PROGRESSIVE PULMONARY FIBROSIS (PPF): CURRENT TREATMENTS AND FUTURE ASPECTS

Dr Maria Kokosi
Consultant in Respiratory Medicine
Royal Brompton Hospital
Guy's & St Thomas' NHS Foundation Trust
London, UK

Vall d'Hebron University Hospital
6th June 2025

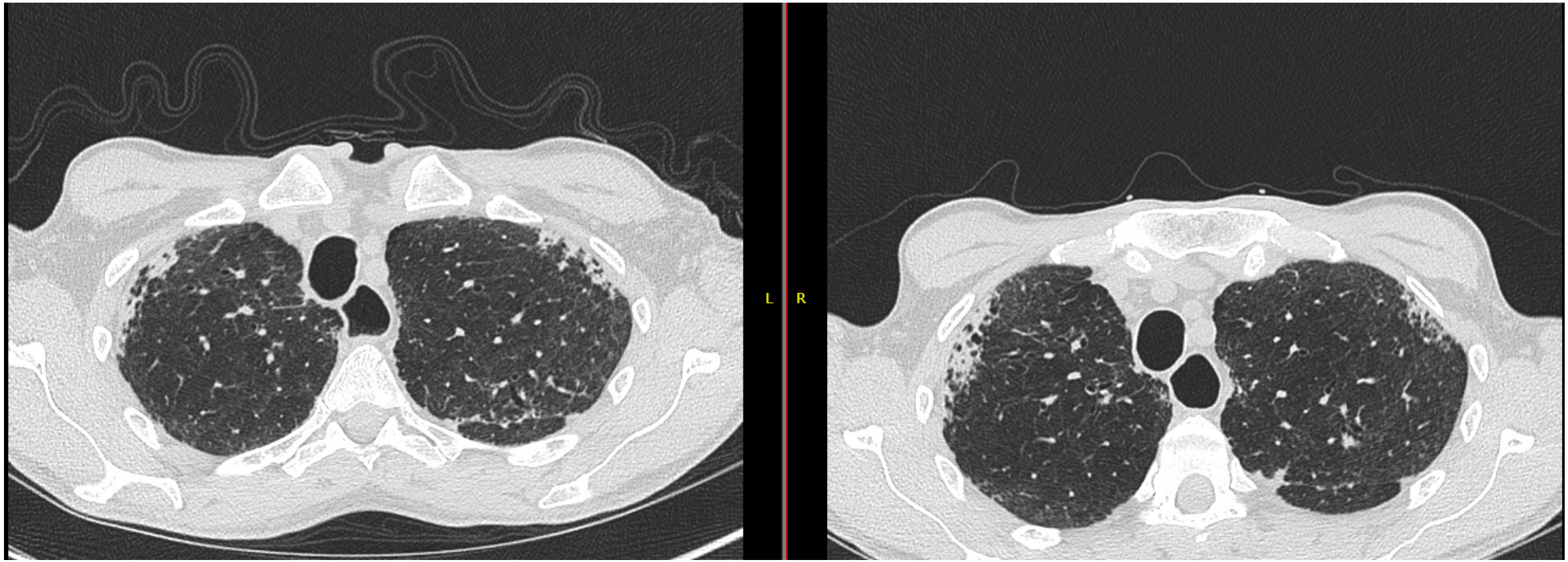
I will cover

- Definition and underlying diagnoses
- Criteria for progression
- Treatment
- Risk factors
- Future aspects

58 yr old male with diffuse systemic sclerosis associated ILD

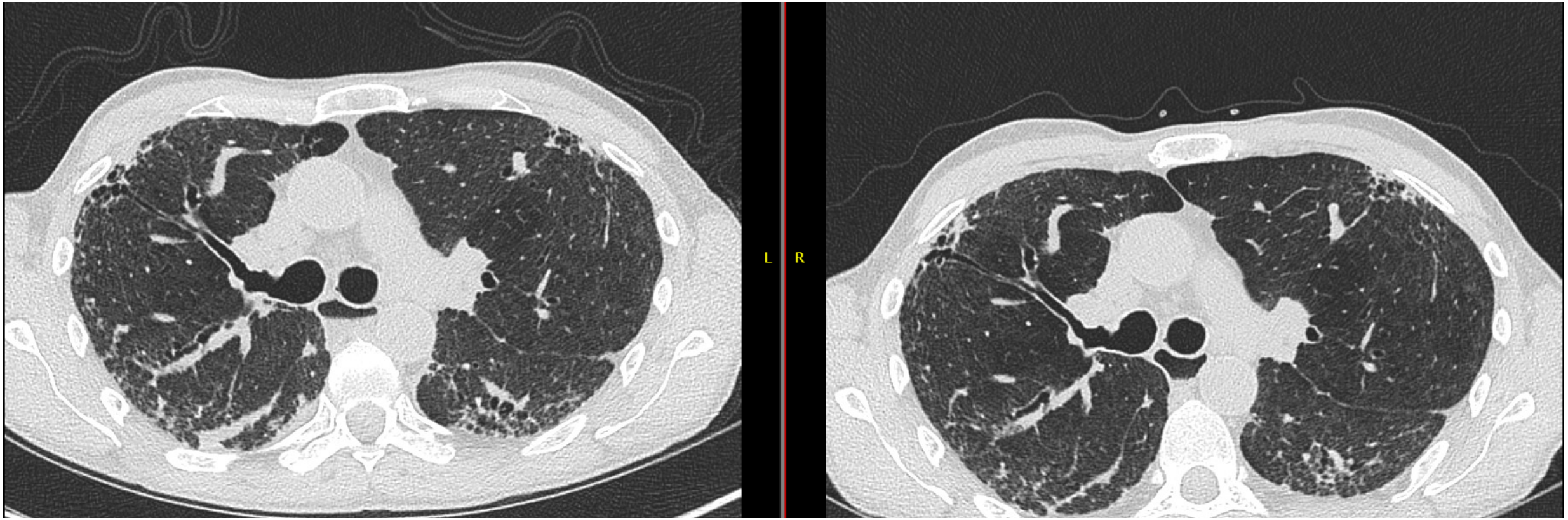
2024

2022



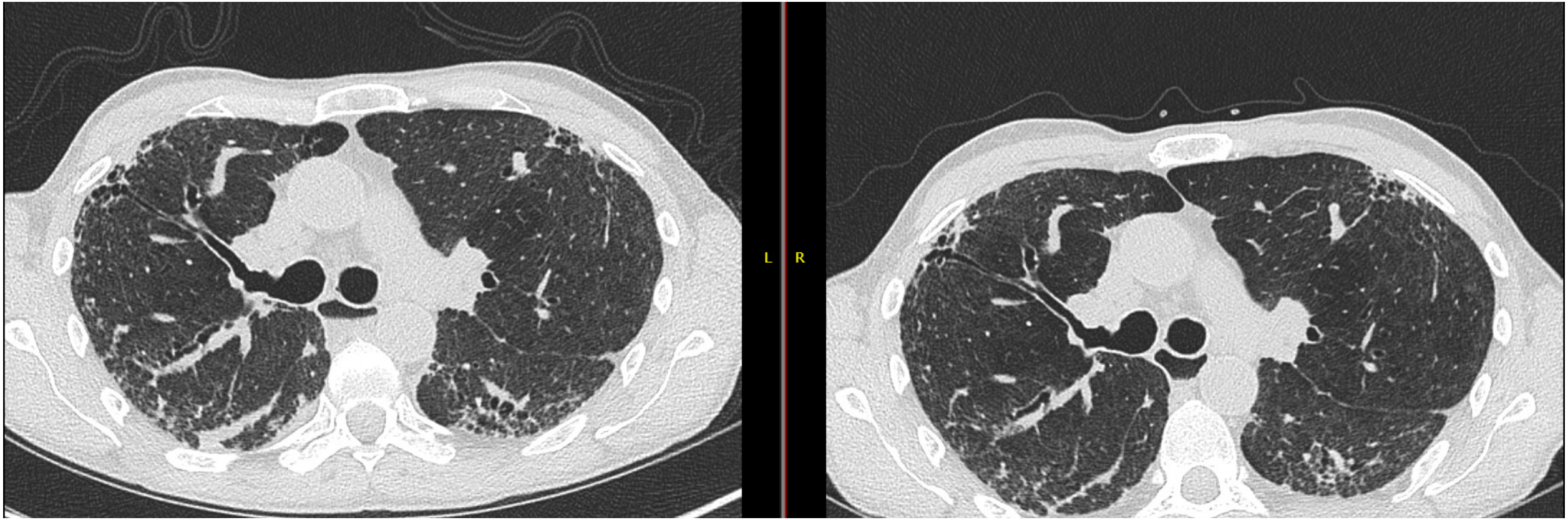
2024

2022



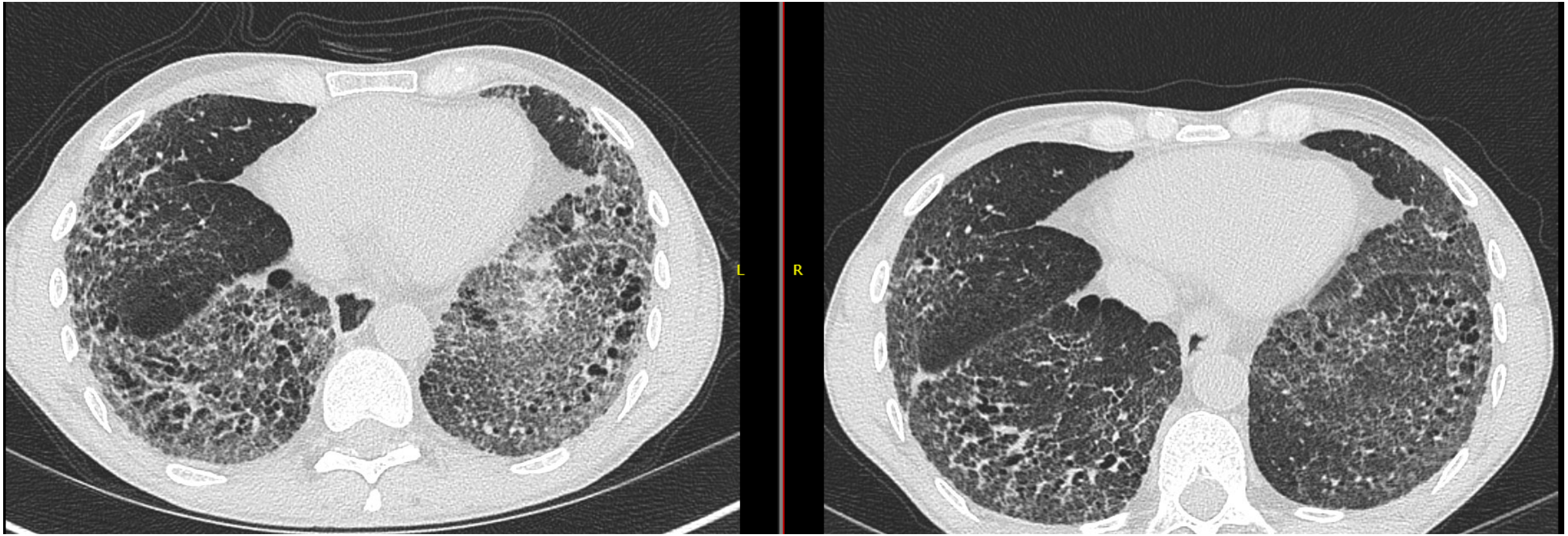
2024

2022



2024

2022



Cyclophosphamide in 2022 by the Rheumatologists

On prednisolone 10mg daily and Mycophenolate 1g twice daily since

	Test 1	Test 2	Test 3	Test 4	Test 5	% Pred	SR
Date	24.06.22	12.07.23	16.10.23	22.10.24	03.01.25		
FEV 1	2.63	2.34	2.54	2.27	2.07	67.5	-2.02
FVC	3.12	2.79	2.81	2.52	2.28	57.3	-2.85
VC MAX	3.12	2.79	2.87	2.52	2.28		
FEV 1 % FVC	84.26	84.04	90.36	89.97	90.81	117.6	2.01
PEF	9.47	6.11	9.02	7.97	7.86	100.9	0.06
MEF 75	9.39	6.09	8.76	7.94	7.21	104.0	0.16
MEF 50	4.23	4.15	4.61	4.84	5.28	129.5	0.91
MEF 25	0.83	0.92	1.64	1.58	1.62	229.8	1.52
FET	4.91	3.94	3.83	3.08	4.78		
PIF	5.72	5.02	5.81	5.07	5.19	88.8	
MMEF	3.02	2.88	3.94	3.80	4.02	161.1	1.38

TLCO	3.03	2.19	2.26	2.07	2.03	24.8	-6.27
TLCOc	3.37	2.47	2.56	2.20	2.22	27.2	-5.97
VA	4.01	3.49	3.66	3.48	3.35	57.7	-3.82
KCO	0.76	0.63	0.62	0.60	0.60	42.8	-4.10
KCOc	0.84	0.71	0.70	0.63	0.66	46.8	-3.76
IVC	2.98	2.60	2.79	2.52	2.26	51.6	-4.02
Hb	11.50	11.20	11.00	12.70	11.90		

Definition of PPF

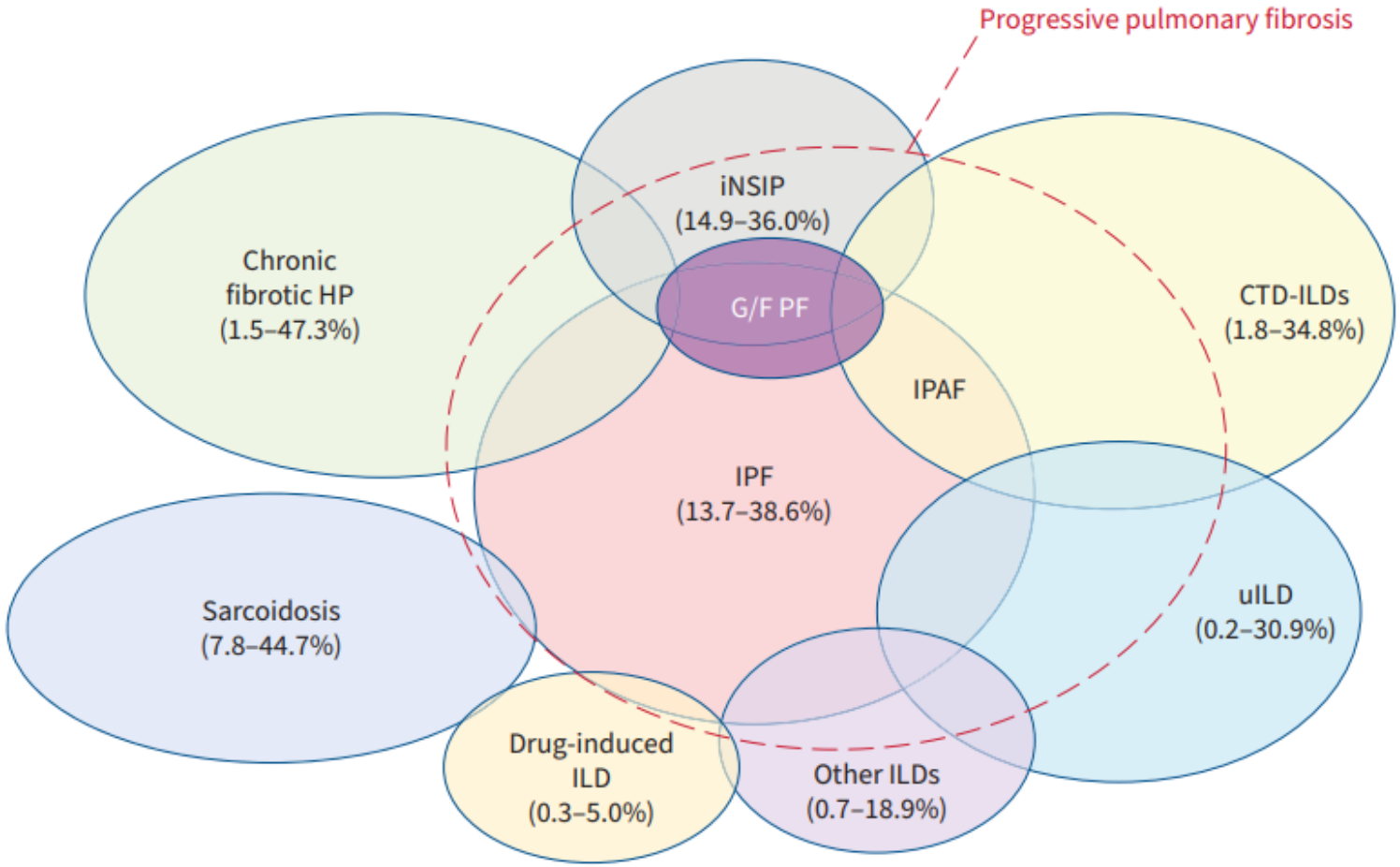
Progressive fibrosis despite appropriate management for the given ILD

We need to differentiate between PPF at first presentation and PPF despite treatment

18-32% of non-IPF F-ILDS progress despite initial treatment within 61-80 months

Faverio P et al. Respiration 2020
Nasser M et al. Eur Respir J 2021
Simpson T et al. Eur Respir J 2021

Spectrum of ILDs associated with progressive fibrosis



Cottin V. Eur Respir Rev 2019

Accurate initial diagnosis is crucial

Accurate initial management

Prognosis: are they likely to progress?

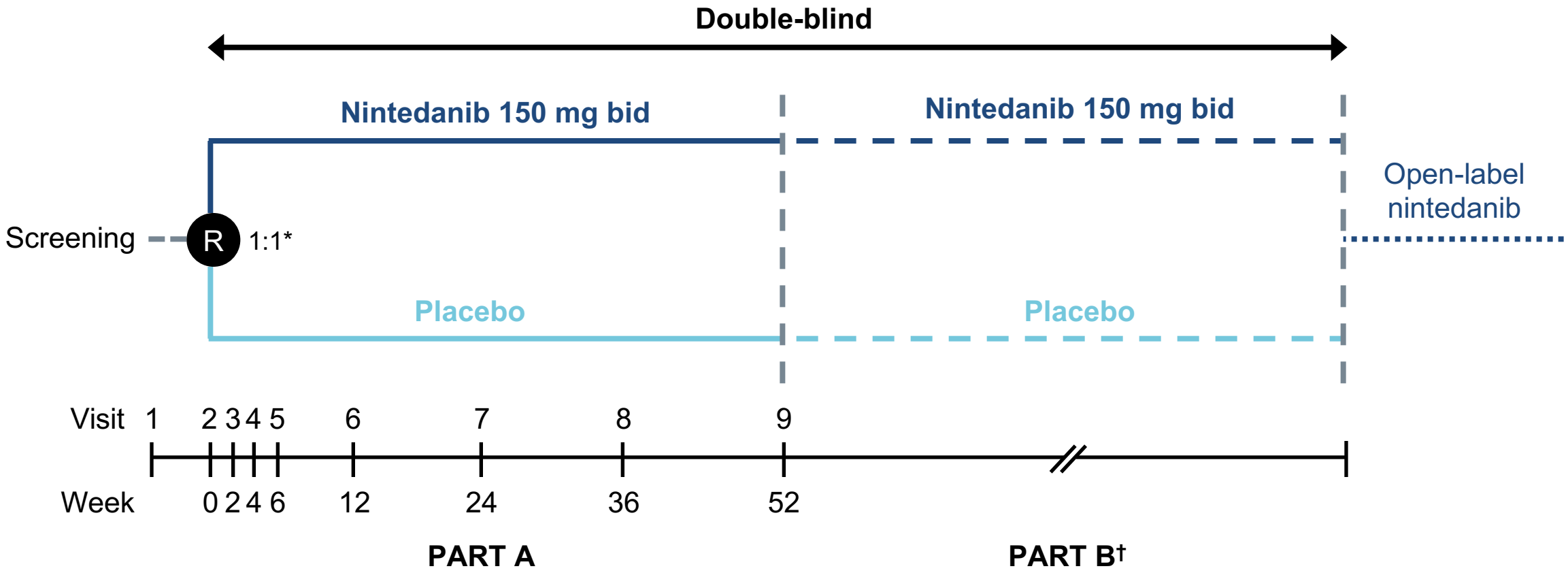
Frequency and type of monitoring

What is appropriate management?

- Removal of potential causative factors
- In some patients with limited ILD and low risk of progression, it will be careful observation
- In many patients, it will be immunomodulation
- In some (e.g. asbestosis), no treatment and ongoing observation
- In several ILD entities, robust evidence is lacking, with the approach based on retrospective studies and clinical experience

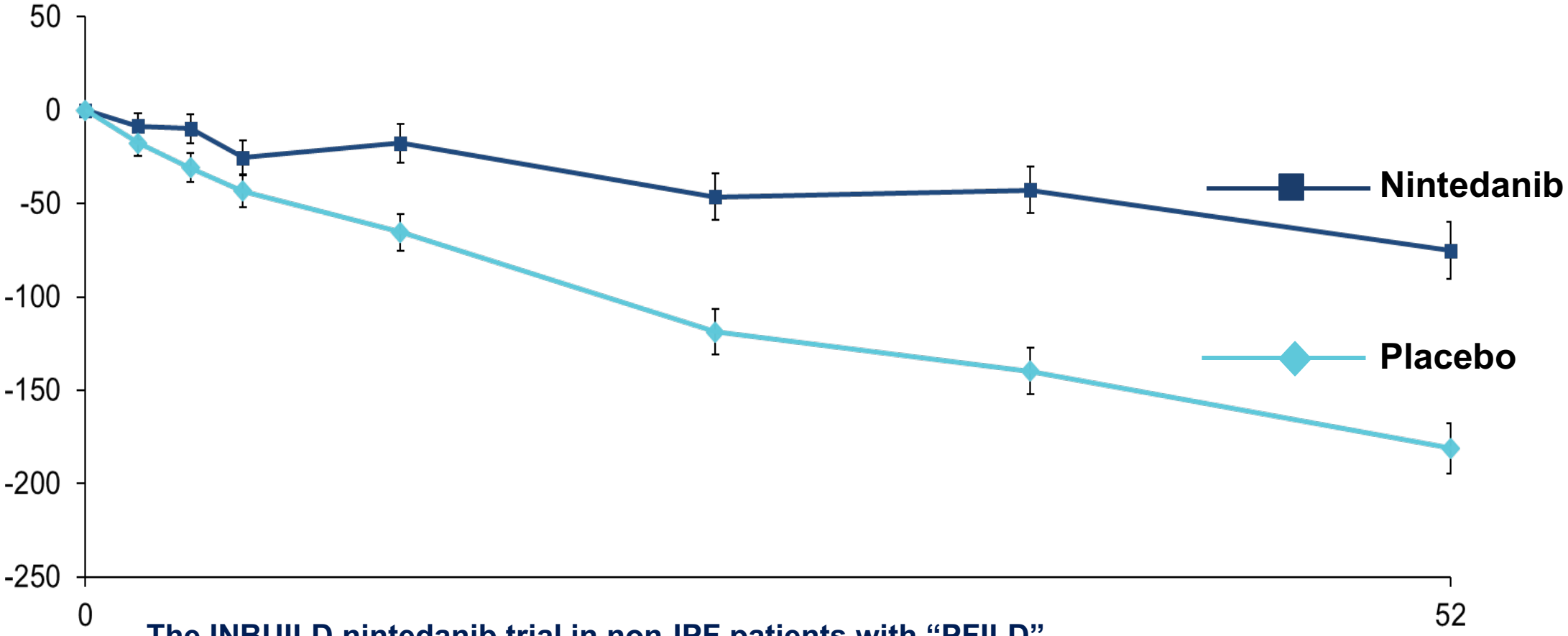
ANTIFIBROTIC THERAPY IN PPF

INBUILD trial design



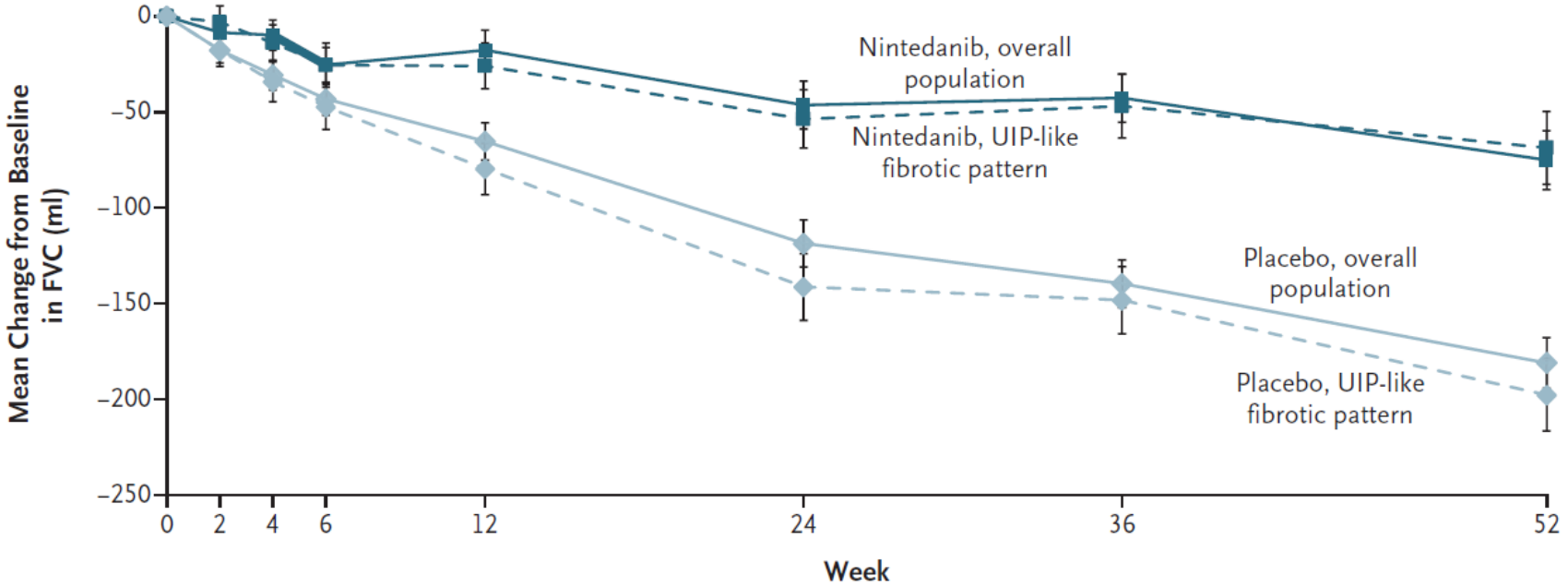
*Randomisation was stratified by HRCT pattern (UIP-like fibrotic pattern only or other fibrotic patterns) based on central review.
†Visits to occur every 16 weeks until end of treatment. bid, twice daily; R, randomisation; UIP, usual interstitial pneumonia.
Flaherty KR, et al. N Engl J Med 2019

Change from baseline in FVC (mL) over 52 weeks



The INBUILD nintedanib trial in non-IPF patients with "PFILD"

Flaherty KR, et al. N Engl J Med 2019

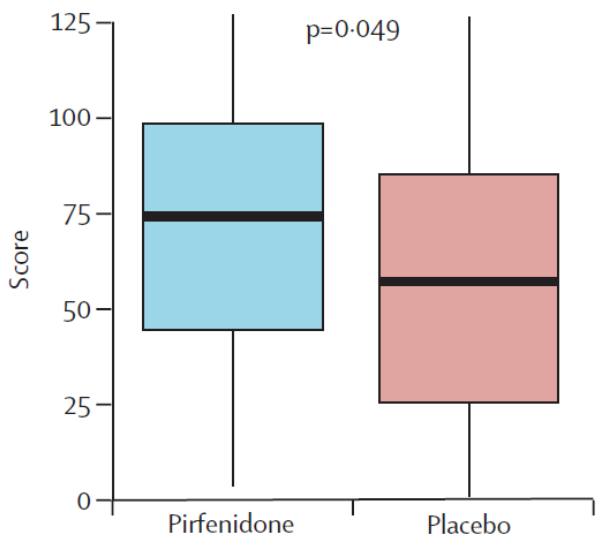


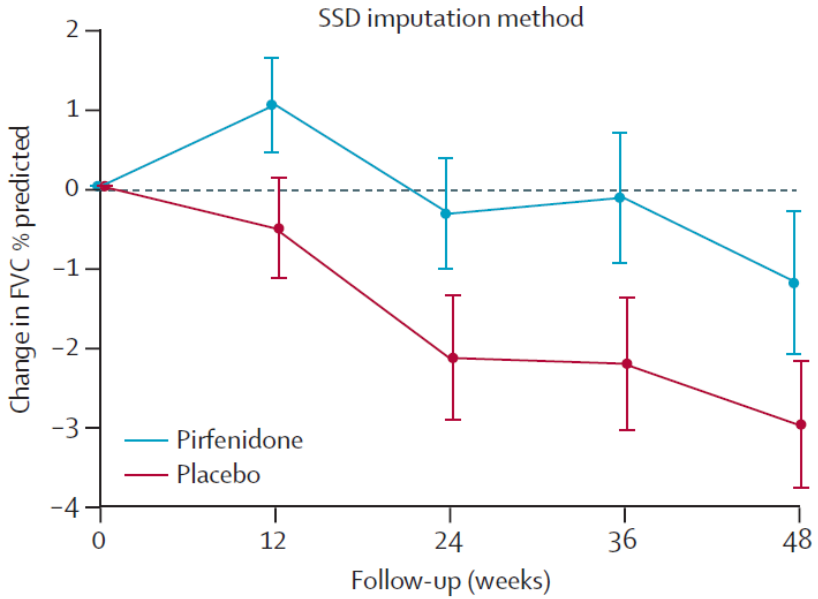
No. of Patients								
Overall population								
Nintedanib	332	326	320	322	314	298	285	265
Placebo	331	325	326	325	320	311	296	274
Patients with UIP-like fibrotic pattern								
Nintedanib	206	203	200	199	193	180	171	160
Placebo	206	202	202	201	197	190	176	162

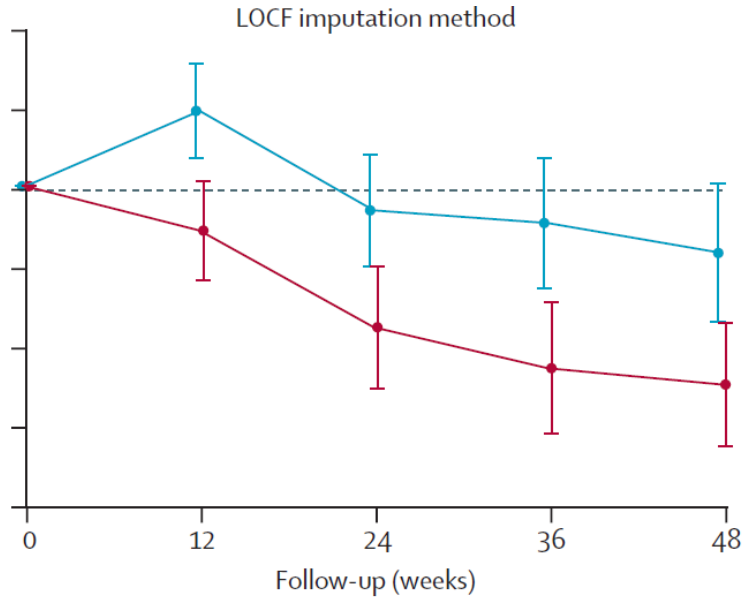
The INBUILD nintedanib trial in non-IPF patients with "PFILD"

Flaherty KR, et al. N Engl J Med 2019

RELIEF TRIAL





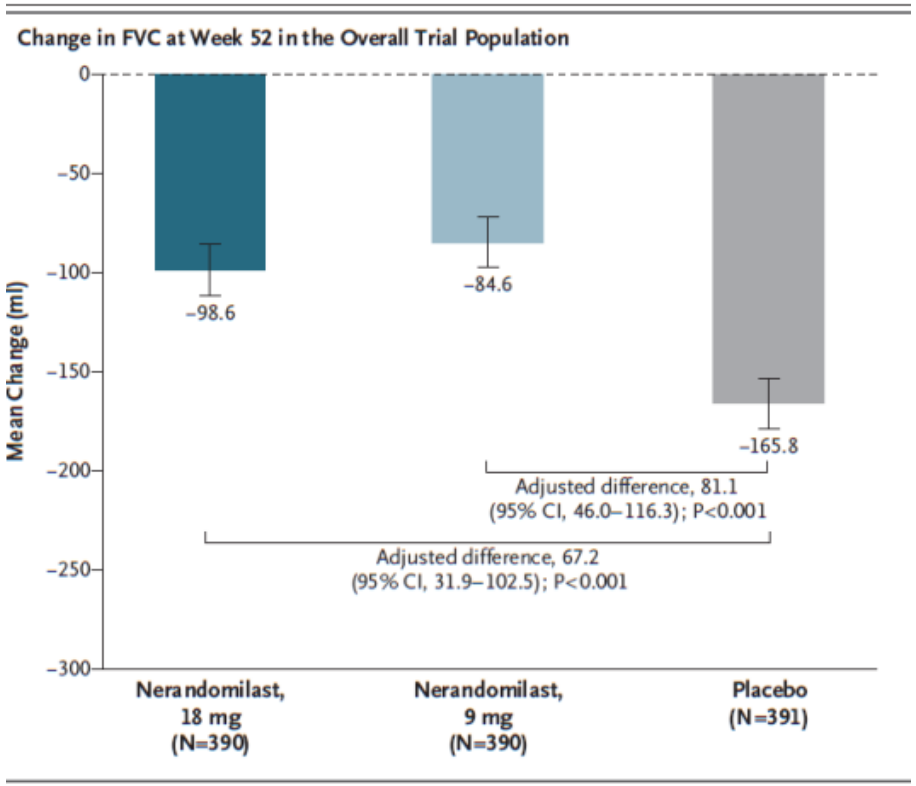


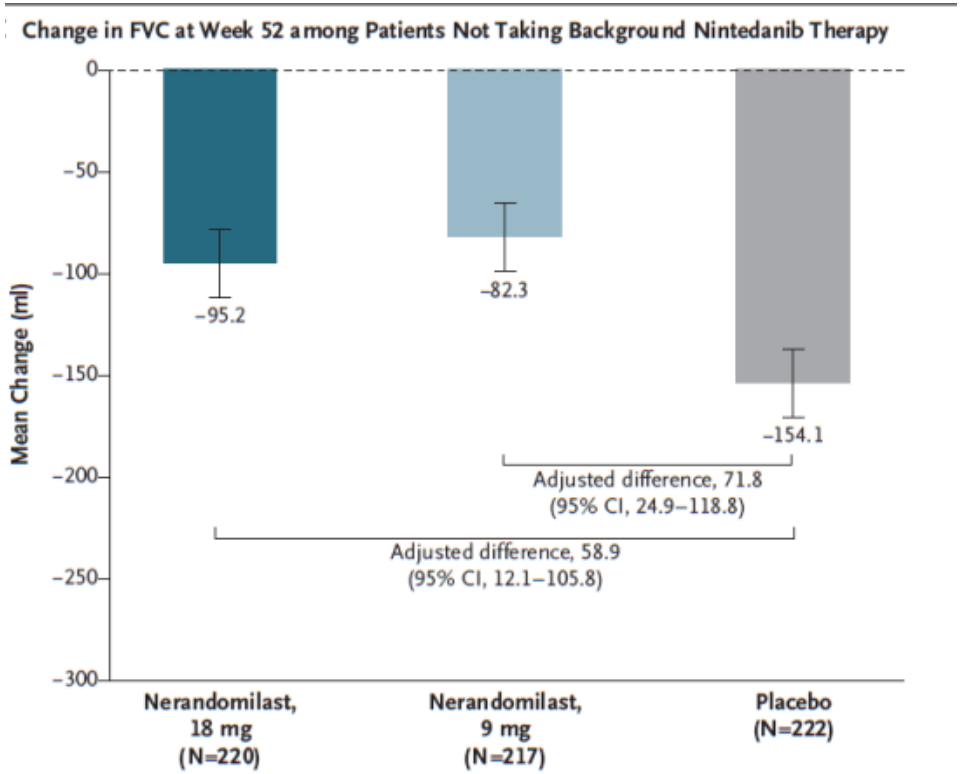
Behr J et al. Lancet Respir Med 2021

Nerandomilast in Patients with Progressive Pulmonary Fibrosis

Toby M. Maher, M.D.,[1,2] Shervin Assassi, M.D.,[3] Arata Azuma, M.D.,[4,5] Vincent Cottin, M.D.,[6] Anna-Maria Hoffmann-Vold, M.D.,[7,8] Michael Kreuter, M.D.,[9,10] Justin M. Oldham, M.D.,[11] Luca Richeldi, M.D.,[12] Claudia Valenzuela, M.D.,[13] Marlies S. Wijsenbeek, M.D.,[14] Emmanuelle Clerisme-Beaty, M.D.,[15] Carl Coeck, M.D.,[16] Hui Gu, Ph.D.,[17] Ivana Ritter, M.D.,[15] Arno Schlosser, M.Sc.,[18] Susanne Stowasser, M.D.,[15] Florian Voss, Ph.D.,[19] Gerrit Weimann, M.D.,[15] Donald F. Zoz, M.D.,[20] and Fernando J. Martinez, M.D.,[21] for the FIBRONEER-ILD Trial Investigators*

This article was published on May 19, 2025, and updated on May 22, 2025, at NEJM.org.





How does one define progression?

INBUILD criteria: Inclusion criteria for progression

Patients with non-IPF fibrotic ILD required to meet ≥1 of the following criteria for progression in the 24 months before screening, despite management:

- **Relative decline in FVC ≥10% predicted**
- **Relative decline in FVC ≥5–<10% predicted and worsened respiratory symptoms**
- **Relative decline in FVC ≥5–<10% predicted and increased extent of fibrosis on HRCT**
- **Worsened respiratory symptoms and increased extent of fibrosis on HRCT**

Flaherty KR et al. N Engl J Med 2019

Definitions of progression used in other anti-fibrotic trials in non-IPF progressive fibrosis

RELIEF: Progression despite conventional therapy within previous 6-24 months defined as:

- Annual absolute decline in FVC ≥ 5% based on at least three measurements

UILD: Deterioration within the last 6 months, defined as:

- FVC absolute decline >5%, or
- significant symptomatic worsening attributable to ILD progression (patients allowed to continue on stable dose immunosuppression)

Behr J et al Lancet Respir Med. 2021 May. Maher et al Lancet Respir Med. 2020.

AMERICAN THORACIC SOCIETY DOCUMENTS

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

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

Table 4. Definition of Progressive Pulmonary Fibrosis

Definition of PPF
In a patient with ILD of known or unknown etiology other than IPF who has radiological evidence of pulmonary fibrosis, PPF is defined as at least two of the following three criteria occurring within the past year with no alternative explanation*:
1 Worsening respiratory symptoms
2 Physiological evidence of disease progression (either of the following): a. Absolute decline in FVC ⩾5% predicted within 1 yr of follow-up b. Absolute decline in D_{LCO} (corrected for Hb) ⩾10% predicted within 1 yr of follow-up
3 Radiological evidence of disease progression (one or more of the following): a. Increased extent or severity of traction bronchiectasis and bronchiolectasis b. New ground-glass opacity with traction bronchiectasis c. New fine reticulation d. Increased extent or increased coarseness of reticular abnormality e. New or increased honeycombing f. Increased lobar volume loss

Multidimensional approach to identify patients with progression of ILD

Raghu et al Am J Respir Crit Care Med. 2022

Issues with the ATS/ERS/JRS/ALAT guidelines for defining PPF

- A large decline in DLco, not associated with FVC change, can be a manifestation of pulmonary vasculopathy, which is not necessarily linked to severity of ILD (for example in CTD-ILD)

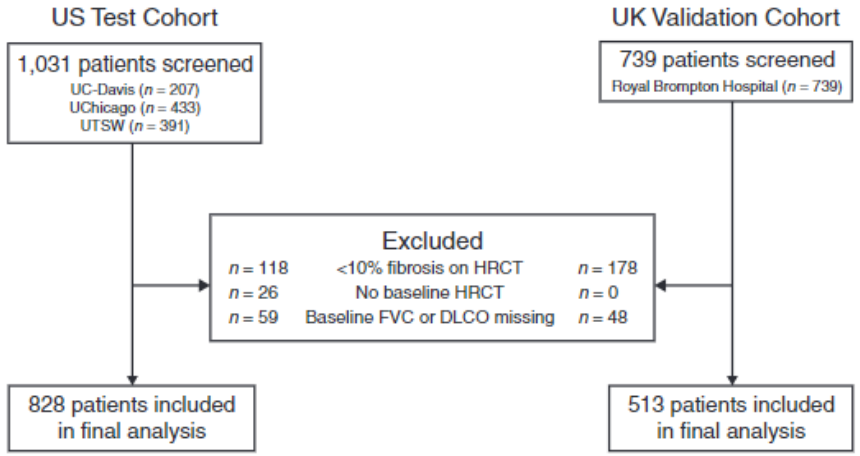
- The chosen threshold of absolute decline in DLCO by at least 10% is not based on validated data

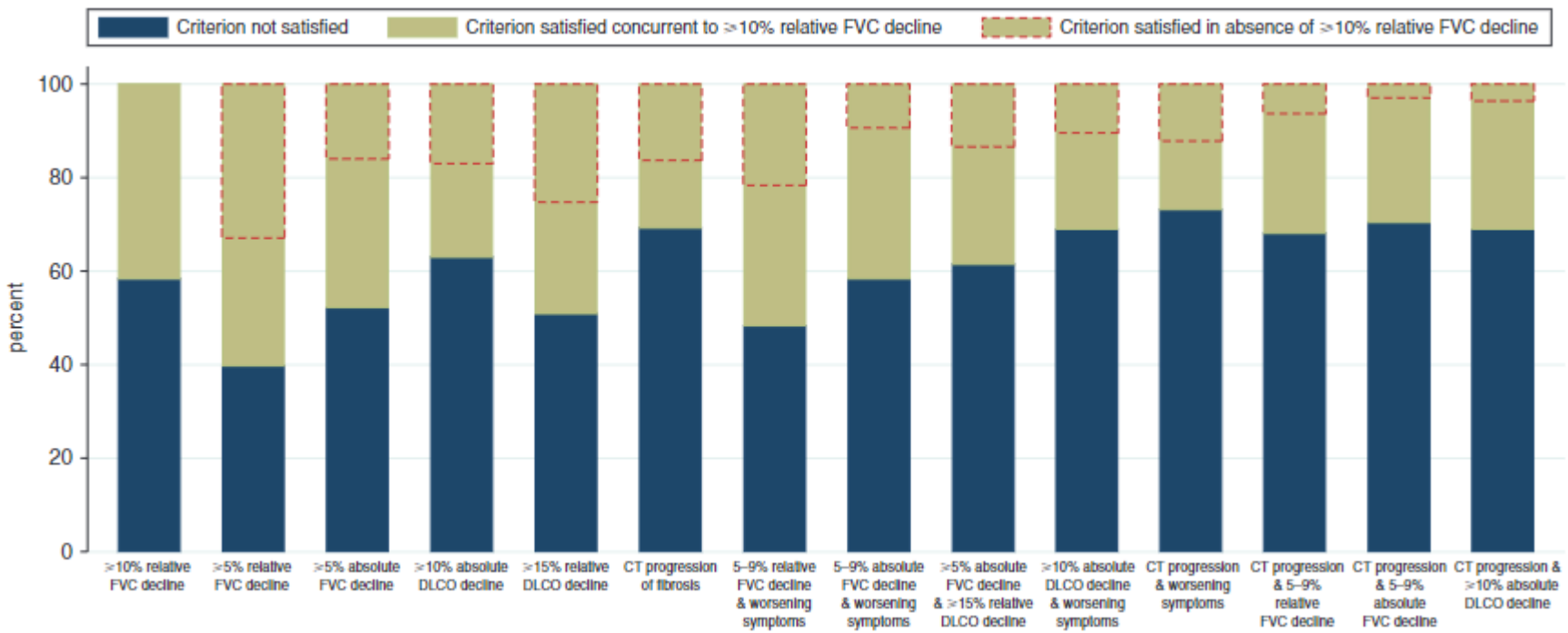
- The guidelines require disease progression within a 12-month time interval. However rate of progression varies between patients and most recent trials of PPF included longer periods. The limit of 12 months would exclude patients who are progressing over longer periods

Wells AU. Curr Opin Pulm Med. 2023

Validation of Proposed Criteria for Progressive Pulmonary Fibrosis

Janelle Vu Pugashetti[1,2*], Ayodeji Adegunsoye[3*], Zhe Wu[4,5], Cathryn T. Lee[3], Anand Srikrishnan[6], Sahand Ghodrati[2], Vivian Vo[2], Elisabetta A. Renzoni[4,5], Athol U. Wells[4,5], Christine Kim Garcia[7], Felix Chua[4,5], Chad A. Newton[6‡], Philip L. Molyneaux[4,5‡], and Justin M. Oldham[1‡]



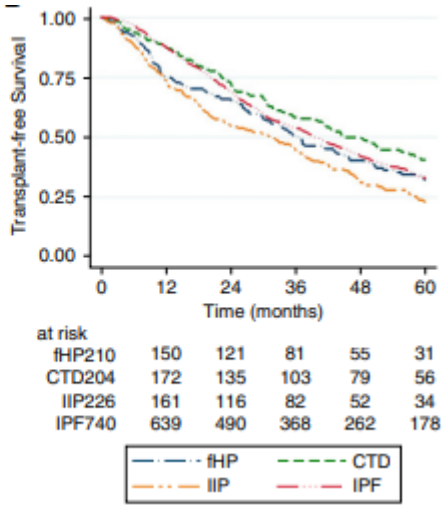


Progression evaluated over four years

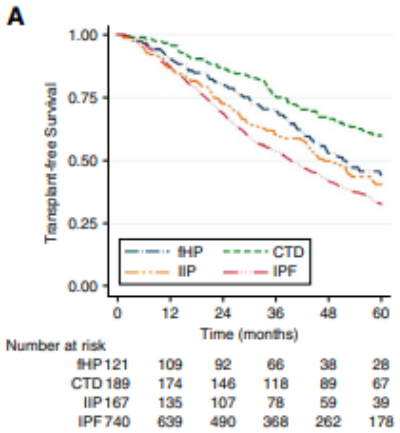
Am J Respir Crit Care Med. 2023

	Combined cohort HR (95% CI)
≥10% relative FVC decline	3.1 (2.5-3.9)
5-9% relative FVC decline	2.6 (2.0-3.4)
≥15% relative DLCO decline	2.2 (1.7-2.8)
CT worsening fibrosis	2.0 (1.5-2.7)
5-9% relative FVC decline & worsening symptoms	2.4 (1.9-3.1)
5-9% relative FVC decline & ≥15% DLCO decline	2.3 (1.7-3.0)
Worsening of CT fibrosis & symptoms	2.3 (1.7-3.1)

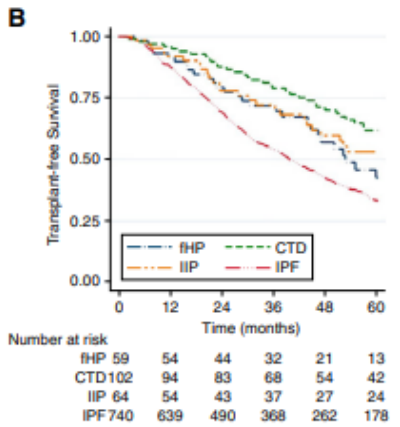
≥10% relative FVC decline



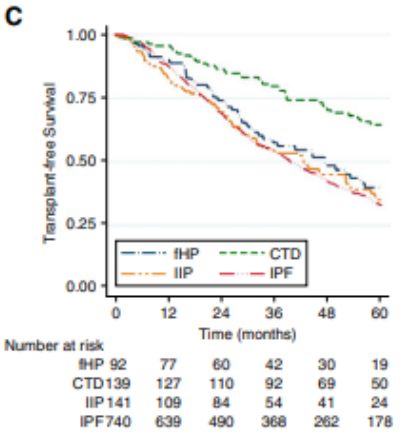
5-9% relative FVC decline



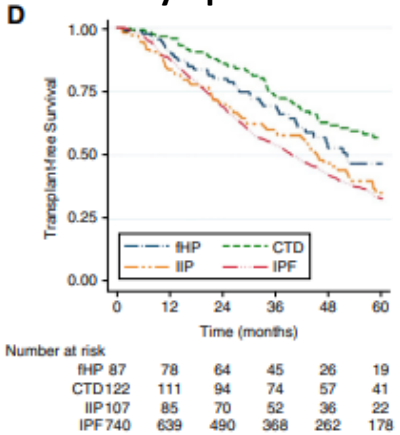
>15% relative DLCO decline



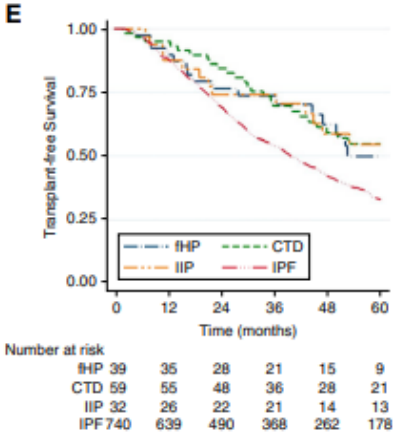
CT progression of fibrosis



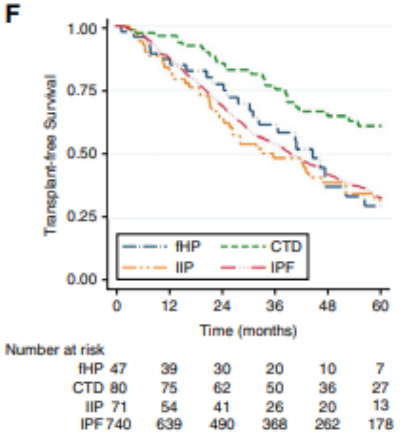
5–9% relative FVC decline & worsening symptoms



5–9% FVC relative decline & >15% relative DLCO decline



Worsening of CT fibrosis & symptoms



Am J Respir Crit Care Med. 2023

- ½ of the cohort experienced ⩾10% FVC decline over four years

- ⩾10% relative FVC decline was the strongest predictor of subsequent reduced transplant-free survival, irrespective of ILD type

- Three additional stand-alone PPF criteria in the absence of ⩾10% relative FVC decline (5–9% relative FVC decline, ⩾15% relative D_{LCO} decline, and CT worsening) and three combinations of symptomatic, physiologic, and radiologic worsening, were also associated with reduced transplant-free survival in patients with non-IPF fibrotic ILD in both test and validation cohorts

- Compared to connective tissue disease-ILD, both fibrotic hypersensitivity pneumonitis and non IPF idiopathic interstitial pneumonias more frequently experienced disease progression and had a greater risk of death after satisfying PPF criteria

Pugashetti et al Am J Respir Crit Care Med. 2023 Jan 1;207(1):69-76.

How does one define progression in clinical practice?

1) No “one-size-fits-all” definition of progression exists. In the real world, various combinations of increasing respiratory symptoms, reductions in FVC and/or DLCO and/or increasing fibrosis on HRCT scan are used

2) Progression is progression, whether in 6 months or more insidiously

3) The frequency of lung function tests in follow-up monitoring must be decided on a case-by-case basis, but should be every 3-6 months in patients at risk

1) Serial HRCT should be used to identify progressive fibrosis when serial symptomatic and pulmonary function data are inconclusive

Rajan SK et al Eur Respir J. 2023

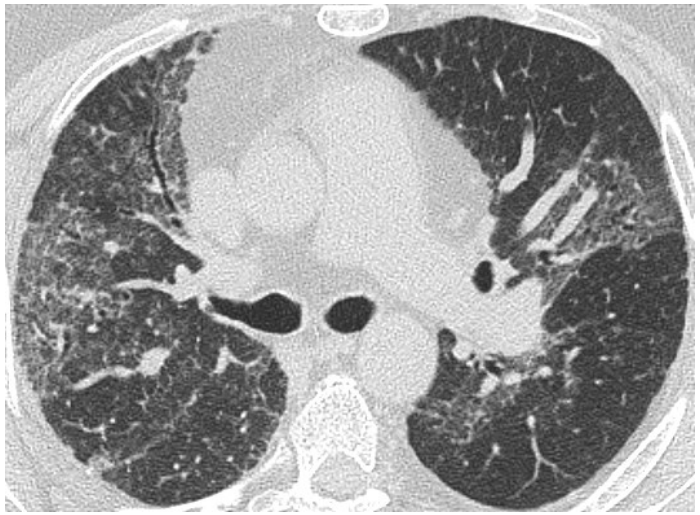
What is best management in PPF ?

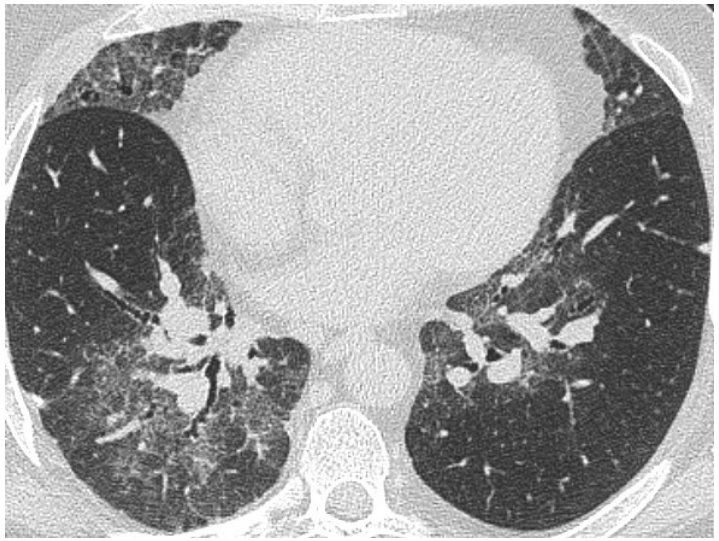
When (non-IPF) ILD is progressing despite ongoing “standard” treatment, how do we know whether to:

- Intensify immunomodulatory treatment
- Introduce anti-fibrotic therapy but not immunomodulation
- Introduce anti-fibrotic therapy and continue immunomodulation
- Introduce anti-fibrotic therapy and stop immunomodulation

CASE

- 47-year-old man
- Presents in 2017 with 6-month history of worsening breathlessness
- No identifiable exposures at home or work
- FVC: 57% predicted
  DLCO: 36% predicted
- SpO_2: 97% at rest
  6MWT: 450m, SpO_2 93%
- BAL: 20% lymphocytosis, 5 % neutrophils
- Echocardiogram: normal, no suggestion of PH





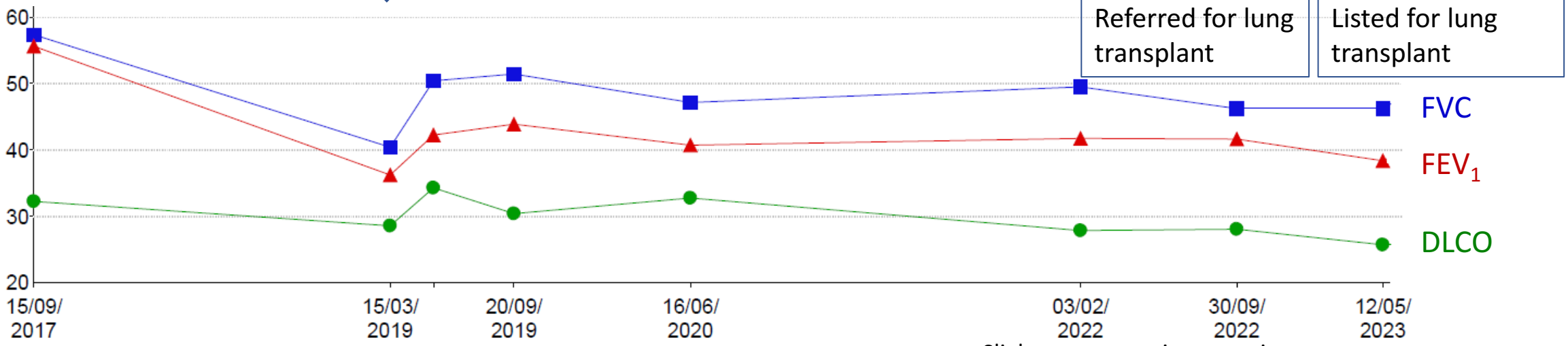
VATS biopsy:
in keeping with fibrotic HP (bronchocentric inflammatory changes and fibrosis, including occasional small poorly formed non- necrotising granulomas)

Low dose steroids and azathioprine

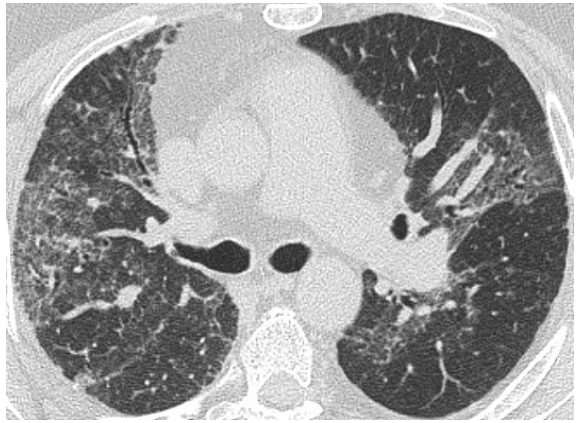
IV MP

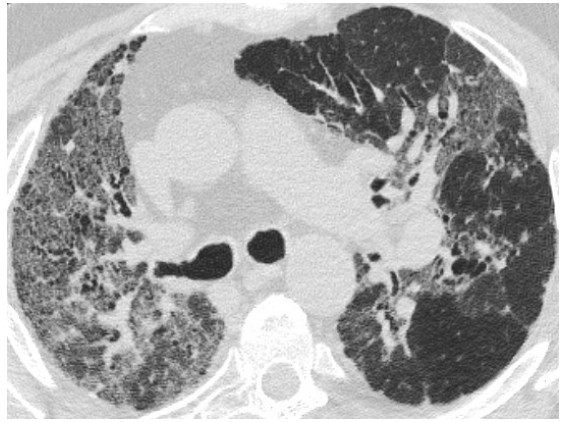
Switch to MMF and ongoing low dose steroids

Starts nintedanib and continues MMF



- Slight symptomatic worsening, although still working full time
- 6MWT: SpO2 drops to 83%
- Echo no PH, normal BNP





Consider increasing immunosuppression

- Morphology (CT / Histology / Bronchoalveolar Lavage) suggestive of inflammatory component
- Background autoimmune disease
- Extrapulmonary inflammation
- Previous response to increased anti-inflammatory treatment
- Patient wishes

Consider avoiding or stopping immunomodulation

- In advanced fibrotic ILD, particularly if extensive honeycombing and/or extensive traction bronchiectasis
- In elderly and/or frail patients
- Recurrent infections
- Absence of BAL lymphocytosis
- Patient wishes

Treatment decisions always case by case

Rajan SK et al. Eur Respir J 2023. Mackintosh JA et al. Eur Respir Rev 2021. Behr J et al. Pneumologie 2023.

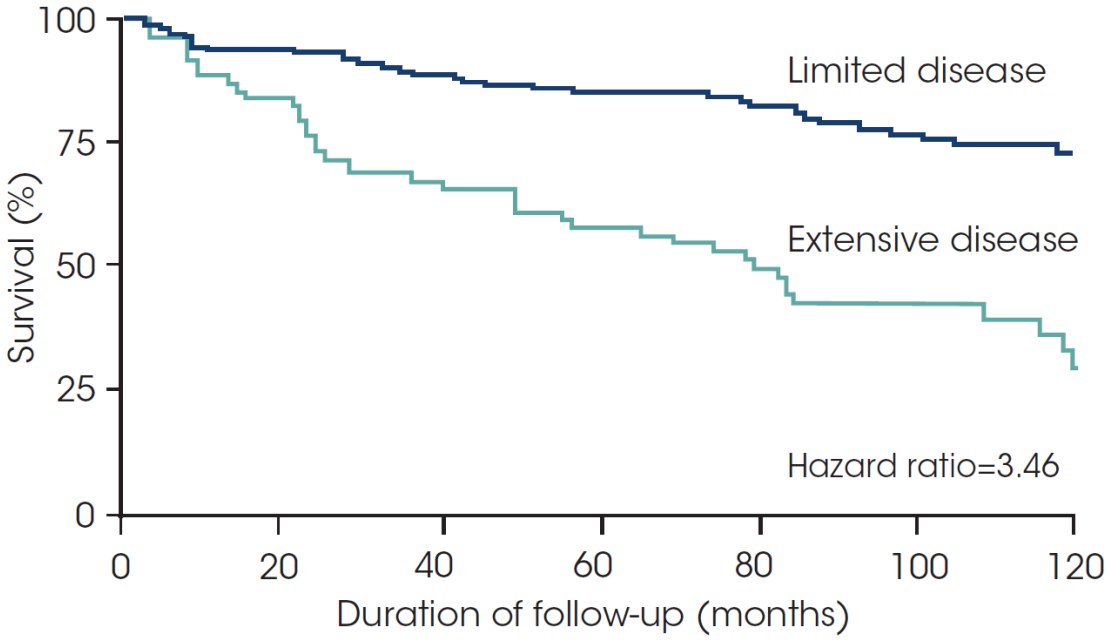
Are there any risk factors for progression across different non IPF ILD entities?

Risk stratification for progression: plan follow-up accordingly

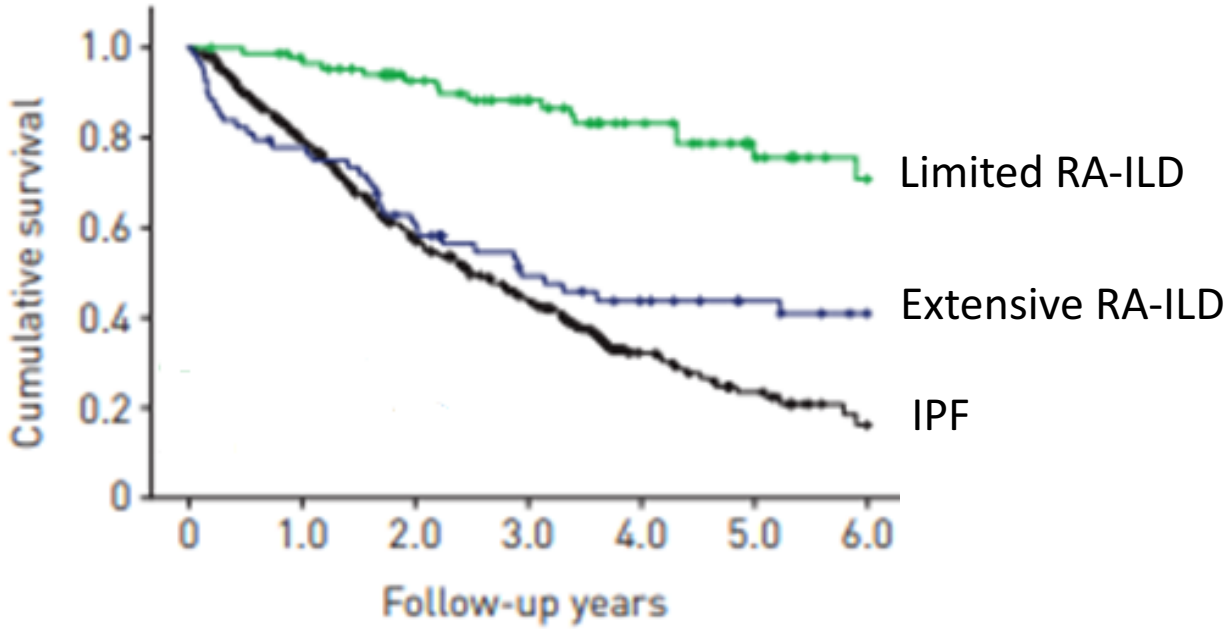
- **Severe disease: “fibrosis begets fibrosis”**
- **A UIP pattern (**definite**UIP on CT}**
- **Older age: senescent pathways**
- **Family history of fibrotic ILD**
- **Short telomeres**

Extensive fibrosis is bad news….

Systemic sclerosis-ILD (SSc-ILD)



Rheumatoid arthritis-ILD (RA-ILD)

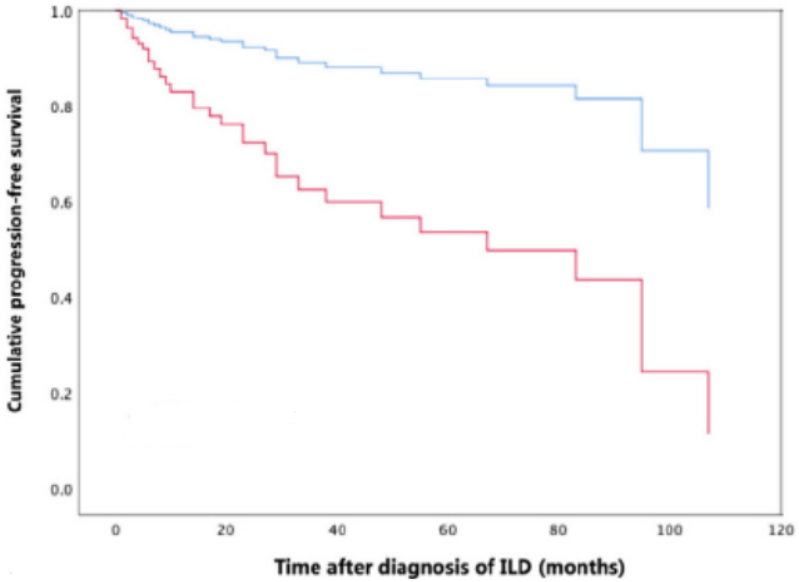


Goh NS, et al. Am J Respir Crit Care Med. 2008
Kim EJ et al. Eur Respir J 2010

Usual interstitial pneumonia as a stand-alone diagnostic entity: the case for a paradigm shift?

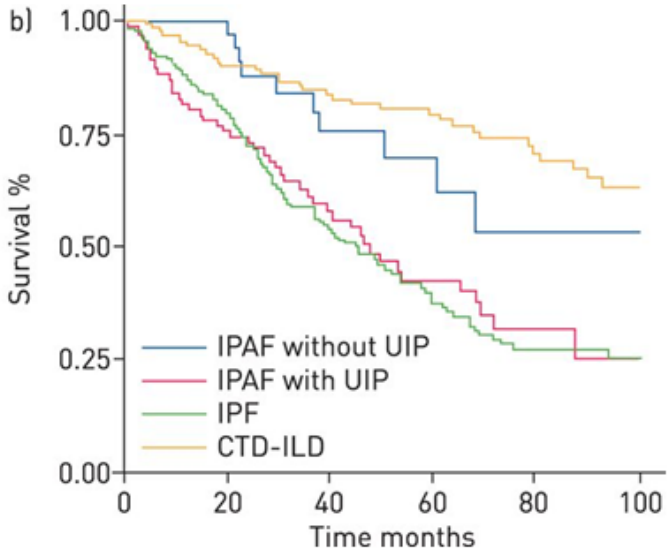
Moisés Selman, Annie Pardo, Athol U Wells

RA-ILD



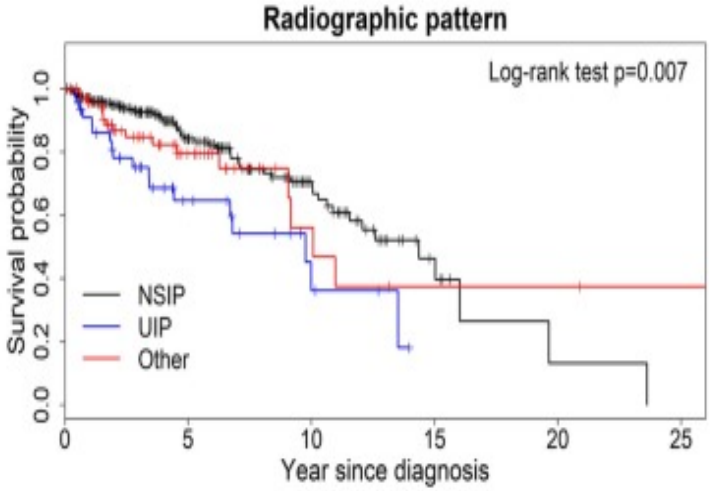
Chen N et al Semin Arthritis Rheum. 2022;55:152004.

IPAF



Oldham JM et al. Eur Respir J 2016;47:1767-75.

CTD-ILD

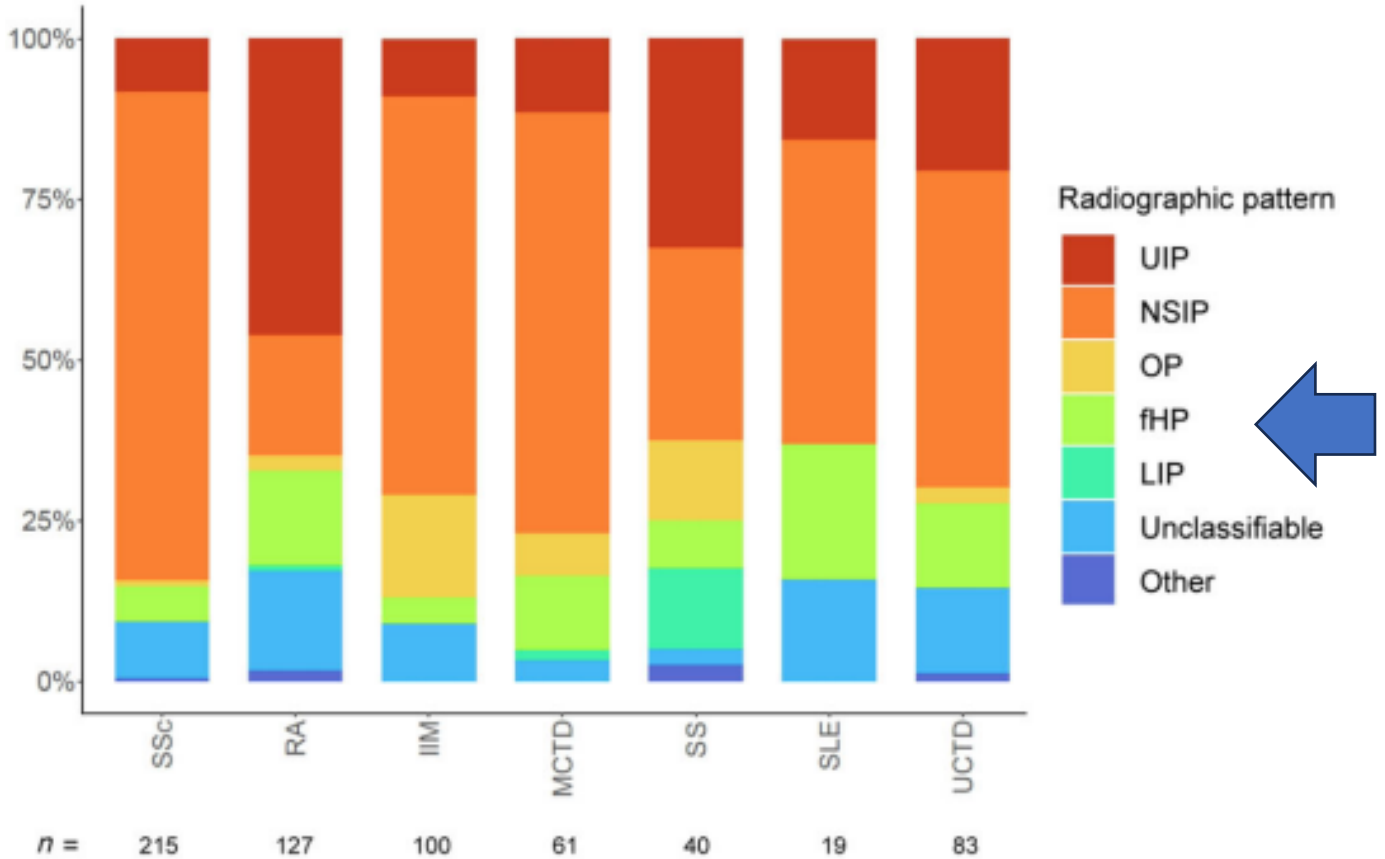


Chan C et al. BMC Pulm Med 2019;19:192.

Lung imaging patterns in connective tissue disease–associated interstitial lung disease impact prognosis and immunosuppression response

Canadian registry with 645 CTD-ILD patients: SSc (*n* = 215), RA (*n* = 127), inflammatory myopathies (*n* = 100) and others

CT patterns reviewed by expert radiologists

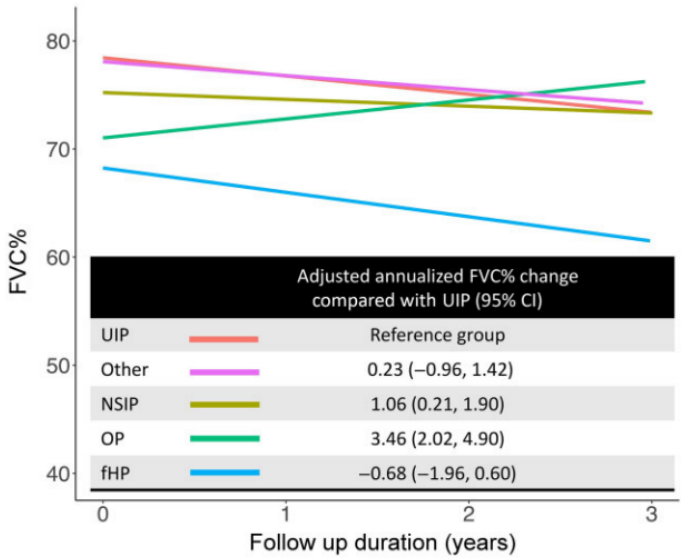


UIP: usual interstitial pneumonia; NSIP: non specific interstitial pneumonia; OP: organising pneumonia; fHP: fibrotic hypersensitivity pneumonitis (airway centred pattern)

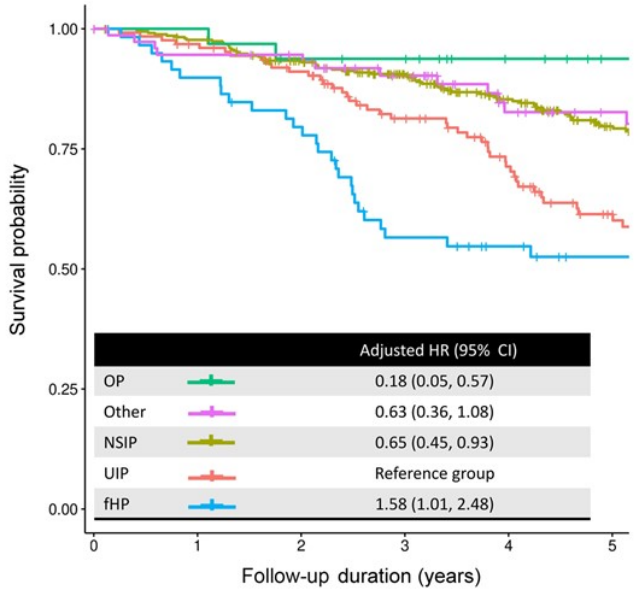
Zheng et al Rheumatology (Oxford). 2024

Lung imaging patterns in connective tissue disease–associated interstitial lung disease impact prognosis and immunosuppression response

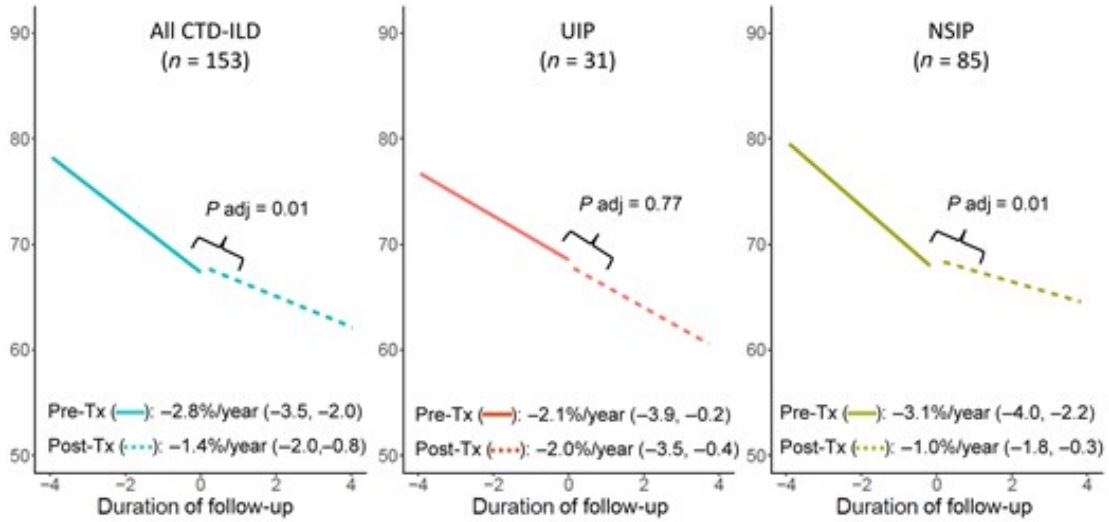
FVC decline



Mortality



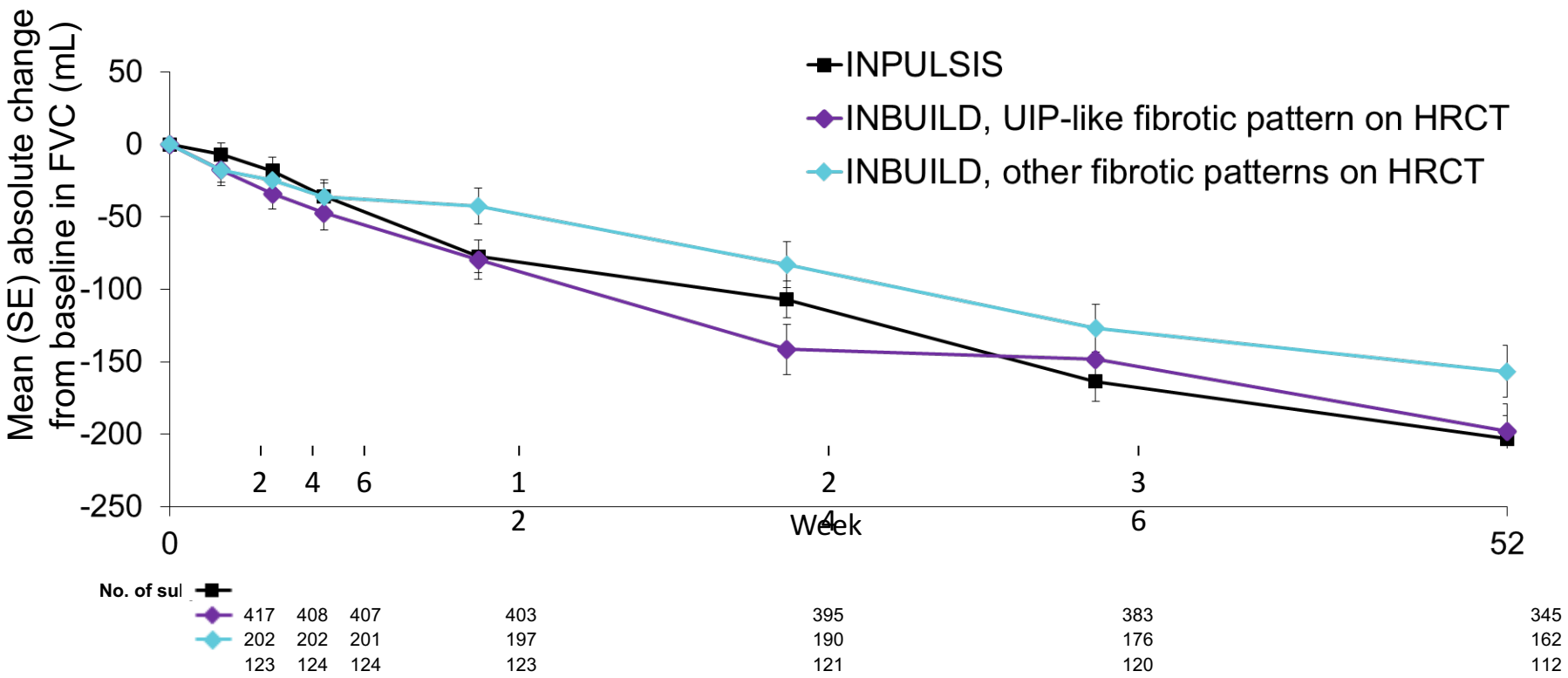
Response to immunosuppression



UIP: usual interstitial pneumonia; NSIP: non specific interstitial pneumonia; OP: organising pneumonia; fHP: fibrotic hypersensitivity pneumonitis (airway centred pattern)

Zheng et al Rheumatology (Oxford). 2024

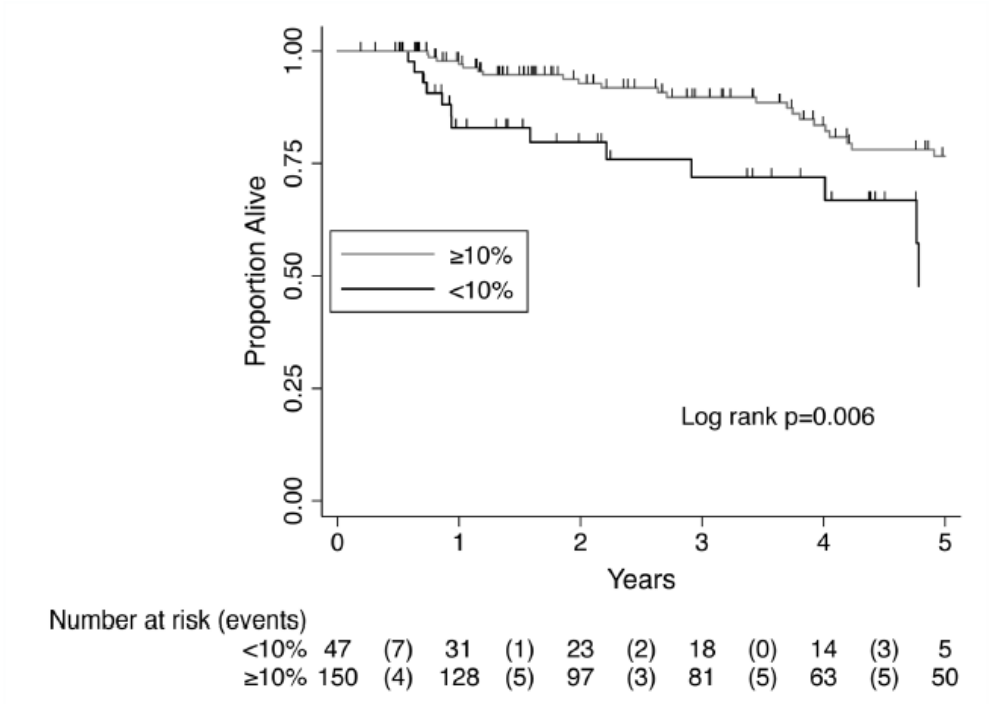
Change in FVC over time in placebo arms: previous progression despite optimal management predicts further progression



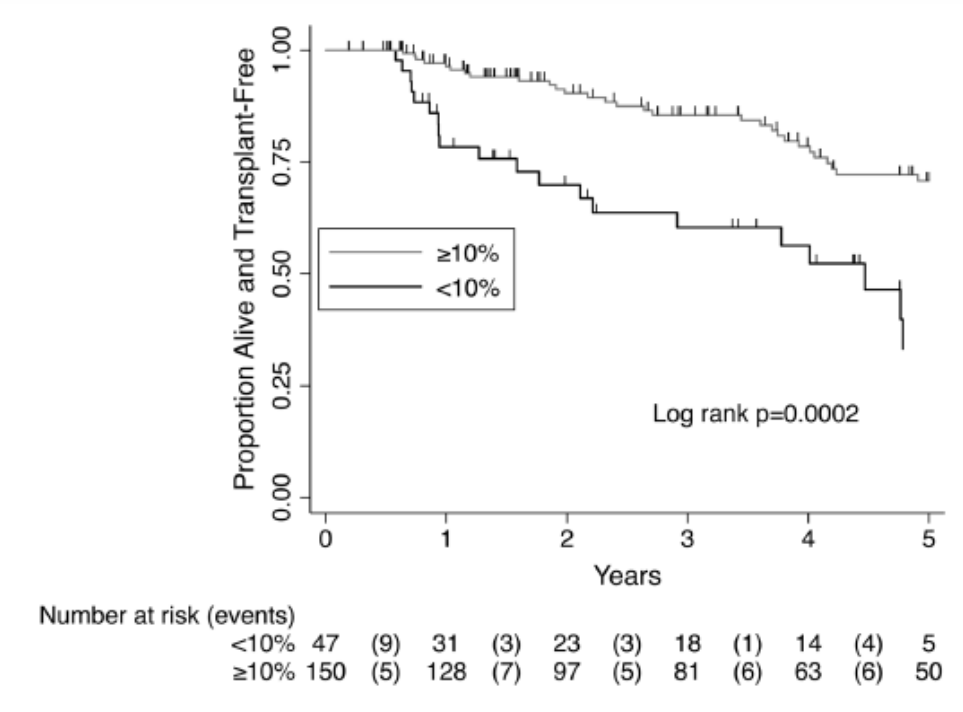
Brown KK, Martinez FJ, Walsh SLF, et al. The natural history of progressive fibrosing interstitial lung diseases. Eur Respir J. 2020

cHP with normal telomere length has better prognosis

Survival



Transplant free survival



Brett L et al. Lancet Resp Med. 2017

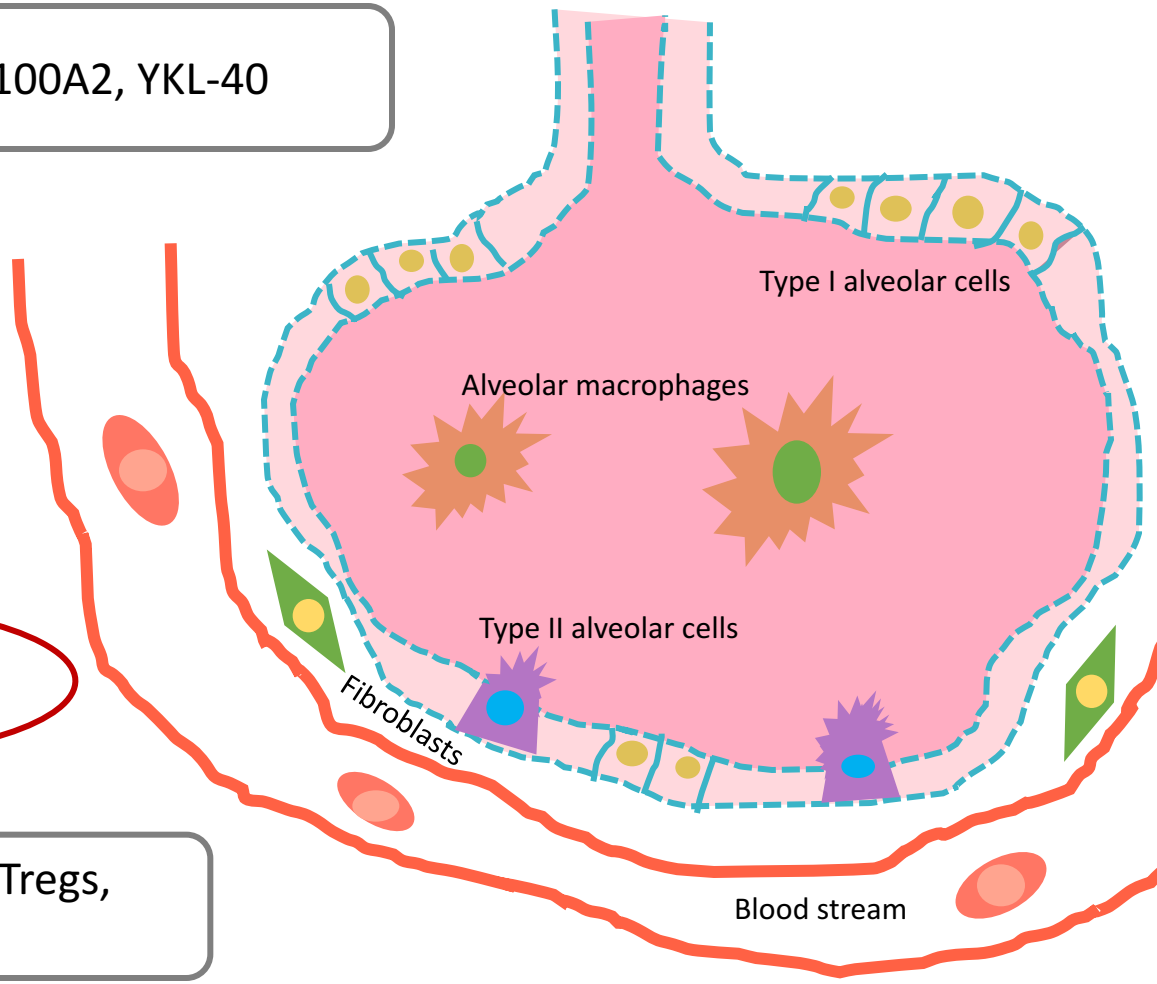
Serum Biomarkers

Innate immunity

CCL18, S100A2, YKL-40

Alveolar epithelial cell dysfunction

KL-6, SP-A, SP-D, CK-18



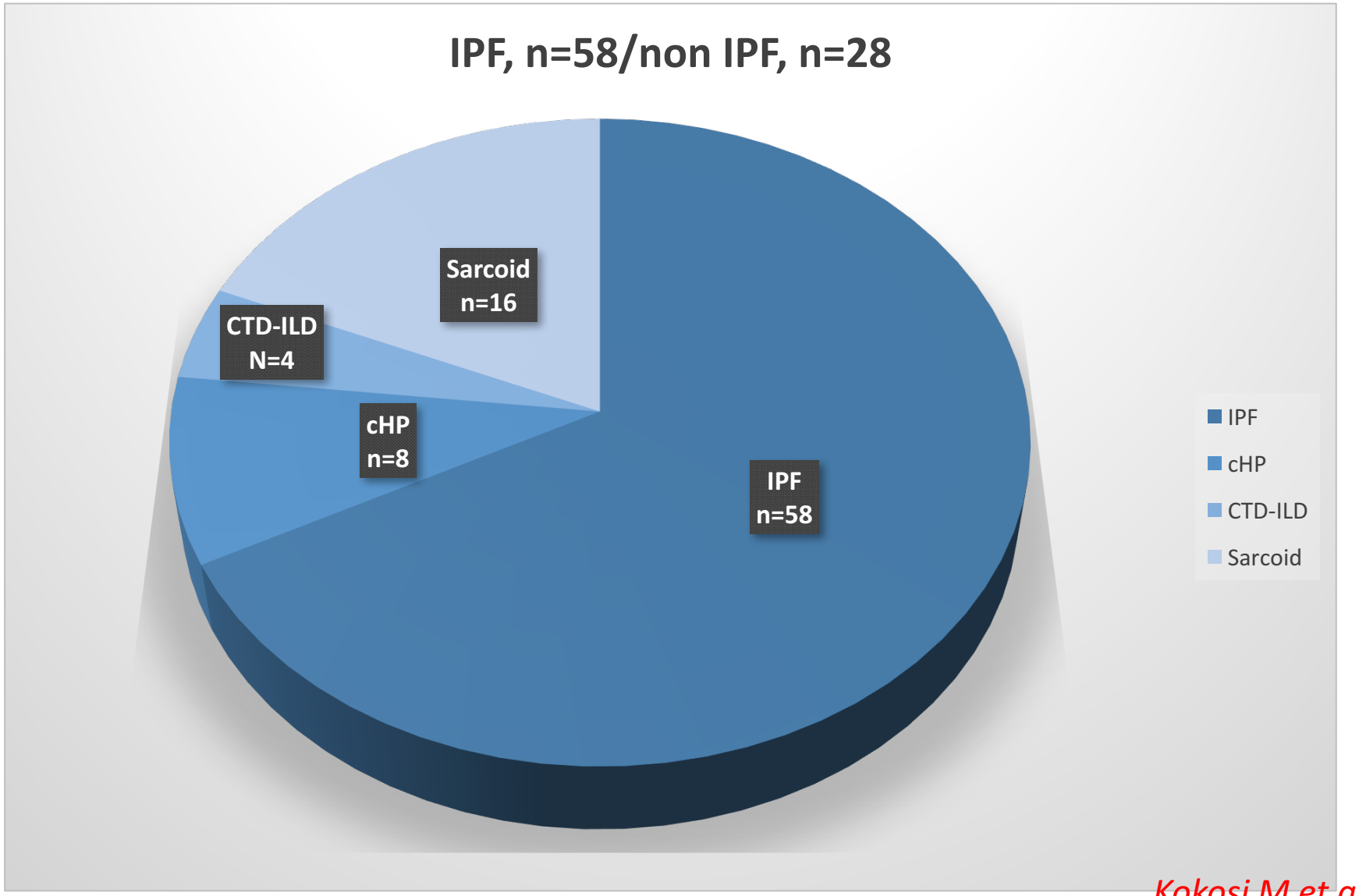
Adaptive Immunity

CXCL13, HSP70, Tregs, a-defensins, ILs

ECM remodelling & fibroproliferation

MMPs, Periostin, LOXL, Fibrocytes, Osteopontin

Pilot data (n=86)



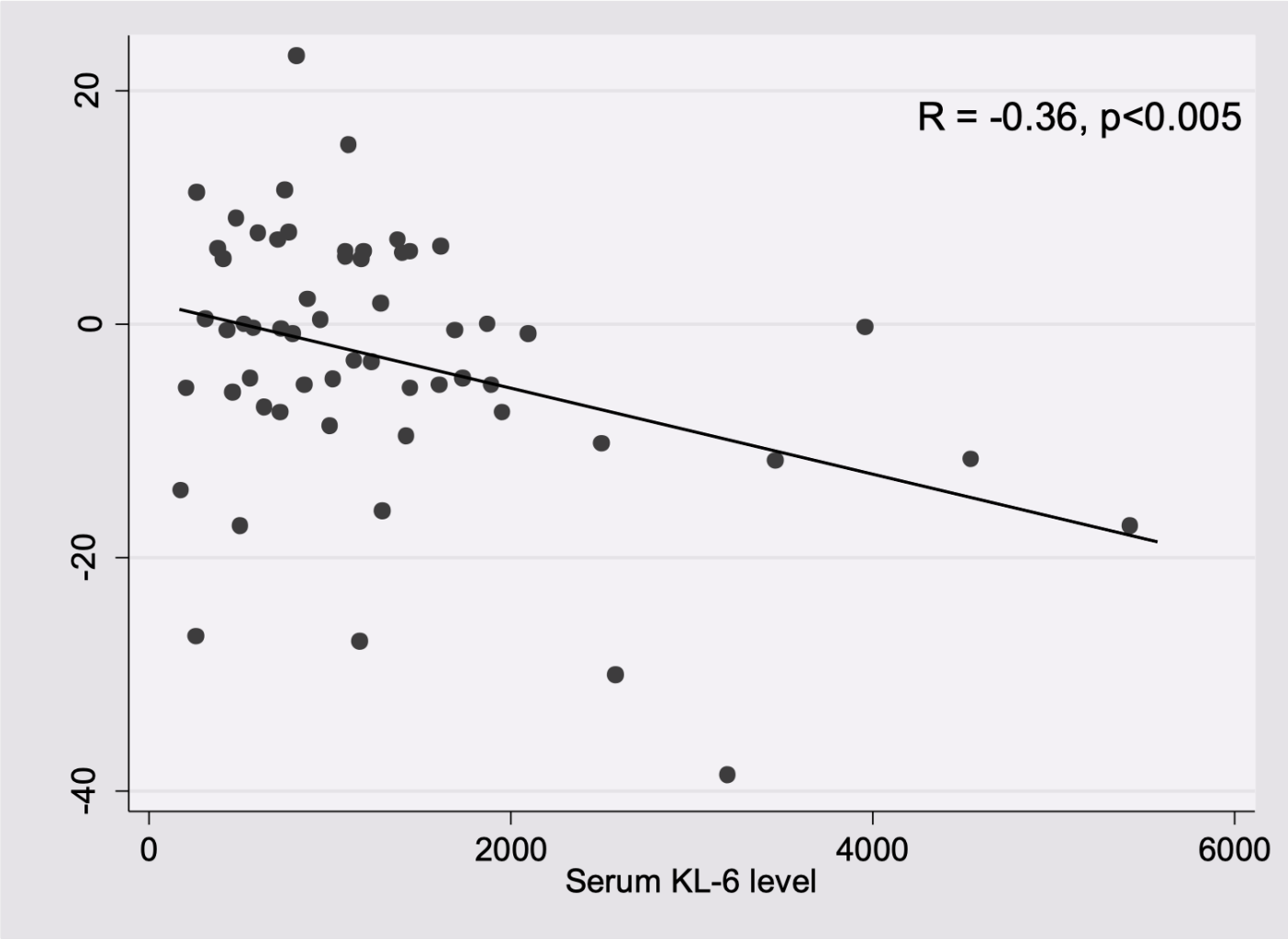
Kokosi M et al.in progress

Results

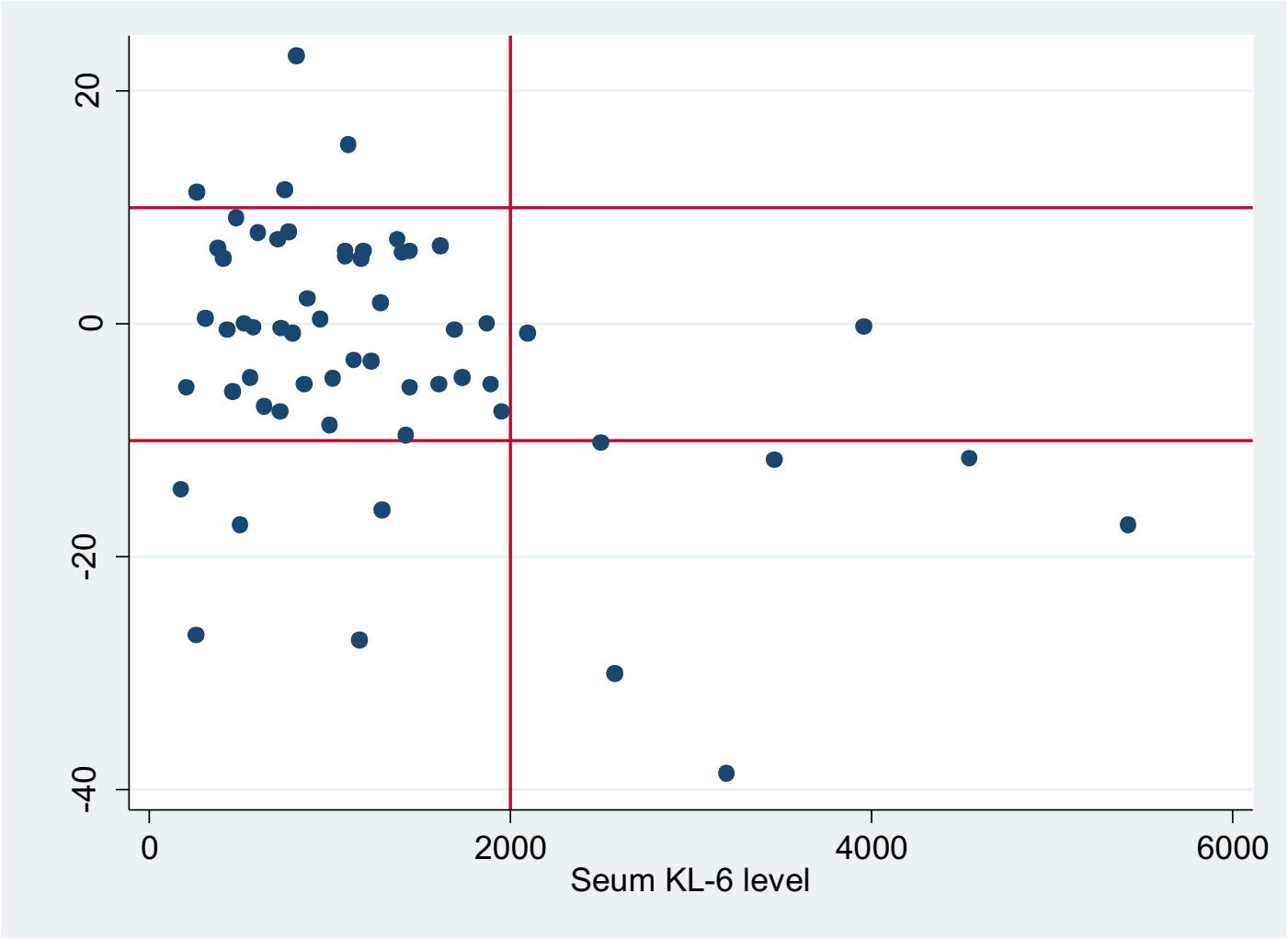
Gender , male/female	65/21
Age, years	68.5 ± 12.0
KL-6 level in the IPF cohort, U/mL	1240 ± 765
KL-6 level in the non-IPF cohort, U/mL	1302 ± 270
FVC, % predicted	75.6 ± 19.4
DLco, % predicted	49.7 ± 18.0

- DLco was the most powerful determinant of KL-6 levels (R^2=0.19)
- Serum KL-6 was equally elevated in IPF and non IPF patients
- This remained the case after adjustment for disease severity

Follow up data, n=58



Results

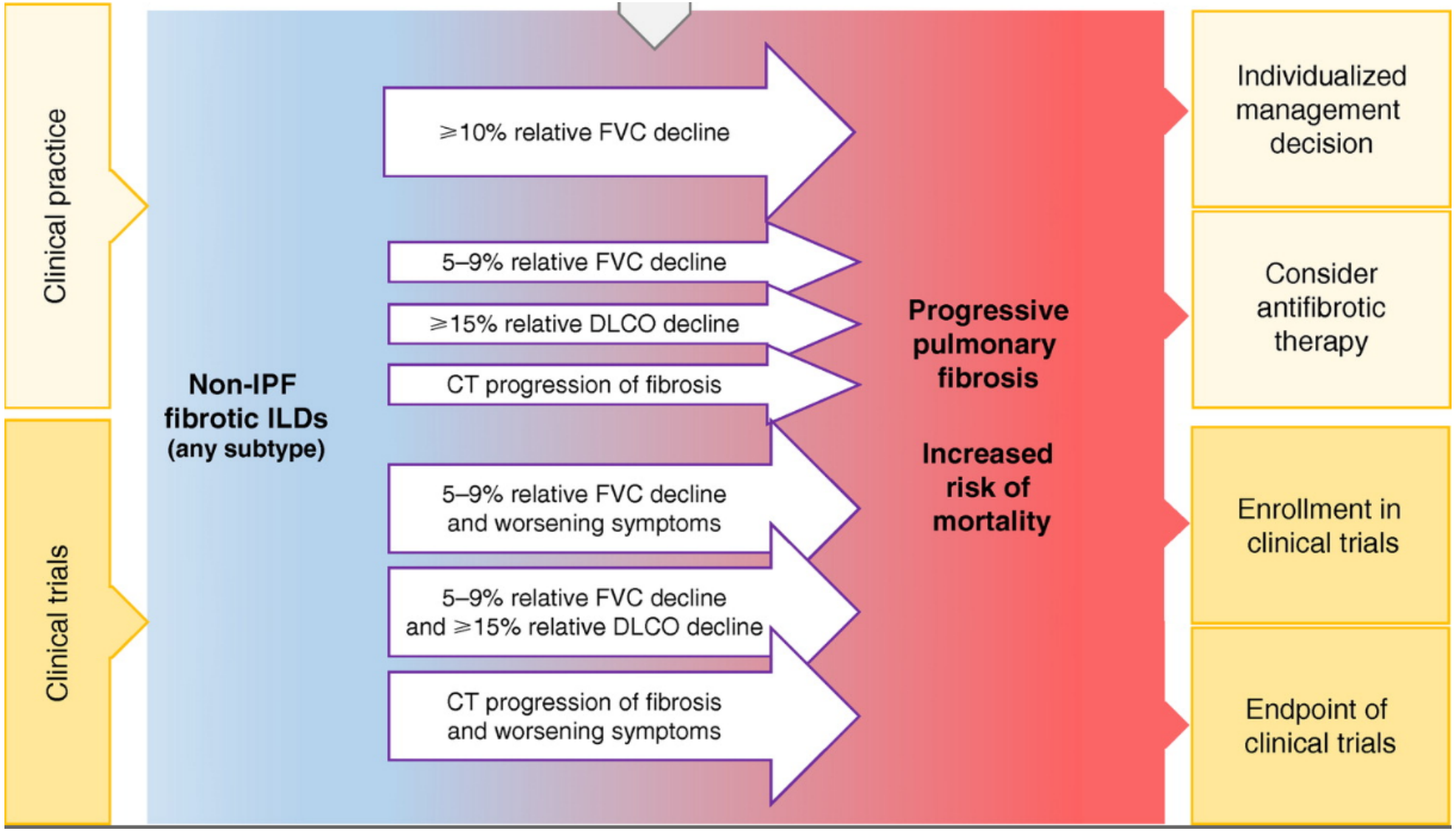


- Patients with FVC improvement did not have high KL6 levels
- The 8 patients with KL6 levels >2000 included six decliners (75%)
- The 50 patients with KL6 levels<2000 included only five decliners (10%)
- The difference between 6/8 and 5/50 is highly significant, p<0.0005

Royal Brompton & Harefield NHS Foundation Trust

- Serum KL-6 levels were elevated across the progressive fibrosis phenotype with no difference between the IPF and non IPF cohort
- Lack of discrimination between the two groups supports the idea that epithelial damage is a unifying feature among the fibrosing ILDs
- KL-6 seems to be a good candidate for prognosis in the progressive fibrotic phenotype

Algorithm derived from the study by Pugashetti and colleagues



Cottin V. Criteria for Progressive Pulmonary Fibrosis: Getting the Horse Ready for the Cart. Am J Respir Crit Care Med. 2023 Jan 1;207(1):11-13.

In conclusion

- A substantial proportion of patients with non-IPF fibrotic ILD are estimated to progress despite appropriate management
- PPF is identified by decline in lung function, worsening symptoms, and increased fibrosis on imaging, with variable criteria across studies
- Predicting which individuals will develop PPF remains challenging: close monitoring, including regular lung function tests, is needed to detect worsening disease early
- PPF is associated with high rates of death and must be identified promptly
- Research into early recognition of the progressive fibrosing phenotype, the role and timing of combination treatment urgently needed


SOUTH BROMPTON HOSPITAL BLOCK


Welcome to
Royal Brompton
Hospital
NHS

Thank you