Progressive fibrosing ILD

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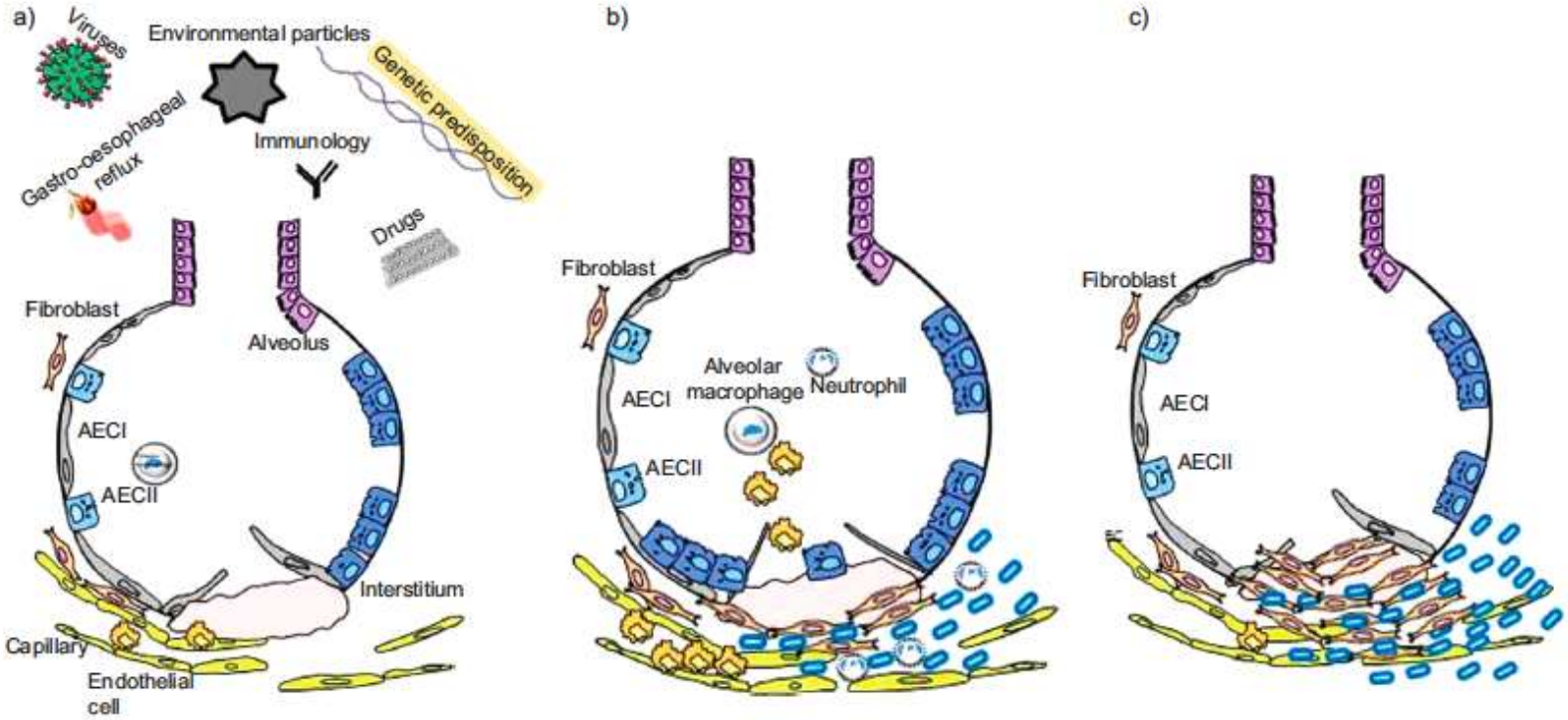
DM seminar

28-08-2020

Division

- Background
- Definition
- Pathophysiology
- Biomarkers
- Radiology
- Treatment

Induction and progression of fibrosis



Injury

- Epithelial damage
- Endothelial damage
- Destruction of alveolar capillary basement membrane
- Vascular leak
- Platelet activation
- Fibrin clot activation

Epithelial–fibroblastic interaction

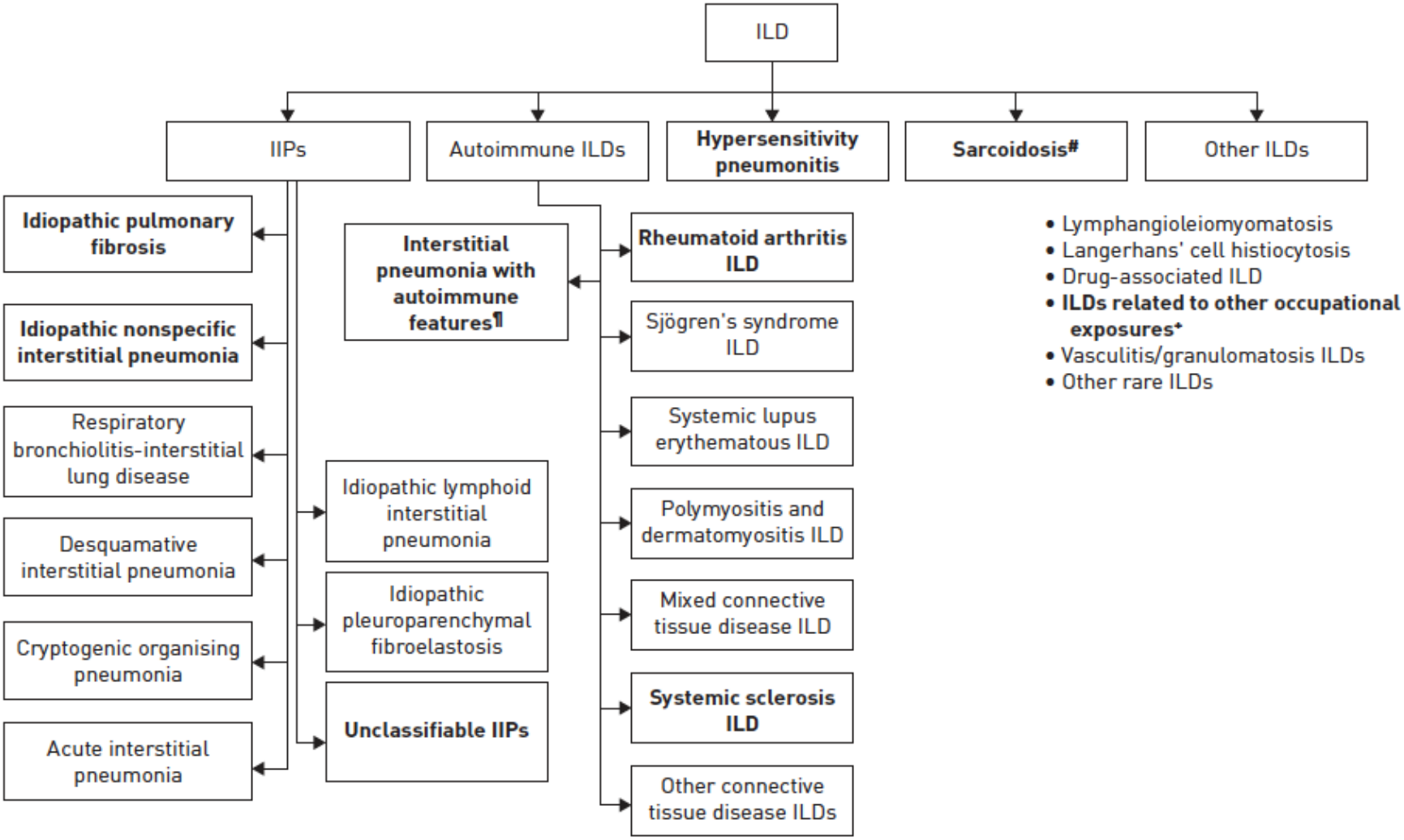
- Release of profibrotic cytokines
- (Myo)fibroblast recruitment, proliferation and differentiation
- Provisional matrix formation
- Angiogenesis
- Defective re-epithelialisation

Aberrant repair and fibrosis

- Exaggerated ECM accumulation
- Lack of matrix degradation
- Progressive lung remodelling
- Honeycomb changes

Eur Respir J 2013; 41: 1207–1218

Types of interstitial lung disease



https://doi.org/10.1183/16000617.0076-2018
Eur Respir Rev 2018; 27: 180076

ATS-Classification of the Idiopathic Interstitial Pneumonias

TABLE 1. REVISED AMERICAN THORACIC SOCIETY/EUROPEAN RESPIRATORY SOCIETY CLASSIFICATION OF IDIOPATHIC INTERSTITIAL PNEUMONIAS: MULTIDISCIPLINARY DIAGNOSES

Major idiopathic interstitial pneumonias
Idiopathic pulmonary fibrosis
Idiopathic nonspecific interstitial pneumonia
Respiratory bronchiolitis–interstitial lung disease
Desquamative interstitial pneumonia
Cryptogenic organizing pneumonia
Acute interstitial pneumonia
Rare idiopathic interstitial pneumonias
Idiopathic lymphoid interstitial pneumonia
Idiopathic pleuroparenchymal fibroelastosis
Unclassifiable idiopathic interstitial pneumonias*

ATS-Classification of the Idiopathic Interstitial Pneumonias

TABLE 3. 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

Future definition and taxonomy of IPF ?

Splitting IPF and precision medicine

Tried to identify endotypes based on genetic and molecular studies

Failed

Lumping IPF with other fibrotic diseases: the progressive fibrotic phenotype

Evidence?

Data indicative of IPF-like disease progression in subgroups of patients with other progressive fibrotic lung diseases

- IPF-like outcomes in
  - CHP with a histological or CT pattern of UIP
  - RA with a histological or CT pattern indicative of UIP
  - IPAF with a histological or CT pattern indicative of UIP
- Outcomes intermediate between IPF and other progressive fibrotic diseases in patients with unclassifiable ILD
- Reports of patients with drug-induced lung disease exhibiting a fatal progressive fibrotic phenotype despite drug withdrawal
- IPF-like outcomes in patients with idiopathic NSIP with disease progression at 6–12 months (as judged by serial FVC trends)
- Linkage between serial decline in FVC and mortality in CHP, SSc-ILD and rheumatoid lung, similar to that seen in IPF

https://doi.org/10.1183/16000617.0076-2018
Eur Respir Rev 2018; 27: 180076

Evidence?

Data indicative of pathogenetic mechanisms common to IPF and other progressive fibrotic lung diseases

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

https://doi.org/10.1183/16000617.0076-2018
Eur Respir Rev 2018; 27: 180076

What about in real world?

Progressive fibrosing interstitial lung diseases: current practice in diagnosis and management

Marlies Wijsenbeek[a], Michael Kreuter[b], Amy Olson[c], Aryeh Fischer[d], Elisabeth Bendstrup[e], Christopher D. Wells[f], Christopher P. Denton[g], Baher Mounir[h], Leila Zouad-Lejour[h], Manuel Quaresma[h] and Vincent Cottin[i]

From May–June 2017 through online survey collected data from 243 pulmonologists, 203 rheumatologists and 40 internists across France, Germany, Italy, Japan, Spain, UK and US who had managed 10 patients with non-IPF ILDs in the past year, including those with progressive fibrosing ILDs

Progressive fibrosing ILD were defined in the survey as those with fibrosis detected by high resolution computed tomography (HRCT) (reticular abnormality with traction bronchiectasis with or without honeycombing) that were progressing in terms of worsening of lung function (FVC and/or DLCO) and/or respiratory symptoms and/or chest images

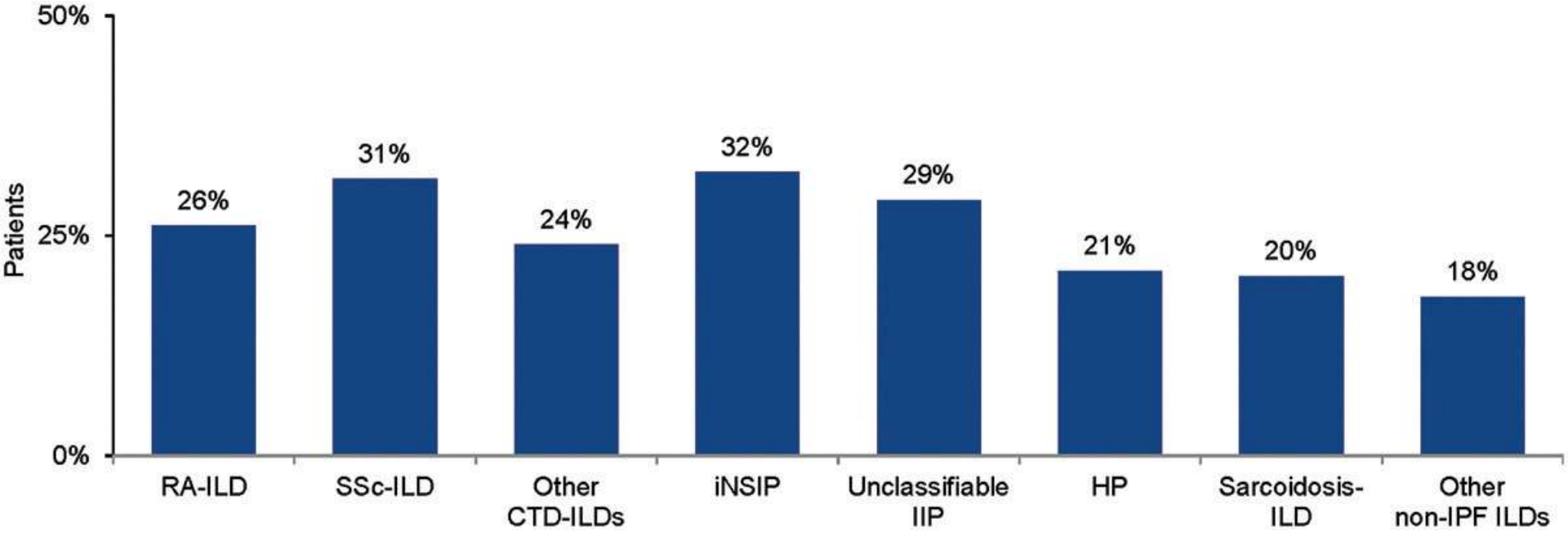
CURRENT MEDICAL RESEARCH AND OPINION 2019, VOL. 35, NO. 11, 2015–2024

Patient journey in non-IPF progressive fibrosing ILDs

	Average time (months)	Average time (months)	Average time (months)	Average time (months)
RA-ILD	11.5	15.2	11.0	41.6
SSc-ILD	9.3	12.3	9.6	33.0
Other CTD-ILDs	11.0	13.9	11.2	38.3
iNSIP	9.3	12.0	8.9	31.1
Unclassifiable IIP	10.3	11.4	9.2	29.7
HP	8.6	13.6	10.4	40.0
Sarcoidosis-ILD	8.8	14.6	11.7	45.2
Other ILDs	9.9	12.7	11.1	33.7

CURRENT MEDICAL RESEARCH AND OPINION 2019, VOL. 35, NO. 11, 2015–2024

Patients with non-IPF ILDs who develop a progressive fibrosing phenotype



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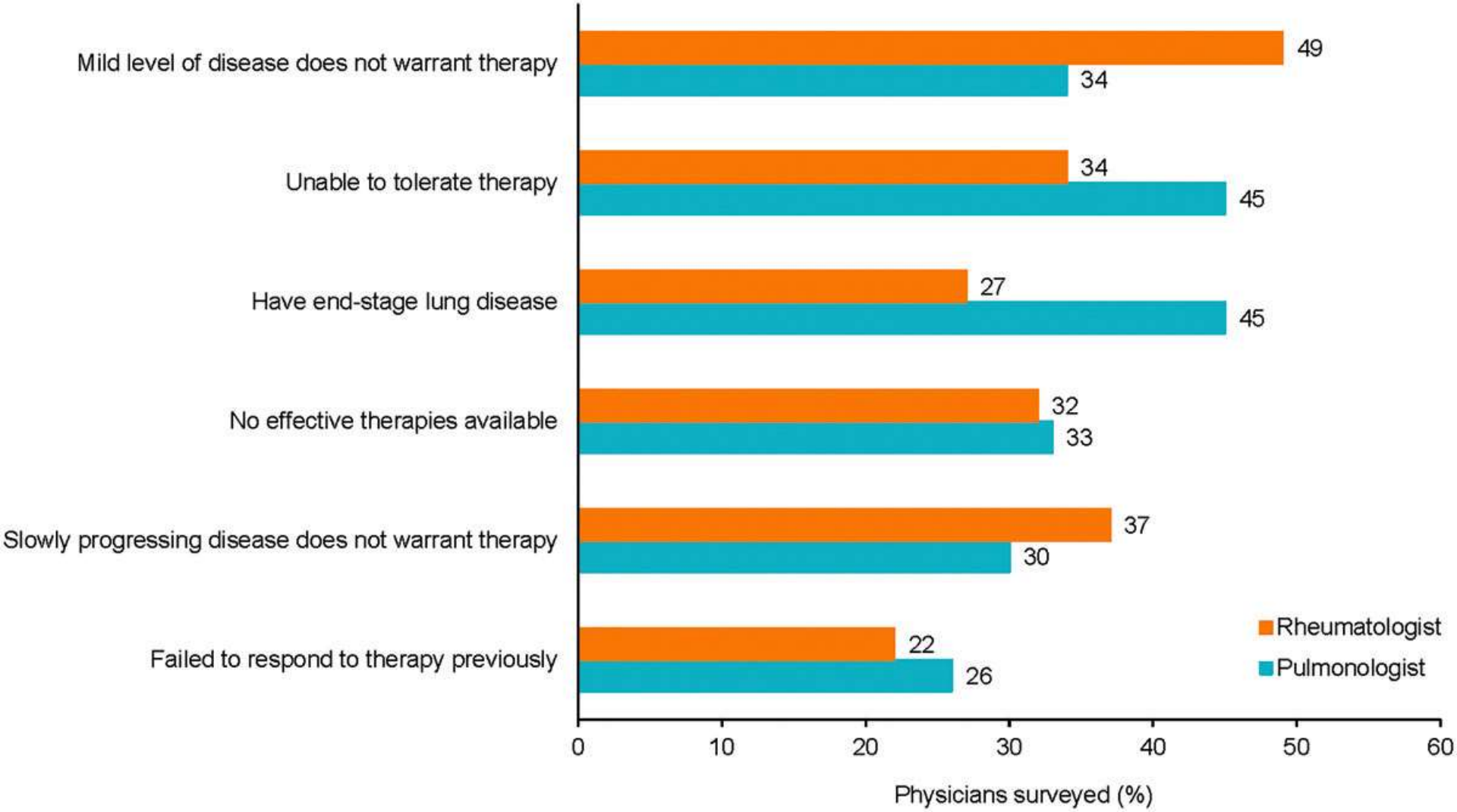
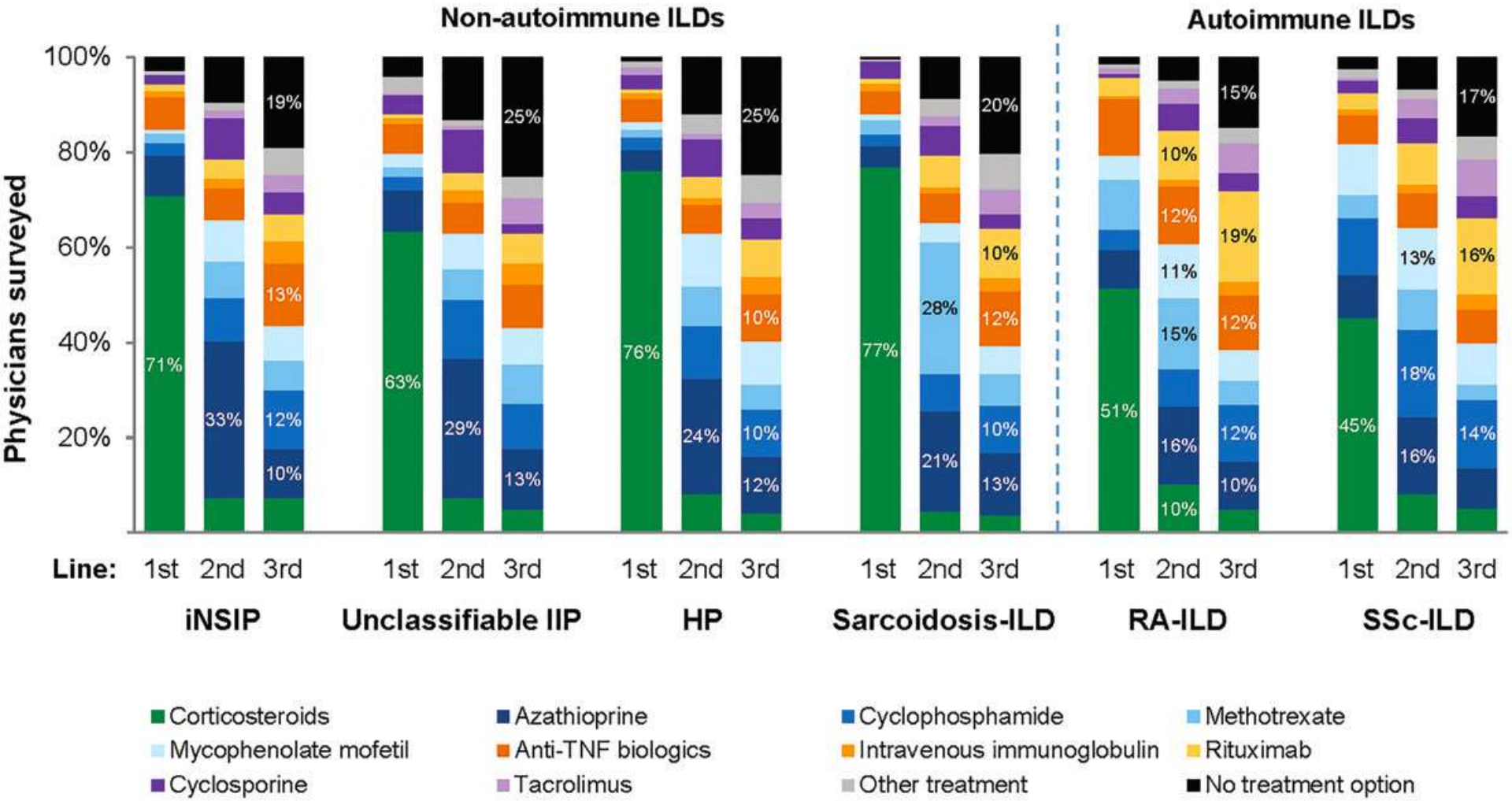
Reasons why patients with non-IPF progressive fibrosing ILDs did



Agents used as first-, second- and third-line treatments for fibrotic ILDs



In conclusion

- 18–32% of patients diagnosed with non-IPF ILDs will develop a progressive fibrosing phenotype
- 25–50% of patients with progressive fibrosing ILDs did not receive any drug therapy in the past year.
- Mortality is similar to patients with IPF prior to the availability of therapies

CURRENT MEDICAL RESEARCH AND OPINION 2019, VOL. 35, NO. 11, 2015–2024

The natural history of progressive fibrosing interstitial lung diseases

Kevin K. Brown[1], Fernando J. Martinez[2], Simon L.F. Walsh[3], Victor J. Thannickal[4], Antje Prasse[5], Rozsa Schlenker-Herceg[6], Rainer-Georg Goeldner[7], Emmanuelle Clerisme-Beaty[8], Kay Tetzlaff[8,9], Vincent Cottin[10] and Athol U. Wells[3,11]

- Address the question of similarity between IPF and other fibrosing ILDs with a progressive phenotype, data from the placebo group in the overall population in the INBUILD trial were compared with pooled data from the placebo groups of the INPULSIS trials
- Both are randomised, double-blind, placebo-controlled trial with a 52-week treatment period

Inclusion criteria

INPULSIS trials

- Aged ⩾40 years and had a clinical diagnosis of IPF.
- FVC ⩾50% predicted and DLCO⩾30% and <80% predicted
- Subjects were randomised 3:2 to receive nintedanib or placebo.

INBUILD trial-(randomised 1:1)

- Age >18yr
- Physician diagnosed PF-ILDs(nine options: iNSIP, unclassifiable IIP, HP, RA-ILD, mixed connective tissue disease-associated ILD (MCTD-ILD), SSc-ILD, exposure-related ILD, sarcoidosis and other fibrosing ILD)

INBUILD trial-Inclusion criteria

- FVC of **>45%** and DLCO of **30 to 80%** of the predicted value
- Fibrosing ILD-reticular abnormality with traction bronchiectasis with or without honeycombing with an extent of >10% on an HRCT scan (taken within the previous ⩽12 months)
- Progressive Interstitial lung disease-At least one of the following criteria within the last 24 months despite standard treatment (other than nintedanib and pirfenidone)
  - Relative decline in the FVC of at least 10% of the predicted value
  - Relative decline in the FVC of 5-10% of the predicted value **PLUS** worsening of respiratory symptoms **OR** an increased extent of fibrosis on high-resolution CT
  - Worsening of respiratory symptoms **PLUS** an increased extent of fibrosis on HRCT

Analysis

- Analysed measures of longitudinal disease behaviour: annual rate of decline in FVC (mL·year−1), observed absolute change from baseline in FVC (mL) over time, the proportions of subjects with relative declines in FVC of >5% predicted and >10% predicted at Week 52, and all-cause mortality
- Subgroups of subjects with a UIP-like fibrotic pattern on HRCT and with other fibrotic patterns on HRCT in the INBUILD trial were compared with patients with IPF in the INPULSIS trials

Analysis

- Course of ILD in the placebo group of the INBUILD trial was assessed in the following five diagnostic groups: iNSIP, unclassifiable IIP, HP, autoimmune ILDs (RA-ILD, SSc-ILD, MCTD-ILD, plus subjects with an autoimmune disease noted in the “Other fibrosing ILDs” category of the case report form) and other ILDs (sarcoidosis, exposure-related ILDs and selected diagnoses from “Other fibrosing ILDs”)

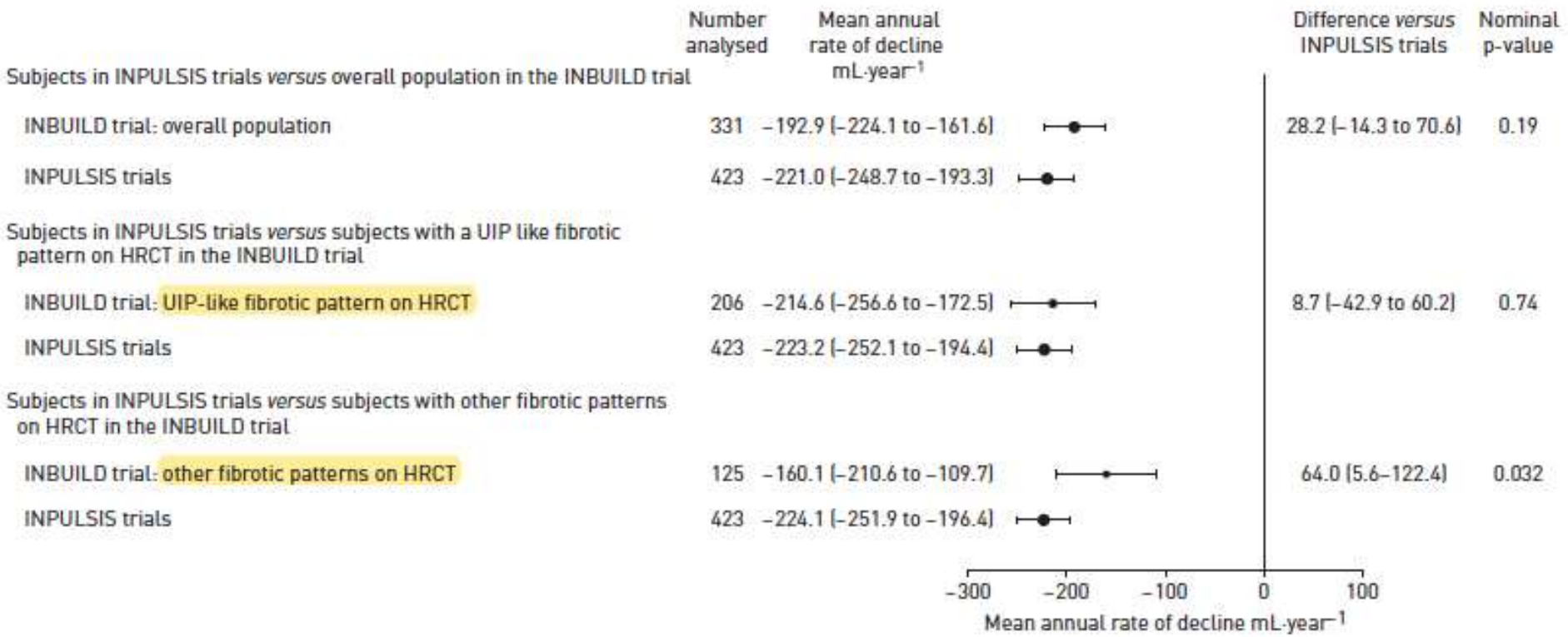
Results

TABLE 1 Baseline characteristics of subjects in the INBUILD and INPULSIS trials

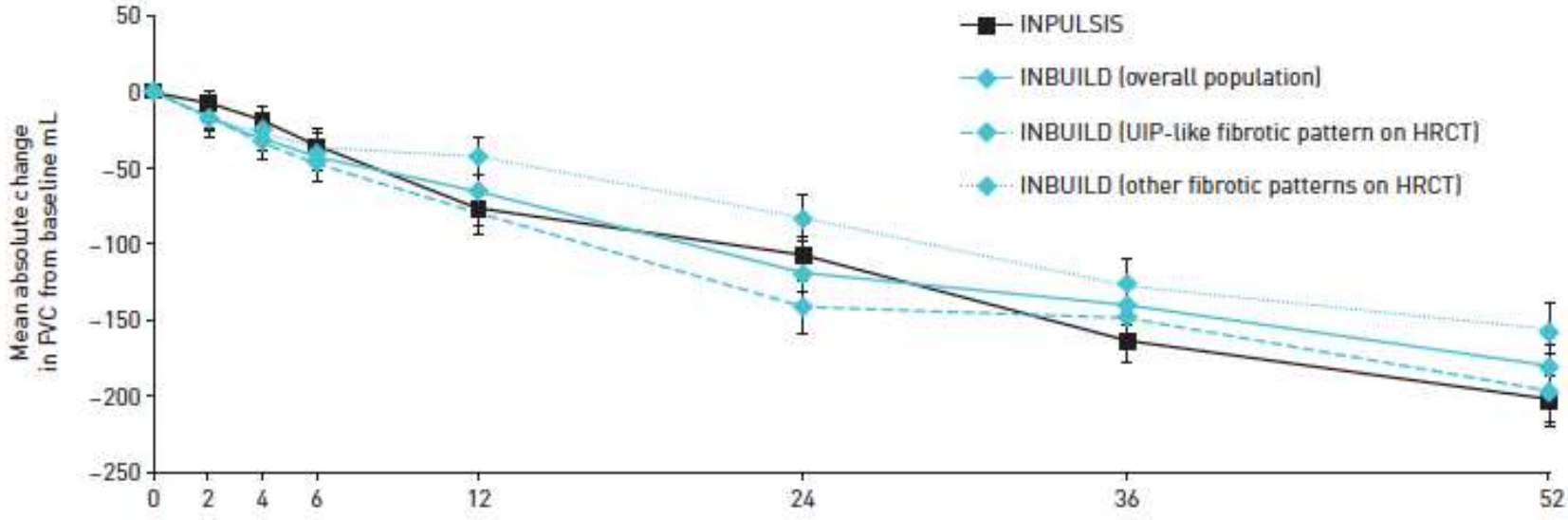
Characteristic	INBUILD trial (overall population)		INPULSIS trials (pooled)	
	Nintedanib (n=332)	Placebo (n=331)	Nintedanib (n=638)	Placebo (n=423)
Male sex	179 (53.9)	177 (53.5)	507 (79.5)	334 (79.0)
Age years	65.2±9.7	66.3±9.8	66.6±8.1	67.0±7.9
Former or current smoker	169 (50.9)	169 (51.1)	464 (72.7)	301 (71.2)
FVC mL	2340±740	2321±728	2714±757	2728±810
FVC % predicted	68.7±16.0	69.3±15.2	79.7±17.6	79.3±18.2
D_{LCO}[#] % predicted	44.4±11.9	47.9±15.0	47.4±13.5	47.0±13.4

Data are presented as n (%) or mean±SD. D_{LCO}: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity. [#]: corrected for haemoglobin level.

Annual rate of decline in FVC



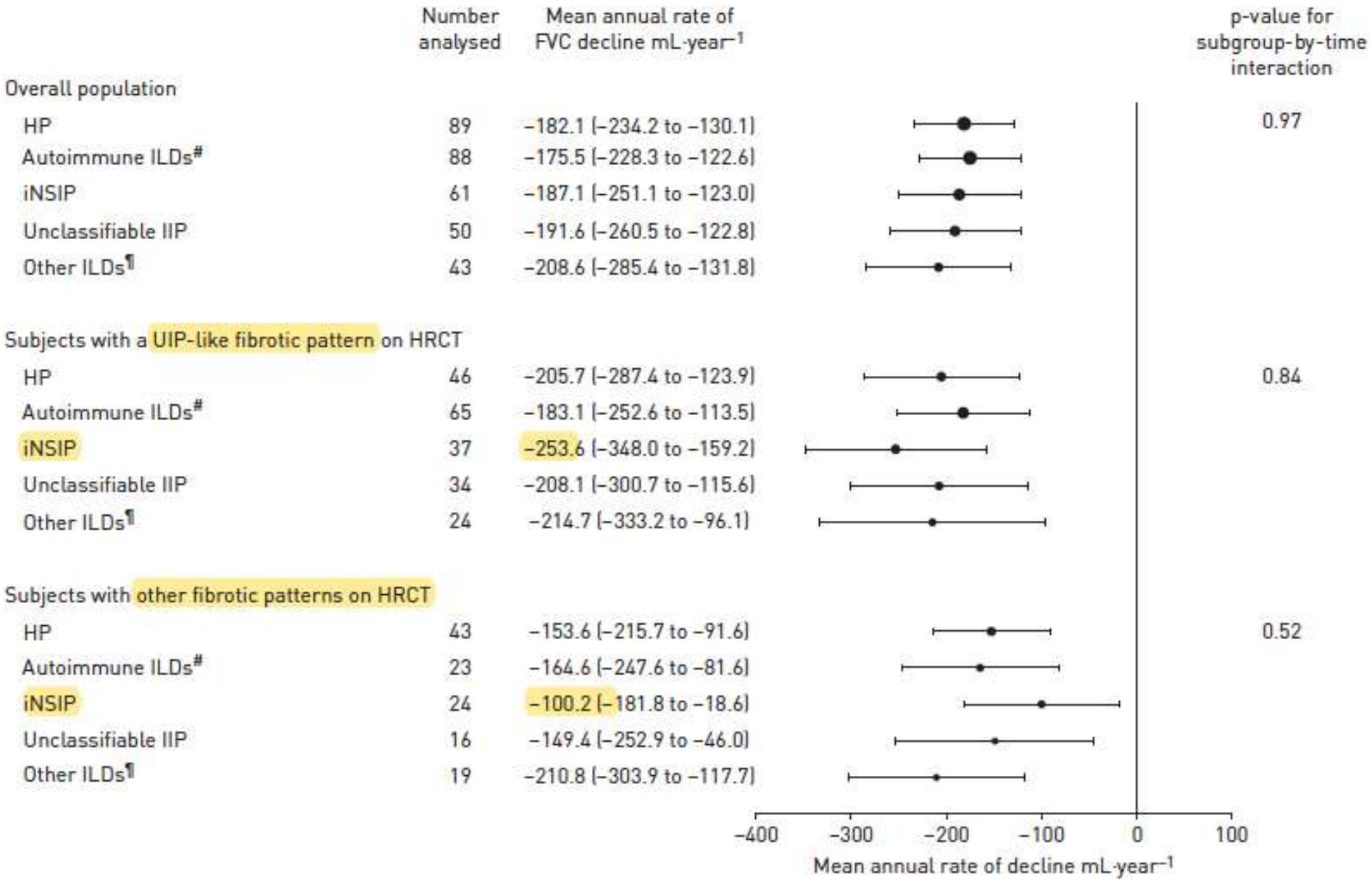
Annual rate of decline in FVC



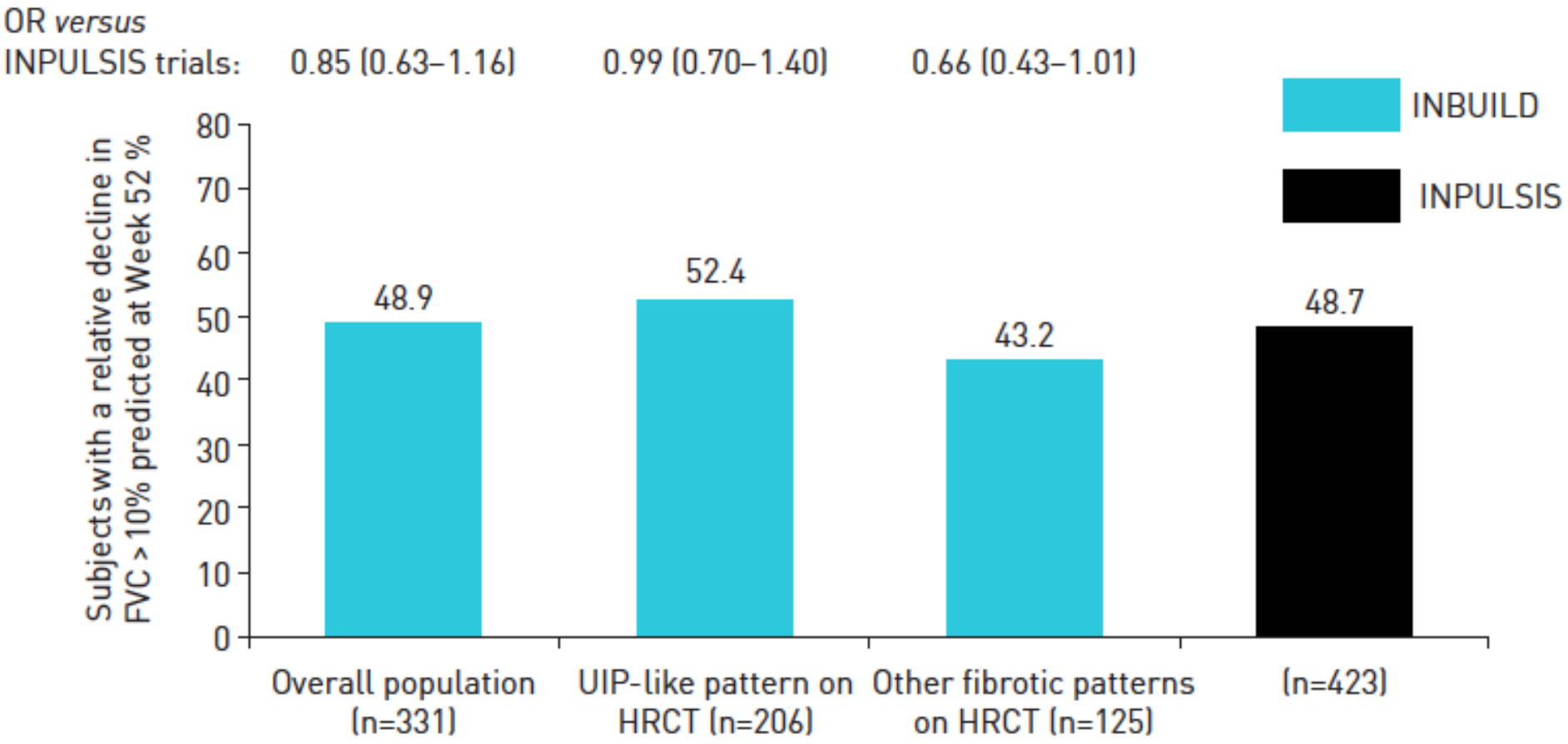
Number of subjects							
INPULSIS	417	408	407	403	395	383	345
INBUILD (overall population)	325	326	325	320	311	296	274
INBUILD (UIP-like fibrotic pattern)	202	202	201	197	190	176	162
INBUILD (other fibrotic patterns)	123	124	124	123	121	120	112

FIGURE 2 Observed change in forced vital capacity (FVC) from baseline (mean (SE)) over 52 weeks in the placebo groups of the INPULSIS and INBUILD trials. HRCT: high-resolution computed tomography; UIP: usual interstitial pneumonia.

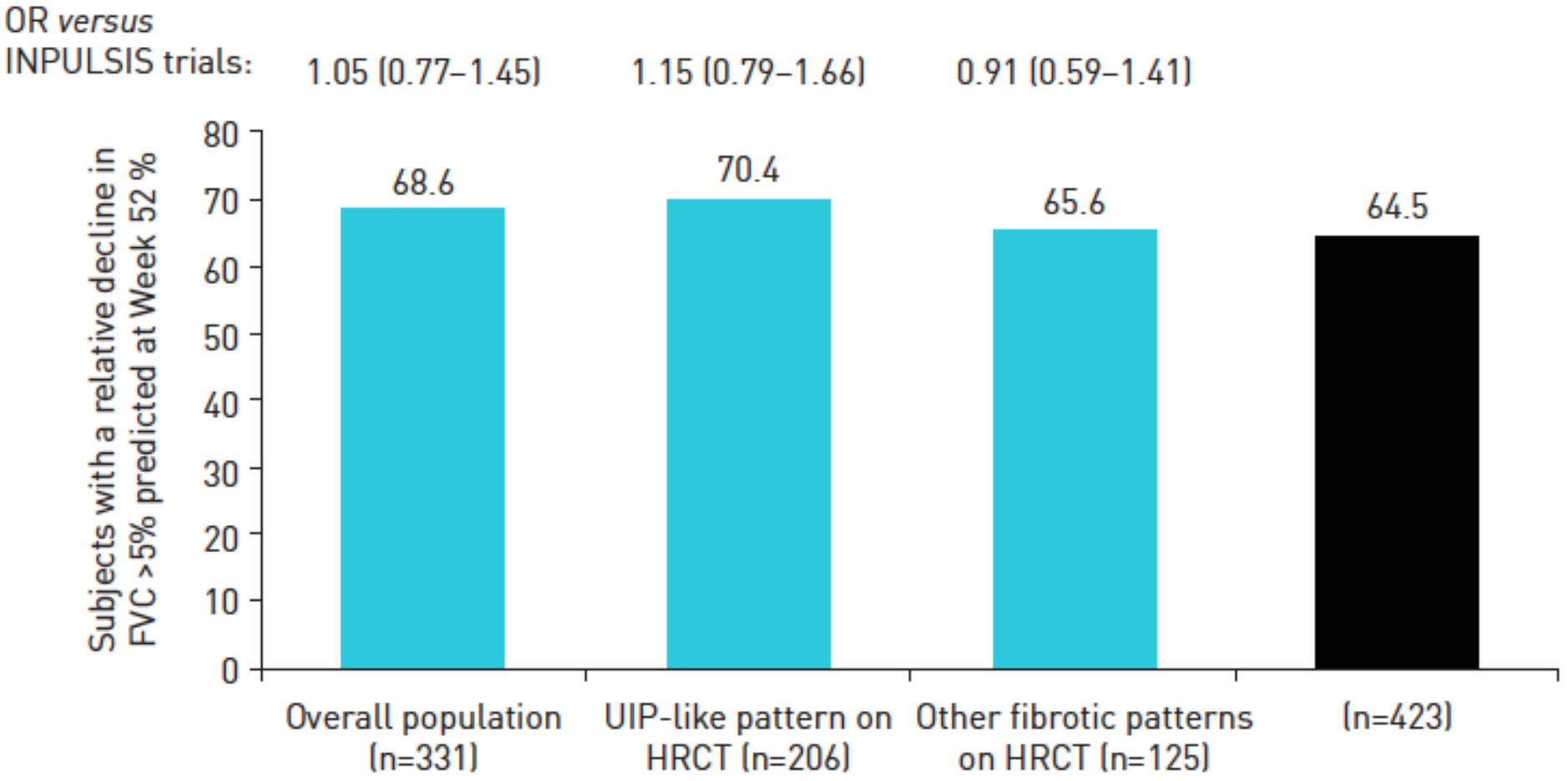
Decline in FVC-in sub groups of ILD



Proportion of subjects who had a relative decline in forced vital capacity (FVC) >10% predicted at Week 52



Proportion of subjects who had a relative decline in forced vital capacity (FVC) >5% predicted at Week 52



Proportion of subjects who died over 52 weeks in the placebo groups of the INBUILD and INPULSIS trials

TABLE 2 Proportion of subjects who died over 52 weeks in the placebo groups of the INBUILD and INPULSIS trials

	INBUILD trial			INPULSIS trials (n=423)
	Overall population (n=331)	UIP-like fibrotic pattern on HRCT (n=206)	Other fibrotic patterns on HRCT (n=125)	
Deaths over 52 weeks	17 (5.1)	16 (7.8)	1 (0.8)	33 (7.8)
Hazard ratio *versus* INPULSIS trials[#]	0.63 (0.35–1.13)	0.97 (0.53–1.76)	0.10 (0.01–0.70)	
Nominal p-value[¶]	0.12	0.92	0.004	

Data are presented as n (%) or hazard ratio (95% CI), unless otherwise stated. UIP: usual interstitial pneumonia; HRCT: high-resolution computed tomography; CI: confidence interval. [#]: based on a Cox regression model with terms for patient population (idiopathic pulmonary fibrosis (IPF) *versus* non-IPF); [¶]: based on a log-rank test.

Mortality and its association with relative decline of >10% predicted in forced vital capacity

TABLE 3 Relationship between relative decline in forced vital capacity (FVC) >10% predicted and time to death over 52 weeks in the placebo groups of the INBUILD and INPULSIS trials

	INBUILD trial[#]		INPULSIS trials (n=423)
	Overall population (n=331)	UIP-like fibrotic pattern on HRCT (n=206)	
Deaths over 52 weeks	17 (5.1)	16 (7.8)	33 (7.8)
Relationship[¶]			
Hazard ratio[+]	3.64 (1.29–10.28)	3.35 (1.16–9.64)	3.95 (1.87–8.33)
p-value[§]	0.015	0.025	<0.001

Data are presented as n (%) or hazard ratio (95% CI), unless otherwise stated. UIP: usual interstitial pneumonia; HRCT: high resolution computed tomography; CI: confidence interval. [#]: as the number of subjects with other fibrotic patterns on HRCT who died was one, the relationship between a relative decline in FVC >10% predicted and mortality could not be analysed; [¶]: relationship between relative decline in FVC >10% predicted and time to death; [+]: based on a Cox regression model with relative decline in FVC >10% predicted as a time-dependent variable; [§]: based on a Wald test.

Relationship between relative decline in forced vital capacity (FVC) >10% predicted and time to death up to the second database lock-19 months

TABLE 4 Relationship between relative decline in forced vital capacity (FVC) >10% predicted and time to death up to the second database lock[#] in the placebo group of the INBUILD trial

	Overall population (n=331)	Subjects with a UIP-like fibrotic pattern on HRCT (n=206)	Subjects with other fibrotic patterns on HRCT (n=125)
Deaths up to second database lock[#]	45 (13.6)	36 (17.5)	9 (7.2)
Relationship[¶]			
Hazard ratio[+]	3.48 (1.71–7.10)	3.64 (1.65–8.06)	2.88 (0.59–14.09)
p-value[§]	<0.001	0.001	0.192

Data are presented as n (%) or hazard ratio (95% CI), unless otherwise stated. UIP: usual interstitial pneumonia; HRCT: high-resolution computed tomography; CI: confidence interval. [#]: the second database lock took place after all patients had completed the follow-up visit or had entered the open-label extension study. The median follow-up was approximately 19 months. Analysis over a similar time period in the INPULSIS trials was not possible as they were 52-week trials; [¶]: relationship between relative decline in FVC >10% predicted and time to death; [+]: based on a Cox regression model with relative decline in FVC >10% predicted as a time-dependent variable. The assessment in the overall population also included the stratification variable (UIP-like fibrotic pattern *versus* other fibrotic patterns on HRCT); [§]: based on a Wald test.

In conclusion

- Fibrosing ILDs the presence of a UIP-like fibrotic pattern on HRCT is associated with more rapid disease progression
- But mortality is similar over long periods
- Rate of decline in FVC was similar across subgroups with different diagnoses

Definition

- No uniformly accepted criteria

Patients meeting any of the following criteria within a 24-month period have experienced disease progression:

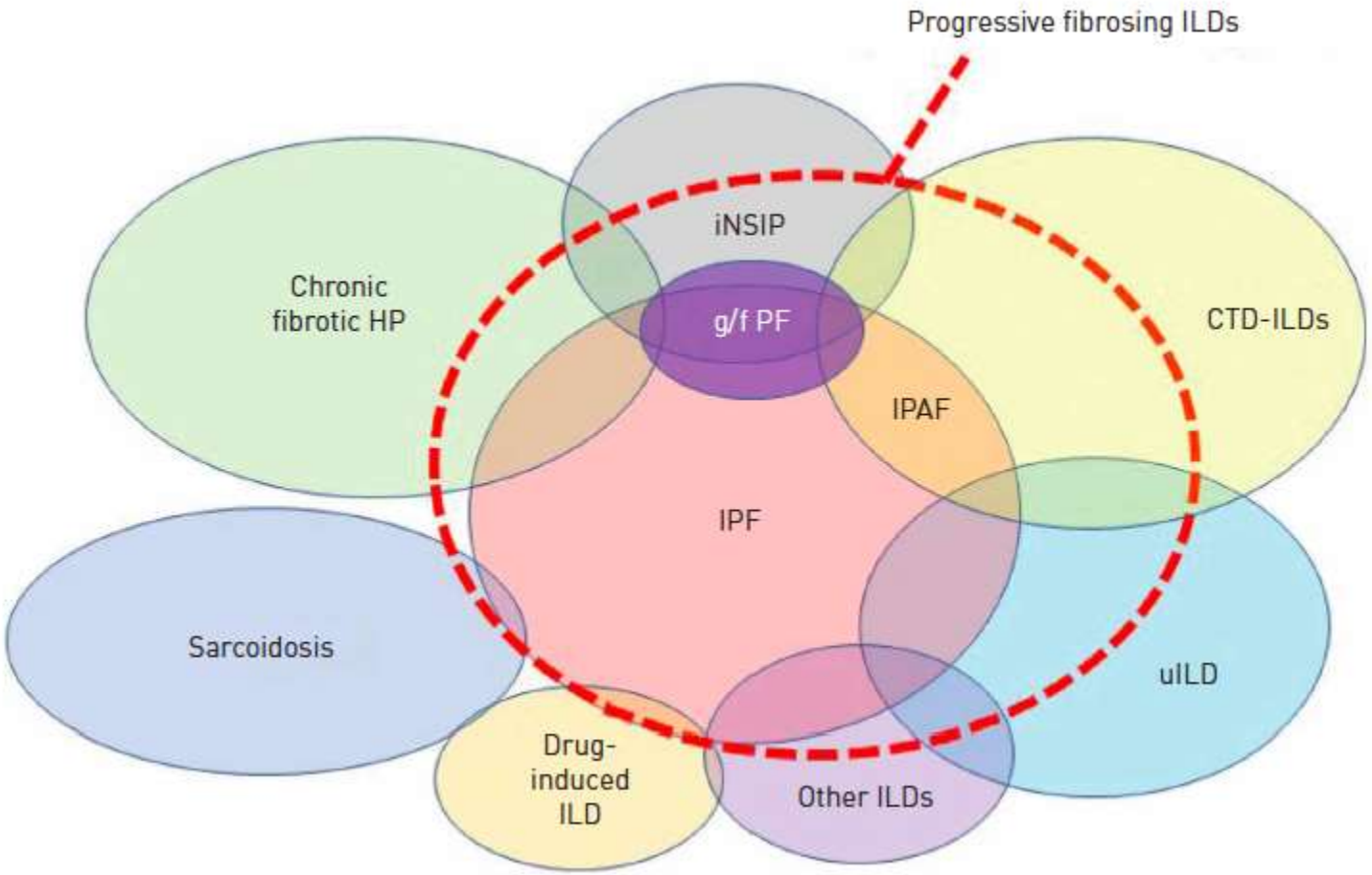
- Relative decline of ⩾10% in forced vital capacity(FVC)
- Relative decline of ⩾15% in DLCO

or

- Worsening symptoms or a worsening radiological appearance accompanied by a ⩾5–<10% relative decrease in FVC

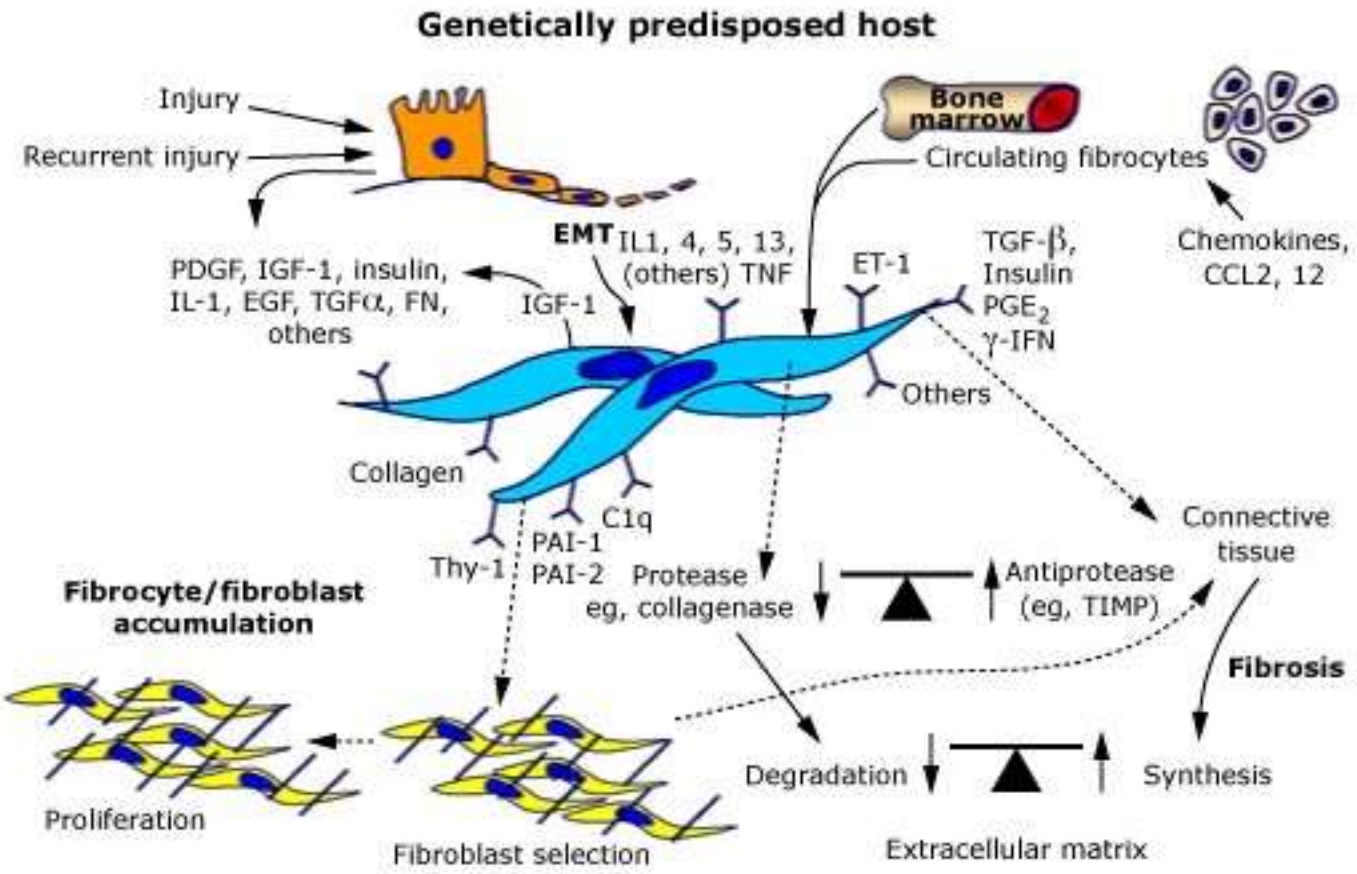
Vincent Cottin et.al Eur Respir Rev 2018; 27: 180076

ILD associated with a progressive fibrosing phenotype

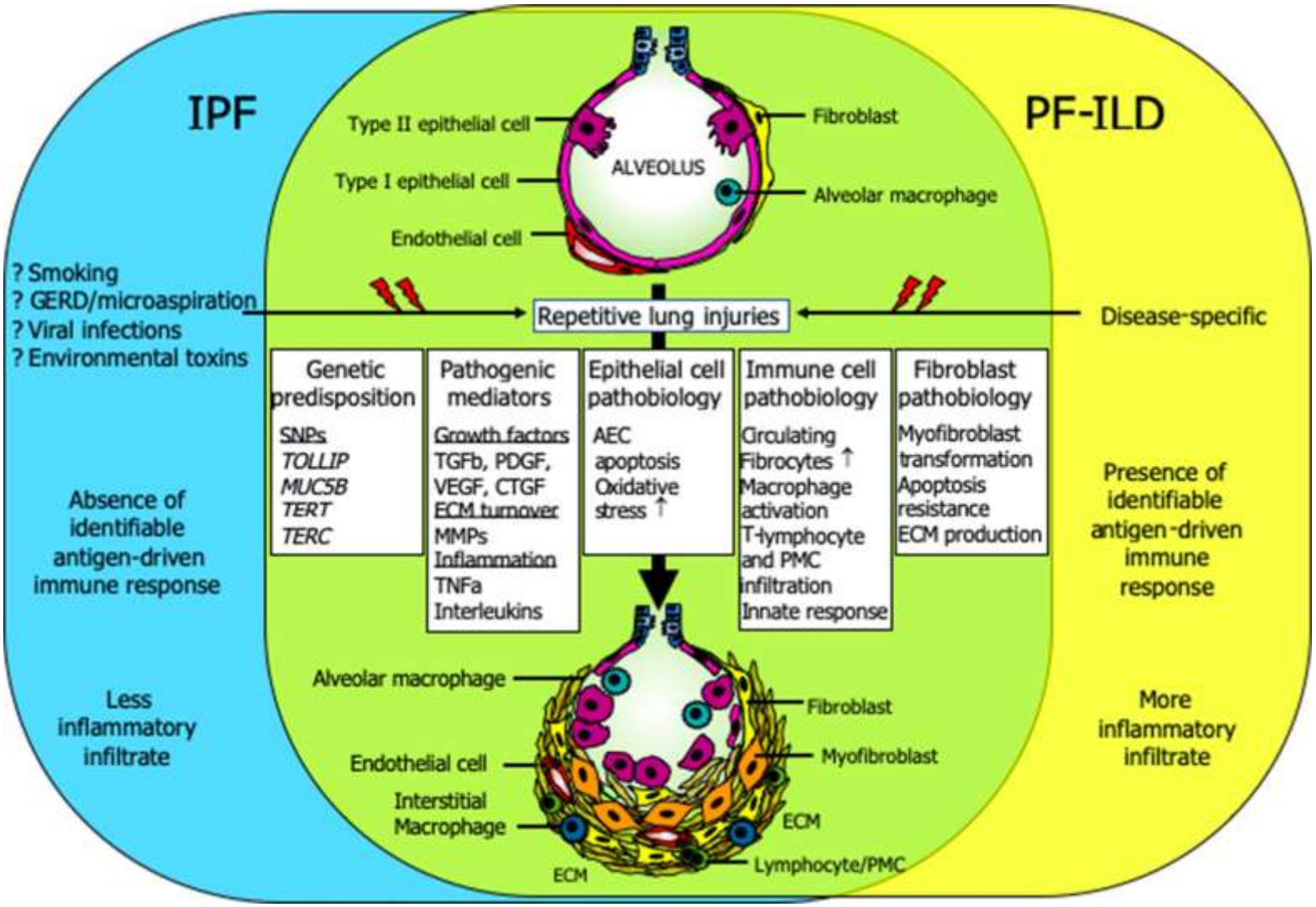


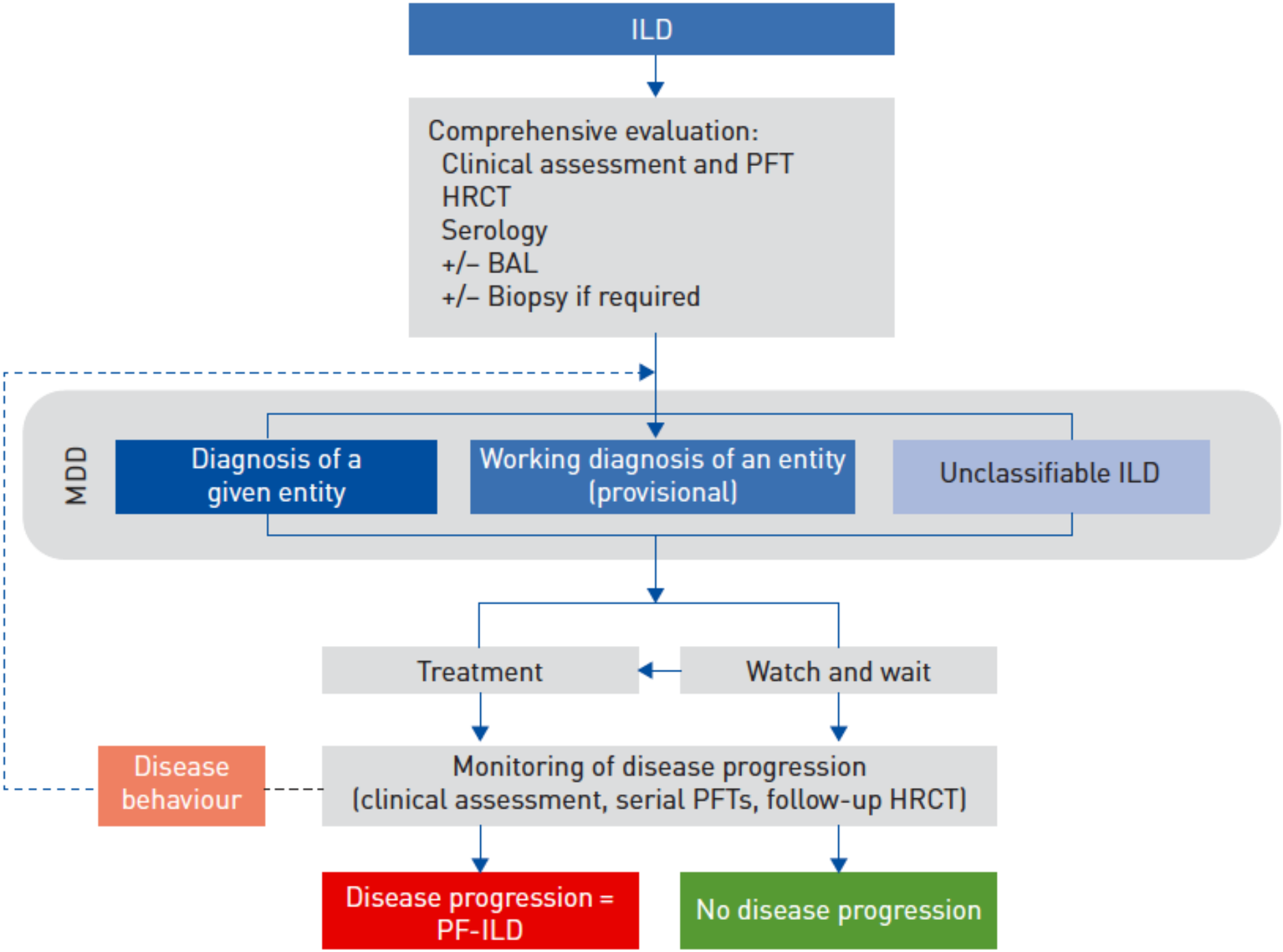
Vincent Cottin et.al Eur Respir Rev 2019; 28: 190109

Pathogenesis of IPF



Pathogenesis of PF-ILD




ILD
Comprehensive evaluation:
Clinical assessment and PFT
HRCT
Serology
+/– BAL
+/– Biopsy if required
MDD
Diagnosis of a given entity
Working diagnosis of an entity (provisional)
Unclassifiable ILD
Treatment
Watch and wait
Disease behaviour
Monitoring of disease progression (clinical assessment, serial PFTs, follow-up HRCT)
Disease progression = PF-ILD
No disease progression

Role of biomarkers ?

Diagnostic and Prognostic Biomarkers for Chronic Fibrosing Interstitial Lung Diseases With a Progressive Phenotype

Yoshikazu Inoue, MD, PhD; Robert J. Kaner, MD; Julien Guiot, MD, PhD; Toby M. Maher, MD, PhD; Sara Tomassetti, MD; Sergey Moiseev, MD; Masataka Kuwana, MD, PhD; and Kevin K. Brown, MD

A biomarker may be defined as ***"any substance, structure, or process that can be measured in the body or its products and influences or predicts the incidence of outcome or disease"***

- Molecular (protein and RNA) markers that can be quantified in biological tissue or fluids (eg, whole blood, serum, BAL fluid [BALF], induced sputum) that reflect physiologic or pathologic processes or that reflect pharmacologic responses to a therapeutic intervention

Biomarkers-classification

- Biomarkers by Mechanistic Pathway
  - Epithelial Cell Dysfunction
  - ECM Turnover
  - Immune Dysregulation
- Risk and Predisposition Biomarkers
- Diagnostic Biomarkers
- Prognostic Biomarkers

Risk and Predisposition Biomarkers

TABLE 1] Risk and Predisposition Biomarkers

Disease	Mechanistic Pathway	Biomarker	Disease Subcategory[a]
IPF	Epithelial cell dysfunction and ECM remodeling	*MUCB5*[26-28] *TERT*, *TERC*[29,30] *FAM13A*, *RTEL1*[31]	...
	Immune dysregulation	*TOLLIP*[32] HLA[33]	...
Chronic fibrosing ILDs with a progressive phenotype	Epithelial cell dysfunction and ECM remodeling	*MUCB5*	RA-ILD[34]
	Immune dysregulation	HLA	Sarcoidosis,[35,36] SSc-ILD,[37] RA-ILD[38,39]

HLA = human leukocyte antigen; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; RA-ILD = rheumatoid arthritis-associated ILD; SSc-ILD = systemic sclerosis-associated ILD.

[a]For chronic fibrosing ILDs with a progressive phenotype.

Diagnostic Biomarkers

Disease	Mechanistic Pathway	Biomarker	Disease Subcategory[a]
Chronic fibrosing ILDs with a progressive phenotype	Epithelial cell dysfunction and ECM remodeling	KL-6	IIP, HP, CTD-ILD, sarcoidosis, asbestosis, iNSIP[13,38,52-55]
		SP-A, SP-D	HP, iNSIP, SSc-ILD[13,38,56,57]
		CC16	SSc-ILD, sarcoidosis, asbestosis[58-60]
		MMP-1, MMP-7, MMP-12	Sarcoidosis, RA-ILD, SSc-ILD[61-67]
		TIMP-1	SSc-ILD[13,38]
		Periostin	NSIP, cryptogenic organizing pneumonia[24]
	Immune dysregulation	CCL18, CCL2	SSc-ILD[68-72]
		CCL15, CCL18	Sarcoidosis[42,73] iNSIP,[74] SSc-ILD[13,75]
		S100A8, S100A9	RA-ILD,[64] sarcoidosis[42]
		CXCL10	SSc-ILD[63,69,76]
		IL-4, IL-6, IL-7, IL-8	Sarcoidosis[42,77]
		IL-12, IL-18, sIL-2R	
		Anti-topoisomerase I, anti-U1 RNP, anti-U3 RNP, anti-U11/U12 RNP, anti-endothelial cell antibodies	SSc-ILD[38]
		CRP	Sarcoidosis[42,77]
		SAA	Sarcoidosis[42,77]
		Anti-MX1	iNSIP[78]

Prognostic Biomarkers

Disease	Mechanistic Pathway	Biomarker	Disease Subcategory[a]
Chronic fibrosing ILDs with a progressive phenotype	Epithelial cell dysfunction and ECM remodeling	KL-6	iNSIP, HP, CTD-ILD, SSc-ILD[56,57,74,101-112]
		SP-A, SP-D	iNSIP, HP, SSc-ILD[13,38,57,113]
		YKL-40	HP, SSc-ILD, sarcoidosis[114-117]
		MMP-7	HP[118]
		MMP-12, TIMP-1	SSc-ILD[119,120]
		CC16	SSc-ILD[60]
		Tenascin C	SSc-ILD, sarcoidosis, HP[97,121,122]
		CA 19-9	CTD-ILD, SSc-ILD[123-125]
		CA-125	CTD-ILD, SSc-ILD[118,123-125]
		VCAM-1	CTD-ILD, HP[118]
	Immune dysregulation	S100A9	iNSIP[74]
		CCL2, CCL18	SSc-ILD[69,71,72,126-129]
		IL-6, IL-2	SSc-ILD[100,130]
		CRP	SSc-ILD[108]
		IFN-γ	RA-ILD[64,131]
		CXCL4, CXCL10, CX3CL1	SSc-ILD[78]
		CXCL13	CTD-ILD, HP[118]
		Anti-MX1	iNSIP[78]
		Anti-citrullinated protein	RA-ILD
		Chitotriosidase	Sarcoidosis[42]

Imaging?

Labelling as fibrosis

Study	Population & agent	Criteria used
INBUILD	n=663, progressive fibrosing ILD Nintedanib	>10% on an HRCT scan (taken within the previous ⩽12 months)
SENSCIS	n=580, SSc-pulmonary fibrosis Nintedanib	>10% on an HRCT scan (taken within the previous ⩽12 months)
NCT02821689	n=60, CADM with ILD Pirfenidone	worsening of fibrosis on HRCT with >10% increase of HRCT score
NCT03099187	n=252, nonclassifiable ILD Pirfenidone	Extent of fibrosis >10% on HRCT
NCT03260556 PirFS	60-with sarcoidosis 40-with Fibrotic HP Pirfenidone	Evidence of >20% fibrosis on high resolution cat scan

Diagnostic entity	HRCT findings	Histopathologic findings
IPF	Definite or possible UIP pattern	Typical UIP pattern
CTD-ILD or IPAF	UIP or NSIP pattern most common	Prominent lymphoid hyperplasia
		Germinal center formation
		Pleuritis, pleural adhesions
Chronic HP	Mosaic perfusion	Airway-centered lesions (peribronchiolar interstitial pneumonia, peribronchiolar giant cells and poorly formed granulomas, and chronic bronchiolitis
	Air trapping	Centrilobular or airway-centered accentuation of fibrosis
	Relative sparing of the lung bases	Peribronchiolar metaplasia
Stage IV sarcoidosis	Upper lobe and peribronchovascular distribution	Centrilobular, lymphangitic, and/or mass-like areas of fibrosis
	Consolidative fibrotic masses	Residual granulomas or giant cells within areas of dense fibrosis
	Perilymphatic nodules	Honeycomb change and bronchiolectasis that is central (not subpleural as in UIP)
Asbestosis	Pleural plaque formation	Presence of asbestos bodies
		Pleural plaques with "basket-weave" pattern of hyalinized collagen

CT Features of the UIP:Differentiating CTD–Associated ILD From IPF

OBJECTIVE. A substantial proportion of cases of usual interstitial pneumonia (UIP) are due to connective tissue disease (CTD)-associated interstitial lung disease (ILD). The purpose of this study was to determine whether specific CT findings can help differentiate a UIP pattern of CTD-ILD from a UIP pattern of idiopathic pulmonary fibrosis (IPF) and whether these signs are associated with survival.

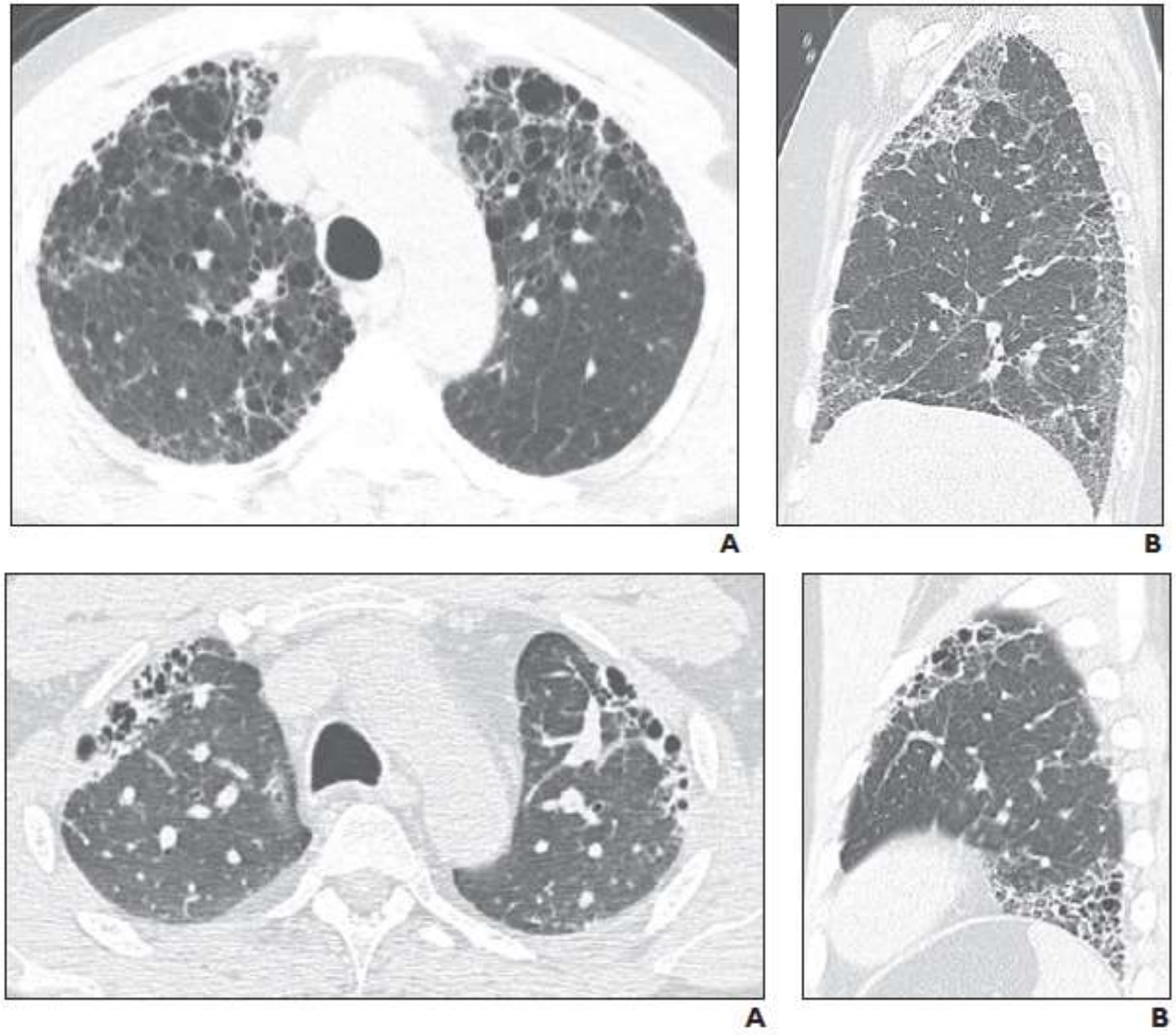
MATERIALS AND METHODS. Adults visiting an ILD clinic from 2006 to 2015 enrolled in a research registry with a multidisciplinary diagnosis of CTD-ILD or IPF and a UIP pattern at high-resolution CT were included in the study. In these subjects with CT findings of UIP due to either IPF or CTD-ILD, three CT findings anecdotally associated with CTD-ILD were assessed for diagnostic accuracy: the "straight-edge" sign, the "exuberant honeycombing" sign, and the "anterior upper lobe" sign. Survival assessments were performed with univariate and multivariable techniques.

RESULTS. The subjects included 63 patients who had CTD-ILD and 133 patients who had IPF with a UIP pattern at CT. All three CT signs were significantly more common in subjects with CTD-ILD than those with IPF (prevalence, 22.2–25.4% for CTD-ILD, 6.0–12.8% for IPF; $p = 0.028$ to < 0.001). The highest specificity (94.0%) and sensitivity (25.4%) were seen for the straight-edge sign. No CT sign was associated with survival in multivariable analysis.

CONCLUSION. Although UIP is usually associated with IPF, the index of suspicion for CTD-ILD should be raised in the care of patients with any of the three CT signs. A thorough workup for CTD-ILD should be pursued, including referral to the rheumatology department.

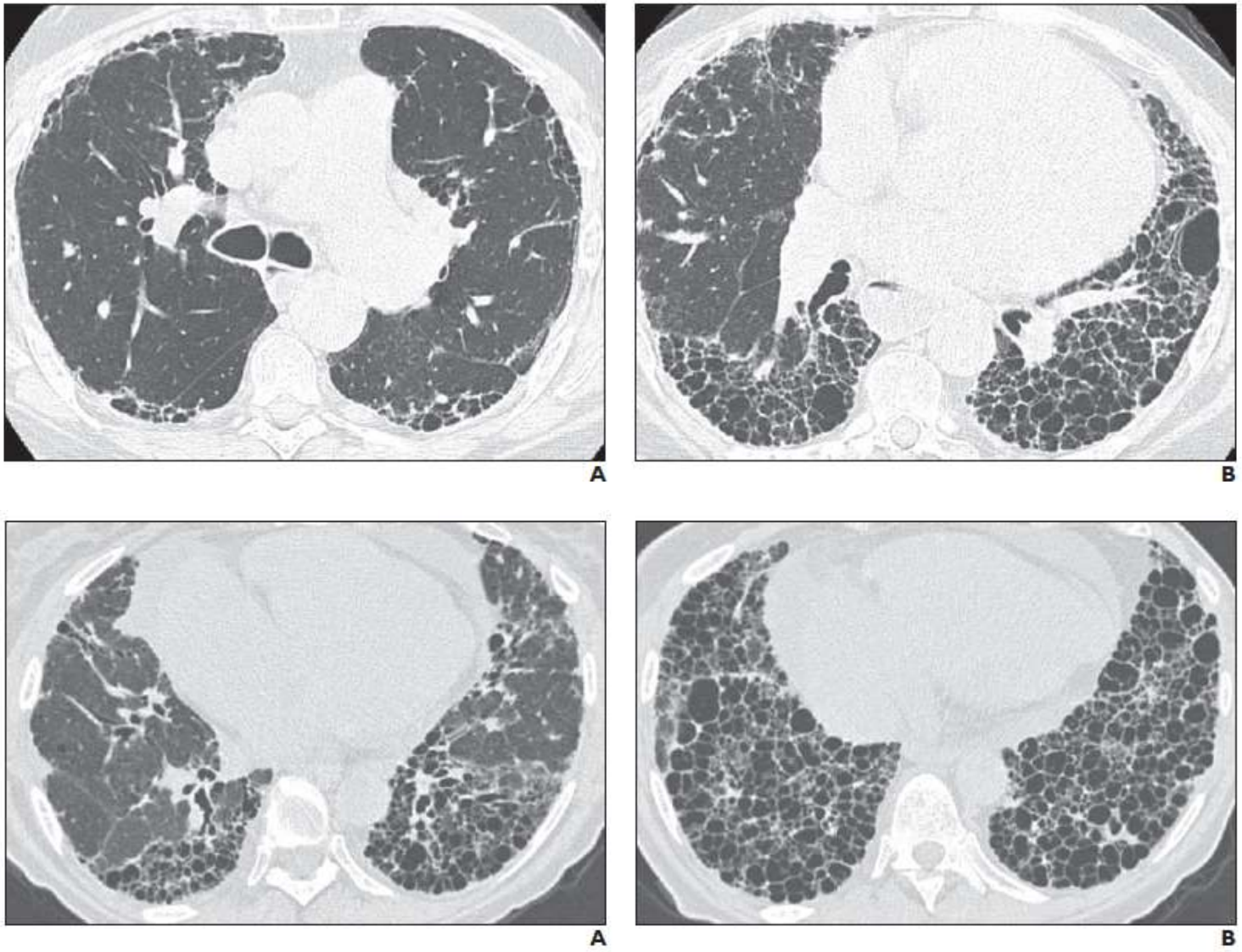
Anterior upper lobe sign

Concentration of fibrosis within the anterior aspect of the upper lobes (with relative sparing of the other aspects of the upper lobes) and concomitant lower lobe involvement (“anterior upper lobe” sign)



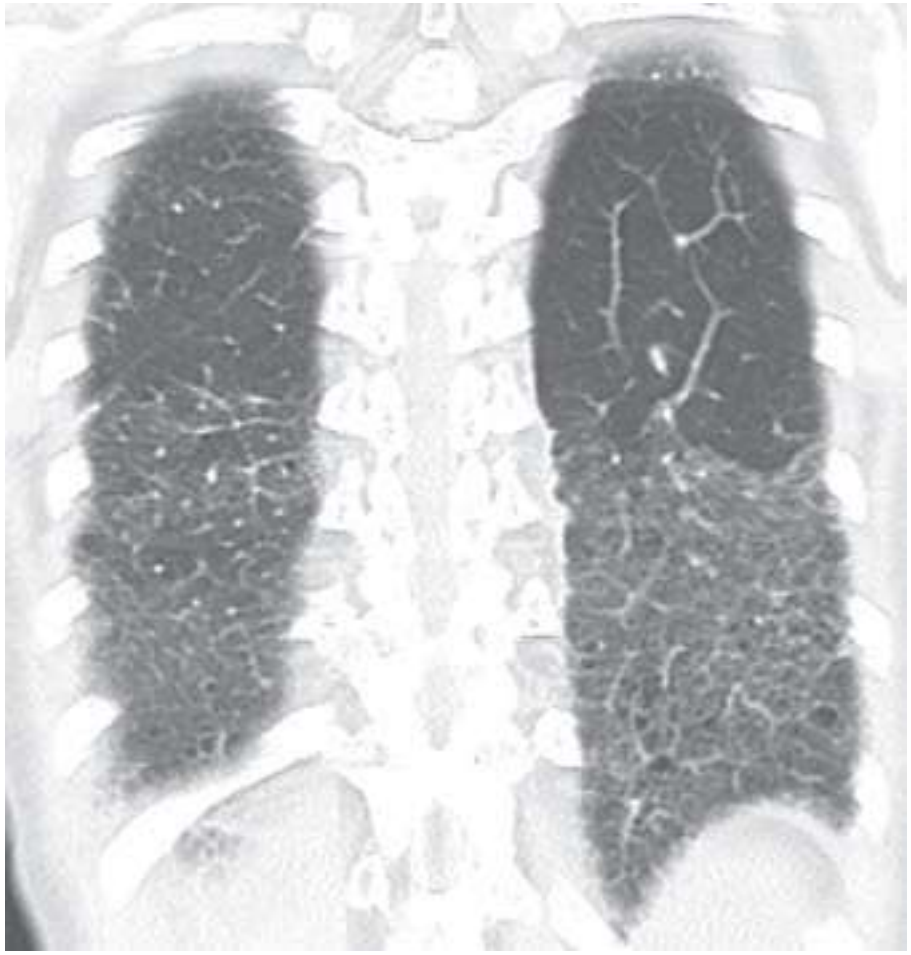
Exuberant honeycombing sign

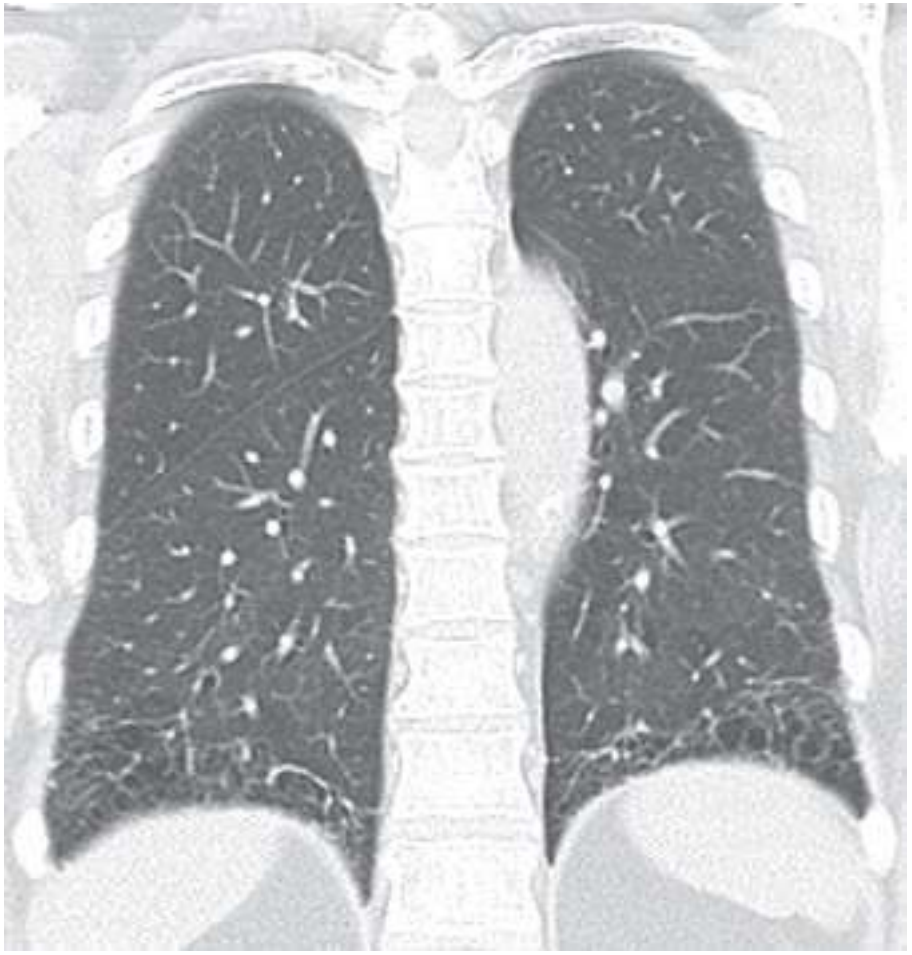
Exuberant honeycomb-like cyst formation within the lungs constituting greater than 70% of fibrotic portions of lung (“exuberant honeycombing ” sign)



Straight-edge sign

Isolation of fibrosis to the lung bases with sharp demarcation in the craniocaudal plane without substantial extension along the lateral margins of the lungs on coronal images (“straight-edge” sign)





Performance of Specific CT Signs

TABLE 3: Performance of Specific CT Signs in Differentiation of Connective Tissue Disease–Associated Interstitial Lung Disease (CTD-ILD) From Idiopathic Pulmonary Fibrosis (IPF) in Patients With Usual Interstitial Pneumonia CT Pattern

CT Sign	Percentage of Patients With IPF With CT Sign ($n = 133$)	Percentage of Patients With CTD-ILD With CT Sign ($n = 63$)	Sensitivity (%)	Specificity (%)	Positive Likelihood Ratio	Negative Likelihood Ratio	*p*
Anterior upper lobe	12.8 (17)	25.4 (16)	25.4	87.2	1.99	0.86	0.028[a]
Exuberant honeycombing	6.0 (8)	22.2 (14)	22.2	94.0	3.69	0.83	< 0.001[a]
Straight edge	6.0 (8)	25.4 (16)	25.4	94.0	4.22	0.79	< 0.001[a]
More than one sign	4.5 (6)	23.8 (15)	23.8	95.5	5.28	0.80	< 0.001[a]
Any CT sign	19.5 (26)	42.9 (27)	42.9	80.5	2.19	0.71	< 0.001

Note—Values in parentheses are number of subjects.
[a]Statistically significant.

Survival

TABLE 4: Cox Unadjusted and Adjusted Models of Survival of Patients With Connective Tissue Disease and Idiopathic Pulmonary Fibrosis with a Usual Interstitial Pneumonia CT Pattern

Variable	Unadjusted			Adjusted		
	Hazard Ratio	95% CI	*p*	Hazard Ratio	95% CI	*p*
Age	1.019	1.006–1.032	0.005[a]	1.022	1.006–1.038	0.007[a]
Male sex	1.64	1.199–2.253	0.002[a]	1.555	1.053–2.297	0.027[a]
Smoking history (pack-years)	1.007	1.002–1.012	0.010[a]	1.002	0.996–1.009	0.428
Forced vital capacity	0.987	0.979–0.995	0.003[a]	0.99	0.979–1.000	0.065
D_{LCO}	0.984	0.977–0.991	< 0.001[a]	0.988	0.978–0.998	0.015[a]
CTD-ILD	0.675	0.489–0.932	0.017[a]	1.117	0.773–1.703	0.606
CT signs						
Anterior upper lobe	0.654	0.445–0.961	0.031[a]	0.82	0.522–1.289	0.390
Exuberant honeycombing	0.792	0.496–1.264	0.329	0.98	0.582–1.65	0.938
Straight edge	0.684	0.442–1.057	0.087	0.872	0.547–1.391	0.566

Note—CTD-ILD = connective tissue disease–associated interstitial lung disease, D_{LCO} = diffusing capacity of the lung for carbon monoxide.
[a]Statistically significant.

Treatment

Treatment

- No treatment guidelines have been issued by an international professional association for forms of ILD other than IPF and SSc-ILD
- Available options
  - Immuno-suppresents
  - Antifibrotic agents
  - Supportive care
  - Lung transplantation

Problem is ?

TABLE 1 Proposed criteria that may be used in clinical practice to assess disease progression in fibrotic interstitial lung diseases

Lung function	Rate of decline in FVC (mL·year^{-1})
	Absolute or relative changes in FVC (mL or % predicted)
	Absolute or relative changes in D_{LCO} % predicted
Exercise capacity	Absolute change in 6-min walk test distance
	Change in oxygen saturation nadir during 6-min walk test
	Change in maximal exercise capacity
Symptoms and patient-reported outcomes	Change in symptoms
	Change in everyday life exercise capacity
	Questionnaires on shortness of breath, cough, and/or quality of life
Acute worsening	Acute exacerbation of fibrosis (idiopathic or triggered)
	Non-elective hospitalisation for a respiratory cause
HRCT	Change in the extent or texture of fibrotic features on HRCT
	Change in quantitative fibrosis scores on HRCT[#]
Need for supportive care	Initiation of ambulatory oxygen therapy at exercise
	Initiation of supplemental oxygen therapy at rest, or change in flow of oxygen
Serum biomarkers	None validated
	Not yet applicable in clinical practice

As these criteria are intended to guide individual decisions in clinical practice, they may differ from end-points used in clinical trials [17]. Most clinicians would make management decisions based on a combination of variables. HRCT: high-resolution computed tomography; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide. [#]: not yet routinely available.

Antifibrotic agents

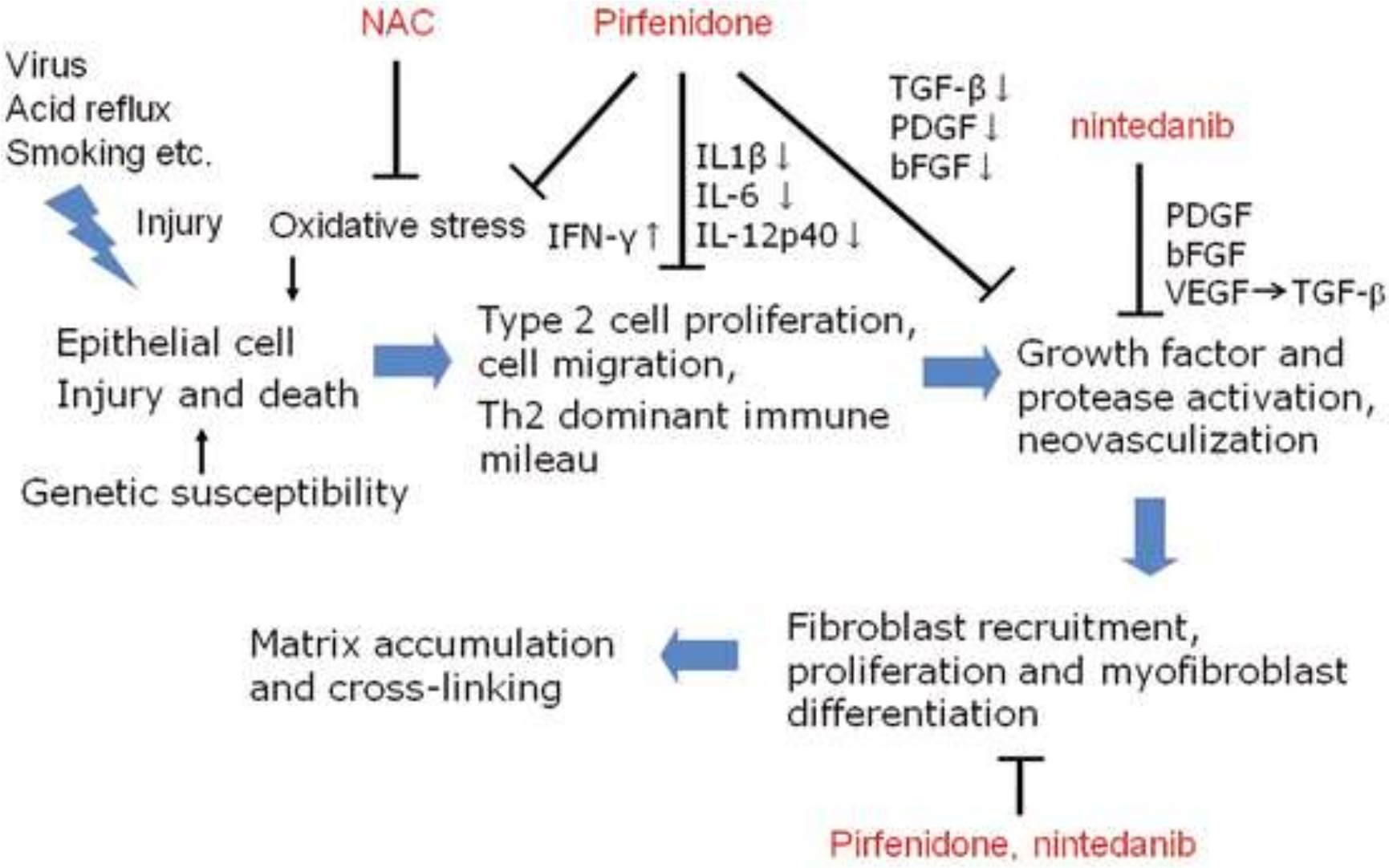


TABLE 1 Major randomised controlled trials of antifibrotics among patients with idiopathic pulmonary fibrosis (IPF)

	Phase	Patients	Intervention	Duration	Primary outcome(s)	Key secondary outcome(s)
Nintedanib						
TOMORROW [25]	II	432	Randomised to 1 of 4 doses nintedanib or placebo	52 weeks	Annual rate of FVC decline 60 mL·year^{-1} in nintedanib 150 mg twice daily group *versus* 190 mL·year^{-1} in placebo group	Lower incidence of AE-IPF, small decrease in SGRQ with nintedanib 150 mg twice daily
INPULSUS I [7]	III	515 IPF patients	Randomised 3:2 ratio to nintedanib 150 mg twice daily or placebo	52 weeks	Annual rate of decline FVC −114.7 mL nintedanib *versus* −239.9 mL placebo (p<0.01)	No significant difference in time to first AE or proportion with AE
INPULSIS II [7]	III	551 IPF patients	Randomised 3:2 ratio to nintedanib 150 mg twice daily or placebo	52 weeks	Annual rate of decline FVC −113.6 mL nintedanib *versus* −207.3 mL placebo (p<0.01)	Increase in time to first AE in nintedanib group and lower proportion with AE in nintedanib group; significant small increase in SGRQ in nintedanib group
Pirfenidone						
CAPACITY I (004) [26]	III	435 IPF patients	Randomised 2:1:2 pirfenidone 2403 mg·day^{-1}, pirfenidone 1197 mg·day^{-1} or placebo	72 weeks	Mean decline FVC −8% pirfenidone *versus* −12.4% placebo (p<0.01)	Decreased proportion of patients with ⩾10% decline in FVC; prolonged PFS
CAPACITY II (006) [26]	III	344 IPF patients	Randomised 1:1 pirfenidone 2403 mg·day^{-1} or placebo	72 weeks	Mean decline FVC −9% pirfenidone *versus* −9.6% placebo (p=0.5)	Reduced decline in 6MWD
ASCEND [8]	III	555 with IPF (surgical biopsy required if possible UIP)	Randomised to pirfenidone 801 mg three times daily or placebo	52 weeks	Proportion of patients with ⩾10% decline in FVC or death reduced by 47.9% pirfenidone *versus* placebo (p<0.01)	Decreased decline in 6MWD, improved PFS

The NEW ENGLAND JOURNAL of MEDICINE

Basket trail

ORIGINAL ARTICLE

Nintedanib for Systemic Sclerosis–Associated Interstitial Lung Disease

Oliver Distler, M.D., Kristin B. Highland, M.D., Martina Gahlemann, M.D., Arata Azuma, M.D., Aryeh Fischer, M.D., Maureen D. Mayes, M.D., Ganesh Raghu, M.D., Wiebke Sauter, Ph.D., Mannaig Girard, M.Sc., Margarida Alves, M.D., Emmanuelle Clerisme-Beaty, M.D., Susanne Stowasser, M.D., Kay Tetzlaff, M.D., Masataka Kuwana, M.D., and Toby M. Maher, M.D., for the SENSCIS Trial Investigators*

Nintedanib is an intracellular tyrosine kinase inhibitor

Randomized, double blind, placebo-controlled, parallel-group trial

Performed in 32 countries

Inclusion & Exclusion criteria

- ≥18 years of age
- SS-according to ACR/EULAR classification
- Onset of the first non-Raynaud's symptom within 7 years before screening
- HRCT showing fibrosis affecting at least 10% of the lungs
- FVC ≥40% of the predicted and DLco 30 -89% of the predicted value
- Patients receiving IS at least 6 months before randomization

Exclusion criteria

- Deranged LFT(AST, ALT, TB >1.5 ULN) or CLD
- CrCl <30ml/min
- FEV1/FVC <0.7
- Significant P-HTN
- Other significant pulmonary abnormality
- Life expectancy <2.5 yerars
- Pregnancy
- Severe skin involvement

Intervention & outcomes

- 1:1 randomization 150mg BD nintedanib or placebo
- Stratified - to Anti-topoisomerase I antibody
- Primary efficacy evaluation-at 52 week(<100week)

Primary:

- Annual rate of decline in FVC

Secondary:

- Absolute change in modified Rodnan skin score
- Change in SGRQ score
- Others

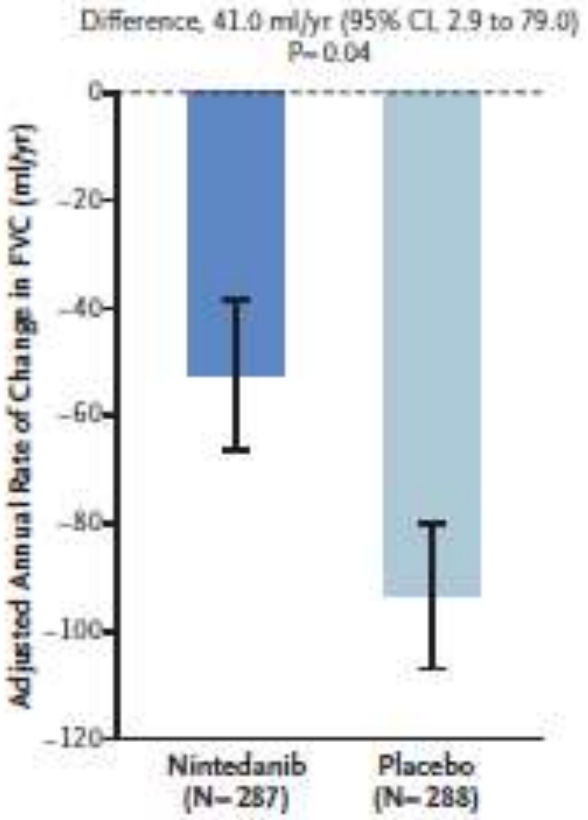
Table 1. Baseline Characteristics of the Patients.*

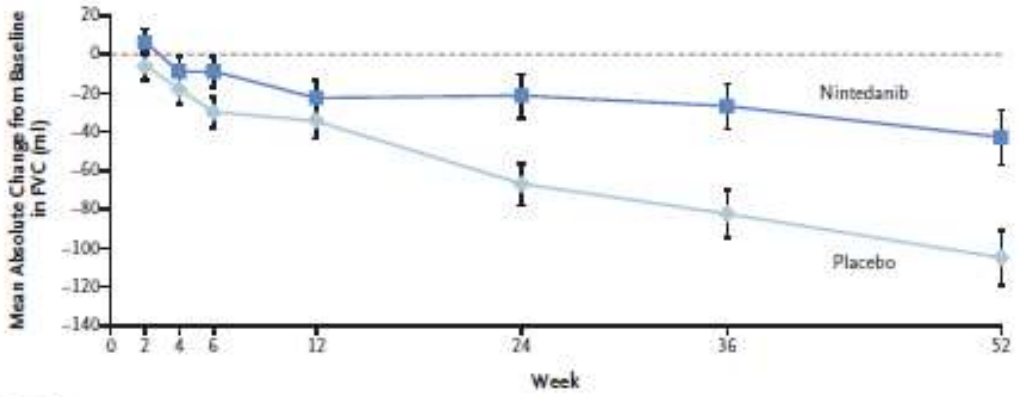
Characteristic	Nintedanib (N=288)	Placebo (N=288)
Female sex — no. (%)	221 (76.7)	212 (73.6)
Age — yr	54.6±11.8	53.4±12.6
Diffuse cutaneous systemic sclerosis — no. (%)	153 (53.1)	146 (50.7)
Years since the onset of the first non-Raynaud's symptom		
Median	3.4	3.5
Range	0.3–7.1	0.4–7.2
Extent of fibrosis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

Results

Mean duration of exposure to nintedanib was 10.5±3.4 months

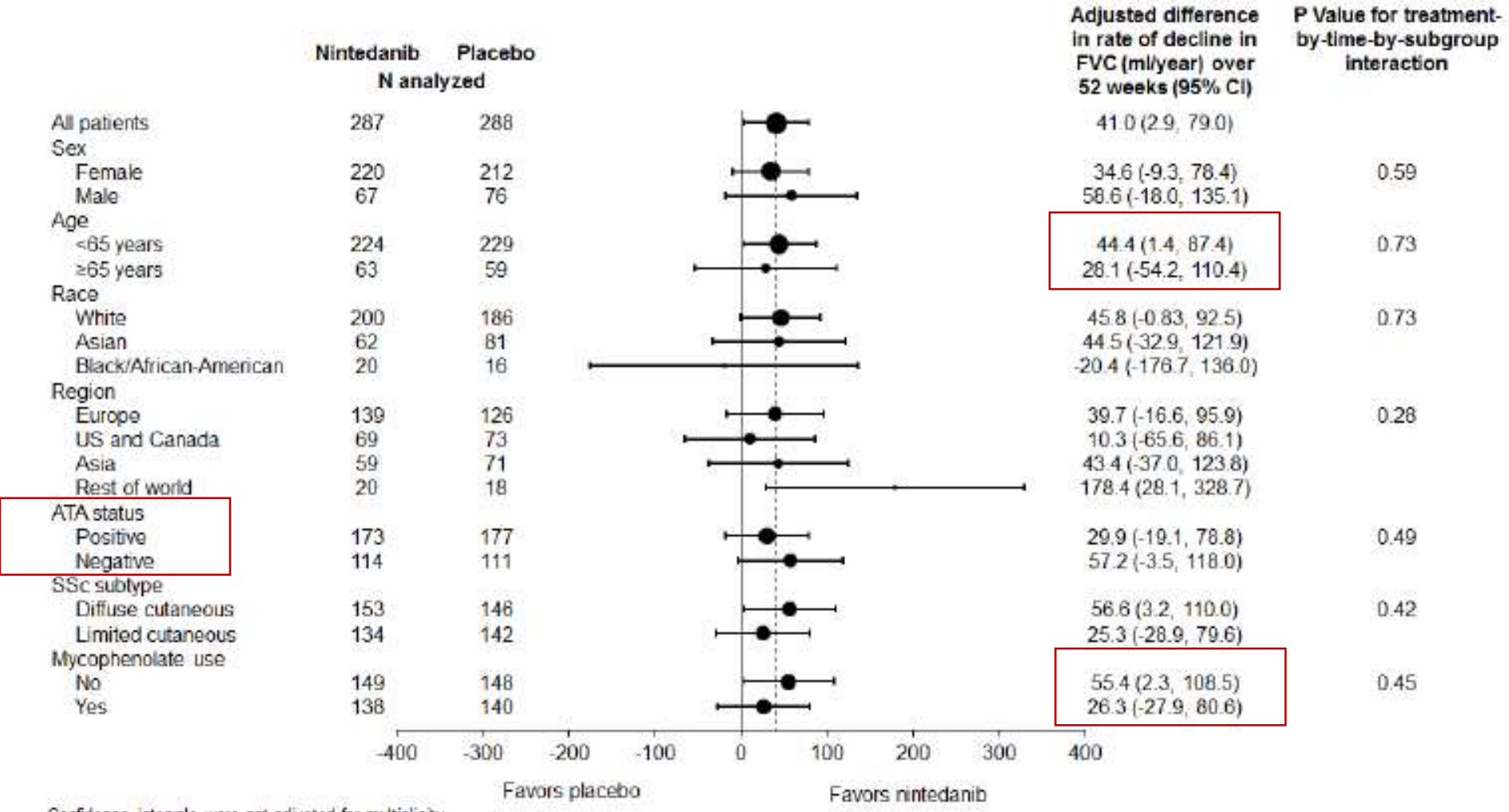
The adjusted annual rate of change in FVC over a 52-week period was lower in the nintedanib group than in the placebo group (−52.4 ml/yr vs. −93.3 ml/yr; difference, 41.0 ml/yr; 95% confidence interval [CI], 2.9 to 79.0; P = 0.04)





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

Section H: Pre-specified subgroup analyses of the annual rate of decline in FVC (mL) over 52 weeks (primary endpoint) based on baseline characteristics



Confidence intervals were not adjusted for multiplicity
ATA denotes anti-topoisomerase I antibody

Results

- The annual rates of change in FVC in patients on MMF at baseline were −40.2 ml/year in the nintedanib group and −66.5 ml/year in the placebo group
- Corresponding rates in patients not on MMF at baseline were −63.9 ml/year and −119.3 ml/year
- Results of key secondary end points did not differ significantly
- Change in modified Rodnan skin score was −2.17 in the nintedanib Vs −1.96 placebo group (D−0.21; 95% CI;−0.94/0.53).
- Change in total score on the SGRQ was 0.81 in the nintedanib Vs−0.88 in the placebo group (D-1.69; 95% CI, −0.73 to 4.12)

Results

End Point	Nintedanib	Placebo	Difference (95% CI)
Primary end point			
Annual rate of decline in FVC assessed over 52 weeks — ml/yr	−52.4±13.8	−93.3±13.5	41.0 (2.9 to 79.0)†
Key secondary end points			
Absolute change from baseline in modified Rodnan skin score at week 52	−2.17±0.27	−1.96±0.26	−0.21 (−0.94 to 0.53)‡
Absolute change from baseline in total score on the SGRQ at week 52	0.81±0.88	−0.88±0.87	1.69 (−0.73 to 4.12)§
Other secondary end points			
Absolute change from baseline in FVC at week 52 — ml	−54.6±13.9	−101.0±13.6	46.4 (8.1 to 84.7)§
Annual rate of decline in FVC — % of predicted value	−1.4±0.4	−2.6±0.4	1.2 (0.1 to 2.2)§
Absolute change from baseline in DL_{CO} at week 52 — % of predicted value	−3.21±0.54	−2.77±0.54	−0.44 (−1.94 to 1.06)§
Absolute change from baseline in net digital ulcer burden at week 52	0.03±0.05	0.06±0.04	−0.03 (−0.16 to 0.09)§
Patients with an absolute decline from baseline in FVC of >5 percentage points of the predicted value at week 52 — no./total no. (%)	59/287 (20.6)	82/288 (28.5)	0.65 (0.44 to 0.96)§¶
Patients with an absolute decline from baseline in FVC of >10 percentage points of the predicted value at week 52 — no./total no. (%)	20/287 (7.0)	24/288 (8.3)	0.82 (0.44 to 1.52)§¶
Patients with a relative decline from baseline in FVC, measured in milliliters, of >5% at week 52 — no./total no. (%)	95/287 (33.1)	125/288 (43.4)	0.65 (0.46 to 0.91)§¶
Patients with a relative decline from baseline in FVC, measured in milliliters, of >10% at week 52 — no./total no. (%)	48/287 (16.7)	52/288 (18.1)	0.91 (0.59 to 1.41)§¶

Table 3. Adverse Events.*

Event	Nintedanib (N=288)	Placebo (N=288)
	no. of patients (%)	
Any adverse event	283 (98.3)	276 (95.8)
Most common adverse events†		
Diarrhea	218 (75.7)	91 (31.6)
Nausea	91 (31.6)	39 (13.5)
Skin ulcer	53 (18.4)	50 (17.4)
Vomiting	71 (24.7)	30 (10.4)
Cough	34 (11.8)	52 (18.1)
Nasopharyngitis	36 (12.5)	49 (17.0)
Upper respiratory tract infection	33 (11.5)	35 (12.2)
Abdominal pain	33 (11.5)	21 (7.3)
Fatigue	31 (10.8)	20 (6.9)
Weight decrease	34 (11.8)	12 (4.2)
Severe adverse event‡	52 (18.1)	36 (12.5)
Serious adverse event§	69 (24.0)	62 (21.5)
Fatal adverse event	5 (1.7)	4 (1.4)
Adverse event leading to discontinuation of the intervention	46 (16.0)	25 (8.7)

- Diarrhoea (and other GI adverse effects) and Transamnitis(>3xULN) were more common in nintedanib group
- Rate of adverse effectss leading to discontinution of drug was also more in trial group
- 10 patients in trial group and 9 patients in placebo group died

In conclusion

- Nintedanib is effective in reducing the decline in FVC in patients with ILD associated with systemic sclerosis
- Annual rate of decline in FVC among placebo received patients INPULSIS trials11 (−93.3 ml in SENSIS vs. −223.5 ml in the INPULSIS trials)
- Similar change in FVC when compared to SLS-I
- No improvement in Health related quality of life
- Does not support nintedanib as a disease-modifying agent for systemic sclerosis as a whole (i.e., nintedanib does not address other organ complications)

ORIGINAL ARTICLE

Nintedanib in Progressive Fibrosing Interstitial Lung Diseases

K.R. Flaherty, A.U. Wells, V. Cottin, A. Devaraj, S.L.F. Walsh, Y. Inoue, L. Richeldi, M. Kolb, K. Tetzlaff, S. Stowasser, C. Coeck, E. Clerisme-Beaty, B. Rosenstock, M. Quaresma, T. Haeufel, R.-G. Goeldner, R. Schlenker-Herceg, and K.K. Brown, for the INBUILD Trial Investigators*

INBUILD trial was not designed or powered to provide evidence for a benefit of nintedanib in specific ILD subgroups, exploratory subgroup analyses based on grouped ILD diagnoses

Nintedanib in patients with progressive fibrosing interstitial lung diseases—subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial

*Athol U Wells, Kevin R Flaherty, Kevin K Brown, Yoshikazu Inoue, Anand Devaraj, Luca Richeldi, Teng Moua, Bruno Crestani, Wim A Wuyts, Susanne Stowasser, Manuel Quaresma, Rainer-Georg Goeldner, Rozsa Schlenker-Herceg, Martin Kolb on behalf of the INBUILD trial investigators**

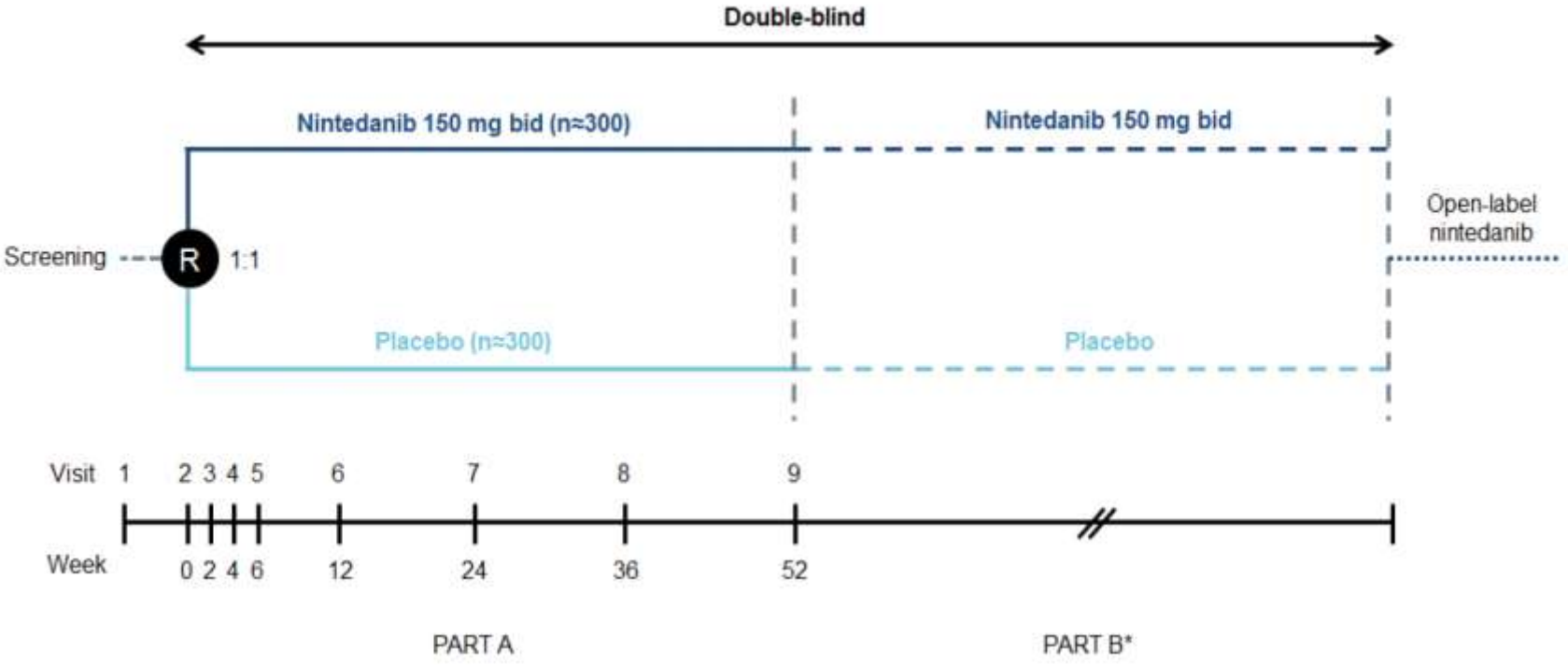
- Randomized, double blind (placebo-controlled, parallel-group) trial
- 153 sites in 15 countries (Europe)
- From Feb 2017 to Apr 2018

Inclusion criteria

- Age >18yr
- Physician diagnosed PF-ILDs
- FVC of **>45%** and DLCO of **30 to 80%** of the predicted value
- Progressive Interstitial lung disease
- Fibrosing ILD (imaging)

Exclusion criteria

- Patients who were treated with IS or previous treatment with nintedanib or pirfenidone
- T bilirubin, AST, ALT>1.5 times the ULN,
- chronic liver disease (CTP A/B/C)
- creatinine clearance <30 mL/min
- significant PAH
- severe uncontrolled hypertension
- Pregnant, nursing women
- Life expectancy>2.5yrs



Primary outcome

- Rate of decline in FVC at 52wk

Secondary outcome

- Absolute change in total score on K-BILD questionnaire at 52 wk
- Acute exacerbation of ILD or death at 52wk
- Death at 52 wk

Characteristic	Nintedanib (N=332)	Placebo (N=331)
Male sex — no. (%)	179 (53.9)	177 (53.5)
Age — yr	65.2±9.7	66.3±9.8
Former or current smoker — no. (%)	169 (50.9)	169 (51.1)
UIP-like fibrotic pattern on high-resolution CT — no. (%)	206 (62.0)	206 (62.2)
Criteria for disease progression in previous 24 mo — no. (%)		
Relative decline in FVC of ≥10% of predicted value	160 (48.2)	172 (52.0)
Relative decline in FVC of 5% to <10% of predicted value plus worsening of respiratory symptoms or increased extent of fibrosis on high-resolution CT	110 (33.1)	97 (29.3)
Worsening of respiratory symptoms and increased extent of fibrosis on high-resolution CT	62 (18.7)	61 (18.4)
FVC		
Mean value — ml	2340±740	2321±728
Percent of predicted value	68.7±16.0	69.3±15.2
Diffusing capacity for carbon monoxide†		
Mean value — mmol/min/kPa	3.5±1.2	3.7±1.3
Percent of predicted value	44.4±11.9	47.9±15.0
Total score on K-BILD questionnaire‡	52.5±11.0	52.3±9.8

	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 idiopathic interstitial pneumonia	64 (19.3)	50 (15.1)
Other ILDs*	38 (11.4)	43 (13.0)

Data are no (%) of patients.

*Included sarcoidosis, exposure-related ILDs and selected other terms in “Other fibrosing ILDs”.

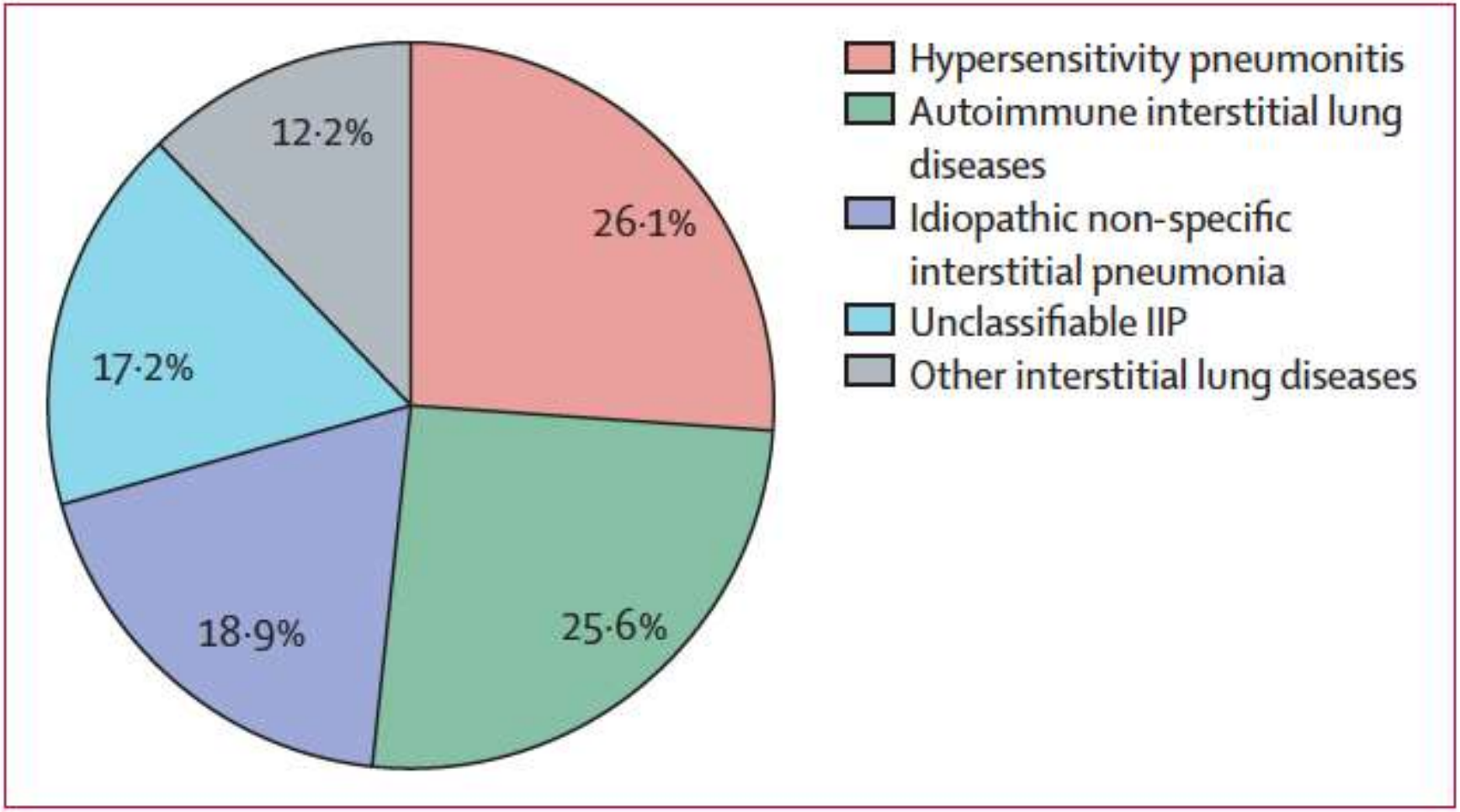
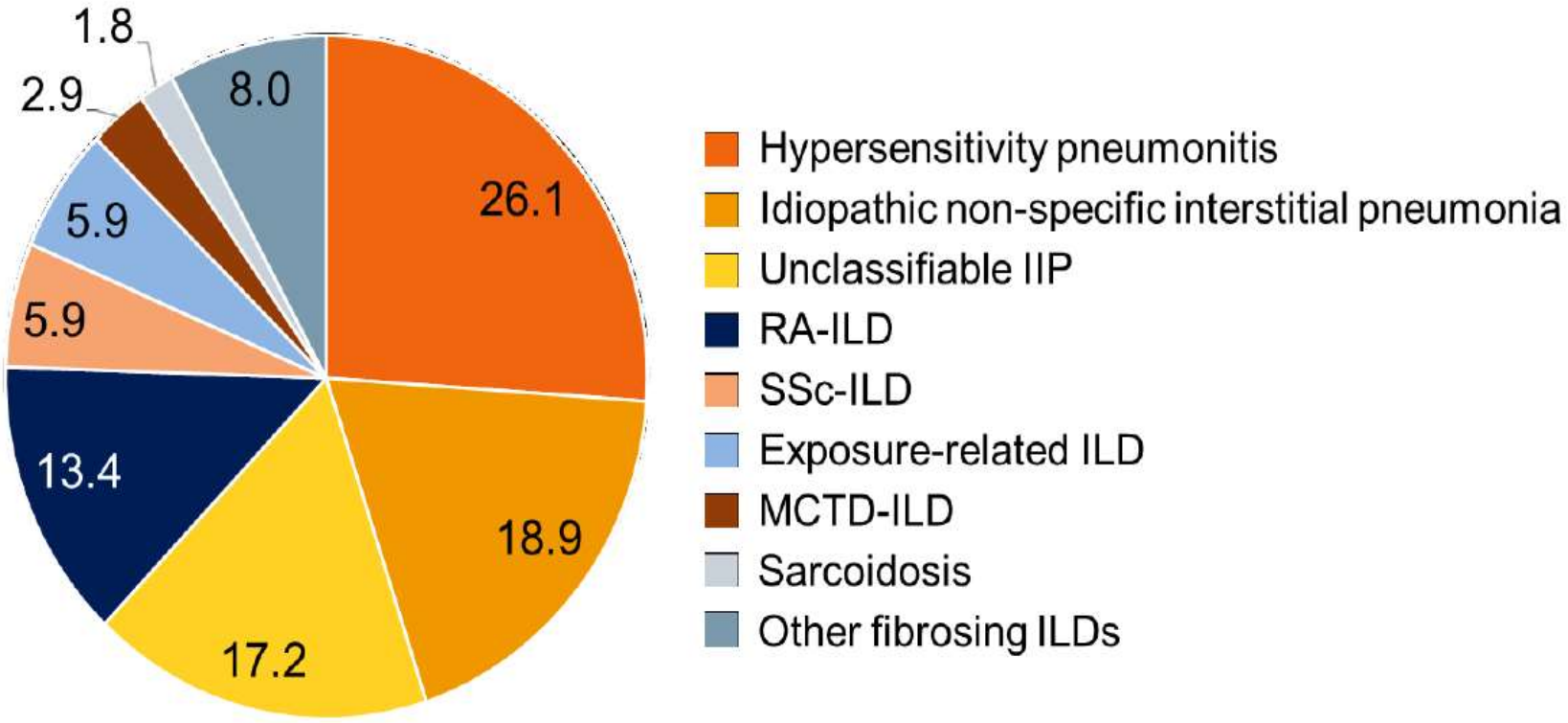
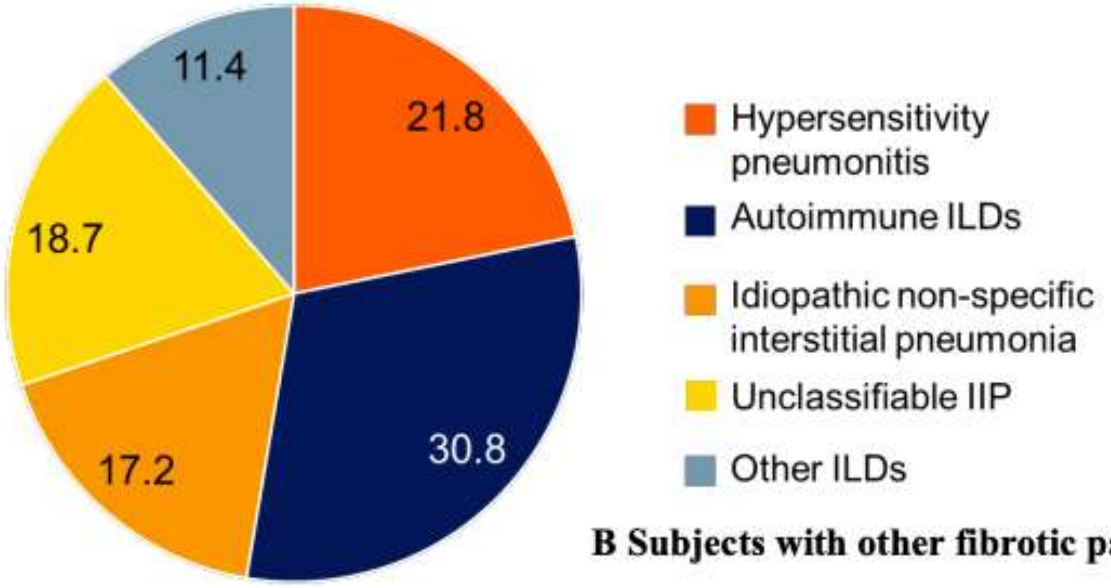


Figure 1: **Interstitial lung disease diagnoses in five groups (overall population)**
Autoimmune interstitial lung diseases (ILDs)=those associated with rheumatoid arthritis, systemic sclerosis, mixed connective tissue disease, plus autoimmune ILDs in the other fibrosing ILDs category. Other ILDs=sarcoidosis, exposure-related ILDs and other terms in the other fibrosing ILDs category.

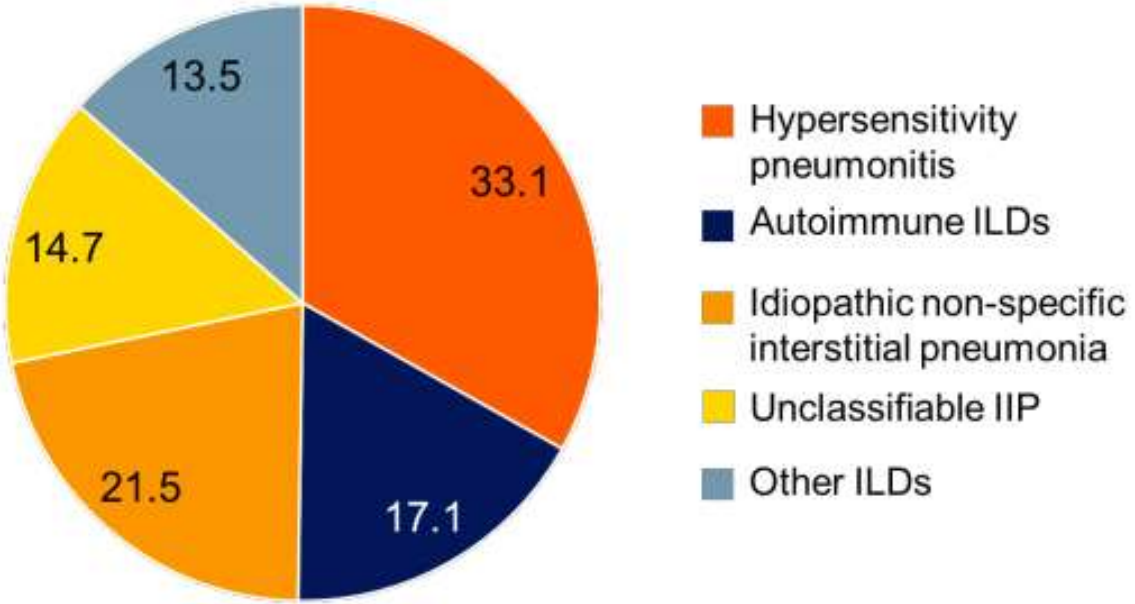
ILD DIAGNOSIS IN OVERALL POPULATION



A Subjects with a UIP-like fibrotic pattern on HRCT



B Subjects with other fibrotic patterns on HRCT



Baselines characteristics

	HP (n=173)	iNSIP (n=125)	Unclassifiable IIP (n=114)	RA-ILD (n=89)	SSc-ILD (n=39)	MCTD-ILD (n=19)	Exposure-related ILDs (n=39)	Sarcoidosis (n=12)	Other fibrosing ILDs* (n=53)
Male, n (%)	89 (51.4)	63 (50.4)	62 (54.4)	54 (60.7)	9 (23.1)	4 (21.1)	36 (92.3)	5 (41.7)	34 (64.2)
Age (years), mean (SD)	65.5 (8.3)	65.4 (9.4)	68.4 (9.4)	66.9 (9.6)	58.4 (10.0)	64.5 (9.5)	69.4 (10.4)	63.1 (14.4)	63.5 (11.0)
Former or current smoker, n (%)	91 (52.6)	43 (34.4)	62 (54.4)	57 (64.0)	8 (20.5)	6 (31.6)	33 (84.6)	4 (33.3)	34 (64.2)
FVC, mL, mean (SD)	2244 (739)	2351 (761)	2286 (730)	2394 (694)	2229 (618)	2082 (407)	2551 (597)	2188 (497)	2588 (931)
FVC, % predicted, mean (SD)	65.2 (14.2)	71.3 (17.3)	69.8 (15.4)	71.5 (16.2)	69.7 (12.7)	71.1 (12.5)	67.9 (14.6)	64.9 (16.8)	70.5 (17.5)
DLco % predicted, mean (SD)†	45.3 (14.4)	47.4 (12.5)	45.2 (11.9)	47.7 (15.6)	47.7 (12.9)	51.4 (18.2)	44.9 (14.7)	39.9 (6.0)	44.2 (12.1)

Baseline characteristics

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

Data are n (%) or mean (SD). *Included sarcoidosis, exposure-related ILDs and selected other terms in other fibrosing interstitial lung diseases such as pleuroparenchymal fibroelastosis, and cryptogenic organising pneumonia. †Corrected for haemoglobin.

***Table 1*: Baseline characteristics**

Primary end result

End Point	Nintedanib (N=332)	Placebo (N=331)	Difference (95% CI)
Primary end point			
Rate of decline in the FVC at 52 wk — ml/yr†			
Overall population	−80.8±15.1	−187.8±14.8	107.0 (65.4 to 148.5)‡
Patients with a UIP-like fibrotic pattern	−82.9±20.8	−211.1±20.5	128.2 (70.8 to 185.6)‡
Patients with other fibrotic patterns	−79.0±21.6	−154.2±21.2	75.3 (15.5 to 135.0)§

Figure S4A. Between-group adjusted difference in the annual rate of decline in FVC (mL/year) over 52 weeks in the overall population (primary endpoint). The bars indicate the standard error.

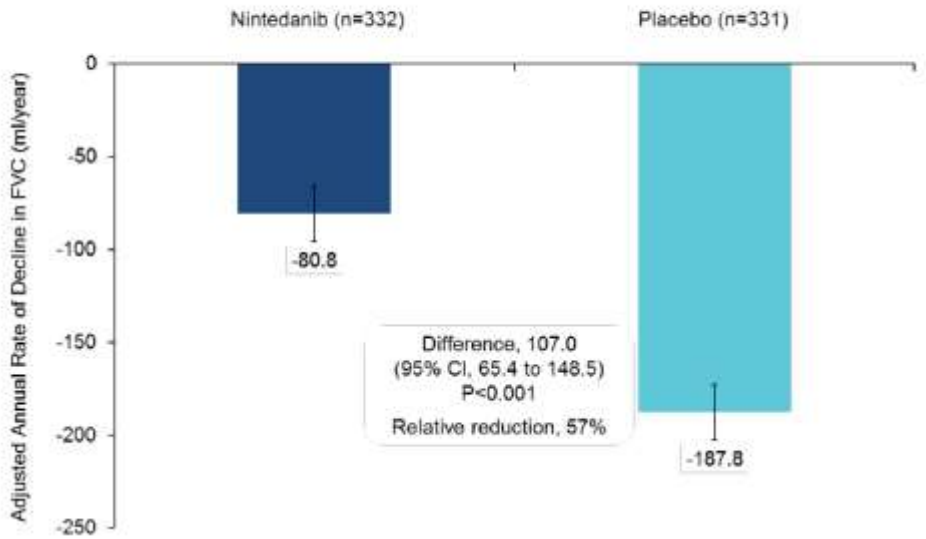


Figure S4B. Between-group adjusted difference in the annual rate of decline in FVC (mL/year) over 52 weeks in patients with a UIP-like fibrotic pattern on HRCT (primary endpoint). The bars indicate the standard error.

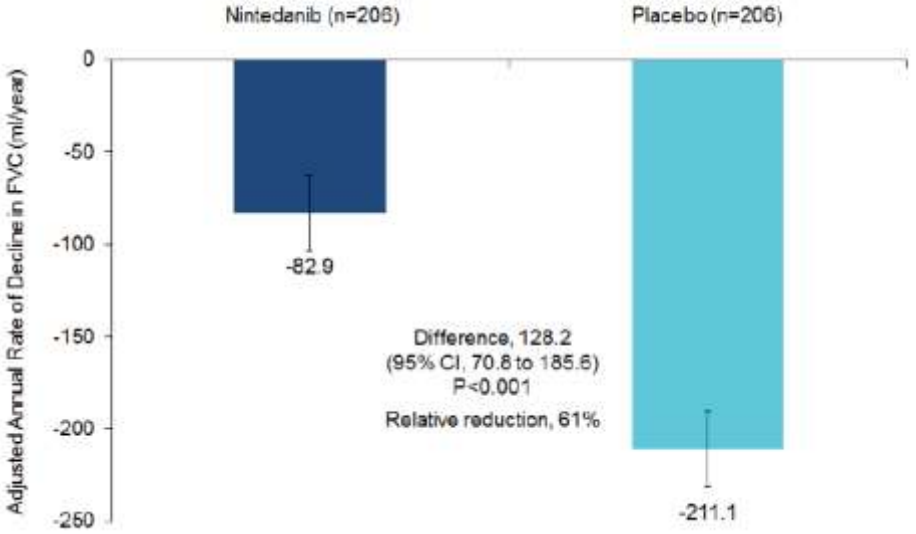
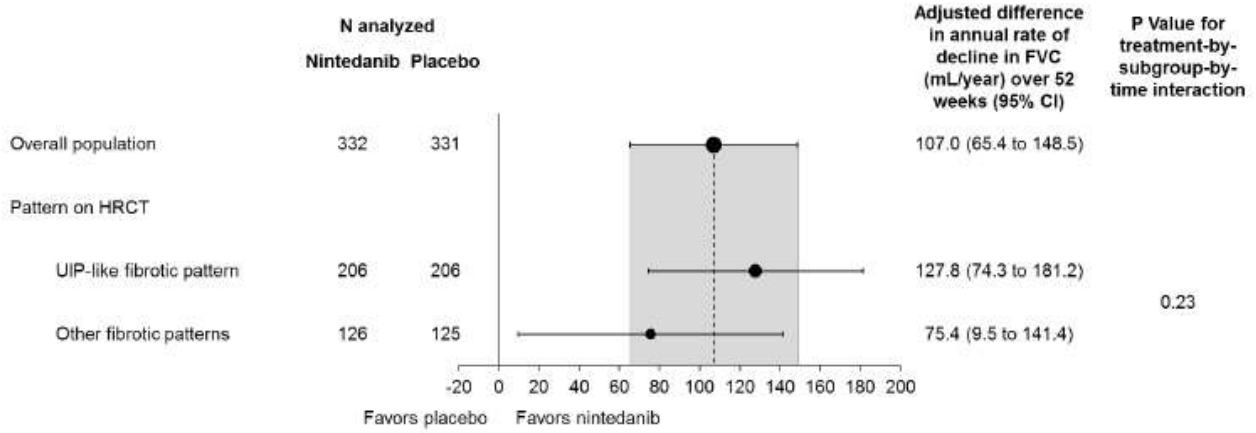


Figure S7. Between-group adjusted difference in the annual rate of decline in FVC (mL/year) over 52 weeks in subgroups by HRCT pattern



Five groups

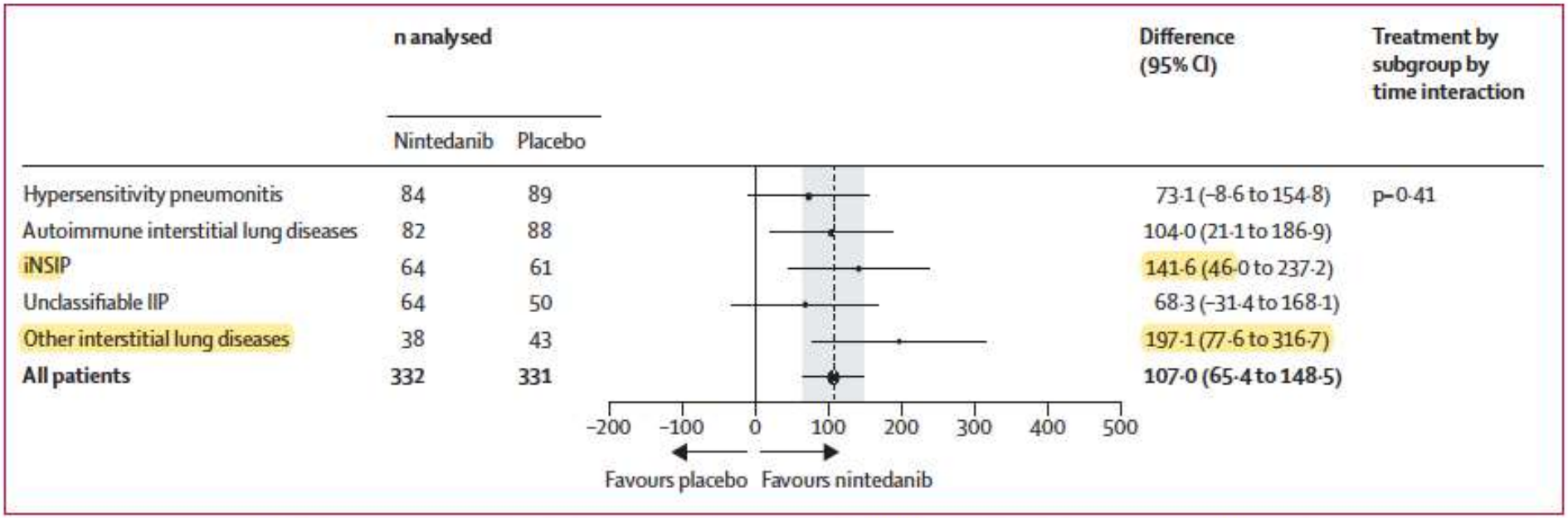
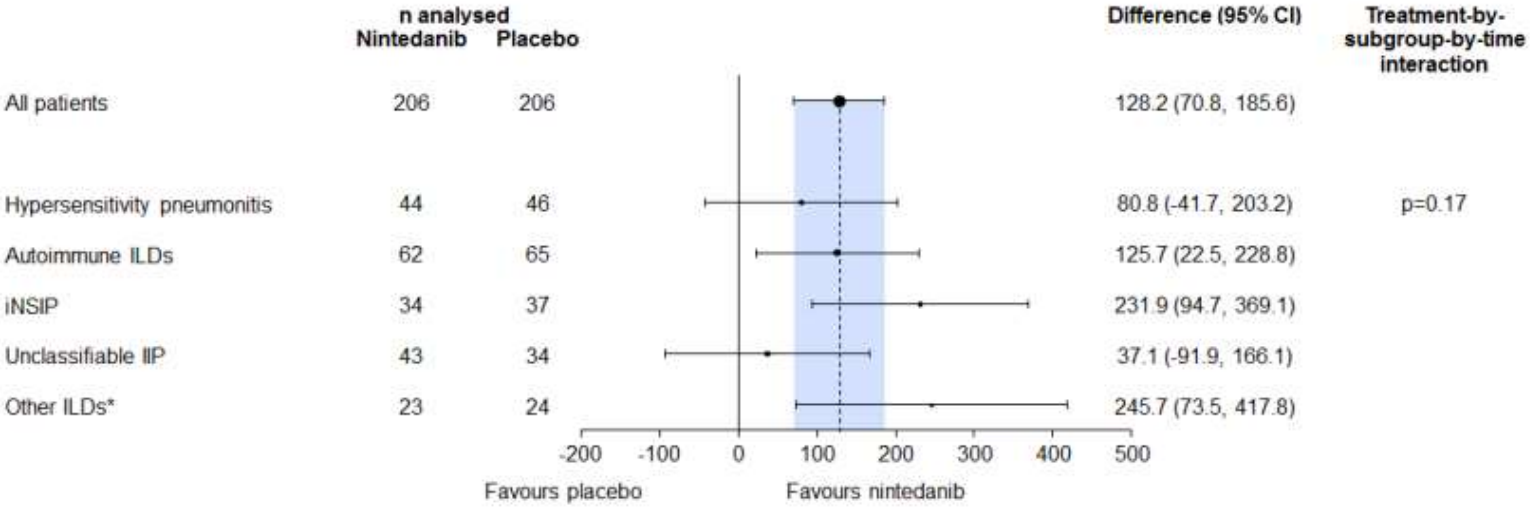


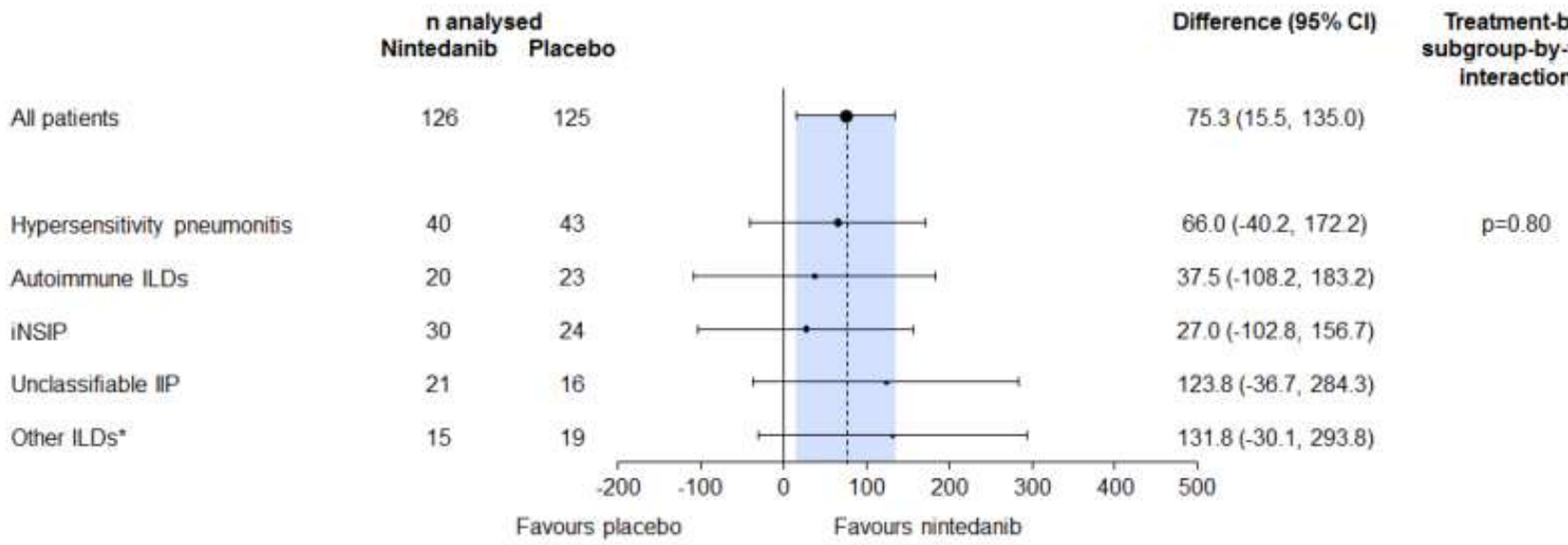
Figure 2: **Annual rate of decline in forced vital capacity (mL/year) in five groups by interstitial lung disease diagnosis (overall population)**
iNSIP=idiopathic non-specific interstitial pneumonia. IIP=idiopathic interstitial pneumonia. Other interstitial lung diseases (ILDs)=sarcoidosis, exposure-related ILDs and other terms in the other fibrosing ILDs category.

A Subjects with a UIP-like fibrotic pattern on HRCT



*Included sarcoidosis, exposure-related ILDs and selected other terms in "Other fibrosing ILDs".

B Subjects with other fibrotic patterns on HRCT



*Included sarcoidosis, exposure-related ILDs and selected other terms in "Other fibrosing ILDs".

No diagnostic group drove the treatment effect in the overall population

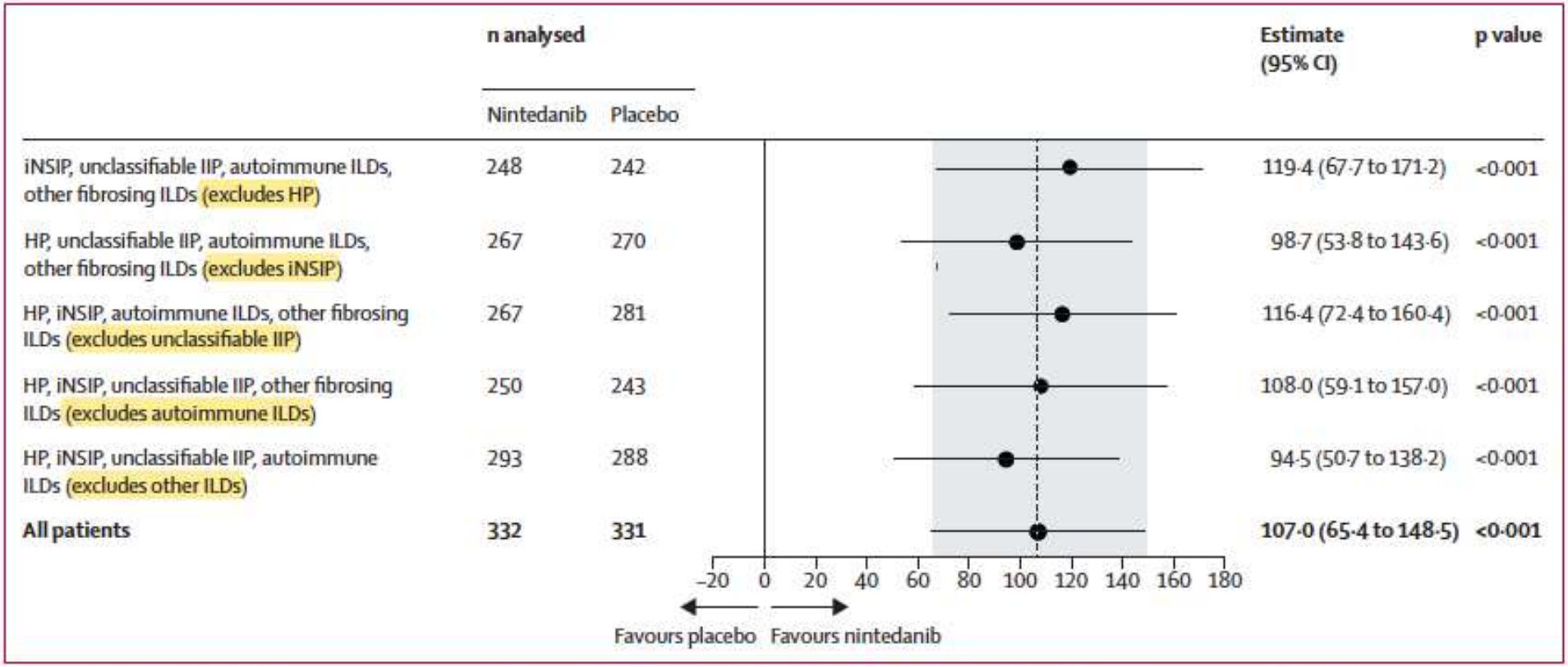
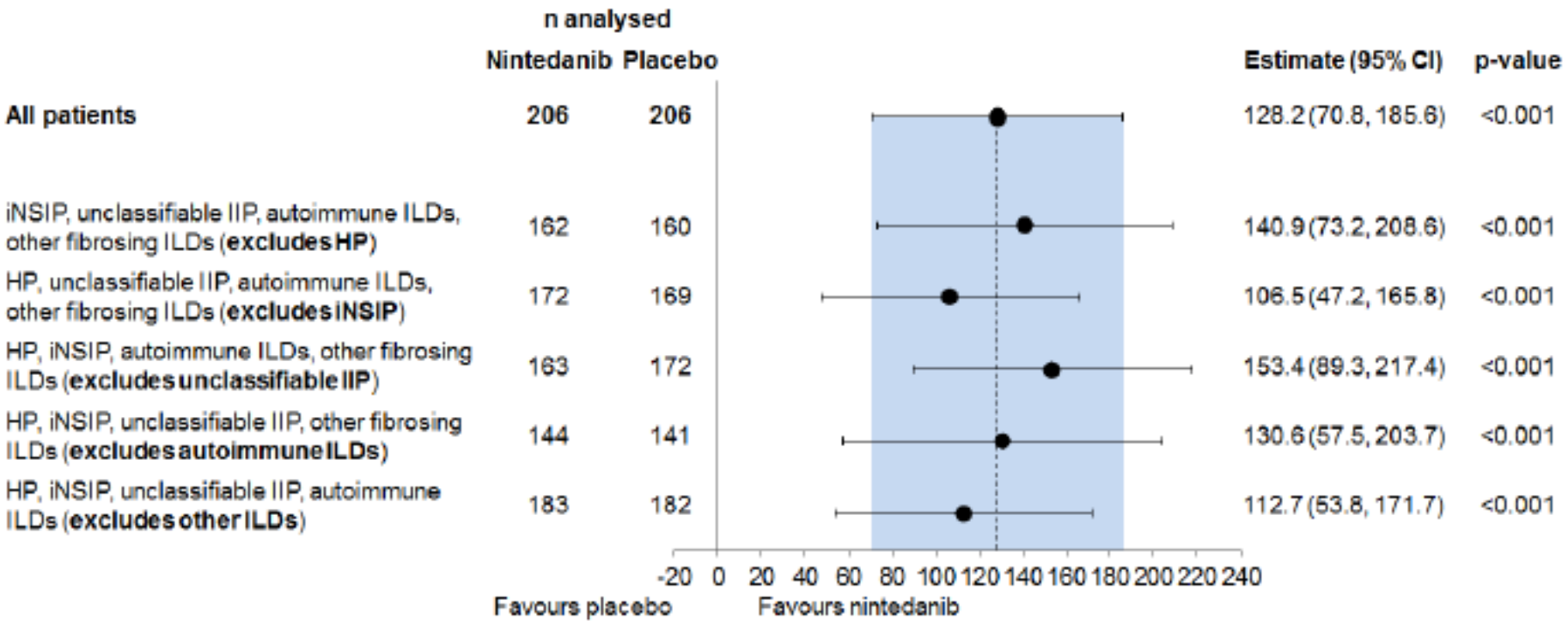


***Figure 3*: Annual rate of decline in forced vital capacity (mL/year) with one of the five groups by interstitial lung disease diagnosis excluded at a time (overall population)**

iNSIP=idiopathic non-specific interstitial pneumonia. IIP=idiopathic interstitial pneumonia. ILD=interstitial lung disease. HP=hypersensitivity pneumonitis.

A Subjects with a UIP-like fibrotic pattern on HRCT



B Subjects with other fibrotic patterns on HRCT

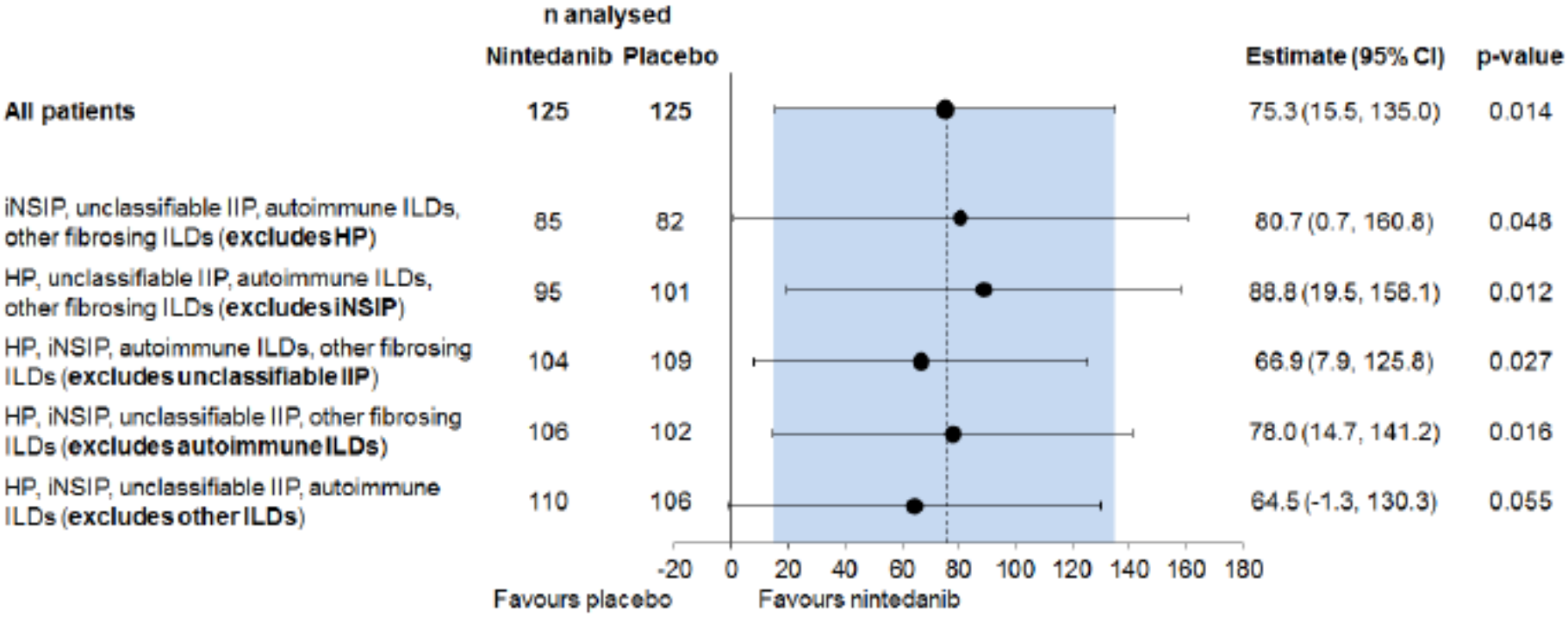
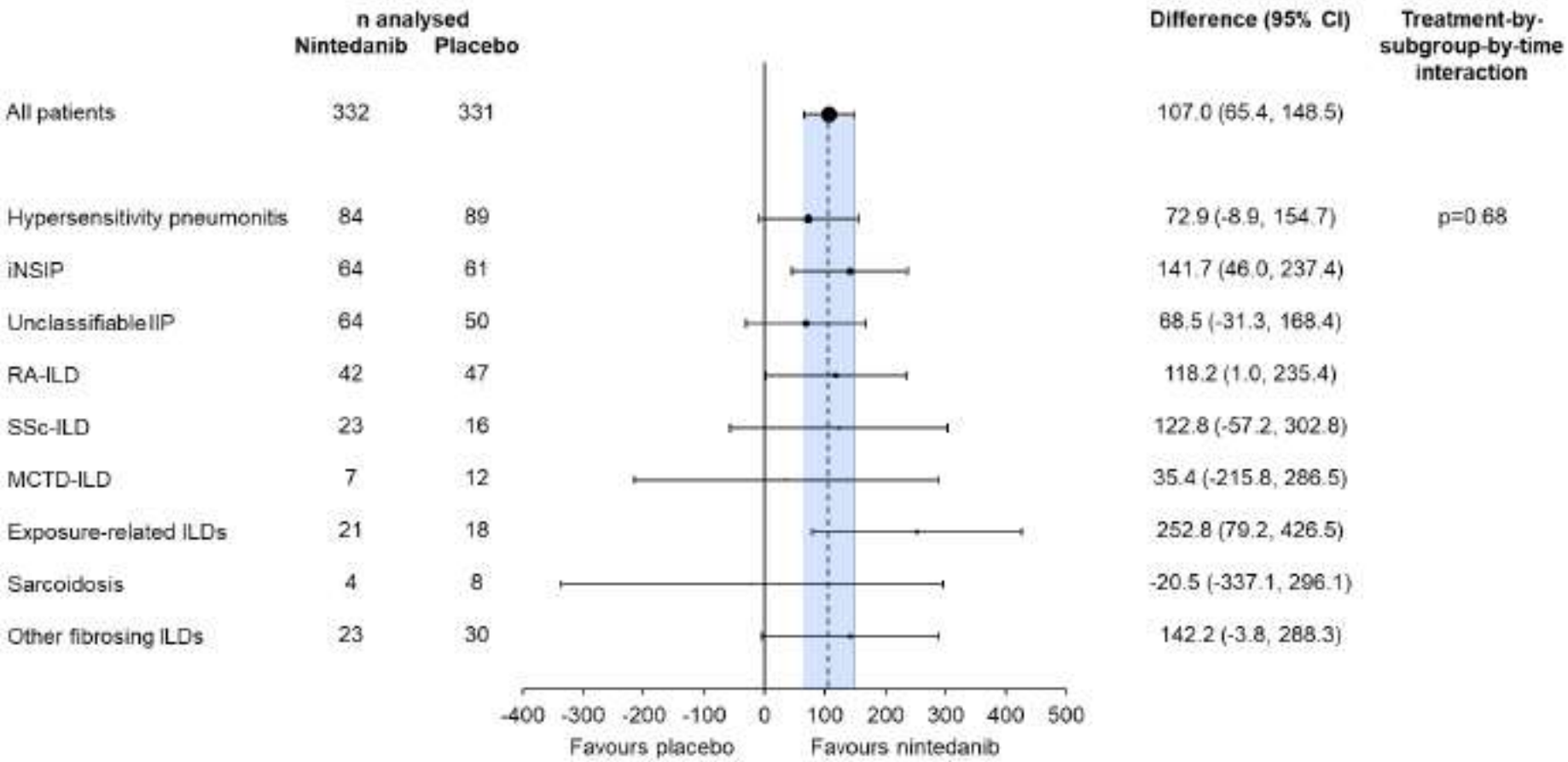


Figure S5. Annual rate of decline in FVC (mL/year) in 9 subgroups by ILD diagnosis noted in the case report form (overall population). FVC=forced vital capacity. IIP=idiopathic interstitial pneumonia. ILD=interstitial lung disease. iNSIP=idiopathic non-specific interstitial pneumonia. MCTD=mixed connective tissue disease. RA=rheumatoid arthritis. SSc=systemic sclerosis.



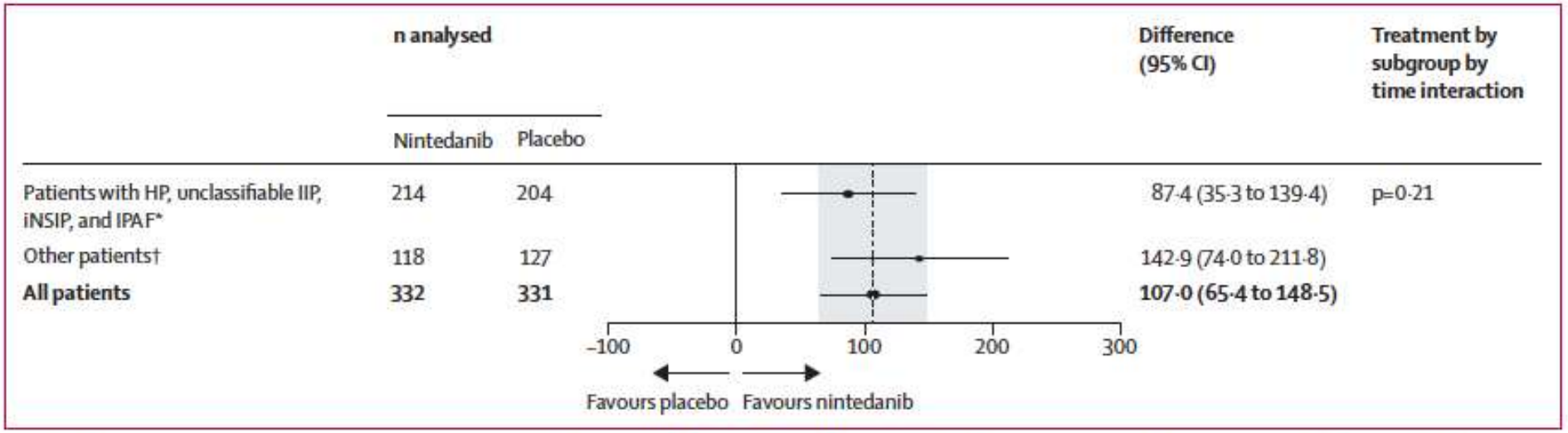


Figure 4: **Annual rate of decline in forced vital capacity (mL/year) in patients with a diagnosis likely to be considered as a differential diagnosis of IPF (hypersensitivity pneumonitis, unclassifiable idiopathic interstitial pneumonia, idiopathic non-specific interstitial pneumonia, or interstitial pneumonia with autoimmune features) versus all other patients (overall population)**

HP=hypersensitivity pneumonitis. IIP=idiopathic interstitial pneumonia. iNSIP=idiopathic non-specific interstitial pneumonia. IPAF=interstitial pneumonia with autoimmune features. *IPAF was based on selected terms in other fibrosing interstitial lung diseases. †ILD associated with rheumatoid arthritis and systemic sclerosis, mixed connective tissue disease-ILD, sarcoidosis, exposure-related ILDs, and selected other terms in other fibrosing ILDs.

	Hypersensitivity pneumonitis		Autoimmune interstitial lung diseases		Idiopathic non-specific interstitial pneumonia		Unclassifiable idiopathic interstitial pneumonia		Other ILDs*	
	Nintedanib (n=84)	Placebo (n=89)	Nintedanib (n=82)	Placebo (n=88)	Nintedanib (n=64)	Placebo (n=61)	Nintedanib (n=64)	Placebo (n=50)	Nintedanib (n=38)	Placebo (n=43)
Any adverse event	83 (99%)	85 (96%)	79 (96%)	79 (90%)	54 (84%)	48 (79%)	64 (100%)	46 (92%)	37 (97%)	38 (88%)
Most frequent adverse events†										
Diarrhoea	59 (70%)	24 (27%)	52 (63%)	24 (27%)	41 (64%)	11 (18%)	45 (70%)	9 (18%)	25 (66%)	11 (26%)
Nausea	24 (29%)	13 (15%)	22 (27%)	10 (11%)	16 (25%)	1 (2%)	25 (39%)	3 (6%)	9 (24%)	4 (9%)
Bronchitis	10 (12%)	11 (12%)	13 (16%)	13 (15%)	4 (6%)	8 (13%)	7 (11%)	7 (14%)	7 (18%)	8 (19%)
Nasopharyngitis	11 (13%)	11 (12%)	10 (12%)	13 (15%)	9 (14%)	9 (15%)	12 (19%)	6 (12%)	2 (5%)	1 (2%)
Dyspnoea	11 (13%)	16 (18%)	6 (7%)	10 (11%)	3 (5%)	2 (3%)	10 (16%)	6 (12%)	6 (16%)	10 (23%)
Vomiting	21 (25%)	7 (8%)	14 (17%)	6 (7%)	11 (17%)	2 (3%)	12 (19%)	0	3 (8%)	2 (5%)
Cough	11 (13%)	17 (19%)	2 (2%)	6 (7%)	4 (6%)	4 (7%)	10 (16%)	8 (16%)	6 (16%)	9 (21%)
Decreased appetite	8 (10%)	9 (10%)	15 (18%)	1 (1%)	8 (13%)	3 (5%)	11 (17%)	1 (2%)	6 (16%)	3 (7%)
Headache	9 (11%)	12 (13%)	7 (9%)	4 (5%)	5 (8%)	4 (7%)	10 (16%)	3 (6%)	4 (11%)	0
Alanine aminotransferase increased	11 (13%)	4 (4%)	14 (17%)	3 (3%)	8 (13%)	2 (3%)	8 (13%)	1 (2%)	2 (5%)	2 (5%)
Progression of ILD‡	3 (4%)	10 (11%)	3 (4%)	7 (8%)	5 (8%)	9 (15%)	5 (8%)	8 (16%)	0	5 (12%)
Weight decreased	9 (11%)	4 (4%)	10 (12%)	1 (1%)	7 (11%)	1 (2%)	12 (19%)	5 (10%)	3 (8%)	0
Aspartate aminotransferase increased	11 (13%)	3 (3%)	11 (13%)	4 (5%)	8 (13%)	1 (2%)	7 (11%)	2 (4%)	1 (3%)	2 (5%)
Abdominal pain	14 (17%)	2 (2%)	7 (9%)	2 (2%)	2 (3%)	1 (2%)	9 (14%)	0	2 (5%)	3 (7%)
Severe adverse event§	19 (23%)	22 (25%)	13 (16%)	16 (18%)	9 (14%)	10 (16%)	15 (23%)	13 (26%)	4 (11%)	12 (28%)
Serious adverse event¶	29 (35%)	34 (38%)	28 (34%)	28 (32%)	14 (22%)	17 (28%)	25 (39%)	17 (34%)	11 (29%)	14 (33%)
Fatal adverse event	4 (5%)	4 (4%)	3 (4%)	4 (5%)	2 (3%)	5 (8%)	0	1 (2%)	2 (5%)	3 (7%)
Adverse event leading to permanent treatment discontinuation	16 (19%)	6 (7%)	14 (17%)	9 (10%)	13 (20%)	5 (8%)	14 (22%)	7 (14%)	8 (21%)	7 (16%)

In conclusion

- Absolute treatment effect b/w group difference (of FVC) was 107ml vs 109 ml in comparison to INPULSIS trial
- Supports the hypothesis that progressive fibrosing ILDs have a similar pathobiologic mechanism, irrespective of clinical diagnosis

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

Inclusion criteria

- Age 18 to 85 years
- Unclassifiable ILD (Cannot be grouped into a category with high/moderate confidence after MDD)
- Progressive disease i.e, Absolute FVC decline > 5% or symptomatic worsening in last 6 months
- >10% fibrosis on HRCT(within past 1 year)
- FEV1/FVC >0.7
- FVC > 45% of predicted value
- DLCO >30% of predicted value
- 6MWD>150m

Exclusion criteria

- Diagnosis with moderate or high confidence of NSIP and any ILD with an identifiable cause
- Diagnosis of IPF independent of confidence level
- History of Unstable angina/MI in past 6 months
- Treatment with steroids(>15 mg /d of prednisolone or equivalent)/any immunosuppressant other than MMF within 4 weeks of screening (Patient on MMF should be on it for at least 3 months prior to screening)

- Eligible patients assigned in 1:1 ratio
- Oral pirfenidone 2403 mg daily or placebo
- Given for 24 weeks
- Home spirometry using hand held micro spirometer every day
- Efficacy outcomes and safety outcomes assessed q 4 wk at site visit

Primary Outcome/End points

- Mean change in FVC(ml) at 24 weeks measured by hand held spirometer

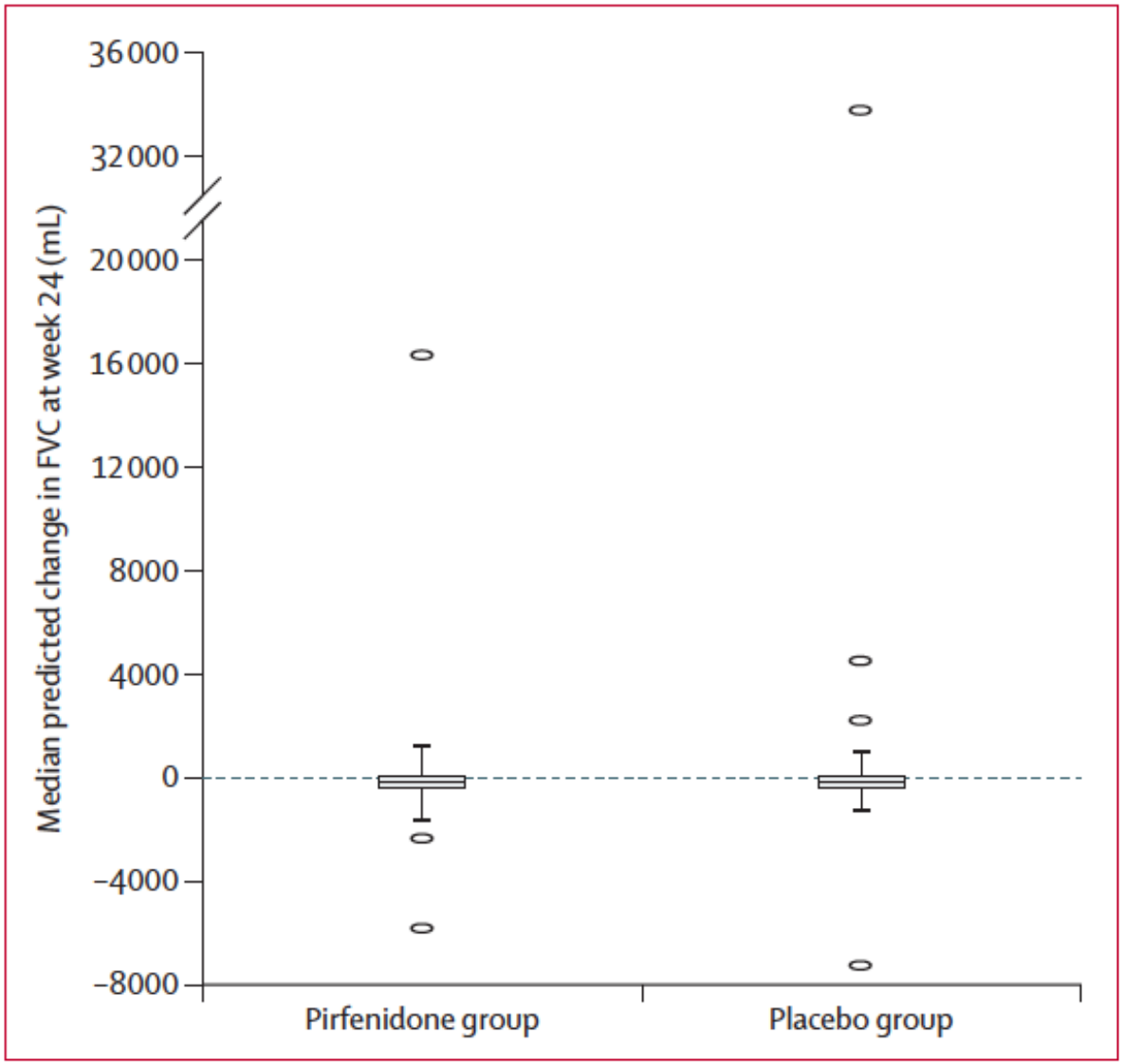
Secondary Endpoints

- Change in percent predicted FVC measured by site spirometry
- Proportion of patients with >5% and >10% absolute or relative decline in % predicted FVC measured by site spirometry
- Change in % predicted DL_{CO}
- Change in 6MWD
- Change in UCSD-SOBQ, LCQ and SGRQ score
- Change in visual analogue cough scale

	Pirfenidone (n=127)	Placebo (n=126)
Age at screening, years	70·0 (61·0–76·0)	69·0 (63·0–74·0)
Sex		
Men	70 (55%)	69 (55%)
Women	57 (45%)	57 (45%)
Race		
White	120 (94%)	123 (98%)
Black	1 (1%)	2 (2%)
Asian	5 (4%)	0
Native American or Alaskan Native	1 (1%)	0
Other	0	1 (1%)
Body-mass index, kg/m²	28·6 (26·5–32·9)	29·3 (26·2–32·7)
Previous surgical lung biopsy	40 (31%)	48 (38%)
Percent predicted FVC	71·0% (59·0–87·3)	71·5% (58·0–88·0)
Percent predicted DLco	44·6% (36·9–53·5)	48·0% (38·4–59·0)
Percent predicted FEV_1	75·0% (62·0–88·0)	76·0% (62·0–92·7)
FEV_1/FVC ratio	0·82 (0·78–0·86)	0·84 (0·78–0·87)
6MWD, m	372·0 (303·0–487·0)	395·0 (325·0–472·0)
Concomitant treatment with mycophenolate mofetil	23 (18%)	22 (17%)
IPAF diagnosis	15 (12%)	18 (14%)
Concomitant treatment with mycophenolate mofetil	6 (5%)	6 (5%)
Unclassifiable ILD diagnosis		
Low-confidence rheumatoid arthritis-ILD	0	0
Low-confidence systemic sclerosis-ILD	0	1 (1%)
Low-confidence undifferentiated connective tissue disease-ILD	3 (2%)	2 (2%)
Low-confidence chronic hypersensitivity pneumonitis-ILD	10 (8%)	9 (7%)
Low-confidence idiopathic non-specific interstitial pneumonia-ILD	4 (3%)	3 (2%)
Low-confidence sarcoidosis-ILD	0	0
Low-confidence myositis-ILD	0	0
Low-confidence other defined ILD	1 (1%)	0
Unclassifiable ILD	93 (73%)	93 (74%)

- Baseline characteristics were similar b/w two groups
- ~ 75% had diagnosis of uILD

Results – Primary End Point

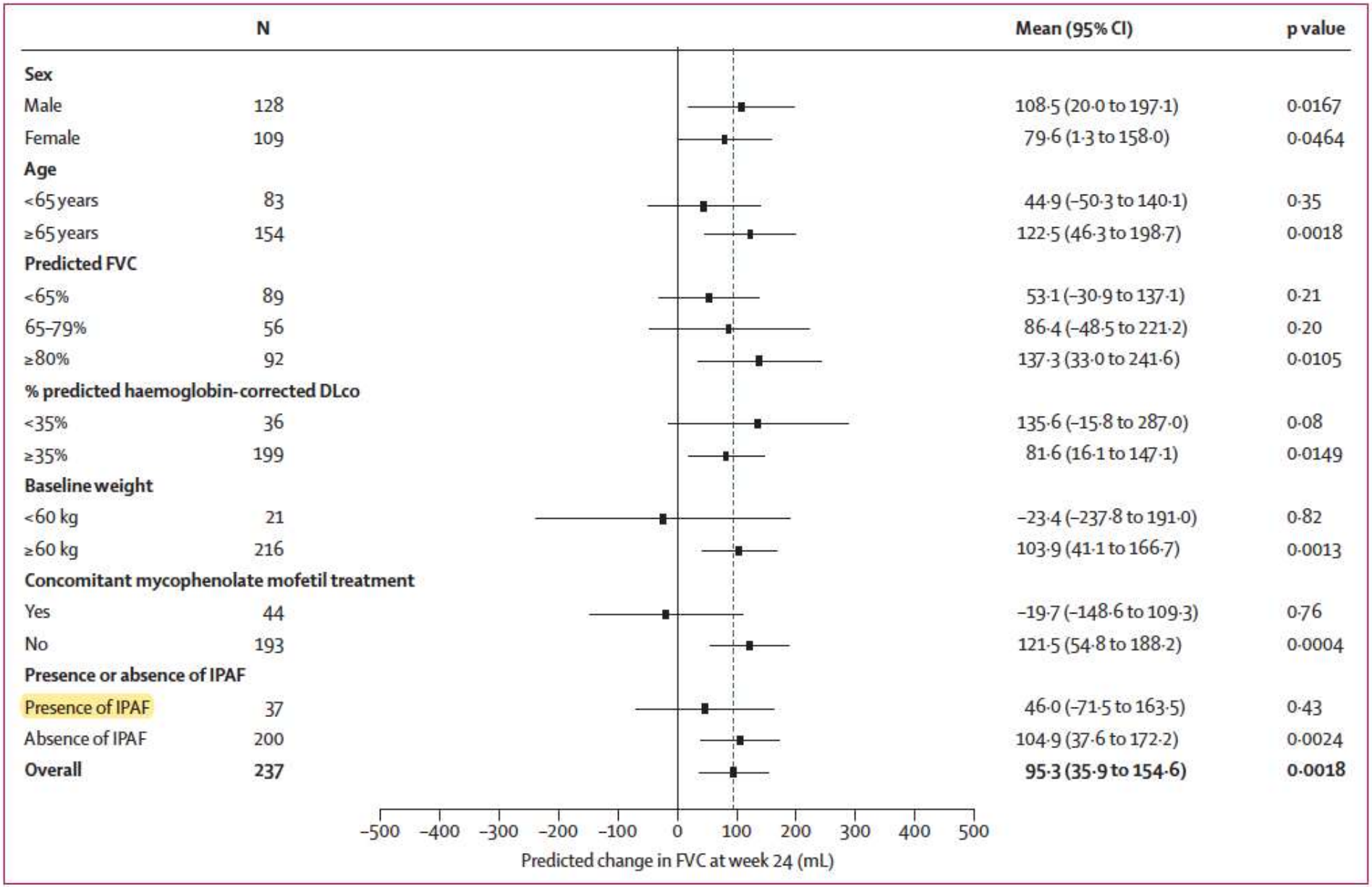


	Pirfenidone	Placebo
FVC change	-87.7ml (-338.1 – 148.6)	-157.1ml (-370.9 – 70.1)

	Pirfenidone (n=127)	Placebo (n=126)
Change in FVC from baseline measured by site spirometry		
Mean, mL	20·0* (7·6)	−80·0† (7·6)
Median, mL	0·0 (−160·0 to 120·0)	−90·0 (−210·0 to 30·0)
Mean, % predicted	−0·4%* (6·9)	−2·5%† (9·2)
Median, % predicted	0·0% (−4·8 to 4·0)	−2·0% (−7·0 to 1·5)
Change in percent predicted DLco from baseline		
Mean	−0·7%‡ (7·1)	−2·5%§ (8·8)
Median	−1·0% (−4·1 to 3·2)	−2·0% (−6·0 to 1·7)
Change in 6MWD from baseline		
Mean, m	−2·0¶ (68·1)	−26·7‖ (79·3)
Median, m	0·0 (−39·0 to 40·0)	−12·0 (−53·5 to 10·5)

Data are mean (SD) or median (Q1–Q3). For some of the analyses, only patients with data available for the relevant outcome measure at week 24 were included, thus patient numbers vary from that included in the intention-to-treat population. FVC=forced vital capacity. DLco=carbon monoxide diffusing capacity. 6MWD=6-min walk distance. *n=101. †n=112. ‡n=97. §n=110. ¶n=99. ‖n=108.

Table 3: **Descriptive secondary outcome variables at week 24 in the intention-to-treat population (n=253)**



Treatment benefit was observed regardless of age, sex, lung function, and IPAF

Results – Secondary outcomes

	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.

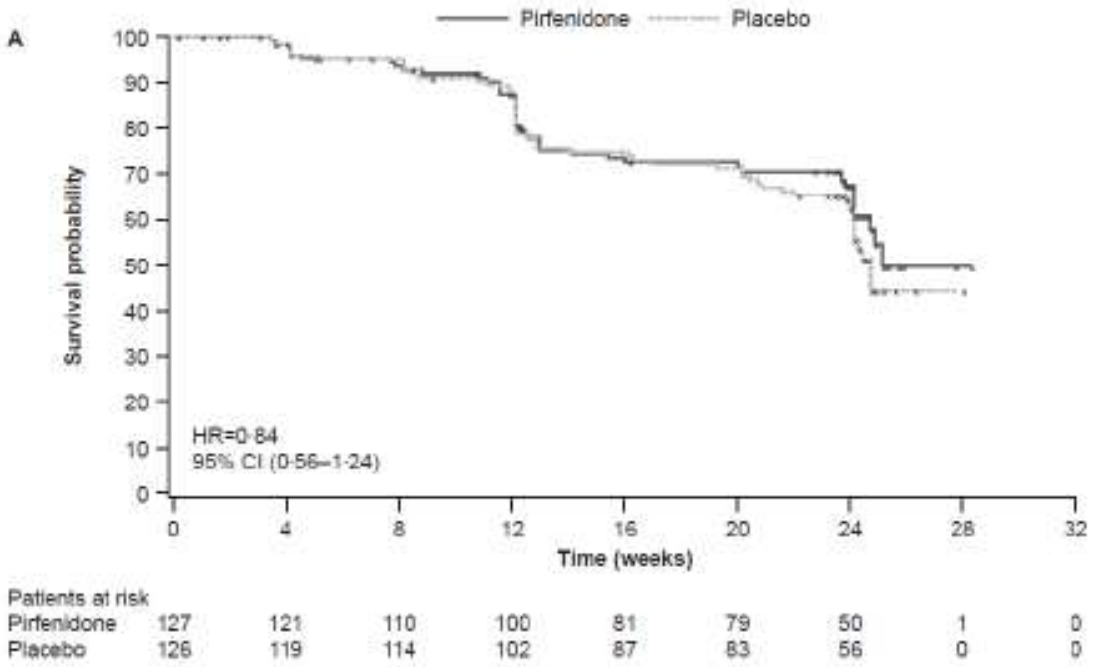
Table 2: **Secondary and prespecified exploratory outcomes at week 24 in the intention-to-treat population (n=253)**

Results – Secondary outcomes

Parameter	Pirfenidone	Placebo	Pirfenidone *vs* placebo
Change from baseline to Week 24 in SGRQ score			
Total score			
Mean (SD)	0·05 (12·5)*	0·85 (13·4)†	–
Median (Q1, Q3)	–0·37 (–7·6, 7·0)	0·60 (–7·0, 9·4)	–
Rank ANCOVA	–	–	0·16
Symptoms component			
Mean (SD)	–1·69 (19·2)‡	–0·66 (15·4)§	–
Median (Q1, Q3)	0 (–15·4, 9·7)	0·41 (–9·9, 9·4)	–
Activities component			
Mean (SD)	1·25 (14·6)*	2·22 (13·1)†	–
Median (Q1, Q3)	0 (–6·7, 6·7)	0·05 (–6·7, 12·1)	–
Impacts component			
Mean (SD)	–0·18 (13·9)*	1·07 (17·5)†	–
Median (Q1, Q3)	–1·24 (–7·6, 8·0)	–0·22 (–8·3, 11·7)	–
Change from baseline to Week 24 in UCSD-SOBQ score			
Mean (SD)	5·21 (18·7)¶	5·30 (22·1)‖	–
Median (Q1, Q3)	4·00 (–7·5, 14·5)	1·00 (–8·0, 20·0)	–
Rank ANCOVA	–	–	0·78
Change from baseline to Week 24 in cough VAS score, mm			
Mean (SD)	–2·52 (26·7)**	0·78 (30·1)††	–
Median (Q1, Q3)	0 (–15·5, 10·0)	0 (–15·0, 20·0)	–
Rank ANCOVA	–	–	0·30

Results – Secondary outcomes

No significant b/w group difference in PFS



	Pirfenidone (n=127)	Placebo (n=124)
Any treatment-emergent adverse events	120 (94%)	101 (81%)
Any treatment-related treatment-emergent adverse events	90 (71%)	57 (46%)
Any serious treatment-emergent adverse events*	18 (14%)	20 (16%)
Any severe treatment-emergent adverse events	29 (23%)	28 (23%)
Any treatment-related, severe treatment-emergent adverse events	6 (5%)	2 (2%)
Treatment-emergent adverse events of special interest†	0	0
Treatment-emergent adverse events leading to death	1 (1%)	1 (1%)
Treatment-related, treatment-emergent adverse events leading to death	0	0
Treatment-emergent adverse events leading to treatment discontinuation	19 (15%)	5 (4%)
Treatment-related, treatment-emergent adverse events leading to treatment discontinuation	16 (13%)	1 (1%)
Treatment-related treatment-emergent adverse events known to be associated with pirfenidone		
Gastrointestinal disorder‡	60 (47%)	32 (26%)
Photosensitivity§	10 (8%)	2 (2%)
Rash¶	13 (10%)	9 (7%)
Dizziness	10 (8%)	4 (3%)
Weight decrease	10 (8%)	1 (1%)
Fatigue	16 (13%)	12 (10%)

In conclusion

- Planned statistical model could not be applied to the primary endpoint data
- Results for the key secondary endpoints support the conclusion that 24 weeks of treatment with pirfenidone slows disease progression when compared with placebo
- Treatment with pirfenidone slows disease progression in progressive fibrosing unclassifiable ILD
- Acceptable safety and tolerability profile

In conclusion

- Result is similar to the treatment benefit observed on mean decline in FVC in a prespecified pooled analysis of the phase 3 trials of pirfenidone in IPF, in which an absolute treatment difference of 104 mL was observed for pirfenidone versus placebo after 24 weeks of treatment, increasing to 148 mL after 52 weeks of treatment
- Patients with IPF given placebo in the ASCEND phase 3 trial of pirfenidone showed a linear slope of decline in FVC of 280 mL at week 52, whereas patients with unclassifiable ILD given placebo in our study had a mean decline of 113·0 mL at week 24 measured using site spirometer

Chronic HP

- One RCT(placebo) of an 8-week course of prednisone Vs placebo in acute HP (farmer's lung) shows improvement in pulmonary function in both groups initially, but no differences in pulmonary function between the two groups at 1 year
- Retrospective study-MMF or azathioprine had a small but significant improvement in DLCO after 1 year of treatment and required lower doses of corticosteroids

Chronic HP

- SHIBATA.et al reported a series of 23 patients with cHP treated with pirfenidone. In n=16 vital capacity decreased by 292±78 mL over the 6 months prior to pirfenidone and decreased by 152±56 mL over the 6 months after pirfenidone
- BUENDIA-ROLDAN et.al-29 patients with cHP randomised to pred+AZT Vs pred+AZT+pirfenidone. In pirfenidone arm had improvement in 6MWD at 9 months' follow-up

Ongoing clinical trials of antifibrotic medications in Chronic HP

	Name	Phase	Patients	Intervention	Duration	Primary outcome	Key secondary outcomes
NCT02958917 [90]	Study of Efficacy and Safety of Pirfenidone in Patients with Fibrotic Hypersensitivity Pneumonitis	N/A	40 patients with fibrotic hypersensitivity pneumonitis	Pirfenidone 801 mg three times daily or placebo	52 weeks	Mean change in FVC	PFS, ⩾5% mean change FVC, acute exacerbation, 6MWD
NCT02496182 [89]	Pirfenidone in the Chronic Hypersensitivity Pneumonitis Treatment (Picheon)	II/III	n=60, cHP	Pirfenidone (1800 mg or 1200 mg total daily dose) or placebo in addition to conventional therapy (prednisone and azathioprine)	52 weeks	Change in FVC	Inflammation and fibrosis grade on HRCT (Kazerooni scale), 6MWD, SGRQ score

Cyclophosphamide	SLS I	2 mg/kg/d PO X 1 year	Slowerrate of annual decline in % predicted FVC:-1% (-2.6% in placebo arm)
MMF	SLS II	1500 mg BD X 2 years	Improved % predicted FVC at2 years by+2.2% (similarto 1-year oral CYC Rx arm +2.9%)
Nintedanib	SENSCIS	150 mg BD X 1 year	Slowerrate of annual decline in FVC by about 40 mL (-52 vs -93 mL) No difference in rate of annual decline in % predicted FVC: -1.4% (-2.6% in placebo arm)

Systemic sclerosis

Agent	Major RCTs	Dose	Outcome
Cyclophosphamide	SLS I	2 mg/kg/d PO X 1 year	Slowerrate of annual decline in % predicted FVC:-1% (-2.6% in placebo arm)
MMF	SLS II (phase 3) N-580	1500 mg BD X 2 years	Improved % predicted FVC at2 years by+2.2% (similarto 1-year oral CYC Rx arm +2.9%)
Nintedanib	SENSCIS	150 mg BD X 1 year	Slowerrate of annual decline in FVC by about 40 mL (-52 vs -93 mL) No difference in rate of annual decline in % predicted FVC: -1.4% (-2.6% in placebo arm)

Systemic sclerosis-on going

	Name	Phase	Patients	Intervention	Duration	Primary outcome	Key secondary outcomes
NCT03221257 [95]	Scleroderma Lung Study III – Combining Pirfenidone with Mycophenolate (SLSIII)	II	n=150, SSc-pulmonary fibrosis	Pirfenidone (target dose 801 mg three times daily) or placebo+MMF (target dose of 1500 mg twice daily)	18 months	Change in FVC % pred	Change *D*LCO % pred, change modified Rodan Skin Score, SGRQ, dyspnoea assessment score, change from baseline ILD by computer-quantified HRCT

RA-ILD

- UIP is the most common pattern in RA-ILD
- Mutation in the MUC5B promoter seen in many patients with IPF is also associated with RA-ILD (RA-UIP in particular)

	Name	Phase	Patients	Intervention	Duration	Primary outcome	Key secondary outcomes
NCT02808871 [99]	Phase II Study of Pirfenidone in Patients with RA-ILD (TRAIL1)	II	270 patients with RA-ILD	Pirfenidone 801 mg three times daily or placebo	52 weeks	Composite end-point: ⩾10% decline in FVC or death	Relative decline D_{LCO} (⩾15%), relative decline in FVC (⩾10%), acute exacerbation, dyspnoea scores, SGRQ

Myositis- CADM

- 65% of patients with CADM may have ILD
- Positive serum MDA5 antibody is associated with rapidly progressive with high associated mortality
- LI et al conducted an open-label prospective study of pirfenidone added on to existing immunosuppressive therapy for patients with CADM and ILD (n=30) compared to retrospective matched controls (n=27).
- Statistically significant difference in mortality in the pirfenidone group was absent
- subgroup analyses - subacute ILD (disease 3–6 months' duration, n=10) 1-year survival was improved (90%) compared to that in controls (n=9; 44%)
- The same effect was not seen for patients with acute ILD (<3 months)
- 85% of patients in the pirfenidone group were MDA5+ compared to only 57% in the control group, which makes the finding that the pirfenidone group with subacute disease had improved survival more striking

Myositis- CADM

	Name	Phase	Patients	Intervention	Duration	Primary outcome	Key secondary outcomes
NCT02821689 [94]	Pirfenidone in Progressive ILD Associated with Clinically Amyopathic Dermatomyositis	IV	n=60, CADM with ILD	1800 mg pirfenidone total per day or placebo added on to existing treatment	52 weeks	Overall survival	Change in HRCT score, change in PFT from baseline

Sarcoidosis

	Name	Phase	Patients	Intervention	Duration	Primary outcome	Key secondary outcomes
NCT03260556 [100]	Pirfenidone for Progressive Fibrotic Sarcoidosis (PirFS)	IV	60 patients with sarcoidosis and >20% fibrosis on HRCT (stable immunosuppressive medications and/or ⩽ 20 mg prednisone/ day for 2 months prior allowed)	Pirfenidone 801 mg three times daily or placebo	24 months	Time until clinical worsening	Change in FVC, change in composite physiologic index

Unclassifiable PF-ILD

	Name	Phase	Patients	Intervention	Duration	Primary outcome	Key secondary outcomes
NCT03099187 [97]	A Study of Pirfenidone in Patients with Unclassifiable Progressive Fibrosing Interstitial Lung Disease	II	n=252, nonclassifiable ILD (cannot be classified to a specific category of ILD with moderate or high level of confidence with MDD)	Pirfenidone (801 mg three times daily) or placebo (stable dose MMF allowed)	24 weeks	Rate of decline in FVC over 24 weeks	Change in FVC (% pred), change in D_{LCO} (% pred), change in FVC of >5%, change in FVC of >10%, change in 6MWD, change in symptom scores (dyspnoea, cough), SGRQ score, AE-IPF, PFS

Parameter	Comparison b/w two arms
FVC decline	95.3 ml lower(X MCID)
Absolute/ Relative decline in percent predicted FVC of >5/10%	In lesser number of patients
6MWD decline	Lower(24.7 m lower)(X MCID)
>15% decline in Dlco	lower
>50m decline in 6MWD	similar
PRO	similar
PFS	similar

Progressive Non-IPF Lung Fibrosis

	Name	Phase	Patients	Intervention	Duration	Primary outcome	Key secondary outcomes
DRKS00009822 [96]	Exploring Efficacy and Safety of Pirfenidone for Progressive, Non-IPF Lung Fibrosis (RELIEF)	II	Collagen vascular disease-associated fibrosis, fibrotic NSIP, cHP, asbestos-related lung fibrosis	Pirfenidone (801 mg three times daily) or placebo	48 weeks	Absolute change in FVC (%) from baseline to week 48	Time to disease worsening, change in D_{LCO}, 6MWD, SGRQ and EQ-5D

Summary

- PF-ILD can be recognized as basket entity regardless of etiology
- Look carefully into clinical, radiology and spirometry data before labelling as progressive fibrosing ILD
- We can use anti fibrotic agents(take feasibility into account) in selected population
- Large RCT are needed