Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Pneumonitis with Immunotherapy

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#LearnACI

Disclosures

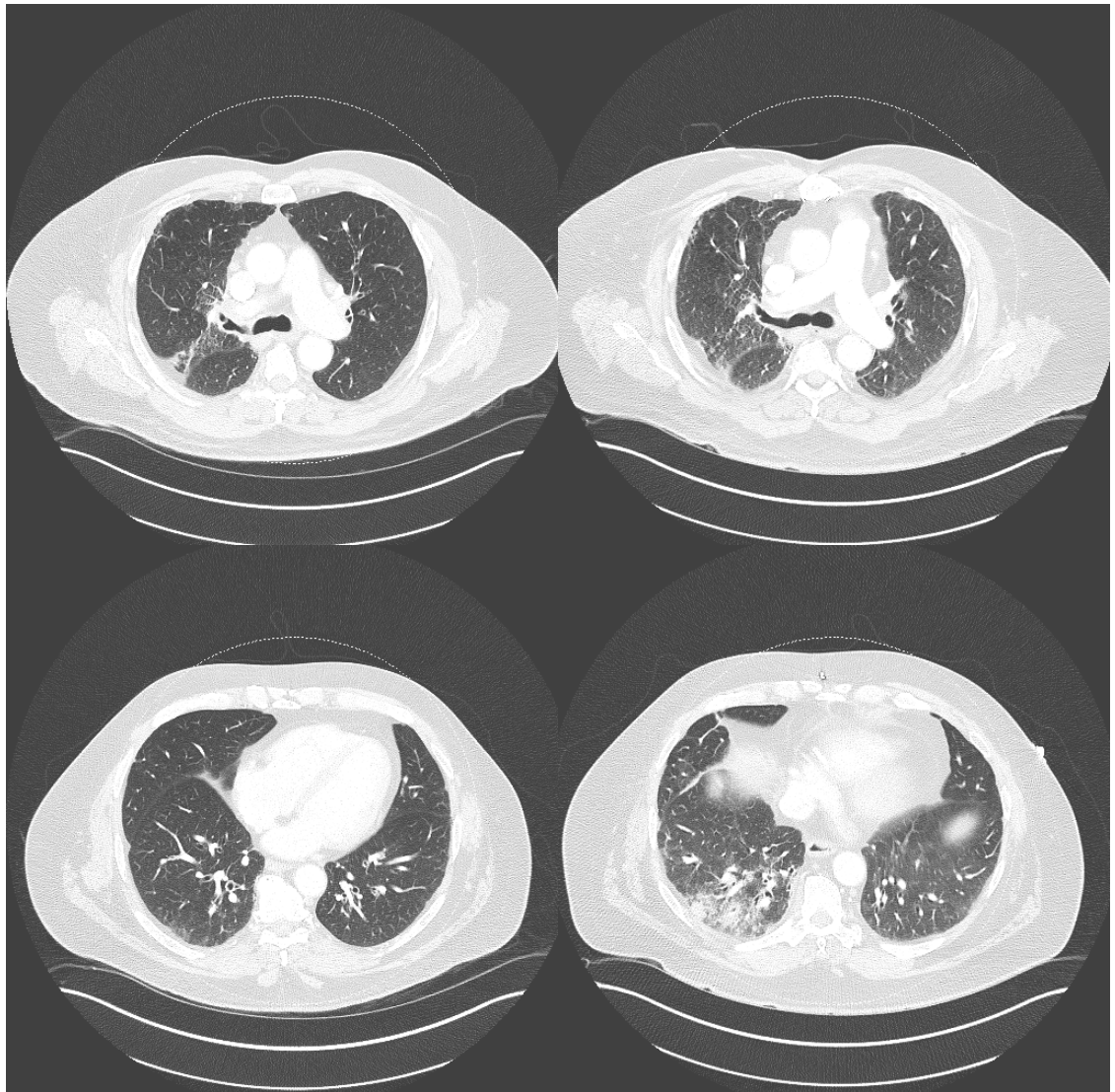
- Research funding (to institution) from Genentech, Nektar Therapeutics, Merck, GlaxoSmithKline, Novartis, Jounce Therapeutics, Bristol Myers Squibb, Eli Lilly, Adaptimmune, Shattuck Lab, Gilead.
- Advisory Board: GlaxoSmithKline, Shattuck Lab, Bristol Myers Squibb, AstraZeneca
- Speaker fees: AstraZeneca, Nektar Therapeutics
- I will be discussing non-FDA approved indications during my presentation.

- Case presentation
- Incidence of pneumonitis, Risk factors
- Recognizing and treating pneumonitis
- Conclusions

Case Review

- 72 yo gentleman w metastatic lung adenocarcinoma
- PMHx: 20 pack/year smoking hx, HTN, dyslipidemia, CAD w coronary artery stents
- KRAS/TP53 co-mutant, PD-L1 TPS 90%
- 1st line therapy, Pembrolizumab started in July 2017 with very good PR
- No irAEs until mid March 2019
- Clinic visit for consideration of 24th cycle Pembrolizumab with response assessment scan

Baseline Pneumonitis?



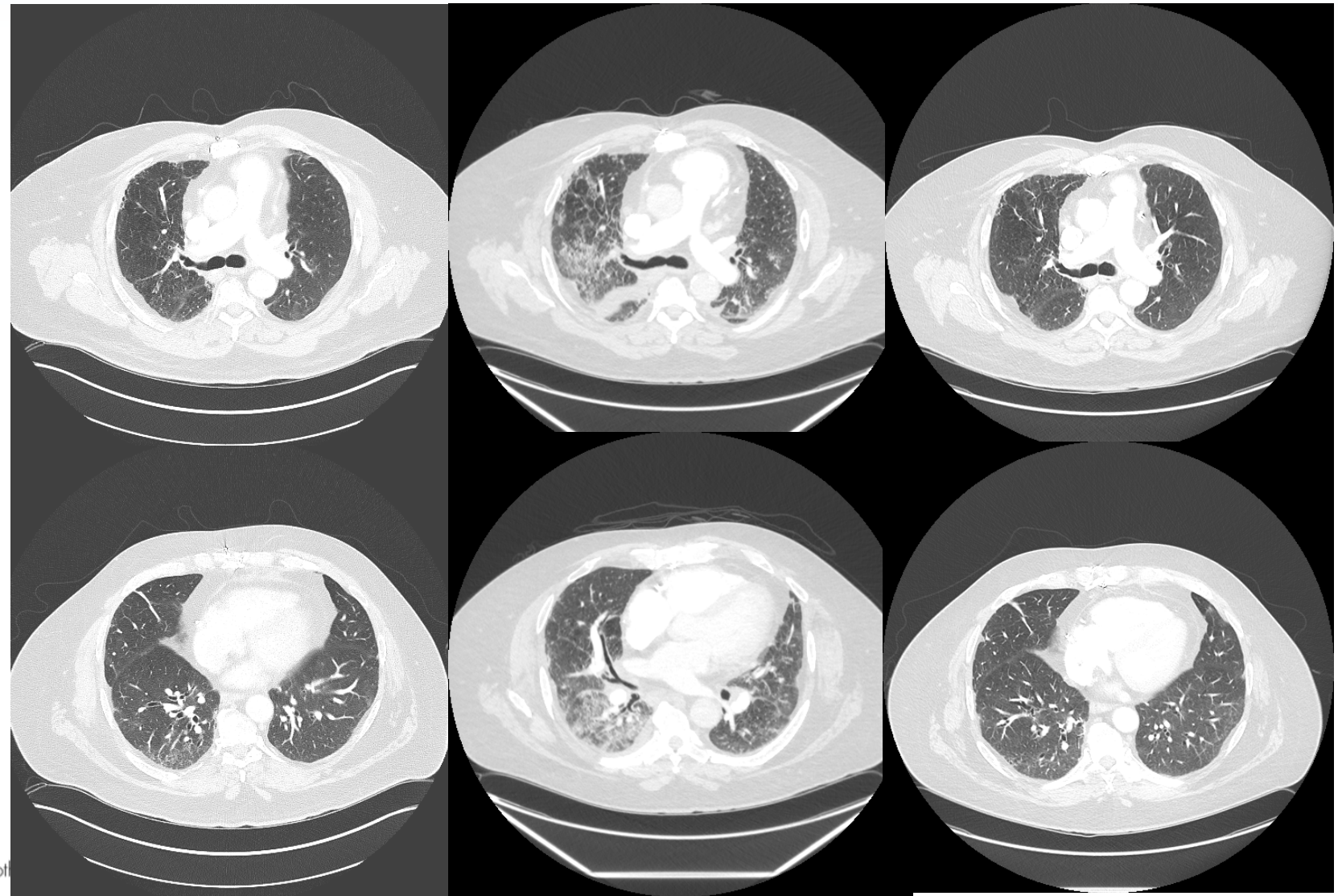
Case Review

- O2 sat 96% (Baseline), asymptomatic,
- ROS & Clinical exam
- Preliminary diagnosis, Grade 1 Pneumonitis
- Therapy placed on hold, Pulm consultation requested, reviewed alarming symptoms
- 3 days later in pulm consult, O2 sat 72%

Resolution

Second Pneumonitis

Resolution of 2nd pneumonitis



Trigger? Baseline risk factors? Early predictors? How to manage? Risk of flares? Re-challenge?

Pneumonitis, as a particular irAE of interest in NSCLC

- Most common fatal irAE (accounts for 35% anti PD-1/PD-L1 related deaths)

- In a meta-analysis of 22 solid tumor studies;
  - In NSCLC pneumonitis all grade 4.1% and Grade ≥3 1.8%
  - Highest incidence compared with RCC and melanoma

Nishino M. et al JAMA Onc 2016
Su Q. et al Front. Immunol. 2019
Khunger M et al. Chest. 2017
Fukihara J et al. Clin. Lung Ca. 2019

Pneumonitis after Immunotherapy for Lung Cancer

- 1% of patients on CTLA-4 inhibitors, 5% of patients on PD-1/PD-L1 inhibitors. Higher incidence with combination ICI therapy
- Median onset is typically 3-4 months
- Typical symptoms include cough, wheezing, shortness of breath, chest tightness, low-grade fevers
- Clinical manifestations are typically a non-infectious pneumonia or interstitial lung disease

Nishino, JAMA Onc 2016
Su, Front. Immunol. 2019
Khunger, Chest 2017
Fukihara, Clin. Lung Ca 2019
Suresh J Thorac Oncol 2018

Pneumonitis, as a particular irAE of interest in NSCLC

In NSCLC therapy rates possibly increase by

- Interstitial lung dx
- Preexisting obs lung dx (COPD)
- With chest radiation
- With treatment in combination with TKI

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Sears, C.R.et al. ATS Research Statement 2019

Pneumonitis, as a particular irAE of interest in NSCLC

In NSCLC therapy rates possibly increase by

Interstitial lung dx

Preexisting obs lung dx (COPD)

Smoking or smoking-related histology (e.g. Sq Cell) is associated with higher rates of pneumonitis*

Number of studies have identified that ILD is associated with a higher risk for pneumonitis.

-Yamaguchi et al – IPF vs. no IPF 35% vs. 6%

-Shimoji et al – prior ILD OR 6.29; 95% CI, 2.34-16.92

-Yamaguchi et al – prior ILD OR 5.92; 95% CI 2.07–18.54

-Nakanishi et al – prior ILD OR 6.6; 95 % CI 1.7-24.7

Yamaguchi et al. Lung Cancer 2018
Shimoji et al. JAMA Netw Open. 2020
Yamaguchi et al. BMC Cancer. 2021.
Nakanishi et al. Respir Investig. 2019.
Yamaguchi et al. Lung Cancer 2021

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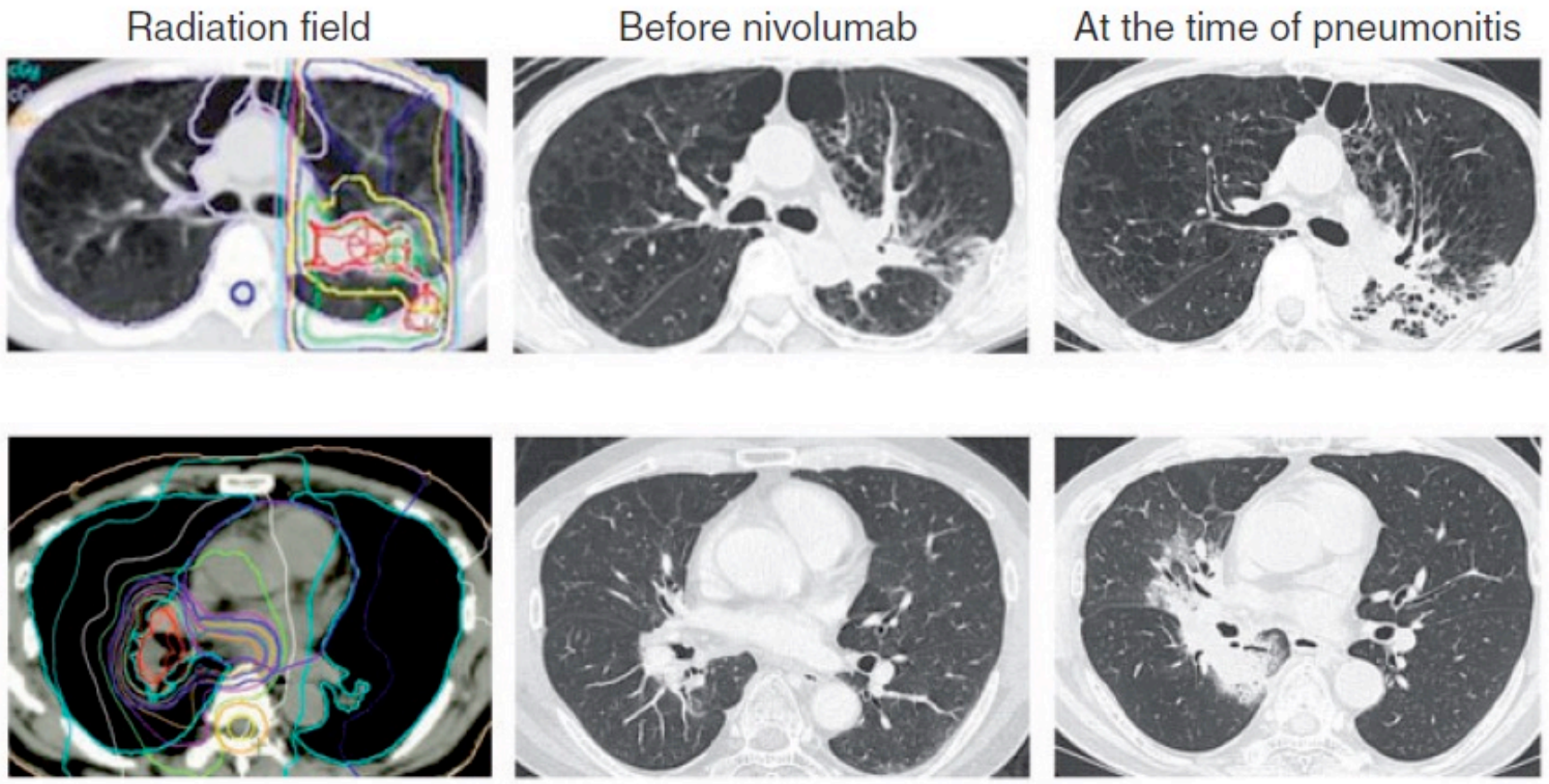
Radiation



Shibaki, R. Ann.Oncol. 2017

Radiation (Non-metastatic dx (Stage IIIB)

PACIFIC STUDY

Stage III NSCLC, unresectable

Definitive RT (54 to 66 Gy) + Chemotherapy (platinum based)

R

- Durvalumab
- Placebo

Any grade pneumonitis or radiation pneumonitis 33
Pneumonitis (RT and/or IO) G≥3, 3.4%
Discontinuation rate 5%, 1% mortality attributable to pneumonitis

Radiation (Non-metastatic dx (Stage IIIB)

KN-799 STUDY

Stage III NSCLC, unresectable

→ Pembrolizumab* +Carboplatin+ Pemetrexed +definitive** RT

→ Pembrolizumab* +Carboplatin+ Paclitaxel +definitive RT**

*Pembrolizumab up to a year
**RT given with cycle 2 and 3 systemic therapy

Pneumonitis (RT and/or IO) G≥3, 8%
Discontinuation rate 33%,
Cohort A 3.6%-Cohort B 1% mortality attributable to pneumonitis

Pneumonitis, as a particular irAE of interest in NSCLC

In NSCLC therapy rates possibly increase by

- Interstitial lung dx
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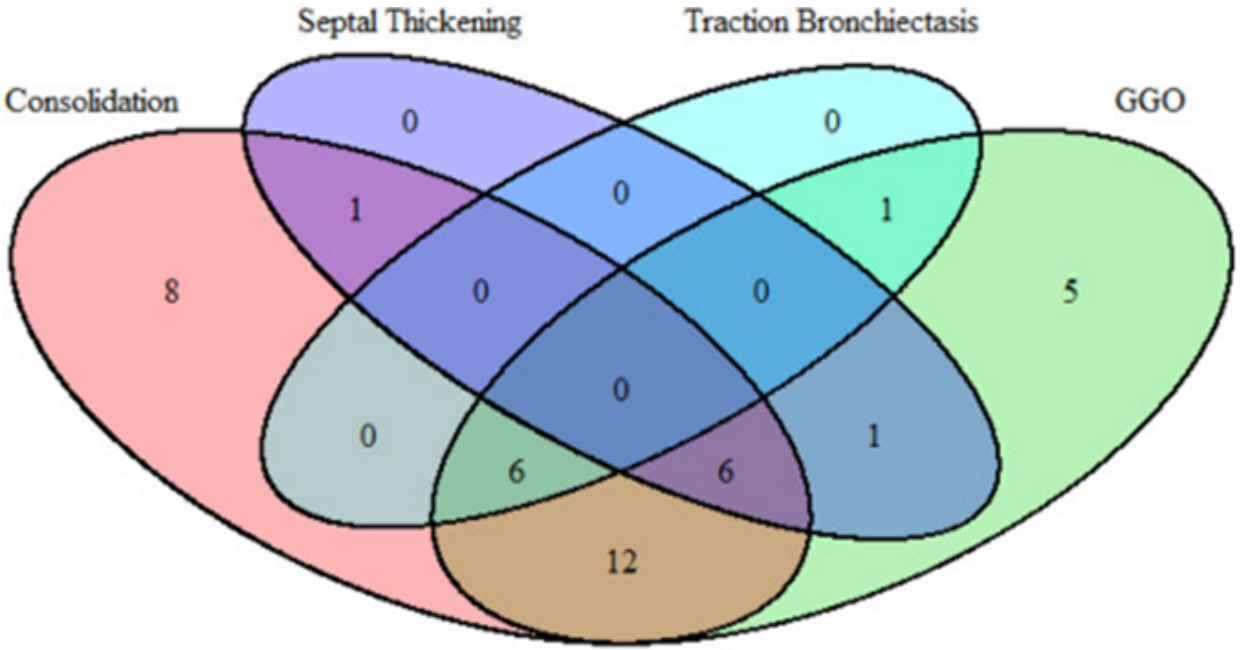
Clinical and Pathologic Subtypes of Pneumonitis

Organizing pneumonia (about half of patients)

Interstitial pneumonitis (about 1/3 of patients)

Mixed pattern (about 15% of patients)



Naidoo, J Clin Oncol 2017
Suresh, J Thorac Oncol 2018

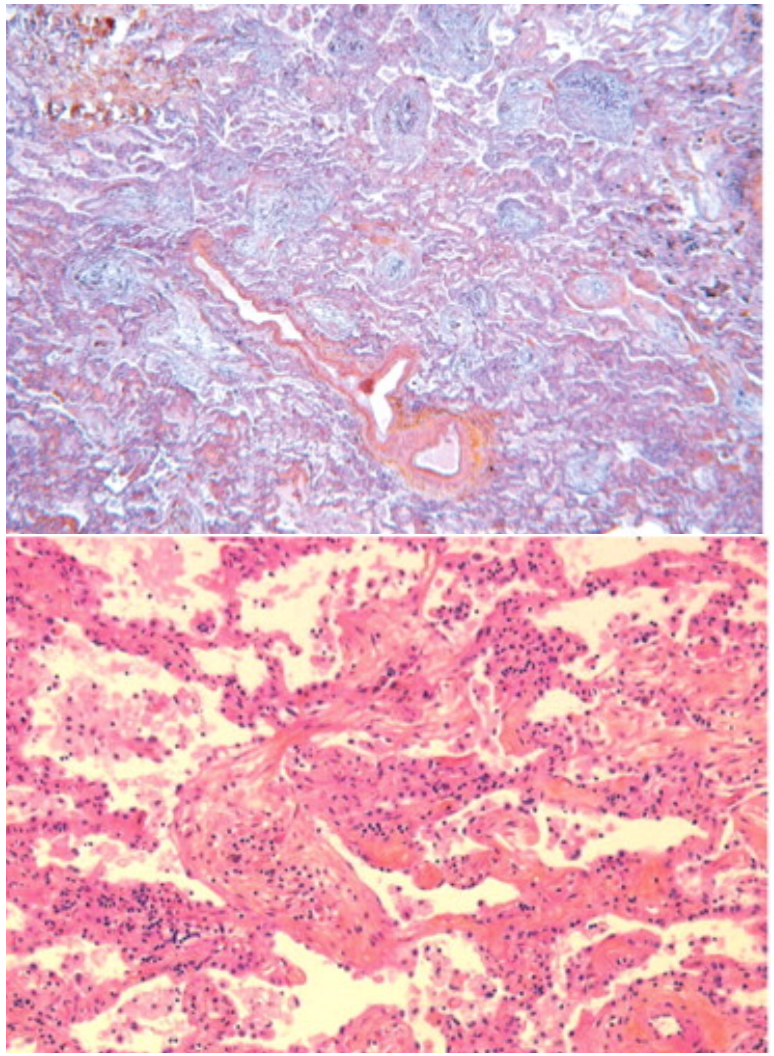
Organizing Pneumonia

"Organizing" pneumonia due to deposition of fibrous tissue in untreated cases

Despite fibrous plugs in airspaces, OP is very treatable

Untreated OP can spontaneously

- resolve
- "smolder" with waxing/waning infiltrates
- progress to fatal lung injury

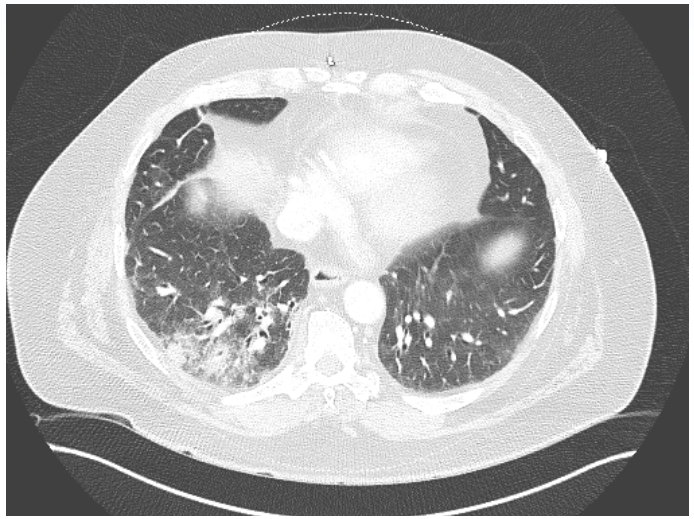


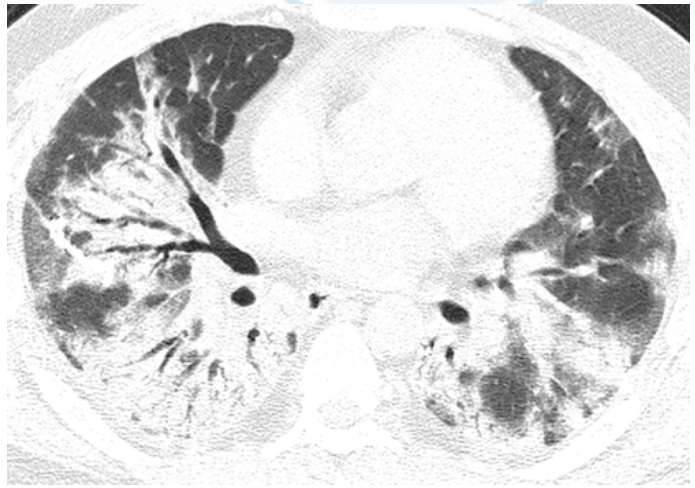
Cordier, Eur Resp J 2006

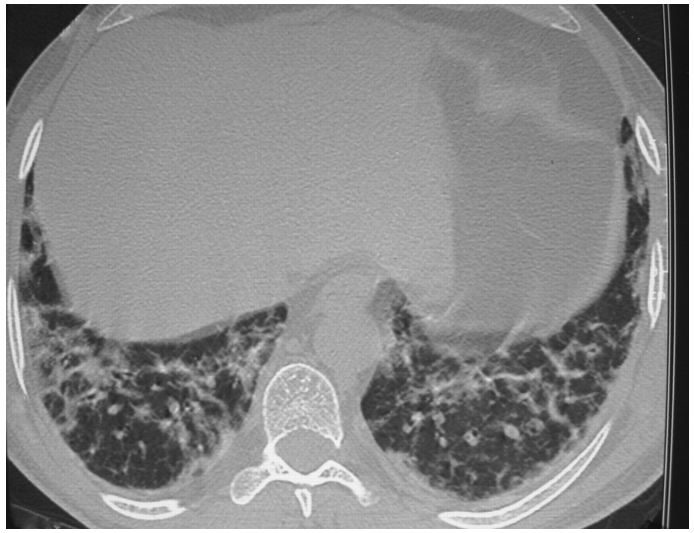
Organizing Pneumonia

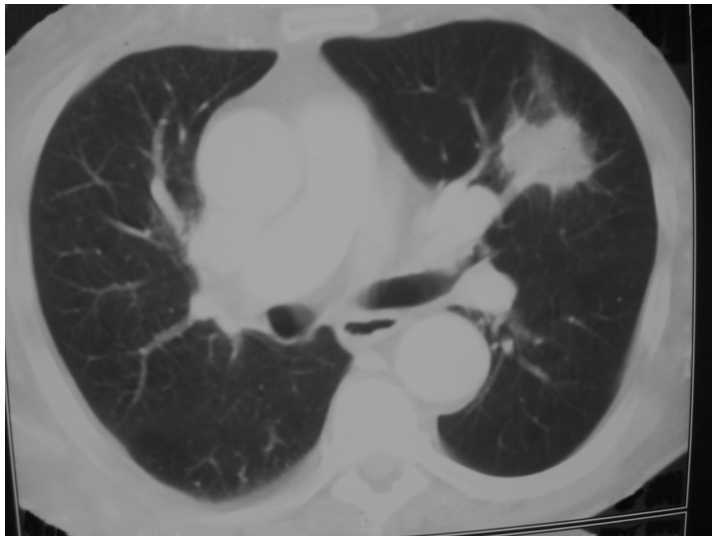
OP has many radiological forms

- "typical" OP: peripheral bilateral ground-glass or consolidative lesions
- "infiltrative" OP with widespread interstitial infiltrates and ground-glass opacities
- Solitary lesions which can mimic fungal infections









Cordier, Eur Resp J 2006
Lee, Am J Roentgenol 2010

Grading Pneumonitis (CTCAE 5.0)

Grade 1 – asymptomatic, only seen on radiology (Confined to one lobe of the lung or <25% of lung parenchyma-clinical or diagnostic observation only*)

Grade 2 – minor symptoms interfering with activities of daily life (Involves more than one lobe of the lung or 25%-50% of lung parenchyma*; medical intervention indicated; limiting instrumental ADL)

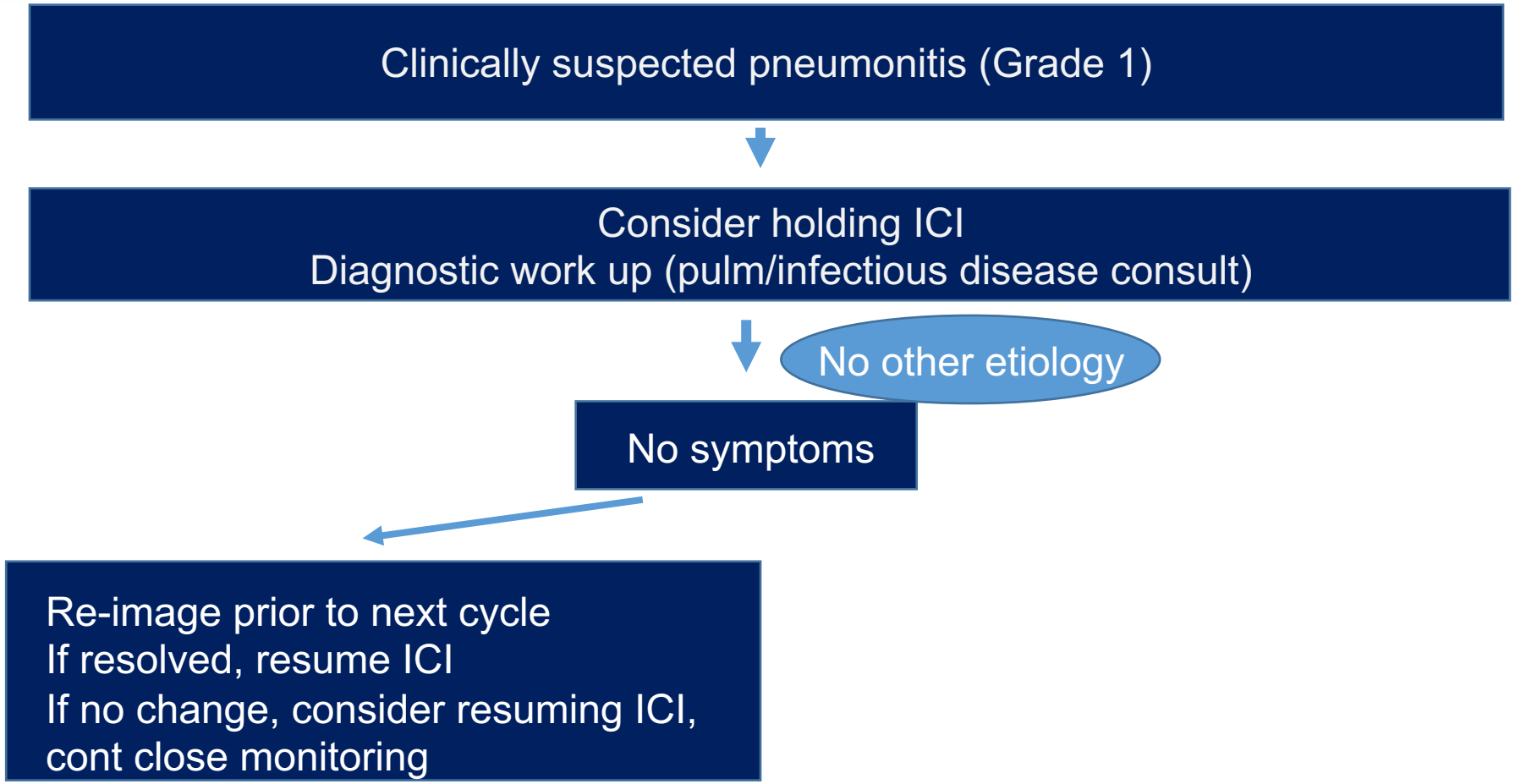
Grade 3 – severe symptoms limiting self-care (usually hypoxemic)(involves all lung lobes or 50% of lung parenchyma*)

Grade 4 – life-threatening respiratory compromise (usually requiring ICU admission)

Grade 5 – death

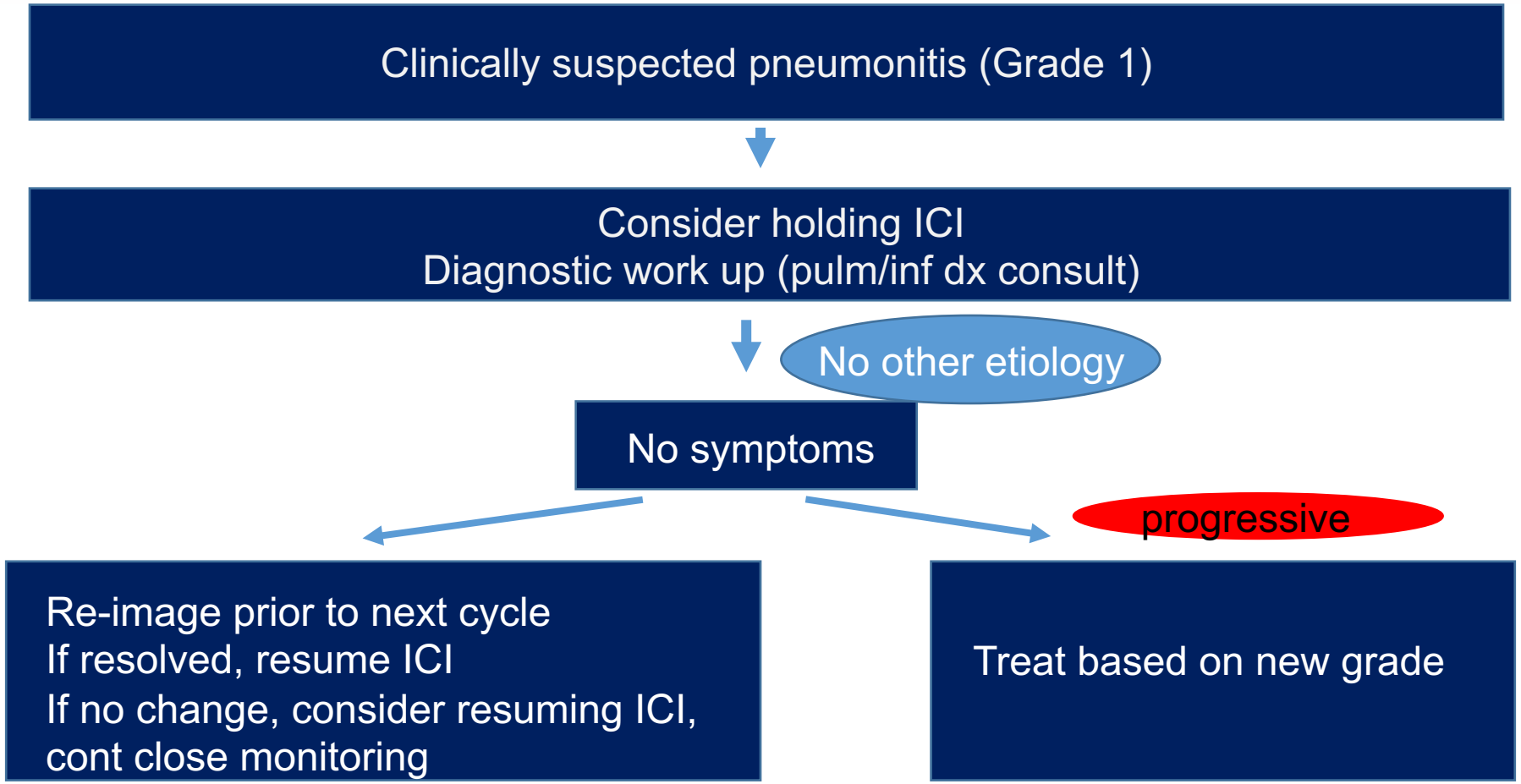
*ASCO guideline (JCO 2021)

Clinically suspected pneumonitis (Grade 1)



SITC, ASCO guidelines

Clinically suspected pneumonitis (Grade 1)



SITC, ASCO guidelines

Recommended Workup

- Initial workup should include
  - Clinical evaluation (pum consult)
  - Non-contrast chest CT
- Pulmonary function testing to compare to prior results
  - Pneumonitis typically presents with reduced total lung capacity or diffusing capacity
  - Can help distinguish from COPD exacerbations, although reports of ICI-related bronchiolitis exist
- Bronchoscopy is indicated to evaluate for infections
- Biopsy can be helpful to distinguish pneumonitis from disease progression or infection
- If volume overload is suspected, suggest prompt cardiology evaluation and potentially echocardiogram to evaluate for myocarditis

Balagani, JIPO 2018

Clinically suspected pneumonitis (Grade 2)

Consider hospitalization
-Hold ICI therapy
-Consider infectious work up, COVID 19 eval, BAL, Lung bx
-Prednisone/methylprednisolone 1mg/kg/d

If improvement

Taper steroids over 4 weeks
Consider re-challenging case to case basis

SITC, ASCO guidelines

Clinically suspected pneumonitis (Grade 3-4)

Consider hospitalization
-Hold ICI therapy
-Consider BAL, Lung bx
-Prednisone/methylprednisolone 1mg/kg/d

If improvement

Taper steroids over 4 weeks
Consider re-challenging case to case basis

If NO improvement/worsening

Hospitalization
Pulmonary consultation with BAL (if feasible). Consider biopsy
iv methylprednisone 2mg/kg
-if improve reduce to 1mg/kg/d of prednisone or equivalent and taper over 2 months.
-if no response add infliximab (if no response)

SITC, ASCO guidelines

Steroid-Refractory Pneumonitis

- Most second-line therapies are only supported by case reports or case series
- Our practice is to use infliximab (5 mg/kg, single dose)
  - Case series from MDACC showed a 20% response
  - In a mixed cancer population, infliximab reduced duration of steroid use (42 patients with pneumonitis)
- Limited evidence for:
  - Tocilizumab
  - Plasmapheresis/IVIG
  - Cyclophosphamide or mycophenolate
- *Key area for investigation*

Abu-Sbeih JIPO 2018

Conclusion and Future Directions

- Combination strategies including immune checkpoint inhibitors result in higher rates of response, but also higher rates of toxicity
- Real-world rates of pneumonitis are high (10-20%) and result in the highest treatment-related mortality of all irAEs in NSCLC
- Oncologists and pulmonary specialists should collaborate to identify and treat pneumonitis
- Further work is needed to
  - Understand risk factors for pneumonitis
  - Standardize first-line and second-line pneumonitis treatments
  - Develop risk mitigation strategies, including biomarkers and real-time monitoring