Άλλες χρόνιες προοδευτικά εξελισσόμενες ινοποιές διάμεσες Πνευμονοπάθειες

Assoc. Professor Katerina Antoniou

ERS ILD Assembly Secretary

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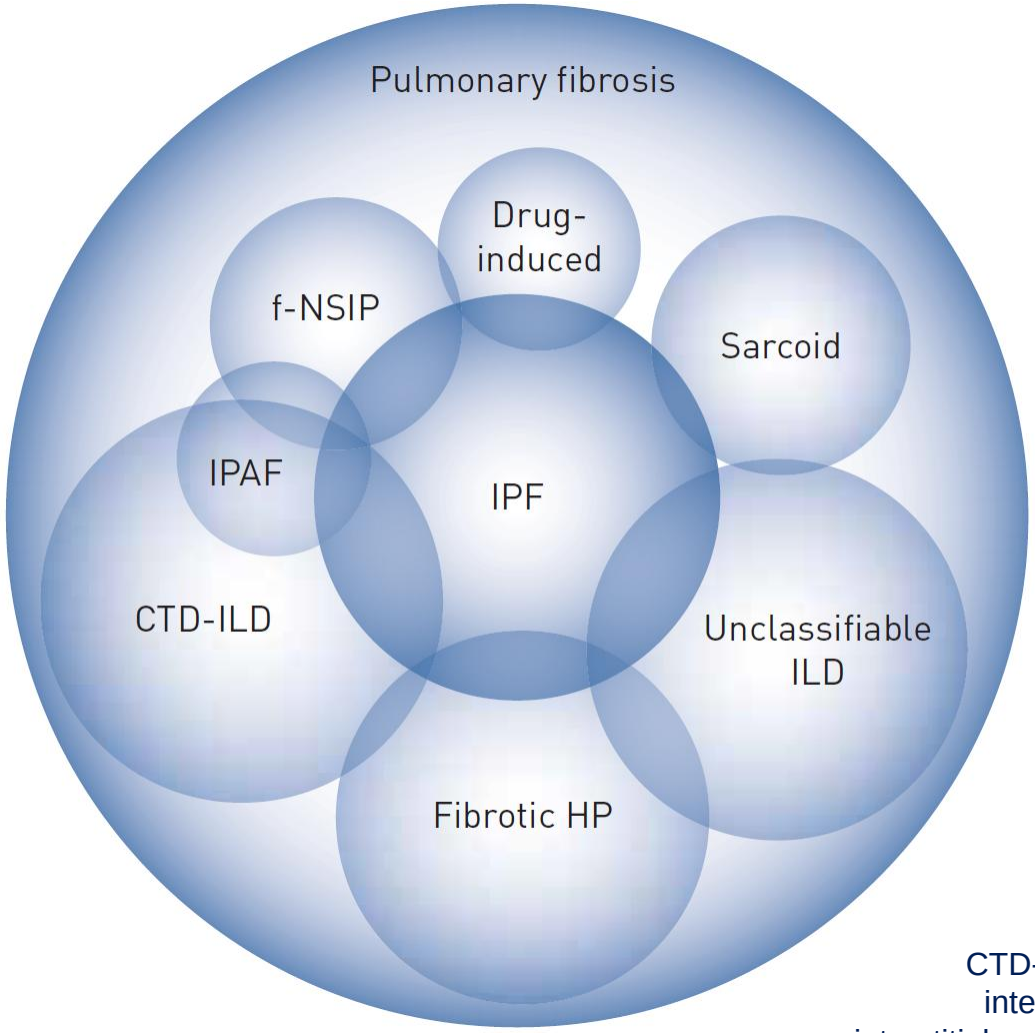
28ο ΠΑΝΕΛΛΗΝΙΟ Πνευμονολογικό ΣΥΝΕΔΡΙΟ

The “progressive fibrotic phenotype” is here to stay

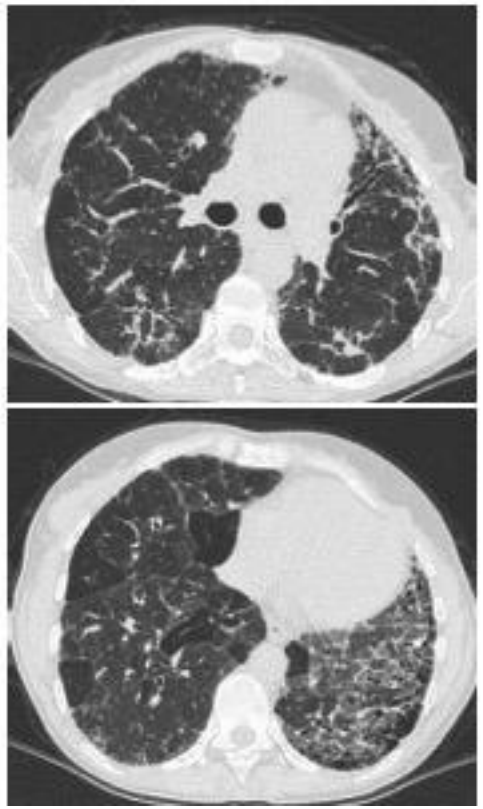


CTD-ILD, Connective tissue disease associated with interstitial lung disease; f-NSIP, fibrotic non-specific interstitial pneumonia; HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis

Wells AU, et al. *Eur Respir J.* 2018;17:pii1800692

Clinical case (#1)

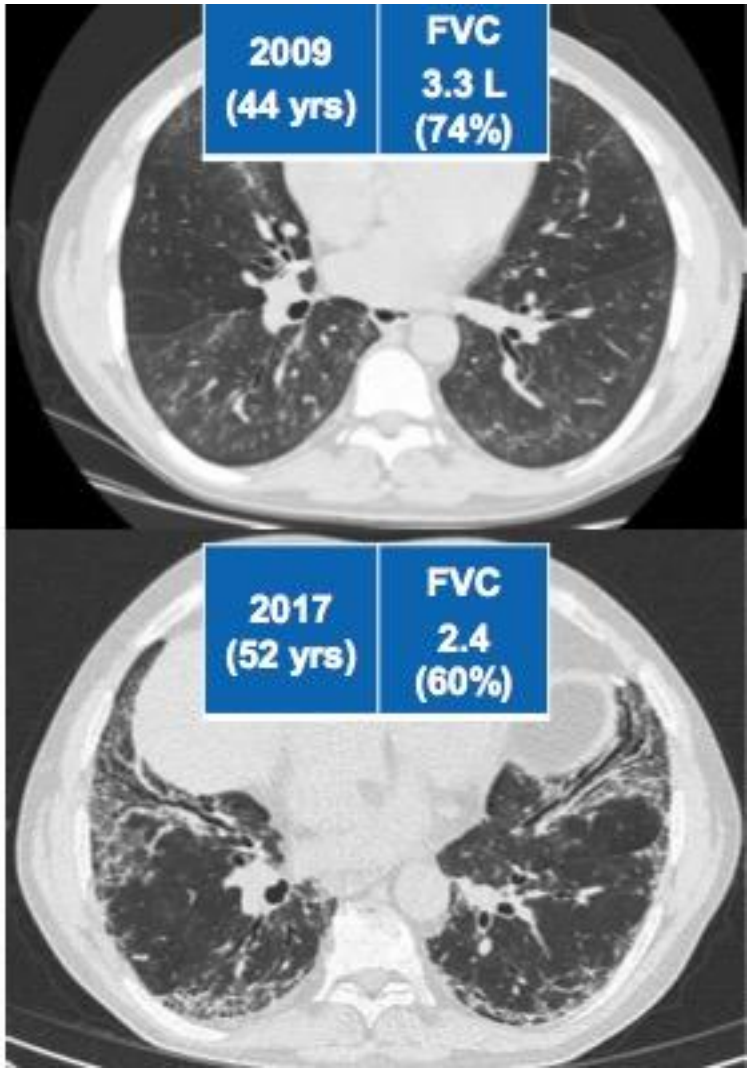
- 49-year-old female, non-smoker
- Familial ILD, no mutation identified
- Unclassifiable ILD with autoimmune features (IPAF)
- Pathology: possible UIP with diffuse lymphoplasmacytic infiltration (without lymphoid follicles)
- Treatment: prednisone



Date	FVC	DLco
Year 1	2.40 (77%)	53%
Year 2	2.37 (77%)	48%
Year 3	1.66 (54%)	39%

Clinical case (#2)

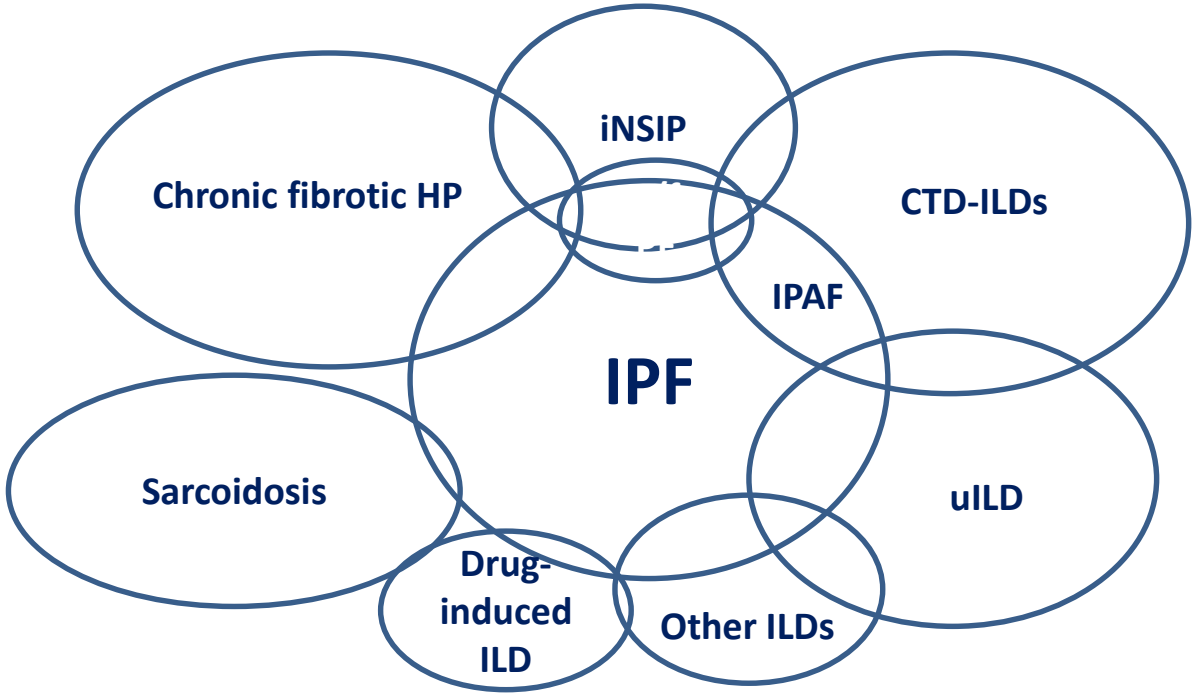
- 44-year-old male at diagnosis (2008)
- Ex-smoker
- No medical history, exposure, or autoimmunity
- VATS biospy: fibrosing NSIP
- Received long-term oral prednisone and immunosuppressants



Limitations of the current approach

Although corticosteroids and immunosuppressants have traditionally been used to treat fibrosing ILDs, other than in patients with SSc-ILD, they don't always reduce the progression of disease

Fibrotic Interstitial Lung Diseases

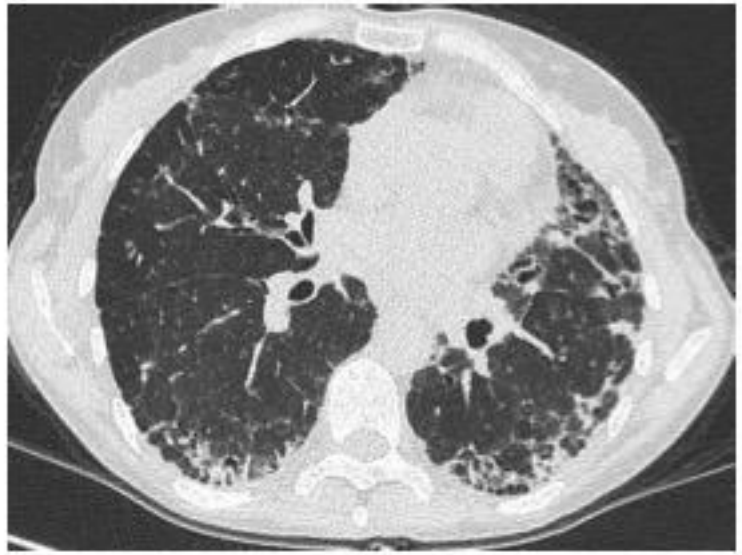


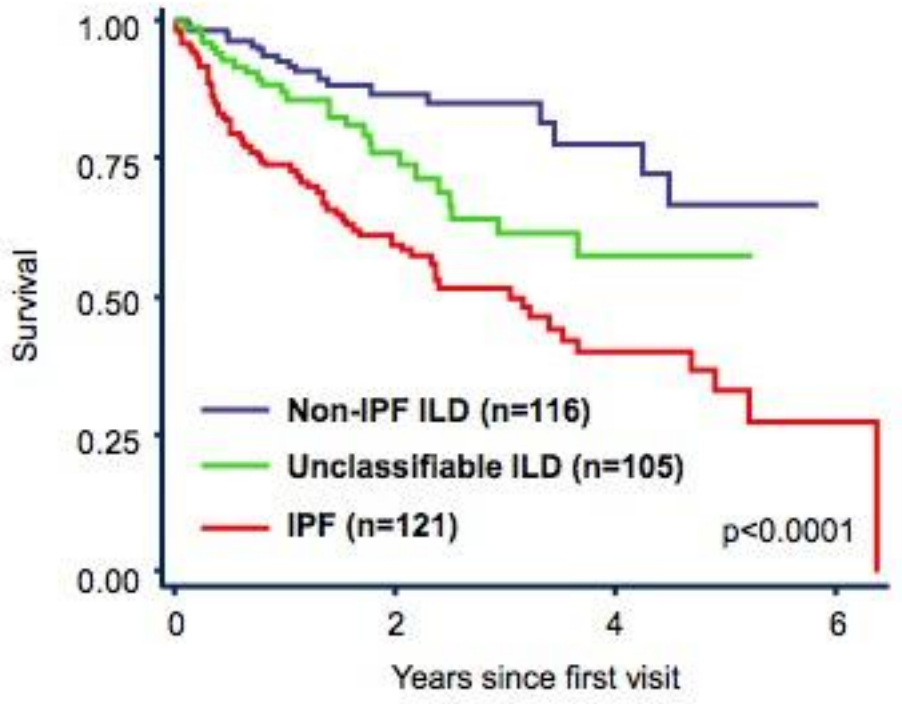
Fibrotic interstitial lung diseases

g/f, genetic/familial.

Cottin V, et al. Eur Respir Rev 2019 (in press).

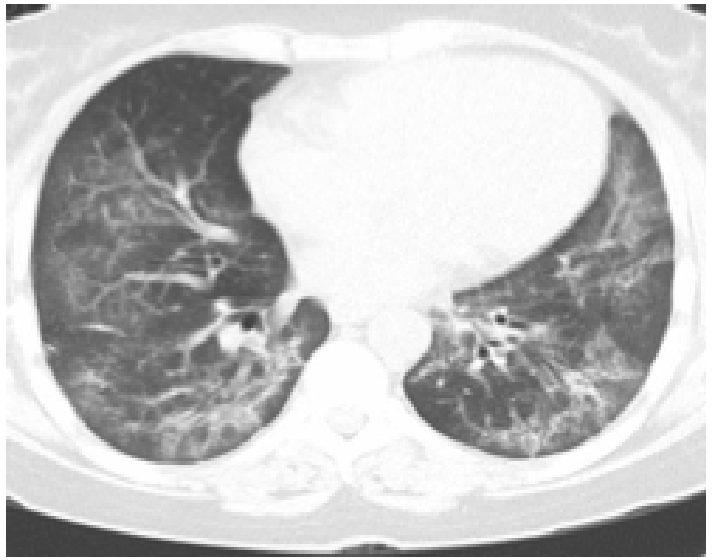
Unclassifiable ILD





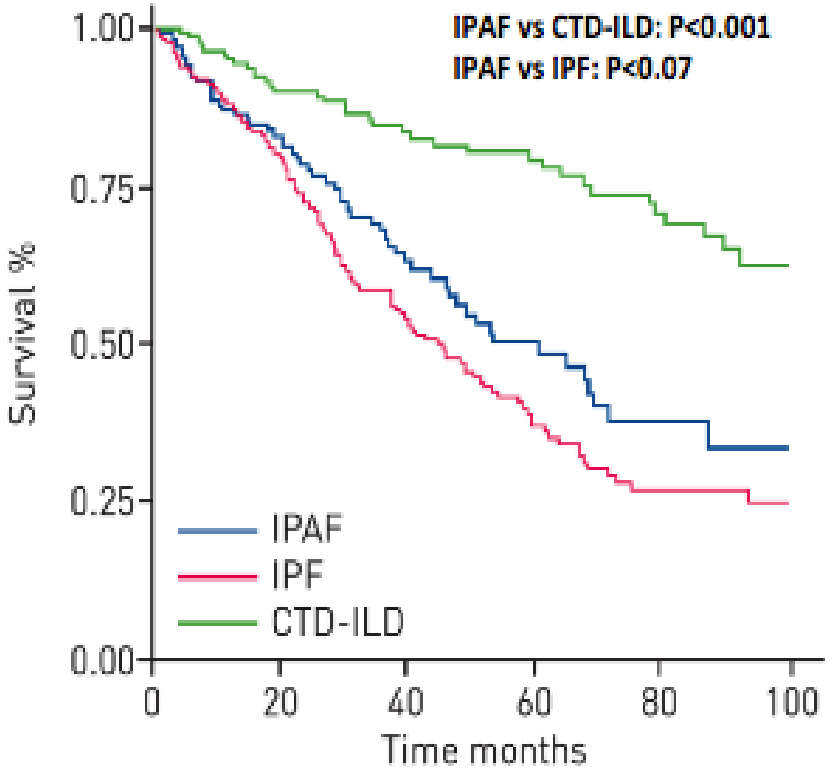
Ryerson CJ, et al. Eur Respir J 2013;42:750-7.
Hyldgaard C, et al. Respirology 2017;22:494-500.

Interstitial Pneumonia with Autoimmune Features_ IPAF



40-year-old woman with clinical features of CTD and ANA at 1:640

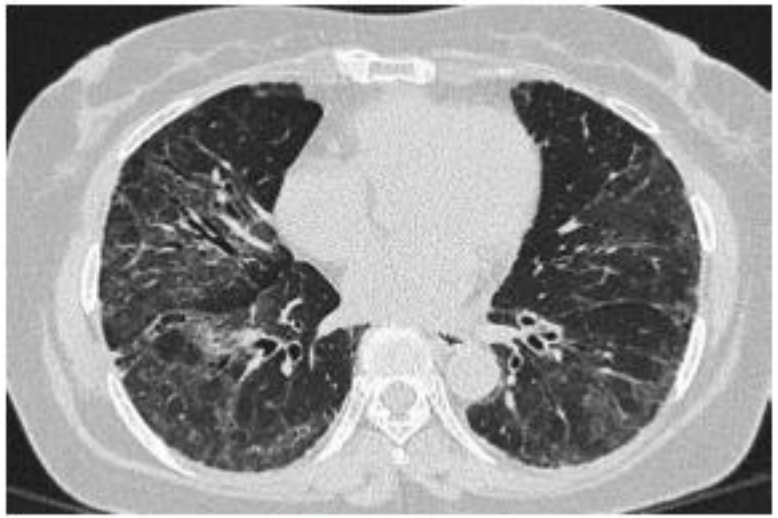
Surgical biopsy: NSIP with OP, lymphoid follicles with germinal centres



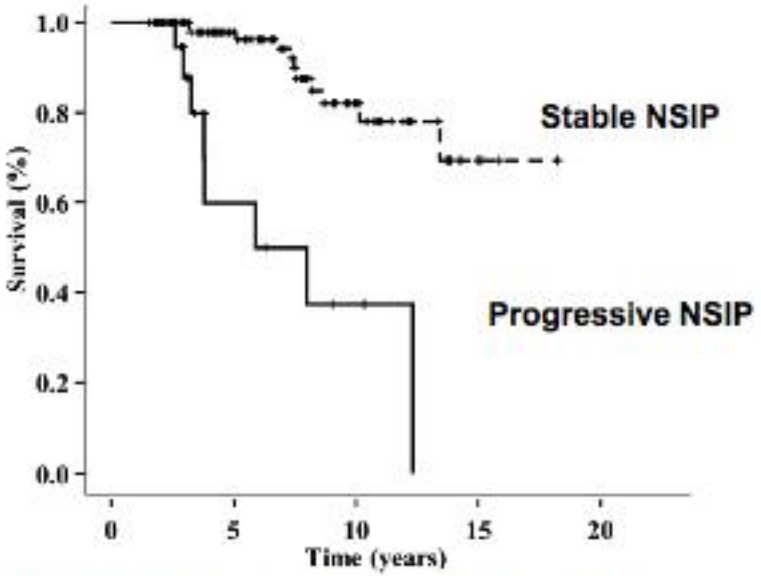
Oldham JM, et al. Eur Respir J 2016;47:1767-75.

Hyldgaard C, et al. Respirology 2017;22:494-500.

NSIP: etiology and progressive phenotype determine prognosis



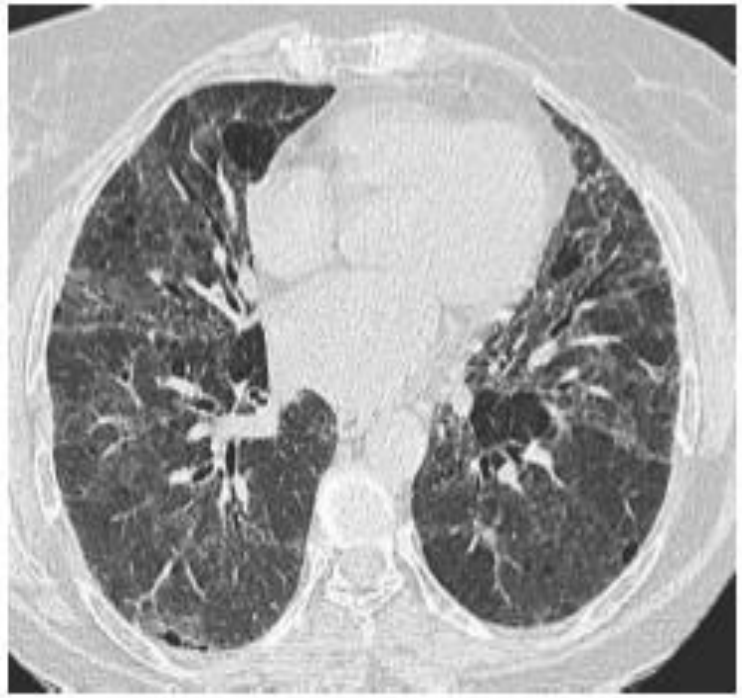
61-year-old woman, idiopathic NSIP

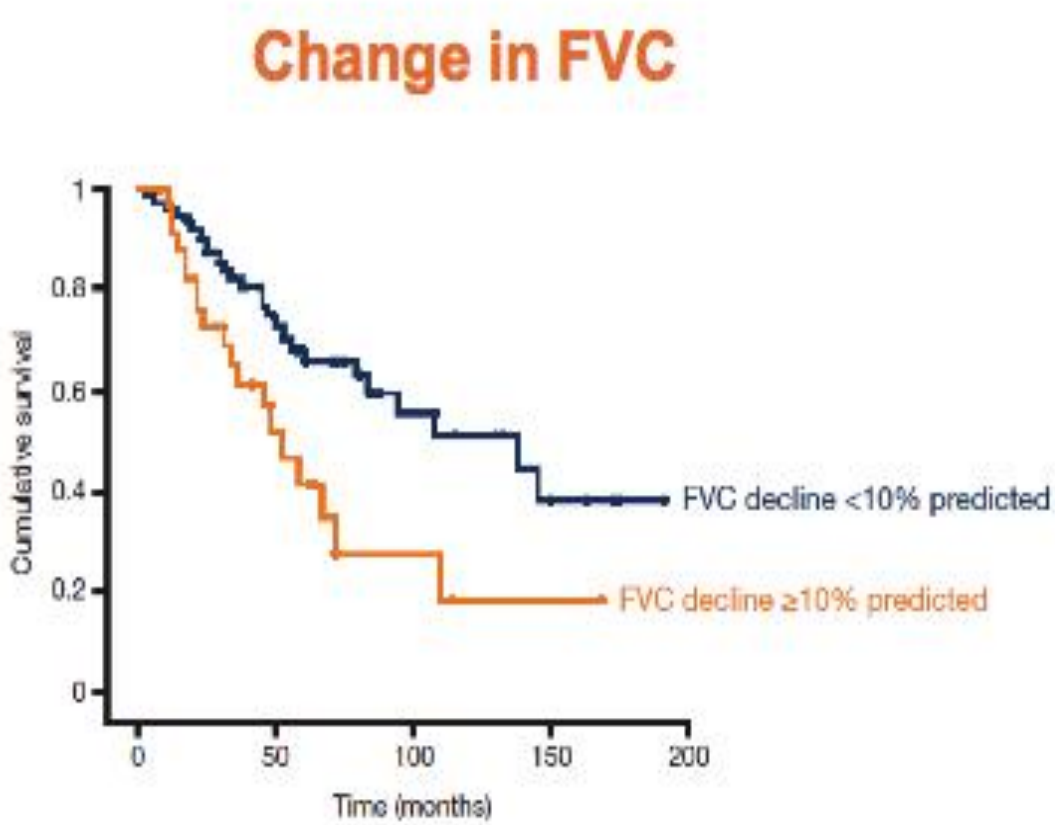


Progressive type defined by relative ≥5%/year decline in the slope of FVC and/or relative ≥7.5%/year decline in the slope of DLco

Yamakawa H, et al. Respirology 2018;23:1032-40.

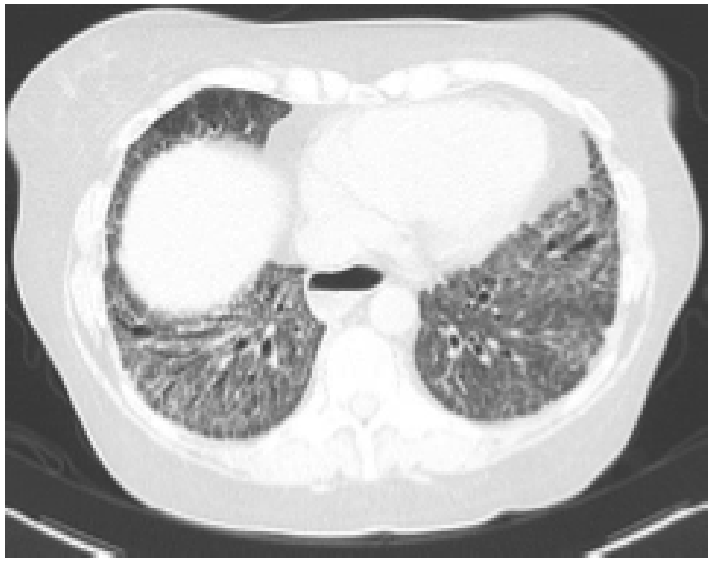
Chronic fibrotic hypersensitivity pneumonitis

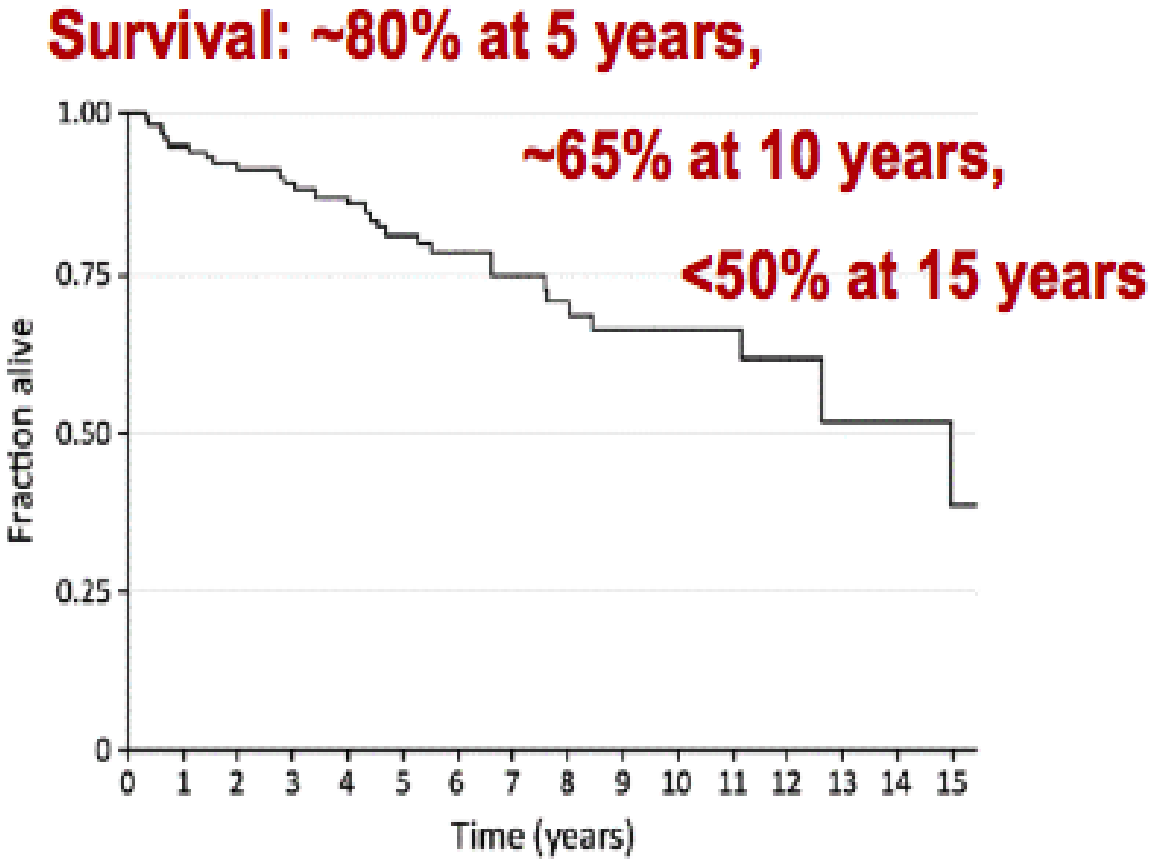




Gimenez A, et al. Thorax 2018;73:391-2.

Systemic sclerosis-associated ILD (SSc-ILD): long-term mortality

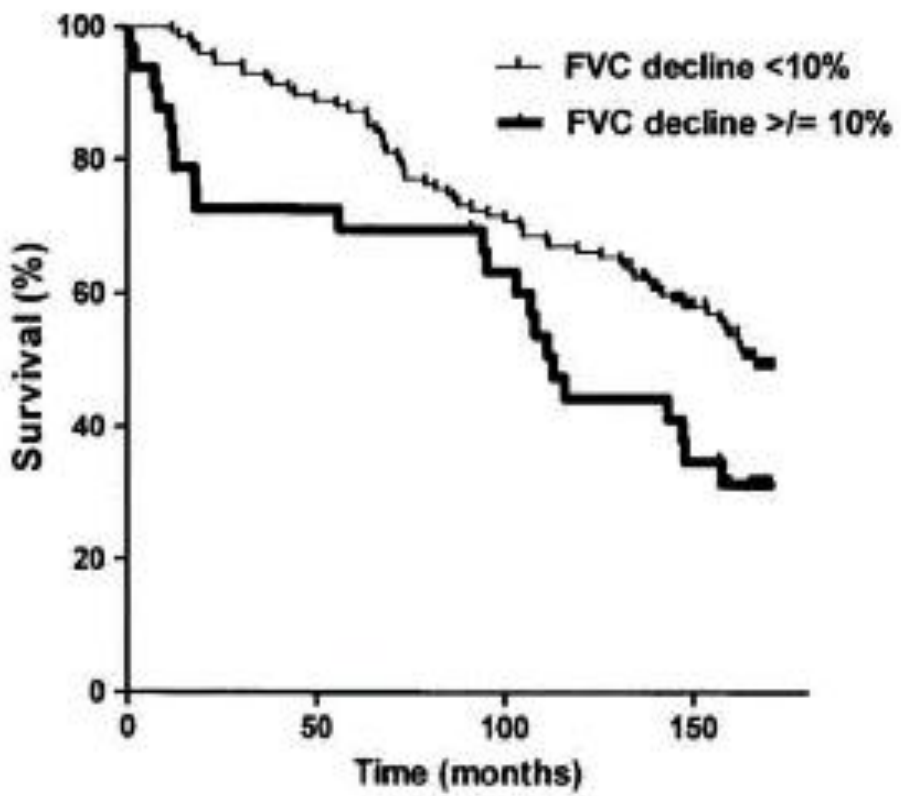




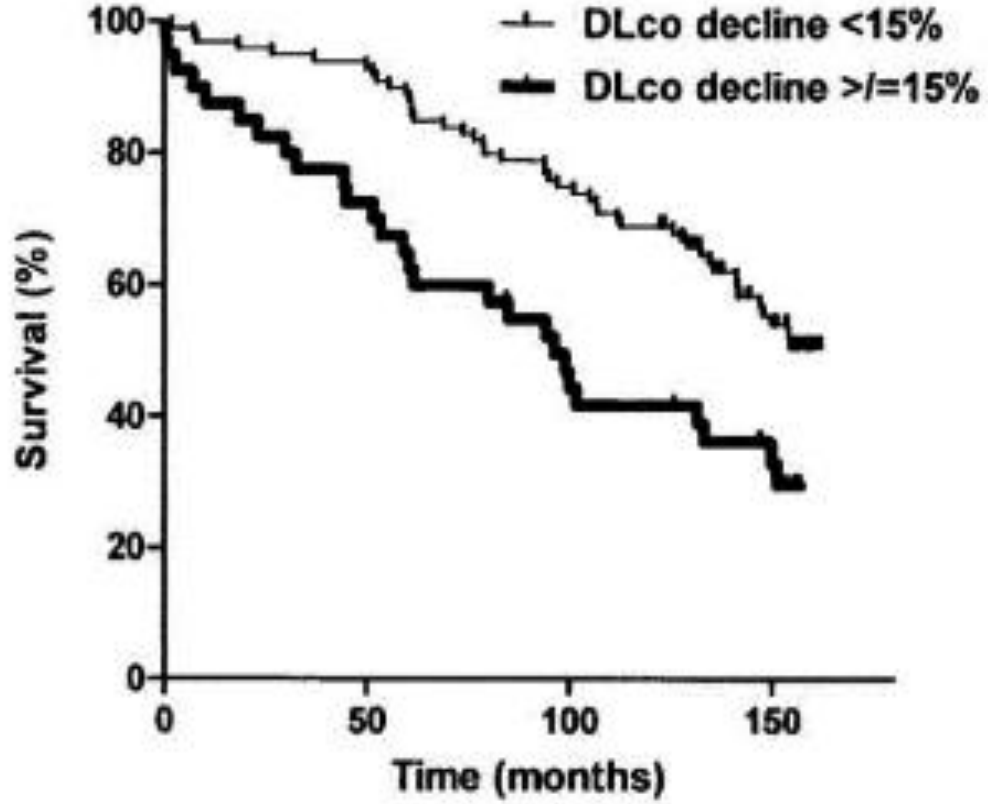
Ryerson CJ, et al. Chest 2015;148:1268-75.

SSc-ILD: prognostic significance of decline in lung function

FVC decline ≥10%



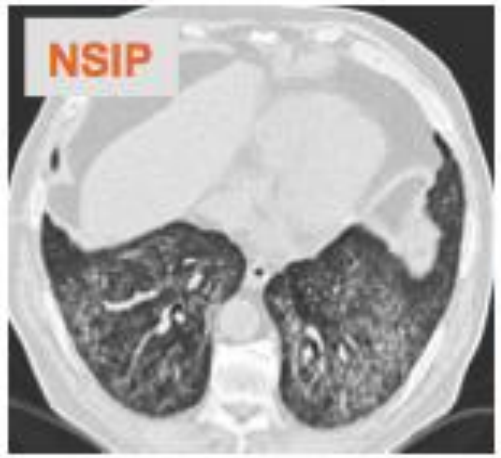
DLco decline ≥15%

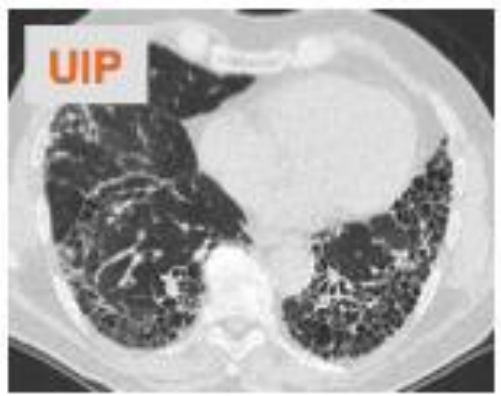


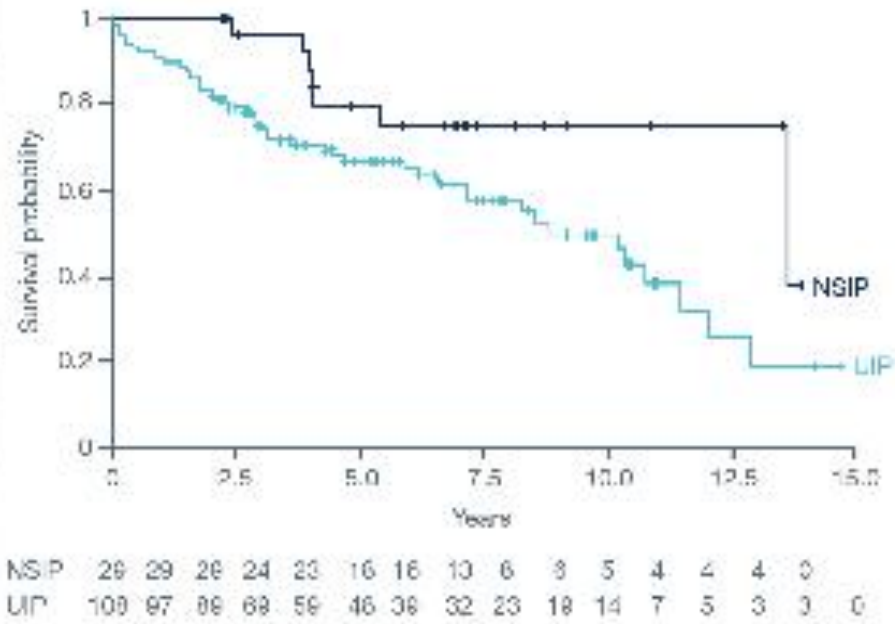
Goh NS, et al. Arthritis Rheum 2017;69:1670-8.

RA-ILD: determinants of prognosis

- HRCT pattern predicts mortality
- Decline in lung function predicts mortality:
  - 10% decline in FVC % predicted at any time after baseline: HR=1.86 (1.26–2.75)

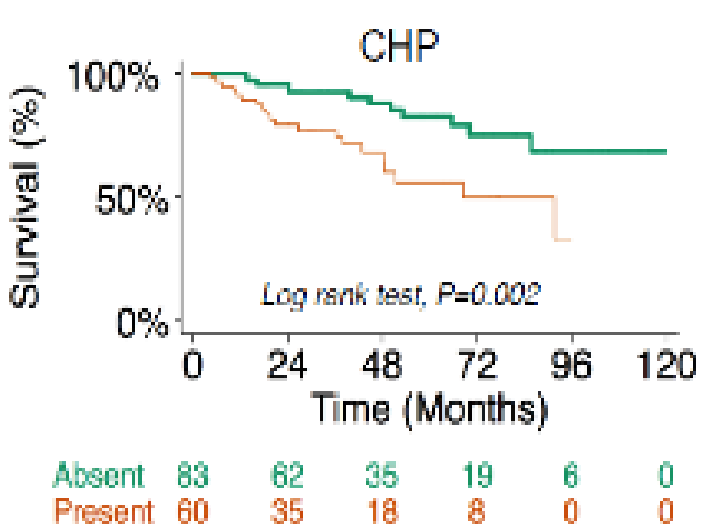


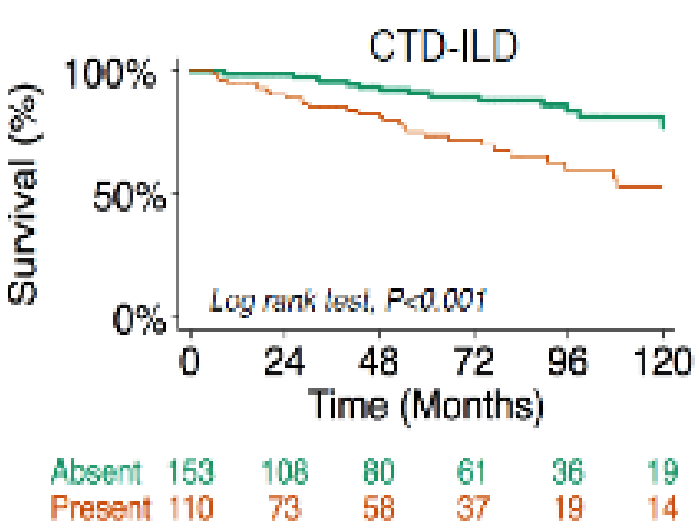


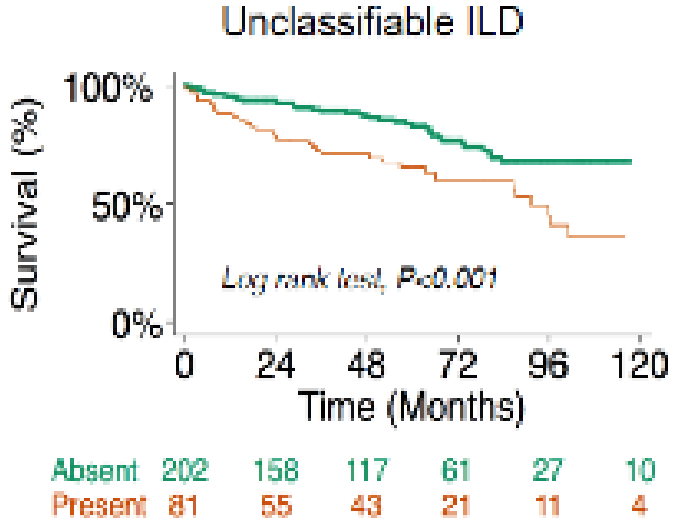


Solomon JJ, et al. Eur Respir J 2016;47:588-96.

Honeycombing on HRCT predicts a progressive phenotype across a wide range of ILDs

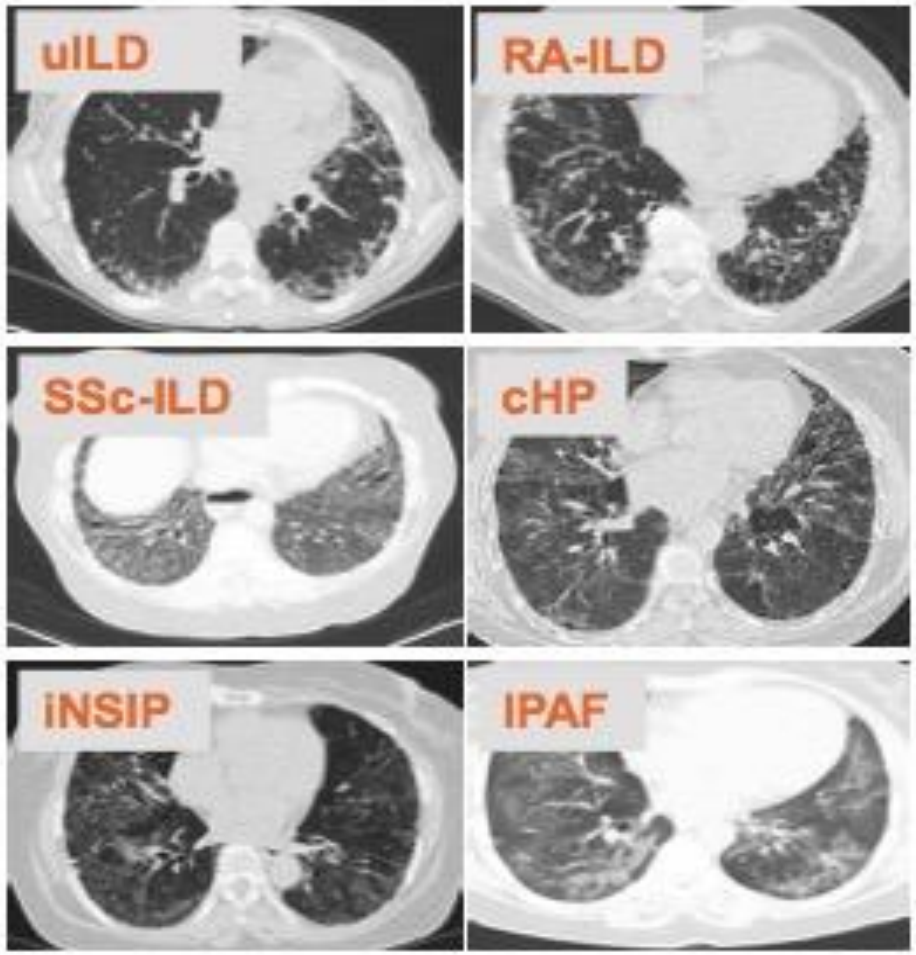






Adegunsoye A, et al. Ann Am Thorac Soc 2019;16:580-8.

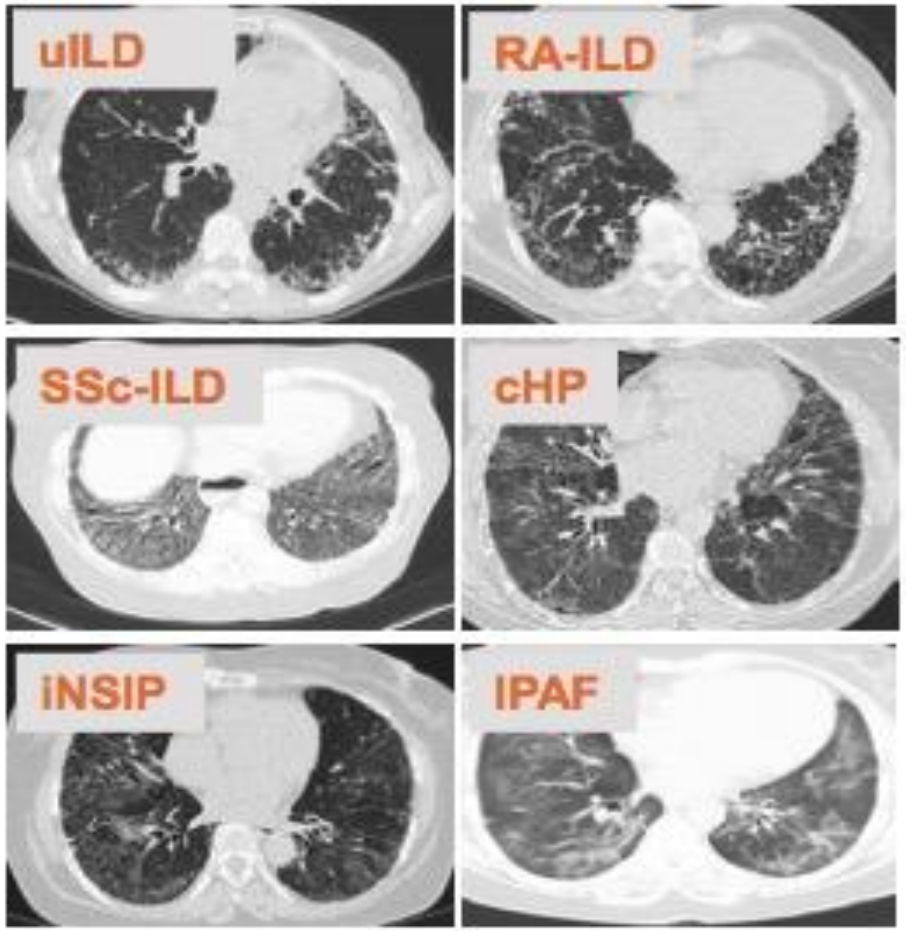
Predictors of disease progression in clinical practice



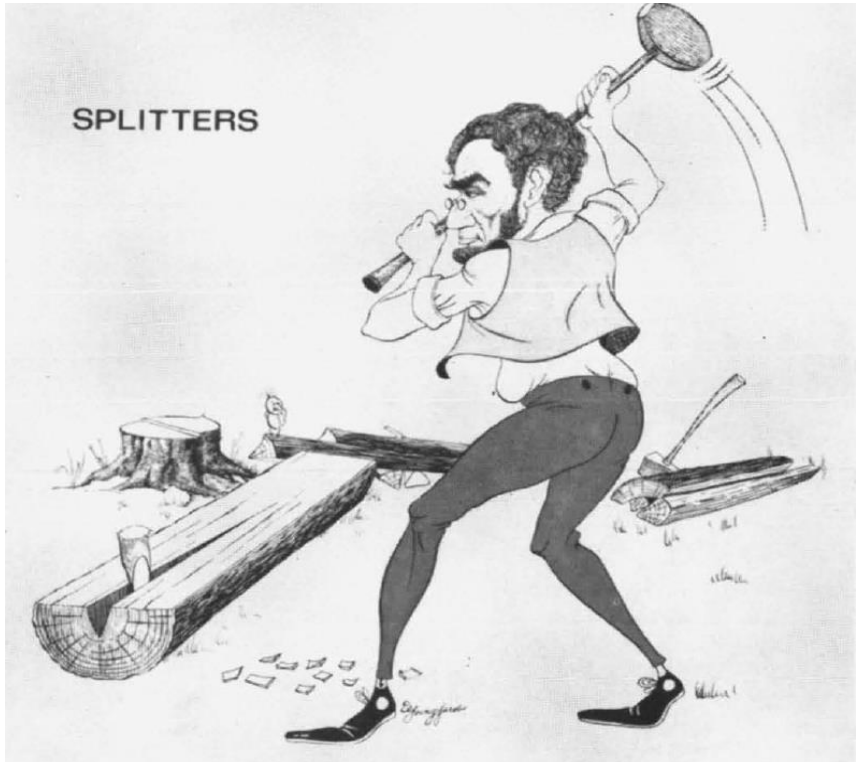
- Demographics, disease phenotype, biomarkers, etc (depending on underlying disease)*
- **Extensive fibrosis on imaging**
- **UIP pattern/honeycombing**
- **Lower pulmonary reserve (FVC and DLco)**

*Example in SSc-ILD: male sex, African-American origin, diffuse cutaneous SSc, anti-Scl70 antibodies.

Indicators of disease progression in clinical practice

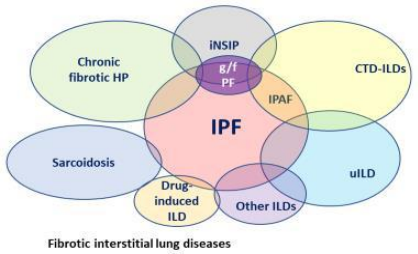


- Progressive symptoms
- **Progressive decline in physiology**
- **Progressive fibrosis on imaging**
- Progression despite first-choice therapy
- Acute exacerbation/respiratory hospitalisation



- **A lumper searches for the big picture**
- Ex: concept of PF-ILD, disease behaviour, shared pathogenetic pathways between IPF and non-IPF fibrotic diseases

- **A splitter prefers to make distinction from observed details and scientific data**
- Ex: genetic testing, precision medicine

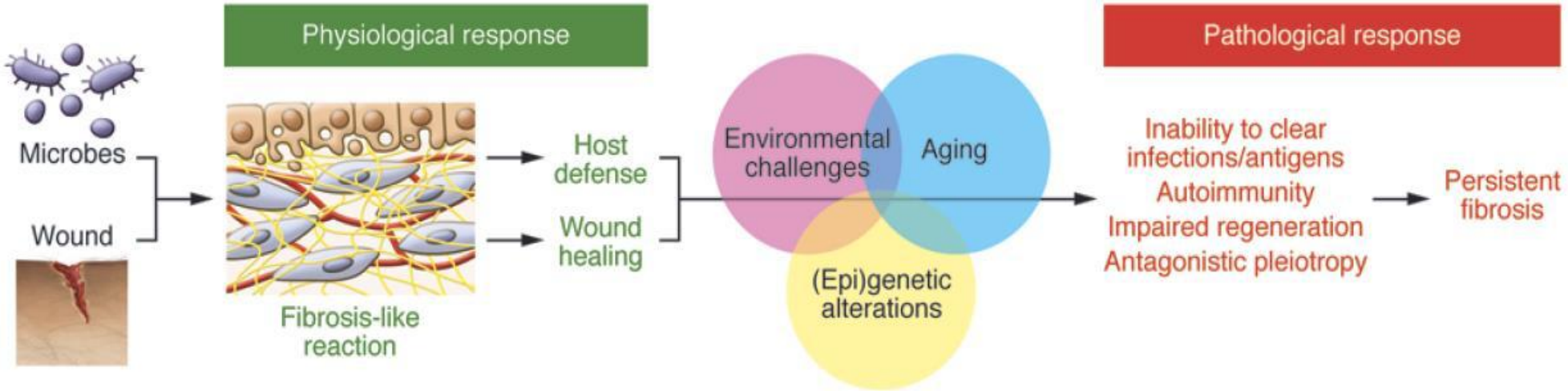


McKusick VA. Perspect Biol Med 1969 Winter;12:298-312.

The Journal of Clinical Investigation REVIEW

Fibrosis: ultimate and proximate causes

Victor J. Thannickal,[1] Yong Zhou,[1] Amit Gaggar,[1] and Steven R. Duncan[2]

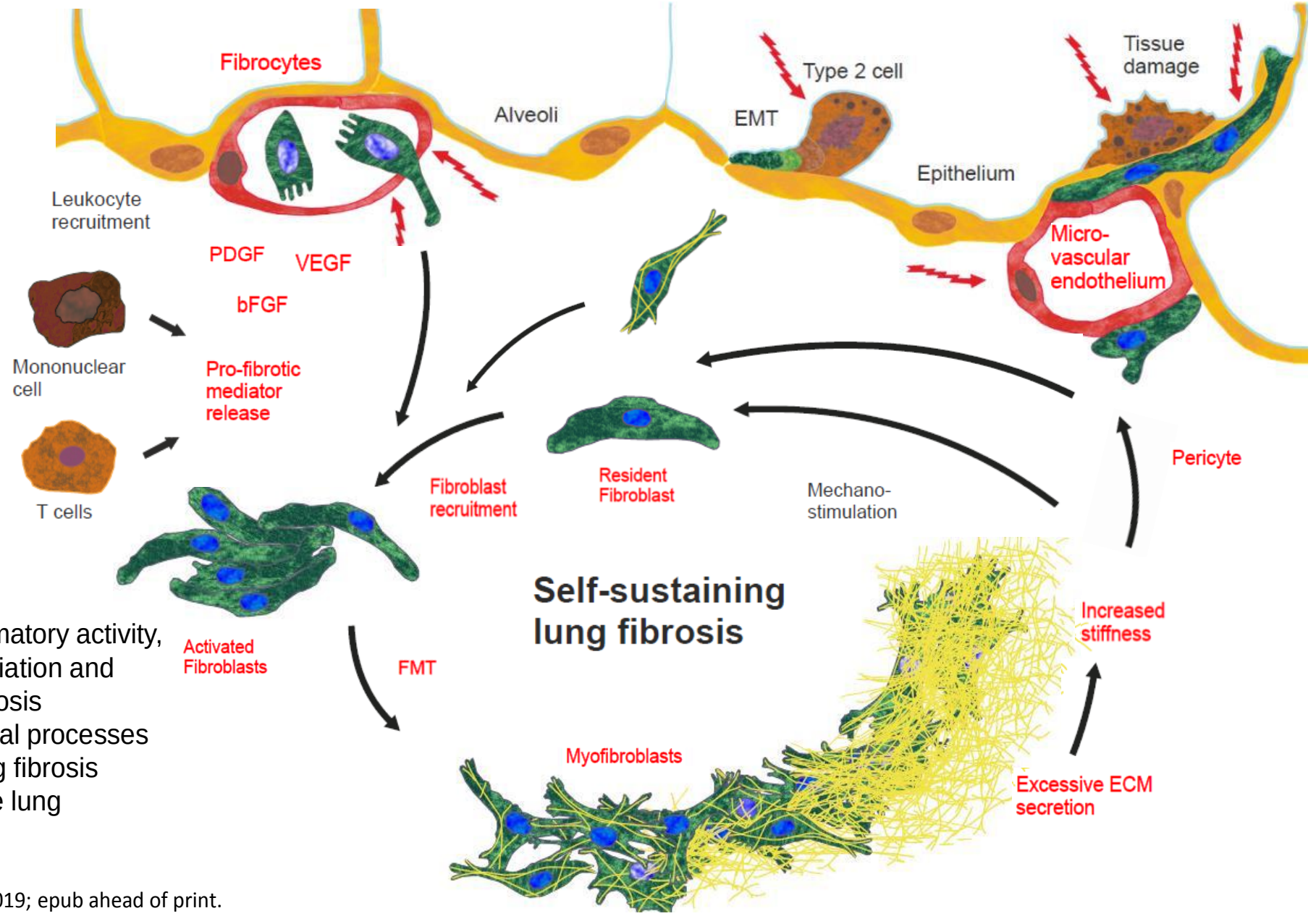


Thannickal VJ, et al. J Clin Invest 2014;124:4673-7.

Shared pathogenetic mechanisms common to IPF and other progressive fibrotic ILDs

Shared mechanism	Diseases
Shared **genetic predilection**	IPF and RA-ILD
Similar links between short **telomere lengths** and mortality	IPF and CHP
Linkage between **alveolar epithelial cell dysfunction/injury** and pulmonary function decline	IPF and SSc-ILD
Pathobiological mechanisms likely to contribute to disease progression: **alveolar stem cell exhaustion/cellular senescence, mitochondrial dysfunction, impaired autophagy, epigenetic modifications, and immune dysregulation**	IPF and SSc-ILD

Wells AU, et al. Eur Respir J 2018;51:1800692.

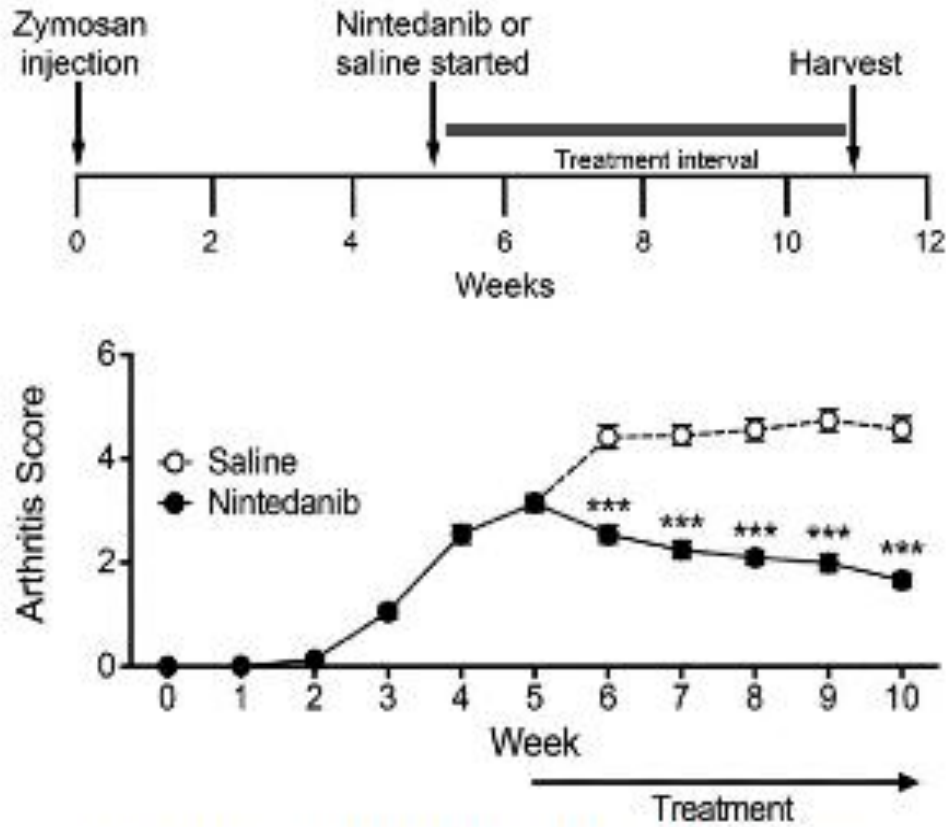


Nintedanib:

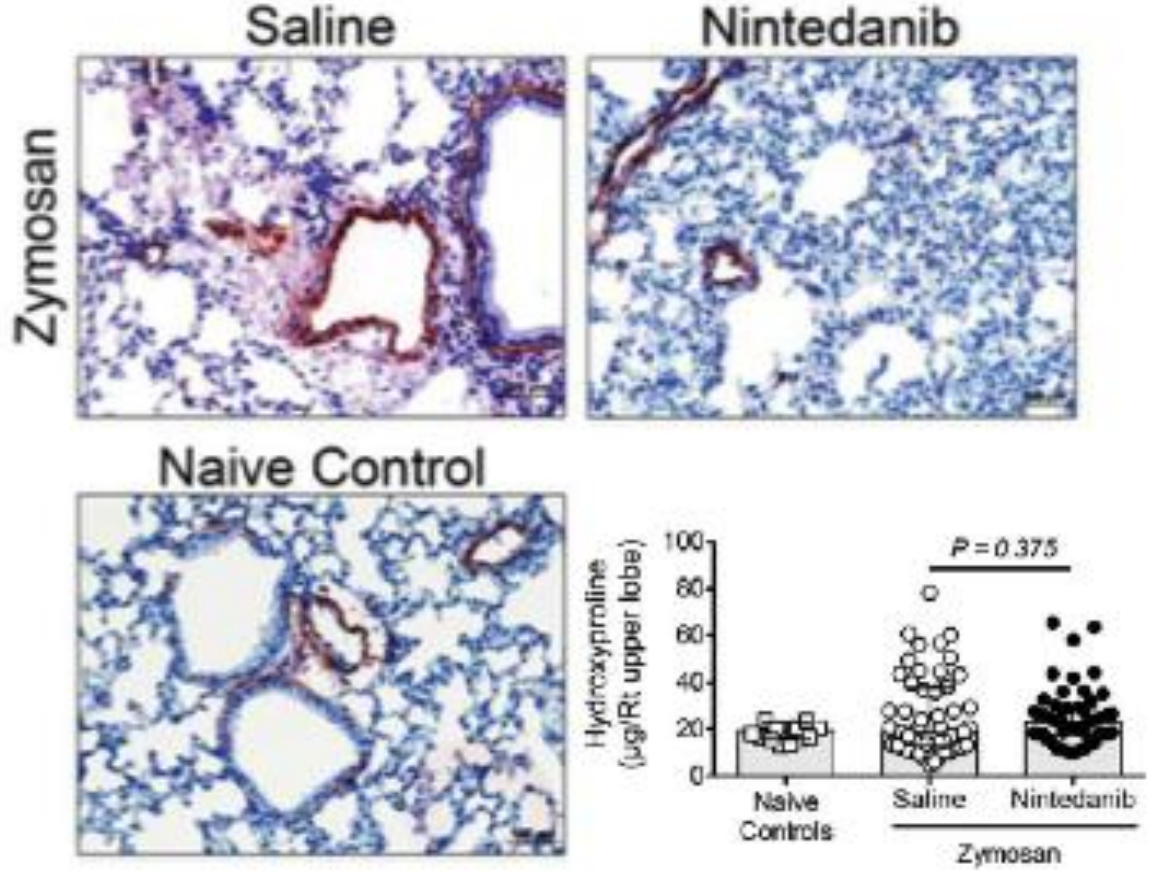
1. Exerts anti-inflammatory activity, attenuating the initiation and progression of fibrosis
2. Inhibits fundamental processes of progressive lung fibrosis
3. Targets cells of the lung vasculature

Wollin L, et al. Eur Respir J 2019; epub ahead of print.

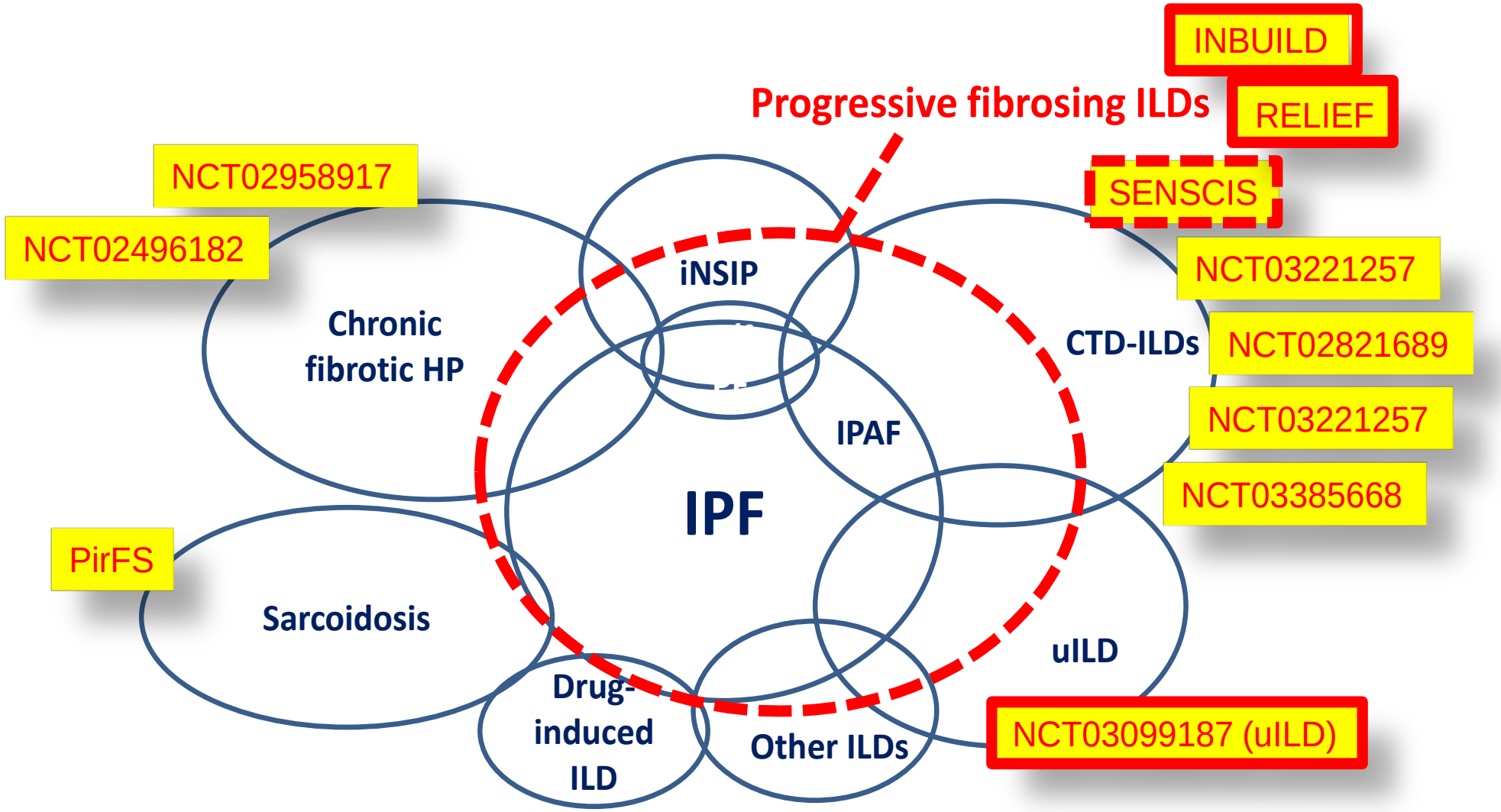
Nintedanib reduces pulmonary fibrosis in a model of RA-ILD
(female SKG mice with arthritis induced by intraperitoneal injection of zymosan)



Nintedanib (60 mg/kg daily via oral gavage)



Redente E, et al. Am J Physiol Lung Cell Mol Physiol 2018;314:L998-1009.



Fibrotic interstitial lung diseases

g/f, genetic/familial.

Cottin V, et al. Eur Respir Rev 2019 (in press).

Real world data

Greek cohort

ORIGINAL ARTICLE
INTERSTITIAL LUNG DISEASE

Efficacy and safety of nintedanib in a Greek multicentre idiopathic pulmonary fibrosis registry: a retrospective, observational, cohort study

Katerina Antoniou[1,7], Katerina Markopoulou[2,7], Argyrios Tzouvelekis[3,7], Athina Trachalaki[1,7], Eirini Vasarmidi[1,7], Jiannis Organtzis[4,7], Vasilios Tzilas[3], Evangelos Bouros[3], Georgia Kounti[2], Christina Rampiadou[2], Serafeim-Chrysovalantis Kotoulas[2], Fotini Bardaka[5], Eleni Bibaki[6], Evangelia Fouka[4], Georgios Meletis[6], Stavros Tryfon[2], Zoe Daniil[5], Despina Papakosta[4] and Demosthenes Bouros[3]

ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Efficacy and safety of nintedanib in a Greek multicentre idiopathic pulmonary fibrosis registry: a retrospective, observational, cohort study

n=244 patients

SAFETY

Table E1. Baseline characteristics of the ITT population.

Number of patients	244
Age, years	71.8±7.5
Sex, n (%)	
Male	193 (79.1)
Female	51 (20.9)
Smoking status, n (%)	
Never smoked	53 (21.9)
Ex-smokers	81 (33.1)
Current smokers	110 (45.1)
Pack-years	52±34.5
HRCT pattern (probable/definite UIP), n (%)	186 (76.4)
CPFE, n (%)	22 (9.0)
Advanced disease (DLco pred ≤35% or FVC pred ≤50%), n (%)	107 (43.8)
FEV_1% pred	78.8±20.2
FVC% pred	73.3±20.7
TLC%	64.9±16.5
DLco% pred	42.6±16.7
Prior pirfenidone treatment, n (%)	29 (11.8)

Table 2. Investigator-reported AEs in the safety population (n=244).

	Number of AEs	Proportion of patients with AE
Total AEs reported	224	55.7%
GI events	173	-
Diarrhoea	110	45.0%
Nausea/vomiting	26	10.7%
Anorexia	18	7.4%
Abdominal pain	11	4.5%
Dyspepsia/bloating	6	2.5%
GI bleeding	2	0.8%
Reduced body weight	16	6.6%
Liver function test elevations	12	4.9%
Weakness	11	4.5%
Ischaemic events[a]	9	2.9%
Hyperpyrexia	1	0.4%
Others	4	1.6%
Reduced dose due to AE	69	28.3%
Discontinuation due to AE	32	13.1%

[a]Ischaemic events defined as myocardial infarction or ischaemic stroke.

Functional effects irrespective of disease severity

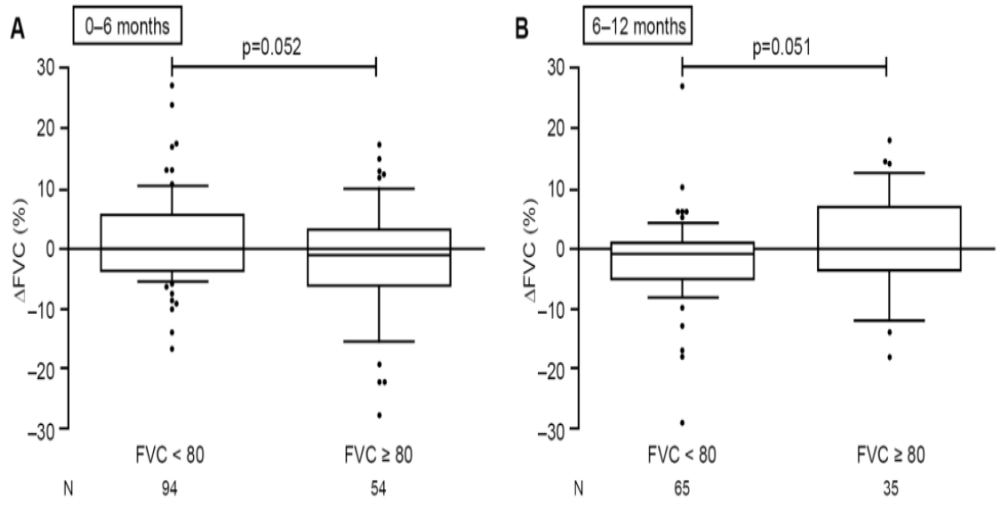
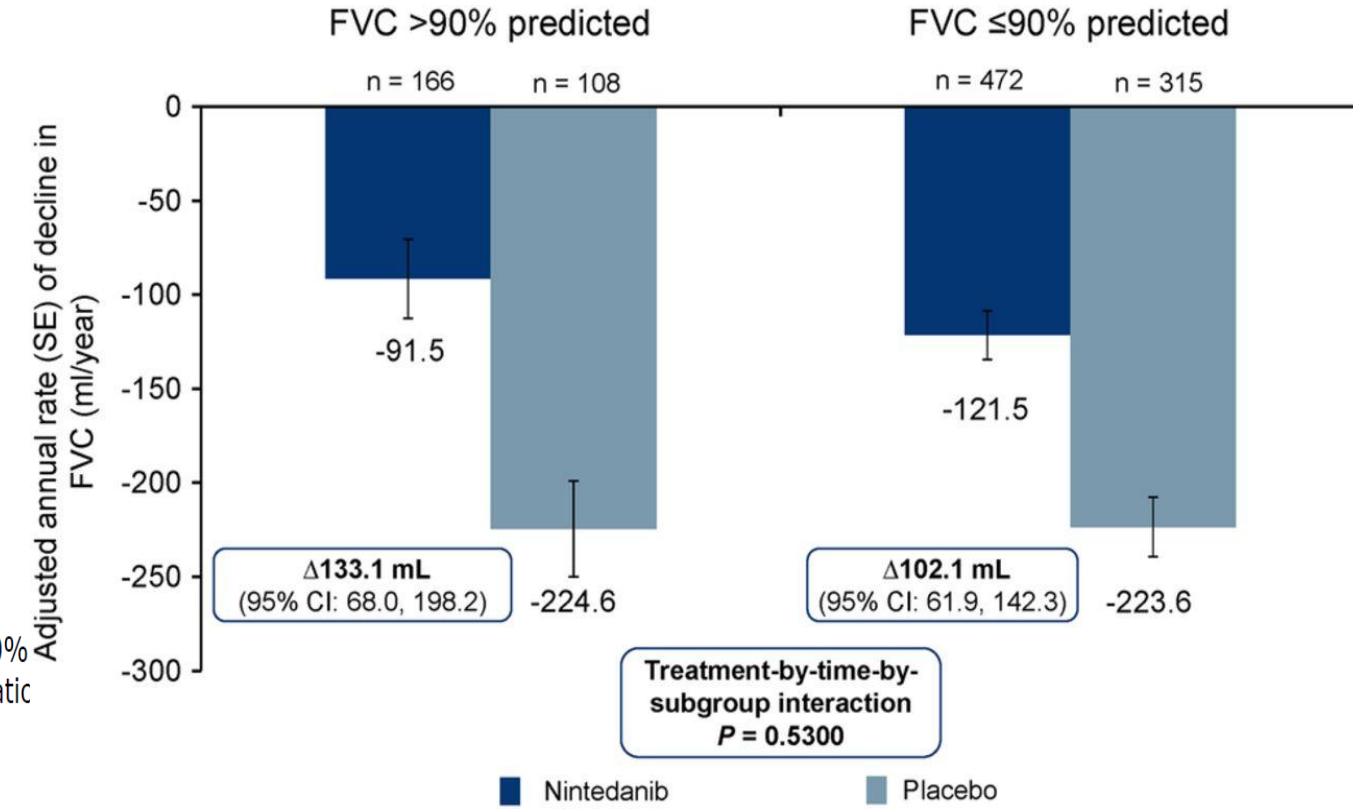


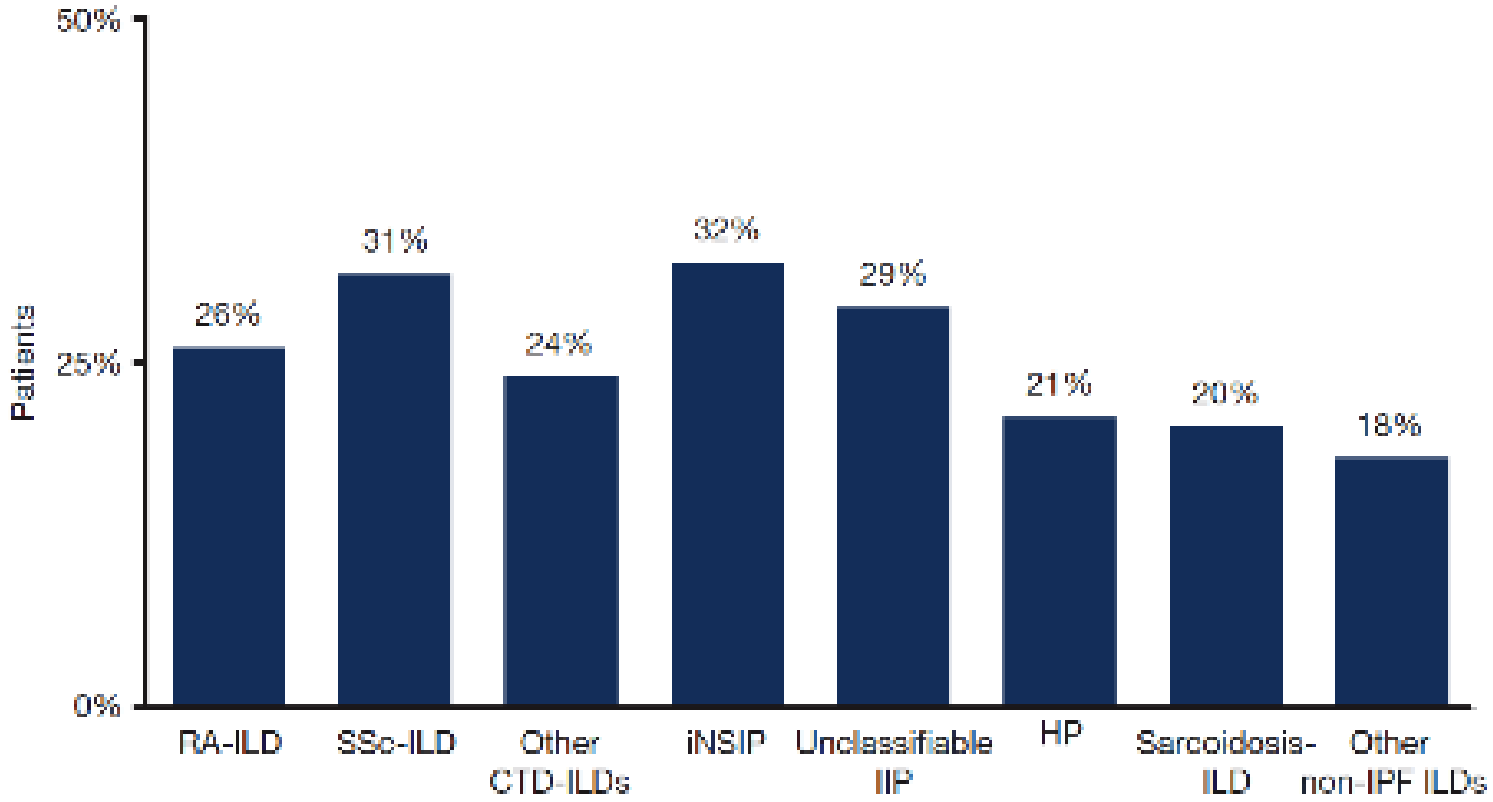
Figure 4. Change in FVC% between 0–6 months and 6–12 months stratified by baseline FVC (<80% [n=151] vs ≥80% [n=91]). Patients were censored from the analysis after death and/or discontinuatic
Abbreviation: FVC, forced vital capacity.

Antoniou et al. ERJ Open Res 2019



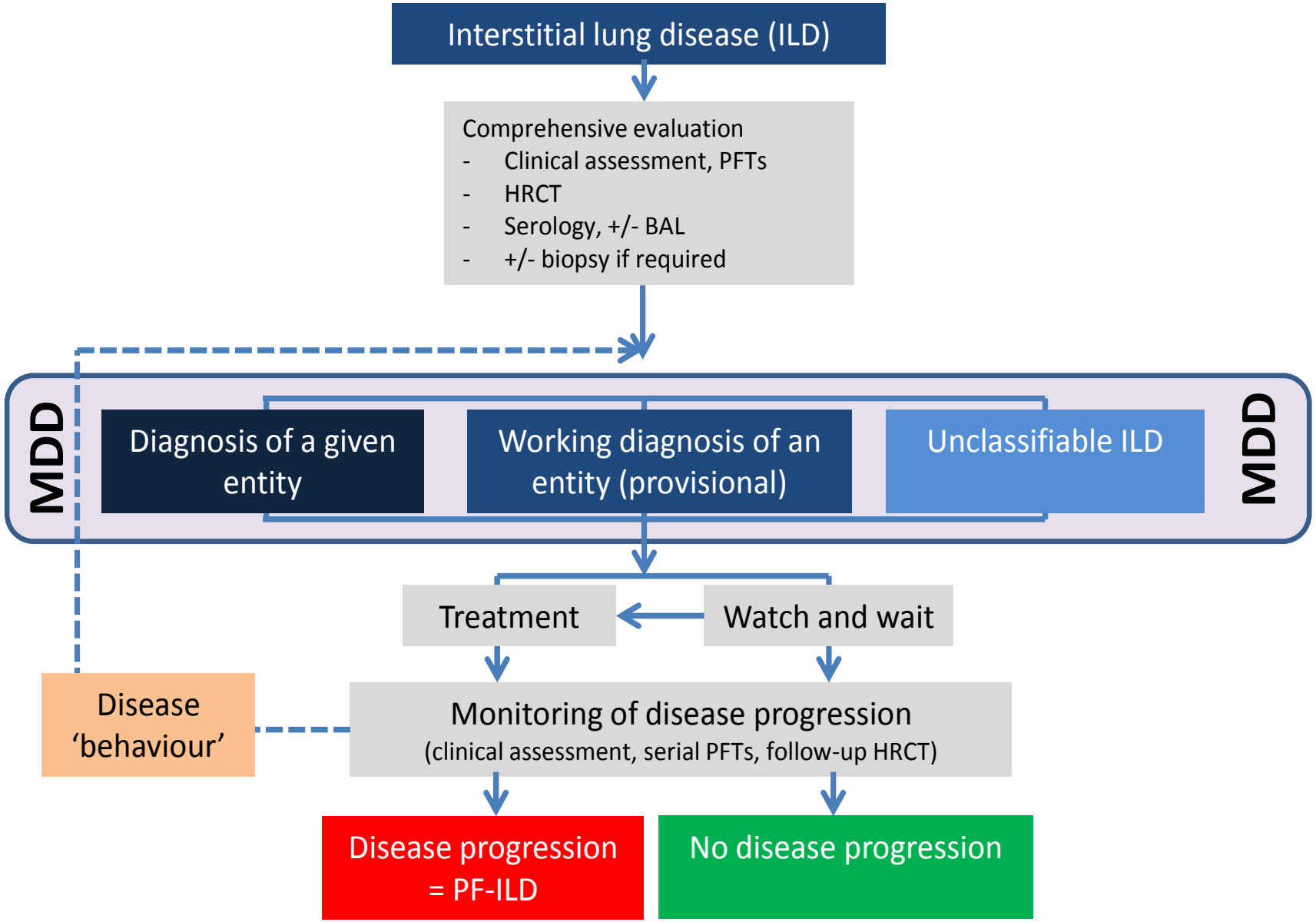
Kolb et al. Thorax 2017;72:340-46

An estimated 18–32% of patients with non-IPF ILDs will develop a progressive fibrosing phenotype



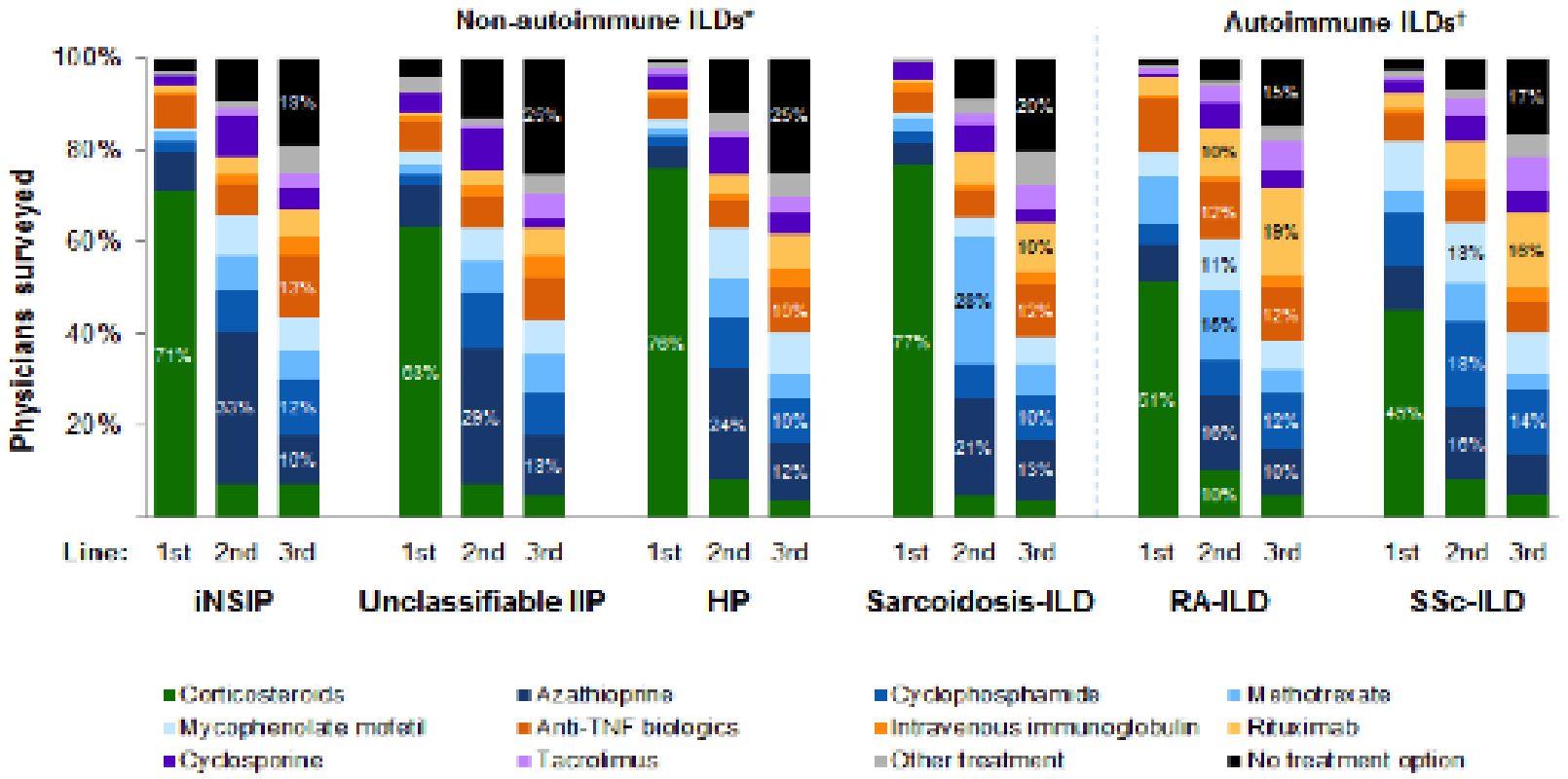
Data from online survey of 243 pulmonologists, 203 rheumatologists, and 40 internists from the US, Japan, Germany, France, Italy, Spain, and the UK

Wijsenbeek M, et al. Presented at ATS International Conference, 18–23 May 2018, San Diego, CA, USA.



Cottin V, et al. Eur Respir Rev 2019 (in press).

Current treatment of fibrosing ILDs other than IPF



Online survey of physicians. *Based on responses from 243 pulmonologists. †Based on responses from 445 pulmonologists and rheumatologists.
Kreuter M, et al. Presented at ATS International Conference, 18–23 May 2018, San Diego, CA, USA.

INBUILD trial design

Do we have data that inform us when the progressive fibrotic phenotype is more likely?

Yes: UIP-like disease, more extensive lung involvement

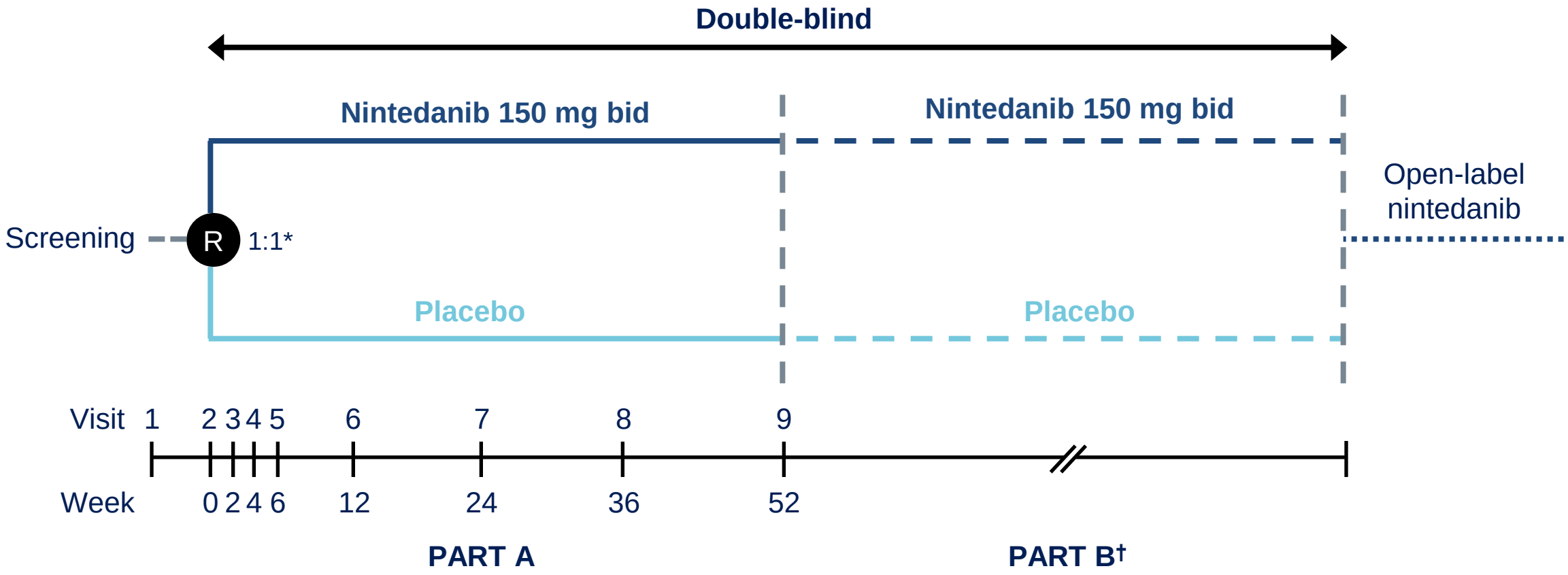
Can the progressive fibrotic phenotype be reliably identified at baseline *in individual patients*?

No

What longitudinal data exist across non-IPF disorders justifying the identification of the progressive fibrotic phenotype based on observed progression despite treatment?

Serial FVC decline consistently predicts mortality

INBUILD trial design



*Randomisation was stratified by HRCT pattern (UIP-like fibrotic pattern only or other fibrotic patterns) based on central review.
†Visits to occur every 16 weeks until end of treatment. bid, twice daily; R, randomisation; UIP, usual interstitial pneumonia.

Flaherty KR, et al. *N Engl J Med.* 2019;381:1718–1727

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, confirmed by central review
- FVC ≥45% predicted
- DLco ≥30%–<80% predicted

DLco, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution computed tomography

Flaherty KR, et al. *N Engl J Med.* 2019;381:1718–1727

Inclusion criteria re: progressive phenotype

Patients were required to meet ≥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–<10% predicted and worsened respiratory symptoms
- Relative decline in FVC ≥5–<10% predicted and increased extent of fibrosis on HRCT
- Worsened respiratory symptoms and increased extent of fibrosis on HRCT

Flaherty KR, et al. *N Engl J Med.* 2019;381:1718–1727

Key exclusion criteria

- Diagnosis of IPF
- FEV_1/FVC <0.7 (pre-bronchodilator)
- Alanine transaminase, aspartate transaminase, or bilirubin >1.5 x upper limit of normal
- Bleeding risk, e.g. full-dose therapeutic anticoagulation or high-dose antiplatelet therapy
- Significant pulmonary arterial hypertension*

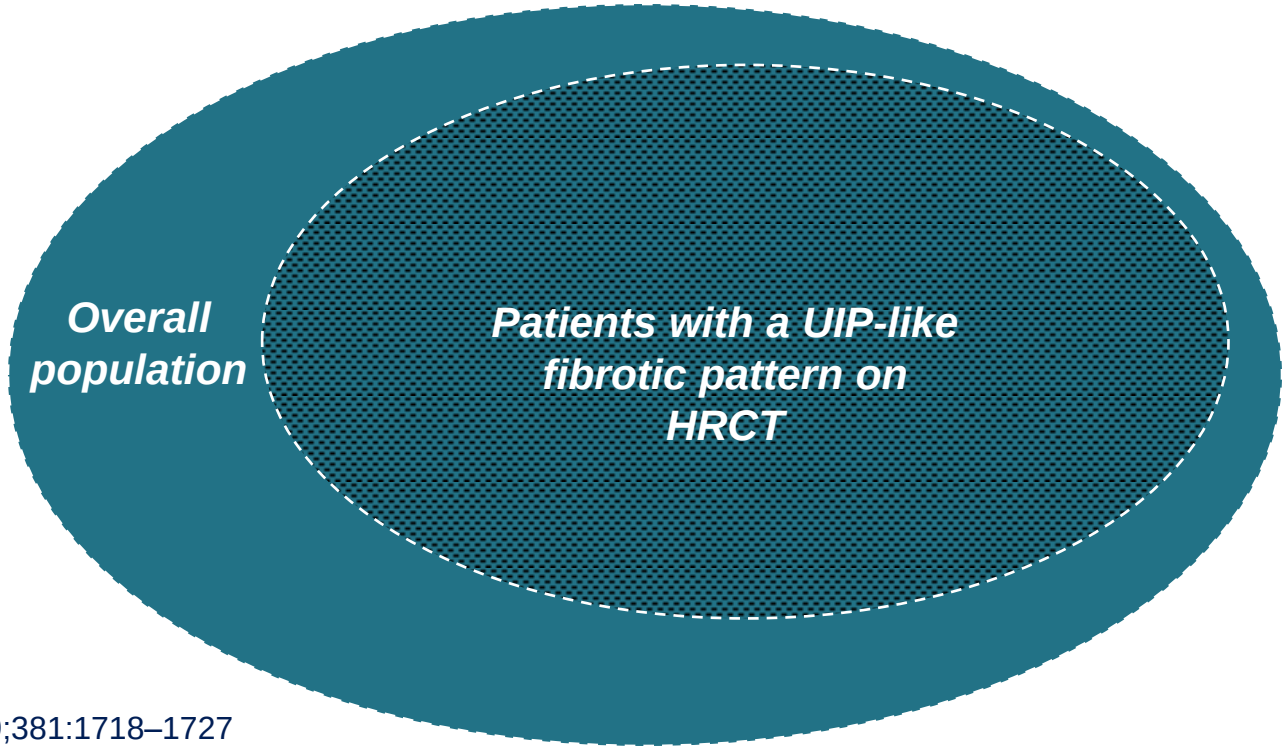
*Previous clinical or echocardiographic evidence of significant right heart failure, history of right heart catheterisation showing a cardiac index ≤2 L/min/m² or pulmonary arterial hypertension requiring parenteral therapy with epoprostenol or treprostinil.

FEV_1, forced expiratory volume in 1 second

Flaherty KR, et al. *N Engl J Med.* 2019;381:1718–1727

Primary endpoint

- The primary endpoint was the annual rate of decline in FVC (mL/year) assessed over 52 weeks
- There were two co-primary analysis populations:



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Main secondary endpoints

- Absolute change from baseline in K-BILD questionnaire total score at week 52
- Time to first acute exacerbation of ILD or death over 52 weeks
- Time to death over 52 weeks

K-BILD, King's Brief Interstitial Lung Disease.

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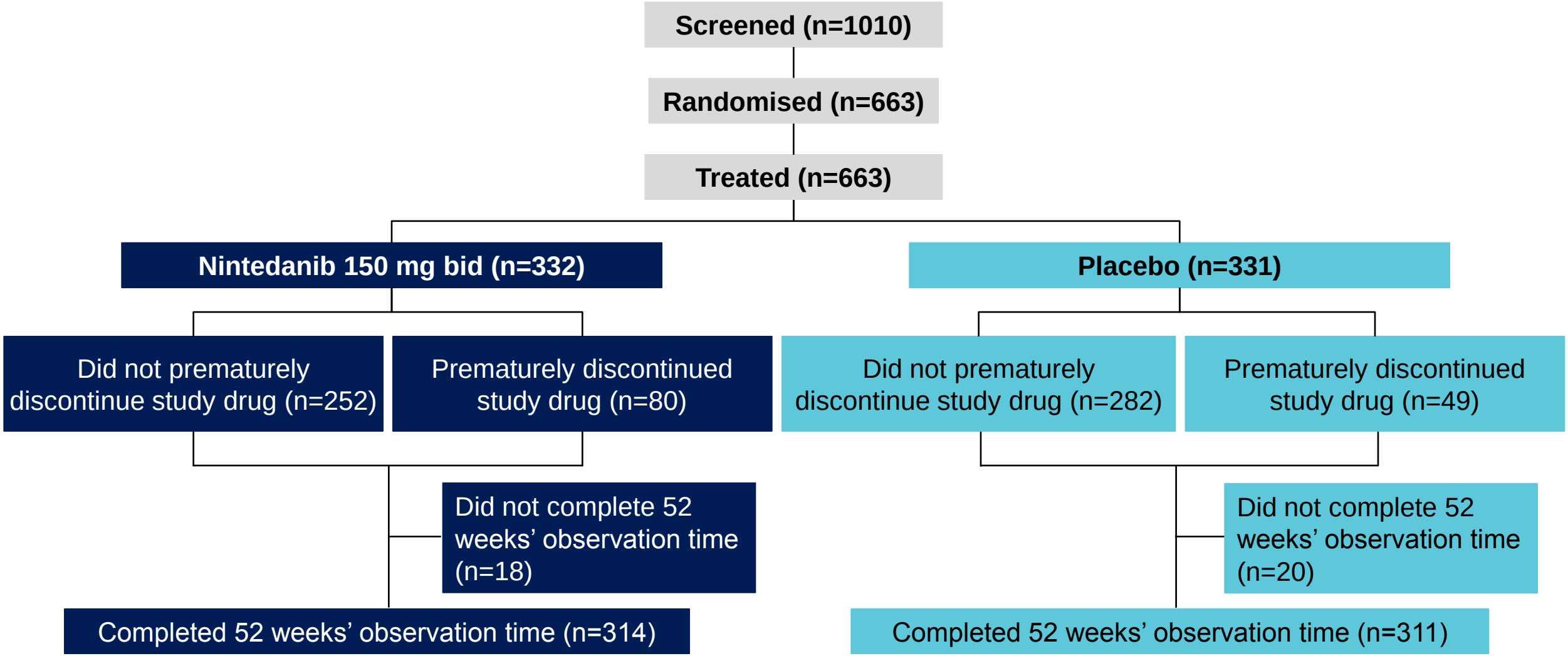
Disposition of overall population over 52 weeks



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INBUILD: Baseline characteristics of overall population

	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)
Current or former smoker, n (%)	169 (50.9)	169 (51.1)
UIP-like fibrotic pattern on HRCT, n (%)	206 (62.0)	206 (62.2)
FVC, mL, mean (SD)	2340 (740)	2321 (728)
FVC, % predicted, mean (SD)	68.7 (16.0)	69.3 (15.2)
DLco, % predicted, mean (SD)*	44.4 (11.9)	47.9 (15.0)
K-BILD questionnaire total score, mean (SD)	52.5 (11.0)	52.3 (9.8)

*Corrected for haemoglobin. Not all patients provided data for all variables.

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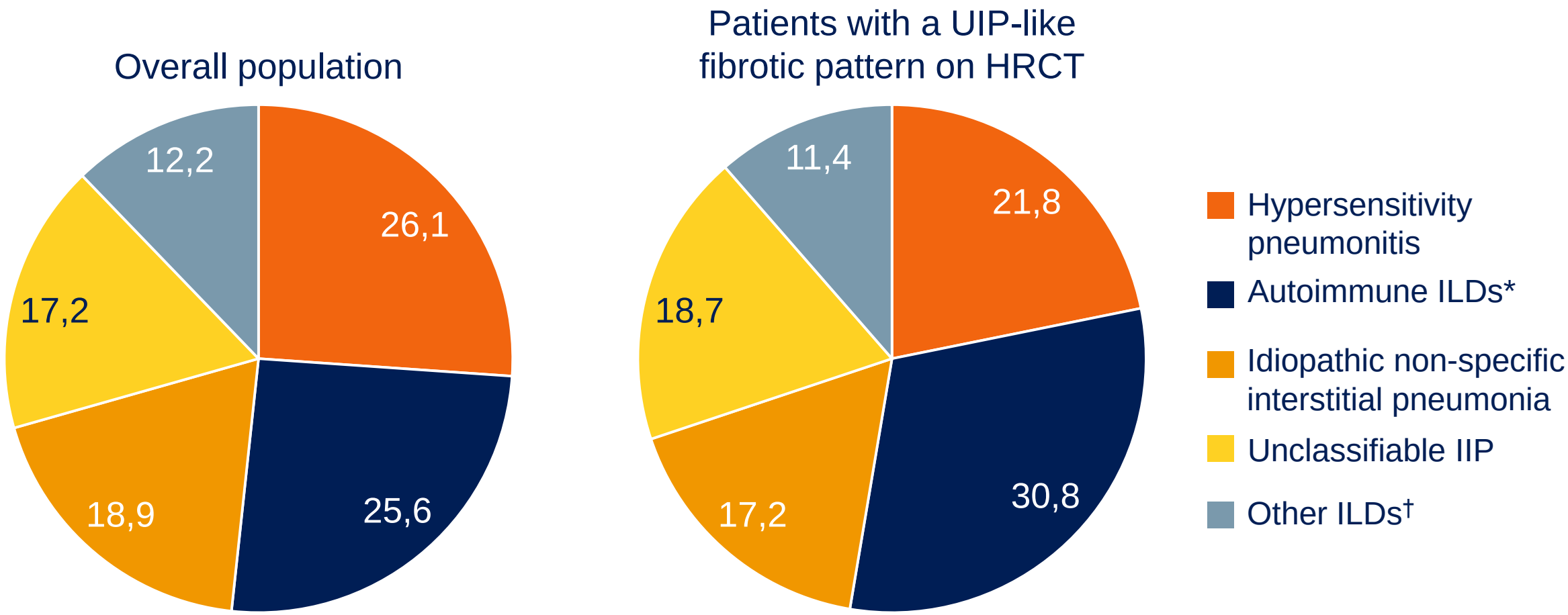
INBUILD: Clinical ILD diagnoses



Data are % of patients. *Included rheumatoid arthritis-associated ILD, systemic sclerosis-associated ILD, mixed connective tissue disease-ILD, and selected other terms in “Other fibrosing ILDs”. †Included sarcoidosis, exposure-related ILDs and selected other terms in “Other fibrosing ILDs”. IIP, idiopathic interstitial pneumonia.

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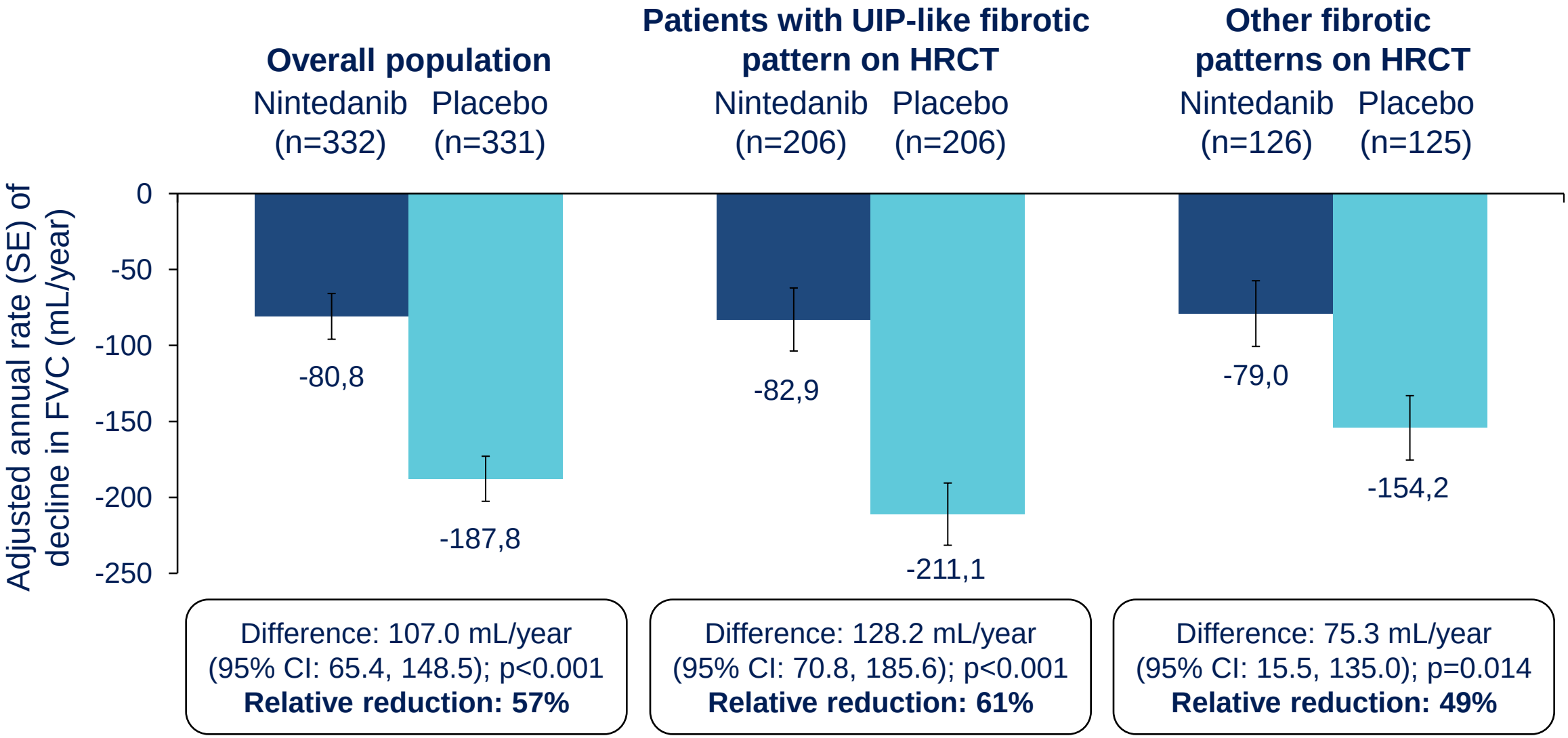
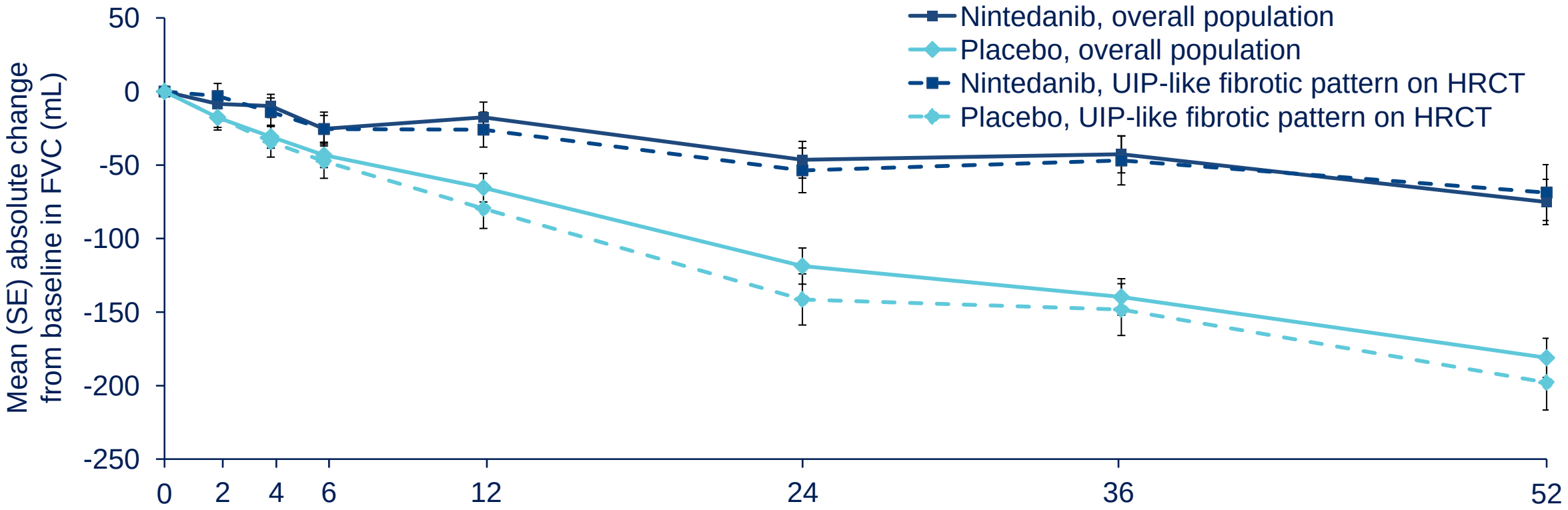
INBUILD: Annual rate of decline in FVC (mL/year) over 52 weeks



Flaherty KR, et al. *N Engl J Med.* 2019;381:1718–1727

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



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

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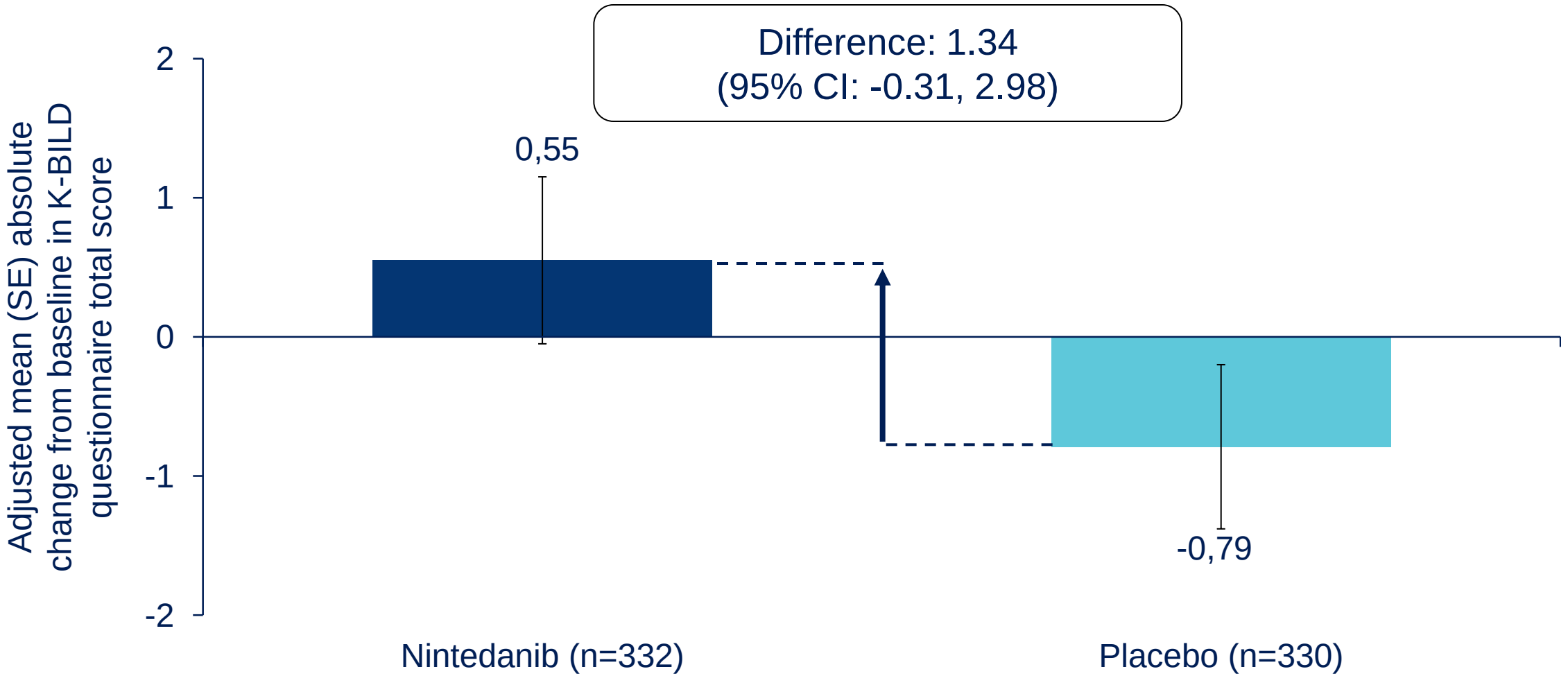
Absolute change from baseline in K-BILD at week 52
Overall population



Scores range from 0 to 100. Higher scores represent better health status.

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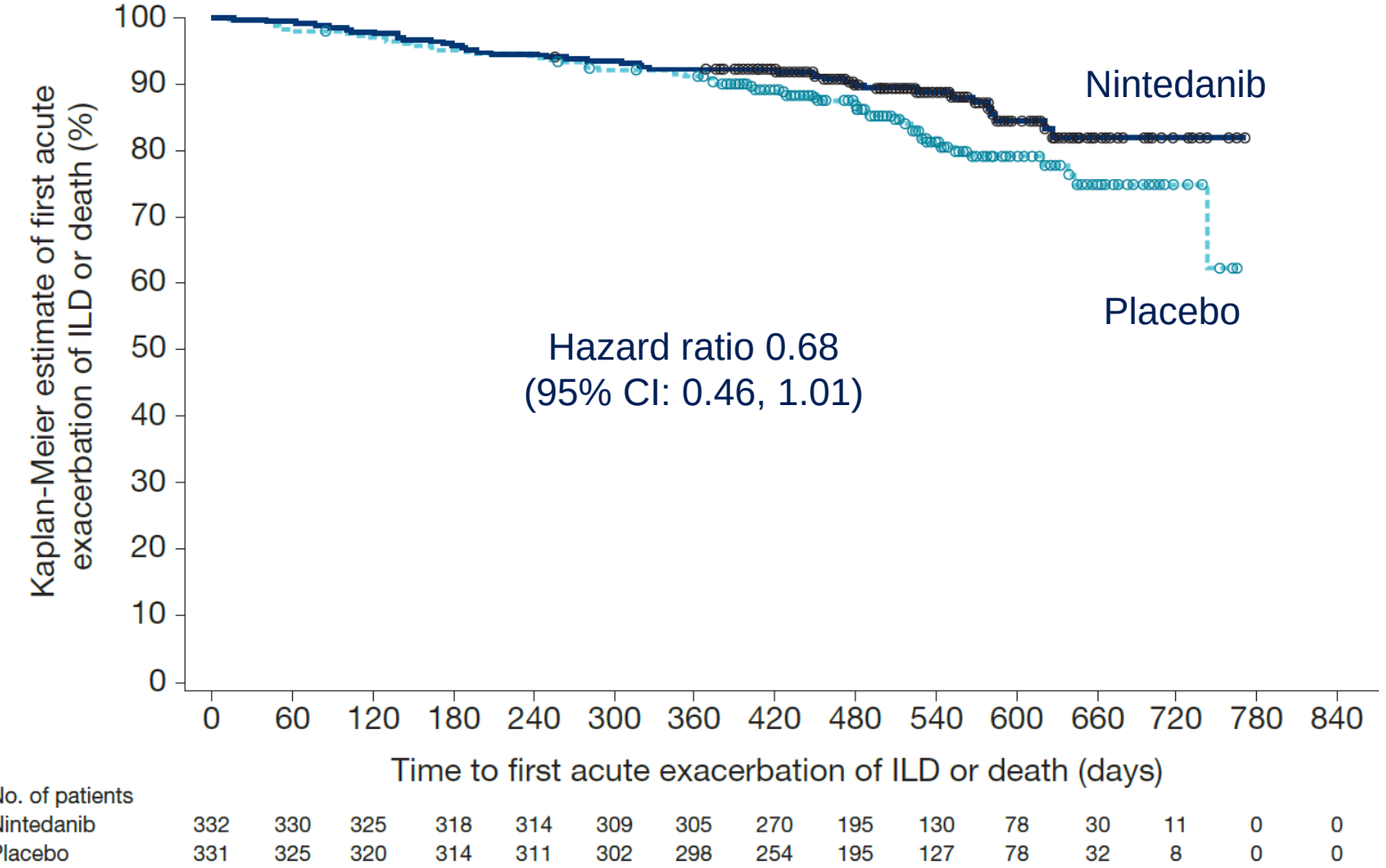
Time to first acute exacerbation of ILD or death (up to first database lock)
Overall population



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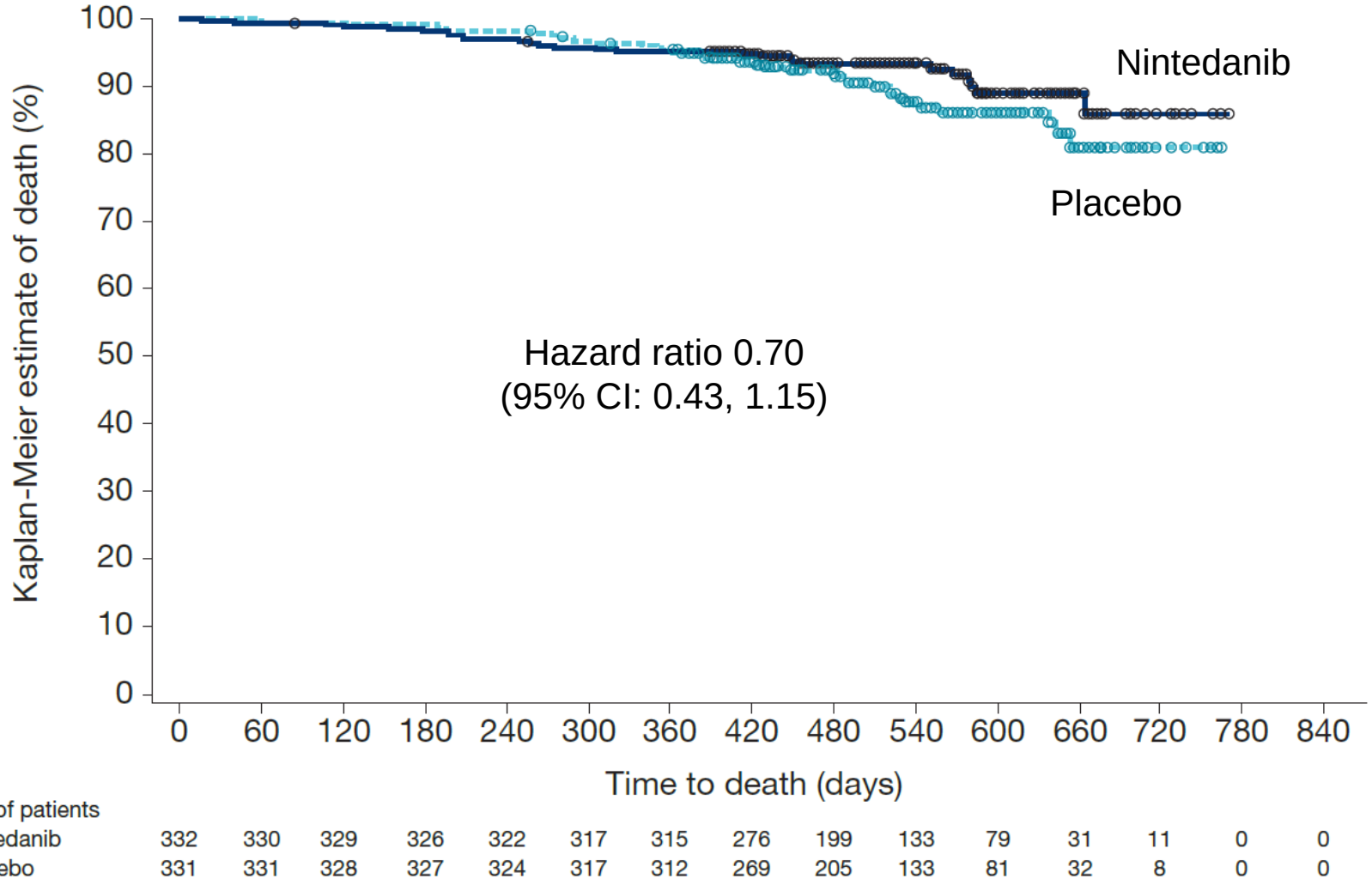
Time to death in overall population



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Most frequently reported adverse events in overall population

	Nintedanib (n=332)	Placebo (n=331)
Diarrhoea	222 (66.9)	79 (23.9)
Nausea	96 (28.9)	31 (9.4)
Bronchitis	41 (12.3)	47 (14.2)
Nasopharyngitis	44 (13.3)	40 (12.1)
Dyspnoea	36 (10.8)	44 (13.3)
Vomiting	61 (18.4)	17 (5.1)
Cough	33 (9.9)	44 (13.3)
Decreased appetite	48 (14.5)	17 (5.1)
Headache	35 (10.5)	23 (6.9)

Data are n (%) of patients with ≥1 such adverse event reported over 52 weeks (or until 28 days after last trial drug intake for patients who discontinued trial drug before week 52). Adverse events based on MedDRA preferred terms that were reported in >10% of patients in either treatment group are shown.

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Most frequently reported adverse events in overall population

	Nintedanib (n=332)	Placebo (n=331)
Alanine aminotransferase increased	43 (13.0)	12 (3.6)
Progression of ILD*	16 (4.8)	39 (11.8)
Weight decreased	41 (12.3)	11 (3.3)
Aspartate aminotransferase increased	38 (11.4)	12 (3.6)
Abdominal pain	34 (10.2)	8 (2.4)

Data are n (%) of patients with ≥1 such adverse event reported over 52 weeks (or until 28 days after last trial drug intake for patients who discontinued trial drug before week 52). Adverse events based on MedDRA preferred terms that were reported in >10% of patients in either treatment group are shown.
*"Progression of ILD" was based on the MedDRA preferred term "interstitial lung disease".

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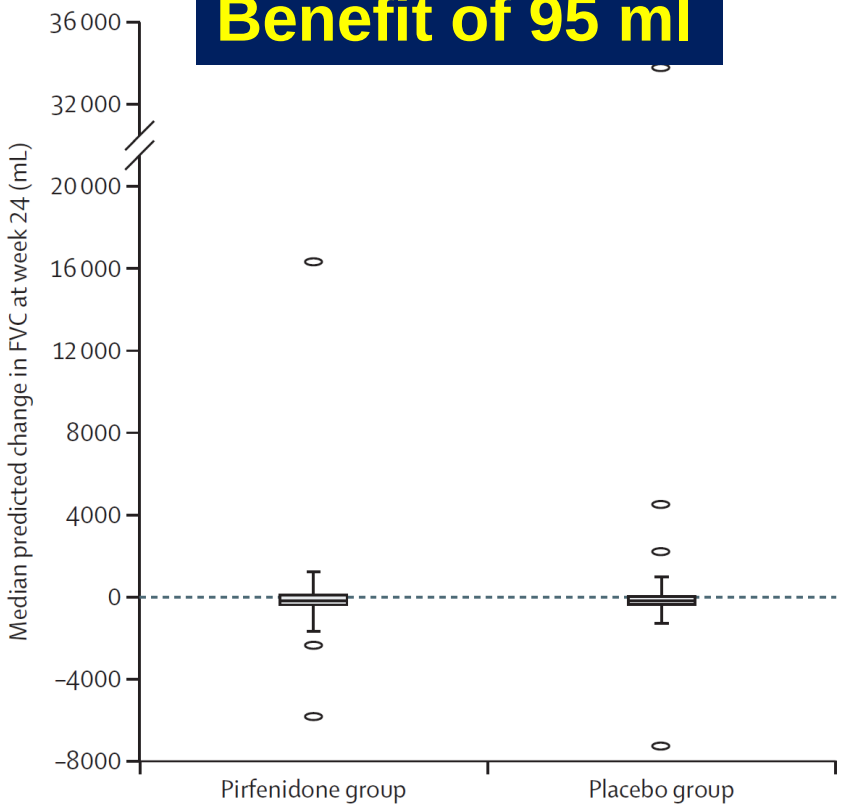
Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial

Toby M Maher, Tamera J Corte, Aryeh Fischer, Michael Kreuter, David J Lederer, Maria Molina-Molina, Judit Axmann, Klaus-Uwe Kirchgaessler, Katerina Samara, Frank Gilberg, Vincent Cottin

Benefit of 95 ml



	Pirfenidone (n=127)	Placebo (n=126)	Pirfenidone *vs* placebo	p value*
Predicted FVC change from baseline measured by site spirometry, mL				
Mean (95% CI)	−17·8† (−62·6 to 27·0)	−113·0‡ (−152·5 to −73·6)	95·3 (35·9 to 154·6)	0·002
Median (Q1–Q3)	−7·5 (−185·4 to 112·3)	−125·8 (−238·2 to 2·2)	118·3	..
FVC change from baseline measured by site spirometry, % predicted				
Rank analysis of covariance	..	..	..	0·038
Patients with >5% decline in FVC	47 (37%)	74 (59%)	0·42 (0·25 to 0·69)§	0·001
Patients with >10% decline in FVC	18 (14%)	34 (27%)	0·44 (0·23 to 0·84)§	0·011
DLco change from baseline, % predicted				
Rank analysis of covariance	..	..	..	0·09
Patients with >15% decline in DLco¶	3 (2%)	11 (9%)	0·25 (0·07 to 0·93)§	0·039
6MWD change from baseline, m				
Rank analysis of covariance	..	..	..	0·040
Patients with >50 m decline in 6MWD¶	36 (28%)	35 (28%)	1·03 (0·59 to 1·78)§	0·92

Data are n (%), unless otherwise specified. FVC=forced vital capacity. DLco=carbon monoxide diffusing capacity. 6MWD=6-min walk distance. *p values for secondary endpoints are not adjusted for multiplicity and are provided for descriptive purposes only. †n=118; only patients with a baseline measurement and at least two post-baseline measurements were included in the analysis. ‡n=119; only patients with a baseline measurement and at least two post-baseline measurements were included in the analysis. §Odds ratio (95% CI). ¶Prespecified exploratory outcome.

Not so progressive…..1/3 FVC>10%, 1/10 DLCO>15%

Predicted FVC change from baseline measured by site spirometry, mL				
Mean (95% CI)	−17·8† (−62·6 to 27·0)	−113·0‡ (−152·5 to −73·6)	95·3 (35·9 to 154·6)	0·002
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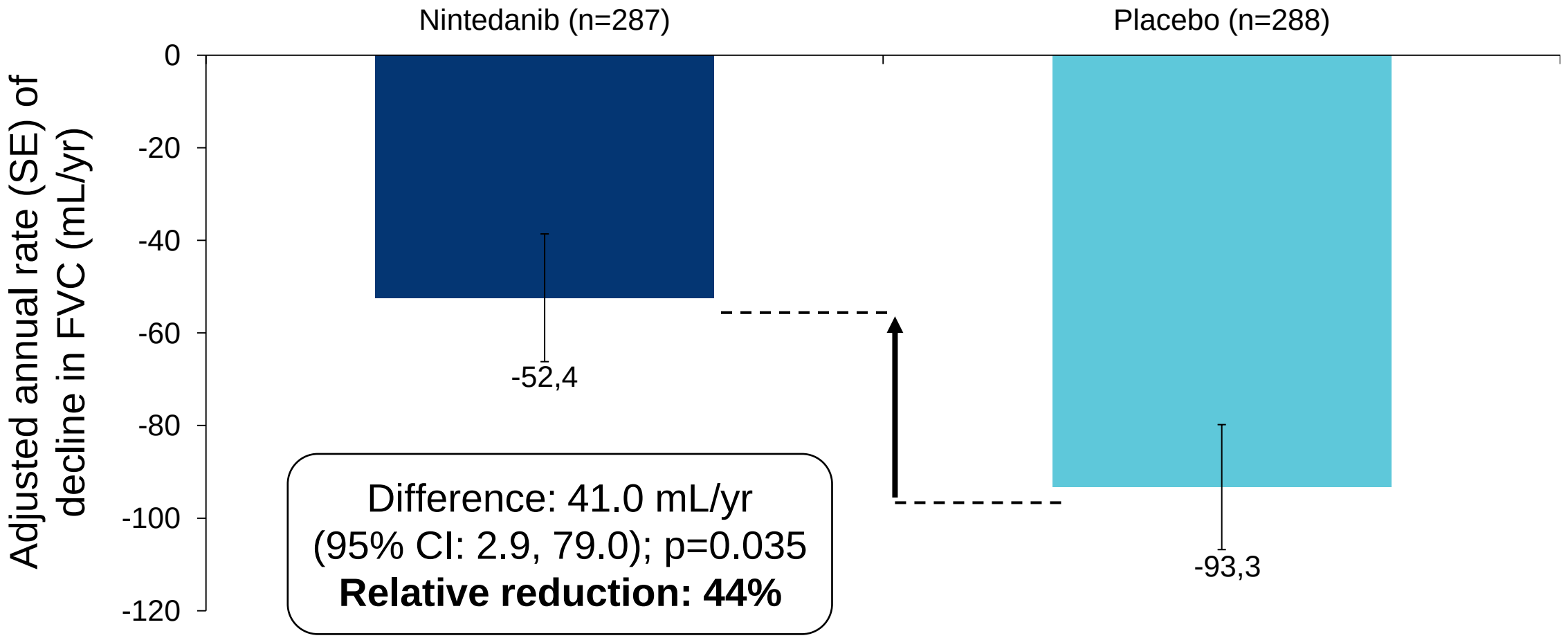
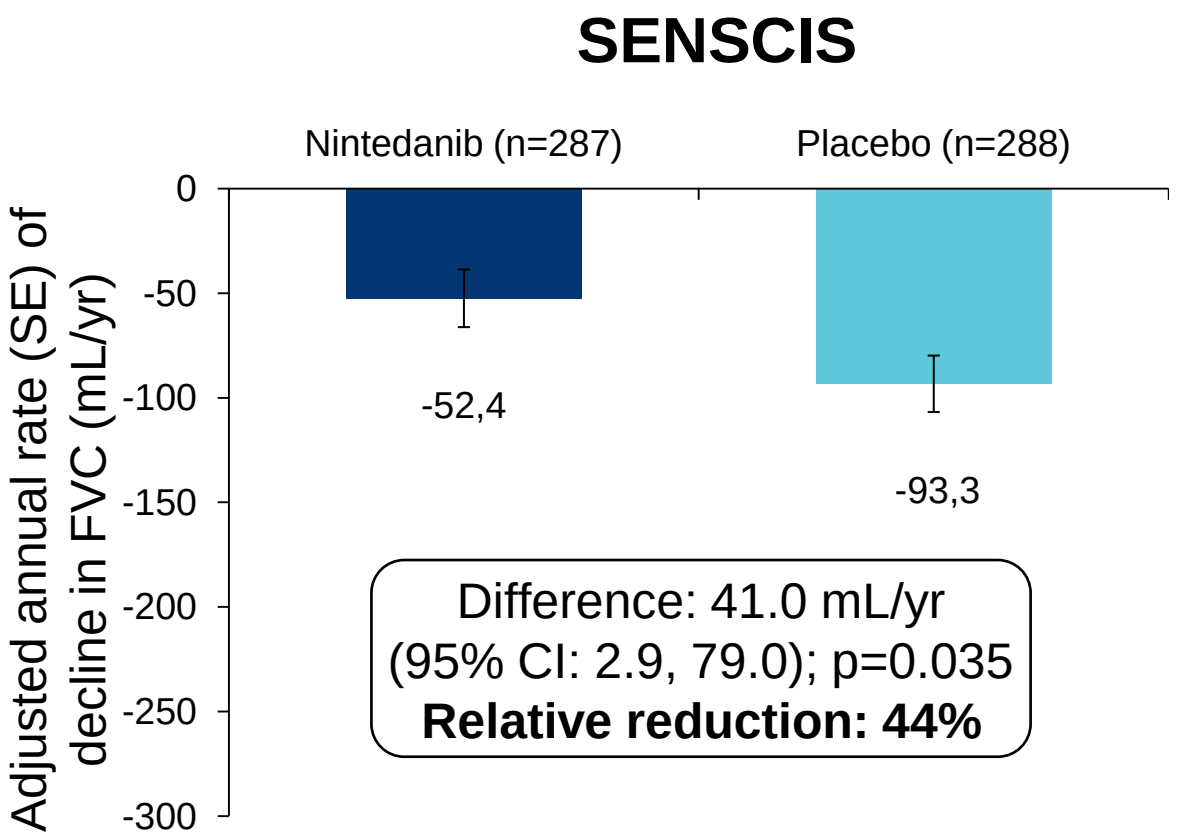
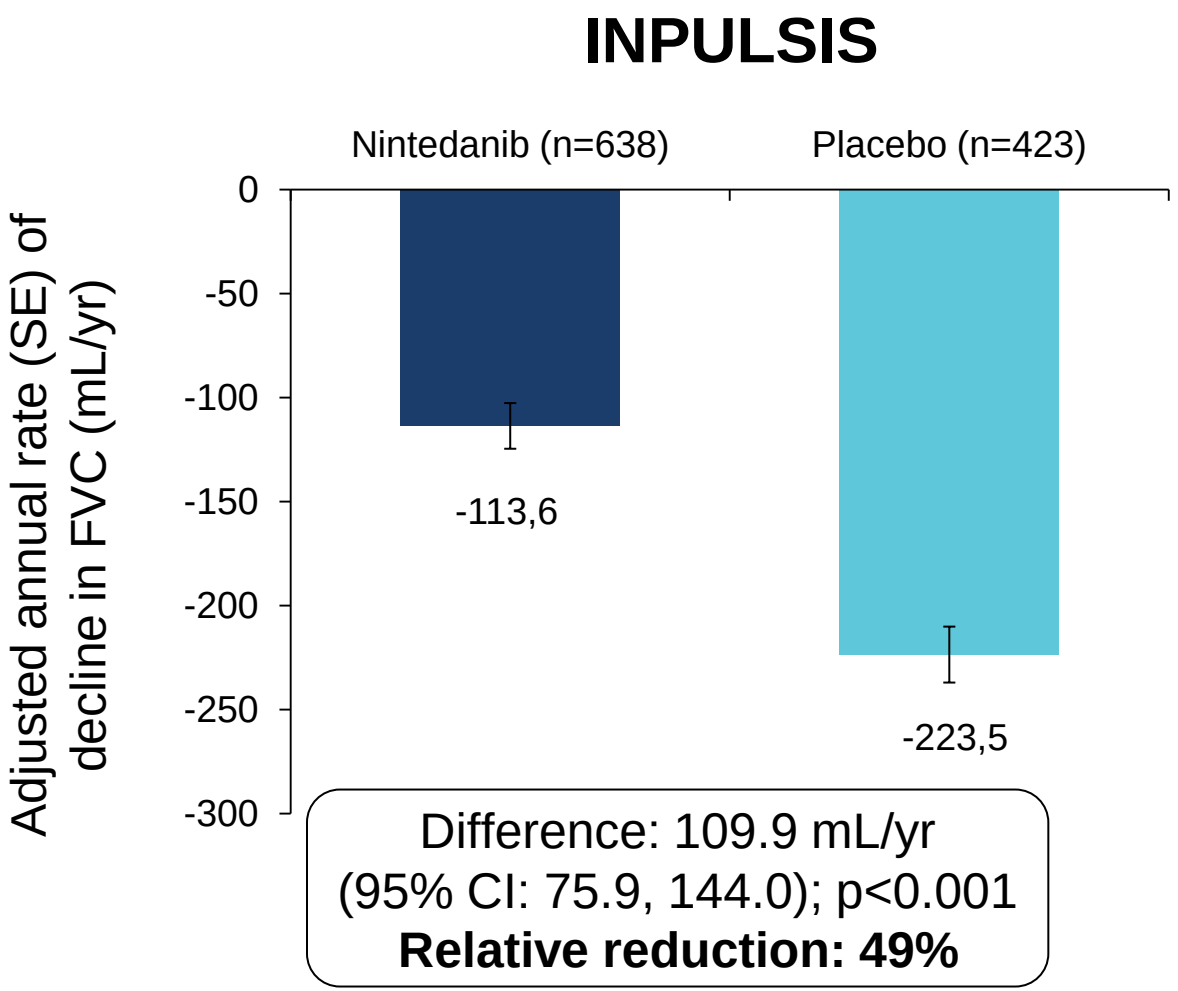
Table 2: **Secondary and prespecified exploratory outcomes at week 24 in the intention-to-treat population (n=253)**

SENSCIS: Annual rate of decline in FVC (mL/yr) over 52 weeks (primary endpoint)



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





PULMONOLOGY

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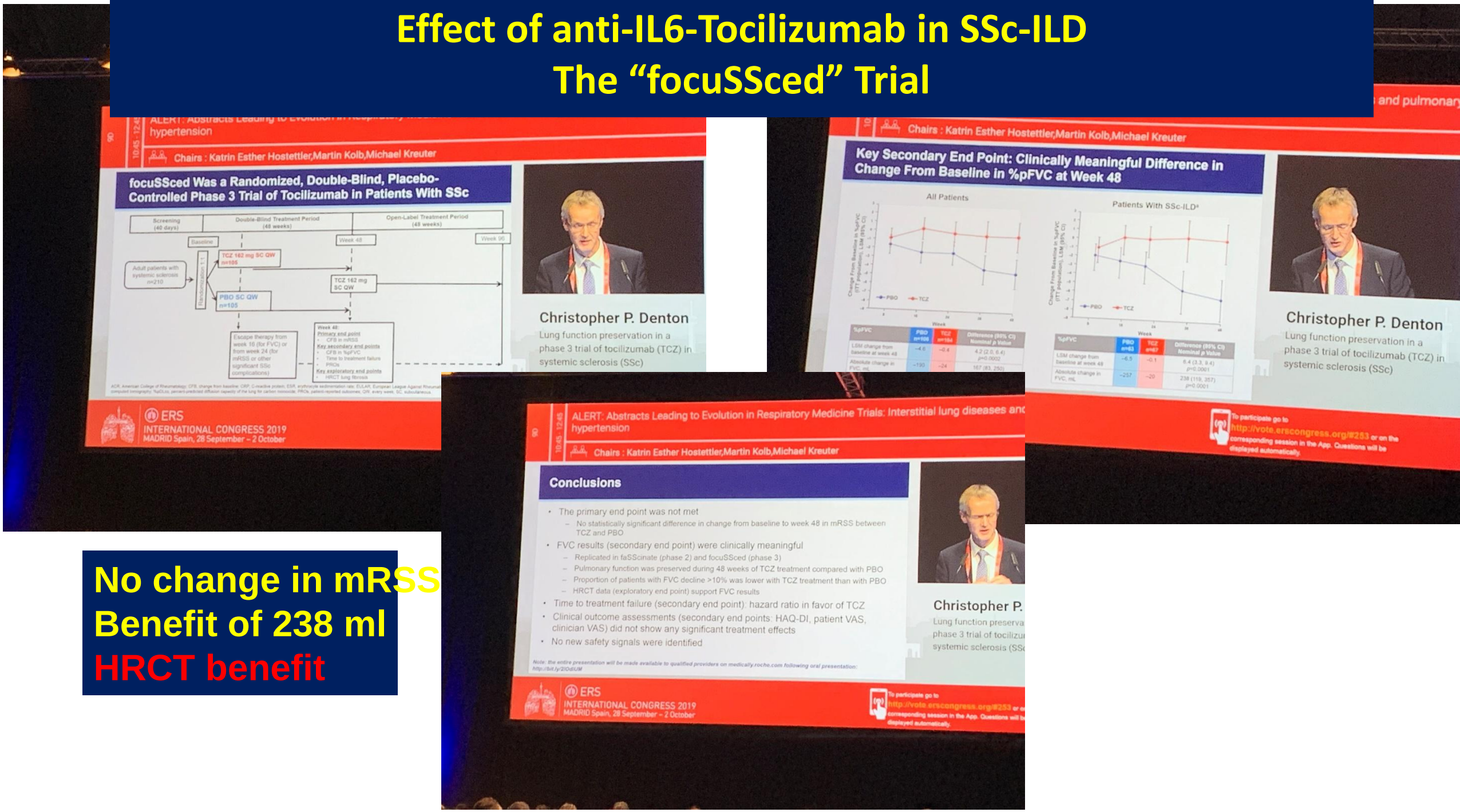
COMMENT

A role of antifibrotics in the treatment of Scleroderma-ILD?

Katerina M. Antoniou[a,*], Athina Trachalaki[a], Argyris Tzouvelekis[b], Venerino Poletti[c,d], Eirini Vasarmidi[a], Petros Sfikakis[e], Demosthenes Bouros[b]

[a] *Department of Respiratory Medicine, Medical School, University of Crete, Heraklion, Greece*
[b] *Medical School, National and Kapodistrian University of Athens, First Academic Department of Pneumonology, Interstit*

Effect of anti-IL6-Tocilizumab in SSc-ILD
The “focuSSced” Trial



No change in mRSS
Benefit of 238 ml
HRCT benefit

Key messages

- A proportion of patients with fibrosing ILDs other than IPF develop a progressive phenotype

- There are commonalities between the progressive fibrosing ILDs and IPF regarding clinical behaviour, progressive loss of lung function, high mortality, as well as in the pathogenetic processes involved irrespective of etiology

- Patients with progressive lung fibrosis can be identified in clinical practice by adequate monitoring especially serial lung function

A GREAT THANK YOU !!!!!!!!!!