울산대학교병원
ULSAN UNIVERSITY HOSPITAL

Landmark studies in IPF

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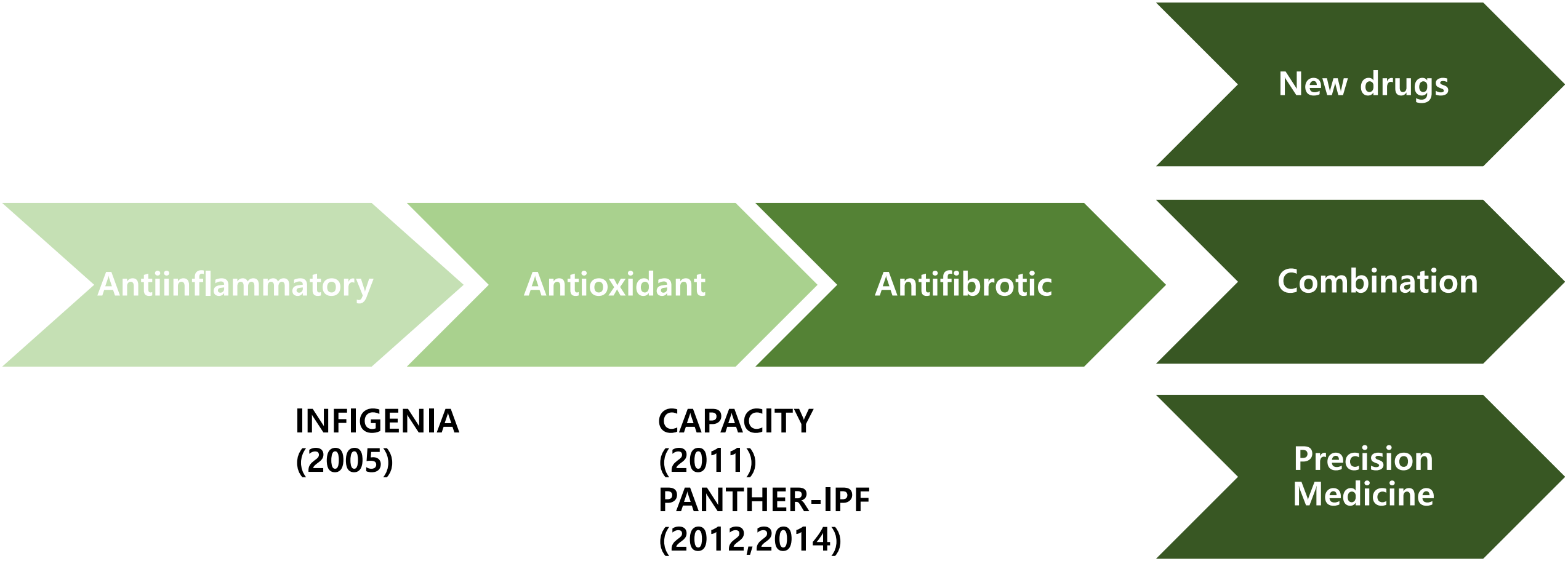
| 울산대학교병원 | 호흡기내과 | 제갈양진

Guideline for IPF treatment

Agent	2015 Guideline	2011 Guideline
New and revised recommendations		
Anticoagulation (warfarin)	Strong recommendation against use*	Conditional recommendation against use‡
Combination prednisone + azathioprine + *N*-acetylcysteine	Strong recommendation against use†	Conditional recommendation against use†
Selective endothelin receptor antagonist (ambrisentan)	Strong recommendation against use†	Not addressed
Imatinib, a tyrosine kinase inhibitor with one target	Strong recommendation against use*	Not addressed
Nintedanib, a tyrosine kinase inhibitor with multiple targets	Conditional recommendation for use*	Not addressed
Pirfenidone	Conditional recommendation for use*	Conditional recommendation against use†
Dual endothelin receptor antagonists (macitentan, bosentan)	Conditional recommendation against use†	Strong recommendation against use*
Phosphodiesterase-5 inhibitor (Sildenafil)	Conditional recommendation against use*	Not addressed
Unchanged recommendations		
Antiacid therapy	Conditional recommendation for use‡	Conditional recommendation for use‡
N-acetylcysteine monotherapy	Conditional recommendation against use†	Conditional recommendation against use†
Antipulmonary hypertension therapy for idiopathic pulmonary fibrosis-associated pulmonary hypertension	Reassessment of the previous recommendation was deferred	Conditional recommendation against use‡
Lung transplantation: single vs. bilateral lung transplantation	Formulation of a recommendation for single vs. bilateral lung transplantation was deferred	Not addressed

Paradigm changes in IPF treatment



INFIGENIA

The NEW ENGLAND JOURNAL of MEDICINE

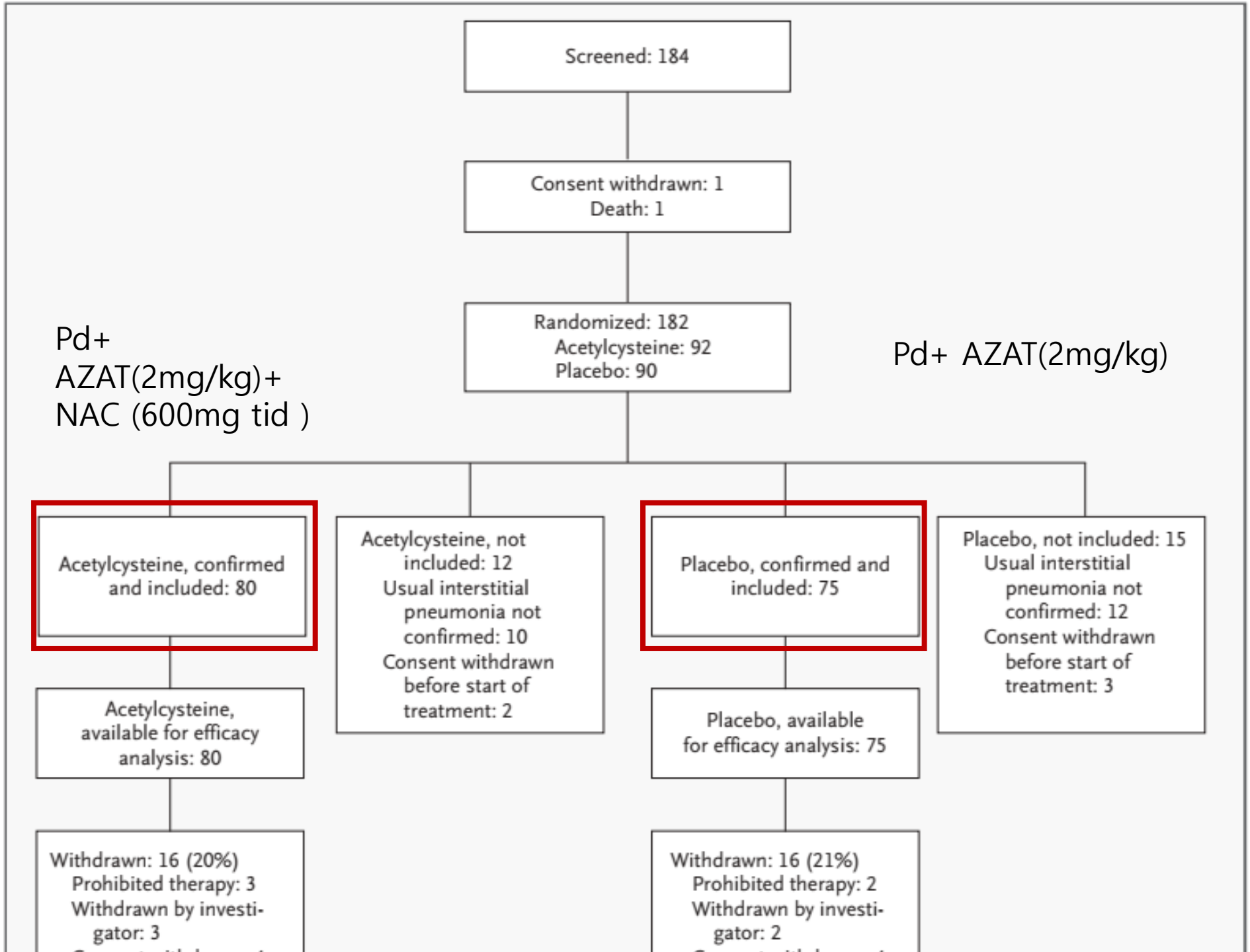
ORIGINAL ARTICLE

High-Dose Acetylcysteine in Idiopathic Pulmonary Fibrosis

Maurits Demedts, M.D., Juergen Behr, M.D., Roland Buhl, M.D., Ulrich Costabel, M.D., P.N., Richard Dekhuijzen, M.D., Henk M. Jansen, M.D., William MacNee, M.D., Michiel Thomeer, M.D., Benoit Wallaert, M.D., François Laurent, M.D., Andrew G. Nicholson, M.D., Eric K. Verbeken, M.D., Johny Verschakelen, M.D., Christopher D.R. Flower, M.D., Frédérique Capron, M.D., Stefano Petruzzelli, M.D., Paul De Vuyst, M.D., Jules M.M. van den Bosch, M.D., Eulogio Rodriguez-Becerra, M.D., Giuseppina Corvasce, Ph.D., Ida Lankhorst, M.D., Marco Sardina, M.D., and Mauro Montanari, Ph.D., for the IFIGENIA Study Group*

Pd+ AZAT(2mg/kg)
vs.
Pd+ AZAT(2mg/kg)+ NAC (600mg tid)

N Engl J Med 2005;353:2229-42

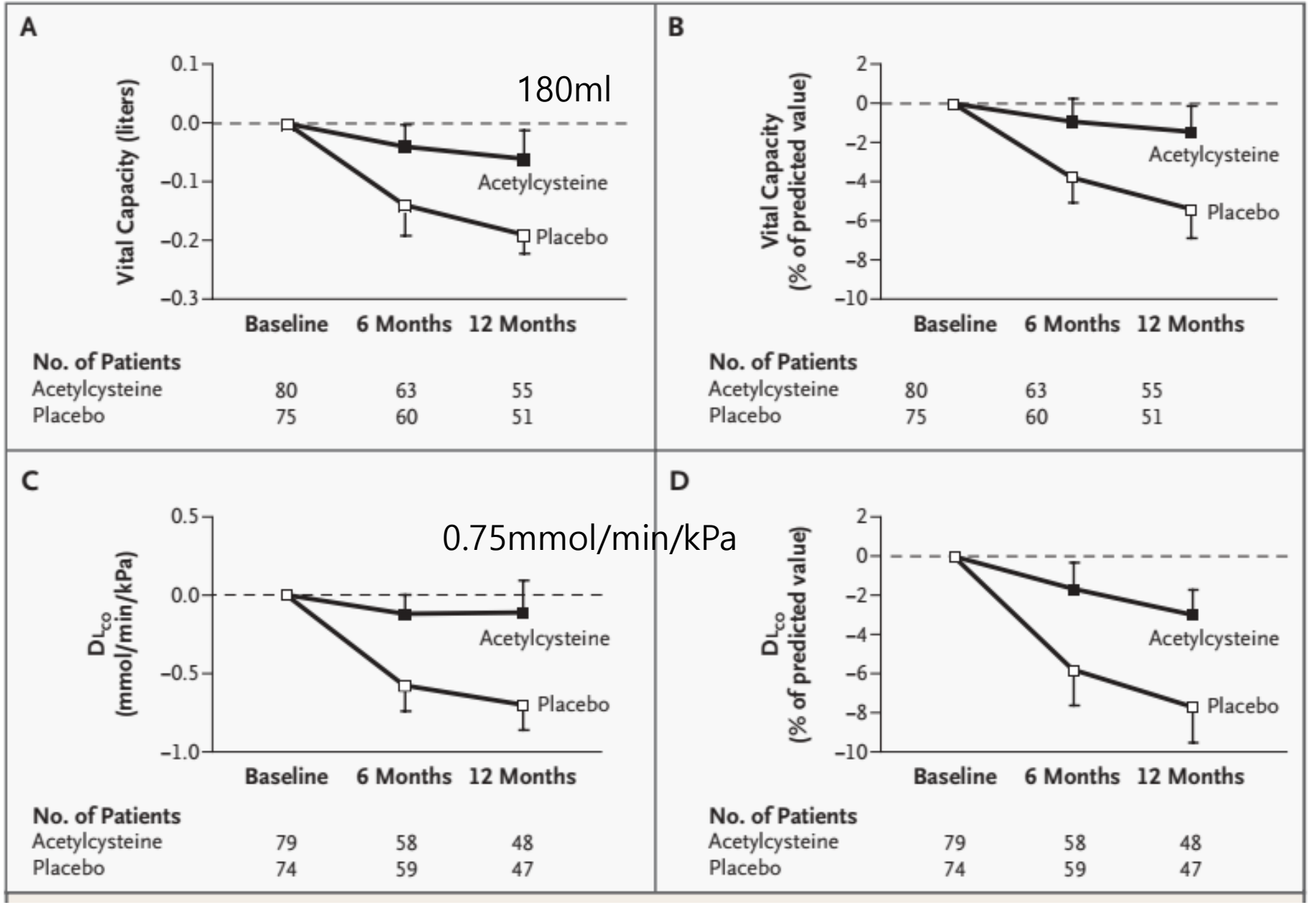


Pd+
AZAT(2mg/kg)+
NAC (600mg tid)

Pd+ AZAT(2mg/kg)

N Engl J Med 2005;353:2229-42

PFT changes at 6 and 12 months



P=0.02

P=0.003

N Engl J Med 2005;353:2229-42

PANTHER-IPF

The NEW ENGLAND JOURNAL of MEDICINE

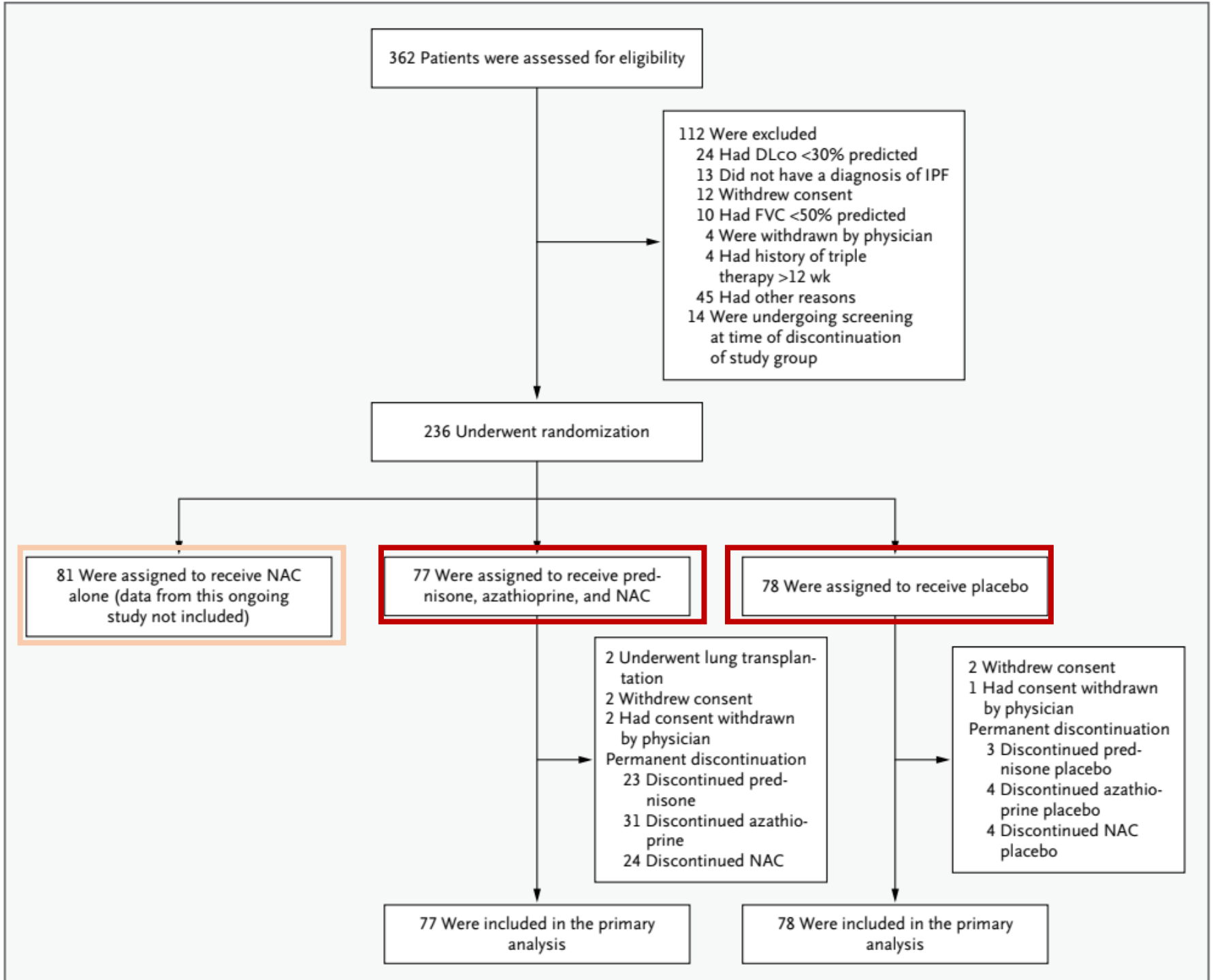
ORIGINAL ARTICLE

Prednisone, Azathioprine, and N-Acetylcysteine for Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network*

ABSTRACT

N Engl J Med 2012;366:1968-77.

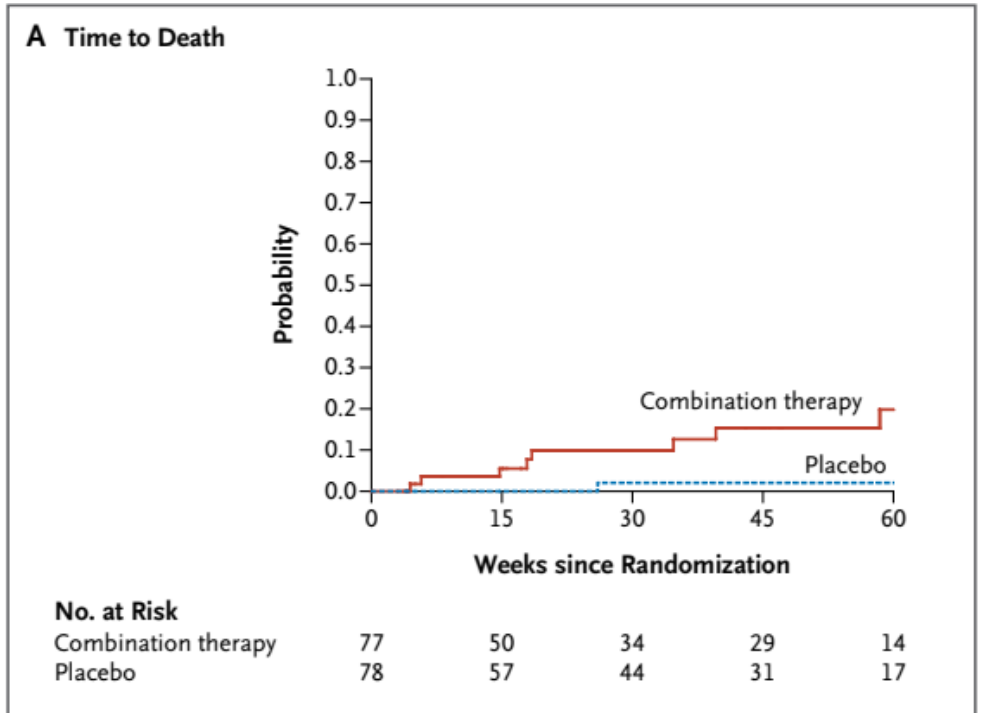


PD+AZAT+ NAC

vs.

Placebo

N Engl J Med 2012;366:1968-77.



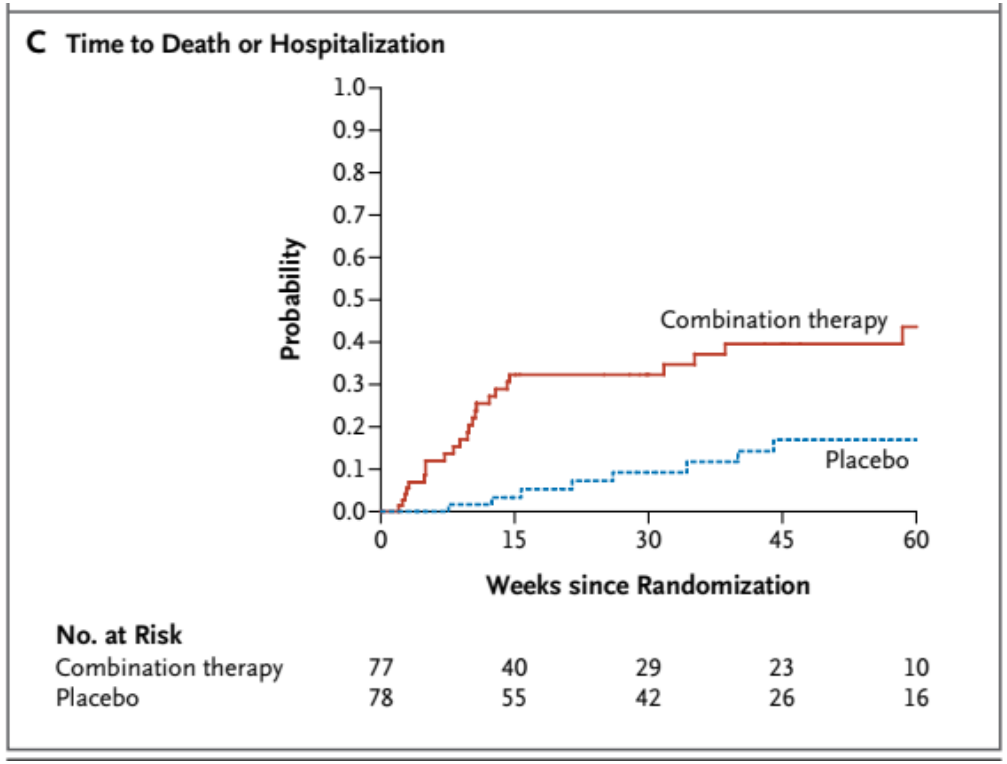


Figure 2. Kaplan–Meier Curves for the Time until Death, Disease Progression, or Hospitalization.

Shown are the time until death (Panel A), until a composite of death or disease progression (defined as a decrease in the forced vital capacity of ≥10%) (Panel B), or until a composite of death or hospitalization (Panel C). Combination therapy refers to a three-drug regimen consisting of prednisone, azathioprine, and *N*-acetylcysteine.

N Engl J Med 2012;366:1968-77.

CAPACITY

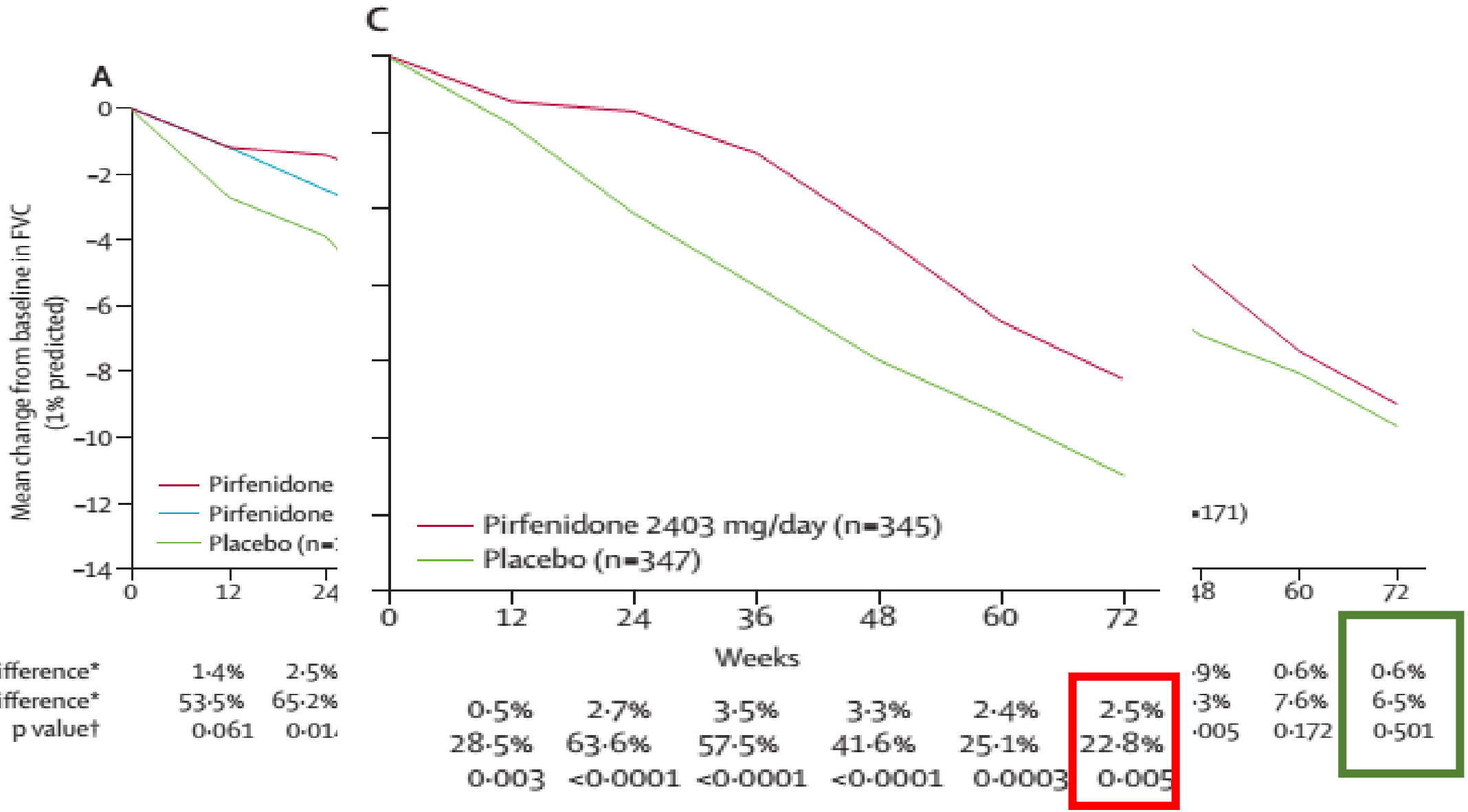
Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials

Paul W Noble, Carlo Albera, Williamson Z Bradford, Ulrich Costabel, Marilyn K Glassberg, David Kardatzke, Talmadge E King Jr, Lisa Lancaster, Steven A Sahn, Javier Szwarcberg, Dominique Valeyre, Roland M du Bois, for the CAPACITY Study Group

- 110 centres in 13 countries
- 40–80 years
- Dx of IPF in the previous 48 months
- 50% ≤FVC ≤ 90%
- 35% ≤ DLco ≤ 90%
- 6MWD ≥150 m

Lancet 2011; 377: 1760–69

FVC changes



Noble et al. Lancet 2011; 377: 1760–69

The NEW ENGLAND JOURNAL of MEDICINE

2067-2069 FREE

ORIGINAL ARTICLES

May 29, 2014

Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

L. Richeldi and Others

2071-2082 FREE

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

T.E. King, , and Others

2083-2092 FREE

Randomized Trial of Acetylcysteine in Idiopathic Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network

INPULSIS

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 29, 2014 VOL. 370 NO. 22

Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

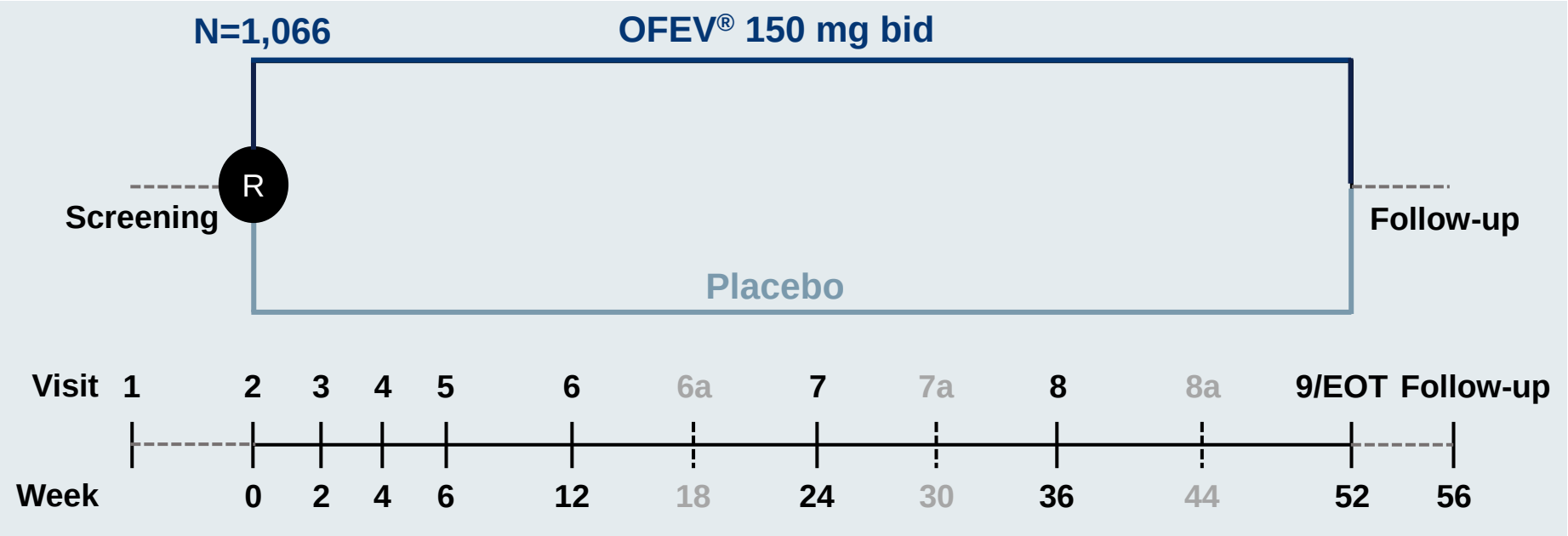
Luca Richeldi, M.D., Ph.D., Roland M. du Bois, M.D., Ganesh Raghu, M.D., Arata Azuma, M.D., Ph.D., Kevin K. Brown, M.D., Ulrich Costabel, M.D., Vincent Cottin, M.D., Ph.D., Kevin R. Flaherty, M.D., David M. Hansell, M.D., Yoshikazu Inoue, M.D., Ph.D., Dong Soon Kim, M.D., Martin Kolb, M.D., Ph.D., Andrew G. Nicholson, D.M., Paul W. Noble, M.D., Moisés Selman, M.D., Hiroyuki Taniguchi, M.D., Ph.D., Michèle Brun, M.Sc., Florence Le Maulf, M.Sc., Mannaïg Girard, M.Sc., Susanne Stowasser, M.D., Rozsa Schlenker-Herceg, M.D., Bernd Disse, M.D., Ph.D., and Harold R. Collard, M.D., for the INPULSIS Trial Investigators*

INPULSIS-Inclusion criteria

- 1066 patients
- 205 sites in 24 countries in the Americas, Europe, Asia, and Australia.
- Nintedanib: placebo 3:2
- ≥40 years
- Dx of IPF in the previous 5Ys
- FVC ≥ 50%
- 30% ≤ DLco ≤ 79%

Richeldi et al. N Engl J Med 2014;370:2071-82

INPULSIS™ trials: Study design[1,2]

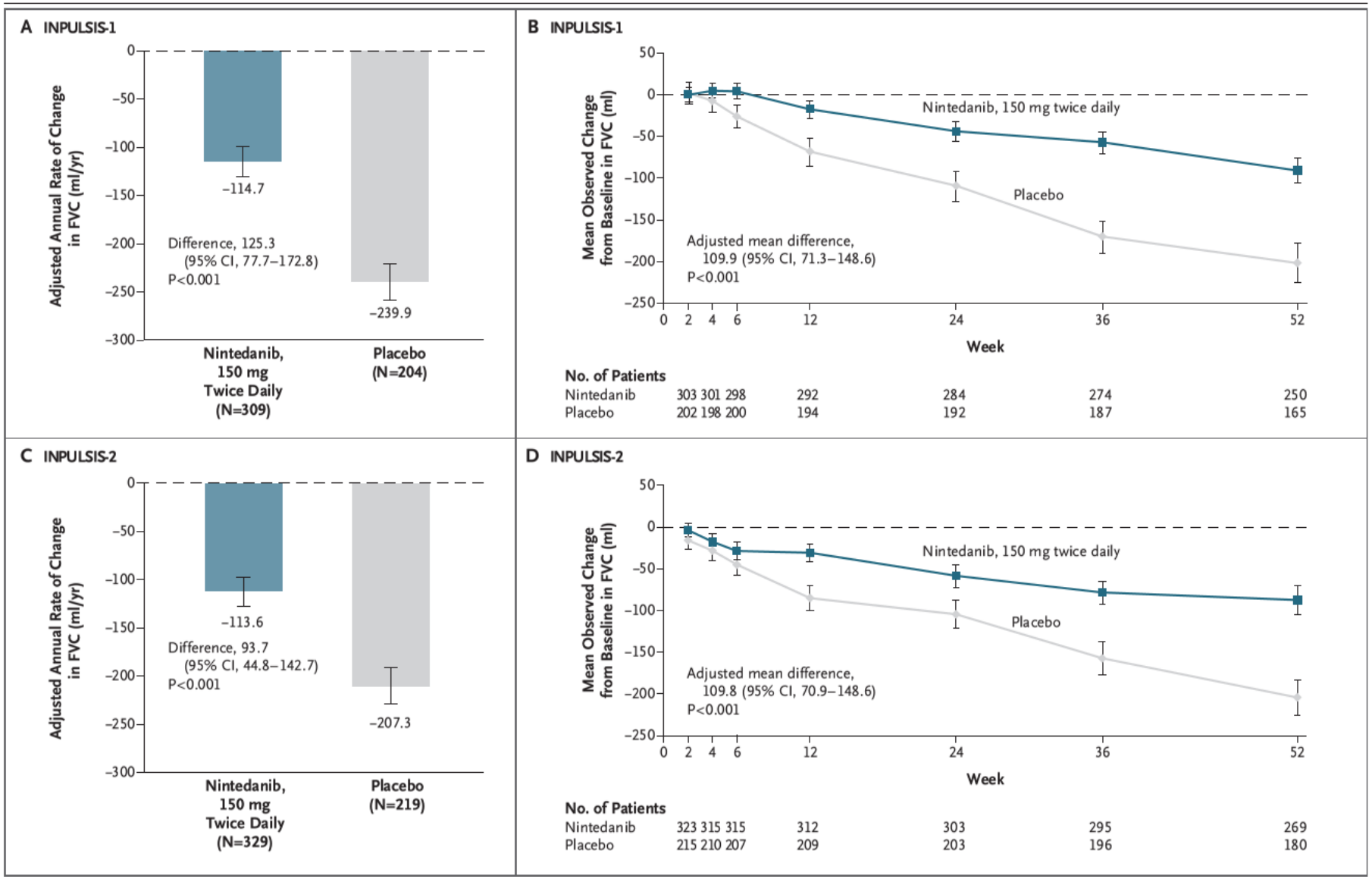


- Two double-blind, placebo-controlled Phase III studies with replicate design (INPULSIS™-1 and -2)
- 52-week treatment period followed by 4-week follow-up
- 3:2 randomisation ratio for OFEV®:placebo
- Treatment interruption and/or dose reduction to 100 mg bid allowed to manage adverse events
- Patients who prematurely discontinued trial drug were asked to attend all visits as planned

- Visits 6a, 7a and 8a were for blood sampling for laboratory tests only.
  Bid; twice-daily; EOT, end of treatment; R, randomisation.
  1. Richeldi L, et al. N Engl J Med 2014; 370: 2071–2082; **2**. Richeldi L, et al. Respir Med 2014; 108: 1023–1030.

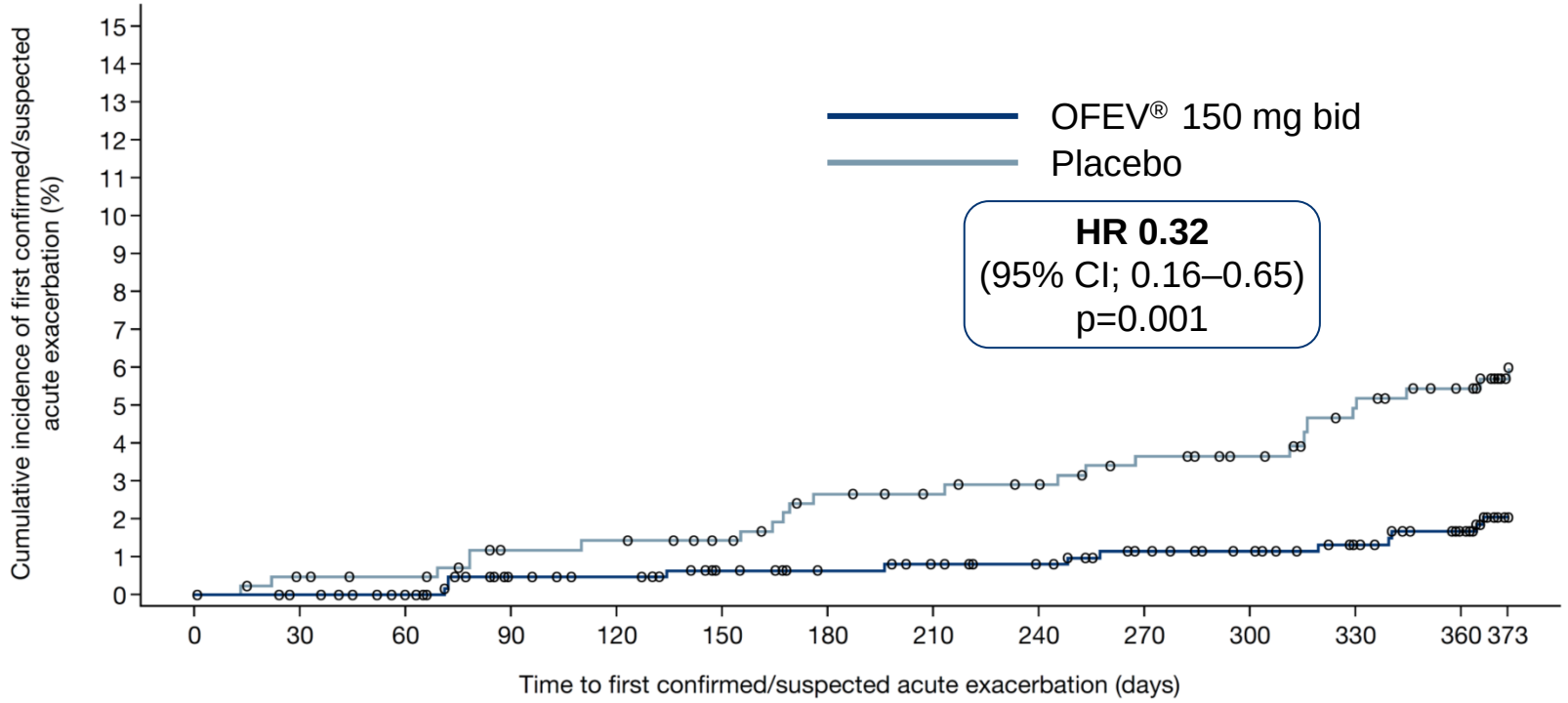
Annual rate of decline in FVC

INPULSIS



Richeldi et al. N Engl J Med 2014;370:2071-82

Time to first AE : Pooled data



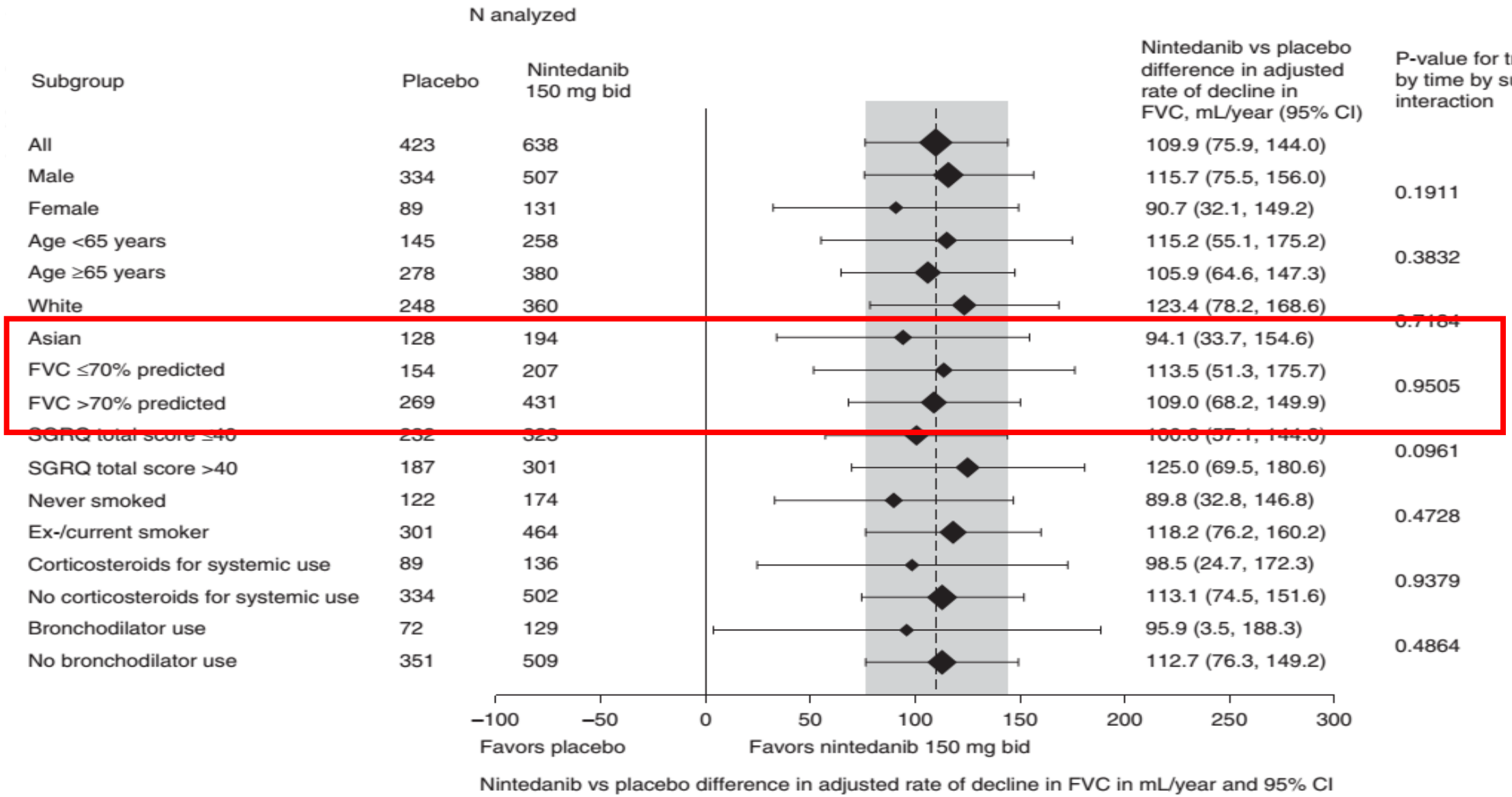
No. of patients														
OFEV®	638	634	629	613	610	602	597	593	589	580	572	563	548	503
Placebo	423	419	416	409	408	404	396	393	390	384	380	371	363	345

	OFEV® 150 mg bid (n=638)	Placebo (n=423)
Patients with ≥1 acute exacerbation, n (%)	12 (1.9)	24 (5.7)

- Bid, twice-daily; CI, confidence interval; HR, hazard ratio.
  Richeldi L, et al. N Engl J Med 2014; 370: 2071–2082.

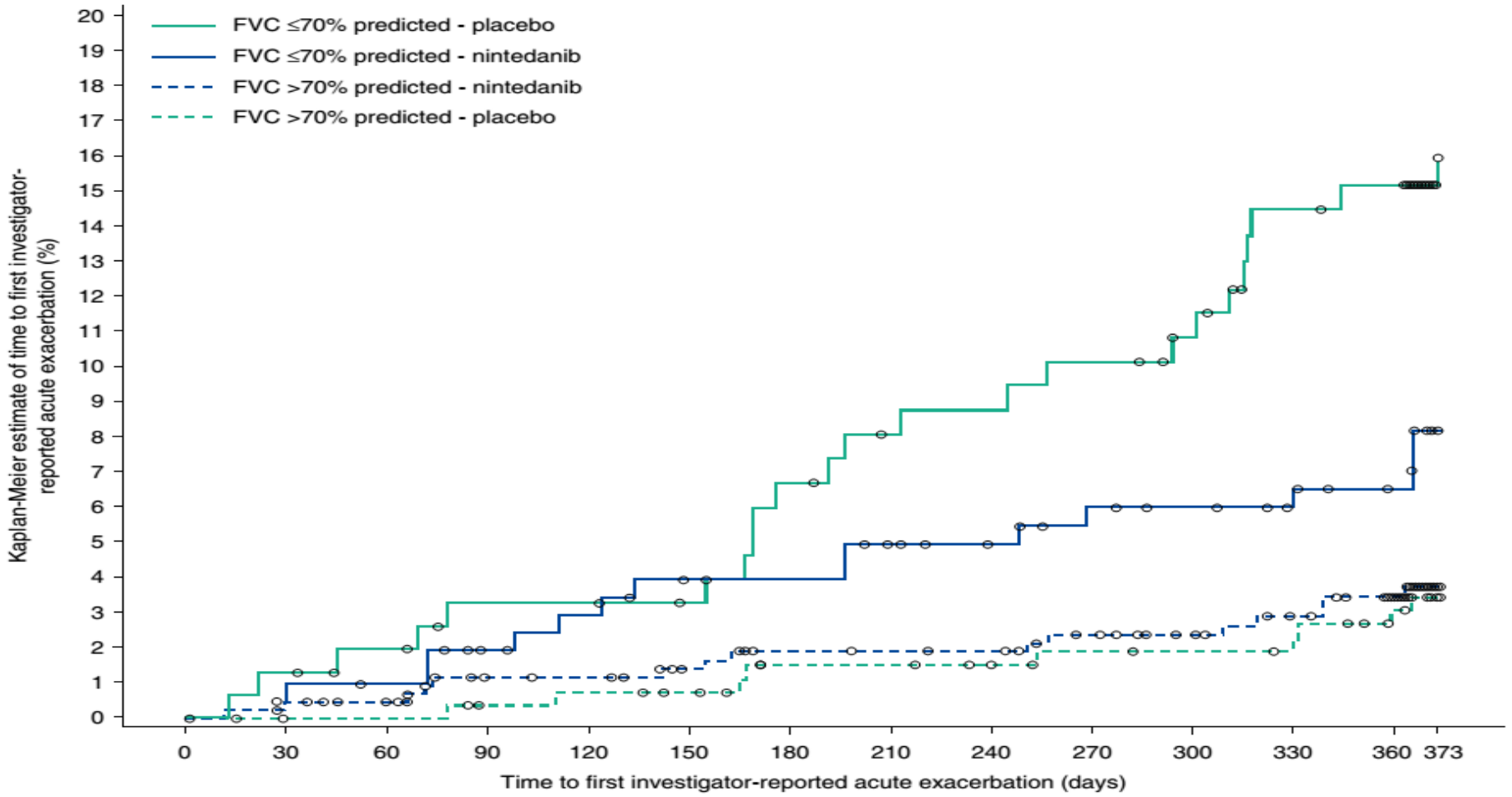
Efficacy of Nintedanib in Idiopathic Pulmonary Fibrosis across Prespecified Subgroups in INPULSIS

Ulrich Costabel[1]. Yoshikazu Inoue[2]. Luca Richeldi[3]. Harold R. Collard[4]. Inga Tschoepe[5]. Susanne Stowasser[6].



Costabel et al. AM J RESPIR CRIT CARE MED 2016;193:178-185

Time to first AE in subgroups by baseline FVC



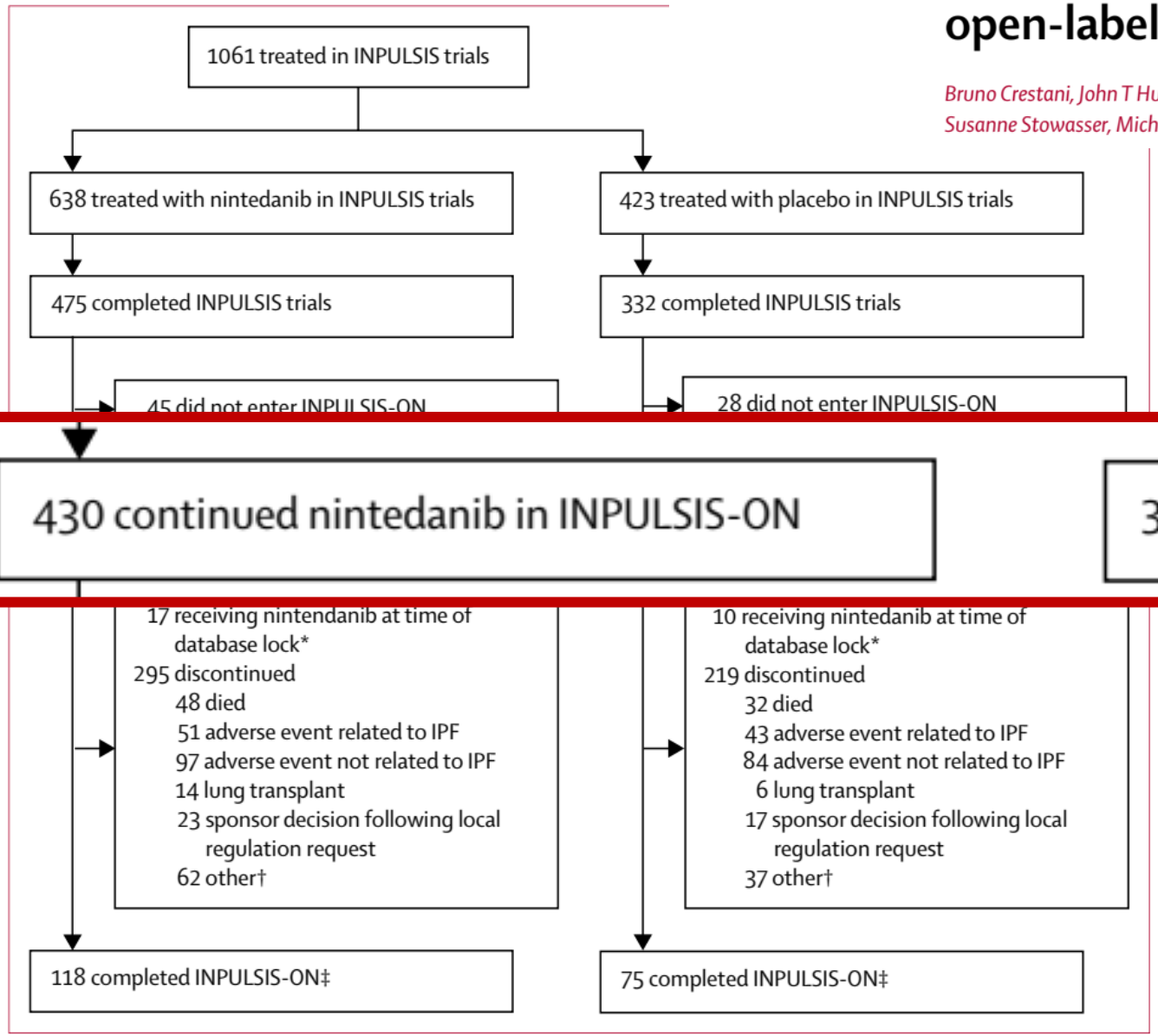
No. of patients														
FVC ≤70% predicted – placebo	154	152	148	144	144	142	137	133	132	130	126	118	116	106
FVC ≤70% predicted – nintedanib	207	205	203	198	195	191	190	186	183	179	177	174	169	160
FVC >70% predicted – nintedanib	431	427	424	411	410	404	399	398	397	391	385	379	368	332
FVC >70% predicted – placebo	269	267	267	264	263	261	256	256	254	251	250	249	243	235

Costabel et al. AM J RESPIR CRIT CARE MED 2016;193:178-185

INPULSIS-ON

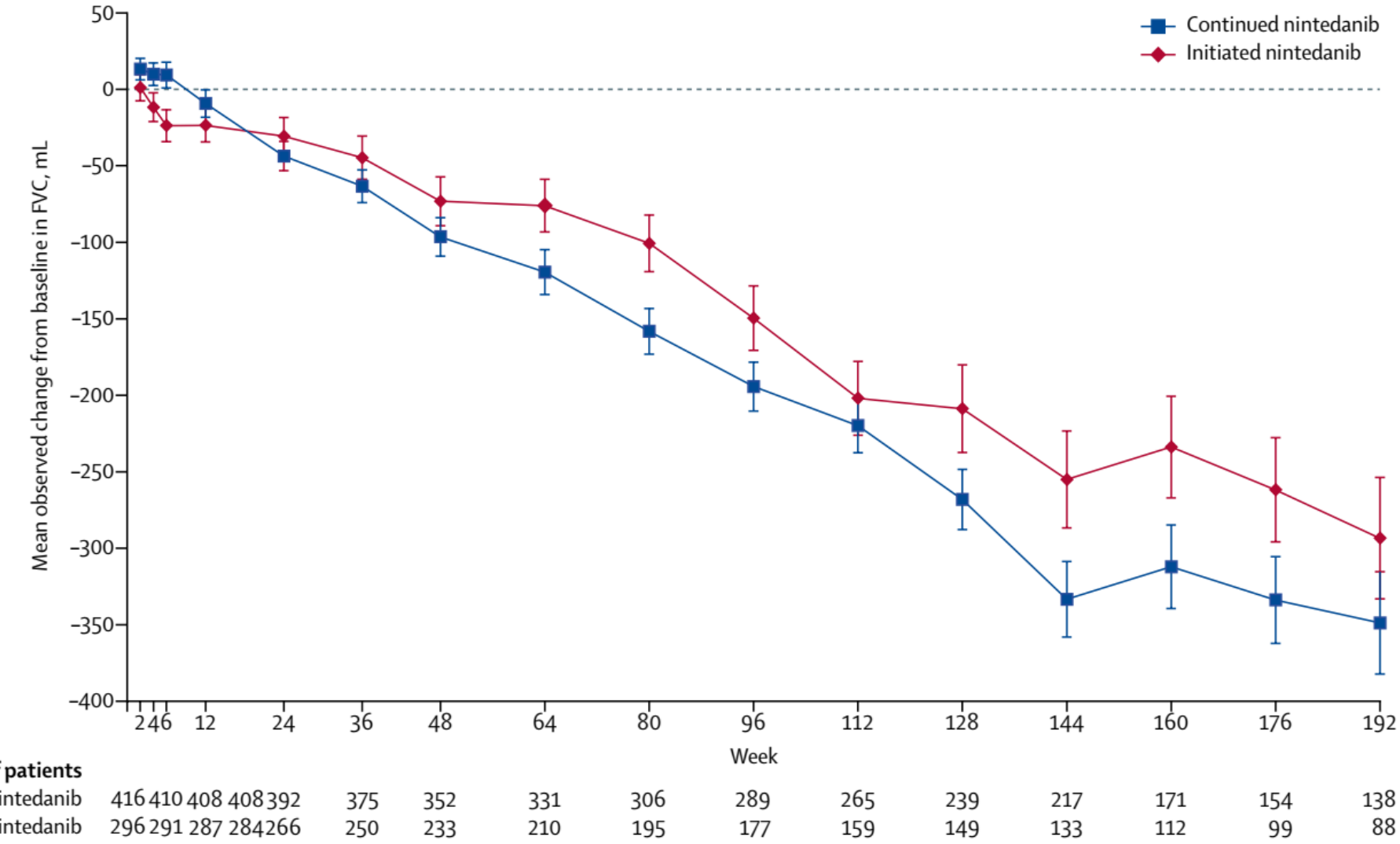
Long-term safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis: results from the open-label extension study, INPULSIS-ON

Bruno Crestani, John T Huggins, Mitchell Kaye, Ulrich Costabel, Ian Glaspole, Takashi Ogura, Jin Woo Song, Wibke Stansen, Manuel Quaresma, Susanne Stowasser, Michael Kreuter



Lancet Respir Med 2019;7: 60–68

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	138
Initiated nintedanib	296	291	287	284	266	250	233	210	195	177	159	149	133	112	99	88

Lancet Respir Med 2019;7: 60–68

Major adverse CV events, MI, and bleeding

	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)
Major adverse cardiovascular events	26	4·4	11	2·7	40	3·6	17	2·4
Myocardial infarction (broad scope)	18	3·0	5	1·2	14	1·3	5	0·7
Myocardial infarction (narrow scope)	11	1·8	2	0·5	13	1·2	4	0·6
Bleeding	94	15·8	42	10·2	93	8·4	48	6·7

Major adverse cardiovascular events were based on fatal adverse events included in the Medical Dictionary for Regulatory Activities (MedDRA) system organ classes "cardiac disorders" and "vascular disorders"; fatal and non-fatal events in the subordinate standardised MedDRA query (SMQ) "myocardial infarction"; stroke based on selected preferred terms from the subordinate SMQs "haemorrhagic cerebrovascular conditions" and "ischemic cerebrovascular conditions"; and the MedDRA preferred terms "sudden death", "cardiac death", and "sudden cardiac death". Myocardial infarction was based on events in the subordinate SMQ "myocardial infarction". SMQs include narrow and broad terms; narrow terms are those that are highly likely to represent the condition of interest whereas broad terms are all possible cases, including some that may prove to be of little or no interest on closer inspection. Bleeding was based on the SMQ "haemorrhage terms [excluding laboratory terms]".

Lancet Respir Med 2019;7: 60–68

ASCEND

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., Ian Glaspole, M.B., B.S., Ph.D., Marilyn K. Glassberg, M.D., Eduard Gorina, M.D., Peter M. Hopkins, M.D., David Kardatzke, Ph.D., Lisa Lancaster, M.D., David J. Lederer, M.D., Steven D. Nathan, M.D., Carlos A. Pereira, M.D., Steven A. Sahn, M.D., Robert Sussman, M.D., Jeffrey J. Swigris, D.O., and Paul W. Noble, M.D., for the ASCEND Study Group*

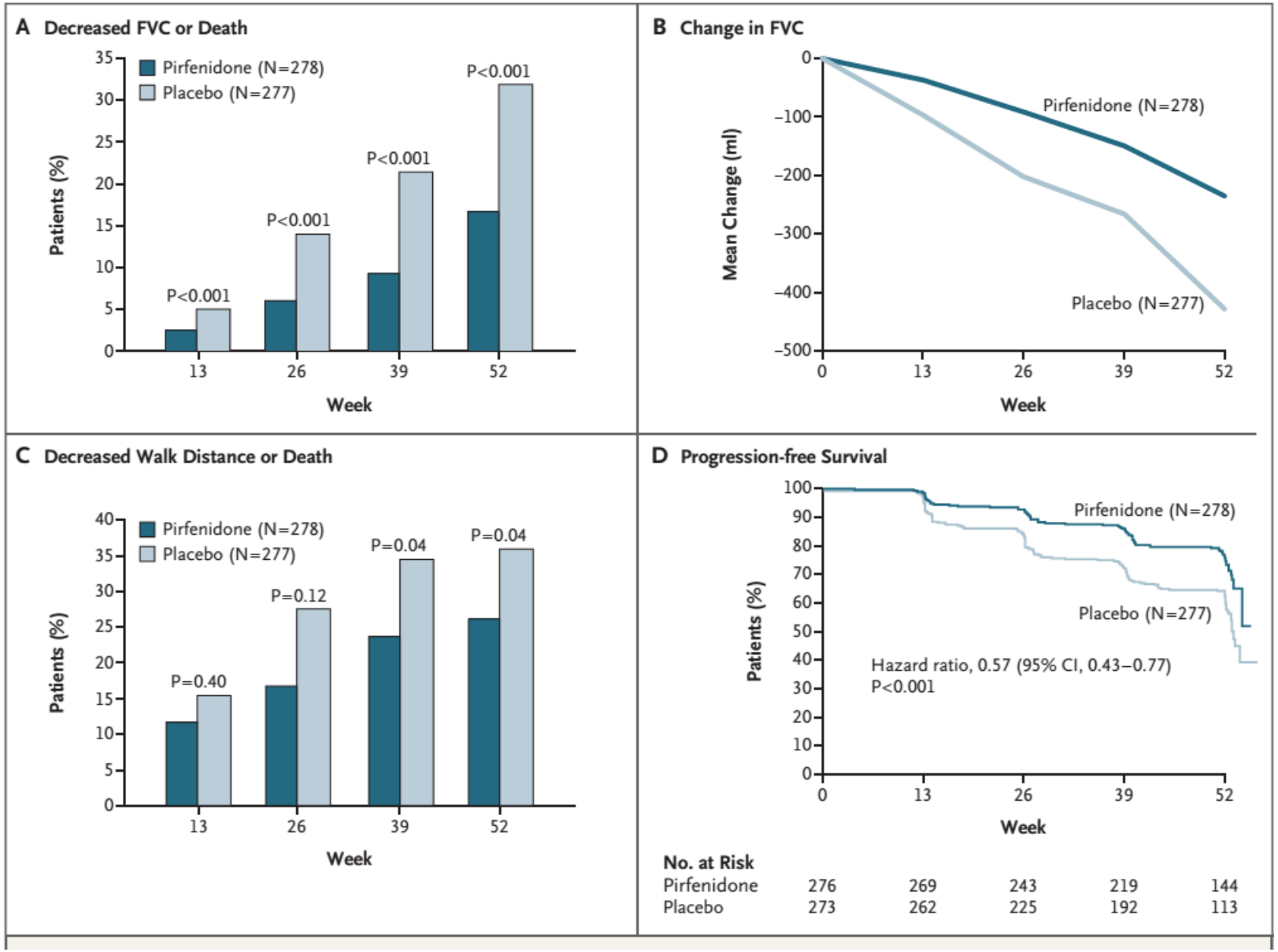
ASCEND- Inclusion criteria

- 555 patients
- 127 sites in 9 countries Pirefenidone 2403mg : placebo 1:1
- 40–80 years
- 50% ≤FVC ≤ 90%
- 30% ≤ DLco ≤ 90%
- 6MWD ≥150 m

King, Jr et al. N Engl J Med 2014;370:2083-92

Primary and Secondary outcome

ASCEND



King, Jr et al. N Engl J Med 2014;370:2083-92

Mortality

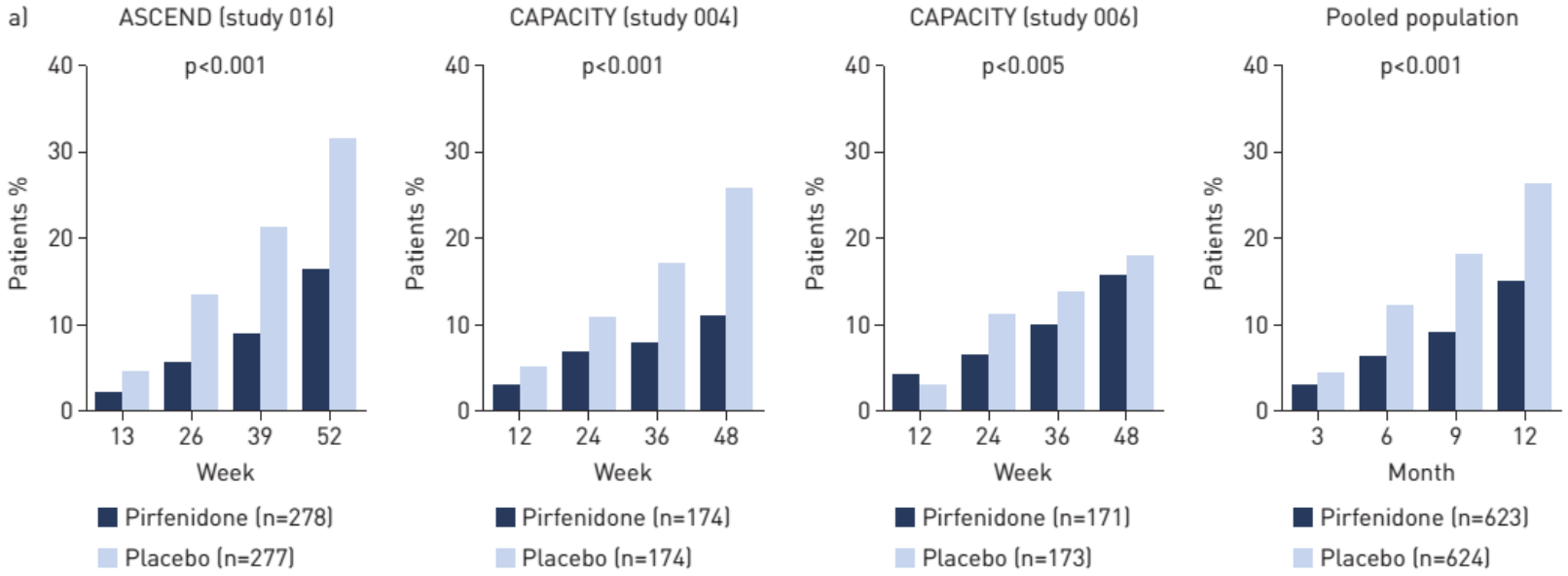
ASCEND & CAPACITY

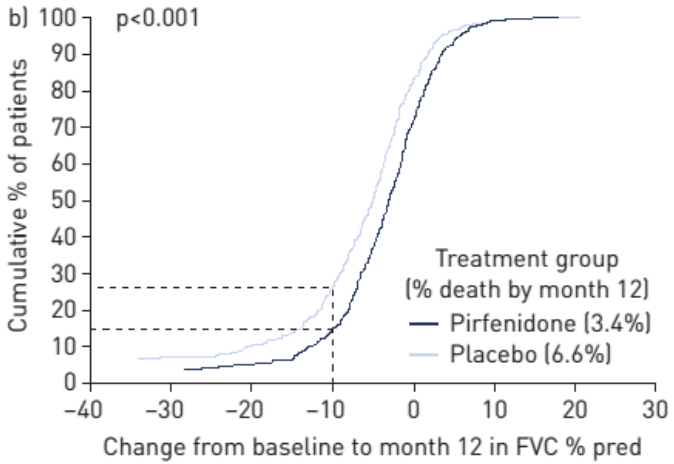
Variable	Pirfenidone	Placebo	Hazard Ratio (95% CI)†	P Value‡
ASCEND trial				
No. of patients	278	277		
Death — no. (%)				
From any cause	11 (4.0)	20 (7.2)	0.55 (0.26–1.15)	0.10
Related to idiopathic pulmonary fibrosis§	3 (1.1)	7 (2.5)	0.44 (0.11–1.72)	0.23
Pooled data from ASCEND and CAPACITY trials				
No. of patients	623	624		
Death — no. (%)				
From any cause	22 (3.5)	42 (6.7)	0.52 (0.31–0.87)	0.01
Related to idiopathic pulmonary fibrosis§	7 (1.1)	22 (3.5)	0.32 (0.14–0.76)	0.006

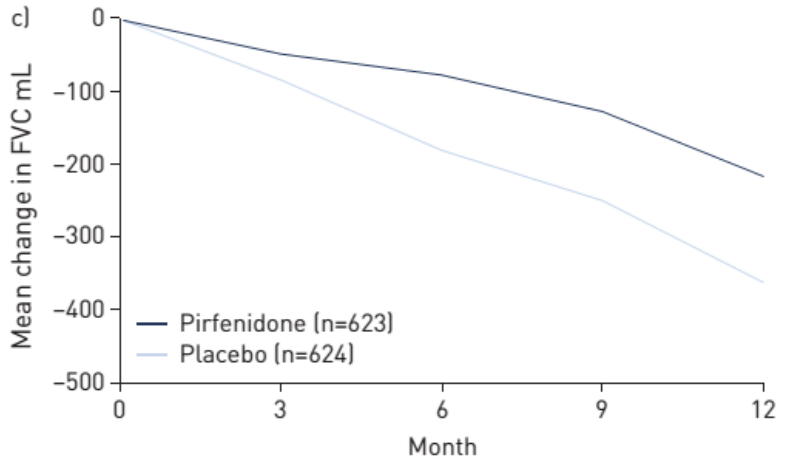
King, Jr et al. N Engl J Med 2014;370:2083-92

Pooled data from ASCEND and CAPACITY

Proportion of patients with (FVC) % decline ⩾10% or death







Absolute difference mL	36	104	123	148
Relative difference %	43.5	57.3	49.1	40.7
Rank ANCOVA p-value	<0.001	<0.001	<0.001	<0.001

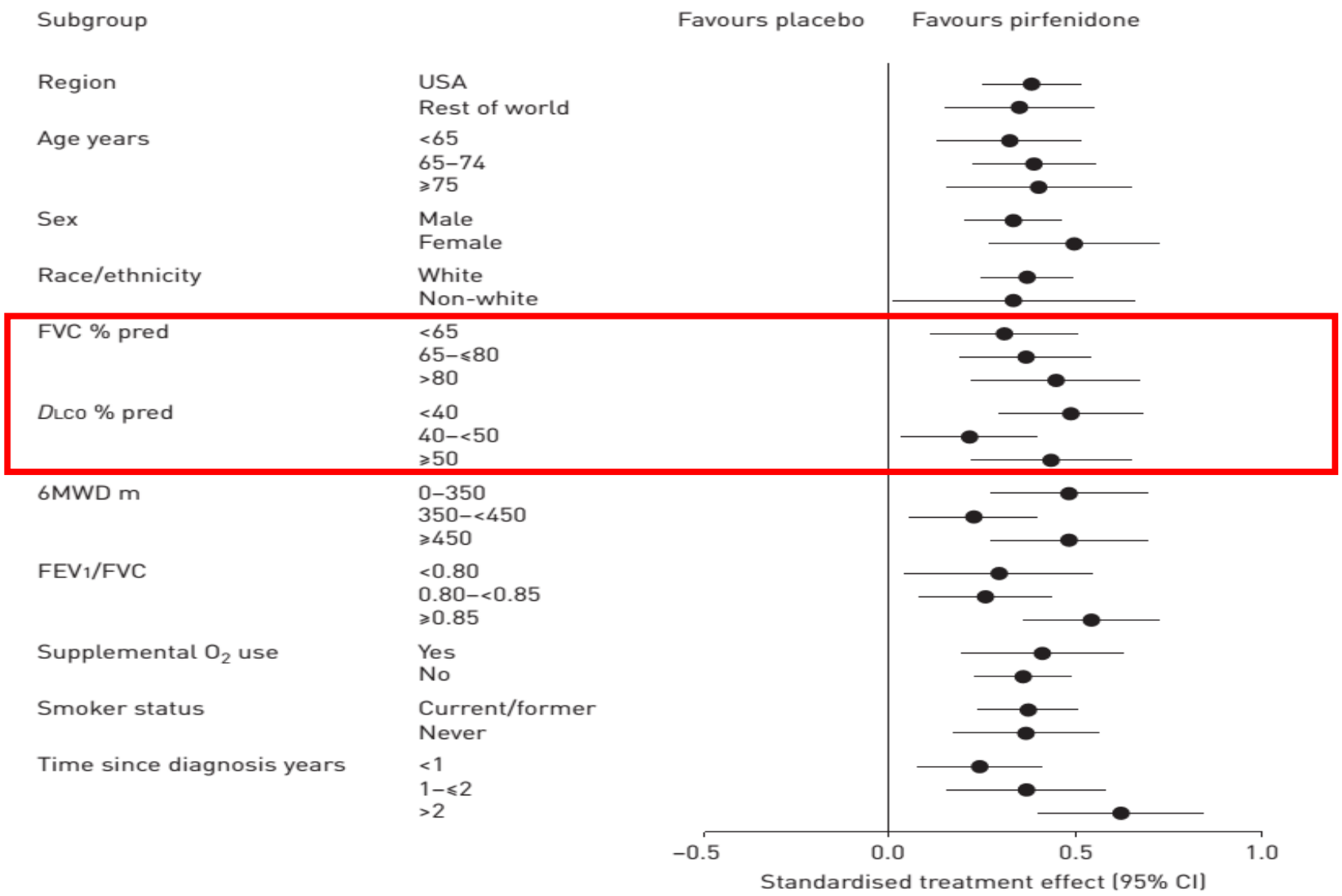
Noble et al. Eur Respir J 2016; 47: 243–253

Disease progression proportions (Post-hoc analysis of CAPACITY/ASCEND)

Outcome at 12 Months	Baseline FVC ≥80%	Baseline FVC <80%	Baseline GAP Stage I	Baseline GAP Stage II-III
Pooled placebo population, n	170	454	235	387
FVC, % of patients				
≥10% decline or death	21.8	28.0	21.7	28.9
No decline	21.2	16.3	20.4	15.8
6MWD, % of patients				
≥50-m decline or death	24.1	38.8	26.6	39.7
No decline	37.3	33.4	37.3	32.9
UCSD SOBQ, % of patients				
≥20-point change in UCSD SOBQ score or death	18.0	36.4	21.4	37.5
No decline	37.1	24.9	36.8	23.1

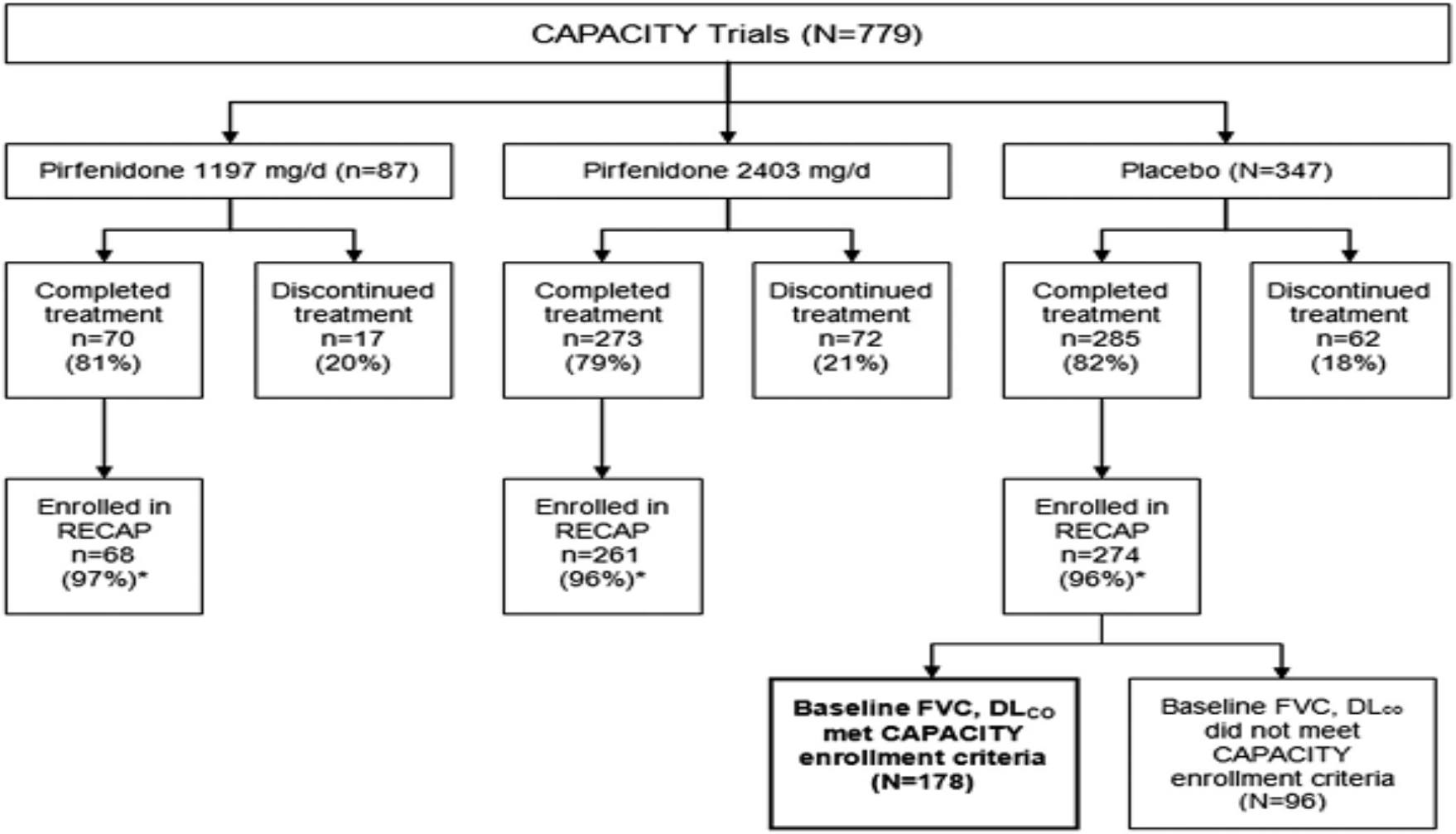
Albera et. Al Eur Respir J 2016;48:843-851

Pooled data from ASCEND and CAPACITY



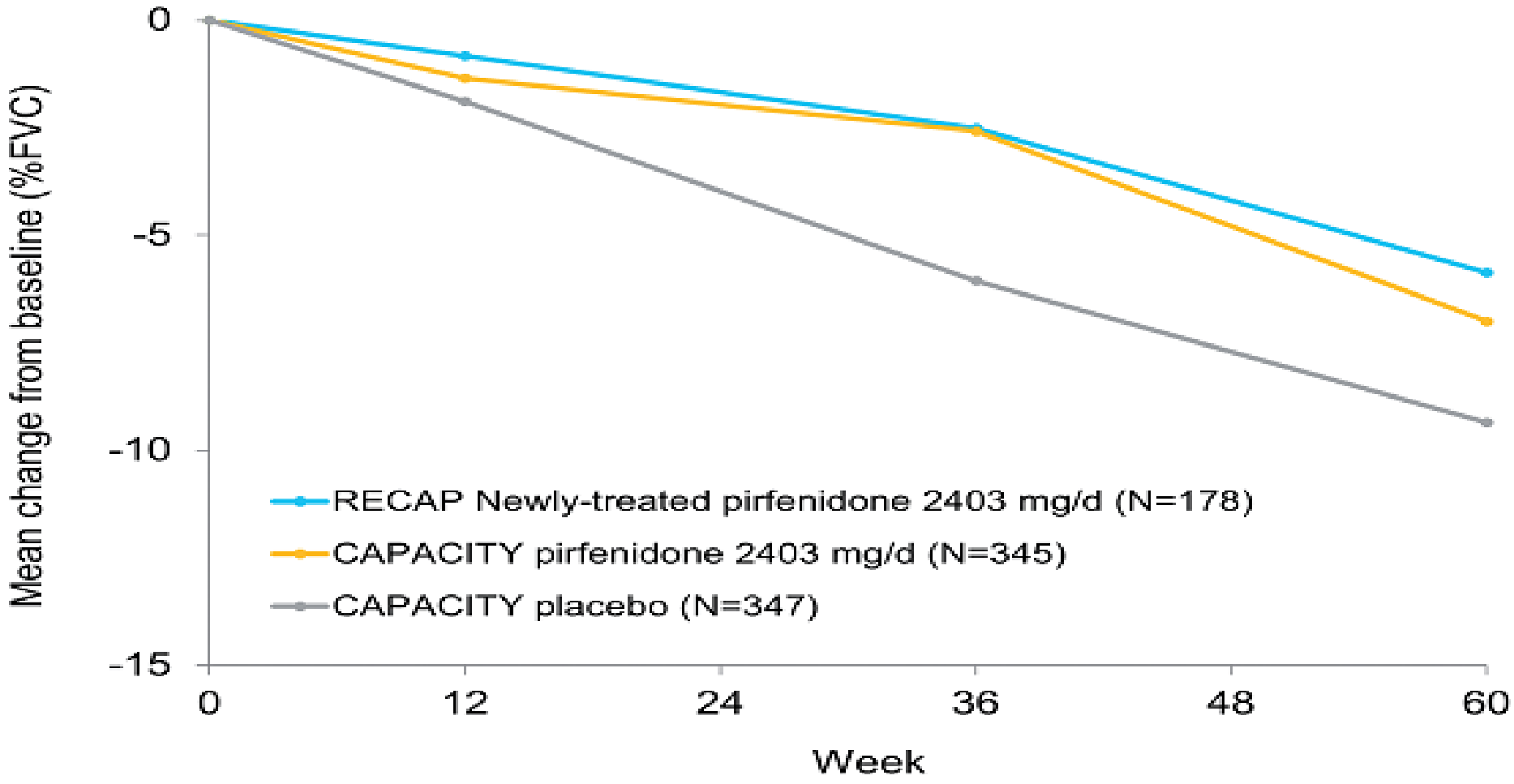
Noble et al. Eur Respir J 2016; 47: 243–253

RECAP: An open-label extension of pirfenidone in IPF



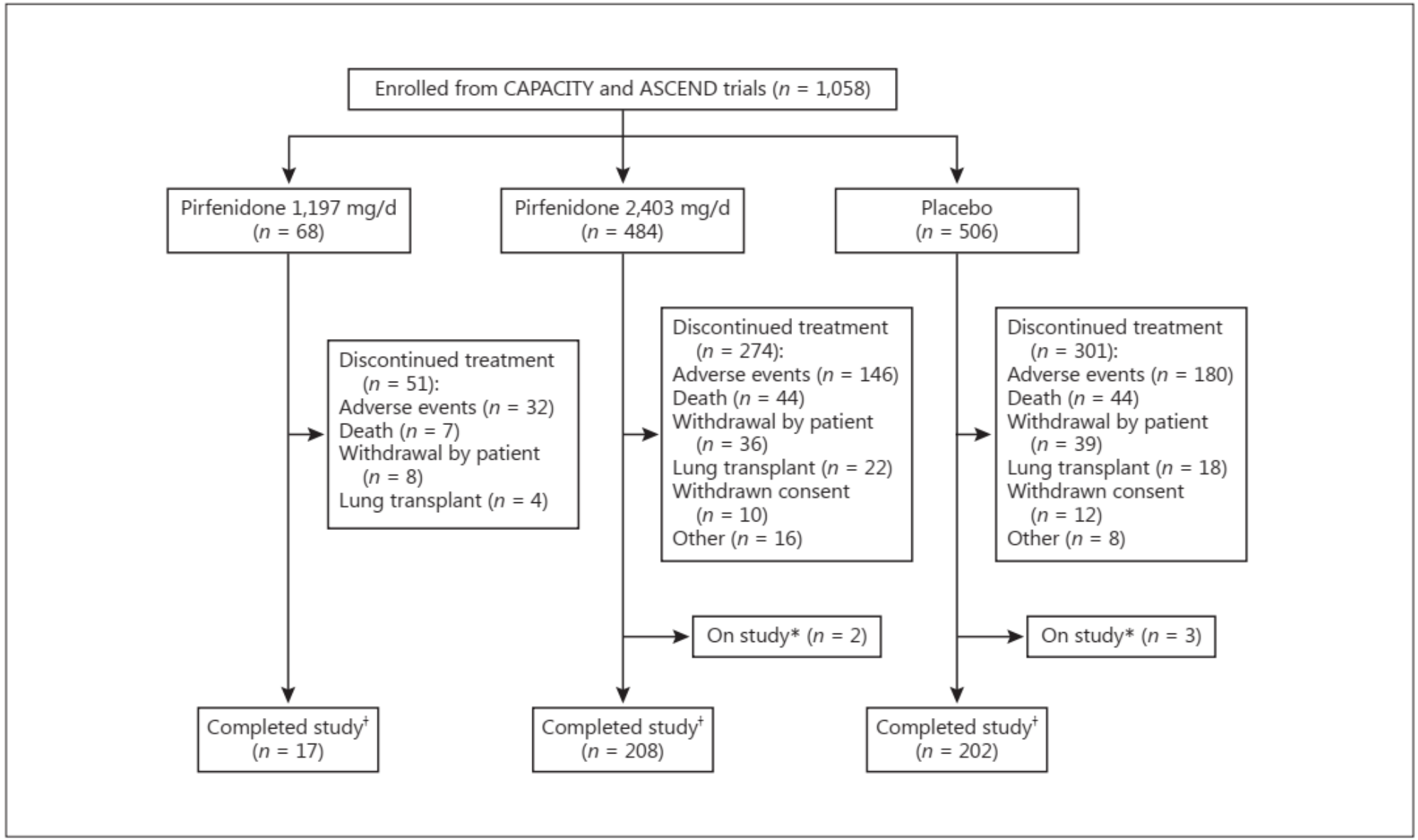
Costabel et al. Sardoidosis Vasc Diffuse Lung Dis. 2014;31:198-205

RECAP: An open-label extension of pirfenidone in IPF



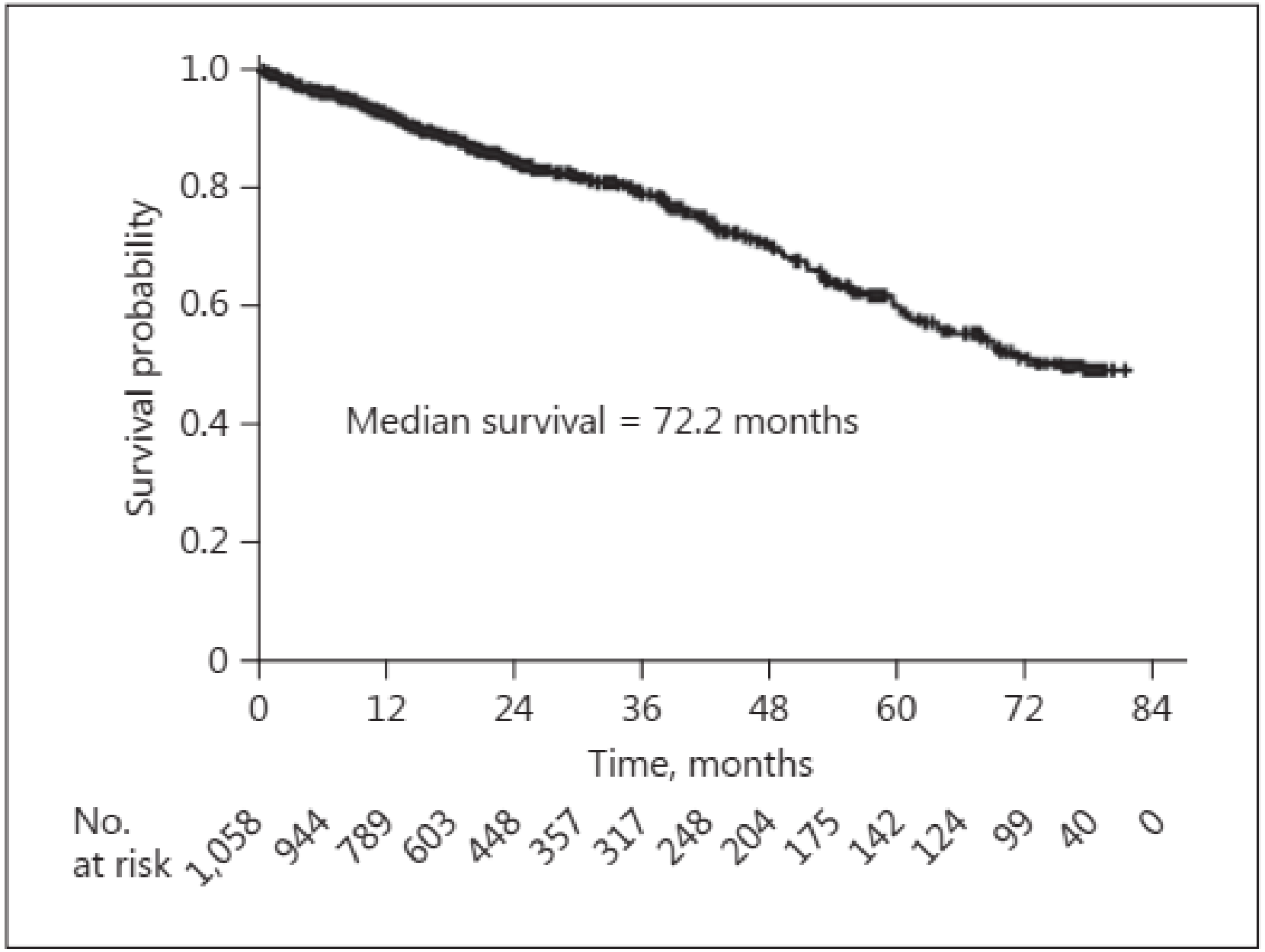
Costabel et al. Sardoidosis Vasc Diffuse Lung Dis. 2014;31:198-205

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



Costabel et al. Respiration 2017;94:408–415

RECAP: On-treatment survival from the first dose of pirfe



Costabel et al. Respiration 2017;94:408–415

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Randomized Trial of Acetylcysteine in Idiopathic Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network*

ABSTRACT

N Engl J Med 2014;370:2093-101.

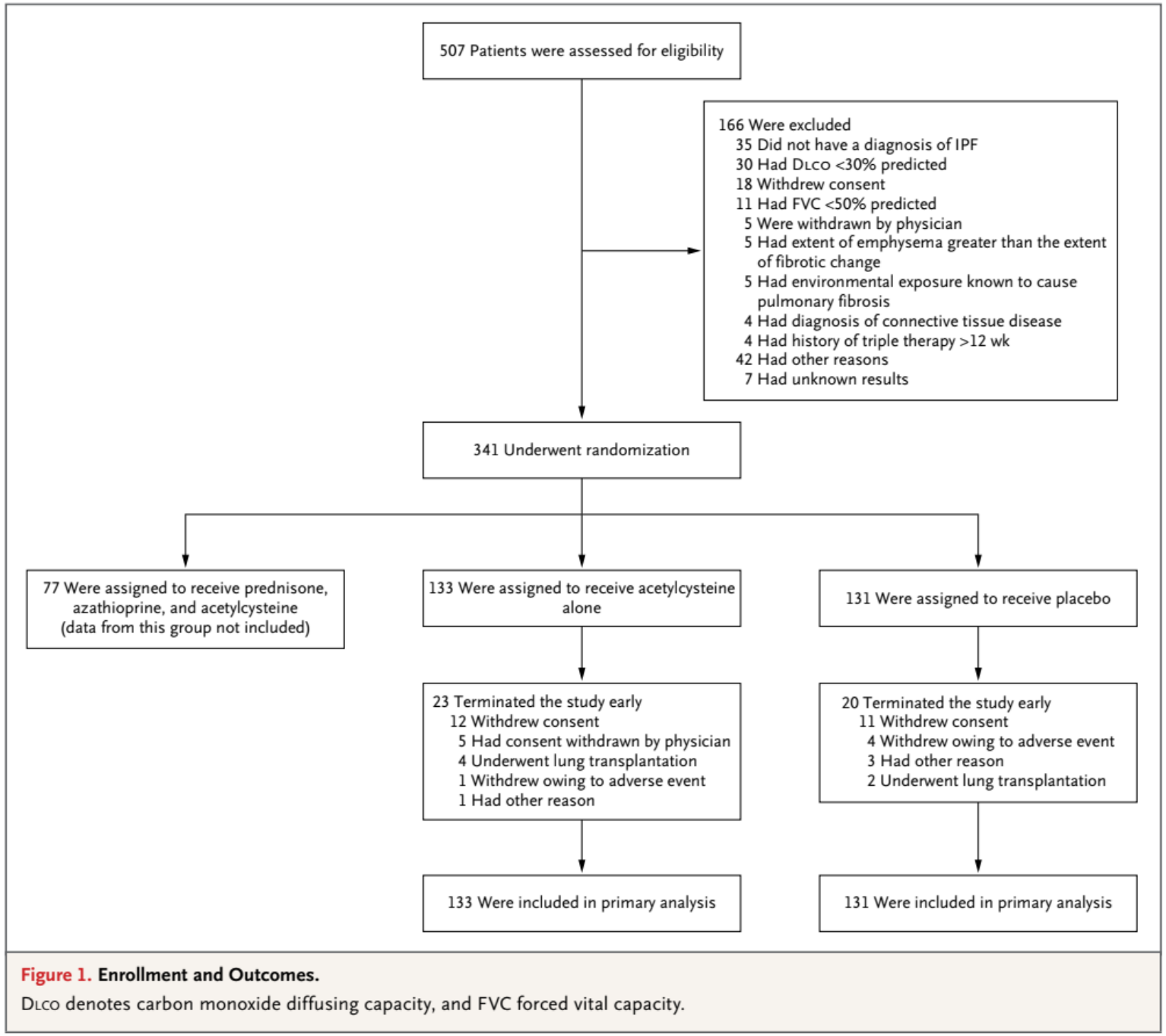
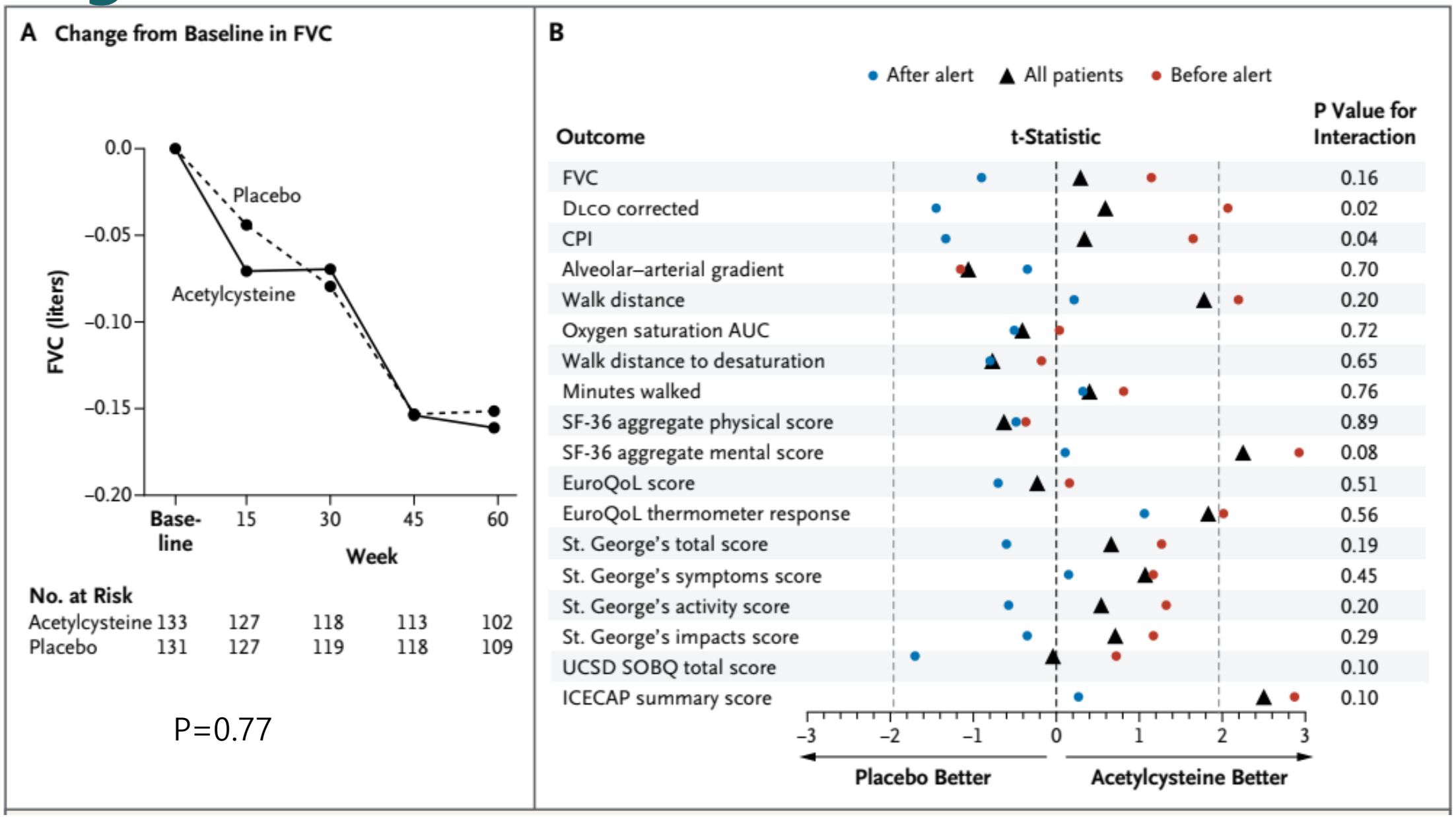


Figure 1. Enrollment and Outcomes.

DLCO denotes carbon monoxide diffusing capacity, and FVC forced vital capacity.

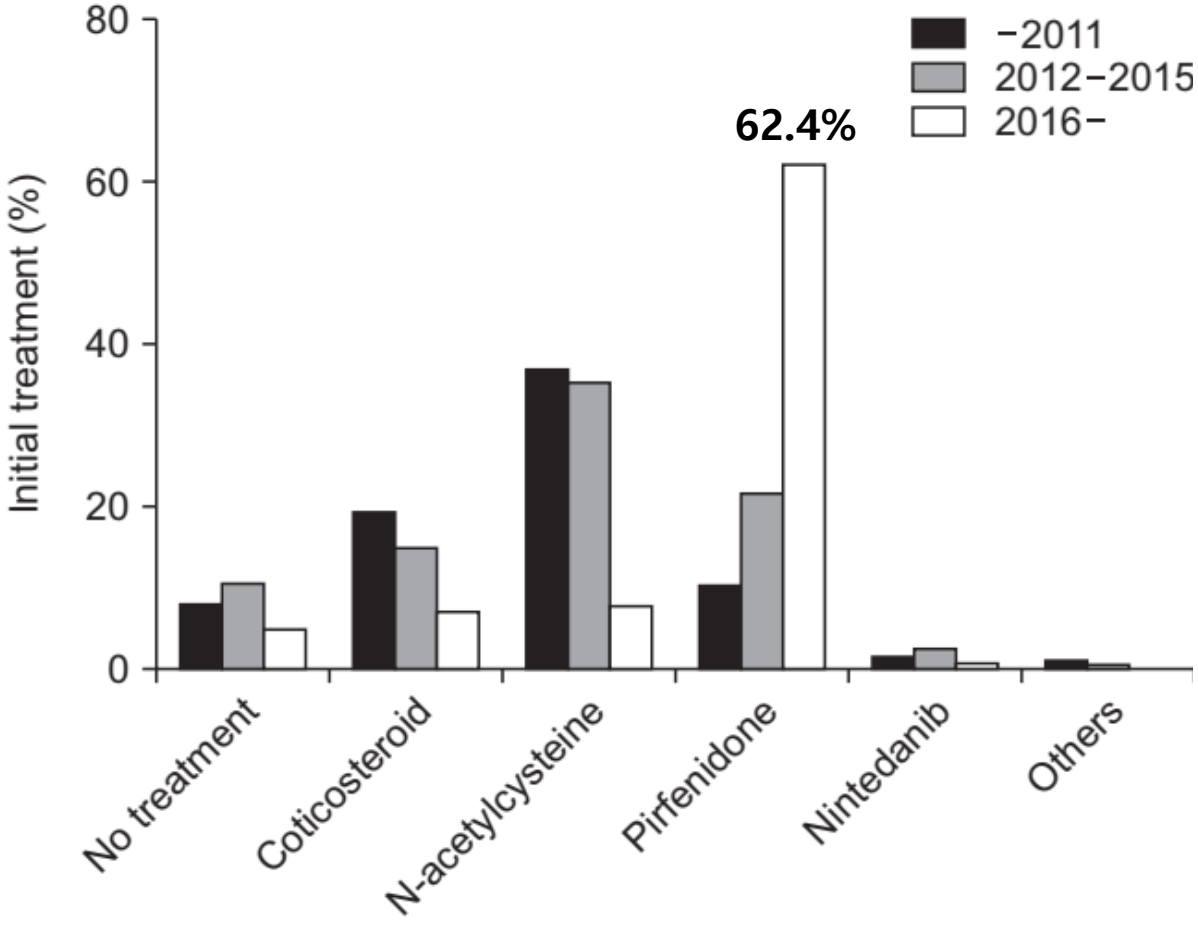
Engl J Med 2014;370:2093-101.

Changes from baseline in FVC

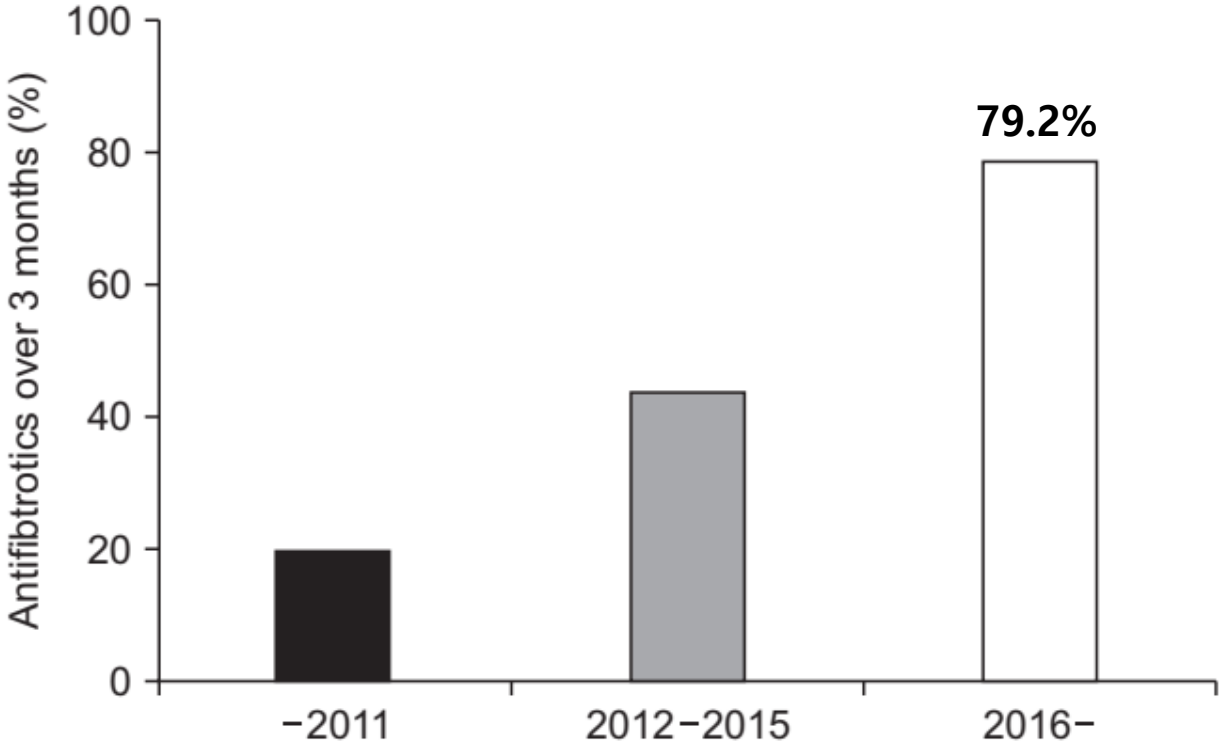


N Engl J Med 2014;370:2093-101.

Treatment of IPF in Korea



Initial Treatment



Treatment with antifibrotics over 3months

Tuberc Respir Dis, Published online Dec. 13, 2021

ORIGINAL ARTICLE

TOLLIP, *MUC5B*, and the Response to *N*-Acetylcysteine among Individuals with Idiopathic Pulmonary Fibrosis

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- chromosome 11p15.5
- *TOLLIP* encodes toll interacting protein (TOLLIP)

  : inhibitory adaptor protein acting downstream from the toll-like receptors(TLRs).
- *MUC5B* encodes a highly glycosylated mucin-5B precursor protein (Mucin-5B)

  :contributes to airway mucus production

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PANTHER cohort baseline characteristics &genotypes

Characteristic	Genotyped (*n* = 154)			Nongenotyped (*n* = 161)			*P* Value
	Placebo Arm (*n* = 54)	NAC Arm (*n* = 60)	PAN Arm (*n* = 40)	Placebo Arm (*n* = 66)	NAC Arm (*n* = 61)	PAN Arm (*n* = 34)	
Age, mean (SD)	66.1 (7.9)	67.9 (8.7)	69.7 (6.8)	66.8 (8.2)	67.8 (8.2)	67 (7.7)	0.39
Male, n (%)	39 (72.2)	47 (78.3)	31 (77.5)	53 (80.3)	51 (83.6)	27 (79.4)	0.79
Ever-smoker, n (%)	41 (75.9)	44 (73.3)	28 (70)	50 (75.8)	46 (76.7)	24 (70.6)	0.96
FVC, % predicted, mean (SD)	73.2 (14.7)	73 (15.7)	71.2 (15.2)	74 (13.8)	73 (15.8)	67.6 (15.5)	0.43
D_{LCO}, % predicted, mean (SD)	46.4 (11.7)	43.9 (10.9)	43 (10.6)	44.7 (12.1)	46.2 (10.8)	39.9 (9.4)	0.11
Death, n (%)	2 (3.7)	1 (1.7)	4 (10)	1 (1.5)	3 (4.9)	4 (11.8)	0.1
FVC decline ⩾ 10%, n (%)	12 (22.2)	11 (18.3)	6 (15)	17 (25.8)	17 (27.9)	3 (8.8)	0.23
Hospitalization, n (%)	8 (14.8)	8 (13.3)	13 (32.5)	10 (15.2)	9 (14.8)	8 (23.5)	0.17
Transplant, n (%)	1 (1.9)	3 (5)	1 (2.5)	1 (1.5)	1 (1.6)	1 (2.9)	0.45
Composite endpoint,† n (%)	17 (31.5)	19 (31.7)	19 (47.5)	24 (36.4)	26 (42.6)	12 (35.3)	0.52
SNP (gene) genotype, n (%)							
rs5743890 (*TOLLIP*) AA/AG/GG	43/10/0 (81/19/0)	52/8/0 (87/13/0)	30/6/0 (83/17/0)	—	—	—	0.72
rs5743894 (*TOLLIP*) AA/AG/GG	29/21/4 (54/39/7)	31/25/4 (52/42/6)	18/17/5 (45/43/12)	—	—	—	0.83
rs3750920 (*TOLLIP*) CC/CT/TT	14/23/17 (26/43/31)	13/30/16 (22/51/27)	6/24/10 (15/60/25)	—	—	—	0.55
rs5743854 (*TOLLIP*) CC/CG/GG	44/10/0 (81/19/0)	55/5/0 (92/8/0)	37/3/0 (93/7/0)				0.19
rs35705950 (*MUC5B*) GG/GT/TT	20/29/5 (37/54/9)	14/42/4 (23/70/7)	11/23/6 (28/57/15)	—	—	—	0.3

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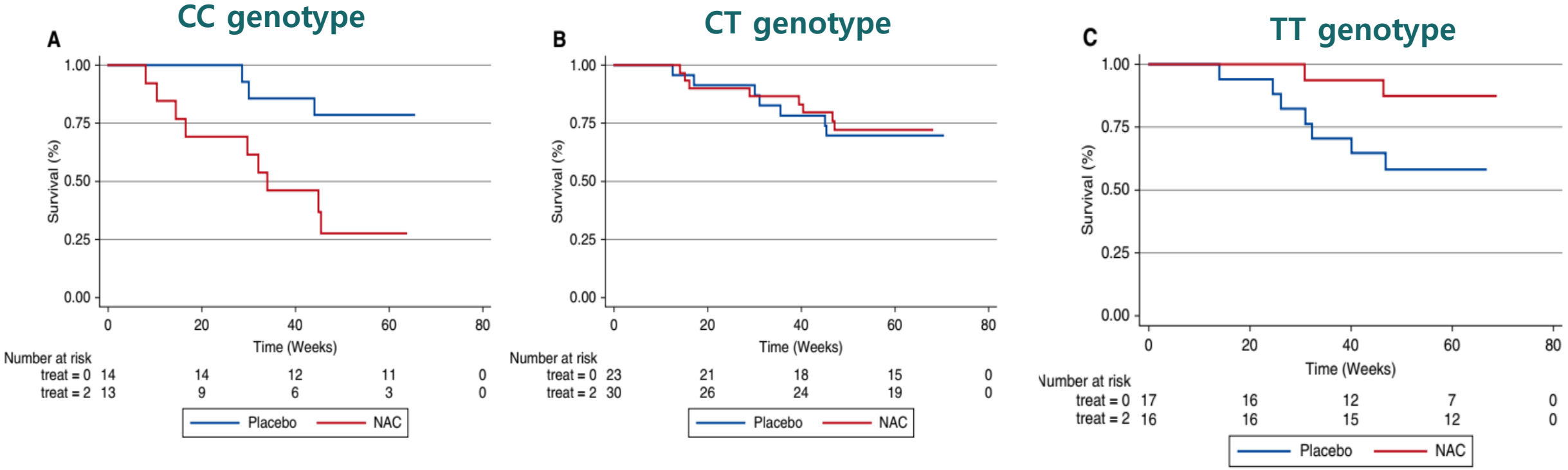
Composite endpoint-free survival



This investigation demonstrates that the genetic makeup of individuals with IPF may influence their response to N-acetylcysteine therapy. These findings also highlight the importance of pharmacogenetics in IPF and support systematic biospecimen collection in IPF clinical trials so that genetic subgroups predisposed to treatment-related benefit or harm can be identified.

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BMC Pulmonary Medicine

STUDY PROTOCOL Open Access

Design and rationale for the prospective treatment efficacy in IPF using genotype for NAC selection (PRECISIONS) clinical trial

Anna J. Podolanczuk[1*†], John S. Kim[2†], Christopher B. Cooper[3], Joseph A. Lasky[4], Susan Murray[5], Justin M. Oldham[6], Ganesh Raghu[7], Kevin R. Flaherty[6], Cathie Spino[5], Imre Noth[2], Fernando J. Martinez[1] and for the PRECISIONS Study Team

Abstract

Background: Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease with few treatment options. *N*-acetylcysteine (NAC) is a well-tolerated, inexpensive treatment with antioxidant and anti-fibrotic properties. The National Heart, Lung, and Blood Institute (NHLBI)-sponsored PANTHER (Prednisone Azathioprine and NAC therapy in IPF) trial confirmed the harmful effects of immunosuppression in IPF, and did not show a benefit to treatment with NAC. How-

Methods: The PRECISIONS trial will randomize 200 patients with IPF and the *TOLLIP* rs3750920 TT genotype 1:1 to oral *N*-acetylcysteine (600 mg tablets taken three times a day) or placebo for a 24-month duration. The primary

lung transplantation, or death from any cause. Secondary endpoints include change in patient-reported outcome scores and proportion of participants with treatment-emergent adverse events. Biospecimens, including blood, buccal, and fecal will be collected longitudinally for future research purposes. Study participants will be offered enrollment in a home spirometry substudy, which explores time to 10% relative FVC decline measured at home, and its comparison with study visit FVC.

Discussion: The sentinel observation of a potential pharmacogenetic interaction between NAC and *TOLLIP* polymorphism highlights the urgent, unmet need for better, molecularly focused, and precise therapeutic strategies in IPF. The PRECISIONS clinical trial is the first study to use molecularly-focused techniques to identify patients with IPF most likely to benefit from treatment. PRECISIONS has the potential to shift the paradigm in how trials in this condition are designed and executed, and is the first step toward personalized medicine for patients with IPF.

Future Treatment

- Anti Connective tissue growth factor Ab
  :Pamrevlumab (FG-3019)

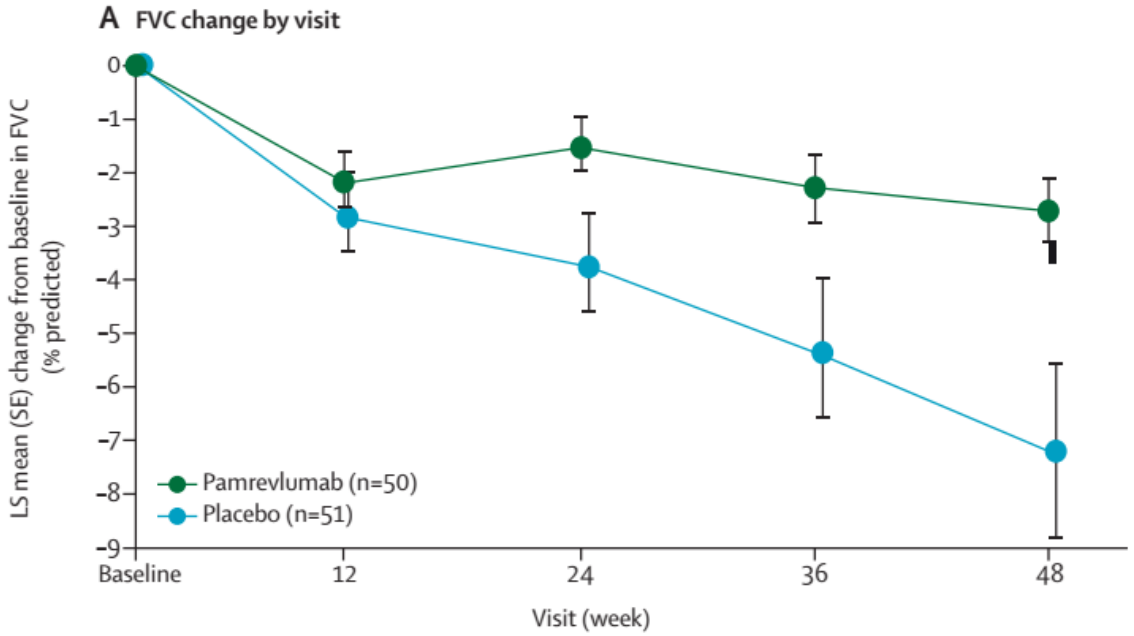
- Preferential Phosphodiesterase 4B
  : BI 1015550

Pamrevlumab, an anti-connective tissue growth factor therapy, for idiopathic pulmonary fibrosis (PRAISE): a phase 2, randomised, double-blind, placebo-controlled trial

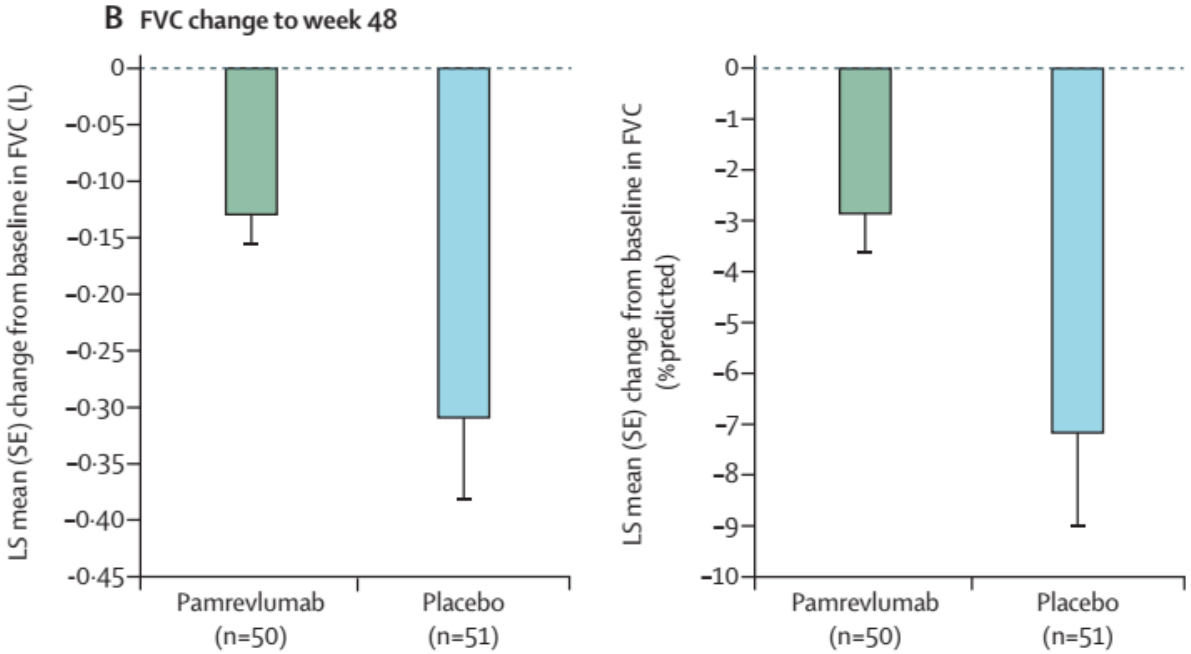
Luca Richeldi, Evans R Fernández Pérez, Ulrich Costabel, Carlo Albera, David J Lederer, Kevin R Flaherty, Neil Ettinger, Rafael Perez, Mary Beth Scholand, Jonathan Goldin, Kin-Hung Peony Yu, Thomas Neff, Seth Porter, Ming Zhong, Eduard Gorina, Elias Kouchakji, Ganesh Raghu*

Richeldi et al. Lancet Respir Med 2020;8: 25–33

PRAISE : phase 2



Pamrevlumab	−2·2 (0·6)	−1·5 (0·5)	−2·3 (0·7)	−2·7 (0·6)
Placebo	−2·8 (0·8)	−3·8 (0·9)	−5·3 (1·3)	−7·2 (1·7)
Absolute difference	0·6 (0·9)	2·3 (1·1)	3·0 (1·5)	4·5 (1·8)
95% CI	(−1·3 to 2·5)	(0·1 to 4·4)	(0·1 to 6·0)	(0·9 to 8·0)
Relative difference	22·2%	59·8%	57·0%	62·4%
p value	0·51	0·042	0·044	0·014



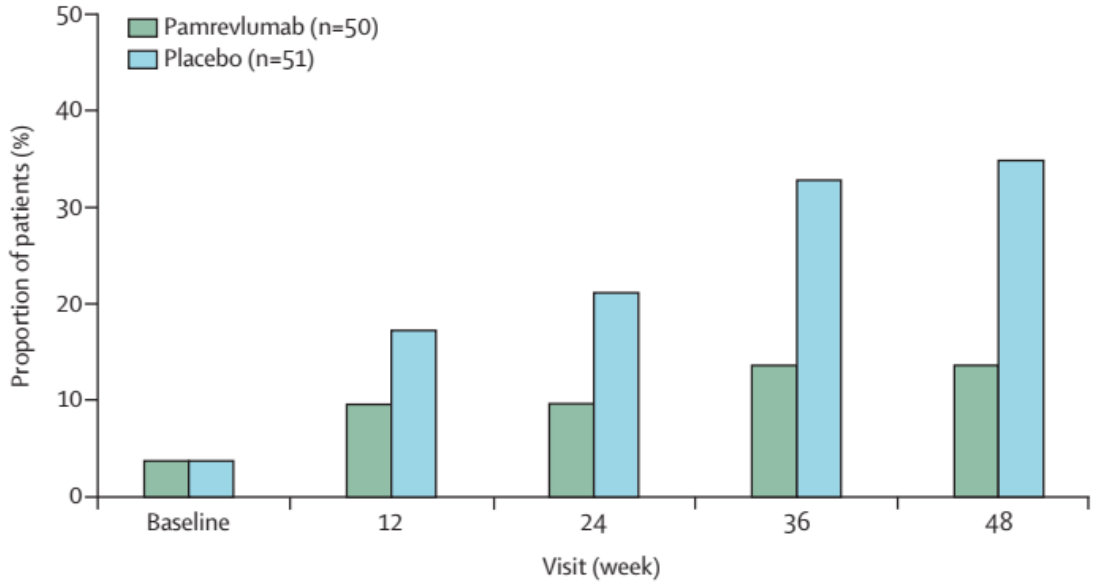
LS mean (SE)	−0·1 (0)	−0·3 (0·1)	−2·9 (0·8)	−7·2 (1·9)
95% CI of LS mean	(−0·2 to −0·1)	(−0·5 to −0·2)	(−4·4 to −1·3)	(−10·8 to −3·5)
Absolute difference	0·2 (0·1)		4·3 (2·0)	
95% CI of difference	(0·0 to 0·3)		(0·4 to 8·3)	
Relative difference	57·9%		60·3%	
p value	0·025		0·033	

Richeldi et al. Lancet Respir Med 2020;8: 25–33

PRAISE : phase 2

	Pamrevlumab (n=50)	Placebo (n=53)
Any adverse event*	48 (96%)	52 (98%)
Serious adverse events	12 (24%)	8 (15%)
All reported deaths†	3 (6%)	6 (11%)
Adverse events leading to treatment or study discontinuation	10 (20%)	10 (19%)
Serious adverse events leading to treatment or study discontinuation	3 (6%)	7 (13%)
Infusion-associated adverse events	20 (40%)	14 (26%)
Most frequent adverse events‡		
Respiratory tract infection	15 (30%)	11 (21%)
Cough	14 (28%)	23 (43%)
Dyspnoea	14 (28%)	11 (21%)
Idiopathic pulmonary fibrosis	10 (20%)	9 (17%)
Fatigue	10 (20%)	4 (8%)
Urinary tract infection	10 (20%)	4 (8%)
Nasopharyngitis	9 (18%)	5 (9%)
Sinusitis	8 (16%)	8 (15%)
Diarrhoea	8 (16%)	4 (8%)
Nausea	7 (14%)	7 (13%)
Headache	4 (8%)	6 (11%)
Bronchitis	2 (4%)	6 (11%)

FVC decline ≥10% or Death



Pamrevlumab	3 (6·0%)	3 (6·0%)	5 (10·0%)	5 (10·0%)
Placebo	7 (13·7%)	9 (17·6%)	15 (29·4%)	16 (31·4%)
Absolute difference	−7·7	−11·6	−19·4	−21·4
95% CI	(−19·2 to 3·8)	(−24·0 to 0·7)	(−34·4 to −4·4)	(−36·6 to −6·2)
Relative difference	−56·3%	−66·0%	−66·0%	−68·1%
p value	0·23	0·09	0·022	0·013

Richeldi et al. Lancet Respir Med 2020;8: 25–33

Phase 3 trial Zephyrus I

Title	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Pamrevlumab in Subjects With Idiopathic Pulmonary Fibrosis (IPF)
Study drugs	Pamrevlumab (30mg/kg iv every 3 weeks vs. placebo), 1:1 allocation
Inclusion criteria	IPF Dx <7 years, HRCT :≥10% to <50% reticulation and <25% honeycombing FVC >45% and <95%, DLco ≥25% and ≤90% Not currently receiving treatment for IPF with an approved therapy
Tx period	48 weeks
enrollment	356participants
Primary outcome	Change in FVC (L) [Time Frame: Baseline to Week 48]
Start date	June 18, 2019
Completion date	June 30, 2024

Phase 3 trial Zephyrus II

Title	Zephyrus II: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Pamrevlumab in Subjects With Idiopathic Pulmonary Fibrosis (IPF)
Study drugs	Pamrevlumab (30mg/kg iv every 3 weeks vs. placebo), 1:1 allocation
Inclusion criteria	IPF Dx <7 years, HRCT :≥10% to <50% reticulation and <25% honeycombing FVC >45% and <95%, DLco ≥25% and ≤90% Previously treated with an approved IPF therapy but discontinued at least 1 week prior
Tx period	48 weeks and open-label extension phase for 48weeks
Estimated enrollment	340 participants
Primary outcome	Time to Disease Progression [Time Frame: Up to Week 48]
Start date	September 30, 2020
Completion date	May 31, 2023

Preferential Phosphodiesterase 4B

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of a Preferential Phosphodiesterase 4B Inhibitor for Idiopathic Pulmonary Fibrosis

Luca Richeldi, M.D., Ph.D., Arata Azuma, M.D., Ph.D., Vincent Cottin, M.D., Ph.D., Christian Hesslinger, Ph.D., Susanne Stowasser, M.D., Claudia Valenzuela, M.D., Marlies S. Wijsenbeek, M.D., Ph.D., Donald F. Zoz, M.D., Florian Voss, Ph.D., and Toby M. Maher, M.D., Ph.D., for the 1305-0013 Trial Investigators*

Richeldi et al. N Engl J Med 2022;386:2178-87.

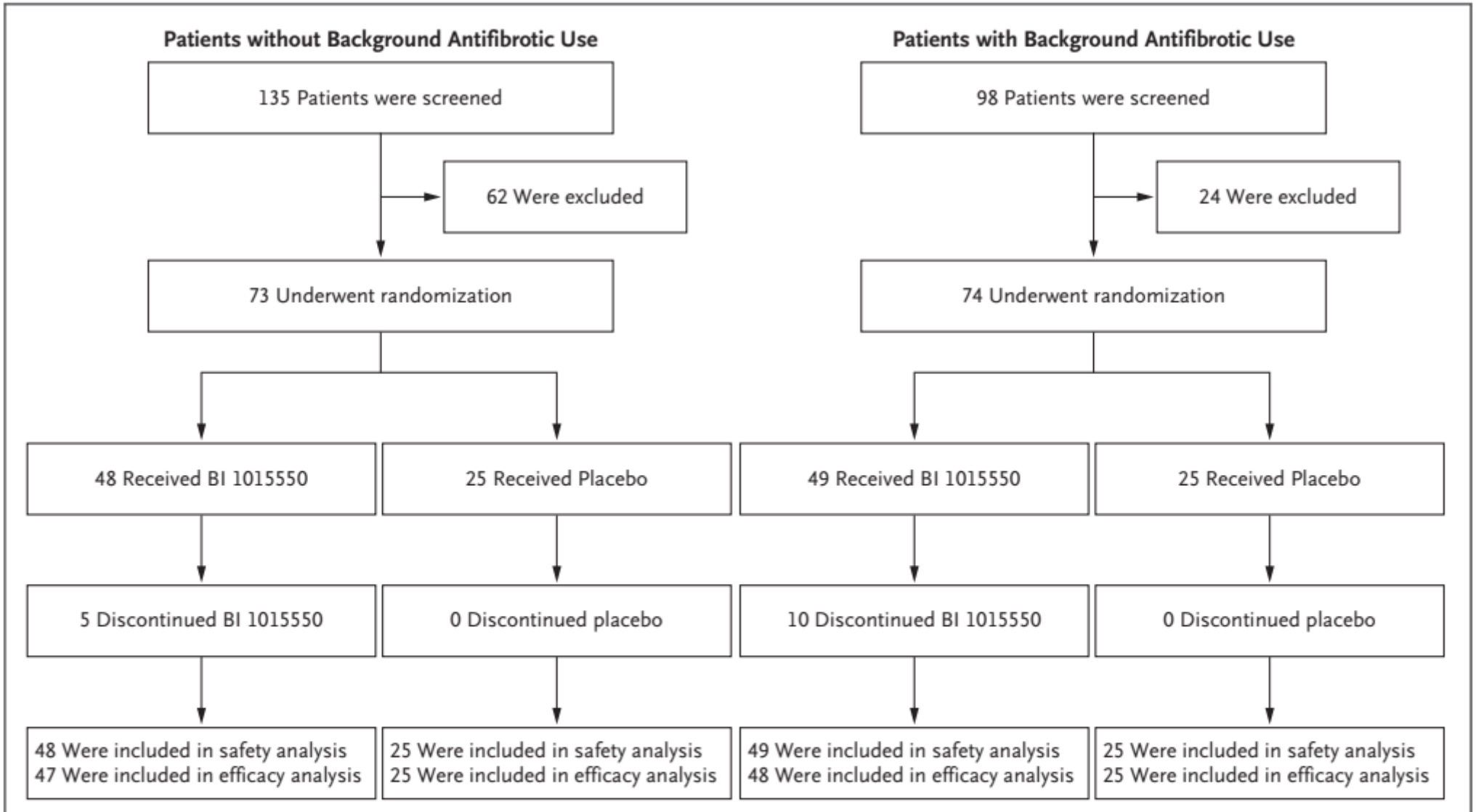
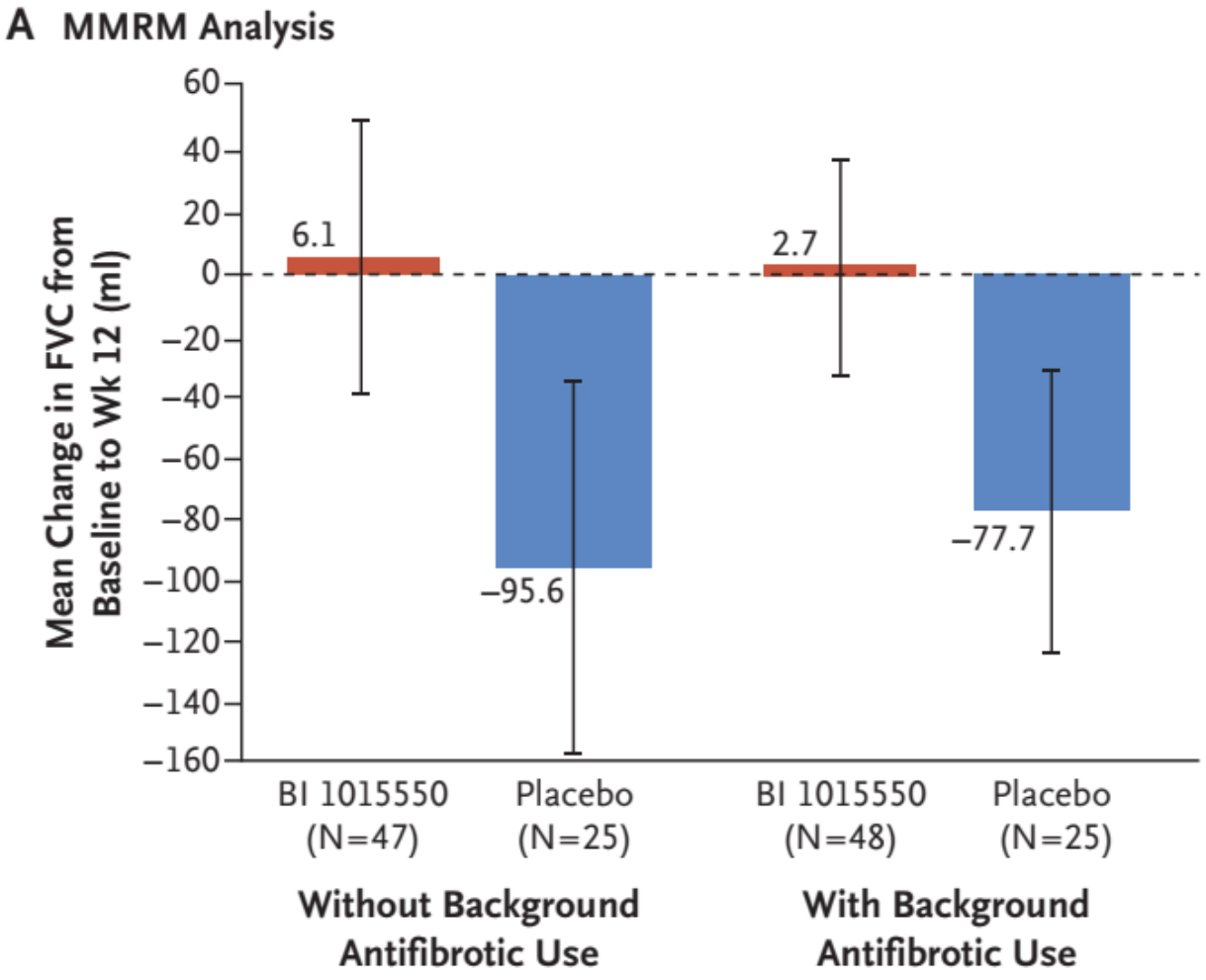


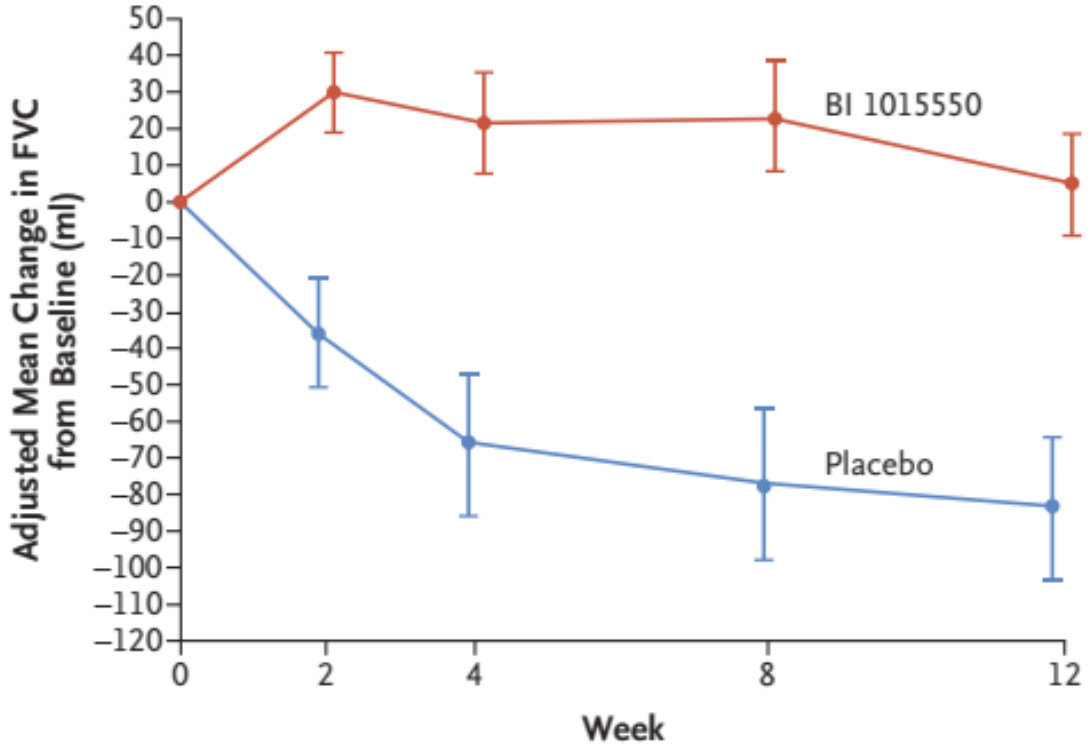
Figure 1. Randomization and Follow-up of the Patients.

Among patients without background antifibrotic use, reasons for premature discontinuation of BI 1015550 included adverse events (in three patients), withdrawal from the trial (in one), and other reason (in one). Among patients with background antifibrotic use, all those who prematurely discontinued BI 1015550 did so because of adverse events. Two patients (one in each cohort) were not included in the efficacy analysis because they did not have postbaseline data on lung function.

Richeldi et al. N Engl J Med 2022;386:2178-87.

Mean change in FVC





No. of Patients				
BI 1015550	90	89	87	81
Placebo	49	50	50	49

Richeldi et al. N Engl J Med 2022;386:2178-87.

Phase 3 trial

Title	A Double Blind, Randomized, Placebo-controlled Trial Evaluating the Efficacy and Safety of BI 1015550 Over at Least 52 Weeks in Patients With Idiopathic Pulmonary Fibrosis (IPF)
Study drugs	BI 1015550 high dose, low dose, placebo
Inclusion criteria	IPF Dx, HRCT :≥10% to <50% reticulation and <25% honeycombing FVC ≥45% and DLco ≥25% and ≤90% No or on a stable therapy with nintedanib or pirfenidone
Tx period	52 weeks
Estimated enrollment	963 participants
Primary outcome	Absolute change from baseline in Forced Vital Capacity (FVC) (mL) at Week 52
Start date	September 19, 2022
Completion date	November 30, 2024

Take Home Messages

- N-Acetylcysteine
  - -INFIGENIA
  - -PANTHER-IPF
- Pirfenidone
  - CAPACITY
  - ASCEND
- Nintedanib
  - INPULSIS
- New drugs