
  days afte
- ❑ **Fate of a**
  - ***Death***
    - Effe
    - B ce
      wee
  - ***Transitic***
    4 doses
    earlier
    - Circ
      function/die after a year or longer
    - Circulating memory B cells: may loose function/die after many years

Agent	Half-life (days)	Steady state concentration reached (weeks)
Ipilimumab	14.7	9
Nivolumab	25	12
Pembrolizumab	14-27	18
Atezolizumab	27	6-9
Avelumab	6	4 - 6
Durvalumab	21	16



Steroid-Refractory Pneumonitis

- Definition: No clinical improvement after 48-72 hours of therapy
- Most second-line therapies are only supported by case reports or case series
- Our practice is to use infliximab (5 mg/kg, single dose)
  - Mixed cancer population (42 patients with pneumonitis)
  - Case series from MDACC showed a 20% response
- Limited evidence for:
  - Tocilizumab
  - Plasmapheresis/IVIG
  - Cyclophosphamide
  - Mycophenolate
- *Key area for investigation*

Lai KA J *Immunotherapy Precision Onc* 2020

Recurrent ICI Pneumonitis following initial lung IrAE

- Any IrAE recurrence after ICI rechallenge – 55%
- Pneumonitis recurrence after ICI rechallenge: 28 – 33%
- Unprovoked pneumonitis (“Pneumonitis flare”): 10-15%
- Provoked and unprovoked events after rechallenge are typically earlier in onset and more severe than the first event
- Increased risk of recurrence correlated with shorter steroid treatment at first event and dual therapy rechallenge
- Recurrent event may be the same as initial IrAE, a different IrAE or both

Simonaggio A et al. **JAMA Oncol** 2019
Asher, N. et al. *Immuno-oncology* 2019

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Criteria for ICI Resumption after IrAE

- Return to pneumonitis Grade 1 or less **OR** return to clinical/radiographic baseline
- Corticosteroid dose is less than 10 mg/day of prednisone or its equivalent
- The patient is not receiving any other immunosuppressive agents for treatment of pneumonitis

Champiat S. et al. *Ann Oncol* 2016
Thompson J. *JNCCN* 2019

Pneumonitis following Immune Checkpoint Inhibition: Summary

- ❑ Infrequent but potentially fatal complication of immune checkpoint inhibition
- ❑ Should be considered in all patients with new or worsening pulmonary symptoms and new/worsening pulmonary infiltrates following ICI therapies
- ❑ Knowledge of onset of symptoms following ICI therapies, risk factors typical clinical presentation, and treatment guidelines is key to good outcomes

Questions?

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