IPF 의 새로운 약물치료 : 현재와 미래

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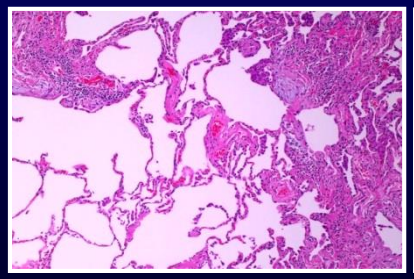
Contents

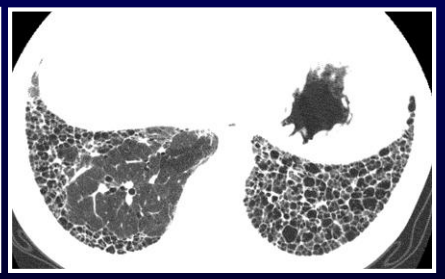
- Pharmacotherapy for IPF: current status
  - update of two antifibrotic agents
  - limits in the real-world

- Pharmacotherpay for IPF: future potential
  - high dose tablets
  - combination treatment
  - new antifibrotic agents

Idiopathic Pulmonary Fibrosis
definition

- A specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occuring in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of UIP.

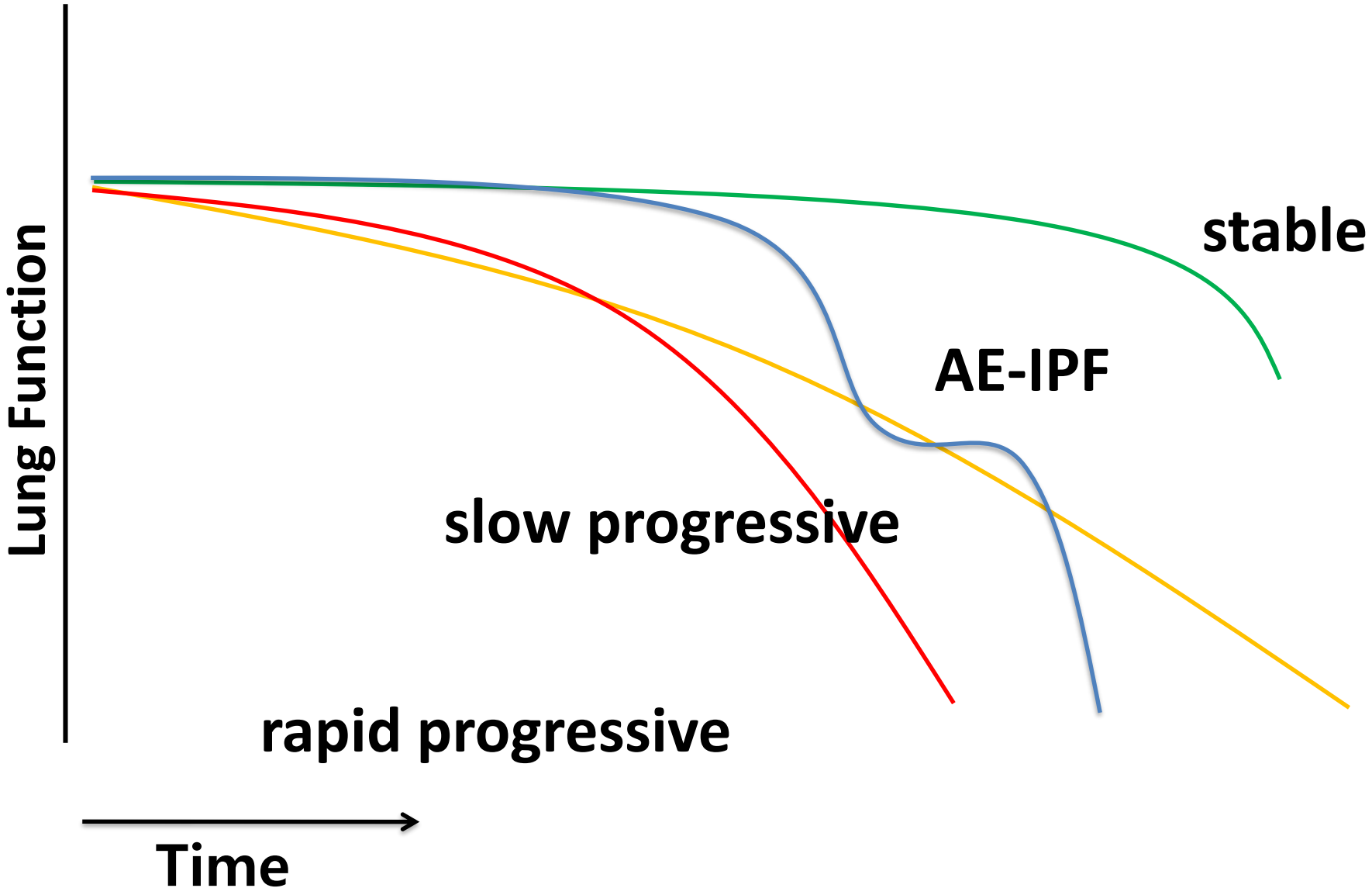




UIP: usual interstitial pneumonia

Am J Respir Crit Care Med. 2011;183:788

IPF – Natural history



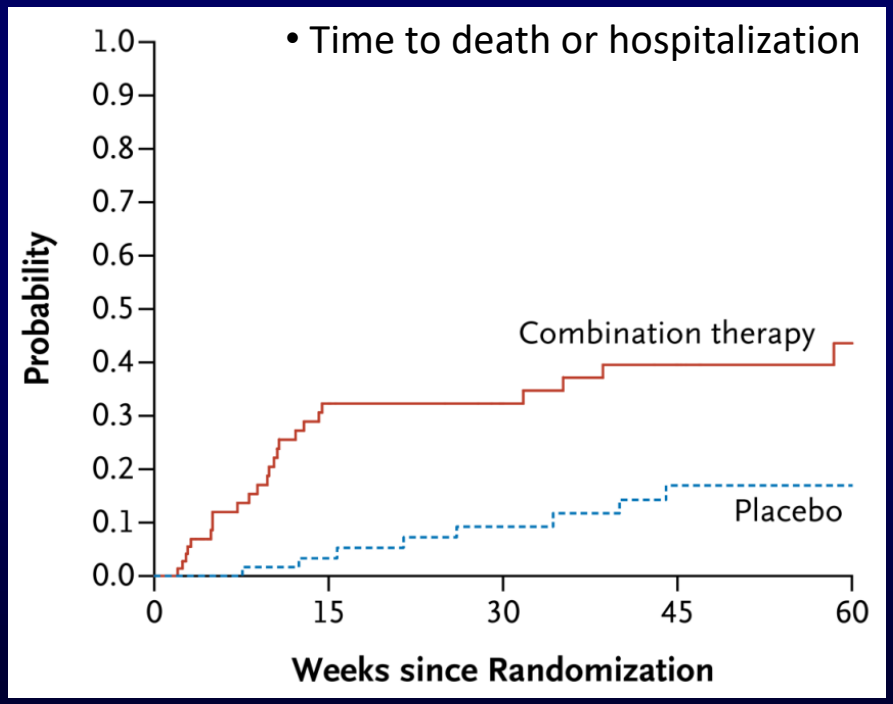
AE-IPF: Acute exacerbation of IPF

Am J Respir Crit Care Med. 2011;183:788

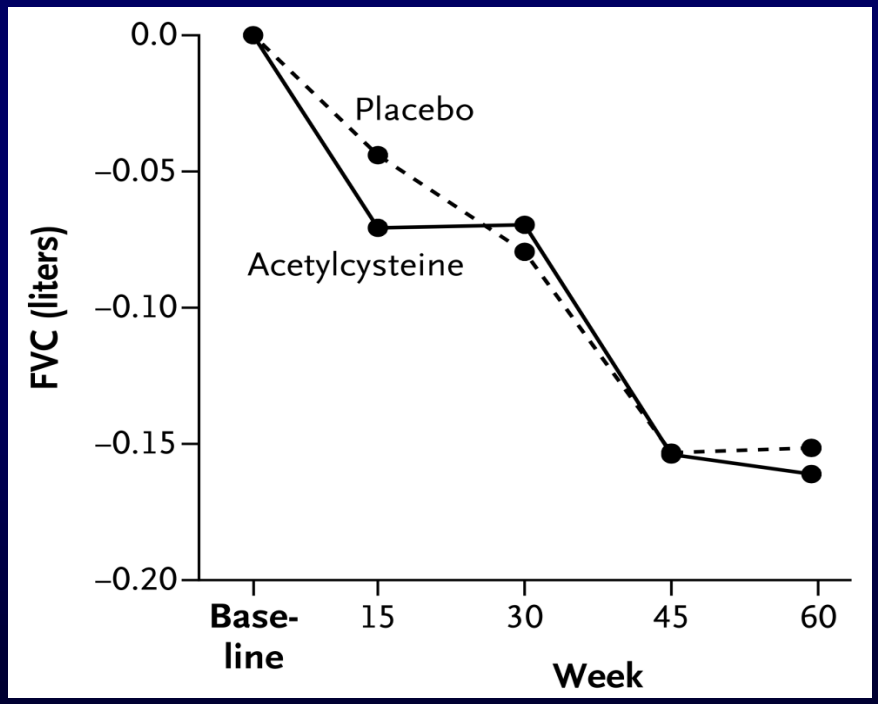
Prednisone, Azathioprine, and N-Acetylcysteine for Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network*

- Triple combination

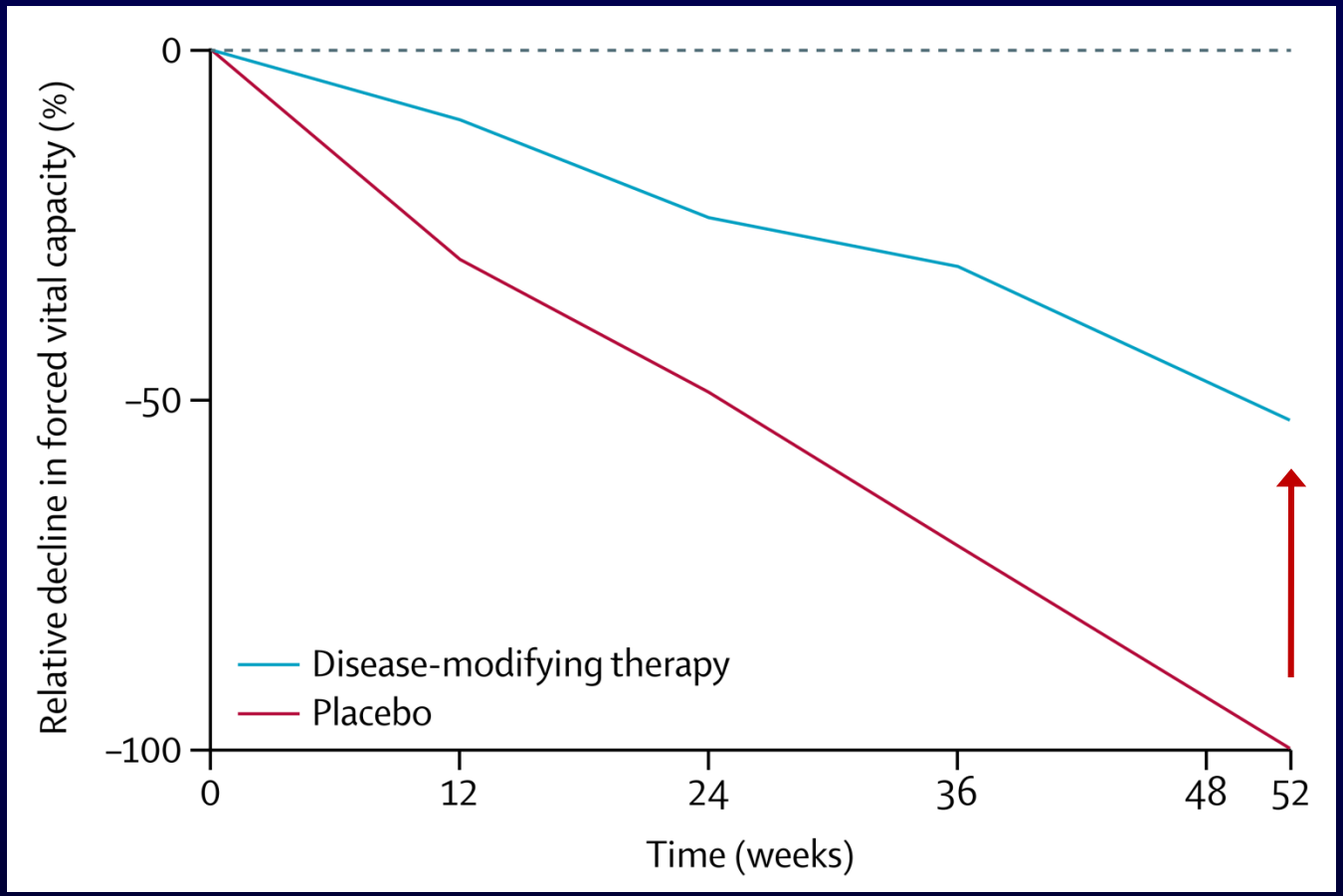


- N-acetylcysteine



N Engl J Med. 2012;366:1968, N Engl J Med. 2014;370:2093

Effect of disease modifying therapy on lung function decline



Lancet 2017;389:1941-52

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

IPF guidelines 2018

KATRD

2. 특발성폐섬유증

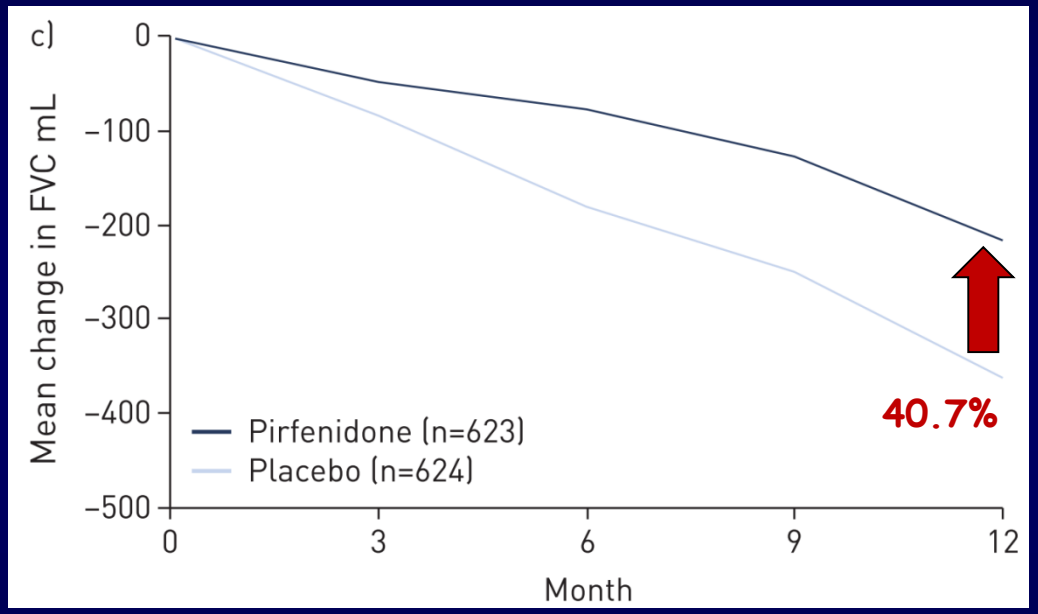
권고사항

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

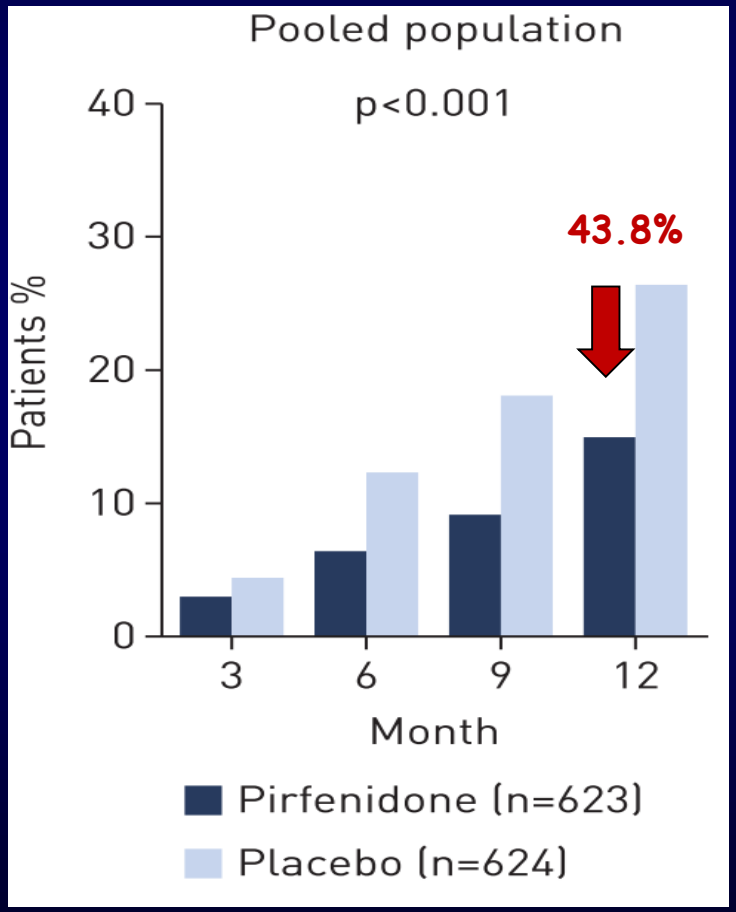
2018 간질성 폐질환 임상진료지침

Pirfenidone: Change in FVC/Progression

- Change in FVC



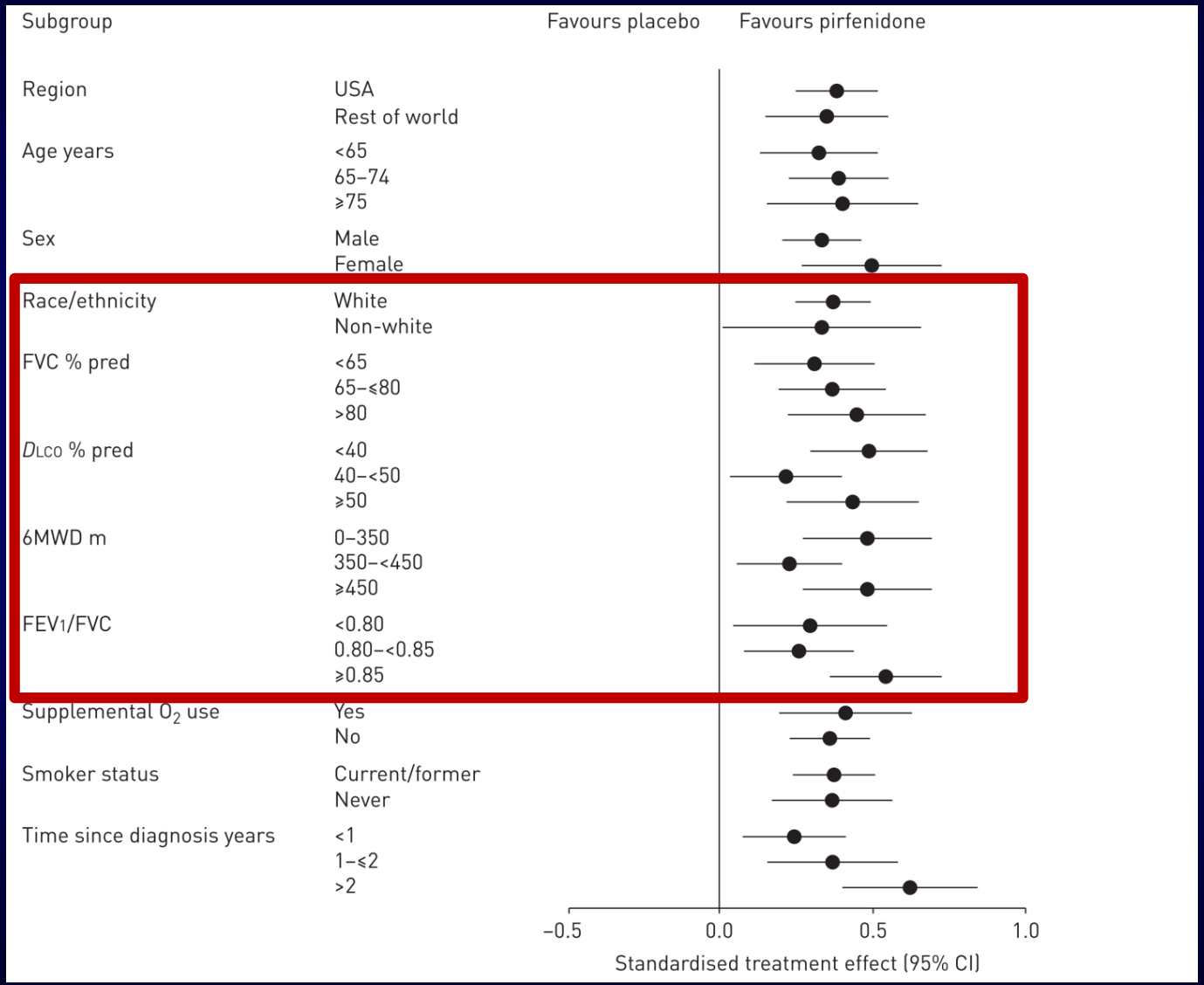
- Decreased FVC or Death



* ASCEND + CAPACITY (N=1247)

Eur Resp J 2016;47:243

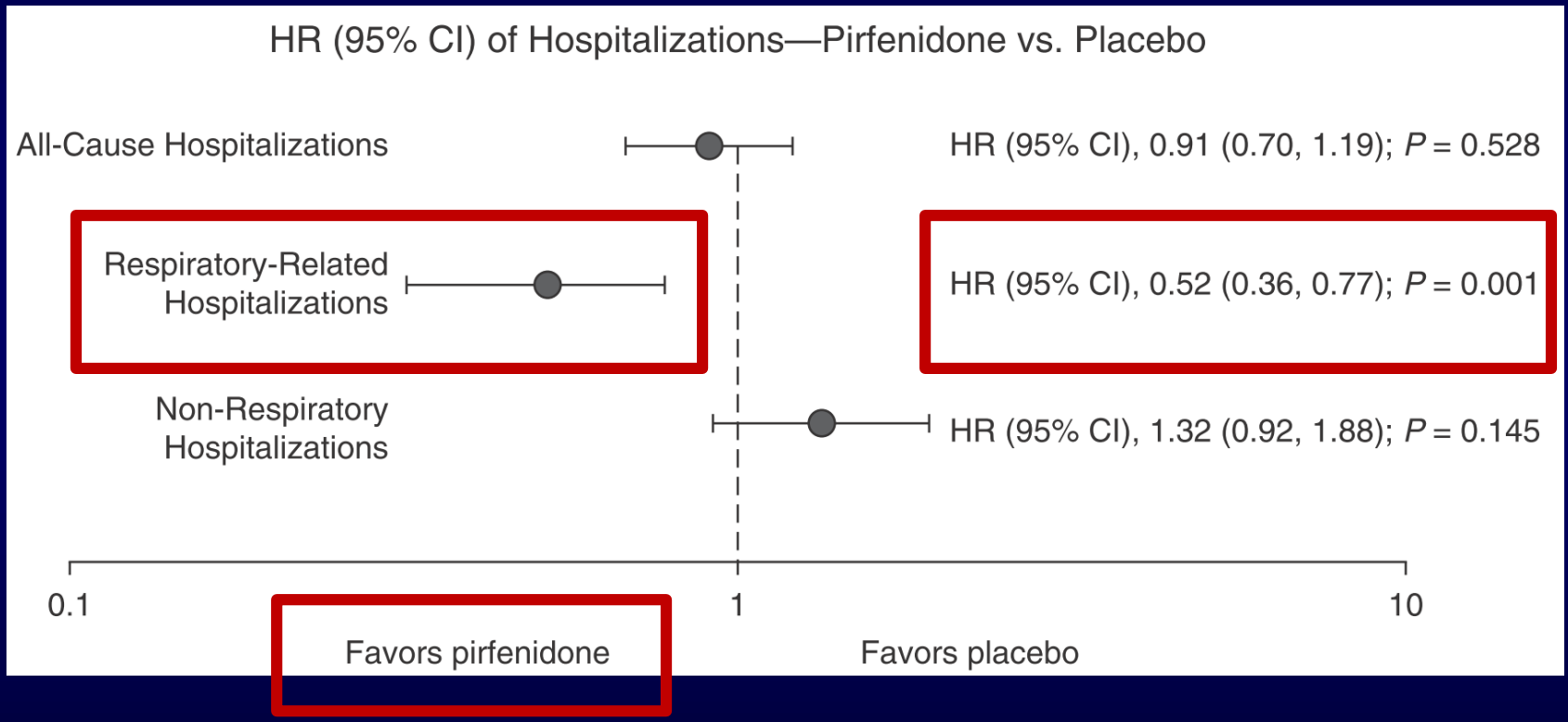
Pirfenidone: Subgroup Analysis



* ASCEND + CAPACITY (N=1247)

Eur Resp J 2016;47:243

Pirfenidone: risk of first nonelective hospitalization



* ASCEND + CAPACITY (N=1247)

Am J Repir Crit Care Med 2017;196:756

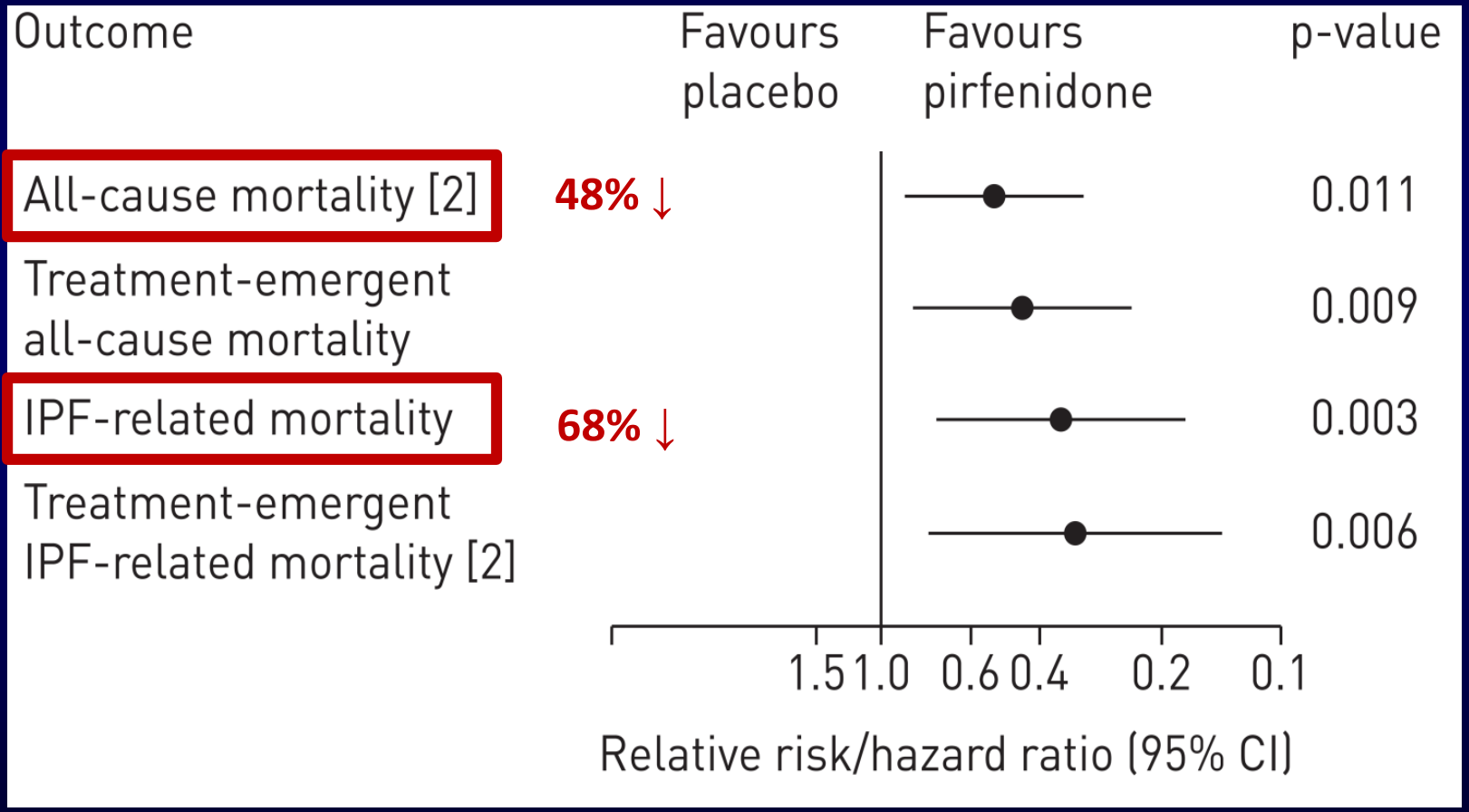
Pirfenidone: risk of death after nonelective hopitalization

	Hazard Ratio	95% Confidence Interval	*P* Value
All-cause hospitalization (n = 221*)			
Unadjusted	0.49	0.28–0.86	0.013
Adjusted for propensity score†	0.56	0.32–0.99	0.047
Respiratory-related hospitalization (n = 115*)			
Unadjusted	0.55	0.28–1.08	0.082
Adjusted for propensity score†	0.50	0.25–1.03	0.061
Non–respiratory-related hospitalization (n = 124*)			
Unadjusted	0.67	0.26–1.74	0.412
Adjusted for propensity score†	0.73	0.27–1.97	0.537

* ASCEND + CAPACITY (N=1247)

Am J Repir Crit Care Med 2017;196:756

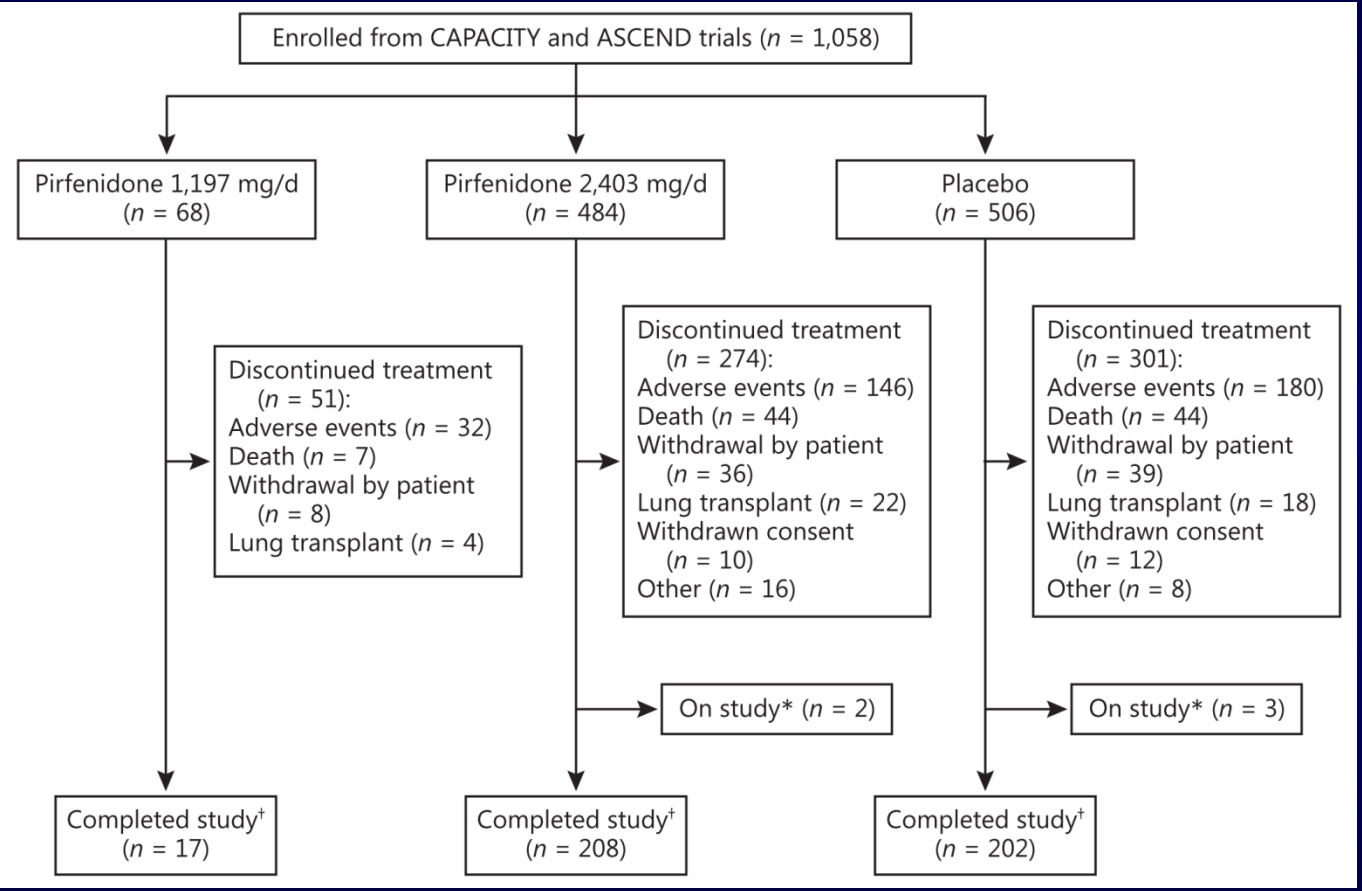
Pirfenidone: Survival



* ASCEND + CAPACITY (N=1247)

Eur Resp J 2016;47:243

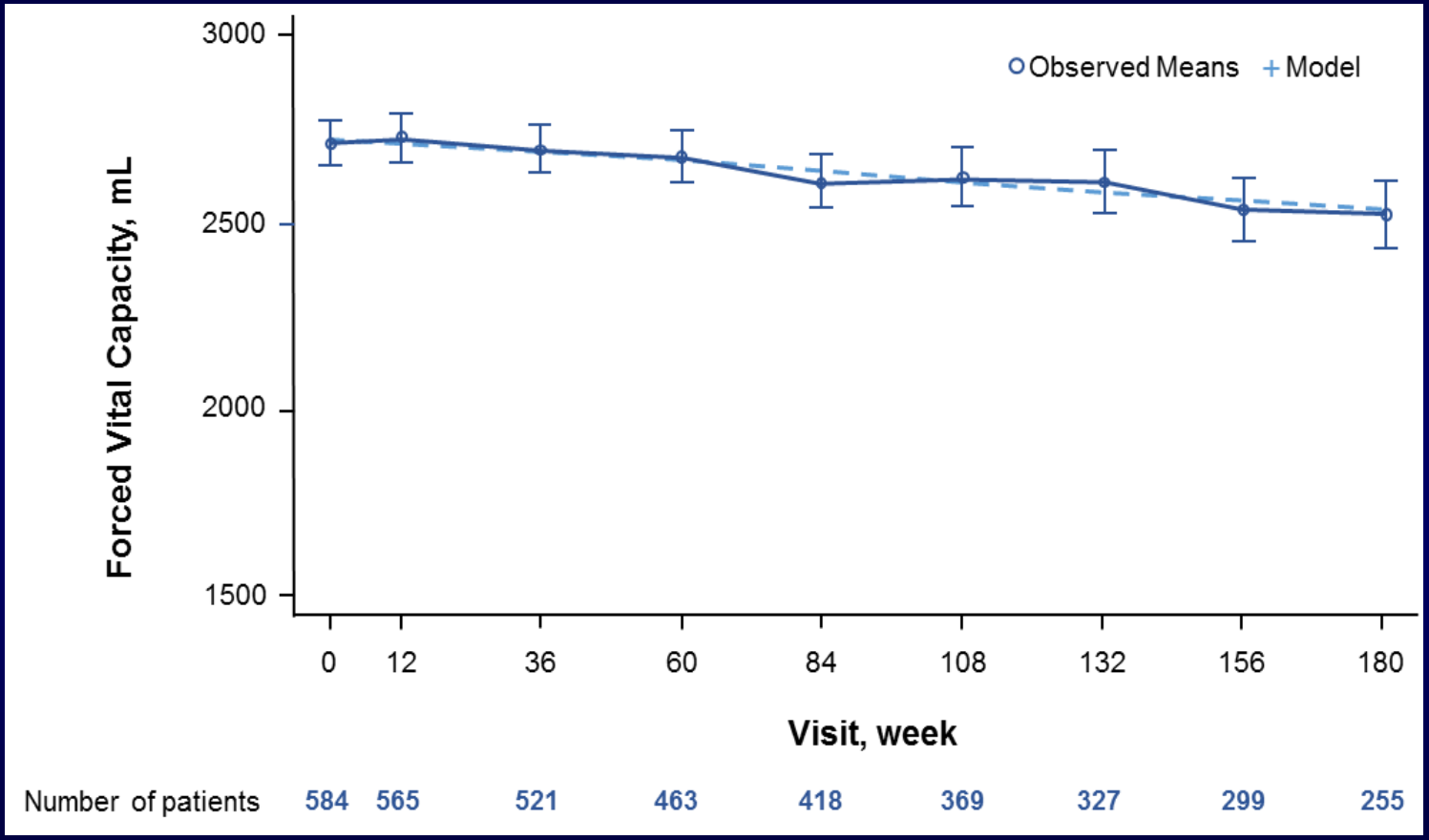
Long term safety of Pirfenidone: RECAP



- Open label extension study (1,058 entered)
- Median (range) of exposures: <u>88 (0-349) weeks</u>

Respiration 2017;94:408

Annualized rate of FVC decline



- FVC decline: 144.3 (6.0) mL/year

* CAPACITY (N=584), linear mixed effects model

Respiration 2017;94:408

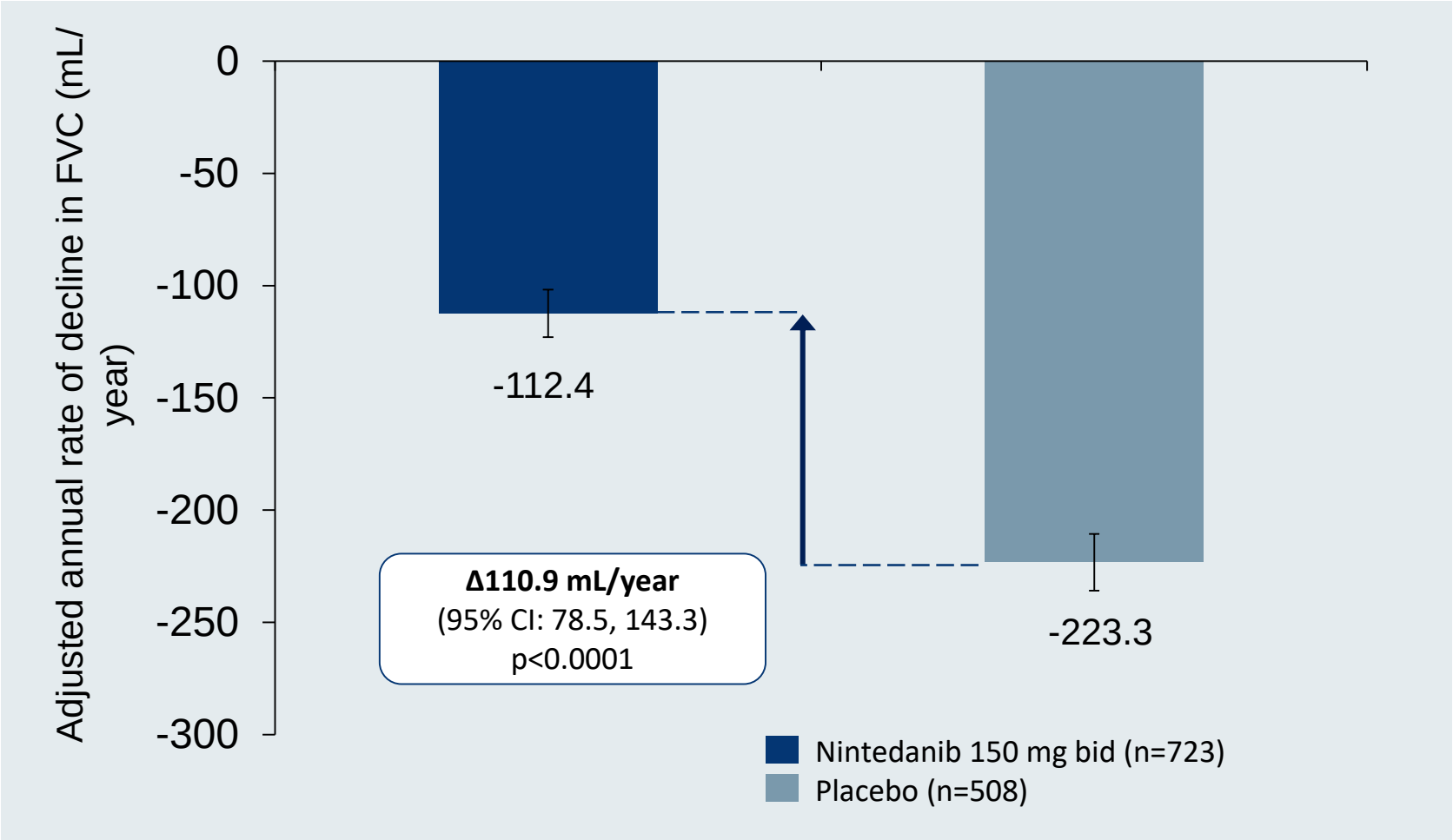
Treatment emergent adverse events

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%

Respiration 2017;94:408

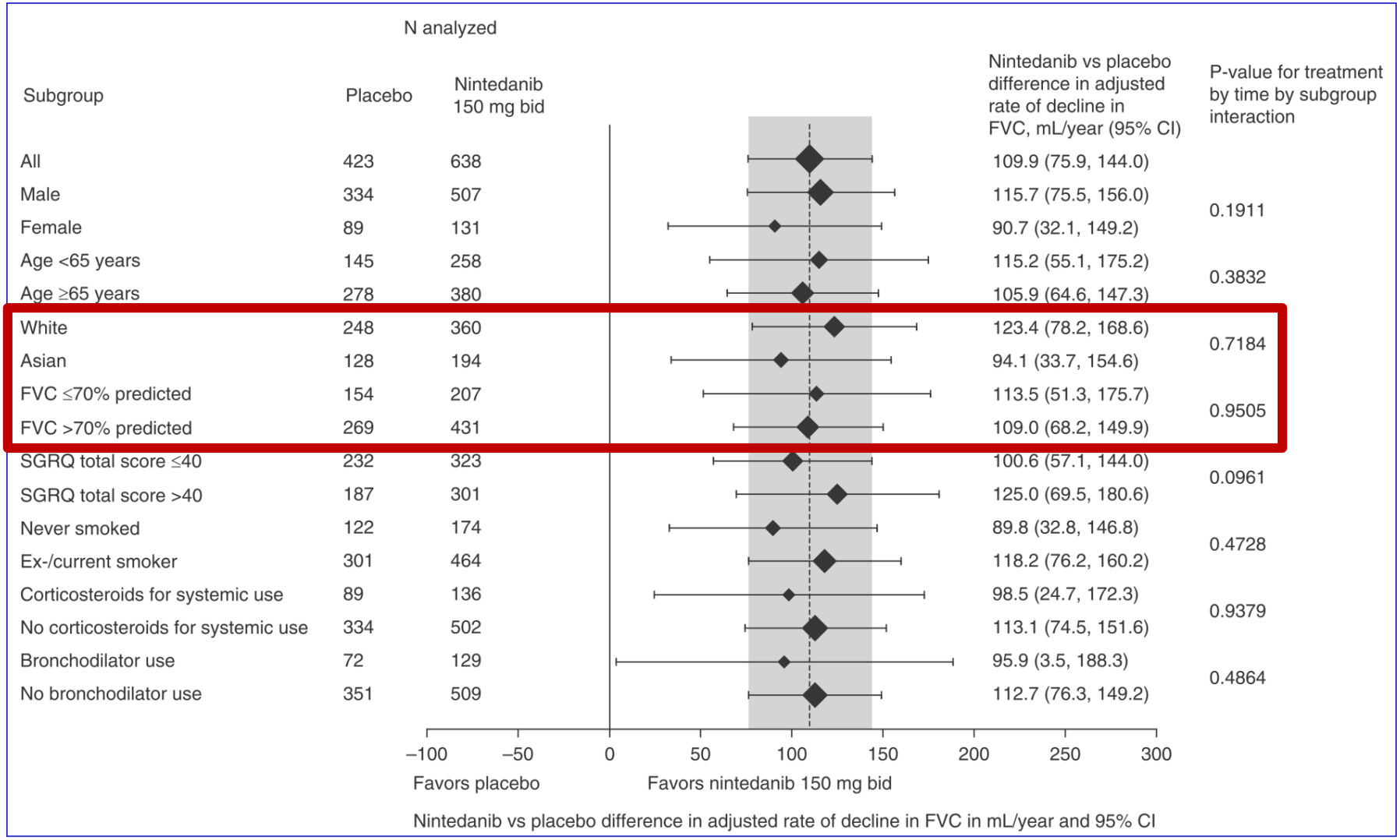
Nintedanib: Annual decline rate in FVC



* INPULSIS + TOMORROW (N=1231)

Respir Med 2016;113:74

Nintedanib: Subgroup Analysis

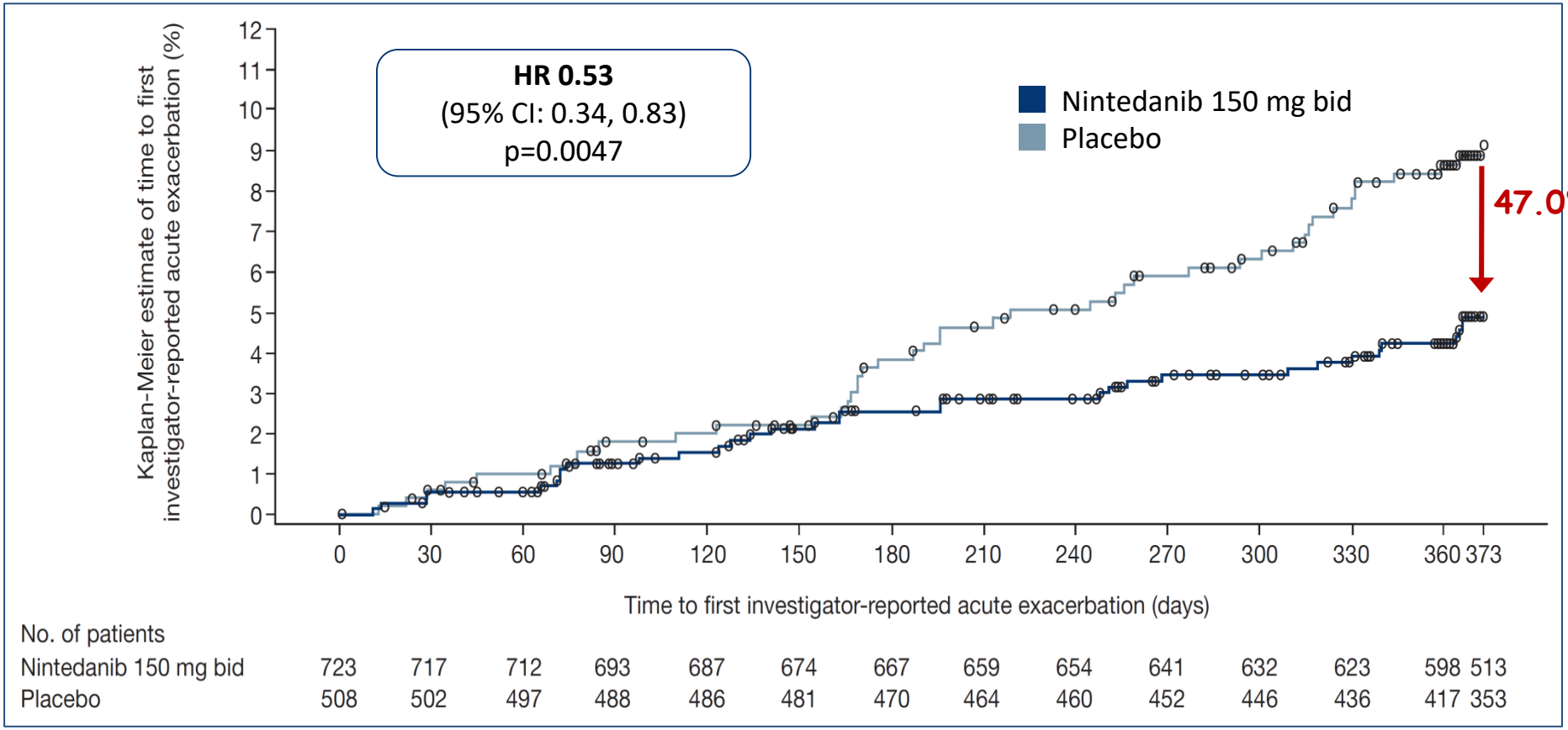


* INPULSIS (N=1061)

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

Nintedanib: Acute exacerbation

- Time to first acute exacerbation



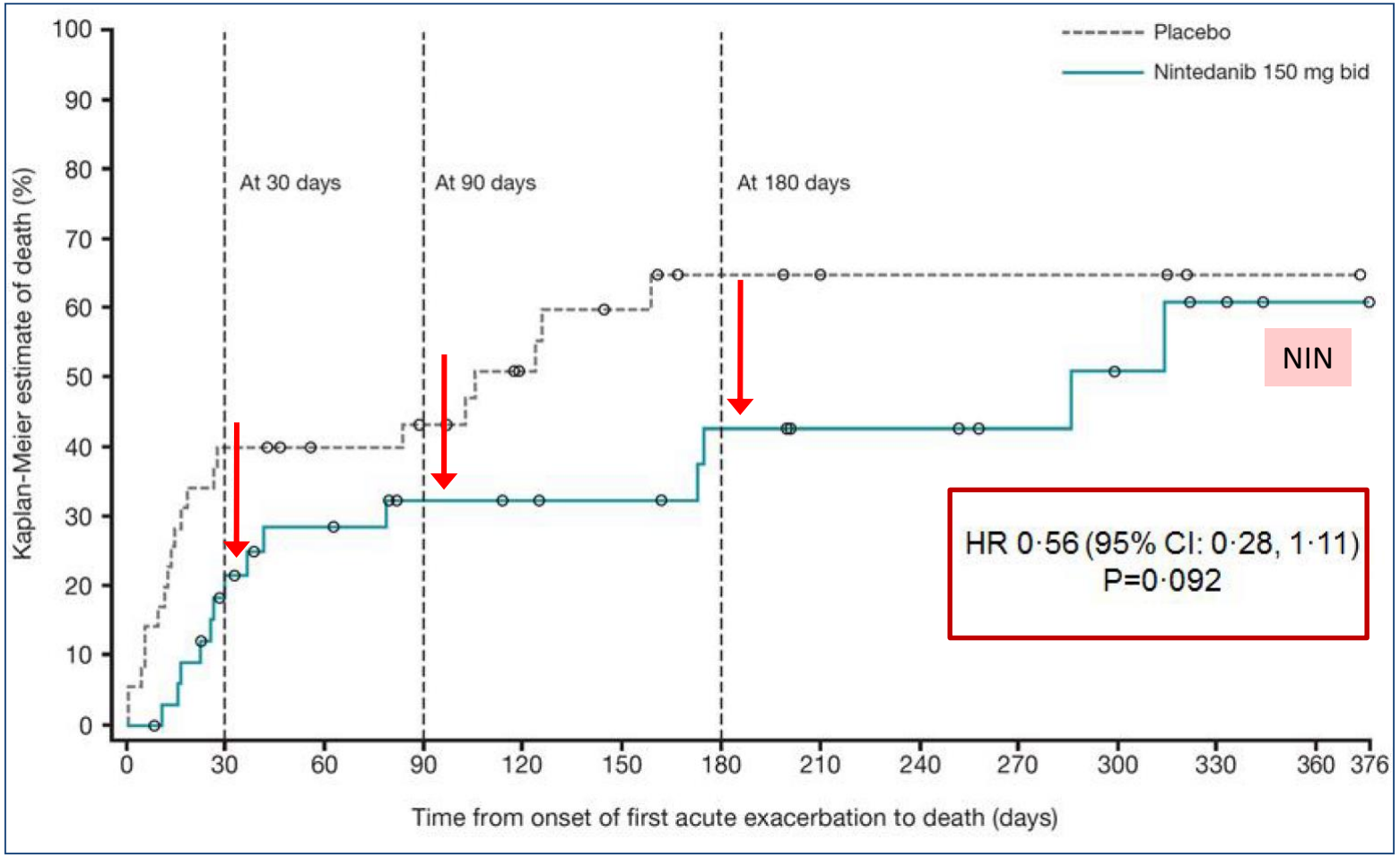
4.6 vs. 8.7%/yr

* INPULSIS + TOMORROW (N=1231)

Respir Med 2016;113:74

Nintedanib: risk of death after acute exacerbation

- Time to death following investigator-reported AE



* INPULSIS (N=1061)

Eur Respir J 2017;49:1601339

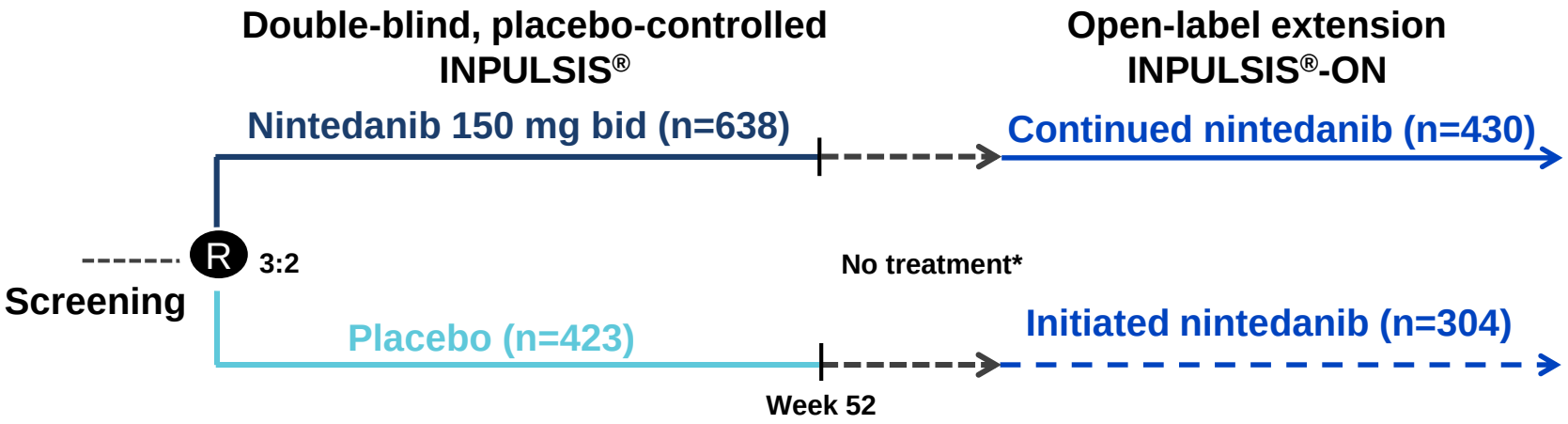
Nintedanib: Survival

	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	

* INPULSIS + TOMORROW (N=1231)

Respir Med 2016;113:74

Long-term safety of Nintedanib: INULSIS-ON

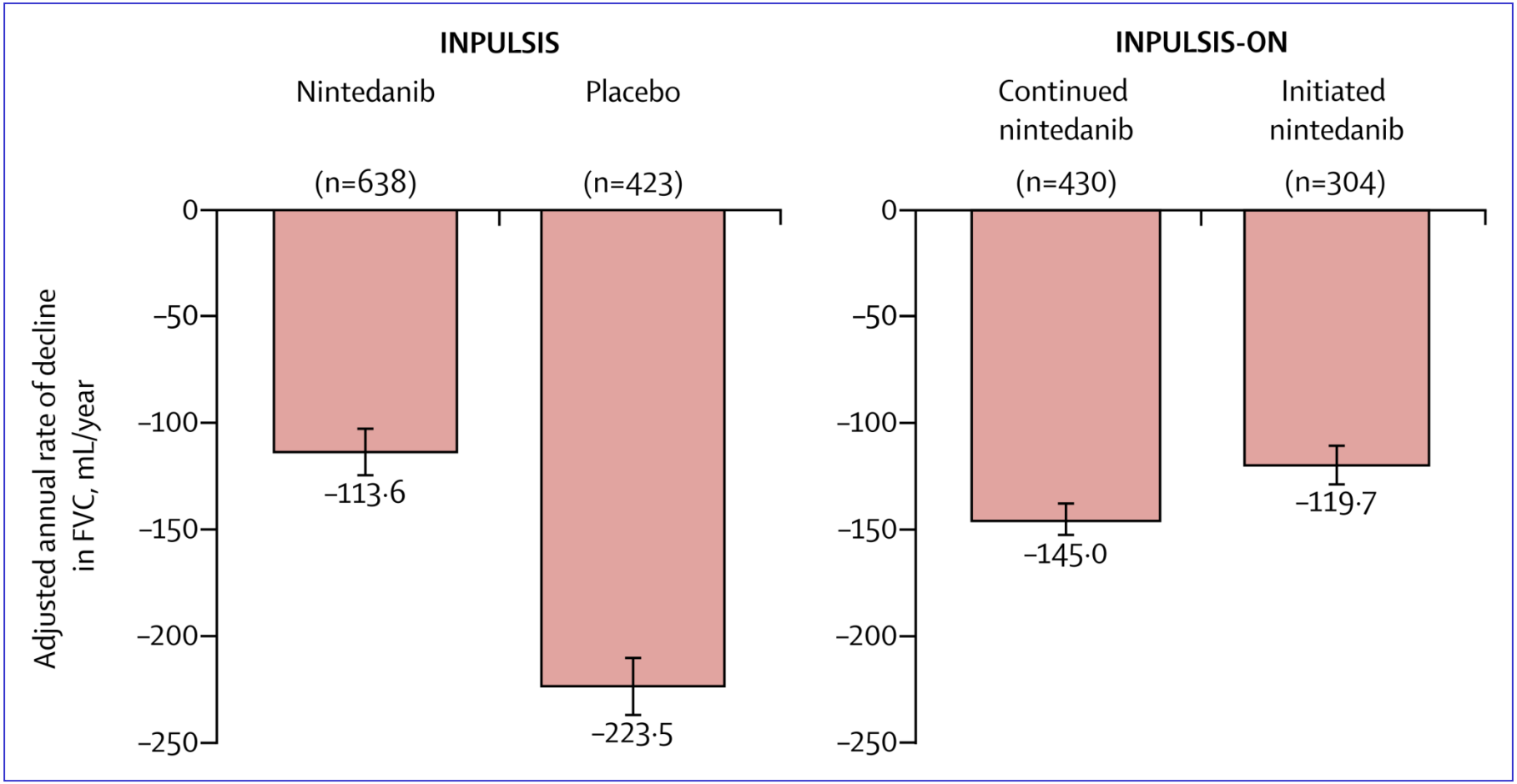


- Total exposure time (median): 44.7 [11.9-68.3] months

  (INPULSIS-ON: 31.5 [0-56.3] months)

Lancet Respir Med 2019;7(1):60

Annual rate of decline over 192 weeks



Lancet Respir Med 2019;7(1):60

Most frequent adverse events

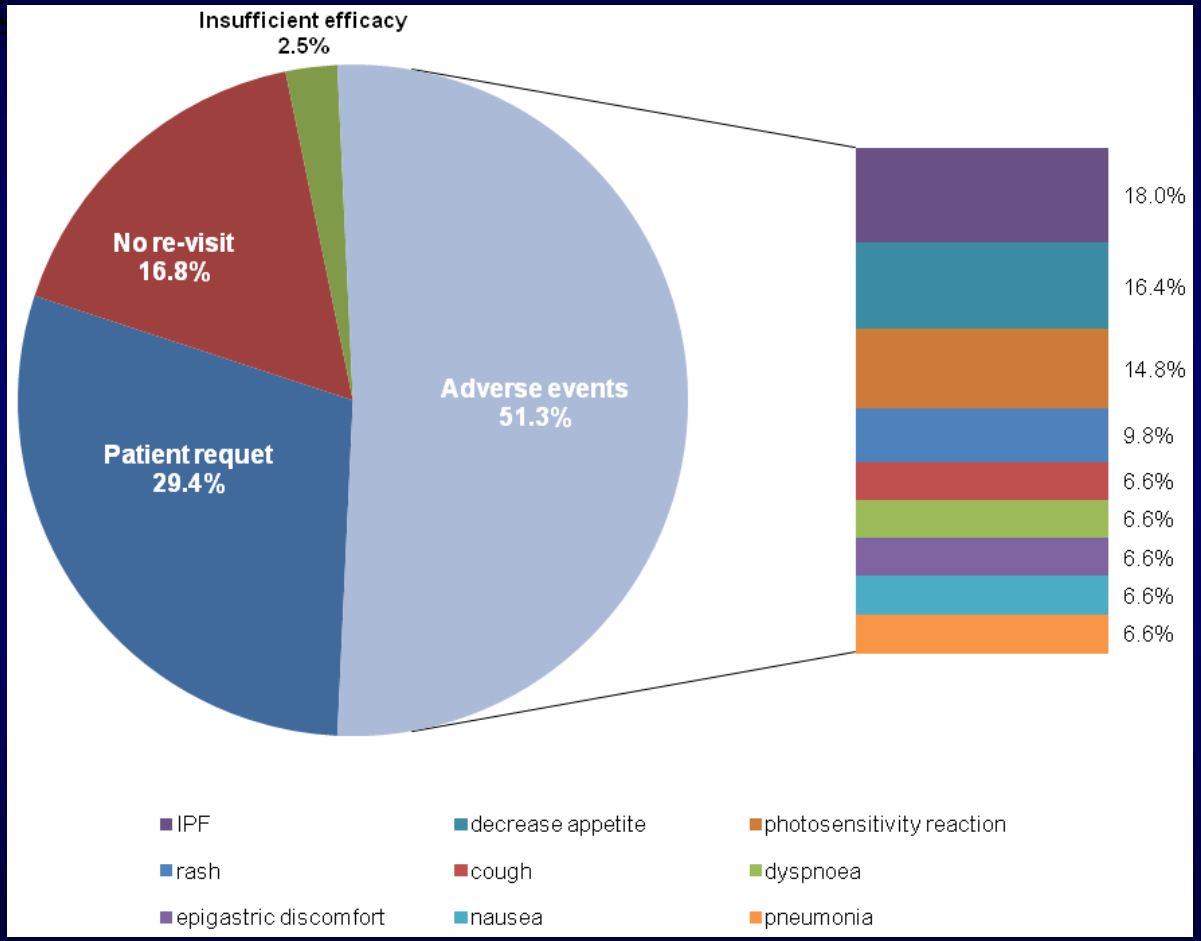
	INPULSIS®				INPULSIS®-ON			
	Nintedanib (n=638)		Placebo (n=423)		Continued nintedanib (n=430)		Initiated nintedanib (n=304)	
	Events, n	Event rate (per 100 PEY)	Events, n	Event rate (per 100 PEY)	Events, n	Event rate (per 100 PEY)	Events, n	Event rate (per 100 PEY)
Diarrhoea	671	112.6	106	25.6	655	62.5	499	73.7
Nausea	208	34.9	29	7.0	90	8.6	111	16.4
Nasopharyngitis	117	19.6	91	22.0	131	12.5	118	17.4
Vomiting	102	17.1	11	2.7	78	7.4	76	11.2
Cough	96	16.1	67	16.2	129	12.3	91	13.4
Bronchitis	92	15.5	62	15.0	159	15.2	96	14.2
Decreased appetite	75	12.6	26	6.3	51	4.9	67	9.9
Upper respiratory infection	72	12.1	55	13.3	117	11.2	53	7.8
Progression of IPF*	70	11.8	73	17.7	143	13.6	95	14.0
Dyspnoea	50	8.4	51	12.3	102	9.7	66	9.7

PEY, patient exposure–years. Adverse events with rate >12 per 100 PEY in any group shown by preferred term in Medical Dictionary for Regulatory Activities (MedDRA). * Corresponds to MedDRA term 'IPF', which included disease worsening and IPF exacerbations.

Lancet Respir Med 2019;7(1):60

Pirespa: reasons for discontinuation

Change in FVC

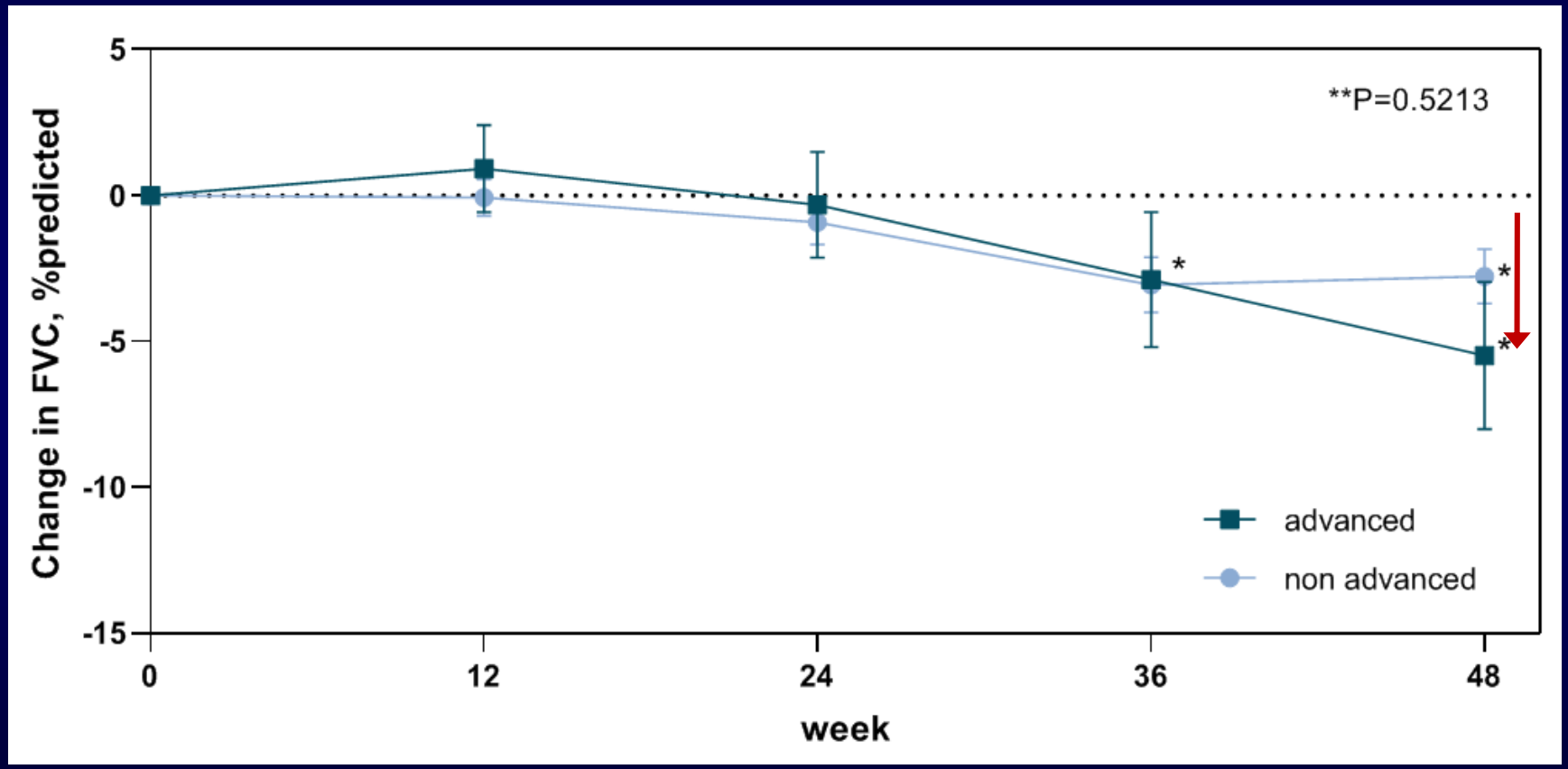


- Duration of exposures (median: 298 days)
- Discontinuation in 119 patients (54.3% of total 219 patients)

Total exposure time: 40.7 months (11.9/63.1 months)

Pirespa: change in FVC

Change in FVC

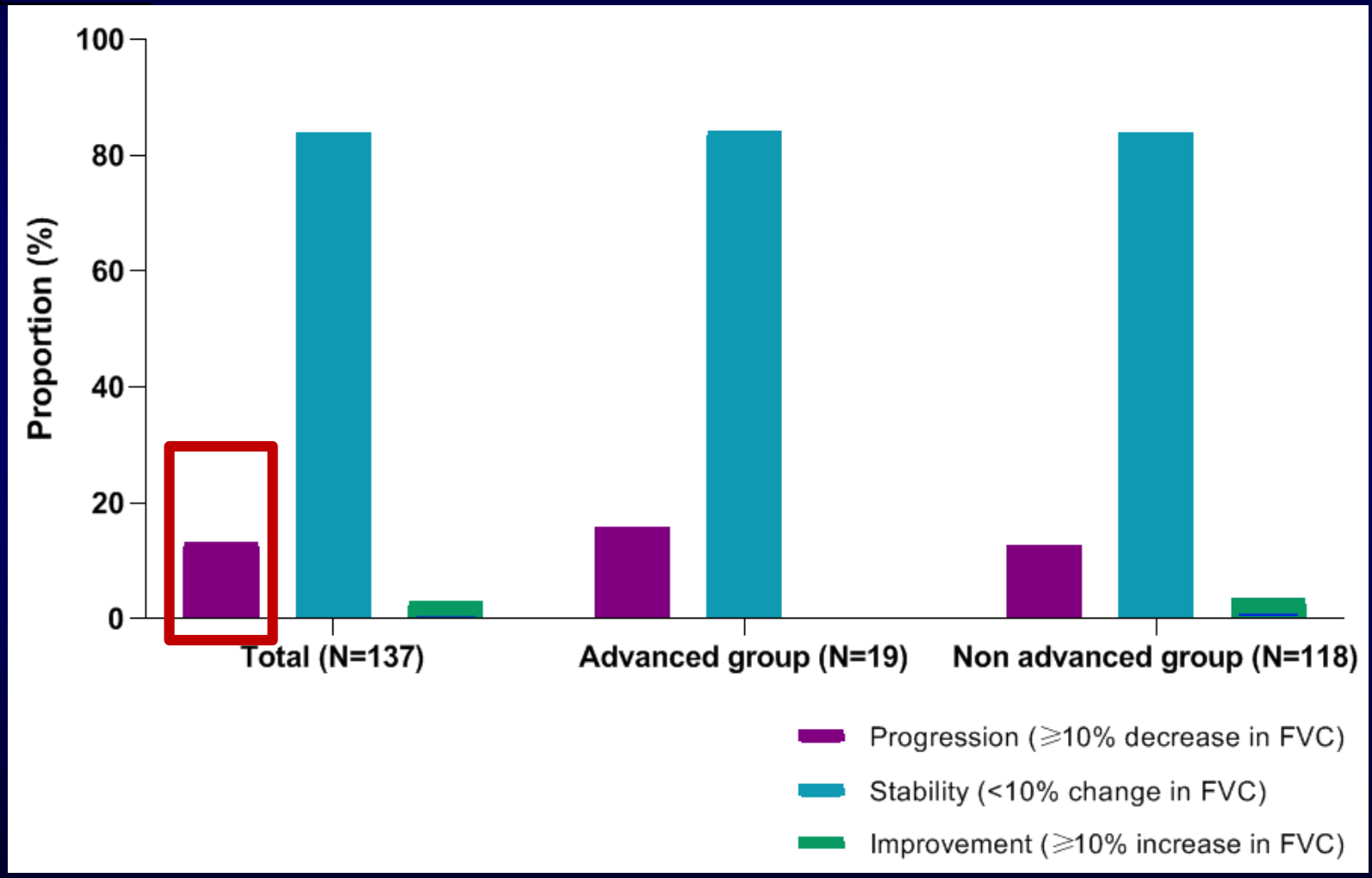


* Mixed-model repeated measures methods, *p <0.05, ** the interaction p-value

Total exposure time: 40.7 months (11.9/63.1 months)

Pirespa: categorical changes in FVC

Change in FVC



Total exposure time: 40.7 months (11.9/63.1 months)

Maintenance with high dose tablets

After the full dose of three 267 mg tablets or capsules TID is well tolerated, transition patients to one 801 mg tablet TID for a maintenance option with fewer pills per day

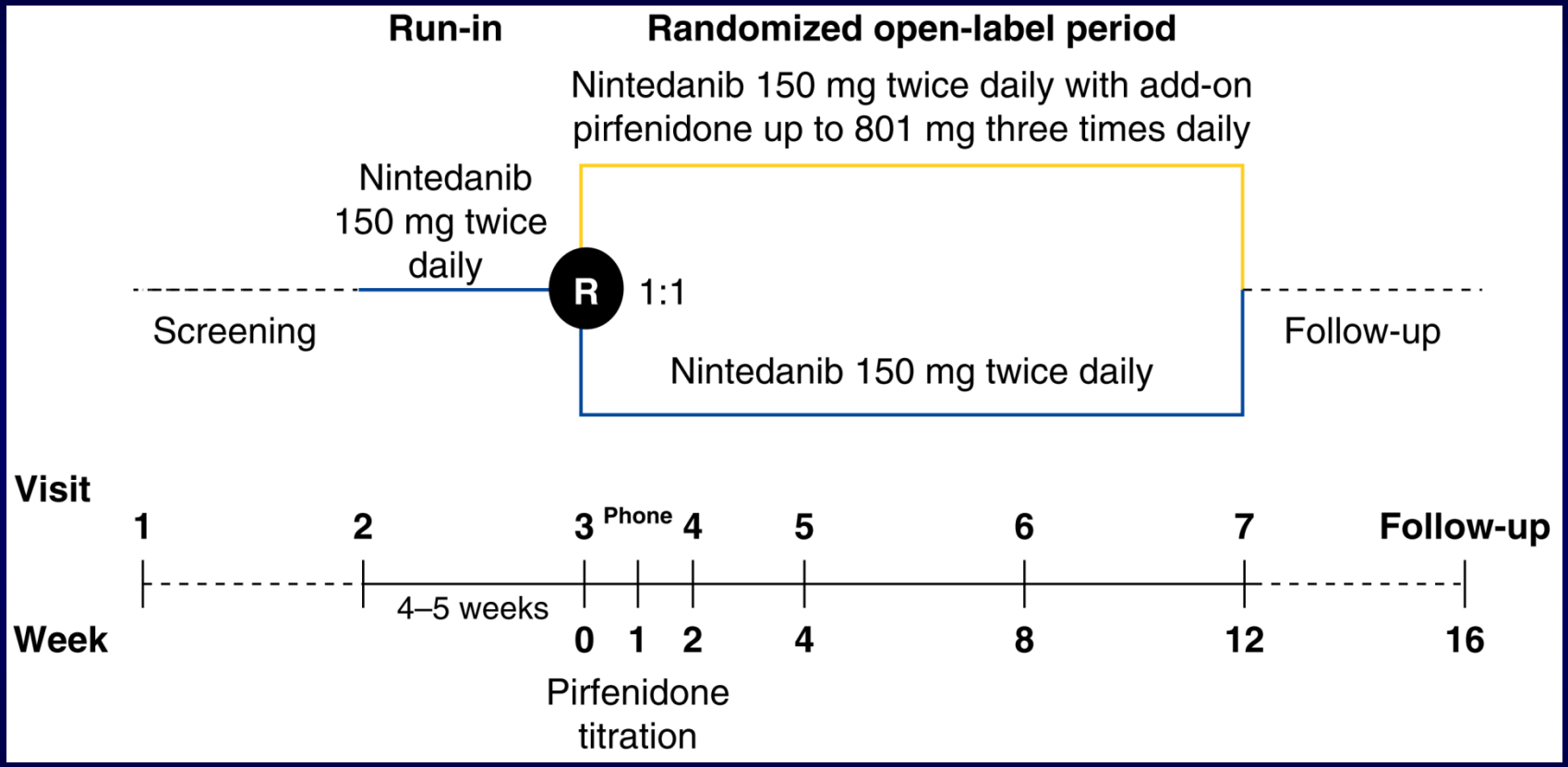
Combination therapy: the future of management for idiopathic pulmonary fibrosis?

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

Nintedanib with add-on Pirfenidone : INJOURNEY Trial



- Open-label, randomized trial (n=105)
- FVC ≥ 50 % predicted
- Percentage of patients with on–treatment GI adverse events

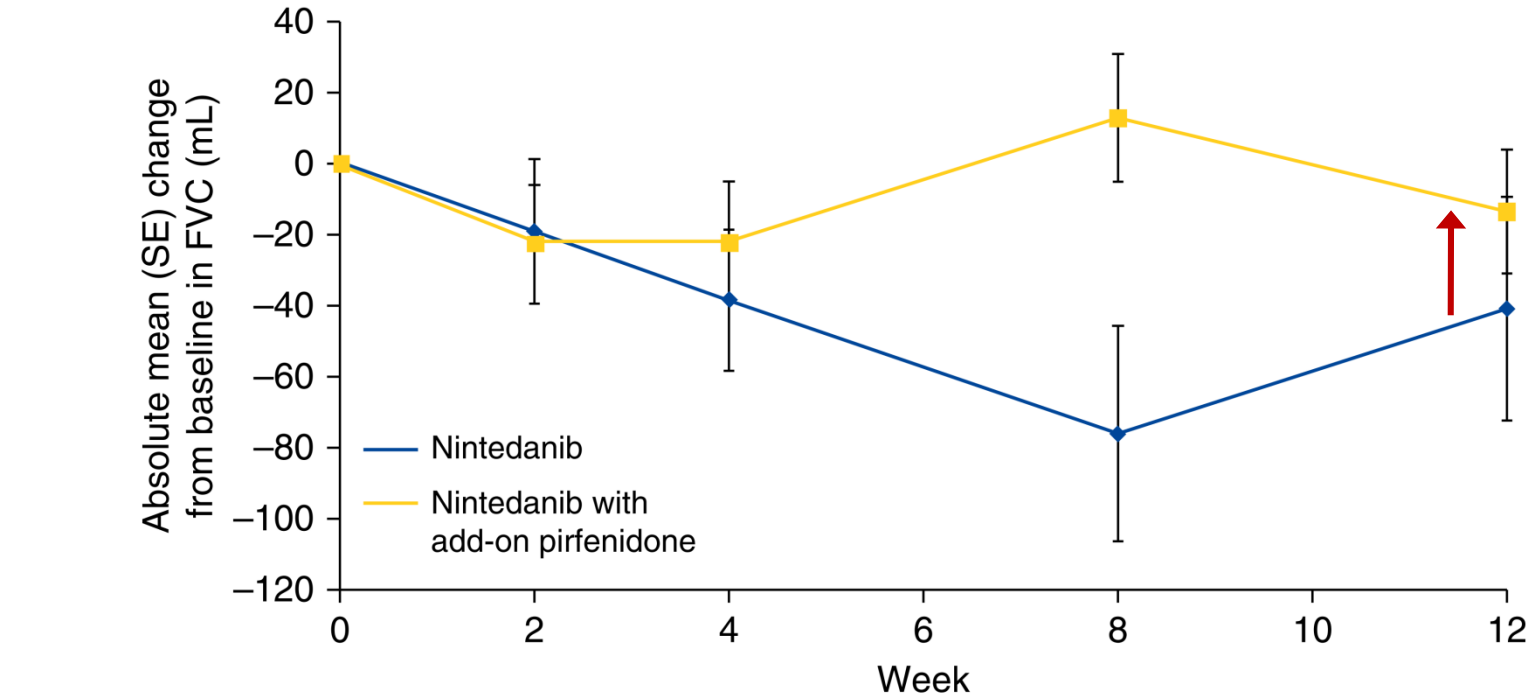
Am J Respir Crit Care Med 2018;197(3):356

Adverse events

	Nintedanib 150 mg bid with add-on pirfenidone (n=53)	Nintedanib 150 mg bid (n=51)
Any adverse event(s)	47 (88.7)	45 (88.2)
Most frequent adverse events*		
Diarrhea	20 (37.7)	16 (31.4)
Nausea	22 (41.5)	6 (11.8)
Vomiting	15 (28.3)	6 (11.8)
Fatigue	10 (18.9)	6 (11.8)
Upper abdominal pain	7 (13.2)	4 (7.8)
Decreased appetite	6 (11.3)	5 (9.8)
Dyspnea	2 (3.8)	8 (15.7)
Headache	7 (13.2)	1 (2.0)
Any serious adverse event(s)†	2 (3.8)	5 (9.8)
Any fatal adverse event(s)	0	0

- On-treatment GI adverse events: NIN/PFD (69.8%) vs. NIN (52.9%)

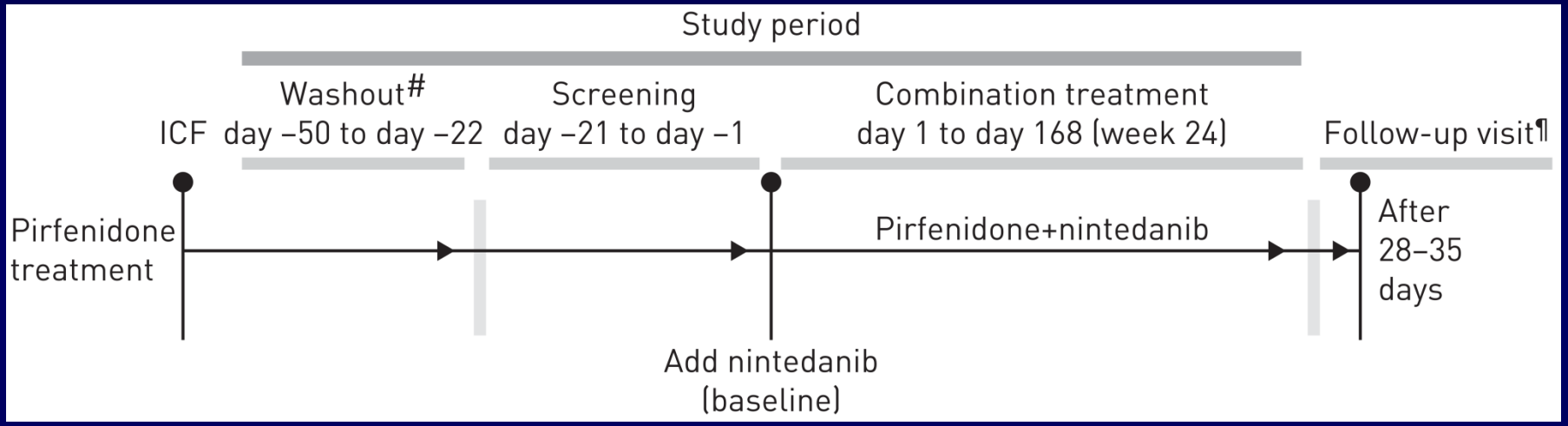
Changes from baseline in FVC



n					
Nintedanib	51	49	48	45	44
Nintedanib with add-on pirfenidone	53	52	50	50	48

- Mean absoulte change: NIN/PFD (-13.3ml) vs. NIN (-40.9 ml)

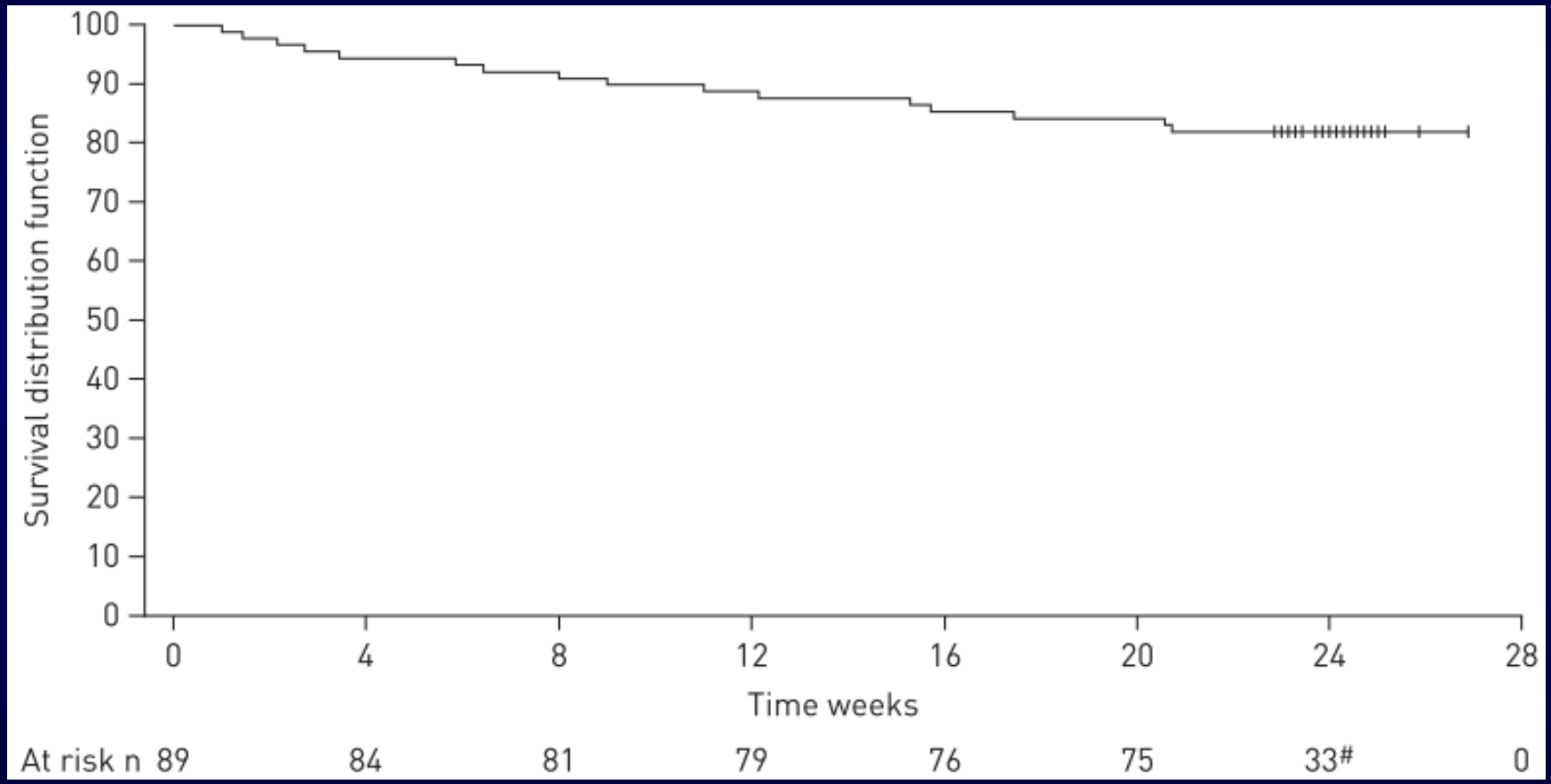
Nintedanib added-on Pirfenidone



- 24 week, single-arm, open-label, phase IV (n=89)
- FVC ≥ 50 % predicted, DLco ≥ 30% predicted. PFD ≥ 16 weeks (stable dose ≥ 28 d)
- Proportion of patients who completed 24 weeks of combination

Eur Respir J 2018;52:1800230

Time to discontinuation



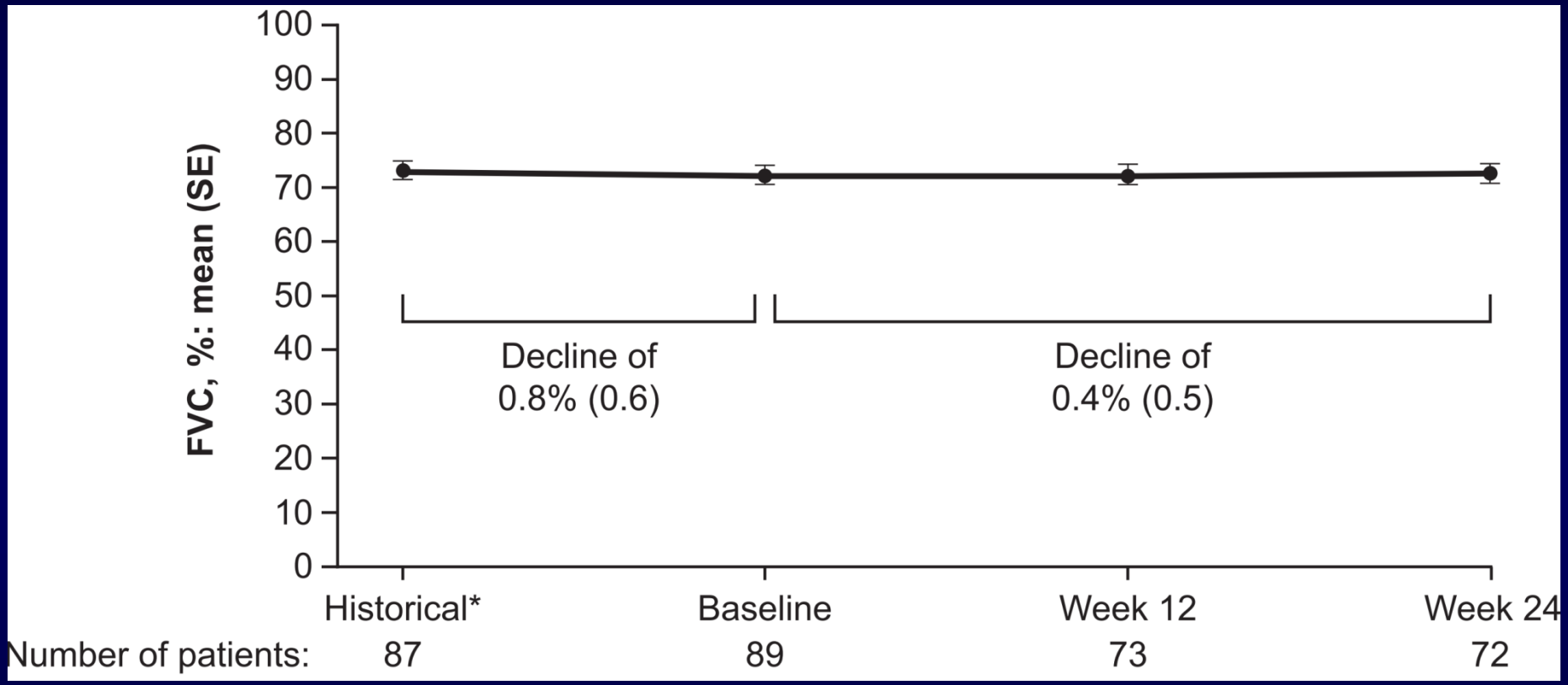
- 69 (78%) completed 24 weeks of treatment (discontinued d/t TEAE: 13 [14.6%])

Eur Respir J 2018;52:1800230

Common treatment-emergent adverse events

	Patients with at least one TEAE[¶]	Patients with at least one TEAE related to pirfenidone only[+]	Patients with at least one TEAE related to nintedanib only[+]	Patients with at least one TEAE related to both pirfenidone and nintedanib[+]
TEAEs occurring in ⩾5% of patients				
⩾1 TEAE	88 (99)			
⩾1 treatment-related TEAE	74 (83)	15 (17)	67 (75)	26 (29)
Diarrhoea	44 (49)	2 (2)	38 (43)	5 (6)
Nausea	41 (46)	3 (3)	31 (35)	12 (14)
Vomiting	21 (24)	1 (1)	16 (18)	7 (8)
Decreased appetite	14 (16)	2 (2)	7 (8)	5 (6)
Fatigue	11 (12)	0	8 (9)	3 (3)
Dyspepsia	8 (9)	1 (1)	6 (7)	1 (1)
Headache	8 (9)	0	7 (8)	1 (1)
Weight decreased	6 (7)	1 (1)	3 (3)	2 (2)
Photosensitivity or rash TEAEs	7 (8)	4 (5)	2 (2)	1 (1)
Abdominal pain upper	5 (6)	1 (1)	2 (2)	2 (2)
Dizziness	5 (6)	0	4 (5)	1 (1)
TEAEs leading to discontinuation				
⩾1 TEAE	13 (15)			
⩾1 treatment-related TEAE	11 (12)	0	10 (11)	1 (1)
Nausea	4 (5)	0	3 (3)	1 (1)
Diarrhoea	4 (5)	0	3 (3)	1 (1)
Fatigue	2 (2)	0	2 (2)	0
Weight decreased	2 (2)	0	2 (2)	0
Deep vein thrombosis	1 (1)	0	1 (1)	0
Epigastric discomfort	1 (1)	0	1 (1)	0
Malaise	1 (1)	0	1 (1)	0
Migraine	1 (1)	0	1 (1)	0
Vomiting	1 (1)	0	1 (1)	0

Changes in FVC



- Mean time from assessment of historical value to screening : 3.0±1.9 months

Eur Respir J 2018;52:1800230

ORIGINAL ARTICLE

A Controlled Trial of Sildenafil in Advanced Idiopathic Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network*

Primary outcome*: presence or absence of an improvement of a t least 20% in the 6-minute walk distance at 12 weeks, as comp ared with baseline*

Key secondary outcomes *included changes in the 6-minute wal k distance, degree of dyspnea, and quality of life*

N Engl J Med 2010;363:620

STEP-IPF – results

"The use of sildenafil did not cause a significant difference in the proportion of p atients with an improvement of 20% or more in the 6-minute walk distance at 1 2 weeks (..9/89 in sildenafil vs 6/91 in placebo, p=0.39..). There were small differ ences favoring sildenafil in some secondary outcomes, including the degree of d yspnea and quality of life."

Characteristic	Sildenafil (N=89)	Placebo (N=91)	Absolute Difference†	P Value
	mean change (95% confidence interval)			
Dyspnea				
Score on Borg Dyspnea Index after walk test‡	0.04 (–0.30 to 0.37)	0.37 (0.04 to 0.70)	–0.34 (–0.81 to 0.14)	0.16
Shortness of Breath Questionnaire‡	0.22 (–3.10 to 3.54)	6.81 (3.53 to 10.08)	–6.58 (–11.25 to –1.92)	0.006
Quality of life				
St. George's Respiratory Questionnaire‡				
Total score	–1.64 (–3.91 to 0.64)	2.45 (0.17 to 4.72)	–4.08 (–7.30 to –0.86)	0.01
Symptoms score	–3.58 (–7.02 to –0.13)	2.15 (–1.30 to 5.61)	–5.73 (–10.61 to –0.85)	0.02
Activity score	–1.15 (–3.68 to 1.38)	2.49 (0.00 to 4.99)	–3.64 (–7.20 to –0.09)	0.04
Impacts score (social function)	–0.88 (–3.78 to 2.02)	2.82 (–0.03 to 5.67)	–3.70 (–7.76 to 0.37)	0.07

N Engl J Med 2010;363:620

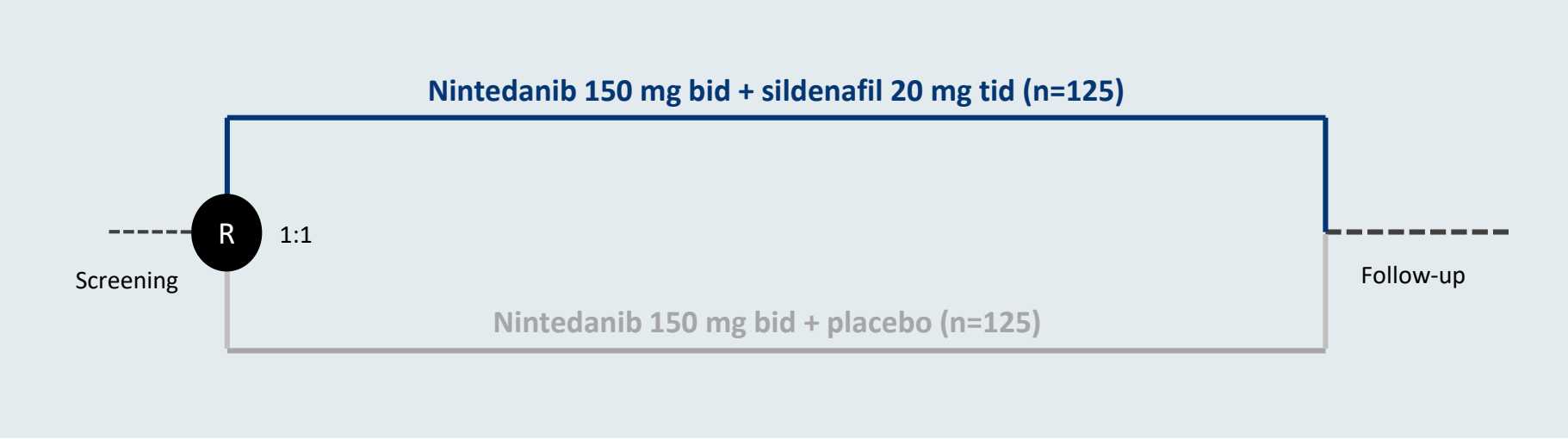
STEP-IPF – death and AE-IPF

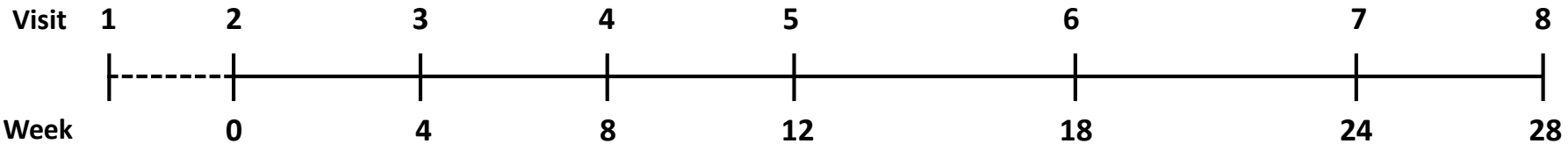
Table 3. Death and Acute Exacerbation.

Variable	Sildenafil (N=89)	Placebo (N=91)	P Value
Death from any cause — no (%)*			
12 wk	2 (2)	4 (4)	0.43
24 wk	3 (3)	9 (10)	0.08
28 wk	4 (5)	11 (13)	0.07
Acute exacerbation — no./total no. (%)			
Period 1	2/89 (2)	4/91 (4)	0.68
Period 2	1/78 (1)	3/83 (4)	0.62
All patients	3/89 (3)	7/91 (8)	0.33

N Engl J Med 2010;363:620

INSTAGE trial design

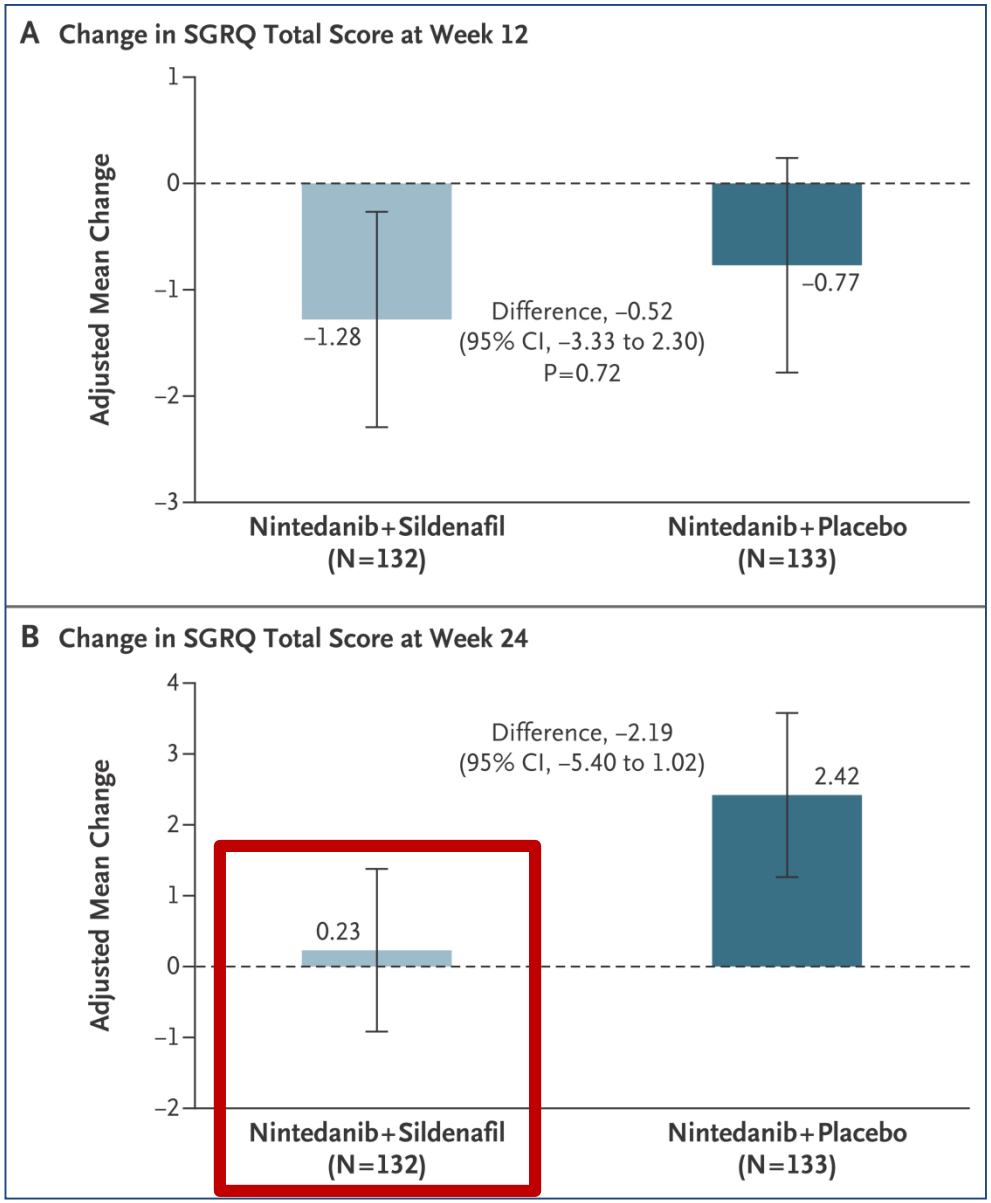




- 24 week, double blinded, RCT, phase III (n=274)
- DLco ≤ 35 % predicted.
- Change from baseline in the total score on the SGRQ at week 12

N Engl J Med 2018;379:1722

Change from baseline in the SGRQ score



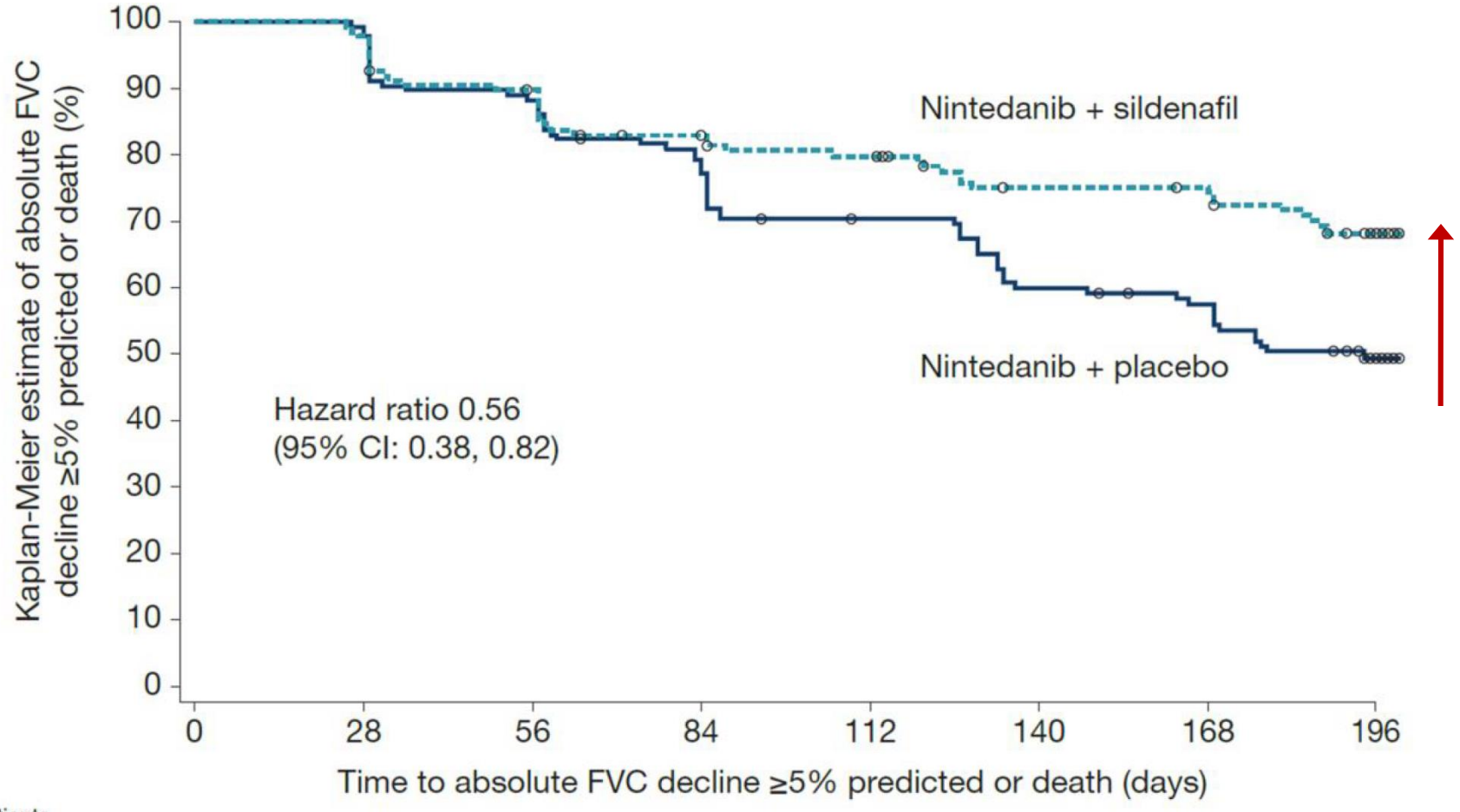
N Engl J Med 2018;379:1722

Adverse events

Event	Nintedanib + Sildenafil (N=137)	Nintedanib + Placebo (N=136)
	no. of patients (%)	
Any adverse event	133 (97.1)	127 (93.4)
Most frequent adverse events†		
Diarrhea	79 (57.7)	66 (48.5)
Nausea	22 (16.1)	14 (10.3)
Headache	21 (15.3)	10 (7.4)
Decreased appetite	20 (14.6)	23 (16.9)
Cough	20 (14.6)	13 (9.6)
Vomiting	19 (13.9)	10 (7.4)
Dyspnea	18 (13.1)	13 (9.6)
Severe adverse event‡	35 (25.5)	40 (29.4)
Serious adverse event§	37 (27.0)	44 (32.4)
Fatal adverse event	12 (8.8)	13 (9.6)
Adverse event leading to premature discontinuation of nintedanib only	2 (1.5)	3 (2.2)
Adverse event leading to premature discontinuation of sildenafil or placebo only	6 (4.4)	2 (1.5)
Adverse event leading to premature discontinuation of nintedanib plus either sildenafil or placebo	19 (13.9)	23 (16.9)
Major adverse cardiovascular event¶	4 (2.9)	6 (4.4)

N Engl J Med 2018;379:1722

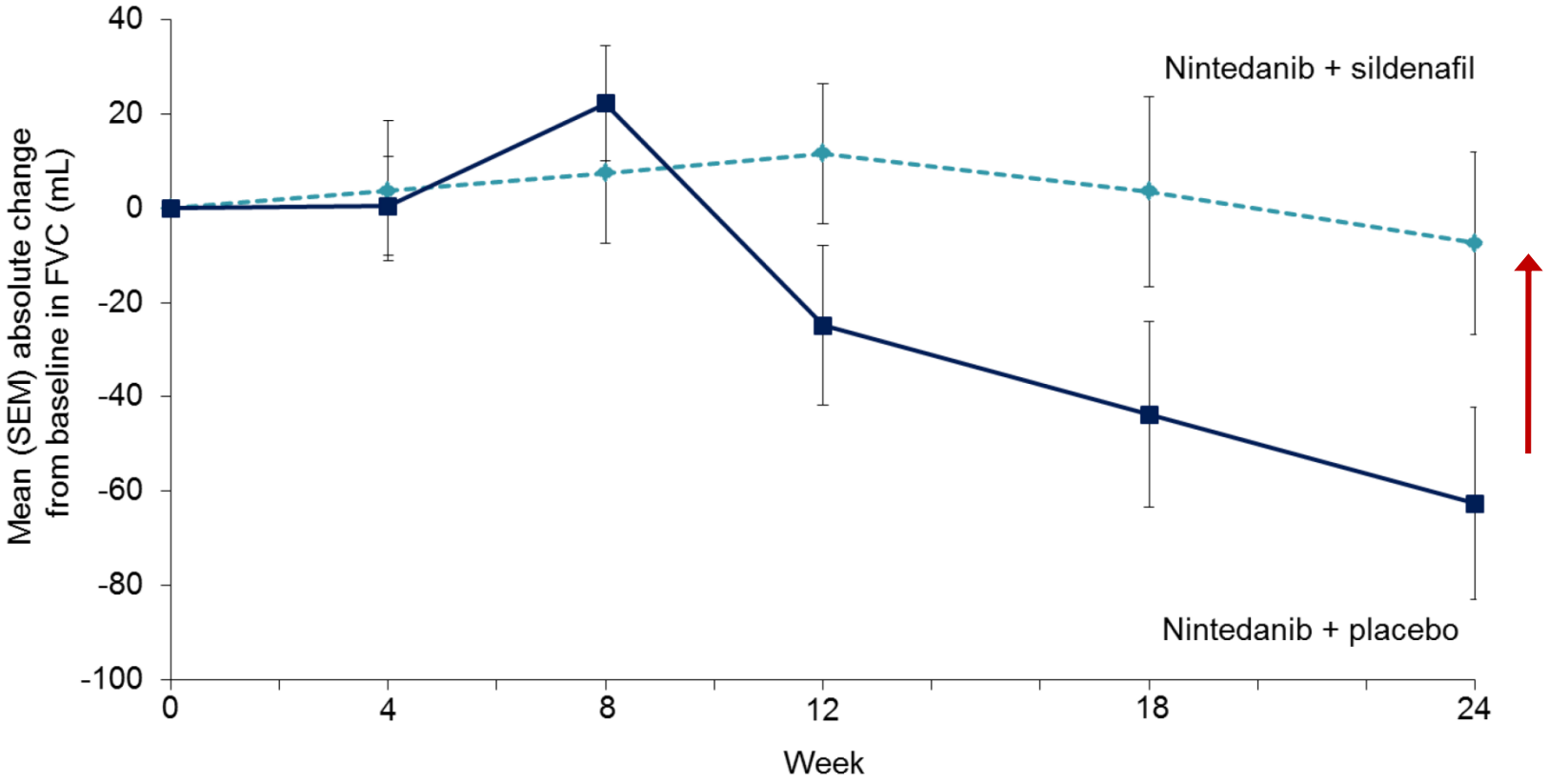
Time to FVC decline ≥ 5% pred. or death



No. of patients								
Nintedanib + sildenafil	137	134	120	109	103	92	91	76
Nintedanib + placebo	136	135	120	107	93	79	73	57

N Engl J Med 2018;379:1722

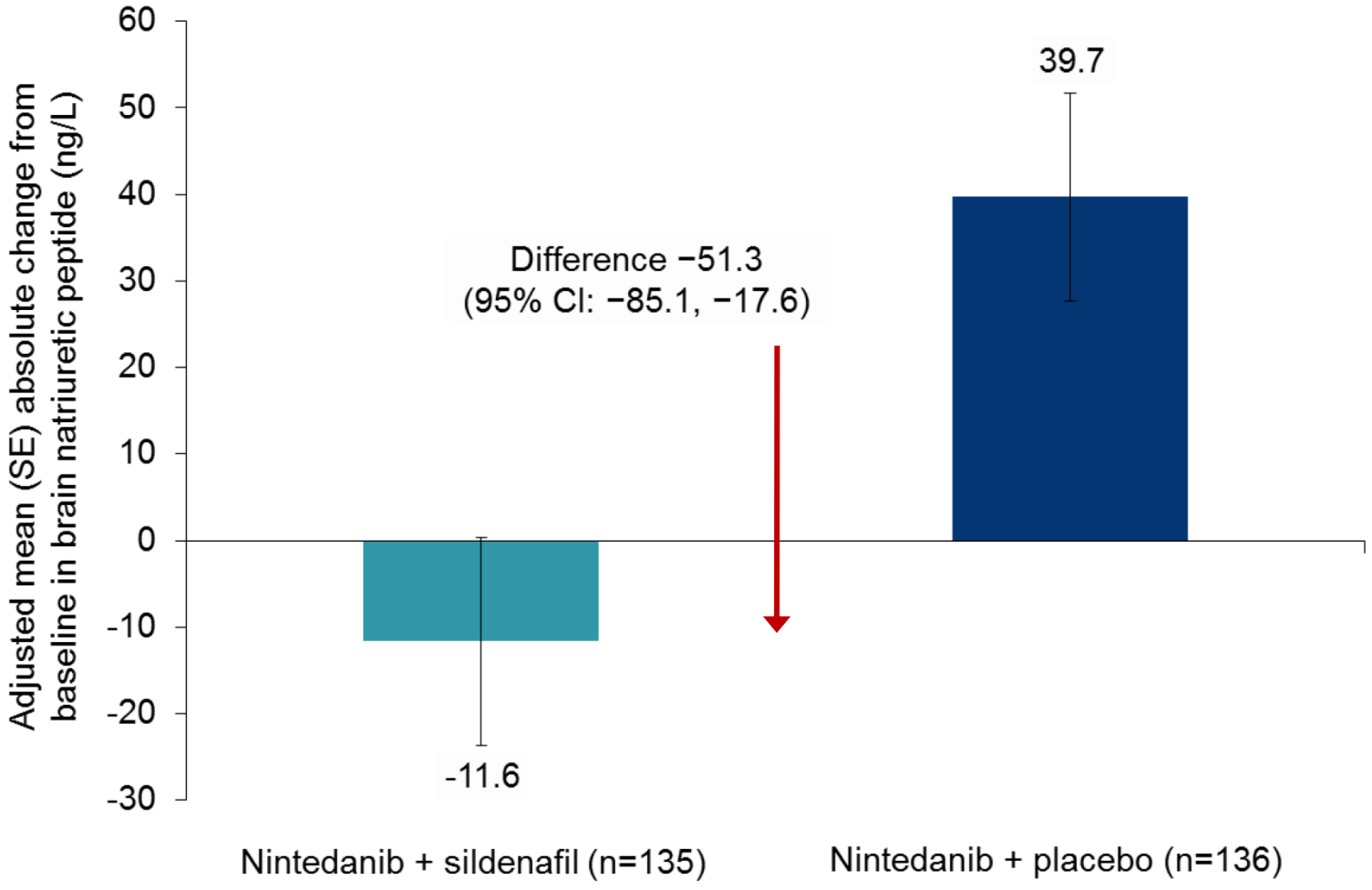
Change from baseline in FVC over time



No. of patients						
Nintedanib + sildenafil	137	132	124	119	109	109
Nintedanib + placebo	136	135	126	124	112	108

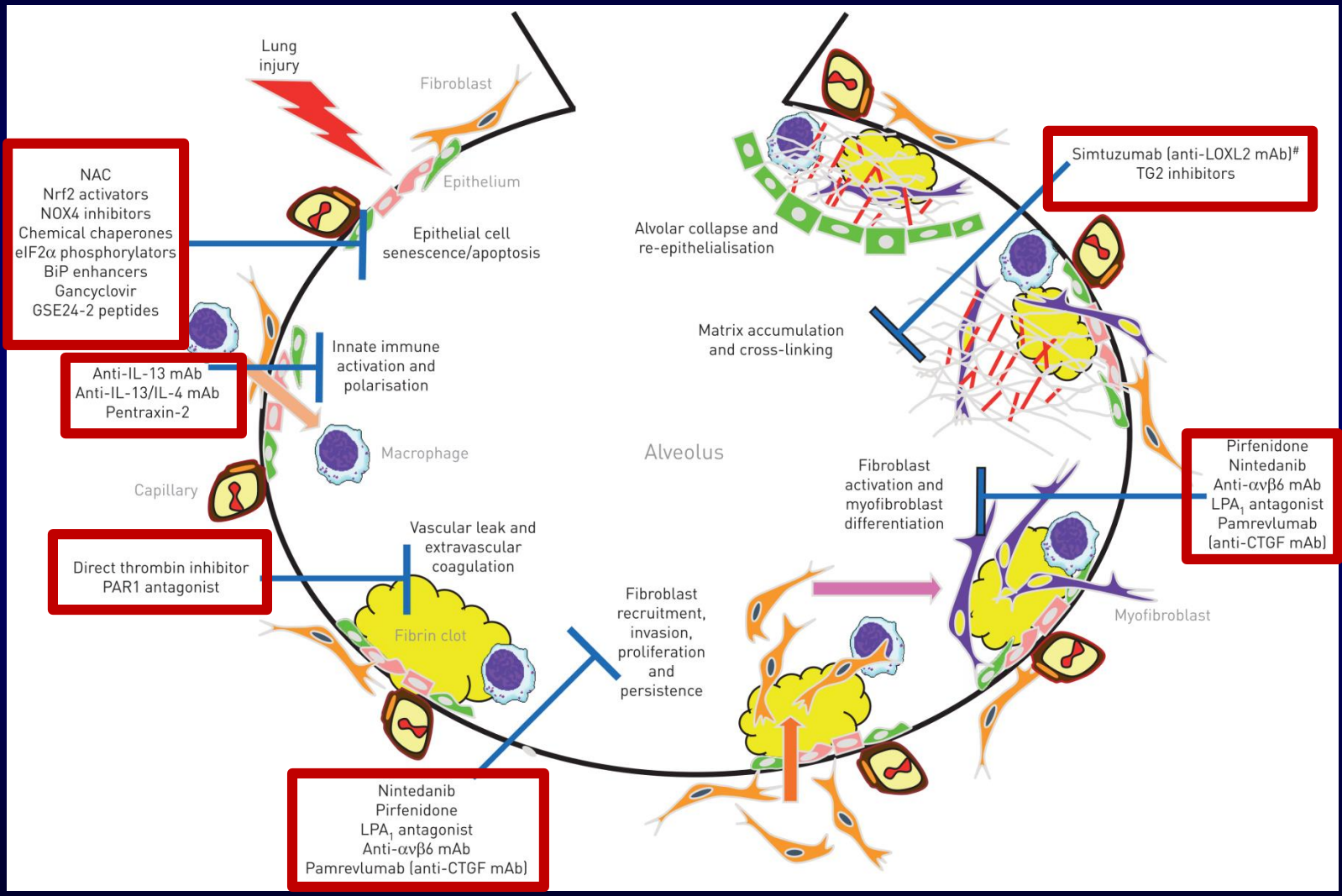
N Engl J Med 2018;379:1722

Change from baseline in BNP at week 24



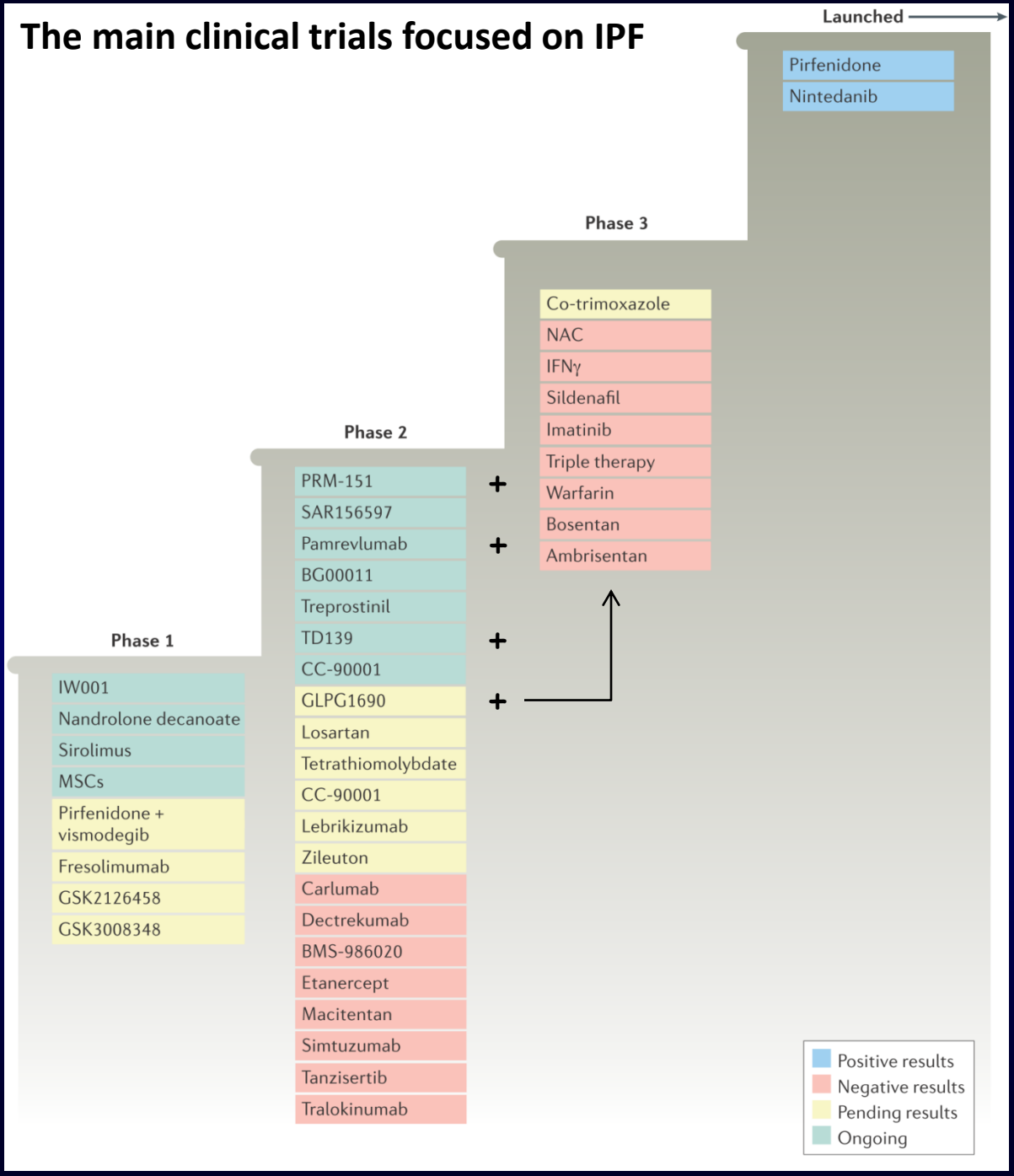
N Engl J Med 2018;379:1722

Targeting aberrant responses to injury



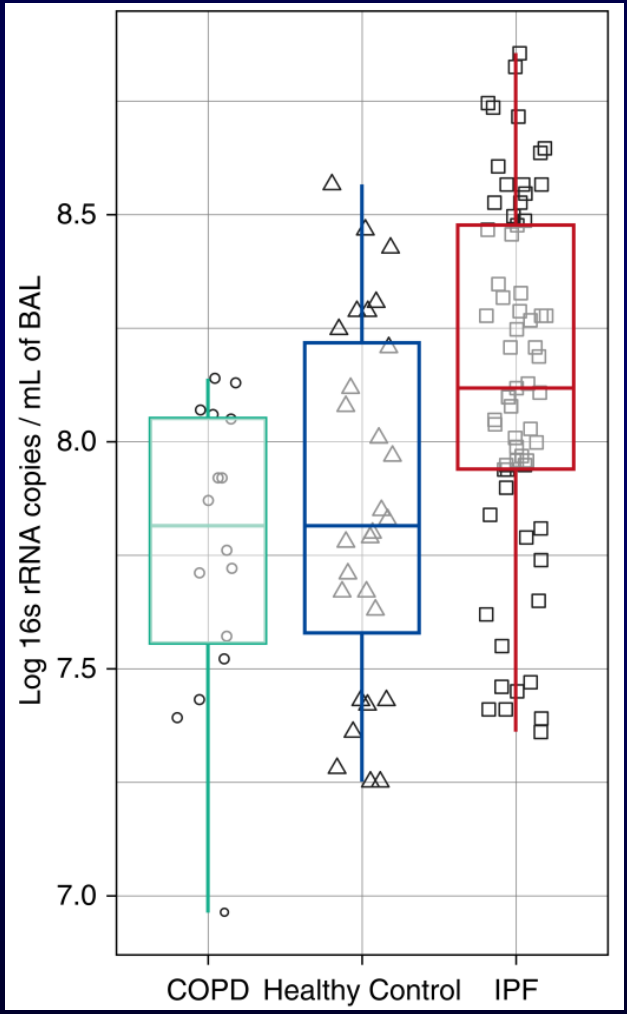
Eur Respir Rev 2017;26:170071

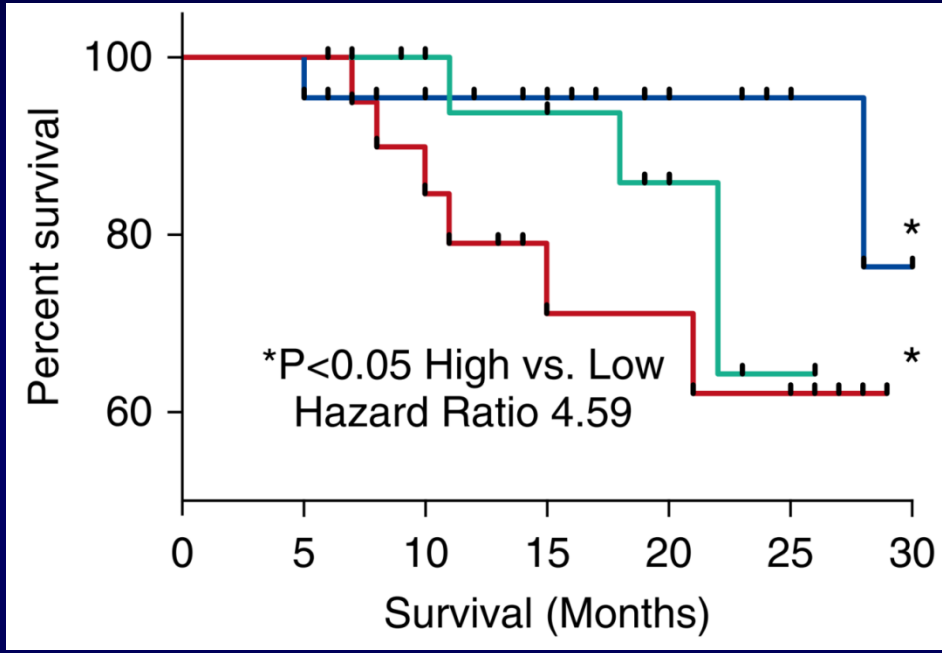
The main clinical trials focused on IPF



Nature review 2017

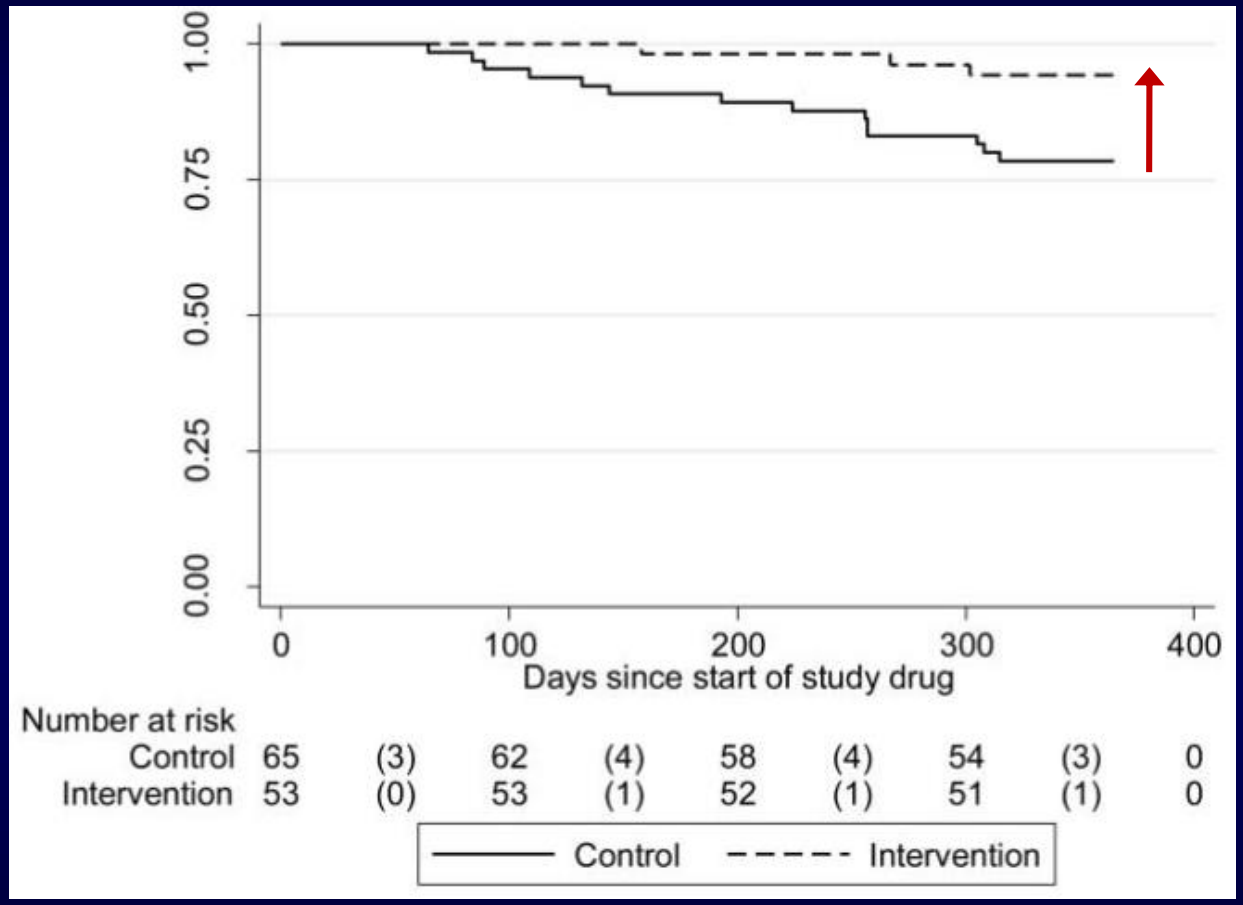
Bacterial burden is increased in IPF





Am J Respir Crit Care Med 2014;190(8):906

Co-trimoxazole improve survival in IPF

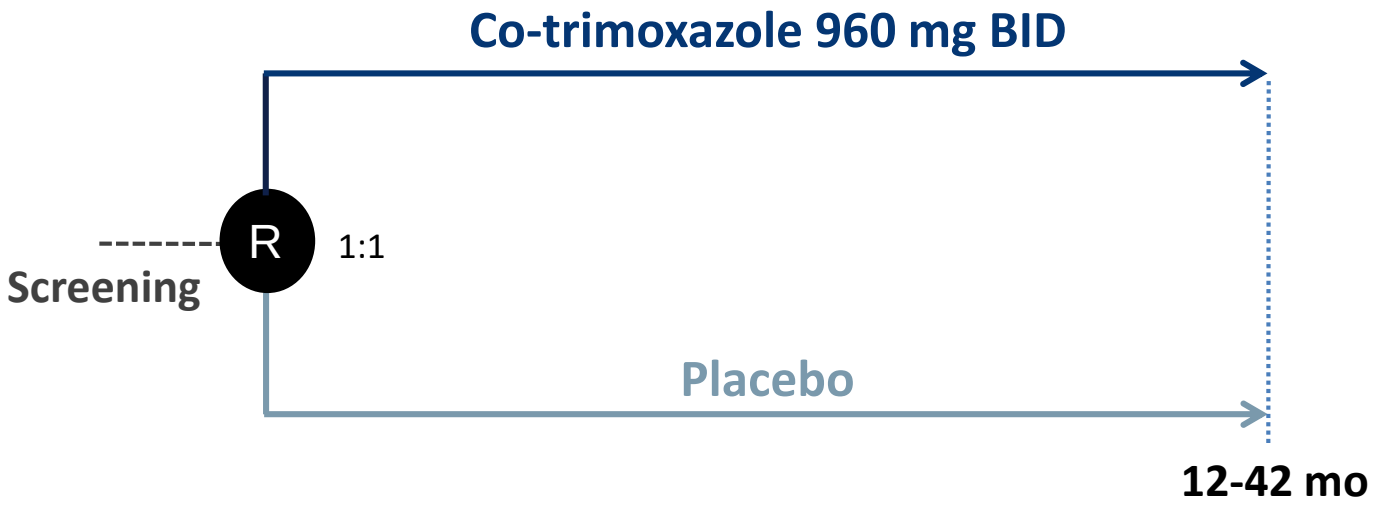


- 181 fibrotic IIP (89% IPF)
- QOL ↑, oxygen requirement ↓, death (HR 0.21), infection ↓

Thorax 2013;68:155

The Efficacy and Mechanism Evaluation of Treating Idiopathic Pulmonary fibrosis with the Addition of Co-trimoxazole (EME-TIPAC): study protocol for a randomised controlled trial

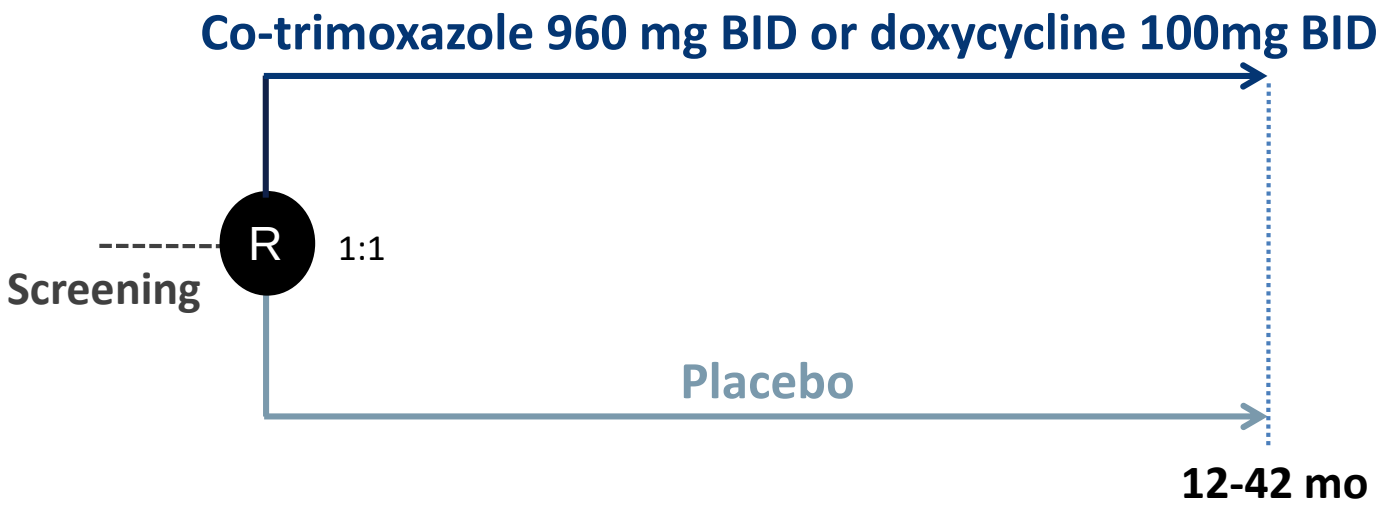
Matthew Hammond[1*], Allan B. Clark[1], Anthony P. Cahn[2], Edwin R. Chilvers[3], William Duncan Fraser[4], David M. Livermore[4], Toby M. Maher[5], Helen Parfrey[6], Ann Marie Swart[1], Susan Stirling[1], David Thickett[7], Moira Whyte[8] and Andrew Wilson[4]



- Randomized, double blinded, placebo-controlled, phase 3 (n=330)
- FVC ≤ 75 % pred.
- Time to death, transplant or first non-elective hospital admission

Trials 2018;9:89

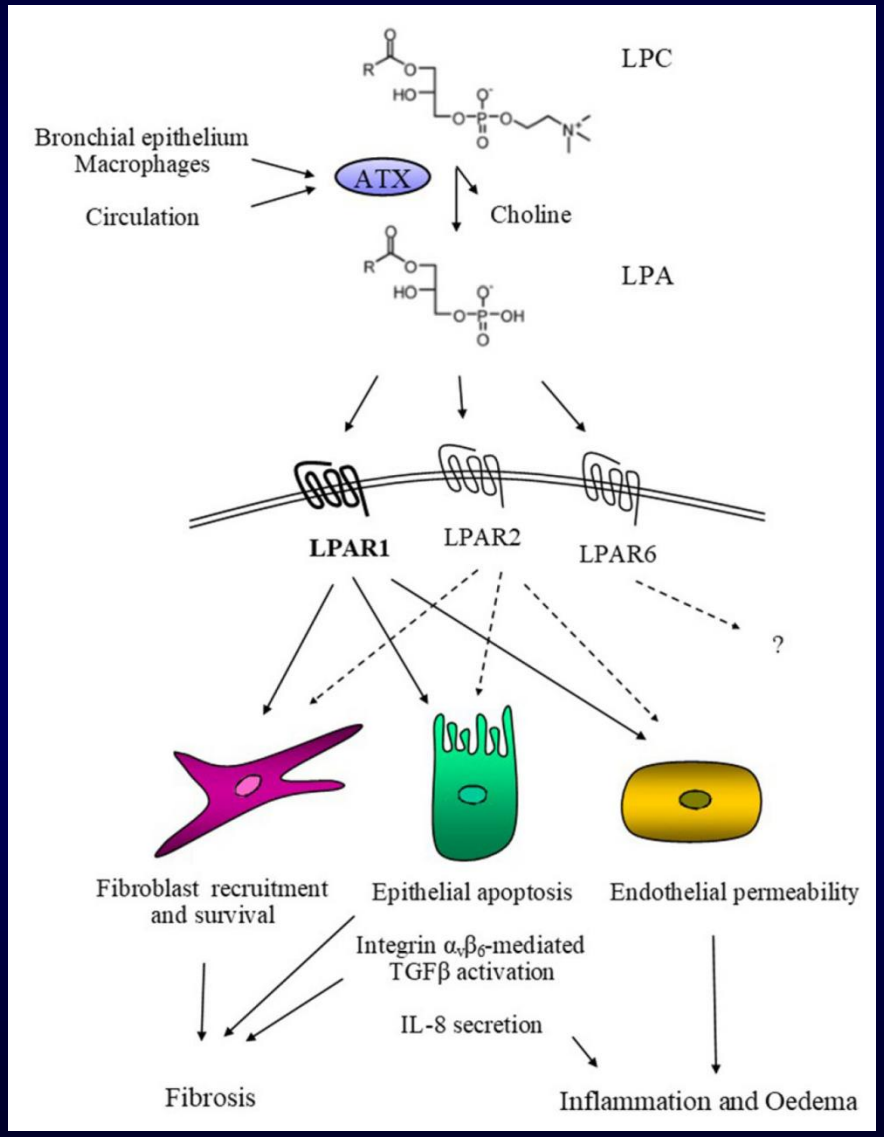
Study of Clinical Efficacy of Antimicrobial Therapy Strategy Using Pragmatic Design in IPF (CleanUP-IPF)



- Randomized, open-label, placebo-controlled, phase 3 (n=500)
- ≥ 40 years of age
- Time to first non-elective, respiratory hospitalization or all-cause mortality

www.clinicaltrials.gov

Autotaxin: mode of action

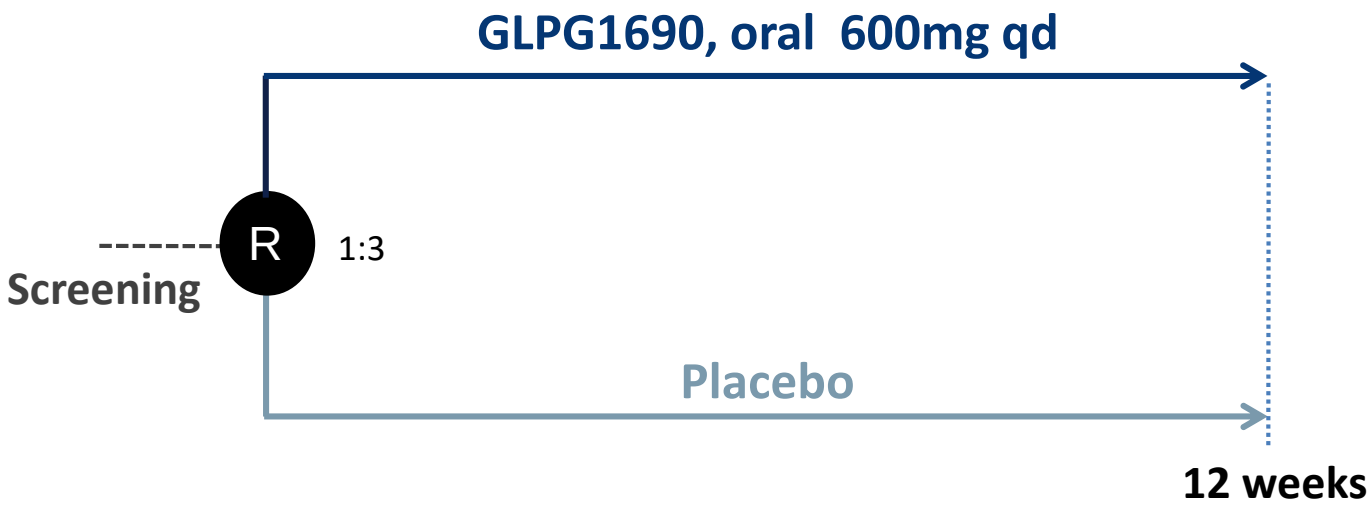


Lysophosphatidic acid

Front. Med. 2018;5:180

Safety, tolerability, pharmacokinetics, and pharmacodynamics of GLPG1690, a novel autotaxin inhibitor, to treat idiopathic pulmonary fibrosis (FLORA): a phase 2a randomised placebo-controlled trial

Toby M Maher, Ellen M van der Aar, Olivier Van de Steen, Lisa Allamassey, Julie Desrivot, Sonia Dupont, Liesbeth Fagard, Paul Ford, Ann Fieuw, Wim Wuyts



- Randomized, double blinded, placebo-controlled ,phase 2a (n=23)
- FVC ≥ 50 % pred., DL_{CO} ≥ 30 % pred.
- Safety, tolerability, pharmacokinetics, and pharmacodynamics

Lancet Respir Med 2018;6:627

Treatment emergent adverse events

	Placebo group (n=6)	GLPG1690 group (n=17)
≥1 event	4 (67%)	11 (65%)
≥1 serious event	2 (33%)	1 (6%)
≥1 event resulting in death	0	0
≥1 event by worst severity		
Mild	0	4 (24%)
Moderate	3 (50%)	6 (35%)
Severe	1 (17%)	1 (6%)
≥1 event related to treatment	0	2 (12%)
≥1 event leading to temporary discontinuation of study drug	0	2 (12%)
≥1 event leading to permanent discontinuation of study drug	1 (17%)	1 (6%)

- Infections and respiratory, thoracic, and mediastinal disorders

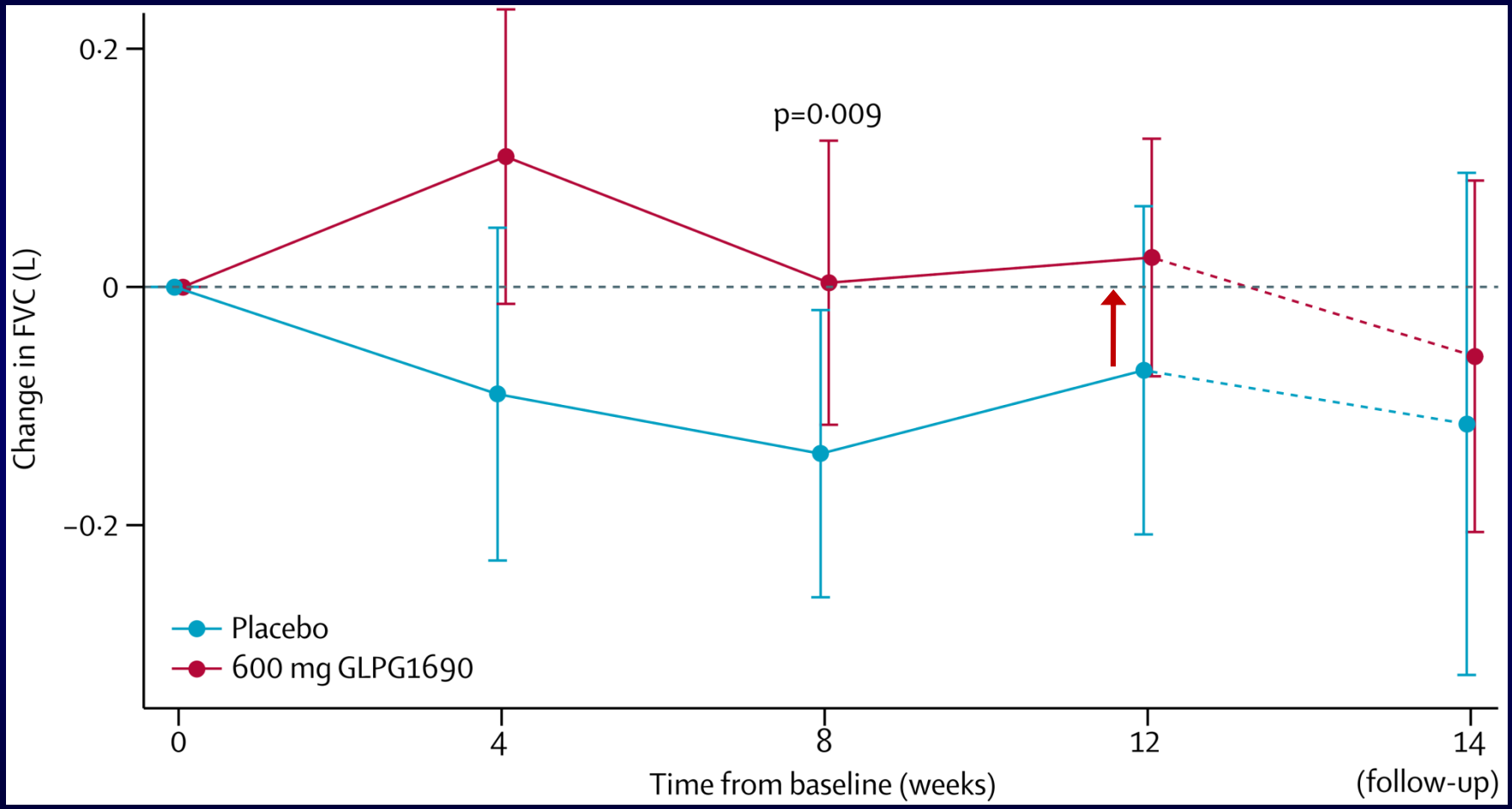
Lancet Respir Med 2018;6:627

Treatment emergent adverse events

	Placebo group (n=6)		GLPG1690 group (n=17)	
	Number of patients (%)	Number of events	Number of patients (%)	Number of events
Infections and infestations	3 (50%)	8	7 (41%)	10
Lower respiratory tract infection	2 (33%)	3	2 (12%)	3
Nasopharyngitis	1 (17%)	1	2 (12%)	2
Orchitis	1 (17%)	1	0	0
Urinary tract infection	1 (17%)	3	0	0
Respiratory, thoracic, and mediastinal disorders	2 (33%)	4	4 (24%)	8
Cough	1 (17%)	1	2 (12%)	2
Dyspepsia	1 (17%)	1	2 (12%)	2
Productive cough	0	0	2 (12%)	2
Haemothorax	1 (17%)	1	0	0
Pneumothorax spontaneous	1 (17%)	1	0	0
Gastrointestinal disorders	2 (33%)	2	2 (12%)	2
Diarrhoea	2 (33%)	2	1 (6%)	1

Lancet Respir Med 2018;6:627

Mean changes in FVC from baseline



- Mean change from baseline in FVC at week 12: 25 ml vs. -70 ml

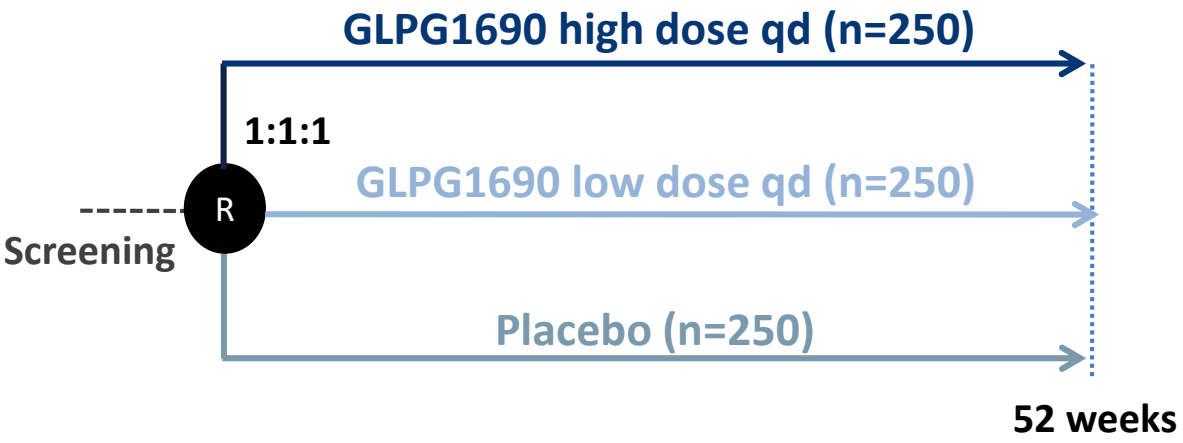
Lancet Respir Med 2018;6:627

Galápagos

GLPG1690 in IPF Patients in addition to local standard of care

ISABELA

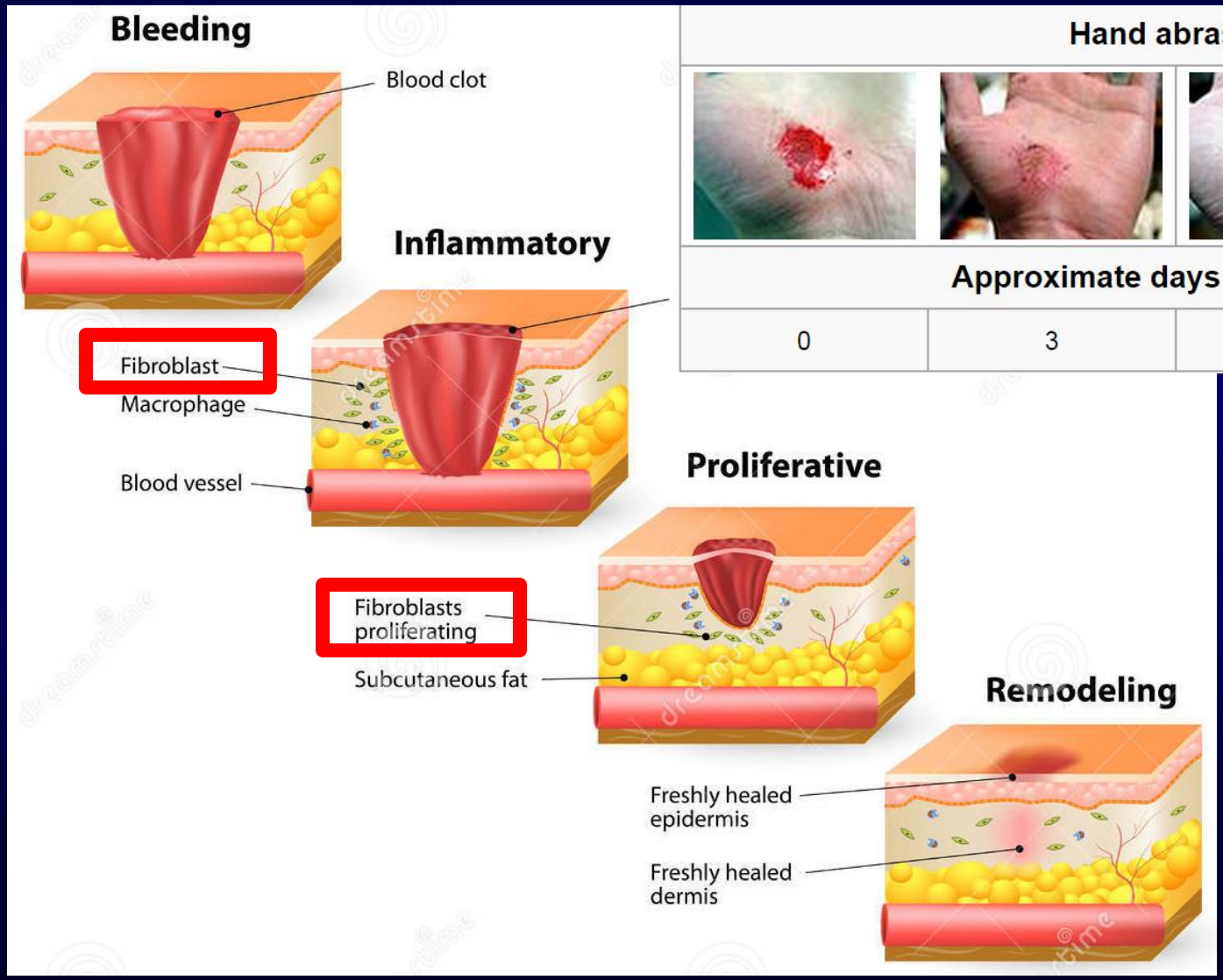
- ISABELA 1 & 2

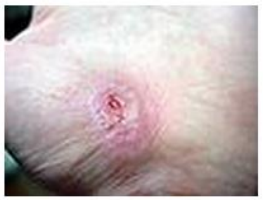
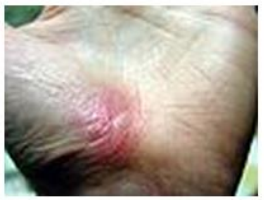


- Randomized, double blinded, placebo-controlled, phase 3 (n=1500)
- FVC ≥ 45 % pred., DL_{CO} ≥ 30 % pred.
- Rate of decline of FVC (in mL) over a period of 52 weeks

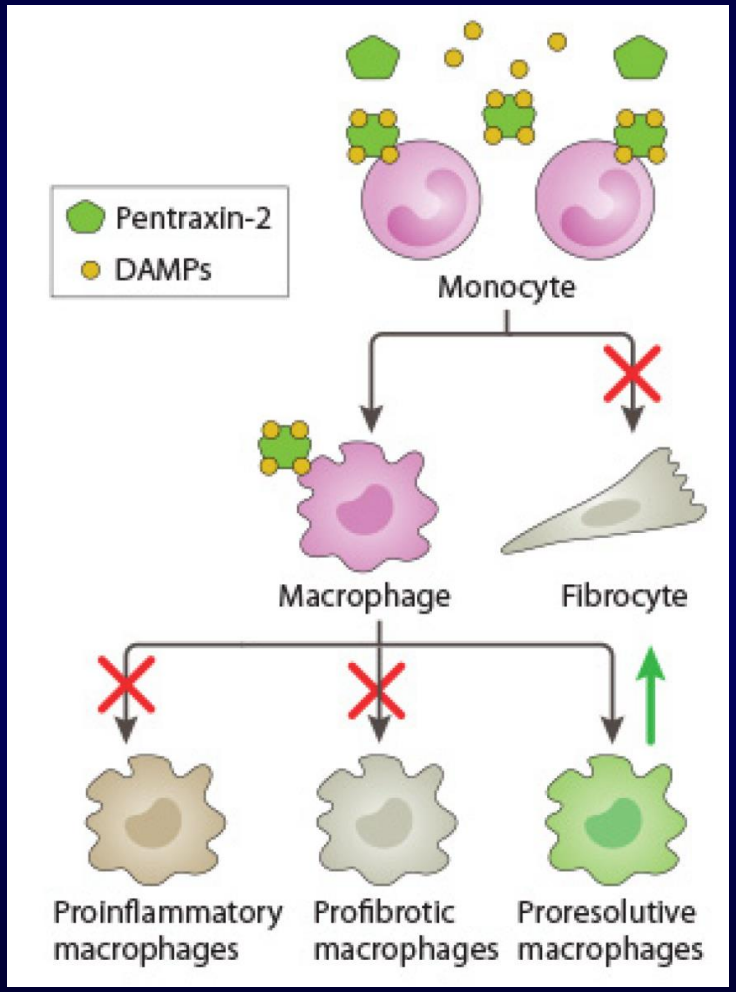
www.clinicaltrials. gov

Fibrosis: Wound Healing Process



Hand abrasion			
			
Approximate days since injury			
0	3	17	30

Pentraxin 2: mode of action

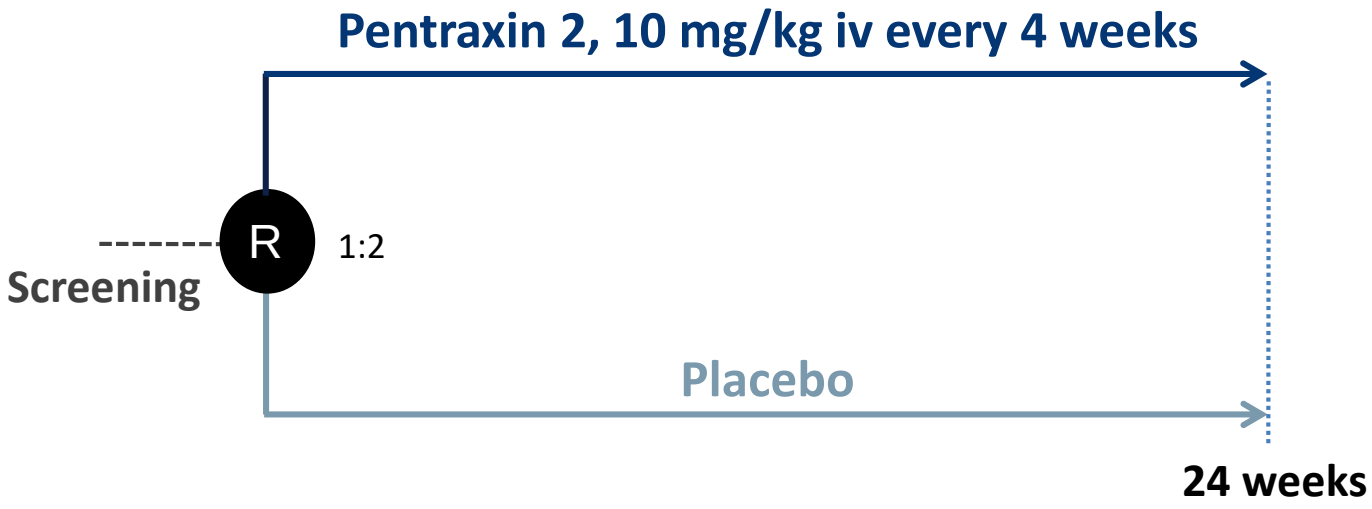


Front Immunol 2018;9:2328

Effect of Recombinant Human Pentraxin 2 vs Placebo on Change in Forced Vital Capacity in Patients With Idiopathic Pulmonary Fibrosis

A Randomized Clinical Trial

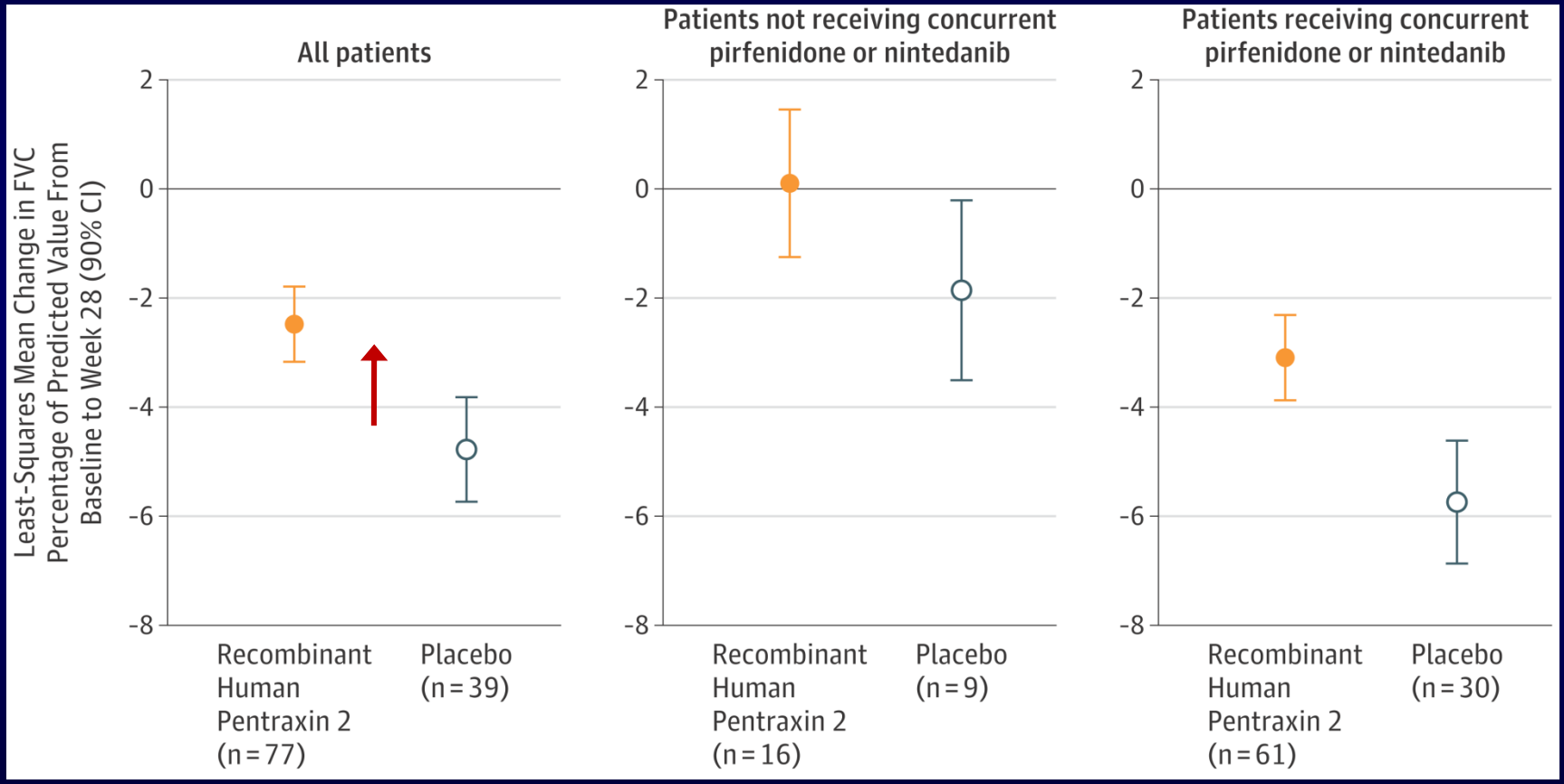
Ganesh Raghu, MD; Bernt van den Blink, MD, PhD; Mark J. Hamblin, MD; A. Whitney Brown, MD; Jeffrey A. Golden, MD; Lawrence A. Ho, MD; Marlies S. Wijsenbeek, MD; Martina Vasakova, MD, PhD; Alberto Pesci, MD; Danielle E. Antin-Ozerkis, MD; Keith C. Meyer, MD; Michael Kreuter, MD; Hugues Santin-Janin, PhD; Geert-Jan Mulder, MD; Brian Bartholmai, MD; Renu Gupta, MD; Luca Richeldi, MD



- Randomized, double blinded, placebo-controlled, phase 2 (n=117)
- FVC 50-90 % pred., DL_{CO} 25-90 % pred.
- Change from baseline to week 28 in FVC

JAMA 2018;319:2299

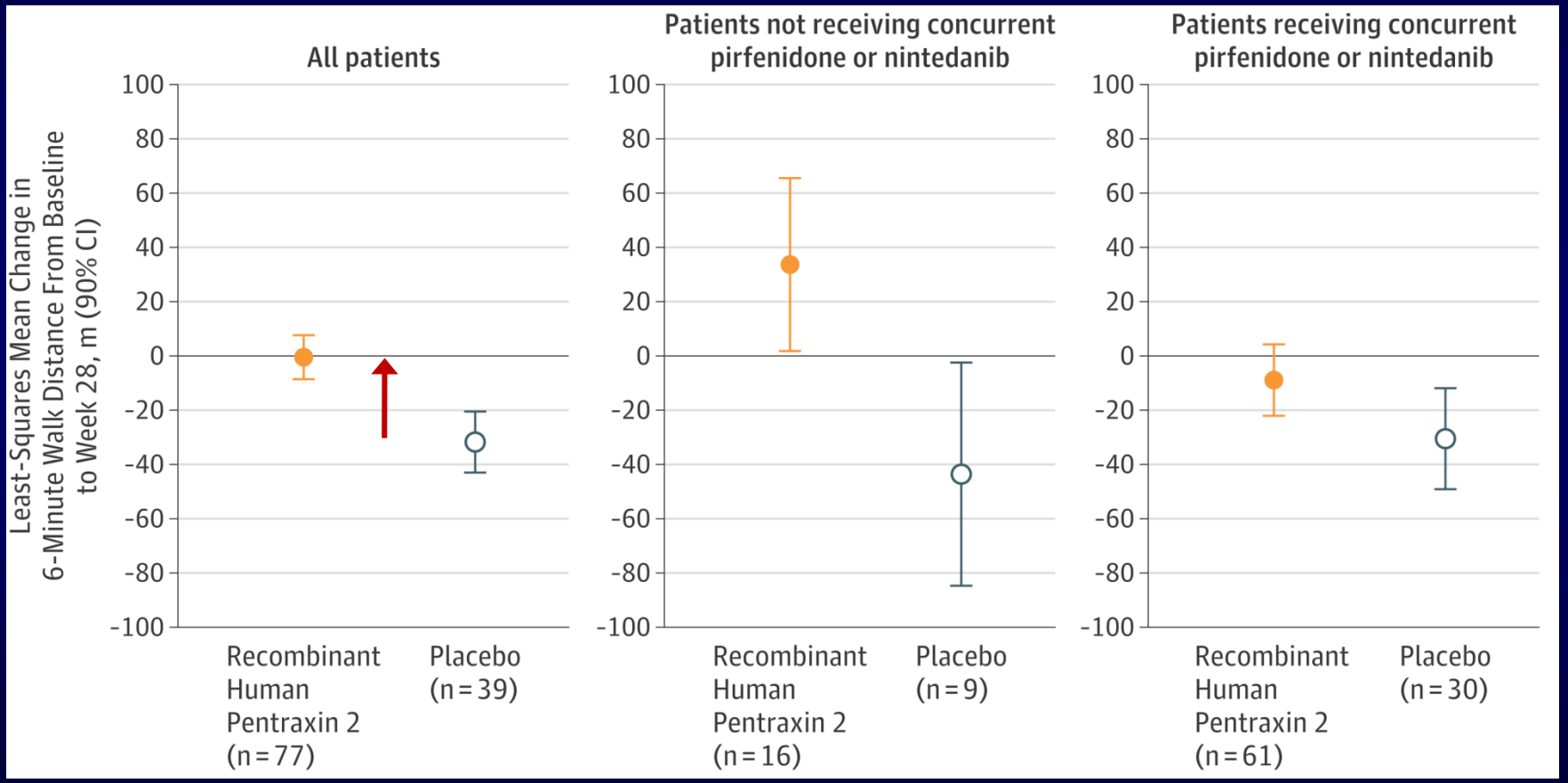
Changes in FVC



- Least-squares mean change; 95.7% completed study; difference 2.3 (95% CI, 1.1-3.5; p=0.01)

JAMA 2018;319:2299

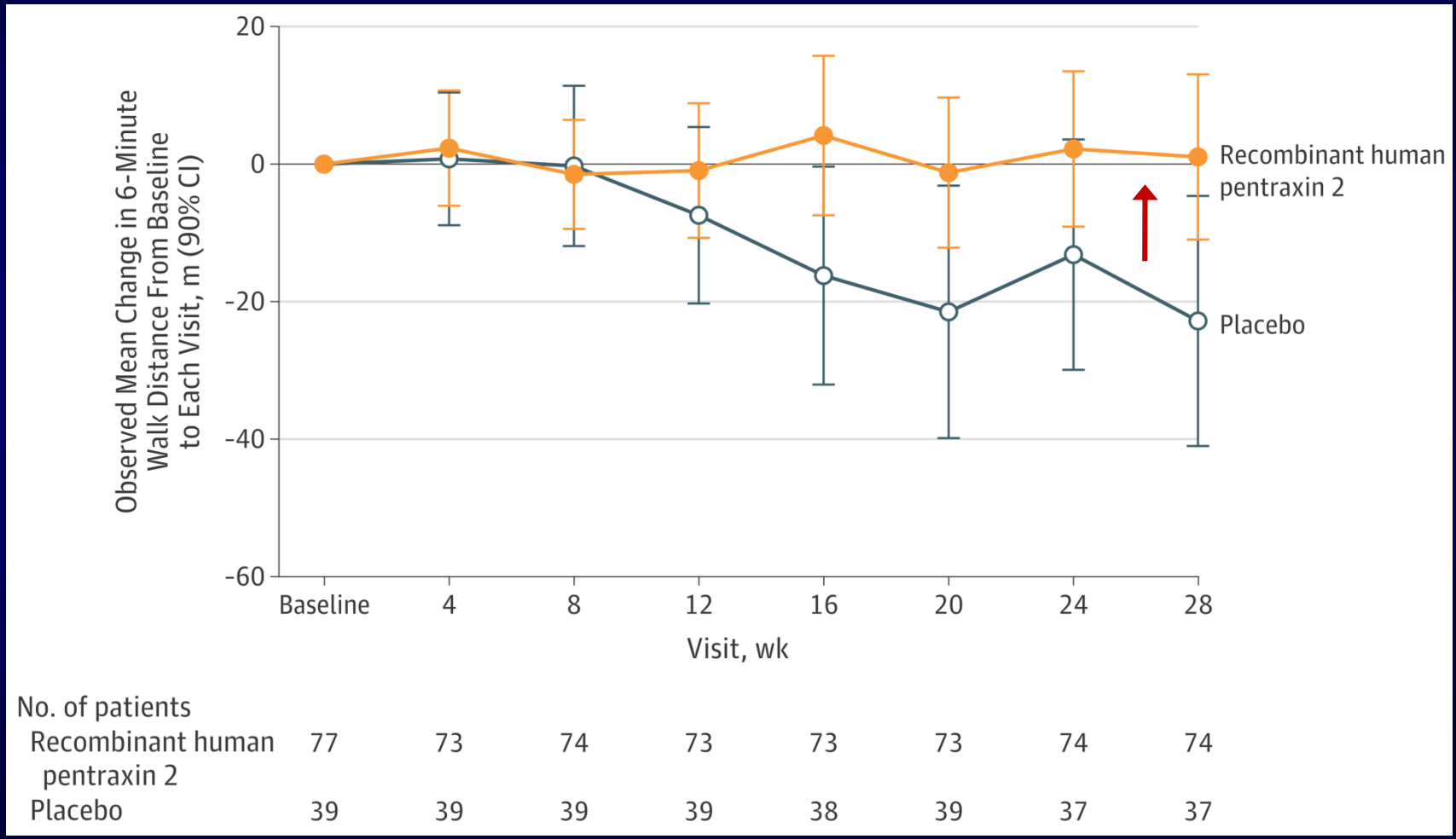
Changes in 6 minute walk distance



- Least-squares mean change; difference 31.3 (90% CI, 17.4-45.1; p<0.01)

JAMA 2018;319:2299

Changes in 6 minute walk distance



- Observed mean change

JAMA 2018;319:2299

Adverse events

Events	No. (%) of Patients With Event	
	Recombinant Human Pentraxin 2 (n = 77)	Placebo (n = 39)
Any adverse event	71 (92)	36 (92)
Most frequent adverse events[b]		
Cough	14 (18)	2 (5)
Fatigue	13 (17)	4 (10)
Nasopharyngitis	12 (16)	9 (23)
Headache	11 (14)	3 (8)
Idiopathic pulmonary fibrosis	11 (14)	5 (13)
Diarrhea	9 (12)	2 (5)
Bronchitis	8 (10)	5 (13)
Dyspnea	7 (9)	4 (10)
Upper respiratory tract infection	7 (9)	5 (13)
Back pain	3 (4)	4 (10)
Severe adverse events[c]	7 (9)	2 (5)
Serious adverse events[d]	6 (8)	4 (10)
Fatal adverse events	0	1 (3)
Adverse events leading to discontinuation	2 (3)	1 (3)
Pneumonia	0	1 (3)
Lung carcinoma cell type unspecified stage II	1 (1)	0
Idiopathic pulmonary fibrosis	1 (1)	0

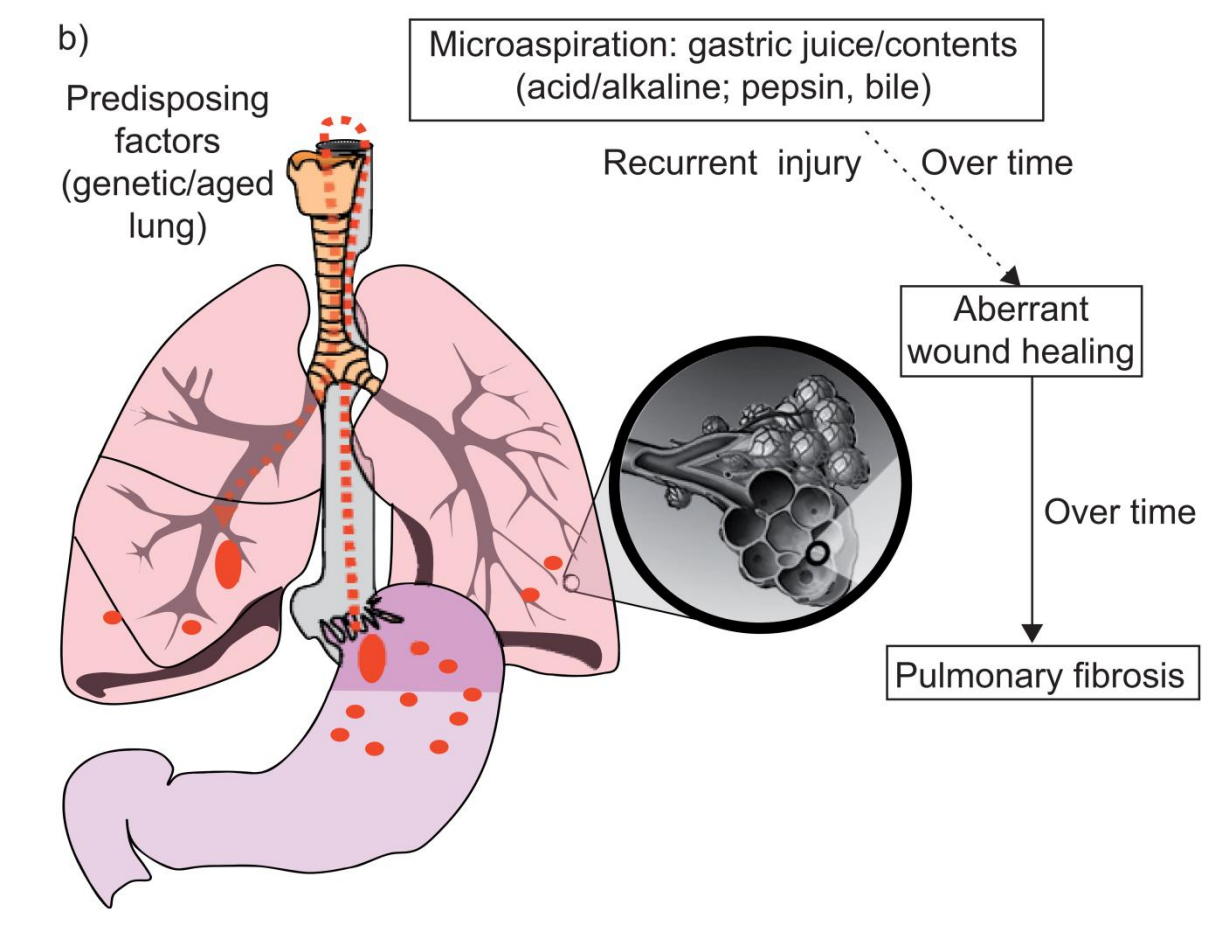
JAMA 2018;319:2299

Summary

- Pharmacotherapy for IPF: current status
  - acute exacerbation, survival, long-term safety
  - limited in terms of tolerance and efficacy

- Pharmacotherpay for IPF: future potential
  - high dose tablets: tolerance ↑
  - combination treatment: efficacy ↑
  - new antifibrotic agents: efficacy ↑

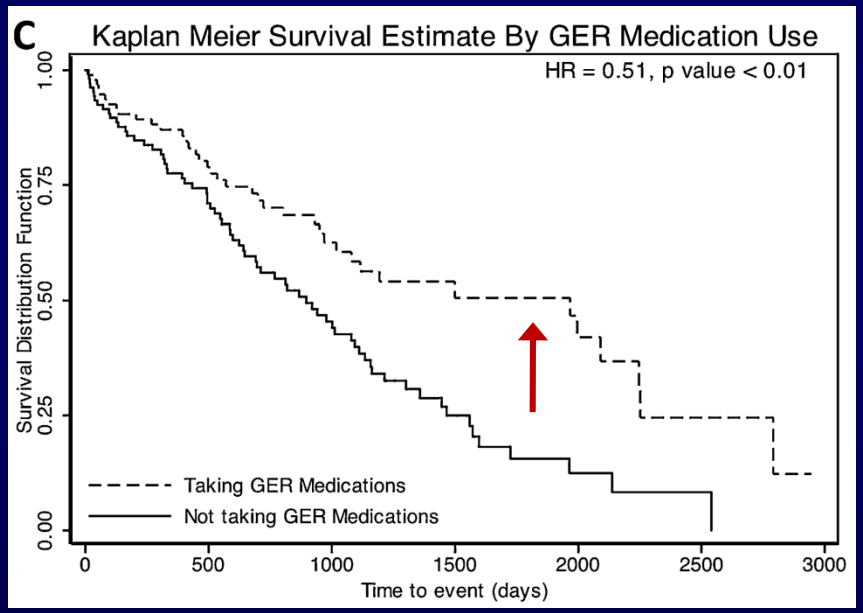
Gastro-esophageal reflux and microaspiration in IPF



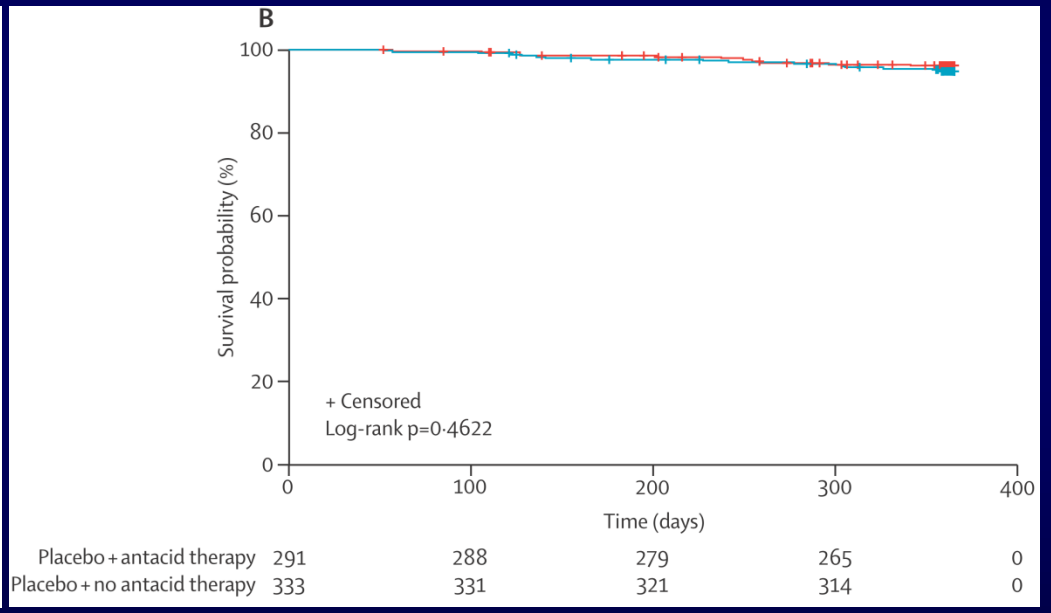
Eur Respir J 2012;39:242

Anti-acid therpy in IPF

- Better prognosis



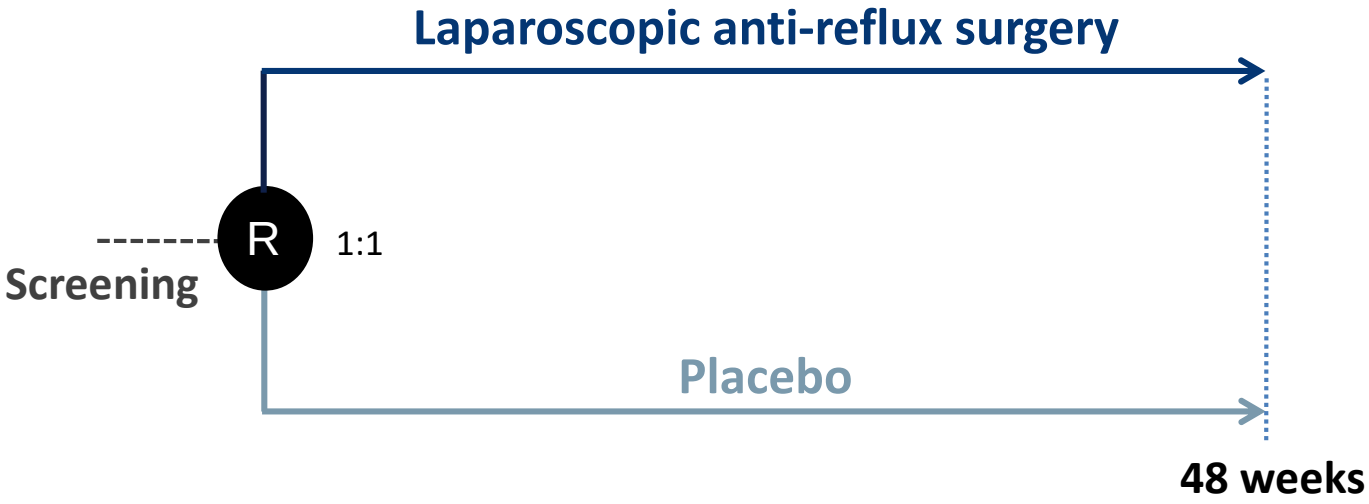
- No impact on outcome

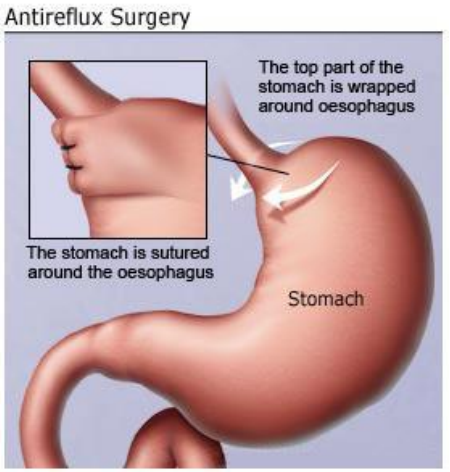


Am J Repir Crit Care Med 2011;184:1390, Lancet Respir Med 2016;4:381

Laparoscopic anti-reflux surgery for the treatment of idiopathic pulmonary fibrosis (WRAP-IPF): a multicentre, randomised, controlled phase 2 trial

Ganesh Raghu, Carlos A Pellegrini, Eric Yow, Kevin R Flaherty, Keith Meyer, Imre Noth, Mary Beth Scholand, John Cello, Lawrence A Ho, Sudhakar Pipavath, Joyce S Lee, Jules Lin, James Maloney, Fernando J Martinez, Ellen Morrow, Marco G Patti, Stan Rogers, Paul J Wolters, Robert Yates, Kevin J Anstrom, Harold R Collard

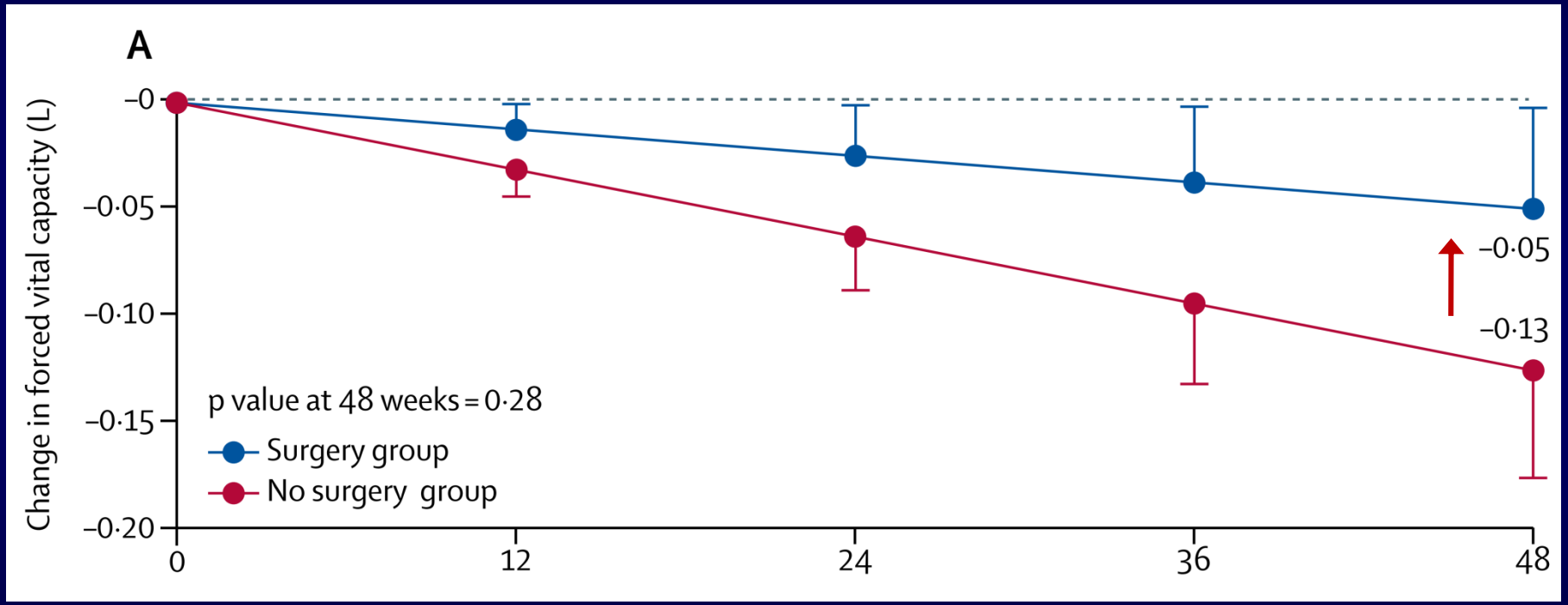




- Randomized, unblinded, placebo-controlled, phase 2 (n=58)
- FVC ≥ 50 % pred. abnormal acid GERD (DeMeester score of ≥ 14.7)
- Change from baseline to week 48 in FVC

Lancet Respir Med 2018;6:707

Changes in FVC

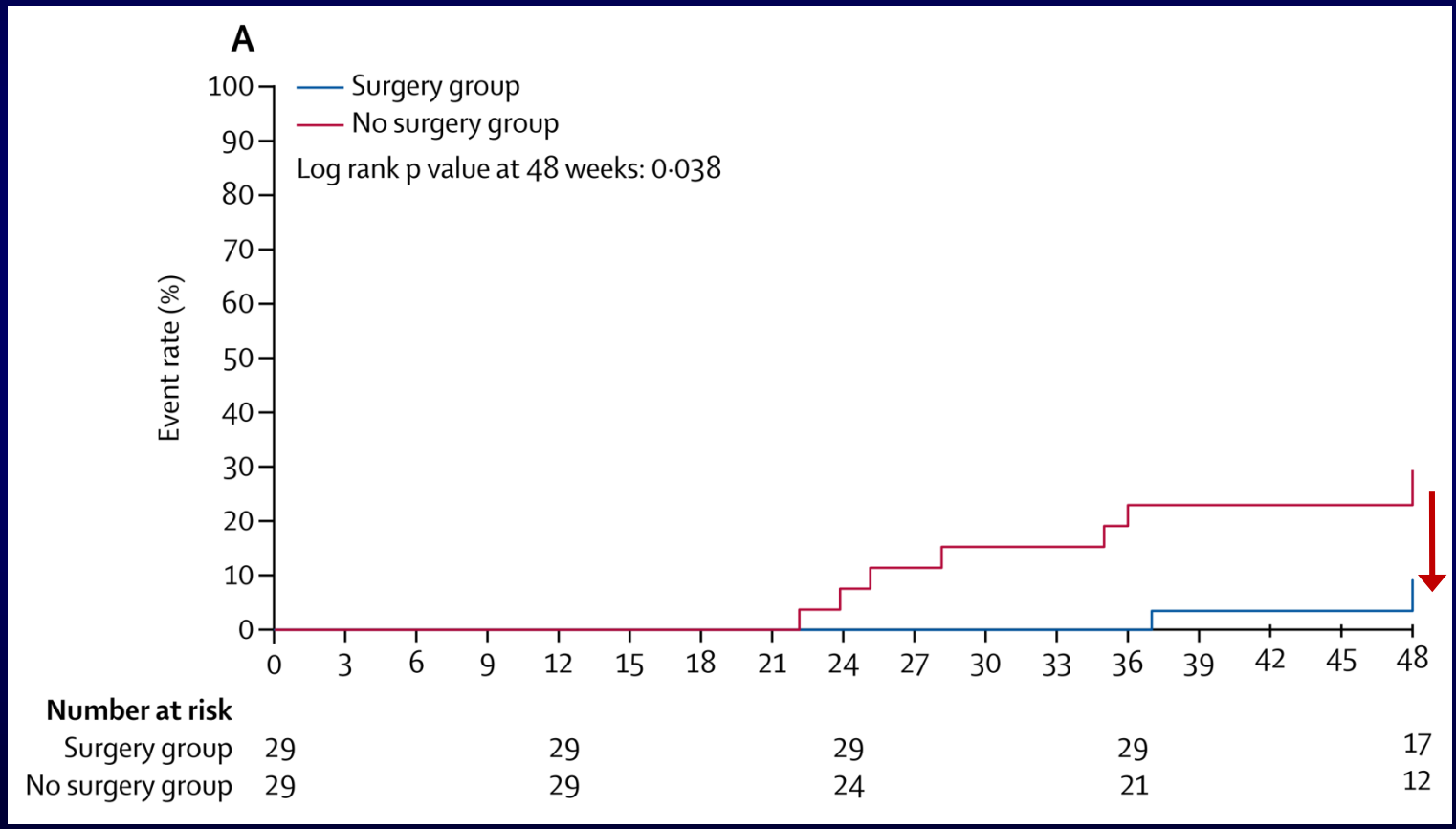


- Mixed effect models for repeated measures

Lancet Respir Med 2018;6:707

Time to the composite endpoint

- 10% decline in FVC or death



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Secondary endpoints

	Surgery (n=29)	No surgery (n=29)	p value
Clinical events*			
Acute exacerbation	1 (3%)	4 (16%)	0·19
Respiratory hospitalisation	2 (7%)	6 (21%)	0·25
Non-elective hospitalisation	5 (17%)	8 (28%)	0·35
Lung transplantation	0	1 (3%)	>0·99
Disease progression†			
Death	1 (3%)	4 (18%)	0·13
10% FVC decline or death	2 (9%)	7 (29%)	0·038
10% FVC decline, acute exacerbation, or death	2 (9%)	7 (28%)	0·048
Respiratory hospitalisation or death	2 (9%)	5 (19%)	0·16
Non-elective hospitalisation or death	5 (17%)	7 (26%)	0·50
10% FVC decline, 5 point UCSD Shortness of Breath Questionnaire increase, respiratory hospitalisation, or death	15 (57%)	15 (56%)	0·74

- Dysphagia (29%) and abdominal distention (14%) after surgery

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Summary

- Pharmacotherapy for IPF: current status
  - acute exacerbation, survival, long-term safety
  - limited in terms of tolerance and efficacy

- Pharmacotherpay for IPF: future potential
  - high dose tablets: tolerance ↑
  - combination treatment: efficacy ↑
  - new antifibrotic agents: efficacy ↑