Respiratory Review of 2017: ILD

APR. 15. 2017

울산의대 서울아산병원

송진우

Contents

- Treatment:
  - Pirefnidone
  - Nintedanib
  - Combination (PFD+NAC; PANORAMA study)
  - MMF in SSc-ILD (Scleroderma lung study II)
- Early interstitial lung disease (ILA)
- Guidelines: Aex of IPF, LAM

IPF guidelines 2015

ATS/ERS/JRS/ALAT

"The majority of patients would want the intervention, but a significant mino rity would not."	"The majority of patients would not want the intervention, but a significant minority would."

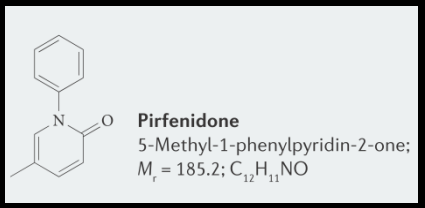
Strong YES	Weak YES*	Weak NO	Strong NO
			
Lung transplant **Oxygen**	**Antacids** **Nintedanib** **Pirfenidone**	**Sildenafil** **NAC** **Bosentan** **Macitentan**	**Warfarin** **Ambrisentan** **NAC+Aza+Pred** **Imatinib**

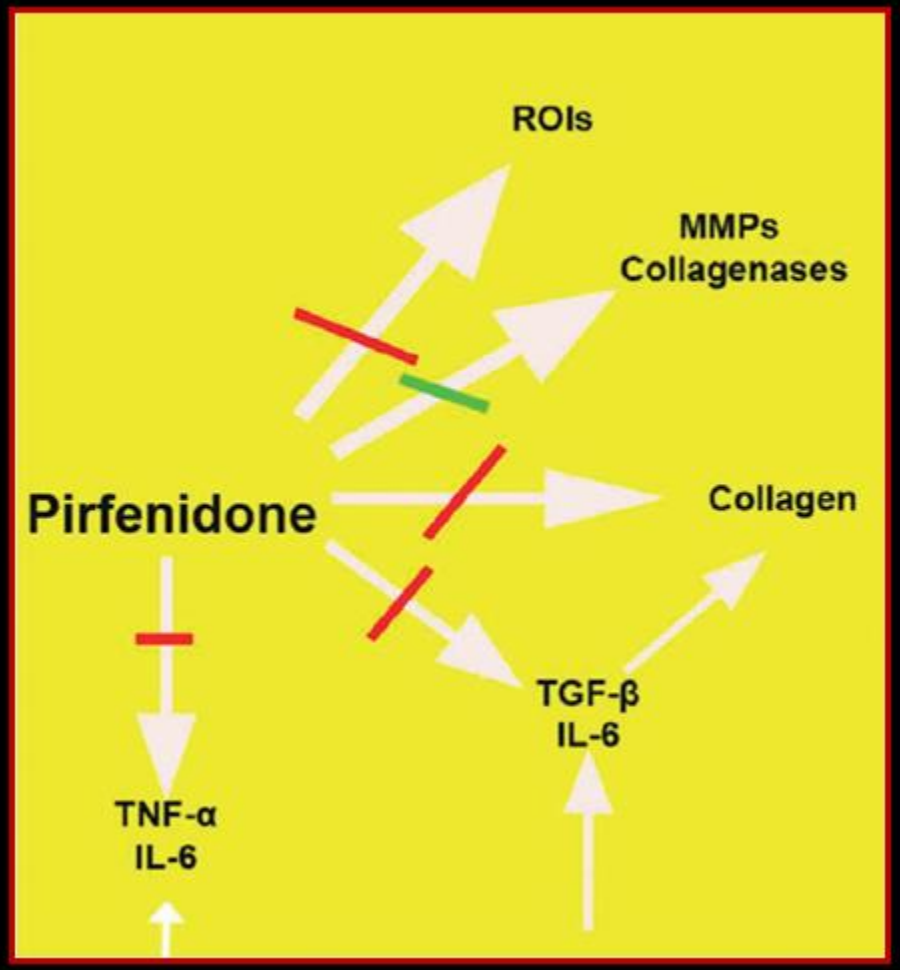
* Conditional recommendation for use

Am J Resp Crit Care Med 2015;192:e3

Pirfenidone

Possible Mechanisms

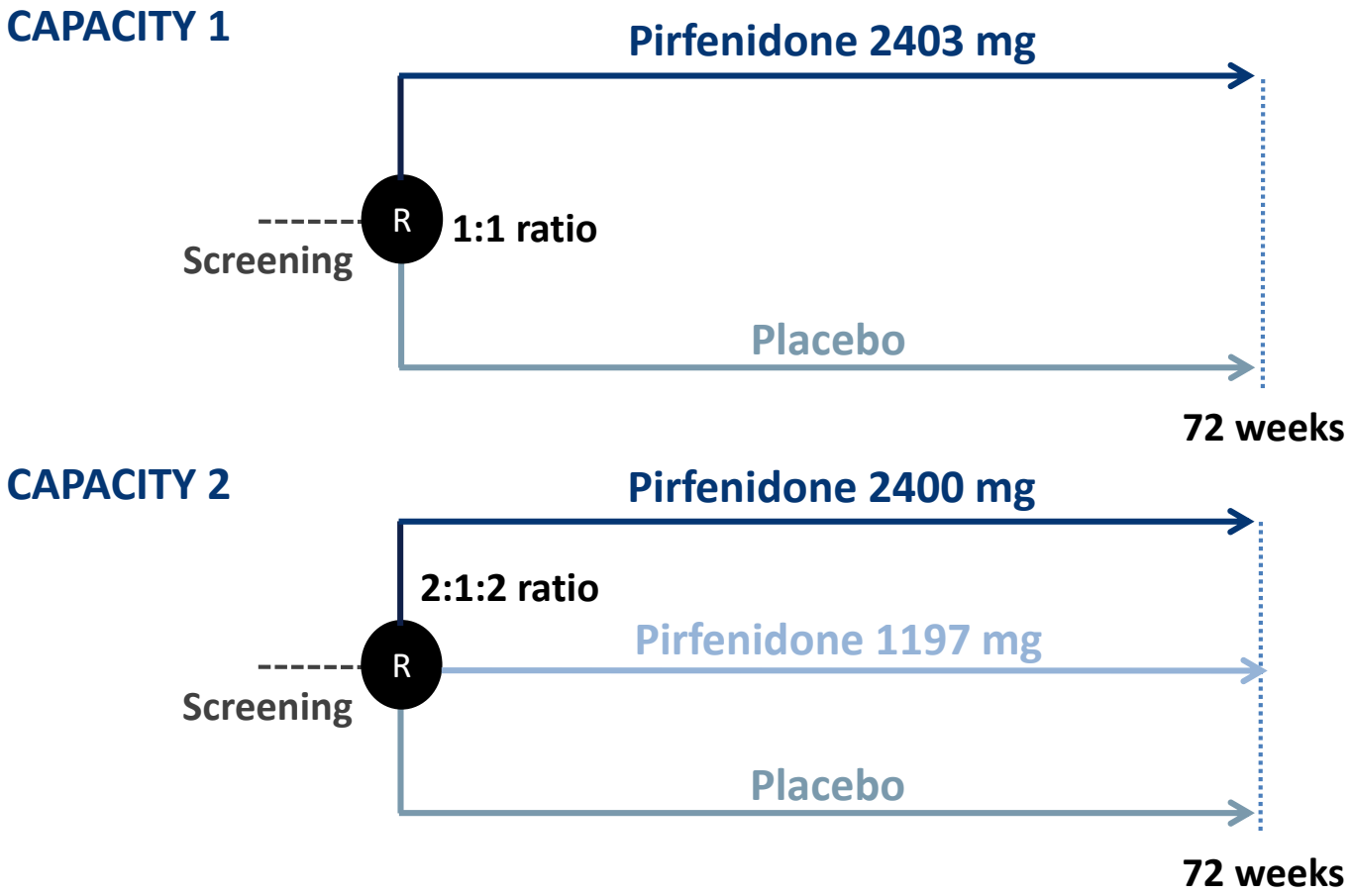




Anti-fibrotic, Anti-inflammatory, Anti-oxidant

Clin Respir J. 2012;6:131

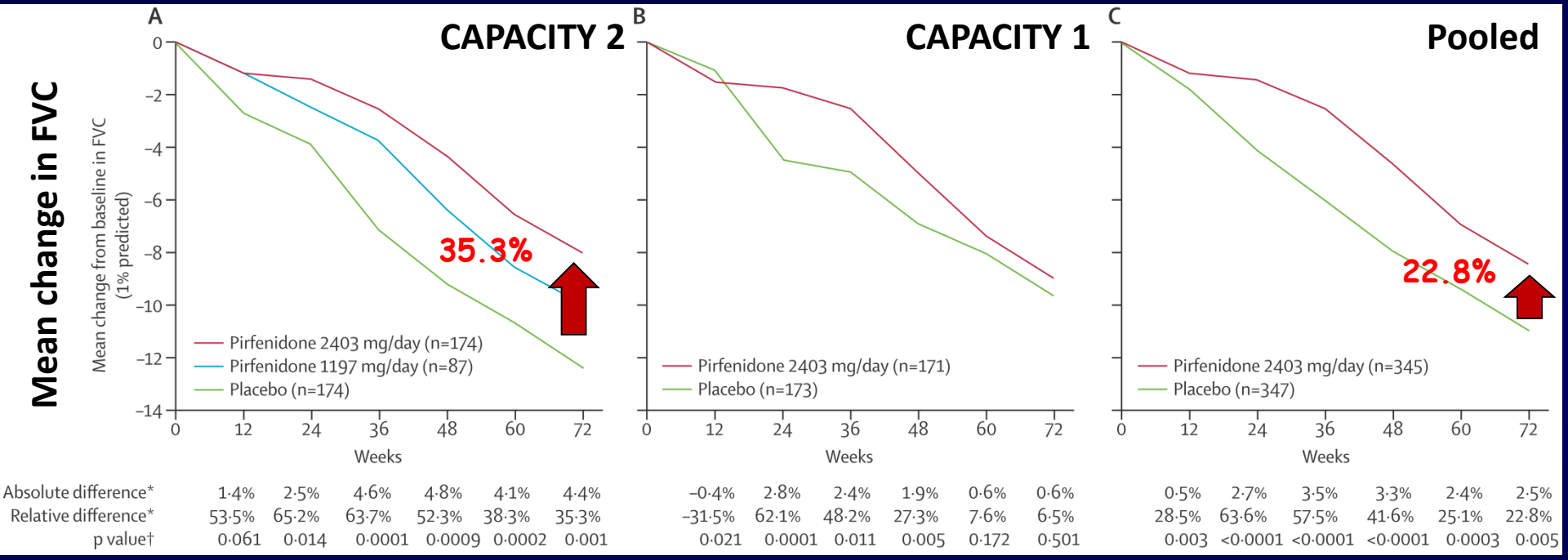
Pirfenidone : CAPACITY Trials



- CAPACITY 1: 344, CAPACITY 2: 435 radomized (Australia, Europe, and North America)
- FVC ≥ 50% predicted, DL_{CO} ≥ 35% predicted (either ≤ 90%), FEV1/FVC ≥ 0.7
- Change from baseline in % predicted FVC

Lancet 2011; 377: 1760

Pirfenidone : CAPACITY Trials



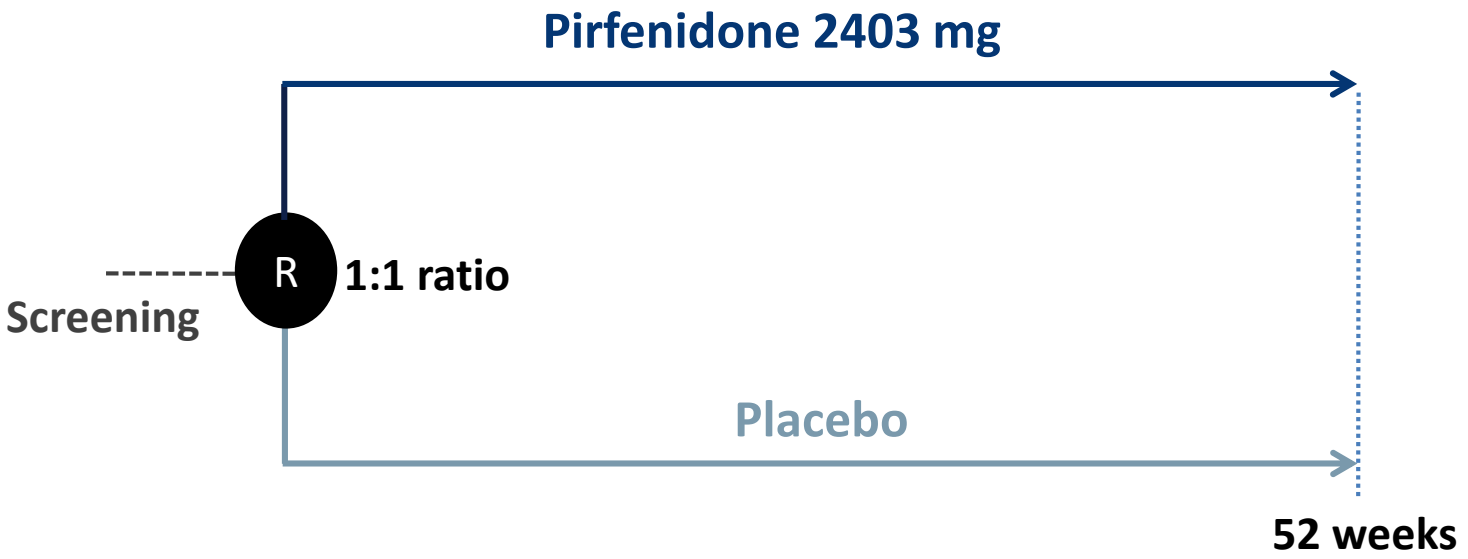
Absolute difference*	1·4%	2·5%	4·6%	4·8%	4·1%	4·4%
Relative difference*	53·5%	65·2%	63·7%	52·3%	38·3%	35·3%
p value†	0·061	0·014	0·0001	0·0009	0·0002	0·001

Absolute difference*	−0·4%	2·8%	2·4%	1·9%	0·6%	0·6%
Relative difference*	−31·5%	62·1%	48·2%	27·3%	7·6%	6·5%
p value†	0·021	0·0001	0·011	0·005	0·172	0·501

Absolute difference*	0·5%	2·7%	3·5%	3·3%	2·4%	2·5%
Relative difference*	28·5%	63·6%	57·5%	41·6%	25·1%	22·8%
p value†	0·003	<0·0001	<0·0001	<0·0001	0·0003	0·005

Lancet 2011; 377: 1760

Pirfenidone : ASCEND Trial

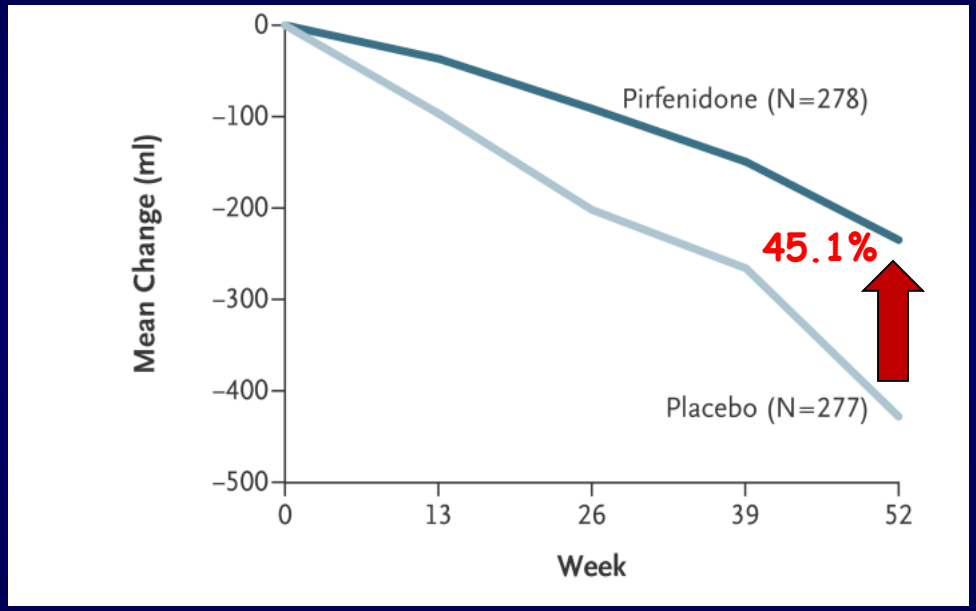


- 555 randomized, 522 included in analysis
- FVC 50-90% predicted, DL_{CO} 35-90% predicted, FEV1/FVC ≥ 0.8
- Change from baseline in % predicted FVC

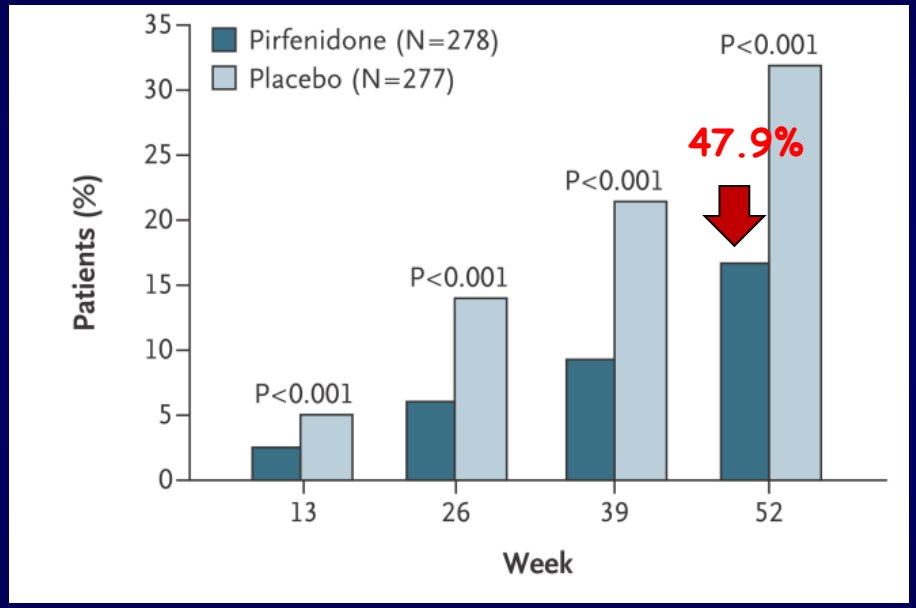
NEJM 2014;370:22

Pirfenidone : ASCEND Trial

Change in FVC



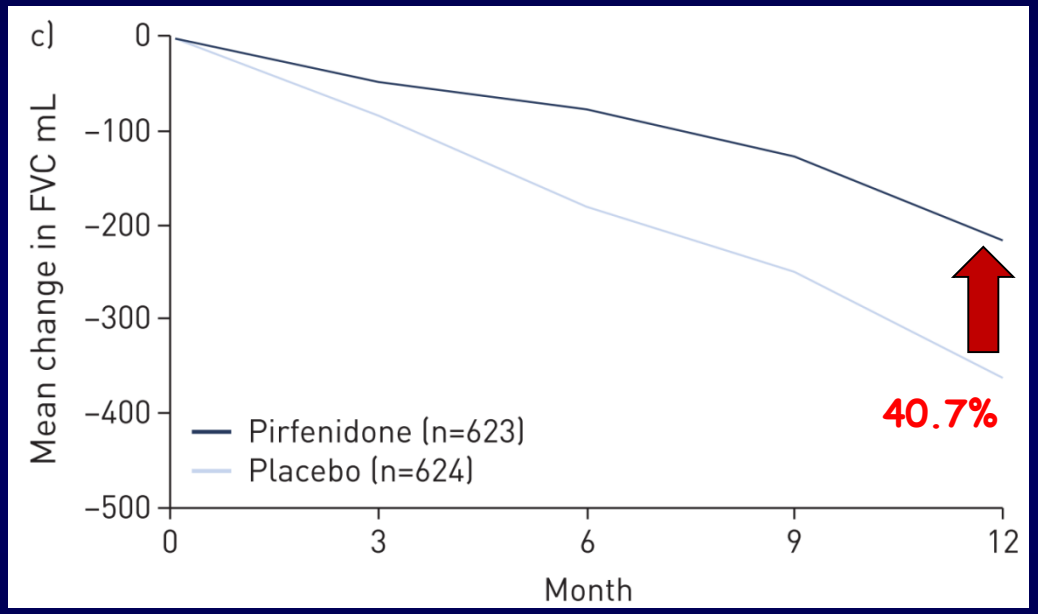
Decreased FVC or Death



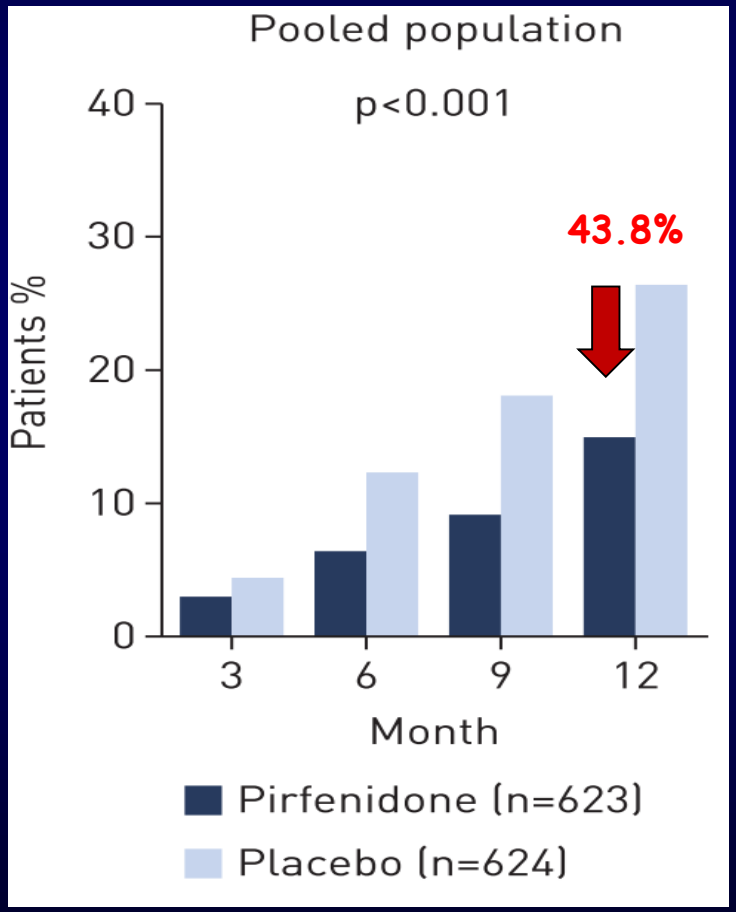
NEJM 2014;370:22

Pooled Data Analysis: *ASCEND and CAPACITY Trials (n=1247)*

Change in FVC



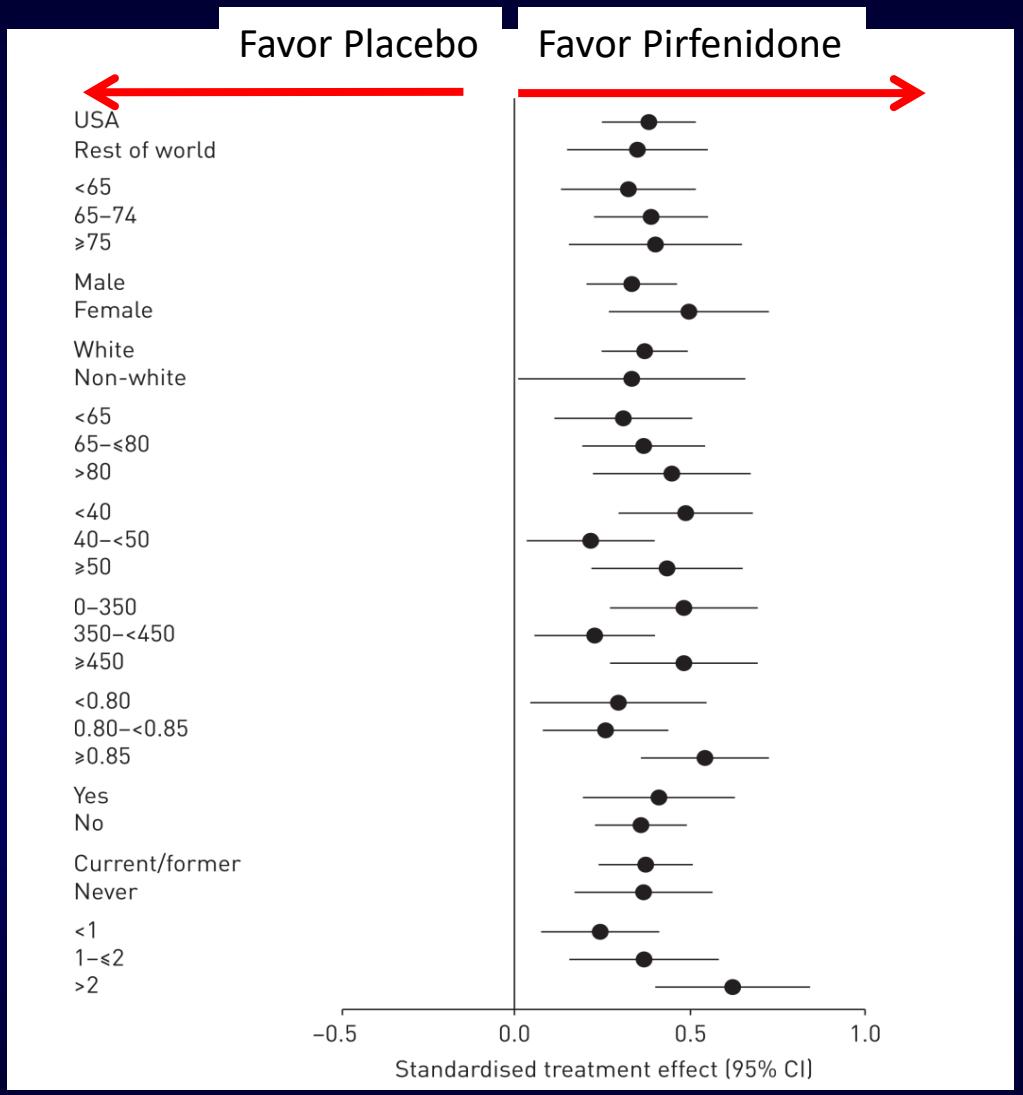
Decreased FVC or Death



ERJ 2016;47:243

Subgroup Analysis of FVC Outcome

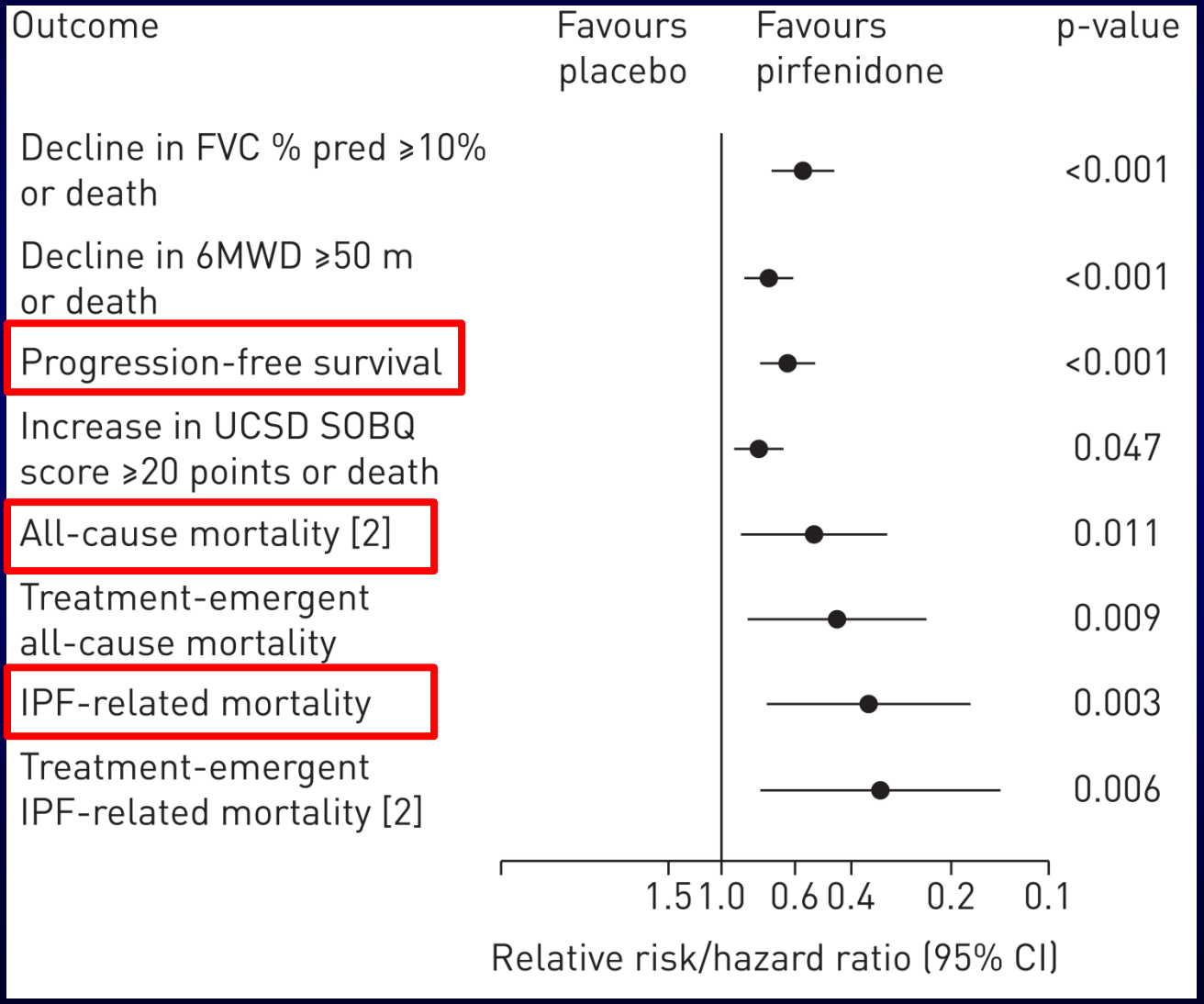
- Region
- Age
- Sex
- Race
- FVC
- DLco
- 6MWD
- FEV_1/FVC
- O_2 use
- Smoking
- Time since diagnosis



A consistent magnitude of treatment effect across all strata for each demographic variable and baseline measure of disease status

ERJ 2016;47:243

Pooled Data Analysis: *ASCEND and CAPACITY Trials (n=1247)*



ERJ 2016;47:243

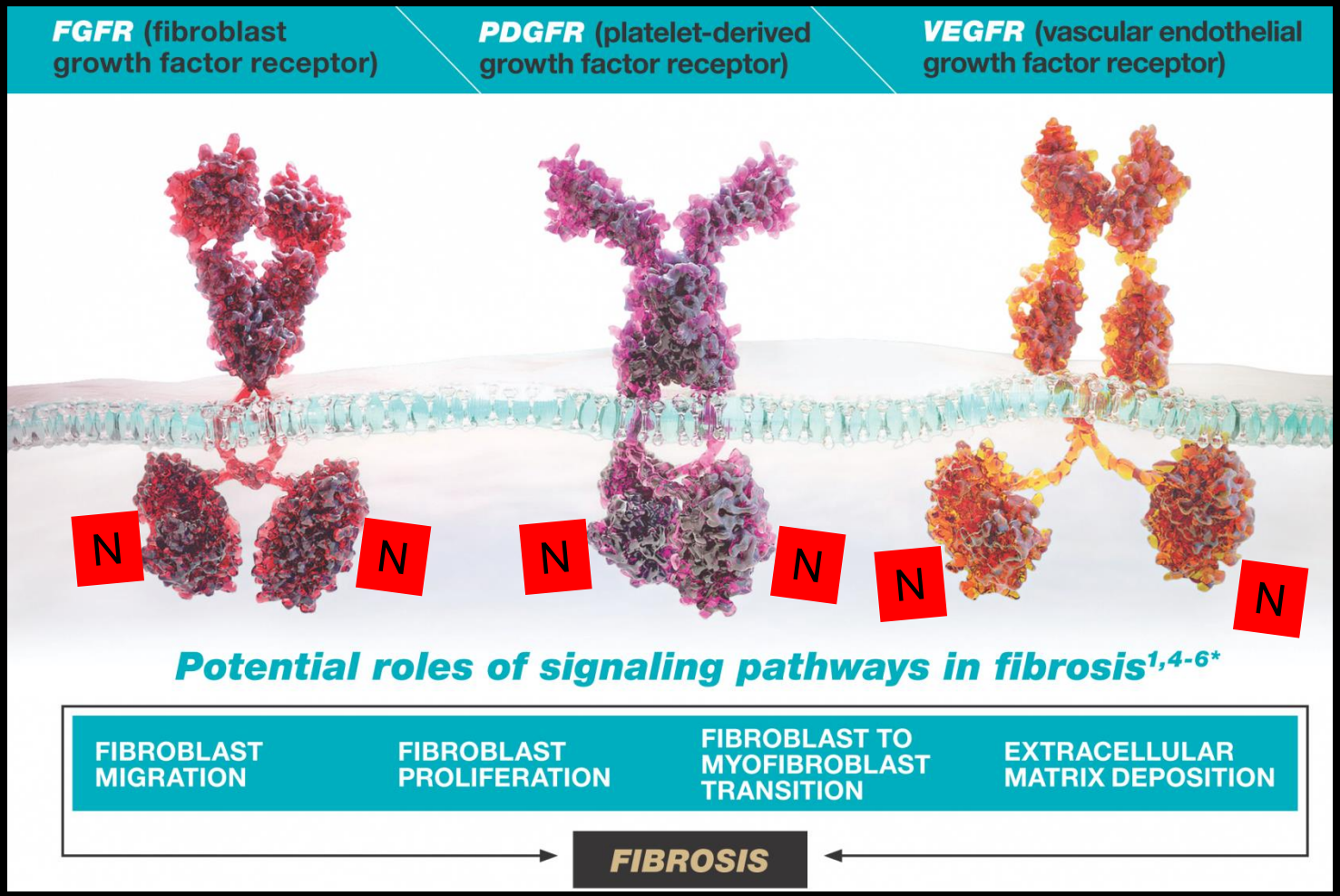
Pooled Data Analysis: *ASCEND and CAPACITY Trials (n=1247)*

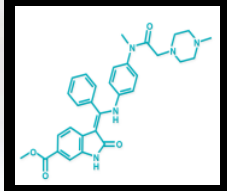
	Pirfenidone	Placebo
Subjects n	623	624
Nausea	35.5	15.1
Cough	23.1	24.0
Diarrhoea	24.6	18.8
Upper respiratory tract infection	22.6	20.2
Fatigue	23.0	16.8
Headache	20.5	18.1
Rash	29.2	9.0
Nasopharyngitis	15.1	15.9
Dyspnoea	13.2	16.0
Dizziness	16.7	10.1
Dyspepsia	17.8	6.7
Bronchitis	11.1	13.1
Idiopathic pulmonary fibrosis	8.5	14.4
Vomiting	12.7	6.1
Anorexia	12.4	4.3
Gastro-oesophageal reflux disease	10.3	5.6

GI and Skin AEs occurred more frequently in the pirfenidone group .

ERJ 2016;47:243

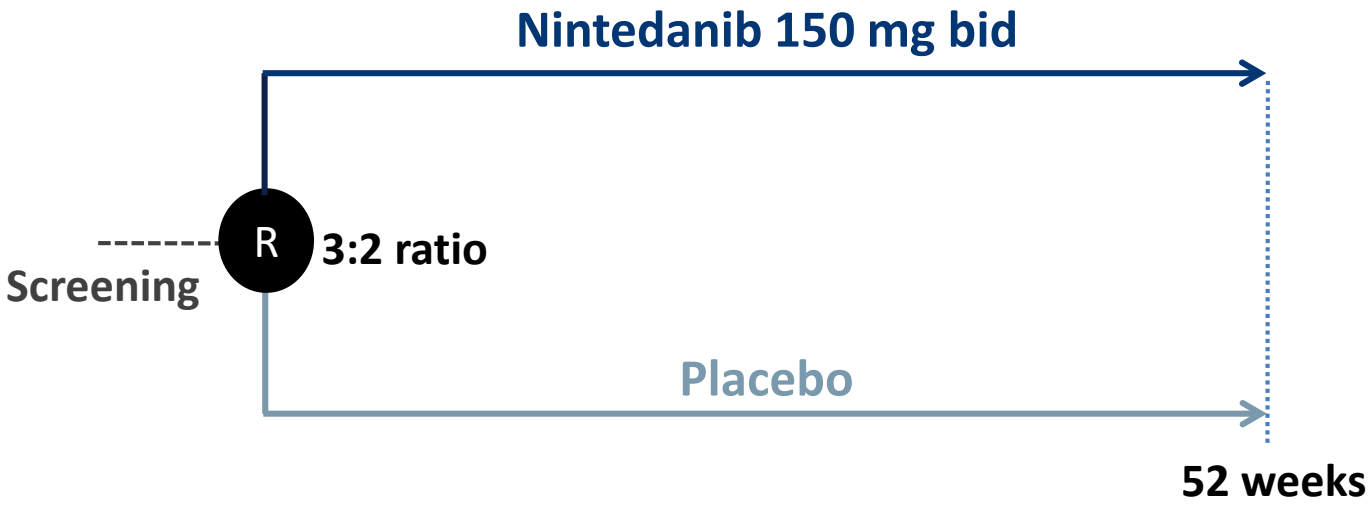
Nintedanib





Nintedanib is a potent inhibitor of tyrosine kinase receptors involved in lung fibrosis.

Nintedanib : INPULSIS Trial

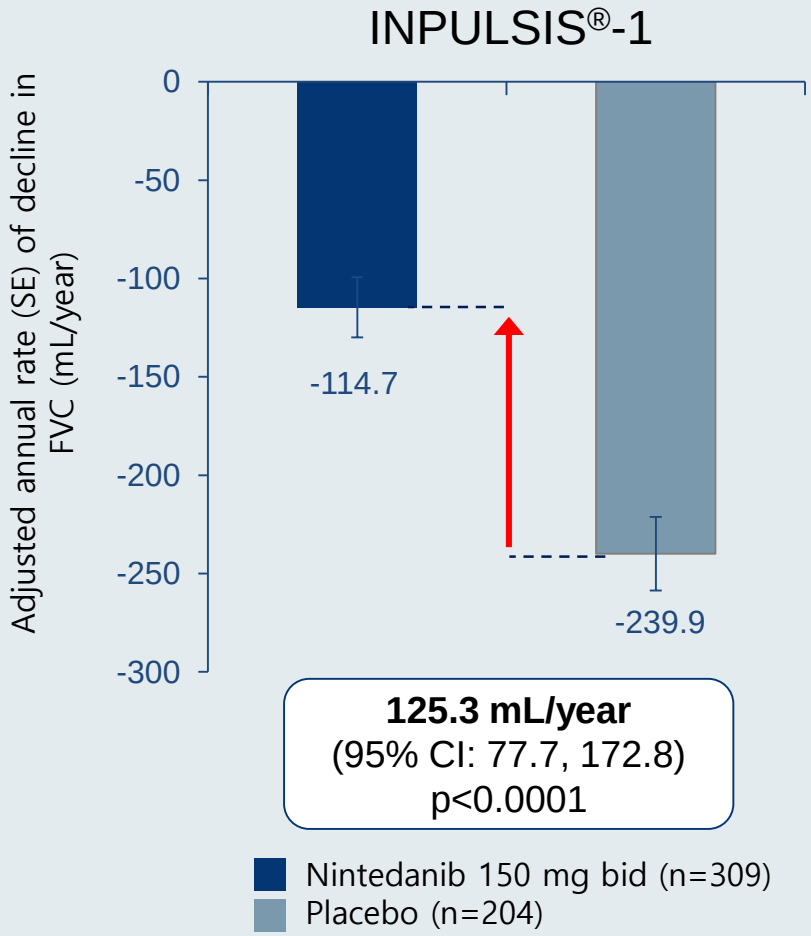


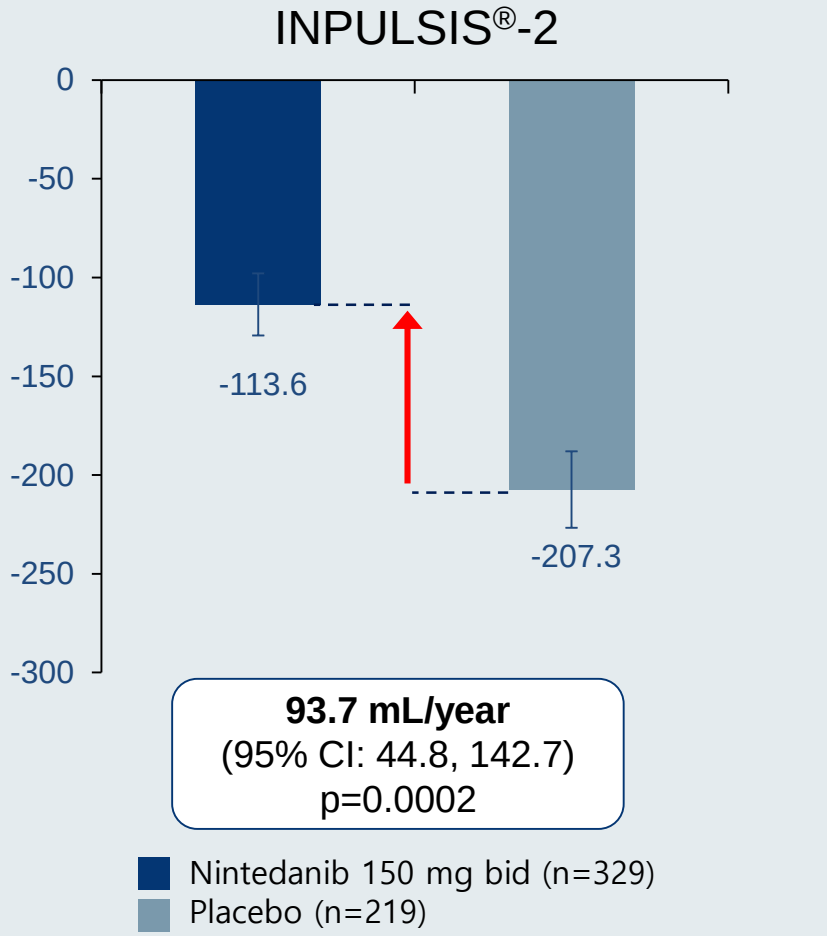
- INPULSIS-1: 515, INPULSIS-2: 513 randomized
- FVC ≥ 50% predicted, DL_{CO} 30-79% predicted
- the annual rate of decline in FVC (ml/year)

NEJM 2014;370:22

Nintedanib : INPULSIS Trial

Annual rate of decline in FVC

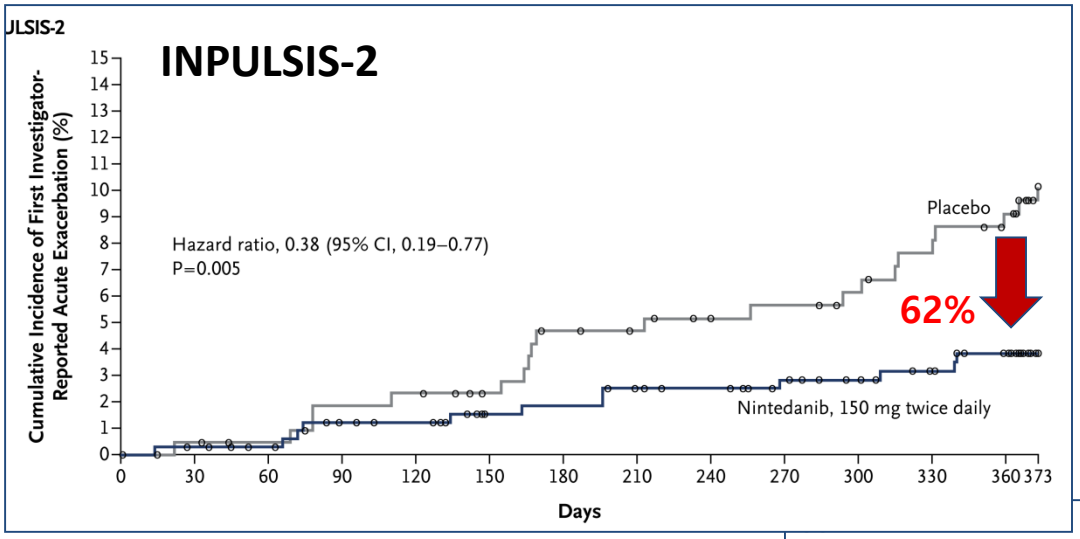


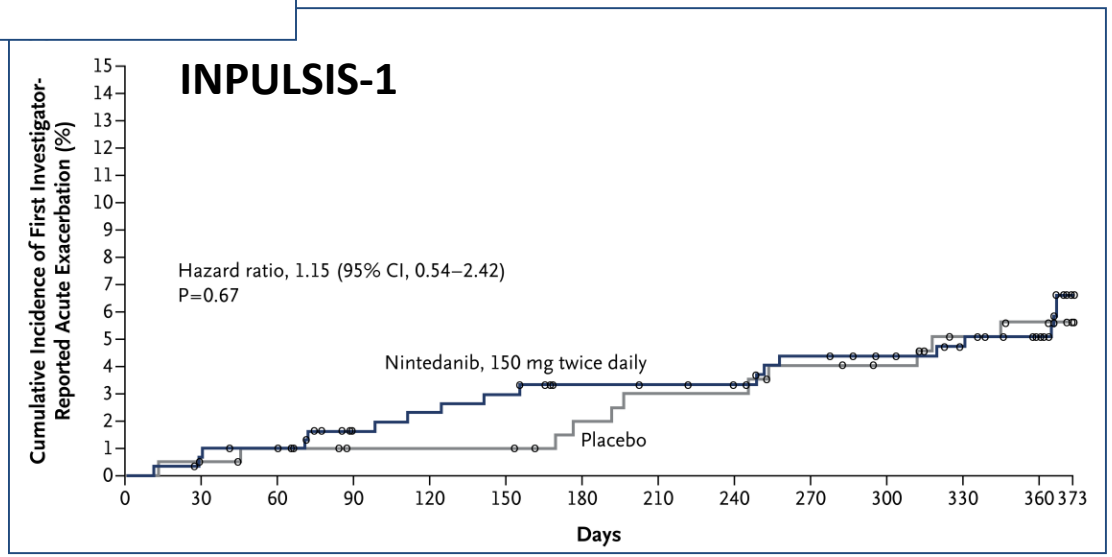


NEJM 2014;370:22

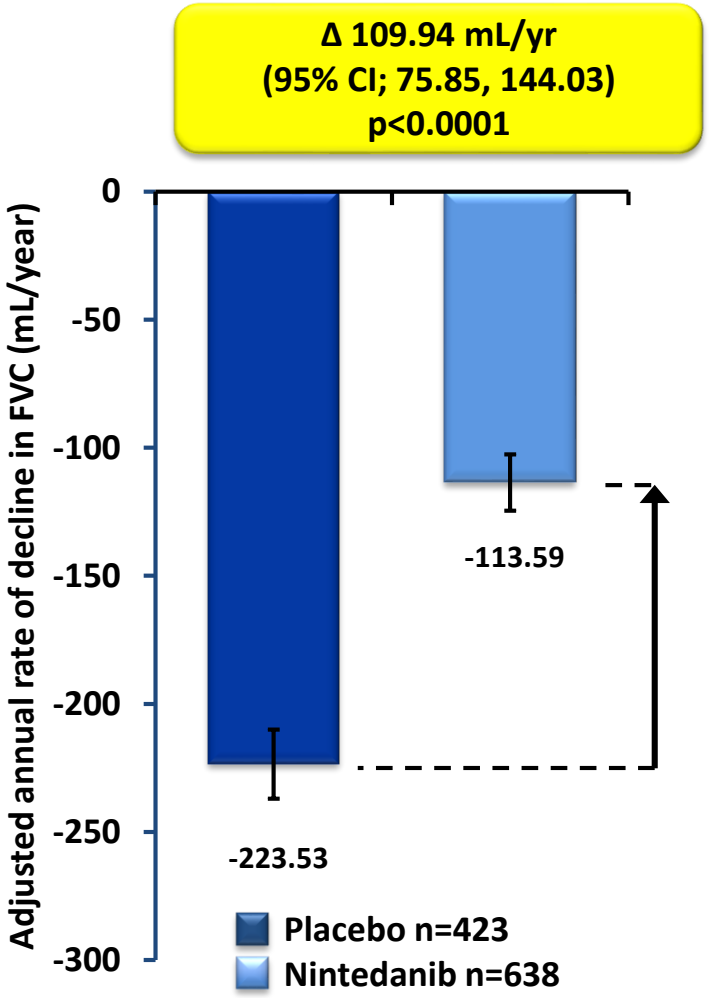
Nintedanib : INPULSIS Trial

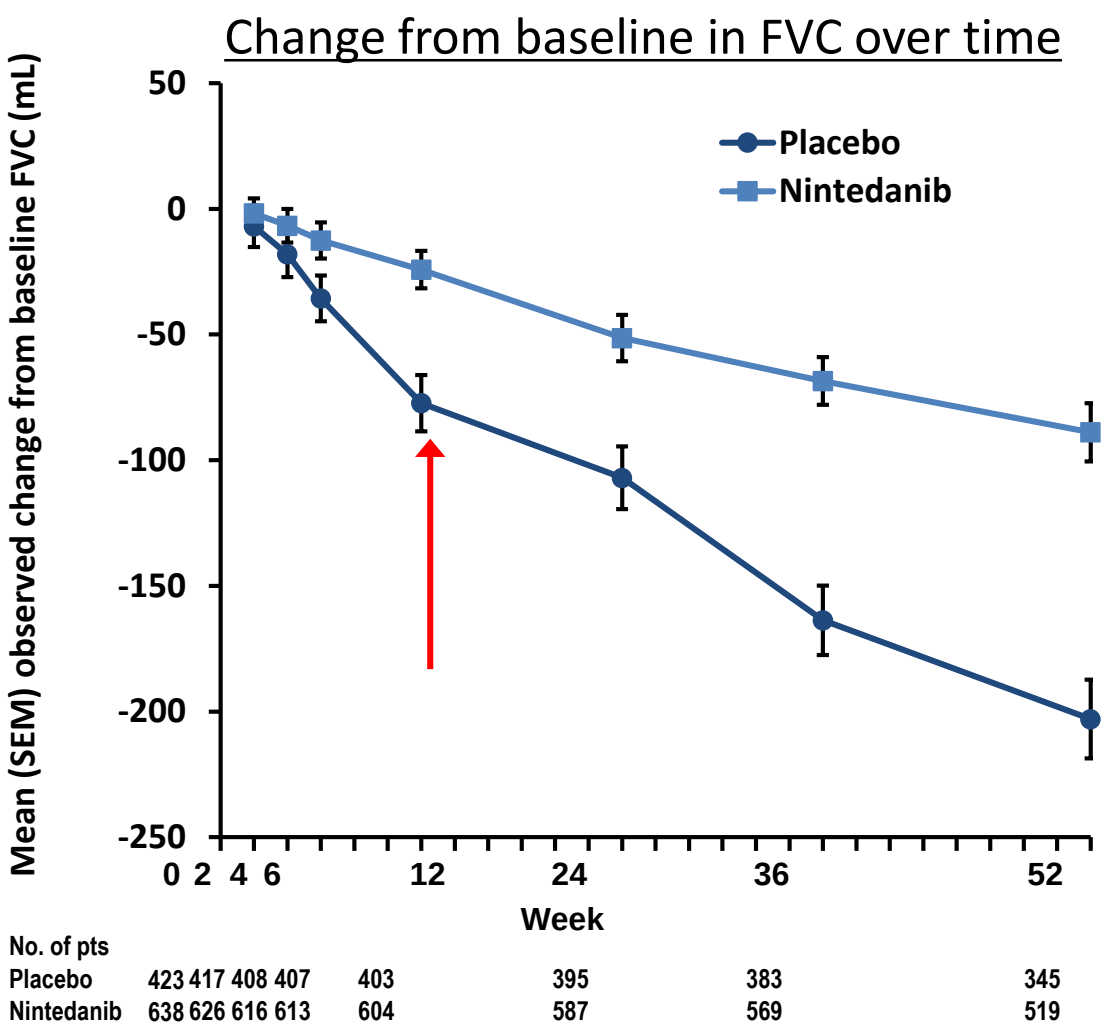
Acute Exacerbation (investigator-reported)





Pooled Data Analysis: *INPULSIS 1 and 2 Trials (n=1061)*





Am J Respir Crit Care Med. 2016;193:178

Subgroup Analysis of FVC Outcome

Sex

Age

Race

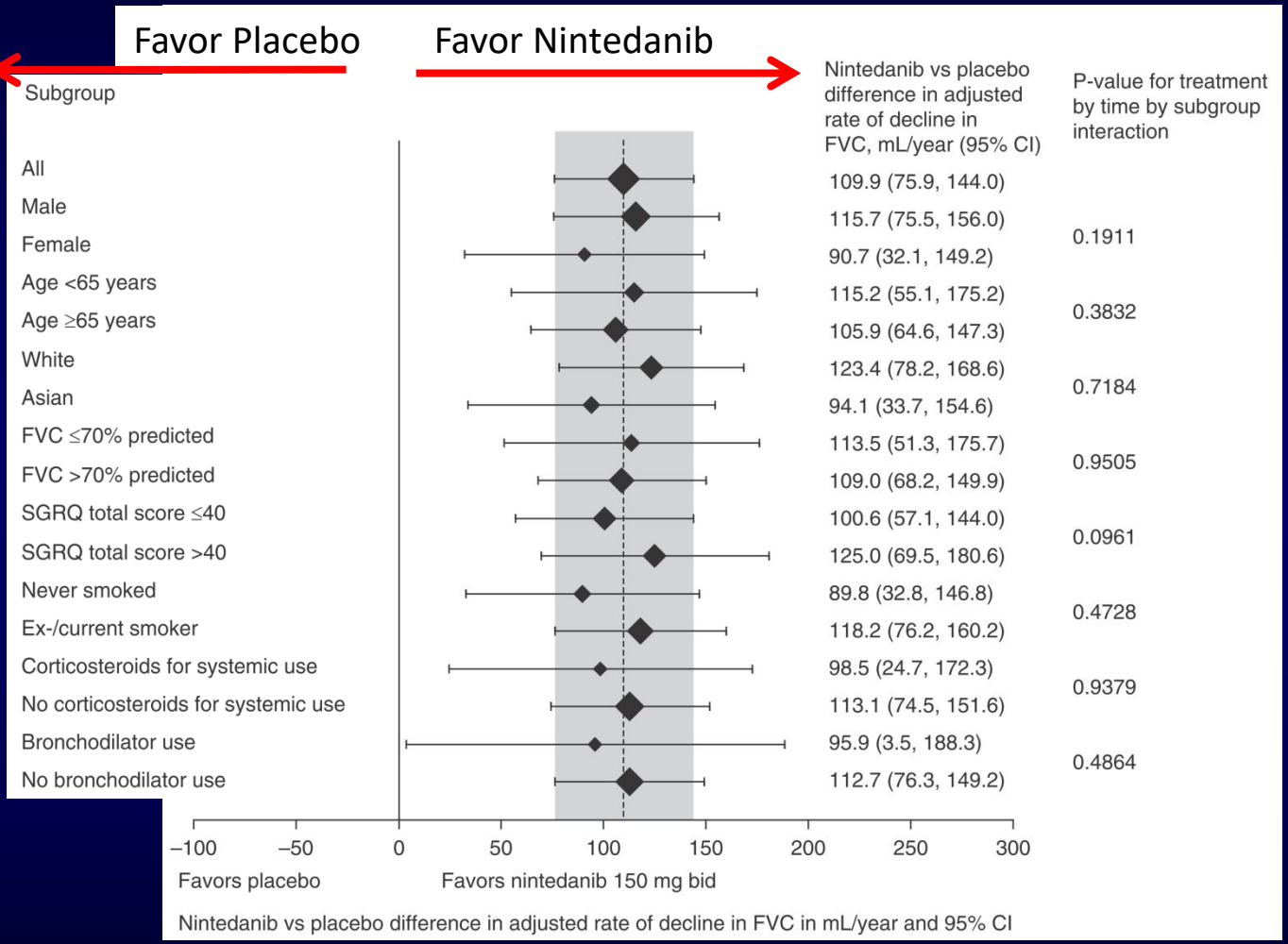
FVC

SGRQ

Smoking

Steroid

Bronchodilator

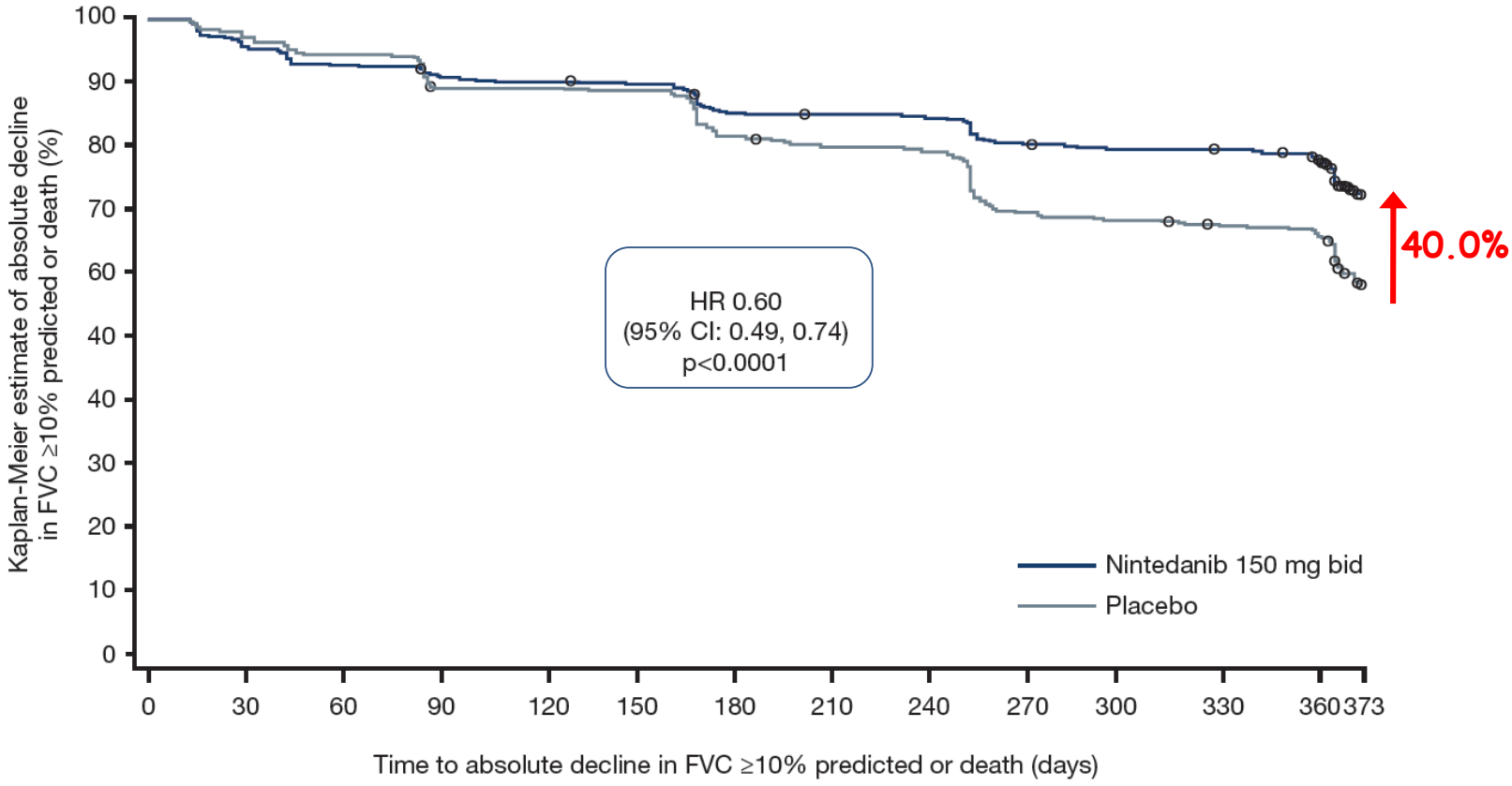


Nintedanib demonstrated a consistent treatment effect on the annual rate of decline in FVC across all subgroups.

Am J Respir Crit Care Med. 2016;193:178

Pooled Data Analysis: *INPULSIS 1 and 2 Trials (n=1061)*

Time to Disease Progression

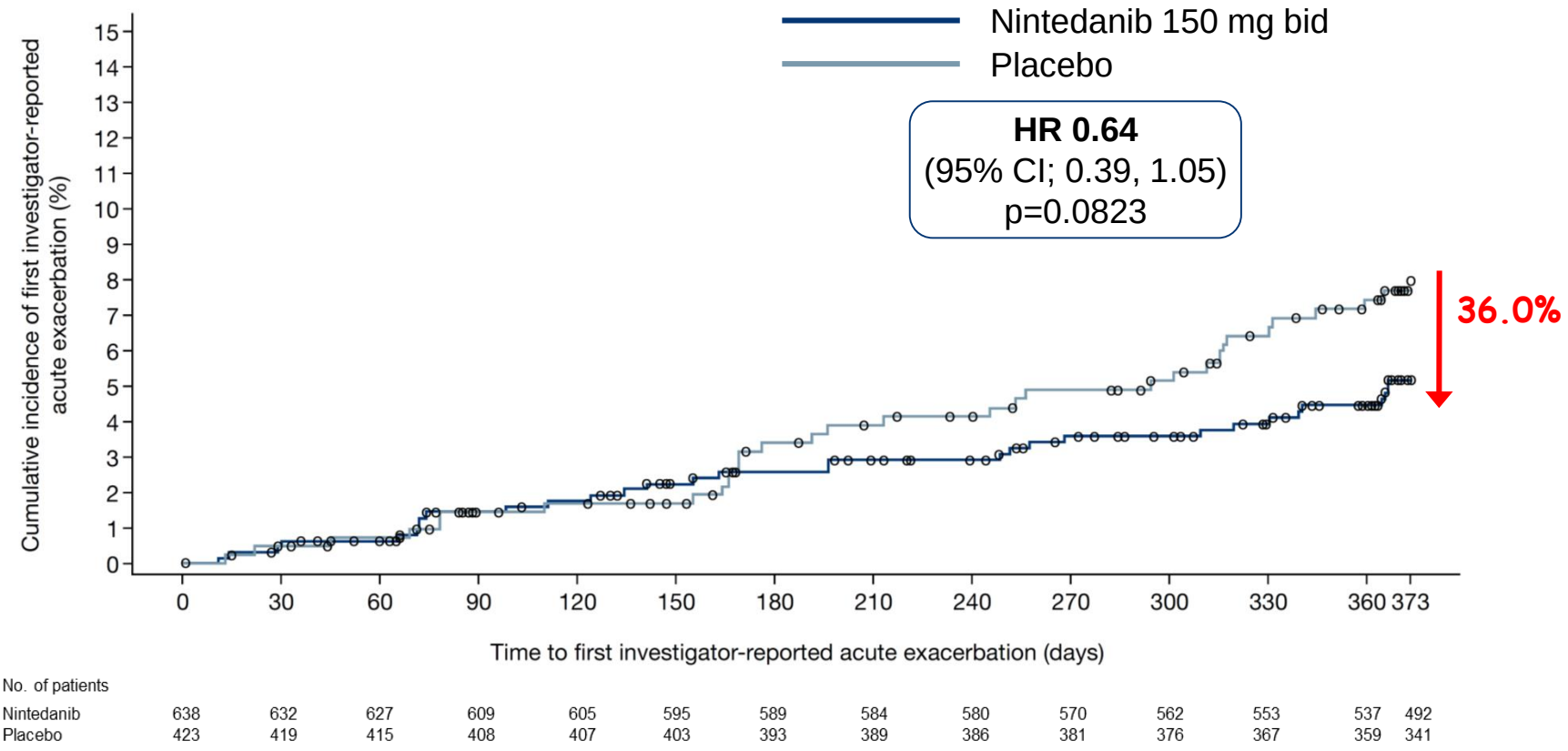


Number at risk													
Nintedanib 150 mg bid	638	611	593	581	576	571	543	540	537	510	505	503	492 415
Placebo	423	411	400	377	377	375	345	337	333	293	288	283	277 232

Am J Respir Crit Care Med. 2016;193:178

Pooled Data Analysis: *INPULSIS 1 and 2 Trials (n=1061)*

Time to First Acute Exacerbation (Investigator-reported)



	Nintedanib 150 mg bid (n=638)	Placebo (n=423)
Patients with ≥1 acute exacerbation, n (%)	31 (4.9)	32 (7.6)

Am J Respir Crit Care Med. 2016;193:178

Pooled Data Analysis: *INPULSIS 1 and 2 Trials (n=1061)*

Adverse Events

N (%)	Nintedanib 150 mg bid (n=638)	Placebo (n=423)
Diarrhea	398 (62.4)	78 (18.4)
Nausea	156 (24.5)	28 (6.6)
Nasopharyngitis	87 (13.6)	68 (16.1)
Cough	85 (13.3)	57 (13.5)
Progression of IPF†	64 (10.0)	61 (14.4)
Bronchitis	67 (10.5)	45 (10.6)
Dyspnea	49 (7.7)	48 (11.3)
Decreased appetite	68 (10.7)	24 (5.7)
Vomiting	74 (11.6)	11 (2.6)

Am J Respir Crit Care Med. 2016;193:178

Pooled Data Analysis: *INPULSIS 1 and 2 Trials (n=1061)*

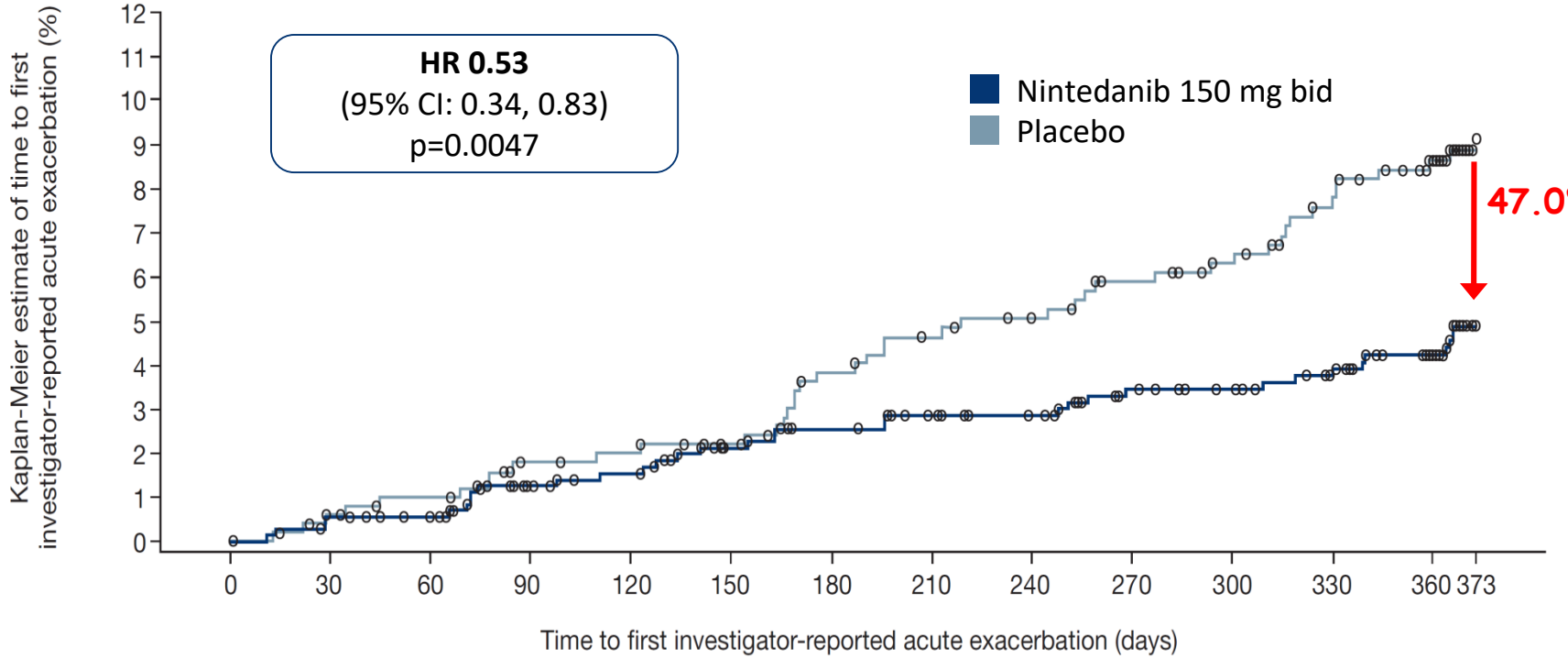
Liver Enzyme Elevation

	Nintedanib 150 mg bid (n=638)	Placebo (n=423)
Patients with maximum elevations in AST and/or ALT, n (%)		
≥3x ULN	32 (5.0)	3 (0.7)
≥5x ULN	14 (2.2)	1 (0.2)
≥8x ULN	5 (0.8)	1 (0.2)
Patients with maximum elevations in total bilirubin, n (%)		
≥1.5x ULN	15 (2.4)	3 (0.7)
≥2x ULN	3 (0.5)	2 (0.5)
Patients with maximum elevations in AP, n (%)		
≥1.5x ULN	37 (5.8)	4 (0.9)
≥2x ULN	17 (2.7)	1 (0.2)

Am J Respir Crit Care Med. 2016;193:178

Pooled Data Analysis: *INPULSIS and TOMORROW Trials (n=1231)*

Time to first acute exacerbation



No. of patients													
Nintedanib 150 mg bid	723	717	712	693	687	674	667	659	654	641	632	623	598 513
Placebo	508	502	497	488	486	481	470	464	460	452	446	436	417 353

	Nintedanib 150 mg bid (n=723)	Placebo (n=508)
Patients with ≥1 acute exacerbation, %	4.6	8.7

Respir Med 2016;113:74

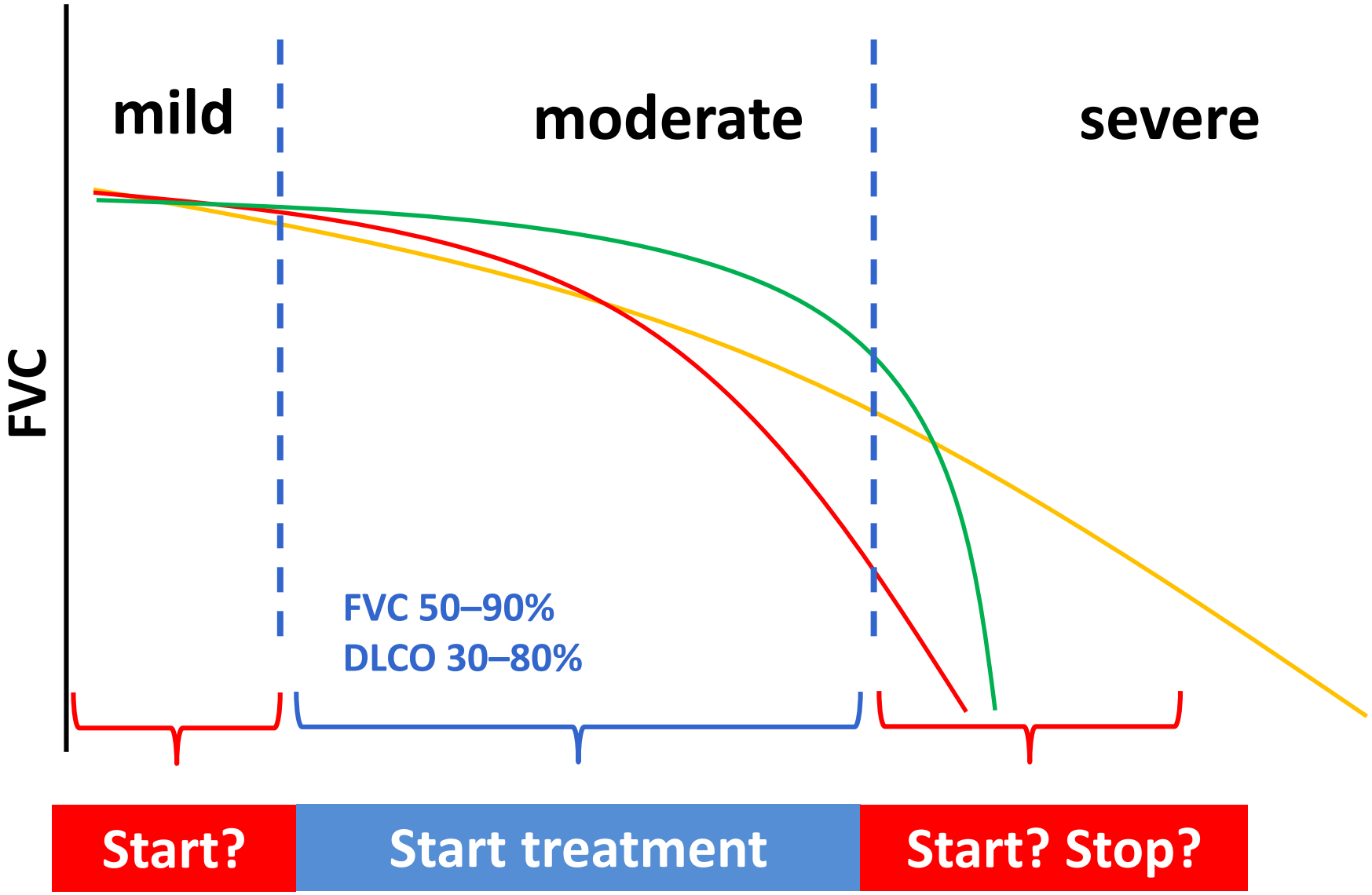
Pooled Data Analysis: *INPULSIS and TOMORROW Trials (n=1231)*

Mortality

	Nintedanib 150 mg bid (n=723)	Placebo (n=508)
All-cause mortality		
Deaths, n (%)	42 (5.8)	42 (8.3)
HR (95% CI)	0.70 (0.46, 1.08)	
p-value	0.0954	
On-treatment mortality		
On-treatment deaths, n (%)	25 (3.5)	34 (6.7)
HR (95% CI)	0.57 (0.34, 0.97)	
p-value	0.0274	
Respiratory mortality		
Deaths due to respiratory cause, n (%)	26 (3.6)	29 (5.7)
HR (95% CI)	0.62 (1.37, 1.06)	
p-value	0.0779	

Respir Med 2016;113:74

IPF – Clinical trial spectrum



Efficacy of pirfenidone in patients with idiopathic pulmonary fibrosis with more preserved lung function

- The pooled population: CAPACITY/ASCEND
  - N=1247 (pirfenidone 2403 mg/d or placebo)

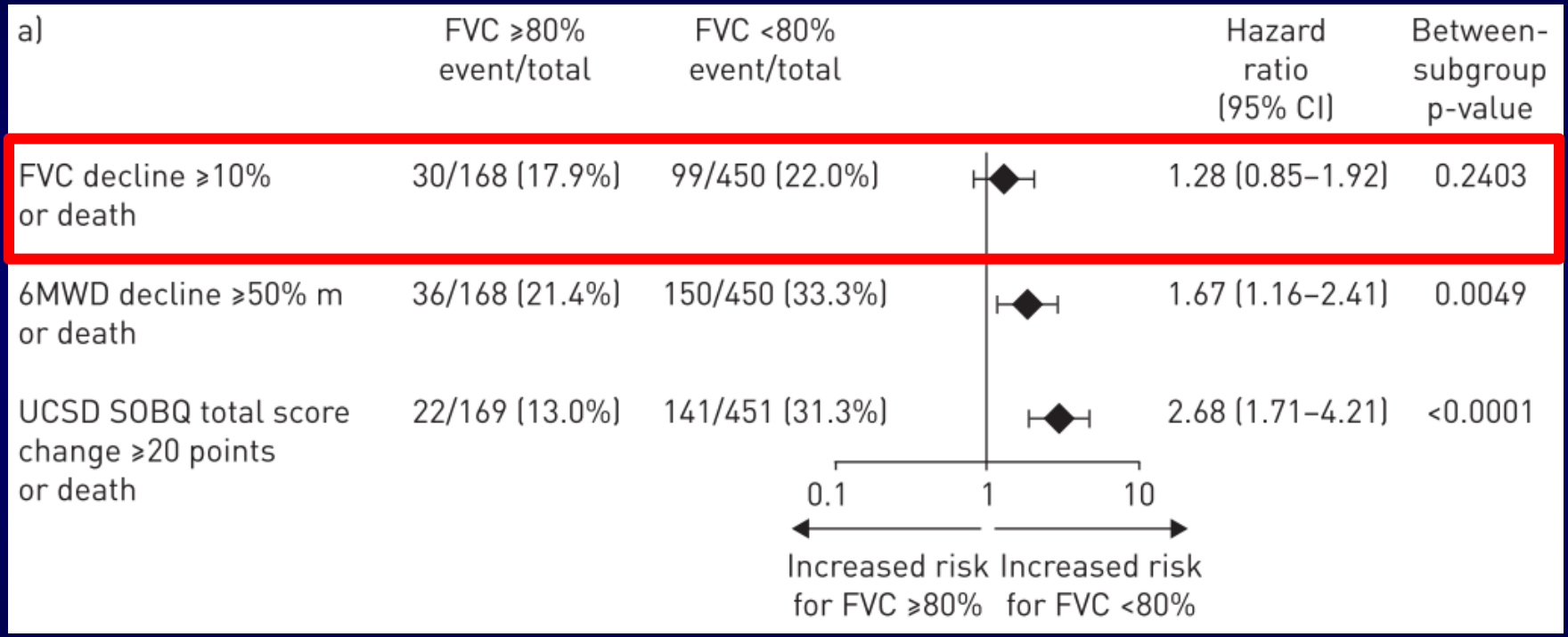
- Stratified into two different sets of subgroups defined by baseline FVC (≥80%, <80%) and GAP stage(GAP1, GAP2-3).

- Efficacy outcomes (FVC, 6MWD, UCSD SOBQ) were analyzed at 12 months.

ERJ 2016;48:843

Pirfenidone in Mild IPF

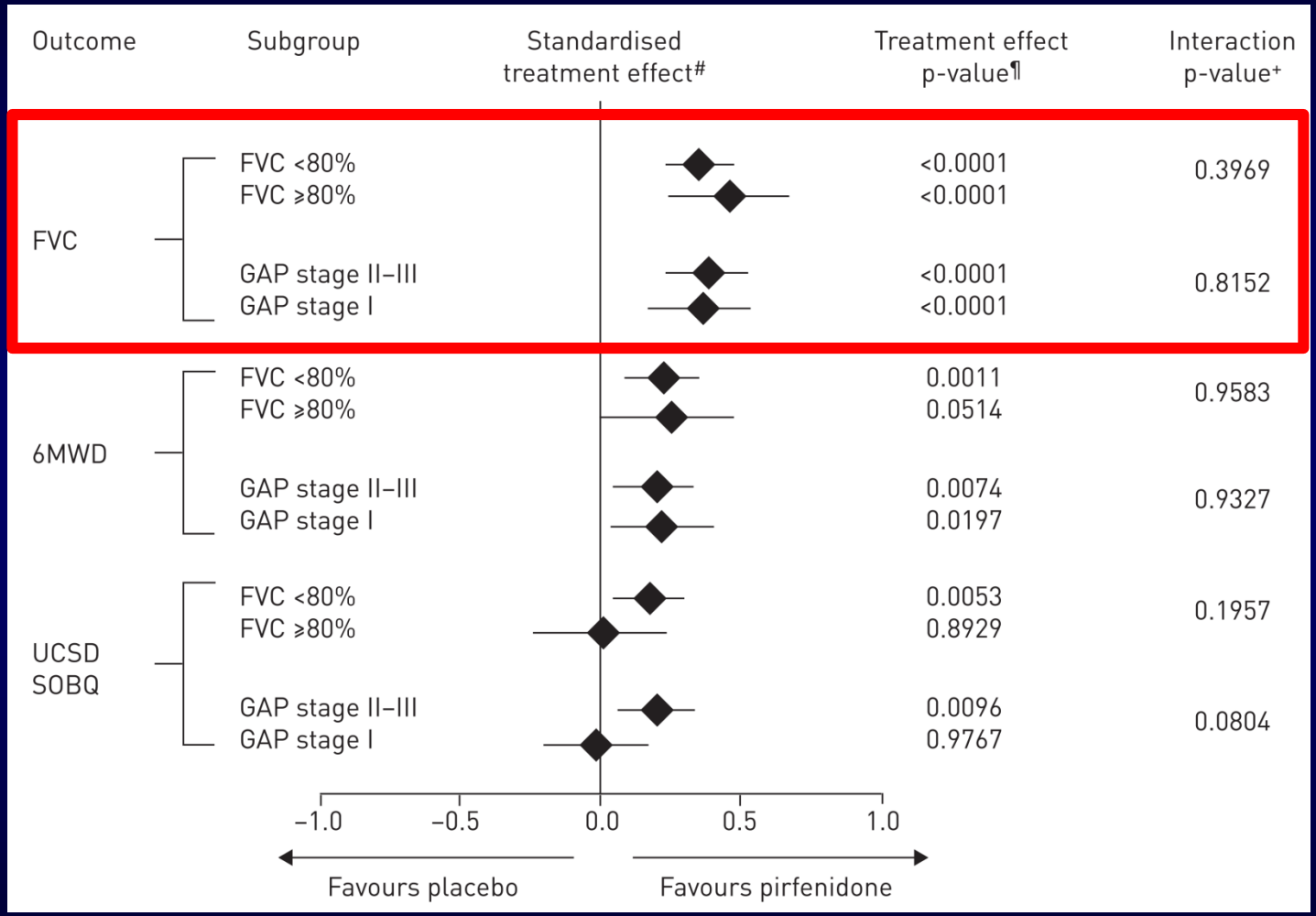
Placebo group (N=624)



Patients with both more preserved (FVC ≥ 80% or GAP stage I) and less preserved (FVC <80% or GAP stage II–III) lung function at baseline demonstrated clinically significant disease progression at 12 months.

ERJ 2016;48:843

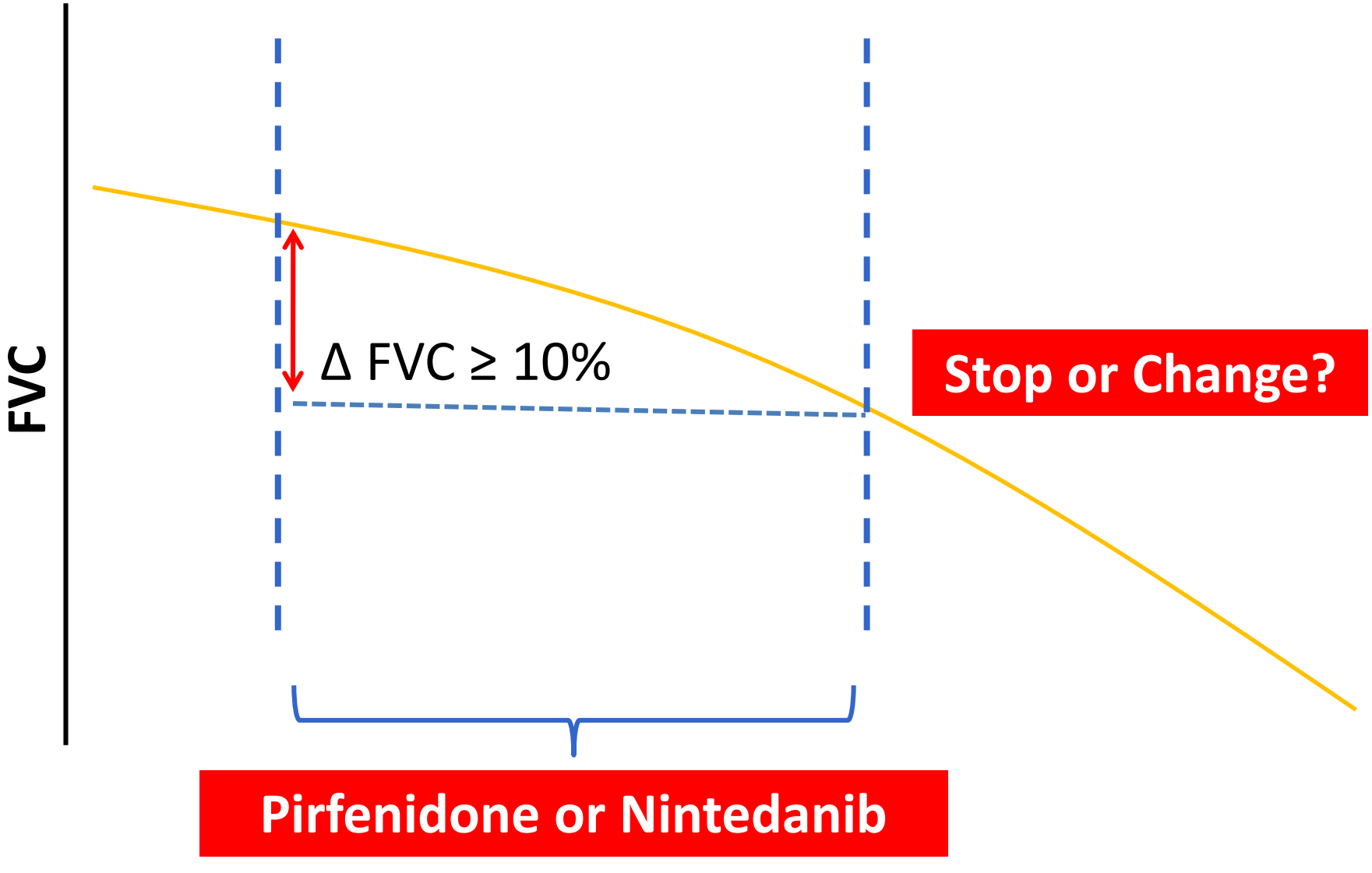
Pirfenidone in Mild IPF



The magnitude of pirfenidone treatment effect on functional measures was comparable in both subgroups of patients.

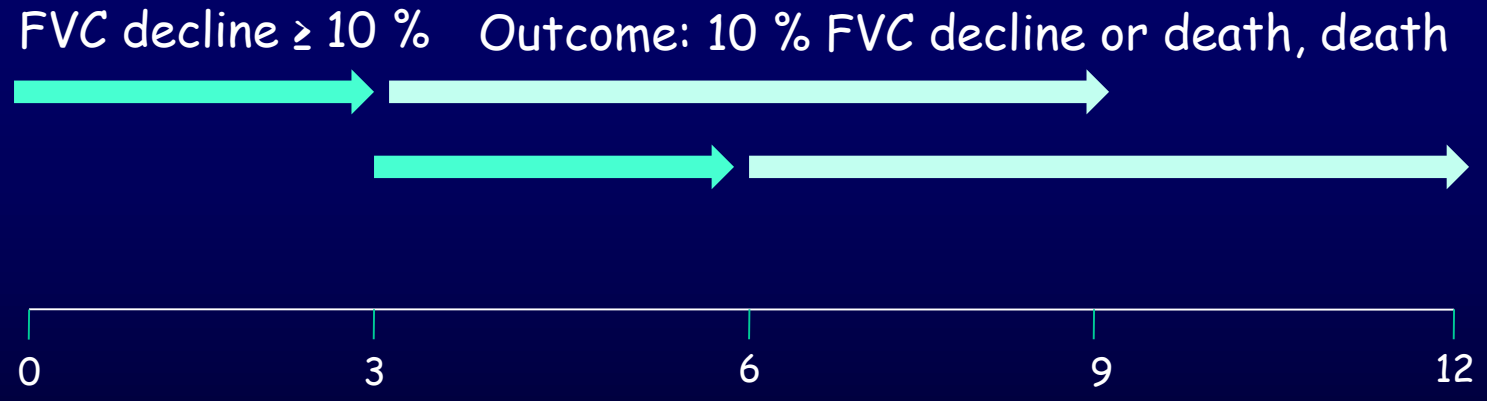
ERJ 2016;48:843

Is It Treatment Failure?



Effect of continued treatment with pirfenidone following clinically meaningful declines in forced vital capacity: analysis of data from three phase 3 trials in patients with idiopathic pulmonary fibrosis

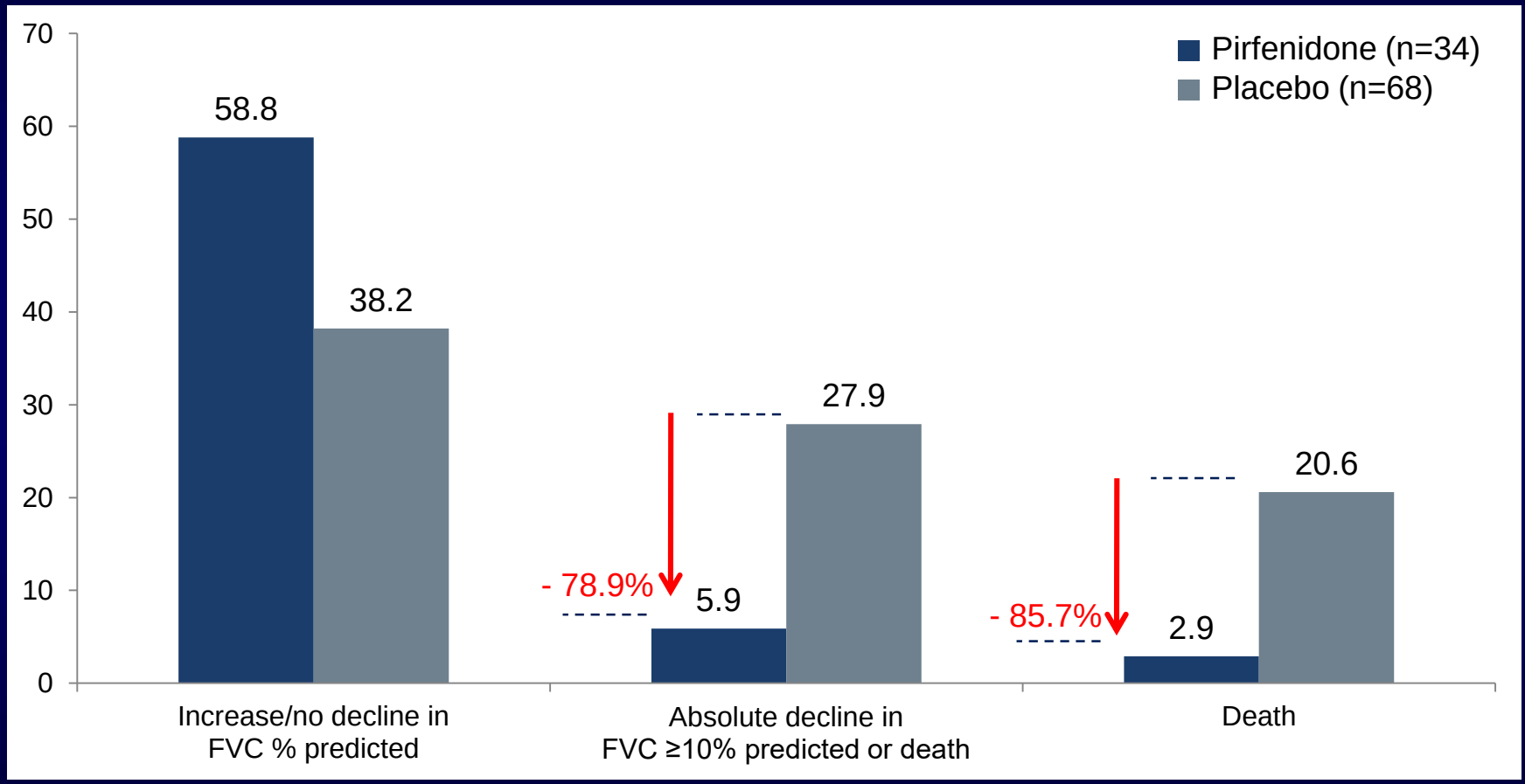
Assessment of treatment outcomes following a ≥ 10% decline in FVC
: pooled pupulation (n=1247)



* ASCNED + CAPACITY

Thorax, 2016;71:429

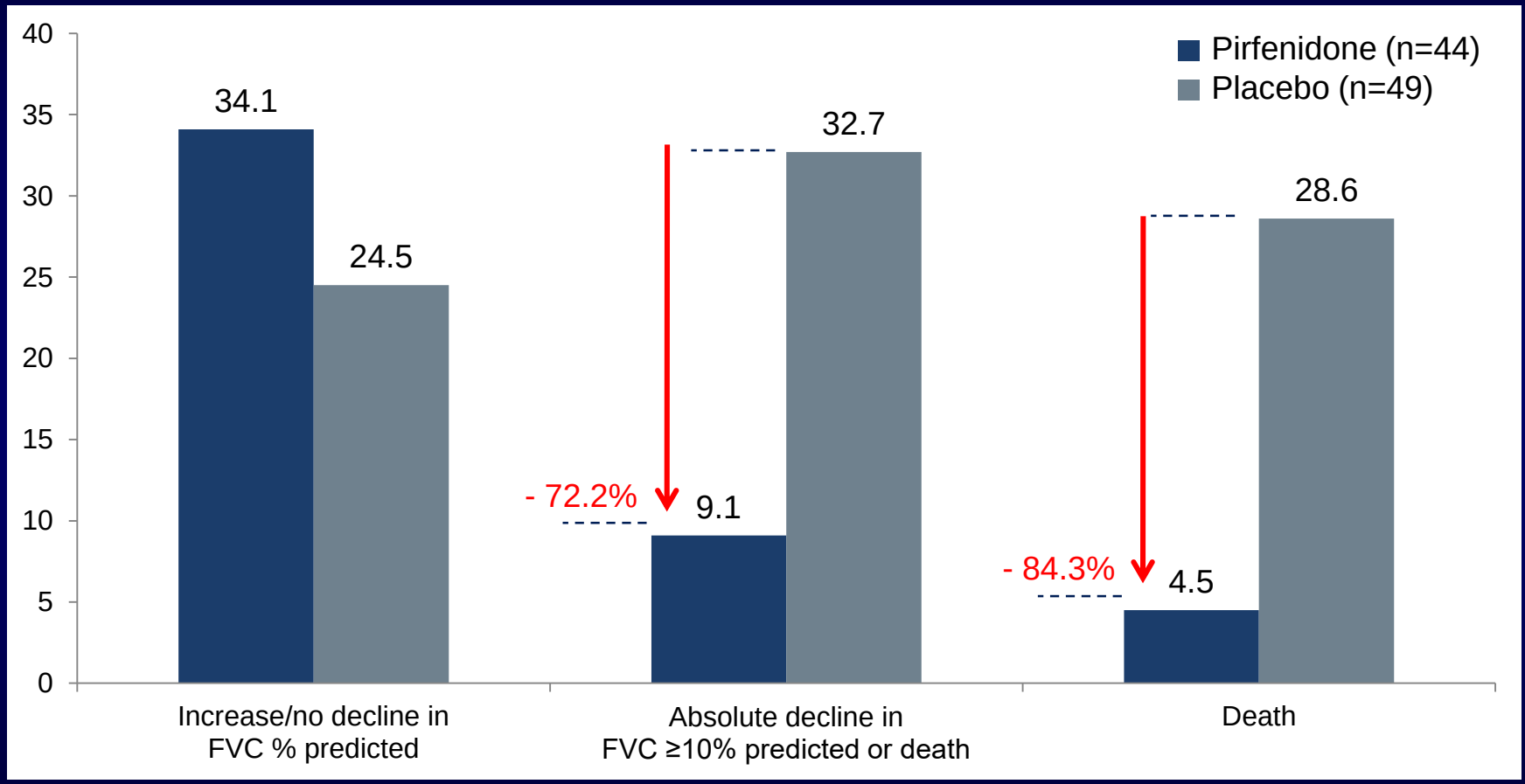
Outcomes after 6 months of continued treatment following an initial decline in FVC % pred. ≥ 10 %



Continuing treatment with pirfenidone despite evidence of disease progression confers a meaningful benefit.

Thorax, 2016;71:429

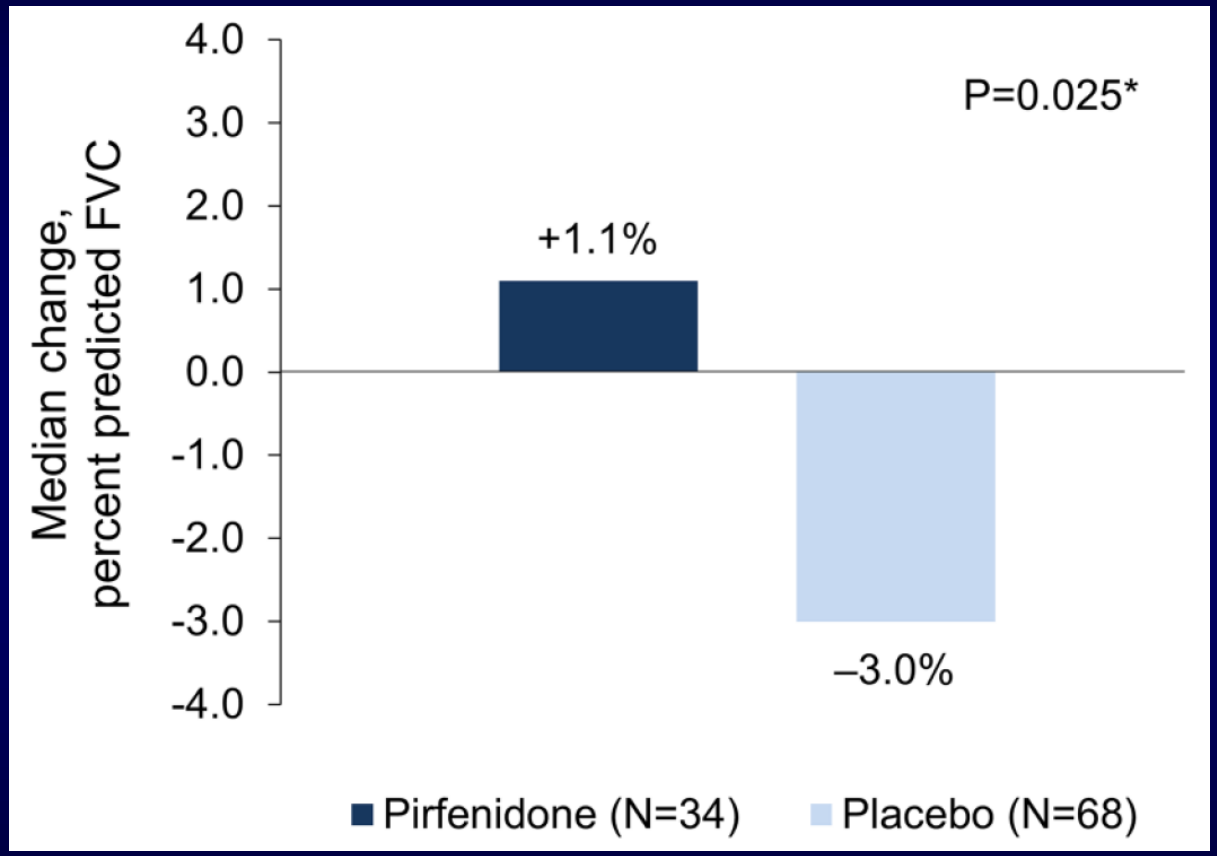
Outcomes after 6 months of continued treatment following hospitalisation



Continuing treatment with pirfenidone despite evidence of disease progression confers a meaningful benefit.

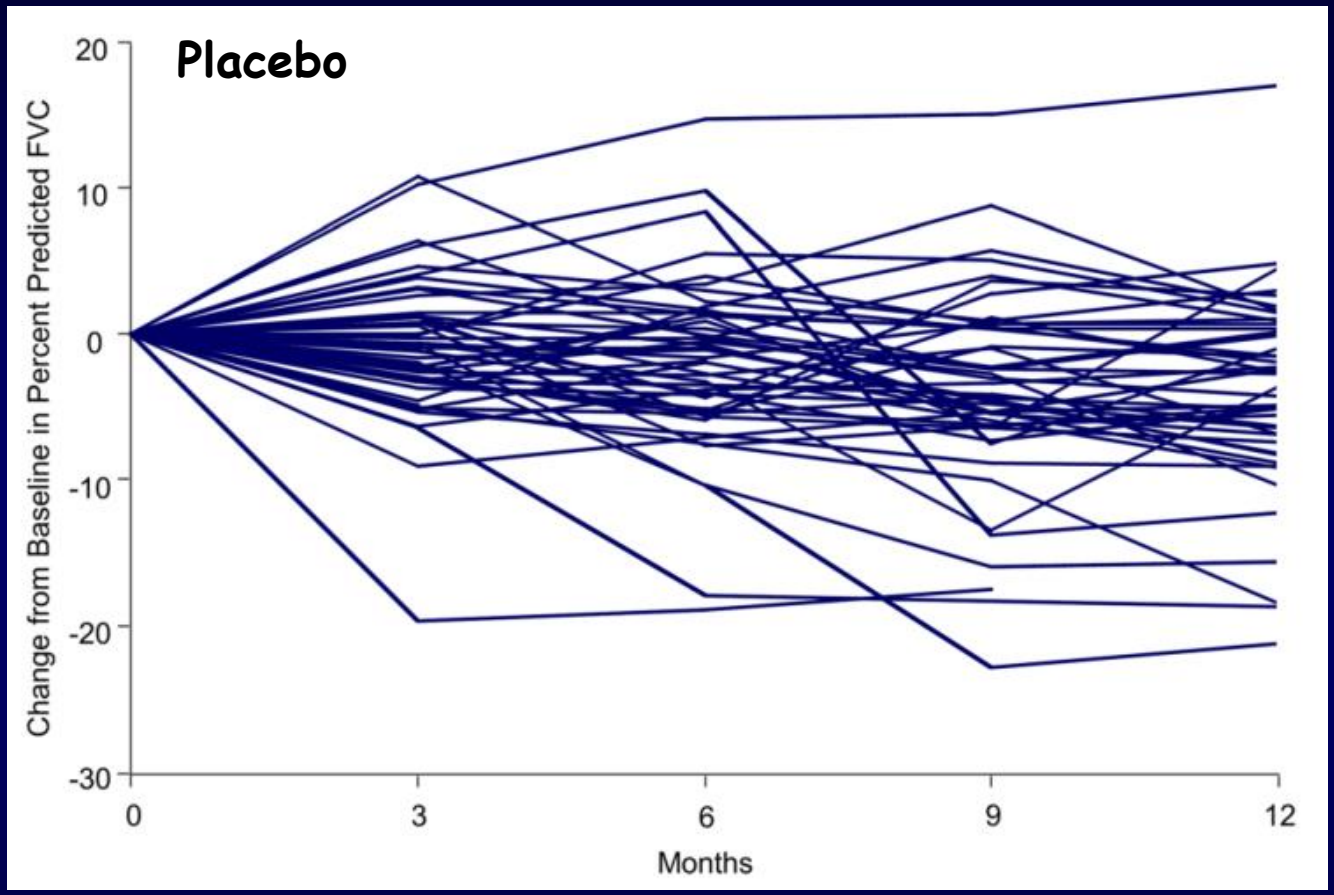
Thorax, 2016;71:429

Median change in % pred. FVC during the 6 month period following an initial decline in FVC ≥ 10 %



Thorax, 2016;71:429

Change from baseline to 1 year in % predicted FVC



Longitudinal FVC data from patients with IPF showed substantial intrasubject variability, underscoring the inability to reliably assess therapeutic response using serial FVC trends.

Thorax, 2016;71:429

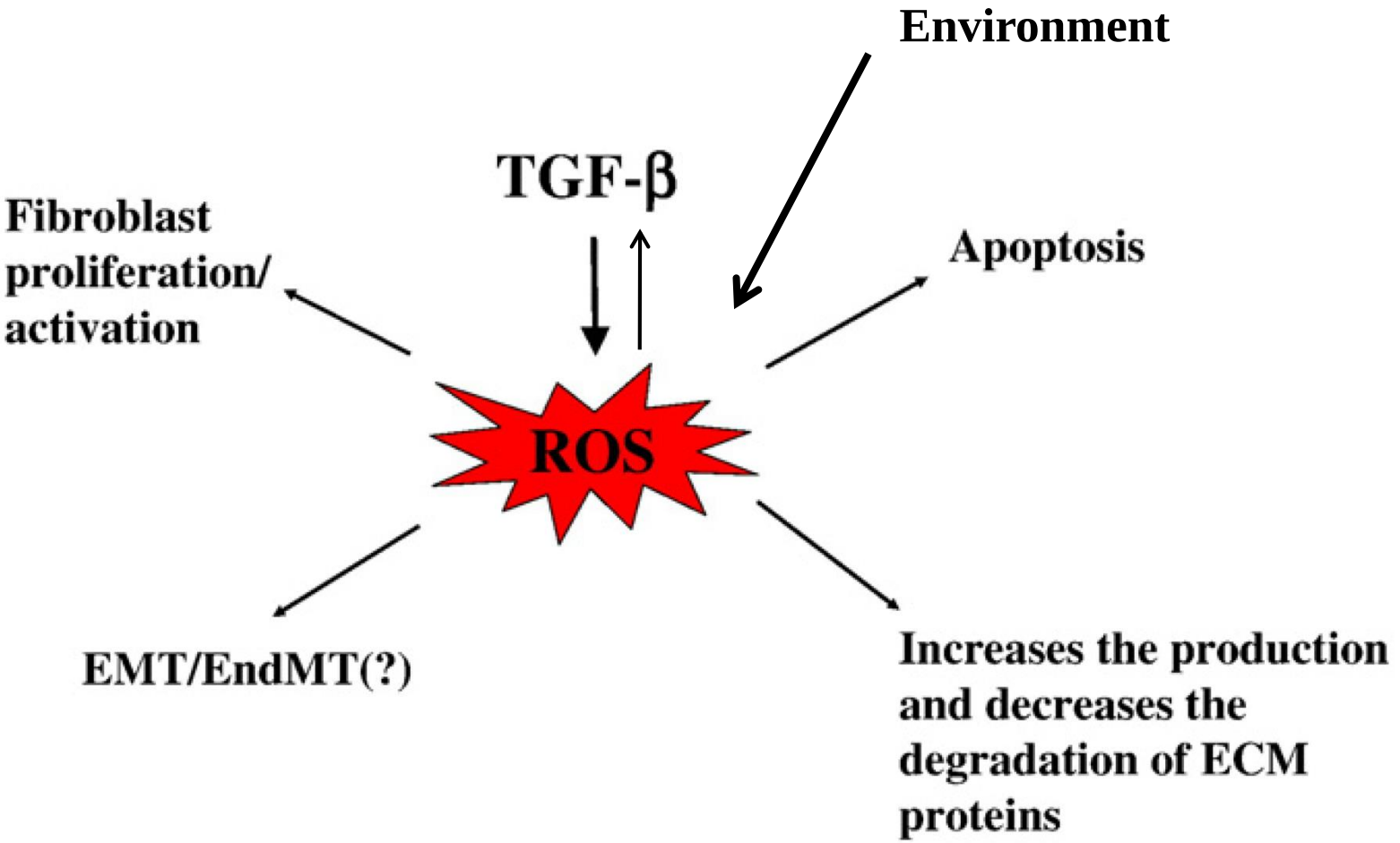
Combination therapy: the future of management for idiopathic pulmonary fibrosis?

Wim A Wuyts, Katerina M Antoniou, Keren Borensztajn, Ulrich Costabel, Vincent Cottin, Bruno Crestani, Jan C Grutters, Toby M Maher, Venerino Poletti, Luca Richeldi, Carlo Vancheri, Athol U Wells

	Pathways targeted	Example of efficacious combination therapy
COPD[43,44]	Longacting β agonists, longacting muscarinic antagonists, inhaled corticosteroids, phosphodiesterase 4 inhibitor	Longacting β agonists with longacting muscarinic antagonists; longacting β agonists with inhaled corticosteroids; glycopyrronium with indacaterol; umeclidinium with vilanterol; longacting β agonists with inhaled corticosteroids and vilanterol
Asthma[45,46]	Longacting β agonists, longacting muscarinic antagonists, inhaled corticosteroids	Longacting β agonists with inhaled corticosteroids, longacting muscarinic antagonists with inhaled corticosteroids
Pulmonary arterial hypertension[47–49]	Guanylate cyclase–phosphodiesterase-5 pathway; endothelin receptor pathway; prostanoid pathway	Riociguat in addition to background therapy with an endothelin receptor antagonist or a prostanoid; macitentan in addition to background sildenafil; ambrisentan with tadalafil

Lancet Resp Med 2014;11:933

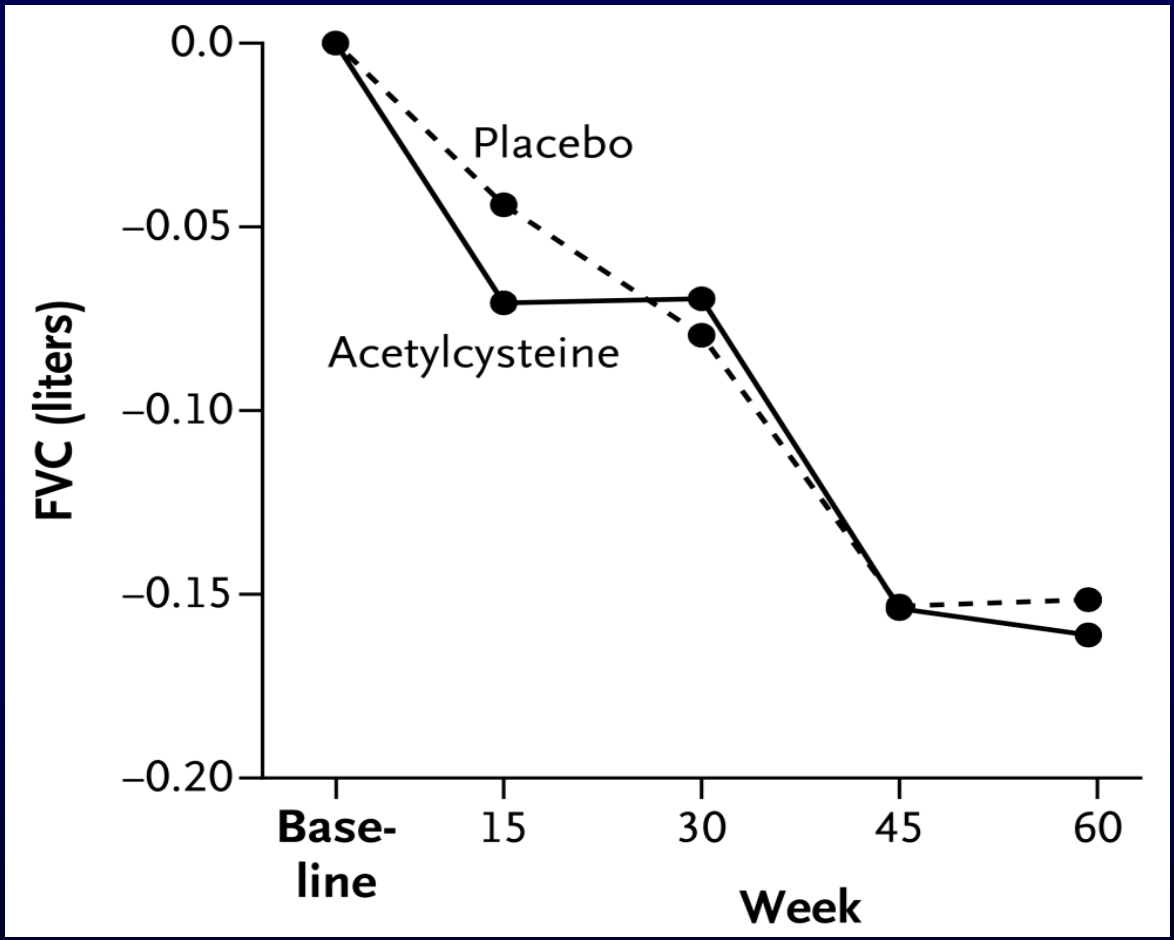
ROS contribute to Fibrogenesis



Free Radic Biol Med 2010;48:1

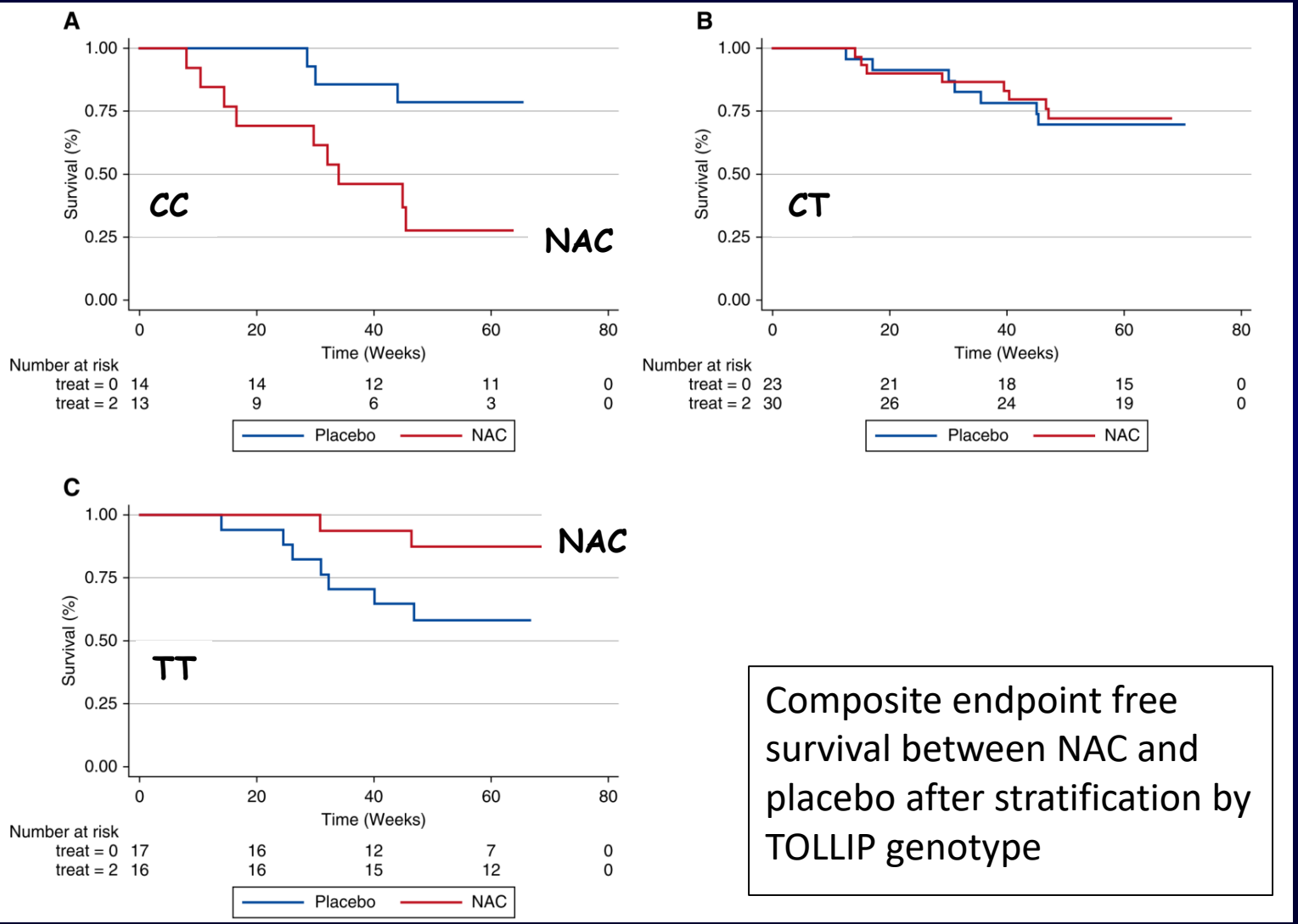
N-acetylcysteine: PANTHER Trial

Change in FVC



N Engl J Med. 2014;370:2093

Survival between NAC and Placebo Groups after Stratification by TOLLIP Genotype



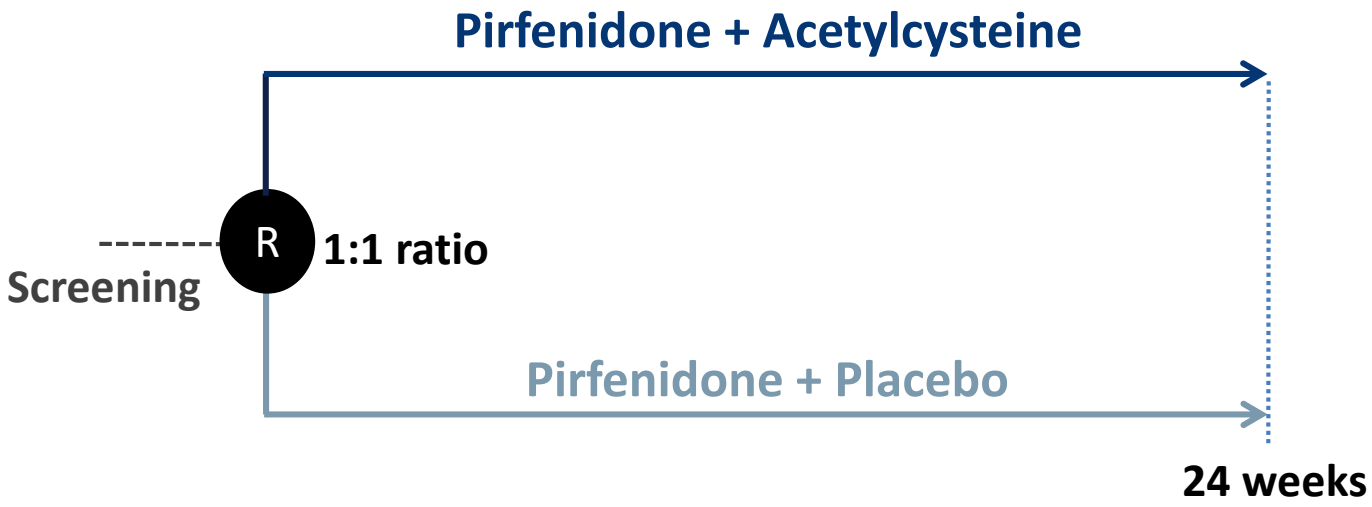
Composite endpoint free survival between NAC and placebo after stratification by TOLLIP genotype

Adjusted for age, sex, FVC and diffusing capacity; TOLLIP: toll-interacting protein

Am J Respir Crit Care Med. 2015;192:1475

Safety and tolerability of acetylcysteine and pirfenidone combination therapy in idiopathic pulmonary fibrosis: a randomised, double-blind, placebo-controlled, phase 2 trial

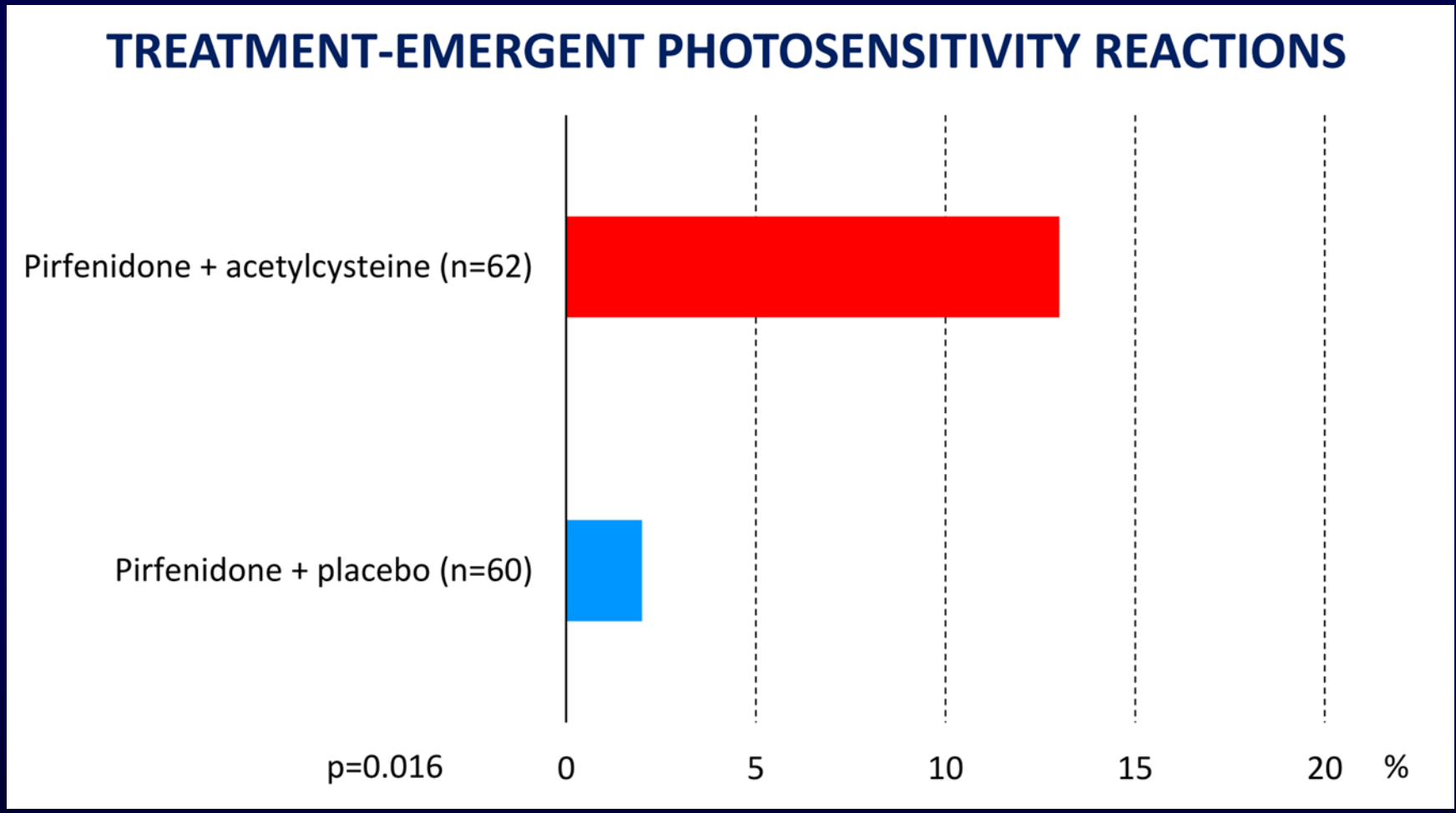
Jürgen Behr, Elisabeth Bendstrup, Bruno Crestani, Andreas Günther, Horst Olschewski, C Magnus Sköld, Athol Wells, Wim Wuyts, Dirk Koschel, Michael Kreuter, Benoît Wallaert, Chin-Yu Lin, Jürgen Beck, Carlo Albera



- 48 sites, 123 randomized
- FVC 50-90% predicted, DL_{CO} 30-90% predicted
- Established on Pirfenidone (≥ 1608 mg/d, ≥ 8 weeks) before
- Assessment for adverse events/FVC, Dlco, 6MWD

Lancet Respir Med 2016;4:445

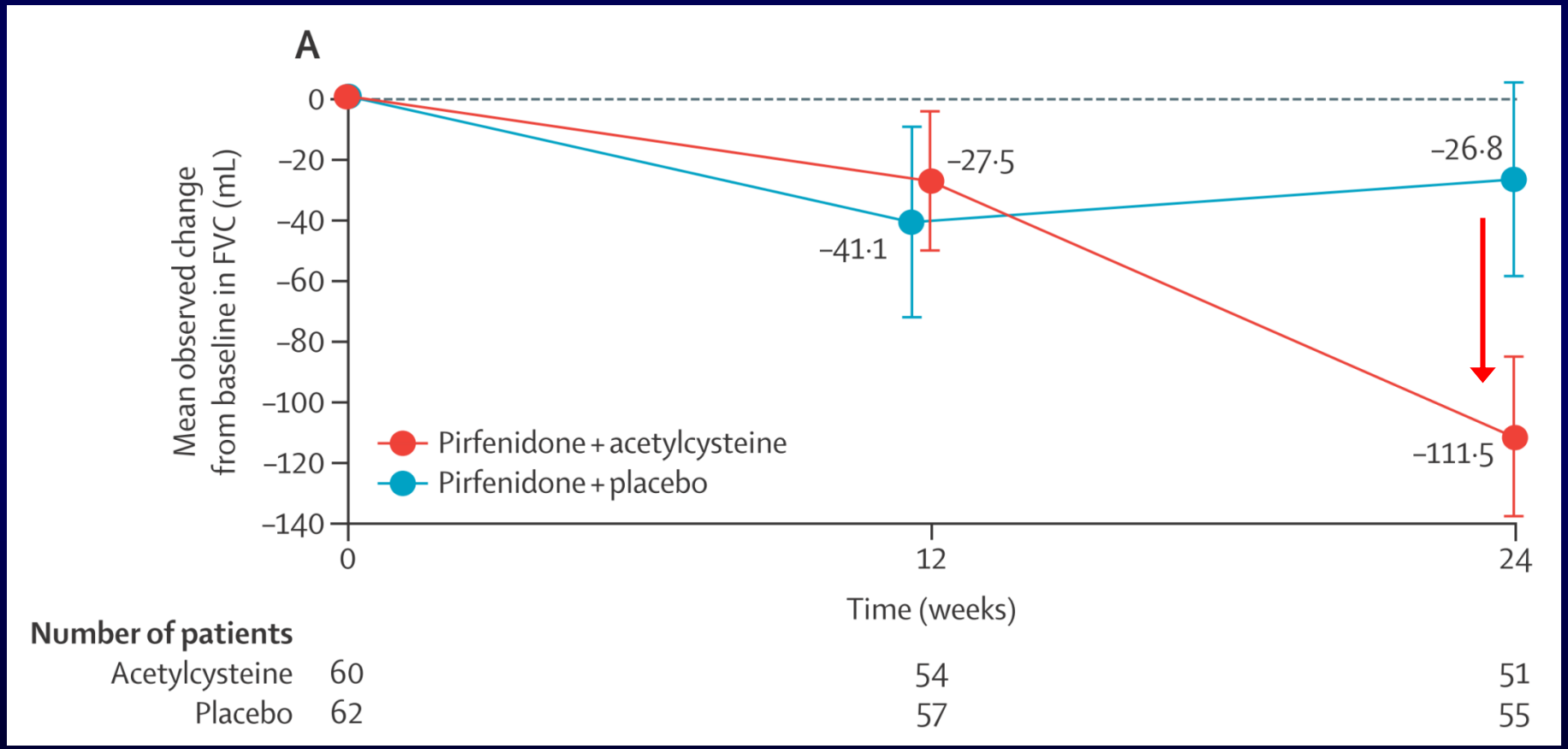
PFD + *NAC*: PANORAMA Study



Lancet Respir Med 2016;4:445

PFD + *NAC*: PANORAMA Study

Change in FVC



125.6 mL [NAC] vs. 34.3 mL/6 mo [PBO]; difference -91.3 mL, p=0.031

Lancet Respir Med 2016;4:445

ILD is the most common Pulmonary Manifestation in CTD

	SSc	RA	Sjögren's	MCTD	PM/DM	SLE
Airways	-	++	++	+	-	+
ILD	+++	++	++	++	+++	+
Pleural	-	++	+	+	-	+++
Vascular	+++	+	+	++	+	+
DAH	-	-	-	-	-	++

Chron Respir Dis. 2011;8(1):53

Scleroderma

- At autopsy: 74 to 100%
- Alton and Turner-Warwick:

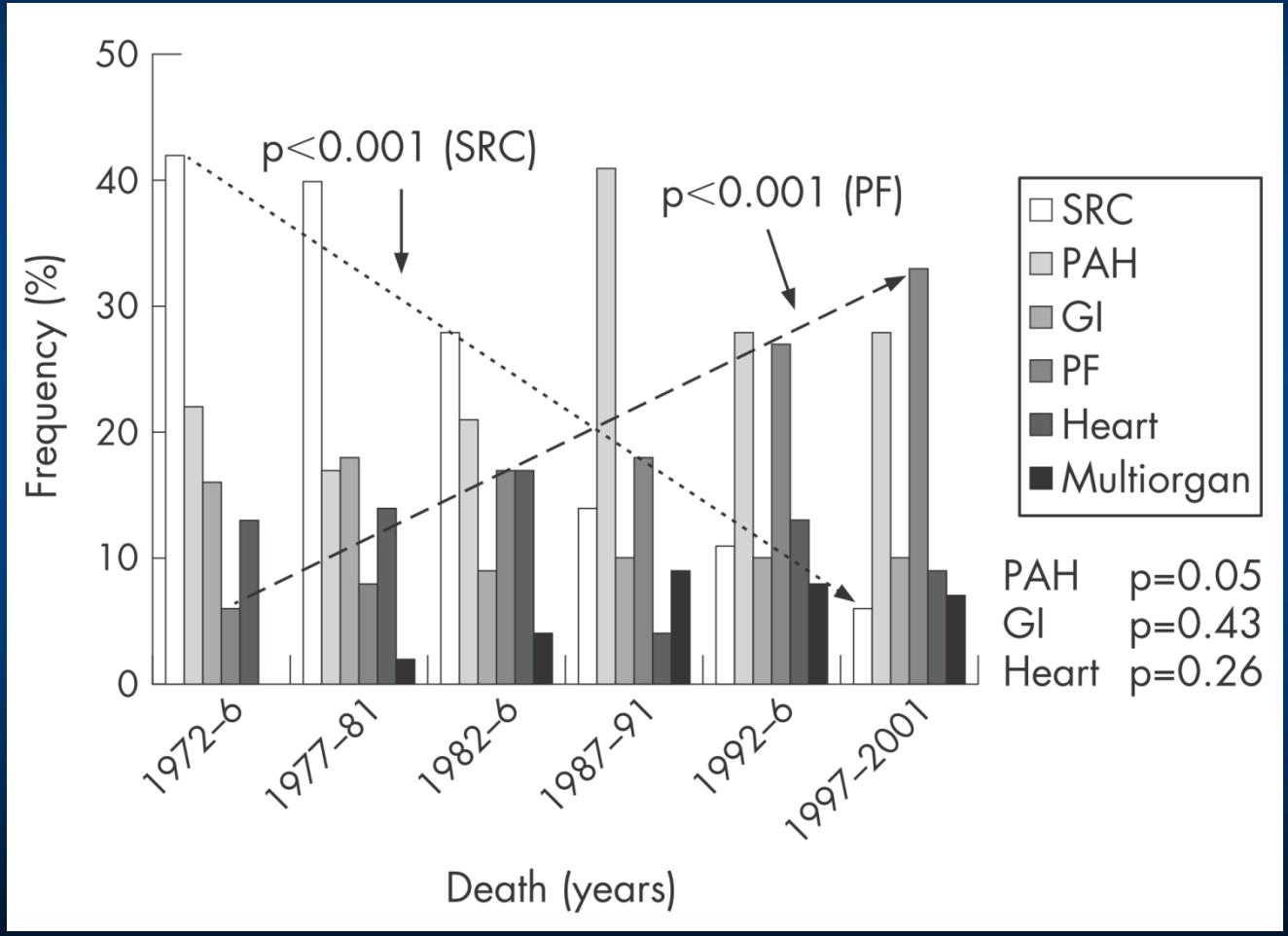
  Symptoms: 54%,

  Chest X-ray: 53%,

  PFT: 92%
- Steen: moderately severe ILD: 27%

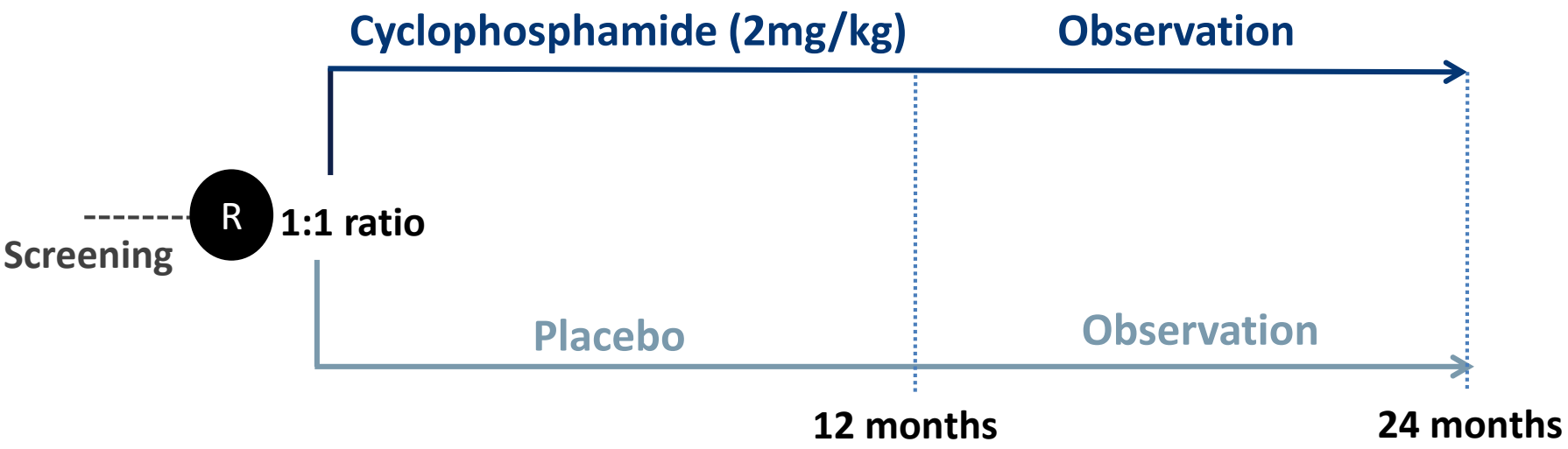
  severe ILD: 13%

ILD is the major cause of death in SSc



Ann Rheum Dis. 2007;66:940

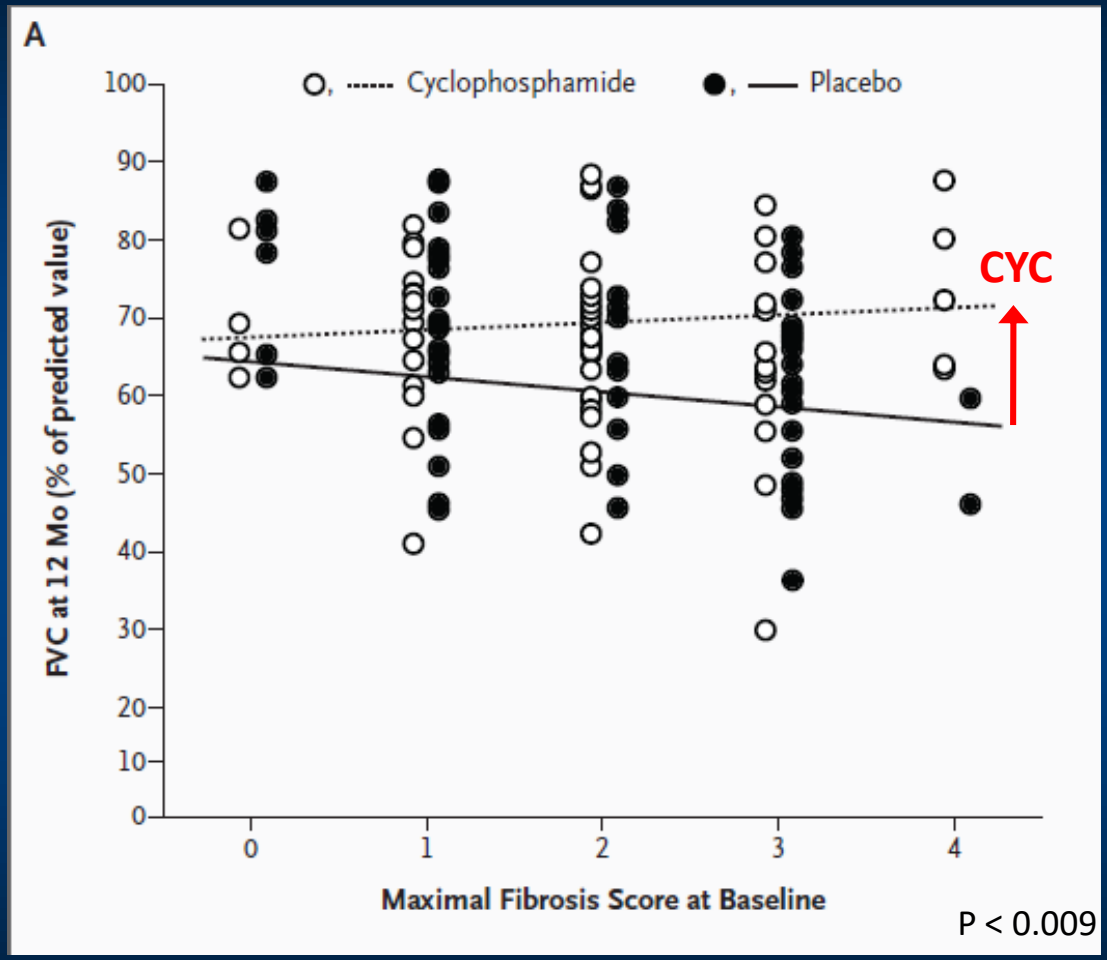
Cychlophosphamide in SSc-ILD : The Scleroderma Lung Study



- Randomized, double blind, placebo-controlled trial
- 158 enrolled, 109 completed
- Change from baseline in % predicted FVC
- Changes in TLC, DLco, DL_{VA}, HAQ, SF-36, Skin thickenss

N Engl J Med 2006;354:25

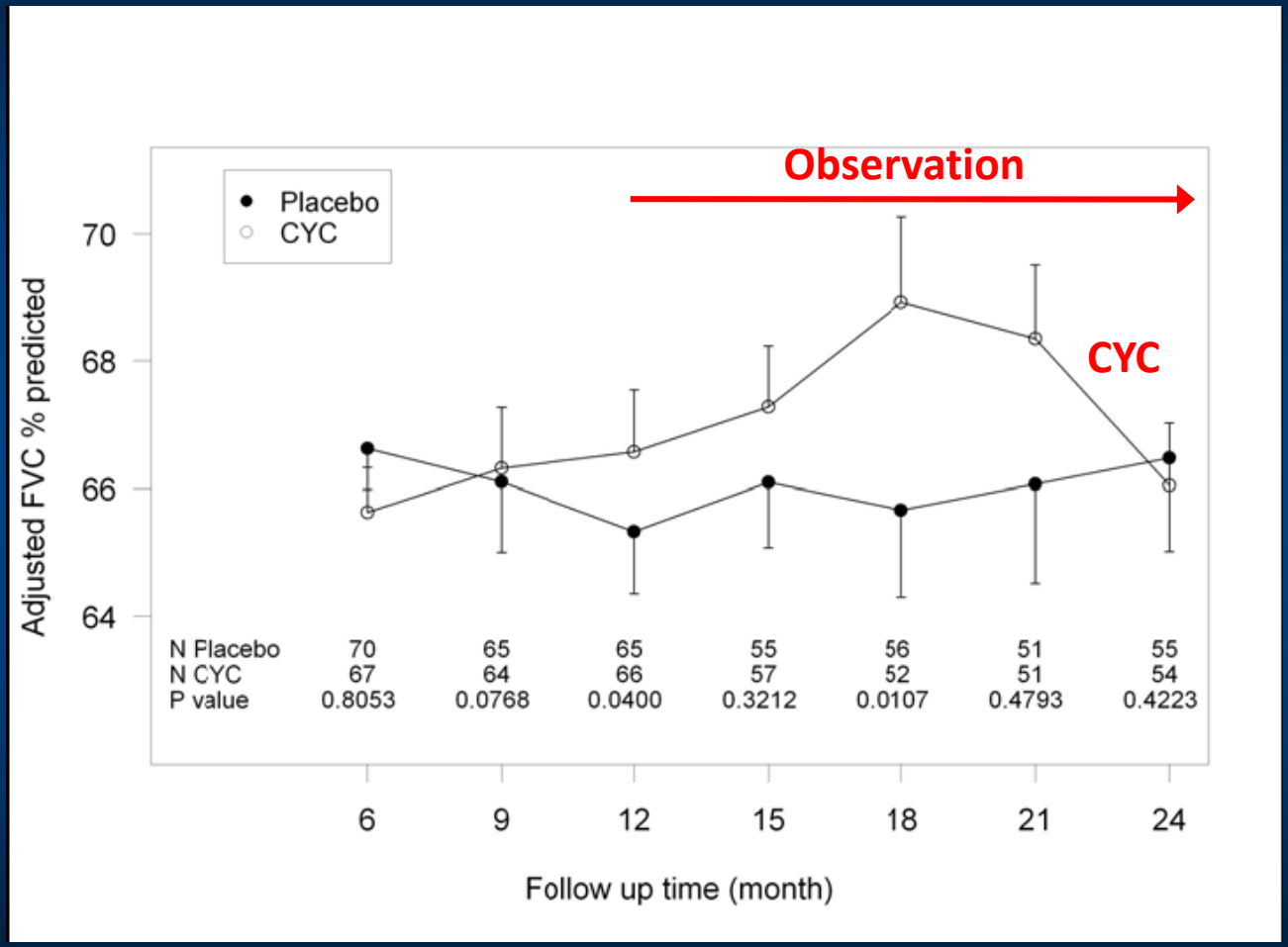
Changes in FVC at 12 months



- Mean absolute difference in FVC: 2.53 % at 12 months (p<0.03)
- CYC improved dyspnea, skin thickening, functional ability and QOL.

N Engl J Med 2006;354:25

Effects of 1-Year Treatment with CYC on Outcomes at 2 Years



- Beneficial effects of CYC on pulmonary function and health status continued to increase through 18 months, after which they dissipated.

Am J Respir Crit Care Med. 2007;176:1026

Adverse Events during follow-up

Event	Cyclophosphamide Group		Placebo Group	
	Year 1	Year 2	Year 1	Year 2
	number of patients			
Adverse event				
Hematuria	9	1	3	2
Leukopenia†	19	0	0	0
Neutropenia†	7	0	0	0
Anemia	2	2	0	1
Pneumonia	5	1	1	0
Serious adverse event‡				
Probably related to treatment	2	4	0	0
Possibly related to treatment	3	4	2	5
Not related to treatment	15	19	14	17
Total	20	27	16	22
Death	2	4	3	3

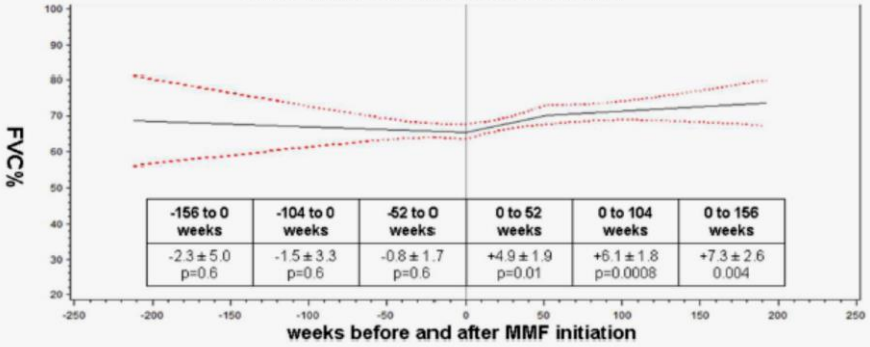
The CYC group showed more freqeuntly leukopenia and neutropenia ($p<0.05$)

N Engl J Med 2006;354:25

Mycophenolate Mofetil in CTD-ILD

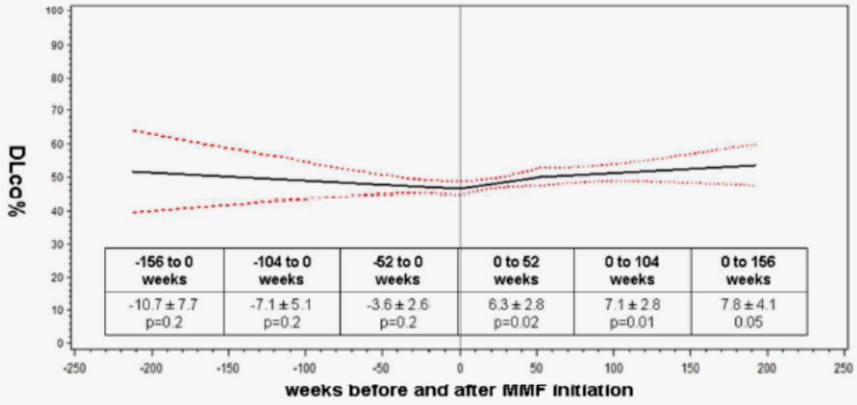
- 125 subjects with a variety of CTD treated for a median 897 days (SSc 44, PM-DM 32, RA 18)
- In 13 (10%), MMF was discontinued. (GI 3, DP 2, LFT 2, INF 1, cytopenia 1)
- Improvements in % FVC from MMF initiation to:
  - 52 weeks; 4.9% ± 1.9%, p = 0.01
  - 104 weeks 6.1% ± 1.8%, p = 0.0008
  - 156 weeks 7.3% ± 2.6%, p = 0.004
- Improvements in %DLco from MMF initiation to:
  - 52 weeks; 6.3% ± 2.8%, p = 0.02
  - 104 weeks; 7.1% ± 2.8%, p = 0.01

Figure 3A. Plot of mixed-effects model estimates for FVC% over time for the entire cohort



solid line=mean; dashed red lines=95% confidence bands

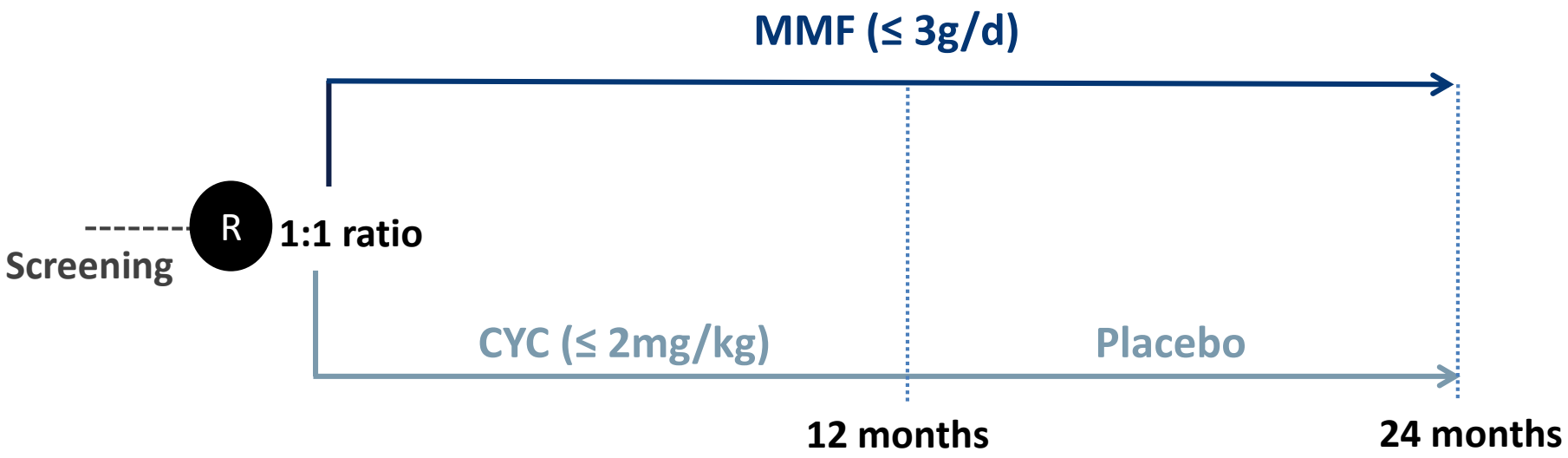
Figure 3B: Plot of mixed-effects model estimates for DLco% over time for the entire cohort



solid line=mean; dashed red lines=95% confidence bands

J Rheumatol 2013;40:640

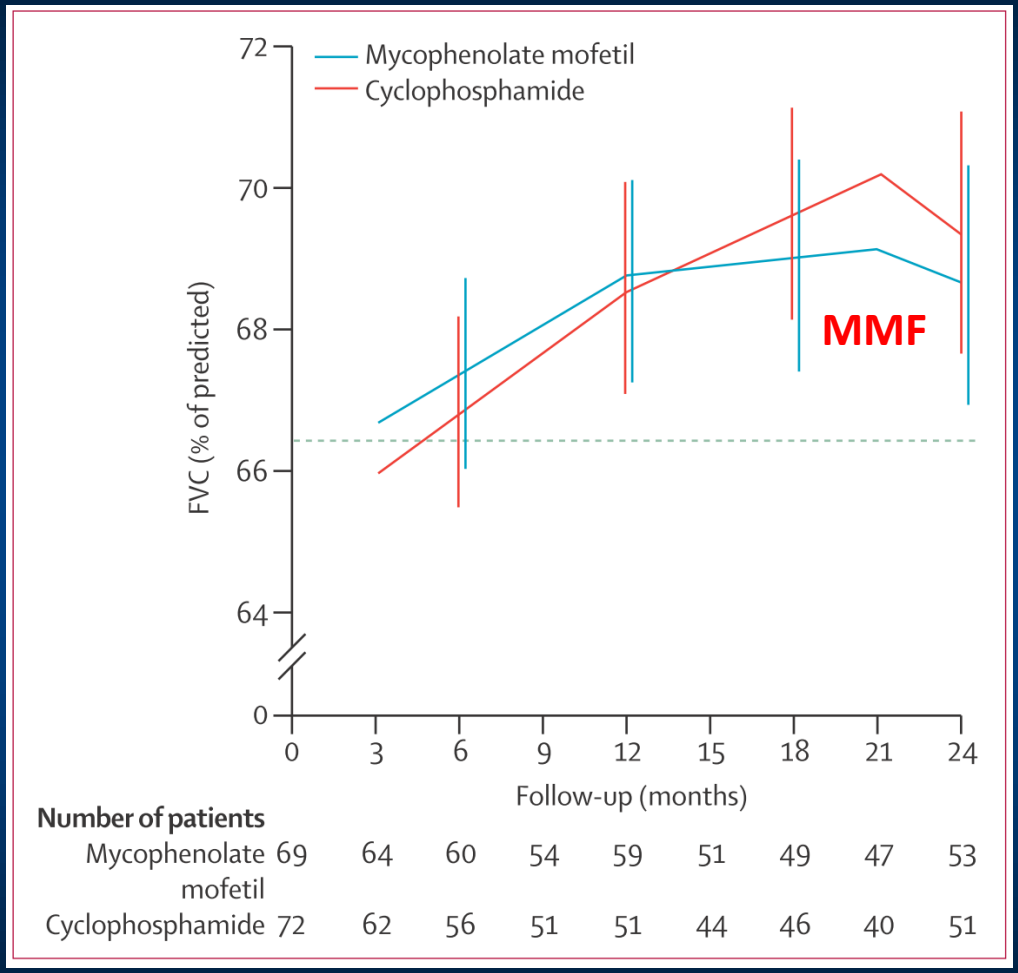
Mycofenolate Mofetil in SSc-ILD: The Scleroderma Lung Study II



- Randomized, double blind
- 142 enrolled, 106 completed, MMF (2yrs) vs. CYC (1yr)
- Change in % predicted FVC
- Changes in % predicted TLC, Dlco, TDI, mRSS and QILD scores

Lancet Resp Med 2016;4:708

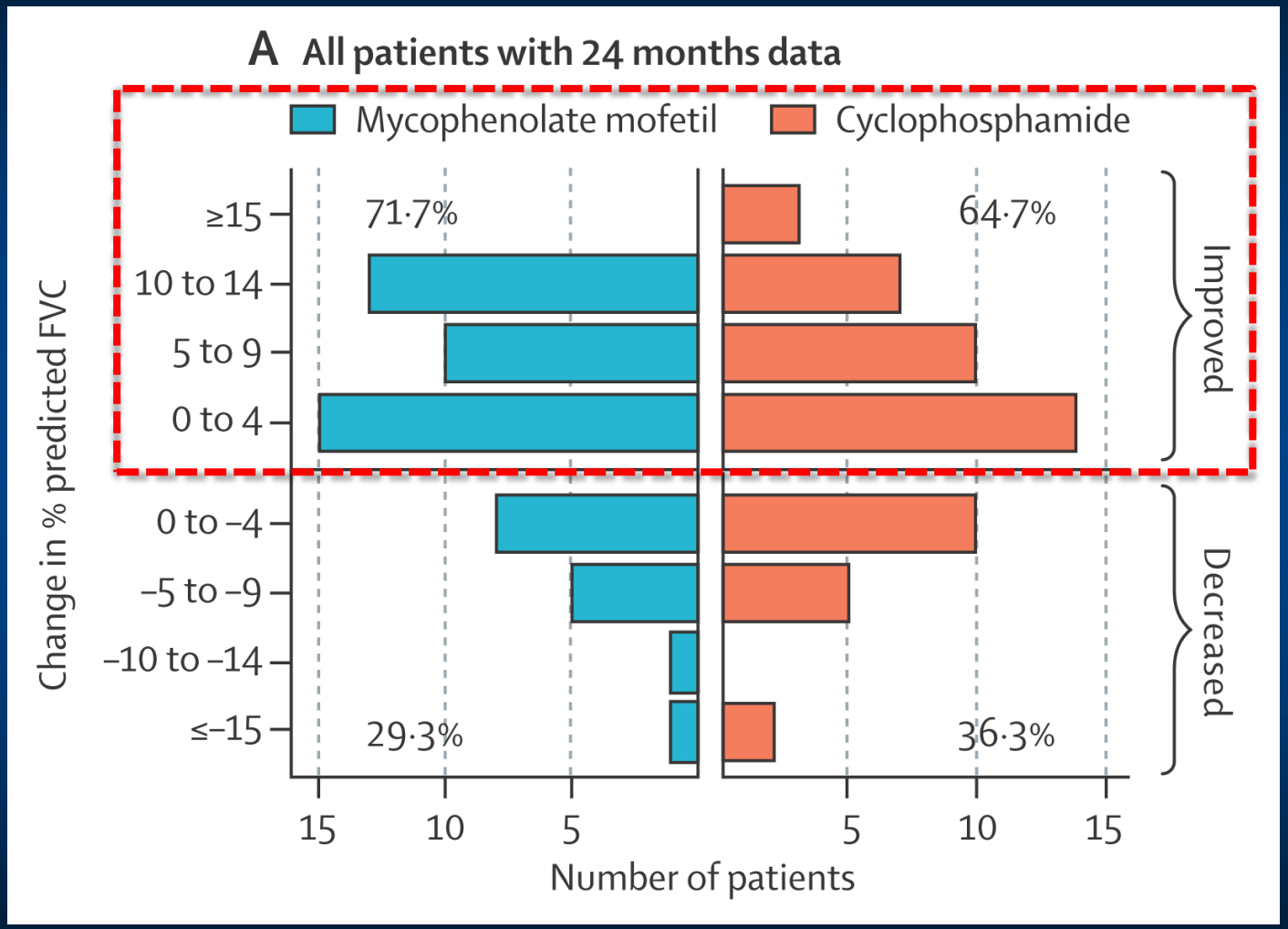
Change in FVC at 24 months



- At 24 months, the improvement in % FVC was comparable .
- Fewer premature withdrawals were noted in the MMF arm (20 vs. 32; p=0.019).

Lancet Resp Med 2016;4:708

Categorical Change in FVC



Most patients in each group had improving FVC (MMF 71·7 vs. CYC 64·7%; p=0·55)

Lancet Resp Med 2016;4:708

Adverse Events

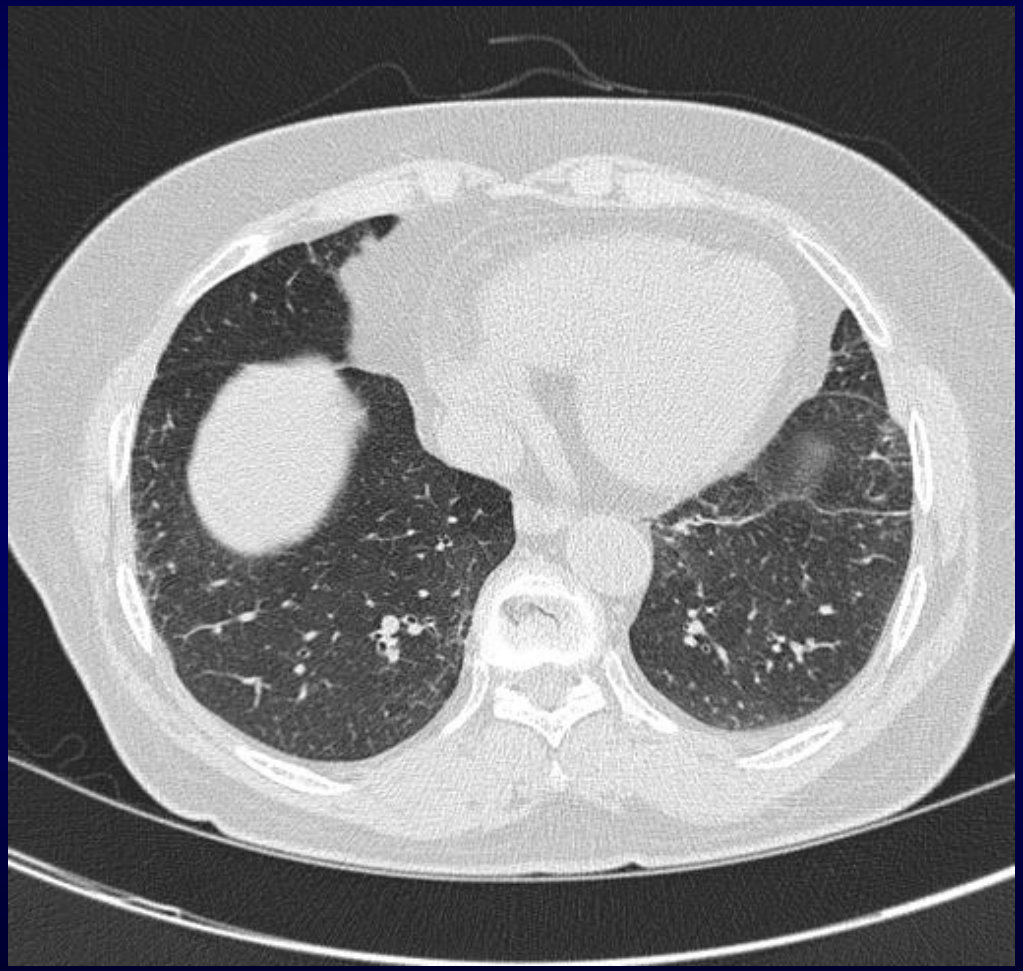
	Mycophenolate mofetil		Cyclophosphamide	
	Adverse events	Patients (n=69)	Adverse events	Patients (n=73)
Adverse events*				
Leucopenia†	5	4 (6%)	51	30 (41%)
Neutropenia	3	3 (4%)	7	5 (7%)
Anaemia	18	8 (12%)	26	13 (18%)
Thrombocytopenia	0	0	7	4 (6%)
Haematuria	3	3 (4%)	2	2 (3%)
Pneumonia	6	5 (7%)	4	4 (6%)
Serious adverse events‡				
Total	42	27 (39%)	36	22 (30%)
Related to treatment§	3	3 (4%)	8	7 (10%)
Related to underlying disease§	16	9 (13%)	16	13 (18%)
Due to other causes§¶	22	14 (20%)	11	6 (8%)
Unknown cause§	3	3 (4%)	3	3 (4%)
Death	..	5 (7%)	..	11 (15%)

- Leukopenia/thrombocytopenia were less frequent in the MMF arm ($p<0.05$).

Lancet Resp Med 2016;4:708

Early Interstitial Lung Disease

Interstitial lung abnormalities (ILA)



Nondependent changes $\geq$ 5% of lung

JAMA 2016;315(7):672

Prevalence of ILA

Author	Cohort	Subjects	No.	Prev.
GR Washko (2011)	COPD Gene study	Smokers $\geq$ 10PYRS 45-80 yrs NH-white and black	2416	8%
N.Sverzellati (2011)	Multicentric Italian Lung Detection trial	Smokers $\geq$ 20 PYRS Age $\geq$ 49 yrs	692	9.3%
GM Hunninghake (2013)	Framingham Heart Study-MDCT2 study	General population NH-white	2633	7%
GY Jin (2013)	National Lung Screening Trial	Smokers $\geq$ 30PYS 55-74 yrs White and Minority (9.2%; Asian 2.0%)	884	9.7%
Tracy J.Doyle (2014)	Brigham and Women's Hospital Rheumatoid Arthritis Sequential study	Rheumatoid arthritis patient	91	37.4%

NEJM 2011; 364:897, NEJM 2013; 368:2192, Radiology 2013; 268:563, ERJ 2011;38:392, Chest 2014;146(1):41

Clinical impacts of ILA

- More respiratory symptoms (Cough, SOB)
- More restrictive lung deficit (OR 2.3)
  - Less COPD (OR 0.53)
- Reduced 6MWD (OR 1.9)
- Association with MUC5B promotor polymorphism (OR 2.8)

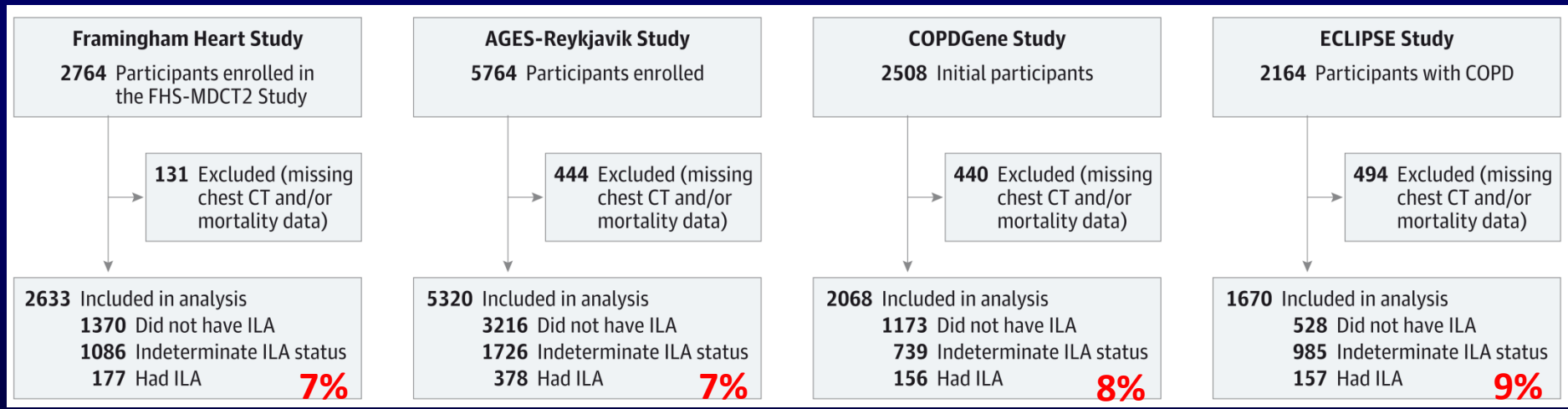
- Mortality ?
- Progression ?

N Engl J Med 2011; 364:897
Am J Respir Crit Care Med 2012;185:756
N Engl J Med 2013; 368:2192-2200
JAMA 2016;315(7):672

Association Between Interstitial Lung Abnormalities and All-Cause Mortality

Rachel K. Putman, MD; Hiroto Hatabu, MD, PhD; Tetsuro Araki, MD, PhD; Gunnar Gudmundsson, MD, PhD; Wei Gao, MS; Mizuki Nishino, MD; Yuka Okajima, MD; Josée Dupuis, PhD; Jeanne C. Latourelle, DSc; Michael H. Cho, MD, MPH; Souheil El-Chemaly, MD, MPH; Harvey O. Coxson, PhD; Bartolome R. Celli, MD; Isis E. Fernandez, MD; Oscar E. Zazueta, MD; James C. Ross, PhD; Rola Harmouche, PhD; Raúl San José Estépar, PhD; Alejandro A. Diaz, MD; Sigurdur Sigurdsson, BSc, MSc; Elías F. Gudmundsson, MSc; Gudny Eiríksdottír, MSc; Thor Aspelund, MSc, PhD; Matthew J. Budoff, MD; Gregory L. Kinney, PhD; John E. Hokanson, MPH, PhD; Michelle C. Williams, MD; John T. Murchison, MD; William MacNee, MD; Udo Hoffmann, MD, MPH; Christopher J. O'Donnell, MD, MPH; Lenore J. Launer, PhD; Tamara B. Harrris, MD, MS; Vilmundur Gudnason, MD, PhD; Edwin K. Silverman, MD, PhD; George T. O'Connor, MD; George R. Washko, MD; Ivan O. Rosas, MD; Gary M. Hunninghake, MD, MPH; for the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) and COPDGene Investigators

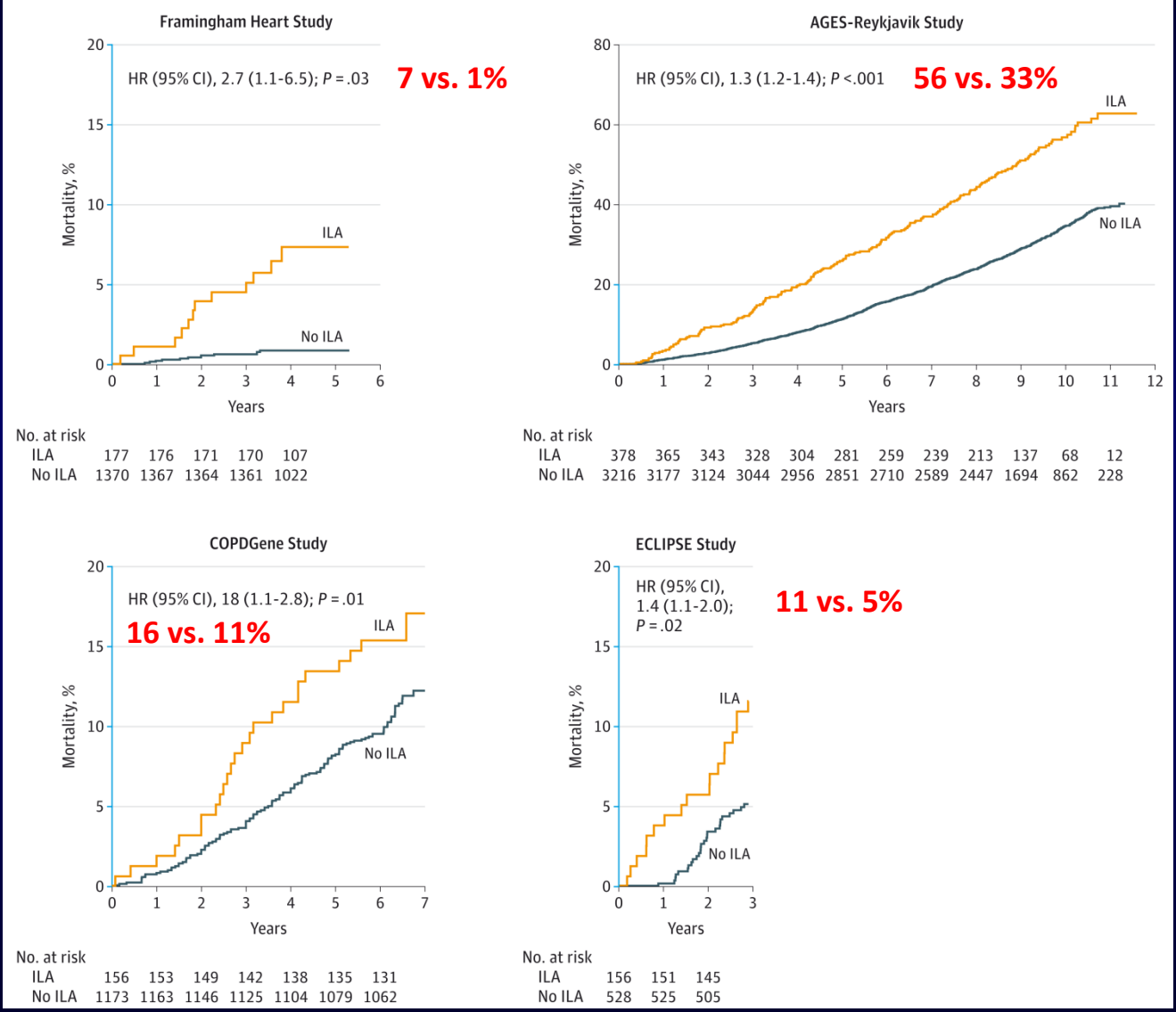
Participant Flow for Each Studies



ILAs were present in 7 - 9% of the participants from each studies.

JAMA 2016;315(7):672

Mortality Rates by ILA Status for Each Studies



There were <u>more deaths (HR 1.3-2.7)</u> among participants with ILA.

JAMA 2016;315(7):672

Mortality, ILA and Cause of Death for the AGES-Reykjavik Study

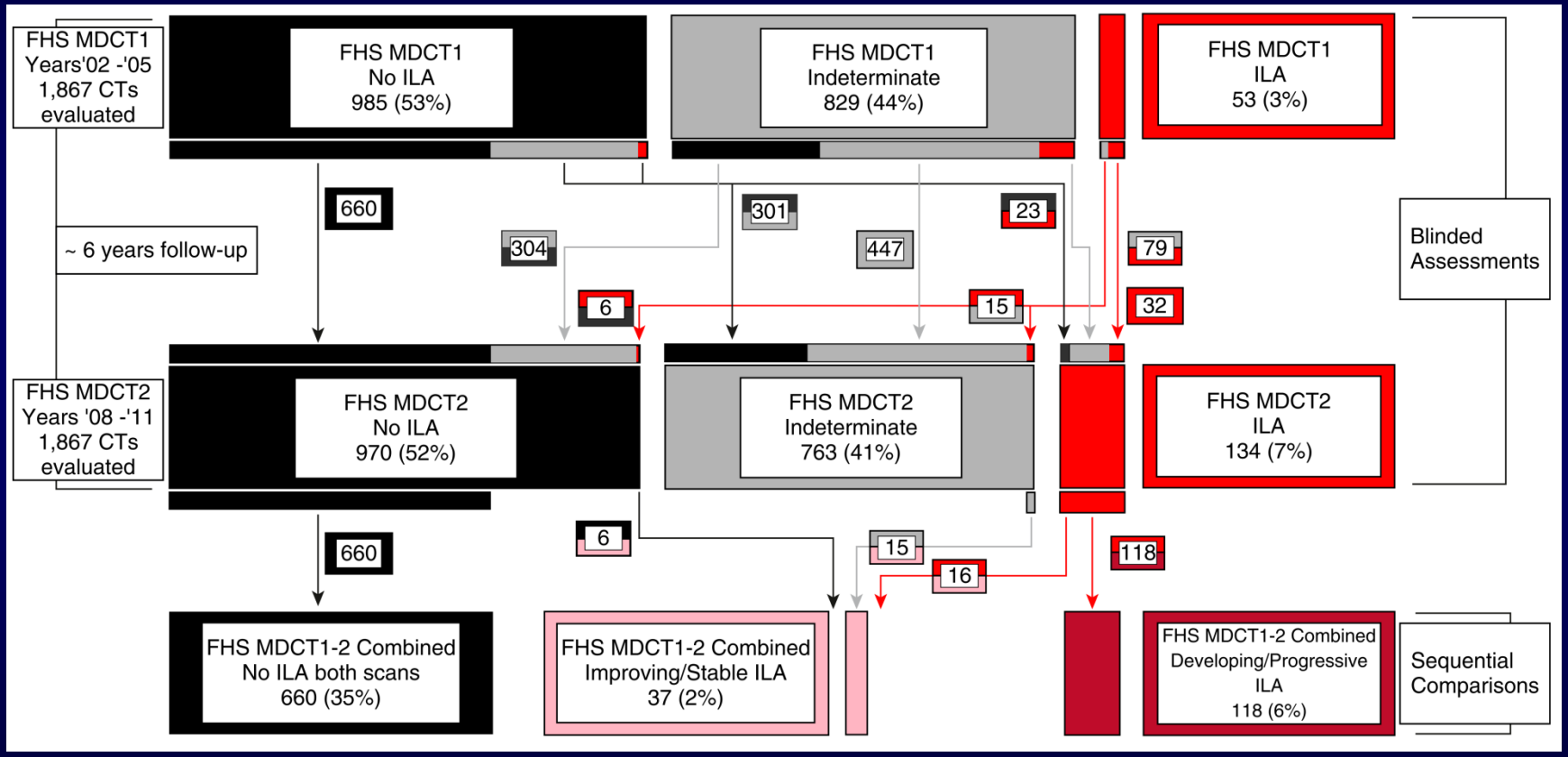
	No. (%)[a]			
	ILA	Indeterminate	No ILA	Overall
No. of participants	378	1726	3216	5320
Deaths				
Total	115 (100)	382 (100)	468 (100)	965
Cardiovascular[b]	48 (42)	161 (42)	204 (44)	413
Cancer[c]	29 (25)	111 (29)	151 (32)	291
Respiratory[d]	15 (13)	22 (6)	20 (4)	57
Pulmonary fibrosis	7	1	0	8
Other	8	21	20	49
Other[e]	23 (20)	88 (23)	93 (20)	204

In the AGES-Reykjavik cohort, the higher rate of mortality could be explained by a higher rate of death due to respiratory disease, specifically pulmonary fibrosis.

JAMA 2016;315(7):672

Development and Progression of Interstitial Lung Abnormalities in the Framingham Heart Study

Tetsuro Araki[1,2*], Rachel K. Putman[3*], Hiroto Hatabu[1,2], Wei Gao[4,5], Josée Dupuis[4,5], Jeanne C. Latourelle[6,7], Mizuki Nishino[2,8], Oscar E. Zazueta[3], Sila Kurugol[8], James C. Ross[8,9], Raúl San José Estépar[2,8], David A. Schwartz[10], Ivan O. Rosas[3], George R. Washko[3], George T. O'Connor[4,11], and Gary M. Hunninghake[1,3]



During the follow-up period 660 (35%) participants did not have ILA on either CT scan, 37 (2%) had stable to improving ILA, and 118 (6%) had ILA with progression.

Am J Respir Crit Care Med. 2016;194:1514

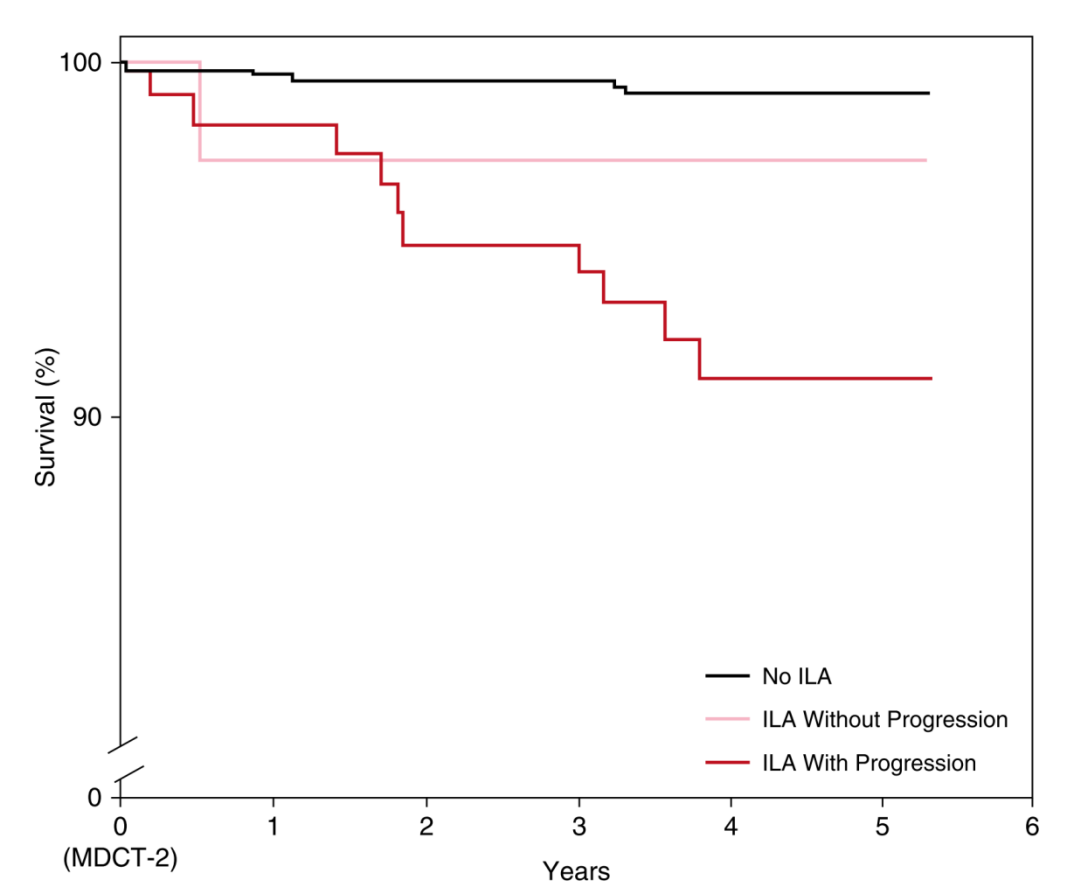
Baseline Characteristics of Participants Stratified by ILA Status

	No ILA (*n* = *660*; *35%*) (1)	ILA without Progression (*n* = *37*; *2%*) (2)	ILA with Progression (*n* = *118*; *6%*) (3)
Age, yr	49 ± 10	58 ± 11	65 ± 11
Sex, female, n (%)	296 (45)	20 (54)	53 (45)
Race, white, n (%)	660 (100)	37 (100)	118 (100)
Body mass index	28 ± 6	30 ± 6	28 ± 5
Pack-years smoking	16 ± 16	26 ± 19	24 ± 21
Current smokers, n (%)¶	48 (7)	9 (25)	6 (5)
Former smokers, n (%)	263 (40)	14 (39)	61 (52)
Never smokers, n (%)	349 (53)	13 (36)	51 (43)
MUC5B genotype, n (%)			
G/G	529 (80)	27 (73)	78 (66)
G/T	125 (19)	10 (27)	36 (31)
T/T	6 (1)	0	4 (3)

Increasing age and increasing copies of the MUC5B promoter polymorphism were associated with ILA progression.

Am J Respir Crit Care Med. 2016;194:1514

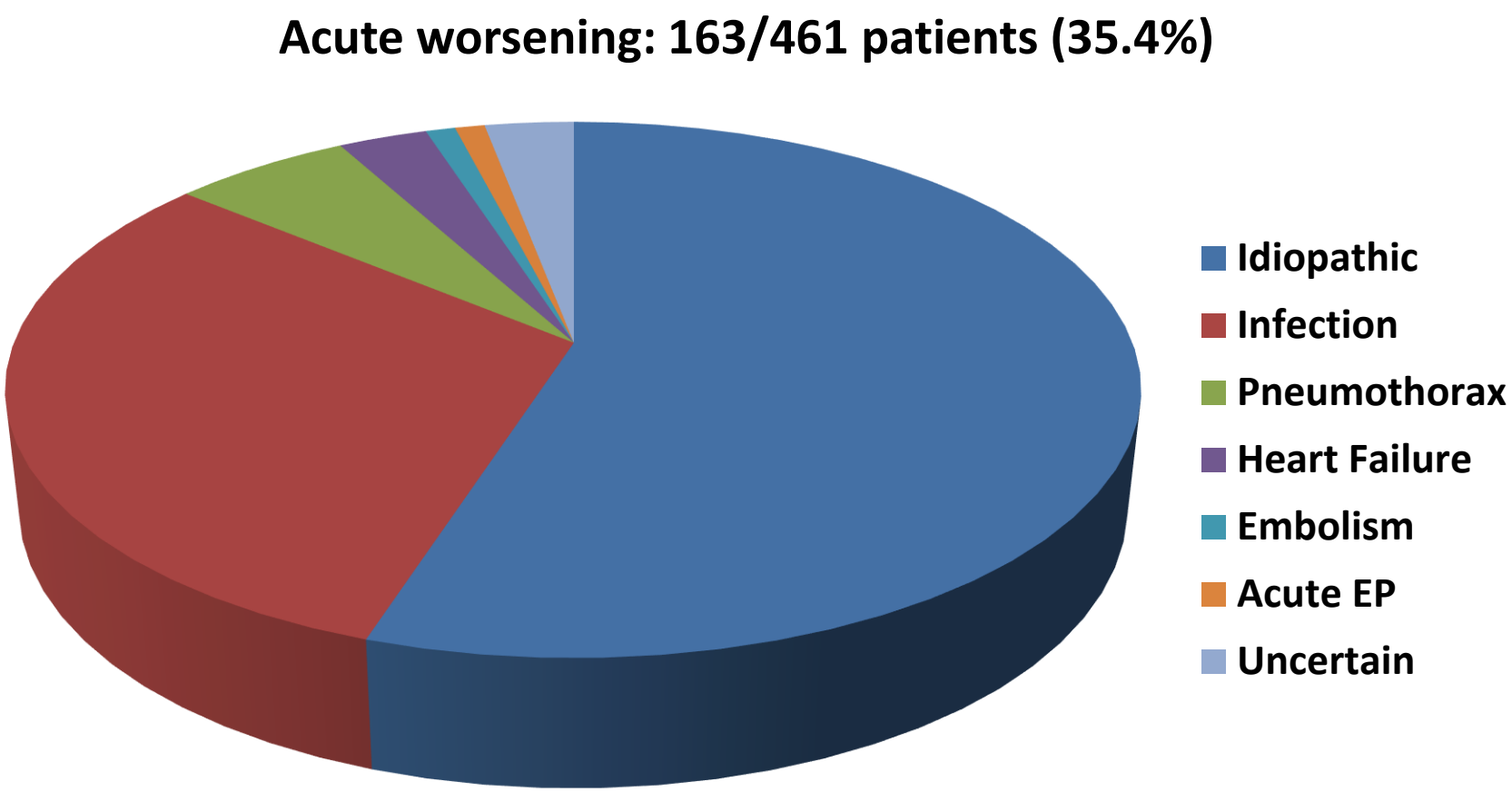
Comparison of Survival Curves



Over a median follow-up time of approximately 4 years, ILA progression was associated with an increase in the risk of death (hazard ratio, 3.9; 95% confidence interval, 1.3–10.9; P = 0.01) when compared with those without ILA.

Am J Respir Crit Care Med. 2016;194:1514

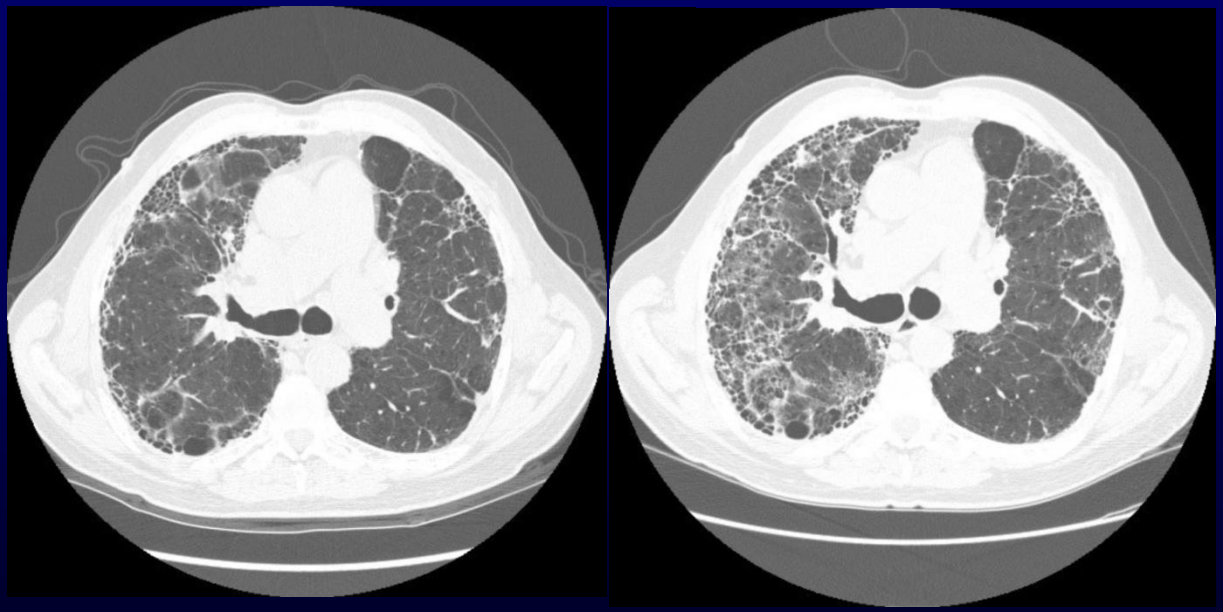
Acute worsening of IPF



ERJ 2011; 37:356

Definition: Acute Exacerbation

- An acute, clinically significant deterioration of unidentifiable cause in a patient with underlying IPF



Am J Respir Crit Care Med. 2007;176:636

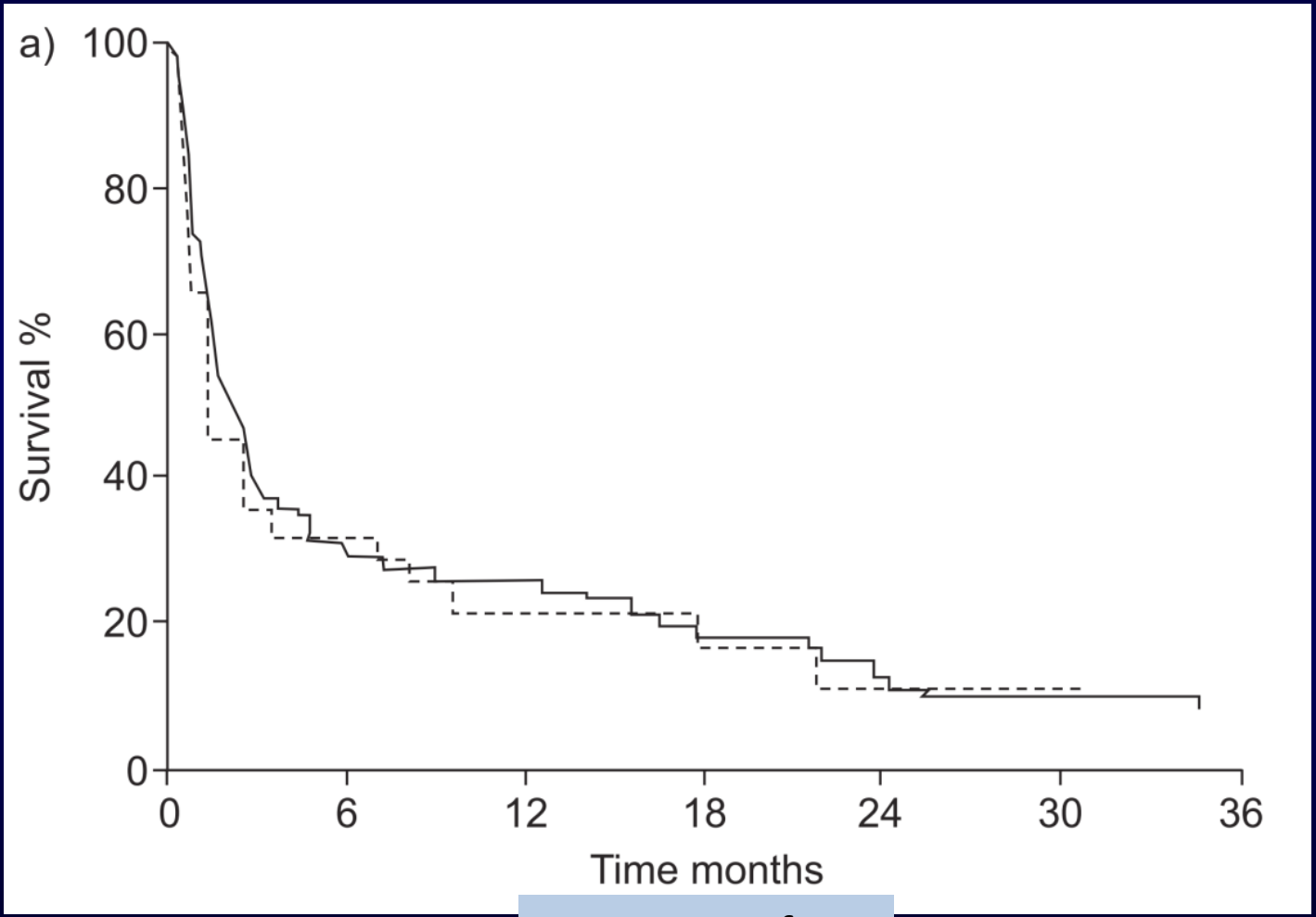
Diagnostic Criteria: 2007

Previous or concurrent diagnosis of IPF
Unexplained worsening of dyspnea within 30 days
HRCT with new bilateral GGA ± Con superimposed on a background reticular or honeycomb pattern c/w UIP
No evidence of pulmonary infection by endotracheal aspirate or BAL
Exclusion of alternative causes, including the following: heart failure, embolism, identifiable causes of ALI

- Suspected Aex: who fail to meet all five criteria due to missing data

Am J Respir Crit Care Med. 2007;176:636

Comparison of Survival Curves between AEx and infection



From onset of AEx

ERJ 2011; 37:356

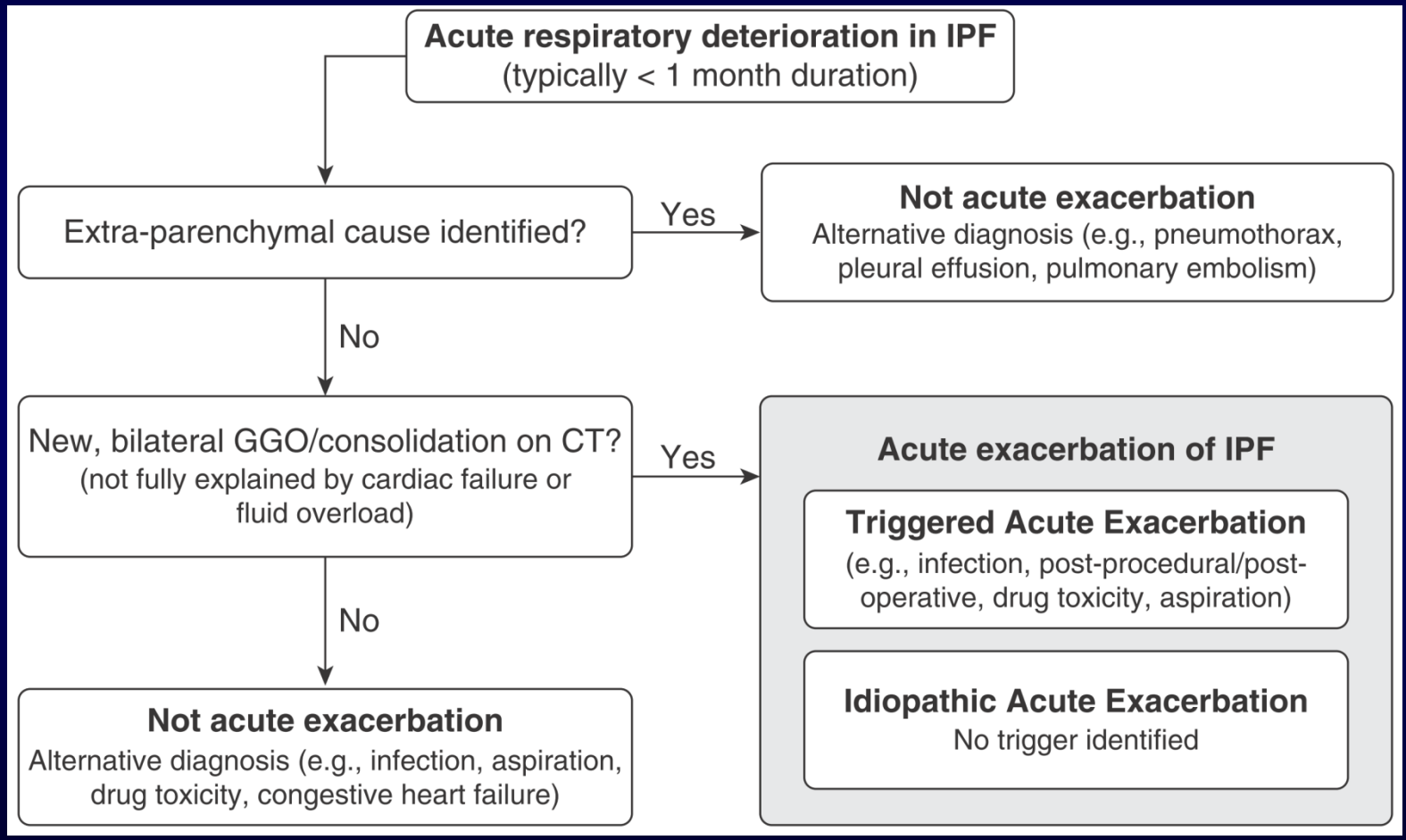
Diagnostic Criteria: 2016

- Revised definition: an acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality

Previous or concurrent diagnosis of IPF
Acute worsening of dyspnea typically within 30 days
CT with new bilateral GGA ± Con superimposed on a background c/w UIP pattern
Deterioration not fully explained by cardiac failure or fluid overload

Am J Respir Crit Care Med. 2016;194:265

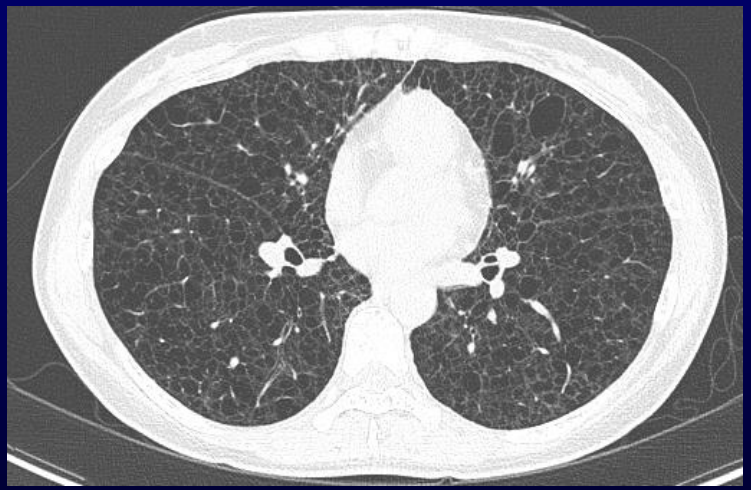
Evaluation of Acute Respiratory Deterioration in IPF

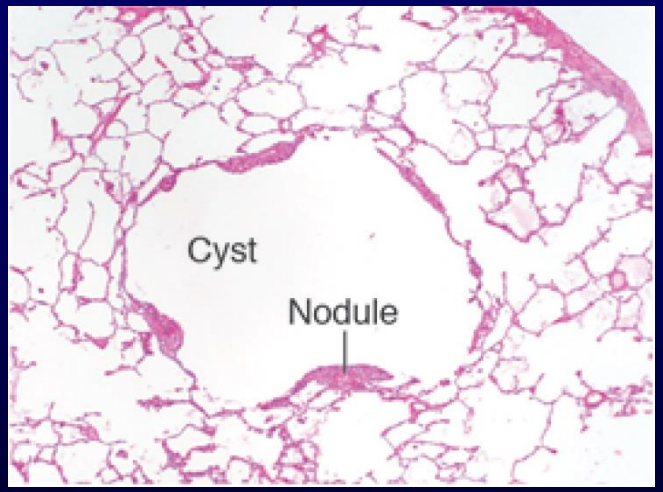


Am J Respir Crit Care Med. 2016;194:265

Lymphangioleiomyomatosis (LAM)

- Uncommon, progressive and often fatal lung disease of young women characterized by smooth muscle cell infiltration and cystic destruction of lung tissue





Chest 2008;133(2):507

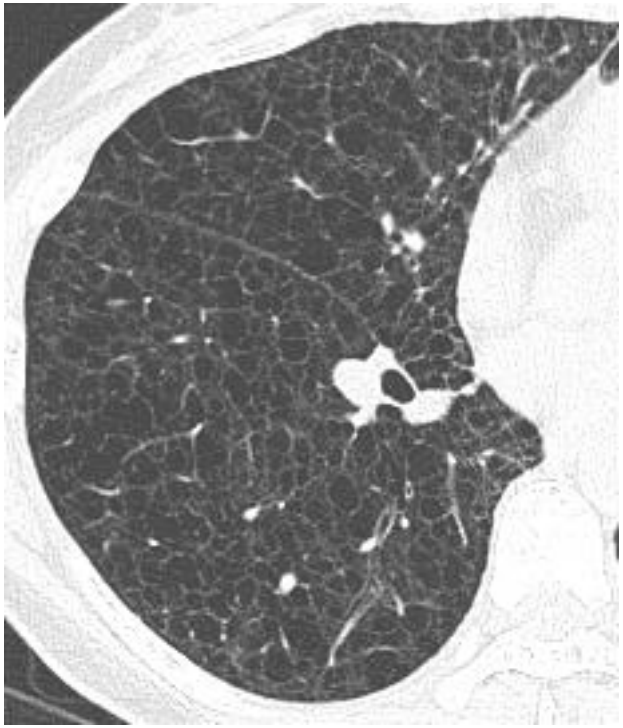
Clinical Features of LAM

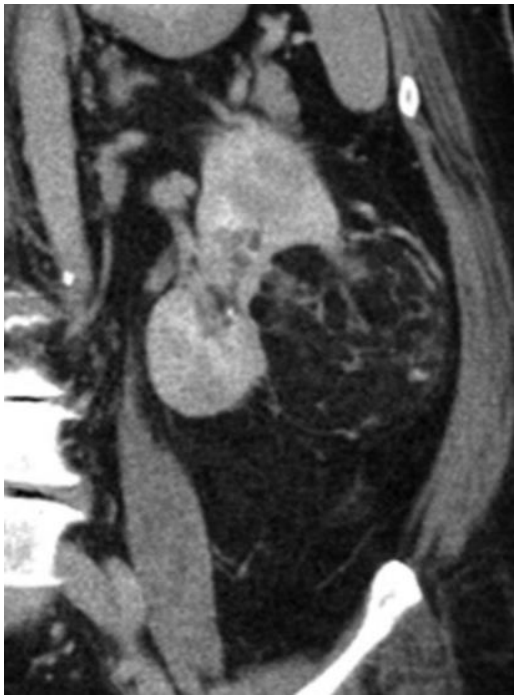
- Average age at diagnosis: 35 years (3-85 yrs)
- Occurs in women >> men
- Rate of decline in lung function: 3-15 % per year
- Disease course 10 years after symptoms onset
  - 55 % of pts are breathless.
  - 20 % of pts are on oxygen.
  - 10 % of pts are deceased.
- Median survival: 8.5-29 years
- No cure

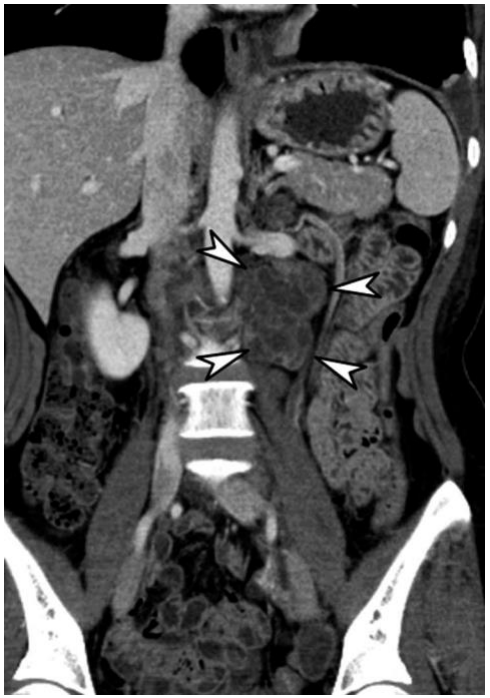
Thorax 2004:59:800

European Respiratory Society guidelines for the diagnosis and management of lymphangioleiomyomatosis

S.R. Johnson*, J.F. Cordier*, R. Lazor, V. Cottin, U. Costabel, S. Harari, M. Reynaud-Gaubert, A. Boehler, M. Brauner, H. Popper, F. Bonetti, C. Kingswood and the Review Panel of the ERS LAM Task Force

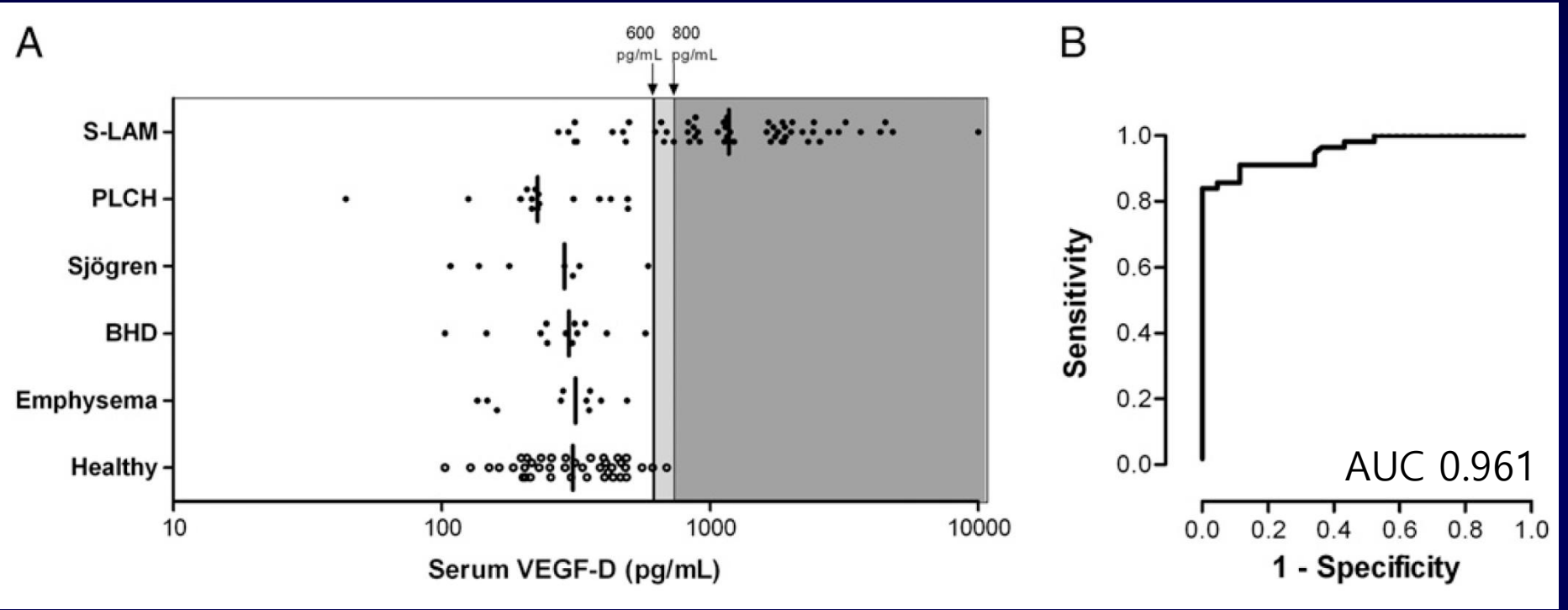






Eur Resp J 2010;35:14

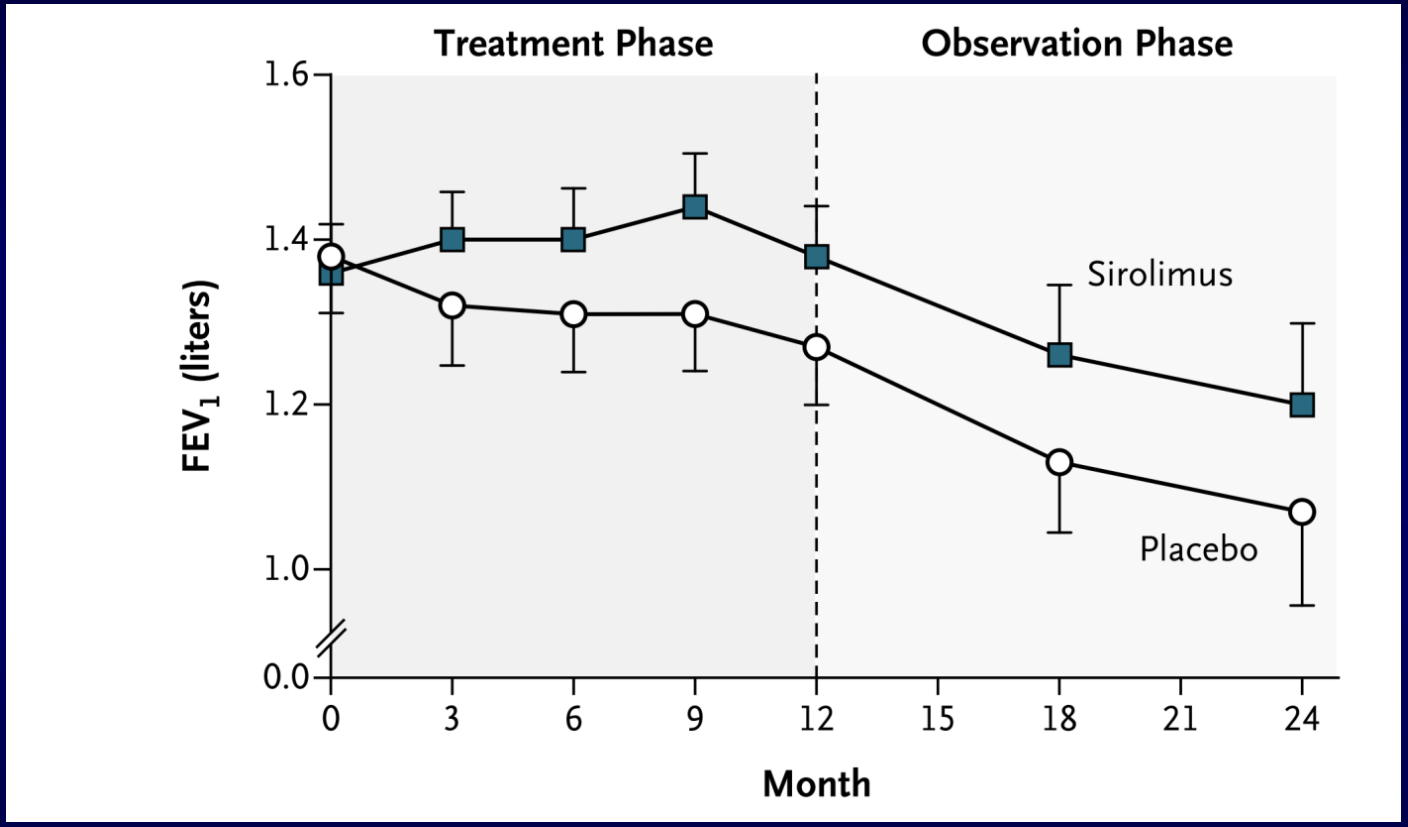
Serum VEGF-D 800 pg/ml is diagnostic for LAM



A serum VEGF-D level of 800 pg/mL in a woman with typical cystic changes on high-resolution CT (HRCT) scan is diagnostically specific for S-LAM and identifies LAM in women with TSC. A negative VEGF-D result does not exclude the diagnosis of LAM.

Chest 2010;138(3):674

Sirolimus : MILES Trial



	0 to 12 mo	12 to 24 mo	0 to 24 mo
Sirolimus	1±2 ml/mo	-14±3 ml/mo	-150±170 ml
Placebo	-12±2ml/mo	-8±2 ml/mo	-180±100 ml

NEJM 2011;364:1595

Official American Thoracic Society/Japanese Respiratory Society Clinical Practice Guidelines: Lymphangioleiomyomatosis Diagnosis and Management

"The majority of patients would want the intervention, but a significant mino rity would not."	"The majority of patients would not want the intervention, but a significant minority would."

Strong YES

Sirolimus
VEGF-D

Weak YES*

Weak NO

Doxycycline
Hormonal therapy

Strong NO

* Conditional recommendation for use

Am J Respir Crit Care Med. 2016;194:265

SUMMARY

- Treatment
  - consistent efficacy and safety of PFD and NIN
  - efficacy of PFD in early and progressed group
  - mmf in SSc
- Early ILD (ILA)
  - all cause mortality
  - progression
- Guidelines:
  - AEx in IPF
  - LAM