Antifibrotic Treatment Options for Fibrotic ILD

Gamze KIRKIL

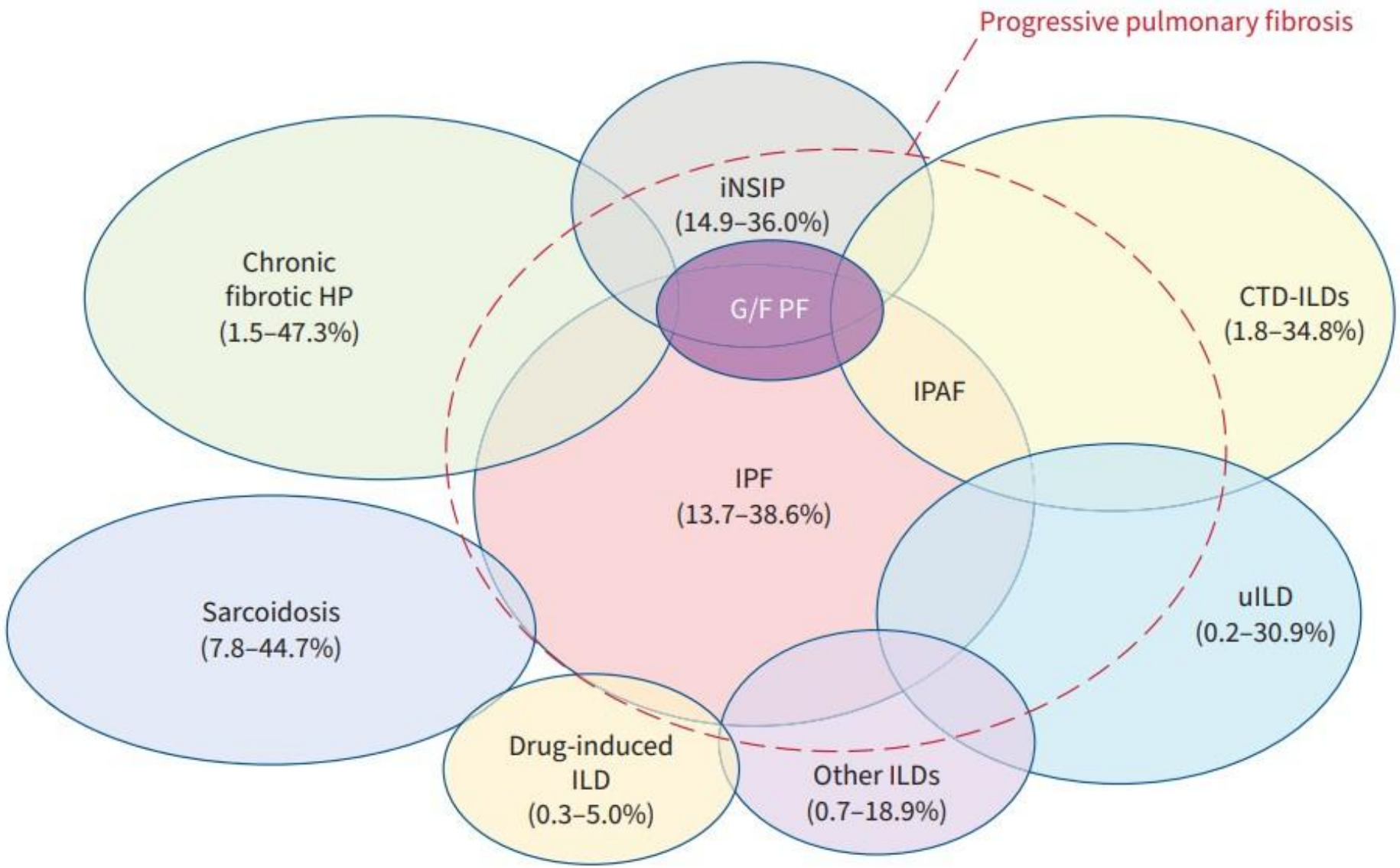
Fırat Üniversitesi Tıp Fakültesi

Göğüs Hastalıkları AD

Fibrotic ILD classification

TABLE 1 Underlying common diagnoses of patients with fibrosing interstitial lung diseases (ILDs)
Idiopathic
Idiopathic interstitial pneumonia
Idiopathic non-specific interstitial pneumonia
Cryptogenic organising pneumonia with supervening fibrosis
Idiopathic desquamative interstitial pneumonia
Idiopathic lymphocytic interstitial pneumonia
Non-idiopathic
Connective tissue disease-ILDs
Fibrotic hypersensitivity pneumonitis
Exposure-related ILDs (asbestosis, silicosis, *etc.*)
Drug-induced ILDs (amiodarone, nitrofurantoin, *etc.*)
Sarcoidosis
Anti-neutrophilic cytoplasmic auto-antibody-associated vasculitis
Unclassifiable ILD
Although idiopathic pulmonary fibrosis is a progressive *and* fibrosing ILD, it is a separate, well-defined entity and has not been considered as part of potentially progressive pulmonary fibrosis for this statement.

Rajan SK, et al. Eur Respir J 2023



Rajan SK, et al. Eur Respir J Rev 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)	<0.000006
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

Treatment of pulmonary fibrosis

IPF treatment

Antifibrotics

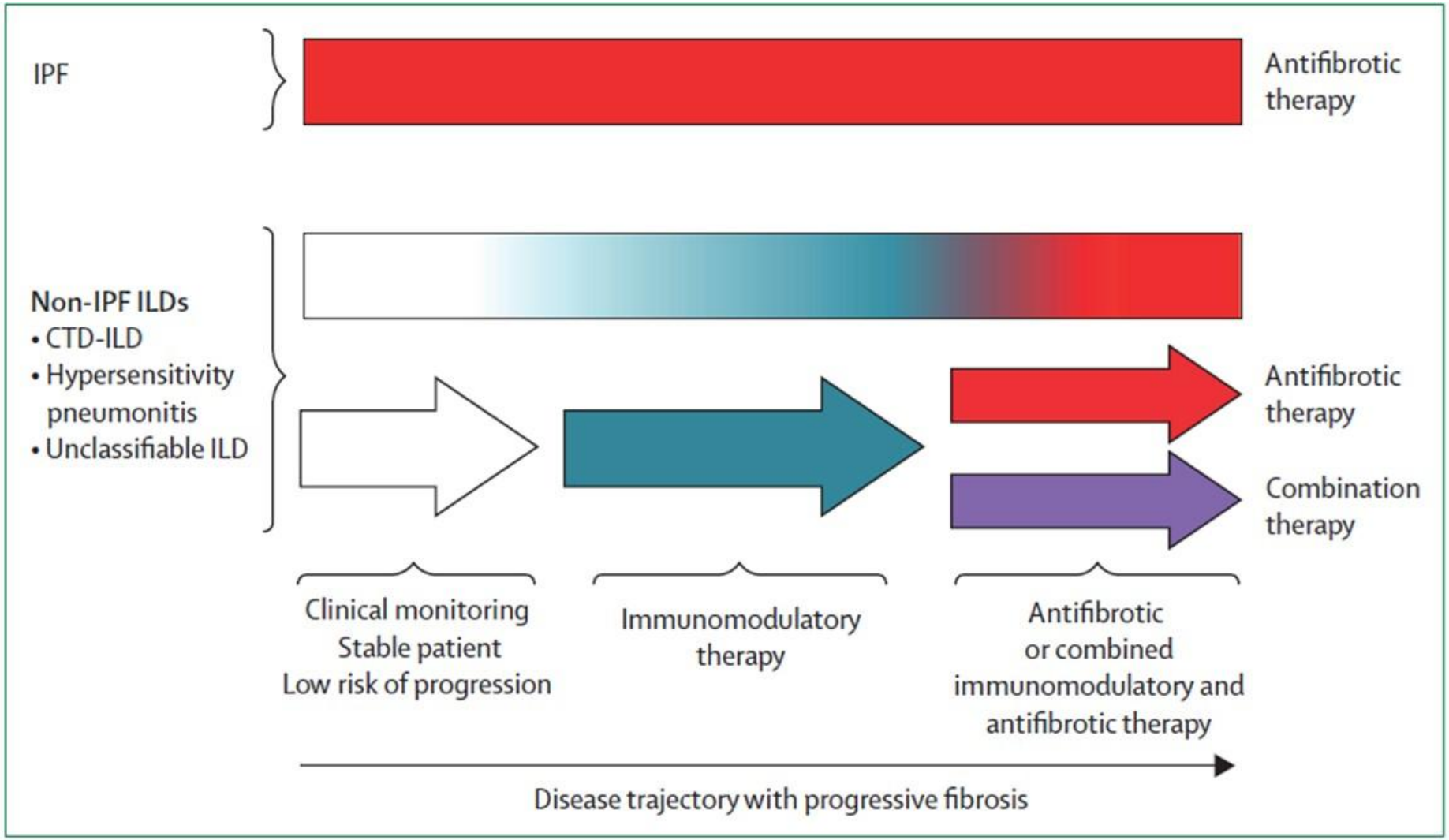
Non-IPF Treatment

Immunomodulators/immunosuppressants

If progresses

Antifibrotics

When Antifibrotics?



Johannson KA, et al. Lancet 2021

IPF Treatment

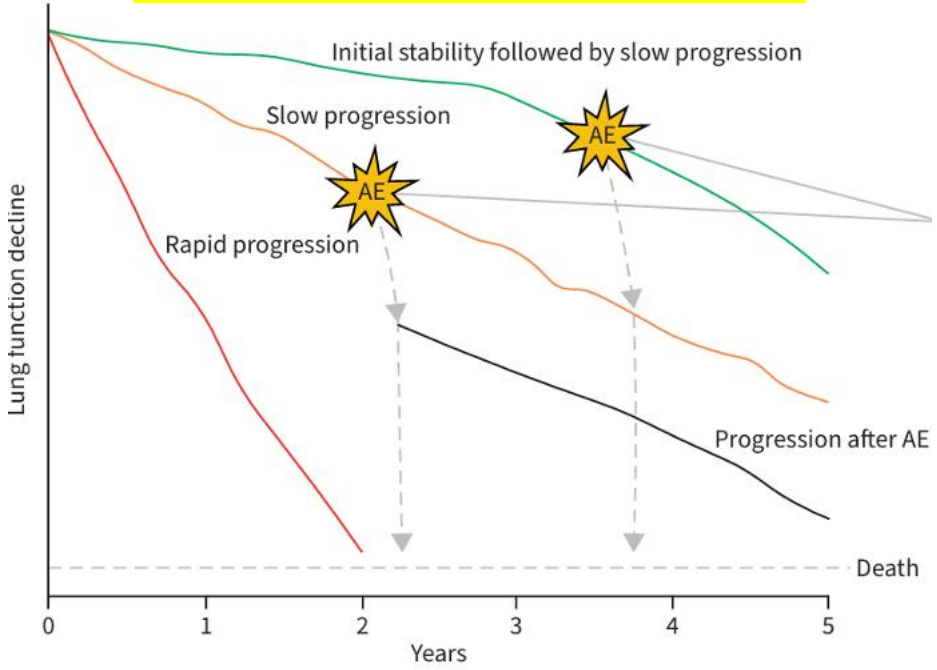
Concerns regarding antifibrotic treatment in IPF

1. When should treatment initiated?
2. Which antifibrotic agent should be preferred?
3. Is there a role for combination therapies?
4. When should treatment be considered ineffective? Should treatment be discontinued?

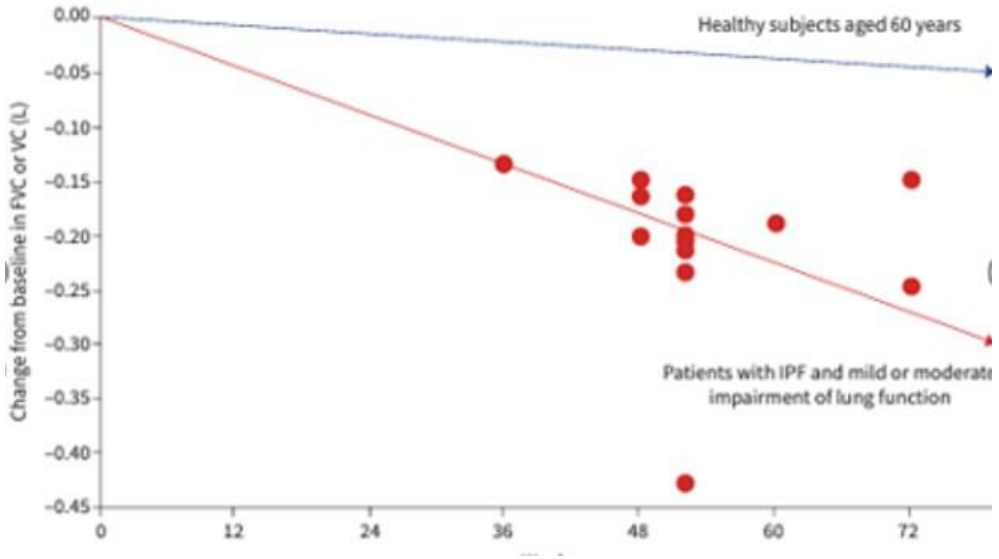
When should treatment initiated?

As soon as the diagnosis is made!!!

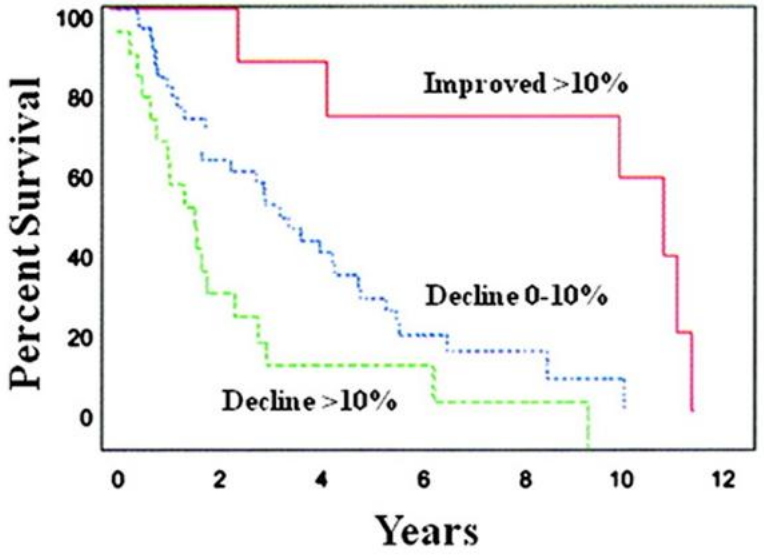
Clinical course of IPF is variable



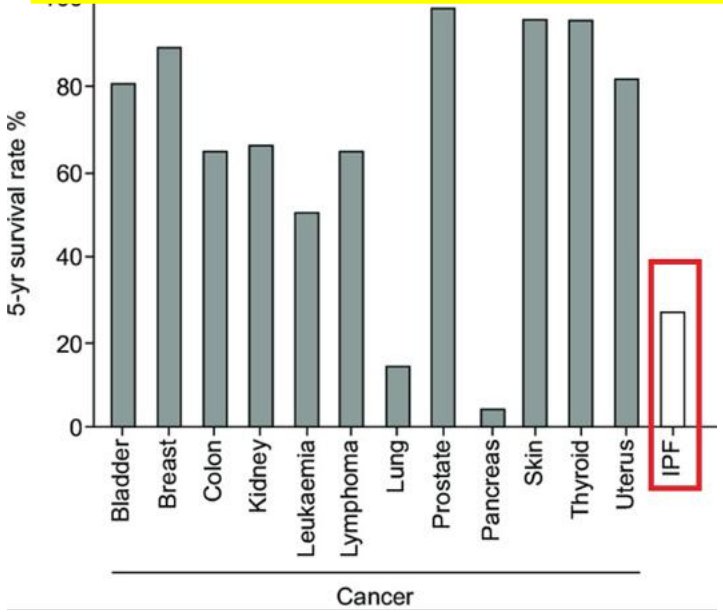
FVC loss is progressive



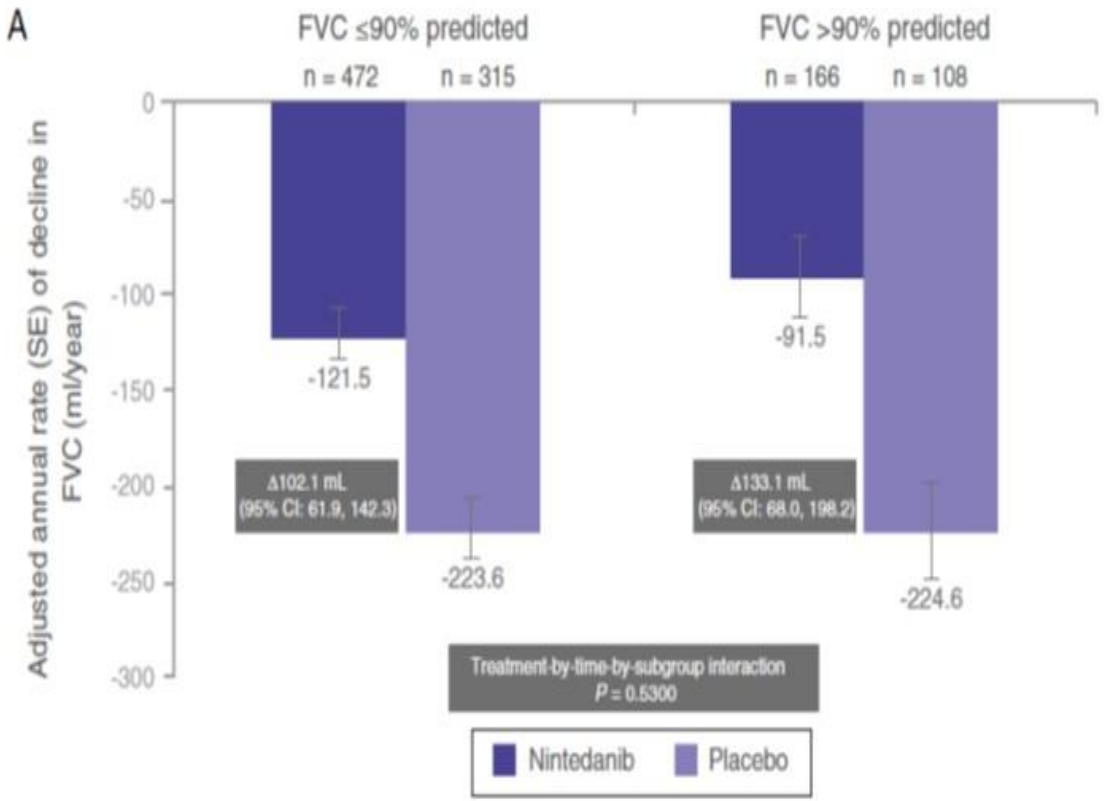
Decrease in FVC is related with mortality



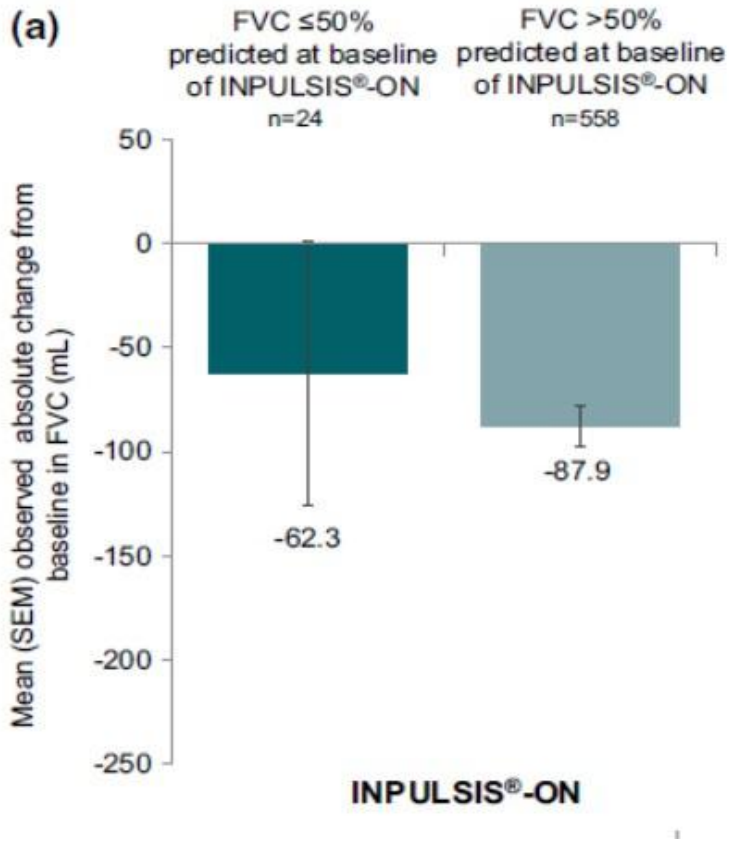
IPF prognosis is poor



The stage of the disease does not alter the response to treatment



Kolb M, et al. Thorax 2017



Wuyts WA, et al. Lung 2016

Adv Ther (2023) 40:3937–3955
https://doi.org/10.1007/s12325-023-02565-3

Check for updates

ORIGINAL RESEARCH

Efficacy and Safety of Pirfenidone in Advanced Versus Non-Advanced Idiopathic Pulmonary Fibrosis: Post-Hoc Analysis of Six Clinical Studies

Jürgen Behr · Steven D. Nathan · Ulrich Costabel ·
Carlo Albera · Wim A. Wuyts · Marilyn K. Glassberg ·
Harold Haller Jr · Giuseppe Alvaro · Frank Gilberg · Katerina Samara ·

Table 2 Efficacy outcomes across the pooled ASCEND/CAPACITY studies, RECAP study, and SP-IPF study (efficacy populations)

	Pooled ASCEND/CAPACITY[a]				RECAP[b]		SP-IPF[a]
	Advanced[c]		Non-advanced[d]		Advanced[c]	Non-advanced[d]	Advanced[c]
	Pirfenidone	Placebo	Pirfenidone	Placebo	Pirfenidone	Pirfenidone	Placebo + pirfenidone
	n = 90	*n* = 80	*n* = 533	*n* = 544	*n* = 187	*n* = 409	*n* = 89
Mean (SE) annual rate of change in FVC volume, mL	− 150.9 (30.2)	− 277.6 (33.5)	− 128.7 (13.6)	− 216.7 (13.4)	− 141.5 (11.7)	− 153.5 (7.6)	− 93.0 (46.4)
Absolute difference in mean, mL	126.7		88.0		NA	NA	NA
Relative difference in mean, %	45.6		40.6				
p-value for pirfenidone versus placebo	0.0035		< 0.0001				
Categorical change in FVC ≥ 10% or death, *n* (%)	17 (18.9)	34 (42.5)	75 (14.1)	130 (23.9)	NA	NA	NA
OR (95% CI)	0.32 (0.16, 0.63)		0.52 (0.38, 0.71)		NA	NA	NA
p-value for pirfenidone versus placebo	0.0008		< 0.0001				
Mean (SD) change from baseline to Week 52 in 6MWD, m	− 62.7 (108.3)	− 112.4 (142.1)	− 25.7 (100.4)	− 45.5 (111.4)	NA	NA	NA
Relative difference in mean, %	49.7		19.8				
Rank ANCOVA *p*-value[e]	0.0477		0.0031				
Categorical change in 6MWD ≥ 50 m or death, *n* (%)	39 (43.3)	48 (60.0)	114 (21.4)	166 (30.5)	NA	NA	NA
OR (95% CI)	0.51 (0.28, 0.94)		0.62 (0.47, 0.82)		NA	NA	NA
p-value for pirfenidone versus placebo	0.0305		0.0006				

Reimbursement in our country

SGK Etkin kodu: SGKGA9

Teşhis kodu: 05.03- Diffüz İnterstisyel Akciğer Hastalıkları

ICD kodu: J84.1 - İdiyopatik Pulmoner Fibrozis

Başlama Kriteri: Karbonmonoksit difüzyon kapasitesi (DLCO) ≥%30, Forced Vital Kapasitesi (FVC) ≥%50 iken akciğer biyopsisi ve/veya toraks yüksek çözünürlüklü bilgisayarlı tomografi (HRCT) ile IPF tanısı konmuş ve bununla birlikte bağ dokusu belirteçleri açısından değerlendirilmiş hastalarda antifibrotik tedavi başlanır. Sağlık kurulu raporunda DLCO ve FVC değerlerinin yanı sıra;

a) **HRCT ile tanı konuldu ise görüntüleme raporunun tarih ve sayısı veya**
b) **Akciğer biyopsisi ile tanı konuldu ise patoloji raporunun tarih ve sayısı ile birlikte bağ dokusu belirteçleri negatif olan hastalarda bu durumun belirtilmesi, bağ dokusu belirteçleri pozitif olan hastalarda romatolojik açıdan değerlendirilerek bağ dokusu hastalığı-akciğer tutulumunun olmadığının belirtilmesi gerekmektedir.**

Devam Kriteri: Hastalar her 12 ayda bir yeniden değerlendirilmelidir. Bu değerlendirmelerde;

a) **FVC değerinde bir önceki sağlık kurulu raporu değerine göre (ataklar dışında) ≥%10 düşme düşme olması ilaca yanıtsızlık olarak kabul edilir ve tedavi sonlandırılır.**
b) **Tedavinin devamı için düzenlenen raporlarda ilaç başlama kriterleri aranmaz. Tedavinin devamı için FVC değerinde bir önceki sağlık kurulu raporu değerine göre (ataklar dışında) ≥%10 düşme düşme olmadığı her raporda belirtilmelidir.**

Raporun Düzenleneceği Sağlık Kurumu: Üçüncü basamak sağlık kurumları

Raporu Düzenleyecek Hekimler: En az üç göğüs hastalıkları uzman hekimi

Rapora İstinaden Reçete Yazabilecek Hekimler: Tüm göğüs hastalıkları uzman hekimlerince reçetelenir

Maksimum Rapor Süresi: 1 yıl

Which antifibrotic agent should be preferred?

TABLE 4 Comparison of antifibrotic agents

	Pirfenidone	Nintedanib
Number of tablets [85]	3–12[#]	2
Side effects [86–88]	Nausea, anorexia, weight loss, photosensitivity, rash, elevated liver enzymes	Diarrhoea, weight loss, elevated liver enzymes
Outdoor occupation/hobby [86]		+
Anticoagulation therapy [89]	+	
Ischaemic heart disease [87, 89]	+	
Cost [90][¶]		
Newly planned/major surgery [91]	+	
Impact on quality of life [85]	+	+
Prevention of acute exacerbation and/or respiratory-related hospitalisations [92–94]	+	+

A "+" possibly denotes the preferred drug of choice. [#]: pill burden will vary, depending on the strengths available in different countries; [¶]: it is important to understand that the cost of these drugs varies across countries, insurance providers and healthcare providers (public *versus* private).

Rajan SK, et al. Eur Respir J Rev 2023

Review

July 01, 2026 EDT

Comparative Efficacy of Nintedanib and Pirfenidone in Idiopathic Pulmonary Fibrosis: A Systematic Review and Bayesian Network Meta-analysis

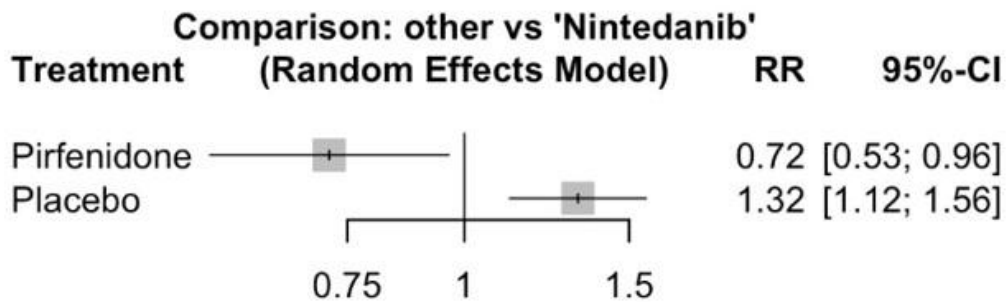
Christopher Fay, D.O.

nintedanib pirfenidone IPF FVC

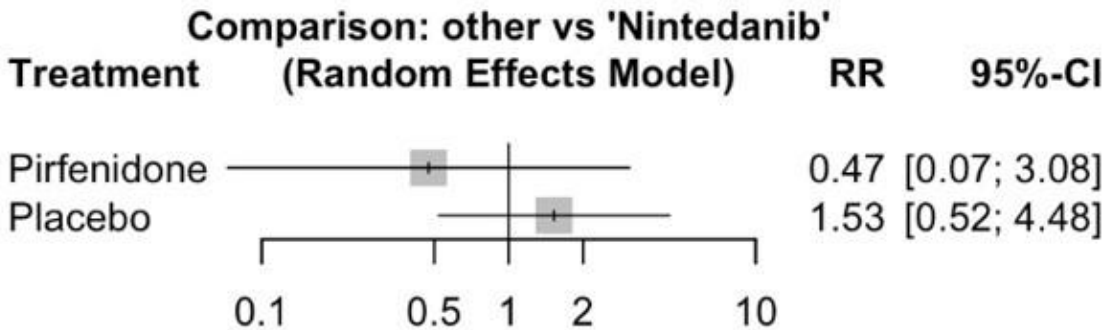
CCBY-4.0 • https://doi.org/10.62186/001c.163657

Synthesis Results

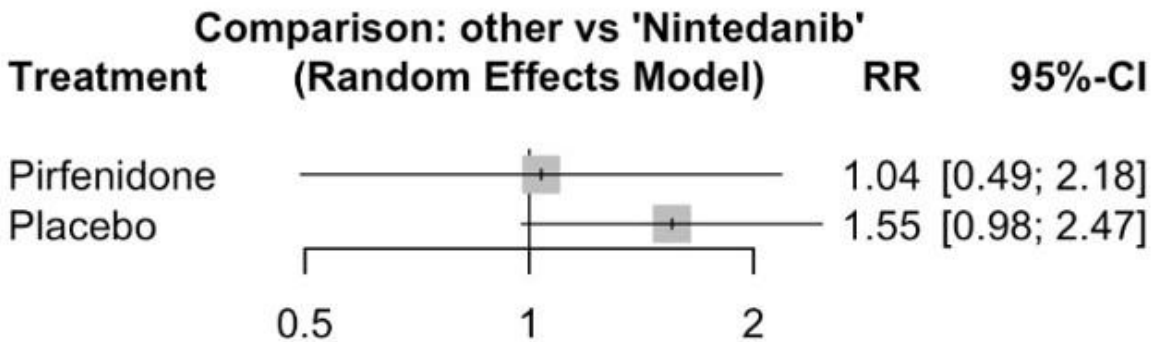
≥10% FVC Decline: All four trials reported data on ≥10% FVC decline from 52-72 weeks. In the random-effects network meta-analysis, both pirfenidone and nintedanib significantly reduced the risk of FVC decline when compared to placebo: nintedanib had an RR of 0.76 (95% CI 0.64–0.89; $p < 0.001$), and pirfenidone had an RR of 0.54 (95% CI 0.43–0.69; $p < 0.001$). Indirect comparison showed pirfenidone to be superior to nintedanib (RR 0.72; 95% CI 0.53–0.96; $p = 0.027$). Heterogeneity was negligible ($I^2 = 0\%$, $\tau^2 = 0$; Cochran's Q $p = 0.43$), indicating consistent effects across studies.



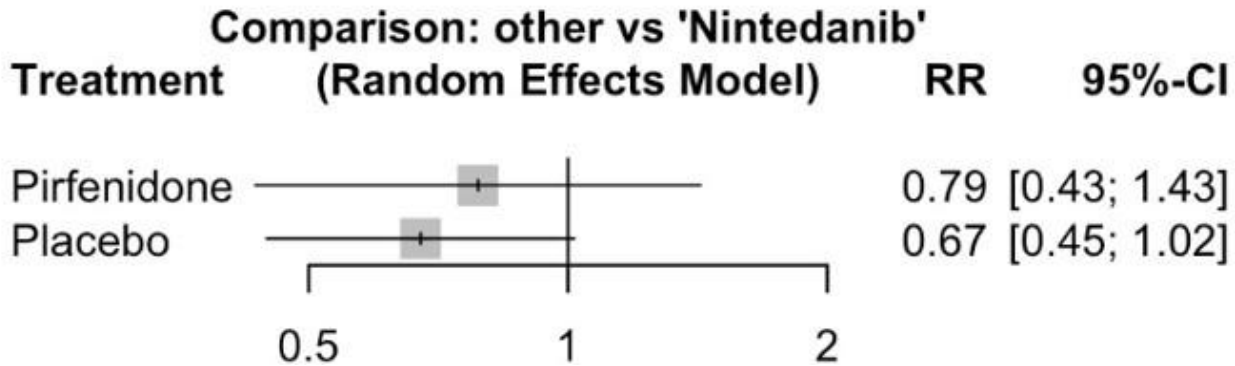
Exacerbation/hospitalization: Three trials (INPULSIS-1, INPULSIS-2, ASCEND) contributed exacerbation/hospitalization data. Pirfenidone decreased exacerbation risk when compared to placebo (RR 0.31; 95% CI 0.15–0.64; p = 0.002), whereas nintedanib did show reduced risk of exacerbations but this result did not reach statistical significance. (RR 0.64; 95% CI 0.39–1.06; p = 0.08). On indirect comparison, pirfenidone reduced the risk of exacerbations/hospitalizations but this result also did not achieve significance (RR 0.48; 95% CI 0.20–1.17; p = 0.11). Heterogeneity was substantial (I^2 = 78.5%, τ^2 = 0.47; Q p = 0.03) likely reflecting a difference in endpoint definitions.



All-cause mortality: All 4 trials reported data contributing to all-cause mortality at one year. Neither pirfenidone or nintedanib significantly impacted mortality when compared to placebo. nintedanib's RR was 0.64 (95% CI 0.40–1.02; p = 0.06), and pirfenidone's RR was 0.67 (95% CI 0.37–1.19; p = 0.17). Indirect comparisons between these two agents yielded an RR of 1.04 (95% CI 0.49–2.18; p = 0.92). Between-study variability was low (I^2 = 0%, τ^2 = 0; Q p = 0.91).



Treatment discontinuation: All four trials reported rates of discontinuation due to adverse effects. Nintedanib trended towards increased rates of discontinuation, but this was not statistically significant (RR 1.48; 95% CI 0.98–2.24; p = 0.06). In contrast pirfenidone's rate of discontinuation was similar to placebo (RR 1.17; 95% CI 0.76–1.79; p = 0.48). Using indirect comparisons, pirfenidone was associated with a 21% lower risk of discontinuation when compared with nintedanib (RR 0.79; 95% CI 0.43–1.43; p = 0.43). Moderate heterogeneity was observed (I^2 = 45.5%, τ^2 = 0.04; Q p = 0.16).



Is there a role for combination therapies?

JOURNAL ARTICLE

Nintedanib with Add-on Pirfenidone in Idiopathic Pulmonary Fibrosis. Results of the INJOURNEY Trial

Get access >

Carlo Vancheri ✉, Michael Kreuter, Luca Richeldi, Christopher J. Ryerson, Dominique Valeyre, Jan C. Grutters, Sabrina Wiebe, Wibke Stansen, Manuel Quaresma, Susanne Stowasser ... Show more

American Journal of Respiratory and Critical Care Medicine, Volume 197, Issue 3, February 2018, Pages 356–363, https://doi.org/10.1164/rccm.201706-1301OC

Published: 01 February 2018 **Article history** ▾

Gastrointestinal (GI) side effects occurred in 37 of 53 patients (69.8%) receiving combination therapy, and in 27 of 51 patients (52.9%) receiving nintedanib alone.

No change in nintedanib steady-state plasma concentration

At week 12, **the change in FVC was -13.3** (17.4) ml in the **combination group** and **-40.9** (31.4) ml in the **nintedanib group**

Original Article

J Thorac Dis 2023;15(11):5913-5921 | https://dx.doi.org/10.21037/jtd-23-946

Safety and tolerability of combination treatment with pirfenidone and nintedanib in patients with idiopathic pulmonary fibrosis: a systematic review and meta-analysis

Jonghoo Lee[1#], Jae-Uk Song[2#]

4 clinical studies involving 191 patients

29% of patients discontinue treatment during the study period

Serious adverse event rate: 10%; **overall adverse event rate: 82%**

Gastrointestinal (GI) adverse events are the most frequent

Acute attacks observed in 7% of patients

Archivos de Bronconeumología 62 (2026) 301–309

Sociedad Española de Neumología y Cirugía Torácica SEPAR

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Original Article

Nintedanib Combined With Pirfenidone in Patients With Idiopathic Pulmonary Fibrosis or Progressive Pulmonary Fibrosis: A Long-Term Retrospective Multicentre Study (Combi-PF)

Corentin Meersseman[a,b], Elisa Martínez Besteiro[c], Nicolas Romain-Scelle[d,e], Bruno Crestani[f,g], Sylvain Marchand-Adam[h,i], Hilario Nunes[j,k], Lidwine Wémeau-Stervinou[l], Raphael Borie[f,g], Rémi Diesler[a,b], Claudia Valenzuela[c], Vincent Cottin[a,b,*], OrphaLung network

Multicenter, retrospective study

38 patients (84.2% with IPF)

Adverse events occurred in **84.2%** of patients (serious adverse events in 28.9%); weight loss (52.6%), diarrhea (36.8%), abdominal pain (28.9%)

Treatment was discontinued in 26.3% of patients

Mean duration of combination therapy: 12.8 months

FVC decline: **-26.7 mL/month before** treatment initiation, **-11.1 mL/month during combination therapy**

Mean survival: 28.5 months

Conclusion:

Although no new safety signal arose, combination therapy is challenging in real-world setting due to poor tolerability especially weight loss. It can nevertheless be a viable treatment option in some patients, particularly as a bridge to lung transplantation. Further studies are needed to confirmthe efficacy of this combined therapeutic strategy

When should treatment be considered ineffective?
Should treatment be discontinued?

JOURNAL ARTICLE

Effect of Continued Treatment with Pirfenidone Following a ≥10% Relative Decline in Percent Predicted Forced Vital Capacity in Patients with Idiopathic Pulmonary Fibrosis (IPF)

Get access >

Steven D. Nathan, MD, Carlo Albera, MD, Ulrich Costabel, MD, PhD, Ian Glaspole, MD, Marilyn Glassberg, MD, Lisa Lancaster, MD, David J. Lederer, MD, MS, Carlos A. Pereira, PhD, Jeffrey Swigris, MD, Bann-Mo Day, BS ... Show more

American Journal of Respiratory and Critical Care Medicine, Volume 193, Issue Supplement_1, May 2016, Page A4995, https://doi.org/10.1164/ajrccm-conference.2016.193.1_MeetingAbstracts.A4995

Published: 01 May 2016

A subgroup analysis of the **CAPACITY and ASCEND** trials shows that among patients who experienced a >10% decline in FVC by the 6th month of treatment, those who continued therapy had a smaller decline in FVC and a lower risk of death compared to those who discontinued treatment

Pharmacological Treatment of Idiopathic Pulmonary Fibrosis (Update) and Progressive Pulmonary Fibroses: S2k Guideline of the German Respiratory Society

Jürgen Behr[a] Francesco Bonella[b] Björn Christian Frye[c] Andreas Günther[d]
Lars Hagmeyer[e] Jörg Henes[f] Philipp Klemm[g] Dirk Koschel[h]
Michael Kreuter[i,j] Gabriela Leuschner[a] Dennis Nowak[k] Antje Prasse[l]
Bernd Quadder[m] Helmut Sitter[n] Ulrich Costabel[b]

Guidelines

Respiration
DOI: 10.1159/000540856

Received: July 4, 2024
Accepted: July 24, 2024
Published online: September 9, 2024

R19	Recommendation
⇑⇑	In the light of the high mortality of IPF, an antifibrotic therapy which is well tolerated by the patient shall be continued without limitation or until lung transplantation, possibly including a switching between the two approved drugs
	Consensus strength 100%

R20	Recommendation
⇑⇑	The antifibrotic treatment shall be discontinued when side effects, in spite of symptomatic therapy, dose reductions, or temporary interruptions of treatment, cannot be controlled
	Consensus strength 100%

The obligation to terminate treatment in our country

SGK Etkin kodu: SGKGA9

Teşhis kodu: 05.03- Diffüz İnterstisyel Akciğer Hastalıkları

ICD kodu: J84.1 - İdiyopatik Pulmoner Fibrozis

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a) HRCT ile tanı konuldu ise görüntüleme raporunun tarih ve sayısı veya
b) Akciğer biyopsisi ile tanı konuldu ise patoloji raporunun tarih ve sayısı ile birlikte bağ dokusu belirteçleri negatif olan hastalarda bu durumun belirtilmesi, bağ dokusu belirteçleri pozitif olan hastalarda romatolojik açıdan değerlendirilerek bağ dokusu hastalığı-akciğer tutulumunun olmadığının belirtilmesi gerekmektedir.

Devam Kriteri: Hastalar her 12 ayda bir yeniden değerlendirilmelidir. Bu değerlendirmelerde;

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b) Tedavinin devamı için düzenlenen raporlarda ilaç başlama kriterleri aranmaz. Tedavinin devamı için FVC değerinde bir önceki sağlık kurulu raporu değerine göre (ataklar dışında) ≥ %10 düşme düşme olmadığı her raporda belirtilmelidir.

Non-IPF Treatment

Two-phase pharmacotherapy in non-IPF fibrotic ILD

1. Short-term treatment for rapidly reversible ILD

2. Long-term treatment for slow progressive ILD

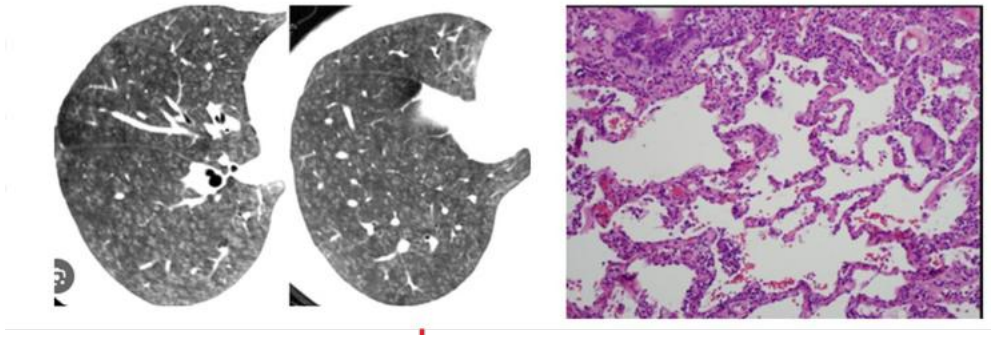
Ryerson, et al. ERJ 2021

Short-term treatment for rapidly reversible ILD

Is there potential for rapidly reversible ILD?

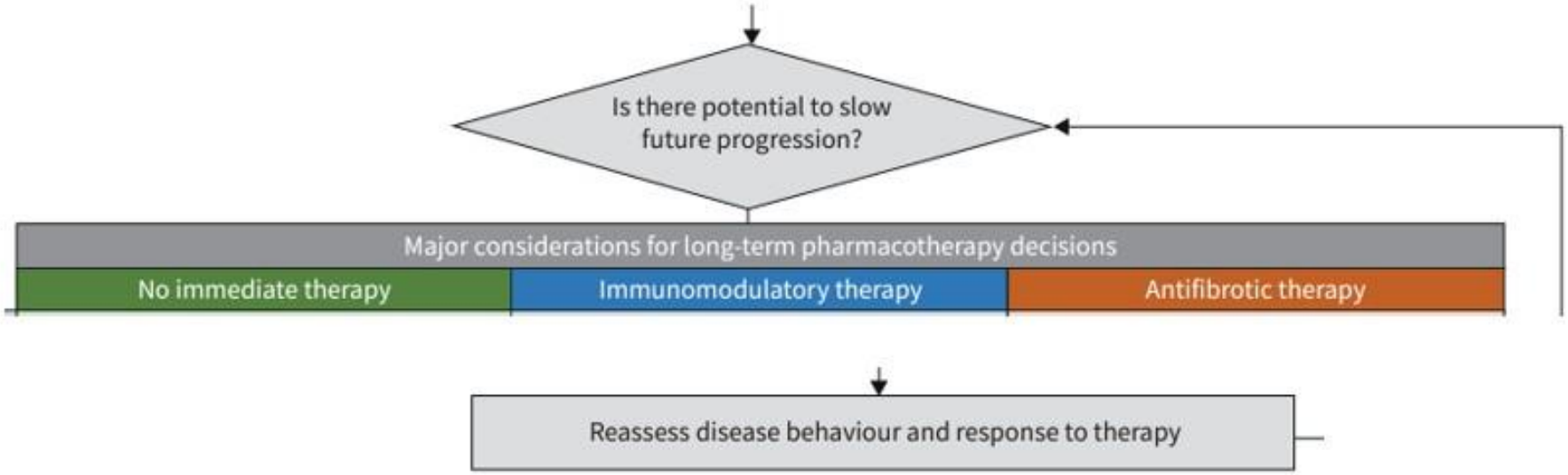
	Major considerations for short-term pharmacotherapy decisions *e.g.* moderate- to high-dose glucocorticoid therapy
Clinical features	Acute or subacute worsening over days to weeks
Radiological features	Significant ground-glass or organising pneumonia on HRCT
Pathological features	Significant cellularity or organising pneumonia on biopsy

Nonfibrotik HP



Ryerson, et al. ERJ 2021

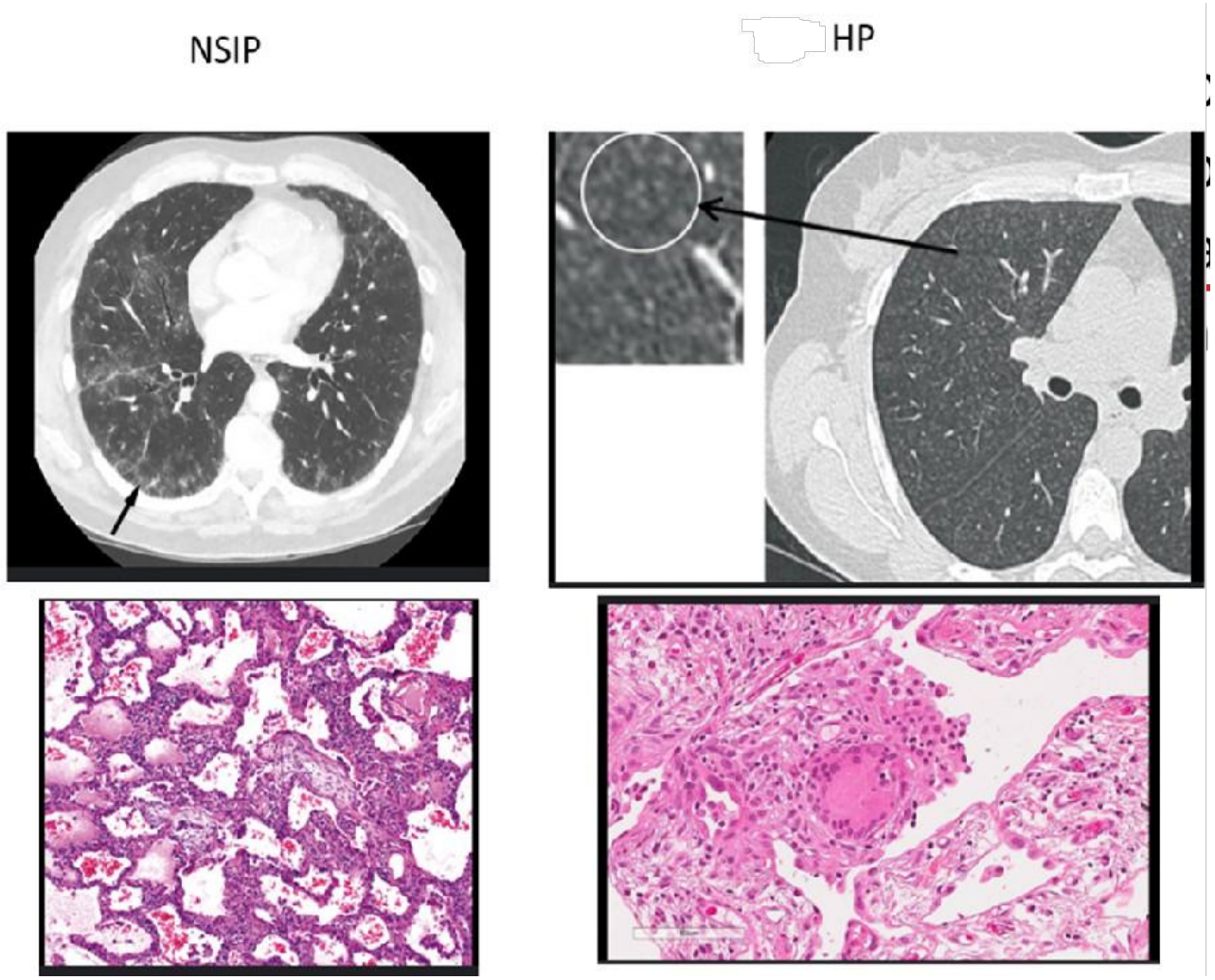
Long-term treatment for slow progressive ILD



Ryerson, et al. ERJ 2021

When immunomodulators?

	Immunomodulatory therapy
Clinical features	Progressive or severe symptoms Significant or progressive lung function abnormalities Younger age Female sex Clinical or serological CTD features HP exposure
Radiological features	Substantial extent of disease NSIP or typical HP pattern Ground-glass opacities (especially with subpleural sparing) Absence of honeycombing, severe traction bronchiectasis, coarse reticular opacities
Pathological features	BAL lymphocytosis Interstitial cellularity Lymphoid follicles Noninfectious, non-necrotising granulomatous inflammation Organising pneumonia



Ryerson, et al. ERJ 2021

When should we discontinue immunosuppressive therapy?

TABLE 5 Likelihood of a benefit after prolonged therapy with immunosuppressants in progressive pulmonary fibrosis

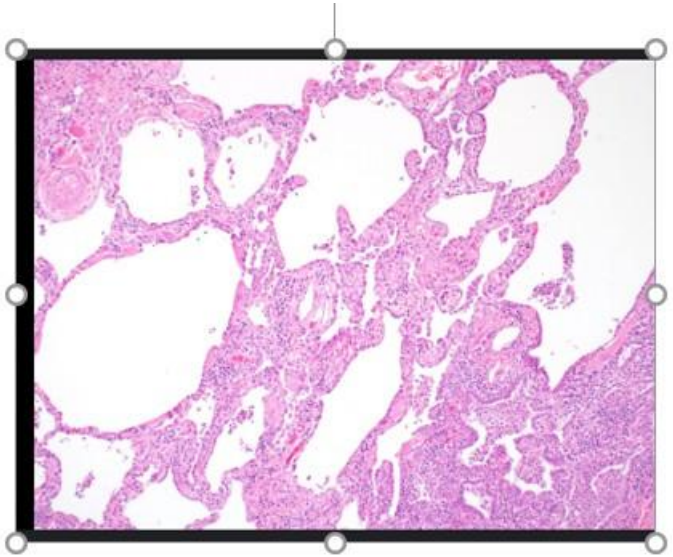
Increased likelihood of a benefit after prolonged therapy with immunosuppressants	Decreased likelihood of a benefit after prolonged therapy with immunosuppressants
OP pattern	UIP pattern
NSIP patterns	Older age
Myositis-ILD	Recurrent infections
Younger age	Absence of clinical or physiological improvement, with increased risk of side effects
Non-pulmonary symptoms that flare up on stoppage	
Previous objective response to corticosteroids and/or immunosuppressive therapy in the disease course	

Rajan SK, et al. Eur Respir J Rev 2023

When should we consider antifibrotic therapy?

	Antifibrotic therapy
Clinical features	Progressive or severe symptoms Significant or progressive lung function abnormalities (especially if despite immunomodulatory Rx) Older age Male sex Significant smoking history
Radiological features	Substantial extent of disease UIP or probable UIP pattern Honeycombing Fibrosis dominated by honeycombing and/or severe traction bronchiectasis and/or coarse reticular opacities
Pathological features	Fibroblast foci Honeycomb change





Ryerson, et al. ERJ 2021

Behr J, et al. AJRCCM 2024

	Dominant Inflammatory Disease with Sustained Response to Antiinflammatory Therapy	Stable/Irreversible Disease without Need for Specific Therapy	Dominant Fibrotic Disease with Beneficial Response to Antifibrotic Therapy
Patient characteristics	Younger female patients, never-smokers, clinical signs of inflammation (elevated temperature, night sweat), extrapulmonary inflammatory manifestations (e.g., polyarthritis, polyserositis, myositis, vasculitis)	ND	Older male patients, ex-smokers (or active smokers), positive family history of fibrotic ILD
Functional severity Prior treatment response and disease behavior	Mild to moderate Positive response to antiinflammatory therapy (i.e., prednisone with or without cell cycle inhibitors)	Mild to moderate Nonresponse to antiinflammatory therapy Patients with documented "stable disease" clinically, functionally, and on HRCT (i.e., no change over time for ≥1 yr)	More advanced Nonresponse to antiinflammatory therapy History of acute exacerbation
Diagnosis	CTD or cellular HP	ND	Absence of a CTD diagnosis
Biomarker (blood)	Positive autoimmune serologies and elevated CRP	ND	Absence of CTD biomarkers; short leukocyte telomere length (<10th percentile)
BAL	Lymphocytosis in the context of a nonfibrotic HRCT pattern	ND	Neutrophilia and absence of lymphocytosis
HRCT morphology	NSIP pattern and/or extensive ground glass Organizing pneumonia pattern Absence of UIP pattern or features of fibrosis	Absence of UIP pattern or significant features of it	UIP pattern or features of UIP (honeycombing, traction bronchiectasis or bronchiolectasis, extensive subpleural reticulation) Extensive fibrosis Fibrotic HP with UIP pattern or radiologic features of UIP pattern Absence of NSIP or OP pattern UIP pattern Histologic features of fHP Absence of inflammatory features potentially suggesting CTD ILD
Histology	NSIP pattern (cellular) Absence of fibroblast foci and microscopic honeycombing Peribronchiolar granulomatous inflammation, as seen in HP Organizing pneumonia	ND	

Check for updates

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

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 (Table 4):

1. worsening respiratory symptoms;
2. physiological evidence of disease progression, as defined below; and
3. radiological evidence of disease progression, as defined below.

1. Absolute decline in FVC of ⩾5% within 1 year of follow-up.
2. Absolute decline in $D_{L_{CO}}$ (corrected for Hb) of ⩾10% within 1 year of follow-up.

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

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.*

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). Remarks: Standard

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]

[1]Bombay Hospital Institute of Medical Sciences and Bhatia Hospital, Mumbai, India. [2]National French Reference Coordinating Center for Rare Pulmonary Diseases, Louis Pradel Hospital Hospices Civils de Lyon, Université Claude Bernard Lyon 1, INRAE, Member of ERN-LUNG, Lyon, France. [3]CK Birla Hospitals, Kolkata, India. [4]Johns Hopkins School of Medicine, Baltimore, MD, USA. [5]University of Michigan, Ann Arbor, MI, USA. [6]Department of Medicine, National Jewish Health, Denver, CO, USA. [7]All India Institute of Medical Sciences, New Delhi, India. [8]Royal Brompton Hospital/Imperial College London, London, UK. [9]Narayana Health, Bengaluru, India. [10]Breach Candy Hospital, Mumbai, India. [11]Department of Rheumatology, Centre for Arthritis and Rheumatism Excellence, Kochi, India. [12]University of Technology, Sydney, Australia. [13]Department of Radiology, Royal Brompton Hospital, London, UK. [14]Picture This by Jankharia, Mumbai, India. [15]Department of Pathology, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi, India. [16]European Idiopathic Pulmonary Fibrosis Federation (EU-IPFF), Peterborough, UK. [17]Pulmonology Unit, GB Morgagni Hospital/ University of Bologna, Forlì, Italy. [18]Hospital Britanico de Buenos Aires, Buenos Aires, Argentina. [19]Bhatia Hospital and PD Hinduja Hospital, Mumbai, India. [20]Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India. [21]Firestone Institute for Respiratory Heath, St Joseph's Healthcare and McMaster University, Hamilton, ON, Canada. [22]Interstitial Lung Disease Unit, Royal Brompton and Harefield NHS Foundation Trust, London, UK. [23]Co-senior authors.

Eur Respir J 2023; 61: 2103187 [

- There is no standardised management regimen that can be applied to all PPF
- **Initial treatment** should be based on the precise **primary diagnosis**
- Apart from IPF, SSc-ILD and, possibly, rheumatoid arthritis-associated ILD (UIP), **antifibrotic medication should not be considered as a first-line therapy**
- The group does not advise general upfront combination therapy
- **Antifibrotics may be administered sequentially in the context of PPF**

Pharmacological Treatment of Idiopathic Pulmonary Fibrosis (Update) and Progressive Pulmonary Fibroses: S2k Guideline of the German Respiratory Society

Jürgen Behr[a] Francesco Bonella[b] Björn Christian Frye[c] Andreas Günther[d] Lars Hagmeyer[e] Jörg Henes[f] Philipp Klemm[g] Dirk Koschel[h] Michael Kreuter[i,j] Gabriela Leuschner[a] Dennis Nowak[k] Antje Prasse[l] Bernd Quadder[m] Helmut Sitter[n] Ulrich Costabel[b]

R6	Recommendation
⇑⇑	Non-autoimmune PPF patients shall be treated with anti-inflammatory agents if an inflammatory component is suspected to contribute to the progression of pulmonary fibrosis after other measures such as antigen avoidance or restriction/limitation of exposure have been considered. The therapy shall be determined in the context of an ILD MDD (ILD Board)

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Published online: September 9, 2024

R7	Recommendation
⇑	Progressive rheumatoid arthritis-associated ILD (RA-ILD) should be treated with anti-inflammatory drugs. The therapy

R8	Recommendation
⇑	Progressive Sjögren's-associated ILD should be treated with anti-inflammatory drugs

R11	Recommendation
⇑	Progressive myositis-associated ILD (MA-ILD) should be treated with anti-inflammatory therapy. The therapy shall be chosen in the context of an ILD MDD (ILD Board)

R12	Recommendation
⇑	Patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) should be treated with anti-inflammatory drugs

R32	Recommendation
⇑	Anti-inflammatory therapy should be discontinued in non-autoimmune and autoimmune PPF if progression or complications (especially infections) or uncontrollable side effects occur over an appropriate monitoring period

R18	Recommendation
⇑⇑	PPF patients shall be started on antifibrotic therapy if other appropriate treatments for the specific diagnosis (e.g., anti-inflammatory therapy, exposure avoidance) were not sufficiently effective. The decision regarding the therapy for a specific patient shall be made in the context of an ILD MDD (ILD Board)

R14	Recommendation
⇑⇑	PPF patients shall be treated with nintedanib. Therapy initiation shall be determined in the context of an ILD MDD (ILD Board)

R15	Recommendation
⇑	PPF patients should be treated with pirfenidone if antifibrotic therapy with nintedanib was not sufficiently effective or has been discontinued due to side effects

Progresif Fenotipli Diğer Kronik Fibrozan İnterstisyel Akciğer Hastalıkları SUT KOŞULU

SGK Etkin kodu: SGKGA9

Teşhis kodu: 05.03- Diffüz İnterstisyel Akciğer Hastalıkları

ICD kodu: J84.0, J84.1, J84.8, J84.9 - Progresif Fenotipli Diğer Kronik Fibrozan İnterstisyel Akciğer Hastalıkları

Başlama Kriteri: Karbonmonoksit difuzyon kapasitesi (DLCO) ≥ %30, Forced Vital Kapasitesi (FVC) ≥ %50 ve toraks yüksek çözünürlüklü bilgisayarlı tomografi (HRCT) ile %10'dan fazla fibrozis alanı varlığı gösteren atak dışında aşağıda tanımlanan progresif pulmoner fibrozis kriterlerinden en az ikisini karşılayan progresif fenotipli diger kronik fibrozan interstisyel akciger hastalarında nintedanib ile tedaviye başlanması halinde bedeli **Kurumca** karşılanır.

a) Solunum semptomlarında kötüleşme

b) Hastalık progresyonunun fizyolojik kanıtı: Forced Vital Kapasitesi (FVC)'nde %5 ve üzerinde ve/veya Karbonmonoksit difüzyon kapasitesi (DLCO)'nde %10 ve üzerinde düşüş olması,

c) Hastalık progresyonunun radyolojik kanıtı: Bir önceki görüntüleme ile kıyaslamalı değerlendirme sonucu sağlık kurulu raporunda belirtilmelidir. SUT maddesinde belirtilen Radyolojik Progresyon kriterlerinden en az birinin gösterilmesi gerekmektedir.

i. traksiyon bronşiektazisi ve bronşiolektazisi yaygınlığı veya şiddetinde artış,
ii. yeni gelişen buzlu cam alanları veya traksiyon bronşiektazileri
iii. yeni gelişen ince retikülasyon,
iv. retiküler anormalliğin yaygınlığı veya yoğunluğunda artış,
v. yeni gelişen veya artan bal peteği görünümü,
vi. volüm kaybında artış

Devam Kriteri: Hastalar her 12 ayda bir yeniden değerlendirilmelidir. Bu değerlendirmelerde;

a) **FVC değerinde bir önceki sağlık kurulu raporu değerine göre (ataklar dışında) ≥ %10 düşme olması ilaca yanıtsızlık olarak kabul edilir ve tedavi sonlandırılır.**
b) **Tedavinin devamı için düzenlenen raporlarda ilaç başlama kriterleri aranmaz. Tedavinin devamı için FVC değerinde bir önceki sağlık kurulu raporu değerine göre (ataklar dışında) ≥ %10 düşme olmadığı her raporda belirtilmelidir.**

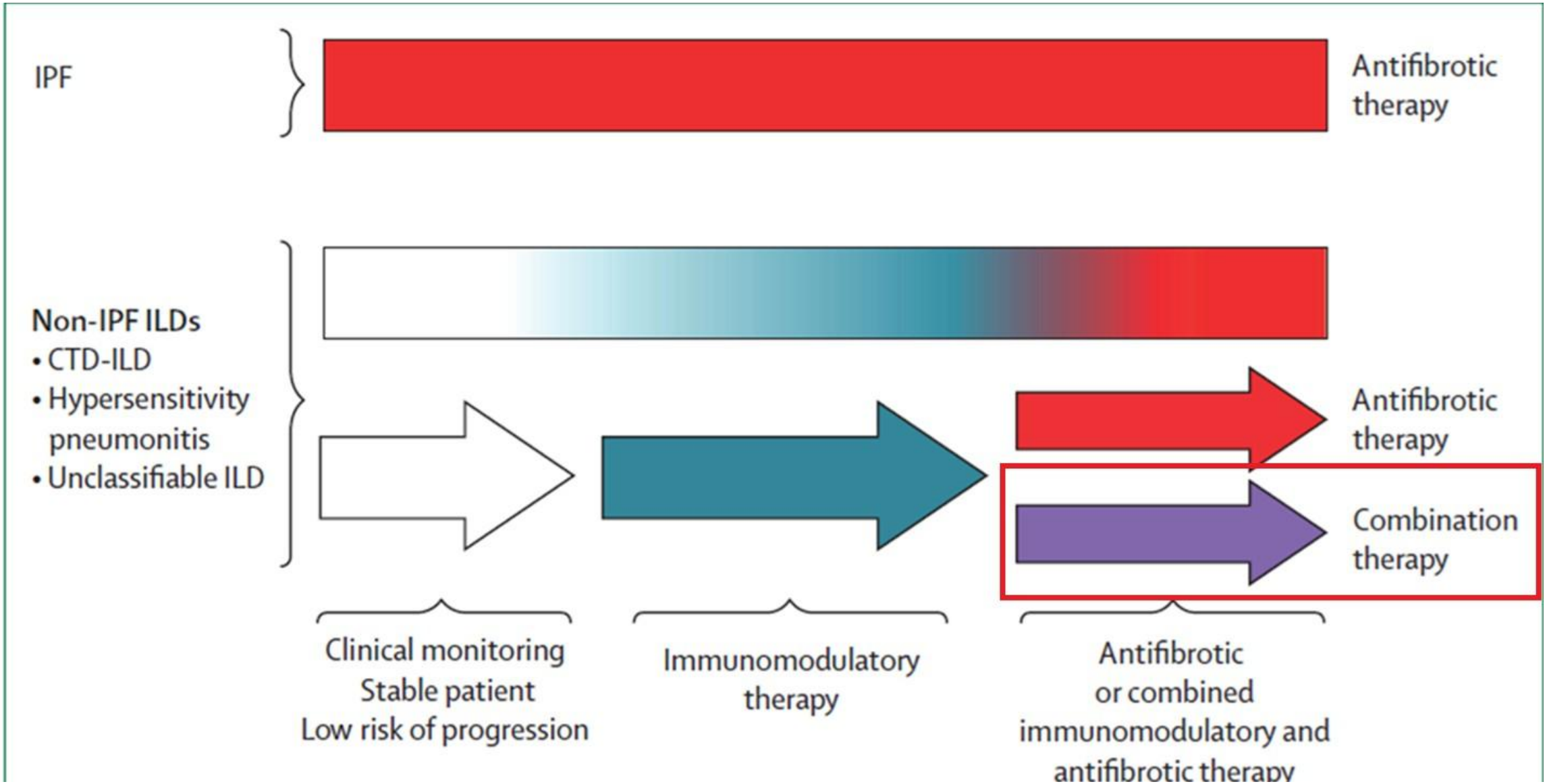
Raporun Düzenleneceği Sağlık Kurumu: Üçüncü basamak sağlık kurumları

Raporu Düzenleyecek Hekimler: Göğüs hastalıkları uzman hekimlerince

Rapora İstinaden Reçete Yazabilecek Hekimler: Tüm göğüs hastalıkları uzman hekimleri

Maksimum Rapor Süresi: 1 yıl

Combination treatment for non-IPF fibrotic ILD



Johannson KA, et al. Lancet 2021

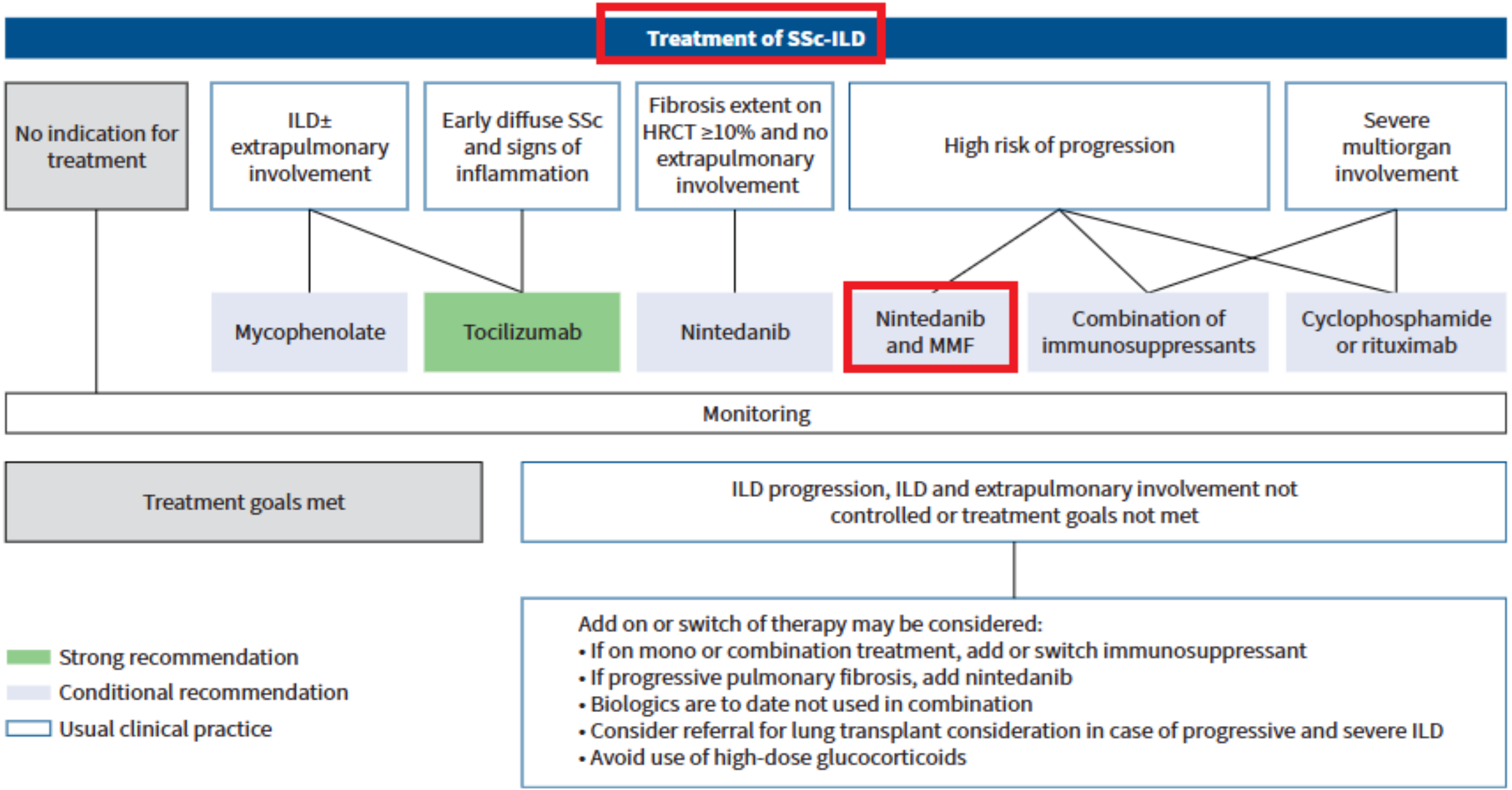
ERS/EULAR clinical practice guidelines for connective tissue disease-associated interstitial lung disease

Developed by the task force for connective tissue disease-associated interstitial lung disease of the European Respiratory Society (ERS) and the European Alliance of Associations for Rheumatology (EULAR)

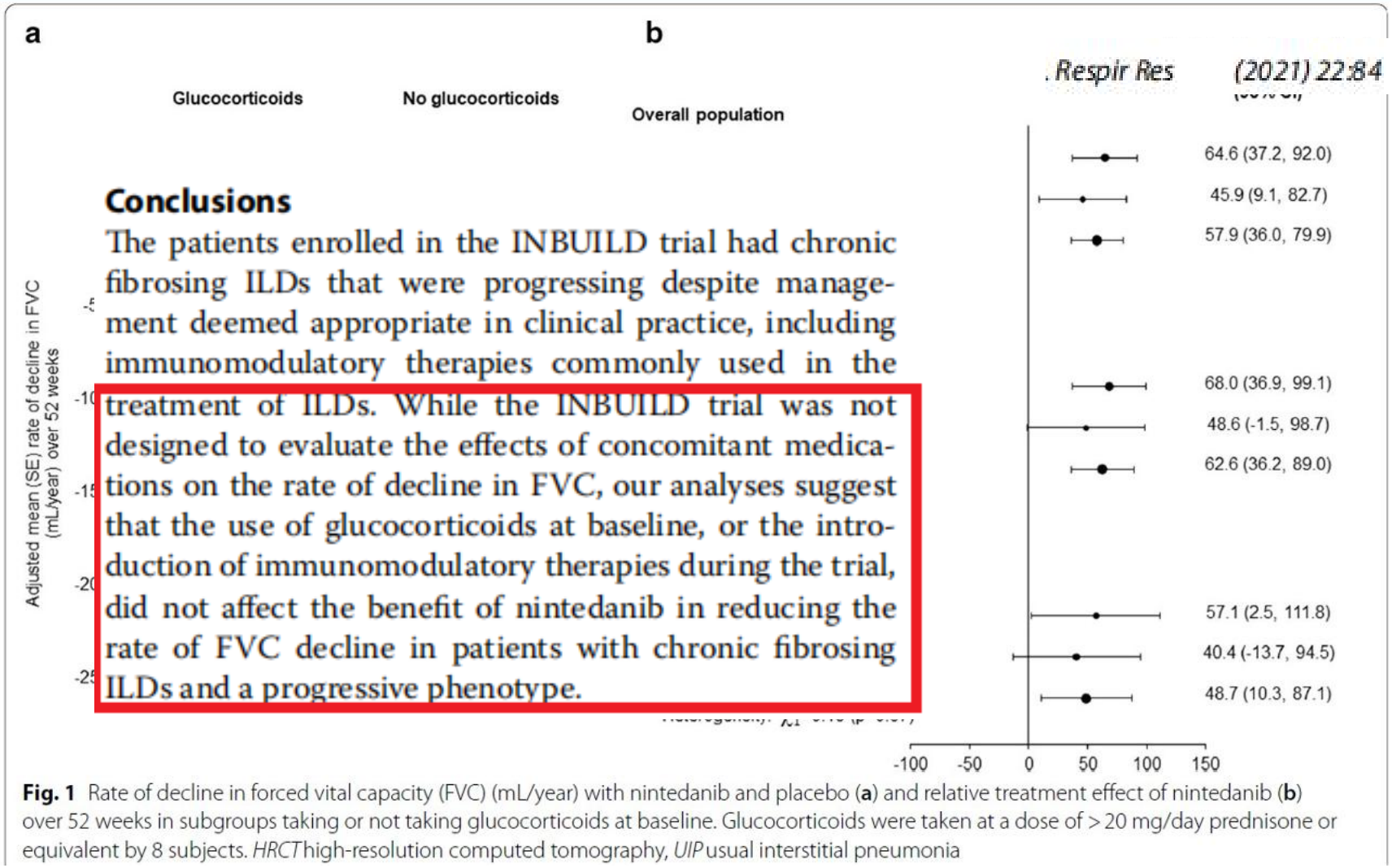
Endorsed by the European Reference Network on rare respiratory diseases (ERN-LUNG)

Katerina M. Antoniou[1,36], Oliver Distler[2,36], Ana-Maria Gheorghiu[3], Catharina C. Moor[4], Jens Vikse[5,6,7], Nikoleta Bizymi[1], Ilaria Galetti[8], Graham Brown[9,†], Elena Bargagli[10], Yannick Allanore[11], Tamera J. Corte[12], Philippe Dieudé[13], Vincent Cottin[14], Benjamin A. Fisher[15,16], Aurelie Fabre[17,18], Jon T. Giles[19], Michael Kreuter[20], Ingrid E. Lundberg[21,22], Venerino Poletti[23], Britta Maurer[24], Elisabetta A. Renzoni[25], Ulf Müller-Ladner[26], Mary E. Strek[27], Nicola Sverzellati[28], Paul Studenic[21,29], Jibril Mohammed[30], Blin Nagavci[31], Tanja Stamm[32], Thomy Tonia[33], Bruno Crestani[34,36] and Anna-Maria Hoffmann-Vold[2,35,36]

Eur Respir J 2026; 67: 2402533


Treatment of SSc-ILD
No indication for treatment
ILD± extrapulmonary involvement
Early diffuse SSc and signs of inflammation
Fibrosis extent on HRCT ≥10% and no extrapulmonary involvement
High risk of progression
Severe multiorgan involvement
Mycophenolate
Tocilizumab
Nintedanib
Nintedanib and MMF
Combination of immunosuppressants
Cyclophosphamide or rituximab
Monitoring
Treatment goals met
ILD progression, ILD and extrapulmonary involvement not controlled or treatment goals not met
Add on or switch of therapy may be considered:
• If on mono or combination treatment, add or switch immunosuppressant
• If progressive pulmonary fibrosis, add nintedanib
• Biologics are to date not used in combination
• Consider referral for lung transplant consideration in case of progressive and severe ILD
• Avoid use of high-dose glucocorticoids
Strong recommendation
Conditional recommendation
Usual clinical practice

Does combination therapy alter the effect of antifibrotics?



. Respir Res (2021) 22:84

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

Cottin V, et al. Respir Res 2021

Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSCIS trial

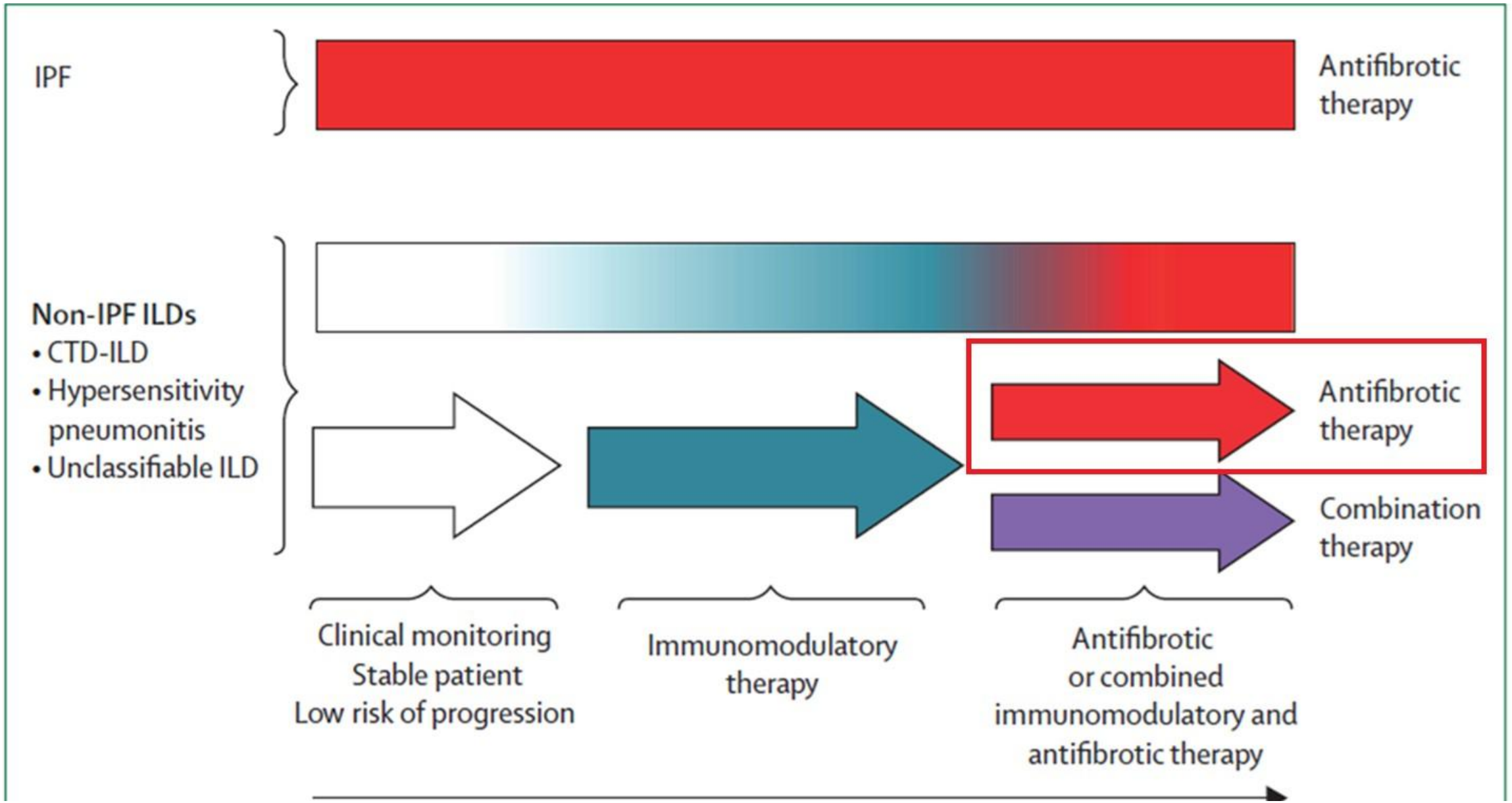
Kristin B Highland, MD [a,*] · Prof Oliver Distler, MD [b,*] · Prof Masataka Kuwana, MD [c] · Prof Yannick Allanore, MD [d] · Prof Shervin Assassi, MD [e] · Prof Arata Azuma, MD [f] · et al. Show more

The Lancet Respiratory Medicine
Volume 9, Issue 1, January 2021, Pages 96-106

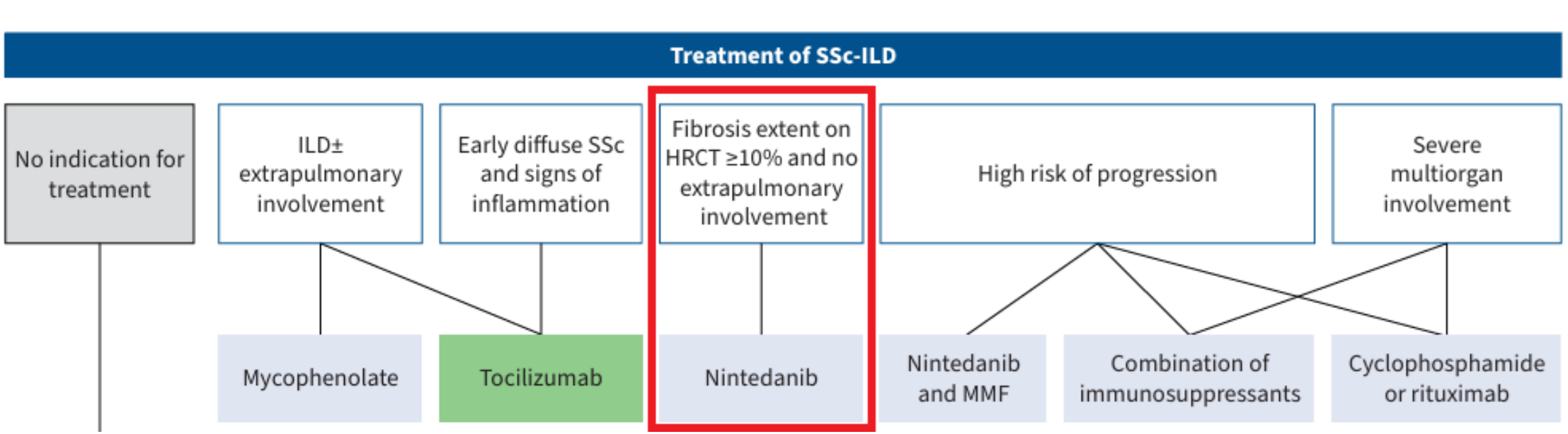
288 patients treated with nintedanib, 139 of whom received nintedanib + MMF
288 patients treated with placebo, 140 of whom received placebo + MMF
Decline in FVC among those treated with nintedanib + MMF: –40.2 mL/year
Decline in FVC among those treated with placebo + MMF: –66.5 mL/year
Annual decline in FVC among patients not receiving MMF: –63.9 mL for those treated with nintedanib, and –119.3 mL for those treated with placebo

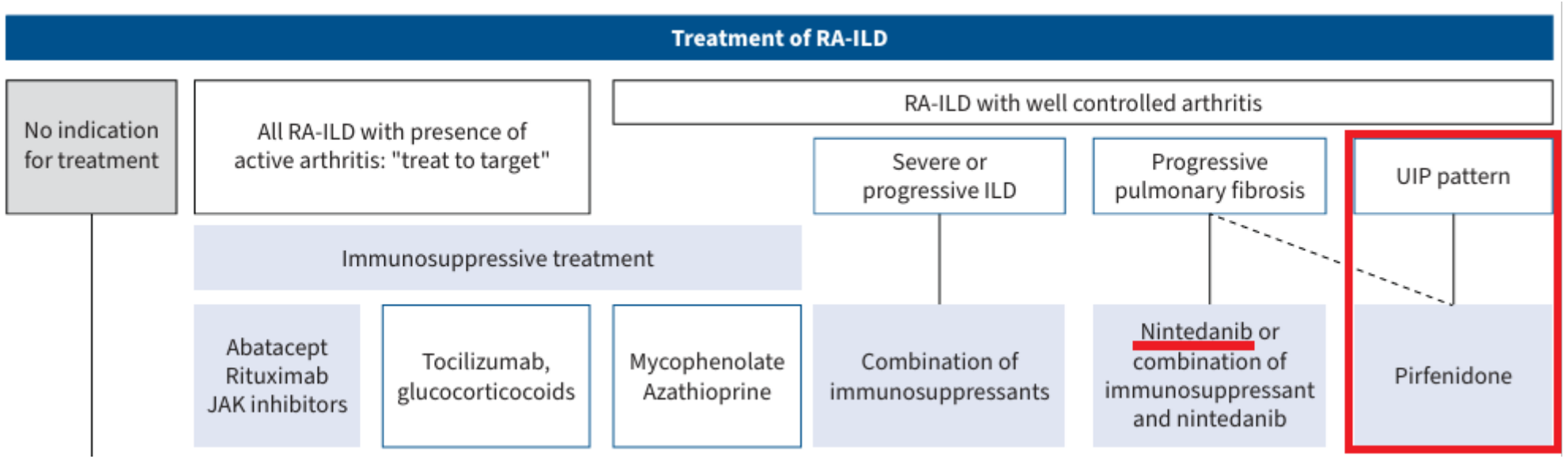
Interpretation

Nintedanib reduced the progression of interstitial lung disease both in patients with SSc-ILD who were and were not using mycophenolate at baseline, with no heterogeneity in its treatment effect detected between the subgroups. The adverse event profile of nintedanib was similar in the subgroups by mycophenolate use. Our findings suggest that the combination of mycophenolate and nintedanib offers a safe treatment option for patients with SSc-ILD. More data are needed on the benefits of initial combination therapy versus a sequential approach to treatment of SSc-ILD.



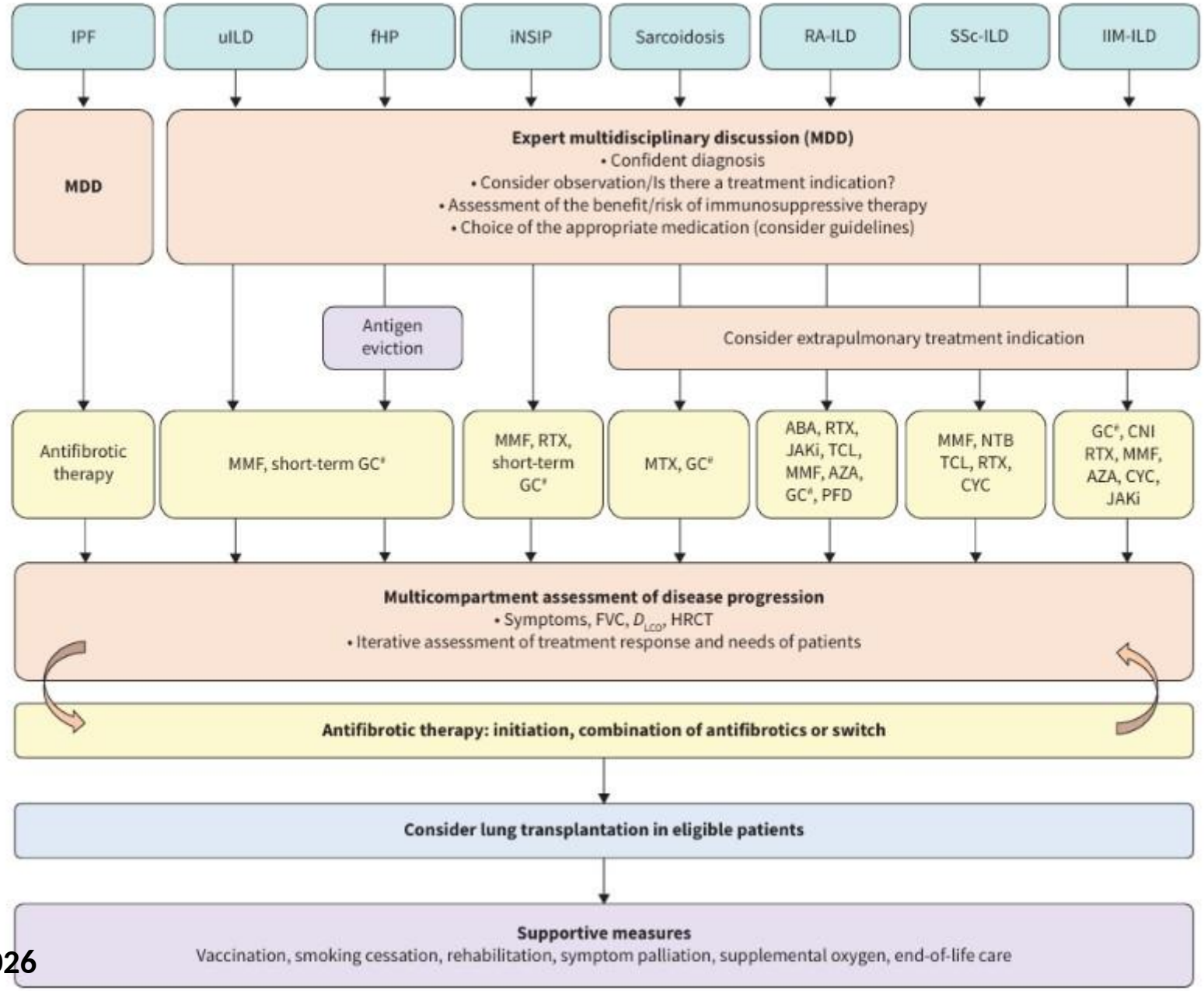
Johannson KA, et al. Lancet 2021





Antoniou KM, et al. Eur Respir J 2026

Algorithm for the management of f-ILD



Cottin V, et al. Eur Respir J 2026