La terapia della malattia interstiziale polmonare nella sclerodermia (SSc-ILD): è ancora un unmet need ?

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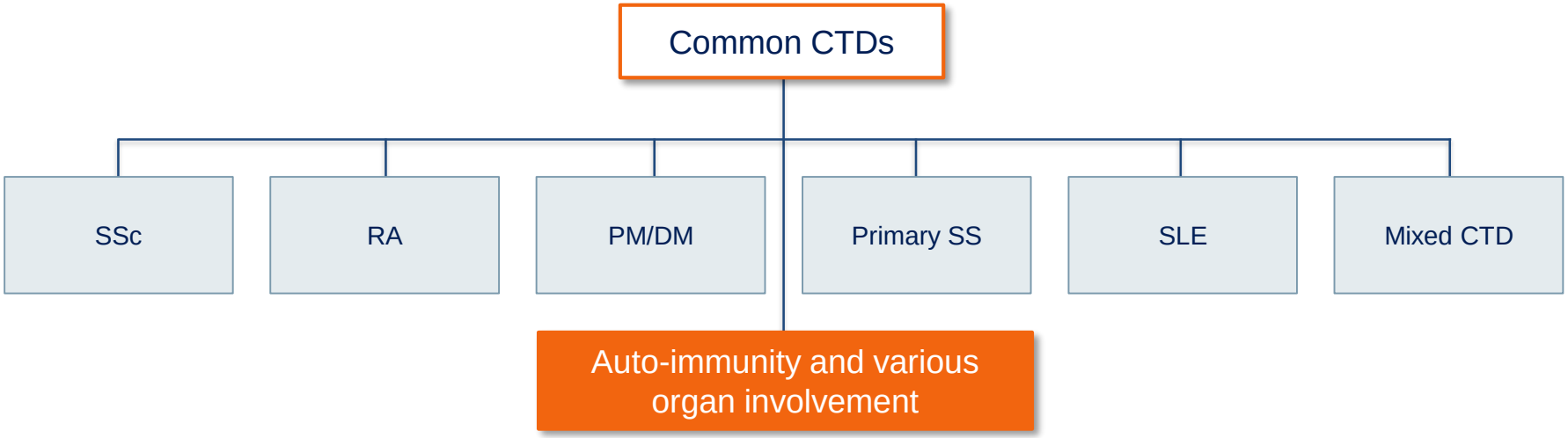
S.C.U. PNEUMOLOGIA

CTDs are a heterogeneous group of systemic disorders



Pulmonary complications, including ILD, are common in CTDs and are associated with significant morbidity and mortality

Solomon JJ, Fischer A. *J Intensive Care Med* 2015;30:392–400

The prevalence of ILD varies by CTD type, with the highest rate observed in SSc[1,2]

CTD-ILD	Prevalence of CTD[1]	Prevalence of ILD[2]
SSc	**26***	**70–90%**
RA	0.5–2%†	4–68%
SS	3%‡	10–30%
Mixed CTD	3.8*	20–85%
PM/DM	Unknown	15–70%
SLE	15–50*	2–10%

*Number of cases per 100,000 persons; †Percentage of the general population; ‡In patients aged >50 years

1. Koo SM, Uh ST. *Korean J Intern Med* 2017;32:600–10; 2. Wallace B *et al. Curr Opin Rheumatol* 2016;28:236–45

Clinical outcomes for patients with CTD-ILD are poor[1]

	SSc	RA	SS	Mixed CTD	PM/DM	SLE
Clinical ILD*	≤45%	7.7%	11–15%	54%	15–78%	11%
ILD-cause mortality	Unknown[1] (but leading cause of death in SSc)[2]	10–20%	5-year survival: 84%	Unknown	From subclinical to rapidly progressive and fatal	50%

Pulmonary involvement is one of the leading causes of morbidity and mortality in CTD[3]

*Clinical ILD is defined as patients who had radiological abnormality and respiratory symptoms and/or impaired lung function related to CTD-ILD

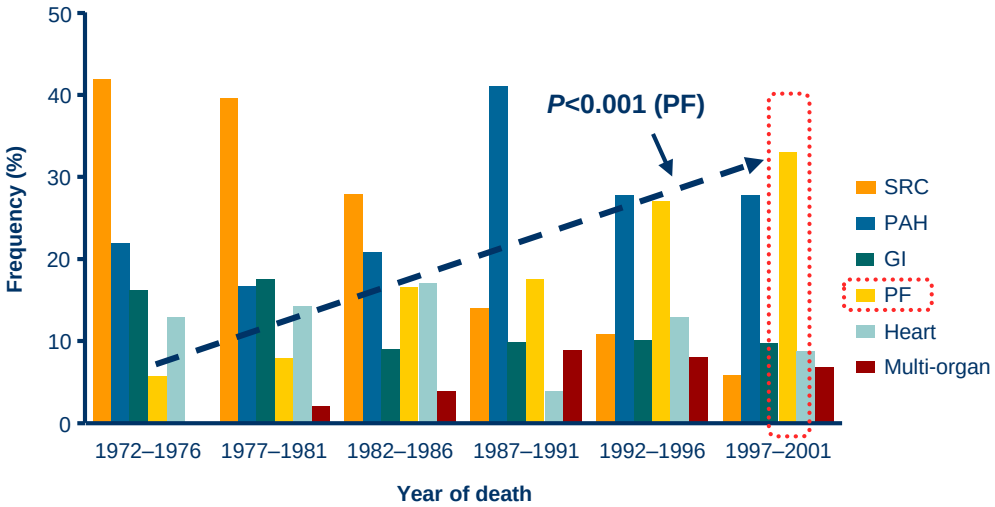
1. Koo SM, Uh ST. *Korean J Intern Med* 2017;32:600–10;
2. Volkmann ER *et al. Ann Am Thorac Soc* 2016;13:2045–56;
3. Lammi MR *et al. Curr Respir Med Rev* 2015;11:163–74

SSc-ILD is associated with substantial morbidity and mortality

Pulmonary fibrosis (a manifestation of ILD) is a major predictor of poor hospitalization outcomes in patients with SSc[1]

Median survival of patients with SSc-ILD is 5–8 years[2]

Changes in the causes of death in SSc over the last 30 years (n=5603)[3]

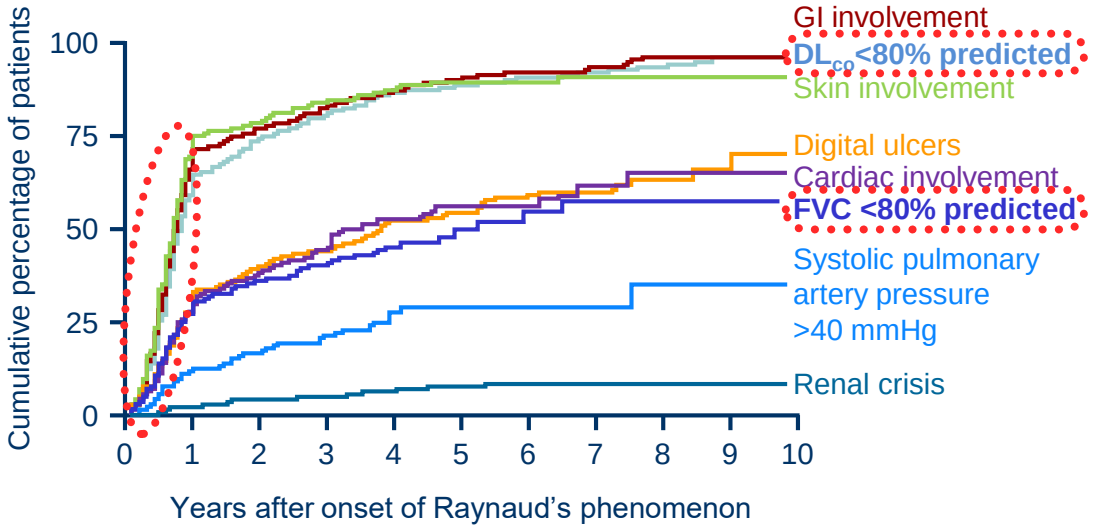


Pulmonary fibrosis is currently the leading cause of mortality in SSc, accounting for approximately a third of deaths[3,4]

1. Chung L *et al. Rheumatology* 2007;46:1808–13; 2. Altman RD *et al. Arthritis Rheum* 1991;34:403–13;
3. Steen VD & Medsger TA. *Ann Rheum Dis* 2007;66:940–4; 4. Tyndall AJ *et al. Ann Rheum Dis* 2010;669:1809–15

ILD develops early in the disease course of SSc

Organ involvement in patients (cumulative percentage) with early SSc[1*]
(after onset of Raynaud's phenomenon; n=695)



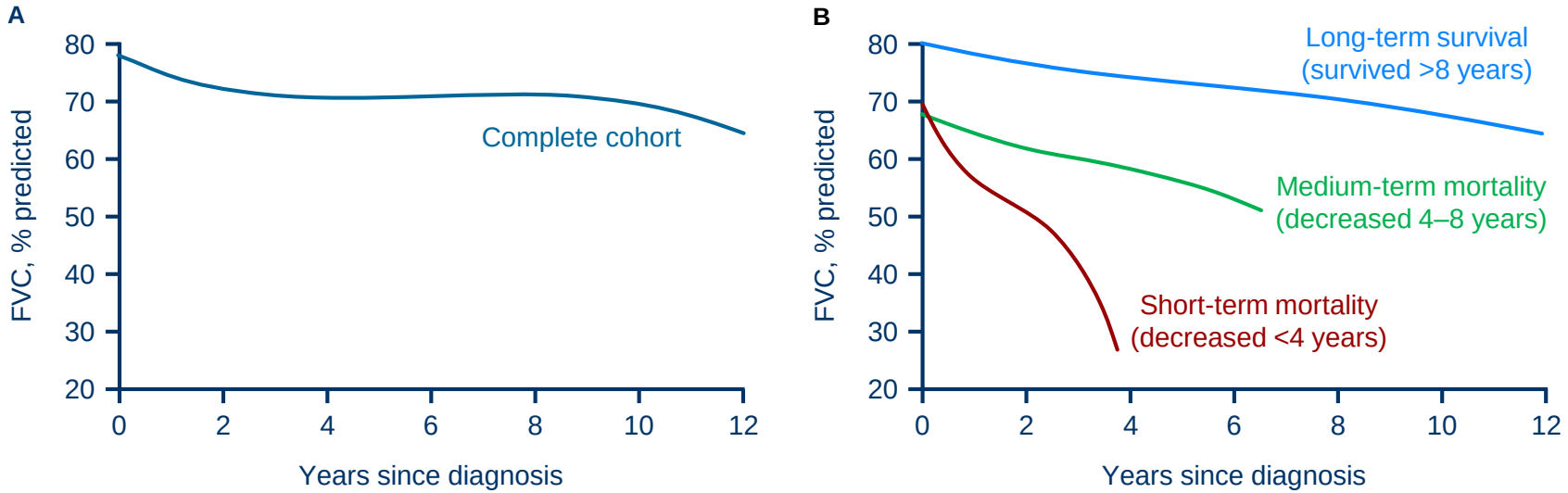
Pulmonary involvement is evident 1 year after presentation of Raynaud's phenomenon

*Skin involvement was defined as modified Rodnan skin score of ≥2 at any part of the body; cardiac involvement was defined as the presence of diastolic dysfunction, conduction blocks, left ventricular ejection fraction <50% or a pericardial effusion; systolic pulmonary artery pressure was estimated by echocardiography

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

SSc-ILD may continue to progress in different patient subgroups

Progression of FVC (% predicted) in 171 patients with SSc-ILD overall (complete cohort; A) and when categorized by prognosis (B)[1]



The consistent decline in FVC % predicted among patient subgroups categorized by prognosis highlights the importance of continued monitoring of patients with SSc-ILD[1]

1. Guler SA *et al. Ann Am Thorac Soc* 2018;15:1427–33

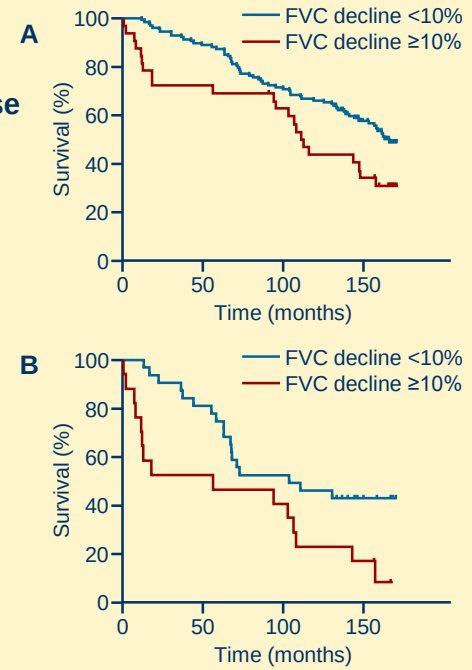
Changes in FVC and DL_{CO} over 12 and 24 months predict 15-year mortality

PFT trends at 12 months[1]

Decline* in FVC ≥10% predicted and mortality in whole cohort (A), and those with extensive disease (B)

Significant predictors of mortality in whole cohort:

- Categorical decline* in FVC (≥10% and ≥15% predicted)
- Categorical decline* in DL_{CO} (≥15% predicted)
- Composite categorical decline*

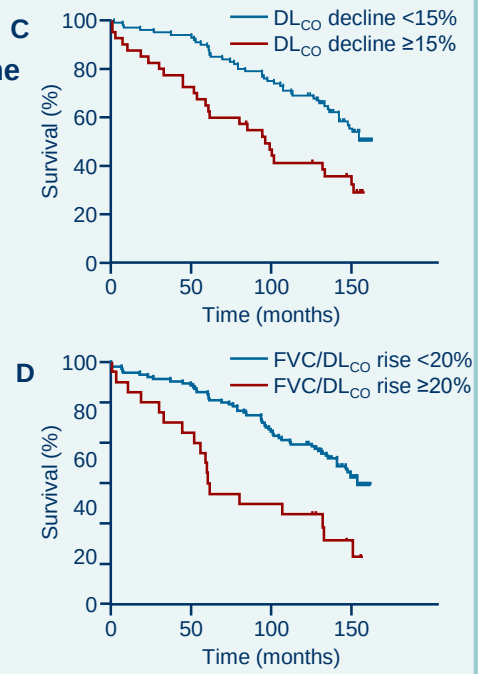


PFT trends at 24 months[1]

Decline* in DL_{CO} ≥15% predicted and mortality in the whole cohort (C), and increase in FVC:DL_{CO} ≥20% (D)

Significant predictors of mortality in whole cohort:

- Categorical decline* in DL_{CO} (≥15% predicted)
- Categorical decline* in K_{CO} (≥10% predicted)
- Increases* in FVC:DL_{CO} (≥15% and ≥20%)



*Declines or increases were computed as percentage changes relative to absolute values at baseline

1. Goh NS *et al. Arthritis Rheumatol* 2017;69:1670–8

Diagnosis of SSc-ILD can be challenging so early and regular screening is required

Challenges of diagnosis:[1,2]

- Heterogeneous presentation and disease course
- Non-specific symptoms
- Subclinical disease is common

Early and regular screening is therefore essential to ensure early detection of SSc-ILD before significant progression occurs[1]

1. Wallace B *et al. Curr Opin Rheumatol* 2016;28:236–45; 2. Chowaniec M *et al. Reumatologia* 2018;56:249–54

The NEW ENGLAND JOURNAL of MEDICINE

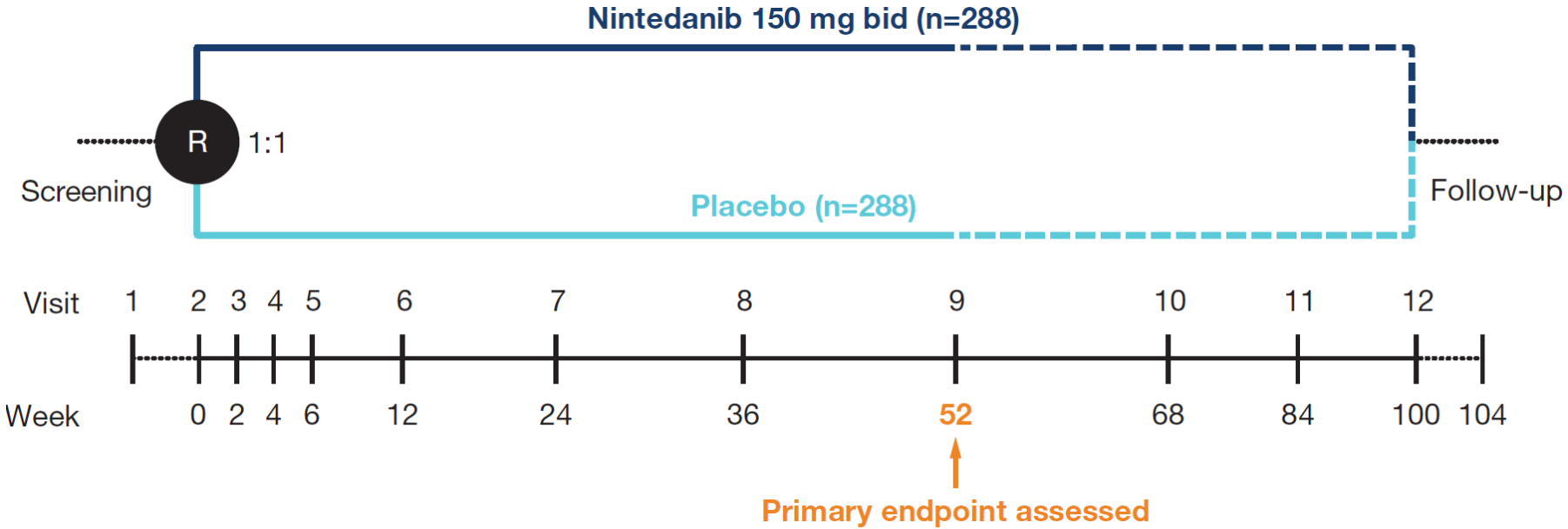
ORIGINAL ARTICLE

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*

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

Trial design



- **Patients remained on blinded treatment until the last patient had reached week 52 but for no longer than 100 weeks**

Randomized patients were stratified by anti-topoisomerase antibody (ATA) status (positive or negative). Dose reductions from 150 mg bid to 100 mg bid and treatment interruptions were permitted to manage adverse events.
bid, twice daily; R, randomization.
Distler O et al. N Engl J Med. 2019. doi:10.1056/NEJMoa1903076C

Key eligibility criteria

Key inclusion criteria[1]

- SSc[2] with first non-Raynaud symptom <7 years from screening
- ≥10% fibrosis of the lungs, confirmed by central assessment of an HRCT scan performed ≤12 months before screening
- FVC ≥40% predicted
- DLco 30–89% predicted

Key exclusion criteria

- Significant pulmonary hypertension*
- >3 digital ulcers or history of severe digital necrosis requiring hospitalization

*Defined as previous clinical or echocardiographic evidence of significant right heart failure, history of right heart catheterization showing a cardiac index ≤2 l/min/m², or pulmonary hypertension requiring parenteral therapy with epoprostenol/treprostinil.

1. Distler O et al. N Engl J Med. 2019. doi:10.1056/NEJMoa1903076C
2. van den Hoogen F, et al. Arthritis Rheum 2013;65:2737–47.

Background medications

- 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

Primary and key secondary endpoints

Primary endpoint

- Annual rate of decline in FVC (mL/year) assessed over 52 weeks

Key secondary endpoints:

- Absolute change from baseline in mRSS at week 52
- Absolute change from baseline in SGRQ total score at week 52

FVC, forced vital capacity; mRSS, modified Rodnan skin score; SGRQ, St George's Respiratory Questionnaire.

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

Baseline characteristics (1/3)

	Nintedanib (n=288)	Placebo (n=288)
Age, years, mean (SD)	54.6 (11.8)	53.4 (12.6)
Female, n (%)	221 (76.7)	212 (73.6)
BMI, kg/m^2, mean (SD)	25.9 (4.8)	25.8 (5.1)
Race, n (%)		
White	201 (69.8)	186 (64.6)
Asian	62 (21.5)	81 (28.1)
Black/African-American	20 (6.9)	16 (5.6)
American Indian/Alaska Native/Native Hawaiian/other Pacific Islander	3 (1.0)	3 (1.0)

Race data are from patients who selected one race. Four patients ticked two boxes.

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

Baseline characteristics (2/3)

	Nintedanib (n=288)	Placebo (n=288)
Type of SSc, n (%)		
Diffuse cutaneous	**153 (53.1)**	**146 (50.7)**
Limited cutaneous	135 (46.9)	142 (49.3)
mRSS, mean (SD)	11.3 (9.2)	10.9 (8.8)
Years since onset of first non-Raynaud symptom, median (minimum, maximum)	3.4 (0.3, 7.1)	3.5 (0.4, 7.2)
Anti-topoisomerase I (anti-Scl-70) antibody positive, n (%)	173 (60.1)	177 (61.5)
Taking mycophenolate, n (%)	**139 (48.3)**	**140 (48.6)**

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

Baseline characteristics (3/3)

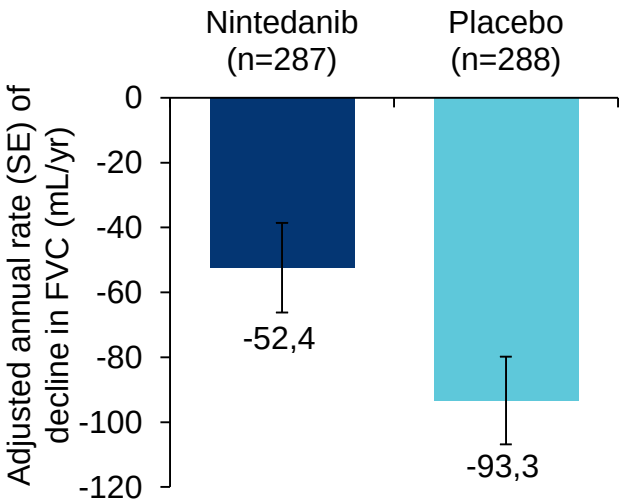
	Nintedanib (n=288)	Placebo (n=288)
Extent of fibrosis on HRCT, mean (SD)	36.8 (21.8)	35.2 (20.7)
FVC, mL, mean (SD)	2459 (736)	2541 (816)
FVC, % predicted, mean (SD)	72.4 (16.8)	72.7 (16.6)
DLco, % predicted, mean (SD)*	52.9 (15.1)	53.2 (15.1)
SGRQ total score, mean (SD)	40.7 (20.2)	39.4 (20.9)

*Corrected for hemoglobin.

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

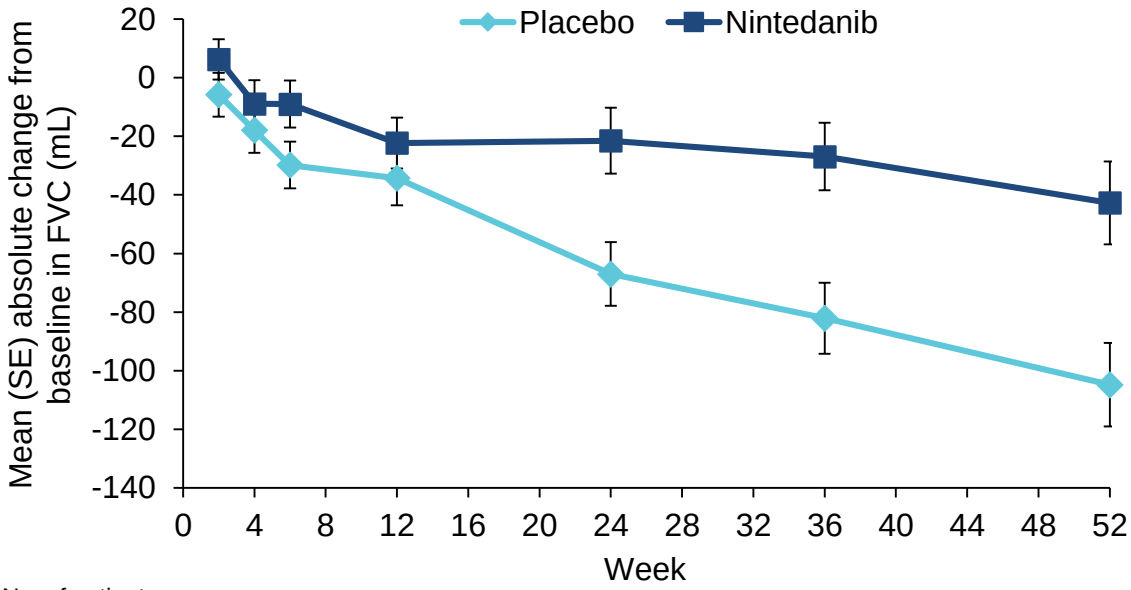
Decline in FVC over 52 weeks

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

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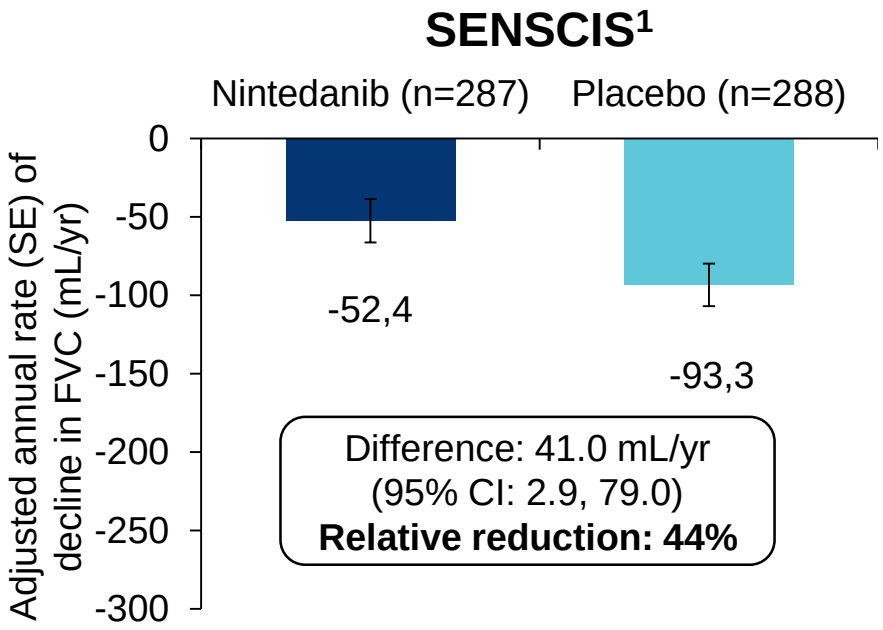
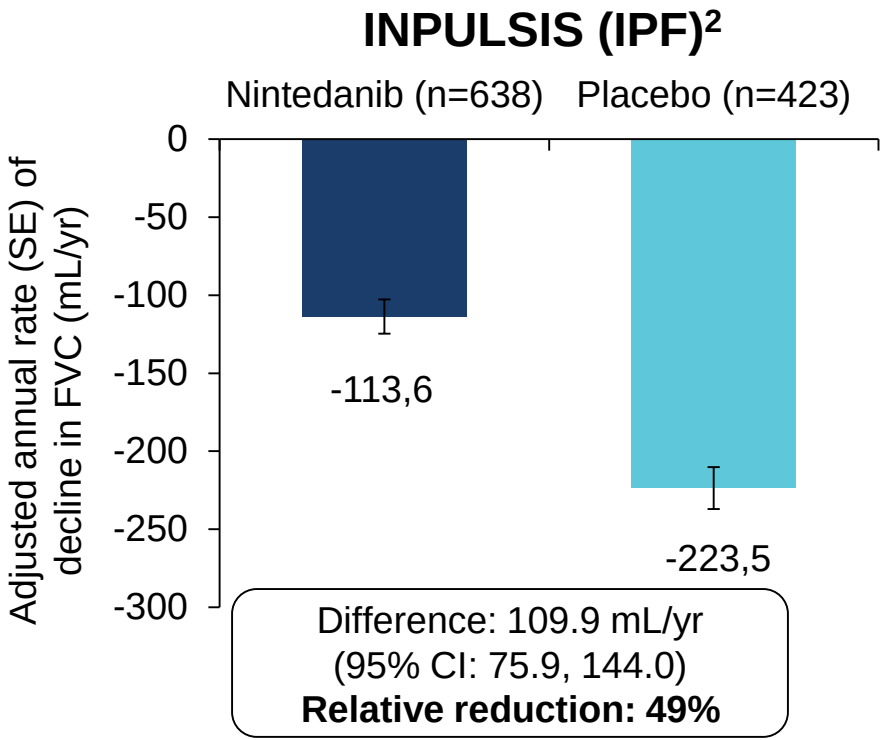
Annual rate of decline in FVC (mL/yr)



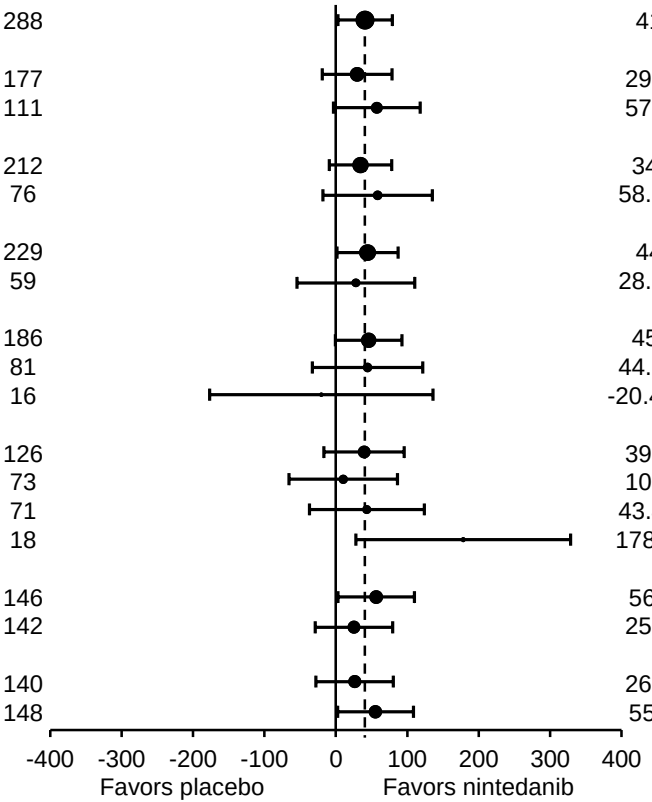


1. Distler O et al. N Engl J Med. 2019. doi:10.1056/NEJMoa1903076C

2. Richeldi L, et al. N Engl J Med 2014;370:2071-82.

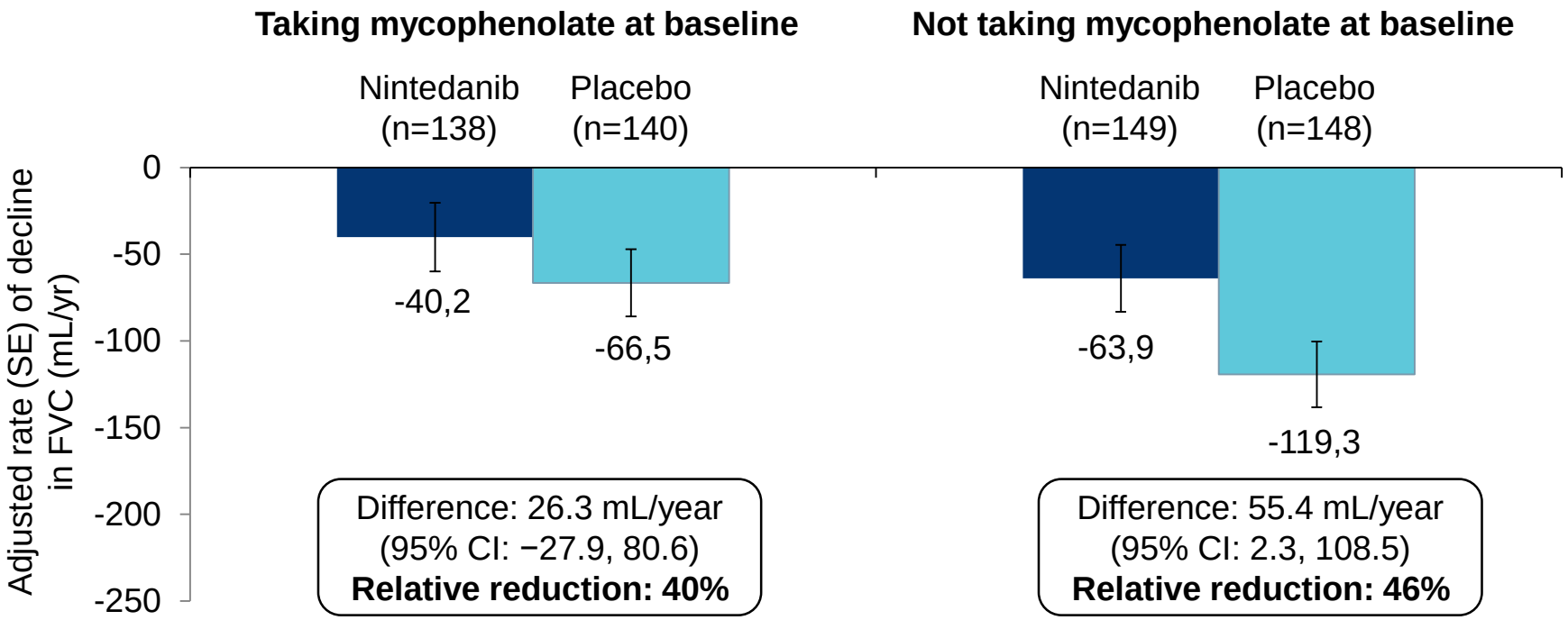
Pre-specified subgroup analyses of primary endpoint

		n analyzed Nintedanib	n analyzed Placebo	Difference (95% CI)	Treatment-by-time-by-subgroup interaction
All patients		287	288	41.0 (2.9, 79.0)	
ATA I (anti-Scl-70) status	Positive	173	177	29.9 (-19.1, 78.8)	p=0.491
	Negative	114	111	57.2 (-3.5, 118.0)	
Gender	Female	220	212	34.6 (-9.3, 78.4)	p=0.594
	Male	67	76	58.6 (-18.0, 135.1)	
Age	<65 years	224	229	44.4 (1.4, 87.4)	p=0.730
	≥65 years	63	59	28.1 (-54.2, 110.4)	
Race	White	200	186	45.8 (-0.8, 92.5)	p=0.725
	Asian	62	81	44.5 (-32.9, 121.9)	
	Black/African-American	20	16	-20.4 (-176.7, 136.0)	
Region	Europe	139	126	39.7 (-16.6, 95.9)	p=0.277
	Canada and USA	69	73	10.3 (-65.6, 86.1)	
	Asia	59	71	43.4 (-37.0, 123.8)	
	Rest of world	20	18	178.4 (28.1, 328.7)	
SSc subtype	Diffuse cutaneous	153	146	56.6 (3.2, 110.0)	p=0.420
	Limited cutaneous	134	142	25.3 (-28.9, 79.6)	
Mycophenolate use	Yes	138	140	26.3 (-27.9, 80.6)	p=0.452
	No	149	148	55.4 (2.3, 108.5)	



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



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

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

Most frequent adverse events

	Nintedanib (n=288)	Placebo (n=288)
Diarrhea	218 (75.7)	91 (31.6)
Nausea	91 (31.6)	39 (13.5)
Vomiting	71 (24.7)	30 (10.4)
Skin ulcer	53 (18.4)	50 (17.4)
Cough	34 (11.8)	52 (18.1)
Nasopharyngitis	36 (12.5)	49 (17.0)
Upper respiratory tract infection	33 (11.5)	35 (12.2)
Abdominal pain	33 (11.5)	21 (7.3)
Fatigue	31 (10.8)	20 (6.9)
Weight decreased	34 (11.8)	12 (4.2)

Adverse events reported over 52 weeks plus 28-day post-treatment period in >10% of patients in either treatment group.
Data are n (%) of patients with ≥1 such adverse event coded based on MedDRA preferred terms.

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

The NEW ENGLAND JOURNAL of MEDICINE

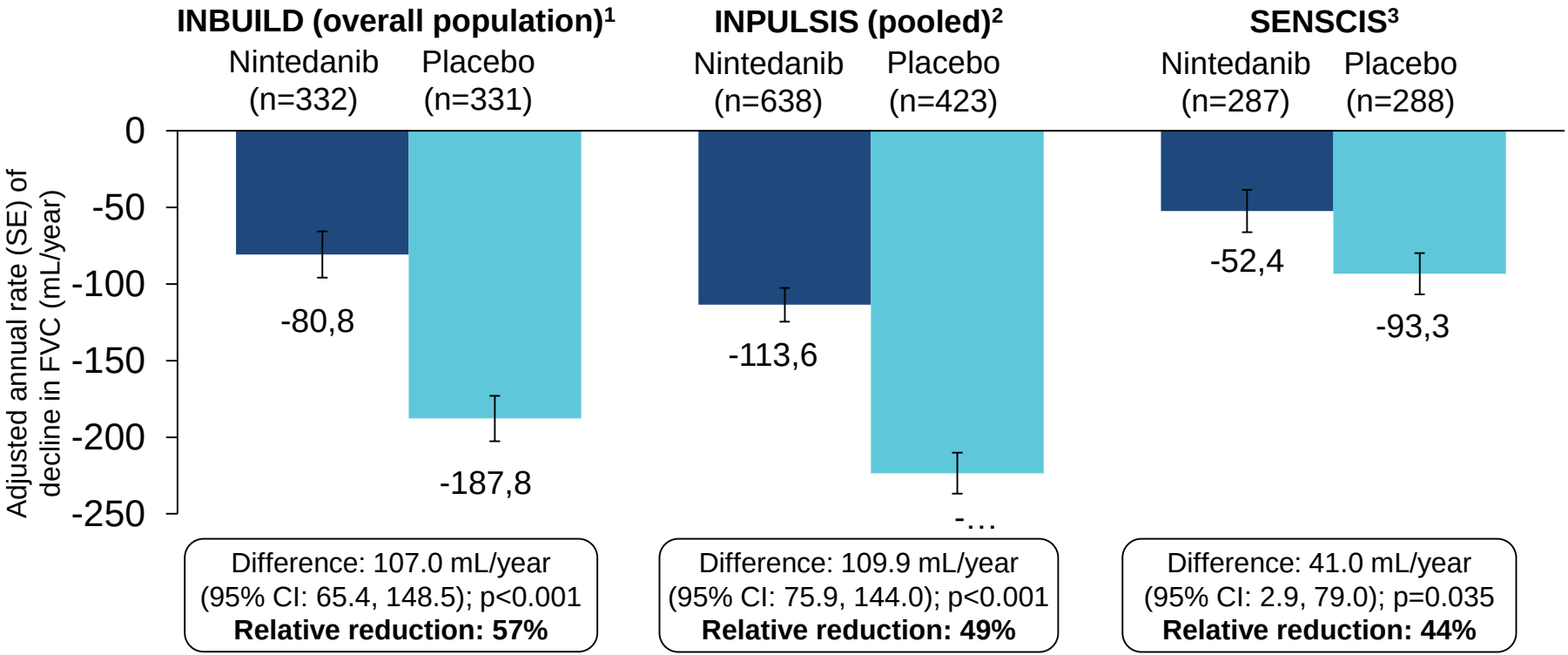
ORIGINAL ARTICLE

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*

Flaherty KR, et al. N Engl J Med 2019; doi: 10.1056/NEJMoa1908681.

INBUILD, INPULSIS and SENSCIS: Annual rate of decline in FVC (mL/year) over 52 weeks



1. Flaherty KR, et al. N Engl J Med 2019; doi: 10.1056/NEJMoa1908681, 2. Richeldi L, et al. N Engl J Med 2014;370:2071–82; 3. Distler O, et al. N Engl J Med 2019;380:2518–28;.

SENSCIS: Summary

- The SENSCIS trial included a broad range of patients with SSc-ILD, including almost 50% of patients with limited cutaneous SSc and almost 50% taking mycophenolate at baseline
- Similar to observations in IPF, nintedanib reduced ILD progression in patients with SSc-ILD, as demonstrated by a reduction in the annual rate of decline in FVC of 44% compared with placebo
- Nintedanib reduced ILD progression consistently across pre-specified patient subgroups with different baseline characteristics
- No effect of nintedanib was observed on skin fibrosis assessed using the mRSS, or on health-related quality of life assessed using the SGRQ
- The safety and tolerability profile of nintedanib in the SENSCIS trial was consistent with that observed in patients with IPF

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