Υπάρχουσες και αναδυόμενες θεραπείες σ

Ζωή Δανιήλ
Καθηγήτρια Πνευμονολογίας
Πανεπιστήμιο Θεσσαλίας

The birth of IPF - 2001

American Thoracic Society

American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias

THIS JOINT STATEMENT OF THE AMERICAN THORACIC SOCIETY (ATS), AND THE EUROPEAN RESPIRATORY SOCIETY (ERS) WAS ADOPTED BY THE ATS BOARD OF DIRECTORS, JUNE 2001 AND BY THE ERS EXECUTIVE COMMITTEE, JUNE 2001

Importance of IPF

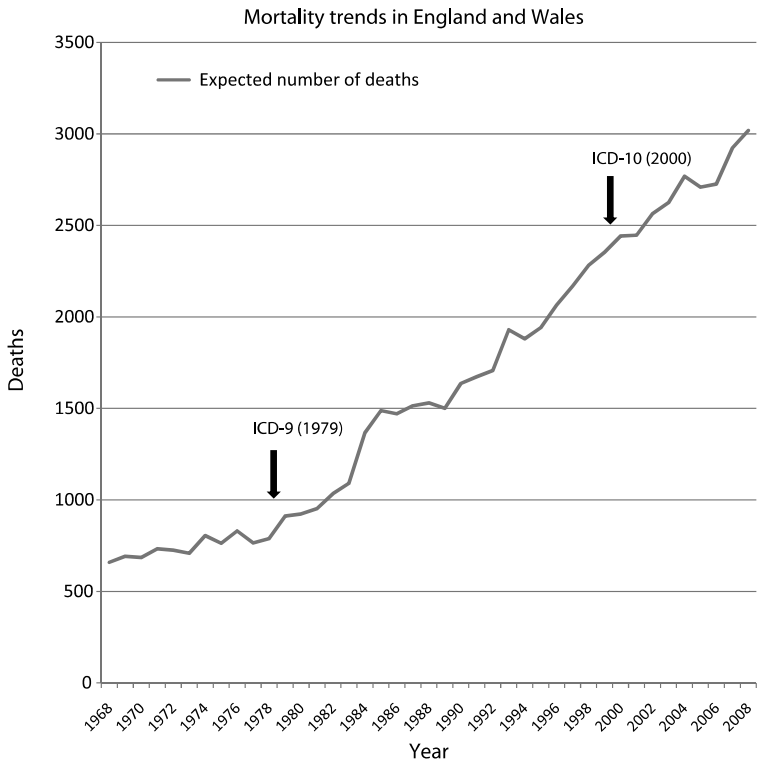


Figure 1 Estimated number of deaths from idiopathic pulmonary fibrosis clinical syndrome, age standardised to the 2008 population of England and Wales. ICD, International Classification of Diseases.

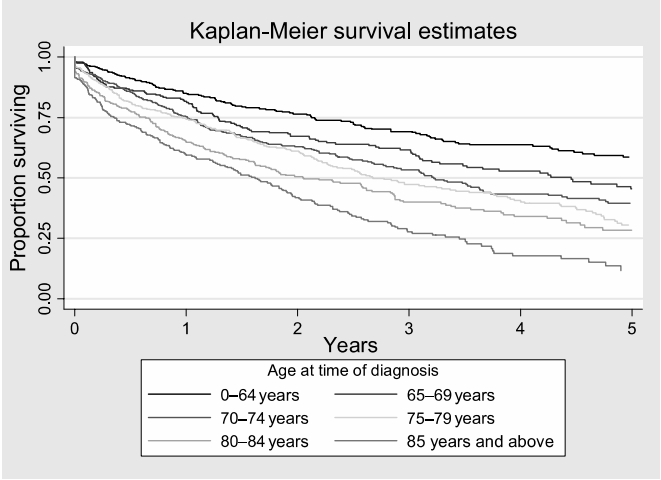
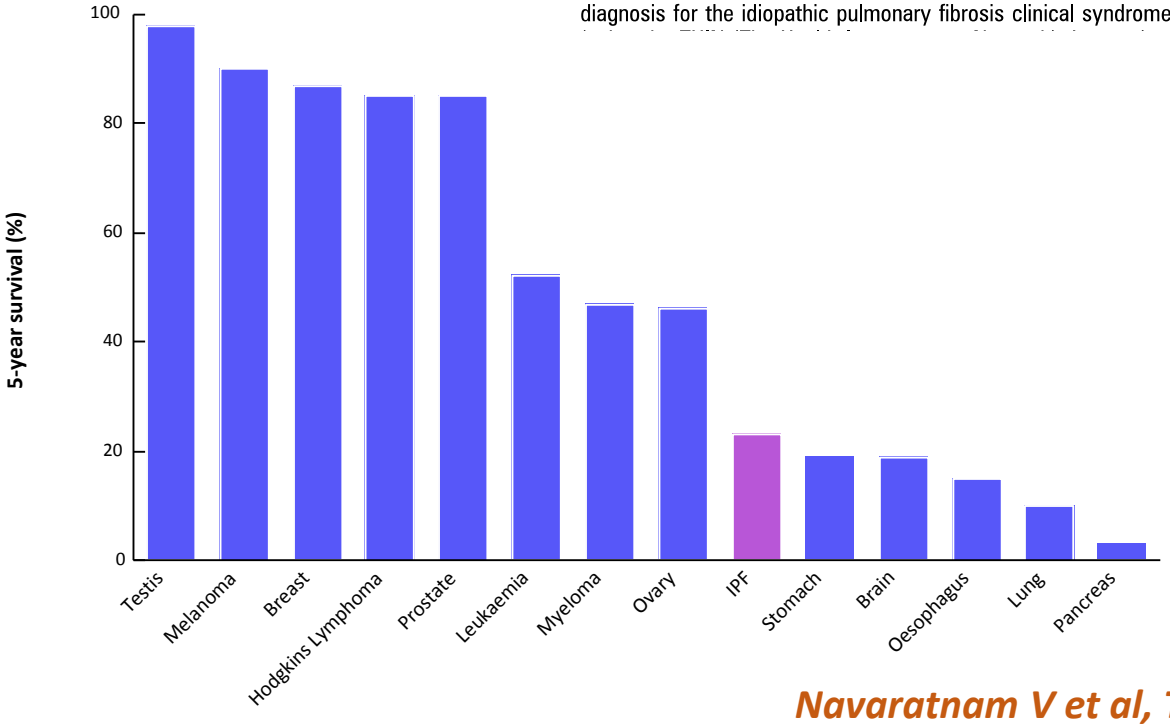
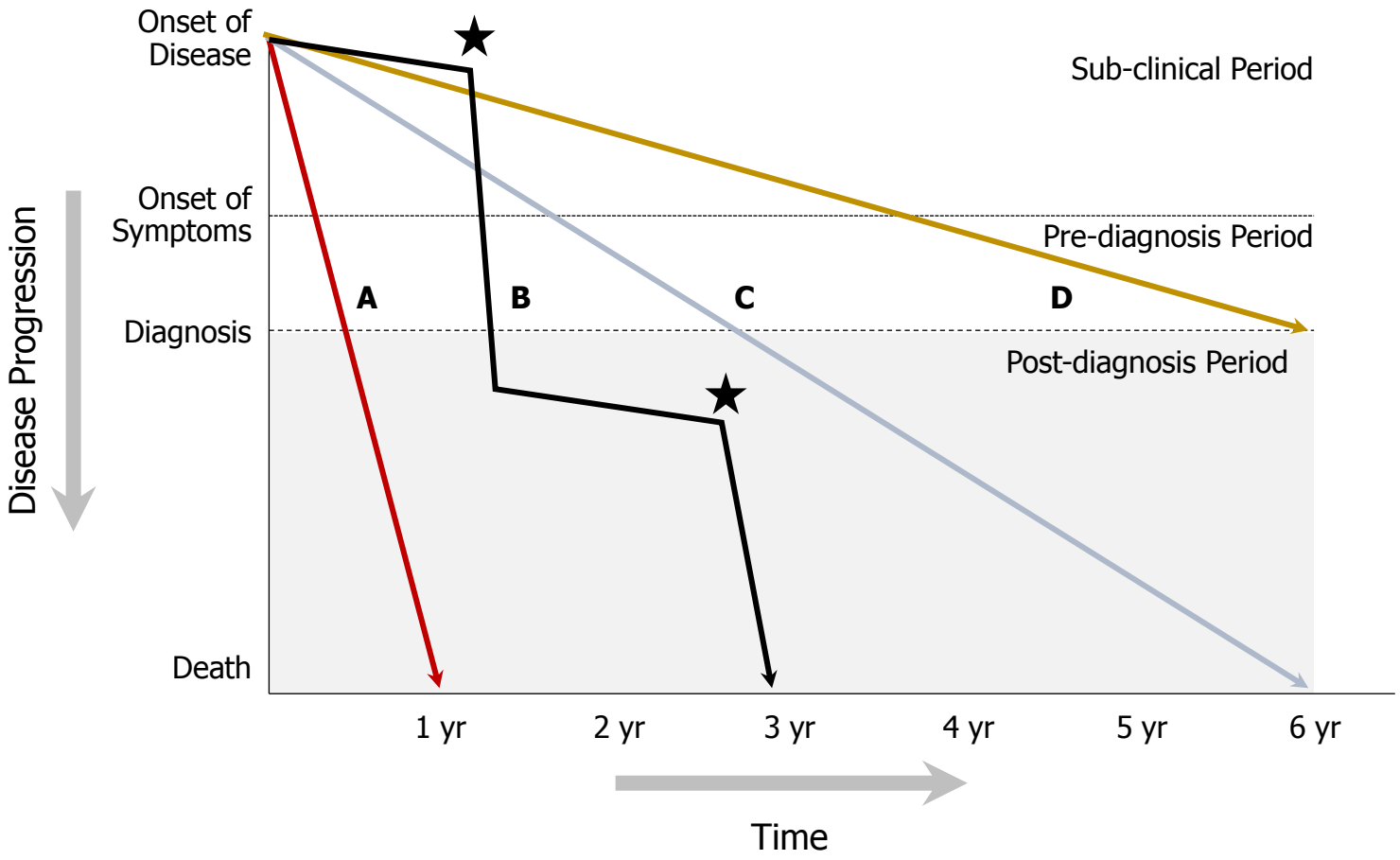


Figure 2 Kaplan—Meier survival estimate stratified by age at time of diagnosis for the idiopathic pulmonary fibrosis clinical syndrome cohort



Navaratnam V et al, Thorax 2011

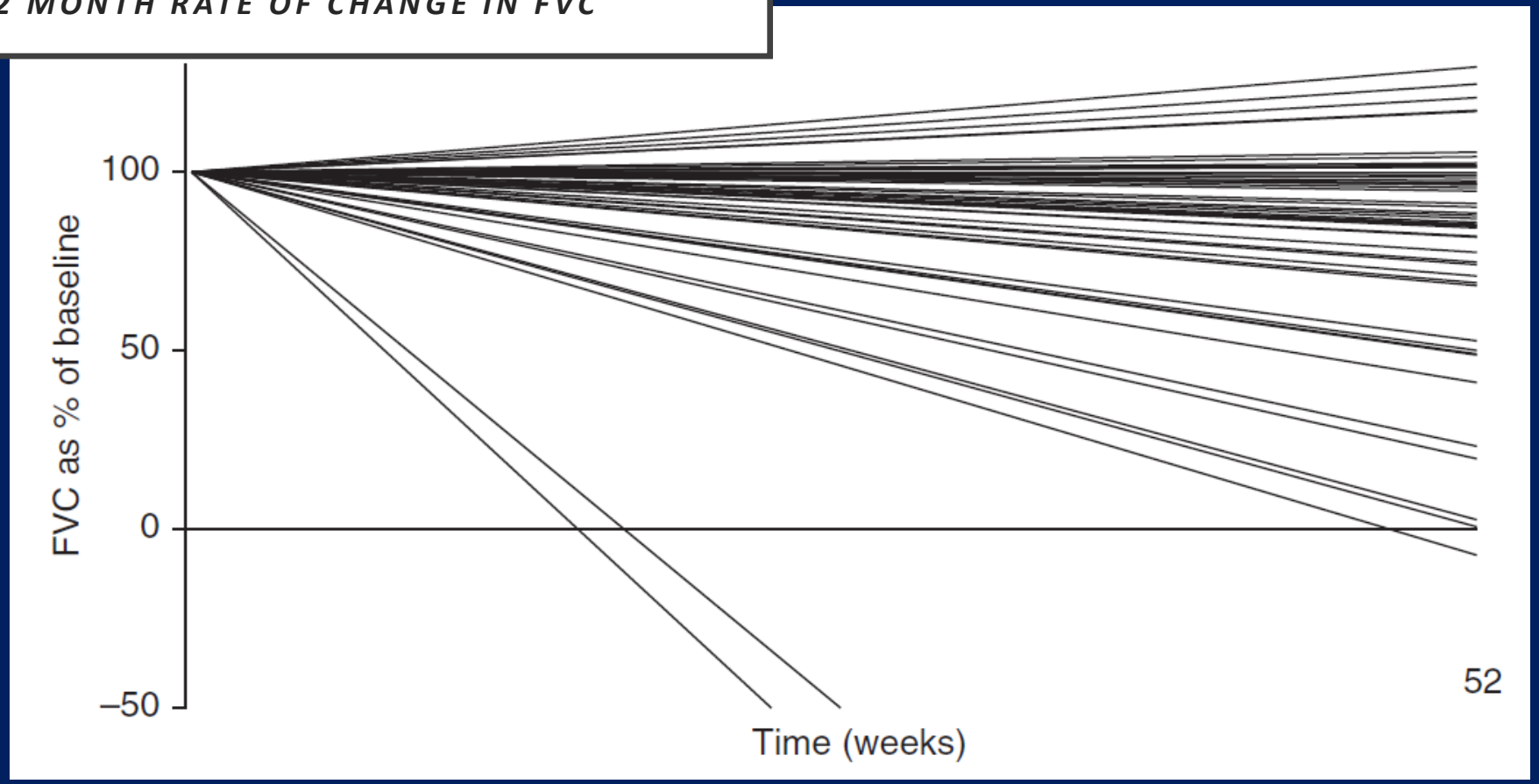
IPF disease progression



Ley B et al, Am J Respir Crit Care Med 2011

DAY BY DAY DISEASE PROGRESSION

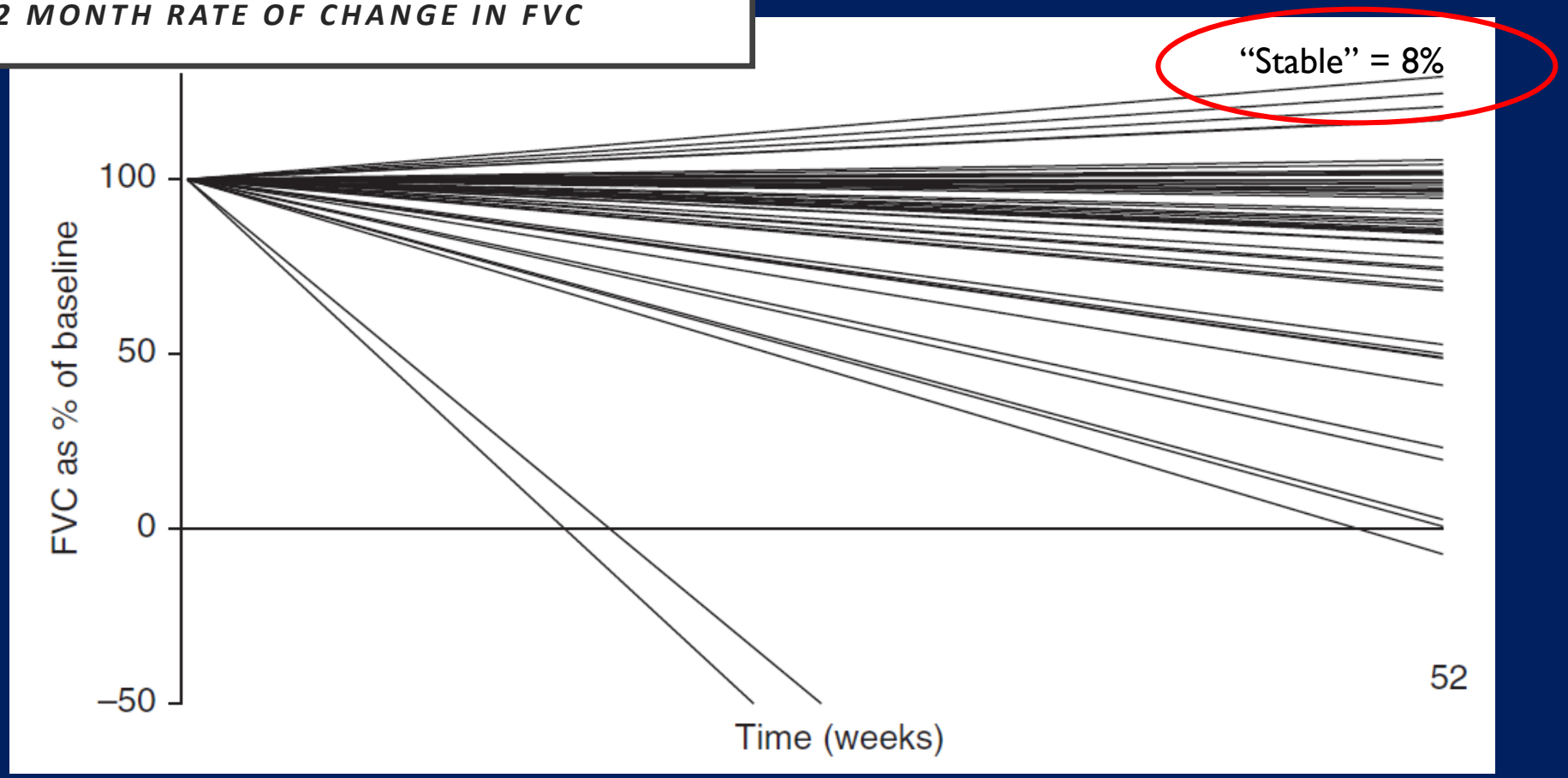
12 MONTH RATE OF CHANGE IN FVC



Russell AM. et al. Am J Respir Crit Care Med 2016

DAY BY DAY DISEASE PROGRESSION

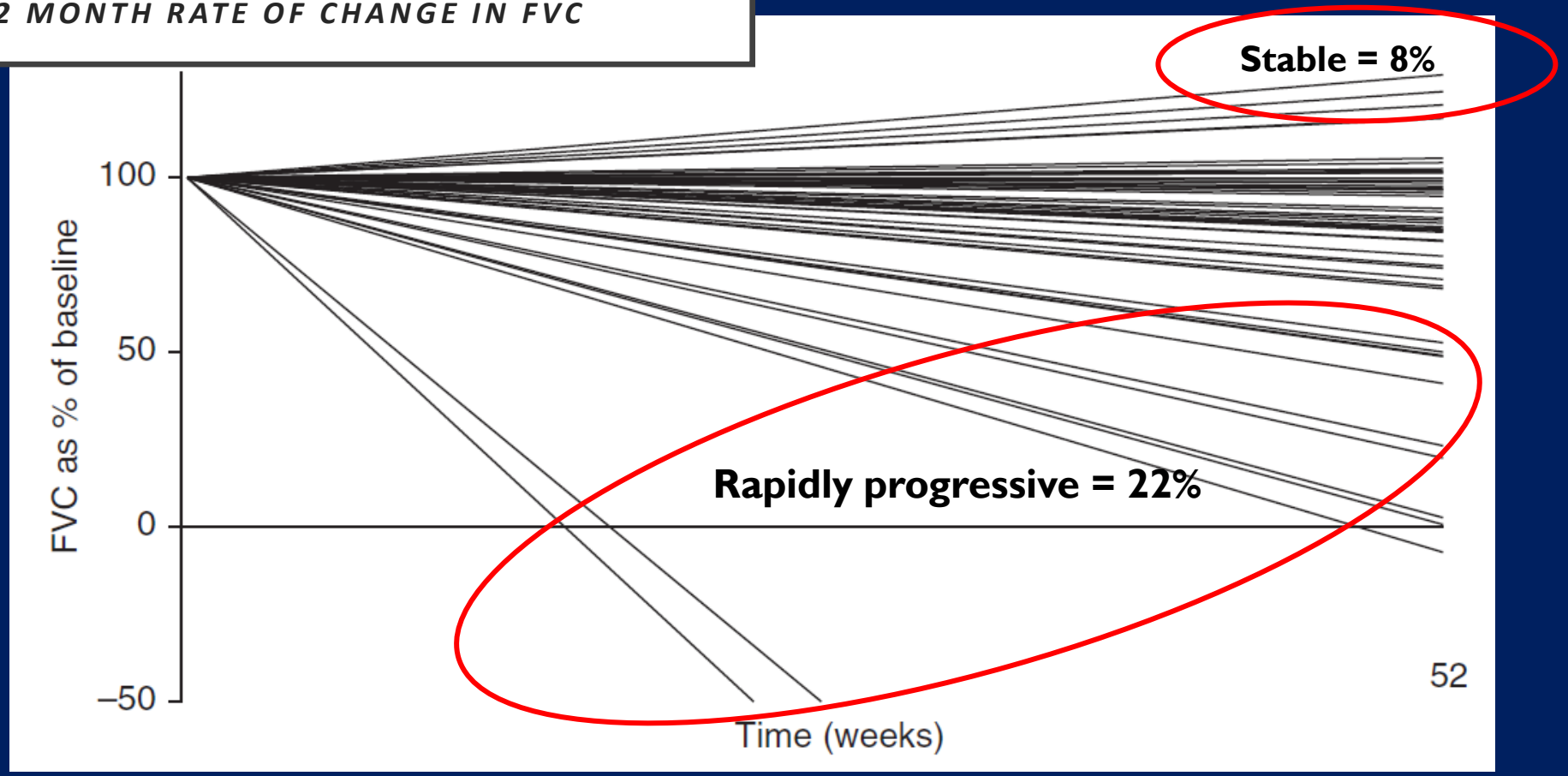
12 MONTH RATE OF CHANGE IN FVC



Russell AM. et al. Am J Respir Crit Care Med 2016

DAY BY DAY DISEASE PROGRESSION

12 MONTH RATE OF CHANGE IN FVC



Russell AM. et al. Am J Respir Crit Care Med 2016

Gazing into the crystal ball:

can treatment response be predicted in IPF?

There is still a major unmet need for ***biomarkers*** to identify

- individuals who are most likely to benefit from treatment (predictive biomarkers) and
- for measuring an individual's treatment response (pharmacodynamic biomarkers)

Michael Kreuter, Toby Maher

Lancet Respir Med 2018

IPF - Treatment

The birth of IPF - 2001

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The NEW ENGLAND JOURNAL of MEDICINE

May 2014

ORIGINAL ARTICLES

Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

L. Richeldi and Others

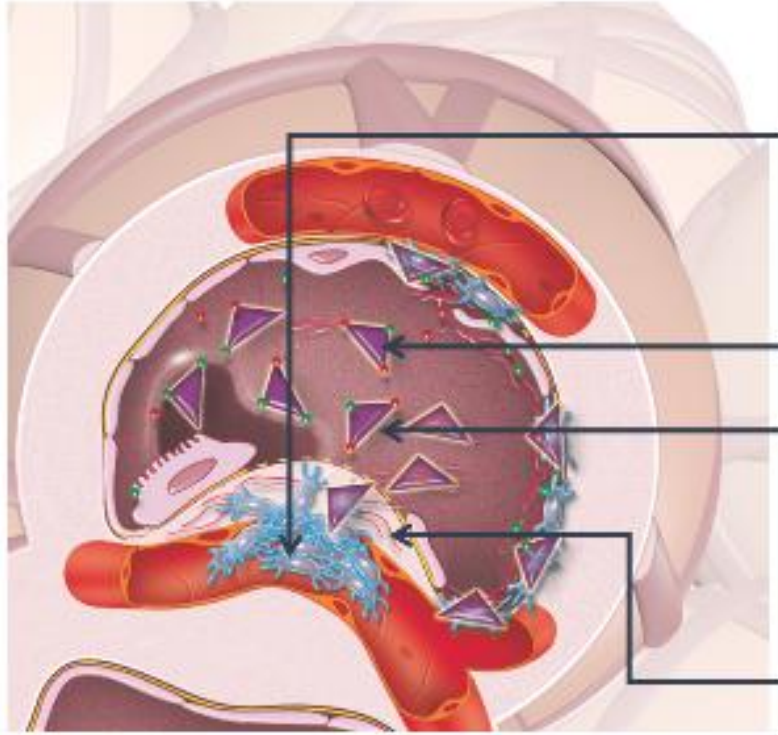
Free Full Text | CME

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

T.E. King, Jr., and Others

Free Full Text

Pirfenidone

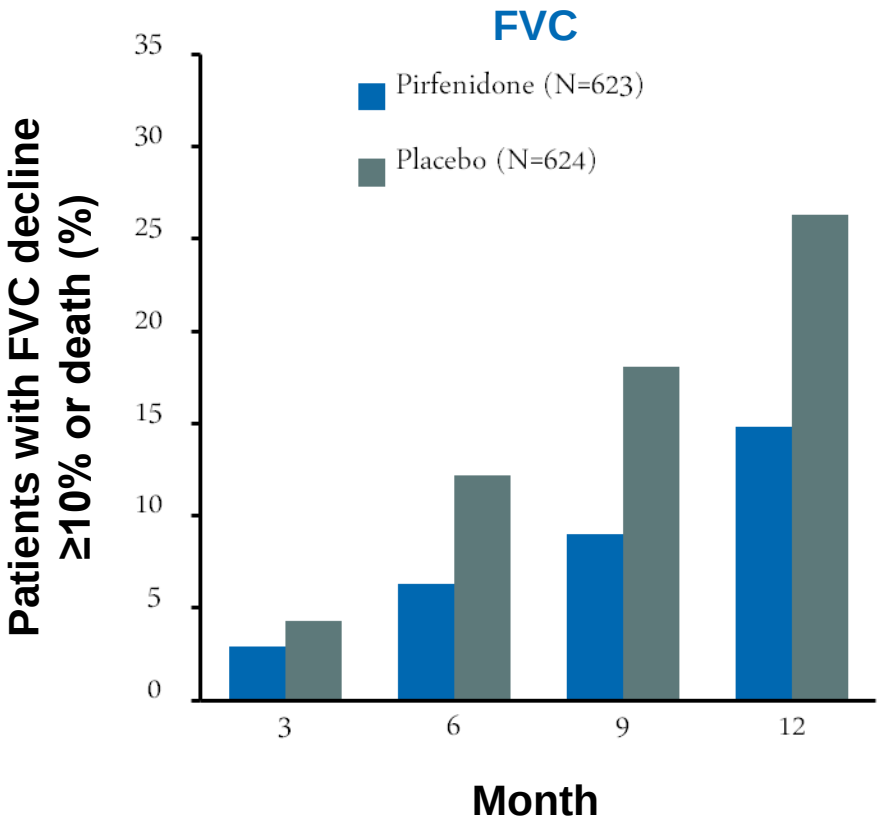


Pirfenidone

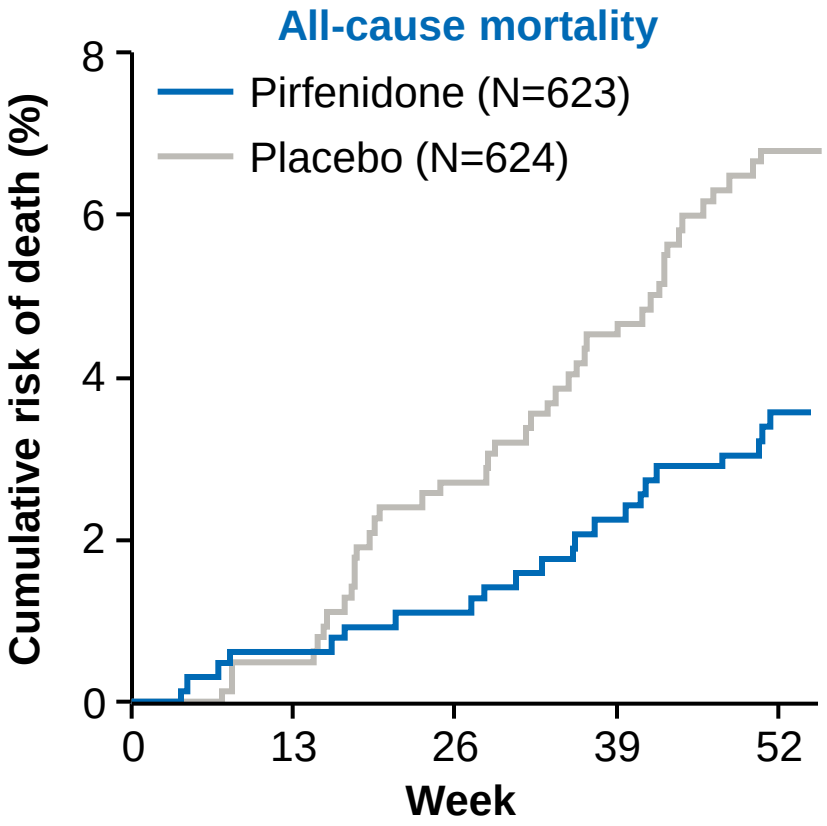
- Pirfenidone attenuates fibroblast proliferation[1,7]
- Pirfenidone inhibits the synthesis and acivity of TGF-β, a potent mediator of lung fibrosis[7-13]
- Pirfenidone inhibits TNF-α synthesis, another fibrotic mediator and inflammatory cytokine[3,6 7]
- Pirfenidone inhibits collagen production[1 2,5,8]

Data from animal and *in vitro* studies

Summary of key clinical endpoints in pooled analyses of pirfenidone Phase III trials at 1 year



	3	6	9	12
Relative difference, %	33.2	48.6	50.4	43.8
p value	<0.0001	<0.0001	<0.0001	<0.0001



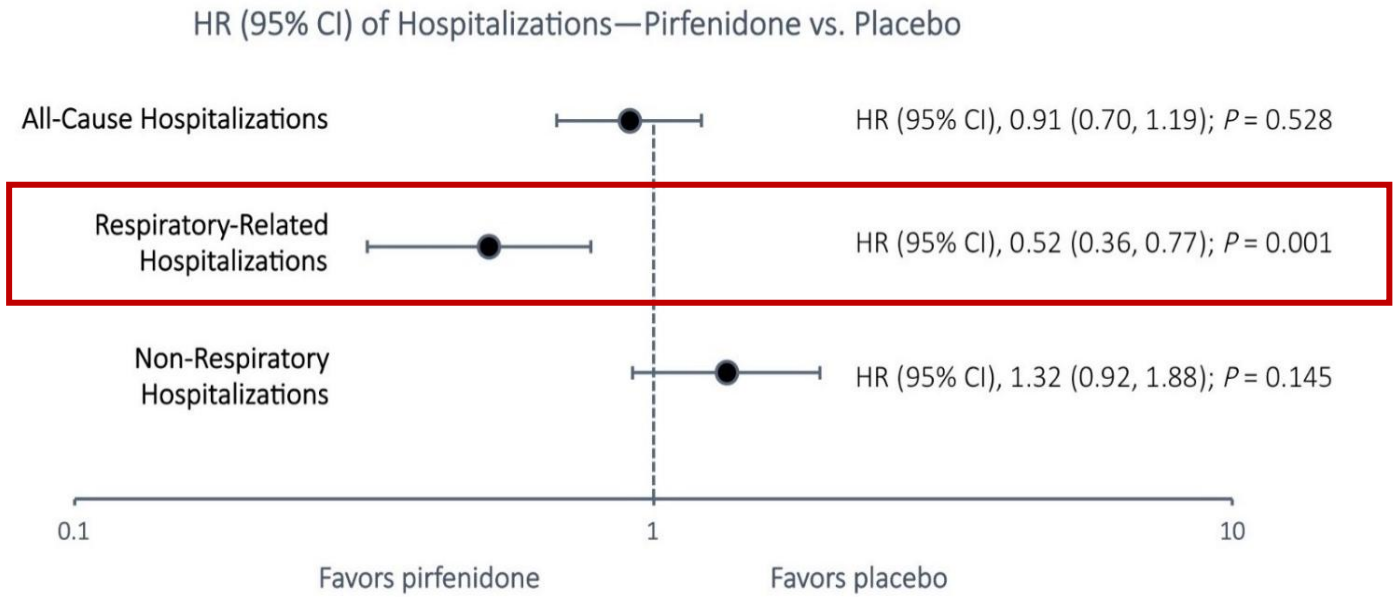
HR 0.52 (95% CI: 0.31, 0.87)*; p=0.011

*Assessed at Weeks 12, 24, 36 and 48 in CAPACITY and Weeks 13, 26, 39 and 52 in ASCEND

CI, confidence interval; FVC, forced vital capacity; HR, hazard ratio

Noble PW et al. Eur Respir J 2016

Clinical outcomes – respiratory hospitalizations



Pirfenidone may reduce the risk of non-elective respiratory-related hospitalizations by 48% over 12 months

Ley B, et al. Am J Resp Crit Care Med, 2017

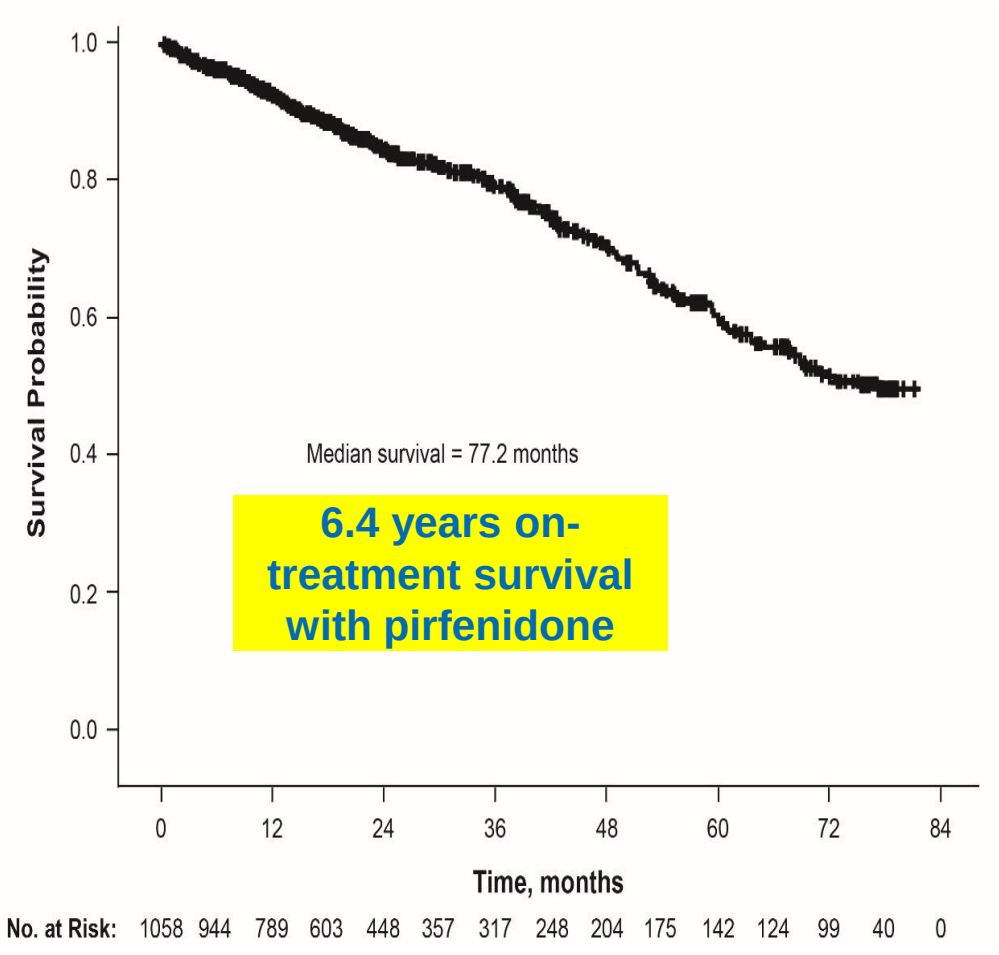
Clinical outcomes – death after hospitalizations

Pirfenidone may reduce the risk of death after all-cause hospitalization by 44% over 12 months

	Hazard ratio	95% CI	*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 hospitalizations (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 hospitalizations (n=124*)			
Unadjusted	0.67	0.26–1.74	0.412
Adjusted for propensity score†	0.73	0.27–1.97	0.537

Ley B, et al. Am J Resp Crit Care Med, 2017

Clinical outcomes – additional mortality data



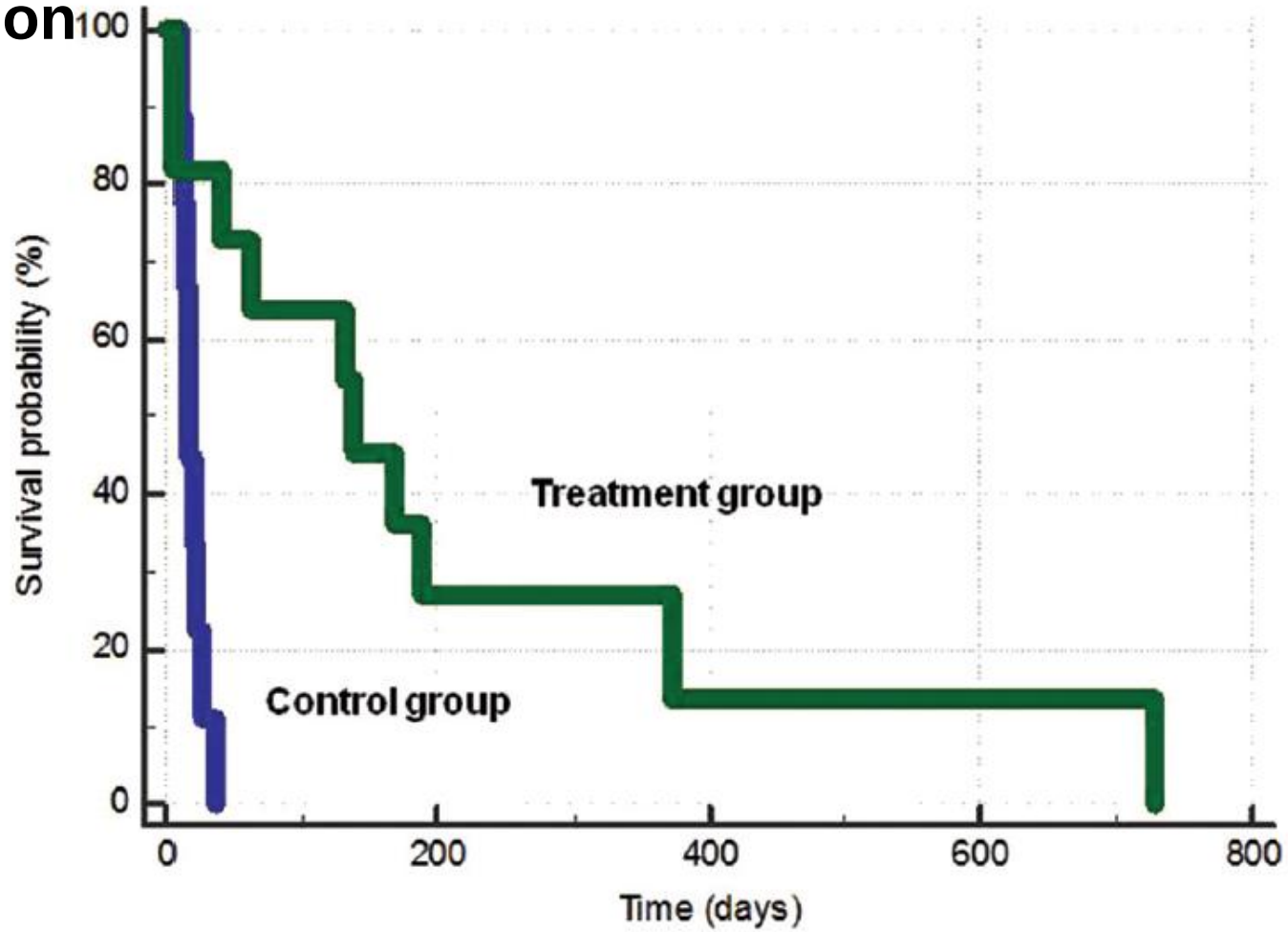
The **median on-treatment survival** from the first dose of 2403 mg/day pirfenidone* in the RECAP study was **77.2 months**

*Assume 1 month = 30.4375 days.

Costabel et al. Respiration 2017

Pirfenidone improves the survival of patients with idiopathic pulmonary fibrosis hospitalized for acute exacerbation

- The survival rate of the patients in the treatment group was 70.0% (±10.2%) at 15 days, 45.0% (±11.1%) at 30 days, 35.0% (±10.7%) at 60 days and 7.5% (±6.6%) at 370 days (maximum length of the follow-up period).
- The stratified log rank test showed that the patients in the treatment group survived for a **significantly longer time** than those in the control group (median survival time: 137.0 [95% CI, 39.0–373.0] versus 16.0 [95% CI, 14.0–22.0] days; p=.0009)



Kaplan–Meier estimates of survival function after RICU admission, stratified according to the group of origin.

Vianelloa A. et al. CURRENT MEDICAL RESEARCH AND OPINION, 2019

Pirfenidone in patients with idiopathic pulmonary fibrosis and more advanced lung function impairment

Steven D. Nathan[a,*], Ulrich Costabel[b], Carlo Albera[c,1], Jürgen Behr[d], Wim A. Wuyts[e], Klaus-Uwe Kirchgaessler[f], John L. Stauffer[g], Elizabeth Morgenthien[g], Willis Chou[g,2], Susan L. Limb[g], Paul W. Noble[h]

Respiratory Medicine 153 (2019) 44–51

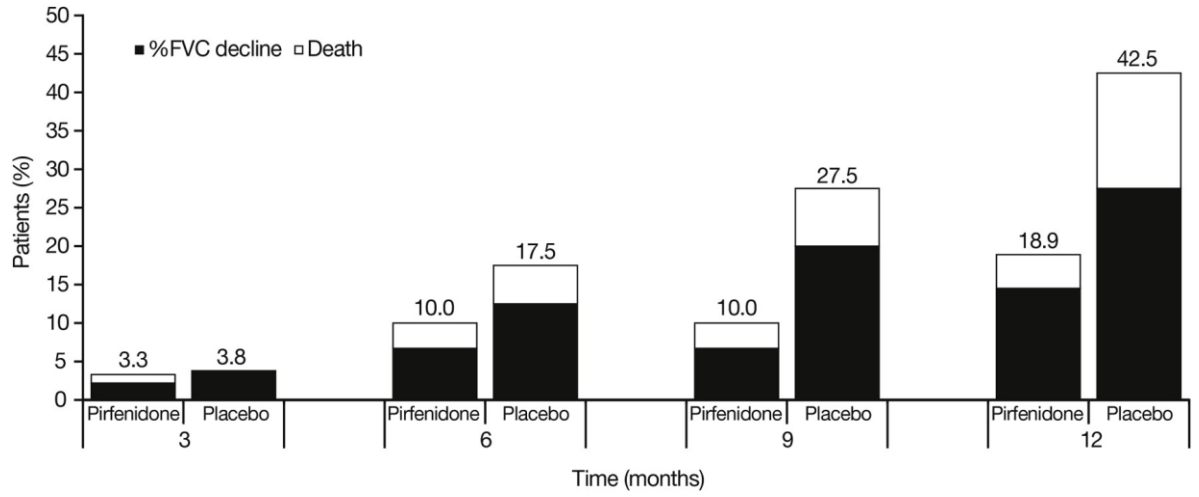


Fig. 2. Percentage of patients with more advanced lung function impairment who experienced ≥10% absolute %FVC decline or all-cause mortality over time. %FVC, percent predicted forced vital capacity.

IPF and more advanced lung function impairment, defined as
percent predicted forced vital capacity (%FVC) < 50% and/or
percent predicted carbon monoxide diffusing capacity < 35%.

Table 2
Time-to-event analyses and NNT calculations for pirfenidone versus placebo for all-cause mortality and composite outcomes over 52 weeks in patients with more advanced lung function impairment who received pirfenidone 2,403 mg/day or placebo in ASCEND and CAPACITY.

Outcome, *n (%)*	Patients with more advanced lung function impairment[a] *N* = 170			
	Pirfenidone *n* = 90	Placebo *n* = 80	HR (95% CI)	NNT
All-cause mortality	4 (4.4)	12 (15.0)	0.28 (0.09–0.86) $p = 0.0180$[b]	10
≥10% absolute %FVC decline or all-cause mortality	19 (21.1)	35 (43.8)	0.40 (0.23–0.69) $p = 0.0006$[b]	5
Respiratory hospitalisation or all-cause mortality	12 (13.3)	22 (27.5)	0.45 (0.22–0.91) $p = 0.0219$[b]	8
≥10% absolute %FVC decline or respiratory hospitalisation or all-cause mortality	25 (27.8)	40 (50.0)	0.46 (0.28–0.76) $p = 0.0018$[b]	5

CI, confidence interval; %DLco, percent predicted carbon monoxide diffusing capacity; %FVC, percent predicted forced vital capacity; HR, hazard ratio; NNT, number-needed-to-treat.

[a] %FVC < 50% and/or %DLco < 35%.

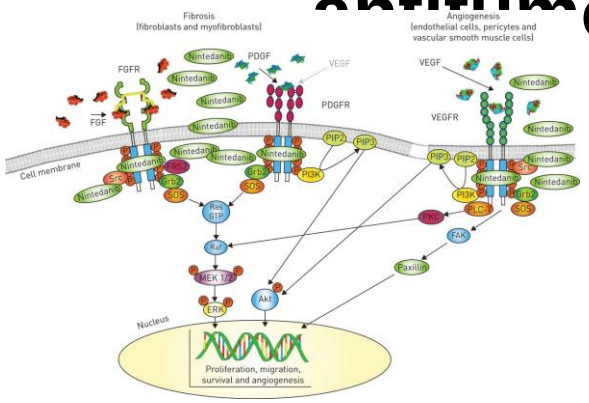
[b] *P*-value is from a log-rank test stratified by study.

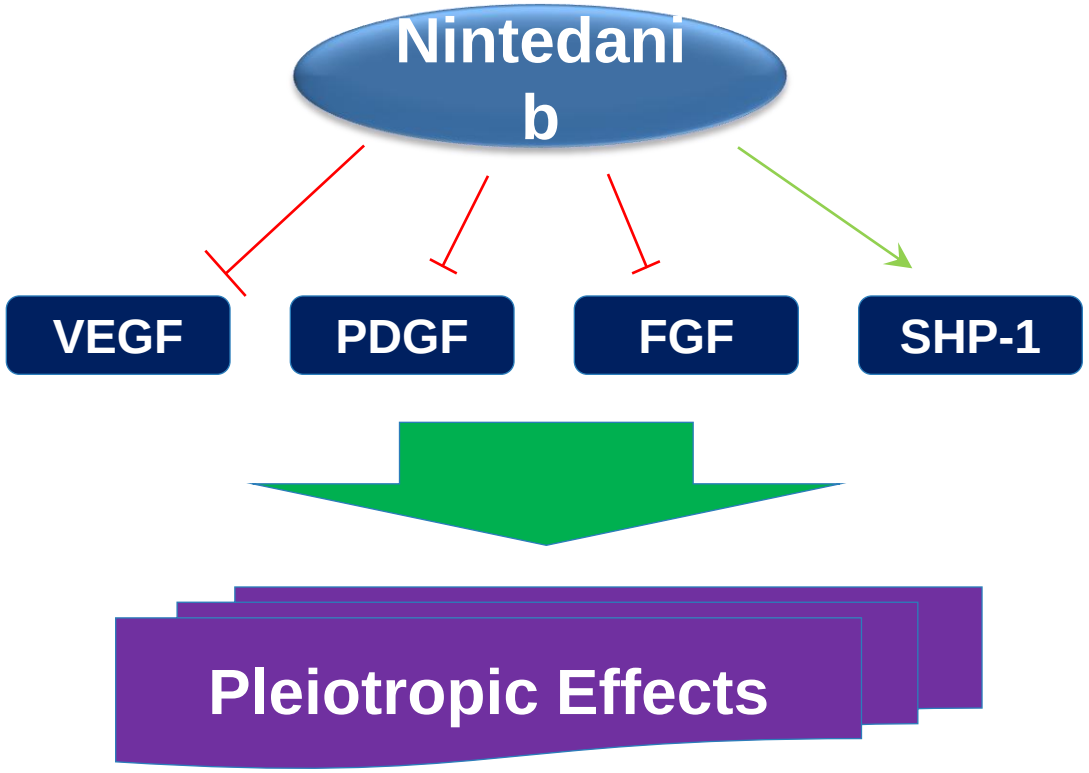
But tolerability needs to be managed… ASCEND trial

Patients (%)	**Pirfenidone** (N=278)	**Placebo** (N=277)
Cough	25.2	29.6
Nausea	**36.0**	**13.4**
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
Idiopathic pulmonary fibrosis	9.4	18.1
Bronchitis	14.0	13.0
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 flux	**11.9**	**6.5**
Insomnia	**11.2**	**6.5**

Mechanisms of Nintedanib Action

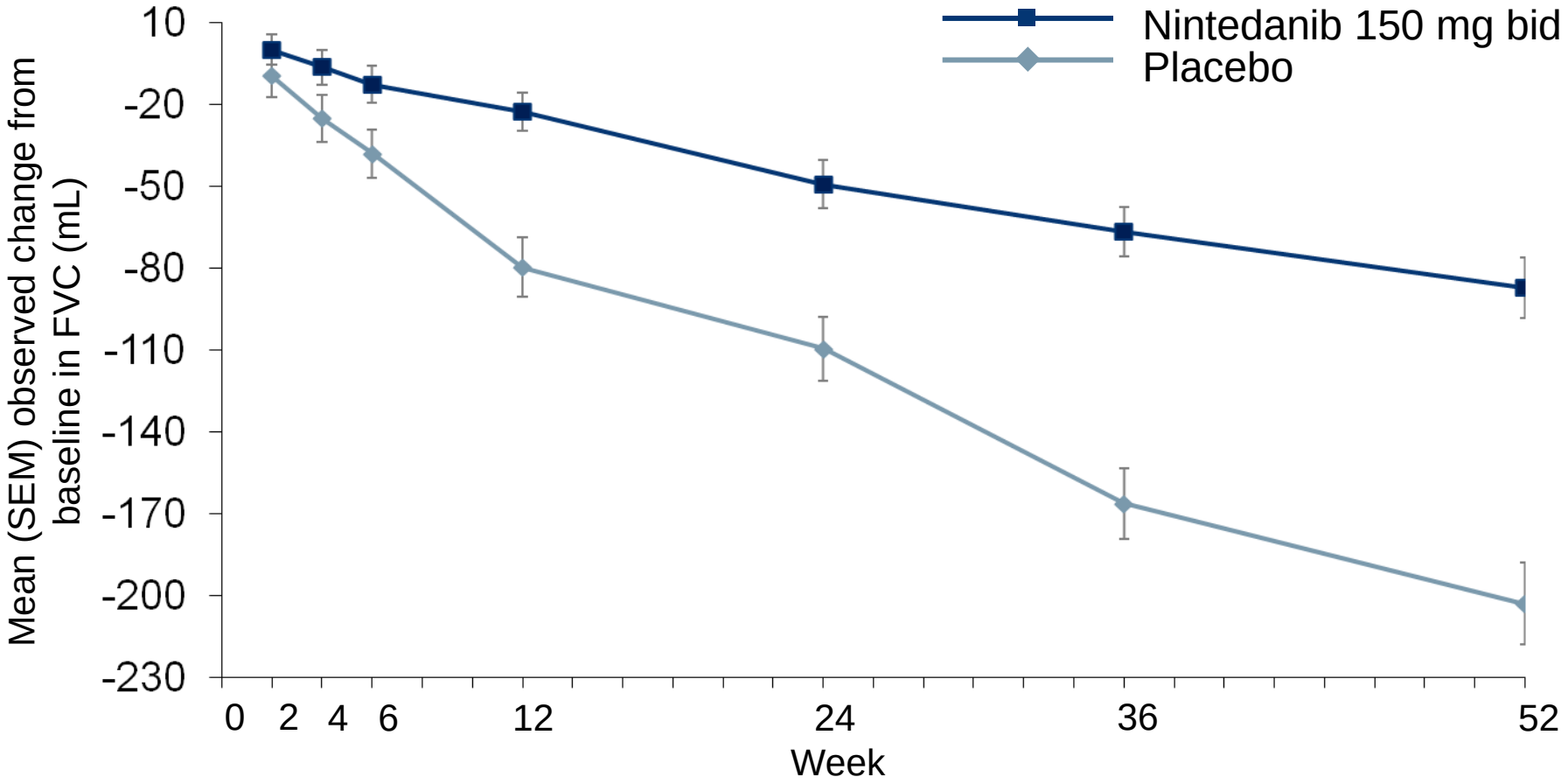
- **Triple kinase inhibitor**
- **Phosphatase activator**
- **Antiangiogenic, antitumor activity**





Hilberg F, et al. Cancer Res. 2008
Tai WT, et al. J Hepatol. 2014

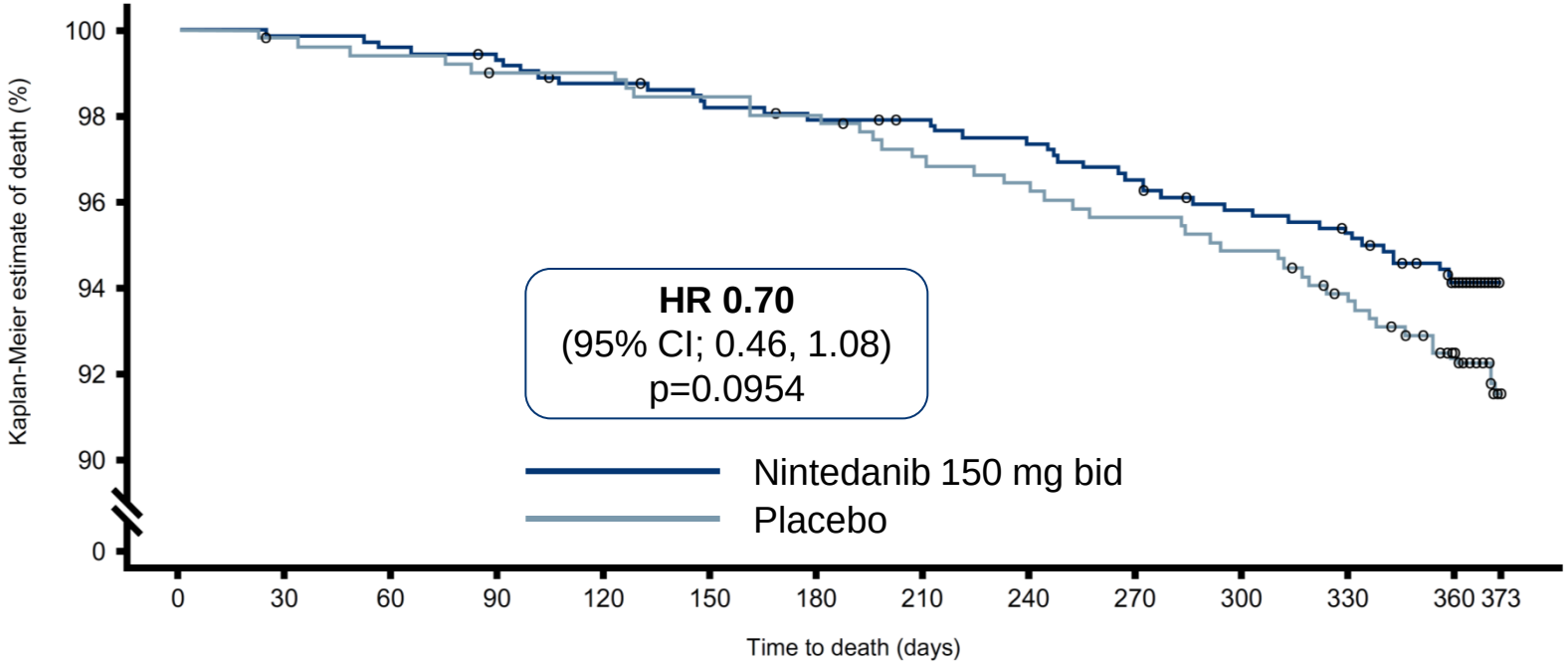
Changes in FVC over time in the TOMORROW and INPULSIS® trials



No. of patients							
Nintedanib	709	699	695	685	664	639	580
Placebo	497	490	490	484	475	460	408

Richeldi L et. al. Respiratory Medicine (2016)

All-cause mortality over 52 weeks: Pooled data from TOMORROW and INPULSIS®

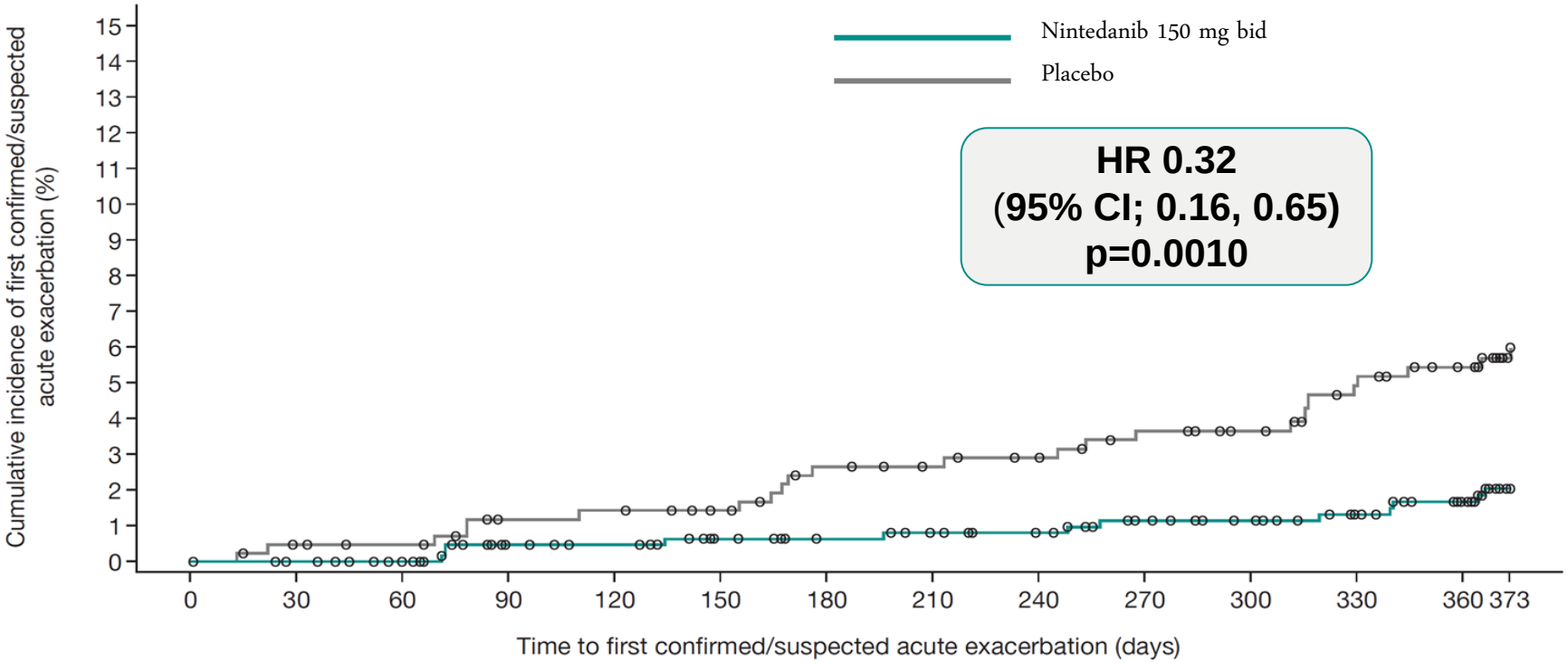


No. of patients													
Nintedanib 150 mg bid	723	722	720	717	712	707	704	702	698	692	685	680	660 562
Placebo	508	506	504	501	501	498	496	490	487	483	479	471	453 375

	Nintedanib 150 mg bid (n=723)	Placebo (n=508)
Patients who died, n (%)	42 (5.8)	42 (8.3)

Richeldi L et. al. Respiratory Medicine (2016)

TIME TO FIRST CONFIRMED OR SUSPECTED ACUTE EXACERBATION PER ADJUDICATION



No. of patients														
Nintedanib	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

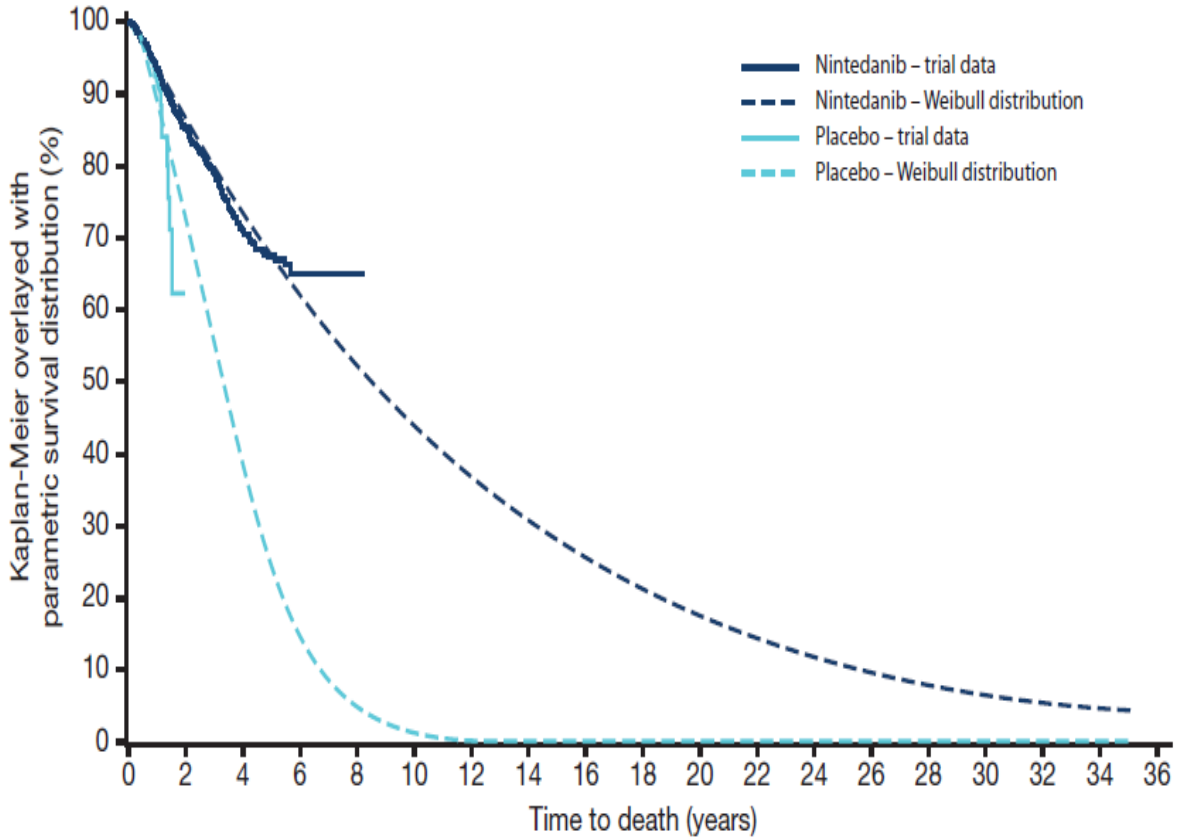
	Nintedanib 150 mg bid (n=638)	Placebo (n=423)
Patients with ≥1 acute exacerbation, n (%)	12 (1.9)	24 (5.7)

Richeldi L, et al. N Engl J Med. 2014

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)

Survival outcomes with long term nintedanib



- Mean (95% CI) survival was estimated as 11.6 (9.6, 14.1) years in nintedanib-treated patients and 3.7 (2.5, 5.4) years in placebo-treated patients; median survival was estimated as 8.5 years in nintedanib-treated patients and 3.3 years in placebo-treated patients

Am J Respir Crit Care Med 2018

ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Efficacy and safety of nintedanib in a Greek multicen
fibrosis registry: a retrospective, observational, cohor

Katerina Antoniou[1*], Katerina Markopoulou[2*], Argyrios T
Eirini Vasarmidi[1*], Jiannis Organtzis[4*], Vasilios Tzilas[3], Eva
Christina Rampiadou[2], Serafeim-Chrysovalantis Kotoulas
Evangelia Fouka[4], Georgios Meletis[6], Stavros Tryfon[2], Zo
Demosthenes Bouros[3].

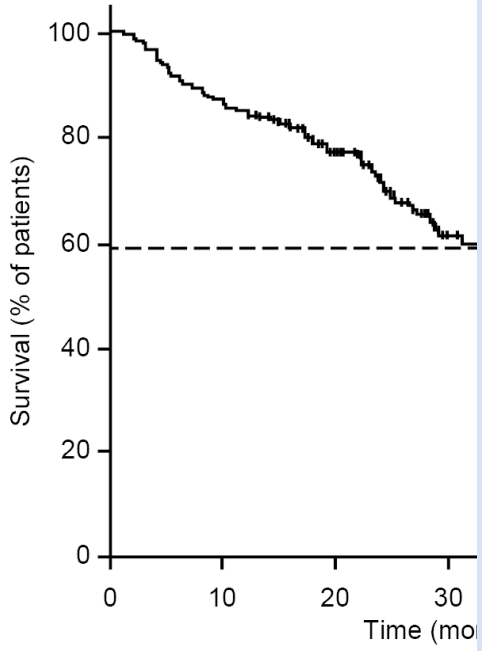
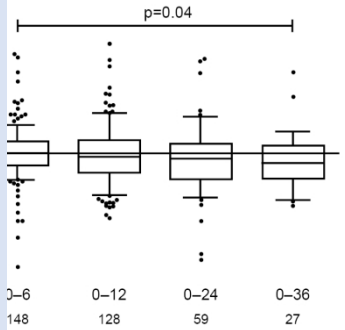


Table 2. Investigator-reported AEs in the safety population (n=244).

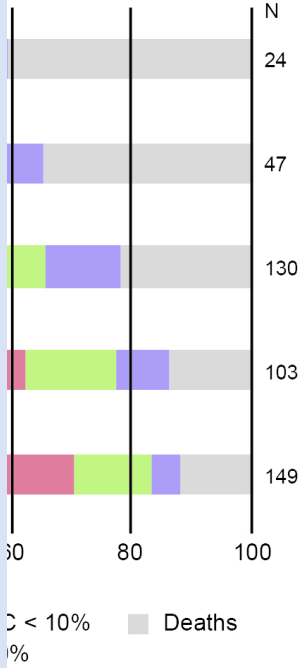
	Number of AEs	Proportion of patients with AE
Total AEs reported	224	55.7%
GI events	173	-
Diarrhoea	110	45.0%
Nausea/vomiting	26	10.7%
Anorexia	18	7.4%
Abdominal pain	11	4.5%
Dyspepsia/bloating	6	2.5%
GI bleeding	2	0.8%
Reduced body weight	16	6.6%
Liver function test elevations	12	4.9%
Weakness	11	4.5%
Ischaemic events[a]	9	2.9%
Hyperpyrexia	1	0.4%
Others	4	1.6%
Reduced dose due to AE	69	28.3%
Discontinuation due to AE	32	13.1%

[a]Ischaemic events defined as myocardial infarction or ischaemic stroke.

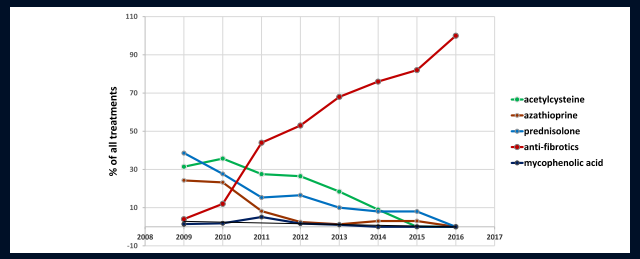
Abbreviations: AE, adverse event; GI, gastrointestinal.

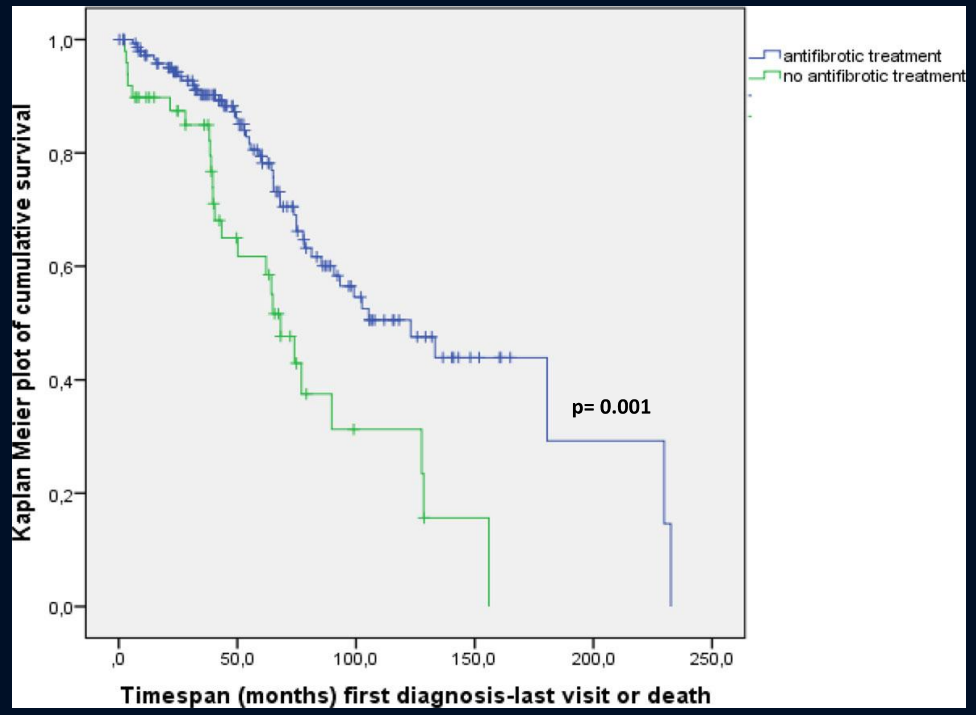


d 24–36 months. B: Change from baseline
red from the analysis after death and/or
capacity; pred, predicted.



The European IPF registry (eurIPFreg): baseline characteristics and survival of patients with idiopathic pulmonary fibrosis

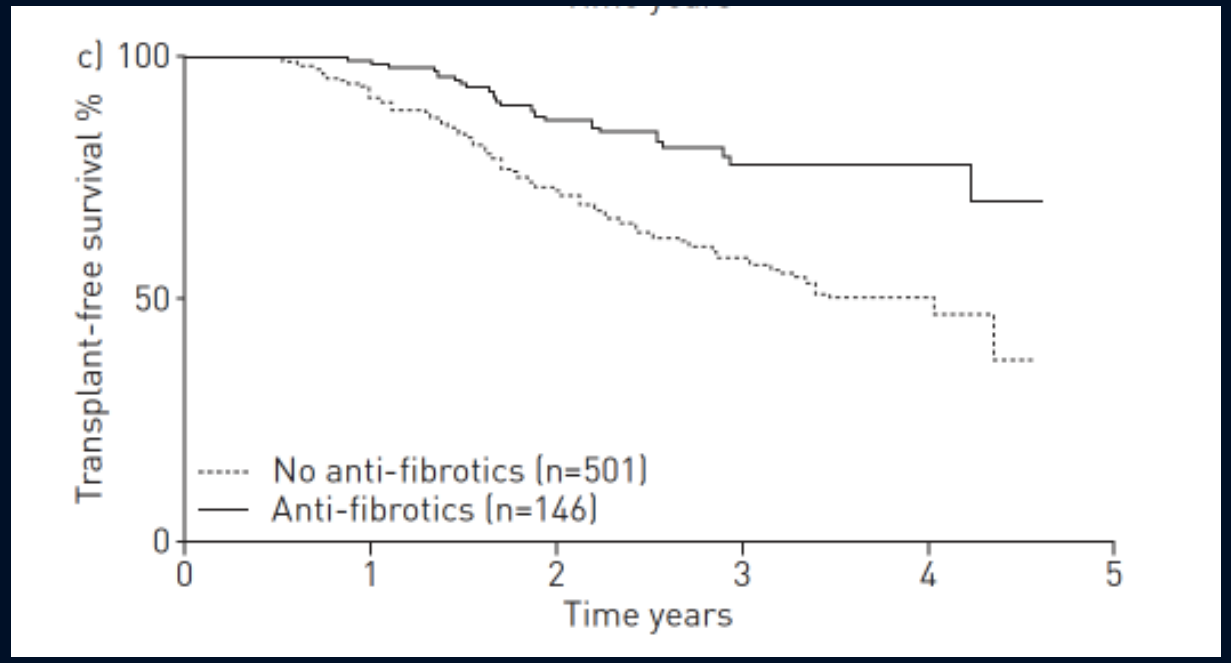




Guenther et al. Respir Res 2018

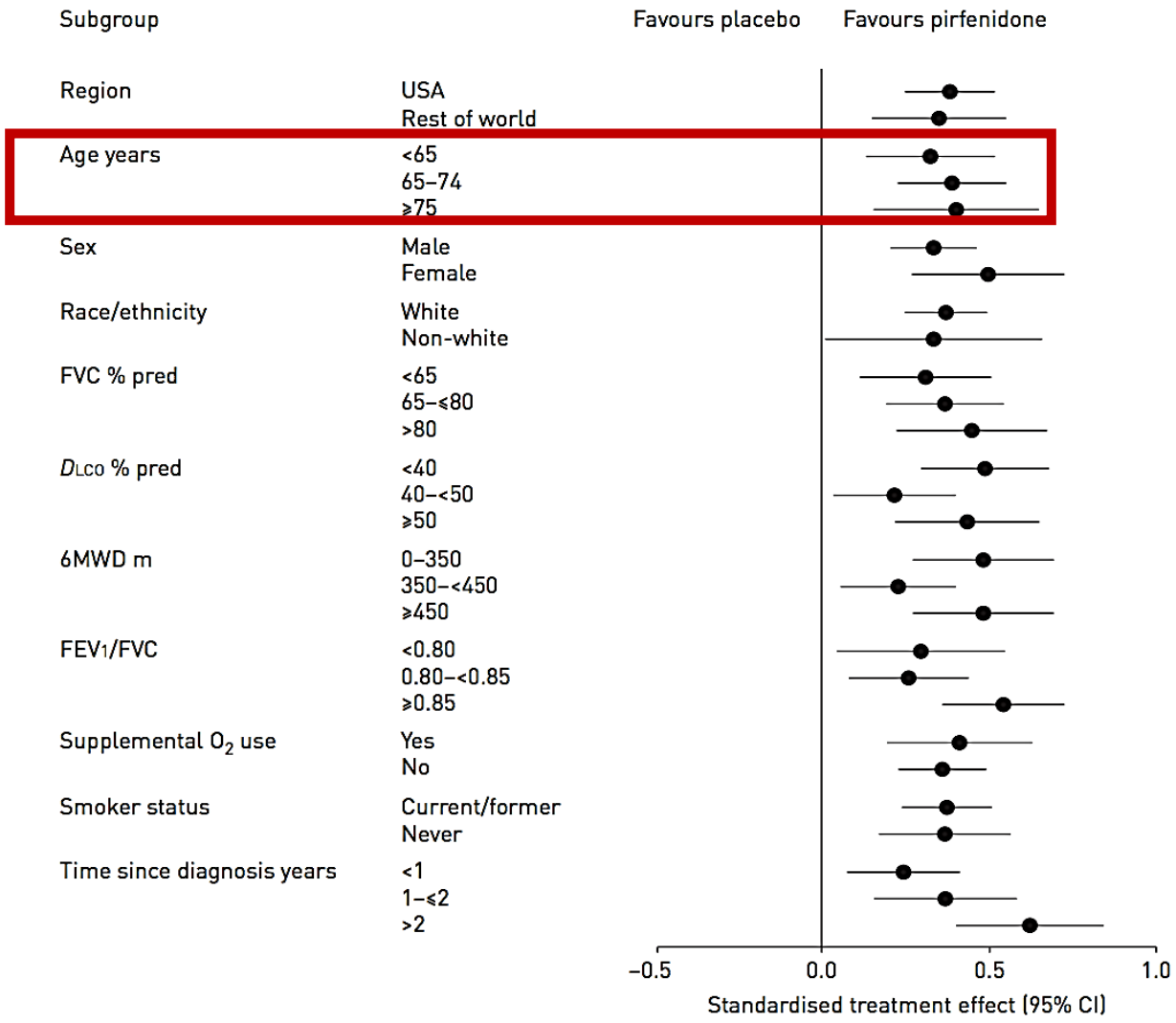
Baseline characteristics of idiopathic pulmonary fibrosis: analysis from the Australian Idiopathic Pulmonary Fibrosis Registry

Helen E. Jo[1,2], Ian Glaspole[3,4], Christopher Grainge[5], Nicole Goh[3,6], Peter M.A. Hopkins[7], Yuben Moodley[8], Paul N. Reynolds[9], Sally Chapman[9], E. Haydn Walters[10], Christopher Zappala[11], Heather Allan[12], Gregory J. Keir[13], Andrew Hayen[14], Wendy A. Cooper[14], Annabelle M. Mahar[15], Samantha Ellis[15], Sacha Macansh[12] and Tamera J. Corte[1,2]



Jo et al Eur Respir J 2016

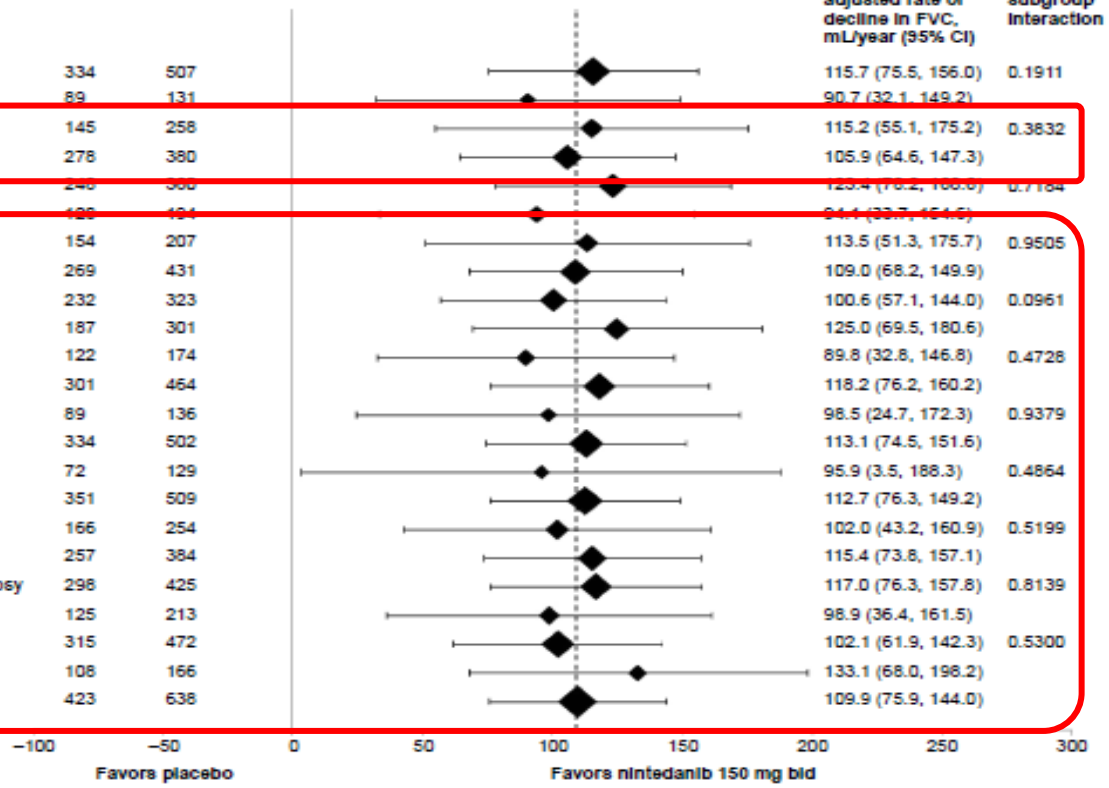
Pirfenidone works across major patient subgroups…



Noble PW et al. Eur Resp J 2016

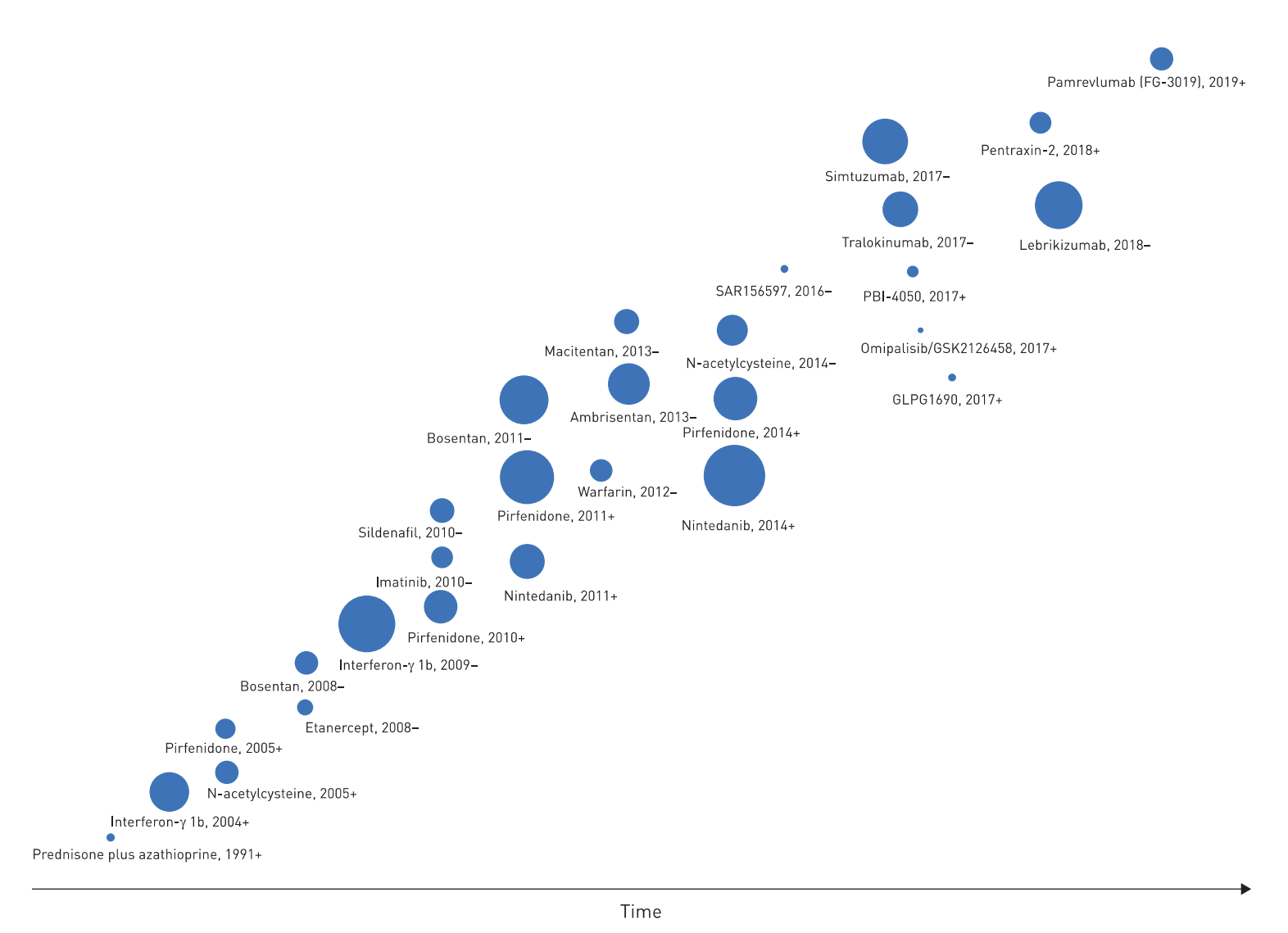
Nintedanib works across major patient subgroups…

Subgroup	N analyzed Placebo	N analyzed Nintedanib 150 mg bid	Nintedanib vs placebo difference in adjusted rate of decline in FVC, mL/year (95% CI)	*P*-value for treatment by time by subgroup interaction
Male	334	507	115.7 (75.5, 156.0)	0.1911
Female	89	131	90.7 (32.1, 149.2)	
Age <65 years	145	258	115.2 (55.1, 175.2)	0.3832
Age ≥65 years	278	380	105.9 (64.6, 147.3)	
White	246	366	123.4 (76.2, 166.6)	0.7184
Asian	120	124	94.1 (33.7, 154.5)	
FVC ≤70% predicted	154	207	113.5 (51.3, 175.7)	0.9505
FVC >70% predicted	269	431	109.0 (68.2, 149.9)	
SGRQ total score ≤40	232	323	100.6 (57.1, 144.0)	0.0961
SGRQ total score >40	187	301	125.0 (69.5, 180.6)	
Never smoked	122	174	89.8 (32.8, 146.8)	0.4728
Ex-/current smoker	301	464	118.2 (76.2, 160.2)	
Corticosteroids for systemic use	89	136	98.5 (24.7, 172.3)	0.9379
No corticosteroids for systemic use	334	502	113.1 (74.5, 151.6)	
Bronchodilator use	72	129	95.9 (3.5, 188.3)	0.4864
No bronchodilator use	351	509	112.7 (76.3, 149.2)	
Emphysema at baseline	166	254	102.0 (43.2, 160.9)	0.5199
No emphysema at baseline	257	384	115.4 (73.8, 157.1)	
Honeycombing on HRCT and/or confirmation of UIP pattern by biopsy	298	425	117.0 (76.3, 157.8)	0.8139
Features of possible UIP pattern on HRCT and no biopsy	125	213	98.9 (36.4, 161.5)	
FVC ≤90% predicted	315	472	102.1 (61.9, 142.3)	0.5300
FVC >90% predicted	108	166	133.1 (68.0, 198.2)	
All	423	638	109.9 (75.9, 144.0)	



Bonella et al, Drug Design Development & Therapy 2015:9

IPF - the future



Somogyi V, et al. Eur Respir Rev 2019

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
Lung cancer[41,42]	Crosslinking of DNA (platinum); microtubule toxin (vinorelbine); nucleoside analogue; gemcitabine; EGFR (erlotinib, gefitinib)	Platinum-based drug (cisplatin or carboplatin) with vinorelbine or gemcitabine; so-called traditional cytotoxic drugs and inhibitors of EGFR
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

Table 2: **Combination regimens used in other chronic lung diseases**

Lancet Respir Med. 2014

Lancet Resp Med 2014; 11: 933-42

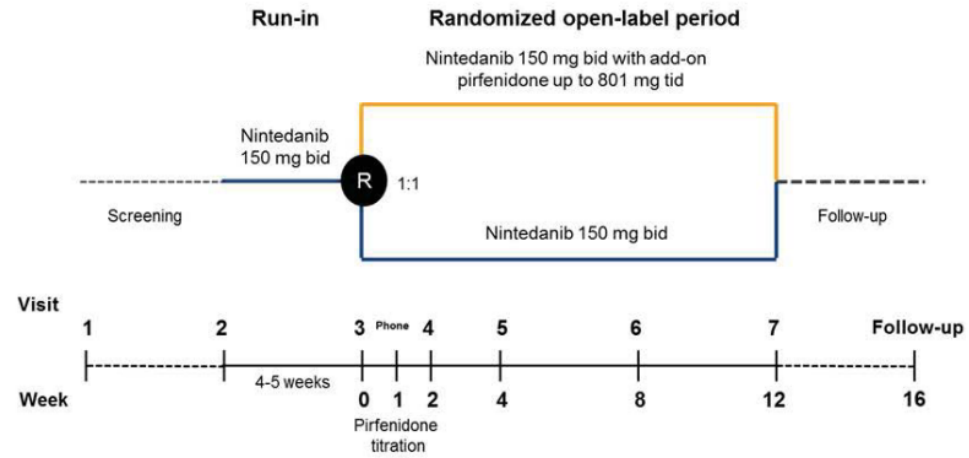
Nintedanib with Add-on Pirfenidone in Idiopathic Pulmonary Fibrosis

Results of the INJOURNEY Trial

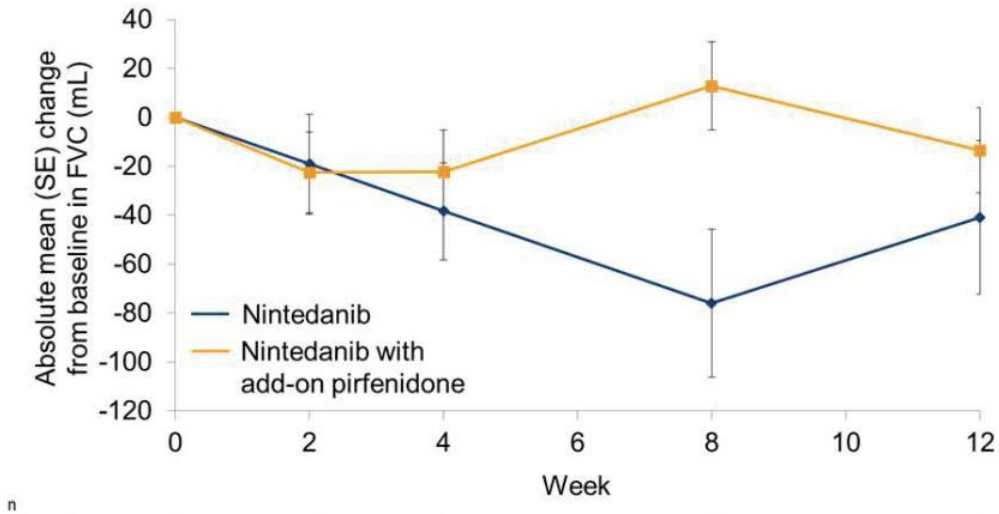
Carlo Vancheri[1], Michael Kreuter[2], Luca Richeldi[3], Christopher J. Ryerson[4], Dominique Valeyre[5], Jan C. Grutters[6,7], Sabrina Wiebe[8], Wibke Stansen[9], Manuel Quaresma[2,9], Susanne Stowasser[9], and Wim A. Wuyts[10]; on behalf of the INJOURNEY Trial Investigators

Table 4. Adverse Events

	Nintedanib 150 mg Twice Daily with Add-on Pirfenidone (*n* = 53)	Nintedanib 150 mg Twice Daily (*n* = 51)
Any adverse events	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 events†	2 (3.8)	5 (9.8)
Any fatal adverse events	0	0



R, randomization.



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

Vanchieri C, et al Am J Respir Crit Care Med 2018

Safety of nintedanib added to pirfenidone treatment for idiopathic pulmonary fibrosis

Kevin R. Flaherty[1], Charlene D. Fell[2], J. Terrill Huggins[3], Hilario Nunes[4], Robert Sussman[5], Claudia Valenzuela[6], Ute Petzinger[7], John L. Stauffer[8], Frank Gilberg[9], Monica Bengus[9] and Marlies Wijsenbeek[10]

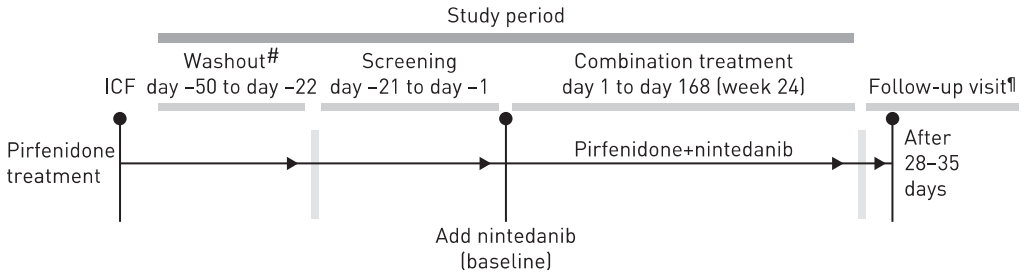


TABLE 2 Summary of common treatment-emergent adverse events (TEAEs) and TEAEs leading to discontinuation (safety population#)

	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

Combined pirfenidone and nintedanib use for 24 weeks was tolerated by the majority of patients with IPF and associated with a similar pattern of TEAEs expected for either treatment alone. These results encourage further study of combination treatment with pirfenidone and nintedanib in patients with IPF.

Flaherty KA, et al Eur Respir J 2018

Trials of Pirfenidone and nintedanib in combination

Trials of pirfenidone and nintedanib in combination

- Nintedanib added to pirfenidone[4] and pirfenidone added to nintedanib (INJOURNEY)[5]
  - Safety and tolerability profile similar to Phase III trials, with a slightly higher discontinuation rate
  - Short duration, no placebo controls
  - No robust efficacy data

1. Parker J, et al. ATS 2017;195:A7606; 2. Raghu G, et al. *Lancet Respir Med.* 2017;5:22–32;
3. Clinicaltrials.gov identifier: NCT02550873; 4. Flaherty KR, et al. *Eur Respir J.* 2018;52:1800230;
5. Vancheri C, et al. *Am J Respir Crit Care Med*. 2018;197:356–363

Proton Pump Inhibitors in IPF: A Call for Clinical Trials

Yohannes T. Ghebre[1,2]*

[1] *Department of Radiation Oncology, Baylor College of Medicine, Houston, TX, United States,* [2] *Section of Pulmonary and Critical Care Medicine, Department of Medicine, Baylor College of Medicine, Houston, TX, United States*

The recent FDA approval of two drugs, pirfenidone and nintedanib, for the treatment of idiopathic pulmonary fibrosis (IPF) has fueled interest in the development of additional drugs to treat the disease or its major clinical complications including cough and acute exacerbations. Since 2015, there are at least a dozen active interventional studies that are testing the efficacy of novel pharmacotherapies, exercise or stem cells in modifying the disease process in IPF. Additionally, there are combinatorial studies evaluating the effectiveness of pirfenidone or nintedanib in combination with other agents. However, there remains an urgent need for clinical trials to prospectively evaluate the efficacy of existing drugs with promising retrospective data, such as proton pump inhibitors (PPIs), in IPF. Several retrospective cohorts have provided tantalizing data supporting the beneficial effect of PPIs in patients with well-defined IPF. This review provides the general outlook of pharmacotherapies in IPF, and highlights preclinical and retrospective clinical data to make a case for randomized controlled clinical trials of PPIs in IPF.

Lancet Respir Med 2018

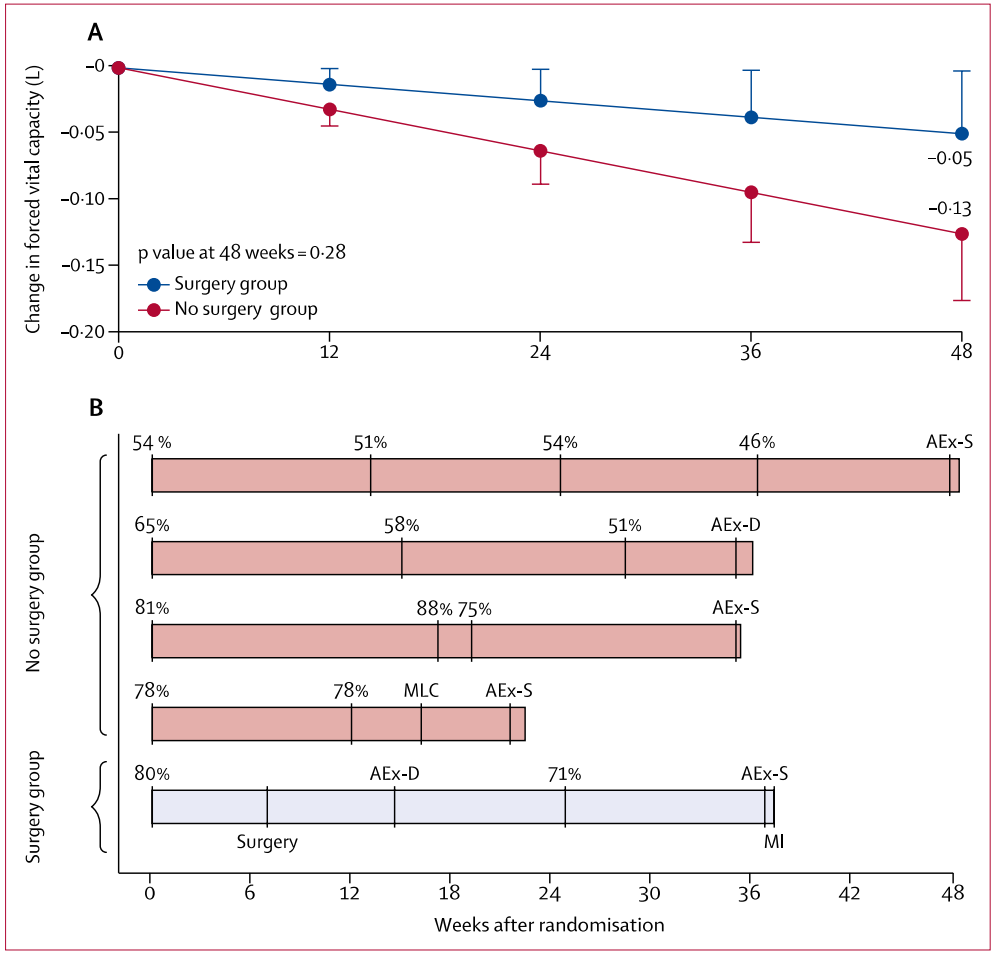


Figure 2: **Change in forced vital capacity and deaths by treatment group**
(A) The mean change in forced vital capacity from randomisation to week 48. Error bars are standard error.
(B) The disease course of the five patients who died during the study. Percentages are measured forced vital capacity in percentage of predicted and acute exacerbations. Each bar ends at the time of the patient's death. MLC=metastatic lung cancer. MI=myocardial infarction. AEx-D=definite acute exacerbations. AEx-S=suspected acute exacerbations.

Anti-acid therapy in idiopathic pulmonary fibrosis: insights from the INPULSIS® trials

Ulrich Costabel[1], Jürgen Behr[2], Bruno Crestani[3], Wibke Stansen[4], Rozsa Schlenker-Herceg[5], Susanne Stowasser[4] and Ganesh Raghu[6*]

Costabel *et al. Respiratory Research* (2018) 19:167

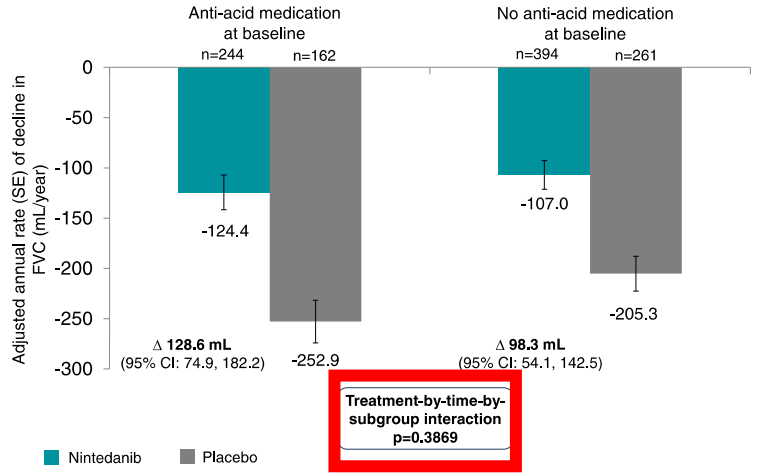
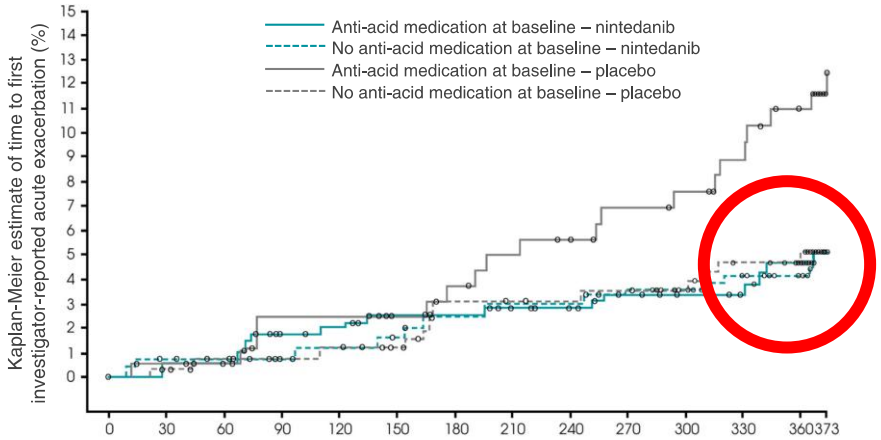
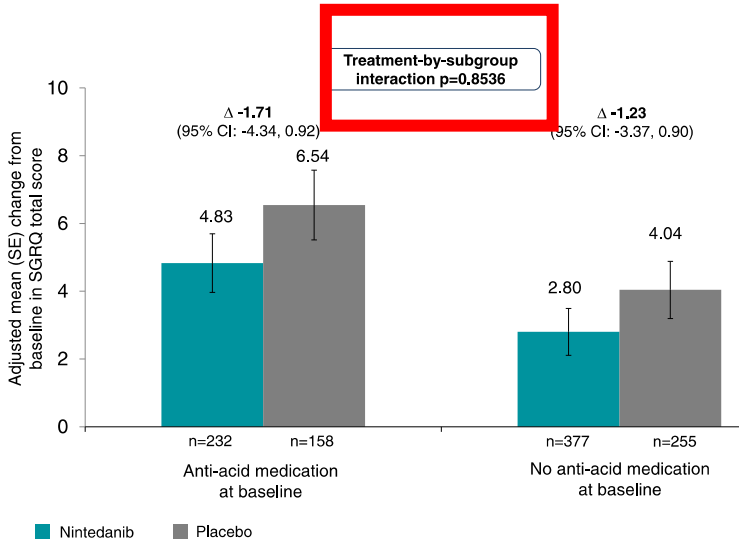


Fig. 1 Annual rate of decline in FVC

Time to first acute exacerbation





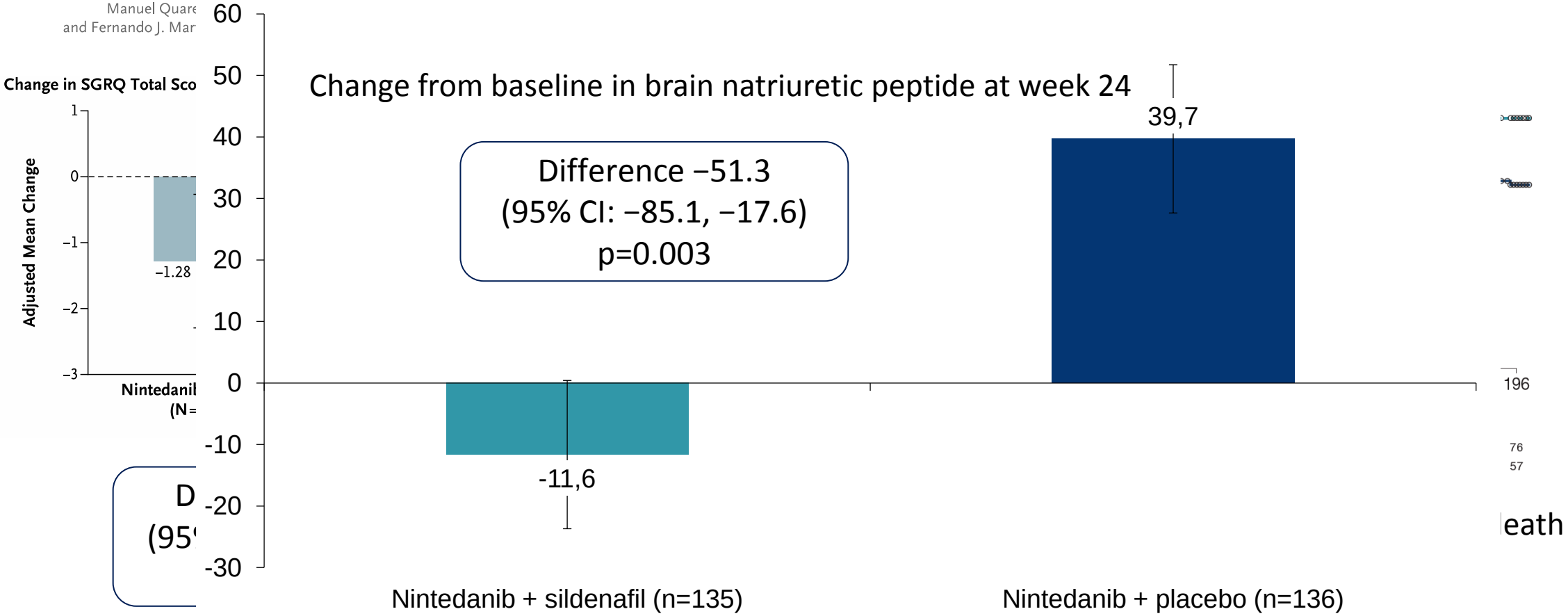
Change from baseline in SGRQ total score

ORIGINAL ARTICLE

Nintedanib plus Sildenafil in Patients with Idiopathic Pulmonary Fibrosis

N Engl J Med 2018;379:1722-31.

Martin Kolb, M.D., Ganesh Raghu, M.D., Athol U. Wells, M.D.,
Jürgen Behr, M.D., Lu
Manuel Quare
and Fernando J. Mar



patients with IPF and a DLCO of 35% or less

Jürgen Behr,[1] Steven D. Nathan,[2] Sergio Harari,[3] Wim Wuyts,[4] Nesrin Mogulkoç Bishop,[5] Demosthenes Borous,[6] Katerina Antoniou,[7] Julien Guiot,[8] Mordechai Kramer,[9] Klaus-Uwe Kirchgaessler,[10] Monica Bengus,[10] Frank Gilberg,[10] Athol U. Wells[11]

- **Baseline Characteristics of All Patients Randomized in a Phase IIb Trial of Sildenafil Added to Pirfenidone in Patients With Advanced Idiopathic Pulmonary Fibrosis and Risk of Pulmonary Hypertension**

- Screening/run-in failure occurred in 96/271 patients (35.4%), mainly based on eligibility criteria related to advanced IPF and risk of PH.
- All randomized patients (N=177) were included; mean age was 68.6 years, 75.7% were male and mean time from IPF diagnosis was 3.1 y

- ***Additional values reported in MA29957 included: mean mPAP on RHC was 28.1 mmHg (n=32), echocardiogram (ECHO) peak TRV was 3.5 m/s (n=158) and sPAP was 57.5 mmHg (n=157). Mean 6MWD was 290.7 m.***

ATS 2019

Other Molecular Targets

- Coagulation (Warfarin)
- Collagen scaffold (LOXL2I: GS-6624)
- Renin-angiotensin System (losartan)
- Telomerase (Nandrolone decanoate)
- Hemoglobin modifiers (GBT440)
- Hormone analogs (Octreotide)

Other Anti-fibrotic Agents

- TD139 (Galectin-3 inhibitor)
- GSK2126458 (mTOR/PI3Kinhibitor)
- IW001 (Anti-Collagen Type V)
- PRM151 (Recombinant human serum amyloid P protein)
- GLPG1690 (Autotaxin inhibitor)
- Tipelukast (inhibitor of leukotriene receptor, lipoxygenase and PDE)
- Rituximab (anti-CD20 monoclonal antibody)
- BMS-986020 (inhibitor of lysophosphatidic acid receptor)

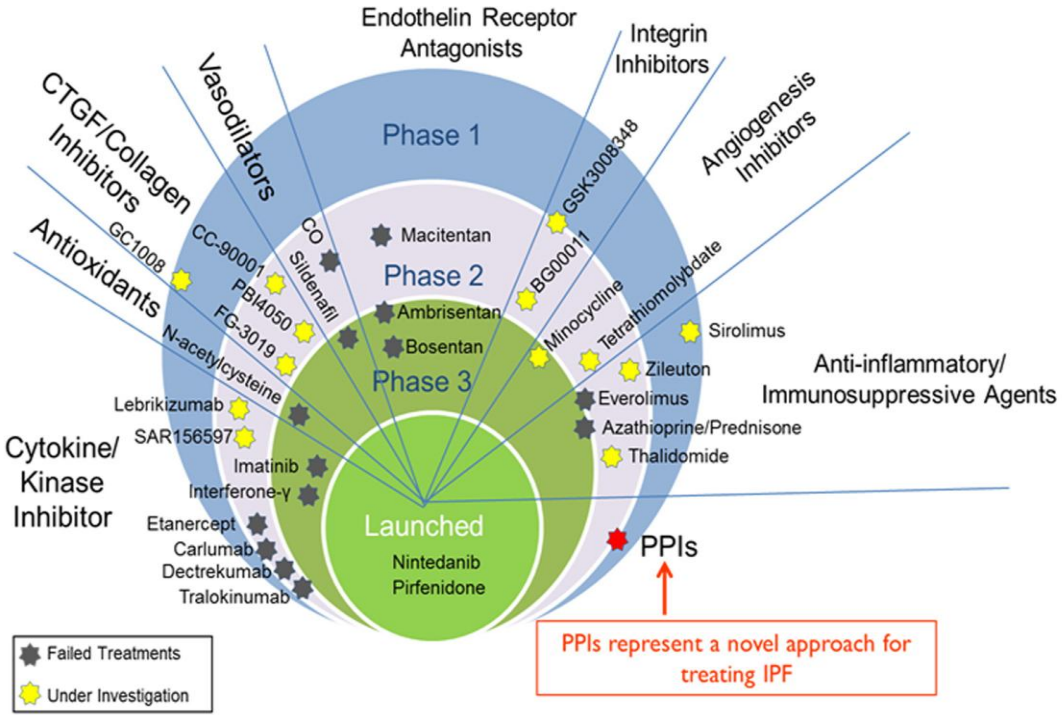


TABLE 2 Current phase II–III trials in idiopathic pulmonary fibrosis (IPF)

	Mechanism of action	Clinical trial identifier	Study description	Primary outcome measures	Phase of development	Treatment duration
PRM-151	Recombinant form of human SAP	NCT02550873	Randomised, double-blind, placebo controlled	Change from baseline in FVC % pred	II	28 weeks
Simtuzumab	Anti-LOX antibody	NCT01769196	Randomised, double-blind, placebo-controlled	The effect of simtuzumab (GS-6624) on progression-free survival	II	148 weeks
Tipelukast	Leukotriene antagonists	NCT02503657	Randomised, double-blind, placebo controlled	Change from baseline FVC at 26 weeks	II	26 weeks
Tralokinumab	Anti IL-13 antibody	NCT01629667	Randomised dose-ranging	Change from baseline FVC % pred at week 52	II	52 weeks
SAR156597	Anti IL-4 and IL-13 antibody	NCT01529853	Randomised, double-blind, placebo-controlled	Safety/tolerability: number of participants with adverse events	II	6 weeks
Lebrikizumab	Anti IL-13 antibody	NCT01872689	Randomised, double-blind, placebo-controlled	Annualised rate of decrease in FVC % pred over 52 weeks	II	52 weeks
BG00011	Anti-integrin antibody	NCT03573505	Randomised, double-blind, placebo-controlled	Yearly rate of change in FVC	II	52 weeks
Pamrevlumab (FG-3019)	Anti-CTGF antibody	NCT01890265	Randomised, double-blind, placebo-controlled	Change from baseline in FVC % pred at week 48	II	48 weeks
PBI-4050	GPR84 antagonist/ GPR40 agonist	NCT02538536	Open-label, single arm, exploratory, observational study	Number of subjects with abnormal laboratory values and/or adverse events that are related to treatment	II	20 weeks
KD025	Selective inhibitor of ROCK2	NCT02688647	Randomised, phase 2, open-label	Change in FVC in baseline to 24 weeks	II	24 weeks
CC-90001	Kinase inhibitor targeting JNKs	NCT03142191	Randomised, double-blind, placebo-controlled	Percentage point change in FVC % pred	II	24 weeks
GLPG1690	Autotaxin-LPA inhibitor	NCT02738801	Randomised, double-blind, parallel group, placebo-controlled	Safety, tolerability, pharmacokinetic and pharmacodynamic properties of GLPG1690	II	12 weeks
Omipalisib/ GSK2126458	Inhibitor of PI3K/Akt pathway	NCT01725139	Randomised, double-blind, placebo-controlled	To explore a number of doses of GSK2126458 for engagement of pharmacology after short-term dosing	I	7–10 days
Sirolimus	mTOR inhibitor	NCT01462006	Double-blind placebo-controlled pilot study	Change in peripheral blood concentration of $CXCR4^+$ fibrocytes; number of subjects with drug side-effects	NA	22 weeks
Rituximab	Antibody targeting CD20	NCT01969409	Randomised, double-blind, placebo-controlled	Titres of anti-HEp-2 autoantibodies, by indirect immunofluorescence assays over 9 months	II	36 weeks
Co-trimoxazole or doxycycline	Antimicrobial drugs	NCT02759120	Randomised, un-blinded, phase III	Time to first non-elective, respiratory hospitalisation or all-cause mortality	III	9 months

SAP: serum amyloid P; FVC: forced vital capacity; LOX: lysyl oxidase; IL: interleukin; CTGF: connective tissue growth factor; GPR: G protein-coupled receptor; ROCK: ρ-associated coiled-coil containing protein kinase; JNK: Jun N-terminal kinase; LPA: lysophosphatidic acid; PI3K/Akt: phosphoinositide 3-kinase/protein kinase B. mTOR: mammalian target of rapamycin; CXCR: C-X-C chemokine receptor; HEp: human epithelial cell.

Somogyi V, et al. Eur Respir Rev 2019

Promising Phase II studies

- Autotaxin inhibitor (GLPG1690)
- Recombinant human pentraxin 2 (PRM-151)
- Pamrevlumab (anti-CTGF)
- Anti-integrin-αvβ6 (BG00011; STX-100)
- PBI4050

JAMA | Preliminary Communication

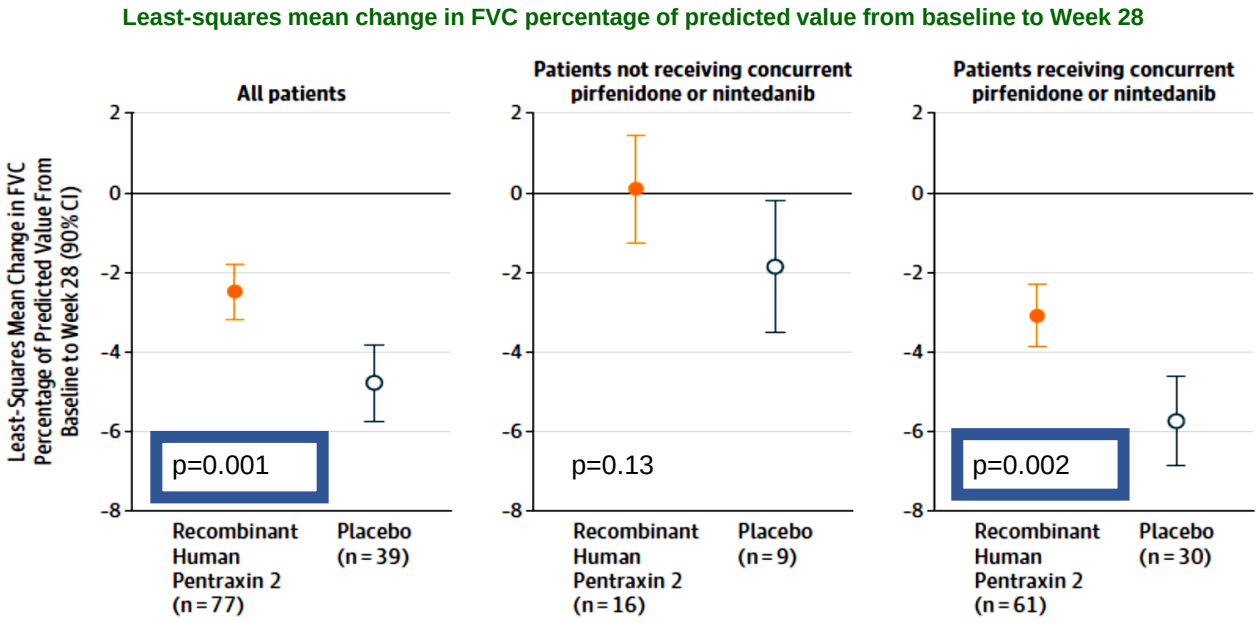
Effect of Recombinant Human Pentraxin 2 vs Placebo on Change in Forced Vital Capacity in Patients With Idiopathic Pulmonary Fibrosis

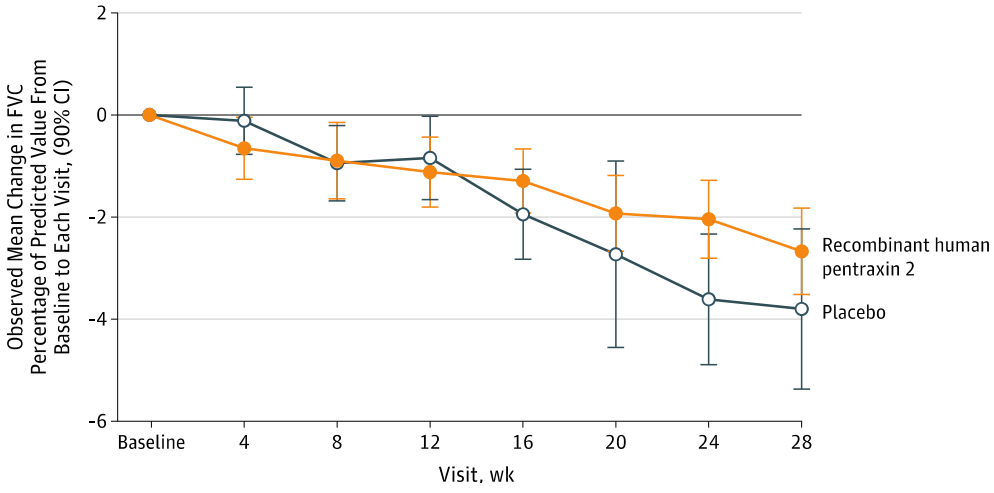
A Randomized Clinical Trial

JAMA. doi:10.1001/jama.2018.6129

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

Recombinant human pentraxin 2 in IPF: change in FVC (primary outcome)





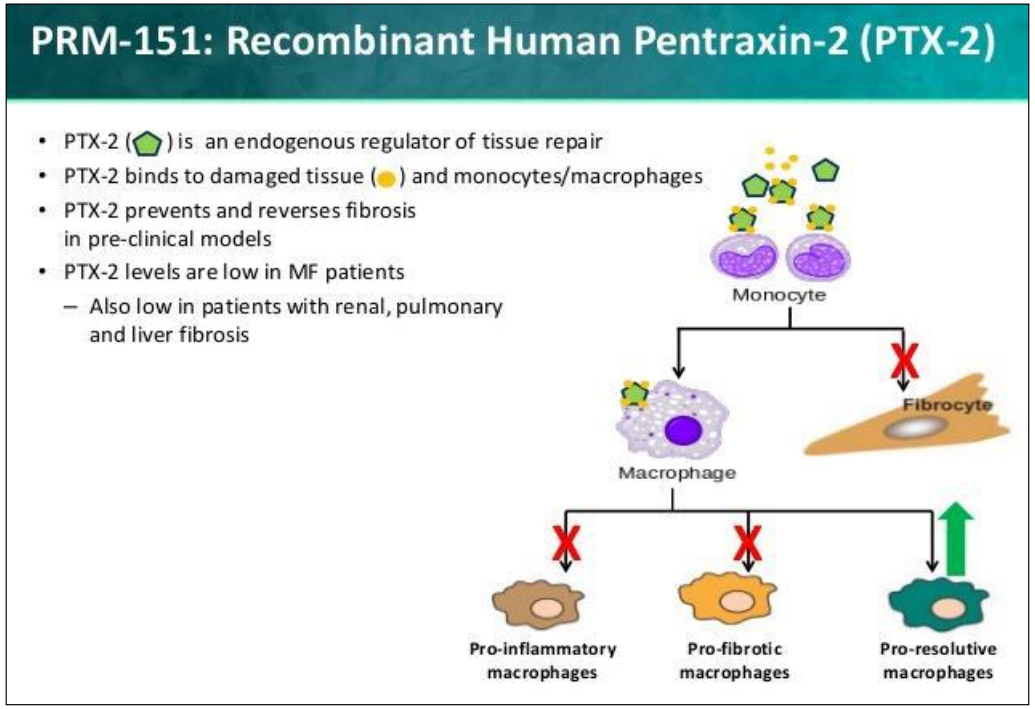
CONCLUSIONS AND RELEVANCE In this preliminary study, recombinant human pentraxin 2 vs placebo resulted in a slower decline in lung function over 28 weeks for patients with idiopathic pulmonary fibrosis. Further research should more fully assess efficacy and safety.

Human pentraxin 2 protein treatment for IPF

*Argyris Tzouvelekis, Vassilios Tzilas, Katerina M Antoniou, *Demosthenes Bouros*

Lancet Respir Med. 2019

Recombinant human pentraxin 2 in IPF: effect on FVC



MF, myelofibrosis

Raghu G. et al. *JAMA.* 2018;319:2299–2307

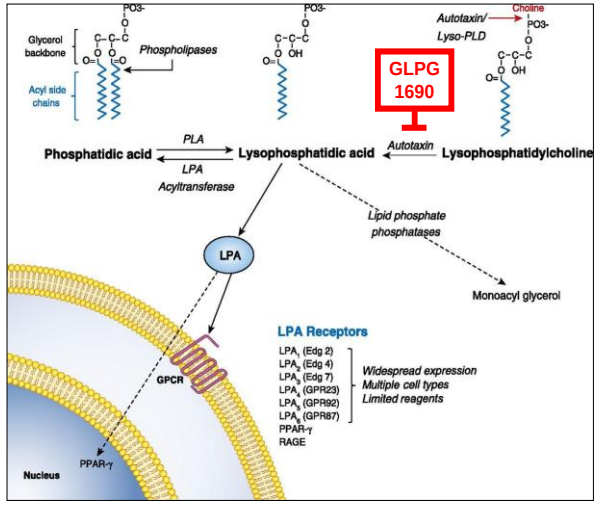
Safety, tolerability, pharmacokinetics, and pharmacodynamics of GLPG1690, a novel autotaxin inhibitor, to treat idiopathic pulmonary fibrosis (FLORA): a phase 2a randomised placebo-controlled trial

Lancet Respir Med 2018

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

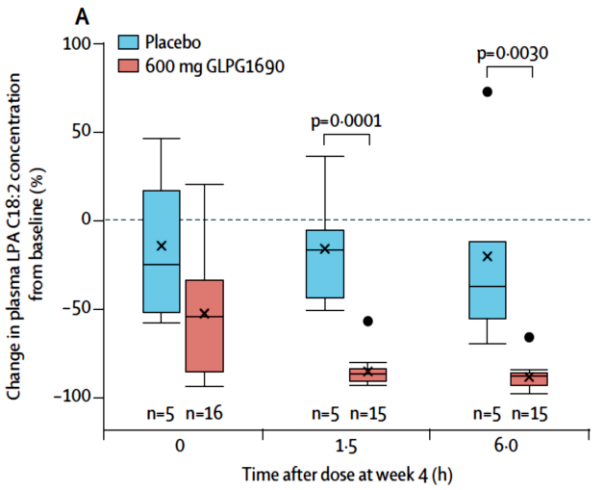
GLPG1690, a novel autotaxin inhibitor, to treat IPF: a Phase IIa study

Mechanism of action



GPCR, G-protein-coupled receptor; LPA, lysophosphatidic acid; PLA, phospholipase A; PPAR, peroxisome proliferator activated receptor; RAGE, receptor for advanced glycation end products

'Target engagement': GLPG1690 → serum LPA C18:2 ↓↓



Knowlden S, et al. *J Immunol*. 2014;192:851–857;
Maher TM, et al. *Lancet Respir Med*. 2018;8:627–635

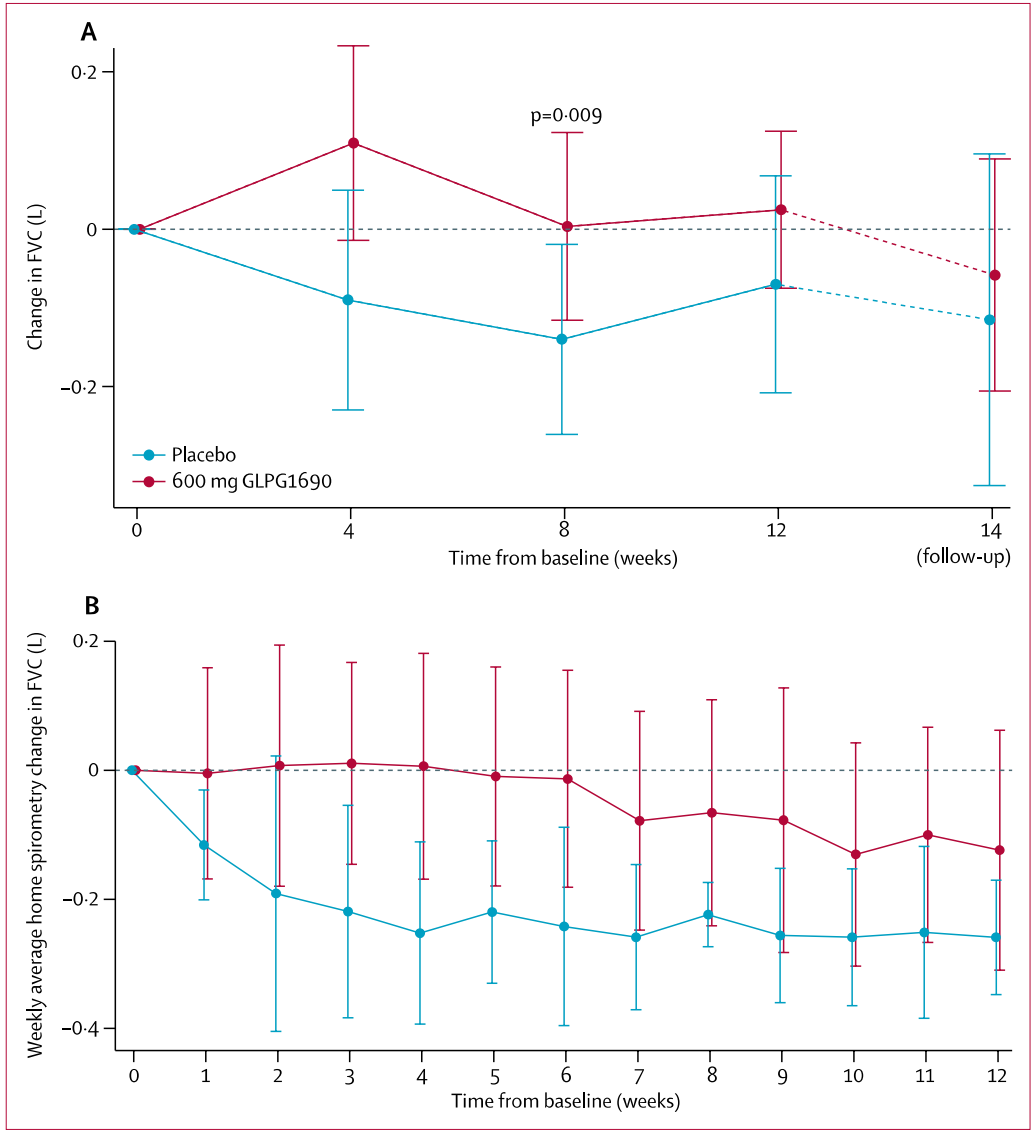
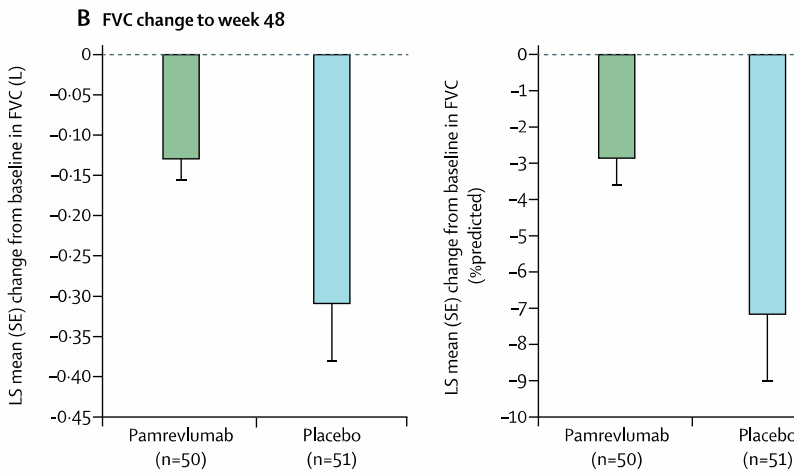


Figure 3: Mean (95% CI) changes in FVC from baseline in the placebo and GLPG1690 groups in the intention-to-treat population

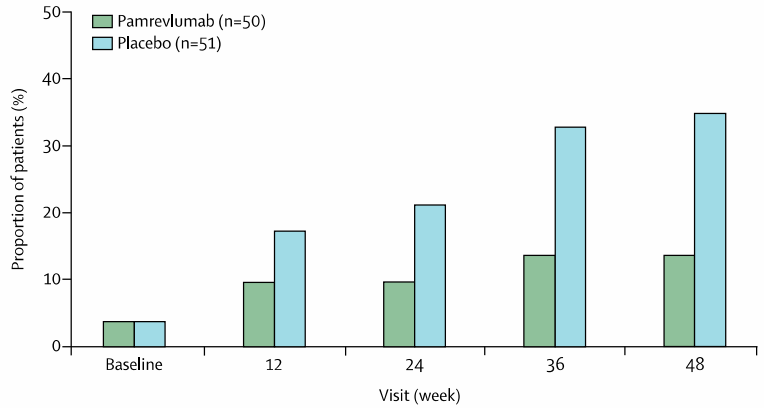
Pamrevlumab, an anti-connective tissue growth factor therapy, for idiopathic pulmonary fibrosis (PRAISE): a phase 2, randomised, double-blind, placebo-controlled trial

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*

Lancet Respir Med 2019



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 -
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	



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

Figure 3: **Proportion of patients with decline in percentage of predicted FVC of 10% or greater, or death, by visit**

In conclusion, data from this study suggest that pamrevlumab has the potential to be an important therapeutic option for patients with idiopathic pulmonary fibrosis. The efficacy and safety of pamrevlumab 30 mg/kg administered by intravenous infusion every 3 weeks will be tested further in the ongoing phase 3, randomised, placebo-controlled trial (ZEPHYRUS; NCT03955146) in patients with idiopathic pulmonary fibrosis.

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

Justin M. Oldham[1*], Shwu-Fan Ma[1*], Fernando J. Martinez[2], Kevin J. Anstrom[3], Ganesh Raghu[4], David A. Schwartz[5], Eleanor Valenzi[1], Leah Witt[1], Cathryn Lee[1], Rekha Vij[1], Yong Huang[1], Mary E. Strek[1], and Imre Noth[1]; for the IPFnet Investigators

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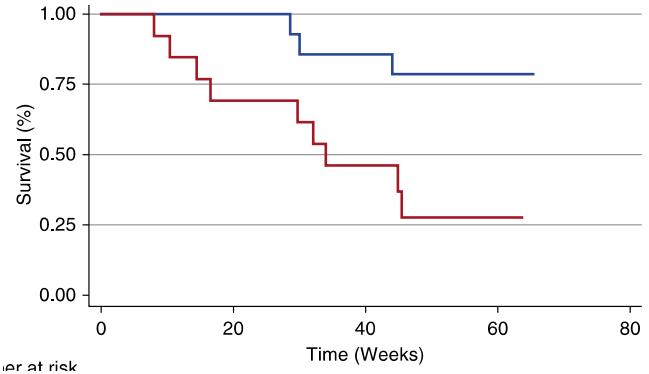
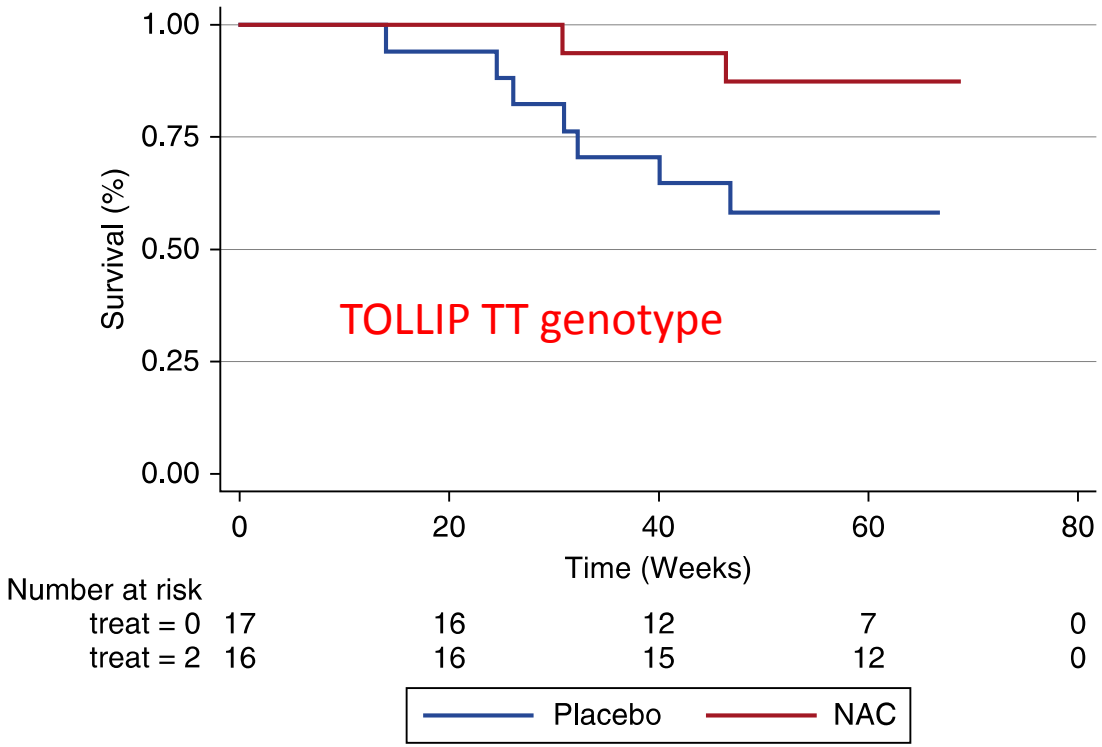
Am J Respir Crit Care Med Vol 192, Iss 12, pp 1475–1482, Dec 15, 2015

Objectives: To determine whether single-nucleotide polymorphisms (SNPs) within *TOLLIP* and *MUC5B* modify the effect of interventions in subjects participating in the Evaluating the Effectiveness of Prednisone, Azathioprine, and *N*-Acetylcysteine in Patients with Idiopathic Pulmonary Fibrosis (PANTHER-IPF) clinical trial.

Conclusions: NAC may be an efficacious therapy for individua with IPF with an rs3750920 (*TOLLIP*) TT genotype, but it was associated with a trend toward harm in those with a CC genotype.



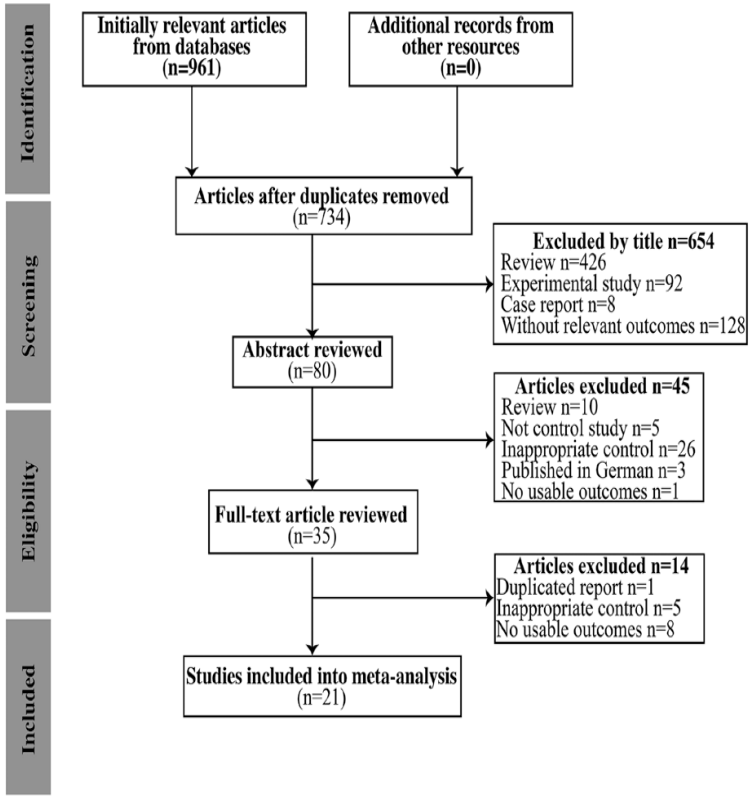


In those with a TT genotype, NAC therapy is associated with improved survival compared with placebo ($P_{logrank} = 0.06$; HR 0.14 ; 95% CI 0.02–0.83; P = 0.03)

EXPERIMENTAL AND THERAPEUTIC MEDICINE 18: 802-816, 2019

Efficacy and safety of *N*-acetylcysteine therapy for idiopathic pulmonary fibrosis: An updated systematic review and meta-analysis

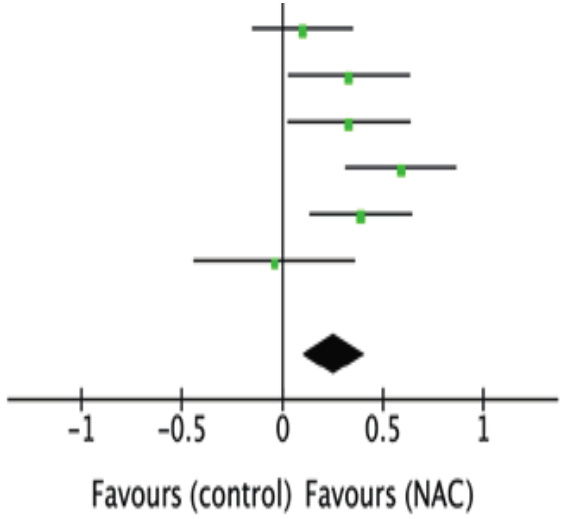
FANCHAO FENG[1*], JIARUI ZHANG[2*], ZHICHAO WANG[1], QI WU[1] and XIANMEI ZHOU[1,3]



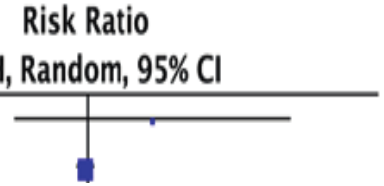
Huang-QY 2015	2.6	0.6	37	2.5	0.5	37	13.5%	0.10 [-0.15, 0.35]
Jiang-AG 2009	2.6	0.37	13	2.27	0.42	13	11.6%	0.33 [0.03, 0.63]
Liu-Y 2015	2.86	0.78	40	2.53	0.61	40	11.5%	0.33 [0.02, 0.64]
Nan-QQ 2007	3.6	0.36	20	3.01	0.52	20	12.5%	0.59 [0.31, 0.87]
Sakamoto-S 2013	2.1	0.12	11	1.71	0.33	7	13.4%	0.39 [0.14, 0.64]
Yang-ZG 2008	2.56	0.54	17	2.6	0.61	15	8.7%	-0.04 [-0.44, 0.36]
Total (95% CI)			**239**			**231**	**100.0%**	**0.26 [0.10, 0.41]**

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 17.94$, df = 8 (P = 0.02); $I^2 = 55\%$

Test for overall effect: Z = 3.24 (P = 0.001)

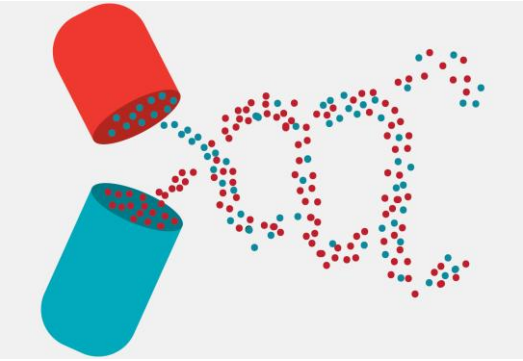


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Bando-M 2010	2	14	0	11	0.7%	4.00 [0.21, 75.66]
Behr-J 2016	46	60	50	62	34.0%	0.95 [0.79, 1.14]



Summary

- Unmet need for *biomarkers*
- Current therapy for IPF: nintedanib and pirfenidone
- Emergence of combination therapy
- Novel disease modifying agents
- Development of personalized therapy

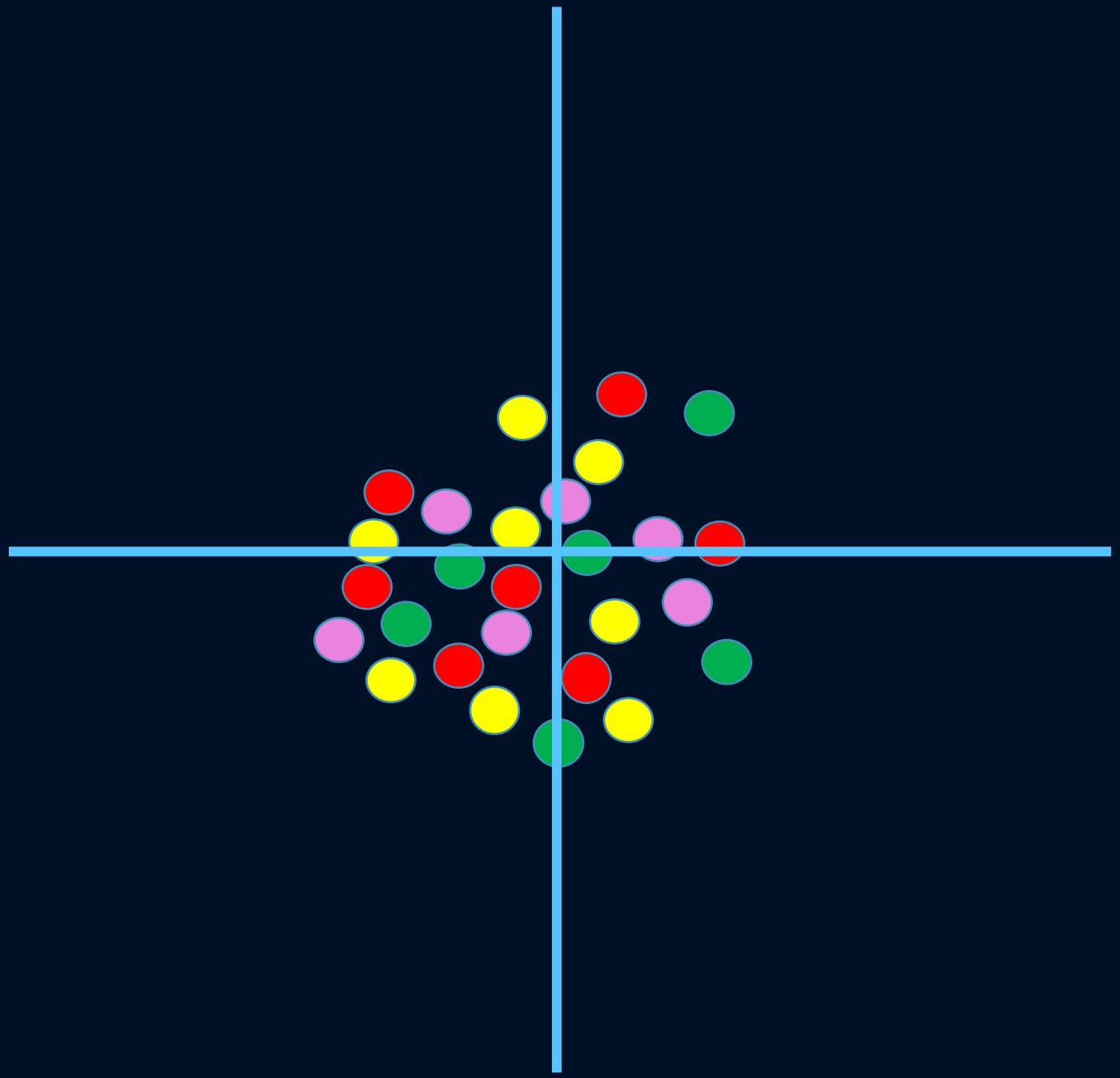


Current and Future Idiopathic Pulmonary Fibrosis Therapy

Fabiana Baldi MD , Giuliana Pasciuto MD ,
Francesco Macagno MD , Loredana Panico MD ,
Luca Richeldi MD

The American Journal of the Medical Sciences (2019)

There is consistent hope for a near future in which IPF therapies will target different pathologic pathways, thus making possible to provide a personalised and effective therapeutic strategy to treat, hopefully cure, IPF.



Personalized Medicine

Αποτελεσματικότητα και ασφάλεια της φαρμακευτικής θεραπείας…

…αλλά και

αναγνώριση των προτιμήσεων και των αναγκών κάθε ασθενούς σχετικά με τη συνολική του φροντίδα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