Progressive Fibrosing ILD (PF-ILD)

[Progress Pulmonary Fibrosis (PPF)]

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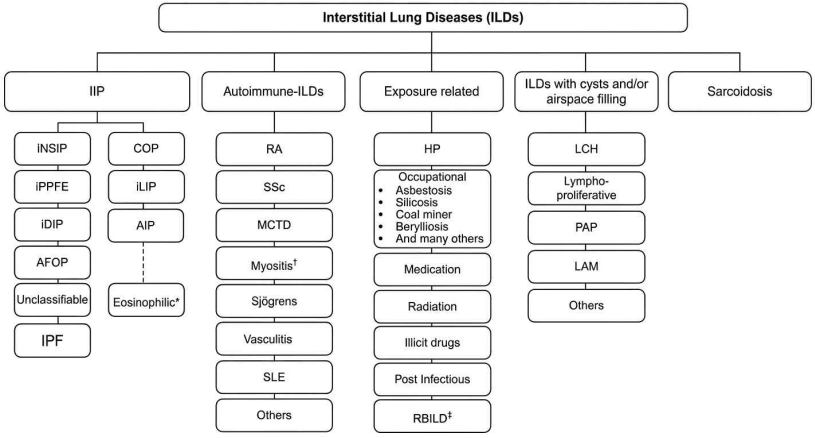
CONTENTS

CONTENTS

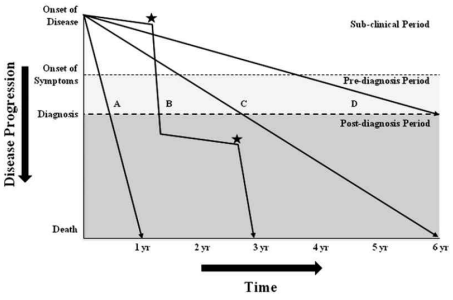
Classification of ILDs

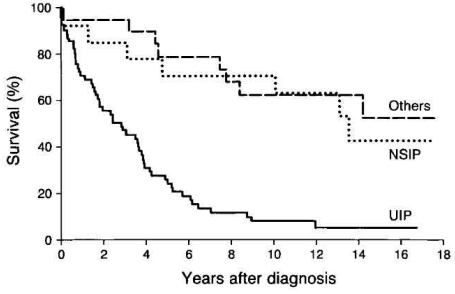


Modified from the original figure (IPF added)

Raghu G *et al. Am J Respir Crit Care Med.* 2022;205(9)

Clinical Course of IPF and Other ILDs

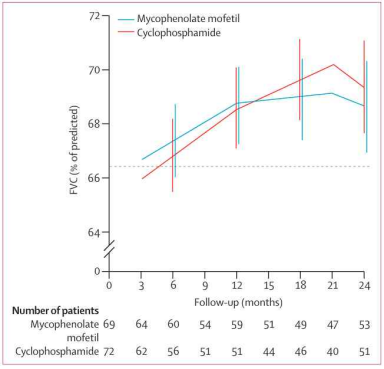


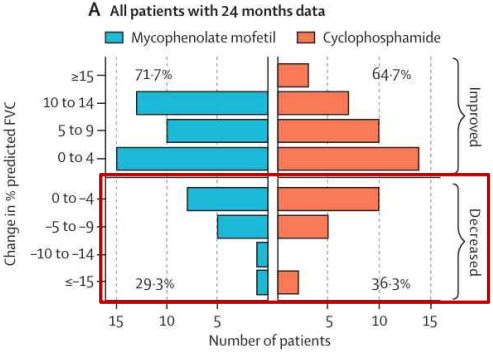


Ley B *et al*. *Am J Respir Crit Care Med*. 2011;183
Bjoraker JA et al. *Am J Respir Crti Care Med*. 1998; 157

Clinical Course of SSc-ILD

- 142 SSc-ILD patients (14 clinical centers) - Prospective RCT (1:1 Oral MMF vs. CYC)
- Outcome: FVC change in 12 months

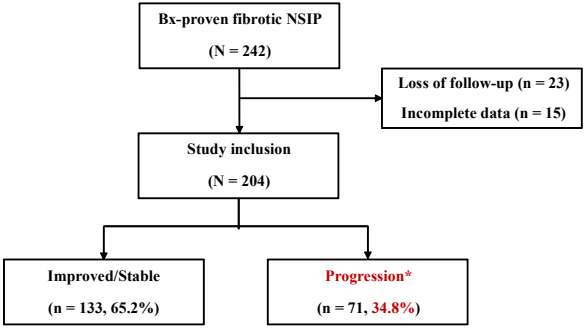




Tashkin DP *et al. Lancet Respir Med.* 2016;9(4)

Clinical Course of Bx-proven NSIP

- 204 Bx-proven fibrotic NSIP patients (Idiopathic and CTD-NSIP) (SMC)

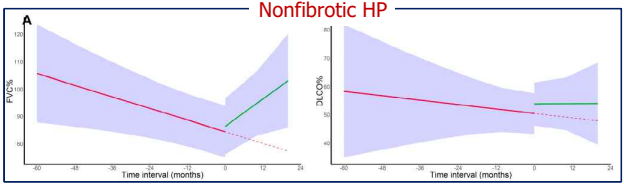


*** Progression defined according to INBUILD criteria**

Cho HK *et al. Ther Adv Respir Dis.* 2022;16

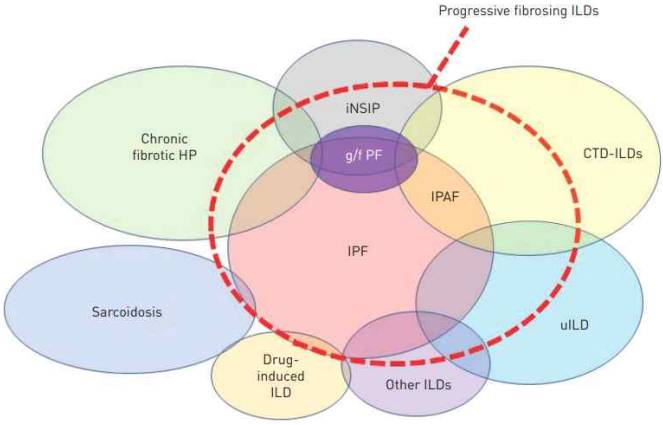
Clinical Course of HP (Fibrotic vs. Nonfibrotic)

- 202 patients with HP (93 nonfibrotic + 109 fibrotic)
- Retrospective observational study (Univ. of Leuven)
- Fibrosis determined by HRCT (Reticulation, traction BE, HC)



De Sadeleer LJ *et al. J Clin Med*. 2019;8

Concept of Progressive Fibrosing ILD



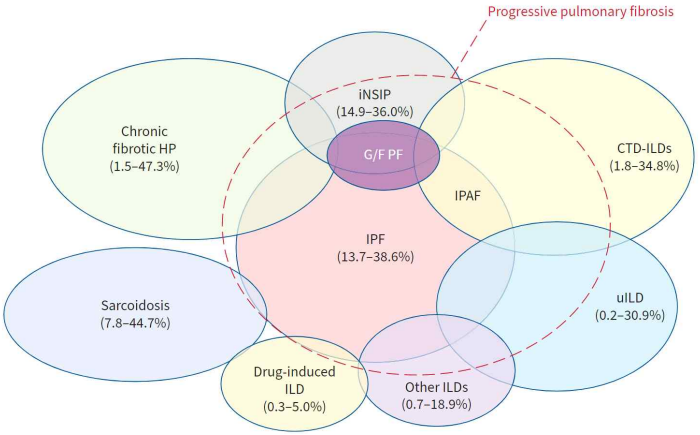
Cottin V. *Eur Respir Rev.* 2019; 28

Concept of Progressive Fibrosing ILD

- Newly suggested classification concept of ILD
- Chronic fibrosing ILD with progressive course (despite treatment)
- Examples of PF-ILD
  - ✓ Idiopathic pulmonary fibrosis
  - ✓ Idiopathic fibrotic NSIP, CTD-ILD (eg. RA-ILD, SSc-ILD), fibrotic HP (chronic HP), unclassifiable ILD, sarcoidosis etc.

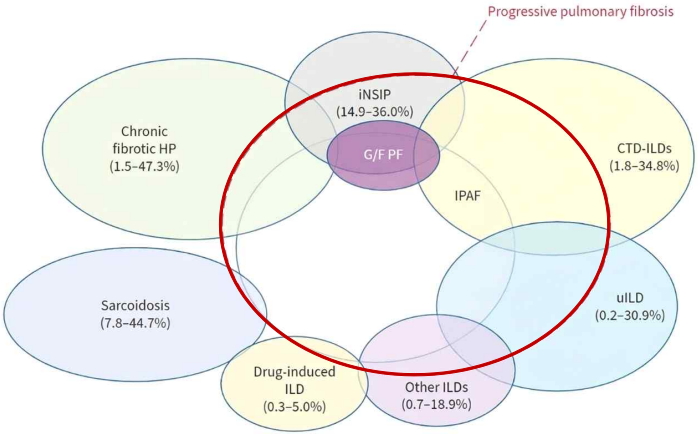
Cottin V. Eur *Respir Rev.* 2019; 28
George PM *et al. Lancet Respir Med.* 2020; 8

Concept of Progressive Pulmonary Fibrosis



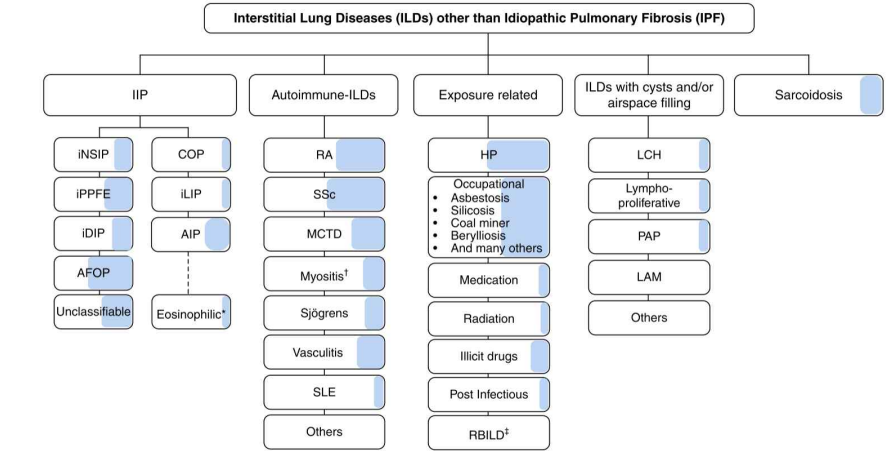
Rajan SK. *Eur Respir Rev*. 2023;61

Concept of Progressive Pulmonary Fibrosis



Rajan SK. *Eur Respir Rev*. 2023;61

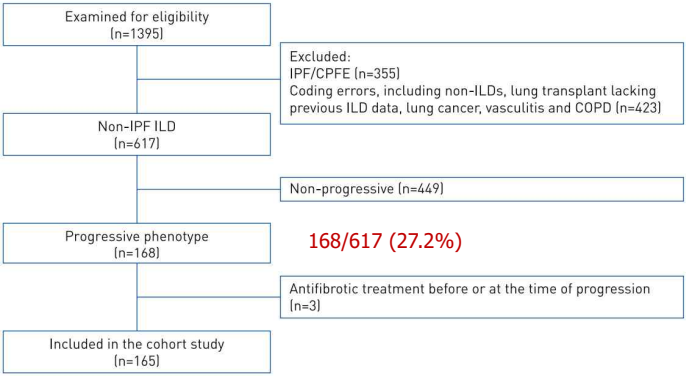
Concept of Progressive Pulmonary Fibrosis



Raghu G *et al. Am J Respir Crit Care Med.* 2022;205(9)

Epidemiology of PPF

- Single center retrospective cohort (France)

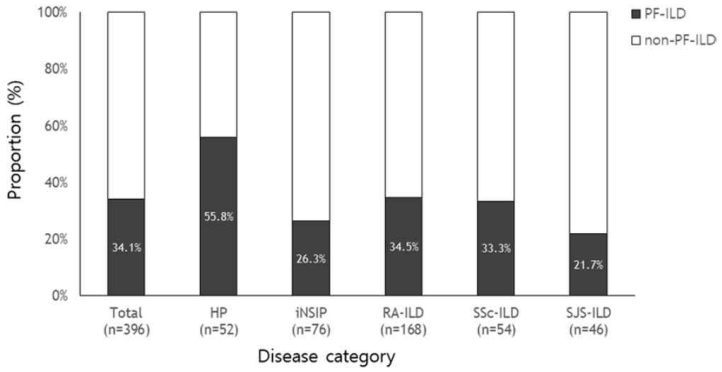


*** Progression defined according to INBUILD criteria**

Nasser M *et al. Eur Respir J.* 2021;57

Epidemiology of PPF

- Single center retrospective cohort (AMC)



*** Progression defined according to INBUILD criteria**

Kwon BS *et al*. *Respir Res*. 2021;22

Clinical Course of PPF vs. IPF

-221.0 mL/y

-192.9 mL/y

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	
INBUILD [UIP-like fibrotic pattern]	202 202 201	197	198	198	192
INBUILD [other fibrotic patterns]	123 124 124	123	121	120	112

Non-IPF PF-ILD 192.9 mL vs. IPF 221.0 mL

Brown KK *et al. Eur Respir J.* 2020; 55(5)

CONTENTS

Definition of PPF

Progressive Pulmonary Fibrosis

- Definition and parameters of "**Fibrosis**"
  - ✓ Radiographic (HRCT) evidence of fibrosis (e.g. reticulation, traction BE, HC etc.)
  - ✓ Extent (e.g. > 10%)

- Definition and parameters of "**Progressive**"
  - ✓ Various definitions
  - ✓ Suggested parameters: FVC decline and/or DLco decline, HRCT extent of progression, symptoms (dyspnea etc.)
  - ✓ Severity and duration

Cottin V. Eur *Respir Rev.* 2019; 28
George PM *et al. Lancet Respir Med.* 2020; 8

Definitions of Fibrosis and Progression

	Term	Fibrosis	Progression
INBUILD (Nintedanib for PF-ILD)	Progressive fibrosing ILD	Fibrosis > 10% of lung (HRCT) (Reticular abnormality with traction BE with/out honeycombing)	• 24 months before screening 1) FVC dec ≥ 10% (Relative) 2) 5% ≤ FVC < 10% (Relative) + worsening Sx or HCRT extent increase 3) Worsening Sx + CT extent increase
RELIEF (PFD for non-IPF ILD)	Progressive fibrotic ILD	Fibrotic lung disease (HRCT)	• Within 6-24 months FVC decline ≥ 5% (Absolute)
uILD (PFD)	Progressive fibrosing unclassifiable ILD	Fibrosis > 10% of lung (HRCT)	• Within 6 months 1) FVC decline ≥ 5% (Absolute) 2) Significant Sx worsening
Cottin V et al.	Progressive fibrosis		• 24 months 1) FVC ≥ 10% (Relative) 2) DLco ≥ 15% (Relative) 3) 5% ≤ FVC < 10% (Relative) + Sx or HRCT worsening
George PM et al.	Progressive fibrosing		• 24 months 1) FVC ≥ 10% (Relative) 2) FVC ≥ 5% (Relative) + DLco ≥ 15% 3) FVC ≥ 5% (Relative) + HRCT extent increase 4) FVC ≥ 5% (Relative) + Sx worsening 5) Sx worsening + HRCT increase

Goos T et al. *J Clin Med.* 2020;9(6)
Cottin V *et al. Eur Respir Rev.* 2018;17
George PM et al. *Lancet Respir Med.* 2020;8

Definition of PPF

Definition of PPF

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 D_{LCO} (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

Definition of abbreviations: ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; PPF = progressive pulmonary fibrosis.
*Although it is critical to exclude alternative explanations of worsening features for all patients with suspected progression, this is particularly important in patients with worsening respiratory symptoms and/or decline in D_{LCO} given the lower specificity of these features for PPF compared with FVC and chest computed tomography.

Raghu G *et al. Am J Respir Crit Care Med.* 2022;205(9)

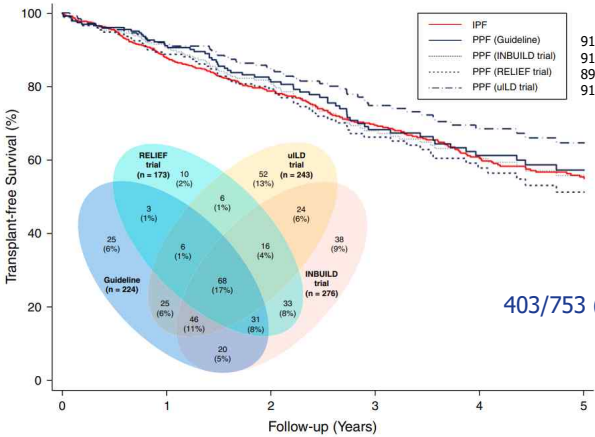
Different Definitions of PPF

- Prospective Austin Health ILD Registry (Australia) + Canadian Registry for Pulmonary Fibrosis (CARE-PF)

Characteristic	Non-IPF (*n* = 753)	PPF				IPF (*n* = 712)
		Guideline (*n* = 224)	INBUILD Trial (*n* = 276)	RELIEF Trial (*n* = 173)	uILD Trial (*n* = 243)	
		(30%)	(37%)	(23%)	(32%)	
Included Patients						
Age at diagnosis, years, *Mdn* (IQR)	61 (51–68)	61 (53–68)	59 (49–67)	61 (51–67)	61 (52–68)	70 (64–75)
Males, *n* (%)	318 (42)	84 (38)	111 (40)	69 (40)	98 (40)	512 (72)
BMI at diagnosis, kg/m^2, *Mdn* (IQR)	28 (25–33)	29 (25–33)	29 (25–33)	29 (25–32)	29 (25–33)	29 (26–32)
Smoking history at baseline						
Ever-smokers, *n* (%)	399 (53)	128 (57)	153 (55)	98 (57)	137 (56)	536 (75)
Pack-years among smokers, *Mdn* (IQR)	16 (7–33)	16 (7–33)	15 (7–30)	16 (8–33)	16 (9–32)	26 (11–39)
Pulmonary function at diagnosis, mean ± SD						
FEV_1/FVC	80 ± 9	80 ± 8	81 ± 7	80 ± 8	79 ± 8	80 ± 8
FEV_1, % predicted	77 ± 19	76 ± 19	73 ± 18	76 ± 18	75 ± 19	83 ± 18
FVC, % predicted	76 ± 19	76 ± 20	72 ± 19	76 ± 19	76 ± 19	79 ± 18
DLCO, % predicted	61 ± 20	60 ± 20	55 ± 17	56 ± 17	58 ± 19	57 ± 18
Non-IPF ILD subtypes, *n* (%)*						
CTD-ILD	372 (49)	120 (32)	163 (44)	99 (27)	130 (35)	—
Fibrotic HP	73 (10)	29 (40)	30 (41)	19 (26)	26 (36)	—
Idiopathic NSIP	10 (1)	2 (20)	4 (40)	2 (20)	4 (40)	—
Sarcoidosis	46 (6)	11 (24)	5 (11)	2 (4)	9 (20)	—
Unclassifiable ILD	169 (22)	47 (28)	57 (34)	42 (25)	51 (30)	—
Other	83 (11)	15 (18)	17 (20)	9 (11)	23 (28)	—
Immunosuppressant use during evaluation period for PPF, *n* (%)†						
Azathioprine	—	49 (22)	103 (37)	57 (33)	39 (16)	—
Cyclophosphamide	—	28 (13)	57 (21)	27 (16)	27 (11)	—
Mycophenolate	—	90 (40)	212 (77)	120 (69)	76 (31)	—
Prednisone	—	83 (37)	170 (62)	101 (58)	72 (30)	—
Rituximab	—	13 (6)	30 (11)	16 (9)	7 (3)	—
Time to meet PPF definition, months, *Mdn* (IQR)	—	11 (7–13)	10 (6–16)	12 (8–16)	5 (3–7)	—

Khor YH *et al. Am J Respir Crit Care Med.* 2023;207(1)

Different Definitions of PPF



403/753 (54%)

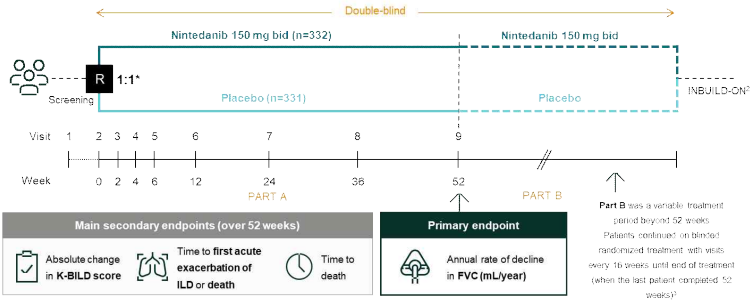
Khor YH *et al. Am J Respir Crit Care Med.* 2023;207(1)

CONTENTS

Nintedanib for PF-ILD (INBUILD trial)

ORIGINAL ARTICLE

Nintedanib in Progressive Fibrosing Interstitial Lung Diseases



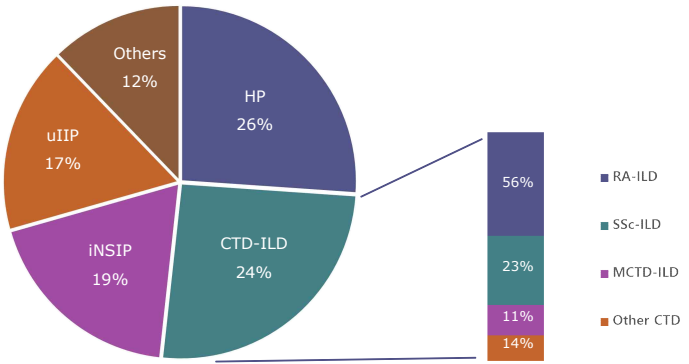
Flaherty KR *et al. N Engl J Med.* 2019; 381(18)

Nintedanib for PF-ILD (INBUILD trial)

- Double-blind placebo-controlled phase 3 trial (15 countries)
- 663 Progressive fibrosing ILD [(HP, CTD-ILD, idiopathic NSIP, uIIP etc.)]
- PF-ILD (Progression within 24 months despite standard treatment)
  - ✓ FVC relative decline ≥10%
  - ✓ 5% ≤ FVC decline < 10% + Worsening respiratory Sx or Increased fibrosis on CT
  - ✓ Worsening respiratory Sx + increased fibrosis on CT
- Exclusion
  - ✓ AZA, CYC, MMF, Tacrolimus, Rituximab, Cytoxan, Steroid (>20mg)
- Protocol
  - ✓ (1:1 ratio) Nintedanib 150mg bid vs. Placebo for 52 weeks
- Outcome
  - ✓ Annual rate of FVC decline
  - ✓ Change of K-BILD, time till 1st AE, and time till death

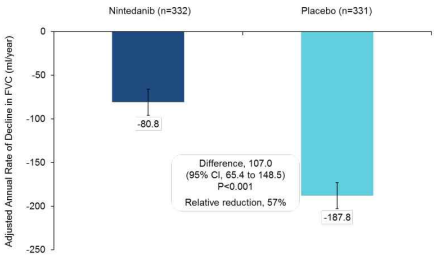
Flaherty KR *et al. N Engl J Med.* 2019; 381(18)

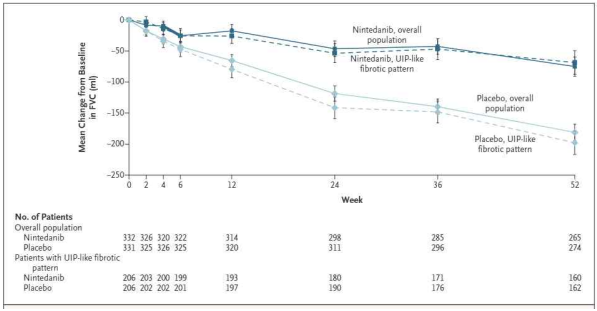
Nintedanib for PF-ILD (INBUILD trial)



Flaherty KR *et al. N Engl J Med.* 2019; 381(18)

Nintedanib for PF-ILD (INBUILD trial)





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

Flaherty KR *et al. N Engl J Med.* 2019; 381(18)

Nintedanib for PF-ILD (INBUILD trial)

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)

Event	Nintedanib (N=332)	Placebo (N=331)
	no. of patients (%)	
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)

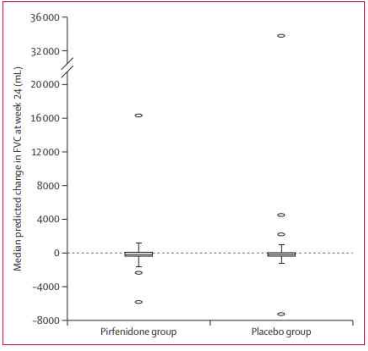
Flaherty KR *et al. N Engl J Med.* 2019; 381(18)

Pirfenidone for Unclassifiable PF-ILD

- Double-blind placebo-controlled phase 2 trial (70 centers)
- 253 unclassifiable ILD
- Patients
  - ✓ Unclassifiable ILD (Not able to classify with moderate to high confidence)
  - ✓ FVC ≥ 45% and DLco ≥ 30% and HRCT fibrosis ≥ 10% and 6 MWD ≥ 150m
  - ✓ FVC absolute decline ≥ 5% or worsening of Sx within 6 months
- Protocol
  - ✓ (1:1 ratio) PFD 2403 mg vs. Placebo for 24 weeks
- Outcome
  - ✓ Mean FVC change (24 weeks) by daily home spirometry
  - ✓ Change in FVC (site spirometry), DLco, 6MWD, UCSD-SOBQ score, SGRQ score

Maher TM *et al. Lancet Respir Med.* 2020;8(2)

Pirfenidone for Unclassifiable PF-ILD



PFD	Placebo
-87.7 mL	-157.1 mL
(-338.1 – 148.6)	(-370.9 – 70.1)

Maher TM *et al. Lancet Respir Med*. 2020;8

Pirfenidone for Unclassifiable PF-ILD

	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

Maher TM *et al. Lancet Respir Med*. 2020;8

Pirfenidone for Unclassifiable PF-ILD

	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%)

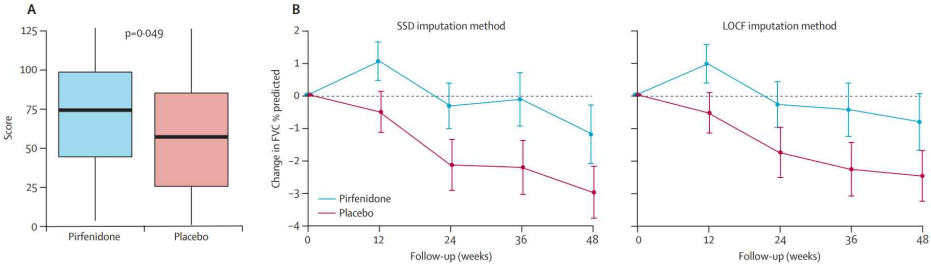
Maher TM *et al. Lancet Respir Med*. 2020;8

Pirfenidone for Non-IPF Lung Fibrosis (RELIEF trial)

- Double-blind placebo-controlled phase 2b trial (RELIEF trial) (17 centers)
- 127 non-IPF lung fibrosis (57 CHP, 37 CVD-ILD, 27 fibrotic NSIP, 6 asbestos-ILD)
- Patients
  - ✓ Annual absolute FVC decline ≥ 5% (Three FVC measurement within 6-24 months)
  - ✓ CVD-LF, Fibrotic NSIP, Chronic HP, Asbestos-induced lung fibrosis
- Protocol
  - ✓ (1:1 ratio) PFD 2403 mg vs. Placebo for 48 weeks
- Outcome
  - ✓ Absolute FVC change (48 weeks)
  - ✓ Change in FVC (categorical), DLco, 6MWT D, SGRQ, PFS, Adverse event

Behr J *et al. Lancet Respir Med.* 2021;9(5)

Pirfenidone for Non-IPF Lung Fibrosis (RELIEF trial)



Behr J *et al. Lancet Respir Med.* 2021;9(5)

Pirfenidone for Non-IPF Lung Fibrosis (RELIEF trial)

	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**

Behr J *et al. Lancet Respir Med.* 2021;9(5)

Pirfenidone for Non-IPF Lung Fibrosis (RELIEF trial)

	Pirfenidone (n=64)	Placebo (n=63)	Total number of SAEs (n=64)	Total number of patients with ≥1 SAE (n=127)
Number of patients with SAEs	26 (41%)	35 (56%)	..	61 (48%)
Infections and infestations	5 (8%)	10 (16%)	15	15 (12%)
General disorders and administration site conditions including disease worsening	2 (3%)	7 (11%)	10	9 (7%)
Respiratory, thoracic, and mediastinal disorders	4 (6%)	4 (6%)	9	8 (6%)
Surgical and medical procedures	4 (6%)	2 (3%)	7	6 (5%)
Cardiac disorders	1 (2%)	5 (8%)	6	6 (5%)
Neoplasms benign, malignant, and unspecified (with cysts or polyps)	2 (3%)	3 (5%)	5	5 (4%)
Injury, poisoning, or procedural complications	1 (2%)	2 (3%)	3	3 (2%)
Investigations	1 (2%)	1 (2%)	2	2 (2%)
Nervous system disorders	2 (3%)	0	2	2 (2%)
Musculoskeletal and connective tissue disorders	2 (3%)	0	2	2 (2%)
Renal and urinary disorders	1 (2%)	1 (2%)	2	2 (2%)
Gastrointestinal disorders	1 (2%)	0	1	1 (1%)
Deaths*	1 (2%)	5 (8%)	..	6 (5%)

Data are n (%) or n. SAEs=serious adverse events. All SAEs are listed according to System Organ Class in the Medical Dictionary for Regulatory Activities, version 22.1 (a full listing of preferred terms is in appendix 1, pp 8-9). *3/5 placebo deaths and 0/5 of pirfenidone deaths were respiratory-related.

Table 3: **Incidence of SAEs at the level of System Organ Class**

Behr J *et al. Lancet Respir Med*. 2021;9(5)

Guidelines on Antifibrotics for PPF

Nintedanib

- We suggest nintedanib for the treatment of PPF in patients who have failed standard management for fibrotic ILD, other than IPF (conditional recommendation, low-quality evidence)
- We recommend research into the efficacy, effectiveness, and safety of nintedanib in specific types of non-IPF ILD manifesting PPF

Pirfenidone

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

Raghu G *et al. Am J Respir Crit Care Med.* 2022;205(9)

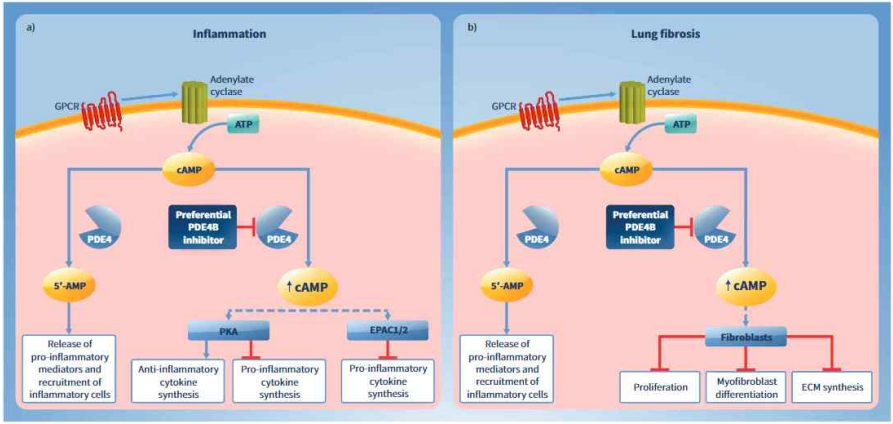
Korean Guidelines on Antifibrotics for PPF

- **권고사항**
  - 전문가 합의에 따라 표준 치료에 실패한 진행성 폐섬유증 환자의 치료제로 nintedanib 사용을 권고한다. (근거 수준: 전문가 합의, 권고등급: 강하게 권고)

- **요약**

  진행성 폐섬유증(Progressive Pulmonary Fibrosis, PPF)는 기존의 Non-IPF ILD 중 적절한 치료에도 불구하고 급속히 섬유화가 진행되는 질환군들을 지칭한다. 임상 증상, 생리학적 근거 및 영상학적 근거 중 최소 두 가지 기준을 만족 시 진단이 가능하다. 치료제로는 전문가 합의에 따라 nintedanib은 조건부 사용을 권고하지만, pirfenidone 사용에 대해서는 추가 연구가 더 필요하다.

Nerandomilast (Preferential PDE4B inhibitor)

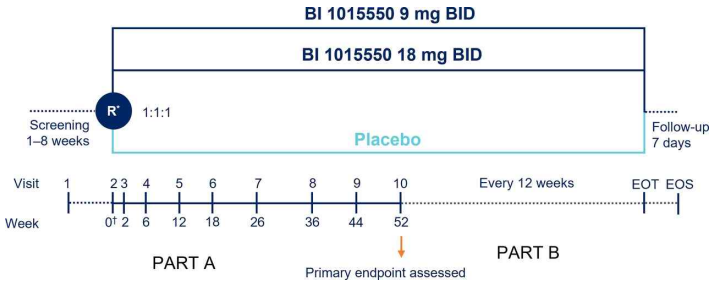


Kolb M *et al. Eur Respir Rev.* 2023; 32:220206

Nerandomilast for PPF (FIBRONEER-ILD trial)

ORIGINAL ARTICLE

Nerandomilast in Patients with Progressive Pulmonary Fibrosis



Maher TM *et al. N Engl J Med.* 2025; 392(22)

Nerandomilast for PPF (FIBRONEER-ILD trial)

- Double-blind placebo-controlled phase 3 trial (403 sites in 44 countries)
- 1176 PPF [(Autoimmune ILD, HP, uIIP, Other ILDs)]
- PPF (Progression within 24 months despite standard treatment)
  - ✓ FVC relative decline ≥10%
  - ✓ 5% ≤ FVC decline < 10% + Worsening respiratory Sx or Increased fibrosis on CT
  - ✓ Worsening respiratory Sx + increased fibrosis on CT
- Exclusion
  - ✓ CYC, Tocilizumab, MMF, Rituximab, PD (≥ 20mg)
- Protocol
  - ✓ (1:1:1 ratio) Nerandomilast 18mg bid vs. 9mg bid vs. placebo for 52 weeks
- Outcome
  - ✓ Absolute change of FVC at 52 week
  - ✓ 1st AE, hospitalization for respiratory cause, or death

Maher TM *et al. N Engl J Med.* 2025; 392(22)

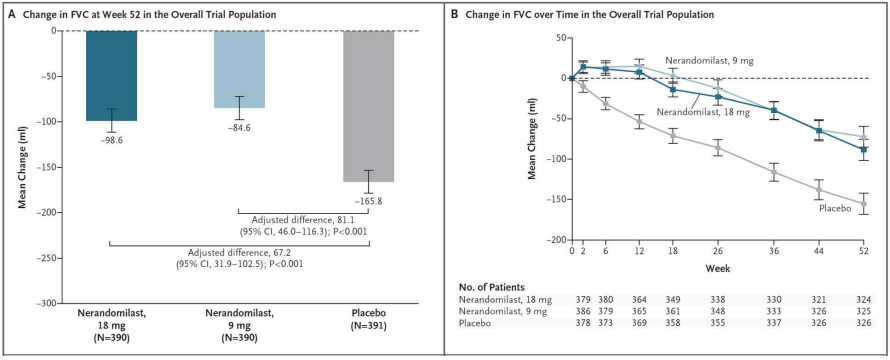
Nerandomilast for PPF (FIBRONEER-ILD trial)

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Nerandomilast, 18 mg (N=391)	Nerandomilast, 9 mg (N=393)	Placebo (N=392)
Male sex — no. (%)	220 (56.3)	203 (51.7)	231 (58.9)
Age — yr	66.0±9.8	66.5±9.8	66.6±10.3
Weight — kg	73.2±17.1	72.1±17.5	73.4±17.9
Smoking status — no. (%)			
Never smoked	191 (48.8)	200 (50.9)	186 (47.4)
Former smoker	189 (48.3)	186 (47.3)	200 (51.0)
Current smoker	11 (2.8)	7 (1.8)	6 (1.5)
Time since diagnosis of ILD — yr	4.6±4.8	4.1±4.3	3.9±3.6
FVC			
Mean value — ml	2381±723	2326±768	2354±766
Percentage of predicted value	70.4±15.5	70.3±15.7	69.7±16.2
Percentage of predicted DLco†	49.4±17.5	48.7±16.8	49.7±16.5
Background nintedanib therapy — no. (%)‡	171 (43.7)	173 (44.0)	170 (43.4)
UIP or UIP-like fibrotic pattern on high-resolution CT — no. (%)	275 (70.3)	290 (73.8)	275 (70.2)
ILD diagnosis			
Autoimmune ILD	113 (28.9)	112 (28.5)	100 (25.5)
Hypersensitivity pneumonitis	73 (18.7)	83 (21.1)	77 (19.6)
Unclassifiable idiopathic interstitial pneumonia	73 (18.7)	76 (19.3)	82 (20.9)
Idiopathic nonspecific interstitial pneumonia	82 (21.0)	73 (18.6)	73 (18.6)
Other ILD	50 (12.8)	49 (12.5)	60 (15.3)
Supplemental oxygen therapy — no. (%)§	117 (29.9)	97 (24.7)	110 (28.1)

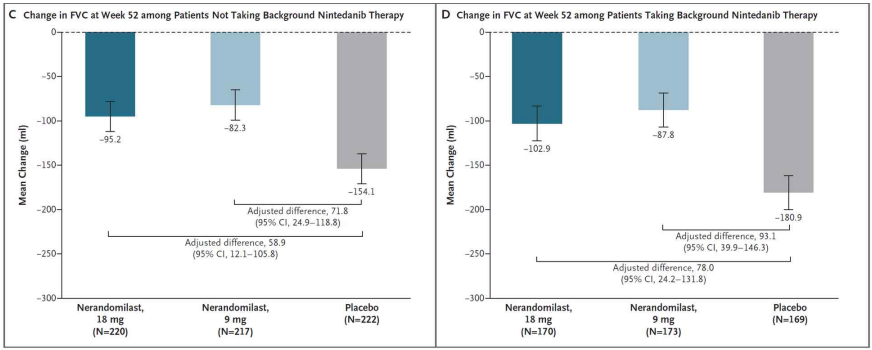
Maher TM *et al. N Engl J Med.* 2025; 392(22)

Nerandomilast for PPF (FIBRONEER-ILD trial)



Maher TM *et al. N Engl J Med.* 2025; 392(22)

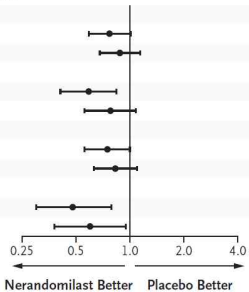
Nerandomilast for PPF (FIBRONEER-ILD trial)



Maher TM *et al. N Engl J Med.* 2025; 392(22)

Nerandomilast for PPF (FIBRONEER-ILD trial)

End Point	Nerandomilast	Placebo	Hazard Ratio (95% CI)	P Value
	no. with event/no. of patients			
Key secondary end point				
Nerandomilast, 18 mg	95/391	122/392	0.77 (0.59–1.01)	0.06
Nerandomilast, 9 mg	110/393	122/392	0.88 (0.68–1.14)	0.34
Acute exacerbation of ILD or death				
Nerandomilast, 18 mg	48/391	83/392	0.59 (0.41–0.84)	
Nerandomilast, 9 mg	65/393	83/392	0.78 (0.56–1.08)	
Hospitalization for respiratory cause or death				
Nerandomilast, 18 mg	84/391	110/392	0.75 (0.56–1.00)	
Nerandomilast, 9 mg	97/393	110/392	0.83 (0.63–1.10)	
Death				
Nerandomilast, 18 mg	24/391	50/392	0.48 (0.30–0.79)	
Nerandomilast, 9 mg	33/393	50/392	0.60 (0.38–0.95)	



Maher TM *et al. N Engl J Med.* 2025; 392(22)

Nerandomilast for PPF (FIBRONEER-ILD trial)

Table 2. Adverse Events over a Period of 52 Weeks.*

Event Category	All Patients			No Background Nintedanib Therapy			Background Nintedanib Therapy†		
	Nerandomilast		Placebo	Nerandomilast		Placebo	Nerandomilast		Placebo
	18 mg (N=391)	9 mg (N=393)	(N=392)	18 mg (N=220)	9 mg (N=220)	(N=222)	18 mg (N=171)	9 mg (N=173)	(N=170)
	number of patients (percent)								
Any event	362 (92.6)	362 (92.1)	360 (91.8)	202 (91.8)	200 (90.9)	202 (91.0)	160 (93.6)	162 (93.6)	158 (92.9)
Most frequent events‡									
Diarrhea	143 (36.6)	116 (29.5)	97 (24.7)	59 (26.8)	33 (15.0)	35 (15.8)	84 (49.1)	83 (48.0)	62 (36.5)
Cough	58 (14.8)	49 (12.5)	55 (14.0)	35 (15.9)	24 (10.9)	31 (14.0)	23 (13.5)	25 (14.5)	24 (14.1)
URT infection	46 (11.8)	39 (9.9)	60 (15.3)	31 (14.1)	26 (11.8)	44 (19.8)	15 (8.8)	13 (7.5)	16 (9.4)
Covid-19	42 (10.7)	41 (10.4)	58 (14.8)	26 (11.8)	20 (9.1)	27 (12.2)	16 (9.4)	21 (12.1)	31 (18.2)
Condition aggravated	28 (7.2)	46 (11.7)	57 (14.5)	12 (5.5)	24 (10.9)	34 (15.3)	16 (9.4)	22 (12.7)	23 (13.5)
Depression	40 (10.2)	38 (9.7)	44 (11.2)	23 (10.5)	21 (9.5)	24 (10.8)	17 (9.9)	17 (9.8)	20 (11.8)
Nasopharyngitis	34 (8.7)	45 (11.5)	39 (9.9)	16 (7.3)	21 (9.5)	18 (8.1)	18 (10.5)	24 (13.9)	21 (12.4)
Anxiety	37 (9.5)	40 (10.2)	37 (9.4)	22 (10.0)	20 (9.1)	20 (9.0)	15 (8.8)	20 (11.6)	17 (10.0)
Nausea	40 (10.2)	30 (7.6)	26 (6.6)	13 (5.9)	9 (4.1)	8 (3.6)	27 (15.8)	21 (12.1)	18 (10.6)
Weight decreased	42 (10.7)	27 (6.9)	23 (5.9)	23 (10.5)	11 (5.0)	9 (4.1)	19 (11.1)	16 (9.2)	14 (8.2)
Event leading to discontinuation of trial regimen									
Any	39 (10.0)	32 (8.1)	40 (10.2)	19 (8.6)	16 (7.3)	23 (10.4)	20 (11.7)	16 (9.2)	17 (10.0)
Diarrhea	10 (2.6)	5 (1.3)	2 (0.5)	3 (1.4)	0	0	7 (4.1)	5 (2.9)	2 (1.2)
Event leading to interruption of trial regimen	69 (17.6)	68 (17.3)	59 (15.1)	28 (12.7)	31 (14.1)	30 (13.5)	41 (24.0)	37 (21.4)	29 (17.1)
Serious events§									
Any	130 (33.2)	125 (31.8)	138 (35.2)	65 (29.5)	68 (30.9)	82 (36.9)	65 (38.0)	57 (32.9)	56 (32.9)
Fatal event	8 (2.0)	14 (3.6)	20 (5.1)	5 (2.3)	10 (4.5)	11 (5.0)	3 (1.8)	4 (2.3)	9 (5.3)

Maher TM *et al. N Engl J Med.* 2025; 392(22)

Takeaway (I)

Concept of PPF

- Fibrotic ILD other than IPF with progression
- Fibrotic HP, CTD-ILD, Idiopathic NSIP, unclassifiable ILD etc.

Clinical Significance of PPF

- 30-40% of Non-IPF ILD
- Fast decline of pulmonary function (similar to that of IPF)
- Poor prognosis (mortality)

Takeaway (II)

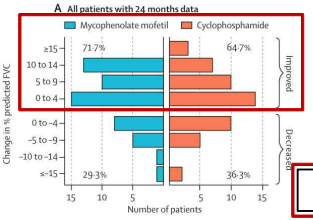
Diagnosis of PPF

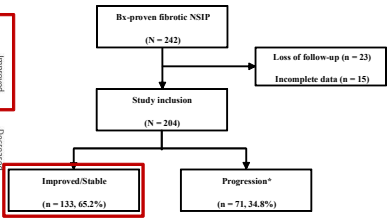
- Based on symptoms, physiology (FVC and DLco), and CT features
- Various definitions (from clinical trials and expert opinion)
- Criteria proposed by ATS/ERS/JRS/ALAT (2022)
- Further research including validation is required

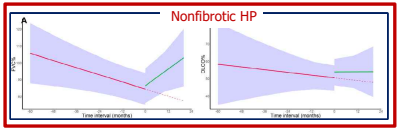
Treatment of PPF

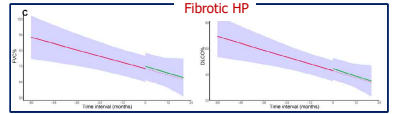
- Nintedanib (Recommended)
- Pirfenidone (Further research required)
- Nerandomilast
  - ✓ Preferential PDE4B inhibitor
  - ✓ Reduce lung function decline, possible mortality benefit

Progression despite Treatment…









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