



울산대학교병원  
ULSAN UNIVERSITY HOSPITAL

# 간질성폐질환의 최신지견

*Antifibrotic therapy in IPF and PF-ILD*

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HOSPITAL



# INPULSIS and ASCEND - 2014

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### Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

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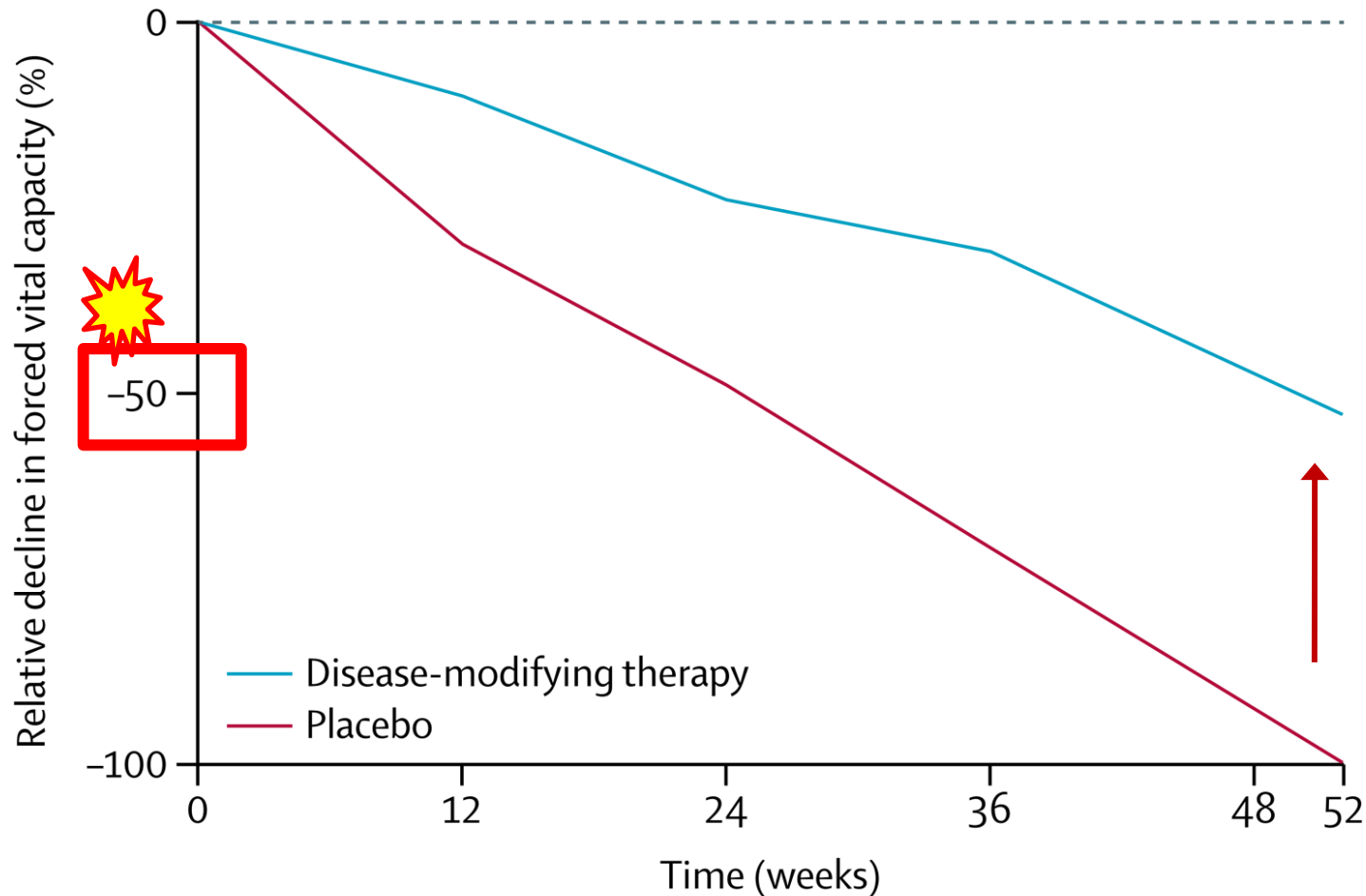
*The* NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

### A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

Talmadge E. King, Jr., M.D., Williamson Z. Bradford, M.D., Ph.D.,  
Socorro Castro-Bernardini, M.D., Elizabeth A. Fagan, M.D.,  
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# Effect of disease modifying therapy on lung function decline



# After INPULSIS and ASCEND

1. Post hoc analysis, pooled analysis
2. Real world study
3. PF-ILD (progressive fibrosing interstitial lung disease)

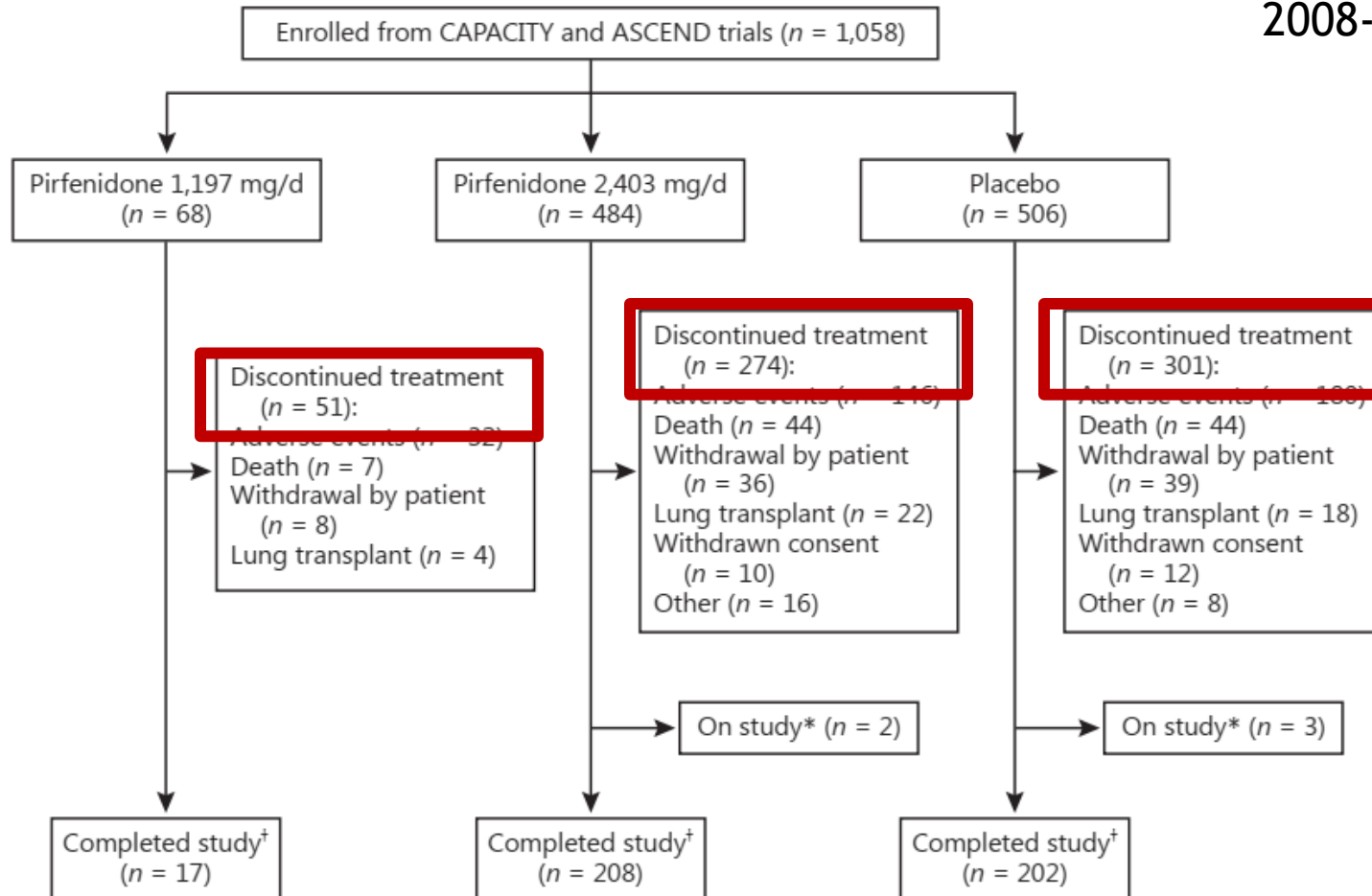
# Real world experience of pirfenidone and nintedanib

Pirfenidone - RECAP, PASSPORT

Nintedanib - INPULSIS- on

# RECAP: Open-label study of the long-term safety of pirfenidone in patients with IPF

2008-2015



# RECAP: Adverse events

**Table 2.** Summary of TEAEs ( $n = 1,058$ )

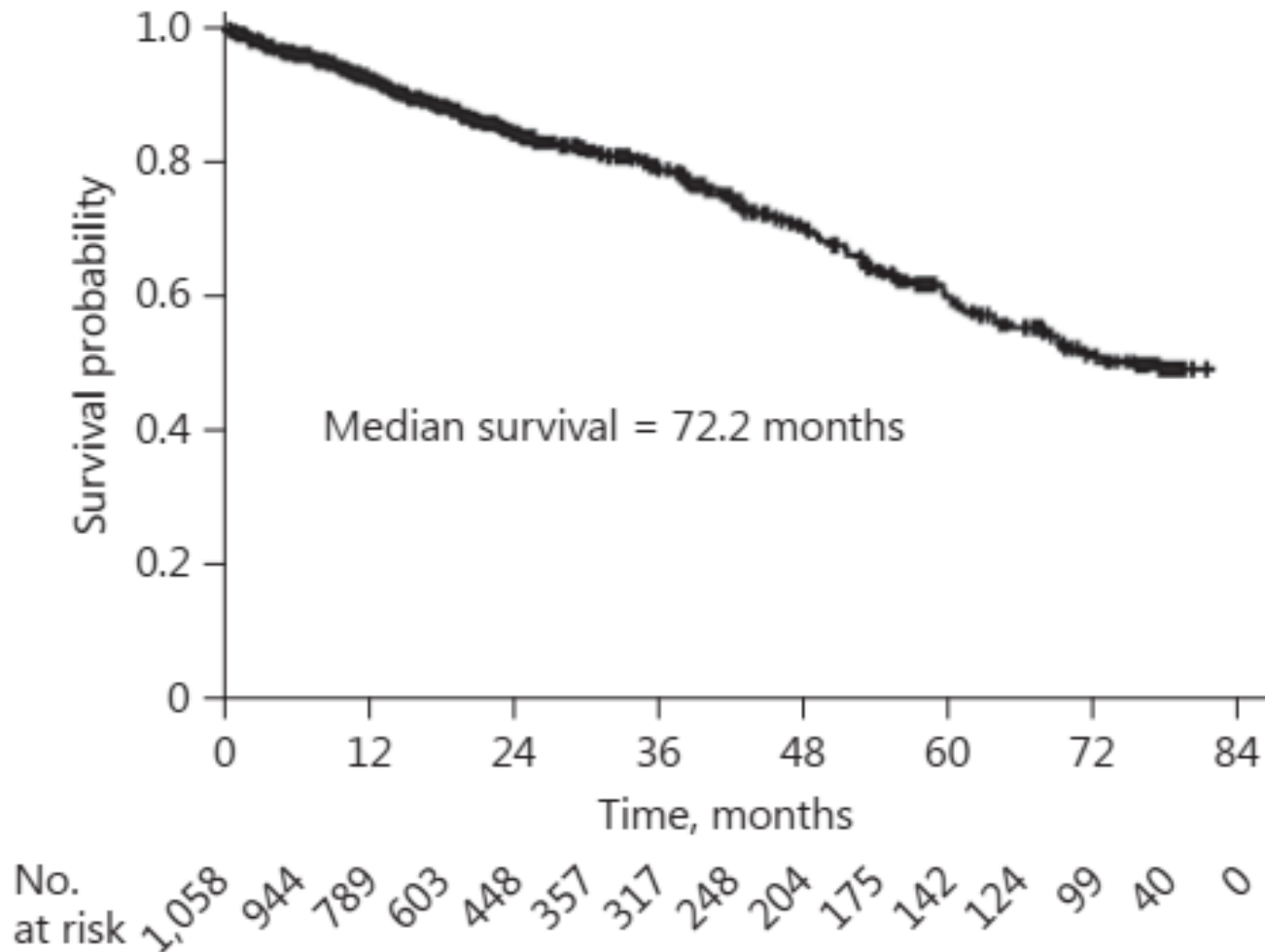
TEAEs	$n$ (%)	Adjusted rate <sup>1</sup>	
		events, $n$	rate per 100 PEY <sup>2</sup>
<i>TEAEs with incidence in <math>\geq 15\%</math> of patients</i>			
<b>Total</b>	<b>1,037 (98.0)</b>	<b>17,422</b>	<b>701.9</b>
IPF	355 (33.6)	547	22.0
Upper RTI	295 (27.9)	523	21.1
Bronchitis	260 (24.6)	485	19.5
Cough	331 (31.3)	436	17.6
<b>Nausea</b>	<b>305 (28.8)</b>	<b>433</b>	<b>17.4</b>
Dyspnea	327 (30.9)	420	16.9
Nasopharyngitis	202 (19.1)	359	14.5
<b>Diarrhea</b>	<b>242 (22.9)</b>	<b>357</b>	<b>14.4</b>
<b>Fatigue</b>	<b>210 (19.8)</b>	<b>251</b>	<b>10.1</b>
Dizziness	176 (16.6)	226	9.1

**Table 3.** Summary of TEAEs resulting in pirfenidone withdrawal with incidence in  $\geq 1\%$  of patients ( $n = 1,058$ )

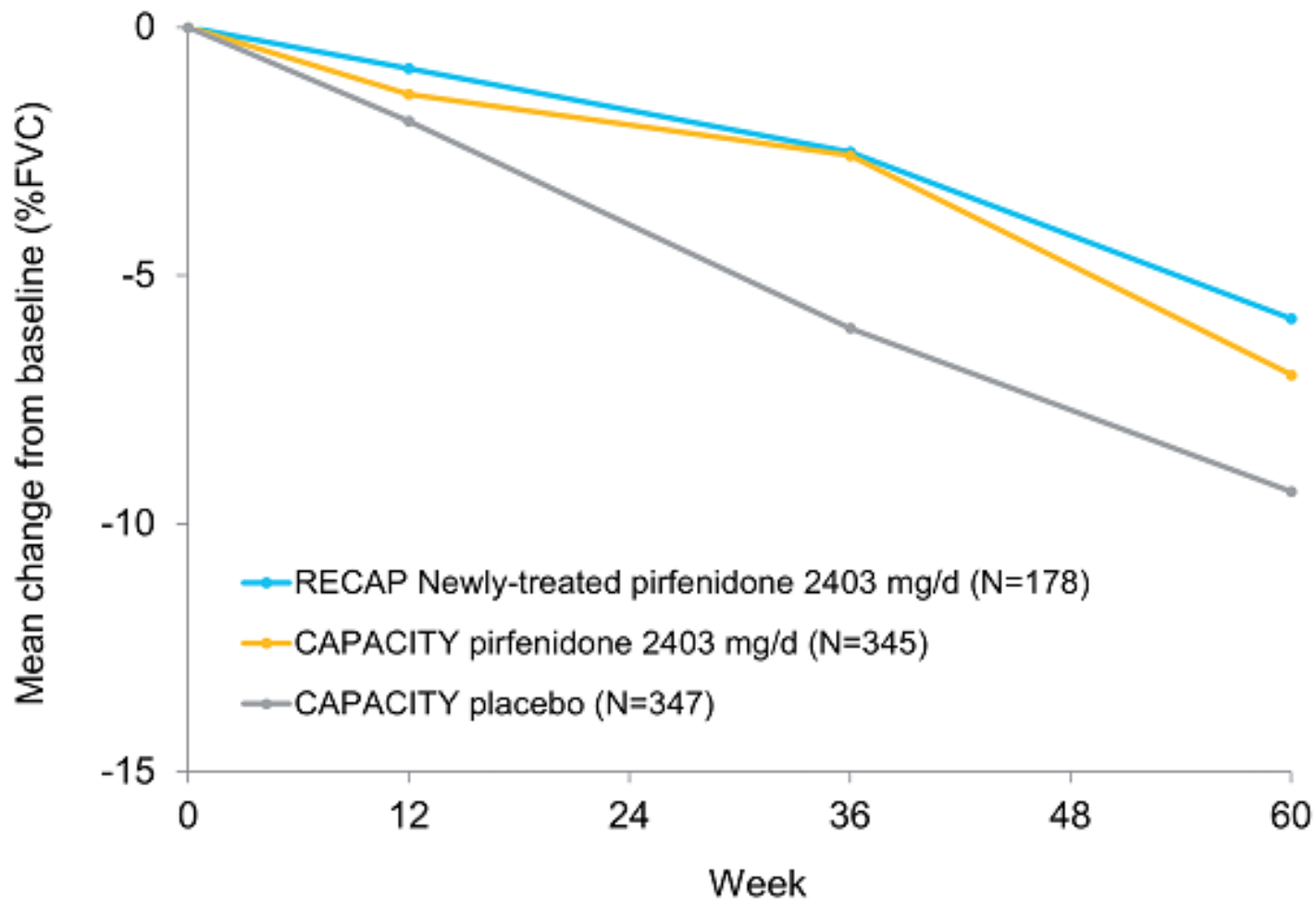
TEAEs	$n$ (%)	Adjusted rate <sup>1</sup>	
		events, $n$	rate per 100 PEY <sup>2</sup>
<b>Total</b>	<b>444 (42.0)</b>	<b>444</b>	<b>17.9</b>
IPF	178 (16.8)	178	7.2
Pneumonia	13 (1.2)	13	0.5
Respiratory failure	13 (1.2)	13	0.5
Acute respiratory failure	12 (1.1)	12	0.5
<b>Rash</b>	<b>12 (1.1)</b>	<b>12</b>	<b>0.5</b>
<b>Nausea</b>	<b>11 (1.0)</b>	<b>11</b>	<b>0.4</b>

**ADRs** occurred in 786 patients (**74.3%**). **Discontinuation** of pirfenidone due to an ADR occurred in 120 patients (**11.3%**; 4.8 per 100 PEY).

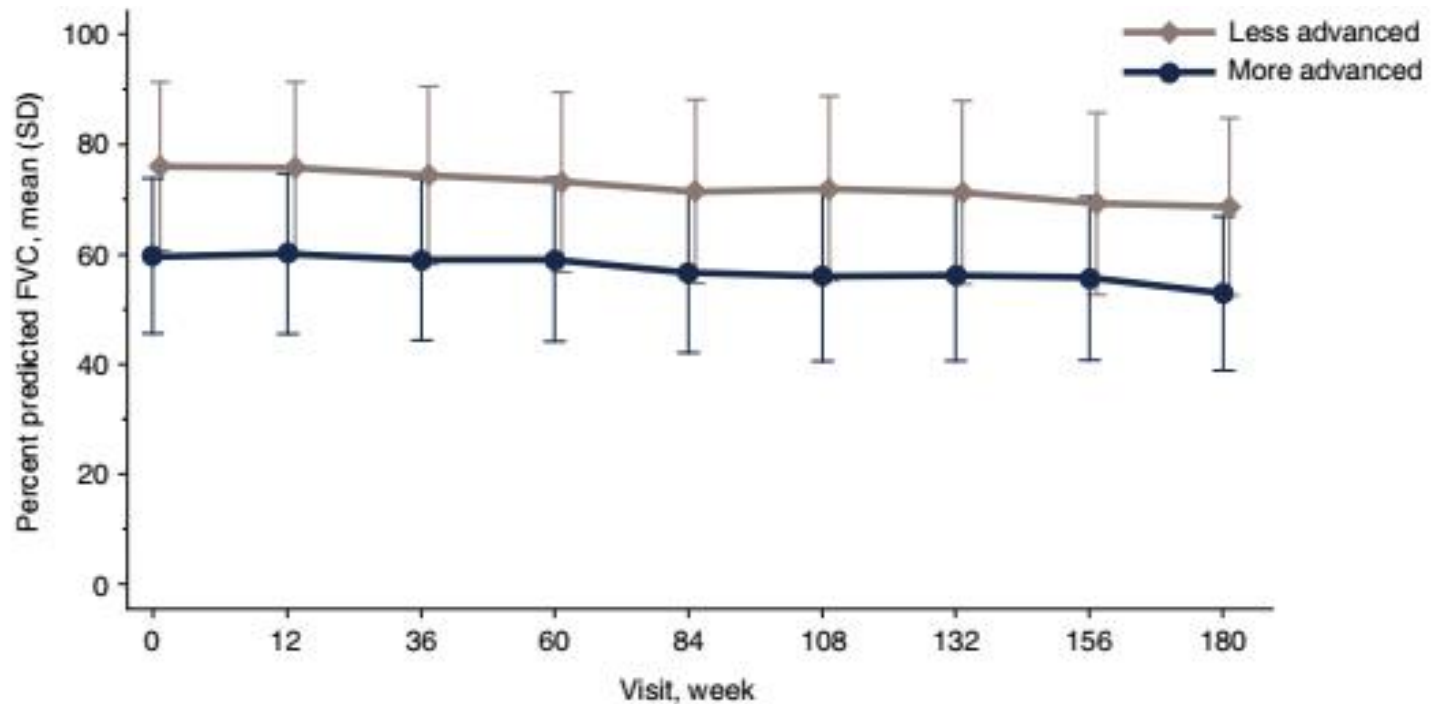
# RECAP: On-treatment survival from the first dose of pirfenidone



# RECAP: FVC changes by Initiation time



# RECAP: FVC over time by IPF severity



## Number of patients\*

Less advanced	400	392	376	343	318	287	258	237	208
More advanced	184	170	142	117	97	80	67	60	46

more advanced :FVC <50% and/or DLco <35%

less advanced :FVC ≥50% and DLco ≥35%

# PASSPORT-multicentre, prospective , observational, post-authorisation study

European Medicines Agency (EMA), a post-authorisation safety study

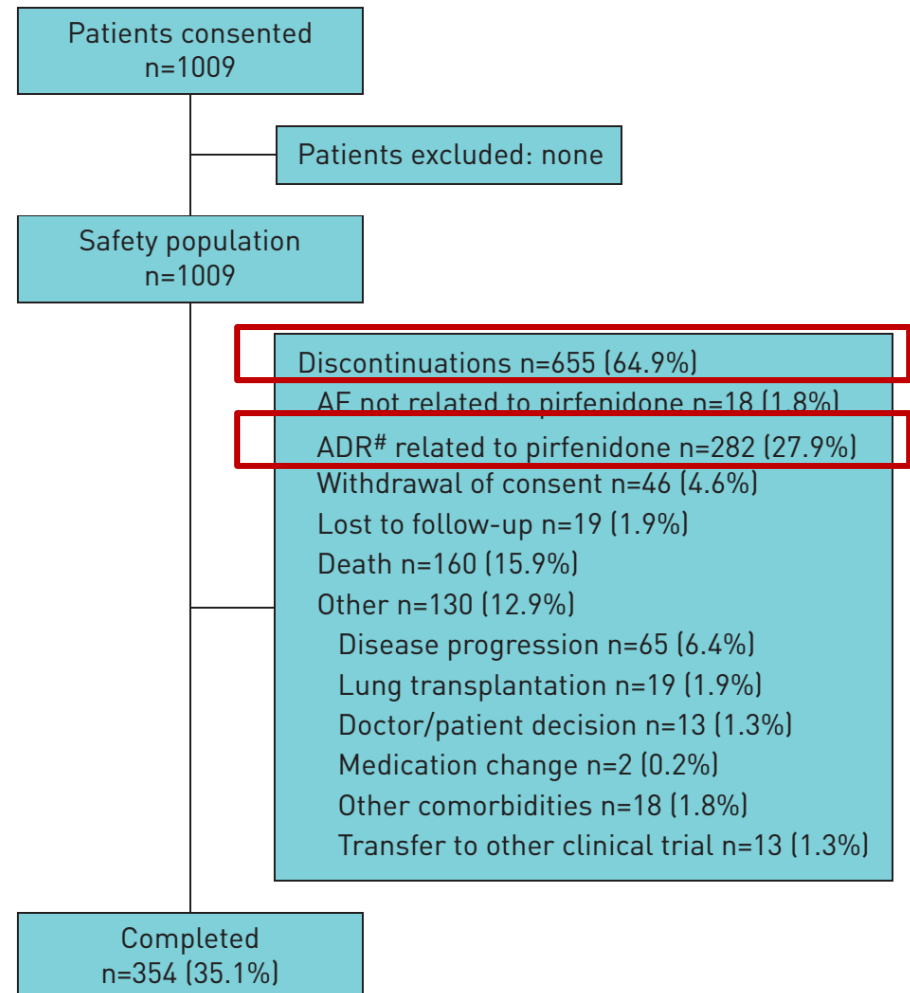
Male 80%

Time since IPF diagnosis  $1.7 \pm 3.0$  yrs

FVC  $66.0 \pm 16.1\%$

FVC <50% 14.9%

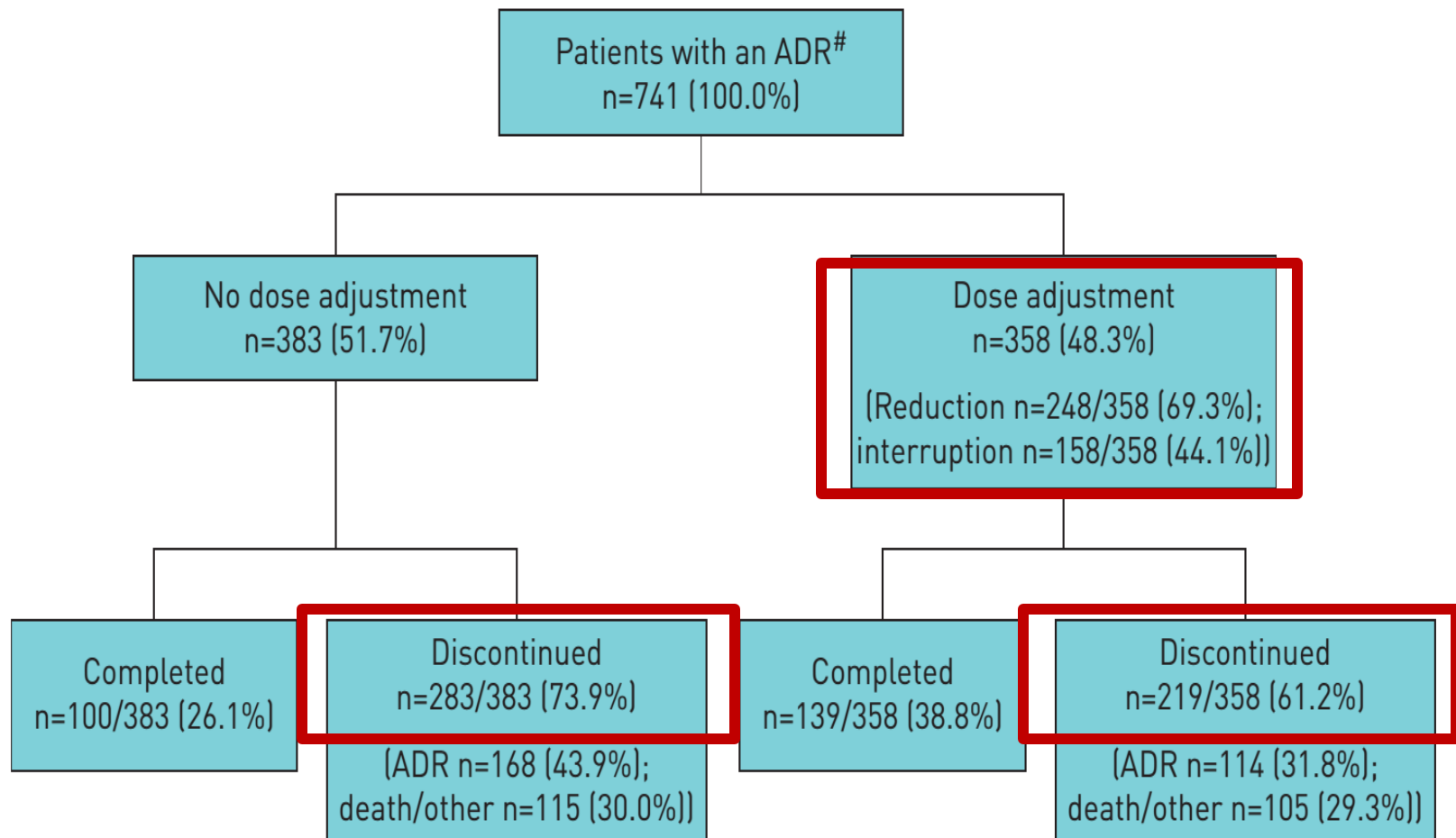
2Yr FU



# PASSPORT-Adverse drug reactions

	Total events	Patients with event	Exposure-adjusted event rate <sup>+</sup>	Patients with event in first 30 days	Patients with events resulting in permanent discontinuation of pirfenidone
<b>Any ADR</b>	2167	741 (73.4)		379 (37.6)	290 (28.7)
<b>Most common ADRs (≥5% of patients)</b>					
Nausea	227	208 (20.6)	181.2	113 (11.2)	41 (4.1)
Fatigue	194	187 (18.5)	154.9	101 (10.0)	15 (1.5)
Decreased appetite	172	163 (16.2)	137.3	69 (6.8)	17 (1.7)
Decreased weight	172	161 (16.0)	137.3	59 (5.8)	32 (3.2)
Rash	135	123 (12.2)	107.8	15 (1.5)	32 (3.2)
Diarrhoea	111	96 (9.5)	88.6	44 (4.4)	21 (2.1)
Dizziness	69	65 (6.4)	55.1	30 (3.0)	5 (0.5)
Photosensitivity reaction	61	59 (5.8)	48.7	5 (0.5)	15 (1.5)

# PASSPORT-Adverse drug reactions

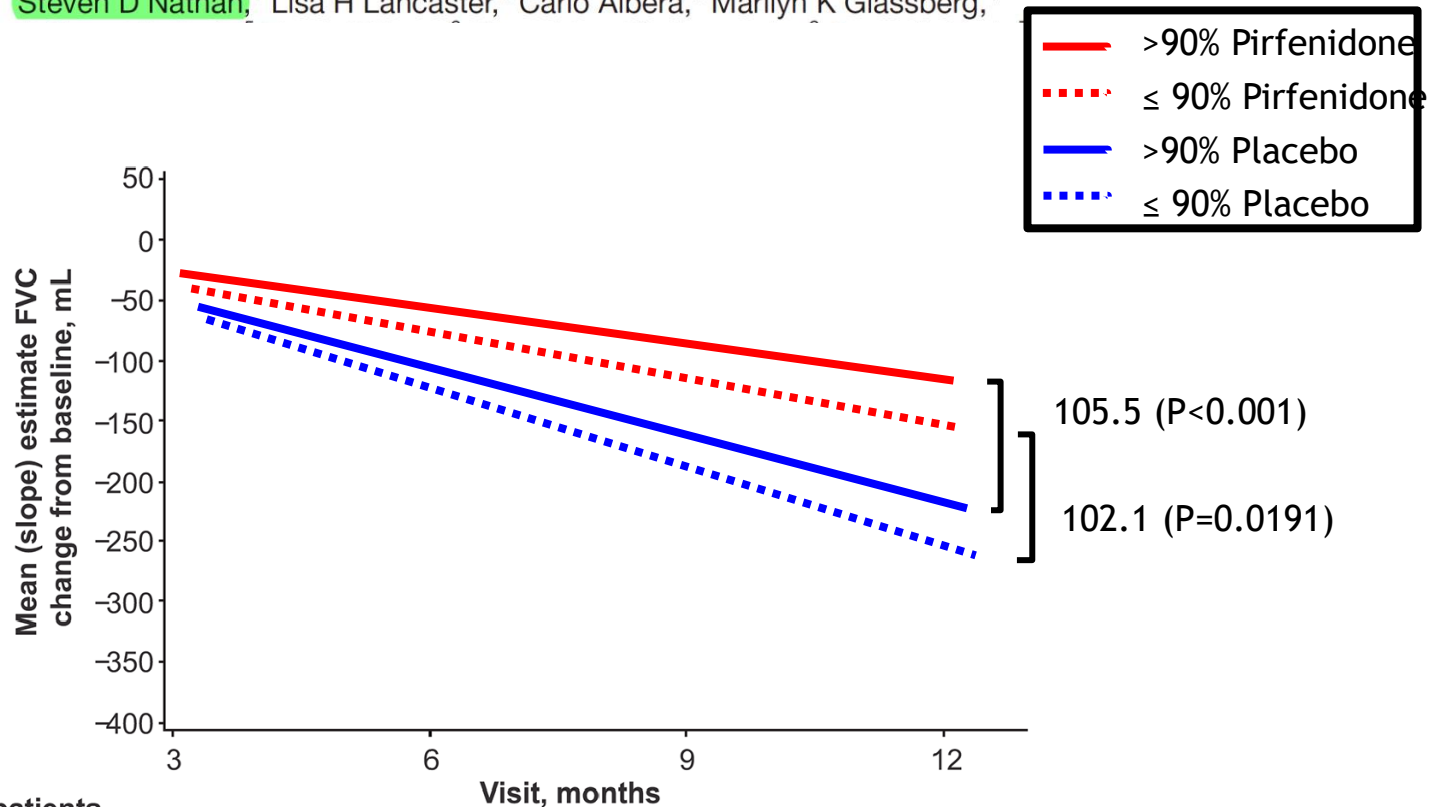


# PASSPORT-Risk factors for discontinuation

Predictor of early discontinuation <sup>¶</sup>	Comparison	OR (95% CI)	p-value
<b>At 6 months</b>			
Age	Continuous	1.06 (1.03–1.08)	<0.0001
Female sex	Yes versus no	1.59 (1.06–2.33)	0.0228
Steroid use prior to study	Yes versus no	1.64 (1.10–2.43)	0.0148
<b>At 12 months</b>			
Age	Continuous	1.06 (1.04–1.08)	<0.0001
Female sex	Yes versus no	1.52 (1.04–2.17)	0.0288
Steroid use prior to study	Yes versus no	1.48 (1.02–2.17)	0.0406
Underlying pulmonary disease <sup>+</sup>	Yes versus no	0.72 (0.50–1.03)	0.0748
<b>During entire study</b>			
Age	Continuous	1.03 (1.01–1.05)	0.0009
Female sex	Yes versus no	1.54 (1.08–2.22)	0.0193
BMI	Continuous	0.96 (0.92–0.99)	0.0127
UK patients	Yes versus no	1.65 (1.14–2.39)	0.0081
Current alcohol use	Yes versus no	0.73 (0.53–1.01)	0.0555
Years since IPF diagnosis	Continuous	1.04 (0.99–1.09)	0.1245
Ex-/current smoker	Yes versus no	1.30 (0.94–1.79)	0.1111

# Dose modification and dose intensity during treatment with pirfenidone: analysis of pooled data from three multinational phase III trials

Steven D Nathan,<sup>1</sup> Lisa H Lancaster,<sup>2</sup> Carlo Albera,<sup>3</sup> Marilyn K Glassberg,<sup>4</sup>



**Number of patients**

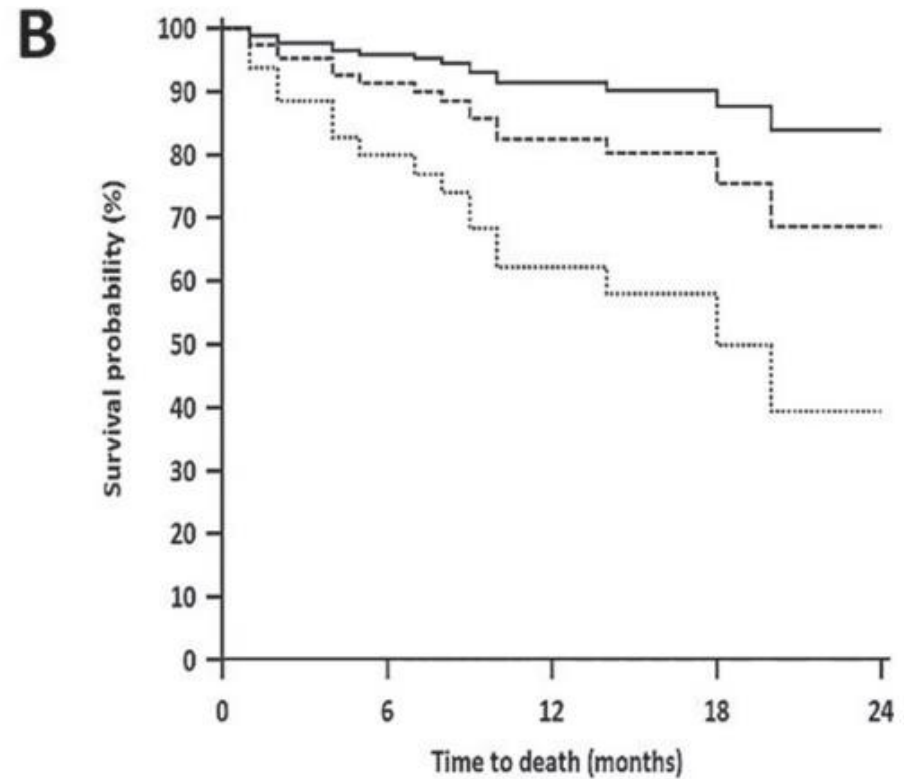
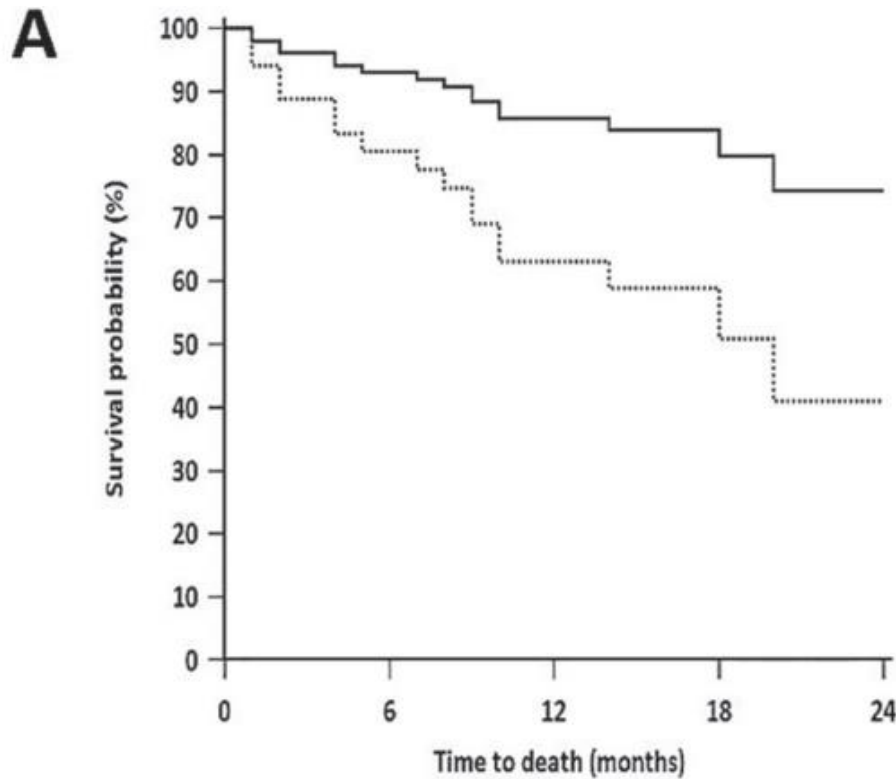
>90% Pirfenidone	417	409	396	392
≤90% Pirfenidone	193	182	169	167
>90% Placebo	545	531	508	497
≤90% Placebo	59	60	52	52

# Full dose vs. Reduced dose

**Table 2.** Tolerated dose/dose range of pirfenidone (primary outcome) and reasons for discontinuation among study subjects started on pirfenidone (n = 115)

<b>Tolerated dose/dose range</b>	<b>Number (percentage)</b>
2400 mg	49 (42.6)
1800 mg to < 2400 mg	34 (29.6)
1200 mg to < 1800 mg	12 (10.4)
600 mg to < 1200 mg	5 (4.3)
<b>Reasons for discontinuation (n = 22)</b>	<b>Number (percentage)</b>
Discontinued due to an adverse drug reaction	15 (68.2)
Patient's choice	4 (18.2)
Progression prompting a switch to nintedanib	2 (9.1)
Financial constraint	1 (4.5)

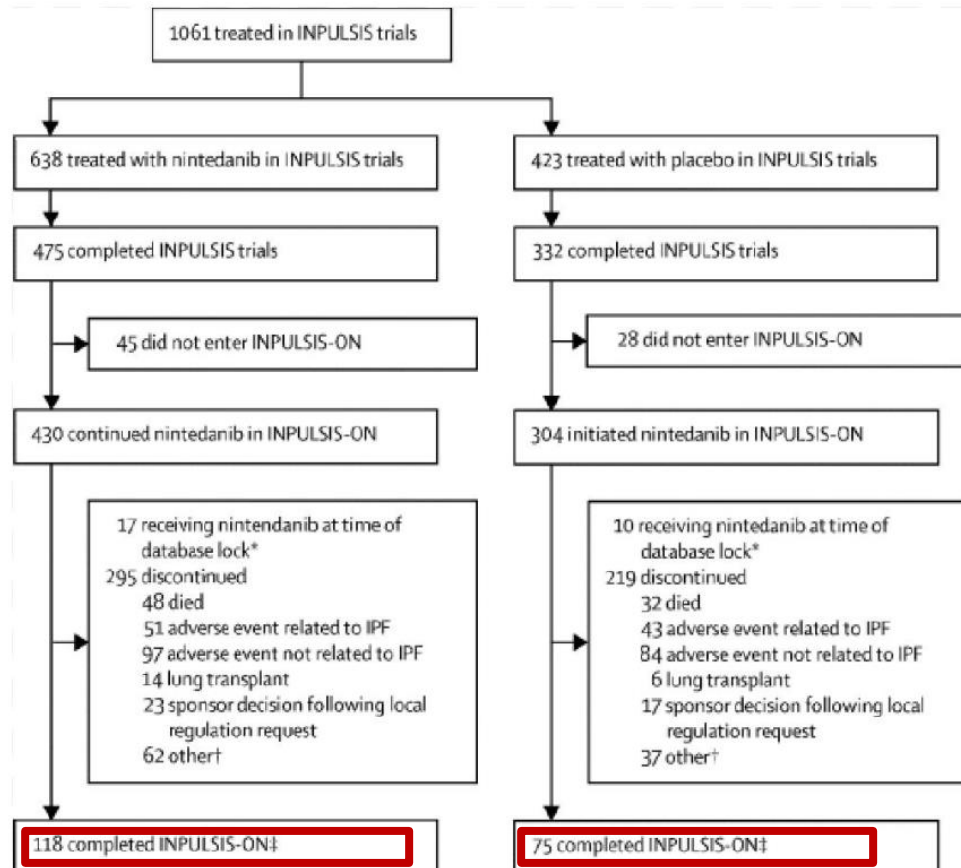
# Full dose vs. Reduced dose



Numbers at risk

Pirfenidone	59	43	32	9	0	Full dose	24	17	13	3	0
No pirfenidone	21	12	7	2	0	Reduced dose	35	26	19	6	0
						No pirfenidone	21	12	7	2	0

# INPULSIS-ON : Long-term safety and tolerability of nintedanib, the open-label extension study

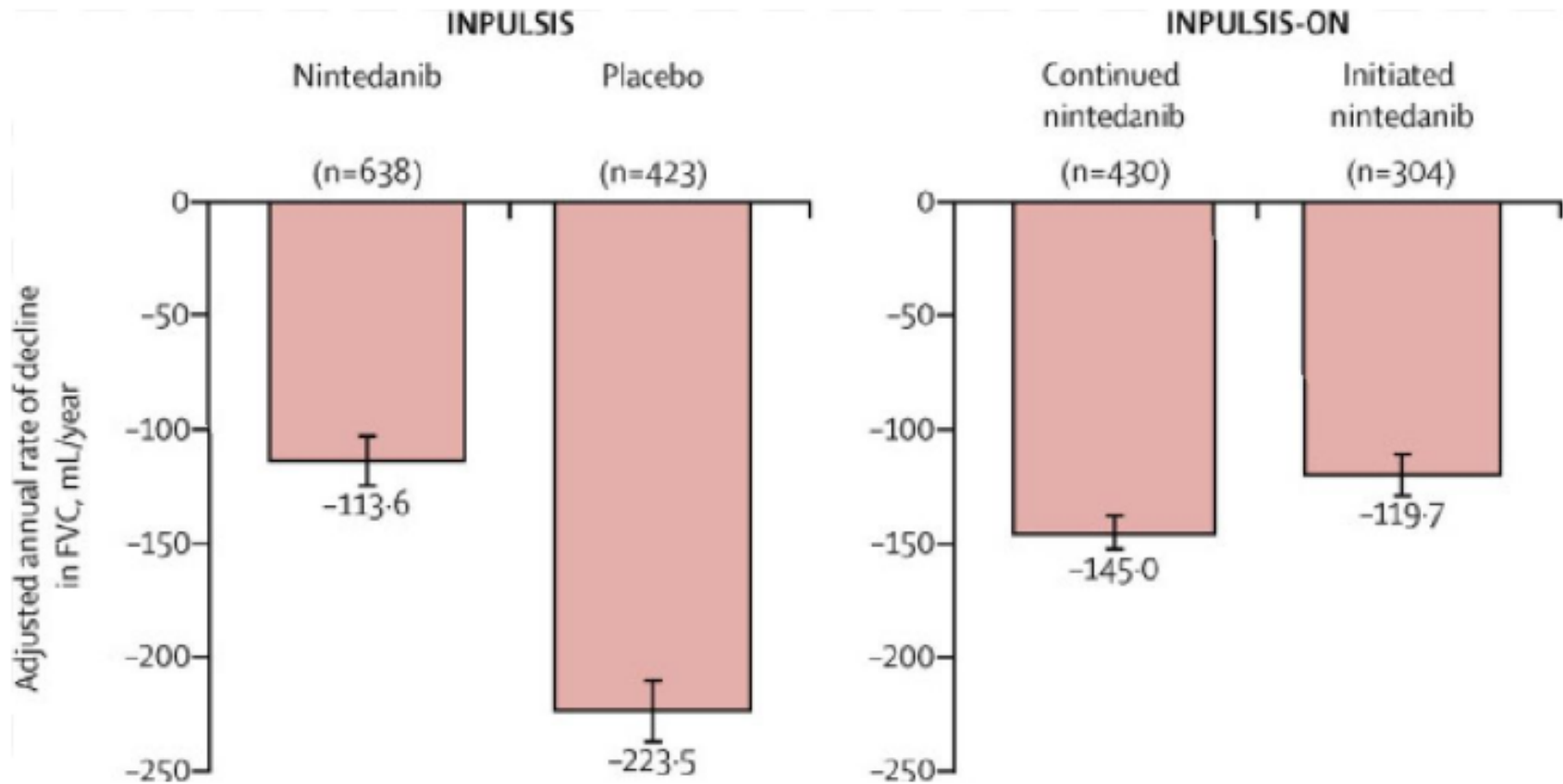


Median exposure of nintedanib 31.5 months (0.0-56.3)

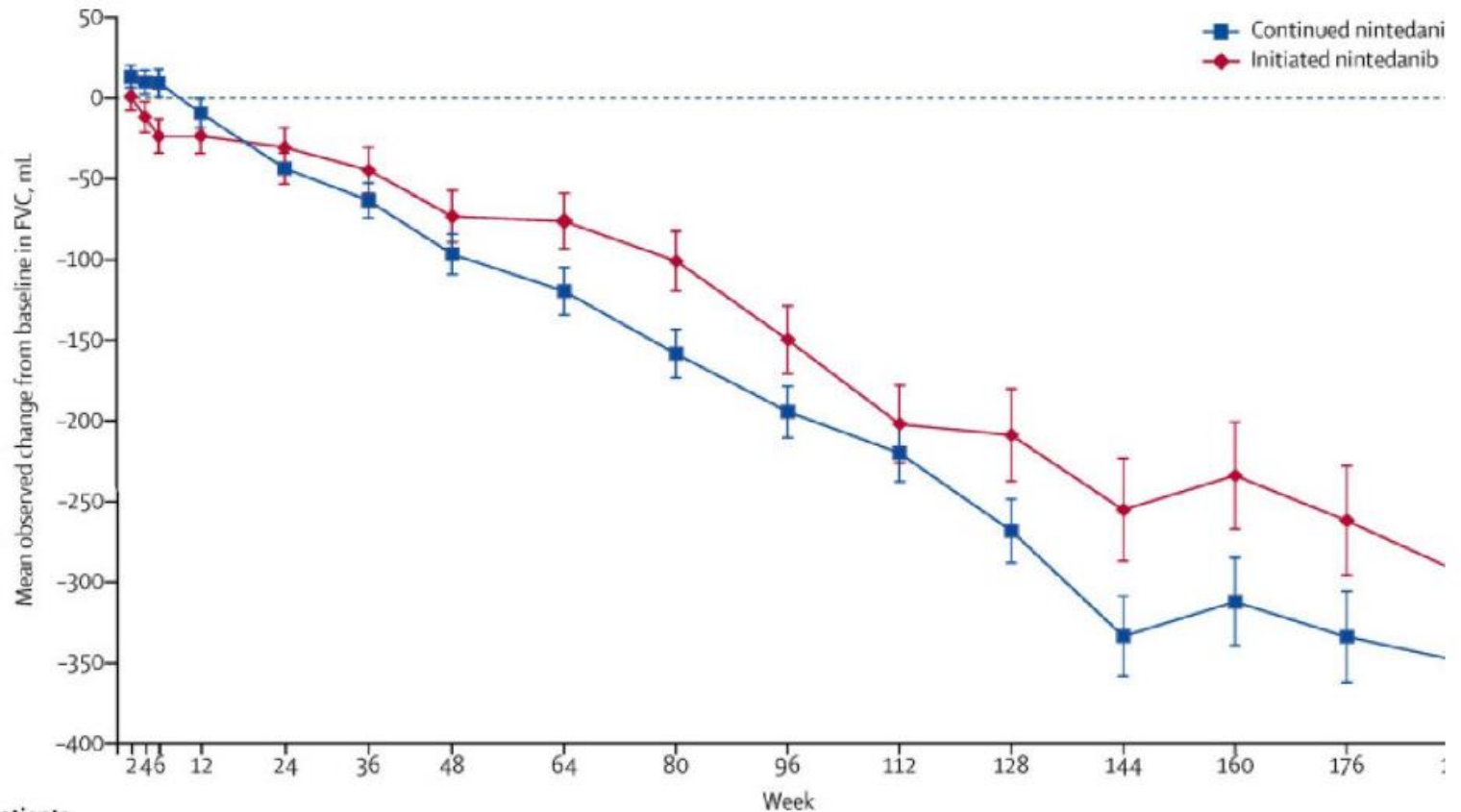
# INPULSIS-ON :Most frequent adverse events

	INPULSIS				INPULSIS-ON			
	Nintedanib (n=638)		Placebo (n=423)		Continued nintedanib (n=430)		Initiated nintedanib (n=304)	
	Number of events	Event rate (per 100 patient exposure-years)	Number of events	Event rate (per 100 patient exposure-years)	Number of events	Event rate (per 100 patient exposure-years)	Number of events	Event rate (per 100 patient exposure-years)
Diarrhoea	671	112.6	106	25.6	667	60.1	509	71.2
Bronchitis	92	15.5	62	15.0	166	15.0	101	14.1
Nasopharyngitis	117	19.6	91	22.0	139	12.5	125	17.5
Progression of IPF † (tbl4fn1)	70	11.8	73	17.7	152	13.7	103	14.4
Cough	96	16.1	67	16.2	133	12.0	94	13.2
Nausea	208	34.9	29	7.0	95	8.6	113	15.8
Upper respiratory tract infection	72	12.1	55	13.3	125	11.3	55	7.7
Dyspnoea	50	8.4	51	12.3	108	9.7	72	10.1
Vomiting	102	17.1	11	2.7	80	7.2	77	10.8
Weight decreased ‡ (tbl4fn2)	64	10.7	15	3.6	67	6.0	66	9.2
Decreased appetite	75	12.6	26	6.3	53	4.8	67	9.4
Abdominal pain	68	11.4	10	2.4	34	3.1	49	6.9

# INPULSIS-ON :Annual rate of decline in FVC over 52weeks



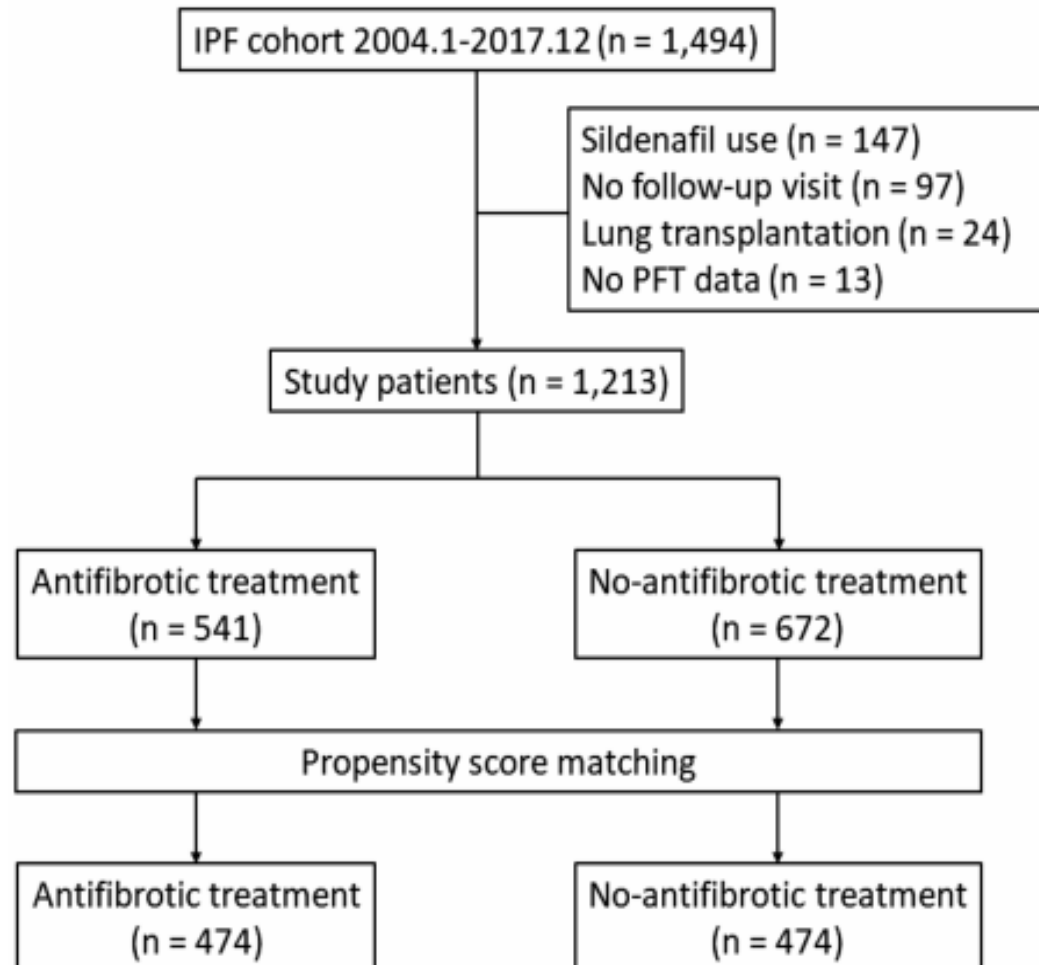
# INPULSIS-ON :Change from baseline in FVC in INPULSIS-ON



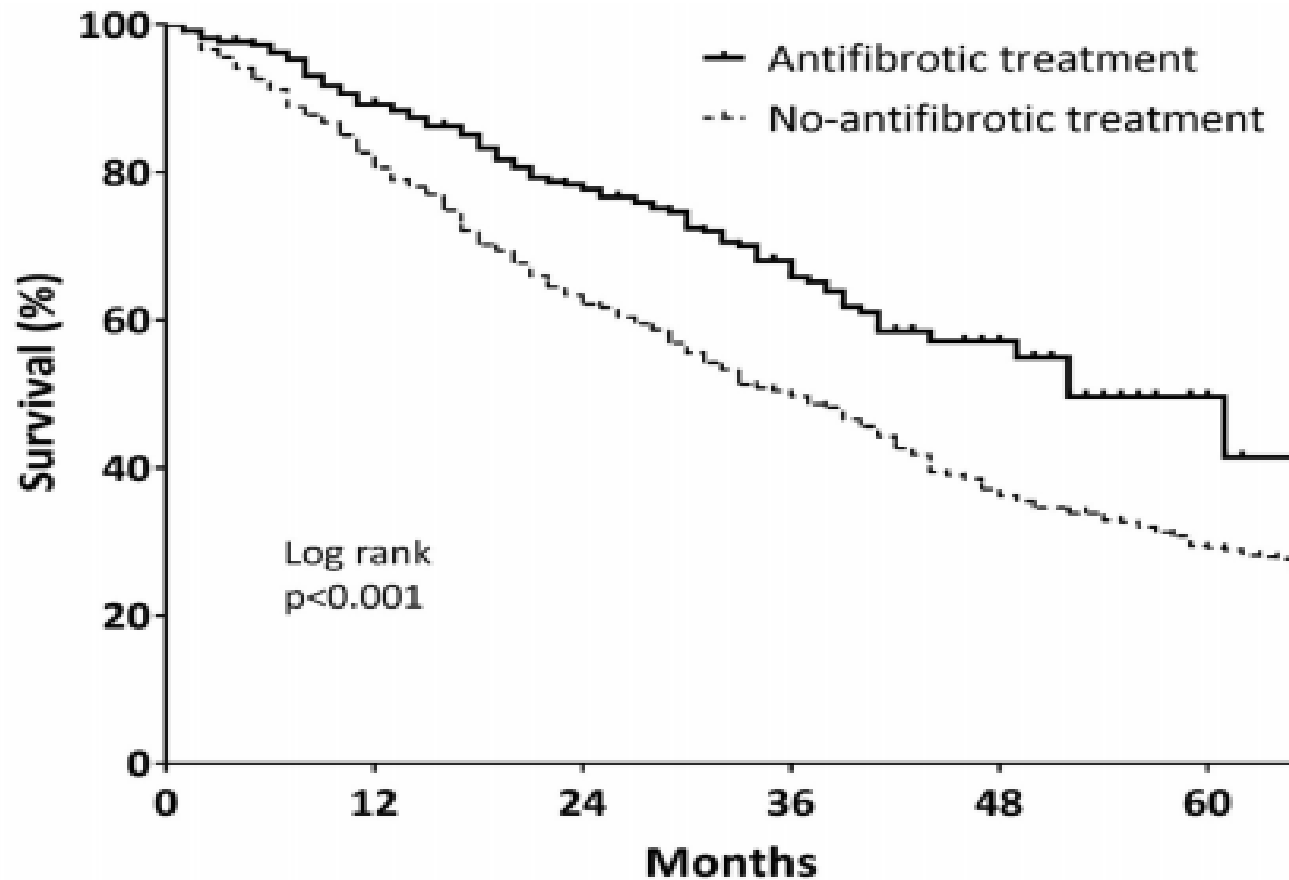
## Number of patients

Continued nintedanib	416	410	408	408	392	375	352	331	306	289	265	239	217	171	154
Initiated nintedanib	296	291	287	284	266	250	233	210	195	177	159	149	133	112	99

# Survival with or without antifibrotic treatment



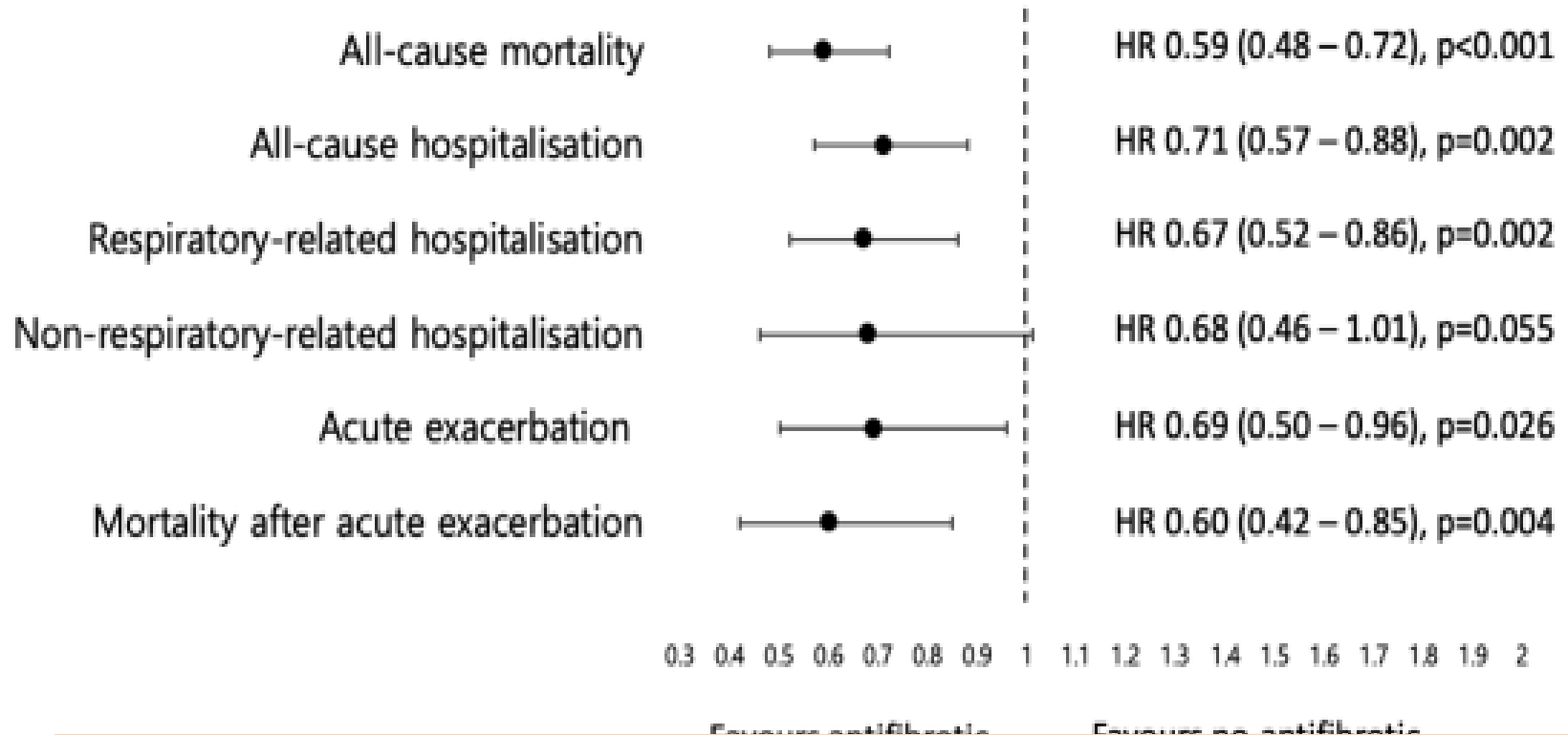
# Survival with or without antifibrotic treatment



Number at risk

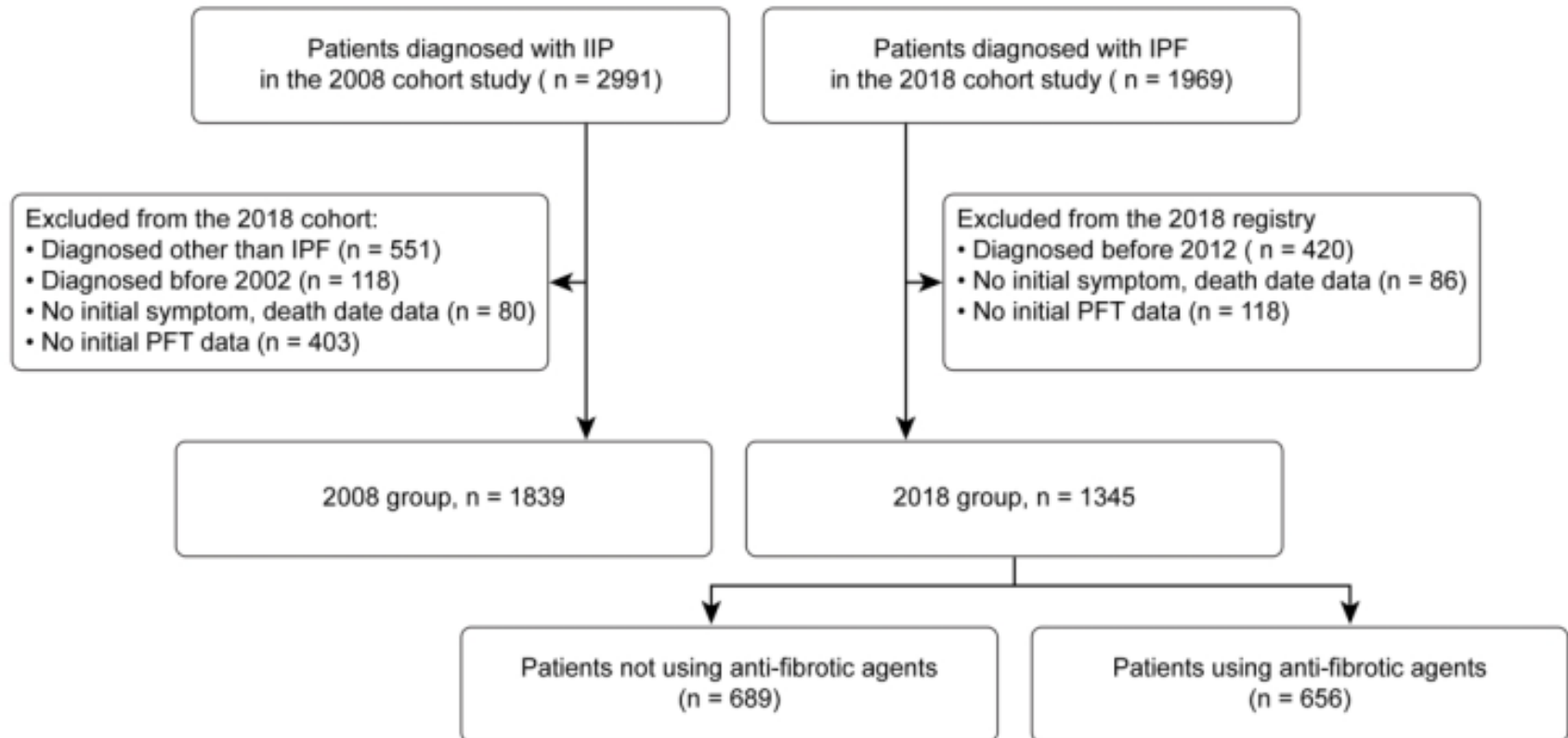
Antifibrotic	474	393	240	122	28	8
No-antifibrotic	474	392	294	224	160	122

# Outcomes with or without antifibrotic treatment

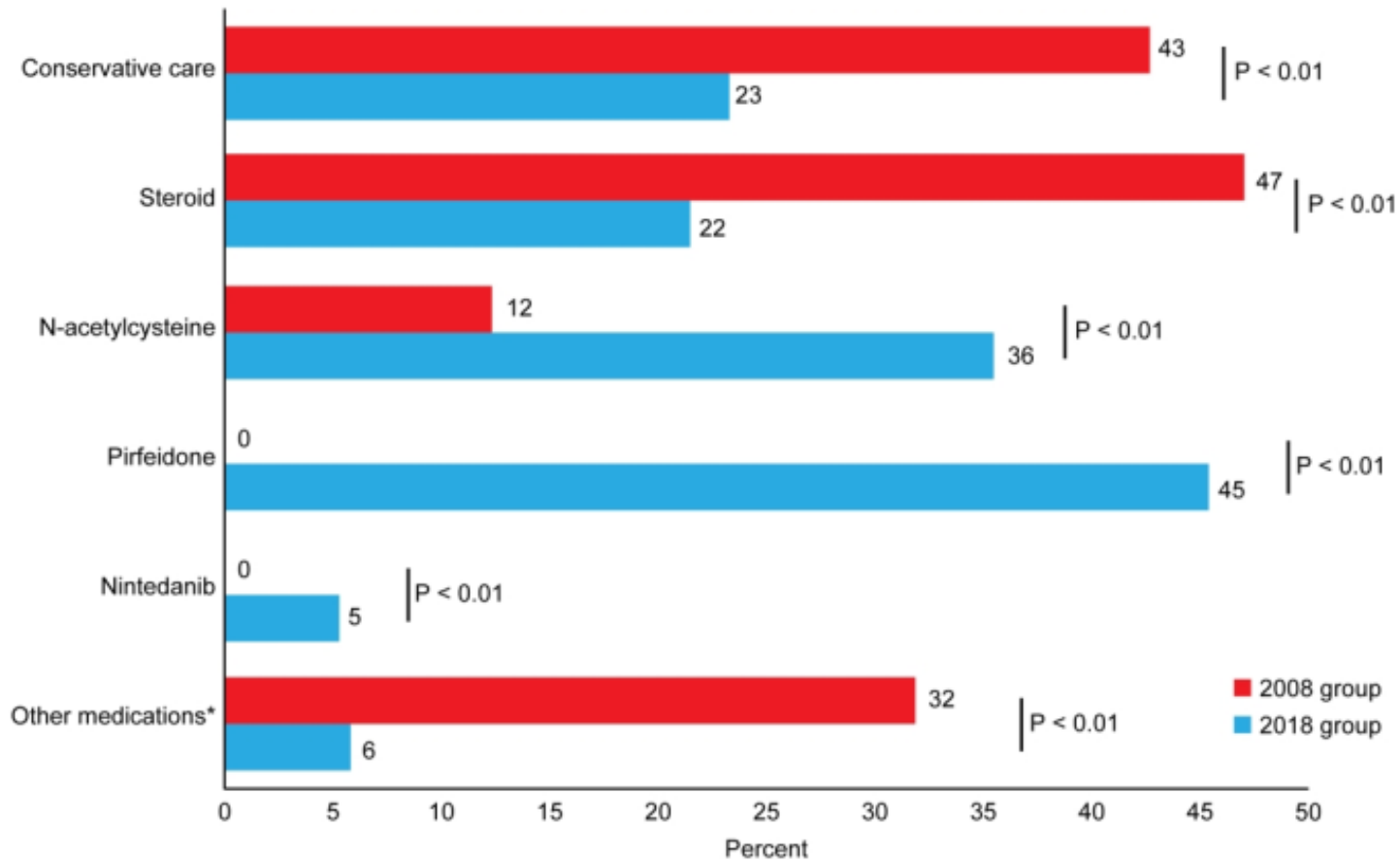


Our results suggest that antifibrotic treatment may reduce the risks of all-cause mortality, hospitalization, acute exacerbation, and mortality after acute exacerbation in patients with IPF.

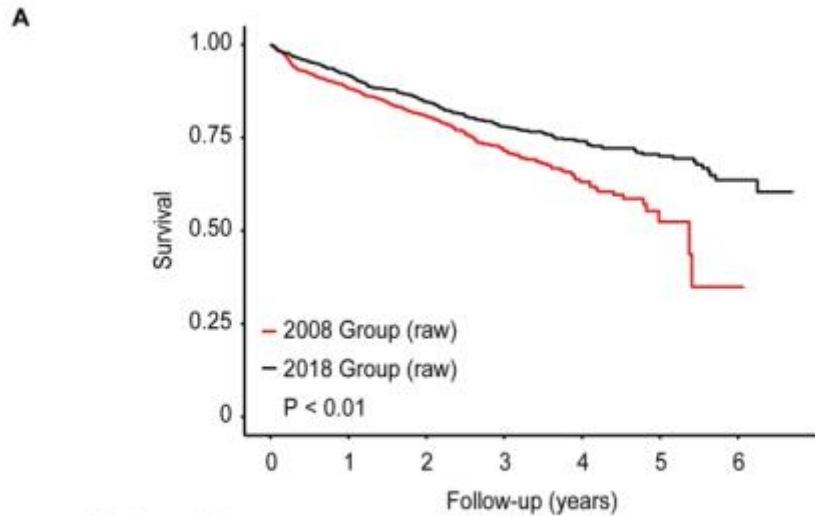
# Longitudinal Changes in Clinical Features, Management, and Outcomes of Idiopathic Pulmonary Fibrosis: A Nationwide Cohort Study



# Longitudinal changes in the use of pharmacologic agents

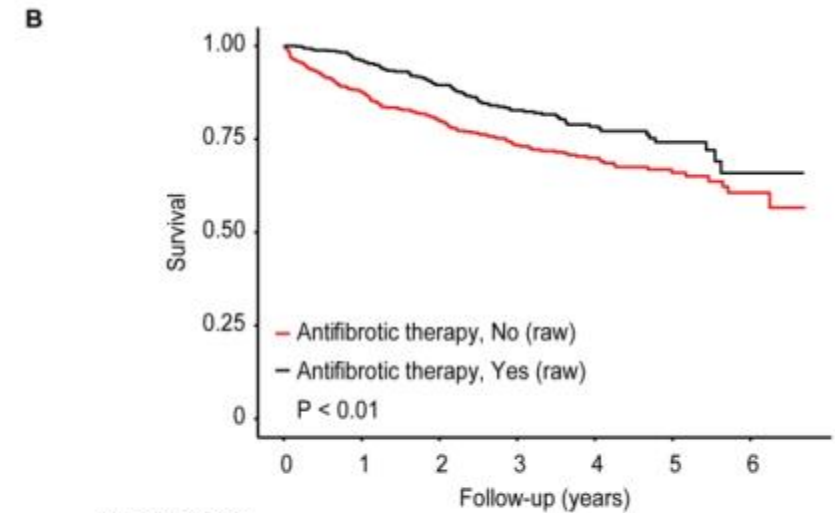


# Longitudinal changes in the use of pharmacologic agents



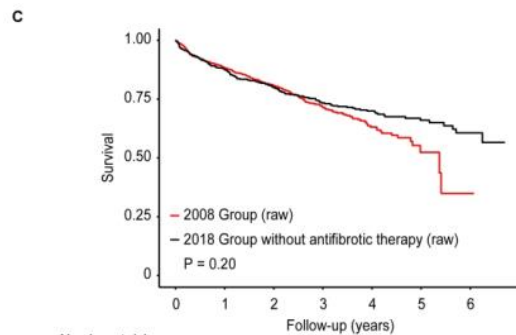
Number at risk

2008 group	1839	1219	909	909	698	556	461
2018 group	1345	1100	920	778	584	436	335



Number at risk

Antifibrotic therapy, No	689	564	482	424	324	252	199
Antifibrotic therapy, Yes	656	536	438	354	260	184	136



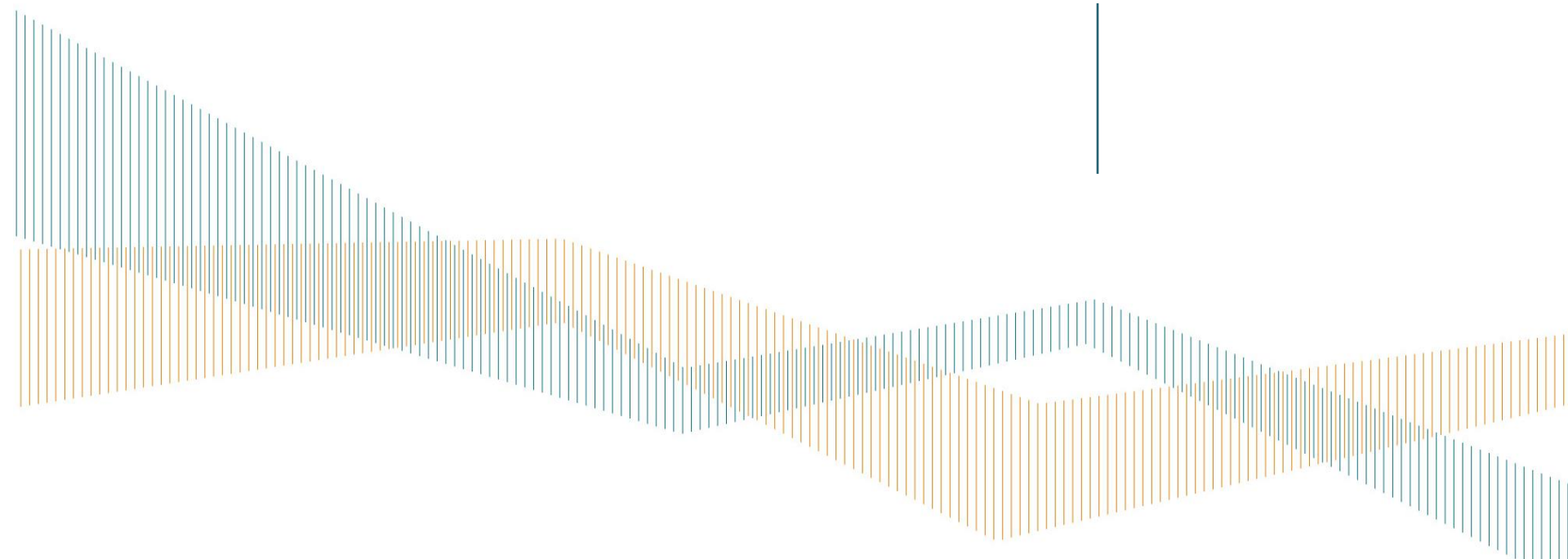
Number at risk

2008 group	1839	1219	909	698	556	476	461
2018 group without anti-fibrotic therapy	689	564	482	424	324	252	199

# Summary of real world data of antifibrotic therapy in IPF

- ✓ Antifibrotic therapy 는 IPF 에서 FVC 의 악화를 감소시키며 그 효과는 투여시기나 병의 중증도와 무관하다. 더 나아가 생존을 연장시킬 수도 있다.
- ✓ nintedanib 과 pirfenidone 의 효과와 부작용은 3상 연구와 비슷하다.
- ✓ Full dose 에 비해 reduced dose 는 효과가 적으므로 약제 부작용에 대해 적극적으로 치료할 필요가 있다. 그러나 reduced dose 라 할 지라도 계속 복용하는 것이 중단하는 것 보다 더 좋은 예후를 보인다.
- ✓ 약제 부작용이 있을 때 약을 잠시 중단하거나 용량을 줄이는 등의 적극적인 대처는 약의 중단을 줄일 수 있다.

# PF-ILD



# Definition of PF ILD



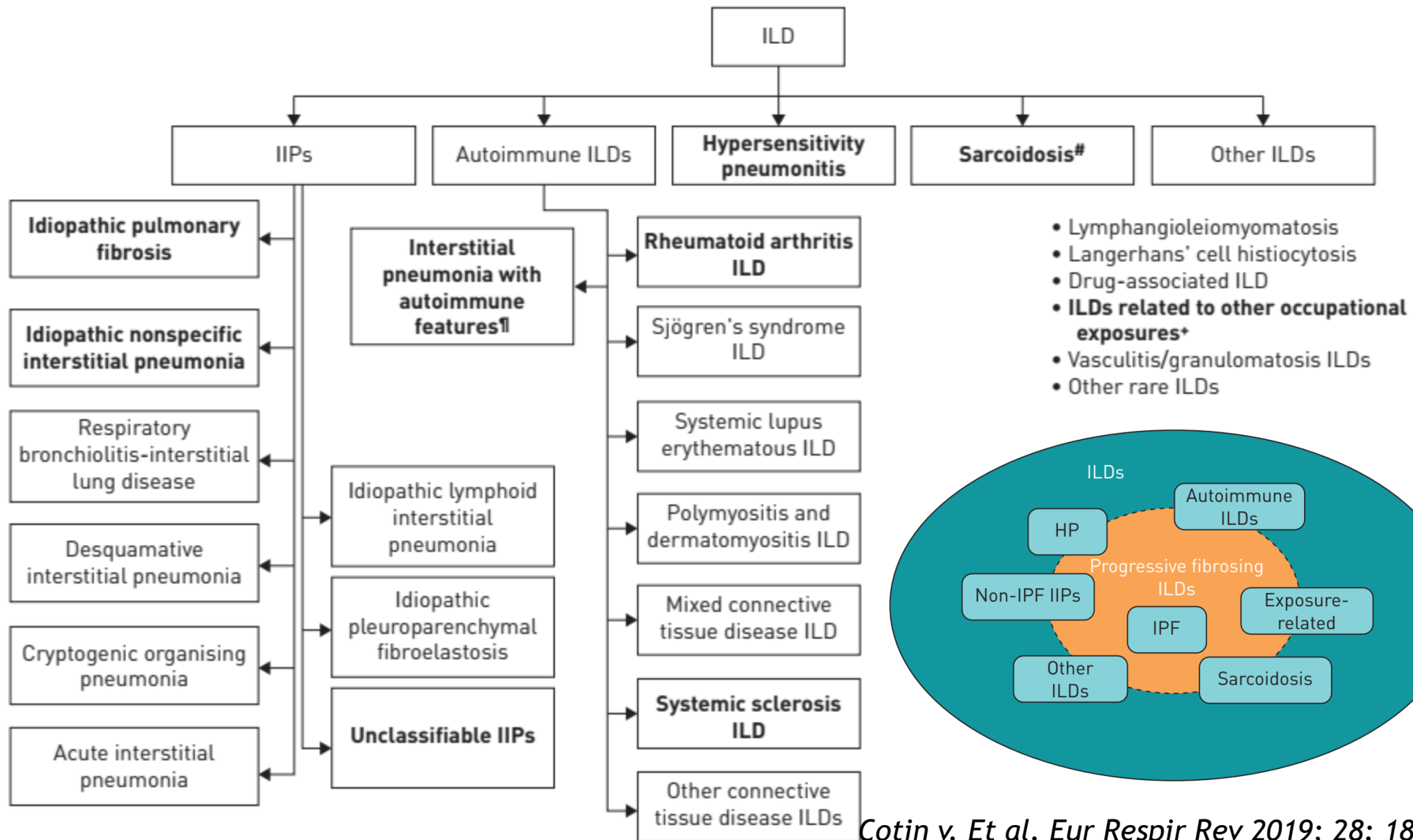
The terminology “**progressive fibrosing ILDs**” has been coined to describe ILD in patients who, **independent of the classification of the ILD**, at some point in time exhibit a **progressive fibrosing phenotype**.

# Criteria for disease progression

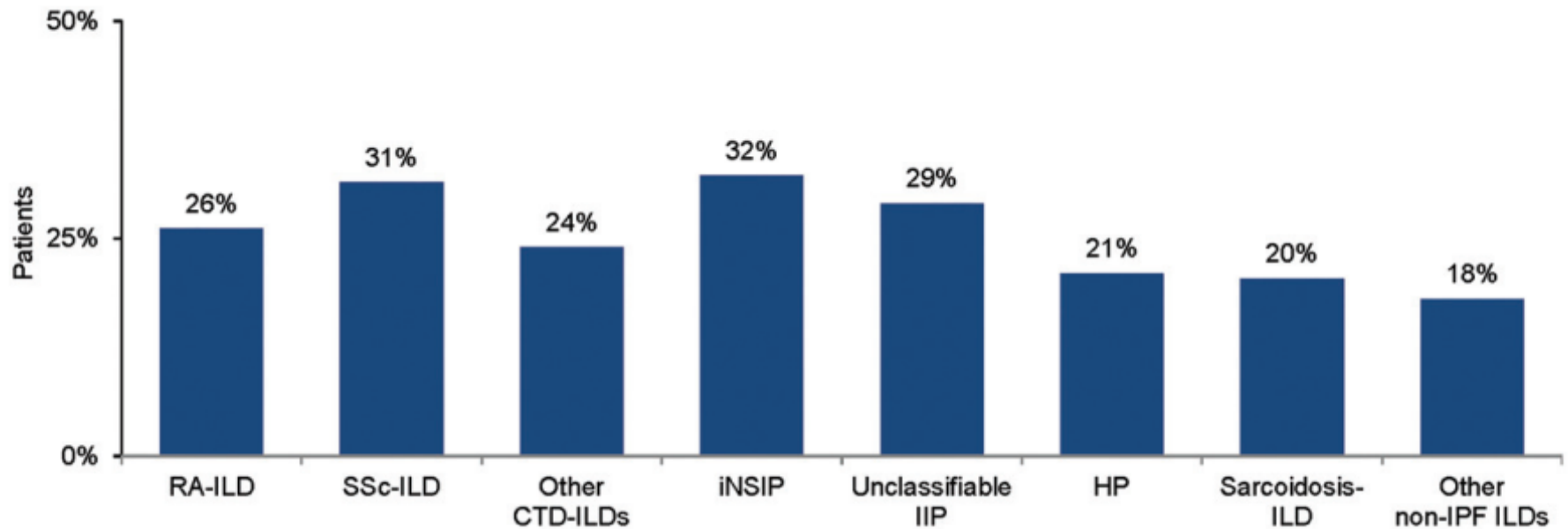
Clinical trial	Design	Criteria for disease progression				Study duration	Outcomes
		Time frame	Pulmonary function	Symptoms	HRCT		
Nintedanib in non-IPF PF-ILD [4 <sup>■</sup> ]	Phase 3, double-blinded, placebo, RCT	24 months	FVC $\geq$ 10% decline (relative) or two of these: FVC 5–10% decline (relative)	Worsening symptoms	Increased extent of fibrosis	52 weeks	Annual rate of decline in FVC at 52 weeks: between-group difference 107.0–ml (95% CI 65.4–148.5)
Pirfenidone in progressive unclassifiable ILD [5 <sup>■</sup> ]	Phase 2, double-blinded, placebo, RCT	6 months	FVC > 5% decline (absolute)	Worsening symptoms		24 weeks	Predicted mean change in FVC over 24 weeks <sup>a</sup> : between-group difference 95.3–ml (95% CI 35.9–154.6)
Pirfenidone in non-IPF PF-ILD (RELIEF) [41]	Phase 2, double-blinded, placebo, RCT	12 months	FVC $\geq$ 5% decline (absolute)			48 weeks	Absolute change in percentage predicted FVC over 48 weeks: favored pirfenidone <sup>b</sup>
Pirfenidone in patients with RA-ILD (TRAIL1) [42]	Phase 2, double-blinded, placebo, RCT	12 months	FVC $\geq$ 10% decline (relative) or FVC 5–10% decline (relative) and DLCO $\geq$ 15% decline (relative)			52 weeks	The composite endpoint of decline in percentage predicted FVC of at least 10% or death: not completed

# Types of ILD

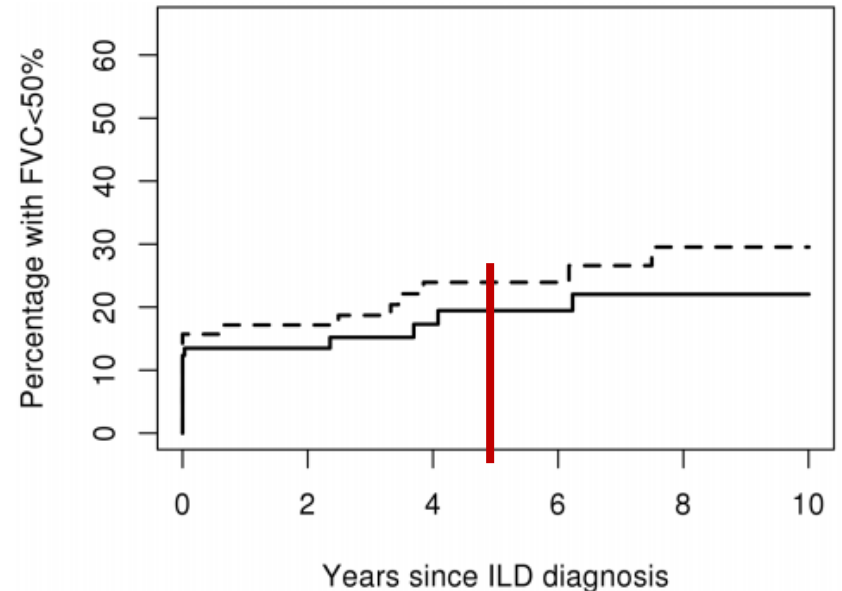
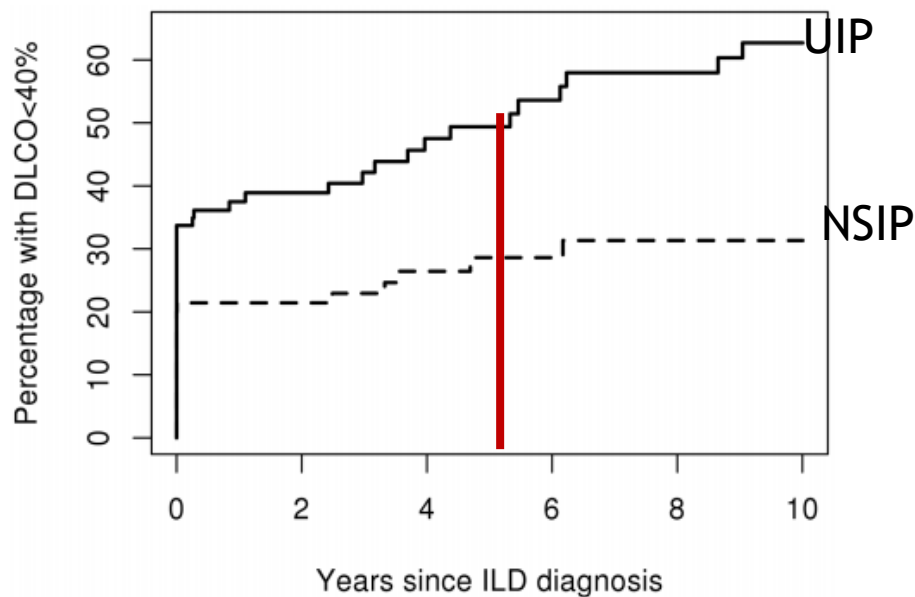
:Most likely to have a progressive-fibrosing phenotype



# Non-IPF ILDs developing PF-ILD

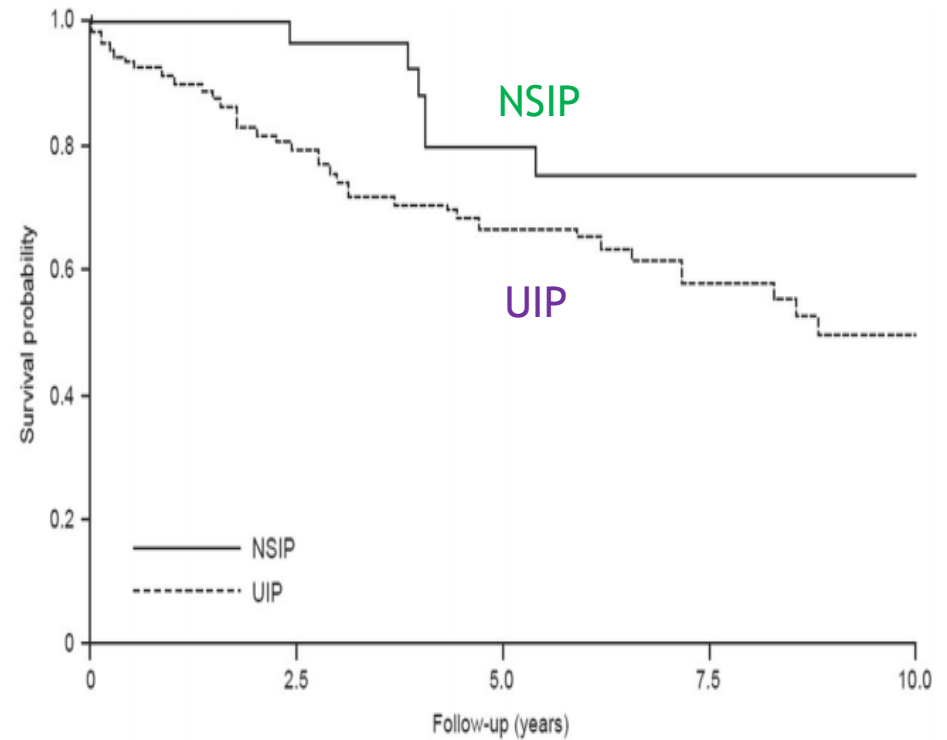
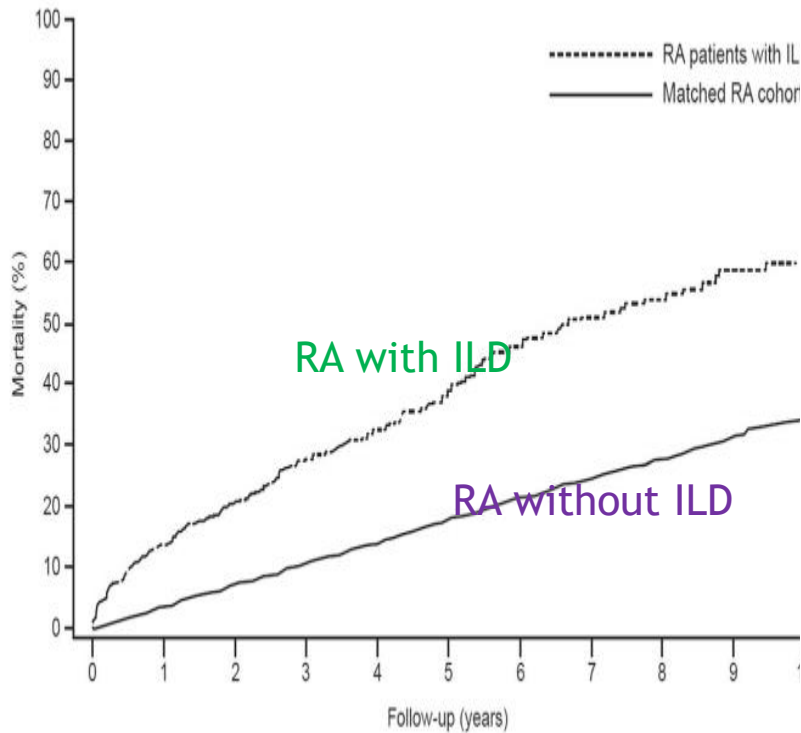


# Progressive decline of lung function in RA-ILD



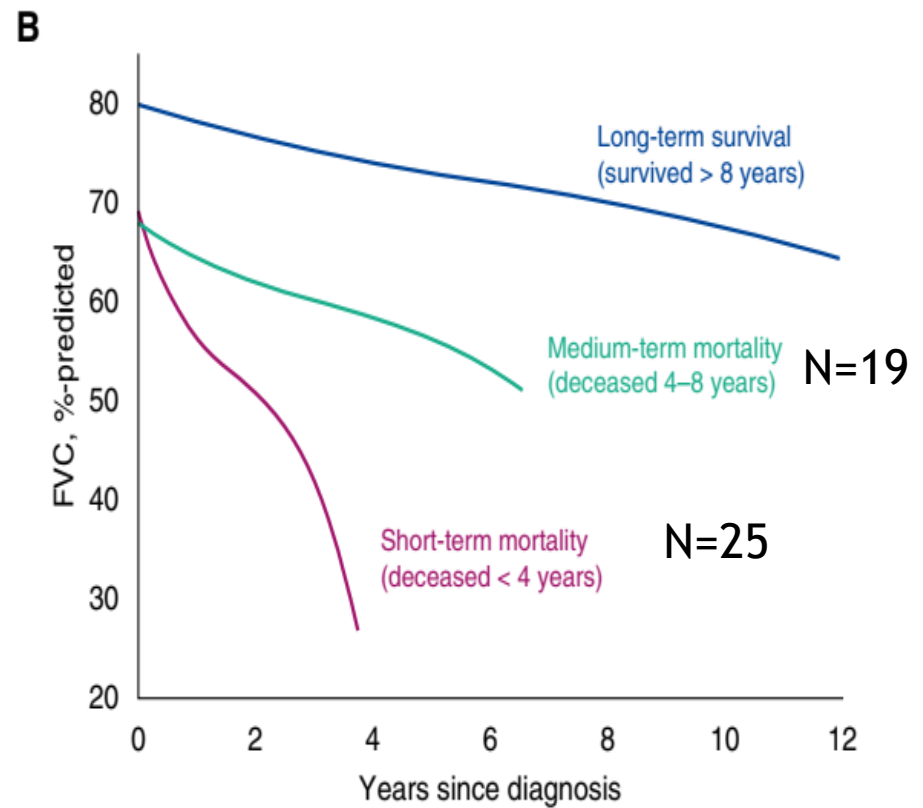
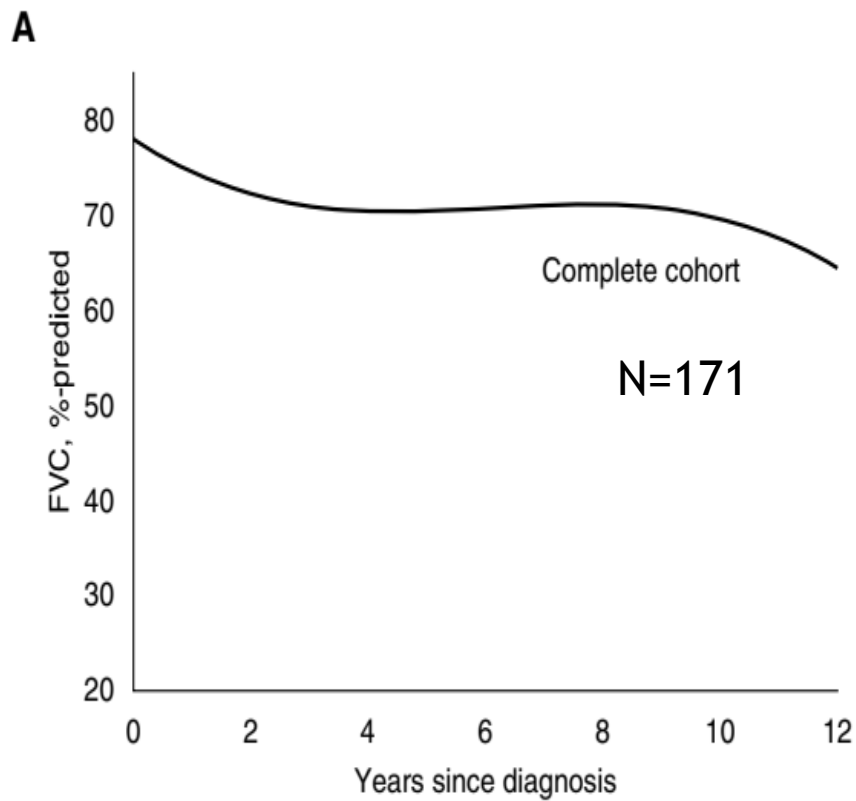
A third of patients required supplemental oxygen, 40% developed DLCO < 40% predicted and 22% developed FVC < 50% predicted by 5 years after ILD diagnosis.

# ILDs in Rheumatoid arthritis and survival



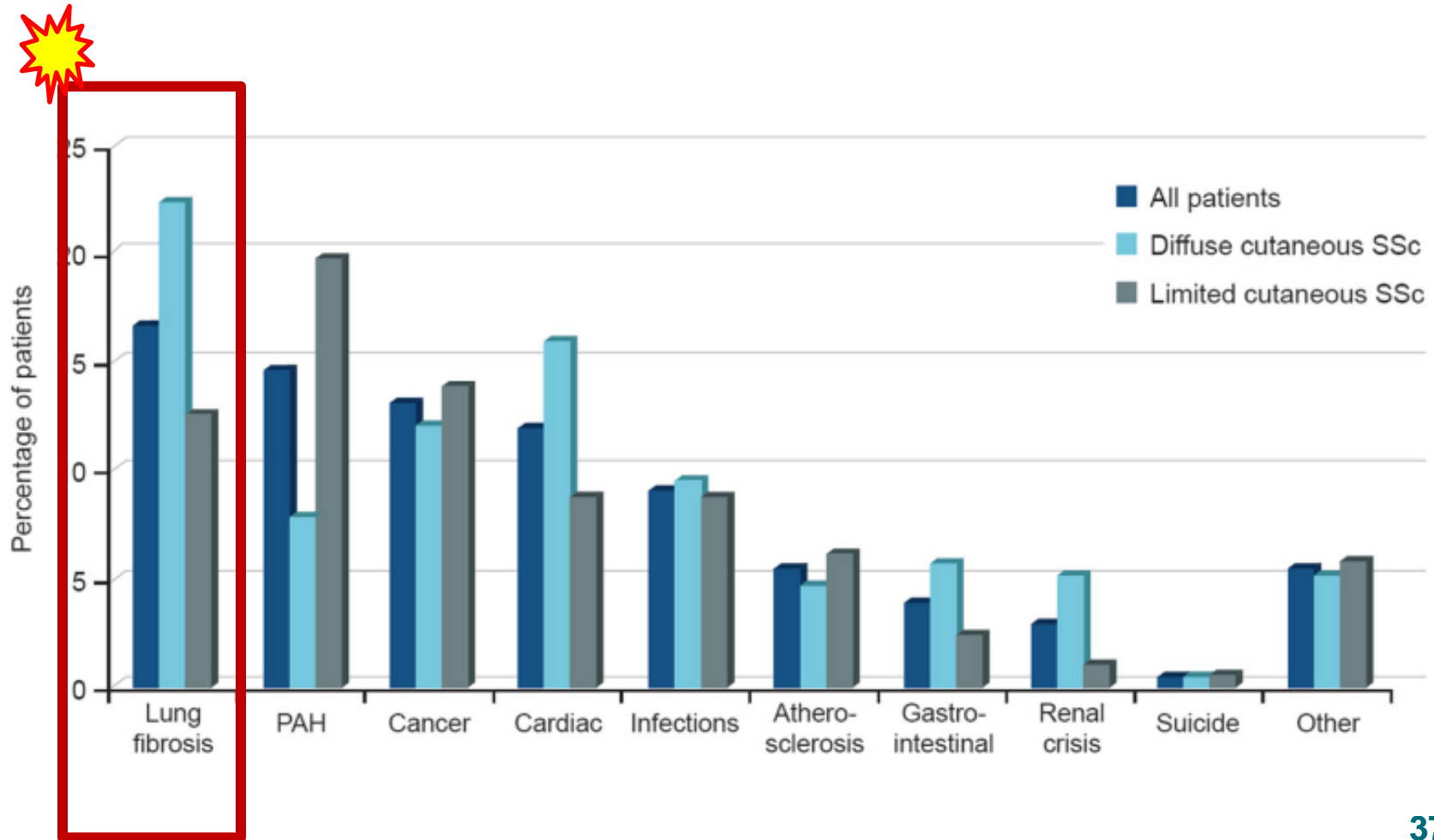
NSIP	29	29	29	24	23	18	16	13	8	6	5
UIP	108	97	89	69	59	48	39	32	23	19	14

# Specific phenotypes of disease progression in SSc-ILD

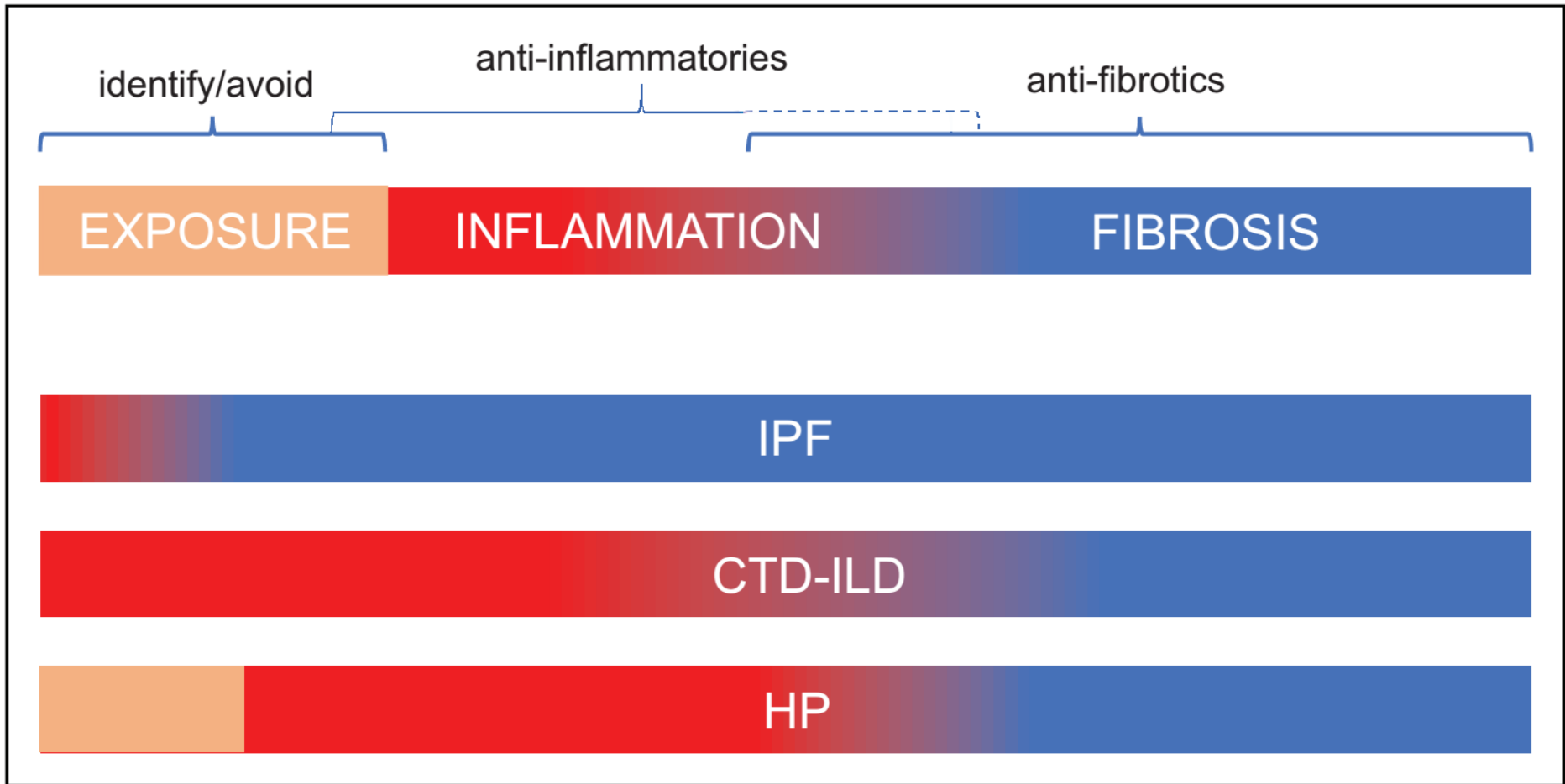


# Cause of death in pts with SSc

:The European Scleroderma Trials and Research (EUSTAR)



# Overlapping pathogenesis of PF-ILD



**Early Phase (Underlying Disease-Specific)**

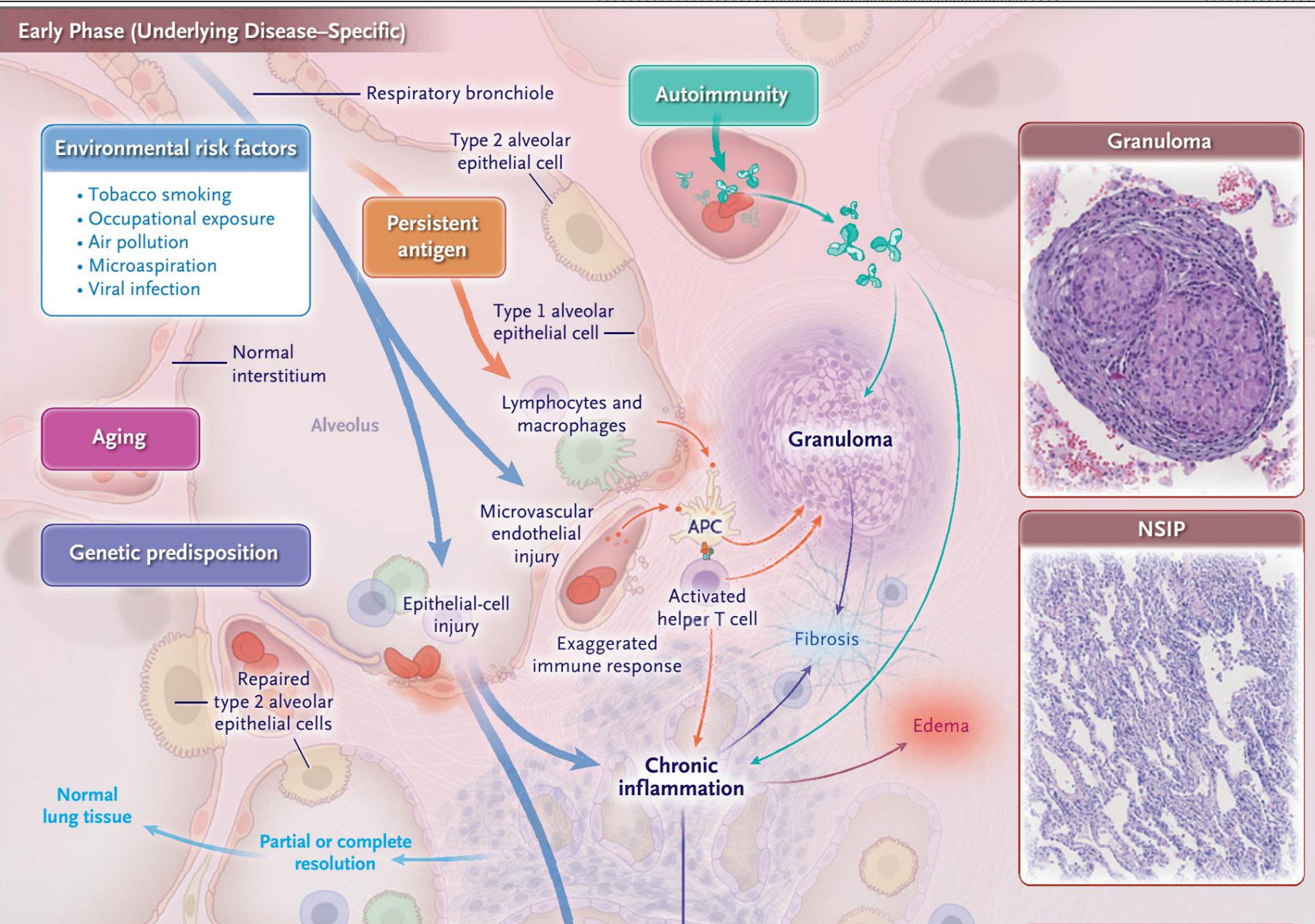
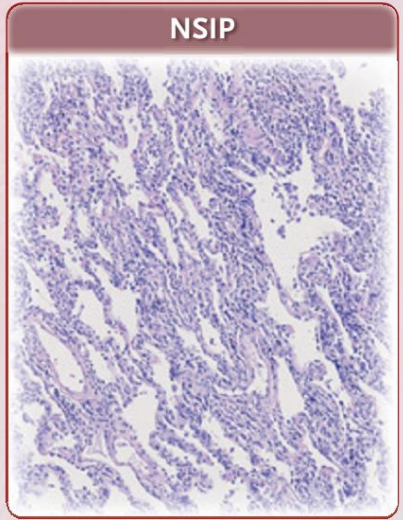
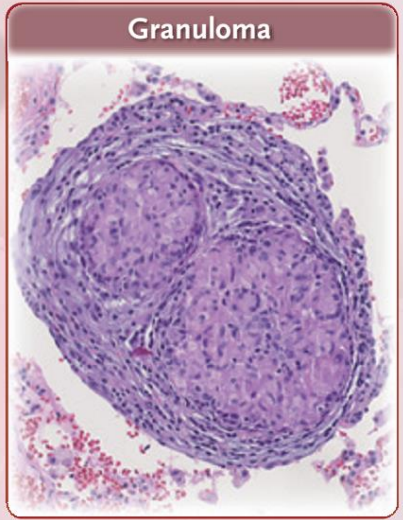
- Environmental risk factors**
- Tobacco smoking
  - Occupational exposure
  - Air pollution
  - Microaspiration
  - Viral infection

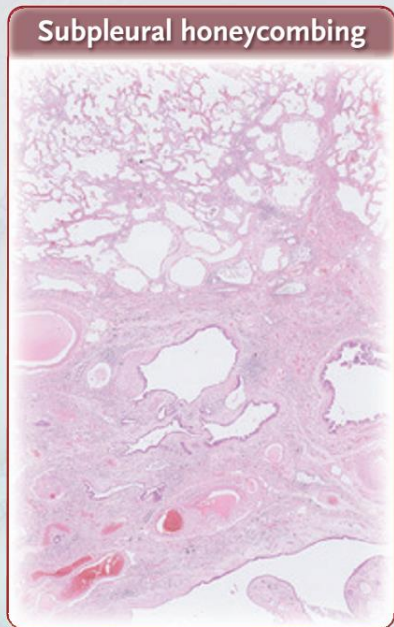
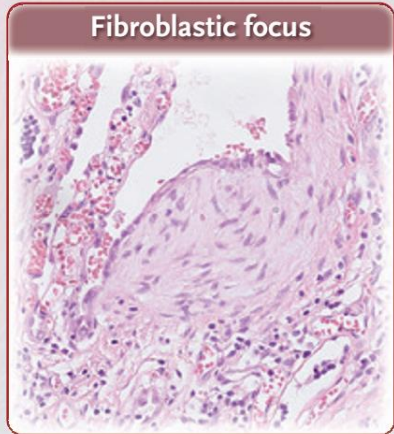
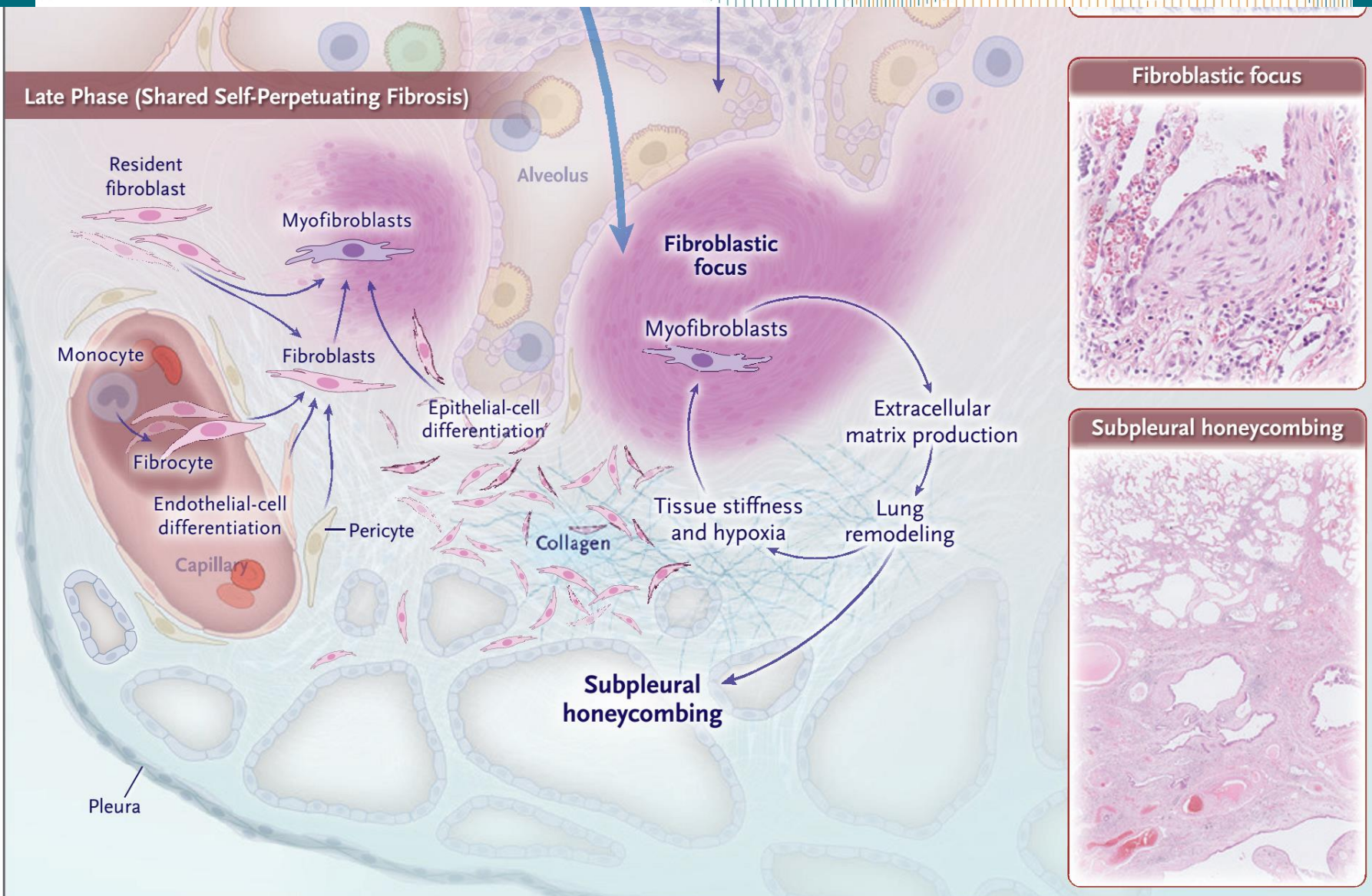
**Aging**

**Genetic predisposition**

**Persistent antigen**

**Autoimmunity**





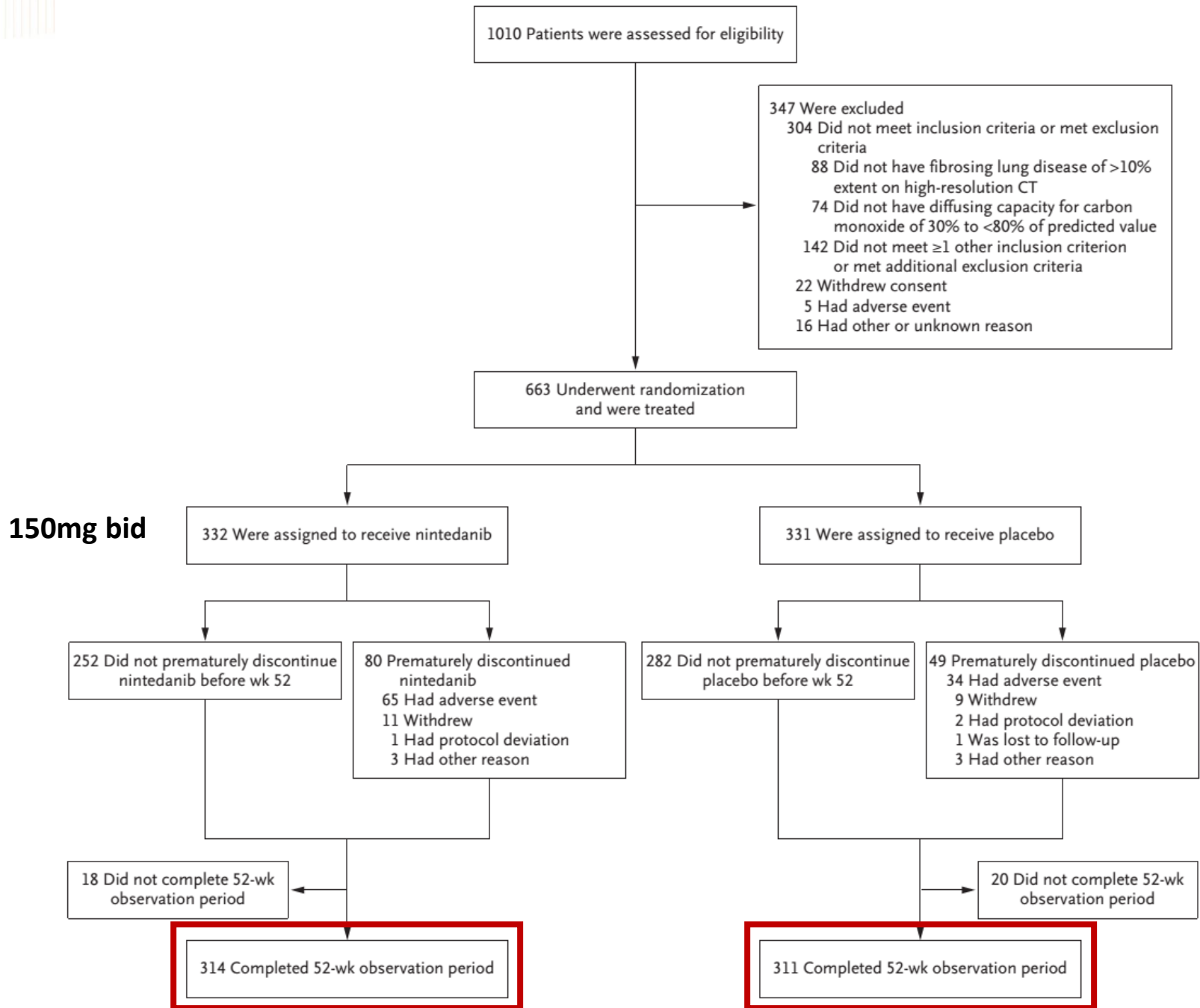
ORIGINAL ARTICLE



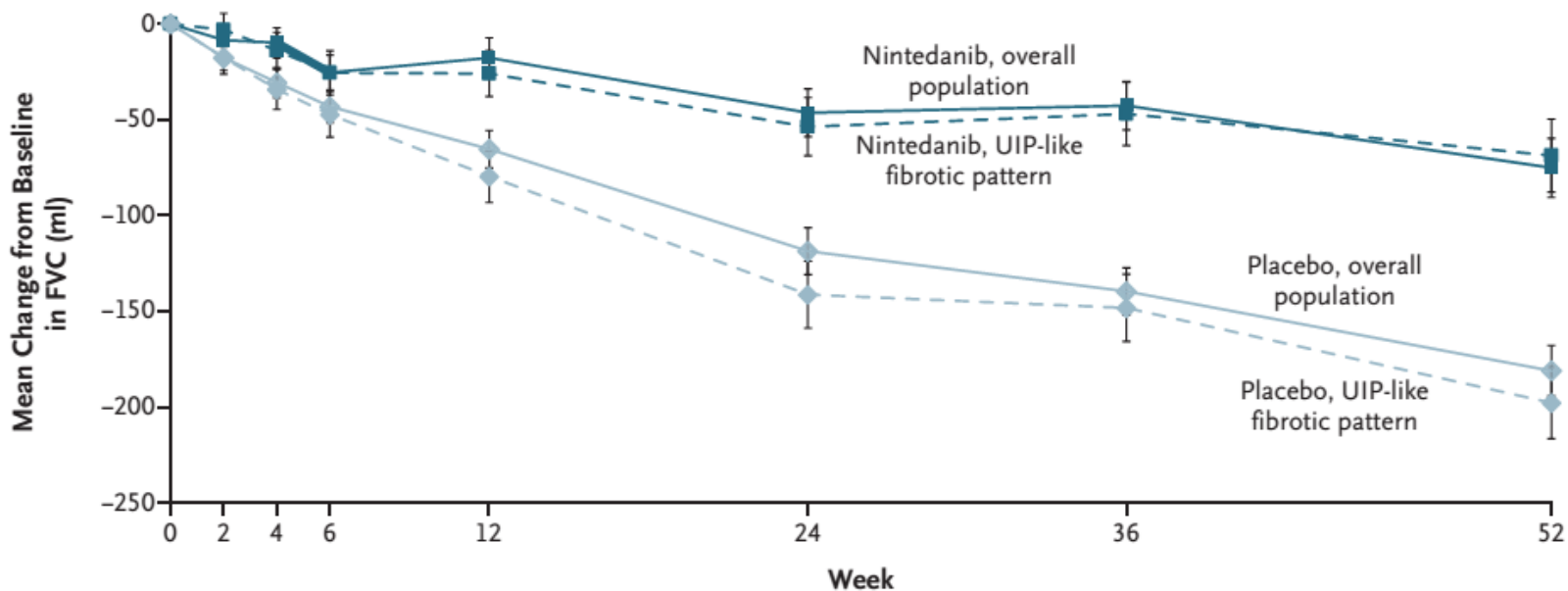
**Nintedanib** in Progressive Fibrosing  
Interstitial Lung Disease

K.R. Flaherty, A.U. Wells  
M. Kolb, K. Tetzlaff, S.  
M. Quaresma, T. Haeuf  
fc

- ✓  $\geq 18$  years
- ✓ physician-diagnosed fibrosing ILD other than IPF
- ✓  $> 10\%$  of lung volume on HRCT
- ✓ at least one of the following criteria for progression of ILD within the 24 months
  - relative decline of FVC  $\geq 10\%$
  - $5\% \leq$  decline FVC  $< 10\%$  & worsening symptoms or increased extent of fibrosis on high-resolution CT
  - worsening of respiratory symptoms & an increased extent of fibrosis
- ✓ FVC  $\geq 45\%$  and  $30\% \leq$  DLco  $< 80\%$



# INBUILD: Decline from baseline in FVC



## No. of Patients

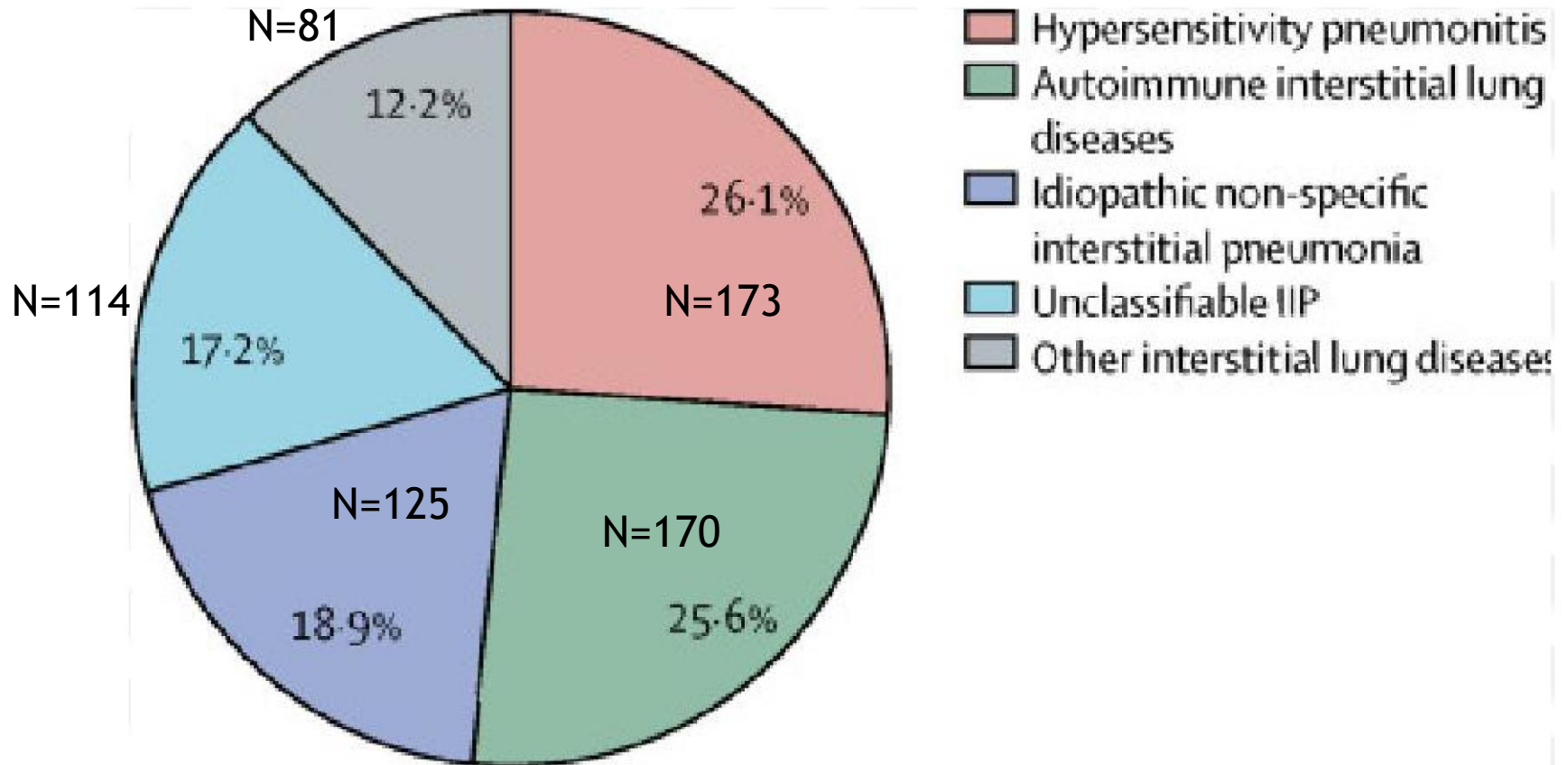
### Overall population

Nintedanib	332	326	320	322	314	298	285	265
Placebo	331	325	326	325	320	311	296	274

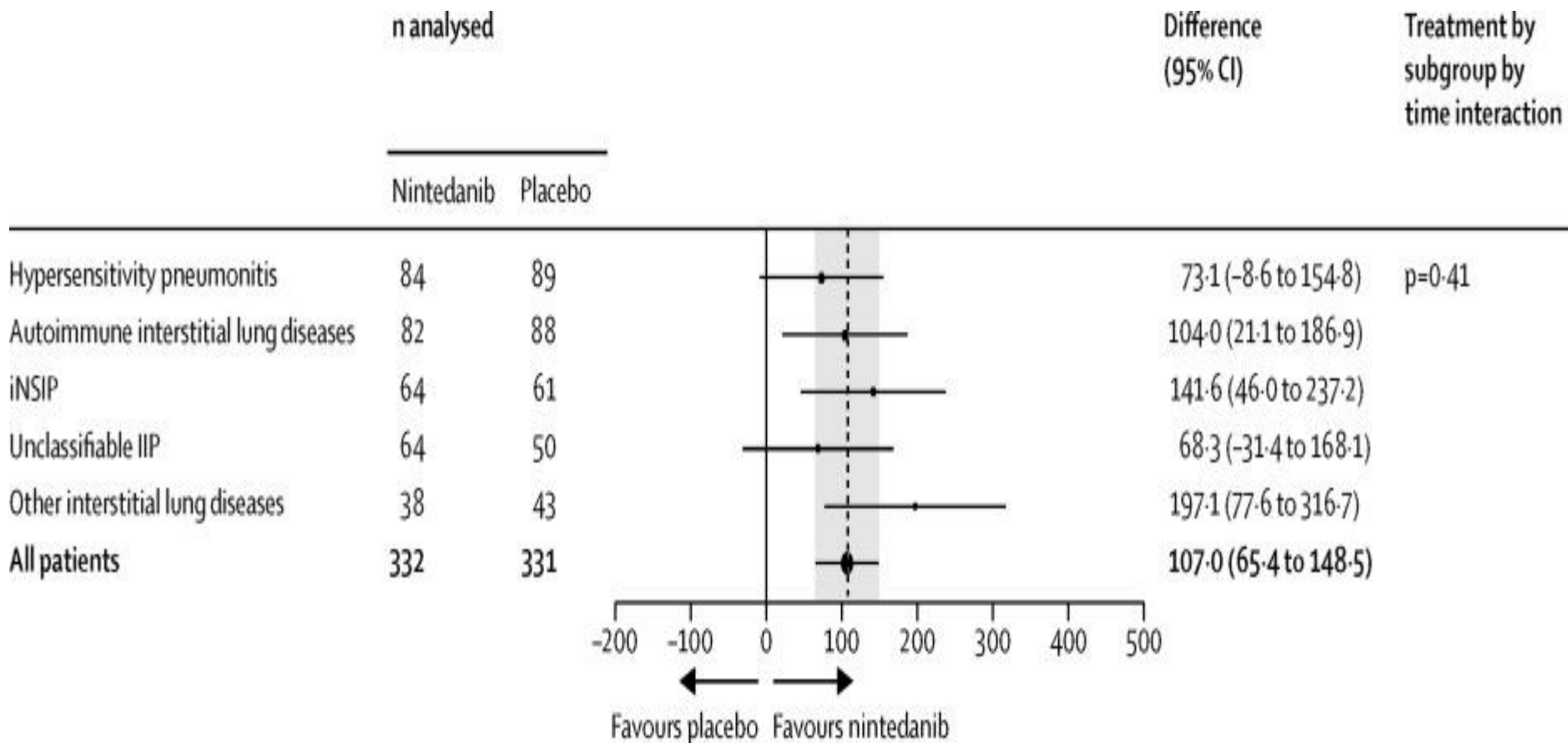
### Patients with UIP-like fibrotic pattern

Nintedanib	206	203	200	199	193	180	171	160
Placebo	206	202	202	201	197	190	176	162

# INBUILD: The distribution of participants



# INBUILD: subgroup analysis



# SENSIS-Nintedanib in SSc-ILD

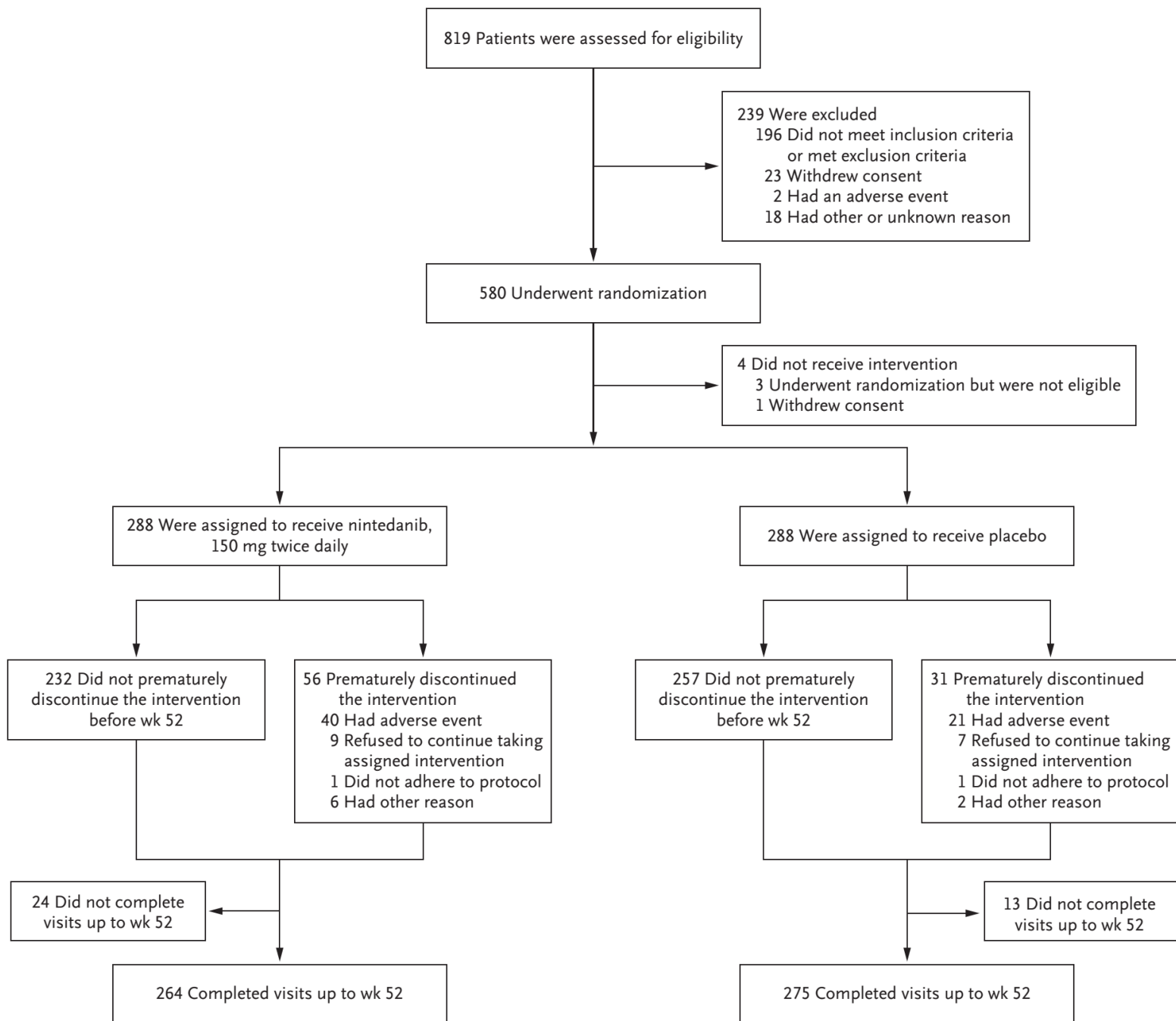
The NEW ENGLAND JOURNAL of MEDICINE

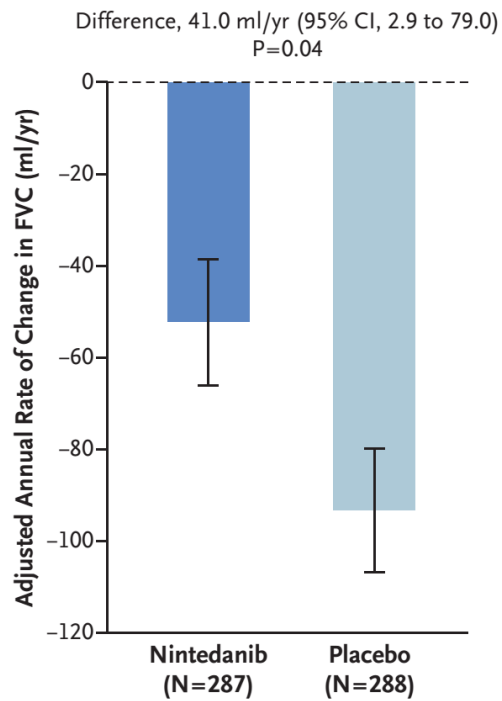
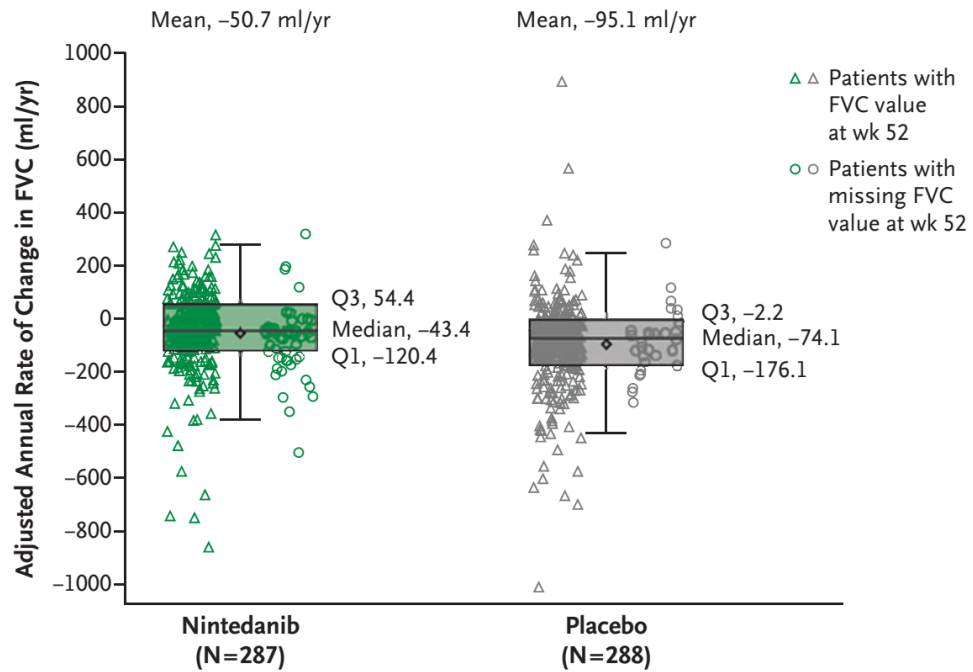
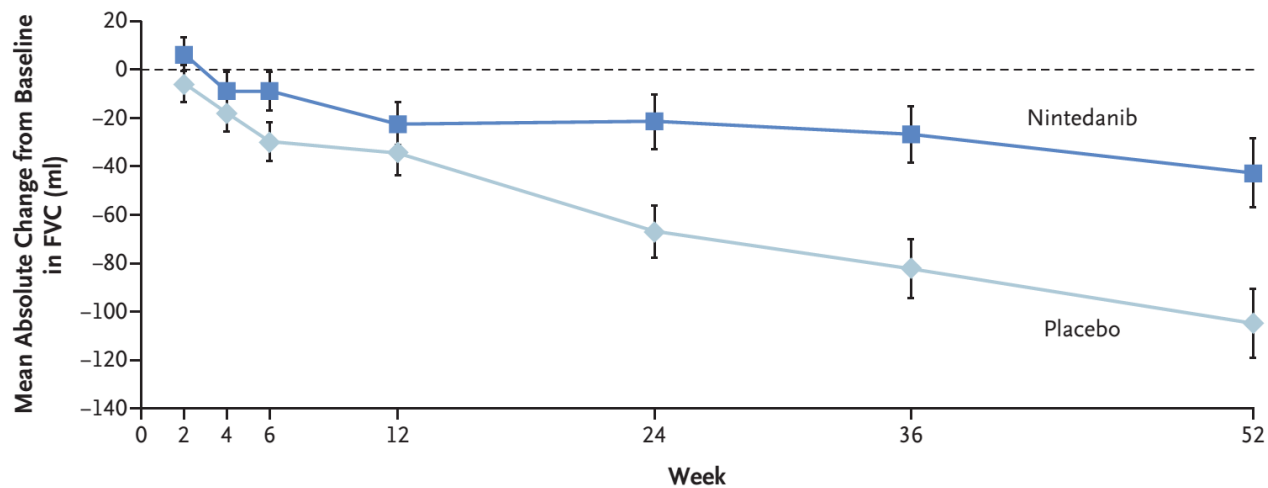
## ORIGINAL ARTICLE

- ✓ November 2015 - October 2017
- ✓  $\geq 18$  years of age
- ✓ onset of the first non-Raynaud's symptom  $\leq 7$  years
- ✓ HRCT  $\leq 12$  months before screening
- ✓ Fibrosis affecting at least  $\geq 10\%$  of the lungs
- ✓ FVC  $\geq 40\%$  and Dlco 30-89%
- ✓ PD  $\leq 10$  mg /day
- ✓ MMF or MTX at a stable dose  $\geq 6$ M

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tors\*



**A****B****C****No. of Patients**

Nintedanib	288	283	281	273	278	265	262	241
Placebo	288	283	281	280	283	280	268	257

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

Toby M Maher,<sup>1,2</sup> Tamera J Corte,<sup>3,4</sup> Aryeh Fischer,<sup>5</sup> Michael Kreuter,<sup>6</sup> David J Lederer,<sup>7</sup> Maria Molina-Molina,<sup>8,9</sup> Judit Axmann,<sup>10</sup> Klaus-Uwe Kirchgaessler,<sup>10</sup> Vincent Cottin<sup>11,12</sup>

Treatment period  
Weeks 1 to 24

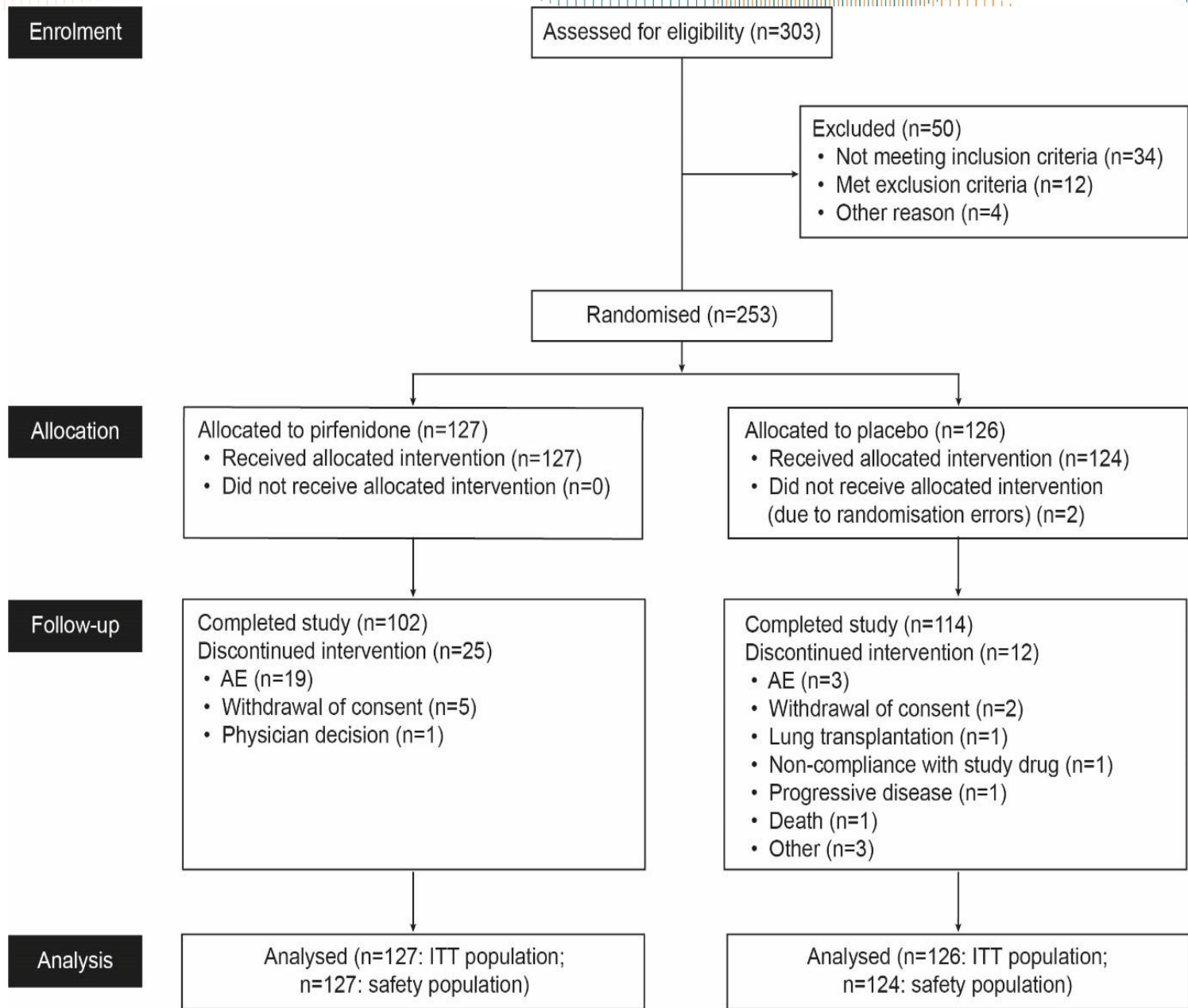
## Description of inclusion criteria

- ▶ Extent of fibrosis >10% on HRCT (visual scoring) within the last 12 months.
- ▶ Spirometry criteria: FVC  $\geq$ 45% predicted, DLco  $\geq$ 30% predicted, FEV<sub>1</sub>/FVC ratio  $\geq$ 0.7.
- ▶ 6MWD  $\geq$ 150 m.
- ▶ Progressive disease: absolute decline in per cent predicted FVC >5% or significant symptomatic worsening not due to cardiac, pulmonary, vascular or other causes in the previous 6 months.

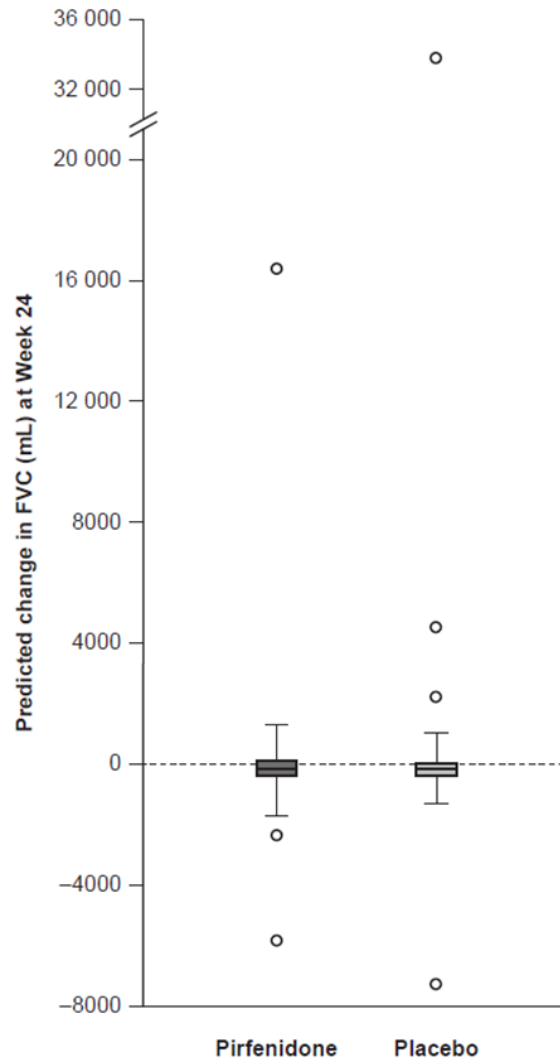
We  
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ICF†

p visit‡  
28

pirfenidone or placebo (1:1)

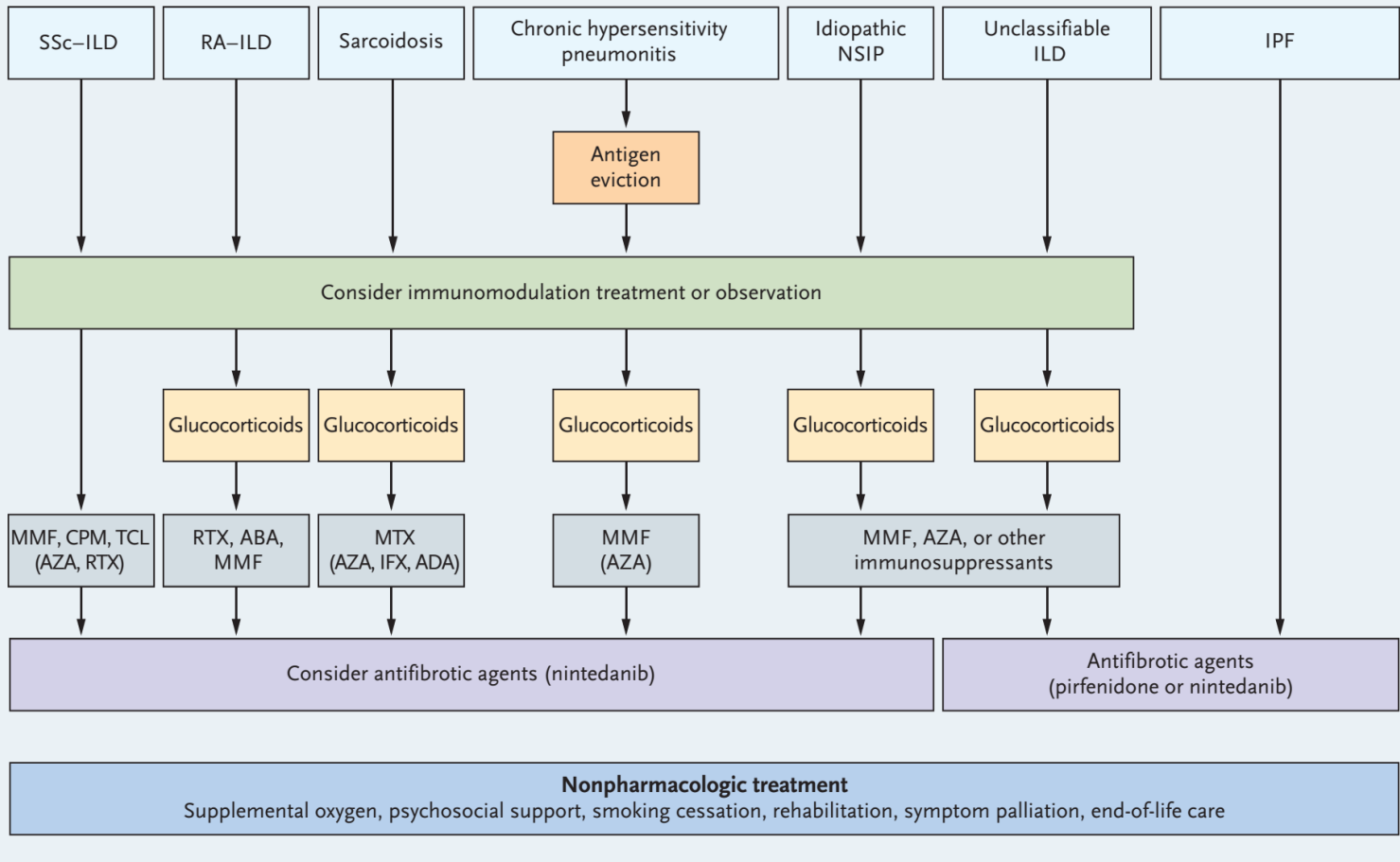


# Change in FVC (mL) measured by daily home spirometry



FVC change (mL) from baseline at Week 24	Pirfenidone	Placebo
Mean	-17.9	116.6
Median	-87.7	-157.1

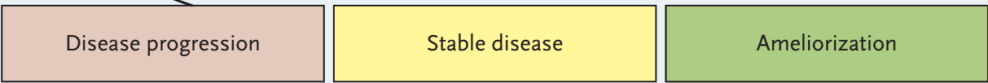
**Management**



Reconsider Management

Regular Follow-up

**Monitoring of Disease Course**





울산대학교병원  
ULSAN UNIVERSITY HOSPITAL

***Thank you!***

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