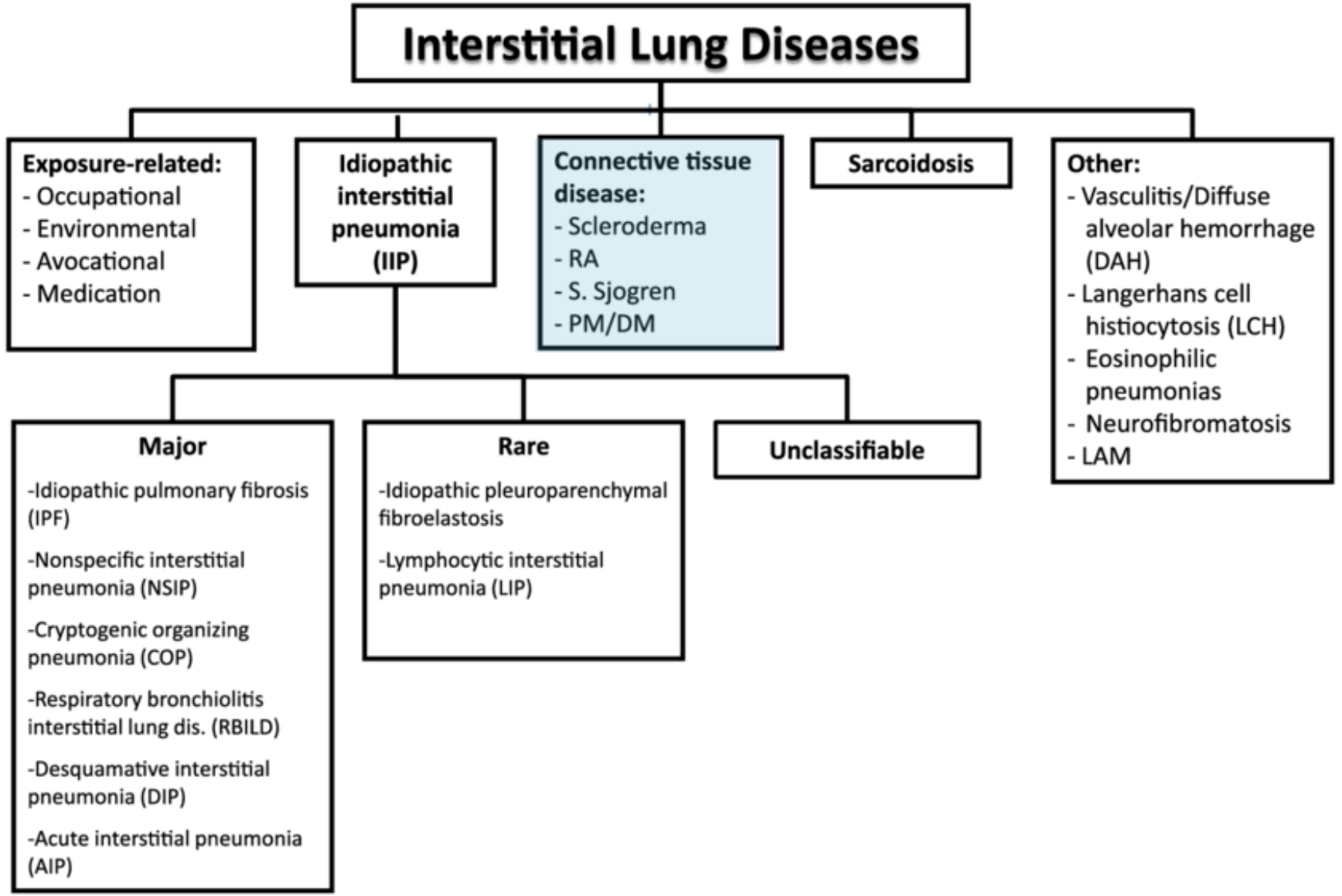
Landmark studies in CTD-ILD

가톨릭대학교 의과대학 호흡기 내과 김용현


Interstitial Lung Diseases
Exposure-related:
- Occupational
- Environmental
- Avocational
- Medication
Idiopathic interstitial pneumonia (IIP)
Connective tissue disease:
- Scleroderma
- RA
- S. Sjogren
- PM/DM
Sarcoidosis
Other:
- Vasculitis/Diffuse alveolar hemorrhage (DAH)
- Langerhans cell histiocytosis (LCH)
- Eosinophilic pneumonias
- Neurofibromatosis
- LAM
Major
-Idiopathic pulmonary fibrosis (IPF)
-Nonspecific interstitial pneumonia (NSIP)
-Cryptogenic organizing pneumonia (COP)
-Respiratory bronchiolitis interstitial lung dis. (RBILD)
-Desquamative interstitial pneumonia (DIP)
-Acute interstitial pneumonia (AIP)
Rare
-Idiopathic pleuroparenchymal fibroelastosis
-Lymphocytic interstitial pneumonia (LIP)
Unclassifiable

CTD or collagen vascular diseases

Systemic lupus erythematosus
Systemic sclerosis
Sjogren's syndrome
Rheumatoid arthritis
Polymyositis/dermatomyositis
Mixed connective tissue disease
Undifferentiated connective tissue disease (UCTD)

Most common CTD-associated pulmonary manifestations

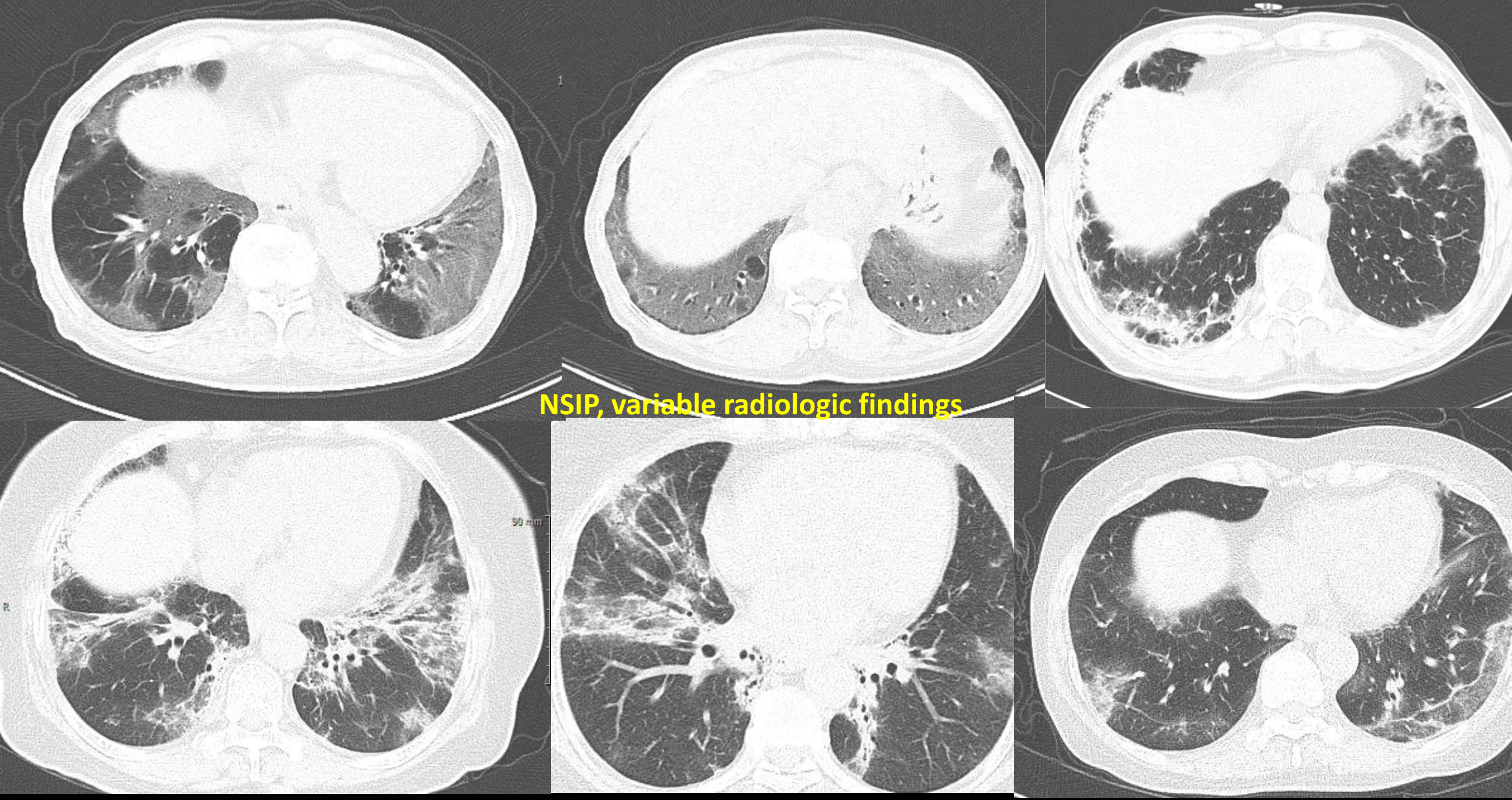
	SSc	RA	Primary SjS	MCTD	PM/DM	SLE
Airways	–	++	++	+	–	+
ILD	+++	++	++	++	+++	+
Pleural	–	++	+	+	–	+++
Vascular	+++	–	+	++	+	+
DAH	–	–	–	–	–	++

The clinical presentations

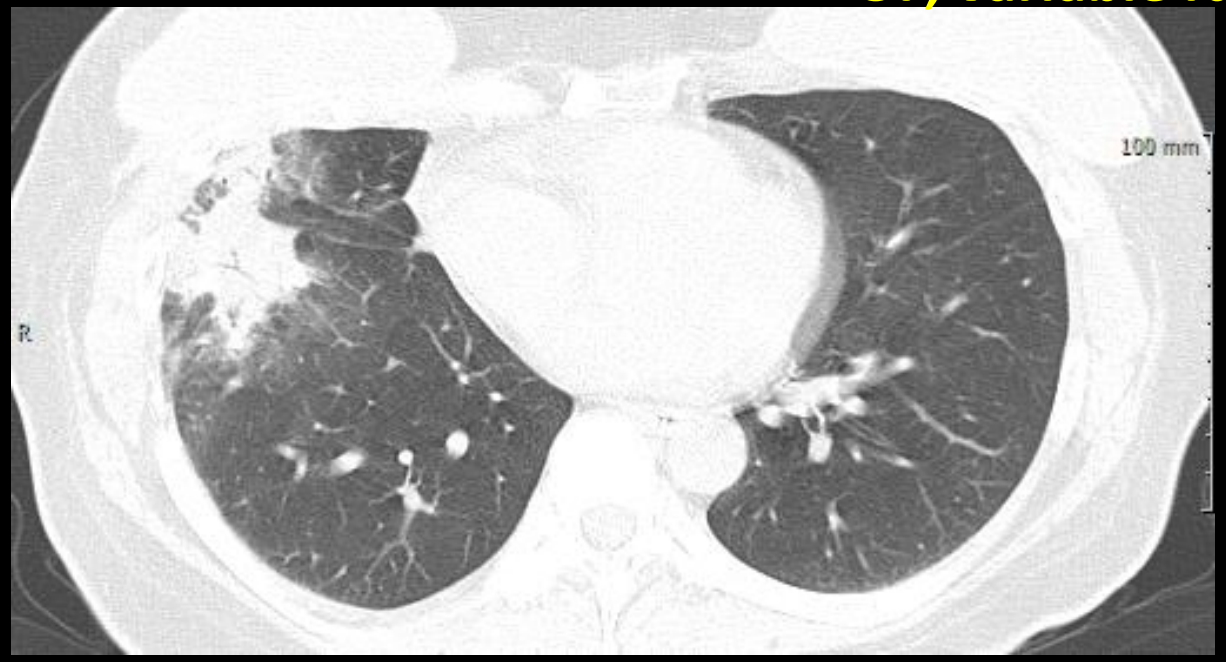
- Acute or subacute
- Chronic and/or progressive

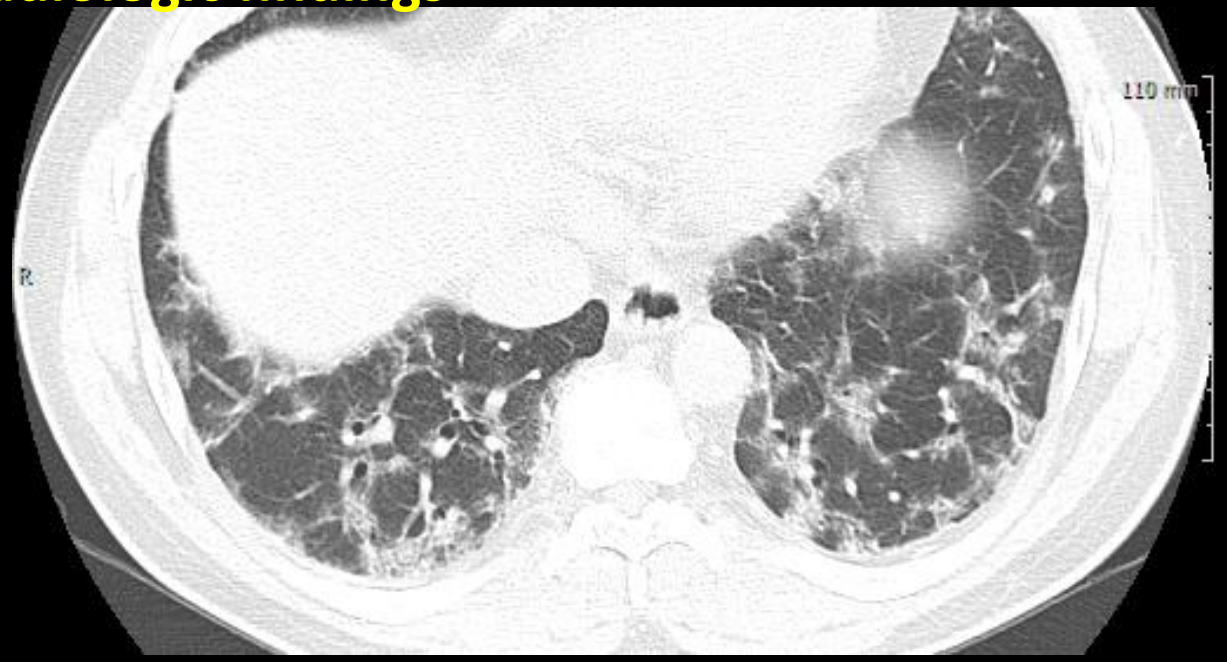
- Variable ILD patterns on radiologic and pathologic view

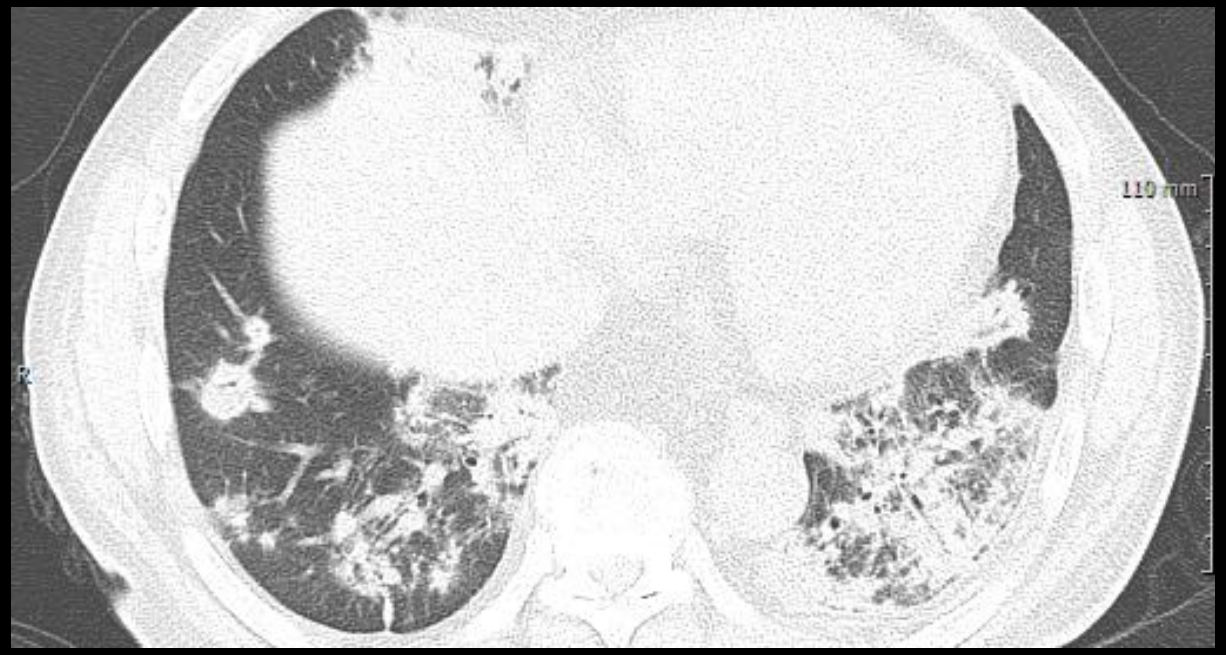
- Not essentially specific lung presentation dependent on specific CTD subtype

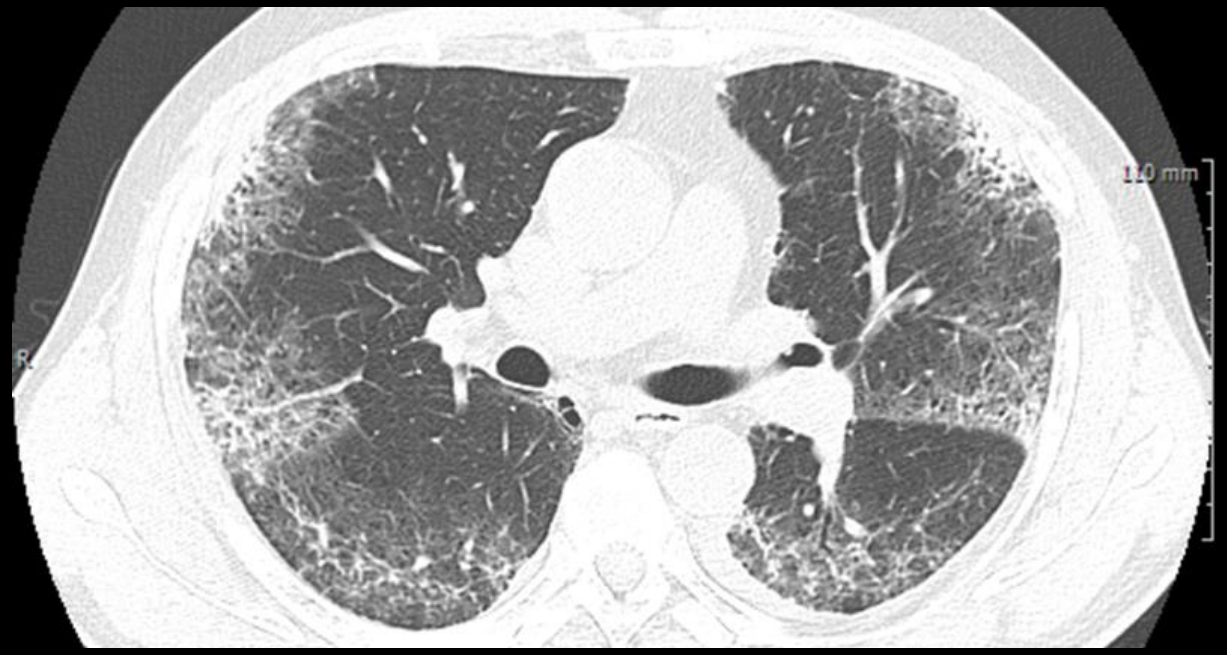

NSIP, variable radiologic findings

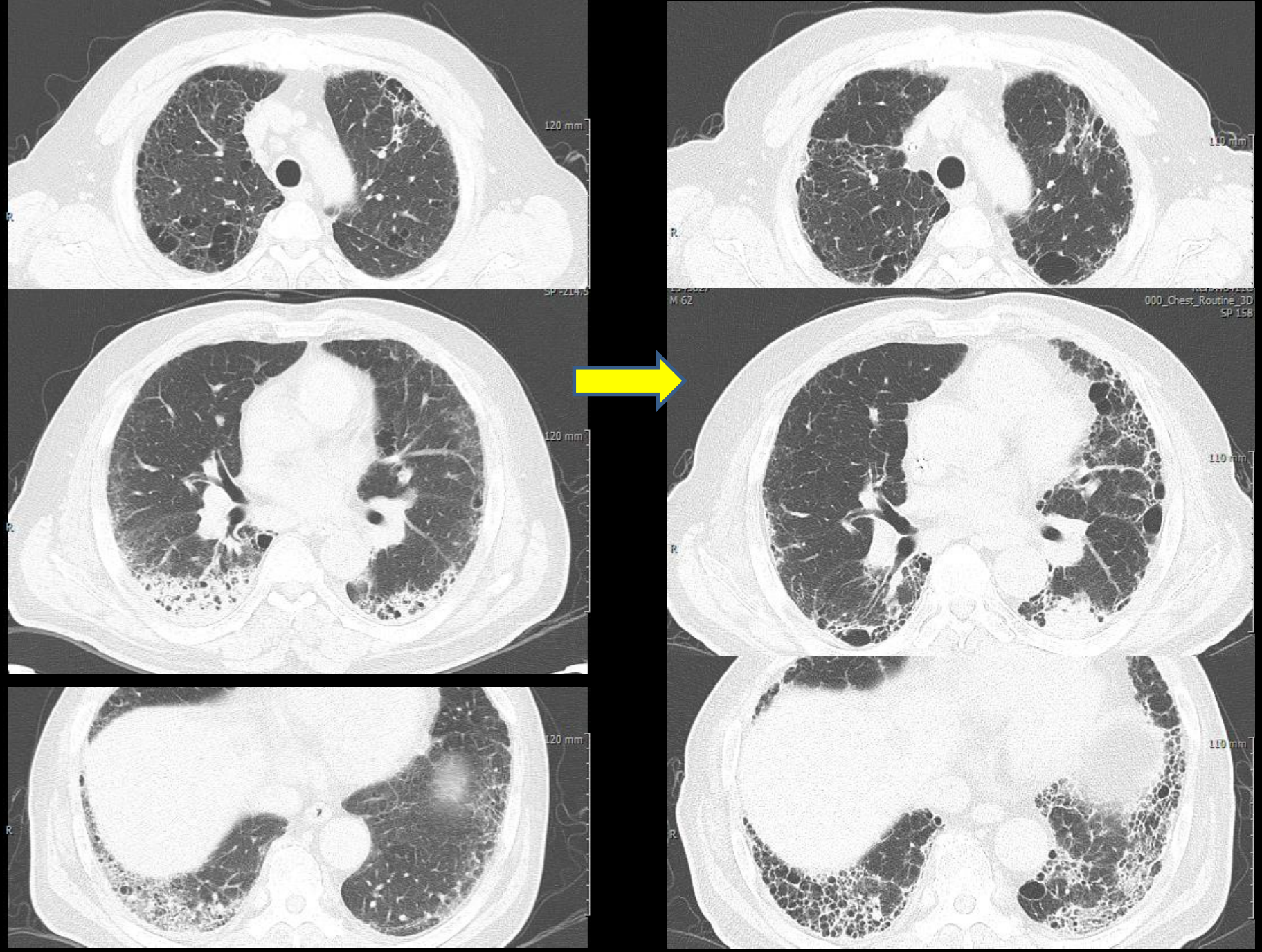
OP, variable radiologic findings











Longitudinal changes of HRCT findings over time

RCT (2000-2018) reporting Treatment and Adverse Effects of medical therapy in CTD-ILD

- DM/PM-ILD and antisynthetase syndrome-ILD : RCT (0)
- Rheumatoid arthritis ILD : RCT (0)
- pSS-ILD, MCTD-ILD, and SLE-ILD : RCT (0)

- SSc-ILD (No of studies/No of patients)
  - AZA (2 /105)
  - CYC (6/474)
  - MMF (2/183)
  - RTX (1/60)
  - TCZ (1/87)

Cyclophosphamide versus Placebo in Scleroderma Lung Disease (SLS I)

- 158 patients with scleroderma, restrictive lung physiology, dyspnea, and evidence of inflammatory ILD on examination of BAL fluid and HRCT or both

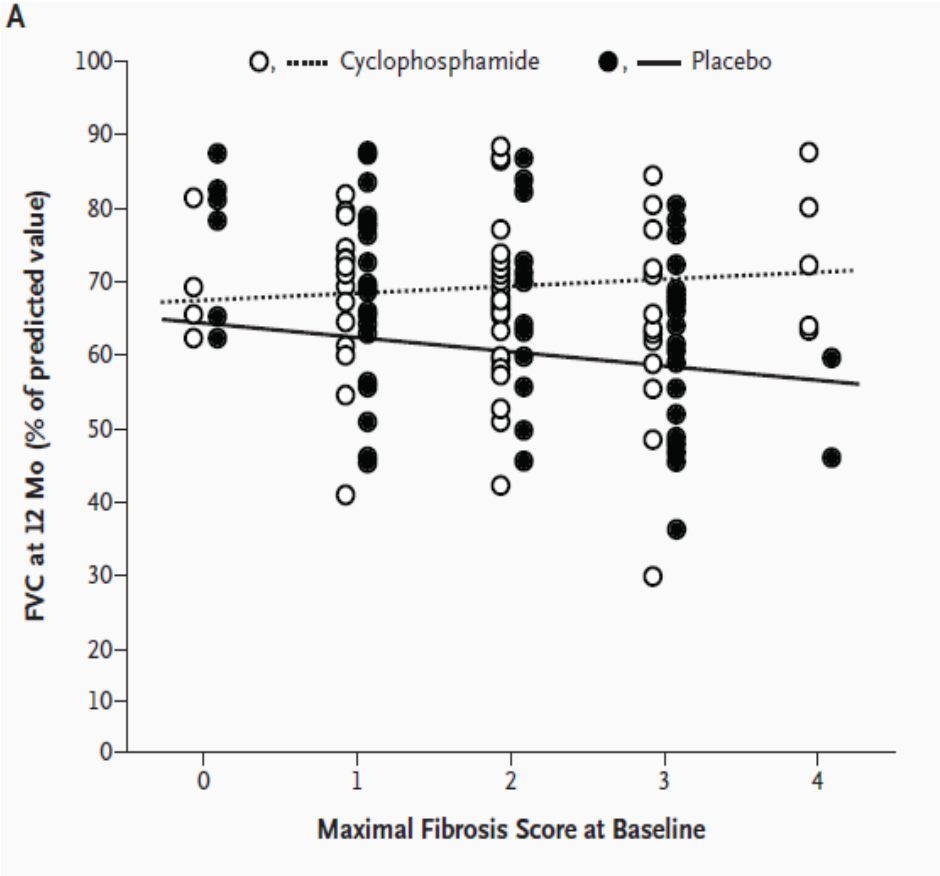
- Active alveolitis
  - BAL fluid (defined as neutrophilia of ≥3 percent, eosinophilia of ≥2 percent, or both)
  - Or on thoracic CT, any ground-glass opacity

N Engl J Med 2006;354:2655-66

Table 1. Baseline Characteristics of 158 Patients.*

Characteristic	All Patients (N=158)	Cyclophosphamide Group (N=79)	Placebo Group (N=79)
Age (yr)			
Mean	47.9±1.0	48.2±1.4	47.5±1.4
Range	19.6–83.1	28.9–81.5	19.6–83.1
Female sex (% of patients)	70.3	75.6	64.6
Duration of scleroderma (yr)			
Mean	3.2±0.2	3.2±0.3	3.1±0.2
Range	0.04–12.0	0.04–12.0	0.2–6.8
Diffuse scleroderma-related disease (% of patients)	59.5	62.8	57.7
FVC (% of predicted)	68.1±1.0	67.6±1.5	68.6±1.5
FEV_1:FVC (% of predicted)	82.8±0.6	82.8±1.0	82.8±0.8
Total lung capacity (% of predicted)	69.6±1.1	69.6±1.5	69.4±1.5
Functional residual capacity (% of predicted)	73.6±1.5	75.2±2.0	71.7±2.2
Residual volume (% of predicted)	70.7±2.1	72.3±3.1	69.0±2.9
D_LCO (% of predicted)	47.2±1.1	47.0±1.6	47.4±1.6
MIP (cm of water)	88.7±2.7	84.1±3.5	92.5±4.1
MEP (cm of water)	91.8±3.2	87.9±4.5	95.2±4.6
Focal score for the Mahler Dyspnea Index	5.7±0.2	5.7±0.2	5.7±0.2
Visual-analogue score for breathing	28.4±2.1	27.2±2.8	29.5±3.1
Cough (% of patients)	69.5	71.1	68.0
SF-36 score			
Physical component	33.5±0.9	32.6±1.3	34.3±1.2
Mental component	49.8±0.9	48.6±1.2	50.7±1.2

Cyclophosphamide versus Placebo in Scleroderma Lung Disease (SLS I)



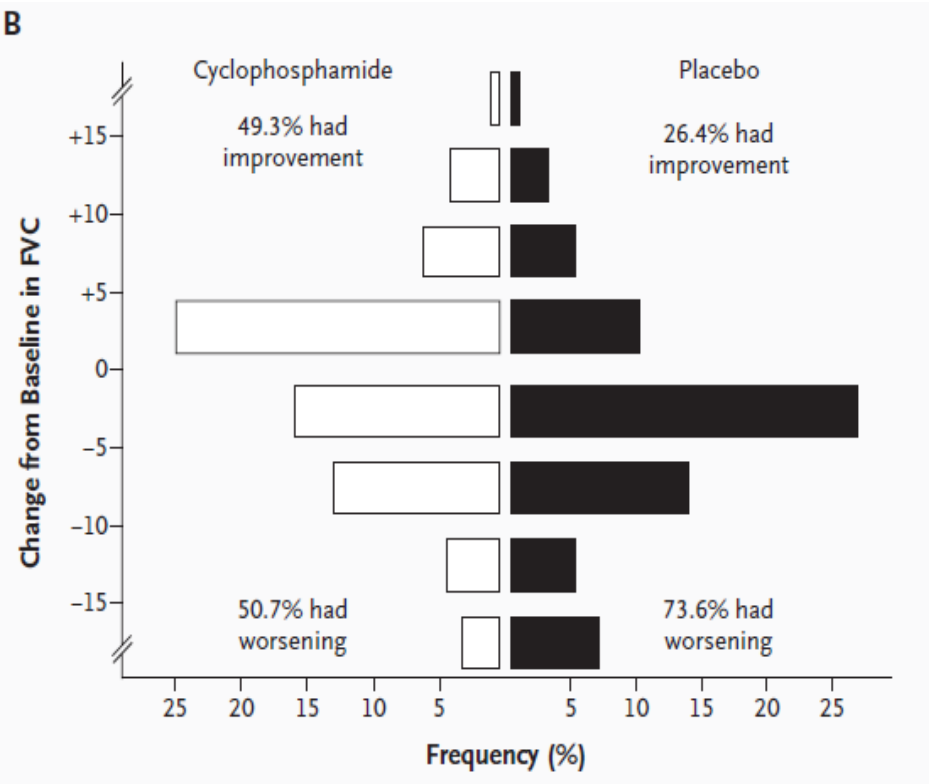


Table 2. Change in Values from Baseline to Month 12.*

Characteristic	Baseline Value	Value at 12 Mo	Difference
Cyclophosphamide group			
FVC (% of predicted)	67.6±1.3	66.6±1.7	−1.0±0.92†
Total lung capacity (% of predicted)	70.4±2.1	70.5±1.8	−0.3±1.82†
DLCO (% of predicted)	47.2±1.6	42.8±1.7	−4.2±1.16
Placebo group			
FVC (% of predicted)	68.3±1.5	65.6±1.6	−2.6±0.9
Total lung capacity (% of predicted)	67.9±1.9	64.7±1.9	−2.8±1.2
DLCO (% of predicted)	47.9±1.7	44.3±2.1	−3.5±1.0
Score on Mahler Dyspnea Index			
According to baseline instrument	5.6±0.42		
According to transitional dyspnea index (focal score)‡		−1.5±0.43	
Cough (%)	55.9	67.2	
Score for HAQ disability index	0.70±0.09	0.86±0.10	0.16±0.06
SF-36 score			
Physical component	35.1±1.4	33.2±1.4	−1.9±1.2
Mental component	50.8±1.4	50.9±1.5	0.1±1.5

Cyclophosphamide ;
Small but significant improvement in the FVC and TLC at 12 months

Adverse Events and Serious Adverse Events

Event	Cyclophosphamide Group		Placebo Group	
	Year 1	Year 2	Year 1	Year 2
	number of patients			
Adverse event				
Hematuria	9	1	3	2
Leukopenia†	19	0	0	0
Neutropenia†	7	0	0	0
Anemia	2	2	0	1
Pneumonia	5	1	1	0
Serious adverse event‡				
Probably related to treatment	2	4	0	0
Possibly related to treatment	3	4	2	5
Not related to treatment	15	19	14	17
Total	20	27	16	22
Death	2	4	3	3

Effects of 1-Year Treatment with Cyclophosphamide on Outcomes at 2 Years in Scleroderma Lung Disease

Donald P. Tashkin[1], Robert Elashoff[2], Philip J. Clements[1], Michael D. Roth[1], Daniel E. Furst[1], Richard M. Silver[3], Jonathan Goldin[4], Edgar Arriola[5], Charlie Strange[3], Marcy B. Bolster[2], James R. Seibold[6], David J. Riley[6], Vivien M. Hsu[6], John Varga[7], Dean Schraufnagel[7], Arthur Theodore[8], Robert Simms[8], Robert Wise[9], Fred Wigley[9], Barbara White[9], Virginia Steen[10], Charles Read[10], Maureen Mayes[11], Ed Parsley[11], Kamal Mubarak[12], M. Kari Connolly[13], Jeffrey Golden[13], Mitchell Olman[14], Barri Fessler[14], Naomi Rothfield[15], Mark Metersky[15], Dinesh Khanna[1], Ning Li[2], and Gang Li[2], for the Scleroderma Lung Study Research Group*

What This Study Adds to the Field

The present report provides the first evidence that, during an additional year of follow-up in the same patients off of study drug, the benefits of cyclophosphamide persist for several additional months, but are generally no longer apparent at 2 years.

Am J Respir Crit Care Med Vol 176. pp 1026–1034, 2007

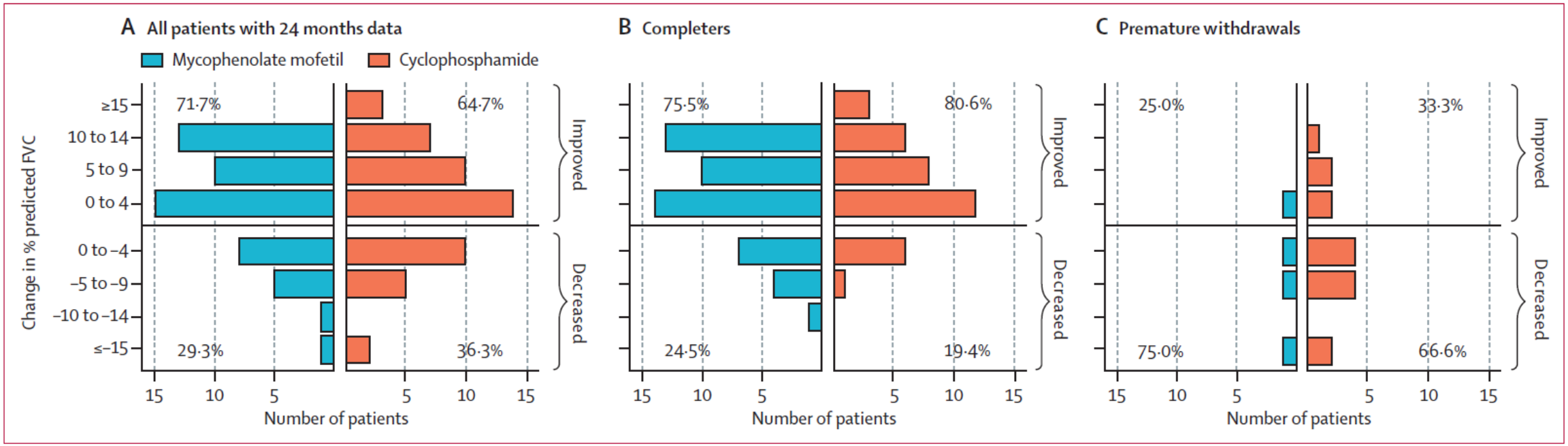
Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial

Design to receive either mycophenolate mofetil (1500 mg twice daily) for 24 months or oral cyclophosphamide (2·0 mg/kg per day) for 12 months followed by placebo for 12 months

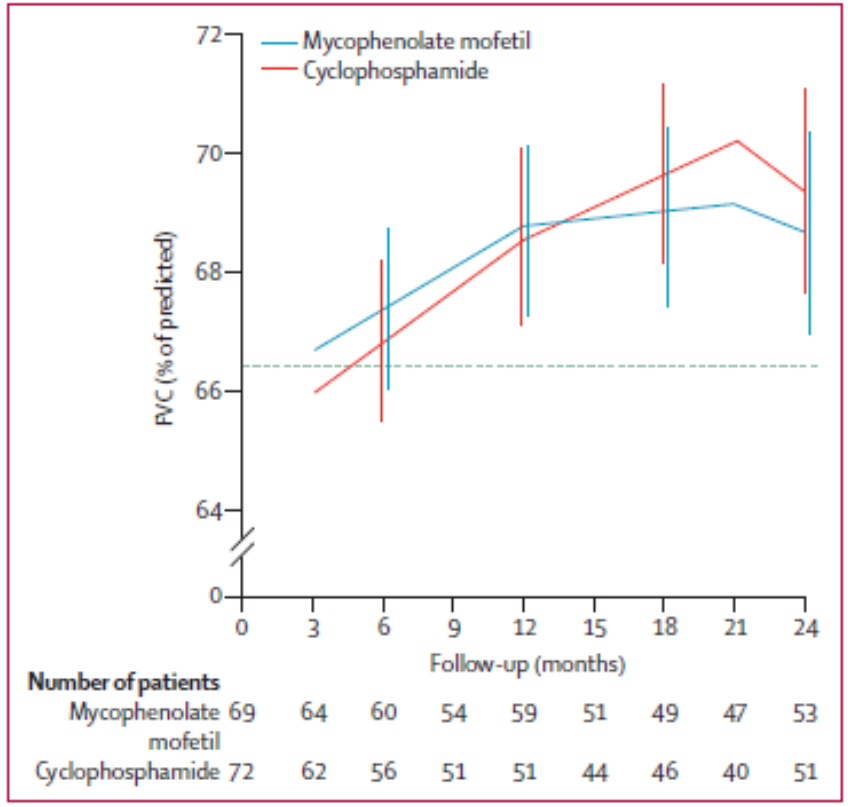
The primary endpoint : change in FVC as a percentage of the predicted normal value (FVC %) over the course of 24 months

Lancet Respir Med 2016; 4: 708–19

Frequency distribution of changes from baseline to 24 months in % predicted FVC



Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II)



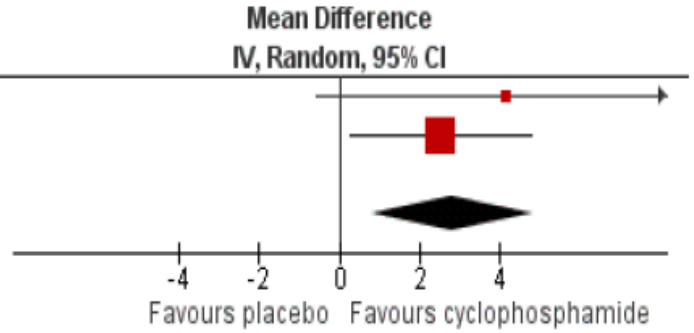
	Mycophenolate mofetil		Cyclophosphamide	
	Adverse events	Patients (n=69)	Adverse events	Patients (n=73)
Adverse events*				
Leucopenia†	5	4 (6%)	51	30 (41%)
Neutropenia	3	3 (4%)	7	5 (7%)
Anaemia	18	8 (12%)	26	13 (18%)
Thrombocytopenia	0	0	7	4 (6%)
Haematuria	3	3 (4%)	2	2 (3%)
Pneumonia	6	5 (7%)	4	4 (6%)
Serious adverse events‡				
Total	42	27 (39%)	36	22 (30%)
Related to treatment§	3	3 (4%)	8	7 (10%)
Related to underlying disease§	16	9 (13%)	16	13 (18%)
Due to other causes§¶	22	14 (20%)	11	6 (8%)
Unknown cause§	3	3 (4%)	3	3 (4%)
Death	..	5 (7%)	..	11 (15%)

Lancet Respir Med 2016; 4: 708–19

Forest plot of comparison
: Cyclophosphamide versus placebo, FVC % and DLco% predicted

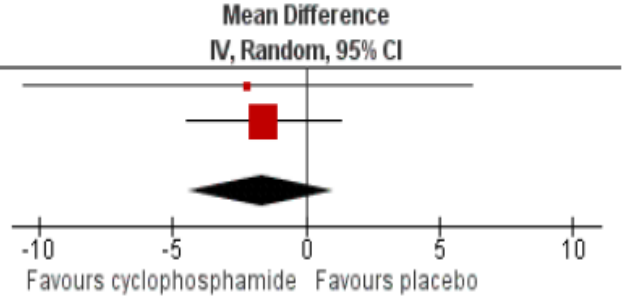
Study or Subgroup	Mean Difference	SE	Cyclophosphamide Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Hoyles 2006	4.19	2.4286	22	23	18.3%	4.19 [-0.57, 8.95]
Tashkin 2006	2.53	1.148	73	72	81.7%	2.53 [0.28, 4.78]
Total (95% CI)			**95**	**95**	**100.0%**	**2.83 [0.80, 4.87]**

Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 1 (P = 0.54); I² = 0%
Test for overall effect: Z = 2.73 (P = 0.006)



Study or Subgroup	Mean Difference	SE	Favours cyclophosphamide Total	Cyclophosphamide Total	Weight	Mean Difference IV, Random, 95% CI
Hoyles 2006	-2.2	4.2848	19	18	10.6%	-2.20 [-10.60, 6.20]
Tashkin 2006	-1.6	1.4729	73	72	89.4%	-1.60 [-4.49, 1.29]
Total (95% CI)			**92**	**90**	**100.0%**	**-1.66 [-4.39, 1.07]**

Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 1.19 (P = 0.23)

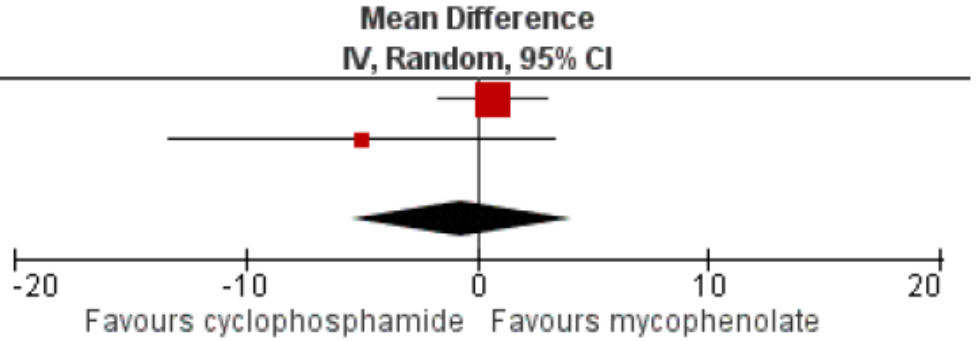


Cochrane Database of Systematic Reviews 2018

Forest plot of comparison
: Cyclophosphamide versus mycophenolate, FVC % and DLco% predicted

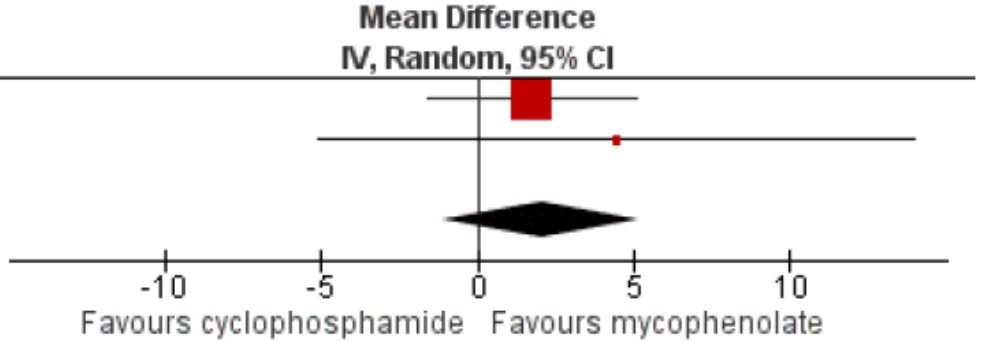
Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Random, 95% CI
Tashkin 2016	0.69	1.1877	75.9%	0.69 [-1.64, 3.02]
Zhang 2015	-4.99	4.256	24.1%	-4.99 [-13.33, 3.35]
Total (95% CI)			**100.0%**	**-0.68 [-5.44, 4.08]**

Heterogeneity: Tau² = 6.37; Chi² = 1.65, df = 1 (P = 0.20); I² = 39%
Test for overall effect: Z = 0.28 (P = 0.78)



Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Random, 95% CI
Tashkin 2016	1.74	1.7041	89.1%	1.74 [-1.60, 5.08]
Zhang 2015	4.47	4.8629	10.9%	4.47 [-5.06, 14.00]
Total (95% CI)			**100.0%**	**2.04 [-1.11, 5.19]**

Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 1 (P = 0.60); I² = 0%
Test for overall effect: Z = 1.27 (P = 0.20)



Cochrane Database of Systematic Reviews 2018

Cyclophosphamide and mycophenolate for SSc-ILD

- Small benefit of 1 year of treatment with cyclophosphamide in terms of % FVC when compared with placebo
- Significant improvement in dyspnea, functional ability, the health-related quality of life, and skin thickness with cyclophosphamide
- The benefits of cyclophosphamide are generally no longer apparent at 2 years
- No significant different when cyclophosphamide was compared with mycophenolate at 12months
- Risk of adverse effects was increased in the cyclophosphamide groups versus mycophenolate

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

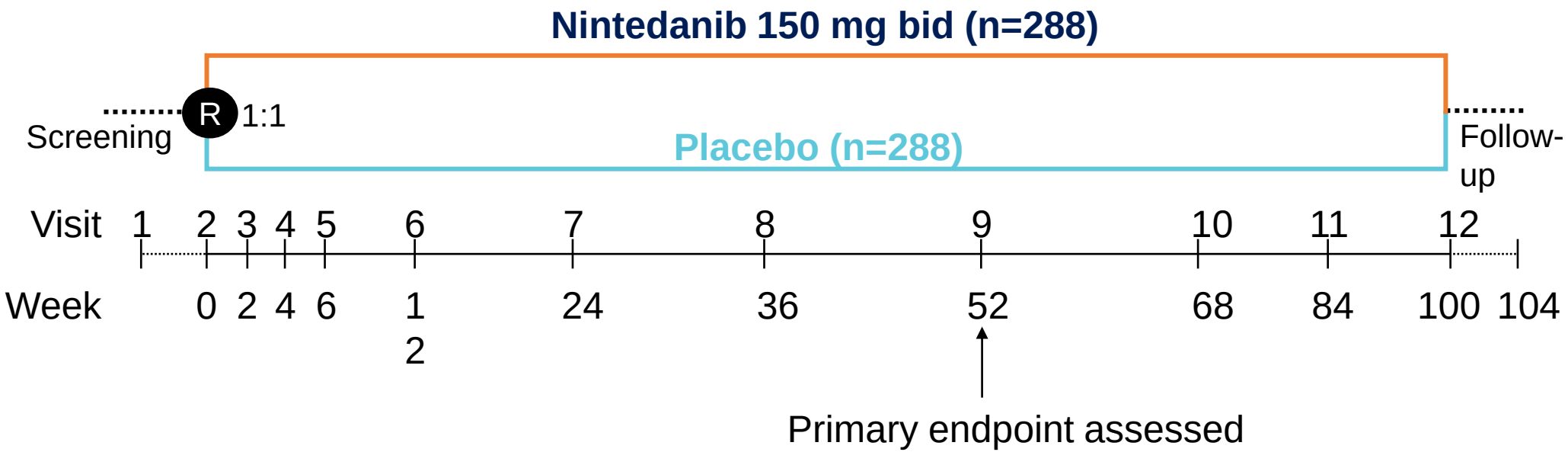
Nintedanib for Systemic Sclerosis–Associated Interstitial Lung Disease

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*

SENSCIS Trial

N Engl J Med 2019;380:2518-28

SENSCIS: Trial design

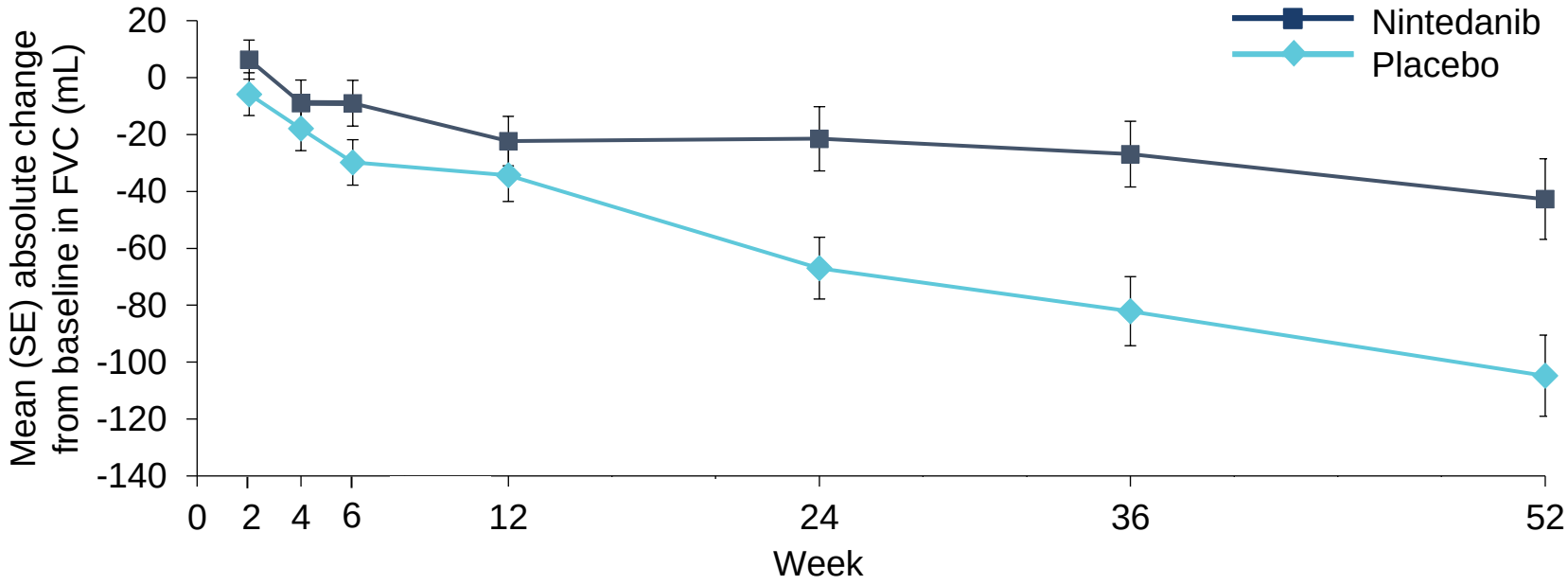


Randomised patients were stratified by anti-topoisomerase antibody (ATA) status (positive or negative).
Patients remained on blinded treatment until the last patient had reached week 52 but for no longer than 100 weeks.
bid, twice daily; R, randomisation.

Table 1. Baseline Characteristics of the Patients.*

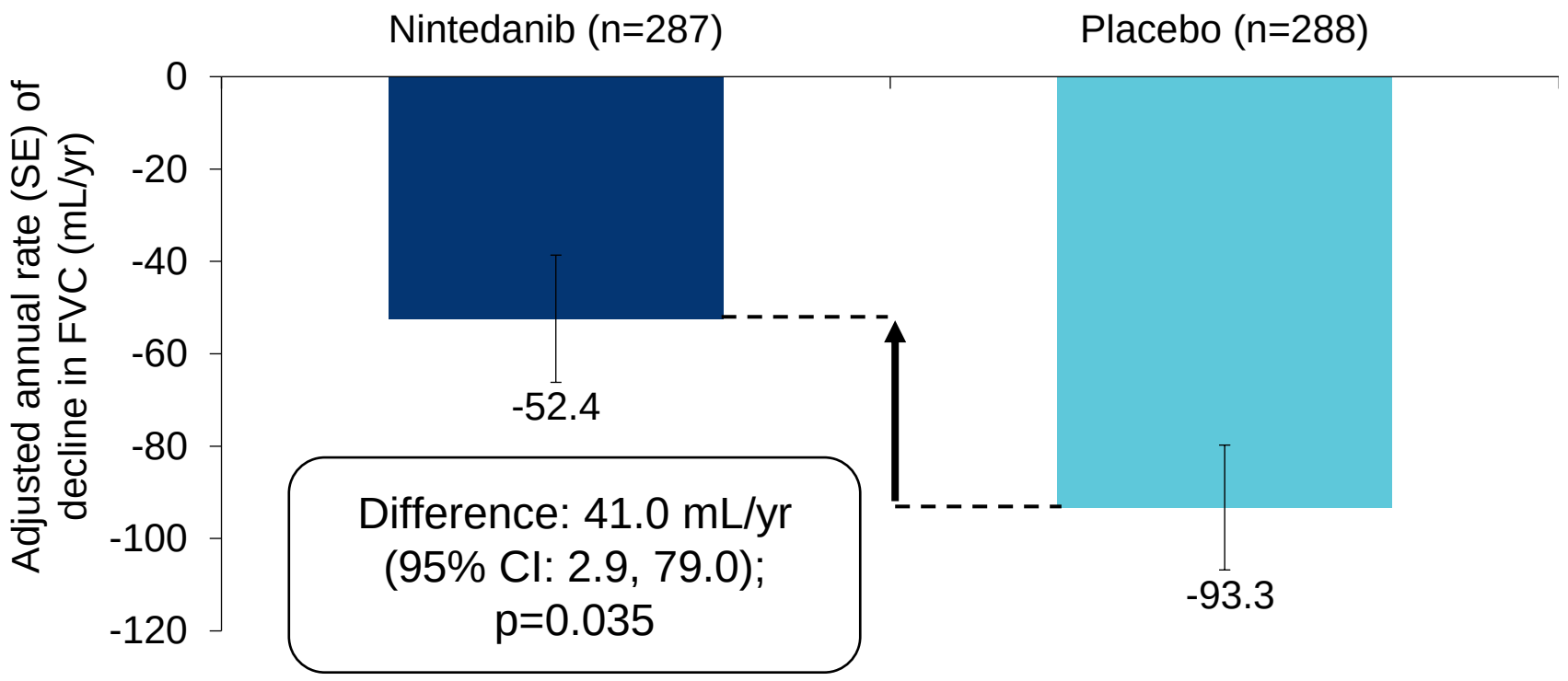
Characteristic	Nintedanib (N = 288)	Placebo (N = 288)
Female sex — no. (%)	221 (76.7)	212 (73.6)
Age — yr	54.6±11.8	53.4±12.6
Diffuse cutaneous systemic sclerosis — no. (%)	153 (53.1)	146 (50.7)
Years since the onset of the first non-Raynaud's symptom		
Median	3.4	3.5
Range	0.3–7.1	0.4–7.2
Extent of fibrosis of the lungs on high-resolution CT — %	36.8±21.8	35.2±20.7
FVC — ml	2459±736	2541±816
FVC — % of predicted value	72.4±16.8	72.7±16.6
DL_{CO} — % of predicted value†	52.9±15.1	53.2±15.1
Antitopoisomerase antibody positive — no. (%)‡	173 (60.1)	177 (61.5)
Modified Rodnan skin score§	11.3±9.2	10.9±8.8
Patients with diffuse cutaneous systemic sclerosis	17.0±8.7	16.3±8.9
Patients with limited cutaneous systemic sclerosis	4.9±4.2	5.4±4.1
Total score on the SGRQ¶	40.7±20.2	39.4±20.9
Score on the HAQ-DI‖	0.65±0.70	0.55±0.58
Scaled score on the FACIT-Dyspnea questionnaire**	47.01±9.64	45.67±9.90
Receiving mycophenolate — no. (%)	139 (48.3)	140 (48.6)
Receiving methotrexate — no. (%)	23 (8.0)	15 (5.2)

Change from baseline in FVC (mL) over 52 weeks



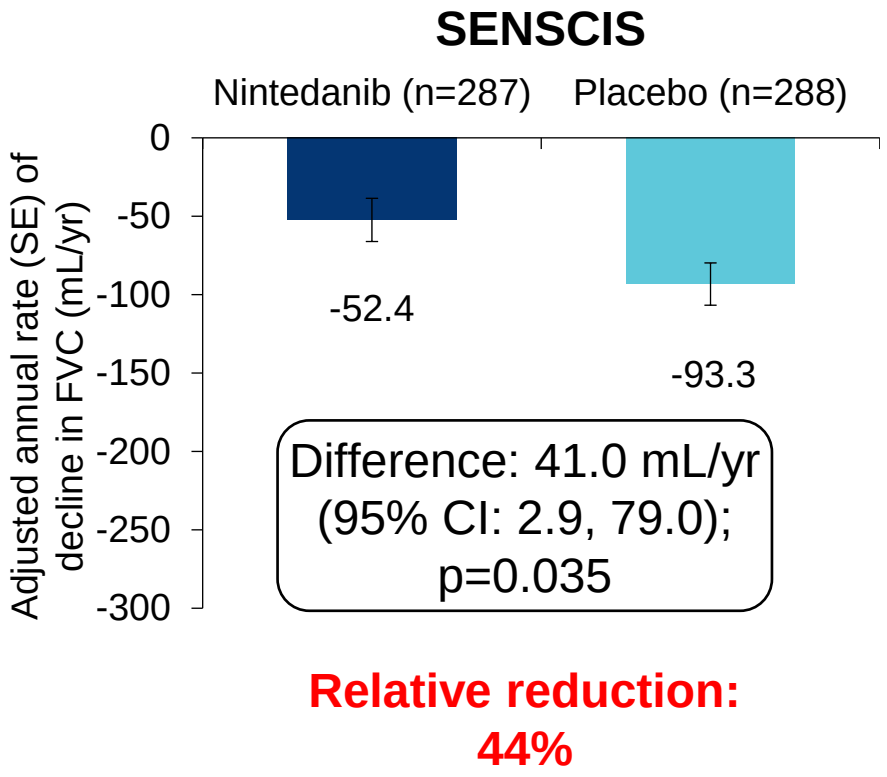
No. of patients								
Nintedanib	288	283	281	273	278	265	262	241
Placebo	288	283	281	280	283	280	268	257

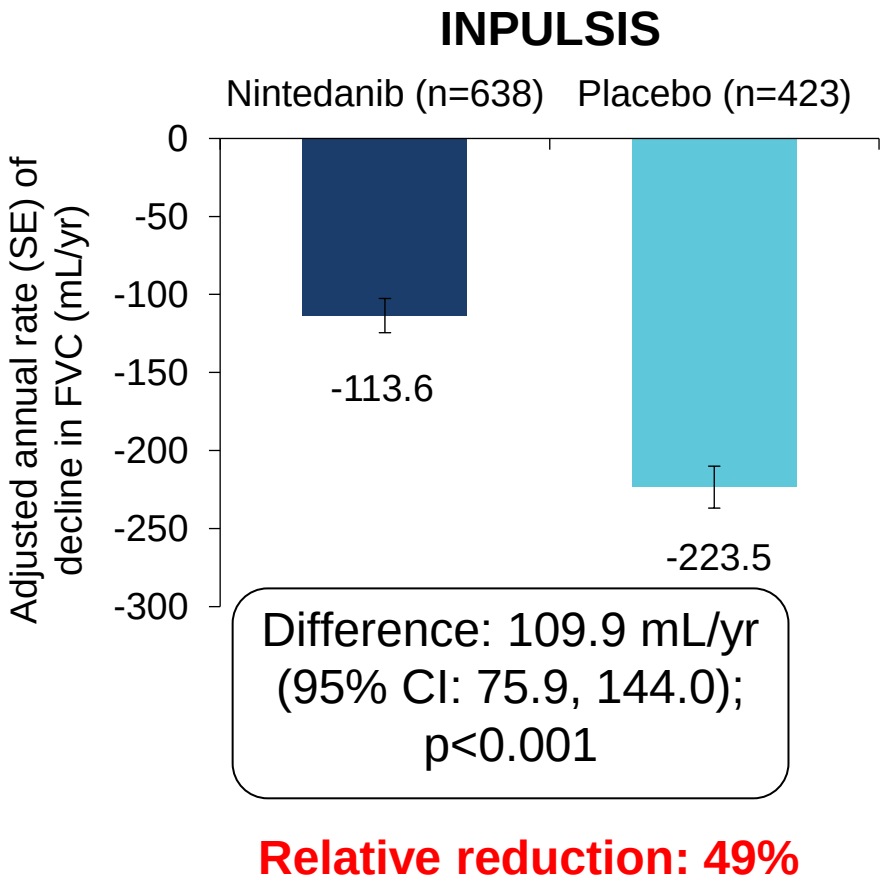
Annual rate of decline in FVC (mL/yr) over 52 weeks



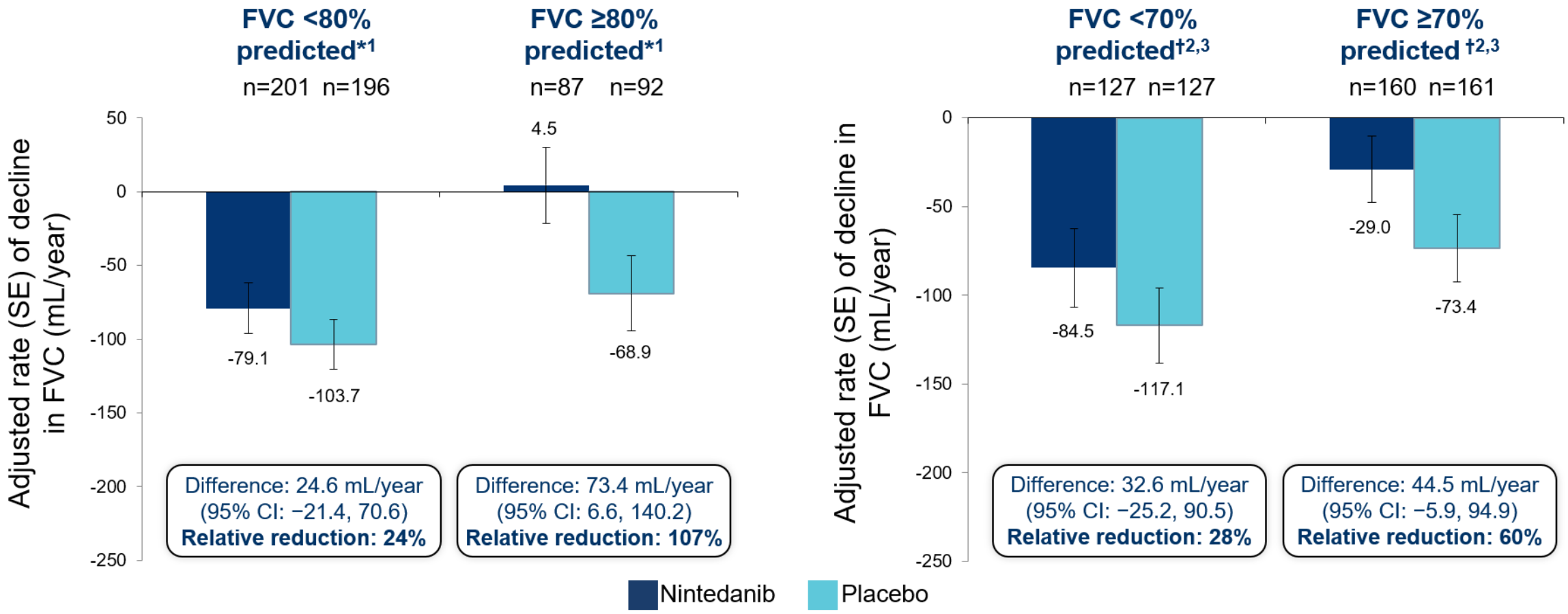
Relative reduction: 44%

SENSCIS and INPULSIS: Annual rate of decline in FVC (mL/yr)



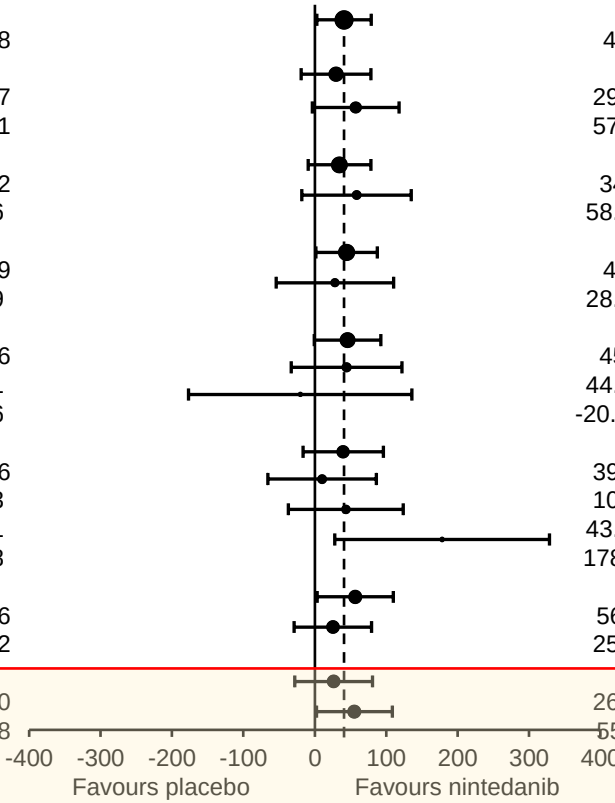


Nintedanib reduced the rate of decline in FVC in patients with more and less preserved lung function



Pre-specified subgroup analyses

		n analysed Nintedanib	n analysed Placebo	Difference (95% CI)	Treatment-by-time-by-subgroup interaction
All patients		287	288	41.0 (2.9, 79.0)	
ATA 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)	



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*

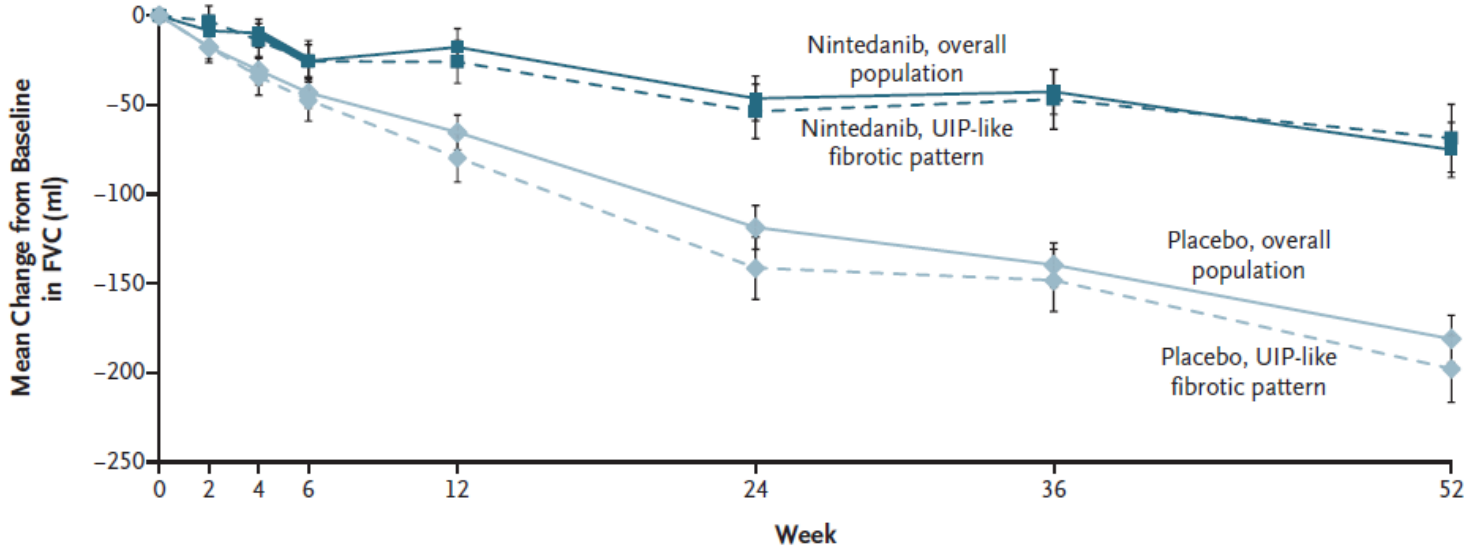
INBUILD Clinical Trials

INBUILD: Clinical ILD diagnoses in overall population

	Nintedanib (n=332)	Placebo (n=331)
Hypersensitivity pneumonitis	84 (25.3)	89 (26.9)
Autoimmune ILDs	82 (24.7)	88 (26.6)
Rheumatoid arthritis-associated ILD	42 (12.7)	47 (14.2)
Systemic sclerosis-associated ILD	23 (6.9)	16 (4.8)
Mixed connective tissue disease-associated ILD	7 (2.1)	12 (3.6)
Other autoimmune ILDs	10 (3.0)	13 (3.9)
Idiopathic non-specific interstitial pneumonia	64 (19.3)	61 (18.4)
Unclassifiable IIP	64 (19.3)	50 (15.1)
Other fibrosing ILDs*	38 (11.4)	43 (13.0)

Data are n (%) of patients. *In the nintedanib and placebo groups, respectively, 21 (6.3%) and 18 (5.4%) patients had exposure-related ILDs and 4 (1.2%) and 8 (2.4%) patients had sarcoidosis. IIP, idiopathic interstitial pneumonia.

Decline from Baseline in Forced Vital Capacity
(total of 663 patients)



No. of Patients								
Overall population								
Nintedanib	332	326	320	322	314	298	285	265
Placebo	331	325	326	325	320	311	296	274
Patients with UIP-like fibrotic pattern								
Nintedanib	206	203	200	199	193	180	171	160
Placebo	206	202	202	201	197	190	176	162

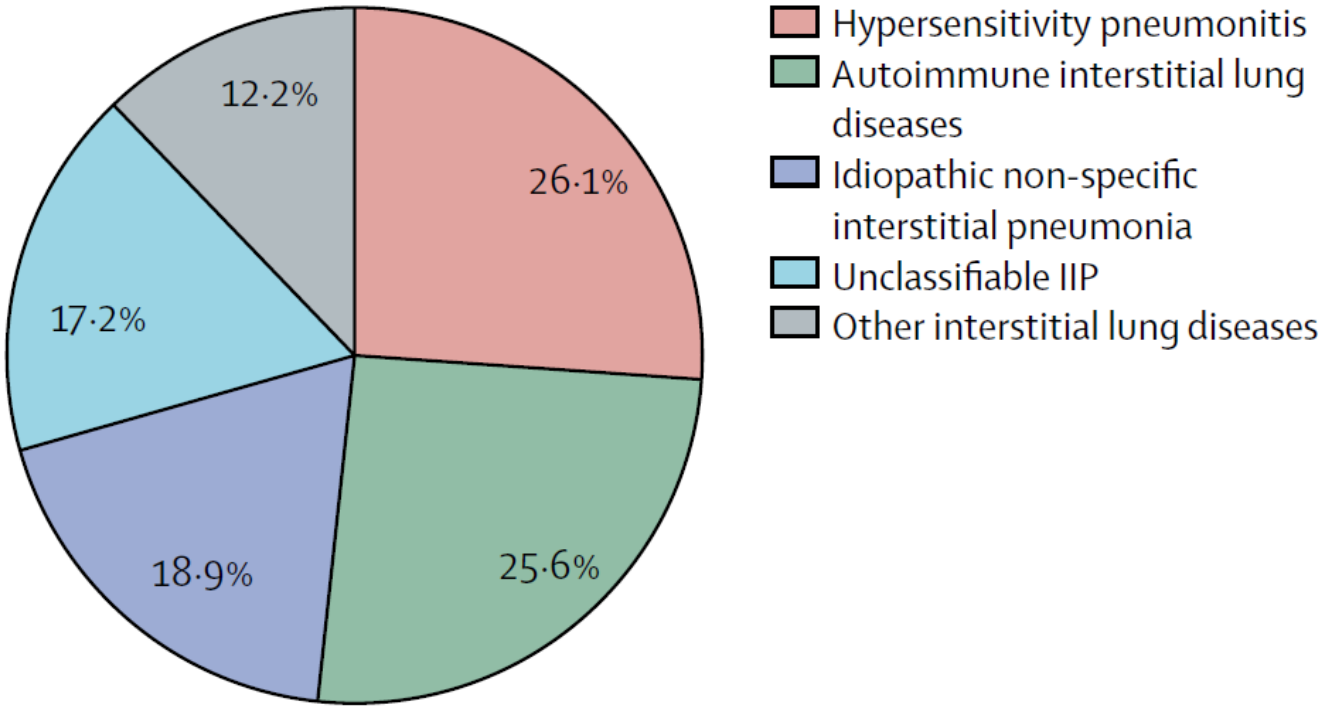
Nintedanib

Placebo

Baseline characteristics

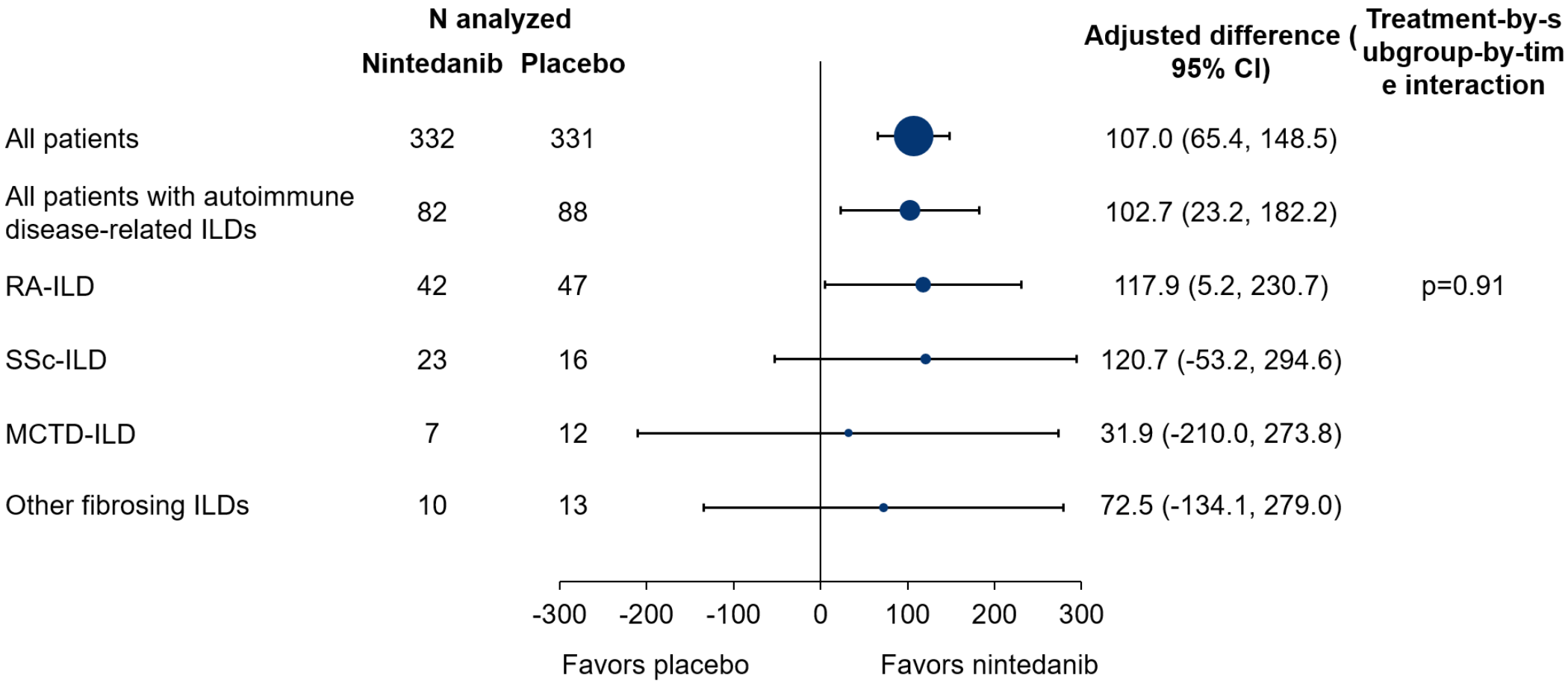
	HP (n=173)	Autoimmune ILD (n=170)	Idiopathic NSIP (n=125)	Unclassifiable IIP (n=114)	Other ILDs* (n=81)
Male	89 (51%)	80 (47%)	63 (50%)	62 (54%)	62 (77%)
Age, years	65·5 (8·3)	64·3 (10·6)	65·4 (9·4)	68·4 (9·4)	66·2 (11·2)
Former or current smoker	91 (53%)	85 (50%)	43 (34%)	62 (54%)	57 (70%)
UIP-like fibrotic pattern on HRCT	90 (52%)	127 (75%)	71 (57%)	77 (68%)	47 (58%)
Forced vital capacity, mL	2244 (739)	2330 (699)	2351 (761)	2286 (730)	2548 (727)
Forced vital capacity, % predicted	65·2 (14·2)	70·9 (14·9)	71·3 (17·3)	69·8 (15·4)	68·4 (16·6)
Diffusing capacity of the lung for carbon monoxide, % predicted†	45·3 (14·4)	48·0 (15·1)	47·4 (12·5)	45·2 (11·9)	43·2 (12·2)

Nintedanib in patients with PF-ILD subgroup analyses in the INBUILD trial



Lancet Respir Med 2020;8: 453–60

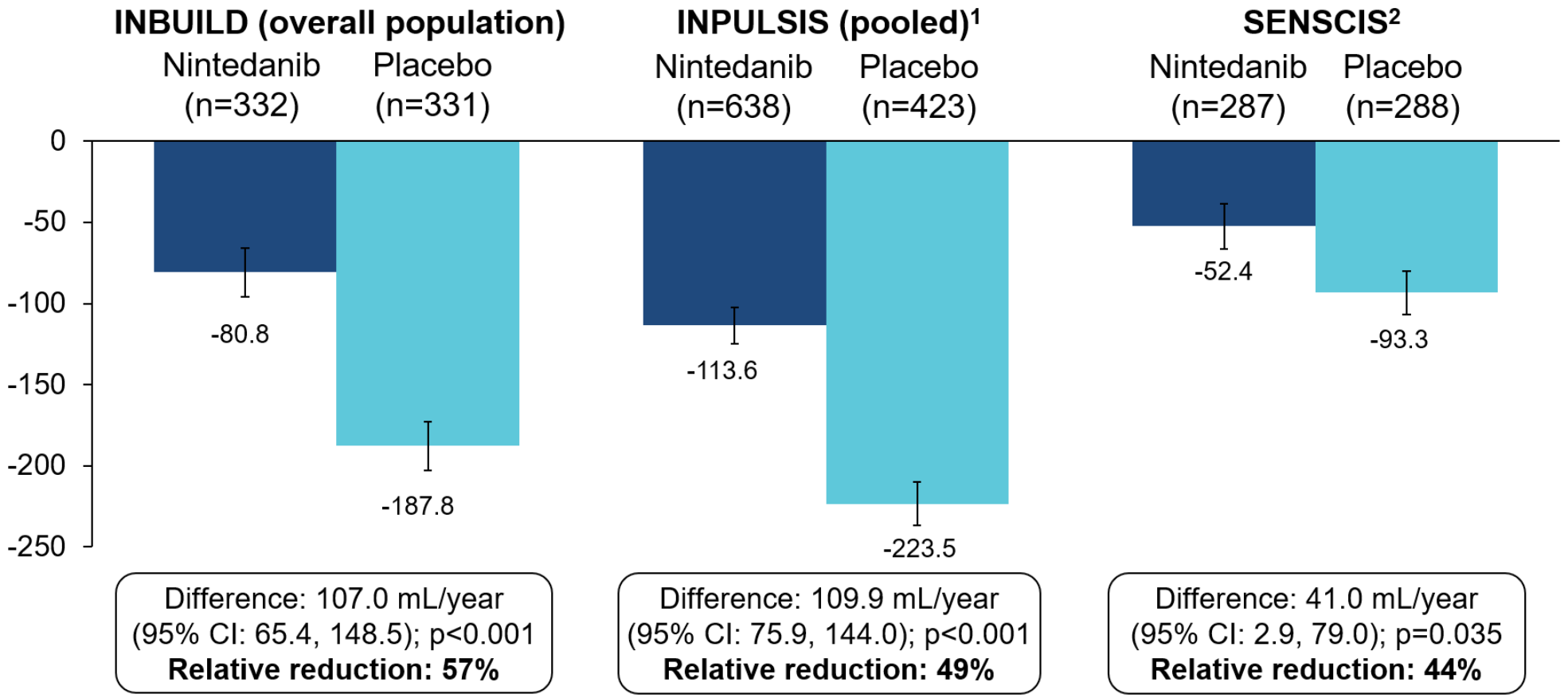
INBUILD : Rate of decline in FVC over 52 weeks in subgroups



Proportion of subjects who died over 52 weeks in the placebo groups

	Overall population (n=331)	UIP-like fibrotic pattern on HRCT (n=206)	Other fibrotic patterns on HRCT (n=125)	INPULSIS trials (n=423)
Deaths over 52 weeks	**17 (5.1)**	**16 (7.8)**	**1 (0.8)**	**33 (7.8)**
Hazard ratio versus INPULSIS trials	0.63 (0.35–1.13)	0.97 (0.53–1.76)	0.10 (0.01–0.70)	

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



1. Richeldi L, et al. N Engl J Med 2014;370:2071–82; 2. Distler O, et al. N Engl J Med 2019;380:2518–28.

SENSCIS® inclusion criteria[1]

- SSc according to 2013 ACR/ EULAR criteria
- Disease duration less than 7 years
- ≥10% extent of lung fibrosis on HRCT
- FVC ≥40% predicted
- DL_{CO} 30–89% predicted
- No need for progression criteria prior to inclusion in the trial

INBUILD® inclusion criteria[2]

- ILD other than IPF with features of diffuse fibrosing lung disease (reticular abnormality with traction bronchiectasis, with or without honeycombing)
- >10% extent of lung fibrosis on HRCT
- FVC ≥45% predicted
- DL_{CO} of 30–79% predicted
- Met ≥1 of the following criteria for ILD progression in the 24 months before screening, despite management:
  - Relative decline in FVC ≥10% predicted
  - Relative decline in FVC ≥5 to <10% predicted and worsened respiratory symptoms
  - Relative decline in FVC ≥5 to <10% predicted and increased extent of fibrosis on HRCT
  - Worsened respiratory symptoms and increased extent of fibrosis on HRCT

ACR, American College of Rheumatology; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; EULAR, European League Against Rheumatism; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; SSc, systemic sclerosis

1. Distler O *et al. N Engl J Med* 2019;380:2518–28; 2. Flaherty KR *et al. N Engl J Med* 2019;381:1718–27

Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial

Dinesh Khanna, Celia J F Lin, Daniel E Furst, Jonathan Goldin, Grace Kim, Masataka Kuwana, Yannick Allanore, Marco Matucci-Cerinic, Oliver Distler, Yoshihito Shima, Jacob M van Laar, Helen Spotswood, Bridget Wagner, Jeffrey Siegel, Angelika Jahreis, Christopher P Denton*, for the focuSSced investigators†*

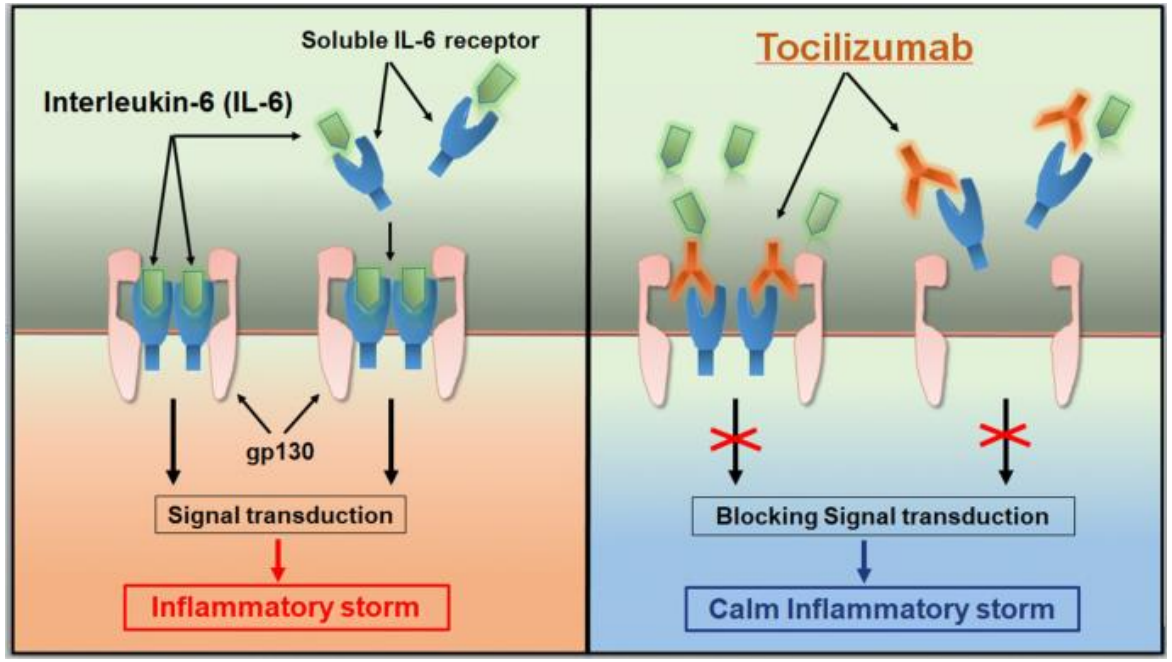
FocuSSced trial

- Subcutaneous tocilizumab 162 mg or placebo weekly for 48 weeks
- The primary endpoint : the difference in change from baseline to week 48 in mRSS
- The secondary endpoint : FVC % predicted at week 48

Lancet Respir Med 2020; 8: 963–74

Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial

Dinesh Khanna, Celia J F Lin, Daniel E Furst, Jonathan Goldin, Grace Kim, Masataka Kuwana, Yannick Allanore, Marco Matucci-Cerinic, Oliver Distler, Yoshihito Shima, Jacob M van Laar, Helen Spotswood, Bridget Wagner, Jeffrey Siegel, Angelika Jahreis, Christopher P Denton*, for the focuSSced investigators†*



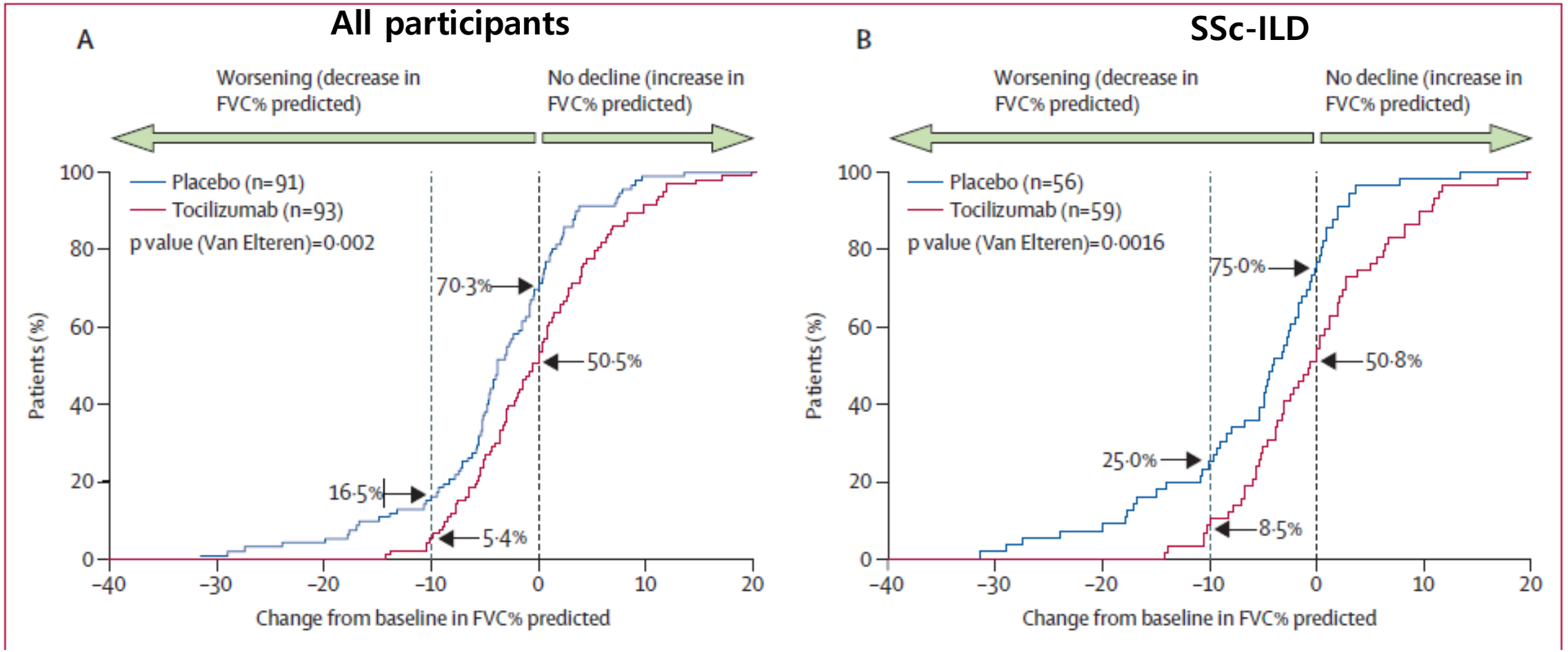
- Monoclonal antibody against the interleukin-6 receptor (IL-6R)
- Used for the treatment of RA and COVID-19 ARDS

Baseline characteristics

- Early, active SSc patients
- Preserved lung function
- SSc ILD: 65% (placebo), 67% (Tocilizumab)

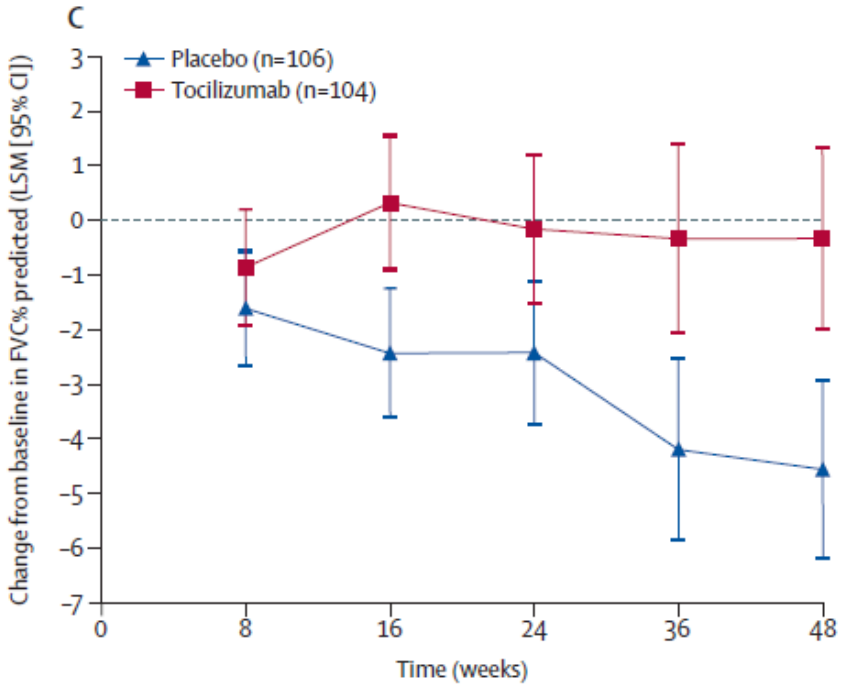
	Placebo group (n=106)	Tocilizumab group (n=104)
Female	90 (85%)	81 (78%)
Age, years	49·3 (12·6)	47·0 (12·2)
Former or existing smoker	40 (38%)	32 (31%)
Race		
American Indian or Alaskan native	3 (3%)	1 (1%)
Asian	9 (9%)	16 (15%)
Black or African American	3 (3%)	2 (2%)
White	90 (85%)	85 (82%)
Other	1 (1%)	0
Duration of SSc, months		
Mean (SD)	23·1 (17·0)	22·2 (16·0)
Median (IQR)	17·9 (9·4–33·2)	17·2 (9·0–34·9)
FVC% predicted*		
Mean (SD)	83·9 (15·0)	80·3 (14·4)
Median (IQR)	85·9 (72·4–95·9)	80·0 (69·3–90·2)
%DLCO predicted, Hb corrected*	n=105	n=104
Mean (SD)	76·8 (18·6)	74·4 (19·2)
Median (IQR)	75·6 (65·7–85·8)	71·5 (59·1–89·3)
Baseline SSc-ILD†	68/104 (65%)	68/102 (67%)
Baseline QLF-LM	n=84	n=73
Mean (95% CI)‡	4·2 (2·4–6·0)	5·4 (3·0–7·8)
Median (IQR)	2·1 (1·0–4·4)	1·8 (0·7–4·9)
Baseline QLF-WL	n=102	n=100
Mean (95% CI)‡	1·8 (1·2–2·4)	2·7 (1·8–3·5)
Median (IQR)	1·1 (0·5–2·1)	1·2 (0·5–3·0)
Baseline QILD-WL	n=102	n=100
Mean (95% CI)‡	14·1 (12·0–16·1)	16·9 (14·1–19·6)
Median (IQR)	12·3 (7·5–20·2)	14·2 (7·0–24·4)

Results


A
All participants
Worsening (decrease in FVC% predicted)
No decline (increase in FVC% predicted)
Placebo (n=91)
Tocilizumab (n=93)
p value (Van Elteren)=0·002
70·3%
50·5%
16·5%
5·4%
Patients (%)
Change from baseline in FVC% predicted
B
SSc-ILD
Worsening (decrease in FVC% predicted)
No decline (increase in FVC% predicted)
Placebo (n=56)
Tocilizumab (n=59)
p value (Van Elteren)=0·0016
75·0%
50·8%
25·0%
8·5%
Patients (%)
Change from baseline in FVC% predicted

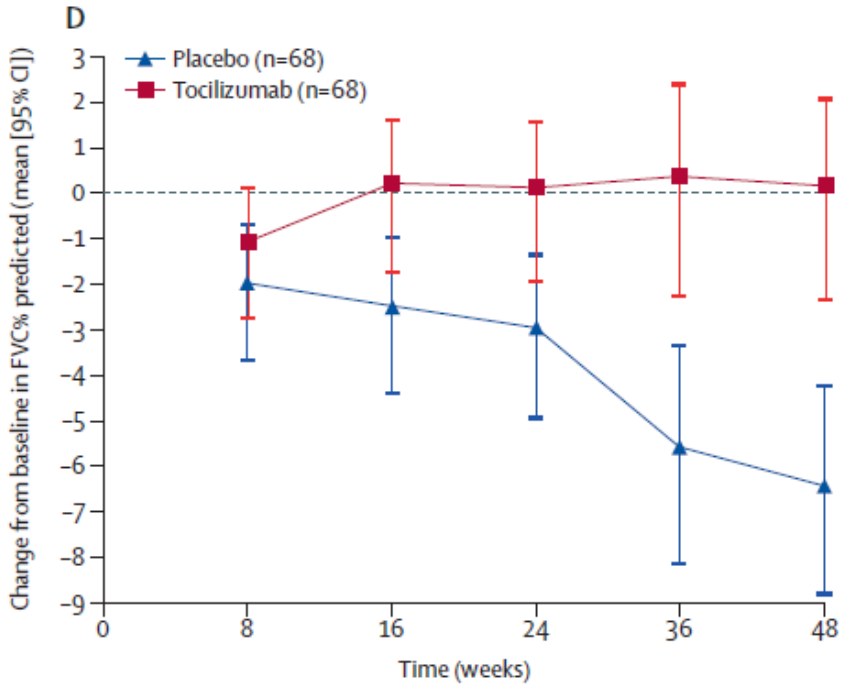
Results

All participants



	Placebo n=106	Tocilizumab n=104	
LSM change from baseline at week 48	−4·6	−0·4	4·2 (95% CI 2·0 to 6·4); nominal p=0·0002

SSc-ILD



Tocilizumab might preserve lung function

	Intention-to-treat population				Participants with SSc-ILD*			
	Placebo group (n=106)	Tocilizumab group (n=104)	Difference between treatment groups†	p value	Placebo group (n=68)	Tocilizumab group (n=68)	Difference between treatment groups†	p value
FVC% predicted change from baseline								
Median (95% CI)	−3·9 (−4·8 to −1·6); n=91	−0·6 (−2·4 to 0·9); n=93	3·3 (0·9–4·8)	Nominal p=0·002	−4·0 (−5·3 to −1·7); n=56	−0·6 (−3·2 to 2·0); n=59	3·4 (0·4–5·6)	Nominal p=0·002
LSM (95% CI)	−4·6; n=104	−0·4; n=104	4·2 (2·0–6·4)	Nominal p=0·0002‡	−6·4; n=66	−0·1; n=68	6·5 (3·4–9·5)	Nominal p<0·0001‡
FVC% predicted ≥10% decline	15/91 (17%)	5/93 (5%)	NA§	..	14/56 (25%)	5/59 (9%)	NA§	..
Improvement in FVC% predicted (increase ≥0%)	26/91 (29%)	43/93 (46%)	NA§	..	13/56 (23%)	27/59 (46%)	NA§	..
Absolute change from baseline in FVC, mL								
Week 24, LSM (95% CI)	−101; n=104	−13; n=104	88 (24–152)	Nominal p=0·008‡	−133; n=66	−15; n=68	118 (31–205)	Nominal p=0·008‡
Week 48, LSM (95% CI)	−190; n=104	−24; n=104	167 (83–250)	Nominal p=0·0001‡	−255; n=66	−14; n=68	241 (124–358)	Nominal p<0·0001‡

ORIGINAL ARTICLE

Long-Term Safety and Efficacy of Tocilizumab in Early Systemic Sclerosis–Interstitial Lung Disease

Open-Label Extension of a Phase 3 Randomized Controlled Trial

Dinesh Khanna[1], Celia J. F. Lin[2*], Daniel E. Furst[3,4], Bridget Wagner[2], Mauro Zucchetto[5], Ganesh Raghu[6], Fernando J. Martinez[7], Jonathan Goldin[8], Jeffrey Siegel[2‡], and Christopher P. Denton[9]; for the focuSSced Investigators

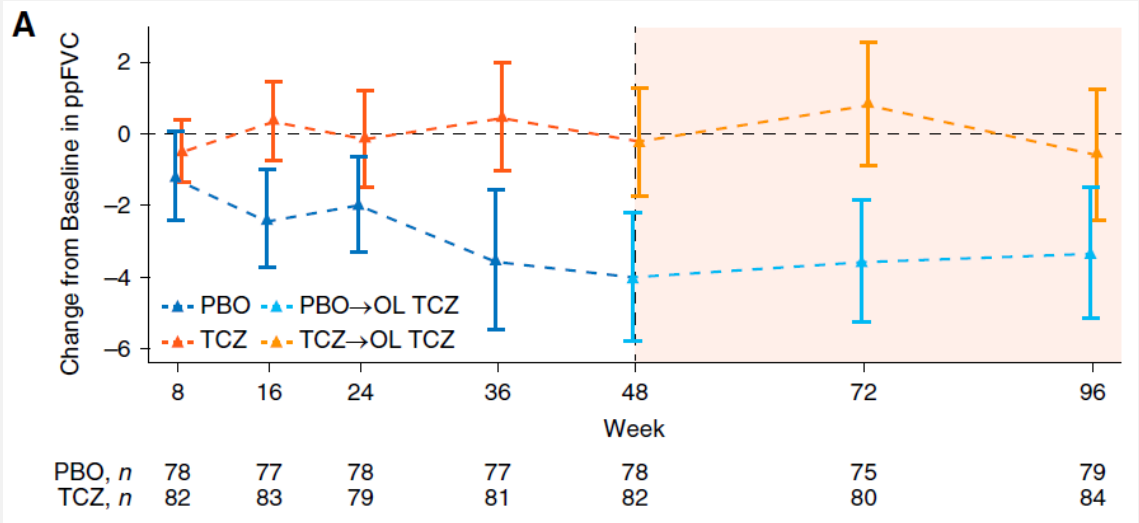
Patients completed FocuSSed trial

→ transitioned to open-label weekly injections of tocilizumab 162 mg for another 48 weeks

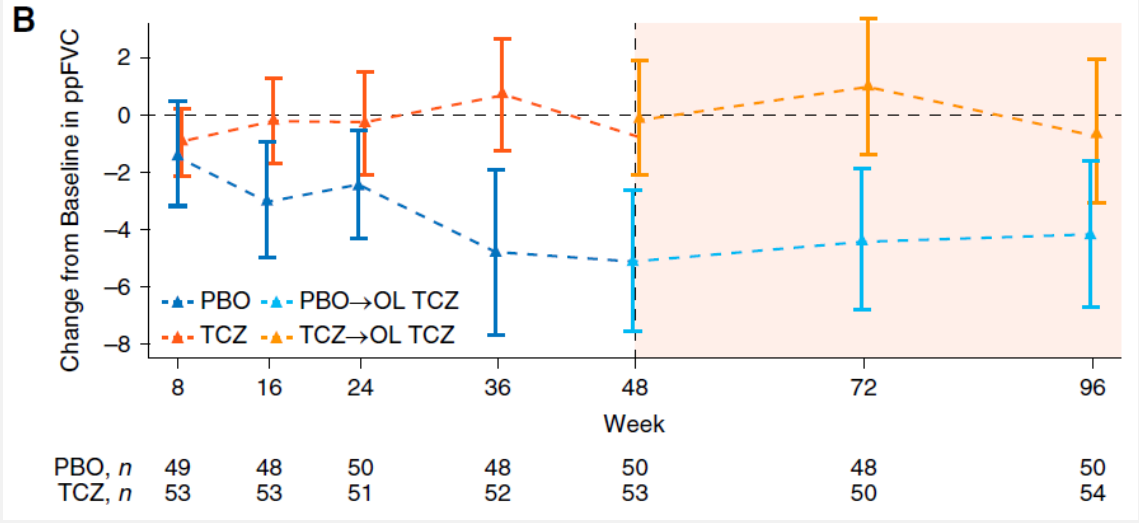
Am J Respir Crit Care Med 2022; 205 (6) 674–684

FVC % pred mean (95% CI) change from baseline to Week 96

All participants



SSc-ILD



Change from Baseline to Week 48 or 96 and from Weeks 48 to 96 in FVC, % Pred. DLCO, and mRSS in Patients with SSc–ILD

	Double-Blind, Baseline to Week 48		Double-Blind + Open-Label, Baseline to Week 96		Open-Label, Week 48 to Week 96	
	PBO	TCZ	PBO-TCZ	Continuous-TCZ	PBO-TCZ	Continuous-TCZ
Absolute FVC, ml						
Mean (95% CI)	−197.2 (−301.6 to −92.8)	−11.1 (−83.8 to 61.6)	−157.6 (−255.9 to −59.3)	−28.9 (−116.9 to 59.1)	39.6 (−28.3 to 107.5)	−15.3 (−80.1 to 49.5)
Median	−105.0	−20.0	−105.0	−40.0	35.0	0.0
n	50	53	50	54	50	53
ppFVC						
Mean (95% CI)	−5.1 (−7.6 to −2.6)	−0.1 (−2.1 to 2.0)	−4.1 (−6.7 to −1.6)	−0.6 (−3.1 to 2.0)	0.9 (−0.8 to 2.7)	−0.4 (−2.3 to 1.5)
Median	−3.1	−0.6	−3.3	−1.0	1.0	0.0
n	50	53	50	54	50	53
ppD_{LCO}						
Mean (95% CI)	−1.4 (−5.2 to 2.3)	0.1 (−3.1 to 3.2)	−5.6 (−8.7 to −2.6)	1.3 (−2.1 to 4.7)	−3.8 (−7.2 to −0.3)	1.6 (−1.0 to 4.2)
Median (95% CI)	−1.6 (−4.6 to 1.0)	−0.6 (−3.1 to 3.9)	−5.6 (−7.5 to −1.0)	1.0 (−4.1 to 4.4)	−2.8 (−8.2 to 1.3)	1.7 (−2.1 to 4.6)
n	43	47	46	51	43	47
mRSS						
Mean (95% CI)	−6.2 (−8.3 to −4.2)	−7.1 (−8.5 to −5.7)	−9.2 (−11.2 to −7.3)	−9.4 (−11.0 to −7.9)	−3.1 (−4.1 to −2.0)	−2.3 (−3.2 to −1.4)
Median	−6.0	−7.0	−9.0	−8.5	−2.0	−2.0
n	50	54	51	54	50	54

Definition of abbreviations: CI = confidence interval; mRSS = modified Rodnan skin score; PBO = placebo; ppD_{LCO} = percent predicted D_{LCO}; ppFVC = percent predicted FVC; TCZ = tocilizumab.

Completers are patients with change from baseline measurements at Week 96. Negative change indicates improvement in mRSS.

Nintedanib and Tocilizumab

- Nintedanib has a beneficial effect by reducing the rate of decline in FVC in patients with CTD-ILD, including SSc-ILD

- Tocilizumab preserved lung function, slowing decline in FVC, in patients with early SSc, including those with ILD

Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): a double-blind, double-dummy, randomised, controlled, phase 2b trial

*Toby M Maher, Veronica A Tudor, Peter Saunders, Michael A Gibbons, Sophie V Fletcher, Christopher P Denton, Rachel K Hoyles, Helen Parfrey, Elisabetta A Renzoni, Maria Kokosi, Athol U Wells, Deborah Ashby, Matyas Szigeti, Philip L Molyneaux, on behalf of the RECITAL Investigators**

- ✓ **Randomly assigned (1:1) to receive rituximab (1000 mg at weeks 0 and 2 IV) or cyclophosphamide (600 mg/m² body surface area every 4 weeks IV for six doses)**
- **The primary endpoint : rate of change in FVC at 24 weeks compared with baseline**

The RECITAL study, Lancet Respir Med 2023; 11: 45–54

Study population

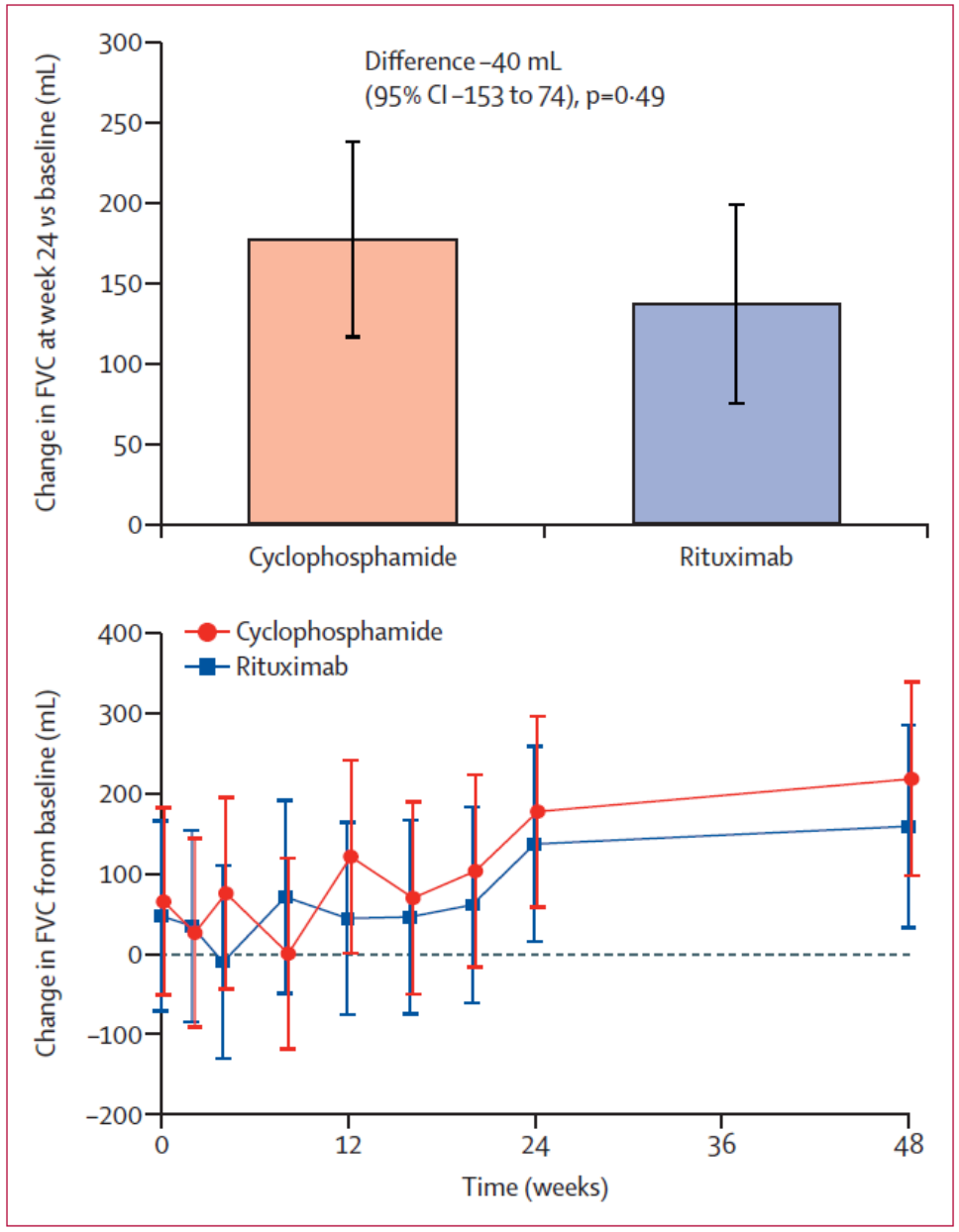
	Cyclophosphamide group (n=48)	Rituximab group (n=49)
Age, years	56·7 (11·6)	56·6 (11·4)
Sex		
Female	35 (73%)	31 (63%)
Male	13 (27%)	18 (37%)
Race and ethnicity*		
Asian	7 (15%)	9 (18%)
Black	5 (10%)	7 (14%)
White	34 (71%)	32 (65%)
Any other ethnic group	2 (4%)	1 (2%)
Connective tissue disease type		
Idiopathic inflammatory myositis	22 (46%)	22 (45%)
Systemic sclerosis	19 (40%)	18 (37%)
Mixed connective tissue disease	7 (15%)	9 (18%)
Years since onset of connective tissue disease	4·8 (6·2)	4·5 (7·6)
FVC, L	2·23 (0·85)	2·25 (0·77)
FVC, % of predicted	71% (20)	68% (17)
DL_{CO}, mL/min per kPa	3·35 (1·42), n=46	3·46 (1·33), n=45
DL_{CO}, % of predicted	40% (14), n=46	40% (14), n=45
SpO_2 on room air, %	96% (2)	97% (2)
6 min walk distance, m	363 (111)	356 (126)
EQ-5D score	55 (20)	58 (22)
GDA score	5·03 (1·76), n=40	4·58 (1·97), n=38
KBILD score	46·1 (20·3)	51 (21·2)
SGRQ score	55·8 (20·0), n=47	52·1 (17·6), n=45

Data are mean (SD) or n (%). FVC=forced vital capacity. DL_{CO}=diffusing capacity of the lung for carbon monoxide. SpO_2=arterial oxygen saturation. EQ-5D=European Quality of Life Five-Dimension. GDA=global disease activity (physician-assessed). KBILD=King's Brief Interstitial Lung Disease. SGRQ=St George's Respiratory Questionnaire. *Self-reported.

Primary and secondary endpoints

	Cyclophosphamide group		Rituximab group		Adjusted difference (95% CI)	p value
	n	Change from baseline	n	Change from baseline		
FVC, mL						
24 weeks	45	99 (329)	43	97 (234)	−40 (−153 to 74)	0·493
48 weeks	42	138 (440)	35	112 (249)	−58 (−178 to 62)	0·345
DL_{CO}, mL/min per kPa						
24 weeks	44	0·058 (0·706)	38	0·264 (0·573)	0·186 (−0·054 to 0·425)	0·425
48 weeks	38	0·131 (1·080)	32	0·288 (0·612)	0·117 (−0·137 to 0·372)	0·372
6 min walk distance, m						
24 weeks	46	10·4 (78·6)	40	10·9 (74·2)	−0·72 (−24·76 to 23·32)	0·953
48 weeks	39	15·1 (82·8)	32	−6·8 (69·8)	−22·46 (−48·43 to 3·51)	0·090
EQ-5D score						
24 weeks	43	3·5 (20·5)	41	6·2 (17·7)	3·06 (−3·05 to 9·18)	0·326
48 weeks	40	−1·2 (23·5)	35	3·9 (15·8)	4·77 (−1·73 to 11·27)	0·150
GDA score						
24 weeks	37	−2·9 (2·1)	35	−2·8 (1·8)	−0·14 (−0·85 to 0·57)	0·700
48 weeks	33	−2·9 (2·5)	26	−1·7 (2·3)	0·90 (0·11 to 1·68)	0·025
KBILD score						
24 weeks	45	9·4 (20·8)	42	8·8 (17·0)	0·40 (−5·73 to 6·52)	0·899
48 weeks	43	5·6 (25·6)	35	6·4 (16·2)	1·15 (−5·34 to 7·64)	0·728
SGRQ score						
24 weeks	42	−4·8 (19·6)	39	−3·4 (15·4)	0·63 (−5·64 to 6·91)	0·843
48 weeks	40	−6·4 (24·3)	35	−3·2 (16·6)	2·82 (−3·69 to 9·34)	0·396

Rituximab was not superior to cyclophosphamide



Adjusted rate of change in FVC in the cyclophosphamide and rituximab groups at week 24

Adjusted change in FVC from baseline to week 48

Rituximab was associated with fewer adverse events

	Cyclophosphamide group (n=50)	Rituximab group (n=51)
All events	646	445
Blood and lymphatic system disorders	3 (<1%)	0
Cardiac disorders	10 (2%)	6 (1%)
Ear and labyrinth disorders	2 (<1%)	1 (<1%)
Eye disorders	16 (2%)	9 (2%)
Gastrointestinal disorders	170 (26%)	71 (16%)
General disorders and administration site conditions	91 (14%)	52 (12%)
Hepatobiliary disorders	1 (<1%)	1 (<1%)
Immune system disorders	0	2 (<1%)
Infections and infestations	50 (8%)	46 (10%)
Injury, poisoning, and procedural complications	8 (1%)	5 (1%)
Investigations	11 (2%)	8 (2%)
Metabolism and nutrition disorders	5 (1%)	3 (1%)
Musculoskeletal and connective tissue disorders	44 (7%)	40 (9%)
Nervous system disorders	72 (11%)	35 (8%)
Psychiatric disorders	9 (1%)	10 (2%)
Renal and urinary disorders	8 (1%)	1 (<1%)
Reproductive system and breast disorders	5 (1%)	4 (1%)
Respiratory, thoracic, and mediastinal disorders	94 (15%)	101 (23%)
Skin and subcutaneous tissue disorders	38 (6%)	32 (7%)
Surgical and medical procedures	1 (<1%)	0
Vascular disorders	7 (1%)	16 (4%)

Data are number of events (% of total events reported per cohort).

Table 3: Adverse events by system, organ, and class, reported to week 48 for all randomised participants

Safety, tolerability, and efficacy of pirfenidone in patients with rheumatoid arthritis-associated interstitial lung disease: a randomised, double-blind, placebo-controlled, phase 2 study

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Randomly assigned (1:1) to receive 2403 mg oral pirfenidone or placebo daily

The primary endpoint : the incidence of the composite endpoint of a decline from baseline in % predicted FVC of 10% or more or death during the 52-week treatment

Lancet Respir Med 2023; 11: 87–96

Study population

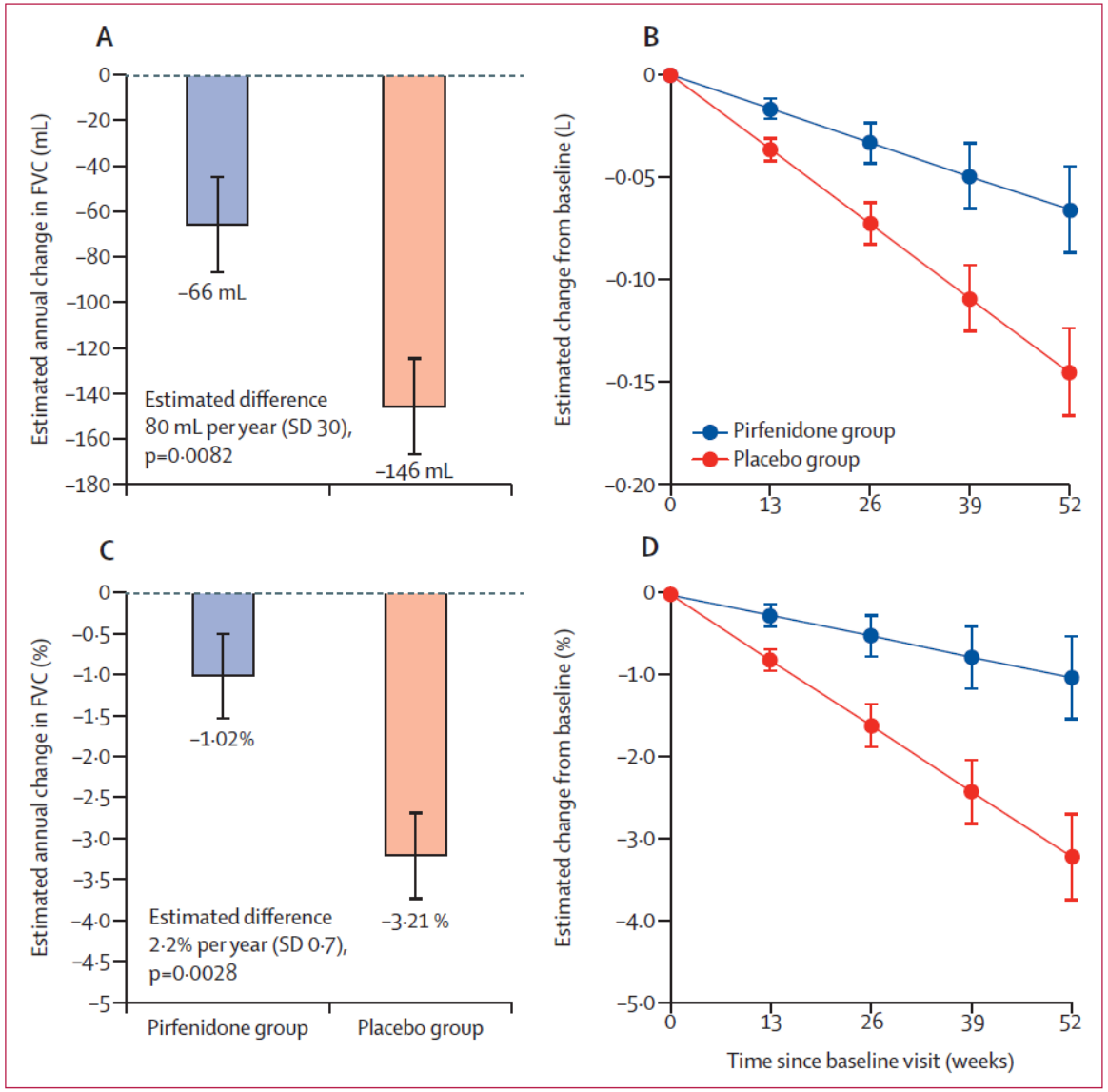
	Pirfenidone group (n=63)	Placebo group (n=60)
Age (years)	66·0 (61·0–74·0)	69·5 (63·5–74·5)
Sex		
Female	25 (40%)	21 (35%)
Male	38 (60%)	39 (65%)
Predominant HRCT pattern		
UIP	34 (54%)	47 (78%)
NSIP	9 (14%)	4 (7%)
LIP	0	3 (5%)
Indeterminate	20 (32%)	6 (10%)
DMARDs		
DMARD use	56 (89%)	50 (83%)
Conventional only, all HRCT patterns	13 (21%)	13 (22%)
Conventional only, UIP	8 (13%)	10 (17%)
Biologic only, all HRCT patterns	24 (38%)	22 (37%)
Biologic only, UIP	10 (16%)	17 (28%)
Conventional and biologic, all HRCT patterns	19 (30%)	15 (25%)
Conventional and biologic, UIP	11 (18%)	12 (20%)
Race		
White	56 (89%)	56 (93%)
Black or African American	2 (3%)	1 (2%)
Asian	4 (6%)	0
American Indian or Alaska Native	1 (2%)	0
Unknown or not reported	0	3 (5%)
Pulmonary physiology		
Percent predicted FVC	69·4 (14·8)	70·4 (14·2)
FVC (L)	2·6 (0·8)	2·6 (0·8)
Percent predicted DLCO	50·0 (12·6)	47·6 (12·8)
DLCO (mL/min per mmHg)	12·0 (4·3)	10·9 (4·4)
HRCT		
CT extent of fibrosis	20·8 (9·8)	24·2 (11·8)

Data are mean (SD) or n (%). The conventional DMARDs were azathioprine, mycophenolate, methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine. The biologic DMARDs were infliximab, adalimumab, etanercept, rituximab, abatacept, rituximab, tocilizumab, tofacitinib, certolizumab pegol, golimumab, sarilumab, anakinra, baricitinib, upadacitinib, and filgotinib. DLCO=diffusing capacity for carbon monoxide. DMARD=disease-modifying antirheumatic drugs. FVC=forced vital capacity. HRCT=high-resolution CT. LIP=lymphocytic interstitial pneumonia. NSIP=non-specific interstitial pneumonia. UIP=usual interstitial pneumonia.

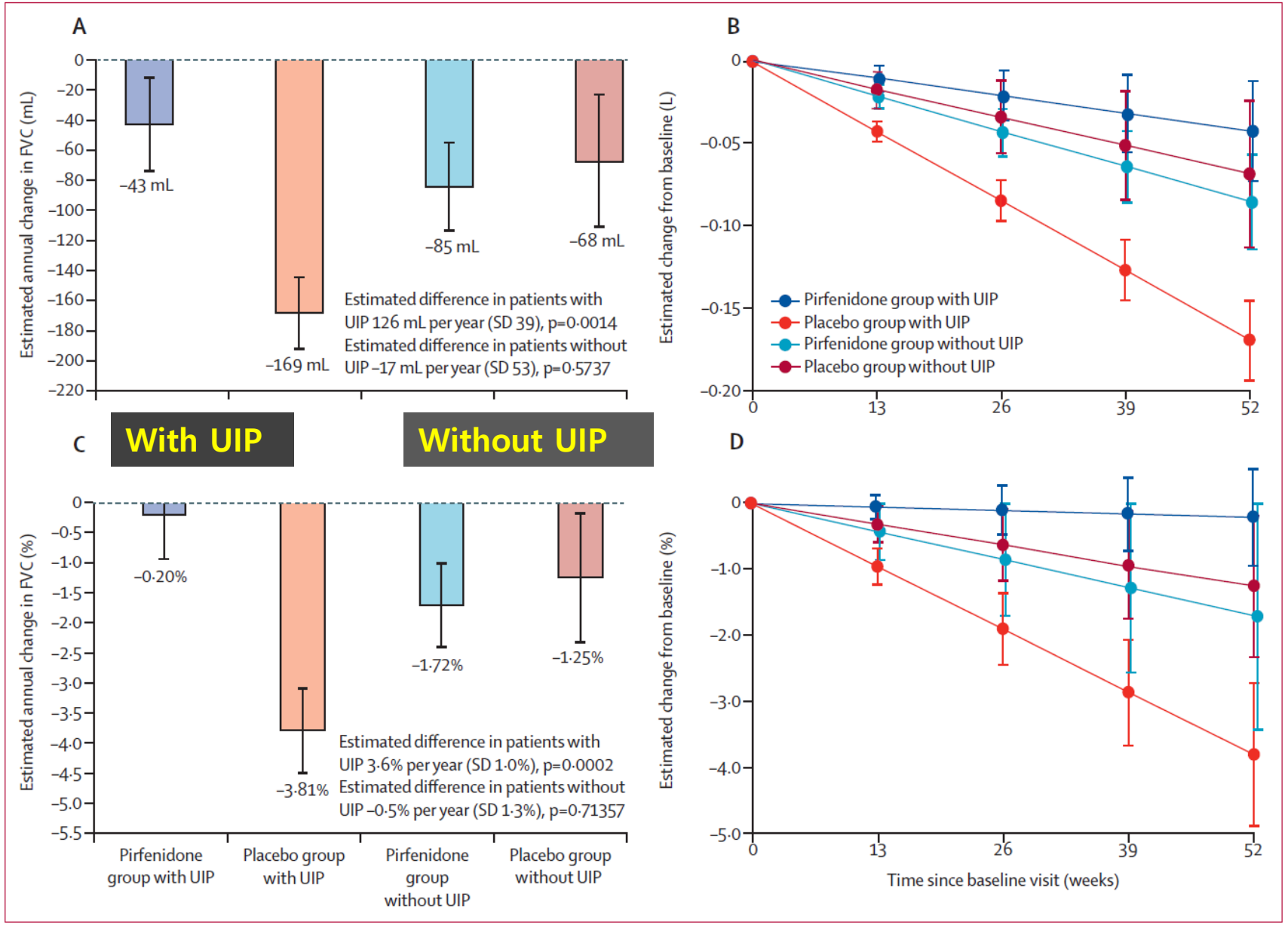
Not meeting the composite primary endpoint

	Pirfenidone group (n=63)	Placebo group (n=60)	p value
Primary endpoint			
Decline in percent predicted FVC by 10% or more or death	7 (11%)	9 (15%)	0·48

Estimated change in FVC and percent predicted FVC



Estimated change in FVC and percent predicted FVC by HRCT pattern



Summary

- The Scleroderma Lung Study ; SLS-I,2006 and SLS-II,2016 (cyclophosphamide and Mycophenolate in SSc-ILD)
- The SENSCIS trial, 2019 (Nintedanib in SSc-ILD)
- The INBUILD trial, 2019 (Nintedanib in CTD-ILD)
- The focuSSced trial, 2020 (In 2021, the FDA approved tocilizumab for the treatment of SSc-ILD)
- The TRAIL1,2023 (pirfenidone in RA-ILD)
- The RECITAL study, 2023 (rituximab in CTD-ILD)