

Scleroderma – Approach in management of ILD

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Interstitial Lung Disease Interdisciplinary Network

Sunday 4th October 2026

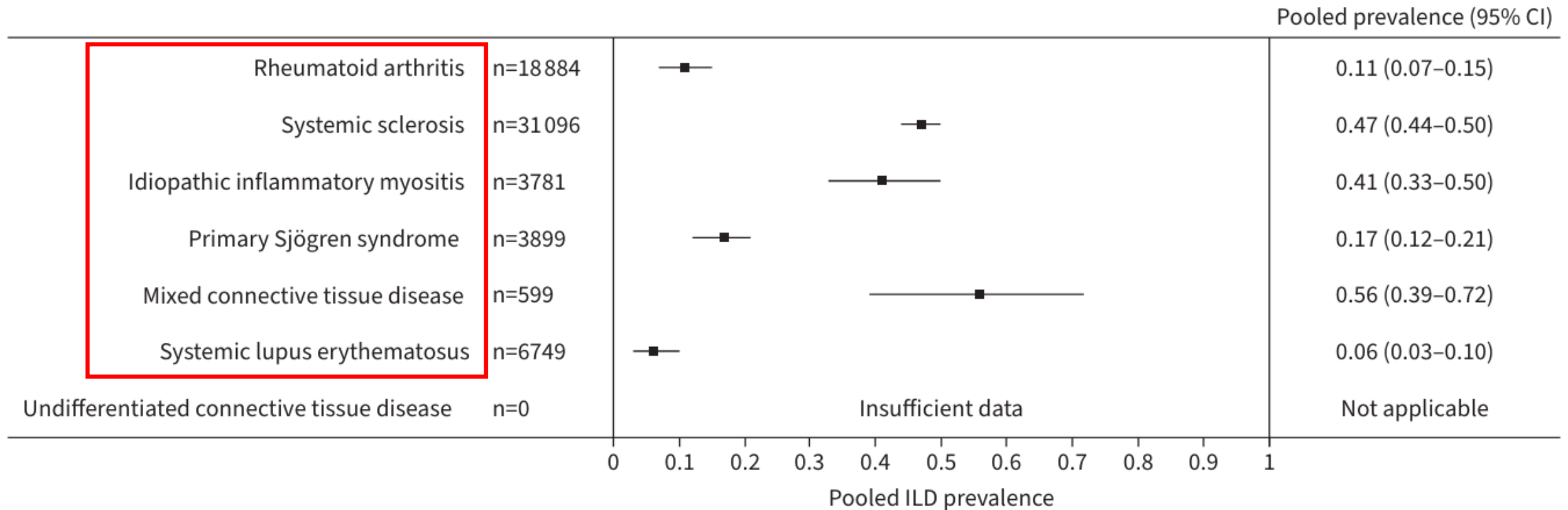
Disclosures

- Speaker/research grants from Boehringer Ingelheim, Mestag and Engitix

Overview of presentation

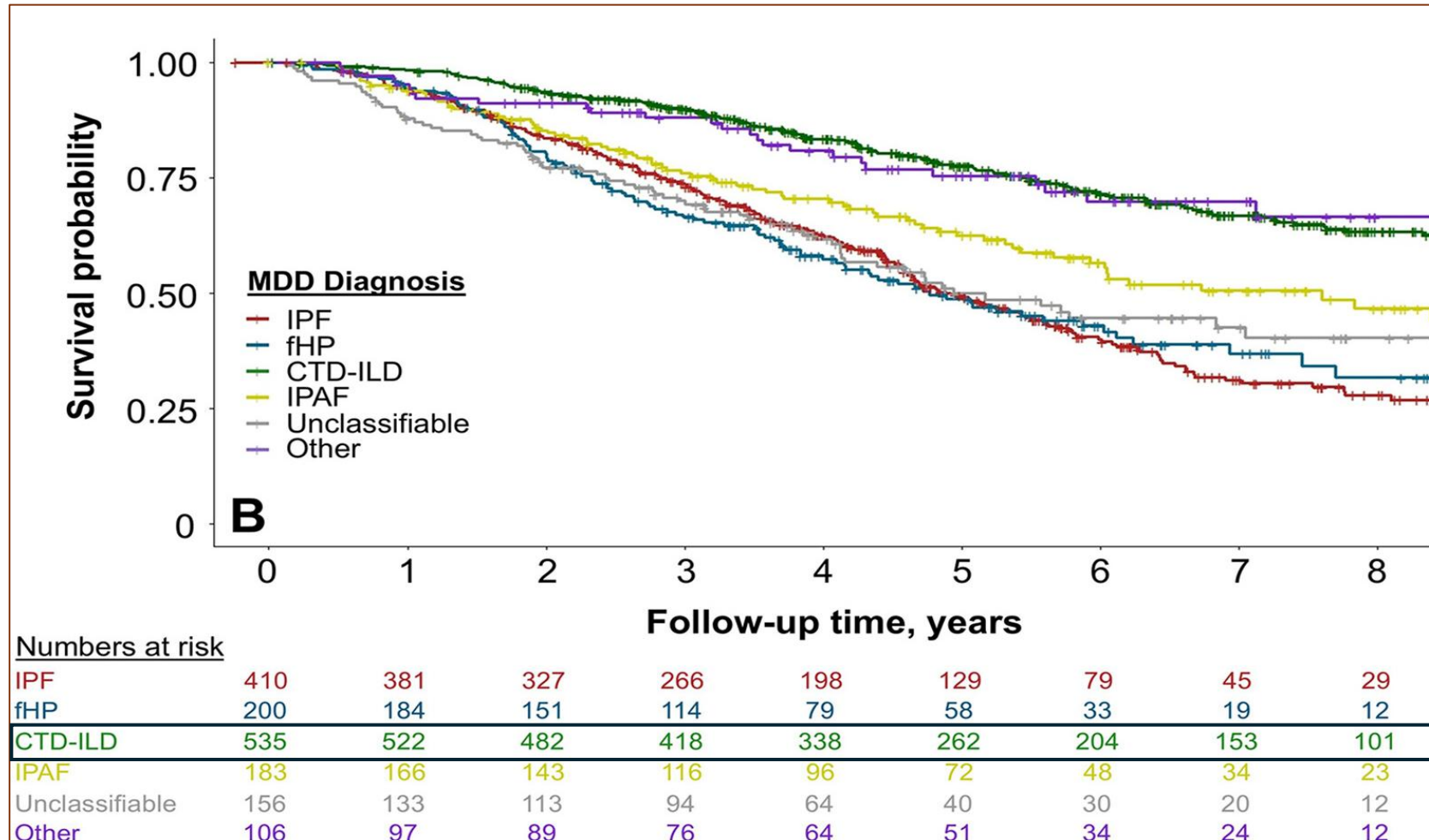
- Guidelines and recommendations
 - SSc-focussed
- Management
 - Screening
 - Treatment
- Multidisciplinary discussion tailors individualised management

Prevalence of ILD across CTDs

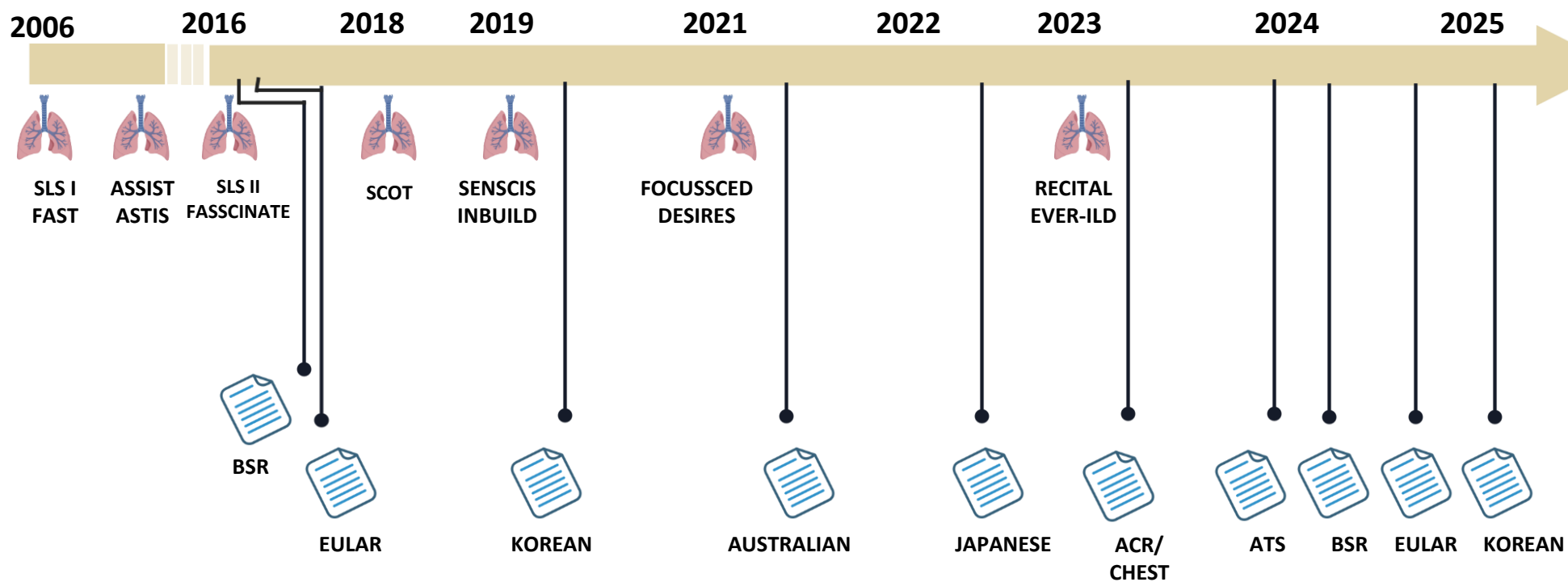


Up to 40% of CTD-ILD may develop progressive pulmonary fibrotic phenotype

Differential survival trajectories across fibrotic ILD subtypes



Evolving SSc therapeutic landscape



Denton CP, et al. Rheumatology (Oxford). 2016 Oct;55(10):1906-10.
 Kowal-Bielecka O, et al. Ann Rheum Dis. 2017 Aug;76(8):1327-1339
 Koo SM, et al. Tuberc Respir Dis (Seoul). 2019 Oct;82(4):285-297.
 Jee AS, et al. Respirology. 2021 Jan;26(1):23-51.
 Raghu G, et al. Am J Respir Crit Care Med. 2024 Jan 15;209(2):137-152.

Kuwana M, et al. Expert Rev Respir Med. 2023 Jan;17(1):71-80.
 Denton CP, et al. Rheumatology (Oxford). 2024 Nov 1;63(11):2956-2975
 Del Galdo F, et al. Ann Rheum Dis. 2025 Jan;84(1):29-40.
 Oh JH, et al. Tuberc Respir Dis (Seoul). 2025 Apr;88(2):247-263
 Johnson SR, et al. Arthritis Rheumatol. 2024 Aug;76(8):1201-1213. .

Guidelines for autoimmune rheumatic diseases-ILD

AMERICAN THORACIC SOCIETY DOCUMENTS

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

③ 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. Volkman, 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

BSR Guidelines

The 2024 British Society for Rheumatology guideline for management of systemic sclerosis

Christopher P. Denton ^{1,*}, Enrico De Lorenzis ², Elen Roblin ³, Nina Goldman ¹, Begonya Alcacer-Pitarch ², Emma Blamont ⁴, Maya H. Buch ⁵, Maresa Carulli ⁶, Caroline Cotton ⁷, Francesco Del Galdo ², Emma Derrett-Smith ⁸, Karen Douglas ⁹, Sue Farrington ⁴, Kim Fligelstone ³, Luke Gompels ¹⁰, Bridget Griffiths ¹¹, Ariane Herrick ¹², Michael Hughes ⁵, Clare Pain ¹², Georgina Pantano ¹³, John D. Pauling ¹⁴, Athiveeraramapandian Prabu ⁸, Nuala O'Donoghue ¹⁵, Elisabetta A. Renzoni ¹⁶, Jeremy Royle ¹⁷, Muditha Samaranayaka ¹⁸, Julia Spierings ¹⁹, Aoife Tynan ³, Louise Warburton ²⁰, Voon H. Ong ¹

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

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EUROPEAN RESPIRATORY JOURNAL
ERS OFFICIAL DOCUMENTS
K.M. ANTONIOU ET AL

ERS/EULAR clinical practice guidelines for connective tissue disease-associated interstitial lung disease

Developed by the task force for connective tissue disease-associated interstitial lung disease of the European Respiratory Society (ERS) and the European Alliance of Associations for Rheumatology (EULAR)

Endorsed by the European Reference Network on rare respiratory diseases (ERN-LUNG)

Raghu G, et al. Am J Respir Crit Care Med. 2024 Jan 15;209(2):137-152
Denton CP, et al. Rheumatology (Oxford). 2016 Oct;55(10):1906-10.
Johnson SR, et al. Arthritis Rheumatol. 2024 Aug;76(8):1182-1200.
Johnson SR, et al. Arthritis Rheumatol. 2024 Aug;76(8):1201-1213
Antonίου KM, et al. Eur Respir J 2026; 67: 2402533

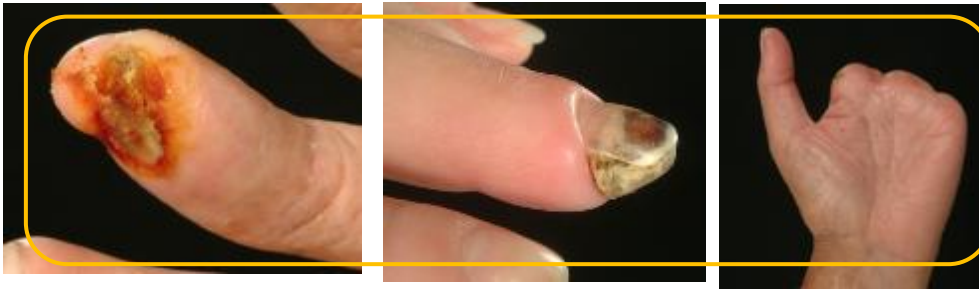
Spectrum of scleroderma diseases



With permission [Royal Free cohort]

Overview of major SSc complications – unmet need

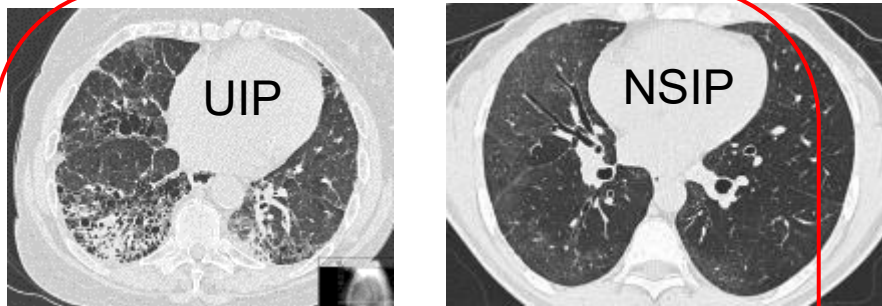
Digital vasculopathy



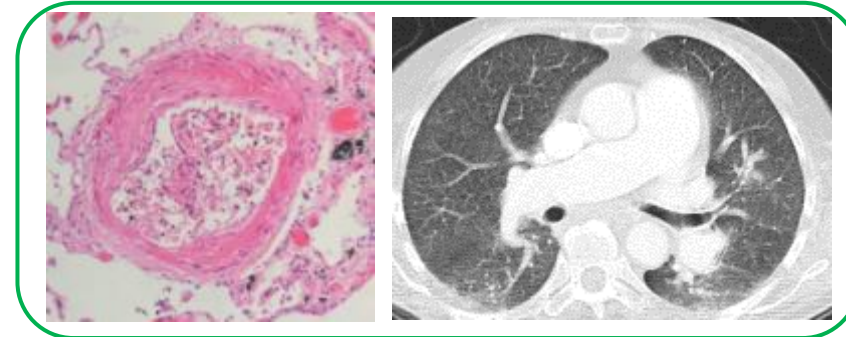
Gastrointestinal



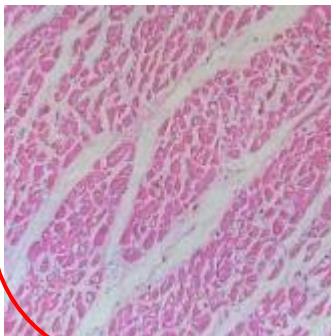
Lung fibrosis



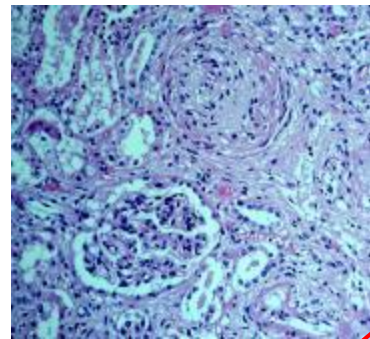
Pulmonary hypertension



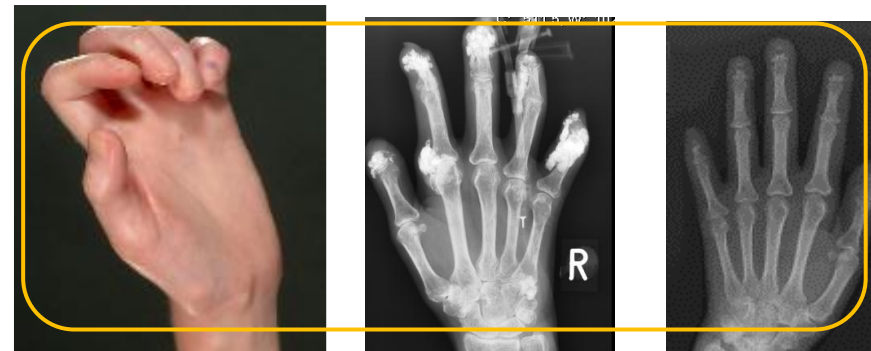
Cardiac



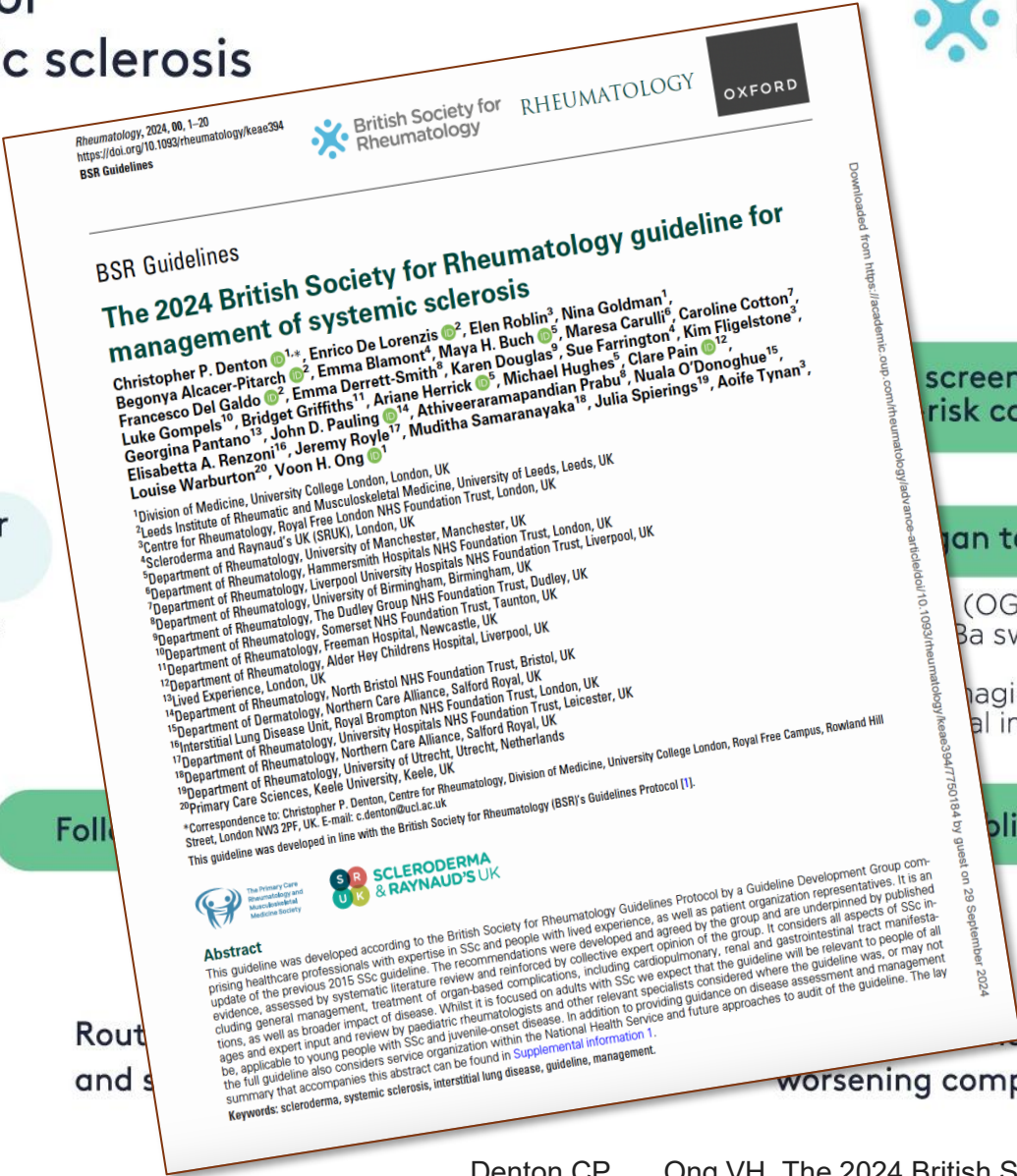
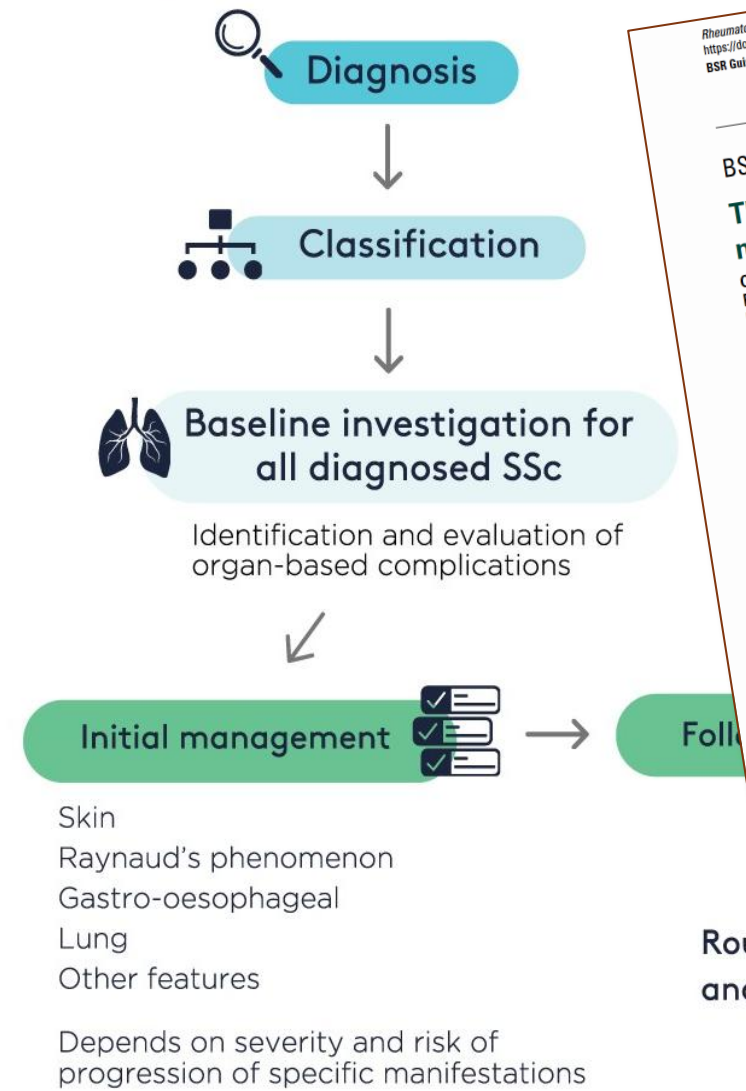
Renal



Musculoskeletal Calcinosis Acro-osteolysis



Overarching principles for management of systemic sclerosis



screening
risk cases

an testing

(OGD,
Ba swallow,

aging
al imaging

olished disease

worsening complications

Denton CP, ... Ong VH. The 2024 British Society for Rheumatology guideline for management of systemic sclerosis. Rheumatology (Oxford). 2024 Nov 1;63(11):2956-2975.

Integrative management of systemic sclerosis: multidisciplinary approach

Research

- SMART database of 3000 SSc patient cohort
- Bioresource of research tissue
- Focus on fibrosis, vascular and immunological perturbation

ILD

- Consultant-led ILD clinic
- Brompton RF SSc Radiology network MDT
- Joint Brompton MDT clinic
- Lung transplant referral with Harefield/Papworth
- AHP services
 - CNS
 - Pharmacist

PAH

- National PAH service
- Collaborative SSc PAH outreach network
- Cardiac MR imaging and echocardiogram

Dermatology

- Joint dermatology MDT clinics
- National referral centre for scleromyxedema and localised SSc

Renal

- Joint renal clinic
- Referral centre for renal crisis

Global management of systemic sclerosis – treatment considerations

Neurological

Neurological complications of SSc require multi-speciality management with careful exclusion of other relevant causes 1C
Peripheral Sensory neuropathy of the feet is common 2C

ILD

MMF is recommended as first line treatment with rituximab or cyclophosphamide i.v. as alternative 1B
Consider adding rituximab or tocilizumab to MMF for progressive disease 2C
Nintedanib recommended for progressive pulmonary fibrosis 1B

PAH

PAH diagnosis by right heart catheter and treatment 1A initiated by a designated Pulmonary Hypertension Centres 1B
Anticoagulation is not recommended in PAH-SSc 1B

Renal

ACEi should be used in all cases of diagnosed SRC 1A
Glucocorticoid treatment avoided in adult SSc due increased SRC risk 1A
Renal biopsy should be considered when diagnosis uncertain 1C
Referral for renal transplantation in cases without significant renal recovery 1B

Skin

MMF is first line treatment for skin fibrosis in dcSSc 1C
Antihistamines are often used for itch 2C
Options for telangiectasia include skin camouflage, pulsed dye laser or intense pulsed light therapy 2C

Musculoskeletal

Musculoskeletal manifestations of SSc may benefit from immunomodulatory treatments given for other complications 1C

Digital ulcers

Severe digital vasculopathy with new tissue necrosis or critical ischaemia requires urgent clinical assessment 1C
Sildenafil (or tadalafil) as 1st line agent in DU healing and secondary prevention and bosentan as second line treatment 1C
Expert opinion supports use of IV prostanooids in promoting DU healing 1C



Fatigue and Health related Quality of Life

Physical and occupational therapy may improve quality of life, pain, and fatigue 2C

Cardiac

Immunosuppression with MMF for SSc- pHI when investigation suggests myocardial inflammation 2C
Glucocorticoids and other bDMARDs may be added if appropriate and/or cyclophosphamide 2C

Gastrointestinal

PPI and/or H2 receptor antagonists for reflux 1C
Parenteral nutrition for severe malnutrition 1B
Intermittent or rotational antibiotics SIBO 2B
Anti-diarrhoeal agents or laxatives 2B
Surgical intervention should be avoided 1C

Reproductive health

Sexual dysfunction needs engagement of gynaecology, urology, and sexual health clinical services 1C
For planned pregnancy in SSc identify significant organ dysfunction and discontinue harmful medication 1C
Pregnancy management requires integrated multi-disciplinary care 2C

Raynaud's phenomenon

Calcium channel blockers and other vasodilators may be considered in management of SSc-RP 1B
Expert opinion suggests that PDE5i are effective as 2nd line agent for refractory SSc-RP 1B
For rescue therapy in severe SSc-RP IV prostanooids may be considered 1C

KEY:

- Life-threatening complications
- Non-lethal morbidity that has major impact on people with SSc

Clinical trials

- Observational and interventional trials
- Academic and industrial-led studies
- Collaborative PAH studies
- RFC and UCL partnership

Network

- ASCT with UCLH and Netherlands
- RheumNET CTD network
- Outreach clinics in South England
- International MDT – Belfast, Malaysia

Gastroenterology

- Joint gastroenterology MDT clinic
- Nutritional and dietetic referral
- Gut physiology – Louise Ryan Unit
- Pelvic health physiotherapy

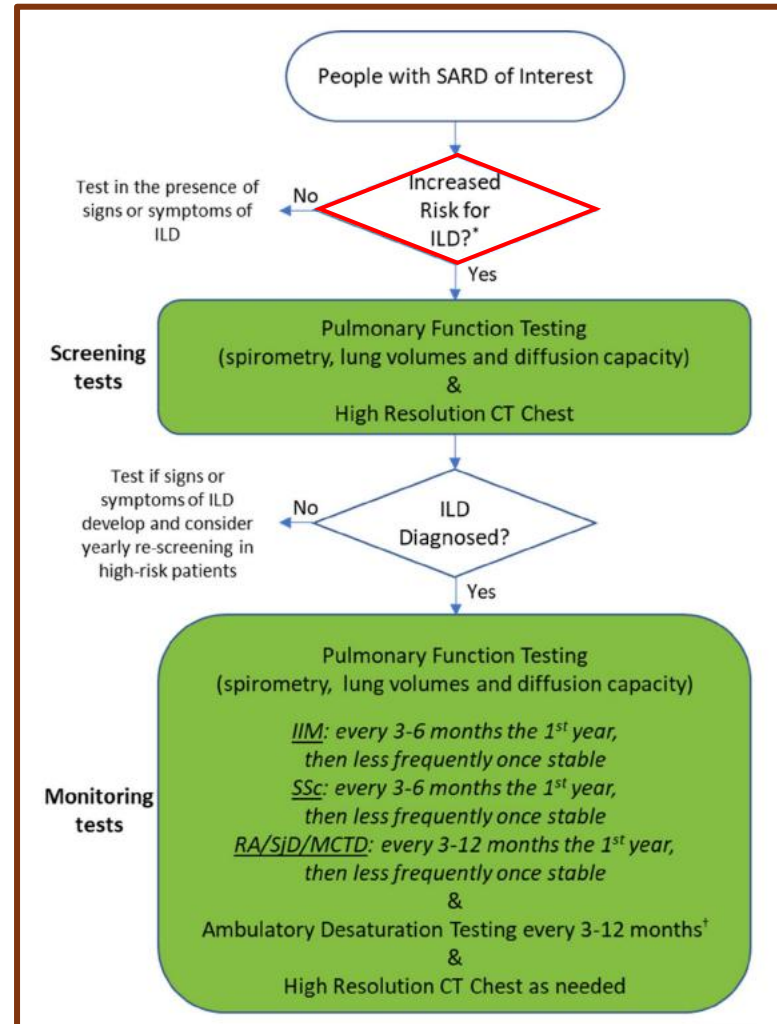
Vascular

- Nurse-led DU and Raynauds clinics
- Angioplasty

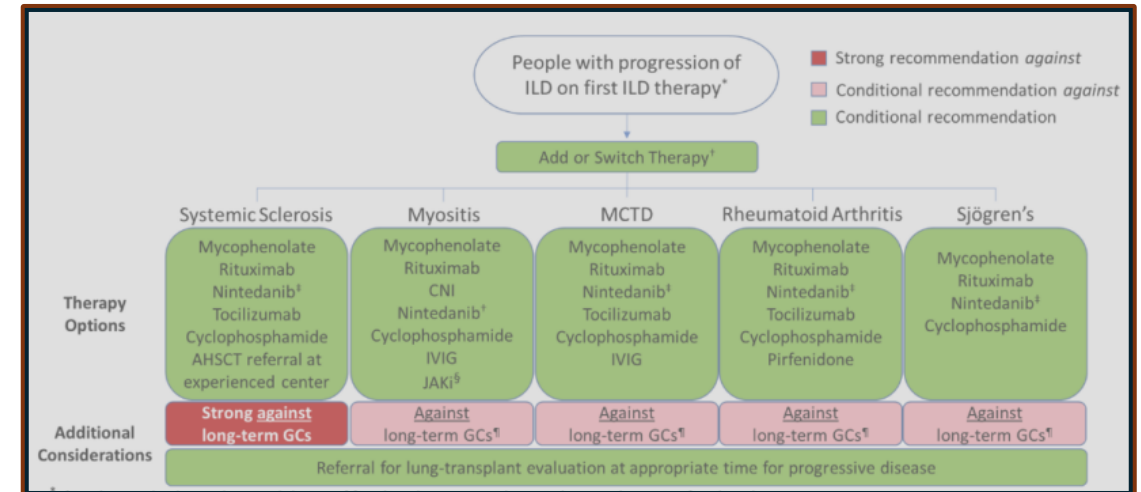
Plastics and hand surgery

- Autologous lipotransfer
- Botox injection
- Digital terminalisation
- Digital sympathectomy

ACR/CHEST guidelines for SARD-ILD



	Systemic Sclerosis	Myositis	MCTD	Rheumatoid Arthritis	Sjögren's
First-line ILD therapy	Preferred Mycophenolate [†] Tocilizumab Rituximab	Mycophenolate [†] Azathioprine Rituximab CNI	Mycophenolate [†] Azathioprine Rituximab	Mycophenolate [†] Azathioprine Rituximab	Mycophenolate [†] Azathioprine Rituximab
Additional options	Cyclophosphamide Nintedanib Azathioprine	JAKi Cyclophosphamide	Tocilizumab Cyclophosphamide	Cyclophosphamide	Cyclophosphamide
+ Glucocorticoids	Strong recommendation against GCs	Short-term GCs [*]	Short-term GCs [*]	Short-term GCs [*]	Short-term GCs [*]



Risk of development of ILD in SARDs

General risk factors

- Male
- Smoking
- Older age
- **Autoantibodies**

Myositis

SSc

MCTD

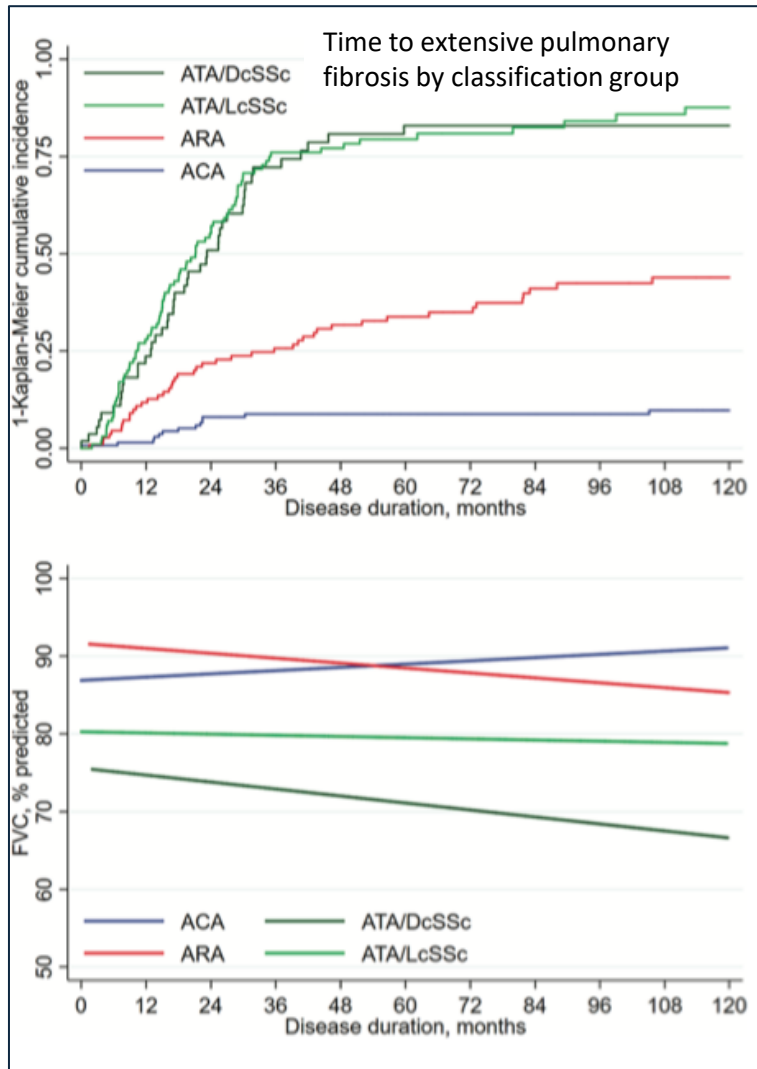
Rheumatoid arthritis

Autoantibodies	Staining on ANA test with indirect immunofluorescence	Prevalence of antibody	Clinical associations except ILD	Prevalence of ILD and its disease behavior
Antisynthetase	ANA negative, cytoplasmic	15–30% in IIM, but found in patients without apparent myositis or DM skin rashes; rare in children	Myositis, arthritis, mechanic's hands, called ASS	90% develop ILD, mainly ILD that stabilizes over time after treatment with immunosuppressive agents, but recurrence is common
Anti-MDA5	ANA negative, cytoplasmic	10–30% of DM, both classic and clinically amyopathic DM; also found in children	Severe skin vasculopathy, arthritis	80% develop ILD, often rapidly progressive ILD, but some have mild ILD resembling ASS
Anti-PM/Scl	Nucleolar	25% of SSc-myositis overlap, 3–6% of SSc	Younger age at disease onset, myositis, lcSSc, arthritis	35–87% have ILD with a better functional outcome
Anti-Ku	Speckled	15% of SSc-myositis overlap; 9% in myositis cohort; 2% in SSc cohort	Younger age at disease onset, myositis, lcSSc, arthritis, DM skin rashes, fewer vascular manifestations such as digital ulcer	Up to 76% have ILD with a better functional outcome
Anti-topo I	Speckled or homogeneous	20–30% of SSc	dcSSc, digital ulcer early in the disease course	80% develop ILD, of which up to 30–50% have progressive fibrosing ILD
Anti-Th/To	Nucleolar	2–5% of SSc	lcSSc, pulmonary arterial hypertension, less digital ulcer	Up to 50% develop ILD, of which 30% have progressive fibrosing ILD
Anti-U11/U12 RNP	Speckled	1–3% of SSc	Both dcSSc/lcSSc, gastrointestinal involvement, cancer in close temporal relationship to onset of SSc	80% develop ILD, which is often severe and associated with increased mortality
Anti-EIF2B	ANA negative, cytoplasmic	<1% of SSc	dcSSc	Up to 100% have ILD
Anti-U1RNP	Speckled	5–35% of patients presenting SSc or overlap syndrome; 100% in MCTD	Younger age at disease onset, arthritis, myositis, lcSSc, pulmonary arterial hypertension	Up to 35% have ILD, of which 20% classified as severe
RF	ANA negative	70–80% in RA	Extra-articular manifestations, especially in high titer	10–40% have ILD, including UIP and NSIP; risk of acute exacerbation
ACPA	ANA negative	70–80% in RA	Progression of joint destruction, MACE	10–40% have ILD, including UIP and NSIP; risk of acute exacerbation

ANA positive and ENA negative SSc-ILD cohorts

Anti-RuvBL1/2	Speckled	RuvBL1/2 double hexamer	1-2%	Diffuse and myositis overlap	Higher frequency in men and higher age of onset with myositis including cardiac involvement and gut dysmotility	
Anti-RNPC-3	Speckled	Small nuclear ribonucleoproteins U11 and U12	3-5%	Diffuse and limited	Coexisting PAH and GI disease and myositis and malignancy	
Anti-BICD2	speckled and/or nucleolar ?	Bicaudal D protein	20-35%	Diffuse	Associated myositis, may coexist with ACA	
Anti-NOR90	Nucleolar punctate	??	2-3%	Limited	Good prognosis	Variably associated with increased risk of ILD
Anti-PRMT5	enzyme belonging to arginine methyltransferases	Unknown	31%	?Diffuse	May coexist with ATA	
Anti-TERF1	Unknown	??	9%	Limited and diffuse	May occur with anti-Ku and anti-U1RNP	

Prediction of significant lung fibrosis by Scl70 antibody



	HR	95% CI		p-value
FVC<70% prediction				
Baseline FVC	0.84	0.79	0.89	<0.001
Male	1.92	1.16	3.16	0.011
Anti-topoisomerase antibody	1.68	1.05	2.69	0.030
Baseline FVC*Time (years)	1.02	1.01	1.03	<0.001
FVC<50% prediction				
Baseline FVC	0.91	0.89	0.94	<0.001
Multivariable Cox regression analysis for predictors of time to FVC<70% and FVC<50% in SSc-ILD				

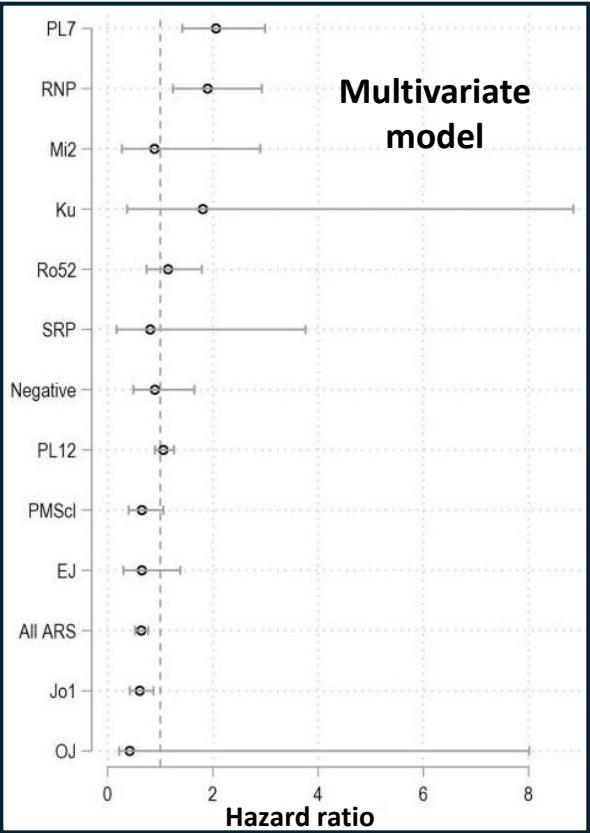
Autoantibody assays

- 52 subjects who tested positive for anti-Scl-70 antibody but without clinical SSc¹
 - 48 subjects (92.3%) was judged negative by Anti-Scl-70 antibody on immunodiffusion method
 - 18 subjects were negative for ANA by indirect immunofluorescence
- Standardisation in autoimmune serology is lacking
- If commercial immunoassays are inconsistent with clinical presentation, false-positive result should be considered
- Lower agreement reported for anti-fibrillarin and Th/To and anti-PM-Scl and Ku²

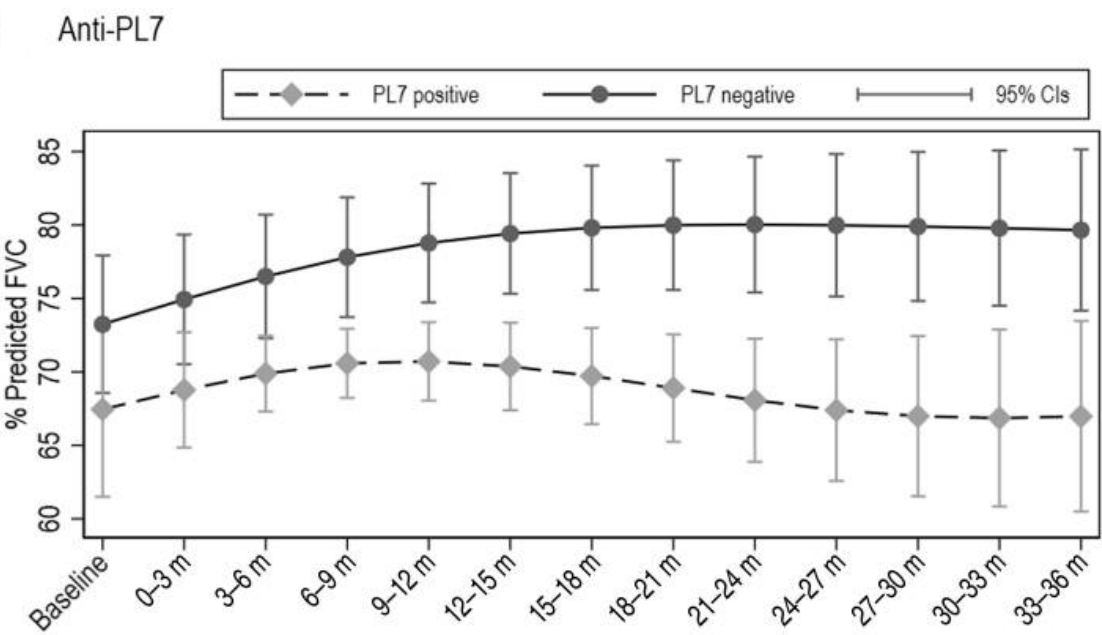
¹Lam BH, et al. False positive anti-Topoisomerase I (Scl-70) antibody results in clinical practice: A case series from a scleroderma referral center. Semin Arthritis Rheum. 2022 Oct;56:152052.

²Alkema W, et al. Autoantibody profiles in systemic sclerosis; a comparison of diagnostic tests. Autoimmunity. 2021 May;54(3):148-155.

Differential outcome with anti PL7 antibody in myositis ILD cohort

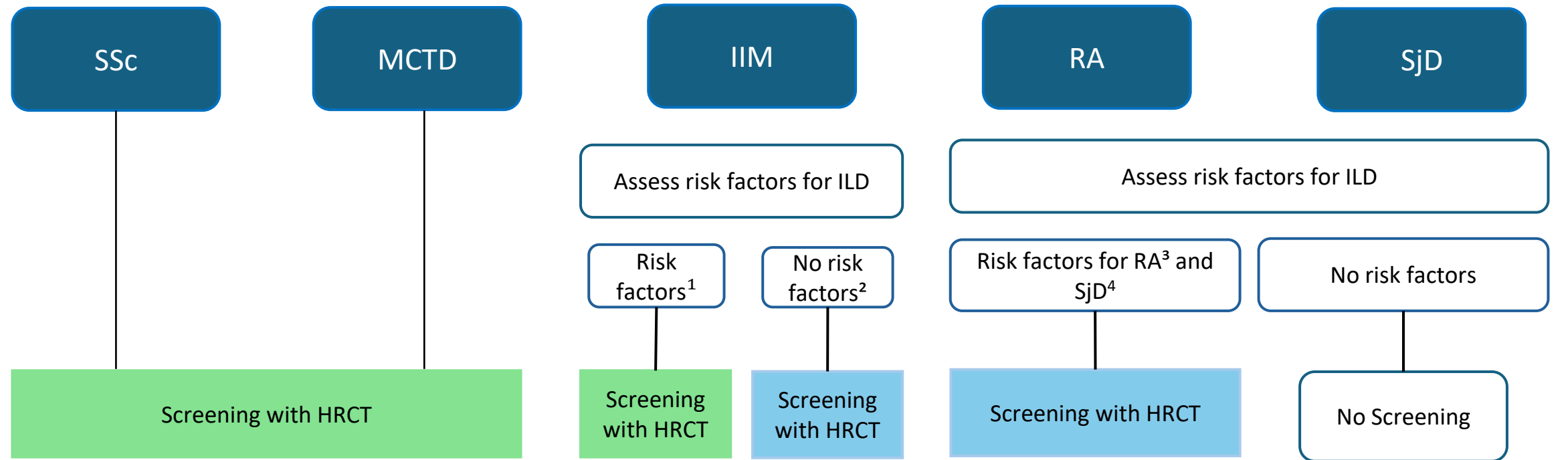


			Univariate model		Multivariate model	
Antibody	Number of patients	Number reaching end point	HR (95% CI)	P value	HR (95% CI)	P value
Primary end point—all-cause mortality						
Jo1	126	21	0.56 (0.35, 0.91)	0.020	0.61 (0.42, 0.87)	0.006
PL12	44	10	0.90 (0.47, 1.73)	0.748	1.06 (0.90, 1.26)	0.482
PL7	26	11	2.29 (1.22, 4.31)	0.010	2.06 (1.42, 2.99)	<0.001



- Increased mortality among antiMDA5 early on, and anti-PL7 cohort
- Anti-PL7+ was linked with a slow FVC decline from 12 months onwards.

Screening of CTD for ILD



Consider in every patient:

- Assessment of respiratory symptoms
- Lung function tests (FVC and DLCO) in case of symptoms or CT abnormalities

■ Conditional recommendation
■ Strong recommendation
▬ Clinical practice

¹IIM: anti-synthetase syndrome, clinical amyopathic dermatomyositis, presence of mechanic hands, arthritis, anti-synthetase, anti-MDA-5 and anti-Ro52 antibodies

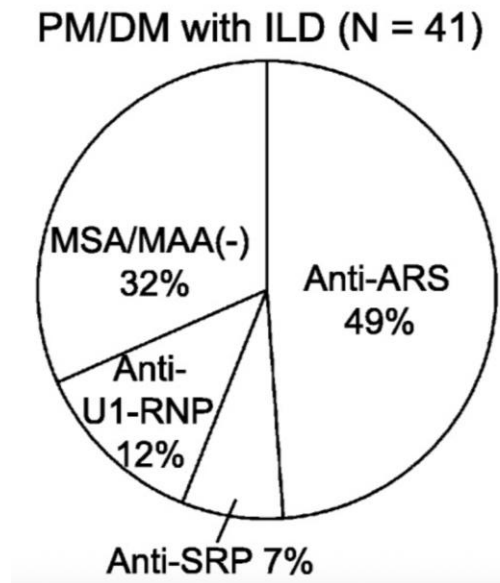
²IIM: except patients with inclusion body myositis

³RA: older age, smoking history, elevated rheumatoid factor, anti-CCP antibodies, increased inflammatory markers, male sex and high RA disease activity

⁴SjD: older age, active extra-pulmonary organ involvement and increased inflammatory markers

For CTDs with high ILD prevalence, screen irrespective of risk factors

- All patients with myositis regardless of symptoms should be screened for ILD (expert opinion) ¹
- Patients can present with clinical features consistent with IIM-ILD without myositis-specific antibody.
 - 32% of PM/DM with ILD MSA/MAA negative compared with 49% with anti-ARS²
 - Similar LF trajectory and lower steroid responsiveness compared with those MSA positive ²
 - None of the risk factors in IIM are definitively linked to presence or absence of ILD
- SSc patients may have significant fibrotic CT extent with minimal, if any, cough or dyspnoea
- RA patients “with multiple risk factors “ should be screened



¹Hallowell RW, Paik JJ. Clin Exp Rheumatol. 2022 Feb;40(2):373-383.

²Yoshifuji, H et al. *Autoimmunity*. 2006; 39:233-241

Summary of screening approaches in RA ILD based on risk factor

RA-ILD Risk factors	ANCHOR-RA	ACR/CHEST guidelines	ERS/EULAR	ESPOIR	SAIL-RA	Four Factor Score
Male gender	☒	☒	☒	☒	☒	
Age onset 60 yr old	☒	☒	☒	☒	☒	☒
Suggest patients with high-risk CTDs including RA to be screened with CT at baseline for ILD						
Podolanczuk AJ, et al. Approach to the Evaluation and Management of Interstitial Lung Abnormalities: An Official American Thoracic Society Clinical Statement. Am J Respir Crit Care Med. 2025 Jul;211(7):1132-1155.						
Extra-articular features	☒					
MUC5B promoter variant				☒		
Acute phase response			☒			
Obesity		☒				

Sparks JA, et al. BMC Rheumatol. 2024 May 21;8(1):19.
Johnson SR, et al. Arthritis Rheumatol. 2024 Aug;76(8):1201-1213.
Juge PA, et al. Arthritis Rheumatol. 2022 Nov;74(11):1755-1765.
McDermott GC, et al. Lancet Rheumatol. 2025 Dec;7(12):e851-e863.
Koduri GM, et al. Rheumatol Int. 2023 Aug;43(8):1515-1523.
Antoniou KM et al. Eur Respir J. 2026 Jan 22;67(1):2402533.

Proposed screening strategy for ILD in early RA

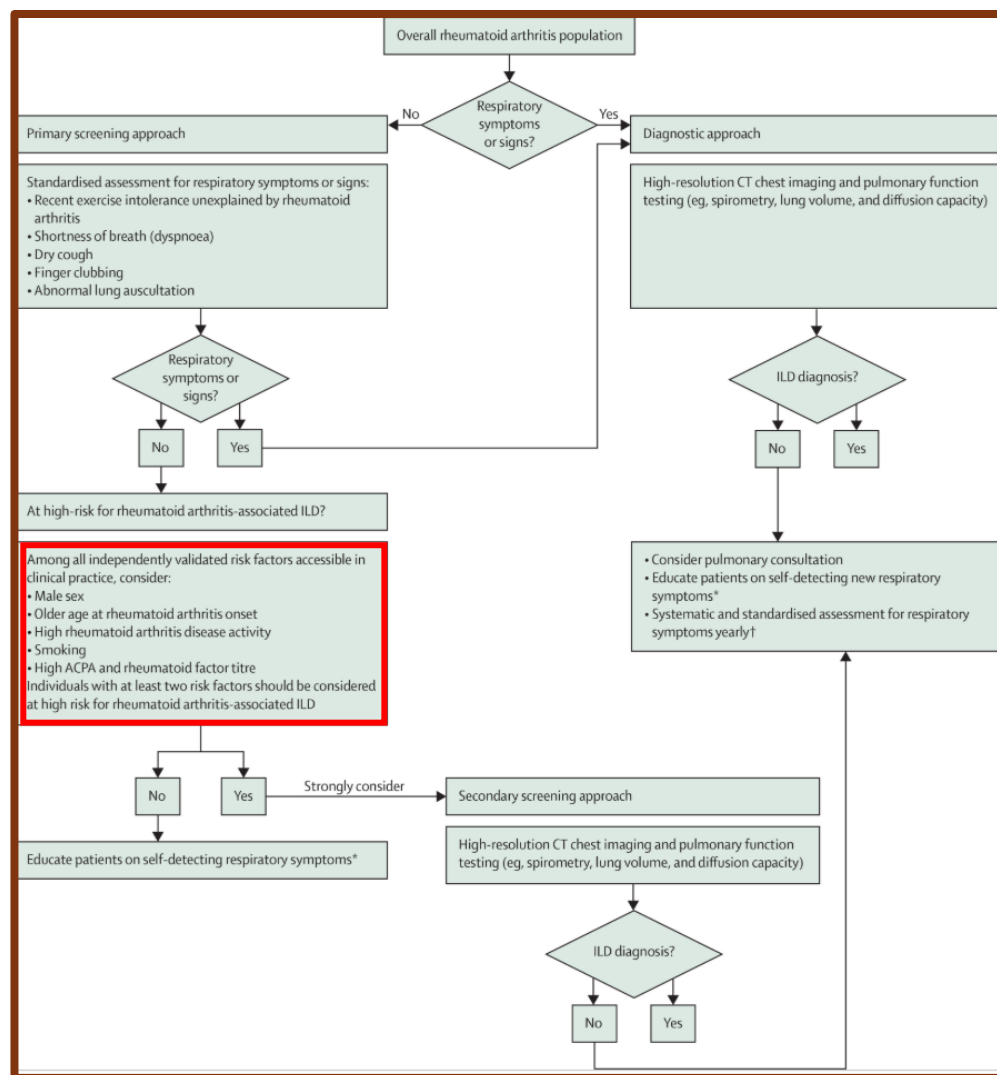
	RA-ILD cases/ denominator in stratum* (%)	Unadjusted OR (95% CI)	Multivariable† OR (95% CI)
Demographics			
Age at rheumatoid arthritis diagnosis			
<60 years	6/99 (6%)	1 (ref)	1 (ref)
≥60 years	13/64 (20%)	3.95 (1.42–11.02)	3.87 (1.33–11.27)
Sex at birth			
Male	6/38 (16%)	1.62 (0.57–4.59)	2.64 (0.79–8.84)
Female	13/125 (10%)	1 (ref)	1 (ref)
Lifestyle			
Smoking status			
Never	10/104 (10%)	1 (ref)	..
Ever	9/59 (15%)	1.69 (0.65–4.44)	..
Pack-years, per unit	19/163 (12%)	1.00 (0.99–1.01)	..
BMI			
Underweight or normal (<25 kg/m ²)	4/43 (9%)	1 (ref)	..
Overweight (≥25–<30 kg/m ²)	8/58 (14%)	1.56 (0.44–5.56)	..
Obese (≥30 kg/m ²)	7/62 (11%)	1.24 (0.34–4.53)	..
Rheumatoid arthritis characteristics			
Anti-CCP titre‡			
Negative	8/74 (11%)	1 (ref)	..
>1–3 × ULN	1/17 (6%)	0.52 (0.06–4.42)	..
>3 × ULN	9/68 (13%)	1.26 (0.46–3.47)	..
Rheumatoid factor titre‡			
Negative	8/102 (8%)	1 (ref)	..
>1–3 × ULN	3/21 (14%)	1.96 (0.47–8.10)	..
>3 × ULN	7/35 (20%)	2.94 (0.98–8.81)	..
Extra-articular manifestations			
No	18/154 (12%)	1 (ref)	..
Yes	1/9 (11%)	0.94 (0.11–8.00)	..
Disease activity			
Remission or low§	4/88 (5%)	1 (ref)	1 (ref)
Moderate or high§	15/75 (20%)	5.25 (1.66–16.61)	7.00 (1.95–25.13)

- n = 172
- Median disease duration 0.79 years
- DAS-28-ESR 3.08
- Disease activity
 - Moderate or high 46%
- Anti-CCP positive 74%
- Rheumatoid factor positive 68%

Prevalence of ILD in new onset RA was 11% including

- 11% of patients having >30% lung involvement on HRCT
- 35% having a forced vital capacity <80%

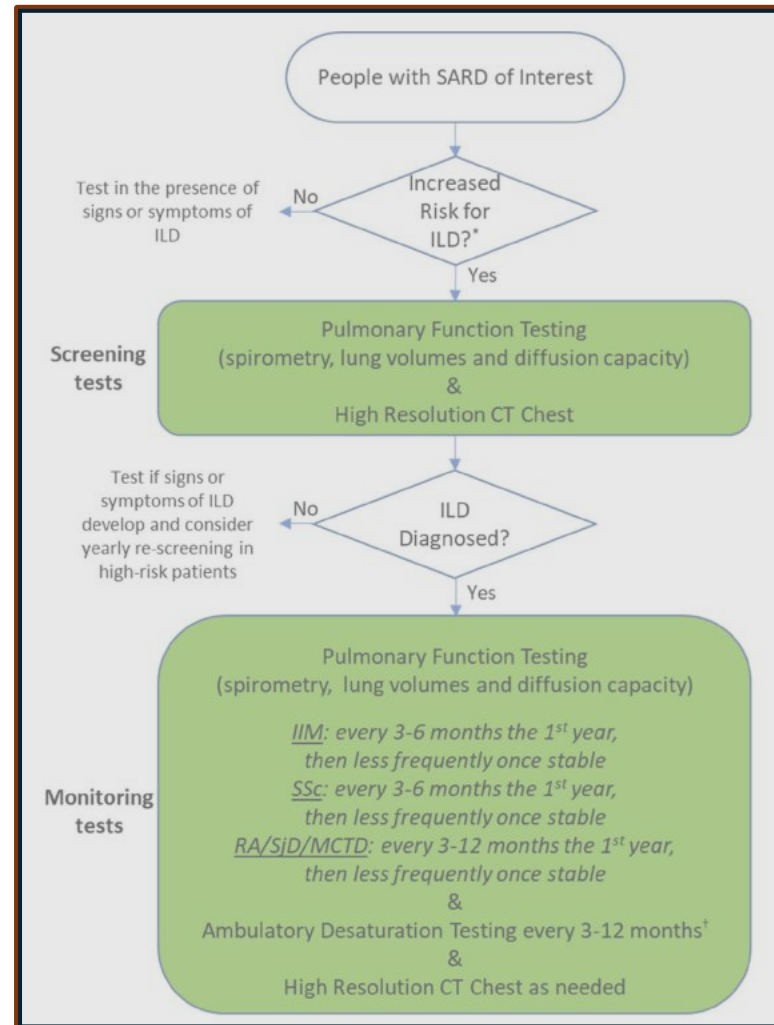
Screening algorithm for ILD in patients with rheumatoid arthritis



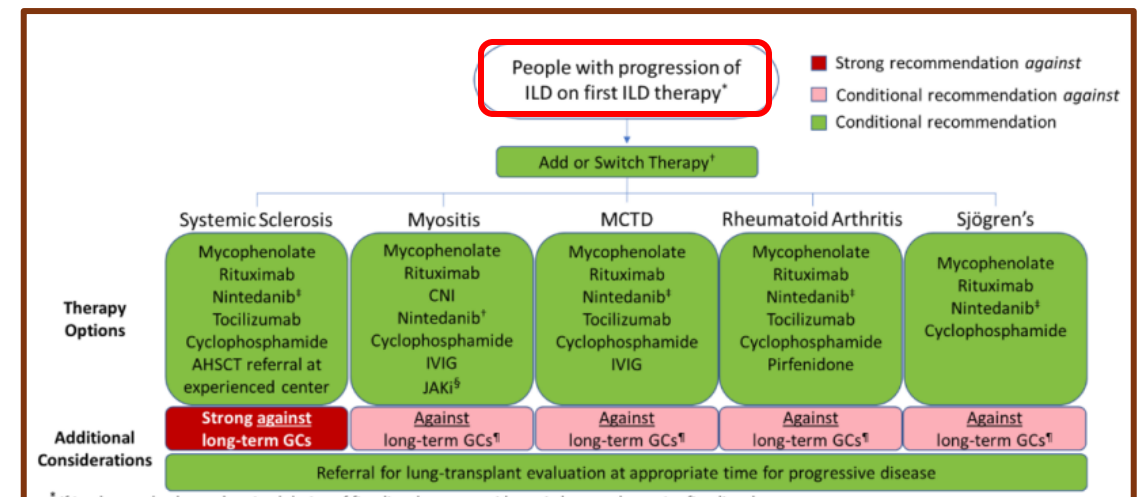
- Two-step screening strategy
 - Primary
 - Secondary
- Symptom and sign assessment
- HRCT and PFT
- PFT as alternative in low resource areas

Solomon JJ, et al. Lancet Respir Med. 2026 Jun 5:S2213-2600(26)00094-9.

ACR/CHEST guidelines for SARD-ILD

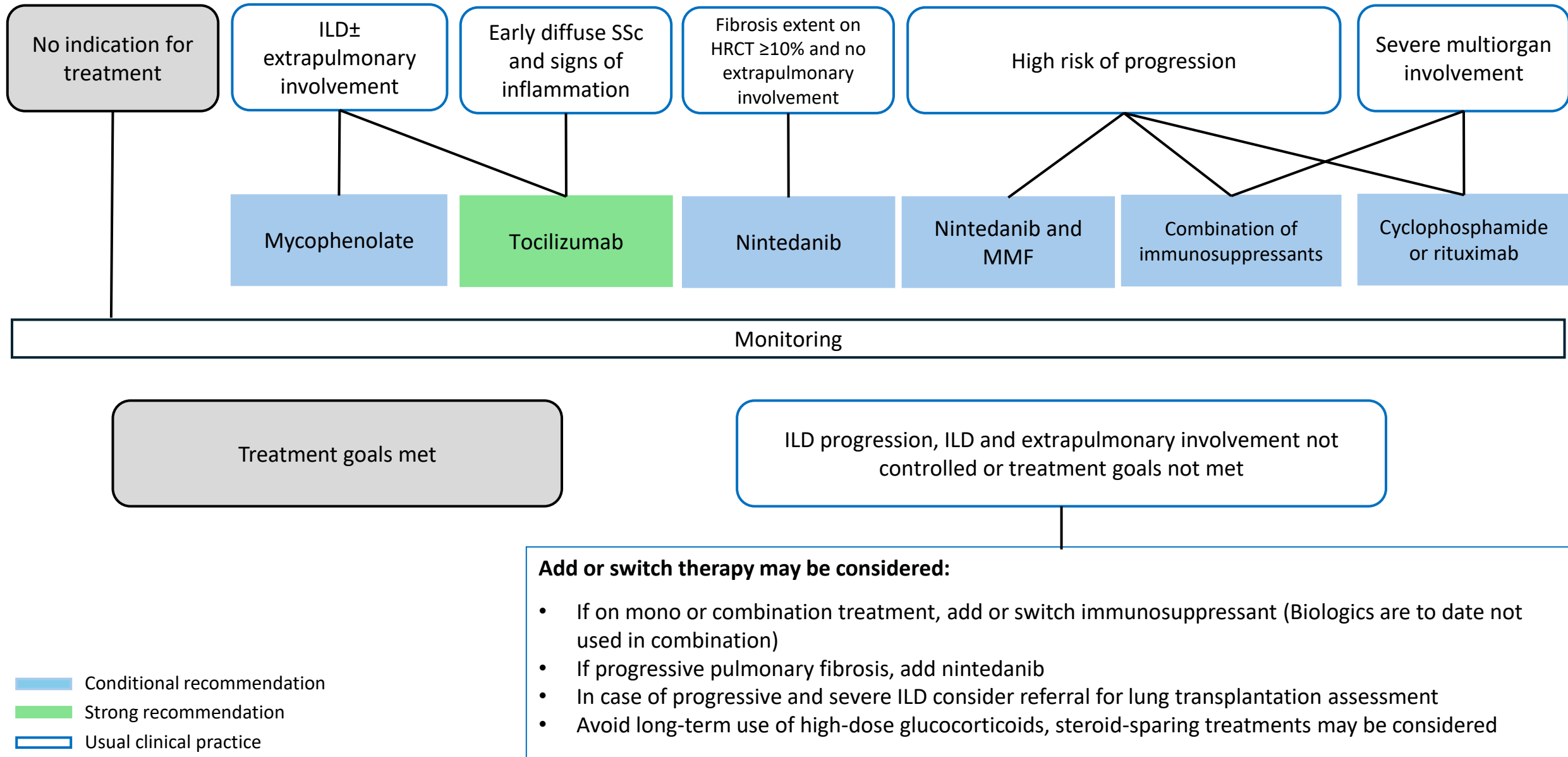


	Systemic Sclerosis	Myositis	MCTD	Rheumatoid Arthritis	Sjögren's
Preferred	Mycophenolate [†] Tocilizumab Rituximab	Mycophenolate [†] Azathioprine Rituximab CNI	Mycophenolate [†] Azathioprine Rituximab	Mycophenolate [†] Azathioprine Rituximab	Mycophenolate [†] Azathioprine Rituximab
Additional options	Cyclophosphamide Nintedanib Azathioprine	JAKi Cyclophosphamide	Tocilizumab Cyclophosphamide	Cyclophosphamide	Cyclophosphamide
+ Glucocorticoids	Strong recommendation against GCs	Short-term GCs*	Short-term GCs*	Short-term GCs*	Short-term GCs*



Johnson SR, et al.. Arthritis Rheumatol. 2024 Aug;76(8):1201-1213.
 Johnson SR, et al. Arthritis Rheumatol. 2024 Aug;76(8):1182-1200.

Treatment of SSc-ILD



Steroids and risk of hypertensive scleroderma renal crisis

- Prior use of high dose glucocorticoid frequently precedes the development of SRC.
- A case control study matched 106 patients with renal crisis to other scleroderma patients based on features that would be associated with increased risks for renal crisis or the use of steroids¹
 - Patients who received high dose prednisone (>15mg/day) were 3 times more likely to develop renal crisis in the next 6 months.
- More SRC cases were exposed to glucocorticoids prior to SRC compared with control cases of SSc without SRC²
- Steroid exposure prior to SRC has also been associated with worse outcomes³
 - For every milligram of prednisone, the risk of death increased by 4% (hazard ratio [HR] 1.04, 95% CI 1.02, 1.07, $p < 0.01$)
- Prior exposure to ACEi may associate with worse mortality from SRC⁴
- No effect on skin or lung progression in dcSSc⁵
- Steroids were associated with worse outcomes in patients with severely reduced FVC⁶

¹Steen VD, Medsger TA, Jr. Arthritis Rheum 1998; 41(9):1613-9

²Guillevin L et al. Rheumatology (Oxford). 2012 Mar;51(3):460-7.

³Hudson M, et al. Semin Arthritis Rheum, 2014. 43(5): 666-72

⁴Hudson M, et al. Semin Arthritis Rheum. 2014 Apr;43(5):666-72.

⁵Griffiths-Jones DJ, et al. Rheumatology (Oxford) 2023 Sep 1;62(9):3133-3138.

⁶Mongin D, et al. Arthritis Care Res (Hoboken). 2025 May;77(5):649-657.

⁶Adler Set al. Arthritis Res Ther 2018; 20:17

Impact of mycophenolate on lung function and skin activity in early diffuse scleroderma

Arthritis & Rheumatism

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Efficacy and Safety of Lenabasum, a Cannabinoid Type 2 Receptor Agonist, in a Phase 3 Randomized Trial in Diffuse Cutaneous Systemic Sclerosis

Robert Spiera,¹ Masataka Kuwana,² Dinesh Khanna,³ Laura Hummers,⁴ Tracy M. Frech,⁵ Wendy Stevens,⁶ Marco Mahucci-Cerina,⁷ Suzanne Kafaja,⁸ Oliver Distler,⁹ Joe-Bum Jun,¹⁰ Yair Levy,¹¹ Piotr Leszczynski,¹² Jessica Gordon,¹³ Virginia Stein,¹⁴ Eun Bong Lee,¹⁵ Tomasz Jankowski,¹⁶ Irena Litinsky,¹⁷ Lorina Chung,¹⁸ Vivien Hsu,¹⁹ Maureen Mayes,²⁰ Nora Sandorf,²¹ Robert W. Simms,²² Stephanie Vinay,²³ Jenka de Vries-Bouwstra,²⁴ Scott Constantine,²⁵ Nancy Deterluk,²⁶ Quinn Dinh,²⁷ Bradley J. Bloom,²⁸ Daniel E. Furst,²⁹ Barbara White,³⁰ and Christopher P. Denton,³¹ on behalf of the RESOLVE-1 Study Group

Objective. This phase 3 study was undertaken to investigate the efficacy and safety of lenabasum, a cannabinoid type 2 receptor agonist, in patients with diffuse cutaneous systemic sclerosis (dcSSc).
Methods. A multinational double-blind study was conducted in 265 dcSSc patients who were randomized and dosed 1:1:1 with lenabasum 20 mg, lenabasum 5 mg, or placebo, each twice daily and added to background treatments, including immunosuppressive therapies (IST).
Results. The primary end point, the American College of Rheumatology combined response index in dcSSc (ACR-CRIS), at week 52 for lenabasum 20 mg twice a day versus placebo, was not met, with CRIS score of 0.856 versus 0.887 ($P = 0.4972$, using mixed models repeated measures [MMRM]). The change in the modified Rodnan skin thickness (mRSS) at week 52 for lenabasum 20 mg twice a day versus placebo was -6.7 versus -8.1 ($P = 0.1165$, 0.887 ($P = 0.4972$, using mixed models repeated measures [MMRM]). The change in the modified Rodnan skin thickness (mRSS) at week 52 for lenabasum 20 mg twice a day versus placebo was -6.7 versus -8.1 ($P = 0.1165$, 0.887 ($P = 0.4972$, using mixed models repeated measures [MMRM]). Prespecified analyses showed higher CRIS scores, greater improvement in mRSS, and lower decline in forced vital capacity in patients on background mycophenolate and those who were taking IST for ≤ 1 year. No deaths or excess in serious or severe adverse events related to lenabasum were observed.
Conclusion. A benefit of lenabasum in dcSSc was not demonstrated. Most patients were treated with background IST, and treatment with mycophenolate in particular was associated with better outcomes. These findings support the use of IST in the treatment of dcSSc and highlight the challenge of demonstrating a treatment effect when investigational treatment is added to standard of care IST. These findings have relevance to trial design in SSc, as well as to clinical care.

INTRODUCTION

Patients with diffuse cutaneous systemic sclerosis (dcSSc) have proximal skin thickening on the limbs or trunk and variable involvement of the lungs, heart, kidneys, gastrointestinal tract, and musculoskeletal system [1,2]. The general health status of

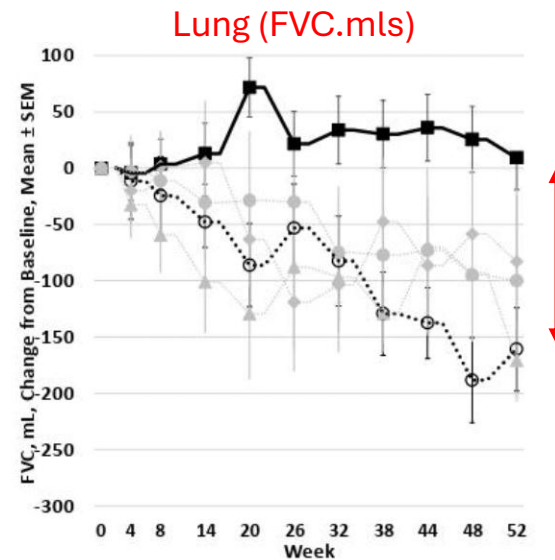
these patients is often markedly impaired, with greater chronic disease burden and increased mortality compared with the general population [3,4].

Approved treatments in North America for SSc are limited to nintedanib and tocilizumab, which are indicated for treatment of interstitial lung disease in SSc [5]. Other immunosuppressive

agents, including mycophenolate mofetil (MMF), cyclophosphamide (CYC), azathioprine (AZA), and tacrolimus (TAC), are used off-label for the treatment of SSc [6]. MMF is the most commonly used off-label agent, with a CRIS score of 0.856 versus 0.887 ($P = 0.4972$, using mixed models repeated measures [MMRM]). The change in the modified Rodnan skin thickness (mRSS) at week 52 for lenabasum 20 mg twice a day versus placebo was -6.7 versus -8.1 ($P = 0.1165$, 0.887 ($P = 0.4972$, using mixed models repeated measures [MMRM]). Prespecified analyses showed higher CRIS scores, greater improvement in mRSS, and lower decline in forced vital capacity in patients on background mycophenolate and those who were taking IST for ≤ 1 year. No deaths or excess in serious or severe adverse events related to lenabasum were observed.

Efficacy end point	Lenabasum 20 mg	Lenabasum 5 mg	Placebo
ACR CRIS	0.89 (p=0.49)	0.83 (p=0.35)	0.89
MRSS	-6.7 (p=0.12)	-7.1 (p=0.50)	-8.1
FVC%	1.6 (p=0.53)	2.2 (p=0.52)	-1

Impact of background MMF in early dcSSc (< 24 months)



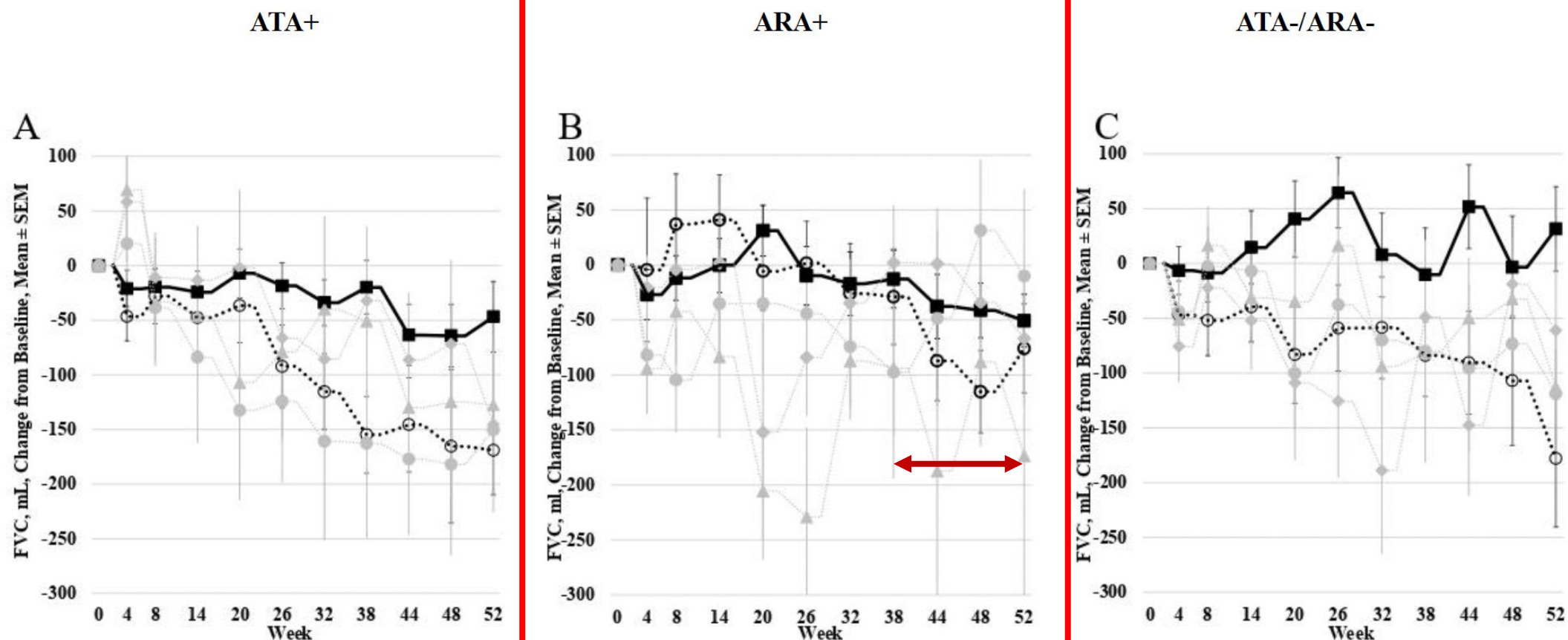
■ MMF n=181
○ no IST n=66

◆ MTX n=62
▲ Steroids n=89
● Other IST n=87

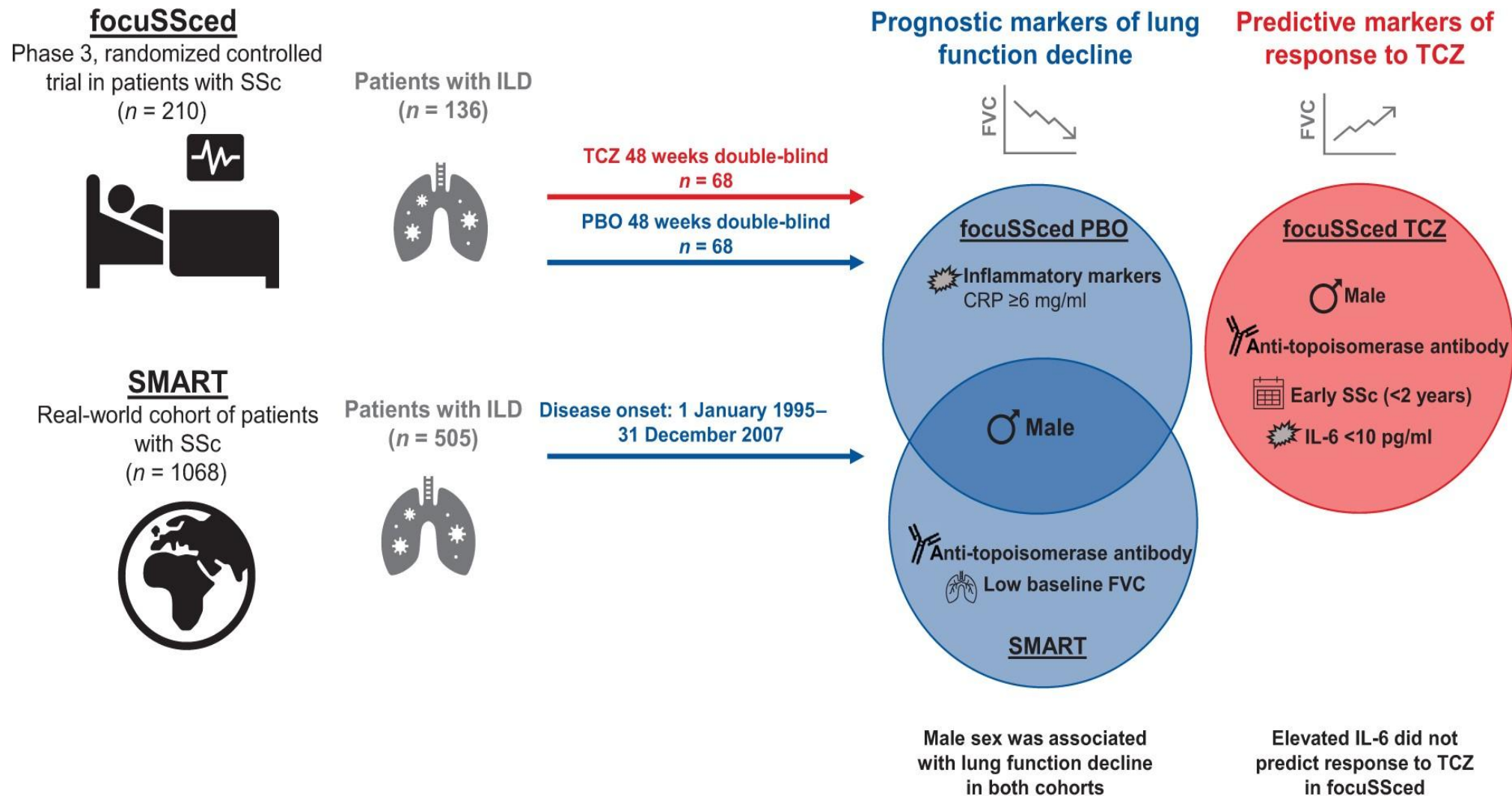
- Improvement in transitional dyspnoea index
 - 24% achieved the MCID for TDI (SLS II)
- Improvement in St George's respiratory questionnaire over 24 months
 - 25% achieved the MCID for SGRQ over 24 months

Volkman ER, et al. ACR Open Rheumatol. 2020 Jun;2(6):362-370.

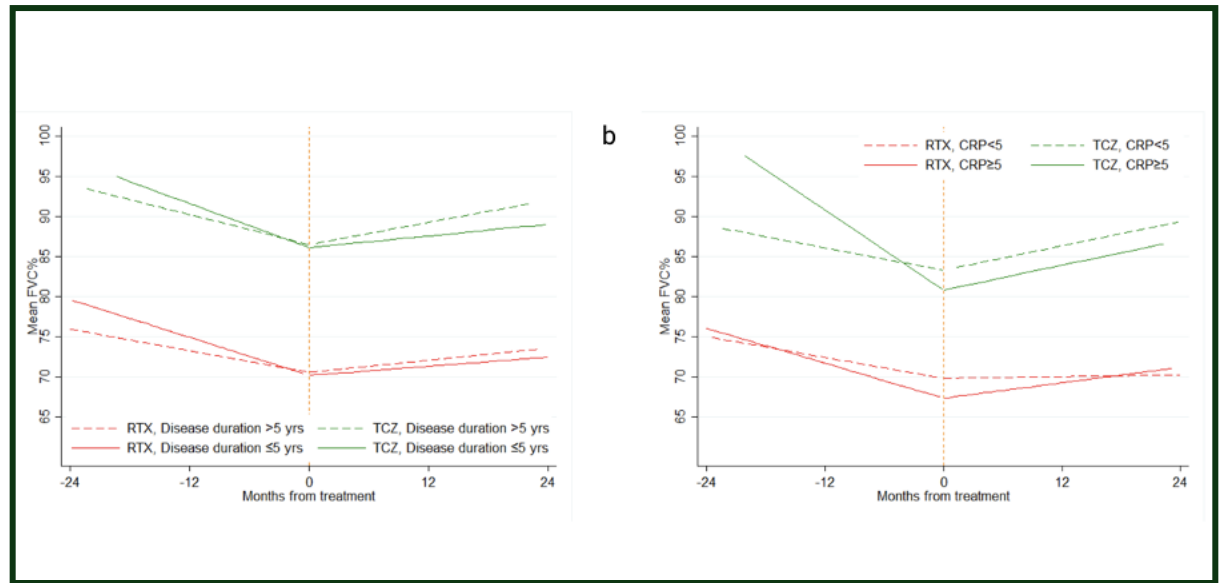
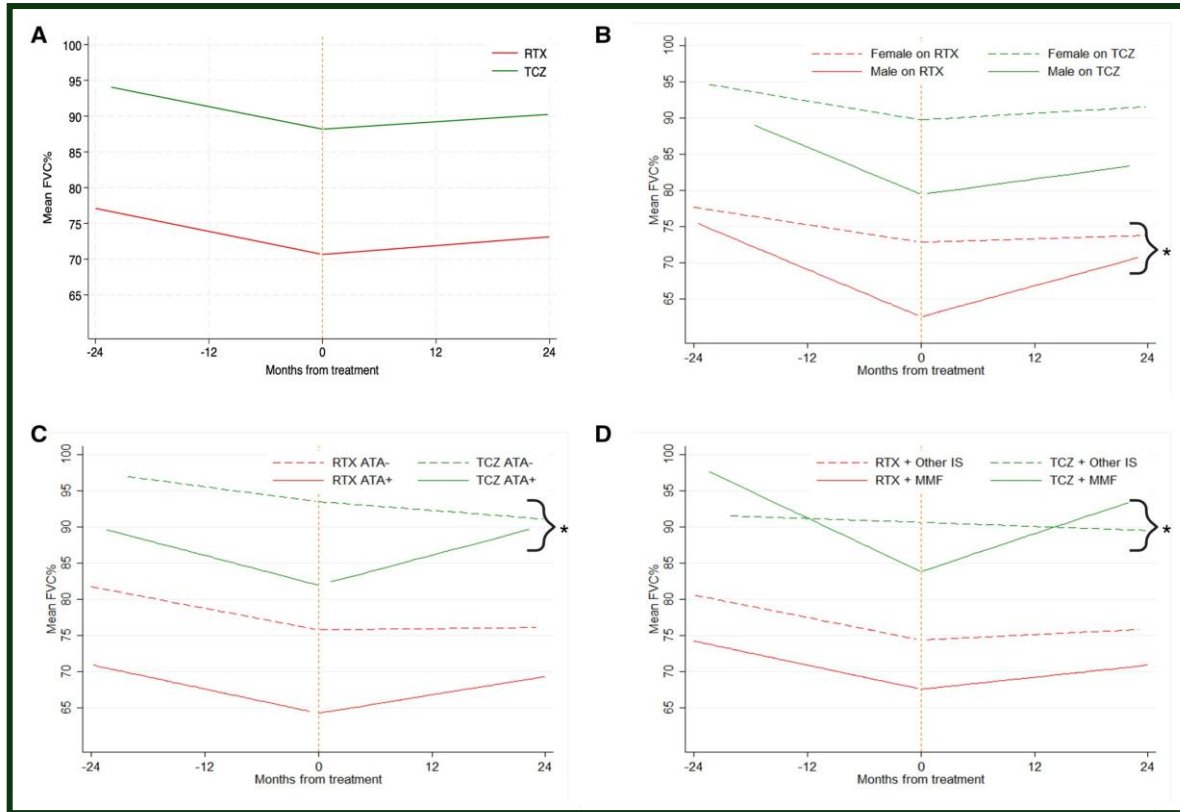
Differential lung function response among hallmark antibody subgroups



ATA as prognostic marker of lung decline and response to tocilizumab



Combination MMF and biologics prevents lung function decline in SSc-ILD



- Impact on lung function independent of disease duration and inflammatory response

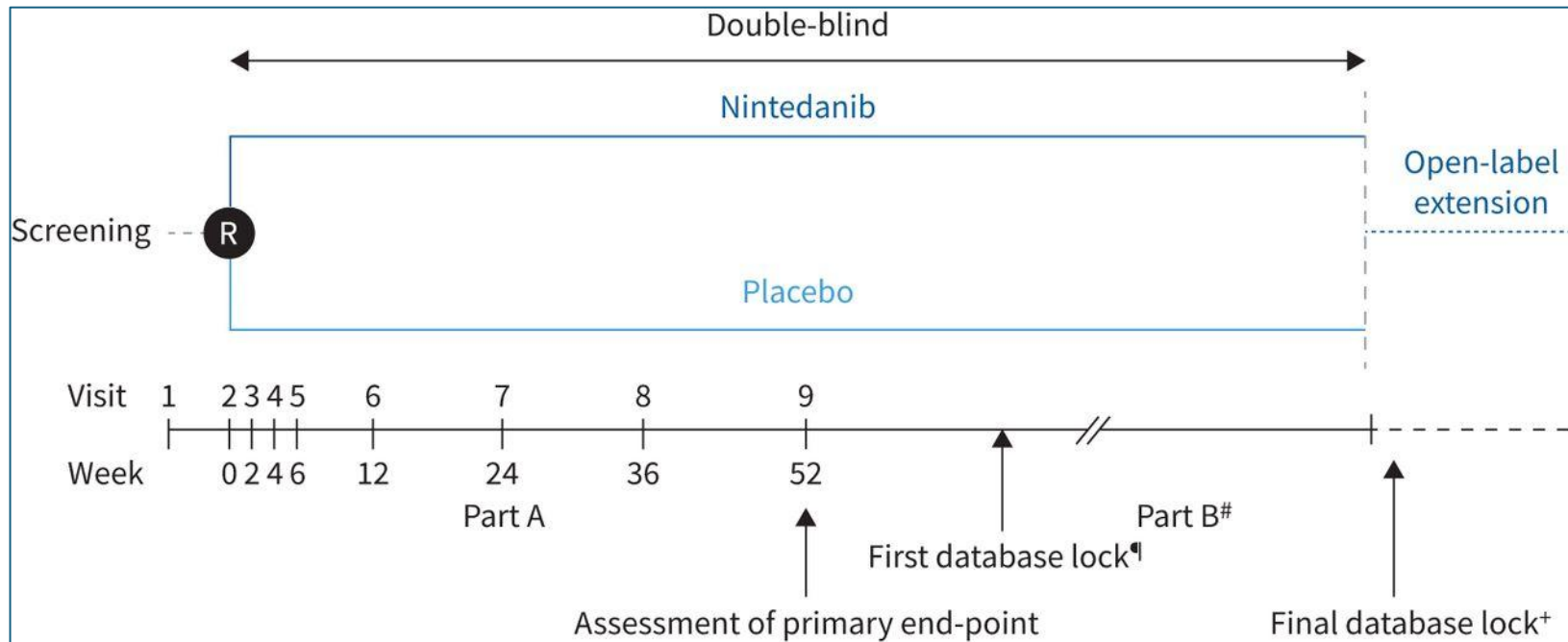
- ATA positive patients had a greater response to tocilizumab patients than those who were ATA negative ($p = 0.04$)
- Concurrent MMF on biologic initiation was significantly associated with increased %FVC in response to tocilizumab ($p=0.04$), but not rituximab ($p=0.91$)

Definition of progressive pulmonary fibrosis

Criteria or definition	Key components	Timeframe	Notes	References
ATS/ERS/JRS/ALAT 2022 (official PPF criteria)	≥2 of the following: - Worsening respiratory symptoms - Absolute decline in FVC ≥5% - Radiologic progression (HRCT)	Within 12 mo	Most recent criteria; awaits validation in SSc-ILD	Raghu et al ⁵
PF-ILD criteria (INBUILD criteria)	- Relative decline in FVC ≥10% predicted or - Relative decline in FVC ≥5% to <10% predicted and worsened respiratory symptoms or - Relative decline in FVC ≥5% to <10% predicted and increased extent of fibrosis on HRCT or - Worsened respiratory symptoms and increased extent of fibrosis on HRCT	Within 24 mo	Broader than ATS definition; used to select patients for INBUILD trial and the FIBRONEER-ILD trial	Flaherty et al ¹⁰
OMERACT criteria	- Relative decline in FVC ≥10% predicted or - Relative decline in FVC ≥5% to <10% predicted with a ≥15% relative decline in DLco	12 mo		Khanna et al ⁹
EUSTAR criteria	- Absolute decline in FVC ≥10% predicted or - Absolute decline in FVC ≥5% to <10% predicted with a ≥15% absolute decline in DLco	12 mo		De Lorenzis et al ¹¹
FVC decline alone	Absolute decline in FVC ≥5% or ≥10%	6–24 mo	Common in earlier studies before composite criteria were introduced	

Treatment of progressive non-IPF ILD

- INBUILD study



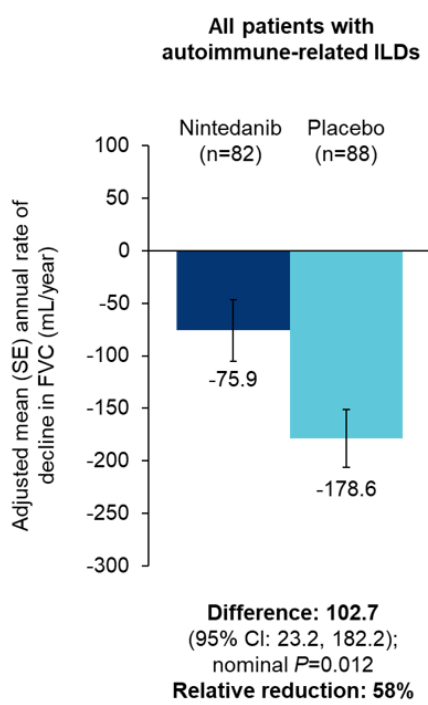
Inclusion criteria

≥ 1 criteria over last 24 months

- Age > 18
- Progressive disease over 24 months of screening*
- Fibrosing lung disease with disease extent > 10%
- Stable CTD
- DLCO 30-80% predicted
- FVC >45% predicted

Nintedanib reduced the rate of decline in FVC over 52 weeks versus placebo by 57% in the overall population

Nintedanib in progressive autoimmune ILD



Definition of progression

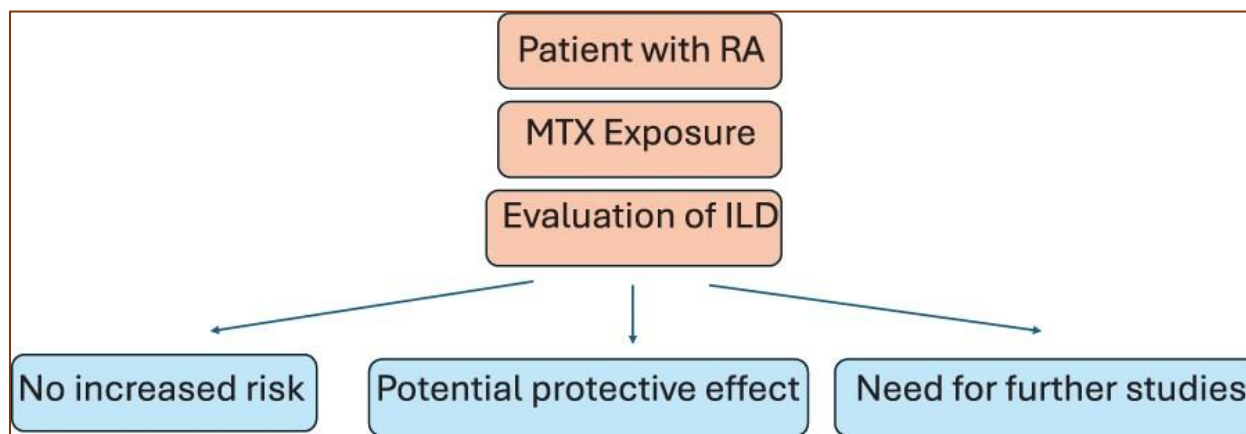
≥ 1 criteria over last 24 months

- Relative decline in FVC ≥ 10% predicted
- Relative decline in FVC% ≥ 5 to 10% predicted with worsening respiratory symptoms
- Relative decline in FVC% ≥ 5 to 10% predicted with increasing fibrotic changes on HRCT chest
- Worsening respiratory symptoms and increased fibrotic extent on HRCT chest

	Mean FVC %pred	Mean DLCO %pred
RA ILD (n=89)	71.5	47.7
SSc ILD (n=39)	69.7	47.7
MCTD ILD (n=19)	71.1	51.4

In subgroup analyses, no heterogeneity was detected in the effect of nintedanib versus placebo on the rate of FVC decline across autoimmune disease subgroups

MTX use is not prohibited in CTD-ILD

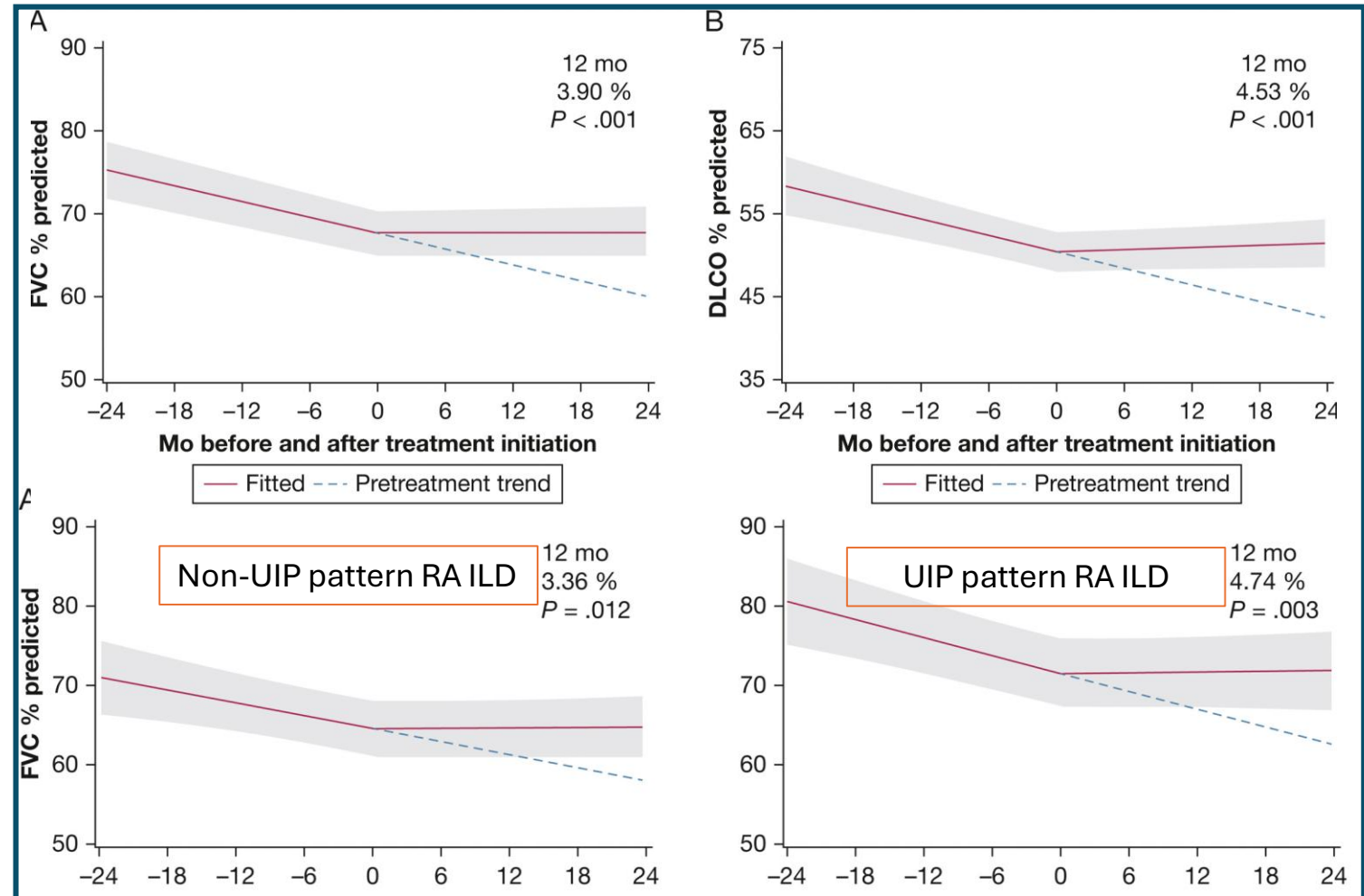


- Methotrexate use has not been linked to the development of fibrotic rheumatoid arthritis-associated ILD
- Data on ILD risk from other DMARDs remains inconclusive or insufficient.
- Do not systematically discontinue or contraindicate initiation of methotrexate
- Evaluate the risk–benefit of methotrexate in case of severe ILD (theoretical consequences of the occurrence of methotrexate-induced pneumonitis)

Dawson JK, et al. Rheumatology (Oxford). 2002 Mar;41(3):262-7.
Juge PA, et al. Eur Respir J. 2021 Feb 11;57(2):2000337.
Ibfehl EH, et al Rheumatology (Oxford). 2021 Jan 5;60(1):346-352.
Severo CR, et al. J Bras Pneumol. 2022 Dec 2;48(6):e20220145.
Kur-Zalewska J, et al. PLoS One. 2021 Apr 16;16(4):e0250339.

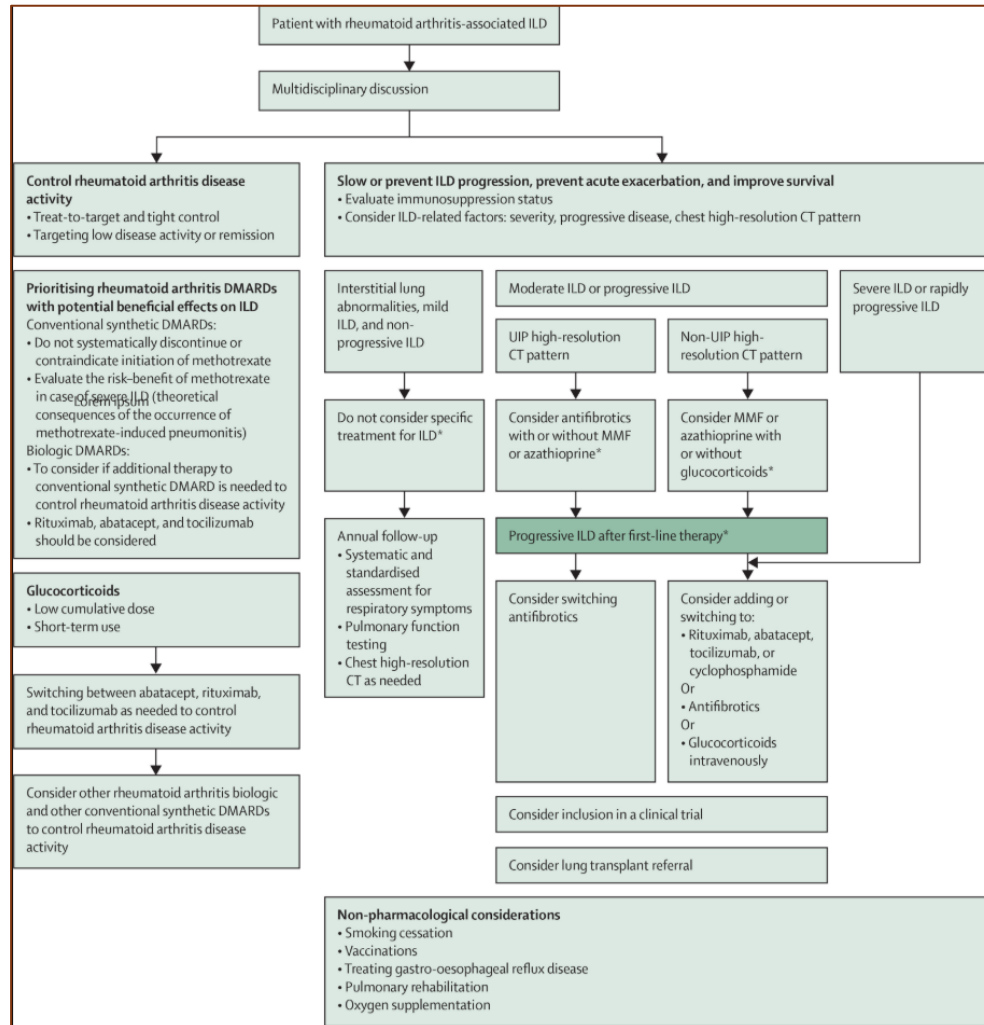
How does immunosuppression impact pulmonary function trajectory in RA-associated ILD?

- Retrospective study RA-ILD (n-212)
- DMARDs and biologic initiated for RA-ILD
 - 92 patients (43.4%) azathioprine,
 - 77 patients (36.3%) mycophenolate mofetil,
 - 43 patients (20.3%) rituximab
- Lacks prospective validation



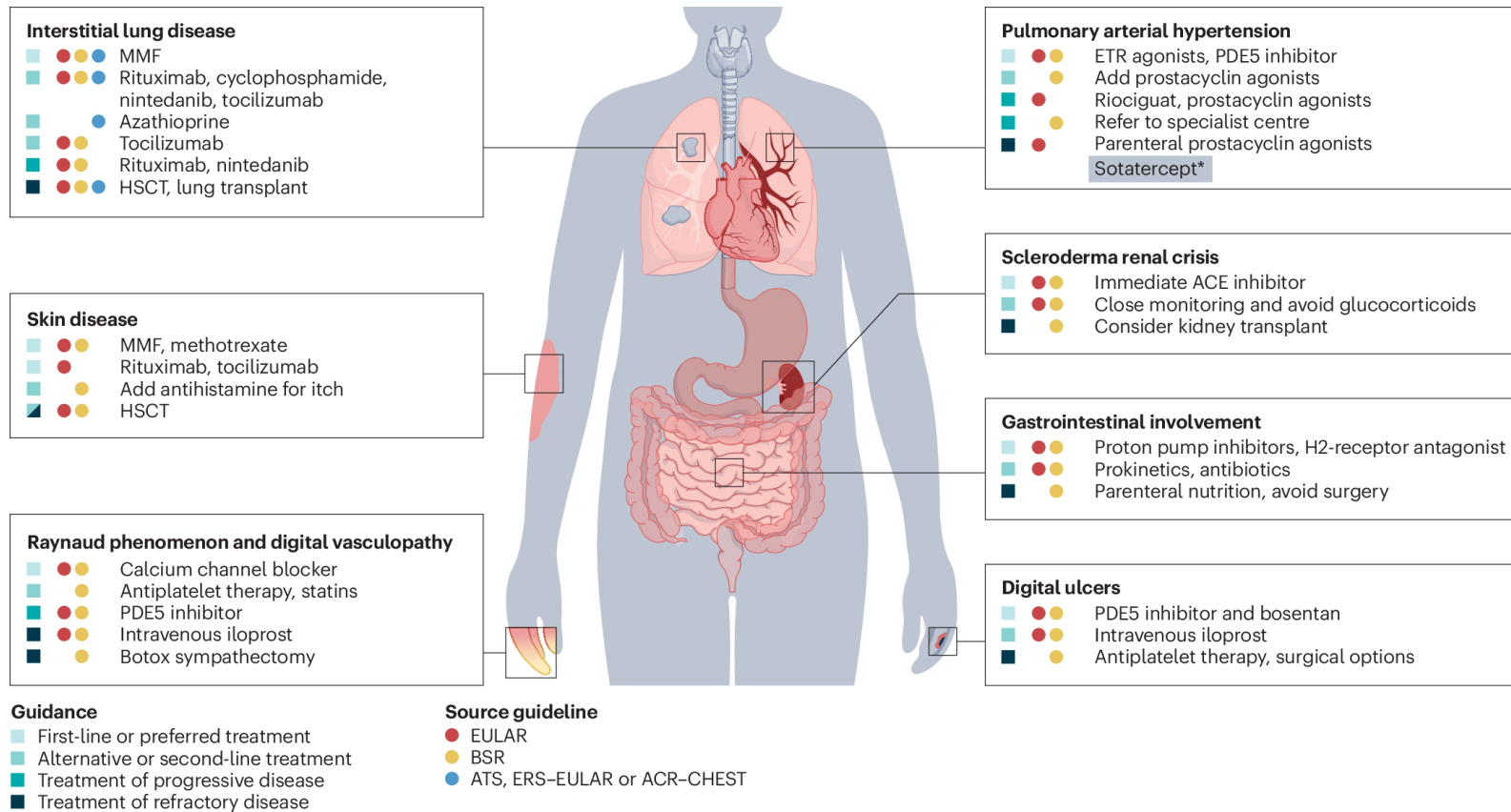
Matson SM, et al. Treatment Outcomes for Rheumatoid Arthritis-Associated Interstitial Lung Disease: A Real-World, Multisite Study of the Impact of Immunosuppression on Pulmonary Function Trajectory. Chest. 2022 Dec 5:S0012-3692(22)04205-2.

Treatment of RA – ILD



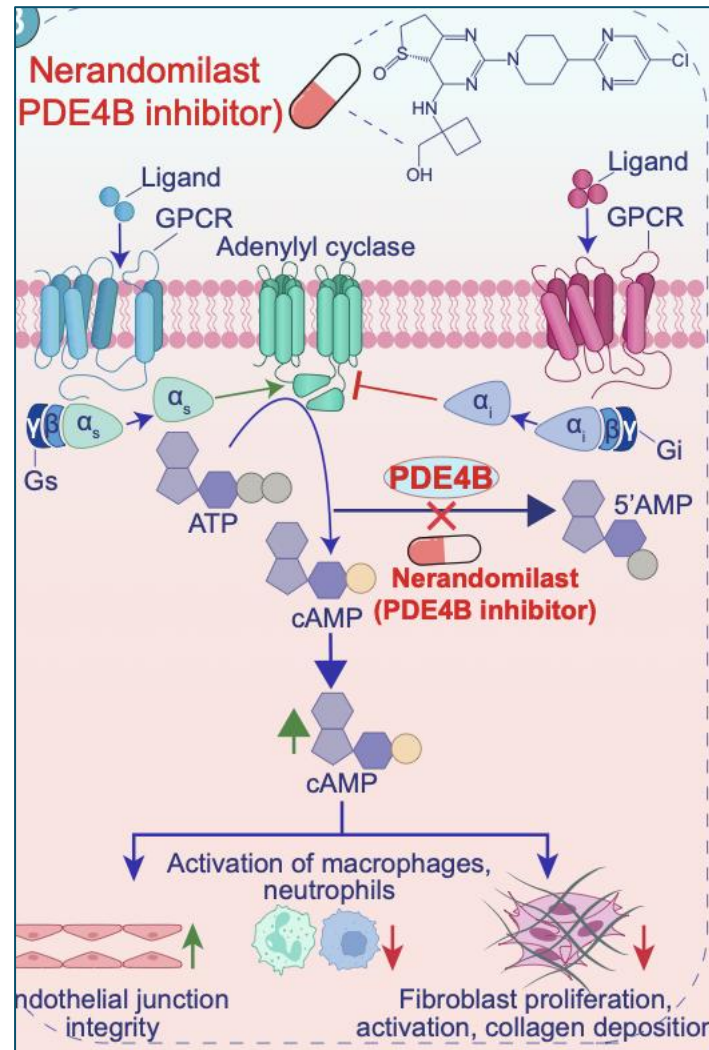
- Based on expert consensus
- *Address pulmonary and extrapulmonary activity*
- Non RA DMARD immunosuppressants
 - MMF, Azathioprine, CYA, steroids
- RA DMARD immunosuppressants
 - MTX
- Biologics
 - Abatacept, RTX, JAKi
- Antifibrotics

Management considerations of SSc ILD – therapeutics



- Multisystem disease
- Risk of immunosuppression
- Tolerability to antifibrotic
- Coexisting cardiac disease and pulmonary hypertension
- Emphysema and PPFE
- Access to lung transplantation

Targeting PDE4B in progressive pulmonary fibrosis

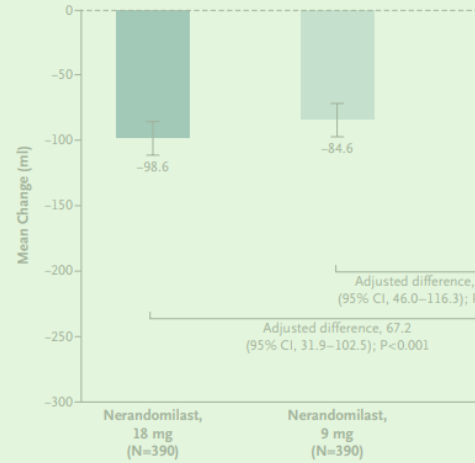


Schniertshauer D, et al *Rheumatology*, Volume 64, Issue Supplement_3, April 2025

Maher TM, et al. N Engl J Med. 2025 Jun 12;392(22):2203-2214.

Nerandomilast slows progression of ILD

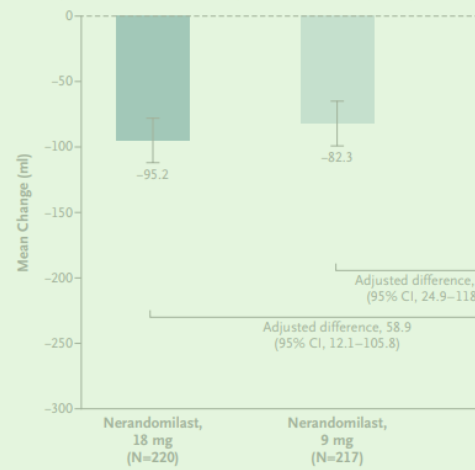
A Change in FVC at Week 52 in the Overall Trial Population



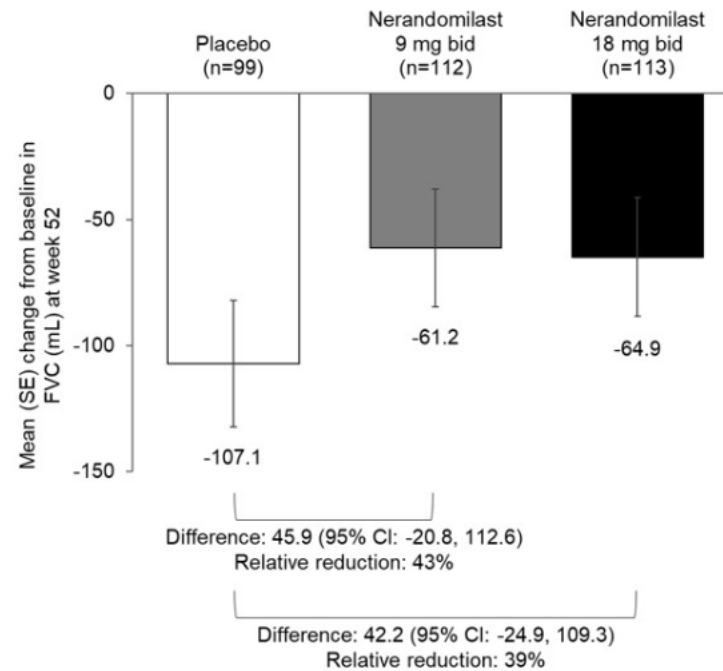
B Change in FVC over Time in the Overall Trial Population



C Change in FVC at Week 52 among Patients Not Taking Background Nintedanib



Subgroup analysis for autoimmune ILD (n=325)



FVC 71.5 % DLCO 51.5 %
34.2% NTD

RA 36.3%

SSc 23.1%

MCTD 14.5%

Diarrhoea 28%

Discontinuation 7%

Hoffmann-Vold A, et al. Efficacy and Safety of Nerandomilast in Patients with Autoimmune Disease-Related Progressive Pulmonary Fibrosis: Subgroup Analysis of the FIBRONEER-ILD trial [abstract]. *Arthritis Rheumatol.* 2025; 77 (suppl 9).

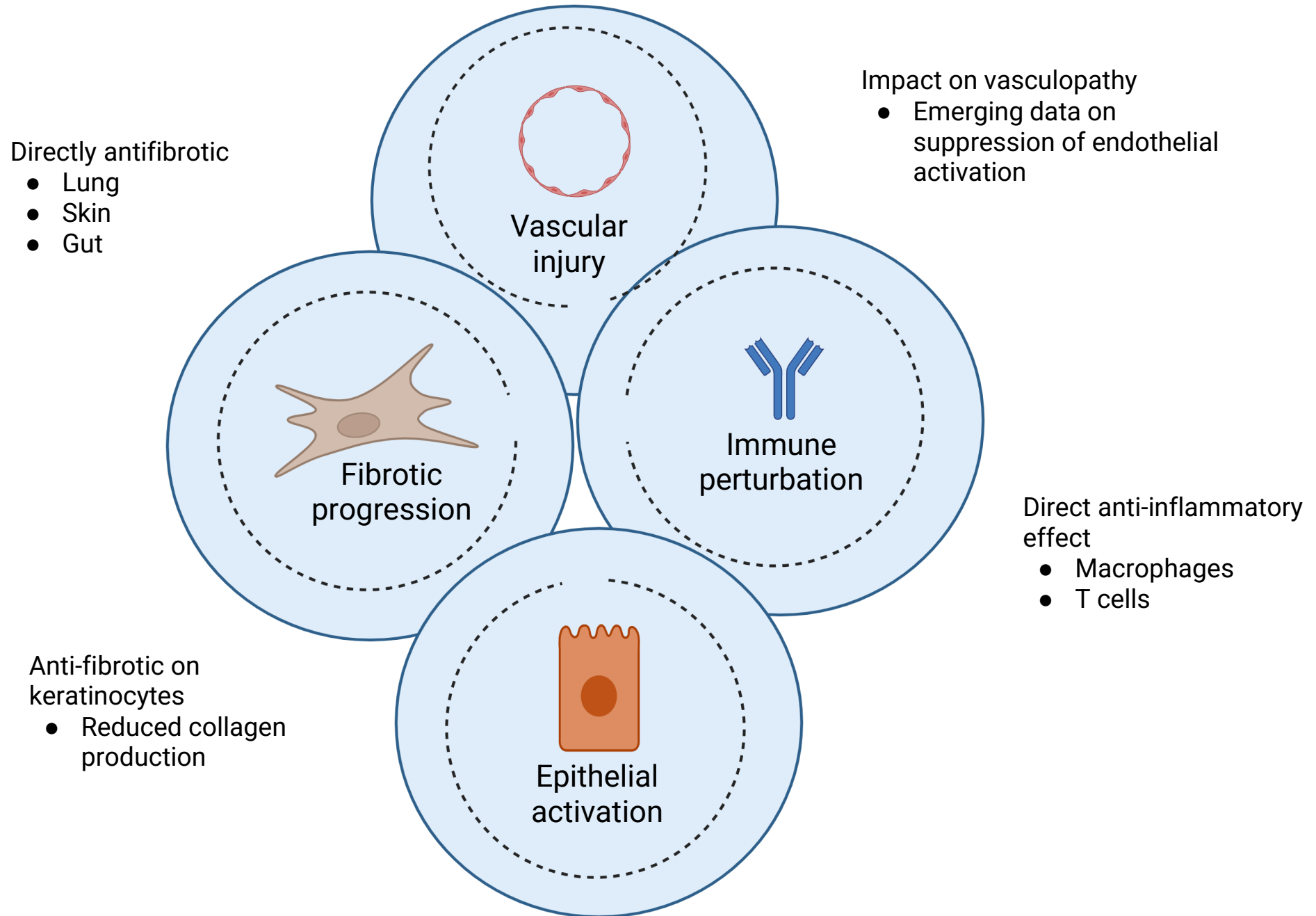
Pooled analysis of FIBRONEER-IPF and FIBRONEER-ILD trials indicated a nominally significant reduction in the risk of death by 43% among cohort on 18mg (HR 0.57 [CI: 0.41-0.78])

Pulmonary Fibrosis. *N Engl J Med.* 2025 Jun 12;392(22):2203-2214.

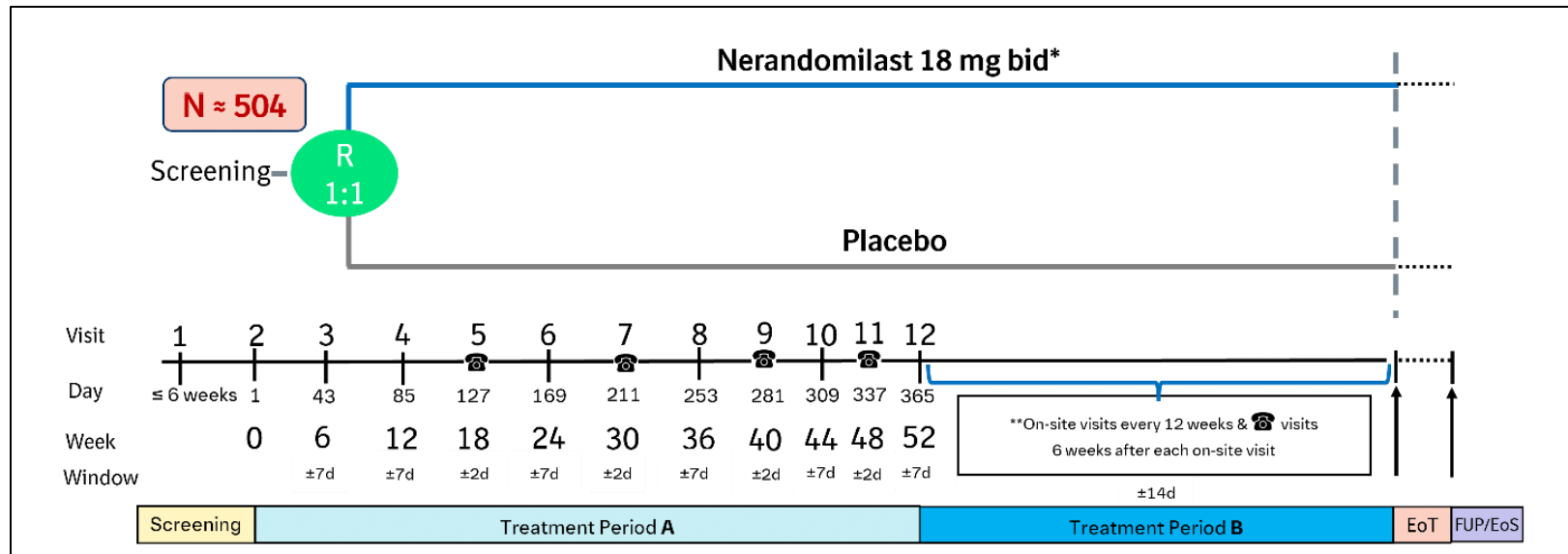
	Nerandomilast, 9 mg (N=393)	Placebo (N=392)
	203 (51.7)	231 (58.9)
	66.5±9.8	66.6±10.3
	72.1±17.5	73.4±17.9
	200 (50.9)	186 (47.4)
	186 (47.3)	200 (51.0)
	7 (1.8)	6 (1.5)
	4.1±4.3	3.9±3.6
	2326±768	2354±766
	70.3±15.7	69.7±16.2
	48.7±16.8	49.7±16.5
	173 (44.0)	170 (43.4)
	290 (73.8)	275 (70.2)
	112 (28.5)	100 (25.5)
	83 (21.1)	77 (19.6)
	76 (19.3)	82 (20.9)
	73 (18.6)	73 (18.6)
	49 (12.5)	60 (15.3)
	97 (24.7)	110 (28.1)

last in Patients with Progressive

Pre-clinical supportive data of biological effects of nerandomilast in SSc



Phase III study Nerandomilast in SSc



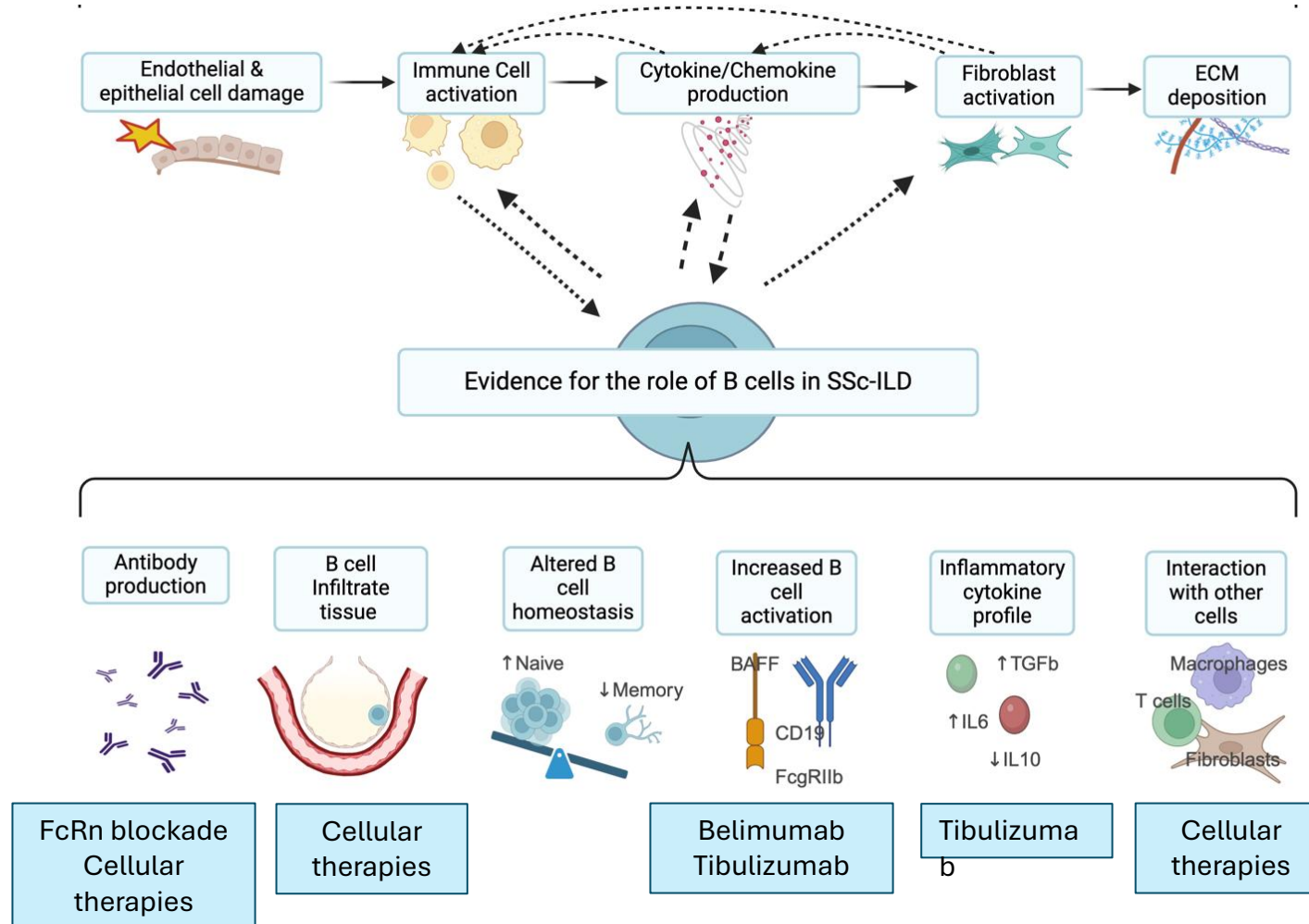
Time to the first occurrence of disease progression or all-cause death:

- Adjudicated SSc-related clinically meaningful disease progression or complications*,

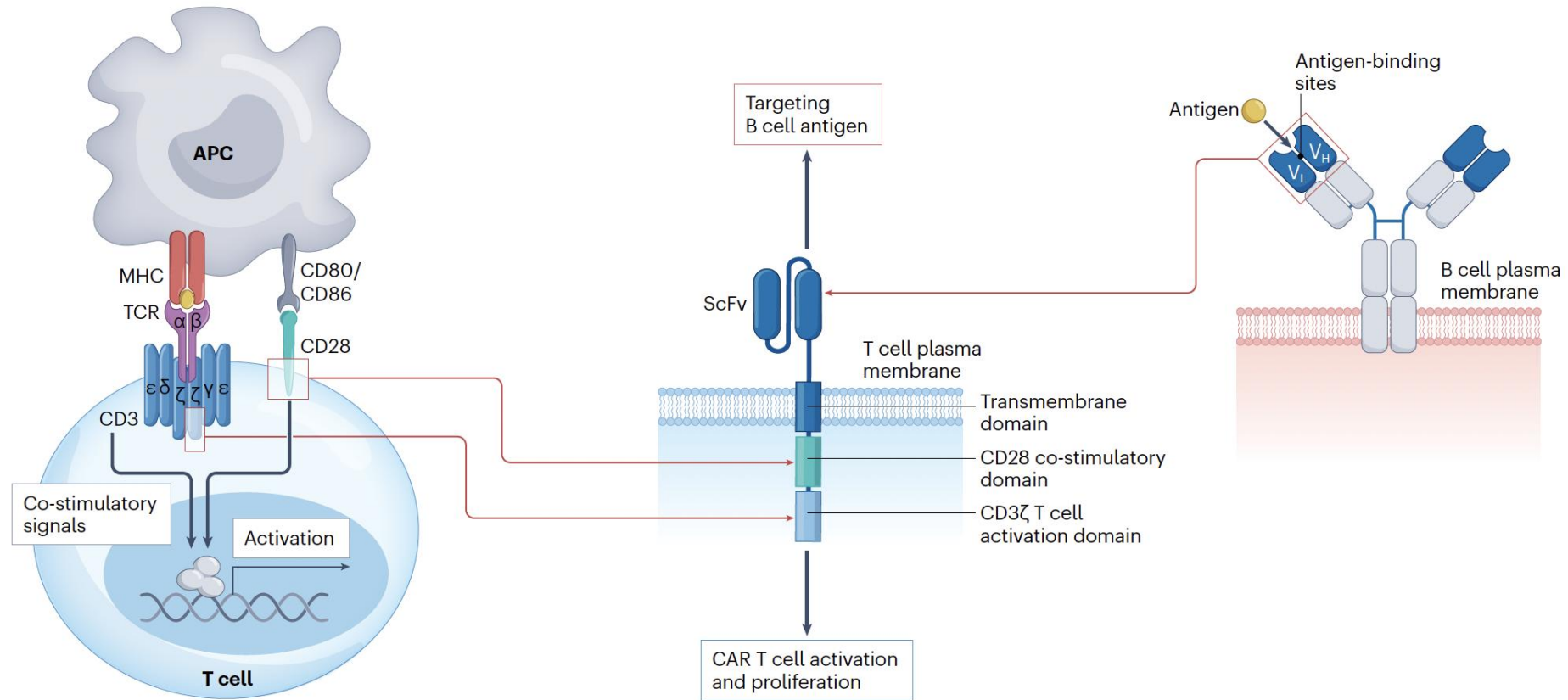
or

- Absolute decline in FVC% predicted $\geq 5\%$, or
- Relative increase in mRSS $\geq 25\%$ and absolute increase in mRSS ≥ 5 points, or
- All-cause death

Targeting B cells in SSc

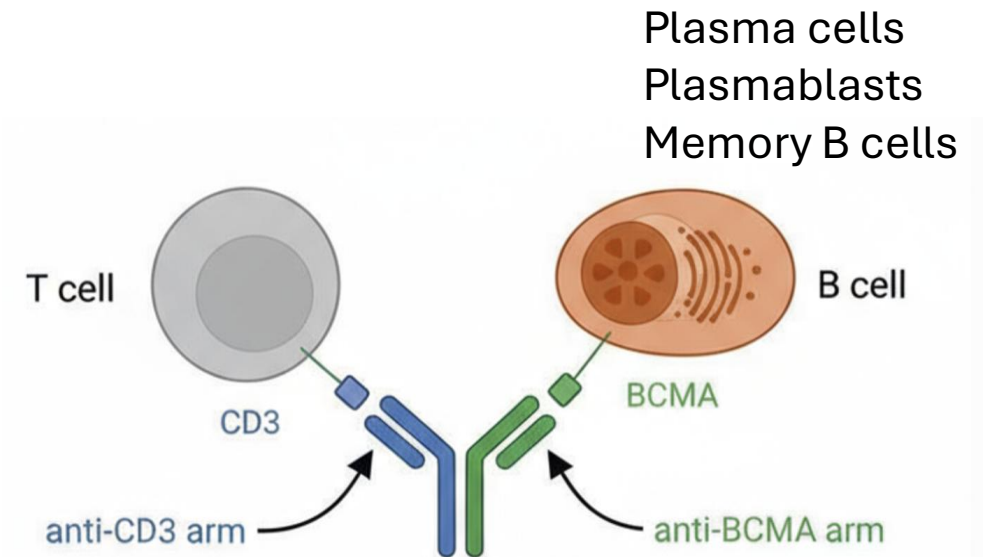


Structure of CAR



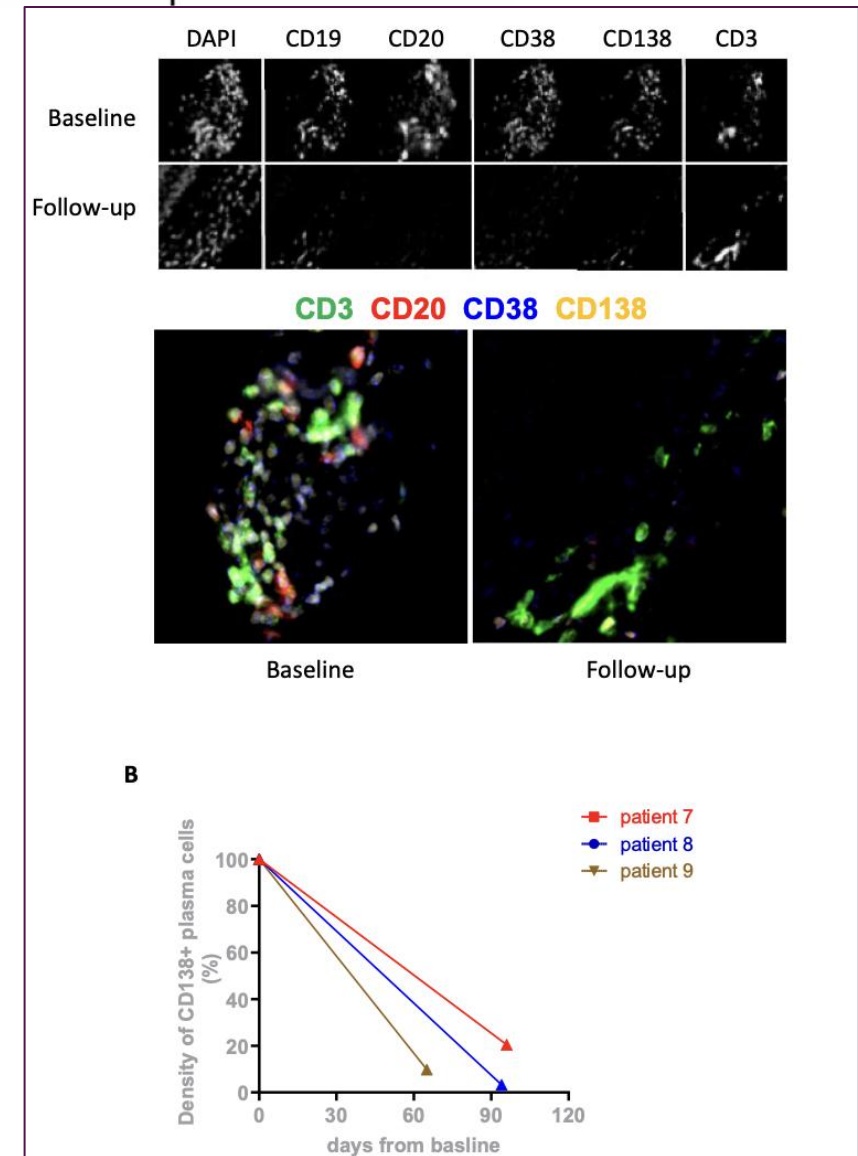
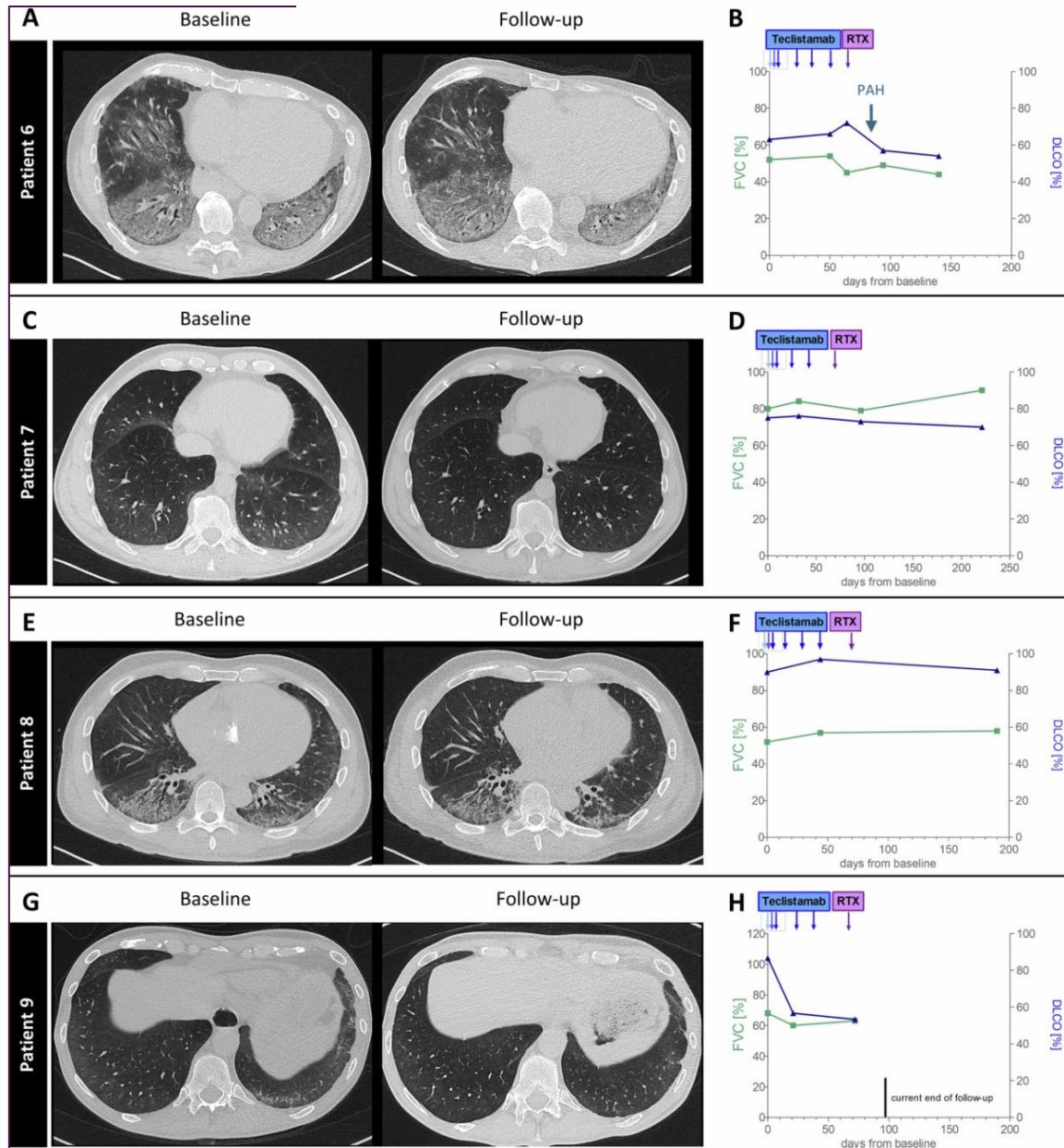
BCMA T-Cell Engager therapy in SSc-ILD

Characteristics	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
General					
Age (years)	65	52	56	46	46
Sex	Male	Male	Male	Male	Male
Inflammatory subtype*	-	+	+	+	+
Disease duration (years)	18	2	4	3	1
Autoantibodies					
Anti-topoisomerase 1	+	+	+	+	-
Others	-	-	-	-	Anti-fibrillarin; ACPA
Skin					
dcSSc	+	+	+	+	+
mRSS	21	22	28	38	23
Lung: SSc-ILD					
CT pattern	cNSIP	CPFE	cNSIP	NSIP	NSIP
FVC, % predicted	52	80	52	68	54
DLCO-VA, % predicted	63	75	90	104	83
History of smoking (PY)	0	80**	0	40	10
Heart: SSc-pHI					
Pathologic CMR	+	+	+	+	+
LV-EF (%)	57	61	67	41	54
ECG abnormalities	+	+	+	+	-
Increased hsTnT	+	+	+	+	+
GI					
Upper GI***	+	+	+	+	+
Weight loss	14 kg / 10 years	15 kg / 1 year	10 kg / 4 years	10 kg / 2 years	18 kg / 1 year
Musculoskeletal					
Arthritis and myositis	-	-	-	+	+
TFRs	3	6	3	+	12
Vascular					
Ischemic ulcers	Pitting scars	+	+	+	-
SSc-PH	-	-	-	-	-
Previous immunomodulatory/antifibrotic therapies					
Mycophenolate	+	+	+	-	+
MTX	-	+	+	+	-
Nintedanib	-	-	+	-	+
Cyclophosphamide	+	-	-	+	+
Tocilizumab	-	-	-	-	-
RTX	-	-	+	+	+
Others	Aza-thioprine	Hydroxy-chloroquine	-	-	-



Düsing, C., *et al.* Bispecific T cell engagers for treatment-refractory autoimmune connective tissue diseases. *Nat Med* (2026).

	teclistamab cycle 1							teclistamab cycle 2		teclistamab cycle 3		RTX maintenance	
days from baseline	+0	+1	+2	+3	+4	+5	+6	~14days after cycle 1		~14days after cycle 2		~14days after cycle 3	
teclistamab s.c. / RTX i.v.	0.06 mg/kg		0.3 mg/kg		1.5 mg/kg			1.5 mg/kg		1.5 mg/kg		RTX 1g	
monitoring	CRS/ICANS every 4h												

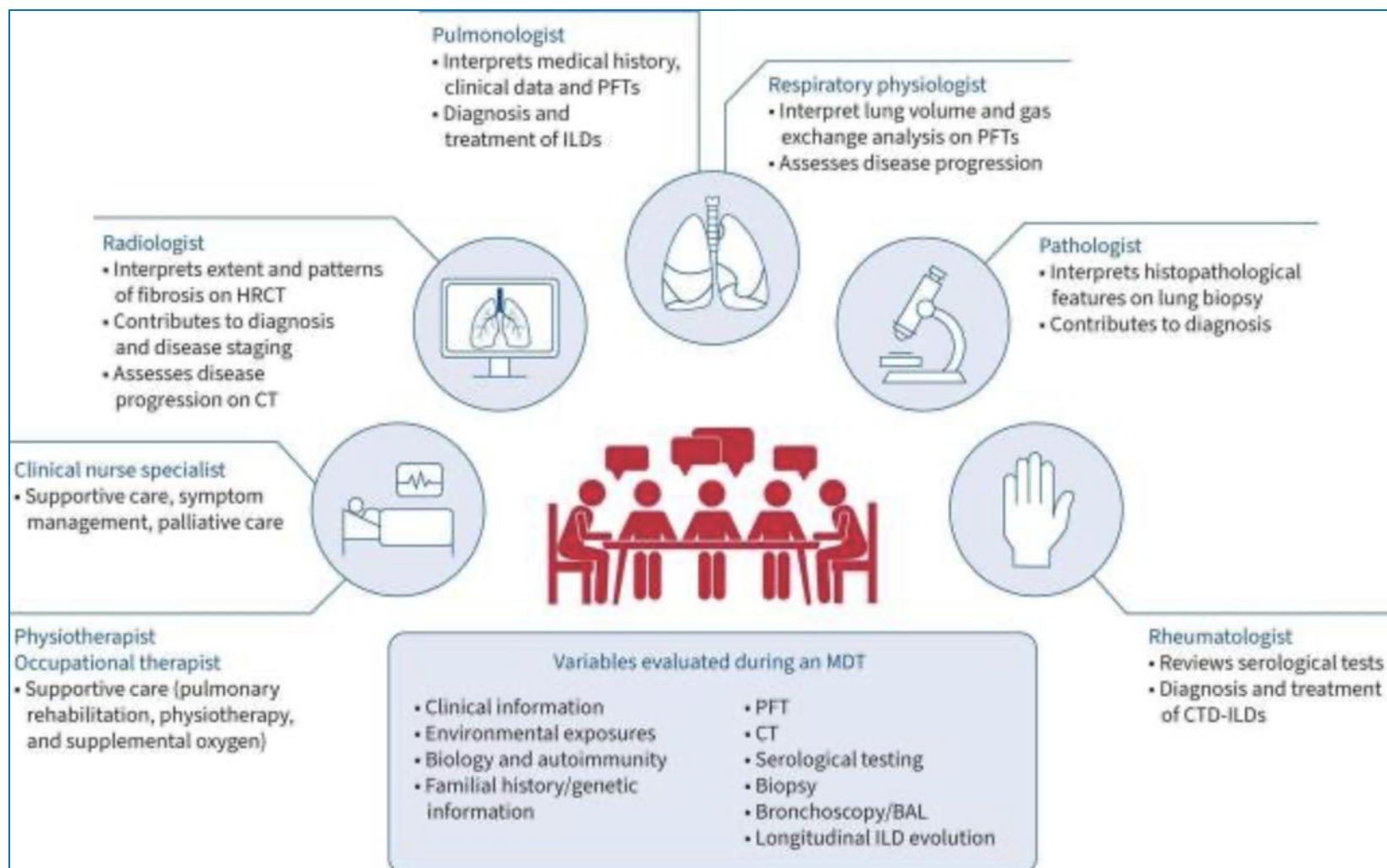


Düsing, C., *et al.* Bispecific T cell engagers for treatment-refractory autoimmune connective tissue diseases. *Nat*

UPDATED: Novartis halts autoimmune CAR-T trials after 3 deaths, as BMS also pauses studies

By Marissa Russo · Aug 31, 2026 6:25pm





Only one-third of multidisciplinary teams include a rheumatologist²

Cottin V, et al. Multidisciplinary teams in the clinical care of fibrotic interstitial lung disease: current perspectives. Eur Respir Rev. 2022 Sep 7;31(165):220003.

²Richeldi L, et al. The characterisation of interstitial lung disease multidisciplinary team meetings: a global study. ERJ Open Res. 2019 Apr 1;5(2):00209-2018.

Conclusions

- Guidelines and recommendations are largely complementary
 - Evolution of combination immunosuppressives and biologics
 - Antifibrotic for PPF
- Significant need for studies to address evidence gaps for specific CTD ILDs
- Exciting trials into cellular strategies tempered with caution
 - Not generalisable to all CAR T constructs
- MDTs key to optimising the diagnosis and management of patients

Many thanks to

- Our patients
- The “Scleroderma team” at Royal Free
- Research Funders
- Colleagues in many institutions and organisations
- UKSSG colleagues
- International collaborators – EUSTAR, WSF, SCTC and FESCA



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