ILD Collaborative

Project ECHO

Scleroderma-ILD

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Disclosures

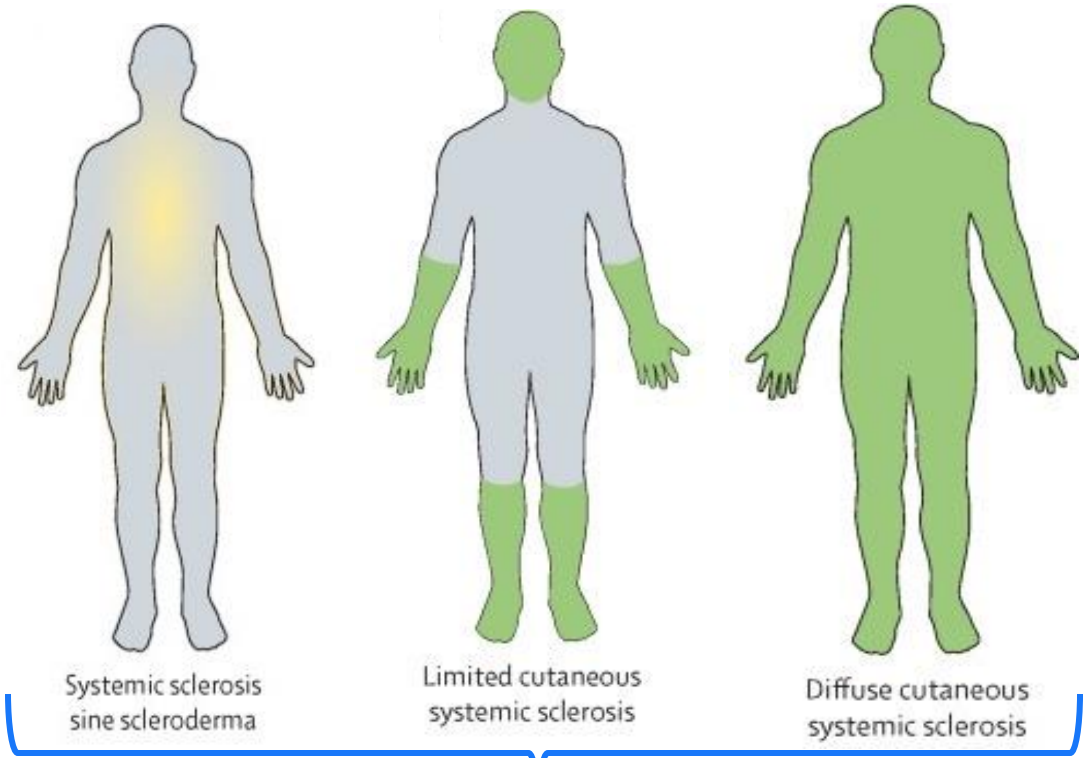
- Advisory board fees for Boerhinger Ingelheim
- Indirect clinical trial research funding from Boerhinger Ingelheim, Daewoong Pharmaceuticals, Pliant Therapeutics, and Avalyn Pharma Inc

Learning objectives

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

Definitions

- Scleroderma-ILD = ILD in the presence of scleroderma
  - By definition, ILD = systemic involvement → all scleroderma ILD is "systemic sclerosis" SSc-ILD



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

ILD can occur in any

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 *(sufficient criterion)*	-	9
Skin thickening of the fingers *(only count the higher score)*	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the MCP but proximal to the PIP)	4
Fingertip lesions *(only count the higher score)*	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	-	2
Abnormal nailfold capillaries	-	2
PAH or ILD *(max score is 2)*	PAH	2
	ILD	2
Raynaud Phenomenon	-	3
SSc-related autoantibodies *(max score is 3)*	Anticentromere Anti-Scl-70 (anti-topoisomerase) Anti-RNP polymerase III	3

Van den Hoogen *et al.* (2013). *Arthritis Rheum.* 65:2737

Autoantibodies in scleroderma

Antibody	Frequency	Clinical associations	Organ involvement
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

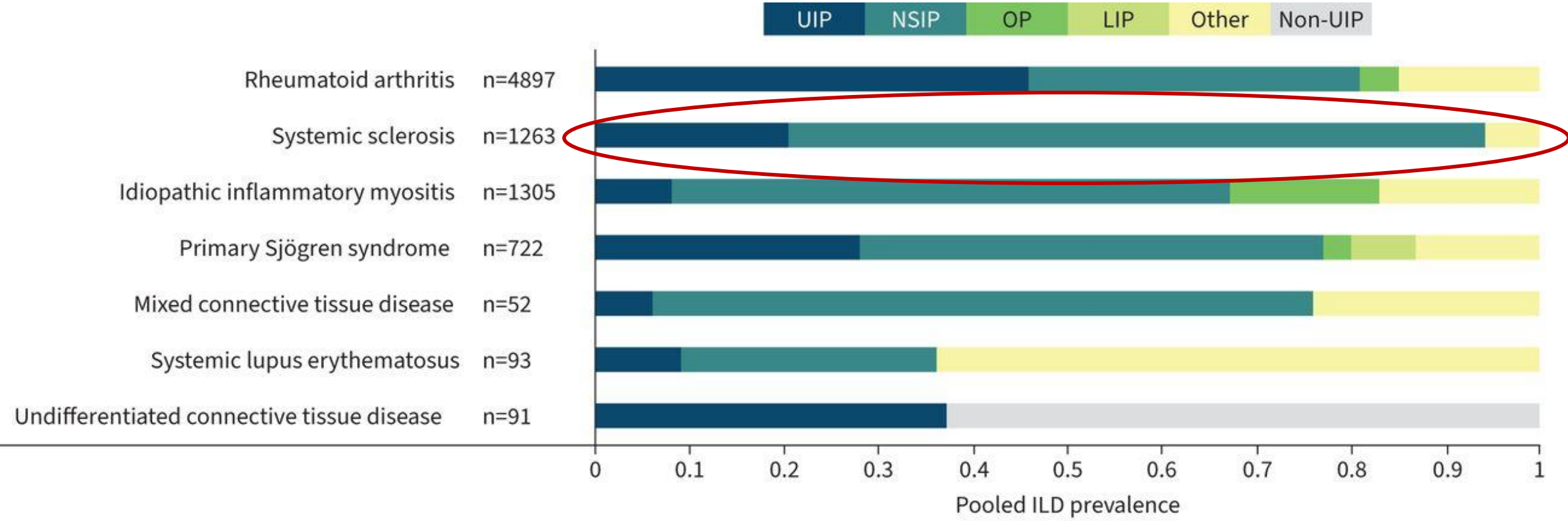
Highly specific (>99.5%)

20-50% sensitive

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

Perelas, *et al*. (2020). *Lancet Respir Med*. 8:304-20
Tyndall *et al*. (2010). *Ann Rheum Dis*. 69:1809-1815.

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DOI 10.1002/art.42860

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

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

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 COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

Arthritis & Rheumatology
Vol. 76, No. 8, August 2024, pp 1182–1200
DOI 10.1002/art.42861

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

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

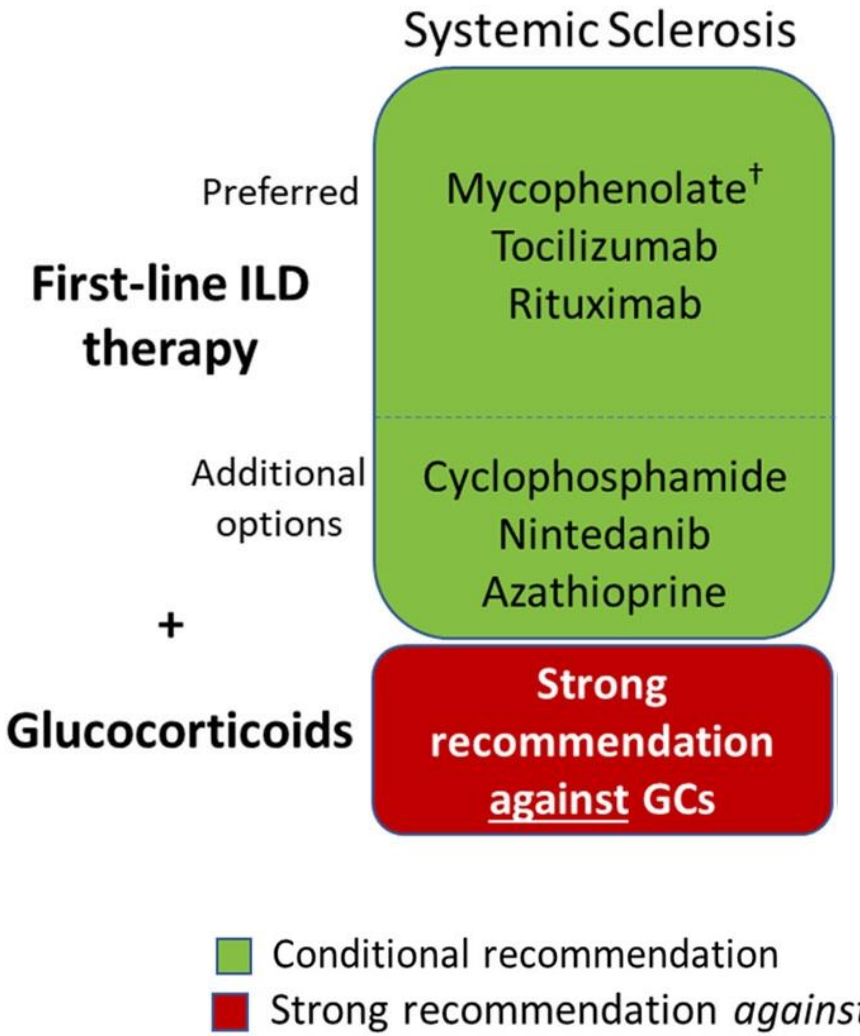
ATS guidelines

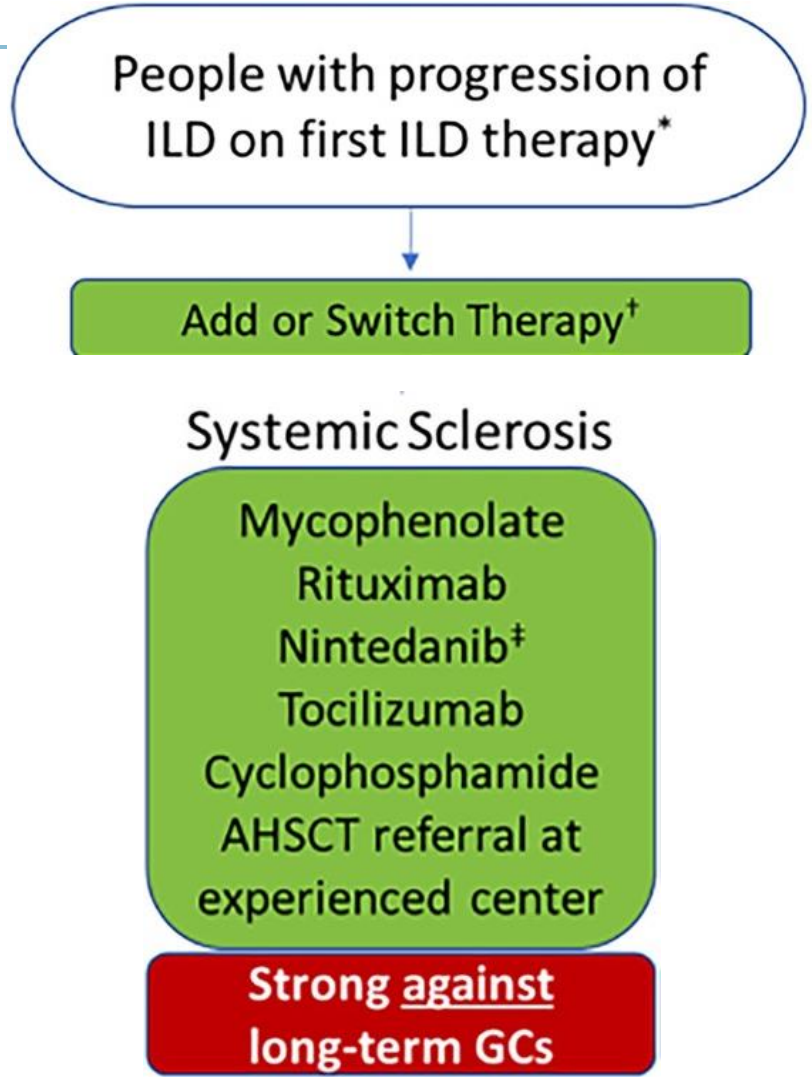
Treatment Recommendations

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

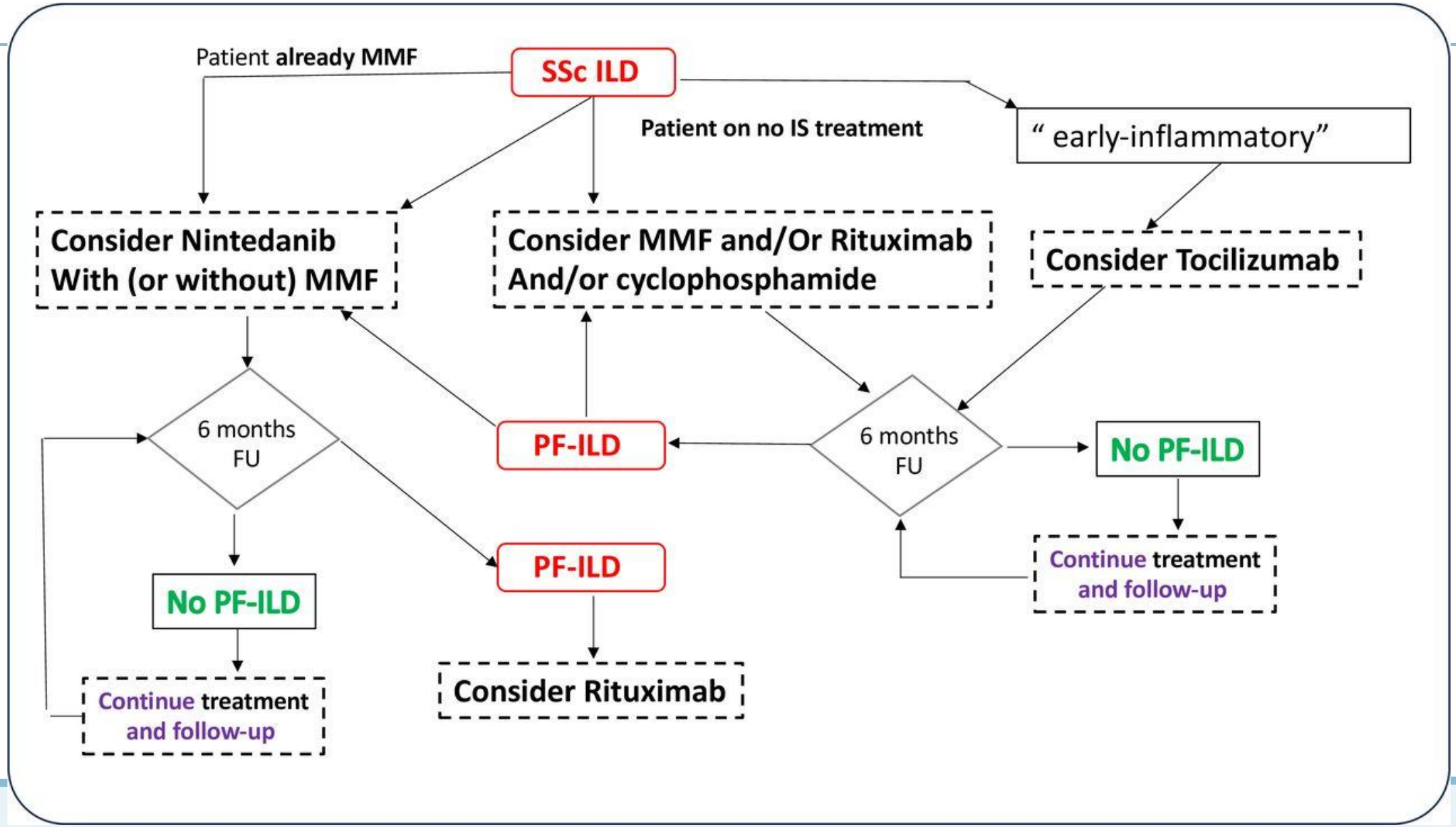
ACR/CHEST guidelines





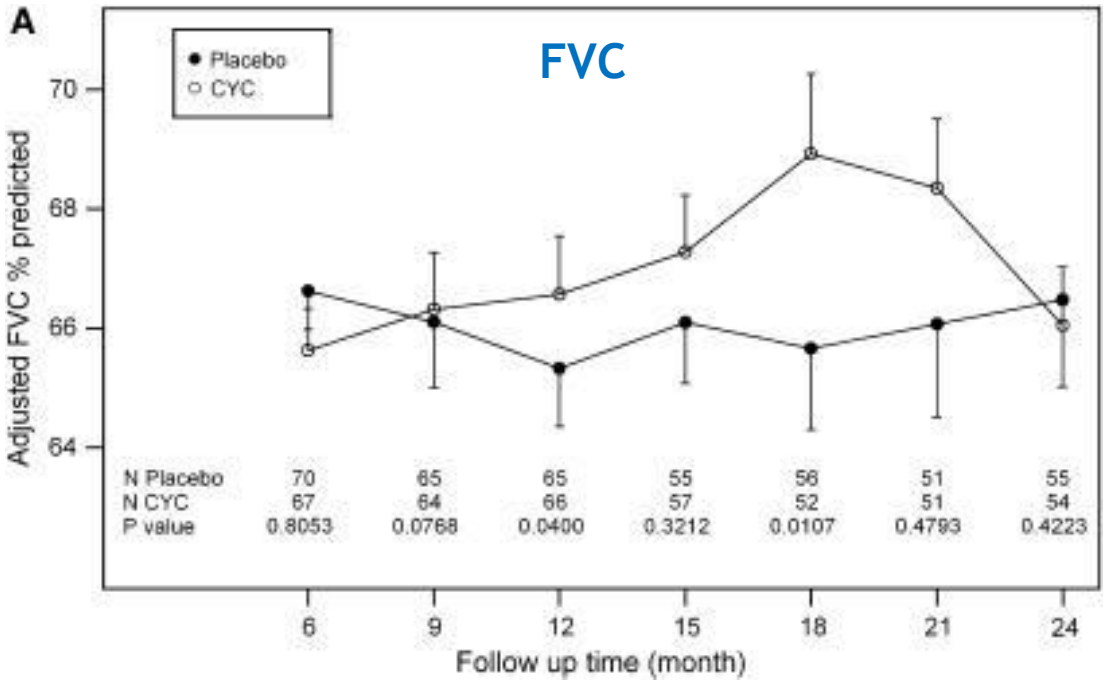
Johnson *et al.* (2024). *Arthritis Rheumatol.* 76(8): 1051

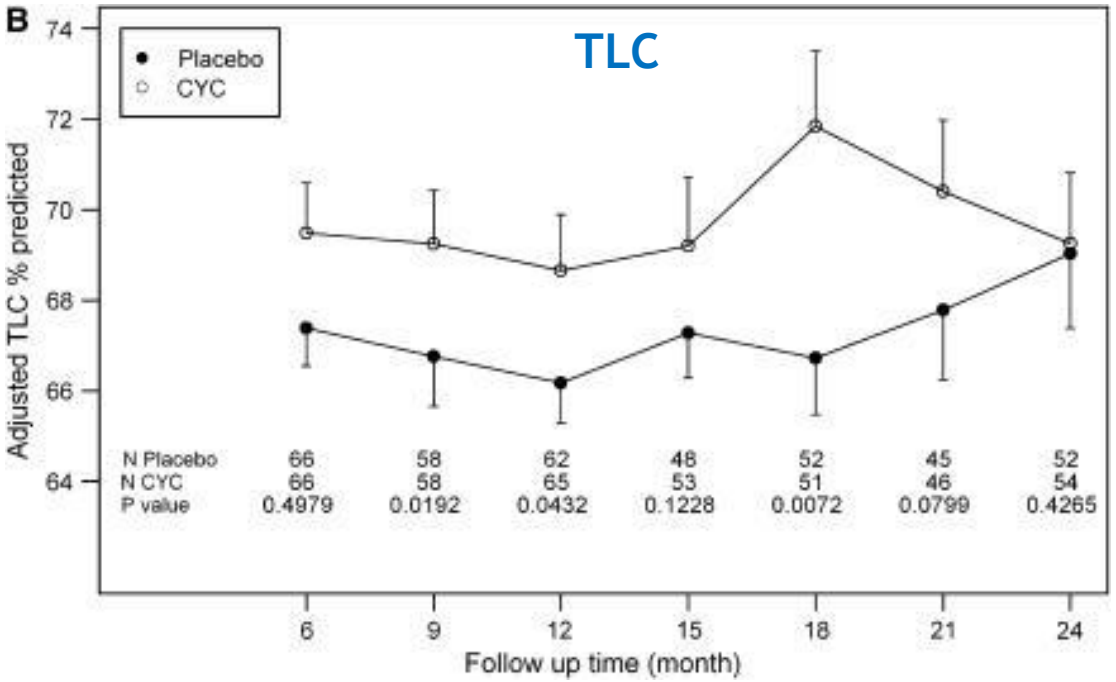
EULAR guidelines



Del Gado (2024). *Annals Rheum Dis.* doi: 10.1136/ard-2024-226430

Cyclophosphamide (CYC)





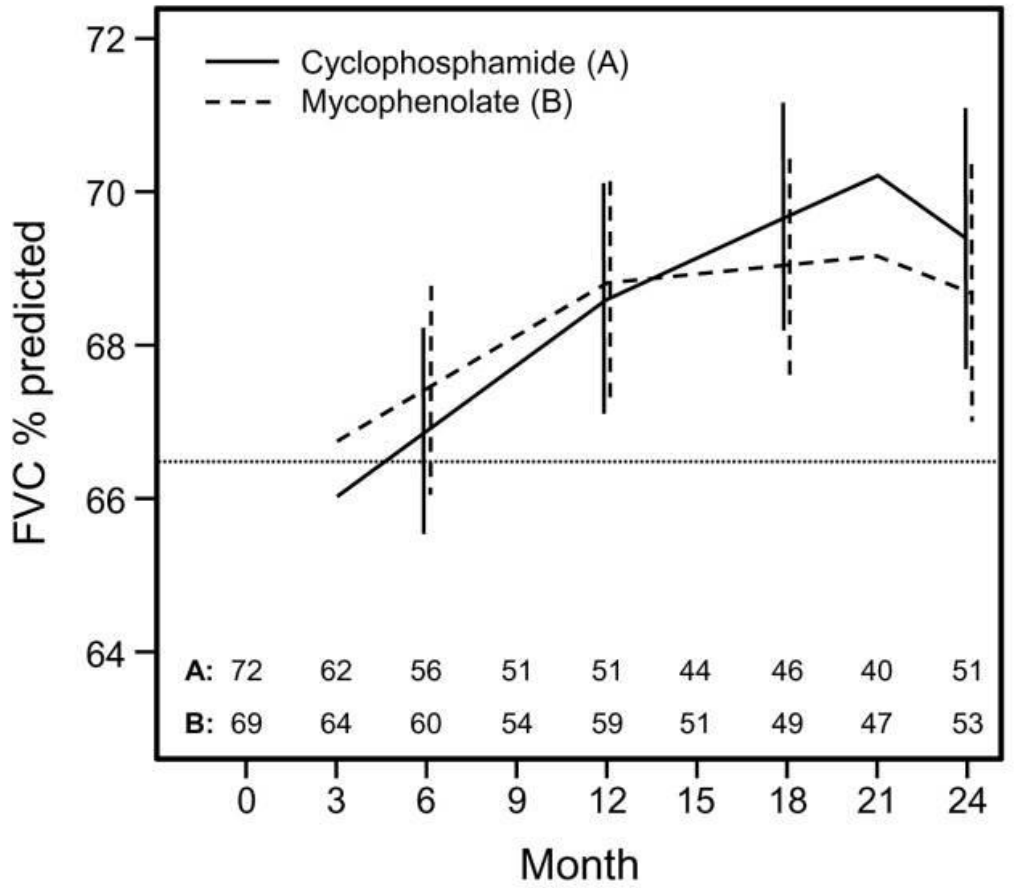
SLS I: 158 patients with inflammatory SSc-ILD; RCT double blind placebo-controlled trial
PO CYC vs placebo x1 year
CYC better than placebo (FVC, TLC, not DLCO) at 12 months but effects wane after 18 months
AE: hematuria, leukopenia, neutropenia

Tashkin, *et al*. (2006). *NEJM*.354(25):2655-66
Tashkin *et al*. (2007). *AJRCCM*. 176 (1026)

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 AE with CYC
- More withdrew CYC arm early



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

Rituximab

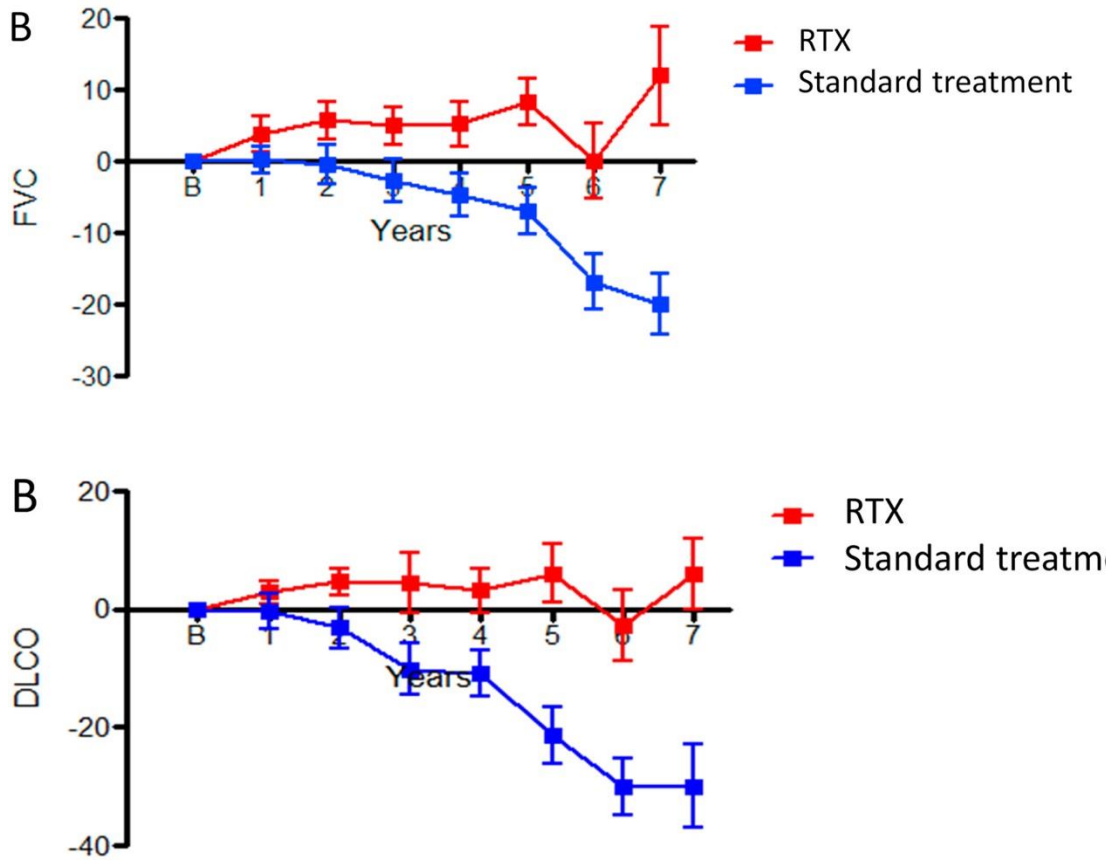
- 3 RCTs: 2 without *a priori* confirmation of ILD
- Small, underpowered studies
- Range of dosing and duration
- Meta-analysis: rituximab attenuated decline in FVC % predicted by 3.3%; varied DLCO effect
- No mortality* or QoL benefit; improved skin scores
- Well tolerated *vs* placebo

*24 weeks

Ebata *et al.* (2021). *Lancet Rheumatol.* 3: E489
Ebata *et al.* (2022). *Lancet Rheumatol.* 4(8)
Caldas *et al* (2021). *Advances in Rheumatology.* 61:15
Raghu *et al.* (2024). *AJRCCM.* 209 (2):137-152
Boonstra *et al.* (2017). *RMD Open* 3:e000384.
Daoussis *et al.* (2010). *Rheumtology.* 49:271.

Rituximab

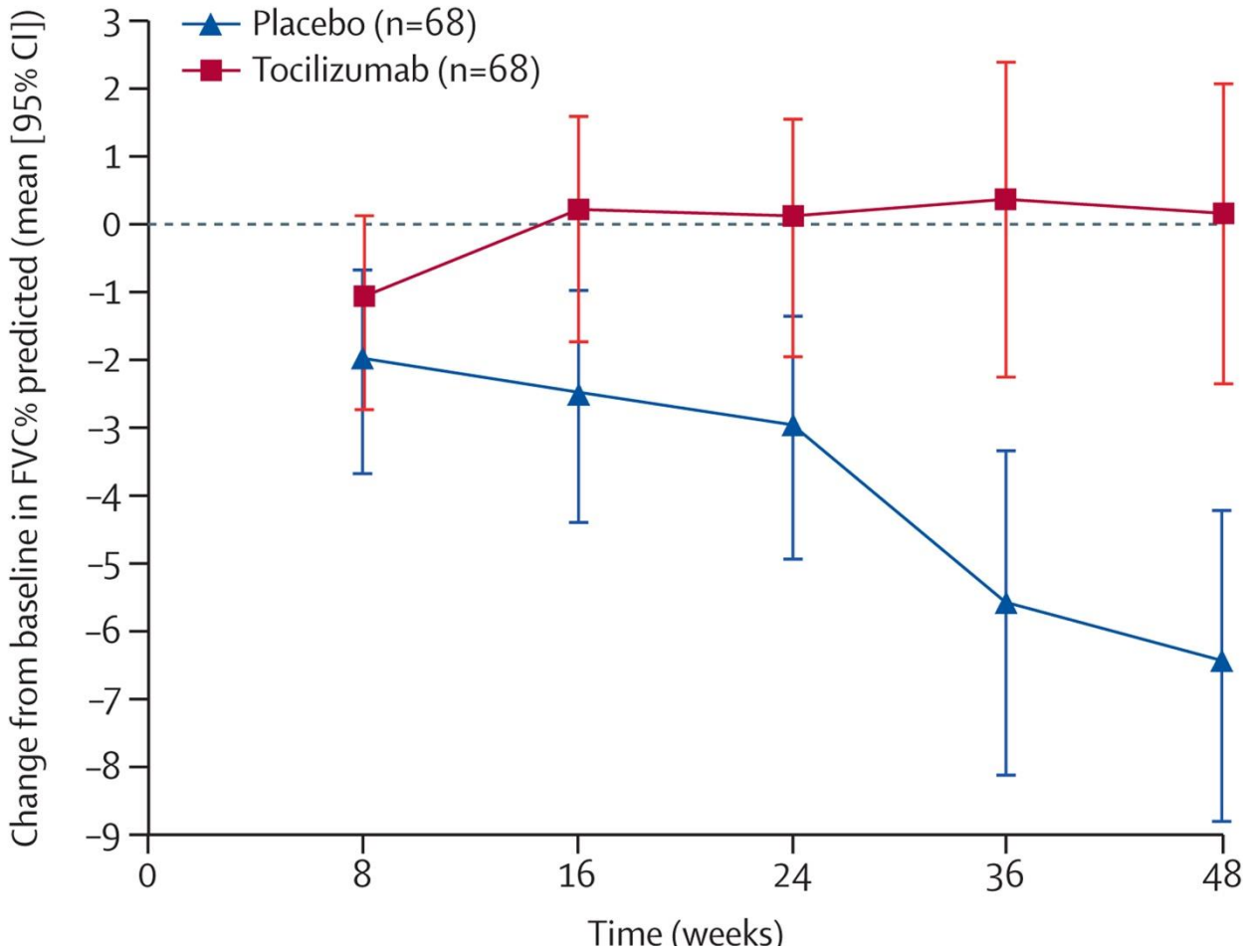
- SSc-ILD (51 pts): 33 ritux; 18 with conventional therapy (MMF, MTX, AZA)
- Median 4 years follow up
- Improved relative FVC and DLCO



Daoussis *et al.* (2010). *Rheumtology*. 49:271.

Tocilizumab

- FaSScinate (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

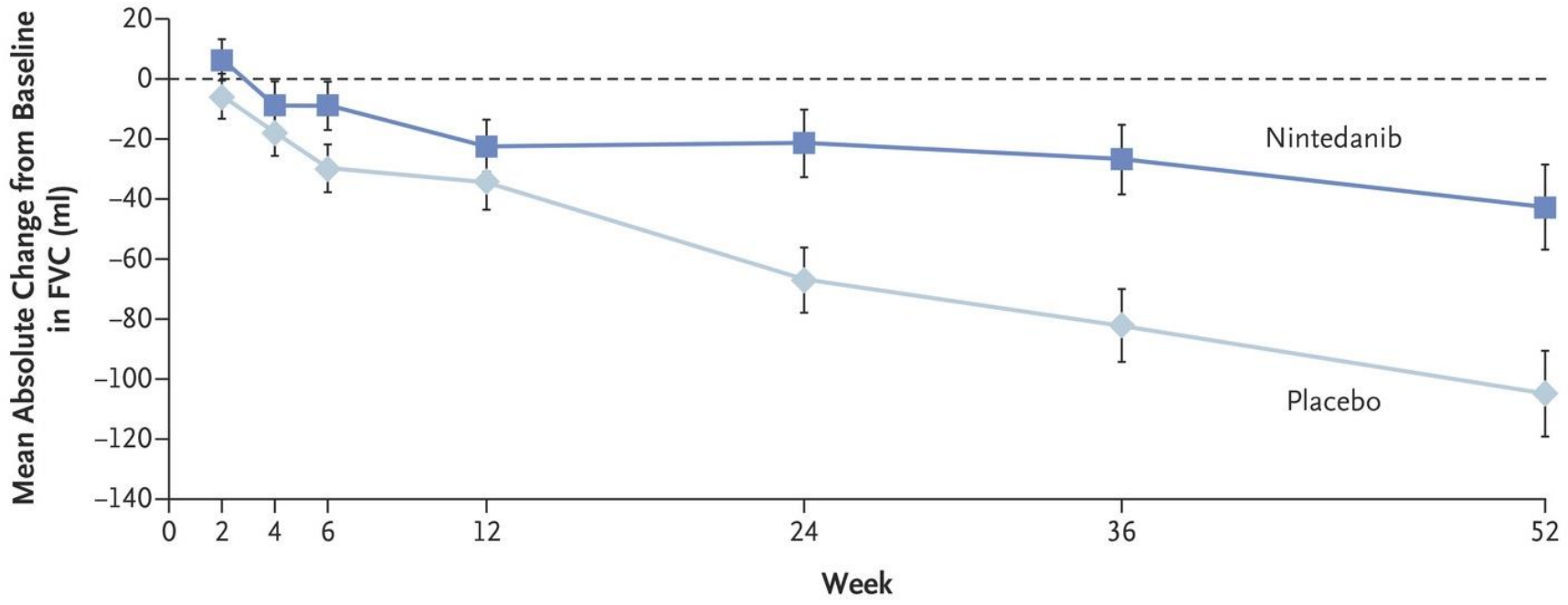


Khanna *et al.* (2020). *Lancet Respir Med*. 8:963-74

Antifibrotics in SSc-ILD

Nintedanib

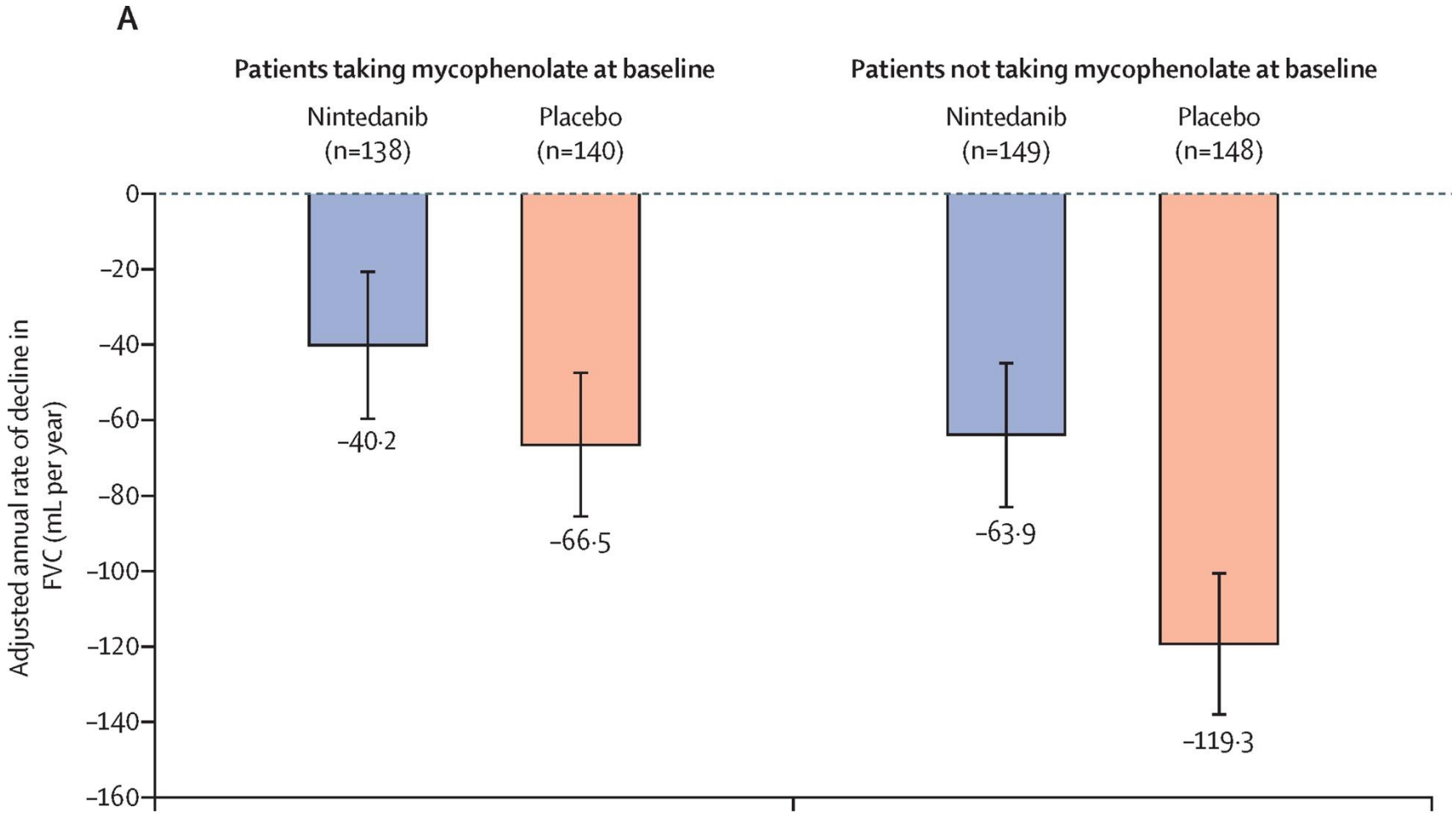
SENSCIS: phase III, 576 subjects with SSc-ILD; background MMF allowed (~50%)



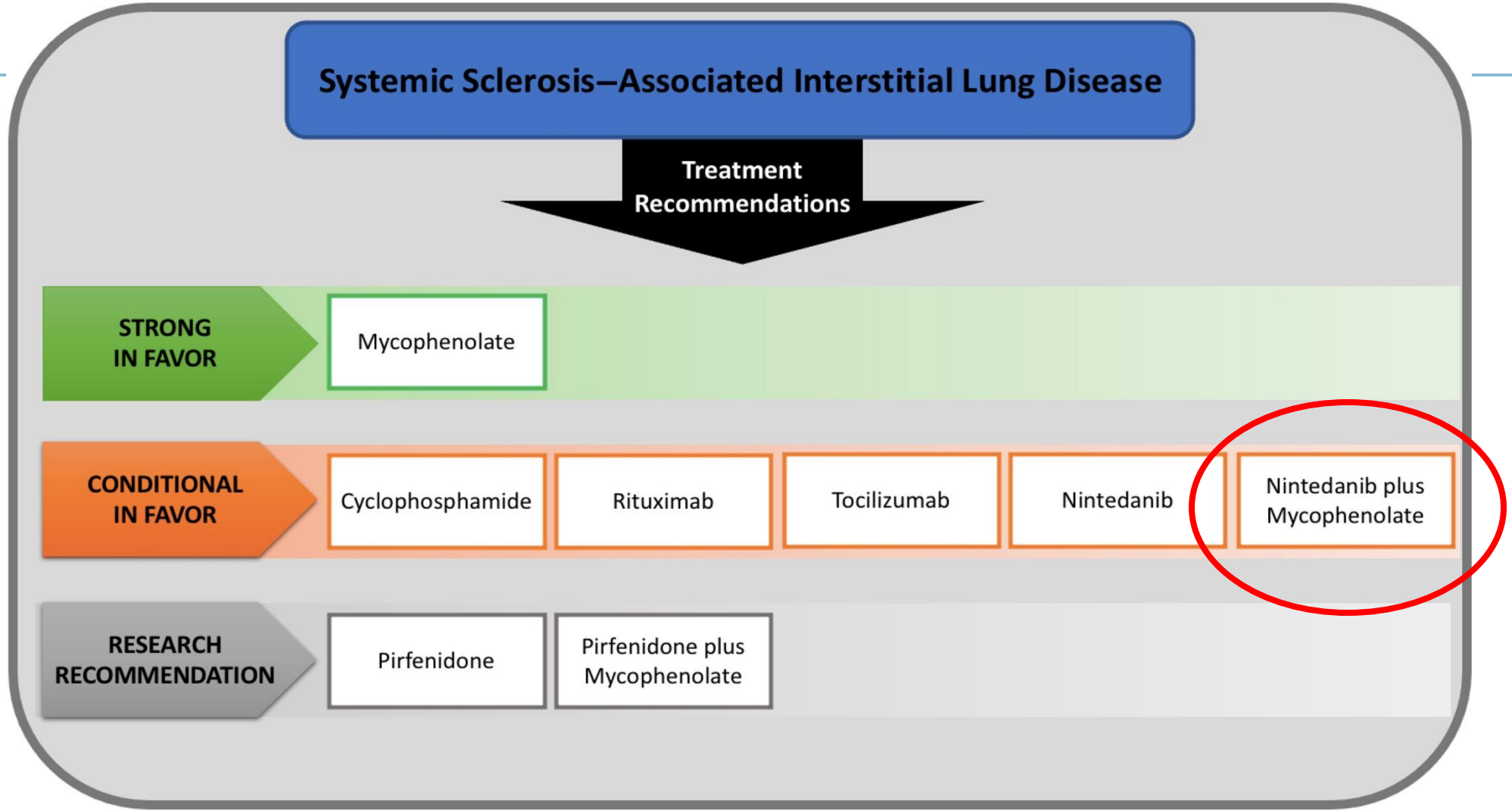
No. of Patients								
Nintedanib	288	283	281	273	278	265	262	241
Placebo	288	283	281	280	283	280	268	257

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

Nintedanib



r, *et al*. (2019). *NEJM*. 380:2518
Highland *et al* (2021). *Lancet Resp Med*. 9(1). 96.

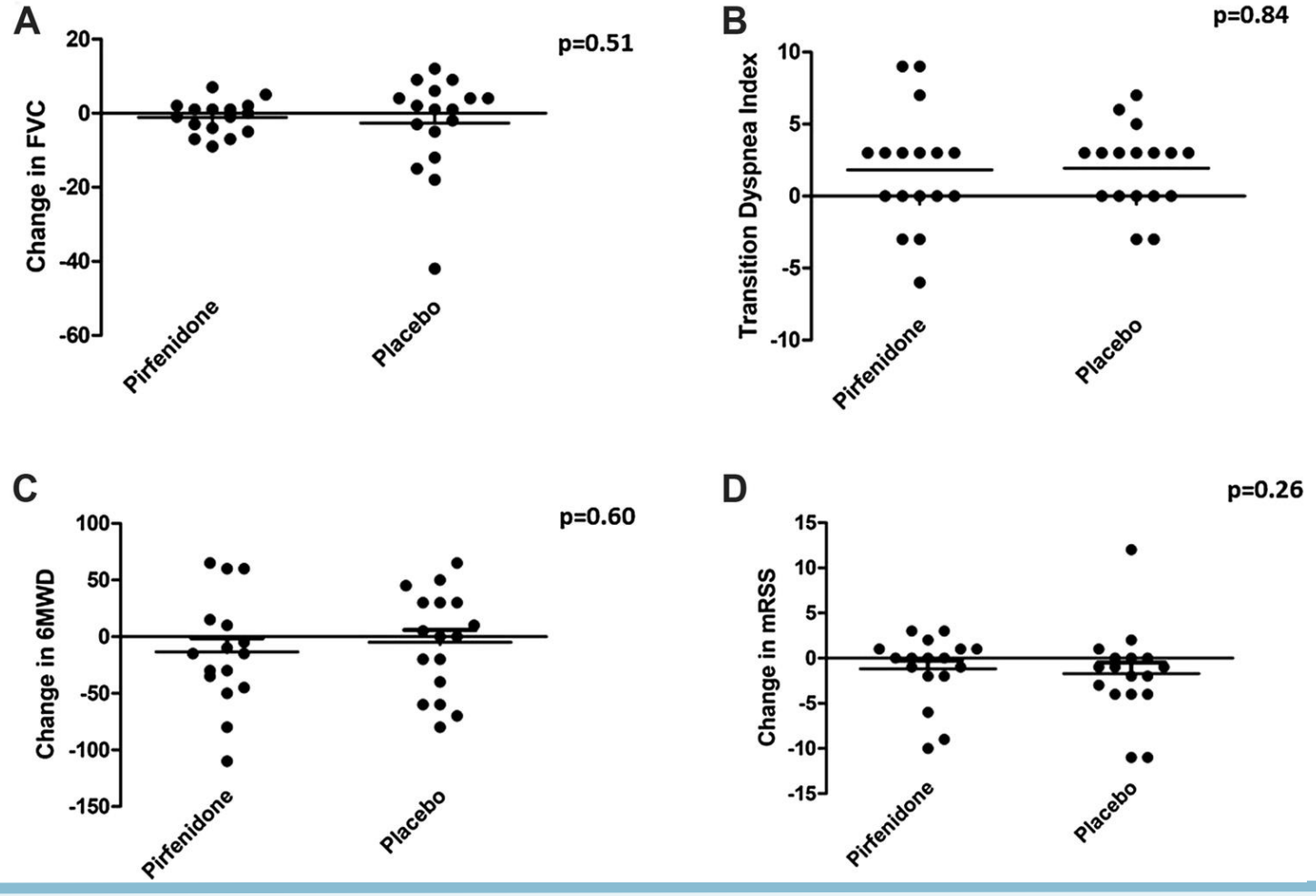


Raghu *et al.* (2024). *AJRCCM.* 209 (2):137-152

Pirfenidone

Research recommendation

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

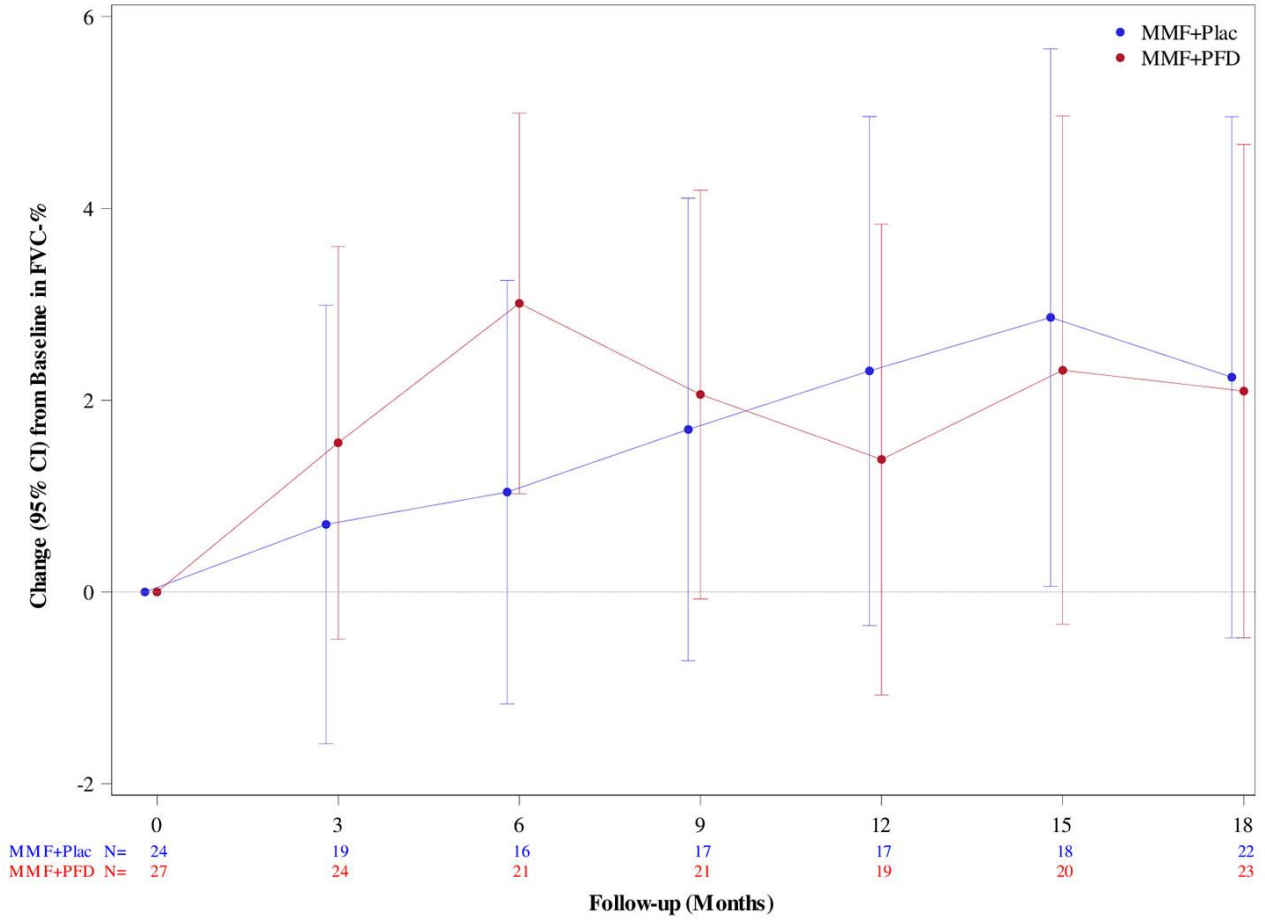


Acharya *et al.* (2020). *Rheumatol Int*. 40(5):703

Pirfenidone + MMF?

Research recommendation

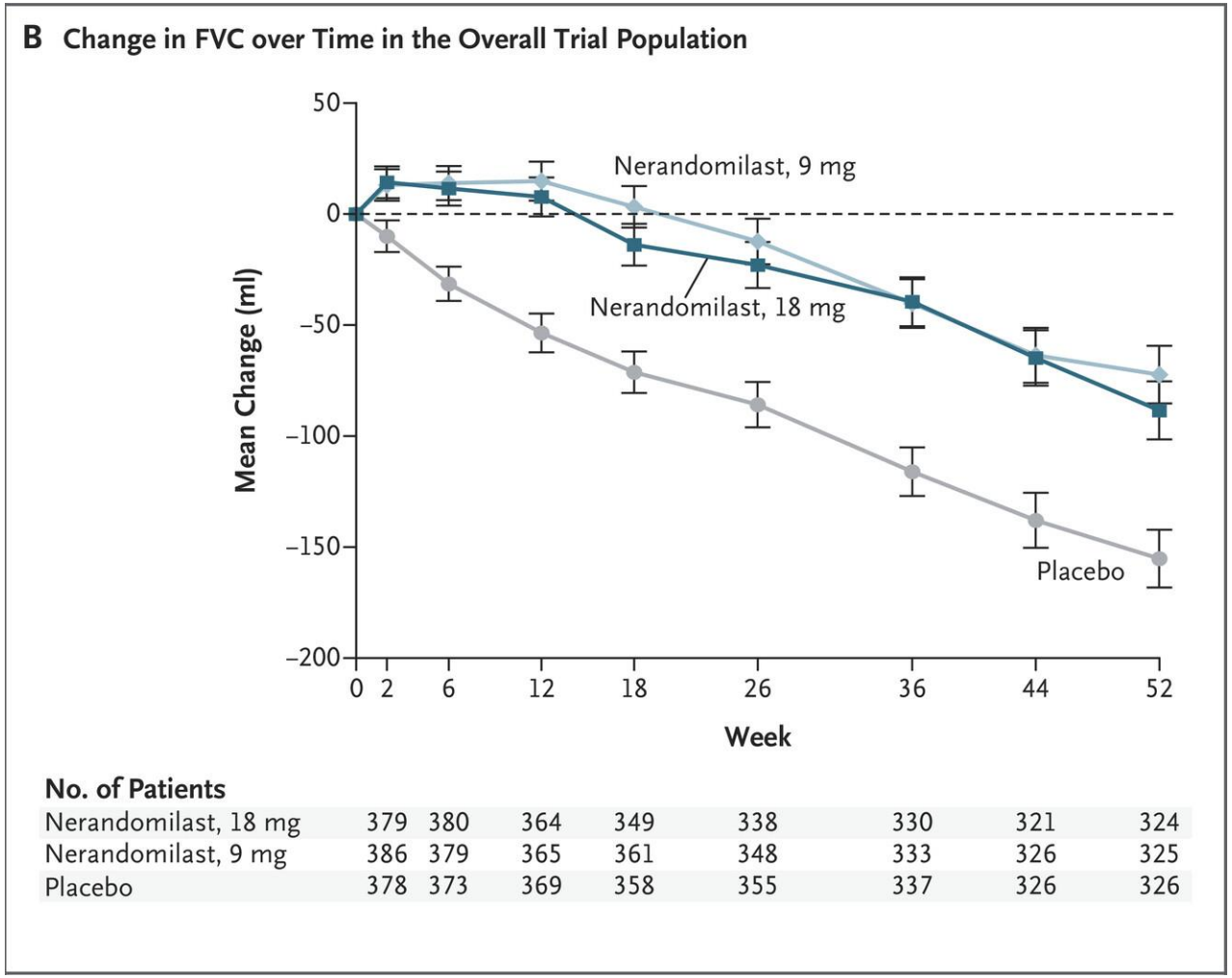
- LOTUSS trial: phase II trial for tolerability over 16 weeks
- SLS III: pirfenidone + MMF *vs* placebo + MMF
  - Aborted due to inability to enroll (51 of 150 intended participants)



Khanna, et al. *(2016). J Rheumatol*. 43:1672
Khanna *et al. (2022) ACR abstractpirefnidne*

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



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
- 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

Questions/comments