ILD Collaborative

Project ECHO

Scleroderma-associated ILD: Treatment approaches and challenges

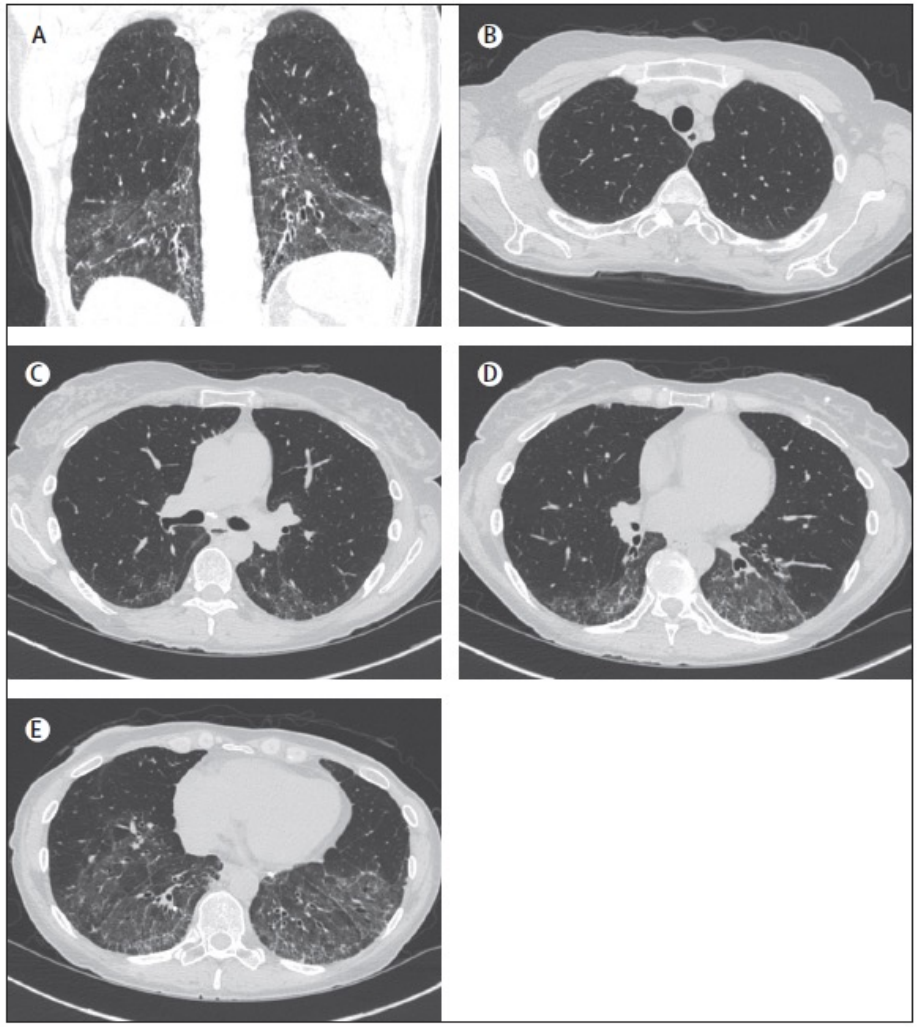
Robert Hallowell, MD

Disclosures

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

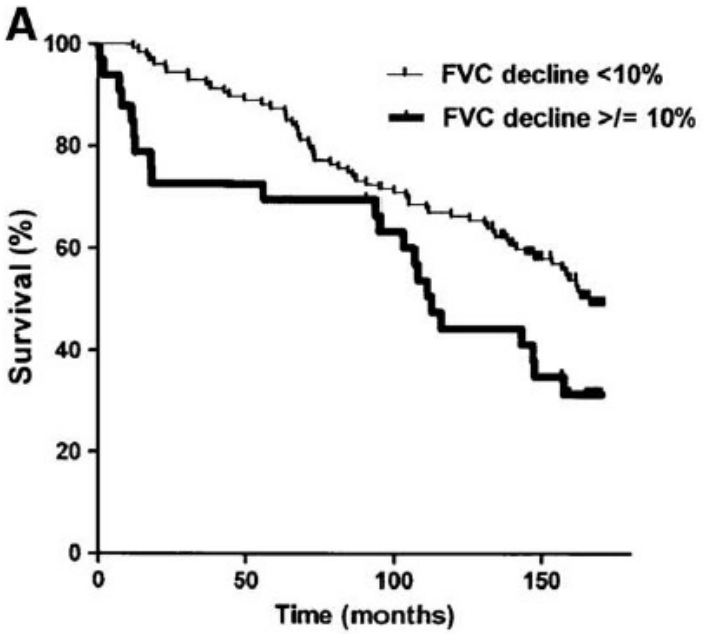
ILD is common in SSc

- 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%



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

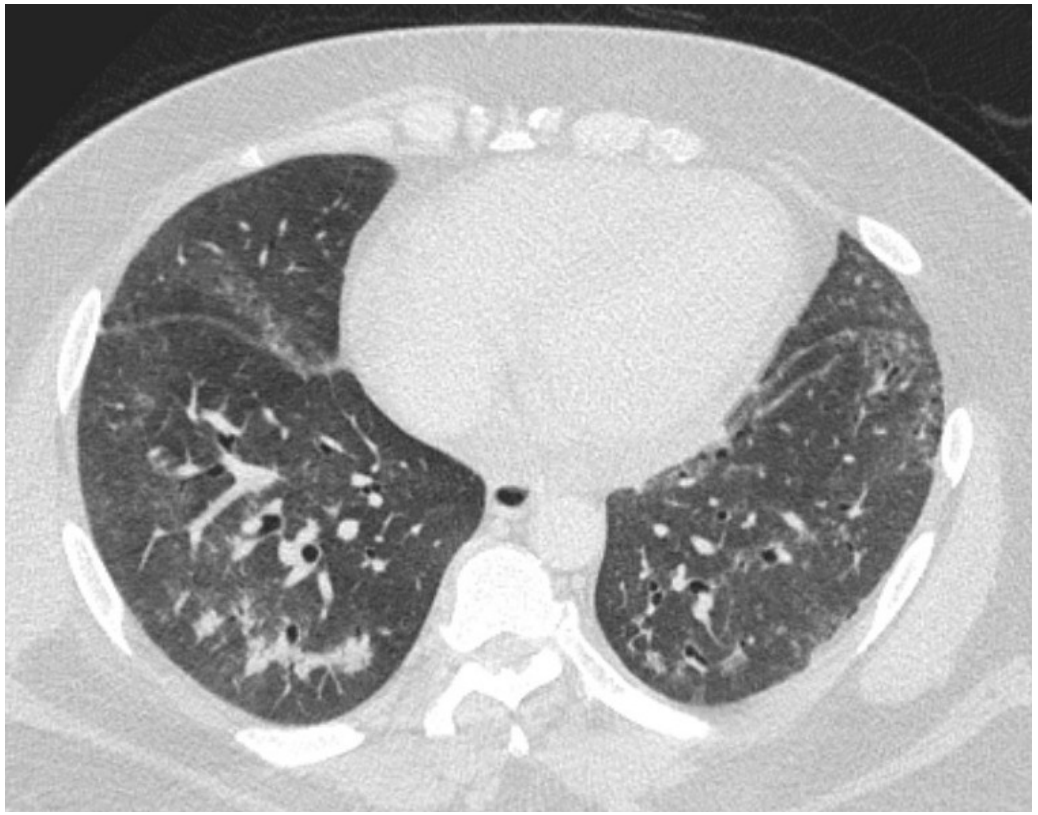
- 5860 SSc patients in the EULAR trials and EUSTAR cohort
- Cause of death analyzed for 234/284 cases
- 33% of deaths attributed to a pulmonary cause; 19% pulmonary fibrosis

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

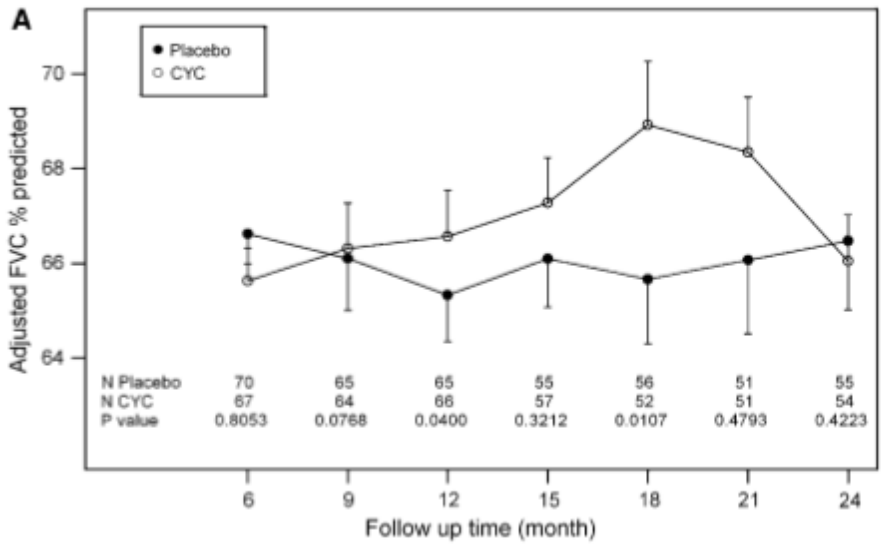
Novel Biomarkers

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

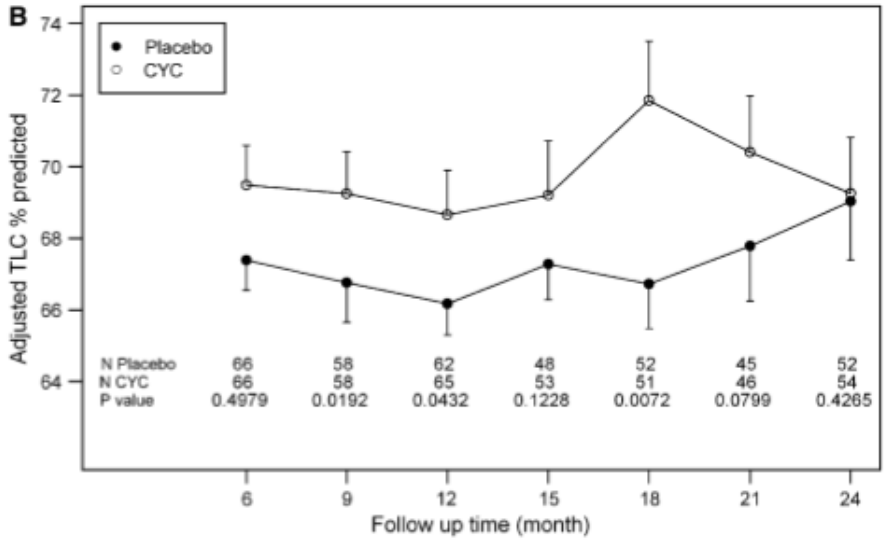
Scleroderma Lung Study 1

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

FVC



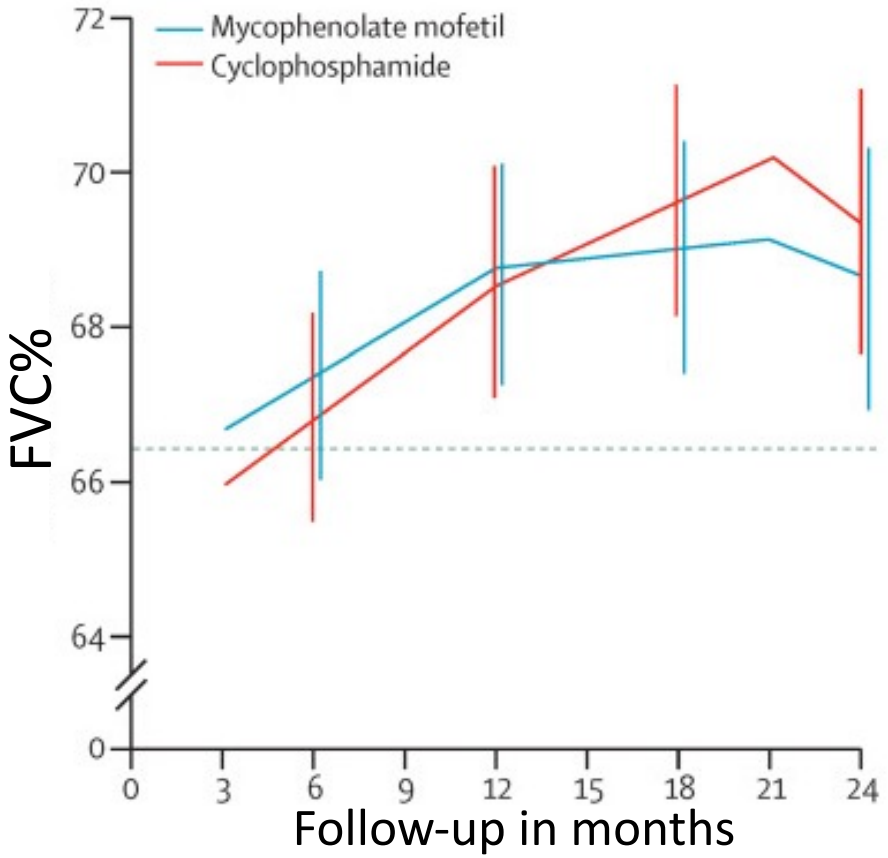
TLC



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:

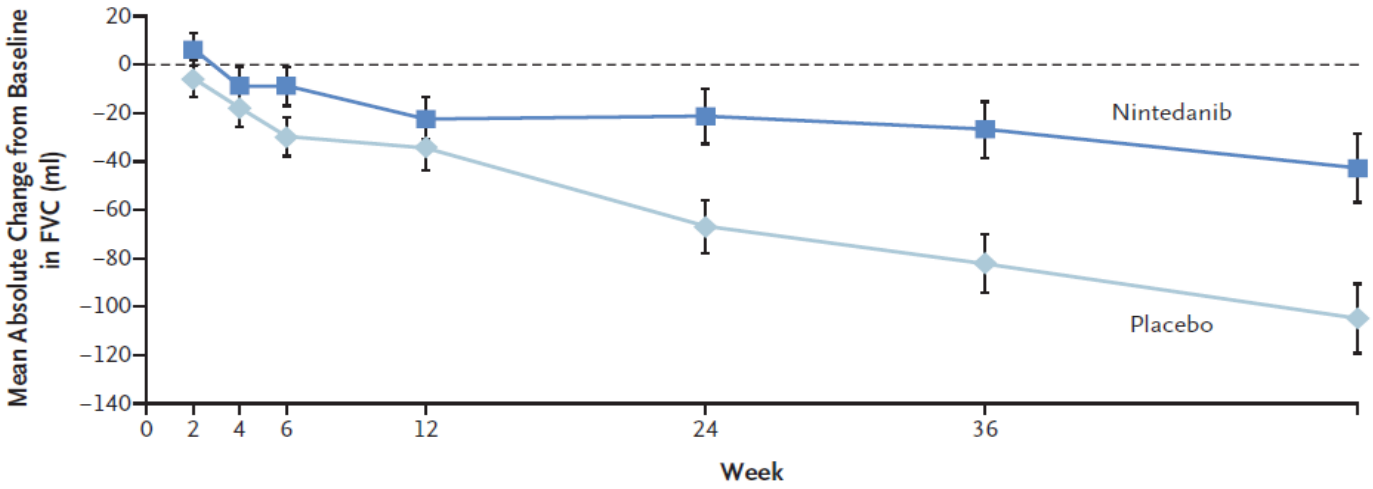
Leukopenia, anemia, thrombocytopenia.

More withdrew early

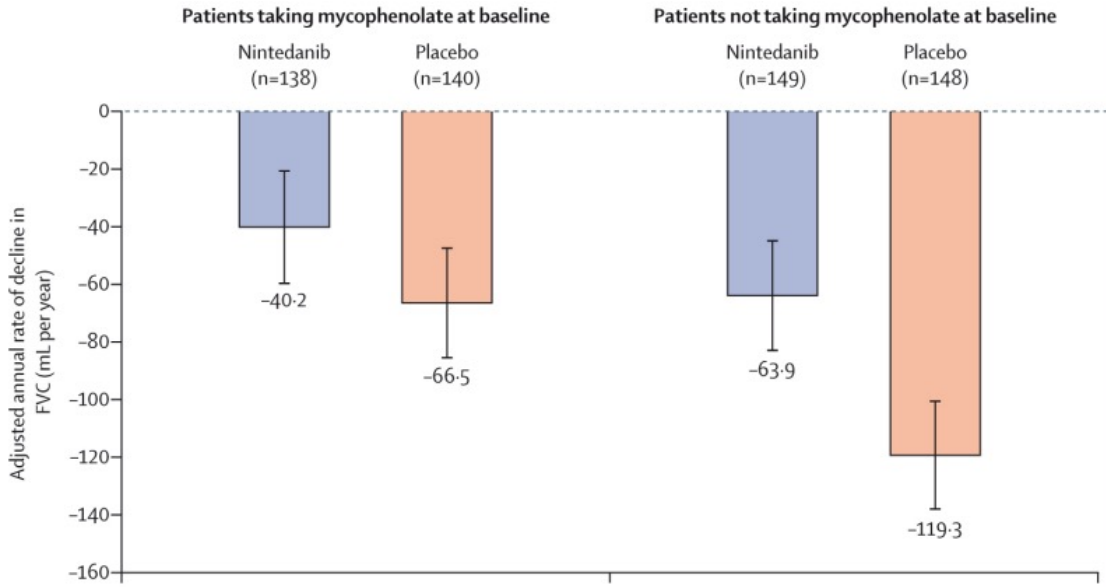
from CYC or failed (34 vs 20)

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

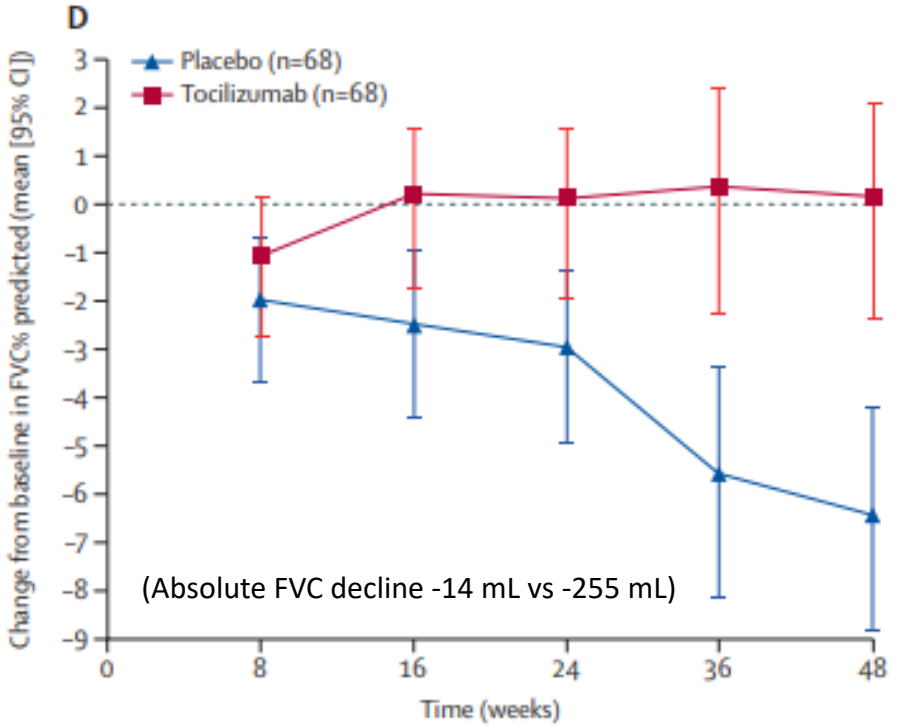
Primary endpoint (change in mRSS) not met

Absolute FVC decline of at least 10%:

Placebo 17%

Toci 5%

FVC Least Sq Mean change



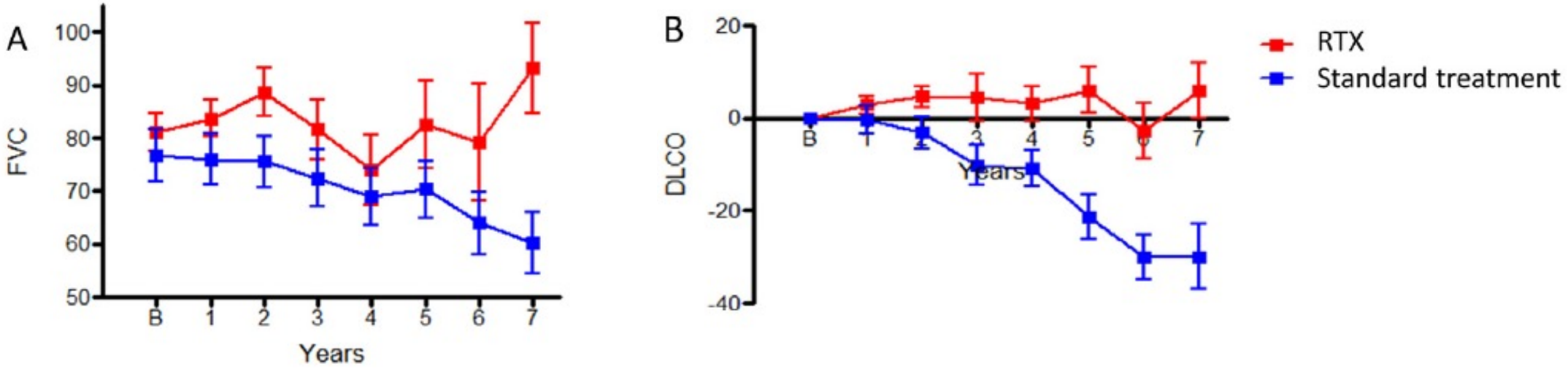
Comparing the randomized SSc-ILD trials

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

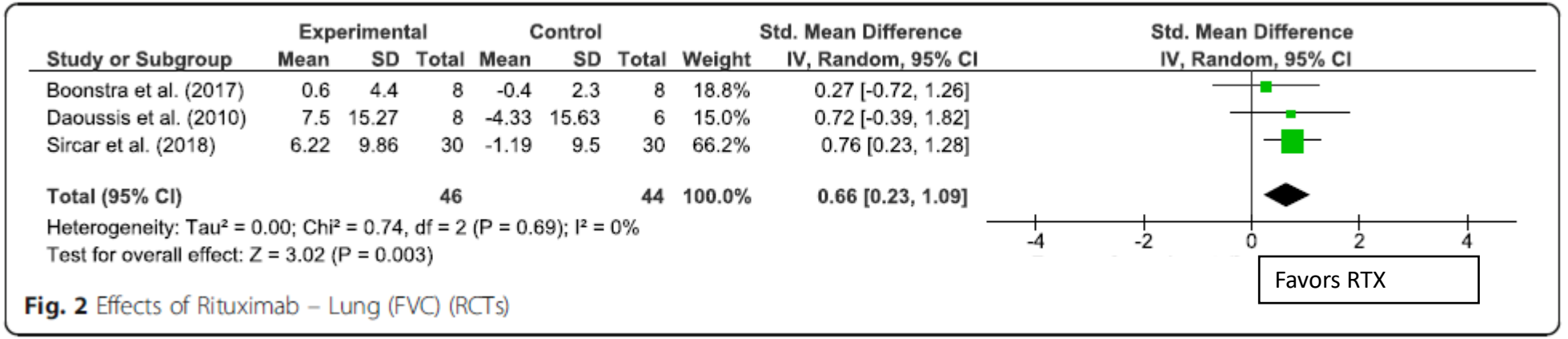
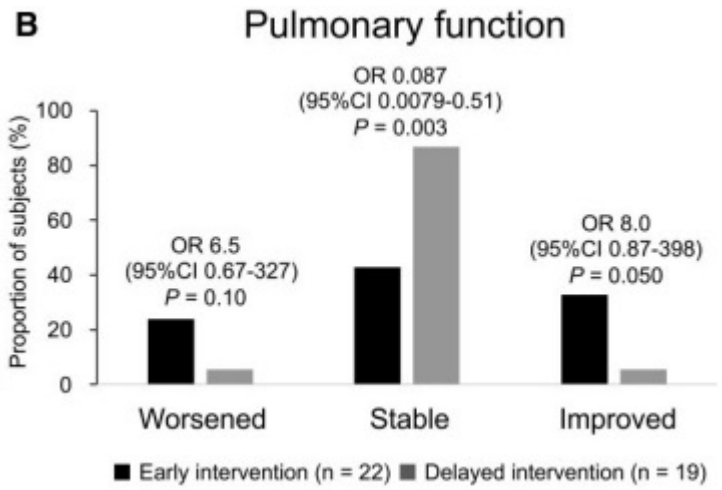
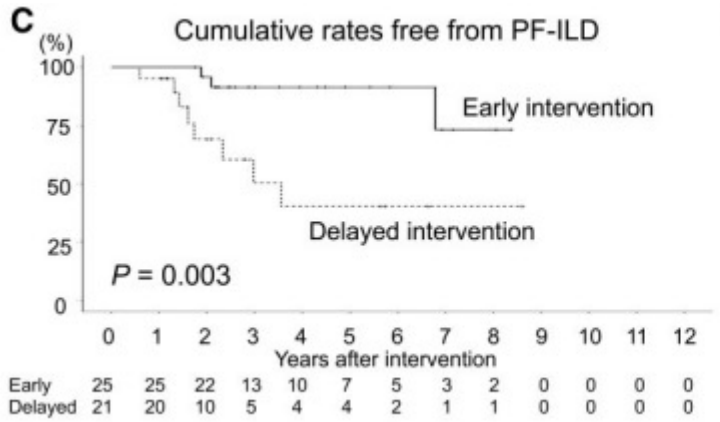


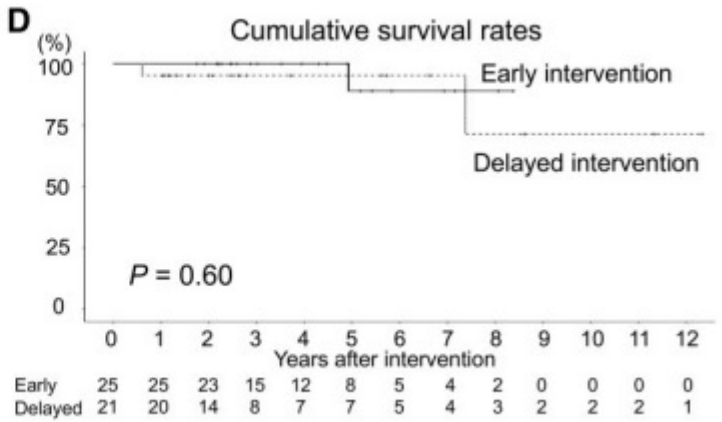
Fig. 2 Effects of Rituximab – Lung (FVC) (RCTs)

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