PULMONARY COMPLICATIONS OF IMMUNOTHERAPY

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Disclosures

- I serve on an advisory board for Sanofi, Regeneron, Triveni, Apogee
- I have sponsored research grants from:
  - Sanofi
  - Regeneron
  - NIH

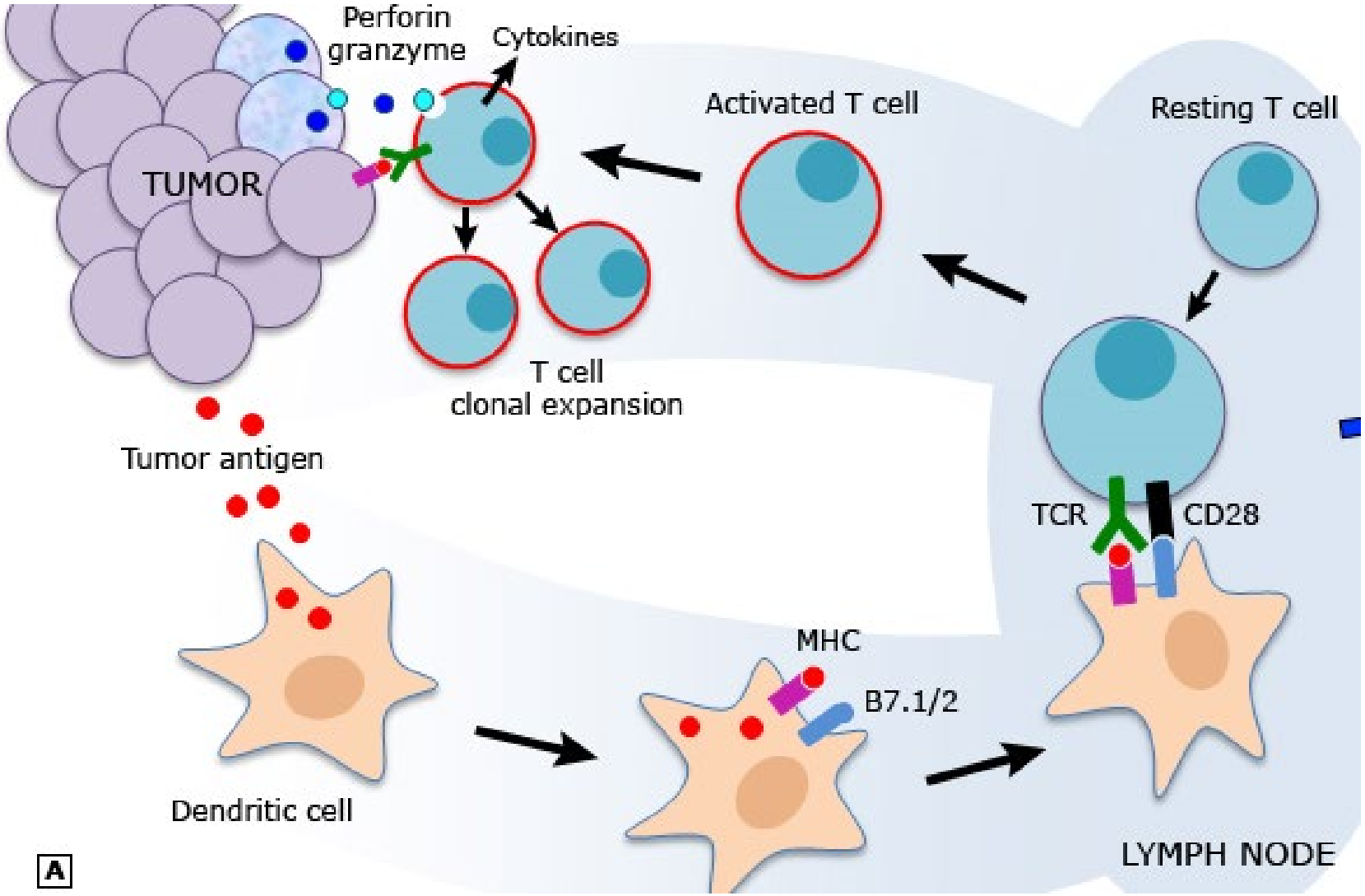
Immunotherapy

- Treatment of disease by altering the immune response:
  - Induction
  - Enhancement
  - Suppression
  - Polarization

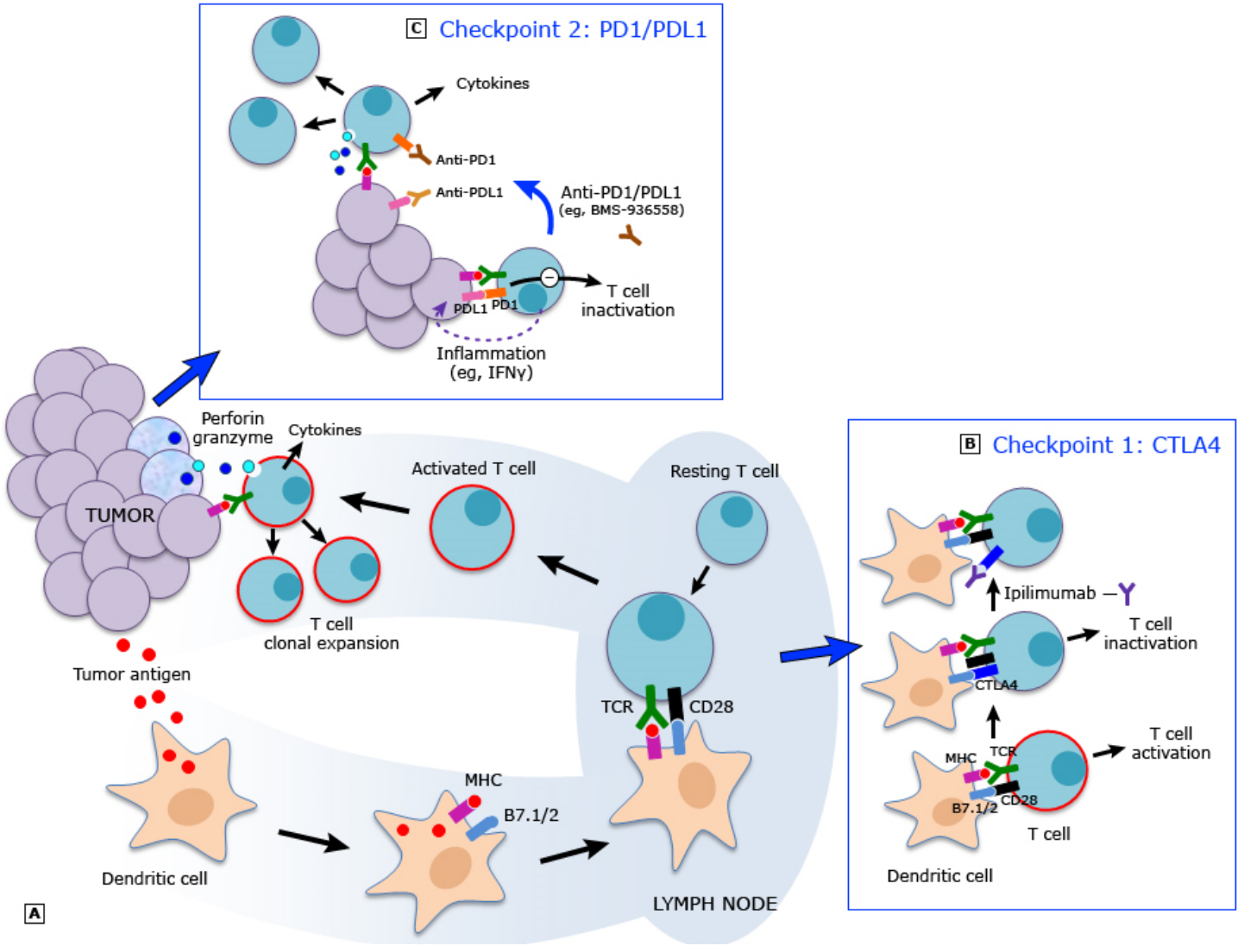
Cancer Immunoediting

- Immunosurveillance can limit tumor development
  - Tumors as non-self or altered-self
  - Both innate and adaptive immunity required
- Higher incidence of malignancies in immunosuppressed individuals
- Immune infiltrates seen in tumors
- Paraneoplastic syndromes may result from immune activation (e.g. polymyositis)
- Immune escape via immunosuppression within the tumor microenvironment
  - Immune checkpoints

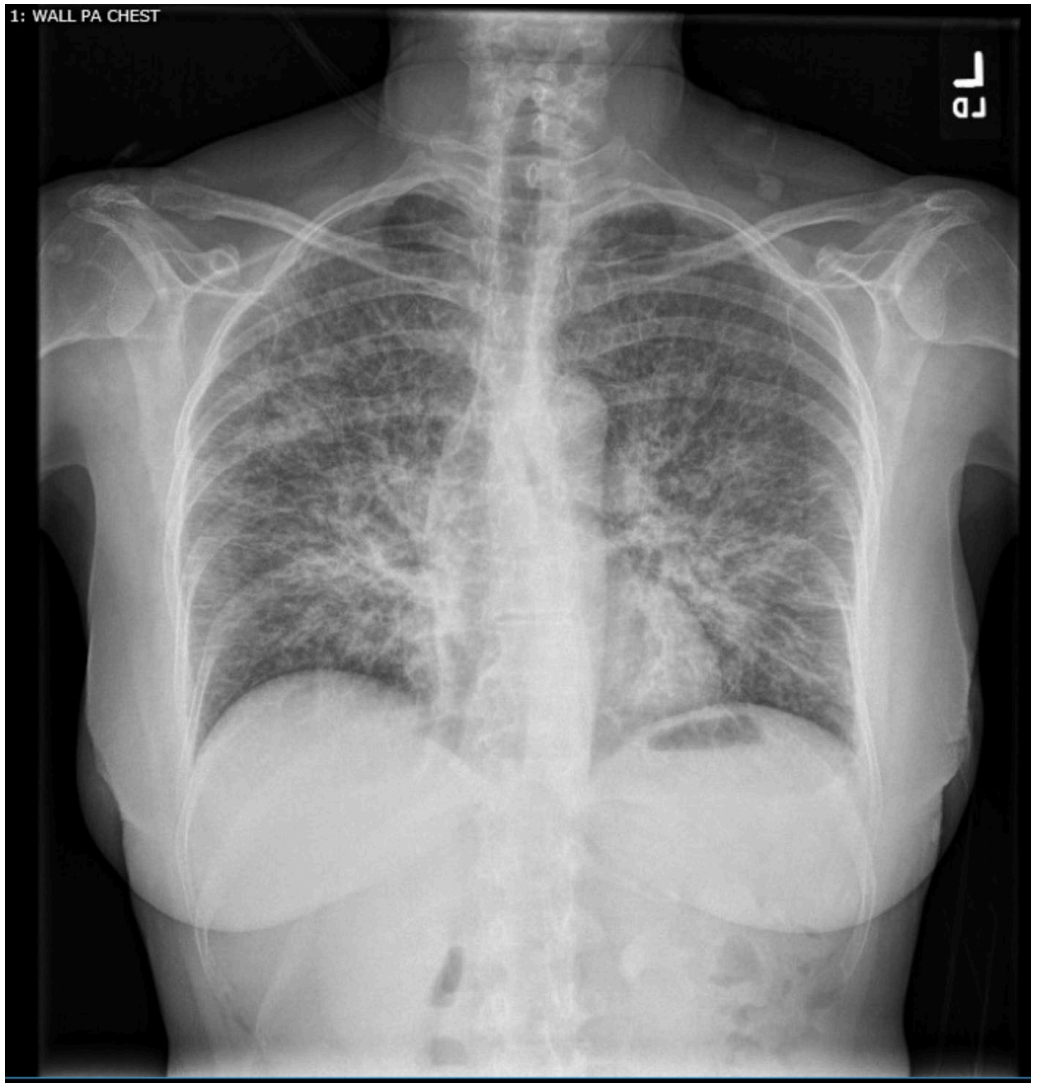
Anti-Tumor Immune Activation



Immune Checkpoint Inhibition

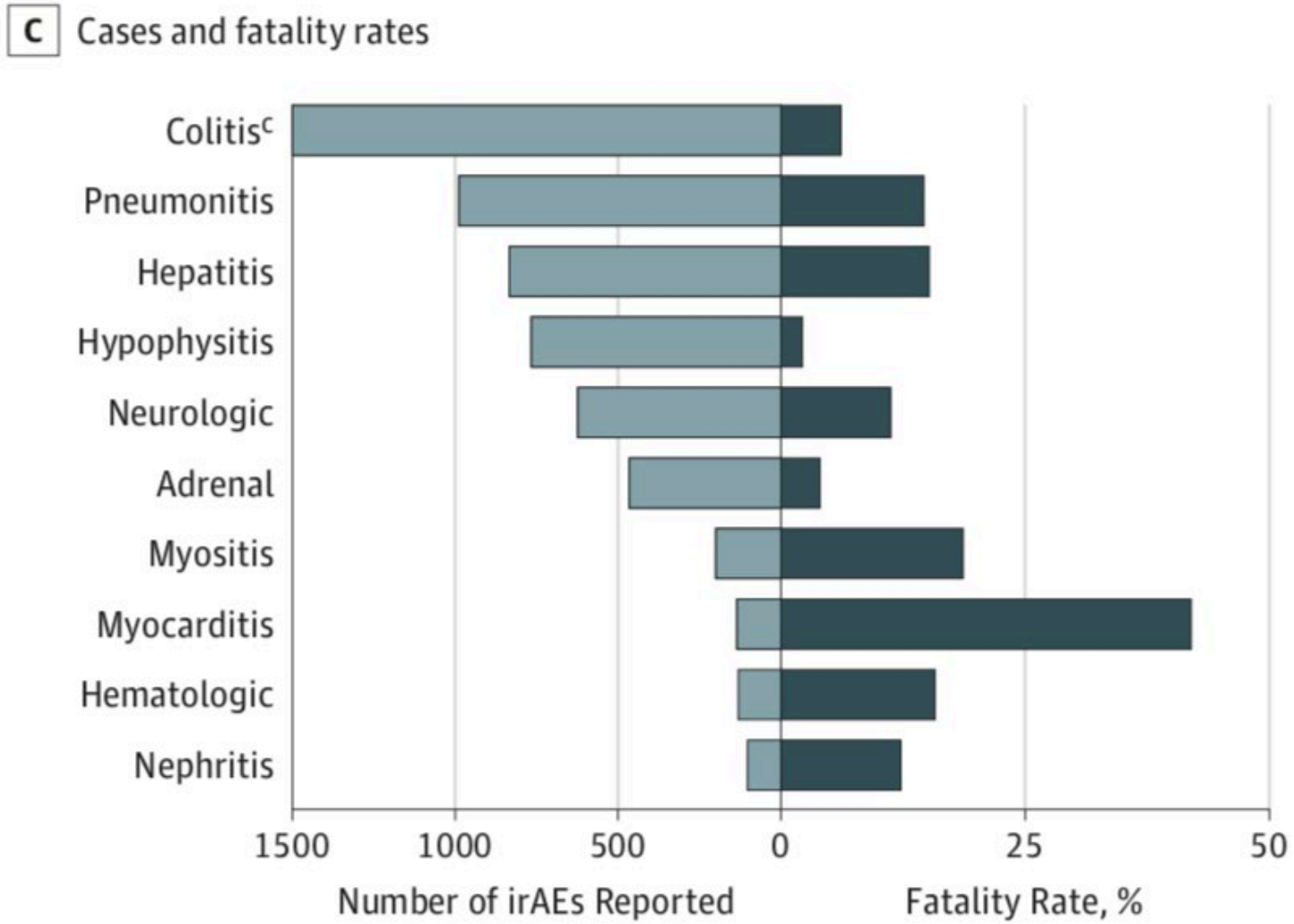


Immune-related adverse event - irAE– Pneumonitis



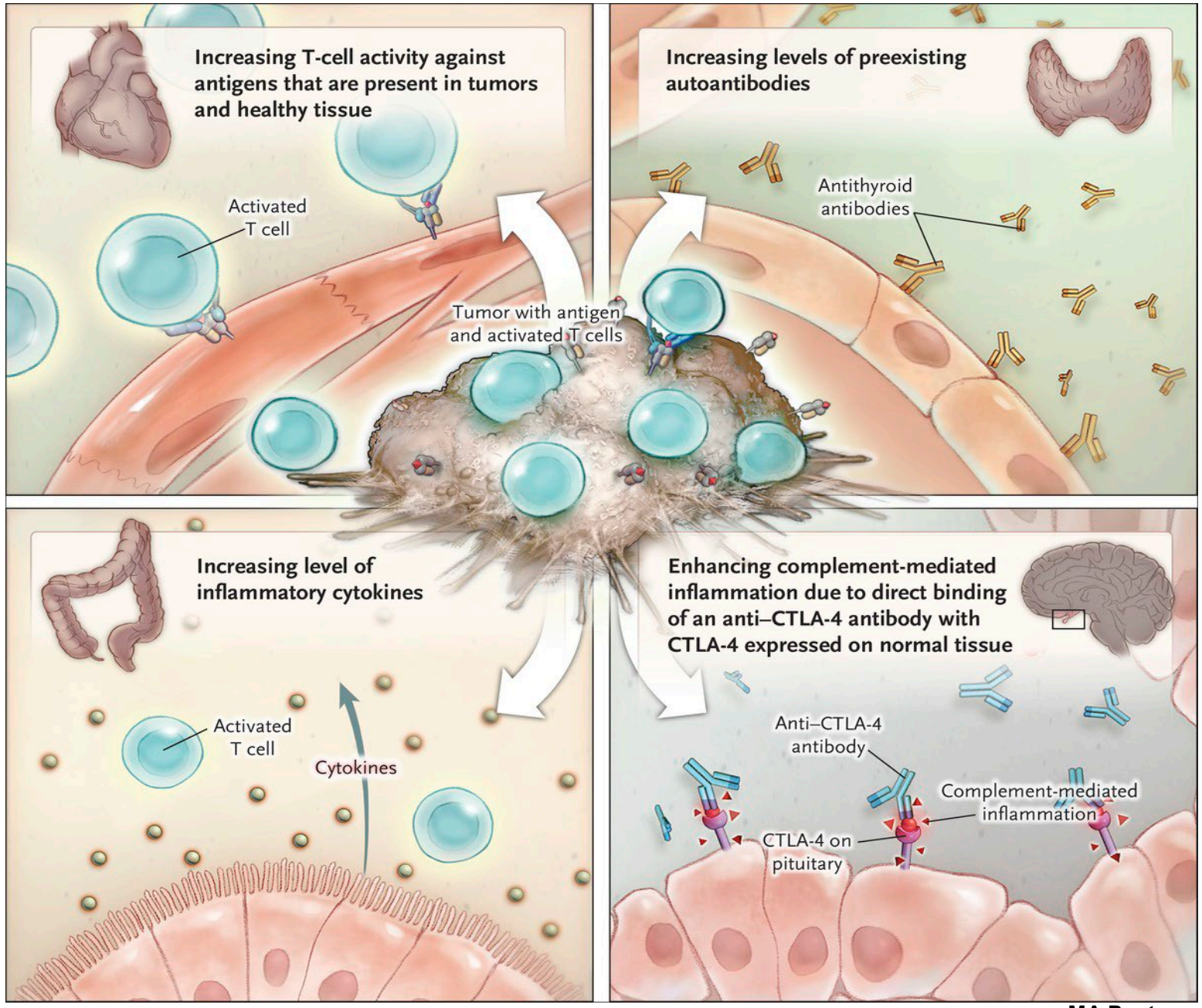
Postow, M et al. N Engl J Med 2018; 378:158-168
Nishino M et al. N Engl J Med 2015;373:288-290.
Naidoo, N et al. J Clin Onc 2017;35:709-717.

Pneumonitis most common cause of death from irAE in patients receiving PD-1/PD-L1treatment.



Wang D et al. *JAMA Oncol*. 2018;4(12):1721-1728.

Possible Mechanisms Underlying Immune-Related Adverse Events.



MA Postow et al. N Engl J Med 2018;378:158-168.

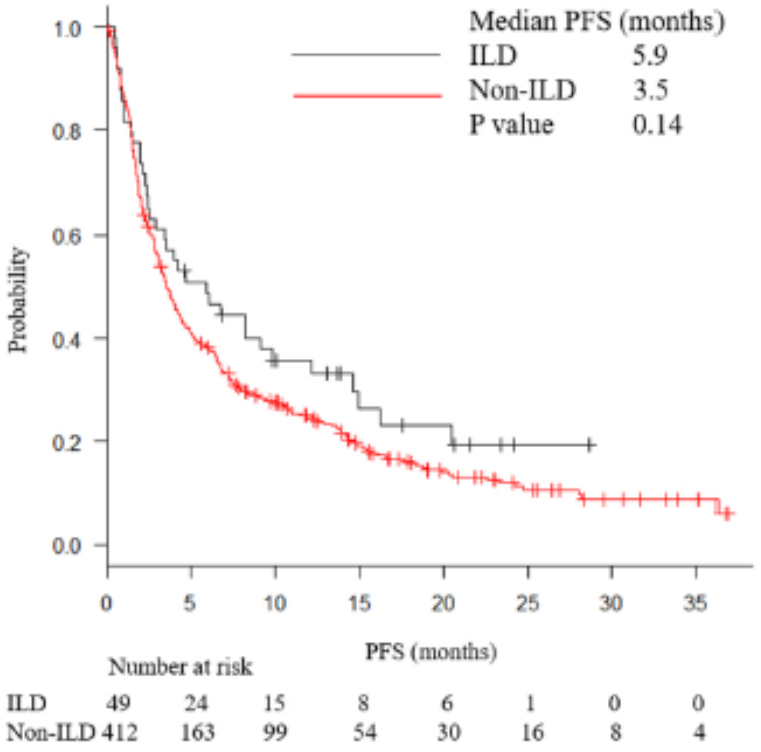
Epidemiology of Pneumonitis

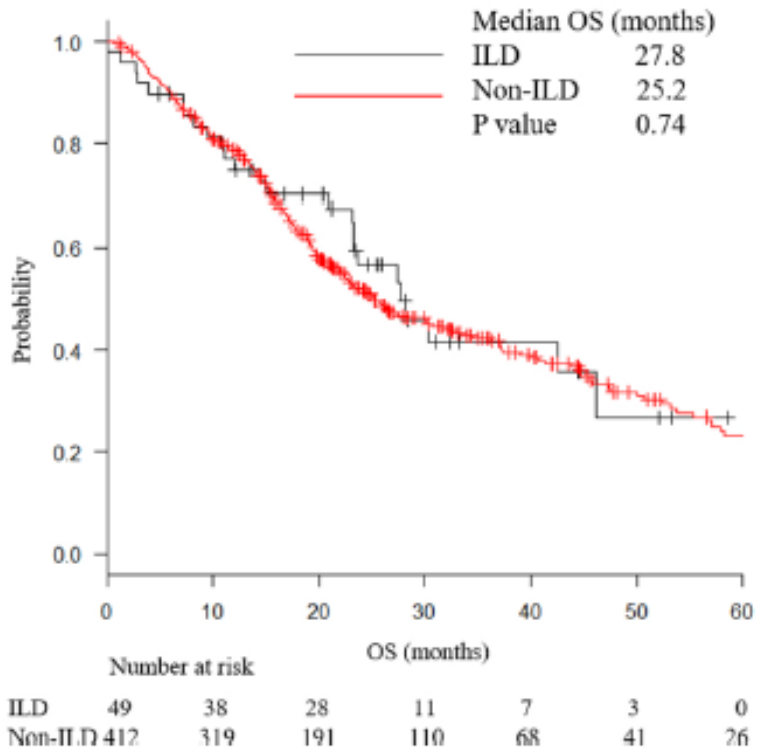
- Incidence depends on type of treatment:
  - PD-1 inhibitors have ~4-5% reported incidence, 0.8% grade 3/4
  - CTLA-4 inhibitors have ~1% incidence
  - Combination PD-1/CTLA-4 treatment associated with 10% incidence
- Median time to onset is 3 months, however wide range (2-24 months) and it can occur months after discontinuation
- Risk factors:
  - NSCLC, RCC associated with 2-to-3-fold higher incidence than melanoma
  - One study indicates the incidence in NSCLC could approach 20% for all grades
  - Reduced risk seen in adenocarcinoma subtype of NSCLC, although mortality in this subgroup is higher
  - **Pre-existing lung disease confers increased risk**

Cho JY et al. Lung Cancer. 2018 Nov;125:150-156.
Suresh K et al. J Thorac Oncol. 2018 Dec;13(12):1930-1939.

Outcomes of ICI in ILD patients

- Retrospective study of 469 patients of whom 41 had ILD
- 20% had UIP pattern
- Pneumonitis more common
  - 30% vs 9%
  - Including ≥Gr3





Tasaka Y, et al. Lung Cancer. 2021 May;155:120-126.

Ground glass score predicts pneumonitis

- 48 patients with NSCLC and ILD
- 48% non-IPF
- 7 patients (14%) developed pneumonitis
  - 3 died

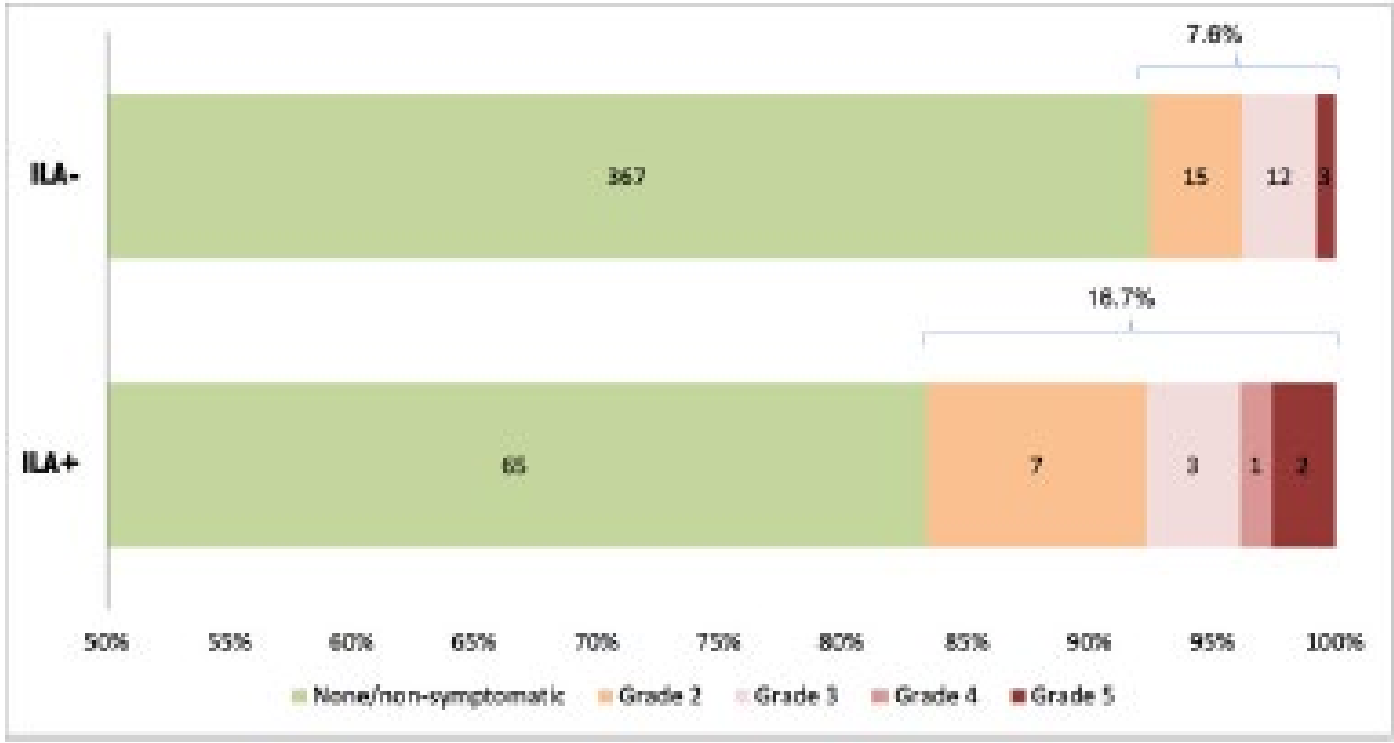
- Scoring system:
  - 3 slices of each CT
  - Scored for 3 different things:
    - Low attenuation areas
    - Fibrosis
    - Ground glass attenuation (GGA)

	Chemotherapy cohort			ICI cohort		
Variable	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Age < 70	0.64	0.18–2.28	0.49	1.33	0.15–12.1	0.80
Pack-years ≥ 40	0.94	0.22–4.02	0.93	1.50	0.15–14.9	0.73
Steroid therapy prior to treatment	0.91	0.17–4.91	0.91			
UIP pattern	0.71	0.17–2.98	0.64	1.32	0.07–25.5	0.85
Ground-glass attenuation score	2.62	1.06–6.47	**0.037**	653	4.30–99,000	**0.01**

Nishiyama N, et al. Int J Clin Oncol. 2020 Feb;25(2):282-291.

Experience at MGH

- Cohort of 475 patients with NSCLC who received ICI
- 78 (16%) had ILA
- Individual radiologic features associated with pneumonitis:
  - Ground glass
  - Mosaic attenuation
- Another predictor was prior thoracic radiation



Petranovic M, et al. Clin Lung Cancer. 2023 Dec;24(8):682-688.e5.

Checkpoint Inhibitor Pneumonitis Across Lung Diseases: ILD vs COPD vs Controls

BACKGROUND

CIP is an adverse effect of ICIs.

Risk may differ in ILD vs COPD.

KEY FINDINGS

CIP Incidence:
ILD 4.6%
COPD 1.9%
Controls 1.5%

Earlier CIP in ILD:
HR 2.49

CIP Recurrence:
ILD 0.156 *vs*
COPD 0.040

Mortality

ILD 8.9% *VS* COPD 12.3%

Respiratory failure & ICU rates: ~20–21% & ~16% (both higher than controls)

INTERPRETATION

ILD = highest CIP risk, earlier onset, more recurrence → requires increased surveillance

COPD = lower CIP risk but higher mortality, probably due to higher attention paid to ILD patients

STUDY DESIGN

- Retrospective TriNetX cohort
- Lung cancer patients receiving ICIs
- Groups: ILD, COPD, Control
- Propensity matching 1:1:1
- Outcomes: CIP incidence, time to onset, recurrence, mortality, ICU/respiratory failure

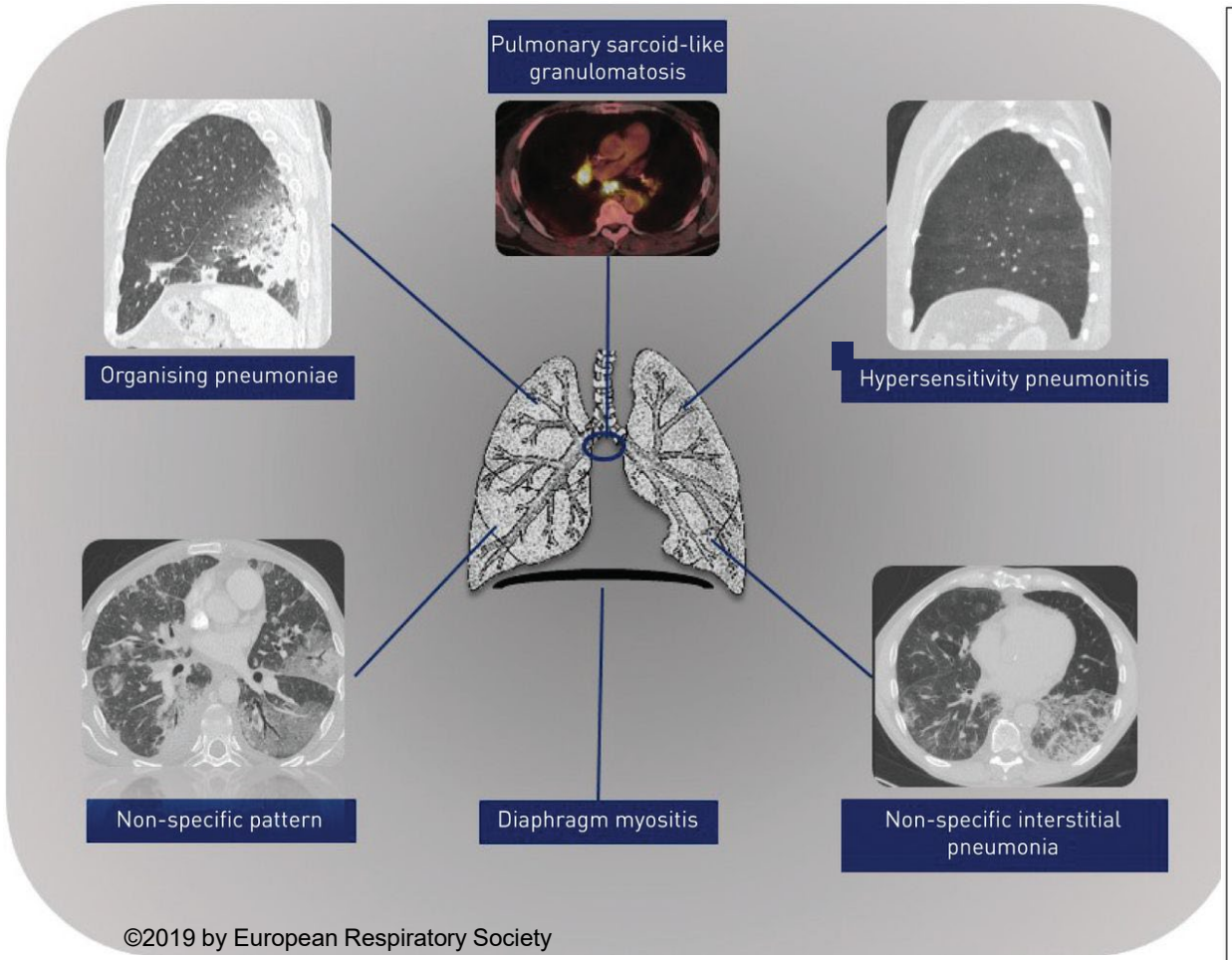
Respirology 2026 Apr;31(4):361-36

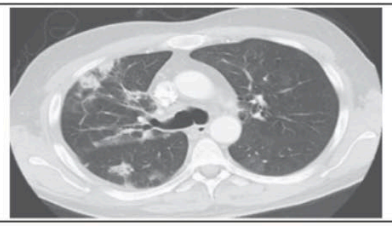
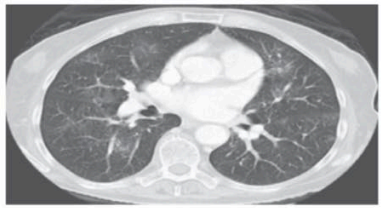
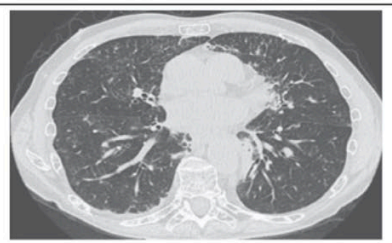
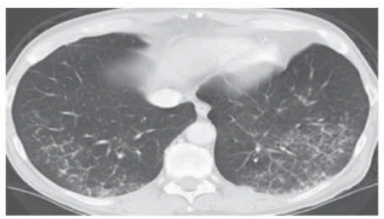
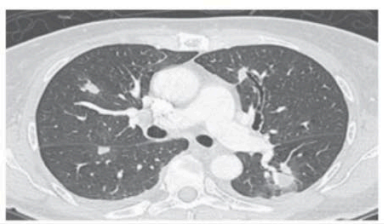
Clinical Presentation

- Most commonly symptoms are:
  - Dyspnea (53%)
  - Cough (35%)
  - Fever (12%)
  - Chest pain (7%)
- Up to 30% of patients are asymptomatic at presentation.
- Over 50% of patients will experience additional IRAE

Naidoo J et al. J Clin Oncol 35:709-717.
Nishino M et al. Clin Cancer Res: 22 (24).

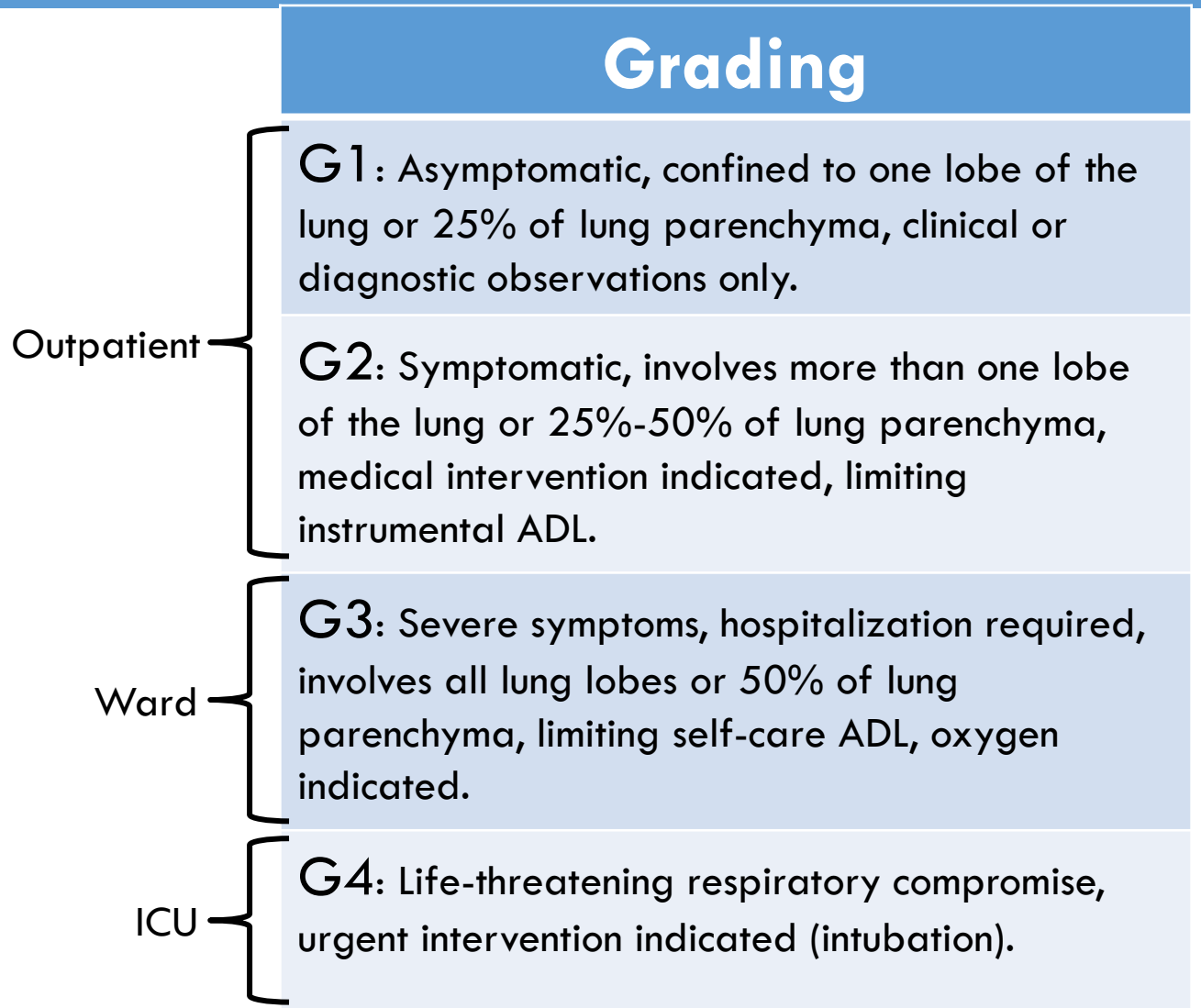
Imaging



Radiologic Subtypes	Representative Image	Description
Cryptogenic organizing pneumonia-like (n = 5, 19%)		Discrete patchy or confluent consolidation with or without air bronchograms Predominantly peripheral or subpleural distribution
Ground glass opacities (n = 10, 37%)		Discrete focal areas of increased attenuation Preserved bronchovascular markings
Interstitial (n = 6, 22%)		Increased interstitial markings, interlobular septal thickening Peribronchovascular infiltration, subpleural reticulation Honeycomb pattern in severe patient cases
Hypersensitivity (n = 2, 7%)		Centrilobular nodules Bronchiolitis-like appearance Tree-in-bud micronodularity
Pneumonitis not otherwise specified (n = 4, 15%)		Mixture of nodular and other subtypes Not clearly fitting into other subtype classifications

Myriam Delaunay et al. Eur Respir Rev 2019;28:190012
Brahmer JR et al. J Clin Oncol 36:1714-1768.

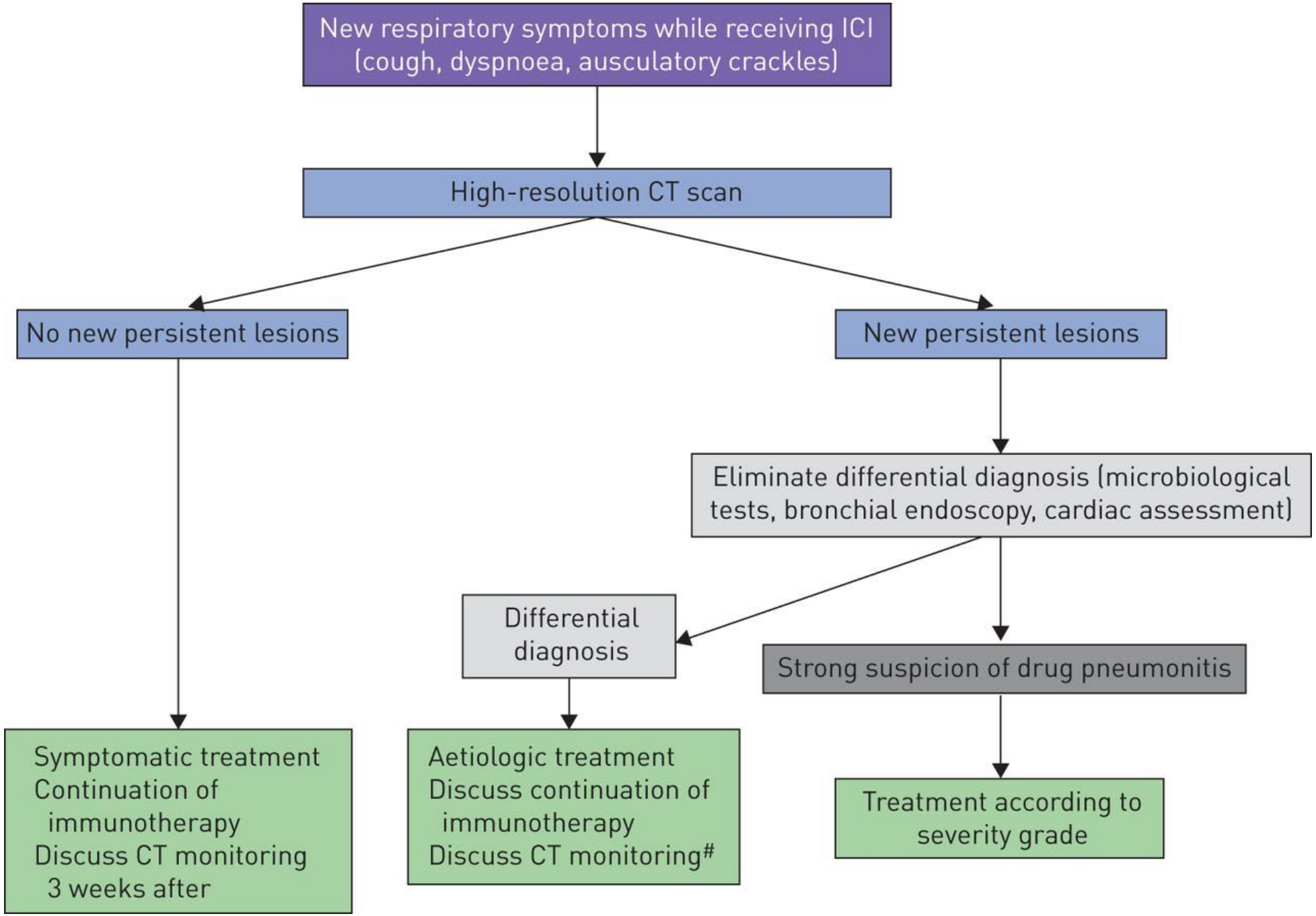
Pneumonitis Grading



Brahmer JR et al. J Clin Oncol 36:1714-1768.

Diagnosis - Initial Evaluation

- There is no gold standard diagnostic test
- Primary modality is imaging in the right clinical setting
  - CT chest
  - Exam with SpO2/ambulatory SpO2
  - Non-invasive infectious work-up
  - Consider bronchoscopy with BAL/TBBx



Myriam Delaunay et al. Eur Respir Rev 2019;28:190012

Bronchoscopy

- No clear guidelines
  - Diagnostic uncertainty
  - Potential infection
  - ? Metastatic disease
  - ??? everyone who can tolerate it
- Pathology: cellular interstitial pneumonia, granulomatous inflammation, DAD/acute lung injury, organizing pneumonia
- Prior to starting ICI on patients with existing ILDs

Initial Treatment

	Grading	Management
Outpatient	G1: Asymptomatic, confined to one lobe of the lung or 25% of lung parenchyma, clinical or diagnostic observations only.	? hold drug, repeat chest CT in 3-4 weeks. Can resume drug if radiographic improvement. If no improvement, treat as **grade 2**.
Outpatient	G2: Symptomatic, involves more than one lobe of the lung or 25%-50% of lung parenchyma, medical intervention indicated, limiting instrumental ADL.	Hold drug, start prednisone 1 mg/kg/day and taper over 4-8 weeks. Consider bronch, abx. Monitor every 3 days. If no improvement by 3 days, treat as **grade 3**.
Ward	G3: Severe symptoms, hospitalization required, involves all lung lobes or 50% of lung parenchyma, limiting self-care ADL, oxygen indicated.	Permanently stop drug. Hospitalize patient. Start IV methylprednisone BID. Start IV antibiotics. Consult pulm, consider bronchoscopy. If no improvement in 48 hours, treat as **grade 4**.
ICU	G4: Life-threatening respiratory compromise, urgent intervention indicated (intubation).	Consider adding tocilizumab, MMF, and/or IVIG.

Brahmer JR et al. J Clin Oncol 36:1714-1768.

Steroid Course

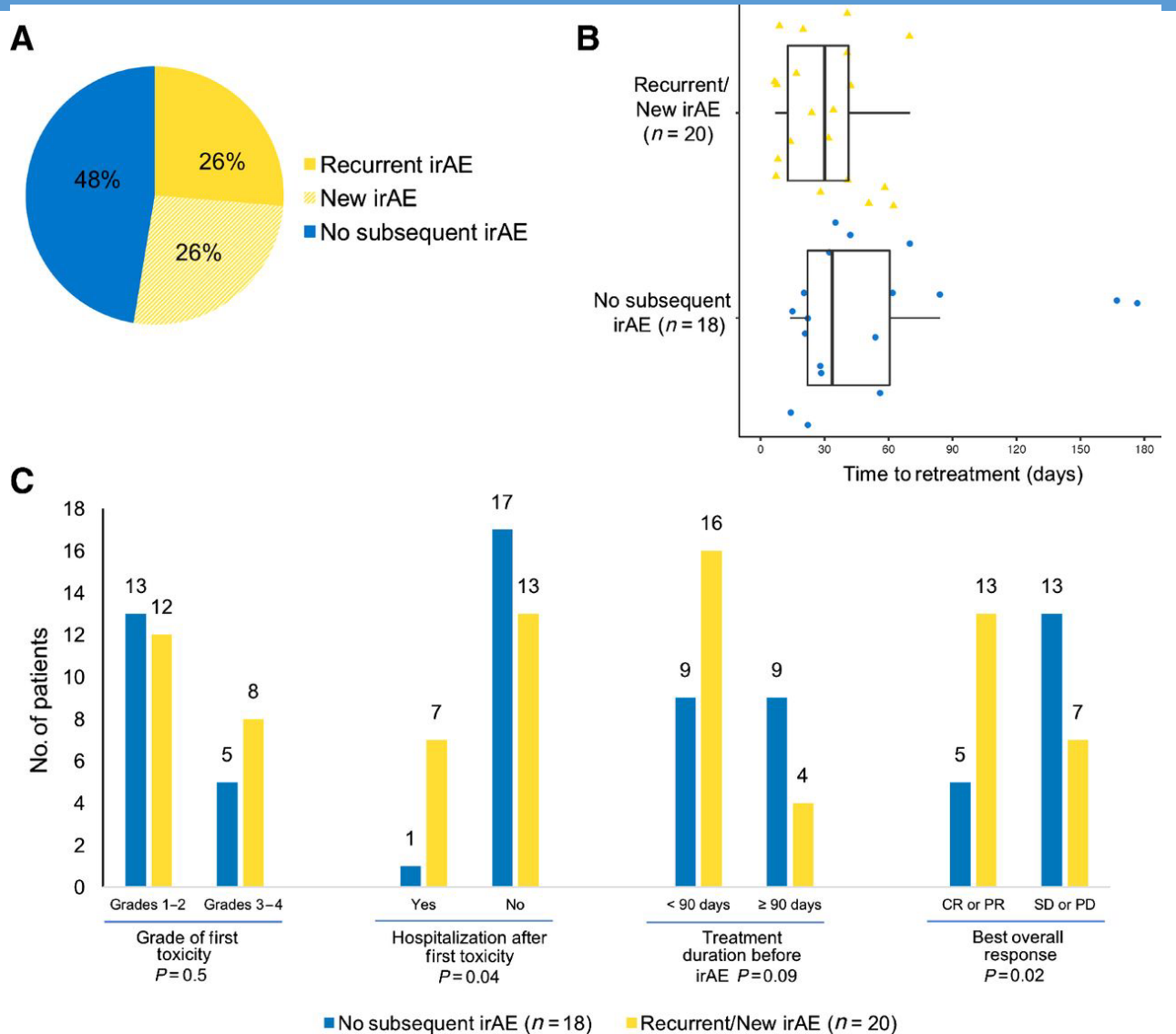
- Short course (6 weeks) – Grade 1-2 with improvement in imaging and symptoms at 2 weeks.
- Medium course (12 weeks) – Grade 3 or Grade 1-2 with slow improvement
- Long course – 6 months or more – Grade 3 or 4, recurrent disease with prior tapers. Consider steroid-sparing agent (MMF, Imuran)

Steroid Refractory Pneumonitis

*Patients with no improvement or worsening of pneumonitis with initial treatment with systemic steroids

- IVIG (Balaji et al, prospective trial ongoing infliximab vs IVIG)
- Tocilizumab (Stroud et al, grade 3/4 pneumonitis)
- Infliximab
  - Conflicting results, positive in single case reports but all negative outcomes in more recent retrospective studies (Naidoo, Balaji et al); high infectious complication rates
- MMF
  - Beattie et al, 2020: Rate of improvement with infliximab 20% (4/20, more severe cases), MMF 83% (5/6); 90 day survival 35% vs 100%
- BMJ 2024: MMF and IVIG for steroid-resistant pneumonitis, followed by tocilizumab if the first two agents fail

Re-treating with Immunotherapy
Risk of recurrence 30-50%



Cancer Immunol Res. 2018;6(9):1093-1099

Summary

- Pneumonitis is a relatively common complication of immunotherapy with significant morbidity and mortality
- Diagnosis largely based on imaging and clinical assessment
  - Grading 1 to 4
- ? Role for bronchoscopy
- If detected should consider hold of therapy and primary treatment with corticosteroids
- More severe disease, refractory disease, and recurrent disease should prompt consideration of secondary agents (MMF, toci)
- Can consider re-challenge with ICI if pneumonitis resolved and not prior severe disease

Steroid dependent pneumonitis

*Patients who initially responded to steroids, but subsequently developed recurrent pneumonitis in the context of steroid tapering, in the absence of ICI rechallenge

- BAL w/ persistent lymphocytosis, path w/ organizing pneumonia and lymphocytic infiltration (Naidoo et al, 2020)
- Worsening at 10mg daily, requiring extended course >12 weeks (median duration 37 weeks)
- More common with combination ICI therapy
- Clinical course similar to natural history of COP