PNEUMOLOGIA 2018

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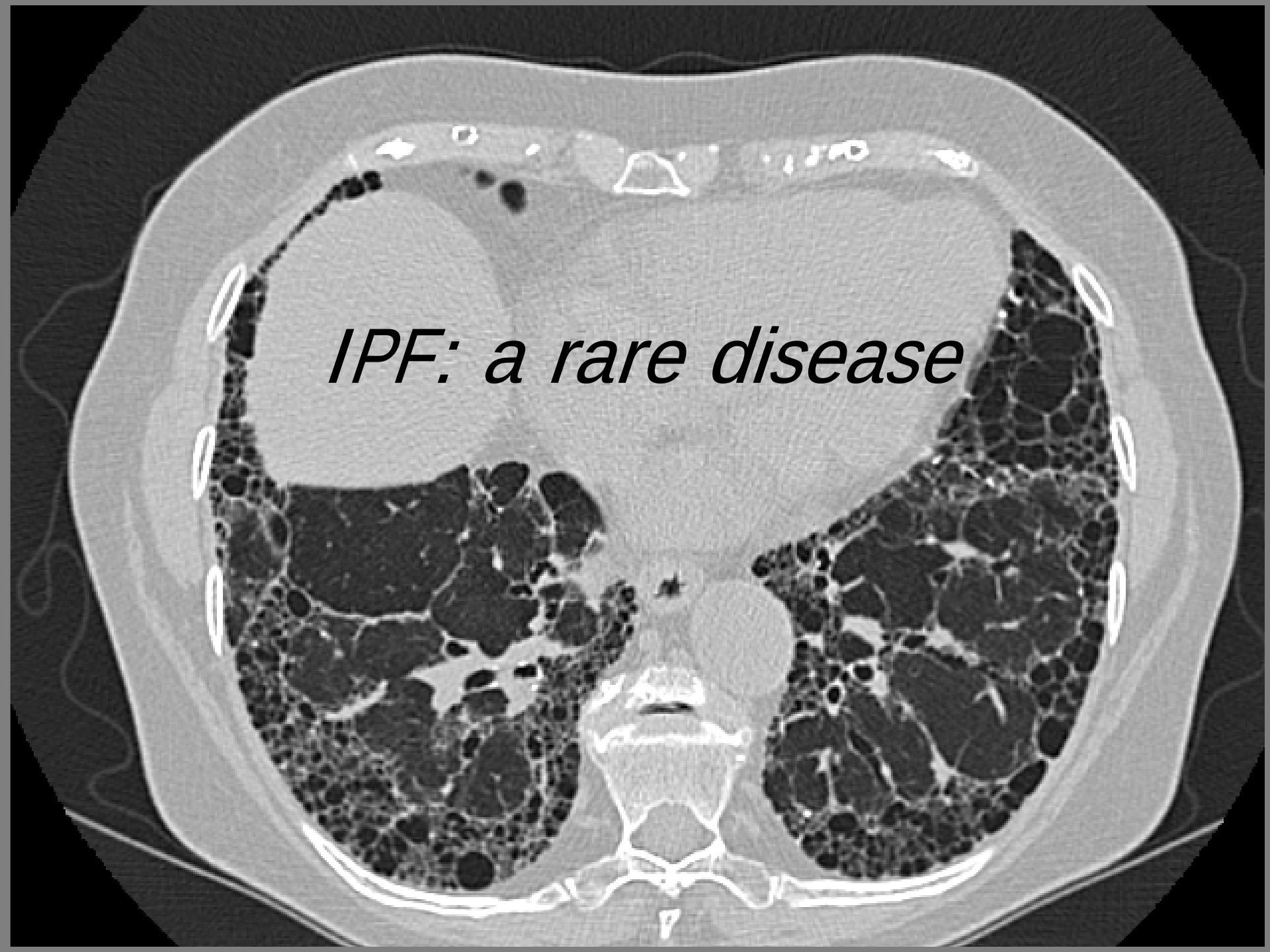
Gli studi italiani sull'IPF

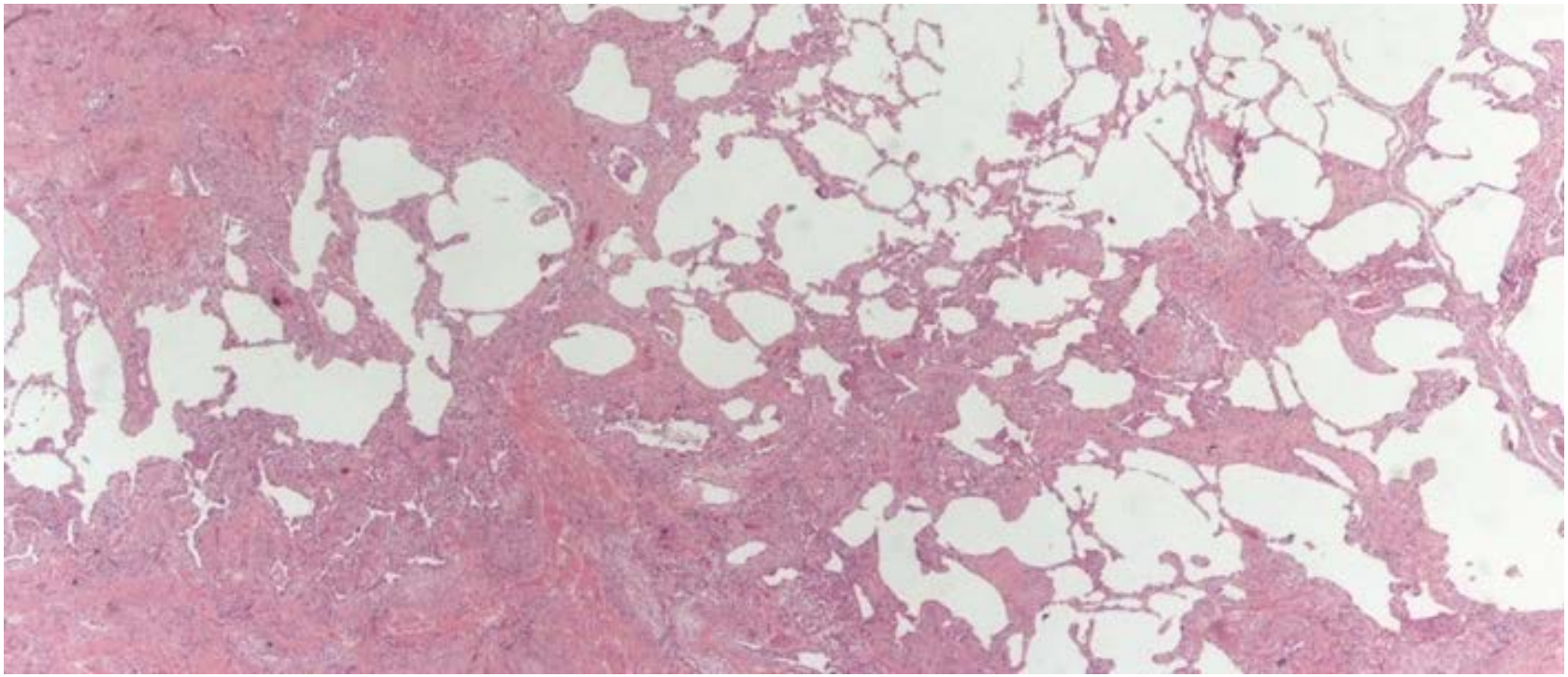
Antonella Caminati

U.O. di Pneumologia e Terapia Semi Intensiva
Servizio di Fisiopatologia Respiratoria ed Emodinamica Polmonare
Osp. San Giuseppe - MultiMedica, Milano


IPF: a rare disease

Results of clinical research

The recent positive results of the pirfenidone and nintedanib phase III trials demonstrate *that agents targeting the biologic processes that drive fibrosis can reduce the progression of IPF*



A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis

King TE et al. NEJM 2014; 370: 2083

2014-2015: the begin of the new era of IPF

Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis

Richeldi L et al. NEJM 2014; 370: 2071

Randomized trial of acetylcysteine in idiopathic pulmonary fibrosis

NEJM 2014; 370: 2093

Where We're Going…

Anti-inflammatory

Immunosuppression

Immunomodulation

Anti-oxidant

Anti-fibrotic

Stem cells?

Antiproliferative

Statement ATS/ERS 2000

Steroids and/or immunosuppressant

Statement ATS/ERS/JRS/ALAT 2011

No therapy approved

Pirfenidone

Nintedanib

Combined therapy?

1950s **1990s** **2009** **2018**

Currently, where is no a cure for IPF

Today, we have a therapy

IPF: Where we are today

- It is clear that treatment decisions and the clinical management of patients with IPF should be based primarily on the findings of randomized controlled trials
- Randomized clinical trials have increased our knowledge in several aspects of IPF
- Many promising compounds for IPF treatment have not shown efficacy when evaluated in phase II and III clinical trials

Lessons learned from clinical trials

- Remarkable accomplishments
  - also in an orphan disease as IPF: several multicenter randomized clinical trials
  - clinical investigators, sponsors, patients join hands and work together
  - placebo arm/placebo controls (no more ethical)
  - better understanding of natural course of IPF
- myths clarified with facts and figures
- opinions/consensus of expert opinions proven wrong by evidence
- standard of care improved by sparing patients from toxic/harmful drugs

Lessons learned from clinical trials

- Almost all clinical trials: patients with mild –moderate impairment in FVC and DLCO and followed 48-60 weeks
- Patients are relatively stable during this interval
- FVC decline is about 200 ml/yr in placebo group
- FVC is not a predictor of hospitalization/acute exacerbation
- Feasibility of enrolling patients with severe/advanced pulmonary function impairment demonstrated
- Other than standard physiological/clinical assessment of disease progression, no other cellular/molecular/genetic biomarkers have been utilized

Nintedanib and pirfenidone

- Approval for treatment for IPF (FDA and EMA)

  "Blanket treatment" (regardless of status of disease and/or comorbid conditions)

- Results of phase 3 clinical trials in a precise subgroup of patients with IPF
- Decline in FVC decreases over 1 yr without symptomatic relief
- Significant side effects (GI in both; rash with pirfenidone)
- Tolerated by patients in the context of clinical trials

..but real life is not a clinical trial...

Unkown effects:

- whether the lower rate of decline in FVC in patients lasts beyond 1 yr in patients with mild –moderate impairment (PFTs)
- applicable to the entire spectrum of patients with IPF, especially those with severe functional impairment and/or known comorbidities
- Long term effects and if tolerated in patients in “real world”
- ***Is one better than the other? No head-to-head comparison***
- ***if used sequential or in combination with both or with other drugs***
- ***Cost effective-benefit-ratio***

RCTs:

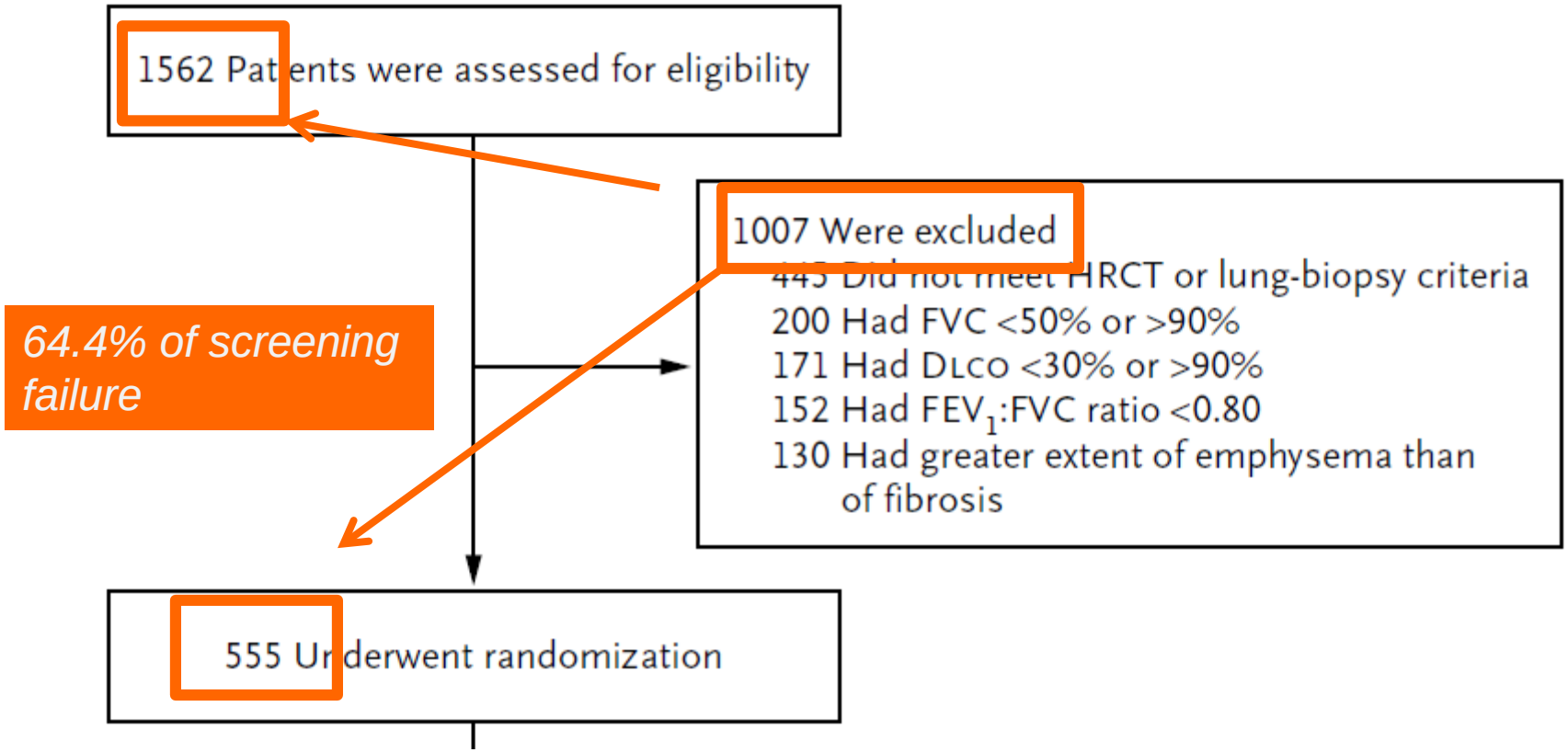
are recognized as the “gold standard” for evaluating treatment outcomes

have ***high internal validity***

are representative for a little sample of the “real” patients

- The patient populations in the clinical trials may be not representative of the whole IPF population
- Few patients in the trials have the comorbidities that would normally be seen in clinical practice
- General severity of IPF (according to mean baseline FVC or VC values across the randomized controlled trials) is likely to be less severe in the trials than in clinical practice
- Screening failure in randomized trials is usually relevant

For example, in ASCEND study….



Screening failure in INPULSIS trials: 28-31%

Screening failure in PANTHER study: 32.7%

Real life studies:

are designed to evaluate treatment outcomes,
but unlike RCTs they adopt usual care settings and procedures in non-selected patients, thus mimicking everyday clinical practice, which provides ***high external validity***.

Mortality in randomized trials studying IPF is much lower than expected

It is therefore unclear if IPF patients enrolled in clinical trials always reflect the prognosis and progression of IPF

	Death in placebo group n (%)
PANTHER	3/131 (2.3)
INPULSIS	33/423 (7.8)
ASCEND	20/277 (7.2)
ASCEND + CAPACITY	42/624 (6.7)
INSIGHT-IPF	41/451 (9.1)

IPF patients in this prospective real-life large registry (451 pts) had a more severe disease, a higher symptom burden, more compromised quality of life, and a higher mortality compared to recent randomized controlled trials. Behr J, ERS 2014

Controlled clinical trial results vs real world observations

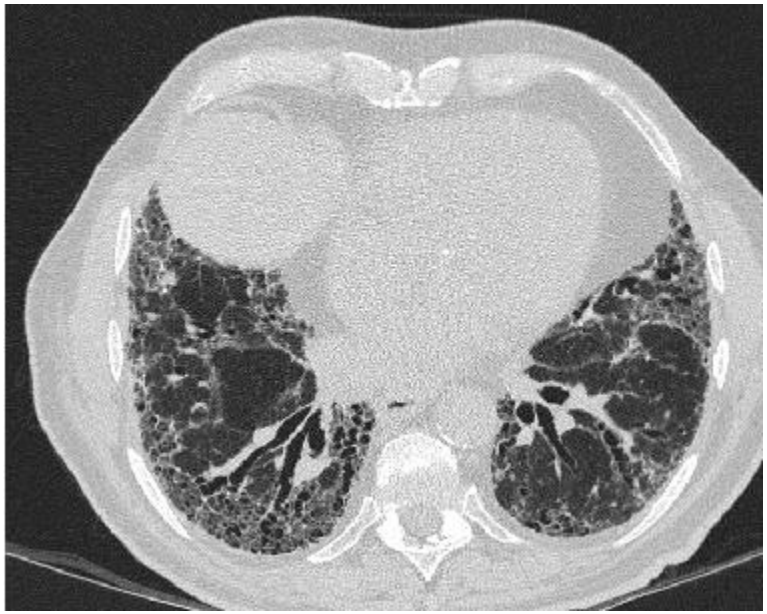
Will the treatment work in the real world?
That's the issue often raised by the favorable outcome of a formal clinical trial

It's so important that special terminology has been developed for it: "the gap between efficacy and effectiveness" - ***efficacy*** meaning proof in a carefully controlled trial, and ***effectiveness*** meaning success in the circumstances of everyday life

From clinical trial to real life: an Italian experience

Efficacy of Pirfenidone for Idiopathic Pulmonary Fibrosis: an Italian real life study

S. Harari, A. Caminati, C. Albera, C. Vancheri, V. Poletti, A. Pesci, F. Luppi, C. Saltini, C. Agostini, E. Bargagli i, A. Sebastiani, A. Sanduzzi, V. Giunta, R. Della Porta, G.P. Bandelli, S. Puglisi, S. Tomassetti, A. Biffi, S. Cerri, A. Mari, F. Cinetto, F. Tirelli, G. Farinelli, M. Bocchino, C. Specchia, M. Confalonieri.



Respir Med. 2015 Jul;109(7):904-1

Matherials and Methods

We conducted a national, retrospective, unsponsored, observational study of patients with IPF treated with pirfenidone:

Inclusion criteria:

* Diagnosis of IPF confirmed by HRCT UIP pattern and/or surgical lung biopsy (according to 2011 IPF guidelines);
* Mild, moderate and severe stage of disease;
* Availability of functional follow-up data at least 12 months before and at least 12 months after starting Pirfenidone;

Matherials and Methods

Study design:

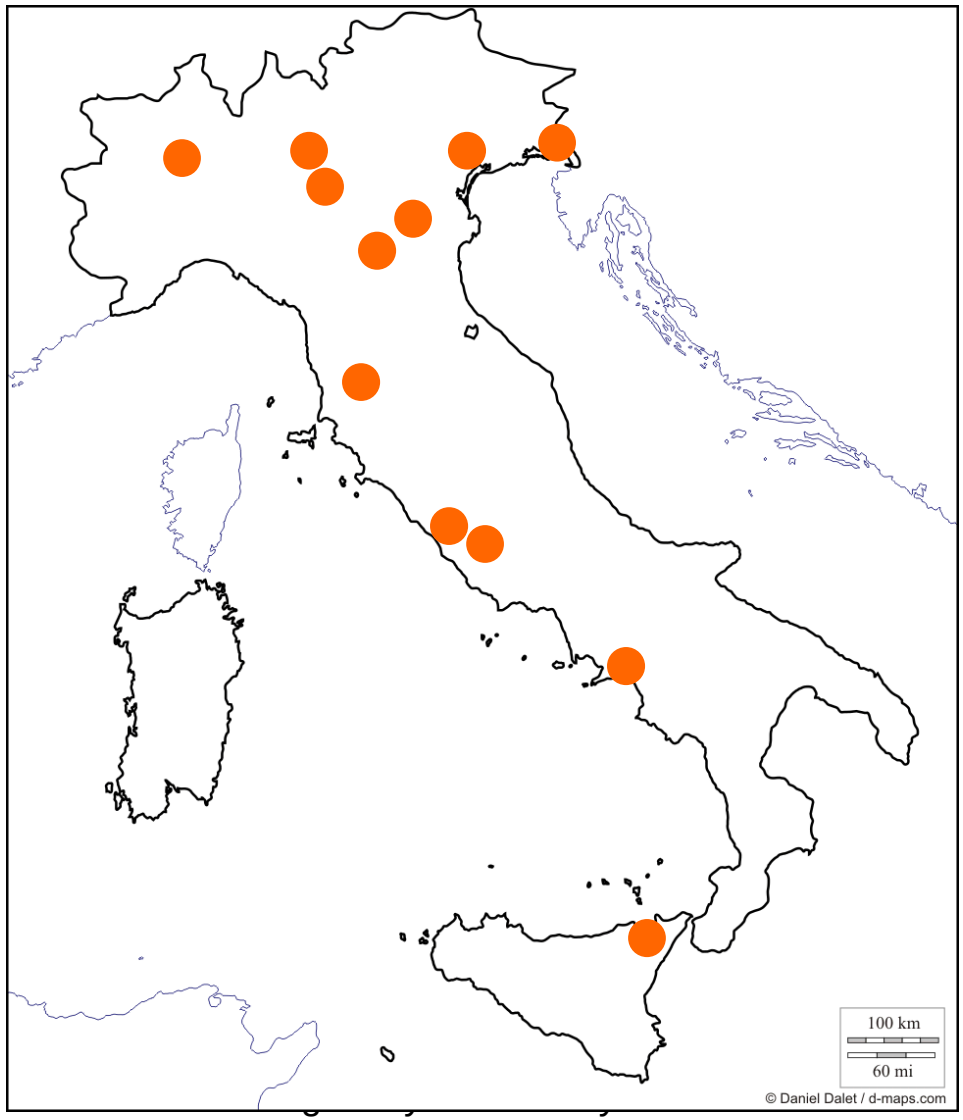
- Each subject is control of himself;
- The time (at least 12 months) before starting pirfenidone have the role of control period;
- Each subject is monitored in a period before the assumption of the drug and in the period after

Matherials and Methods

- **Primary End-point:**
  - Evaluation of the slope of decline of FVC% 1-year before and 1-year after starting PT;

- **Secondary End-points:**
  - Distance walked on 6MWT; DLCO change

Patients' characteristics at baseline – first pirfenidone prescription (N=128)



Variable	Levels	N (%)
Age at baseline (years)*	<=60	17 (13.3)
	61-65	20 (15.6)
	65+	91 (71.1)
Smoking status	Ex-smoker	97 (75.8)
	Non smoker	27 (21.1)
	Smoker	4 (3.1)
Histological diagnosis	No	96 (75.0)
	Yes	32 (25.0)
Clinical/Radiological diagnosis	Uncertain	20 (15.6)
	No	3 (2.3)
	Yes	105 (82.0)
Cortisone	No	53 (41.4)
	Yes	75 (58.6)
Azathioprine	No	97 (75.8)
	Yes	31 (24.2)
N-Acetylcysteine	No	75 (58.6)
	Yes	53 (41.4)

* * Mean time from diagnosis of IPF to first pirfenidone prescription: 2 years (SD 1.8 years)

Results

PFTs and 6MWT distance at baseline (first pirfenidone prescription)

	N	Mean (SD)	Min-Max
FVC %	128	0.75 (0.18)	0.35-1.43
DLCO	120	11.27 (4.02)	1.52-26.40
DLCO%	120	0.47 (0.15)	0.17-1.20
Distance (m) (w/o O2 support)	63	442 (101)	250-750
Distance (m) (w O2 support)	25	360 (86)	150-490

GAP index and stage at baseline (first pirfenidone prescription)

	Predictor	N (%)
G - Gender	Female	32 (25.0)
	Male	96 (75.0)
A – Age	<=60	17 (13.3)
	61-65	20 (15.6)
	65+	91 (71.1)
P - Physiology	FVC %	
	>=0.75	59 (46.1)
	0.50-0.75	67 (52.3)
	<0.50	2 (1.6)
	DLCO %	
	>0.55	26 (20.3)
	0.36-0.55	75 (58.6)
	<=0.35	19 (14.8)
	missing	8 (6.3)

	Predictor	N (%)	Median, (Min-Max)
GAP index			4 (1-6)
Stage	I (GAP index 0-3)	48 (37.5)	
	II (GAP index 4-5)	64 (50.0)	
	III (GAP index 6-8)	8 (6.3)	
	missing	8 (6.3)	

Results

Changes in PFTs. All patients (N=128)

Parameter	Time	Mean* (95% CI)	% change**	Difference in % change	p-value***
FVC %	1-yr before	0.80 (0.77, 0.84)	-	-	
	baseline	0.75 (0.72, 0.79)	-6.3%	-	
	1-yr after	0.74 (0.70, 0.77)	-1.3%	4.9%	0.065
DLCO	1-yr before	12.28 (11.45, 13.11)	-	-	
	baseline	11.27 (10.60, 11.95)	-8.2%	-	
	1-yr after	9.78 (8.90, 10.66)	-13.2%	5.0%	0.355
DLCO%	1-yr before	0.51 (0.48, 0.55)	-	-	
	baseline	0.47 (0.44, 0.49)	-7.8%	-	
	1-yr after	0.40 (0.37, 0.43)	-14.9%	-7.1%	0.249

* based on predicted values at 1-yr before, at baseline and at 1-yr after estimated from a linear mixed model;

** first % change reported: (baseline-1yr before)/(1yr before); second % change reported: (1 yr after-baseline)/(baseline);

*** based on the null hypothesis first % change=second % change;

Results

Changes in PFTs by FVC % group at baseline (>0.75 vs <=0.75)

		FVC% >0.75 at baseline				FVC% <=0.75 at baseline			
Parameter	Time	Mean* (95% CI)	%change**	Difference in % change	p ***	Mean* (95% CI)	%change**	Difference in % change	p***
FVC %	1-yr before	0.92 (0.88, 0.96)	-	-		0.71 (0.67, 0.74)	-	-	
	baseline	0.91 (0.88, 0.94)	-1.1%	-		0.62 (0.59, 0.66)	-12.7%	-	
	1-yr after	0.88 (0.84, 0.91)	-3.3%	-2.2%	0.332	0.62 (0.58, 0.65)	0.0%	12.7%	0.006
p-value for homegeneity of difference in % changes between strata***:0.002									
DLCO	1-yr before	13.22 (12.05, 14.39)	-	-		11.46 (10.33, 12.58)	-	-	
	baseline	12.33 (11.38, 13.29)	-6.7%	-		10.34 (9.44, 11.24)	-9.8%	-	
	1-yr after	11.24 (9.96, 12.50)	-8.8%	-2.1%	0.792	8.49 (7.31, 9.67)	-17.9%	-8.1%	0.317
p-value for homegeneity of difference in % changes between strata*:0.618**									
DLCO %	1-yr before	0.55 (0.50, 0.60)	-	-		0.48 (0.43, 0.52)	-	-	
	baseline	0.91 (0.47, 0.55)	-7.3%	-		0.43 (0.39, 0.46)	-10.4%	-	
	1-yr after	0.45 (0.41, 0.50)	-11.8%	-4.5%	0.605	0.35 (0.30, 0.39)	-18.6%	-8.2%	0.279
p-value for homegeneity of difference in % changes between strata***:0.707									

*based on predicted values at 1-yr before, at baseline and at 1-yr after estimated from a linear mixed model; ** first % change reported: (baseline-1yr before)/(1yr before); second % change reported: (1 yr after-baseline)/(baseline); *** based on the null hypothesis first % change=second % change;

Results

Changes in PFTs by stage at baseline (I vs II/III)

		STAGE I at baseline				STAGE II/III at baseline			
Parameter	Time	Mean* (95% CI)	%change**	Difference in % change	p***	Mean* (95% CI)	%change**	Difference in % change	p***
FVC %	1-yr before	0.87 (0.82, 0.93)	-	-		0.77 (0.72, 0.81)	-	-	
	baseline	0.85 (0.80, 0.89)	-2,3%	-		0.70 (0.66, 0.74)	-9,1%	-	
	1-yr after	0.81 (0.75, 0.86)	-4.7%	-2.4%	0.713	0.69 (0.64, 0.73)	-1.4%	7.7%	0.007
	p-value for homegeneity of difference in % changes between strata***:0.041								
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%	-		10.11 (9.30, 10.92)	-9.8%	-	
	1-yr after	11.20 (9.83, 12.56)	-13.8%	-7.0%	0.305	8.79 (7.67, 9.90)	-13.1%	-3.2%	0.739
	p-value for homegeneity of difference in % changes between strata*:0.570**								
DLCO %	1-yr before	0.58 (0.53, 0.63)	-	-		0.47 (0.43, 0.51)	-	-	
	baseline	0.94 (0.51, 0.58)	-6.9%	-		0.41 (0.38, 0.44)	-12.8%	-	
	1-yr after	0.46 (0.41, 0.50)	-14.8%	-7.9%	0.113	0.35 (0.31, 0.39)	-14.6%	-1.9%	0.897
	p-value for homegeneity of difference in % changes between strata***:0.259								

* based on predicted values at 1-yr before, at baseline and at 1-yr after estimated from a linear mixed model; ** first % change reported: (baseline-1yr before)/(1yr before); second % change reported: (1 yr after-baseline)/(baseline); *** based on the null hypothesis first % change=second % change;

Results

Changes in 6MWT distance by stage at baseline (I vs II/III)

		STAGE I at baseline				STAGE II/III at baseline			
Parameter	Time	Mean* (95% CI)	%change**	Difference in % change	p ***	Mean* (95% CI)	%change**	Difference in % change	p***
Distance w/o O2	1-yr before	456 (413, 496)	-	-		447 (406, 487)	-	-	
	baseline	437 (404, 470)	-4.1%	-		430 (400, 459)	-3.8%	-	
	1-yr after	438 (393, 482)	0.1%	4.2%	0.513	405 (365, 444)	-5.8%	-2.0%	0.771
	p-value for homegeneity of difference in % changes between strata***:0.497								
Distance w O2	1-yr before	357 (270, 445)	-	-		454 (363, 566)	-	-	
	baseline	369 (333, 444)	8.8%	-		341 (307, 374)	-26.7%	-	
	1-yr after	329 (262, 397)	-15.3%	-24.1%	0.207	367 (329, 406)	7.9%	34.5%	0.021
	p-value for homegeneity of difference in % changes between strata***:0.013								

* based on predicted values at 1-yr before, at baseline and at 1-yr after estimated from a linear mixed model; ** first % change reported: (baseline-1yr before)/(1yr before); second % change reported: (1 yr after-baseline)/(baseline); *** based on the null hypothesis first % change=second % change;

Conclusions

In this real life national experience:

→ Pirfenidone has been administered even to patients with moderate-severe disease;

→In general population:

- The drug reduces the slope of decrease of FVC% (p= 0,065);

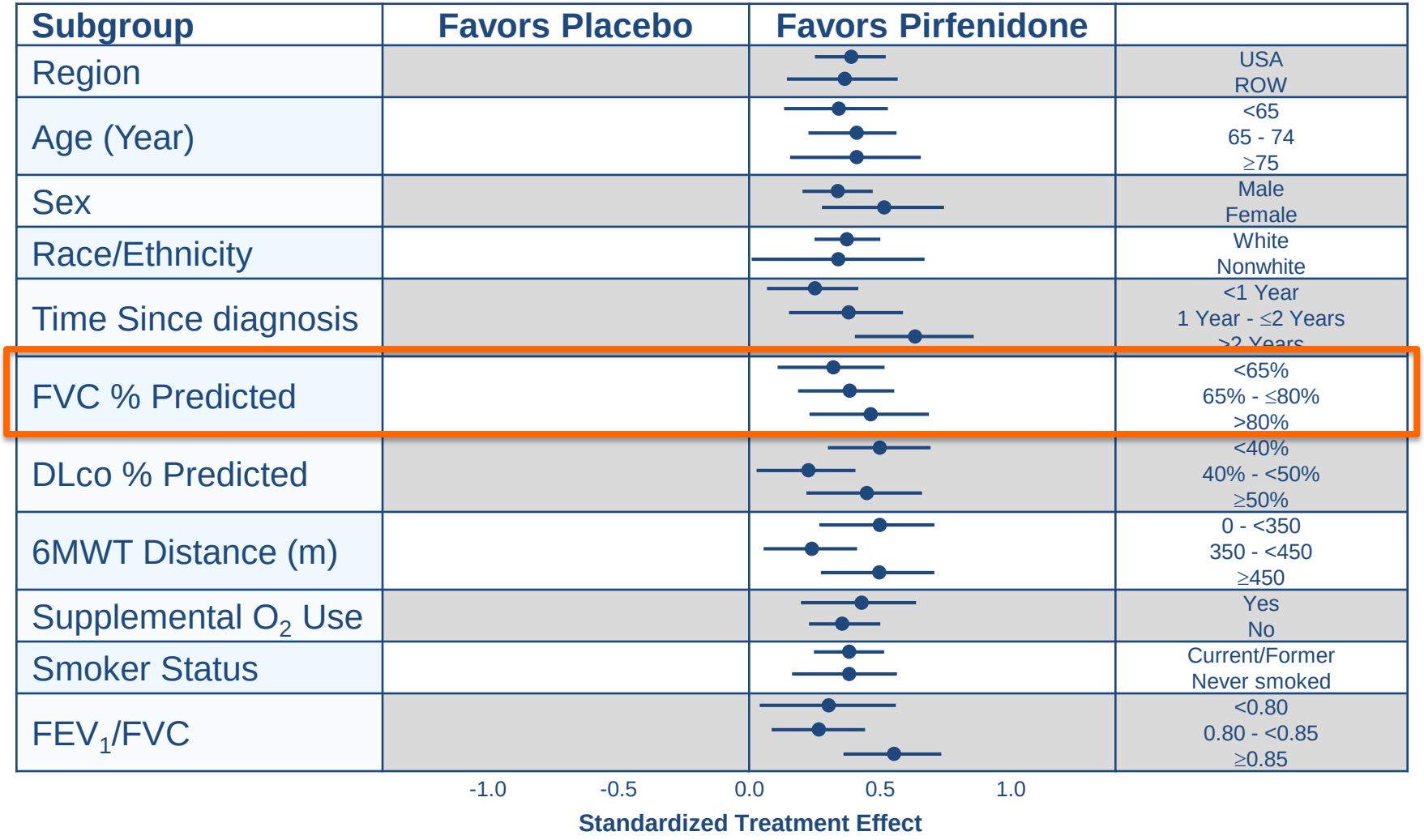
→ Splitting the whole population in two groups according to FVC% (>0,75 or <0,75 at baseline) and GAP index:

- The pirfenidone effect is more evident in moderate-severe patients;

This important findings need further investigations

Treatment effect observed across subgroups:

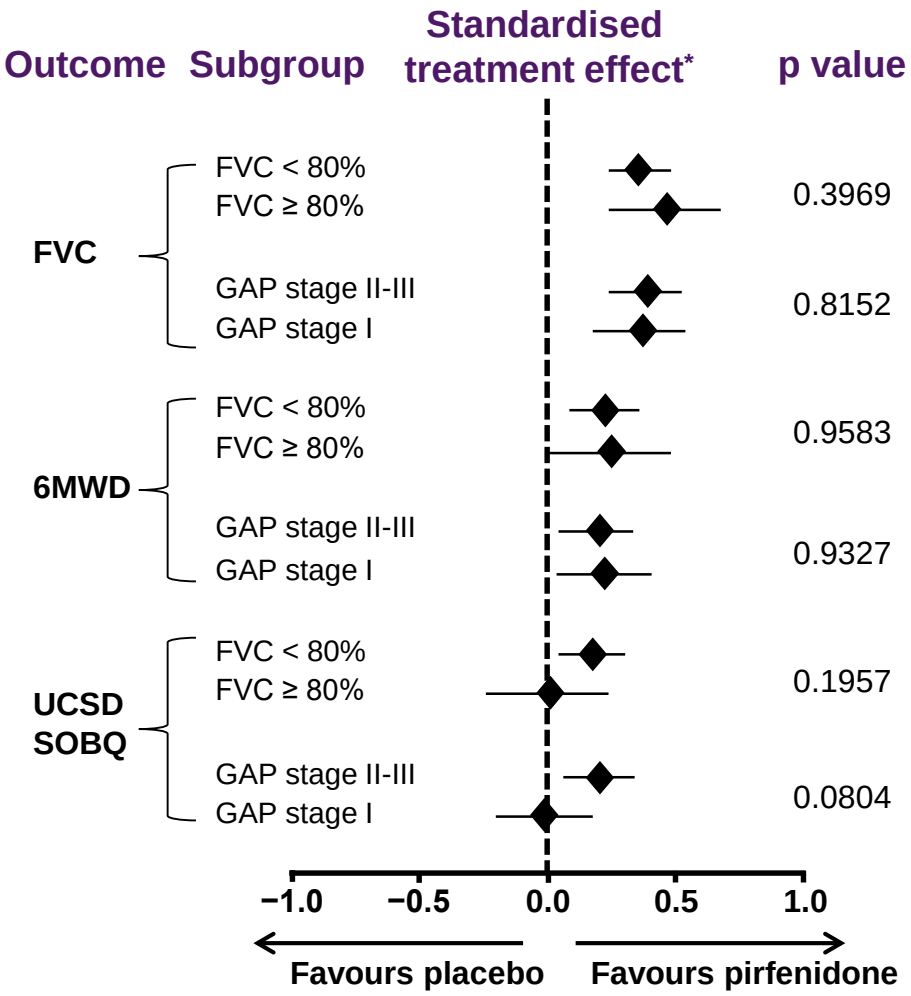
%FVC change at 1 year in the pooled ASCEND and CAPACITY population*†



* Rank ANCOVA Model With Standardized Effects; † Statistical test for interaction provides no evidence that treatment effect is different at different levels of any of the covariates, except time since IPF diagnosis (p=0.034)

TE. King ERS 2014

Pirfenidone has a beneficial effect in patients with FVC ≥80% or GAP stage I



Pirfenidone had a similar effect in patients with FVC ≥80% vs <80% and GAP stage I vs II/III

Pirfenidone is efficaciuos in patients with more preserved lung function

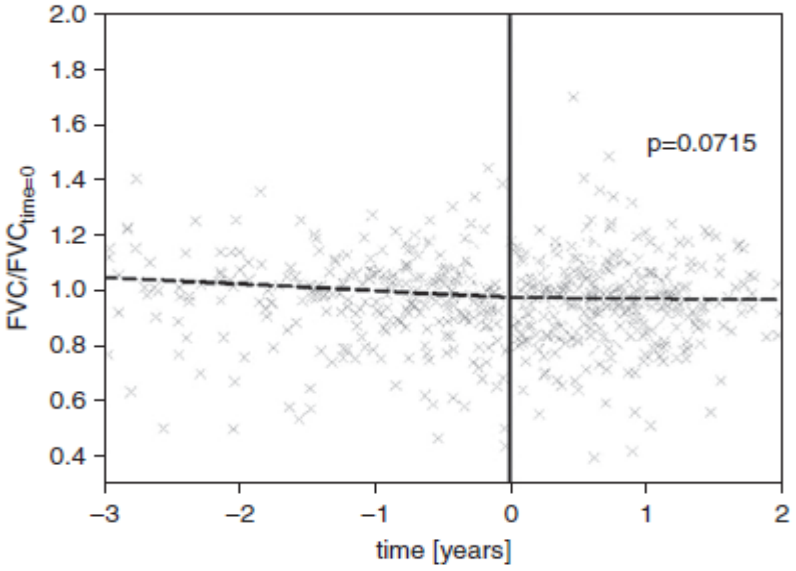
Patients n=1247

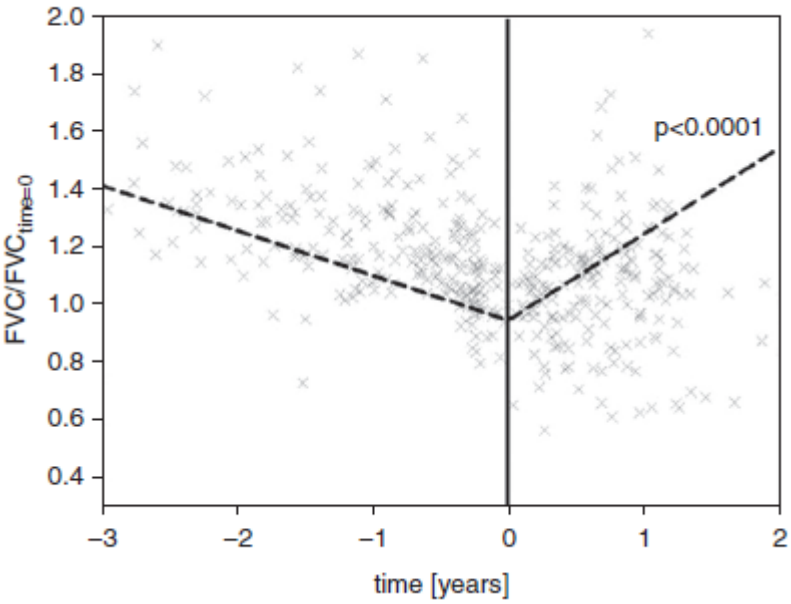
*For FVC and 6MWD: treatment difference = pirfenidone–placebo; for UCSD SOBQ, treatment difference = placebo–pirfenidone

Albera C et al. Eur Respir J 2016;48:843

Intraindividual response to treatment with pirfenidone in idiopathic pulmonary fibrosis

Loeh B et al. Am J Respir Crit Care Med 2015; 191: 110

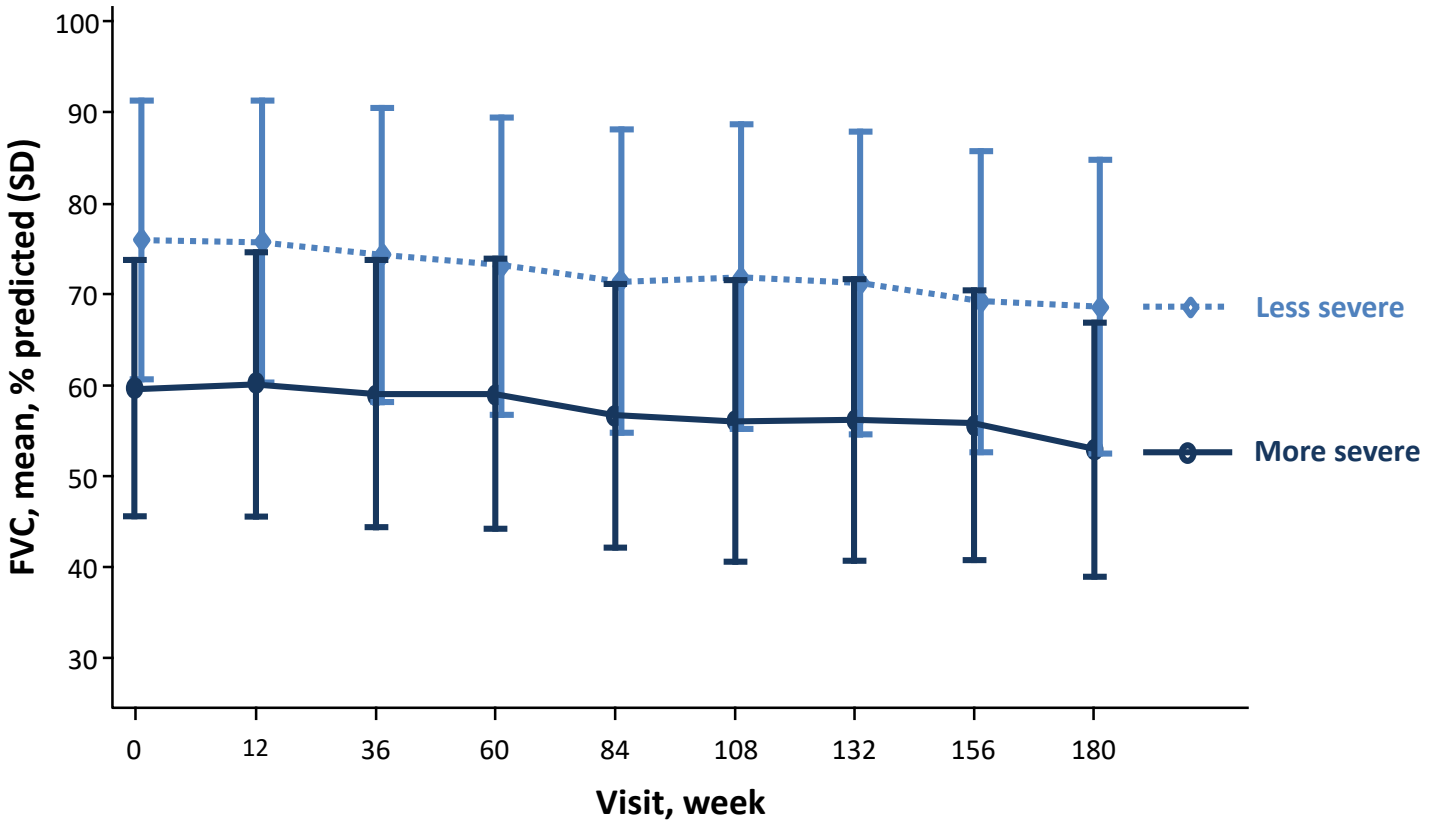




- Two patients cohorts in German and Italy
- Retrospective analysis, **197 pts**
- **R**esponse to pirfenidone in this “real-life” patient cohorts is favorable in the patient population as a whole, but most pronounced in those patients with the greatest decline in FVC evident before treatment.


How to treat severe IPF?
Are pirfenidone and nintedanib indicated also in these patients?

Course of mean FVC over time by severity of lung function impairment at baseline in RECAP

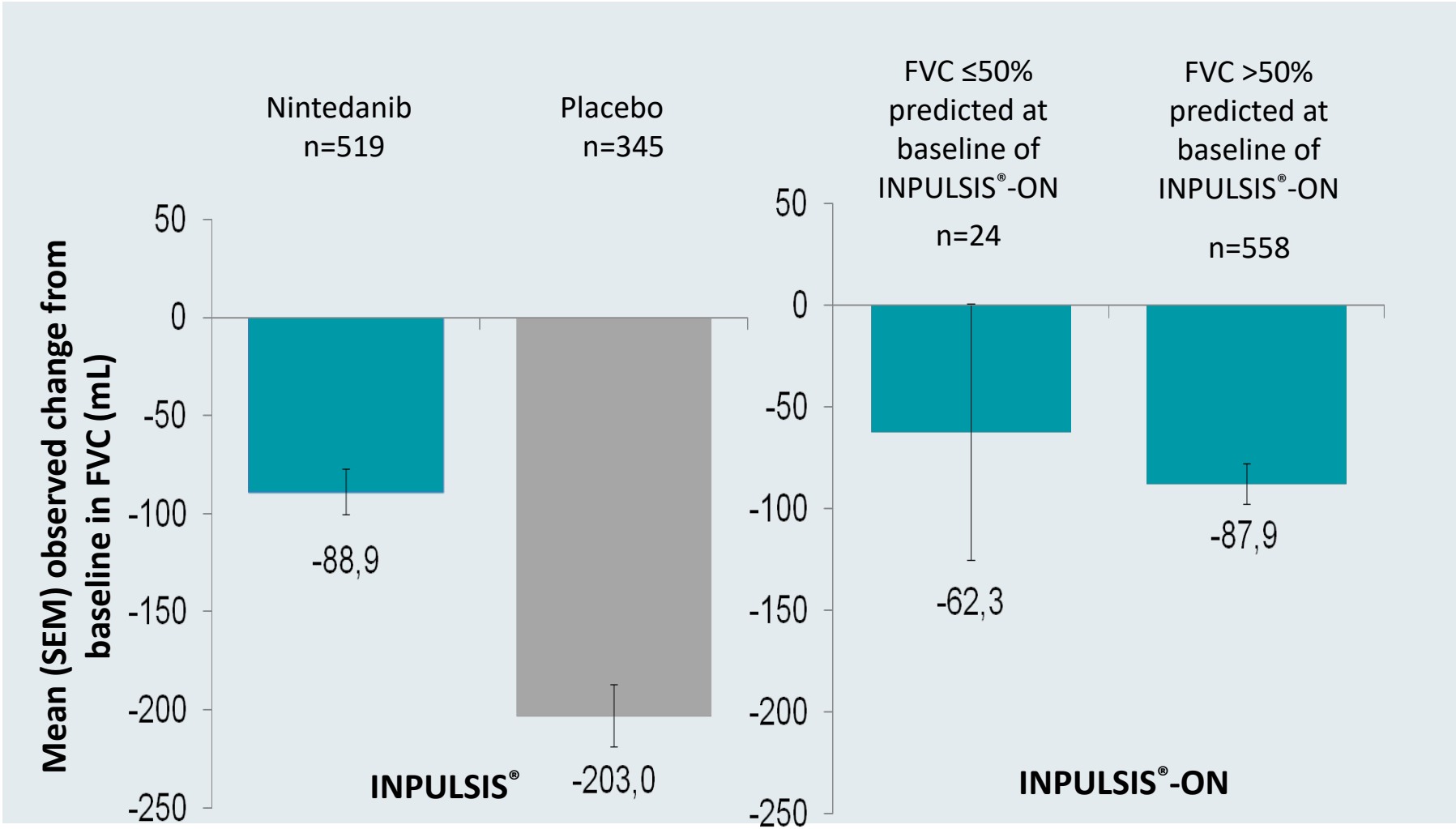


Number of patients*									
Less severe	400	392	376	343	318	287	258	237	208
More severe	184	170	142	117	97	80	67	60	46

* Patients with missing baseline values were excluded.

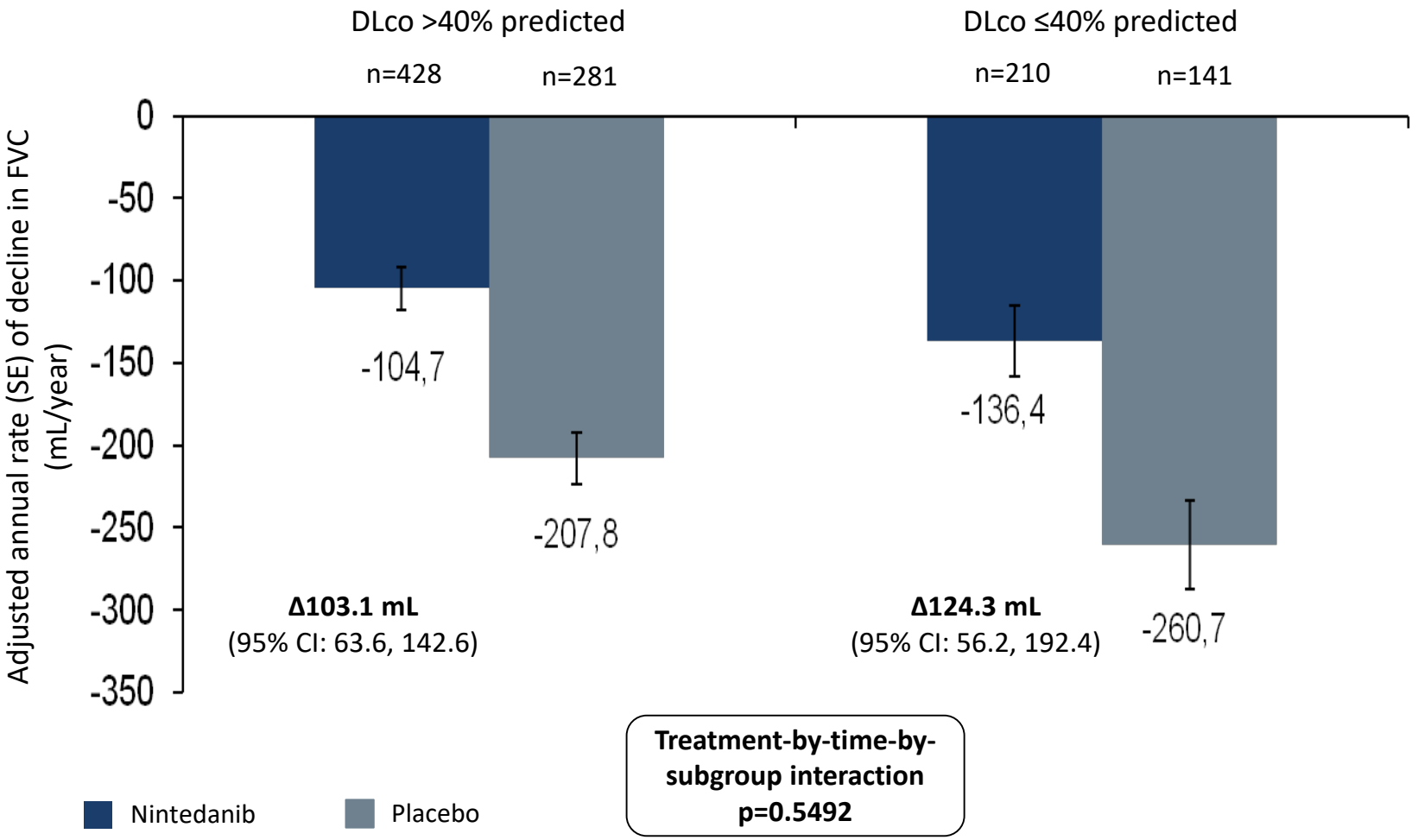
Costabel U. et al. ERS 2016

Change in FVC from baseline to week 52 of INPULSIS® and from baseline to week 48 of INPULSIS®-ON



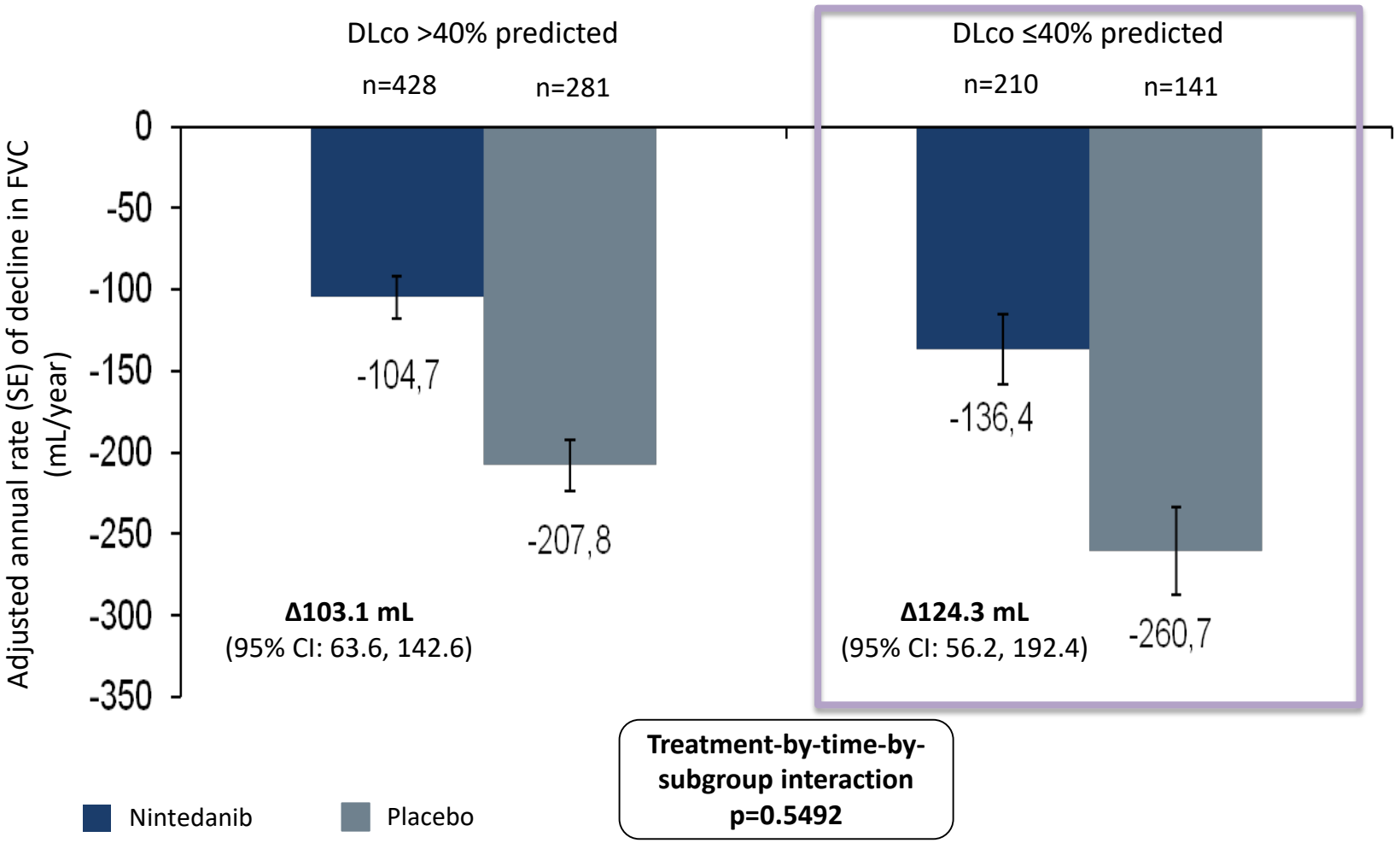
Wuyts WA, et al. Lung 2016

Annual rate of decline in FVC by DLco % predicted at baseline



Maher TM et al. Presented at the European Respiratory Congress 2016 in London

Annual rate of decline in FVC by DLco % predicted at baseline



Maher TM et al. Presented at the European Respiratory Congress 2016 in London

A real life multicenter national study on the use of nintedanib in moderate to severe IPF patients

Harari S, Caminati A, Poletti V, Confalonieri M, Gasparini S, Lacedonia D, Luppi F, Pesci A, Sebastiani A, Spagnolo P, Vancheri C, Balestro E, Bonifazi M, Cerri S, De Giacomi F, Della Porta R, Foschino Barbaro MP, Fui A, Pasquinelli P, Rosso R, Tomassetti S, Specchia C, Rottoli P.

Respiration, 2018; doi: 10.1159/000487711

Matherials and Methods

We conducted a national, retrospective, unsponsored, observational study of patients with IPF treated with Nintedanib

Inclusion criteria:

- Diagnosis (definite or probable) of IPF (according to 2011 IPF guidelines);
- Severe stage of disease (FVC ≤50% e/o DLCO ≤35%, at baseline);
- Availability of functional follow-up data at least 6 (± 2) months before, at the starting therapy point and at least 6 (± 2) months after starting therapy;

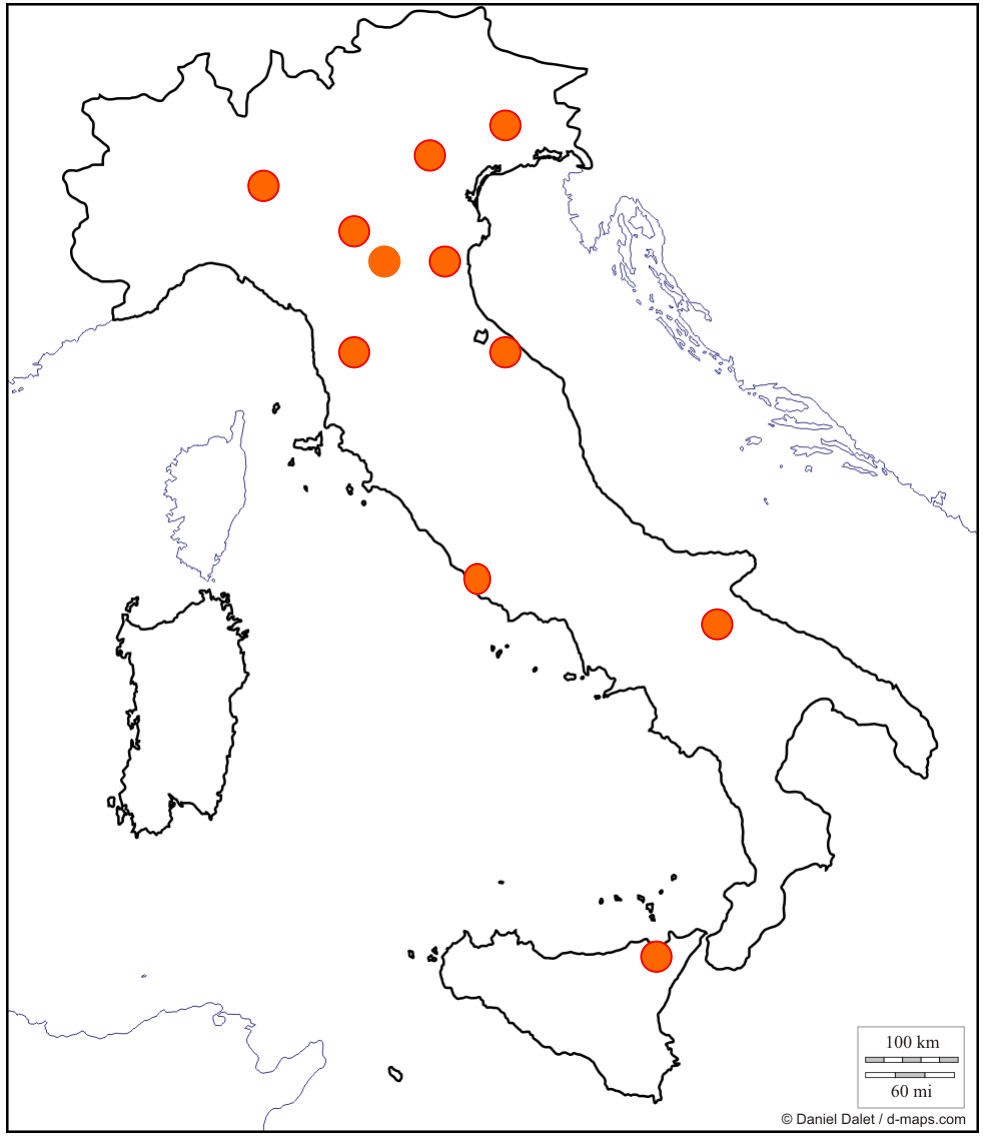
Matherials and Methods

- Primary End-point:
  - Evaluation of the slope of decline of FVC% 6-months before and 6-months after starting nintedanib;

- Secondary End-points:
  - Distance walked on 6MWT; DLCO change

Differences between post and pre-treatment changes of lung function parameters have been tested using Wilcoxon signed-rank test

Patients' characteristics at baseline – first nintedanib prescription (N=41)



Gender N (%)	Female	7 (17)
	Male	34 (83)
Age (years)*	55-64	7 (17)
	65-74	20 (49)
	75+	14 (34)
Smoking status	Ex-smoker	28 (68)
	Non smoker	11 (27)
	Smoker	2 (5)
Histological diagnosis	No	35 (85)
	Yes	6 (15)
Clinical/Radiological diagnosis	Definite UIP	26 (63)
	Probable UIP	13 (32)
	Possible UIP	2 (5)
Cortisone	No	17 (41)
	Yes	24 (59)
Pirfenidone	No	34 (82.9)
	Yes	7 (17.1)
N-Acetylcysteine	No	36 (88)
	Yes	5 (12)
Time from diagnosis (months) ****	0-5	11 (27)
	6-11	12 (29)
	>12	18 (44)

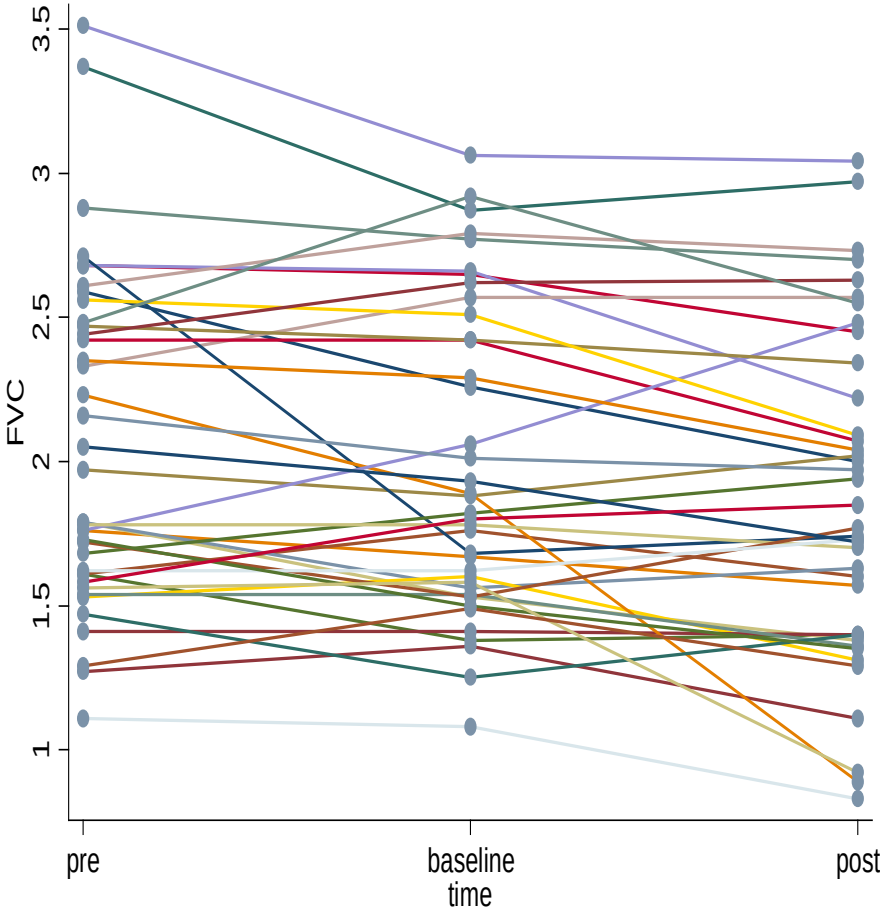
* mean age 70 years ± SD 8 years

** mean time from diagnosis 20 months ± SD 28 months)

PFTs 6 months before, at baseline (first prescription nintedanib) and 6 months after

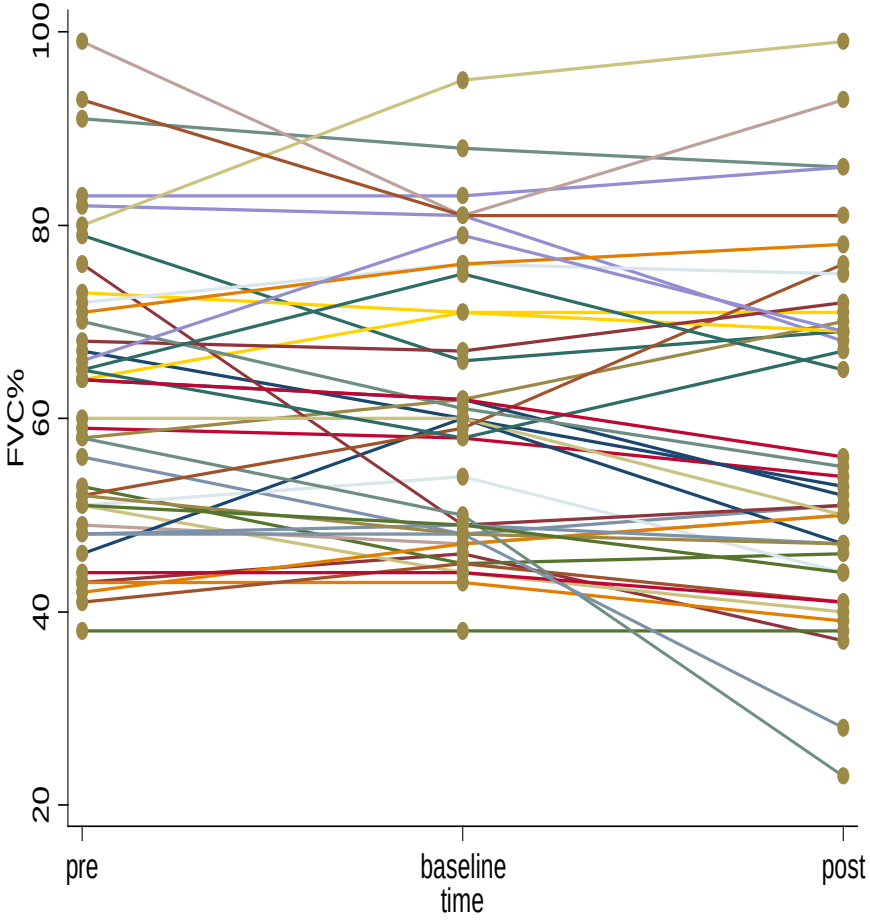
Parameter	N	Time	Mean (SD)	Changes (95%CI)	difference in changes (SD)	p-value
FVC	39	pre	2.05(0.58)	-	-	
	39	baseline	1.99(0.54)	-0.07(-0.15;0.02)	-	
	39	post	1.87(0.58)	-0.12(-0.20;-0.04)	-0.06(0.36)	0.22
FVC %	41	pre	61.83(15.25)	-		
	41	baseline	60.63(14.57)	-1.20(-3.78;1.39)		
	41	post	58.00(17.77)	-2.63(-5.21;-0.06)	-1.44(12.36)	0.34
DLCO	26	pre	32.73(8.56)	-		
	26	baseline	26.54(5.70)	-6.19(-9.26;-3.12)		
	26	post	29.23(12.08)	2.69(-1.54;6.93)	8.88(15.30)	0.004
FEV1	37	pre	1.72(0.45)	-		
	37	baseline	1.70(0.46)	-0.02(-0.10;0.05)		
	37	post	1.60(0.44)	-0.11(-0.18;-0.03)	-0.08(0.38)	0.15
FEV1%	39	pre	67.62(16.02)	-		
	39	baseline	66.67(15.62)	-0.95(-4.43;2.53)		
	39	post	63.62(17.66)	-3.05(-5.64;-0.46)	-2.10(15.62)	0.37
TLC	15	pre	3.85(1.13)	-		
	15	baseline	3.78(1.03)	-0.07(-0.34;0.20)		
	15	post	3.73(1.01)	-0.05(-0.48;0.38)	-0.02(1.07)	1
TLC%	17	pre	59.06(13.73)	-		
	17	baseline	58.71(13.46)	-0.35(-4.34;3.64)		
	17	post	57.65(13.16)	-1.06(-6.60;4.48)	-0.71(15.74)	0.83

ΔFVC as absolute value



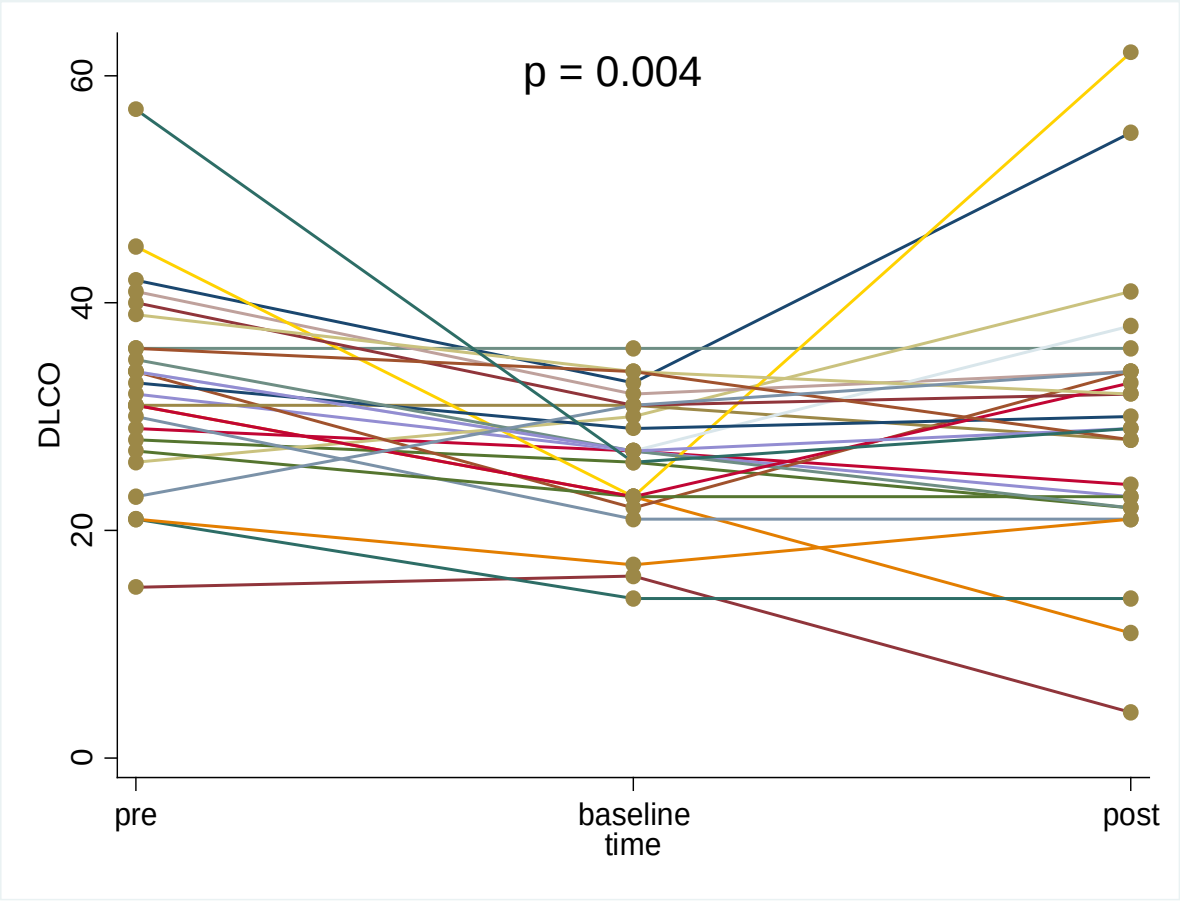
p = 0.22

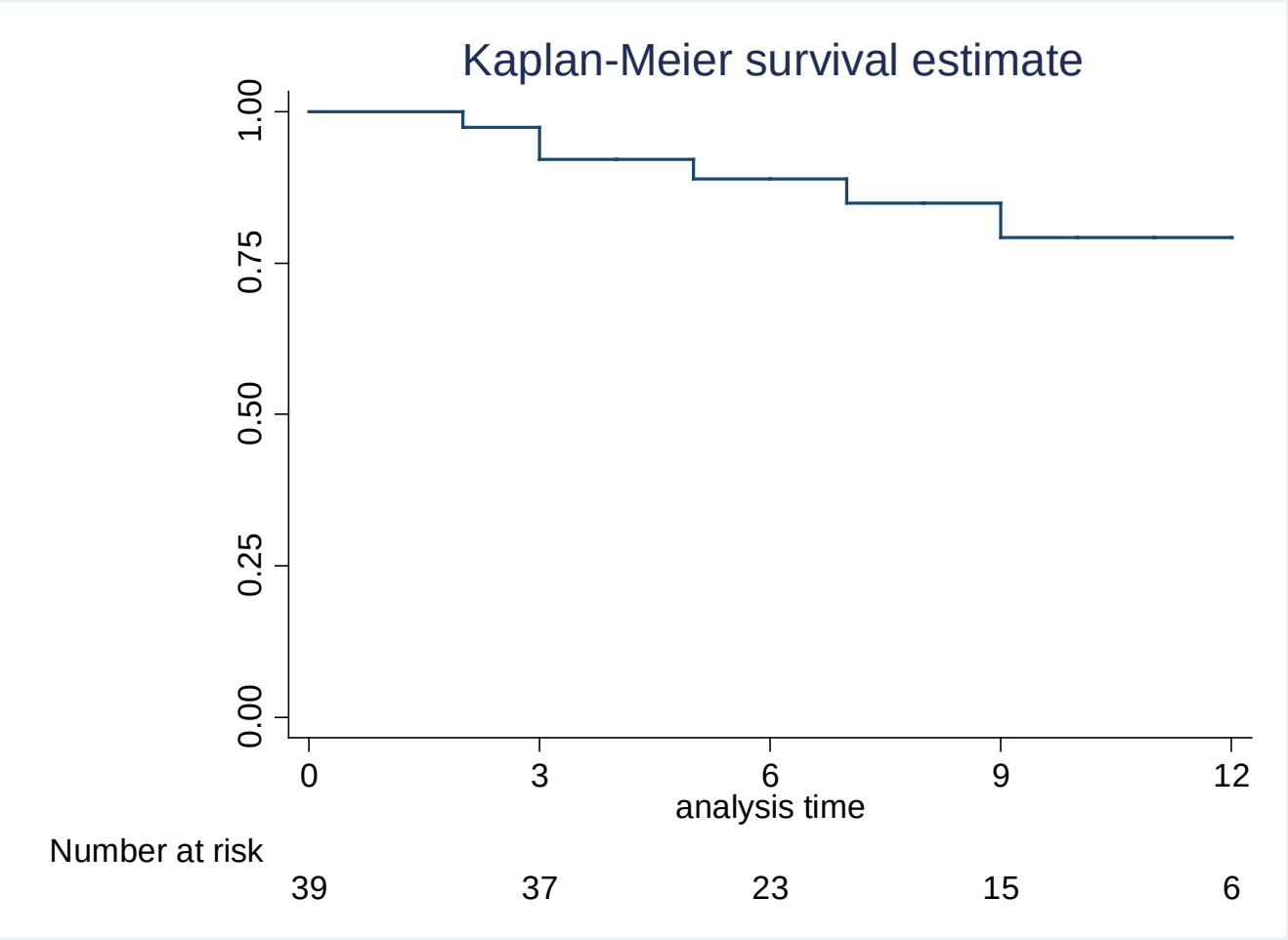
ΔFVC as percent of the predicted value



p = 0.34

Δ DLCO pre, at baseline and post 6 months (N=26)





Survival at 3 moths **0.92** [95% CI: 0.78 - 0.97]
Survival at 6 months **0.89** [95% CI: 0.73 - 0.96]
Survival at 12 months **0.79** [95% CI: 0.58 - 0.91]

Conclusions

This nationwide multicenter experience in patients with severe IPF shows that nintedanib slows down the rate of decline of absolute and % predicted DLCO, but does not impact significantly on the decline of FVC or other lung function parameters.


How predict the course of disease?

The prognostic role of Gender-Age-Physiology system in idiopathic pulmonary fibrosis patients treated with pirfenidone

Harari S , Caminati A, Confalonieri M, Poletti V, Vancheri C, Pesci A, Rogliani P, Luppi F, Agostini C, Rottoli P, Sanduzzi Zamparelli A, Sebastiani A, Della Porta R, Salton F, Messore B, Tomassetti S, Rosso R, Biffi A, Puxeddu E, Cerri S, Cinetto F, Refini RM, Bocchino ML, Di Michele L, Specchia C, Albera C for the ILDINET (Interstitial Lung Diseases Italian Network).

Clin Respir J, under review

Matherials and Methods

We conducted a national, retrospective, unsponsored, observational study

Inclusion criteria:

All patients who received at least 6 months of treatment with pirfenidone and who had pulmonary function data available at six months after pirfenidone initiation where included in the study and followed up.

Purpose of this study was ***the validation*** of the GAP system evaluated after six months of pirfenidone therapy in predicting the subsequent risk of death in an Italian population of patients affected by IPF.

The primary outcome was all-cause mortality ascertained. Lung transplantation was treated as a competing risk.

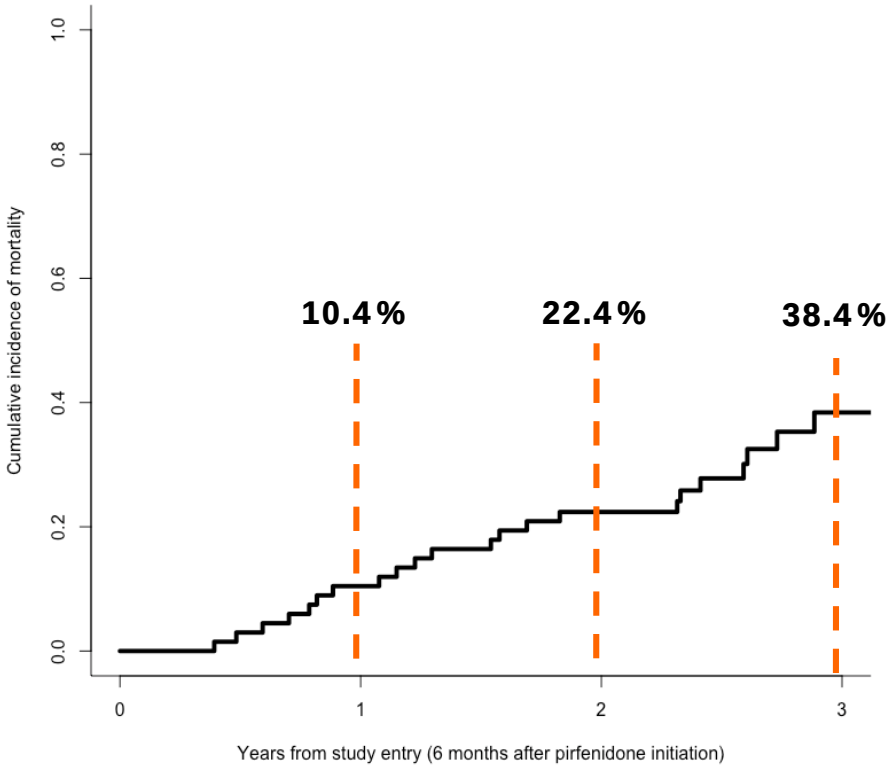
Patients' characteristics (N=68)

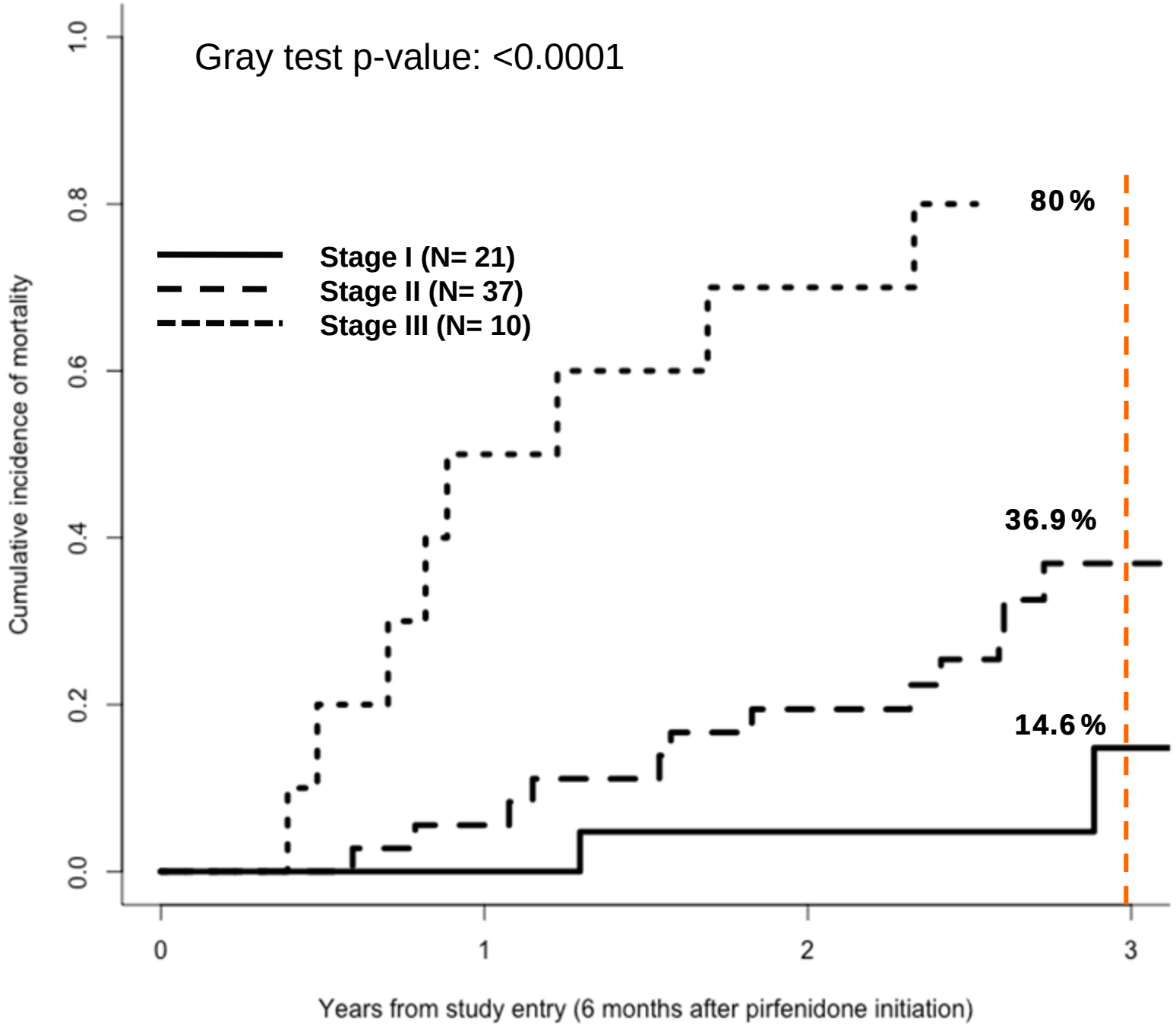
Characteristic	Levels	N (%)
Gender	Female	16 (24)
	Male	52 (76)
Age (years)*	≤60	7 (10)
	61-65	12 (18)
	>65	49 (72)
Smoking status	Ex-smoker	50 (74)
	Non smoker	15 (22)
	Smoker	3 (4)
Histological diagnosis	No	49 (72)
	Yes	19 (28)
Cortisone	No	27 (40)
	Yes	41 (60)
Azathioprine	No	50 (74)
	Yes	18 (26)
N-Acetylcysteine	No	38 (56)
	Yes	30 (44)
Time from diagnosis of IPF to start of pirfenidone therapy (years) **	< 1	22 (32)
	1-2	24 (35)
	>2	22 (32)

* Mean age: 69 years (SD: 7.9 years)
** Mean time from diagnosis of IPF to initiation of treatment with pirfenidone: 2 years (SD: 1.9 years)

Cumulative incidence of mortality

Median follow-up time: 2.4 ys
22 deaths (32%)
10 lung transplantation (15%)




Gray test p-value: <0.0001
Stage I (N= 21)
Stage II (N= 37)
Stage III (N= 10)
80 %
36.9 %
14.6 %
Cumulative incidence of mortality
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
Years from study entry (6 months after pirfenidone initiation)

GAP-index and staging system: a simple point-score model and staging system

(provides a simple screening method for determining the average risk of mortality of patients by GAP stage)

GAP-calculator: individual risk calculator

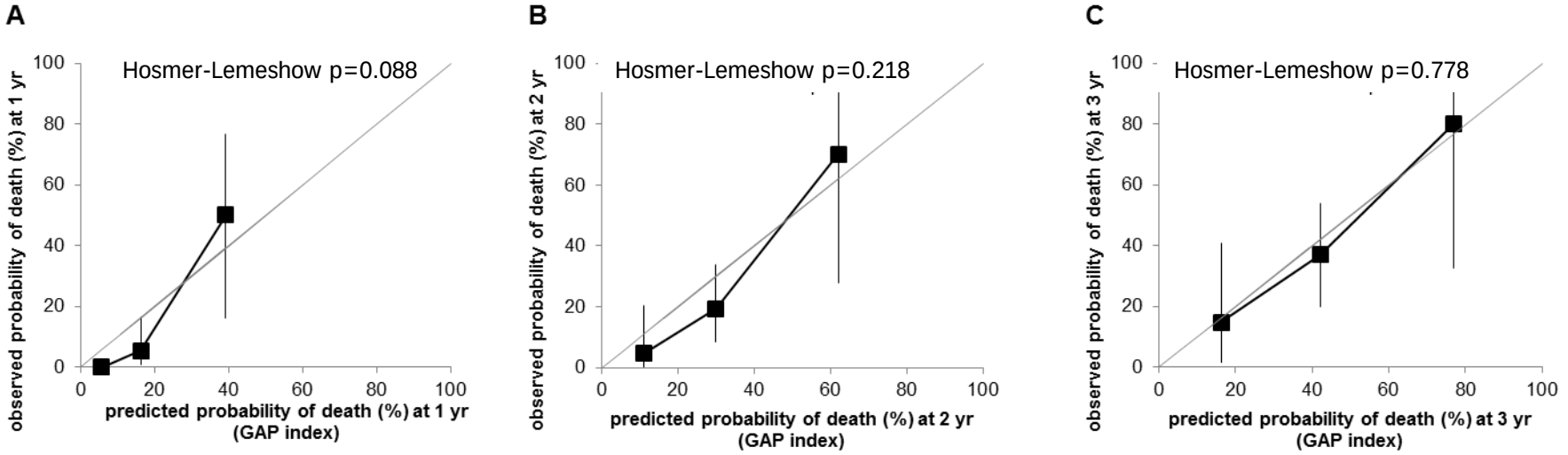
(provides an estimation of individual risk of mortality for those patients in whom a more precise estimation of risk may further inform patient care)

Ley B et al. Ann Intern Med 2012; 156: 684-691

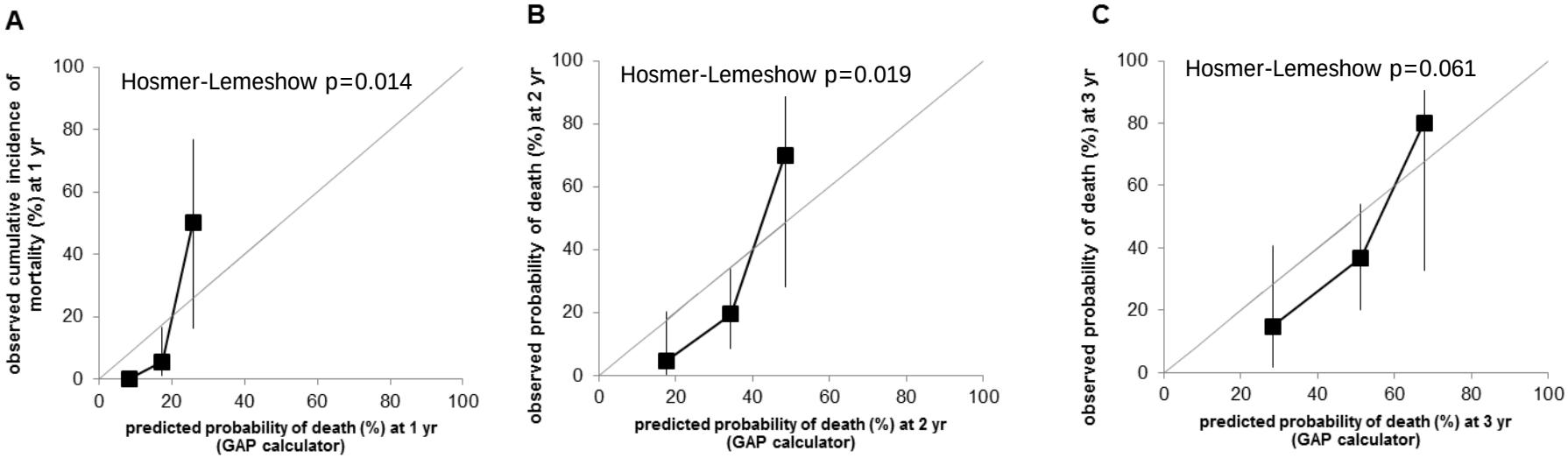
Comparison of predicted and observed cumulative incidence of mortality

Year	GAP stage	Predicted by GAP index	Predicted by GAP Calculator	Observed
1	I	5.6	8.4	0.0
	II	16.2	17.2	5.5
	III	39.2	25.8	50.0
2	I	10.9	17.6	4.7
	II	29.9	34.2	19.4
	III	62.1	48.4	70.0
3	I	16.3	28.3	14.8
	II	42.1	51.2	36.9
	III	76.8	67.8	80.0

GAP index calibration plots



GAP calculator calibration plots



In our cohort, the GAP system was more accurate in predicting mortality than the GAP calculator

The difference between the predicted and observed variables suggests that there may have been important factors (treatment or comorbidities) that were not captured by the GAP model

The re-assessment of the GAP system in the era of new therapies for IPF is an important topic

Conclusions

- It is critical that we continue to encourage patients with IPF to participate in clinical trials of new drug agents that will undoubtedly add benefit to our initial therapies
- Patients with IPF continue to await a cure for their disease, and the unmet medical needs remains high
- With the emergence of novel and effective therapy for patients with IPF, it is clear that IPF care will evolve significantly over the next few years
- Real world studies evaluate the ***effectiveness*** of drugs and may play a role in improving our clinical understanding and practice; ***their role is specific and complements RCTs*** and other forms of research.