진행된 IPF 환자에서 항섬유화제 치료

Pro

가톨릭의대 김 용 현

2018 결핵 및 호흡기학회 춘계학술대회

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*

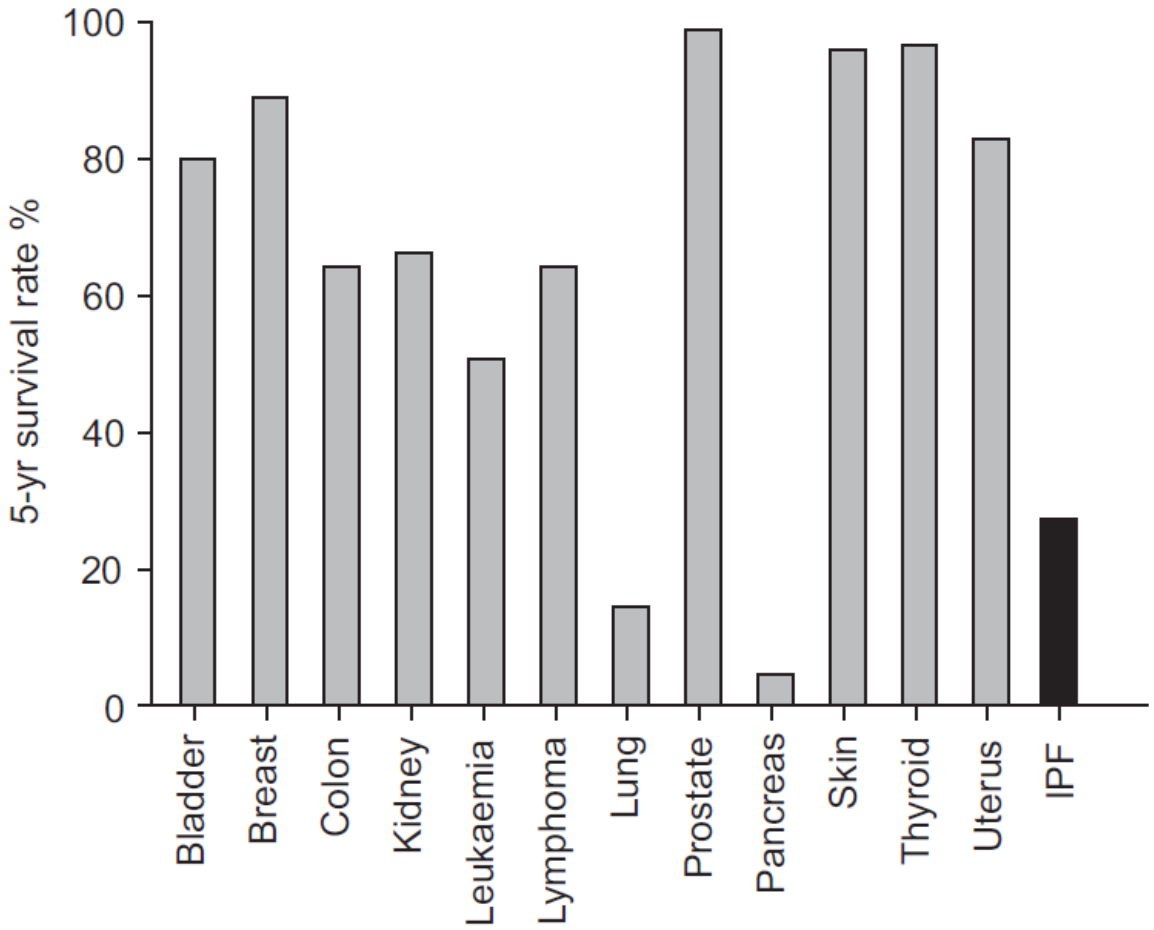
ORIGINAL ARTICLE

FVC >50% pred. & DLco 30-79% pred

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

FVC 50-90% pred. & DLco 30-90% pred

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



Statistics for cancer are from the US National Cancer Institute

Burden of Severe IPF patients in real world

❖ ILD 연구회 2017 IPF registry 환자 코호트 (N= 978)

- Stratification on the lung function (total = 841, missing data 137)

1) FVC > 90% predicted : 18.2% (N=180)
2) FVC <50% (A) 혹은 DLco <35% (B)인 중증환자

   : (A): 9.0%, (B): 7.8%, (A) or (B): **13.0% (N=110)**

3) FEV1/FVC <0.7로 폐쇄성 장애를 동반하지만 명백한 IPF 환자: 6.5% (N=65)

Severe idiopathic pulmonary fibrosis

Patients with FVC <50 % predicted and/or DLco predicted <35% are usually excluded from clinical trials in IPF

A discrepancy from clinical trials to real-life experiences

The circumstance of severe IPF patients are similar to those of patients with an advanced neoplastic disease

Today's Topic

Anti-fibrotic agents are effective for severe IPF patients?

FVC predicted <50% and/or DLco predicted <30 or 35%

The decision to treat or not ?

Balance between effectiveness and treatment-related risk

Pirfenidone for idiopathic pulmonary fibrosis: analysis of pooled data from three multinational phase 3 trials

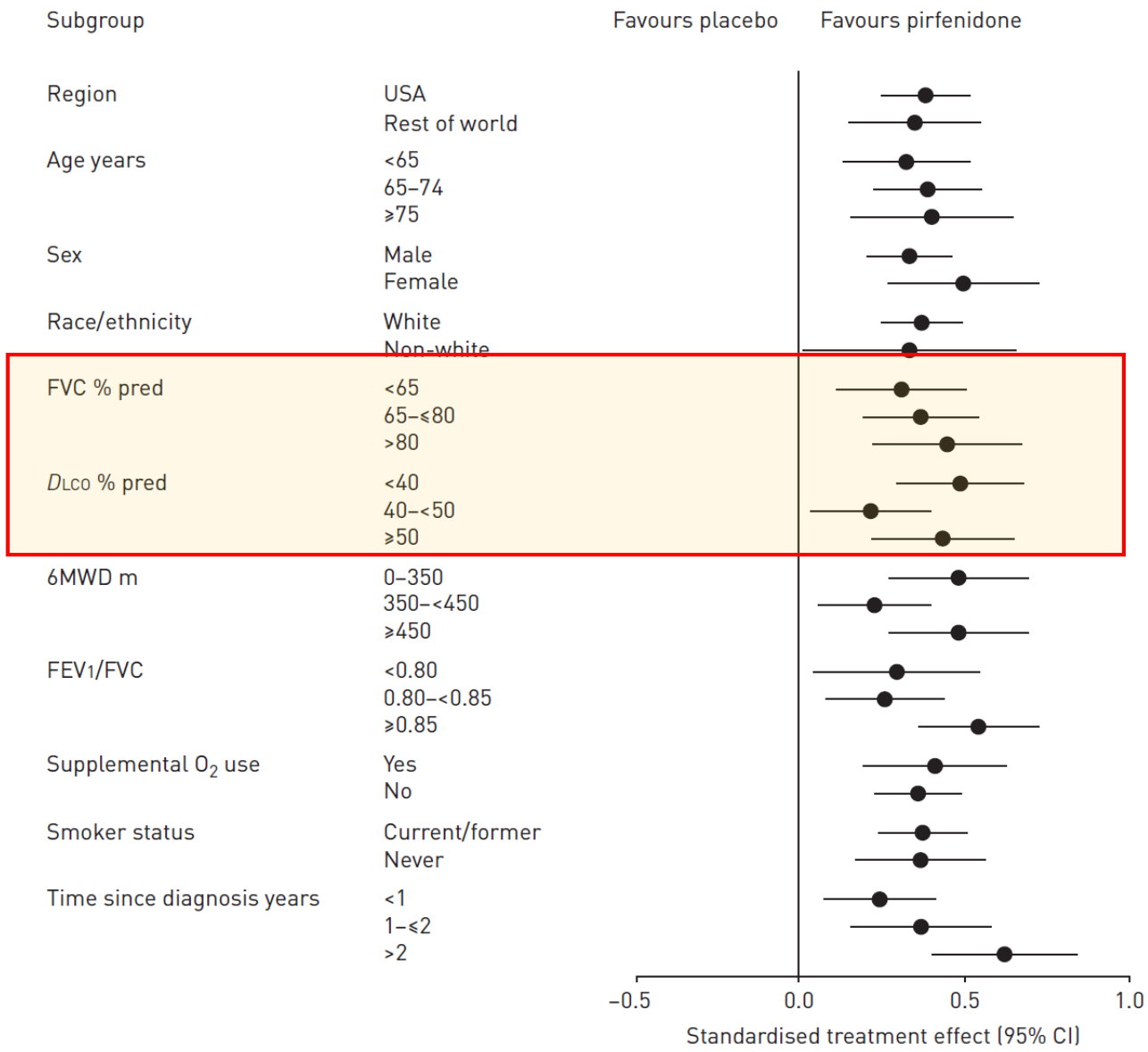
Paul W. Noble[1], Carlo Albera[2], Williamson Z. Bradford[3], Ulrich Costabel[4], Roland M. du Bois[5], Elizabeth A. Fagan[3], Robert S. Fishman[3], Ian Glaspole[6], Marilyn K. Glassberg[7], Lisa Lancaster[8], David J. Lederer[9], Jonathan A. Leff[3], Steven D. Nathan[10], Carlos A. Pereira[11], Jeffrey J. Swigris[12], Dominique Valeyre[13] and Talmadge E. King Jr[14]

Total of 1247 patients
Eligibility criteria for the CAPACITY and ASCEND studies:

FVC % pred ⩾50% and DLCO % pred ⩾35% or 30%

Eur Respir J 2016; 47: 243–253

Subgroup analysis of change in FVC % predicted



Subgroup analysis of safety outcomes at 1 year

	Pirfenidone 2403 mg·day^{-1}					Placebo				
	Subjects n	Grade 3 AE	Grade 4 AE	Serious AE	AE leading to treatment DC	Subjects n	Grade 3 AE	Grade 4 AE	Serious AE	AE leading to treatment DC
FVC % pred										
<65	205	25.4	5.4	23.9	15.1	224	29.0	6.3	27.7	11.2
65–⩽80	272	25.4	2.6	19.1	12.5	230	24.3	5.2	21.7	8.3
>8	146	21.9	2.7	18.5	6.8	170	17.1	4.7	15.9	5.9
***D*LCO % pred**										
<40	207	28.5	3.4	23.7	14.0	211	32.2	9.5	33.6	12.8
40–<50	229	25.3	5.2	23.1	12.7	230	22.6	4.8	20.4	8.3
⩾50	187	19.3	1.6	13.9	9.1	181	16.6	1.7	11.6	4.4

Data are presented as % of patients in each stratum based on events occurring between the first dose and 28 days after the last dose of study drug, unless otherwise stated. AE: adverse event; DC: discontinuation; FVC: forced vital capacity; *D*LCO: diffusing capacity of the lung for carbon monoxide; 6MWD: 6-min walk distance.

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

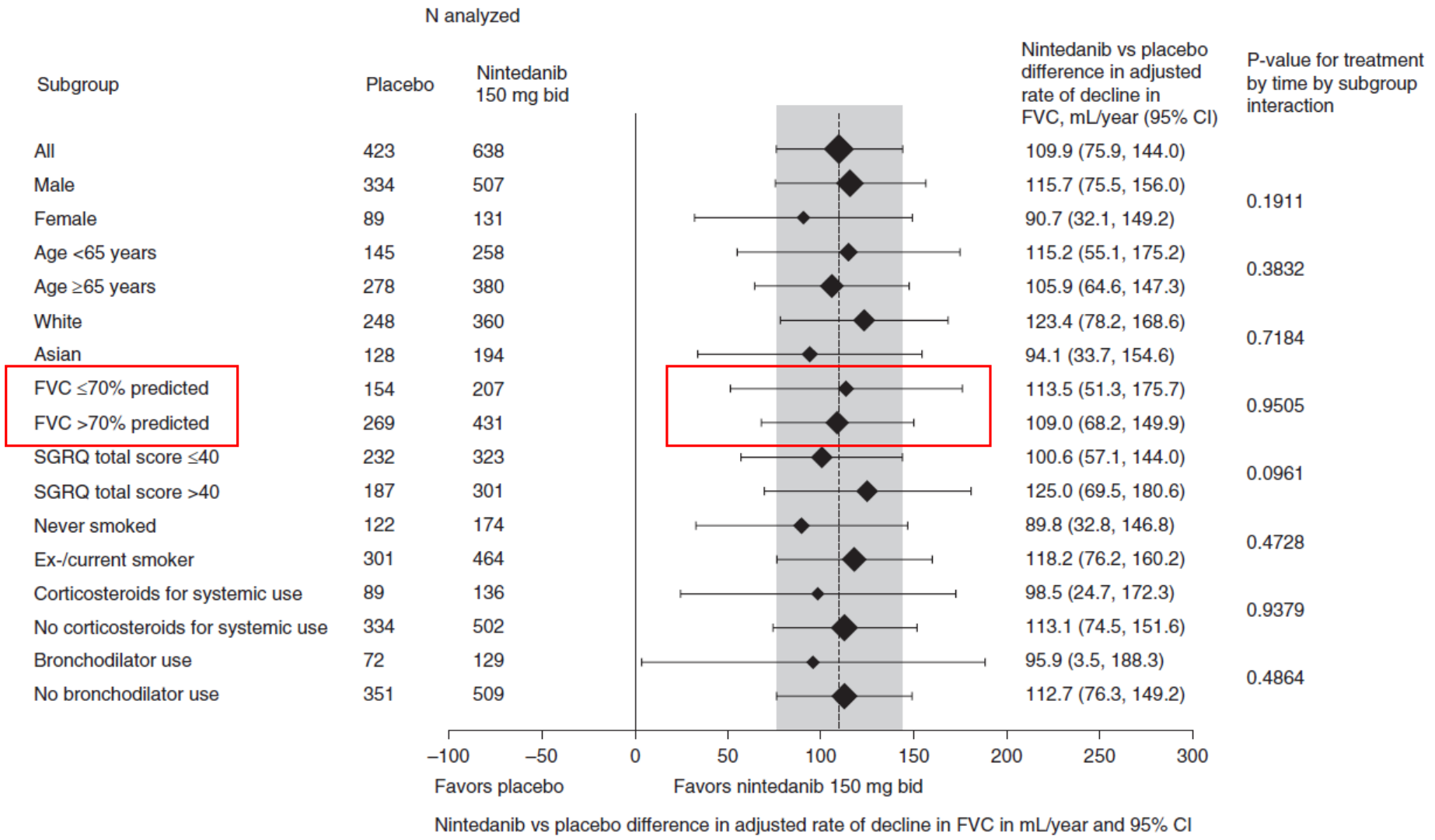
Ulrich Costabel[1], Yoshikazu Inoue[2], Luca Richeldi[3], Harold R. Collard[4], Inga Tschoepe[5], Susanne Stowasser[6], and Arata Azuma[7]

Baseline Characteristics

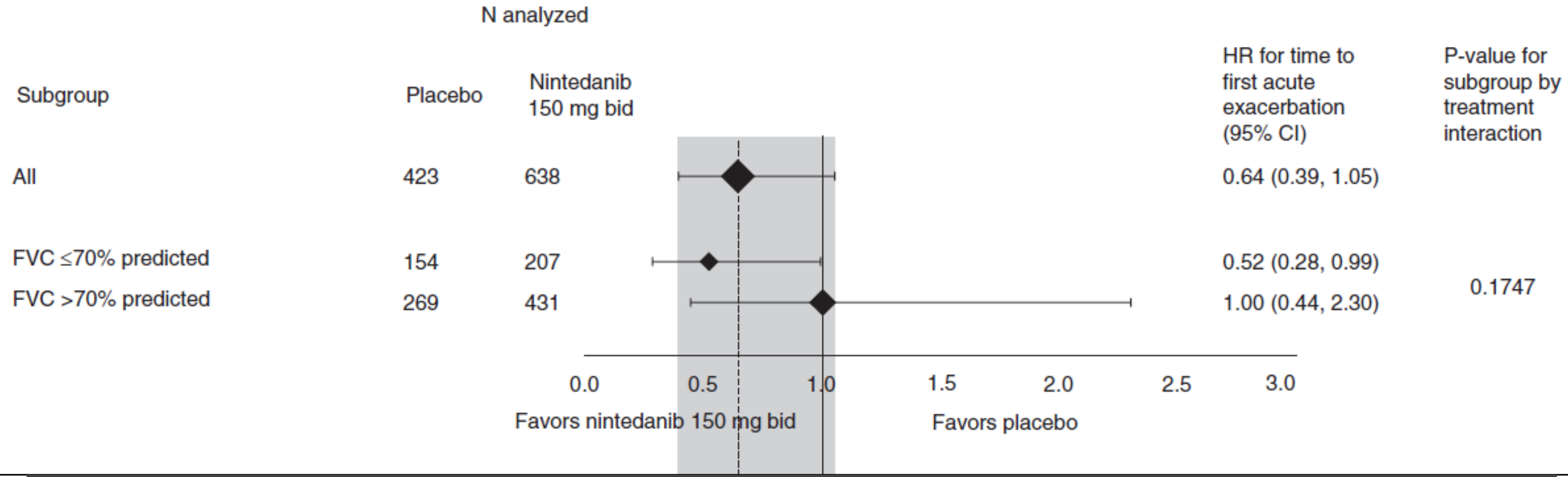
Characteristics	Nintedanib 150 mg Twice Daily (*n* = 638)	Placebo (*n* = 423)	Total (*n* = 1,061)
FVC, ml, mean (SD)	2714 (757)	2728 (810)	2719 (778)
FVC, % predicted, mean (SD)	79.7 (17.6)	79.3 (18.2)	79.6 (17.8)
FEV_1/FVC ratio, %, mean (SD)	81.7 (5.8)	81.7 (6.0)	81.7 (5.9)
D_{LCO}, % predicted, mean (SD)†	47.4 (13.5)	47.0 (13.4)	47.2 (13.5)
Sp_{O_2}, %, mean (SD)	95.9 (2.3)	95.8 (2.0)	95.8 (2.2)
SGRQ total score, mean (SD)‡	39.5 (19.2)	39.6 (18.5)	39.5 (18.9)

Am J Respir Crit Care Med 2016; 193: 178–185

Forest plot for the annual rate of decline in FVC (ml/yr)

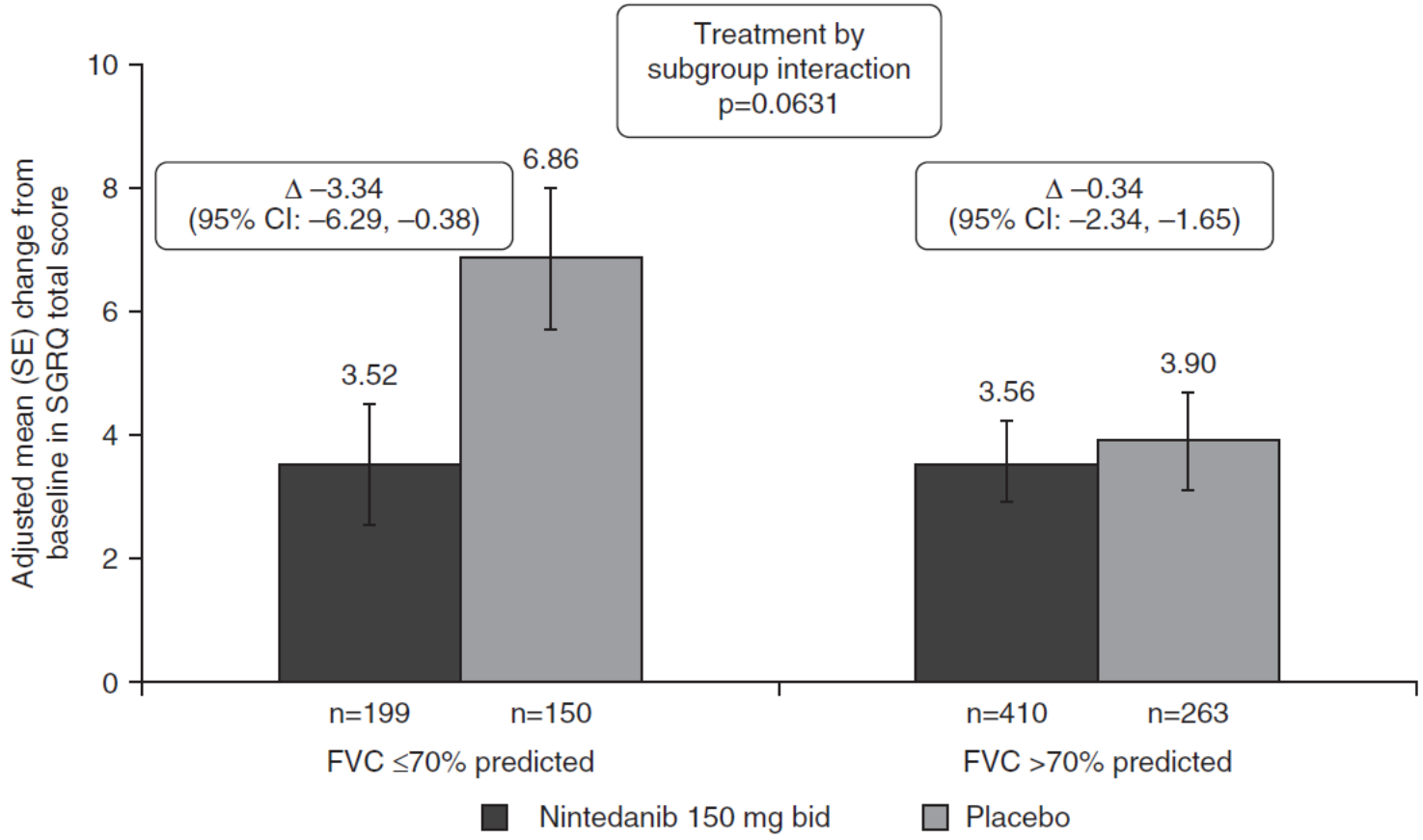


Forest plot for the time to first investigator-reported AE over 52 weeks



IPF patients with more severe reductions in FVC are at greater risk of AE.
Nintedanib may be more likely to provide a benefit on reducing the risk of AE
in individuals with more severe lung function impairment

Change from baseline in SGRQ total score at week 52



from clinical trials to real-life experiences

- Consistent effect of nintedanib or pirfenidone in subgroups of patients with more impaired lung function
  - ✓ on disease progression and /or AE, symptoms

- **But, in more severe (excluded from clinical trials) IPF patients ?**

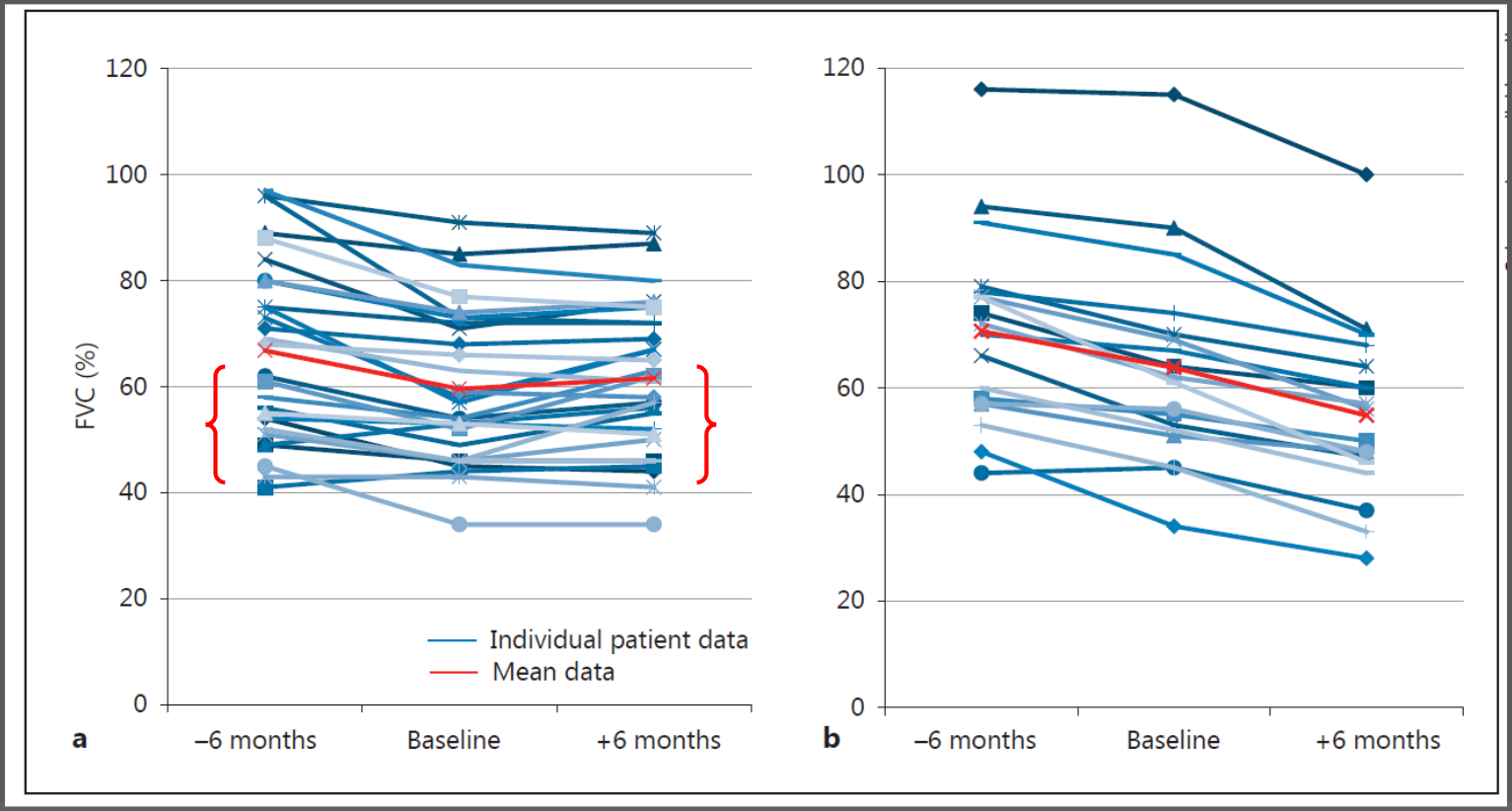
Insights from the German Compassionate Use Program of Nintedanib for the Treatment of Idiopathic Pulmonary Fibrosis

Francesco Bonella[a] Michael Kreuter[b] Lars Hagmeyer[c] Claus Neurohr[d]
Claus Keller[e] Martin J. Kohlhaeufl[f] Joachim Müller-Quernheim[g]
Katrin Milger[d] Antje Prasse[h–j] on behalf of the German Nintedanib
Compassionate Use Consortium

- Older patients
- mean FVC markedly lower than in INPULSIS (64 vs. 80% pred)
- treatment was started on average 5.8 years after IPF diagnosis (1.6 years in the INPULSIS)
- the majority of patients (70%) - pirfenidone for longer than 1 year

Respiration 2016;92:98–106

FVC before and after initiation of treatment with Nintedanib



stable disease (n = 30)

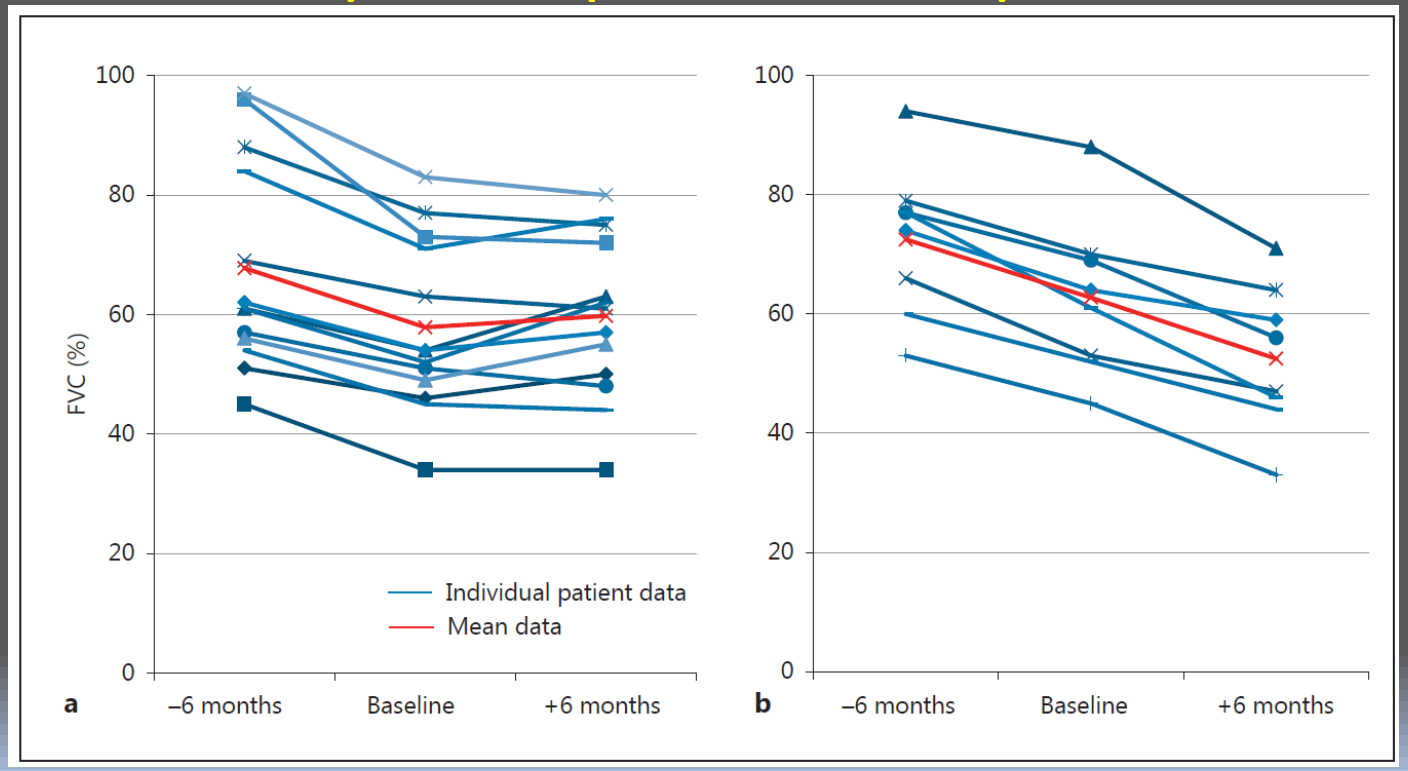
disease progression (n = 18)

The patients (N=21)
who had not responded to pirfenidone in the previous 6 months

- ✓ In stable disease group

FVC change in the 6 months prior to nintedanib
: mean (SEM) -17.3% (6%).

FVC change after 6 months of nintedanib
: mean (SEM) 2% (1.8%).



(stable disease, N = 13)

(disease progression, N=8)

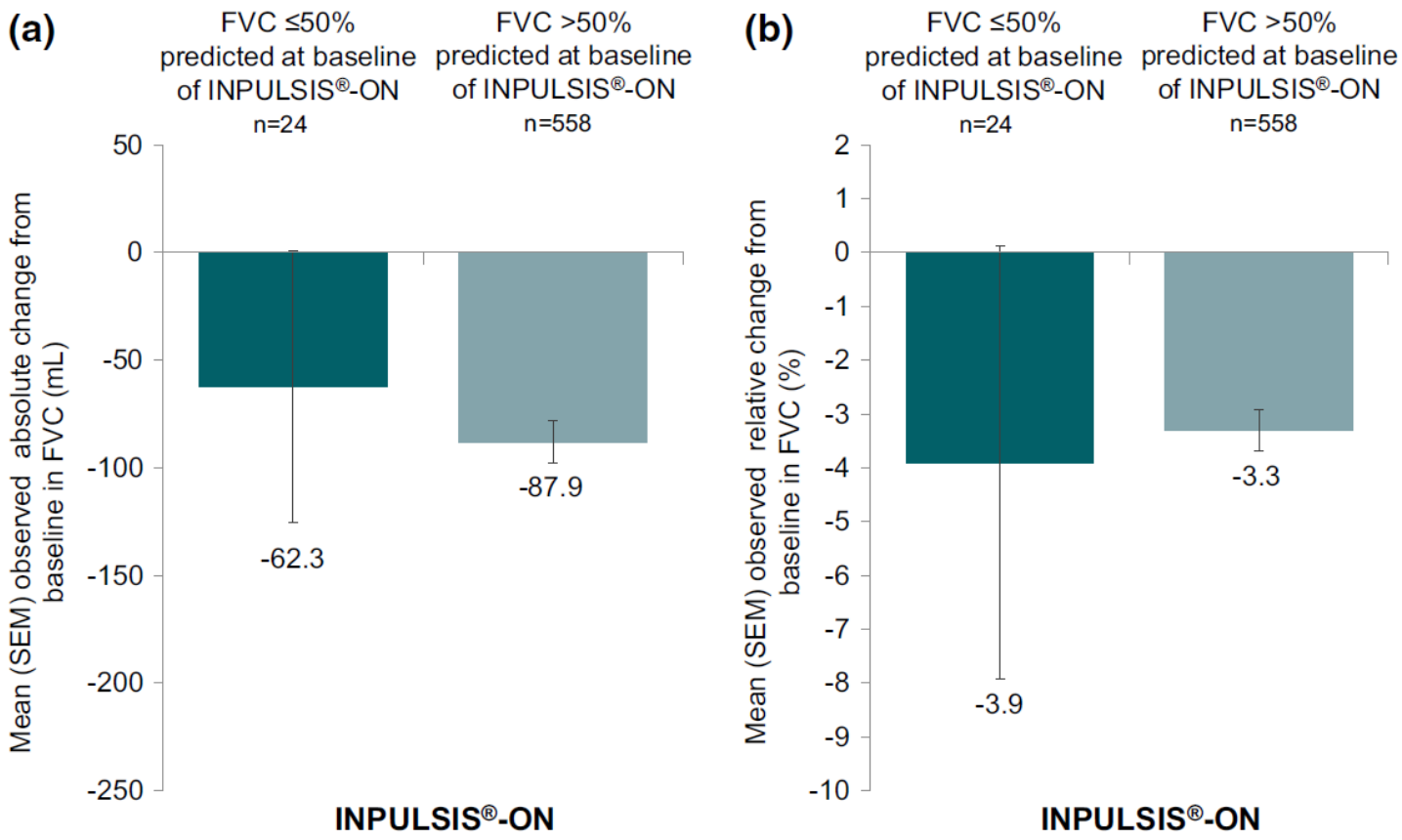
INPULSIS-ON, the open-label extension of the INPULSIS trial

Lung (2016) 194:739–743
DOI 10.1007/s00408-016-9912-1

CrossMark

First Data on Efficacy and Safety of Nintedanib in Patients with Idiopathic Pulmonary Fibrosis and Forced Vital Capacity of ≤50 % of Predicted Value

Absolute change in (a) and relative (b) change in FVC from baseline
FVC to week 48



Adverse events

	INPULSIS®		INPULSIS-ON®	
	Nintedanib ($n = 638$)	Placebo ($n = 423$)	FVC ≤50 % predicted ($n = 41$)	FVC >50 % predicted ($n = 690$)
Any adverse event(s)	609 (95.5)	379 (89.6)	41 (100.0)	649 (94.1)
Most frequent adverse event(s)[a]				
Diarrhoea	398 (62.4)	78 (18.4)	19 (46.3)	446 (64.6)
Nausea	156 (24.5)	28 (6.6)	7 (17.1)	111 (16.1)
Cough	85 (13.3)	57 (13.5)	7 (17.1)	114 (16.5)
Nasopharyngitis	87 (13.6)	68 (16.1)	3 (7.3)	100 (14.5)
Bronchitis	67 (10.5)	45 (10.6)	4 (9.8)	97 (14.1)
Dyspnoea	49 (7.7)	48 (11.3)	10 (24.4)	88 (12.8)
Progression of IPF[b]	64 (10.0)	61 (14.4)	14 (34.1)	104 (15.1)
Weight decreased	62 (9.7)	15 (3.5)	7 (17.1)	75 (10.9)
Severe adverse event(s)[c]	174 (27.3)	99 (23.4)	21 (51.2)	210 (30.4)
Serious adverse event(s)[d]	194 (30.4)	127 (30.0)	26 (63.4)	271 (39.3)
Fatal adverse event(s)	37 (5.8)	31 (7.3)	9 (22.0)	66 (9.6)
Adverse event(s) leading to treatment discontinuation[e]	123 (19.3)	55 (13.0)	17 (41.5)	155 (22.5)
Diarrhoea	28 (4.4)	1 (0.2)	2 (4.9)	37 (5.4)
Progression of IPF[b]	13 (2.0)	21 (5.0)	7 (17.1)	37 (5.4)
Nausea	13 (2.0)	0 (0.0)	1 (2.4)	5 (0.7)
Fatigue	1 (0.2)	1 (0.2)	1 (2.4)	3 (0.4)
Weight decreased	6 (0.9)	1 (0.2)	1 (2.4)	6 (0.9)
Decreased appetite	9 (1.4)	1 (0.2)	0 (0.0)	3 (0.4)

Lung (2016) 194:739–743
DOI 10.1007/s00408-016-9912-1

CrossMark

First Data on Efficacy and Safety of Nintedanib in Patients with Idiopathic Pulmonary Fibrosis and Forced Vital Capacity of ≤50 % of Predicted Value

- The decline in FVC in INPULSIS-ON in both subgroups was similar to that in INPULSIS, suggesting that nintedanib may have a similar effect on disease progression in patients with advanced disease

- A higher proportion of patients with baseline FVC <50 % predicted had serious adverse events (63.4 % vs. 39.3 %) and fatal adverse events (22.0 % vs. 9.6 %).

Baseline characteristics at start of INPULSIS and INPULSIS-ON trials

	INPULSIS®		INPULSIS-ON®	
	Nintedanib ($n = 638$)	Placebo ($n = 423$)	FVC ≤50 % predicted ($n = 41$)	FVC >50 % predicted ($n = 690$)
Age, years, mean (SD)	66.6 (8.1)	67.0 (7.9)	66.9 (8.3)	67.1 (7.8)
Male, n (%)	507 (79.5)	334 (79.0)	32 (78.0)	554 (80.3)
Race, n (%)				
White	360 (56.4)	248 (58.6)	29 (70.7)	401 (58.1)
Asian	194 (30.4)	128 (30.3)	8 (19.5)	207 (30.0)
Black	2 (0.3)	0 (0.0)	0 (0.0)	2 (0.3)
Missing[a]	82 (12.9)	47 (11.1)	4 (9.8)	80 (11.6)
Ex or current smoker, n (%)	464 (72.7)	301 (71.2)	26 (63.4)	501 (72.6)
Weight, kg, mean (SD)	79.2 (16.6)	78.6 (16.5)	78.8 (17.6)	78.2 (16.1)
Body mass index, kg/m^2, mean (SD)	28.1 (4.6)	27.6 (4.6)	27.1 (5.3)	27.5 (4.4)
FVC, mL, mean (SD)	2714 (757)	2728 (810)	1602 (330)	2683 (790)
FVC, % predicted, mean (SD)	79.7 (17.6)	79.3 (18.2)	45.0 (4.6)	78.0 (17.9)
FEV_1/FVC, mean (SD)[b]	81.7 (6.0)	81.7 (5.8)	86.6 (7.4)	81.3 (6.5)

Clinical Investigations

Respiration

Respiration
DOI: 10.1159/000487711

Received: October 11, 2017
Accepted after revision: February 13, 2018
Published online: March 27, 2018

A Real-Life Multicenter National Study on Nintedanib in Severe Idiopathic Pulmonary Fibrosis

Sergio Harari[a] Antonella Caminati[a] Venerino Poletti[b] Marco Confalonieri[c]
Stefano Gasparini[d] Donato Lacedonia[e] Fabrizio Luppi[f] Alberto Pesci[g]
Alfredo Sebastiani[h] Paolo Spagnolo[i] Carlo Vancheri[j] Elisabetta Balestro[i]
Martina Bonifazi[d] Stefania Cerri[f] Federica De Giacomi[g]
Rossana Della Porta[c] Maria Pia Foschino Barbaro[e] Annalisa Fui[k]
Patrizio Pasquinelli[h] Roberta Rosso[j] Sara Tomassetti[b] Claudia Specchia[l, m]
Paola Rottoli[k] for the ILDINET (Interstitial Lung Diseases Italian Network)

Study design

A national, multicenter, retrospective real-life study (ILD Italian Network)

41 patients with FVC ≤50% and/or DLCO ≤35% predicted

Assessment of nintedanib effect at the –6-month, 0, and +6-month time points

Parameter	*N*	Time	Mean (SD)	Changes (95% CI)	Difference in changes (SD)	*p* value
FVC, L	39	T_{-1}	2.05 (0.58)	–	–	
	39	T_0	1.99 (0.54)	−0.07 (−0.15; 0.02)	–	
	39	T_1	1.87 (0.58)	−0.12 (−0.20; −0.04)	−0.06 (0.36)	0.22
FVC%	41	T_{-1}	61.83 (15.25)	–		
	41	T_0	60.63 (14.57)	−1.20 (−3.78; 1.39)		
	41	T_1	58.00 (17.77)	−2.63 (−5.21; −0.06)	−1.44 (12.36)	0.34
D_{LCO}, mmol/min/kPa	22	T_{-1}	5.48 (3.25)	–		
	22	T_0	4.50 (2.77)	−0.98 (−1.60; −0.37)		
	22	T_1	5.03 (3.64)	0.53 (−0.47; 1.53)	1.51 (3.46)	0.03
D_{LCO}%	26	T_{-1}	32.73 (8.56)	–		
	26	T_0	26.54 (5.70)	−6.19 (−9.26; −3.12)		
	26	T_1	29.23 (12.08)	2.69 (−1.54; 6.93)	8.88 (15.30)	0.004
FEV_1, L	37	T_{-1}	1.72 (0.45)	–		
	37	T_0	1.70 (0.46)	−0.02 (−0.10; 0.05)		
	37	T_1	1.60 (0.44)	−0.11 (−0.18; −0.03)	−0.08 (0.38)	0.15
FEV_1%	39	T_{-1}	67.62 (16.02)	–		
	39	T_0	66.67 (15.62)	−0.95 (−4.43; 2.53)		
	39	T_1	63.62 (17.66)	−3.05 (−5.64; −0.46)	−2.10 (15.62)	0.37
TLC, L	15	T_{-1}	3.85 (1.13)	–		
	15	T_0	3.78 (1.03)	−0.07 (−0.34; 0.20)		
	15	T_1	3.73 (1.01)	−0.05 (−0.48; 0.38)	−0.02 (1.07)	1
TLC%	17	T_{-1}	59.06 (13.73)	–		
	17	T_0	58.71 (13.46)	−0.35 (−4.34; 3.64)		
	17	T_1	57.65 (13.16)	−1.06 (−6.60; 4.48)	−0.71 (15.74)	0.83
FVC%/D_{LCO}%	26	T_{-1}	2.17 (0.79)	–	–	
	26	T_0	2.60 (0.97)	0.43 (0.20; 0.66)	–	
	26	T_1	2.87 (2.42)	0.27 (−0.55; 1.10)	0.15 (2.29)	0.73

FVC, forced vital capacity; D_{LCO}, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; TLC, total lung capacity.

Safety and efficacy of pirfenidone in idiopathic pulmonary fibrosis in clinical practice

Ryo Okuda*, Eri Hagiwara, Tomohisa Baba, Hideya Kitamura, Terufumi Kato, Takashi Ogura

Baseline clinical characteristics and laboratory data

Characteristics	
Subjects	76
Male	60
Female	16
Age (yrs)	70.5 ± 8.3
Smoking history	
Never smoker	16
Ex- and current smokers	60
Brinkman index	849 ± 637
Surgical lung biopsy	
Yes	36
No	40
Disease severity	
(criteria of the Japanese Respiratory Society)	
I/II/III/IV/unmeasurable	20/11/15/27/3
(criteria of the USA)	
Mild/moderate/severe/unmeasurable	11/38/11/17
Pulmonary function	
VC (L)	2.05 ± 0.61
VC % pred	66.5 ± 15.8
FVC (L)	2.04 ± 0.61
FVC % pred	65.3 ± 16.1
FEV_1 (L)	1.67 ± 0.48
DLco % pred	55.9 ± 17.8
6MWT	
Distance (m)	313 ± 105
Lowest SpO_2 (%)	86.0 ± 5.5

Data are presented as *n*, *n*(%) or mean ± standard deviation

Respiratory Medicine (2013) 107, 1431 -1437

FVC decline in subpopulations characterized by %FVC and by change in FVC before therapy.

%FVC at initiation of therapy	*n*	Mean change in FVC for 6 months before therapy (ml)	Mean change in FVC for 6 months after therapy (ml)	*p*-Value
%FVC ≥80	4	−60 ± 96	−80 ± 69	0.840
80> %FVC ≥70	11	−130 ± 58	20 ± 70	0.282
70> %FVC ≥60	10	−210 ± 44	−60 ± 63	0.156
60> %FVC	11	−280 ± 72	−80 ± 55	0.074

Decline in FVC for 6 months before therapy	*n*	Mean change in FVC for 6 months before therapy (ml)	Mean change in FVC for 6 months after therapy (ml)	*p*-Value
≥150 ml	16	−350 ± 48	30 ± 58	<0.001
<150 mL	20	−60 ± 20	−100 ± 31	0.274

Paired *t*-test was performed. Values are given as mean ± standard error.

- Pirfenidone was effective even in patients with baseline FVC values of <60%
- Pirfenidone was more effective in the group with a greater decline of FVC prior to therapy

Correlation between anorexia and disease severity

Criteria of the Japanese Respiratory Society		
Disease severity	Anorexia (+)	Anorexia (−)
I	7	13
II	4	7
III	7	8
IV	14	13
Criteria of the USA		
Disease severity	Anorexia (+)	Anorexia (−)
I	4	7
II	17	21
III	5	6

[1)]p = 0.875, [2)]p = 0.651, [3)]p = 0.488. Data are presented as n.

- There was no correlation between anorexia and disease severity

Original article

Efficacy of pirfenidone and disease severity of idiopathic pulmonary fibrosis: Extended analysis of phase III trial in Japan

Yoshio Taguchi[a,*], Masahito Ebina[b], Seishu Hashimoto[a], Takashi Ogura[c], Arata Azuma[d], Hiroyuki Taniguchi[e], Yasuhiro Kondoh[e], Moritaka Suga[f], Hiroki Takahashi[g], Koichiro Nakata[h], Yukihiko Sugiyama[i], Shoji Kudoh[j], Toshihiro Nukiwa[j], Pirfenidone Clinical Study Group in Japan

Respiratoty investigation 53(2015) 279–287

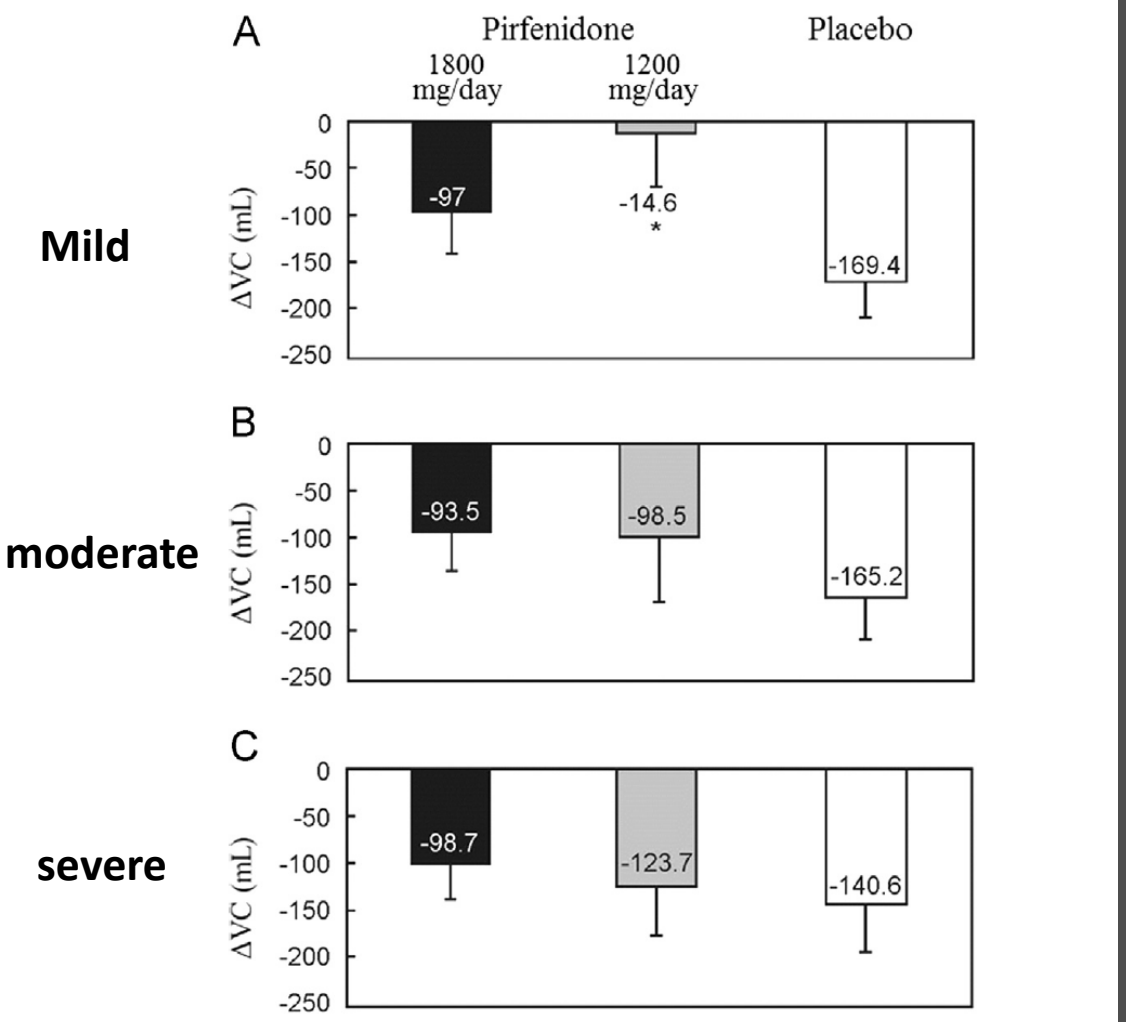
Table 1 – The number of patients in the three sub-populations in the treatment groups.

Group	High-dose pirfenidone *n* (%)	Low-dose pirfenidone *n* (%)	Placebo *n* (%)	Total *n* (%)
Mild	34 (31.4)	21 (38.2)	47 (45.2)	102 (38.6)
Moderate	37 (35.2)	15 (27.3)	38 (36.5)	90 (34.1)
Severe	34 (32.4)	19 (34.5)	19 (18.3)	72 (27.3)
Total	105 (100)	55 (100)	104 (100)	264 (100)

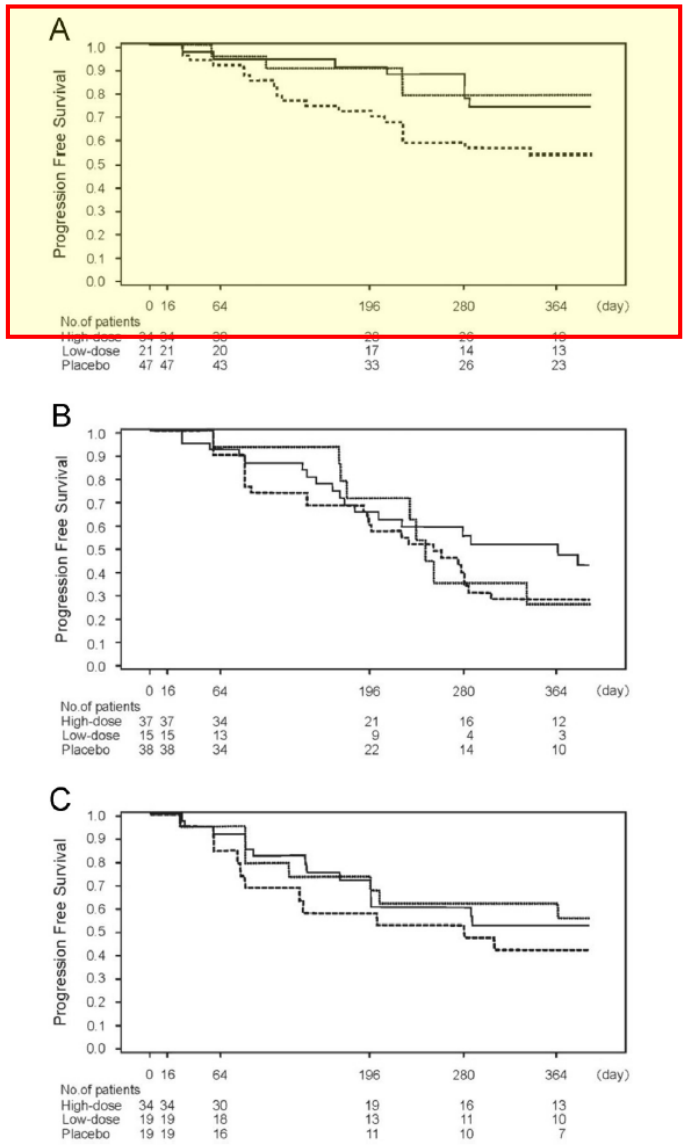
- Shah's classification of IPF severity
  1) % FVC <65%
  2) The lowest SpO2 < 88% with exertion on room air
  3) DLco 50% or less

- definition of disease severity
  1) None of 3 features → mild
  2) 1 of the three features → moderate
  3) 2 or 3 of the three features→ severe

Change in vital capacity from baseline to week 52



Progression-free survival



Original article

Efficacy of pirfenidone and disease severity of idiopathic pulmonary fibrosis: Extended analysis of phase III trial in Japan

Yoshio Taguchi[a,*], Masahito Ebina[b], Seishu Hashimoto[a], Takashi Ogura[c], Arata Azuma[d], Hiroyuki Taniguchi[e], Yasuhiro Kondoh[e], Moritaka Suga[f], Hiroki Takahashi[g], Koichiro Nakata[h], Yukihiko Sugiyama[i], Shoji Kudoh[j], Toshihiro Nukiwa[j], Pirfenidone Clinical Study Group in Japan

✓ Conclusion

- Pirfenidone attenuated VC decline at all grades of severity
- Pirfenidone have better efficacy in the subpopulation with mild-grade IPF

Real life Study

Respiratory Medicine (2015) 109, 904–913

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Efficacy of pirfenidone for idiopathic pulmonary fibrosis: An Italian real life study

Study design

- Observational, retrospective, multicenter (12 ILD centers)
- Stratification of patients (128 patients)
  I. % FVC at baseline (>75% and <75%)
  II. GAP index at baseline (stage I vs. II/III)
- Monitoring lung function decline
  ✓ 1-yr before, Baseline, 1-yr after pirfenidone

Pirfenidone effect in IPF patient with lower FVC

Spirometric parameters and 6MWT distance measured one year before pirfenidone therapy initiation (1-yr before), at the time of treatment entry (baseline), and one year after therapy initiation (1-yr after) in patients stratified by percent predicted FVC (≤75% and >75%) at baseline.

Parameter	Time	FVC at baseline >75% of predicted				FVC at baseline ≤75% of predicted			
		Mean[a] (95% CI)	Change (%)	Difference in change (%)	p-value[d]	Mean[a] (95% CI)	Change (%)	Difference in change (%)	p-value[d]
FVC (% of predicted)	1-yr before	92 (88, 95)	–	–		71 (67, 74)	–	–	
	baseline	91 (88, 94)	−1.1[b]	–		62 (59, 65)	−12.7[b]	–	
	1-yr after	88 (84, 92)	−3.3[c]	−2.2	0.332	62 (58, 65)	0.0[c]	12.7	0.006

Pirfenidone effect in IPF patient with GAP Ⅱ/Ⅲ

Spirometric parameters and 6MWT distance measured one year before pirfenidone therapy initiation (1-yr before), at the time of treatment entry (baseline), and one year after therapy initiation (1-yr after) in patients stratified by GAP stage (I and II/III) at baseline.

		Stage I at baseline				Stage II/III at baseline			
Parameter	Time	Mean[a] (95% CI)	Change (%)	Difference in change (%)	p-value[d]	Mean[a] (95% CI)	Change (%)	Difference in change (%)	p-value[d]
FVC (% of predicted)	1-yr before	87 (82, 93)	–	–		77 (72, 81)	–	–	
	Baseline	85 (80, 89)	−2.3[b]	–		70 (66, 74)	−9.1[b]	–	
	1-yr after	81 (75, 86)	−4.7[c]	−2.4	0.713	69 (64, 73)	−1.4[c]	7.7	0.007
DLCO	1-yr before	13.96 (12.74, 15.17)	–	–		11.21 (10.17, 12.24)	–	–	
	Baseline	13.00 (12.01, 13.99)	−6.9[b]	–		10.11 (9.30, 10.92)	−9.8[b]	–	
	1-yr after	11.20 (9.83, 12.56)	−13.8[c]	−7.0	0.305	8.79 (7.67, 9.90)	−13.1[c]	−3.2	0.739
DLCO (% of predicted)	1-yr before	58 (53, 63)	–	–		47 (43, 51)	–	–	
	Baseline	54 (51, 58)	−6.9[b]	–		41 (38, 44)	−12.8[b]	–	
	1-yr after	46 (41, 50)	−14.8[c]	−7.9	0.113	35 (31, 39)	−14.6[c]	−1.9	0.897
Distance (without suppl. O_2)	1-yr before	456 (413, 498)	–	–		447 (406, 487)	–	–	
	Baseline	437 (404, 470)	−4.1[b]	–		430 (400, 459)	−3.8[b]	–	
	1-yr after	438 (393, 482)	0.1[c]	4.2	0.513	405 (365, 444)	−5.8[c]	−2.0	0.771
Distance (with suppl. O_2)	1-yr before	357 (270, 445)	–	–		464 (363, 566)	–	–	
	Baseline	389 (333, 444)	8.8[b]	–		341 (307, 374)	−26.7[b]	–	
	1-yr after	329 (262, 397)	−15.3[c]	−24.1	0.207	367 (329, 406)	7.9[c]	34.5	0.021

Message from this real life study

Pirfenidone reduced the rate of annual FVC decline (p= 0.065)

Pirfenidone provided significant treatment benefit for patients with moderate-severe disease

It suggests that the drug may also be effective in patients with more advanced disease

Safety and efficacy of pirfenidone in severe Idiopathic Pulmonary Fibrosis: A real-world observational study

Argyrios Tzouvelekis [a, *, 1], Paschalis Ntolios [b, 1], Theodoros Karampitsakos [a], Vasilios Tzilas [a], Stavros Anevlavis [b], Evangelos Bouros [a], Paschalis Steiropoulos [b], Nikolaos Koulouris [a], Grigoris Stratakos [a], Marios Froudarakis [b], Demosthenes Bouros [a]

Retrospective study (N=43)

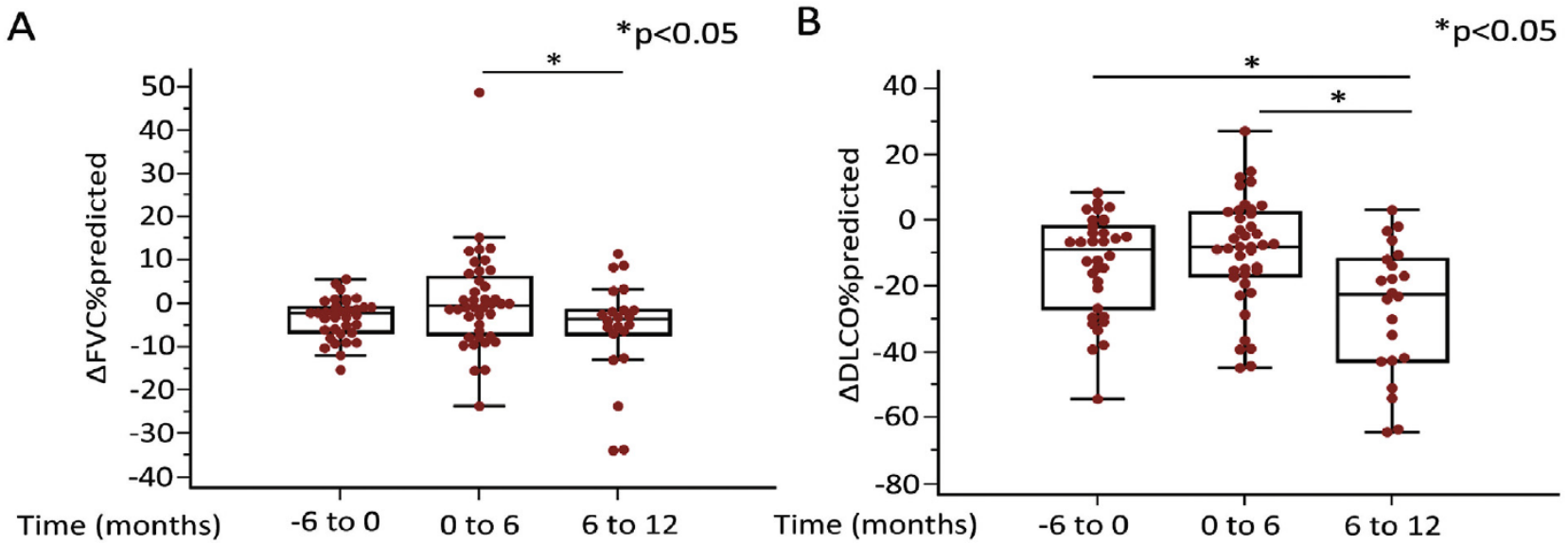
Advanced IPF (FVC% predicted< 50% and/or DLco%

receiving pirfenidone for at least 6 months

Baseline characteristics of subjects included in study. Data are presented as no (total) or mean ± SD.

Characteristics	Baseline data
Total patients enrolled	43
Male/Female	35/8
Age (years ± SD)	66.25 ± 13.25
Never smokers	3
Current or ex-smokers	40
VATS	11
Prior treatment	0
CPFE	8
FVC %pred	63.80 ± 20.36
DLco %pred	27.26 ± 8.02
GAP score (median)	5

Pulmonary Pharmacology & Therapeutics 46 (2017) 48-53



The trend towards stability in both functional indices after 6-months of pirfenidone
However, pirfenidone failed to halt disease progression after one year of treatment

Similar treatment response irrespective of disease severity

	FVC <50% (N=12)	FVC >50% (N=31)	P
Rate of %FVC decline 6 months before treatment	- 7.3 ± 4.3	- 1.3 ± 3.4	P= 0.006
Rate of %FVC decline at 6 months post-treatment initiation	4.7 ± 8.9	0.6 ± 11.8	P= 0.2
Rate of %FVC decline at 12 months post-treatment initiation	- 3.3 ± 10.8	- 6.2 ± 12.2	P=0.7

Journal of
Clinical Medicine

MDPI

Review

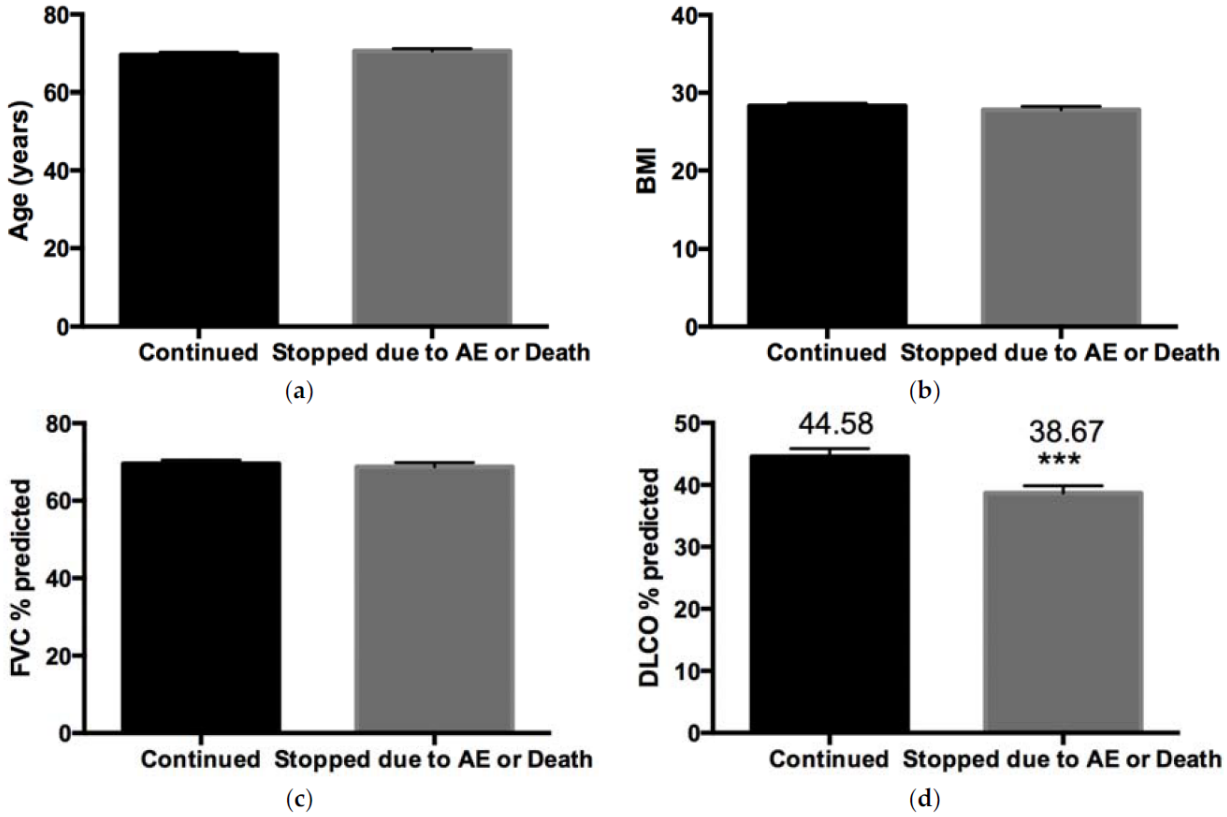
Real World Experiences: Pirfenidone and Nintedanib are Effective and Well Tolerated Treatments for Idiopathic Pulmonary Fibrosis

Gareth Hughes [1,2], Hannah Toellner [3], Helen Morris [1], Colm Leonard [1,2] and Nazia Chaudhuri [1,2,*]

a single centre retrospective observational study, in UK

Pirfenidone

Impact of age, BMI, FVC, and DLCO on discontinuations due to AEs



J. Clin. Med. 2016, 5, 78; doi:10.3390

Official Journal of the Asian Pacific Society of Respirology
Respirology
Editor's Choice
APSR
Respirology (2017) 22, 1171–1178

ORIGINAL ARTICLE

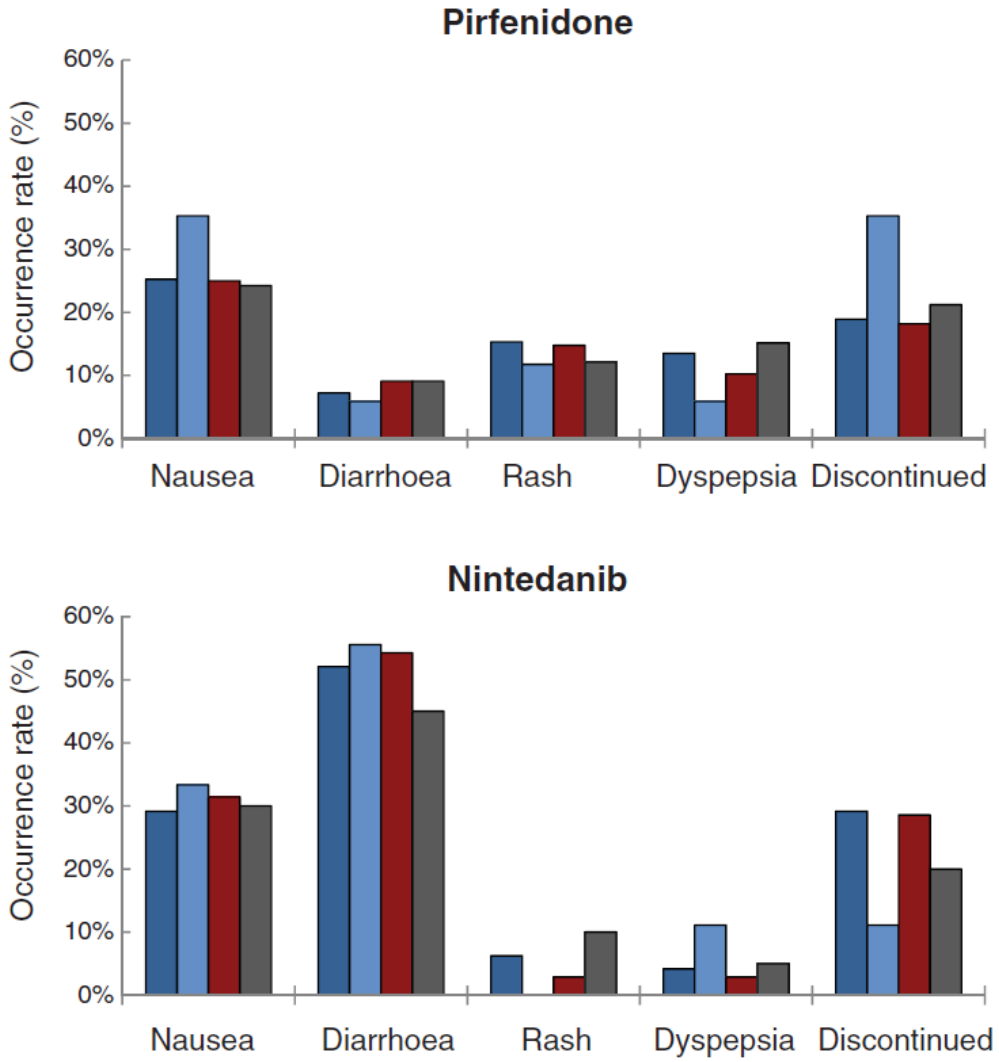
Pirfenidone and nintedanib for pulmonary fibrosis in clinical practice: Tolerability and adverse drug reactions

A total of 186 subjects
IPF and non-IPF lung fibrosis
Subjects had significant respiratory impairment at baseline
The large proportion requiring home oxygen therapy (117 of 186 subjects/ 63%)
Mean diffusion capacity of carbon monoxide (DLCO) was 36±14%

Subjects had significant respiratory impairment at baseline

Table 2 Baseline HRCT and PFTs

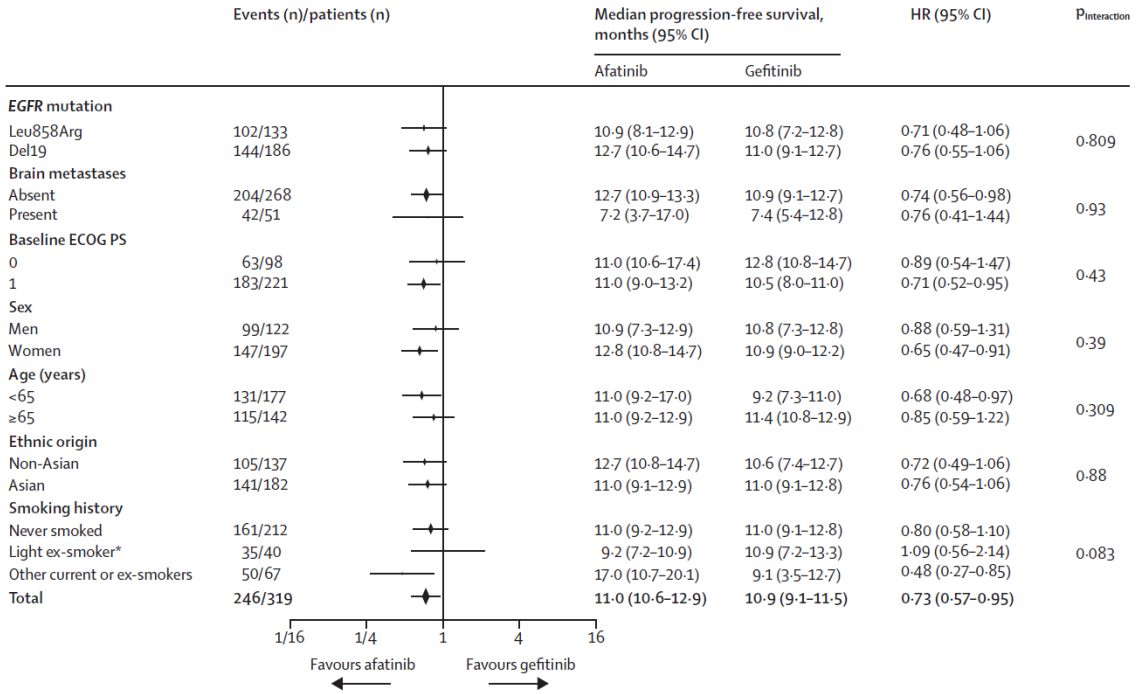
Baseline characteristics	Pirfenidone group (*n* = 129)	Pirfenidone (CAPACITY and ASCEND trials) (*n* = 623)	Nintedanib group (*n* = 57)	Nintedanib (INPULSIS 1 and 2 trials) (*n* = 638)
HRCT pattern, *n* (%)				
Definite UIP pattern	56 (43.4)	n/a[†]	18 (31.6)	n/a[‡]
Possible UIP pattern	42 (32.6)	n/a	15 (26.3)	n/a
Inconsistent with UIP pattern	27 (20.9)	n/a	21 (36.8)	n/a
No HRCT available for review	4 (3.1)	n/a	3 (5.3)	n/a
PFT				
FVC (% predicted)	68 ± 18	71.6	66 ± 17	79.8
DLco (% predicted)	37 ± 14	45.6	35 ± 13	47.4
6-Min walk distance (m)	268 ± 103	404	290 ± 77	n/a



Clinical characteristics associated with disease severity (FVC % pred., DLCO % pred. and home oxygen use) had no association with adverse event frequency and drug discontinuation

, FVC ≥50 (n = 111); , FVC <50 (n = 17); , DLco ≥30 (n = 88); , DLco <30 (n = 33); nintedanib: , FVC ≥50 (n = 48); , FVC <50 (n = 9); , DLco ≥30 (n = 35); , DLco <30 (n = 20).

- What is the effectiveness in other fields of pulmonary disease that is destined to die



	Events (n)/patients (n)	Median progression-free survival, months (95% CI)		HR (95% CI)	$P_{interaction}$
		Afatinib	Gefitinib		
***EGFR* mutation**					
Leu858Arg	102/133	10·9 (8·1–12·9)	10·8 (7·2–12·8)	0·71 (0·48–1·06)	0·809
Del19	144/186	12·7 (10·6–14·7)	11·0 (9·1–12·7)	0·76 (0·55–1·06)	
Brain metastases					
Absent	204/268	12·7 (10·9–13·3)	10·9 (9·1–12·7)	0·74 (0·56–0·98)	0·93
Present	42/51	7·2 (3·7–17·0)	7·4 (5·4–12·8)	0·76 (0·41–1·44)	
Baseline ECOG PS					
0	63/98	11·0 (10·6–17·4)	12·8 (10·8–14·7)	0·89 (0·54–1·47)	0·43
1	183/221	11·0 (9·0–13·2)	10·5 (8·0–11·0)	0·71 (0·52–0·95)	
Sex					
Men	99/122	10·9 (7·3–12·9)	10·8 (7·3–12·8)	0·88 (0·59–1·31)	0·39
Women	147/197	12·8 (10·8–14·7)	10·9 (9·0–12·2)	0·65 (0·47–0·91)	
Age (years)					
<65	131/177	11·0 (9·2–17·0)	9·2 (7·3–11·0)	0·68 (0·48–0·97)	0·309
≥65	115/142	11·0 (9·2–12·9)	11·4 (10·8–12·9)	0·85 (0·59–1·22)	
Ethnic origin					
Non-Asian	105/137	12·7 (10·8–14·7)	10·6 (7·4–12·7)	0·72 (0·49–1·06)	0·88
Asian	141/182	11·0 (9·1–12·9)	11·0 (9·1–12·8)	0·76 (0·54–1·06)	
Smoking history					
Never smoked	161/212	11·0 (9·2–12·9)	11·0 (9·1–12·8)	0·80 (0·58–1·10)	0·083
Light ex-smoker*	35/40	9·2 (7·2–10·9)	10·9 (7·2–13·3)	1·09 (0·56–2·14)	
Other current or ex-smokers	50/67	17·0 (10·7–20·1)	9·1 (3·5–12·7)	0·48 (0·27–0·85)	
Total	**246/319**	**11·0 (10·6–12·9)**	**10·9 (9·1–11·5)**	**0·73 (0·57–0·95)**	

Afatinib versus gefitinib as first-line treatment of patients with *EGFR* mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial

Progression-free survival : median 11·0 months vs 10.9 months
time-to-treatment failure : median 13·7 months vs 11·5 months

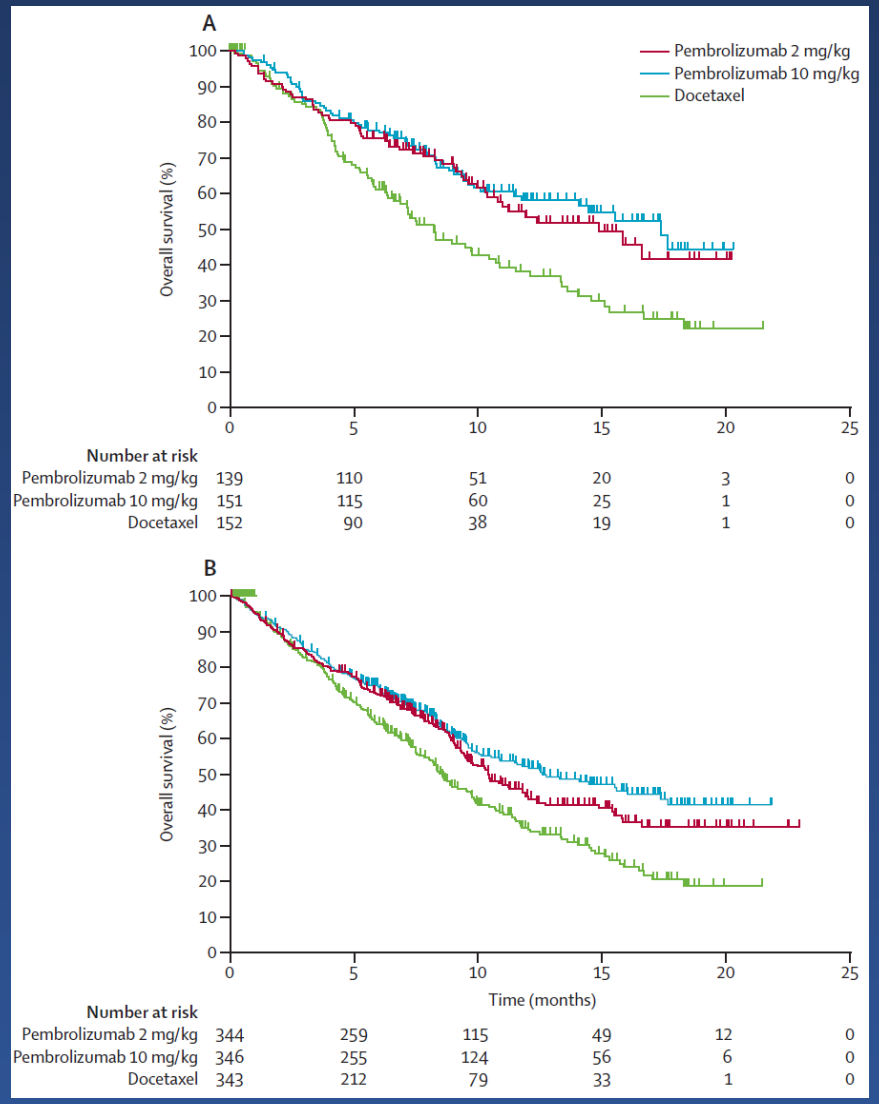
Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial

Roy S Herbst, Paul Baas, Dong-Wan Kim, Enriqueta Felip, José L Pérez-Gracia, Ji-Youn Han, Julian Molina, Joo-Hang Kim, Catherine Dubos Arvis, Myung-Ju Ahn, Margarita Majem, Mary J Fidler, Gilberto de Castro Jr, Marcelo Garrido, Gregory M Lubiniecki, Yue Shentu, Ellie Im, Marisa Dolled-Filhart, Edward B Garon

Pembrolizumab prolongs overall survival and has a favourable benefi t-to-risk profile in patients with previously treated, PD-L1-positive, advanced NSCLC.

Median overall survival

10·4 /12·7 months vs 8.5 months

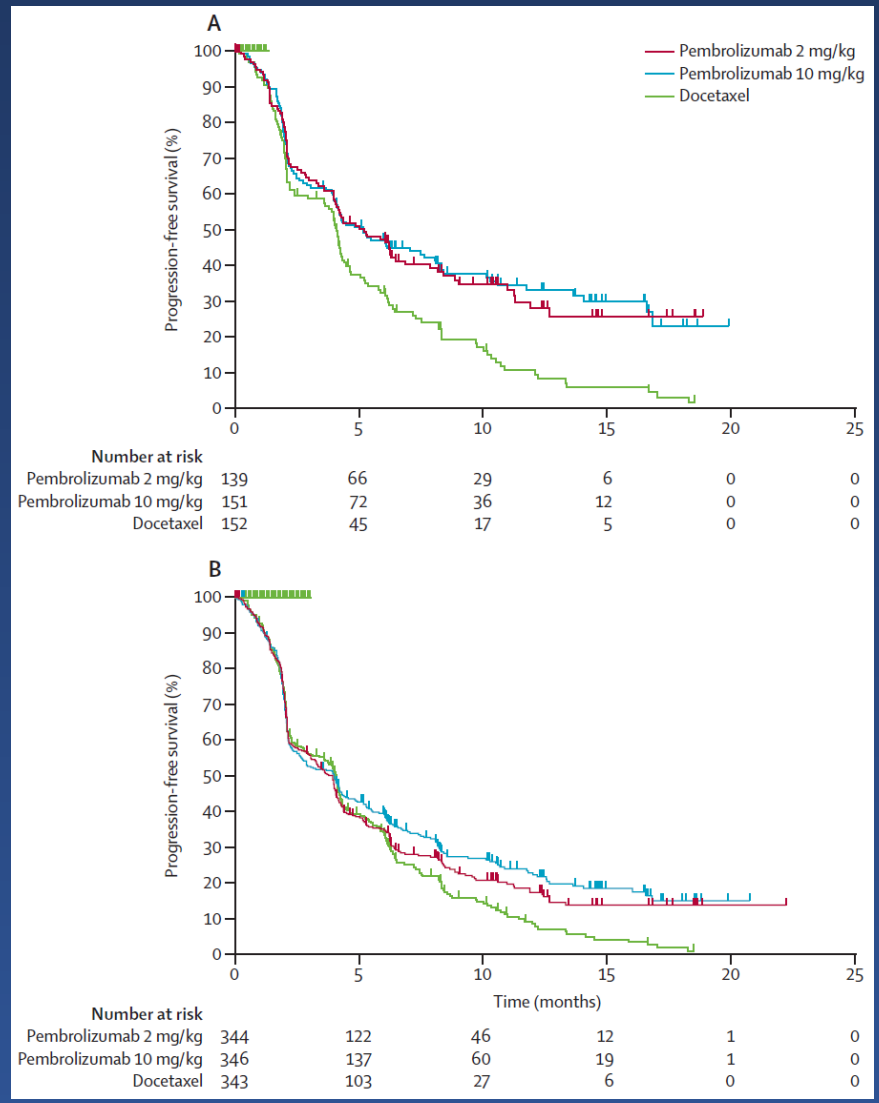


Analysis of overall survival

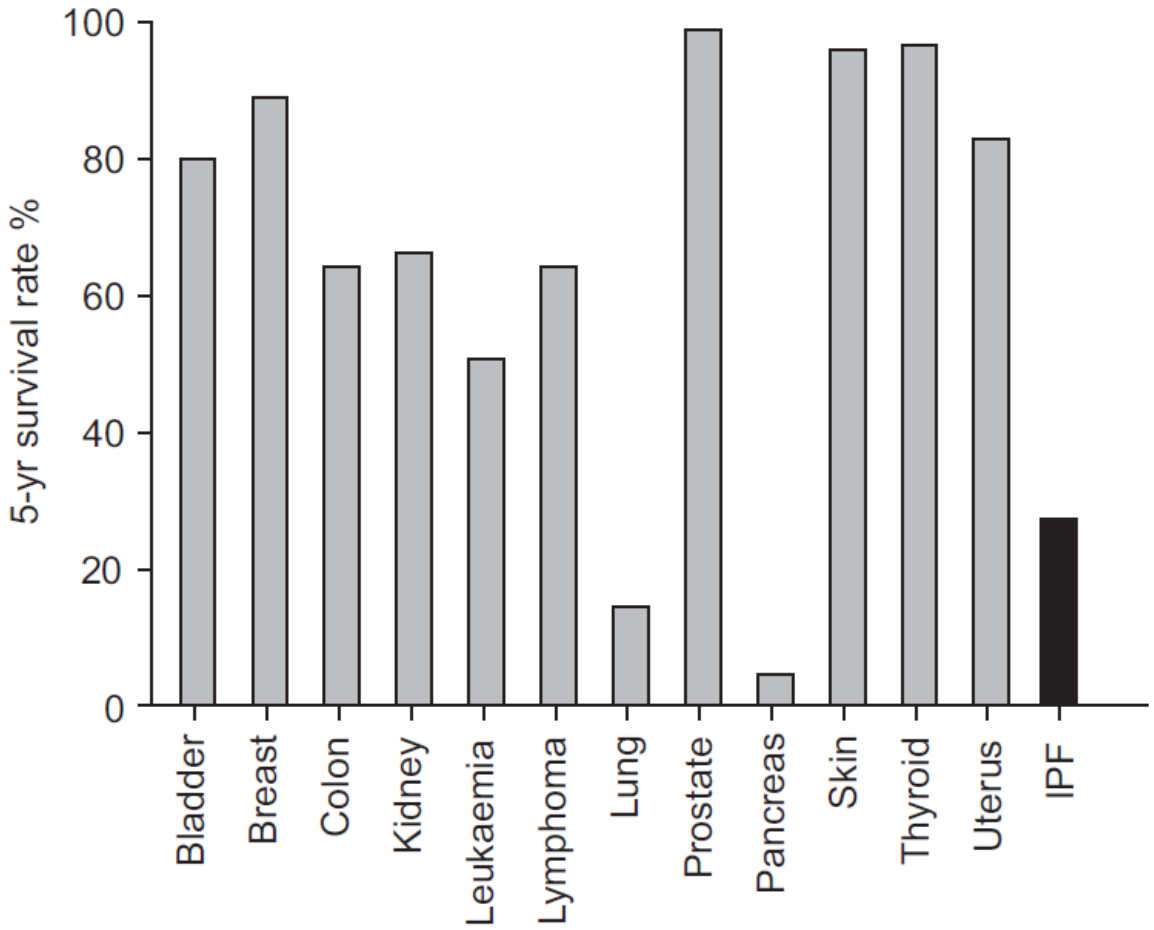
Median progression-free survival

5·0 months vs 4·1 months

5·2 months vs 4·1 months



Analysis of progression-free survival



Statistics for cancer are from the US National Cancer Institute

My opinion

- **From clinical trials to real-life studies**

  A few, but consistent evidences of beneficial effect in severe IPF patients with antifibrotic drugs

  No more increased adverse events-related to antifibrotic drugs in severe IPF patients

- **No alternative medical treatment option in severe IPF patients**

We should consider anti-fibrotic treatment in severe IPF patients