ILD e Sclerosi Sistemica: quando e perché la terapia anti-fibrotica?

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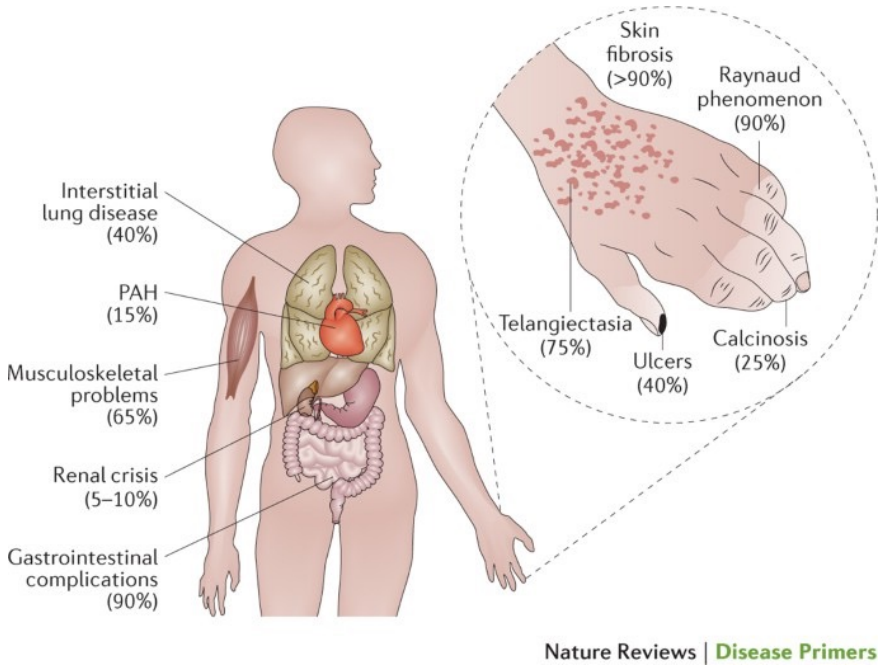
Systemic Sclerosis



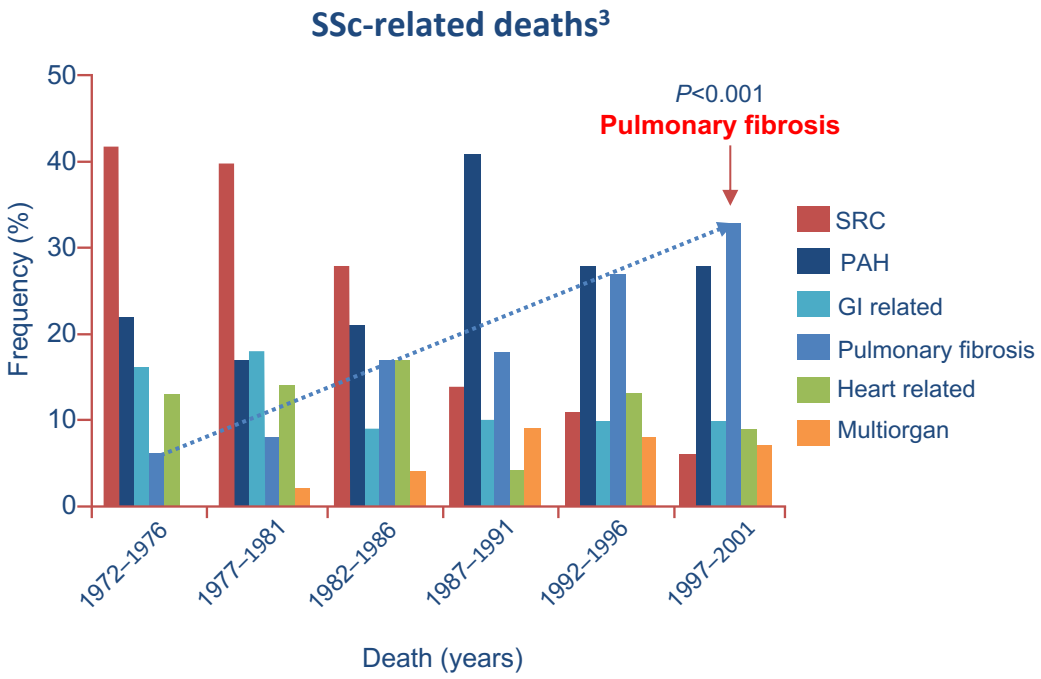
The heterogeneity in terms of clinical involvement gives rise to many difficulties in finding the optimal therapeutic interventions for SSc and, to date, no disease-modifying agents are available.

Lung involvement can appear early after a diagnosis of SSc, with ILD representing the leading cause of SSc-related death[1–3]

ILD prevalence is **53%** and **35%** in patients with **dcSSc and lcSSc**, respectively[4]

~50% of patients with SSc have **ILD when first assessed** by HRCT[2]

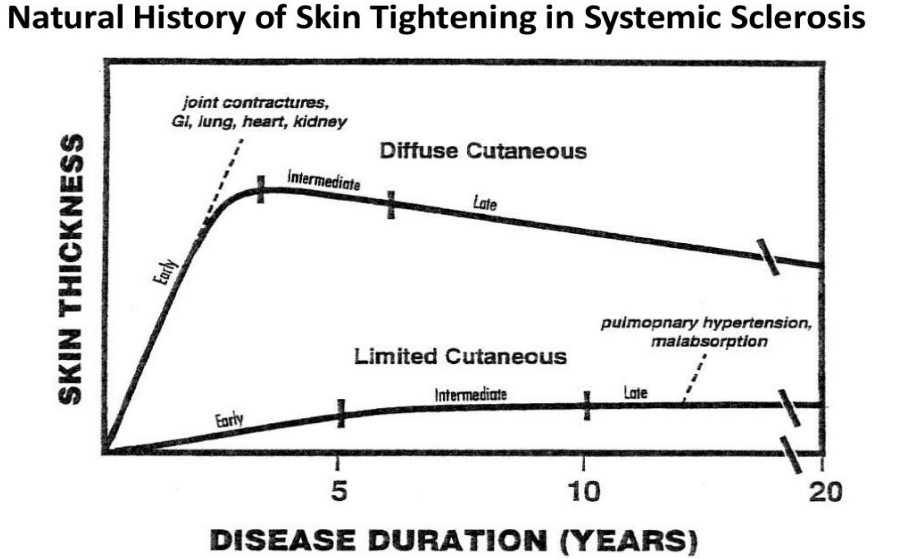
ILD is the leading cause of SSc-related mortality, accounting for **~35% of SSc-related deaths**[3,5]



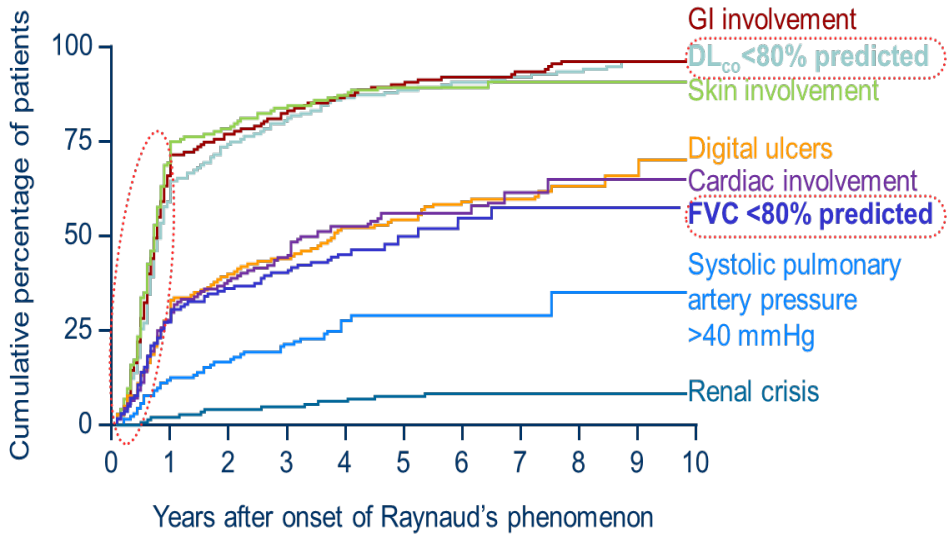
- dcSSc, diffuse cutaneous systemic sclerosis; GI, gastrointestinal; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; lcSSc, limited cutaneous systemic sclerosis; PAH, pulmonary arterial hypertension; SRC, scleroderma renal crisis; SSc, systemic sclerosis

1. Solomon JJ *et al. Eur Respir Rev* 2013;22:6–19; 2. Hoffmann-Vold A-M *et al. Am J Respir Crit Care Med* 2019;200:1258–66; 3. Steen VD, Medsger TA. *Ann Rheum Dis* 2007;86:940–4; 4. Walker UA *et al. Ann Rheum Dis* 2007;66:754–63; 5. Tyndall AJ *et al. Ann Rheum Dis* 2010;69:1809–15

ILD develops early in the disease course of SSc

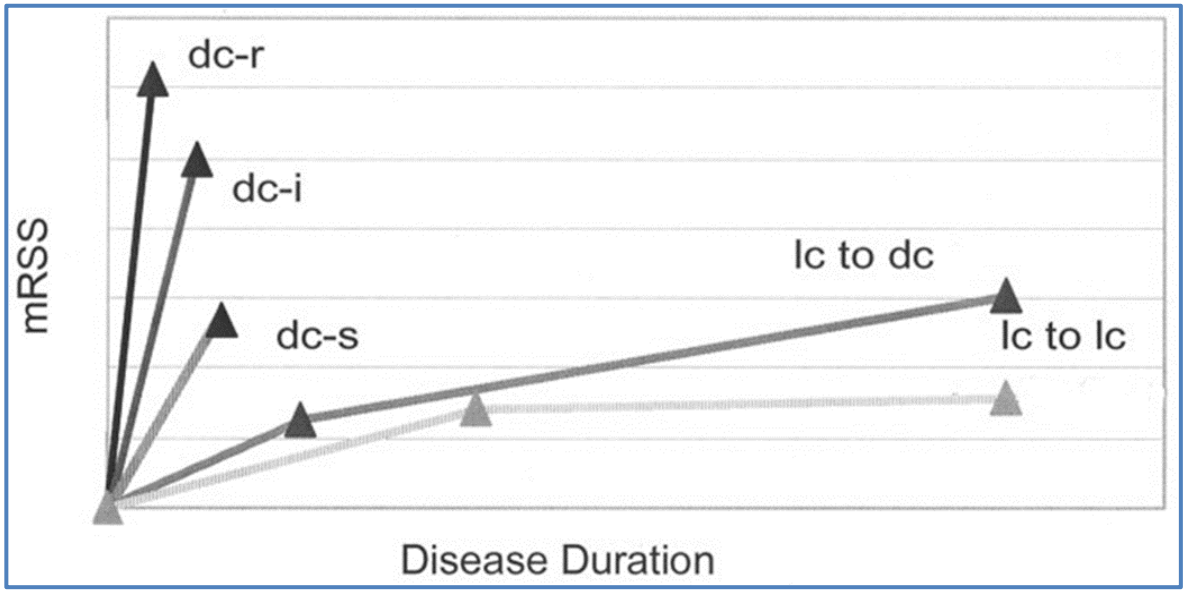


Medsger Rheum Dis N Am 2003;29(2):255-73.

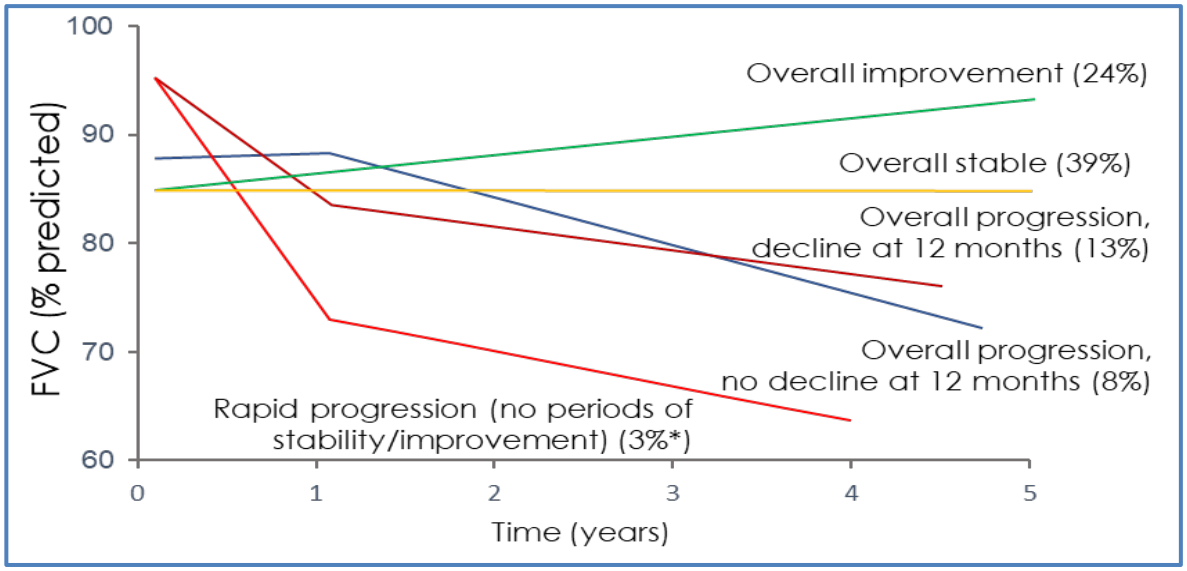


Jaeger VK et al. PLoS One 2016;11:e0163894

Heterogeneous disease course of SSc-Skin and lung involvement



Perera A. et al. Arthritis Rheum 2007



Hoffmann-Vold A-M *et al. Ann Rheum Dis 2020*
Distler O *et al. Eur Resp J* 2020

Heterogeneity of SSc as a therapeutic challenge

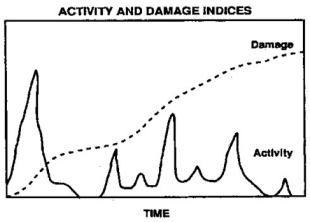
SSc is characterized by a diverse range of clinical manifestations with various trajectories regarding skin fibrosis, organ involvement, and mortality. Capturing the heterogeneity of this systemic disease in a practical approach, feasible in daily practice, remains challenging.

Nonetheless, the identification of homogeneous subsets of SSc patients, sharing predominant pathogenic pathways may help to improve the design of randomized controlled trials (RCTs).

Early stages of the disease have also been identified as a window of opportunity, for the management of diffuse cutaneous systemic sclerosis (dcSSc), but also for the treatment of interstitial lung disease (ILD) .

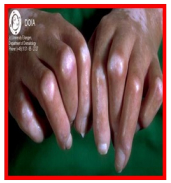
Patients with the highest possibility to have an improvement by the therapies

Distinguishing activity from Damage has long been considered a primary goal in Clinical Rheumatology



Activity
the potentially reversible part of disease process

ACTIVITY INDEXES ASSESS THE CURRENT LEVEL OF INFLAMMATORY, IMMUNOLOGIC, OR CLINICAL MANIFESTATIONS OF DISEASE



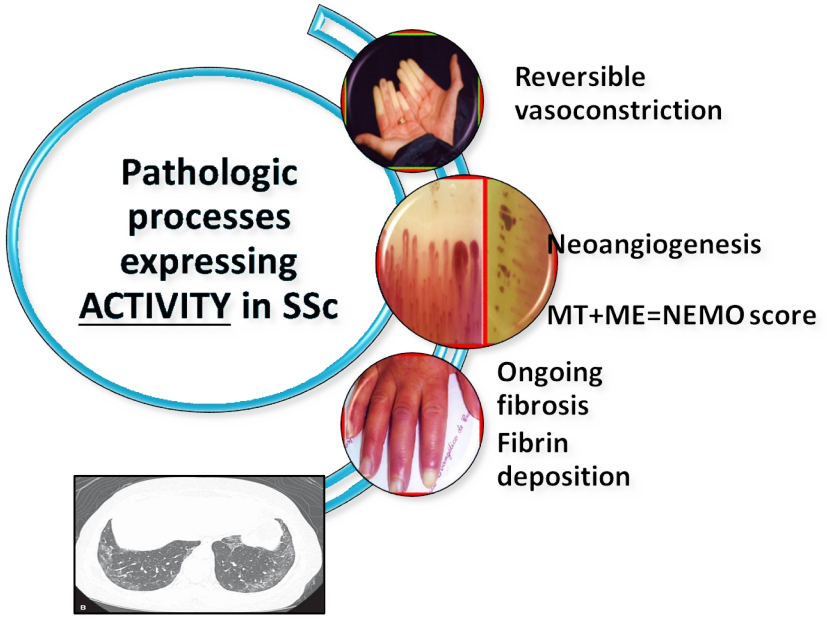
Damage
the irreversible part of it

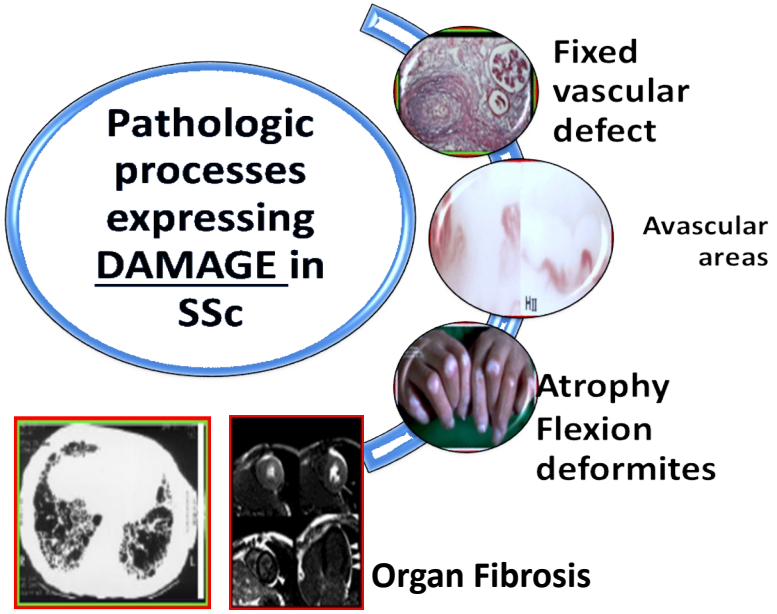
DAMAGE INDEXES QUANTITATE THE IRREVERSIBLE DESTRUCTION OF TISSUE AS A RESULT OF THE DISEASE.

Unfortunately, in SSc……

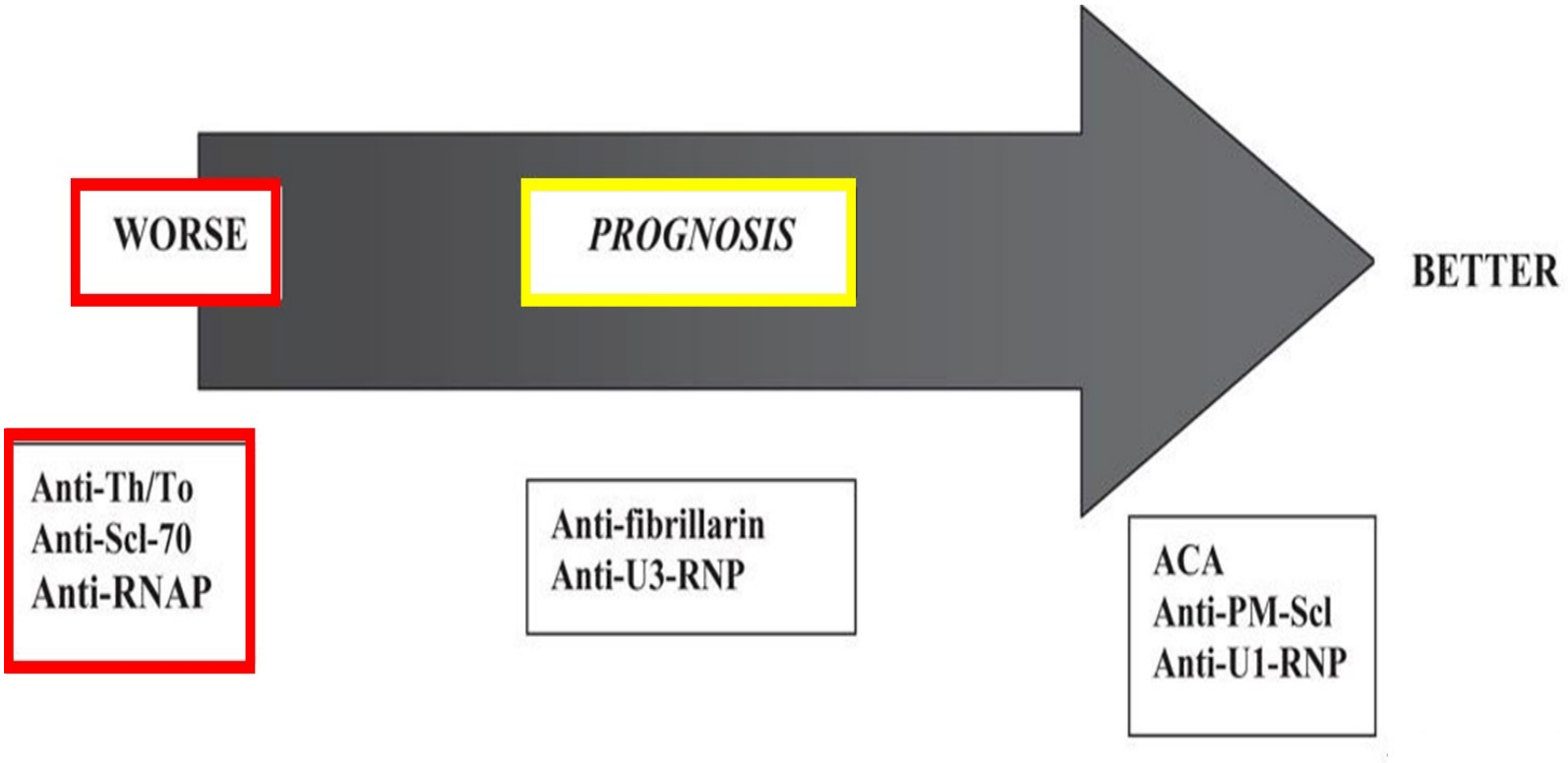
- **No fully validated indexes for assessing overall disease activity in patients with SSc currently exists**
- **No biological markers available as surrogate of disease activity**

Patients with the highest possibility to have an improvement by the therapies

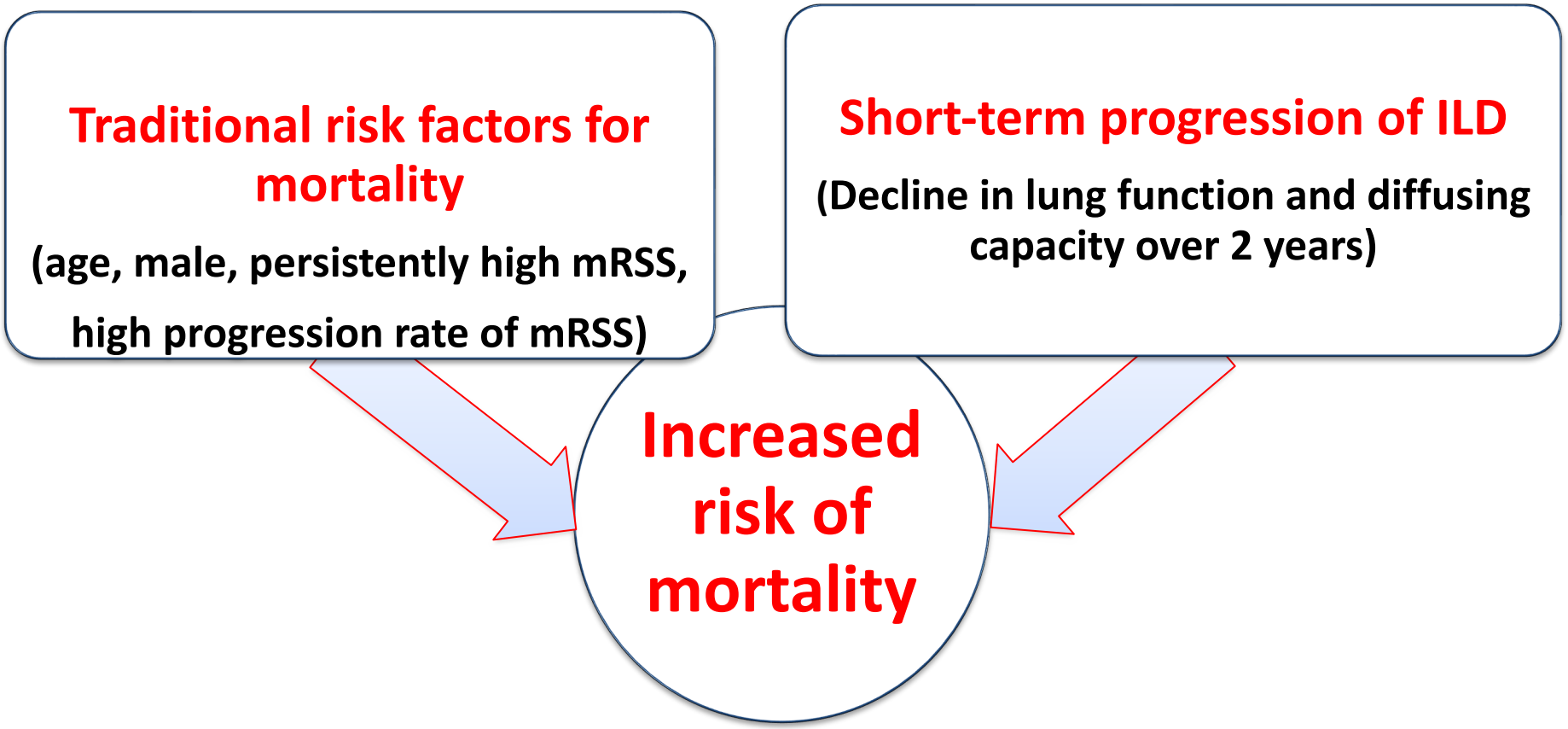




Autoantibodies linked to SSc bad prognosis



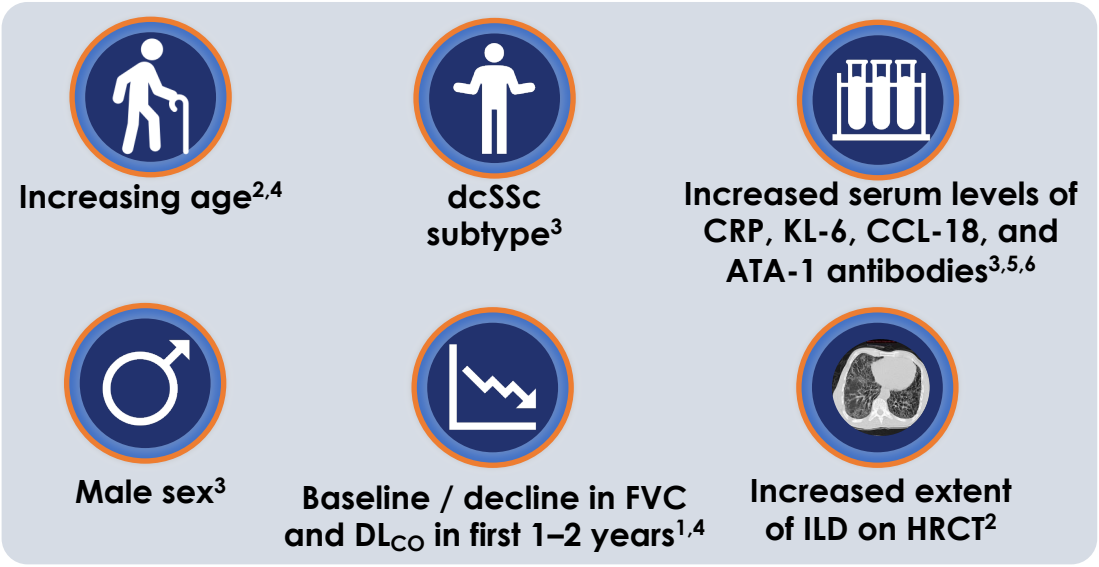
Rate of progression of skin and lung involvement as prognostic factors of mortality in SSc



Volkmann ER et al, Ann Rheum Dis 2018

Due to variable patterns of FVC decline in SSc-ILD, early intervention to preserve lung function may be warranted

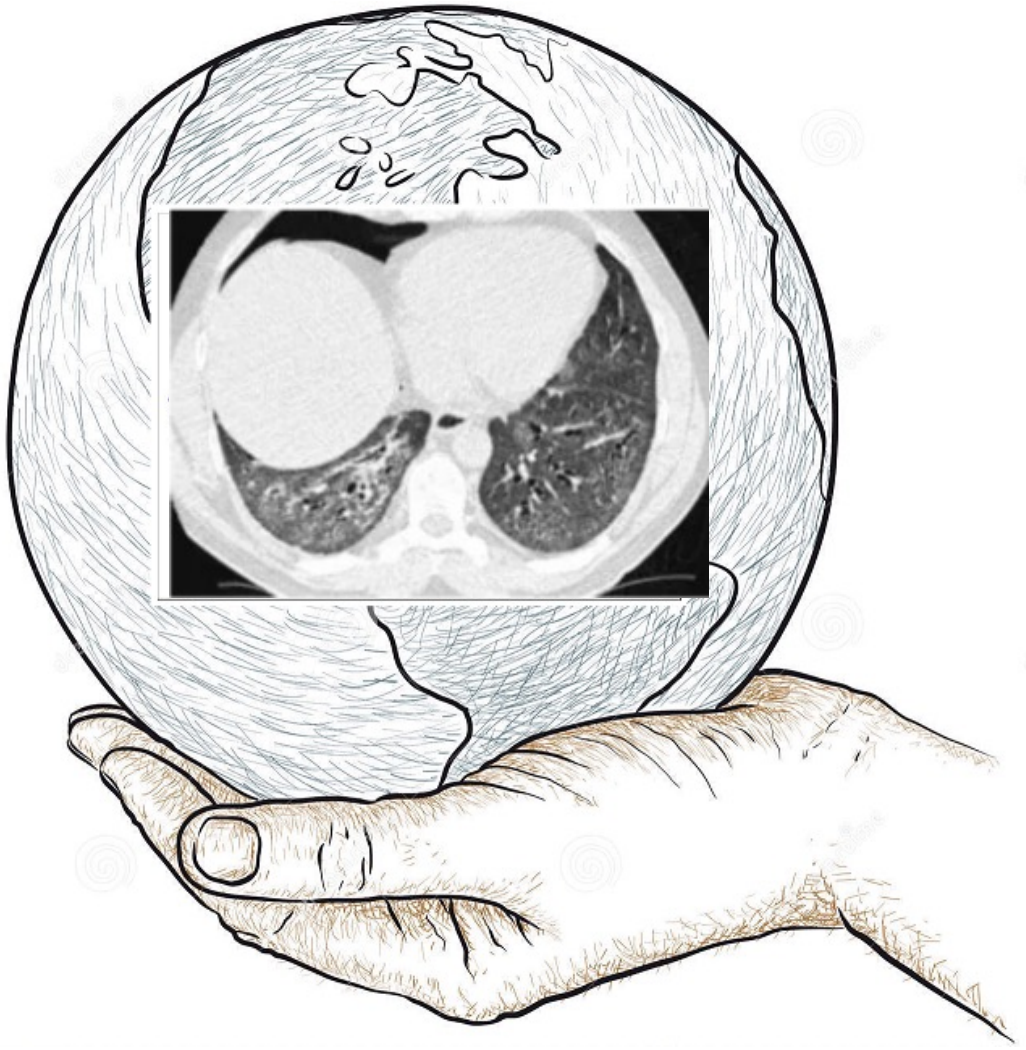
Due to the heterogeneous disease progression of SSc-ILD,
Identifying who and when to treat is challenging



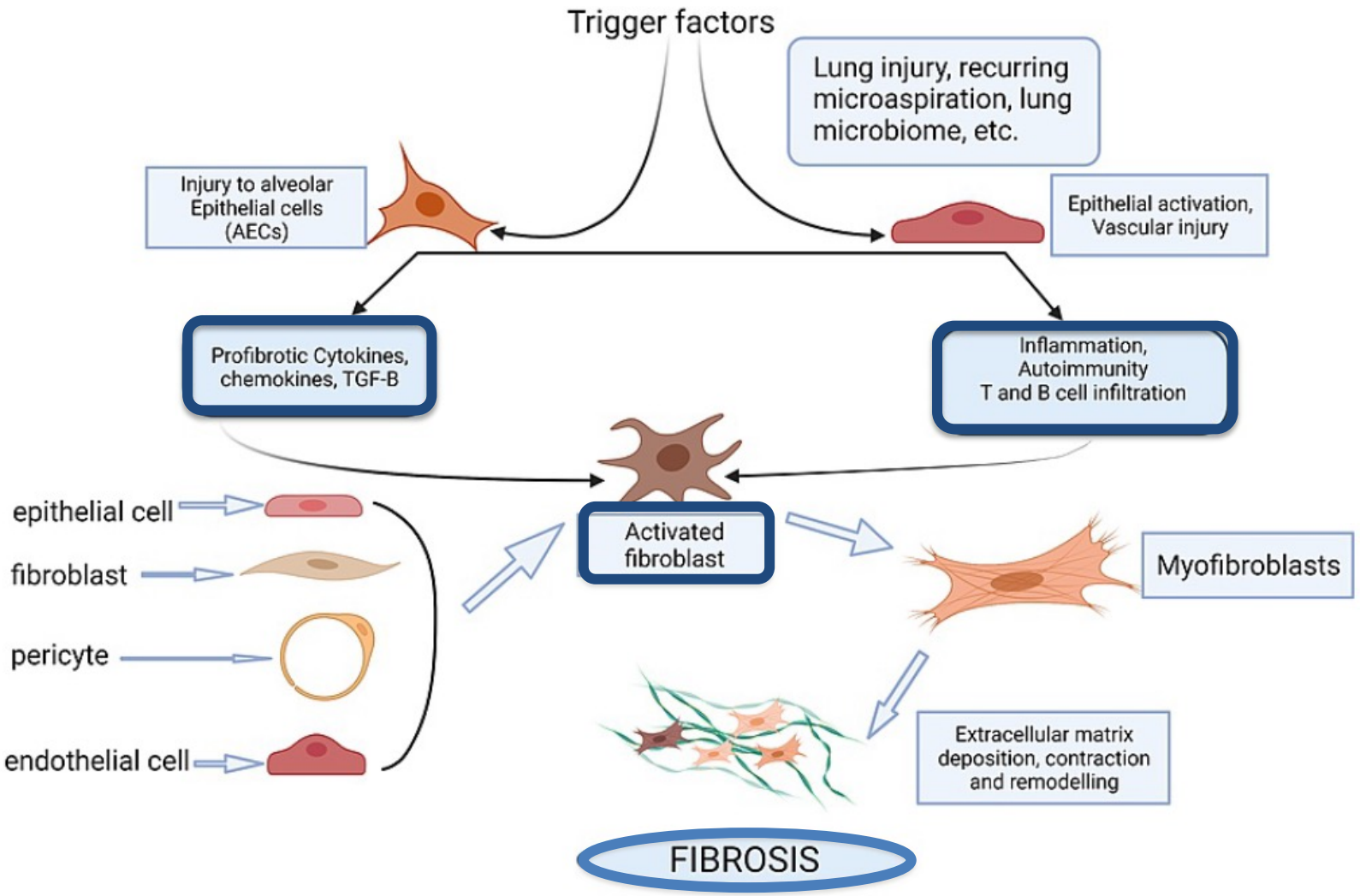
Treatment may be initiated in selected patients with a **high probability of progression** based on **prognostic factors** for progression / mortality.

*8% of those with an overall FVC decline
FVC, forced vital capacity; HRQoL, health-related quality of life; ILD, interstitial lung disease; SSc, systemic sclerosis; SSc-ILD, systemic sclerosis-associated interstitial lung disease
1. Hoffmann-Vold A-M *et al. Ann Rheum Dis* 2021;80:219–27; 2. Jaeger VK *et al. PLoS One* 2016;11:e0163894; 3. Denton CP, Khanna D. *Lancet* 2017;390:1685–99

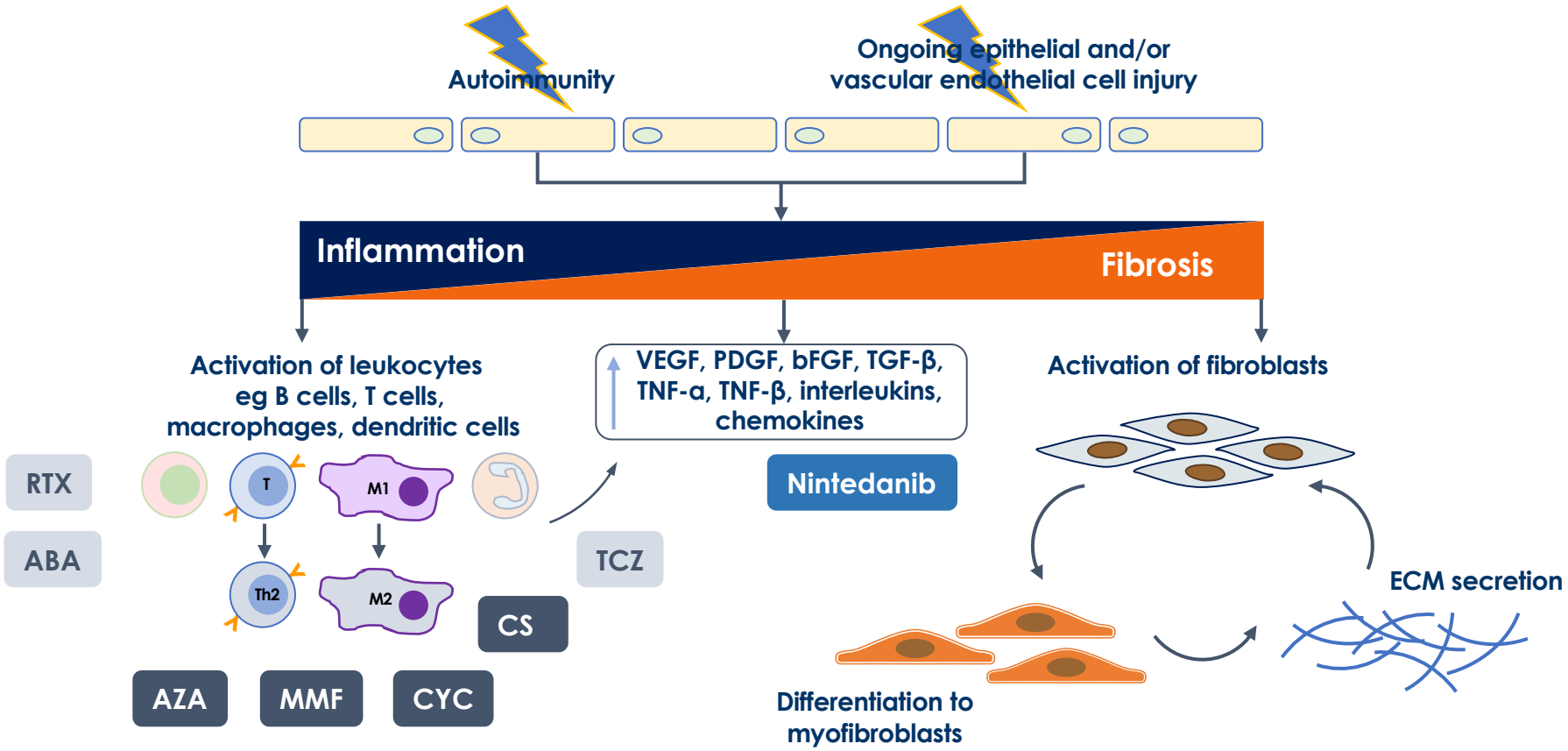
ILD-SSc as an expression of SSc pathogenic pathway



SSc pathogenesis: multiple key actors



Immunomodulatory and antifibrotic treatments for SSc-ILD act on a range of biological pathways



*Nintedanib is the only antifibrotic licensed to treat SSc-ILD and other fibrosing CTD-ILDs if they have a progressive phenotype; †ABA, AZA, CS, CYC, MMF and RTX are not are not licensed for the treatment of SSc-ILD and other CTD-ILDs. TCZ is licensed for slowing the rate of decline in pulmonary function in adult patients with SSc-ILD in the United States only. ABA, abatacept; AZA, azathioprine; bFGF, basic fibroblast growth factor; CS, corticosteroids; CTGF, connective tissue growth factor; CYC, cyclophosphamide; ECM, extracellular matrix; M1, classically activated macrophage; M2, alternatively activated macrophage; MMF, mycophenolate mofetil; PDGF, platelet-derived growth factor; RTX, rituximab; TGF, transforming growth factor; Th2, type 2 T helper cell; TNF, tumor necrosis factor; TCZ, tocilizumab; VEGF, vascular endothelial growth factor. 1. Cottin V. *Eur Respir Rev* 2019;28:190109

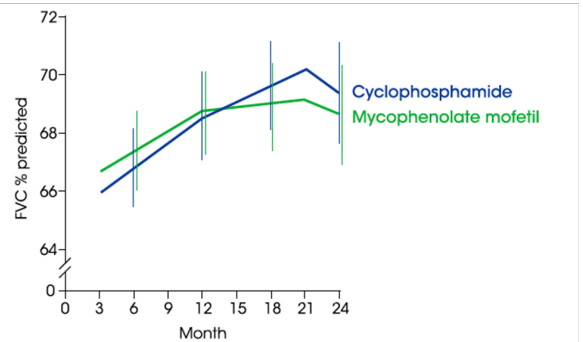
Medications for the treatment of SSc-ILD:

Immunosuppressive agents

SLS II

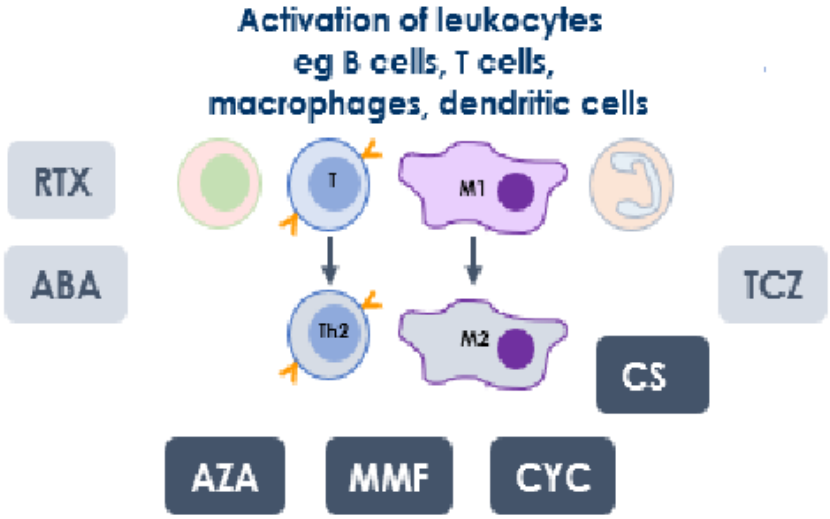
FVC % predicted in patients who received MMF for 2 years vs CYC for 1 year followed by placebo for 1 year

CYC 2 mg/kg/day
vs
MMP 1500 mg twice/day



Number of patients									
Cyclophosphamide	72	62	56	51	51	44	46	40	51
Mycophenolate mofetil	69	64	60	54	59	51	49	47	53

Lancet Resp Med, 2016

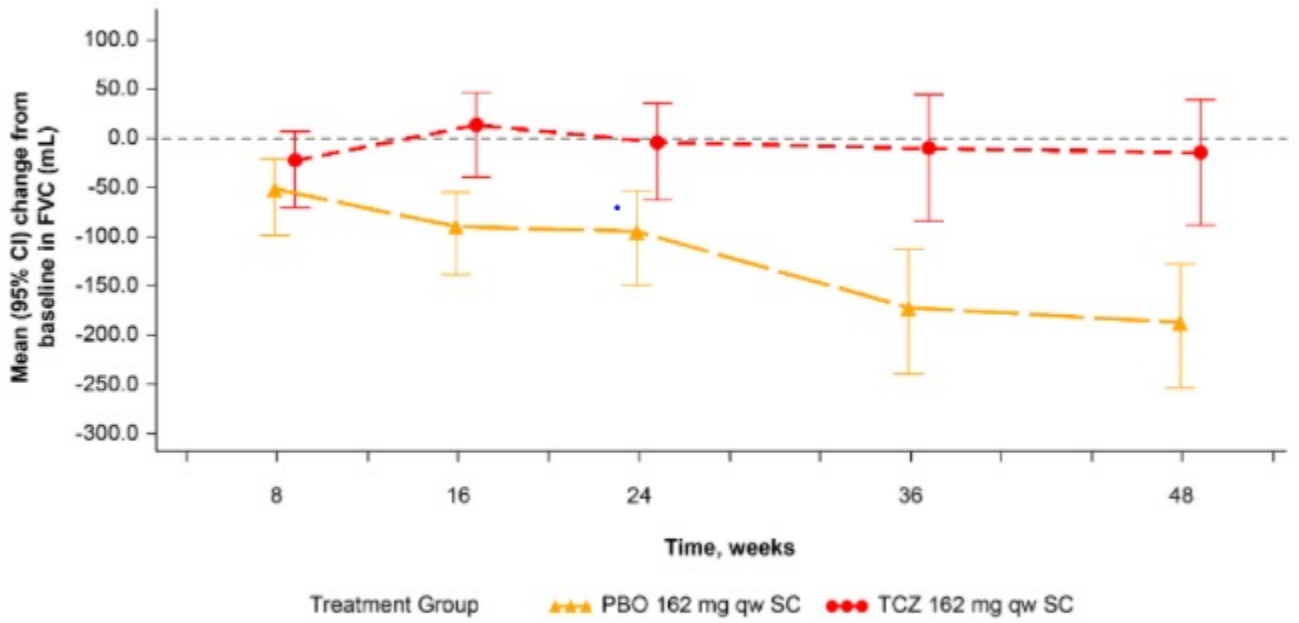


	Study type	N° pts	RTX Dose	Follow-up	mRss	Lung function
Smith et al. 2013	Open Label	8 dcSSc		6 months	Improved	Stable
Lafyatis et al.	Open Label	15 dcSSc	1000mg x 2	12 months	Not Improved	Stable
Daoussis et al. 2010, 2012	RCT (vs other Immunosupp.)	8 dcSSc 6dcSSc controls	4x375mg/m2 Baseline and 6 months	12 months (and 24 months)	Improved (in both groups)	Improved (vs controls)
Bosello et al. 2015	Open Label	20 dcSSc	1000mg x 2	12 months	Improved	Improved
Jordan et al. 2015	Case control (Hystorical)	46 dcSSc 17 lcSSc 25 controls	1000mg x 2 (+variable co-treatments)	6 months	Improved (more in severe pts)	Prevented FVC decline vs controls
Sircar G. et al. 2018	Open label, RCT (RTX vs CYC)	68 dcSSc	1000mg x 2	6 months	Improved	Improved
Ebata S. et al.	Double-blind,RCT (vs placebo)	56 dcSSc	375mg/m2 Once/week for 4 weeks	6 months	Improved	Improved

Medications for the treatment of SSc-ILD:

Immunosuppressive agents

Tocilizumab might preserve lung function in people with early SSc-ILD and elevated acute-phase reactants



A mixed model for repeated measures analysis was implemented.
The analysis included the fixed, categorical effects of treatment, visit, the stratification factor IL-6 level (<10; ≥10 pg/mL) at screening, IL-6 level at screening-by-visit interaction, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction.

Khanna D. et al. Lancet Respir Med 2020 Oct;8(10):963-974

Arthritis & Rheumatology
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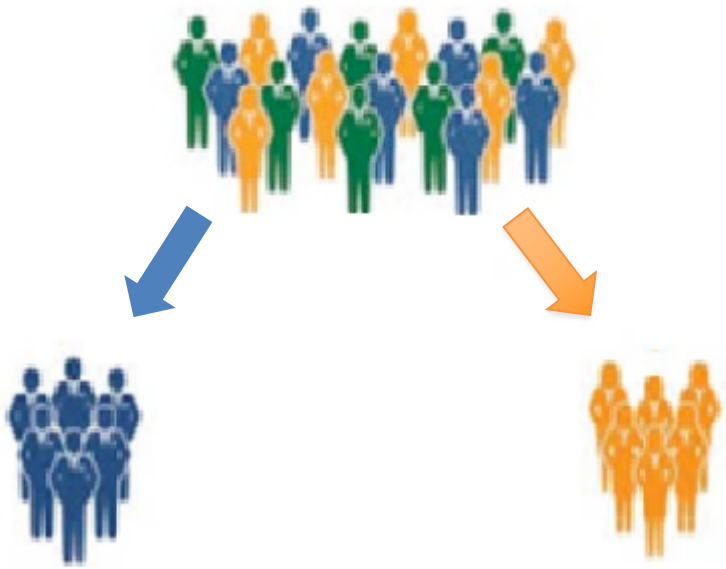
Tocilizumab Prevents Progression of Early Systemic Sclerosis–Associated Interstitial Lung Disease

David Roofeh,[1] Celia J. F. Lin,[2] Jonathan Goldin,[3] Grace Hyun Kim,[3] Daniel E. Furst,[4] Christopher P. Denton,[5] Suiyuan Huang,[1] and Dinesh Khanna,[1] on behalf of the focuSSced Investigators

133 pts from theFocuSSced trial (phase III RCT of TCZ in patients with SSc and progressive skin disease) with ILD.
ILD divided in mild (5-10%), moderate (>10-20%), or severe (>20%) categories

They had numerically lower %FVC and %DLco, higher CRP, and a greater percentage of ATA1 positivity.



Quantitative ILD (QILD) → summation of ground glass opacities, honeycombing, and fibrotic reticulation;

Quantitative lung fibrosis (QLF) → quantitative fibrosis (fibrotic reticulation) alone.

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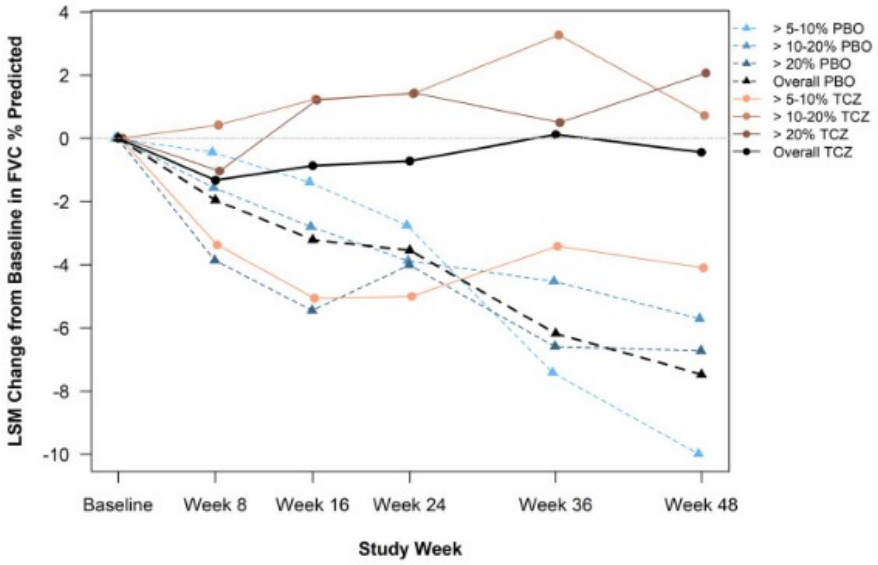
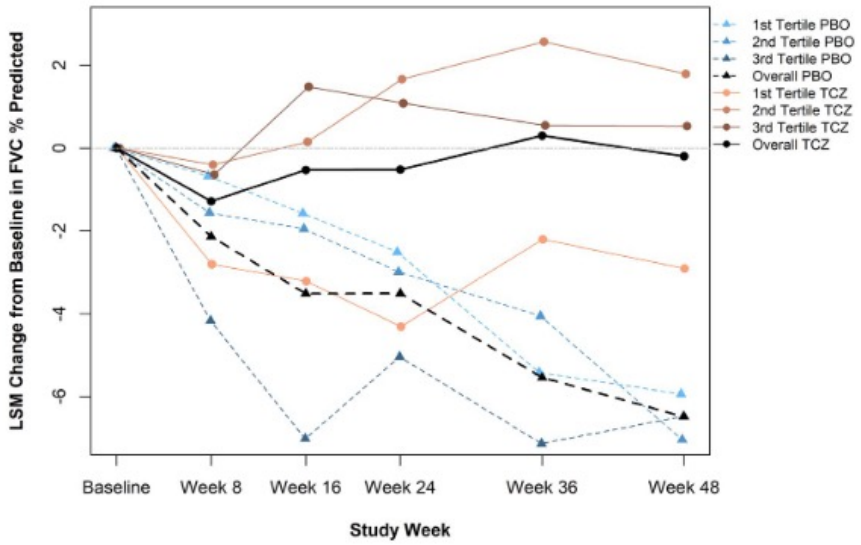
QILD divided in mild (5-10%), moderate (>10-20%), or severe (>20%) categories

The preservation of FVC in the TCZ arm did not vary according to baseline QILD and QLF score



QILD



QLF

Tocilizumab in early SSc-ILD with progressive skin disease stabilized forced vital capacity over 48 weeks, independent of the extent of quantitative radiographic interstitial lung disease or fibrosis.

RHEUMATOLOGY

Letter to the Editor

Rheumatology 2021;0:1–2
doi:10.1093/rheumatology/keab273

Real-world experience of tocilizumab in systemic sclerosis: potential benefit on lung function for anti-topoisomerase-positive patients

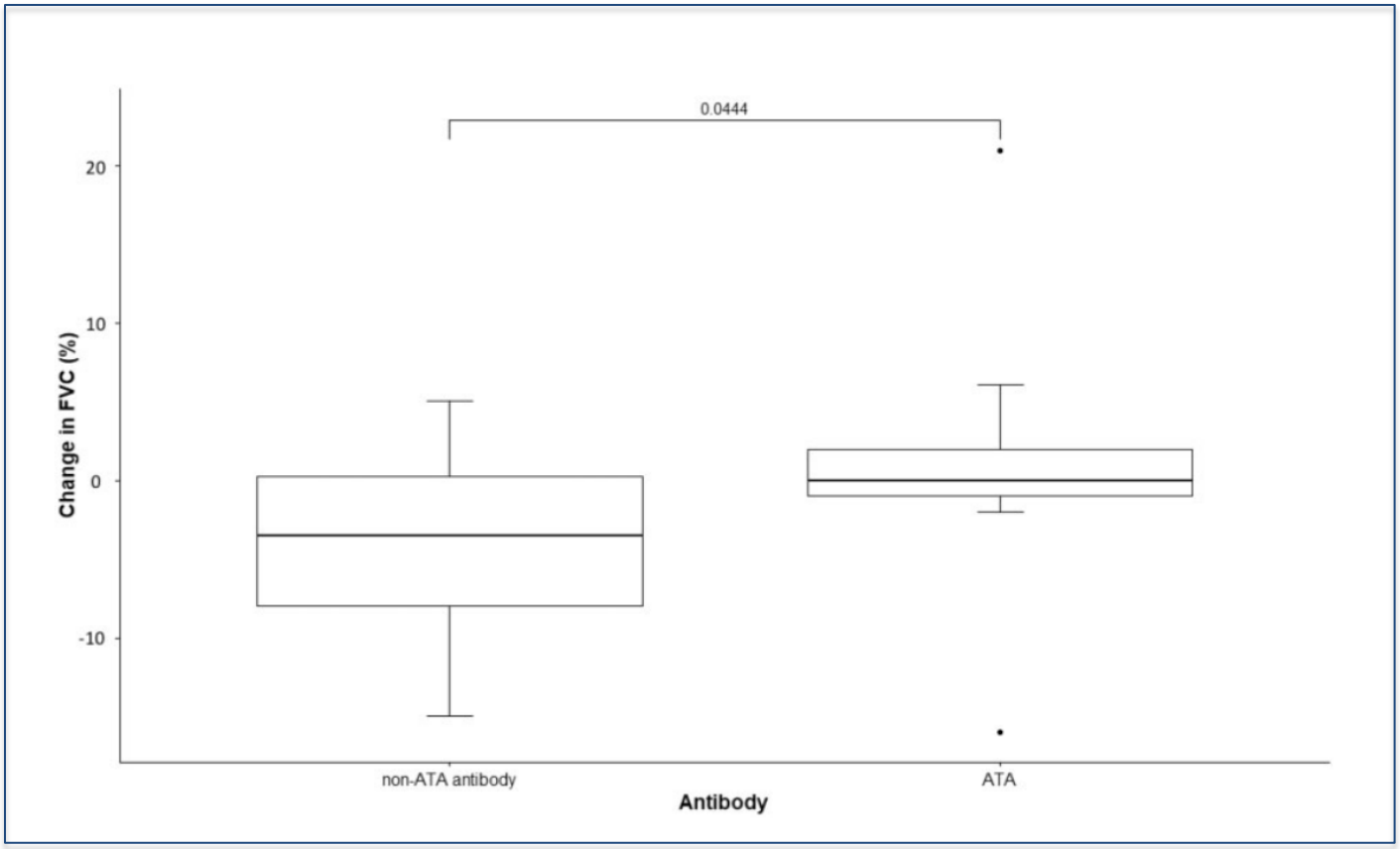
A retrospective study of 31 SSc patients treated with tocilizumab

Potential benefit of tocilizumab on lung function in SSc patients in a real-world setting, especially for ATA-positive cases

The average change in FVC was significantly greater in the non-tocilizumab comparator group (-1.3 vs -4.1) (P 0.016)

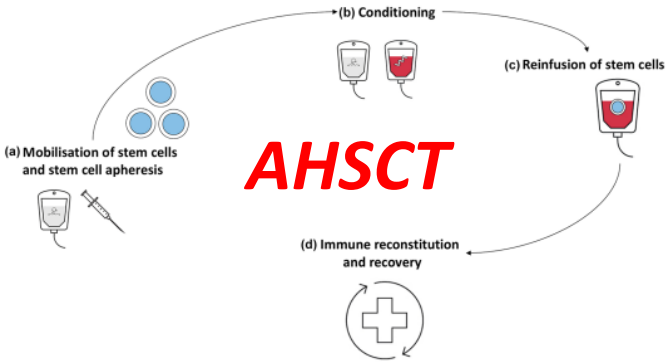
Subgroup analysis revealed a significant difference between autoantibody groups and change in FVC while on tocilizumab (P 0.044)

There was no significant difference in FVC change for patients with ILD prior to initiation of treatment or between early and late-stage disease at time of tocilizumab initiation



Medications for the treatment of SSc-ILD:

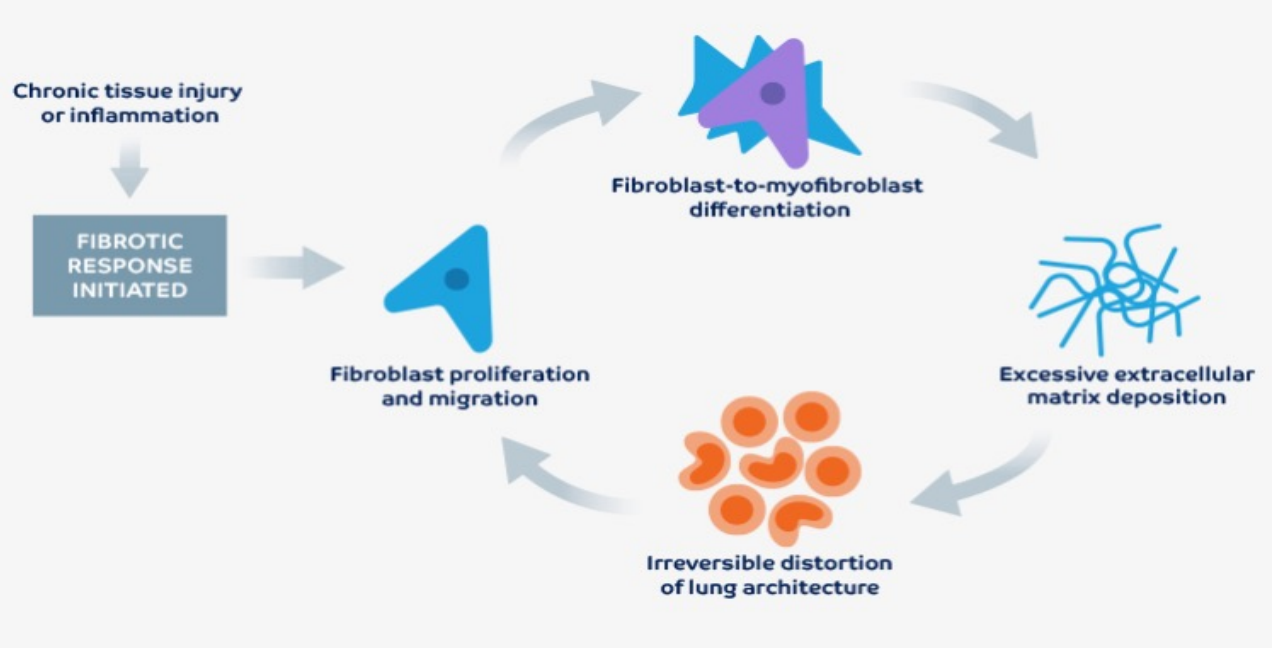
Immunosuppressive agents

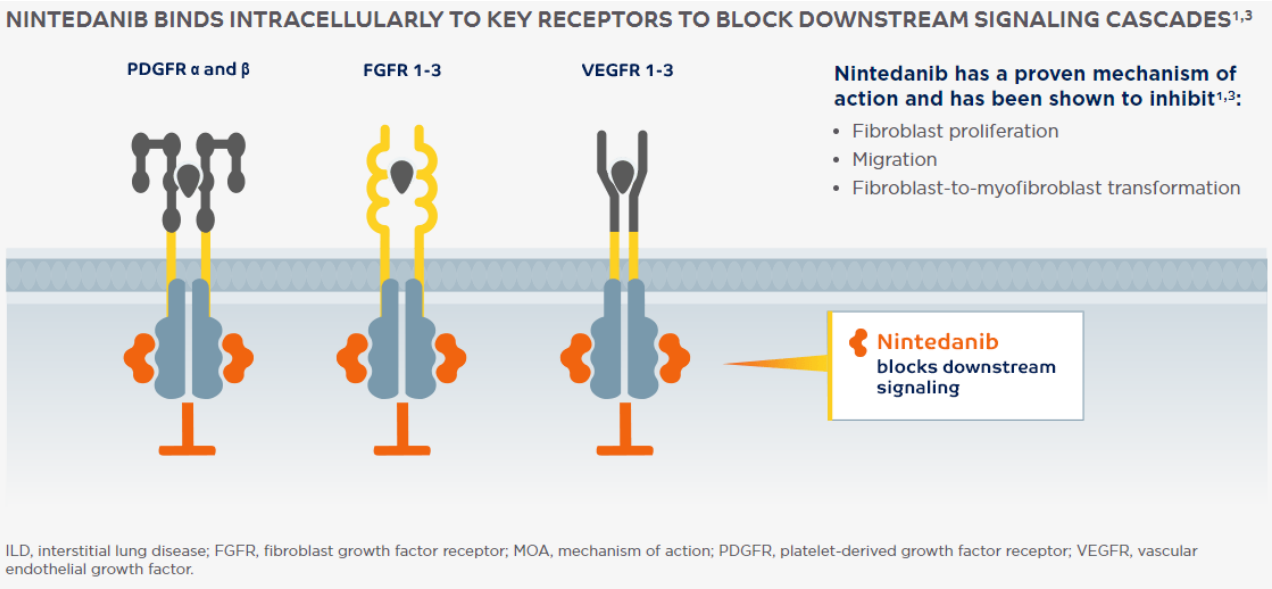


- AHSCT resulted in stabilization and modest improvement of lung volumes
- AHSCT resulted in stabilization and modest improvement of lung disease extent on HRTC
- Lung involvement *per se* was not an inclusion criterion in all SCT trial

Medications for the treatment of SSc-ILD:

Anti-fibrotic agents





ILD, interstitial lung disease; FGFR, fibroblast growth factor receptor; MOA, mechanism of action; PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor.

Nintedanib in fibrosing ILD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nintedanib for Systemic Sclerosis–Associated Interstitial Lung Disease

Oliver Distler, M.D., Kristin B. Highland, M.D., Martina Gahlemann, M.D., Arata Azuma, M.D., Aryeh Fischer, M.D., Maureen D. Mayes, M.D., Ganesh Raghu, M.D., Wiebke Sauter, Ph.D., Mannaig Girard, M.Sc., Margarida Alves, M.D., Emmanuelle Clerisme-Beaty, M.D., Susanne Stowasser, M.D., Kay Tetzlaff, M.D., Masataka Kuwana, M.D., and Toby M. Maher, M.D., for the SENSCIS Trial Investigators*

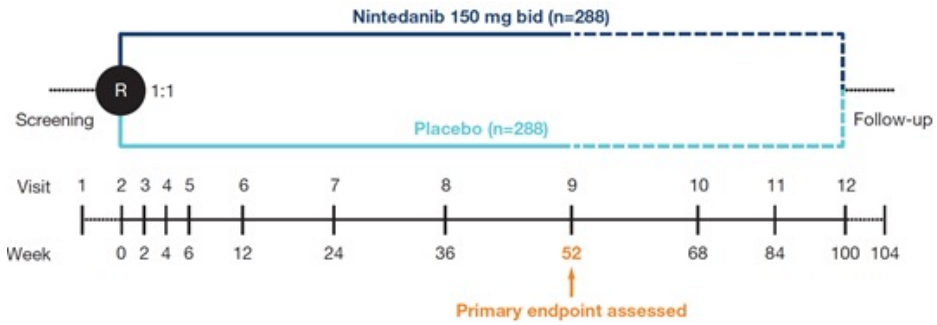
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nintedanib in Progressive Fibrosing Interstitial Lung Diseases

K.R. Flaherty, A.U. Wells, V. Cottin, A. Devaraj, S.L.F. Walsh, Y. Inoue, L. Richeldi, M. Kolb, K. Tetzlaff, S. Stowasser, C. Coeck, E. Clerisme-Beaty, B. Rosenstock, M. Quaresma, T. Haeufel, R.-G. Goeldner, R. Schlenker-Herceg, and K.K. Brown, for the INBUILD Trial Investigators*

N Engl J Med. 2019;380:2518-2528.
N Engl J Med. 2019;381:1718-1727.



SENSCIS® trial population and background medications

- **Age ≥18 years**
- **SSc (based on 2013 ACR/EULAR criteria[1]) with disease onset (first non-Raynaud symptom) <7 years from screening**
- **ILD based on chest HRCT performed within 12 months of screening with ≥10% extent of fibrosis of the lungs (confirmed by central assessment)**
- **FVC ≥40% predicted**
- **DL_{CO} 30–89% predicted**

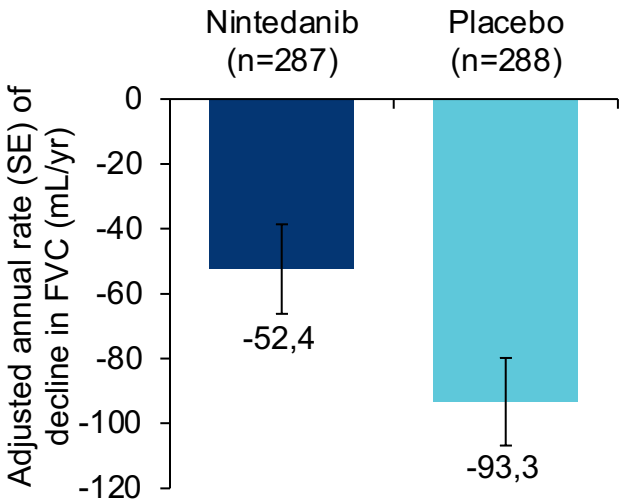
Permitted:

- **Prednisone ≤10 mg/day** or equivalent
- **Stable mycophenolate or methotrexate** for ≥6 months prior to randomization
- Initiation of additional therapy during the trial was permitted in cases of clinically significant deterioration of SSc, at discretion of investigator

Distler O et al. N Engl J Med. 2019. doi:10.1056/NEJMoa1903076C

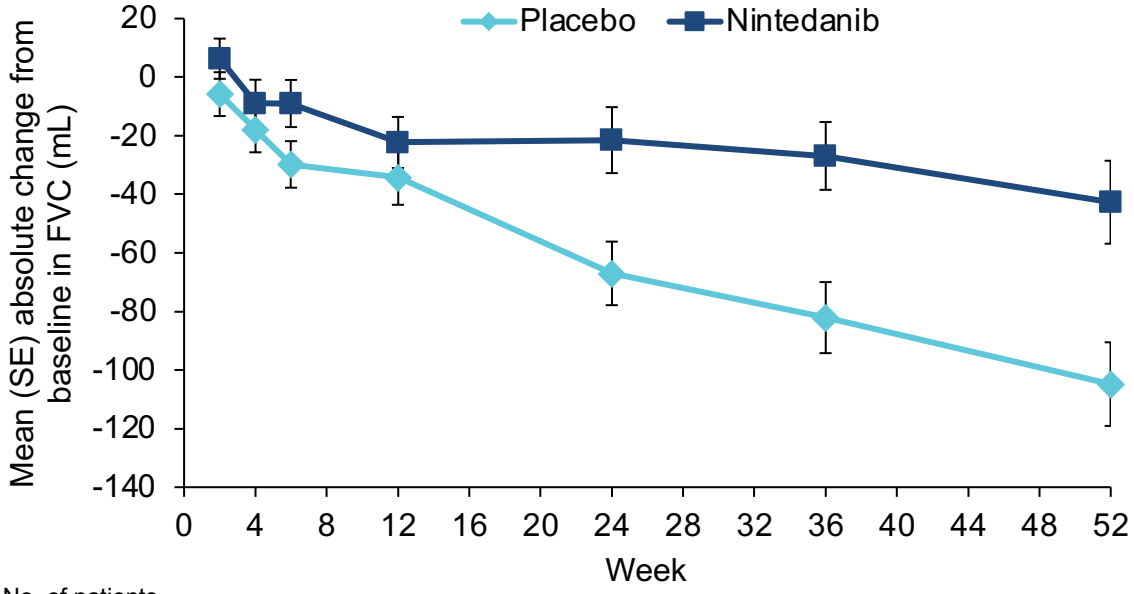
Nintedanib in SSc-ILD and the results of the SENSCIS® trial

Annual rate of decline in FVC (mL/yr) (primary endpoint)



Difference: 41.0 mL/yr (95% CI: 2.9, 79.0); p=0.04
Relative reduction: 44%

Change from baseline in FVC (mL) over 52 weeks



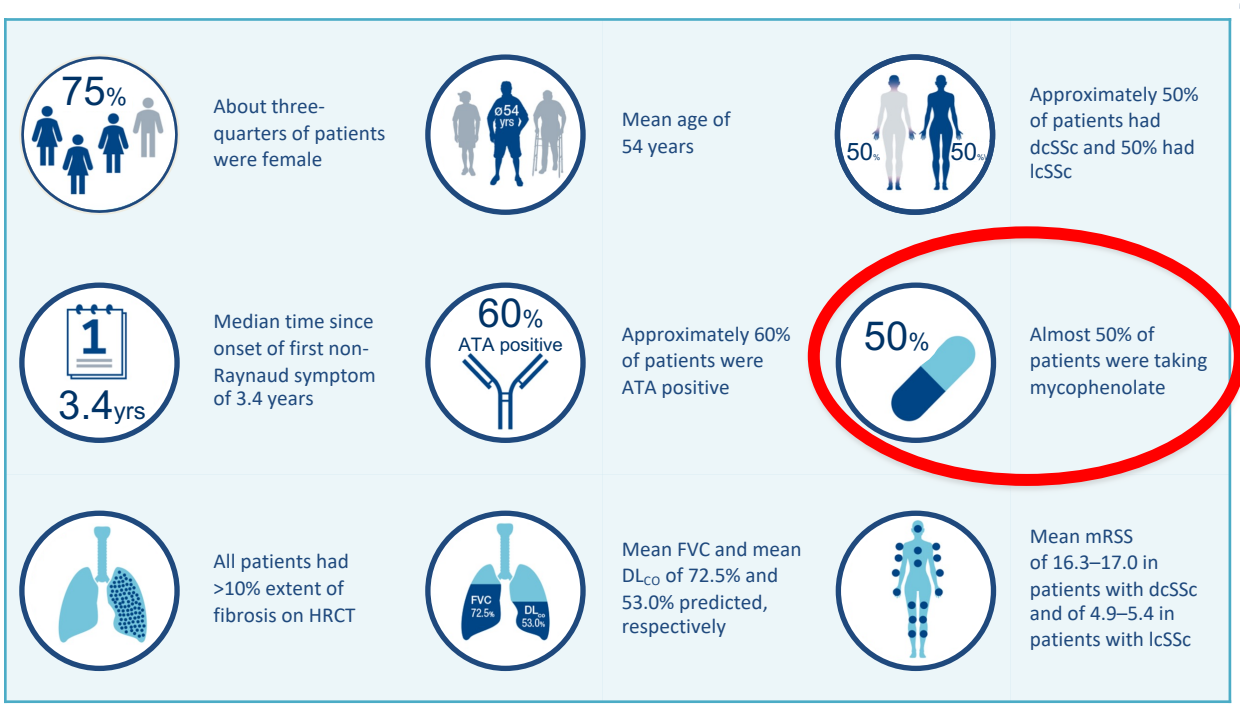
No. of patients

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

Primary endpoint analyzed using random coefficient regression model (with random slopes and intercepts) including ATA status, age, height, gender and baseline FVC (mL) as covariates

Distler O et al. N Engl J Med. 2019. doi:10.1056/NEJMoa1903076C

The baseline characteristics of patients in SENSCIS® are a relevant representation of the general SSc-ILD population



Inclusion of patients with lcSSc and dcSSc and patients receiving and not receiving mycophenolate

+

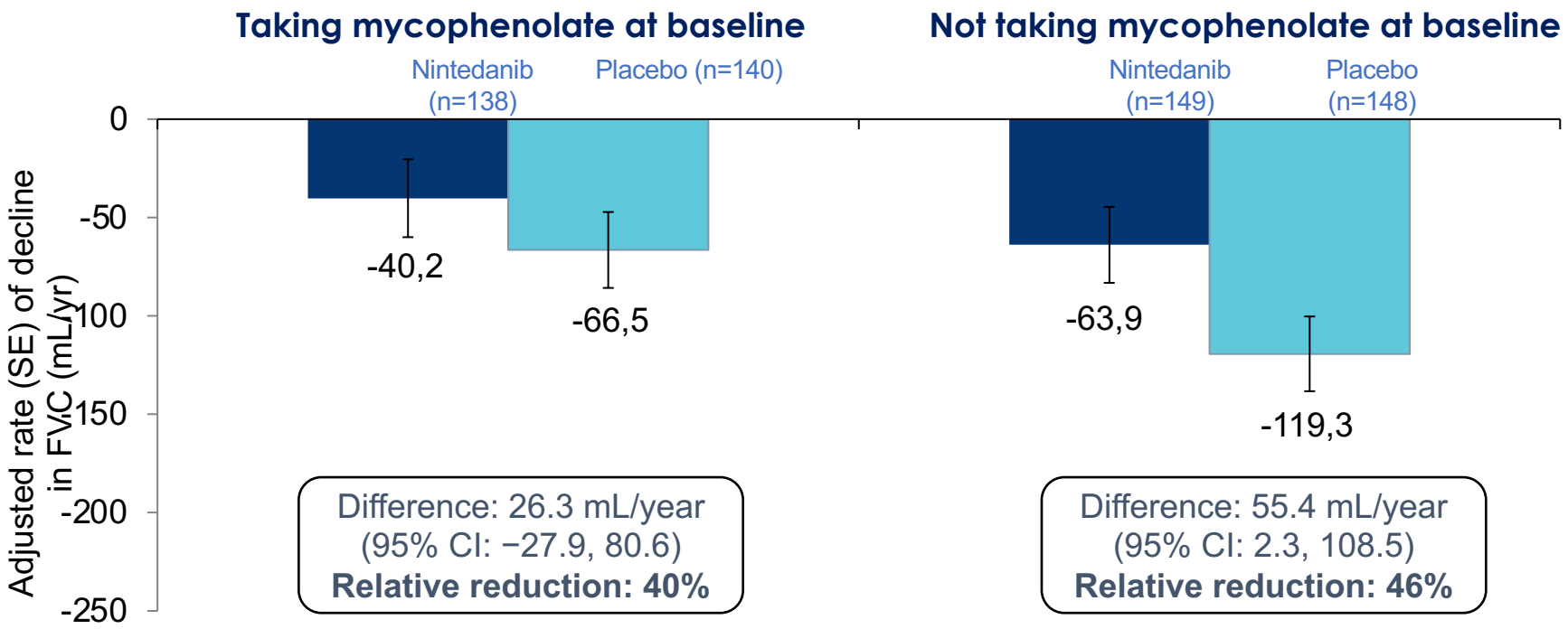
A wide spectrum of lung function impairment

=

Suggests the population is largely reflective of real-world clinical practice

ATA, antitopoisomerase antibody; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; dcSSc, diffuse cutaneous systemic sclerosis; FVC, forced vital capacity; HRCT, high-resolution computed tomography; lcSSc, limited cutaneous systemic sclerosis; mRSS, modified Rodnan Skin Score; SGRQ, St George's Respiratory Questionnaire; SSc-ILD, systemic sclerosis-associated interstitial lung disease. Distler O *et al*. *N Engl J Med* 2019;380:2518–28

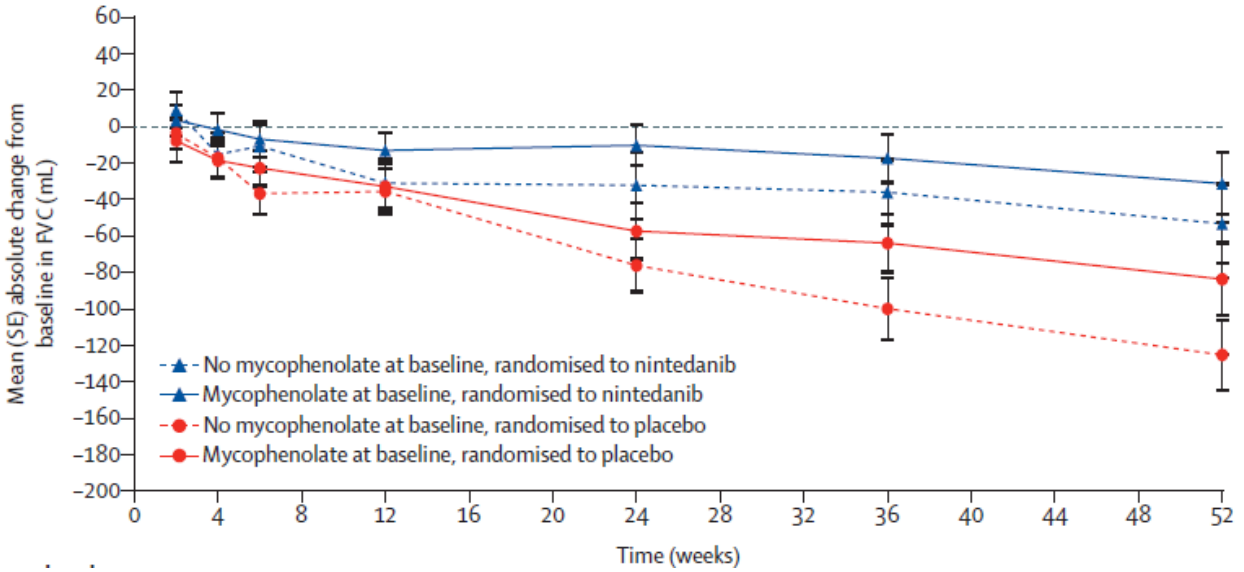
Rate of decline in FVC (mL/yr) over 52 weeks by Mycophenolate use at baseline in the SENSCIS® trial

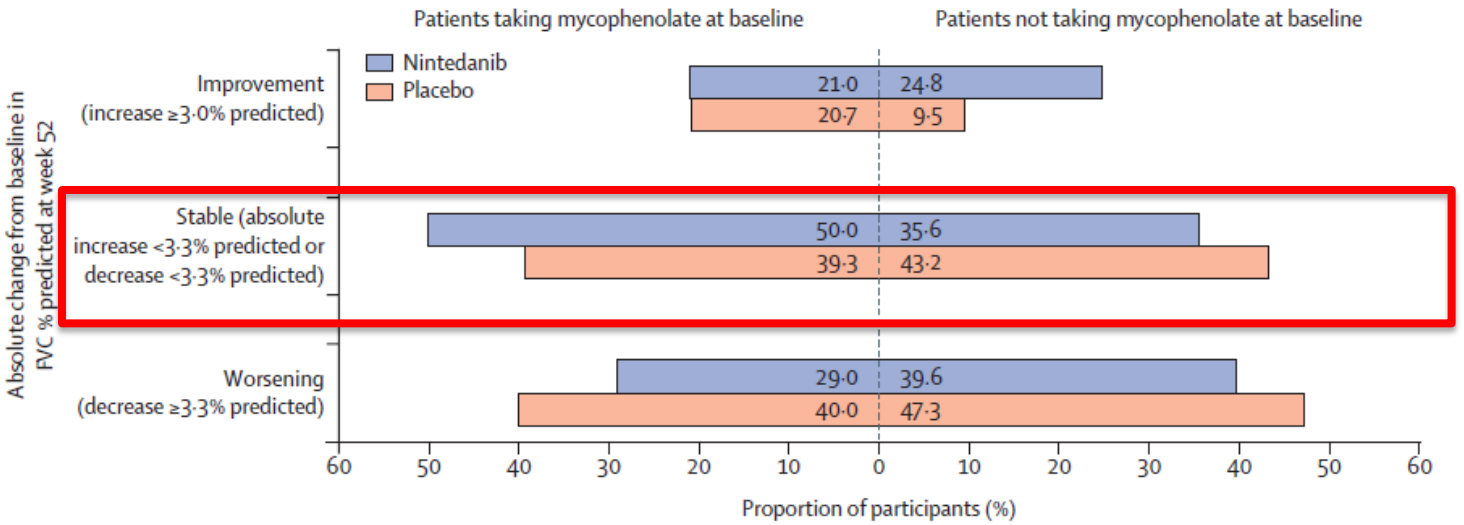


Treatment-by-time-by-subgroup interaction p=0.452

Distler O et al. N Engl J Med. 2019. doi:10.1056/NEJMoa1903076C

Rate of decline in FVC (mL/yr) over 52 weeks by Mycophenolate use at baseline in the SENSCIS® trial





Highland KB et al. *Lancet Respir Med.* 2021; **9**: 96-106

Mycophenolate use in the SENSCIS® trial

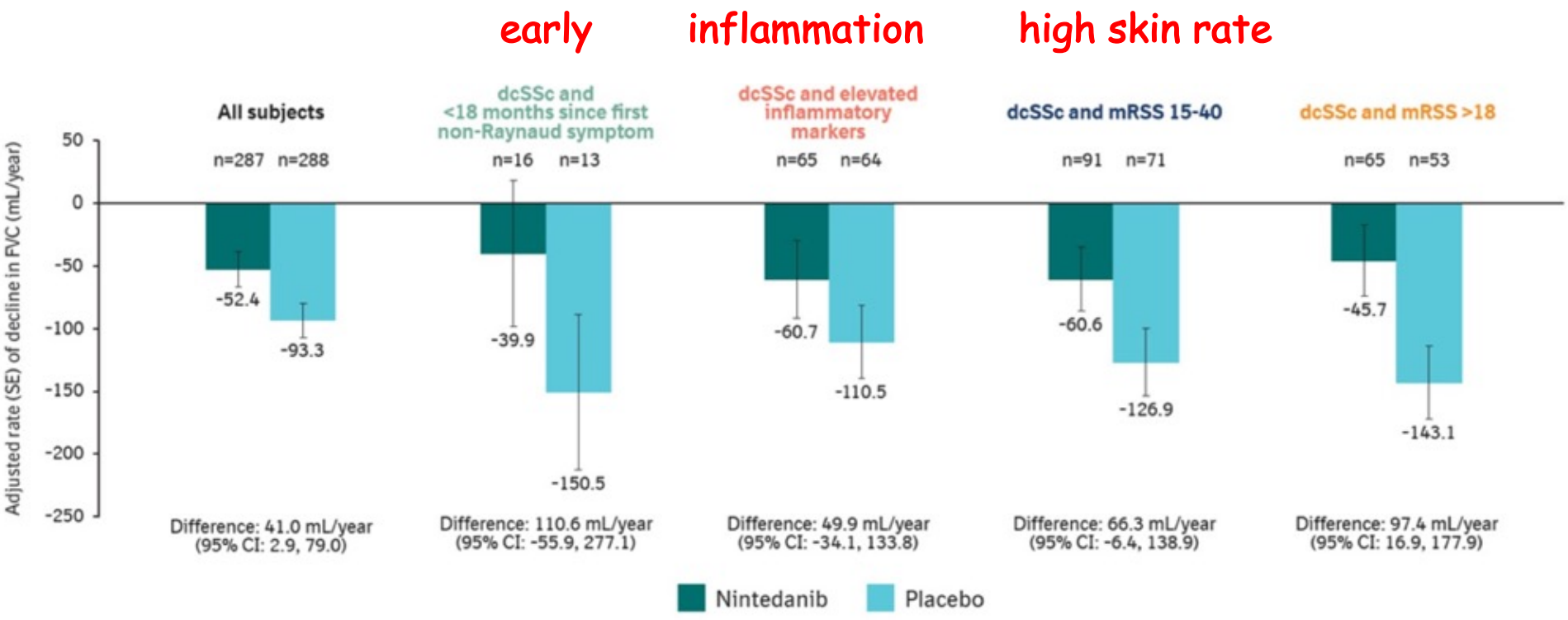
Participants in the SENSCIS trial were not randomised according to mycophenolate use at enrolment, systematic differences probably existed between patients who were taking mycophenolate and those who were not

Higher proportion of patients treated with mycophenolate at baseline had diffuse cutaneous systemic sclerosis, higher mean mRSS, and lower mean percentage of predicted FVC at enrolment, suggesting that patients who were taking mycophenolate might have had more aggressive ILD

Alternatively, a more progressive phenotype might have been present in those not taking mycophenolate because this therapy might have been used previously, but discontinued due to side-effects, worsening systemic sclerosis, or ILD progression

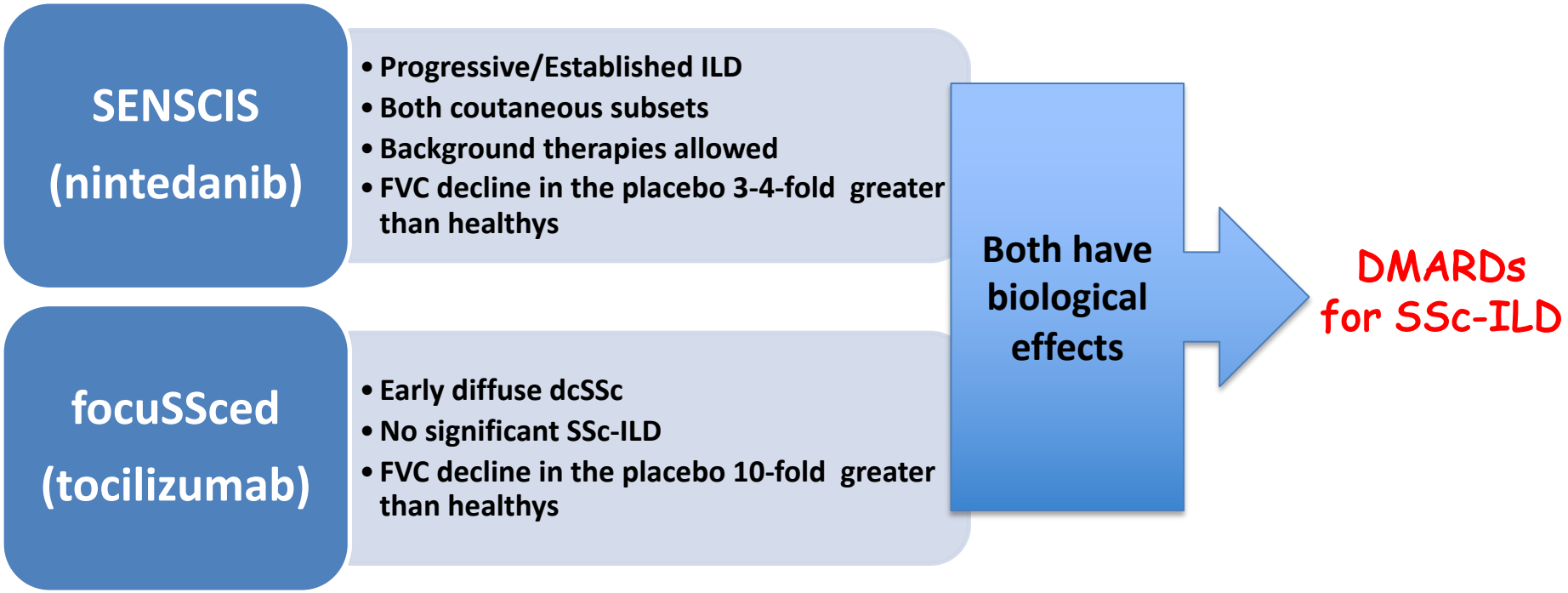
Effect of Nintedanib in SSc-ILD and risk factors for rapid decline in FVC: further analyses of the SCENSIS trial

Rate of decline in FVC (mL/year) over 52 weeks in subjects with dcSSc and risk factors for rapid decline in FVC



Khanna D et al. Effect of nintedanib in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) and risk factors for rapid decline in forced vital capacity: further analyses of the SENSCIS trial. Poster presented at the American College of Rheumatology Convergence Conference, 2021.

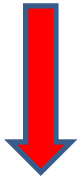
Interpretation of anti-fibrotic and immunosuppressive SSc-ILD RCTs



All patients with SSc should be screened for ILD at baseline, using HRCT, PFTs/exercise tests, and clinical examination[1]

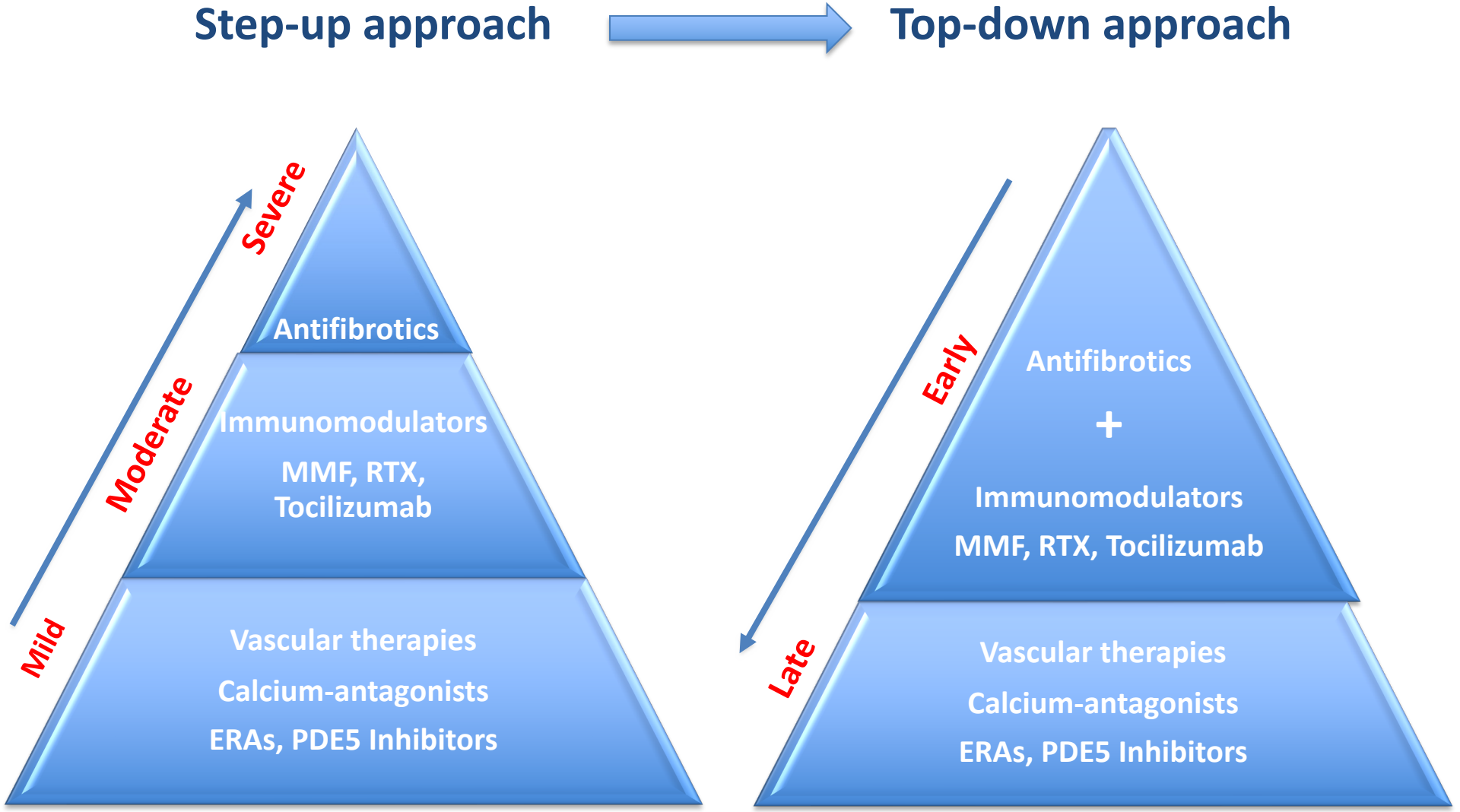
Once SSc-ILD is diagnosed, management options should be considered, with patients then monitored for ILD progression

Progression of SSc-ILD should be monitored using HRCT, PFTs/exercise tests, and clinical symptoms[1]

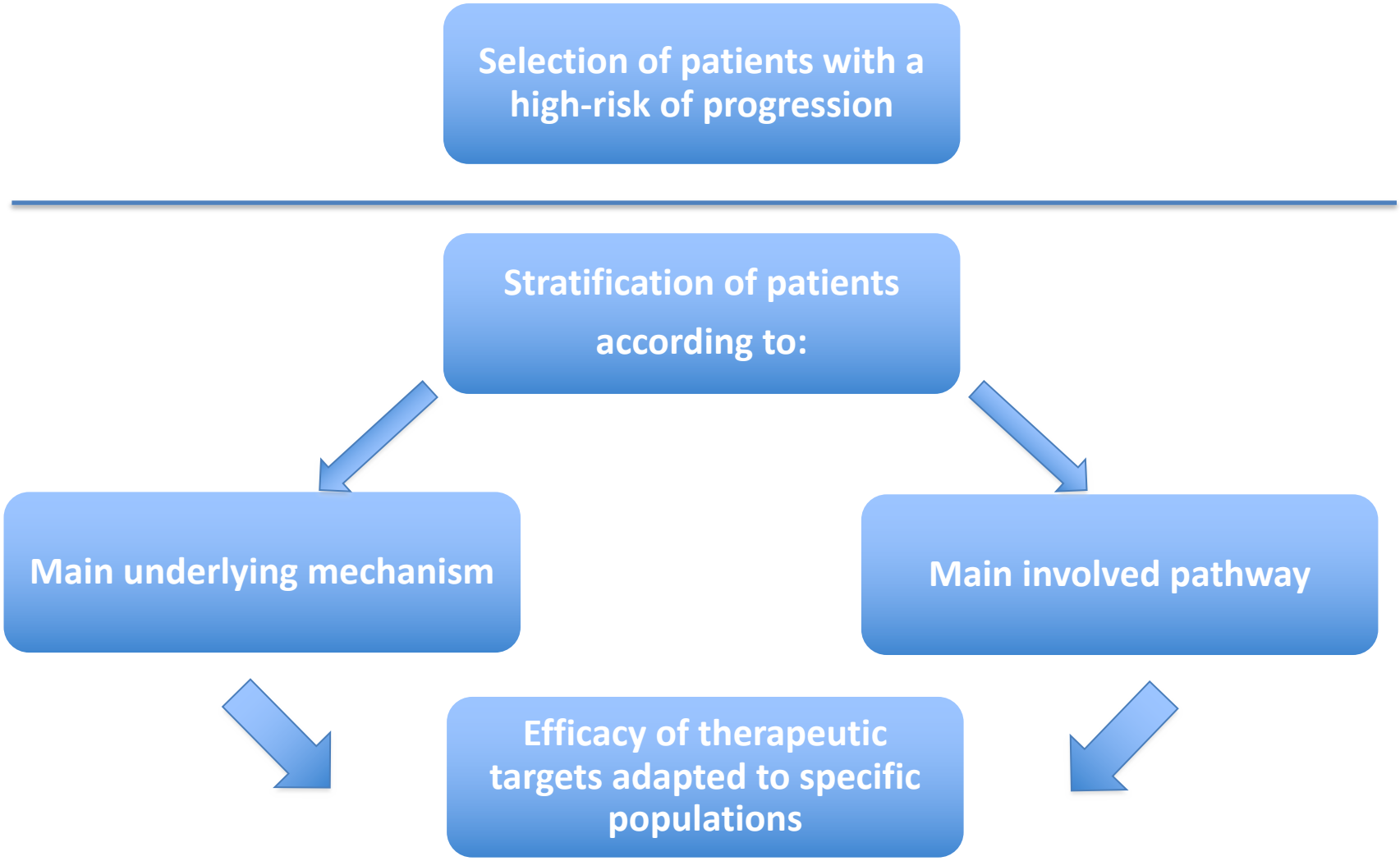


Potential factors to be taken into consideration when choosing between immunosuppressants or antifibrotics in SSc-ILD

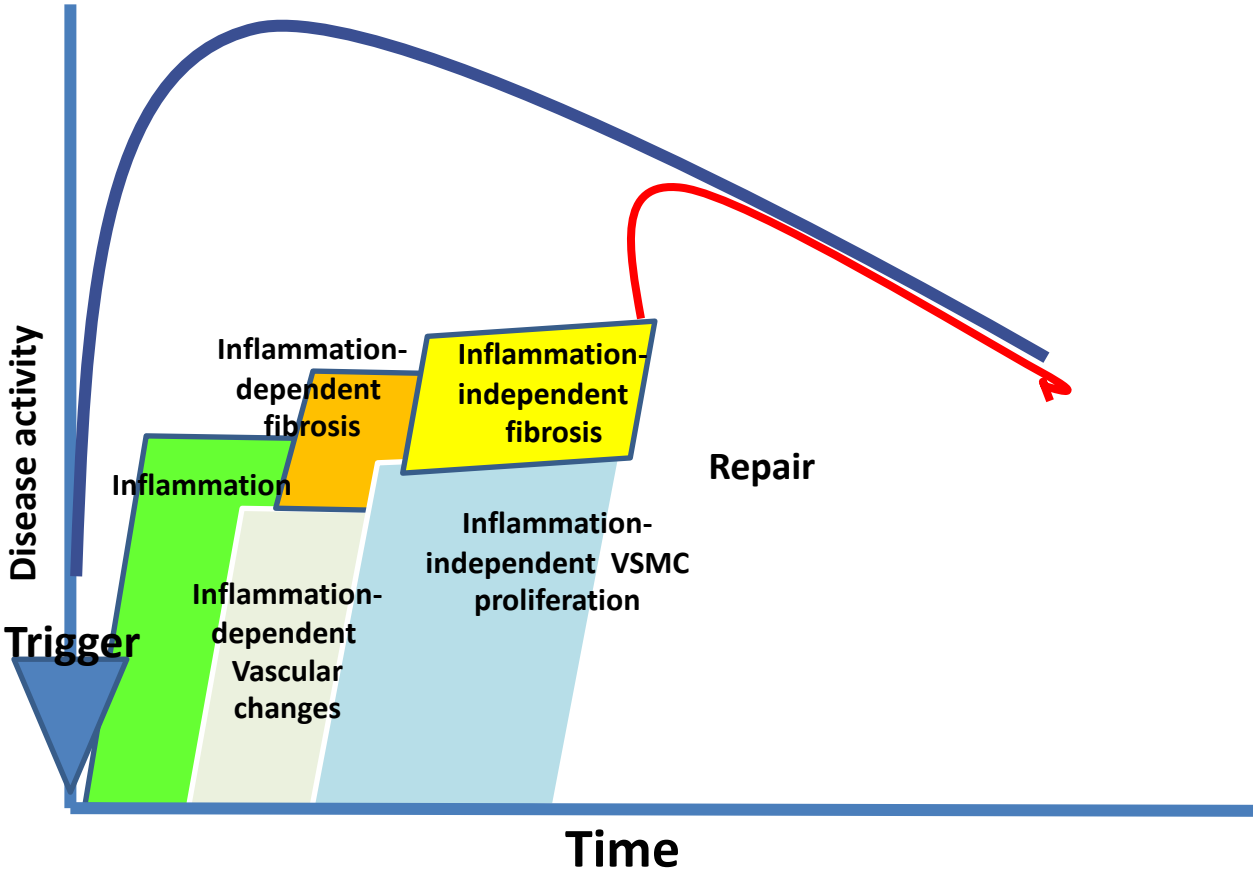
- Early disease duration
- Clinical expression of ILD (lung symptoms, altered function for daily life, abnormal PFTs)
- Extra-pulmonary involvement (Skin and MSK activity)
- Elevated acute phase reactants
- Autoantibody status (anti-topoisomerase I: high risk of progression; ACA: low risk)
- HRCT extent (high risk if >10%)


Step-up approach
Top-down approach
Severe
Moderate
Mild
Antifibrotics
Immunomodulators
MMF, RTX,
Tocilizumab
Vascular therapies
Calcium-antagonists
ERAs, PDE5 Inhibitors
Early
Late
Antifibrotics
+
Immunomodulators
MMF, RTX, Tocilizumab
Vascular therapies
Calcium-antagonists
ERAs, PDE5 Inhibitors

Towards personalized medicine

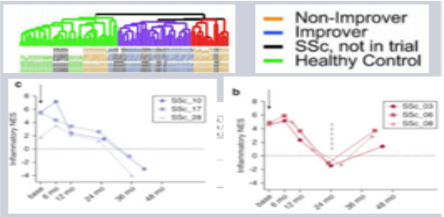
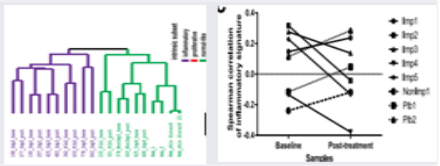
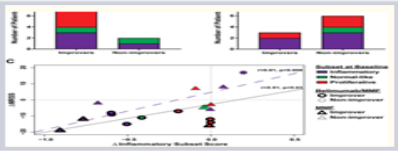
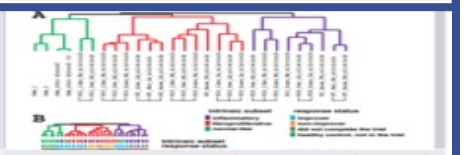
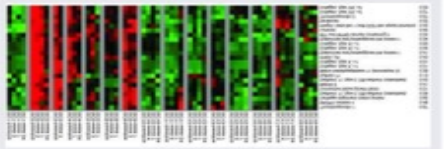


Working model of evolving disease mechanisms in SSc



Gene expression subsets identify patients that improve with therapy

(inflammatory, fibro-proliferative, normal-like, limited cutaneous patterns)

Trial Analyzed	Primary results	
Mycofenolate Mofetil Hinchcliff M. et al. (2013) Toledo D et al. (2018)	Improvers are most often inflammatory while no improvers are most often fibroproliferative; Inflammatory signature decreases with MMF therapy and rebounds upon cessation	
Abatacept Chakravarty EF et al. (2015)	4 of 5 SSc patients who improved with abatacept were inflammatory	
Belimumab (with background MMF) Gordon J (2017)	Improvement coincides with a decrease in inflammatory signature and movement to the normal-like subset	
Nilotinib Gordon J. et al. (2015)	Activation of the TGFb pathway (which spans the inflammatory and fibroproliferative subsets) was important for improvement.	
Fresolimumab Rice L. et al EF (2015) Taroni et al. (2016)	Activation of the TGFb pathway (which spans the inflammatory and fibroproliferative subsets) was important for improvement.	

Improvers typically associated with the inflammatory subset

Improvers associated with the activation of a specific pathway, ie TGFβ

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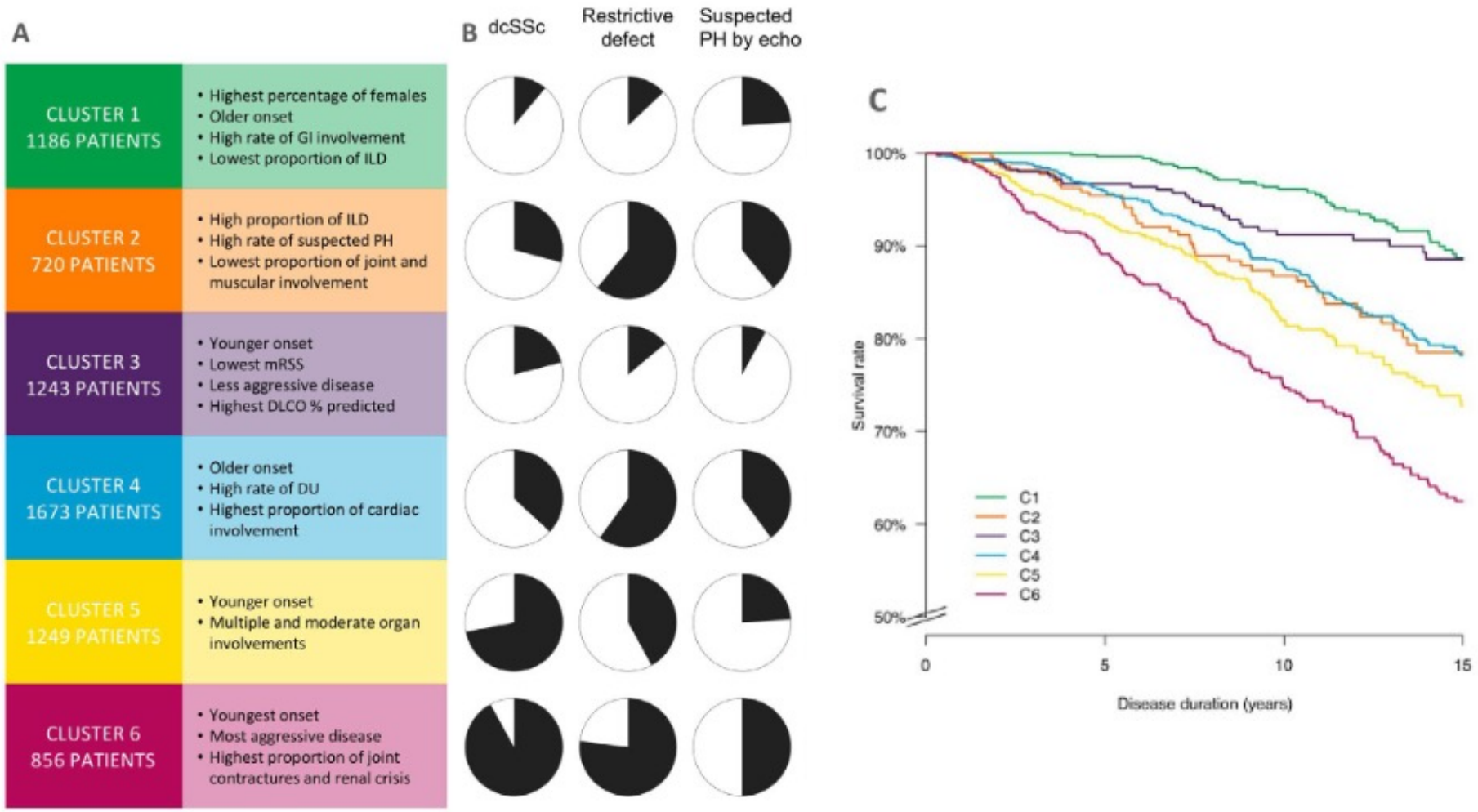
American College of Rheumatology
Empowering Rheumatology Professionals

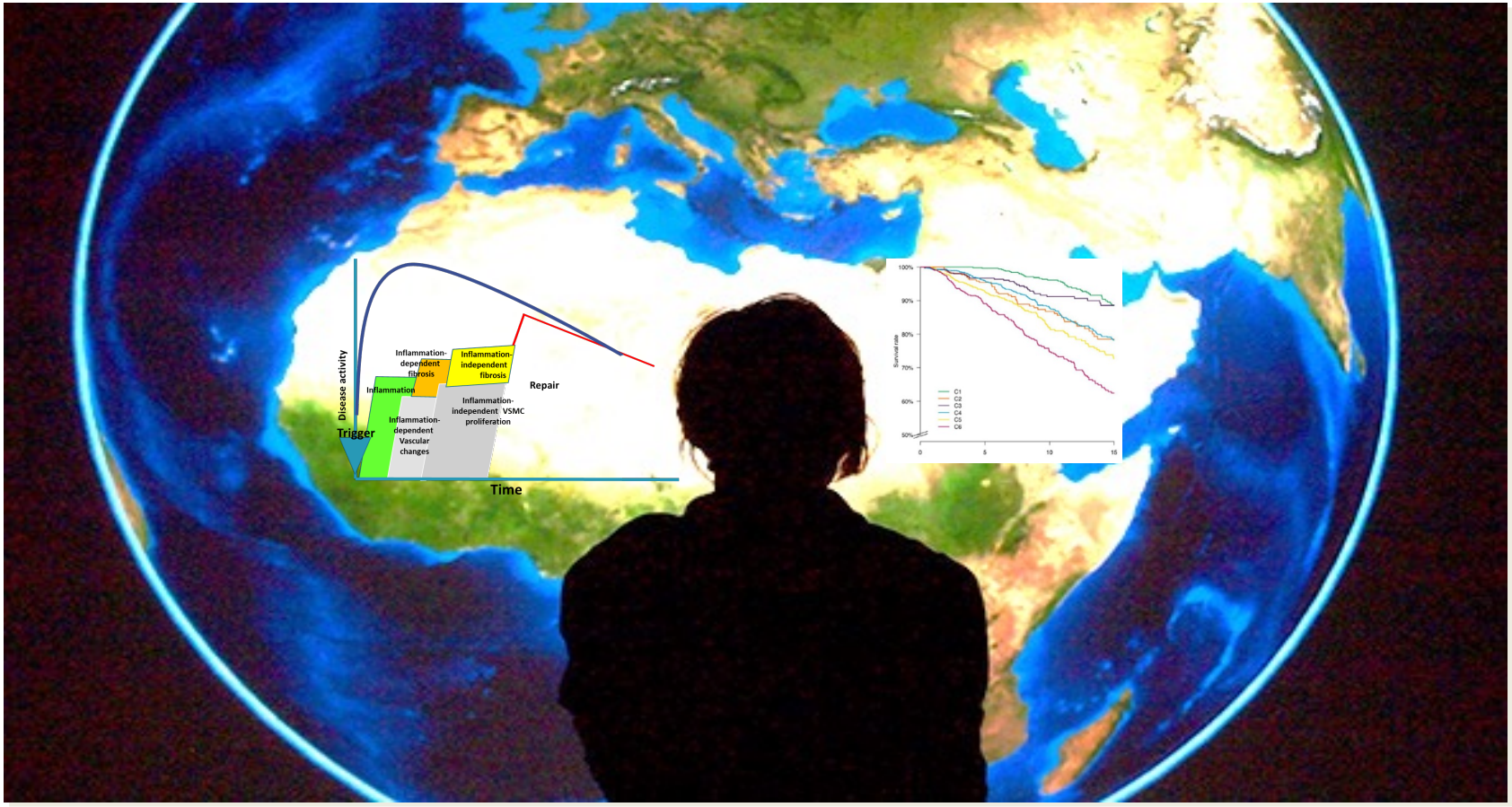
Phenotypes Determined by Cluster Analysis and Their Survival in the Prospective European Scleroderma Trials and Research Cohort of Patients With Systemic Sclerosis

Vincent Sobanski,[1] Jonathan Giovannelli,[2] Yannick Allanore,[3] Gabriela Riemekasten,[4] Paolo Airò,[5] Serena Vettori,[6] Franco Cozzi,[7] Oliver Distler,[8] Marco Matucci-Cerinic,[9] Christopher Denton,[10] David Launay,[1] Eric Hachulla,[1] and the EUSTAR Collaborators



Main characteristics of the 6 clusters (clusters 1–6) of patients with SSc

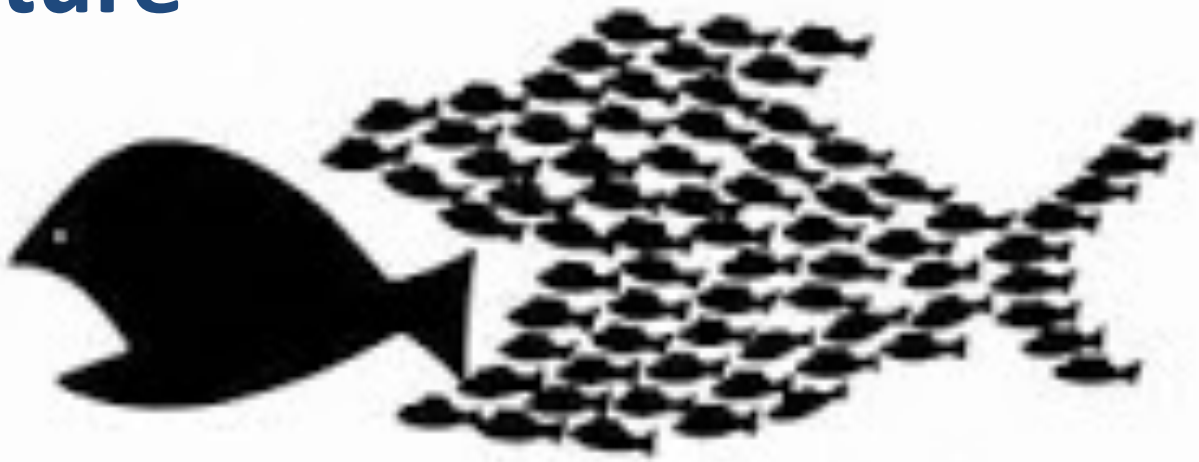
All therapeutic choices in SSc should be the result of disease overview



Multi-disciplinary team is a milestone to increase both safety and efficacy of therapeutic strategies in SSc

The past

The future



Thank you for your attention