PULMONARY COMPLICATIONS OF IMMUNOTHERAPY

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MGH Pulm-Oncology Group

Ben Medoff
Grace Peloquin
Angela Frank
Ming-Hui Fan
Rob Hallowell
Lauren Flynn

Massachusetts General Hospital
Division of Pulmonary & Critical Care Medicine

Disclosures

- I serve on an advisory board for Sanofi/Regeneron
- I have sponsored research grants from:
  - Bayer
  - Boehringer-Ingelheim
  - Sanofi
  - Regeneron
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  - NIH

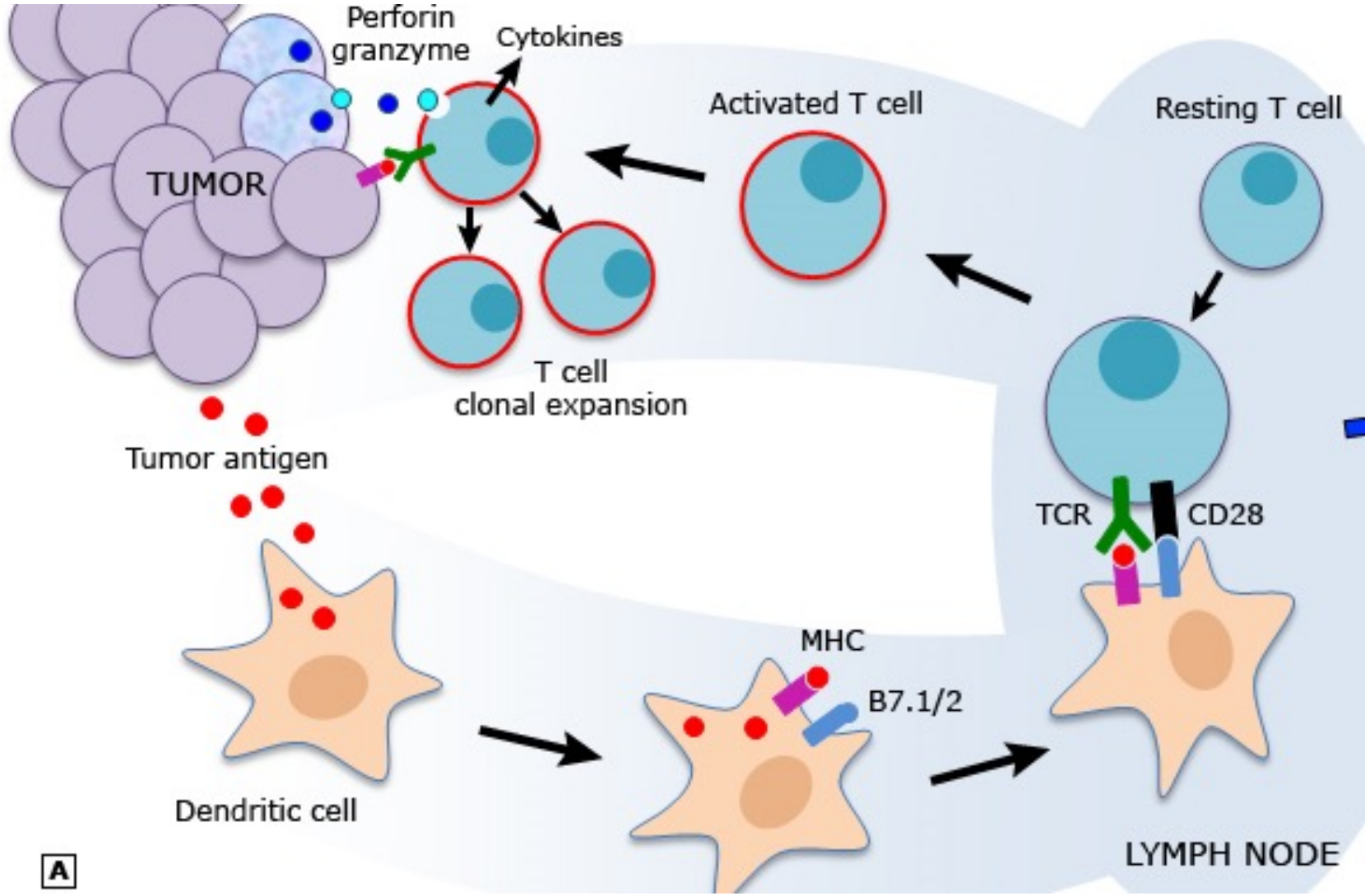
Immunotherapy

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

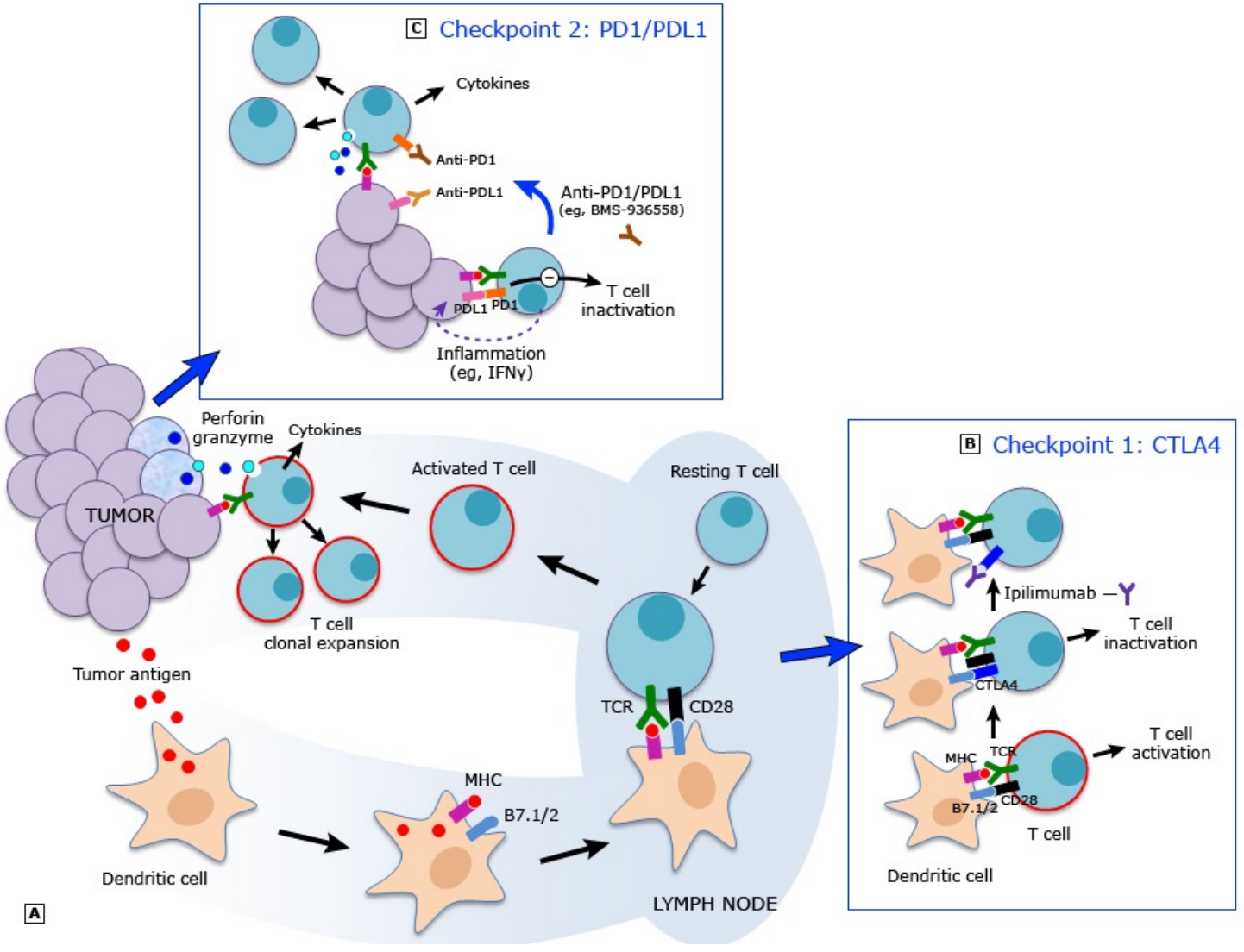
Cancer Immunoediting

- 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

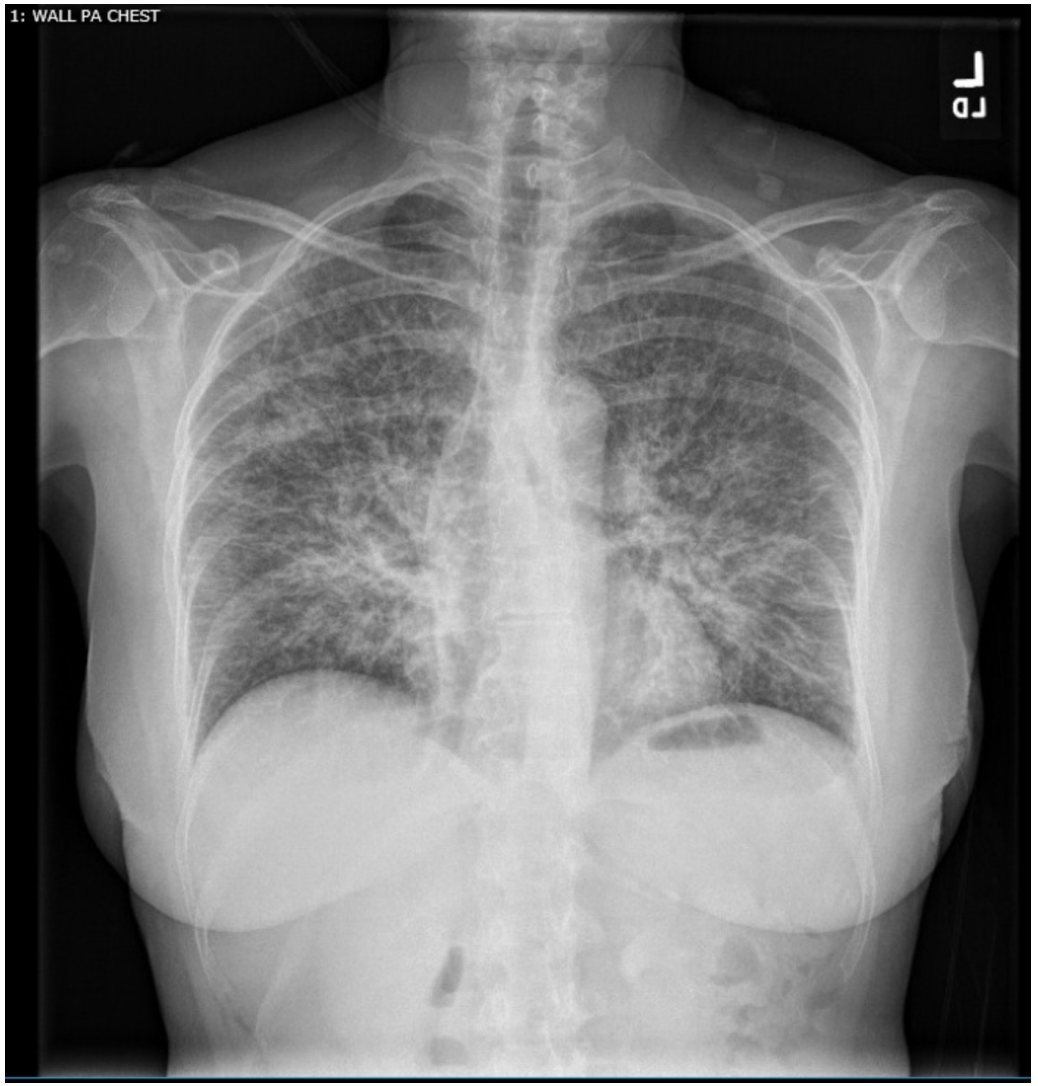
Anti-Tumor Immune Activation



Immune Checkpoint Inhibition

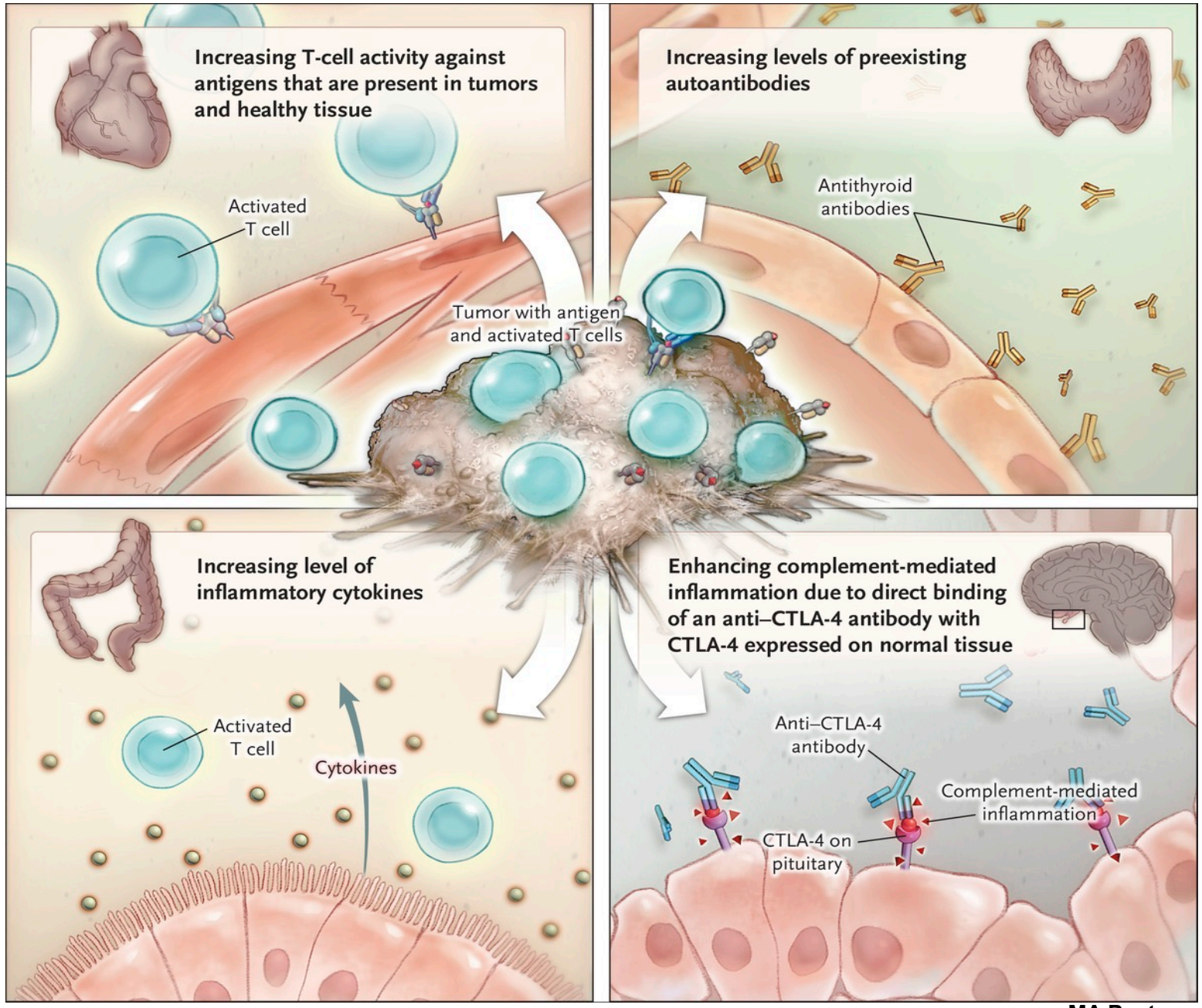


Immune-related adverse event - irAE– Pneumonitis



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.

Possible Mechanisms Underlying Immune-Related Adverse Events.



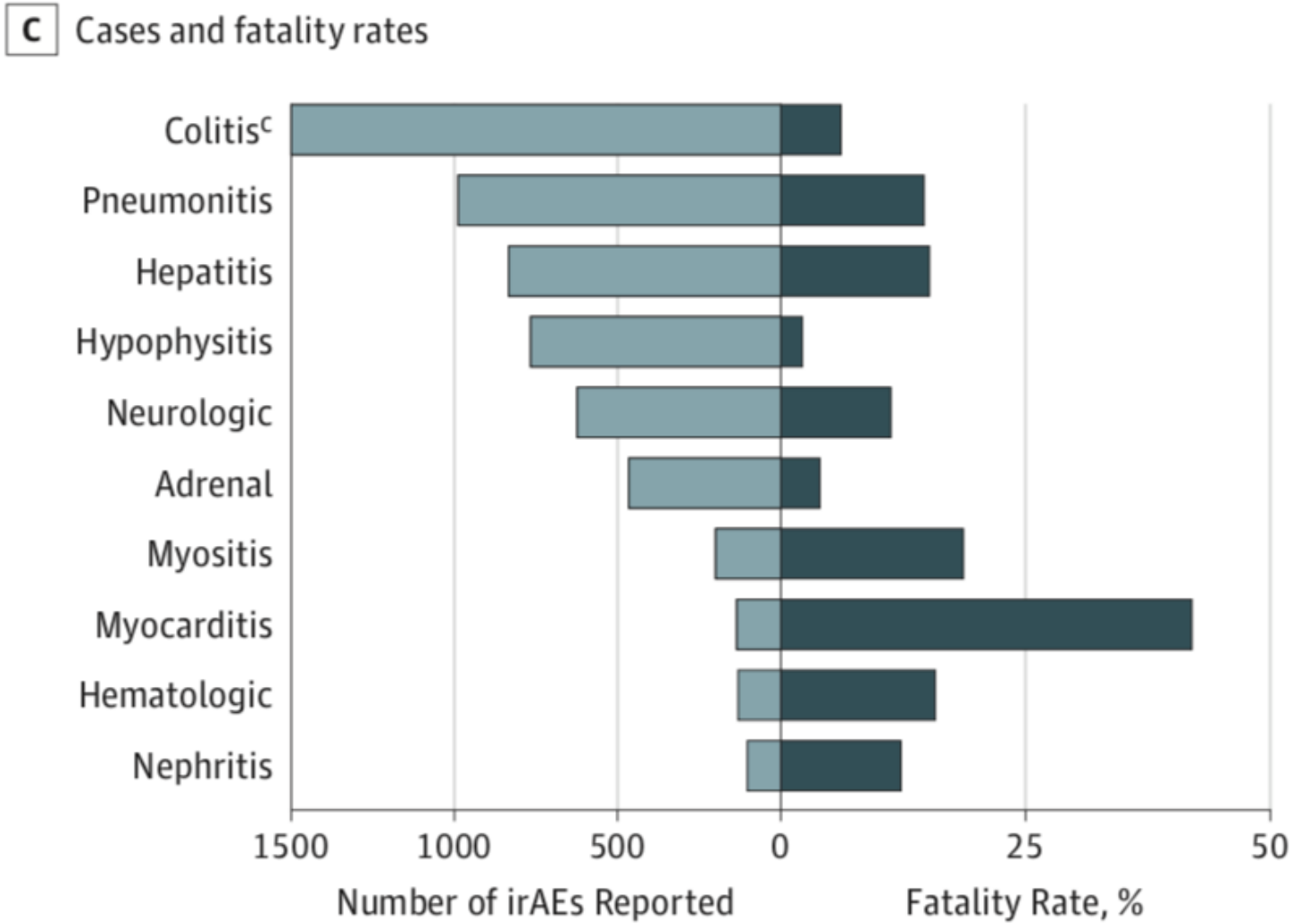
MA Postow et al. N Engl J Med 2018;378:158-168.

Epidemiology of Pneumonitis

- Incidence depends on type of treatment:
  - PD-1 inhibitors have ~4-5% reported incidence (maybe higher), 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 can occur months after discontinuation
- Risk factors:
  - NSCLC, RCC associated with 2-to-3-fold higher incidence than melanoma
  - One study indicates 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 ILD confers 6 to10 fold 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.

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



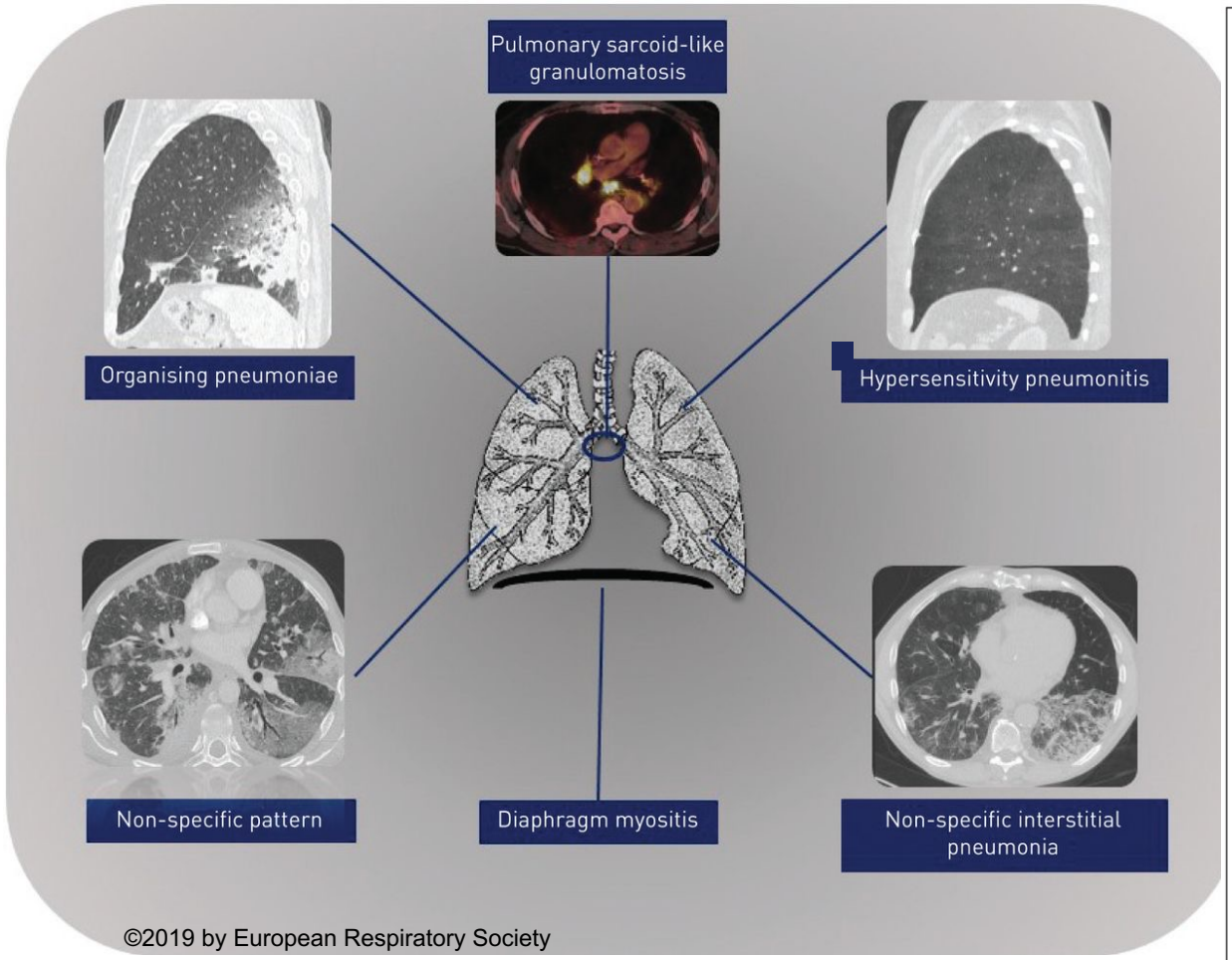
Wang D et al. *JAMA Oncol*. 2018;4(12):1721-1728.

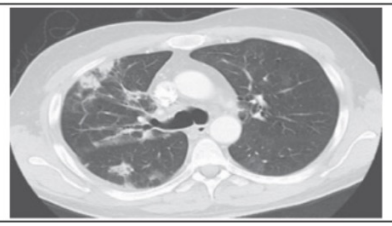
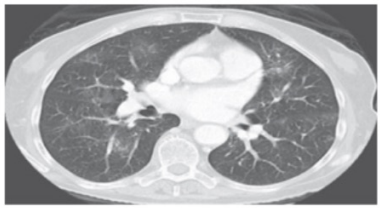
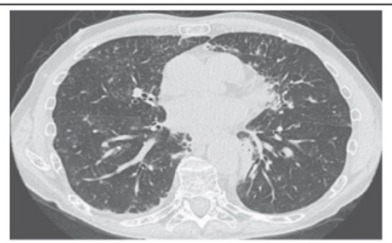
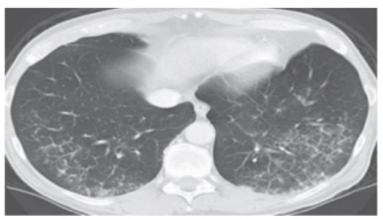
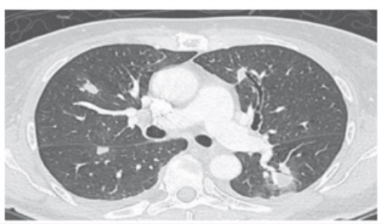
Clinical Presentation

- 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.

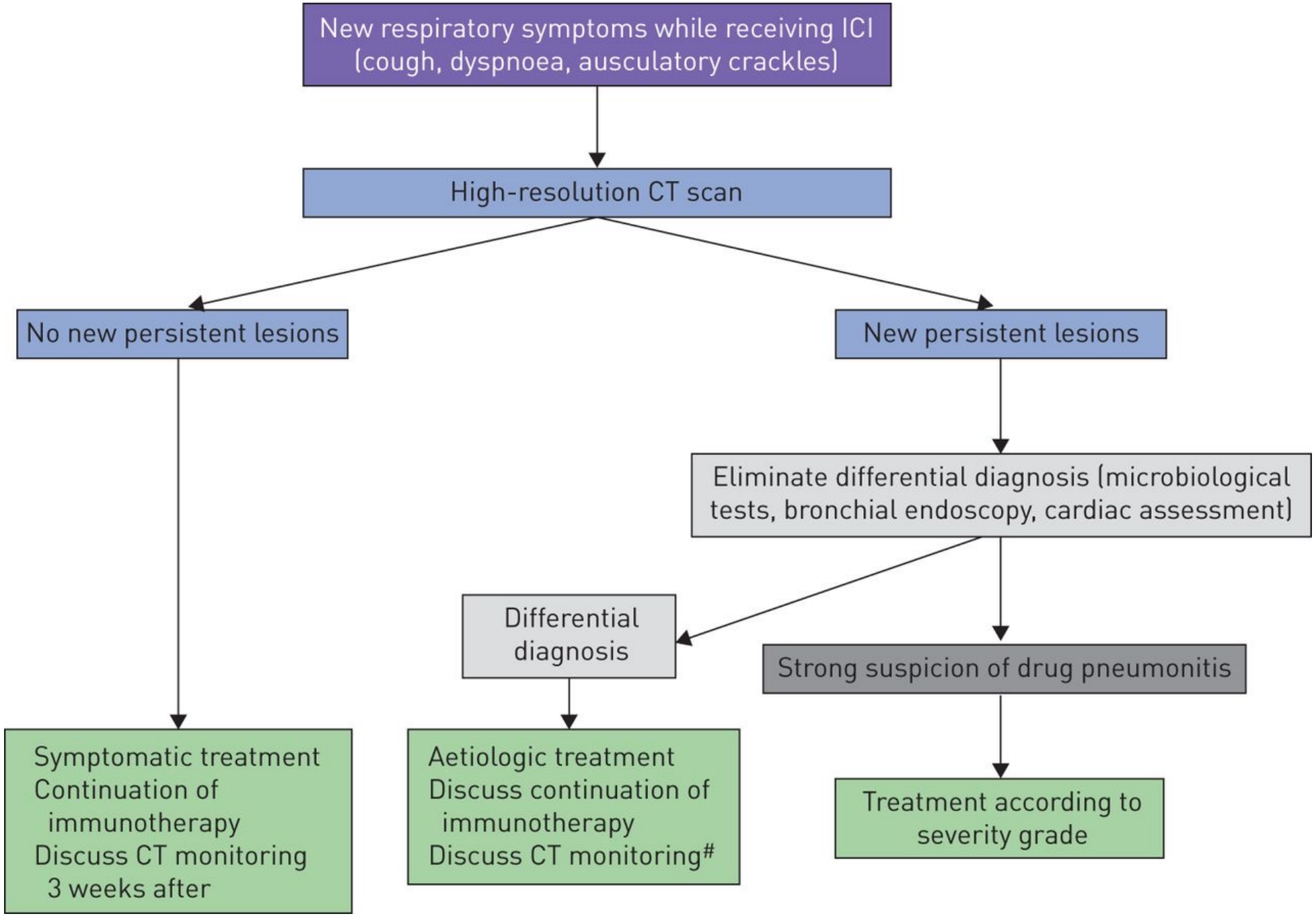
Pneumonitis Grading

	Grading
Outpatient	G1: Asymptomatic, confined to one lobe of the lung or 25% of lung parenchyma, clinical or diagnostic observations only.
Outpatient	G2: Symptomatic, involves more than one lobe of the lung or 25%-50% of lung parenchyma, medical intervention indicated, limiting instrumental ADL.
Ward	G3: Severe symptoms, hospitalization required, involves all lung lobes or 50% of lung parenchyma, limiting self-care ADL, oxygen indicated.
ICU	G4: Life-threatening respiratory compromise, urgent intervention indicated (intubation).

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)

Natural History of irAEs

Recurrent irAEs:
- Occur in the same organ
- Occur at least twice after IO discontinuation

Delayed/late-onset irAEs:
- Occur > 3 months after ICI discontinuation

Chronic irAEs:
- Persist beyond 3 months of ICI discontinuation

Two subtypes:
1) **Chronic + active**: Ongoing inflammation, requires ongoing immunosuppression
2) **Chronic + inactive**: Absence of ongoing inflammation, not requiring ongoing immunosuppression

Patterns of irAEs

Multisystem irAEs:
- Occur concomitantly with another irAE or during treatment for the first irAE
- irAEs occurring in the same or different organ system
- If occurring in the same system, affect different tissues

Response to irAE Treatment

Steroid-unresponsive irAEs:
- No clinical improvement after a standard timeframe of guideline-based irAE-directed steroid therapy
- Steroid-refractory irAEs derived no clinical benefit from steroids

Steroid-resistant irAEs:
- Derived some clinical benefit without resolution of the event

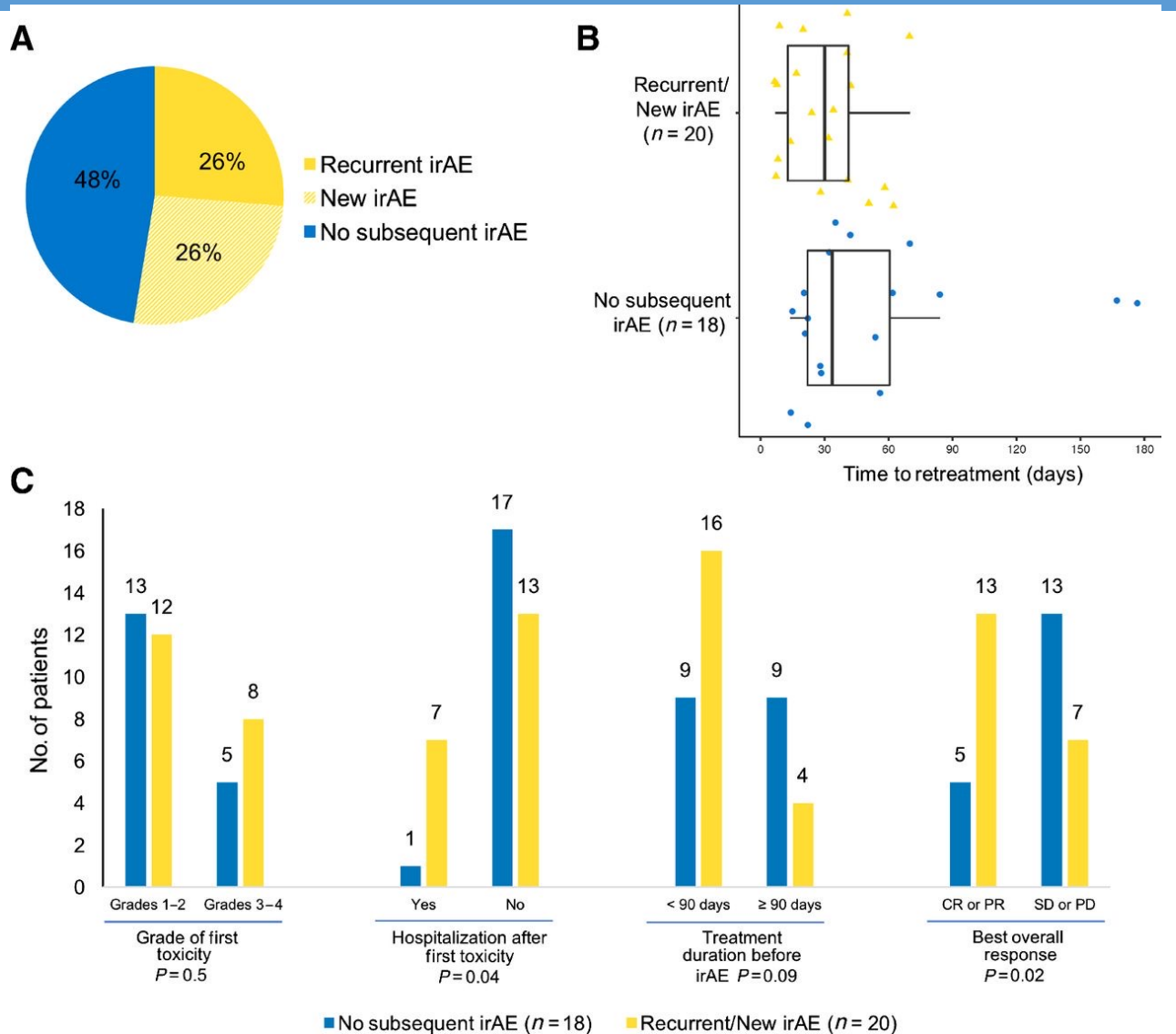
Steroid-dependent irAEs:
- Some improvement with guideline-based irAE-directed steroid therapy, however a taper is not possible.
- irAEs requiring ongoing steroids for ≥12 weeks are "chronically steroid-dependent"

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