Attualità nella terapia della FPI

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Conflict of interests disclosures

Actelion

Boehringer Ingelheim

Roche

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?

Cyclophosphamide

Pirfenidone

Ambrisentan
Sitaxestan

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

Currently, where is no a cure for IPF

Today, we have a therapy

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 (not 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

New antifibrotic Treatments Indicated for Idiopathic Pulmonary Fibrosis offer hopes and Raises Questions

Raghu and Selman, AJRCCM, Feb 1 2015

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***

Some answers:

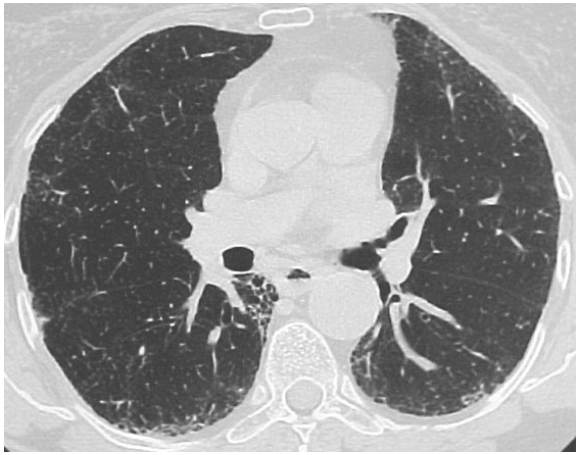
- positive long term effect of both drugs
- well tolerated in patients in “real world”
- also in severe disease
- well tolerated also in combination

When to treat

IPF is a progressive disease

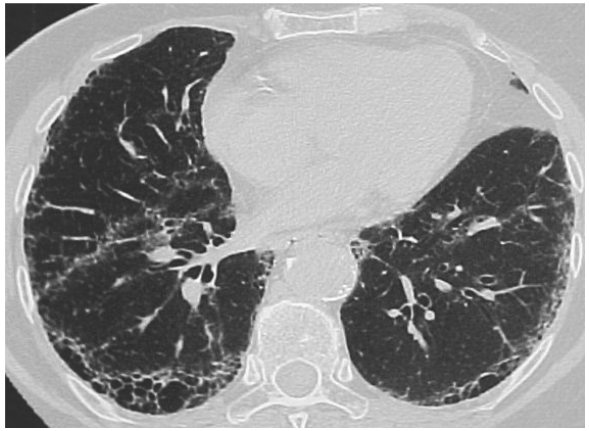
Early:

Reticular



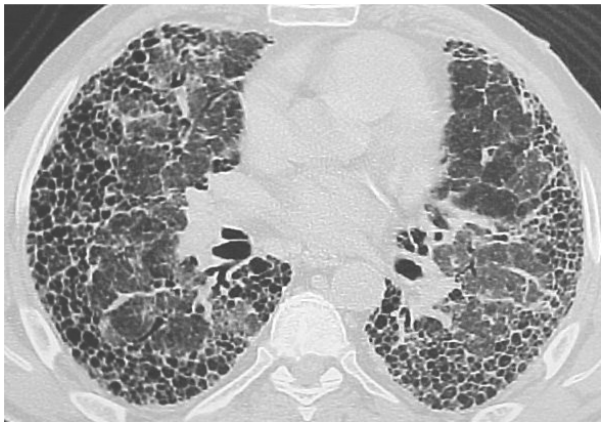
Midcourse:

Subpleural honeycombing



Late:

Diffuse honeycombing



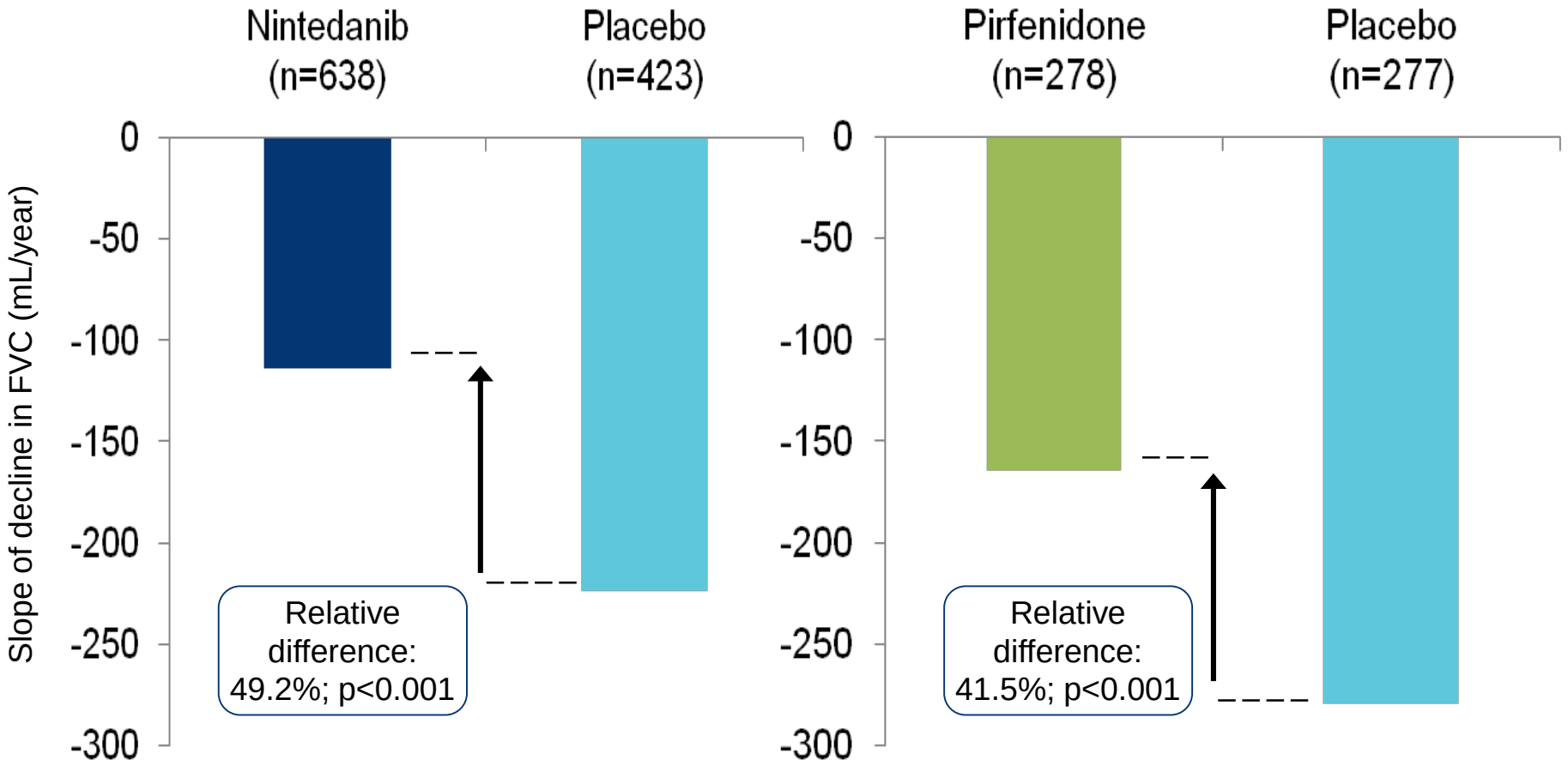
Benefits of early diagnosis

- Due to the progressive nature of IPF, timely diagnosis and immediate initiation of treatment results in significant benefits for patients with IPF
- Treatment of IPF aims to:
  - slow disease progression
  - improve long-term outcomes

- An early diagnosis is important also for:
  - begin earlier evaluation for lung transplantation
  - exclude other more treatable diseases
  - prolong survival

Ley B et al. *Am J Respir Crit Care Med.* 2011;183:431-440
Raghu G, et al. *Am J Respir Crit Care Med.* 2015;192:e2-e19

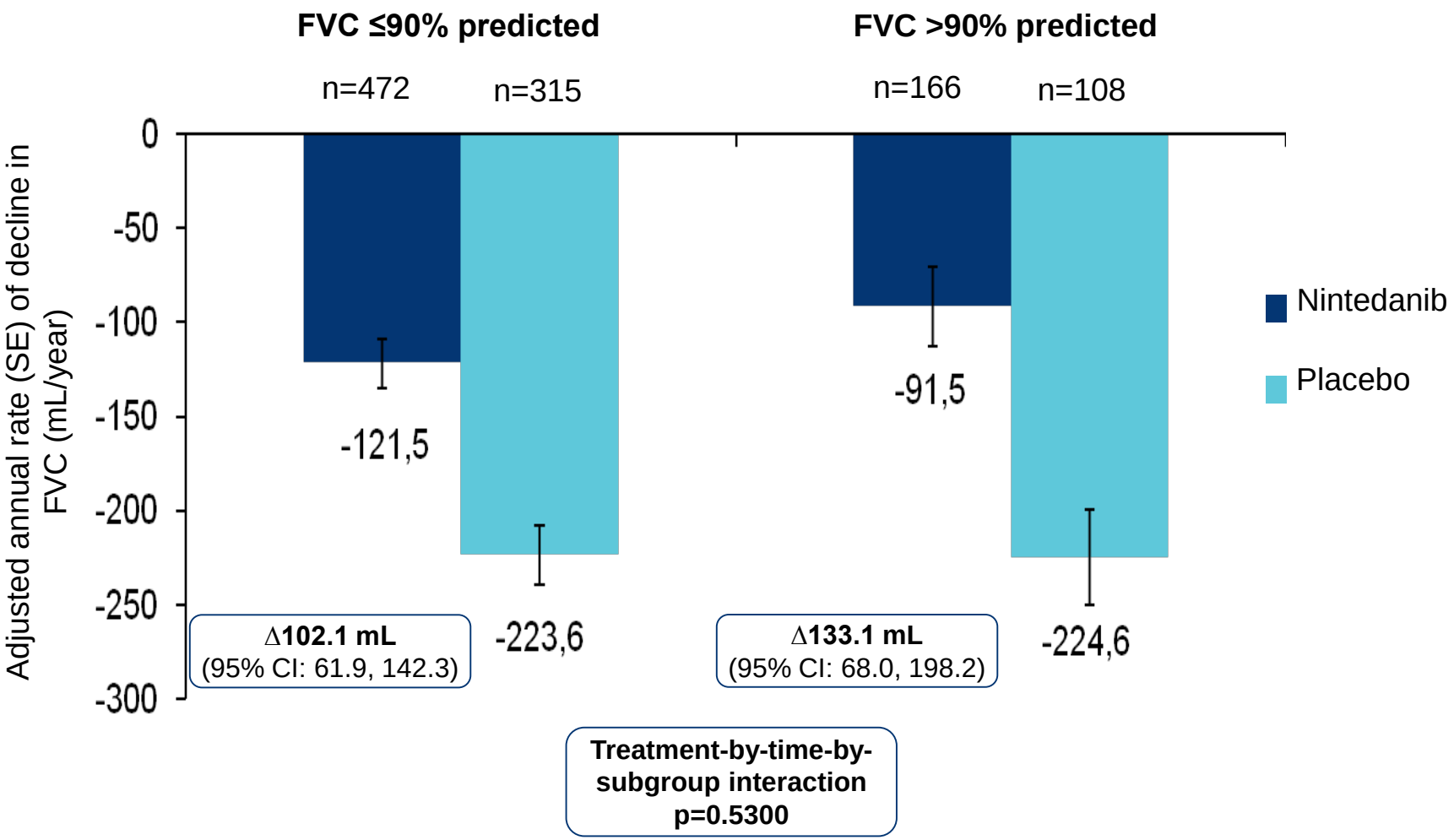
Nintedanib and pirfenidone slow disease progression in IPF



Richeldi L et al. N Engl J Med 2014;370:2071-82.

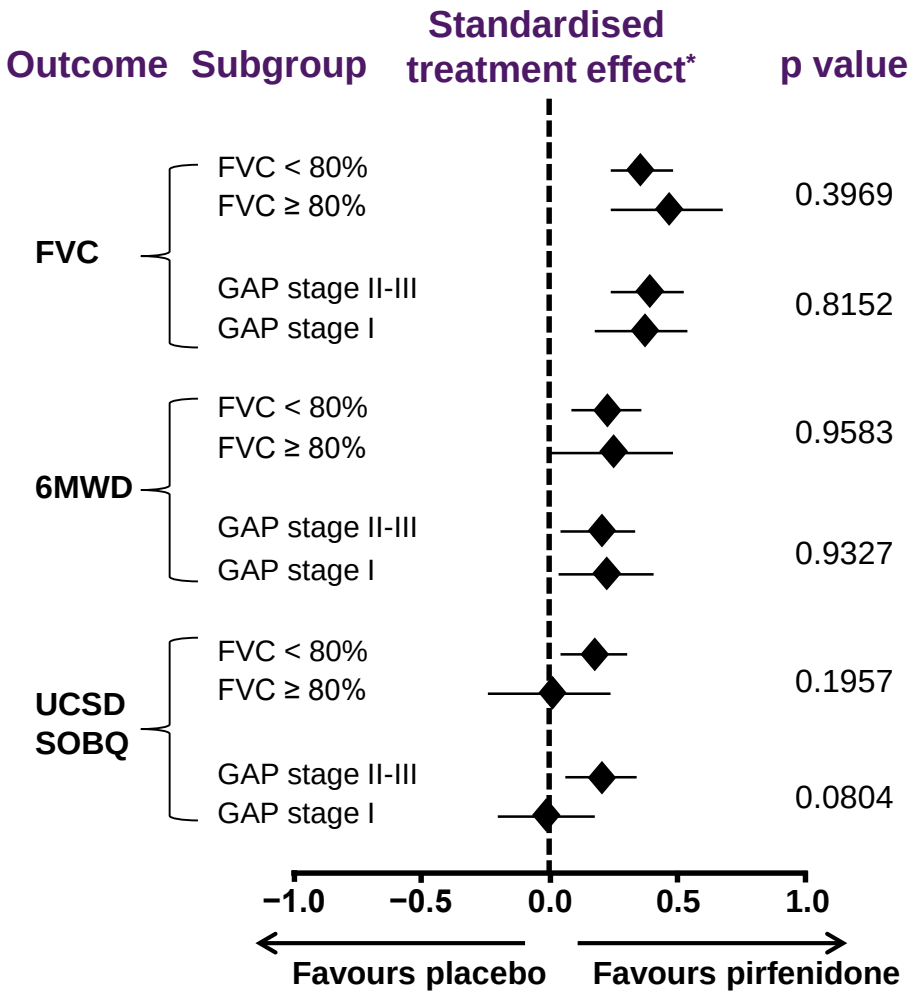
King TE Jr et al. N Engl J Med 2014;370:2083-92.

Nintedanib slows disease progression in patients with preserved lung volumes



Kolb M et al. Thorax 2017;72:340–346.

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

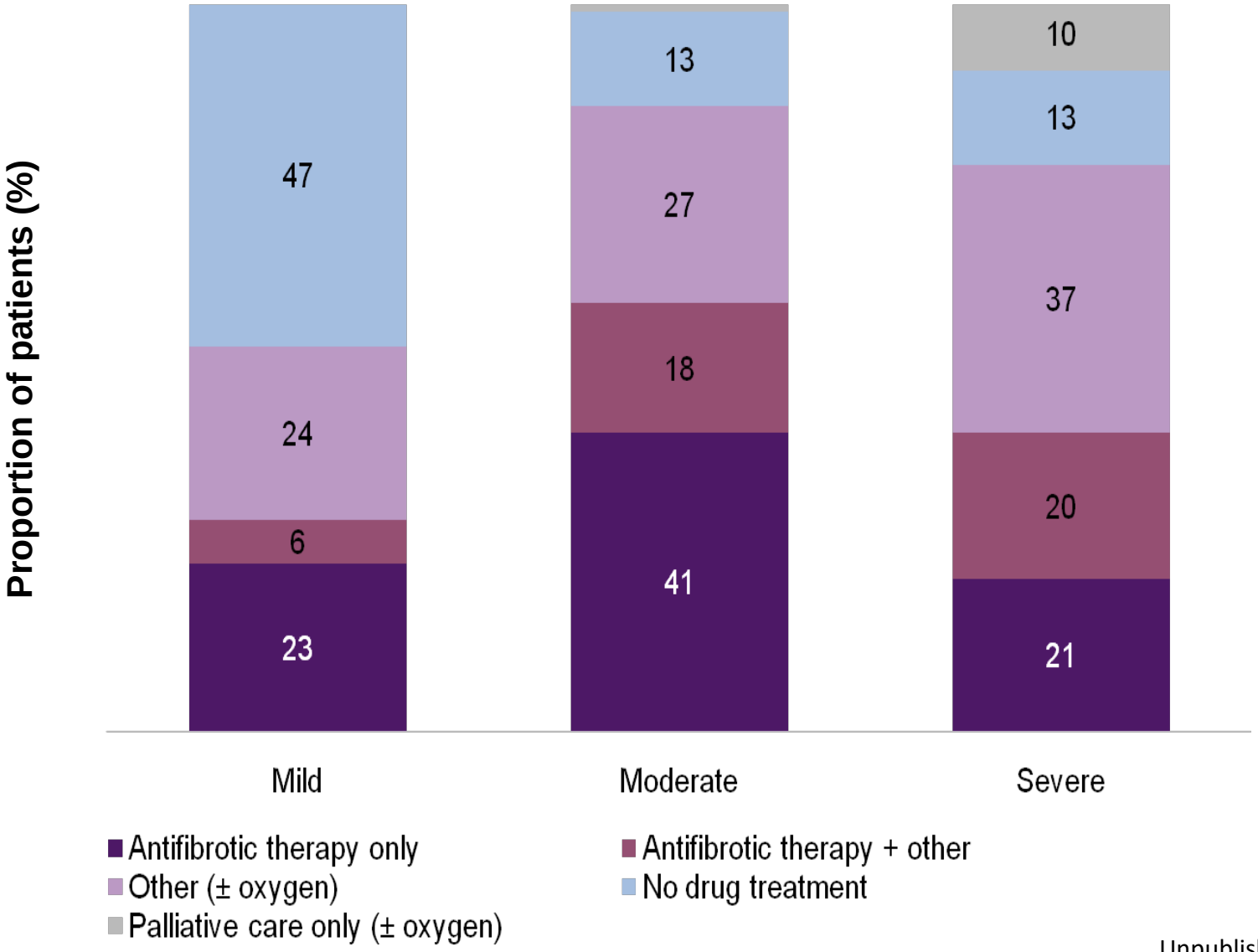
Pirfenidone is efficaciuos in patients with more preserved lung function

Patients n=1247

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

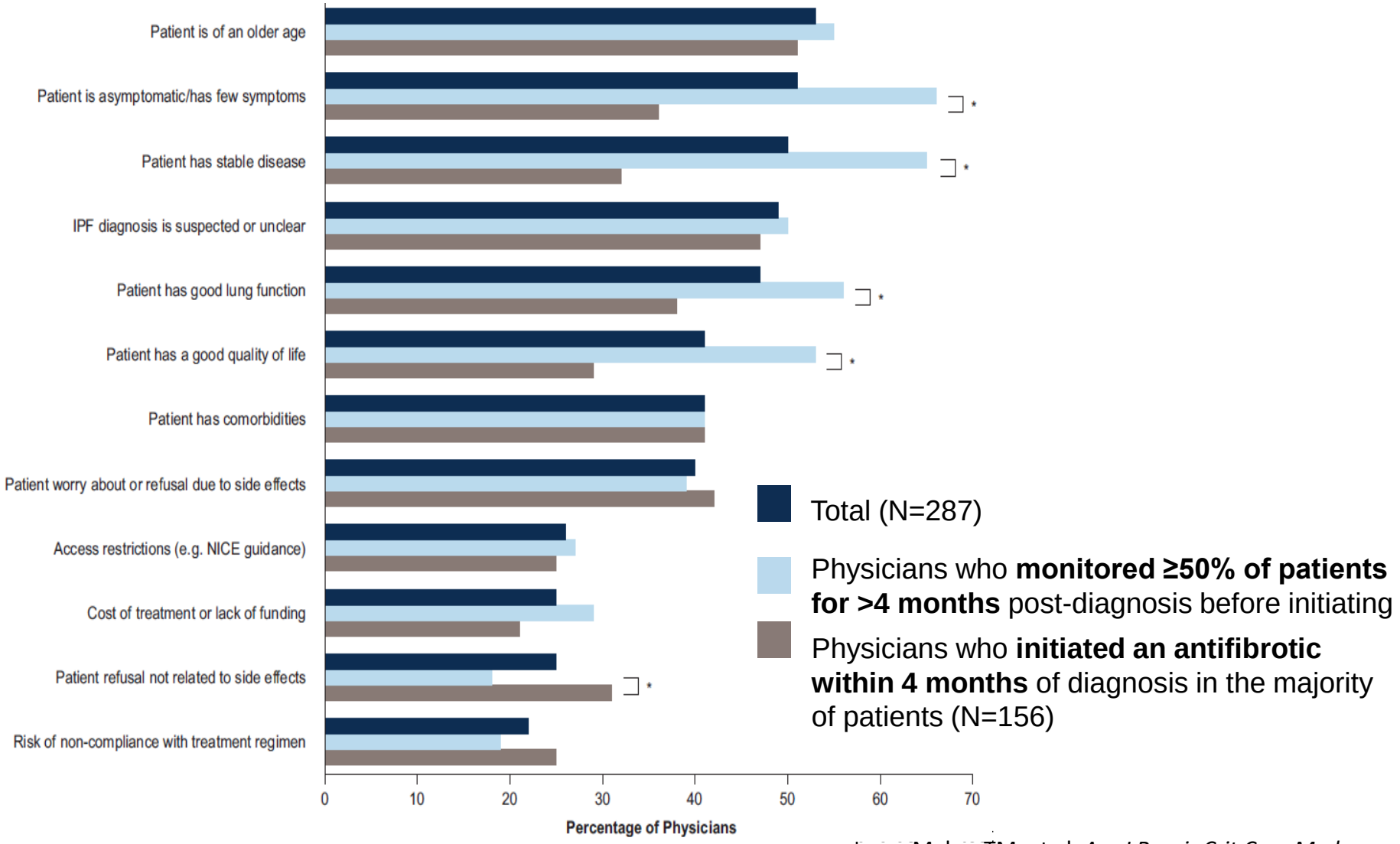
Albera C et al. Eur Respir J 2016;48:843

Patients with mild IPF are less likely to receive treatment



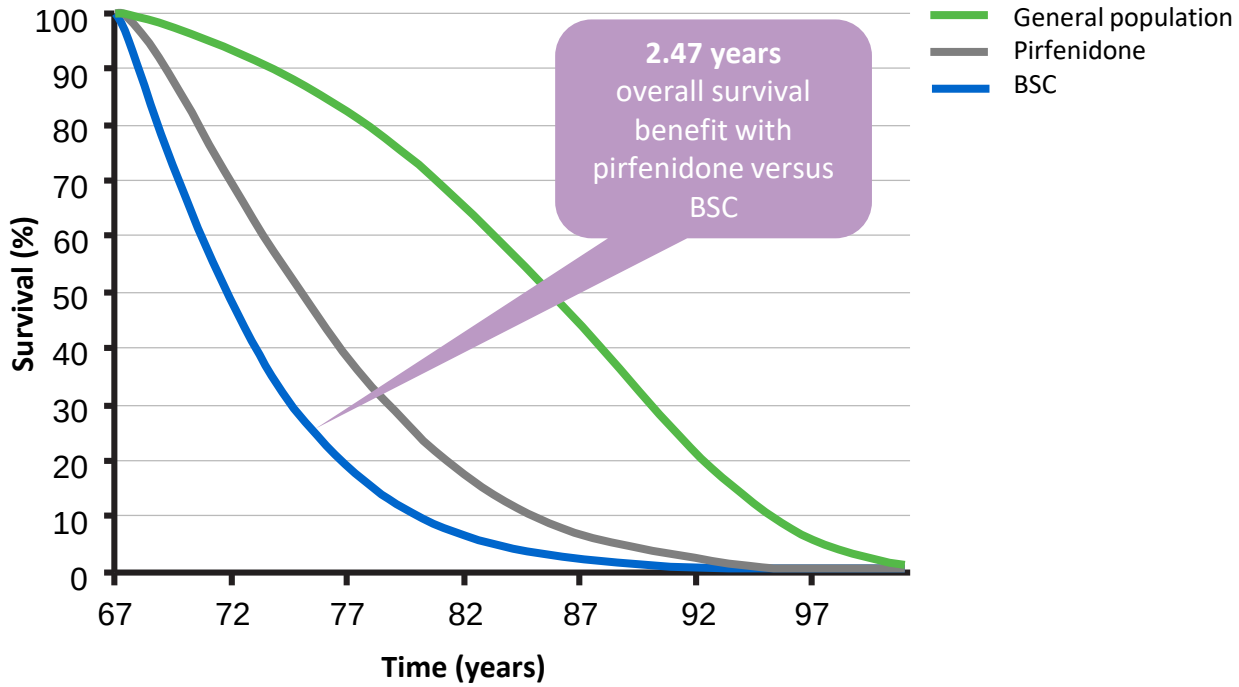
Unpublished data

Reasons cited by physicians for not treating patients with mild IPF



Maher TM, et al. *Am J Respir Crit Care Med* 2017;195:A1123

Transforming the IPF therapeutic landscape



BSC, best supportive care
Data are from a model based on life-long adherence

Fisher M, et al. *J Manag Care Spec Pharm.* 2017;23:S17-S24

How to treat

Which drug do I choose?

	Nintedanib	Pirfenidone
Efficacy (primary endpoint comparison)	~50% slowing of disease progression	~50% slowing of disease progression
Safety	Elevated AST/ALT, MI	Elevated AST/ALT
Tolerability >20%	Diarrhea, nausea	Nausea, rush, diarrhea, fatigue, headache
Dosing	Two times daily	Three times daily
Patient type	Broader population (some possible IPF)	Narrower population (excluded some IPF)
Patient preference	?	?

FVC ≥ 50% and DLCO ≥ 30%

Yrs ≤80; FVC ≥ 50% and DLCO ≥ 35%; 6MWT ≥ 150 m

TEAEs leading to discontinuation in pirfenidone and nintedanib trials

% patients	CAPACITY and ASCEND trials		TOMORROW and INPULSIS trials	
	Pirfenidone (N=623)	Placebo (N=624)	Nintedanib (N=723)	Placebo (N=508)
Any TEAE,%	99.0	97.9	95.3	89.8
Any serious TEAE, %	27.0	28.5	30.0	30.1
Any TEAE leading to treatment discontinuation, %	**14.6**	**9.6**	**20.6**	**15.0**

Main reasons for discontinuation:

- Diarrhoea (5.3%)
- Nausea (2.4%)
- Progression IPF (2.1%)
- Decreased appetite (1.5%)

Most common reasons for treatment discontinuation were:

- Worsening of IPF (11.5%)
- Rash (2.2 %)
- Nausea (1.7%)
- Photosensititivity (0.5%)

While a large proportion of patients experience AEs, the rate of AEs is not a key element to adherence

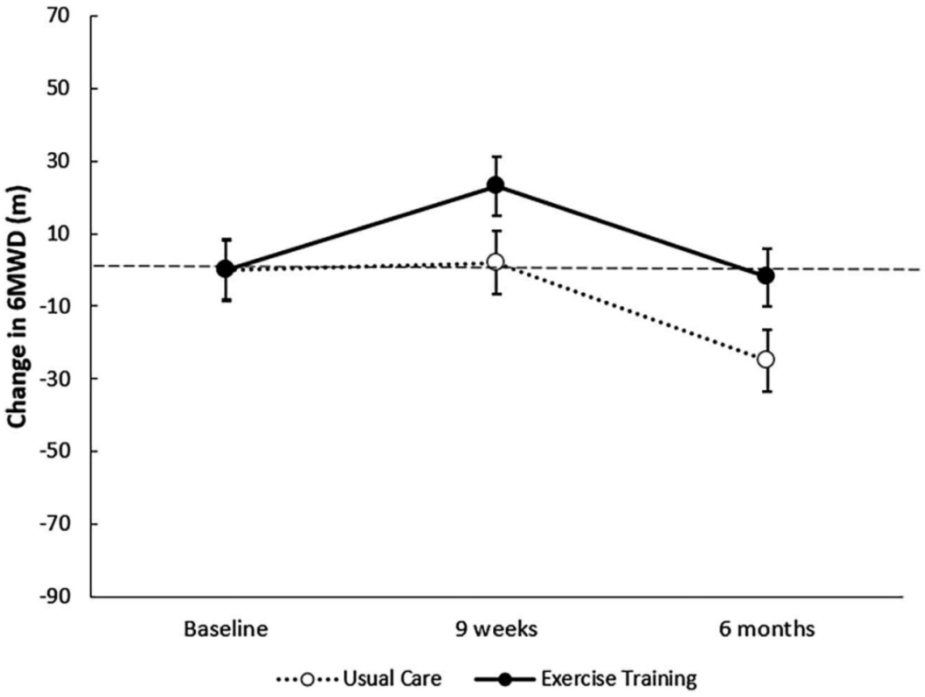
AE, adverse event; TEAE, treatment-emergent adverse event

Lancaster L, et al. *BMJ Open Respir Res* 2016;3:e000105;
Richeldi L, et al. *Respir Med* 2016;113:74–79;
Cottin V. *Exp Opin Drug Safety* 2017;16:857–865

Pulmonary rehabilitation recent data

Results

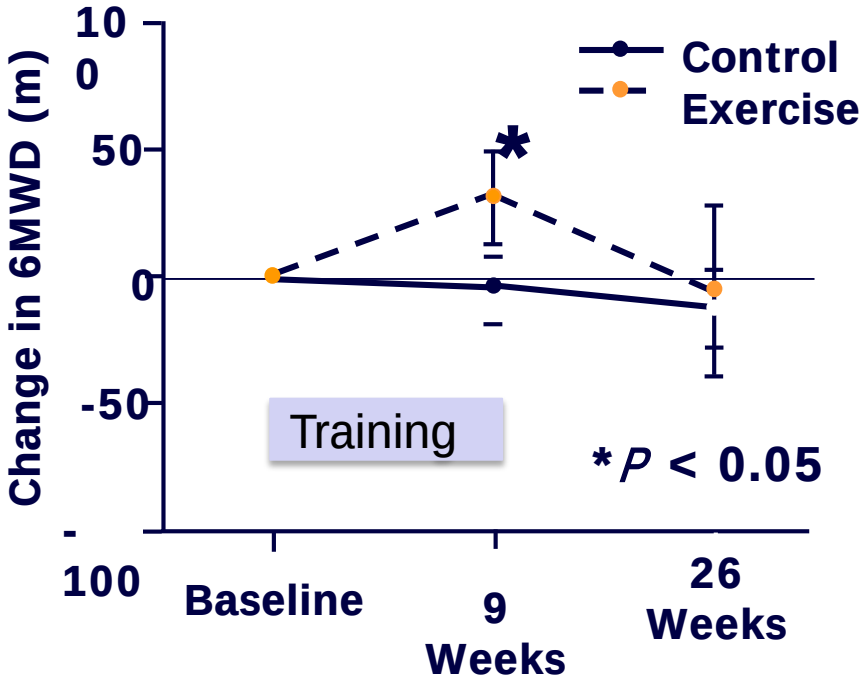
- Exercise resulted in clinically important improvement in:
  - 6MWD
  - Symptoms
  - HRQoL
- Most convincing for:
  - Asbestosis
  - IPF
- To a lesser extent CTD-ILD
- Successful adherence maximises the benefits



CTD-ILD, connective tissue disease-ILD; HRQoL, health-related quality of life

Dowman LM, et al. *Thorax.* 2017;72:610–619

Exercise training effect on 6MWD



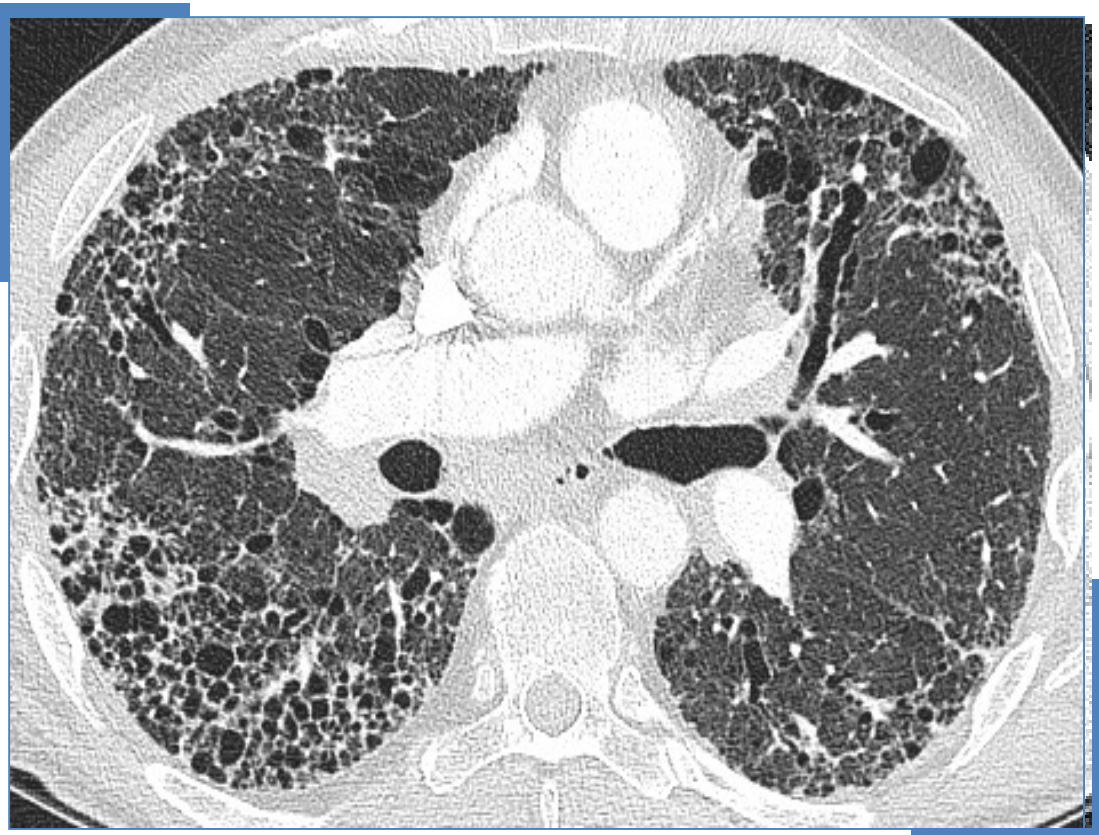
57 subjects (34 with IPF) randomized to 8 weeks of PR or weekly telephone support

- Conclusions
  - -- Exercise training improves exercise capacity and symptoms in patients with ILD
  - – Benefits are not sustained at 6 months

Holland AE, et al. ***Thorax.*** **2008;63:549-554.**

About treatment con/discontinuation

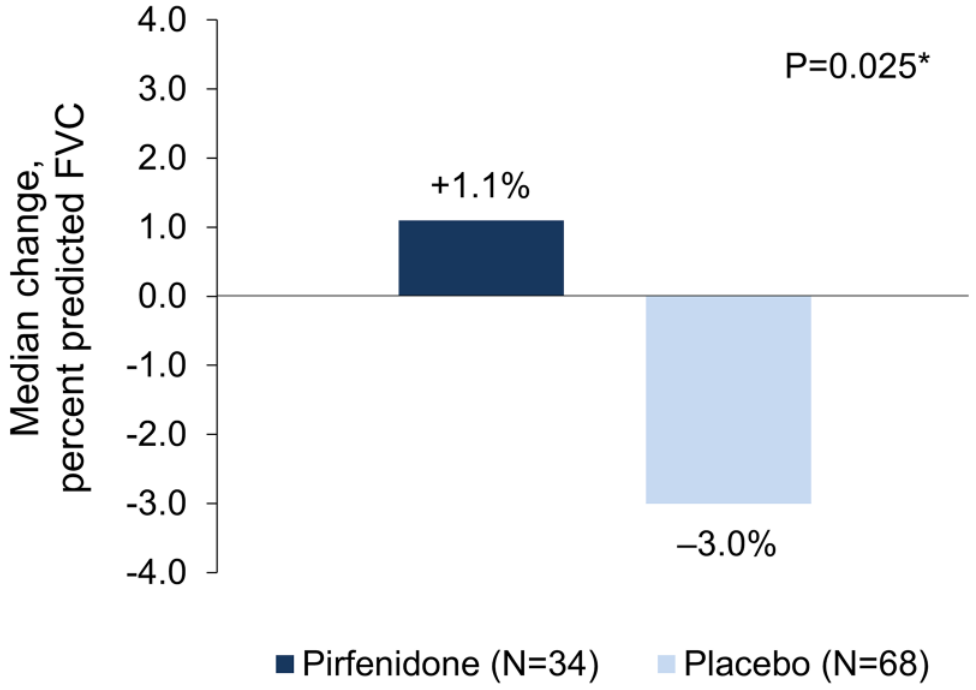
IPF – the challenge



Effect of continued treatment with pirfenidone following clinically meaningful declines in forced vital capacity: analysis of data from three phase 3 trials in patients with idiopathic pulmonary fibrosis

Nathan SD et al. Thorax 2016; 71: 429

	Pirfenidone (N=34)	Placebo (N=68)	P value
≥10% decline in FVC or death	2(5.9%)	19 (27.9%)	0.009
No further decline in FVC	20 (58.8%)	26 (38.2%)	0.059
Death	1 (2.9%)	14 (20.6%)	0.18



Outcome after 6 months of continued treatment following an initial decline in %predicted FVC ≥10%

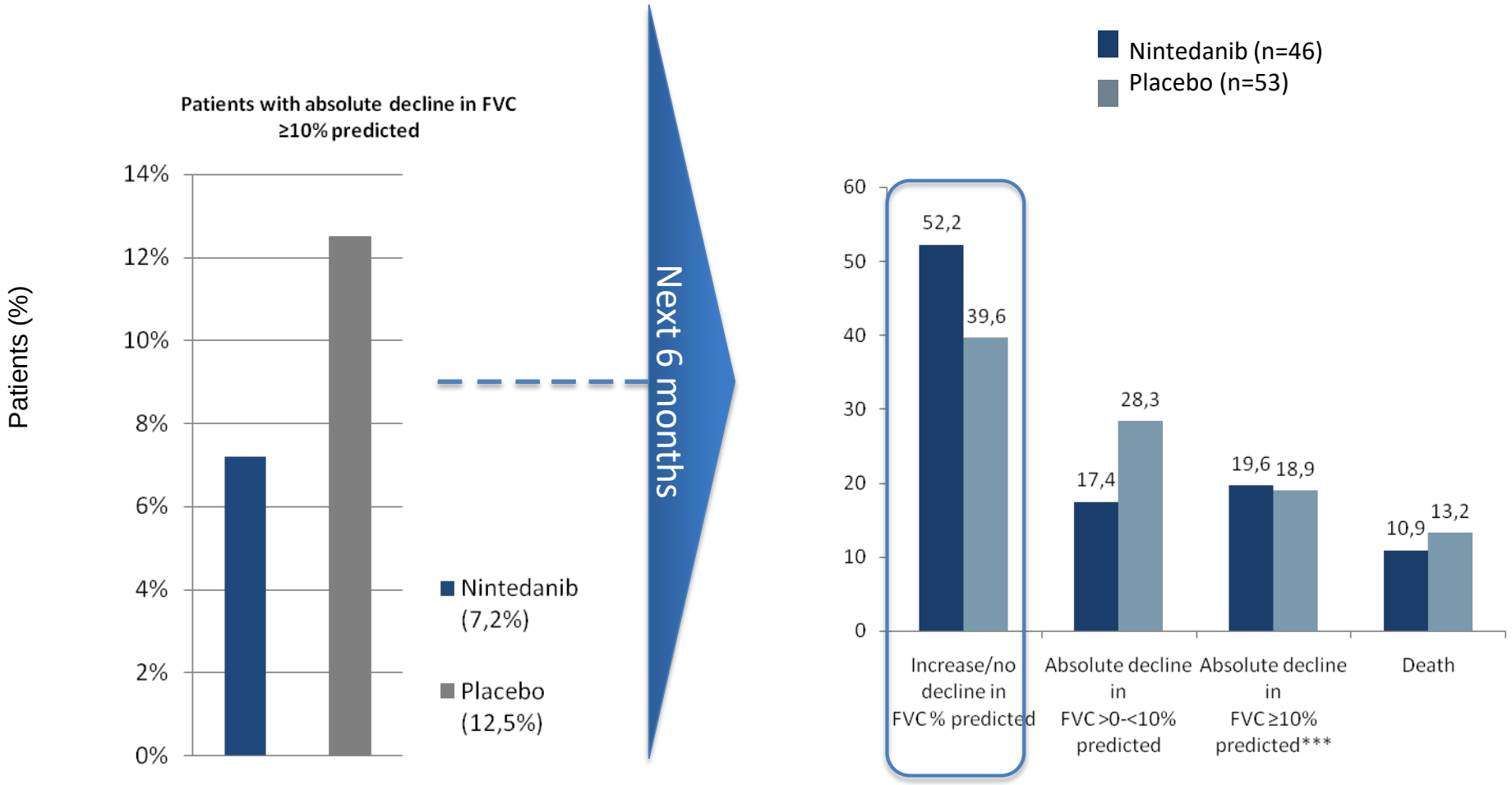
Effect of continued treatment with pirfenidone following clinically meaningful declines in forced vital capacity: analysis of data from three phase 3 trials in patients with idiopathic pulmonary fibrosis

Nathan SD et al. Thorax 2016; 71: 429

Conclusions: Longitudinal FVC data from patients with IPF showed substantial intrasubject variability, underscoring the inability to reliably assess therapeutic response using serial FVC trends.

In patients who progressed during treatment, continued treatment with pirfenidone resulted in a lower risk of subsequent FVC decline or death.

Patients treated with nintedanib with absolute decline in FVC ≥10% predicted in the first 6 months* and their outcome in the next 6 months**



* from baseline to week 24 ** between week 24 and week 52 ***Includes patients with missing FVC data at week 52 for reasons other than death.

Modify from: Richeldi L et al. Presented at the European Respiratory Congress 2016 in London

Nintedanib with add-on pirfenidone in idiopathic pulmonary fibrosis: results of the INJOURNEY trial

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

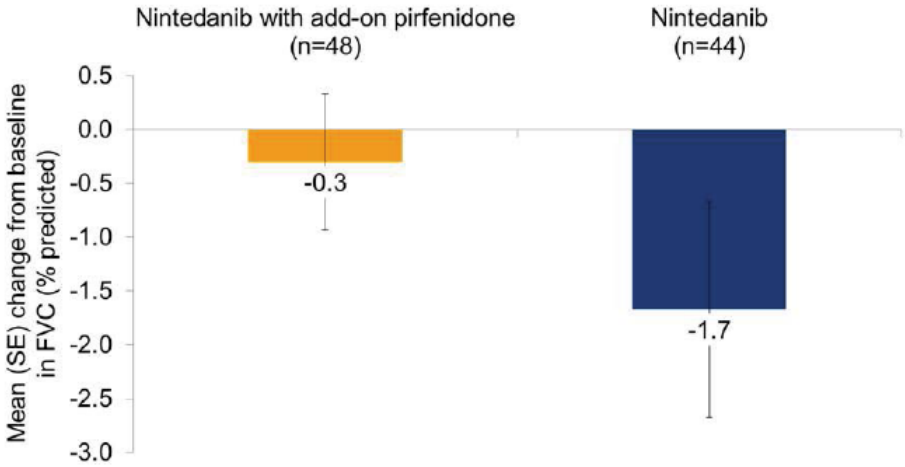
- Nintedanib with add-on pirfenidone had a manageable safety and tolerability profile in patients with IPF, in line with the adverse event profiles of each drug

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

Vancheri et al. Am J Respir Crit Care Med 2017

Nintedanib with add-on pirfenidone in idiopathic pulmonary fibrosis: results of the INJOURNEY trial

- Pre-dose plasma trough concentrations of nintedanib were similar at each time point, irrespective of whether nintedanib 150 mg bid was administered alone or with add-on pirfenidone.
- A smaller numerical decline in FVC over 12 weeks was observed in patients treated with nintedanib with add-on pirfenidone compared with nintedanib alone.
- However, as this trial was not powered for this endpoint and was too short for conclusions to be drawn about the efficacy of combination therapy, these findings should be interpreted with caution

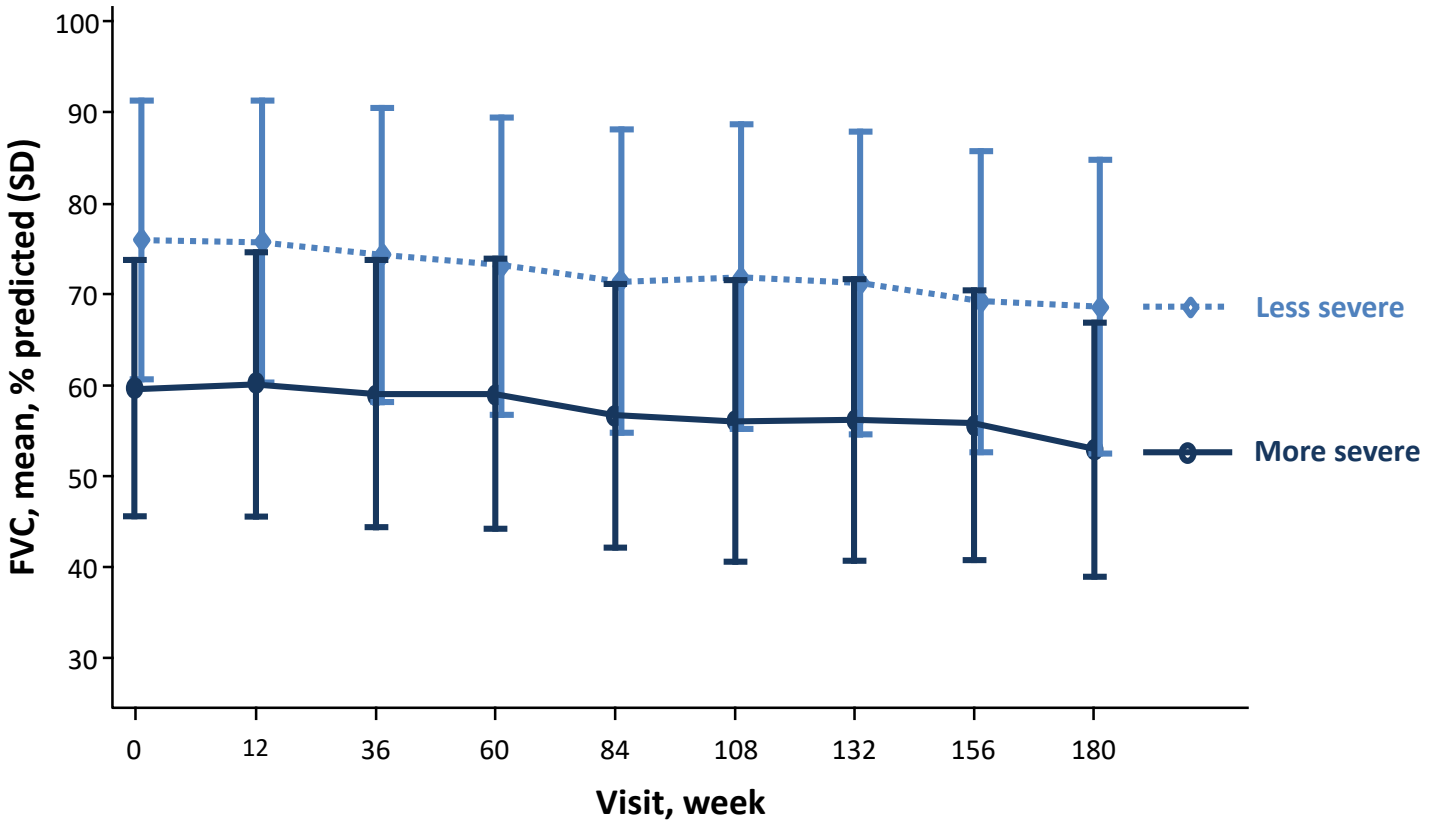


Vancheri et al. Am J Respir Crit Care Med 2017

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

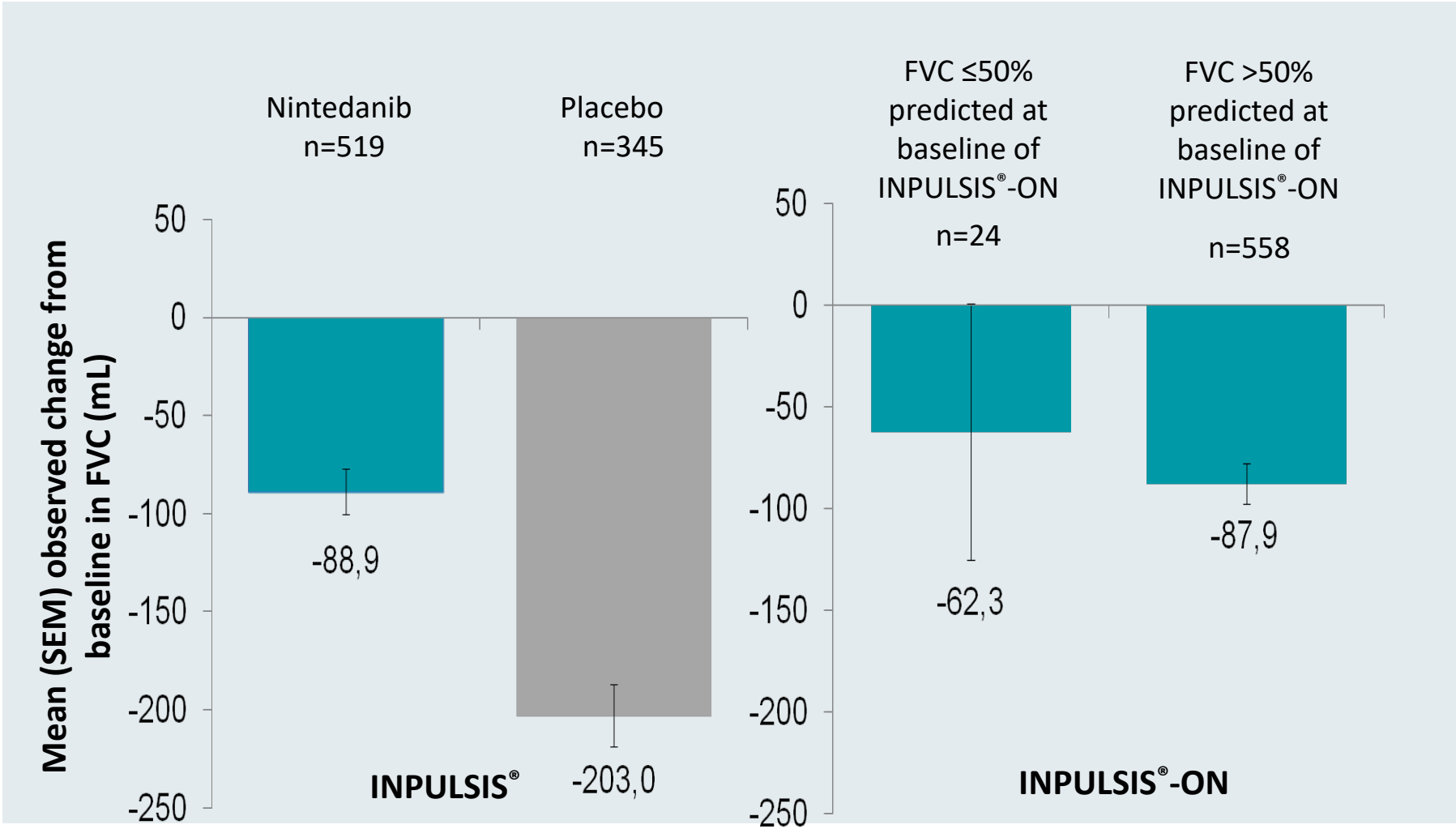


Number of patients*									
Less severe	400	392	376	343	318	287	258	237	208
More severe	184	170	142	117	97	80	67	60	46

* Patients with missing baseline values were excluded.

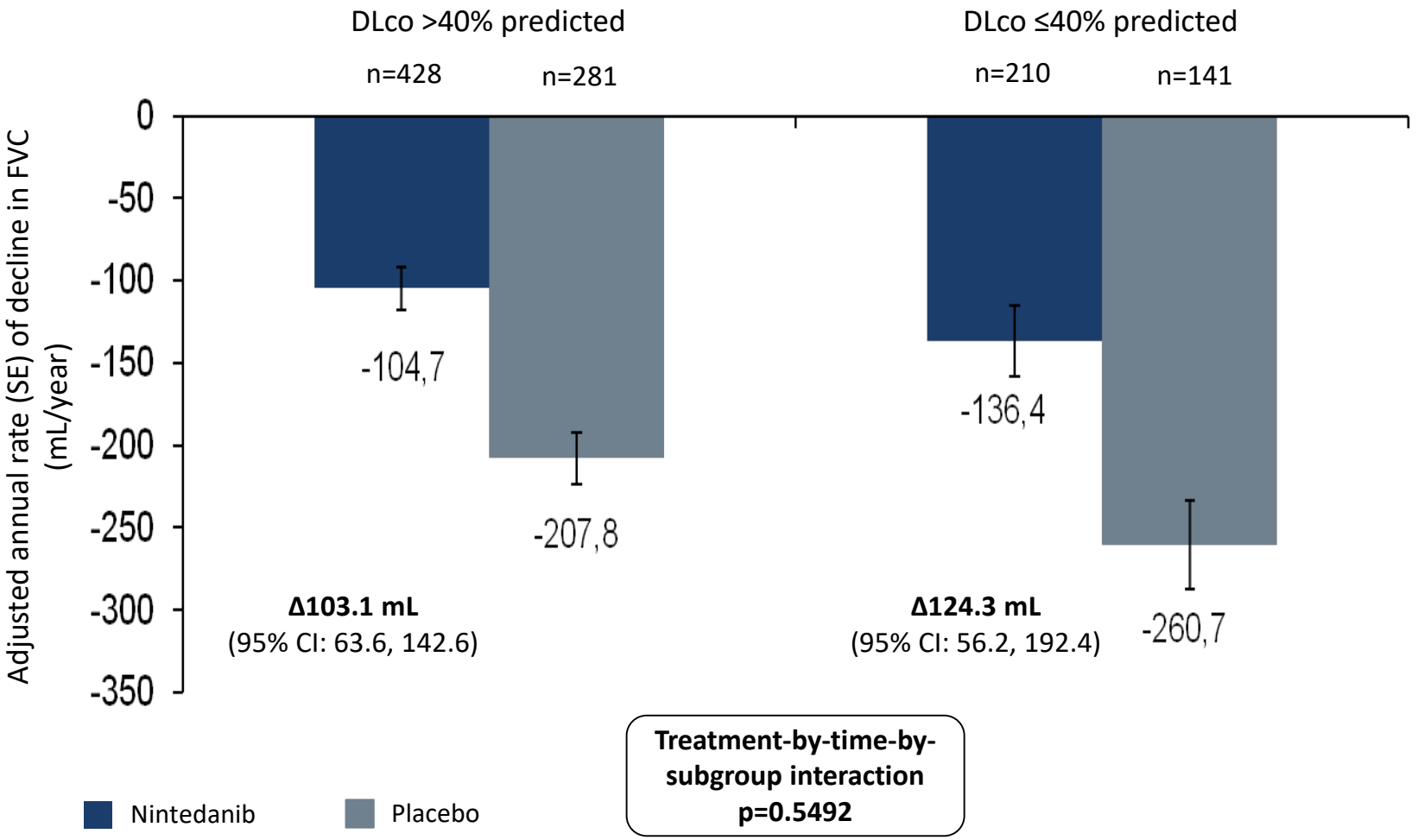
Costabel U. et al. ERS 2016

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



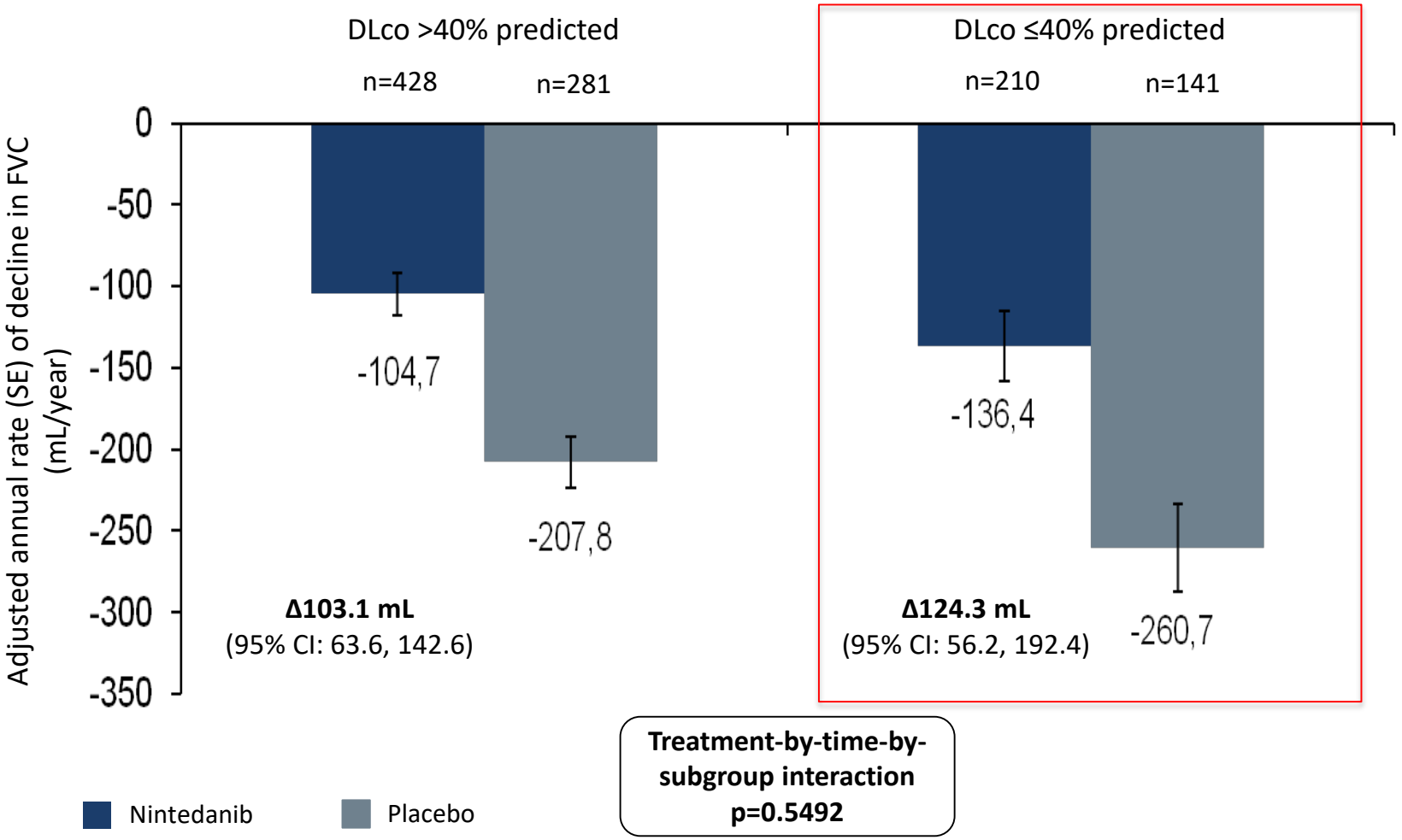
Wuyts WA, et al. Lung 2016

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, Specchia C, Tomassetti S, Rottoli P.

Respiration, in press

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;

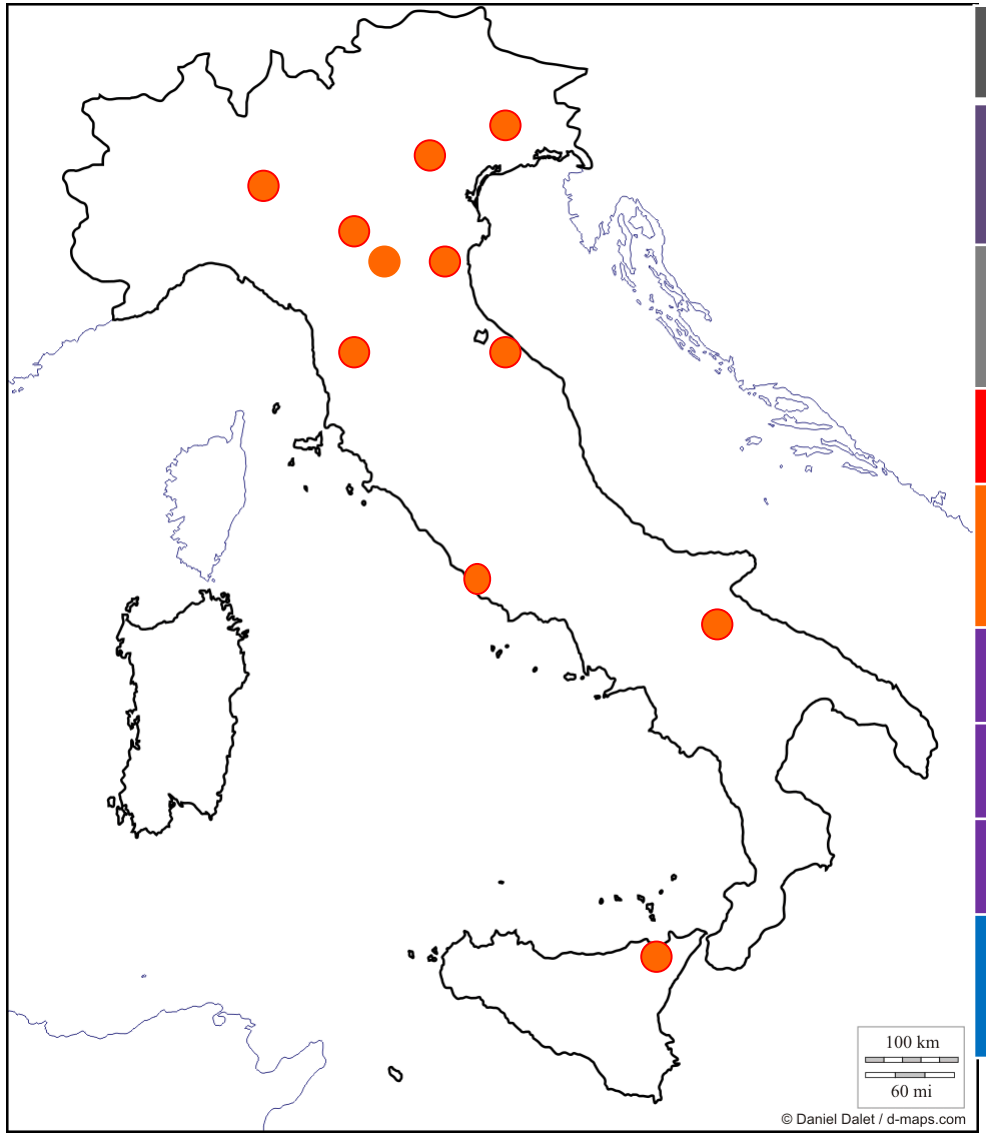
Matherials and Methods

- 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

Table 1. Patients' characteristics at baseline – first nintedanib prescription (N=41)



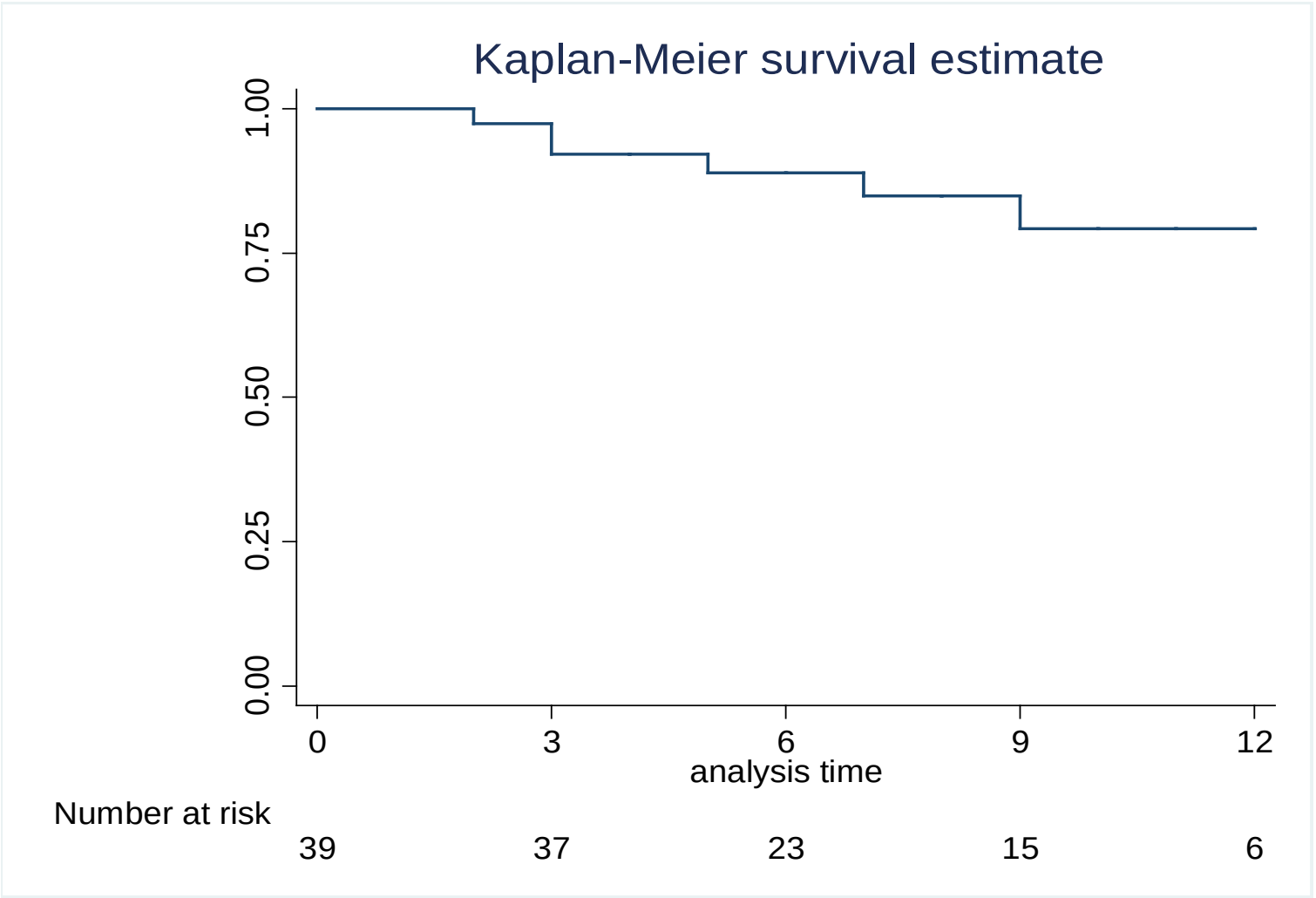
Gender N (%)	**Female**	**7 (17)**
	Male	**34 (83)**
Age (years)*	55-64	7 (17)
	65-74	20 (49)
	75+	14 (34)
Smoking status	Ex-smoker	28 (68)
	Non smoker	11 (27)
	Smoker	2 (5)
Histological diagnosis	No	35 (85)
	Yes	6 (15)
Clinical/Radiological diagnosis	Definite UIP	26 (63)
	Probable UIP	13 (32)
	Possible 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 (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
DLCO 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
DLCO%	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
FEV1 (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
FEV1%	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



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

Forty-one patients with an FVC < 50% predicted and/or a DLCO < 35% predicted at the start of nintedanib were enrolled in the study.

At the 6-month follow-up, the decline of DLCO (both absolute and % 22 predicted) was significantly reduced compared to the pretreatment period

No significant beneficial effect was observed in the other functional parameters analyzed, in particular FVC.

The 1-year survival in this patient 1 population was 79%, calculated from month 6 of therapy with nintedanib

Conclusions

- IPF is a devastating and life-shortening disease
- Symptomatic IPF inevitably progresses
- Rate of progression is the same at all levels of disease severity
- Nintedanib and pirfenidone slow disease progression
- Earlier treatment should magnify benefits of slowing disease
- Quality of life gain should accrue the longer patients live