ILD Collaborative

Project ECHO

# Scleroderma-associated ILD: Update on treatment approaches

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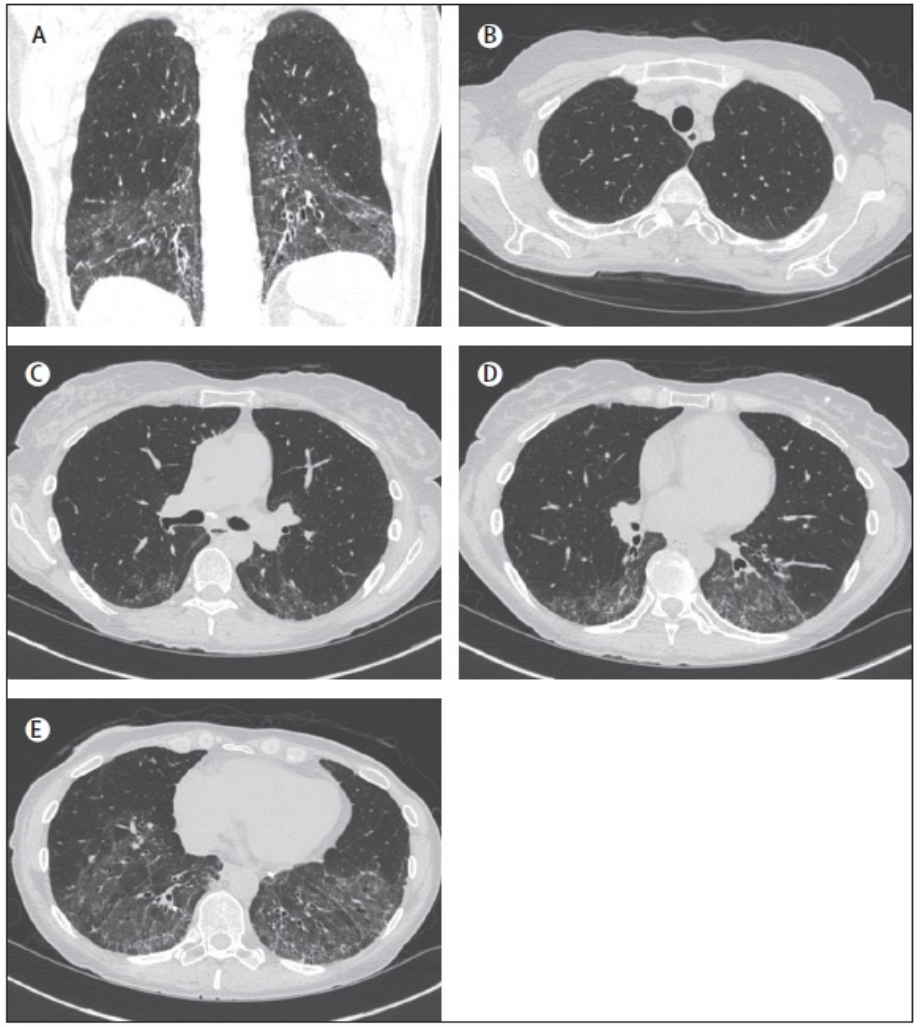
# Disclosures

- Speaking and consulting fees: Boehringer Ingelheim, Genentech, Vicore
- Research trials: Boehringer, Genentech, Galapagos, Hoffmann-La Roche,  Nitto Denko, Vicore
- Authorship fees: UpToDate, Dynamed

# ILD is common in SSc

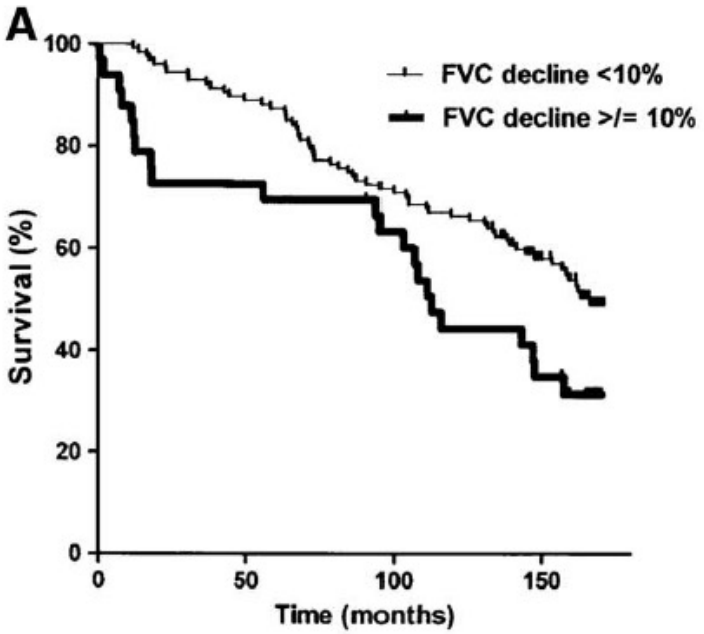
- Seen on CT in up to 80% patients
- Seen on autopsy in up to 90% of patients
- Clinically significant in 30-40% of patients
- 10-year mortality of SSc-ILD up to 40%




Perelas et al. *Lancet Respir Med* 2020;8: 304–20

# ILD is associated with death in SSc

- 162 patients with SSc-ILD
- 12-month PFT trends on 15-year survival
- HR 1.84, p = 0.01




Goh et al. *Arthr & Rheum* Vol. 69, No. 8, Aug 2017, pp 1670–1678

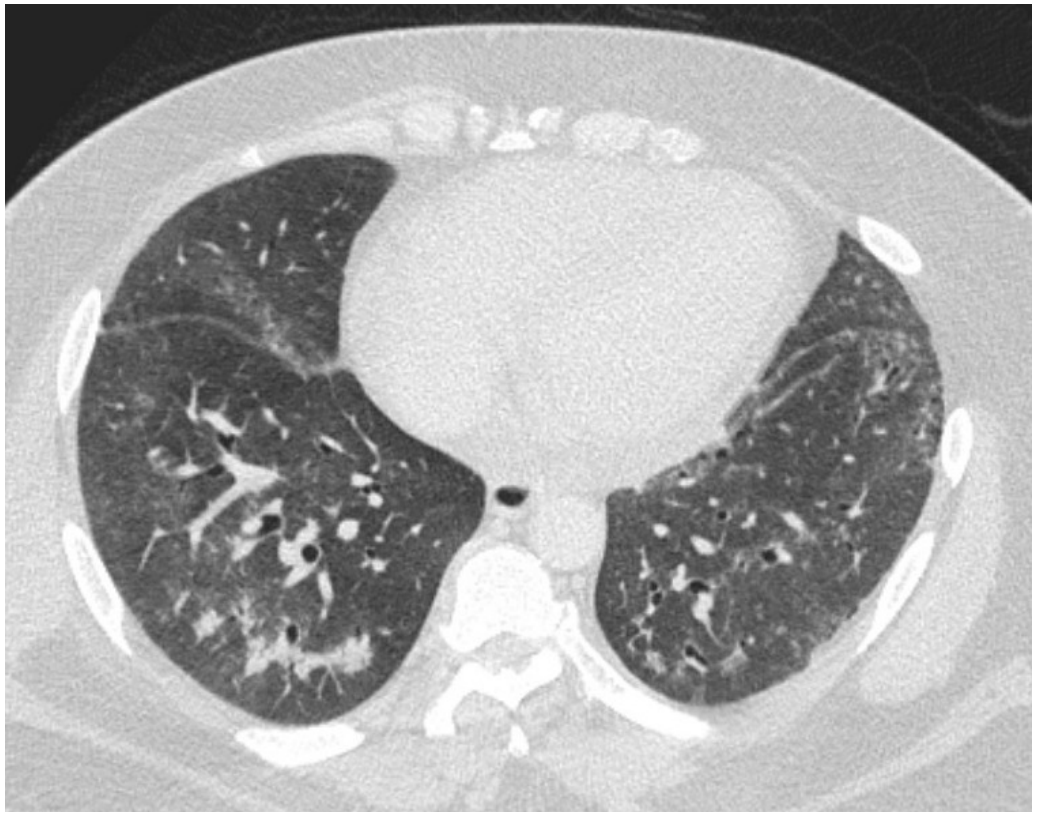
- 5860 SSc patients in the EULAR trials and EUSTAR cohort
- Cause of death analyzed for 234/284 cases
- 33% of deaths attributed to a pulmonary cause; 19% pulmonary fibrosis

**Table 1** Primary causes of death in 234 patients with SSc

| | N | % |
|---|---|---|
| All death cases | 234 | 100 |
| SSc-related death cases | 128 | 55 |
| Pulmonary | 78 | 33 |
| Pulmonary fibrosis | 45 | 19 |
| Isolated PAH | 33 | 14 |
| Myocardial | 33 | 14 |
| Arrhythmia | 14 | 6 |
| Left heart failure | 8 | 3 |
| Right heart failure | 5 | 2 |
| Biventricular heart failure | 4 | 2 |
| Pericarditis (constriction and/or tamponade) | 2 | 1 |
| Renal | 10 | 4 |
| Renal crisis | 10 | 4 |
| Gastrointestinal | 7 | 3 |

Tyndall et al. *Ann Rheum Dis* 2010;69:1809–1815.

# 44 M with diffuse cutaneous SSc
## (+Scl-70, +SSA-52)



# Risk factors for SSc-ILD progression

***Panel 2:*** **Risk factors for systemic sclerosis-associated interstitial lung disease progression**

**Epidemiology**

- Male sex
- Active smoker
- Older age at presentation

**Clinical features**

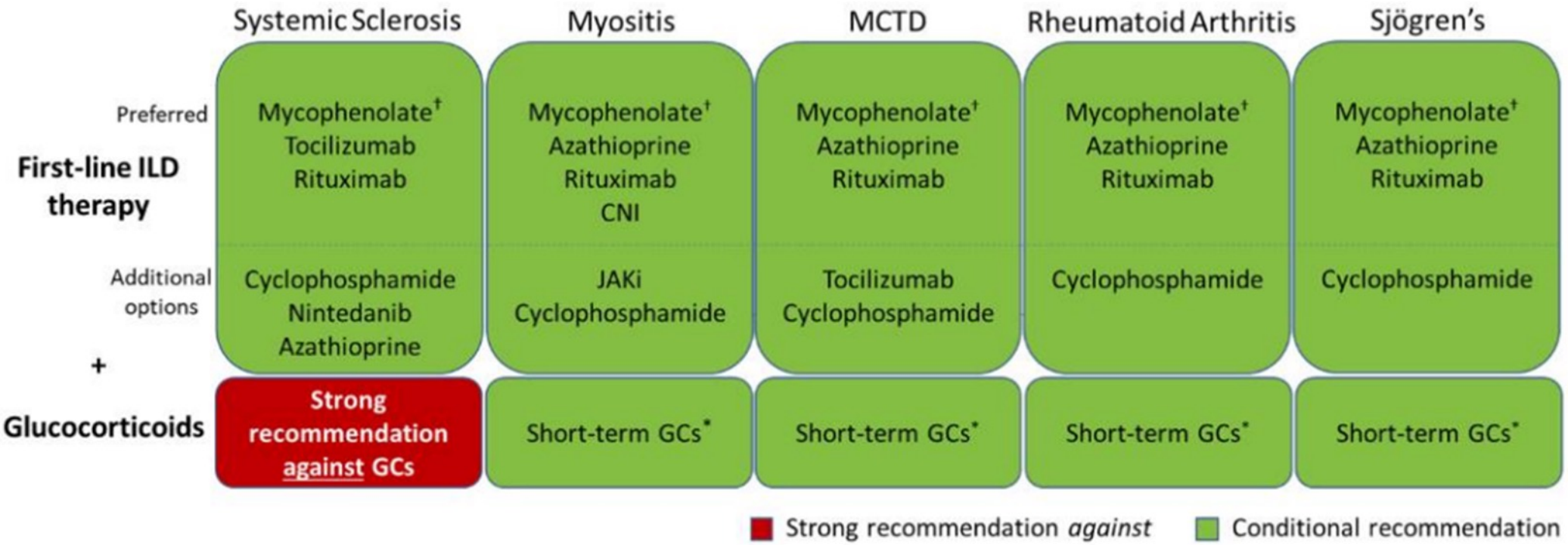
- Digital ulcers
- Arthritis
- Increased oesophageal diameter
- Pulmonary hypertension
- Progressive skin fibrosis
- Renal disease
- Myocardial fibrosis

**Physiology and imaging**

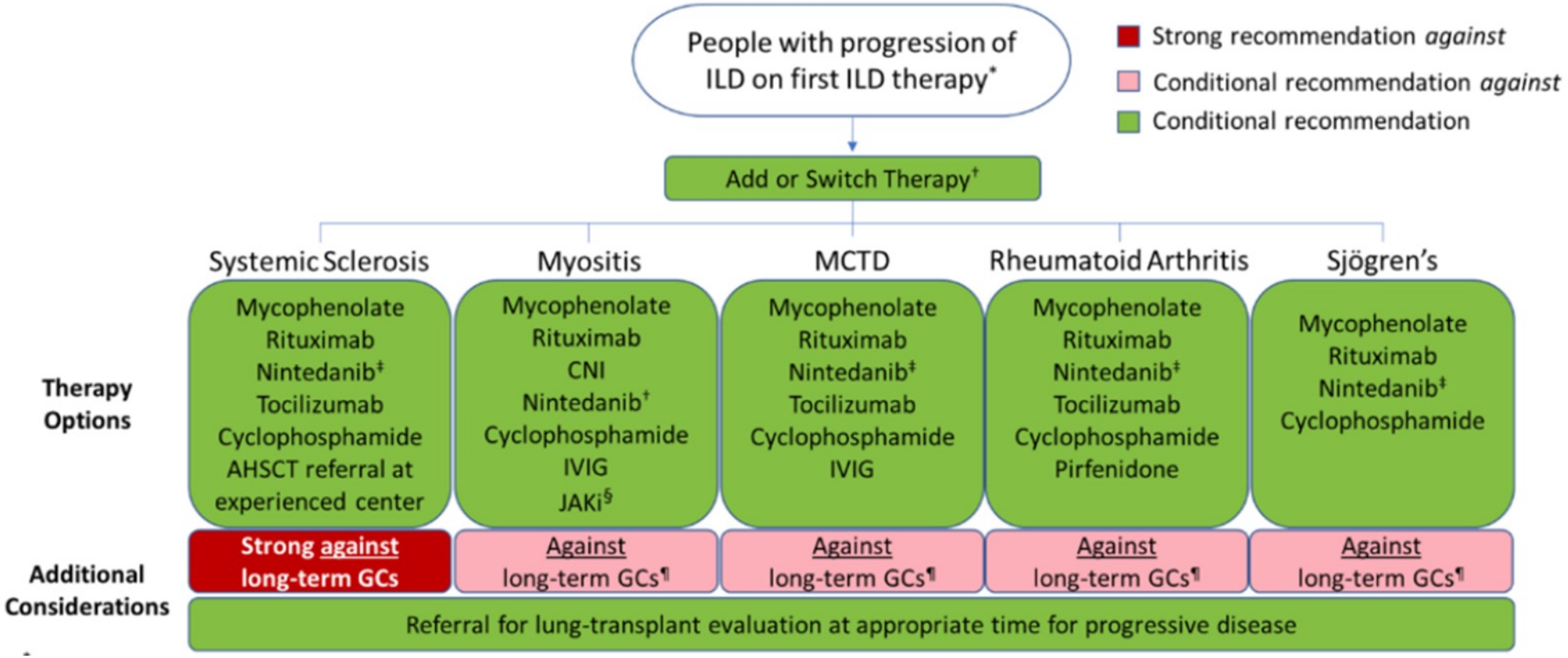
- Forced vital capacity (FVC) decrease of more than 10%
- More than 20% fibrosis on high-resolution CT
- Pulmonary artery-to-aorta ratio of more than 1:1
- FVC decrease of 5–9% with decrease in diffusing capacity for carbon monoxide of more than 15%
- Usual interstitial pneumonia pattern

**Novel Biomarkers**

- Fractional excretion of nitric oxide
- Interleukin 10
- Carbohydrate antigen 15·3
- C-reactive protein
- Monocyte chemoattractant protein 1



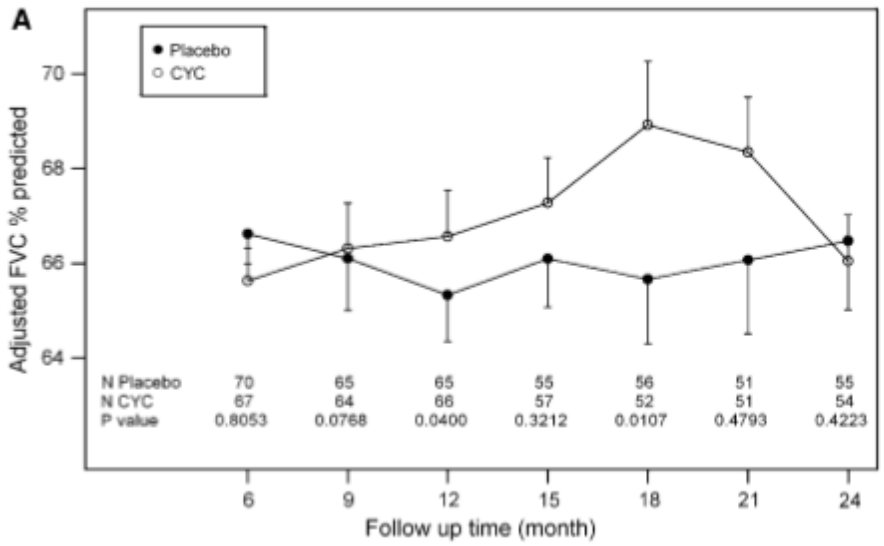

- For people with SARD-ILD, we conditionally recommend against leflunomide, methotrexate, TNFi, and abatacept as first-line ILD treatment options.


People with progression of ILD on first ILD therapy*
Strong recommendation against
Conditional recommendation against
Conditional recommendation
Add or Switch Therapy†
Systemic Sclerosis
Myositis
MCTD
Rheumatoid Arthritis
Sjögren's
Therapy Options
Mycophenolate
Rituximab
Nintedanib‡
Tocilizumab
Cyclophosphamide
AHSCT referral at experienced center
Mycophenolate
Rituximab
CNI
Nintedanib†
Cyclophosphamide
IVIG
JAKi§
Mycophenolate
Rituximab
Nintedanib‡
Tocilizumab
Cyclophosphamide
IVIG
Mycophenolate
Rituximab
Nintedanib‡
Tocilizumab
Cyclophosphamide
Pirfenidone
Mycophenolate
Rituximab
Nintedanib‡
Cyclophosphamide
Additional Considerations
Strong against long-term GCs
Against long-term GCs¶
Against long-term GCs¶
Against long-term GCs¶
Against long-term GCs¶
Referral for lung-transplant evaluation at appropriate time for progressive disease

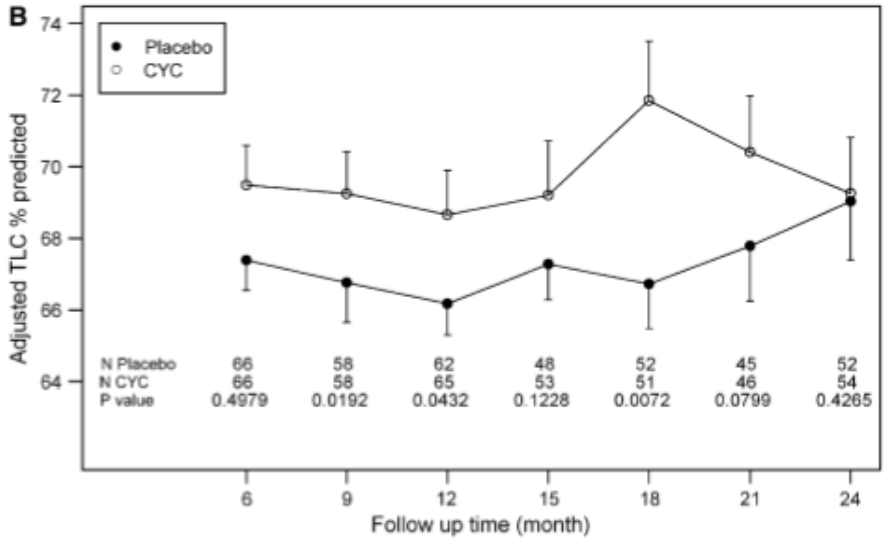
# Scleroderma Lung Study 1

158 patients with inflammatory SSc-ILD
Randomized, double-blind, placebo-controlled trial
Oral cyclophosphamide vs placebo for one year

FVC



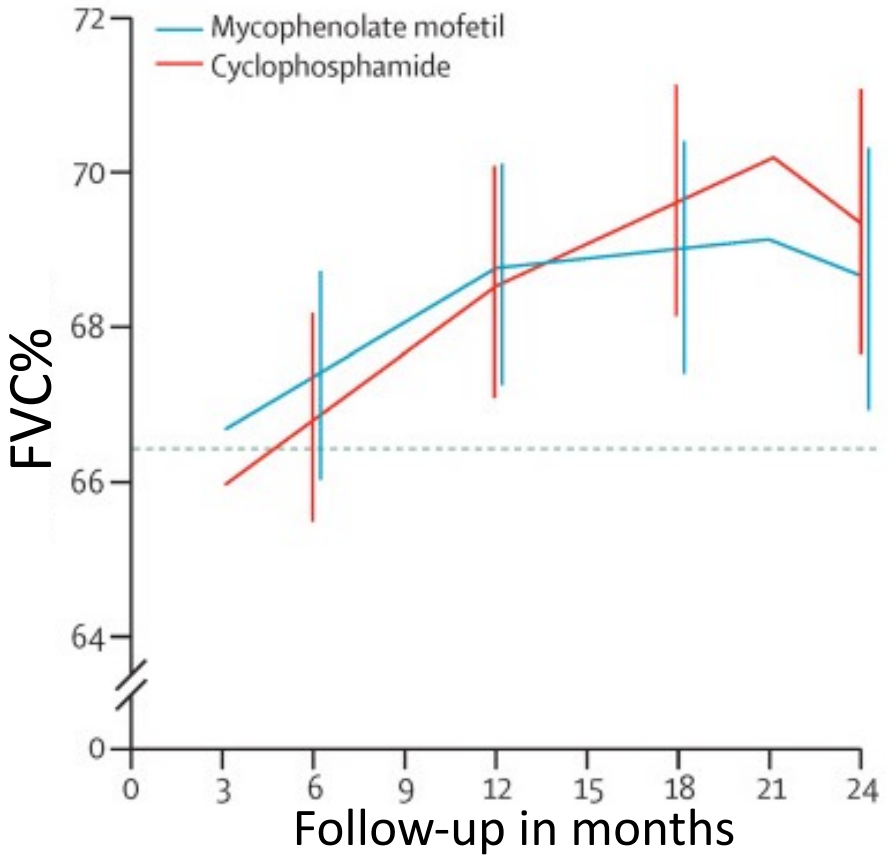

TLC




CYC is better than placebo at 12 months, but the effects wane after 18 months
Adverse events: hematuria, leukopenia, neutropenia

# Scleroderma Lung Study 2

MMF (target dose 1500 mg twice daily) for 24 mo (63 pts)
Oral CYC (target dose 2.0 mg/kg/day) for 12 months, then placebo 12 mo (63 pts)




Also equal in both:

*Skin score*
*Dyspnea*
*HRCT scores*

More AE with CYC:

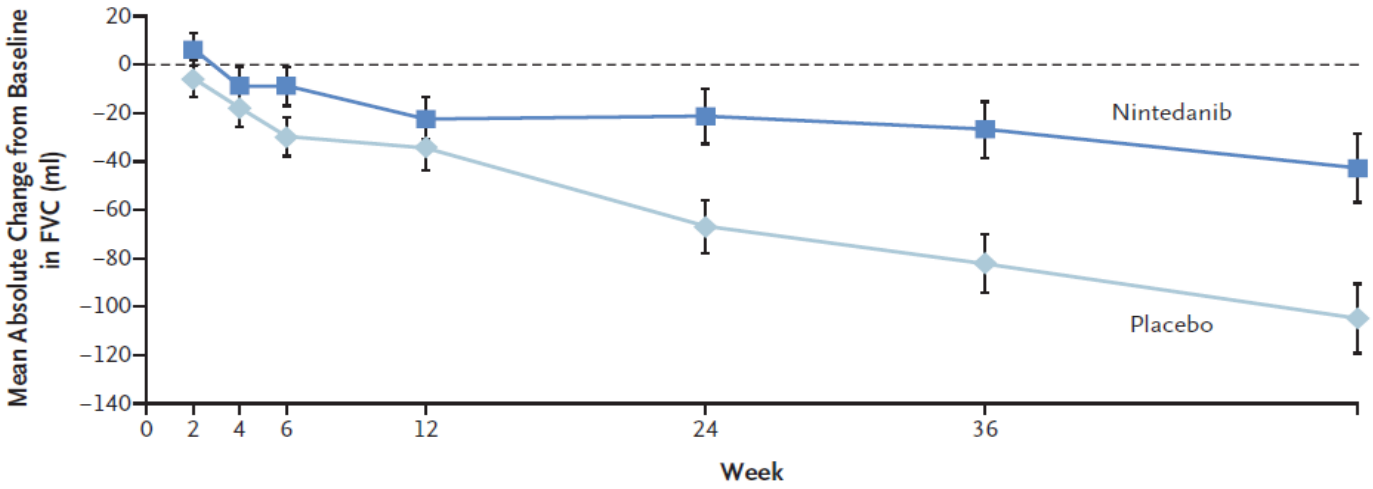
Leukopenia, anemia, thrombocytopenia.

More withdrew early

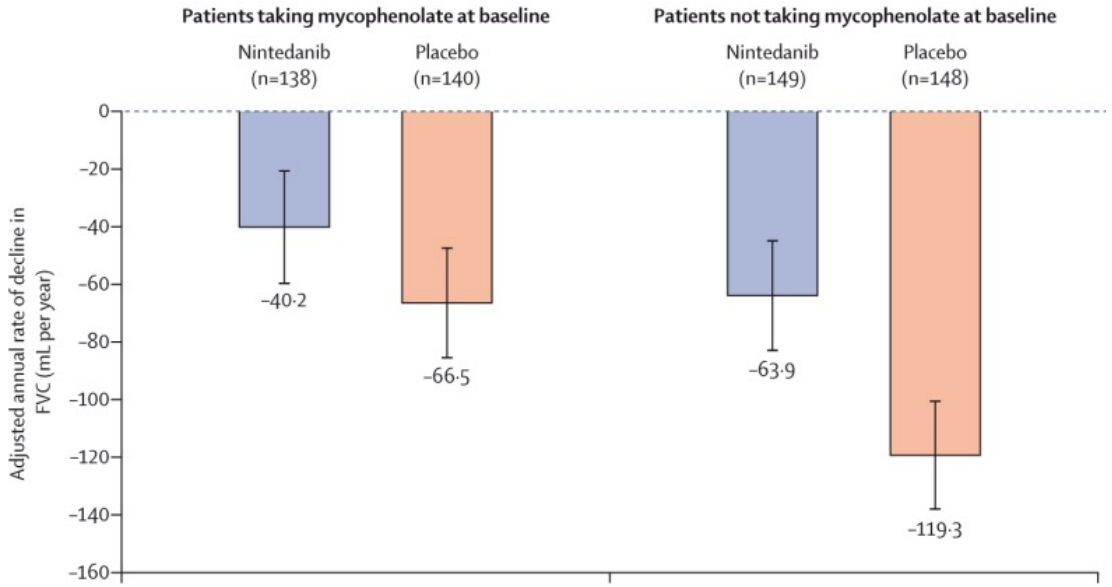
from CYC or failed (34 vs 20)

Tashkin et al. *Lancet Respir Med*. 2016 September ; 4(9): 708–719.

# SENSCIS: Nintedanib for SSc-ILD




- 288 nintedanib; 288 placebo over 52 weeks
- 48.4% were receiving MMF at baseline





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

# FocuSSced: Tocilizumab for SSc-ILD

Phase 3 study of diffuse cutaneous SSc

New active disease and elevated inflammatory markers

≈66% diagnosed with ILD at baseline

210 patients: Toci 162 sc weekly or placebo

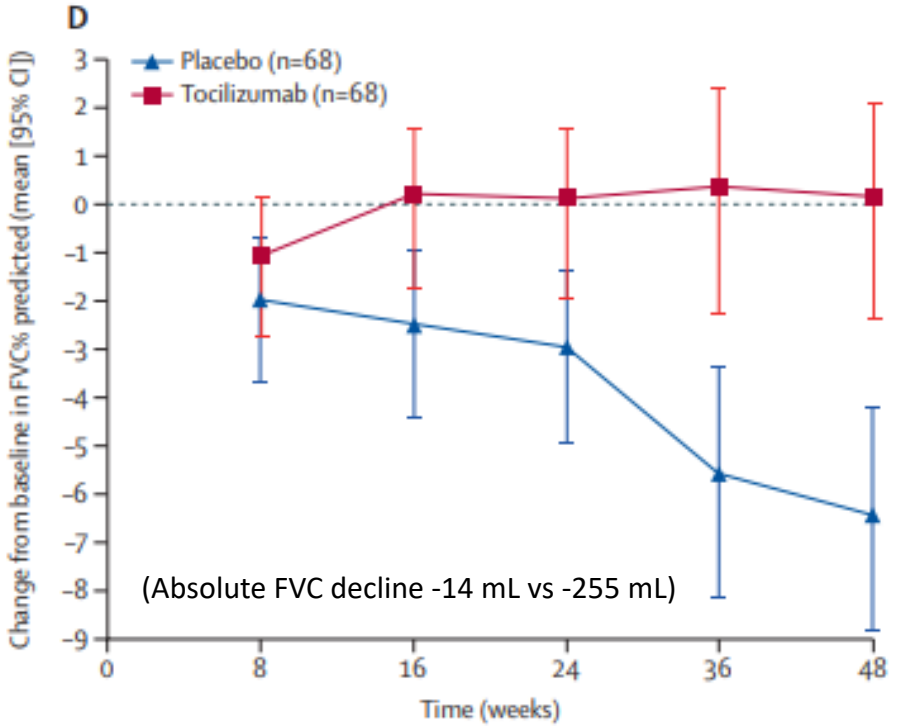
Primary endpoint (change in mRSS) not met

**Absolute FVC decline of at least 10%:**

**Placebo 17%**

**Toci 5%**

FVC Least Sq Mean change



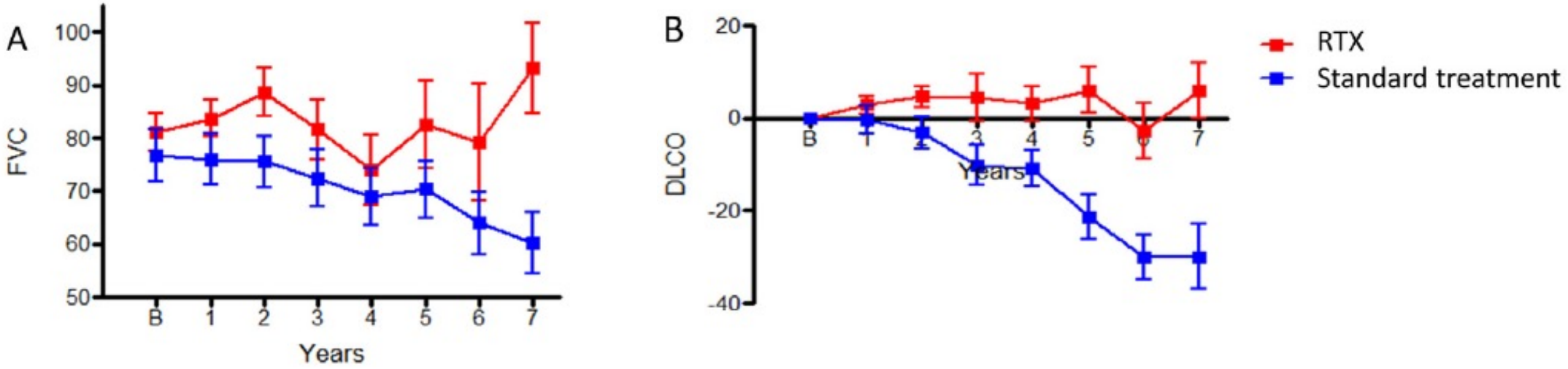
# Comparing the randomized SSc-ILD trials

| **Trial** | **Scleroderma Lung Study 2** (MMF vs CYC) | **SENSCIS** (Nintedanib vs Placebo)* | **FocuSSced** (Tocilizumab vs Placebo) |
|---|---|---|---|
| Mean age (yrs) | 52.3 | 53-54 | **47-49** |
| Median disease duration (yrs) | 2.6 | 3.5 | **1.4-1.5** |
| FVC % predicted | 66.5% | 72-73% | **80-84%** |
| DLCO % predicted | 54% | 53% | **74-77%** |
| Scl-70 positive | 45.5% | 60-62% | 50% |

*48.4% in SENSCIS were receiving MMF at baseline

# Rituximab for SSc-ILD

51 patients with SSc-ILD
- 33 rituximab
- 18 conventional therapy (MMF 10, MTX 6, or AZA 2)
- Followed a median of 4 years



# Rituximab for SSc-ILD

3 randomized controlled trials (90 patients)

7 non-randomized controlled trials (128 patients) were included

5 studies demonstrated statistically significant improvement in FVC at some time during follow-up

Meta-analysis of 3 RCT showed a positive effect of RTX on FVC in SSc-ILD

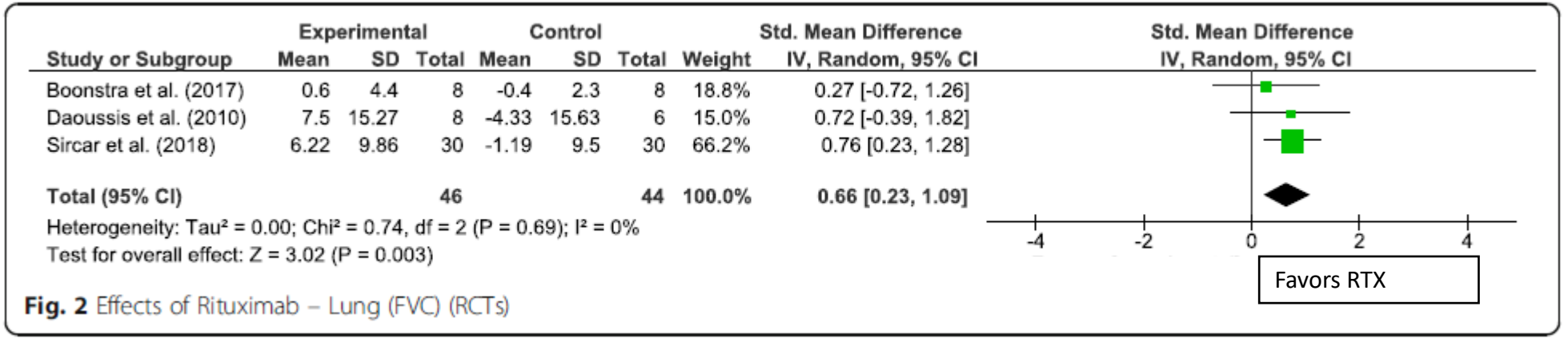
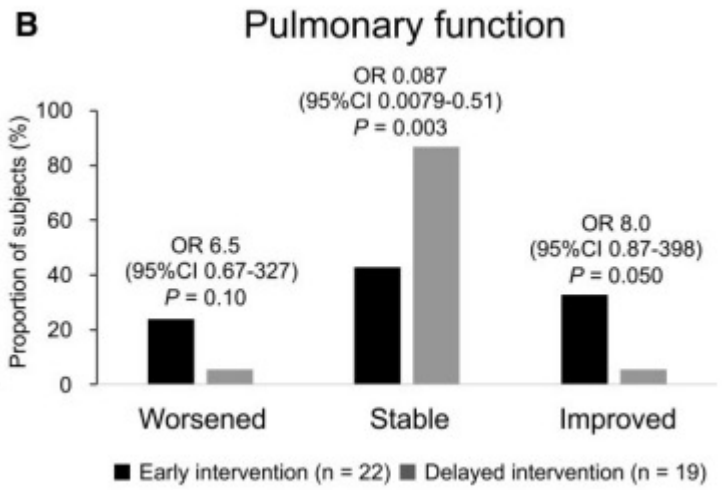
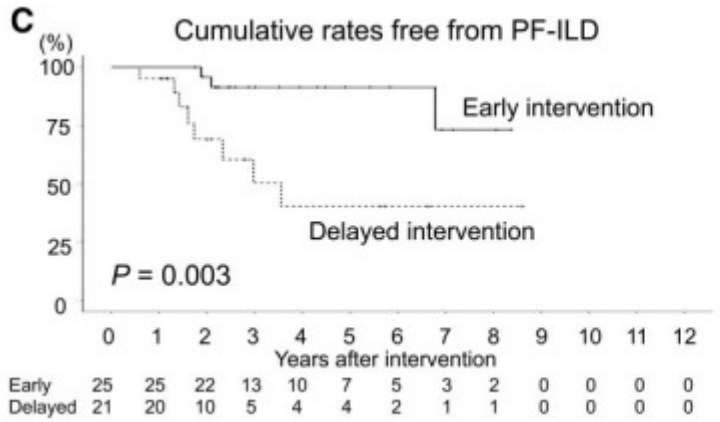


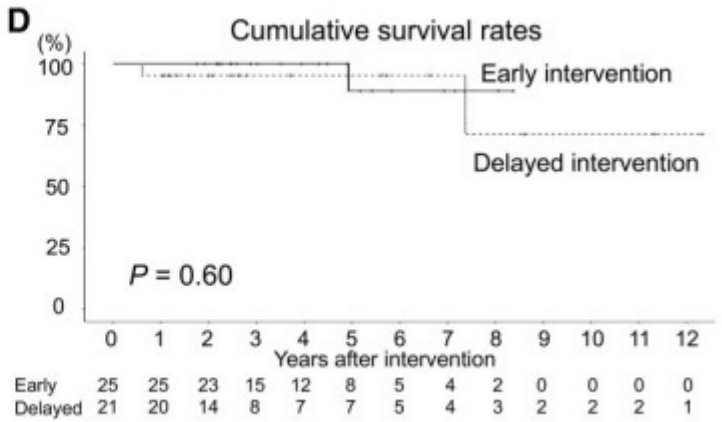

**Fig. 2** Effects of Rituximab – Lung (FVC) (RCTs)

# Treating Scl-ILD earlier might be better

- Single-center, retrospective cohort study
- Patients received CYC, MMF, MTX or TOC within 6 years after disease onset.
- Patients divided into early (< 18 months, n=25) and delayed (> 18 months, n=21) intervention groups based on disease duration



# Summary

- ILD is a common complication of SSc and associated with significant morbidity and mortality
- Early treatment of SSc-ILD is recommended, especially in high-risk patients
- Treatment options include mycophenolate, tocilizumab, rituximab, and nintedanib