

Management of fibrosing ILD in the era of antifibrotic therapy

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Contents

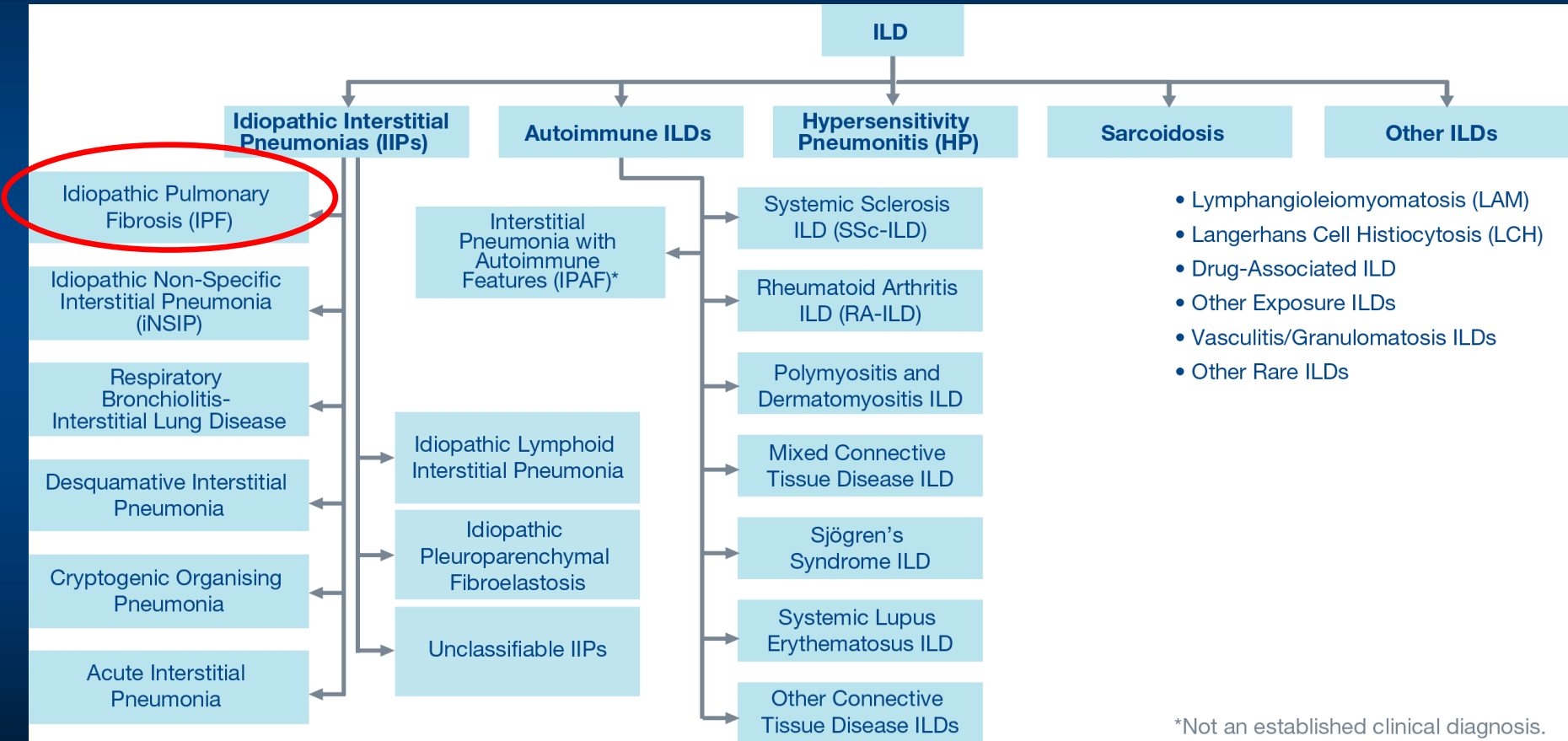
- IPF:
 - current management
 - real-world evidences

- Non-IPF ILD
 - PF-ILD: concept
 - pharmacological management

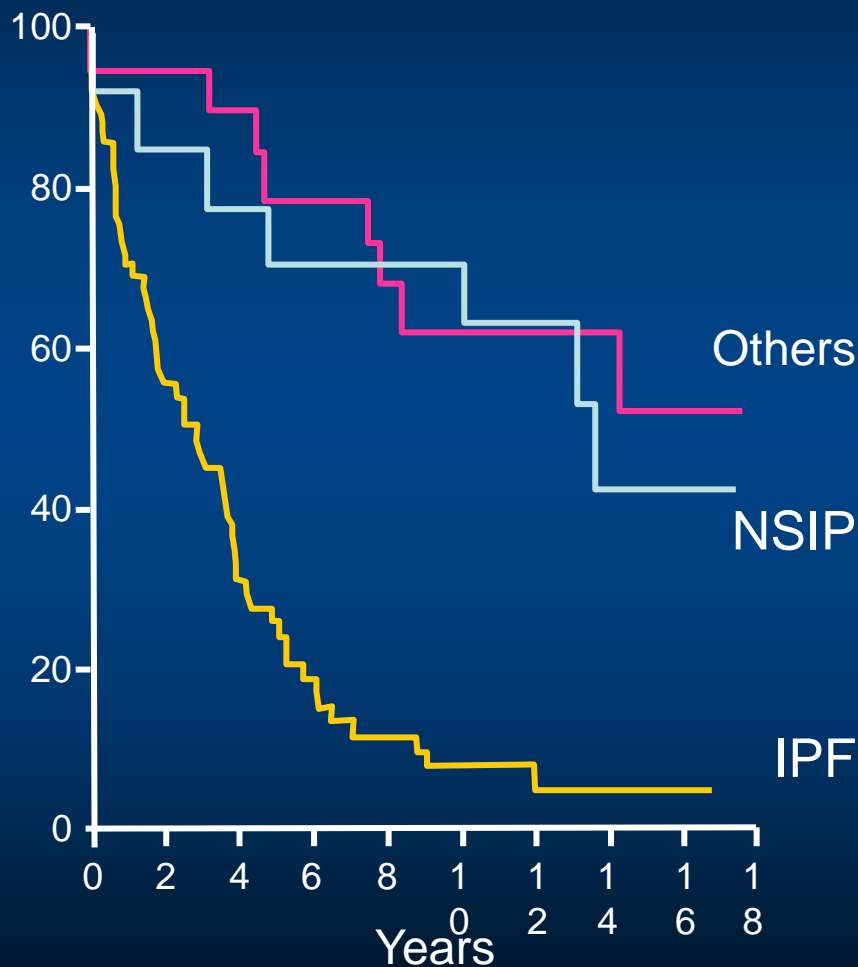
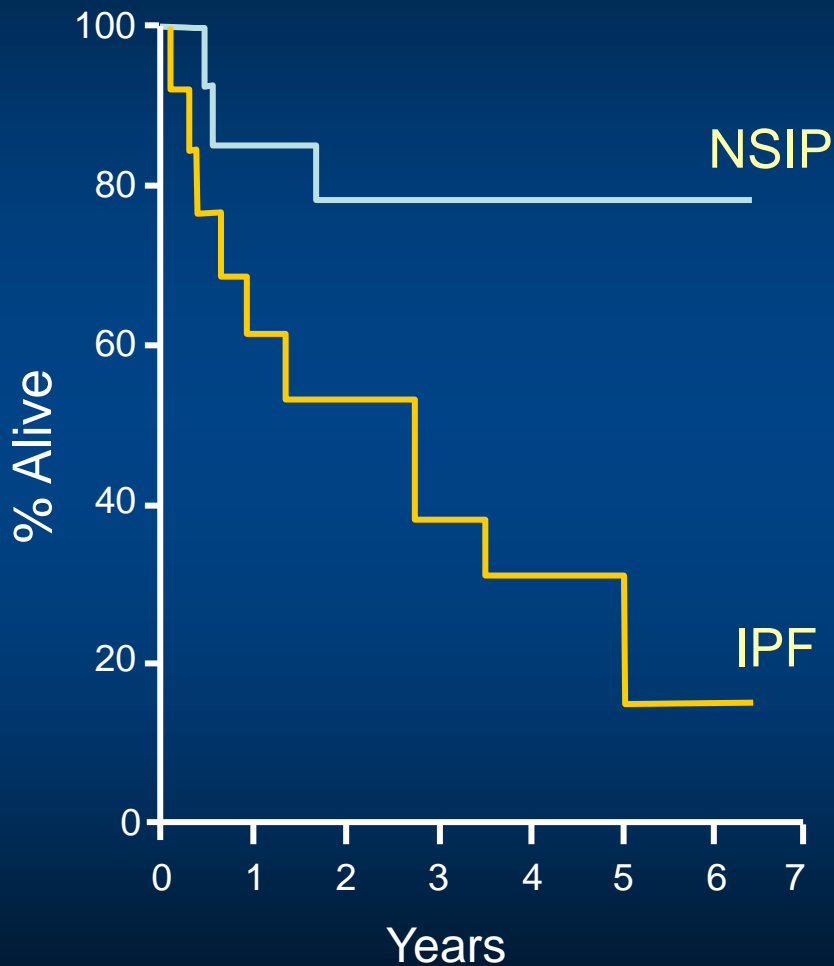
Interstitial Lung Disease

- Diverse group of disorders that involve the distal pulmonary parenchyma
- Patients typically presented with
 - Progressive dyspnea and cough
 - Abnormal pulmonary physiology
 - Abnormal CXR and/or HRCT
- Idiopathic or associated with systemic diseases (CTDs) or environmental exposures

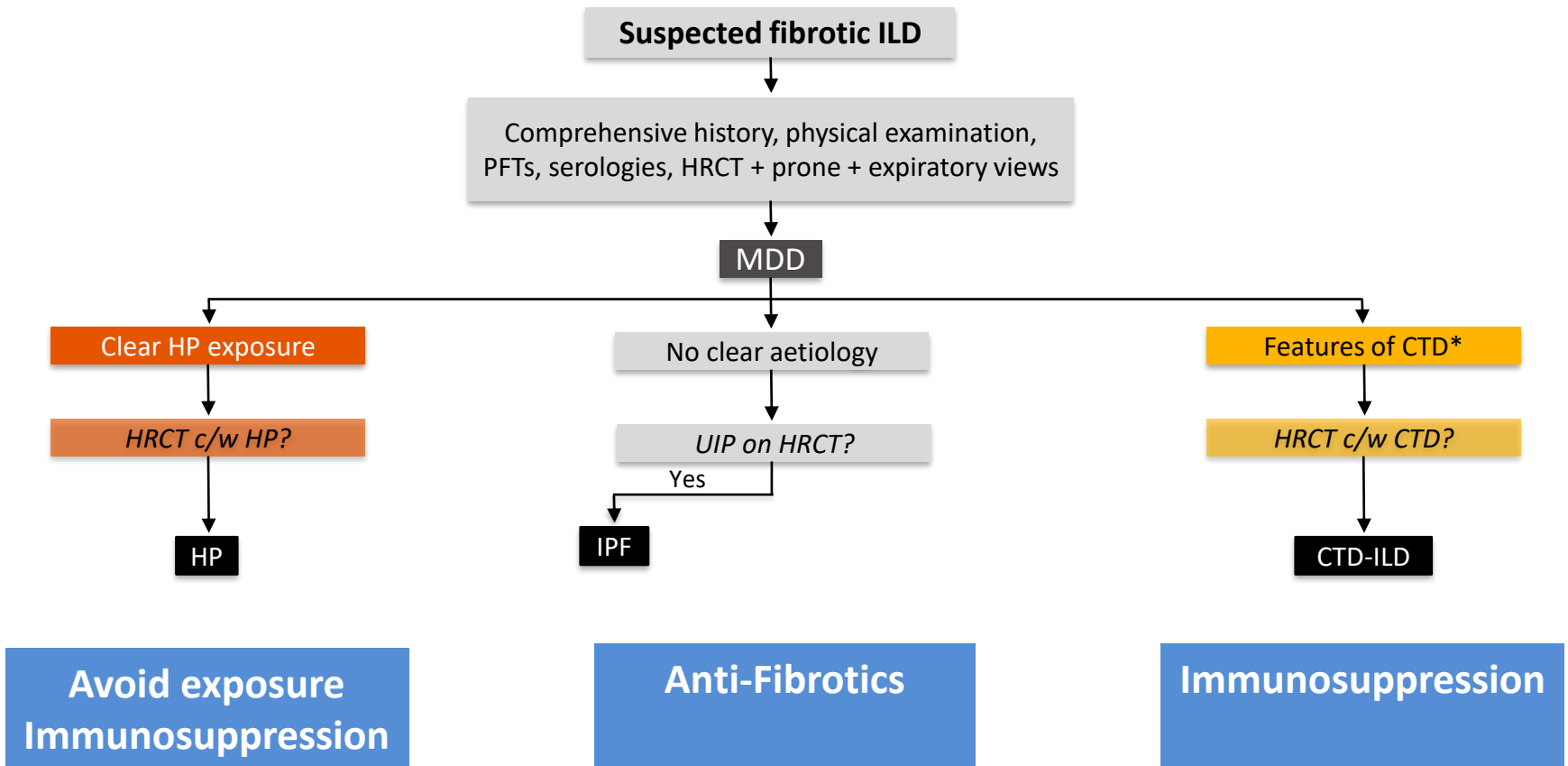
ILD: Classification



IPF confers a poor prognosis

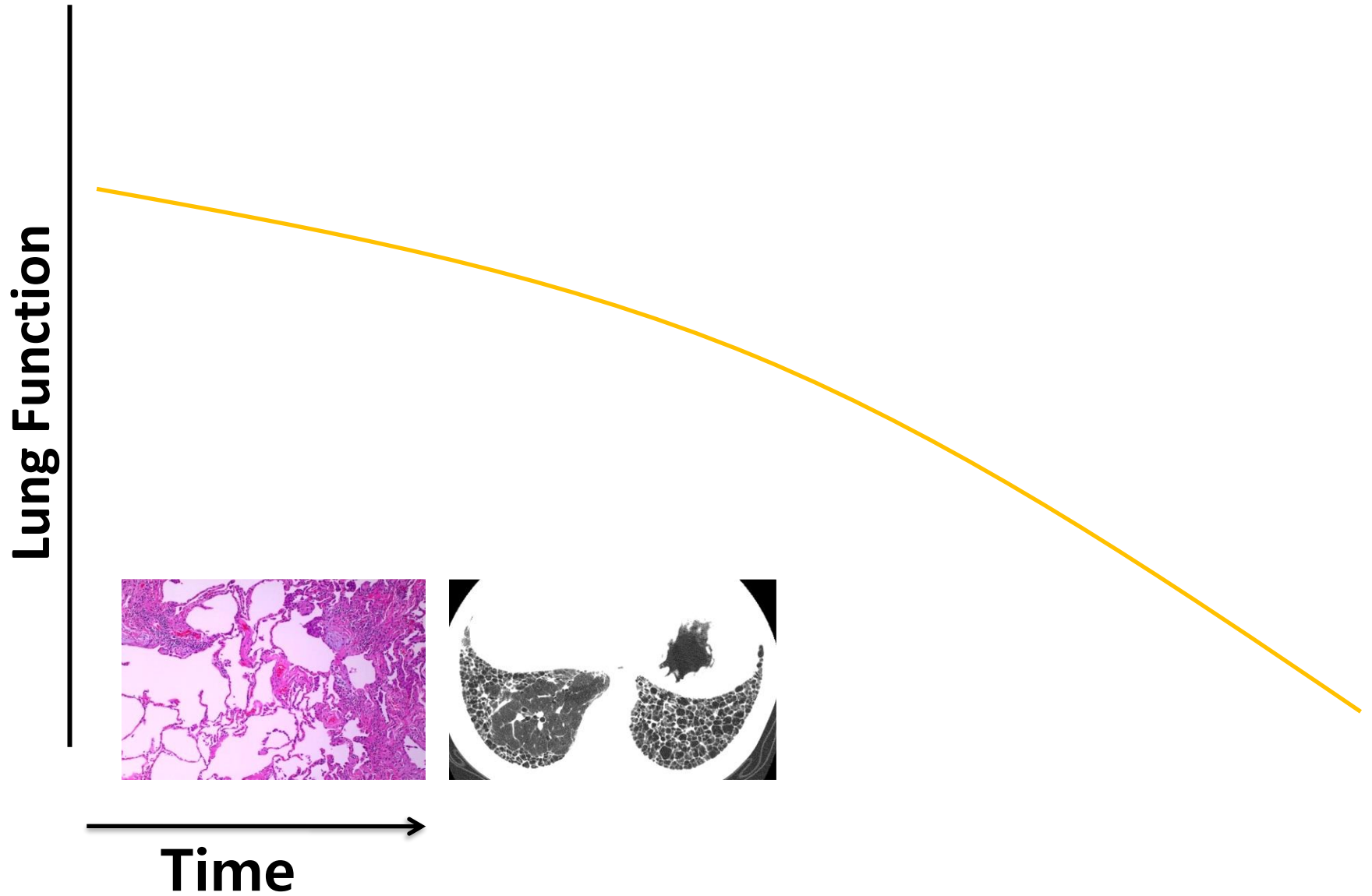


Management of fibrosing-ILD

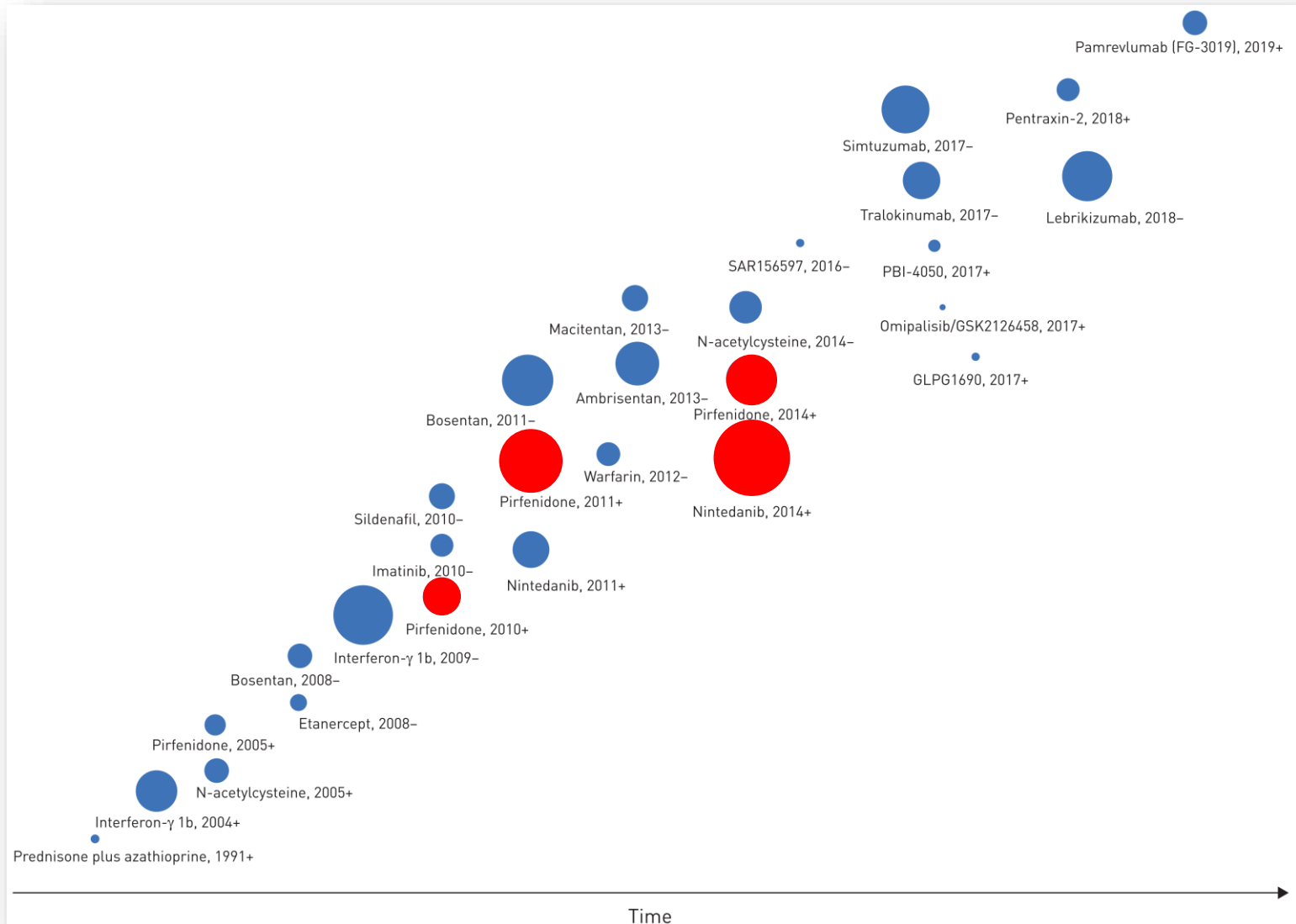


CTD, connective-tissue disease; c/w, consistent with; HP, hypersensitivity pneumonitis; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; MDD, multidisciplinary discussion; PFTs, pulmonary function tests; UIP, usual interstitial pneumonia

IPF-Natural history



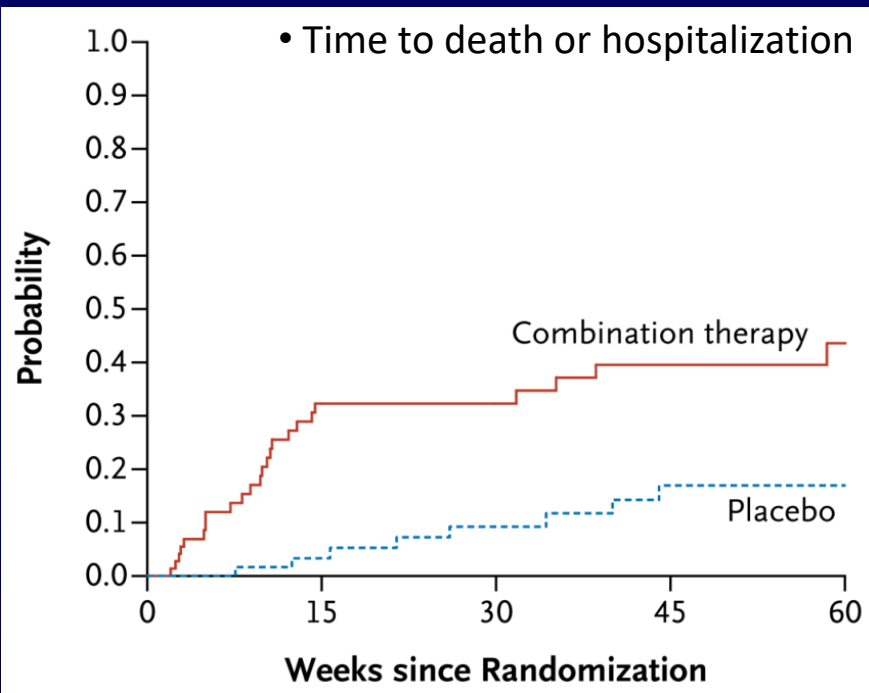
Lessons from clinical trials over the past 10 years



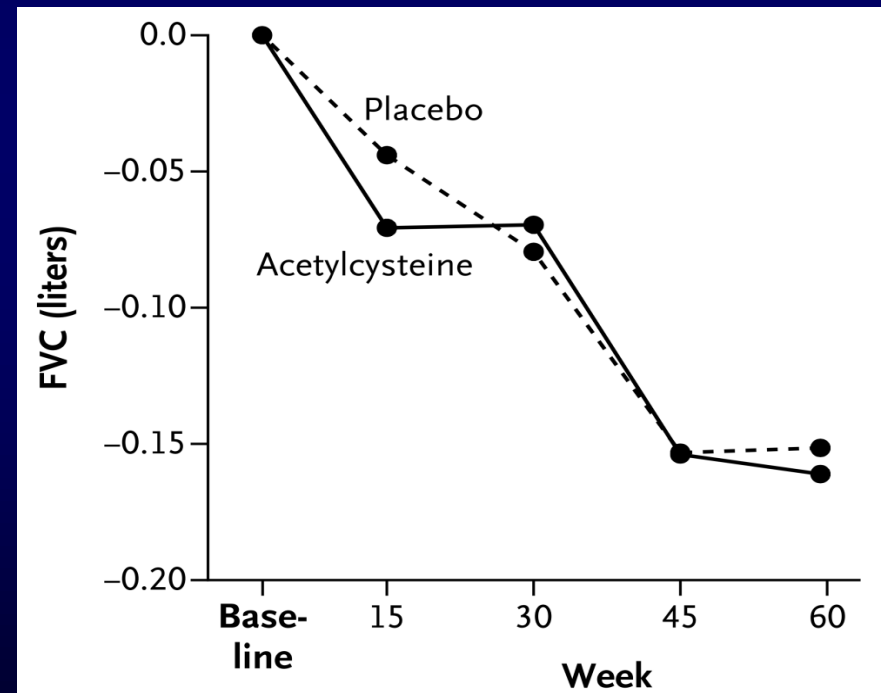
Prednisone, Azathioprine, and N-Acetylcysteine for Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network*

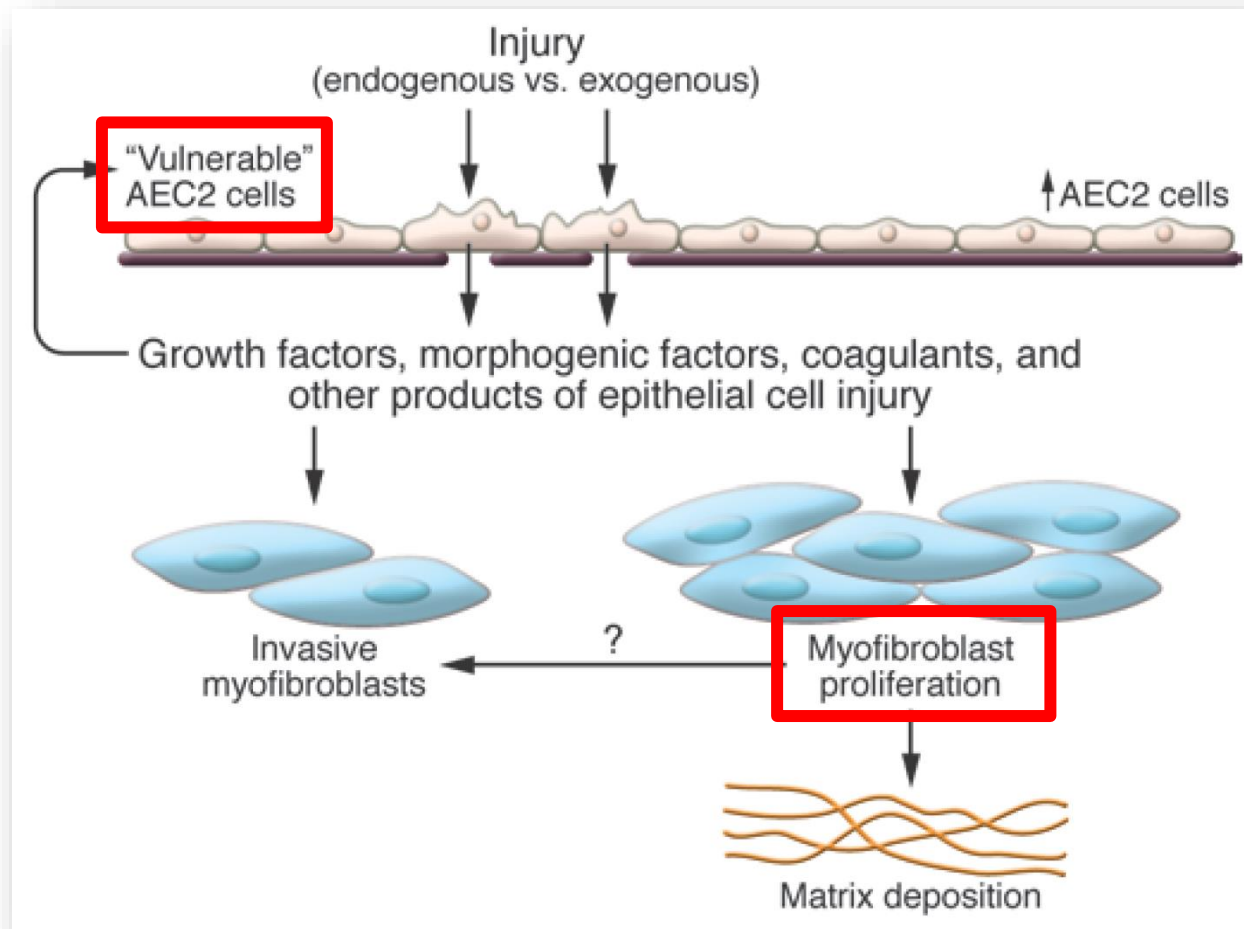
- Triple combination



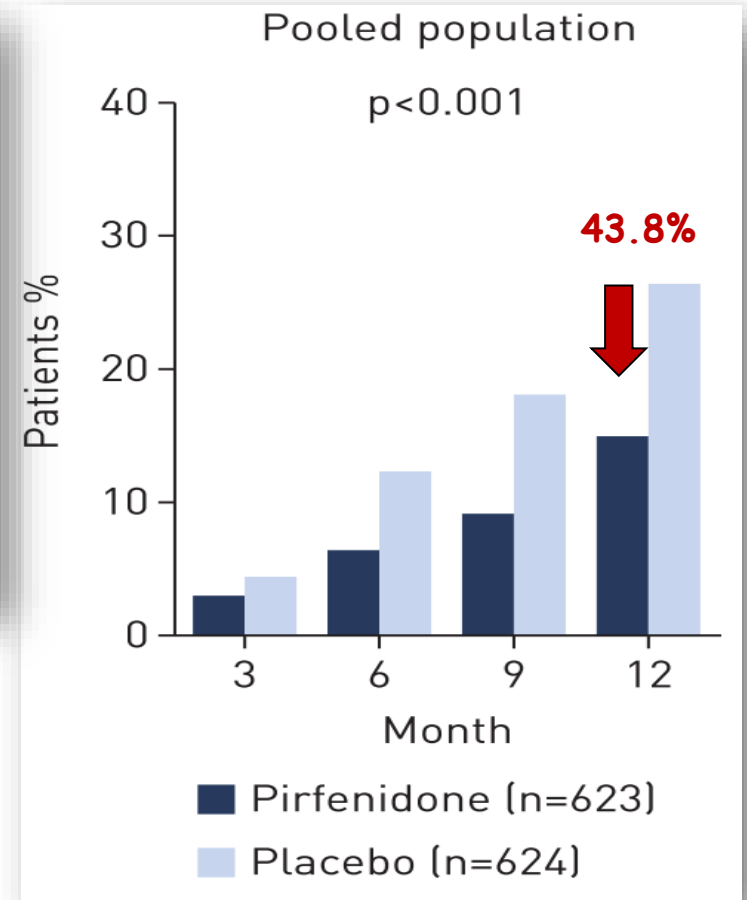
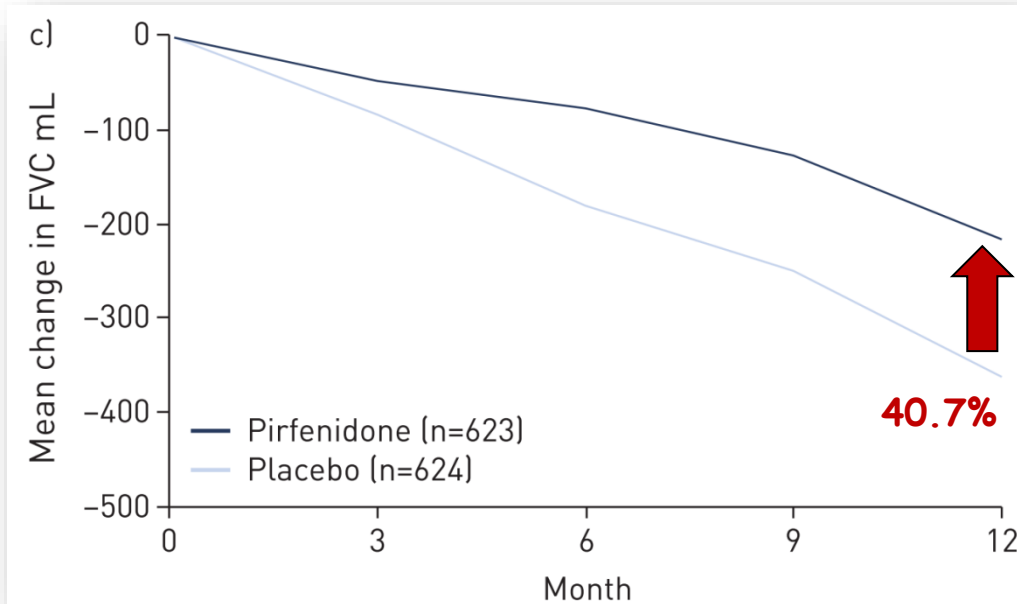
- N-acetylcysteine



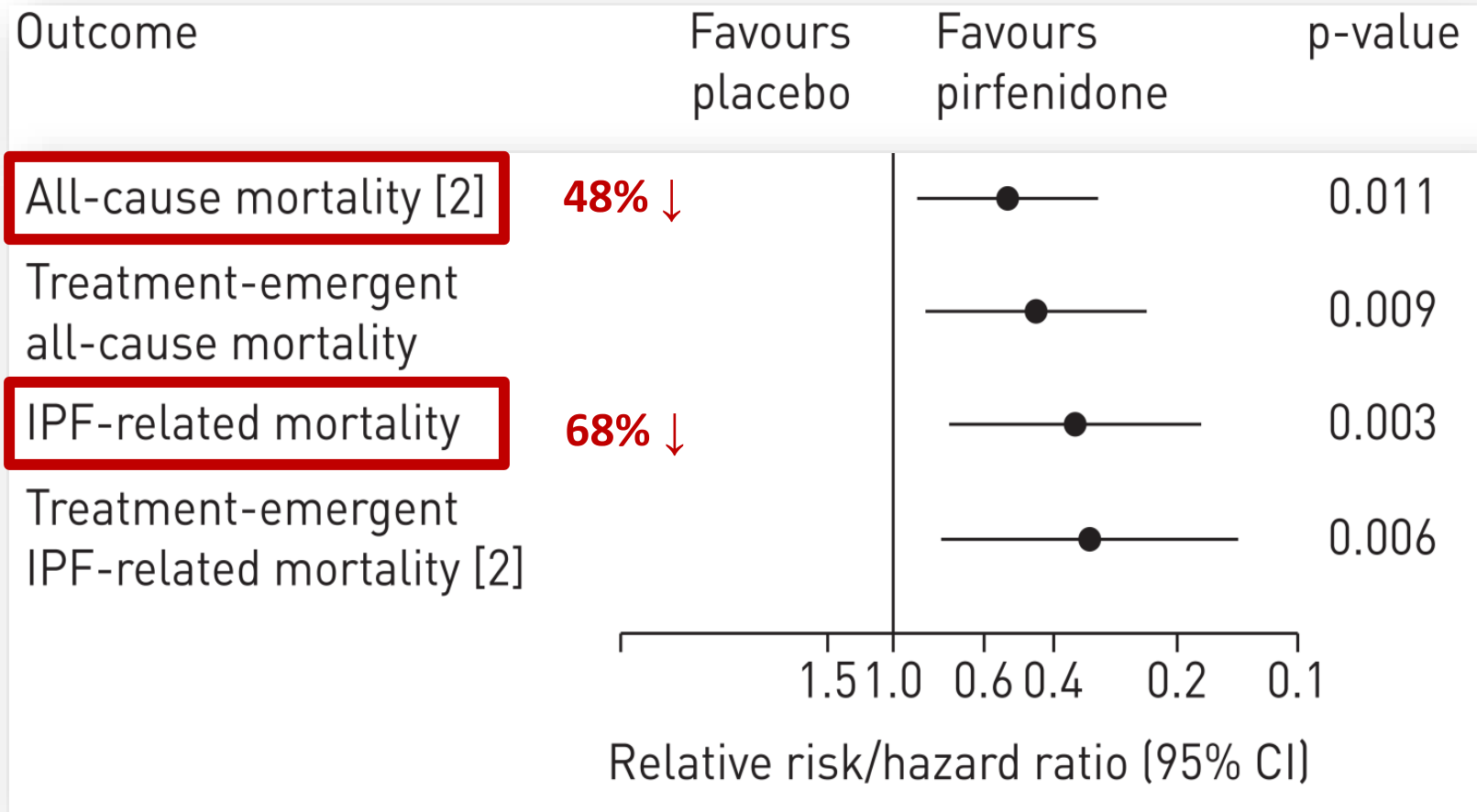
Pathogenesis: abnormal wound healing responses



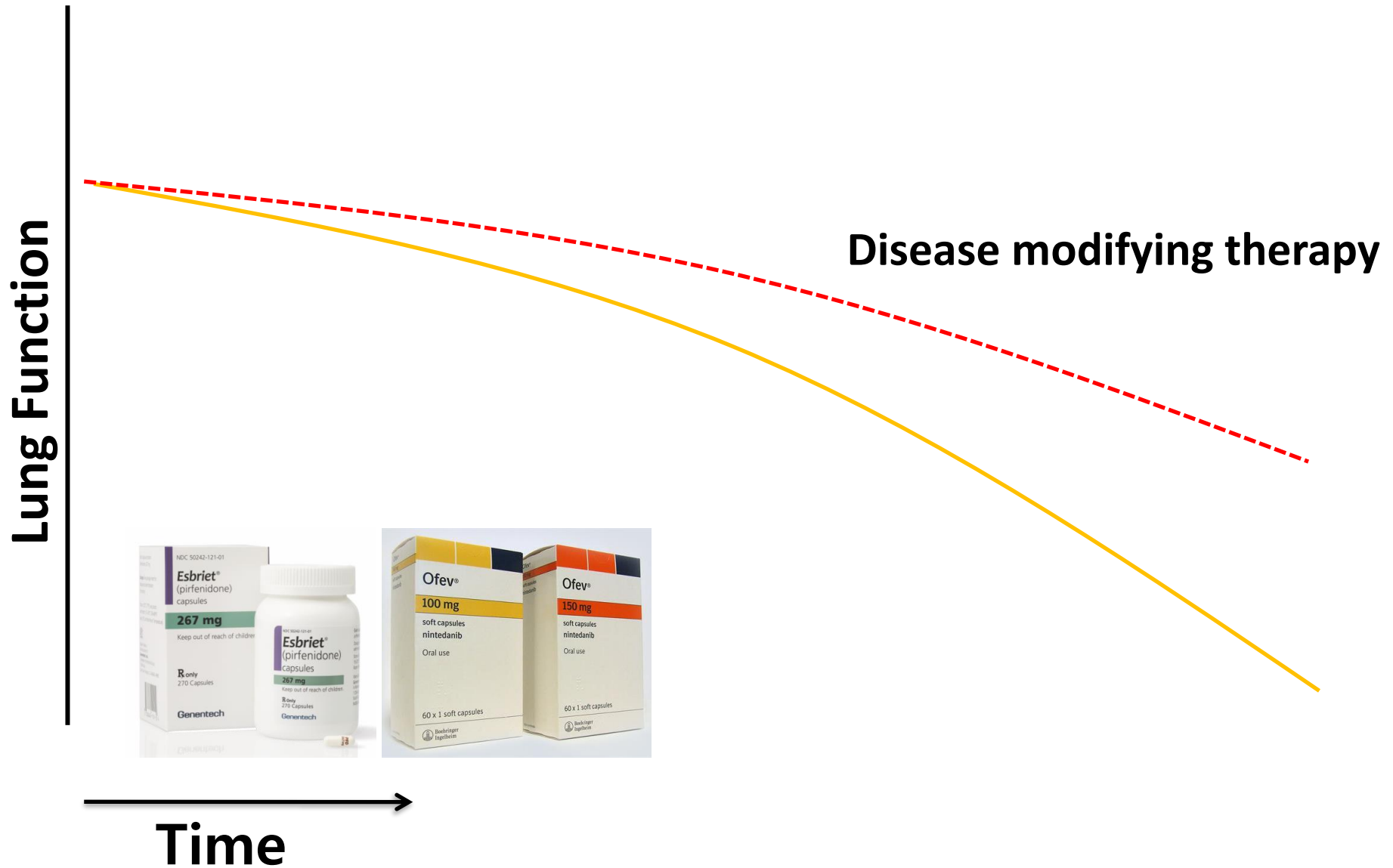
Pirfenidone: Lung function, Progression



Pirfenidone: Survival



Effect of disease modifying therapy on lung function decline



IPF guidelines 2018

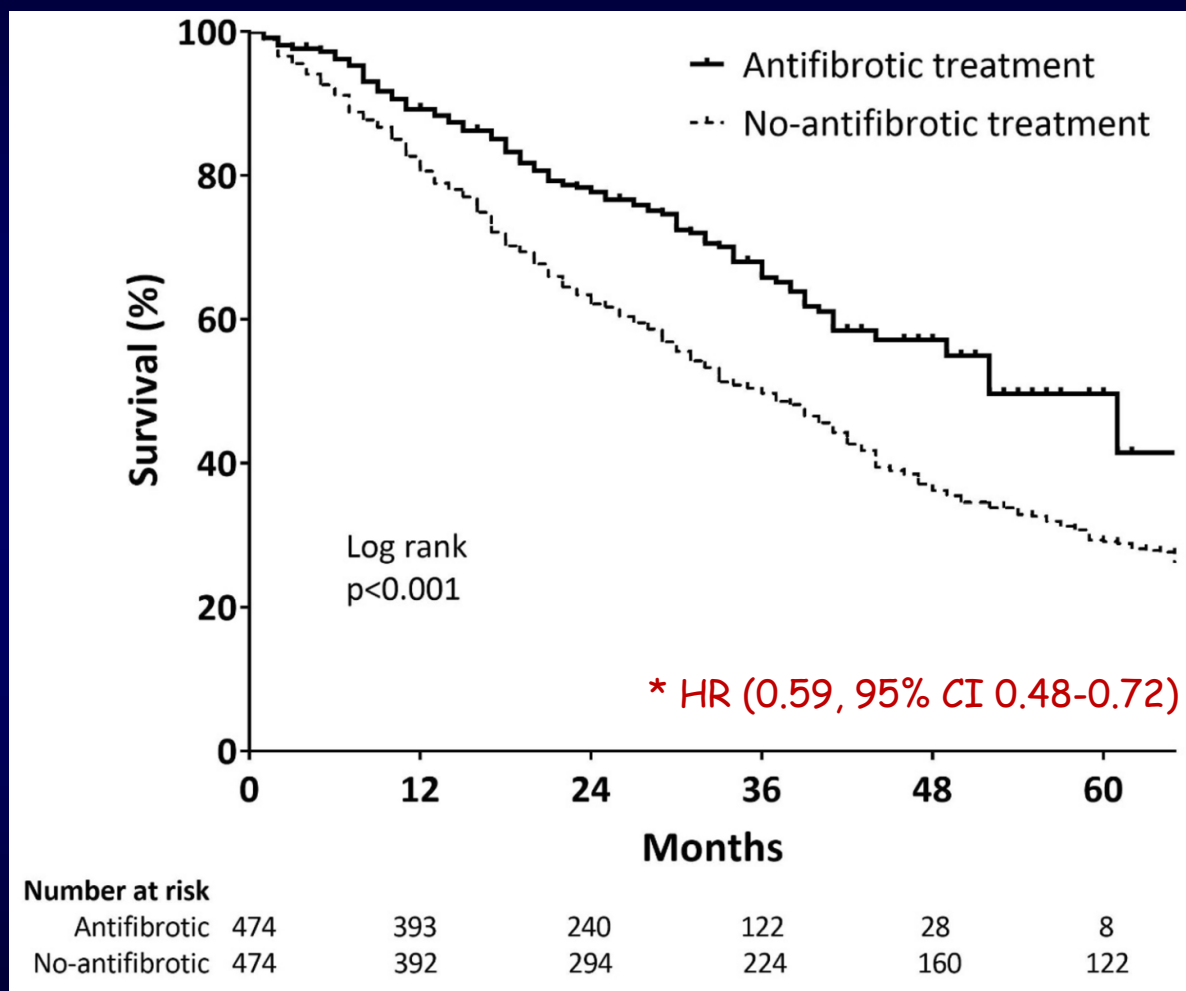
KATRD

2. 특발성폐섬유증

권고사항

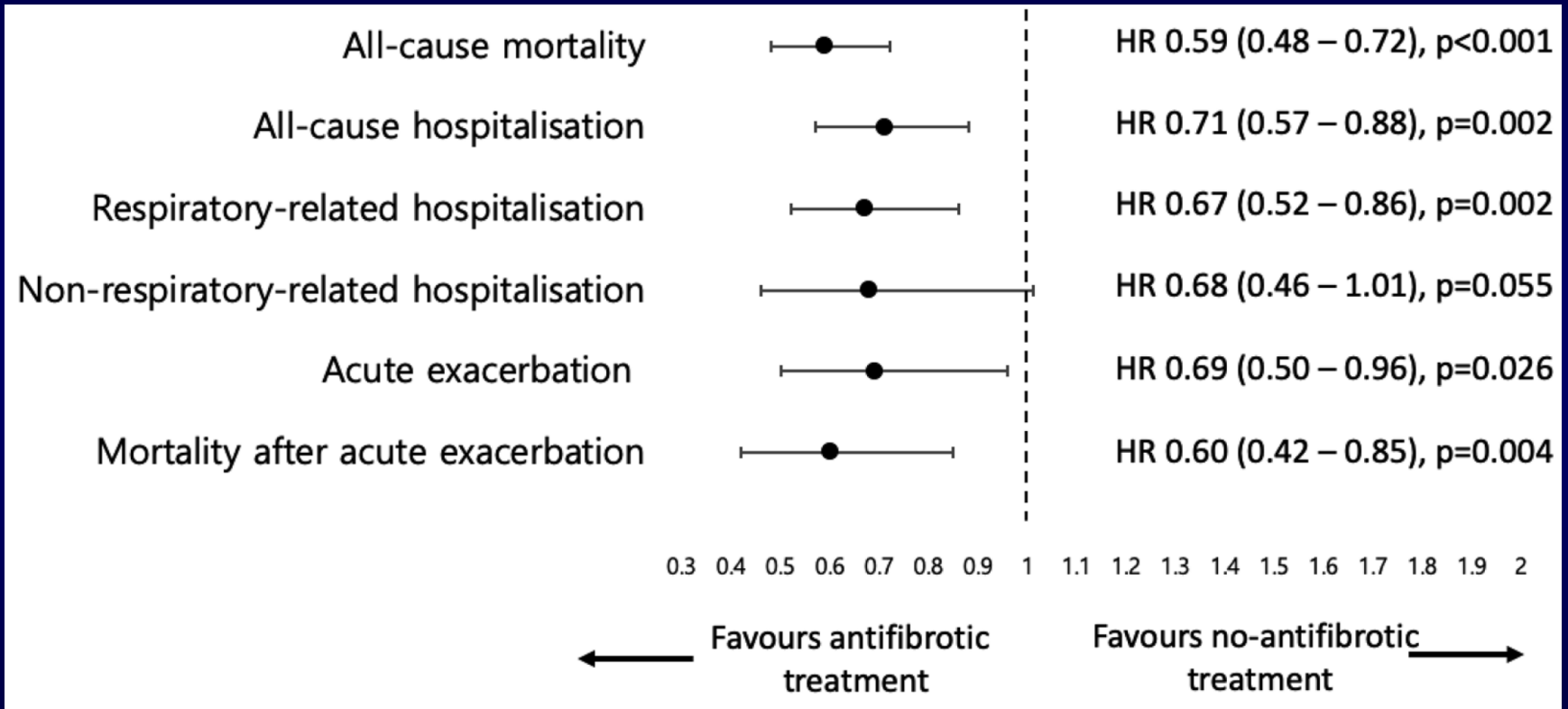
- 특발성폐섬유증(IPF) 환자에서 폐기능(FVC)의 감소로 정의되는 질환의 진행을 늦추기 위하여 Pirfenidone의 사용을 권장한다(근거수준: 보통, 권고수준: 강함)
- 특발성폐섬유증(IPF) 환자에서 폐기능(FVC)의 감소로 정의되는 질환의 진행을 늦추기 위하여 Nintedanib의 사용을 권장한다(근거수준: 보통, 권고수준: 강함)
- 특발성폐섬유증 환자에서 폐이식은 대조군(폐이식 받지 않은 군)에 비해 생존율을 증가시키므로 적절한 시기에 고려한다(근거수준: 보통, 권고수준: 약함)

Pirfenidone: survival in the real-world



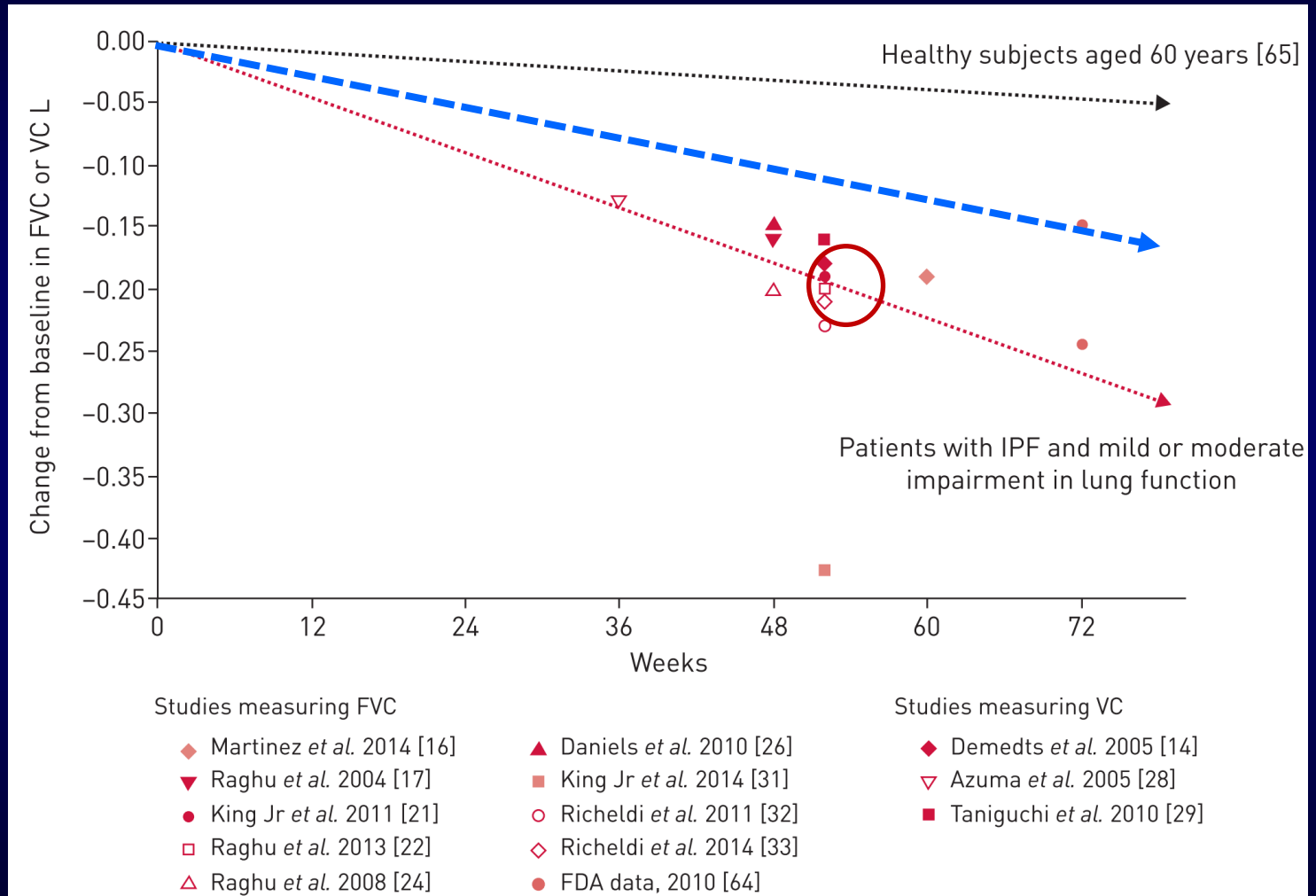
* Asan IPF Cohort (n=1,213; n= 948, propensity score matched)

Pirfenidone: clinical outcomes in the real-world

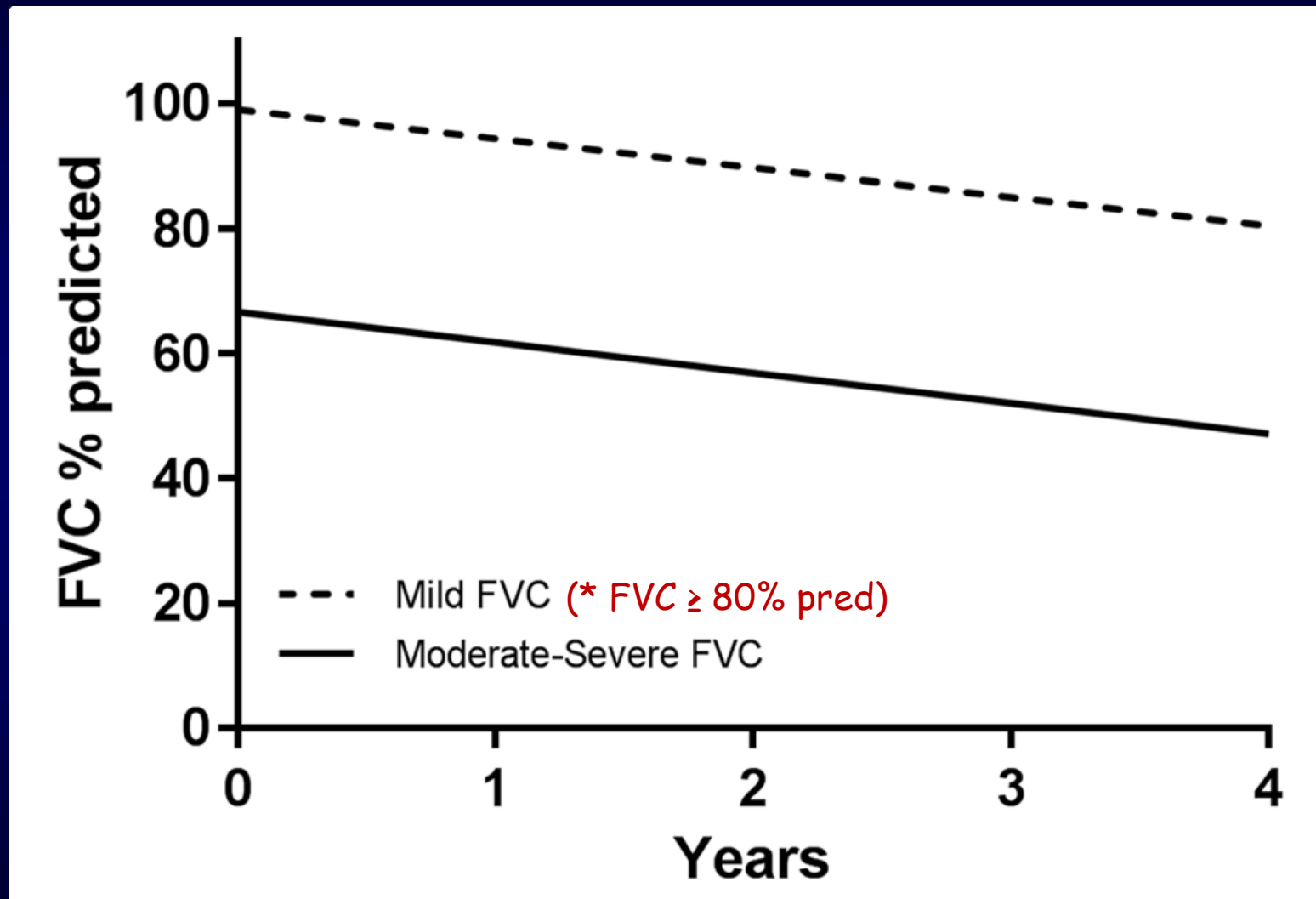


* Asan IPF Cohort (n=1,213; n= 948, propensity score matched)

IPF: natural course of lung function decline in placebo group

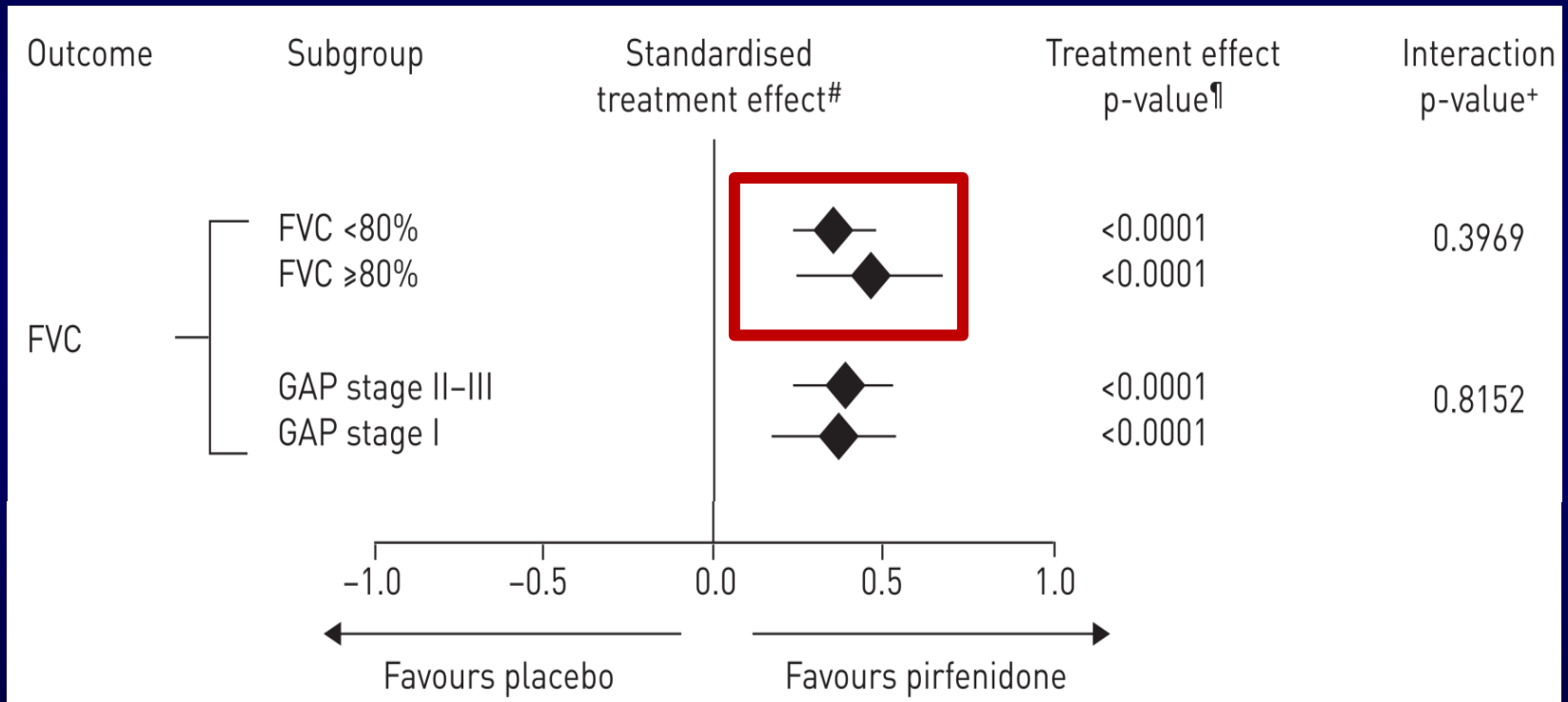


Lung function decline in mild IPF



•Linear mixed model with random intercept and slopes for mild and moderate-severe disease

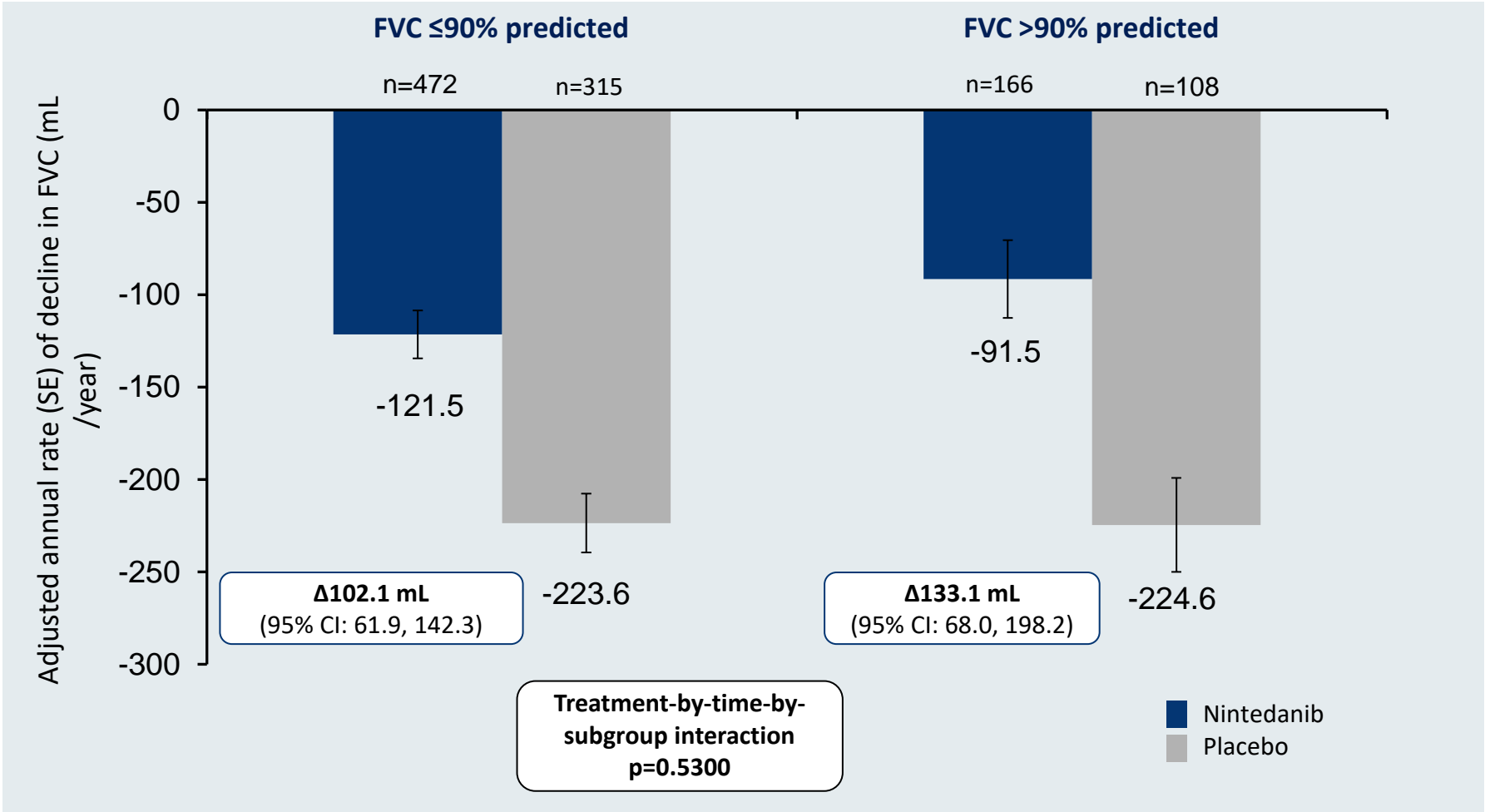
Efficacy of Pirfenidone in mild IPF



* ASCEND + CAPACITY (N=1247)

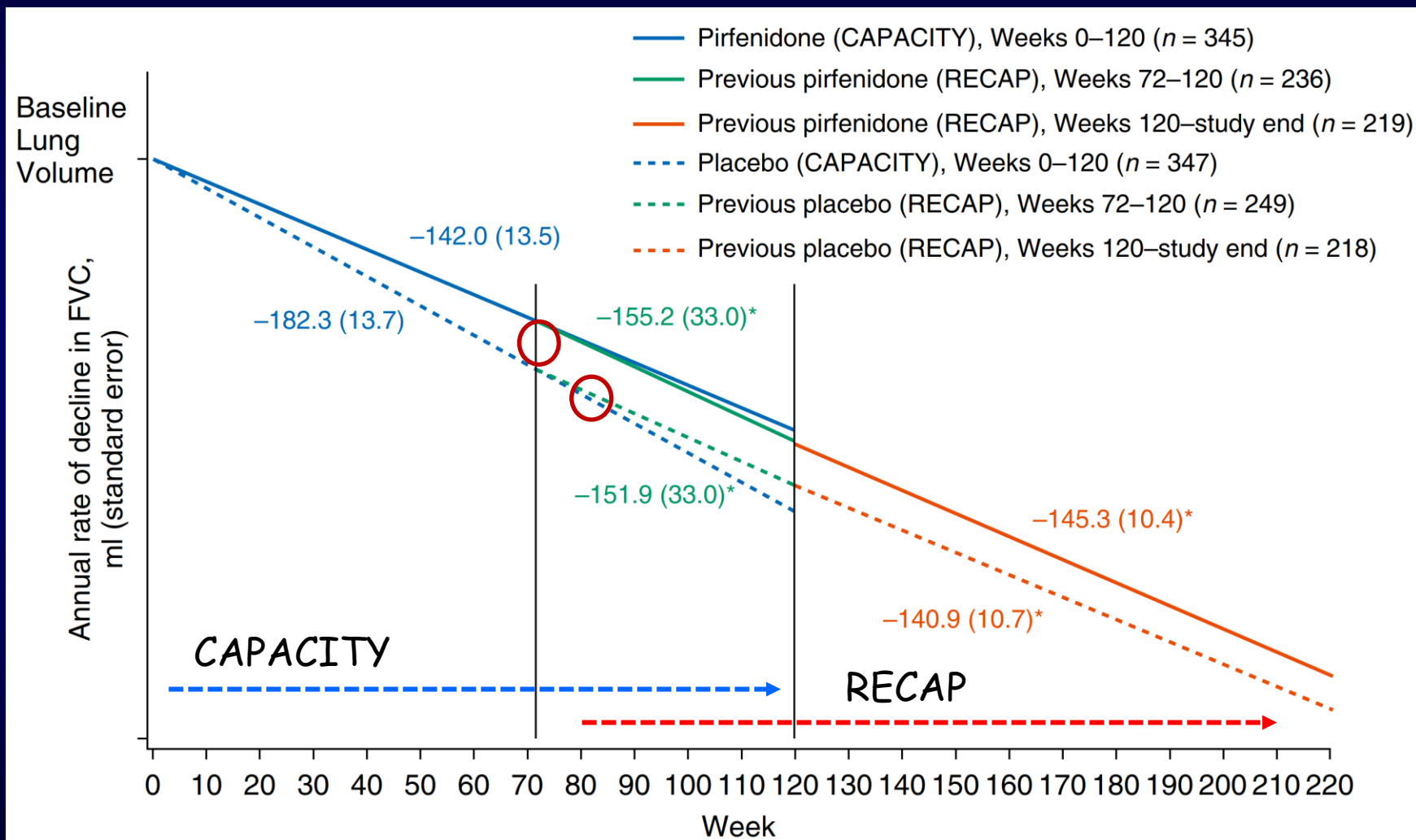
Nintedanib in mild IPF

- Annual rate of decline in FVC



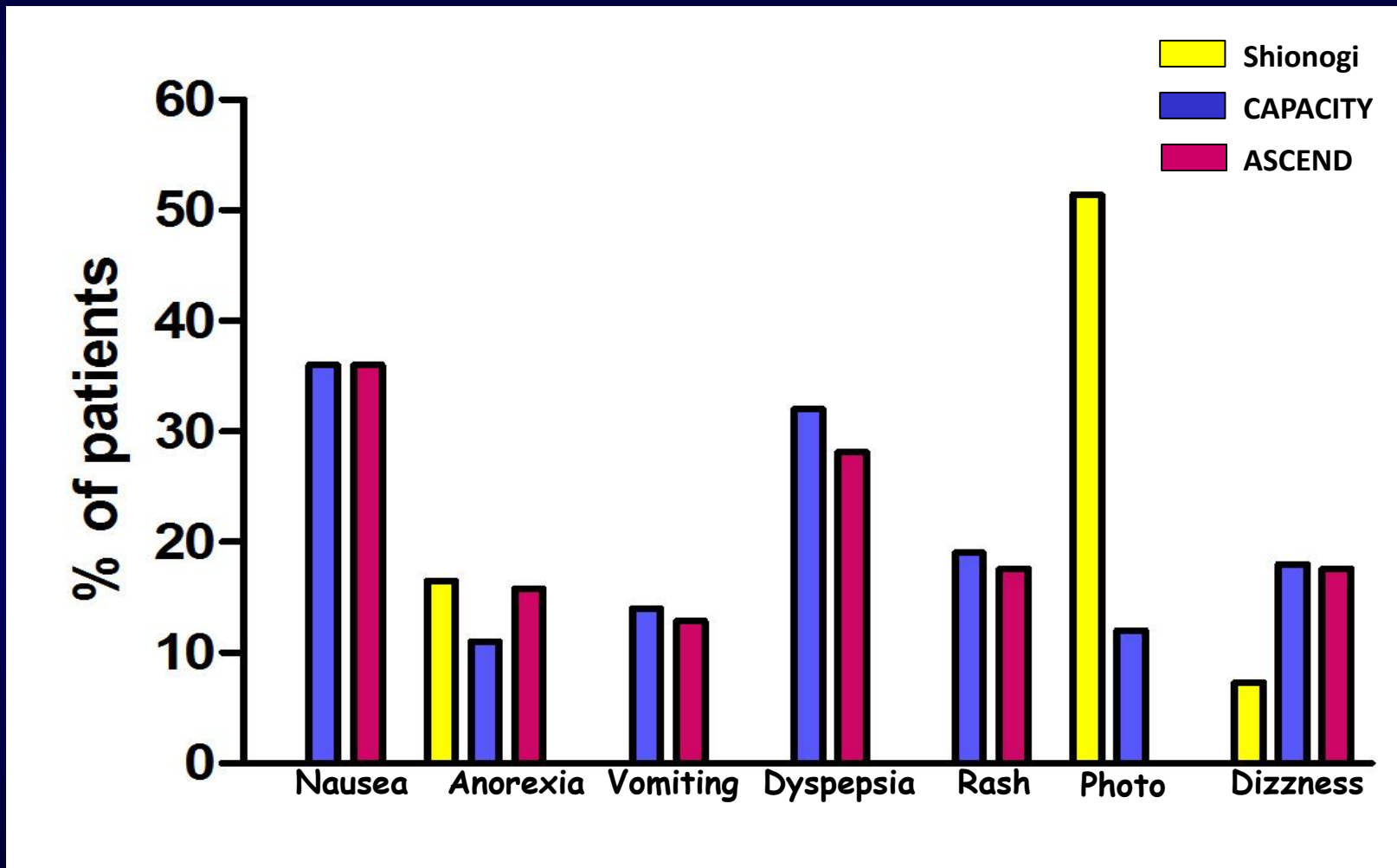
* INPULSIS (N=1061)

FVC decline and timing of pirfenidone initiation



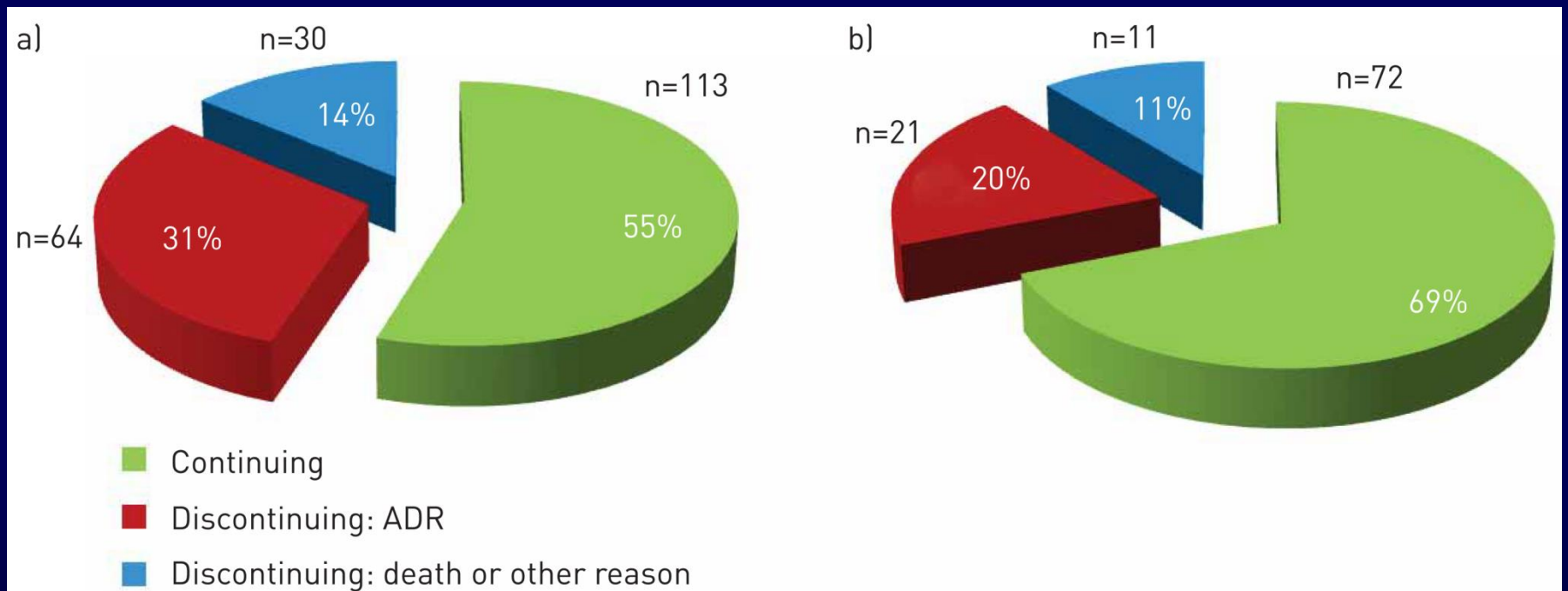
* RECAP (N=485)

Adverse events of pirfenidone



Impact of dose adjustment in case of adverse drug reaction

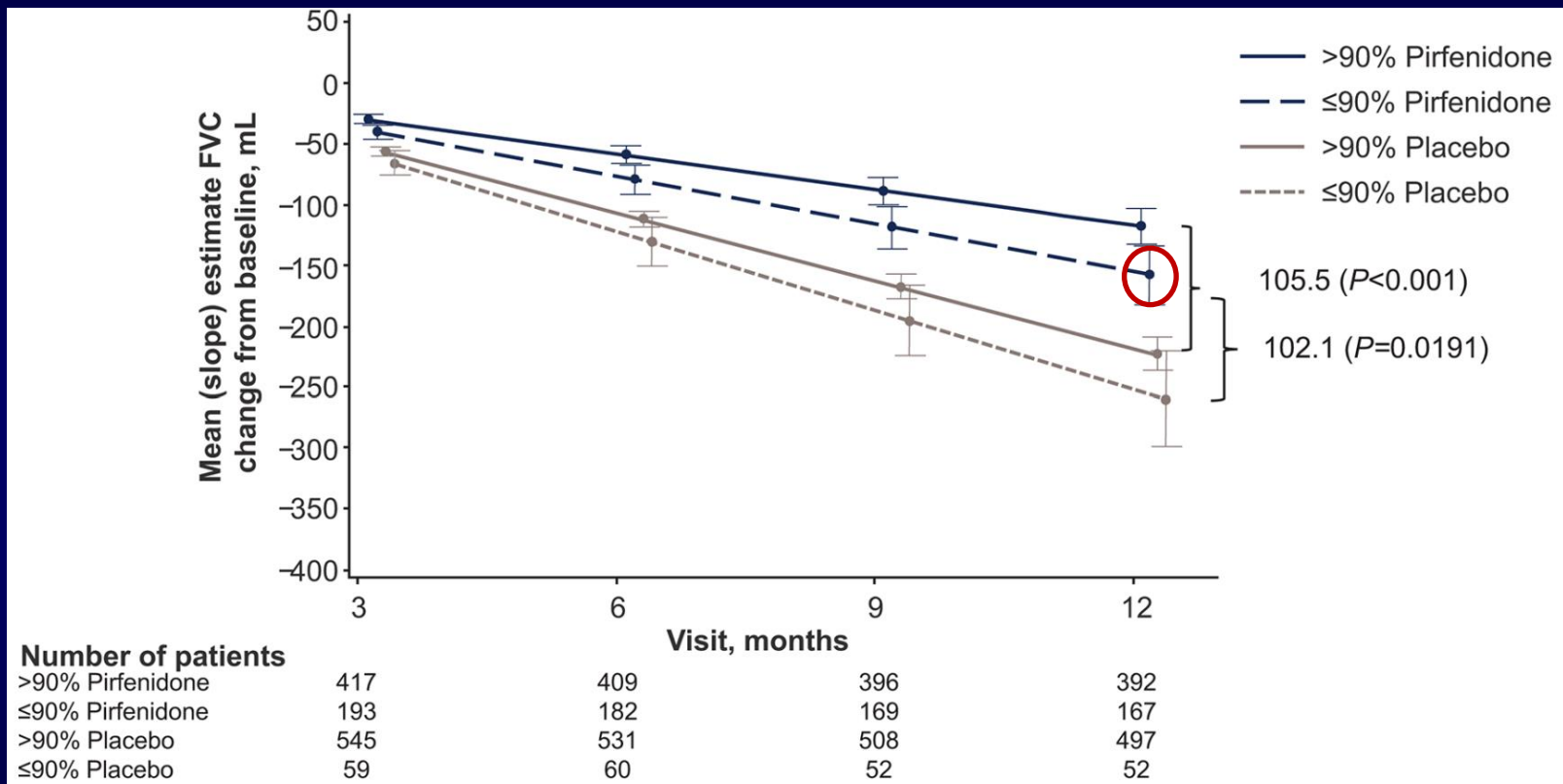
- PASSPORT (prospective observational long term registry for 2 years in Europe)



No dose adjustment

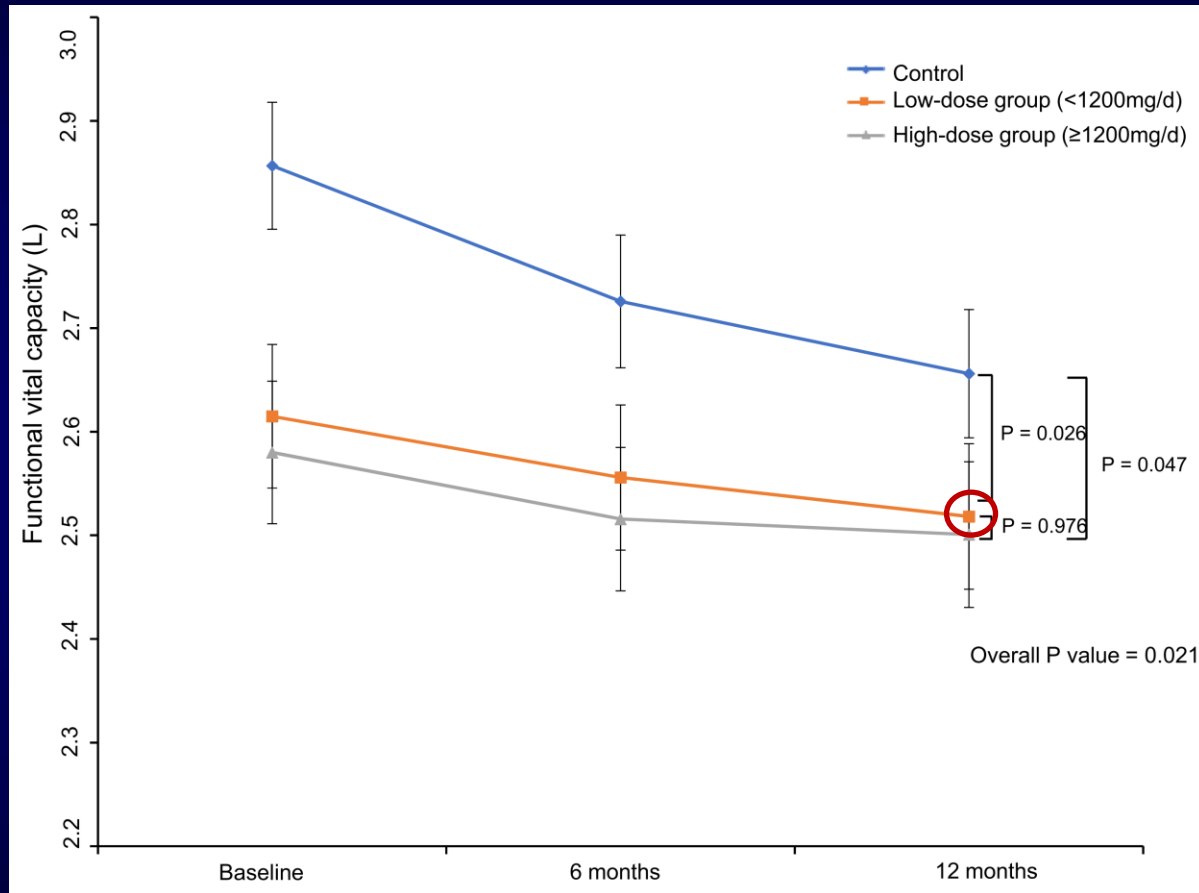
Dose adjustment

FVC change by dose intensity



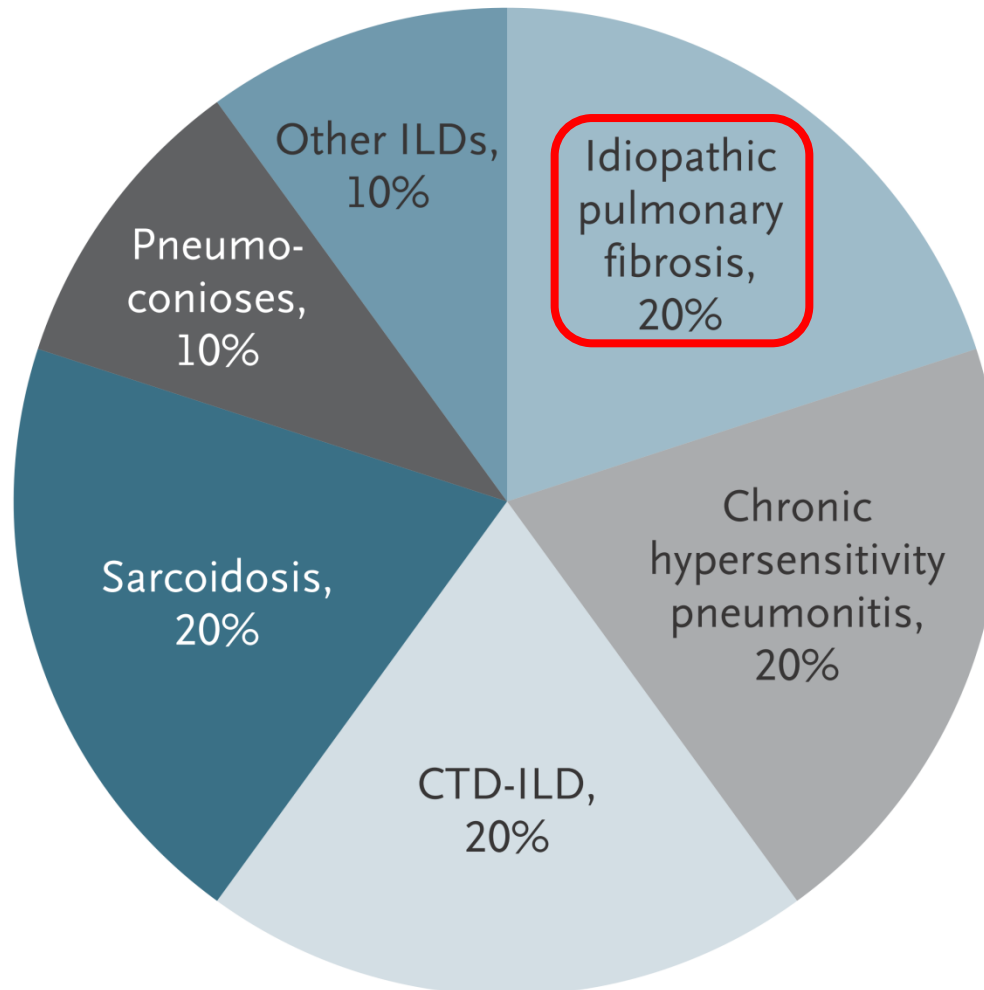
The mean daily actual dose: 2278.4 mg/day (> 90%) and 1575.9 mg/day (≤90%)

FVC change according to pirfenidone dose

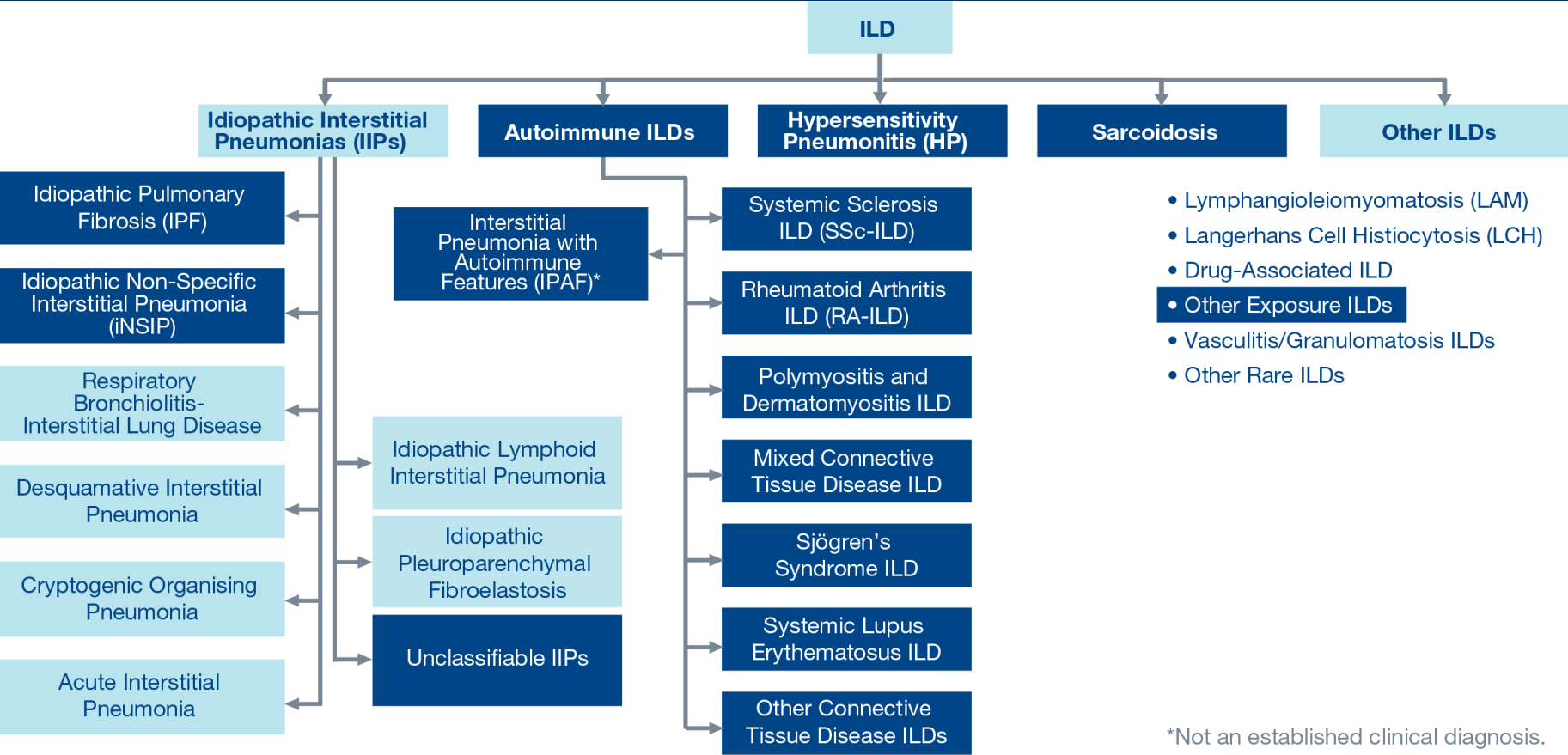


- Adjusted mean change in FVC: -200.7mL (control), -88.4 mL(low), -94.7 mL(high)

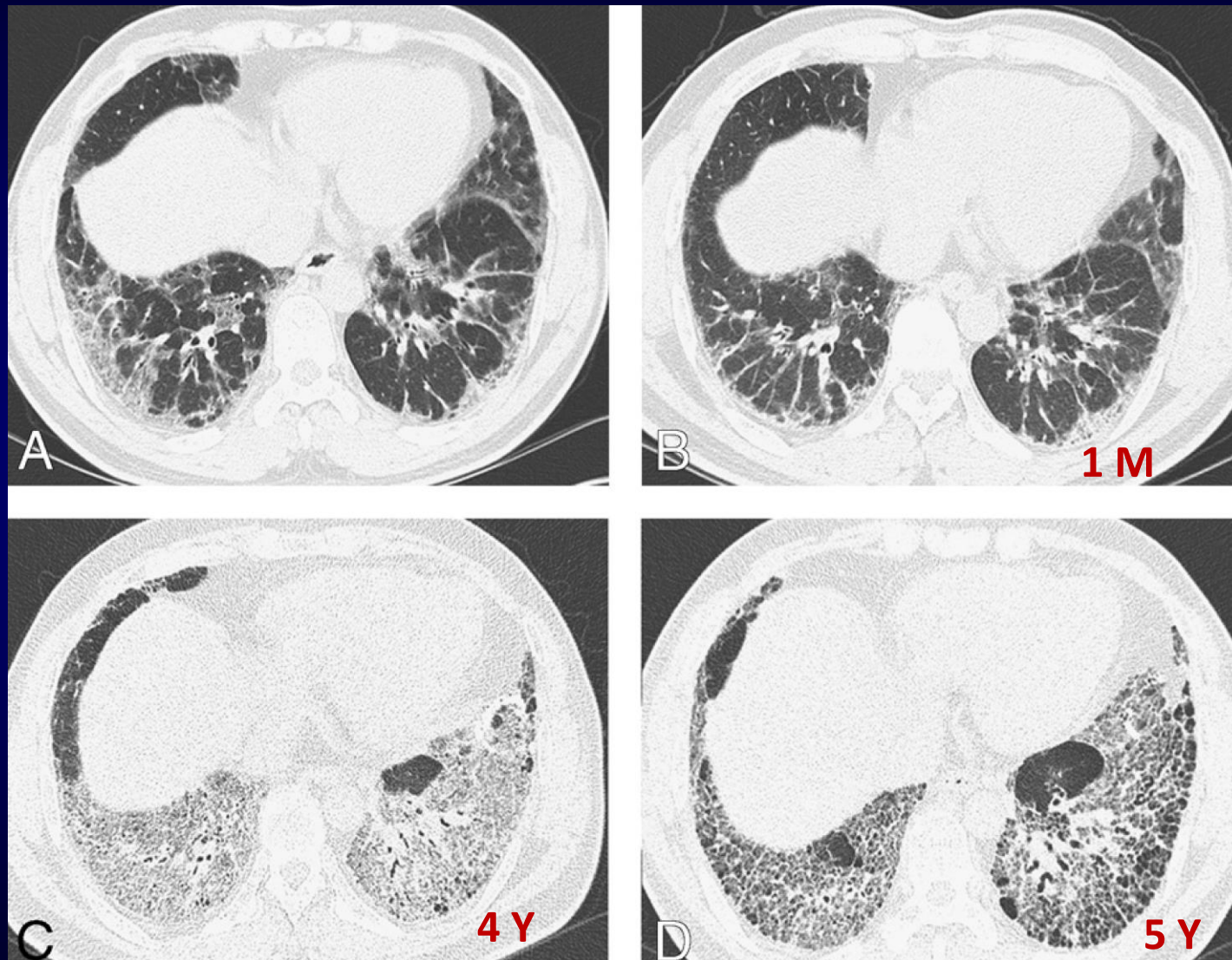
Pulmonary fibrosis is not only IPF: 70-80% have different ILD



Types of ILD likely to have a progressive fibrosing phenotype

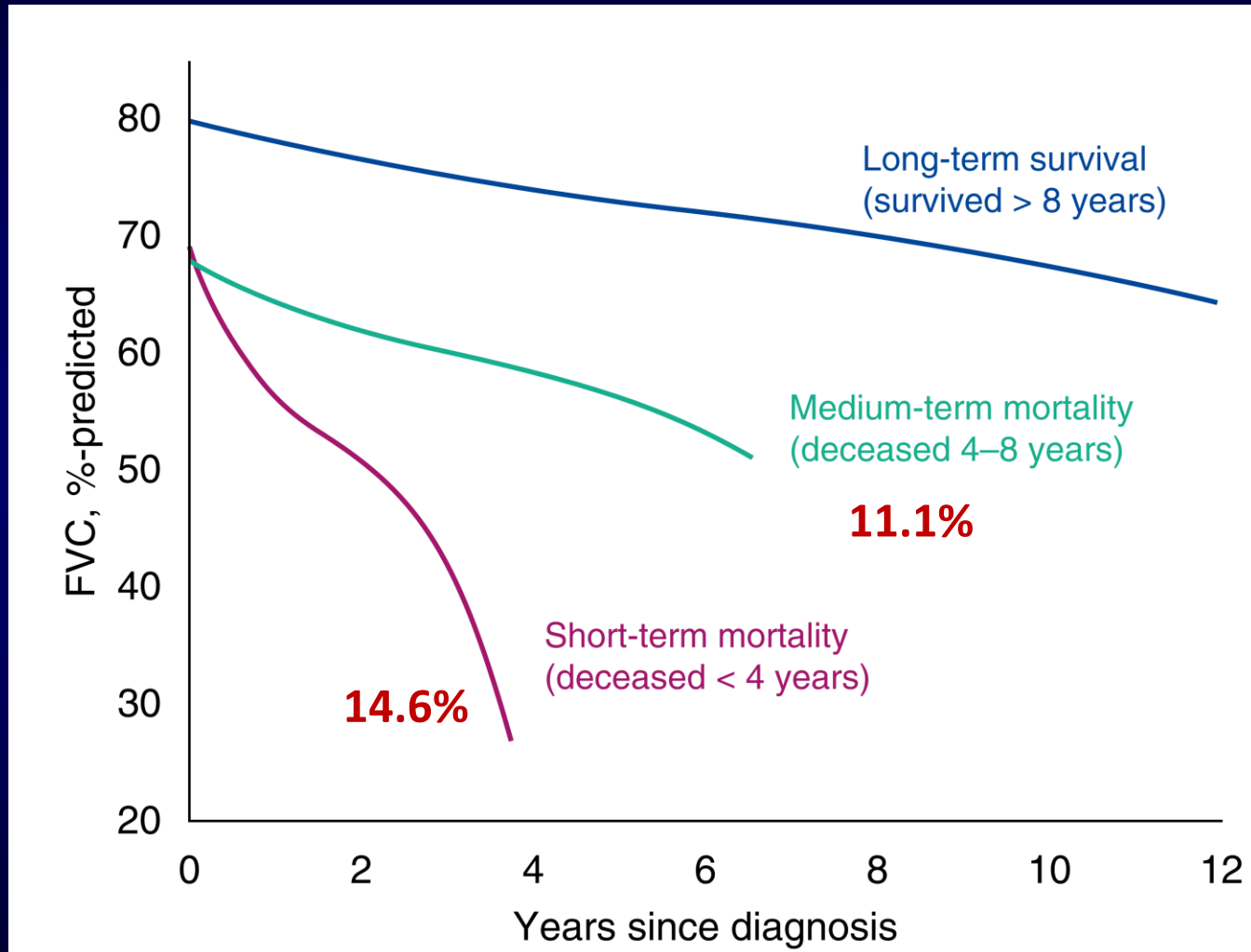


fibrotic NSIP: changes in HRCT



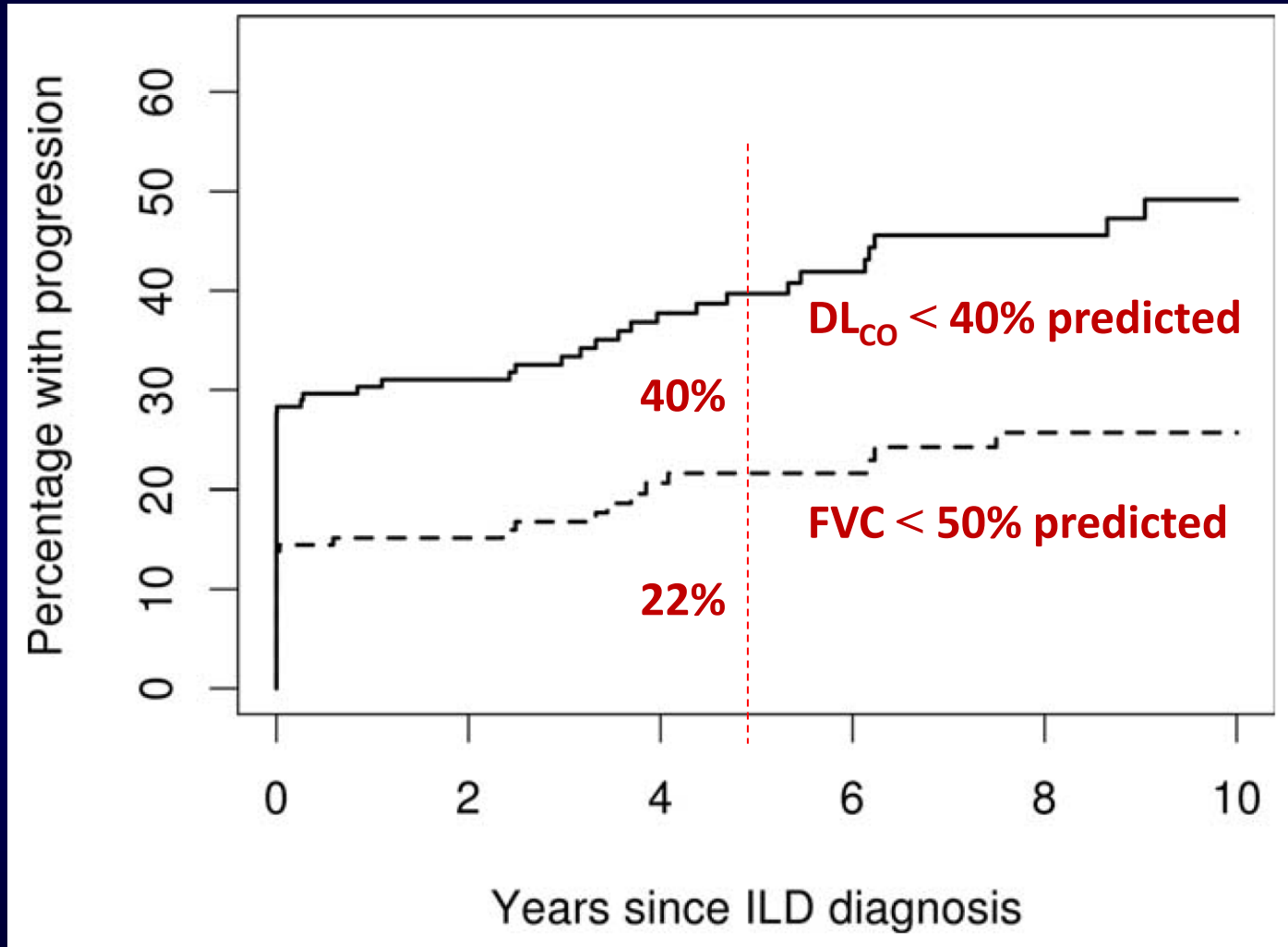
- fibrotic progression: 28% (n=61; Asan iNSIP cohort)

Progression of FVC in SSc-ILD



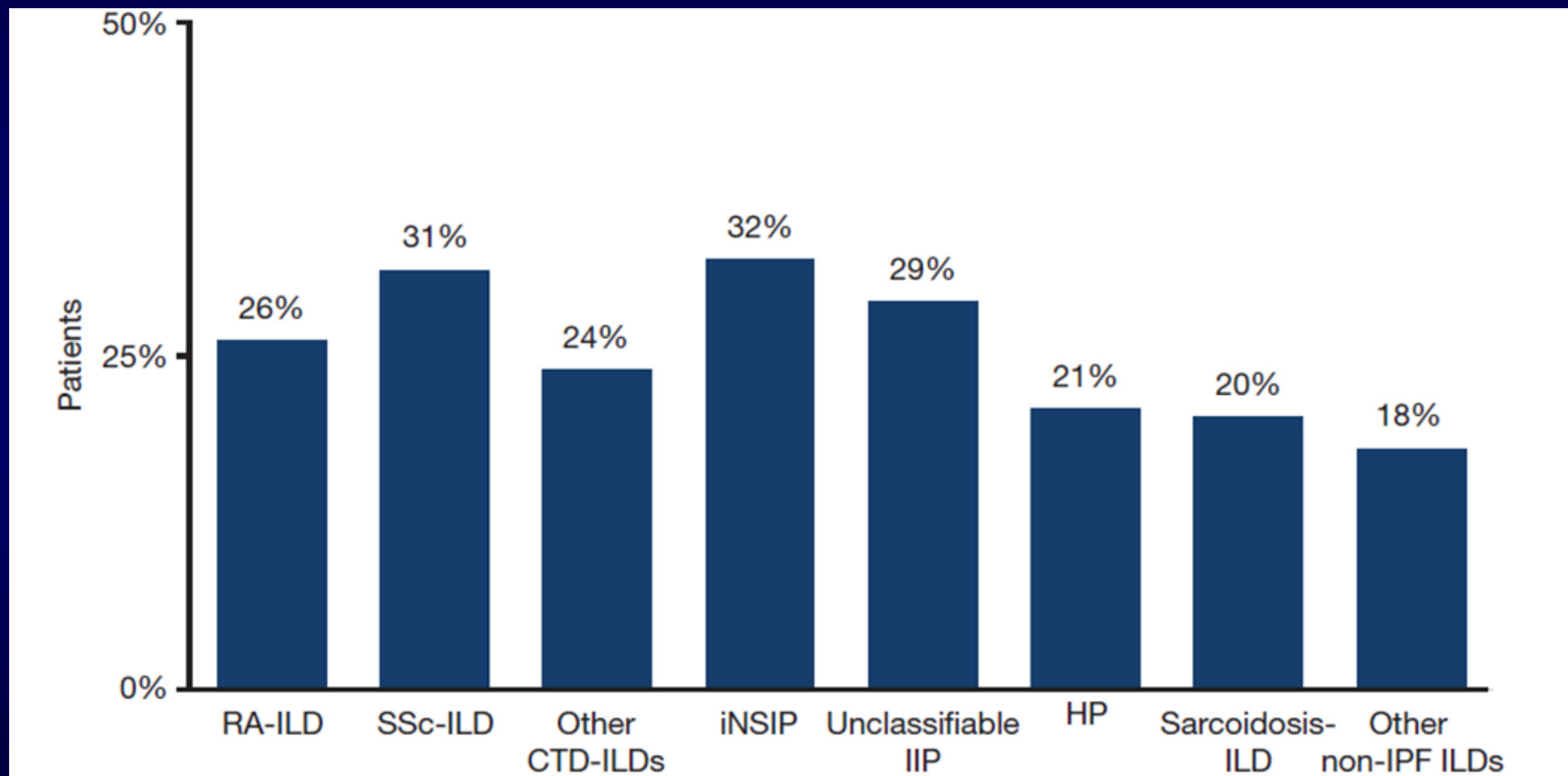
• Univ. of British Columbia SSc-ILD cohort (n=171)

Progression of RA-ILD



- Mayo clinic RA-ILD cohort (n=167), median follow-up: 3.3 years (0.01-14.8 yrs)

Percentage of patients with non-IPF ILDs who develop a progressive fibrosing phenotype



- based on online physician survey (n=486)

IIP: classification according to disease behavior

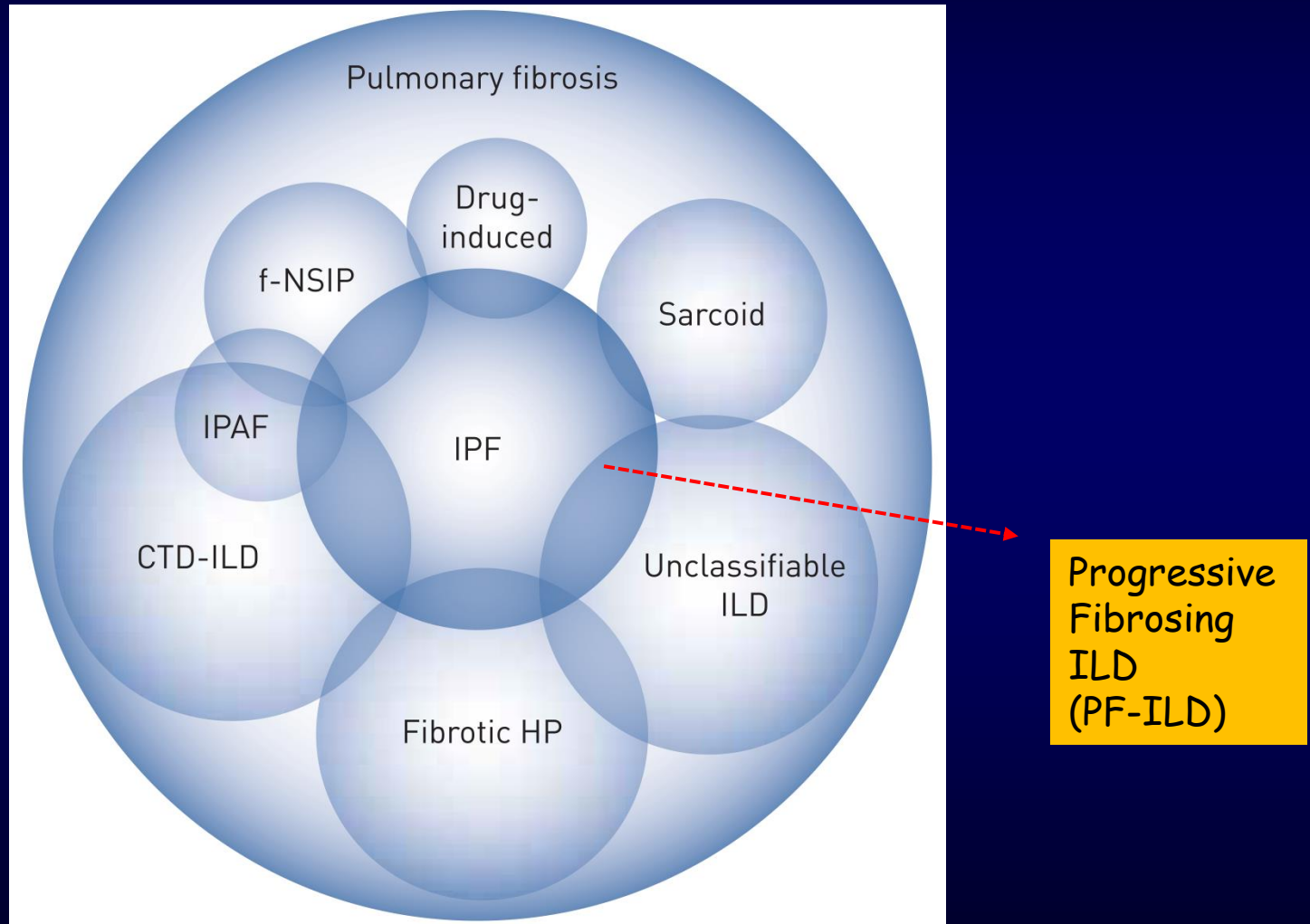
**reversible &
self-limited**



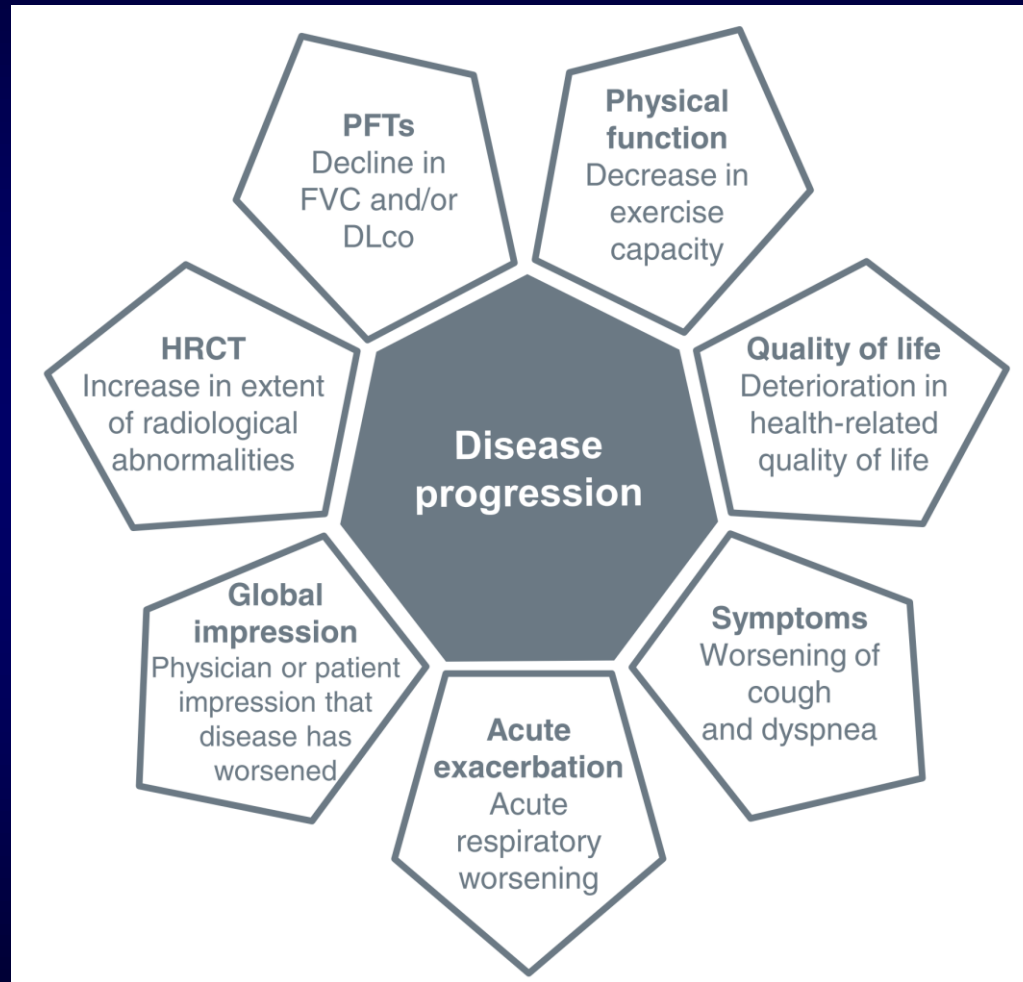
**irreversible &
progressive**

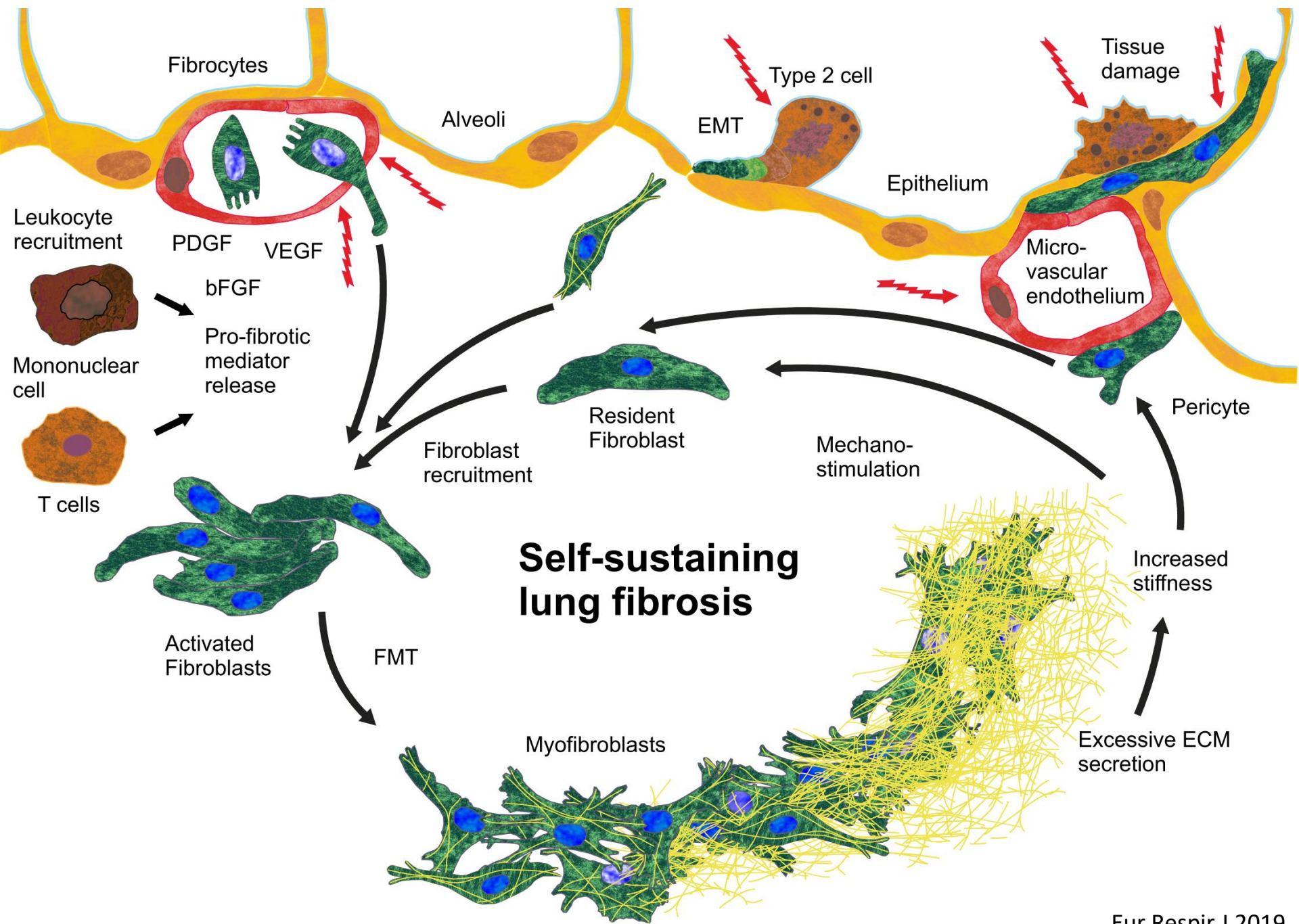
CLINICAL BEHAVIOR	TREATMENT GOAL	MONITORING STRATEGY
Reversible and self-limited (e.g. RB-ILD)	Remove possible cause	Short-term (3-6 months) observation to confirm disease regression
Reversible with risk of progression (e.g. some NSIP, COP, DIP)	Initially for a response and then rationalize longer term therapy	Short-term observation to confirm response: long-term observation to ensure gains are preserved
Stable with residual disease (e.g. some NSIP)	Maintain status	Long-term observation to assess disease course
Progressive, irreversible with potential for stabilization (e.g. some NSIP)	To stabilize	Long-term (3-6 months) observation to assess disease course
Progressive, irreversible despite therapy (e.g. some NSIP, IPF)	To slow progression	Long-term observation to assess disease course and need for transplant or effective palliation

The overlap in longitudinal disease behavior between IPF and other ILDs



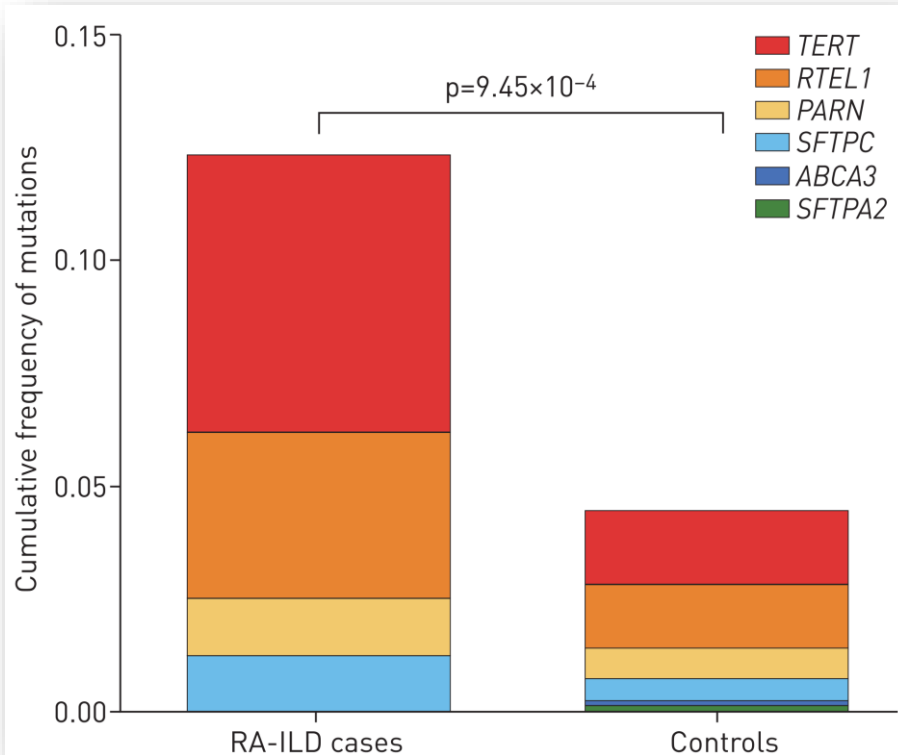
Factors that reflect progression of ILD



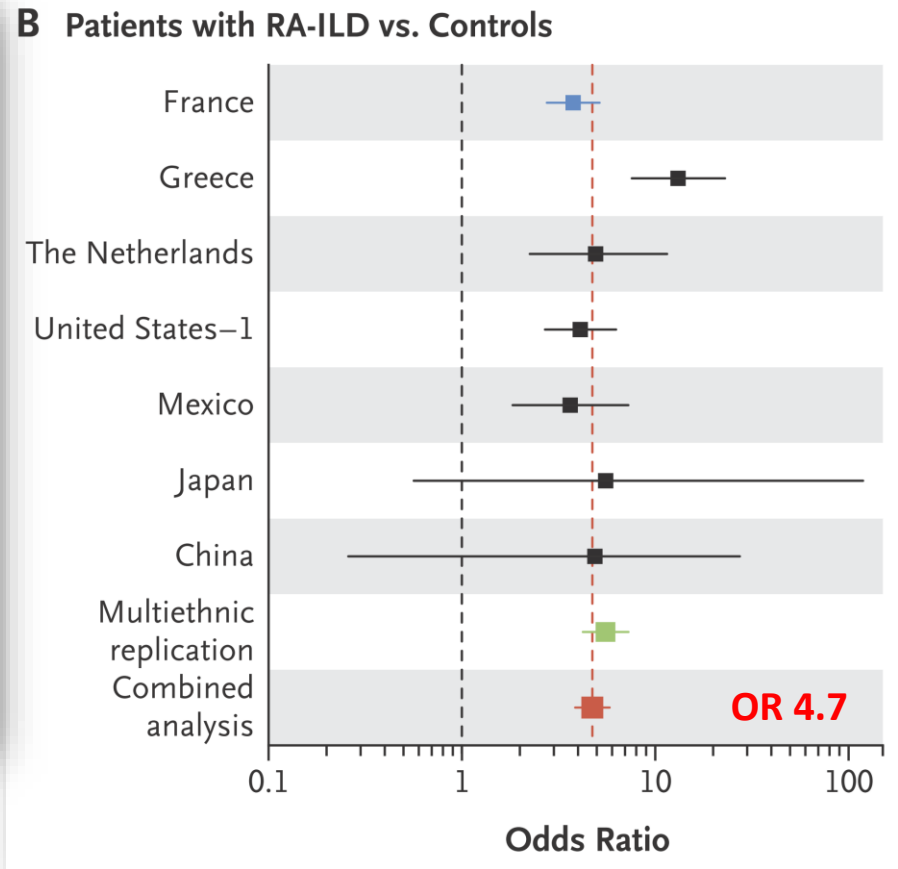


Shared genetic predisposition in RA-ILD and IPF

- Excess of *TERT*, *RTEL1* and *PARN*



- *MUC5B* rs35705950 promoter variant



The NEW ENGLAND JOURNAL *of* MEDICINE

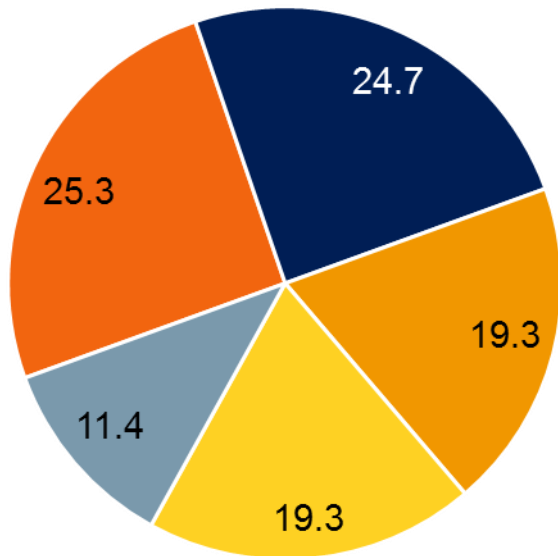
ORIGINAL ARTICLE

Nintedanib in Progressive Fibrosing Interstitial Lung Diseases

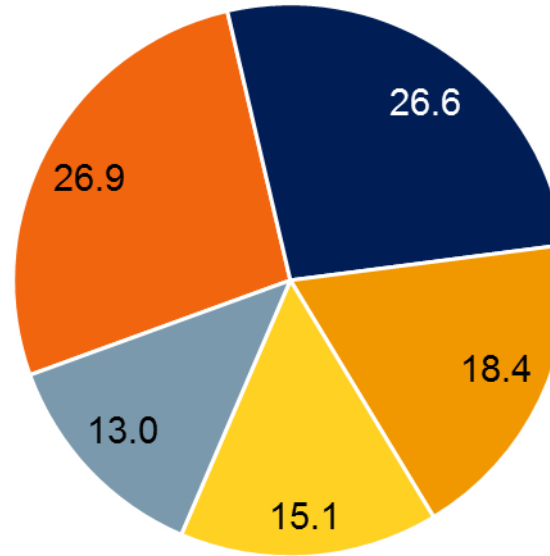
K.R. Flaherty, A.U. Wells, V. Cottin, A. Devaraj, S.L.F. Walsh, Y. Inoue, L. Richeldi,
M. Kolb, K. Tetzlaff, S. Stowasser, C. Coeck, E. Clerisme-Beaty, B. Rosenstock,
M. Quaresma, T. Haeufel, R.-G. Goeldner, R. Schlenker-Herceg, and K.K. Brown,
for the INBUILD Trial Investigators*

Clinical ILD diagnoses

Nintedanib (n=332)



Placebo (n=331)



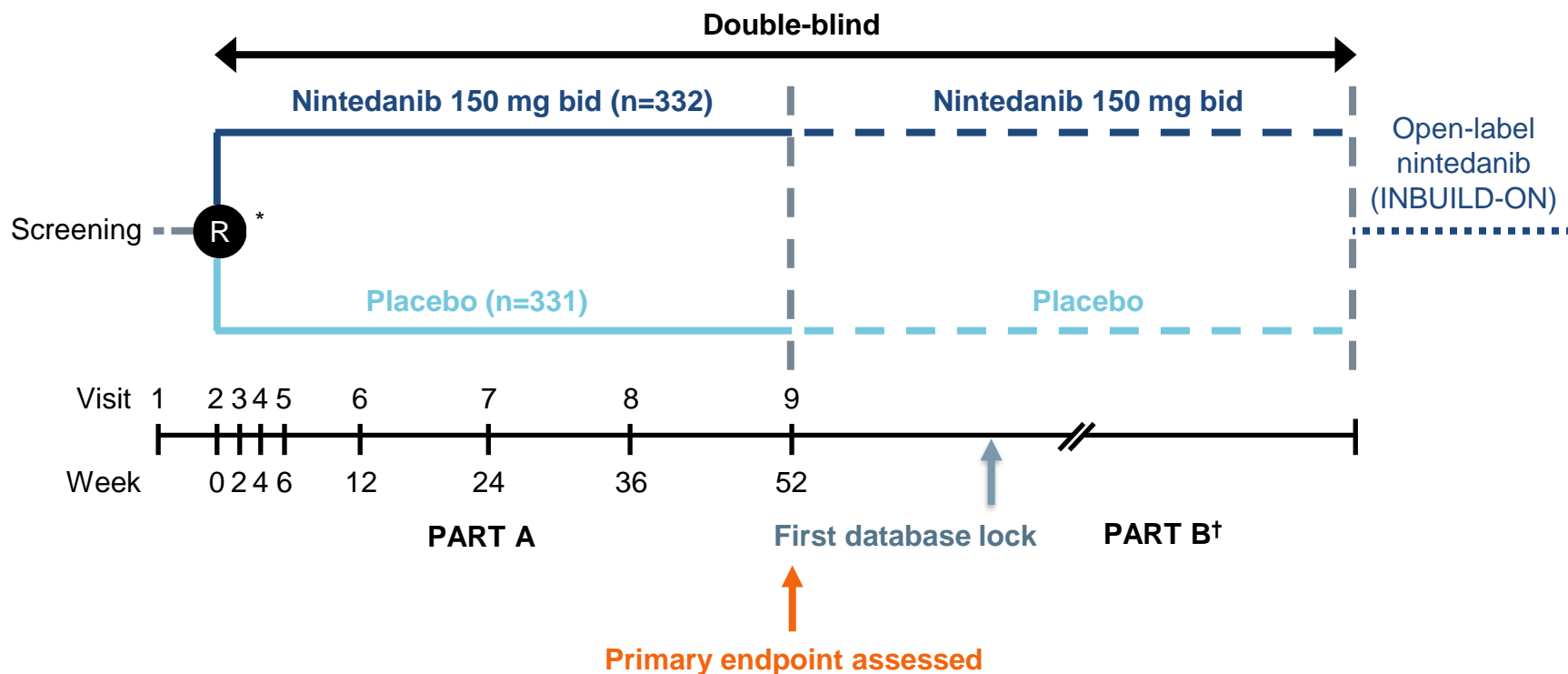
- Hypersensitivity pneumonitis
- Autoimmune ILDs*
- Idiopathic non-specific interstitial pneumonia
- Unclassifiable IIP
- Other ILDs†

* 89 had RA-ILD, 39 had SSc-ILD, 19 had MCTD-ILD, 23 had other autoimmune ILDs

Inclusion criteria

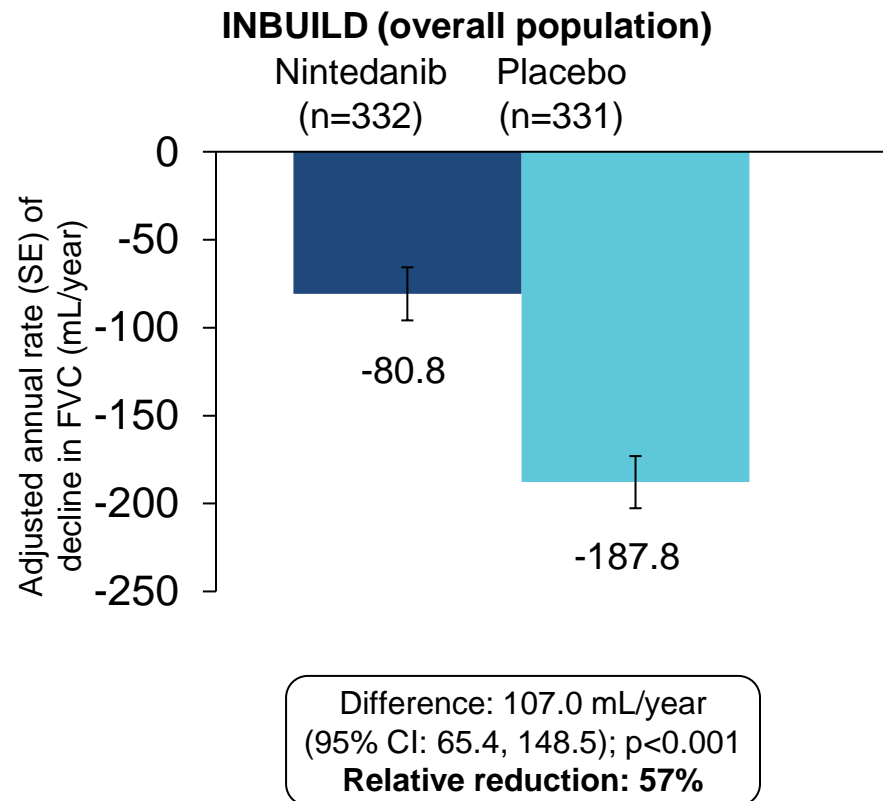
Diagnosis	Physician-diagnosed ILD other than IPF
Fibrosis	Extent of fibrosis > 10% on HRCT
Lung function	FVC \geq 45% predicted, Dlco 30-80% predicted
Progression	\geq 1 of the following criteria in <u>the 24 months</u> before screening, <u>despite</u> standard treatment
	- Relative decline in FVC \geq 10%
	- Relative decline in FVC \geq 5-<10% and worsened respiratory symptoms or increased extent of fibrosis on HRCT
	- Worsened respiratory symptoms and increased extent of fibrosis on HRCT

INBUILD trial: design

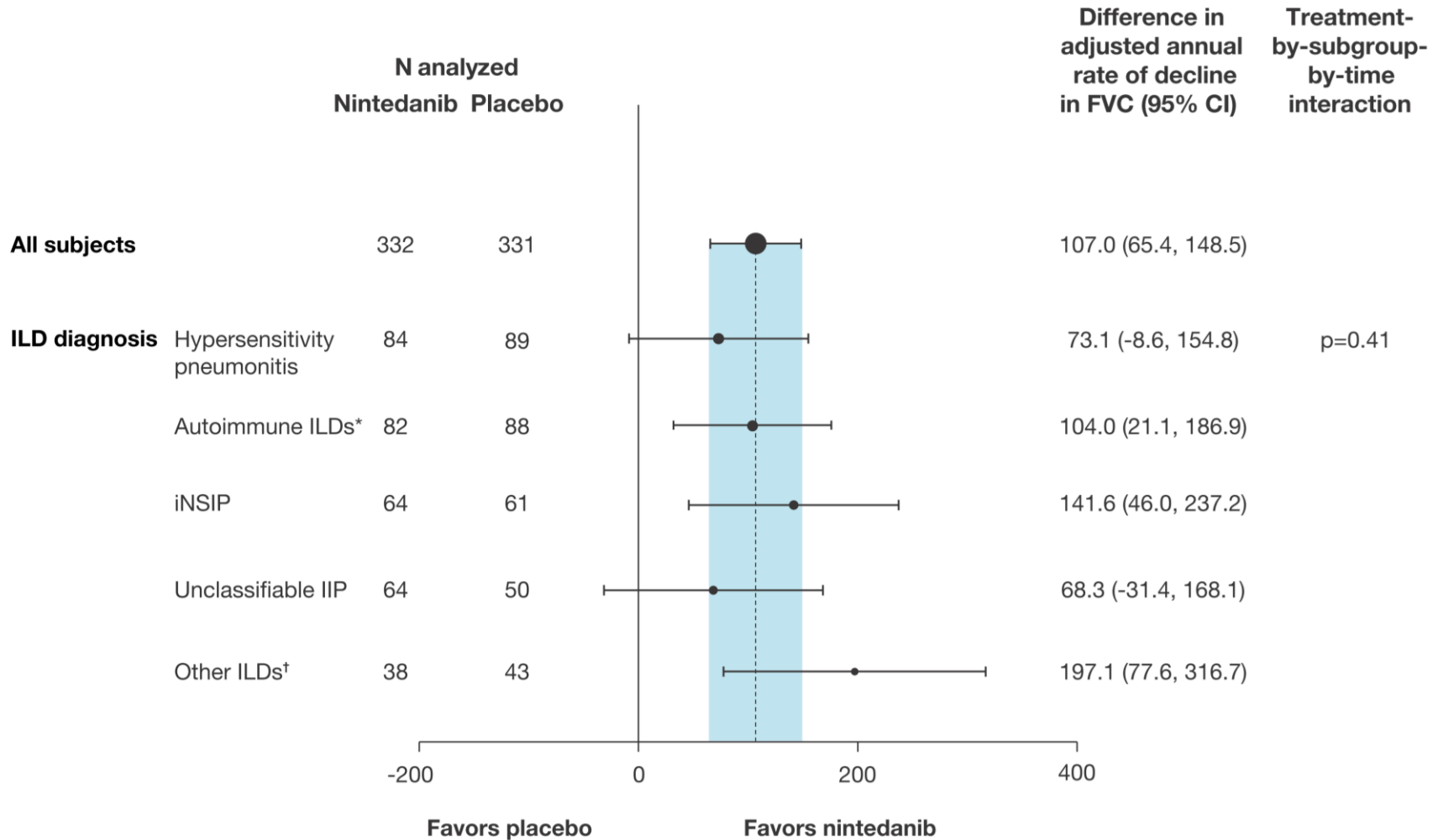


- Annual rate of decline in FVC (mL/year) assessed over 52 weeks

Adjusted annual rate of decline in FVC (mL/year) over 52 weeks



Treatment effect of nintedanib versus placebo on annual rate of decline in FVC in subgroups by ILD diagnosis



Most frequently reported adverse events in overall population

	Nintedanib (n=332)	Placebo (n=331)
Diarrhoea	222 (66.9)	79 (23.9)
Nausea	96 (28.9)	31 (9.4)
Bronchitis	41 (12.3)	47 (14.2)
Nasopharyngitis	44 (13.3)	40 (12.1)
Dyspnoea	36 (10.8)	44 (13.3)
Vomiting	61 (18.4)	17 (5.1)
Cough	33 (9.9)	44 (13.3)
Decreased appetite	48 (14.5)	17 (5.1)
Alanine aminotransferase increased	43 (13.0)	12 (3.6)
Progression of ILD	16 (4.8)	39 (11.8)
Weight decreased	41 (12.3)	11 (3.3)
Aspartate aminotransferase increased	38 (11.4)	12 (3.6)

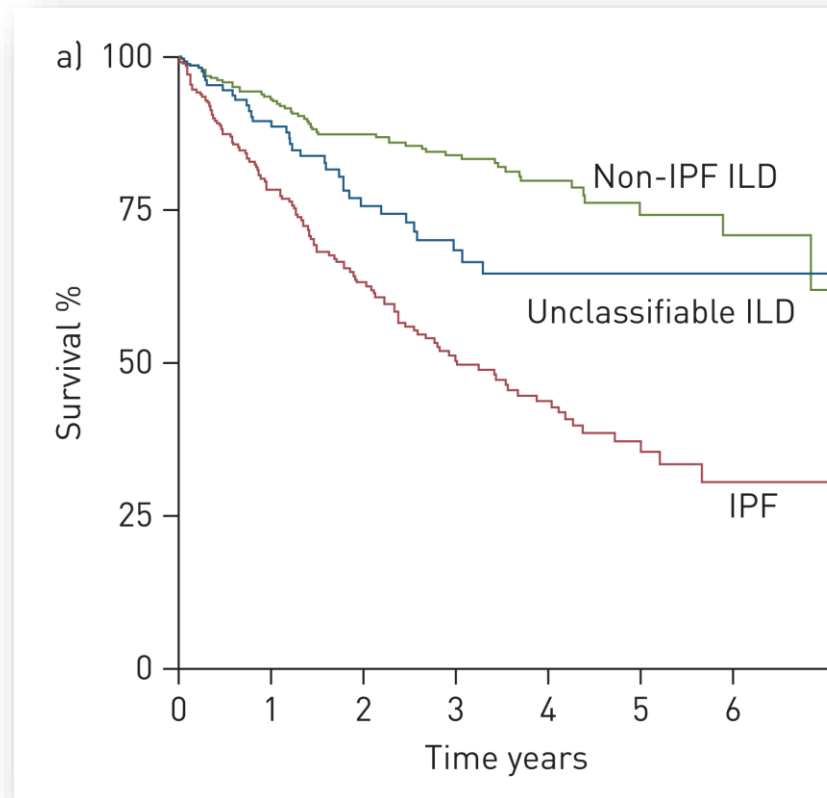
Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial



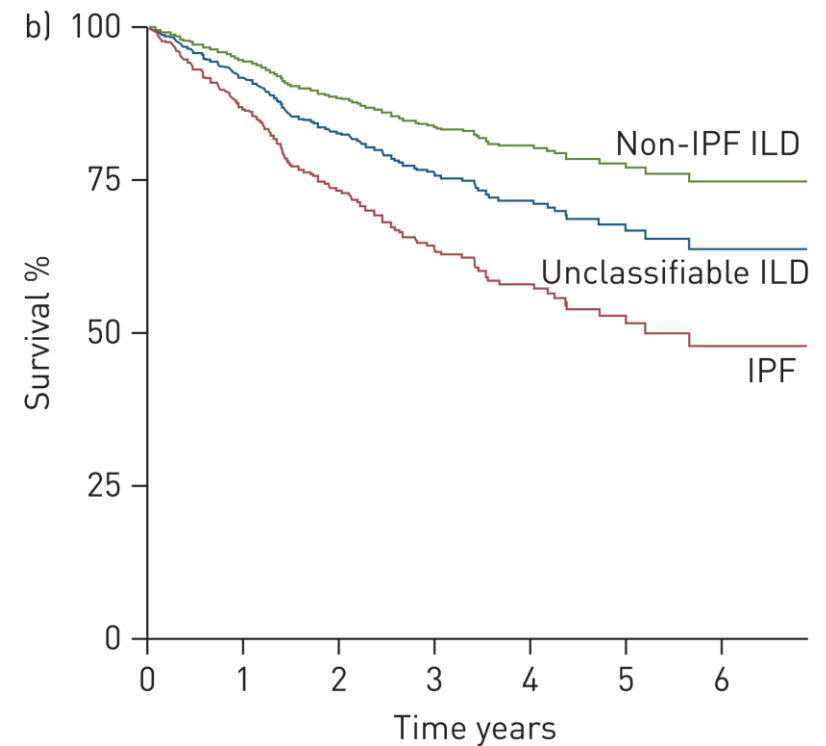
Toby M Maher, Tamera J Corte, Aryeh Fischer, Michael Kreuter, David J Lederer, Maria Molina-Molina, Judit Axmann, Klaus-Uwe Kirchgaessler, Katerina Samara, Frank Gilberg, Vincent Cottin

Unclassifiable ILD

- Unadjusted



- Adjusted for age, sex, FVC, DLco

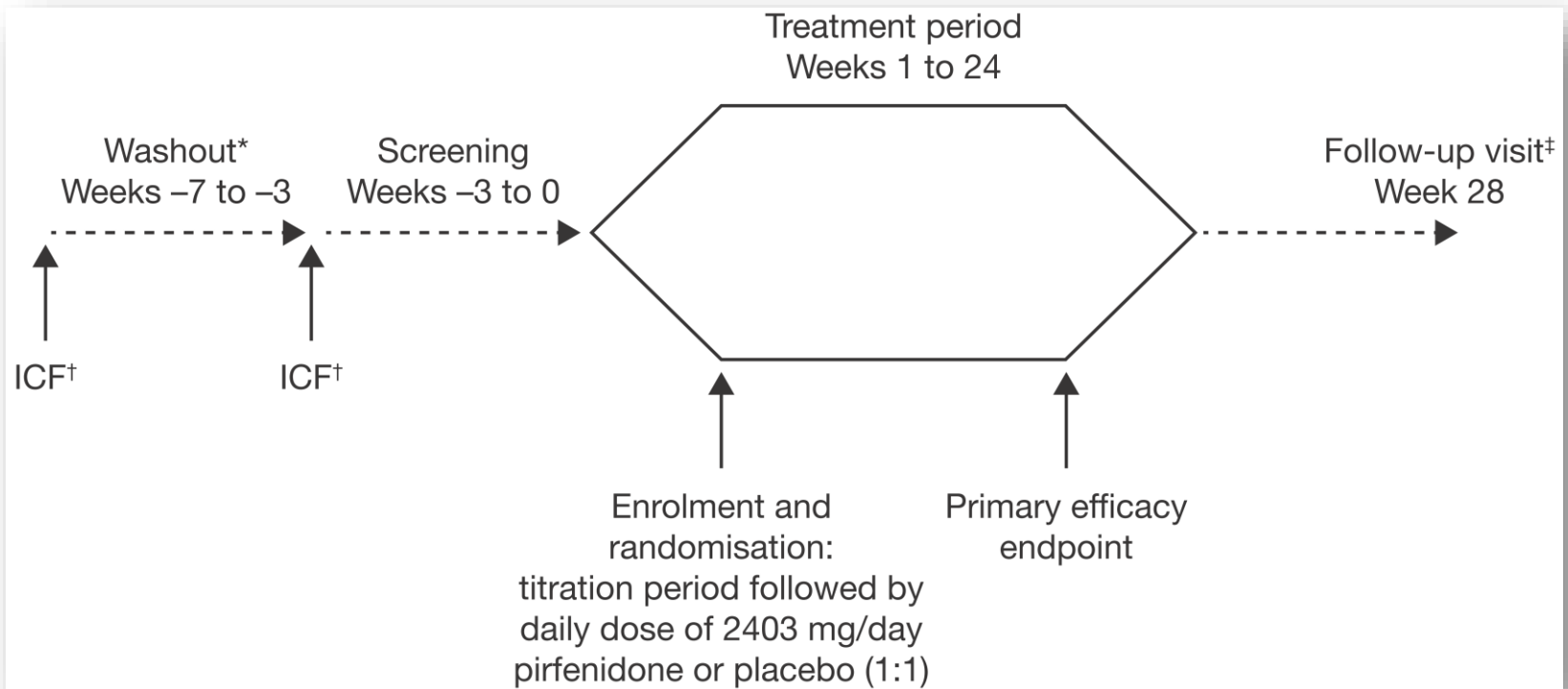


- Unclassifiable ILD is diagnosed in 10% of the ILD cohort.

Inclusion critiera

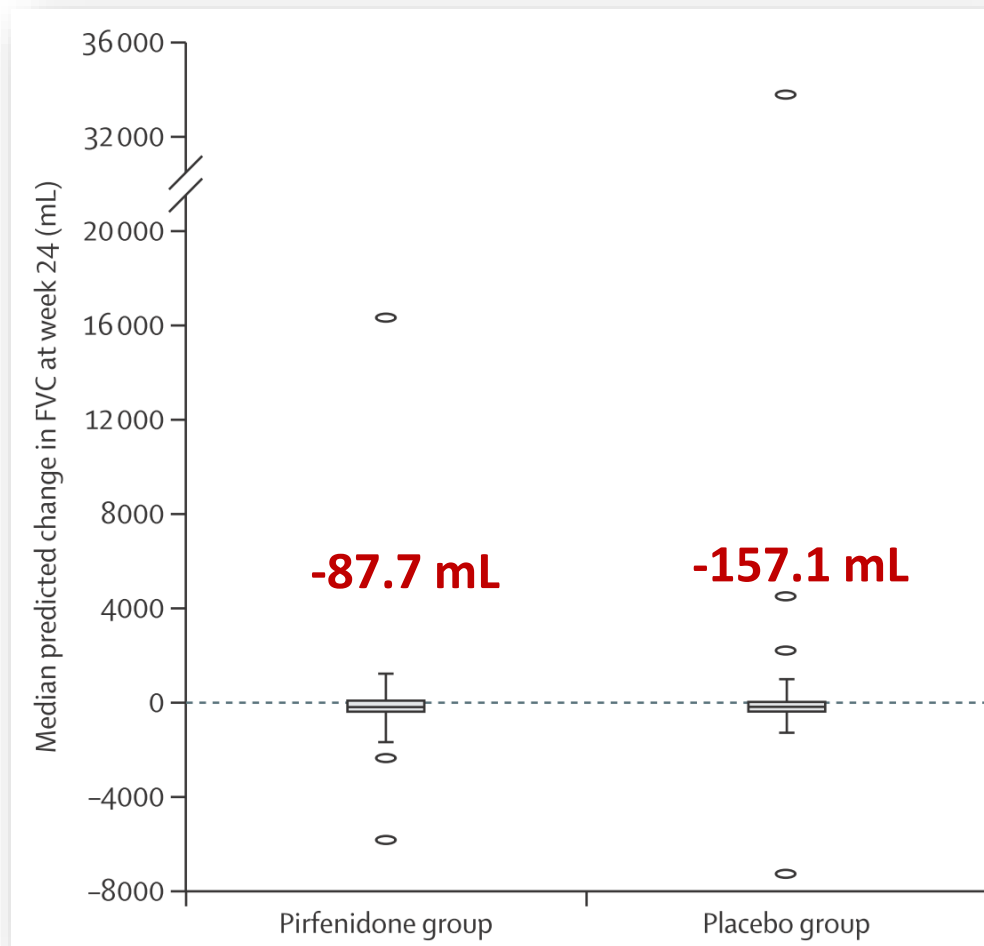
Lung function	FVC \geq 45% predicted, Dlco \geq 30% predicted
Excercise	6MWD \geq 150 m
Fibrosis	Extent of fibrosis $>$ 10% on HRCT
Progression	In the previous 6 months
	- absolute decline in FVC % predicted $>$ 5%
	- significant symptomatic worsening not due to cardiac, pulmonary vascular or other causes

Study Design



- N = 253
- 1' endpoint : change in FVC (in mL) over 24 weeks measured by daily home spirometry

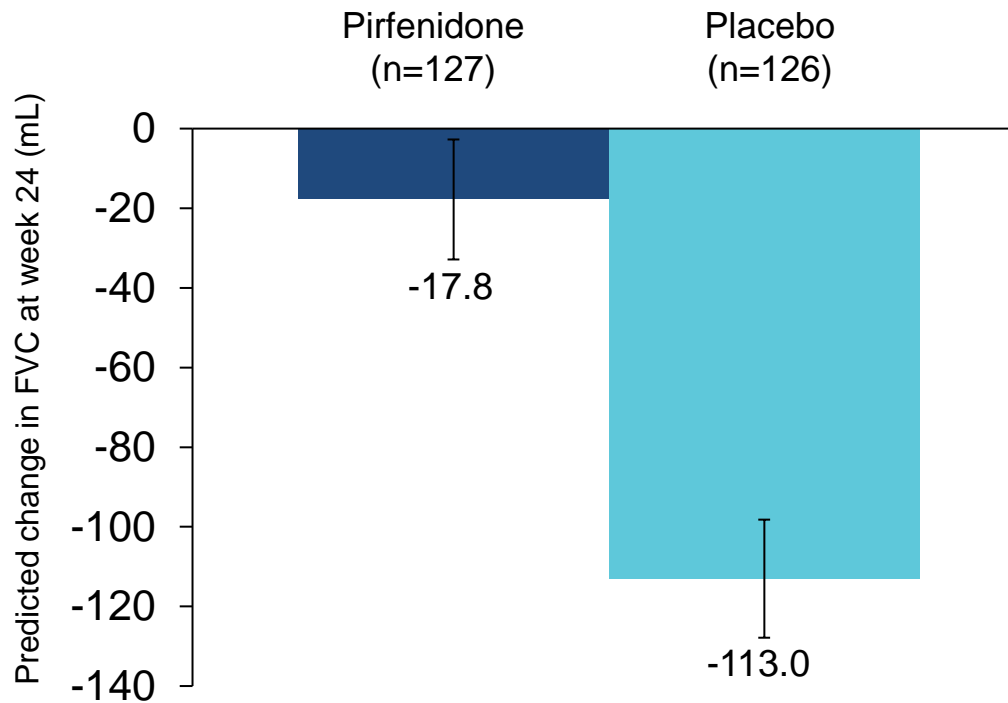
FVC changes from baseline at week 24: home spirometry



* Median predicted FVC (n=253)

Lancet Resp Med 2020;8:147

FVC changes from baseline at week 24: site spirometry



Difference: 95.3 mL/24 weeks
(95% CI: 35.9, 154.6); p=0.002
Relative reduction: 84%

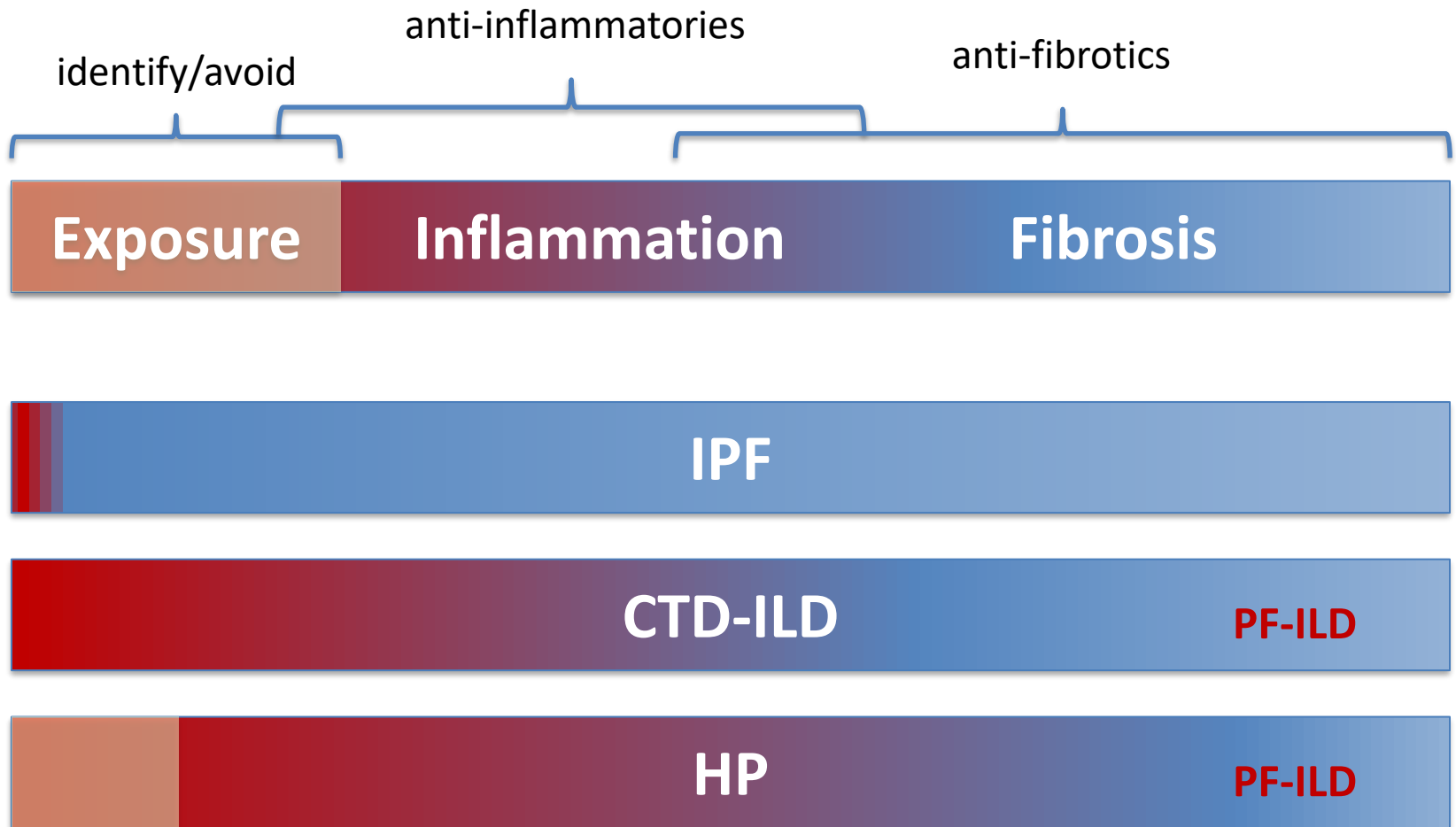
Treatment-emergent adverse events

	Pirfenidone (n=127)	Placebo (n=124)
Treatment-related treatment-emergent adverse events known to be associated with pirfenidone		
Gastrointestinal disorder‡	60 (47%)	32 (26%)
Photosensitivity§	10 (8%)	2 (2%)
Rash¶	13 (10%)	9 (7%)
Dizziness	10 (8%)	4 (3%)
Weight decrease	10 (8%)	1 (1%)
Fatigue	16 (13%)	12 (10%)

Pirfenidone trials of antifibrotic medications in non-IPF fILDs

Name	Phase	No.	Intervention	Duration	Primary outcome
Progressive CADM-ILD	IV	60	PFD vs PBO added on existing Tx	52 weeks	Overall survival
SSc-ILD	II	150	PFD vs PBO added on MMF	18 months	Changes in FVC % pred.
PF with anti-myeloperoxidase Ab	II	15	PFD	52 weeks	Absolute changes in FVC % pred.
RA-ILD	II	270	PFD vs. PBO	52 weeks	> 10% decline in FVC or death
Progressive fibrosis sarcoidosis	IV	60	PFD vs. PBO	24 mo	Time until clinical worsening
Fibrotic HP	II/III	60	PFD vs. PBO added on conventional Tx (pd/aza)	52 weeks	Change in FVC
BOS	II/III	80	PFD vs. PBO added on azithromycin	26 weeks	Change in FEV1

Spectrum of fibrosing-ILD



KFDA approval for Ofev in PF-ILD

제품명	변경항목	변경허가내용	비고
오페브엔질캡슐 100밀리그램 (닌테다닙에실산염) 외 1건	효능·효과	- (적응증 추가) 진행성 표현형을 나타내는 만성 섬유성 간질성폐질환의 치료	안전성유효성 심사완료
	사용상의 주의사항	- 임상시험 결과 정보 추가 등 안전성 정보 반영	
	허가조건	- 위해성관리계획 개정	

- Aug 2020

Summary

- IPF
 - the same efficacy in the real-world patients
 - early treatment and dose modification
- Non-IPF ILD
 - PF-ILD: 20-30%
 - similar efficacy and safety of anti-fibrotic agents