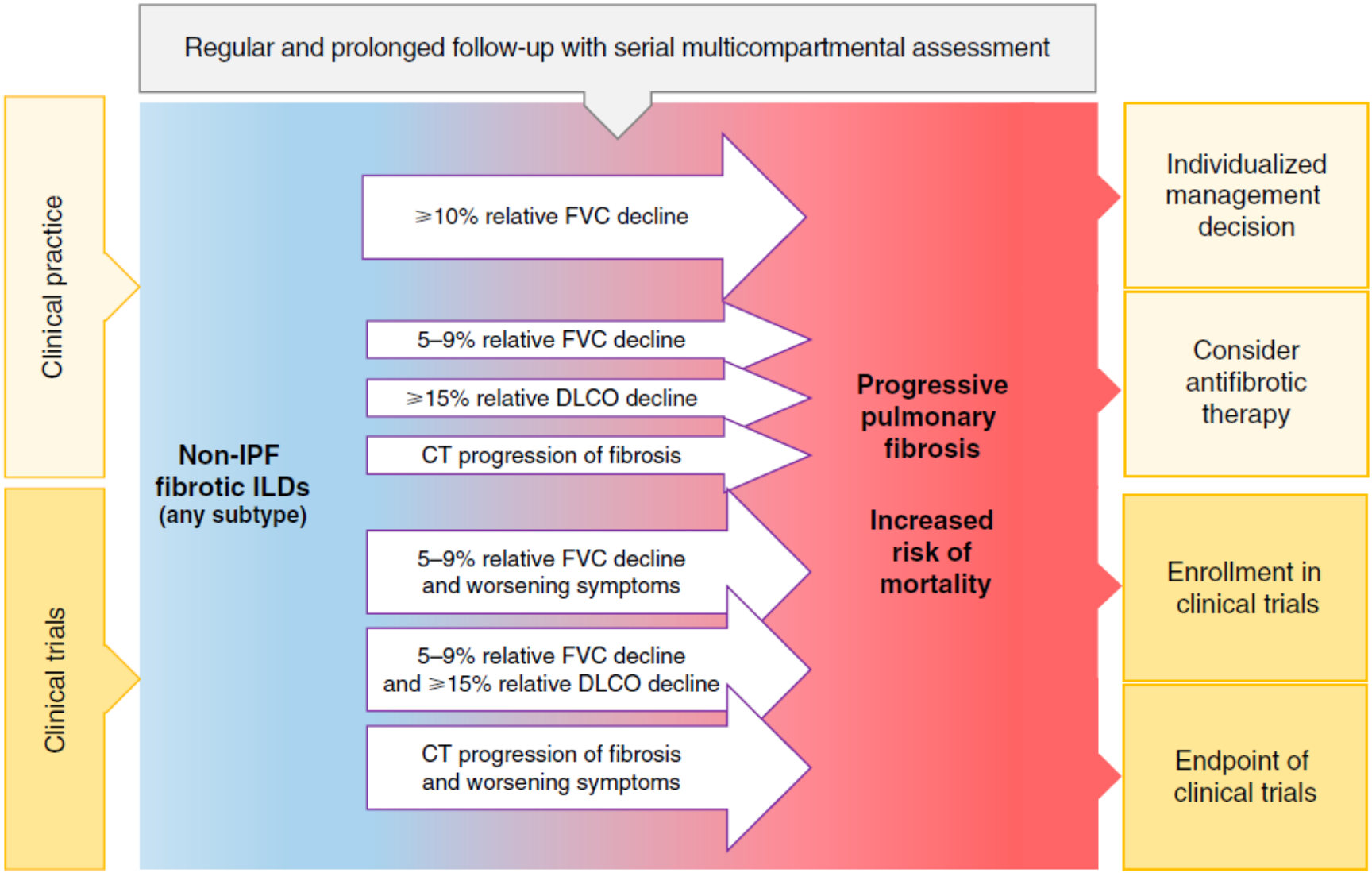
PPF Tedavi Önerileri

Dr Gamze KIRKIL

Fırat Üniversitesi

Göğüs Hastalıkları AD

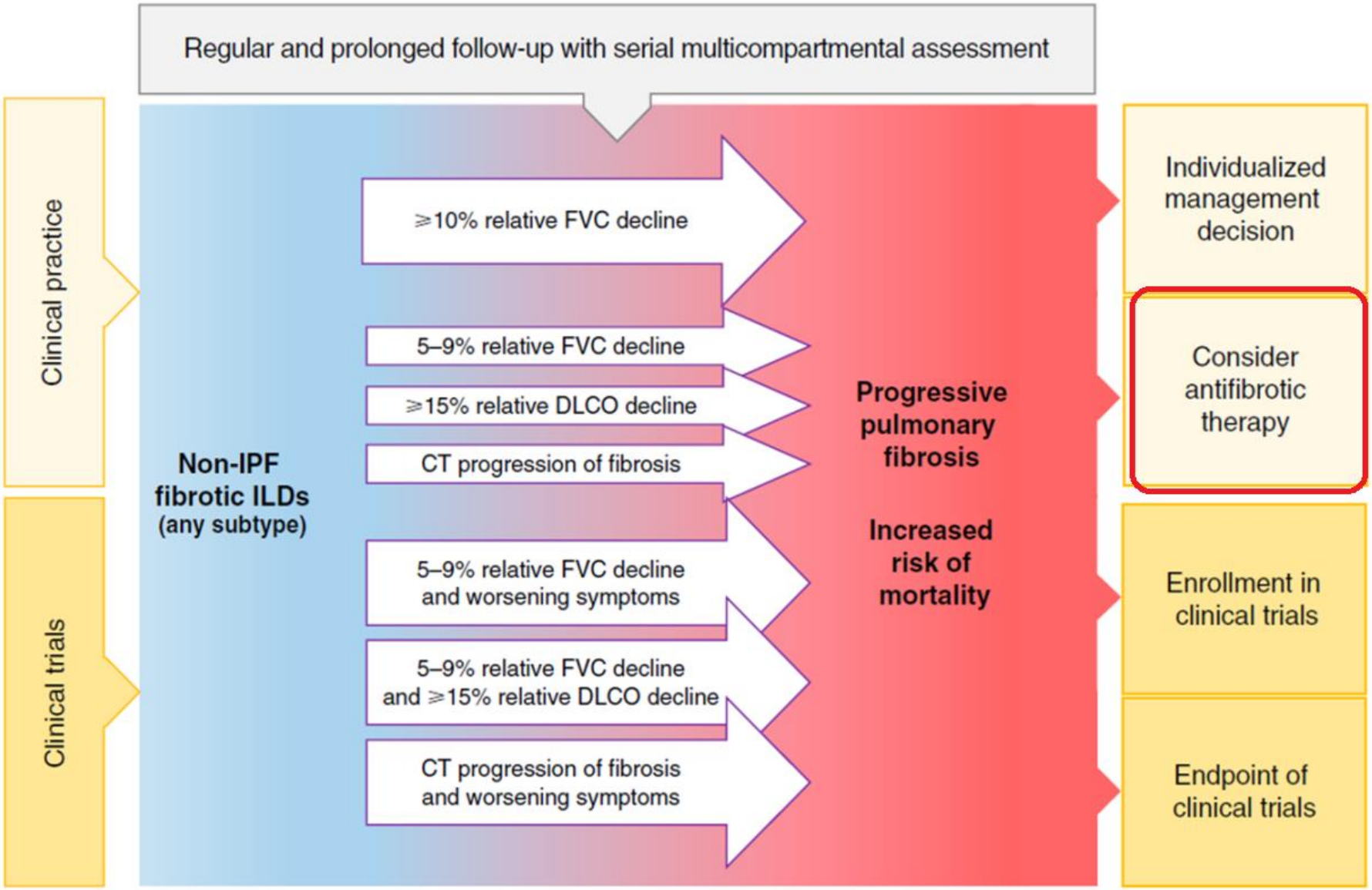


Cottin V. AJRCCM 2023

TABLE 2 Risk factors for the progression of non-idiopathic pulmonary fibrosis interstitial lung diseases (ILDs)

Risk factor	First author (year) [ref.]	Hazard ratio (95% CI)	p-value
General risk factors			
UIP	Flaherty (2019) [2]	1.53 (−0.68–3.74)	NA
BMI	Alakhras (2007) [19]	0.93 (0.89–0.97)	0.002
Oxygen desaturation during 6MWT#	Alfieri (2020) [20]	OR¶ 8.7 (4.42–17.3)	NA
Disease			
Fibrotic hypersensitivity pneumonitis	Gimenez (2018) [21]		
Decline in FVC by ⩾10%	Gimenez (2018) [21]	4.13 (1.96–8.70)	0.005
Lower baseline FVC %	Gimenez (2018) [21]	1.03 (1.01–1.05)	0.003
Antigen identification	Gimenez (2018) [21]	0.18 (0.04–0.77)	0.021
MUC5B^{+}/*TLD*$^{+}$ (gene variants)	Ley (2019) [22]	3.52 (1.87–6.62)	0.00009
Rheumatoid arthritis-ILD	Zamora-Legoff (2017) [9]		
UIP *versus* NSIP	Zamora-Legoff (2017) [9]	3.29 (1.28–8.41)	0.013
High levels of CCP antibody/anti-CCP2 titres^{+}	Khan (2021) [23]	1.05 (1.01–1.10)	0.01
Smoking, 30 pack-years	Kronzer (2021) [24]	OR¶ 6.06 (2.72–13.5)	NA
Fibrotic score on HRCT	Solomon (2016) [25]	1.02 (1.01–1.03)	0.0002
Extent of fibrosis on HRCT	Solomon (2016) [25]	1.12 (1.08–1.17)	<0.00000
Systemic sclerosis	Goh (2017) [26]		
Low baseline FVC <65% and low baseline D_{LCO} ⩽55%	Sánchez-Cano (2018) [27]; Hoffmann-Vold (2019) [28]	OR¶ 1.02 (1.01–1.03)	<0.001
Decline in D_{LCO} >15%	Le Gouellec (2017) [29]	2.03 (1.25–3.29)	<0.005
Decline in K_{CO} >10%	Goh (2017) [26]	2.35 (1.40–3.95)	<0.001
Fibrotic score on HRCT	Ibrahim (2020) [30]	2.52 (1.16–5.49)	0.02
Extent of fibrosis on HRCT (HRCT extent 10–30% and FVC <70%)	Goh (2008) [31]	3.46 (2.19–5.46)	<0.0005

Rajan SK, et al. Eur Respir J 2023; 61: 2103187



Cottin V. AJRCCM 2023

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

Evidence-based Recommendations for Treatment of PPF, Other than IPF

Pirfenidone. *We recommend further research into the 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.*

We suggest nintedanib for the treatment of PPF in patients who have failed standard management for fibrotic ILD, other than IPF

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]

[1]ZS Associates, Global Health Economics and Outcomes Research, New York, New York; [2]Divisions of Epidemiology and Biostatistics, Department of Population Health, and [15]Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, Grossman School of Medicine, New York University Langone Health, New York, New York; [3]Department of Medicine, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, New York; [4]Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, College of Medicine, and [5]Pharmacy Practice and Science Department, College of Pharmacy, University of Kentucky, Lexington, Kentucky; [6]Section of Pulmonary and Sleep Medicine, Department of Medicine, Salem Veterans Affairs Medical Center, Salem, Virginia; [7]Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, Wexner Medical Center, The Ohio State University, Columbus, Ohio; [8]Department of Medicine, School of Medicine, Tufts University, Boston, Massachusetts; [9]Department of Thoracic Surgery and Interventional Pulmonary, Beth Israel Deaconess Medical Center, Harvard Medical School, Harvard University, Boston, Massachusetts; [10]Department of Respiratory and Sleep Medicine, Austin Health, Heidelberg, Victoria, Australia; [11]Faculty of Medicine, University of Melbourne, Melbourne, Victoria, Australia; [12]Library and Knowledge Sciences, National Jewish Health, Denver, Colorado; [13]Department of Medicine, School of Medicine, University of Washington, Seattle, Washington; and [14]Department of Medicine, School of Medicine, Boston University, Boston, Massachusetts

AnnalsATS Volume 19 Number 6 | June 2022

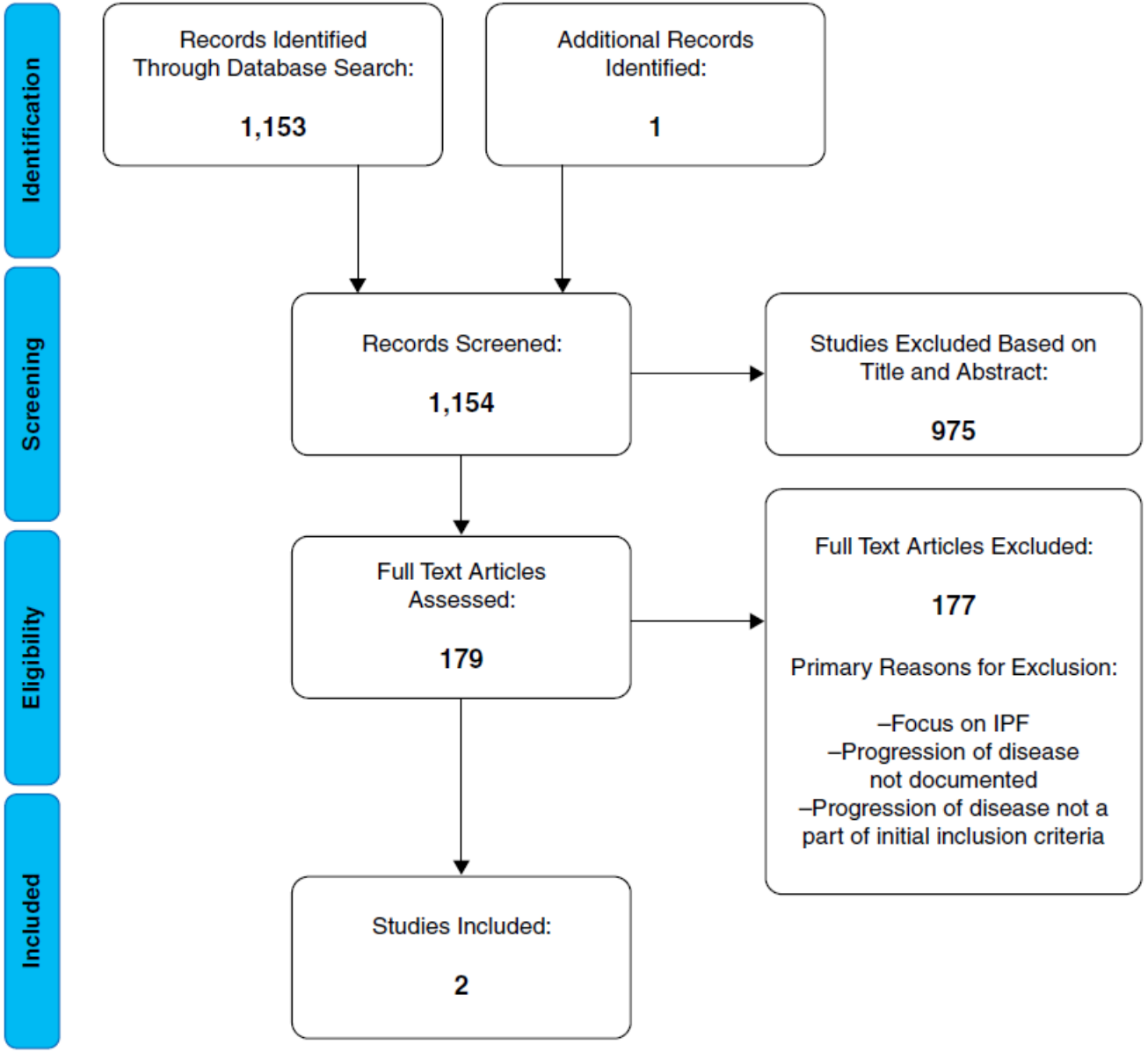


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram. IPF = idiopathic pulmonary fibrosis.

Table 1. Characteristics of studies evaluating pirfenidone versus placebo in PPF

Study (Reference)	Year	Location	Funding	Duration	PPF Diagnostic Criteria	ILD Subtypes
Maher (21)	2020	Fourteen countries: Australia, Belgium, Canada, Czech	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

Study Population	Intervention	Comparator	Study Outcomes
otal 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 admis-sion, *11*) acute exacerbation, *12*) progression-free survival, and *13*) time to death; *adverse events*

Table 1. Characteristics of studies evaluating pirfenidone versus placebo in PPF

Study (Reference)	Year	Location	Funding	Duration	PPF Diagnostic Criteria	ILD Subtypes
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*

Study Population	Intervention	Comparator	Study Outcomes
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*

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

Table 3. Pirfenidone in PPF: important outcomes summary

ILD Subset	MD or RR (95% CI)	Arm Favored	Evidence Quality
All patients with PPF (pirfenidone = 162, control = 158)			
PFT result change			
D_{LCO}, MD, mmol/kPa/min	0.40 (0.10 to 0.70)*	Pirfenidone	Low
D_{LCO} decline >15%, RR	0.27 (0.08 to 0.95)*	Pirfenidone	Low
D_{LCO}% predicted, MD	1.80 (−0.17 to 3.77)	Neither	Low
FEV_1, MD, ml	50 (−50 to 140)	Neither	Low
TLC, MD, L	0.20 (0.0 to 0.4)	Neither	Low
6MWD			
Mean change, MD, m	25.2 (8.3 to 42.1)*	Pirfenidone	Low
Patients with >50-m decline, RR	1.02 (0.69 to 1.51)	Neither	Low
Questionnaire scores, MD			
SGRQ	−1.1 (−4.2 to 2.1)	Neither	Low
UCSD-SOBQ	−0.09 (−5.95 to 5.77)	Neither	Low
LCQ	0.32 (−0.57 to 1.21)	Neither	Low
Cough VAS	−3.30 (−10.91 to 4.31)	Neither	Low
AEs, RR			
GI discomfort	1.83 (1.29 to 2.60)*	Control	Low
Photosensitivity	4.88 (1.09 to 21.8)*	Control	Low
Treatment-emergent AE leading to treatment discontinuation	3.71 (1.43 to 9.63)*	Control	Low
Treatment-related, treatment-emergent AE leading to treatment discontinuation	15.62 (2.10 to 116)*	Control	Low
Any treatment-emergent AE	1.16 (1.06 to 1.27)*	Control	Low
Any treatment-related, treatment-emergent AE	1.54 (1.24 to 1.92)*	Control	Low
Other GI and respiratory AEs†	—	Neither	—

Table 4. Ongoing studies on pirfenidone use in ILD

National Clinical Trial Identifier (Reference)	Study Name	ILD Type	Number of Participants	Study Duration	Primary Endpoint	Projected End Date
NCT03385668 (25)	PIRFENIVAS (Pilot Study of Pirfenidone in Pulmonary Fibrosis with Anti-MPO Antibodies)	Anti-MPO–associated	15	52 wk	Absolute change in FVC% predicted	February 2021
NCT03856853 (26)	Efficacy and Safety of Pirfenidone in Patient with Systemic Sclerosis–associated ILD	Systemic sclerosis–associated	144	52 wk	Relative change from baseline of FVC%	May 2021
NCT03857854 (27)	Efficacy and Safety of Pirfenidone in Patient with Dm-ILD	Dermatomyositis-associated	152	52 wk	Relative change from baseline of FVC%	May 2021
NCT02808871 (28)	TRAIL1 (Phase II Study of Pirfenidone in Patients with RAILD)	Rheumatoid arthritis–associated	270	52 wk	Progression (FVC decline of 10% or greater)–free survival	November 2021
NCT02958917 (29)	Study of Efficacy and Safety of Pirfenidone in Patients with Fibrotic Hypersensitivity Pneumonitis	Fibrotic hypersensitivity pneumonitis	40	52 wk	Mean change from baseline in FVC%	December 2021
NCT03221257 (30)	SLSIII (Scleroderma Lung Study III - Combining Pirfenidone with Mycophenolate)	Systemic sclerosis–associated	150	18 mo	Change from baseline in FVC% predicted	June 2022
NCT04193592 (31)	PEARL (Efficacy and Safety of Pirfenidone Treatment in HPS-ILD)	HPS-associated	50	52 wk	Incidence of decline in FVC% predicted >10%	December 2022

Definition of abbreviations: Dm-ILD = dermatomyositis ILD; FVC = forced vital capacity; HPS = Hermansky-Pudlak syndrome; ILD = interstitial lung disease; MPO = myeloperoxidase; RAILD = rheumatoid arthritis–associated ILD.

NİNTEDANİB

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

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

American Journal of Respiratory and Critical Care Medicine Volume 205 Number 9 | May 1 2022

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). *Remarks: Standard*

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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nintedanib in Progressive Fibrosing Interstitial Lung Diseases

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

N Engl J Med 2019;381:1718-27.

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**

Lancet Respir Med 2020

Nintedanib in Progressive Fibrosing Interstitial Lung Diseases

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

N Engl J Med 2019;381:1718-27.

15 ülke
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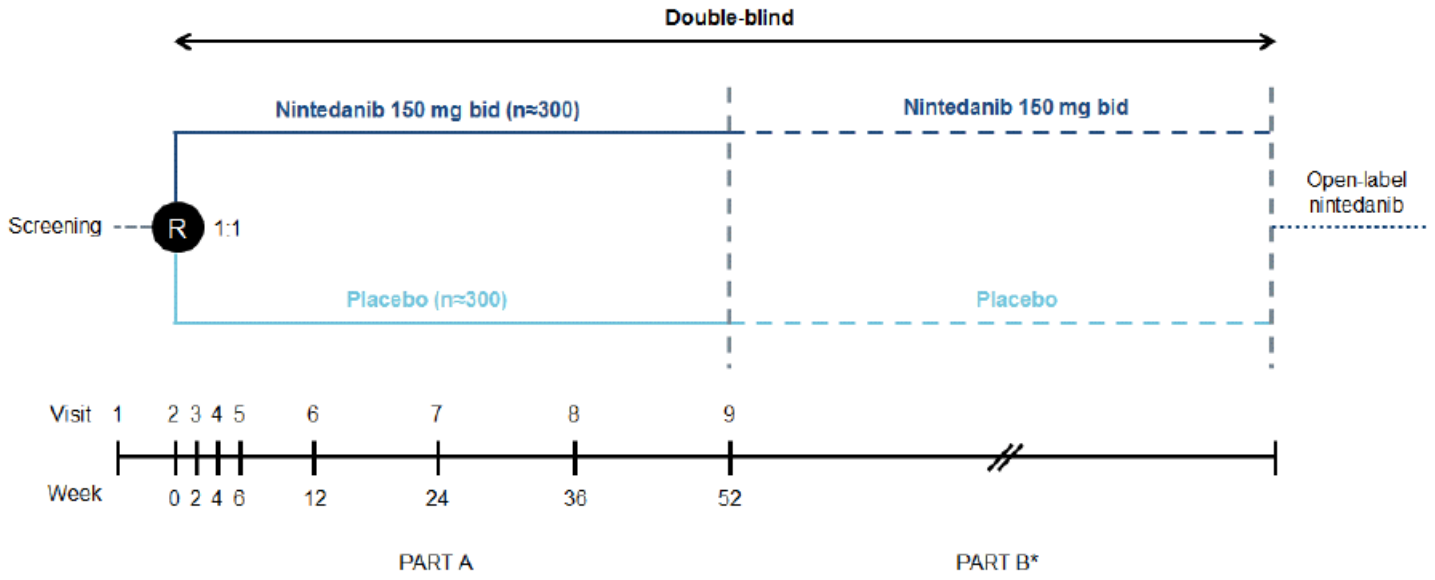
Figure S1A: Overall trial design



R, randomization.
*Visits to occur every 16 weeks until end of treatment.

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

Primer Sonlanım: 52. haftada FVC'de azalma oranı

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

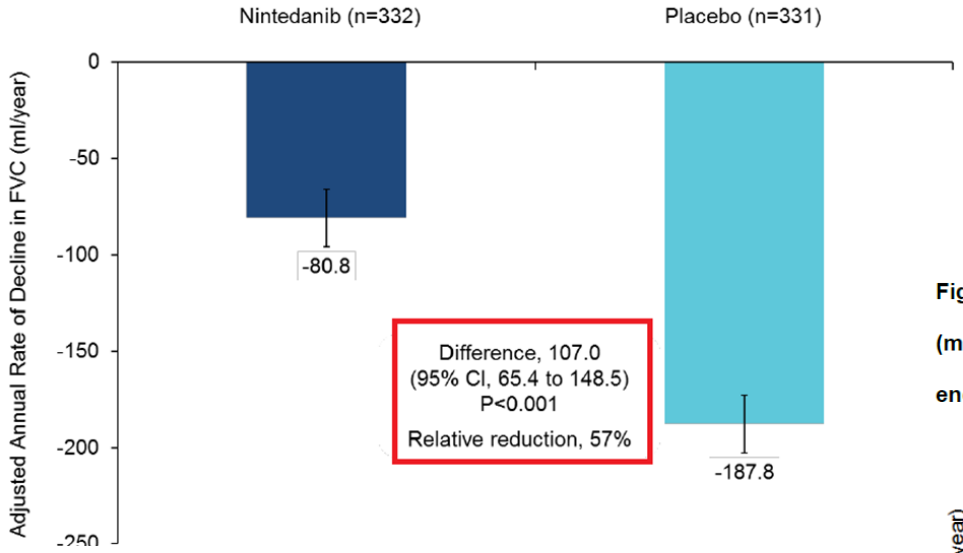


Figure S4B. Between-group adjusted difference in the annual rate of decline in FVC (mL/year) over 52 weeks in patients with a UIP-like fibrotic pattern on HRCT (primary endpoint). The bars indicate the standard error.

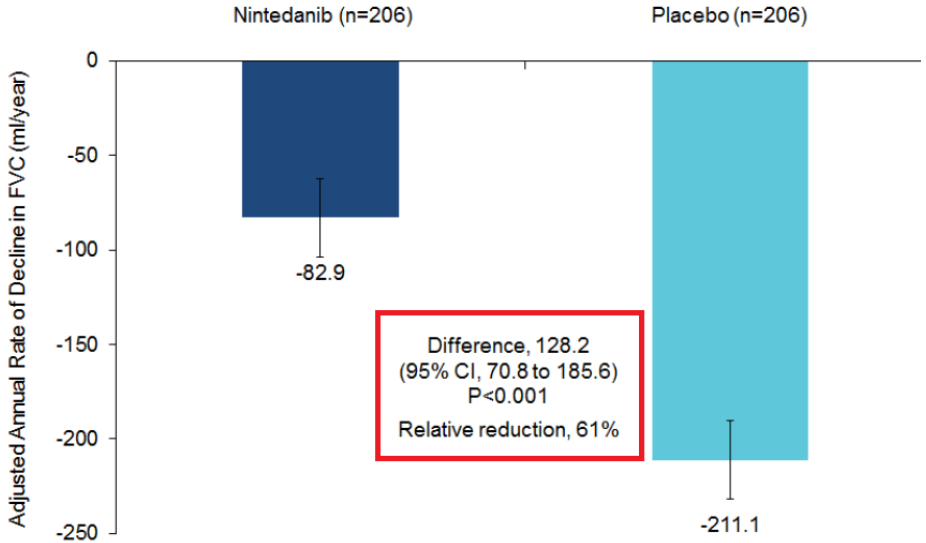


Table 2. Efficacy End Points.*

End Point	Nintedanib (N=332)	Placebo (N=331)	Difference (95% CI)
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)§

A relative decline in FVC of >10% predicted was associated with a more than three-fold increase in the risk of death, both in the overall population and in subjects with a UIP-like fibrotic pattern on HRCT

Table S3. Adverse events in the overall population using data up to first database lock

Event	Nintedanib (n=332)	Placebo (n=331)
	no. of patients (%)	
Any adverse event	325 (97.9)	306 (92.4)
Any adverse event except progression of ILD†	324 (97.6)	305 (92.1)
Most frequent adverse events‡		
Diarrhea	232 (69.9)	84 (25.4)
Nausea	100 (30.1)	33 (10.0)
Vomiting	63 (19.0)	17 (5.1)
Nasopharyngitis	53 (16.0)	48 (14.5)
Decreased appetite	53 (16.0)	21 (6.3)
Alanine aminotransferase increased	48 (14.5)	12 (3.6)
Dyspnea	48 (14.5)	54 (16.3)
Bronchitis	46 (13.9)	57 (17.2)
Weight decreased	43 (13.0)	12 (3.6)
Aspartate aminotransferase increased	43 (13.0)	12 (3.6)
Headache	38 (11.4)	26 (7.9)
Fatigue	34 (10.2)	21 (6.3)
Abdominal pain	34 (10.2)	9 (2.7)
Cough	37 (11.1)	50 (15.1)
Progression of ILD†	24 (7.2)	52 (15.7)
Severe adverse event§	81 (24.4)	97 (29.3)
Serious adverse event¶	138 (41.6)	154 (46.5)
Fatal adverse event	15 (4.5)	30 (9.1)
Fatal adverse event except progression of ILD†	14 (4.2)	26 (7.9)
Adverse event leading to treatment discontinuation	70 (21.1)	45 (13.6)

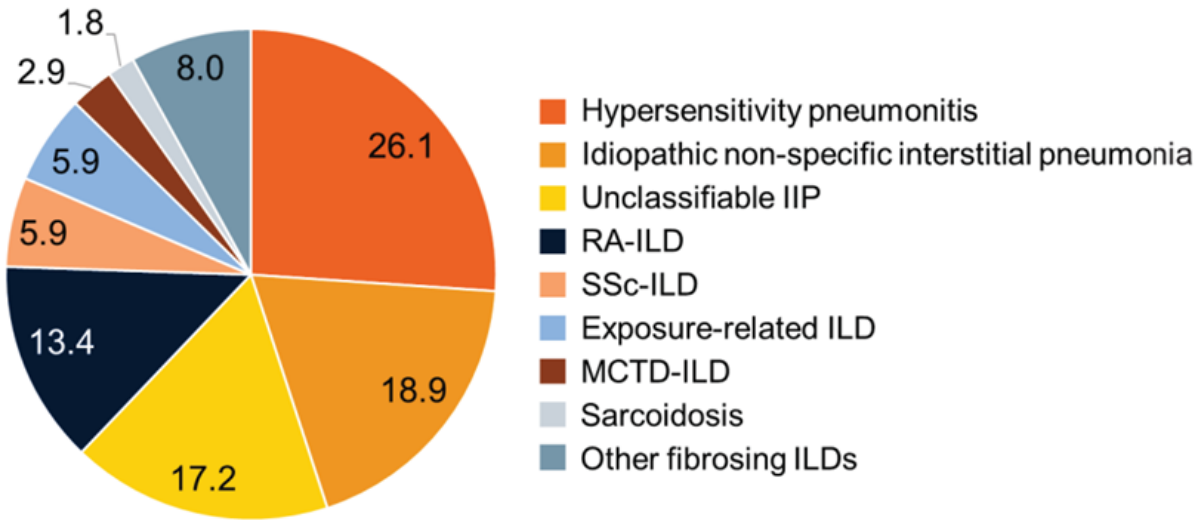
Lancet Respiratory Medicine
2020

P20-02333

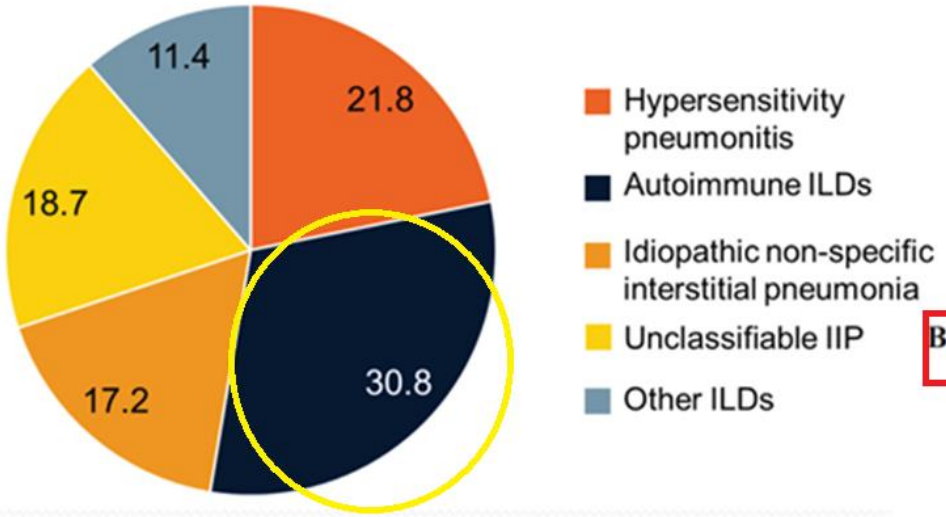
Nintedanib in patients with progressive fibrosing interstitial lung diseases—subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial

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*

Figure S1. ILD diagnoses in 9 subgroups by ILD diagnosis noted in case report form (overall population).



A Subjects with a UIP-like fibrotic pattern on HRCT



B Subjects with other fibrotic patterns on HRCT

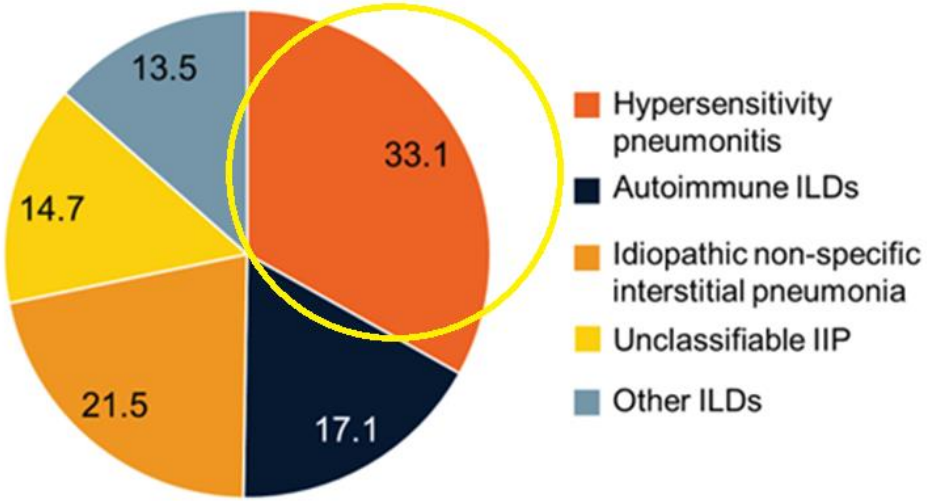


Table S1. Baseline characteristics in 9 subgroups by ILD diagnosis noted in case report form (overall population)

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

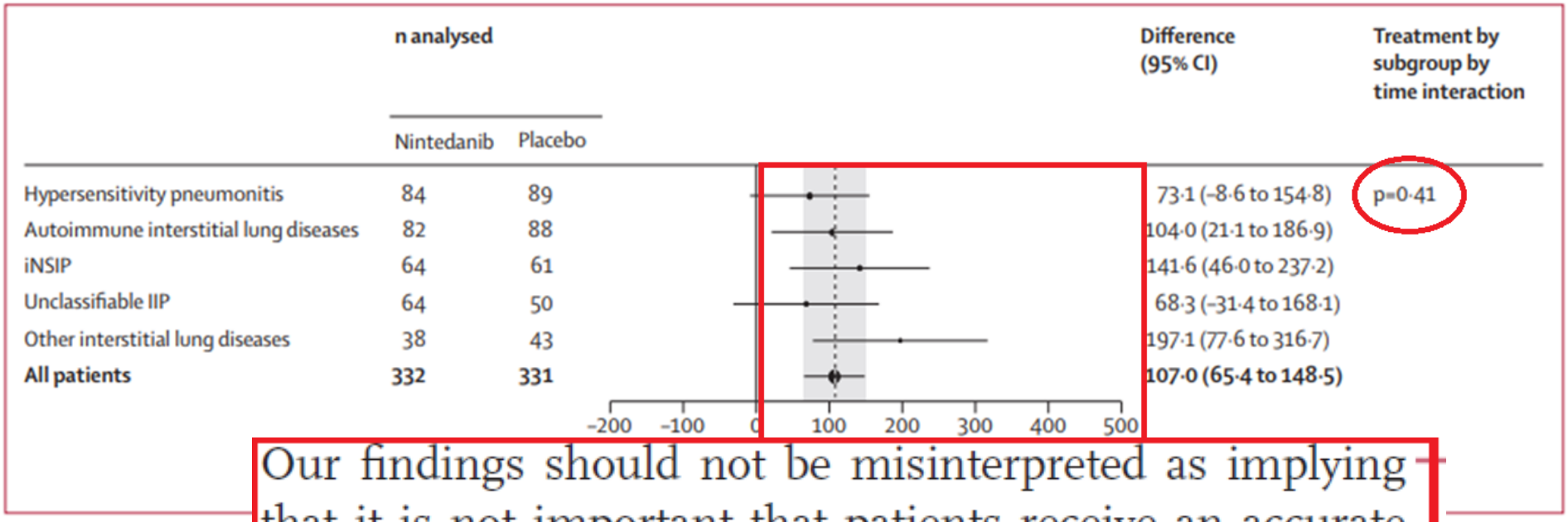


Figure 2: Annual rate of de

Our findings should not be misinterpreted as implying that it is not important that patients receive an accurate ILD diagnosis. An accurate ILD diagnosis remains crucial to the management of individual patients; for example,

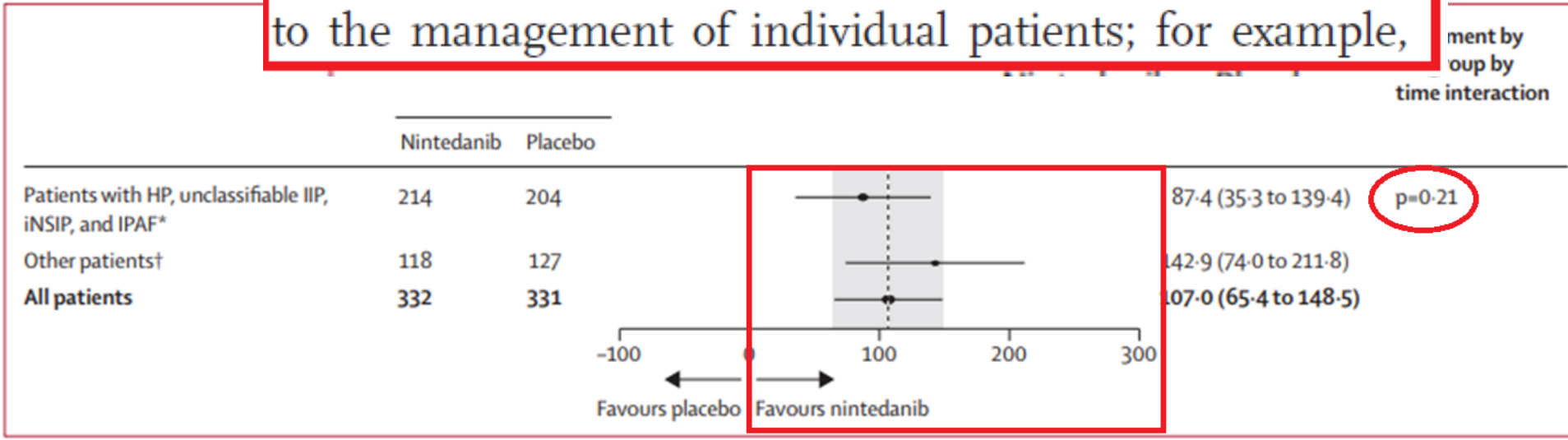


Figure 4: Annual rate of decline in forced vital capacity (mL/year) in patients with a diagnosis likely to be considered as a differential diagnosis of IPF (hypersensitivity pneumonitis, unclassifiable idiopathic interstitial pneumonia, idiopathic non-specific interstitial pneumonia, or interstitial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

Nintedanib in progressive interstitial lung diseases: data from the whole INBUILD trial

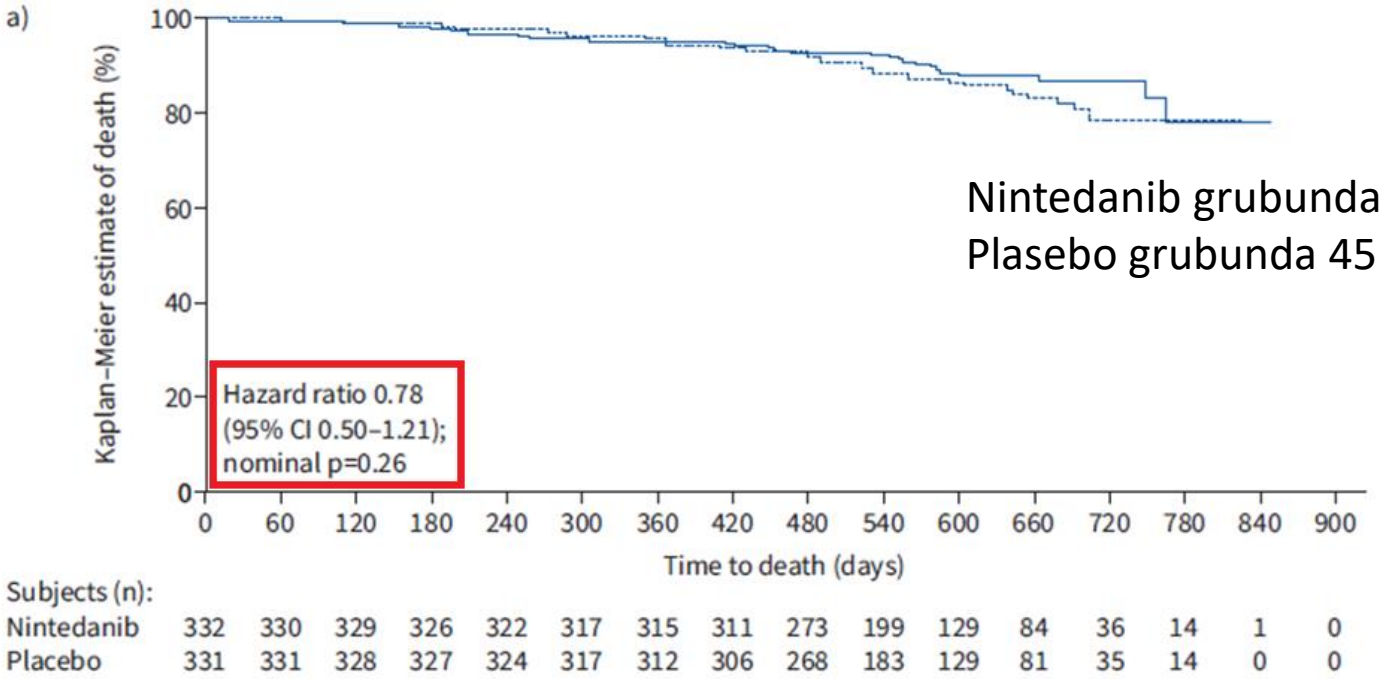
Eur Respir J 2022; 59: 2004538

Kevin R. Flaherty[1], Athol U. Wells[2], Vincent Cottin[3], Anand Devaraj[4,5], Yoshikazu Inoue[6], Luca Richeldi[7], Simon L.F. Walsh[5], Martin Kolb[8], Dirk Koschel[9], Teng Moua[10], Susanne Stowasser[11], Rainer-Georg Goeldner[12], Rozsa Schlenker-Herceg[13] and Kevin K. Brown[14] on behalf of the INBUILD Trial Investigators

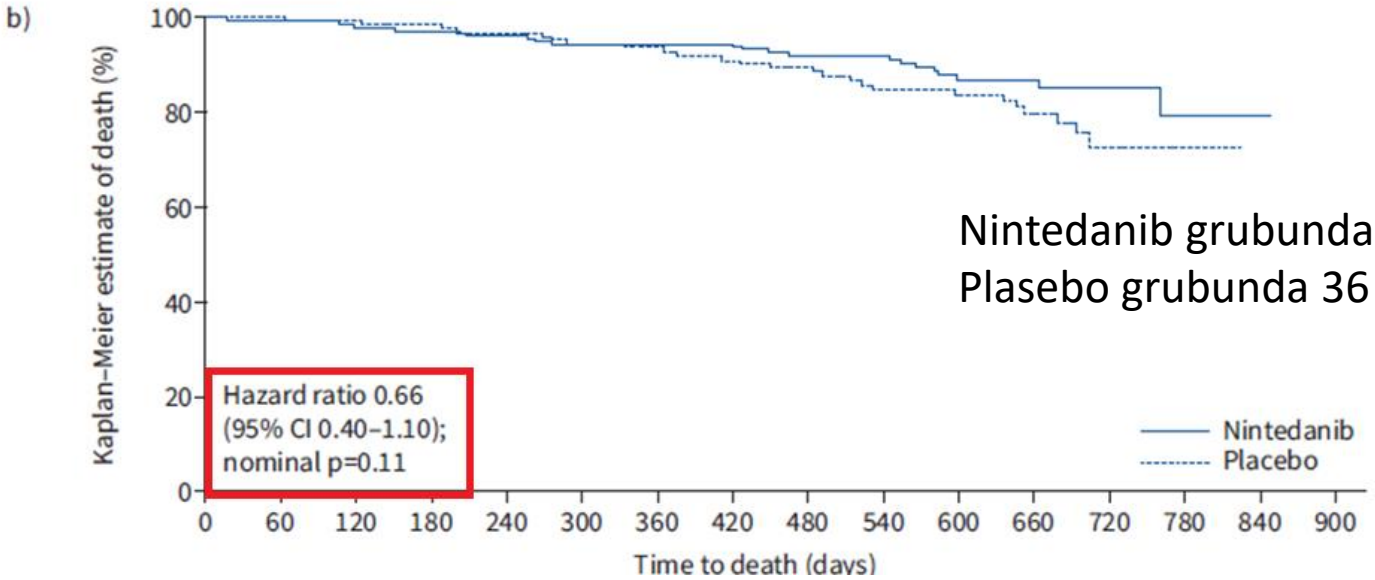
(supplementary table S1). Over the whole trial, mean±SD exposure to trial medication was 15.6±7.2 and 16.8±5.8 months in the nintedanib and placebo groups, respectively; 34.3% and 30.2% of subjects in these groups, respectively, prematurely discontinued trial medication. The median follow-up time for the time-to-event end-points was ~19 months.

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	%37 161 (48.5)	221 (66.8)	%39 101 (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	

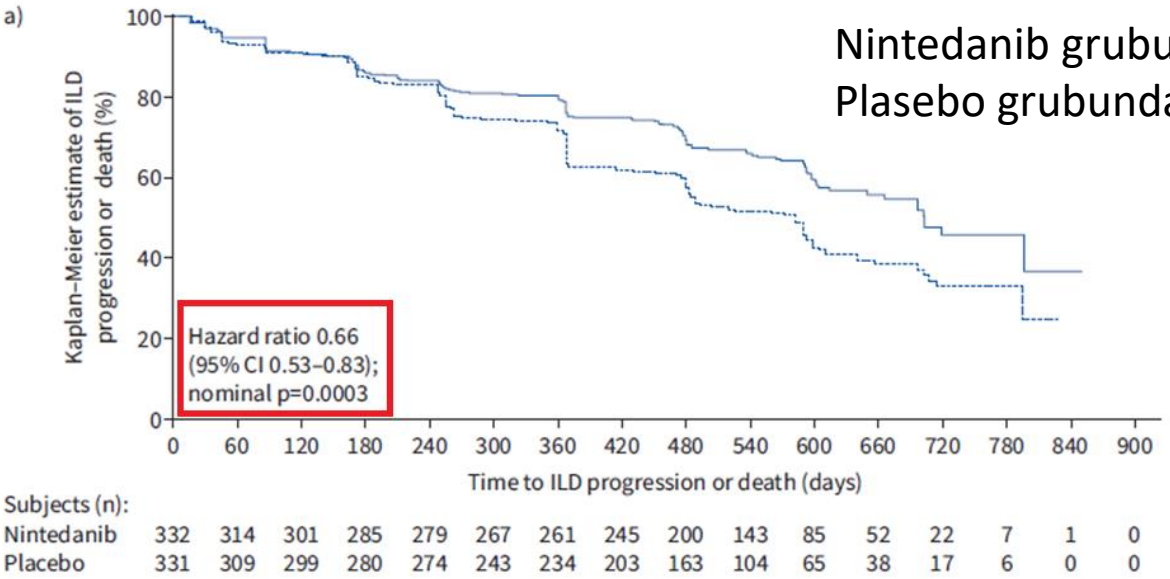


Nintedanib grubunda 36 hasta (%10.8)
Plasebo grubunda 45 hasta (%13.6)



Nintedanib grubunda 25 hasta (%12.1)
Plasebo grubunda 36 hasta (%17.5)

Nintedanib grubunda 134 hasta (%40.4)
Plasebo grubunda 181 hasta (%54.7)



Nintedanib grubunda 90 hasta (%43.7)
Plasebo grubunda 115 hasta (%55.8)

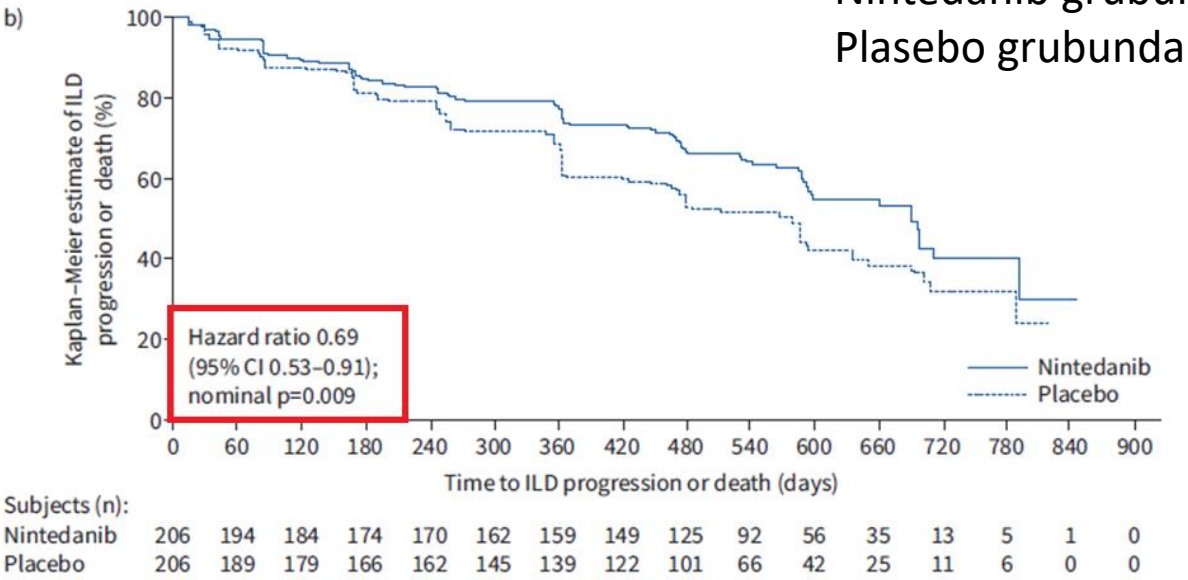
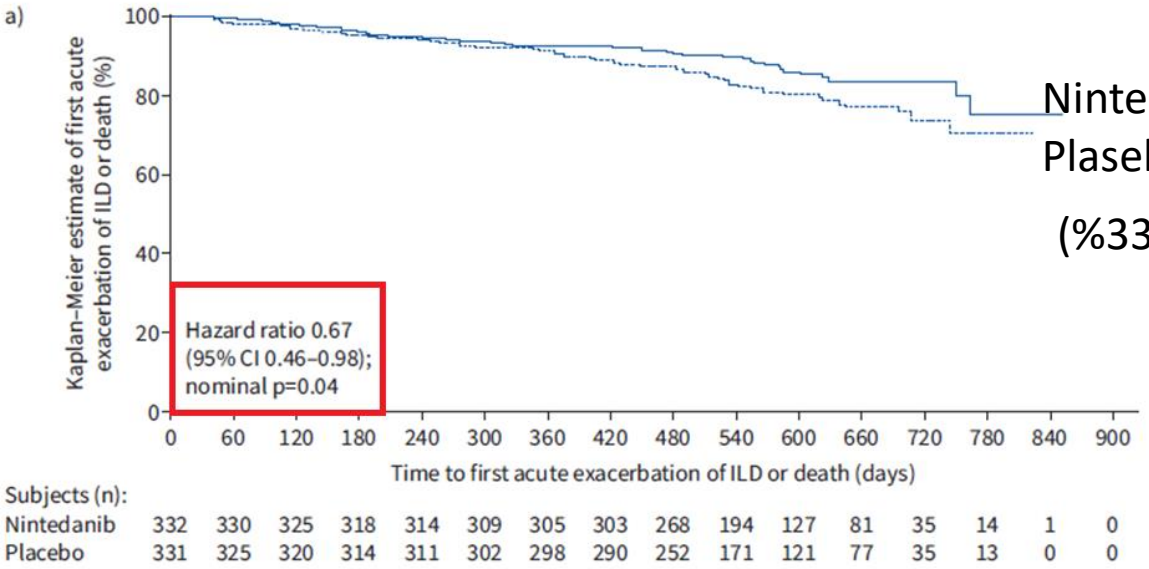
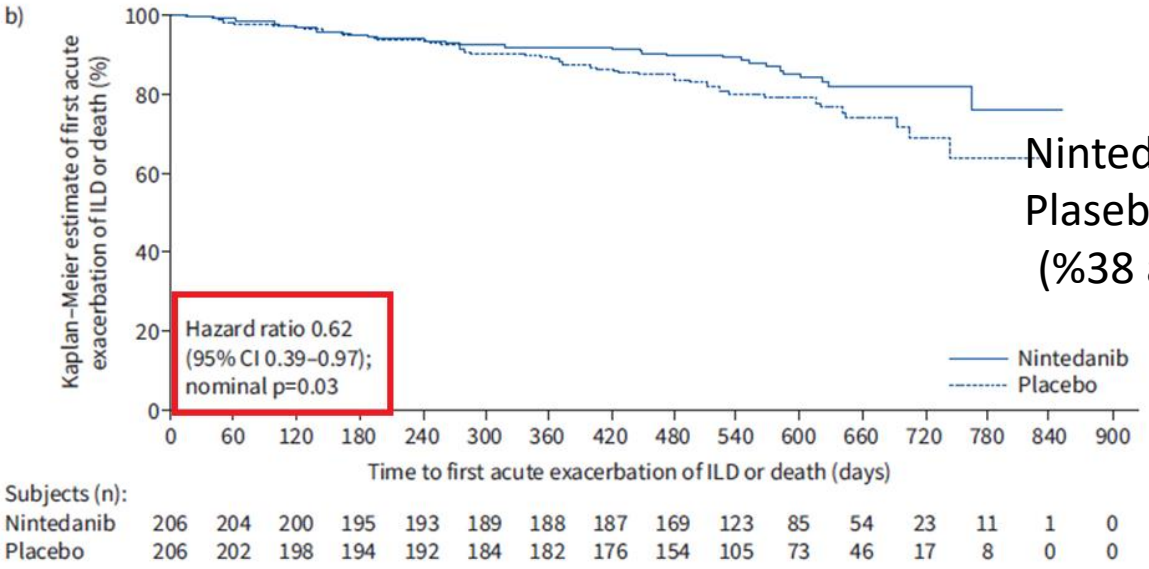


FIGURE 3 Kaplan–Meier estimates of time to progression of interstitial lung disease (ILD) or death in a) the overall population and b) subjects with a usual interstitial pneumonia-like fibrotic pattern on high-resolution computed tomography in the INBUILD trial.



Nintedanib grubunda 46 hasta (%13.9)
Plasebo grubunda 65 hasta (%19.6)

(%33 azalma)



Nintedanib grubunda 31 hasta (%15.0)
Plasebo grubunda 47 hasta (%22.8)
(%38 azalma)

FIGURE 4 Kaplan–Meier estimates of time to first acute exacerbation of interstitial lung disease (ILD) or death in a) the overall population and b) subjects with a usual interstitial pneumonia-like fibrotic pattern on high-resolution computed tomography in the INBUILD trial.

TABLE 2 Rates per 100 patient-years of the most frequent adverse events in the overall population of the INBUILD trial

	Nintedanib (n=332)	Placebo (n=331)
Diarrhoea	136.4	23.0
Nausea	30.8	7.6
Vomiting	17.3	3.5
Decreased appetite	14.0	5.1
Nasopharyngitis	13.9	11.4
Dyspnoea	12.9	13.3
Bronchitis	12.1	15.4
Weight decrease	12.4	3.9
Alanine aminotransferase increased	12.4	2.8
Cough	9.8	12.1
Progression of interstitial lung disease[#]	6.5	12.7
Aspartate aminotransferase increased	10.8	2.8

Clinical Rheumatology (2023) 42:2311–2319
https://doi.org/10.1007/s10067-023-06623-7

ORIGINAL ARTICLE

Effect of nintedanib in patients with progressive pulmonary fibrosis associated with rheumatoid arthritis: data from the INBUILD trial

Eric L. Matteson[1] · Martin Aringer[2] · Gerd R. Burmester[3] · Heiko Mueller[4] · Lizette Moros[5] · Martin Kolb[6]

89 hasta
Ortalama yaş 66.9
% 60.7 erkek
%86.5'inde YRBT'de UIP paterni
Ortalama pred FVC %71.5
Ortalama pred DLco %47.7
RA-İAH tanısına kadar geçen süre 3.6 yıl
%21.3'ü biologic DMARDs,
%53.9'ü non-biologic DMARDs, %73.0'ü steroid

Table 1 Efficacy endpoints in patients with RA-ILD in the INBUILD trial

	Nintedanib ($n = 42$)	Placebo ($n = 47$)
Rate of decline in FVC (mL/year) over 52 weeks		
Rate of decline in FVC (mL/year) over 52 weeks, adjusted mean (SE)	−82.6 (41.3)	−199.3 (36.2)
Difference (95% CI)	116.7 (7.4, 226.1)	
Nominal *p*-value	0.037	
Absolute and relative declines in FVC at week 52		
Relative decline in FVC >10% predicted at week 52, *n* (%)	12 (28.6)	20 (42.6)
Odds ratio (95% CI)	0.48 (0.19 1.25)	
Absolute decline in FVC >10% predicted at week 52, *n* (%)	5 (11.9)	15 (31.9)
Odds ratio (95% CI)	0.31 (0.10, 1.02)	
Time to event endpoints over the whole trial		
Acute exacerbation of ILD or death, *n* (%)	8 (19.0)	15 (31.9)
Hazard ratio (95% CI)	0.54 (0.23, 1.28)	
Nominal *p*-value	0.16	
Hospitalisation or death, *n* (%)	27 (64.3)	26 (55.3)
Hazard ratio (95% CI)	1.36 (0.79, 2.34)	
Nominal *p*-value	0.26	
Respiratory hospitalisation or death, *n* (%)	18 (42.9)	22 (46.8)
Hazard ratio (95% CI)	0.87 (0.46, 1.62)	
Nominal *p*-value	0.65	
Progression of ILD[a] or death, *n* (%)	19 (45.2)	29 (61.7)
Hazard ratio (95% CI)	0.63 (0.35, 1.13)	
Nominal *p*-value	0.12	
Death, *n* (%)	7 (16.7)	9 (19.1)
Hazard ratio (95% CI)	0.86 (0.32, 2.31)	
Nominal *p*-value	0.76	

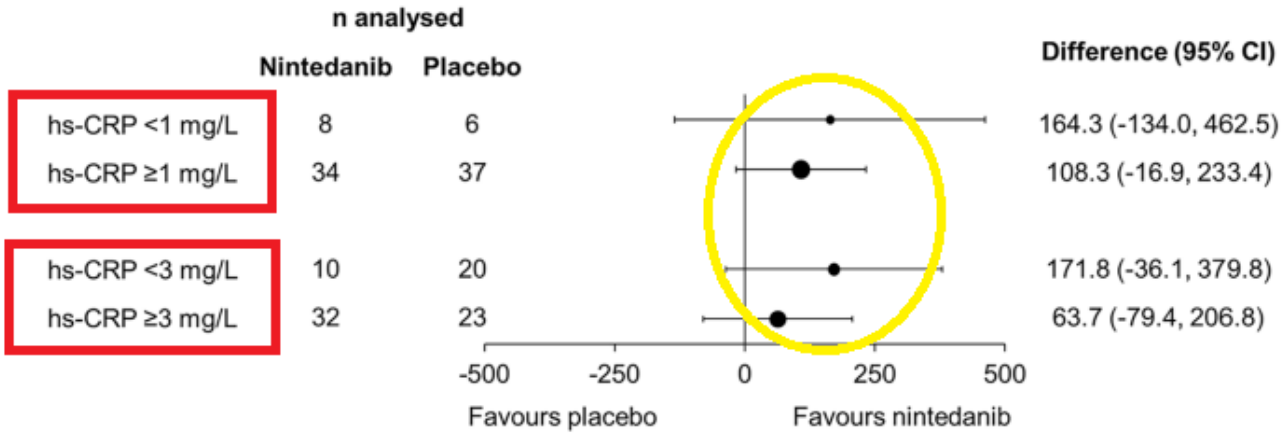


Fig. 2 Rate of decline in FVC (mL/year) over 52 weeks in subgroups of patients with RA-ILD in the INBUILD trial by high sensitivity C-reactive protein (hs-CRP) at baseline. *RA-ILD* rheumatoid arthritis-associated interstitial lung disease

Table 2 Adverse events in patients with RA-ILD in the INBUILD trial

	Nintedanib ($n = 42$)		Placebo ($n = 47$)	
	n (%)	Rate per 100 patient-years	*n* (%)	Rate per 100 patient-years
Any adverse event	42 (100.0)	1124.7	45 (95.7)	425.4
Most frequent adverse events[a]				
Diarrhoea	26 (61.9)	118.0	13 (27.7)	26.0
Bronchitis	9 (21.4)	21.3	14 (29.8)	24.9
Pneumonia	10 (23.8)	19.9	6 (12.8)	9.4
Nausea	9 (21.4)	21.0	6 (12.8)	10.3
Dyspnoea	8 (19.0)	18.1	6 (12.8)	9.6
Nasopharyngitis	4 (9.5)	7.9	7 (14.9)	12.3
Constipation	6 (14.3)	12.8	4 (8.5)	6.4
Arthralgia	5 (11.9)	10.5	5 (10.6)	8.2
Vomiting	5 (11.9)	10.9	4 (8.5)	6.6
Progression of ILD[b]	2 (4.8)	3.8	7 (14.9)	11.3
Abdominal pain	5 (11.9)	11.0	3 (6.4)	4.6
Alanine aminotransferase increased	6 (14.3)	12.5	1 (2.1)	1.5
Back pain	5 (11.9)	10.0	2 (4.3)	3.1
Decreased appetite	5 (11.9)	10.7	1 (2.1)	1.5
Urinary tract infection	5 (11.9)	10.6	1 (2.1)	1.5
Abdominal pain upper	5 (11.9)	10.6	1 (2.1)	1.6
Serious adverse event[c]	26 (61.9)	81.7	29 (61.7)	60.2
Adverse event leading to permanent dose reduction	9 (21.4)	21.5	0	0
Adverse event leading to treatment discontinuation	10 (23.8)	19.2	8 (17.0)	12.2
Most frequent adverse events leading to treatment discontinuation[d]				
Alanine aminotransferase increased	3 (7.1)	5.7	0	0
Diarrhoea	2 (4.8)	3.8	0	0
Aspartate aminotransferase increased	2 (4.8)	3.8	0	0

RESEARCH Open Access

Nintedanib and immunomodulatory therapies in progressive fibrosing interstitial lung diseases

. Respir Res (2021) 22:84

Vincent Cottin[1*], Luca Richeldi[2], Ivan Rosas[3], Maria Otaola[4], Jin Woo Song[5], Sara Tomassetti[6], Marlies Wijsenbeek[7], Manuela Schmitz[8], Carl Coeck[9], Susanne Stowasser[10], Rozsa Schlenker-Herceg[11] and Martin Kolb[12] on behalf of the INBUILD Trial Investigators

Conclusions

The patients enrolled in the INBUILD trial had chronic fibrosing ILDs that were progressing despite management deemed appropriate in clinical practice, including immunomodulatory therapies commonly used in the treatment of ILDs. While the INBUILD trial was not designed to evaluate the effects of concomitant medications on the rate of decline in FVC, our analyses suggest that the use of glucocorticoids at baseline, or the introduction of immunomodulatory therapies during the trial, did not affect the benefit of nintedanib in reducing the rate of FVC decline in patients with chronic fibrosing ILDs and a progressive phenotype.

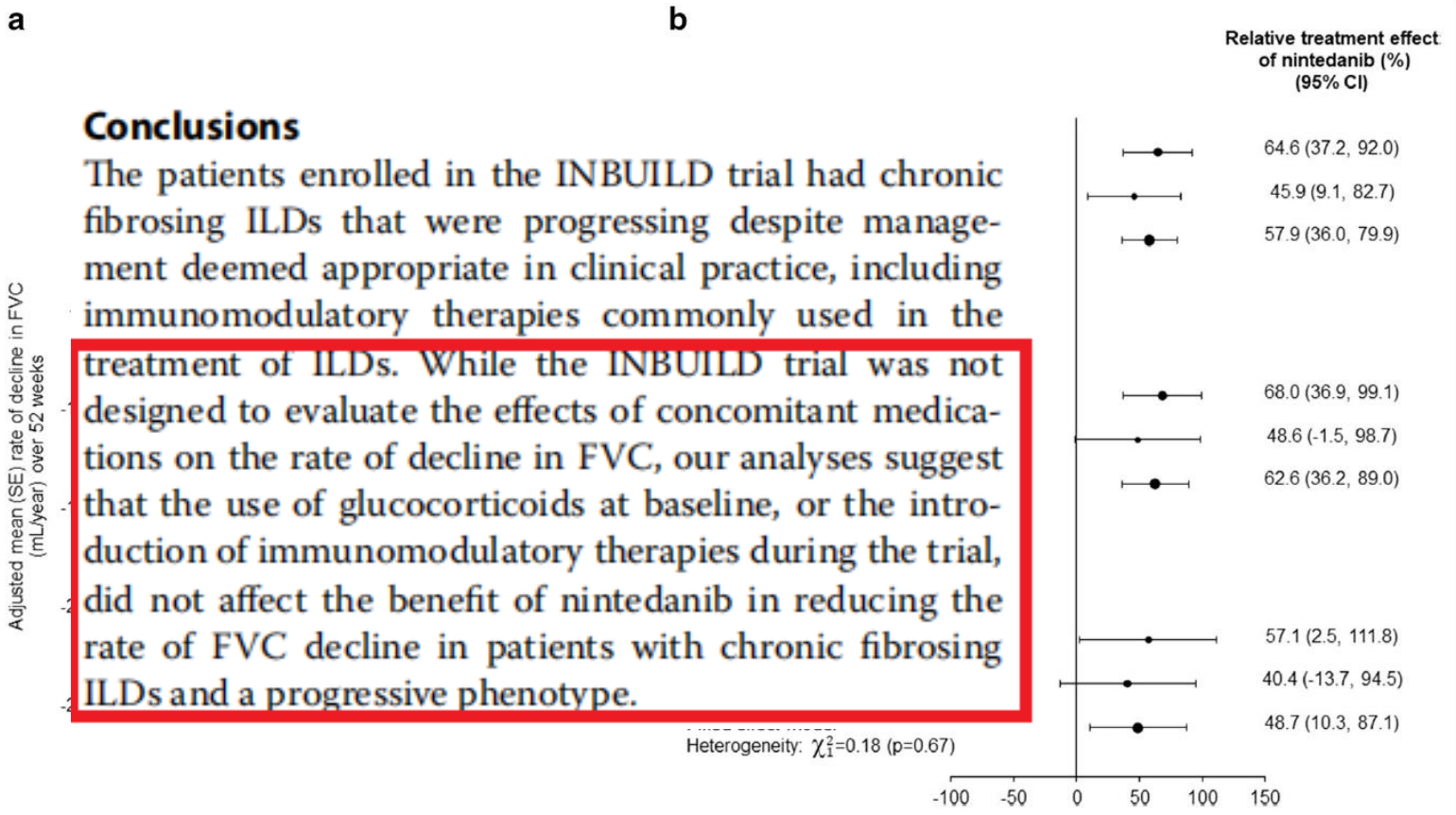


Fig. 1 Rate of decline in forced vital capacity (FVC) (mL/year) with nintedanib and placebo (**a**) and relative treatment effect of nintedanib (**b**) over 52 weeks in subgroups taking or not taking glucocorticoids at baseline. Glucocorticoids were taken at a dose of > 20 mg/day prednisone or equivalent by 8 subjects. *HRCT* high-resolution computed tomography, *UIP* usual interstitial pneumonia

Effect of Nintedanib in Patients with Progressive Pulmonary Fibrosis in Subgroups with Differing Baseline Characteristics

Adv Ther (2023) 40:5536–5546
https://doi.org/10.1007/s12325-023-02668-x

Martin Kolb · Kevin R. Flaherty · Rafael S. Silva ·
Antje Prasse · Carlo Vancheri · Heiko Mueller · Kamila Sroka-Saidi ·
Athol U. Wells · on behalf of the INBUILD trial investigators

Table 1 Time to ILD progression (absolute decline in FVC % predicted ≥ 10%) or death over the whole INBUILD trial in subgroups by baseline characteristics

Baseline characteristic	*n/N* (%) with event		Hazard ratio (95% CI)	Treatment-by-subgroup interaction *p* value
	Nintedanib	Placebo		
Sex				
Male	76/179 (42.5)	105/177 (59.3)	0.62 (0.46, 0.84)	0.66
Female	58/153 (37.9)	76/154 (49.4)	0.72 (0.51, 1.01)	
Age				
< 65 years	49/139 (35.3)	54/121 (44.6)	0.74 (0.50, 1.09)	0.58
≥ 65 years	85/193 (44.0)	127/210 (60.5)	0.64 (0.49, 0.85)	
Race[a]				
White	100/242 (41.3)	137/246 (55.7)	0.65 (0.50, 0.84)	0.93
Asian	32/84 (38.1)	41/80 (51.3)	0.71 (0.45, 1.13)	
Body mass index (BMI)				
< 25 kg/m^2	44/90 (48.9)	59/98 (60.2)	0.74 (0.50, 1.10)	0.85
≥ 25 to < 30 kg/m^2	48/130 (36.9)	61/112 (54.5)	0.65 (0.44, 0.94)	
≥ 30 kg/m^2	42/111 (37.8)	61/121 (50.4)	0.64 (0.43, 0.95)	
Time since diagnosis of ILD				
≤ 1 year	23/67 (34.3)	41/67 (61.2)	0.44 (0.26, 0.74)	0.09
> 1 to ≤ 3 years	54/118 (45.8)	59/112 (52.7)	0.82 (0.56, 1.18)	
> 3 to ≤ 5 years	24/73 (32.9)	34/57 (59.6)	0.50 (0.29, 0.84)	
> 5 years	33/73 (45.2)	47/95 (49.5)	0.88 (0.56, 1.39)	
FVC % predicted				
≤ 50%	25/42 (59.5)	20/33 (60.6)	0.70 (0.38, 1.29)	0.44
> 50 to ≤ 70%	55/154 (35.7)	89/160 (55.6)	0.57 (0.41, 0.80)	
> 70 to ≤ 90%	41/104 (39.4)	50/105 (47.6)	0.80 (0.53, 1.21)	
> 90%	13/32 (40.6)	22/33 (66.7)	0.51 (0.26, 1.03)	
DLco % predicted[b]				
≤ median (43.3%)	82/177 (46.3)	92/150 (61.3)	0.65 (0.48, 0.88)	0.97
> median (43.3%)	51/149 (34.2)	87/178 (48.9)	0.66 (0.46, 0.93)	
CPI				
≤ 45	25/82 (30.5)	57/120 (47.5)	0.61 (0.38, 0.98)	0.77
> 45	108/244 (44.3)	122/208 (58.7)	0.66 (0.51, 0.85)	
GAP stage				
I	41/142 (28.9)	68/152 (44.7)	0.59 (0.40, 0.88)	0.42
II or III	93/190 (48.9)	113/179 (63.1)	0.70 (0.53, 0.93)	
Taking anti-acid therapy[c]				
Yes	88/201 (43.8)	101/180 (56.1)	0.72 (0.54, 0.96)	0.34
No	46/131 (35.1)	80/151 (53.0)	0.58 (0.40, 0.83)	
DMARDs[d]				
Yes	16/43 (37.2)	31/48 (64.6)	0.49 (0.26, 0.91)	0.28
No	118/289 (40.8)	150/283 (53.0)	0.70 (0.55, 0.89)	

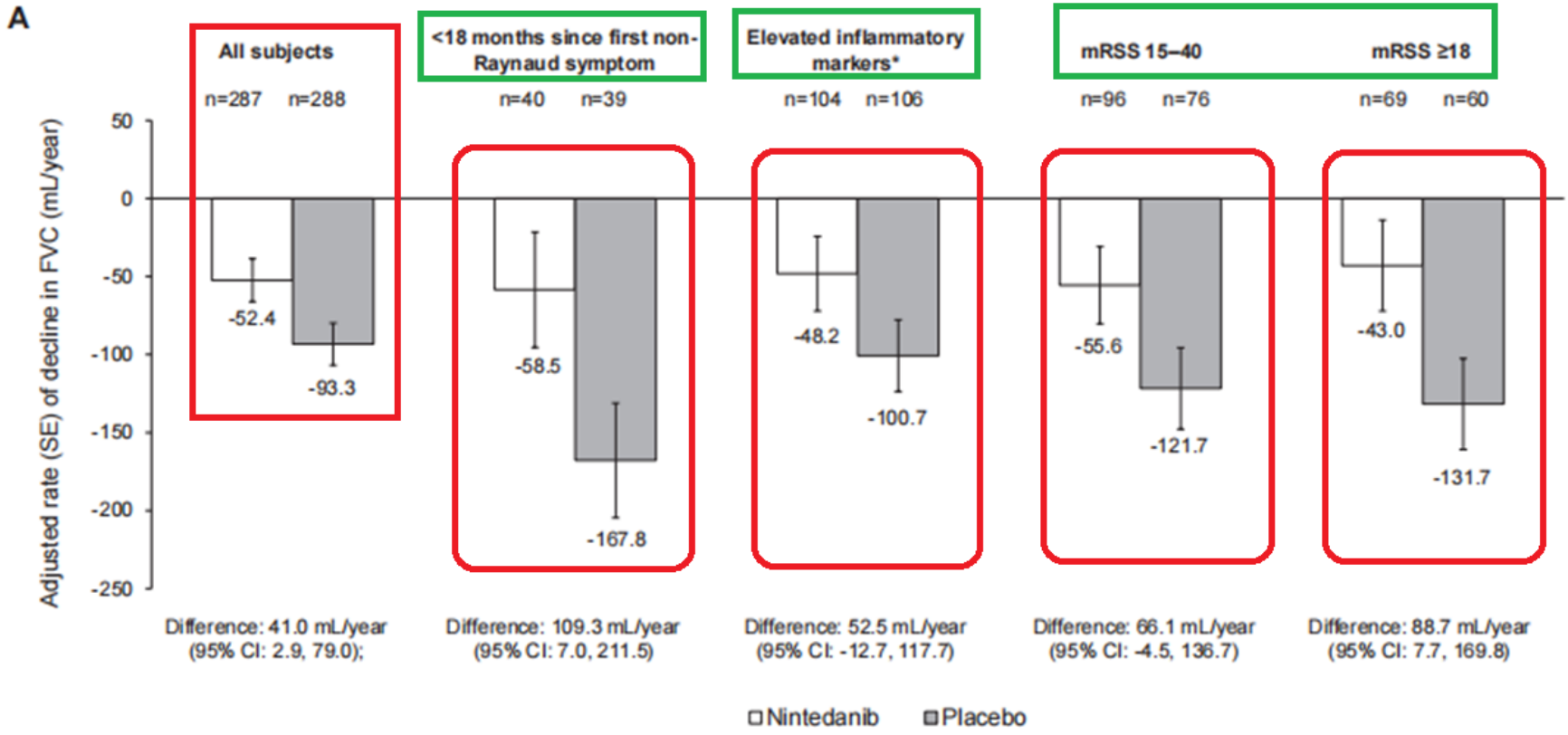
RMD Open
Rheumatic & Musculoskeletal Diseases

SHORT REPORT

Effect of nintedanib in patients with systemic sclerosis-associated interstitial lung disease and risk factors for rapid progression

RMD Open 2023;**9**:e002859. doi:10.1136/rmdopen-2022-002859

Dinesh Khanna ,[1] Toby M Maher ,[2,3] Elizabeth R Volkmann ,[4] Yannick Allanore ,[5] Vanessa Smith ,[6,7,8] Shervin Assassi ,[9] Michael Kreuter ,[10,11] Anna-Maria Hoffmann-Vold ,[12] Masataka Kuwana ,[13] Christian Stock ,[14] Margarida Alves,[15] Steven Sambevski,[15] Christopher P Denton [16]



Antifibrotikler birinci seçenek olarak başlanabilir mi?

- YRBT'de UIP paterni olanlar
- Histopatolojik incelemede UIP paterni olanlar
- 12 ay içinde FVC'de %10 düşme olanlar
- İmmünsüpresif tedavinin potansiyel yan etkileri fazla olanlar

Gibson CD, et al. Lung **2020**
Wong AW, et al. Respir Res **2020**

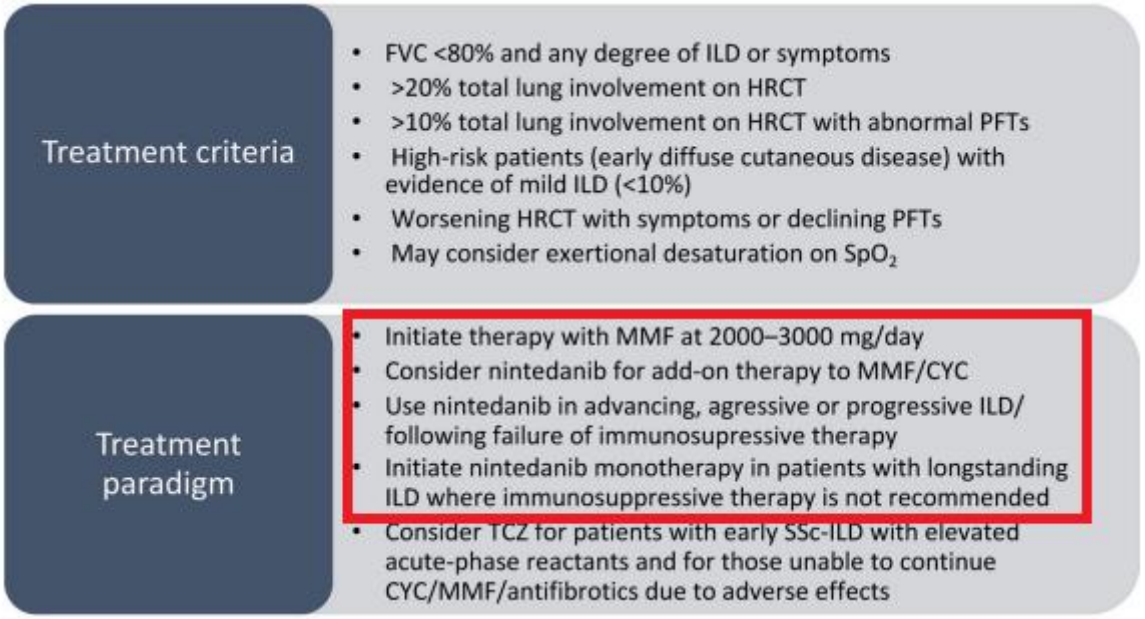
Rahaghi et al. Respiratory Research (2023) 24:6
https://doi.org/10.1186/s12931-022-02292-3

Respiratory Research

RESEARCH Open Access

Expert consensus on the management of systemic sclerosis-associated interstitial lung disease

Franck F. Rahaghi[1*], Vivien M. Hsu[2], Robert J. Kaner[3], Maureen D. Mayes[4], Ivan O. Rosas[5], Rajan Saggar[6], Virginia D. Steen[7], Mary E. Strek[8], Elana J. Bernstein[9], Nitin Bhatt[10], Flavia V. Castelino[11], Lorinda Chung[12], Robyn T. Domsic[13], Kevin R. Flaherty[14], Nishant Gupta[15], Bashar Kahaleh[16], Fernando J. Martinez[3], Lee E. Morrow[17], Teng Moua[18], Nina Patel[9,19], Oksana A. Shlobin[20], Brian D. Southern[21], Elizabeth R. Volkmann[6] and Dinesh Khanna[14*]



Antifibrotikler immünsüpresifler ile eş zamanlı başlanabilir mi?

- uILD'de Pirfenidone+MMF güvenli

  Maher TM, et al. Lancet Respir Med **2020**

- SS-ILD'de Nintedanib+MMF güvenli

  Distler O, et al. N Engl J Med **2019**

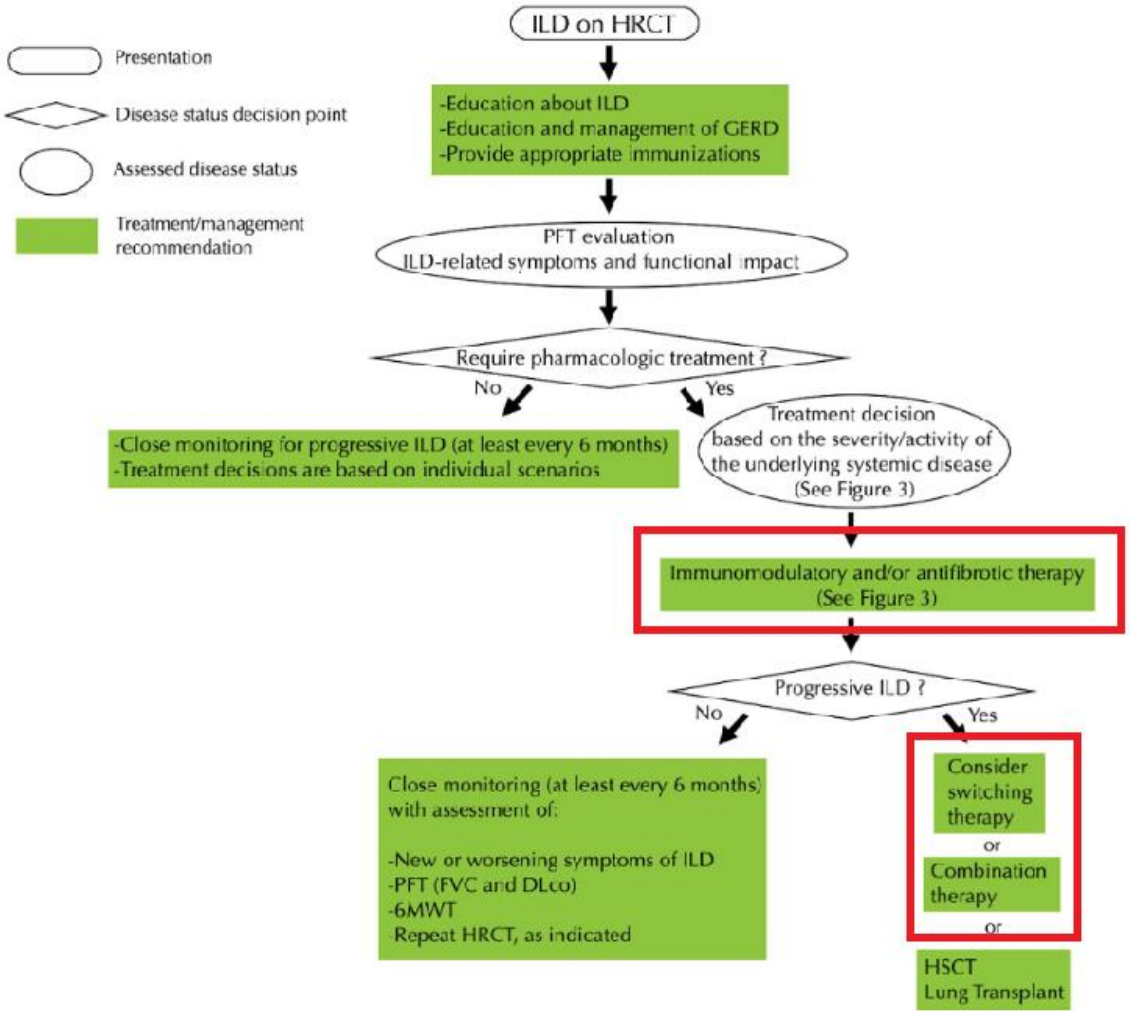
- SS-ILD'de MMF+pirfenidone vs MMF devam ediyor

  U.S. National Library of Medicine. Clinical Trials.gov. Available online: https://www.clinicaltrials.gov/

Systemic Sclerosis–Associated Interstitial Lung Disease: How to Incorporate Two Food and Drug Administration–Approved Therapies in Clinical Practice

Dinesh Khanna,[1] Alain Lescoat,[2] David Roofeh,[1] Elana J. Bernstein,[3] Ella A. Kazerooni,[1] Michael D. Roth,[4] Fernando Martinez,[5] Kevin R. Flaherty,[1] and Christopher P. Denton[6]

Arthritis & Rheumatology
Vol. 74, No. 1, January 2022, pp 13–27
DOI 10.1002/art.41933



Devam eden çalışmalar

International Journal of
Molecular Sciences

MDPI

Review

Efficacy of Pirfenidone and Nintedanib in Interstitial Lung Diseases Other than Idiopathic Pulmonary Fibrosis: A Systematic Review

Francesco Amati [1,2,*], Anna Stainer [1,2], Veronica Polelli [2], Marco Mantero [3,4], Andrea Gramegna [3,4], Francesco Blasi [3,4] and Stefano Aliberti [1,2]

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[4] Department of Pathophysiology and Transplantation, Università degli Studi di Milano, 20122 Milan, Italy
* Correspondence: francesco.amati@hunimed.eu; Tel.: +39-02-8224-3042

Int. J. Mol. Sci. **2023**, *24*, 7849. https://doi.org/10.3390/ijms24097849

Table 2. Ongoing clinical trial on nintendanib [26–37].

NCT Number	Disease	Phase	Enrollment	Study Design	Inclusion Criteria	Primary Outcome	Secondary Outcomes
NCT05065190 [26]	PF-ILD	3	90	Interventional Randomized Quadruple blind	Progressive fibrosis * Fibrosing lung disease on HRCT FVC ≥ 45%	Change in FVC [Time frame 52 weeks]	N/A
NCT05067517 [27]	Progressive Fibrosing Coal Mine Dust-Induced ILD	3	160	Interventional Randomized Triple blind	30% ≤ DLCO < 80%. FVC ≥ 45%	Change in FVC [Time frame 12–24–36–52 weeks]	Change in pulmonary function Absolute change from baseline in the L-PF Symptoms (cough and dyspnea) domain score Absolute change from baseline in the K- BILD total score Progression on HRCT 6MWT Time to all-cause and respiratory mortality Time for progression
NCT05335278 [28]	Myositis Associated ILD	N/A	25	Interventional Open label	Extent of ILD disease ≥ 10% on HRCT done within 12 months of enrolment Progressive disease within 24 months of the screening visit Current and ongoing treatment with immunosuppressive medications, on a stable medication regimen and dosage for at least 6 weeks (considered standard of care medical therapy)	Tolerability AE [Time frame 24 weeks]	Change in FVC Change in DLCO Change in 6MWD
NCT04856111 [29]	COVID-19	4	48	Interventional Randomized Single blind	Post-COVID parenchymal involvement >10% of the lung parenchyma or having persistent reticulation or persistent consolidation despite a trial of glucocorticoids (minimum prednisolone dose of 10 mg/day, or equivalent) for a minimum period of 4 weeks after discharge for the acute COVID-19	Change in the FVC [Time frame 24 weeks]	Proportion of subjects with FVC improvement or stabilization Change in dyspnoea Change in resting oxygen saturation Proportion of subjects with oxygen desaturation on exercise testing Change in the 6MWD Change the SF-36 and K-BILD questionnaires Changes in HRCT scores

Table 2. *Cont.*

NCT Number	Disease	Phase	Enrollment	Study Design	Inclusion Criteria	Primary Outcome	Secondary Outcomes
NCT04619680 [30]	COVID-19	4	170	Interventional Randomized Triple blind	Required one of the following after diagnosis with SARS-CoV-2: - supplemental oxygen through nasal cannula; - high flow oxygen; - non-invasive ventilation or mechanical ventilation or a history of desaturation below 90%; FVC <91% predicted or DLCO <71%	Change in FVC [Time frame 180 days]	Chest CT visual score Change in the SGRQ, K-BILD, LCQ, and SF-36 questionnaires Change in 6MWT Functional Assessment of Chronic Illness Number of deaths due to any or respiratory cause AE
NCT04541680 [31]	COVID-19	3	250	Interventional Randomized Triple blind	1. History of hospitalization for COVID-19 infection documented with positive PCR or positive serology in the previous 2 to 12 months 2. Lung opacities on HRCT involving > 10% of the lung volume with fibrotic features 3. DLCO $\leq$ 70%	Change in FVC [Time frame 12 months]	Change in DLCO Change in 6MWT HRCT lung opacities extension Change in health-related quality of life Evolution of dyspnoea over time AE
NCT04338802 [32]	COVID-19	2	96	Interventional Open Label	18–70 years old. CT examination of patients with multiple fibrotic shadows in both lungs.	Change in FVC [Time frame 8 weeks]	Changes in DLCO Changes in the 6MWT Changes in the HRCT score

Table S3. Adverse events in the overall population using data up to first database lock

NCT04161014 [33]	Pneumoconiosis	2	100	Interventional Open Label	1. Pneumoconiosis diagnosis confirmed at the Occupational MDT 2. Diffuse fibrosing lung disease >10% on HRCT with protocol criteria for progression 3. Asbestosis, silicosis, coal worker's pneumoconiosis, and diffuse dust fibrosis 3. FVC ≥ 45% and DLCO > 30%	Change in FVC [Time frame 36 months]	K-BILD score Time to acute exacerbation Time to referral for lung transplantation Time to death
NCT03805477 [34]	BOS	2	20	Interventional Open Label	Time interval from transplant ≤ 5 years at the time of inclusion Absolute decline of FEV1 ≥ 10% within the past 12 months	AE rate leading to interruption/ discontinuation of study treatment [Time frame 12 months]	Changes in pulmonary function parameters Change in eNO Nitrogen-washout Changes in in 6MWD Cumulative steroid doses Occurrence of GvHD in other organs Disease-free survival of underlying hematologic disease Overall survival
NCT03283007 [35]	BOS	3	80	Interventional Randomized Quadruple Blind	At least 6 months post-lung transplant Progressive BOS **	Change in FEV1 [Time frame 1, 2, 3, 6, 9, 12, and after 13 months]	Exercise tolerance Quality of life improvement Efficacy to hamper FEV1 decrease Efficacy to hamper the progression of BOS Change in oxygen saturation nintedanib tolerance Explanatory parameters of fibrotic pathways
NCT03062943 [36]	LAM	2	30	Interventional Open Label	LAM patients with proven side effects and/or toxicities/contraindications to sirolimus therapy will be eligible for this study.	Change in FEV1 [Time frame 12 months]	AE

Design of a phase III, double-blind, randomised, placebo-controlled trial of BI 1015550 in patients with progressive pulmonary fibrosis (FIBRONEER-ILD)

Ekim 2022'de başladı
Kasım 2024'te bitecek

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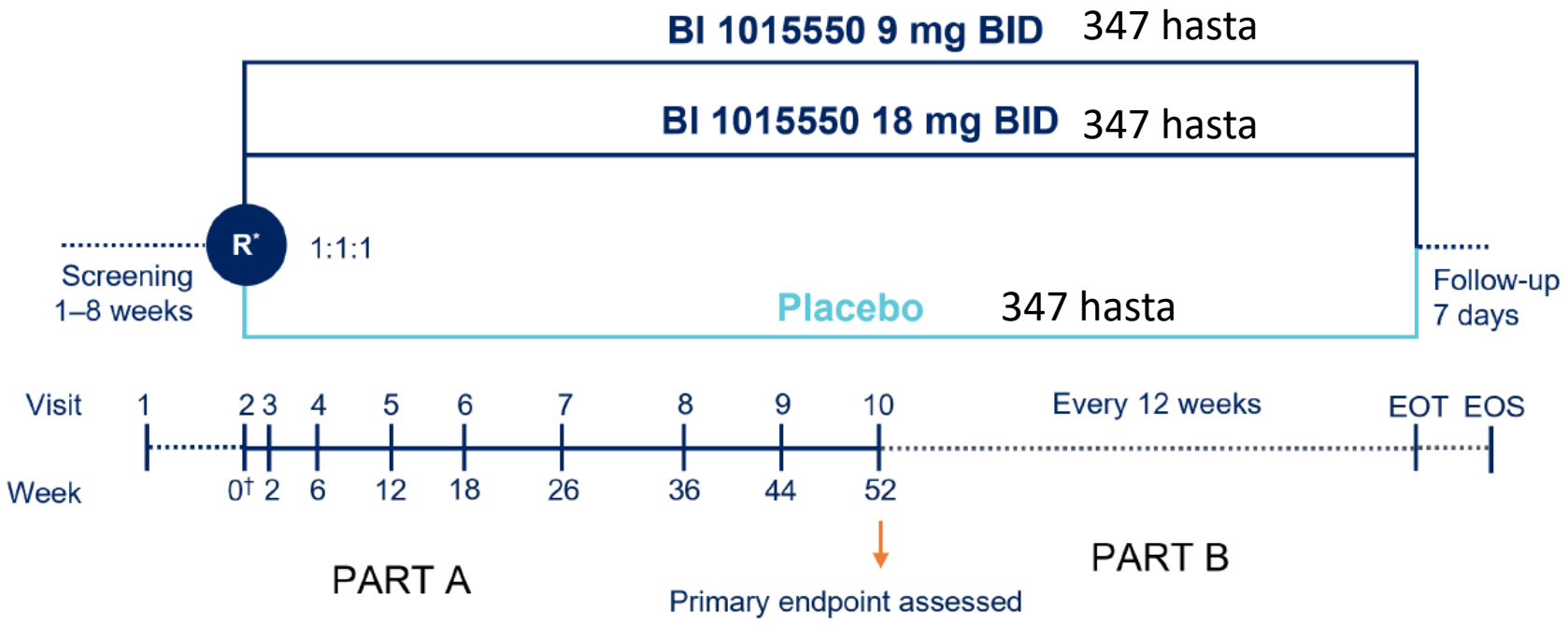

Box 1 Main inclusion and exclusion criteria

Inclusion criteria

⇒ ≥18 years old.

⇒ Presence of fibrotic lung disease with disease extent >10% on HRCT performed within 12 months of visit 1 as confirmed by central review.

⇒ Patients with pulmonary fibrosis other than IPF who manifest progression according to at least one of the following predefined criteria within 24 months of visit 1:
  - ⇒ Relative decline in FVC% predicted of ≥10%.
  - ⇒ Decline in FVC% of ≥5% to <10% with worsening of respiratory symptoms.
  - ⇒ Decline in FVC% predicted of ≥5% to <10% with increasing extent of fibrotic changes on chest imaging.
  - ⇒ Worsening of respiratory symptoms as well as increasing extent of fibrotic changes on chest imaging.

⇒ FVC ≥45% of predicted.

⇒ DLco ≥25% of predicted normal corrected for haemoglobin.

⇒ Patients are either on stable treatment* with nintedanib therapy for at least 12 weeks and plan to stay on this background treatment after randomisation, or not on treatment with nintedanib for at least 8 weeks (eg, either antifibrotic treatment naïve or previously discontinued) and do not plan to start or restart antifibrotic treatment.

⇒ Patients treated with permitted immunosuppressive agents (other than corticosteroids) for an underlying systemic disease (eg, methotrexate, azathioprine) need to be on a stable treatment for at least 12 weeks prior to visit 1 and during the screening period.

Exclusion criteria

⇒ Patients treated with the following medications prior to visit 1:
  - ⇒ Oral corticosteroids >15 mg/day within 4 weeks.
  - ⇒ Cyclophosphamide, tocilizumab or mycophenolate within 8 weeks.
  - ⇒ Rituximab within 6 months.

⇒ Prebronchodilator FEV_1/FVC <0.7 at visit 1.

⇒ Patients with an acute ILD exacerbation within 3 months and/or during the screening period.

⇒ Active, unstable or uncontrolled vasculitis within 8 weeks.

⇒ Any suicidal behaviour (past 2 years) or suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale (past 3 months).

*Stable therapy is defined as a tolerated regimen of nintedanib (no dose change) for at least 12 weeks.

Box 2 Endpoints

Primary endpoint

⇒ Absolute change from baseline in FVC (mL) at week 52.

Key secondary endpoint

⇒ Time to first acute ILD exacerbation, first respiratory hospitalisation or death (whichever occurs first) over the duration of the trial.

Other secondary endpoints

⇒ Time to first acute ILD exacerbation or death over the duration of the trial.

⇒ Time to hospitalisation for respiratory cause or death over the duration of the trial.

⇒ Time to absolute decline in FVC% predicted of >10% from baseline or death over the duration of the trial.

⇒ Time to absolute decline in DLco% predicted of >15% from baseline or death over the duration of the trial.

⇒ Time to death over the duration of the trial.

⇒ Absolute change from baseline in L-PF Symptoms dyspnoea domain score at week 52.

⇒ Absolute change from baseline in L-PF Symptoms cough domain score at week 52.

⇒ Absolute change from baseline in L-PF Symptoms fatigue domain score at week 52.

⇒ Absolute change from baseline in FVC% predicted at week 52.

⇒ Absolute change from baseline in DLco% predicted at week 52.

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REVIEW
S.K. RAJAN ET AL.

Progressive pulmonary fibrosis: an expert group consensus statement

Sujeet K. Rajan [1], Vincent Cottin [2], Raja Dhar[3], Sonye Danoff[4], Kevin R. Flaherty[5], Kevin K. Brown[6], Anant Mohan[7], Elizabeth Renzoni[8], Murali Mohan[9], Zarir Udwadia[10], Padmanabha Shenoy[11], David Currow[12], Anand Devraj[13], Bhavin Jankharia[14], Ritu Kulshrestha[15], Steve Jones[16], Claudia Ravaglia[17], Silvia Quadrelli[18], Rajam Iyer[19], Sahajal Dhooria [20], Martin Kolb [21,23] and Athol U. Wells[22,23]

Eur Respir J 2023; 61: 2103187

Sonuçlar

Farmakolojik Tedaviler

- Tüm PPF hastalarına uygulanacak standart bir tedavi rejimi yoktur
- Başlangıç tedavisi primer tanıya göre başlanmalıdır
- İPF dışında, SSc-İAH ve olasılıkla RA-İAH varlığında antifibrotikler birinci basamak tedavi olarak düşünülmemelidir
- PPF'de kullanılan immünsüpresiften bağımsız olarak antifibrotikler solunum fonksiyonlarındaki düşüşü azaltır

Sonuçlar

Farmakolojik Tedaviler

- Başlangıç tedavisi olarak kombinasyon tedavisi önerilmiyor
- Kombinasyon tedavisi alanlar yan etkiler açısından yakın takip edilmelidir (KCFT, CBC ilk 3 ay aylık, sonra 3 ayda bir)
- PPF varlığında antifibrotikler ardışık olarak başlanabilir
- PPF'de kullanılan immünsüpresiflerin dozu ve süresi hastadan hastaya değişir

Sonuçlar

Nonfarmakolojik Tedaviler

- PPF hastalarına en erken dönemde pulmoner rehabilitasyon başlanmalıdır
- USOT endikasyonları KOAH hastaları ile benzerdir
- Egzersiz desaturasyonu olanlara ambulatuar oksijen önerilir
- Evde NIV uygulaması sadece yaşam kalitesinde artış olduğu gösterilirse devam edilmelidir
- Belirgin kontrendikasyon yoksa erkenden akciğer transplantasyonuna yönlendirme yapılmalıdır