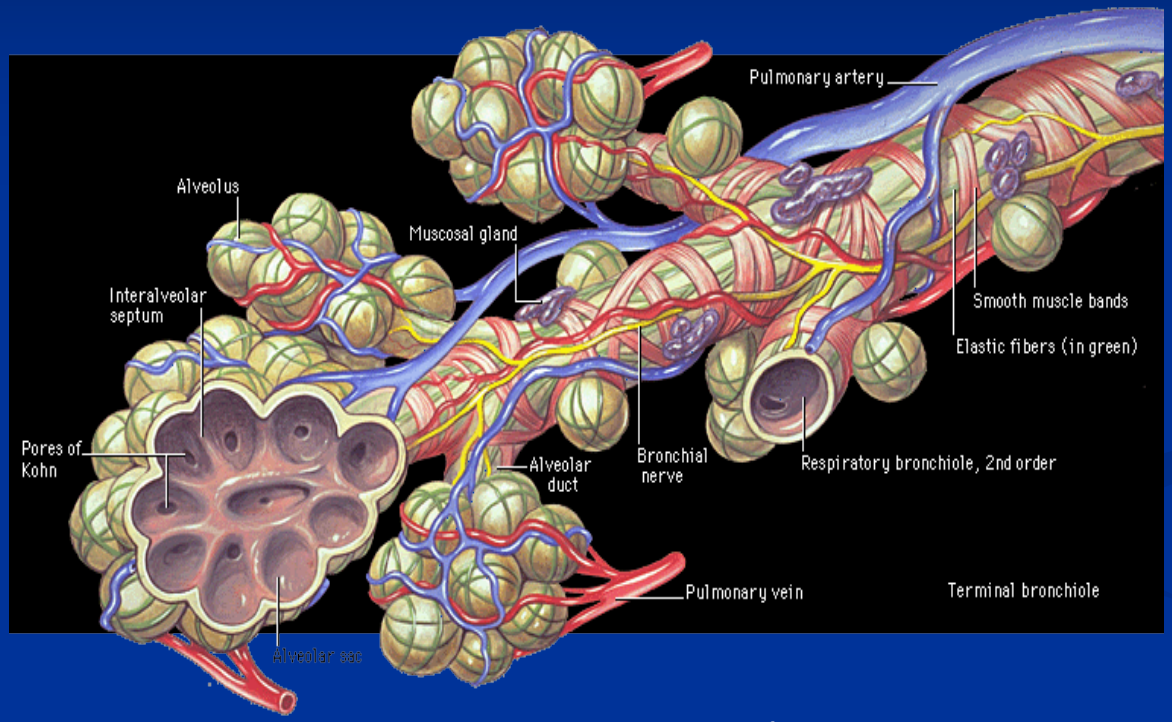
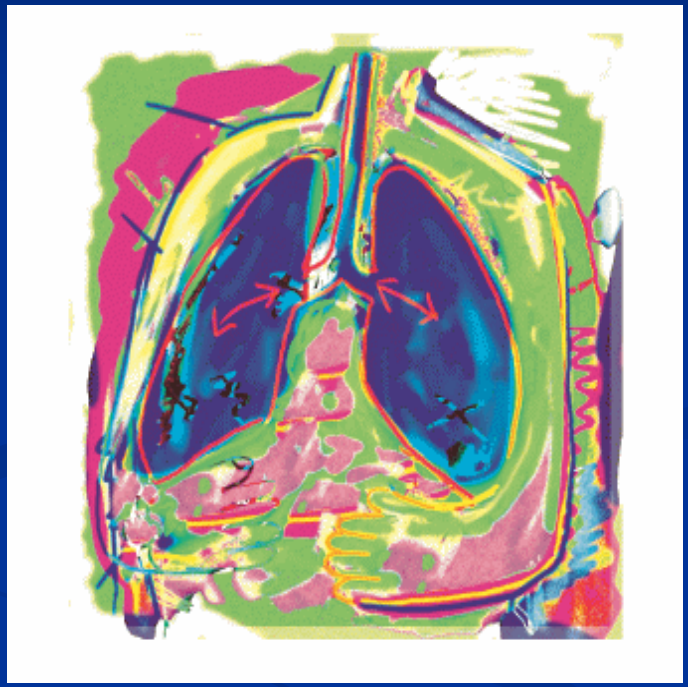
La Terapia della IPF oggi

Pneumologia 2018 – Milano 14-16 giugno





Alberto Pesci

alberto.pesci@unimib.it

Clinica Pneumologica
Università degli Studi di Milano - Bicocca
Ospedale San Gerardo – ASST Monza

Interstitial Lung Disease

Exposure-related:
- Occupational
- Environmental
- Avocational
- Medication

Idiopathic interstitial pneumonia (IIP)

Connective tissue disease:
- Scleroderma
- Rheum. arth
- Sjogren

Sarcoidosis

Other:
- Vasculitis/Diffuse alveolar hemorrhage (DAH)
- Langerhans cell histiocytosis (LCH)
- Eosinophilic pneumonias
- Neurofibromatosis
- LAM

Major

- Idiopathic pulmonary fibrosis (IPF)
- Respiratory bronchiolitis interstitial lung dis. (RBILD)
- Desquamative interstitial pneumonia (DIP)
- Cryptogenic organizing pneumonia (COP)
- Acute interstitial pneumonia (AIP)
- Nonspecific interstitial pneumonia (NSIP)

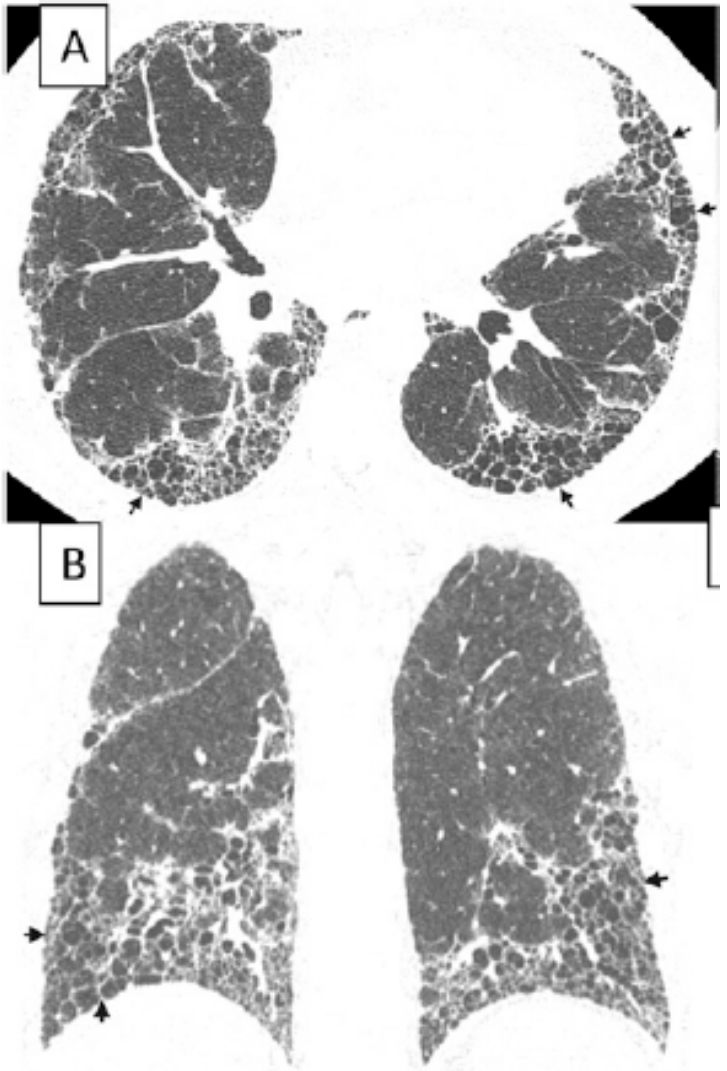
Rare

- Lymphocytic interstitial pneumonia (LIP)
- Idiopathic pleuroparenchymal fibroelastosis

Travis et al. Am J Respir Crit Care Med 2013; 188:733-48

Definition

- IPF is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of UIP



Am J Respir Crit Care Med Vol 183. pp 788–824, 2011

Management IPF

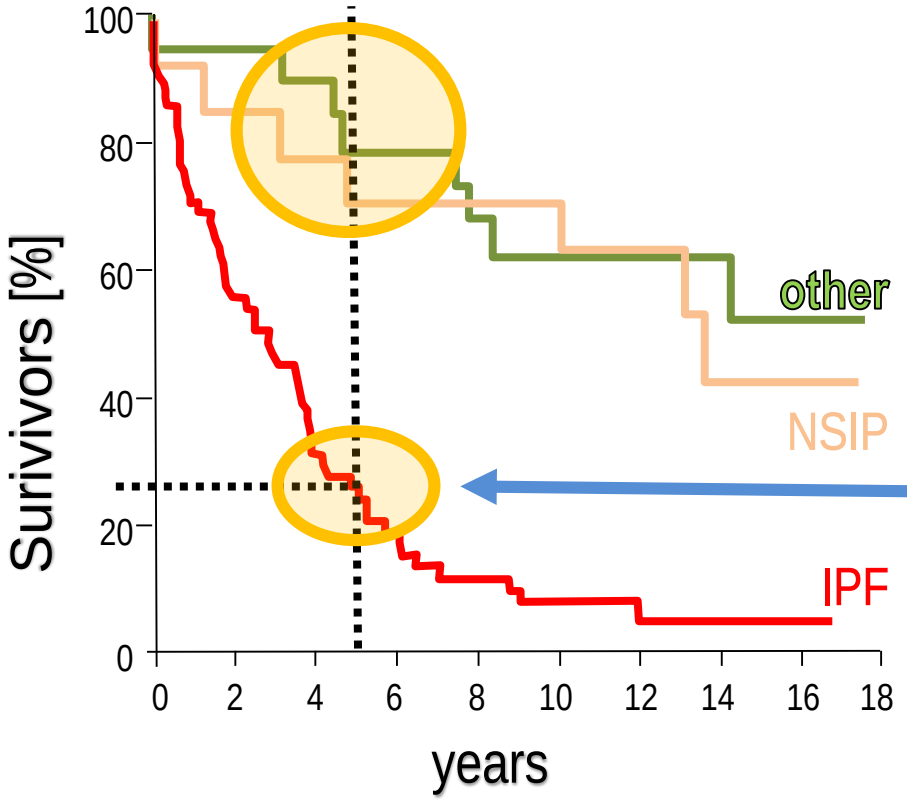
- Riduzione dei fattori di rischio
  - Fumo e Peso
- Educazione del paziente
  - Riunioni di gruppo
- Comorbidità
  - RGE, OSA, CAD, PH
- Ossigenoterapia
  - Notturna, sotto sforzo, a riposo

- Vaccinazioni
  - Influenzale, pneumococco
- Riabilitazione
- Valutazione trapianto
- Palliazione fasi terminali

Terapia Farmacologica

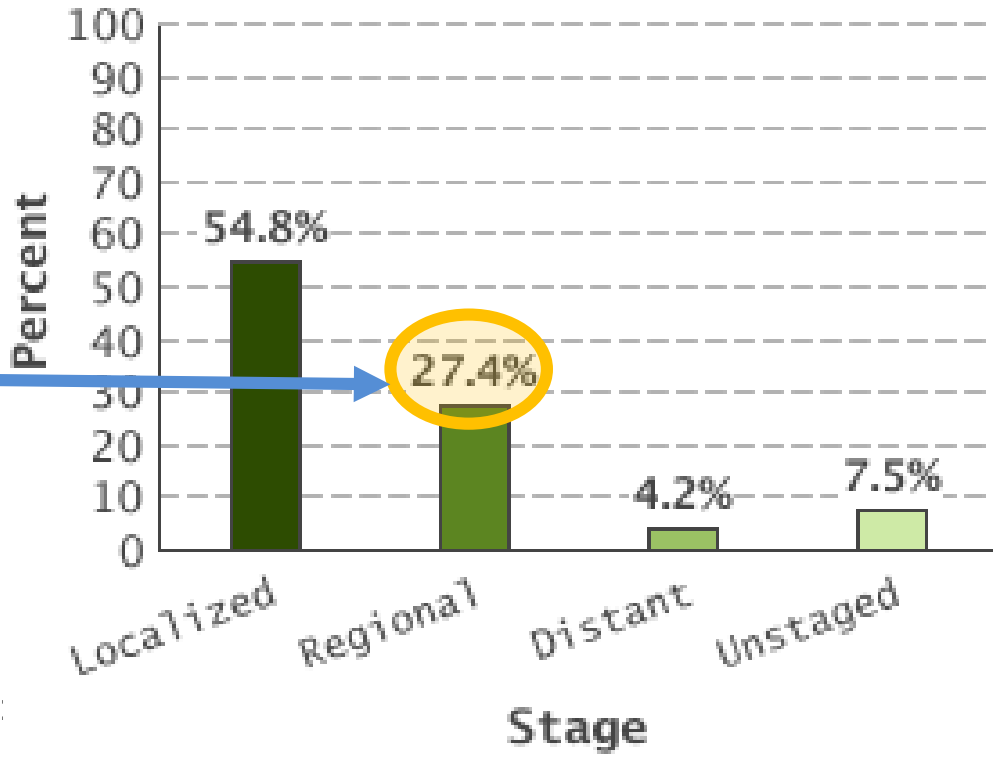
The prognosis of IPF was comparable to that of non methastatic lung cancer

Survival of IPF vs NSIP ad others fibrosing idiopathic ILDs



Bjoraker JA et al.; *Am J Respir Crit Care Med.;* 1998;157

5 years survival rate Lung Cancer 2005-2011

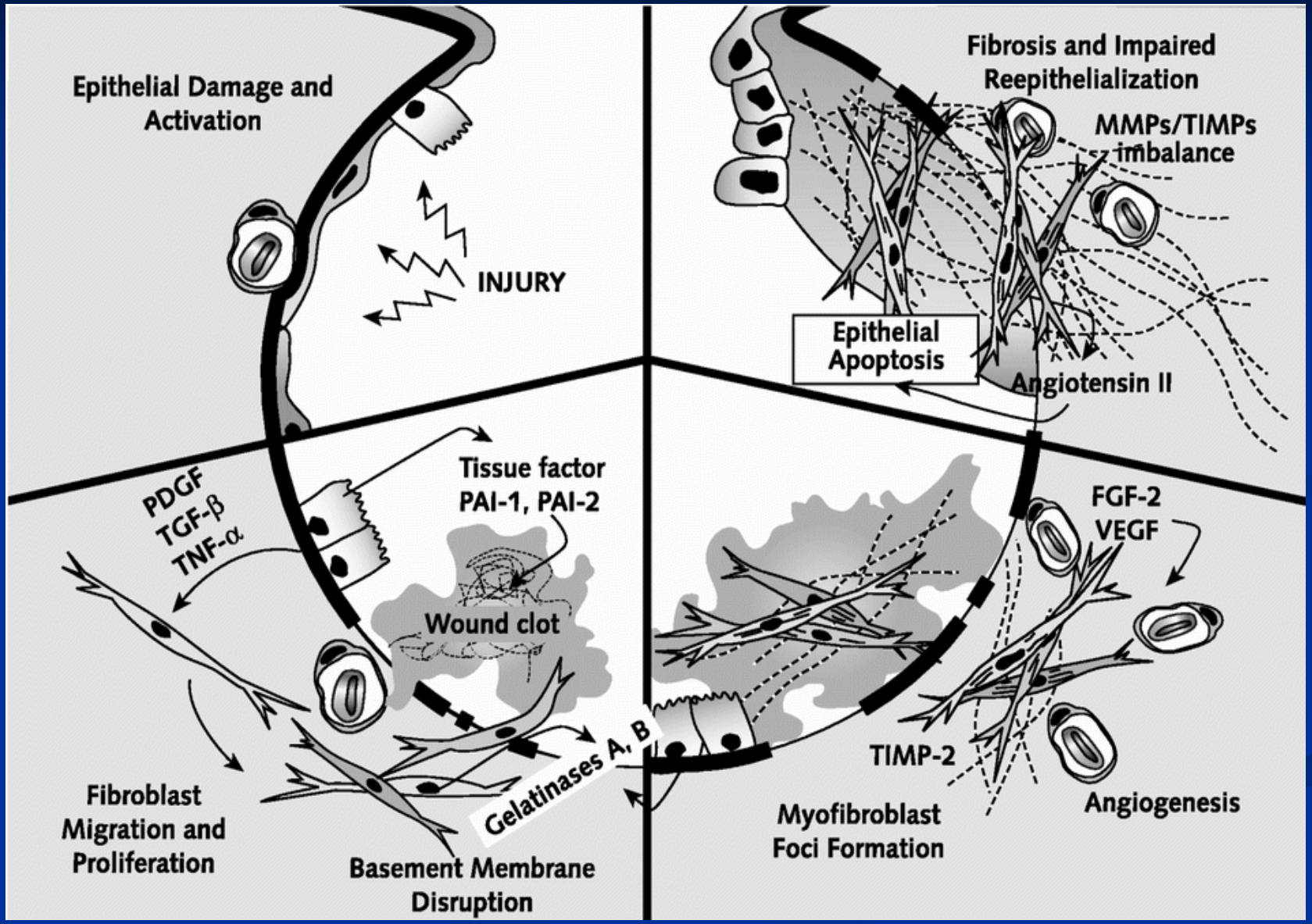


Surveillance, epidemiology and end-results program NTL Cancer Institute, USA

Strong rationale for an early treatment

C.Albera

Patogenesi



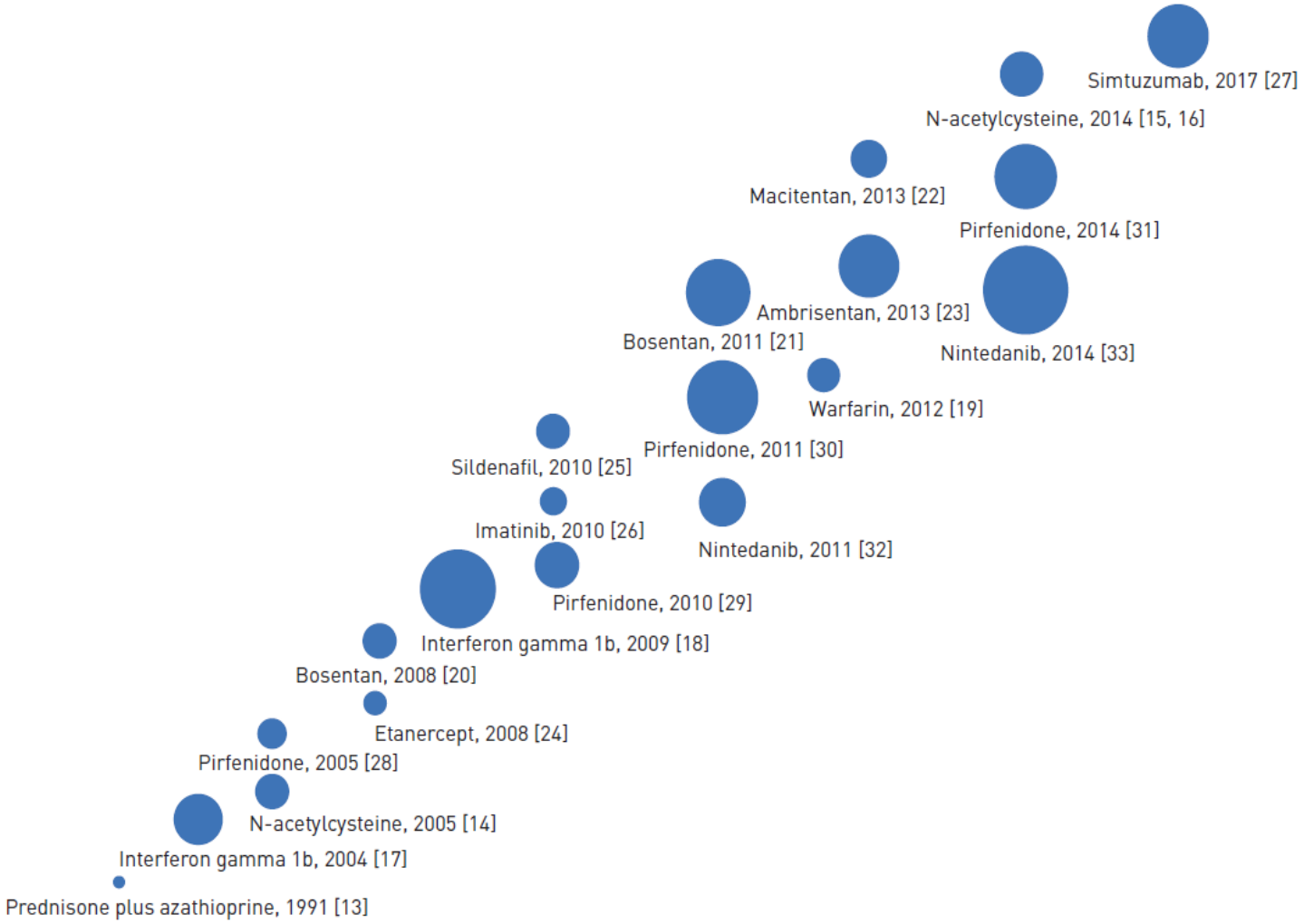
Selman M et al. Ann Intern Med 2001;16:136

Mediators Overexpressed by Epithelial Cells and Their Likely Functions in the Pathogenesis/Progression of Idiopathic Pulmonary Fibrosis

Mediator	Some Putative Profibrotic Roles
Growth factors and related molecules	
Transforming growth factor-beta (TGF-β) (74)	Likely the strongest profibrotic factor. The primary inductor of fibroblast to myofibroblast differentiation and of epithelial to mesenchymal transition
Platelet-derived growth factor (PDGF) (75)	Induces migration and proliferation of fibroblasts
Connective-tissue growth factor (CTGF) (76)	Induced by TGF-β and appears to be a mediator of some of its profibrotic effects. It provokes transcriptional activation of Col1α2
Tumor necrosis factor-alpha (TNF-α) (77)	Induces loss of fibroblast Thy-1 surface expression which is associated with Thy-1 shedding, smad phosphorylation, and myofibroblast differentiation.
Osteopontin (78)	Induces migration and proliferation of fibroblasts and epithelial cells. In fibroblasts, up-regulates TIMP-1 and type I collagen and down-regulates MMP-1 expression. In epithelial cells causes up-regulation and activation of MMP-7.
Insulin-like growth factor-I (IGF-I) (79)	Stimulates collagen production

Selman M, Pardo A. Am J Respir Crit Care Med 2014;189:1161–1172

Double blind, randomised clinical trial over the past 25 years



Raghu G. Eur Respir J 2017

American Thoracic Society Documents

An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management

Ganesh Raghu, Harold R. Collard, Jim J. Egan, Fernando J. Martinez, Juergen Behr, Kevin K. Brown, Thomas V. Colby, Jean-François Cordier, Kevin R. Flaherty, Joseph A. Lasky, David A. Lynch, Jay H. Ryu, Jeffrey J. Swigris, Athol U. Wells, Julio Ancochea, Demosthenes Bouros, Carlos Carvalho, Ulrich Costabel, Masahito Ebina, David M. Hansell, Takeshi Johkoh, Dong Soon Kim, Talmadge E. King, Jr., Yasuhiro Kondoh, Jeffrey Myers, Nestor L. Müller, Andrew G. Nicholson, Luca Richeldi, Moisés Selman, Rosalind F. Dudden, Barbara S. Griss, Shandra L. Protzko, and Holger J. Schünemann, on behalf of the ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis

This Official Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS), the Japanese Respiratory Society (JRS), and the Latin American Thoracic Association (ALAT) Was Approved by the ATS Board of Directors, November 2010, the ERS Executive Committee, September 2010, the JRS Board of Directors, December 2010, and the ALAT Executive Committee, November 2010

This Statement has been formally endorsed by the Society of Thoracic Radiology and by the Pulmonary Pathology Society

Am J Respir Crit Care Med 2011; 183: 788-824

AMERICAN THORACIC SOCIETY DOCUMENTS

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis

An Update of the 2011 Clinical Practice Guideline

Ganesh Raghu, Bram Rochwerg, Yuan Zhang, Carlos A. Cuello Garcia, Arata Azuma, Juergen Behr, Jan L. Brozek, Harold R. Collard, William Cunningham*, Sakae Homma, Takeshi Johkoh, Fernando J. Martinez, Jeffrey Myers, Shandra L. Protzko, Luca Richeldi, David Rind, Moises Selman, Arthur Theodore, Athol U. Wells, Henk Hoogsteden, and Holger J. Schünemann; on behalf of the ATS, ERS, JRS, and ALAT

This guideline is dedicated to the memory of Mr. William Cunningham (June 7, 1935–October 23, 2014).

This official Clinical Practice Guideline of the American Thoracic Society (ATS) was approved by the ATS, May 2015, the European Respiratory Society (ERS), April 2015, the Japanese Respiratory Society (JRS), April 2015, and the Latin American Thoracic Association (ALAT), April 2015

Am J Respir Crit Care Med 2015; 192: e3-e19

	STRONG		WEAK	
TREATMENT	YES	NOT	YES	NOT

Am J Respir Crit Care Med Vol 192; pp e3–e19, 2015

	STRONG		WEAK	
TREATMENT	YES	NOT	YES	NOT
CORTICOSTEROIDS		√		
COLCHICINE		√		
CICLOSPORINE A		√		
INTERFERON ϒ		√		
ETANERCEPT		√		
PREDNISONE+AZA+NAC		√		
ANTICOAGULATION		√		
AMBRISENTAN		√		
IMATINIB		√		

Am J Respir Crit Care Med Vol 192; pp e3–e19, 2015

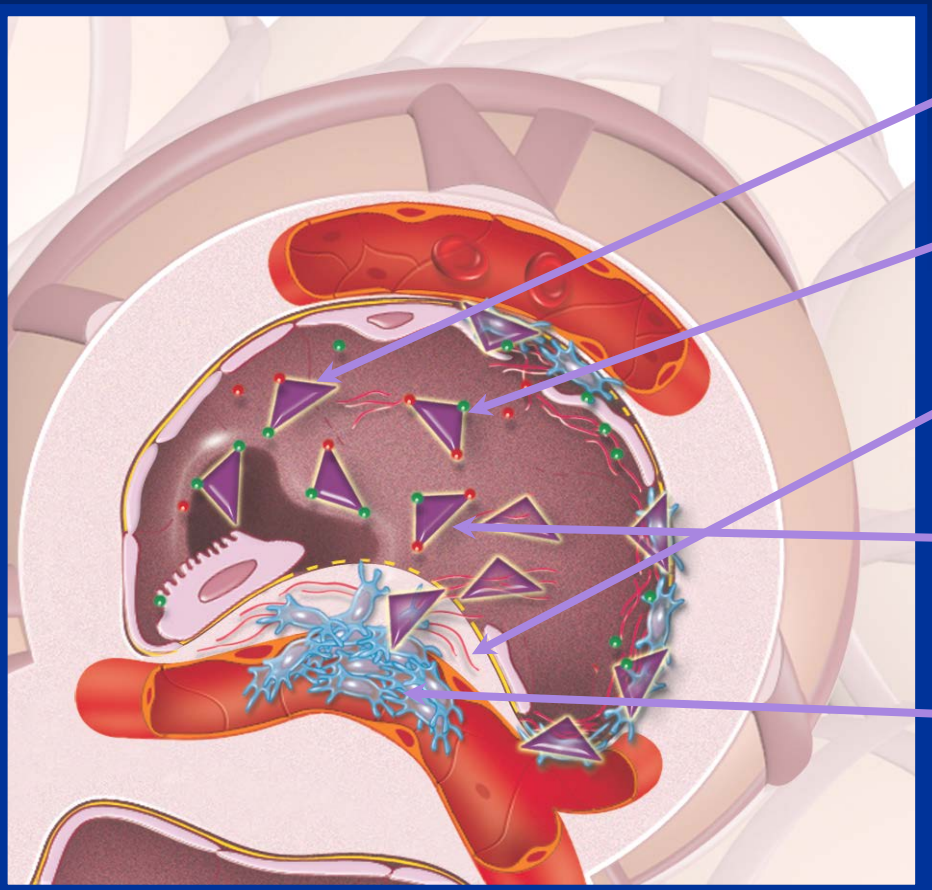
	STRONG		WEAK	
TREATMENT	**YES**	**NOT**	**YES**	**NOT**
CORTICOSTEROIDS		√		
COLCHICINE		√		
CICLOSPORINE A		√		
INTERFERON ϒ		√		
ETANERCEPT		√		
PREDNISONE+AZA+NAC		√		
ANTICOAGULATION		√		
AMBRISENTAN		√		
IMATINIB		√		
BOSENTAN				√
MACITENTAN				√
SILDENAFIL				√
N-ACETYLCYSTEINE				√

Am J Respir Crit Care Med Vol 192; pp e3–e19, 2015

	STRONG		WEAK	
IPF TREATMENT	**YES**	**NOT**	**YES**	**NOT**
CORTICOSTEROIDS		√		
COLCHICINE		√		
CICLOSPORINE A		√		
INTERFERON ϒ		√		
ETANERCEPT		√		
PREDNISONE+AZA+NAC		√		
ANTICOAGULATION		√		
AMBRISENTAN		√		
IMATINIB		√		
BOSENTAN				√
MACITENTAN				√
SILDENAFIL				√
N-ACETYLCYSTEINE				√
PIRFENIDONE			√	
NINTEDANIB			√	

Am J Respir Crit Care Med Vol 192; pp e3–e19, 2015

Pirfenidone Anti-Fibrotic Activity



Pirfenidone

Pirfenidone inhibits TGF-β, a potent mediator of lung fibrosis[1-4]

Pirfenidone inhibits collagen production[5-7]

Pirfenidone inhibits TNF-α synthesis, another fibrotic mediator and inflammatory cytokine[8]

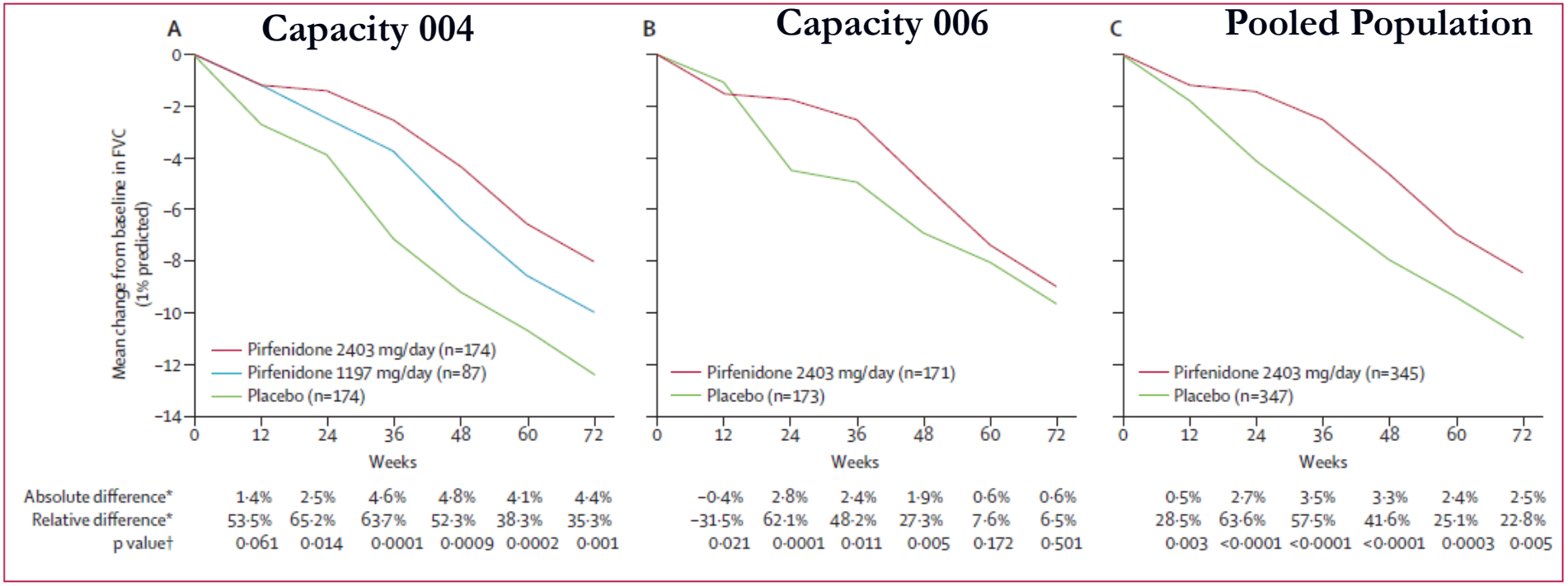
Pirfenidone attenuates fibroblast proliferation[3]

1. Iyer SN et al. J Pharmacol Exp Ther 1999;291:367-73; 2. Iyer SN et al. J Pharmacol Exp Ther 1999;289:211-8;
3. Gurujeyalakshmi G et al. Am J Physiol 1999; 276:L311-8; 4. Oku H et al. Eur J Pharmacol 2008;590:400-8;
5. Lee BS et al. J Clin Endocrinol Metab 1998;83:219-23; 6. Iyer SN et al. J Lab Clin Med 1995;125:779-85;
7. Schelegle ES et al. Proc Soc Exp Biol Med 1997;216:392-7; 8. Grattendick KJ et al. Int Immunopharmacol 2008;8:679-87.

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

www.thelancet.com **Published online May 14, 2011**

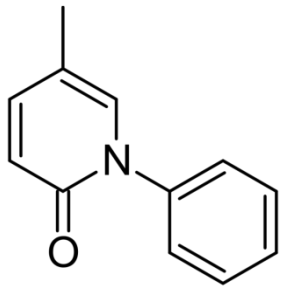


Absolute difference*	1·4%	2·5%	4·6%	4·8%	4·1%	4·4%
Relative difference*	53·5%	65·2%	63·7%	52·3%	38·3%	35·3%
p value†	0·061	0·014	0·0001	0·0009	0·0002	0·001

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

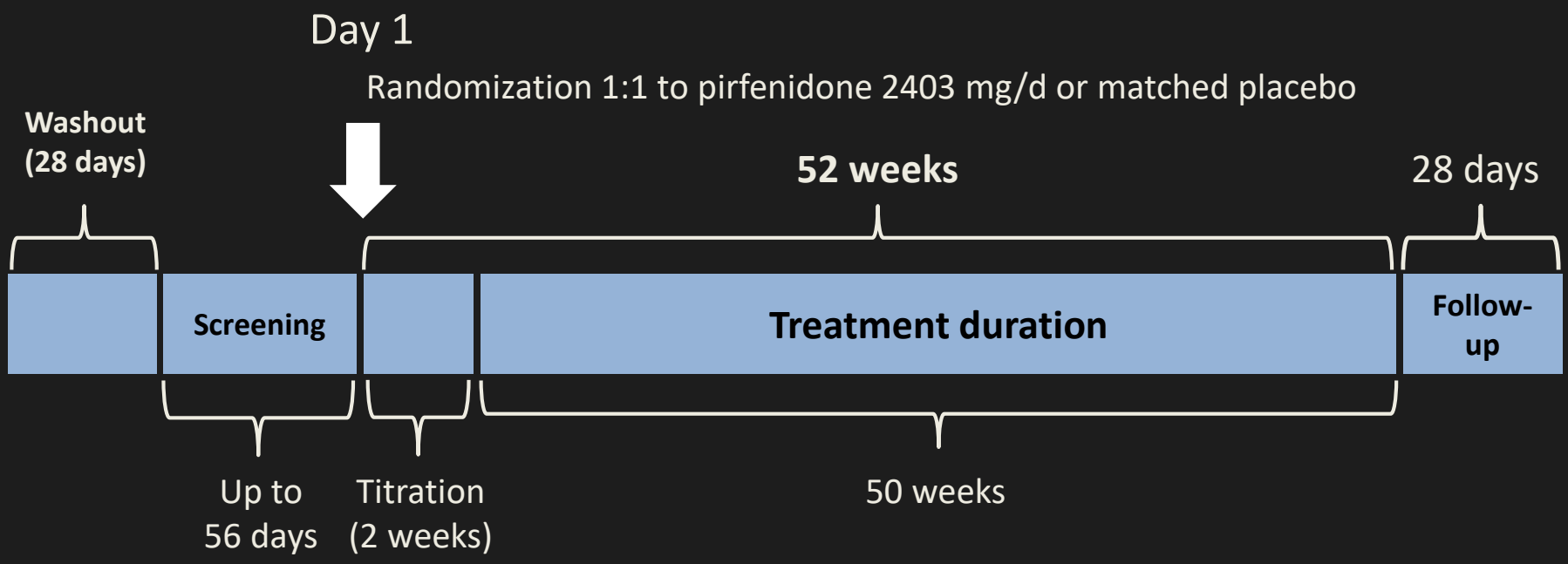
Absolute difference*	0·5%	2·7%	3·5%	3·3%	2·4%	2·5%
Relative difference*	28·5%	63·6%	57·5%	41·6%	25·1%	22·8%
p value†	0·003	<0·0001	<0·0001	<0·0001	0·0003	0·005

Interpretation The data show pirfenidone has a favourable benefit risk profile and represents an appropriate treatment option for patients with idiopathic pulmonary fibrosis.



NEJM 2014; 370: 2083-92

ASCEND Study Design: Randomized, double-blind, placebo controlled trial



Clinical efficacy assessments: Day 1 and weeks 13, 26, 39, 52A/B

127 sites in 9 countries

NEJM 2014; 370: 2083-92

ASCEND Study Design
Primary Endpoint

- Percent of predicted FVC change from baseline to week 52
  - Primary analysis: Rank ANCOVA to test for differences in the distribution between groups
  - Magnitude of effect: Categorical analysis of 2 clinically important thresholds of change:
    - ≥10% decline in %FVC or death
    - No %FVC decline

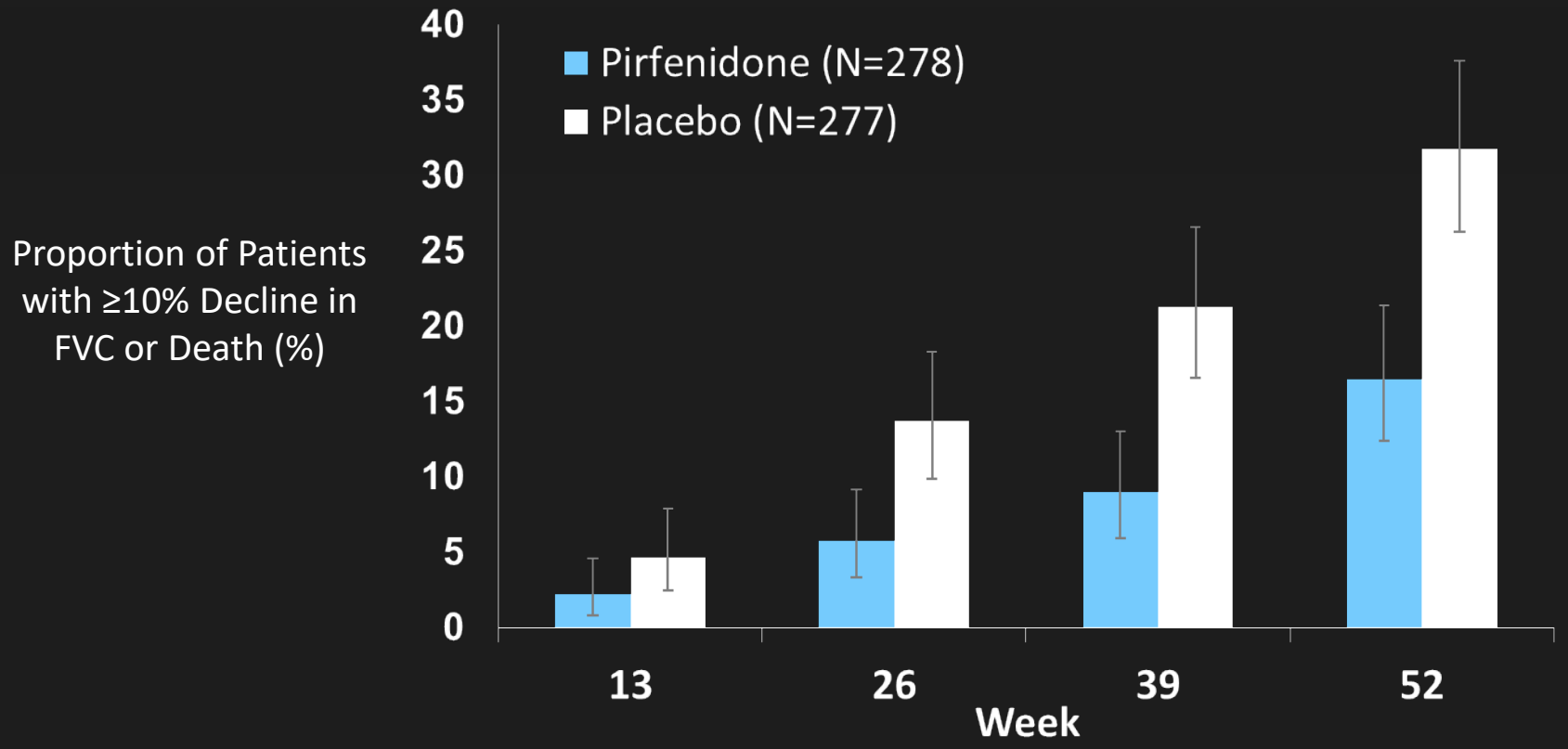
NEJM 2014; 370: 2083-92

ASCEND Study Design
Eligibility

- Age: 40-80 years
- HRCT: Confident diagnosis of IPF
  - Definite UIP, or
  - Possible UIP, with confirmation on SLB
- FVC: ≥50% and ≤90% percent of predicted
- DL_{CO}: ≥30% and ≤90% percent of predicted
- FEV_1/FVC ratio: **≥0.80**
- Centralized review: spirometry, HRCT, SLB, deaths

NEJM 2014; 370: 2083-92

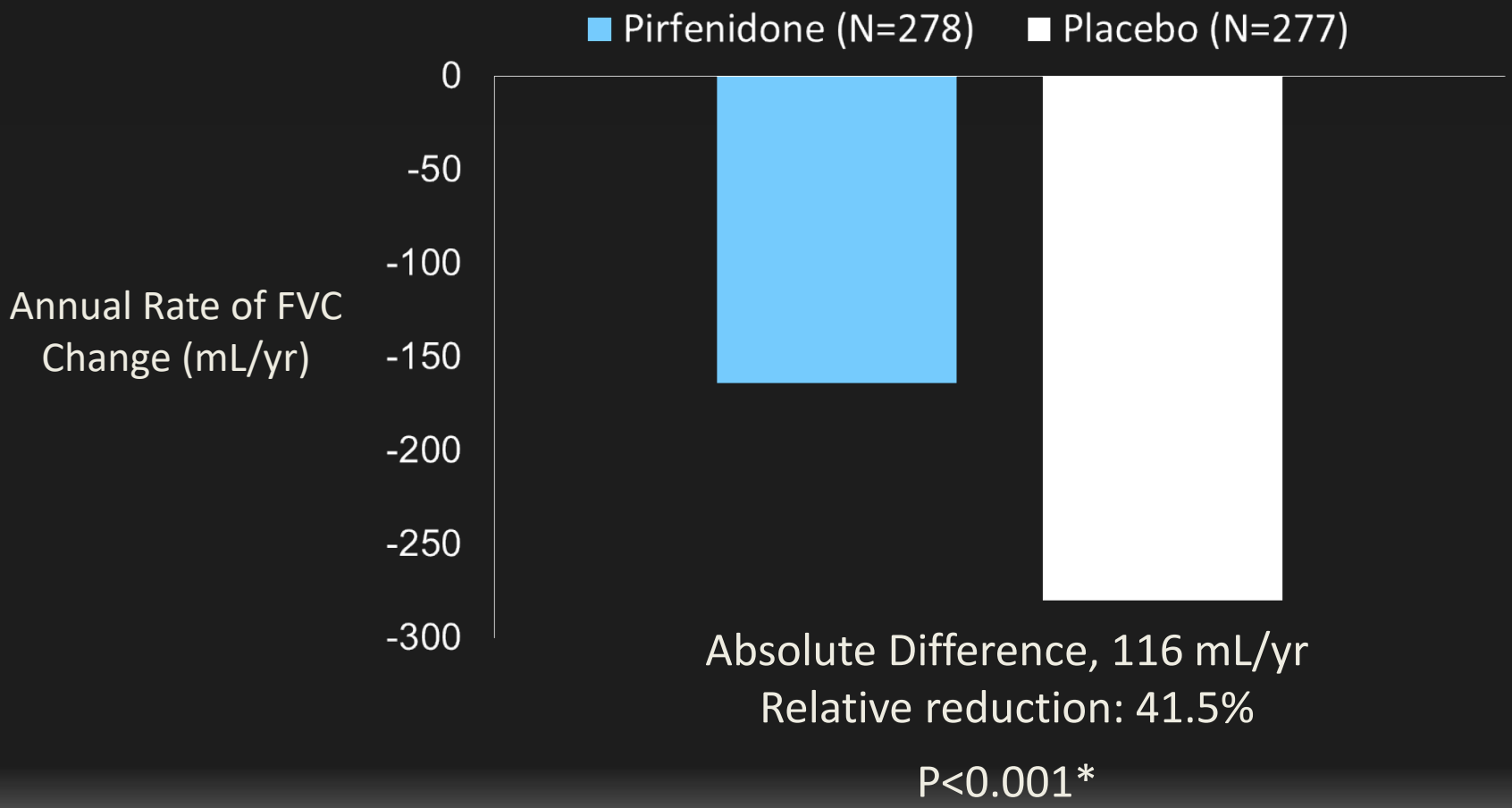
Primary Efficacy Analysis: Treatment with pirfenidone resulted in a significant between-group difference in the rank ANCOVA



Absolute Difference	2.5%	7.9%	12.3%	15.3%
Relative Difference	54.0%	58.0%	57.8%	47.9%
Rank ANCOVA p-value	<0.000001	<0.000001	0.000002	<0.000001

NEJM 2014; 370: 2083-92

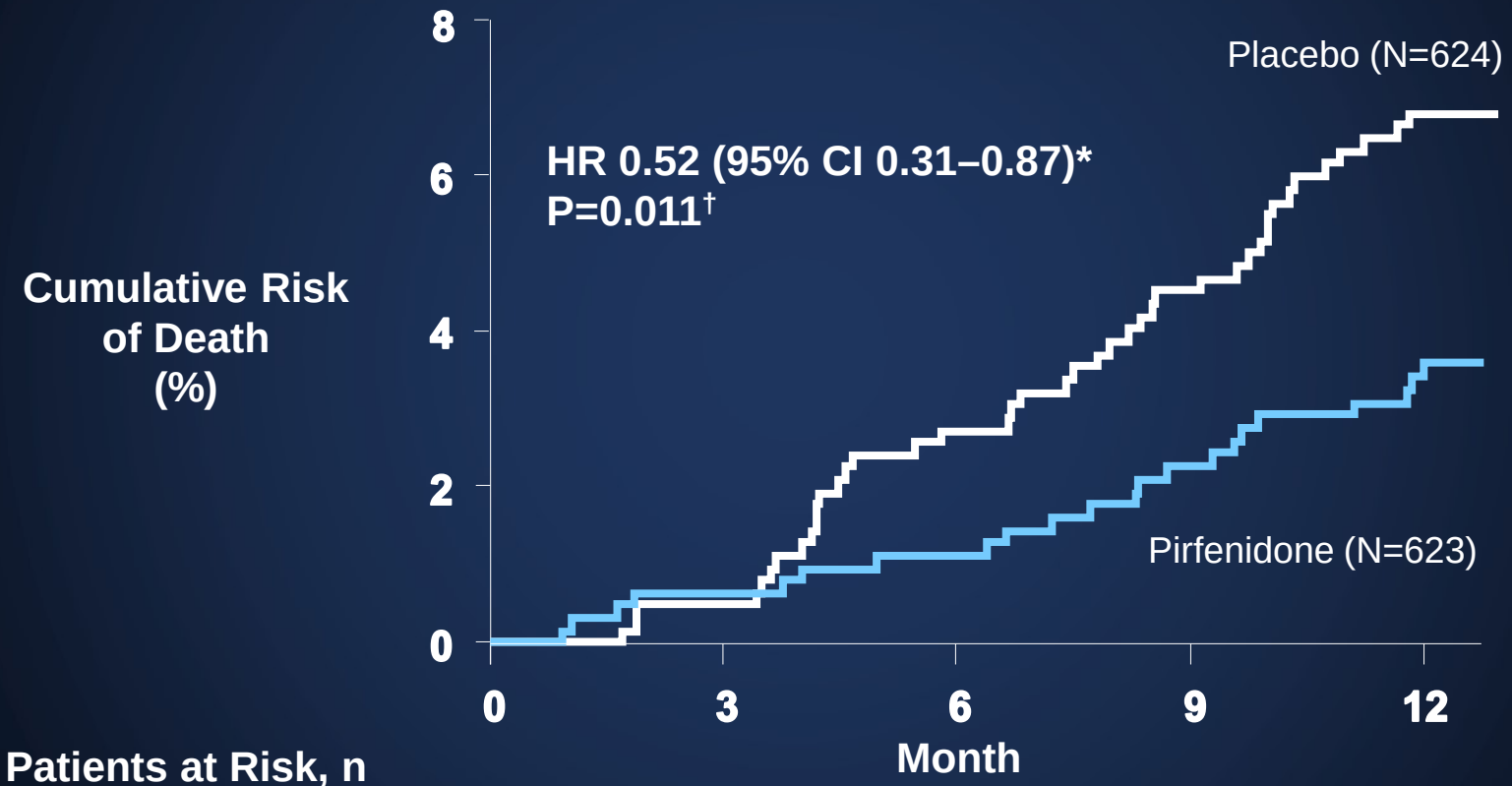
ASCEND Study Supportive Analysis: Annual rate of FVC decline at week 52



Linear slope analysis: Mixed model with linear time effect adjusted for age, height, and sex

NEJM 2014; 371: 1172

Pooled All-cause Mortality (Week 52): Treatment group curves diverge early and continue separating throughout the study period



Patients at Risk, n					
Pirfenidone	623	618	609	596	509
Placebo	624	619	603	586	490

* Cox proportional hazards model
† Log-rank test

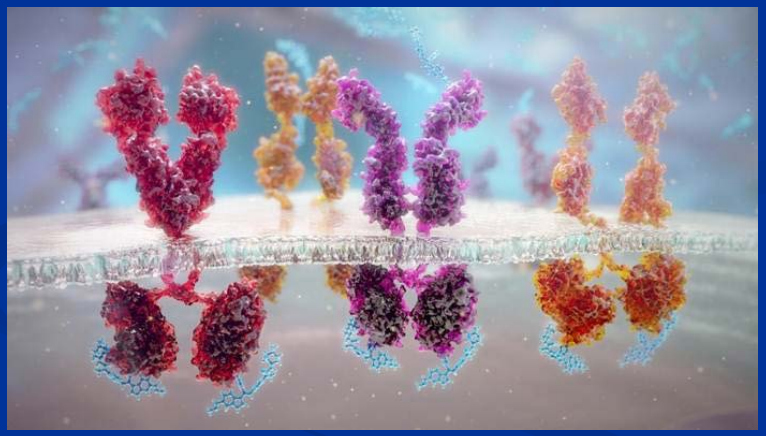
ASCEND Study: GI and skin-related events were more common in the pirfenidone group

Patients (%)	Pirfenidone (N=278)	Placebo (N=277)
Cough	25.2	29.6
Nausea	**36.0**	**13.4**
Headache	25.9	23.1
Diarrhea	22.3	21.7
Upper Respiratory Tract Infection	21.9	20.2
Fatigue	20.9	17.3
Rash	**28.1**	**8.7**
Dyspnea	14.7	17.7
Dizziness	17.6	13.0
Idiopathic pulmonary fibrosis	9.4	18.1
Bronchitis	14.0	13.0
Constipation	11.5	13.7
Back pain	10.8	13.4
Dyspepsia	**17.6**	**6.1**
Nasopharyngitis	11.9	10.8
Anorexia	**15.8**	**6.5**
Vomiting	12.9	8.7
Weight decreased	**12.6**	**7.9**
Gastroesophageal reflux	**11.9**	**6.5**
Insomnia	**11.2**	**6.5**

NEJM 2014; 370: 2083-92

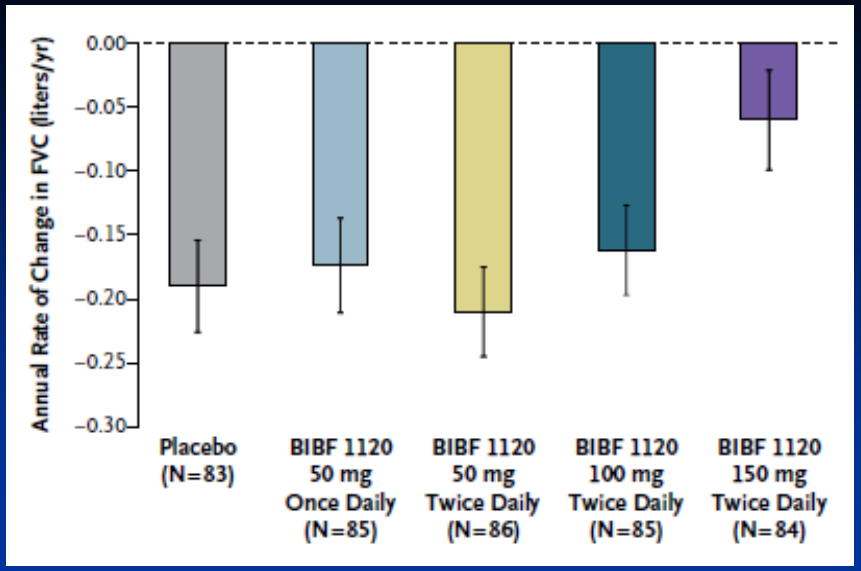
Nintedanib

- Nintedanib
  - An intracellular inhibitor of tyrosine kinases[1,2]
  - Targets FGF, PDGF and VEGF receptors[1,2]
- Phase II TOMORROW study
  - 12 months' treatment with nintedanib 150 mg bid may reduce lung function decline and acute exacerbations in patients with IPF[3]
- INPULSIS trials[4]
  - Two replicate 52-week, randomized, double-blind, Phase III trials



FGF, fibroblast growth factor; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor

1. Hilberg F, et al. Cancer Res 2008;68:4774–82; 2.Wollin L, et al. J Pharmacol Exp Ther 2014;349:209–20;
3. Richeldi L, et al. N Engl J Med 2011;365:1079–87; 4. Richeldi L, et al. N Engl J Med 2014; published online May 18, 2014

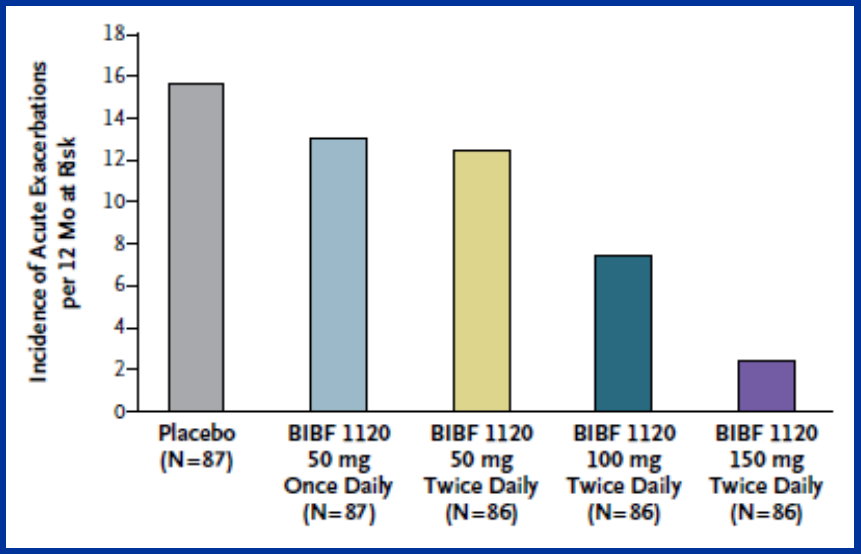


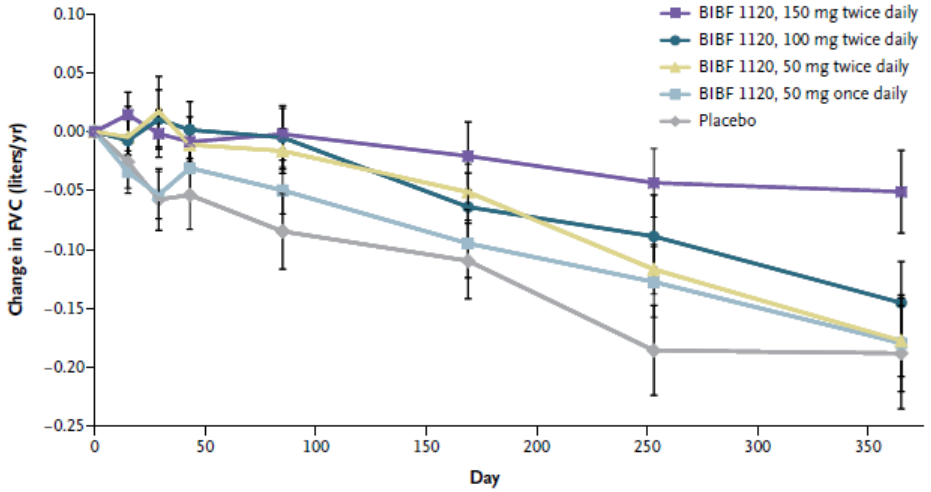
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 22, 2011 VOL. 365 NO. 12

Efficacy of a Tyrosine Kinase Inhibitor in Idiopathic Pulmonary Fibrosis

Luca Richeldi, M.D., Ph.D., Ulrich Costabel, M.D., Moises Selman, M.D., Dong Soon Kim, M.D., David M. Hansell, M.D., Andrew G. Nicholson, D.M., Kevin K. Brown, M.D., Kevin R. Flaherty, M.D., Paul W. Noble, M.D., Ganesh Raghu, M.D., Michèle Brun, M.Sc., Abhya Gupta, M.D., Nolwenn Juhel, M.Sc., Matthias Klüglich, M.D., and Roland M. du Bois, M.D.





No. of Patients	0	15	29	43	85	169	253	365
Total	432	419	416	415	398	385	372	317
Placebo	87	81	82	82	80	79	74	61
50 mg once daily	87	85	82	80	78	72	71	61
50 mg twice daily	86	85	86	86	82	81	80	71
100 mg twice daily	86	84	84	84	80	82	79	67
150 mg twice daily	86	84	82	83	78	71	68	57

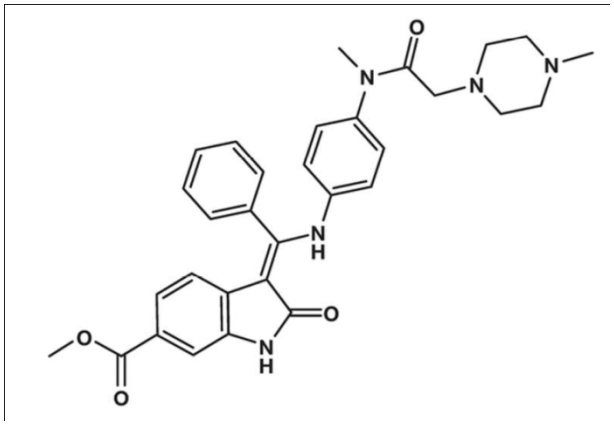
N Engl J Med 2011; 365: 1079

The NEW ENGLAND JOURNAL of MEDICINE

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

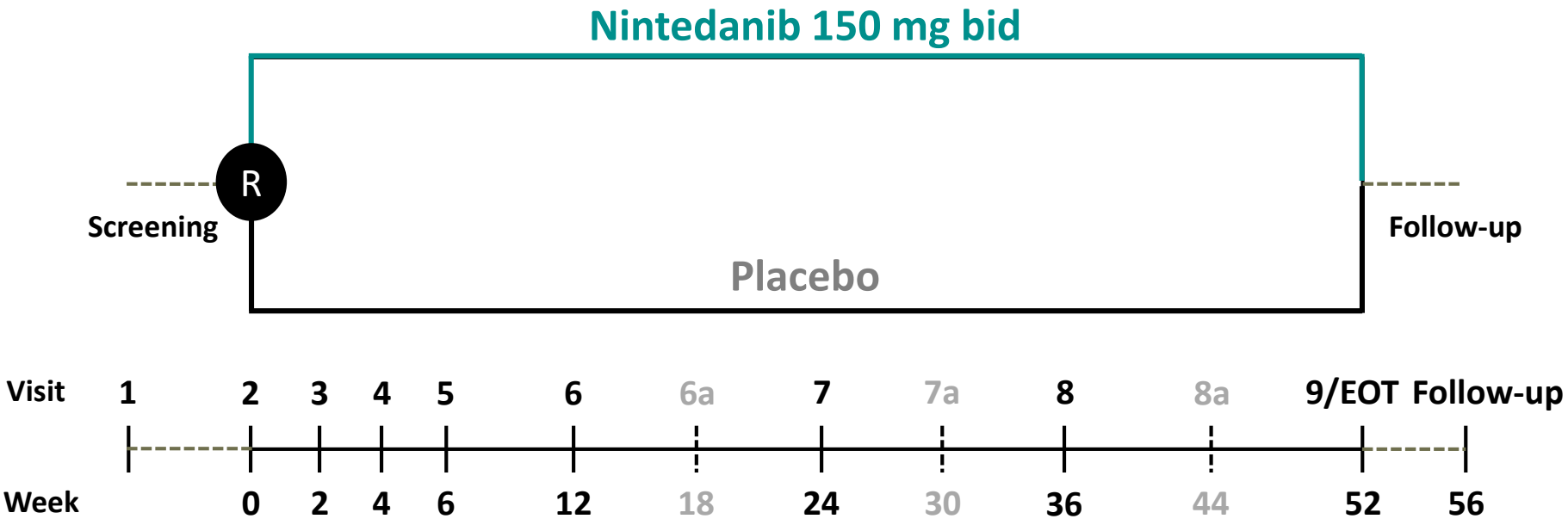
Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

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*



NEJM 2014; 370: 2071-82

INPULSIS 1 AND 2: STUDY DESIGN



- 3:2 randomization ratio for nintedanib : placebo
- Dose 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

Resp Med 2014; 108: 1023-30

ENDPOINTS

Primary endpoint

- Annual rate of decline in FVC (mL/year)

Key secondary endpoints

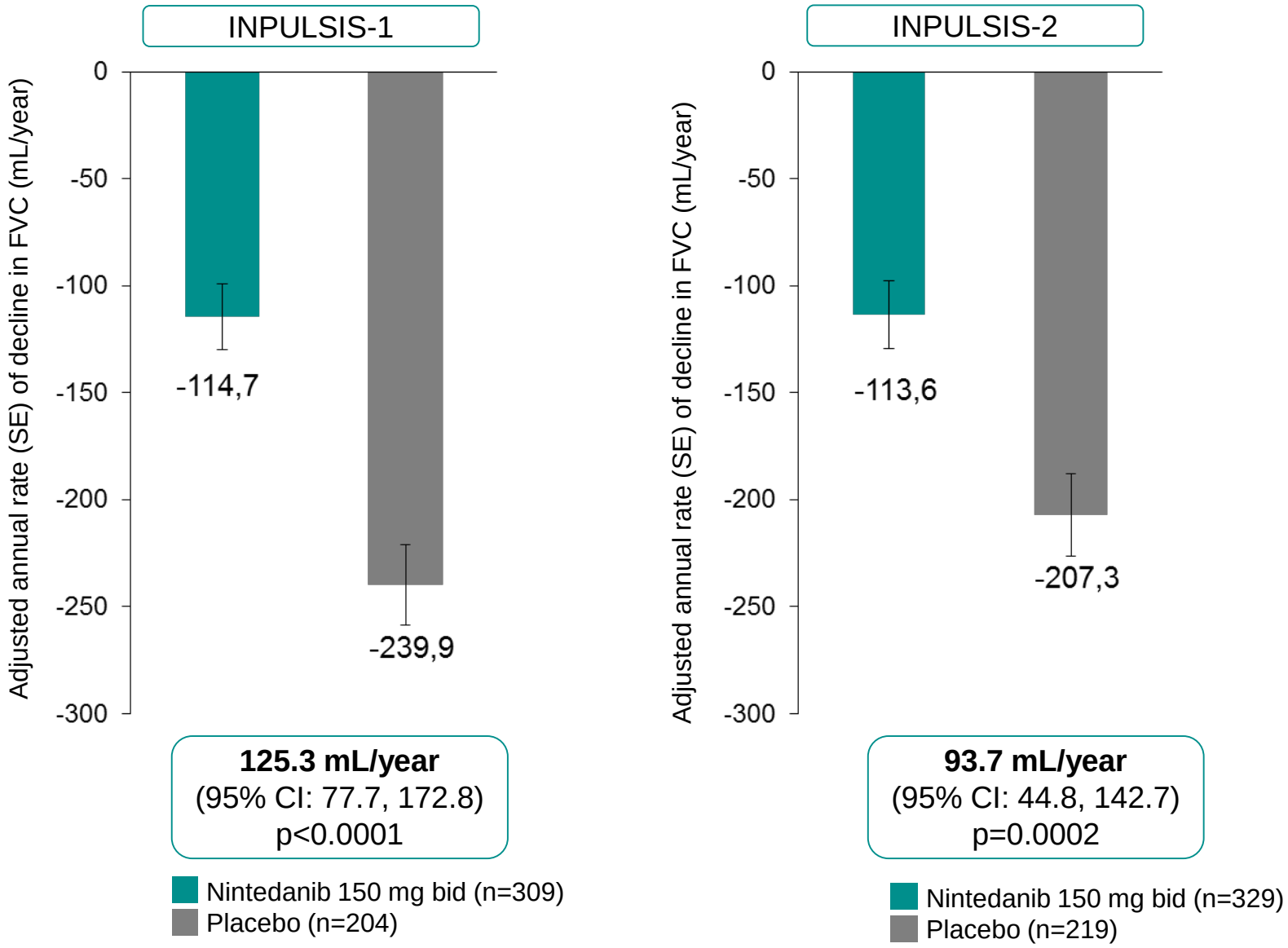
- Time to first acute exacerbation (investigator-reported) over 52 weeks
- Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score over 52 weeks

KEY INCLUSION CRITERIA

- Age ≥40 years
- Diagnosis of IPF within 5 years of randomization
- Chest HRCT performed within 12 months of screening
- FVC ≥50% of predicted value
- DL_{CO} 30–79% of predicted value
- HRCT pattern, and, if available, surgical lung biopsy pattern, consistent with diagnosis of IPF, as assessed centrally by one expert radiologist and one expert pathologist

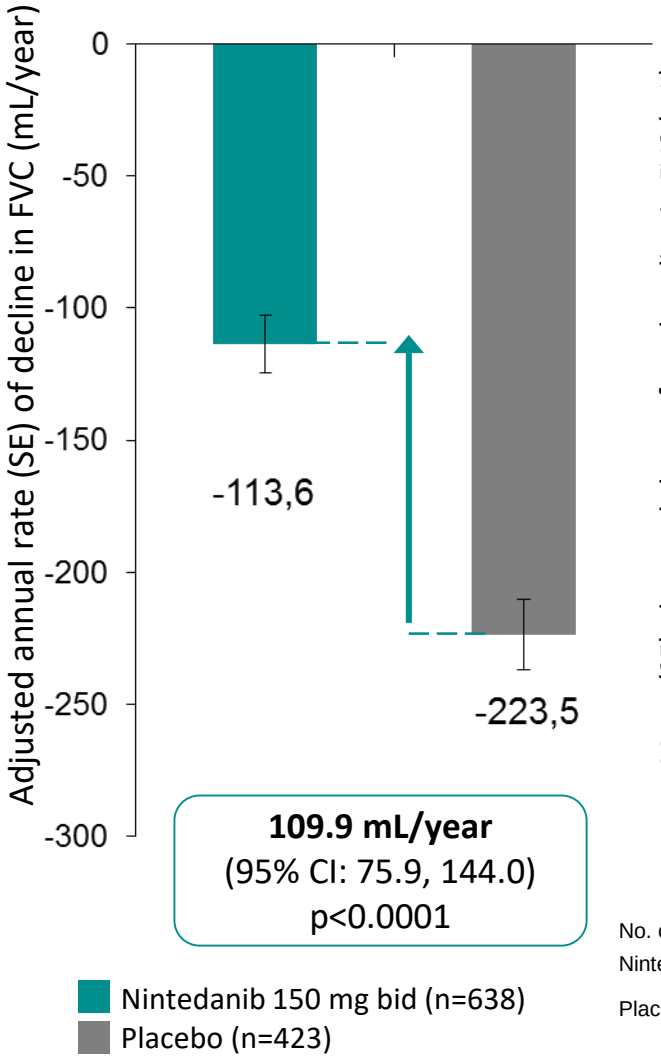
NEJM 2014; 370: 2071-82

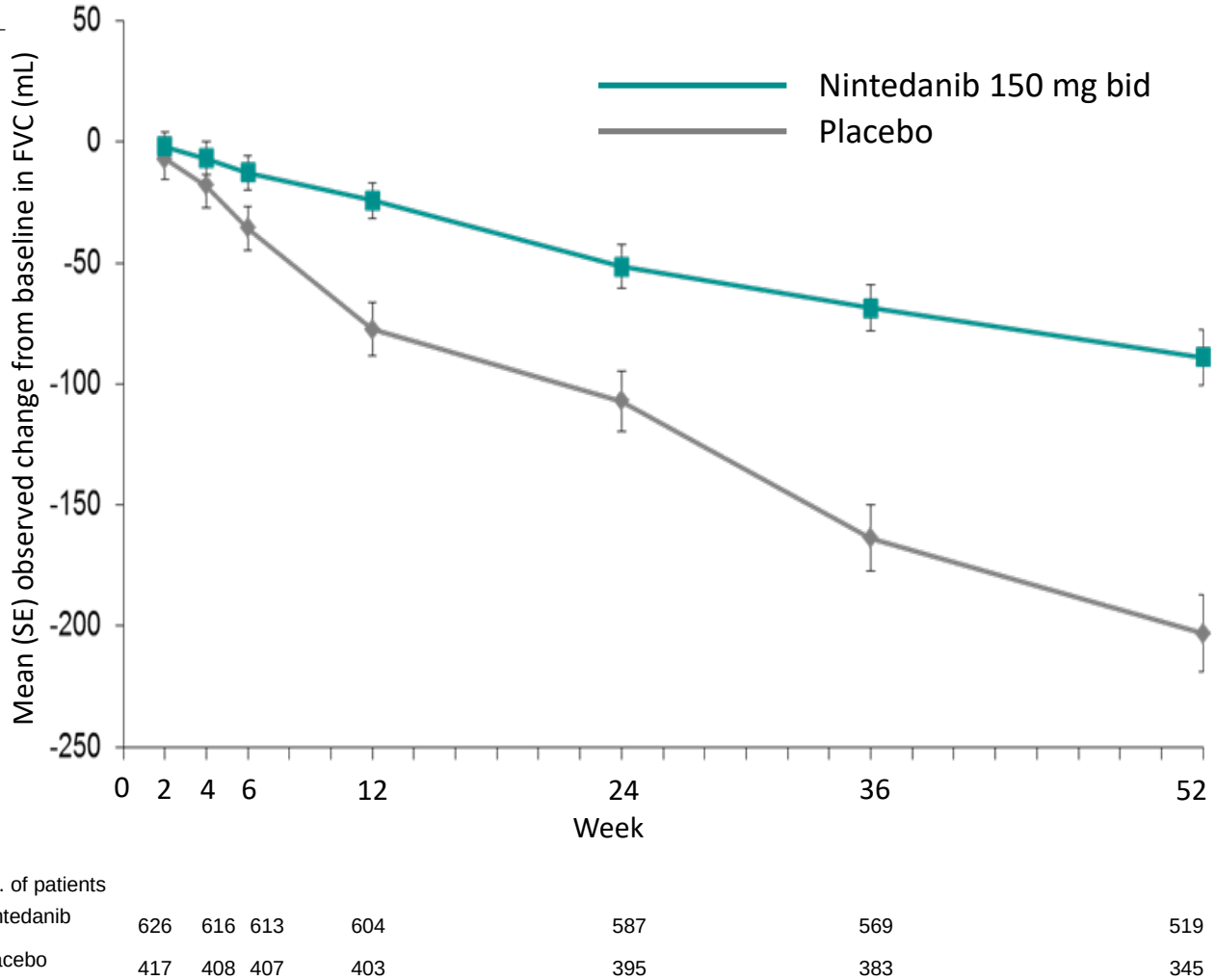
PRIMARY EFFICACY ENDPOINT



NEJM 2014; 370: 2071-82

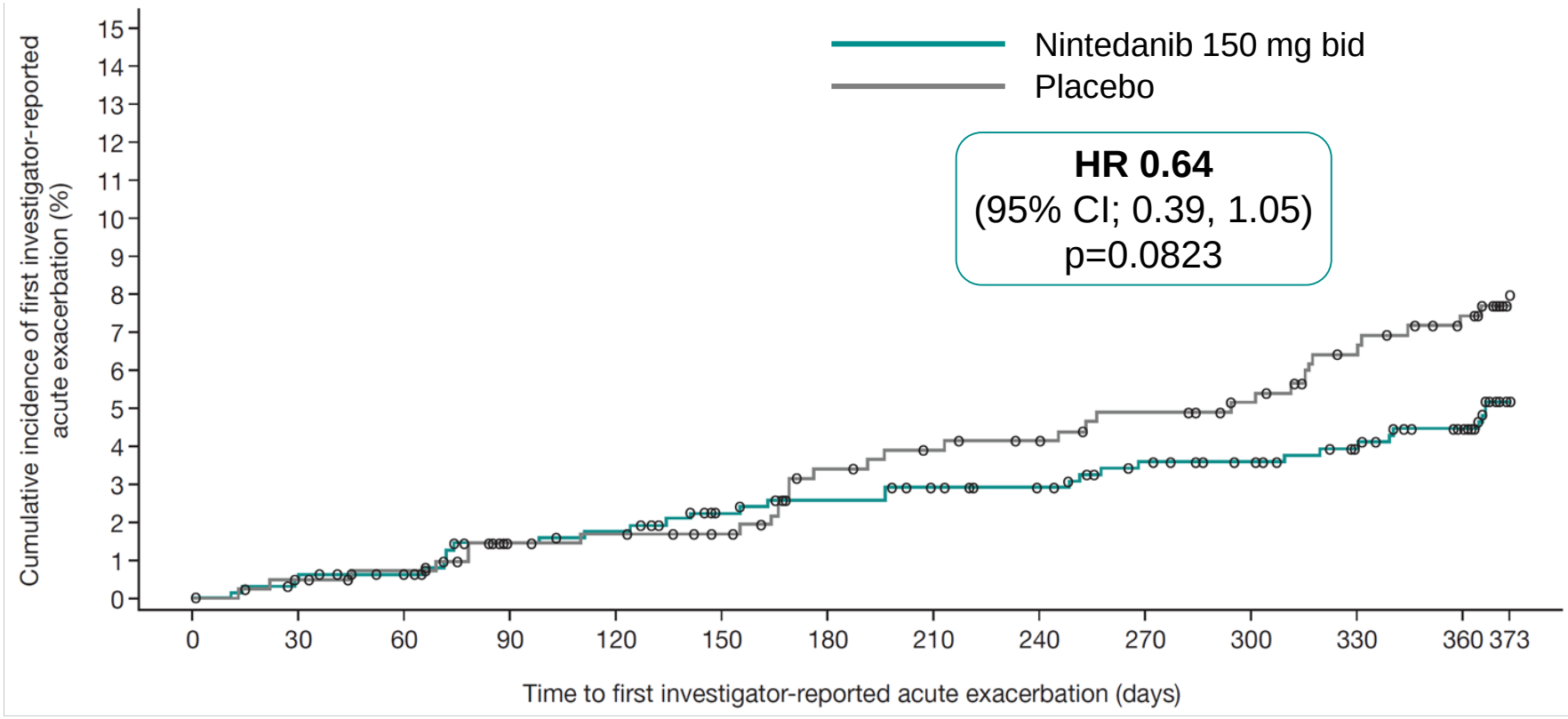
PRIMARY EFFICACY ENDPOINT IN POOLED DATA





NEJM 2014; 370: 2071-82

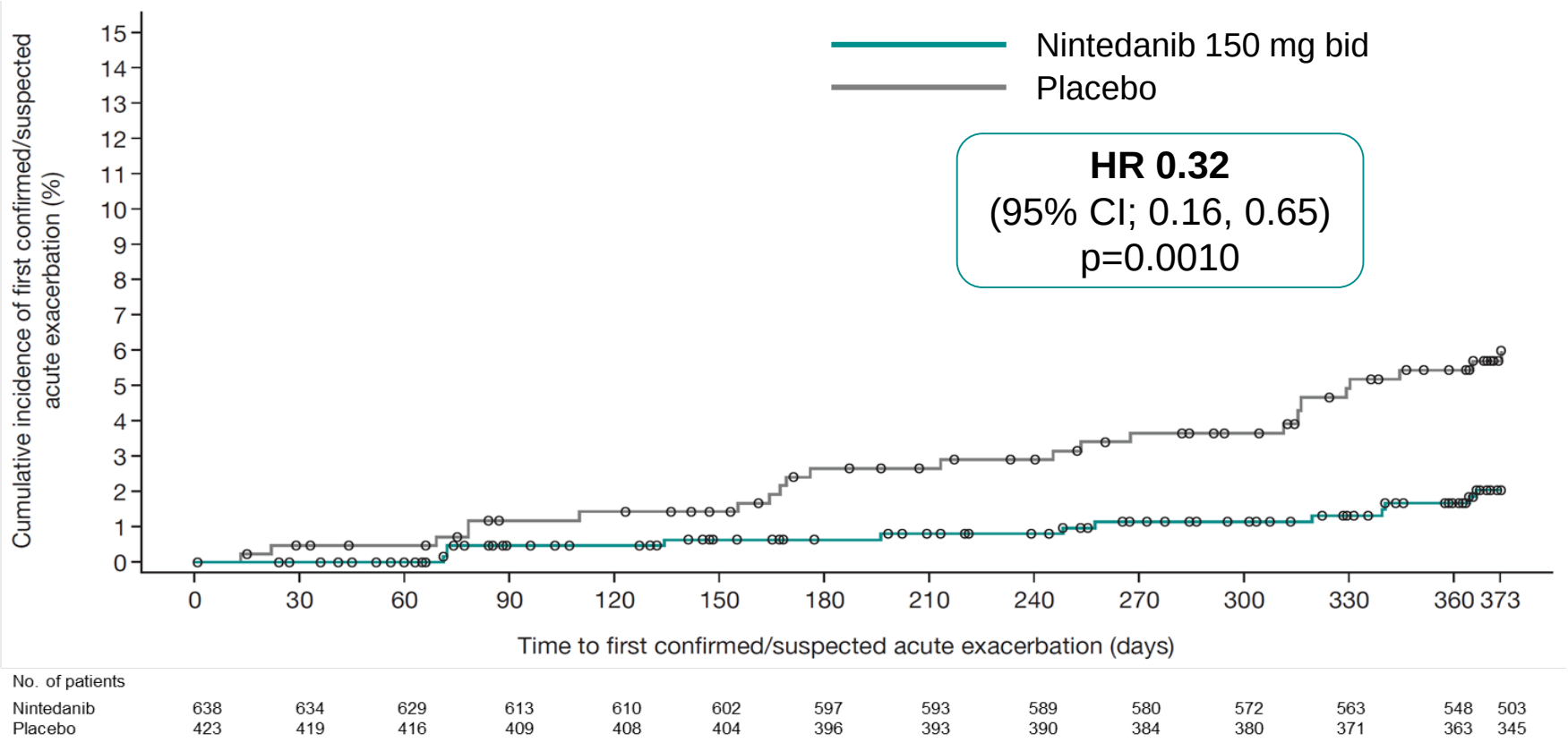
TIME TO FIRST ACUTE EXACERBATION (INVESTIGATOR-REPORTED) IN POOLED DATA



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

NEJM 2014; 370: 2071-82

TIME TO FIRST CONFIRMED OR SUSPECTED ACUTE EXACERBATION PER ADJUDICATION



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

NEJM 2014; 370: 2071-82

MOST FREQUENT ADVERSE EVENTS*

	INPULSIS-1		INPULSIS-2	
No of patients (%)	**Nintedanib 150 mg bid (n=309)**	**Placebo (n=204)**	**Nintedanib 150 mg bid (n=329)**	**Placebo (n=219)**
Diarrhea	190 (61.5)	38 (18.6)	208 (63.2)	40 (18.3)
Nausea	70 (22.7)	12 (5.9)	86 (26.1)	16 (7.3)
Nasopharyngitis	39 (12.6)	34 (16.7)	48 (14.6)	34 (15.5)
Cough	47 (15.2)	26 (12.7)	38 (11.6)	31 (14.2)
Progression of IPF†	31 (10.0)	21 (10.3)	33 (10.0)	40 (18.3)
Bronchitis	36 (11.7)	28 (13.7)	31 (9.4)	17 (7.8)
Upper respiratory tract infection	28 (9.1)	18 (8.8)	30 (9.1)	24 (11.0)
Dyspnea	22 (7.1)	23 (11.3)	27 (8.2)	25 (11.4)
Decreased appetite	26 (8.4)	14 (6.9)	42 (12.8)	10 (4.6)
Vomiting	40 (12.9)	4 (2.0)	34 (10.3)	7 (3.2)
Weight decreased	25 (8.1)	13 (6.4)	37 (11.2)	2 (0.9)

Based on adverse events with onset after first dose and up to 28 days after the last dose of trial medication
*Adverse events with an incidence of >10% in any treatment group. †Corresponds to the MedDRA term 'IPF', which included disease worsening and IPF exacerbations

NEJM 2014; 370: 2071-82

DIARRHEA

	INPULSIS-1		INPULSIS-2	
No of patients (%)	**Nintedanib 150 mg bid (n=309)**	**Placebo (n=204)**	**Nintedanib 150 mg bid (n=329)**	**Placebo (n=219)**
Diarrhea serious adverse event(s)	1 (0.3)	0 (0.0)	1 (0.3)	1 (0.5)
Diarrhea adverse event(s) leading to premature treatment discontinuation	14 (4.5)	0 (0.0)	14 (4.3)	1 (0.5)
Intensity of most severe event, for patients with any diarrhea adverse event(s)				
Mild	103 (54.2)	29 (76.3)	123 (59.1)	31 (77.5)
Moderate	75 (39.5)	9 (23.7)	75 (36.1)	7 (17.5)
Severe	11 (5.8)	0 (0.0)	10 (4.8)	2 (5.0)

NEJM 2014; 370: 2071-82

Nintedanib and Pirfenidone Efficacy in Different IPF Subsets Post Hoc Studies

Fenotipo	Nintedanib	Pirfenidone
IPF early	√	√
IPF severe	√	√
FVC decline >10%	√	√
Sex	√	√
Age	√	√
Race	√	√
GAP index	√	√
Long term	√	√
Possible UIP	√	
Emphysema	√	
Dose reduction	√	√

Pirfenidone – Real-life studies

EFFICACY

STUDIO	# pts	FVC decline	DLCO decline	AE-IPF	Mortality
Okuda et al. (JAPAN) Respir Med 2013;107:1431	76	-207 ml at 6m	-7.9% at 6m	5.3%	-
Chaudhuri et al. (UK) Respir Med 2014; 108:224	40	-0.197 at 9m	+0.367 at 9m	12.8%	30%
Oltmanns et al. (GERMANY) Respiration 2014;88:199	63	-0.3% at 6m -3% at 1 yr	-4% at 6m -9% at 1 yr	8%	20%
Ogura et al. (JAPAN) Respir Investig 2015;53:232	1371	-4.7% at 1yr		12.8%	22.3%
Wijsenbeek et al. (NETHERLANDS & BELGIUM) *Adv Ther* 2015;32:691	63	-0.8% at 6m	-3% at 6m	-	9.5%
Harari et al. (ITALY) Respir Med 2015;109:904-913	128	-4.9%	No effect	-	-
Bando et al. (JAPAN) Intern Med 2016;55:443	502	-30 ml = -0.486% at 1yr	-3.122% at 1yr	-	-
Salih et al. (DENMARK) Eur Clin Respir J 2016;9:32608	113	-164ml = -3.6%	-2.2%	-	11.5%
Tzouvelekis et al. (GREECE) Front Med 2017;4:213	92	-9.25% at 36m	-9.26 at 36m	-	1.25% at 1yr
Tzouvelekis et al. (GREECE) – "SEVERE IPF" *Pulm Pharm & Therap* 2017;46:48-53	43	+0.49 at 6m -5.8 at 1yr	-10.1 at 6m 28.3 at 1 yr	-	49%

Nintedanib – Real-life studies

EFFICACY

STUDIO	# pts	FVC decline	DLCO decline	AE-IPF	MORTALITY
Galli et al. Respirology 2017;22, 1171–1178 (USA)	57	-	-	10.5%	-
Tzouvelekis et al. Pulm Pharmacol Ther 2018;49:61-66 (GREECE)	94	Mean Δ%FVC at 6 m: -1.36 %FVC = 68.1, 68.7, 64.5% at baseline, 6m and 12m	Mean Δ%DLCO at 6 m: -4.00 %DLCO = 44.4, 44.0, 43.7% at baseline, 6m and 12m	3%	-
Brunnemer et al. Respiration 2018;95(5):301-309 (GERMANY)	64	Mean Δ%FVC at 6 months: –1.3 ± 7.9% 53% of pts showed no FVC decline at 6 months	-	2%	-
Harari et al. Respiration 2018 (ITALY) “SEVERE IPF”	41	No difference in ΔFVC% at 6 months: -0.12, p=0.22	%DLCO: 32.73, 26.54, 29.23% at baseline and 6m before and after, p=0.04 Mean Δ%DLCO at 6 months: +2.69, p=0.004		1-year survival: 79%

Pirfenidone – Real-life studies

SAFETY

STUDIO	# pts	INTERRU-ZIONE, %	RIDUZIONE DOSE, %	EFF. COLL. GI, %	INAPPE-TENZA, %	FOTOSEN-SIBILITA', %	AUMENTO ALT/AST, %
Okuda et al. (JAPAN) Respir Med 2013;107:1431	76	18.4	-	11.8	17	18	18.4
Chaudhuri et al. (UK) Respir Med 2014; 108:224	40	15	-	58	-	-	-
Oltmanns et al. (GERMANY) Respiration 2014;88:199	63	20	-	59	30	28	20
Ogura et al. (JAPAN) Respir Investig 2015;53:232	1371	24.3	-	40.1	27.9	14.4	3.1
Duck et al. "IPF CARE program" (UK and AUSTRIA) Adv Ther 2015;32:87	465	16	-	-	-	-	-
Wijsenbeek et al. (NETHERLANDS & BELGIUM) *Adv Ther* 2015;32:691	63	19	-	11.1	25.3	9.5	-
Bando et al. (JAPAN) Intern Med 2016;55:443	502	37.1	-	32.6	-	-	-
Hughes et al. (UK) J Clin Med 2016;5:E78	129	20	20	15	17	7	2
Salih et al. (DENMARK) Eur Clin Respir J 2016;9:32608	113	16	45.2	Nausea: 44.2% Vomiting: 10.6%	39.8	32.7	-
Skold et al. (SWEDEN) Eur Clin Respir J 2016;18:32035	33	6.1	12.1	12.1	-	6.1	-
Galli et al. (USA) Respirology 2017;22, 1171	129	20.9	12.4	Nausea: 26.4% Vomiting: 3.1%	4.7	14.7	3.5
Tzouvelekis et al. (GREECE) Front Med 2017;4:213	92	22.5	-	17.5	-	25	7.5
Tzouvelekis et al. (GREECE) – "SEVERE IPF" *Pulm Pharm & Therap* 2017;46:48-53	43	20.9	32.5	34.9	7	18.6	2.3

Nintedanib – Real-life studies

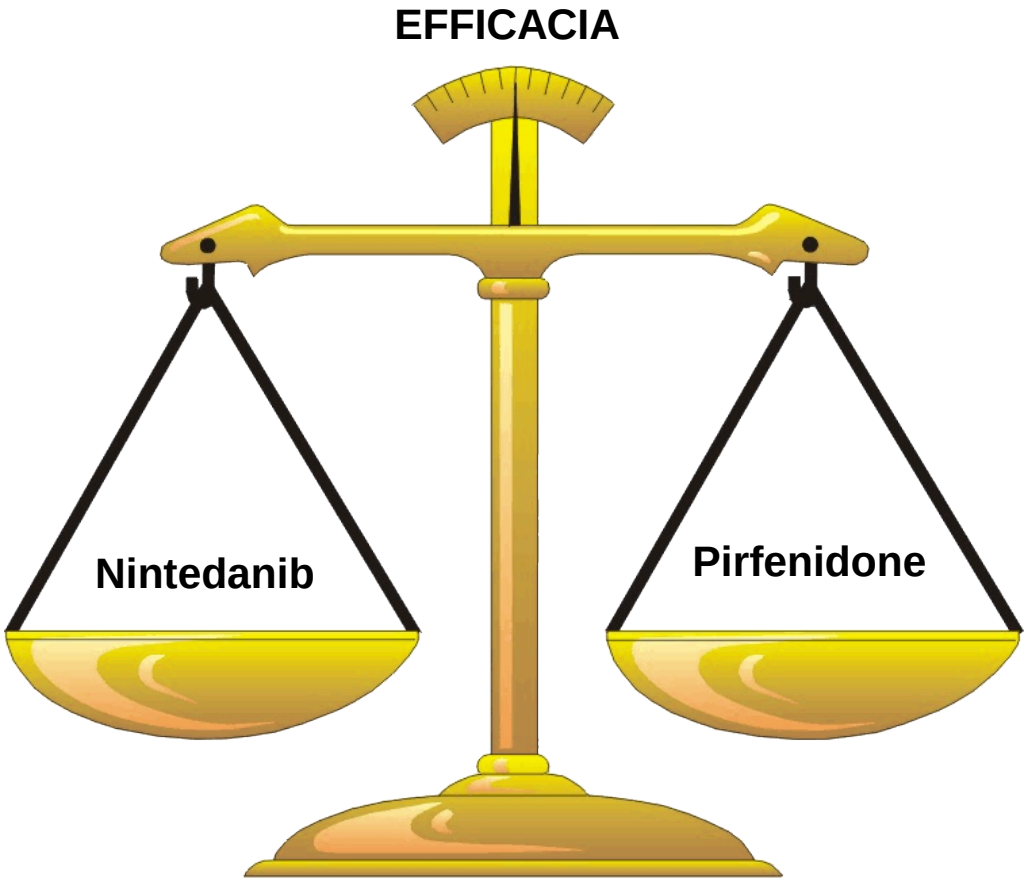
SAFETY

STUDIO	# pts	INTERRU-ZIONE, %	RIDUZIONE DOSE, %	DIARREA, %	NAUSEA, %	AUMENTO ALT/AST, %	SANGUINA-MENTO, %	EVENTI TROMBOEMBOLICI, %
Hughes et al. J Clin Med 2016;5(9):E78 (UK)	124	19	15	24	13	3	1	1
Galli, et al. Respirology 2017;22:1171 (USA)	57	26.3	21.1	52.6	29.8	5.3	1.8	0
Toellner et al. Clin Trans Med 2017;6:41 (UK)	187	13	21	49.7	36.4	9.6	7	1.1
Tzouvelekis et al. Pulm Pharmacol Ther 2018;49:61 (GREECE)	94	21.2	-	55.3	18.1	5.3	2.1	3.1
Brunnemer et al. Respiration 2018;95(5):301-309 (GERMANY)	64	28	13	32.8	3.1	1.6	1.6	3.1

Pirfenidone and Nintedanib: AIFA inclusion criteria for the therapeutic use

	Pirfenidone	Nintedanib
Forced vital capacity (FVC)	**≥ 50%**	**≥ 50%**
Diffusing capacity of the lung for carbon monoxide (DL_{CO})	**≥ 35%**	**≥ 30%**
Age, years	**40 – 80**	**≥ 40**

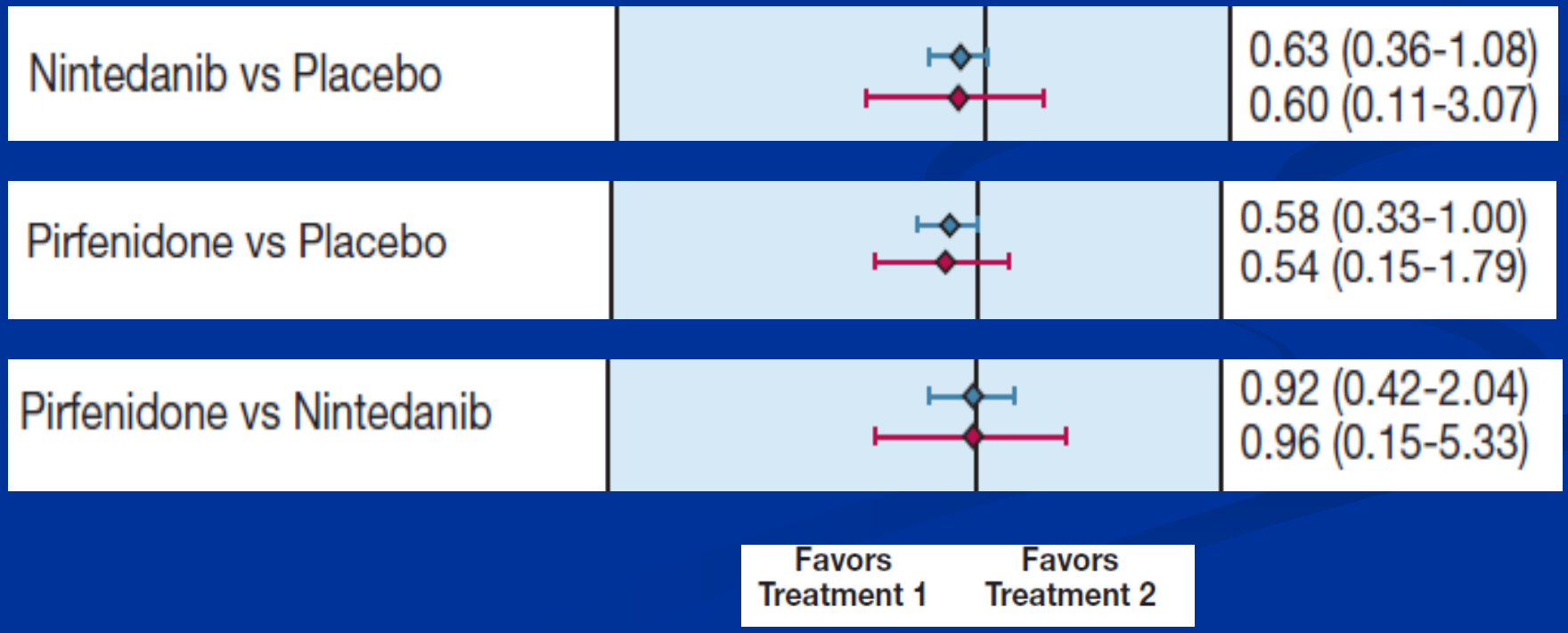
Quale terapia dare al paziente?



Drug Treatment of Idiopathic Pulmonary Fibrosis Systematic Review and Network Meta-Analysis

W J Canestaro, et al. Chest 2016;149:756

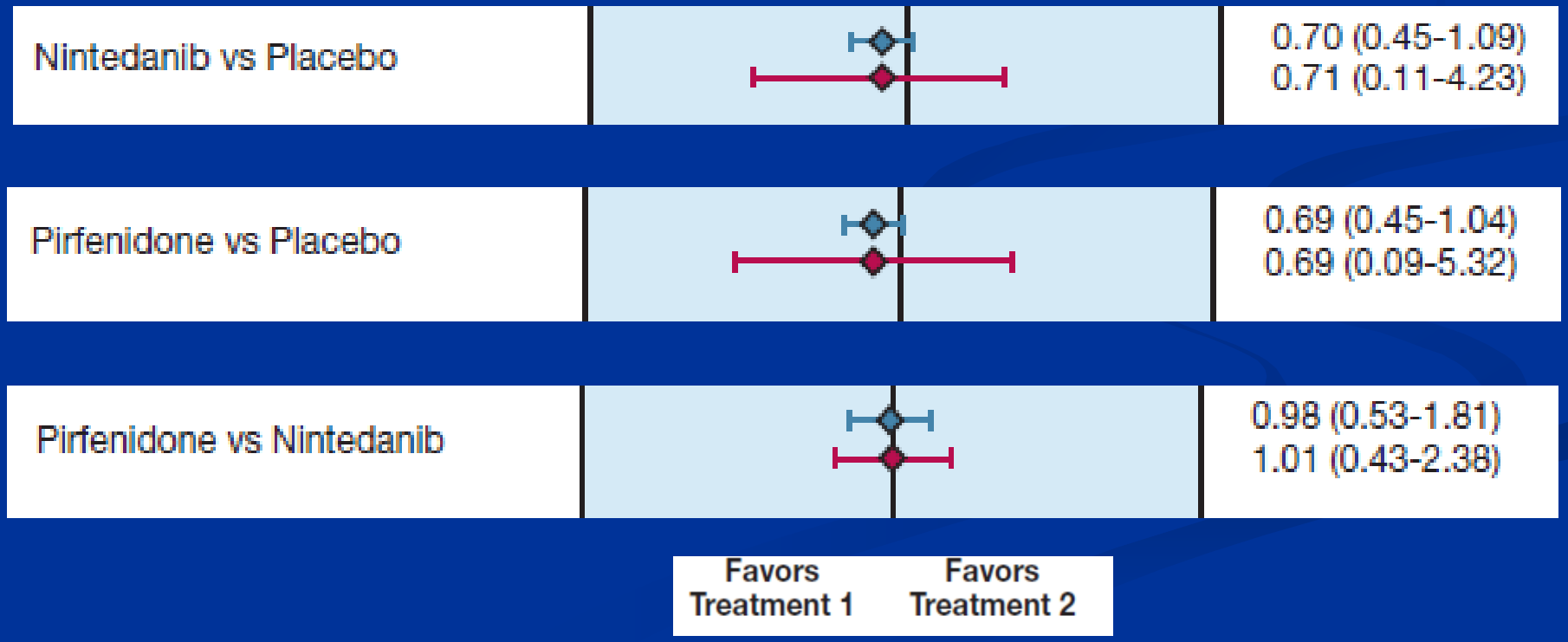
- **Respiratory Death**



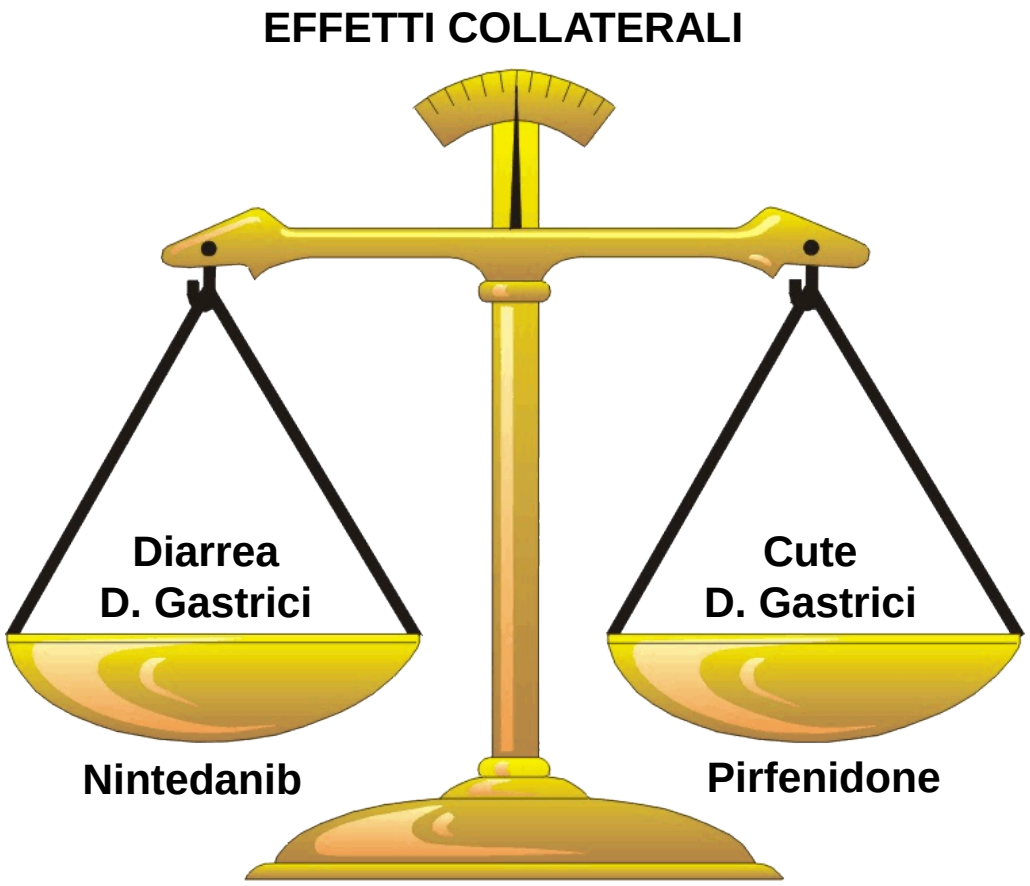
Drug Treatment of Idiopathic Pulmonary Fibrosis Systematic Review and Network Meta-Analysis

W J Canestaro, et al. Chest 2016;149:756

- **All Cause Death**



Quale terapia dare al paziente?



Decidere assieme al Paziente

Paziente
Preferenze
Tolleranza effetti coll.
Stile di vita

Medico
Efficacia del farmaco
Effetti collaterali
Comorbidità

Quale paziente e di quale gravità deve iniziare il trattamento ?

- Gli studi hanno selezionato pazienti lievi-moderati
- Sfortunatamente solo il 27% dei pazienti IPF rientrano in queste categorie*
- FDA approva per IPF, AIFA per severità

*Nathan SD et al. Chest 2011;140:221

Quale paziente e di quale gravità deve iniziare il trattamento ?

- Paziente IPF asintomatico con PFR nei limiti di riscontro occasionale ?

Maher *et al. BMC Pulmonary Medicine* (2017) 17:124
DOI 10.1186/s12890-017-0468-5

BMC Pulmonary Medicine

RESEARCH ARTICLE Open Access

Unmet needs in the treatment of idiopathic pulmonary fibrosis—insights from patient chart review in five European countries

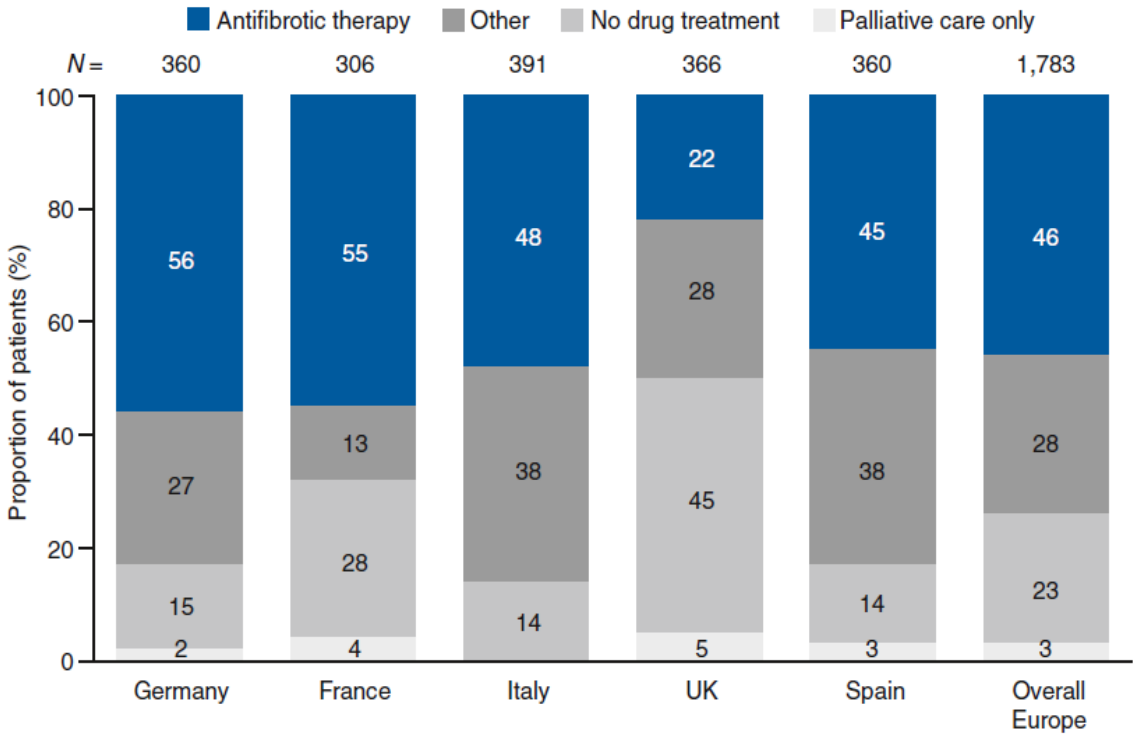


Fig. 1 Proportion of patients that are treated or untreated across European countries. Unweighted data. For individual questions asked, please refer to Additional files 1 and 2

Maher *et al. BMC Pulmonary Medicine* (2017) 17:124
DOI 10.1186/s12890-017-0468-5

BMC Pulmonary Medicine

RESEARCH ARTICLE Open Access

Unmet needs in the treatment of idiopathic pulmonary fibrosis—insights from patient chart review in five European countries

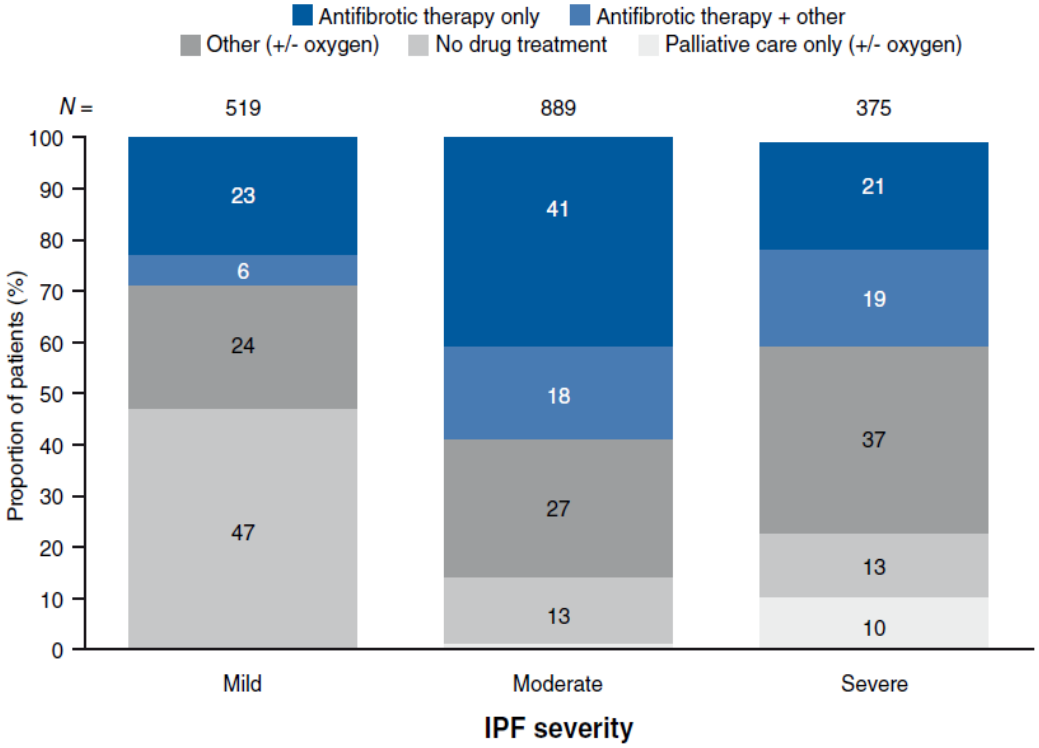


Fig. 3 Overall proportion of treated and untreated patients based on current disease severityClassification of disease severity was based on the subjective determination of individual physicians for each patient. For individual questions asked, please refer to Additional files 1 and 2. *IPF* idiopathic pulmonary fibrosis

Maher *et al. BMC Pulmonary Medicine* (2017) 17:124
DOI 10.1186/s12890-017-0468-5

BMC Pulmonary Medicine

RESEARCH ARTICLE Open Access

Unmet needs in the treatment of idiopathic pulmonary fibrosis—insights from patient chart review in five European countries

The most common reasons given for why the patient was not receiving any drug treatment were:

- lack of, or few, symptoms related to IPF (27%),
- stable disease (26%),
- old age (20%),
- physician-reported good quality of life (20%).

Quale paziente e di quale gravità deve iniziare il trattamento ?

- Paziente IPF asintomatico con PFR nei limiti di riscontro occasionale ?
  - I 2 farmaci funzionano anche con FVC>90%*
  - La prognosi pessima, l'evoluzione non prevedibile, il costante declino della funzione polmonare e la sua correlazione con la mortalità consigliano terapia alla diagnosi

*Albera C, et al. Eur Respir J. 2016;48:843–51

*Kolb M, et al. Thorax. 2017;72:340–6

Quale paziente e di quale gravità deve iniziare il trattamento ?

- Paziente IPF severo (FVC < 50%) ?
  - Sottoanalisi* dei diversi studi dimostrano pari efficacia dei due farmaci nei pazienti sopra e sotto mediana FVC così come studi di real life**
  - Valutare gravità complessiva

*Nathan SD, et al. Thorax. 2016;71:429–35

**Wuits et al, Lung 2017, online first

**Harari S, et al. Respir Med 2015;109:904-13

Per quanto tempo devo continuare il trattamento?

- Abbiamo dati di studi osservazionali a lungo termine (RECAP*, PASSPORT**, ***TOMORROW, §INPULSIS-ON)
- Esperienze real life riferiscono di buona tollerabilità, costante calo FVC, circa 50% in trattamento a 5 anni***

*Costabel U et al. Sacoidosis 2014;31:198
**Cottin V et al. Eur Respir Rev 2015;24:58
***Richeldi et al Thorax 2017, online first
§ Wuits et al Lung 2017, online first
§ Crestani et al ERS 2017
*** Harari S et al. Respir Med 2015;109:904
Okuda R et al. Respir Med 2013; 107:1431
Oltmanns U et al. Respiration 2014;88:199
Chaudhuri N et al. Respir Med 2014;108:224
Behr J et al. Eur Respir J 2015;46:186

Quando sospendere il trattamento?

- Effetti collaterali non gestibili (raramente)
- Nel contesto di una malattia altamente mortale è ragionevole trattare a vita o fino al trapianto tutti i pazienti

Devo sospendere il trattamento prima o dopo il trapianto?

- Delanote I, et al. BMC Pulm Med 2016; 16: 156
- Leuschner G, et al. Respir Med 2017;129:24-30
- Balestro E, et al. Respirology Case Reports 2018;6:4

Devo sospendere il trattamento prima della chirurgia?

- The study demonstrated that acute exacerbations did not occur in 37 out of 39 patients (94.9%, 95% CI 82.7–99.4%; p=0.01)
- The use of pirfenidone before and after surgery is generally safe and significantly reduces the risk of acute exacerbations.

  - Iwata T, et al. Respir Res 2016; 17: 90

Posso usare questi farmaci in altre forme di fibrosi polmonare ?

Nintedanib – All 3 Trials Are Recruiting

- Lymphangioleiomyomatosis (LAM)
- Scleroderma-related ILD (SSc-ILD)
- Progressive fibrosing ILD (PF-ILD)
  - Non-IPF Fibrotic ILD
  - Clinical or radiological progression

ClinicalTrials.gov. Accessed April 2017.

Pirfenidone

- Completed
  - Scleroderma-related ILD
- Recruiting
  - Hypersensitivity pneumonitis
- Not yet recruiting
  - Unclassifiable progressive fibrosing ILD (PF-ILD)
  - ILD with amyopathic dematomyositis
  - RA-ILD

ClinicalTrials.gov. Accessed April 2017.

Come definire il successo o il fallimento del trattamento

- Essendo il corso dell'IPF imprevedibile è impossibile dirlo

Substantial intersubject and intrasubject variability of FVC in IPF in both the magnitude and direction of change

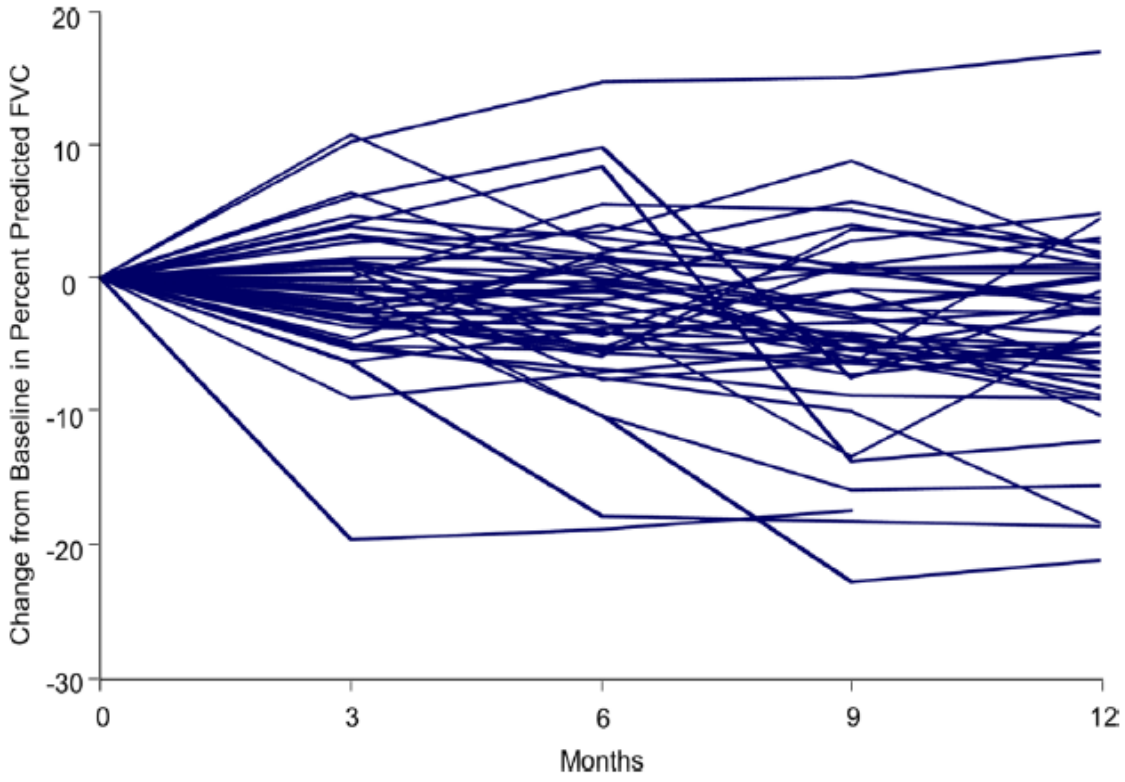


Figure 3 Spaghetti plot of change from baseline to 1 year in per cent predicted FVC*. *Randomly selected patients from the pooled placebo population from the CAPACITY and ASCEND studies (N=50).

Nathan SD, et al. Thorax 2016;0:1–7

Come definire il successo o il fallimento del trattamento

- Essendo il corso dell'IPF imprevedibile è impossibile dirlo
- Caduta della FVC > 10% a 3-6 mesi è sicuramente associata ad una prognosi peggiore
- I dati cumulativi dei vari studi dimostrano, in pazienti con caduta FVC> 10%, prognosi migliore nei trattati rispetto al placebo
- AIFA ha recepito questo messaggio

Posso fare switch tra i due farmaci?

- Lo switch è sicuramente attuabile in caso di effetti collaterali incontrollabili
  - Milger K, et al. Eur Respir J 2015; 46: 1217–1221
  - Ikeda S, et al. BMC Pulm Med 2016;16:38

Posso combinarli?

- Vi sono dati sulla tollerabilità. Costi importanti
  - Ogura T et al. Eur Respir J 2015;45:1382
  - Vancheri et al. Am J Respir Crit Care Med 2017
  - Flaherty KR, et al. 2017 ERS congress, PA2805

Combining Pirfenidone and Nintedanib: Ongoing Studies in Patients with IPF

- **Roche (NCT02598193)**
  - N = 80 patients stable on pirfenidone
  - Nintedanib added
  - Safety/tolerability
  - 24 weeks

- **BI (NCT02579603)**
  - N = 100 patients
  - Nintedanib +/- pirfenidone
  - Safety/tolerability/PK
  - 12 weeks

✓ Enrollment has been completed for both studies

Nintedanib with add-on pirfenidone in IPF: results of the INJOURNEY trial

- 105 were randomized to receive nintedanib 150mg bid alone (n=52) or nintedanib 150mg bid with add-on pirfenidone titrated to 801 mg tid (n=53).

- Nintedanib with add-on pirfenidone had a manageable safety and tolerability profile in patients with IPF, in line with the adverse event profiles of each drug.

Vancheri et al. Am J Respir Crit Care Med 2017

Table 4. Adverse events

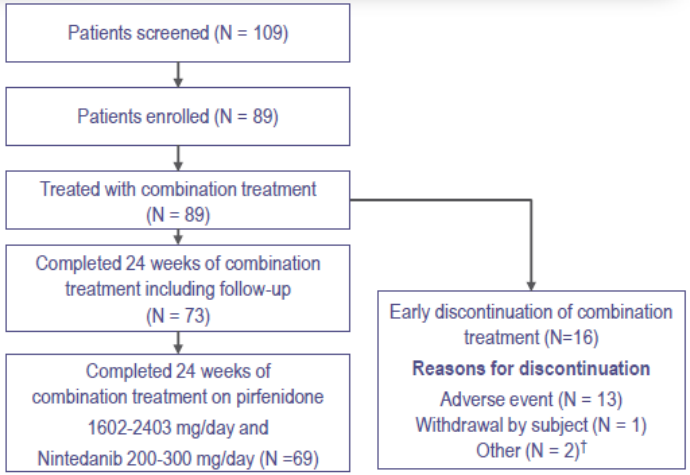
	Nintedanib 150 mg bid with add-on pirfenidone (n=53)	Nintedanib 150 mg bid (n=51)
Any adverse event(s)	47 (88.7)	45 (88.2)
Most frequent adverse events*		
Diarrhea	20 (37.7)	16 (31.4)
Nausea	22 (41.5)	6 (11.8)
Vomiting	15 (28.3)	6 (11.8)
Fatigue	10 (18.9)	6 (11.8)
Upper abdominal pain	7 (13.2)	4 (7.8)
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

Flaherty et al.

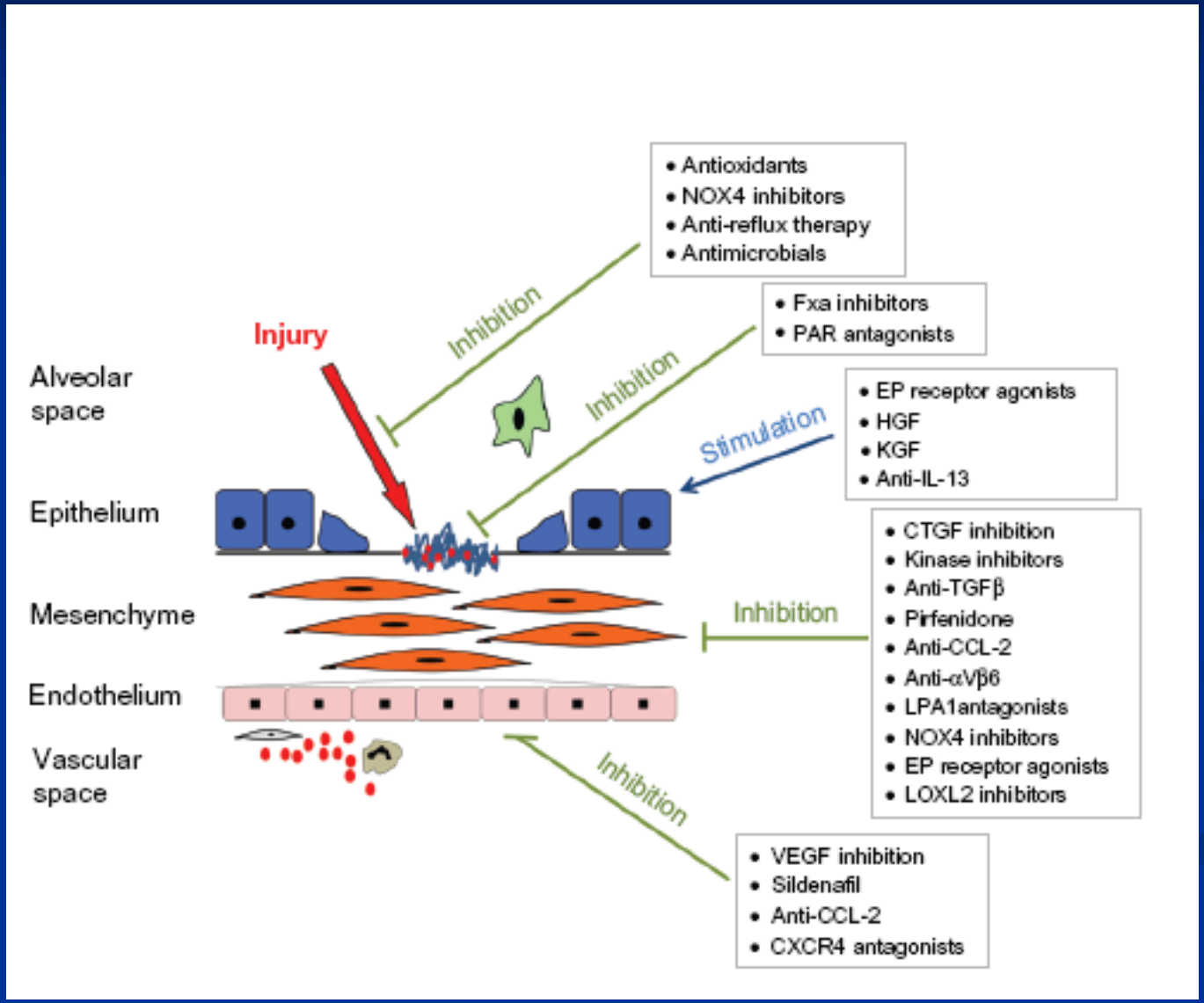
Safety of combined pirfenidone (PFD) and nintedanib (NIN) in patients with IPF

Mon, Sept 11, 12:50pm – 2:40pm, PA2805

- Phase IV, **open-label, single-arm** study evaluating the safety and tolerability of adding NIN to PFD over 24 weeks in **89 patients**
- Combined use of pirfenidone and nintedanib was **tolerated by the majority of patients** and did not reveal differences in the types of TEAEs to that expected with either treatment alone
- Most TEAEs affected the **gastrointestinal system** and were **mild-to-moderate** in severity
- **Exploratory efficacy analyses** showed a **small mean change** from baseline to Week 24

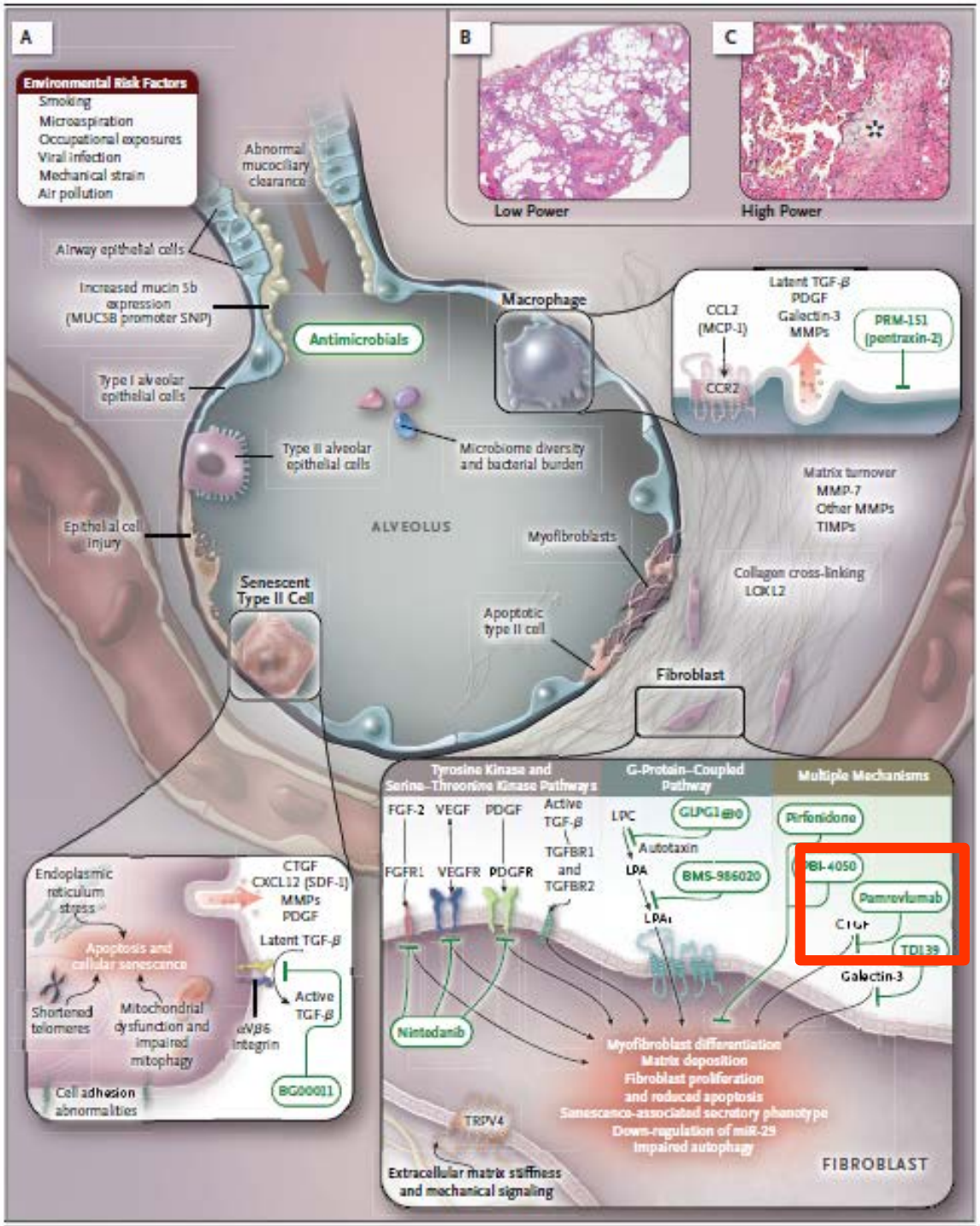


Ongoing Trials with Novel Agents



RCTs for IPF

Intervention	Target	Phase	Status
GSK3008348	αvβ6 integrin	Phase 1	Not yet recruiting
Valganciclovir	Herpesvirus	Phase 1	Not yet recruiting
Omeprazole	Gastric pH, other	Phase 2	Recruiting
KD025	ROCK2	Phase 2	Recruiting
BG00011 (STX-100)	αvβ6 integrin	Phase 2	Recruiting
Pirfenidone + sildenafil	Multiple + PDE5	Phase 2	Recruiting
Tipelukast	LT, PDE3/4, 5-LO	Phase 2	Recruiting
GBT440	Hemoglobin	Phase 2	Recruiting
GLPG1690	Autotaxin	Phase 2	Recruiting
Rituximab	Autoantibodies	Phase 2	Recruiting
Nintedanib + sildenafil	TKs + PDE5	Phase 3	Recruiting
Nebulized fentanyl	Dyspnea	Phase 3	Recruiting
Co-trimoxazole or doxycycline	Lung microbiome	Phase 3	Recruiting
Palliative Care	Your patient	n/a	Recruiting
Home-based rehabilitation	Your patient	---	Recruiting
Azithromycin	Cough	--	Recruiting



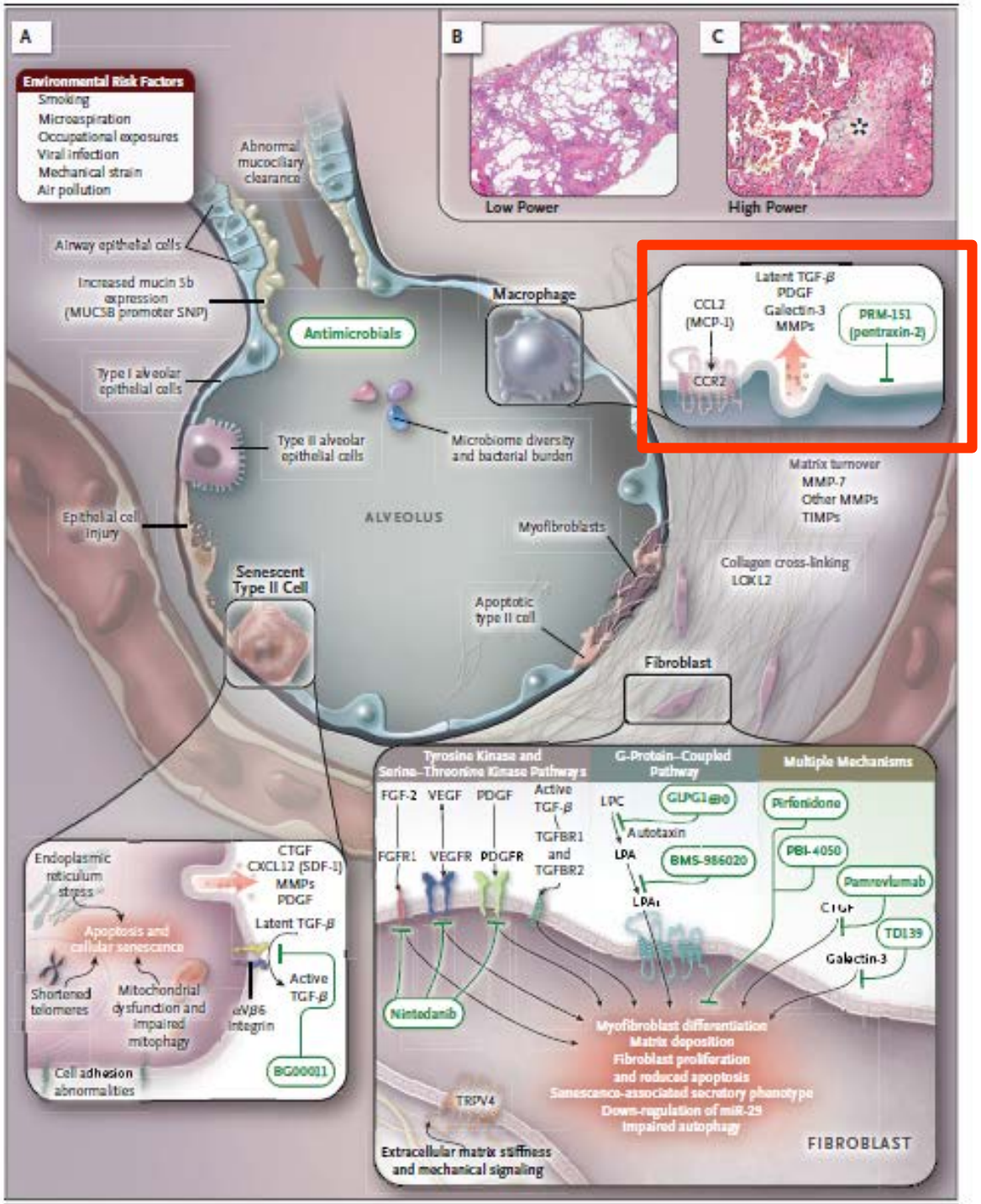
NEJM 2018;378:1811

PRAISE / FIBROGEN- Pamrevlumab (FG-3019)

- Phase 2b randomized, double-blind, placebo-controlled study
- 103 IPF patients with FVC ≥55% and DLCO ≥30% and 10-50% HRCT lung fibrosis were randomized to receive 16 doses of pamrevlumab (30mg/kg IV q3w) or placebo for 48 weeks. Two additional cohorts on stable dosing with pirfenidone (n=36) or nintedanib (n=21) were also enrolled for 24 weeks
- Reduced FVC% decline at 48 weeks: 2.85 vs. 7.17, p = 0.0331
- Reduced FVC absolute decline at 48 weeks: 129 mL vs. 308 mL, p = 0.0249
- Lower proportion of patients with FVC% decline >10% or deaths at 48 weeks: 10% vs. 31.4%, p = 0.0103
- Well tolerated with no safety risks identified during the 48-week study either in monotherapy or in combination with the currently approved standard of care (nintedanib and pirfenidone)

ERS International Congress, Milan 2017 - Symposium “IPF treatment highlights” - N 3400

L. Richeldi



NEJM 2018;378:1811

JAMA | Preliminary Communication

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

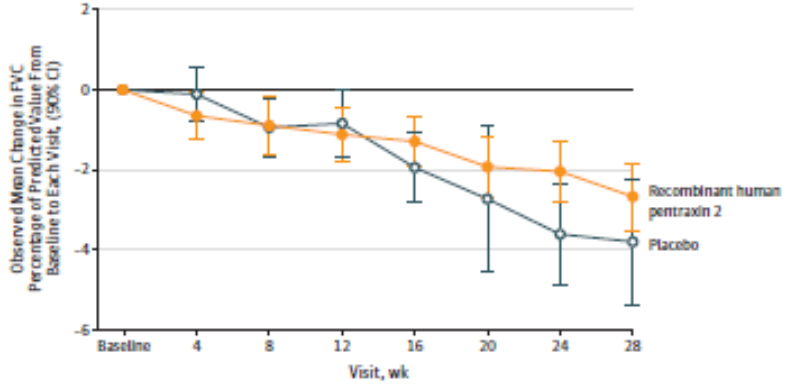
A Randomized Clinical Trial

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

CONCLUSIONS AND RELEVANCE In this preliminary study, recombinant human pentraxin 2 vs placebo resulted in a slower decline in lung function over 28 weeks for patients with idiopathic pulmonary fibrosis. Further research should more fully assess efficacy and safety.

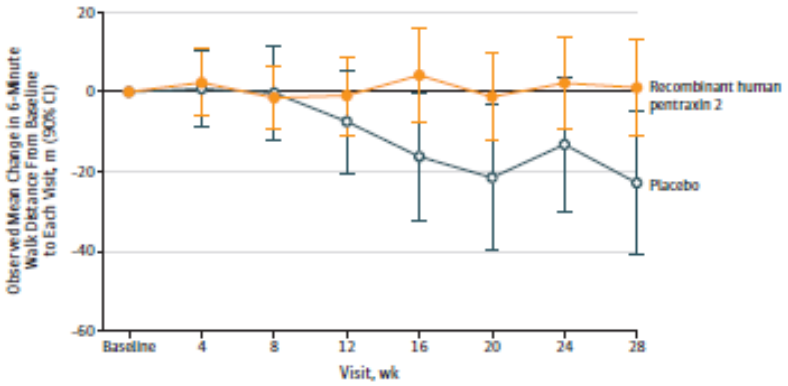
JAMA. doi:10.1001/jama.2018.6129
Published online May 20, 2018.

B Observed mean change in FVC percentage of predicted value from baseline to each visit, all patients

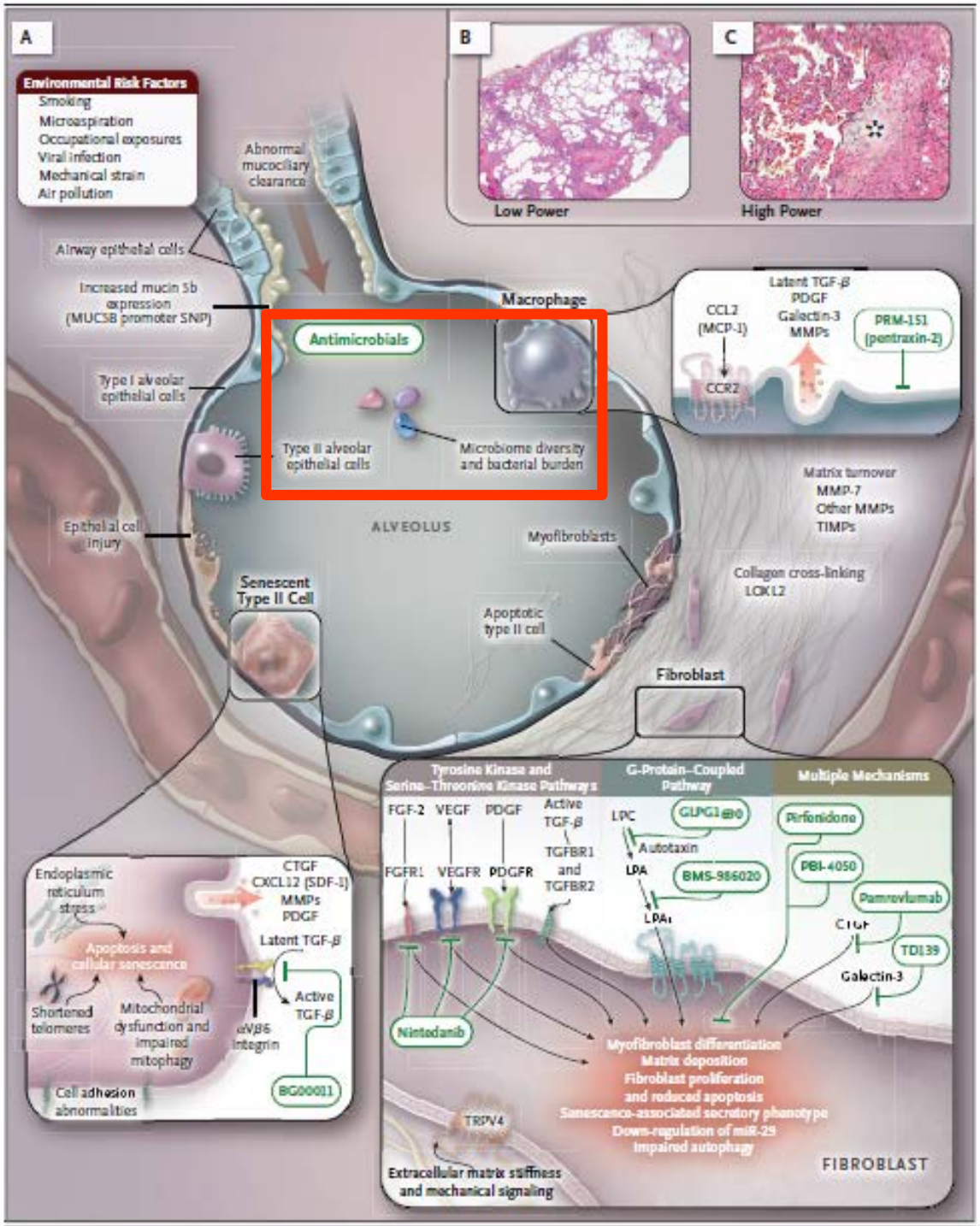


No. of patients								
Recombinant human pentraxin 2	77	69	67	67	68	70	70	67
Placebo	39	35	36	38	37	37	36	35

B Observed mean change in 6-minute walk distance from baseline to each visit, all patients

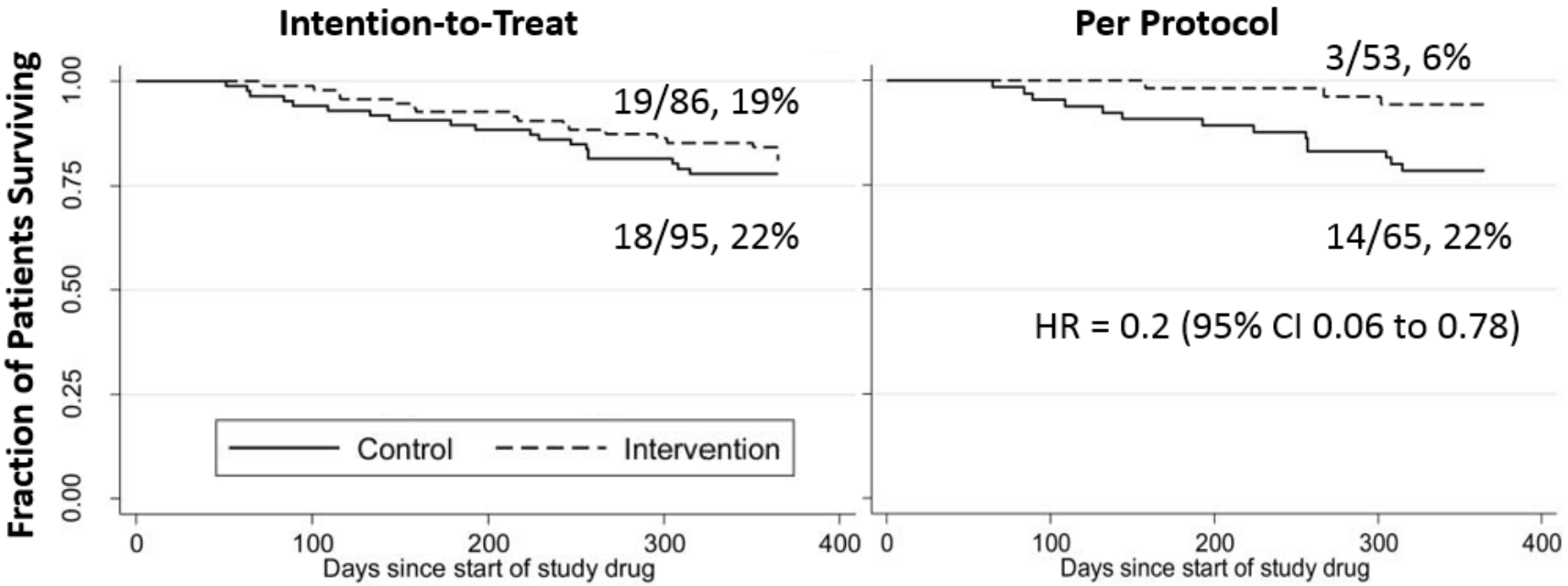


No. of patients								
Recombinant human pentraxin 2	77	73	74	73	73	73	74	74
Placebo	39	39	39	39	38	39	37	37



NEJM 2018;378:1811

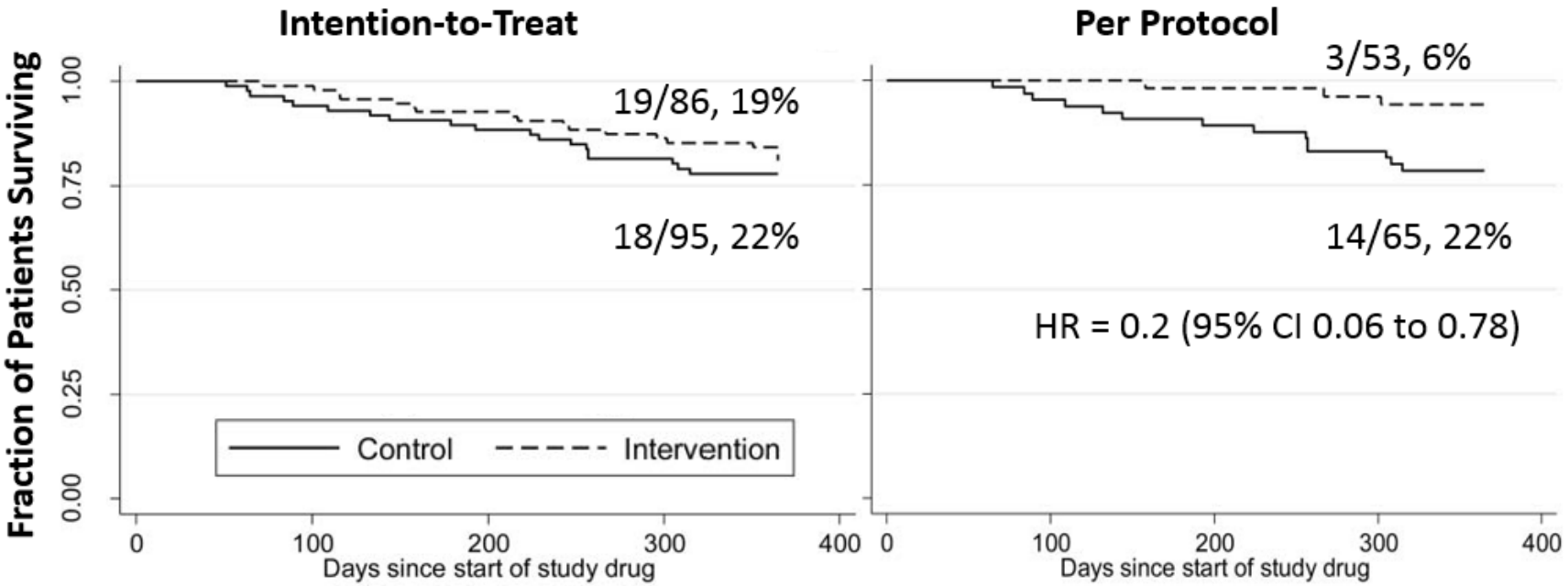
Cotrimoxazole Improves 1 Measure of Mortality



- New trials are currently ongoing
  - UK (ISRCTN17464641)
  - Spain (NCT01777737)

Shulgina L, et al. *Thorax*. 2013;68(2):155-162.

Cotrimoxazole Improves 1 Measure of Mortality



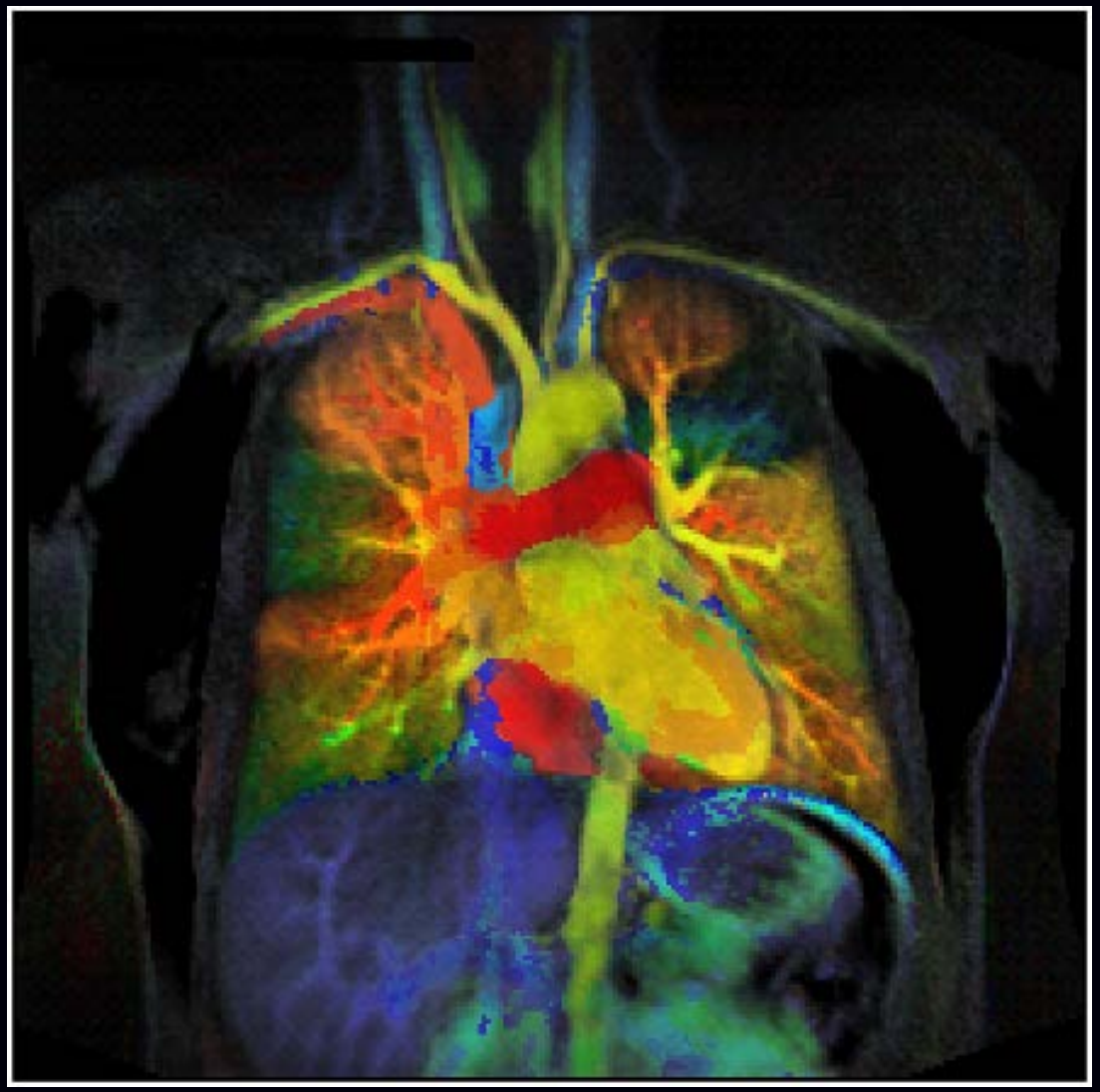
- New trials are currently ongoing
  - UK (ISRCTN17464641)
  - Spain (NCT01777737)

Shulgina L, et al. *Thorax*. 2013;68(2):155-162.

Conclusioni

- La IPF è malattia con prognosi pessima
- La storia naturale è un cronico e persistente peggioramento della funzione respiratoria
- Esistono molecole efficaci nel rallentarne l'evoluzione
- Questi farmaci devono essere usati il più precocemente possibile

Grazie a tutti i presenti della cortese attenzione



Alberto Pesci