# CLINICAL PEARLS *for* Rheumatologists:

## Diagnosing and Managing Fibrosing

# INTERSTITIAL LUNG DISEASES

**WEDNESDAY, OCTOBER 29, 2025**

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**AGENDA**

**I. Introduction**

**II. The F-ILs: An Overview for Rheumatologists**

a. IPF vs SARD-ILD
b. Mechanisms underlying disease development and progression in F-ILDs
c. Survival with SARD-ILD vs interstitial pneumonia
d. Diagnosing

**III. Case #1: Adult patient with possible connective tissues disease-associated ILD**

**IV. Diagnosing F-ILDs**

a. Updated ACR diagnostic guidelines
b. Interpreting from recommended testing methods

**V. Case #2: Adult patient with rheumatoid arthritis-associated interstitial lung disease (RA-ILD)**

**VI. The Evolving F-ILD Treatment Landscape**

a. RA-UIP vs IPF Demographics, Histology, Pathobiology
b. Risk factors for SSc-ILD progression
c. Updated ACR management guidelines
d. Clinical profiles of current and emerging therapies

**VII. Case #3: Adult patient with advanced SSc-associated ILD with possible secondary pulmonary hypertension**

**VIII. Conclusions**

# *Clinical Pearls for Rheumatologists: Diagnosing and Managing Fibrosing Interstitial Lung Diseases*

**FACULTY**

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Professor of Medicine
Cleveland Clinic
Cleveland, Ohio

**PROGRAM DESCRIPTION**

This program explores the pathophysiology, clinical features, and overall burden of fibrosing interstitial lung diseases (F-ILDs), with a focus on idiopathic pulmonary fibrosis (IPF), progressive pulmonary fibrosis (PPF), and systemic autoimmune rheumatic disease–associated ILD (SARD-ILD). Participants will gain strategies to enhance diagnostic accuracy, interpret evidence from clinical trials of emerging therapies, and translate findings into practice. The program also emphasizes the critical role of multidisciplinary collaboration in delivering comprehensive, patient-centered management for individuals living with F-ILDs.

**TARGET AUDIENCE**

This activity is designed to meet the educational needs of rheumatologists.

**LEARNING OBJECTIVES:**

After completing the CME activity, learners should be better able to:

- Describe the pathophysiology, clinical characteristics, and burdens associated with F-ILDs including IPF, PPF, and SARD-ILD
- Improve diagnostic accuracy of F-ILDs including IPF, PPF, and SARD-ILD
- Interpret results from clinical trials assessing new and emerging treatment options for F-ILDs including IPF, PPF, and SARD-ILD
- Implement multidisciplinary teamwork essential for comprehensive management of F-ILDs including IPF, PPF, and SARD-ILD

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# Clinical Pearls for Rheumatologists: Diagnosing and Managing Fibrosing Interstitial Lung Diseases

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0

## Disclosures

- **Kristin B. Highland, MD, MSCR** discloses the following:

| | |
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## Learning Objectives

- Describe the pathophysiology, clinical characteristics, and burdens associated with fibrosing interstitial lung diseases (F-ILDs), including idiopathic pulmonary fibrosis (IPF), progressive pulmonary fibrosis (PPF), and systemic autoimmune rheumatic disease-associated interstitial lung disease (SARD-ILD)
- Improve diagnostic accuracy of F-ILDs, including IPF, PPF, and SARD-ILD
- Interpret results from clinical trials assessing new and emerging treatment options for F-ILDs, including IPF, PPF, and SARD-ILD
- Implement multidisciplinary teamwork essential for comprehensive management of F-ILDs, including IPF, PPF, and SARD-ILD

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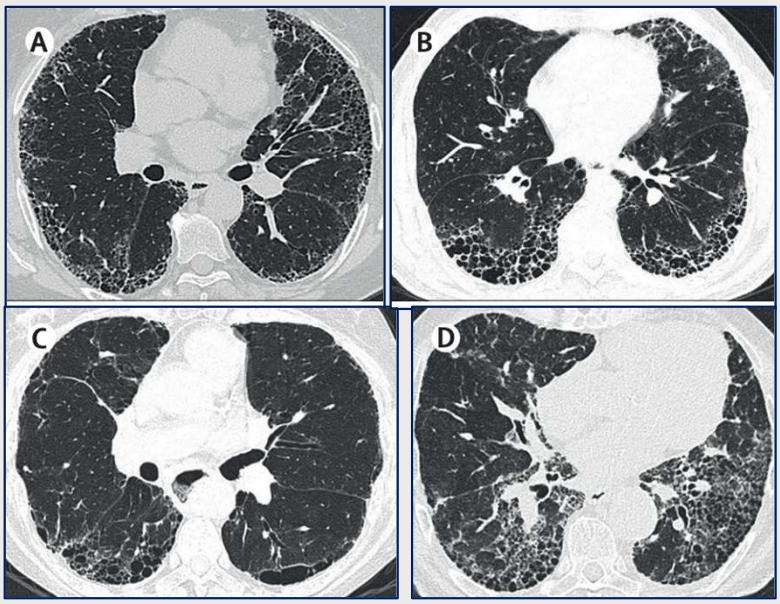
## Audience Response Question
## Which patient has IPF? Which patient has SARD-ILD?

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## "Scar IS Scar"

**Combination of risk factors: the perfect storm**

- Pro-UIP genetic architecture
- Male sex
- Ageing (usually >60 years)
- Smoking or other exposures
- Host factors (eg, diabetes and hypothyroidism)
- Pro-UIP epigenetic reprogramming

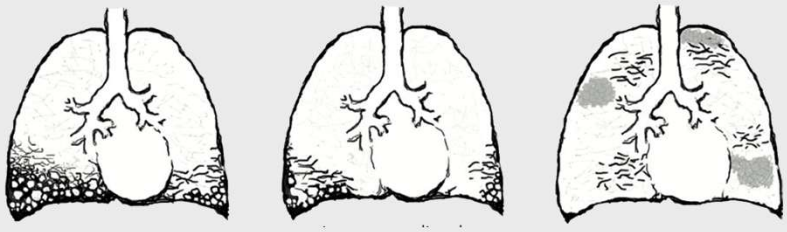
**Appearance of: KRT17 and KRT5 senescent epithelial cells**

**CTHRC1 and HAS1 fibroblasts**

**HLA-DR, CD169, and CD206 macrophages**

**Known-etiology ILD (eg, SARD)**

| Unknown cause | Plus a similar combination of risk factors | With other genetic, environmental, and host background |
|---|---|---|



**IPF** **SARD-UIP** **SARD-NSIP**

Adapted from Selman M, et al. *Lancet Respir Med.* 2023;11(2):188-196.

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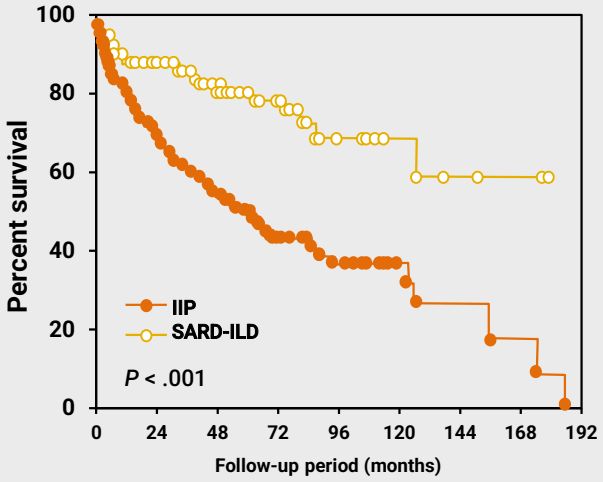
## IT MATTERS: Survival of Patients With SARD-ILD Compared With Idiopathic Interstitial Pneumonia

- N=362 patients with interstitial pneumonia
  - SARD-ILD n=93
  - IIP n=269
- Baseline lung function was not significantly different between groups




Park JH, et al. *Am J Respir Crit Care Med.* 2007;175:705-711.

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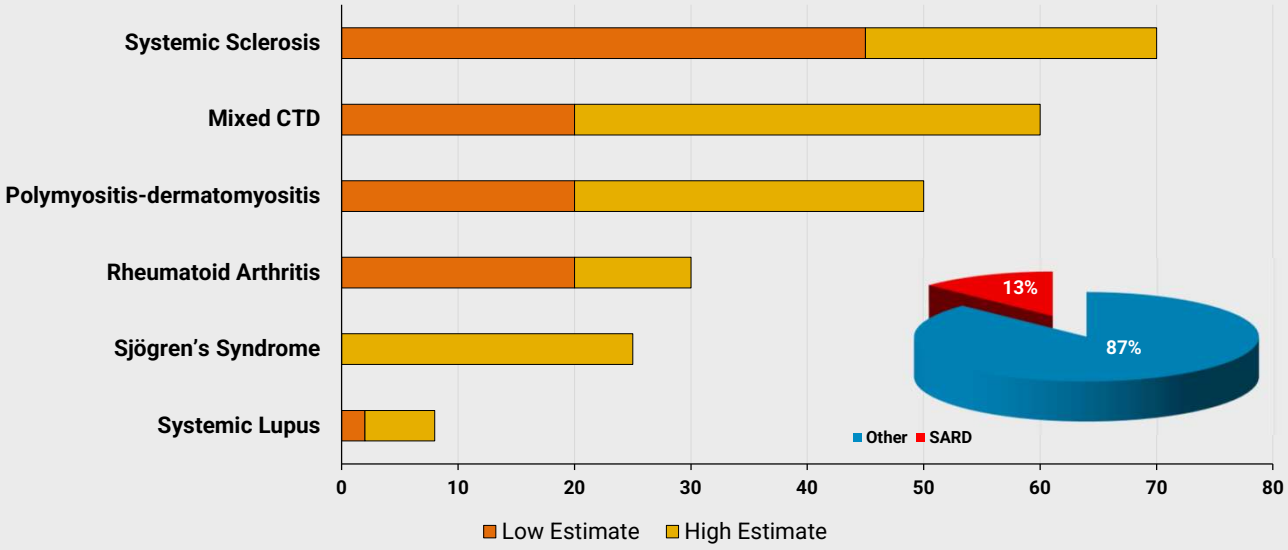
## Frequency of Interstitial Lung Diseases in Systemic Rheumatologic Conditions




Bryson T, et al. *Semin Ultrasound CT MRI*. 2014;35:29-38.

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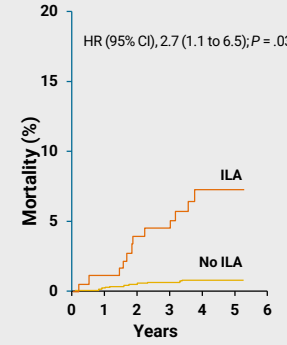
## Association Between Interstitial Lung Abnormalities and All-Cause Mortality

### Framingham Heart Study

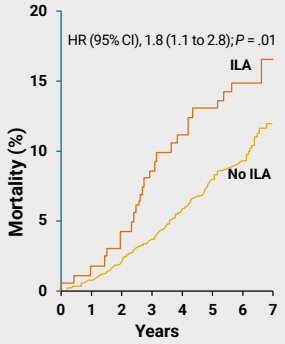



| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| ILA | 177 | 176 | 171 | 170 | 107 | |
| No ILA | 1370 | 1367 | 1364 | 1361 | 1022 | |

### AGES-Reykjavik Study

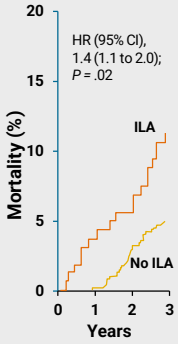

| No. at risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ILA | 378 | 365 | 343 | 328 | 304 | 281 | 259 | 239 | 213 | 137 | 68 | 12 | |
| No ILA | 3216 | 3177 | 3124 | 3044 | 2956 | 2851 | 2710 | 2589 | 2447 | 1694 | 862 | 228 | |

### COPDGene® Study




| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| ILA | 156 | 153 | 149 | 142 | 138 | 135 | 131 |
| No ILA | 1173 | 1163 | 1146 | 1125 | 1104 | 1079 | 1062 |

### ECLIPSE Study




| No. at risk | | | | |
|---|---|---|---|---|
| ILA | 156 | 151 | 145 | |
| No ILA | 528 | 525 | 505 | |

Adjusted for age, sex, race, body mass index, pack-years of smoking, current or former smoking status, and GOLD stage of COPD (except AGES-Reykjavik).

Putnam RK, et al. *JAMA*. 2016;315:672-681.

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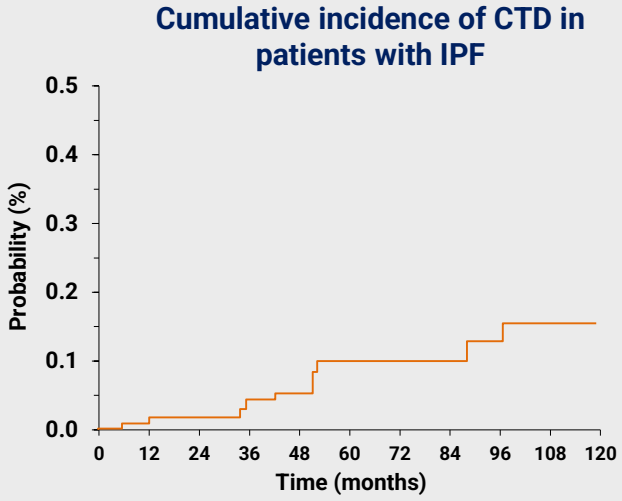
## Diagnosis of IPF May Precede Incident SARDs

Retrospective review of 111 consecutive patients diagnosed with IPF

- None fulfilled any criteria for SARDs within 6 months or more of IPF diagnosis

9.0% developed a SARD during 10 years of follow-up, including

- Rheumatoid arthritis
- Microscopic polyangiitis
- Systemic sclerosis
- Sjögren's syndrome




Kono M, et al. *PLoS One*. 2014;9(4):e94775.

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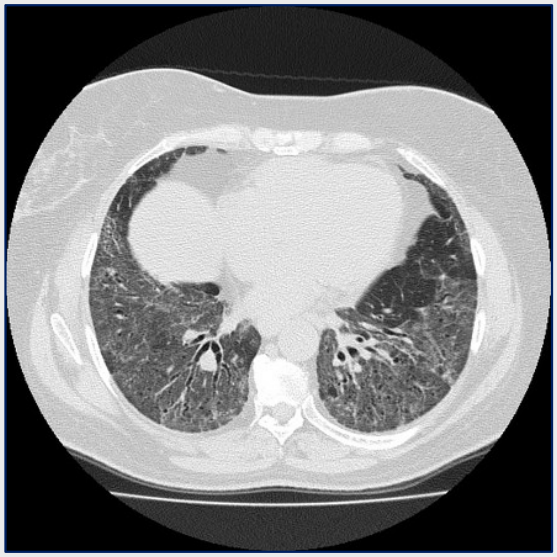
## Case 1

- 49-year-old African American female
- Progressive DOE x 12 months
- ANA 1:320 (speckled)
- No overt CTD signs & symptoms
- FVC 49% predicted
- DLCO 52% predicted
- Referred to rheumatology



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## Interstitial Pneumonia With Autoimmune Features (IPAF): Classification Criteria

Research designation for indeterminate ILD with the following features:

- Presence of interstitial pneumonia, *and*
- Exclusion of alternative etiologies, *and*
- Does not meet the criteria of a defined connective tissue disease, *and*
- At least one feature from at least two domains
  - Clinical
  - Serologic
  - Morphologic

Fischer A, et al. *Eur Respir J*. 2015;46:976-987.

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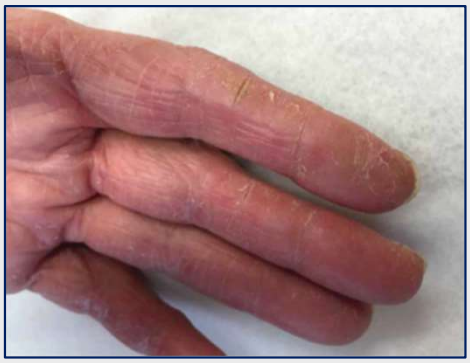
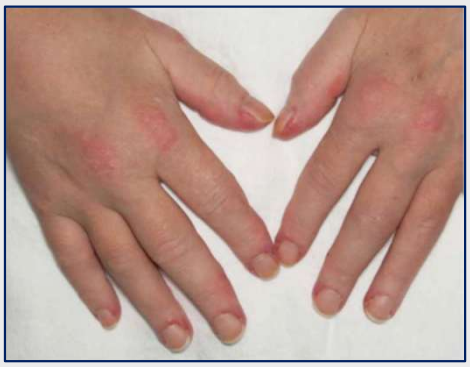
## IPAF Clinical Domain

- Distal digital fissuring (mechanic's hands)
- Distal digital tip ulceration
- Inflammatory arthritis or polyarticular morning stiffness ≥60 min
- Palmar telangiectasia
- Raynaud phenomenon
- Unexplained digital edema
- Unexplained fixed rash on the digital extensor surfaces (Gottron's sign)





Fischer A, et al. *Eur Respir J*. 2015;46:976-987.

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## Audience Response Question

Which of the following serologic findings meets the positive classification criterion for IPAF?

A. Low titer ANA
B. Abnormal anti-CCP
C. Low titer rheumatoid factor
D. Abnormal C-reactive protein

IPF = idiopathic pulmonary fibrosis.

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## IPAF: Serologic Domain

### Not Included in Criteria:

- Low titer ANA
- Low titer rheumatoid factor
- Erythrocyte sedimentation rate
- C-reactive protein
- Creatine phosphokinase
  - May be ordered to screen for dermatomyositis/ polymyositis

### Presence:

- ANA ≥1:320 titer, diffuse, speckled, homogeneous patterns or
  a) ANA nucleolar pattern (any titer) or
  b) ANA centromere pattern (any titer)
- Rheumatoid factor ≥2× upper limit of normal
- Anti-CCP
- Anti-dsDNA
- Anti-Ro (SS-A)
- Anti-La (SS-B)
- Anti-ribonucleoprotein
- Anti-Smith
- Anti-topoisomerase (Scl-70)
- Anti-tRNA synthetase (eg, Jo-1, PL-7, PL-12; others are: EJ, OJ, KS, Zo, tRS)
- Anti-PM-Scl
- Anti-MDA-5

Fischer A, et al. *Eur Respir J*. 2015;46:976-987.

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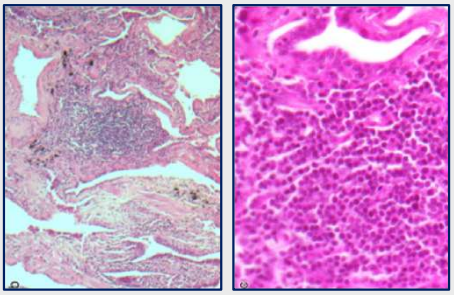
## IPAF: Morphological Domain

- HRCT or histopathology patterns
  - NSIP
  - OP
  - NSIP with OP overlap
  - LIP
- Additional histology patterns
  - Interstitial lymphoid aggregates with germinal centers
  - Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)



- Unexplained multi-compartment involvement
  - Pleural effusion or thickening
  - Pericardial effusion or thickening
  - Intrinsic airway disease
    - Airflow obstruction, bronchiolitis, or bronchiectasis
  - Pulmonary vasculopathy

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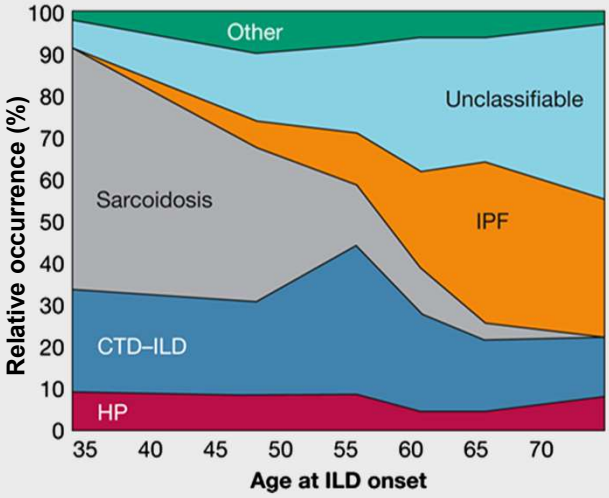
## Comparison of Demographic and Clinical Characteristics Between Patients With IPF/UIP and SARD-UIP

| Variable | IPF (n=88) | SARD (n=67) |
|---|---|---|
| **Age, years** | 64.4 ± 13.5 | 56.8 ± 14.1 |
| **Female, %** | 35 | 72 |
| **Ever smoker, %** | 40 | 19 |
| **Disease duration, months** | 31.7 ± 18.0 | 39.2 ± 18.3 |




Alhamad EH. *J Thorac Dis*. 2015;7(3):386-393. Patterson KC, et al. *Chest*. 2017;151(4):838-844.

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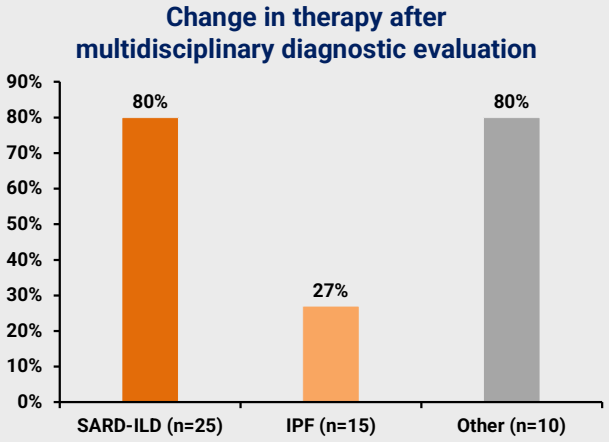
## Impact of Rheumatological Evaluation in the Management of Patients With ILD

- N=50 consecutive patients referred to interdisciplinary ILD clinic over a 12-month period for diagnostic and management recommendations
- 11 (22%) patients with an initial referral diagnosis of IPF or ILD NOS were found to have a SARD
  - 9 (18%) referred with a SARD-ILD diagnosis had a final diagnosis of an alternate SARD-ILD
- Most patients had their treatment regimen changed




By final diagnosis: "Other" includes cryptogenic organizing pneumonia, drug-induced ILD, and vasculitis.

Castelino FV, et al. *Rheumatology*. 2011;50:489-493.

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## Diagnostic Work-up: Clinical Presentation

- Chronic dyspnea (may be overshadowed by extrapulmonary complaints)
  - Acute respiratory failure can occur in IIM and RA
- Cough (dry, nonproductive)
- Fatigue
- Exercise desaturation
- Bibasilar inspiratory crackles
- Can occur before extrapulmonary manifestations
- Severity/activity of ILD does not correlate with severity/activity of extrapulmonary manifestations

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## Video Case Part 1: Proactive Screening in Systemic Sclerosis

https://youtu.be/TH7yGyGzHz0

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## Audience Response Question

Which of the following pulmonary function test findings is most consistent with interstitial lung disease (ILD)?

**A.** Increased total lung capacity and elevated DLCO
**B.** Reduced forced vital capacity (FVC) and impaired DLCO
**C.** Normal spirometry and normal DLCO
**D.** Obstructive flow–volume loop with increased residual volume

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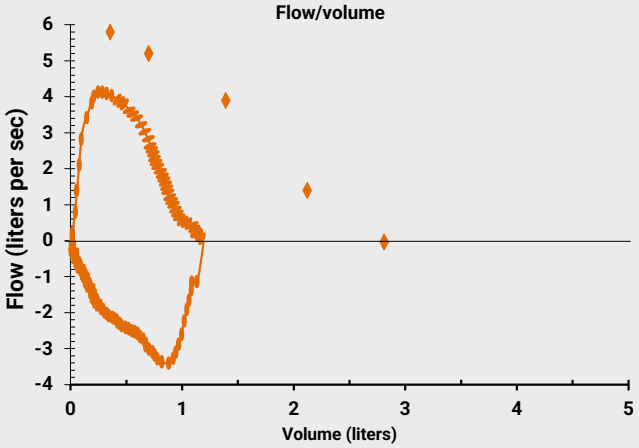
## Pulmonary Function Testing for Suspected ILD

- ILD is characterized by restrictive lung physiology
  - Forced vital capacity (FVC) <80% of control is abnormal; <50% severely abnormal
- Diffusing capacity for carbon monoxide (DLCO) is often impaired
- Patients with concurrent emphysema may exhibit normal lung volumes and spirometry, but reduced DLCO
- Low baseline FVC, decline in FVC, low DLCO, and decline in 6MWT are associated with decreased survival

**Abnormal flow volume indicating restrictive lung physiology**




Wallace B, et al. *Curr Opin Rheumatol*. 2016;28(3):236-245. Vecchi E, et al. *Respir Investig*. 2025;63(3):334-341.

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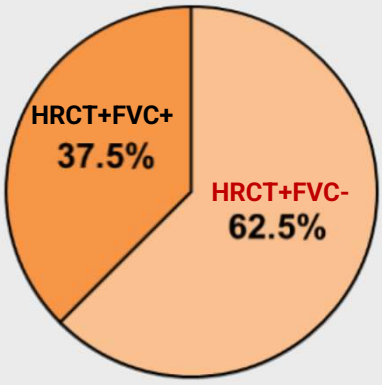
## PFTs Alone May Miss ILD

- N=102 SSc patients
- 64/102 (63.0%) with significant ILD on HRCT
- 27/102 (26.0%) with FVC <80%




**40/64 (62.5%) patients with significant ILD on HRCT had a normal FVC**

**↔ high false negative rate → high risk of missed diagnoses in clinical practice**

Suliman YA, et al. *Arthritis Rheumatol*. 2015;67:3256-3261.

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## focuSSced: Baseline Demographics and Disease Characteristics

| | All patients N=210 | PBO n=106 | TCZ n=104 |
|---|---|---|---|
| Females, % | 81 | 85 | 78 |
| Age, years | 48.2 (12.4) | 49.3 (12.6) | 47.0 (12.2) |
| **Duration of SSc, months** | **22.6 (16.5)** | **23.1 (17.0)** | **22.2 (16.0)** |
| **Total mRSS** | **20.4 (6.8)** | **20.4 (7.0)** | **20.3 (6.7)** |
| **%pFVC** | **82.1 (14.8)** | **83.9 (15.0)** | **80.3 (14.4)** |
| **%pDLCO** | **75.6 (18.9)** | **76.8 (18.6); n=105** | **74.4 (19.2)** |
| HAQ-DI | 1.2 (0.7) | 1.3 (0.7) | 1.1 (0.8) |
| Patient VAS | 56.8 (22.9) | 59.3 (21.3) | 54.3 (24.3) |
| CRP, mg/L | 7.9 (13.1) | 7.0 (11.1) | 8.9 (14.8) |
| ESR, mm/h | 34.8 (17.4) | 34.7 (18.5); n=103 | 34.8 (16.3); n=100 |
| Platelet count, $10^9$/L | 304.9 (92.2) | 298.7 (96.0) | 311.1 (88.2) |
| ANA positive, n/N (%) | 181/196 (92.3) | 90/98 (91.8) | 91/98 (92.9) |
| **Anti-topoisomerase positive, n/N (%)** | **101/200 (50.5)** | **49/100 (49.0)** | **52/100 (52.0)** |
| Anti-RNA polymerase positive, n/N (%) | 35/200 (17.5) | 16/100 (16.0) | 19/100 (19.0) |
| Anti-centromere positive, n/N (%) | 17/200 (8.5) | 9/100 (9.0) | 8/100 (8.0) |
| **SSc-ILD (HRCT visual read), n/N (%)** | **132/206 (64.1)** | **65/104 (62.5)** | **67/102 (65.7)** |

Khanna D, et al. *Ann Rheum Dis.* 2018;77(2):212-220. http://dx.doi.org/10.1136/annrheumdis-2017-211682.

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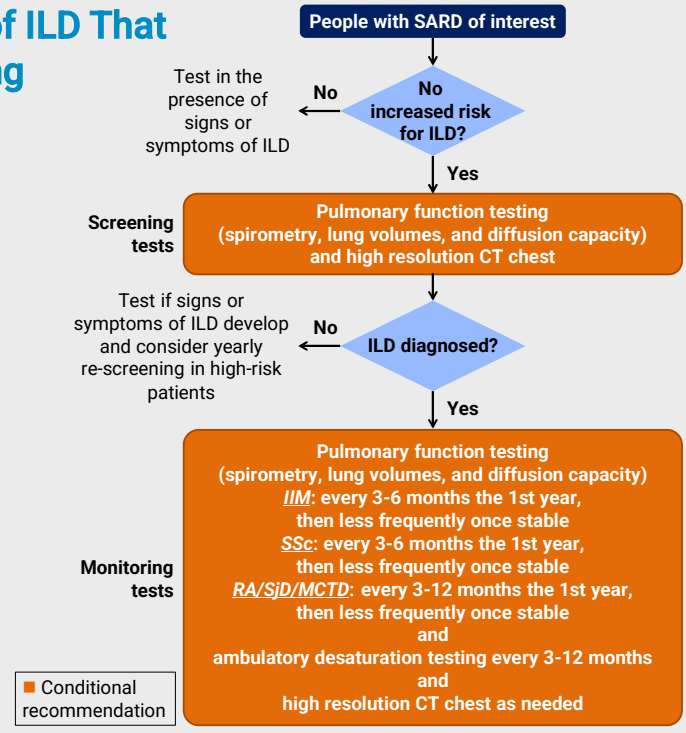
## Risk Factors for the Development of ILD That May Indicate the Need for Screening

| Disease | Risk factors |
|---|---|
| **Systemic sclerosis** | ▪ Anti-Scl-70 positivity, antinuclear antibody with nucleolar pattern<br>▪ Diffuse cutaneous subtype, male sex, African American race<br>▪ Early disease (first 5-7 y after onset)<br>▪ Elevated acute phase reactants |
| **Rheumatoid arthritis** | ▪ High-titer rheumatoid factor, high-titer anti-CCP<br>▪ Cigarette smoking, older age at rheumatoid arthritis onset, high disease activity<br>▪ Male sex, higher body mass index |
| **Idiopathic inflammatory myopathies** | ▪ Anti-synthetase (Jo-1, PL7, PL12, EJ, OJ, KS, Ha, Zo), anti-MDA-5, anti-Ku, anti-Pm/Scl, anti-Ro52 antibody positivity<br>▪ Mechanic's hands, arthritis/arthralgia, ulcerating lesions |
| **Mixed connective tissue disease** | ▪ Dysphagia, Raynaud phenomenon<br>▪ Other systemic sclerosis clinical or laboratory features |
| **Sjögren disease** | ▪ Anti-Ro52 antibody, antinuclear antibody<br>▪ Raynaud phenomenon<br>▪ Older age<br>▪ Lymphopenia<br>▪ Severe dental caries |




Johnson SR, et al. *Arthritis Rheum* 2024;76(8):1201-1213.

23

## Relative Prevalence of Thoracic Findings in SARDs

| | SSc | RA | SLE | DM/PM | MCTD | SjS |
|---|---|---|---|---|---|---|
| ILD overall | +++ | ++ | + | +++ | ++ | ++ |
| NSIP | +++ | ++ | ++ | +++ | ++ | ++ |
| UIP | + | +++ | + | + | + | + |
| OP | + | ++ | + | +++ | + | – |
| LIP | – | + | + | – | – | ++ |
| DAD | ++ | + | ++ | ++ | – | + |

Bryson T, et al. *Semin Ultrasound CT MRI*. 2014;35:29-38.

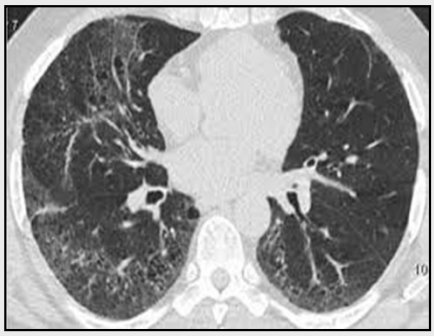
24

## Relative Prevalence of Thoracic Findings in SARDs

| | SSc | RA | SLE | DM/PM | MCTD | SjS |
|---|---|---|---|---|---|---|
| ILD overall | +++ | ++ | + | +++ | ++ | ++ |
| NSIP | +++ | ++ | ++ | +++ | ++ | ++ |
| UIP | + | +++ | + | + | + | + |
| OP | + | ++ | + | +++ | + | – |
| LIP | – | + | + | – | – | ++ |
| DAD | ++ | + | ++ | ++ | – | + |

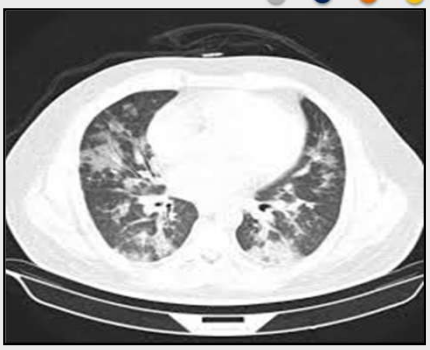
Bryson T, et al. *Semin Ultrasound CT MR*. 2014;35:29-38.

25



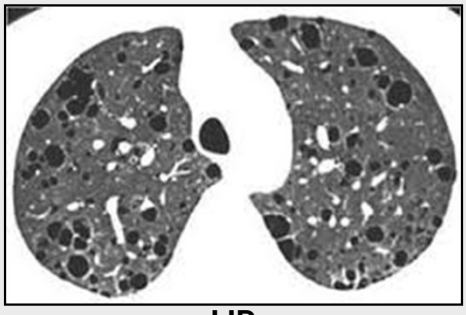
NSIP

NSIP OP overlap

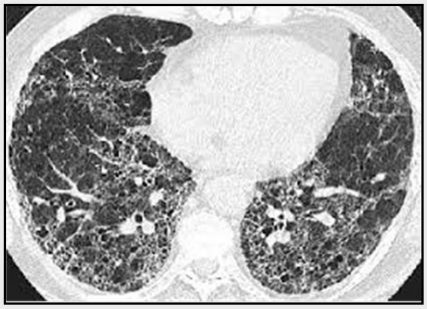


OP

Potentially reversible



LIP



UIP

Not reversible

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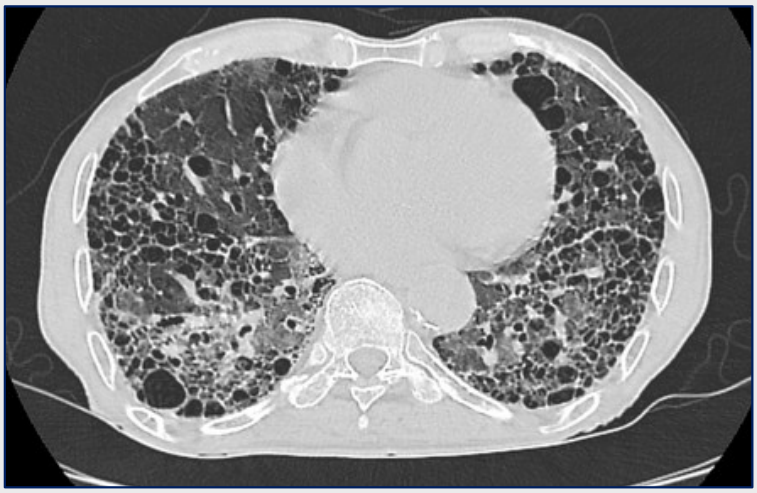
## Case 2

- 70-year-old man referred for IPF
- 30 pack years
- Velcro crackles
- FVC 58% predicted
- DLCO 45% predicted
- Long-standing joint pain in hands “OA by PCP”
  - Mild tenderness with minimal swelling several PIPs and MCPs
  - Morning stiffness ~20 minutes
- RF 98, CCP >200



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## RA-UIP vs IPF: Demographics

| | RA-UIP | IPF |
|---|---|---|
| **Gender** | Males> Females | Males> >Females |
| **Age** | >60 | >60 |
| **Risk factors** | Smoking | Smoking |
| **Race** | Caucasians | Caucasians |
| **Prevalence** | 5% of RA patients | 15-20/100,000 |

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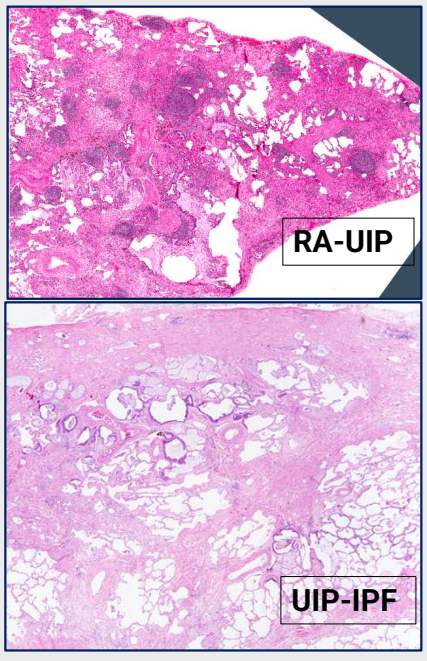
## RA-UIP vs IPF: Histology

| Characteristic | RA-UIP | IPF |
|---|---|---|
| Microscopic honeycombing | Present | Present |
| Temporal heterogeneity | Present | Present |
| Spatial heterogeneity | Present | Present |
| Fibroblastic foci | Some | Many |
| Lymphoid aggregates | Common | Uncommon |
| Interstitial inflammation | Present | Minimal |
| Pleural fibrosis | Common | Uncommon |
| Distribution of fibrosis | Airway centered | Subpleural |

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## RA-UIP vs IPF: Pathobiology

| Mechanism of disease | RA-UIP | IPF |
|---|---|---|
| **Autophagy** | Upregulated→CCP | Upregulated |
| **Mitophagy** | Dysregulated | Dysregulated |
| **Telomere length** | Short | Short |
| **MUC5B association** | Present | Present |
| **TERT, RTEL1, PARN, and SFTPC association** | Present | Present |

*Cryobiopsy and genomic classifier cannot distinguish between IPF and other forms of UIP*

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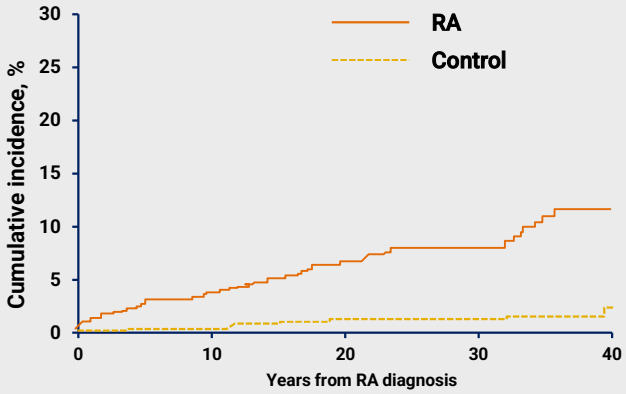
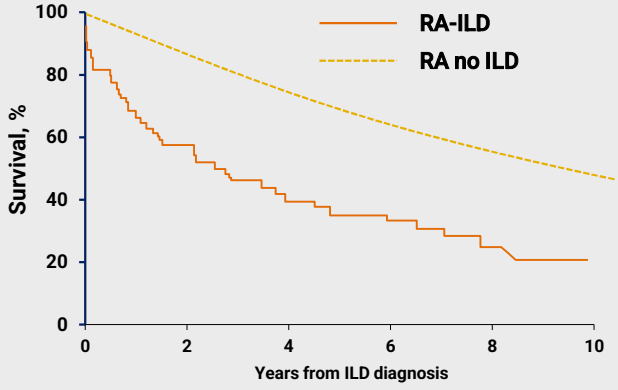
## IT MATTERS:
## RA Associated With Increased Risk of ILD and Death

**Incidence of ILD in RA compared with matched controls**




**Survival in RA-ILD compared with RA overall**




Population-based incidence cohort of patients with RA (n=582) matched with subjects without RA (n=603) followed longitudinally. Lifetime risk of ILD was 7.7% for RA patients vs 0.9% for non-RA subjects (HR=8.96). Risk of death HR=2.86 for RA-ILD vs RA without ILD.

Bongartz T, et al. *Arthritis Rheum*. 2010;62(6):1583-1591.

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## Prevalence of SSc-ILD

| Autopsy | PFTs (TCL <70%) | HRCT | Clinical | Chronic respiratory failure |
|---|---|---|---|---|
| ▪ 75–95% | ▪ 25% | ▪ 47–84% | ▪ cdSSc 50%<br>▪ lcSSc 25% | ▪ 12% |

Reviewed in: Roofeh D, et al. *Curr Opin Rheumatol.* 2019;31:241-249. Steen V, et al. *Arthritis Rheum.* 1994;37:1283-1289.

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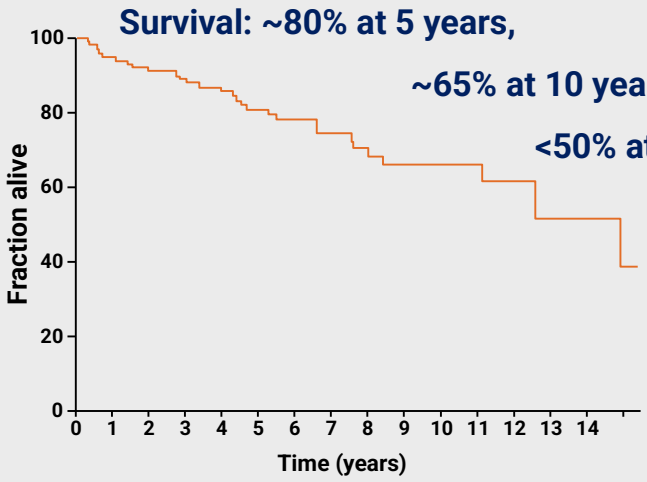
## Long-Term Mortality in SSc-ILD




| Characteristics at SSc-ILD diagnosis | |
|---|---|
| Age, mean (SD) | 54.5 (13.2) |
| Male, % | 16% |
| FVC % predicted, mean (SD) | 81 (20) |
| DLCO % predicted, mean (SD) | 59 (20) |

Ryerson CJ, et al. *Chest.* 2015.;148:1268-1275.

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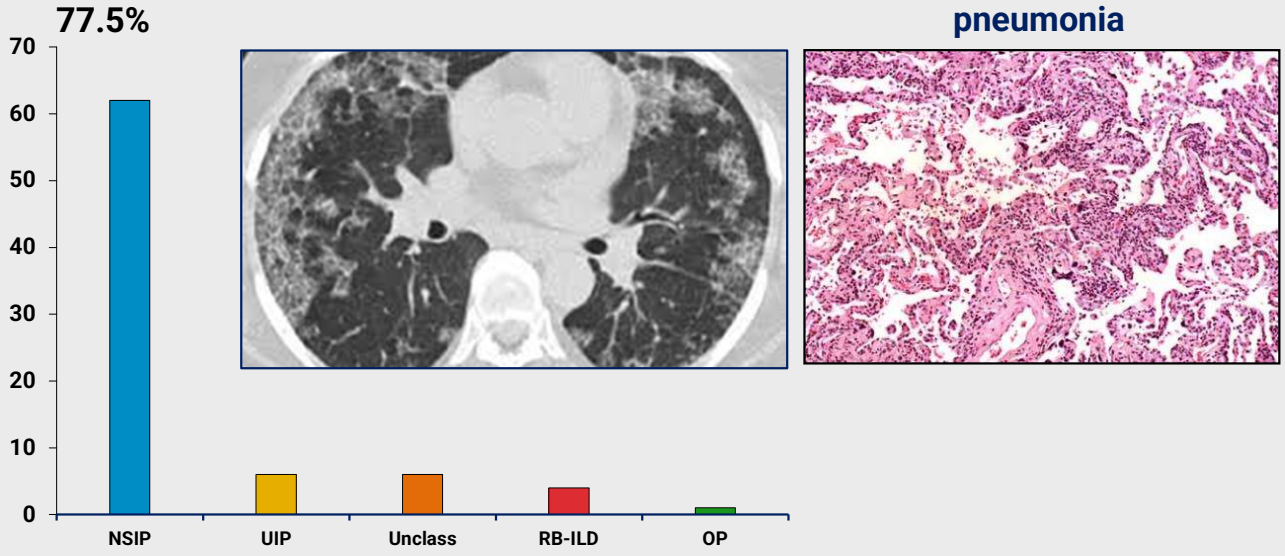
## Histopathology of SSc-ILD (N=80)




Bouros D, et al. *Am J Resp Crit Care Med.* 2002;165:1581-1586.

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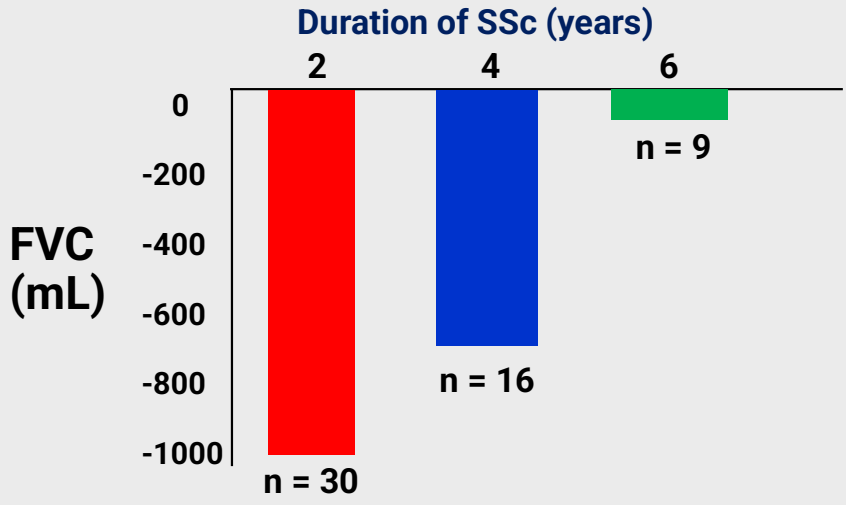
## Rate of FVC Fall in SSc Patients With Severe Restriction




Sheeran RP, et al. *Arthritis Rheum.* 1990;33:S157.

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## Risk Factors for SSc-ILD Progression

- African American race
- Male sex
- Genetic polymorphisms
- Diffuse cutaneous scleroderma variant
- Nailfold capillary abnormalities
- Digital ulcers
- Early disease
- Pulmonary hypertension
- Primary cardiac dysfunction

- Anti-topoisomerase I
- ANCA
- Anticardiolipin
- Anti-Ro52
- Anti-NOR90
- Anti-U11/U12
- Anti-Th/To
- Anti-polymyositis-scleroderma

Perelas A, et al. *Lancet Respir Med*. 2020;8(3):304-320.

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## Video Case Part 2: Early Detection and Next Steps in ILD Care

https://youtu.be/ML4Gh9vsho4

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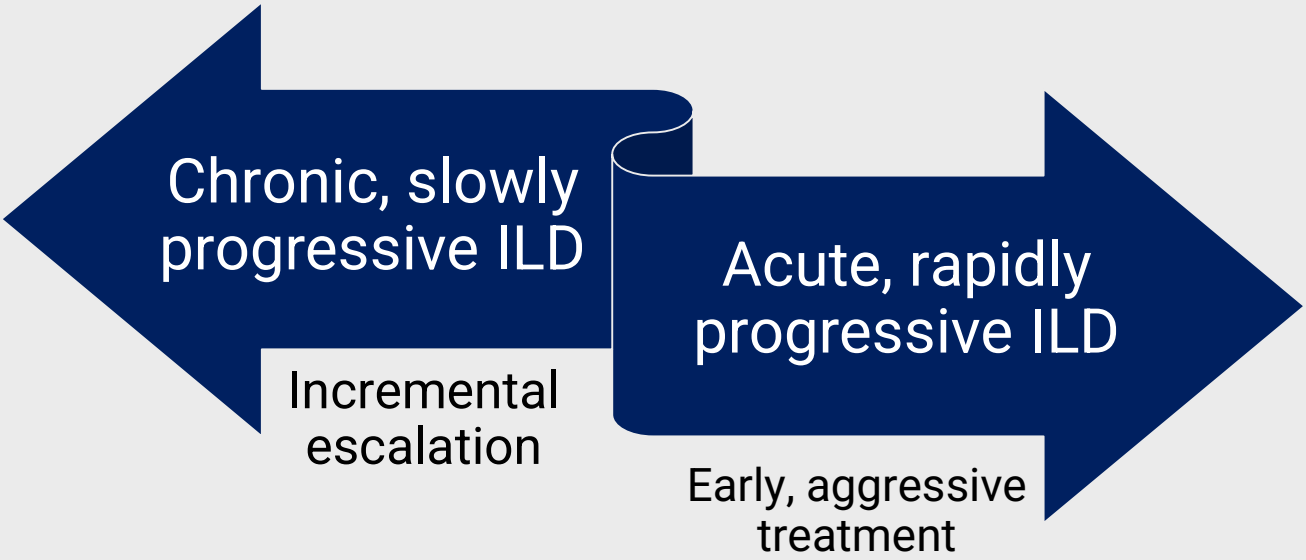
## Management Algorithms for SARD-ILD

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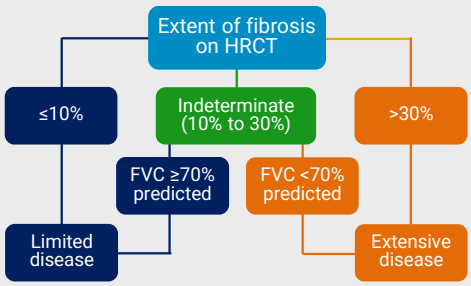
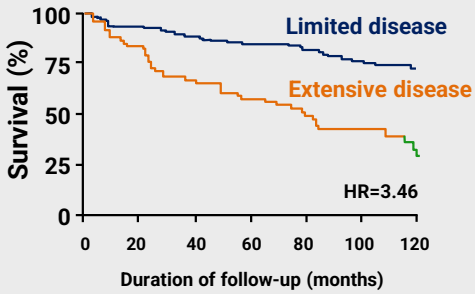
## Who should be treated?




**Extensive disease**

- ≥20% on HRCT or
- Clinical disease progression evidenced by either or both of the following:
  - >10% FVC decline
  - 5% to 9% FVC decline with a 15% DLCO decline

**Less extensive disease**

- Risk factors for progression

Goh NSL, et al. *Am J Respir Crit Care Med*. 2008;177:1248-1254. Perelas A, et al. *Lancet Respir Med*. 2020;8:304-320.

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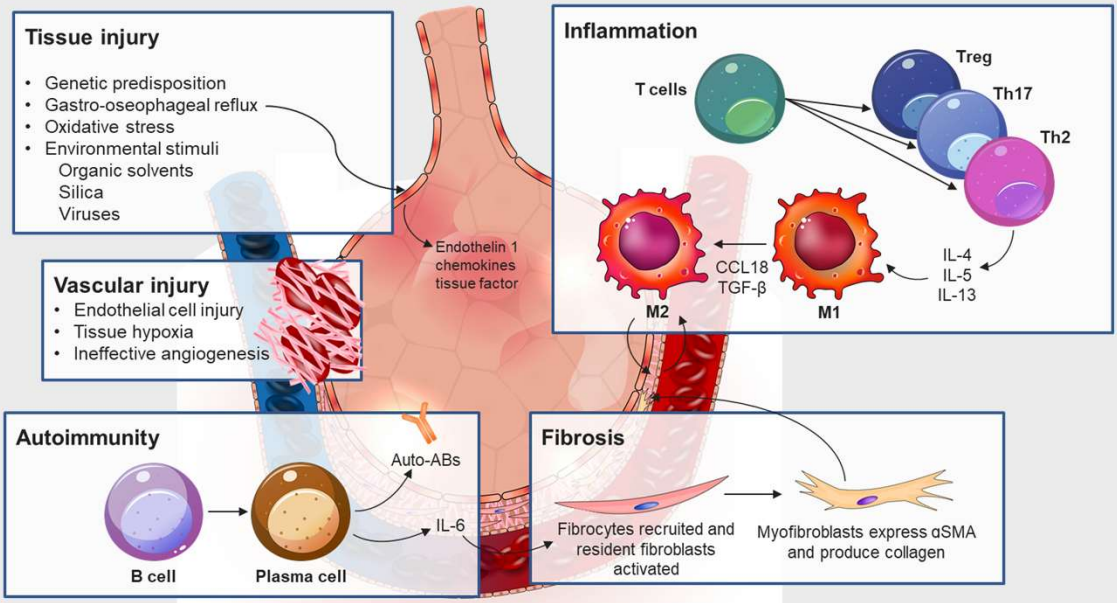
## Pathogenesis of SARD -ILD




Adapted from Perelas A, et al. *Lancet Respir Med*. 2020;8:304-320.

40

## Treatment Approaches for SARD-ILD: Caveats

- Other than in scleroderma, well-powered clinical trials are lacking in this field
- Results appear to be etiology-specific and not translatable across SARDs
- Extrapolating results from IPF to SARD-ILD is not advisable
- Clinical trials are ongoing and need patients

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## Treatment of Systemic Sclerosis-Associated Interstitial Lung Disease: Evidence-based Recommendations

An Official American Thoracic Society Clinical Practice Guideline

**Systemic sclerosis-associated interstitial lung disease**

Treatment recommendations

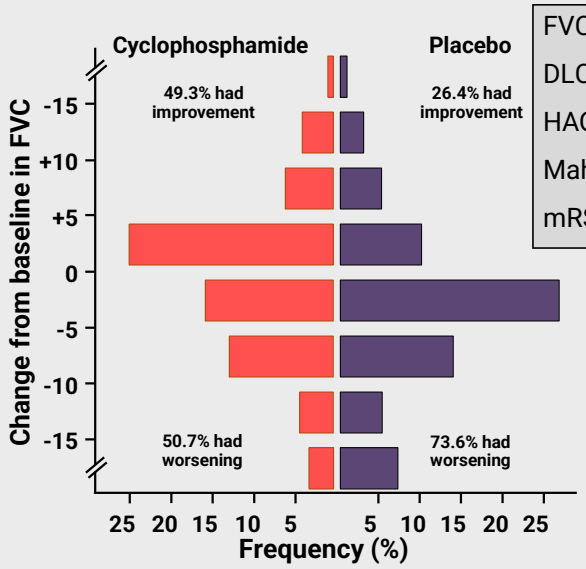
| | |
|---|---|
| STRONG IN FAVOR | Mycophenolate |
| CONDITIONAL IN FAVOR | Cyclophosphamide; Rituximab; Nintedanib; Nintedanib plus mycophenolate |
| RESEARCH RECOMMENDATION | Pirfenidone; Pirfenidone plus mycophenolate |

Summary of treatment recommendations for patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD). The SSc-ILD Guideline Committee.

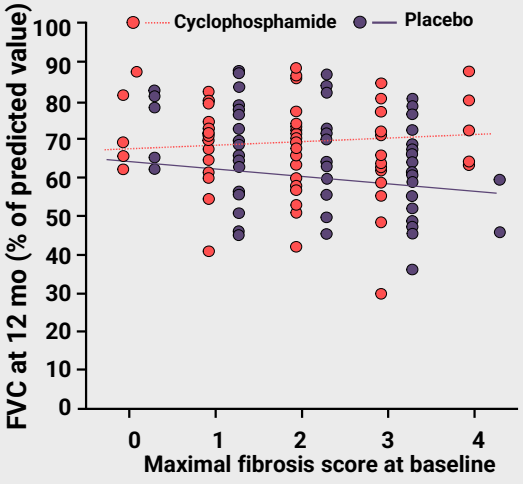
Mycophenolate and cyclophosphamide are not FDA approved for this indication. Raghu G, et al. *Am J Respir Crit Care Med.* 2024;209(2):137-152.

42

## SLS I: Oral Cyclophosphamide vs Placebo




FVC: 2.5%
DLCO: 1%
HAQ: 0.16 units
Mahler: 2.9 units
mRSS: 3.6 units




Cyclophosphamide is not FDA approved for this indication.
Tashkin DP, et al. *N Engl J Med.* 2006;354:25.

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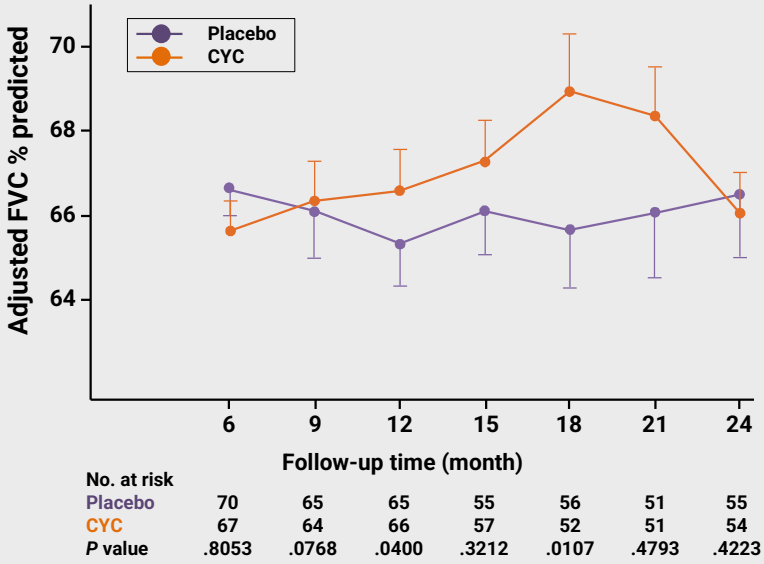
## Effects of 1-Year Treatment With Cyclophosphamide at 2 Years




| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Placebo | 70 | 65 | 65 | 55 | 56 | 51 | 55 |
| CYC | 67 | 64 | 66 | 57 | 52 | 51 | 54 |
| *P* value | .8053 | .0768 | .0400 | .3212 | .0107 | .4793 | .4223 |

### Editorial for SLS I

*"Cyclophosphamide is… arguably the most toxic immunosuppressive agent currently used to treat autoimmune diseases."*

Cyclophosphamide is not FDA approved for this indication.
Tashkin DP, et al. *Am J Respir Crit Care Med*. 2007;176:1026-1034.

Martinez F, et al. *N Engl J Med*. 2006;354(25):2707-2709.

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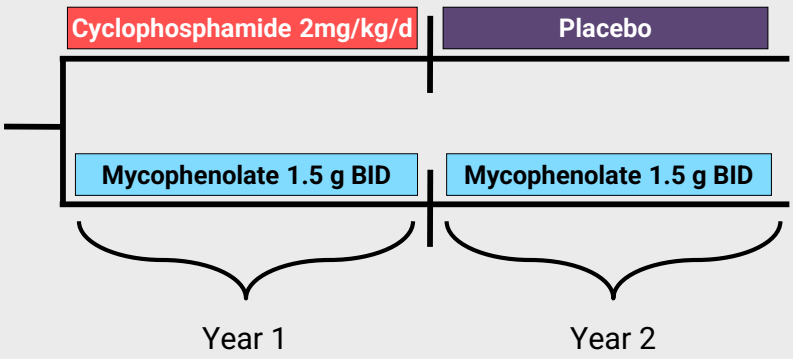
## Scleroderma Lung Study II: Mycophenolate vs Cyclophosphamide




**Primary outcome:** % predicted FVC
**Secondary outcomes:** TLC, DLCO, TDI, HRQoL

Tashkin DP, et al. *Lancet Respir Med* 2016;4:708-719.

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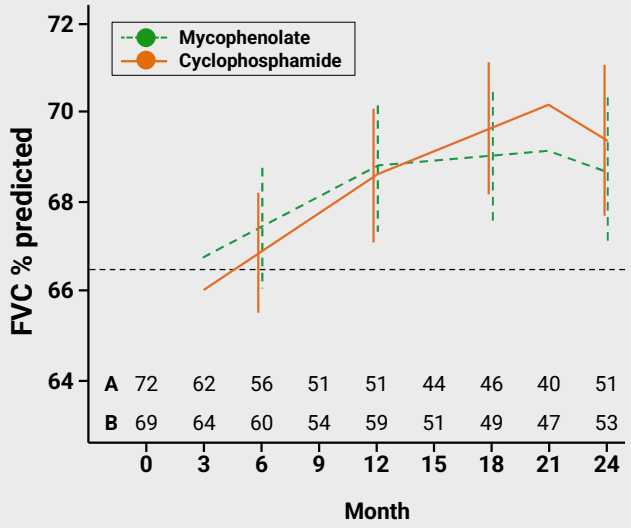
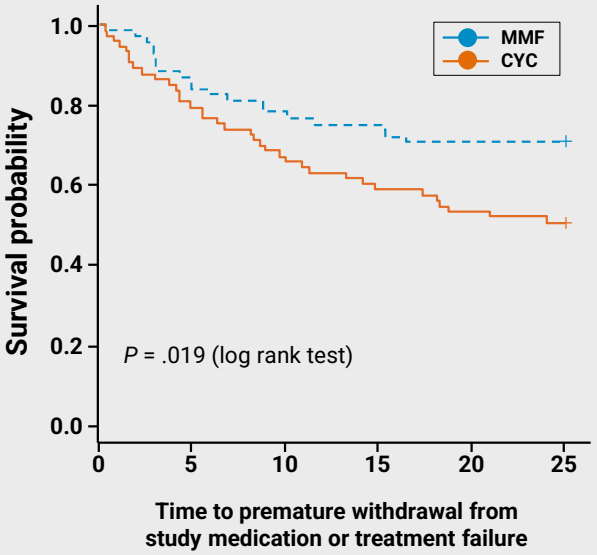
## Scleroderma Lung Study II: Mycophenolate vs Cyclophosphamide




Tashkin DP, et al. *Lancet Respir Med.* 2016;4:708-719.

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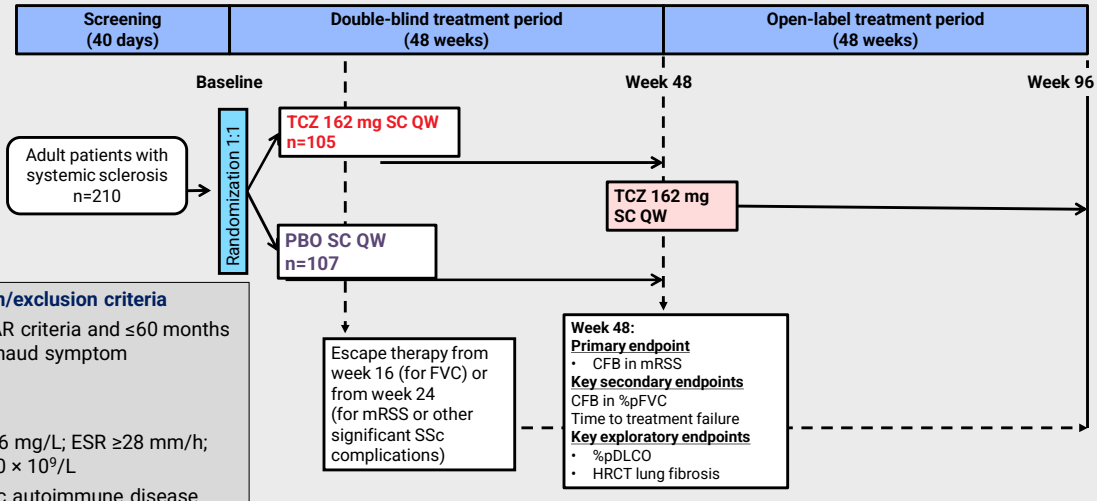
## focuSSced: A Randomized, Double-blind, Placebo-controlled Phase 3 Trial of Tocilizumab in SSc




**Key inclusion/exclusion criteria**

- SSc per ACR/EULAR criteria and ≤60 months from first non-Raynaud symptom
- mRSS 10-35 units
- Active disease
- ≥1 of these: CRP ≥6 mg/L; ESR ≥28 mm/h; platelet count ≥330 × $10^9$/L
- No other rheumatic autoimmune disease
- Other background immunomodulatory therapies not allowed

Khanna D, et al. *Lancet Respir Med.* 2020;8:963-974.

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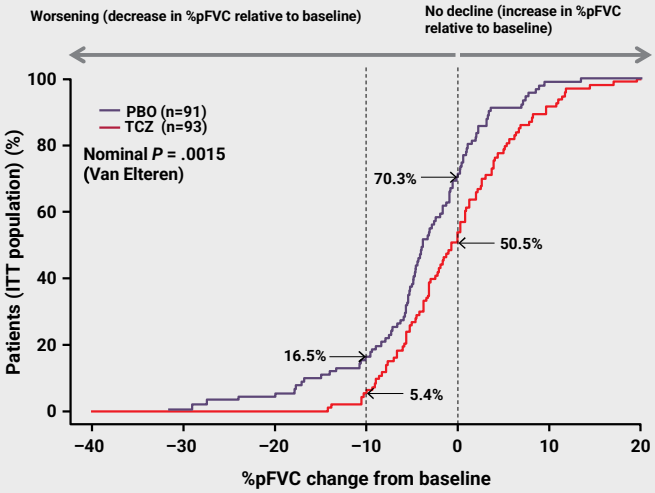
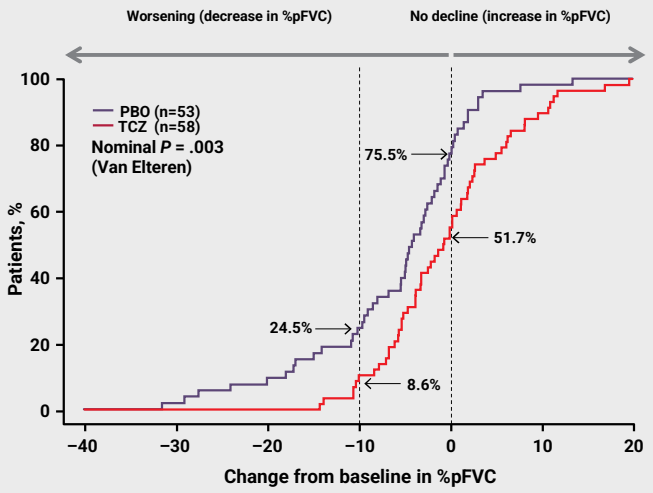
# focuSSced: A Randomized, Double-blind, Placebo-controlled Phase 3 Trial of Tocilizumab in Patients With SSc

## All patients




## Patients with SSc-ILD

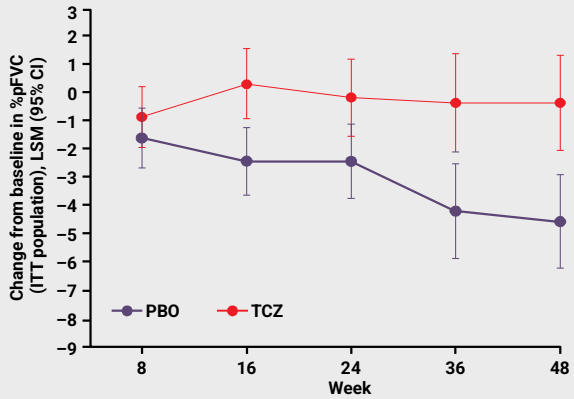



Khanna D, et al. *Lancet Respir Med.* 2020;8:963-974.

48

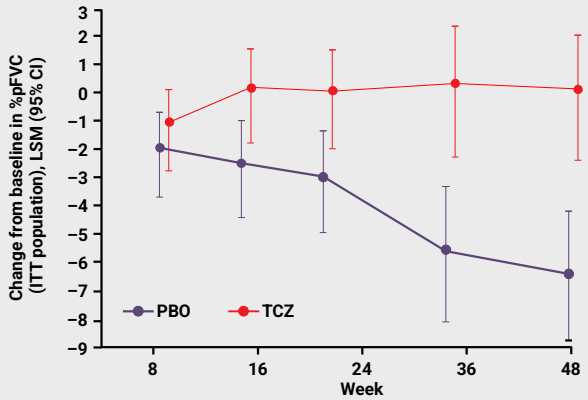
# Key Secondary Endpoint: Clinically Meaningful Difference in Change From Baseline in %pFVC at Week 48

## All patients




| | PBO N=106 | TCZ N=104 | Difference (95% CI) nominal *P* Value |
|---|---|---|---|
| %pFVC change from baseline at week 48 | -4.6 | -0.4 | 4.2 (2.0 to 6.4) *P* = .0002 |
| Absolute change in FVC, mL | -190 | -24 | 167 (83 to 250) *P* = .0001 |

## Patients with SSc-ILD




| | PBO N=63 | TCZ N=67 | Difference (95% CI) nominal *P* Value |
|---|---|---|---|
| %pFVC change from baseline at week 48 | -6.5 | -0.1 | 6.4 (3.3 to 9.4) *P* < .0001 |
| Absolute change in FVC, mL | -257 | -20 | 238 (119 to 357) *P* = .0001 |

Khanna D, et al. *Lancet Respir Med.* 2020;8:963-974.

49

## focuSSced: HRCT Results in Patients With SSc-ILD

| HRCT lung fibrosis score | PBO N=65 | TCZ N=67 | Nominal *P* Value (Van Elteren) |
|---|---|---|---|
| **QLF-LM post hoc analysis**<br>Baseline: median (IQR)<br>Change from baseline | n=36<br>2.7 (1.3 to 6.4) | n=35<br>3.6 (1.4 to 13.2) | .003 |
| **QLF-WL post hoc analysis**<br>Baseline: median (IQR)<br>Change from baseline t | | | < .001 |
| **QILD-WL post hoc analysis**<br>Baseline: median (IQR)<br>Change from baseline to week 48: median (IQR) | n=46<br>14.5 (10.2 to 20.2)<br>1.5 (-2.1 to 5.2) | n=55<br>17.8 (11.4 to 30.1)<br>-1.6 (-4.4 to 0.5) | .01 |

**Tocilizumab**
**FDA approved for SSc-ILD**

Khanna D, et al. *Lancet Respir Med.* 2020;8:963-974.

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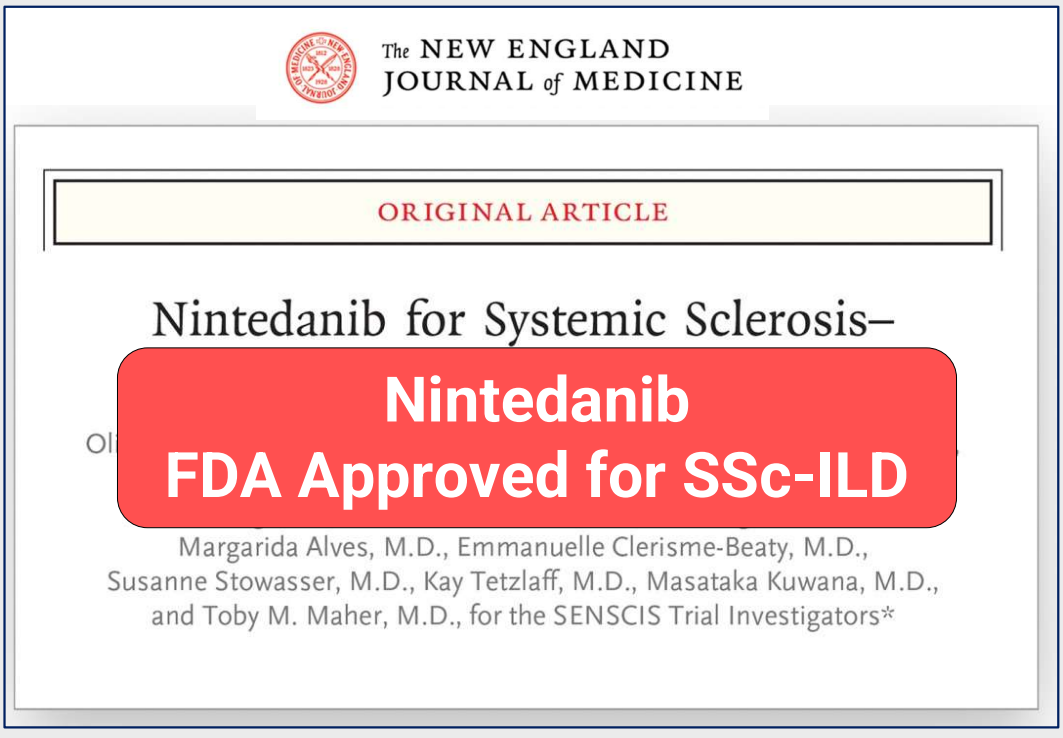


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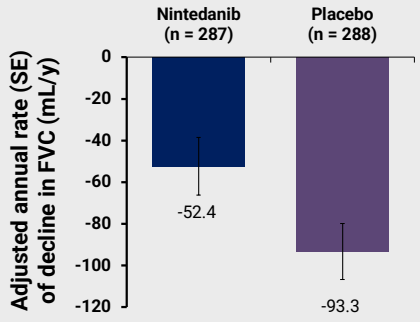
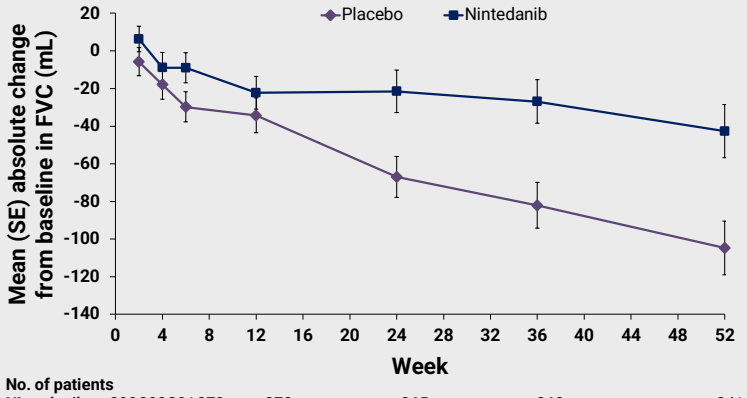
## Decline in FVC Over 52 Weeks

### Annual rate of decline in FVC (mL/y) (primary endpoint)




Difference: 41.0 mL/y (95% CI: 2.9 to 79.0); *P* = .04
**Relative reduction: 44%**

### Change from baseline in FVC (mL) over 52 weeks




| No. of patients | | | | | |
|---|---|---|---|---|---|
| Nintedanib | 288 283 281 273 | 278 | 265 | 262 | 241 |
| Placebo | 288 283 281 280 | 283 | 280 | 268 | 257 |

Distler O, et al. *N Engl J Med.* 2019;380:2518-2528.

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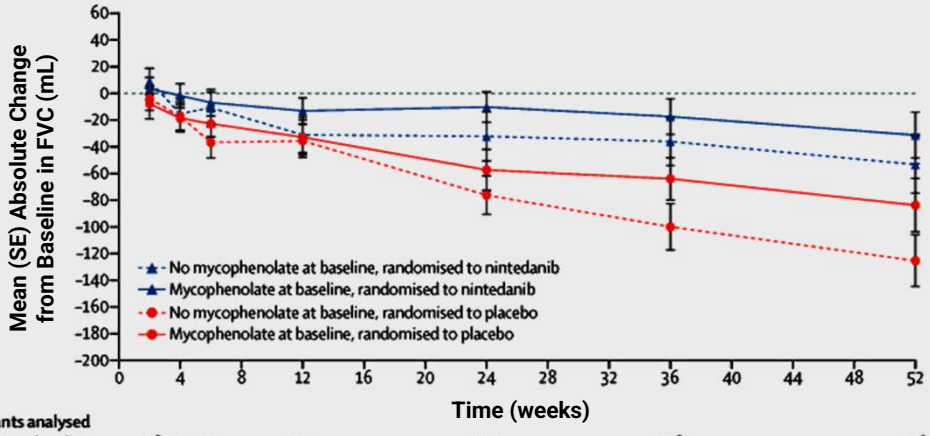
## SENSCIS: Mycophenolate Subgroup Analysis



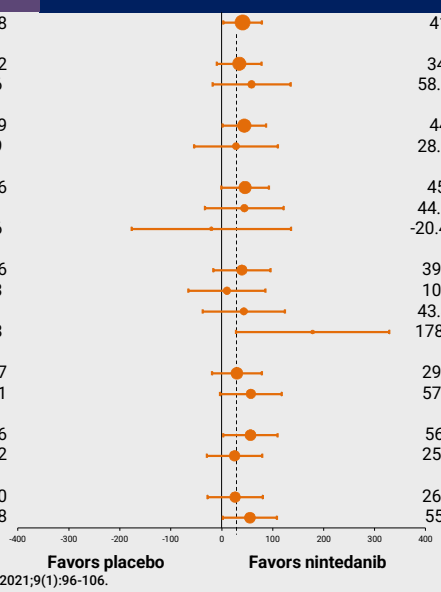

| Number of participants analysed | | | | | |
|---|---|---|---|---|---|
| Nintedanib group, mycophenolate at baseline | 138 134 131 | 135 | 129 | 128 | 116 |
| Nintedanib group, no mycophenolate at baseline | 145 147 142 | 143 | 136 | 134 | 125 |
| Placebo group, mycophenolate at baseline | 136 139 139 | 139 | 137 | 133 | 127 |
| Placebo group, no mycophenolate at baseline | 147 142 141 | 144 | 143 | 135 | 130 |

Mycophenolate is not FDA approved for this indication.
Highland KB, et al. *Lancet Resp Med.* 2021;9(1):96-106.

53

## Subgroup Analyses of Rate of Decline in FVC

| | | n analysed | | Difference (95% CI) | Treatment-by-time-by-subgroup interaction |
|---|---|---|---|---|---|
| | | Nintedanib | Placebo | | |
| **All patients** | | 287 | 288 | 41.0 (2.9 to 79.0) | |
| **Gender** | Female | 220 | 212 | 34.6 (-9.3 to 78.4) | *P* = .59 |
| | Male | 67 | 76 | 58.6 (-18.0 to 135.1) | |
| **Age** | <65 years | 224 | 229 | 44.4 (1.4 to 87.4) | *P* = .73 |
| | ≥65 years | 63 | 59 | 28.1 (-54.2 to 110.4) | |
| **Race** | White | 200 | 186 | 45.8 (-0.8 to 92.5) | *P* = .73 |
| | Asian | 62 | 81 | 44.5 (-32.9 to 121.9) | |
| | Black/African American | 20 | 16 | -20.4 (-176.7 to 136.0) | |
| **Region** | Europe | 139 | 126 | 39.7 (-16.6 to 95.9) | *P* = .28 |
| | Canada and USA | 69 | 73 | 10.3 (-65.6 to 86.1) | |
| | Asia | 59 | 71 | 43.4 (-37.0 to 123.8) | |
| | Rest of world | 20 | 18 | 178.4 (28.1 to 328.7) | |
| **ATA status** | Positive | 173 | 177 | 29.9 (-19.1 to 78.8) | *P* = .49 |
| | Negative | 114 | 111 | 57.2 (-3.5 to 118.0) | |
| **SSc subtype** | Diffuse cutaneous | 153 | 146 | 56.6 (3.2 to 110.0) | *P* = .42 |
| | Limited cutaneous | 134 | 142 | 25.3 (-28.9 to 79.6) | |
| **Mycophenolate use** | Yes | 138 | 140 | 26.3 (-27.9 to 80.6) | *P* = .45 |
| | No | 149 | 148 | 55.4 (2.3 to 108.5) | |




Distler O, et al. *N Engl J Med.* 2019;380:2518-2528. Highland KB, et al. *Lancet Resp Med.* 2021;9(1):96-106.

54

## ACR/ACCP First-Line Therapy Recommendations for SARD-ILD

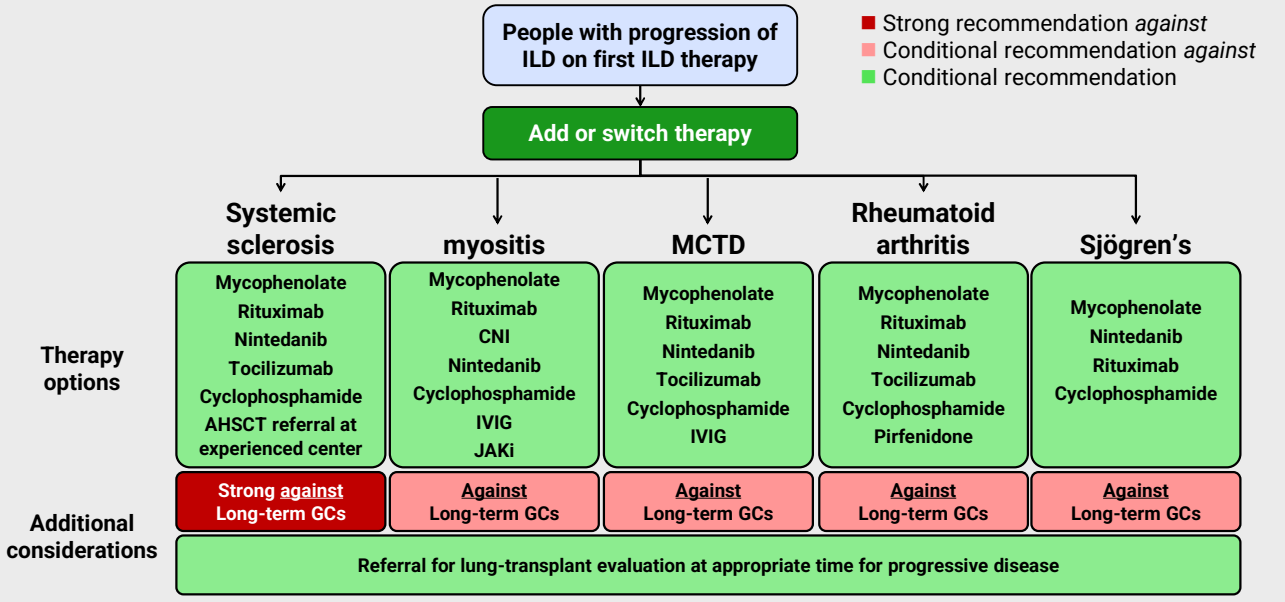
| | Systemic sclerosis | Myositis | MCTD | Rheumatoid arthritis | Sjögren's |
|---|---|---|---|---|---|
| Preferred **First-line ILD therapy** | Mycophenolate<br>Tocilizumab<br>Rituximab | Mycophenolate<br>Azathioprine<br>Rituximab<br>CNI | Mycophenolate<br>Azathioprine<br>Rituximab | Mycophenolate<br>Azathioprine<br>Rituximab | Mycophenolate<br>Azathioprine<br>Rituximab |
| Additional options | Cyclophosphamide<br>Nintedanib<br>Azathioprine | JAKi<br>Cyclophosphamide | Tocilizumab<br>Cyclophosphamide | Cyclophosphamide | Cyclophosphamide |
| + **Glucocorticoids** | Strong recommendation against GCs | Short-term GCs | Short-term GCs | Short-term GCs | Short-term GCs |

■ Strong recommendation *against* ■ Conditional recommendation

Mycophenolate, rituximab, cyclophosphamide, IVIG, and JAK are not FDA-approved for this indication.
Johnson SR, et al. *Arthritis Rheum.* 2024;76(8):1182-1200.

55

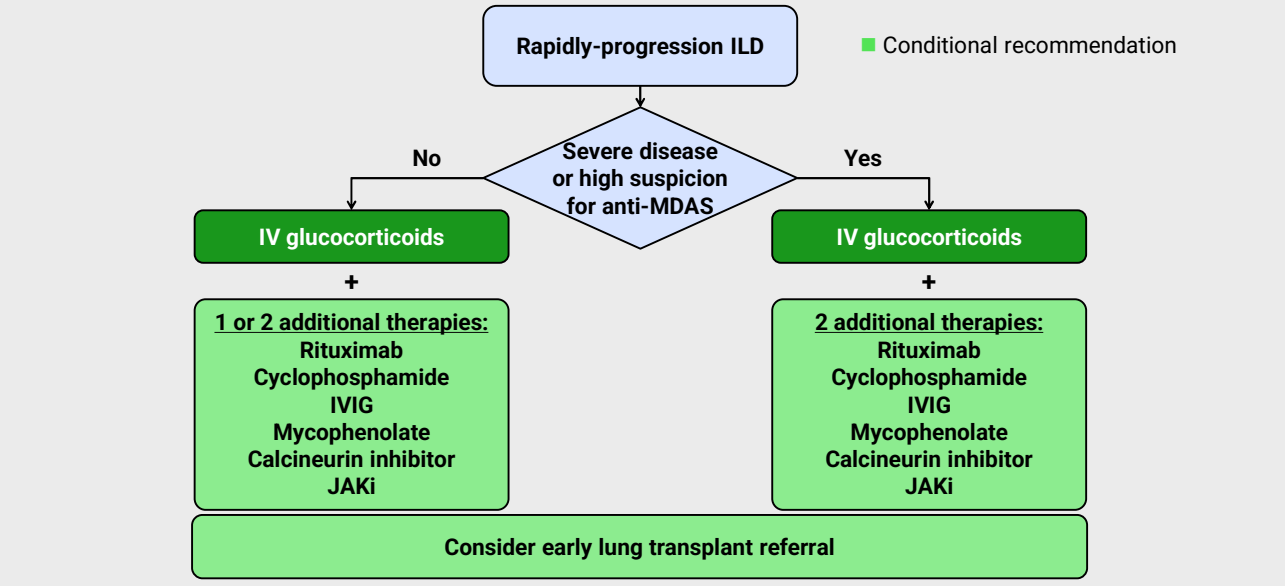
## ACR/ACCP Treatment Algorithm for Progression on First SARD-ILD Therapy




Mycophenolate, rituximab, cyclophosphamide, IVIG, and JAK are not FDA-approved for this indication.
Johnson SR, et al. *Arthritis Rheum.* 2024;76(8):1182-1200.

56

## ACR/ACCP Treatment Algorithm for Rapidly Progressive SARD-ILD




Johnson SR, et al. *Arthritis Rheum.* 2024;76(8):1182-1200.

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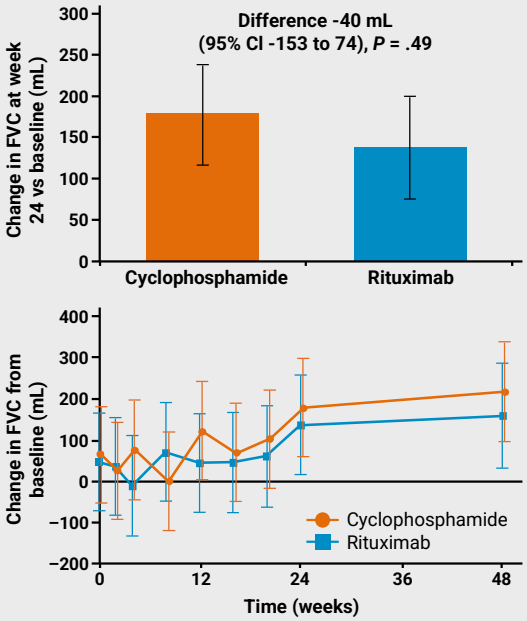
## Recital Trial: Cyclophosphamide vs Rituximab for CTD-ILD

| | Cyclophosphamide group (n=48) | Rituximab group (n=49) |
|---|---|---|
| **Age, years** | 56.7 (11.6) | 56.6 (11.4) |
| **Sex** | | |
| Female | 35 (73%) | 31 (63%) |
| Male | 13 (27%) | 18 (37%) |
| **Race and ethnicity** | | |
| Asian | 7 (15%) | 9 (18%) |
| Black | 5 (10%) | 7 (14%) |
| White | 34 (71%) | 32 (65%) |
| Any other ethnic group | 2 (4%) | 1 (2%) |
| **Connective tissue disease type** | | |
| Idiopathic inflammatory myositis | 22 (46%) | 22 (45%) |
| Systemic sclerosis | 19 (40%) | 18 (37%) |
| Mixed connective tissue disease | 7 (15%) | 9 (18%) |
| **Years since onset of connective tissue disease** | 4.8 (6.2) | 4.5 (7.6) |
| **FVC, L** | 2.23 (0.85) | 2.25 (0.77) |
| **FVC, % of predicted** | 71% (20) | 68% (17) |
| **DLCO, mL/min per kPa** | 3.35 (1.42), n=46 | 3.46 (1.33), n=45 |
| **DLCO, % of predicted** | 40% (14), n=46 | 40% (14), n=45 |
| **SpO, on room air, %** | 96% (2) | 97% (2) |
| **6 min walk distance, m** | 363 (111) | 356 (126) |
| **EQ-5D score** | 55 (20) | 58 (22) |
| **GDA score** | 5.03 (1.76), n=40 | 4.58 (1.97), n=38 |
| **KBILD score** | 46.1 (20.3) | 51 (21.2) |
| **SGRQ score** | 55.8 (20.0), n=47 | 52.1 (17.6), n=45 |

Cyclophosphamide and rituximab are not FDA-approved for this indication.
Maher TM, et al. *Lancet Respir Med.* 2023;11:45-54.




~40% SSc

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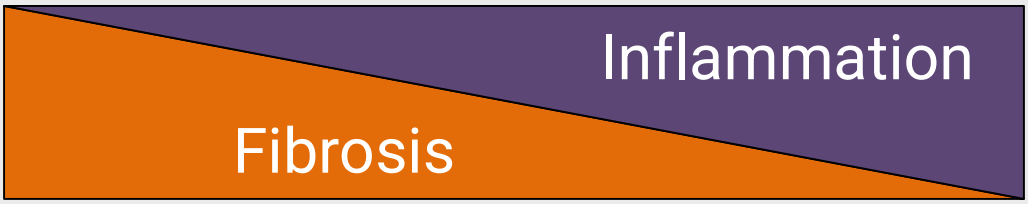
## What are you treating?

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## Audience Response Question

True or false: ILDs generally have patterns of progression that are highly variable during long-term follow-up.

1. True
2. False

IPF = idiopathic pulmonary fibrosis.

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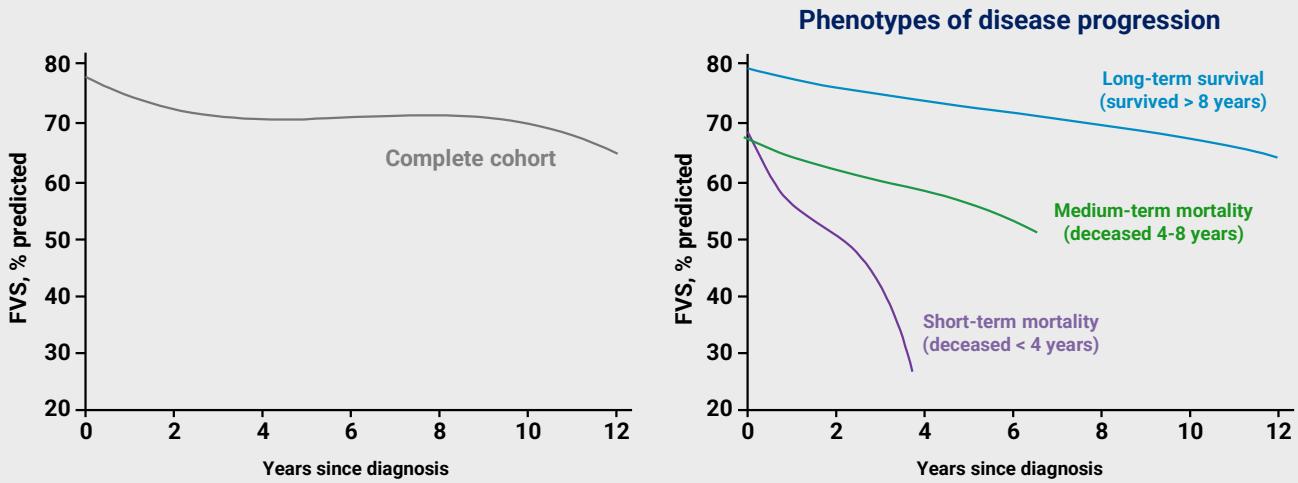
## ILDs Have Distinct Patterns of Progression That Remain Stable During Long-Term Follow-Up




Patients censored with <8 years follow-up were excluded.

Guler S, et al. *Ann Am Thorac Soc.* 2018;5:1427-1433.

61

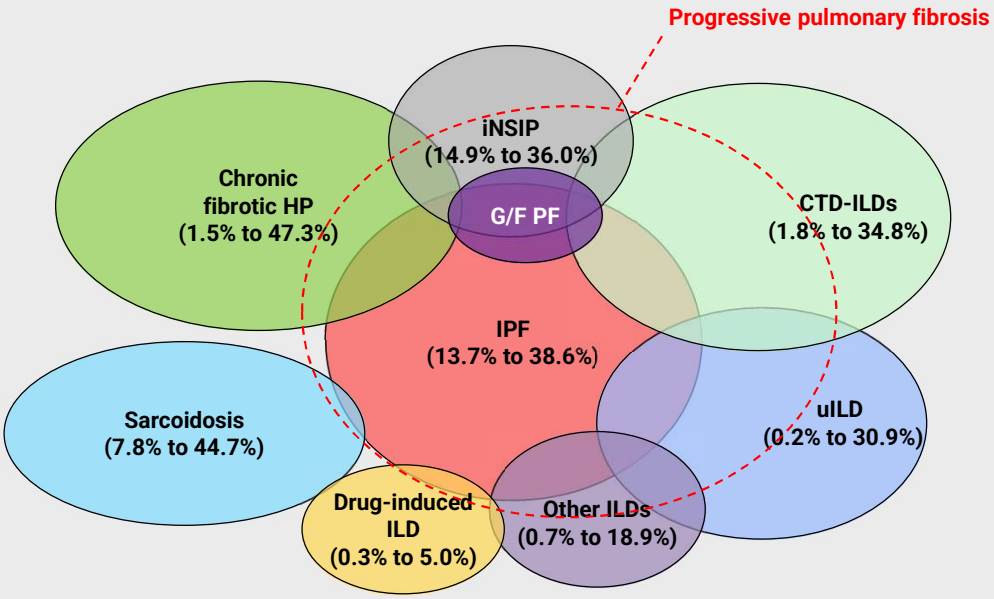
## Criteria for Progressive Pulmonary Fibrosis

| The three diagnostic criteria of PPF | | | |
|---|---|---|---|
| **Domain** | **5-year** | **1-year** | **2-year** |
| **Symptoms** | Worsening respiratory symptoms | Worsening respiratory symptoms | Worsening respiratory symptoms |
| **Pulmonary function** | An absolute decline in FVC% over 5% | An absolute decline in predicted FVC% over 5% or an absolute decline in DLCO% of 10% | An absolute decline in predicted FVC% over 10%, or an absolute decline in predicted FVC% of 5% to 10% |
| **Radiology** | — | Increased fibrosis on HRCT | Increased fibrosis on HRCT |

Chen T, et al. *J Thorac Dis.* 2024;16(2):1034-1043.

62

## Progressive Pulmonary Fibrosis




Rajan SK, et al. *Eur Resp J.* 2023;61:2103187. DOI: 10.1183/13993003.03187-2021.

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Nintedanib in Progressive Fibrosing Interstitial Lung Diseases

K.R. Flaherty, A.U. Wells, V. Cottin, A. Devaraj, S.L.F. Walsh, Y. Inoue, L. Richeldi, M. Kolb, K. Tetzlaff, S. Stowasser, C. Coeck, E. Clerisme-Beaty, B. Rosenstock, M. Quaresma, T. Haeufel, R.-G. Goeldner, R. Schlenker-Herceg, and K.K. Brown, for the INBUILD Trial Investigators*

Flaherty KR, et al. *N Engl J Med* 2019;381(18):1718-1727. doi: 10.1056/NEJMoa1908681.

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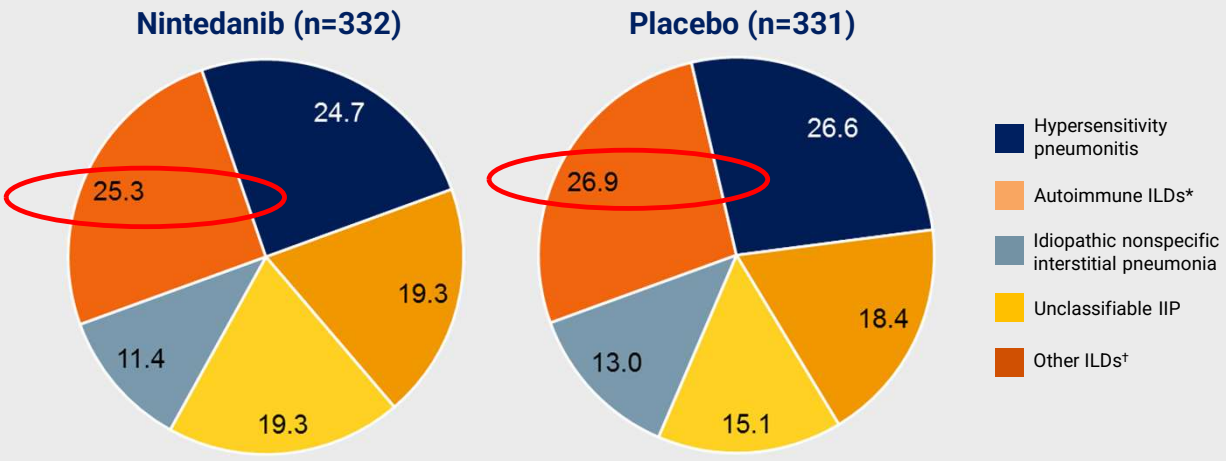
## Clinical ILD Diagnoses in Overall Population




*Included rheumatoid arthritis-associated ILD (nintedanib 12.7%; placebo 14.2%), systemic sclerosis-associated ILD (nintedanib 6.9%; placebo 4.8%), mixed connective tissue disease-ILD (nintedanib 2.1%; placebo 3.6%)

Flaherty KR, et al. *N Engl J Med* 2019;381(18):1718-1727. doi: 10.1056/NEJMoa1908681.

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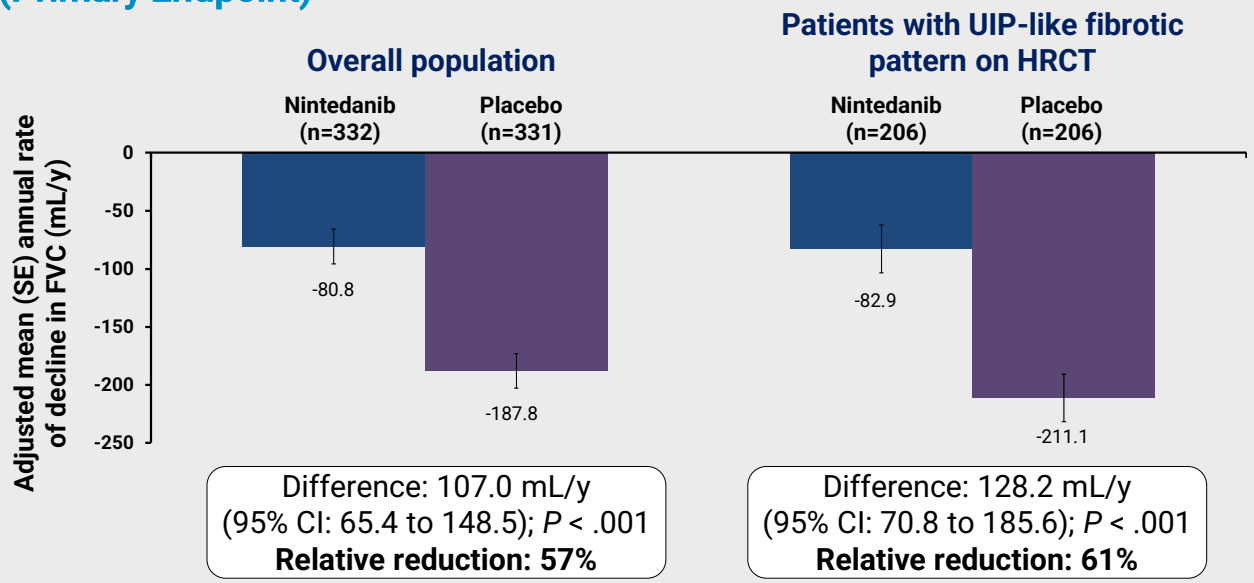
## Adjusted Annual Rate of Decline in FVC (mL/y) Over 52 Weeks (Primary Endpoint)




Flaherty KR, et al. *N Engl J Med* 2019;381(18):1718-1727. doi: 10.1056/NEJMoa1908681.

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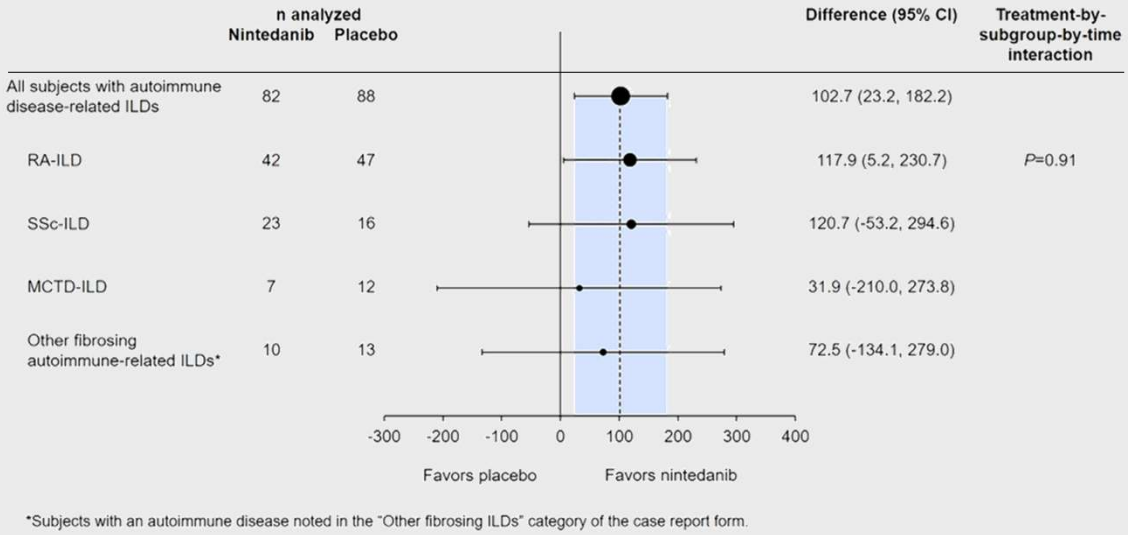
## INBUILD: CTD Subgroup Analysis Rate of Decline in FVC by SARD




*Subjects with an autoimmune disease noted in the "Other fibrosing ILDs" category of the case report form.

Matteson EL, et al. *Arthritis Rheumatol.* 2022;74(6):1039-1047. DOI 10.1002/art.42075.

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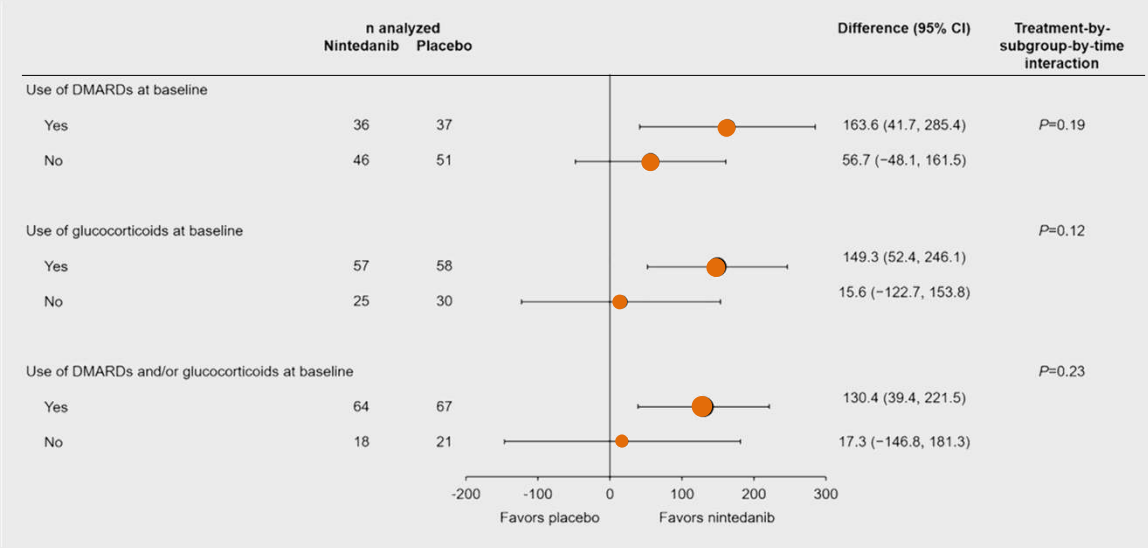
## INBUILD: CTD Subgroup Analysis
## Rate of Decline in FVC by use of DMARDs and Glucocorticoids




Matteson EL, et al. *Arthritis Rheumatol.* 2022;74(6):1039-1047. DOI 10.1002/art.42075.

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## Fibroneer-ILD

- Nerandomilast
  - Phosphodiesterase 4B (PDE4B) inhibitor
  - Anti-inflammatory and anti-fibrotic effects
- N=1,176
- 44 countries
- Progressive pulmonary fibrosis

| Characteristics of the patients at baseline | | | |
|---|---|---|---|
| **Characteristic** | **Nerandomilast 18 mg (N=391)** | **Nerandomilast 9 mg (N=393)** | **Placebo (N=392)** |
| **Male sex — no. (%)** | 220 (56.3) | 203 (51.7) | 231 (58.9) |
| **Age—y** | 66.0±9.8 | 66.5±9.8 | 66.6±10.3 |
| **Weight — kg** | 73.2±17.1 | 72.1±17.5 | 73.4±17.9 |
| **Smoking status — no. (%)** | | | |
| **Never smoked** | 191 (48.8) | 200 (50.9) | 186 (47.4) |
| **Former smoker** | 189 (48.3) | 186 (47.3) | 200 (51.0) |
| **Current smoker** | 11 (2.8) | 7 (1.8) | 6 (1.5) |
| **Time since diagnosis of ILD — y** | 4.6±4.8 | 4.1±4.3 | 3.9±3.6 |
| **FVC** | | | |
| **Mean value — mL** | 2,381±723 | 2,326±768 | 2,354±766 |
| **Percentage of predicted value** | 70.4±15.5 | 70.3±15.7 | 69.7±16.2 |
| **Percentage of predicted DLCO** | 49.4±17.5 | 48.7±16.8 | 49.7±16.5 |
| **Background nintedanib therapy — no. (%)** | 171 (43.7) | 173 (44.0) | 170 (43.4) |
| **UIP or UIP-like fibrotic pattern on high-resolution CT — no. (%)** | 275 (70.3) | 290 (73.8) | 275 (70.2) |
| **ILD diagnosis** | | | |
| **Autoimmune ILD** | 113 (28.9) | 112 (28.5) | 100 (25.5) |
| **Hypersensitivity pneumonitis** | 73 (18.7) | 83 (21.1) | 77 (19.6) |
| **Unclassifiable idiopathic interstitial pneumonia** | 73 (18.7) | 76 (19.3) | 82 (20.9) |
| **Idiopathic nonspecific interstitial pneumonia** | 82 (21.0) | 73 (18.6) | 73 (18.6) |
| **Other ILD** | 50 (12.8) | 49 (12.5) | 60 (15.3) |
| **Supplemental oxygen therapy — no. (%)** | 117 (29.9) | 97 (24.7) | 110 (28.1) |

Maher TM, et al. *N Engl J Med.* 2025;392:2203-2214.

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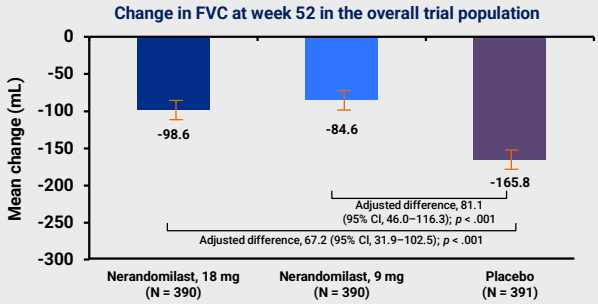
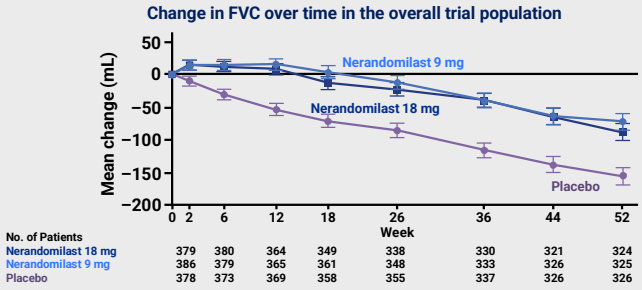
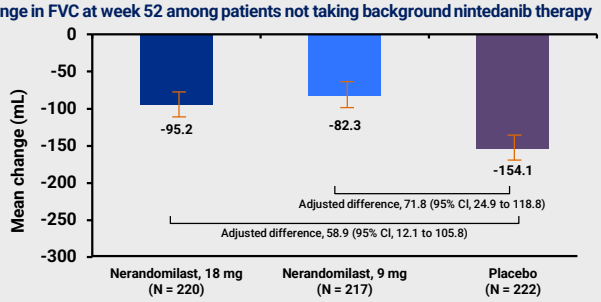
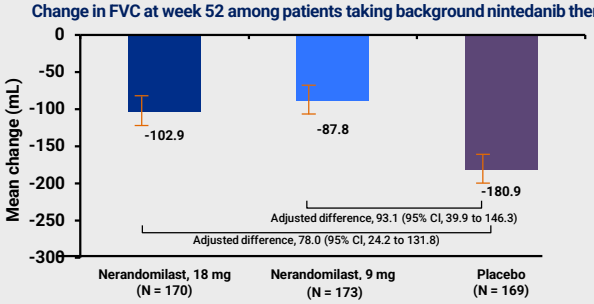
# Fibroneer-ILD: Changes From Baseline to Week 52 in the Forced Vital Capacity (FVC)




Maher TM, et al. *N Engl J Med.* 2025;392:2203-2214.

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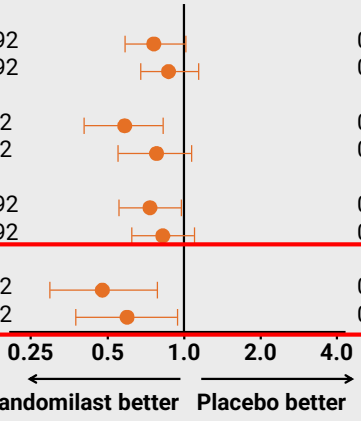
# Fibroneer-ILD: Key Secondary Endpoints

## Analyses of key secondary endpoint and related secondary endpoints up to first database lock

| Endpoint | Nerandomilast | Placebo | Hazard ratio (95% CI) | *P* Value |
|---|---|---|---|---|
| | *no. with event/no. of patients* | | | |
| **Key secondary endpoint** | | | | |
| Nerandomilast 18 mg | 95/391 | 122/392 | 0.77 (0.59 to 1.01) | .06 |
| Nerandomilast 9 mg | 110/393 | 122/392 | 0.88 (0.68 to 1.14) | .34 |
| **Acute exacerbation of ILD or death** | | | | |
| Nerandomilast 18 mg | 48/391 | 83/392 | 0.59 (0.41 to 0.84) | |
| Nerandomilast, 9 mg | 65/393 | 83/392 | 0.78 (0.56 to 1.08) | |
| **Hospitalization for respiratory cause or death** | | | | |
| Nerandomilast 18 mg | 84/391 | 110/392 | 0.75 (0.56 to 1.00) | |
| Nerandomilast 9 mg | 97/393 | 110/392 | 0.83 (0.63 to 1.10) | |
| **Death** | | | | |
| Nerandomilast 18 mg | 24/391 | 50/392 | 0.48 (0.30 to 0.79) | |
| Nerandomilast 9 mg | 33/393 | 50/392 | 0.60 (0.38 to 0.95) | |




Maher TM, et al. *N Engl J Med.* 2025;392:2203-2214.

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## Coming Soon to a Site Near You: Fibroneer-SARD

RMD Open
Rheumatic & Musculoskeletal Diseases

Visit this Journal BMJ

RMD Open. 2024 Dec 23;10(4):e004704. doi: 10.1136/rmdopen-2024-004704

**Rationale for phosphodiesterase-4 inhibition as a treatment strategy for interstitial lung diseases associated with rheumatic diseases**

Martin Aringer [1,✉], Oliver Distler [2], Anna-Maria Hoffmann-Vold [2,3], Masataka Kuwana [4], Helmut Prosch [5], Elizabeth R Volkmann [6]

Author information · Article notes · Copyright and License information

PMCID: PMC11683935 PMID: 39719300

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## Case 3

- 58-year-old woman with diffuse cutaneous systemic sclerosis x 10 years
- ILD diagnosed 8 years ago; on MMF and nintedanib
- Worsening dyspnea on exertion
- HRCT fibrotic NSIP pattern
- FVC 52% predicted, DLCO 25% predicted, FVC/DLCO 2.08
- 6 MWD 265 m, O2 sat 83% predicted
- NT-pro BNP 193

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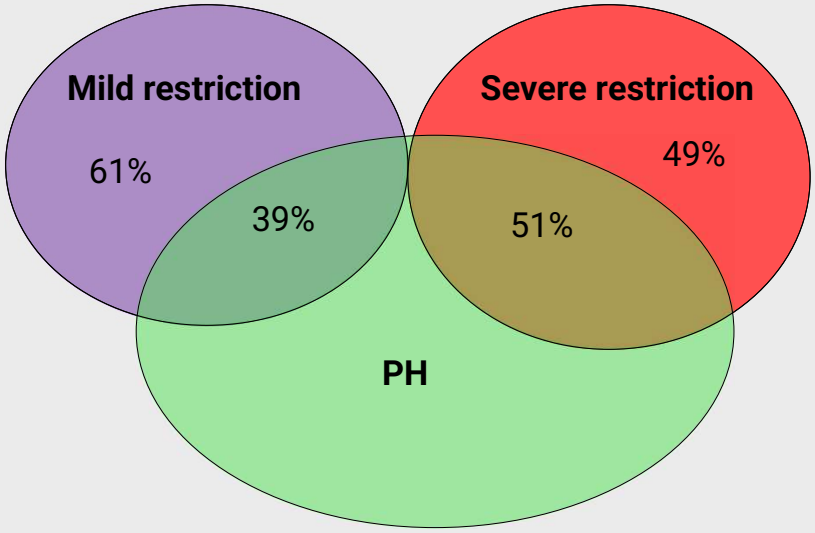
## Combined PH and ILD in SSc (N=619)




Chang B, et al. *J Rheumatol:* 2003;30(11):2398-2405.

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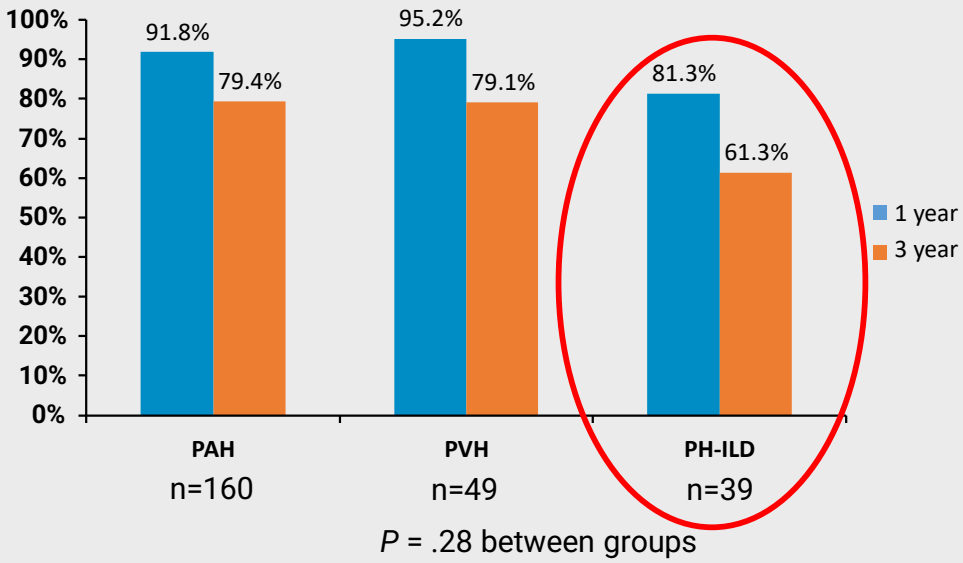
## Survival in SSc Patients by Type of PH




Gordon JK, et al. ACR/AHRP Annual Meeting. November 9-14, 2012. Washington DC. Abstract 1465.

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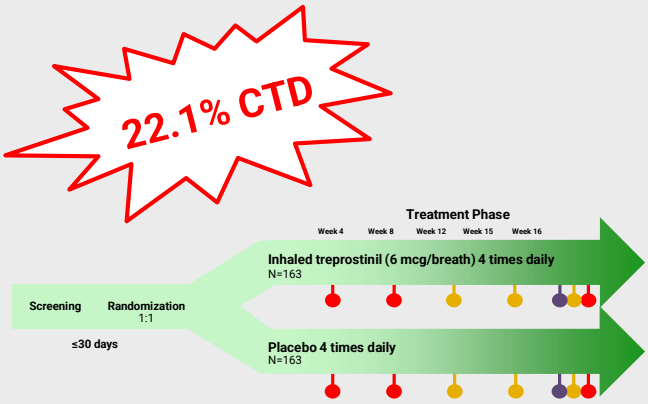
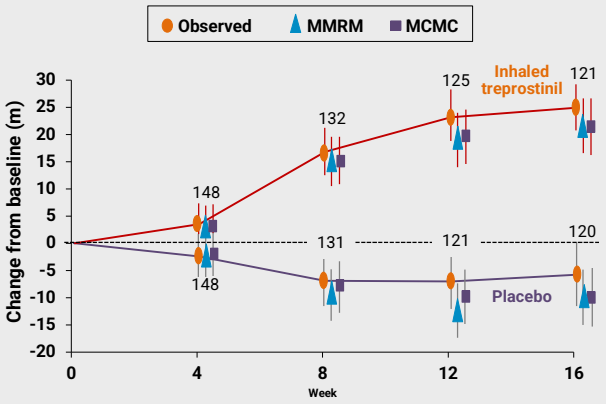
## INCREASE: Inhaled Treprostinil in PH-ILD (n=326)




- Placebo-corrected difference from baseline in peak 6MWD of 31.12 meters (95% CI: 16.85 to 45.39; *P* <. 001)
- 42% reduction in nt-proBNP
- 39% reduction in time to clinical worsening

Waxman A, et al. *N Engl J Med*. 2021;384:325-334.

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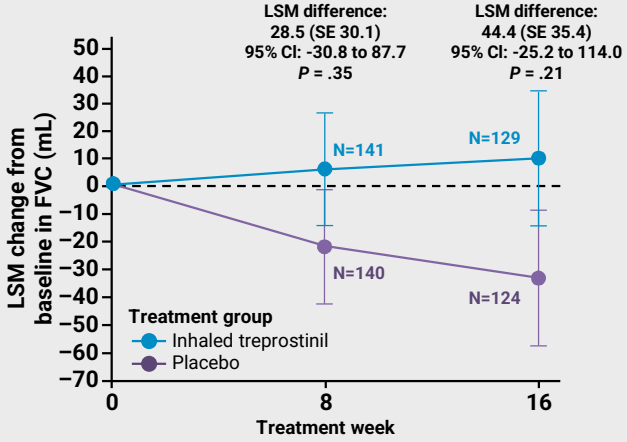
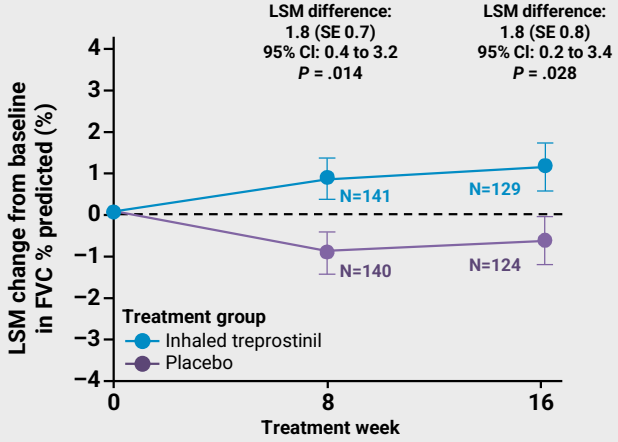
## Safety Endpoint: FVC

- Inhaled treprostinil resulted in placebo-corrected difference in FVC of 28.47 mL and 44.40 mL at weeks 8 and 16, respectively
- Percent predicted FVC at week 8 (1.79%; *P* = .01) and week 16 (1.80%; *P* = .03)




Nathan SD, et al. *N Engl J Med*. 2021;9(11):1266-1274.

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## TETON-2 Pivotal Study of Inhaled Treprostinil Meets Primary Endpoint for the Treatment of Idiopathic Pulmonary Fibrosis

- Placebo corrected improvement in FVC by 95.6 mL ($P < .0001$) at week 52
- Benefits seen across all subgroups
- Statistical improvements in most secondary endpoints
  - Time to first clinical worsening
  - Change in percent predicted FVC
  - Change in King's Brief Interstitial Lung Disease QOL Questionnaire (K-BILD)
  - Diffusion capacity
- Trend towards improvement in
  - Time to first acute exacerbation
  - Survival

**Coming soon:**
- Peer-reviewed publications
- Teton-1
- Teton-PPF

Teton-2 press release. https://ir.unither.com/~/media/Files/U/United-Therapeutics-IR/documents/press-releases/2025/teton-2-press-release.pdf.

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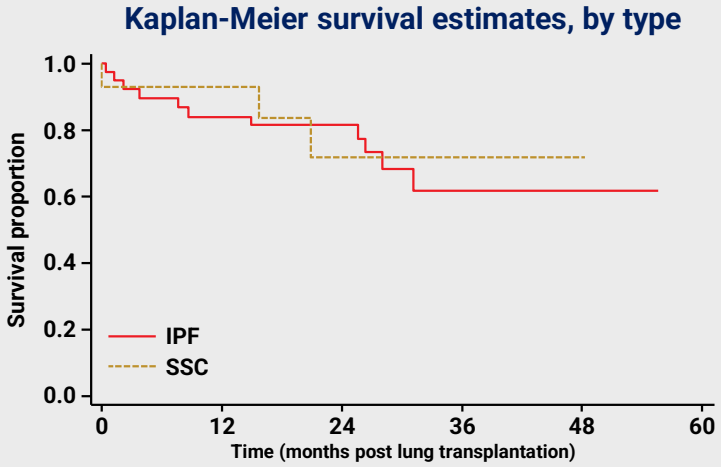
## General Treatment Recommendations for SARD-ILD

- Treatment of comorbidities
  - GERD
  - Pulmonary hypertension
  - Depression
- Supplemental oxygen
- Pulmonary rehabilitation
- Smoking cessation
- Avoidance of environmental triggers
- Vaccinations
- Clinical trials
- Goals of care discussion




Saggar R, et al. *Eur Respir J.* 2010;36:893-900. Johnson SR, et al. *Arthritis Rheumatol.* 2024;76(8):1182-1200.

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## Conclusions

- Work-up for SARDs is an essential component of the evaluation of patients with suspected ILD
- Since interstitial lung disease is a leading cause of morbidity and mortality, clinicians caring for patients with SARDs should be alert for development of ILD
- Pathobiology involves the interplay of disordered fibrotic, immunologic and vascular pathways
- Treatment approaches vary by specific type of SARD and not all patients require treatment
- Fibrosis does not exclude development of pulmonary vasculopathy

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## Thank you!

highlak@ccf.org

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*Clinical Pearls for Rheumatologists: Diagnosing and Managing Fibrosing Interstitial Lung Diseases*

## Toolkit

| Resource | Address |
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