

Scleroderma-ILD

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Disclosures

- Advisory board fees for Boehringer Ingelheim
- Indirect clinical trial research funding from Boehringer Ingelheim, Daewoong Pharmaceuticals, Pliant Therapeutics, and Avalyn Pharma Inc



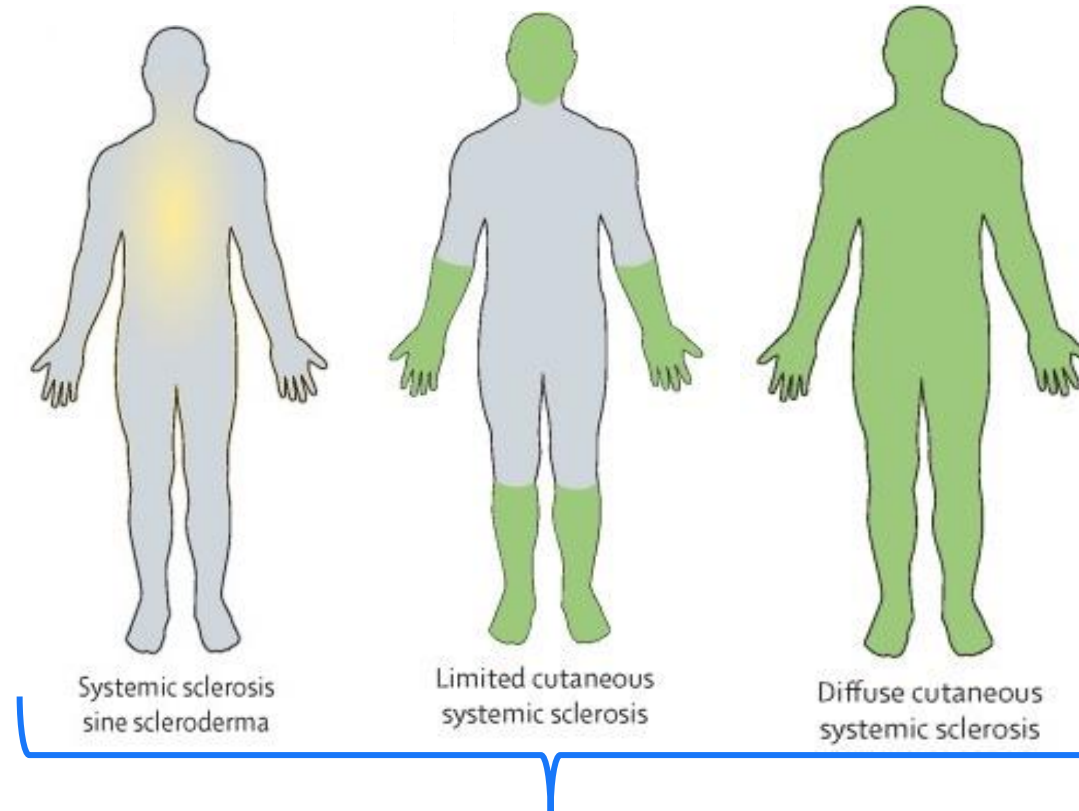
Learning objectives

1. Diagnose SSc-ILD and send appropriate work up
2. Utilize recent guidelines to inform treatment in your clinic



Definitions

- ILD in scleroderma = "systemic sclerosis" or SSc ILD



ILD can occur in any

Lescoat, et al. (2019). *Lancet Rheum.* 1(4):E257

ACR/EULAR criteria for classification of systemic sclerosis

Item	Sub-item(s)	Weight/ score
Skin thickening of the fingers of both hands extending to the MCPs (<i>sufficient criterion</i>)	-	9
Skin thickening of the fingers (<i>only count the higher score</i>)	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the MCP but proximal to the PIP)	4
Fingertip lesions (<i>only count the higher score</i>)	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	-	2
Abnormal nailfold capillaries	-	2
PAH or ILD (<i>max score is 2</i>)	PAH	2
	ILD	2
Raynaud Phenomenon	-	3
SSc-related autoantibodies (<i>max score is 3</i>)	Anticentromere Anti-Scl-70 (anti-topoisomerase) Anti-RNA polymerase III	3

Autoantibodies in scleroderma

Antibody	Frequency	Clinical associations	Organ involvement	Highly specific (>99.5%) 20-50% sensitive
Scl-70 (topoisomerase)	10-40%	Diffuse SSc	ILD > PH	
Centromere	15-40%	Limited SSc	PH, GERD, CREST > ILD	
RNA polymerase III	4-25%	Diffuse SSc	Renal, skin, malignancy, synovitis, myositis	
U3 RNP	<5%	Diffuse SSc	PH, muscle involvement, renal crisis, cardiac involvement	
PM-Scl	4-11%	Overlap syndrome or mixed	Myositis, ILD, sicca, calcinosis, arthritis	
U1 RNP	3-35%	Limited SSc, polymyositis overlaps	Muscle, Raynauds, puffy fingers, arthritis, myositis, MCTD	
Anti-Ku	<3%	Overlap syndrome	Muscle and joint; SLE overlap	
Th/To	1-13%	Limited SSc	ILD	

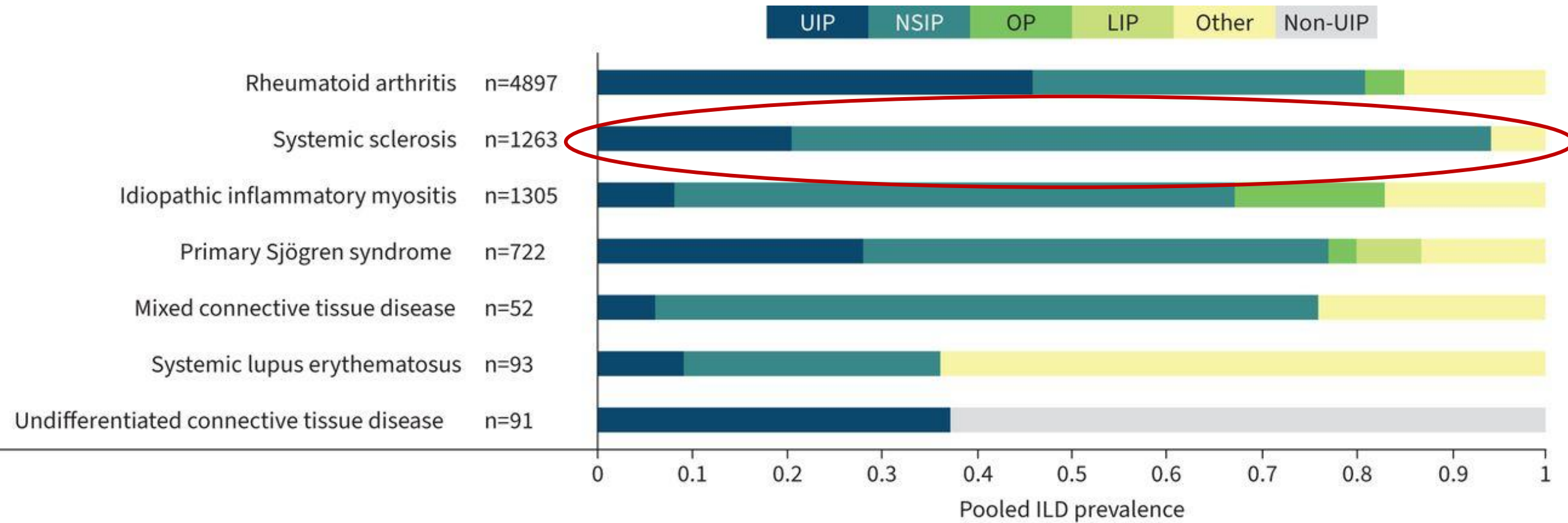


Others not listed: U11/U12, endothelial cell, FBN 1, MMP1 and 3, PDGFR and more

Nihtyanova and Denton. (2010). *Nat Rev Rheumatol*. 6:12
 Kayser et al (2015). *Front Immunol* 6:167



Radiology



Joy, et al. (2023). *Eur Resp Rev.* 32:220210



ILD in scleroderma: common and bad

- 80% with interstitial abnormalities on HRCT
- 90% with lung involvement in autopsy
- 30-40% develop clinical ILD
- 10-year mortality 40%
- Occurs early; < 5 years of first non-Raynaud symptom and almost never > 15 years

5860 SSc patients in the EULAR trials and EUSTAR cohort

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

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2023 American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) Guideline for the Screening and Monitoring of Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Diseases

2023 American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) Guideline for the Treatment of Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Diseases

EULAR recommendations for the treatment of systemic sclerosis: 2023 update

Francesco Del Galdo ^{1,2}, Alain Lescoat ³, Philip G Conaghan ^{1,2},
Eugenia Bertoldo,⁴ Jelena Čolić,⁵ Tânia Santiago ⁶, Yossra A Suliman,^{7,8}
Marco Matucci-Cerinic ⁹, Armando Gabrielli,¹⁰ Oliver Distler ¹¹,
Anna-Maria Hoffmann-Vold ¹², Ivan Castellví ¹³, Alexandra Balbir-Gurman,¹⁴
Madelon Vonk ¹⁵, Lidia Ananyeva,¹⁶ Simona Rednic,¹⁷ Anna Tarasova,¹⁸
Pedrag Ostojic,¹⁹ Vladimira Boyadzhieva,²⁰ Khadija El Aoufy,²¹ Sue Farrington,^{22,23}
Ilaria Galetti,²³ Christopher P Denton ²⁴, Otylia Kowal-Bielecka,²⁵
Ulf Mueller-Ladner,²⁶ Yannick Allanore ²⁷

AMERICAN THORACIC SOCIETY DOCUMENTS

Treatment of Systemic Sclerosis–associated Interstitial Lung Disease: Evidence-based Recommendations An Official American Thoracic Society Clinical Practice Guideline

Ganesh Raghu, Sydney B. Montesi, Richard M. Silver, Tanzib Hossain, Madalina Macrea, Derrick Herman, Hayley Barnes, Ayodeji Adegunsoye, Arata Azuma, Lorinda Chung, Gregory C. Gardner, Kristin B. Highland, Marie Hudson, Robert J. Kaner, Martin Kolb, Mary Beth Scholand, Virginia Steen, Carey C. Thomson, Elizabeth R. Volkmann, Fredrick M. Wigley, Dee Burlile, Karen A. Kemper, Shandra L. Knight, and Marya Ghazipura; on behalf of the American Thoracic Society Assembly on Clinical Problems

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE OF THE AMERICAN THORACIC SOCIETY WAS APPROVED MAY 2023

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Systemic Sclerosis–Associated Interstitial Lung Disease

Treatment Recommendations

ATS guidelines

**STRONG
IN FAVOR**

Mycophenolate

**CONDITIONAL
IN FAVOR**

Cyclophosphamide

Rituximab

Tocilizumab

Nintedanib

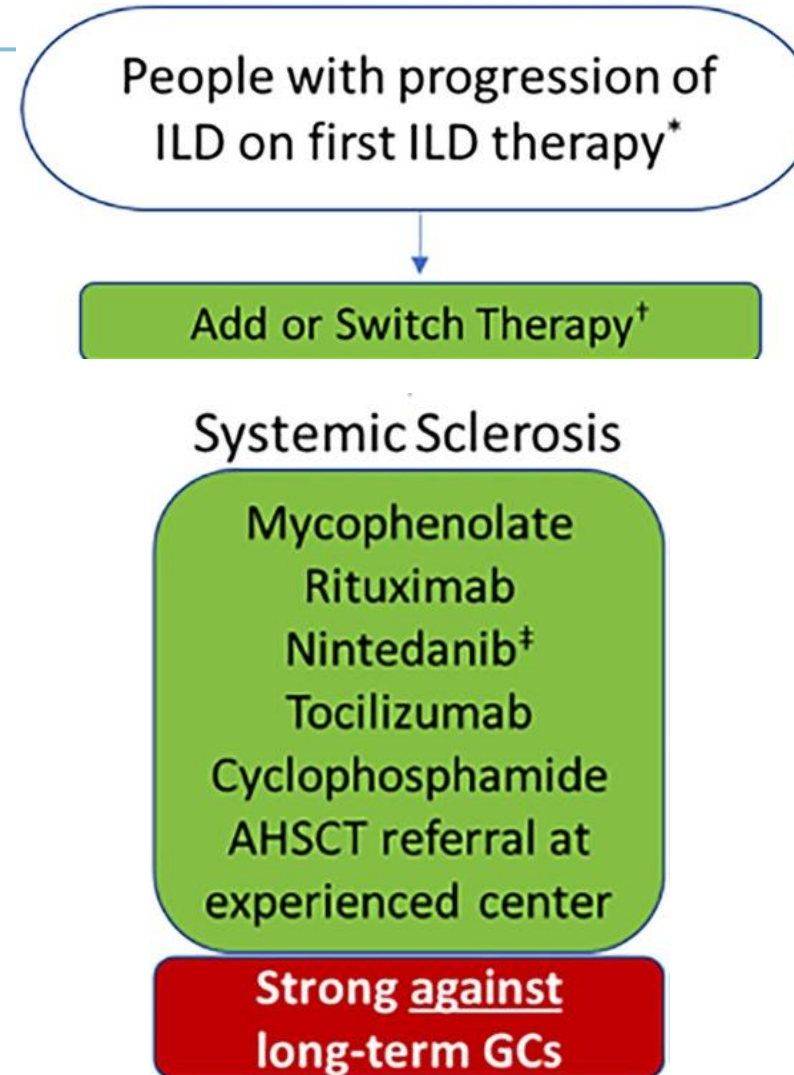
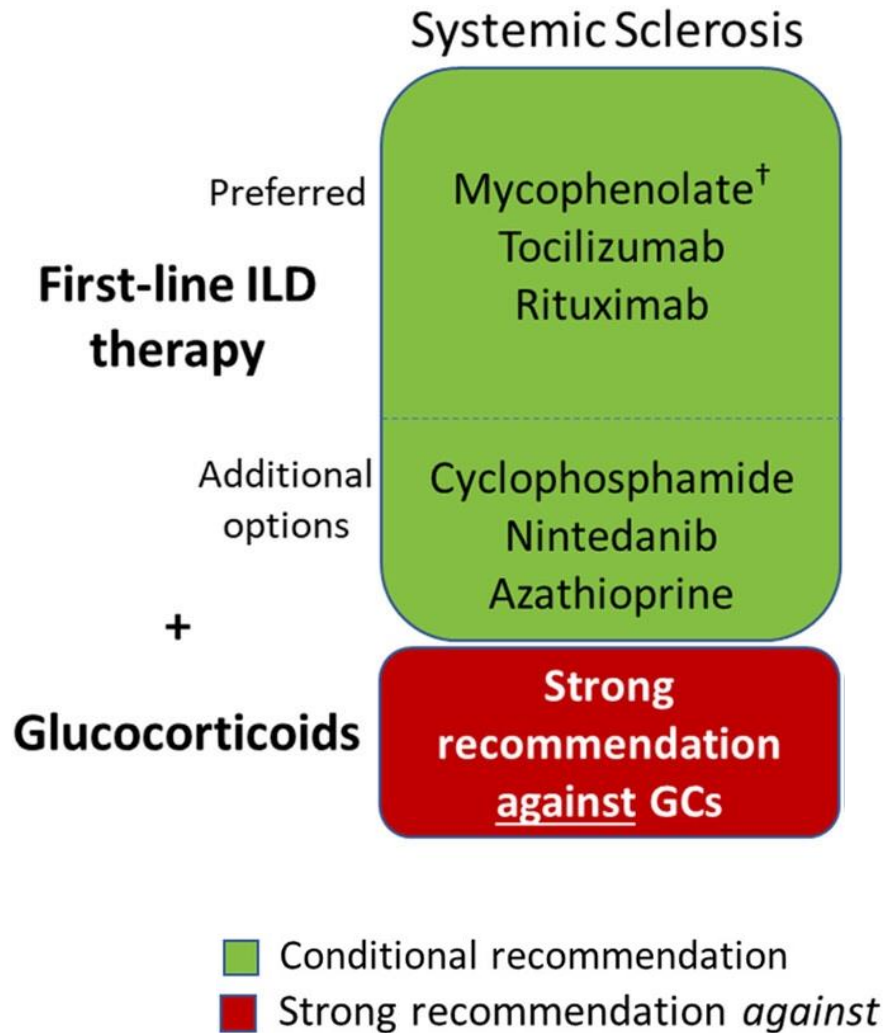
Nintedanib plus
Mycophenolate

**RESEARCH
RECOMMENDATION**

Pirfenidone

Pirfenidone plus
Mycophenolate

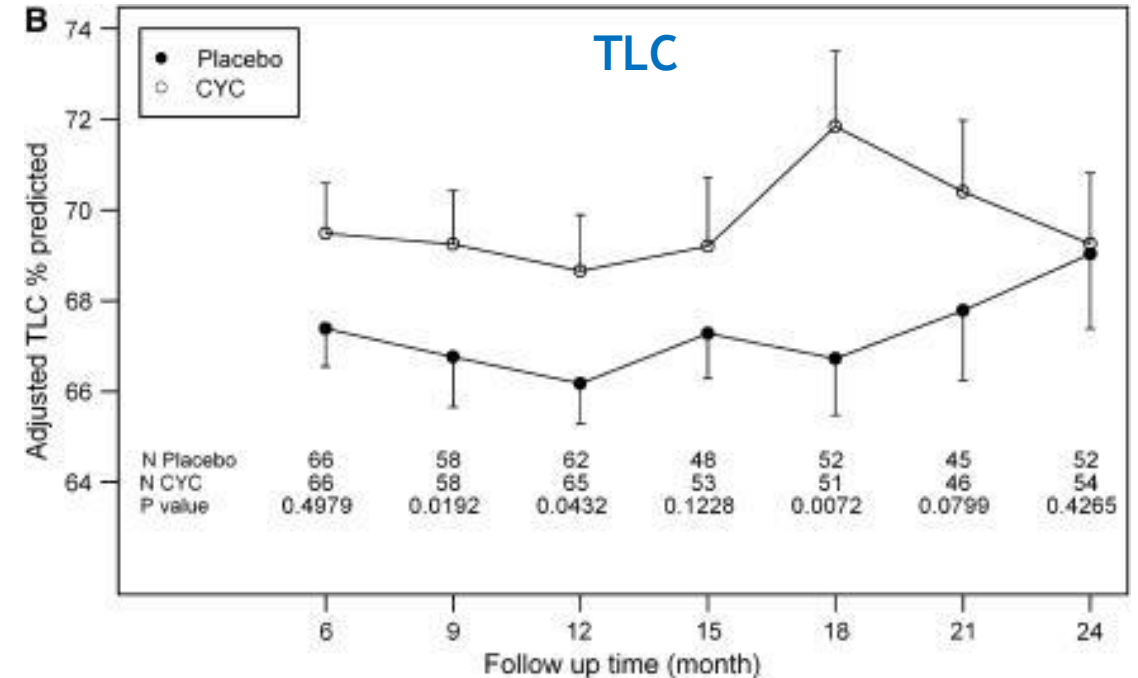
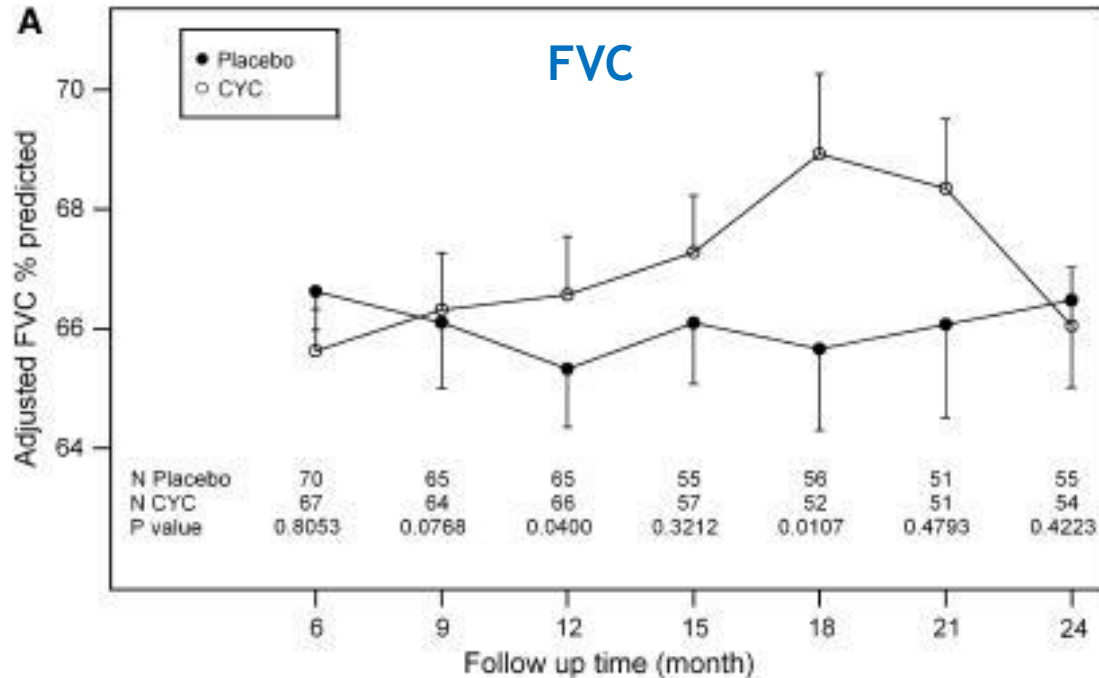
ACR/CHEST guidelines



Johnson et al. (2024). *Arthritis Rheumatol.* 76(8): 1051



Cyclophosphamide (CYC)

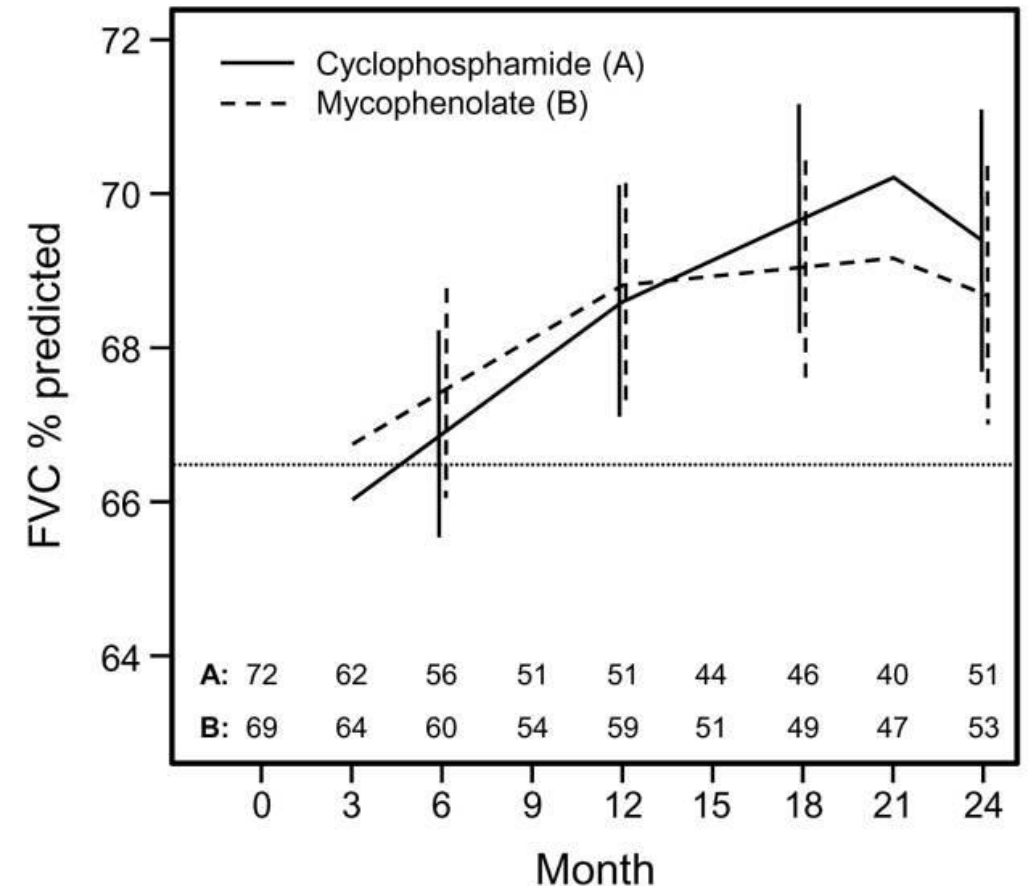


SLS I: 158 patients with inflammatory SSc-ILD; RCT double blind placebo-controlled trial
PO CYC vs placebo x1 year
CYC better than placebo (FVC, TLC, not DLCO) at 12 months but effects wane after 18 months
AE: hematuria, leukopenia, neutropenia

Mycophenolate

SLS II

- PO CYC (2 mg/kg/d) x12 months then placebo x12 months (63 pts) vs MMF (1500 BID) for 24 months (63 pts)
- No difference in FVC or DLCO, dyspnea, skin score, HRCT score
- More adverse events with CYC
- More withdrew CYC arm early



Tashkin, *et al.* (2016). *Lancet Respir Med.* 4(9):708



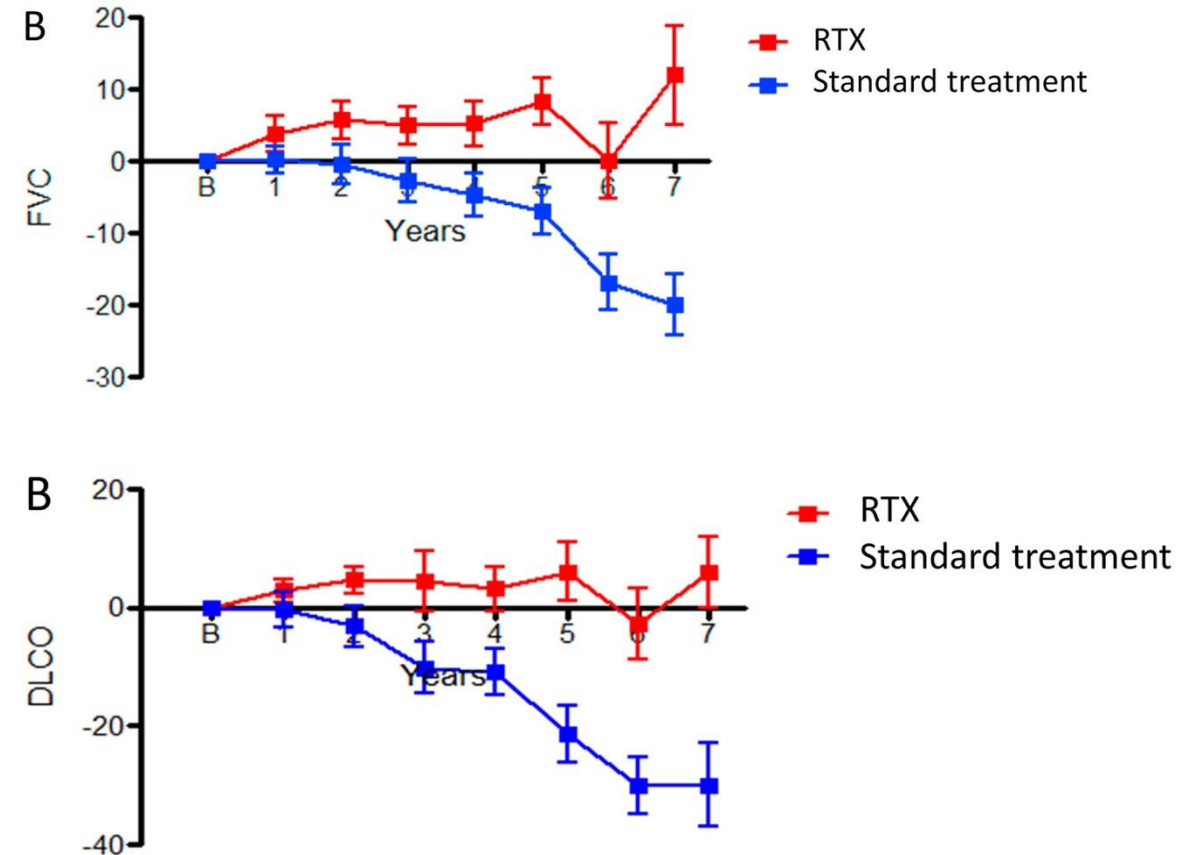
Rituximab

- 3 RCTs: 2 without *a priori* confirmation of ILD
- Small, underpowered studies
- Range of dosing and duration
- Meta-analysis: rituximab attenuated decline in FVC % predicted; varied DLCO effect
- No mortality* or QoL benefit; improved skin scores *24 weeks
- Well tolerated vs placebo



Rituximab

- SSc-ILD (51 pts): 33 ritux; 18 with conventional therapy (MMF, MTX, AZA)
- Median 4 years follow up
- Improved relative FVC and DLCO

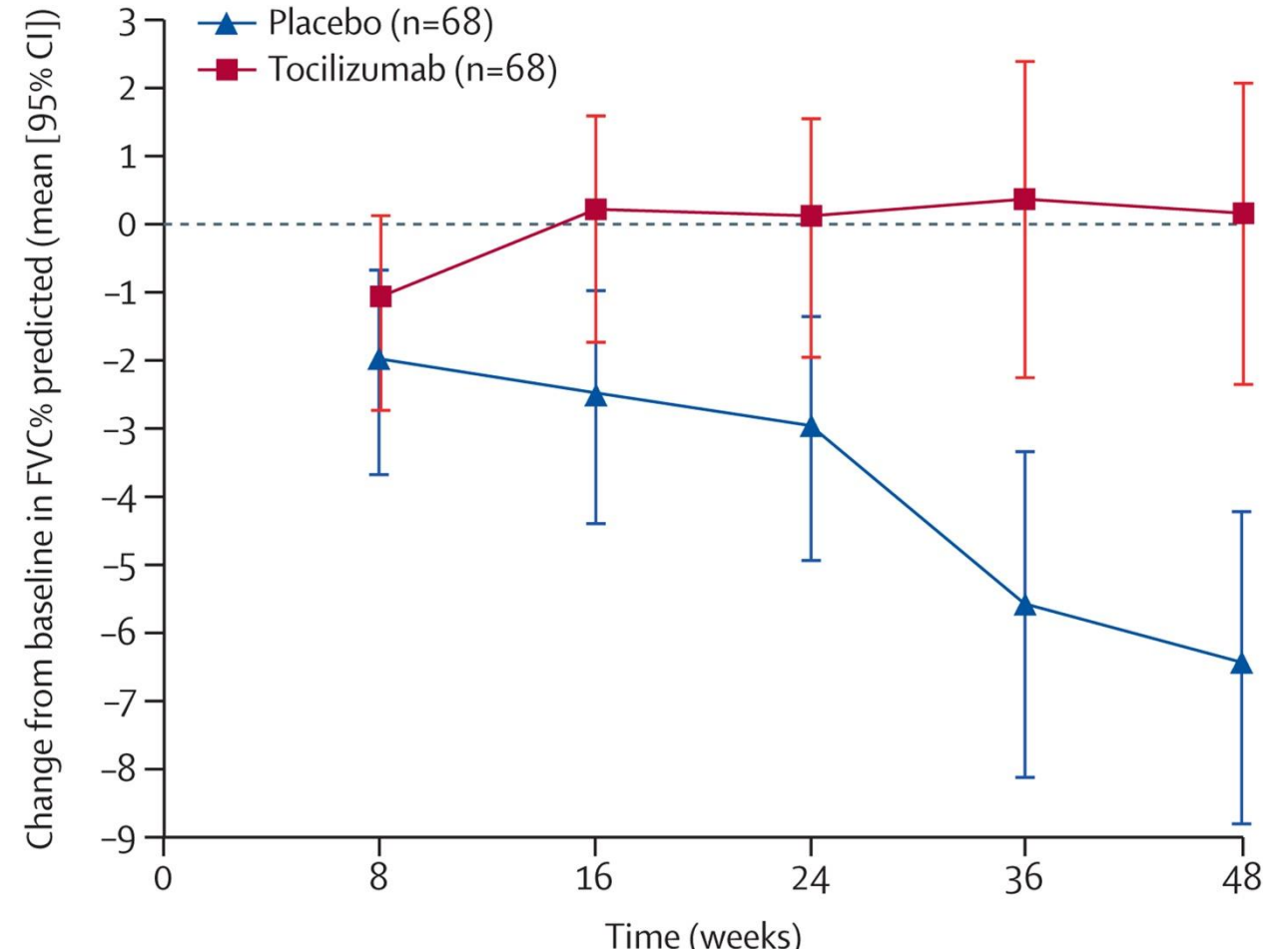


Daoussis et al. (2017). *Semin Arth Rheum.* 46(5):625



Tocilizumab

- FaSSciate (phase II) + focuSSced (phase III)
- Diffuse SSc with new active disease, elevated inflammatory markers
- 65% with ILD at baseline, baseline FVC ~80%; DLCO ~75%
- Change in mRSS was primary outcome (not met)
- Mean change in FVC from baseline at 48 weeks:
 - -14 mL with tocilizumab vs -255 mL with placebo



Khanna et al. (2020). *Lancet Respir Med.* 8:963-74

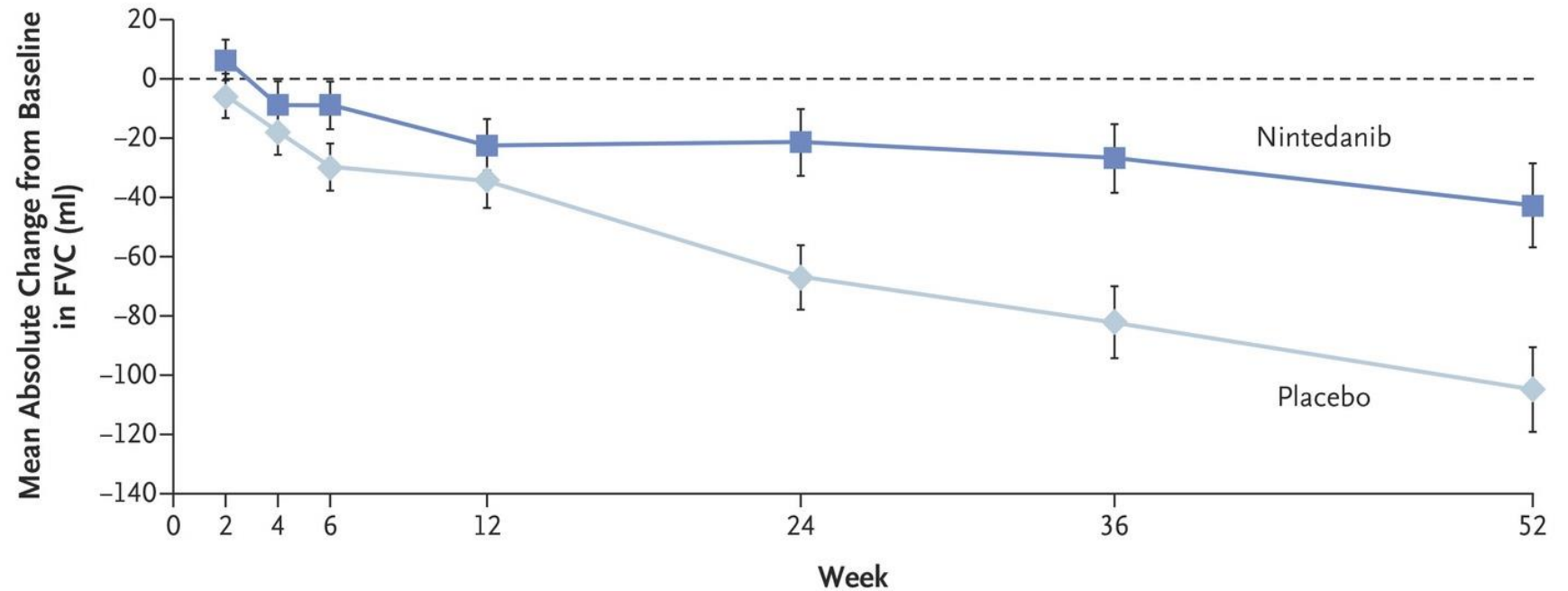


Antifibrotics in SSc-ILD



Nintedanib

SENSCIS: phase III,
576 subjects with
SSc-ILD; background
MMF allowed (~50%)



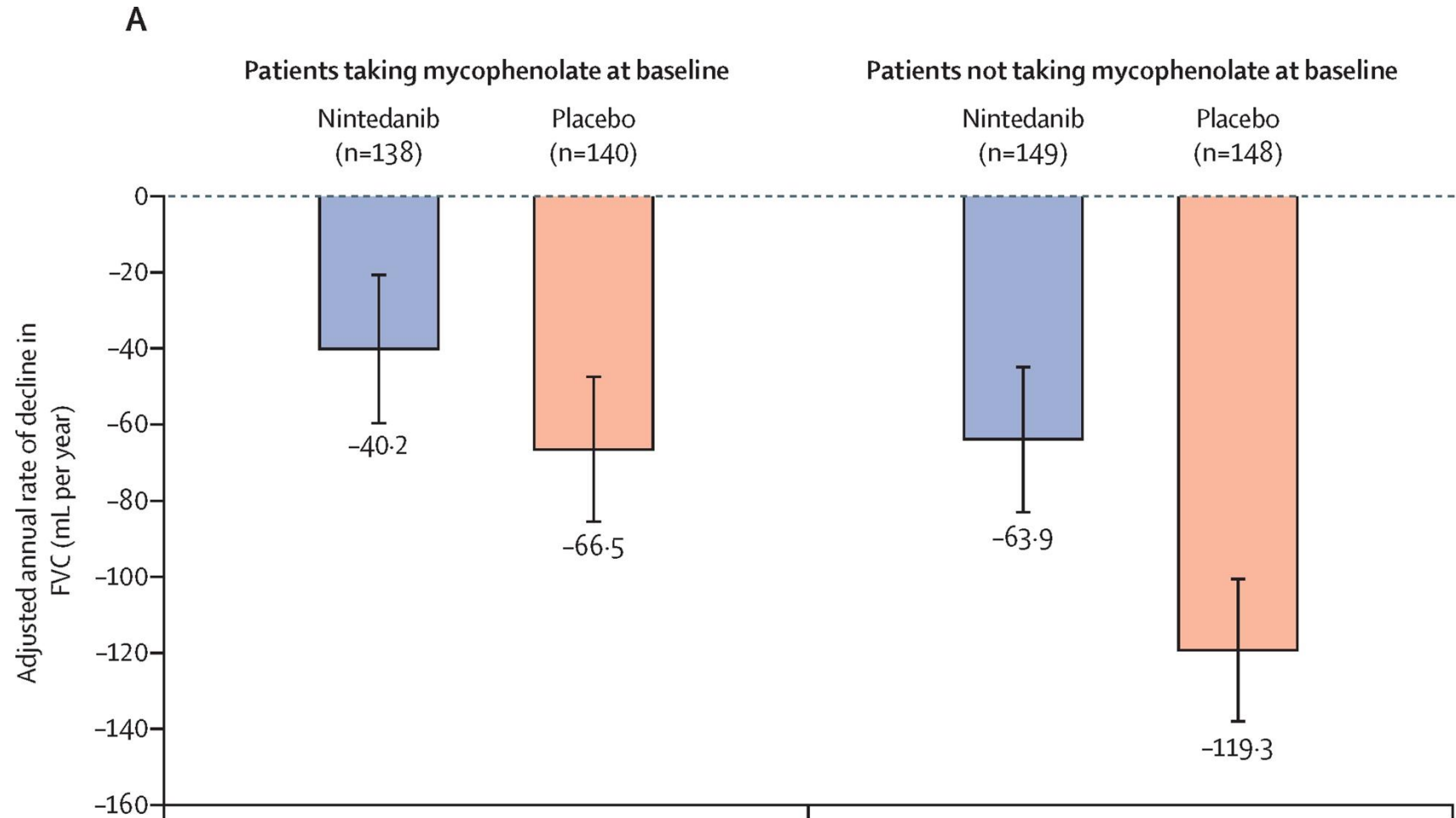
No. of Patients

Nintedanib	288	283	281	273	278	265	262	241
Placebo	288	283	281	280	283	280	268	257

Distler, et al. (2019). *NEJM*. 380:2518



Nintedanib



Systemic Sclerosis–Associated Interstitial Lung Disease

Treatment Recommendations

**STRONG
IN FAVOR**

Mycophenolate

**CONDITIONAL
IN FAVOR**

Cyclophosphamide

Rituximab

Tocilizumab

Nintedanib

Nintedanib plus
Mycophenolate

**RESEARCH
RECOMMENDATION**

Pirfenidone

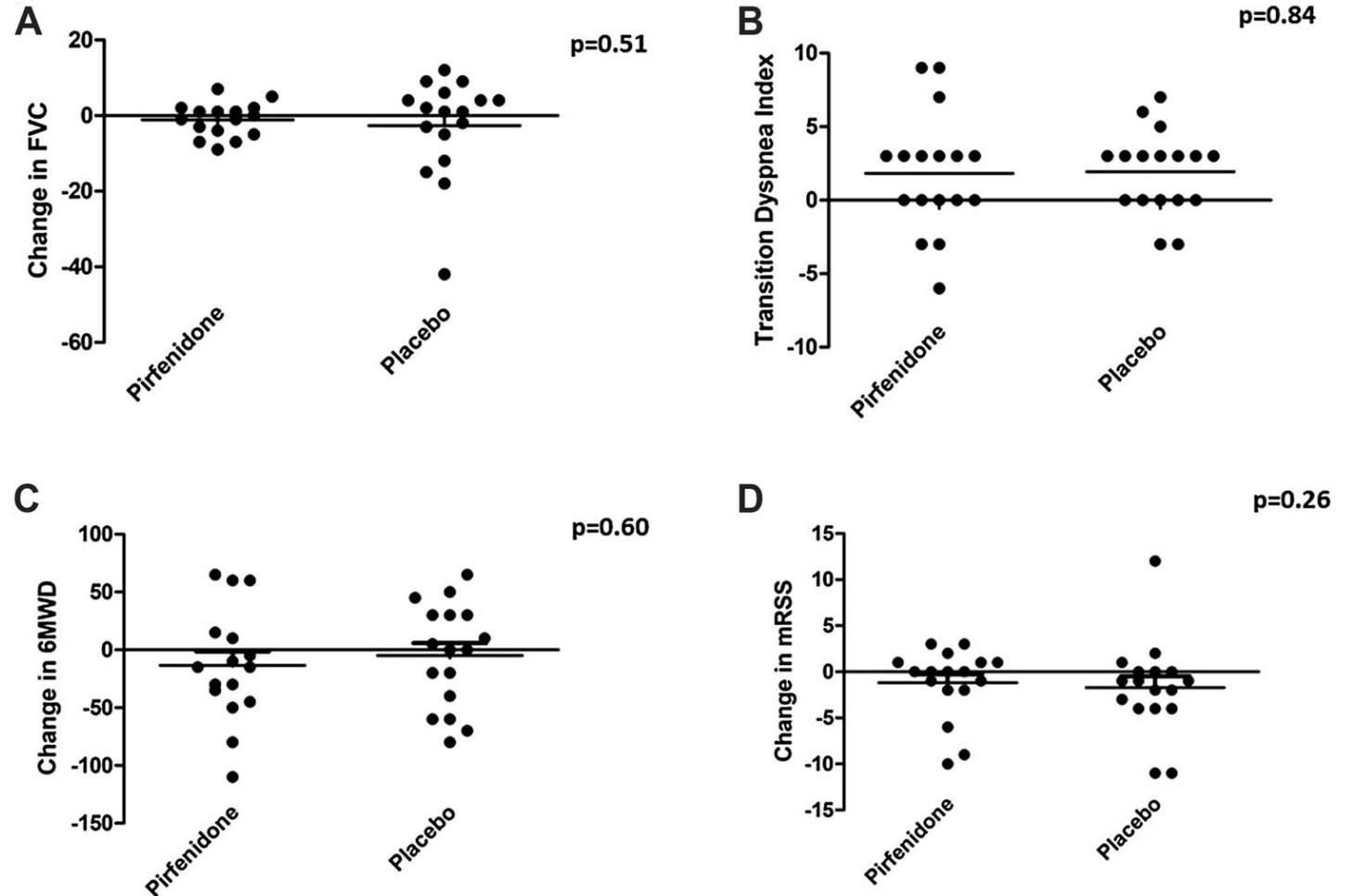
Pirfenidone plus
Mycophenolate

Raghu *et al.* (2024). *AJRCCM*. 209 (2):137-152

Pirfenidone

Research recommendation

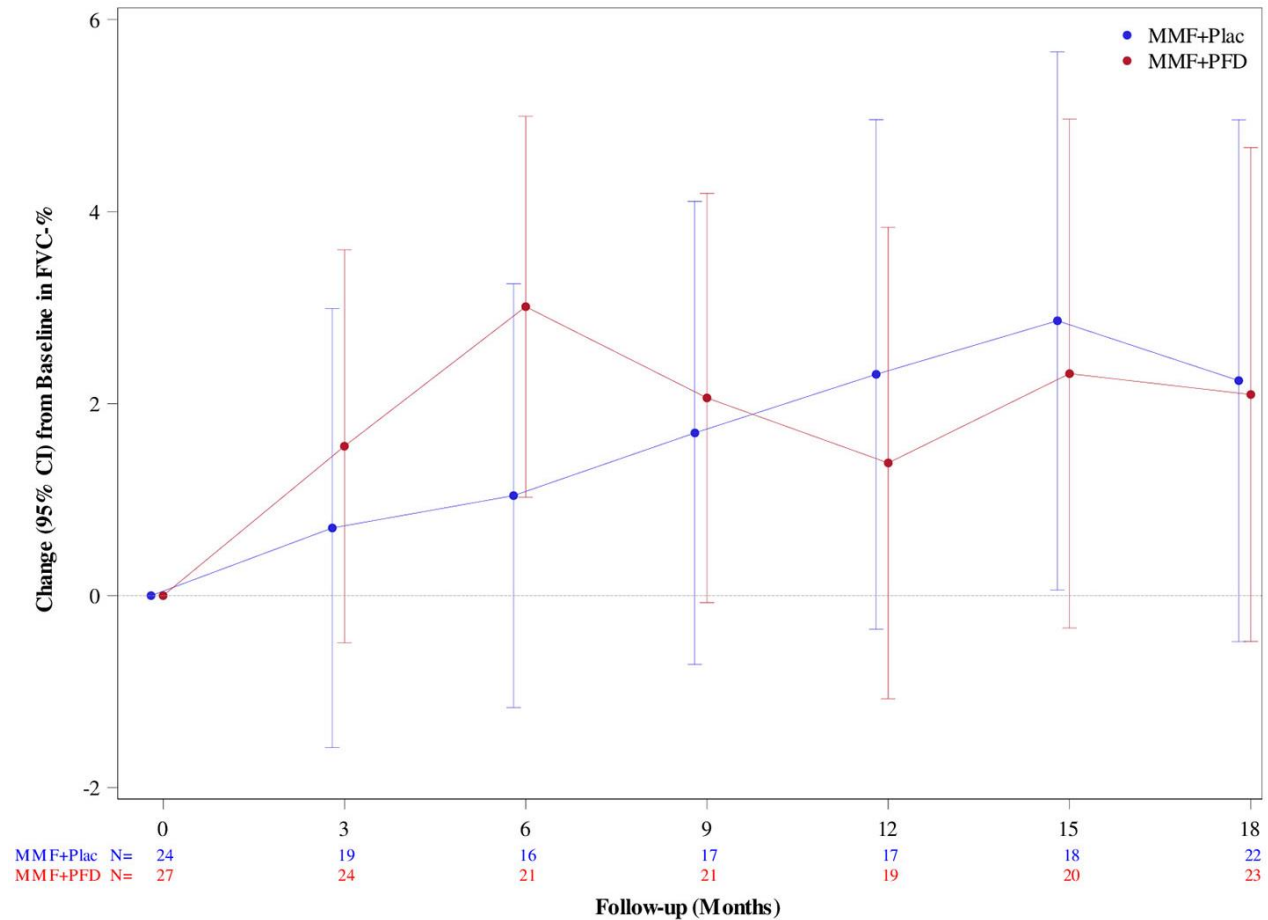
- Small RCT, underpowered (N=34)
- 24 weeks
- Only 6% at target dose
- No benefit (FVC, symptoms, mRSS)



Pirfenidone + MMF?

Research recommendation

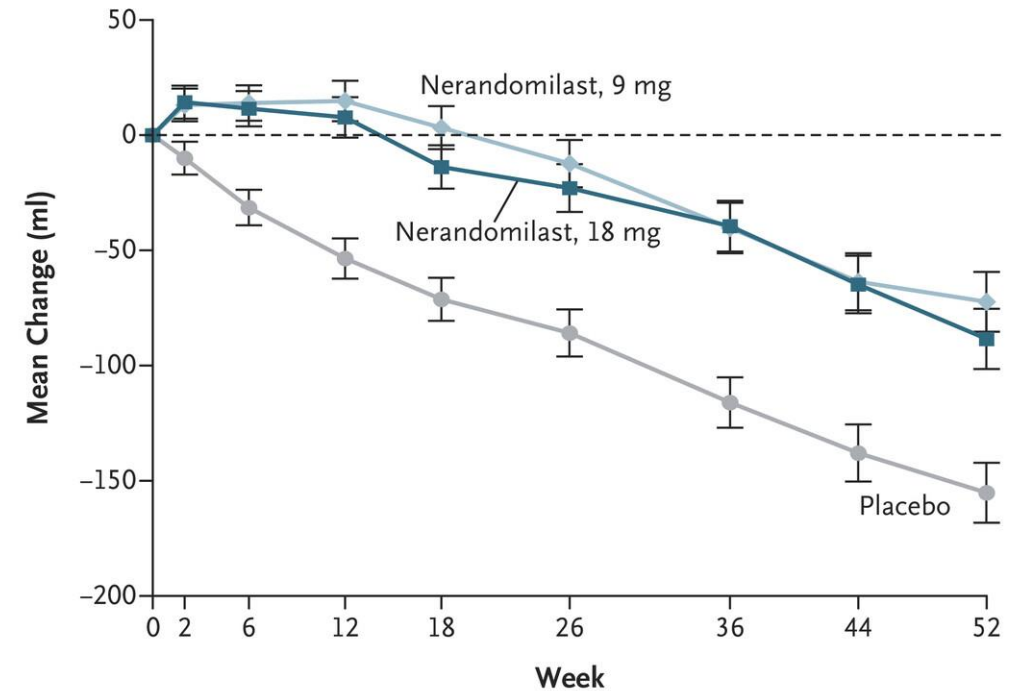
- LOTUSS trial: phase II trial for tolerability over 16 weeks
- SLS III: pirfenidone + MMF vs placebo + MMF
 - Aborted due to inability to enroll (51 of 150 intended participants)



Nerandomilast

- Phosphodiesterase 4B inhibitor with antifibrotic and anti-inflammatory properties
- FIBRONEER PPF study: 1:1:1 placebo controlled study (9 mg BID vs 18 mg BID vs placebo): 1176 patients
- Primary endpoint: absolute change in FVC from baseline at 52 weeks

B Change in FVC over Time in the Overall Trial Population



No. of Patients

Nerandomilast, 18 mg	379	380	364	349	338	330	321	324
Nerandomilast, 9 mg	386	379	365	361	348	333	326	325
Placebo	378	373	369	358	355	337	326	326



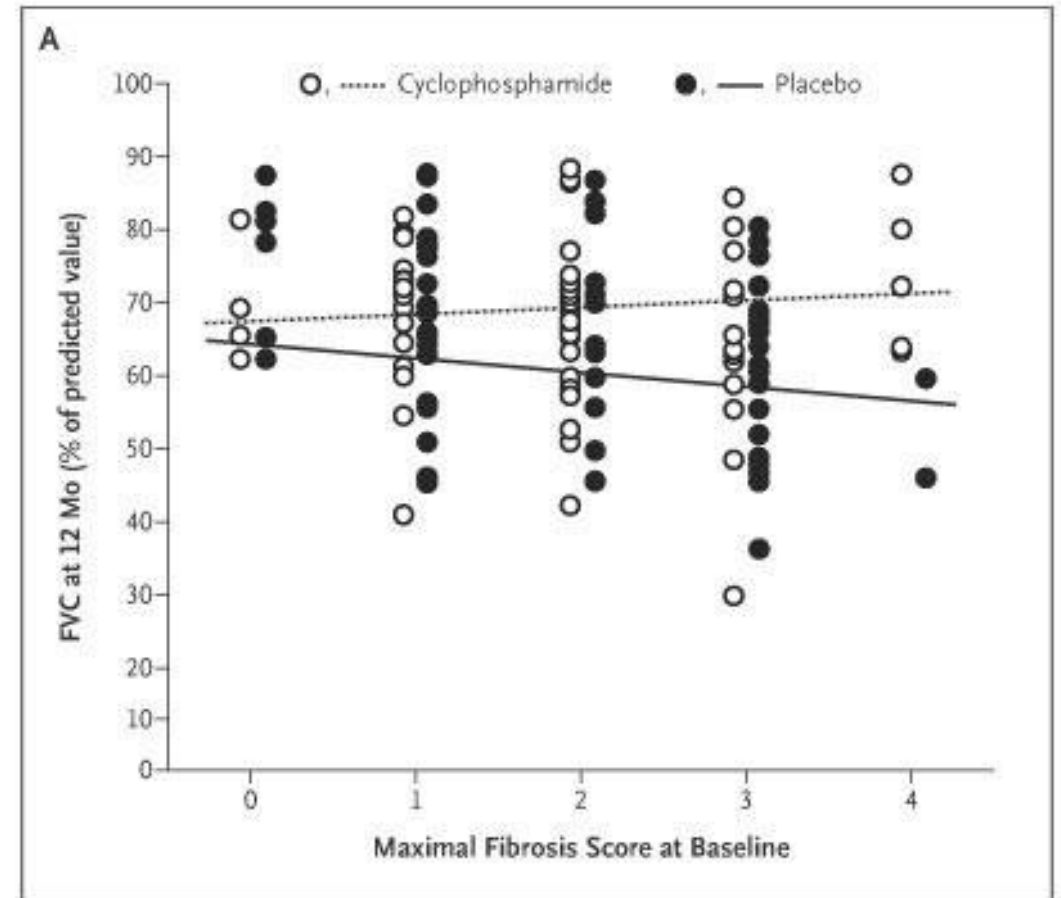
Major unknowns in SSc-ILD treatment

- When to treat: at diagnosis vs stable vs progressing SSc-ILD
 - *E.g.* asymptomatic patient with minimal ILD found on screening CT, normal PFTs?
 - *E.g.* patient with stable disease over 5 years?
- Duration of therapy
- Radiologic subgroups: UIP vs NSIP
- Lingering questions about therapies:
 - Drug formulation or route of MMF or CYC
 - Comparing one therapy vs another

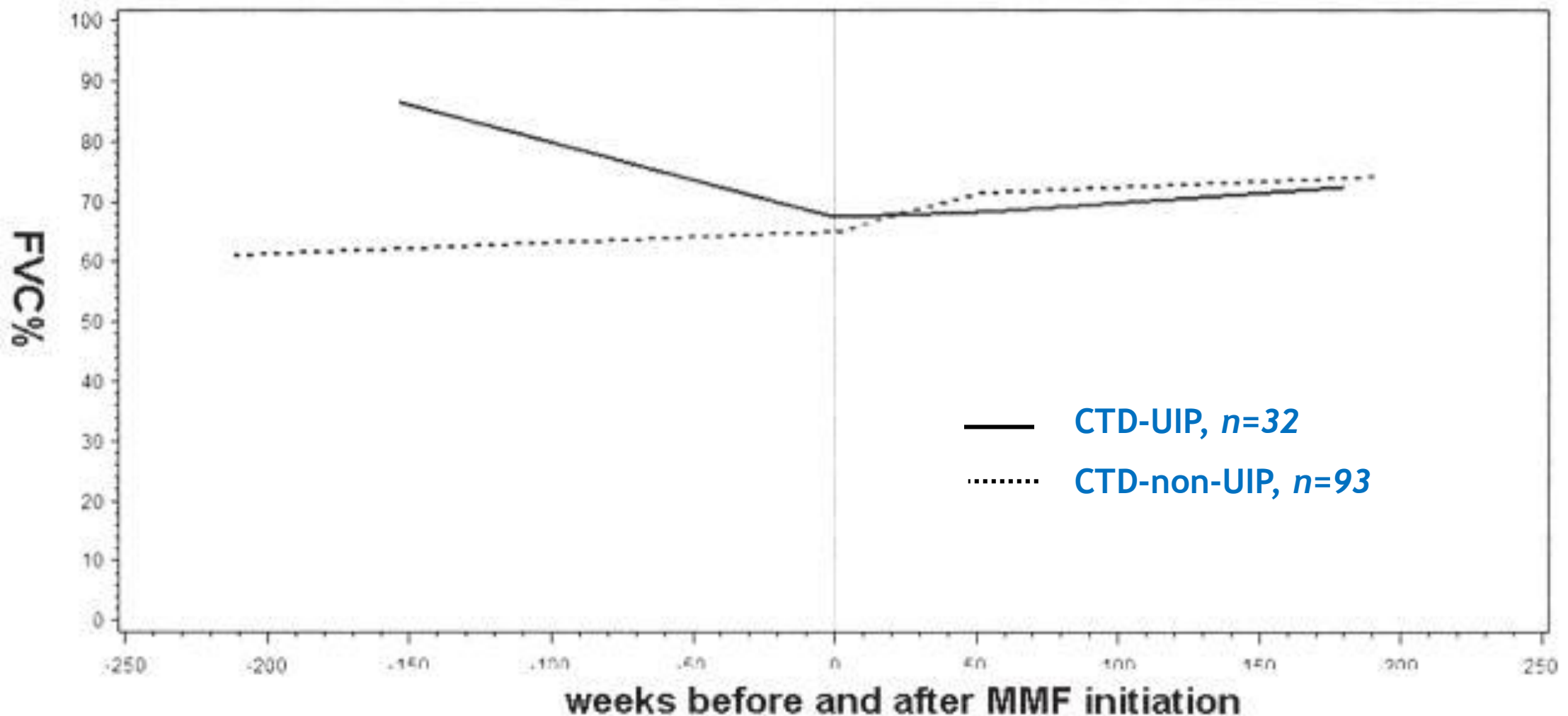


What about usual interstitial pneumonia?

- SLS I
 - “Active alveolitis” + many had fibrosis
 - Favored CYC over placebo for those with *increased* fibrosis scores



MMF in SARD with UIP pattern



Questions / comments