135차 춘계학술대회 (Interactive Learning)

# Progressive Pulmonary Fibrosis (PPF)

## [Progressive Fibrosing-ILD (PF-ILD)]

유홍석

성균관대학교 의과대학
삼성서울병원 호흡기내과

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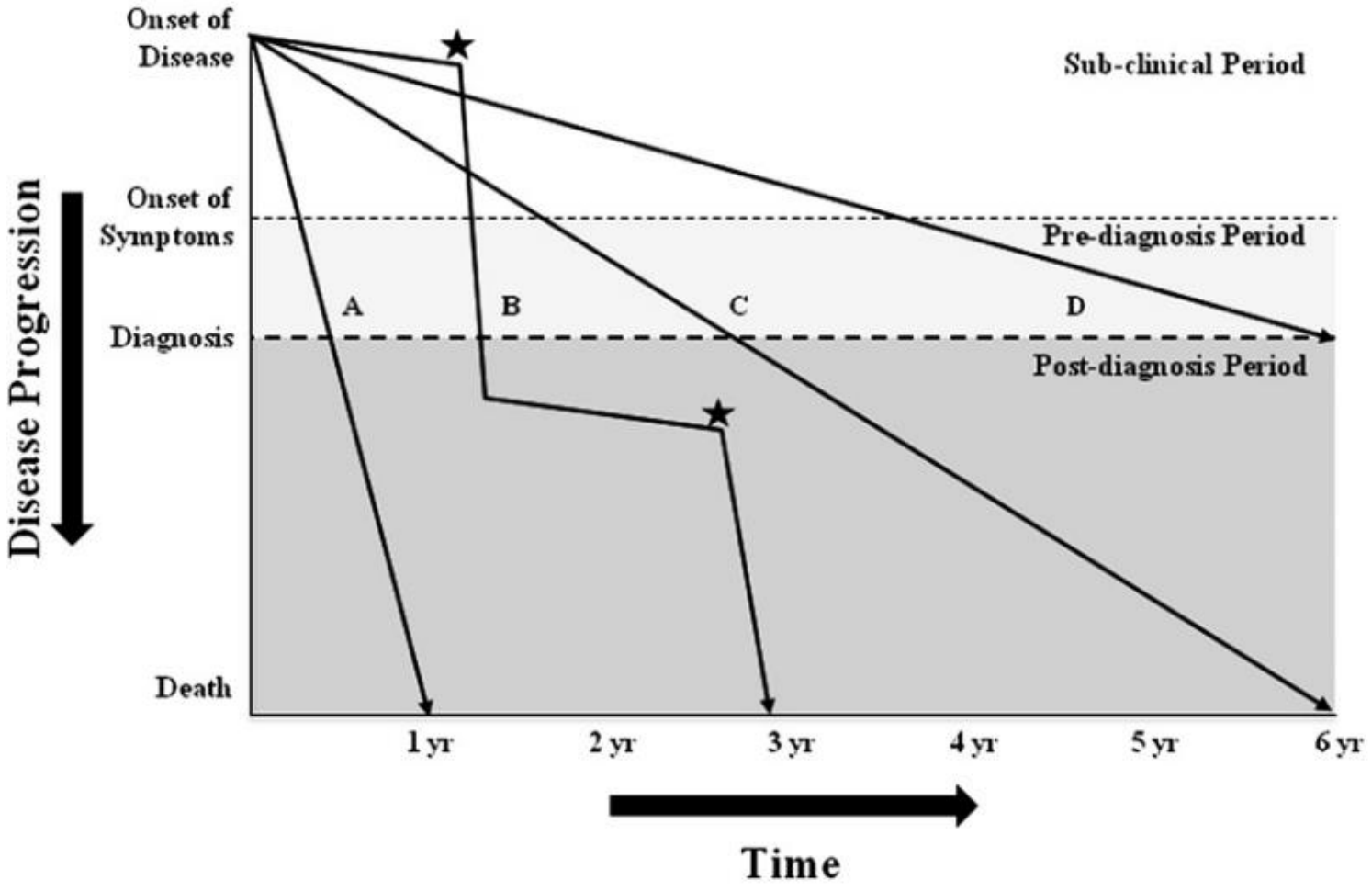
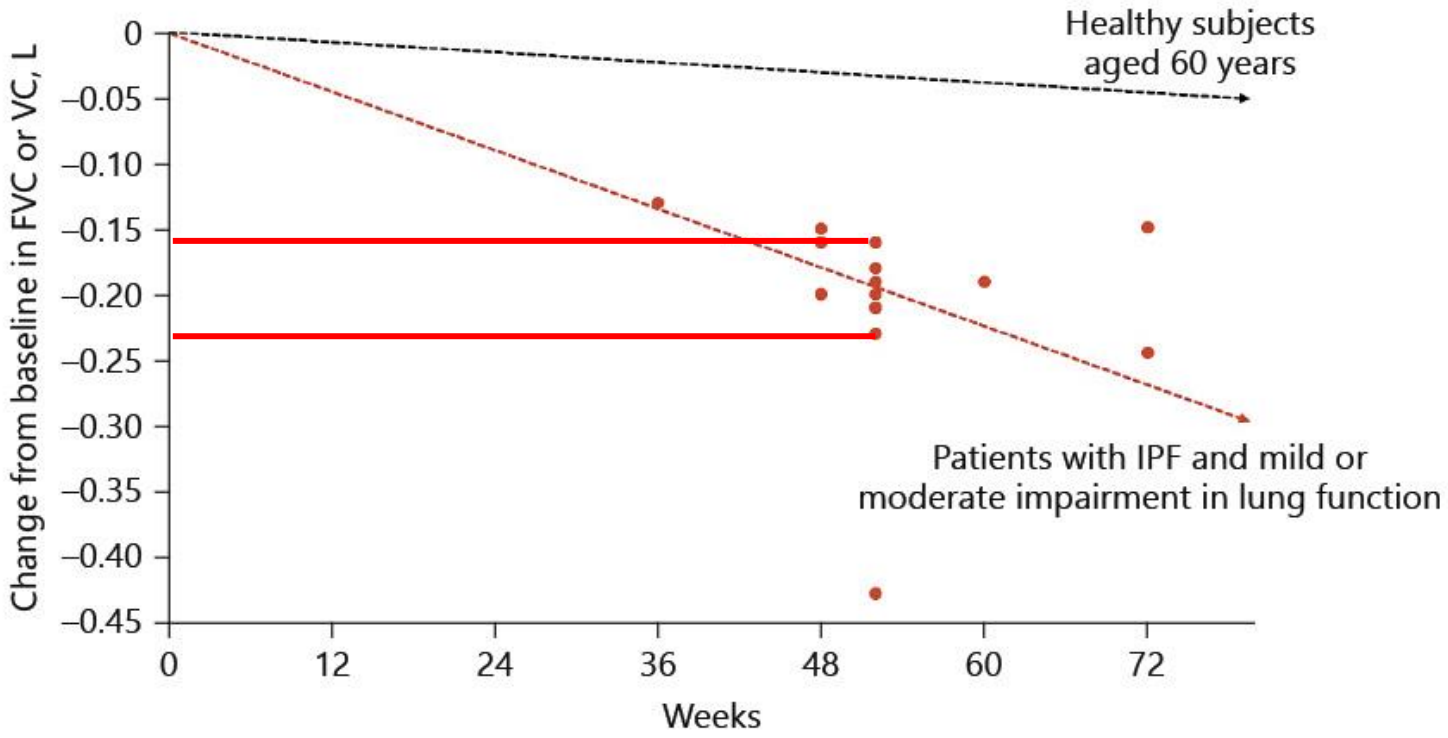
# Clinical Course of IPF



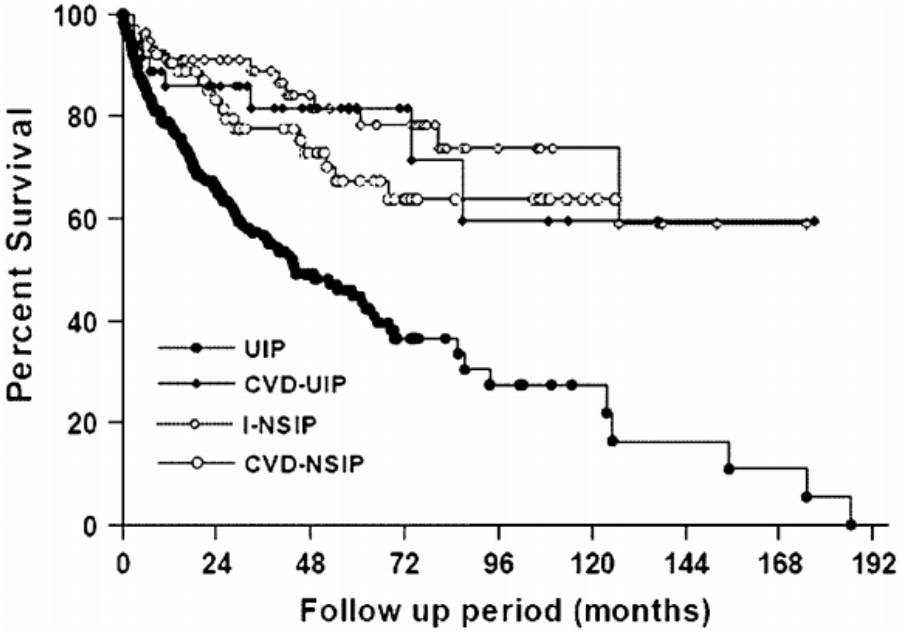

Ley B *et al*. *Am J Respir Crit Care Med*. 2011;183

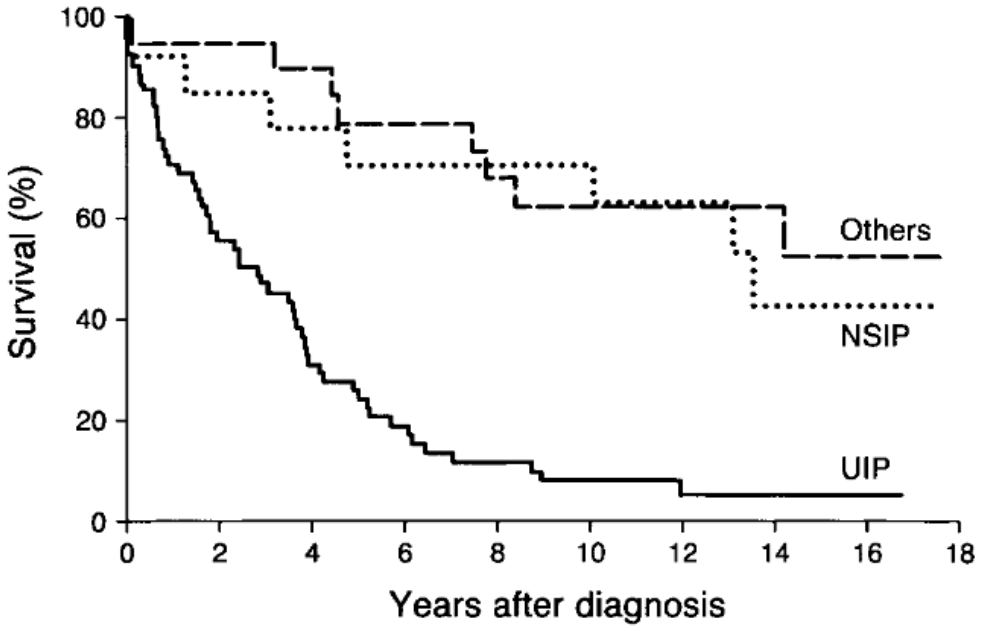
# Clinical Course of IPF




Wuyts WA *et al*. *Respiration*. 2020;99

# Prognosis of ILD



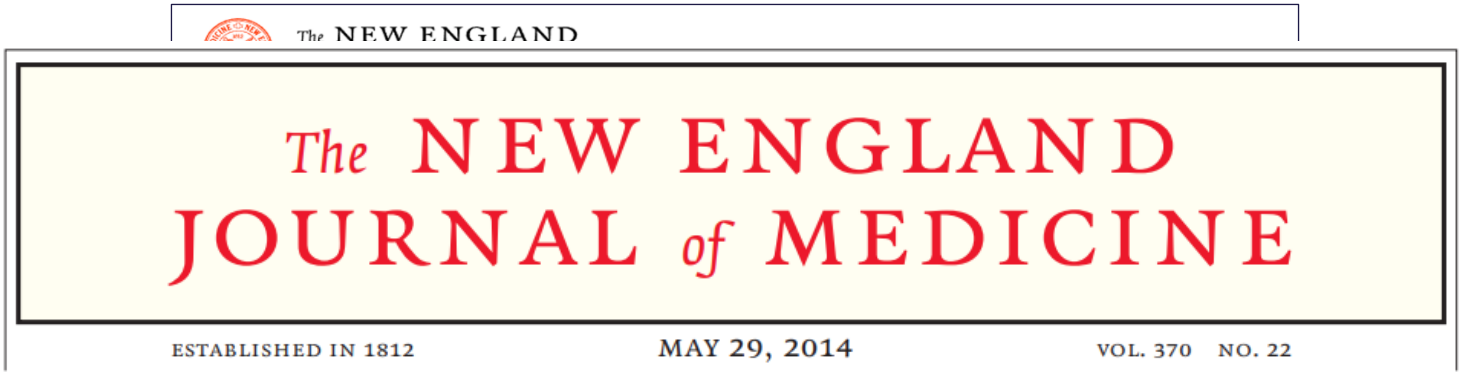

Park JH *et al*. *Am J Respir Crit Care Med*. 2007; 175
Bjoraker JA et al. *Am J Respir Crti Care Med*. 1998; 157

# Clinical Trials of IPF

| Trial | Drug | Endpoint | Outcome |
|---|---|---|---|
| BUILD-I (2008) | Bosentan | 6 MWD at 12 mo | (-) |
| NCT00063869 (2008) | Etanercept | FVC decline, DLco/A-a gradient over 48 wks | (-) |
| INSPIRE (2009) | IFNr-1b | Survival | (-) |
| NCT00131274 (2010) | Imatinib mesylate | Time to disease progression or death over 92 wks | (-) |
| STEP-IPF (2010) | Sildenafil | 6 MWD over 12 weeks<br>Dyspnea score at 6 mo | (-)<br>Improvement in dyspnea |
| BUILD-3 (2011) | Bosentan | Time to disease progression or death over 8-32 wks | (-) |
| ACE-IPF trial (2012) | Warfarin | Time to death or disease progression over 48 wks | (-)<br>Exc mortality in warfarin |
| PANTHER-IPF (2012) | NAC with/without AZAT + PD | FVC decline at 60 weeks | (-)<br>Increased mortality |
| ARTEMIS-IPF (2013) | Ambrisentan | Time to disease progression or death over 4 yrs | (-)<br>Interim analysis |
| MUSIC (2013) | Macitentan | FVC decline over 12 mo | (-) |

Rafii R *et al*. *J Thorac Dis*. 2013;15(1)

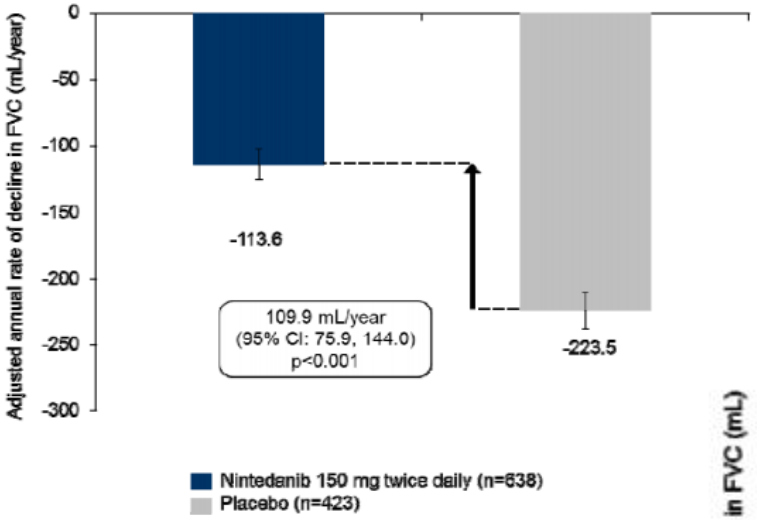
# Antifibrotics in IPF

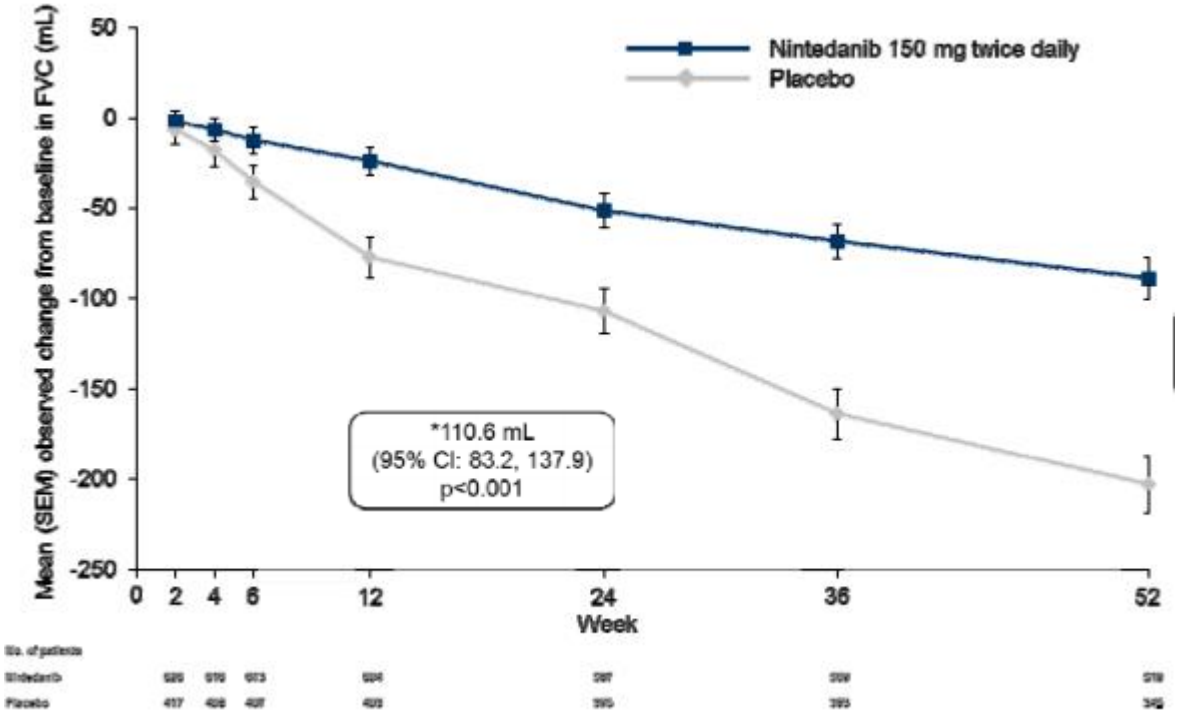





Raghu G *et al*. *N Engl J Med*. 2014; 370; 22
King TE *et al*. *N Engl J Med*. 2014; 370; 22

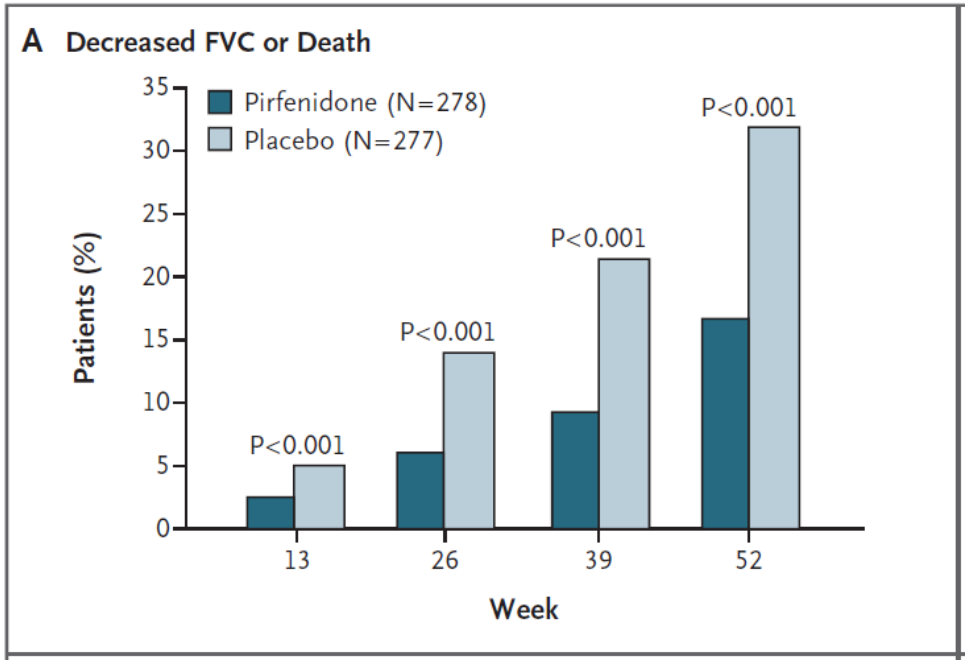
# Nintedanib for IPF (INPULSIS trial)

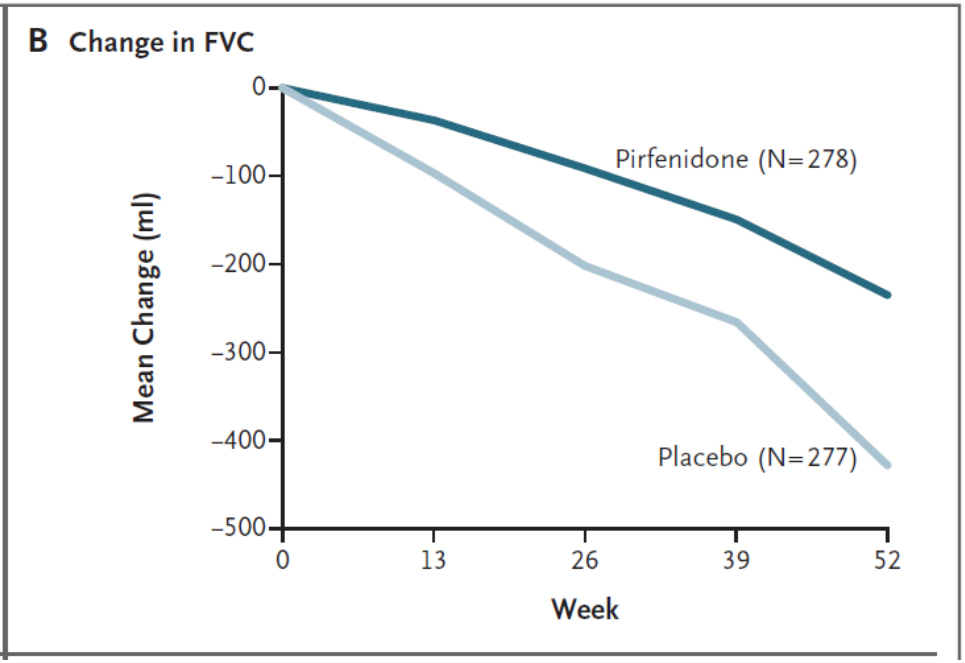



Richeldi L *et al*. *N Engl J Med*. 2014; 370

# Pirfenidone for IPF (ASCEND trial)



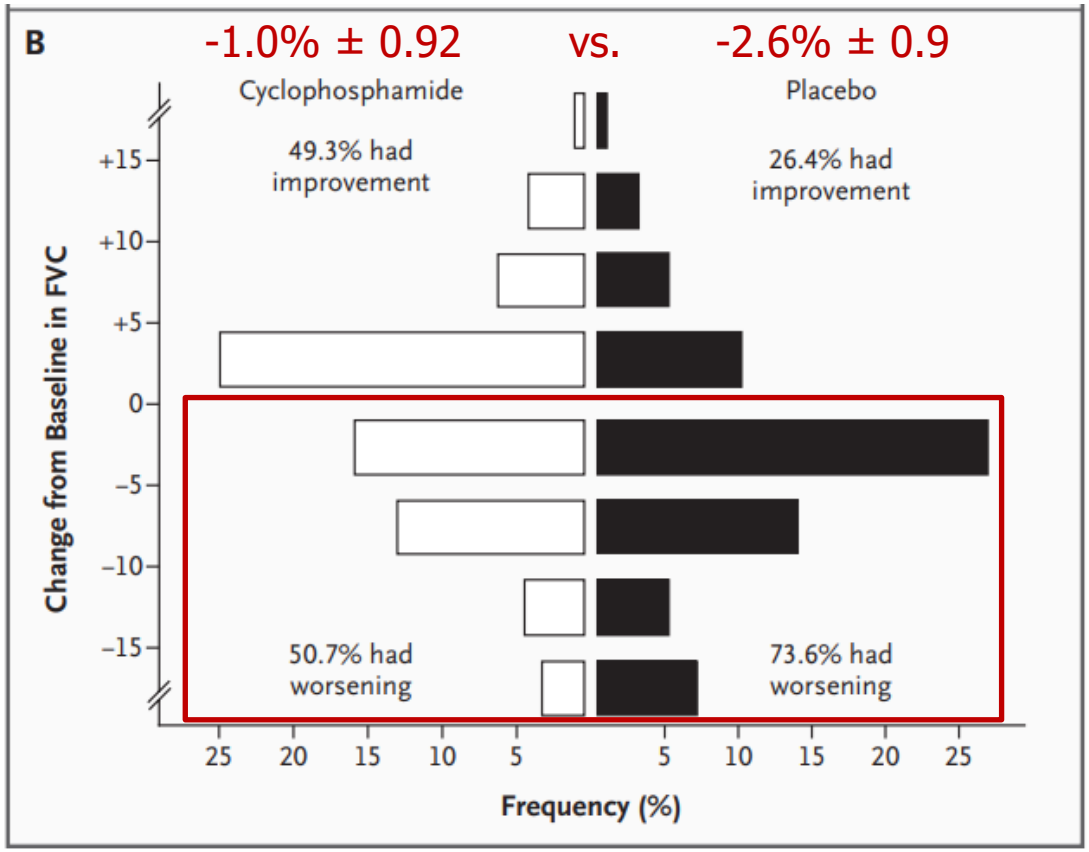

FVC ≥ 10% or death at 52 wk
PFD 16.5% vs. P 31.8%

FVC Decline over 52 weeks
PFD -164mL vs. P -280mL

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

# Systemic Sclerosis-ILD (SSc-ILD)

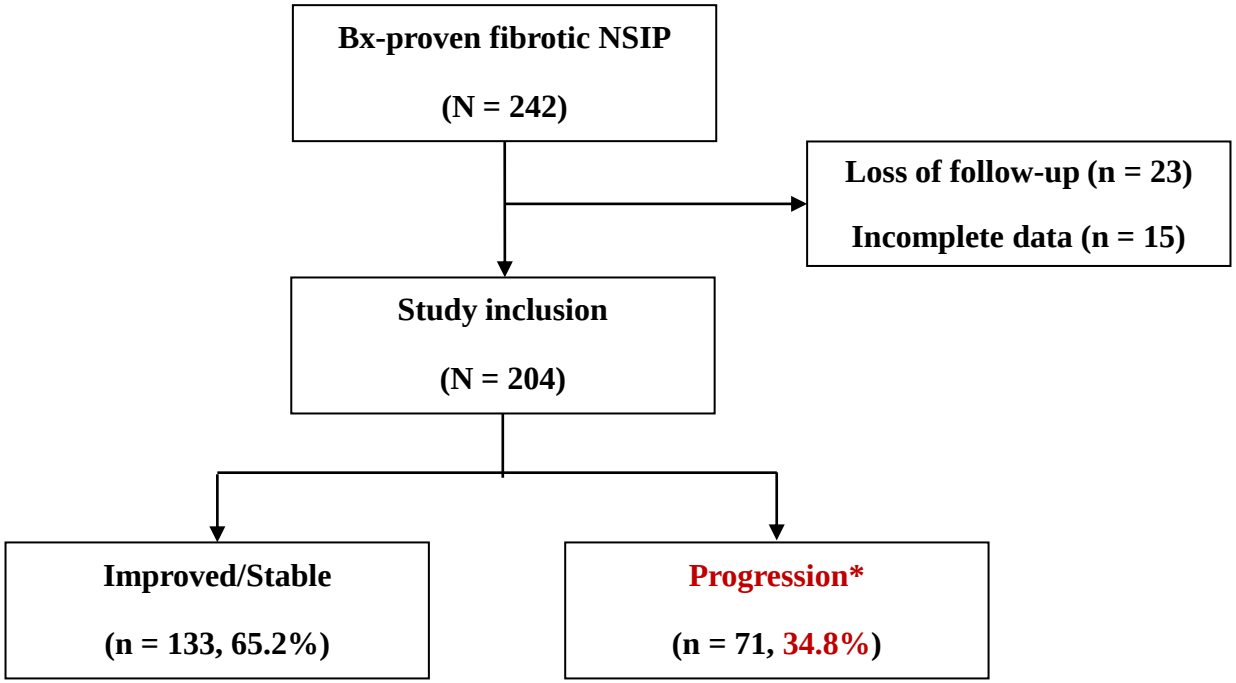
- 158 SSc-ILD patients (13 clinical centers)
- Prospective RCT (1:1 Oral CYC vs. Placebo)
- Outcome: FVC decline at 12 months




Tashkin DP *et al*. *N Engl J Med*. 2006; 354

# Nonspecific Interstitial Pneumonia (NSIP)

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



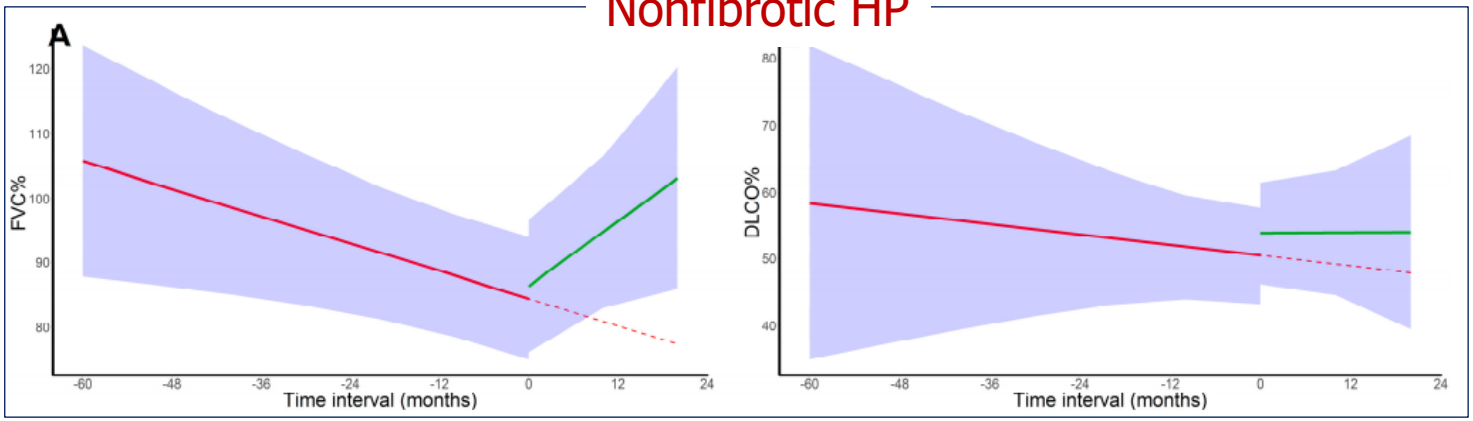

*** Progression defined according to INBUILD criteria**

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

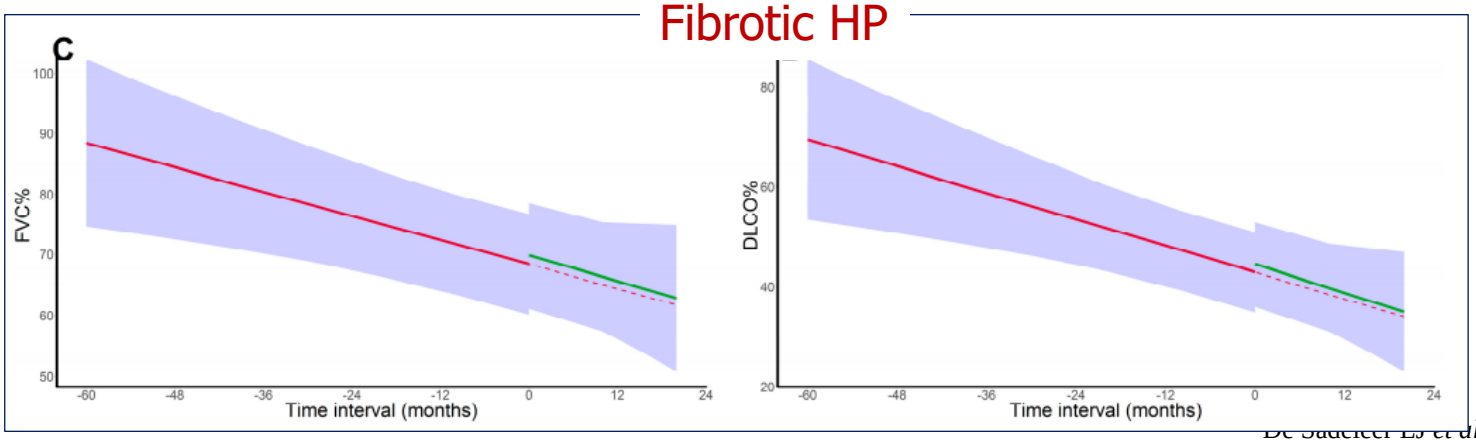
# Prognosis of HP (Fibrosis vs. No fibrosis)

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

## Nonfibrotic HP

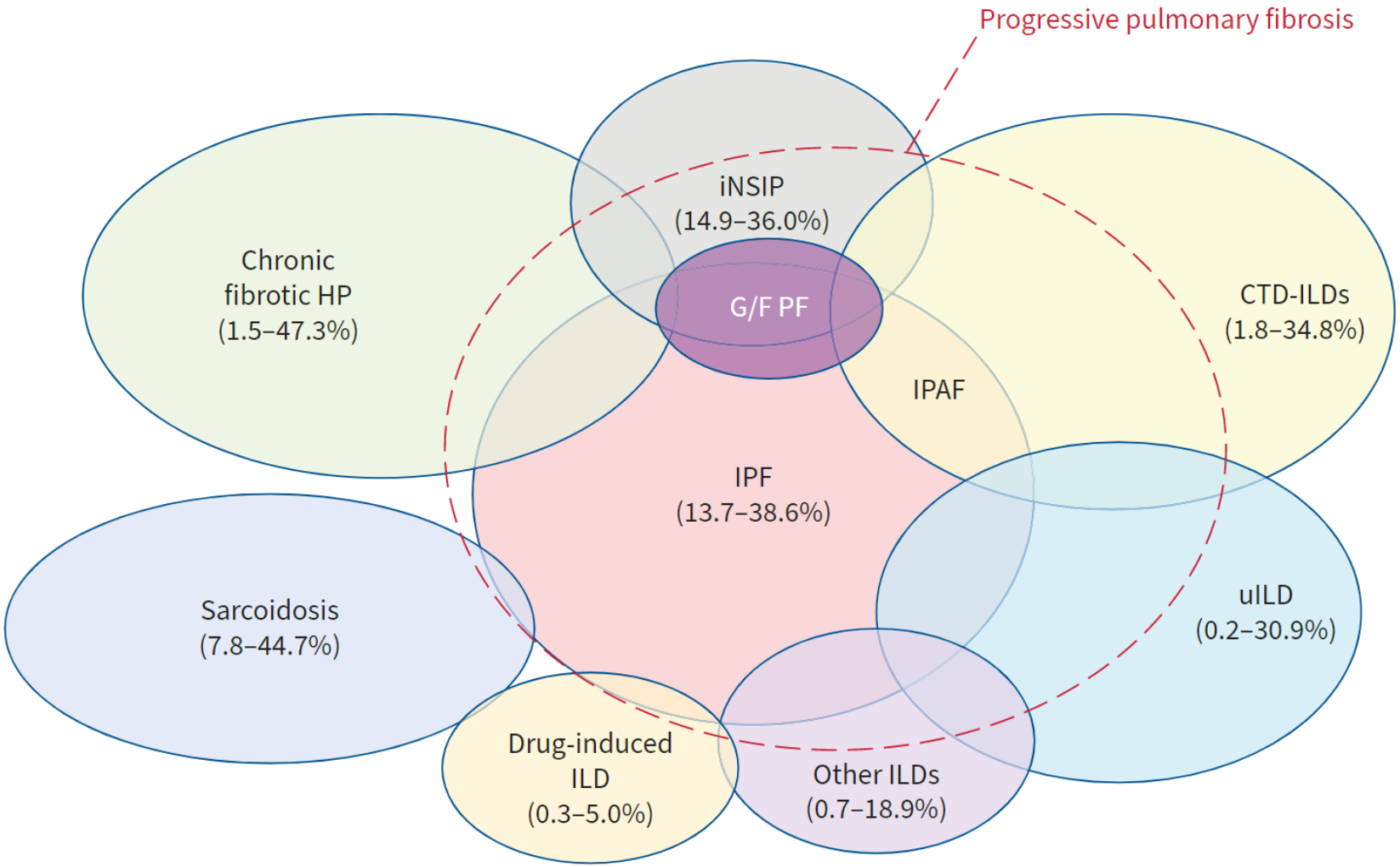



## Fibrotic HP




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

# Concept of PPF



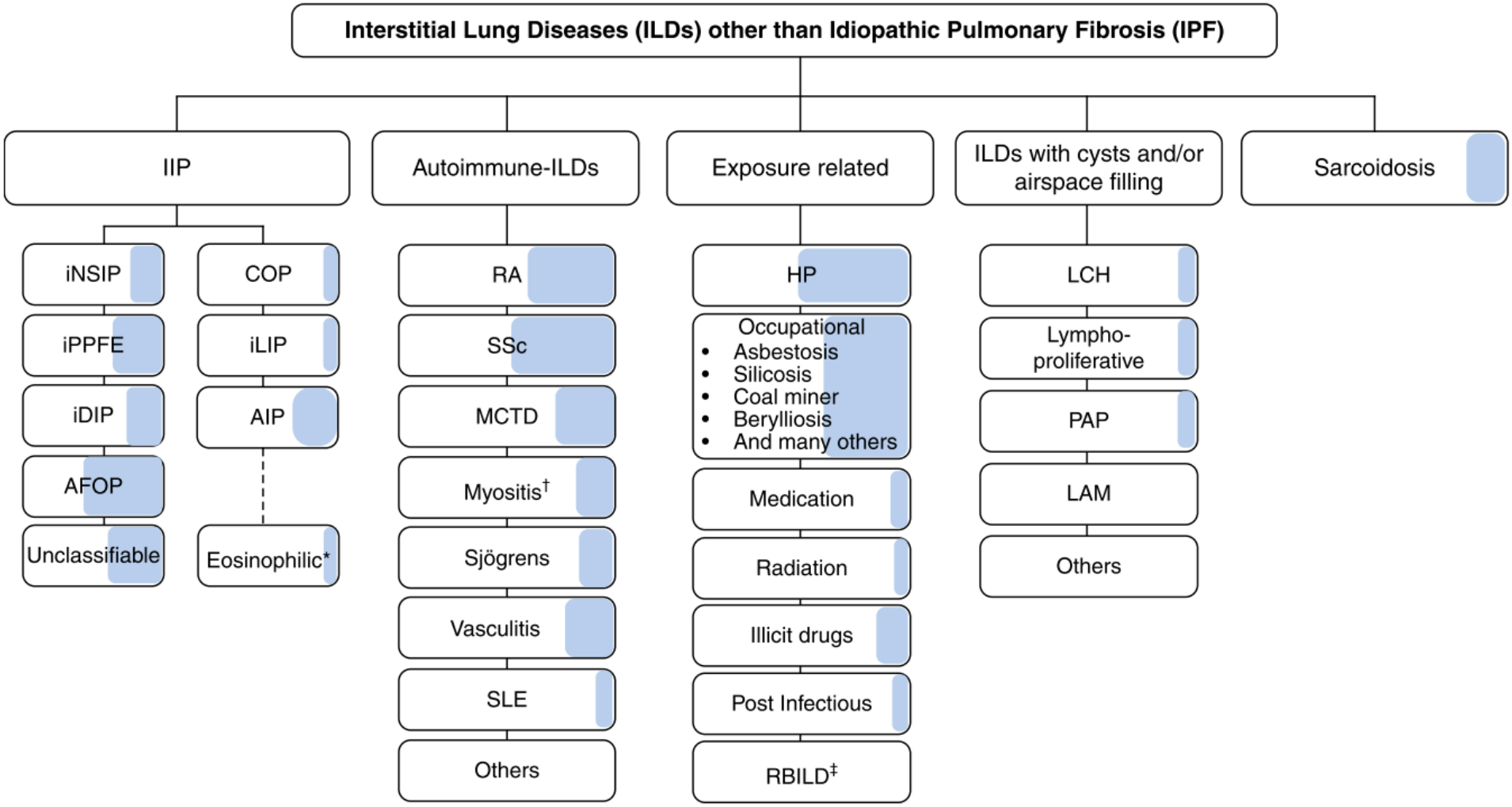

Rajan SK. *Eur Respir Rev*. 2023;61

# Progressive Pulmonary Fibrosis (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

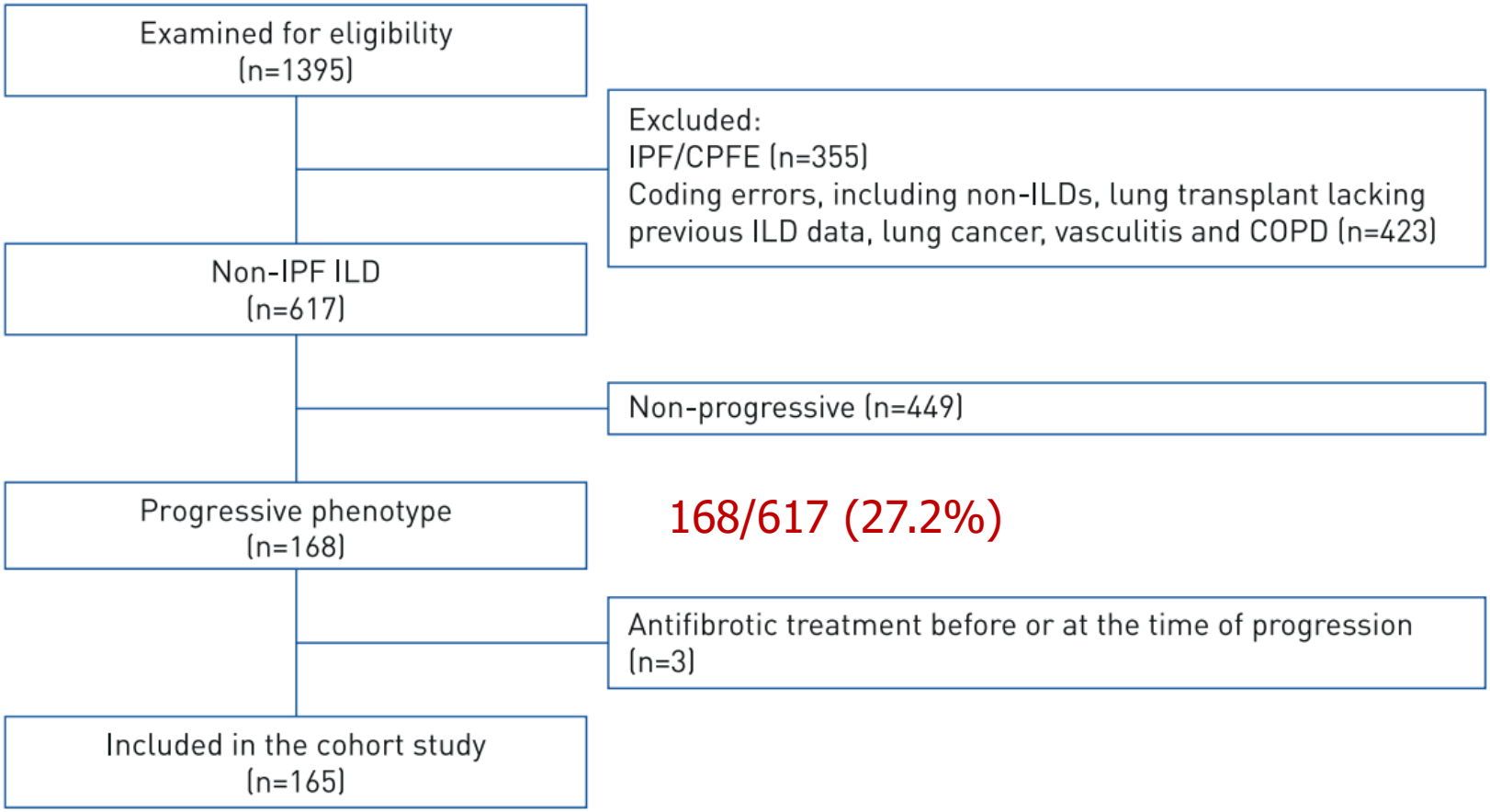
# Concept of PPF




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

# ILD other than IPF with Progressive Phenotype

- Single center retrospective cohort (France)

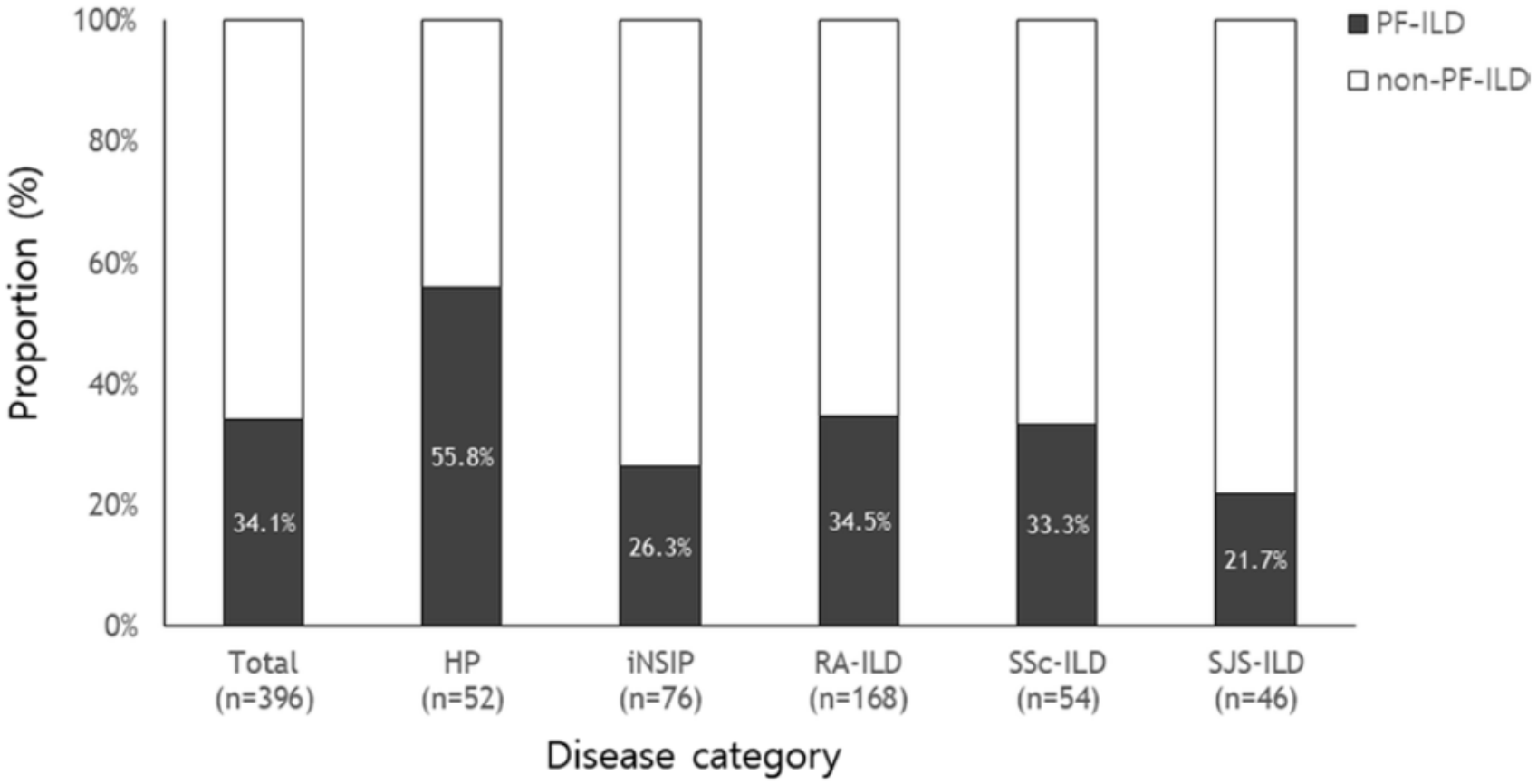



*** Progression defined according to INBUILD criteria**

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

# ILD other than IPF with Progressive Phenotype

- Single center retrospective cohort (AMC)




*** Progression defined according to INBUILD criteria**

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

# Natural History of PF-ILD


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 | |

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

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

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

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# PPF or PF-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 etc.

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

# Definition of PPF or PF-ILD

## Progressive Fibrosing (Fibrotic) ILD

- 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.)
  - ✓ Duration and severity

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

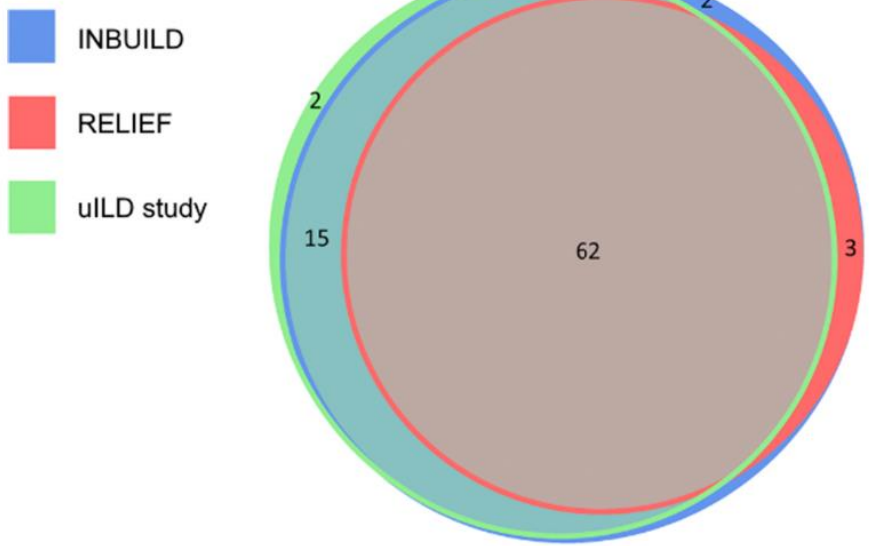
# Definitions of Fibrosis and Progression

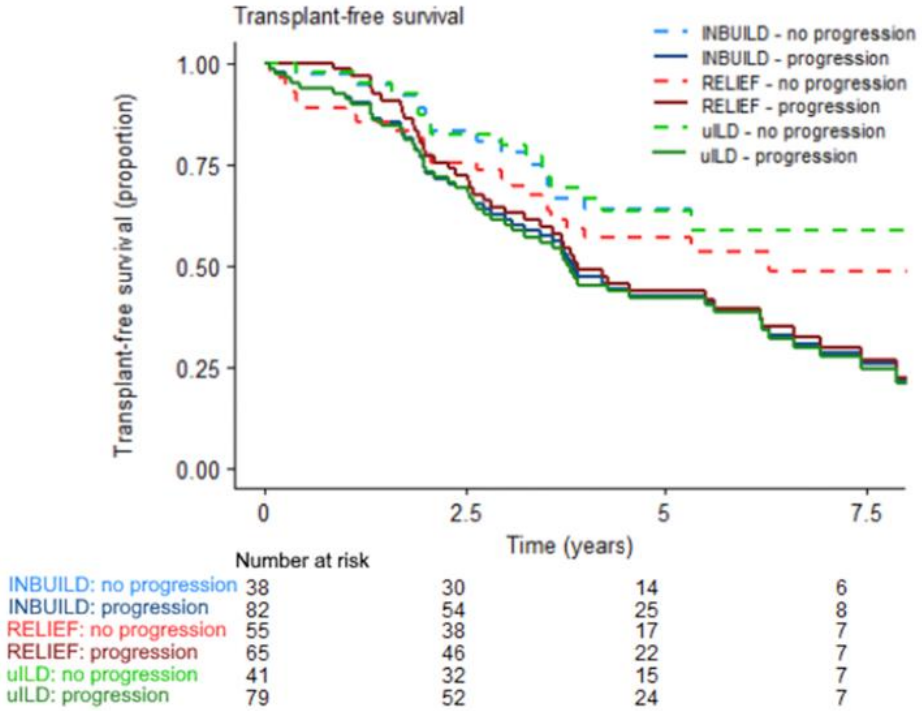
| | Term | Fibrosis | Progression |
|---|---|---|---|
| **INBUILD (Nintedanib for PF-ILD)** | Progressive fibrosing ILD | Fibrosis > 10% of lung (HRCT) (Reticular abnormality with traction BE with/out honeycombing) | • 24 months before screening<br>1) FVC dec ≥ 10% (Relative)<br>2) 5% ≤ FVC < 10% (Relative)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

- 120 non-IPF fibrotic ILD patients (Univ. of Leuven)




Goos T et al. *Respir Med.* 2021;19

# 2022 IPF and PPF Guidelines

AMERICAN THORACIC SOCIETY DOCUMENTS

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

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

Ganesh Raghu, Martine Remy-Jardin, Luca Richeldi, Carey C. Thomson, Yoshikazu Inoue, Takeshi Johkoh, Michael Kreuter, David A. Lynch, Toby M. Maher, Fernando J. Martinez, Maria Molina-Molina, Jeffrey L. Myers, Andrew G. Nicholson, Christopher J. Ryerson, Mary E. Strek, Lauren K. Troy, Marlies Wijsenbeek, Manoj J. Mammen, Tanzib Hossain, Brittany D. Bissell, Derrick D. Herman, Stephanie M. Hon, Fayez Kheir, Yet H. Khor, Madalina Macrea, Katerina M. Antoniou, Demosthenes Bouros, Ivette Buendia-Roldan, Fabian Caro, Bruno Crestani, Lawrence Ho, Julie Morisset, Amy L. Olson, Anna Podolanczuk, Venerino Poletti, Moisés Selman, Thomas Ewing, Stephen Jones, Shandra L. Knight, Marya Ghazipura, and Kevin C. Wilson; on behalf of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax

This official clinical practice guideline was approved by the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax February 2022

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

# 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)

# Considerations for Definition of PPF

- PPF is defined separately from IPF
- PPF is not a diagnosis / PPF is agnostic to the underlying condition
- The criteria reflect multiple clinical trials (not a single trial)
- The criteria have been associated only with prognosis
  - ✓ Unclear if the criteria identify the patients for antifibrotic therapy

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

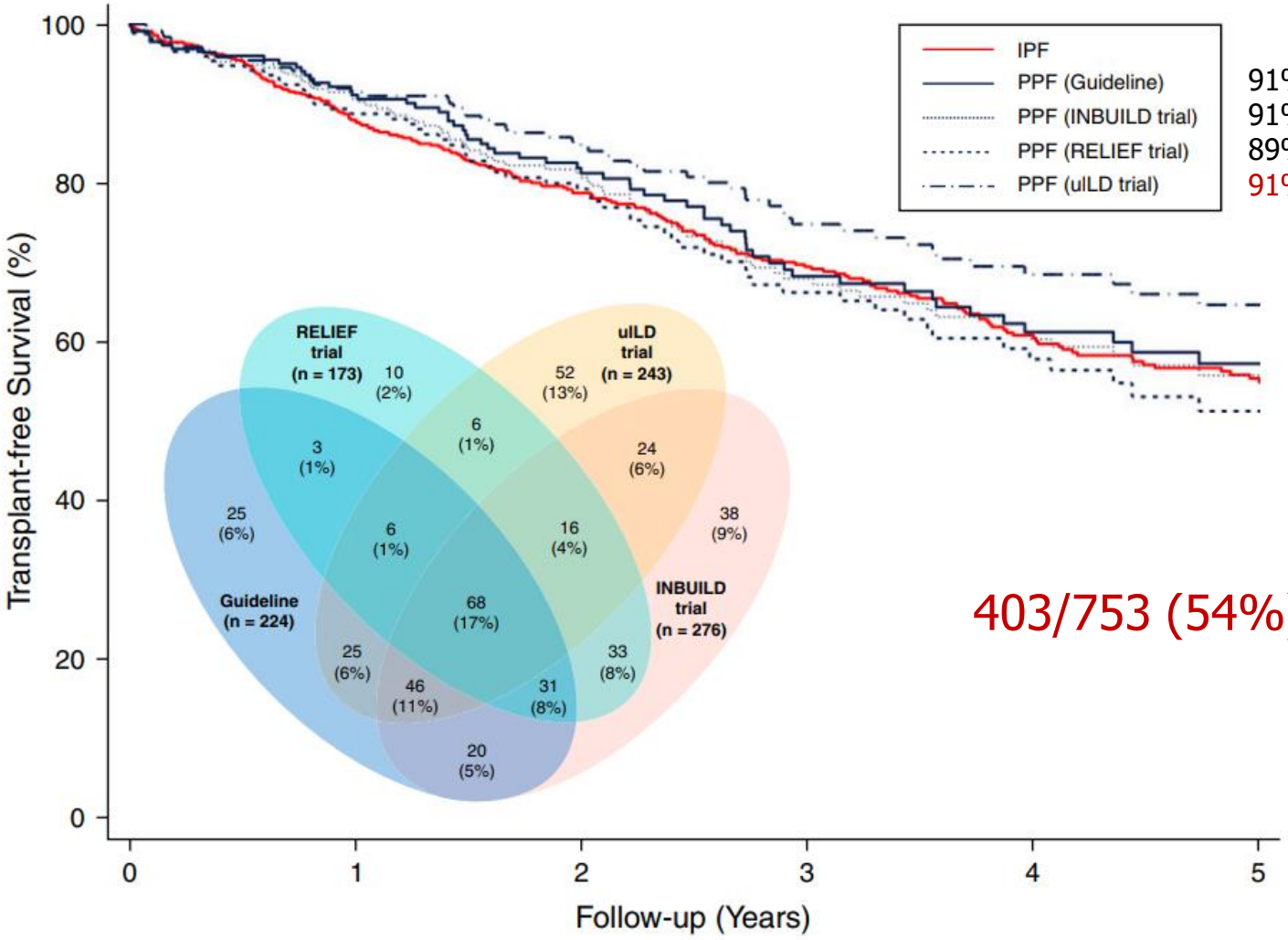
# Prognosis according to New PPF Definition

- 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)

# Prognosis according to New PPF Definition




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

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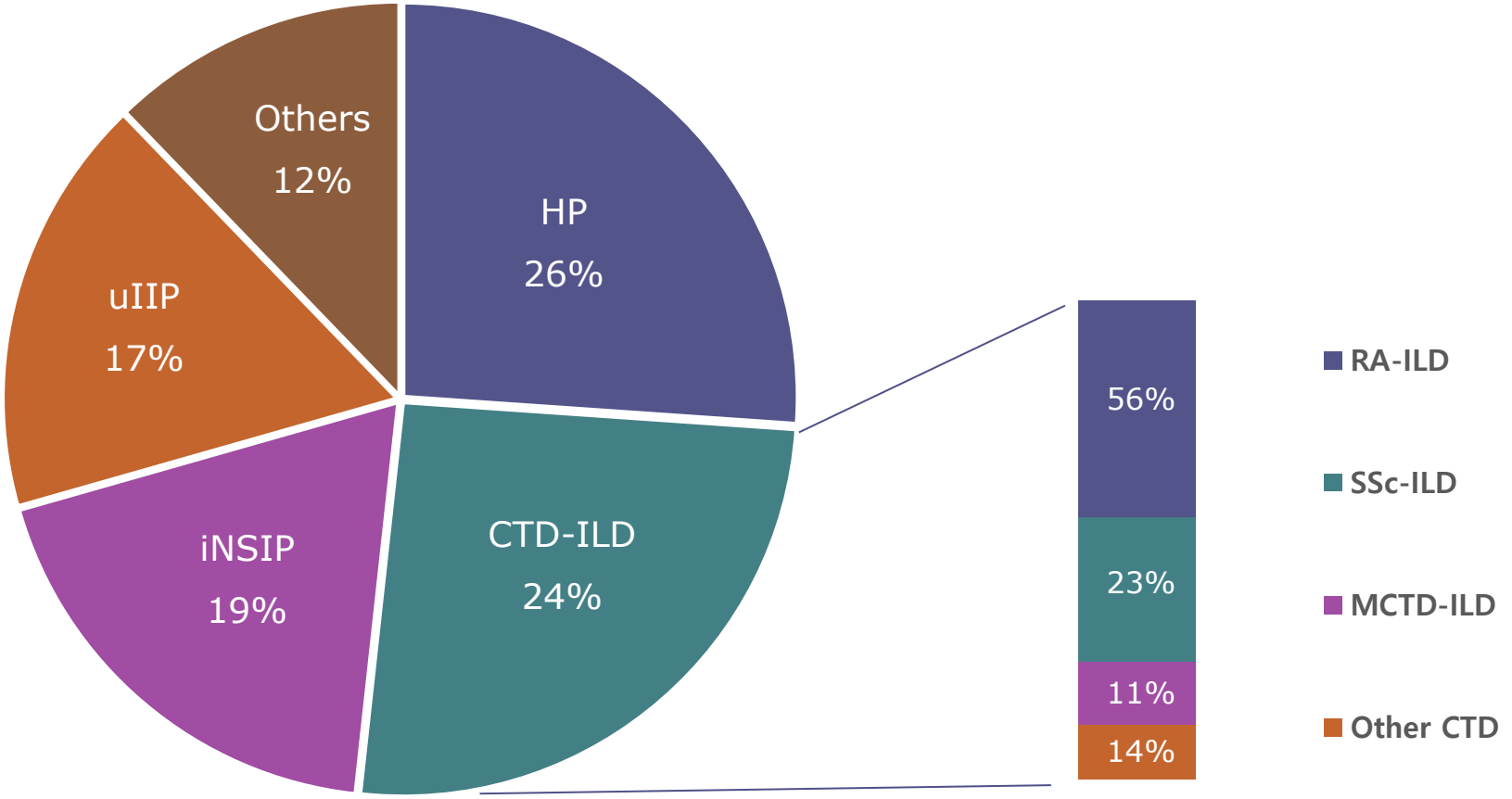
# Nintedanib for PF-ILD (INBUILD trial)

- 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)

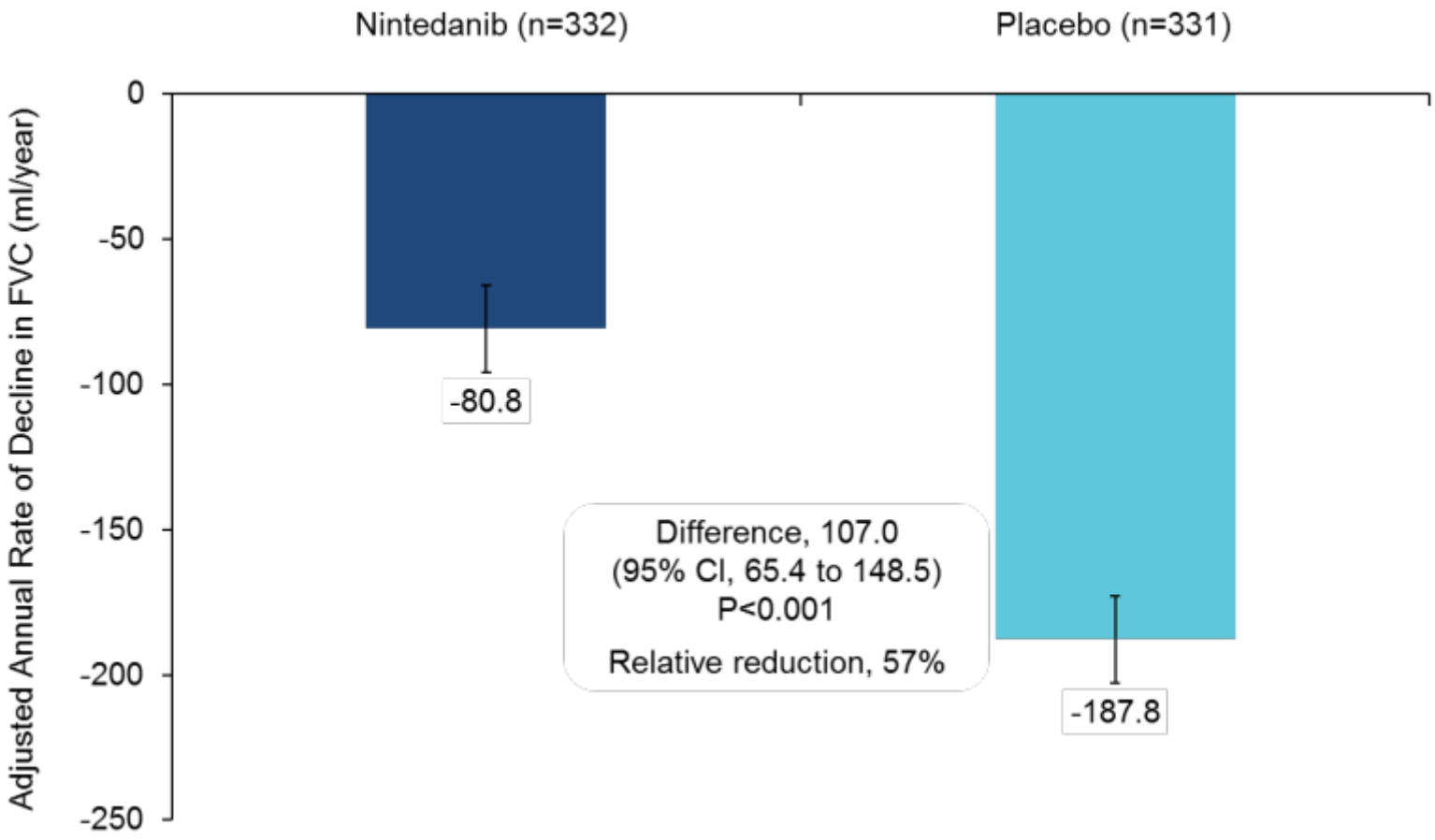
# Nintedanib for PF-ILD (INBUILD trial)

**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 |

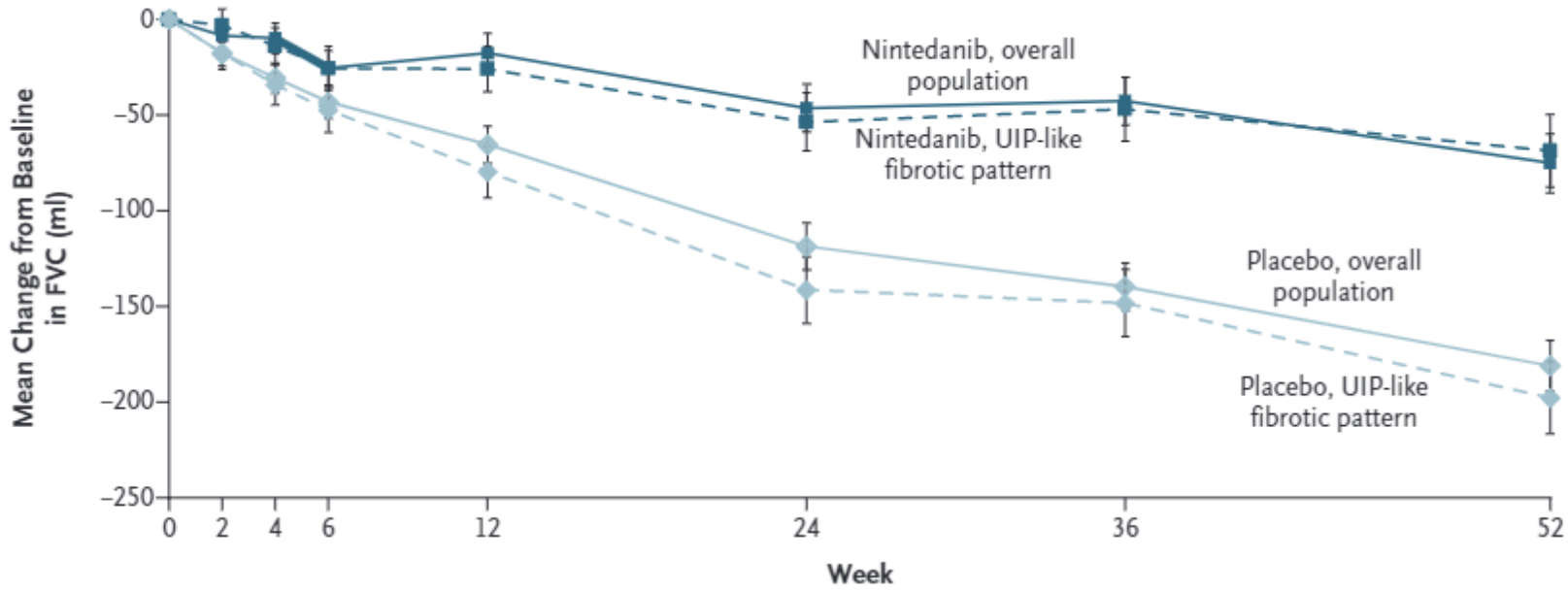
Flaherty KR *et al*. *N Engl J Med*. 2019; 381(18)

# 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)

**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)§‖ |

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)

# Nintedanib for PF-ILD (Subgroup)

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

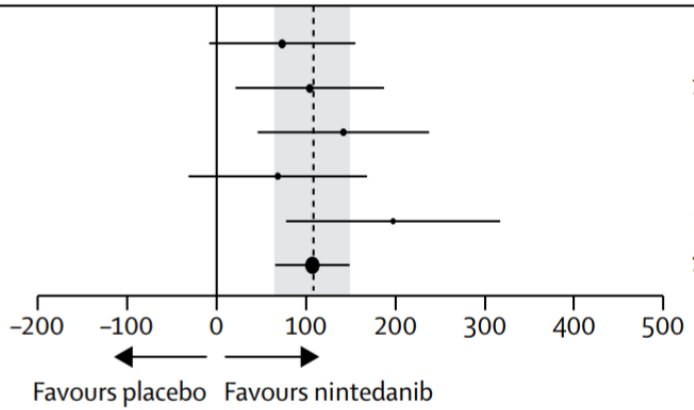
*Athol U Wells, Kevin R Flaherty, Kevin K Brown, Yoshikazu Inoue, Anand Devaraj, Luca Richeldi, Teng Moua, Bruno Crestani, Wim A Wuyts, Susanne Stowasser, Manuel Quaresma, Rainer-Georg Goeldner, Rozsa Schlenker-Herceg, Martin Kolb on behalf of the INBUILD trial investigators**

- Endpoint
  - ✓ Rate of decline in FVC over 52 weeks
  - ✓ Subgroup analysis on 5 prespecified subgroups based on ILD diagnosis

Wells AU *et al*. *Lancet Respir Med*. 2020;8(5)

# Nintedanib for PF-ILD (INBUILD trial)

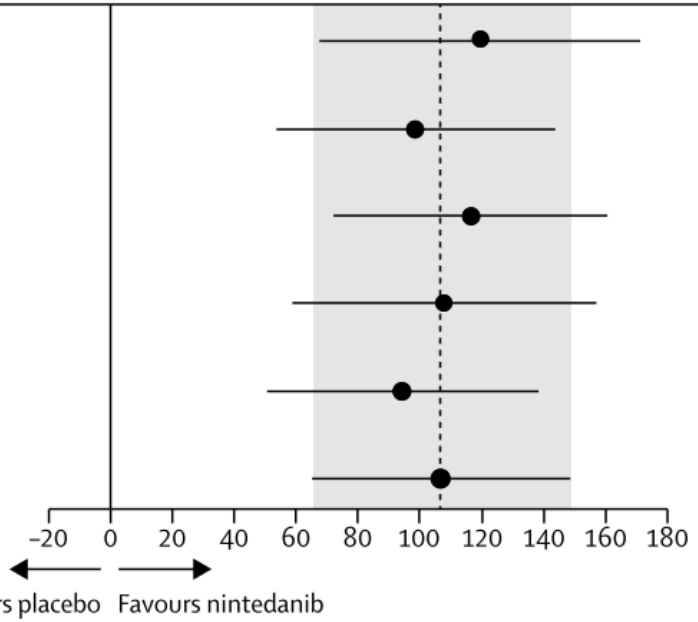
| | n analysed | | Difference (95% CI) | Treatment by subgroup by time interaction |
|---|---|---|---|---|
| | Nintedanib | Placebo | | |
| Hypersensitivity pneumonitis | 84 | 89 | 73·1 (–8·6 to 154·8) | p=0·41 |
| Autoimmune interstitial lung diseases | 82 | 88 | 104·0 (21·1 to 186·9) | |
| iNSIP | 64 | 61 | 141·6 (46·0 to 237·2) | |
| Unclassifiable IIP | 64 | 50 | 68·3 (–31·4 to 168·1) | |
| Other interstitial lung diseases | 38 | 43 | 197·1 (77·6 to 316·7) | |
| **All patients** | **332** | **331** | **107·0 (65·4 to 148·5)** | |




Wells AU *et al*. *Lancet Respir Med*. 2020;8

# Nintedanib for PF-ILD (INBUILD trial)

| | n analysed | | Estimate (95% CI) | p value |
|---|---|---|---|---|
| | Nintedanib | Placebo | | |
| iNSIP, unclassifiable IIP, autoimmune ILDs, other fibrosing ILDs (excludes HP) | 248 | 242 | 119·4 (67·7 to 171·2) | <0·001 |
| HP, unclassifiable IIP, autoimmune ILDs, other fibrosing ILDs (excludes iNSIP) | 267 | 270 | 98·7 (53·8 to 143·6) | <0·001 |
| HP, iNSIP, autoimmune ILDs, other fibrosing ILDs (excludes unclassifiable IIP) | 267 | 281 | 116·4 (72·4 to 160·4) | <0·001 |
| HP, iNSIP, unclassifiable IIP, other fibrosing ILDs (excludes autoimmune ILDs) | 250 | 243 | 108·0 (59·1 to 157·0) | <0·001 |
| HP, iNSIP, unclassifiable IIP, autoimmune ILDs (excludes other ILDs) | 293 | 288 | 94·5 (50·7 to 138·2) | <0·001 |
| **All patients** | **332** | **331** | **107·0 (65·4 to 148·5)** | **<0·001** |



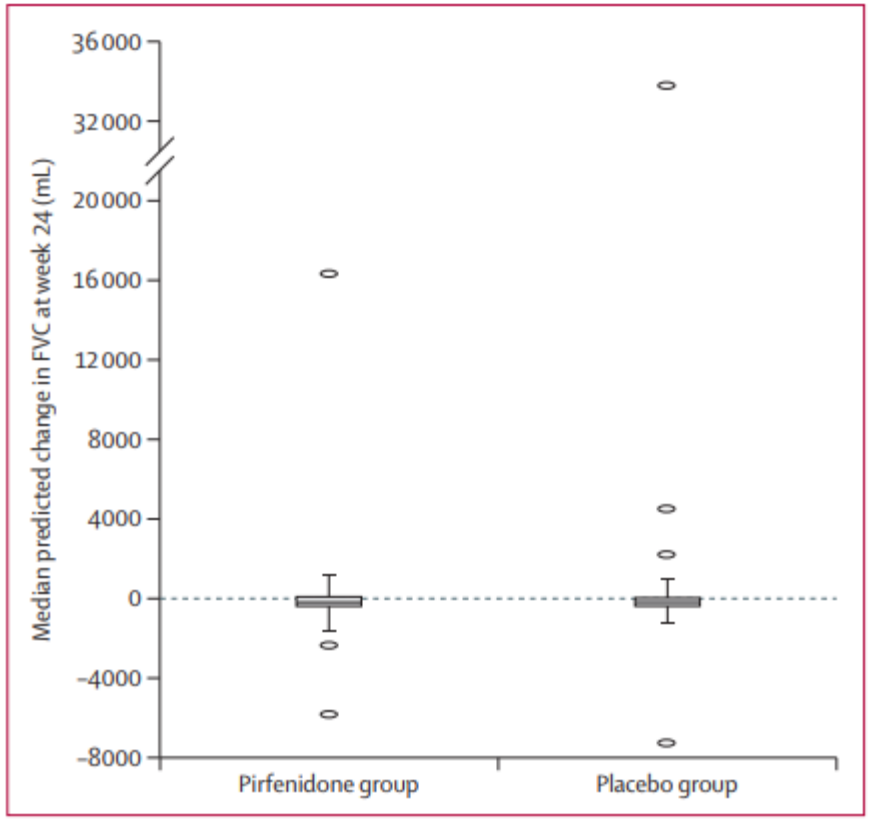

Wells AU *et al*. *Lancet Respir Med*. 2020;8

# 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%) |

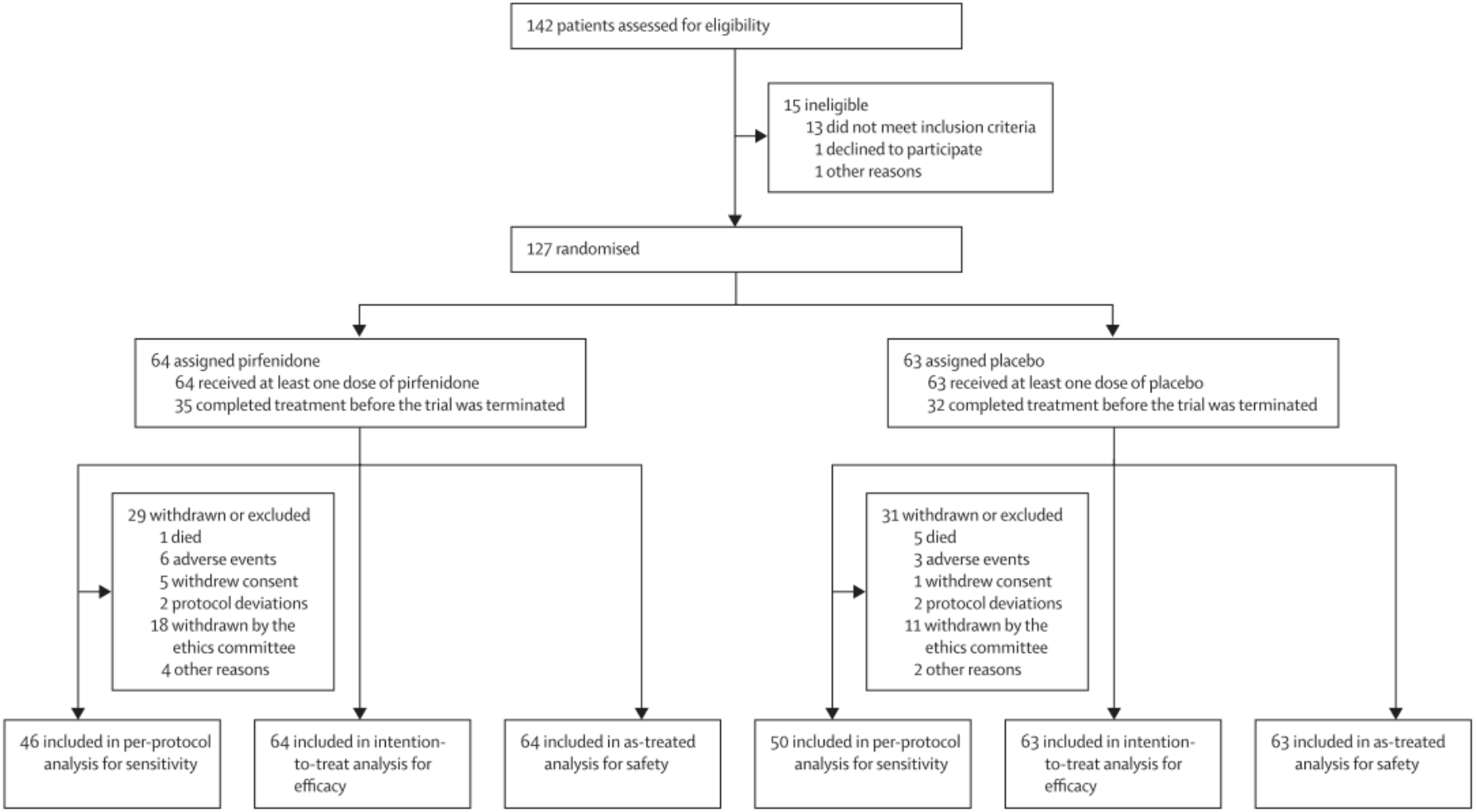
Maher TM *et al*. *Lancet Respir Med*. 2020;8

# 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

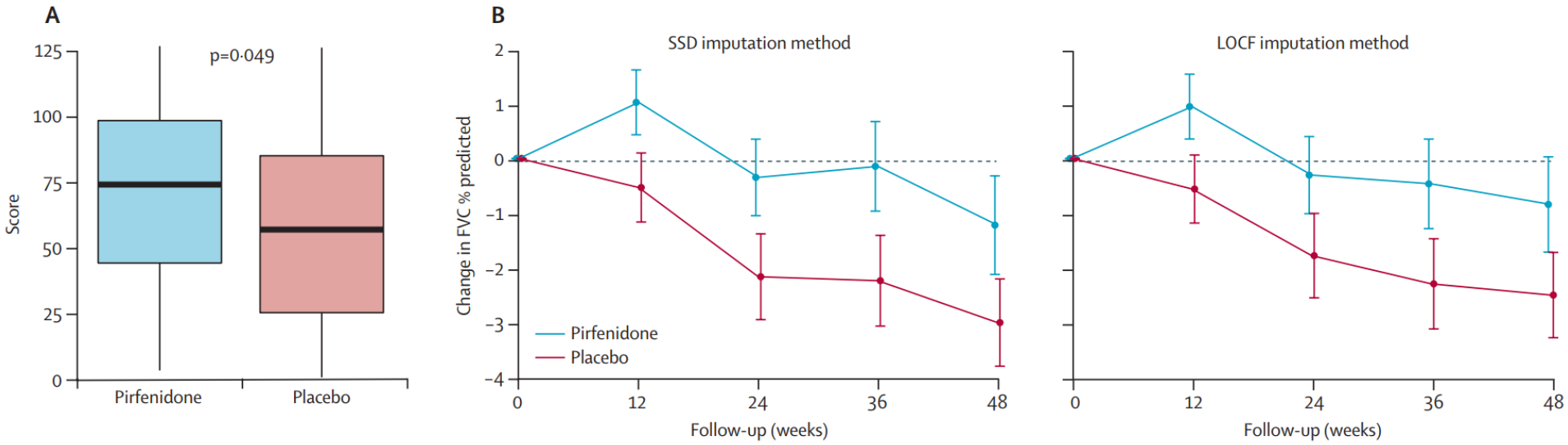
Behr J *et al*. *Lancet Respir Med*. 2021;9(5)

# 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)




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)

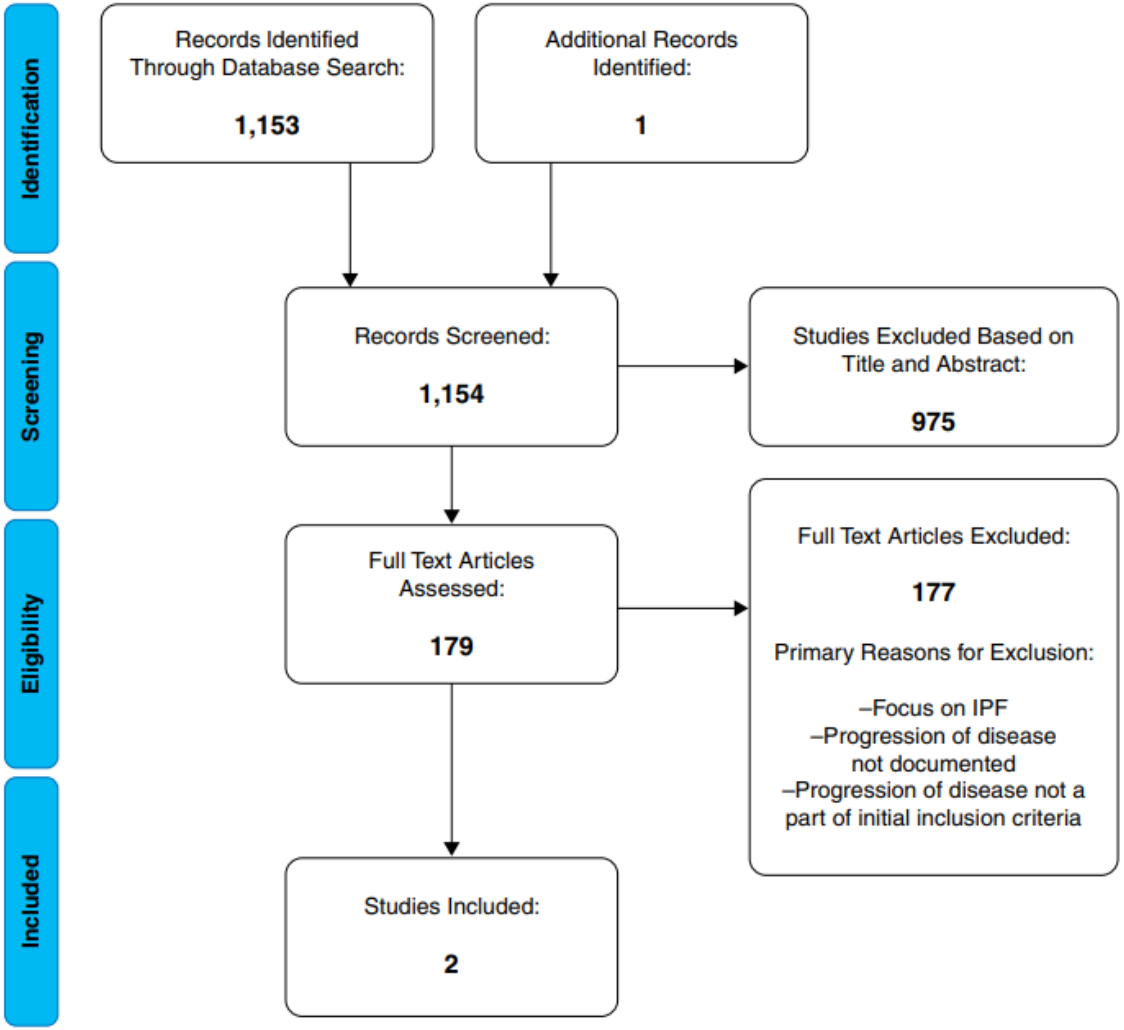
# Pirfenidone for PPF Other Than IPF

## Recommendations

- 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)

# Pirfenidone for PPF Other Than IPF




Ghazipura M et al. *Am J Respir Crit Care Med.* 2022;19(6)

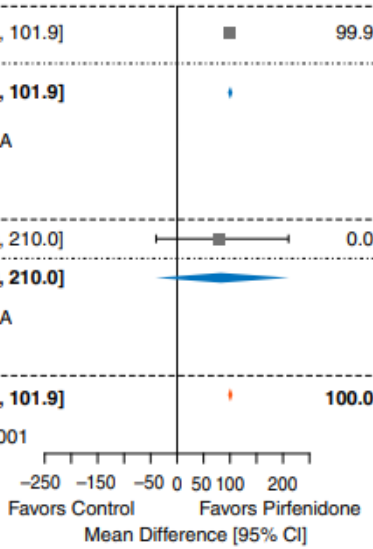
# Pirfenidone for PPF Other Than IPF

**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** | | | **127 \| 126** | **2.10 [0.1, 4.1]** | |

**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

Ghazipura M et al. *Am J Respir Crit Care Med.* 2022;19(6)

# Limitations of Evidence (Pirfenidone)

- Data from low number of patients
- Early termination of study due to futility (RELIEF trial)
- Potential problems of making recommendations specific for uILD
  - ✓ May discourage clinicians in identifying and differentiating ILD

Raghu G *et al*. *Am J Respir Crit Care Med*. 2022;205(9)
Ghazipura M et al. *Am J Respir Crit Care Med.* 2022;19(6)

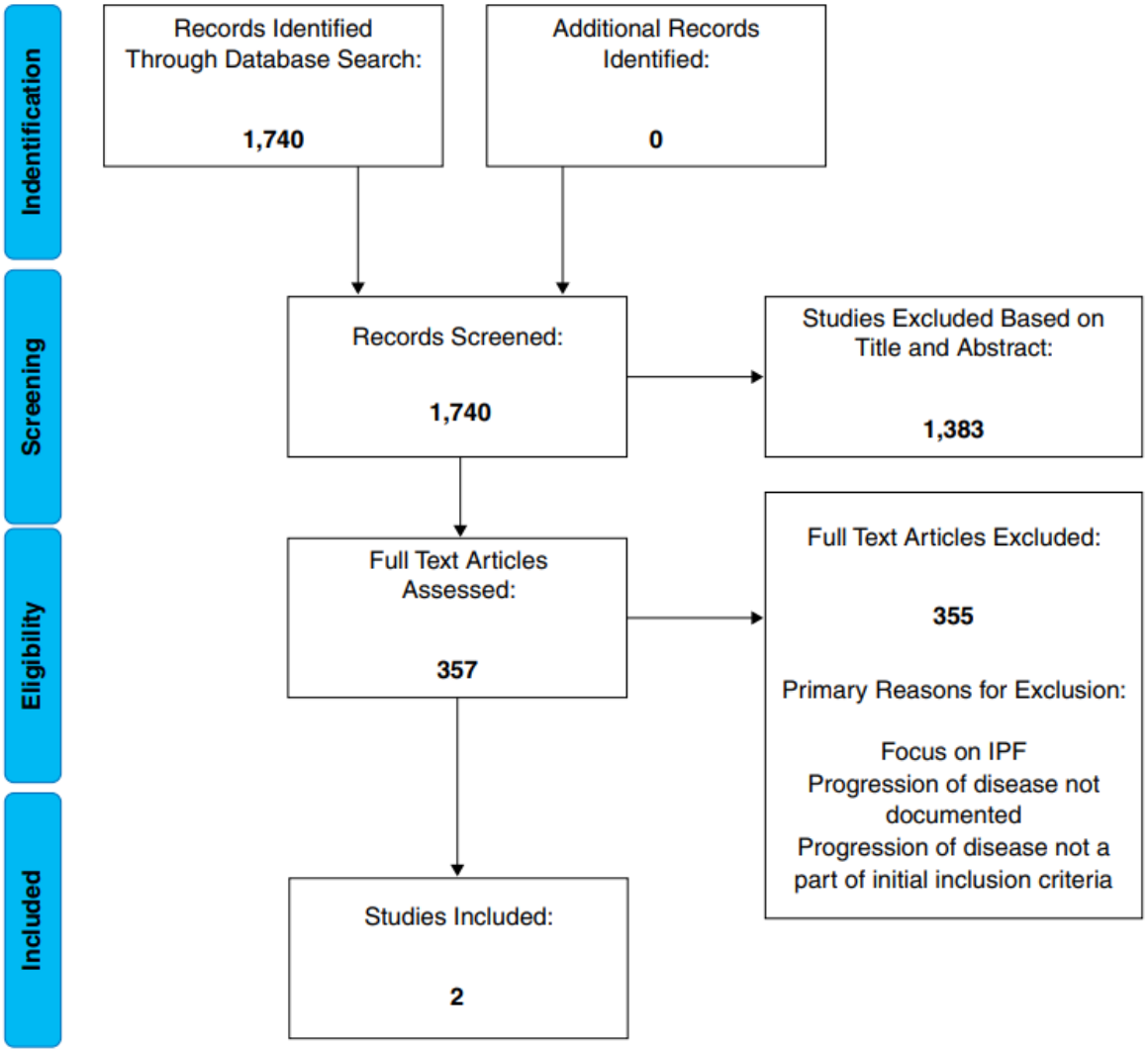
# Nintedanib for PPF Other Than IPF

## Recommendations

- 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)

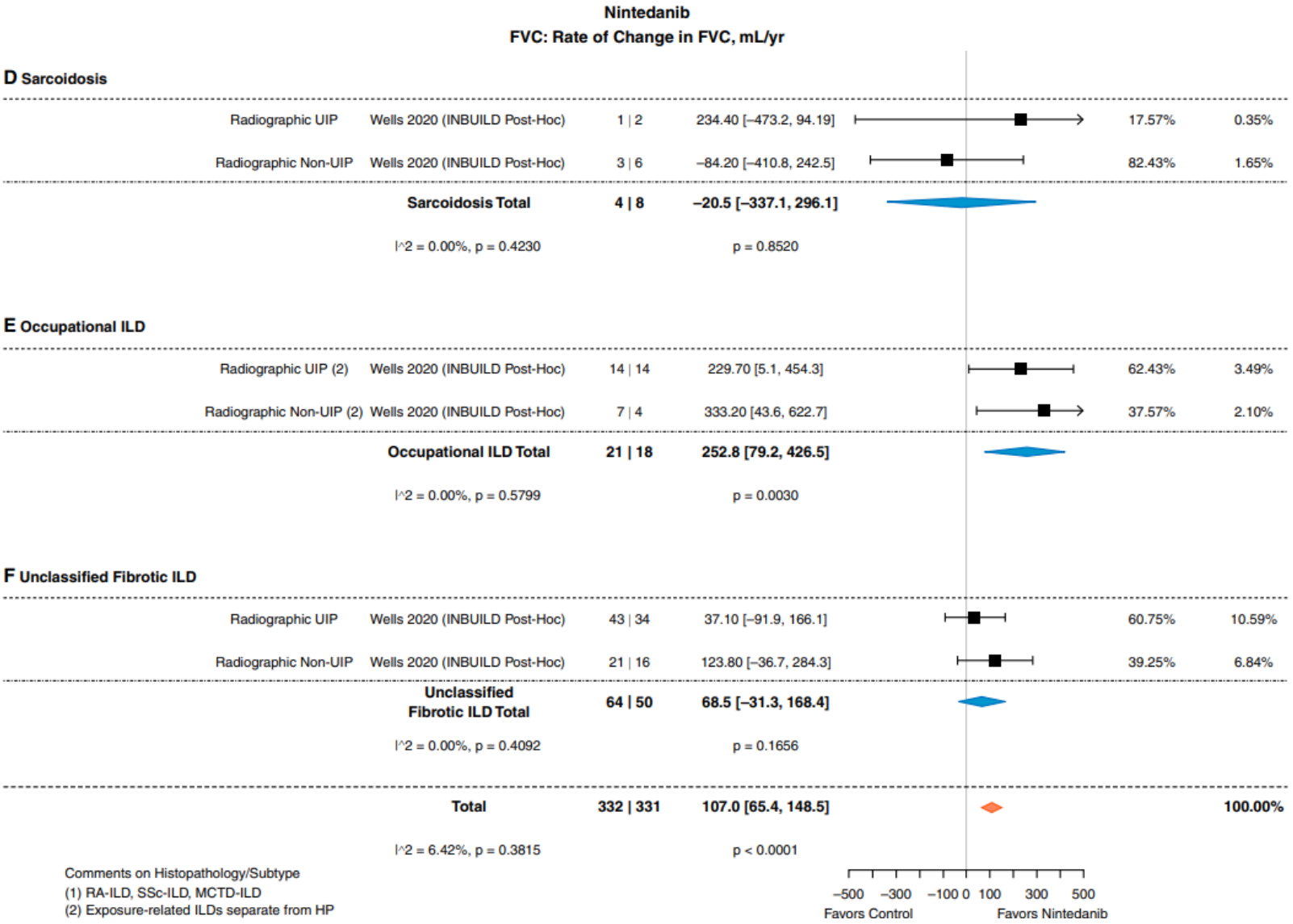
- We recommend research into the efficacy, effectiveness, and safety of nintedanib in specific types of non-IPF ILD manifesting PPF

# Nintedanib for PPF Other Than IPF




Ghazipura M et al. *Am J Respir Crit Care Med.* 2022;19(6)

# Nintedanib for PPF Other Than IPF




Ghazipura M et al. *Am J Respir Crit Care Med.* 2022;19(6)

# Takeaway (I)

## Concept of PPF

- Fibrotic ILD other than IPF with progression (Classification concept)
- CTD-ILD, Fibrotic HP, Idiopathic NSIP, unclassifiable ILD etc.
- Various terms (PF-ILD, Fibrotic ILD with progressive phenotype) → PPF

## Clinical significance of PPF

- Consists 30-50% of non-IPF ILD
- Decline of pulmonary function (similar to that of IPF)
- Poor prognosis (Survival)

# Takeaway (II)

## Diagnosis of PPF

- Definition and criteria proposed by ATS/ERS/JRS/ALAT (2022)
- Symptoms, physiology (Absolute change of FVC, DLco), Radiography (HRCT)
- May evolve over time (validation)

## Treatment of PPF

- Nintedanib
  - ✓ Recommended (in whom standard treatment has failed)
- Pirfenidone
  - ✓ Future research recommended