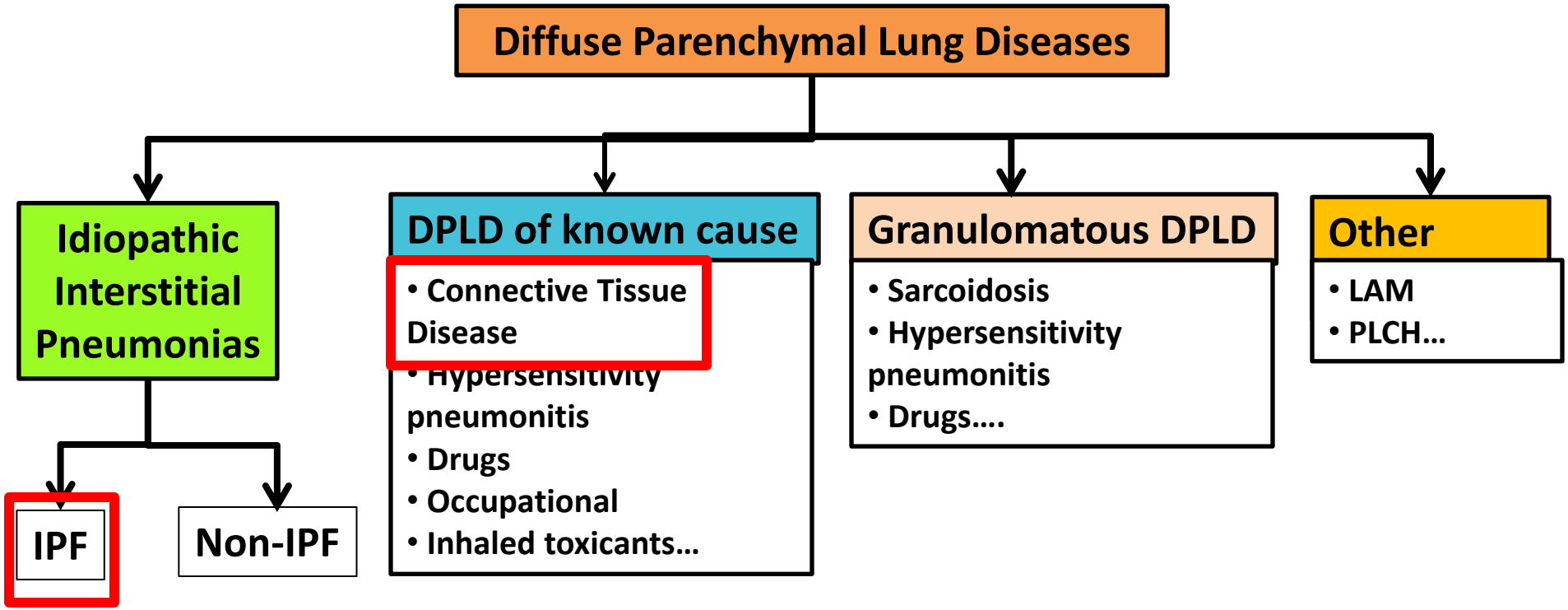
Η θέση του αντι-ινωτικού παράγοντα στη θεραπευτική των ασθενών με νοσήματα του συνδετικού ιστού και διάμεση πνευμονοπάθεια

DPLD classification



Modified from ATS/ERS. Am J Respir Crit Care Med 2002 ;165(2):277-304.

Respiratory involvement in CTDs

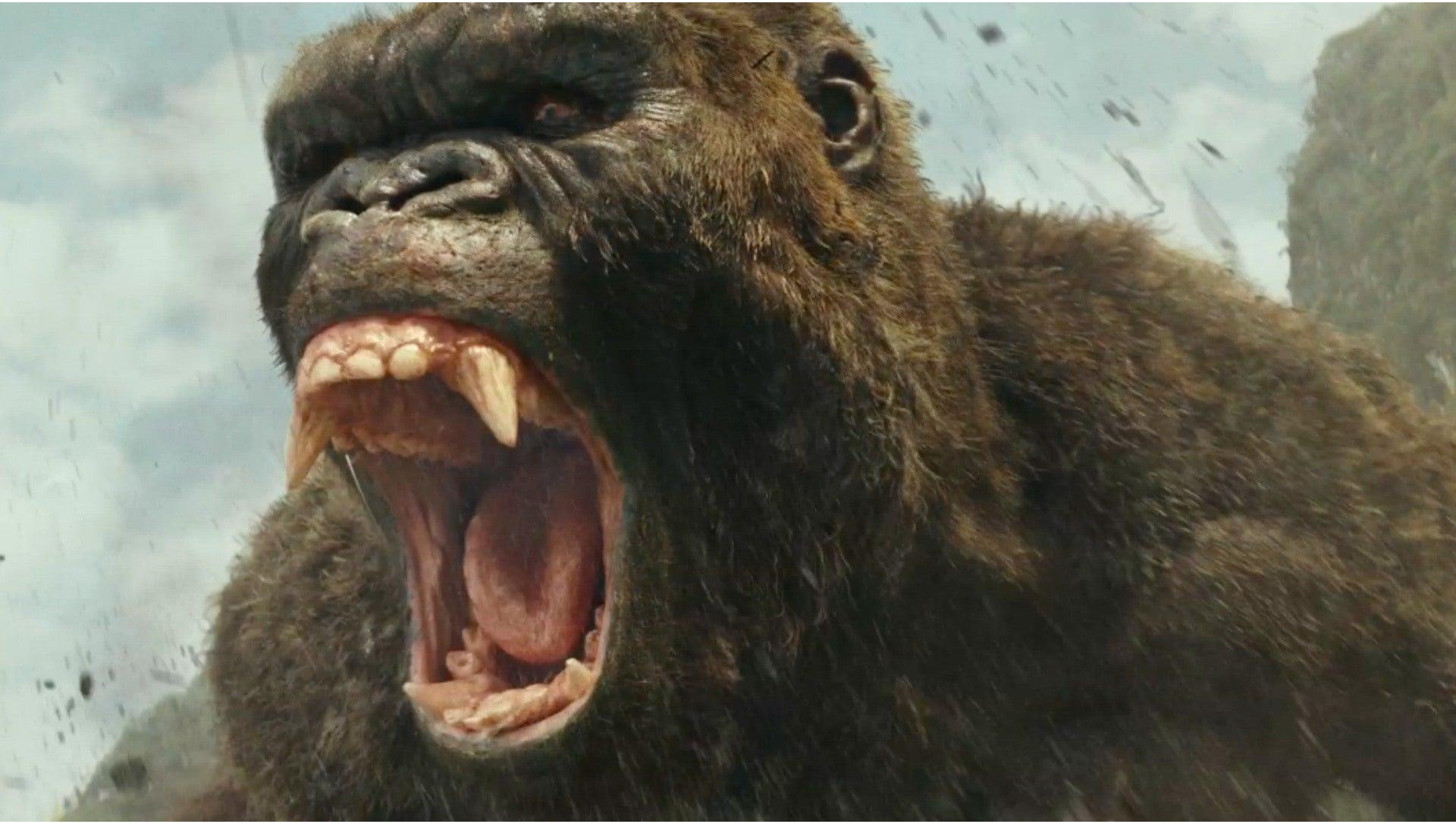
Manifestation	RA	SLE	SS	DM-PM	Sjögren's syndrome	MCTD	AS
Pleural effusion	++	++	±	–	±	+	–
Pleural fibrosis	+	–	–	–	–	–	–
Pneumothorax	+	–	–	–	±	–	+
Pneumomediastinum	–	–	–	+	–	–	–
Upper airway involvement	+	–	–	–	++	–	+
Bronchiolitis/bronchiectasis	+++	+	+	–	+	+	–/±
UIP	++	+	+	++	–/±	+	+
NSIP	+	+	+++	+++	–/±	++	+
Apical fibrobullous disease	±	–	±	–	–	±	++
LIP	–/±	–/±	–/±	–	+	–	–
Lymphoproliferative disorders	±	–	–	–	+	–	–
CPFE	+	–	±	–	–	±	±
DIP/RB-ILD	+	–	+	–	–	–	–
COP/AFOP	+	+	+	++	+	+	–
Eosinophilic pneumonia	–/±	–	–	–	–	–	–
DAD/ARDS	+	++	+	++	–	+	–
Pulmonary nodules	+	–	–	–	–	–	–
Pulmonary infections	+	+++	+	+	±	+	+
Aspiration pneumonia	–	–	++	++	–	+	±
Lung cancer	–	–	++	++	–	+	–
Pulmonary amyloidosis	–/±	–	–	–	–	–	–
PAH	+	+	++	+	–	++	±
DAH/capillaritis	–/±	+	–/±	–/±	–	±	–
Vasculitis	+	+	–	+	–	+	±
Pulmonary thromboembolism	+	++	+	±	–	+	–
Acute reversible hypoxemia	–	+	–	–	–	–	–
Respiratory muscle dysfunction	–/±	+	–	++	–	–	±
Thoracic cage involvement	±	–/±	–	±	–	–	+
Obstructive sleep apnea	±	–	–	–	–	–	++

Papiris, Bouros et al. Respiration 2015;90:2–24

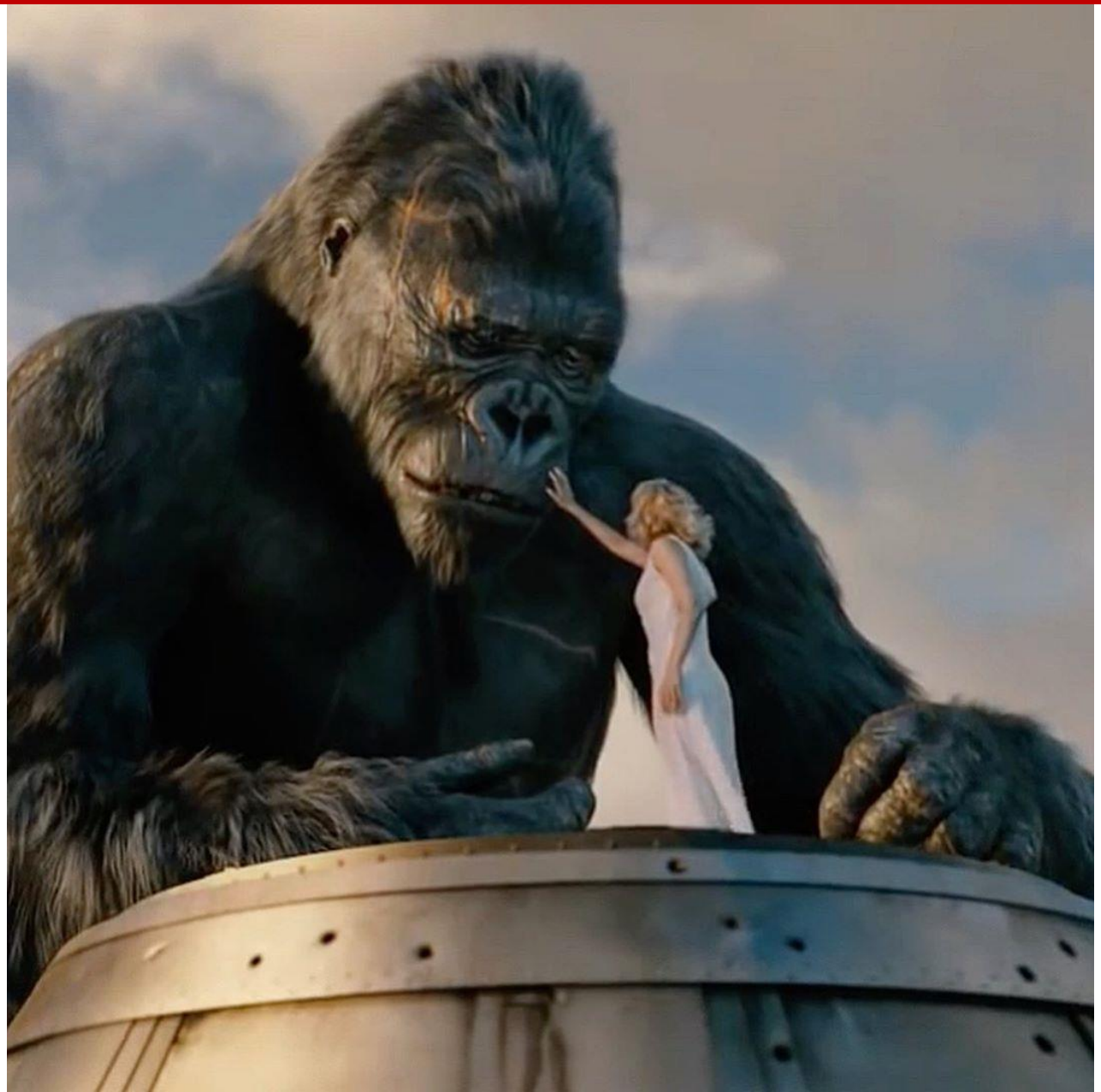
Interstitial Lung Disease in CTD

- **Rheumatoid arthritis: UIP, NSIP**
- **Systemic Sclerosis: NSIP, UIP**
- **Polymyositis-dermatomyositis: OP/NSIP**
- **Sjogren syndrome: NSIP**

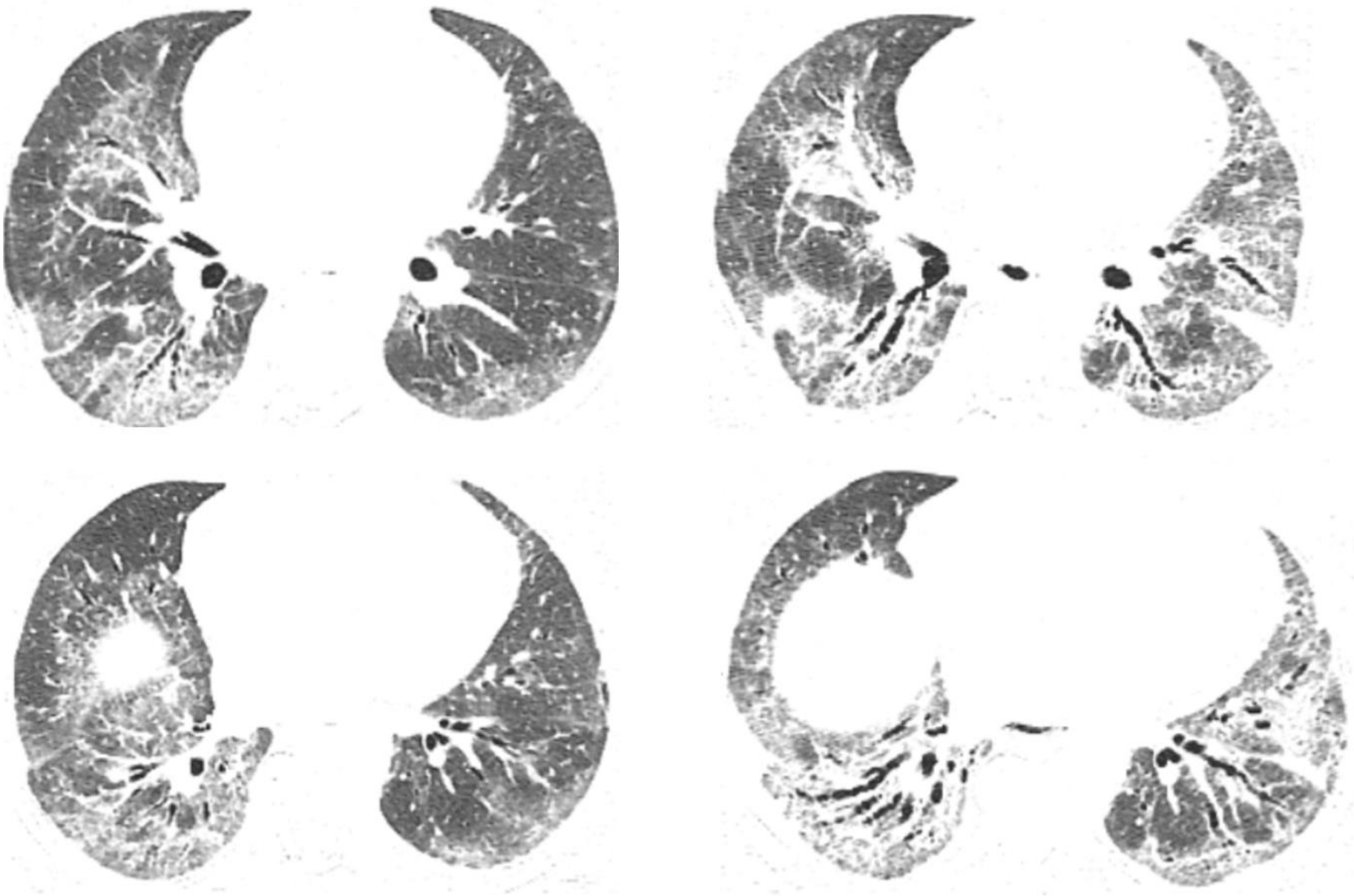
Usual Interstitial Pneumonia



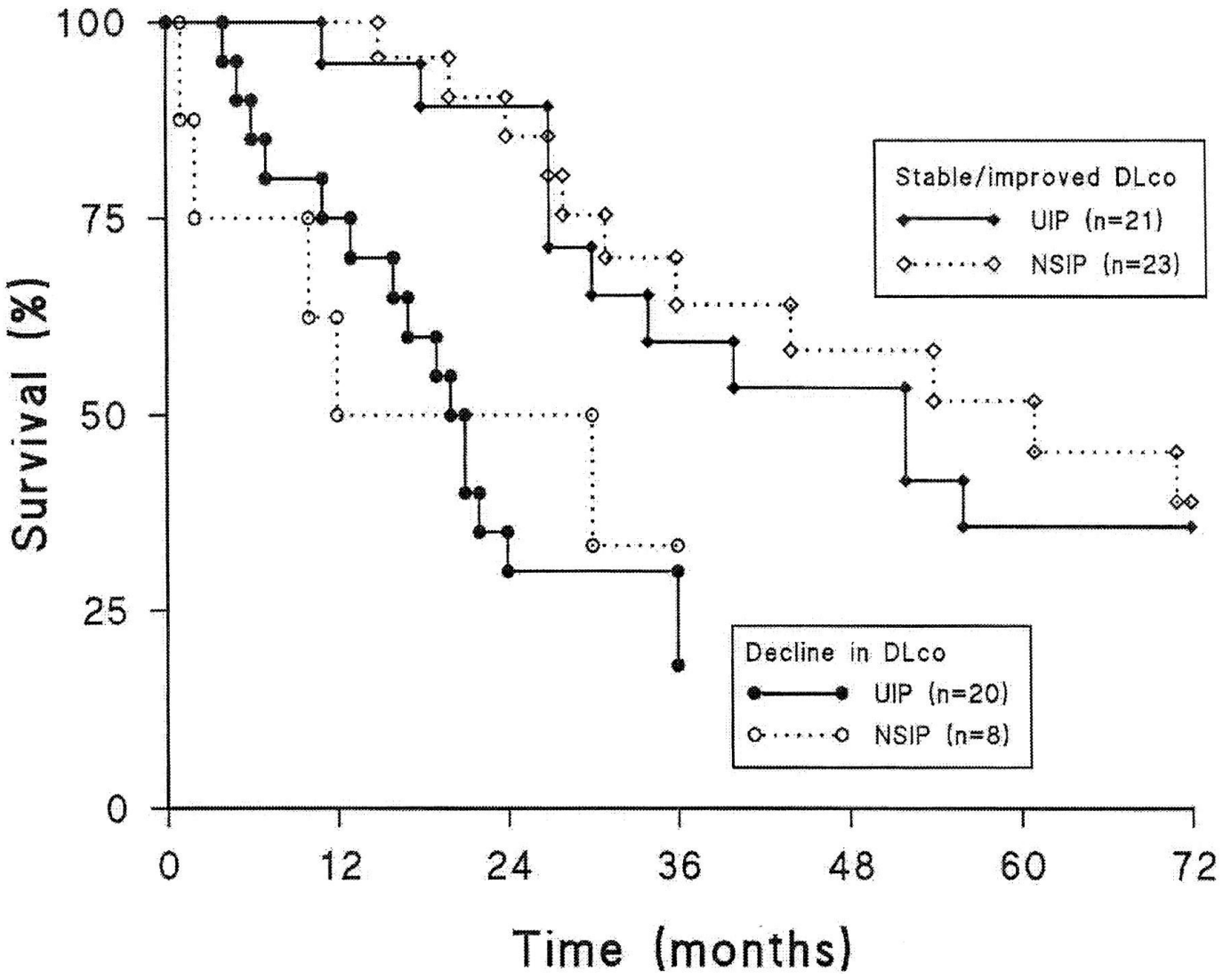
Importance of behavior



48F. Rheumatoid arthritis. Evolution in 3,5 months.



Progression more important than pathology pattern



Am J Respir Crit Care Med. 2003;168(5):531-7

Classification according to ***DISEASE BEHAVIOR***

Idiopathic Interstitial Pneumonias: Classification according to *DISEASE BEHAVIOR*

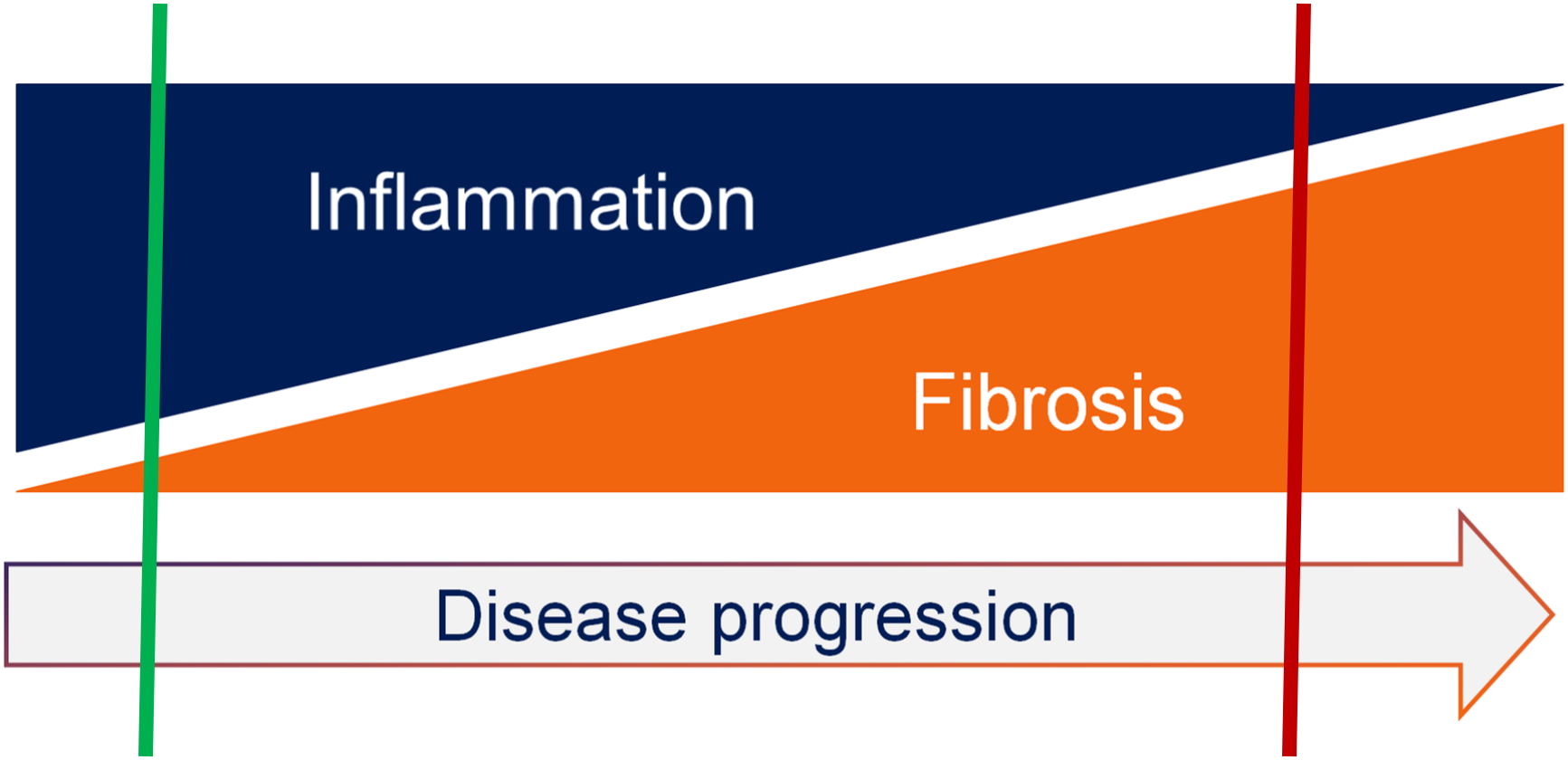
Clinical Behavior	Treatment Goal	Monitoring Strategy
Reversible and self-limited (e.g., many cases of RB-ILD)	Remove possible cause	Short-term (3- to 6-mo) observation to confirm disease regression
Reversible disease with risk of progression (e.g., cellular NSIP and some fibrotic NSIP, DIP, COP)	Initially achieve response and then rationalize longer term therapy	Short-term observation to confirm treatment response. Long-term observation to ensure that gains are preserved
Stable with residual disease (e.g., some fibrotic NSIP)	Maintain status	Long-term observation to assess disease course
Progressive, irreversible disease with potential for stabilization (e.g., some fibrotic NSIP)	Stabilize	Long-term observation to assess disease course
Progressive, irreversible disease despite therapy (e.g., IPF, some fibrotic NSIP)	Slow progression	Long-term observation to assess disease course and need for transplant or effective palliation

Am J Respir Crit Care Med. 2013;188(6):733-48.

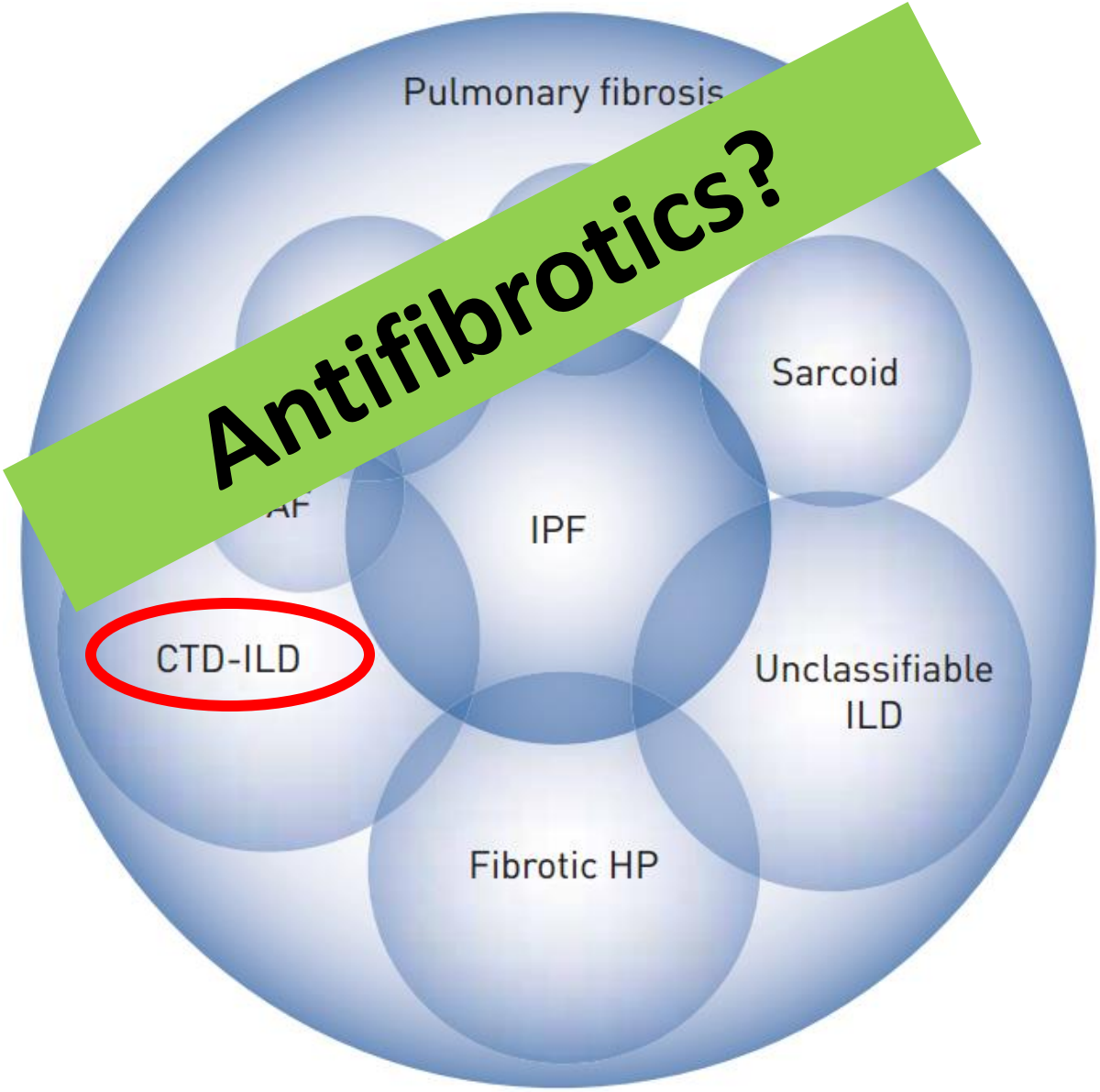
Expanding the paradigm *beyond IIPs*

Clinical Behavior
Reversible (self-limited)
Reversible (risk of progression)
Stable (with residual disease)
Progressive, irreversible (potential for stabilization or slowing progression)

Concept of disease evolution in CTD-ILDs



Longitudinal disease behavior in ILDs



Wells AU et al. Eur Respir J. 2018 May 17;51(5)

INBUILD: Key inclusion criteria

- Age ≥18 years
- Physician-diagnosed ILD other than IPF
- Features of diffuse fibrosing lung disease (reticular abnormality with traction bronchiectasis, with or without honeycombing) of >10% extent on HRCT performed ≤12 months prior to screening, confirmed by central review
- Progressive phenotype
- FVC ≥45% predicted
- DLco ≥30%-<80% predicted

Progressive phenotype (at least one)

A

Relative FVC decline >10%

B

Relative FVC decline 5-10%

Worsening symptoms **OR** Progressive HRCT

C

Worsening symptoms **AND** Progressive HRCT

INBUILD: Baseline characteristics of overall population (1/2)

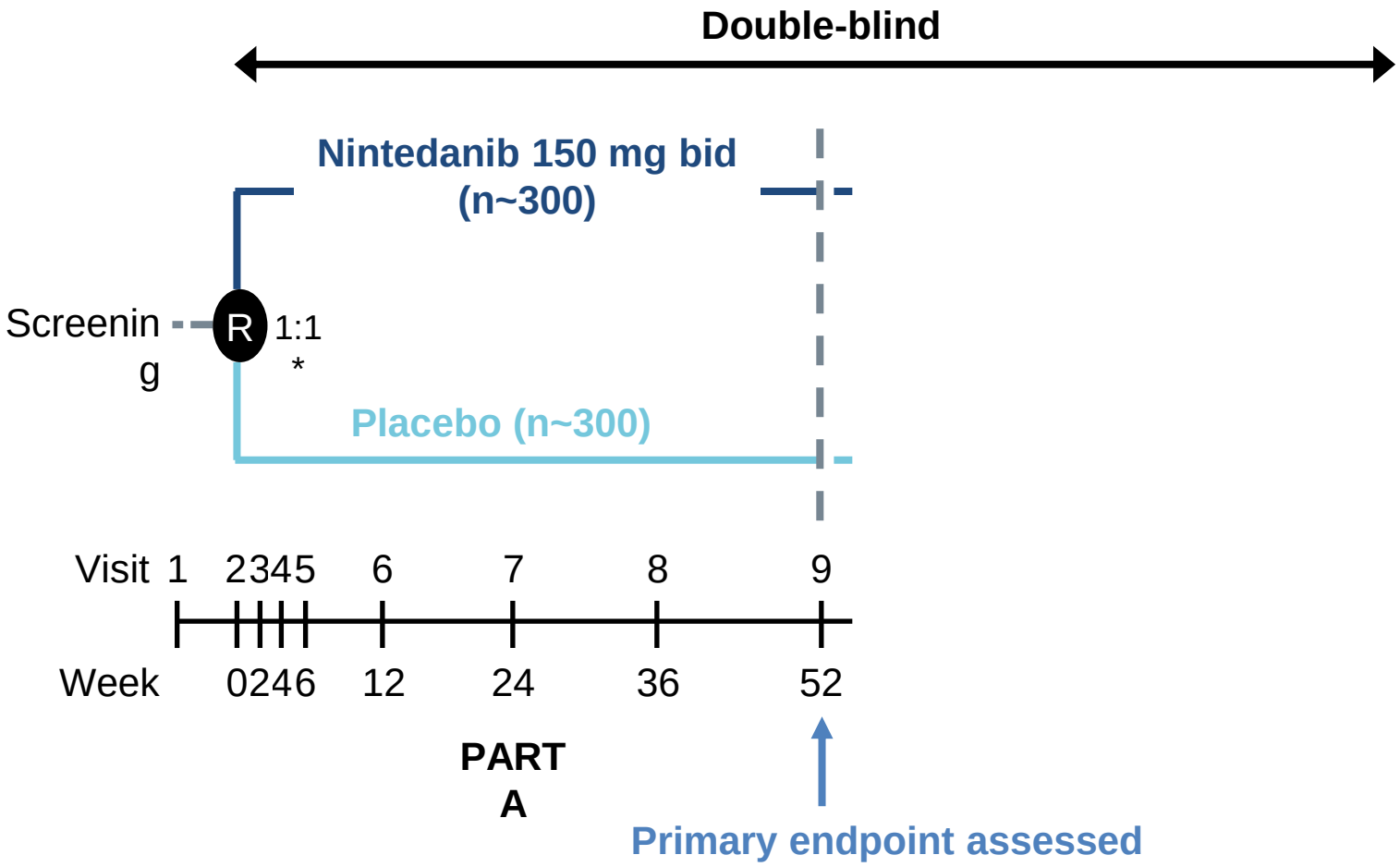
	Nintedanib (n=332)	Placebo (n=331)
Age, years, mean (SD)	65.2 (9.7)	66.3 (9.8)
Male, n (%)	179 (53.9)	177 (53.5)
Body mass index, kg/m^2, mean (SD)	28.1 (5.1)	28.4 (5.5)
Current or former smoker, n (%)	169 (50.9)	169 (51.1)
Race, n (%)*		
White	242 (72.9)	246 (74.3)
Asian	83 (25.0)	80 (24.2)
Black/African-American	5 (1.5)	5 (1.5)
American Indian/Alaska Native/Native Hawaiian/other Pacific Islander	1 (0.3)	0

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.

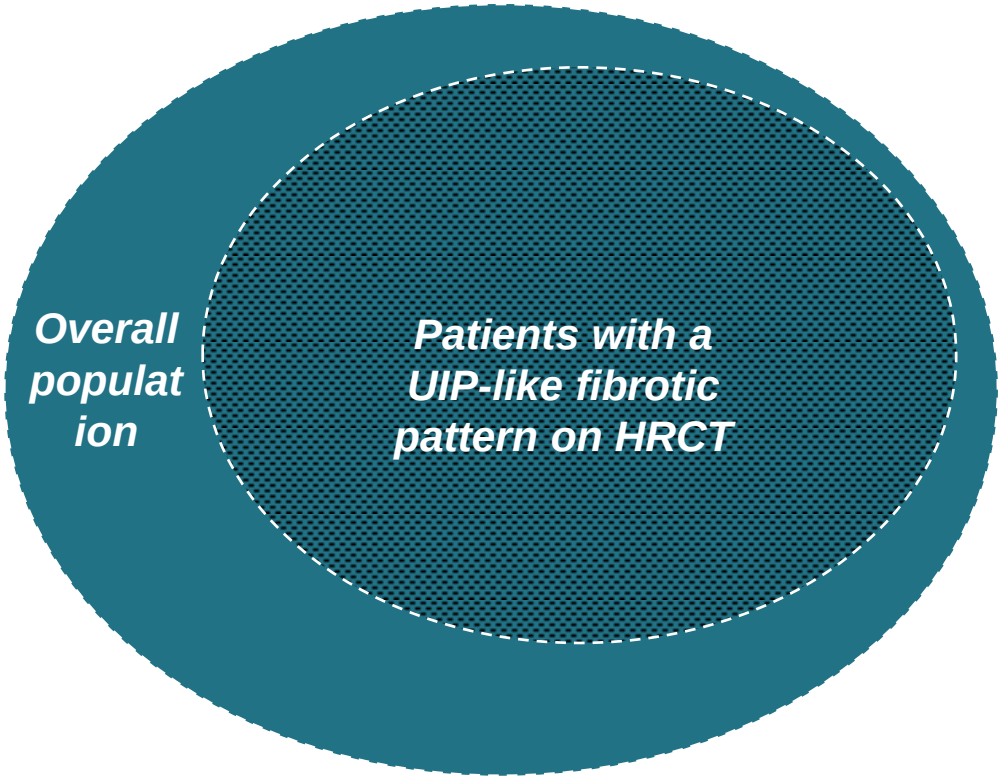
INBUILD: Trial design



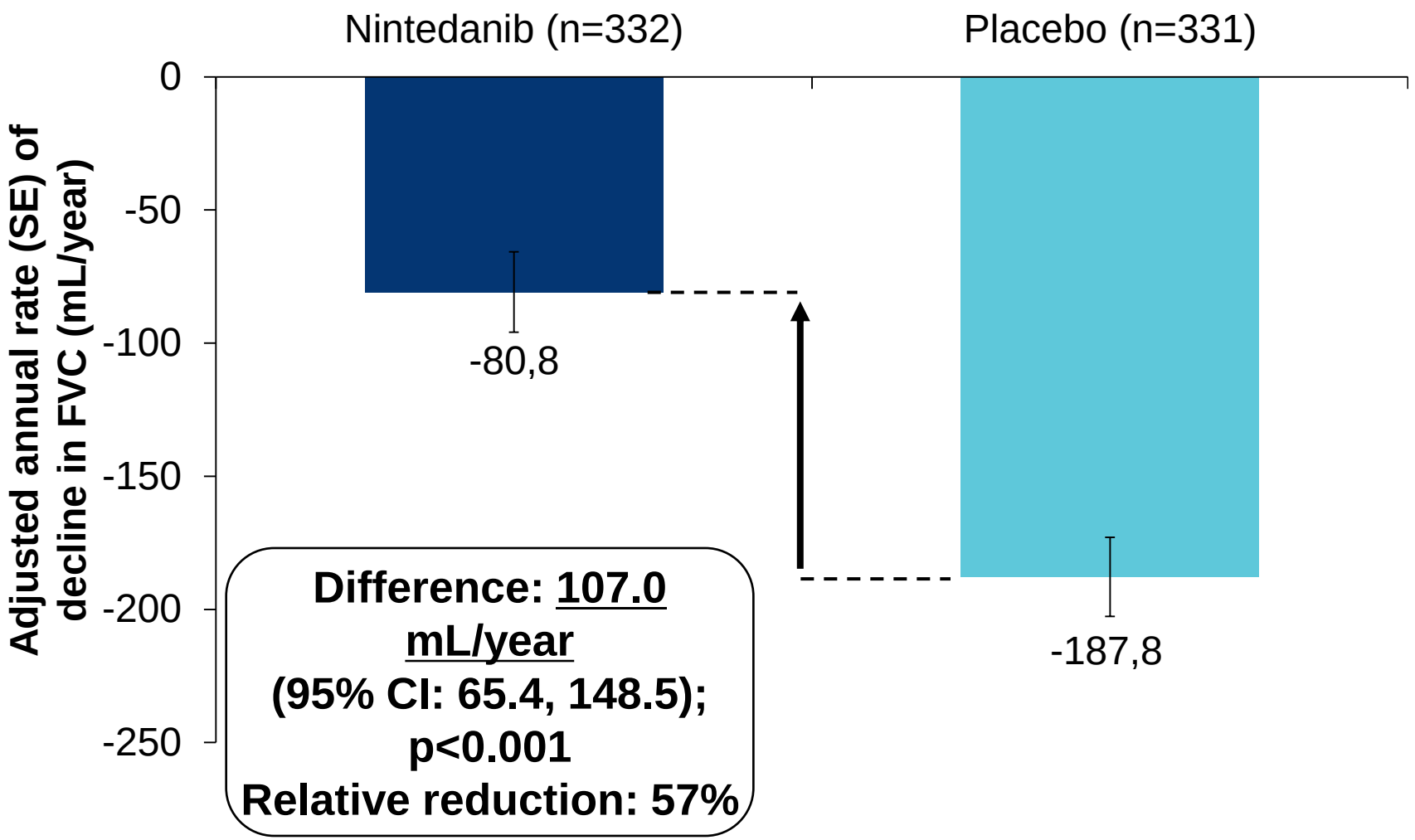
Flaherty K et al; N Engl J Med. 2019 Sep 29.

INBUILD: Primary endpoint

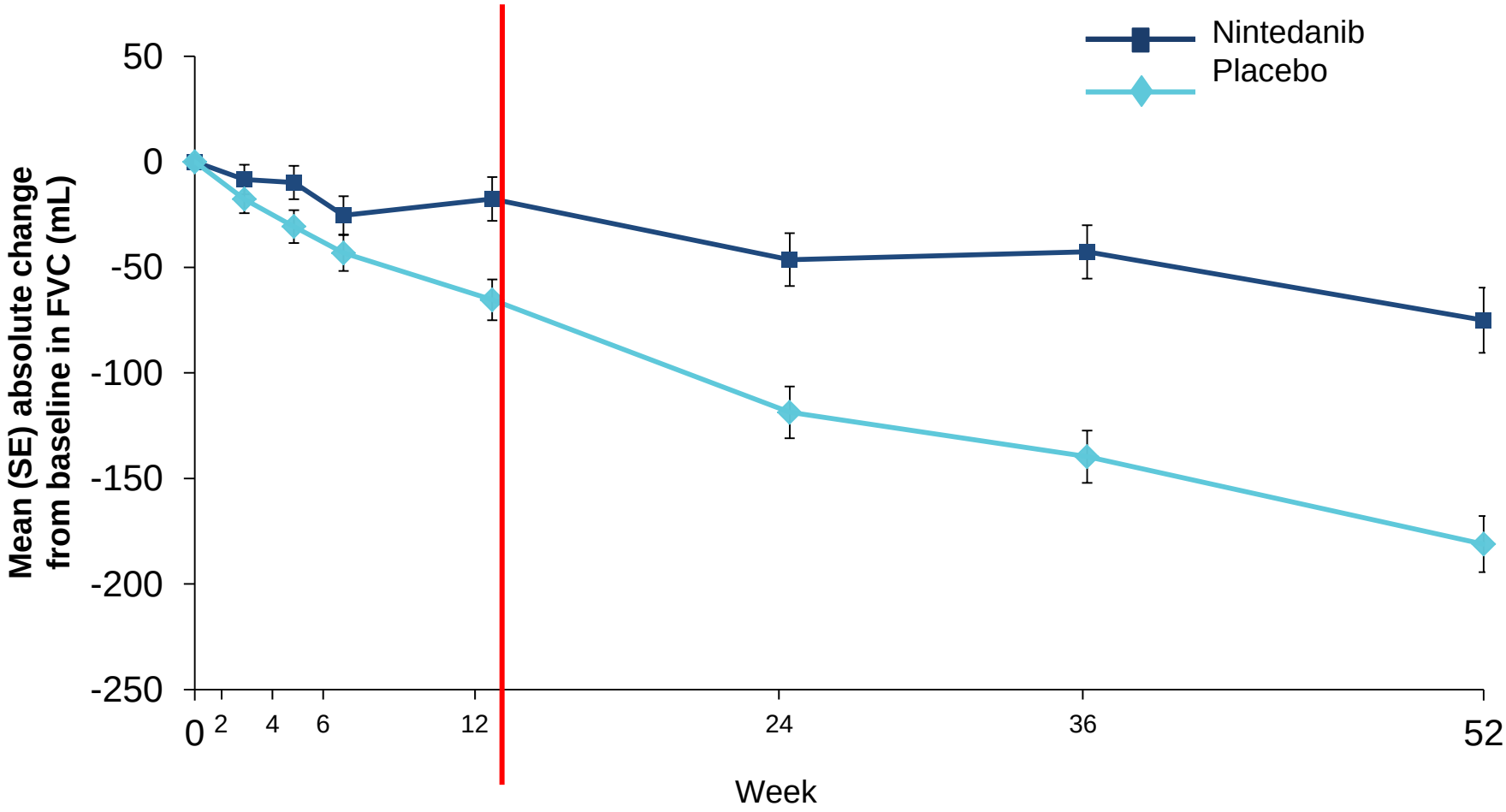
- **Primary endpoint: annual rate of decline in FVC (mL/year) assessed over 52 weeks**



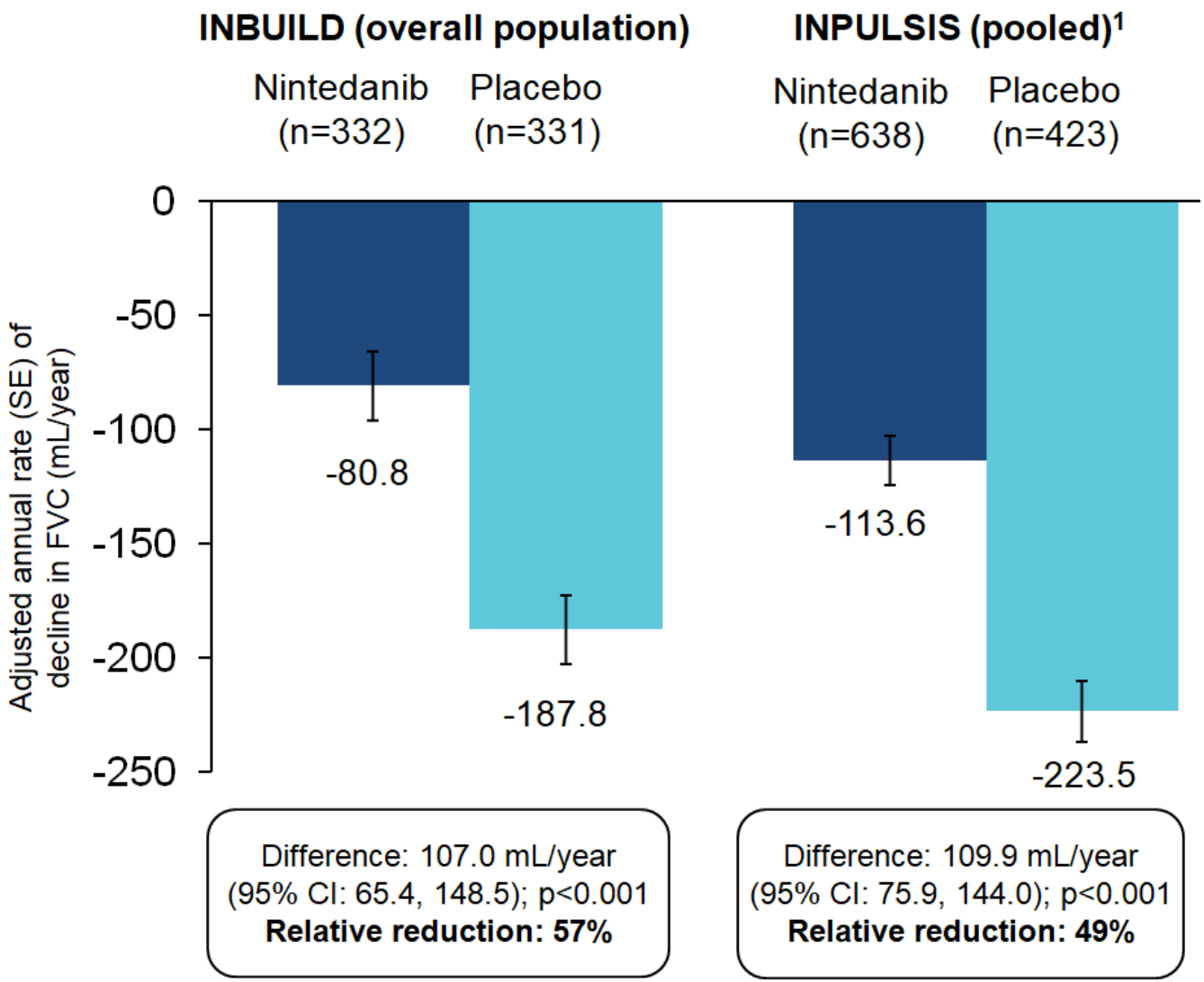
Annual rate of decline in FVC (mL/year) over 52 weeks in overall population



INBUILD: Change from baseline in FVC (mL) over 52 weeks in overall population

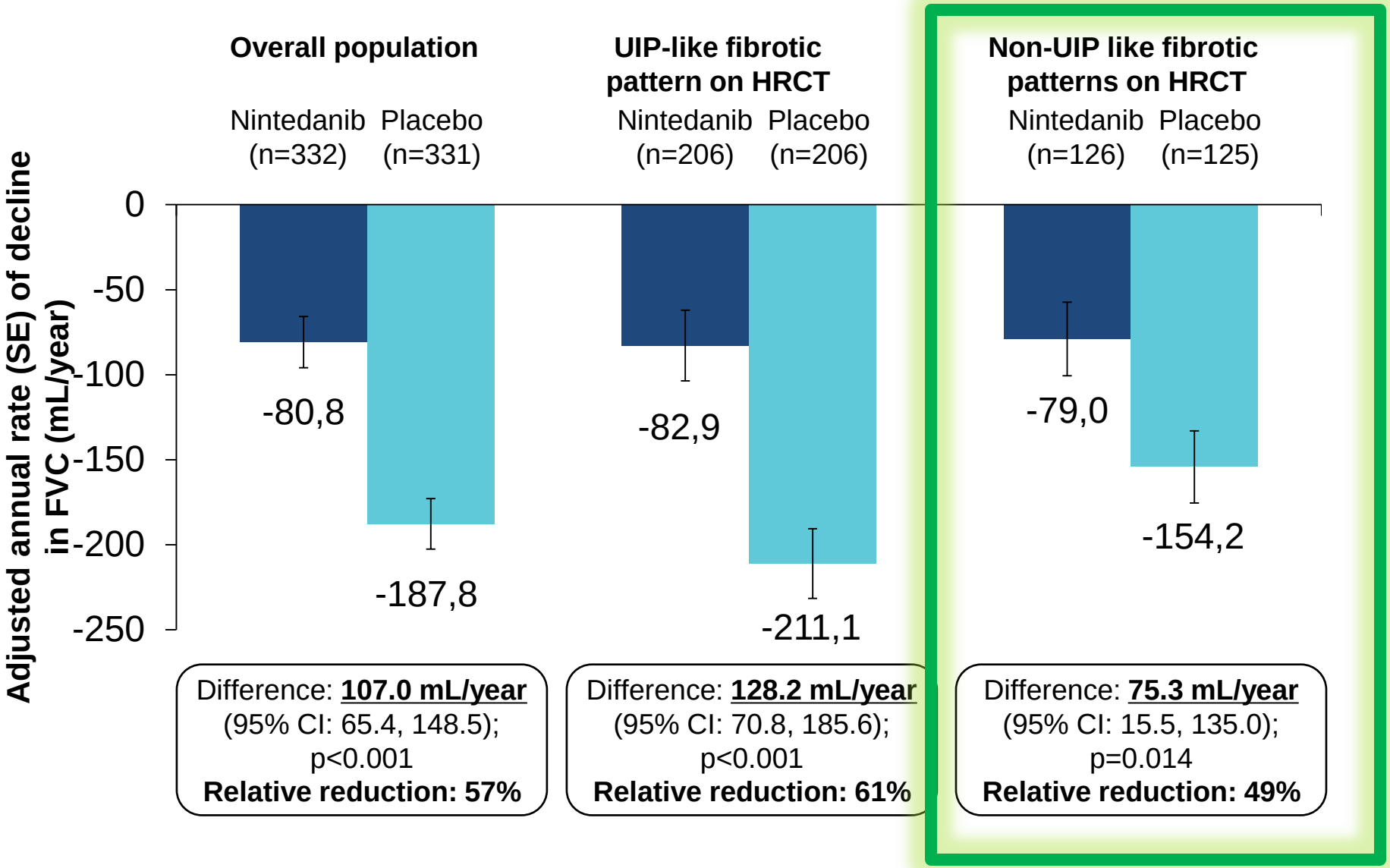


INBUILD and INPULSIS: Annual rate of decline in FVC (mL/year) over 52 weeks



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.

INBUILD: Effect is preserved regardless HRCT pattern



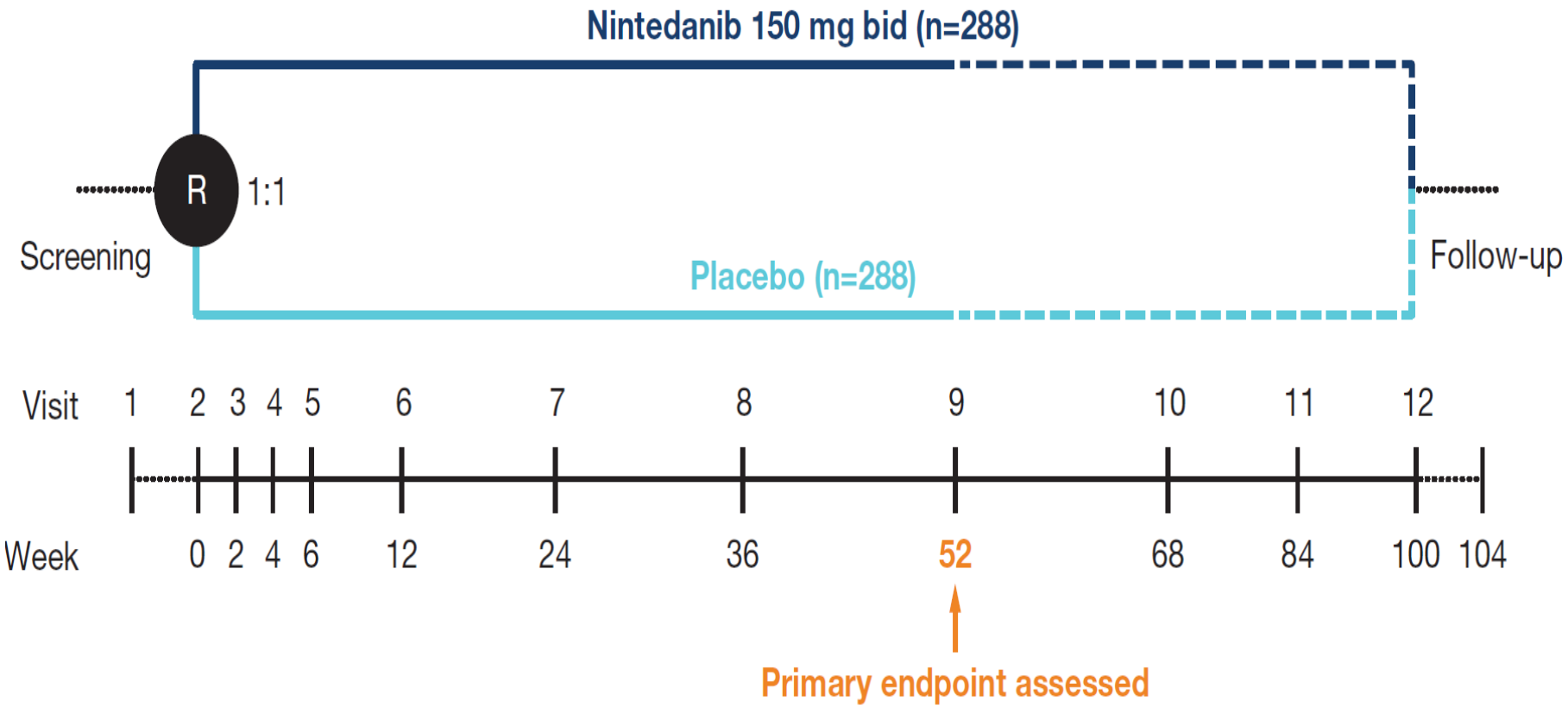
SENCIS trial-Systemic Sclerosis

- ≥ 18 years
- First non-Raynaud's symptom within 7 years before screening
- Extent of fibrosis (HRCT) ≥ 10%
- FVC ≥ 40%
- DLco: 30-89%

PROGRESSION WAS NOT AN INCLUSION CRITERION

Distler O, et al. N Engl J Med 2019;380:2518–28.

SENCIS: Trial design

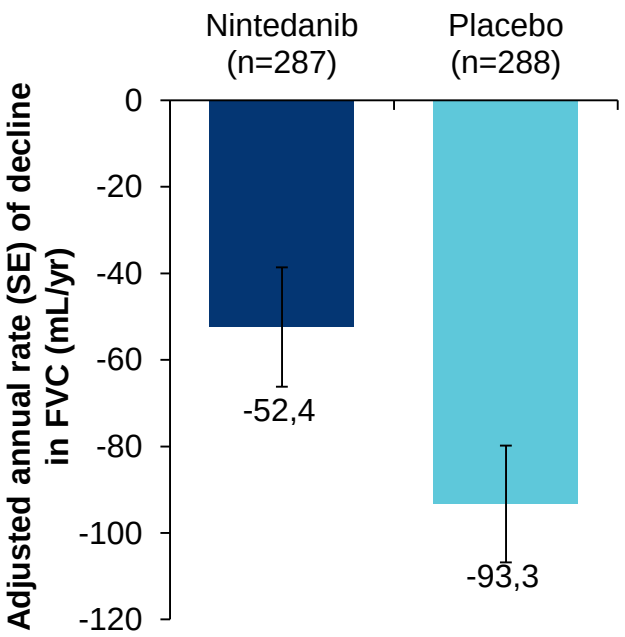


Annual rate of decline in FVC (mL/year) at 52 weeks

Distler O, et al. N Engl J Med 2019;380:2518–28.

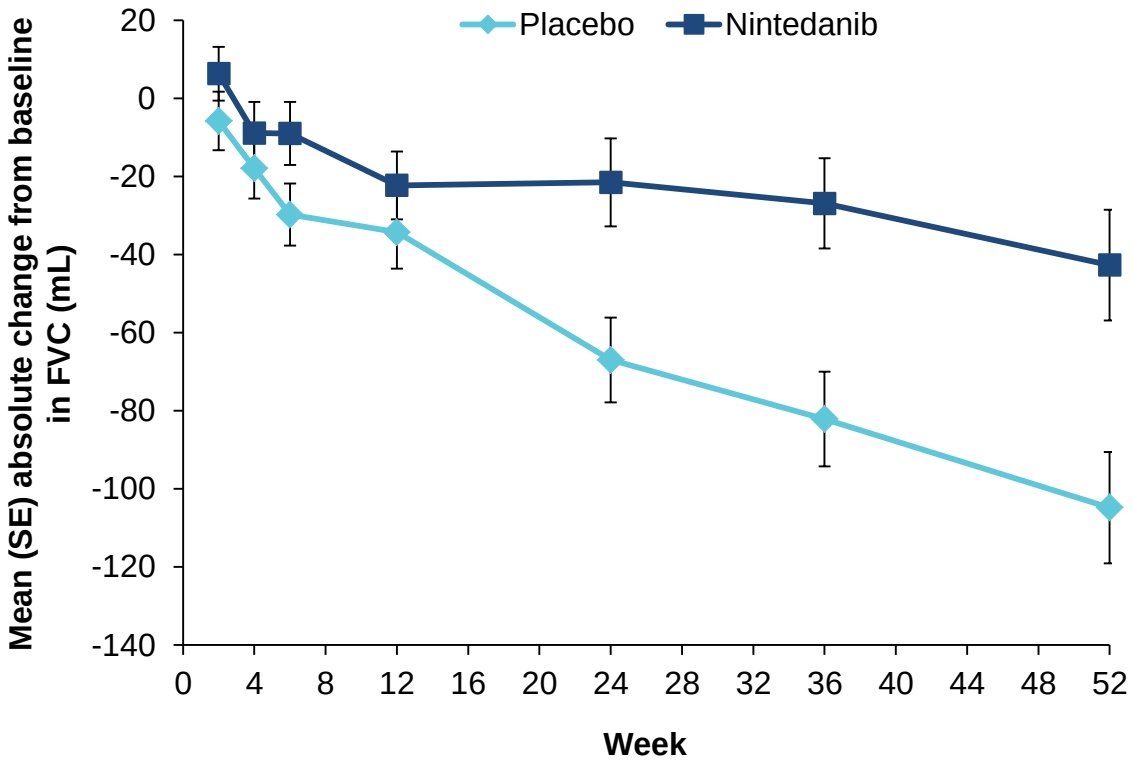
Decline in FVC over 52 weeks

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



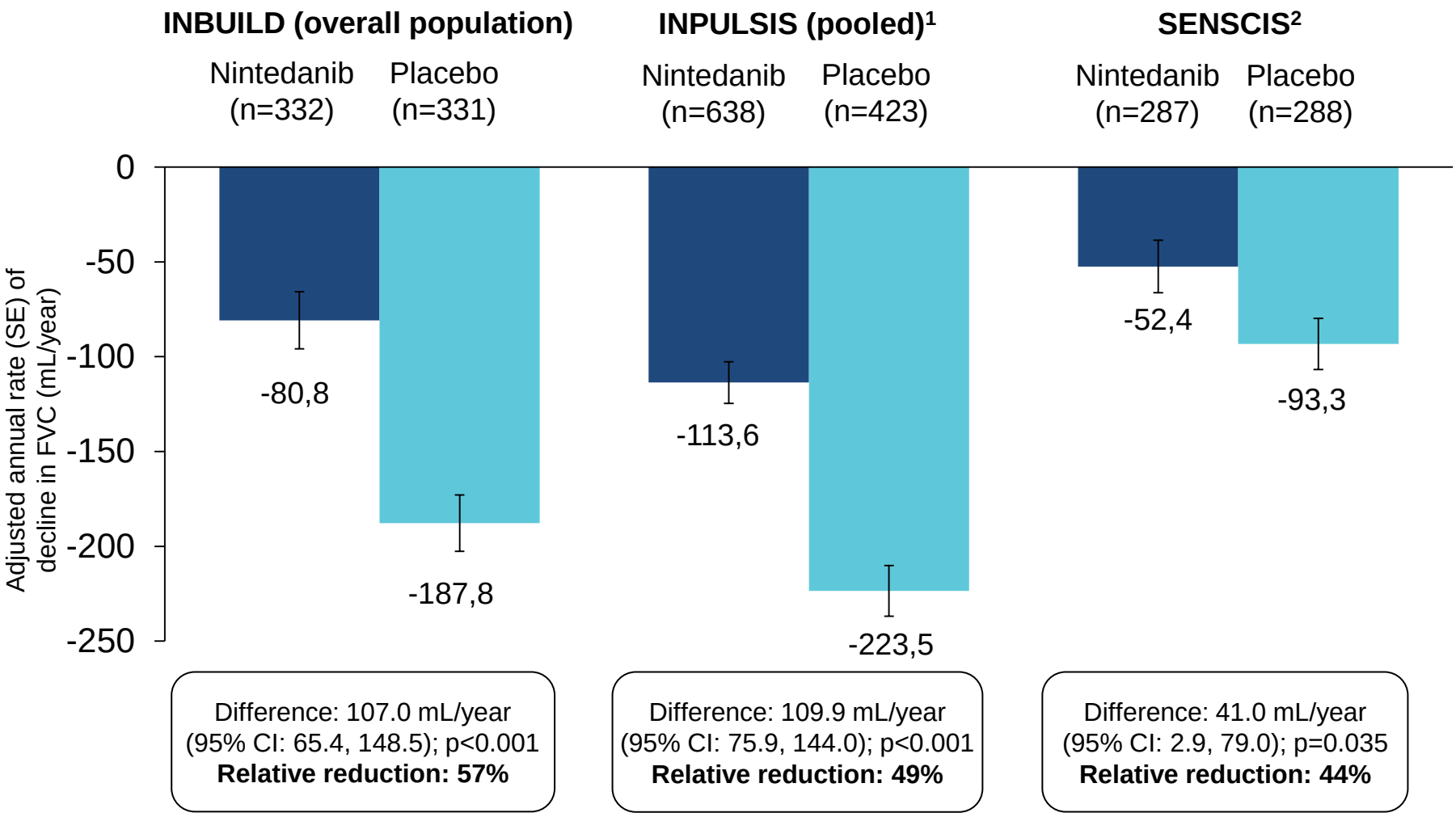
Difference: 41.0 mL/yr (95% CI: 2.9, 79.0); p=0.04
Relative reduction: 44%

Change from baseline in FVC (mL) over 52 weeks



Distler O, et al. N Engl J Med 2019.

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.

AMERICAN THORACIC SOCIETY DOCUMENTS

Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

Pirfenidone. *We recommend further research into the efficacy, effectiveness, and safety of pirfenidone in both 1) non-IPF ILD manifesting PPF in general and 2) specific types of non-IPF ILD manifesting PPF.*

Nintedanib. *We suggest nintedanib for the treatment of PPF in patients who have failed standard management for fibrotic ILD, other than IPF*

Am J Respir Crit Care 2022; 205(9):e18–e47

Progressive phenotype

HRCT

UIP or probable UIP pattern

Pulmonary Function Tests

FVC decline >10%

FVC decline 5-10%

Worsening symptoms

Progressive HRCT

Take home messages

- **Monitor disease progression**

✓ **Clinical**

✓ **Functional**

✓ **Imaging**

- **Ask for previous PFTs, HRCTs**
- **Co-operation with pulmonologists**

- **Ευχαριστώ!**