Progressive Pulmonary Fibrosis Diagnosis And Management

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Objectives

Definition and its evolution

Diagnosis

Treatment In Nutshell

Evidence of Treatment

Follow Up

Research questions

Definition

In a patient with ILD of known or unknown etiology other than IPF who has radiological evidence of pulmonary fibrosis, PPF is defined as at least two of the following three criteria occurring within the past year with no alternative explanation:

1 Worsening respiratory symptoms

2 Physiological evidence of disease progression (either of the following):

a. Absolute decline in FVC >5% predicted within 1 yr of follow-up

b. Absolute decline in DLCO (corrected for Hb) >10% predicted within 1 yr of follow-up

3. Radiological evidence of disease progression (one or more of the following):

a. Increased extent or severity of traction bronchiectasis and bronchiolectasis

b. New ground-glass opacity with traction bronchiectasis

c. New fine reticulation

d. Increased extent or increased coarseness of reticular abnormality

e. New or increased honeycombing

f. Increased lobar volume loss

Raghu G et al, Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2022 1;205(9):e18-e47.

Evolution of criteria in PPF

First author, year, reference	Type of proposal	Criteria of progression	Time period within which progression is assessed
Cottin (2018) [9]	ILD expert statement. Clinical practice.	Relative decline of at least 10% in FVC a relative decline of at least 15% in DLCO or worsening symptoms or a worsening radiological appearance accompanied by a at least 5 to less than 10% relative decrease in FVC	Within a 24-month period
George (2020) [35]	ILD expert statement. Clinical practice.	Relative decline of 10% or more in FVC Relative decline in FVC of 5% or more with decline in DLCO of 15% or more Relative decline in FVC of 5% or more with increased fibrosis on high-resolution CT (HRCT)* Relative decline in FVC of 5% or more with progressive symptoms Progressive symptoms with increased fibrosis on HRCT*	Over 24 months
Flaherty (2019) [24▪▪]	INBUILD clinical trial	Relative decline in FVC at least 10%; or FVC at least 5 to less than 10% and worsening of respiratory symptoms or increased extent of fibrosis on HRCT; or worsening of respiratory symptoms and increased extent of fibrosis on HRCT	Within 24 months
Maher (2020) [36▪]	U-ILD clinical trial	Either more than 5% absolute decline in FVC or significant symptomatic worsening	Within the previous 6 months

Valenzuela C et al, Epidemiology and real-life experience in progressive pulmonary fibrosis. Curr Opin Pulm Med. 2022;1;28(5):407-413.

Behr (2021) [37]	RELIEF clinical trial	Annualized percentage predicted FVC decline at least 5% (absolute)	Within up to 24 months
Raghu 2022 [11▪▪]	International guidelines ATS/ERS/JRS/ALAT	1. Worsening respiratory symptoms; 2. Physiological evidence of disease progression, either of the following: a. Absolute decline in FVC >5% predicted b. Absolute decline in DLCO (corrected for Hb) >10% predicted and 3. Radiological evidence of disease progression, one or more of the following: a. Increased extent or severity of traction bronchiectasis and bronchiolectasis b. New ground-glass opacity with traction bronchiectasis c. New fine reticulation d. Increased extent or increased coarseness of reticular abnormality e. New or increased honeycombing f. Increased lobar volume loss	Within 1 year of follow-up

- The above criteria mentioned are chosen based on the 5 years transplant free survival (TFS)

- Most of these datas are from the IPF studies.

Pugashetti, J.V. et al, *American Journal of Respiratory and Critical Care Medicine, 207* (1), 69-76.

- Dissecting the criteria used for PPF diagnosis, each component of the composite criteria by itself predicts the transplant free survival by itself.

- FVC relative decline ≥ 10% or DLco decline ≥15% and CT chest progression of fibrosis in the absence of FVC decline ≥ 10% better predicted the transplant free survival at 5 years.

- DLco as a isolated criteria for TFS is confounded by pulmonary vasculopathy.

- Using clinical symptoms alone for predicted TFS at 5 years has poor yield for prediction.

Pugashetti, J.V. et al, *American Journal of Respiratory and Critical Care Medicine, 207* (1), 69-76

- Time period for identification of disease progression in most trials is 2 years.

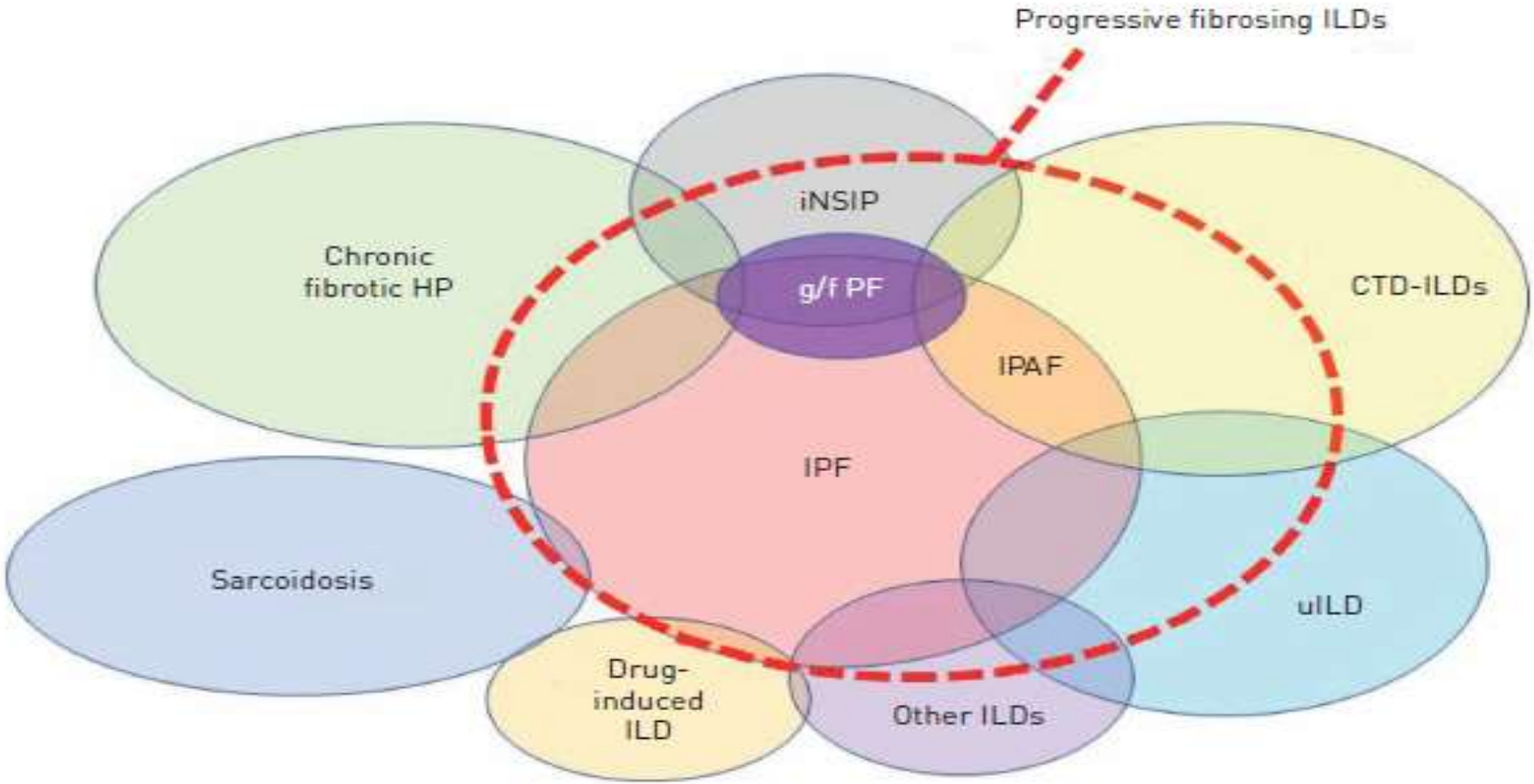
- However, if there is clear cut evidence that the disease is progressing at 3,6,9,12,24 or even 36 months, then one need not wait for the time period criteria to fulfil to call it as a progressive fibrotic ILD.

- The timelines for the criteria need not to be fulfilled to start treatment if the other criteria are clearly satisfied.

Cottin, V. et al, *American Journal of Respiratory and Critical Care Medicine, 206* (10), 1293-1294.

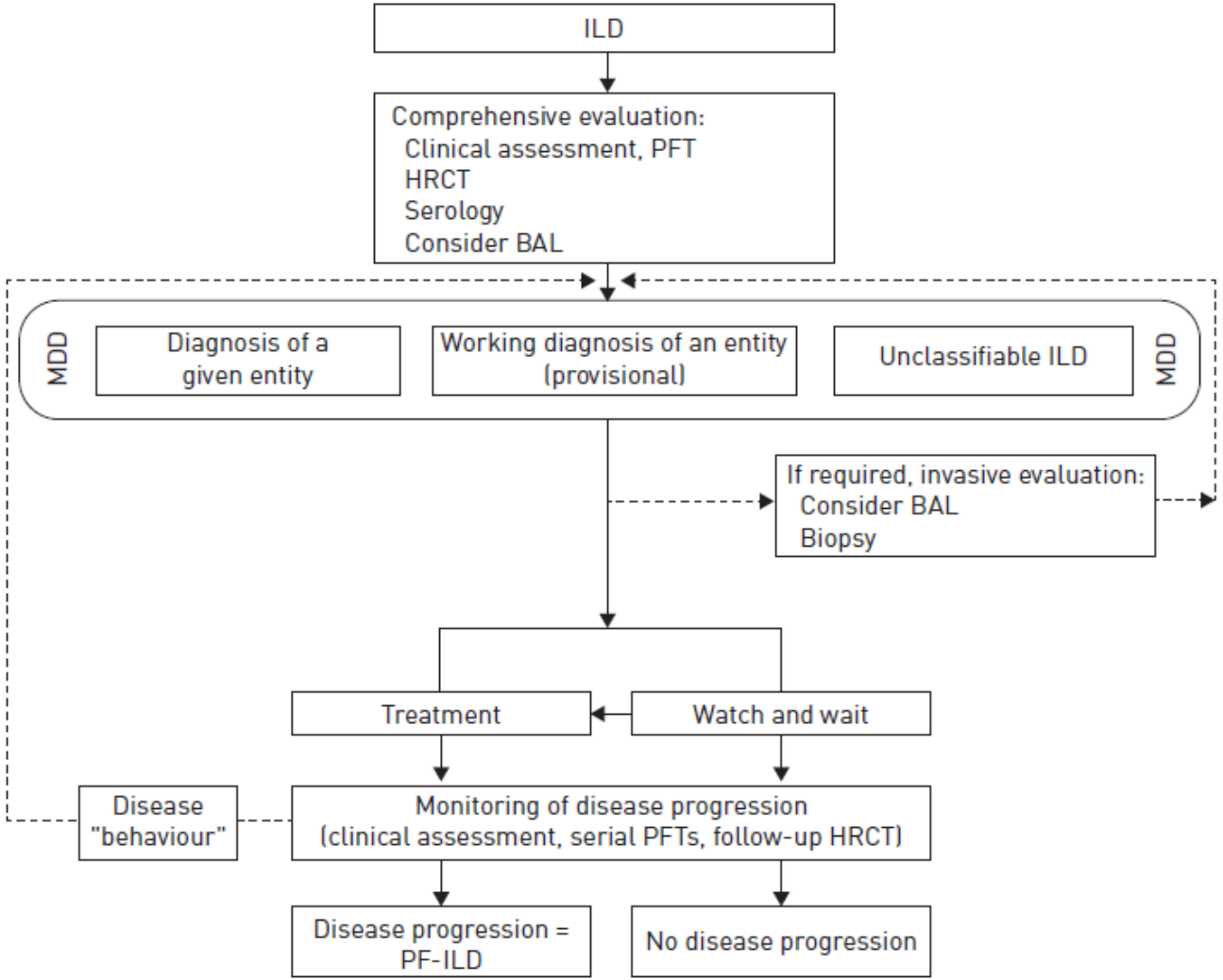
- Prevalence of PPF varies from 18 to 32% globally.
- Prevalence of CTD related ILD progressing to PF-ILD is more compared to other ILD(38.7%) ascertained from various studies.
- The incidence of PPF increases as the age increases.
- “Progression of ILD despite appropriate management qualifies the term “progressive pulmonary fibrosis”

Valenzuela C et al, Epidemiology and real-life experience in progressive pulmonary fibrosis. Curr Opin Pulm Med. 2022 ;1;28(5):407-413.
Rajan SK et al, Progressive pulmonary fibrosis: an expert group consensus statement. Eur Respir J. 2022 14:2103187.



Cottin V. Treatment of progressive fibrosing interstitial lung diseases: a milestone in the management of interstitial lung diseases. Eur Respir Rev. 2019 ;1;28(153):190109.

Overview of diagnosis



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

Risk factor for progression

Older age

Male sex

Lower baseline PFT

Radiographic honeycombing

UIP pattern of injury

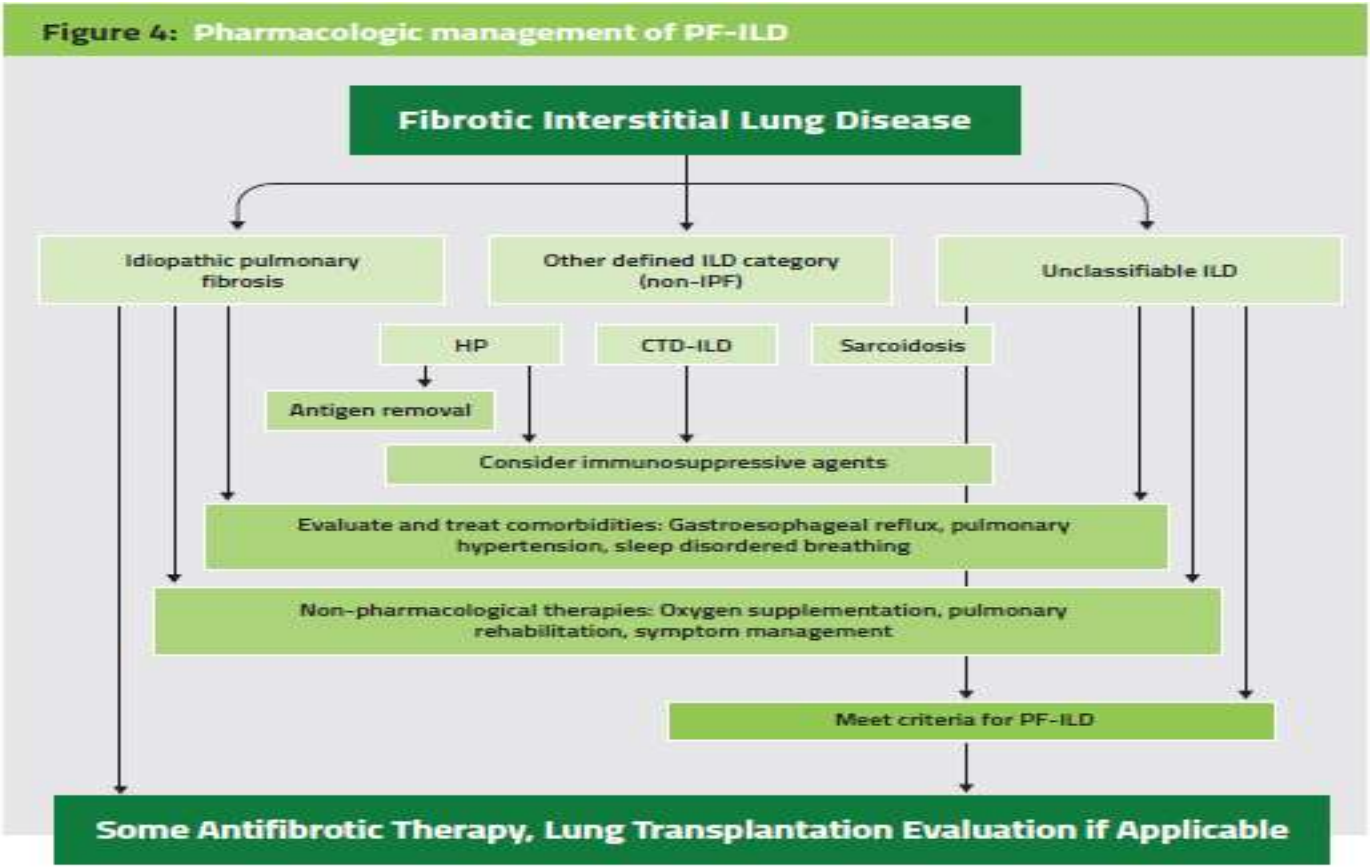
Smoking

Cottin V et. al., Eur Respir Rev 2018; 27: 180076
Copeland CR and Lancaster LH (2021) Management of Progressive Fibrosing Interstitial Lung Diseases (PF-ILD). Front. Med. 8:743977.

Treatment overview

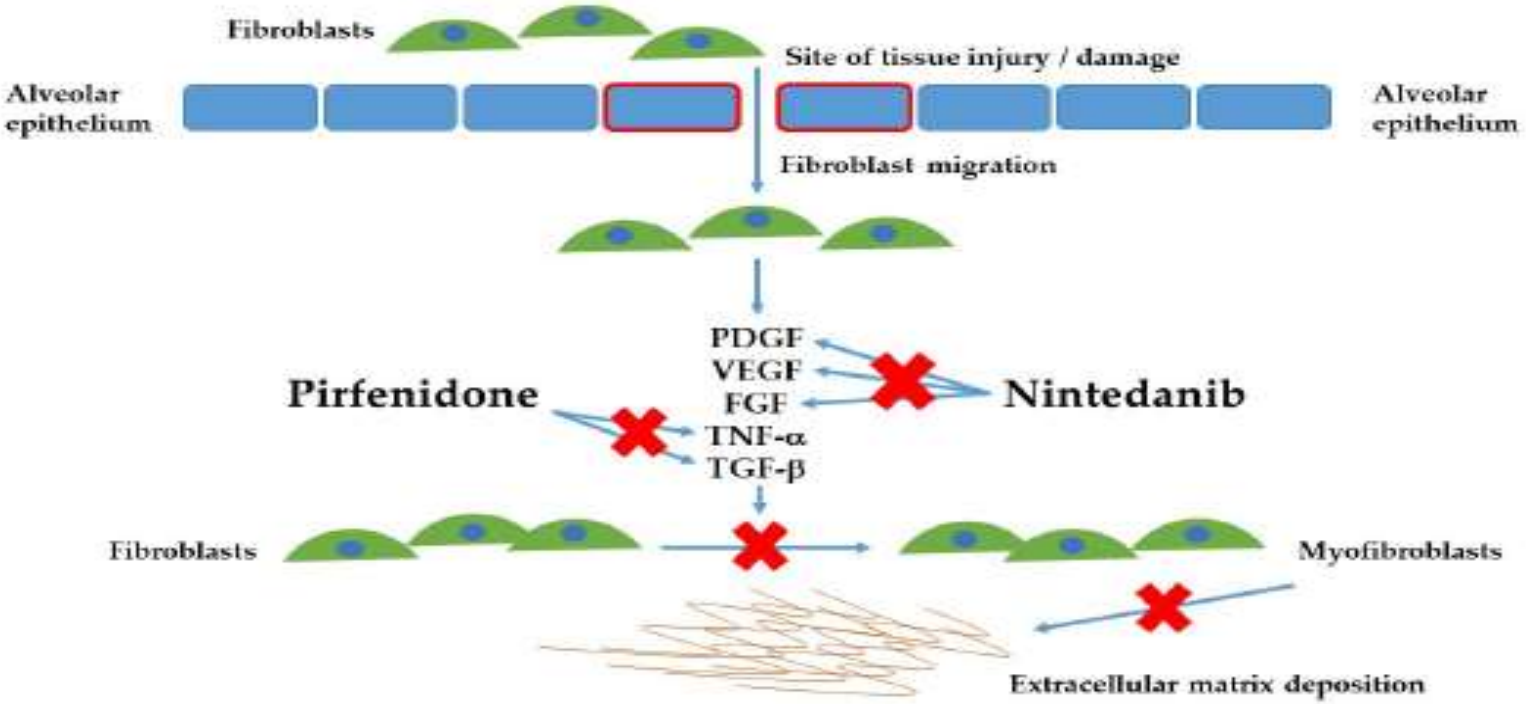
- **Pharmacological**
  - Antifibrotic agents – nintedanib, pirfenidone
  - Immunosupressants
  - Vasodilators
  - Anti-reflux therapy
- **Non-pharmacological**
  - Removal of triggers
  - Oxygen therapy
  - Lung transplantation
  - Vaccination – Influenzae, Pneumococcal vaccination.
  - Pulmonary rehabilitation

Copeland CR and Lancaster LH (2021) Management of Progressive Fibrosing Interstitial Lung Diseases (PF-ILD). Front. Med. 8:743977.
Ats Primer On Progressive Fibrosing Interstitial Lung Diseases



Ats Primer On Progressive Fibrosing Interstitial Lung Diseases

Antifibrotic agents



RESEARCH Open Access

Efficacy of antifibrotic drugs, nintedanib and pirfenidone, in treatment of progressive pulmonary fibrosis in both idiopathic pulmonary fibrosis (IPF) and non-IPF: a systematic review and meta-analysis

James Patrick Finnerty[1,2*], Aravind Ponnuswamy, Prosjenjit Dutta[1], Ammar Abdelaziz[3] and Hafiz Kamil[1]

Finnerty JP et al, Efficacy of antifibrotic drugs, nintedanib and pirfenidone, in treatment of progressive pulmonary fibrosis in both idiopathic pulmonary fibrosis (IPF) and non-IPF: a systematic review and meta-analysis. BMC Pulm Med. 2021 11;21(1):411.

- Total of 13 studies were included. 4 studies were that of non-IPF progressive fibrosis studies.
- 54%(1564/2872) in IPF population and 50%(647/1292) in the non-IPF population were on some immunosupressants.
- FVC decline were similar in the IPF and Non-IPF group. The overall effect size is <0.30.
- Mortality benefit was observed in the IPF group but was not observed in the Non-IPF group.

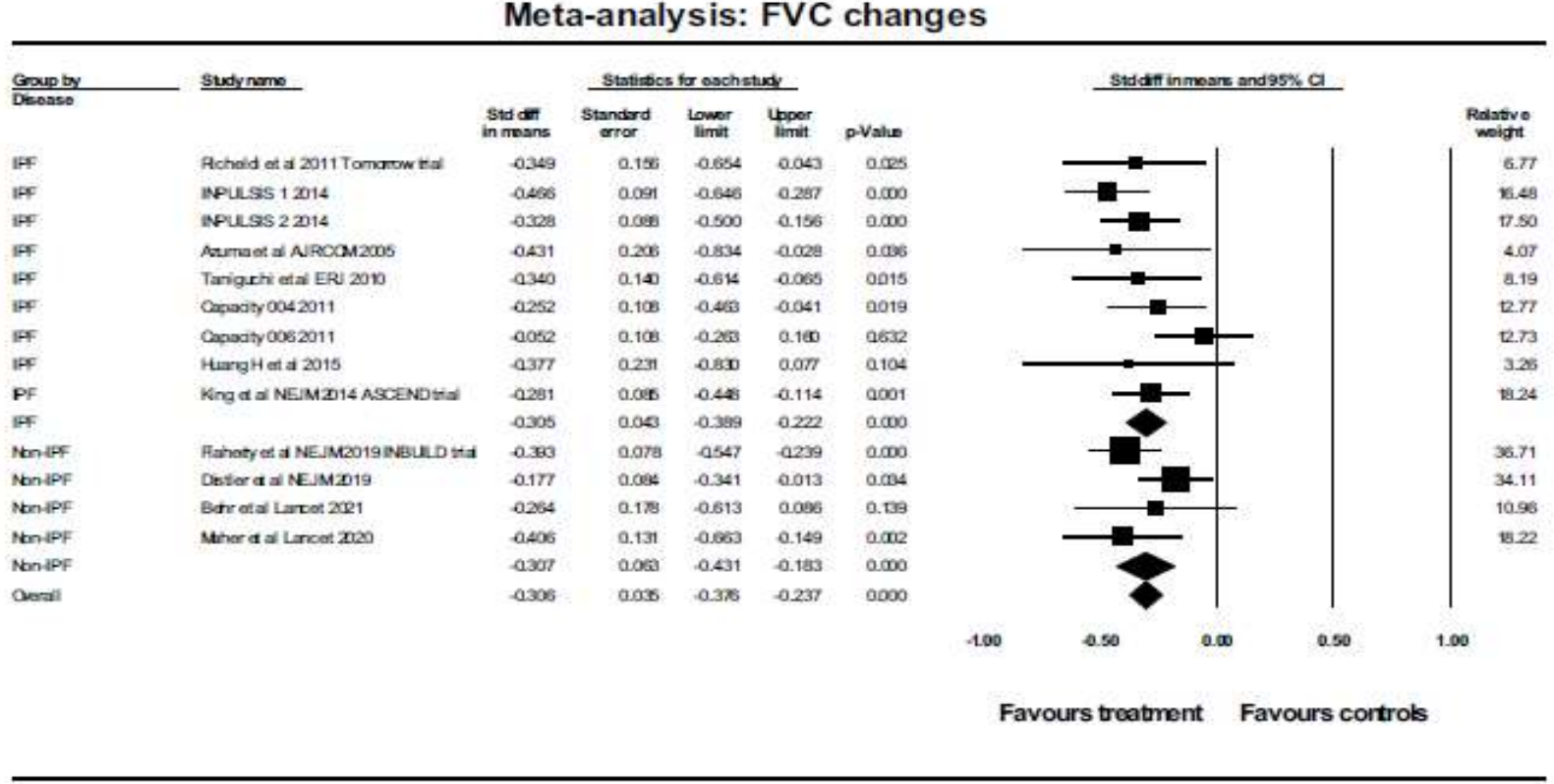


Fig. 4 Comparison of two groups of studies: IPF versus non-IPF for standardised FVC change in response to therapy

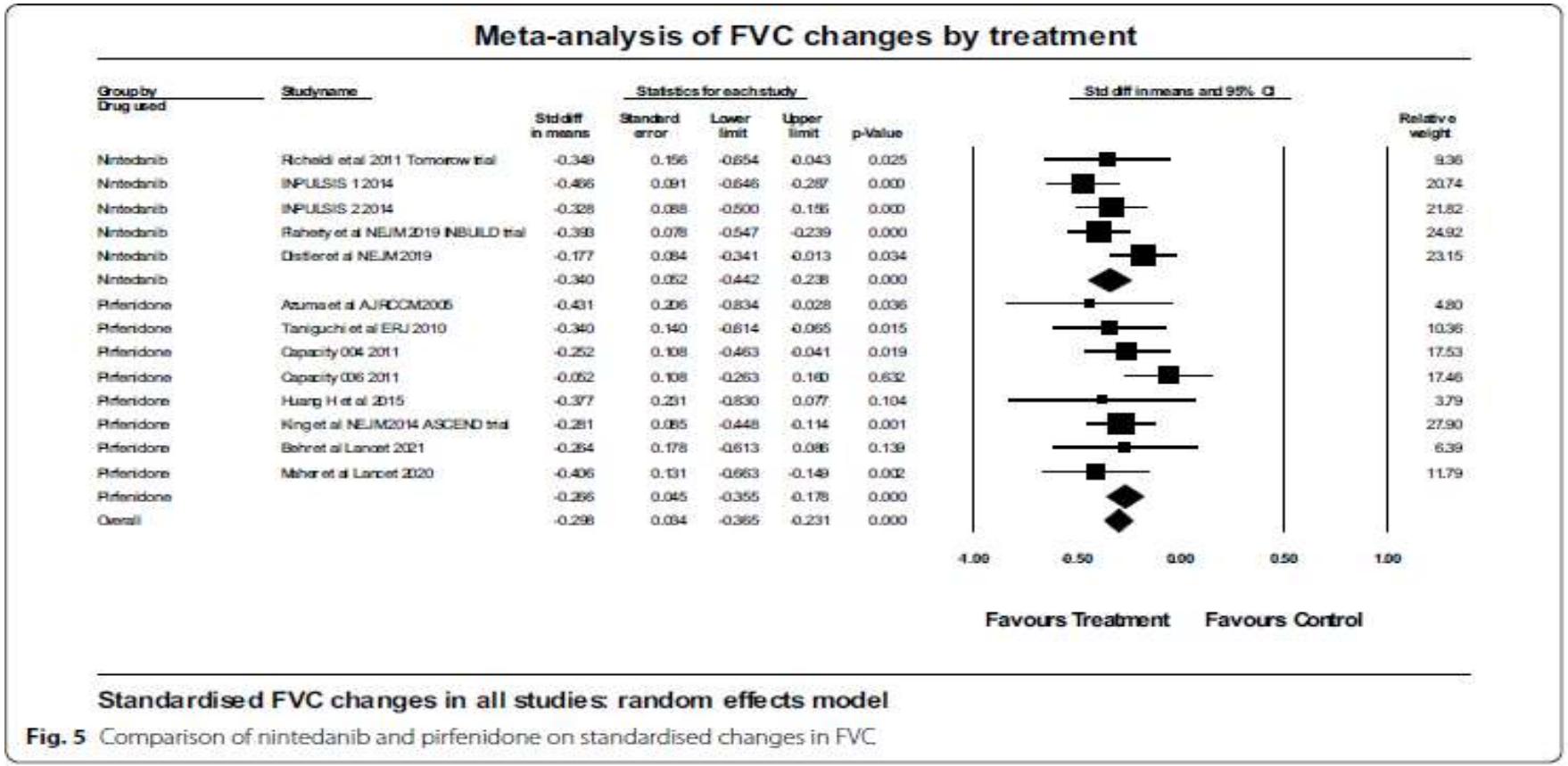


Fig. 5 Comparison of nintedanib and pirfenidone on standardised changes in FVC

Effect size with nintedanib was -0.34 and with pirfenidone was -0.26 with p value <0.001

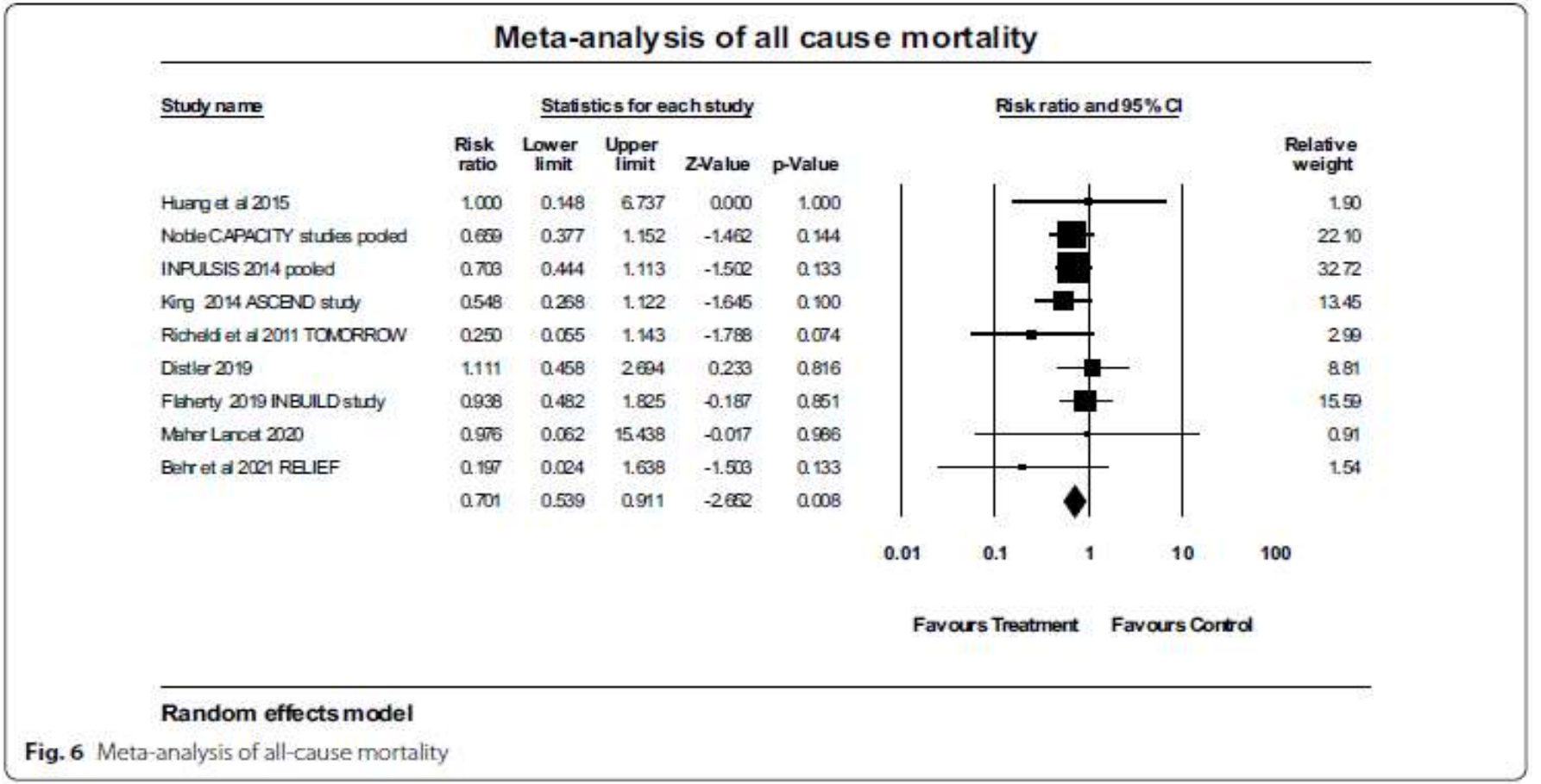


Fig. 6 Meta-analysis of all-cause mortality

Nintedanib

SYSTEMATIC REVIEWS

Nintedanib in Progressive Pulmonary Fibrosis

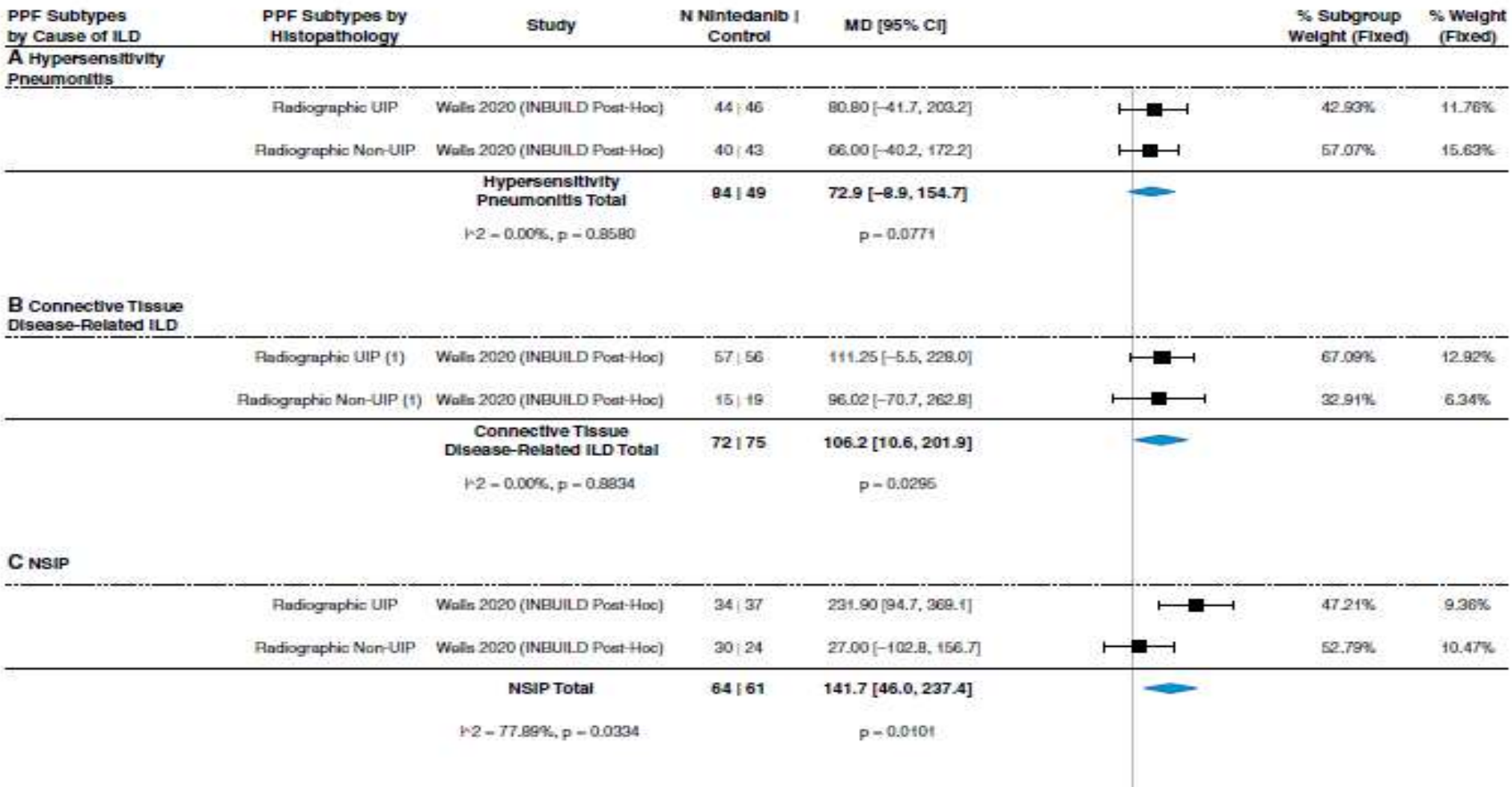
A Systematic Review and Meta-Analysis

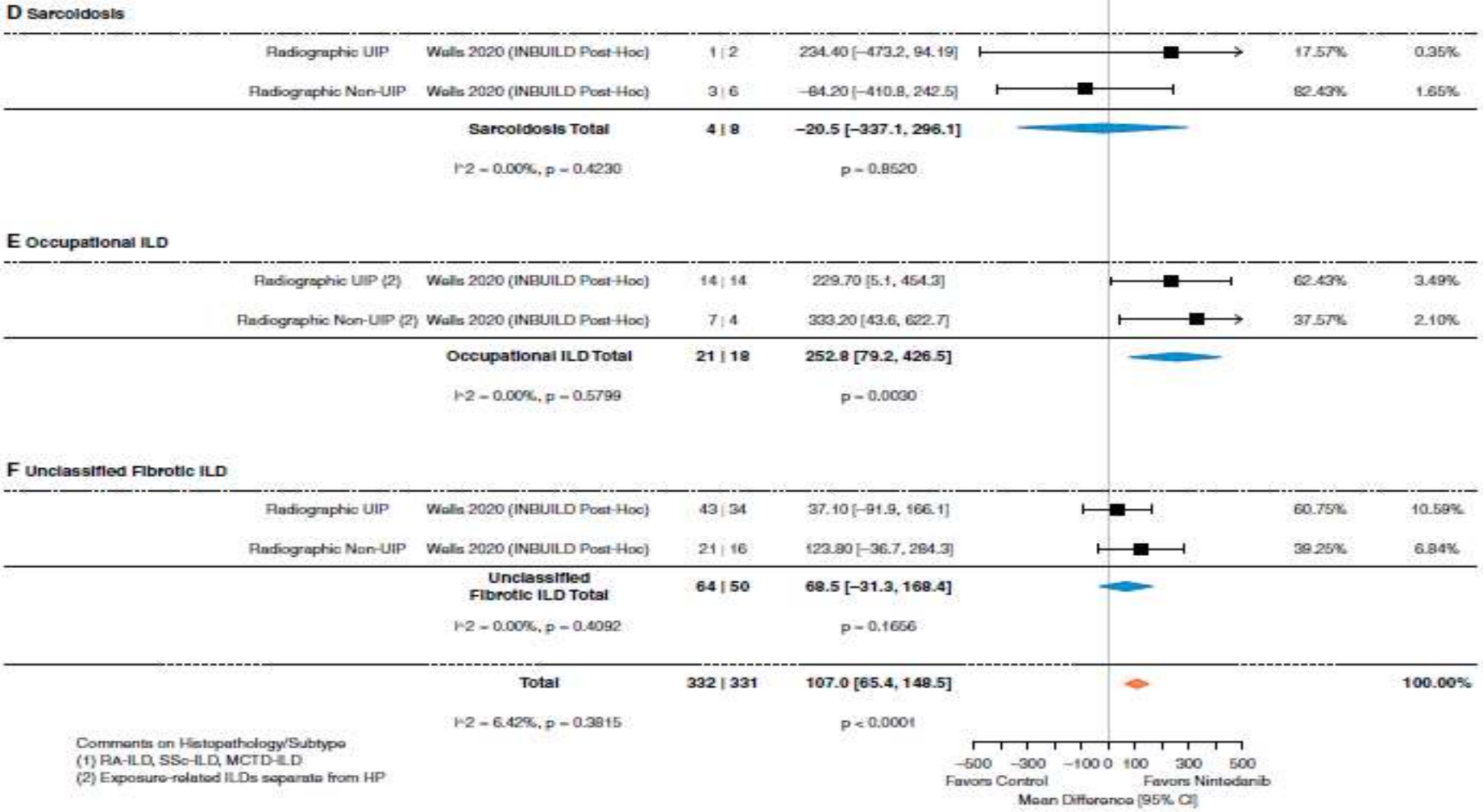
Marya Ghazipura[1,2], Manoj J. Mammen[3], Derrick D. Herman[4], Stephanie M. Hon[5], Brittany D. Bissell[6,7], Madalina Macrea[8], Fayez Kheir[9], Yet H. Khor[10,11], Shandra L. Knight[12], Ganesh Raghu[13], Kevin C. Wilson[14], and Tanzib Hossain[15]

Ghazipura, M. et al, *Annals of the American Thoracic Society, 19* (6), 1040-1049.

Study Name	Year	Location	Funding	Duration	PPF Diagnostic Criteria	ILD Subtypes	Study Population	Intervention	Comparator	Study Outcomes	Risk of Bias
Randomized, double-blind, placebo-controlled trial											
INBUILD (19)	2019	15 countries: Argentina, Belgium, Canada, Chile, China, France, Germany, Italy, Japan, Republic of Korea, Poland, Russian Federation, Spain, UK, USA 153 sites	Boehringer Ingelheim (Pharmaceutical Co.)	52 wk	Adults with fibrosing ILD other than IPF diagnosed by investigator AND presence in the 24 mo preceding study screening of: *1)* FVC predicted decline of at least 10%, or 2) FVC decline 5 to 9% with symptoms or increased fibrosis on HRCT, or *3)* Increased fibrosis on HRCT with worsened respiratory symptoms	*1)* UIP-like fibrotic pattern (definite or probable) of pulmonary fibrosis 2) Other, non-UIP-like fibrotic patterns of pulmonary fibrosis	Total Participants: 663 Intervention: 332 Placebo: 331 UIP-like Fibrotic Pattern of Pulmonary Fibrosis: 412	Nintedanib 150 mg 2 times daily	Placebo 1 tab 2 times daily	Primary: Annual rate of decline in FVC Secondary: *1)* K-BILD score change 2) Time to acute exacerbation *3)* Time to death (mortality) Adverse Events	Not serious
Post hoc analysis of randomized controlled trial											
Wells (22)	2020	15 countries *(as noted above)* 153 sites	Boehringer Ingelheim (Pharmaceutical Co.)	52 wk	Adults with fibrosing ILD other than IPF diagnosed by investigator AND presence in the 24 mo preceding study screening of: *1)* FVC predicted decline of at least 10%, or 2) FVC decline 5 to 9% with symptoms or increased fibrosis on HRCT, or *3)* Increased fibrosis on HRCT with worsened respiratory symptoms	*1)* Chronic HP 2) Autoimmune -RA-ILD -SSc-ILD -MCTD-ILD *3)* Idiopathic NSIP *4)* Unclassifiable IIP 5) Others -Sarcoidosis -Exposure-related	Total Participants: 663 Chronic HP 173 Autoimmune 170 Idiopathic NSIP 125 Unclassifiable IIP 114 Others 81	Nintedanib 150 mg 2 times daily	Placebo 1 tab 2 times daily	Annual rate of decline in FVC Adverse Events	Not Serious

Nintedanib
FVC: Rate of Change in FVC, mL/yr




D Sarcoidosis
Radiographic UIP
Wells 2020 (INBUILD Post-Hoc)
1 | 2
234.40 [−473.2, 94.19]
17.57%
0.35%
Radiographic Non-UIP
Wells 2020 (INBUILD Post-Hoc)
3 | 6
−84.20 [−410.8, 242.5]
82.43%
1.65%
Sarcoidosis Total
4 | 8
−20.5 [−337.1, 296.1]
I^2 = 0.00%, p = 0.4230
p = 0.8520
E Occupational ILD
Radiographic UIP (2)
Wells 2020 (INBUILD Post-Hoc)
14 | 14
229.70 [5.1, 454.3]
62.43%
3.49%
Radiographic Non-UIP (2)
Wells 2020 (INBUILD Post-Hoc)
7 | 4
333.20 [43.6, 622.7]
37.57%
2.10%
Occupational ILD Total
21 | 18
252.8 [79.2, 426.5]
I^2 = 0.00%, p = 0.5799
p = 0.0030
F Unclassified Fibrotic ILD
Radiographic UIP
Wells 2020 (INBUILD Post-Hoc)
43 | 34
37.10 [−91.9, 166.1]
60.75%
10.59%
Radiographic Non-UIP
Wells 2020 (INBUILD Post-Hoc)
21 | 16
123.80 [−36.7, 284.3]
39.25%
6.84%
Unclassified Fibrotic ILD Total
64 | 50
68.5 [−31.3, 168.4]
I^2 = 0.00%, p = 0.4092
p = 0.1656
Total
332 | 331
107.0 [65.4, 148.5]
100.00%
I^2 = 6.42%, p = 0.3815
p < 0.0001
Comments on Histopathology/Subtype
(1) RA-ILD, SSc-ILD, MCTD-ILD
(2) Exposure-related ILDs separate from HP
−500 −300 −100 0 100 300 500
Favors Control
Favors Nintedanib
Mean Difference [95% CI]

- Radiological UIP like pattern has better response to nintedanib than radiological non-UIP pattern.(2/3rd of 663 patients)

- Fibrotic HP, fibrotic sarcoidosis and unclassified ILD are poorly responsive to nintedanib (however the sample size of these ILD subtypes are small)

- Nintedanib does not have influence on time to first exacerbation or any mortality benefit.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nintedanib in Progressive Fibrosing Interstitial Lung Diseases

K.R. Flaherty et. Al.,N Engl J Med 2019;381:1718-27.

Study design	Inclusion criteria	Intervention	End points
Randomized double blinded control trial 15 countries 663 participants included	relative decline in FVC of at least 10% of predicted value, a relative decline in FVC of 5% to less than 10% of predicted value worsening of respiratory symptoms or an increased extent of fibrosis on high-resolution CT, worsening of respiratory symptoms and an increased extent of fibrosis FVC of at least 45% of the predicted value and a diffusing capacity of the lung for carbon monoxide (corrected for hemoglobin) of 30 to less than 80% of the predicted value	1:1 randomization to either placebo or nintedanib	PRIMARY ENDPOINT: FVC decline at 52 week SECONDARY END POINT: Absolute change from baseline in total score on K-BILD questionnaire at 52 wk Acute exacerbation of interstitial lung disease or death at 52 wk — no. with event/total no. (%) Death at 52 wk — no. with event/total no. (%)

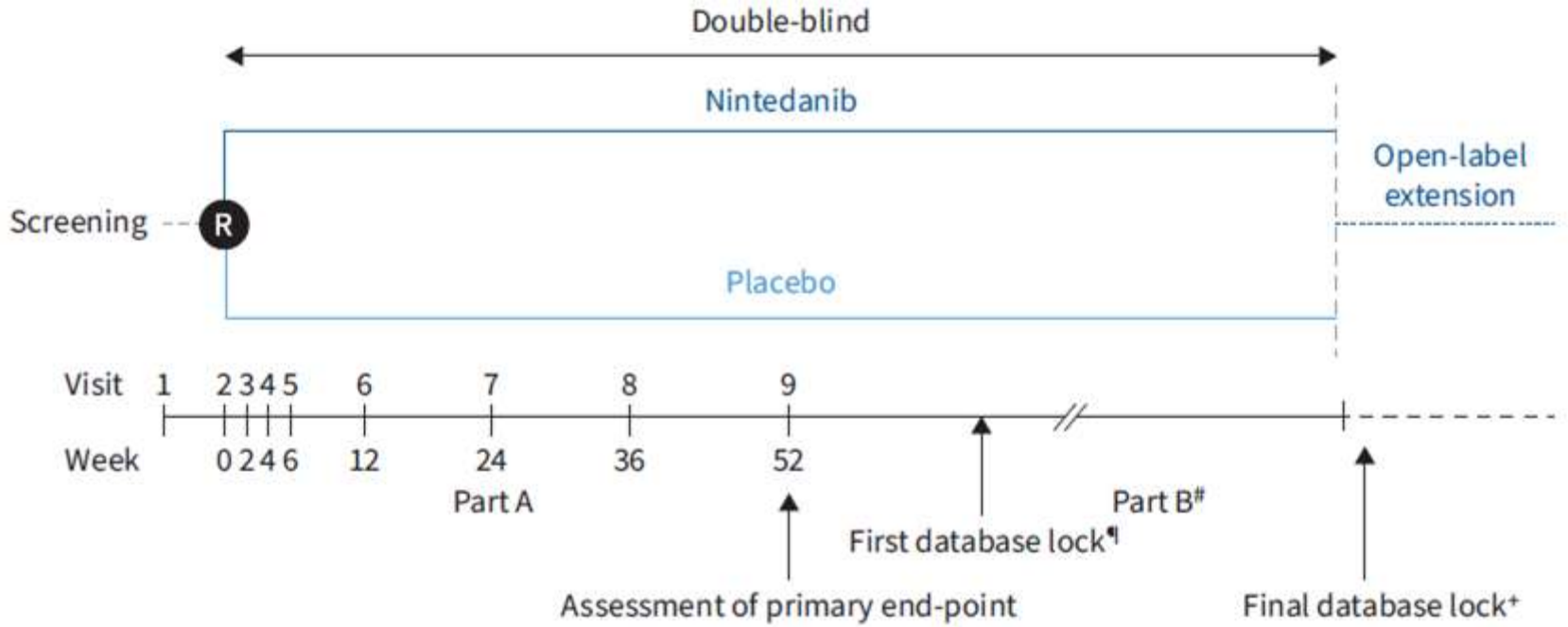


FIGURE 1 INBUILD trial design [4]. R: randomisation 1:1 stratified by high-resolution computed tomography pattern (usual interstitial pneumonia-like fibrotic pattern or other fibrotic patterns). #: visits occurred every 16 weeks until end of treatment; ¶: first database lock took place after the last subject had completed the week 52 visit; +: final database lock took place after all patients had completed the follow-up visit or entered the open-label extension study (INBUILD-ON).

Flaherty KR, et al. Nintedanib in progressive interstitial lung diseases: data from the whole INBUILD trial. Eur Respir J 2022; 59: 2004538

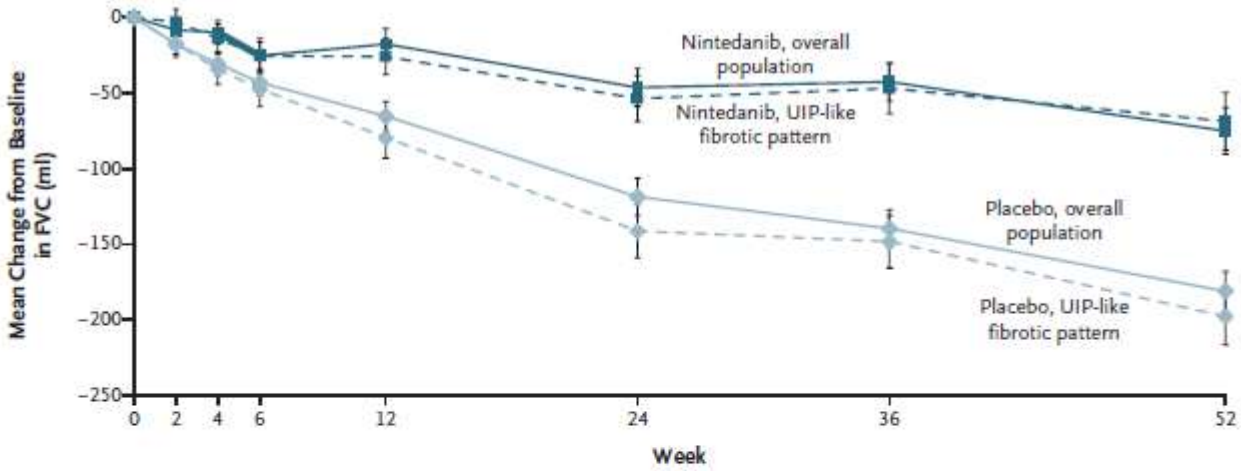
Table 1. Characteristics of the Overall Population at Baseline.*

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

Table 2. Efficacy End Points.*

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)§
Main secondary end points			
Absolute change from baseline in total score on K-BILD questionnaire at 52 wk¶			
Overall population	0.55±0.60	−0.79±0.59	1.34 (−0.31 to 2.98)§
Patients with a UIP-like fibrotic pattern	0.75±0.80	−0.78±0.79	1.53 (−0.68 to 3.74)§
Acute exacerbation of interstitial lung disease or death at 52 wk — no. with event/total no. (%)			
Overall population	26/332 (7.8)	32/331 (9.7)	0.80 (0.48 to 1.34)§
Patients with a UIP-like fibrotic pattern	17/206 (8.3)	25/206 (12.1)	0.67 (0.36 to 1.24)§
Death at 52 wk — no. with event/total no. (%)			
Overall population	16/332 (4.8)	17/331 (5.1)	0.94 (0.47 to 1.86)§
Patients with a UIP-like fibrotic pattern	11/206 (5.3)	16/206 (7.8)	0.68 (0.32 to 1.47)§
Additional end points assessed during period until first database lock			
Acute exacerbation of interstitial lung disease or death — no. with event/total no. (%)			
Overall population	41/332 (12.3)	59/331 (17.8)	0.68 (0.46 to 1.01)§
Patients with a UIP-like fibrotic pattern	28/206 (13.6)	44/206 (21.4)	0.61 (0.38 to 0.98)§
Death — no. with event/total no. (%)			
Overall population	27/332 (8.1)	38/331 (11.5)	0.70 (0.43 to 1.15)§
Patients with a UIP-like fibrotic pattern	20/206 (9.7)	31/206 (15.0)	0.63 (0.36 to 1.10)§

K-BILD – king's brief ILD questionnaire



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

Figure 2. Decline from Baseline in Forced Vital Capacity (FVC).

Shown is the observed mean change from baseline in FVC over the 52-week trial period in the overall population and in patients with an imaging pattern of usual interstitial pneumonia (UIP) on high-resolution computed tomography in the nintedanib group and the placebo group. The I bars indicate the standard error.

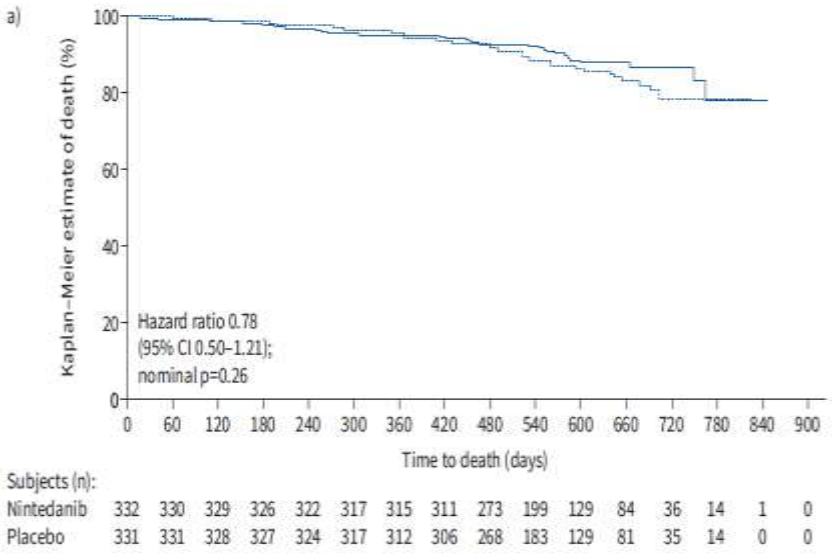
TABLE 1 Time to absolute and relative declines in forced vital capacity (FVC) ⩾5% predicted or ⩾10% predicted using data up to the final database lock in the INBUILD trial

	Overall population		Subjects with UIP-like fibrotic pattern on HRCT	
	Nintedanib (n=332)	Placebo (n=331)	Nintedanib (n=206)	Placebo (n=206)
Absolute decline in FVC ⩾5% predicted	217 (65.4)	263 (79.5)	137 (66.5)	168 (81.6)
Hazard ratio (95% CI)	0.67 (0.56–0.81)		0.64 (0.51–0.80)	
Nominal p-value	<0.0001		<0.0001	
Relative decline in FVC ⩾5% predicted	245 (73.8)	285 (86.1)	152 (73.8)	178 (86.4)
Hazard ratio (95% CI)	0.71 (0.60–0.84)		0.69 (0.55–0.86)	
Nominal p-value	<0.0001		0.0006	
Absolute decline in FVC ⩾10% predicted	114 (34.3)	160 (48.3)	77 (37.4)	99 (48.1)
Hazard ratio (95% CI)	0.64 (0.50–0.81)		0.69 (0.51–0.93)	
Nominal p-value	0.0002		0.0138	
Relative decline in FVC ⩾10% predicted	161 (48.5)	221 (66.8)	101 (49.0)	140 (68.0)
Hazard ratio (95% CI)	0.63 (0.51–0.77)		0.61 (0.47–0.79)	
Nominal p-value	<0.0001		0.0001	

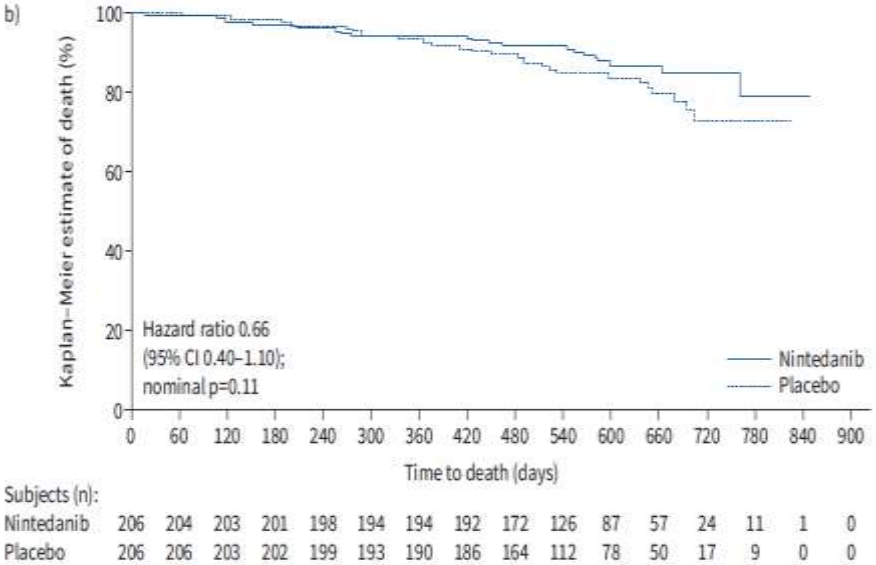
Data are presented as n (%), unless otherwise stated. HRCT: high-resolution computed tomography; UIP: usual interstitial pneumonia.

Flaherty KR, et al. Nintedanib in progressive interstitial lung diseases: data from the whole INBUILD trial. Eur Respir J 2022; 59: 2004538

Kaplan meier curve analysis



- Overall population



- UIP- pattern population

Table 3. Adverse Events in the Overall Population.*

Event	Nintedanib (N = 332)	Placebo (N = 331)
	no. of patients (%)	
Adverse event		
Any	317 (95.5)	296 (89.4)
Any except for progression of interstitial lung disease†	317 (95.5)	295 (89.1)
Most frequent adverse events‡		
Diarrhea	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)
Dyspnea	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)
Alanine aminotransferase increased	43 (13.0)	12 (3.6)
Progression of interstitial lung disease†	16 (4.8)	39 (11.8)
Weight loss	41 (12.3)	11 (3.3)
Aspartate aminotransferase increased	38 (11.4)	12 (3.6)
Abdominal pain	34 (10.2)	8 (2.4)
Severe adverse event§	60 (18.1)	73 (22.1)
Serious adverse event¶	107 (32.2)	110 (33.2)
Fatal adverse event		
Any	11 (3.3)	17 (5.1)
Any except for progression of interstitial lung disease†	10 (3.0)	14 (4.2)
Adverse event leading to treatment discontinuation	65 (19.6)	34 (10.3)
Adverse event leading to permanent dose reduction	110 (33.1)	14 (4.2)

Dose: 150 mg twice daily, in case of adverse effects it can be reduced to 100 mg twice daily

Adverse effects: most commonly diarrhoea and deranged liver function tests.

SYSTEMATIC REVIEWS

Pirfenidone in Progressive Pulmonary Fibrosis

A Systematic Review and Meta-Analysis

Marya Ghazipura[1,2], Manoj J. Mammen[3], Brittany D. Bissell[4,5], Madalina Macrea[6], Derrick D. Herman[7], Stephanie M. Hon[8], Fayez Kheir[9], Yet H. Khor[10,11], Shandra L. Knight[12], Ganesh Raghu[13], Kevin C. Wilson[14], and Tanzib Hossain[15]

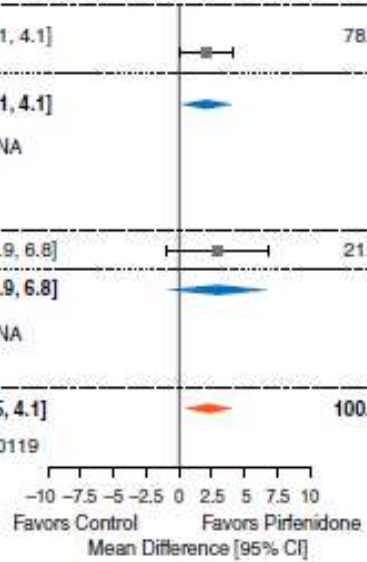
Ghazipura M et al, Pirfenidone in Progressive Pulmonary Fibrosis: A Systematic Review and Meta-Analysis. Ann Am Thorac Soc. 2022;19(6):1030-1039..

- Included 2 studies (RELIEF trial and uILD). Total patients included – 380.
- Studies did not perform subgroup analysis of ILD subtypes for the outcomes neither differentiated the radiological pattern into UIP or non-UIP pattern.
- RELIEF trial which ended prematurely due to slow recruitment (because of strict enrolment criteria) has many imputed values, which makes the study as low evidence based.
- There were no mortality benefit found in this meta-analysis with pirfenidone (sample size small, follow up period is less).

Study (Reference)	Year	Location	Funding	Duration	PPF Diagnostic Criteria	ILD Subtypes	Study Population	Intervention	Comparator	Study Outcomes	Risk of Bias
Maher (21)	2020	Fourteen countries: Australia, Belgium, Canada, Czech Republic, Denmark, Germany, Greece, Ireland, Israel, Italy, Poland, Portugal, Spain, and UK	F. Hoffmann, La Roche Pharmaceutical Co.	24 wk	Adults with fibrosing unclassifiable ILD other than IPF *and* the presence of *1*) FVC predicted decline of at least 5% in the 12 mo preceding enrollment or *2*) significant symptomatic worsening not due to other causes as determined by the investigator in the 6 mo preceding enrollment	Unclassifiable	Total patients: 253; intervention: 127; placebo: 126	Pirfenidone, 801 mg three times daily (2,403 mg total daily)	Placebo, three tablets three times daily	Primary: predicted mean change in the FVC as measured by using home spirometry *(unable to analyze because of variability)*. Secondary: *1*) Change in the FVC predicted as measured by using site spirometry, *2*) 5% FVC decline, *3*) 10% FVC decline, *4*) D_{LCO}, *5*) 6MWD, *6*) UCSD-SOBQ score, *7*) LCQ score, *8*) cough VAS, *9*) SGRQ score, *10*) hospital admission, *11*) acute exacerbation, *12*) progression-free survival, and *13*) time to death; *adverse events*	Not serious
RELIEF (19)	2021	Germany, 17 Sites	German Center for Lung Research and Roche Pharmaceuticals	48 wk	Adults with diagnosed fibrosing ILD other than IPF *and* annual FVC decline of at least 5% predicted assessed by at least three FVC measurements in the 6–24 mo preceding enrollment	*1*) Chronic (fibrotic) HP; *2*) collagen vascular (connective tissue) disease–related RA, SSc, Sjogren syndrome, PM or DM, or MCTD; *3*) NSIP; and *4*) asbestosis-induced lung fibrosis; *results were not reported by subtypes because of small sample sizes*	Total patients: 127; intervention: 64; placebo: 63; stopped because of futility triggered by slow recruitment *(36.5% of intended 374 enrolled)*	Pirfenidone, 534 to 801 mg three times daily (up to 2,403 mg daily)	Placebo, three tablets three times daily	Primary: absolute change in the FVC% predicted from baseline; Secondary: *1*) D_{LCO}, *2*) exercise capacity as measured by using the 6MWD; *3*) time to clinical deterioration; *4*) progression-free survival; *5*) FVC change of at least 5% predicted; *6*) FVC change of at least 10% predicted; and *7*) quality of life as measured by using the SGRQ; *adverse events*	Not Serious*

Pirfenidone
FVC: Mean Change FVC, % Predicted

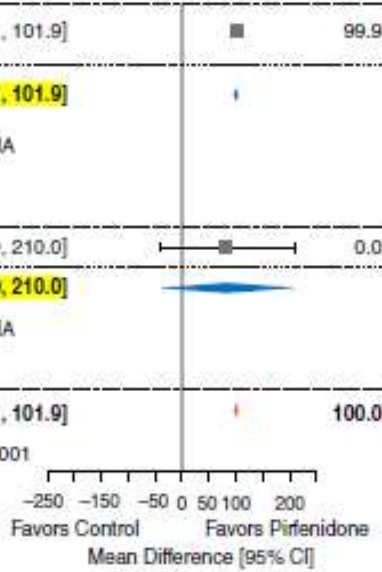
PPF Subtypes by Cause of ILD	Radiographic UIP Pattern	Study	Follow-Up Period	Dosage	N Pirfenidone | Control	MD [95% CI]	% Weight (Random)
A) Unclassified Fibrotic ILD							
	Radiographic Non-UIP	Maher 2020	24 Weeks	Oral 2403 mg/day	127 | 126	2.10 [0.1, 4.1]	78.86%
		Unclassified Fibrotic ILD Total			**127 | 126**	**2.10 [0.1, 4.1]**	
		I^2 = NA, p = NA				p = NA	
B) Other Cause (1)							
	Unspecified UIP	RELIEF 2020	48 Weeks	534–801mg 3x/day	35 | 32	2.97 [–0.9, 6.8]	21.14%
		Other Cause Total			**35 | 32**	**2.97 [–0.9, 6.8]**	
		I^2 = NA, p = NA				p = NA	
		Total			**162 | 158**	**2.3 [0.5, 4.1]**	**100.00%**
		I^2 = 0.00%, p = 0.6958				p = 0.0119	



Comments on ILD Subtype
(1) Collagen/Vascular Disease, Fibrotic Non-Specific Interstitial Pneumonia, Hypersensitivity Pneumonitis and Asbestosis, FVC of 40–90% Predicted, DLCO of 10–90% Predicted, and an Annual Decline of FVC ≥ 5% Predicted

Pirfenidone
FVC: Mean Change FVC, mL

PPF Subtypes by Cause of ILD	Radiographic UIP Pattern	Study	Follow-Up Period	Dosage	N Pirfenidone | Control	MD [95% CI]	% Weight (Random)
A) Unclassified Fibrotic ILD							
	Radiographic Non-UIP	Maher 2020	24 Weeks	Oral 2403 mg/day	127 | 126	100.0 [98.1, 101.9]	99.98%
		Unclassified Fibrotic ILD Total			**127 | 126**	**100.0 [98.1, 101.9]**	
		I^2 = NA, p = NA				p = NA	
B) Other Cause (1)							
	Unspecified UIP	RELIEF 2020	48 Weeks	531–801 mg 3x/day	35 | 32	80.0 [–40.0, 210.0]	0.02%
		Other Cause Total			**35 | 32**	**80.0 [–40.0, 210.0]**	
		I^2 = NA, p = NA				p = NA	
		Total			**162 | 158**	**100.0 [98.1, 101.9]**	**100.00%**
		I^2 = 0.00%, p = 0.7539				p < 0.0001	



Comments on ILD Subtype
(1) Collagen/Vascular Disease, Fibrotic Non-Specific Interstitial Pneumonia, Hypersensitivity Pneumonitis and Asbestosis, FVC of 40–90% Predicted, DLCO of 10–90% Predicted, and an Annual Decline of FVC ≥ 5% Predicted

Table 2. Pirfenidone in PPF: critical outcomes summary

ILD Subset	FVC% Predicted MD (95% CI); Arm Favored; Evidence Quality	FVC MD (95% CI) (*ml*); Arm Favored; Evidence Quality	FVC Decline >5% RR (95% CI); Arm Favored; Evidence Quality	FVC Decline >10% RR (95% CI); Arm Favored; Evidence Quality	Mortality RR (95% CI); Arm Favored; Evidence Quality
All patients with PPF (pirfenidone = 162, control = 158)	2.3 (0.5–4.1)*; pirfenidone; very low	100.0 (98.1–101.9)*; pirfenidone; very low	0.63 (0.48–0.83)*; pirfenidone; low	0.53 (0.31–0.88)*; pirfenidone; low	0.20 (0.02–1.64); neither; low
Radiographic UIP	N/A	N/A	N/A	N/A	N/A
Radiographic non-UIP	N/A	N/A	N/A	N/A	N/A
Fibrotic HP	N/A	N/A	N/A	N/A	N/A
Fibrotic CTD–related	N/A	N/A	N/A	N/A	N/A
Fibrotic idiopathic NSIP	N/A	N/A	N/A	N/A	N/A
Fibrotic sarcoidosis	N/A	N/A	N/A	N/A	N/A
Fibrotic occupational	N/A	N/A	N/A	N/A	N/A
Unclassified fibrotic (pirfenidone = 127, control =124)	2.10 (0.09–4.11)*; pirfenidone; low	100.0 (98.1–101.9)*; pirfenidone; low	0.63 (0.48–0.83)*; pirfenidone; low	0.53 (0.31–0.88)*; pirfenidone; low	N/A

Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial

Jurgan behr et al, *Lancet Respir Med 2021; 9: 476–86*

Study design	Inclusion criteria	Intervention	End points
Randomized double blinded placebo controlled multicentre trial 127 participants included	Adults 18-80 years of age Diagnosis of connective tissue diseaseassociated-ILD, fibrotic non-specific interstitial pneumonia, chronic hypersensitivity pneumonitis, or asbestos-induced lung fibrosis DLCO 25% to 75%(amended 10 to 90%) FVC 40% to 90% predicted	1:1 randomization to either placebo or pirfenidone	PRIMARY ENDPOINT: Absolute change in percentage of predicted FVC from baseline to week 48

Secondary End Point:

progression-free survival

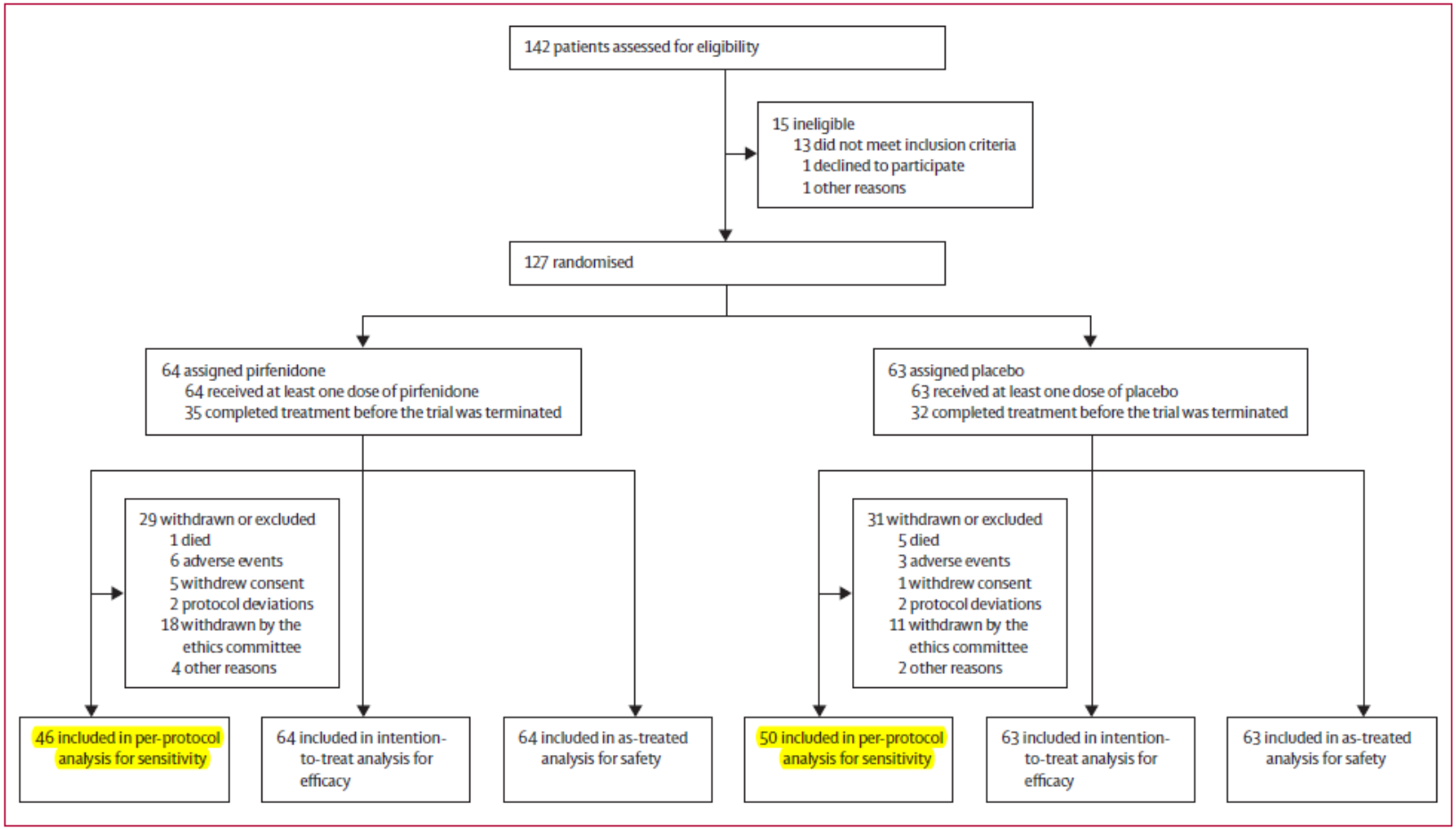
Categorical assessment of relative changes from baseline to week 48 in predicted FVC of less than 5%, 5% to less than 10%, and atleast 10%

DLco

Exercise capacity (6-min walk distance
[6MWD])

Quality of life (St George's Respiratory Questionnaire [SGRQ]), time to clinical deterioration

Safety (frequencies of adverse events and serious adverse events).


142 patients assessed for eligibility
15 ineligible
13 did not meet inclusion criteria
1 declined to participate
1 other reasons
127 randomised
64 assigned pirfenidone
64 received at least one dose of pirfenidone
35 completed treatment before the trial was terminated
63 assigned placebo
63 received at least one dose of placebo
32 completed treatment before the trial was terminated
29 withdrawn or excluded
1 died
6 adverse events
5 withdrew consent
2 protocol deviations
18 withdrawn by the ethics committee
4 other reasons
31 withdrawn or excluded
5 died
3 adverse events
1 withdrew consent
2 protocol deviations
11 withdrawn by the ethics committee
2 other reasons
46 included in per-protocol analysis for sensitivity
64 included in intention-to-treat analysis for efficacy
64 included in as-treated analysis for safety
50 included in per-protocol analysis for sensitivity
63 included in intention-to-treat analysis for efficacy
63 included in as-treated analysis for safety

	Pirfenidone (n=64)	Placebo (n=63)
Age, years	63·2 (10·6)	63·5 (9·1)
Sex		
Men	43 (67%)	32 (51%)
Women	21 (33%)	31 (49%)
Supplemental O_2 at rest	14 (22%)	20 (32%)
Flow rate at rest, L/min	2·2 (0·9)*	2·3 (0·8)†
FVC, % predicted	62·6 (14·5)	62·2 (13·5)
FEV_1, % predicted	68·1 (15·4)	64·4 (14·3)
DLCO, % predicted	38·1 (14·1)	37·7 (14·2)
FEV_1/FVC ratio	86·7 (6·9)	83·8 (7·7)
6MWD, m	357·7 (99·2)	345·2 (110·0)
Any steroid or immunosuppressant therapy	47 (73%)	56 (89%)
Steroid monotherapy	17 (27%)	31 (49%)
Combination therapy with steroids	23 (36%)	22 (35%)
Azathioprine	11 (17%)	11 (18%)
Mycophenolate	7 (11%)	6 (10%)

Data are mean (SD) or n (%). DLCO=diffusing capacity of the lung for carbon monoxide. FVC=forced vital capacity. 6MWD=6-min walk distance. *n=14. †n=20.

***Table 1*: Baseline demographic characteristics in the safety analysis population**

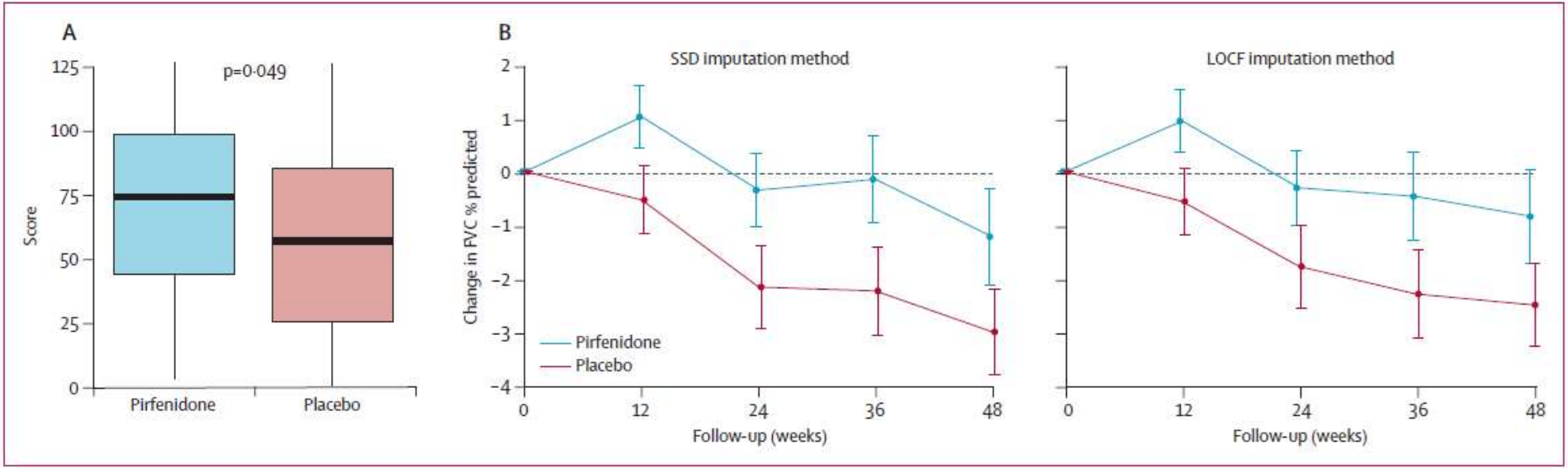


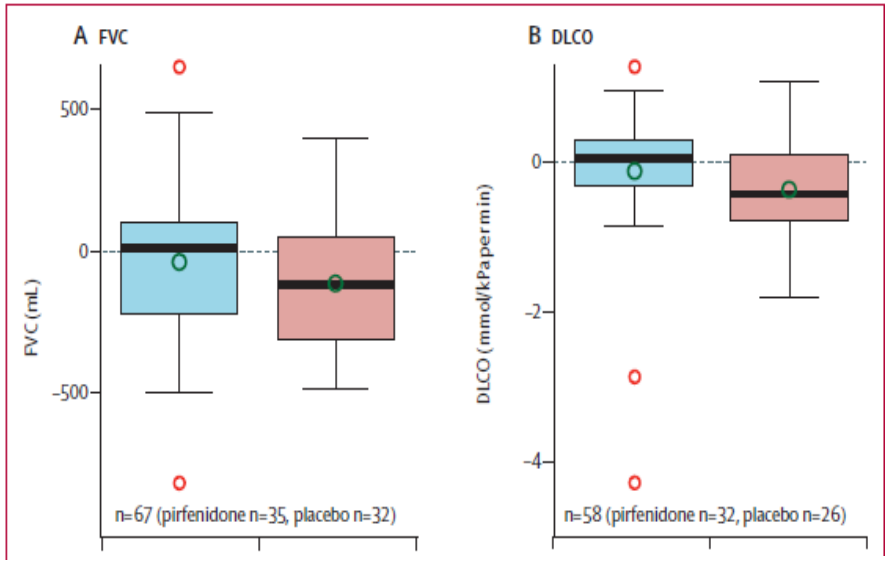
Figure 2: **Absolute change in percentage of predicted FVC and time course for mean change in percentage of predicted FVC from baseline to week 48**

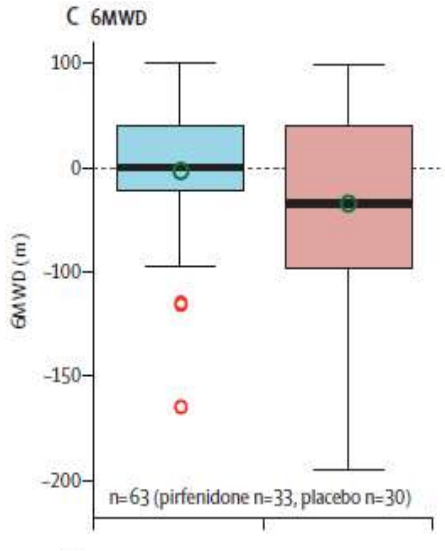
(A) Distribution of Wilcoxon scores (from Mann-Whitney *U* test) for the absolute change in percentage of predicted FVC (FVC % predicted) from baseline to week 48 in the intention-to-treat population (n=127) for the pirfenidone and placebo groups (using the prespecified SSD imputation method for missing data, with deaths ranked worst). (B) Mean changes from baseline in FVC % predicted (SE) over the 48-week trial period in the pirfenidone and placebo groups after imputation of missing values (including those of deceased patients) according to the prespecified SSD method or, alternatively, the post-hoc LOCF imputation method. FVC=forced vital capacity. LOCF=last observation carried forward. SSD=sum of squared differences.

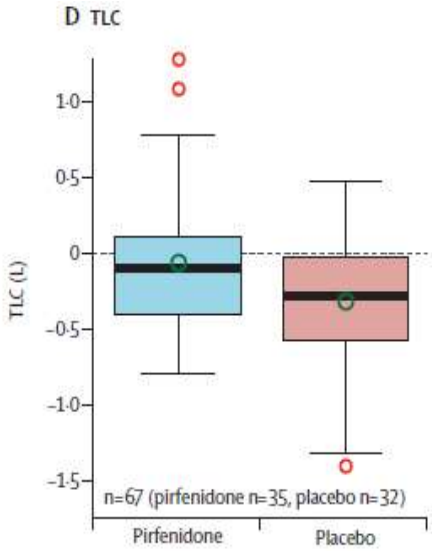
	Baseline				Change from baseline to week 48: within groups				Change from baseline to week 48: pirfenidone vs placebo	p value
	n	Pirfenidone	n	Placebo	n	Pirfenidone	n	Placebo		
FVC, mL	64	2332·5 (798·9)	63	2123·0 (715·7)	35	−36·6 (281·5)	32	−114·4 (225·3)	80·0 (−40·0 to 210·0)	0·21
DLCO, mmol/kPa per min	64	3·4 (1·4)	63	3·2 (1·2)	32	−0·1 (1·0)	26	−0·4 (0·6)	0·4 (0·1 to 0·7)	0·023
6MWD, m	64	357·7 (99·2)	63	345·2 (110·0)	33	−2·7 (74·2)	30	−34·1 (91·0)	28·0 (−15·0 to 75·0)	0·15
TLC, L	64	4·1 (1·2)	63	4·0 (1·0)	35	−0·1 (0·5)	32	−0·3 (0·4)	0·2 (0·0 to 0·4)	0·089
FEV_1, mL	64	2004·2 (636·2)	63	1761·7 (552·2)	35	−76·9 (259·3)	32	−103·1 (182·1)	50·0 (−50·0 to 140·0)	0·27

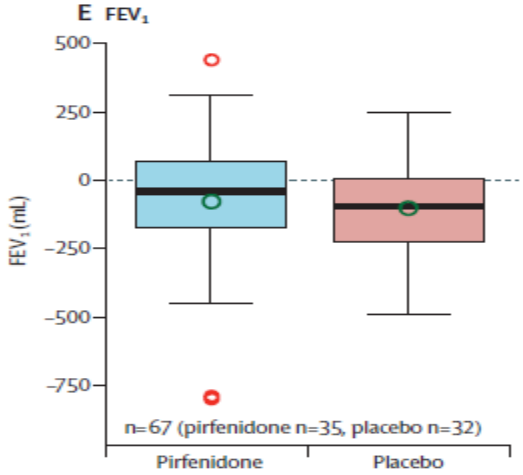
All analyses were done without imputation of missing values. Data are means (SD) at baseline, mean absolute changes (SD) from baseline to week 48, Hodges-Lehmann estimates for median differences (asymptotic 95% CIs) between pirfenidone and placebo, and two-sided p values from Mann-Whitney *U* tests. Note that FVC, TLC, and FEV_1 were assessed in post-hoc analyses. DLCO=diffusing capacity of the lung for carbon monoxide. FVC=forced vital capacity. TLC=total lung capacity. 6MWD=6-min walk distance.

Table 2: **Absolute changes in lung function and exercise capacity from baseline to week 48**


A FVC
FVC (mL)
500
0
-500
n=67 (pirfenidone n=35, placebo n=32)
B DLCO
DLCO (mmol/kPa per min)
0
-2
-4
n=58 (pirfenidone n=32, placebo n=26)


C 6MWD
6MWD (m)
100
0
-100
-150
-200
n=63 (pirfenidone n=33, placebo n=30)


D TLC
TLC (L)
1·0
0·5
0
-0·5
-1·0
-1·5
n=67 (pirfenidone n=35, placebo n=32)
Pirfenidone
Placebo


E FEV1
FEV1 (mL)
500
250
0
-250
-500
-750
n=67 (pirfenidone n=35, placebo n=32)
Pirfenidone
Placebo

- This trial ended prematurely due to strict enrolment criteria.
- Missing values are imputed for the analysis of outcomes. Therefore the evidence is low based.
- More study participants were on immunosupressants in baseline compared to that of INBUILD trial.
- FVC decline in pirfenidone group has not achieved a statistically significant value due to the above reason (p value >0.05).

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

Multicentre, double blind randomized placebo controlled phase 2 trial.

253 patients were included.

Duration was 24 weeks.

Maher et al, the lancet 2020; 8; P147-17

Inclusion Criteria:

Age 18 -85 years.

Fibrosing unclassifiable ILD as diagnosis after multidisciplinary discussion

Predicted FVC >45%

Predicted DLco >30%

>10% fibrosis in HRCT chest in previous 12 months

6 min walk test of minimum 150 metres

FEV1/FVC ratio >0.7

Progressive disease (>5% absolute decline in percent predicted FVC or symptomatic worsening not due to cardiac, pulmonary(other than disease progression) vascular or other causes

End point

Primary endpoint:

Predicted mean change in FVC from baseline over 24 weeks (daily home spirometry)

Secondary endpoint:

Change in FVC from baseline measured by spirometry during clinic visits.

Proportion of patients having >5% or >10% absolute or relative decline in %predicted FVC(site spirometry)

Change in %predicted DLco from baseline

Change in 6MWD from baseline

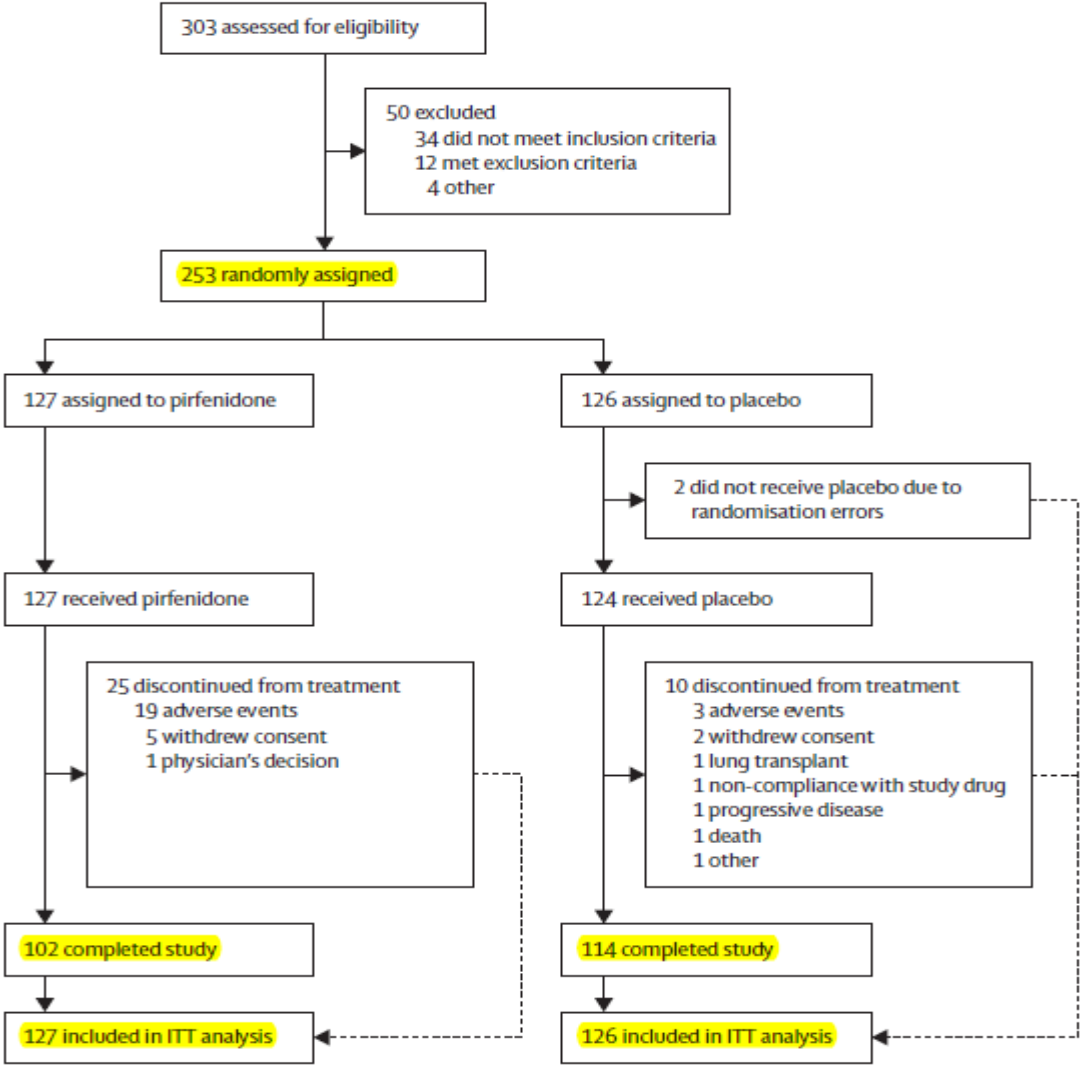
Change in university california san diego-shortness of breath questionnaire score

Change in leicester cough questionnaire score from baseline

Proportion of patients having all-cause and respiratory non-elective hospital admission

Incidence of, and time to first, investigator-reported acute exacerbation

Progression free survival


303 assessed for eligibility
50 excluded
34 did not meet inclusion criteria
12 met exclusion criteria
4 other
253 randomly assigned
127 assigned to pirfenidone
126 assigned to placebo
2 did not receive placebo due to randomisation errors
127 received pirfenidone
124 received placebo
25 discontinued from treatment
19 adverse events
5 withdrew consent
1 physician's decision
10 discontinued from treatment
3 adverse events
2 withdrew consent
1 lung transplant
1 non-compliance with study drug
1 progressive disease
1 death
1 other
102 completed study
114 completed study
127 included in ITT analysis
126 included in ITT analysis

	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%)

	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)**

	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)**

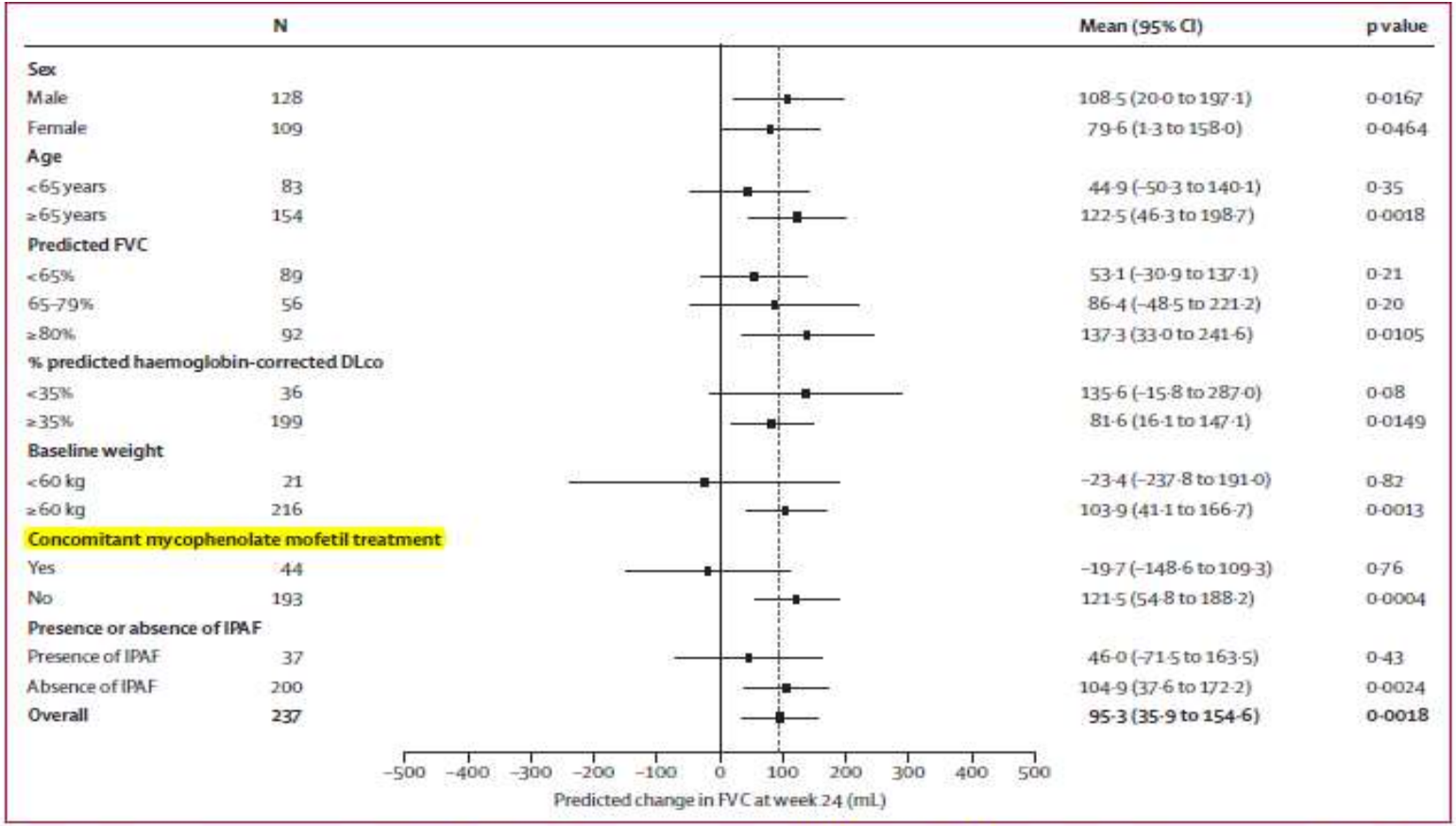


Figure 3: Subgroup analysis of mean change in FVC from baseline at week 24 measured by site spirometry in all patients who had site spirometry at week 8 (n=237)

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 this study, primary pre-specified end point could not be analysed due to implausible data measured by home spirometry.

However, the secondary end points were met and it showed pirfenidone is better than placebo in terms of reducing FVC decline, improving 6MWD and reducing DLco decline.

Treatment benefit was generally observed with pirfenidone regardless of age, sex, lung function, and presence or absence of interstitial pneumonia with autoimmune features.

This study predominately included unclassified-ILD, some of the unclassified-ILD were labelled without biopsy (biopsy could have grouped these ILD into the existing groups).

The short duration of study (24 weeks) in this study, by nature cannot predict the long term outcome.

Real-world impact of antifibrotics on prognosis in patients with progressive fibrosing interstitial lung disease

Takayuki Niitsu ,[1] Kiyoharu Fukushima,[1,2] Sho Komukai,[3,4] So Takata,[1] Yuko Abe,[1] Takuro Nii,[5] Tomoki Kuge,[1] Shinichi Iwakoshi,[6] Takayuki Shiroyama,[1] Kotaro Miyake,[1] Kazuyuki Tujino,[2] Satoshi Tanizaki,[1] Kota Iwahori,[1] Haruhiko Hirata,[1] Keisuke Miki,[2] Masahiro Yanagawa,[7] Noriyuki Takeuchi,[8] Yoshito Takeda,[1] Hiroshi Kida,[2] Atsushi Kumanogoh[1]

Multicentre retrospective observation study

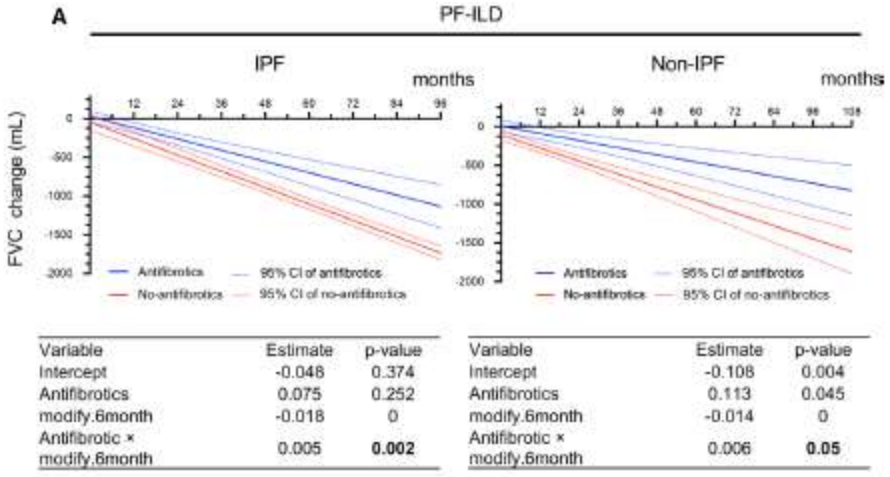
167 PF-ILD (Non-IPF 103) patients were included

Main groups were antifibrotic group and non fibrotic group among IPF and Non-IPF patients.

Non-IPF more than IPF patients were receiving baseline immunosupressive therapy.

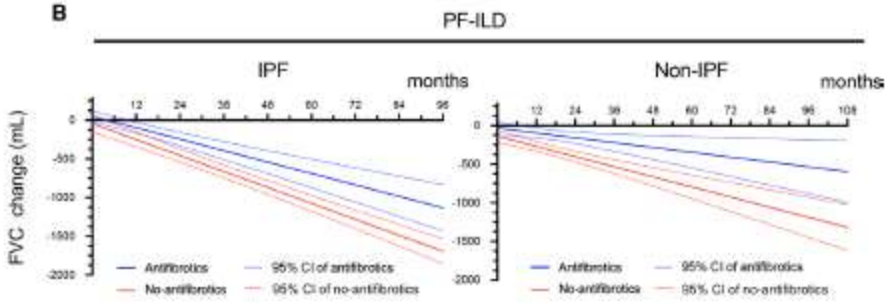
Outcome assessed was FVC decline and overall survival.

Niitsu T, Fukushima K, Komukai S, et al. Real-world impact of antifibrotics on prognosis in patients with progressive fibrosing interstitial lung disease. RMD Open 2023;9:e002667



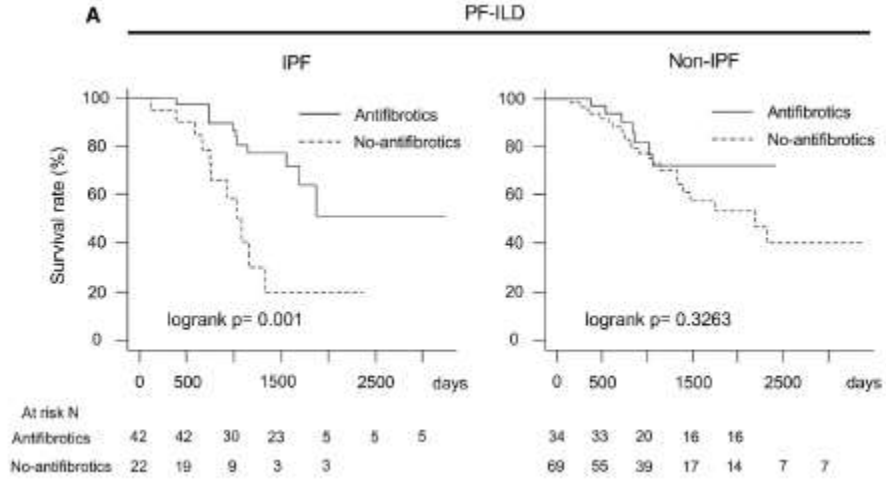
Variable	Estimate	p-value
Intercept	-0.048	0.374
Antifibrotics	0.075	0.252
modify.6month	-0.018	0
Antifibrotic × modify.6month	0.005	**0.002**

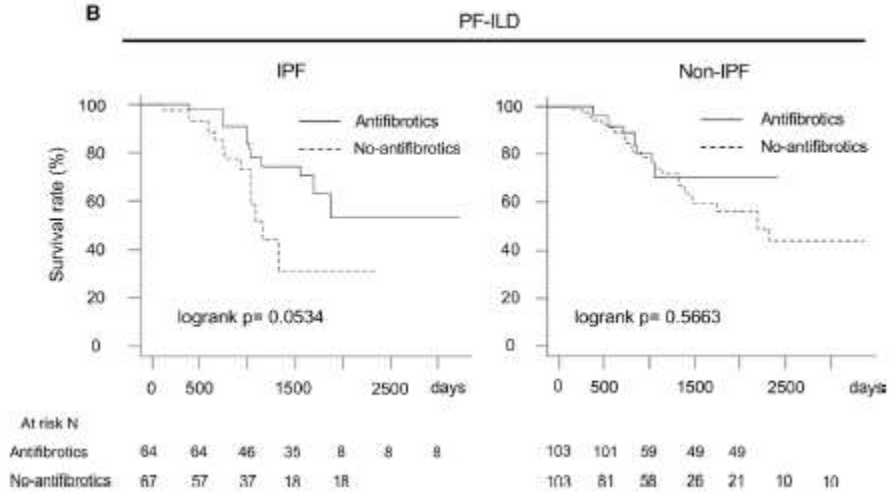
Variable	Estimate	p-value
Intercept	-0.108	0.004
Antifibrotics	0.113	0.045
modify.6month	-0.014	0
Antifibrotic × modify.6month	0.006	**0.05**



Variable	Estimate	p-value
Intercept	-0.044	0.427
Antifibrotics	0.093	0.163
modify.6month	-0.017	0
Antifibrotic × modify.6month	0.005	**0.015**

Variable	Estimate	p-value
Intercept	-0.139	0.005
Antifibrotics	0.104	0.075
modify.6month	-0.011	<0.001
Antifibrotic × modify.6month	0.006	**0.031**





- Retrospective nature of the study, there a risk of selection bias and confounding factors.
- Any benefit of antifibrotic therapy is masked by immunosupressant medications.
- There is no uniformity in the starting of antifibrotic drugs, being a observational study.

Available immunomodulatory therapies

Corticosteroids

Mycophenolate mofetil

Cyclophosphamide

Rituximab

Corticosteroids

Sarcoidosis, crytogenic organising pneumonia, acute hypersentivity pneumonitis and eosinophilic pneumonia generally responds well.

Prednisolone may be used in Ssc related ILD, but the risk of scleroderma related renal crisis when dose >15mg/day particularly in early diffuse disease. Usually steroids are used in combination with other immunosupressants.

No trial evidence for SLE-ILD. Treatment consists of corticosteroids along with other immunosupressants.

IIM-ILD responds well to steroids(First line therapy).

Ajay wanchu et.al.,International Journal of Rheumatic diseases p. 239-242
Sussanna chappelli et. al European Respiratory Review 2015 24: 411-419
Laura van den bosch et.al Therapeutic Advances in Respiratory Disease
Beth wallace et.al, current opin rheumatol 2016;28(3): 236-245

Characteristic of studies reported outcome in chronic interstitial lung disease.

Study	Population	Mean age	Sex (M/F)	Evaluation criteria	Main treatment	Treatment protocol
Marie, 2002‡	DM/PM	54	16/20	PFT	CsA, CYC, AZA	NA
Takada, 2005	PM/DM	49	8/29	PFT	CsA	NA
Wilkes, 2005‡	ARS	45	5/8	PFT	Tacrolimus	Oral, twice daily (0.075 mg/kg) to achieve plasma trough concentration of 5-20 ng/mL.
Yamasaki, 2006	PM/DM	51	4/13	PFT	CYC	500–1000 mg (300–800 mg/m^2 every 4 weeks (6 doses) i.v.
Ideura, 2007	ADM	46	5/13	PFT and HRCT	CS alone, CsA	NA
Sem, 2009	ARS	60	4/7	ATS criteria	Rituximab	1000 mg, at days 0 and 14 (9 patients) 375 mg/m^2/week for 4 weeks (2 patients)
Marie, 2010	PM/Scl antibodies	NA	NA	ATS criteria	CS alone, AZA, CYC	NA
Koreeda, 2010	ARS	59	7/7	ATS criteria	CsA	3 mg/kg/day then adjusted to target the trough level (100–200 ng/mL).
Ingegnoli, 2011	ARS (anti-Jo1)	53	0/15	HRCT	CYC, CsA, CS alone	Seven of the 15 patients were treated with oral cyclosporin A (CsA) 5 mg/kg/day and eight with cyclophosphamide (CYC) pulses (1000 mg/m^2 of body surface) monthly for 6 months followed by 3-monthly maintenance pulses
Marie, 2011	PM/DM	53	43/64	ATS criteria	CS alone, CYC, AZA, MMF	NA
Marie, 2012	ARS	57	3/4	ATS criteria	Rituximab	2 infusions of 1 g at days 0 and 14, third infusion of 1 g at 6-month follow-up
Keir, 2012	PM/DM	49	3/2	PFT	Rituximab	2 infusions of 1 g at days 0 and 14
Labirua-Iturburu, 2013	ARS	42	4/11	ATS criteria	CsA, Tacrolimus	Tacrolimus: oral, twice daily 0.065 mg/kg. Cyclosporine: oral, twice daily 2–5 mg/kg.
Marie, 2013‡	ARS (anti-PL7)	60	7/8	ATS criteria	CS alone, AZA, CYC	CS 1 mg/kg/day AZA 2 mg/kg/day CYC 0.7 g/m^2/month (6 pulses) MMF (30 mg/kg/day).
Marie, 2013‡	ARS (anti-Jo1)	55	25/41	ATS criteria	CS alone, AZA, CYC	CS 1 mg/kg/day AZA 2 mg/kg/day CYC 0.7 g/m^2/month (6 pulses) MMF (30 mg/kg/day)

T. Barba et al. Autoimmunity Reviews 18 (2019) 113–122

Prednisolone is started as 0.5 to 1 mg/kg/day (max 60 mg/day) for 1 month, then followed by 30 to 40 mg/day for next 2 months, then gradually tapered to 5 to 10 mg/day by the end of 6 months.

In a responding patient, treatment should be continued for atleast 1 year before stopping.

Elizabeth A et al, Respirology 2016;21(2):259-68.
up-to-date

Mycophenolate mofetil

MMF is a prodrug of mycophenolic acid, which is noncompetitive selective reversible inhibitor of inosine monophosphate dehydrogenase in stimulated lymphocytes.

It has anti-inflammatory, anti-proliferative and anti-fibrotic properties.

Gastrointestinal and bone marrow suppression are the most observed AEs and are mostly dose dependent and typically occur early in the course of treatment and decrease in frequency with continued use

The optimal daily dose range of MMF is 1.5–3 g in two divided doses. In patients with end-stage renal disease, dose reduction is recommended.

It should be taken either 30 minutes before a meal or 2 hours after the meal. Use of antacids and mineral supplements should be separated by at least 2 hours from time of intake of MMF.

Kevin K Brown et al, The emerging role of mycophenolate mofetil in interstitial lung diseases, Expert Review of Respiratory Medicine, 2021; 15:12, 1539-1549

Authors	No. of Patients	Design	Treatment Duration	FVC		DLco		Steroid Dose (mg)	
				Before mycophenolate mofetil initiation	*After mycophenolate mofetil treatment*	*Before mycophenolate mofetil initiation*	*After mycophenolate mofetil treatment*	*Before mycophenolate mofetil initiation*	*After mycophenola mofetil treatmen*
Chronic HP									
Morisset et al. (2017)	51	Retrospective trial	12 months	65.2% predicted	Increased by 1.3% (P = .103)	49.8% predicted	Increased by 3.9% (P < .001)	12.33	3.7
D Mac Donald et al. (2017)	38	Retrospective trial	24 months	61.1 ± 12.3% predicted	65.1 ± 12.9% predicted	45.3 ± 14.9% predicted	50.9 ± 14.5% predicted	18.9 ± 11.1	5.4 ± 6.1
Fiddler CA et al. (2019)	18	Retrospective trial	12 months	−111 ± 295 mL	Increased by 2.3 ± 319 mL (P = 0.22)	NA		16.2 ± 9.7	8.2 ± 4.2 (P = 0.002)
Systemic Sclerosis-ILD									
Tashkin DP et al (2016)	69	Randomized, double-blind, parallel group	24 months	66.5% predicted	Increased by 2.19%	54.0% predicted	Stabilized	NA	NA
Shenoy PD et al. (2016)	34	Retrospective trial	6 months	53.44 ± 13.69% predicted	55.99 ± 13.47% predicted; (*P* = 0.003); numerical increase in FVC reported in 78.5% of patients	NA	NA	NA	NA
Highland KB et al. (2021)	139	Randomized, double-blind, placebo-controlled trial	52 weeks			NA	NA	NA	NA
Gerbino AJ et al. (2008)	13	Retrospective trial	12 months	Decreased by 5.4% in previous 12 months (P = 0.02)	Increased by 4.2% predicted (P = 0.002)	Decreased by 5.2% in previous 12 months (P = 0.01)	Increased by 1.2% predicted (P = 0.57)	NA	NA
Liossis SNC et al. (2006)	5	Prospective trial	4–6 months	65.6% predicted	76.2% predicted (P = 0.057)	64.2% predicted	75.4% predicted (P = 0.033)	NA	NA
Owen C et al. (2016)	22	Prospective trial	36 months	Stabilized and/improvement	Stabilized and/improvement			NA	NA
Swigris JJ et al. (2006)	28	Retrospective observational study	35.9 patient-years	65% predicted	Increased by 2.3% (P = 0.47)	38% predicted	Increased by 2.6% (P = 0.14)	15	10

Other Connective Tissue Disease-ILD									
Fischer A et al. (2013)	125	Retrospective trial	156 weeks	66.7 ± 16.0% predicted	Increased by 7.3% ± 2.6% (P = 0.004)	47.4 ± 16.4% predicted	Increased by 7.8% ± 4.1% (P = 0.05)	20 mg	5 mg
Santhanam S and Rahulan V (2018) - MCTD - RA - Others	33	Retrospective observational study	24 months	62% predicted 59% predicted 64% predicted	65% predicted 62% predicted 65% predicted	NA	NA	NA	NA
Polymyositis/Dermatomyositis-ILD									
Morganroth PA et al. (2010)	4	Case report	1 year	Complete normalization of pulmonary function				15–60	4
Mira-Avendano IC et al. (2013)	9	Retrospective study	12 months	64% predicted	64% predicted	58% predicted	63% predicted	40	10
Koyama RVL et al. (2017)	1	F/62 years	25 months	Improvement in pulmonary function				10	5
Huapaya JA et al. (2019)	44	Retrospective trial	24 months	72 ± 22.2% predicted	Improved by 3.3% (P = .021)	66.6 ± 26.2% predicted (P = .657)	NA	18.1 ± 12.2	Decreased by 6.9 (P < .001)
Chronic/Refractory Sarcoidosis									
Brill KA et al. (2013)	10	Retrospective trial	12 months	78.8 ± 11.9% predicted	85 ± 9.6% predicted (P = 0.057)	62.9 ± 14.4% predicted	60.3 ± 11.8% predicted (P = 0.721)	14.3 ± 13.3	6.5 ± 2.3 (P = 0.043)
Papiris S et al. (2019)	8	Retrospective trial	12 months	86.2% predicted	92.4% predicted	68.8% predicted	81.1% predicted	15	2.5
Idiopathic Pulmonary Fibrosis									
Nambiar AM et al. (2017)	11	Retrospective trial	12 months	Trend toward decreased decline in FVC by 76.3 mL, 2.4% predicted (P = NS)	NA		NA	NA	NA

Rituximab

Monoclonal antibody targeting CD20 on B-lymphocytes.

Mainly used in CTD-ILD.

Can be used as rescue therapy in patient of treatment refractory fibrosing ILD.

Xu L, Wang F and Luo F (2022), Rituximab for the treatment of connective tissue disease–associated interstitial lung disease: A systematic review and meta-analysis. Front. Pharmacol. 13:1019915

TABLE 1 Baseline clinical characteristics of included studies.

Study	Study design	Country	Population	Patient (*n*)	Sex (F (%)	Mean age (yrs)	Evaluation criteria	Rituximab therapy	Follow-up (months)
Sem et al, (2009)	Retrospective study	Norway	AS-ILD	11	63	59 (23–66)	PFT、HRCT	Rituximab (1,000 mg) on D0 and D14 ($n = 10$) Rituximab (700 mg) on D0 and D14 ($n = 1$)	6
Keir et al, (2014)	Retrospective study	United Kingdom	CTD-ILD	32	33	52.5 ± 10.9	PFT	Rituximab (1,000 mg) on D0 and D14	6–12
Allenbach et al, (2015)	Prospective study	French	AS-ILD	10	20	51 (18–57)	PFT、HRCT、SF-36	Rituximab (1,000 mg) on D0, D15 and M6	12
Bosello et al, (2015)	Prospective study	Italy	SSC-ILD	14	85	41.4 ± 13.1	PFT、HRCT	Rituximab (1,000 mg) on D0 and D14	12
Lepri et al, (2016)	Retrospective study	NA	CTD-ILD	42	75	NA	PFT	NA	12
Sharp et al, (2016)	Retrospective study	United Kingdom	CTD-ILD	24	66	51.4 ± 14.9	PFT、HRCT	Rituximab (1,000 mg) on D0 and D14	6–12
Yuzaiful (2017)	Retrospective study	United Kingdom	RA-ILD	43	64	64 (59–72)	PFT、HRCT	Rituximab (1,000 mg) on D0 and D14	6–12
Sari et al, (2017)	Retrospective study	Turkey	SSC-ILD	14	92	53.2 (46.8–55.5)	PFT	NA	6-?
Doyle et al, (2018)	Retrospective study	United States	AS-ILD	22	80	49 ± 12	PFT、HRCT	NA	12–36
Sircar et al, (2018)	Prospective study	India	SSC-ILD	30	83	34.67 ± 8.13	PFT、HRCT	Rituximab (1,000 mg) on D0 and D15	6
Duarte et al, (2019)	Retrospective study	United Kingdom	RA-ILD	15	66	NA	PFT、HRCT	NA	6–36
Javier (2020)	Retrospective study	Spain	SSC-ILD	24	87.5	58.0 ± 14.0	PFT、HRCT	Rituximab (1,000 mg) on D0 and D15	6–24
Javier (2020)	Retrospective study	Spain	RA-ILD	31	58	61.0 ± 12.0	PFT、HRCT	Rituximab (1,000 mg) on D0 and D15	6–24

Xu L, Wang F and Luo F (2022), Rituximab for the treatment of connective tissue disease–associated interstitial lung disease: A systematic review and meta-analysis. Front. Pharmacol. 13:1019915

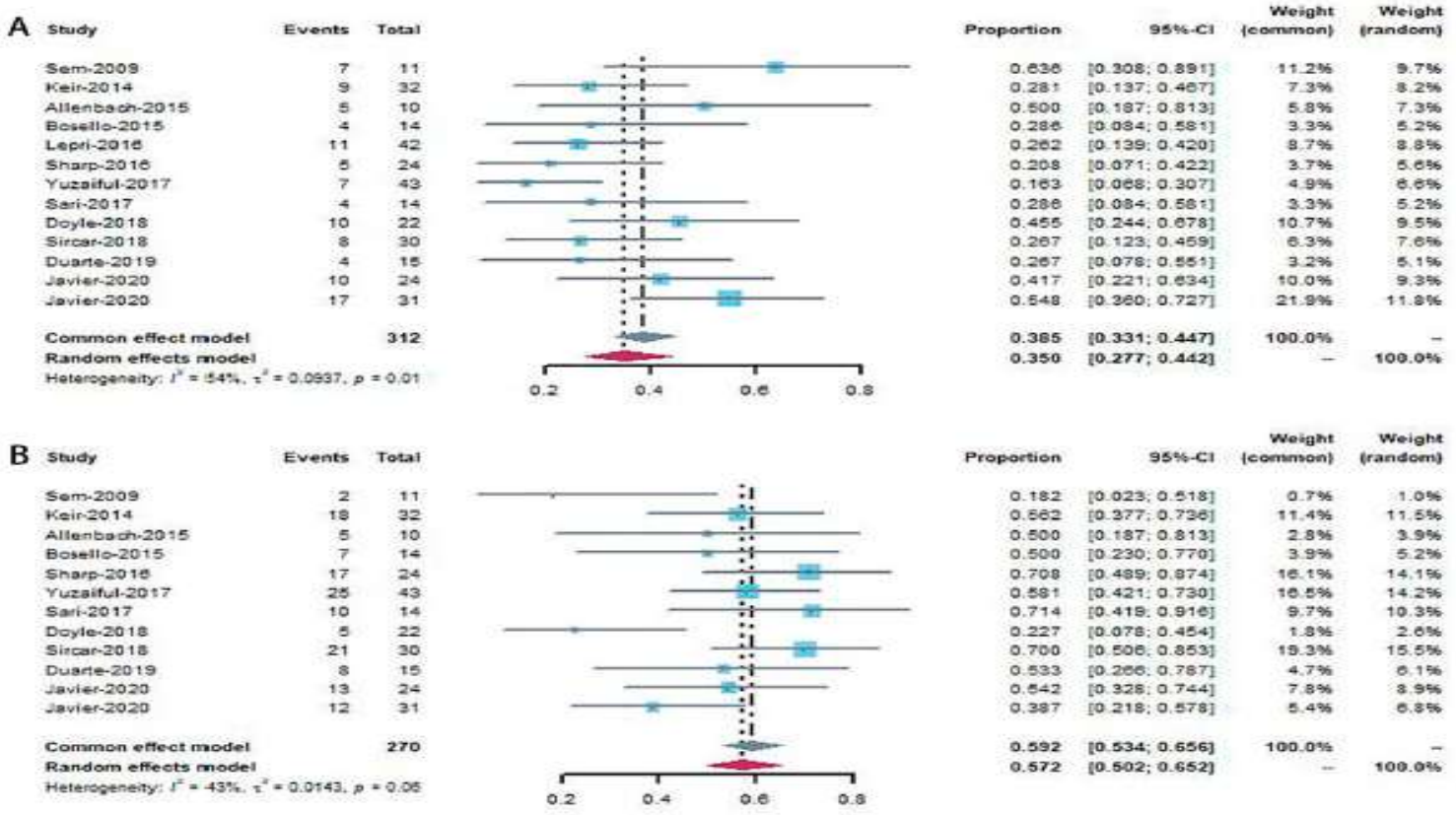


FIGURE 2
Forest plot showing improvement rate **(A)** and stable rate **(B)** to patients using rituximab.

Improvement - increase of ≥ 10% in forced vital capacity (FVC) and/or ≥ 15% in diffusing capacity of carbon monoxide (DLCO)

Worsening - decrease of ≥ 10% in FVC and/or ≥15% in DLCO, or death from progressive ILD

Stable - others that did not meet criteria for either worsening/improving

The improvement rate was estimated to be 35.0% in 312 patients with CTD-ILD, while the stable rate was 59.2%

Patients involved in this meta-analysis have not received antifibrotic treatment.

Dose is 1g intravenously separated by 1 to 2 weeks apart.

Usually preferred in refractory disease.

Cyclophosphamide

An alkylating agent causing cross-linkage of a variety of macromolecules, including DNA, producing cell death amongst resting and dividing lymphocytes.

Robust data is available for systemic sclerosis related ILD.

Dosing is either oral or intravenous

Intravenous is usually preferred, to avoid cumulative toxicity

Oral dosing is 2mg/kg/day with normal renal function

Iv dosing is 500-1000mg/m2 every 4 to 6 weeks.

A total duration of 6 months is usually given.

Cyclophosphamide for connective tissue disease–associated interstitial lung disease (Review)

Barnes H, Holland AE, Westall GP, Goh NSL, Glaspole IN

Meta-analysis of 4 studies

Three studies included only participants with systemic sclerosis, one study included participants with systemic sclerosis, dermatomyositis/ polymyositis, systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA)

Subgroups are not separately analysed

BarnesH et. al., Cyclophosphamide for connective tissue disease–associated interstitial lung disease. Cochrane Database of Systematic Reviews 2018 (1): CD010908.

Figure 4. Forest plot of comparison: 1 Cyclophosphamide versus placebo, outcome: 1.1 FVC % predicted.

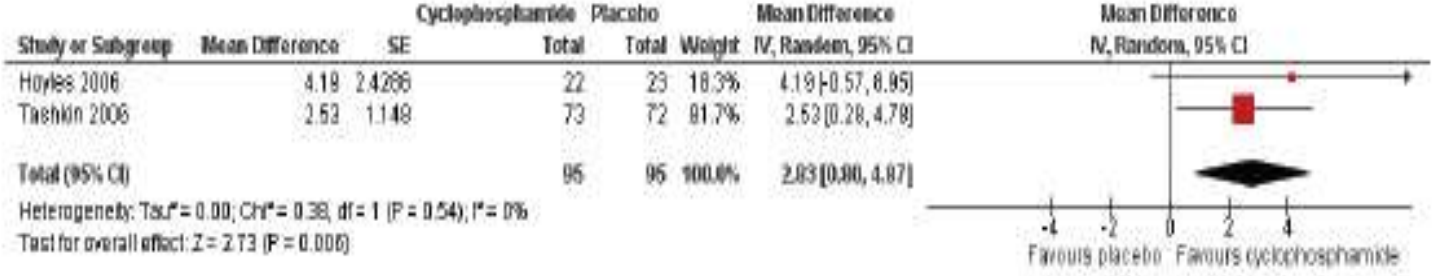


Figure 5. Forest plot of comparison: 1 Cyclophosphamide versus placebo, outcome: 1.2 DLCO % predicted.

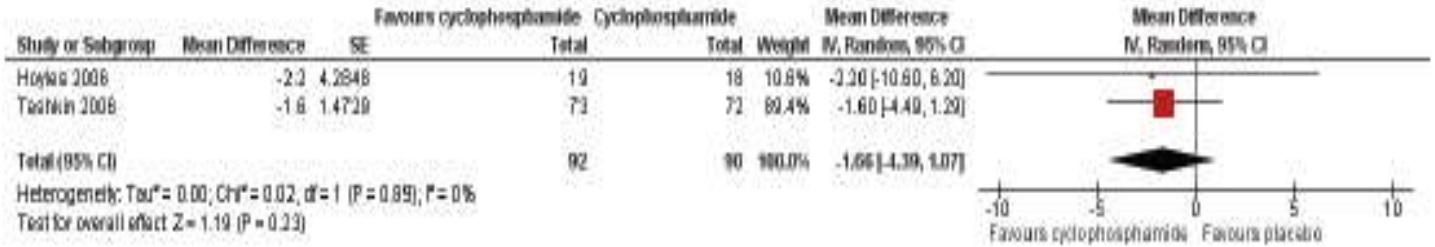


Figure 6. Forest plot of comparison: 2 Cyclophosphamide versus mycophenolate, outcome: 2.2 FVC % predicted at end of study.

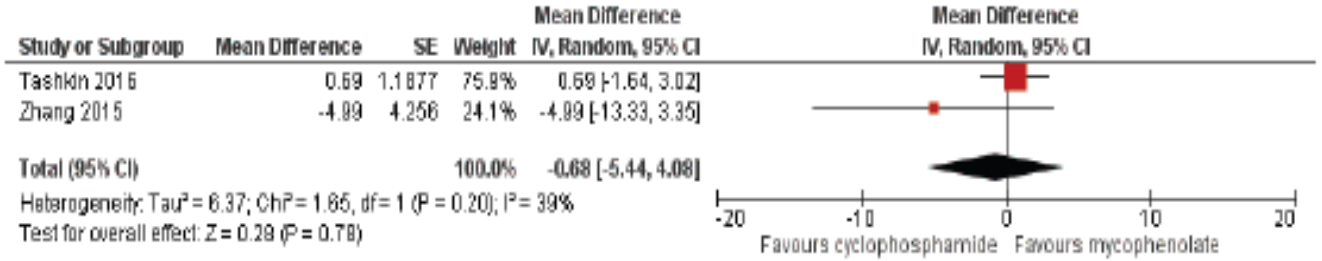
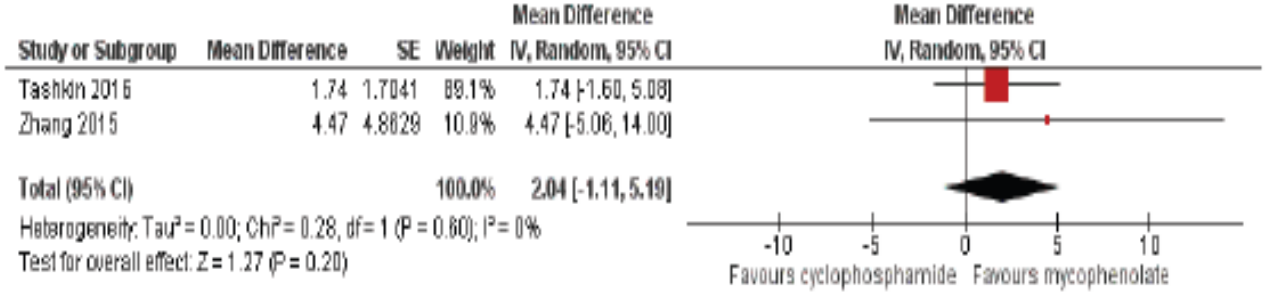


Figure 7. Forest plot of comparison: 2 Cyclophosphamide versus mycophenolate, outcome: 2.4 DLCO % predicted at end of study.



No mortality benefit when cyclophosphamide is compared with Mycophenolate mofetil.

Cyclophosphamide has higher incidence of side effects than mycophenolate mofetil.

Side effects of cyclophosphamide includes bone marrow suppression, hemorrhagic cystitis, bladder cancer (cumulative dose of 100 gm).

Which of the ILD can progress to PF-ILD at higher incidence?

TABLE 2 Underlying clinical diagnoses

Patients	165
Chronic fibrosing hypersensitivity pneumonitis	14 (8.5)
Idiopathic interstitial pneumonia	12 (7.3)
Unclassifiable ILD	52 (31.5)
Interstitial pneumonitis with autoimmune features	2 (1.2)
Autoimmune ILD	77 (46.7)
Rheumatoid arthritis-ILD	7 (4.2)
Systemic sclerosis-ILD	43 (26.1)
Dermatomyositis-ILD	12 (7.3)
Mixed connective tissue disease-ILD	10 (6.1)
Other autoimmune ILD[#]	5 (3.0)
Other ILDs[¶]	10 (6.1)

Data are presented as n or n (%). ILD: interstitial lung disease. [#]: Sjögren syndrome ILD (n=1), systemic lupus erythematosus (n=1), others (n=3); [¶]: exposure-related ILD (n=2), other fibrosing ILD (n=5), sarcoidosis (n=3).

Nasser M, Larrieu S, Si-Mohamed S, et al. Progressive fibrosing interstitial lung disease:a clinical cohort (the PROGRESS study). Eur Respir J 2021; 57: 2002718

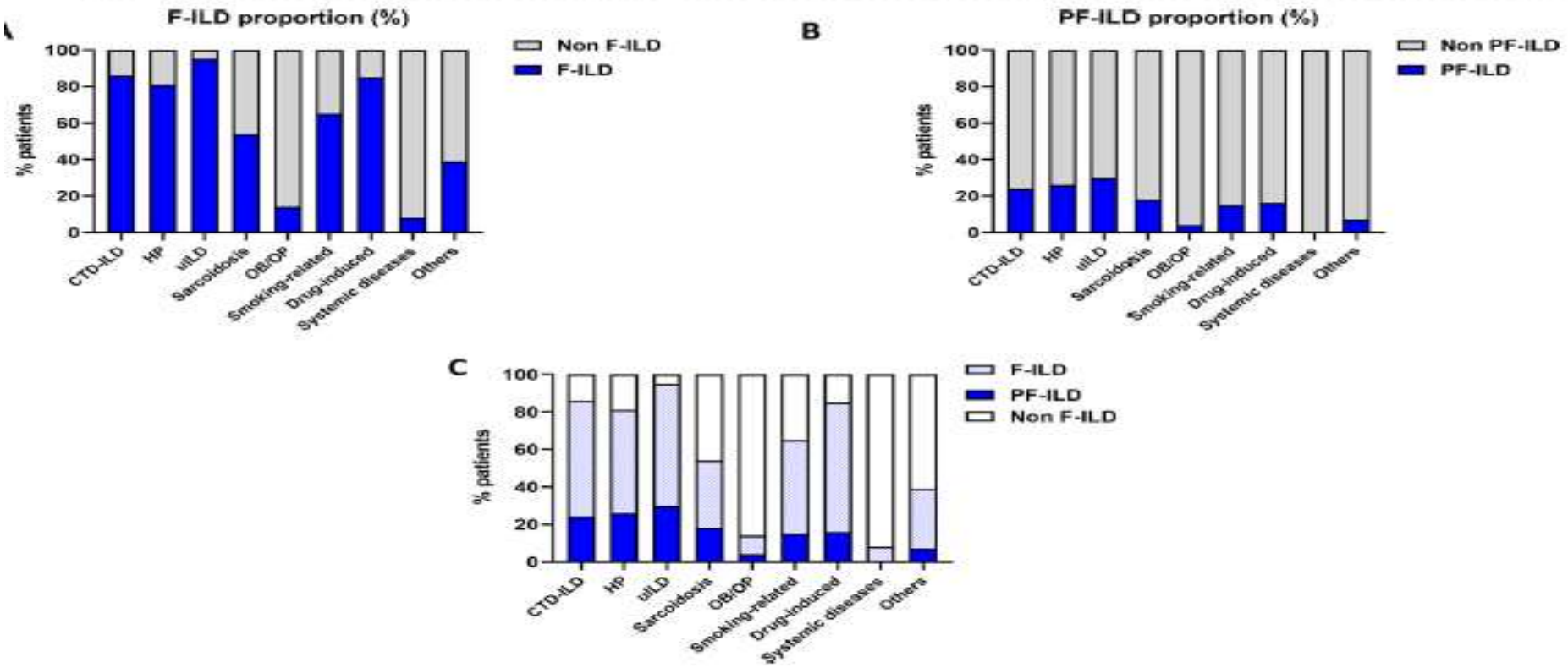
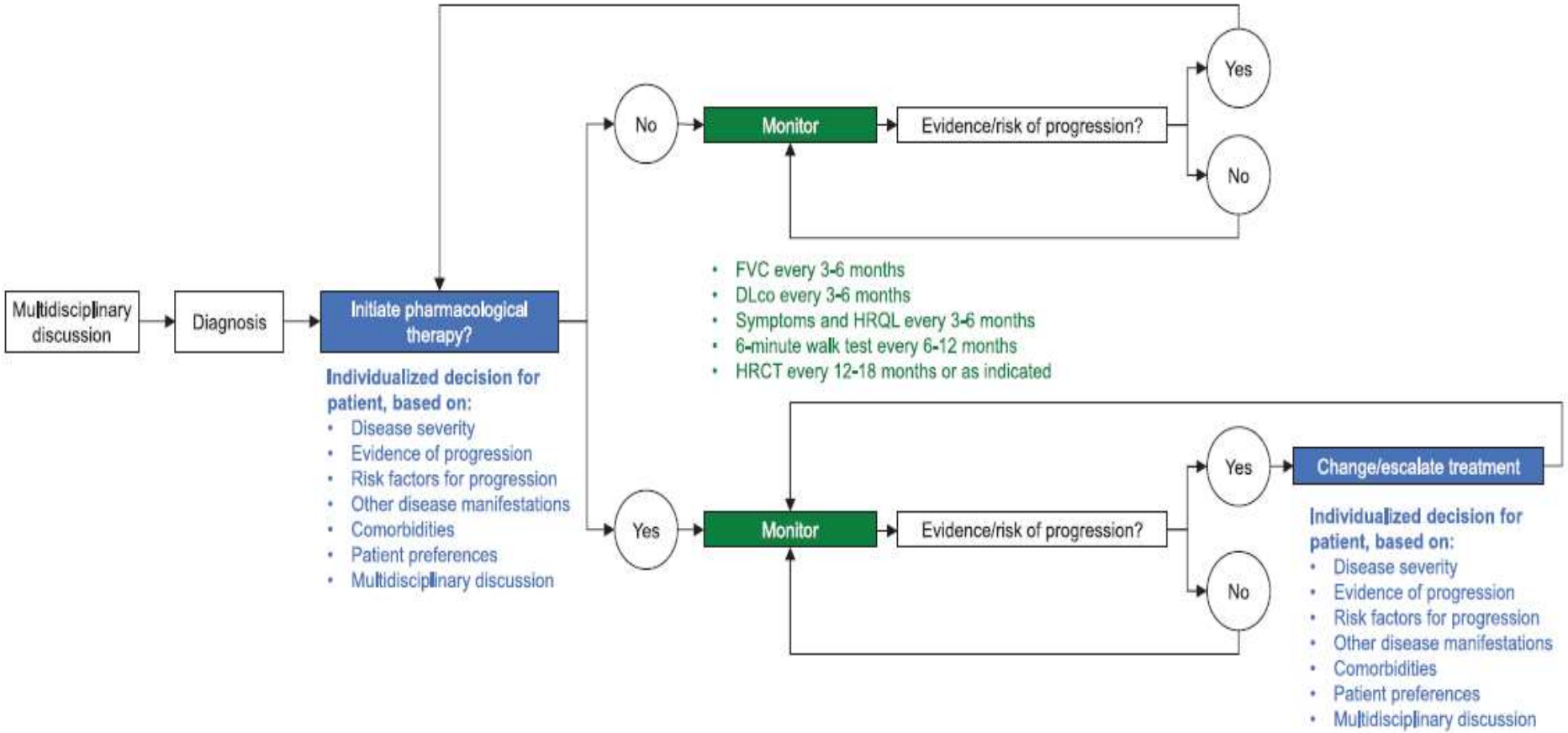


Figure 2. Proportion of fibrosing ILD (panel A), progressive and fibrosing ILD (panel B) and merge (panel C) within ILD subgroups.

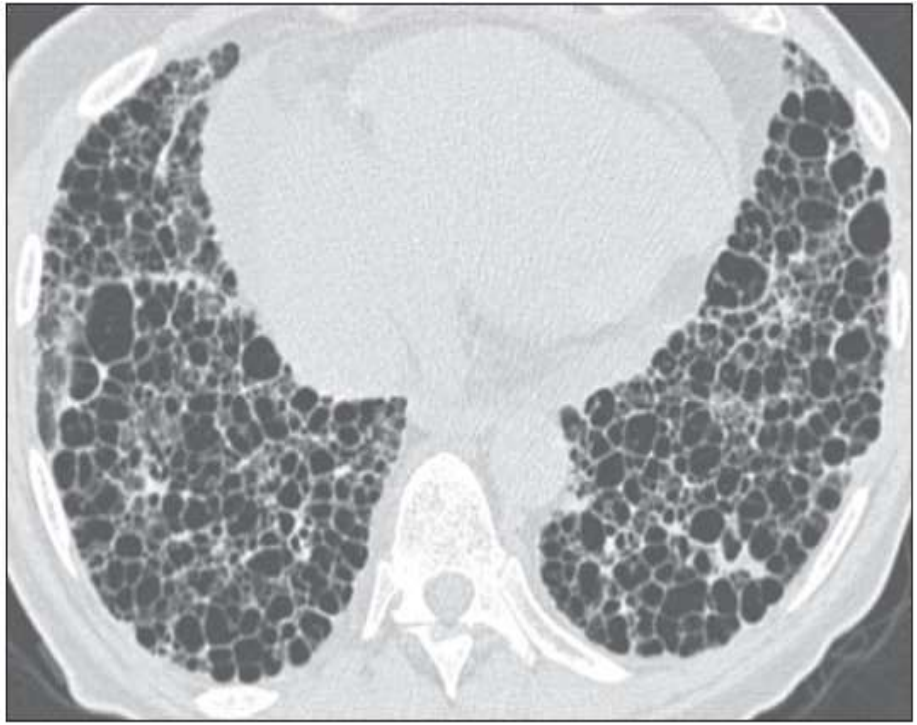
How to follow up patients of PF-ILD?



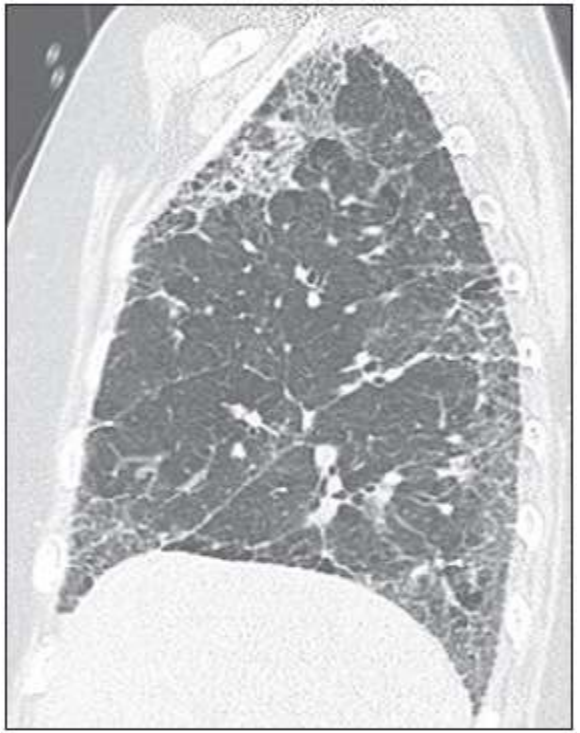
Anoop M. Nambiar et. al.,Ther Adv Respir Dis. 2021;15:17534666211039771

- Radiological UIP pattern progress faster than the non-UIP pattern.
- Fibrotic lesion in lung has -500HU.(normal lung -850HU)
- UIP pattern from non-IPF can be differentiated from IPF by signs like exuberent honeycombing, anterior upper lobe sign and straight edge sign. These usually occurs with CTD-ILD.

Abu Qubo A et al, The Role of Radiology in Progressive Fibrosing Interstitial Lung Disease. Front Med (Lausanne). 2022 13;8:679051.

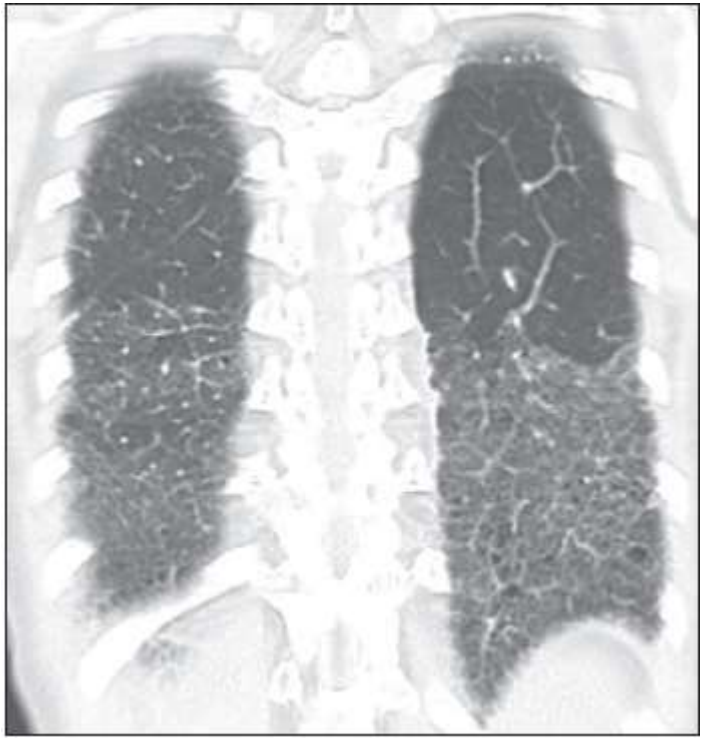


Exuberent honeycombing sign



Anterior lobe sign

Chung JH et al, CT Features of the Usual Interstitial Pneumonia Pattern: Differentiating Connective Tissue Disease-Associated Interstitial Lung Disease From Idiopathic Pulmonary Fibrosis. AJR Am J Roentgenol. 2018;210(2):307-313.



Straight edge sign

Chung JH et al, CT Features of the Usual Interstitial Pneumonia Pattern: Differentiating Connective Tissue Disease-Associated Interstitial Lung Disease From Idiopathic Pulmonary Fibrosis. AJR Am J Roentgenol. 2018;210(2):307-313

For fibrosing ILDs other than IPF, the optimal sequence, combination and timing of use of immunosuppressants, nintedanib, and supportive therapies has not been established.

Oxygen therapy in ILD

Resting hypoxemia (Pao2 < 55 mm Hg);Moderately severe resting hypoxemia (Pao2 <60 mm Hg) with complications of chronic hypoxemia – becomes indication for long term oxygen therapy

Short term oxygen therapy has shown improvement in resting dyspnea. It has shown to increase the exercise capacity but not dyspnea during exercise.

Ambulatory oxygen therapy with portable oxygen cylinders(than portable compressed oxygen cylinders) may improve the quality of life in these patients.

Portable oxygen cylinders has limited use in severe exertional hypoxemia due to higher flow requirment.

Bell EC, Cox NS, Goh N, et al. Oxygen therapy for interstitial lung disease: a systematic review. Eur Respir Rev 2017; 26: 160080

Definitions of oxygen therapy used in ILD

- *Long-term oxygen therapy (LTOT)* in which oxygen is delivered for patients with chronic hypoxemia, for at least 15 hours daily.
- *Ambulatory oxygen therapy (AOT):* Oxygen supplementation during exercise and daily activities for patients who are not hypoxemic at rest but who develop hypoxemia on exercise.
- *Nocturnal oxygen therapy (NOT)* in which oxygen administered overnight alone with no oxygen therapy during daytime hours.
- *Short burst oxygen* in which a brief and intermittent oxygen supplementation used as needed in the absence of hypoxemia.
- *Palliative oxygen therapy (POT):* The use of oxygen for relieving breathlessness in advanced or life-limiting disease in the absence of known hypoxemia.

Shebl E, Modi P, Cates TD. Home Oxygen Therapy. 2022 Jul 4. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022.

Nocturnal desaturation is a independent predictor of mortality in ILD patients.
Nocturnal oxygen supplementation can be given in these populations.

Data for LTOT in ILD comes from COPD trials.

Yet H khor et. Al.,Curr Opin Pulm Med 2020, 26:464–469

Effect of ambulatory oxygen on quality of life for patients with fibrotic lung disease (AmbOx): a prospective, open-label, mixed-method, crossover randomised controlled trial

Summary

Background In fibrotic interstitial lung diseases, exertional breathlessness is strongly linked to health-related quality of life (HRQOL). Breathlessness is often associated with oxygen desaturation, but few data about the use of ambulatory oxygen in patients with fibrotic interstitial lung disease are available. We aimed to assess the effects of ambulatory oxygen on HRQOL in patients with interstitial lung disease with isolated exertional hypoxia.

Methods AmbOx was a prospective, open-label, mixed-method, crossover randomised controlled clinical trial done at three centres for interstitial lung disease in the UK. Eligible patients were aged 18 years or older, had fibrotic interstitial lung disease, were not hypoxic at rest but had a fall in transcutaneous arterial oxygen saturation to 88% or less on a screening visit 6-min walk test (6MWT), and had self-reported stable respiratory symptoms in the previous 2 weeks. Participants were randomly assigned (1:1) to either oxygen treatment or no oxygen treatment for 2 weeks, followed by crossover for another 2 weeks. Randomisation was by a computer-generated sequence of treatments randomly permuted in blocks of constant size (fixed size of ten). The primary outcome, which was assessed by intention to treat, was the change in total score on the King's Brief Interstitial Lung Disease questionnaire (K-BILD) after 2 weeks on oxygen compared with 2 weeks of no treatment. General linear models with treatment sequence as a fixed effect were used for analysis. Patient views were explored through semi-structured topic-guided interviews in a subgroup of participants. This study was registered with ClinicalTrials.gov, number NCT02286063, and is closed to new participants with all follow-up completed.

Findings Between Sept 10, 2014, and Oct 5, 2016, 84 patients were randomly assigned, 41 randomised to ambulatory oxygen first and 43 to no oxygen. 76 participants completed the trial. Compared with no oxygen, ambulatory oxygen was associated with significant improvements in total K-BILD scores (mean 55·5 [SD 13·8] on oxygen *vs* 51·8 [13·6] on no oxygen, mean difference adjusted for order of treatment 3·7 [95% CI 1·8 to 5·6]; p<0·0001), and scores in breathlessness and activity (mean difference 8·6 [95% CI 4·7 to 12·5]; p<0·0001) and chest symptoms (7·6 [1·9 to 13·2]; p=0·009) subdomains. However, the effect on the psychological subdomain was not significant (2·4 [−0·6 to 5·5]; p=0·12). The most common adverse events were upper respiratory tract infections (three in the oxygen group and one in the no-treatment group). Five serious adverse events, including two deaths (one in each group) occurred, but none were considered to be related to treatment.

Interpretation Ambulatory oxygen seemed to be associated with improved HRQOL in patients with interstitial lung disease with isolated exertional hypoxia and could be an effective intervention in this patient group, who have few therapeutic options. However, further studies are needed to confirm this finding.

Role of lung transplantation:

TABLE 1 Criteria for referral and listing for lung transplantation in patients with interstitial lung disease (ILD)

Timing of referral[#]	Timing of listing
Histopathological UIP	Hospitalisation for respiratory decline, pneumothorax or acute exacerbation
Radiographic probable or definite UIP pattern	Desaturation to <88% on 6MWT or >50 m decline in 6MWD over 6 months
FVC <80% or D_{LCO} <40% pred	Pulmonary hypertension on right heart catheterisation or echocardiography
Relative decline in pulmonary function over the past 2 years: FVC ⩾10% or D_{LCO} ⩾15% or FVC ⩾5% with symptomatic or radiographic progression	Absolute decline in pulmonary function over the past 6 months despite appropriate treatment: FVC >10% or D_{LCO} >10% or FVC >5% with radiographic progression
Any resting or exertional oxygen requirement	
For inflammatory ILDs, disease progression despite treatment	

Referral or listing should be considered if meeting any one criterion. UIP: usual interstitial pneumonia; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; 6MWT: 6-min walk test; 6MWD: 6-min walk distance. [#]: earlier referral is recommended for patients with connective tissue disease or familial idiopathic pulmonary fibrosis to address potential extrapulmonary manifestations. Reproduced and modified from [13] with permission.

Kapnadak SG, Raghu G. Lung transplantation for interstitial lung disease. Eur Respir Rev 2021; 30: 210017

Absolute contraindications
Lack of patient willingness or acceptance of transplant
Malignancy with high risk of death or recurrence
GFR <40 mL·min^{-1}·1.73 m^{-2} unless being considered for multi-organ transplant
Acute coronary syndrome within 30 days (excluding demand ischaemia)
Stroke within 30 days
Liver cirrhosis with portal hypertension or synthetic dysfunction unless being considered for multi-organ transplant
Acute liver failure
Acute renal failure with rising creatinine or on dialysis and low likelihood of recovery
Active extrapulmonary infection including septic shock
Active tuberculosis infection
HIV infection with detectable viral load
Severely limited functional status with poor rehabilitation potential
Progressive cognitive impairment
Repeated episodes of nonadherence without evidence of improvement
Active substance use or dependence including current tobacco use, vaping, marijuana smoking or intravenous drug use
Other severe uncontrolled medical condition expected to limit survival after transplant

TABLE 3 Common risk factors for adverse post-lung transplant outcomes in disease
Advanced age
Overweight status
Telomere biology disorders
Prior thoracic surgery
Limited functional status, deconditioning, frailty
Gastro-oesophageal reflux
High-risk atherosclerotic disease
Connective tissue disease manifestations
Corticosteroids, other immunosuppressants
Acute exacerbations
Active mechanical ventilation

TABLE 4 Morbidity rates in survivors at 5 years after lung transplantation for interstitial lung disease

	Idiopathic interstitial pneumonia % of survivors with listed diagnosis	Other interstitial lung diseases % of survivors with listed diagnosis
Hypertension	79.5	80.0
Creatinine >2.5 $mg \cdot dL^{-1}$	35.8	34.4
Chronic dialysis or renal transplant	2.7	2.7
Hyperlipidaemia	63.4	57.1
Diabetes	37.7	33.2

Data from the International Society for Heart and Lung Transplantation 2016 registry [143].

Research questions

- Best time for drug and non-drug interventions in PPF?
- Is there any evidence for early treatment delaying progression, reducing FVC decline?
- Impact of other interventions (pulmonary rehabilitation, oxygen therapy) on the survival of PPF?
- Is there any role of bio-markers in the early detection of PPF that could influence its management?