OFEV® (nintedanib) Capsules for Systemic Sclerosis-associated Interstitial Lung Disease (SSc-ILD)

U.S. Food & Drug Administration

Arthritis Advisory Committee

July 25, 2019

Boehringer Ingelheim

Introduction

Kay Tetzlaff, MD

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Nintedanib Is Effective in Pulmonary Fibrosis

- Nintedanib
  - Small-molecule tyrosine kinase inhibitor
  - Blocks numerous pro-fibrotic pathways implicated in pulmonary fibrosis
  - Established safety and efficacy in idiopathic pulmonary fibrosis (IPF)
  - Approved in >70 countries
- Systemic Sclerosis-associated Interstitial Lung Disease (SSc-ILD) is another fibrosing interstitial lung disease (ILD) that shares similar clinical and pathologic features with IPF

Clinical Development of Nintedanib in Pulmonary Fibrosis

Fibrosing Interstitial Lung Diseases

Idiopathic Pulmonary Fibrosis (IPF)

INPULSIS
Approved

Systemic Sclerosis-assoc. Interstitial Lung Disease (SSc-ILD)

SENSCIS
Under review

Progressive Fibrosing ILDs

INBUILD
Ongoing

Nintedanib in Idiopathic Pulmonary Fibrosis (IPF)

- Efficacy[a]
  - Replicate Phase 3, 52-week trials (INPULSIS-1 and INPULSIS-2)
  - Primary endpoint: Annual rate of decline in Forced Vital Capacity (FVC)
  - Nintedanib reduced the annual rate of decline in FVC by 49% vs placebo, consistent with slowing disease progression in patients with IPF
- Safety
  - >1500 individual patients exposed to nintedanib in IPF clinical trials
  - Long-term exposure in clinical trials up to 68 months

    Median (range): 44.7 months (11.9-68.3 months)
  - Post-marketing exposure >80,000 patient-years

[a] Richeldi L, et al. *N Engl J Med.* 2014;370(22):2071-2078.

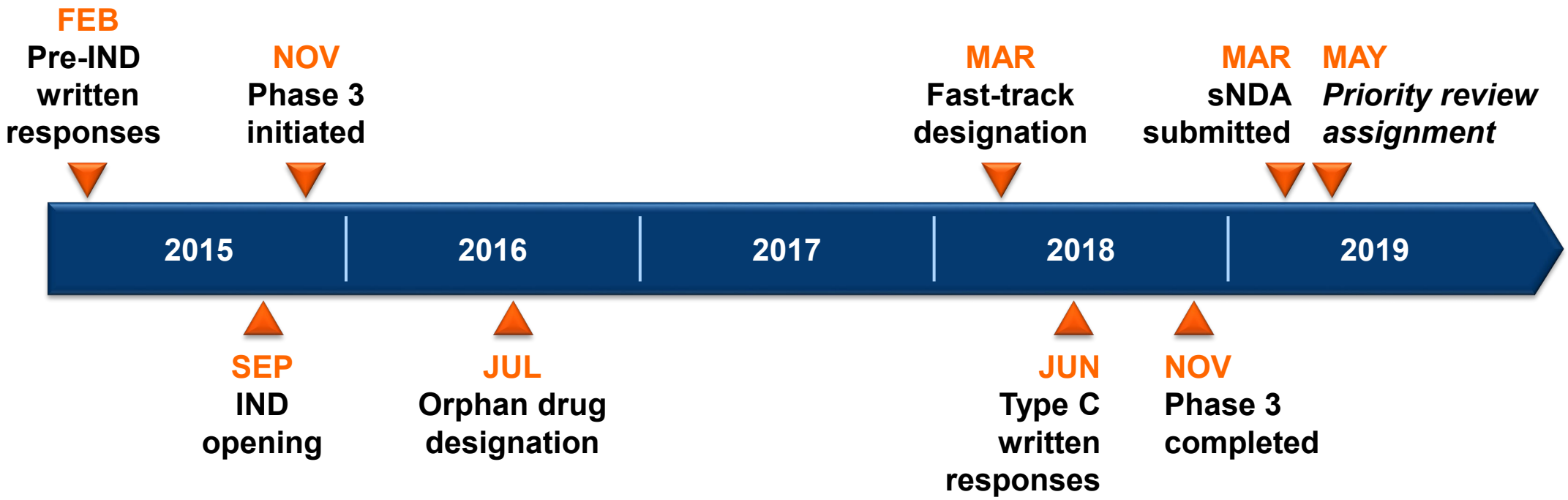
Systemic Sclerosis-associated Interstitial Lung Disease (SSc-ILD)

- Systemic sclerosis (SSc) is a chronic connective tissue disease characterized by progressive fibrosis that has a high disease burden and high rate of mortality
- Interstitial lung disease (ILD) is a common manifestation and the leading cause of death in SSc
- Pulmonary fibrosis is progressive, and associated loss in lung function is irreversible
- Short-term changes in FVC as a surrogate for progression of pulmonary fibrosis may predict mortality in SSc-ILD

Nintedanib in SSc-ILD

- SENSCIS
  - Replicates design of IPF pivotal trials
  - Trial population reflected patients seen in clinical practice
    - Limited and diffuse cutaneous SSc
    - Background mycophenolate allowed
    - Wide range of pulmonary function
- 94% of eligible patients entered open-label extension (SENSCIS-ON)

SSc-ILD Regulatory Milestones



sNDA: Proposed Indication and Dosing

- Proposed new indication

  Treatment of systemic sclerosis-associated interstitial lung disease (SSc-ILD)

- Dosing and dose regimen same as approved for IPF
  - 2 dosage strengths containing 100 mg or 150 mg
  - Intended dosing will be 150 mg twice daily with an option to reduce dose to 100 mg twice daily to manage adverse events

What You Will Hear Today

- SENSCIS is the first placebo-controlled phase 3 study in SSc-ILD that reached the primary endpoint of slowing FVC decline
- Results of SENSCIS are consistent with what we can expect from IPF with regard to the relative FVC benefit
- Safety comparable to experience from IPF
- Nintedanib adds an antifibrotic treatment option with the target of slowing down loss of lung function in SSc-ILD
- Nintedanib has a positive benefit/risk profile

Presenters

Disease Background/Unmet Need	James R. Seibold, MD Scleroderma Research Consultants LLC
Clinical Development Rationale	Susanne Stowasser, MD Boehringer Ingelheim
Efficacy	Emmanuelle Clerisme-Beaty, MD Boehringer Ingelheim
Safety	Veronika M. Kohlbrenner, MD Boehringer Ingelheim
Benefit Risk	Kay Tetzlaff, MD Boehringer Ingelheim
Clinical Perspective	Kevin K. Brown, MD National Jewish Health

Advisors

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Systemic Sclerosis-associated Interstitial Lung Disease (SSc-ILD) Background and Unmet Medical Need

James R. Seibold, MD

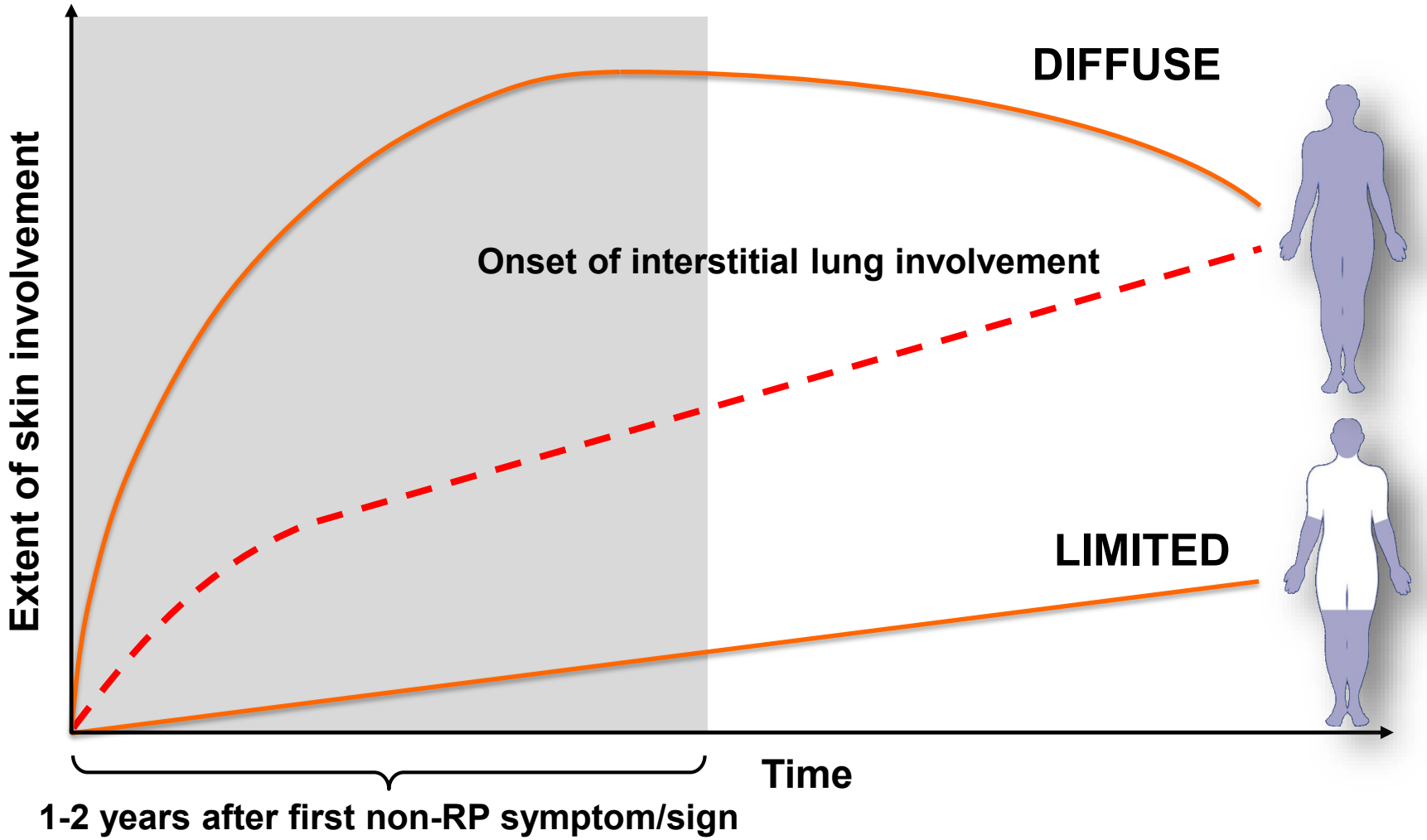
Scleroderma Research Consultants

Epidemiology and Demographics of Systemic Sclerosis in United States

- Annual US incidence: 20 to 24 per million[a,b]
- US prevalence: 276 to 300 per million[a,b]
  - Estimated 70,000 to 100,000 US patients[a]
  - Orphan disease
- ILD occurs in majority of patients[d]
- Female/male ratio: ~4:1[b,c]
- Peak onset ages: 40 to 50 years[b,c]
- More severe in African Americans[e]

[a] United States: Mayes MD, et al. *Arthritis Rheum*. 2003;48:2246-2255.
[b] Barnes and Mayes. *Curr Opin Rheumatol*. 2012;24:165-170.
[c] North America: Bergamasco A, et al. *Clin Epidemiol.* 2019;11:257-273.
[d] Solomon JJ, et al. *Eur Respir Rev*. 2013;22:6-19.
[e] Gelber AC, et al. *Medicine*. 2013;92:191-205.

Progression of Skin and Lung Involvement in Diffuse and Limited Systemic Sclerosis



Comorbid organ involvement

- Raynaud syndrome
- Digital ischemia and ulcers
- Esophageal disease
- Pulmonary hypertension

RP=Raynaud phenomenon

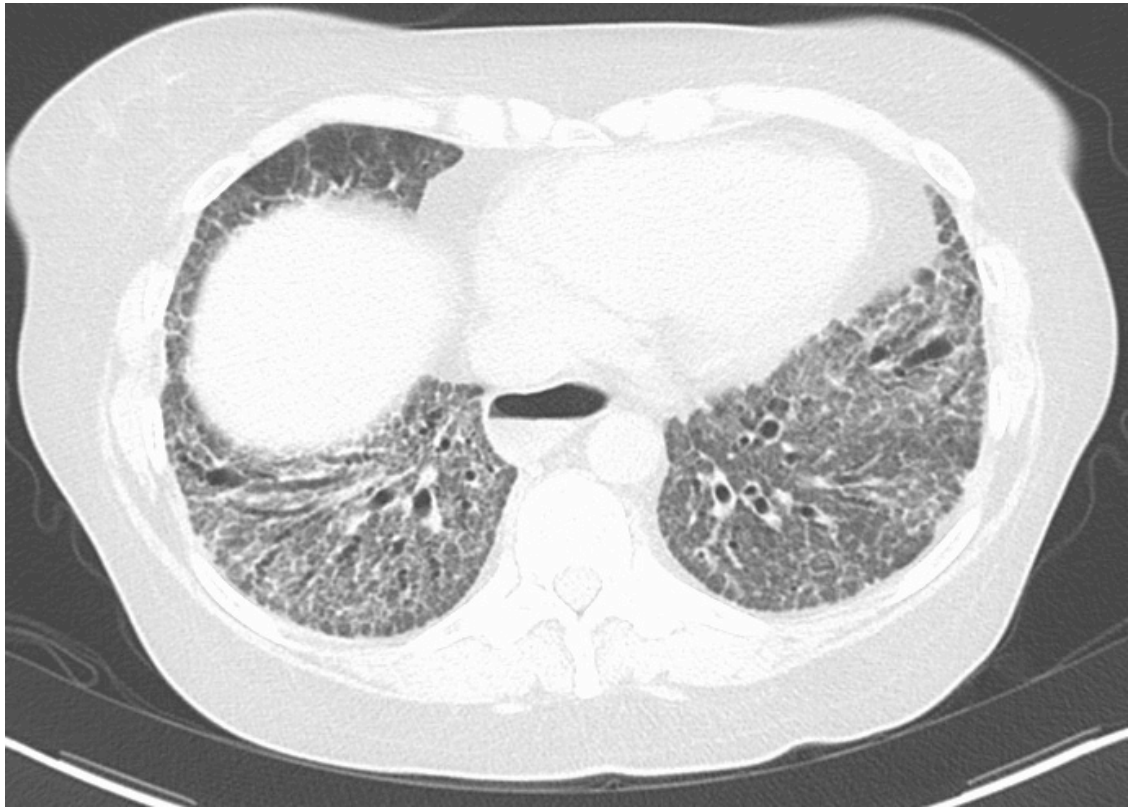
Adapted from Seibold JR. Kelley's *Textbook of Rheumatology*. Saunders 2000. p1211-1239.

The Human Impact of Scleroderma

- Onset in “prime of life”
- Women as family anchor for children and aging parents
- Impact of life-changing illness on career and social activities
- Uncertainty of future clinical course and outcome
- High symptom burden coupled with high risk of mortality
- Only approved therapies are for pulmonary arterial hypertension (PAH)

Systemic Sclerosis-associated Interstial Lung Disease (SSc-ILD)

- ILD is present in the majority of SSc patients
- Fibrotic NSIP is the most common HRCT pattern
- Clinically progressive in ~1/3 cases
- Onset is early and decline is continual
- Median survival 5 to 8 years after diagnosis



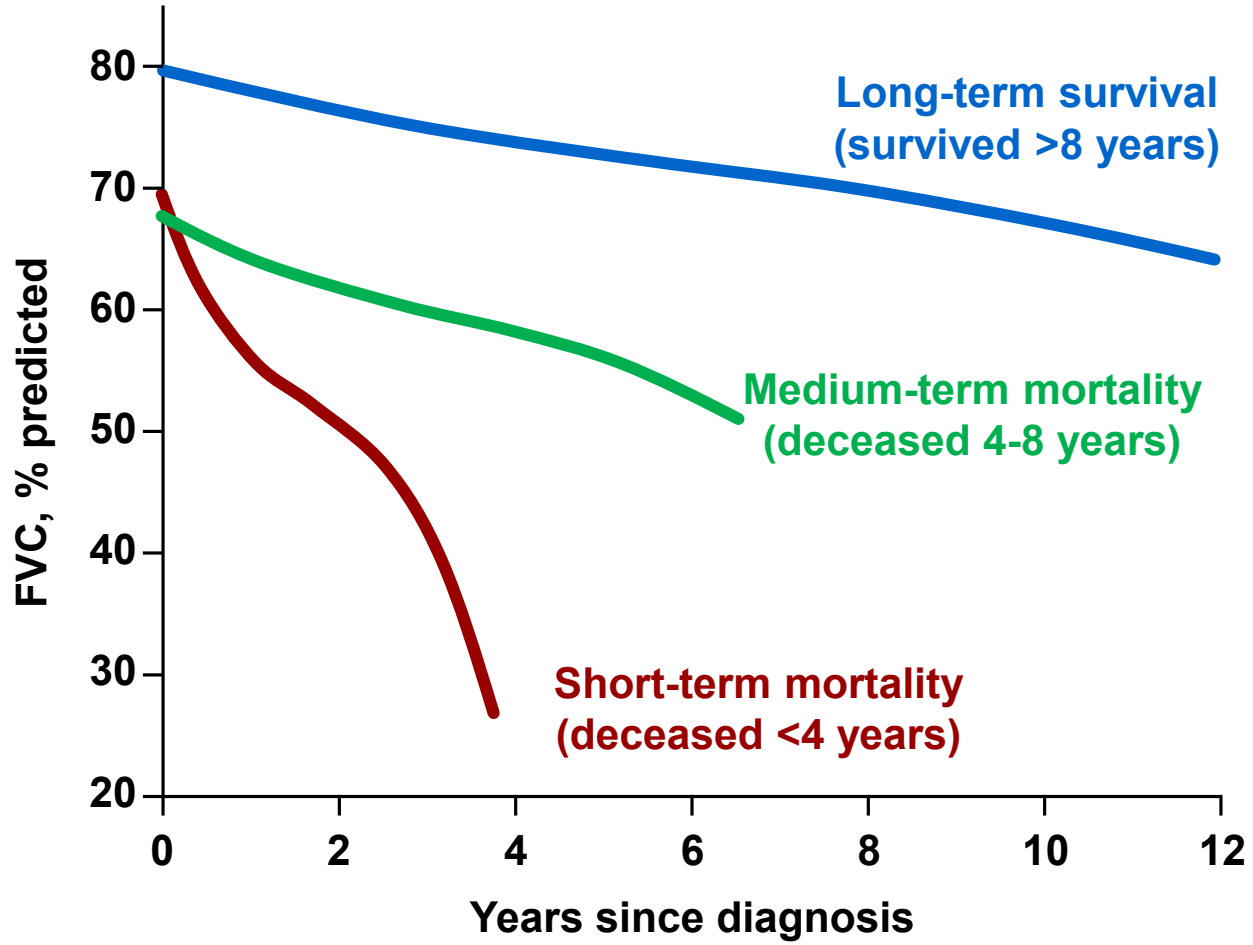
HRCT=high-resolution computed tomography;
NSIP=non-specific interstitial pneumonia.
Solomon JJ, et al. *Eur Respir Rev*. 2013;22:6-19.
Altman RD, et al. *Arthritis Rheum*. 1991;34:403-413.
Image courtesy of T. Maher.

Putative Risk Factors for ILD Progression

- Classification (diffuse vs limited)
- Disease duration <5 yr
- HRCT extent >20%
- FVC <70% predicted
- Presence of antitopoisomerase I antibody (ATA)

Khanna D, et al. *Rheumatoalogy (Oxford)*. 2017;56 (Suppl 5):v27-v32.

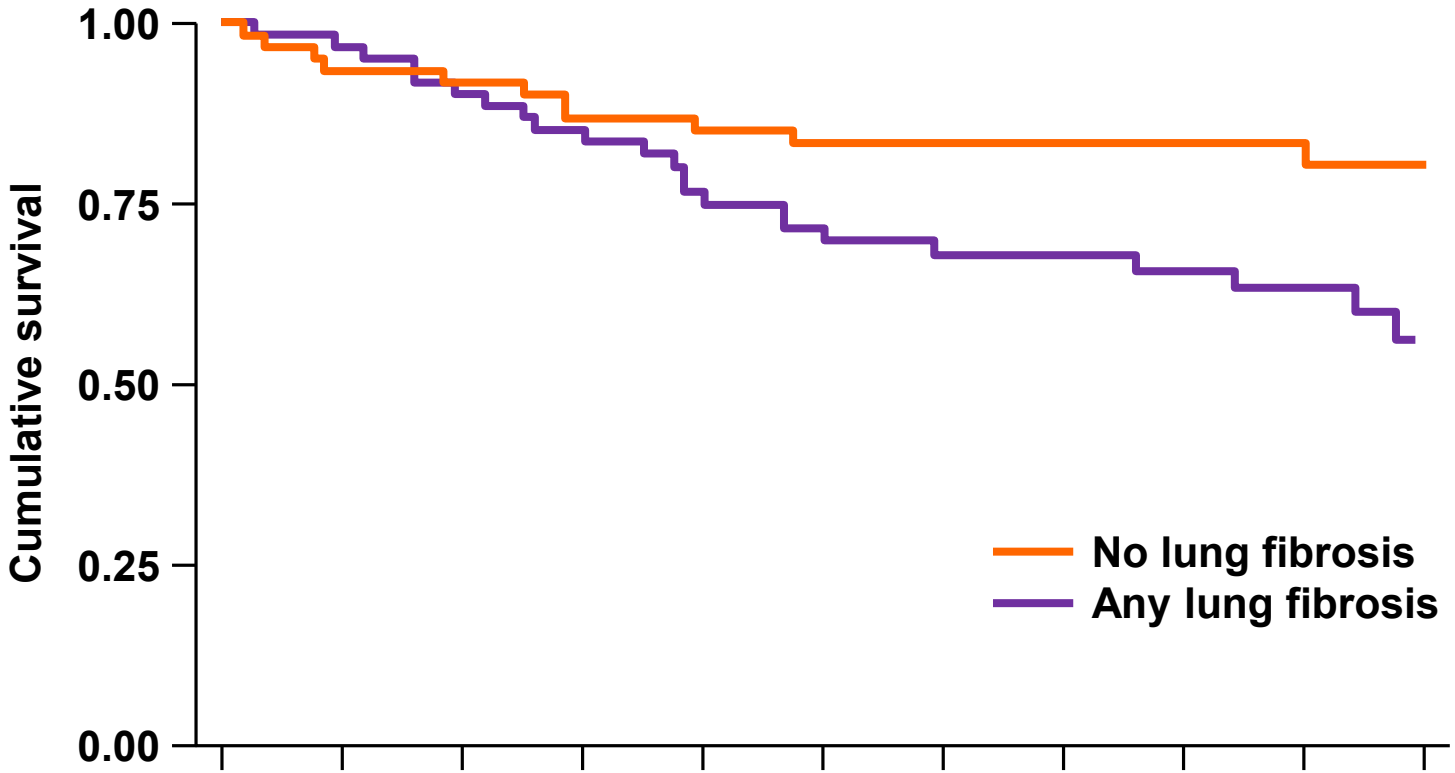
Pace of FVC Decline and Early Mortality in SSc-ILD



Reprinted from Guler SA, et al. *Ann Am Thorac Soc*. 2018;15:1427-1433.

The Presence of ILD Is Associated With Mortality

Nationwide Norwegian SSc Cohort

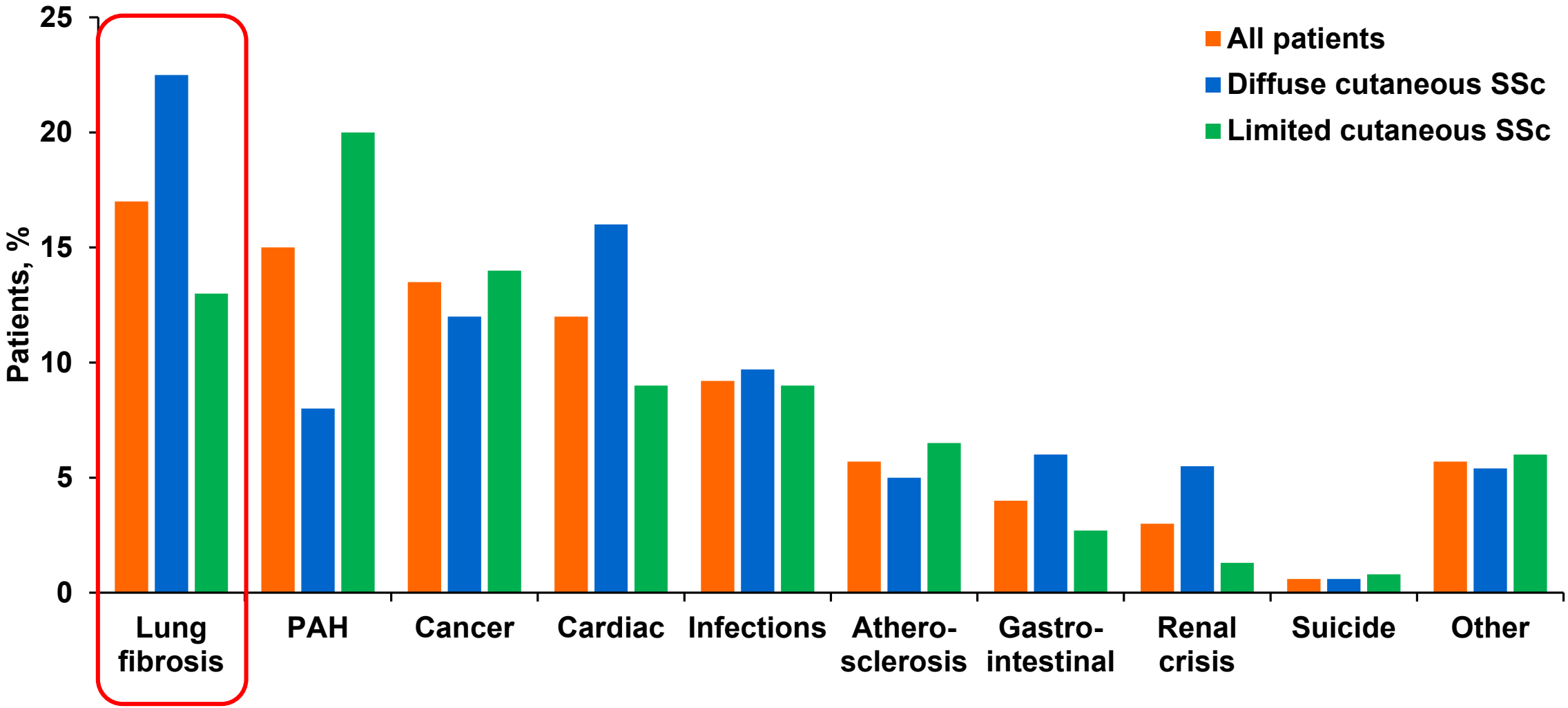


At risk, n						
No lung fibrosis	61	55	50	45	35	20
Any lung fibrosis	61	55	45	36	29	14

Adapted from Hoffmann-Vold AM, et al. *Am J Respir Crit Care Med*. 2019 Jul 16. doi: 10.1164/rccm.201903-0486OC. [Epub ahead of print]

Causes of Death in Patients With SSc

EUSTAR Cohort (N=11,193)



PAH=pulmonary arterial hypertension.

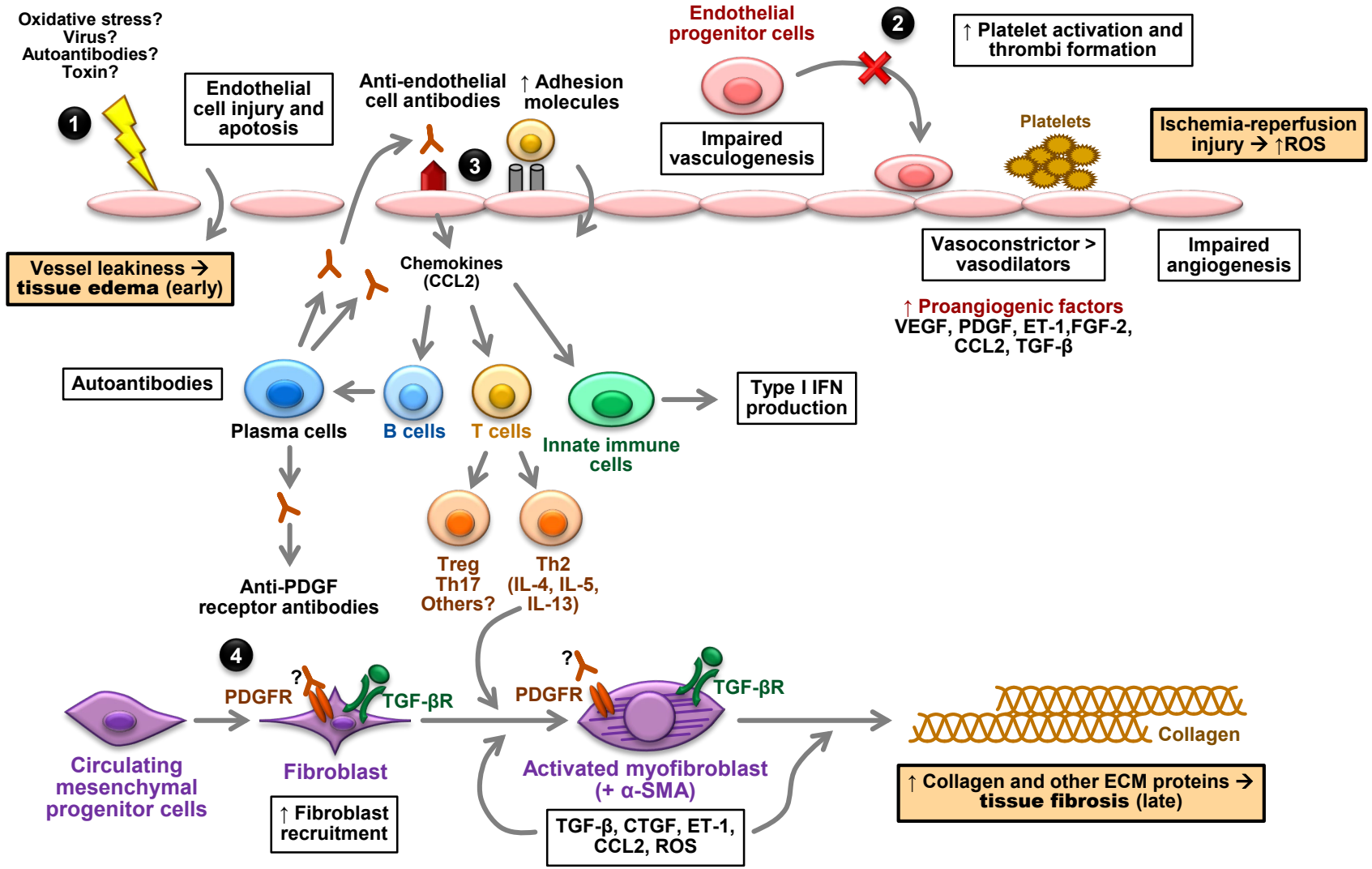
Reprinted from Elhai M, et al. *Ann Rheum Dis*. 2017;76:1897-1905.

A Current View of SSc Pathogenesis: Key Cellular and Molecular Targets

Vascular injury
- Damage
- Defective repair (vasculogenesis)

Immunity
- Adaptive immunity
- Autoantibodies
- Innate immunity

Fibrosis



Adapted from Katsumoto TR, et al. *Annu Rev Pathol*.2011;6:509-537.

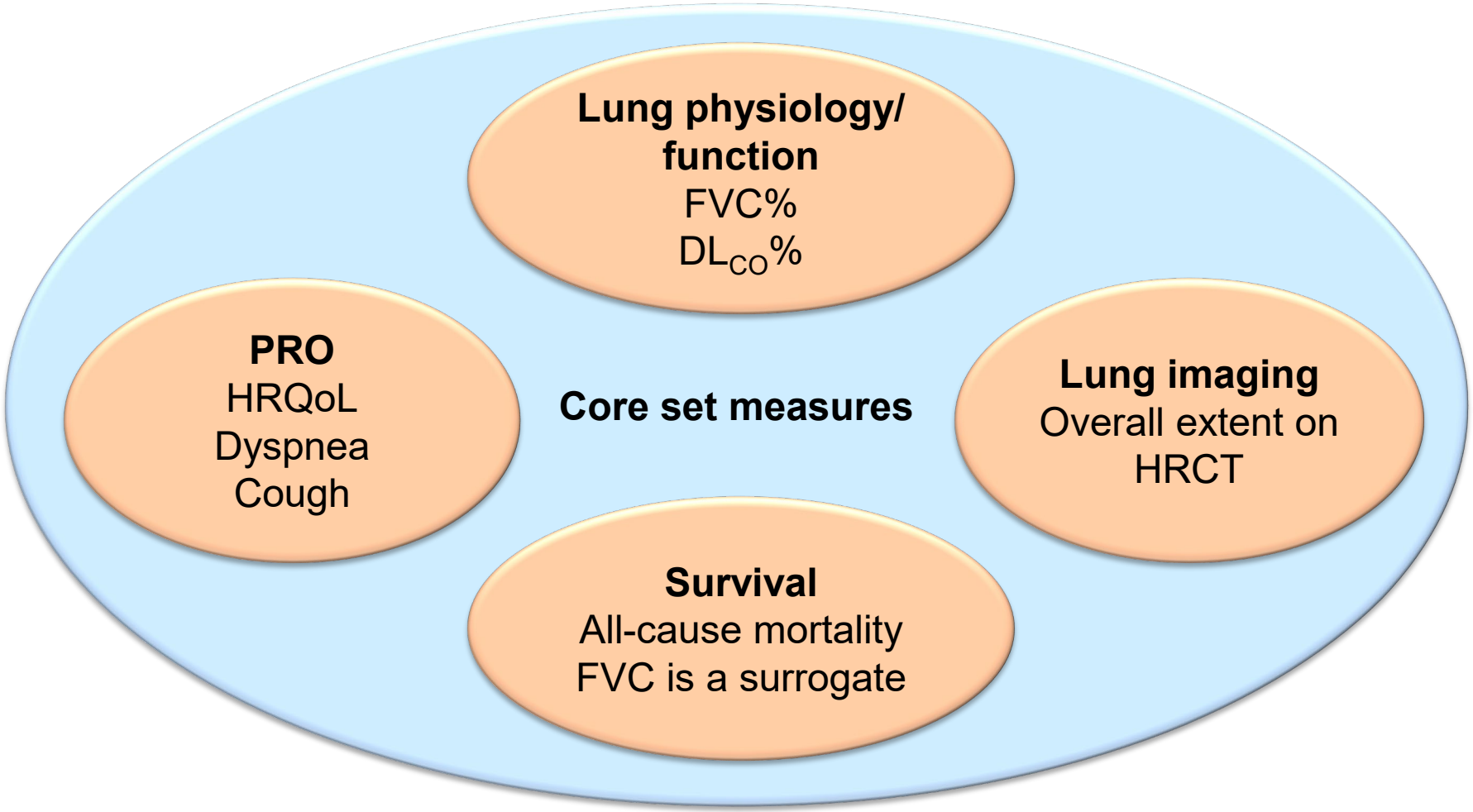
IPF and SSc-ILD Share Pathophysiologic Features but Differ Clinically

	IPF	SSc-ILD
Demographics	Males >70 yr	Females 45-55 yr
Pathology	UIP	NSIP >> UIP
Acute exacerbations	++++	+
Progressivity	Variable	Variable
Pace of decline in FVC	++++	++
Median survival	3-5 yr	5-8 yr

NSIP=non-specific interstitial pneumonia; UIP=usual interstitial pneumonia.

Wells AU, Denton CP. *Nat Rev Rheumatol*. 2014;10:728-739.

OMERACT Criteria for Outcome Assessment in CTD-ILD



CTD-ILD=connective tissue disease-associated interstitial lung disease; DL_{CO}=diffusion capacity of the lung for carbon monoxide; HRQoL=health-related quality of life; PRO=patient-reported outcomes; OMERACT=Outcome Measures in Rheumatoid Arthritis Clinical Trials.

Khanna D, et al. *J Rheumatol*. 2015;42(11):2168-2171.

Forced Vital Capacity

- Amount of air forcibly exhaled after maximum inhalation
- Reproducible, real time quality assurance via flow-volume loop
- Measure of lung elasticity
- Frequently expressed as % predicted to adjust for age, gender, ethnicity, and height
- Healthy individuals lose ~25 mL per year after age 25-30

Assessing Dyspnea in SSc

- Factors affecting dyspnea
  - Musculoskeletal involvement
  - Skeletal muscle perfusion
  - Fatigue/chronic catabolic disorder
  - Left ventricular diastolic disease
  - Pulmonary vascular involvement
  - Sedentary/deconditioned
- Dyspnea PRO for SSc-ILD are lacking

PRO=patient-reported outcomes.

Khanna D, et al. *J Rheumatol*. 2015;42(11):2168-2171.
Buch MH, et al. *Ann Rheum Dis*. 2007;66:169-173.

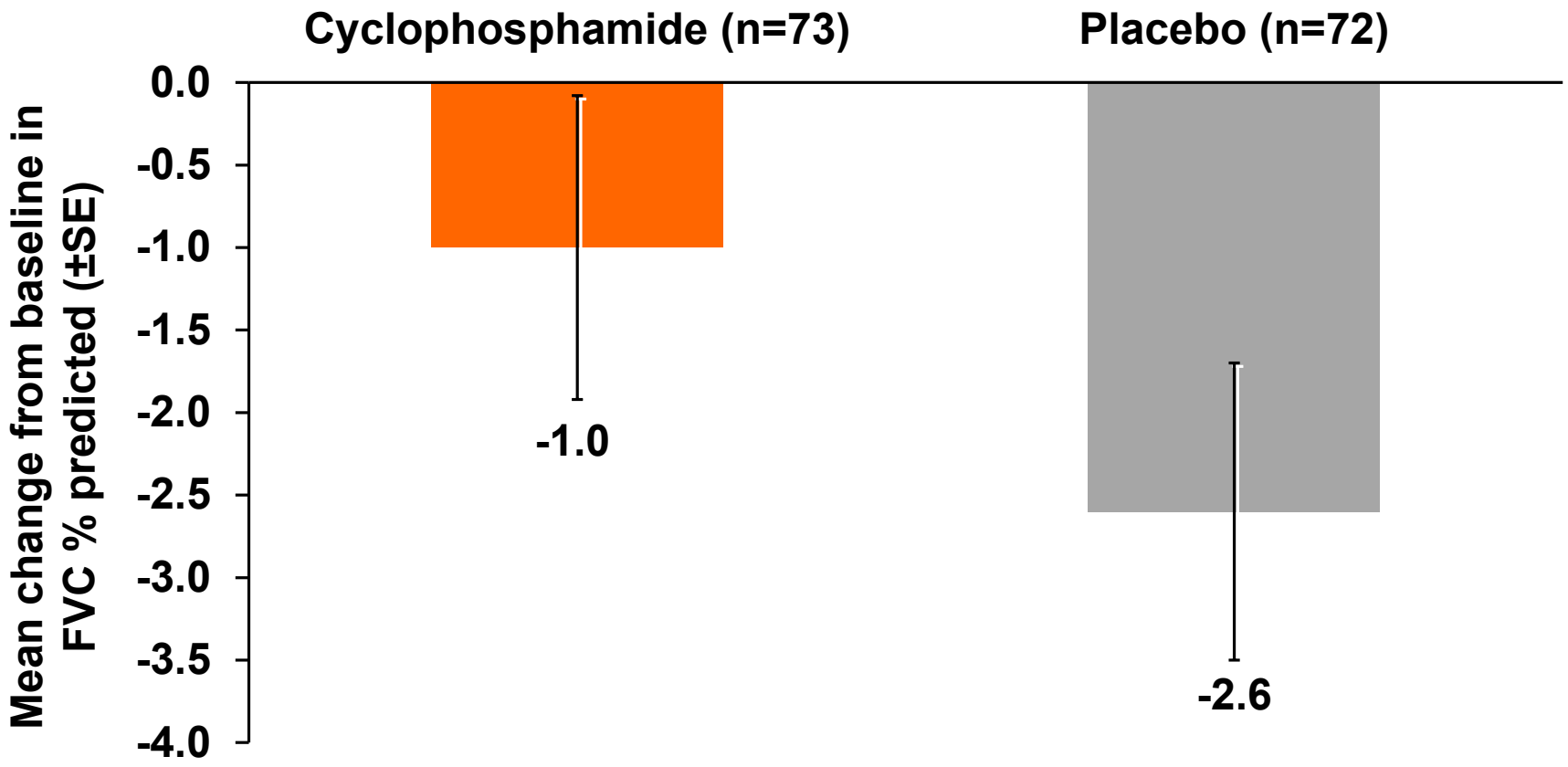
Current Management of SSc-ILD

- No approved therapies
- Prevention or slowing of worsening is therapeutic goal
- Regeneration of alveolar tissue not biologically plausible
- Immunosuppressive therapies used in clinical practice
  - Oral cyclophosphamide (1-2 mg/kg/day)
  - IV cyclophosphamide (750 mg/m^2 BSA monthly × 6)
  - Oral mycophenolate mofetil (1500 mg bid)
  - IV or SC rituximab

bid=twice daily; BSA=body surface area; IV=intravenous; SC=sulocutaneous

Change From Baseline in FVC % Predicted at Month 12 (Primary Endpoint)

Scleroderma Lung Study I



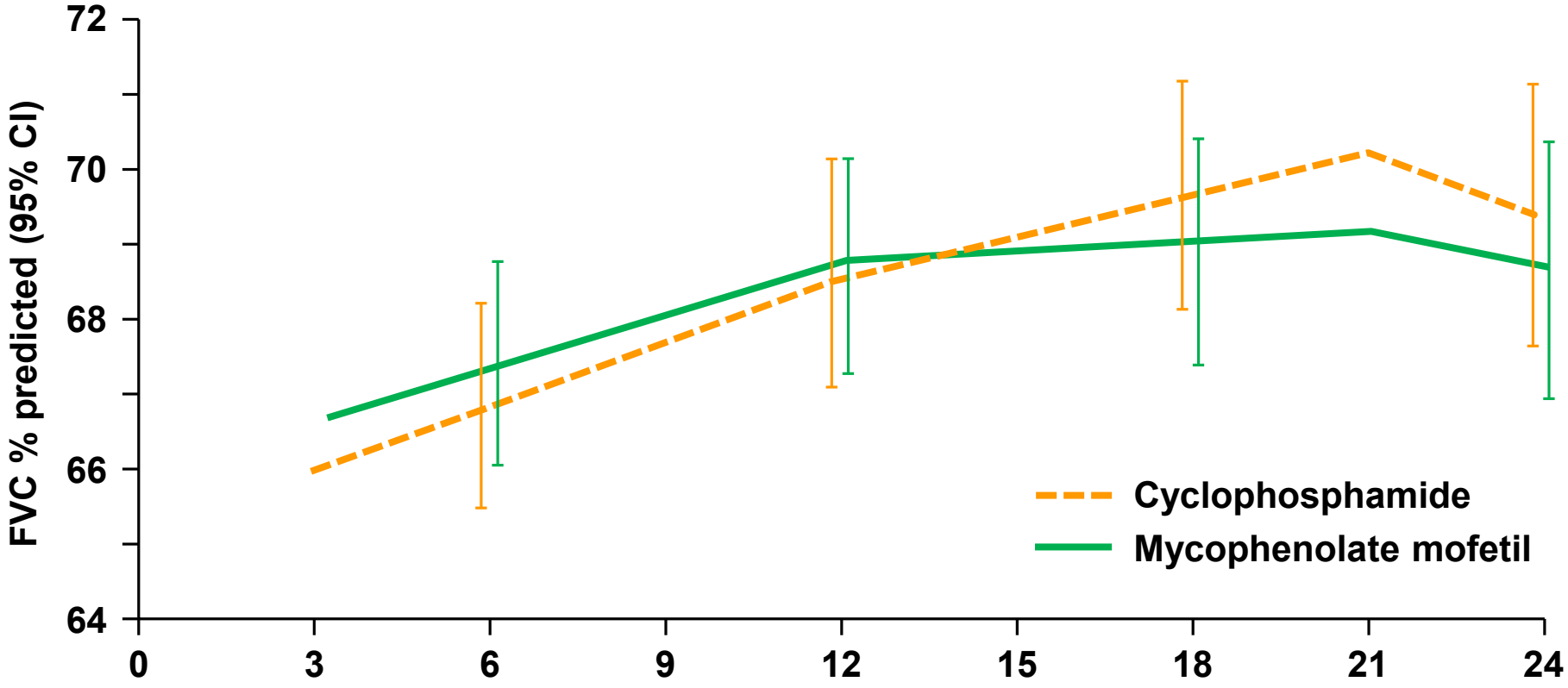
SE=standard error

p<0.05 for cyclophosphamide vs placebo.

Tashkin DP, et al. *N Engl J Med*. 2006;354;2655-2666.

FVC % Predicted Over 24 Months

Scleroderma Lung Study II



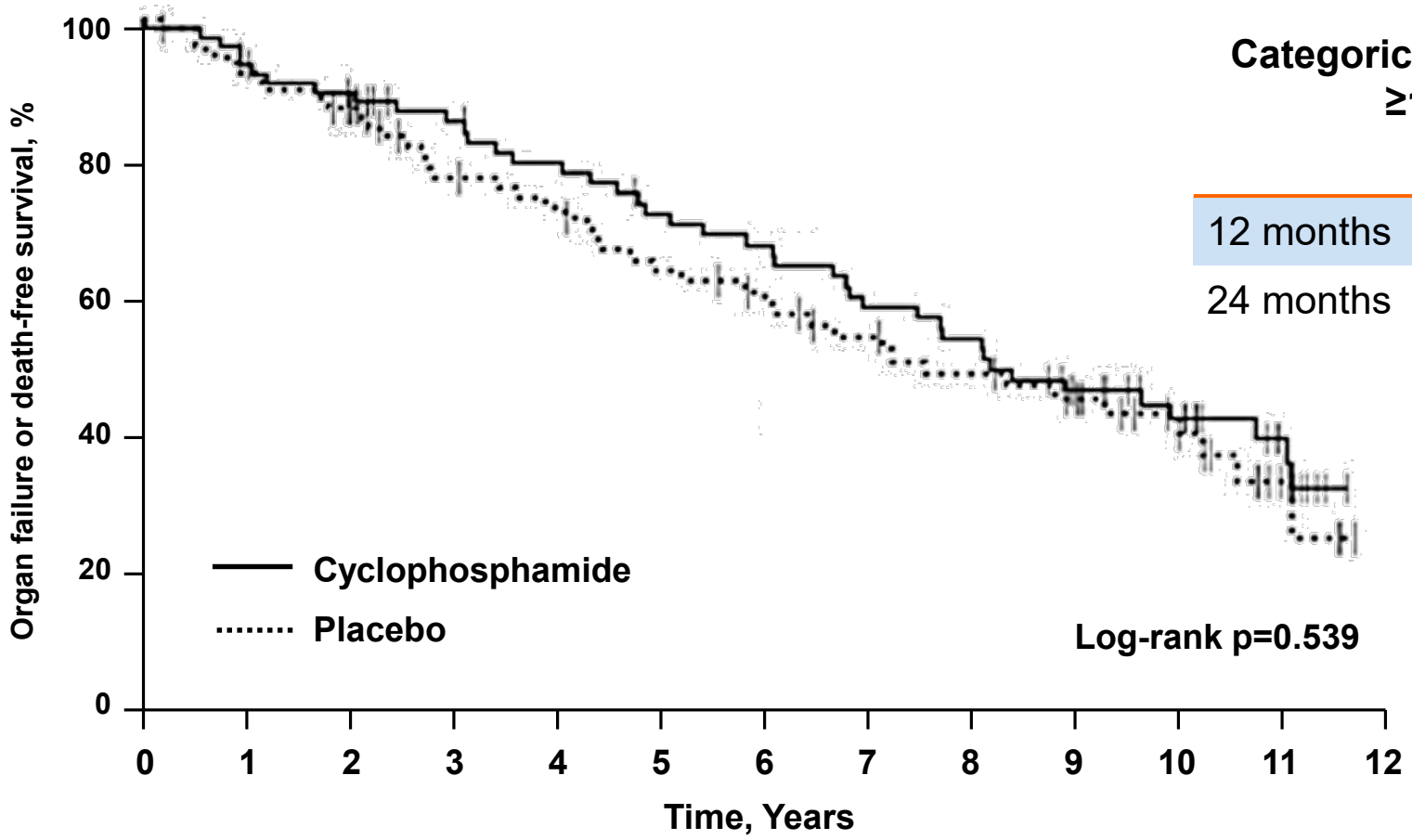
Patients, n									
Cyclophosphamide	72	62	56	51	51	44	46	40	51
Mycophenolate mofetil	69	64	60	54	59	51	49	47	53

CI=confidence interval.

Reprinted from Tashkin DP, et al. *Lancet Respir Med*. 2017;4:708-719, with permission from Elsevier.

Time to Death or Organ Failure From Randomization

Scleroderma Lung Study I



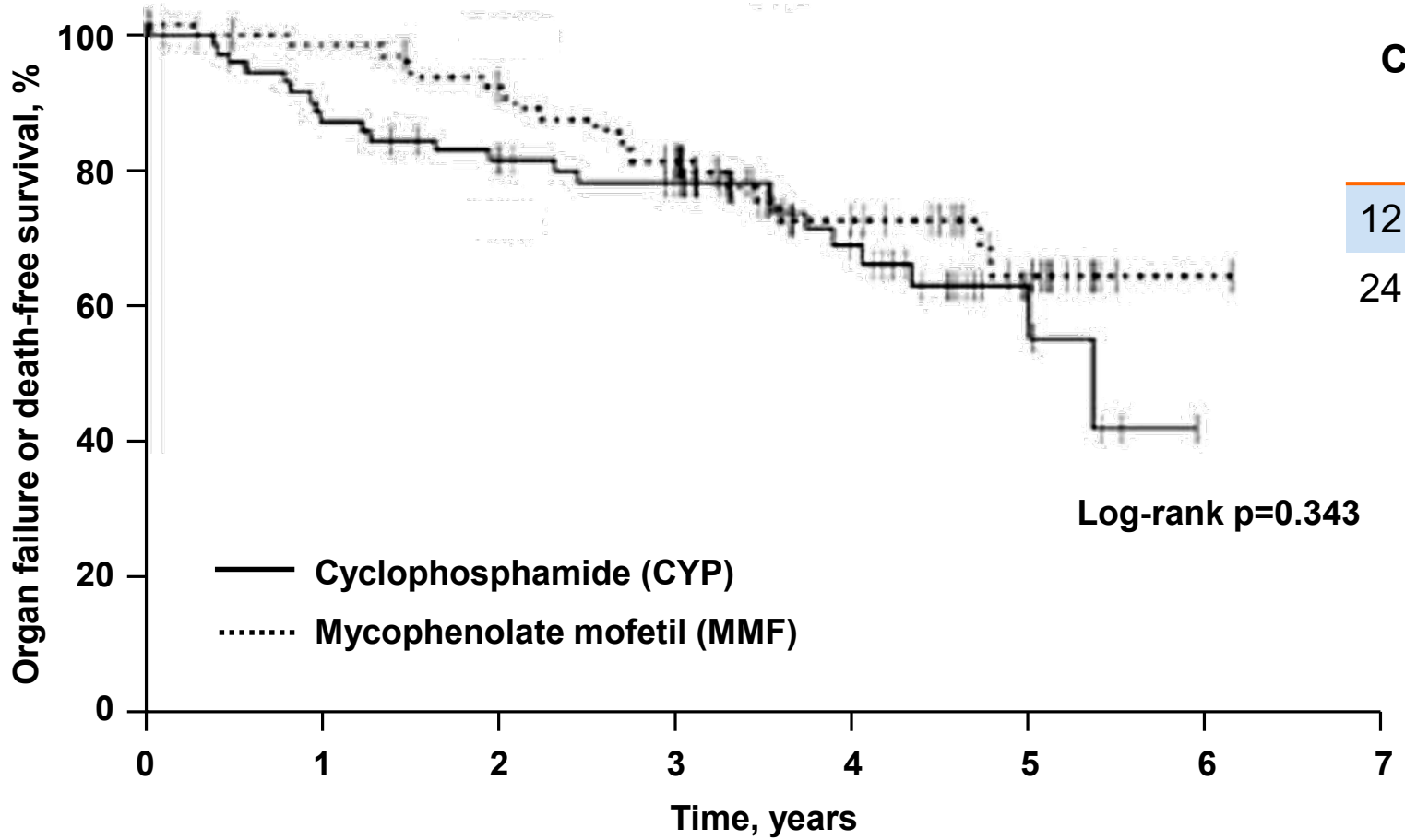
Categorical decline in FVC % predicted ≥10% predicts survival

	HR (95% CI)	p value
12 months	1.79 (0.98, 3.30)	NS
24 months	2.47 (1.27, 4.80)	<0.01

Reprinted from Volkmann ER, et al. *Ann Rheum Dis*. 2019;78:122-130.

Time to Death or Organ Failure From Randomization

Scleroderma Lung Study II



CYP	73	60	53	47	27	8	0
MMF	69	64	58	49	26	16	1	0

Categorical decline in FVC % predicted ≥10% predicts survival

	HR (95% CI)	p value
12 months	8.22 (2.91, 23.22)	<0.0001
24 months	4.02 (1.15, 14.02)	<0.05

Reprinted from Volkmann ER, et al. *Ann Rheum Dis*. 2019;78:122-130.

SSc-ILD Current Status

- High disease burden
- Lung fibrosis is leading cause of death
- Prevention or slowing of worsening is the therapeutic goal
- No approved therapies
- Unapproved immunosuppressive therapies may provide short-term benefit in selected subsets
- Effective antifibrotic therapy is lacking

Clinical Development Rationale for SSc-ILD

Susanne Stowasser, MD

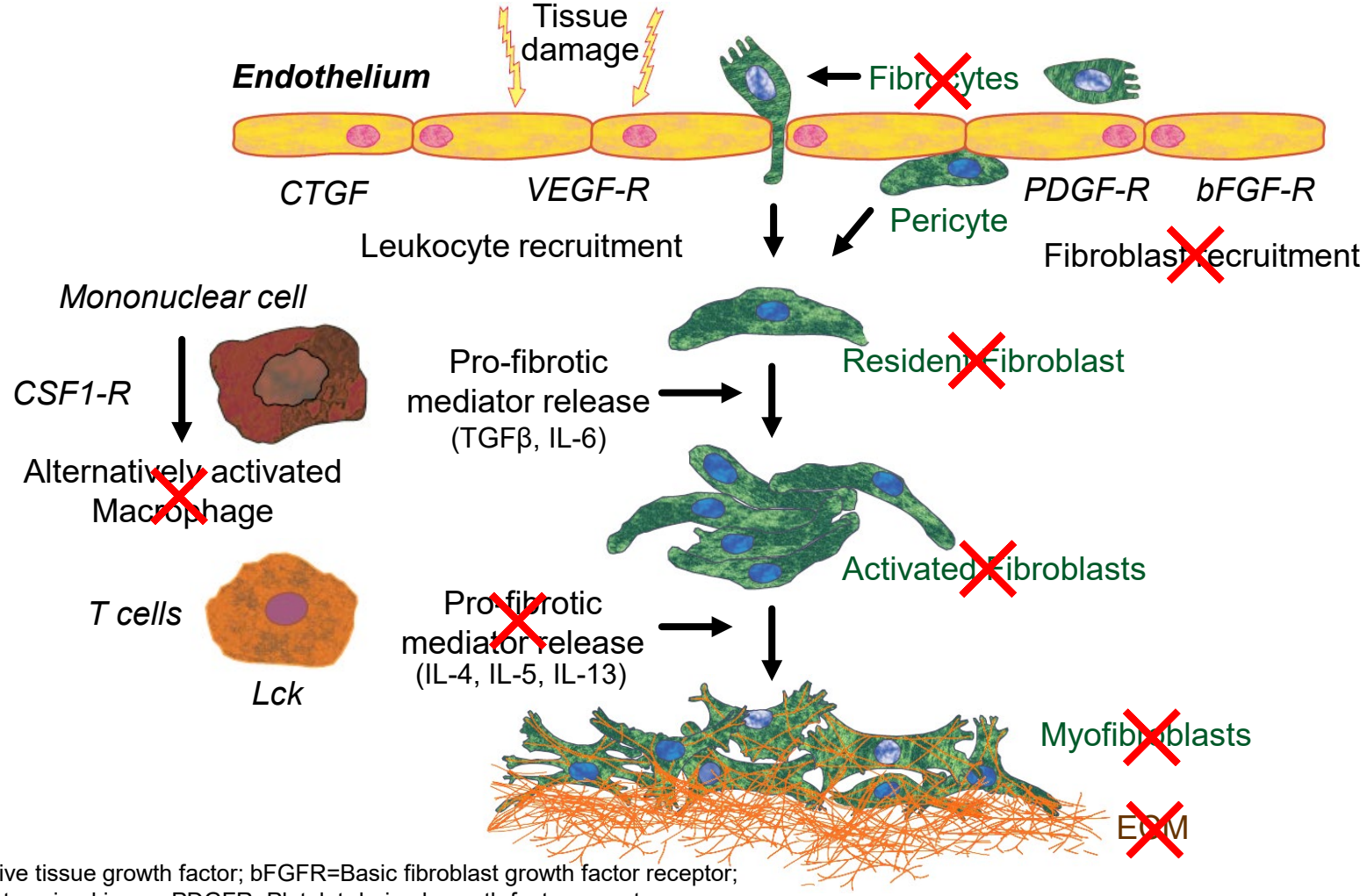
Associate Head Medicine, Therapeutic Area Respiratory Diseases
Boehringer Ingelheim

Rationale for Clinical Development of Nintedanib in SSc-ILD

- High unmet need in SSc-ILD
- Established benefit in IPF
- Similar pathogenesis across fibrosing ILDs with final common pathways of lung fibrosis
- Demonstrated anti-fibrotic activity in different *in vitro* models with human fibroblasts and animal models

Nintedanib Attenuates Signaling Pathways Implicated in Fibrosis

- **Nintedanib** is a small-molecule **tyrosine kinase** inhibitor with a distinct inhibitory spectrum



CSF1R=Colony-stimulating factor 1 receptor; CTGF=Connective tissue growth factor; bFGFR=Basic fibroblast growth factor receptor; IL-4, -5, -6, -13= Interleukin; Lck=Lymphocyte-specific protein tyrosine kinase; PDGFR=Platelet derived growth factor receptor; TGFb=Transforming growth factor beta; VEGFR=Vascular endothelial growth factor receptor.

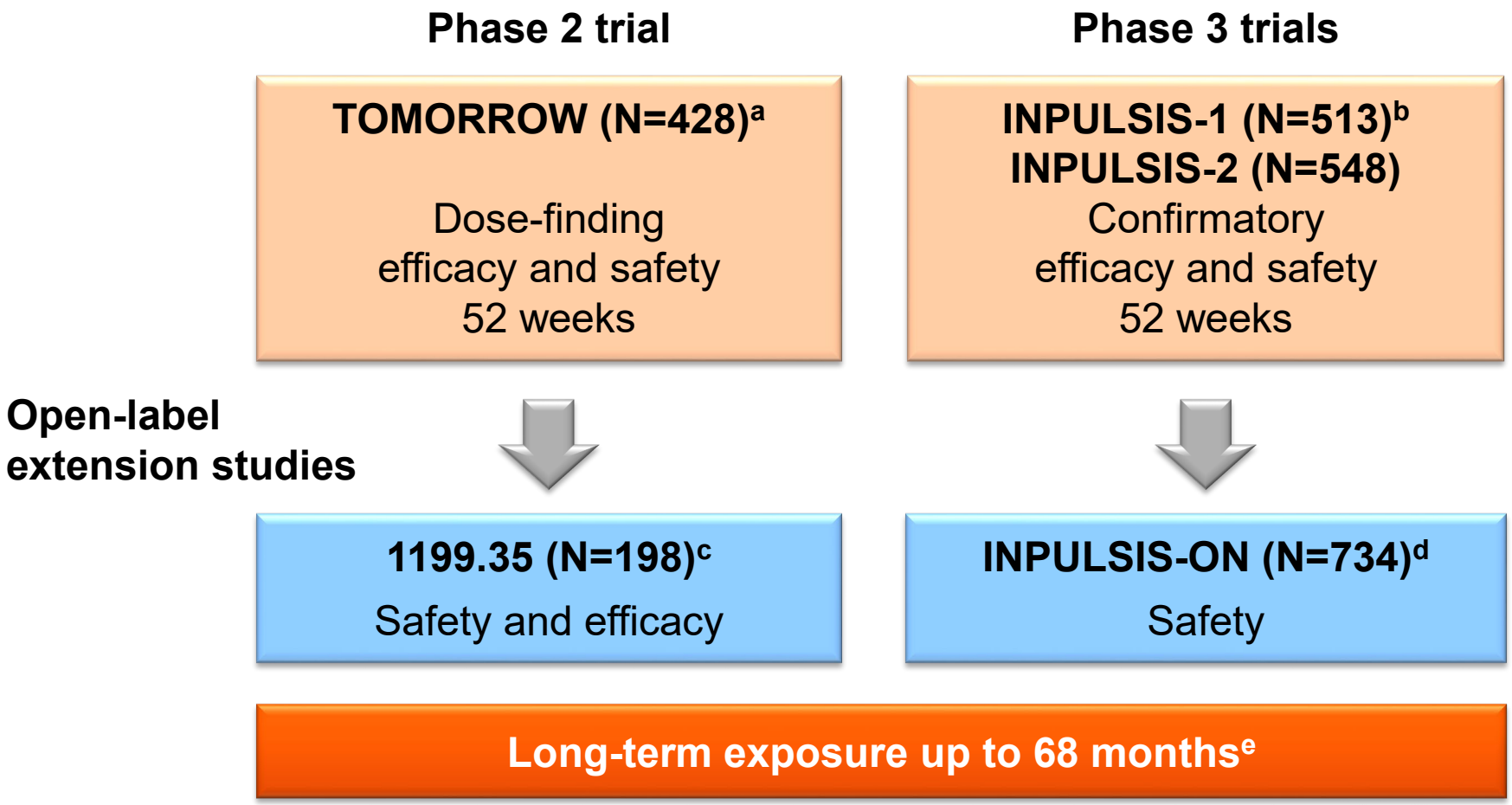
Reprinted from Wollin L, et al. *Journal of Scleroderma and Related Disorders*. 2019. [e-pub ahead of print]

Clinical Development of Nintedanib in Fibrosing Interstitial Lung Diseases

Fibrosing Interstitial Lung Diseases

Idiopathic Pulmonary Fibrosis (IPF)	Systemic Sclerosis-assoc. Interstitial Lung Disease (SSc-ILD)	Progressive Fibrosing ILDs
INPULSIS Approved	**SENSCIS** Under review	**INBUILD** Ongoing

The Nintedanib Program in IPF Is the Foundation for Development in SSc-ILD



[a] Richeldi L, et al. *N Engl J Med*. 2011;365(12):1079-1087; [b] Richeldi L, et al. *N Engl J Med*. 2014;370(22):2071-2082;
[c] Richeldi L, et al. *Thorax*. 2018;73:581-583; [d] Crestani B, et al. *Lancet Resp Med*. 2019;7(1):60-68;
[e] For patients treated with nintedanib in INPULSIS and INPULSIS-ON.

Key Commonalities Across IPF and SSc-ILD Phase 3 Studies

- Dosing regimen
  - Nintedanib 150 mg bid
  - Dose reduction or treatment interruption to manage AEs
- Treatment period: 52 weeks to assess benefit-risk
- Primary endpoint: annual rate of decline in FVC

AE=adverse event.

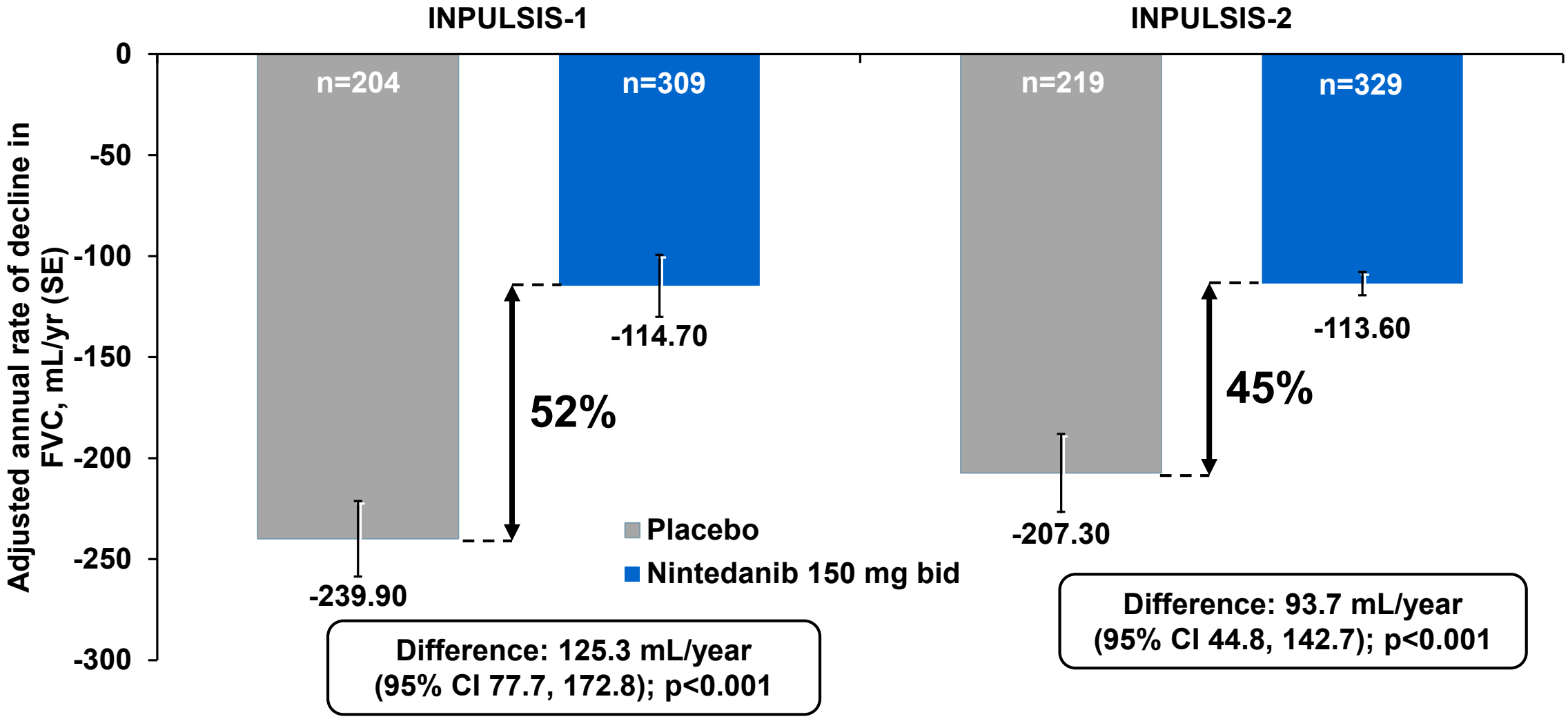
Rationale for FVC as Primary Endpoint in SSc-ILD

- FVC reflects the underlying pathophysiology of the scarring process
- In IPF, FVC is accepted surrogate for clinically meaningful benefit[a]
- In SSc-ILD, FVC decline is associated with mortality[b,c,d,e]
- FVC is the primary outcome in SSc trials that assess ILD progression[f]
- OMERACT CTD-ILD working group proposes FVC as the preferred outcome measure in trials of 1-year duration[g,h]

[a] Karimi-Shah BA, et al. *N Engl J Med*. 2015;372:1189-1191; [b] Goh NS, et al. *Arthritis Rheumatol*. 2017;69:1670-1678; [c] Assassi S, et al. Arthritis Res Ther 2010;12 R166; [d] Volkmann ER, et al. *Ann Rheum Dis*. 2019;78:122-130; [e] Hoffmann-Vold AM, et al. *Am J Respir Crit Care Med*. 2019 Jul 16. doi: 10.1164/rccm.201903-0486OC. [Epub ahead of print]; [f] Caron M, et al. *Eur Respir Rev*. 2018;27:170102; [g] Khanna D, et al. *J Rheumatol*. 2015;42;2168-2171; [h] Saketkoo LA, et al. *J Rheumatol*. 2014;41:4.

Annual Rate of Decline in FVC (Primary Endpoint)

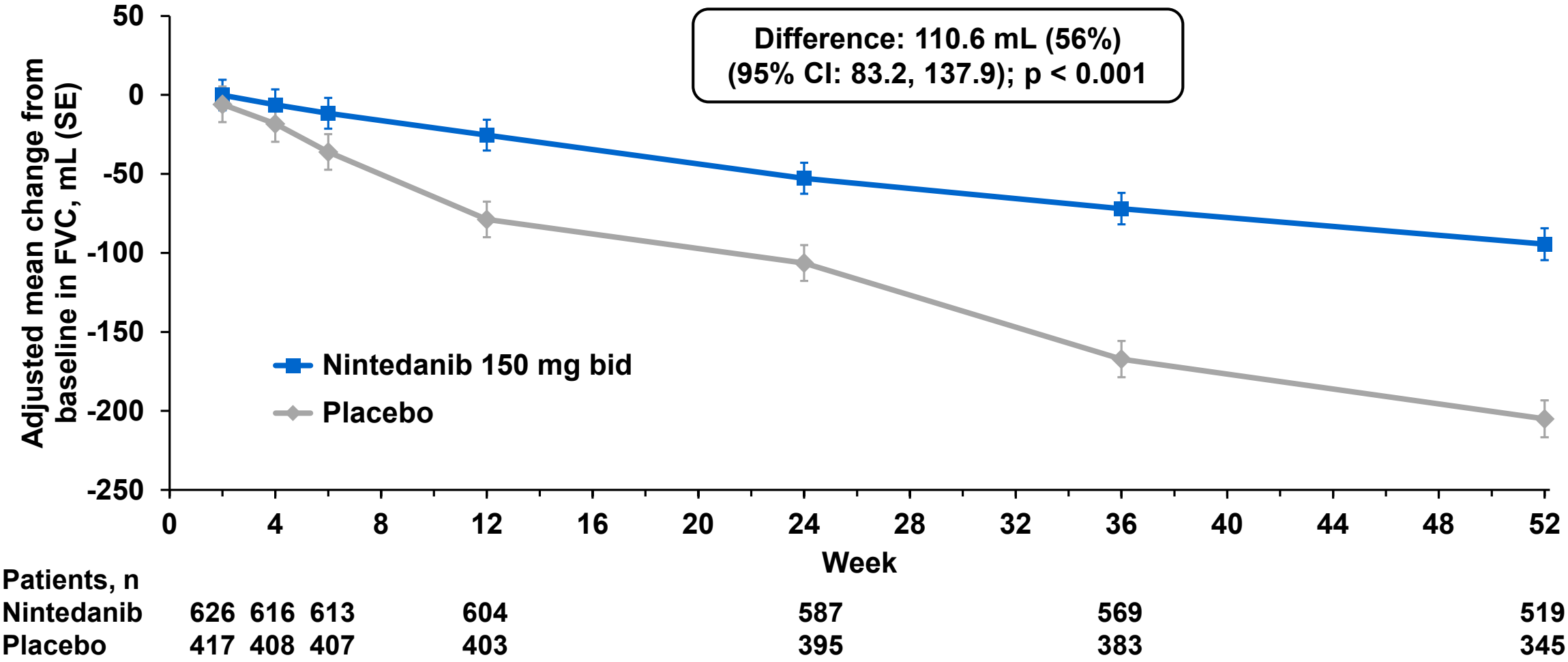
INPULSIS Studies in IPF



Reprinted from Richeldi L, et al. *N Engl J Med.* 2014;370(22):2071-2078.

Adjusted Change From Baseline in FVC

INPULSIS Studies in IPF (Pooled)



[a] Adjusted mean difference vs placebo at Week 52.

Reprinted from Supplement to Richeldi L, et al. *N Engl J Med*. 2014;370(22):2071-2082.

Building on the IPF Experience
SENSCIS Phase 3 Study in SSc-ILD

- Nintedanib addresses the same underlying pathophysiology in IPF and SSc-ILD
- SENSCIS is the largest randomized placebo-controlled trial in SSc-ILD
  - Includes a broad patient population generalizable to clinical practice
- Same dosing regimen with dose reduction/interruption to manage AEs
- Same primary endpoint: annual rate of decline in FVC over 52 weeks

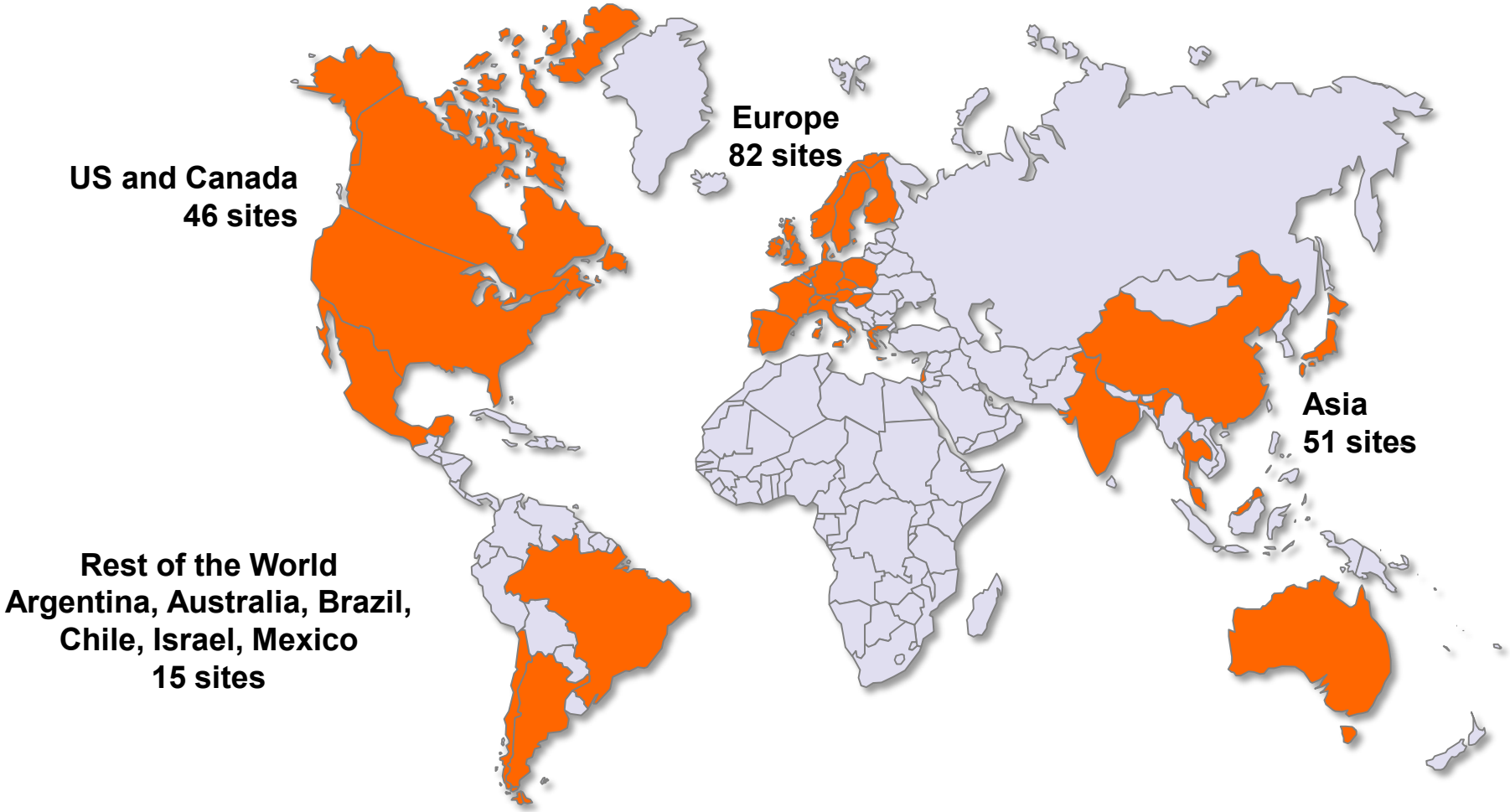
Efficacy of Nintedanib for SSc-ILD

Emmanuelle Clerisme-Beaty, MD

Senior Clinical Program Leader
Boehringer Ingelheim

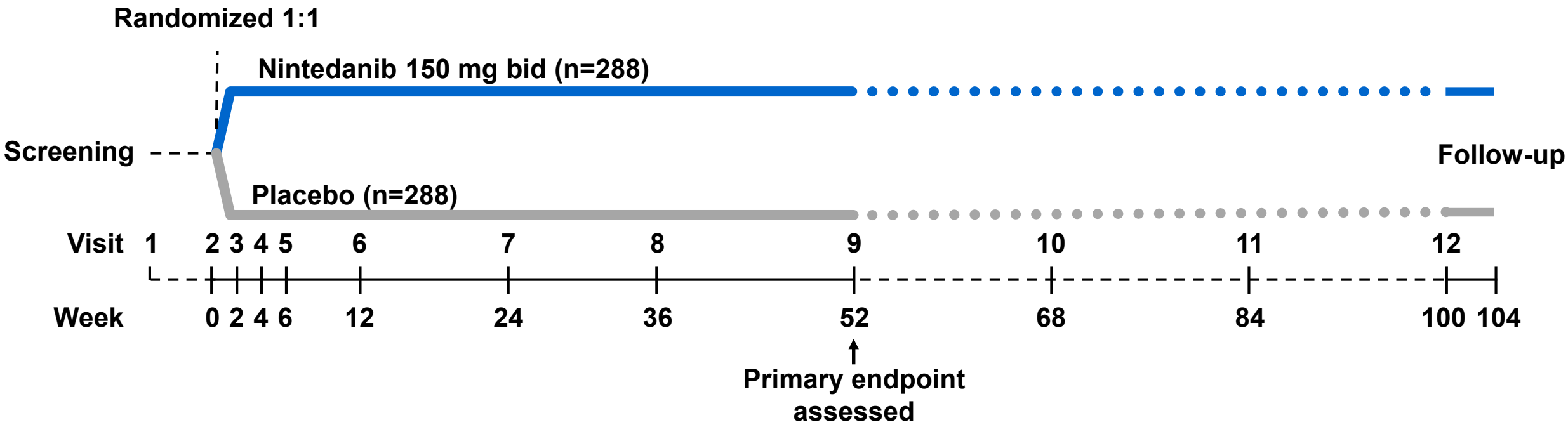
Participating Countries (194 Sites)

SENSCIS



Europe: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, The Netherlands, Norway, Poland, Portugal, Spain, Sweden, Switzerland, United Kingdom.
Asia: China, India, Japan, Malaysia, Thailand.
Rest of the world: Argentina, Australia, Brazil, Chile, Israel, Mexico.

Trial Design
SENSCIS

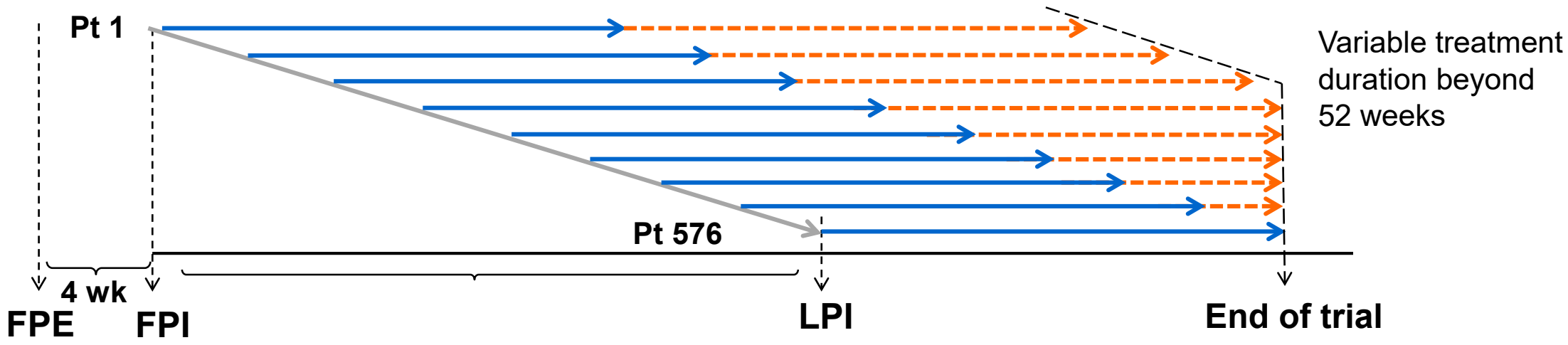


- Stratification by anti-topoisomerase antibody (ATA) status (positive or negative)
- Primary assessment over 52 weeks
- Patients remained on blinded treatment up to 100 weeks *or* until the last patient had reached Week 52

bid=twice daily.

Treatment Duration Beyond 52 Weeks Varied

SENSCIS



52-week treatment period for primary endpoint

Treatment period beyond 52 weeks but ≤100 weeks

- 146 patients (73 per arm) were able to complete 100-week treatment period

FPE=first patients enrolled; FPI=first patient in; LPI=last patient in.

Key Inclusion Criteria
SENSCIS

- Age ≥18 years
- SSc (based on 2013 ACR/EULAR criteria[a]) 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 reviewer)
- FVC ≥40% predicted
- DL_{co} 30% to 89% predicted

ACR/EULAR=American College of Rheumatology/ European League Against Rheumatism; DL_{CO}=diffusing capacity of the lung for carbon monoxide.

[a] van den Hoogen F, et al. *Arthritis Rheum*. 2013;65:2737-2747.

Key Exclusion Criteria
SENSCIS

- ALT or AST or bilirubin >1.5×ULN
- Bleeding risk (eg, requiring full-dose therapeutic anticoagulation or high-dose antiplatelet therapy)
- Myocardial infarction or unstable angina within 6 months of screening
- History of thrombotic event within 12 months of screening
- More than 3 digital ulcers or history of severe digital necrosis requiring hospitalization
- Significant pulmonary hypertension[a]
- History of scleroderma renal crisis
- FEV_1/FVC <70%

ALT=alanine transaminase; AST=aspartate transaminase; FEV_1=forced expiratory volume in 1 second; ULN=upper limit of normal.
[a] 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.

Main Concomitant Medications at Baseline

- Permitted
  - Prednisone (≤10 mg/day or equivalent)
  - Stable therapy with mycophenolate or methotrexate for ≥6 months prior to randomization
- Excluded
  - Cyclophosphamide
  - Azathioprine
  - Rituximab
  - Cyclosporine A

Primary and Key Secondary Endpoints
SENSCIS

- 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

mRSS=modified Rodnan skin score (scores ranges from 0-51);
SGRQ=St George's Respiratory Questionnaire (scores ranges from 0-100).

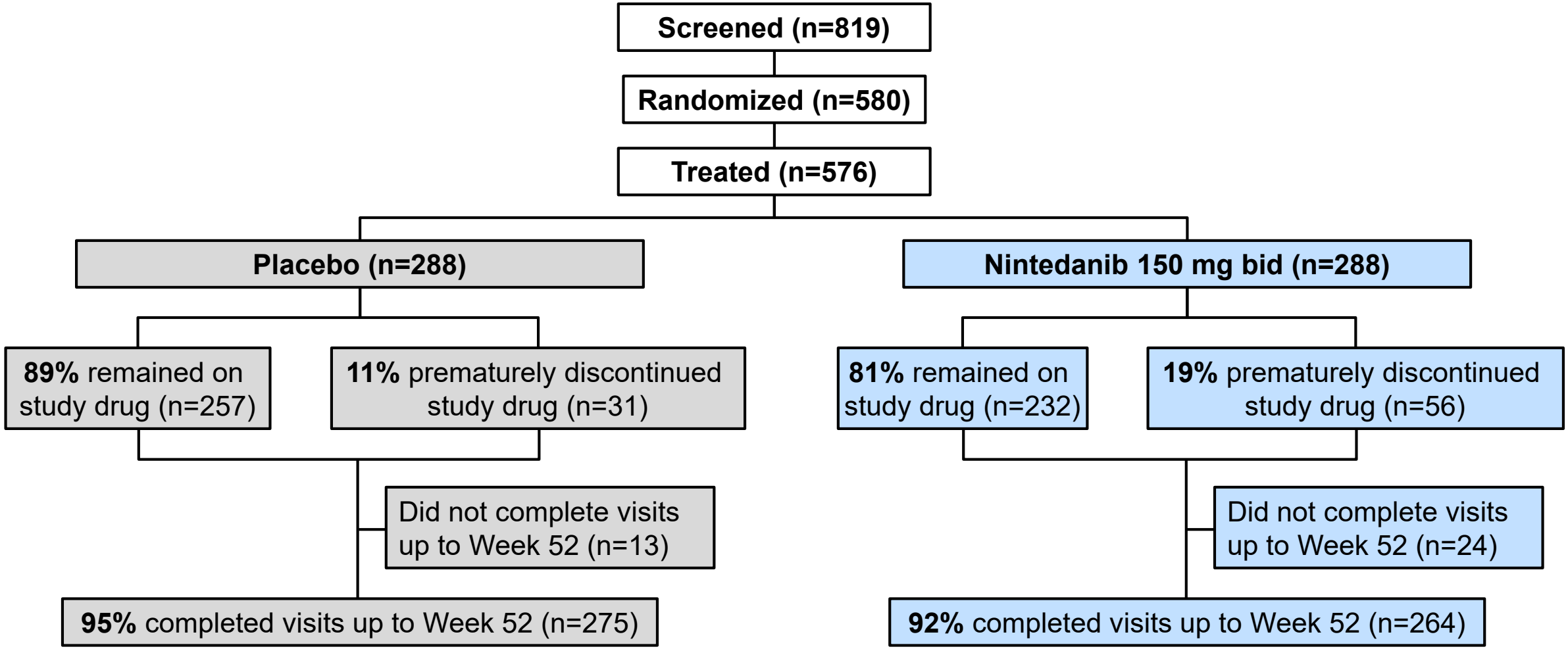
Analysis of Primary Endpoint
SENSCIS

- Hierarchical testing procedure used to protect type I error rate
- Primary endpoint
  - On all measurements taken within first 52 weeks, including those from patients who discontinued study drug or who did not have an FVC measurement at Week 52
  - Slope of FVC decline (mL/year) calculated for every patient and the average compared between treatment groups
  - A random coefficient regression model used with ATA status, age, height, sex, and baseline FVC (mL) as covariates

ATA=anti-topoisomerase antibody.

Disposition of Patients Over 52 Weeks

SENSCIS



Handling of Missing FVC Measurements at Week 52

- Prespecified analyses
  - 78 of 576 treated patients did not provide FVC measurement at Week-52 time window (up to 373 days)
    - 28 of those 78 patients had values just after the window (median 9 days)
- Revised analyses include data from these 28 patients
  - 50 of 576 patients had a missing 52-week FVC value

Baseline Demographics
SENSCIS

	Patients, n (%)	
	Placebo n=288	Nintedanib n=288
Mean age, years (SD)	53.4 (12.6)	54.6 (11.8)
Female, n (%)	212 (73.6)	221 (76.7)
Mean weight, kg (SD)	70.0 (16.4)	69.4 (15.4)
Mean body mass index, kg/m^2 (SD)	25.8 (5.1)	25.9 (4.8)
Race, n (%)[a]		
White	186 (64.6)	201 (69.8)
Asian	81 (28.1)	62 (21.5)
Black/African American	16 (5.6)	20 (6.9)
American Indian/Alaska Native/ Native Hawaiian/other Pacific Islander	3 (1.0)	2 (0.7)

SD=standard deviation.
[a] Data from patients who selected one race. Four patients ticked two boxes.

Baseline Disease Characteristics
SENSCIS

	Placebo n=288	Nintedanib n=288
Type of SSc, n (%)		
Diffuse cutaneous	146 (50.7)	153 (53.1)
Limited cutaneous	142 (49.3)	135 (46.9)
mRSS, mean (SD)	10.9 (8.8)	11.3 (9.2)
Years since onset of first non-Raynaud symptom, median (minimum, maximum)	3.5 (0.4, 7.2)	3.4 (0.3, 7.1)
Anti-topoisomerase antibody positive, n (%)	177 (61.5)	173 (60.1)
Taking mycophenolate, n (%)	140 (48.6)	139 (48.3)
Taking corticosteroids, n (%)	135 (46.9)	152 (52.8)
Taking methotrexate, n (%)	15 (5.2)	23 (8.0)

Baseline Pulmonary Characteristics
SENSCIS

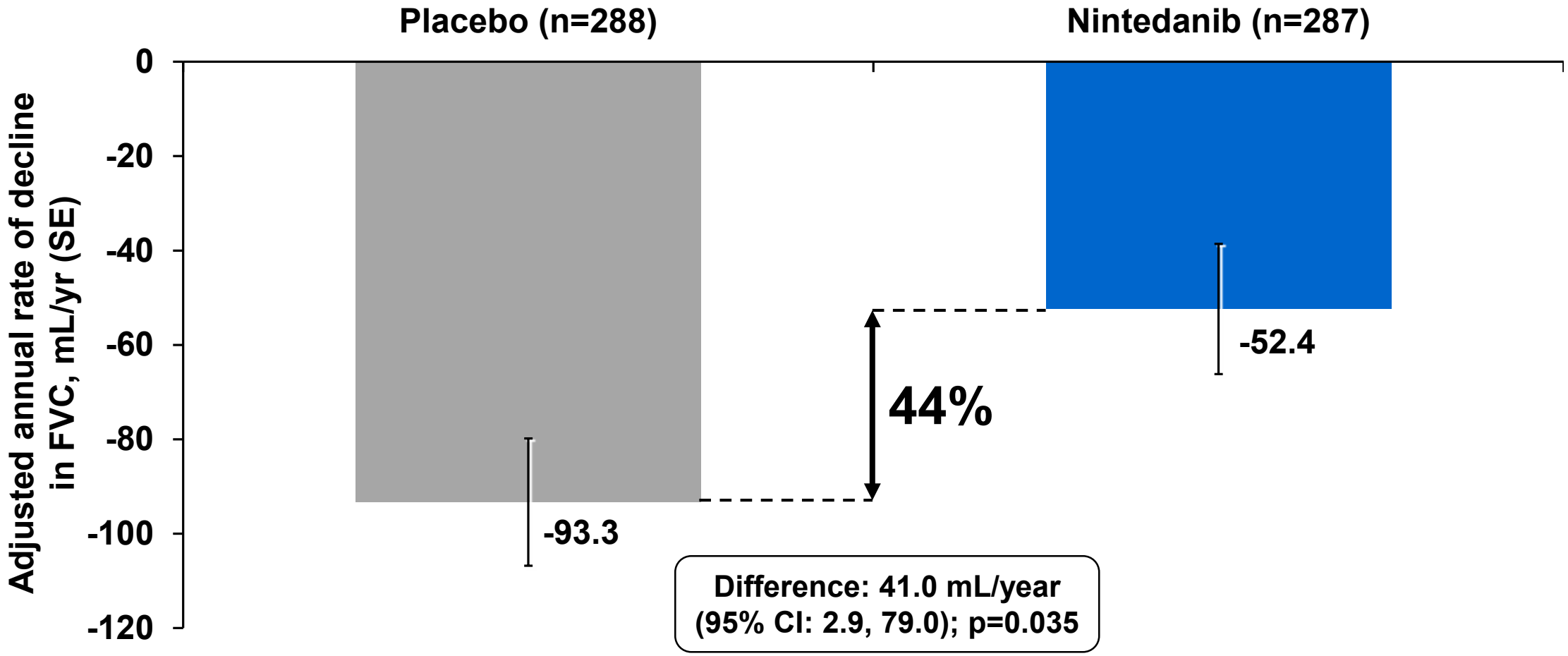
	Placebo n=288	Nintedanib n=288
Mean extent of fibrotic ILD on HRCT, (SD)[a]	35.2 (20.7)	36.8 (21.8)
HRCT features, n (%)		
Reticulation	272 (94.4)	266 (92.4)
Ground glass opacities	246 (85.4)	241 (83.7)
Honeycombing	45 (15.6)	44 (15.3)
Mean FVC, mL (SD)	2541 (816)	2459 (736)
Mean FVC, % predicted (SD)	72.7 (16.6)	72.4 (16.8)
Mean DL_{co}, % predicted (SD)[b]	53.2 (15.1)	52.9 (15.1)
Mean SpO_2, % (SD)	97.5 (2.5)	97.6 (1.9)

SpO_2=peripheral capillary oxygen saturation.
[a] Qualitative assessment by central review by expert radiologist.
[b] Corrected for hemoglobin.

Study Results

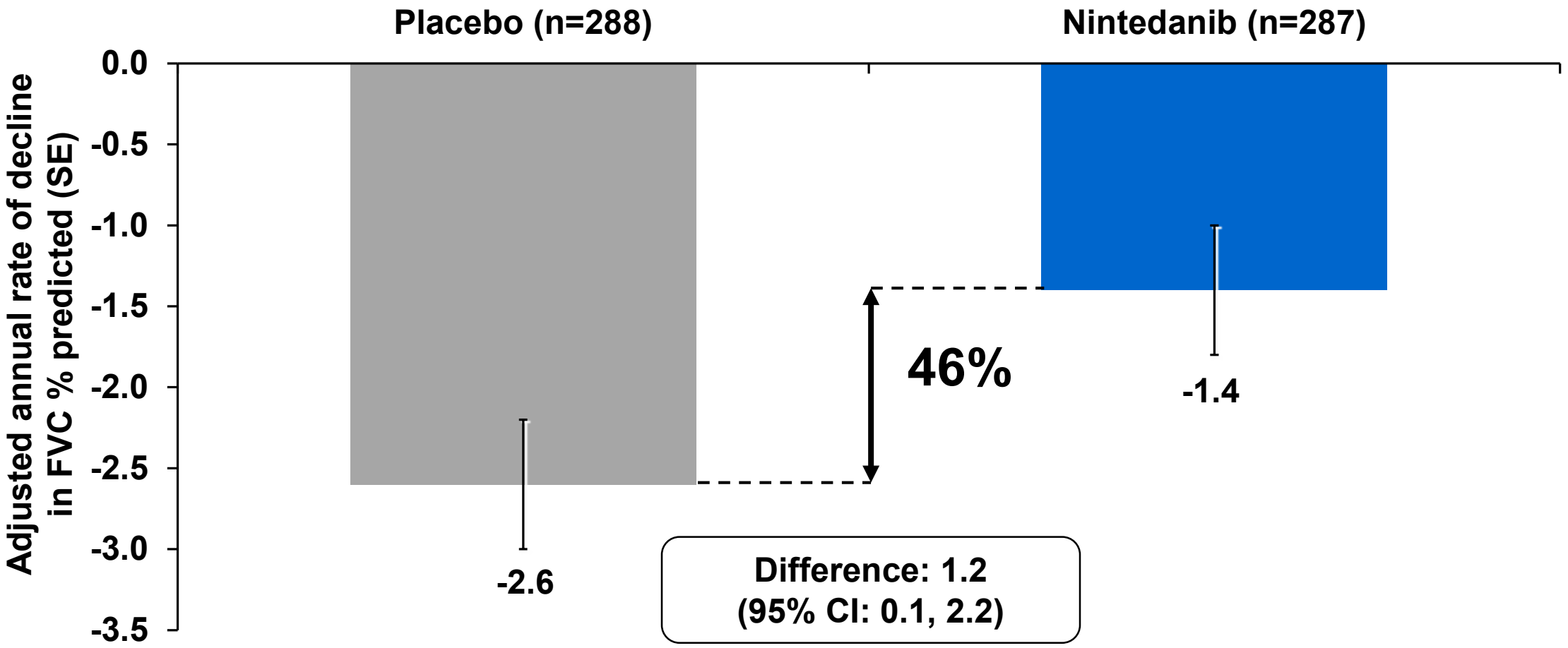
Primary Endpoint: Annual Rate of Decline in FVC (mL/yr) Over 52 Weeks

SENSCIS



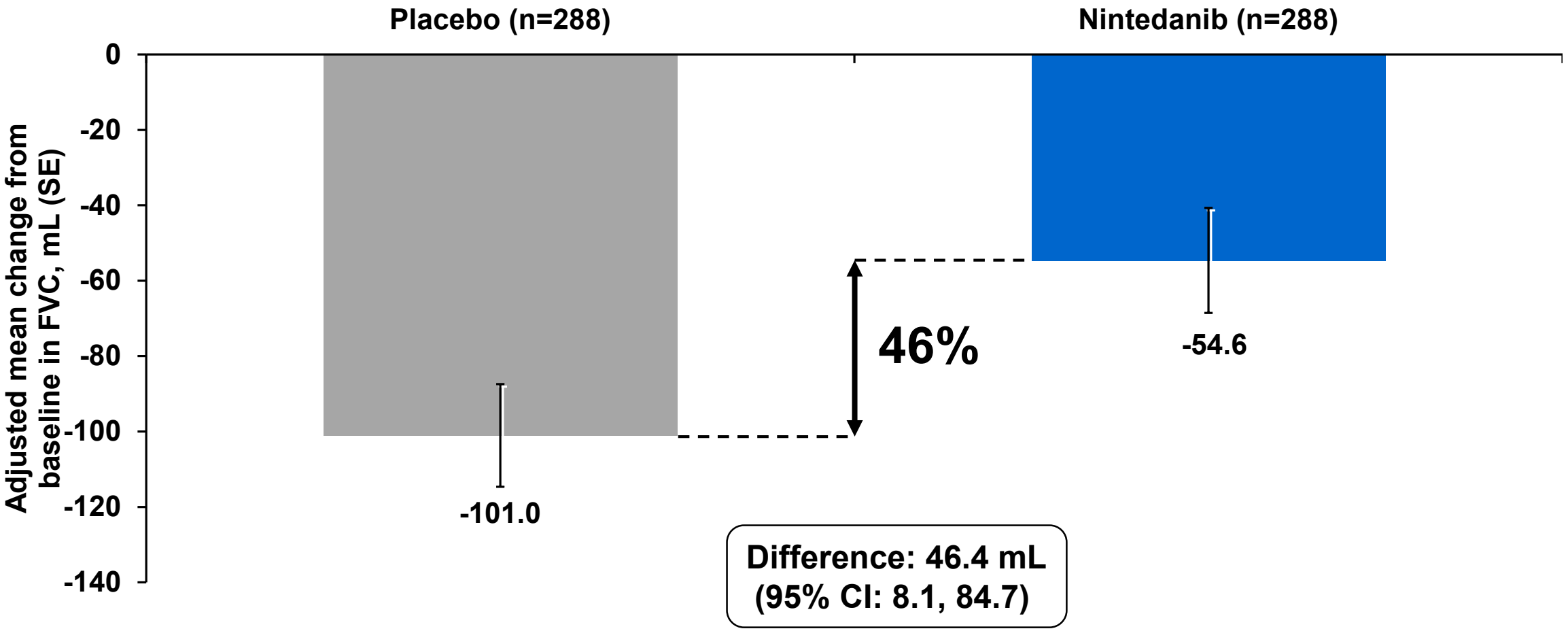
Rate of Decline in FVC % Predicted Over 52 Weeks

SENSCIS



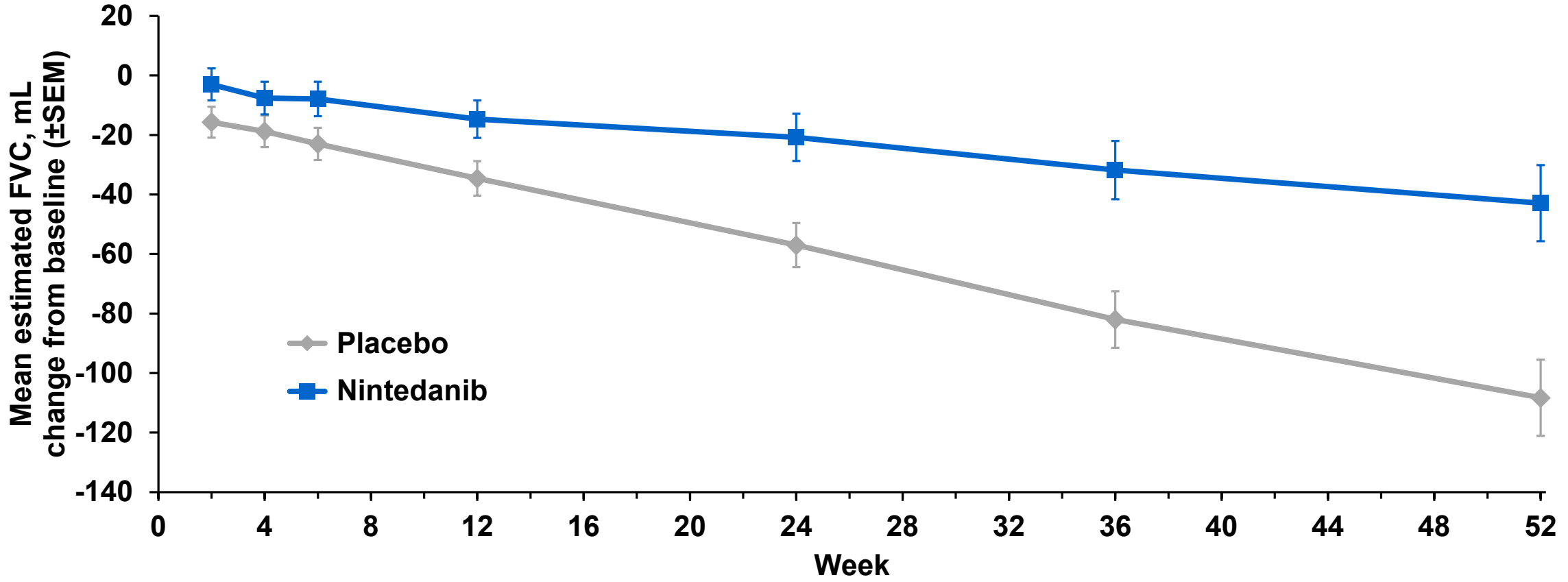
Absolute Change From Baseline in FVC (mL) at Week 52

SENSCIS



Change From Baseline in FVC (mL) Over 52 Weeks

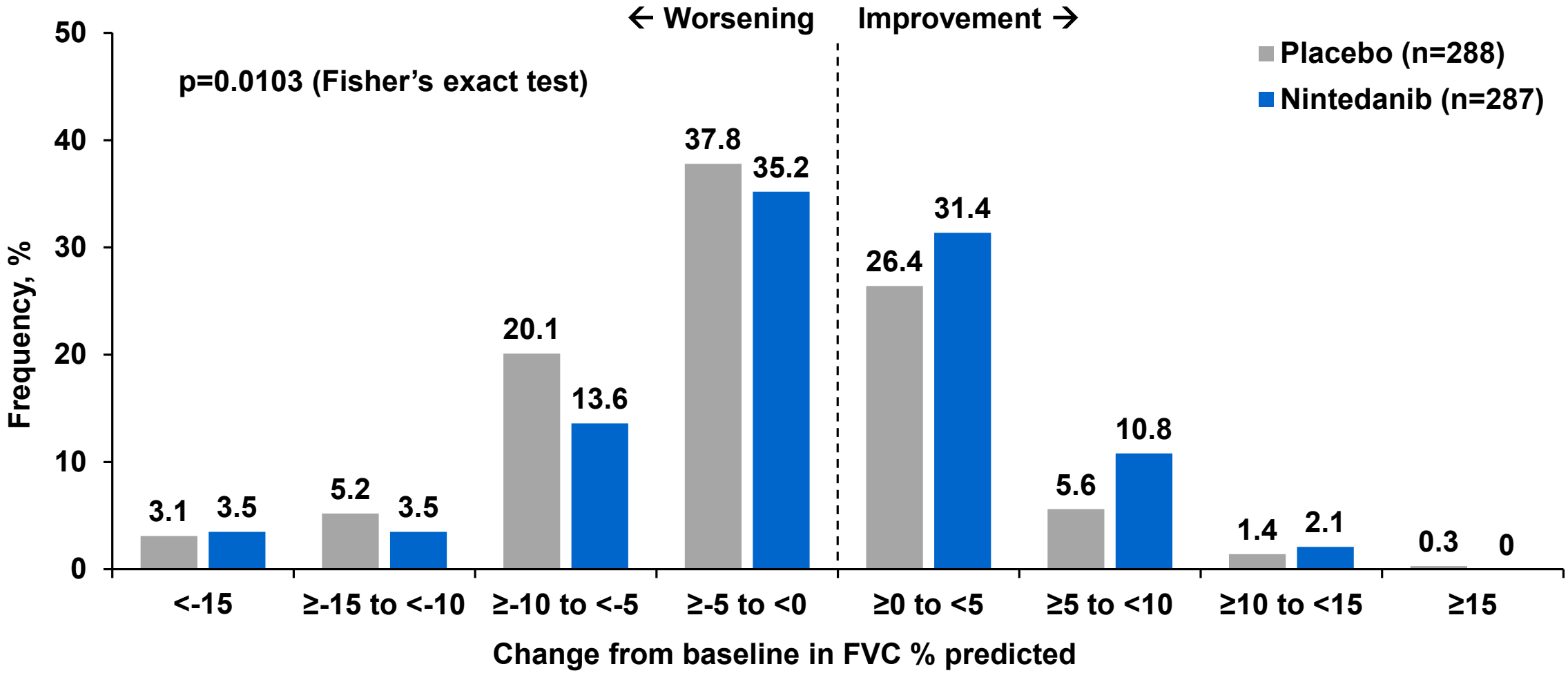
SENSCIS



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

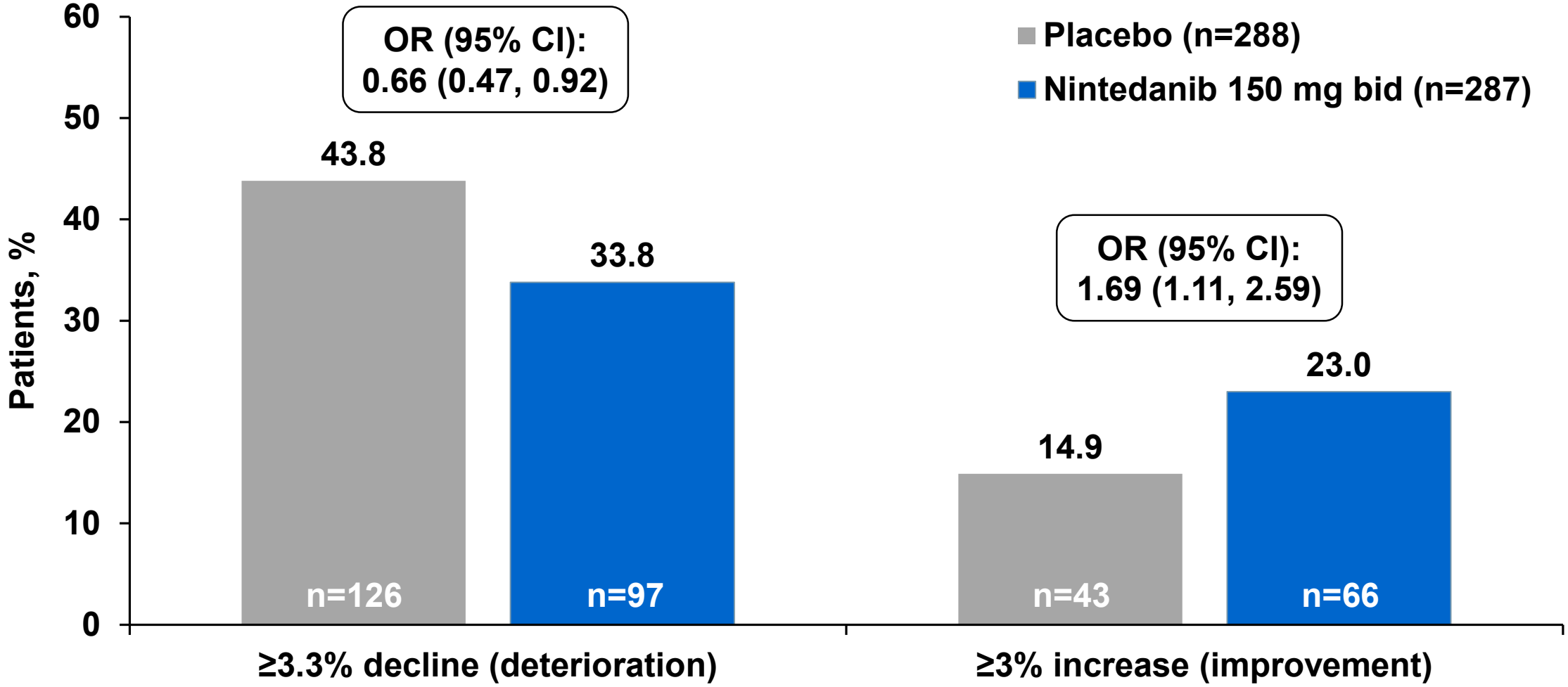
Based on primary analysis model.

Categorical Analysis—Change in FVC % Predicted at 52 Weeks[a]



[a] Worst observation carried forward.

Additional Responder Analysis
Change From Baseline in FVC % Predicted at 52 Weeks[a]



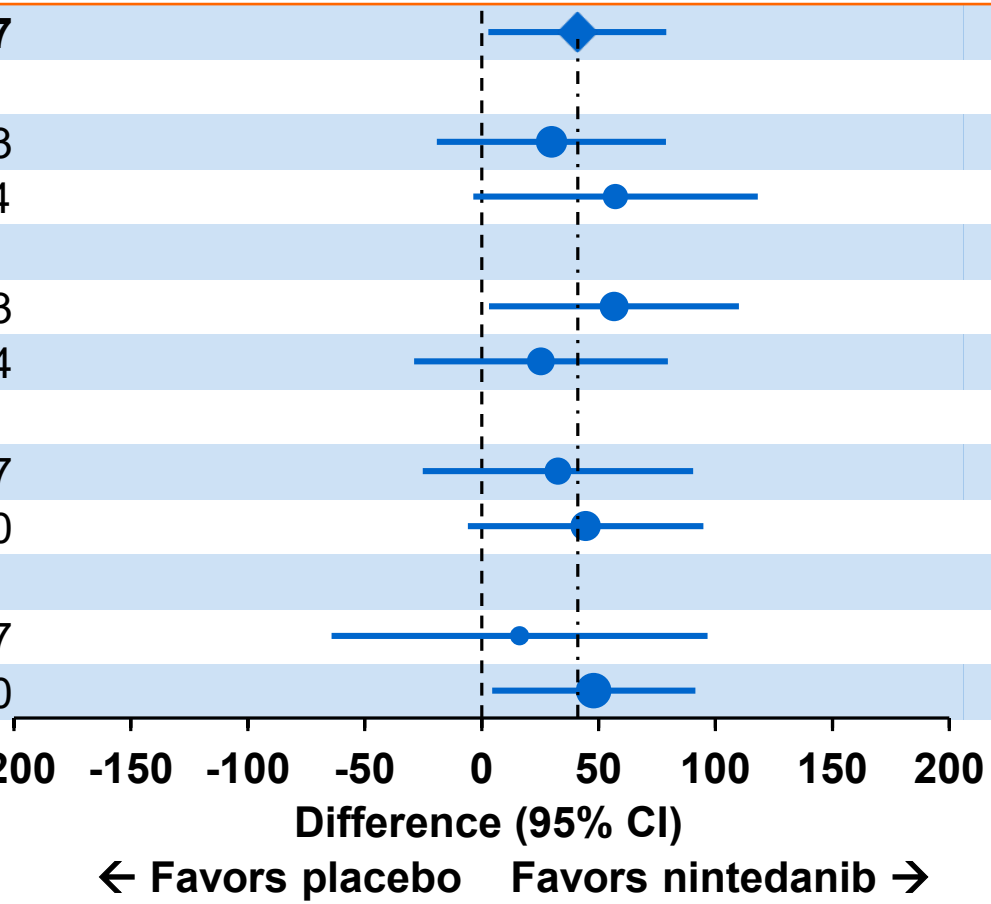
Cut-offs based on Kafaja S, et al. *Am J Respir Crit Care Med*. 2018;197:644-652.

[a] Worst observation carried forward.

Subgroup Analyses of Primary Endpoint 1/2

SENSCIS Treated Set

	Analyzed, n		Difference (95% CI)	p value[a]
	Placebo	Nintedanib		
All patients	**288**	**287**	**41.0 (2.9, 79.0)**	
ATA status				
Negative	177	173	29.9 (-19.1, 78.8)	0.491
Positive	111	114	57.2 (-3.5, 118.0)	
SSc subtype				
Diffuse cutaneous	146	153	56.6 (3.2, 110.0)	0.420
Limited cutaneous	142	134	25.3 (-28.9, 79.6)	
FVC % predicted				
<70% predicted	127	127	32.6 (-25.2, 90.5)	0.762
≥70% predicted	161	160	44.5 (-5.9, 94.9)	
Extent of fibrotic ILD				
<20%	74	57	16.2 (-64.1, 96.5)	0.496
≥20%	214	230	47.9 (4.5, 91.3)	

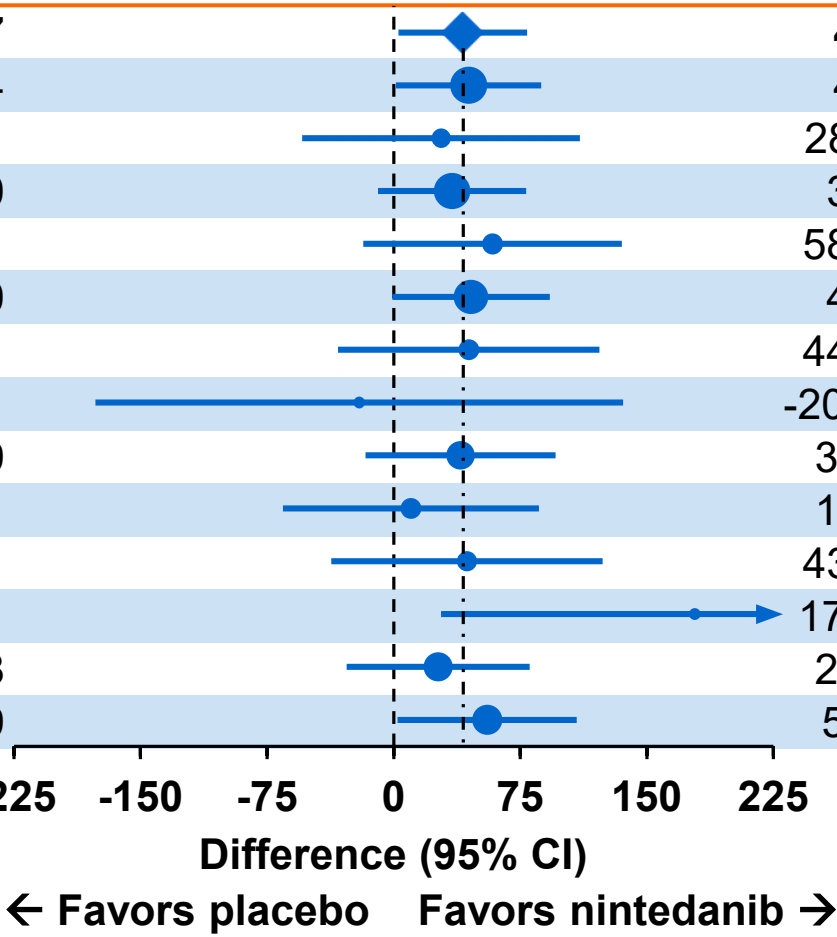


[a] Treatment-by-time-by-subgroup interaction.

Subgroup Analyses of Primary Endpoint 2/2

SENSCIS

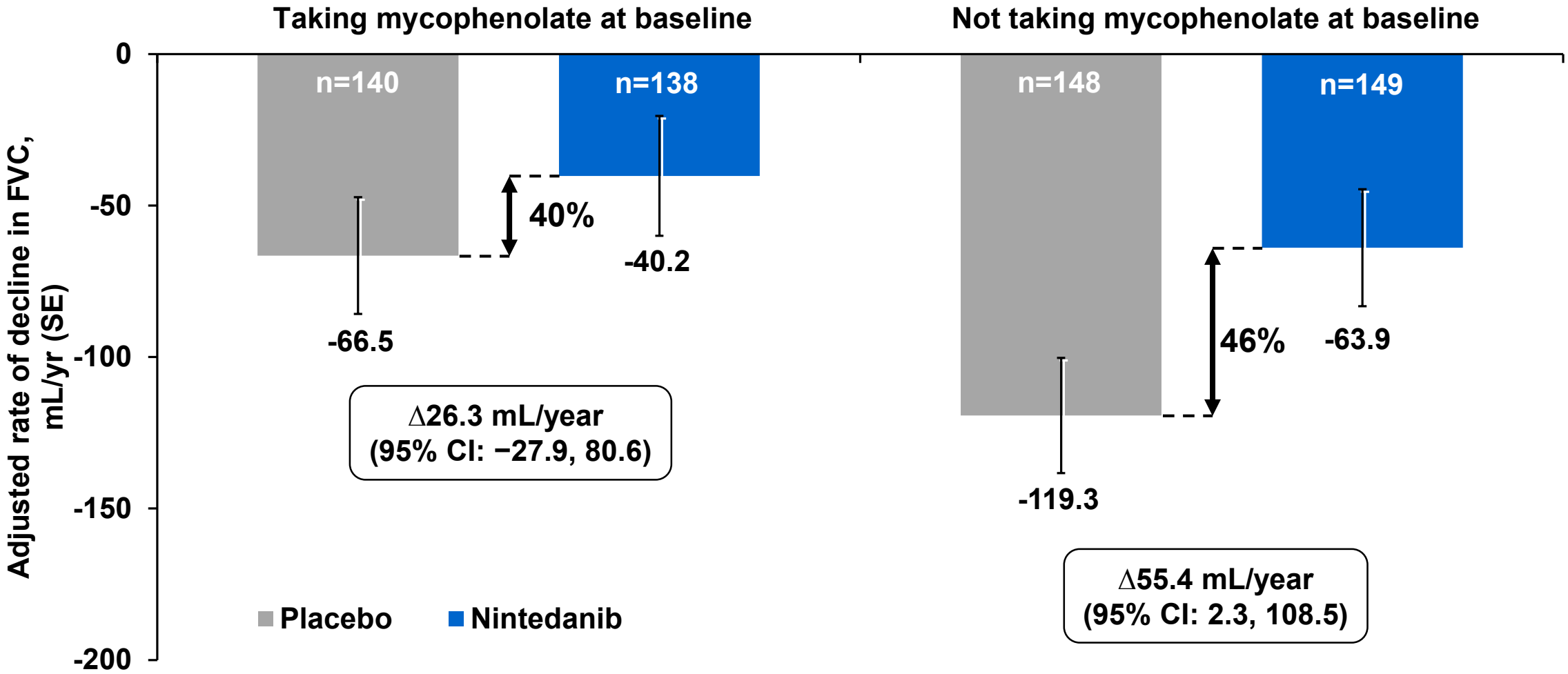
		Analyzed, n		Difference in annual rate of decline in FVC (95% CI)	p value[a]
		Placebo	Nintedanib		
All patients		**288**	**287**	**41.0 (2.9, 79.0)**	
Age	<65 years	229	224	44.4 (1.4, 87.4)	0.730
	≥65 years	59	63	28.1 (-54.2, 110.4)	
Gender	Female	212	220	34.6 (-9.3, 78.4)	0.594
	Male	76	67	58.6 (-18.0, 135.1)	
Race	White	186	200	45.8 (-0.8, 92.5)	0.725
	Asian	81	62	44.5 (-32.9, 121.9)	
	Black/African Am.	16	20	-20.4 (-176.7, 136.0)	
Region	Europe	126	139	39.7 (-16.6, 95.9)	0.277
	Canada and US	73	69	10.3 (-65.6, 86.1)	
	Asia	71	59	43.4 (-37.0, 123.8)	
	Rest of world	18	20	178.4 (28.1, 328.7)	
Mycophenolate	Yes	140	138	26.3 (-27.9, 80.6)	0.452
	No	148	149	55.4 (2.3, 108.5)	



[a] Treatment-by-time-by-subgroup interaction.

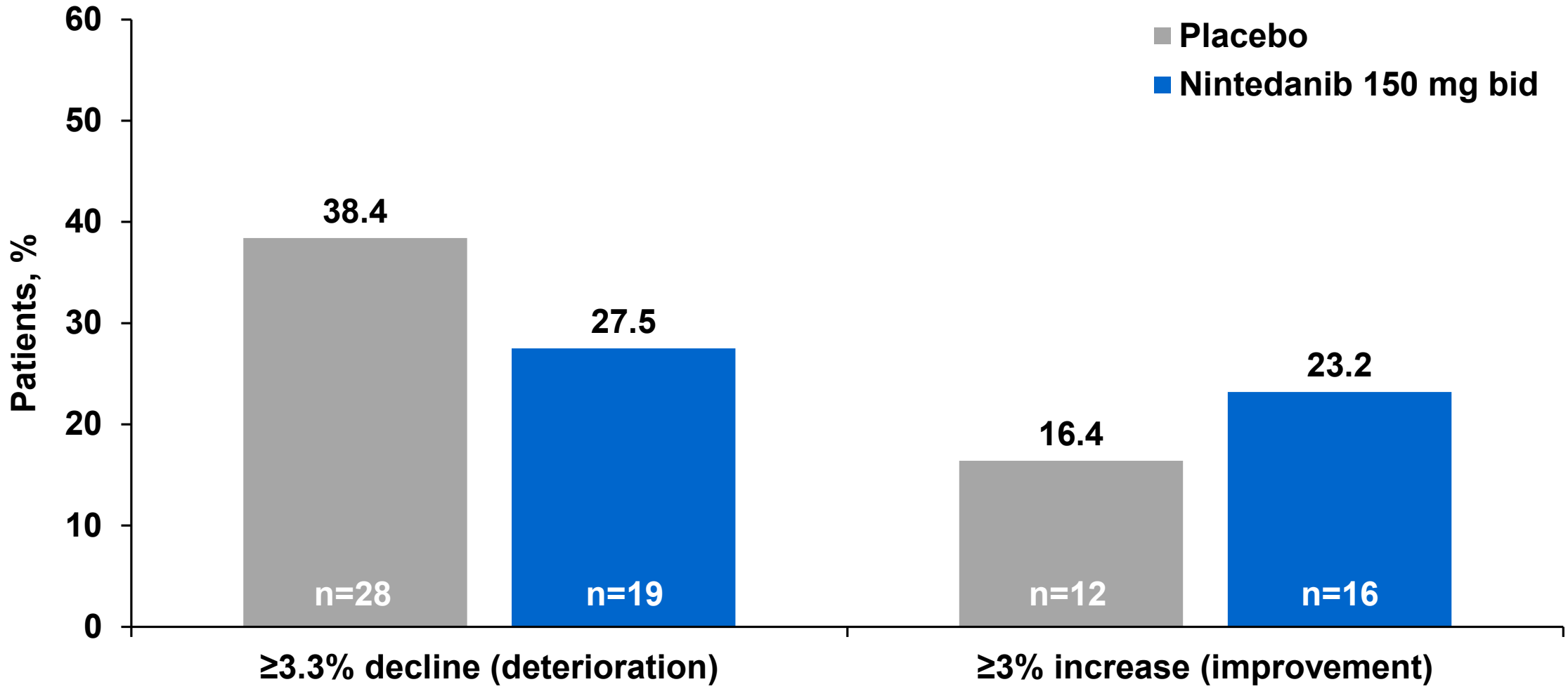
Prespecified Subgroup Analyses of Primary Endpoint by Mycophenolate Use

SENSCIS



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

Responder Analysis for US/Canada



Cut-offs based on Kafaja S, et al. *Am J Respir Crit Care Med*. 2018;197:644-652.
Worst Observation Carried Forward was used for missing data at Week 52.

Key Secondary Endpoints

Key Secondary Endpoints
SENSCIS

Secondary endpoint at Week 52	Placebo	Nintedanib	Adjusted mean difference (95% CI)	p value
mRSS	**n=286**	**n=288**		
Mean baseline (SD)	10.9 (8.8)	11.3 (9.2)		
Adjusted absolute mean change from baseline[a] (SE)	-1.96 (0.26)	-2.17 (0.27)	-0.21 (-0.94, 0.53)	0.579
SGRQ	**n=283**	**n=282**		
Mean baseline (SD)	39.4 (20.9)	40.7 (20.1)		
Adjusted absolute mean change from baseline (SE)	-0.88 (0.87)	0.81 (0.88)	1.69 (-0.73, 4.12)	0.171

- No treatment differences in mRSS or SGRQ between treatment groups

SGRQ=St. George's Respiratory Questionnaire; Scores range from 0 (no impairment) to 100 (worst possible impairment);
MCIDs in IPF are estimated between 5-8 points
Swigris J et al. *Respiratory Medicine* 2010; 104:296-304

Time to Death Over Whole Trial
SENSCIS

	Placebo	Nintedanib
Analyzed, n	288	288
Patients with event, n (%)	9 (3.1)	10 (3.5)
Hazard ratio (95% CI)	1.16 (0.47, 2.84)	
p value	0.754	

- No treatment differences in mortality between treatment groups

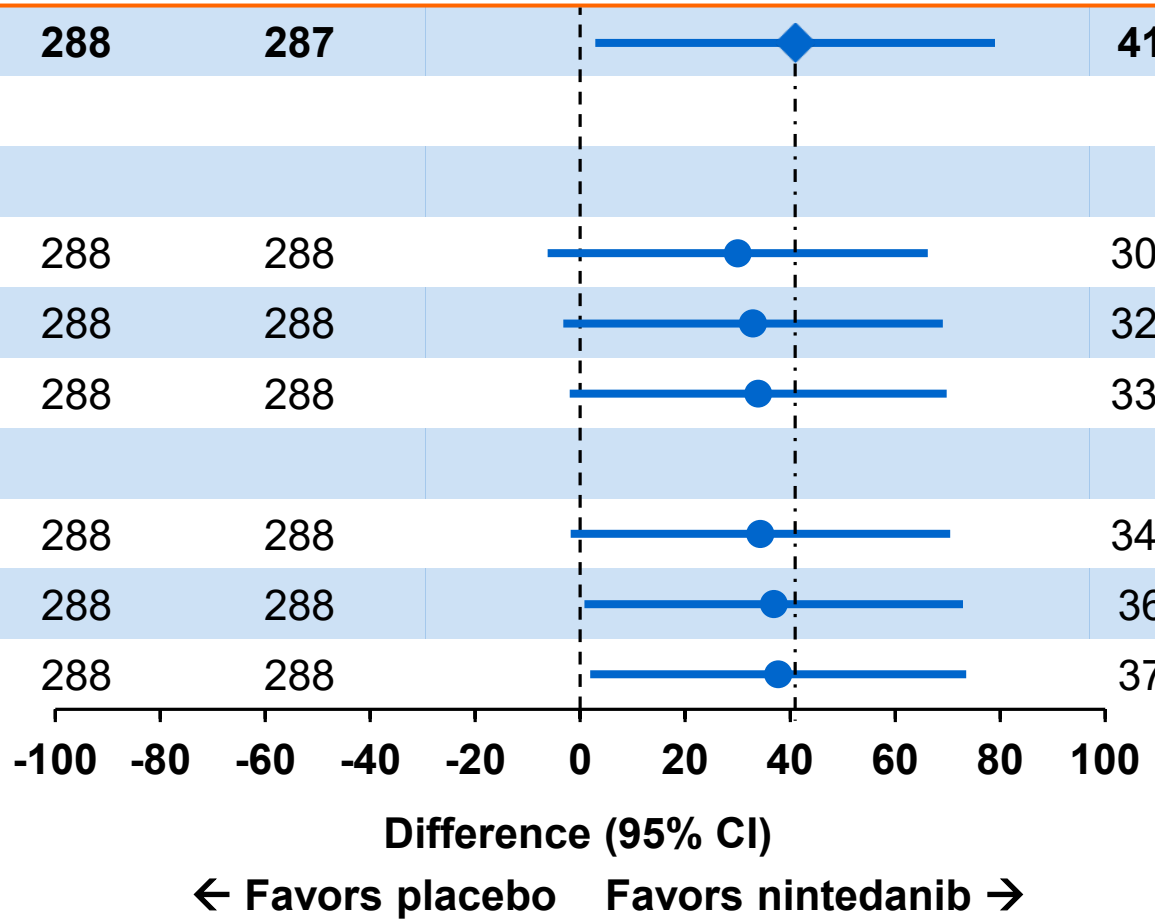
Data from randomization to last contact date on case report form.

Points of Interest

- Sensitivity analysis of primary endpoint
- Tipping point analysis
- Available data over 100 weeks

Annual Rate of Decline in FVC
Prespecified and Revised Sensitivity Analyses

	Analyzed, n		Difference (95% CI)	p value
	Placebo	Nintedanib		
Primary analysis	**288**	**287**	**41.0 (2.9, 79.0)**	**0.035**
Multiple imputation sensitivity analyses				
Prespecified (missing n=78)				
1	288	288	30.0 (-6.2, 66.2)	0.105
2	288	288	32.9 (-3.2, 69.1)	0.074
3	288	288	33.9 (-2.0, 69.8)	0.064
Revised (missing n=50)				
1	288	288	34.3 (-1.8, 70.5)	0.063
2	288	288	36.9 (0.8, 72.9)	0.045
3	288	288	37.7 (1.9, 73.5)	0.039



Tipping Point Analysis

- Post-hoc tipping point analysis
  - FVC missing from 78 patients at 52 weeks
  - Penalty in nintedanib group of 30 mL/year required to lose significance
- Revised tipping point analysis
  - All available data including 28 patients
    (FVC missing from 50 patients at 52 weeks)
  - Penalty of 120 mL/year required to lose significance
- Both analyses support robustness of primary findings

Analysis of FVC Over the Entire Trial (up to 100 Weeks[a])

- Analyses including FVC data collected beyond 52 weeks suggest treatment effect persist
- Using intent-to-treat approach, adjusted treatment difference at 100 weeks compared with placebo was 65.3 mL (95% CI: 6.6, 124.1)

[a] Including all off-treatment data of patients who prematurely discontinued.

Summary of Efficacy Results

- Nintedanib reduced ILD progression in patients with SSc-ILD
  - 44% relative effect on annual rate of FVC decline in SENSCIS similar to that observed in the INPULSIS trials
  - Findings overall consistent across patient subgroups
  - Sensitivity analyses and tipping point analysis support robustness of findings
- No effect of nintedanib observed on mRSS or SGRQ (key secondary endpoints)
- Observed treatment effect is considered clinically meaningful in patients with SSc-ILD

Safety of Nintedanib for SSc-ILD

Veronika M. Kohlbrenner, MD

Director, Global Pharmacovigilance
Boehringer Ingelheim

Safety Overview

- Exposure in SENSCIS
- Summary of adverse events comparing SENSCIS and INPULSIS
- Safety topics of special interest in SENSCIS
- Conclusions

Exposure
SENSCIS

	Placebo n=288	Nintedanib n=288
Mean exposure through 52 weeks, mo (SD)	11.4 (2.4)	10.5 (3.4)
Mean exposure over entire trial,[a] mo (SD)	15.7 (5.7)	14.5 (6.7)
Categorical exposure over entire trial, %		
>6 months	93.4	85.8
>12 months	67.4	60.4
>18 months	37.8	36.8

[a] Entire trial represents up to 100 weeks.

Summary of Adverse Events
SENSCIS and INPULSIS – 52 Weeks

Adverse event	Patients, %			
	SENSCIS		INPULSIS 1 and 2	
	Placebo n=288	Nintedanib n=288	Placebo n=423	Nintedanib n=638
Any AE	95.8	98.3	89.6	95.5
AE leading to discontinuation	8.7	16.0	13.0	19.3
SAE	21.5	24.0	30.0	30.4
AE resulting in death	1.4	1.7	7.3	5.8

SAE=serious adverse event.

Most Common AEs >10%

SENSCIS and INPULSIS – 52 Weeks

	Patients, %			
	SENSCIS		INPULSIS 1 and 2	
Preferred term	Placebo n=288	Nintedanib n=288	Placebo n=423	Nintedanib n=638
Diarrhea	31.6	75.7	18.4	61.6
Nausea	13.5	31.6	6.6	24.5
Vomiting	10.4	24.7	2.6	11.6
Skin ulcer	17.4	18.4	0	0.2
Nasopharyngitis	17.0	12.5	16.1	13.6
Cough	18.1	11.8	13.5	13.3
Weight decrease	4.2	11.8	3.5	9.7
Abdominal pain	7.3	11.5	2.4	8.8
Upper respiratory tract infection	12.2	11.5	9.9	9.1
Fatigue	6.9	10.8	7.8	6.3
Decreased appetite	4.2	9.4	5.7	10.7
Dyspnea	8.7	7.3	11.3	7.7
Bronchitis	8.3	5.6	10.6	10.5

Safety Topics of Special Interest
SENSCIS and INPULSIS – 52 Weeks

	Patients, %			
	SENSCIS		INPULSIS 1 and 2	
Safety topics	Placebo n=288	Nintedanib n=288	Placebo n=423	Nintedanib n=638
Diarrhea	31.6	75.7	18.4	61.6
Hepatic events[a]	4.9	17.4	4.5	17.7
Bleeding events[b]	8.3	11.1	7.8	10.3
MACE[c]	1.7	1.4	2.6	3.6

[a] Combination of 4 hepatic disorder SMQ searches.
[b] SMQ of hemorrhage terms, excluding laboratory.
[c] MACE (as reported by investigator): Composite endpoint of any fatal or non-fatal events in SMQ “myocardial infarction” (broad), any fatal or non-fatal stroke, any fatal events in system organ classes “cardiac disorders” or “vascular disorders,” and the preferred terms “sudden death,” “cardiac death,” or “sudden cardiac death.”
MACE=major adverse cardiovascular events; SMQ = Standardized MedDRA queries.

Diarrhea
SENSCIS – 52 Weeks

	Patients, n (%)	
	Placebo n=288	Nintedanib n=288
Diarrhea events		
AEs	91 (31.6)	218 (75.7)
Mild	61 (21.2)	108 (37.5)
Moderate	27 (9.4)	98 (34.0)
Severe	3 (1.0)	12 (4.2)
SAEs	2 (0.7)	2 (0.7)
Clinical consequence		
Dose reduction	2 (0.7)	57 (19.8)
Premature treatment discontinuation	1 (0.3)	20 (6.9)
Recovered	86/91 (94.5)	202/218 (92.7)

Mild: awareness of signs or symptoms, which are easily tolerated.
Moderate: enough discomfort to cause interference with usual activity.
Severe: incapacitating or causing inability to work or to perform usual activities.

Hepatic Events
SENSCIS – 52 Weeks

	Patients, n (%)	
	Placebo n=288	Nintedanib n=288
Hepatic events[a]		
AEs	14 (4.9)	50 (17.4)
SAEs	1 (0.3)	3 (1.0)
Clinical consequence		
Dose reduction	2 (0.7)	11 (3.8)
Premature treatment discontinuation	1 (0.3)	6 (2.1)

- No cases of hepatic failure
- No liver-related death

[a] Combination of 4 hepatic disorder SMQ searches.

Liver Enzymes and Bilirubin
SENSCIS – 52 Weeks

	Patients, n (%)	
	Placebo n=288	Nintedanib n=288
ALT and/or AST ≥1.5×ULN	11 (3.8)	52 (18.1)
ALT and/or AST ≥3×ULN	2 (0.7)	14 (4.9)
ALT and/or AST ≥5×ULN	1 (0.3)	3 (1.0)
ALT and/or AST ≥8×ULN	1 (0.3)	0
Hy's Law lab constellation[a]	0	0

- Transaminase abnormalities resolved on dose reduction or discontinuation

[a] ALT and/or AST ≥3x ULN and bilirubin ≥2x ULN.
ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal.

Bleeding Events
SENSCIS – 52 Weeks

	Patients, n (%)	
	Placebo n=288	Nintedanib n=288
Bleeding events[a]		
AEs	24 (8.3)	32 (11.1)
SAEs	2 (0.7)	4 (1.4)
Epistaxis	11 (3.8)	8 (2.8)
Skin contusion	3 (1.0)	7 (2.4)
Rectal hemorrhage	0	5 (1.7)
Hematochezia	1 (0.3)	2 (0.7)
Central nervous system bleeding	0	2 (0.7)

- All patients continued study medication uninterrupted

[a]SMQ of hemorrhage terms, excluding laboratory.

Cardiovascular Events
SENSCIS – 52 Weeks

	Patients, n (%)	
	Placebo n=288	Nintedanib n=288
MACE[a]	5 (1.7)	4 (1.4)
Myocardial infarction	3 (1.0)	2 (0.7)
Stroke	1 (0.3)	1 (0.3)
Fatal cardiovascular events	2 (0.7)	1 (0.3)
Adjudicated MACE	3 (1.0)	1 (0.3)
Other cardiovascular events		
Cardiac failure	1 (0.3)	1 (0.3)
Venous thromboembolism	3 (1.0)	4 (1.4)
Pulmonary embolism	1 (0.3)	0
Pulmonary arterial hypertension	4 (1.4)	7 (2.4)
Hypertension	4 (1.4)	11 (3.8)

[a] Major Adverse Cardiovascular Events (as reported by investigator): Composite endpoint of any fatal or non-fatal events in SMQ "myocardial infarction" (broad), any fatal or non-fatal stroke, any fatal events in system organ classes "cardiac disorders" or "vascular disorders," and the preferred terms "sudden death," "cardiac death," or "sudden cardiac death."

Summary of Safety

- Safety and tolerability profile of nintedanib in SSc-ILD is consistent with that observed in IPF
- No new safety findings in SENSCIS
- Common AEs associated with nintedanib were manageable with treatment strategies
- SENSCIS trial results demonstrate the safety of nintedanib in the treatment of patients with SSc-ILD

Benefit/Risk of Nintedanib for SSc-ILD

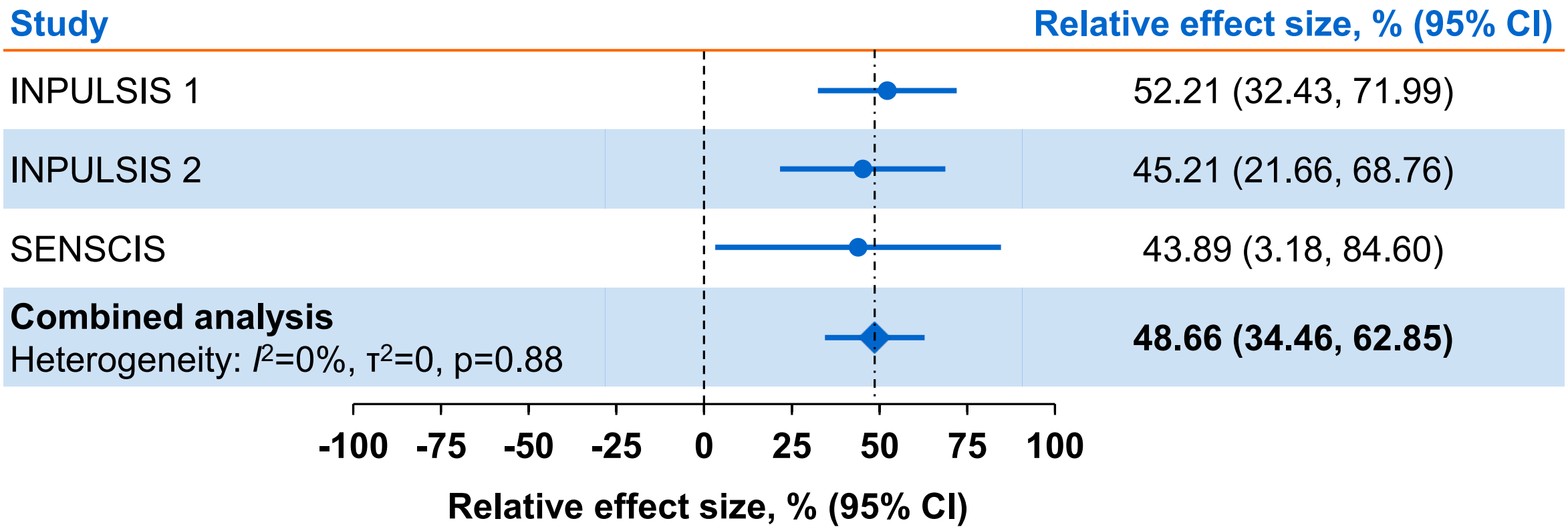
Kay Tetzlaff, MD

Medical Head, Therapeutic Area Respiratory Diseases
Boehringer Ingelheim

Benefit/Risk of Nintedanib in SSc-ILD

- ILD is a common manifestation of SSc and is associated with high mortality
- Progression of SSc-ILD is irreversible
- Nintedanib significantly reduced annual rate of decline in FVC by 44% relative to placebo in a population allowing generalization of results to clinical practice
- Relative treatment effect similar to that in IPF

Consistency of Relative Treatment Effect Across Trials



Benefit/Risk of Nintedanib in SSc-ILD

- Effects considered clinically meaningful, given the
  - Typical age of onset of SSc-ILD
  - Natural progression/gradual lung function decline accumulating over years

- Nintedanib was safe and well tolerated in the SSc-ILD population, and the safety profile was consistent with the experience of nintedanib in IPF

Conclusion

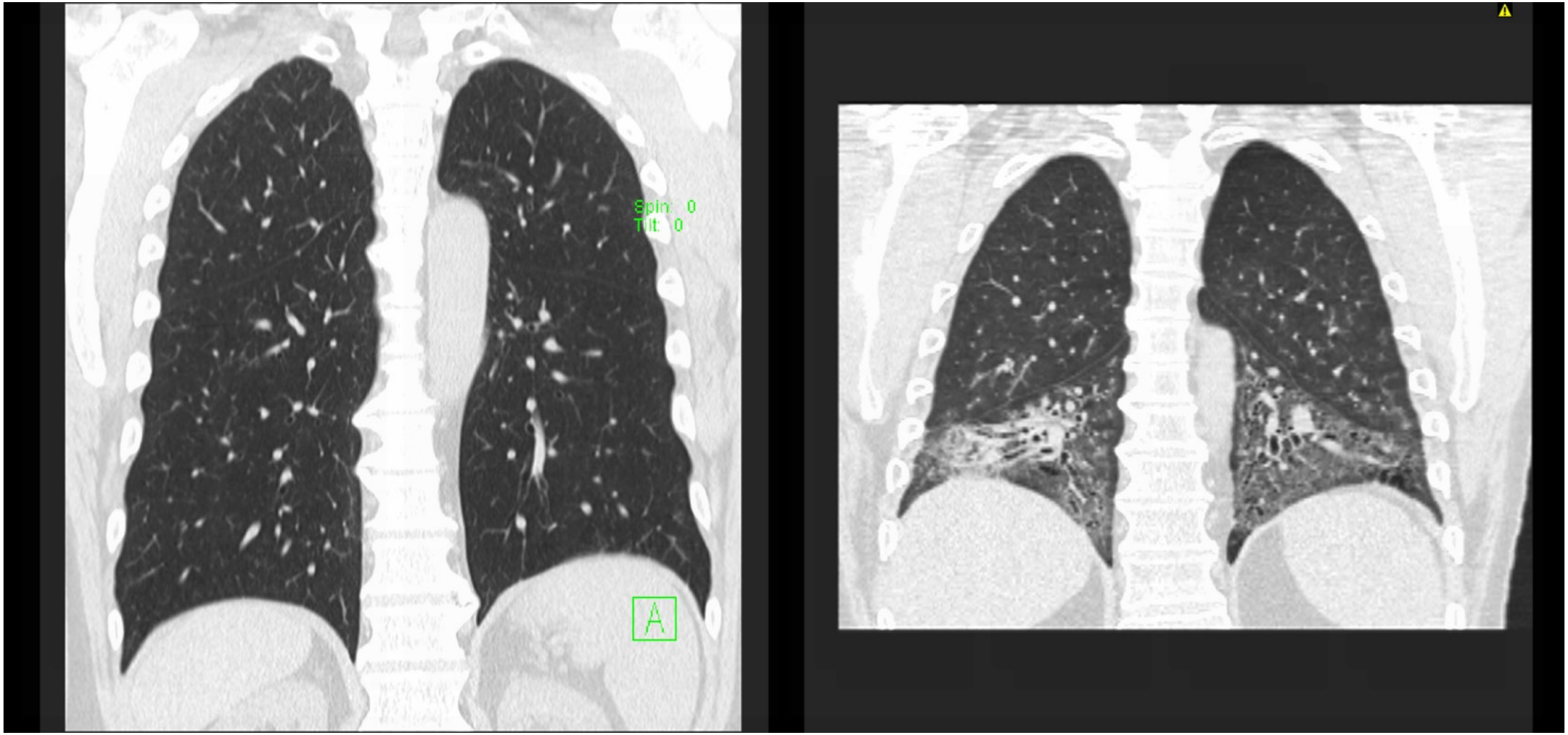
The benefit-risk profile of nintedanib is positive for the treatment of patients with SSc-ILD

Clinical Perspective

Kevin K. Brown, MD

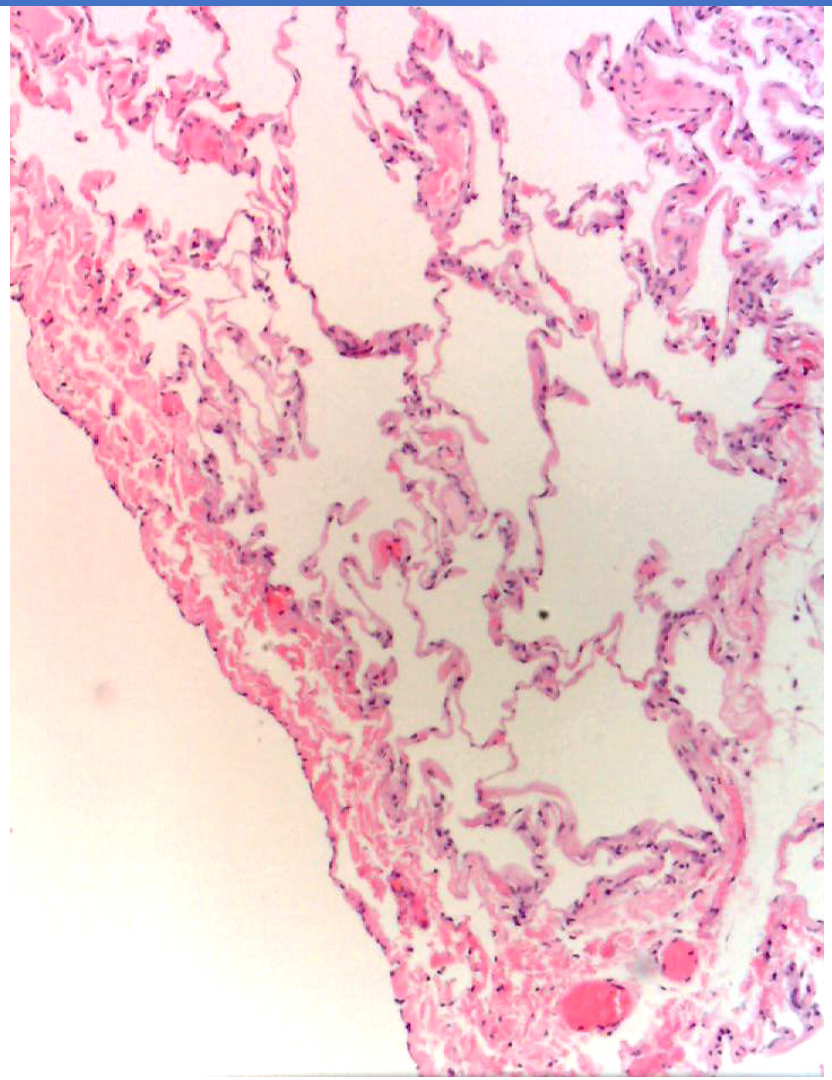
National Jewish Health

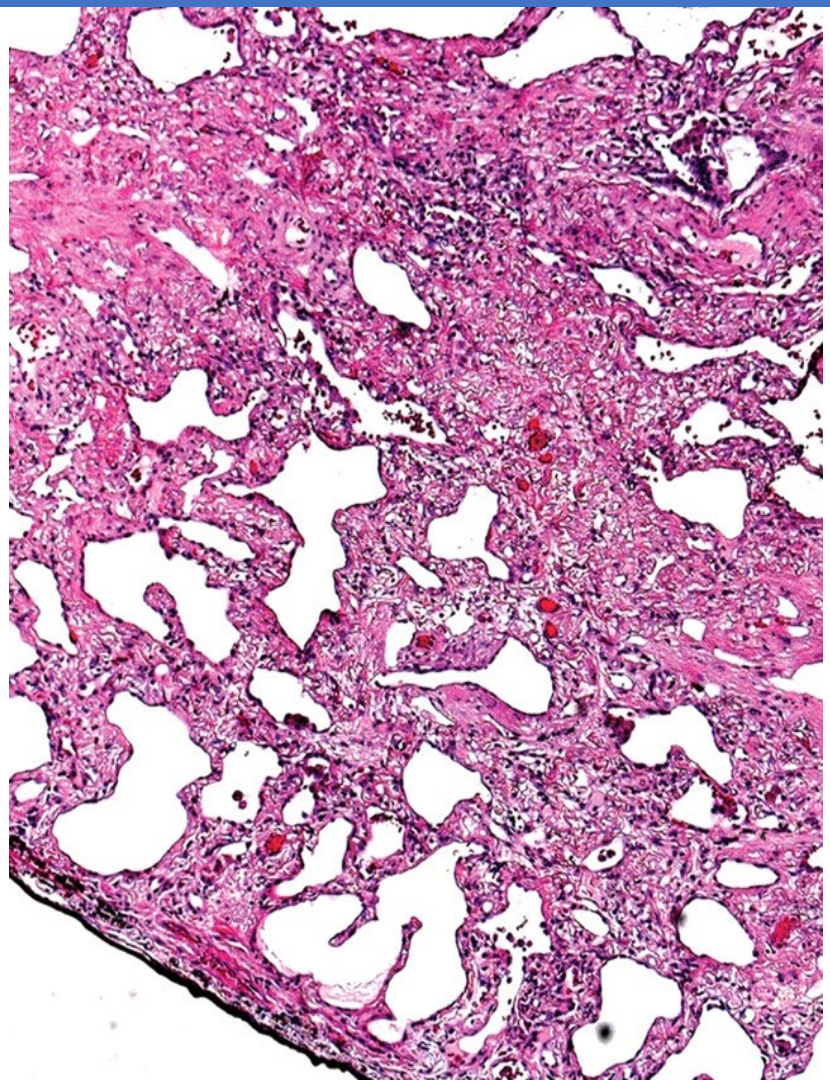
SSc-ILD



Images from K Brown, National Jewish Health.

SSc-ILD





Images from K Brown, National Jewish Health.

One Individual's History of Lung Function Loss

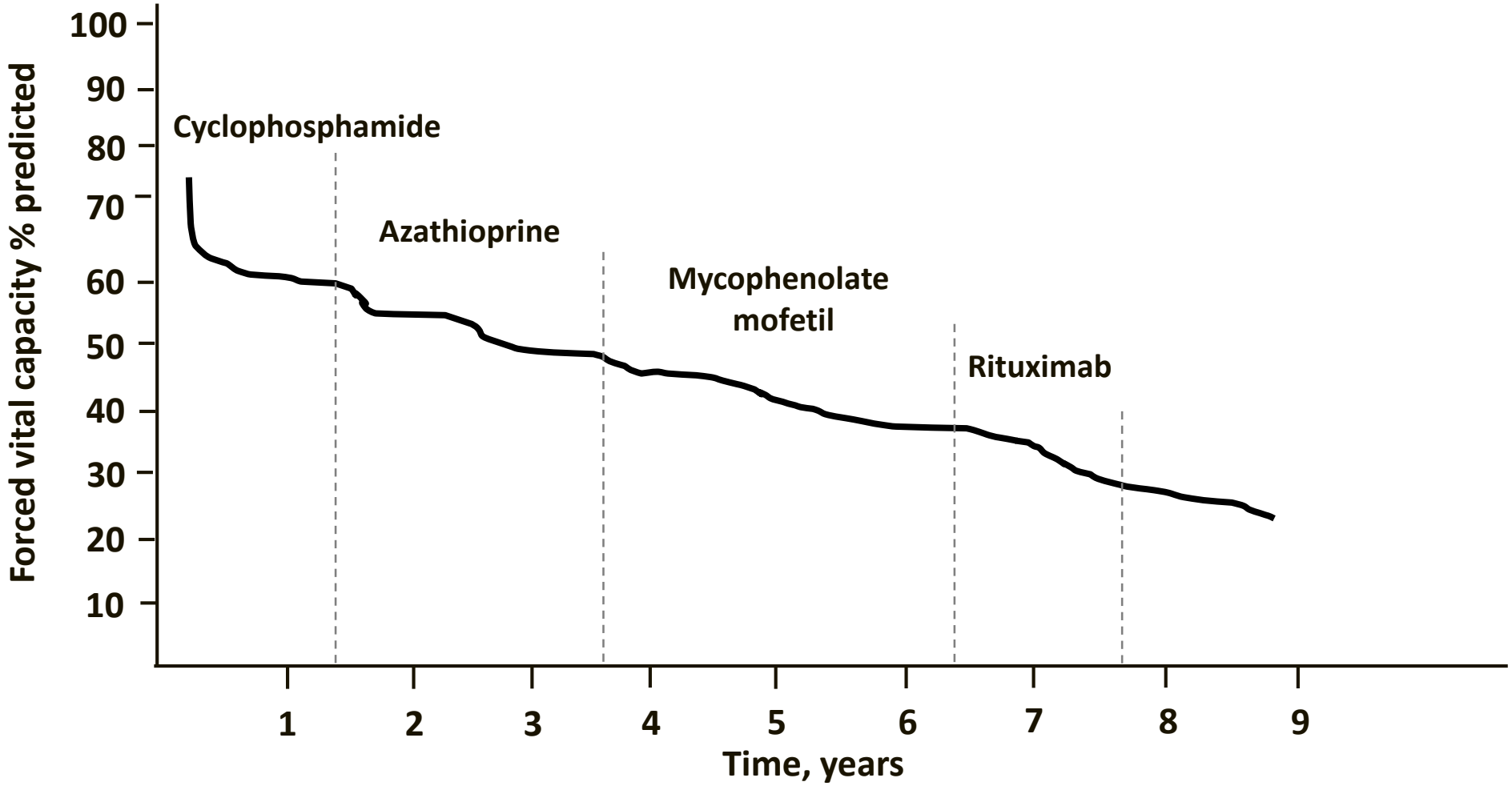
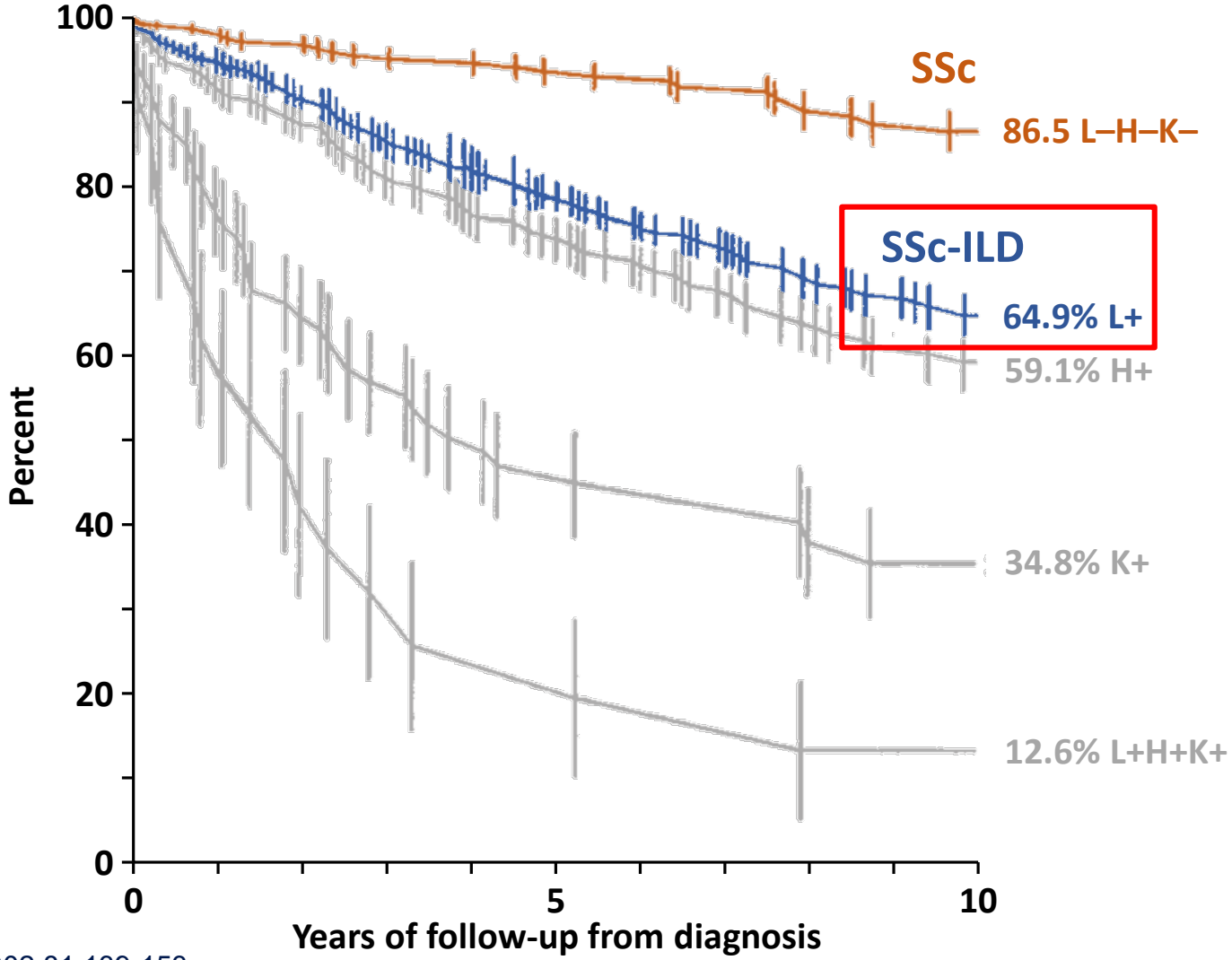


Image from of K Brown, National Jewish Health.

ILD Shortens Survival in Scleroderma

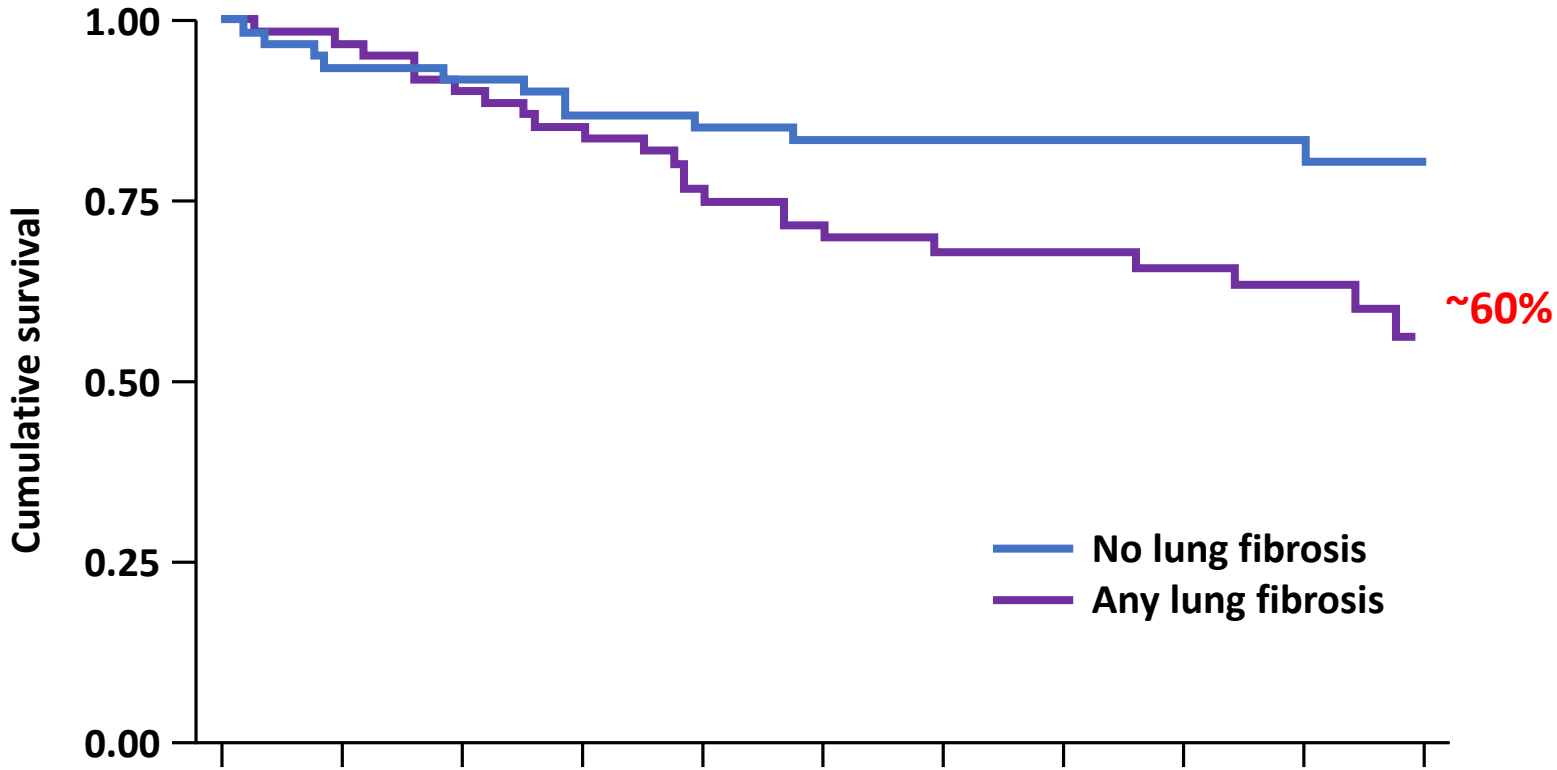
Survival and SSc Organ Involvement



Reprinted from Ferri C, et al. *Medicine.* 2002;81:139-153.

The Presence of ILD Is Associated With Mortality

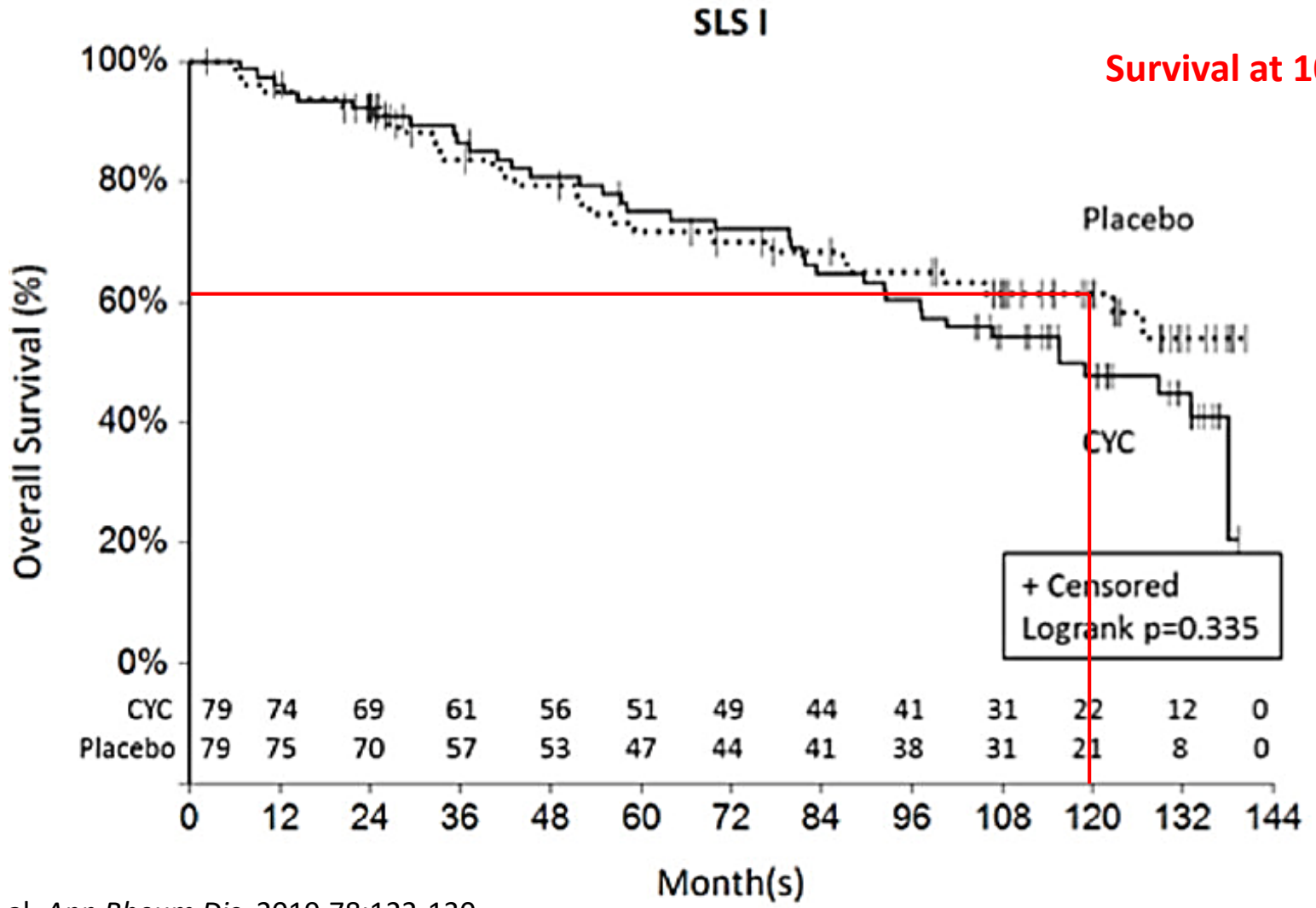
Nationwide Norwegian SSc Cohort



At risk, n						
No lung fibrosis	61	55	50	45	35	20
Any lung fibrosis	61	55	45	36	29	14

Hoffmann-Vold AM, et al. *Am J Respir Crit Care Med*. 2019 Jul 16. doi: 10.1164/rccm.201903-0486OC. [Epub ahead of print]

Anti-inflammatory Therapy Has Not Altered Long-term Survival



Reprinted from Volkmann ER, et al. *Ann Rheum Dis*. 2019;78:122-130.

ATS 2019: Clinical Topics in Pulmonary Medicine

When There Is No Right Answer: A Pro/Con Debate on Controversies in ILD

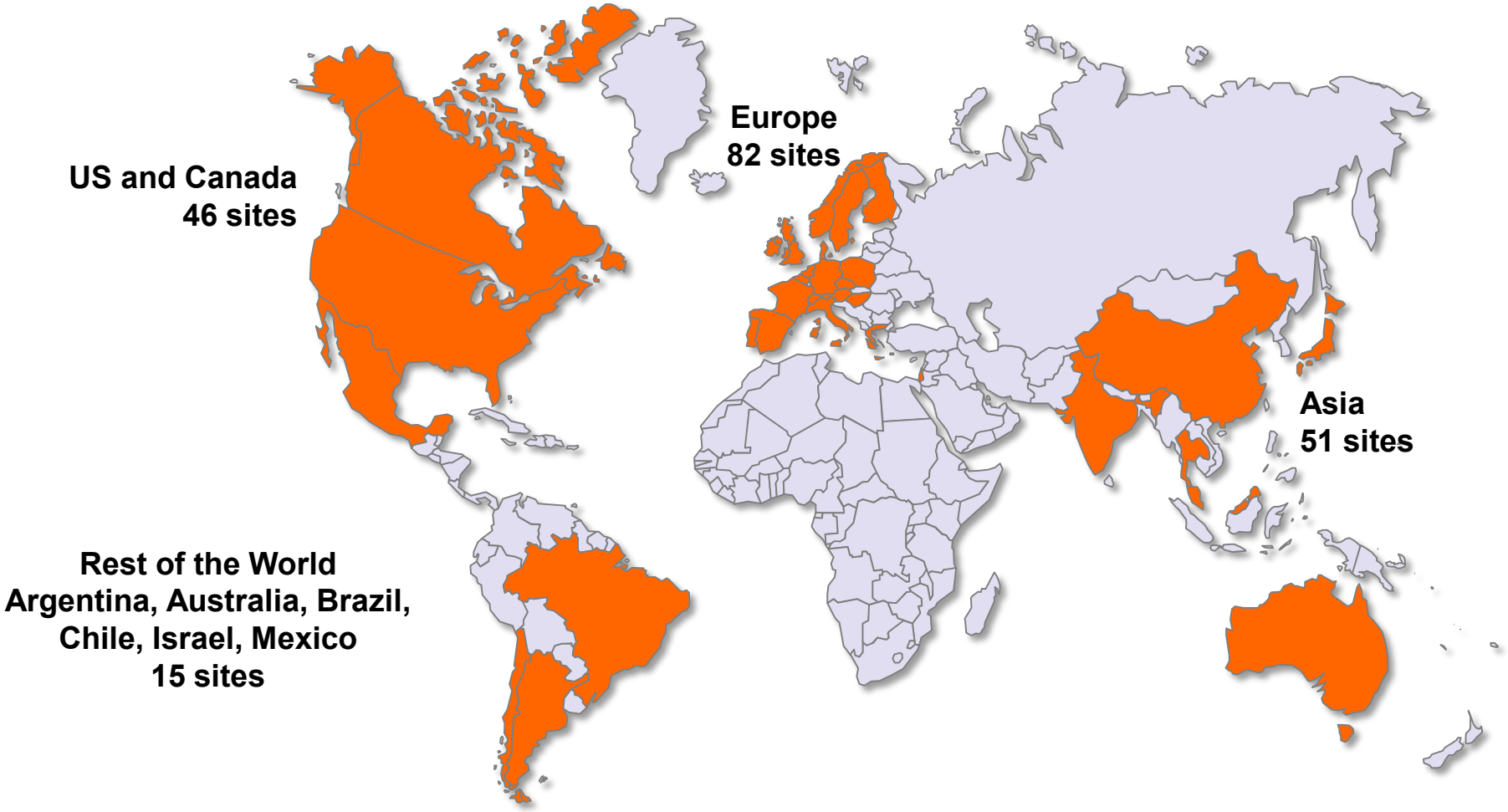
Assemblies on Clinical Problems, Behavioral Science and Health Services Research

9:15 AM - 11:15 AM

Chairing: SM Bhorade, MD, Chicago, IL
R Jablonski, MD, Chicago, IL

9:15	**PRO: Lung Transplant Is a Viable Treatment Option for Scleroderma** MM Crespo, MD, Philadelphia, PA
9:27	**CON: Other Options Should Be Explored for Management of Scleroderma Lung Disease** R Jabonski, MD, Chicago, IL

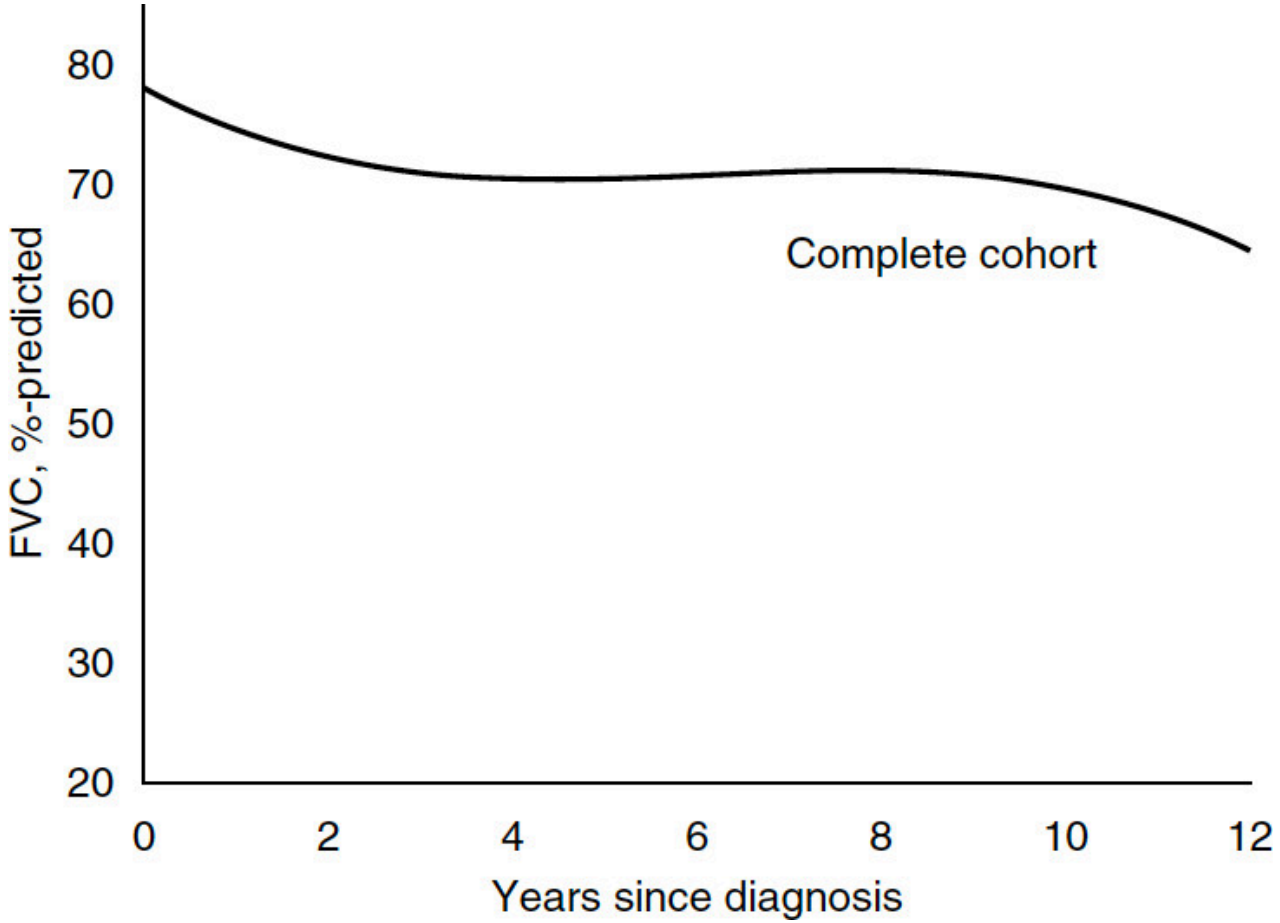
SENSCIS

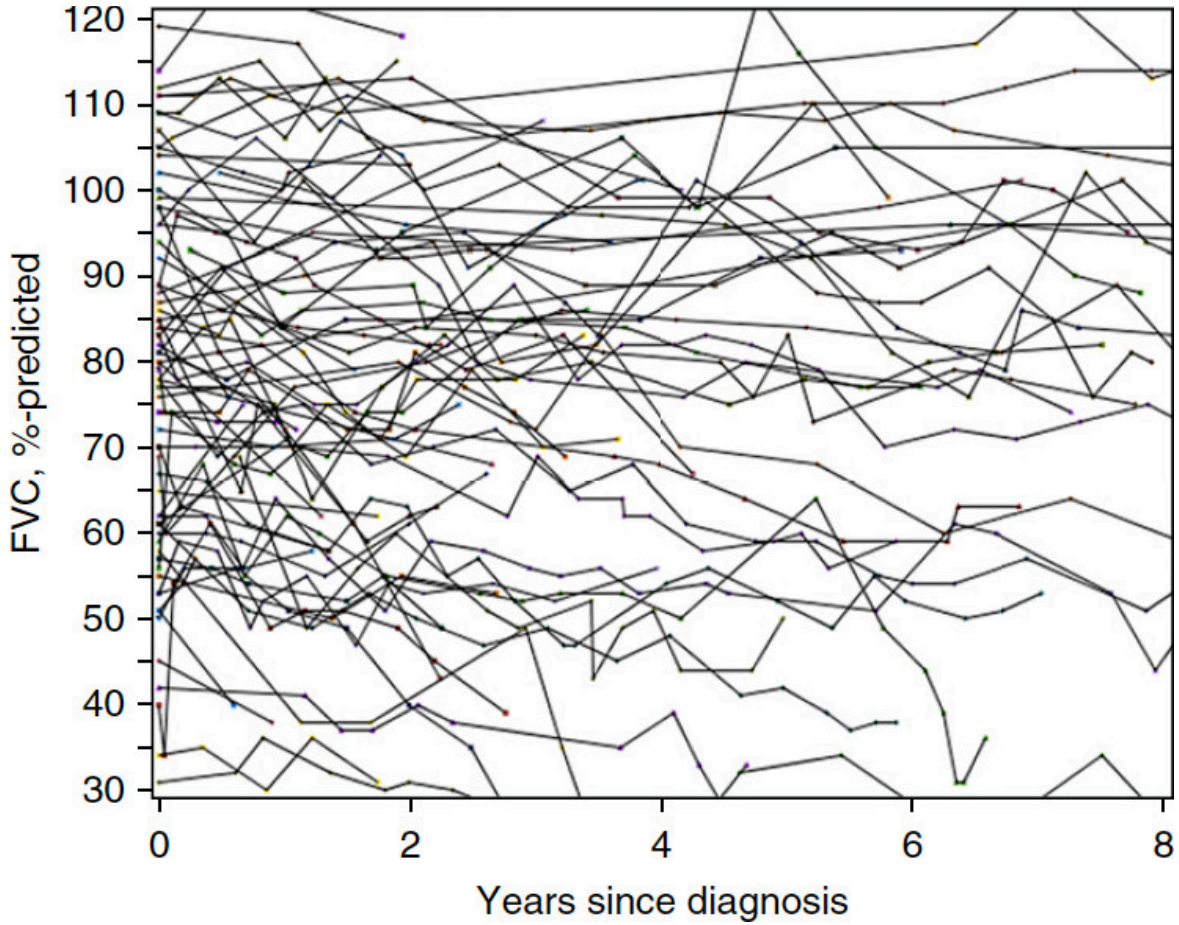

US and Canada
46 sites
Europe
82 sites
Asia
51 sites
Rest of the World
Argentina, Australia, Brazil,
Chile, Israel, Mexico
15 sites

SENSCIS

- Largest placebo-controlled trial ever conducted in SSc-ILD
- Enrolled a broad population reflective of patients treated in clinical practice
- Did not exclude patients receiving available therapies

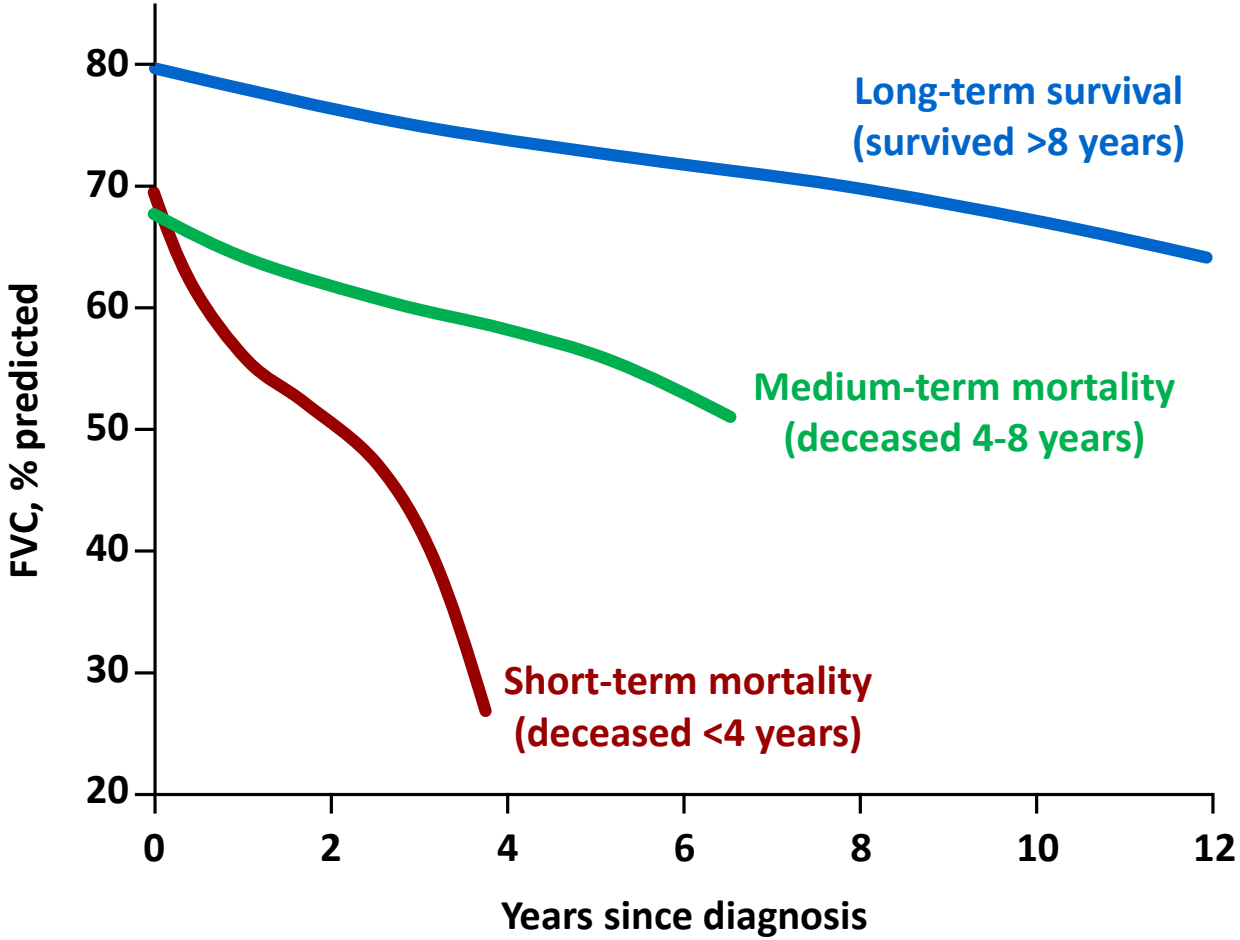
FVC Decline Precedes Mortality in SSc-ILD





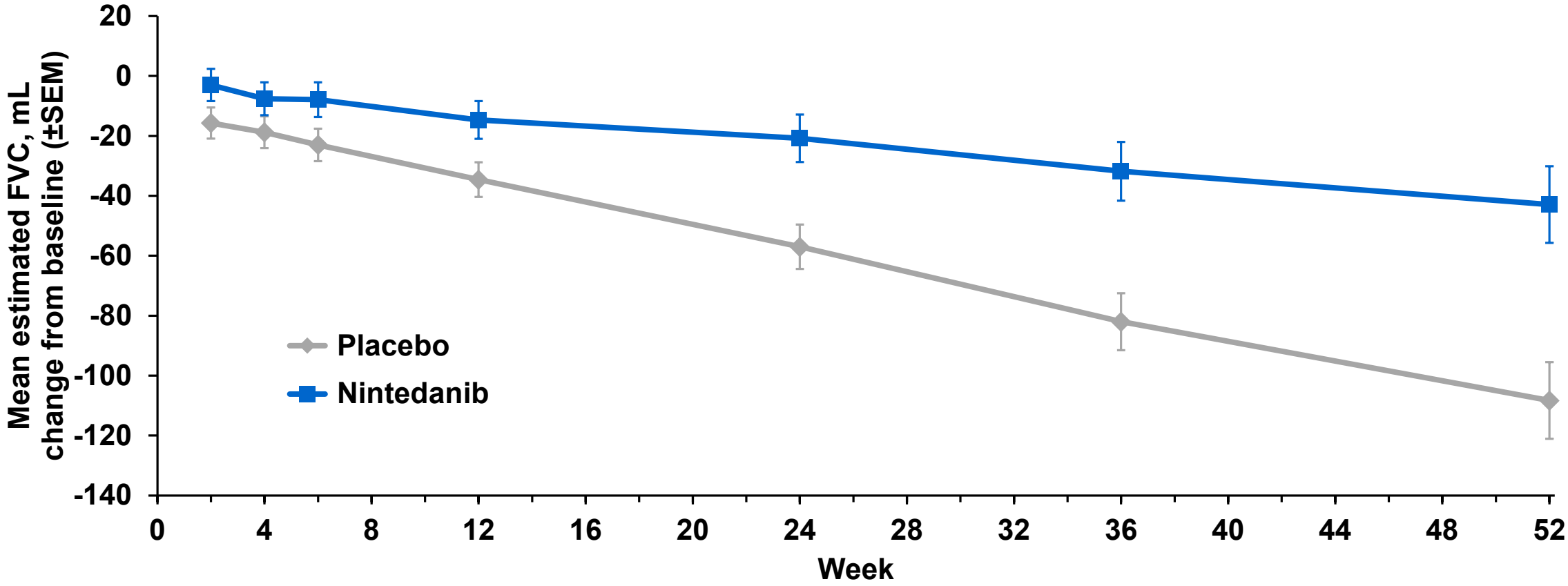
Reprinted from Guler SA, et al. *Ann Am Thorac Soc*. 2018:15(12):1427-1433.

FVC Decline Precedes Mortality in SSc-ILD



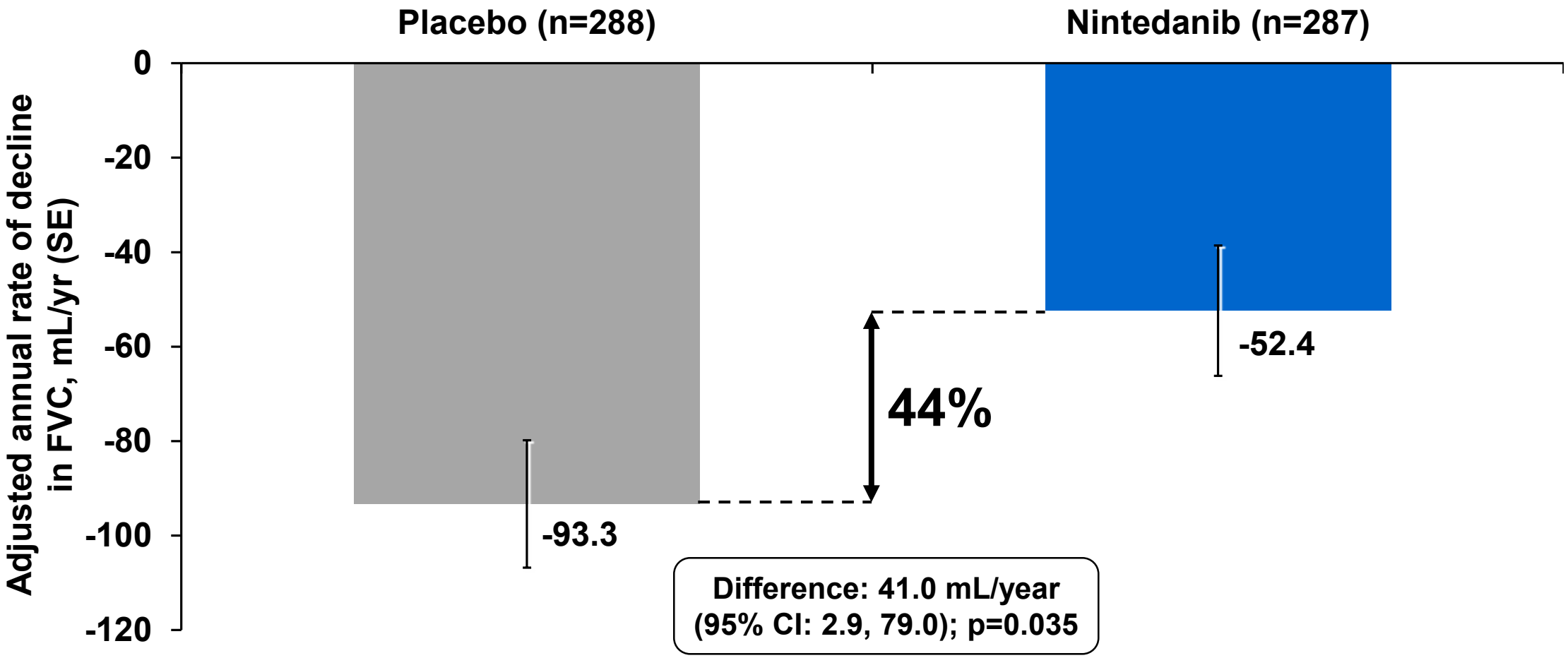
Reprinted from Guler SA, et al. *Ann Am Thorac Soc*. 2018:15(12):1427-1433.

SENSCIS: Mean Absolute Change in FVC



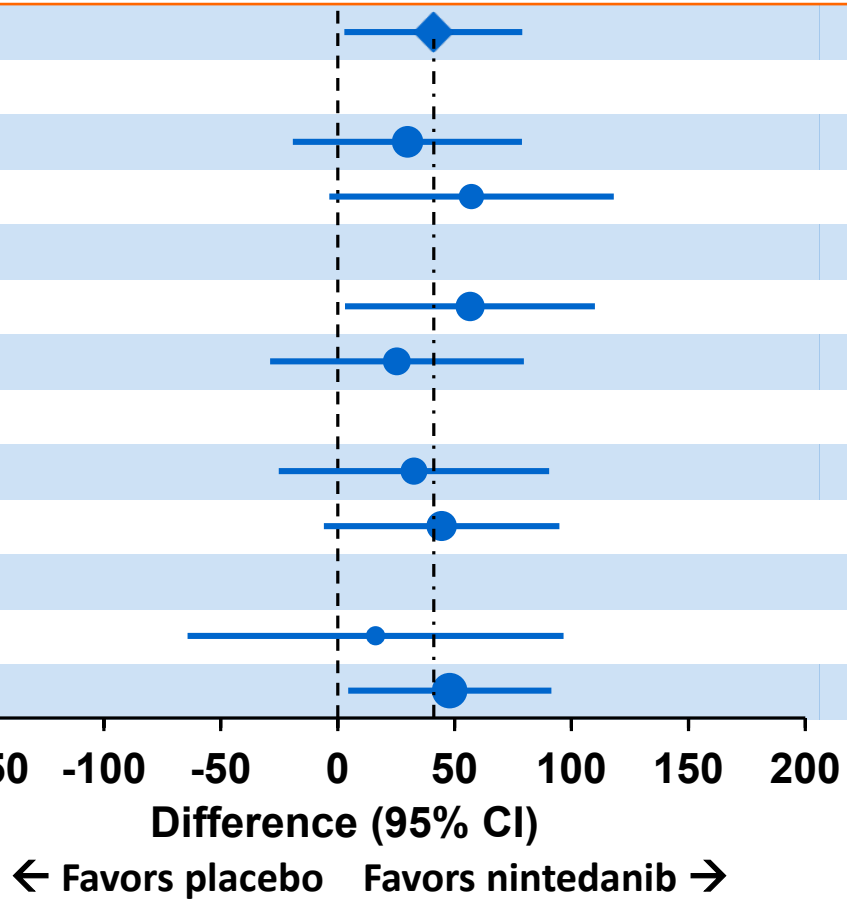
Patients, n													
Placebo	288	283	281	280	283		280		268				257
Nintedanib	288	283	281	273	278		265		262				241

SENSCIS: Adjusted Annual Rate of FVC Decline



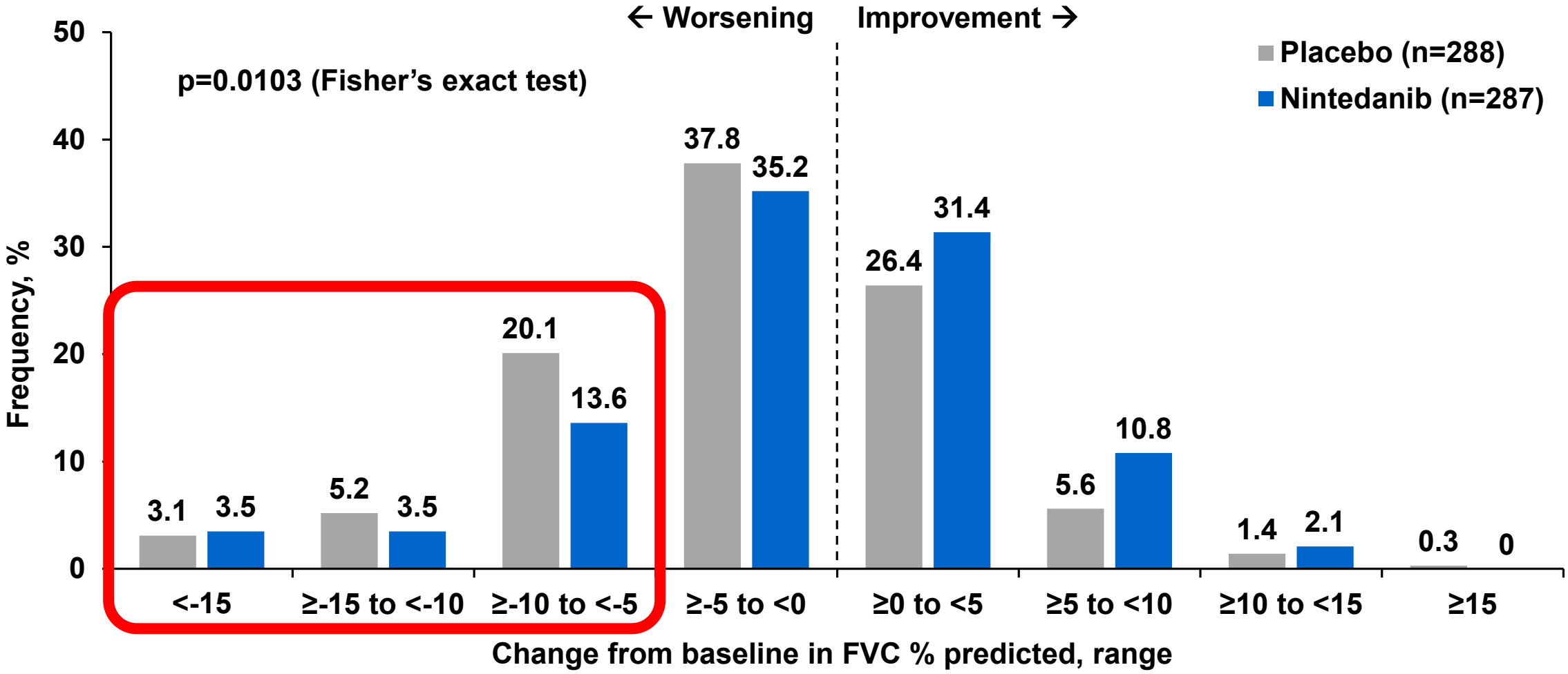
SENSCIS: Additional Subgroup Analyses of Primary Endpoint

	Analyzed, n		Difference (95% CI)	p value[a]
	Placebo	Nintedanib		
All patients	**288**	**287**	**41.0 (2.9, 79.0)**	
ATA status				
Negative	177	173	29.9 (-19.1, 78.8)	0.491
Positive	111	114	57.2 (-3.5, 118.0)	
SSc subtype				
Diffuse cutaneous	146	153	56.6 (3.2, 110.0)	0.420
Limited cutaneous	142	134	25.3 (-28.9, 79.6)	
FVC % predicted				
<70% predicted	127	127	32.62 (-25.22, 90.47)	0.7616
≥70% predicted	161	160	44.47 (-5.93, 94.87)	
Extent of fibrotic ILD				
<20%	74	57	16.21 (-64.10, 96.52)	0.4958
≥20%	214	230	47.90 (4.46, 91.34)	



[a] Treatment-by-time-by-subgroup interaction.

SENSCIS: Categorical Analysis



SSc-ILD—Where We Are…

- Patients with scleroderma are affected in the prime of their lives. They are parents, children, siblings, employers, employees, and caregivers. Their major personal relationships, quality of life, and functional status are all adversely affected
- Lung fibrosis is the leading cause of death
- No approved therapies are available for SSc-ILD
  - Unapproved immunosuppressive therapies may provide short-term benefit in selected subsets
- As with IPF, prevention or slowing of disease progression, as measured by FVC, is a therapeutic goal
- Effective antifibrotic therapy is needed

Medication Use for Hypertension / PAH

SENSCIS – 52 Weeks

Customized drug grouping Preferred name	Patients, n (%) Placebo n=288	 Nintedanib n=288
Antihypertensives	204 (70.8)	210 (72.9)
Nifepidine	66 (22.9)	60 (20.8)
Amlodpine	30 (10.4)	34 (11.8)
Amlodpine besilate	23 (8.0)	23 (8.0)
Bosentan	23 (8.0)	21 (7.3)
Sildenafil	18 (6.3)	20 (6.9)
Sildenafil citrate	13 (4.5)	14 (4.9)
Diltiazem hydrochloride	15 (5.2)	13 (4.5)
Iloprost trometamol	8 (2.8)	8 (2.8)
Iloprost	7 (2.4)	6 (2.1)
Epoprostenol	0	1 (0.3)

Post-hoc Responder Analyses for Absolute Decline From Baseline in FVC % Predicted

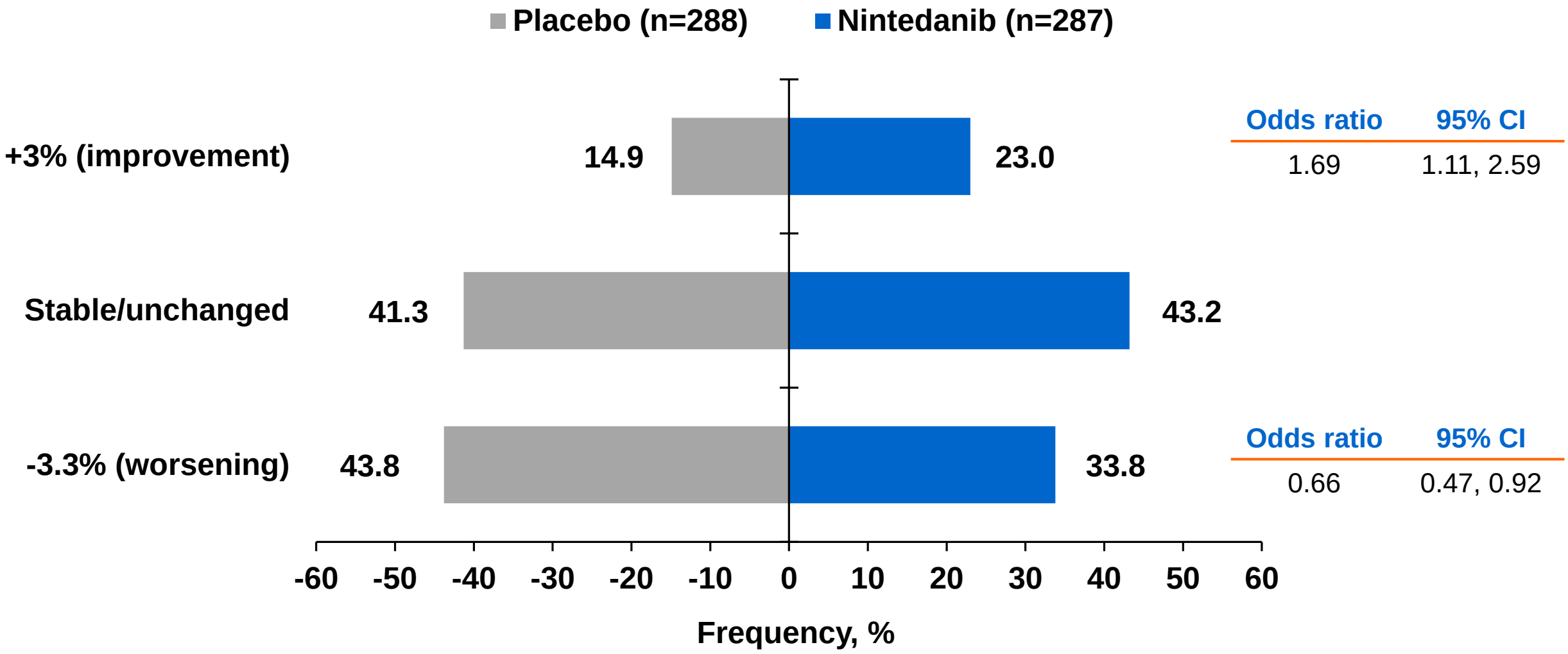
SENSCIS (Worst Value Carried Forward)

	Nintedanib	Placebo
Analyzed, n	287	288
Absolute decline in FVC % predicted at Wk 52, n (%)		
>5% predicted	**59 (20.6)**	**82 (28.5)**
Odds ratio (95% CI)	0.65 (0.44, 0.96)	
p value	0.0287	
>10% predicted	**20 (7.0)**	**24 (8.3)**
Odds ratio (95% CI)	0.82 (0.44, 1.52)	
p value	0.5342	

Percent of patients with disease worsening lower in nintedanib treatment group

Missing values at Week 52 were imputed using a worst value carried forward approach.

Responder Analysis[a]
Change From Baseline in FVC % Predicted at 52 Weeks



[a] Worst observation carried forward.

Restricted Medication Use

SENSCIS – 52 Weeks

	Patients, n (%)			
	Initiated during study treatment		Initiated post treatment	
	Placebo n=288	Nintedanib n=288	Placebo n=288	Nintedanib n=288
Mycophenolate (mofetil, acid, sodium)	4 (1.4)	4 (1.4)	2 (0.7)	2 (0.7)
Methotrexate	1 (0.3)	1 (0.3)	0	1 (0.3)
Added first restricted medication	**9 (3.1)**	**11 (3.8)**	**5 (1.7)**	**10 (3.5)**
Cyclophosphamide	2 (0.7)	5 (1.7)	2 (0.7)	7 (2.4)
Azathioprine	3 (1.0)	0	1 (0.3)	0
Rituximab	1 (0.3)	3 (1.0)	1 (0.3)	1 (0.3)
Tocilizumab	0	1 (0.3)	0	2 (0.7)
Tacrolimus	3 (1.0)	2 (0.7)	1 (0.3)	1 (0.3)

Defintion of Clinically Significant Deterioration
SENSCIS

Clinically significant deterioration is defined as

- Absolute decline since baseline in FVC percent predicted >10% (in the absence of other causes for FVC deterioration[a])
- Relative change from baseline in mRSS of >25% and an absolute change from baseline of >5 patients
- Clinically significant deterioration in other organ systems or clinical parameters at the discretion of the investigator

Initiation of additional therapy, including immunosupressants, was allowed as deemed necessary by the investigator

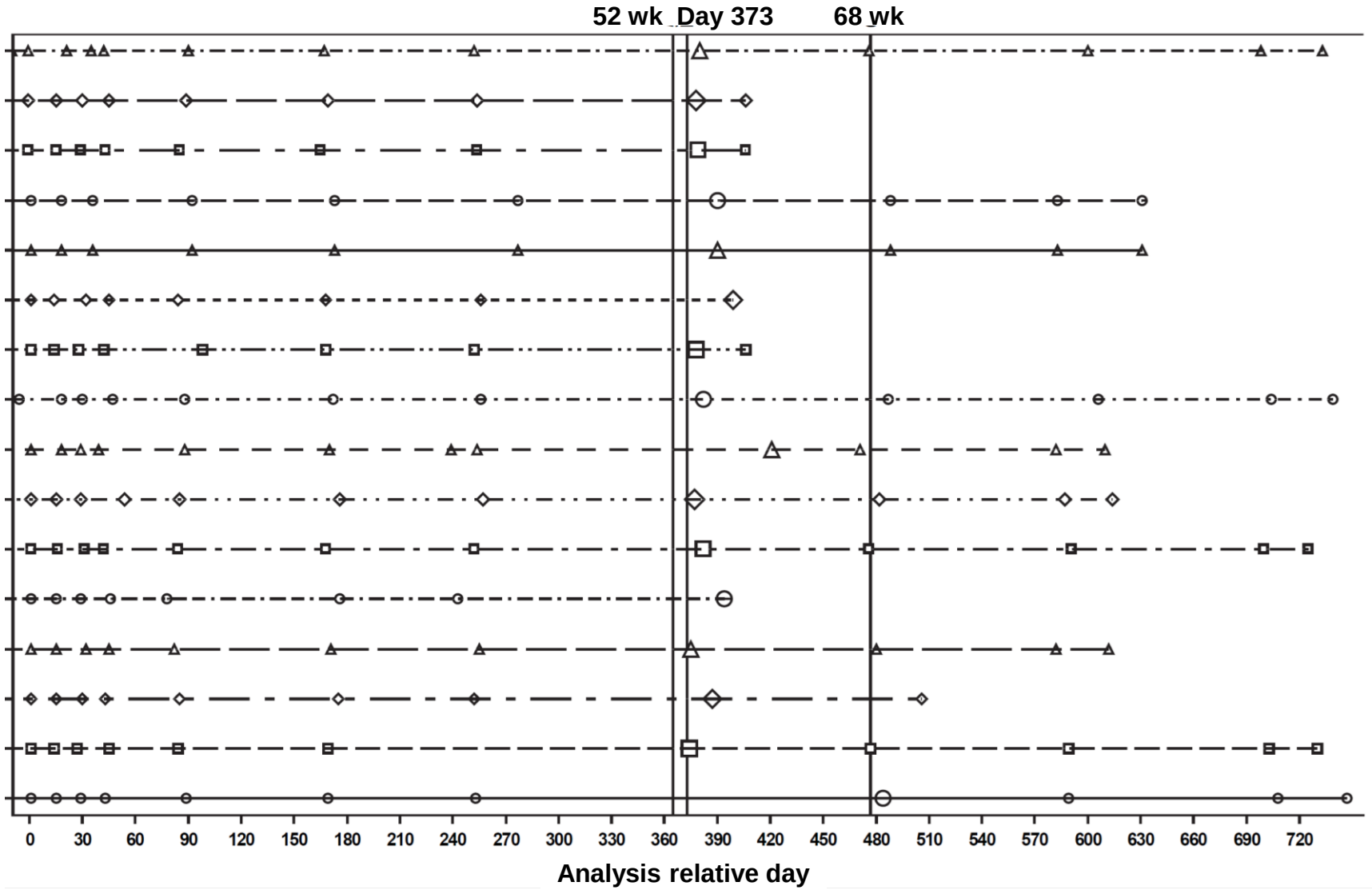
[a] Other causes for FVC decline (ie, respiratory tract infection) should be excluded.

Timing of FVC in Patients With FVC Data After Week 52

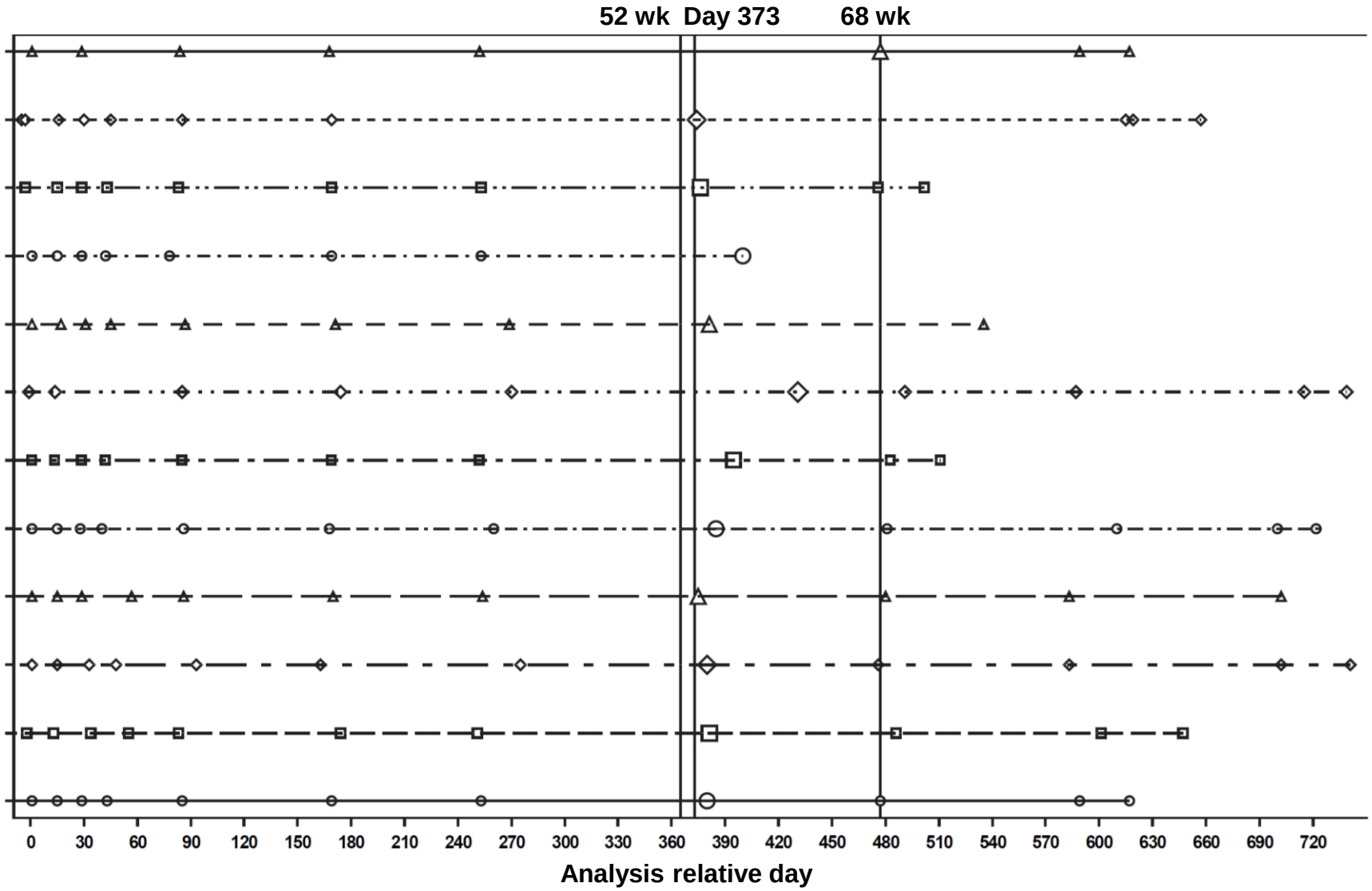
- Time (days) between end of 52 week time window and FVC assessment

	Placebo n=12	Nintedanib n=16
Q1	5.0	5.0
Median	8.0	9.0
Q3	24.5	19.0
Timing ≤28 days, n (%)	10 (83)	14 (88)

Timing of FVC in Patients with FVC Data After Week 52
Nintedanib Group

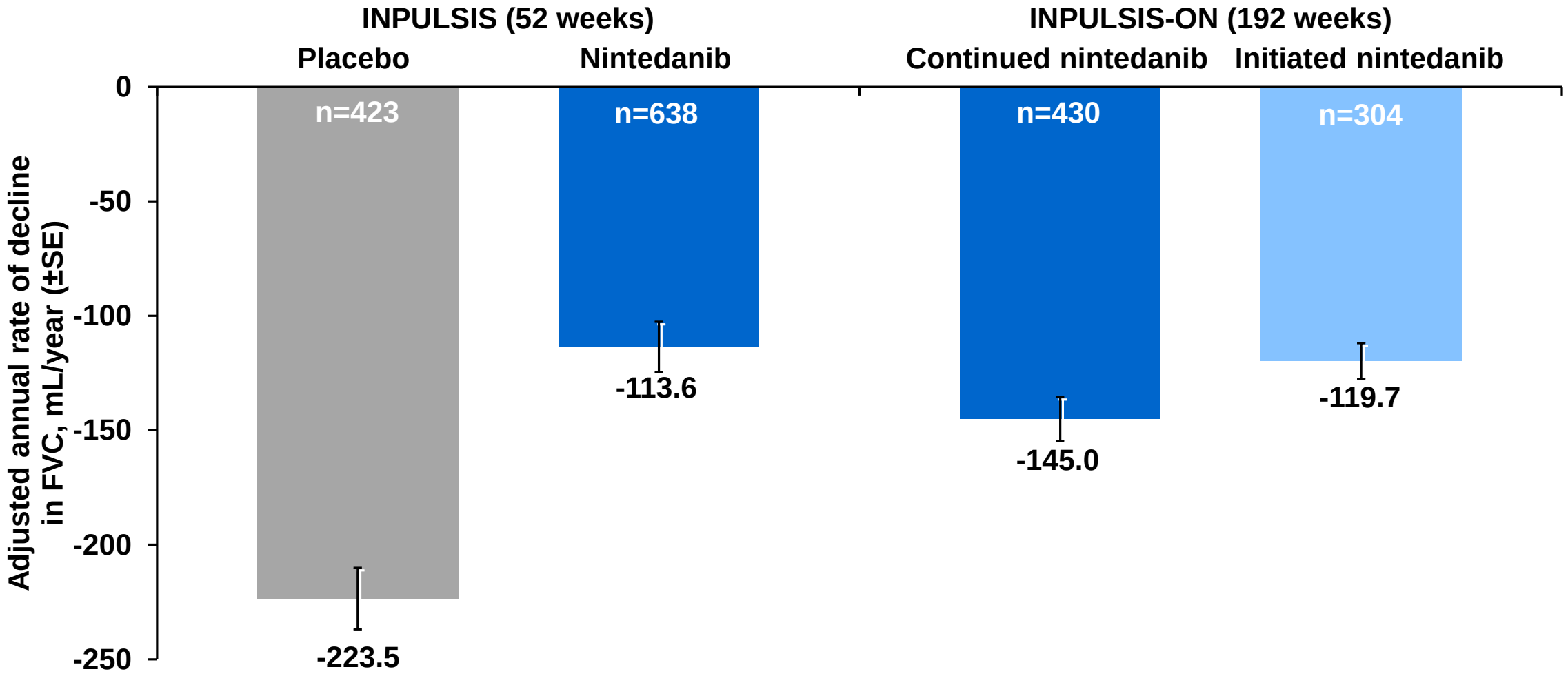


Timing of FVC in Patients with FVC Data After Week 52 Placebo Group



Annual Rate of Decline in FVC

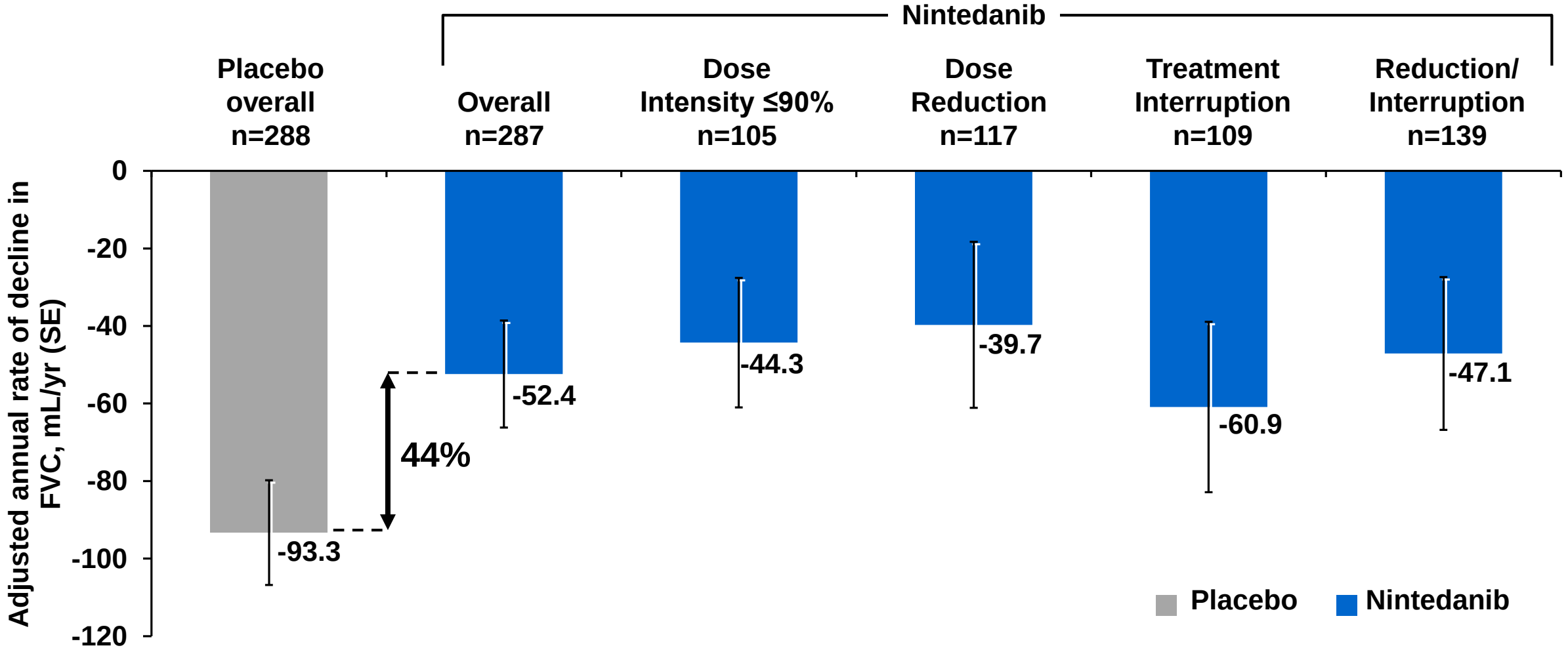
INPULSIS and INPULSIS-ON



Crestani B, et al. *Lancet Respir Med.* 2019;7(1):60-68.

Rate of Decline in FVC (mL/yr) over 52 Weeks by Dose Reductions and Treatment Interruptions

SENSCIS



PRO Strategy

- At the time of the SENSCIS trial no disease-specific PRO measures were available for SSc-ILD.
- Selection of PRO measures informed by recommendations from the **OMERACT CTD-ILD working group**
- Core patient-reported **outcome domains**: **Health-related quality of life** (HRQL), **dyspnea, cough**, and functional status
- In the absence of disease-specific measures, PROs developed for other conditions were utilized to measure these key domains: e.g. SGRQ, FACIT-Dyspnea

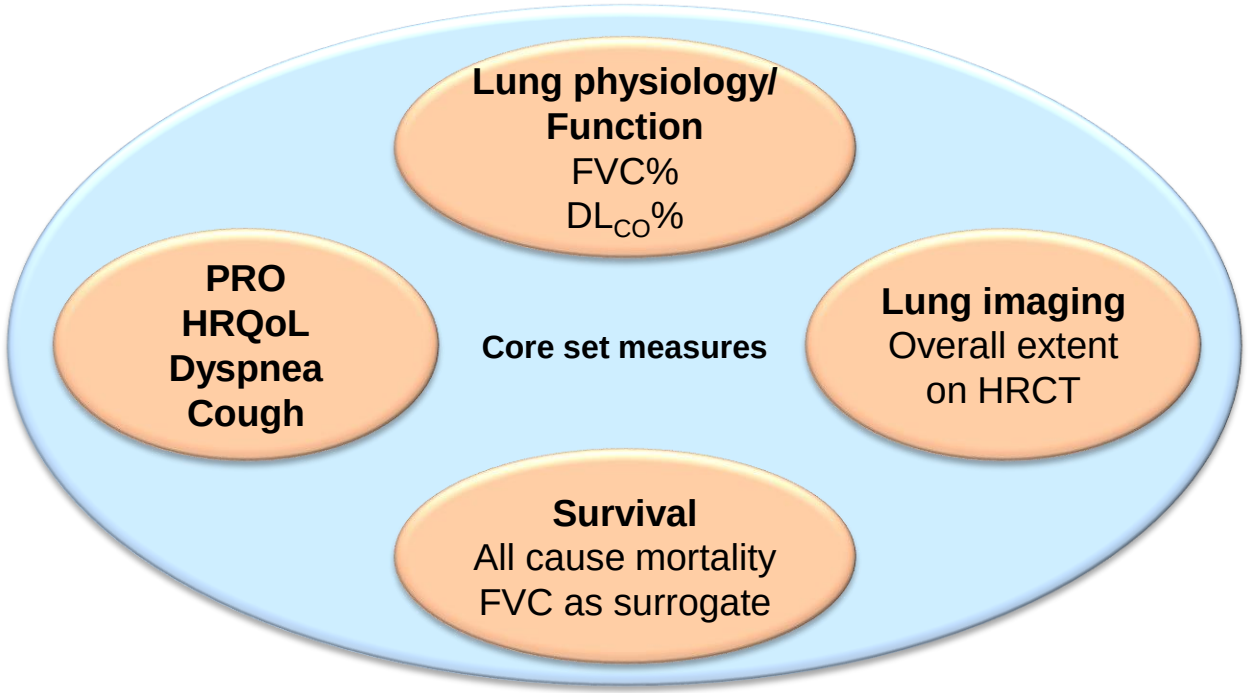


Figure adapted from Khanna D, et al. *J Rheumatol.* 2015;42(11):2168-2171; DOI: https://doi.org/10.3899/jrheum.141182

Treatment Interruptions, Reductions and Discontinuations

SENSCIS – 52 Weeks

	Patients, n (%)	
	Placebo n=288	Nintedanib n=288
Treatment interruption	33 (11.5)	109 (37.8)
Dose reduction	13 (4.5)	117 (40.6)
Dose increase after reduction	2 (0.7)	25 (8.7)
Second dose reduction	0	13 (4.5)
Premature treatment discontinuation	31 (10.8)	56 (19.4)

PRO-Scores: Ability to Detect Change

Mean Change in SGRQ and FACIT-Dyspnea at Week 52 by change in FVC% predicted status (SENSCIS Treated Set)

	FVC decline >10% predicted (n=37)	FVC decline >5 and ≤10% predicted (n=81)	FVC decline >2% and ≤5% predicted (n=95)	FVC |Δ| ≤2 % predicted (n=178)	FVC increase >2% and ≤5% predicted (n=66)	FVC increase >5 and ≤10% predicted (n=33)	FVC increase >10% predicted (n=9)	p Value
SGRQ Total Score	5.5 (17.9)	1.4 (13.8)	-0.6 (15.6)	-1.1 (14.3)	-1.8 (15.6)	-3.4 (11.1)	-3.8 (6.91)	0.1210
FACIT-Dyspnea	3.1 (7.59)	0.9 (6.25)	1.0 (6.75)	-0.0 (6.86)	0.2 (6.81)	-1.2 (6.33)	0.4 (6.17)	0.1786

Changes in SGRQ and FACIT Dyspnea scores do not differ significantly in patients with different responses in FVC

Analysis of variance models (ANOVAs) were used to examine whether mean change in the respective PRO score from Baseline to Week 52 was significantly different among patients in the varying responder groups
SGRQ scores range from 0 (no impairment) to 100 (worst possible impairment)
FACIT Dyspnea scale scores range from 27.7 (raw score=0) to 75.9 (raw score=30). Higher scores represent worse dyspnea or increased functional limitation.

GI AEs by Predisposition[a] to GI Events

SENSCIS – 52 Weeks

MedDRA PT	Patients, n (%)			
	Without predisposition to GI events		With predisposition to GI events	
	Placebo n=53	Nintedanib n=54	Placebo n=235	Nintedanib n=234
Diarrhea	11 (20.8)	38 (70.4)	80 (34.0)	180 (76.9)
Nausea	4 (7.5)	17 (31.5)	35 (14.9)	74 (31.6)
Vomiting	2 (3.8)	11 (20.4)	28 (11.9)	60 (25.6)
Abdominal pain[b]	3 (5.7)	9 (16.7)	29 (12.3)	44 (18.8)
GERD	1 (1.9)	2 (3.7)	21 (8.9)	10 (4.3)

[a] Predisposition to GI events: Patients with reported underlying GERD, esophageal dysphagia, malabsorption, SSc-related diarrhea or constipation.
[b] MedDRA high-level term (related preferred terms grouped by anatomy, pathology, physiology, aetiology, or function).

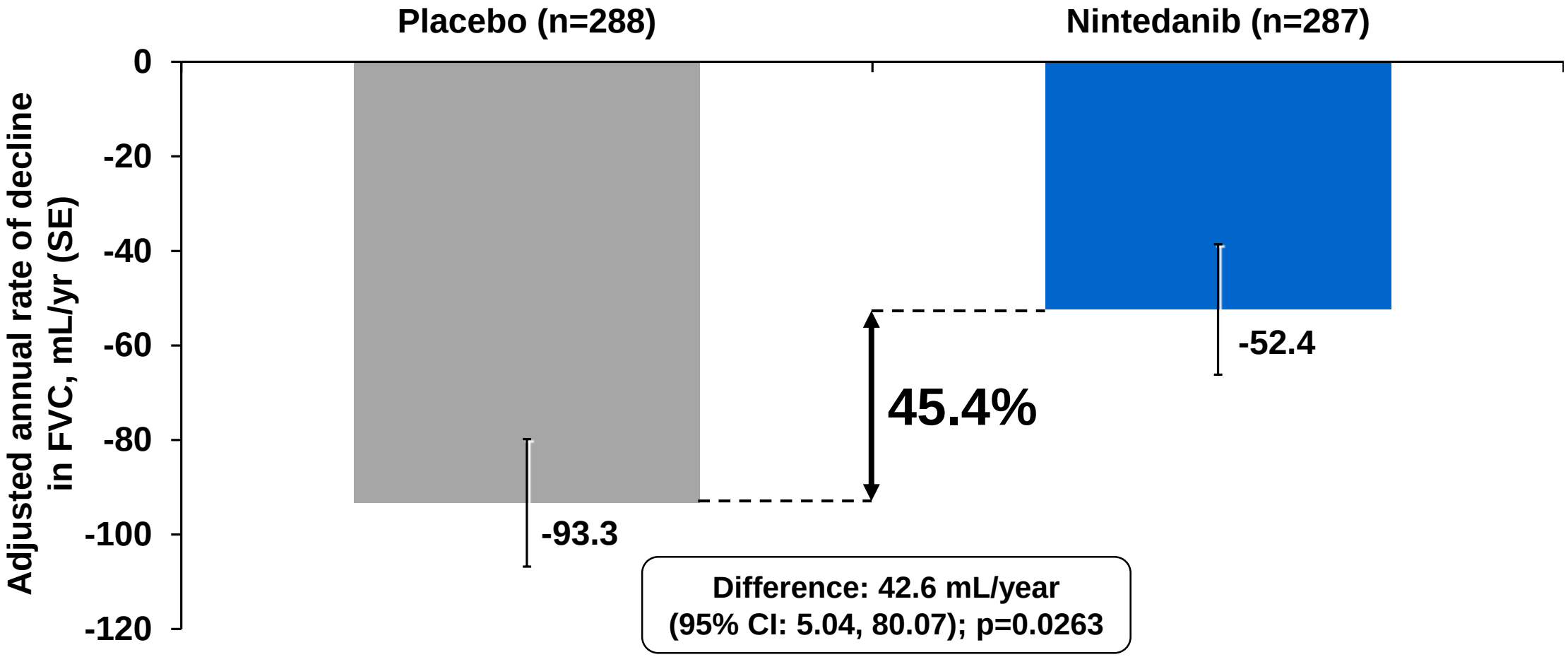
FVC Over Entire Trial – Treatment Policy Strategy

	Adjusted annual rate of decline, mL/yr (SE)	Adjusted difference at 100 weeks, mL (95% CI)
Placebo (n=288)	-88.8 (10.9)	65.3 (6.6, 124.1)
Nintedanib (n=287)	-54.9 (11.1)	

Based on slopes derived from random slope and intercept model as for the primary analysis.
Analysis including all off-treatment data of patients who discontinued treatment prematurely.

Primary Endpoint: Annual Rate of Decline in FVC (mL/yr) Over 52 Weeks

SENSCIS



Similar Nintedanib Plasma Exposure Between Patients With and Without Mycophenolate Co-treatment

Dose-normalized steady state trough plasma concentrations of nintedanib after multiple oral administration twice daily in patients with SSc-ILD without (No) compared to with (Yes) Mycophenolate comedication.