ILD 환자에서의 항섬유화제 사용과 관리

29. JUN. 2024

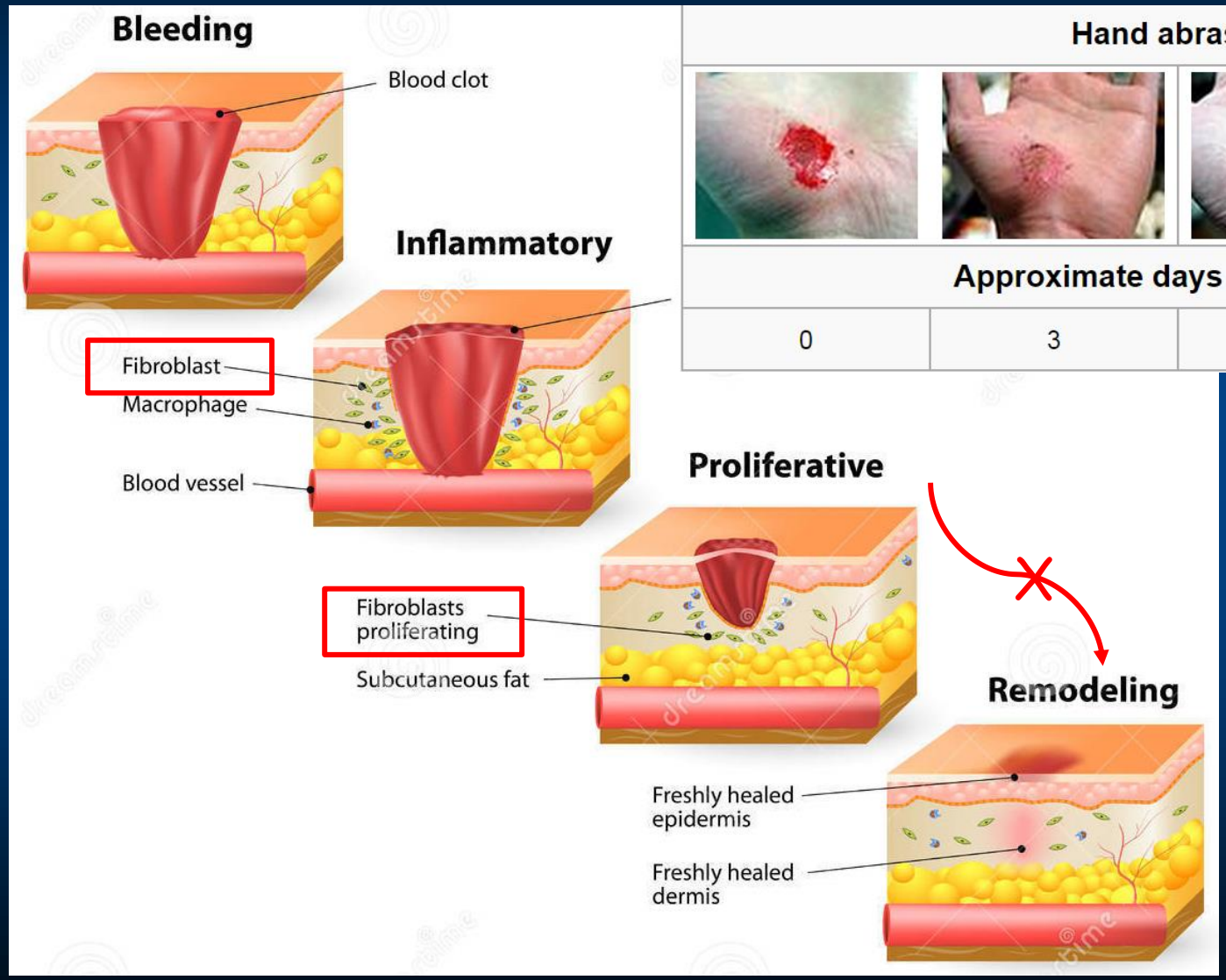
Jin Woo Song

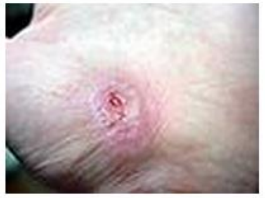
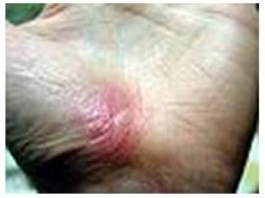
Asan Medical Center, Seoul, Republic of Korea

Contents

- 항섬유화제
  - 소개
  - 유용성
  - 안전성 및 부작용 관리
  - 치료전망

Fibrosis: wound healing process



Hand abrasion			
			
Approximate days since injury			
0	3	17	30

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

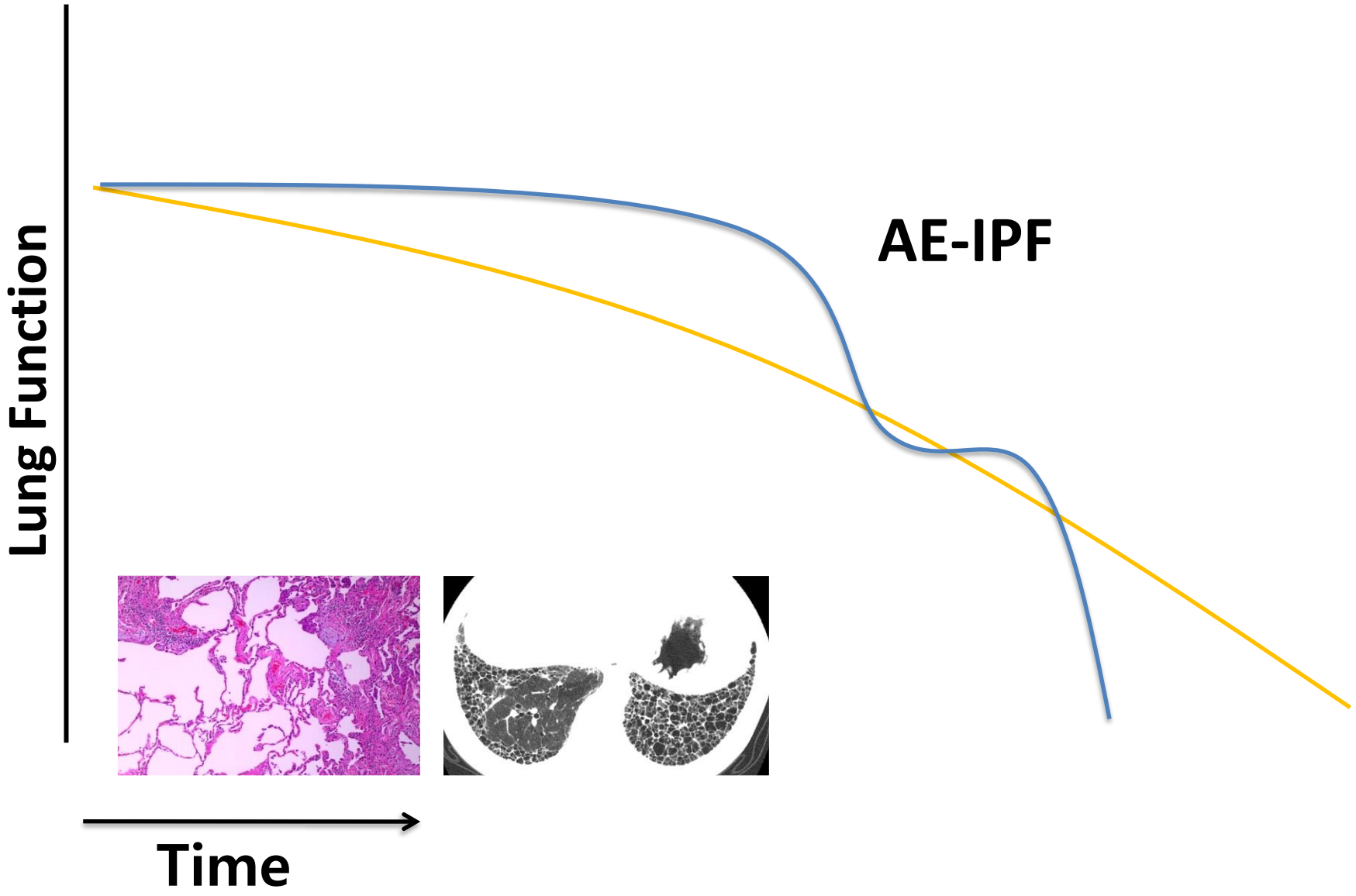
Fibrosis — A Common Pathway to Organ Injury and Failure

Don C. Rockey, M.D., P. Darwin Bell, Ph.D., and Joseph A. Hill, M.D., Ph.D.

- Fibrosis and resultant organ failure account for at least **one third of deaths**.
- Since fibrosis is common and has adverse effects in all organs, it is an **attractive therapeutic target**.
- Contrary to the widely held perception that scar tissue is permanent, the available evidence points to the **hightly plastic nature of organ fibrosis**.

Rocky DC et al. *N Engl J Med* 2015;372:1138-49

IPF is the prototype of progressive fibrosing ILD

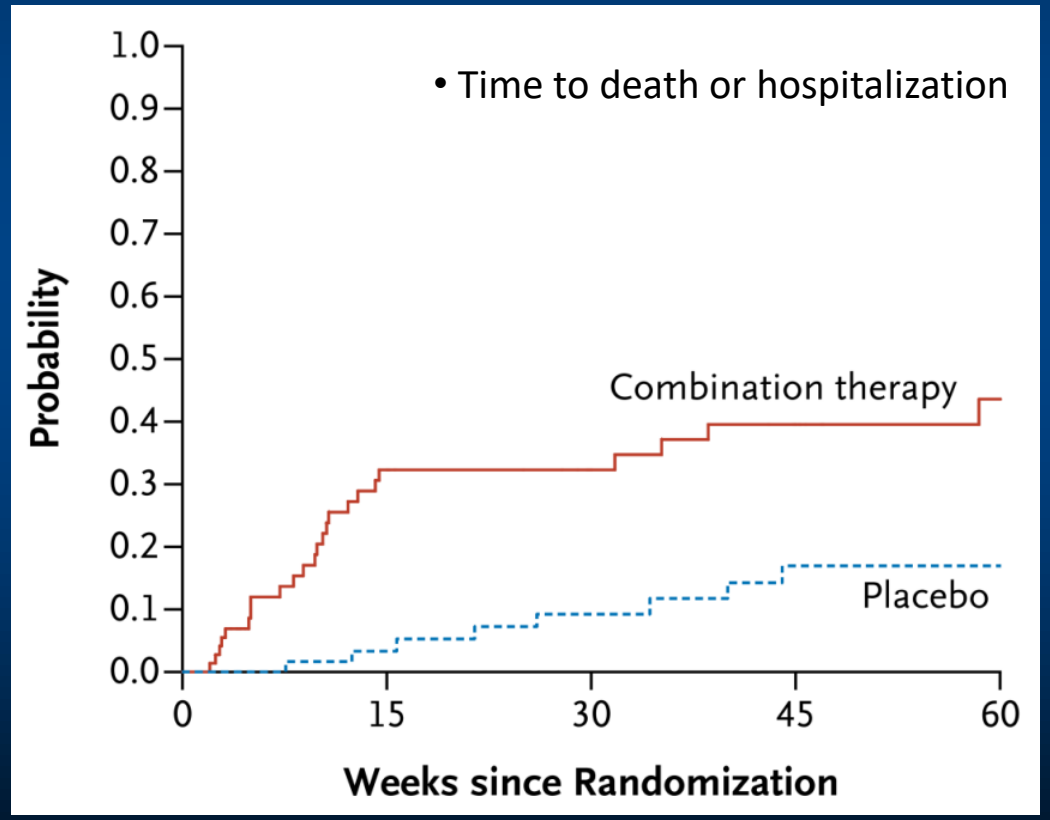


AE: acute exacerbation, IPF: idiopathic pulmonary fibrosis

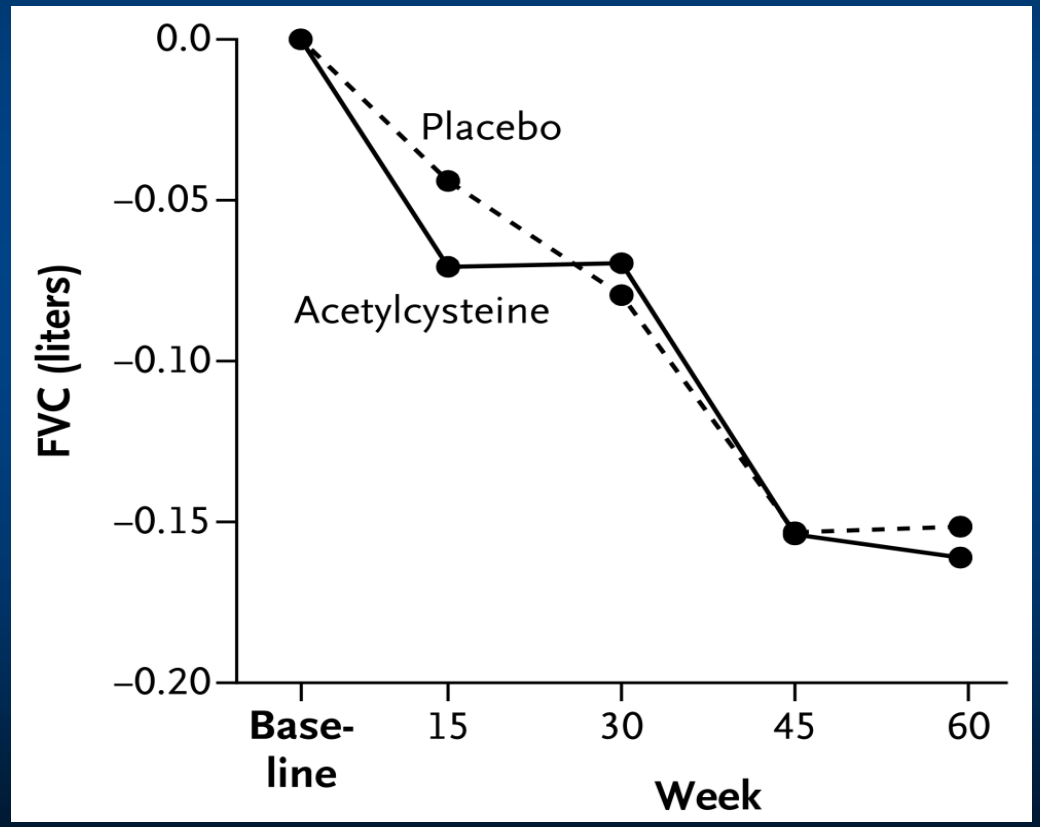
Raghu G et al. *Am J Respir Crit Care Med*. 2011;183:788

IPF (CFA): inflammation driven fibrosis

- Triple combination



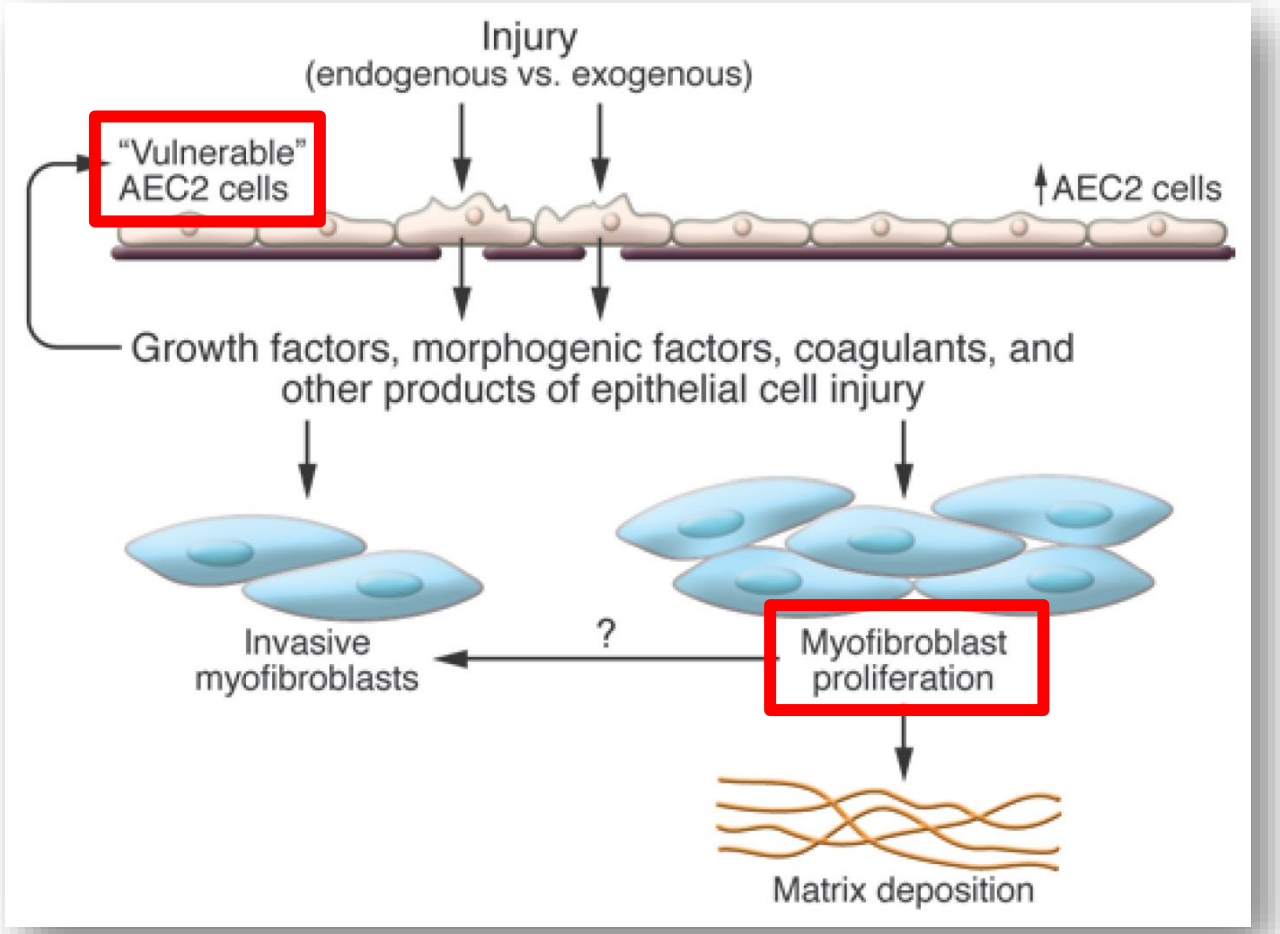
- N-acetylcysteine



CFA: ctyptogenic fibrosing alveolitis

IPF clinical research network, *N Engl J Med*. 2012;366:1968-1977, *N Engl J Med*. 2014;370:2093-2101

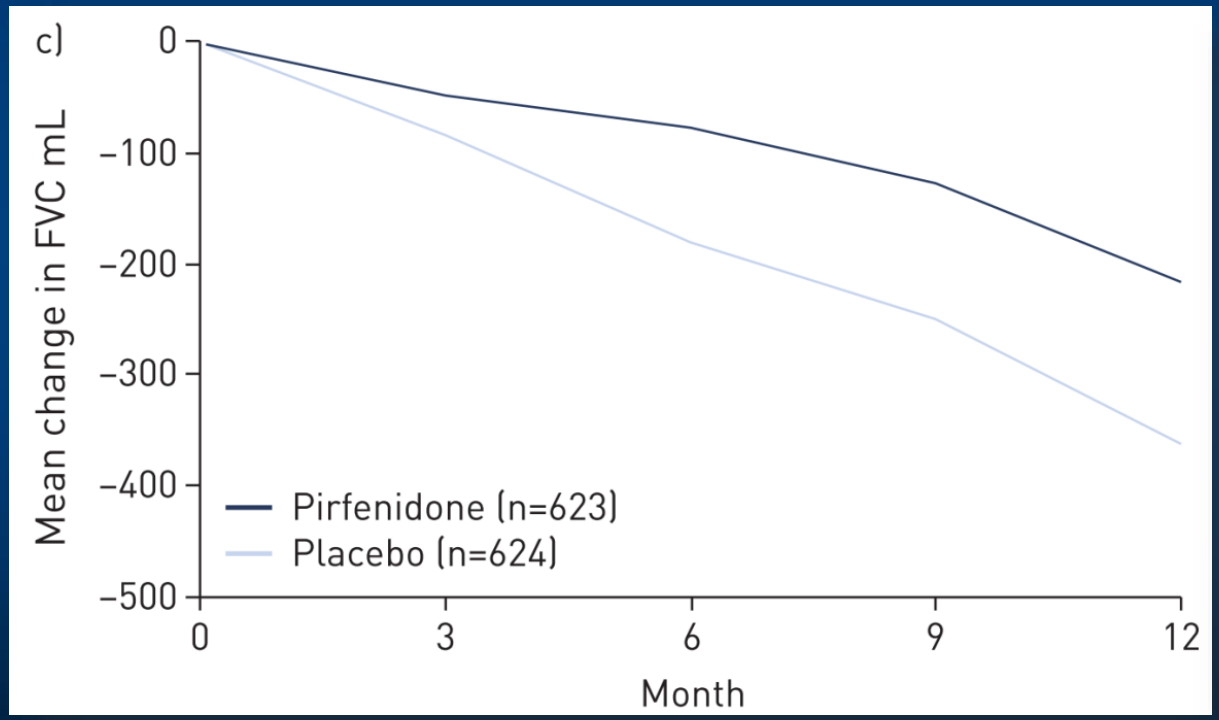
Pathogenesis: abnormal wound healing responses



Noble PW et al. *J Clin Invest*. 2012;122(8):2756-2762

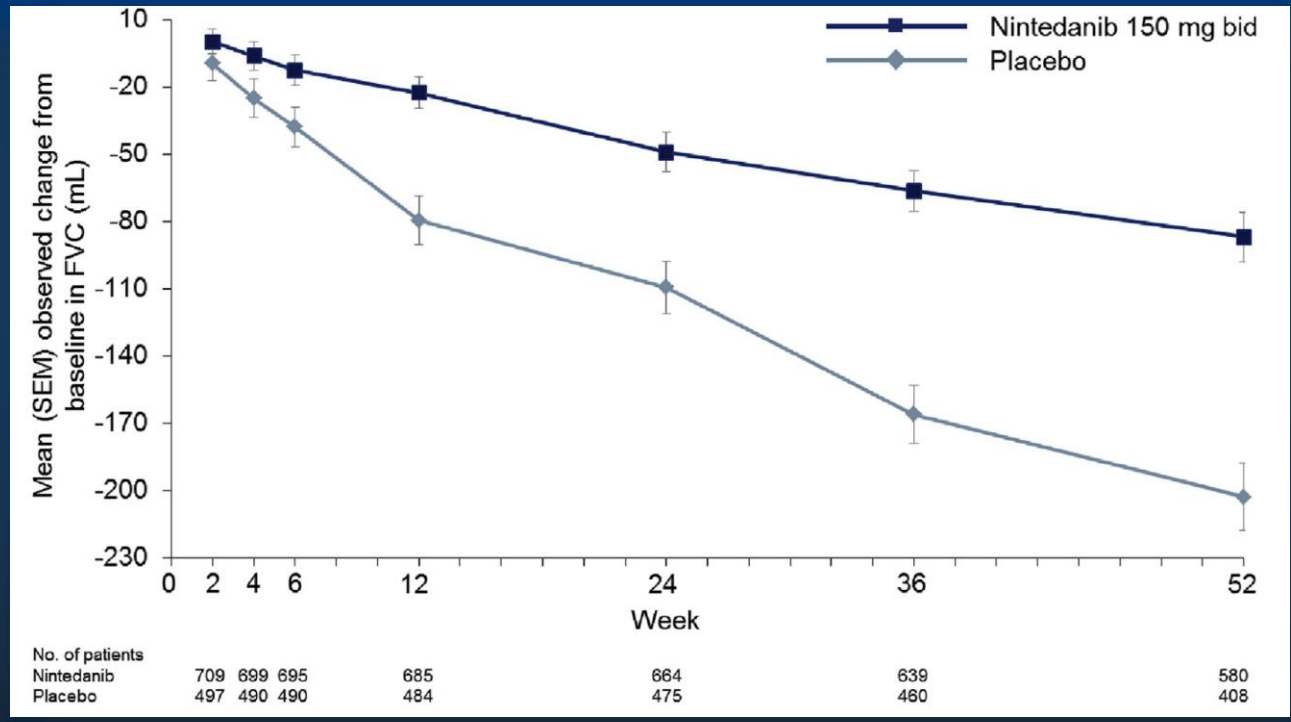
IPF: epithelial dysfunction driven fibrosis

- Pirfenidone



* ASCEND + CAPACITY (N=1247)

- Nintedanib



* TOMORROW+INPULSIS (N=1231)

Noble PW et al. *Eur Resp J* 2016;47:243-253; Richeldi L et al. *Respiratory Medic*ine 2016;113:74-79

KATRD: IPF guideline (2018)

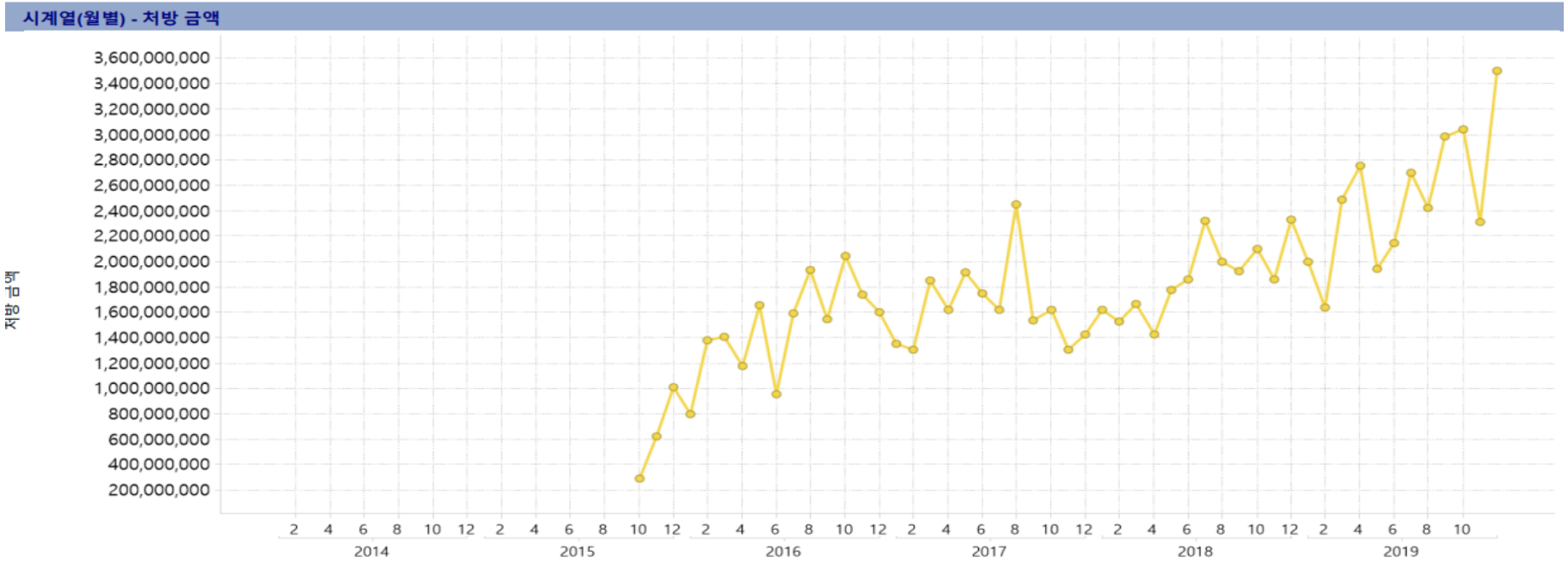
2. 특발성폐섬유증

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)

2018 간질성폐질환 임상진료지침

Pirfenidone: trends of use in South Korea



2012	2015	2017	2018~2019	2020	2021~
2012년 10월 피레스파 발매 (비급여)	2015년 10월 급여 획득 (5,750원/Tab)	2017년 11월 약가 인하 (3,406원/Tab)	2019년 1월 약가 인하 (3,304원/Tab)	2019년 6월 자진 약가 인하 (3,294원/Tab)	
		2017년 12월 일반약 발매	2019년 1월 고용량정 발매		

Issues in the era of antifibrotic therapy

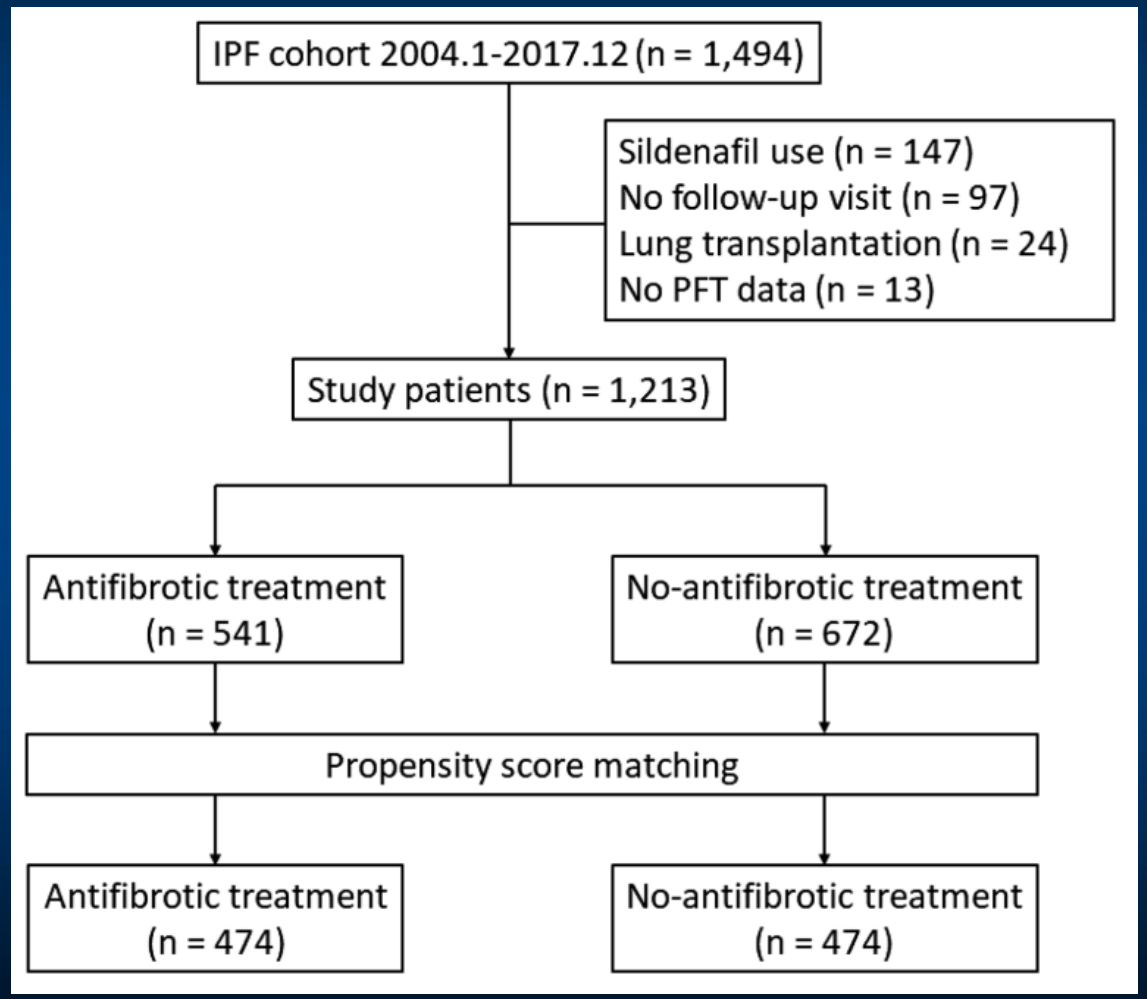
1. Survival
2. When to start treatment ?
3. Dose modification strategy
4. Long term safety and efficacy
5. A progressive fibrosing ILD other than IPF

Pirfenidone in IPF trials: impact on survival

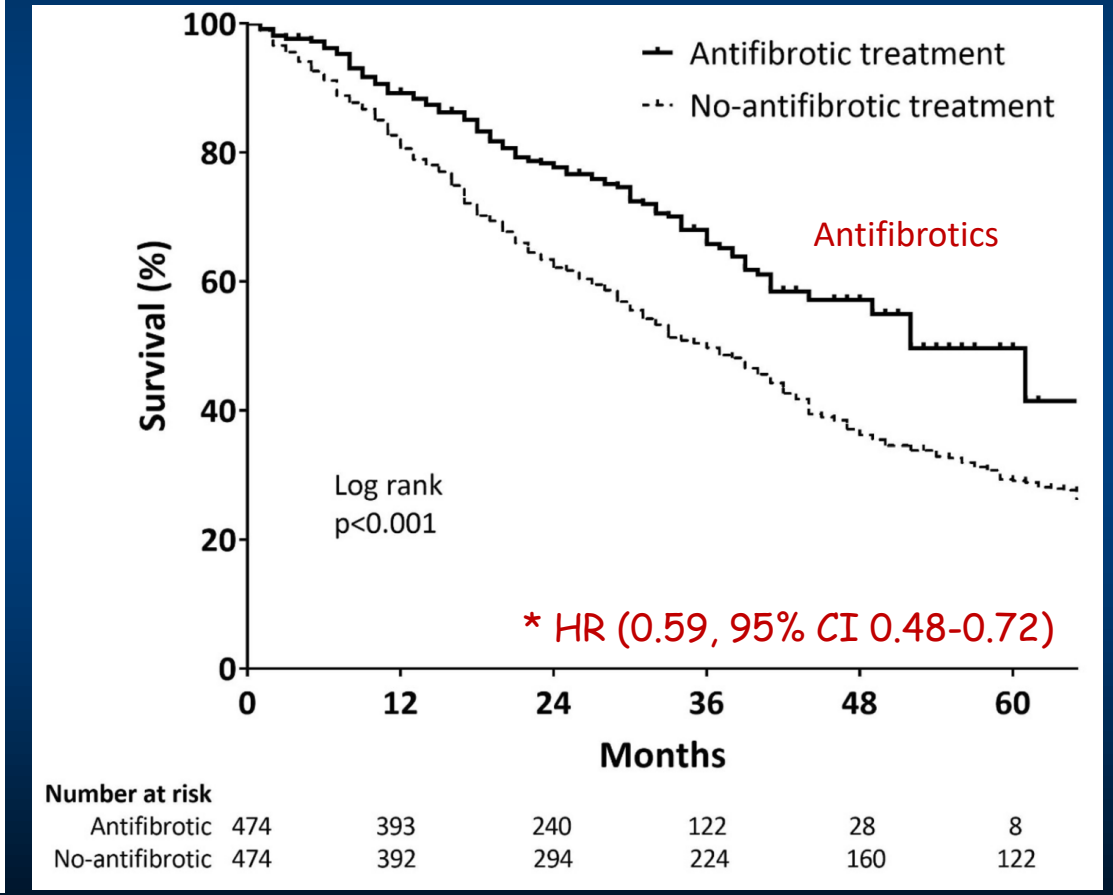
	CAPACITY 004		CAPACITY 006		ASCEND 016*		Study SP2†		Study SP3		Pooled analysis (004, 006, and 016)		Random effects meta-analyses (all trials)	
	Pirfenidone (n=174)	Placebo (n=174)	Pirfenidone (n=171)	Placebo (n=173)	Pirfenidone (n=278)	Placebo (n=277)	Pirfenidone (n=73)	Placebo (n=36)	Pirfenidone (n=108)	Placebo (n=104)	Pirfenidone (n=623)	Placebo (n=624)	Pirfenidone (n=804)	Placebo (n=764)
Week 52														
Deaths, n (%)	5 (2·9%)	13 (7·5%)	6 (3·5%)	9 (5·2%)	11 (4·0%)	20 (7·2%)	0 (0%)	1 (2·8%)	3 (2·8%)	4 (3·8%)	22 (3·5%)	42 (6·7%)	25 (3·1%)	47 (6·2%)
HR (95% CI)	0·37 (0·13–1·04)	..	0·66 (0·24–1·87)	..	0·55 (0·26–1·15)	..	0·16 (0·01–4·13)	..	0·72 (0·16–3·21)	..	0·52 (0·31–0·87)	..	0·53 (0·32–0·85)	..
p	0·0486	..	0·4350	..	0·1045‡	..	0·2721	..	0·6648	..	0·0107	..	0·0092	..
Week 72														
Deaths, n (%)	8 (4·6%)	15 (8·6%)	13 (7·6%)	15 (8·7%)	..	..	..	..	..	..	32 (5·1%)	50 (8·0%)	35 (4·4%)	55 (7·2%)
HR (95% CI)	0·51 (0·22–1·20)	..	0·87 (0·41–1·82)	..	..	..	..	..	..	..	0·63 (0·41–0·98)	..	0·63 (0·41–0·96)	..
p	0·1159	..	0·7043	..	..	..	..	..	..	..	0·0404	..	0·0305	..
End of study														
Deaths, n (%)	11 (6·3%)	17 (9·8%)	16 (9·4%)	17 (9·8%)	..	..	..	..	..	..	38 (6·1%)	54 (8·7%)	41 (5·1%)	59 (7·7%)
HR (95% CI)	0·61 (0·28–1·29)	..	0·95 (0·48–1·87)	..	..	..	..	..	..	..	0·69 (0·46–1·05)	..	0·68 (0·46–1·01)	..
p	0·1911	..	0·8718	..	..	..	..	..	..	..	0·0789	..	0·0585	..

Nathan SD et al. *Lancet Repir Med* 2017;5:33-41

Impact on survival in IPF: a single center study



- Survival

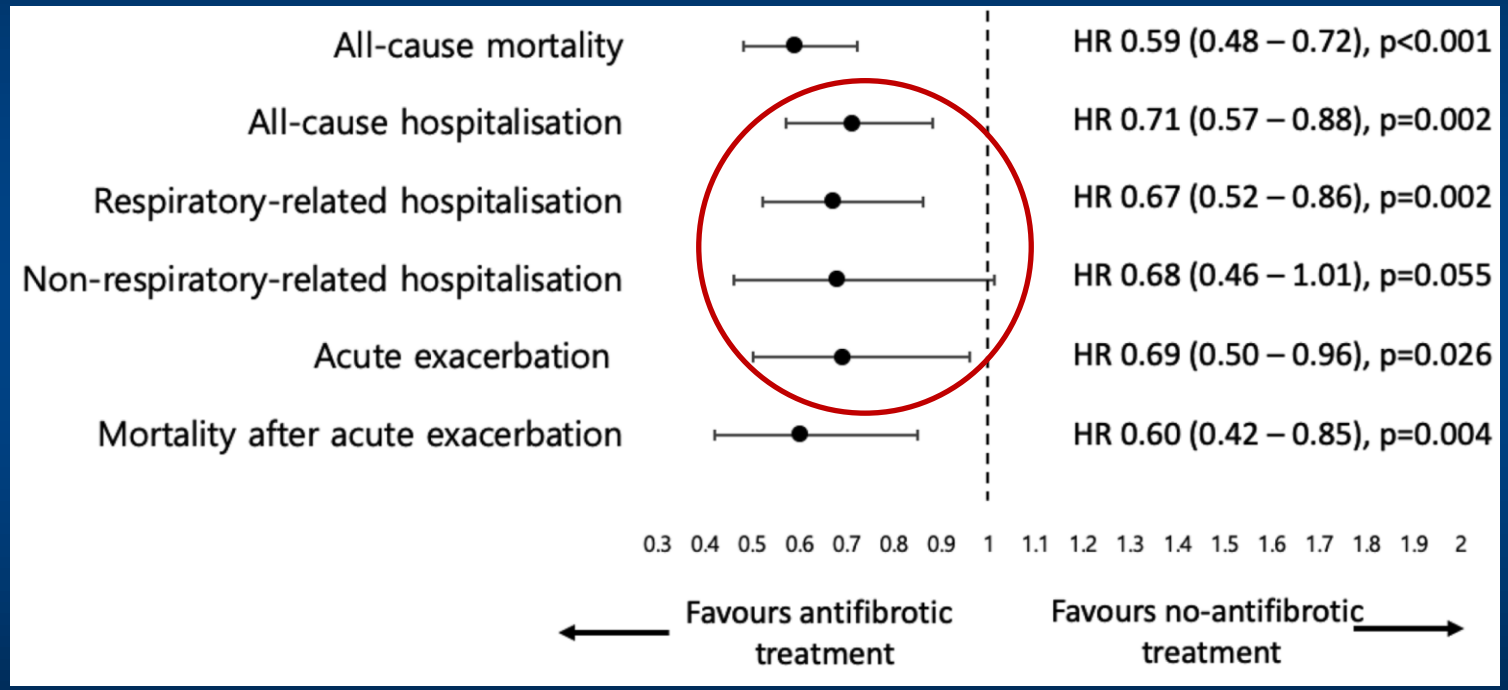


The matched variables were age, sex, body mass index (BMI), FVC, DL_{CO}, corticosteroid use in the 6 months prior to the index date.

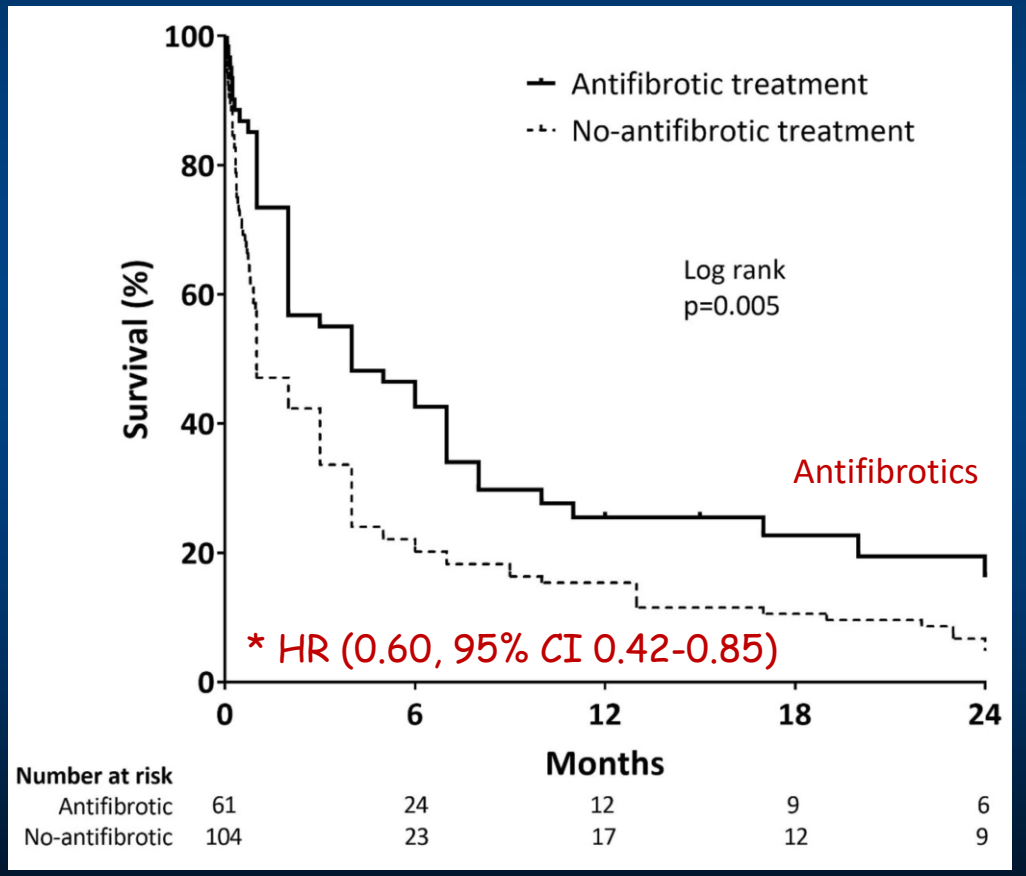
* Asan IPF Cohort (n= 948, propensity score matched)

Kang J et al. *Scientific Reports* 2020;10:15620

Antifibrotic treatment improves clinical outcome in IPF



• Survival after hospitalization

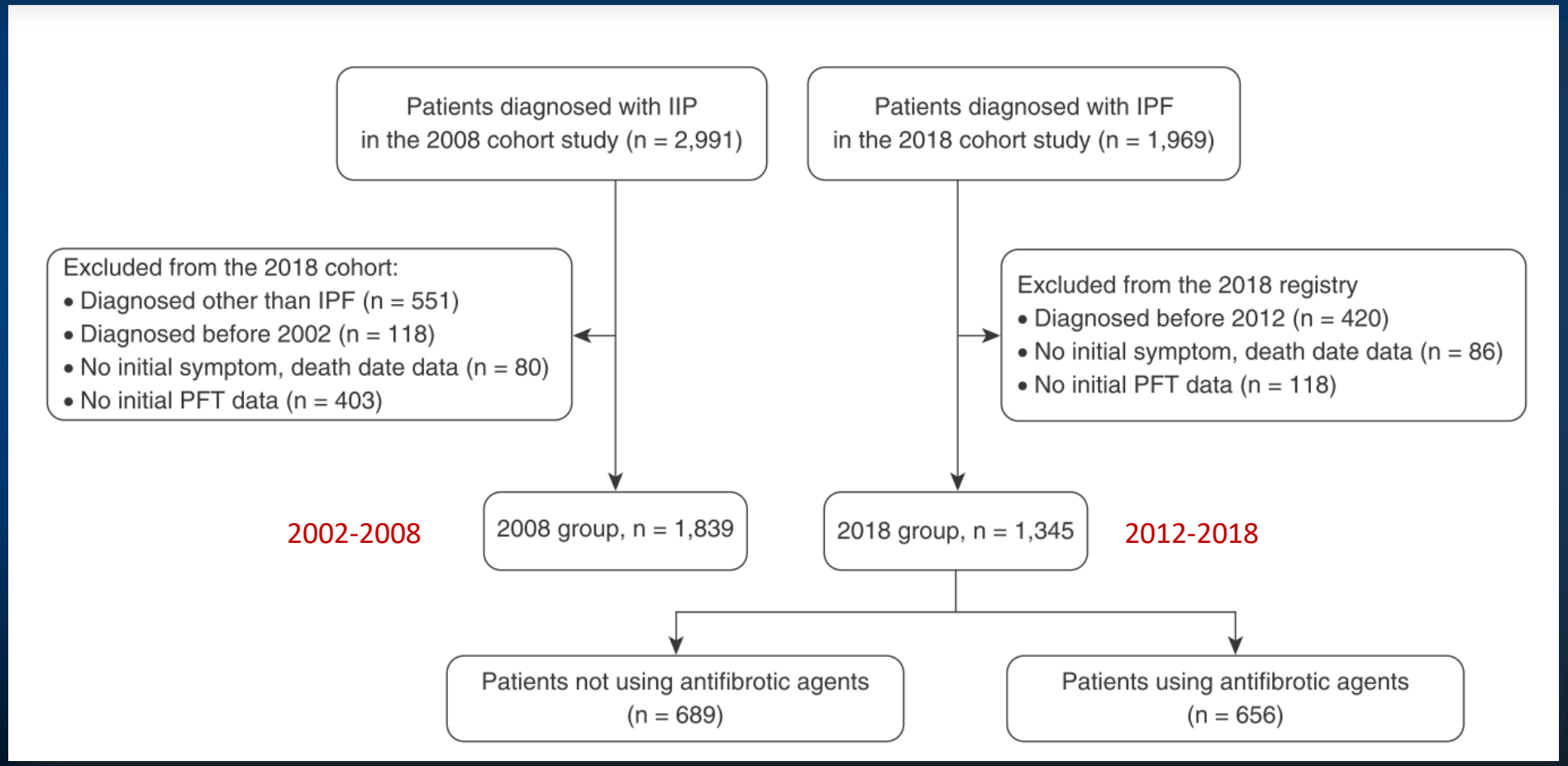


* Asan IPF Cohort (n= 948, propensity score matched)

Kang J et al. *Scientific Reports* 2020;10:15620

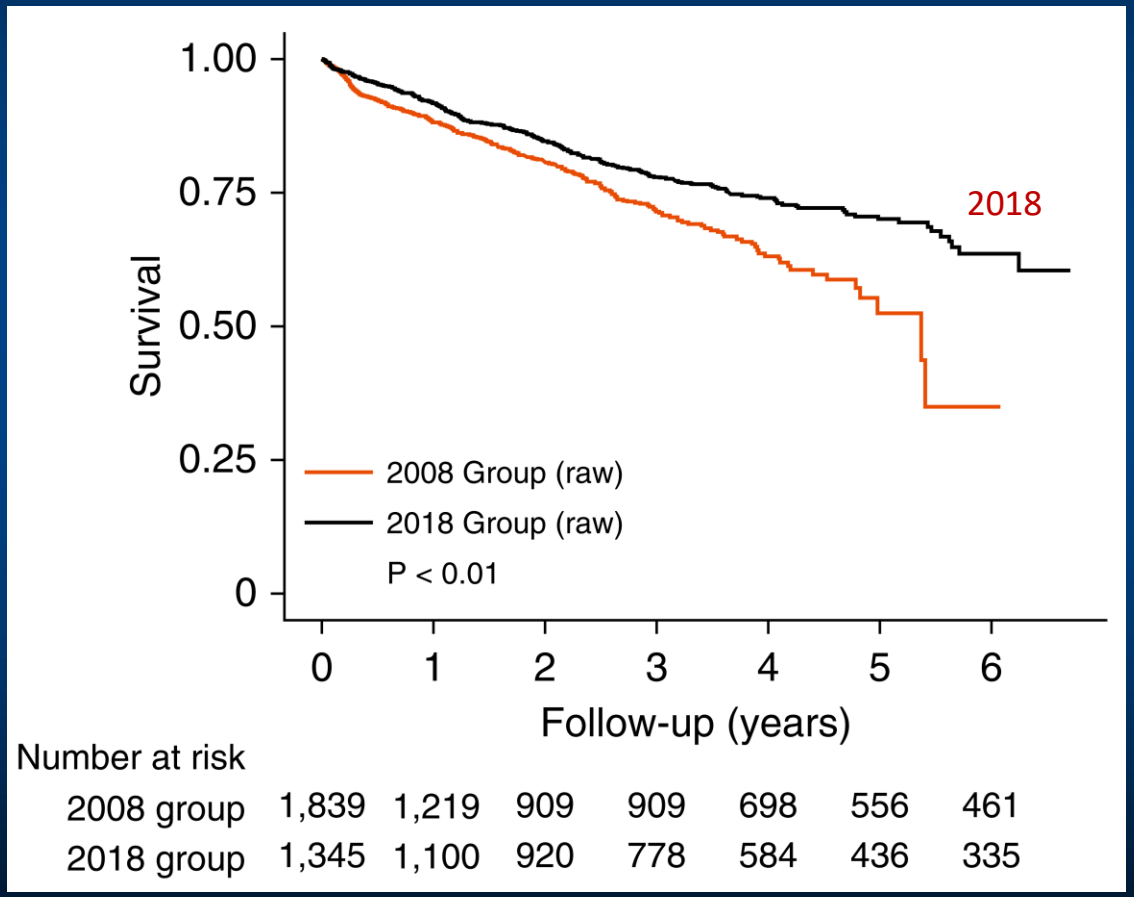
Longitudinal Changes in Clinical Features, Management, and Outcomes of Idiopathic Pulmonary Fibrosis

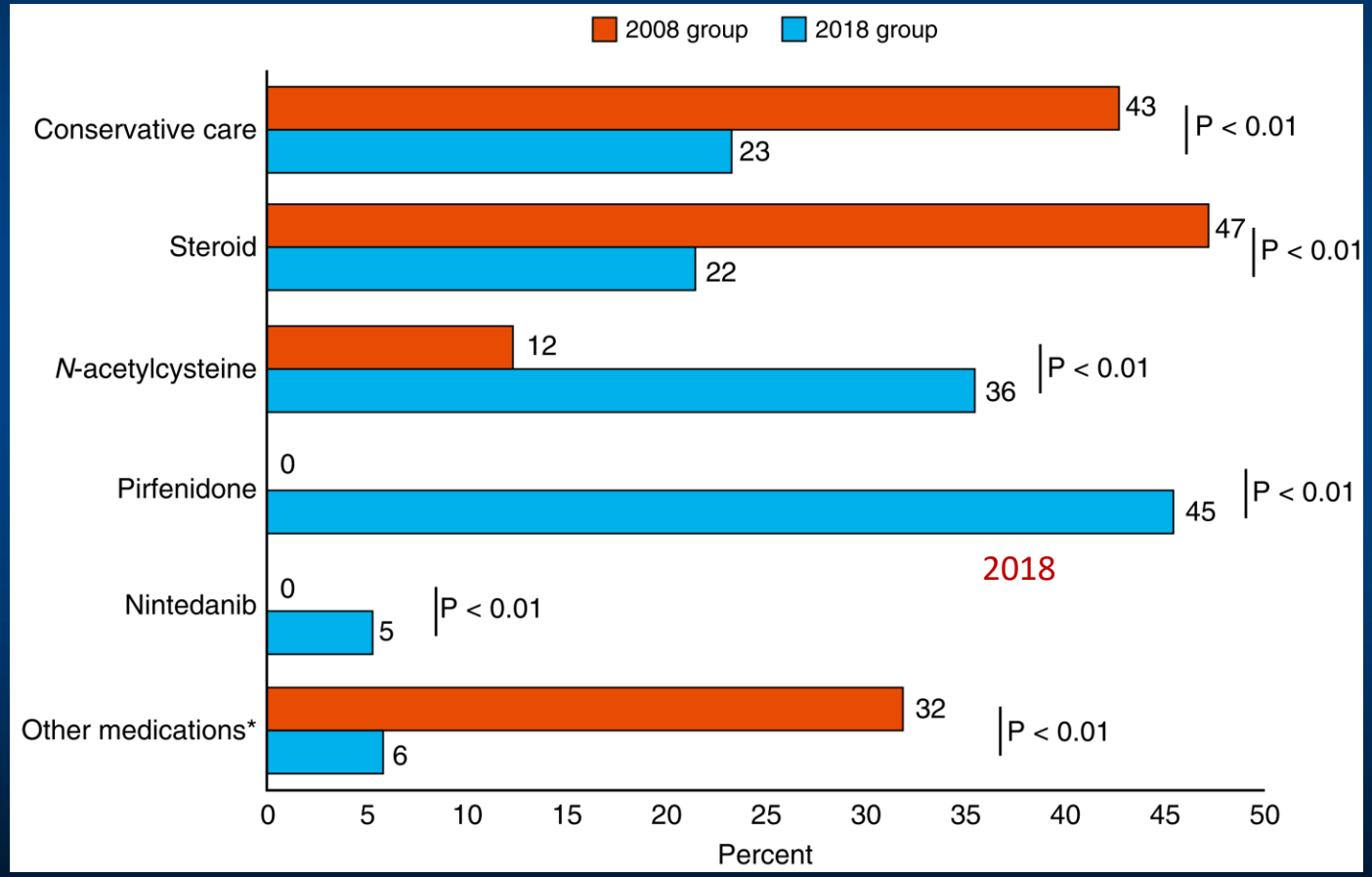
A Nationwide Cohort Study



Moon SW et al. *Ann Am Thorac Soc* 2021;18(5):780-87

Survival and management: 2008 vs. 2018

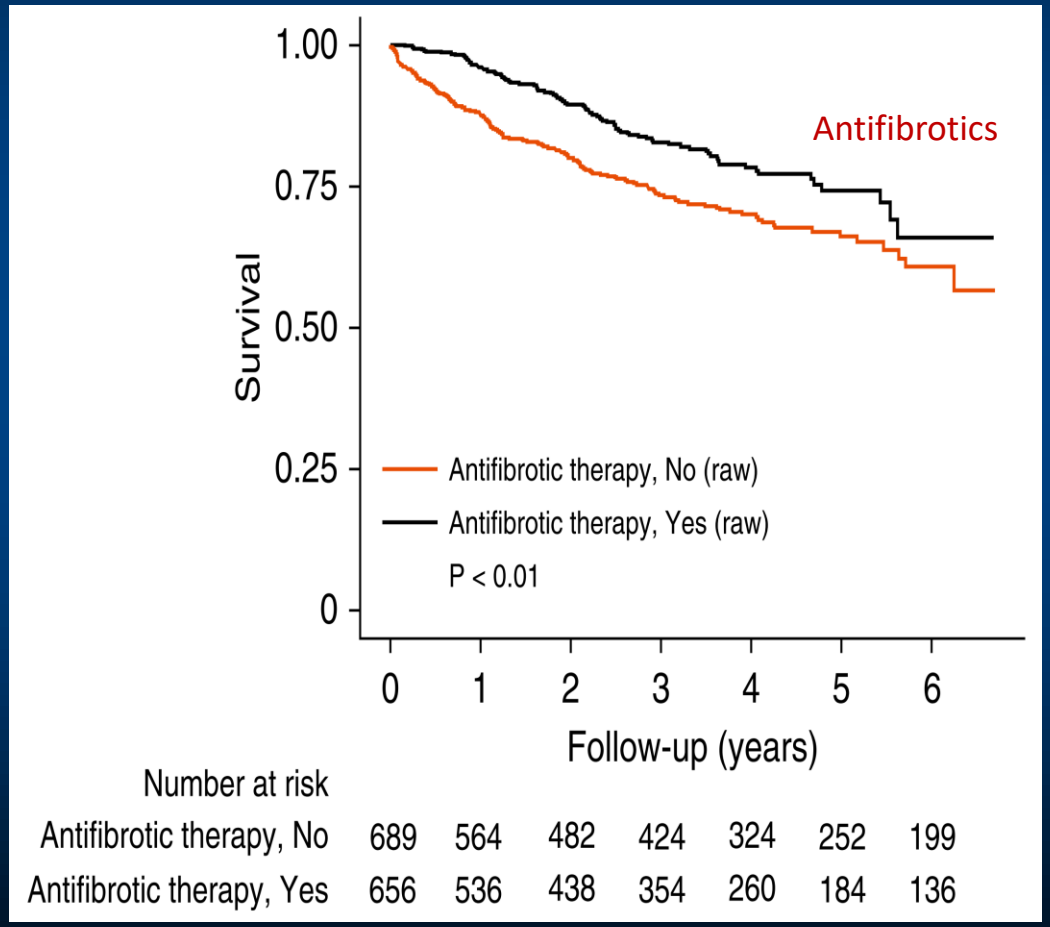




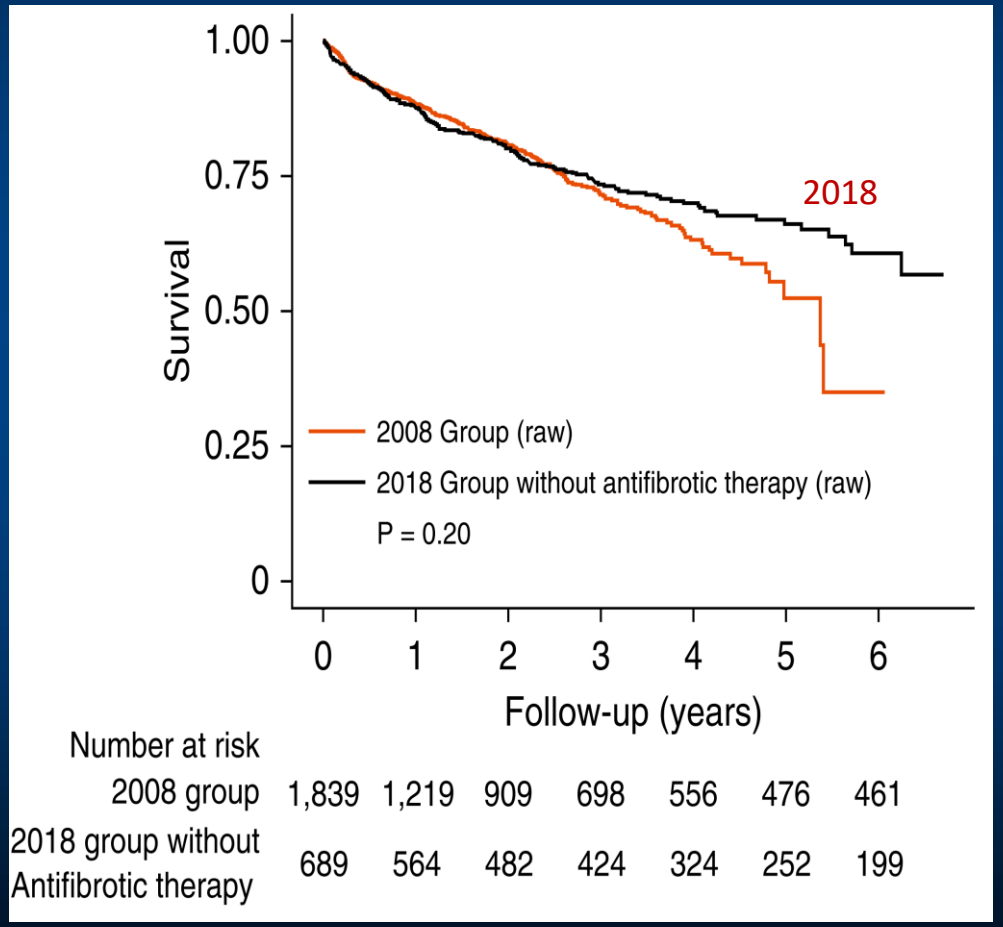
Moon SW et al. *Ann Am Thorac Soc* 2021;18(5):780-87

Comparison of survival according to antifibrotic therapy

- 2018: antifibrotics vs. no antifibrotics



- 2008 vs. 2018 (no antifibrotics)



Moon SW et al. *Ann Am Thorac Soc* 2021;18(5):780-87

Association of long term medication usage with mortality

	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Only conservative care	1.11 (0.83–1.48)	0.47	1.31 (0.96–1.80)	0.09	1.35 (0.98–1.85)	0.07	1.31 (0.96–1.80)	0.09
Steroid	2.41 (1.86–3.12)	<0.01	2.16 (1.63–2.86)	<0.01	1.98 (1.49–2.63)	<0.01	2.16 (1.63–2.86)	<0.01
N-acetylcysteine	0.80 (0.62–1.03)	0.08	0.77 (0.58–1.03)	0.07	0.89 (0.67–1.18)	0.43	0.77 (0.58–1.03)	0.07
Antifibrotic agents	0.59 (0.46–0.76)	<0.01	0.54 (0.41–0.72)	<0.01	0.50 (0.38–0.67)	<0.01	0.54 (0.41–0.72)	<0.01
Other medications*	0.59 (0.29–1.18)	0.14	1.09 (0.45–2.66)	0.85	0.64 (0.30–1.36)	0.24	1.09 (0.45–2.66)	0.85

- Model 1: Unadjusted. Model 2: Adjusted for age, sex, FVC, and DLCO. Model 3: Adjusted for dyspnea, cough symptoms, FVC, DLCO, and the presence of honeycombing on HRCT imaging. Model 4: Adjusted for age, sex, dyspnea, cough symptoms, FVC, DLCO, and the presence of honeycombing on HRCT imaging.

Moon SW et al. *Ann Am Thorac Soc* 2021;18(5):780-87

KATRD: IPF guideline (2023 update)

- **권고사항**
  - 임상적 혹은 조직학적으로 진단된 IPF 환자에서, FVC감소 속도 지연을 위해 Pirfenidone을 사용할 것을 권고한다. (근거수준: 중등도, 권고등급: 강하게 권고)

    투표결과 강하게 권고 7/8, 조건부 권고 1/8,
  - 임상적 혹은 조직학적으로 진단된 IPF 환자에서, 사망률 감소를 위해 Pirfenidone을 사용할 것을 권고한다. (근거수준: 중등도, 권고등급: 강하게 권고)

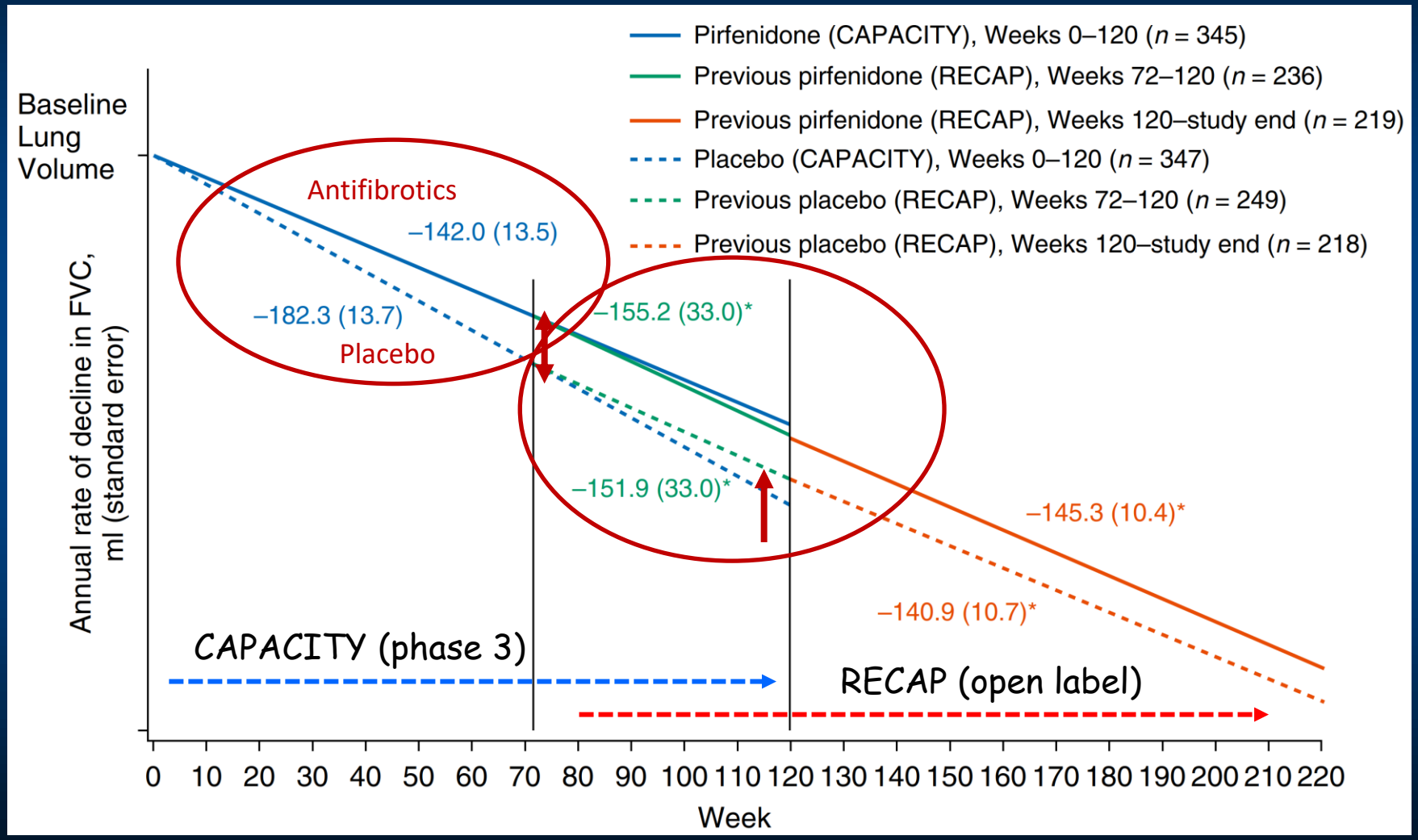
    투표결과 강하게 권고 8/8
  - 임상적 혹은 조직학적으로 진단된 IPF 환자에서, FVC 감소 속도 지연을 위해 Nintedanib을 사용할 것을 권고한다. (근거수준: 중등도, 권고등급: 강하게 권고)

    투표결과 강하게 권고 7/8, 조건부 권고 1/8
  - 임상적 혹은 조직학적으로 진단된 IPF 환자에서, 사망률 감소를 위해 Nintedanib을 사용할 것을 권고한다. (근거수준: 중등도, 권고등급: 강하게 권고)

    투표결과 강하게 권고 5/8, 조건부 권고 3/8

2023 간질성폐질환 임상진료지침(개정)

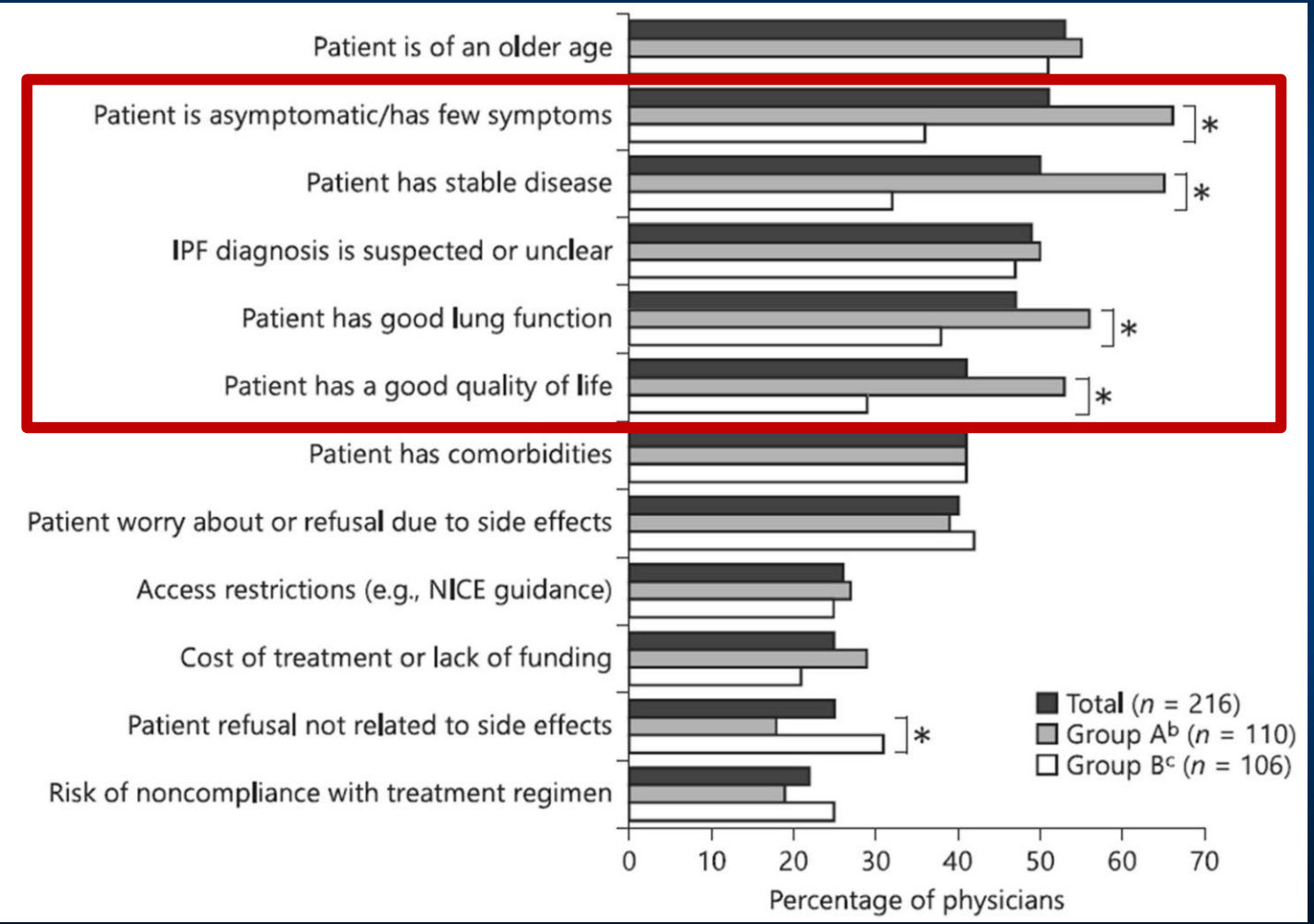
FVC decline and timing of pirfenidone initiation



* RECAP (N=485)

Maher TM et al. *AnnalsATS* 2019;16(7):927-929

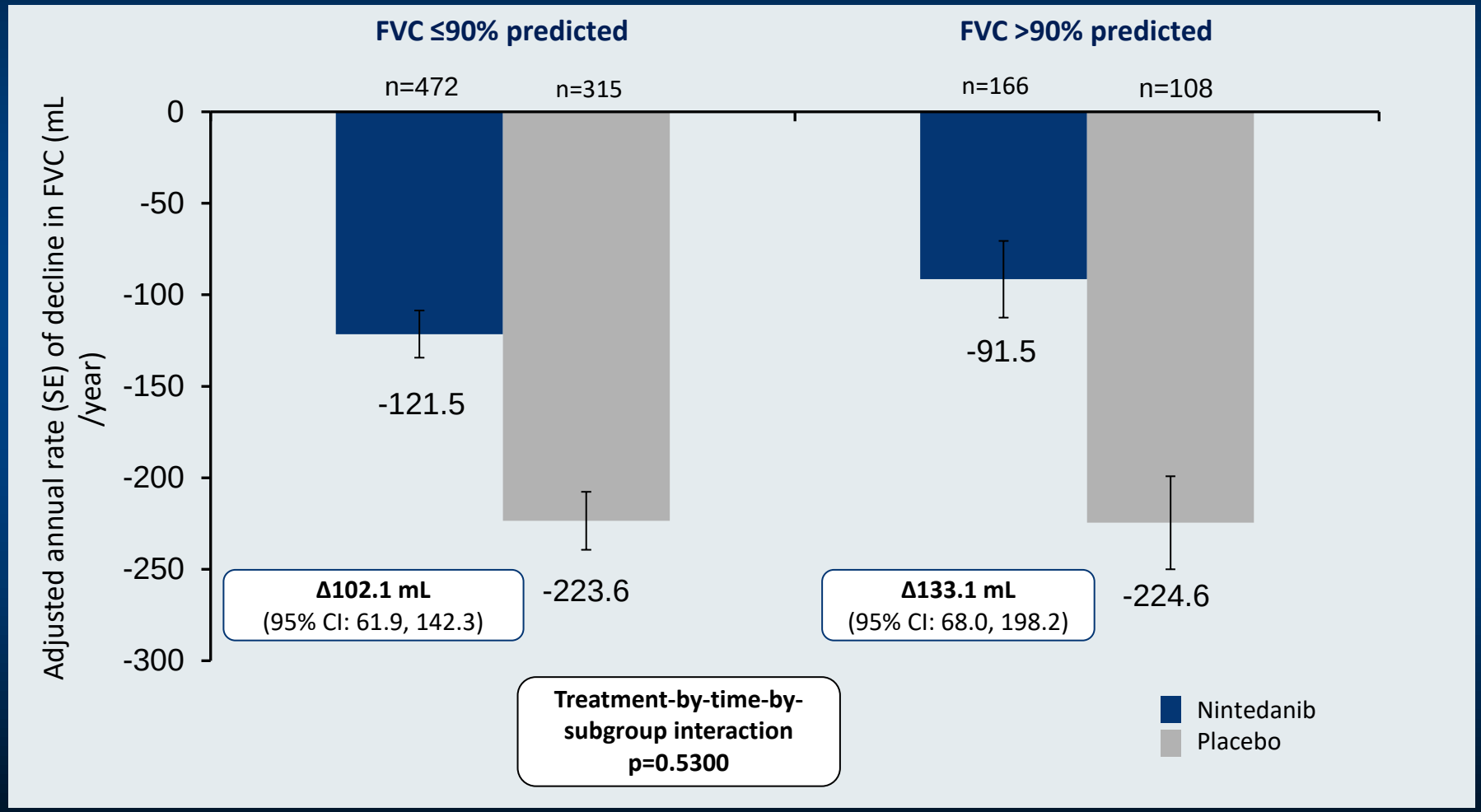
Survey: reasons given by pulmonologists for not treating with mild IPF



Maher TM et al. *Respiratory Research* 2019;20:205

Nintedanib in mild IPF

- Annual rate of decline in FVC

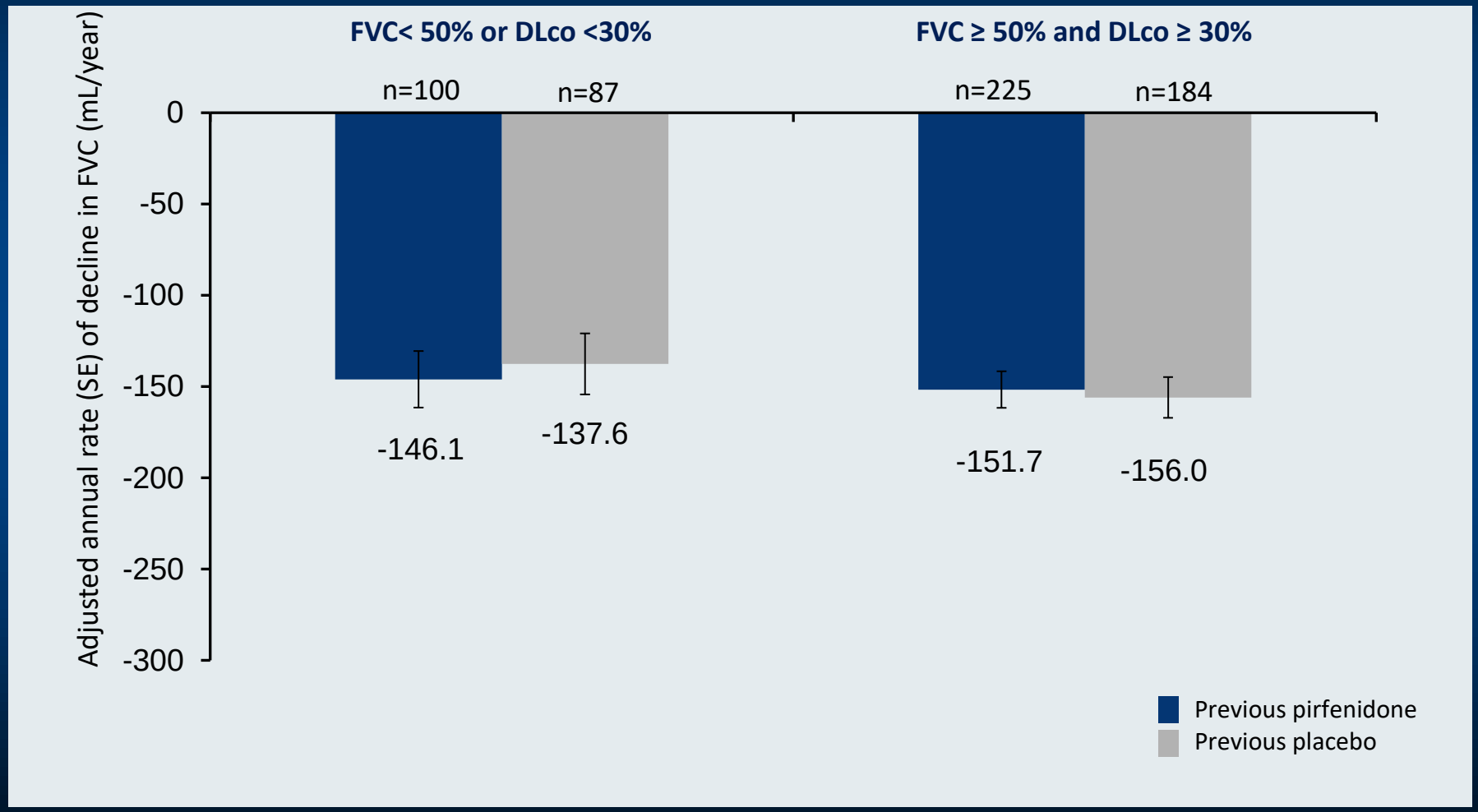


* INPULSIS (N=1061)

Kolb M et al. *Thorax* 2017;72:340-346

Pirfenidone in advanced IPF

- Annual rate of decline in FVC

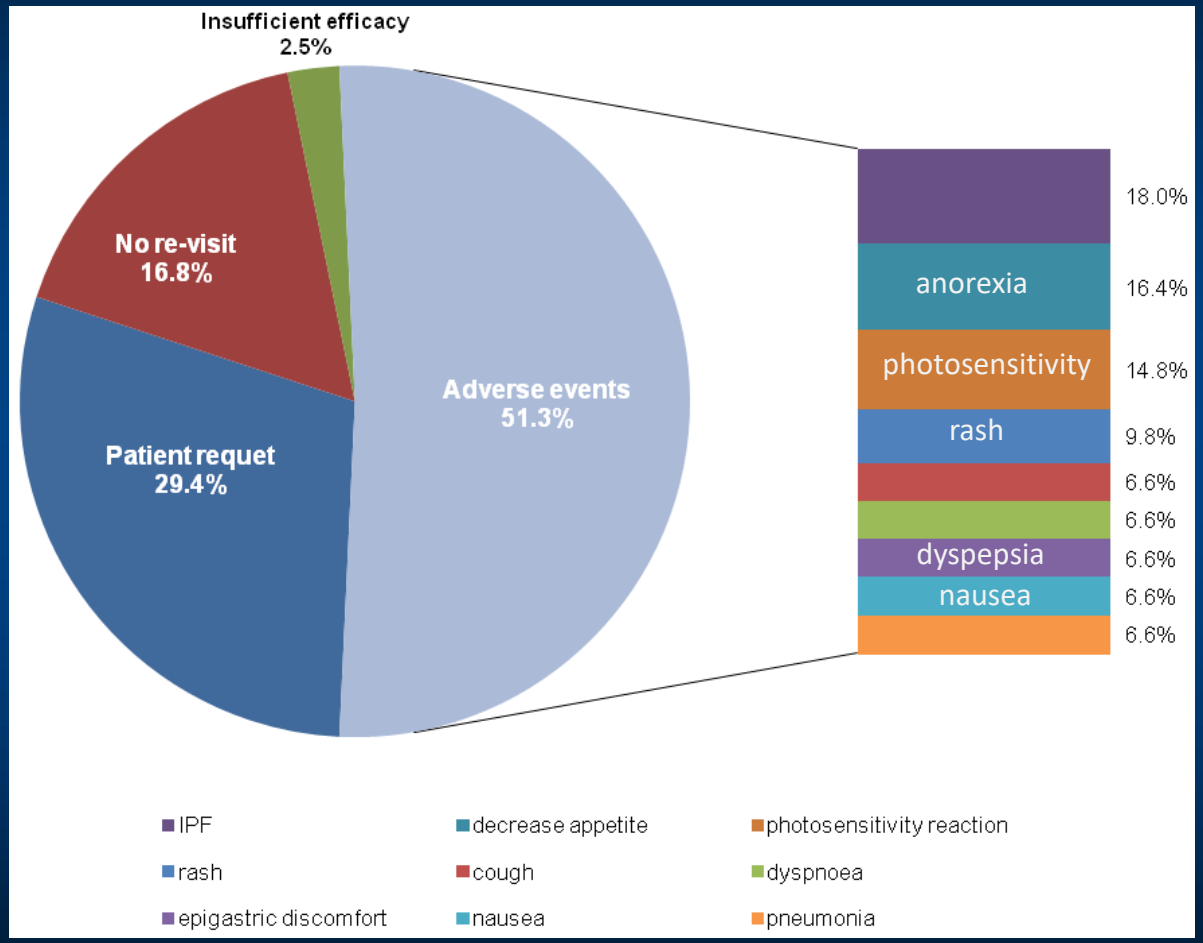


- Median (range) of exposures: 88 (0-349) weeks

* RECAP (N=596)

Costabel et al. *Respiratory Research* 2019;20:55

PIRESPA-PMS: reasons for discontinuation

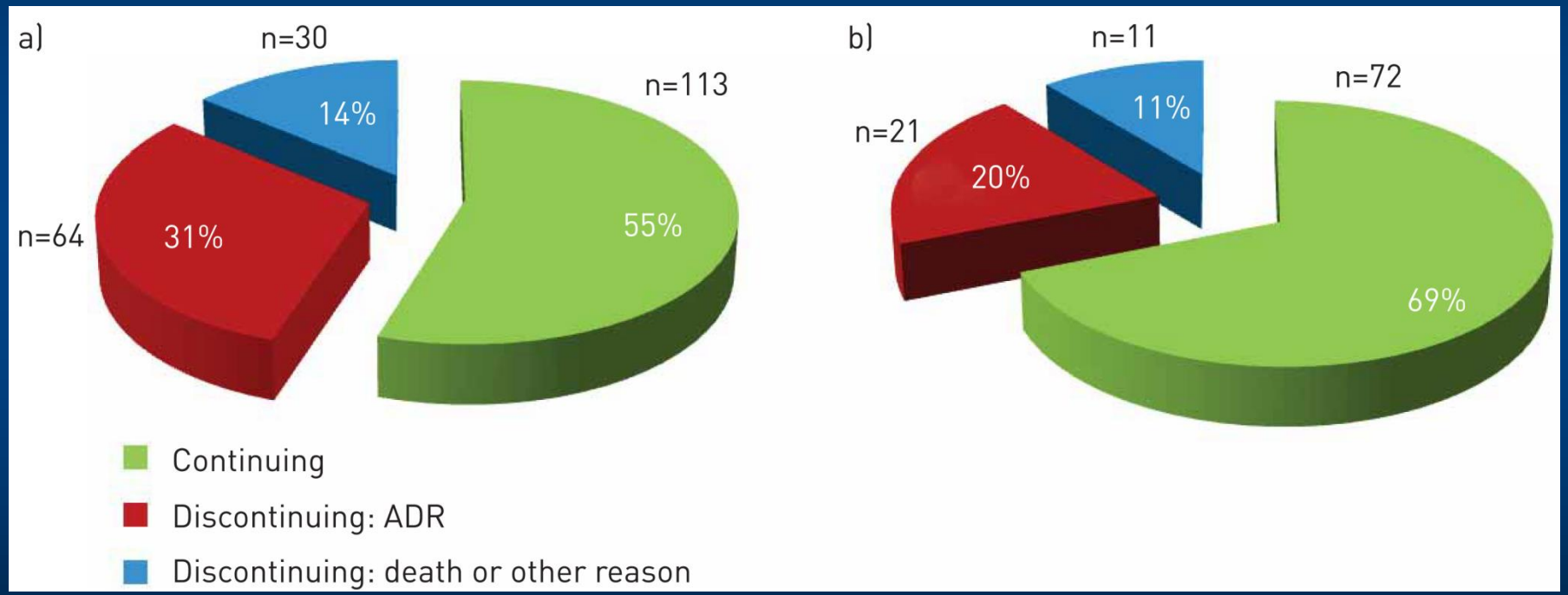


- A multicenter prospective IPF cohort (n=258; 2014-2017)
- Duration of exposures (median: 298 days)
- Discontinuation in 119 patients (54.3% of total 219 patients)

Chung MP et al. *Adv Ther* 2020; 37: 2303-2316

Impact of dose adjustment in case of adverse drug reaction

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

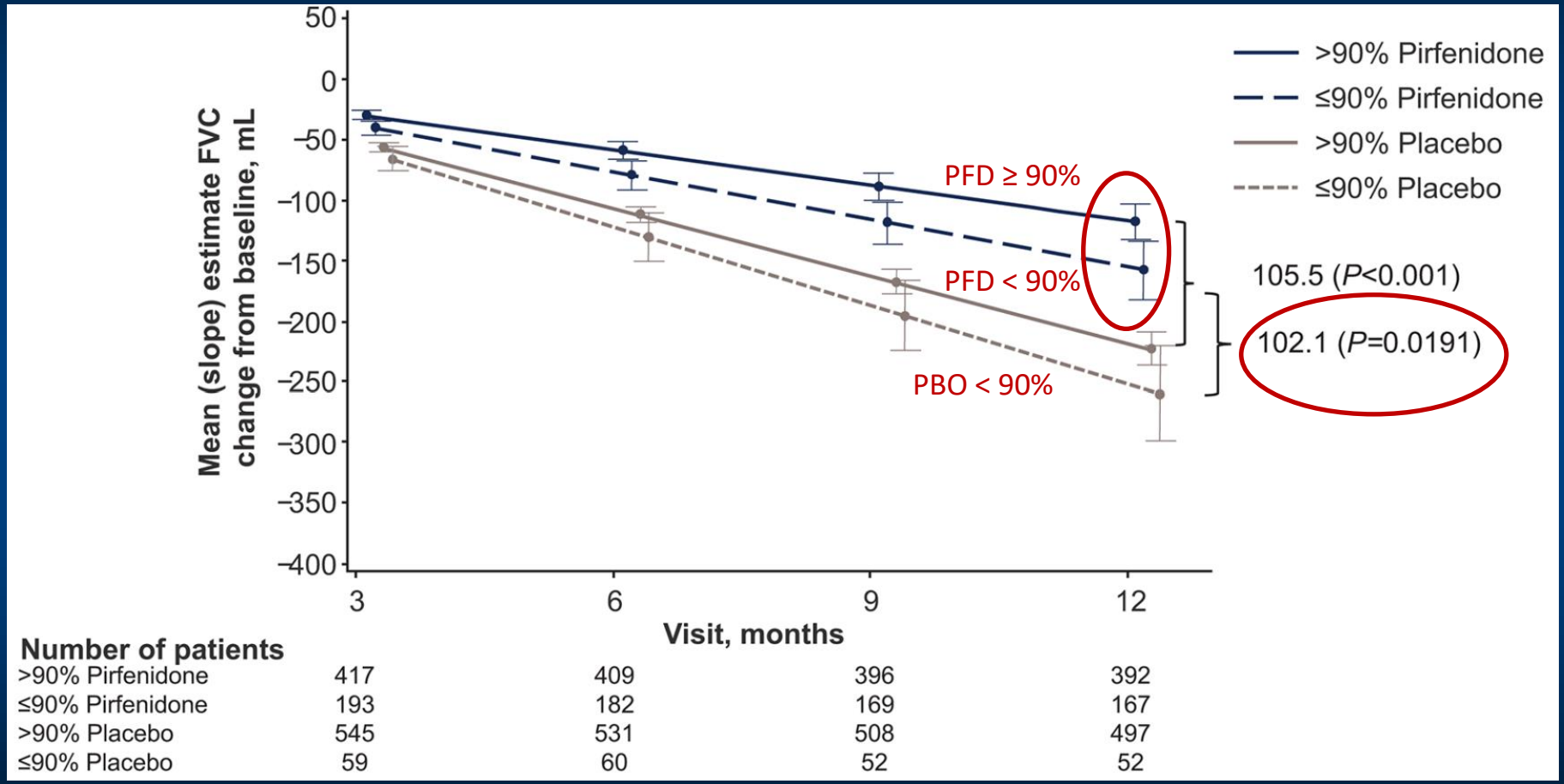


No dose adjustment

Dose adjustment

Cottin V et al. *Eur Respir Rev* 2015; 24: 58-64

FVC change by dose intensity

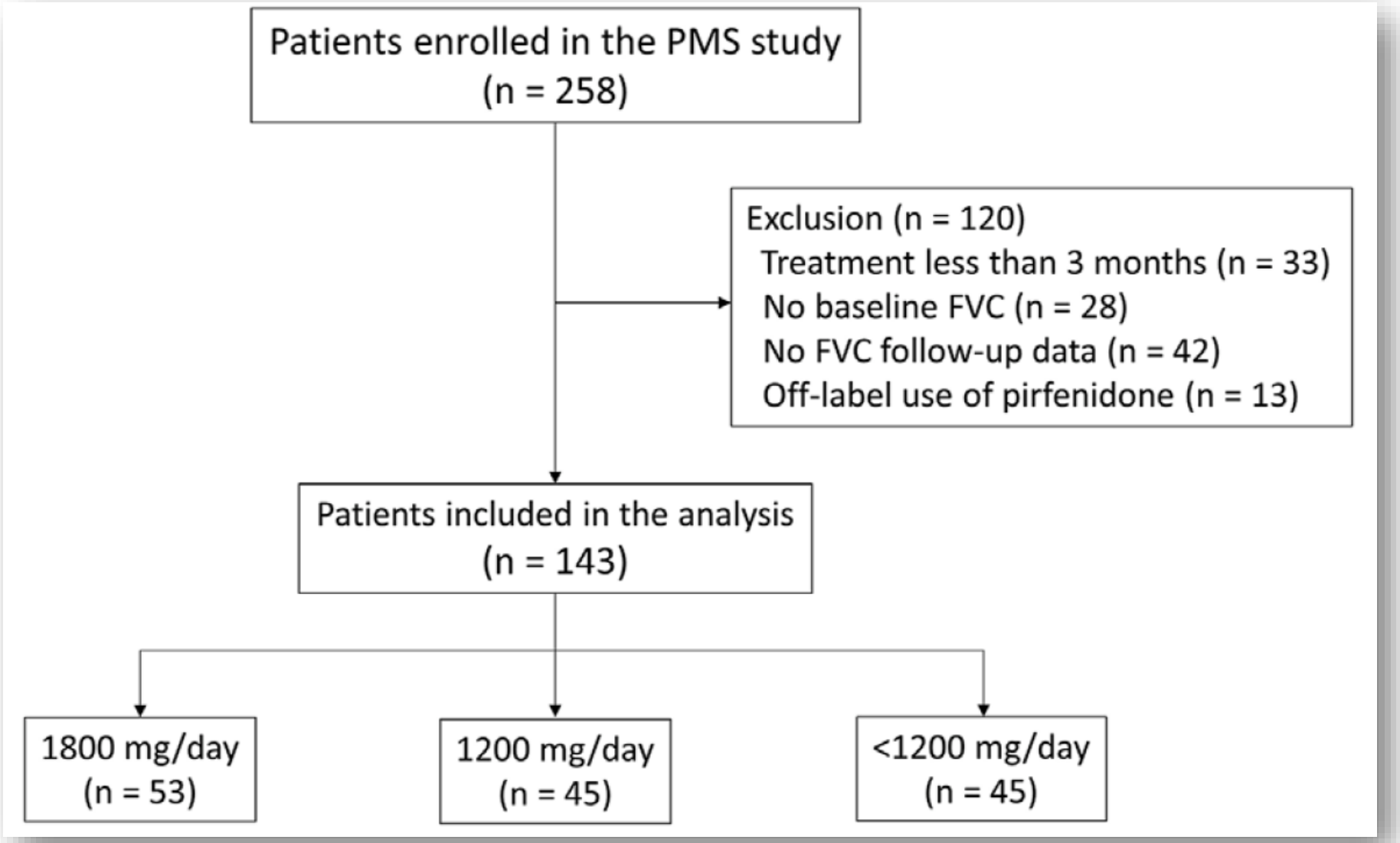


- The mean daily actual dose: 2278.4 mg/day (> 90%) and 1575.9 mg/day (≤90%)

* ASCEND + CAPACITY (N=1247)

Nathan SD et al. *BMJ Open Resp Res* 2018;5:e000323

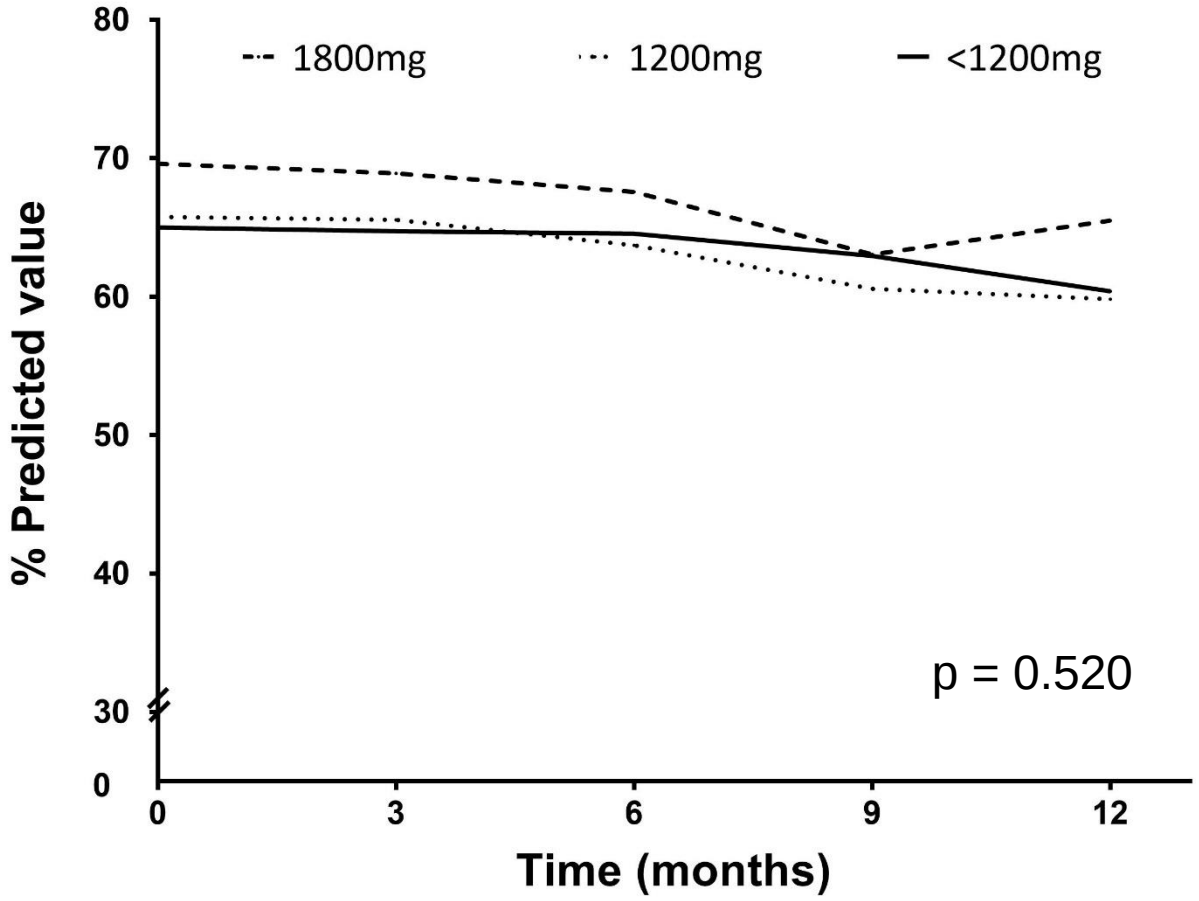
Pirespa-PMS: effect of dose modification on clinical outcome in IPF

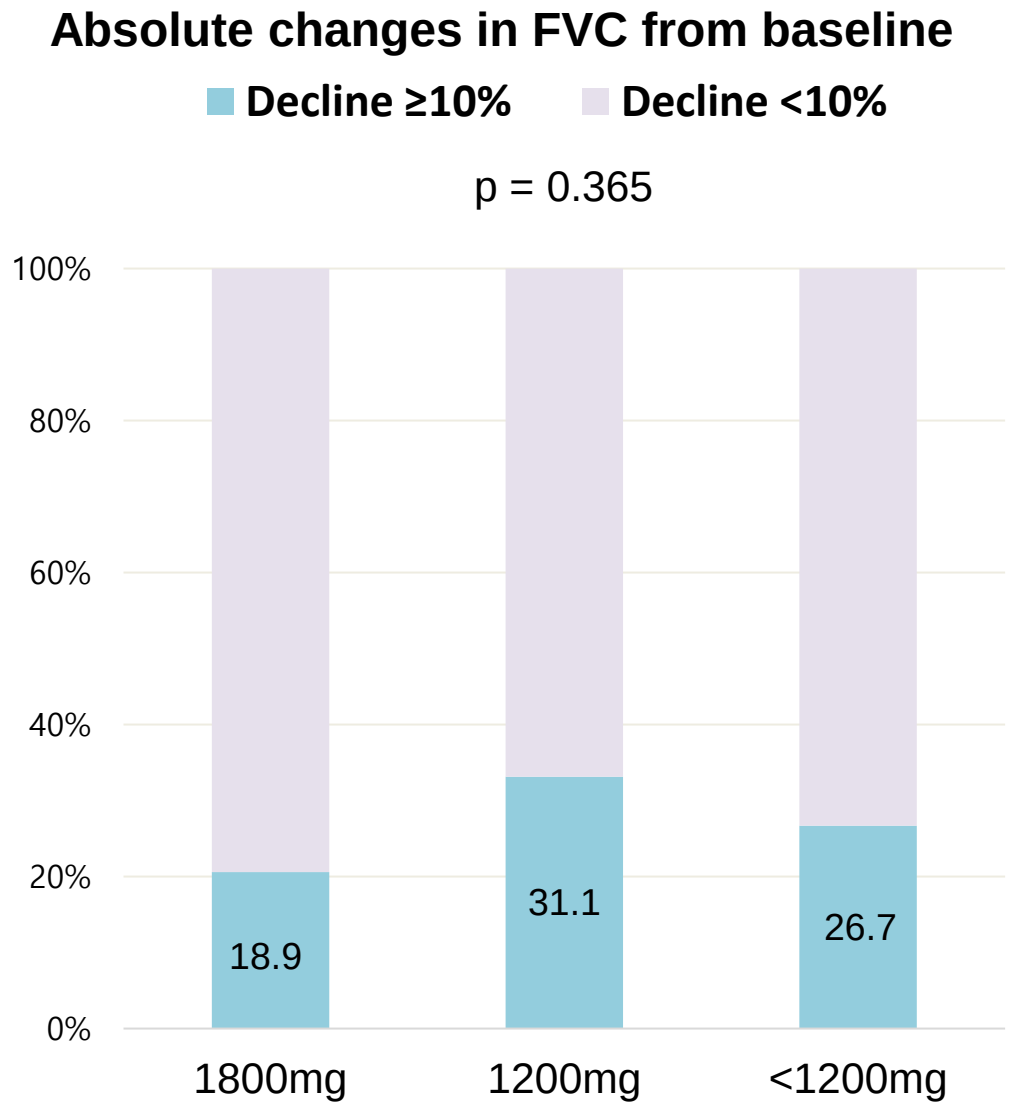


Kang J et al. *Front Pharmacol 2023;13:1025947*

Pirespa-PMS: effect of dose modification on clinical outcome in IPF

- Changes in FVC over 12 months

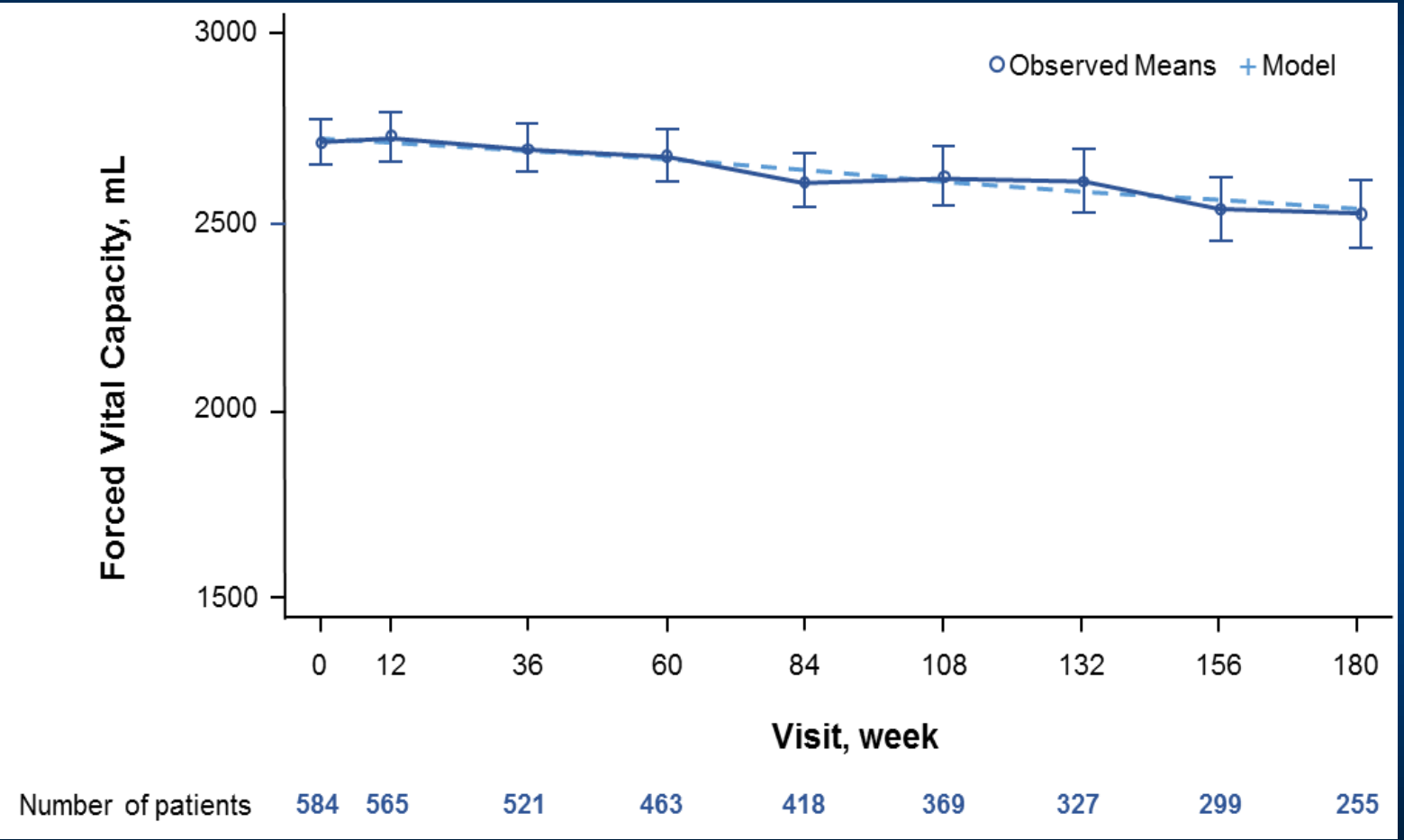




- Age, sex, smoking status, and baseline values of FVC and DL_{CO}, were adjusted in the linear mixed model.

Kang J et al. *Front Pharmacol 2023;13:1025947*

RECAP: annualized rate of FVC decline over 180 weeks



- FVC decline: 144.3 (6.0) mL/year

* CAPACITY (N=584), linear mixed effects model, exposure: 88 (0-349) weeks

Costabel U et al. *Respiration* 2017;94:408-415

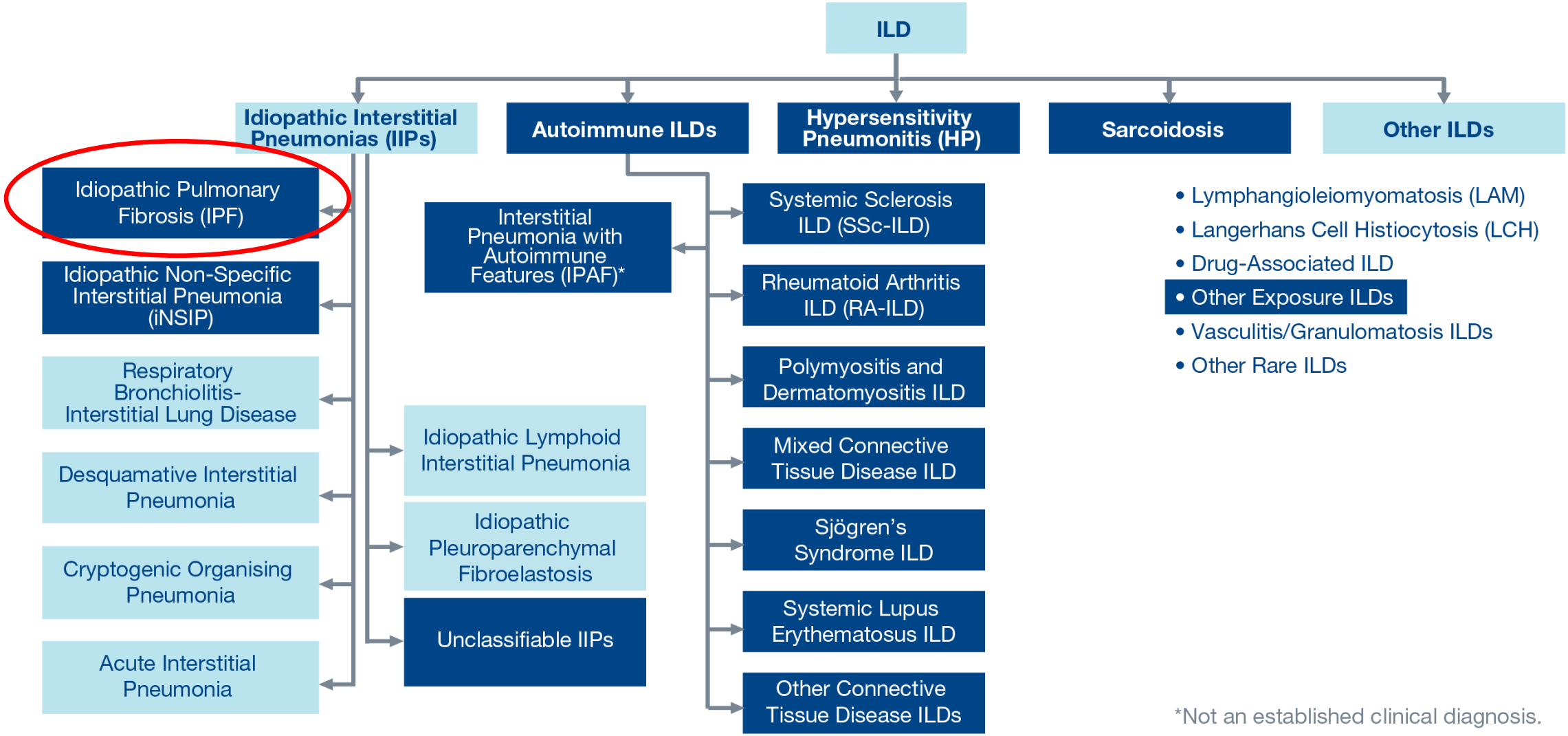
Treatment emergent adverse events

ADR*, %	RECAP (N=1058)	CAPACITY and ASCEND (N=623)
Total	1,037 (98.0)	615 (98.7)
IPF	33.6	8.5
Upper RTI	27.9	22.6
Bronchitis	24.6	11.1
Cough	31.3	23.1
Nausea	28.8	35.5
Dyspnea	30.9	13.2
Nasopharyngitis	19.1	15.1
Diarrhea	22.9	24.6
Fatigue	19.8	23.0
Dizziness	16.6	16.7

* Occurred at rates of at least 15%

Costabel U et al. *Respiration* 2017;94:408-415

Types of ILD likely to have a progressive fibrosing phenotype

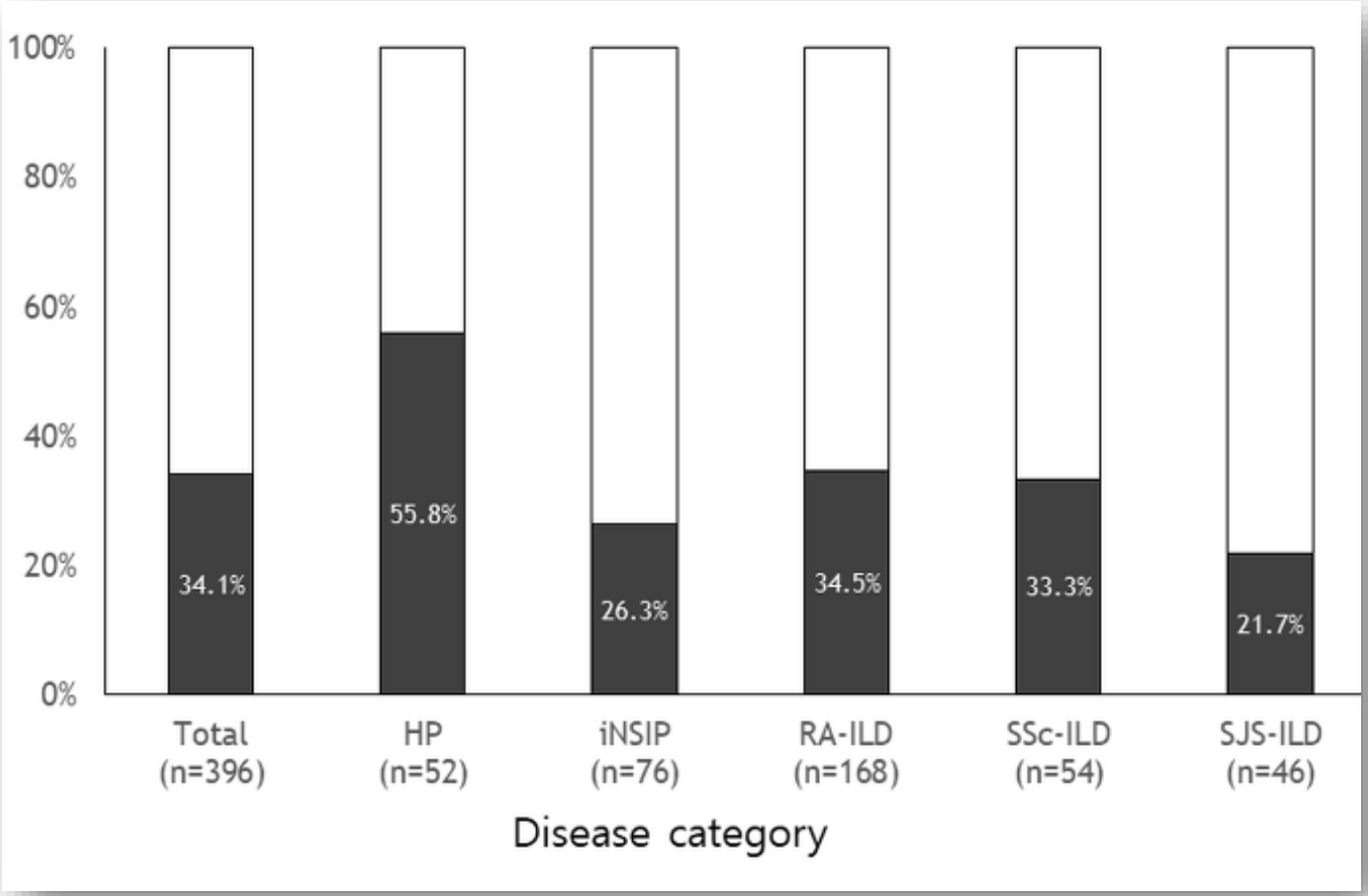


*Not an established clinical diagnosis.

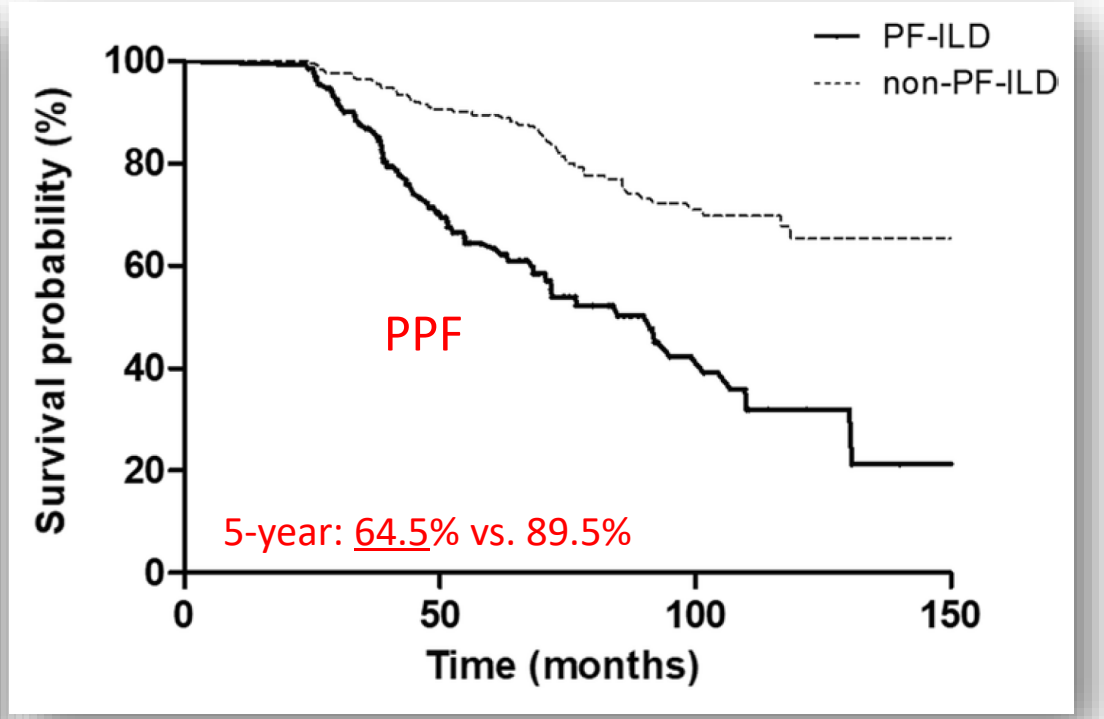
Travis WD, et al. *Am J Respir Crit Care Med*. 2013;188(6):733-48.

PPF: prevalence and outcome in non-IPF ILD

- Prevalence of PPF (N=396)



- Overall survival

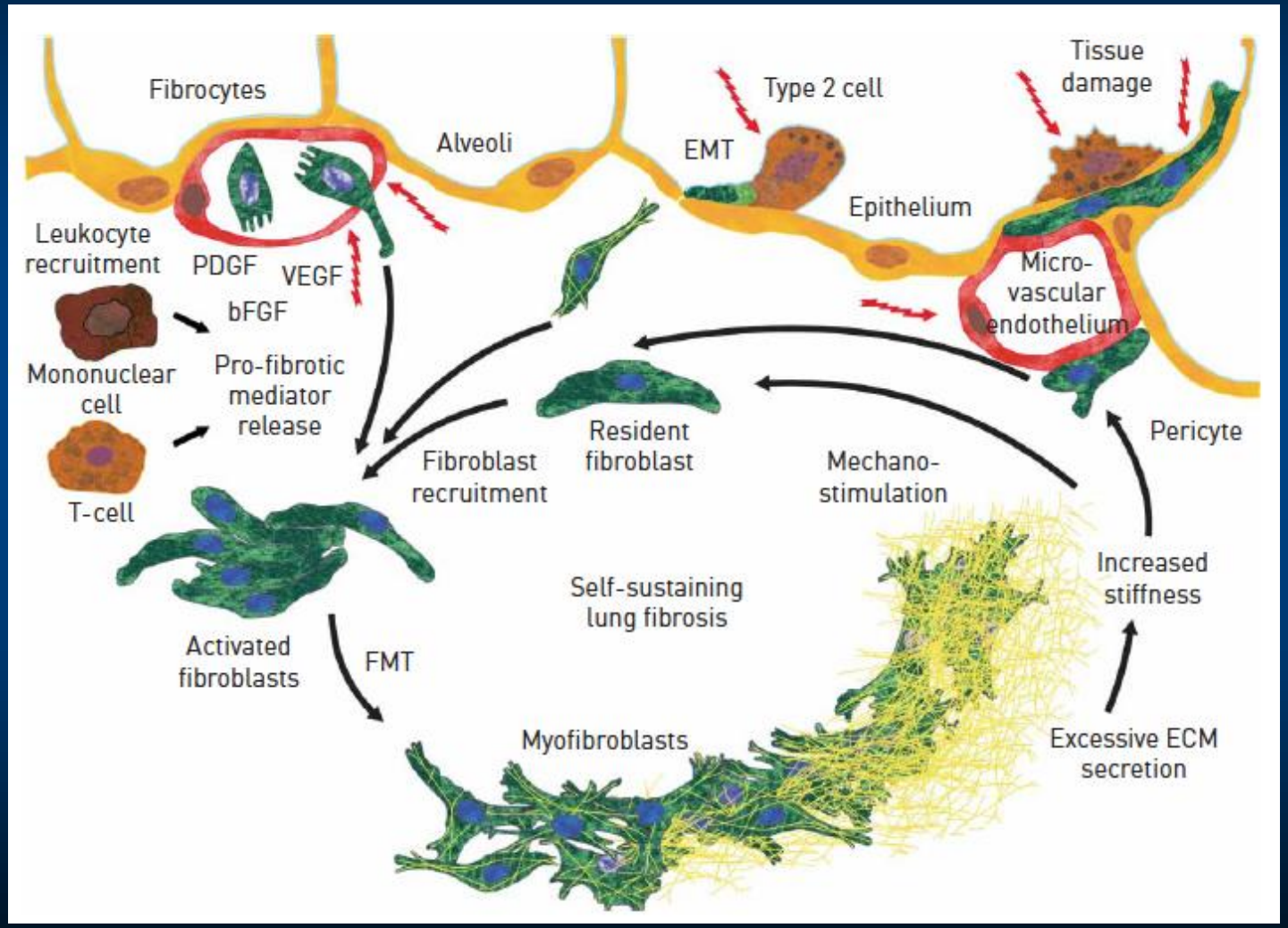


- A single-center retrospective cohort (INBUILD criteria for progression applied)

PPF: progressive pulmonary fibrosis, PF-ILD: progressive fibrosing-ILD

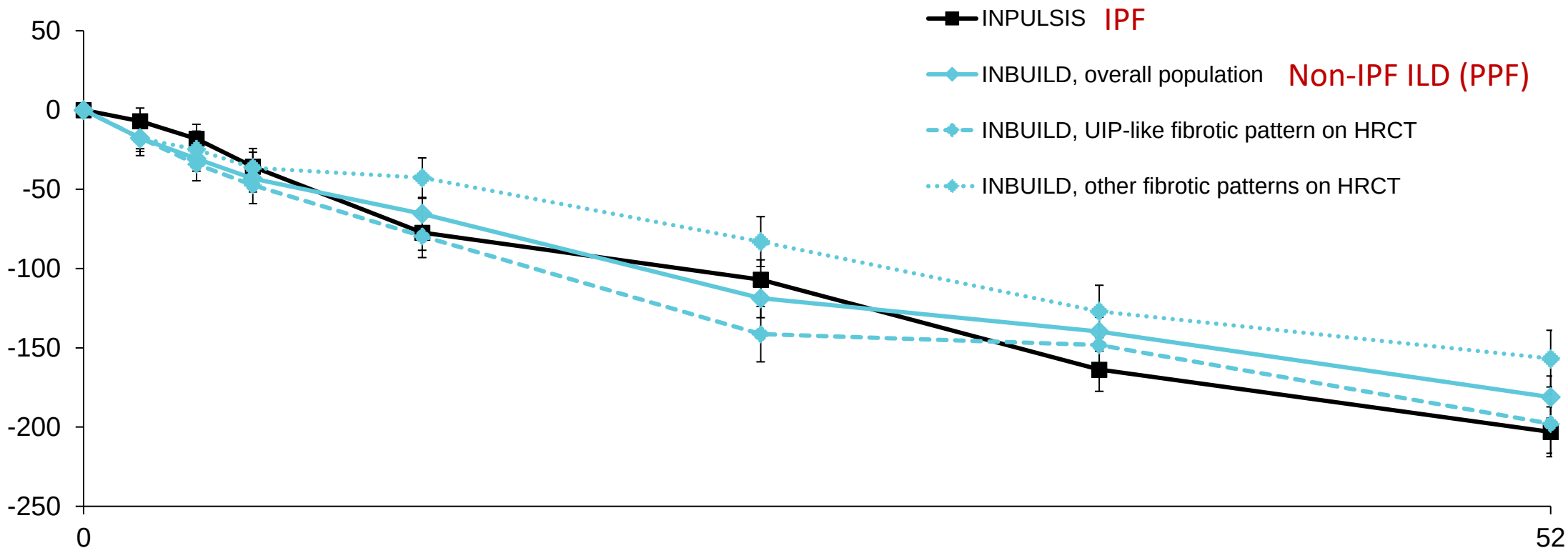
Kwon et al. *Respiratory Research* 2021;22:282

Commonalities: self-perpetuation of pulmonary fibrosis



Wollin L et al, *Eur Respir J* 2019; 54: 1900161.

Observed change in FVC over 52 weeks in the placebo groups of the INBUILD and INPULSIS trials

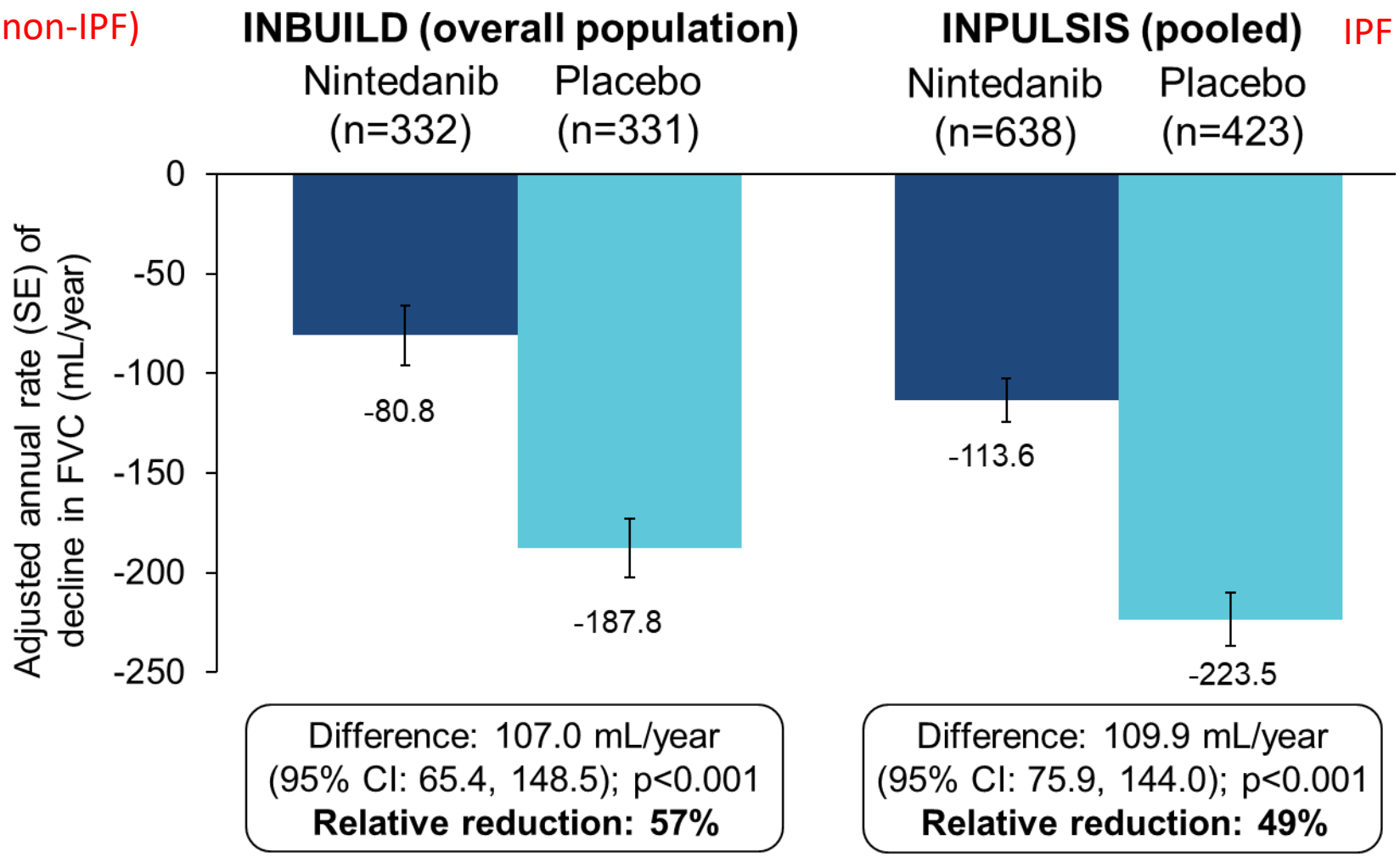


No. of subjects							
INPULSIS	417	408	407	403	395	383	345
INBUILD, overall population	325	326	325	320	311	296	274
INBUILD, UIP-like fibrotic pattern	202	202	201	197	190	176	162
INBUILD, other fibrotic patterns	123	124	124	123	121	120	112

- The INPULSIS trials and the INBUILD trial were randomised, double-blind, placebo-controlled trials with a 52-week treatment period.

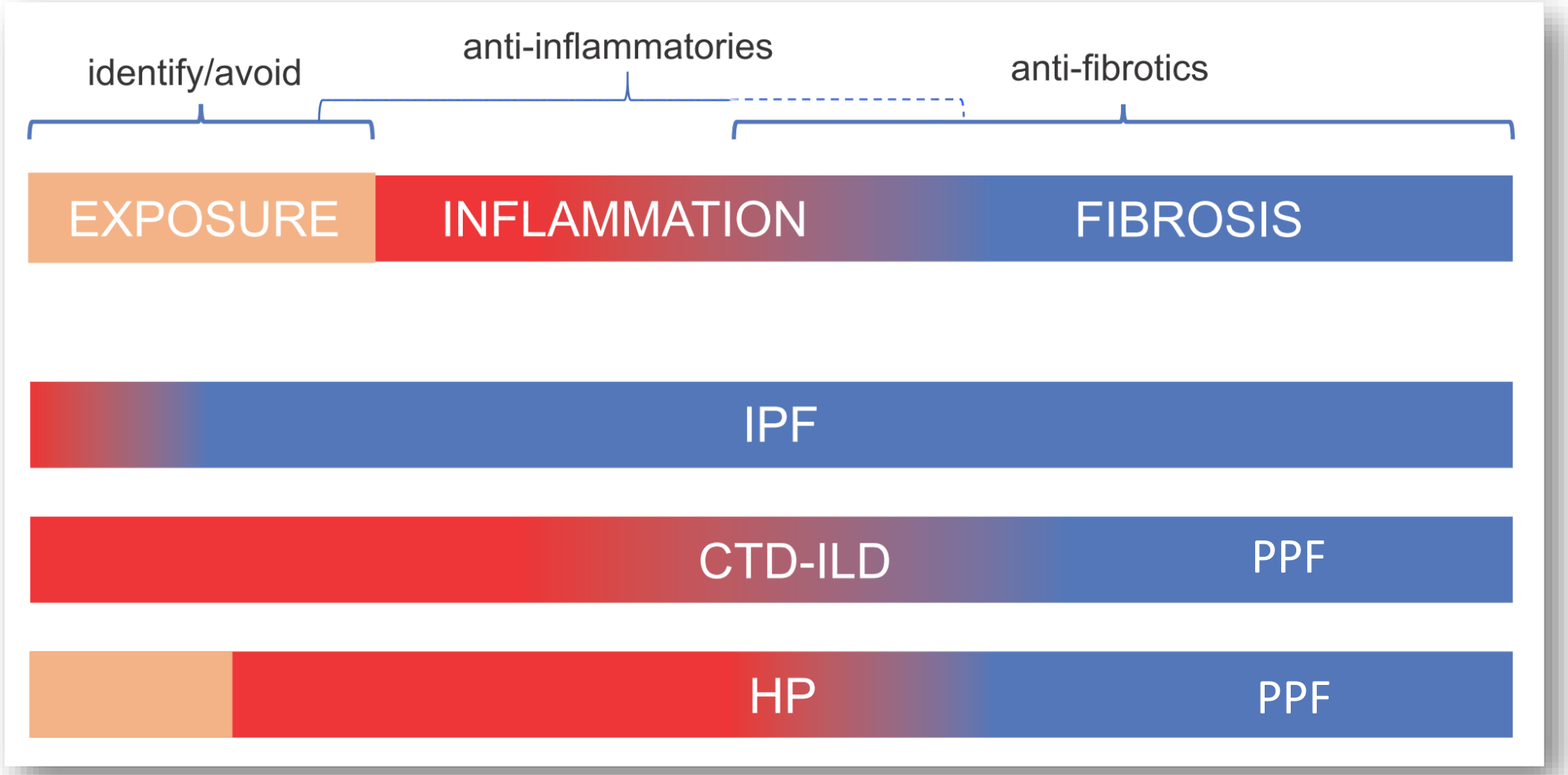
Brown KK et al. *Eur Respir J* 2020;55(6):2000085

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



Flaherty KR, et al. *N Engl J Med*. 2019;381(18):1718-1727.

Spectrum of fibrosing-ILD

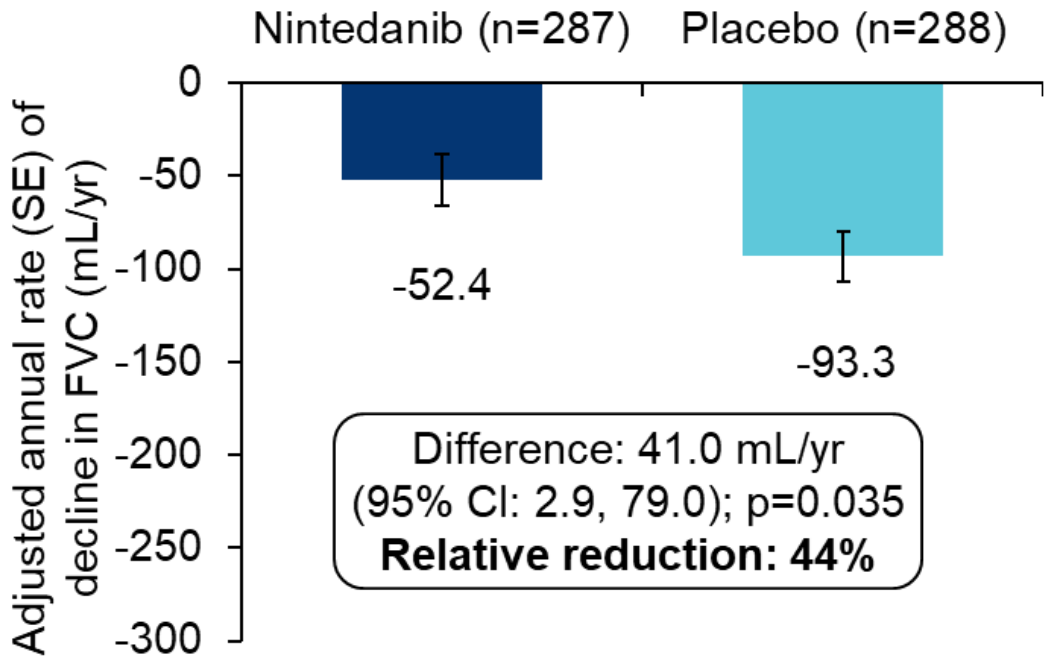


CTD-ILD: connective tissue associated ILD, HP: hypersensitivity pneumonitis

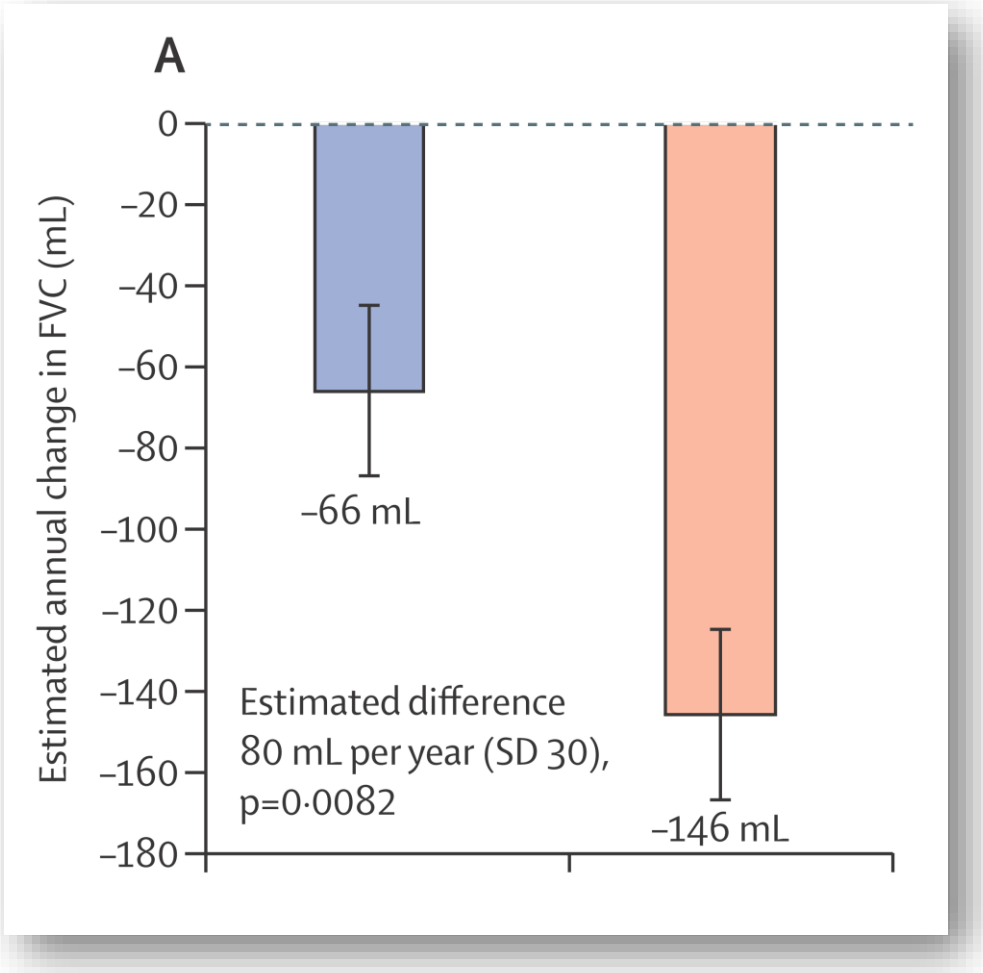
Wongkarnjana A et al. *Curr Opin Pulm Med 2020*; 26:436-442

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

- SENSCIS (nintedanib for SSc-ILD)

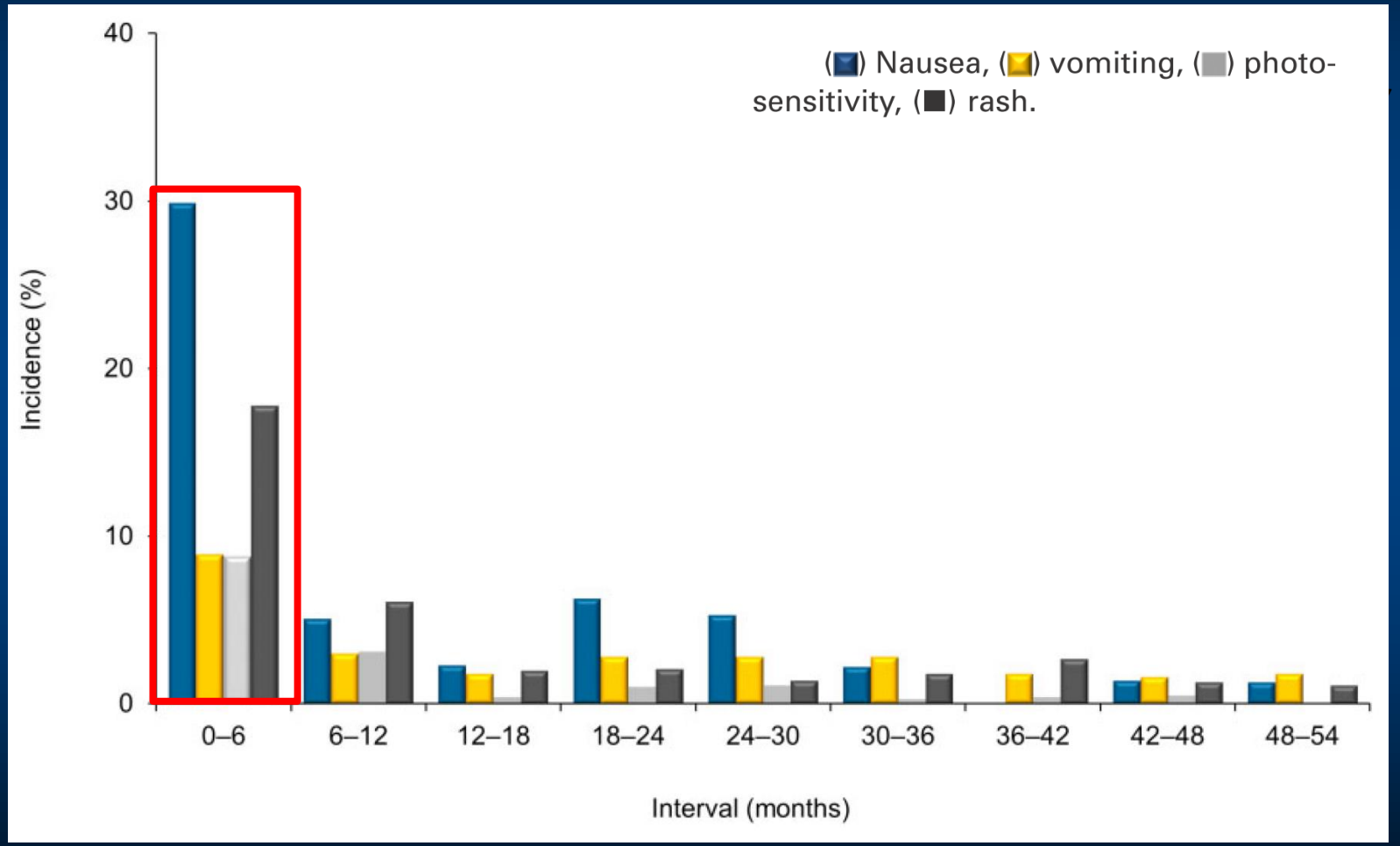


- TRAIL-1 (pirfenidone for RA-ILD)



Distler O et al. *N EnglJ Med* 2019;380:2518-2528, Solomon JJ, et al. *Lancet Resp Med* 2023;11(1):87-96

Incidence of new onset adverse events



* CAPACITY+RECAP (N=789; 2403 mg/d) : the median duration of exposure: 2.6 years (range 1wk-7.7yrs)

Valeyre D et al. *Respirology* 2014;19:740-747

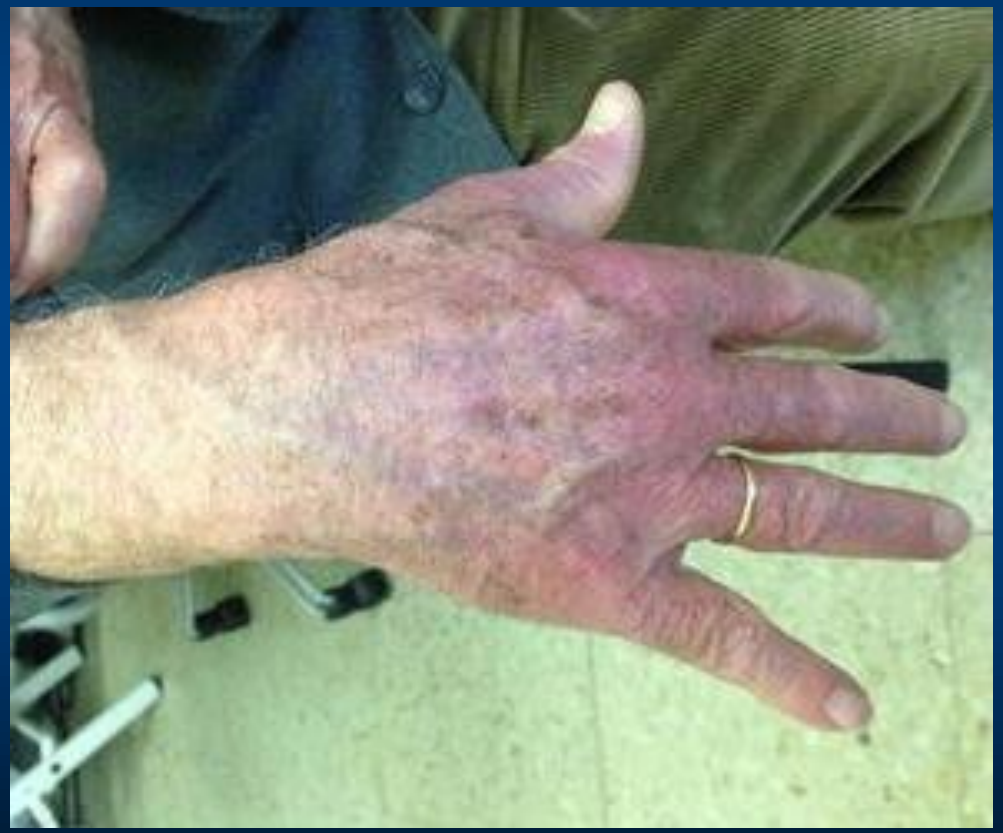
Pirfenidone: GI adverse events

- Pirfenidone reduce the rate of gastric emptying and small intestinal transit.
  → prokinetic agents
  → PPIs and H2RAs improve postprandial fullness.

- Co-administration with food decrease the peak concentration of PFD (AUC unchanged).
  → food intake reduces the risk
  → splitting during a meal

Costable U et al. *Adv Ther* 2014;31(4):375-91

Pirfenidone: skin adverse events



- Sunlight exposure
  - ROS and lipid peroxidation

- Sunscreens (high SPF, UV A & B)
- Clothing, hat, gloves
- Silver sulfadiazine or potent steroid oint

- <u>vs. Allergic reaction</u>

Costable U et al. *Adv Ther* 2014;31(4):375-91

Most diarrhea events in patients receiving nintedanib were mild-to-moderate in intensity

	Nintedanib (n=638)	Placebo (n=423)
Diarrhea, n (%)[1]	398 (62.4)	78 (18.4)

In patients experiencing diarrhea, **~95%** reported events that were **mild-to-moderate** in intensity[1]

Diarrhea occurred most frequently in the **first 3 months** of treatment[1]

<5% of patients discontinued treatment due to diarrhea[1]

Diarrhea led to a dose reduction in **~11%** of patients[2]

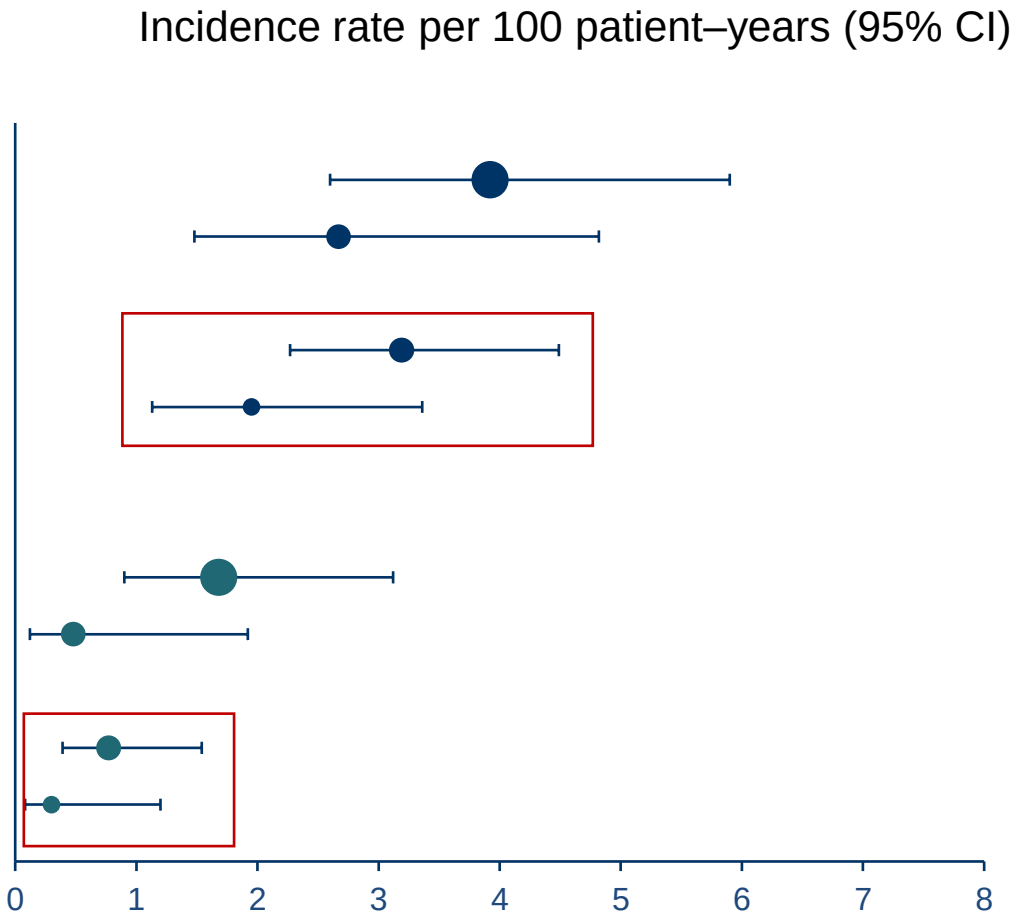
Diarrhea adverse events are manageable for most patients by

- Anti-diarrheal treatment[2]
- Dose reductions (to 100 mg bid) and temporary interruption until diarrhea is resolved[2]

Corte T et al. *Respir Res* 2015;16:116-91

INPULSIS-ON: myocardial infarction rates similar compared to INPULSIS

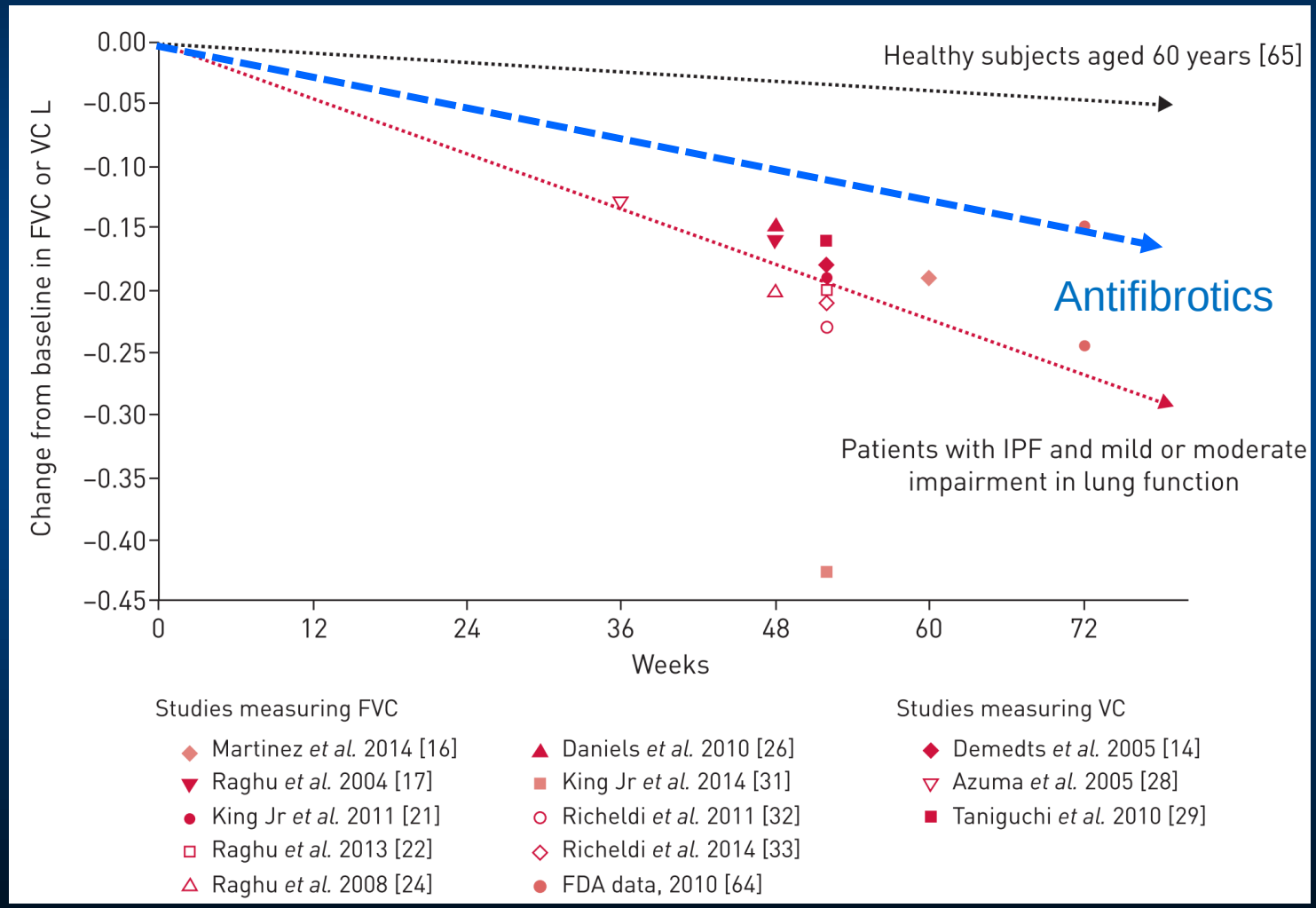
	N	Patients with events, n (%)	Incidence rate* per 100 patient–years (95% CI)
MACE			
INPULSIS®			
Nintedanib	638	23 (3.6)	3.92 (2.60, 5.90)
Placebo	423	11 (2.6)	2.67 (1.48, 4.82)
INPULSIS®-ON			
Continuing nintedanib	430	33 (7.7)	3.19 (2.27, 4.49)
Initiating nintedanib	304	13 (4.3)	1.95 (1.13, 3.36)
Myocardial infarction			
INPULSIS®			
Nintedanib	638	10 (1.6)	1.68 (0.90, 3.12)
Placebo	423	2 (0.5)	0.48 (0.12, 1.92)
INPULSIS®-ON			
Continuing nintedanib	430	8 (1.9)	0.77 (0.39, 1.54)
Initiating nintedanib	304	2 (0.7)	0.30 (0.08, 1.20)



*Number of patients with an event/time at risk
Time at risk was the time from start of treatment until start of first event (patients with event) or end of time at risk (patient without event) plus 1 day
MACE, major adverse cardiovascular events

Crestani B et al. *Eur Respir J* 2017;50:OA3402

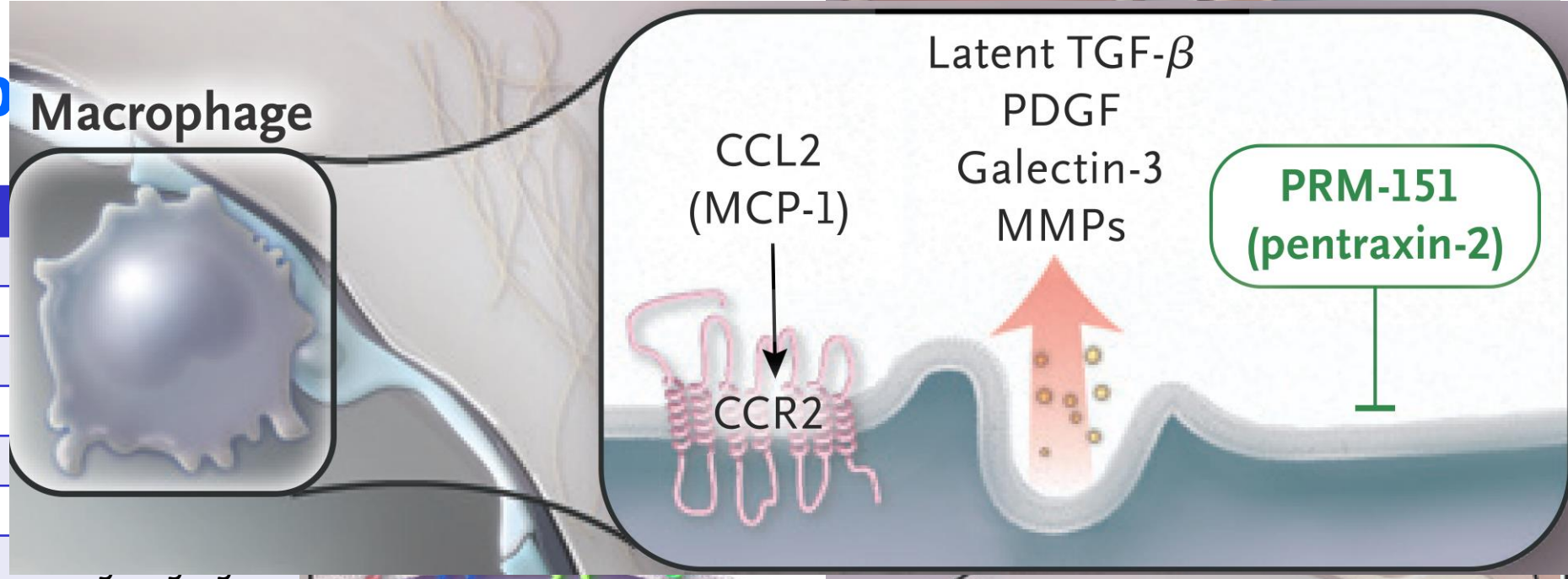
IPF: natural course of lung function decline in placebo groups

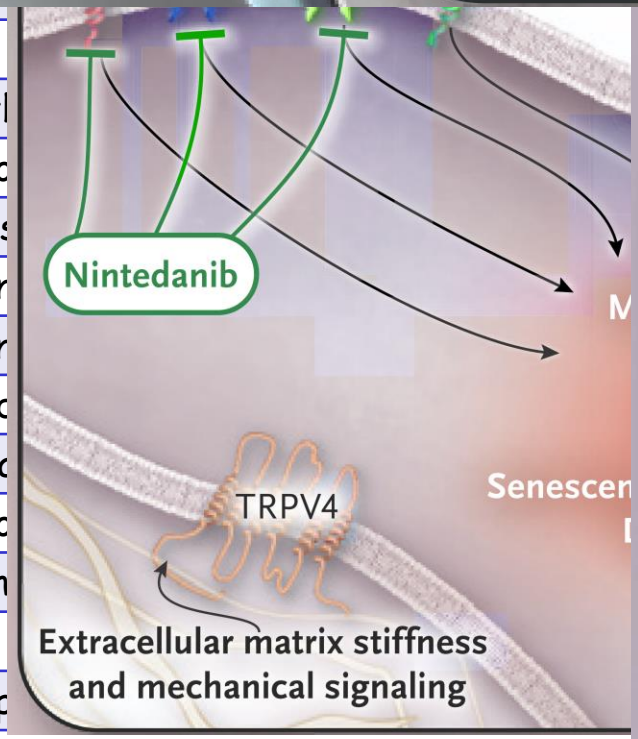


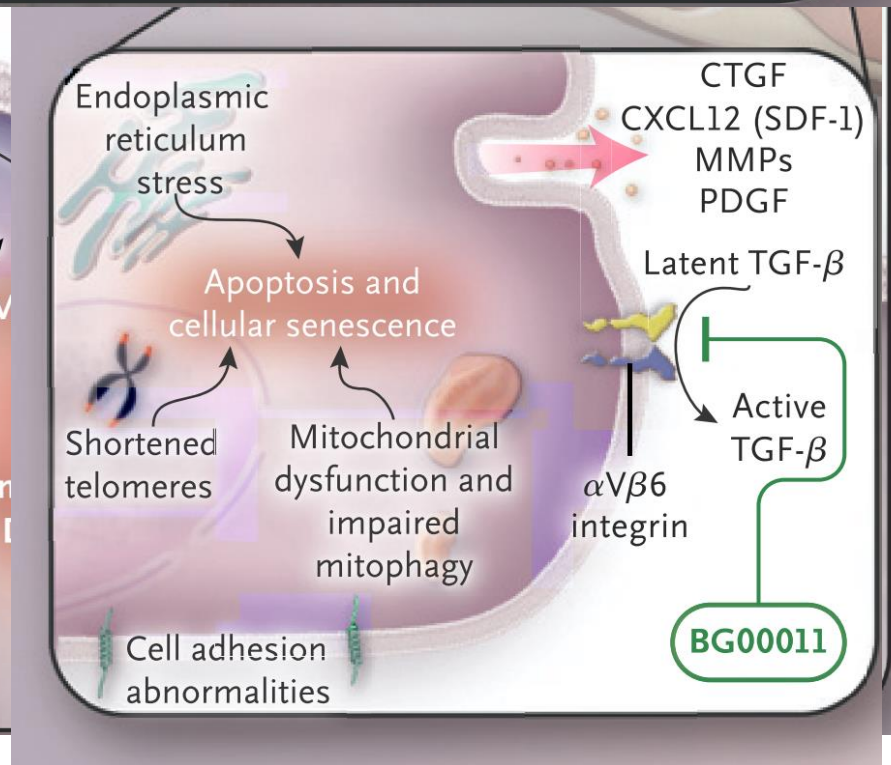
Raghu G et al. *Eur Respir J* 2017;50:1701209

Ongoing/p

Name	Phase	
BI-1015550	III	
RIN-PF-303	III	
BMS-986278	III	
VP-C21	II	
SNDX-6352	II	
HZN-825	II	
ENV-101	II	
LYT-100	II	Deupirfenidone
DWN12088	II	Prolyl-tRNA Synth
BBT-877	II	Autotaxin inhibito
GSK3915393	II	Inhibitor of Trans
GSK218224	II	Belimumab (humar
PLN-74809	II	A selective dual ir
NAL03-202	II	Nalbuphine (opioic
GB44496	II	Vixarelimab (humo
BI 1819479	II	Autotaxin inhibito
BI 1839100	II	Small molecular in
SB17170	II	HMGB1 inhibitor
ARO-MMP7	I/II	MMP-7 siRNA dup

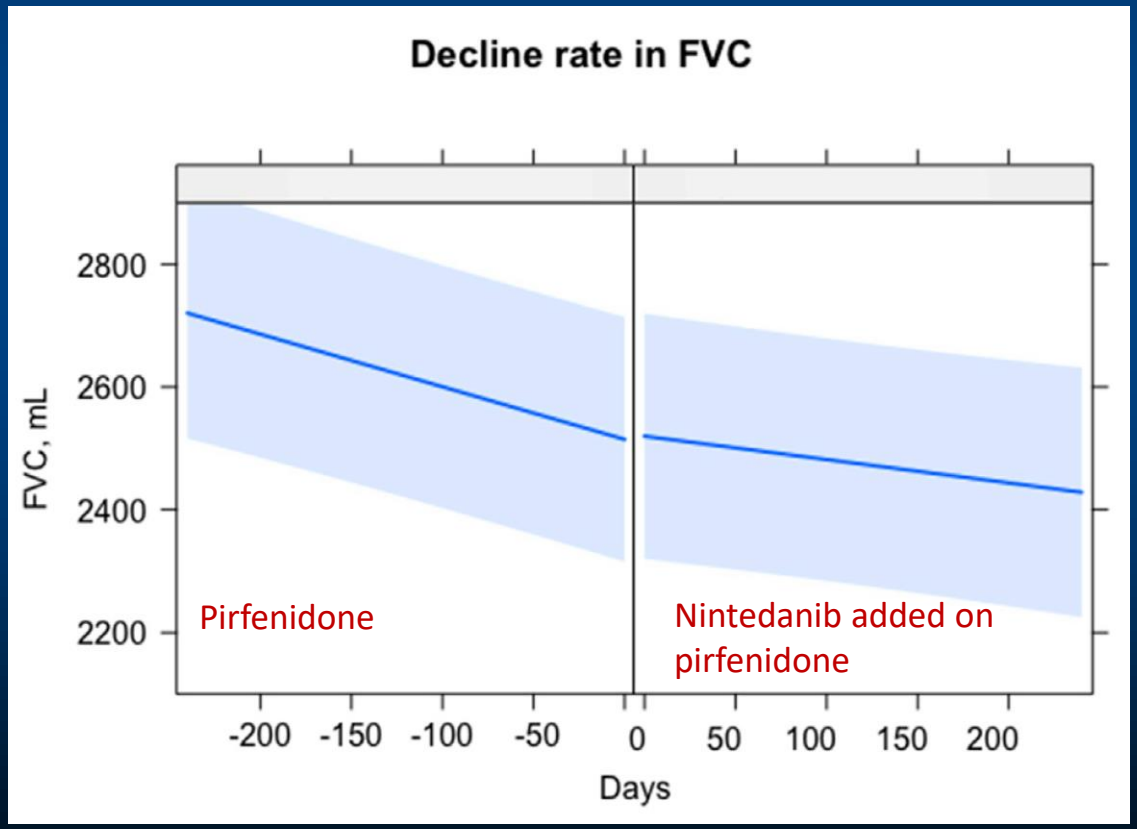






Combination therapy: the future of management for idiopathic pulmonary fibrosis?

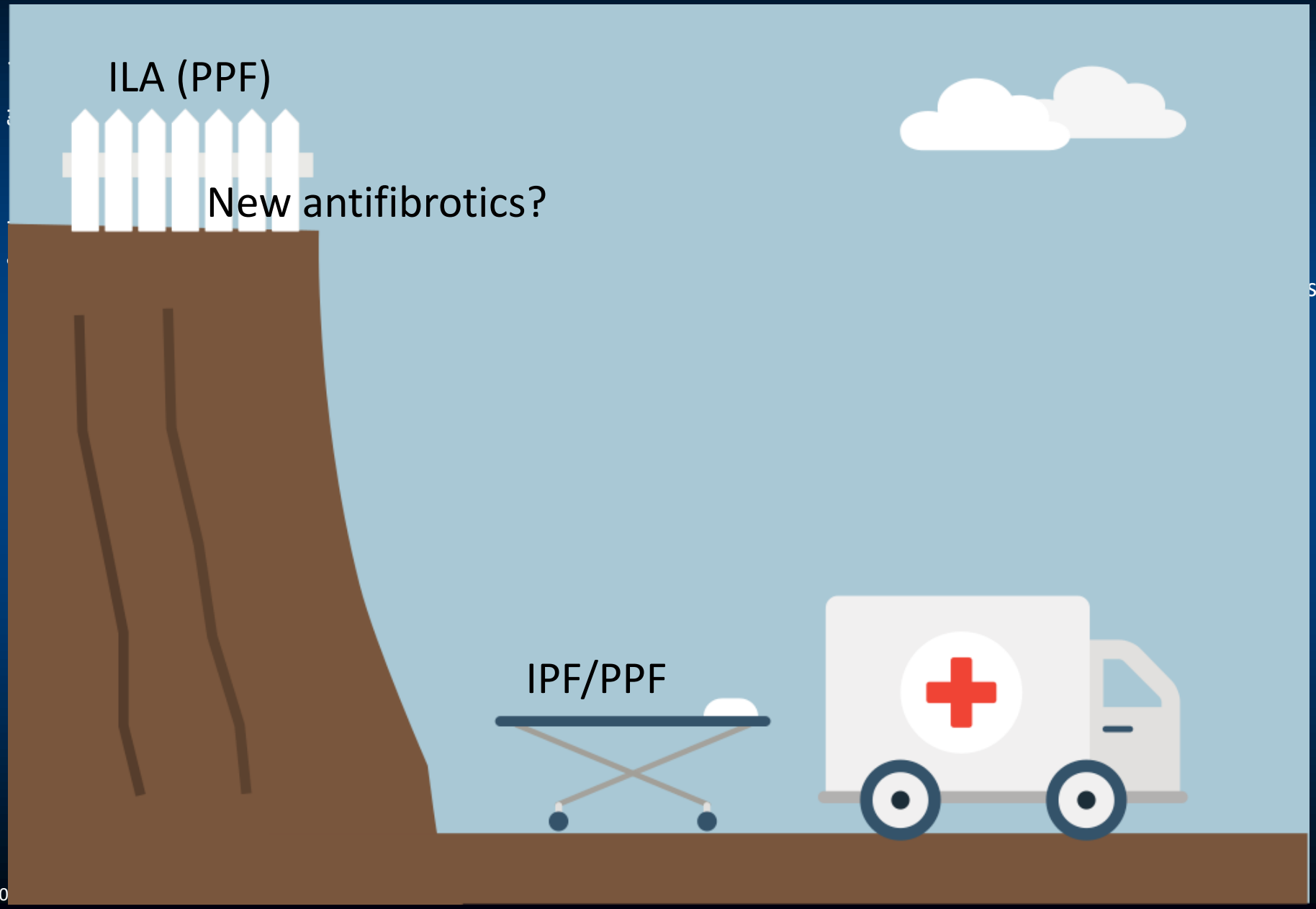
	Pathways targeted
COPD[43,44]	Longacting β agonists, longacting muscarinic antagonists, inhaled corticosteroids, phosphodiesterase 4 inhibitor
Asthma[45,46]	Longacting β agonists, longacting muscarinic antagonists, inhaled corticosteroids
Pulmonary arterial hypertension[47–49]	Guanylate cyclase–phosphodiesterase-5 pathway; endothelin receptor pathway; prostanoid pathway



• A multicenter IPF cohort study (n=45)

Wuyts WA et al. *Lancet Resp Med* 2014;11:933-942, Huh JY et al. *Fronteris in Phamacology* 2023;14:1301923

Spectrum of pulmonary fibrosis



Hunninghake GM et al. Thorax 20

Summary

- Antifibrotic therapy in fibrosing ILD
  - better survival
  - early treatment (even in advanced status)
  - better tolerability by dose modification strategy
  - consistent efficacy and safety in long term use
  - similar efficacy and safety in PPF other than IPF

  - novel targets and strategies underway