Management of ICI Pneumonitis in Lung Cancer Patients

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Lung Cancer Treatment

Chemotherapy **Radiotherapy** **Target therapy: EGFR-TKI, ALK inhibitor** **G-CSF**

Immunotherapy : PD-1/PD-L1 inhibitor

Pneumonitis

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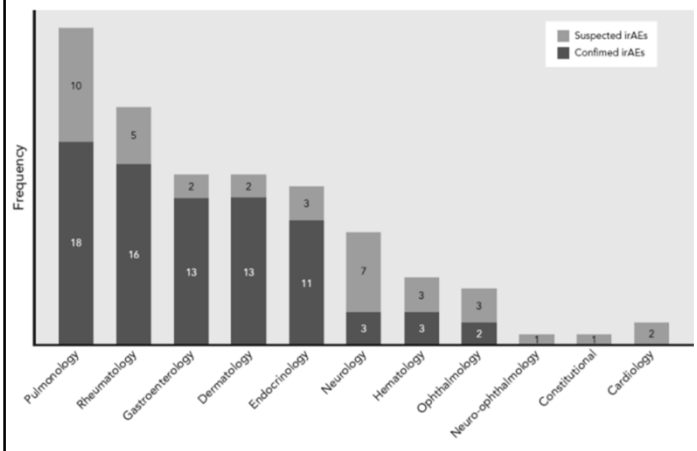
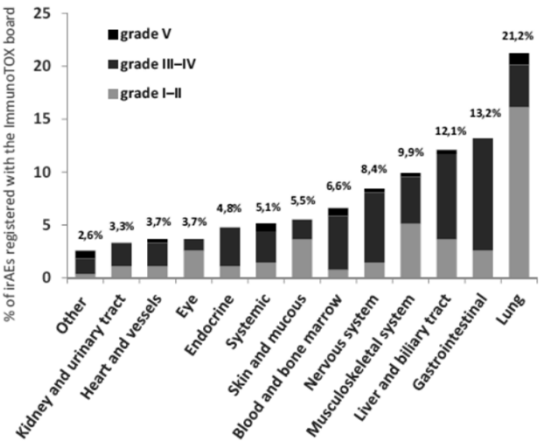
Immune-related AE Referral





J Natl Compr Canc Netw 2019;17(6):712–720
Eur J Cancer. 2020 May;130:39-50

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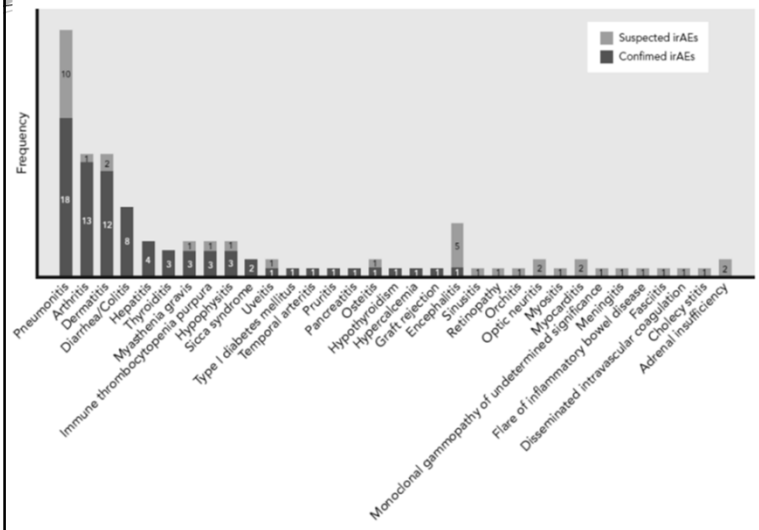
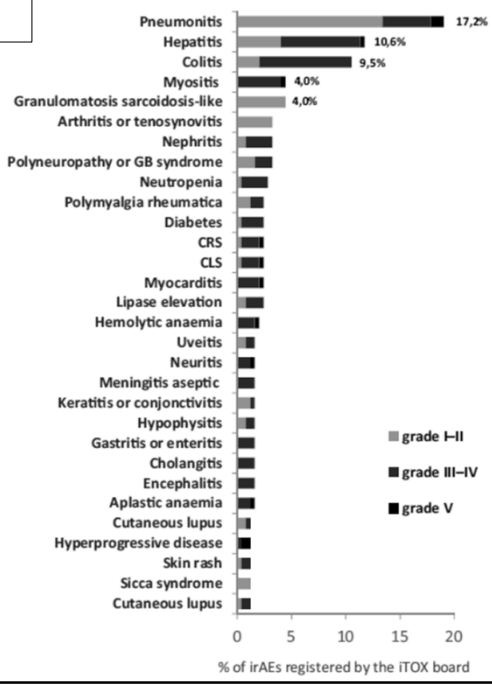
Immune related AE Referral





J Natl Compr Canc Netw 2019;17(6):712–720
Eur J Cancer. 2020 May;130:39-50

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Why irAE pneumonitis so important?

1. The most common side effect that leads to discontinuation of immunotherapy
2. Serious, and potentially life-threatening.

JAMA Oncol 2018;4:1721–1728.
Cancer Treat Rev 2016, 7-18

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Incidence

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PD-1 Inhibitor-Related Pneumonitis: Meta-analysis

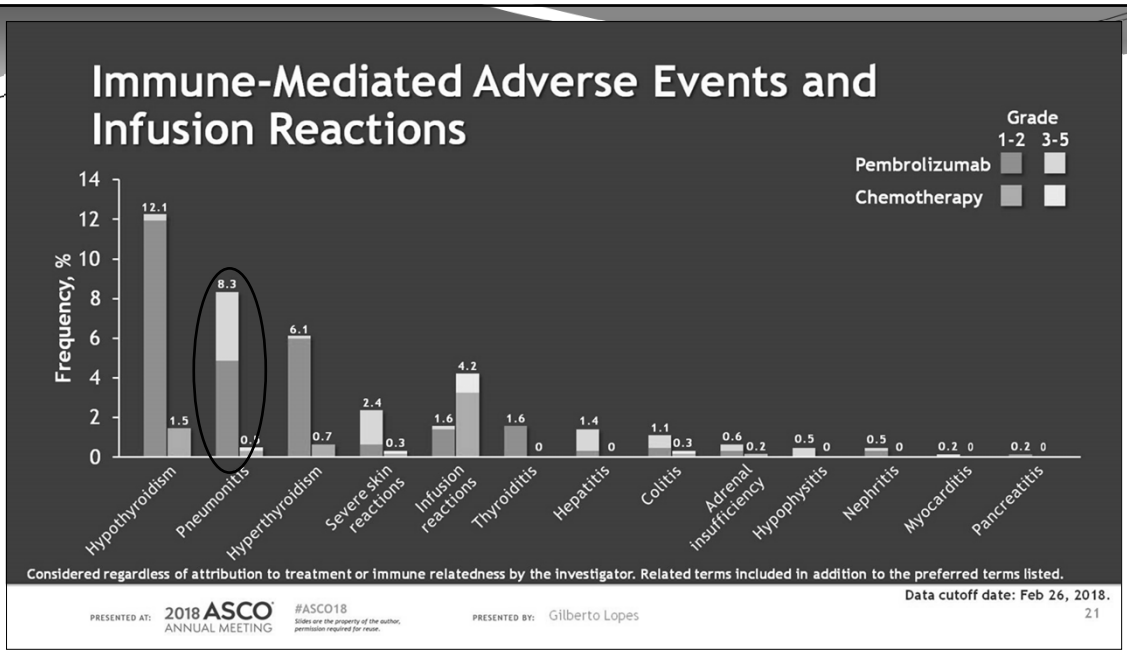
- NSCLC vs. melanoma:
  - all-grade (4.1 vs 1.6%; p = 0.002)
  - grade ≧ 3 (1.8 vs 0.2%; p < 0.001).
- RCC > melanoma for all-grade, NOT for grade ≧3
- Combination therapy > monotherapy:
  - all-grade (p < 0.001) and grade ≧ 3 pneumonitis (p < 0.001).

JAMA Oncol. 2016 Dec 1;2(12):1607-16

PD-1 inhibitors dose and the incidence and risk of pneumonitis: a meta-analysis.

- 16 phase II/III clinical trials (n=6360)
- All-grade/high-grade: 2.92%/1.53% for pneumonitis.
- Risk: PD-1 inhibitors > chemotherapy
- Melanoma patients have the lowest incidence, while NSCLC and RCC patients have the highest.
- No significant differences between high- and low-dose.

Sci Rep. 2017 Mar 8;7:44173



Presented By Gilberto Lopes at 2018 ASCO Annual Meeting

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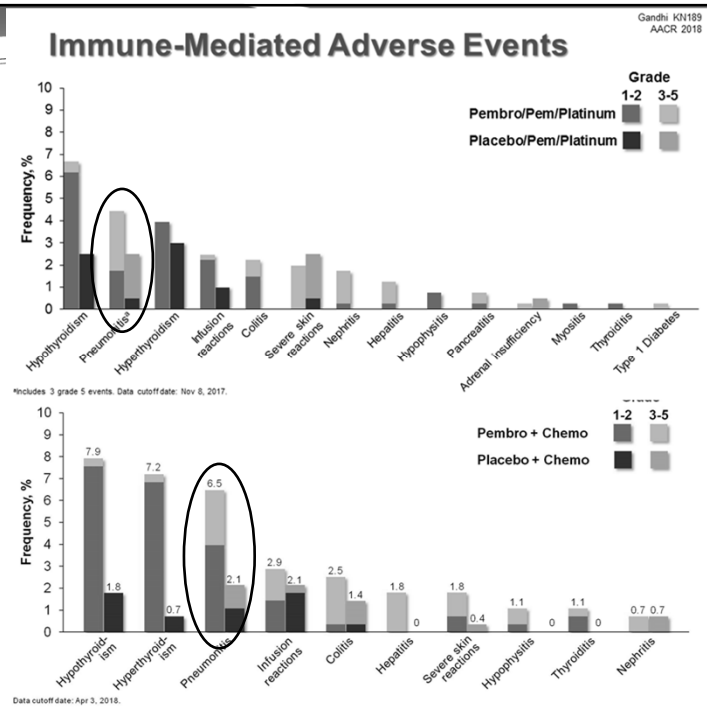
4-6%

KN189

KN407



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Pneumonitis in patients treated with anti–PD1/PD-L1 therapy: Real World Data

- Pneumonitis developed in 43/915 (5%)
- Grade 1/2 (72%)
- 86%(37/43) improved/resolved with drug holding/ immunosuppression.
- Five patients (11.6%) died during pneumonitis course.

J Clin Oncol. 2017 Mar;35(7):709-717

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Incidence of irAE pneumonitis: Real World data

- Among 101 NSCLC patients received ICIs, 22 (21.8%) had iAE pneumonitis
  - 73% (16/22) had a history of radiotherapy ($p < 0.001$).
- Among the 138 patients with NSCLC who received anti-PD1 monotherapy, 20 patients (14.5%) had ir-ILD

2017	2020
3-4%	14.5-21.8%

Front Oncol 2020 Sep 29
J Clin Oncol. 2017 Mar;35(7):709-717
J Thorac Oncol 2020 15: 1317-27

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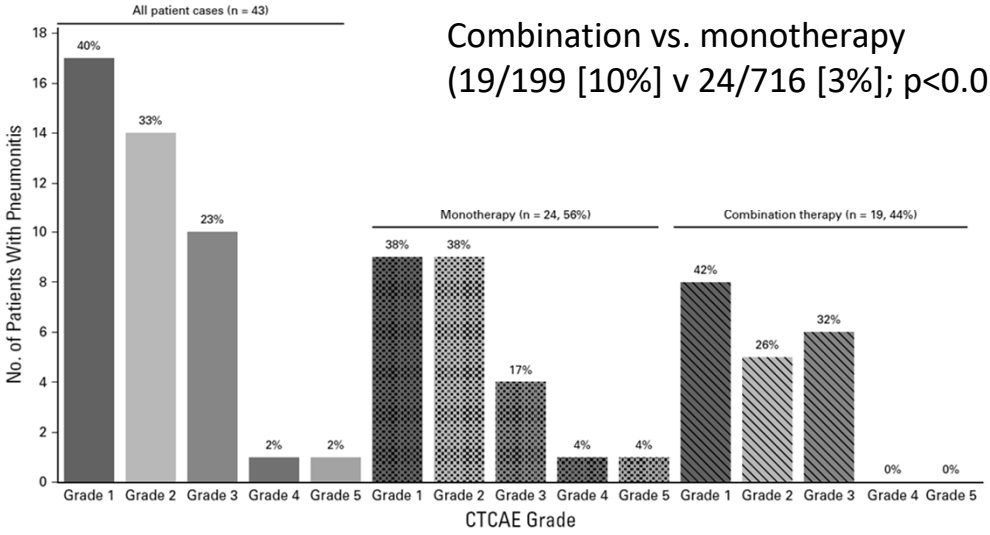

Combination vs. monotherapy
(19/199 [10%] v 24/716 [3%]; p<0.01)

J Clin Oncol. 2017 Mar;35(7):709-717

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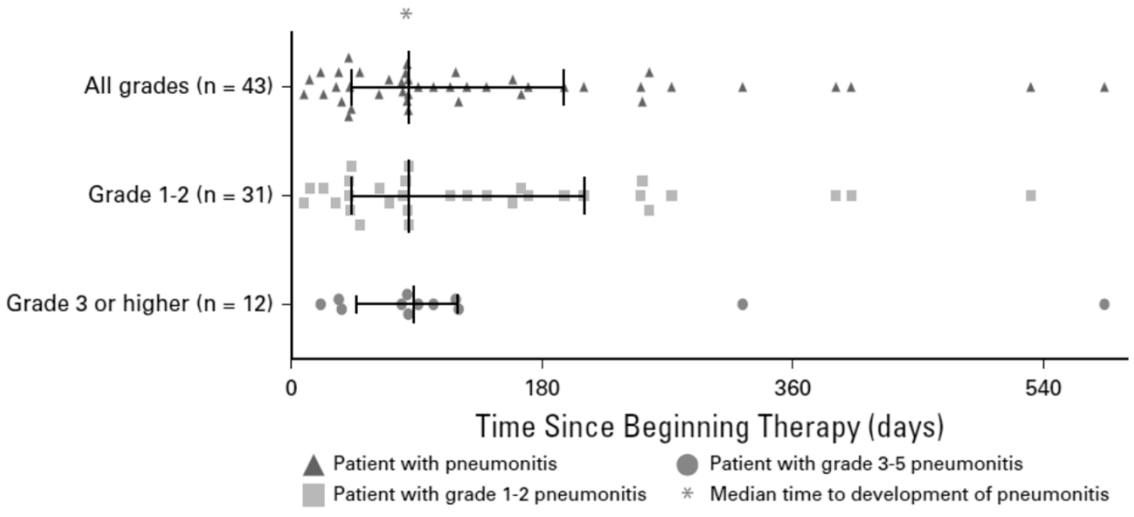
Time to onset: 9 days - 19.2 months



J Clin Oncol. 2017 Mar;35(7):709-717

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Diagnosis

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Diagnosis for anti-neoplastic agent-induced lung diseases

NO clear criteria

history of drug exposure

Exclude other causes

Focal or diffuse inflammation of the lung parenchyma (typically identified on CT)

www.asco.org/supportive-care-guidelines, 2018

Expert Rev Anticancer Ther 2013; 13: 997-1006

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Features of irAE Pneumonitis

- Most common: dyspnea, non-productive cough.
  - 1/3 low-grade: asymptomatic.
- Any new persistent cough or shortness of breath ➔ consider irAE pneumonitis.

Clin Chest Med 38 (2017) 223–232
J Clin Oncol.2017;35(7):709–17

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Differential Diagnosis

Signs/symptoms/Hx Elements	DDx
Hypercarbia	ICI-associated myasthenia gravis
SVT, shock, volume overload	ICI-associated myocarditis
Risk factors for TB	ICI-associated reactivation of TB
Recent cytotoxic chemotherapy	DAH, opportunistic infections
Recent high-dose steroid (for brain/spine metastasis, etc)	PJP, nocardia, other opportunistic infections
Recent XRT	Radiation pneumonitis
Increase in tumor size	Pseudo-progression

Chest 2018; 154(6): 1416-23

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Severity grading for pulmonary irAE

CTCAE Grade	Clinical Presentation
1	Asymptomatic, radiographic changes only
2	Symptomatic, not interfering with ADL
3	Symptomatic, interfering with ADL or with new oxygen requirement
4	Life-threatening, requiring ventilator support
5	Death

Michot JM, Bigenwald C, Champiat S, et al. Eur J Cancer 2016;54:139–48.
https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

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Diagnostic workup for irAE Pneumonitis

- CXR, CT, pulse oximetry
  - For grade 2 or higher: infection workup
- Bronchoscopy and lung biopsy for excluding infection and disease progression.
- Bronchoalveolar lavage: lymphocyte predominate
- No single pathologic finding pathognomonic
  - Granulomatous changes have been reported.
- No serologic biomarkers for diagnosis.

Ann Oncol 2016;27(6):1178–9.
J Clin Oncol 2012;30(17):e156–9.

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Risk Factors for irAE Pneumonitis

- Cancer types: NSCLC,RCC
- Underlying lung diseases/condition: History of smoking, ILD.
- Combination therapy:
  - Immunotherapy + immunotherapy/chemotherapy
- Prior thoracic radiotherapy
- Biomarker/PD-L1 expression?
- Treatment responses?

Clin Chest Med 38 (2017) 223–232

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Radiographic Presentations

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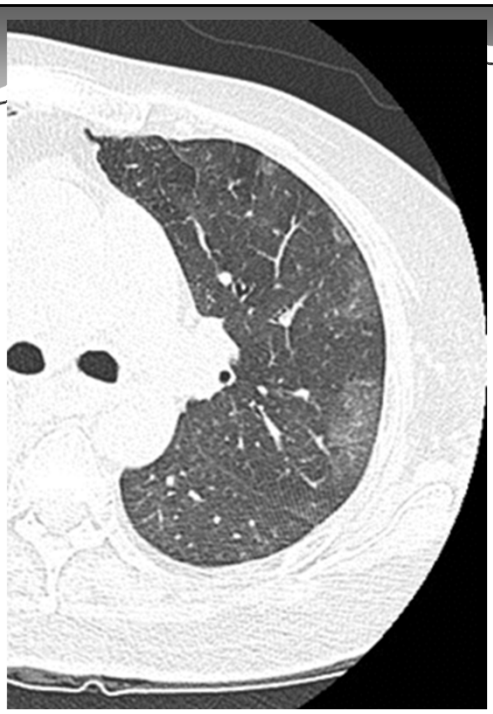

Ground glass opacities (37%)

Discrete focal increased attenuation
Preserved bronchovascular markings

J Clin Oncol. 2017 Mar;35(7):709-717

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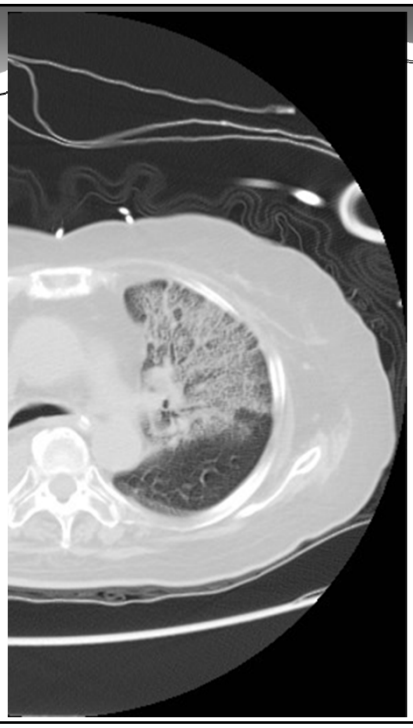

Interstitial pattern (22%)

Increased interstitial markings, interlobular septal thickening
Peribronchovascular infiltration, subpleural reticulation
Honeycomb pattern in severe cases

J Clin Oncol. 2017 Mar;35(7):709-717

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Cryptogenic organizing pneumonia-like (19%)

Discrete patchy or confluent consolidation with/without air bronchograms.
Predominantly peripheral or subpleural distribution

J Clin Oncol. 2017 Mar;35(7):709-717

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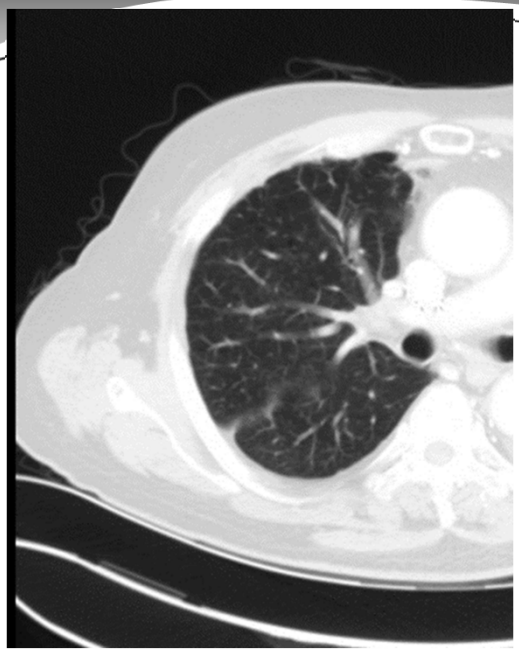

Hypersensitivity (7%)

Centri-lobular nodules
Bronchiolitis-like appearance
Tree-in-bud micro-nodularity

J Clin Oncol. 2017 Mar;35(7):709-717

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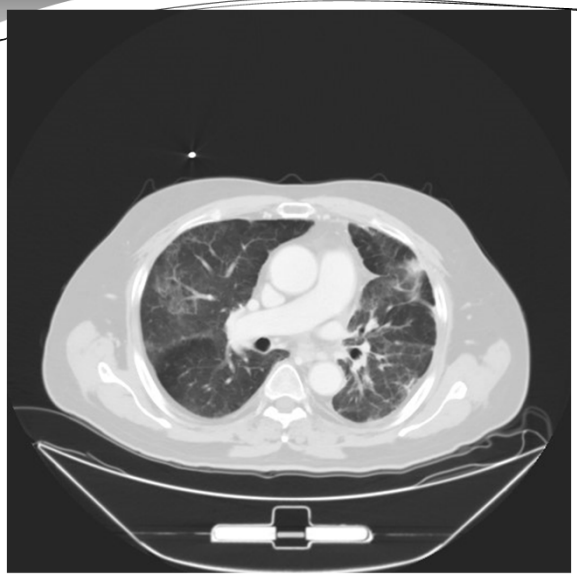

Pneumonitis not otherwise specified (15%)

Mixture of nodular and other subtypes
Not clearly fitting into other subtype classifications

J Clin Oncol. 2017 Mar;35(7):709-717

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Treatments

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Severity grading and recommendations for pulmonary irAE

CTCAE Grade	Clinical Presentation	Fate of Immunotherapy
1	Asymptomatic, radiographic changes only	Cautiously continue
2	Symptomatic, not interfering with ADL	Suspend, temporarily
3	Symptomatic, interfering with ADL or with new oxygenation requirement	Suspend, and likely discontinue
4	Life-threatening, requiring ventilator support	Discontinue permanently
5	Death	

Michot JM, Bigenwald C, Champiat S, et al. Eur J Cancer 2016;54:139–48.
https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

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Severity grading and management recommendations for pulmonary irAE

Grade	Symptoms	Management
1	Asymptomatic, radiographic changes only 1 lobe or < 25%	Hold ICPi with radiographic evidence of pneumonitis progression Monitor patients weekly with history and PE and pulse oximetry; may also offer CXR May offer one repeat CT in 3-4 weeks; A repeat spirometry/DLCO in 3-4 weeks May resume ICPi with radiographic evidence of improvement or resolution. If no improvement, should treat as G2

www.asco.org/supportive-care-guidelines 2018

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Severity grading and management recommendations for pulmonary irAE

Grade	Symptoms	Management
2	Symptomatic, involves more than one lobe of the lung or 25%-50% of lung parenchyma, medical intervention indicated, limiting instrumental ADL	Hold ICPi until resolution to G1 or less Prednisone 1-2 mg/kg/d and taper by 5-10 mg/wk over 4-6 weeks Consider bronchoscopy with BAL Consider empirical antibiotics Monitor every 3 days with history and physical examination and pulse oximetry, consider CXR; No clinical improvement after 48-72 hours of prednisone, treat as G3

www.asco.org/supportive-care-guidelines 2018

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Severity grading and management recommendations for pulmonary irAE

Grade	Symptoms	Management
3-4	G3: Severe symptoms, hospitalization required, involves all lung lobes or >50% of lung parenchyma, limiting self-care ADL, oxygen indicated G4: Life-threatening respiratory compromise, urgent intervention indicated (intubation)	Permanently discontinue ICPi Empirical antibiotics; (methyl)prednisolone IV 1-2 mg/kg/d; No improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g twice a day or IVIG for 5 days or cyclophosphamide Taper corticosteroids over 4-6 weeks Pulmonary and infectious disease consults if necessary Bronchoscopy with BAL +/- transbronchial biopsy Patients should be hospitalized for further management

www.asco.org/supportive-care-guidelines 2018

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Treatment: immunosuppressive agents

- For severe, steroid-refractory case: azathioprine, mycophenolate mofetil, cyclophosphamide, and infliximab (TNF-α Ab)
- Tocilizumab (IL-6 receptor antagonistic antibody)
- Impact on survival remains unclear.
- Azathioprine and mycophenolate have significant delay to effect.
- Most patients die of either acute respiratory failure from pneumonitis or secondary opportunistic infection.

Clin Chest Med 38 (2017) 223–232
Current Oncology Reports (2020) 22:56

Treatment

- The effect of ICI may persist long after discontinuation
- No data of steroid treatment effect on overall survival or response durability.
- In significant irAE, treating complication is more important than therapeutic efficacy.

Clin Chest Med 38 (2017) 223–232

Outcomes

- Most will improve or resolve, with drug cessation alone or corticosteroid treatment.
- Relapses even in absence of re-challenge
- Subsequent relapses:
  - May have radiographic pictures distinct from the initial ones
  - may be more clinically severe
- The relapse irAE typically responds to steroids.
- No guidelines for prediction
- Lack of large-scale prospective study for re-challenge, mostly case reports.

Clin Chest Med 38 (2017) 223–232

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Rechallenge

- No large-scale study concerning recurrence after rechallenge
- Mostly case reports
- 16.7%-20% in retrospective studies (1/5-6)
- Should discuss with the patients and families about the risk of recurrence

JAMA Oncol. 2019 Jun 6;5(9):1310-1317
Chest. 2021 Feb 20.

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Summary

- The incidence is higher compared with the clinical trial data.
- Various radiographic features
- Steroid responsive, not negate antitumor effects
- A multi-disciplinary team including pulmonologist, oncologist, radiologist, and rheumatologist is urgently needed.

Thank You for Your Attention