Fibrosi polmonare idiopatica: quando, come e chi trattare

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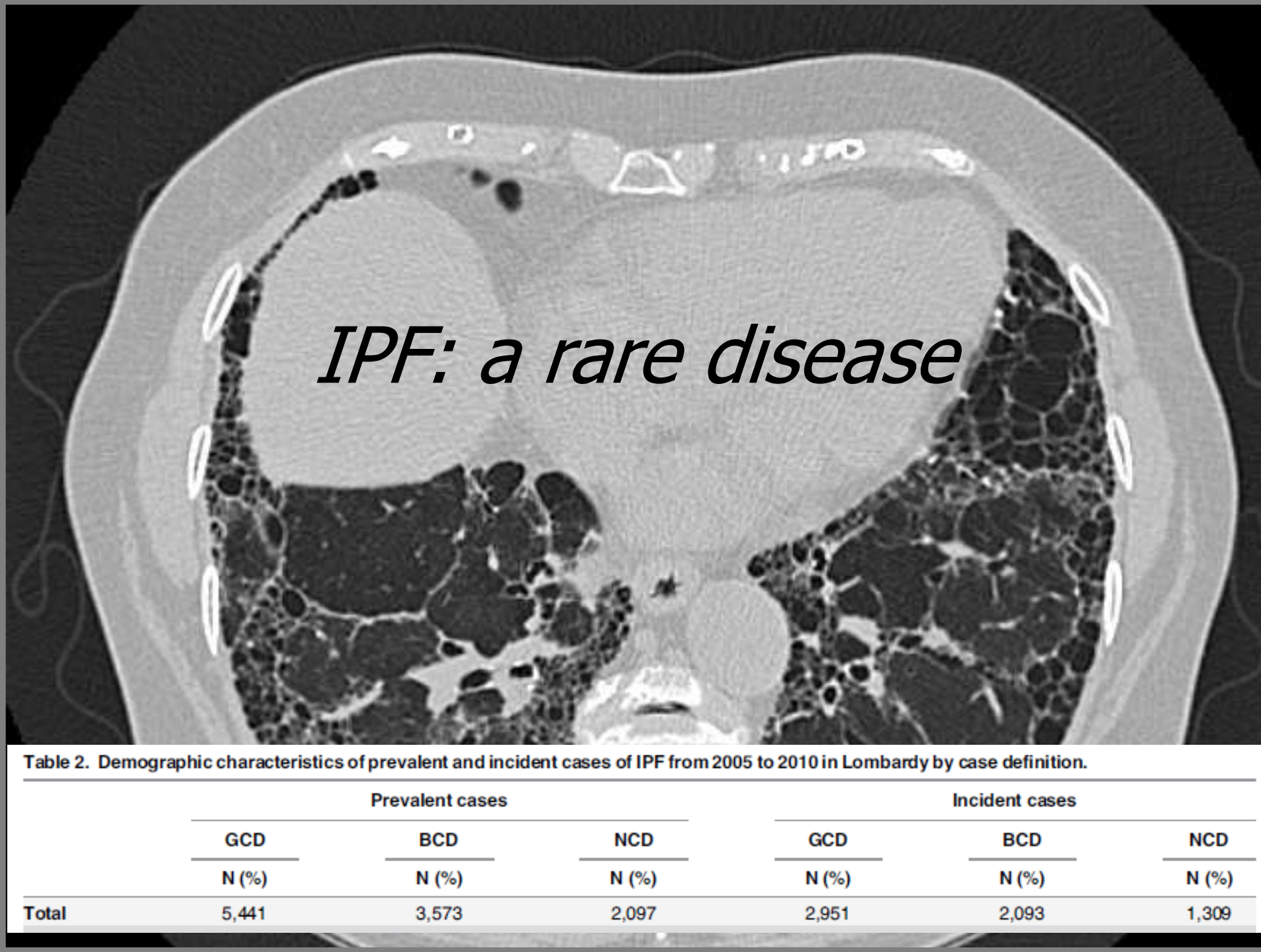
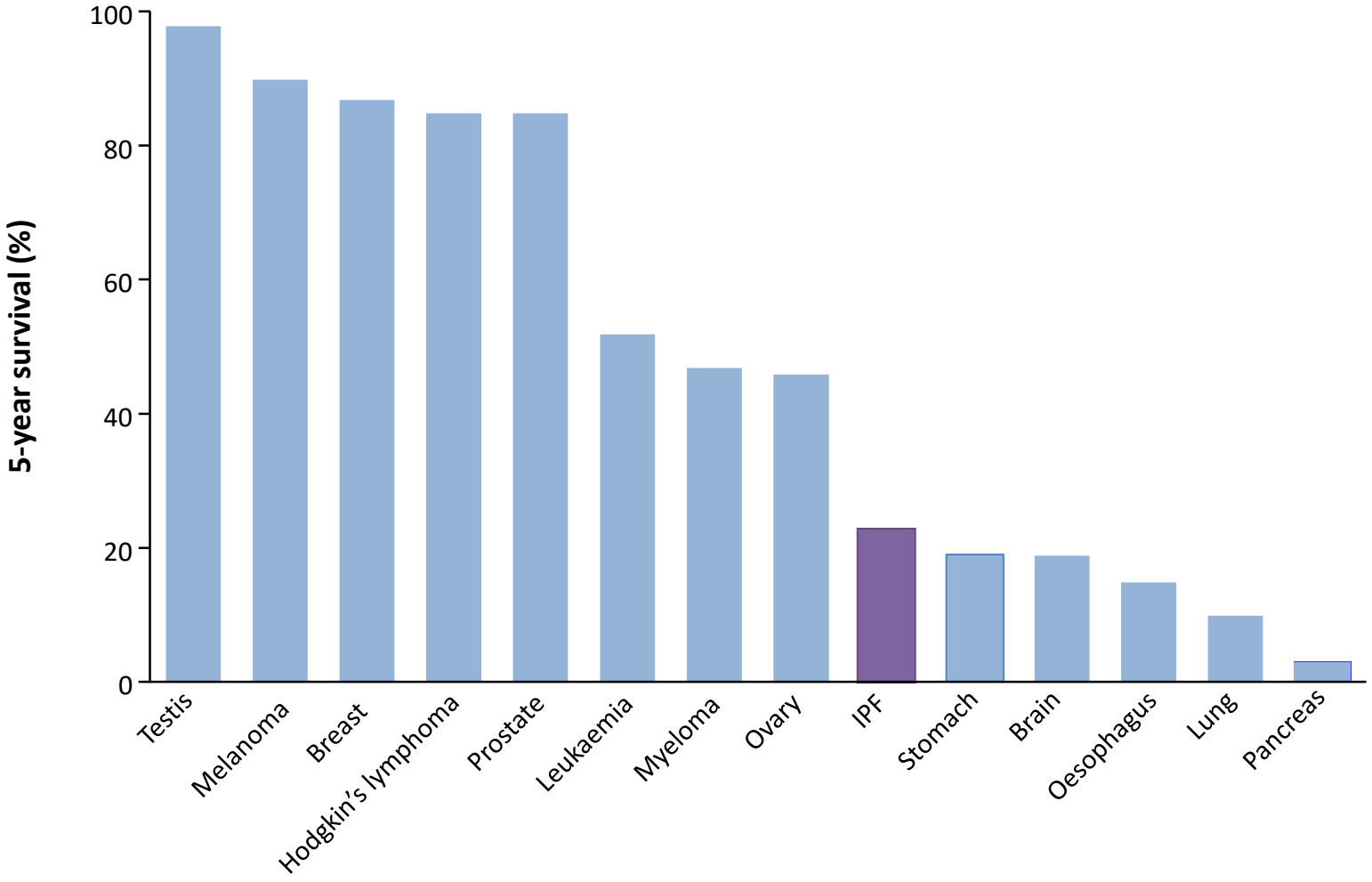


Table 2. Demographic characteristics of prevalent and incident cases of IPF from 2005 to 2010 in Lombardy by case definition.

	Prevalent cases			Incident cases		
	GCD	BCD	NCD	GCD	BCD	NCD
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Total	5,441	3,573	2,097	2,951	2,093	1,309

IPF survival compared with common cancers



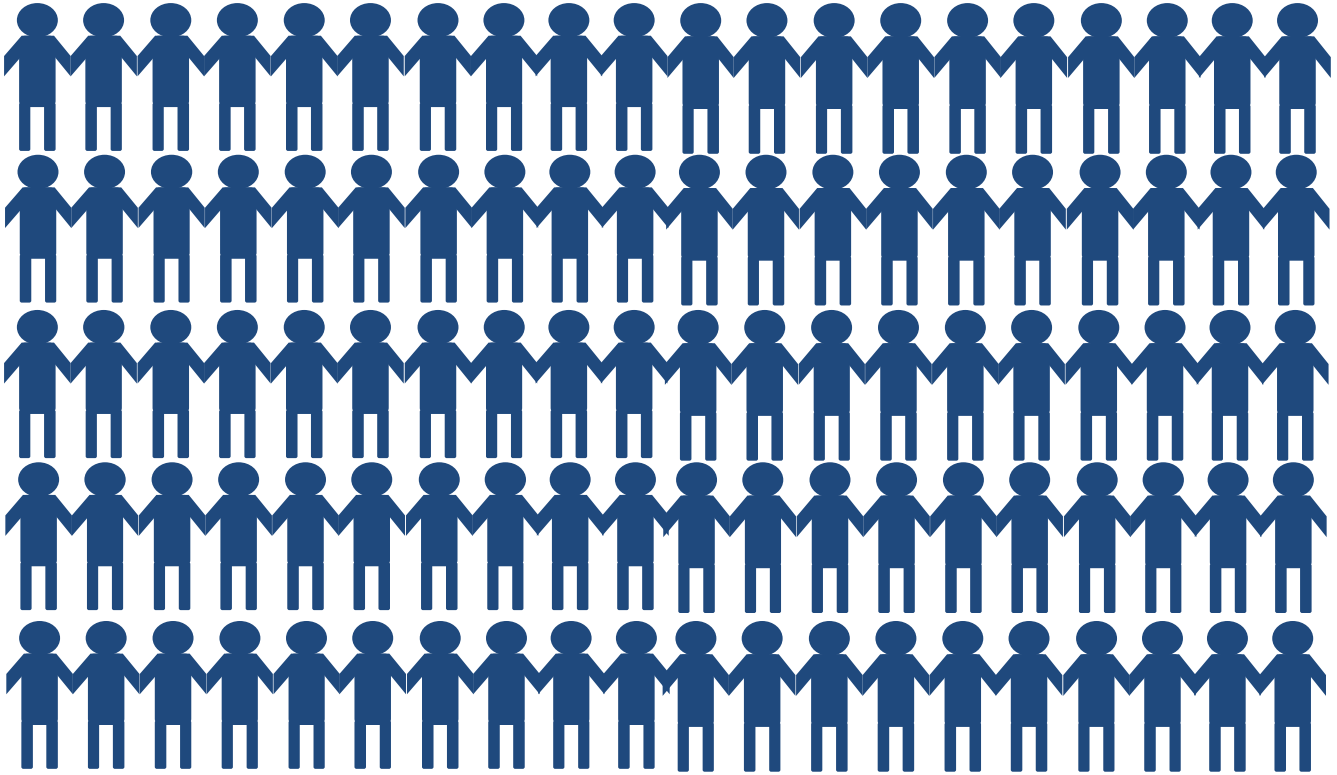
Adapted from Cancer Research UK, Cancer survival for common cancers. Accessed 3 July 2017

Survival following an IPF diagnosis

Alive

Requiring O_2

Dead



Survival following an IPF diagnosis – diagnosis

Survival following an IPF diagnosis – 1 year post-diagnosis

Survival following an IPF diagnosis – 2 years post-diagnosis

Survival following an IPF diagnosis – 3 years post-diagnosis

Survival following an IPF diagnosis – 4 years post-diagnosis

Survival following an IPF diagnosis – 5 years post-diagnosis

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?

Cyclophosphamide

Pirfenidone

Ambrisentan
Sitaxestan

1950s 1990s 2009 2017

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:

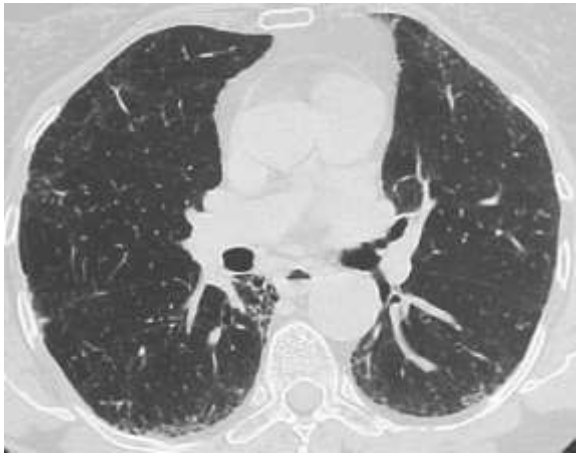
- positive long term effect of both drugs
- well tolerated in patients in “real world”
- also in severe disease
- well tolerated also in combination

When to treat

IPF is a progressive disease

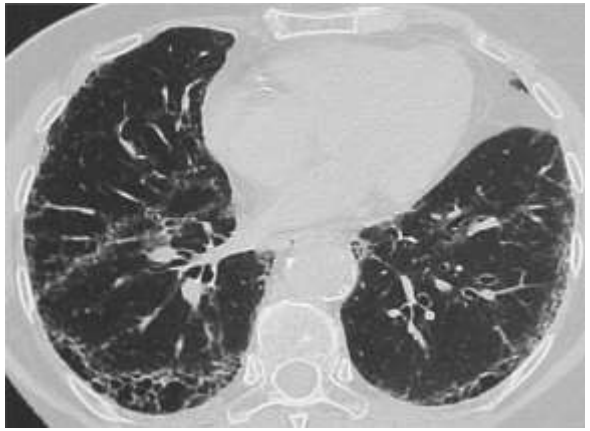
Early:

Reticular



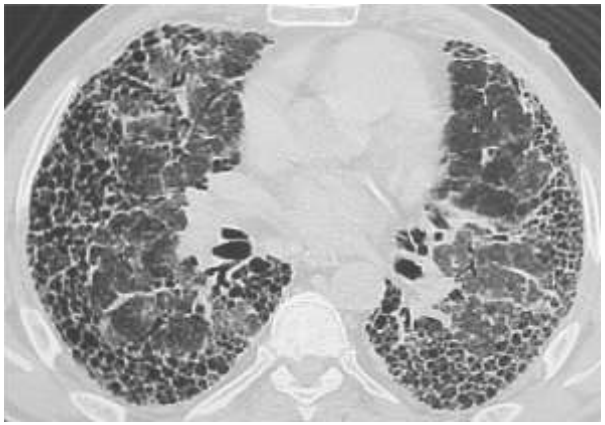
Midcourse:

Subpleural honeycombing



Late:

Diffuse honeycombing



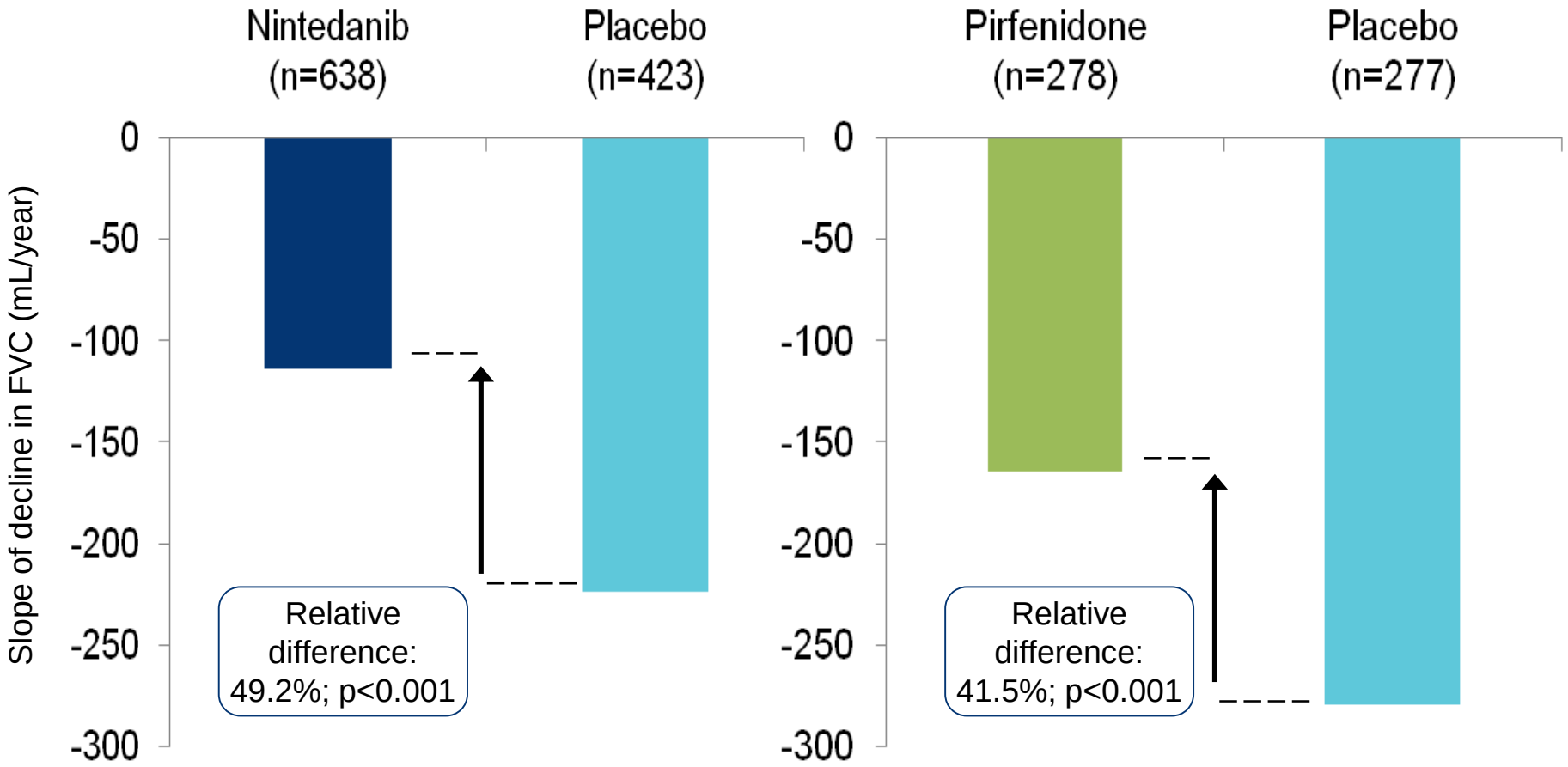
Benefits of early diagnosis

- 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

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

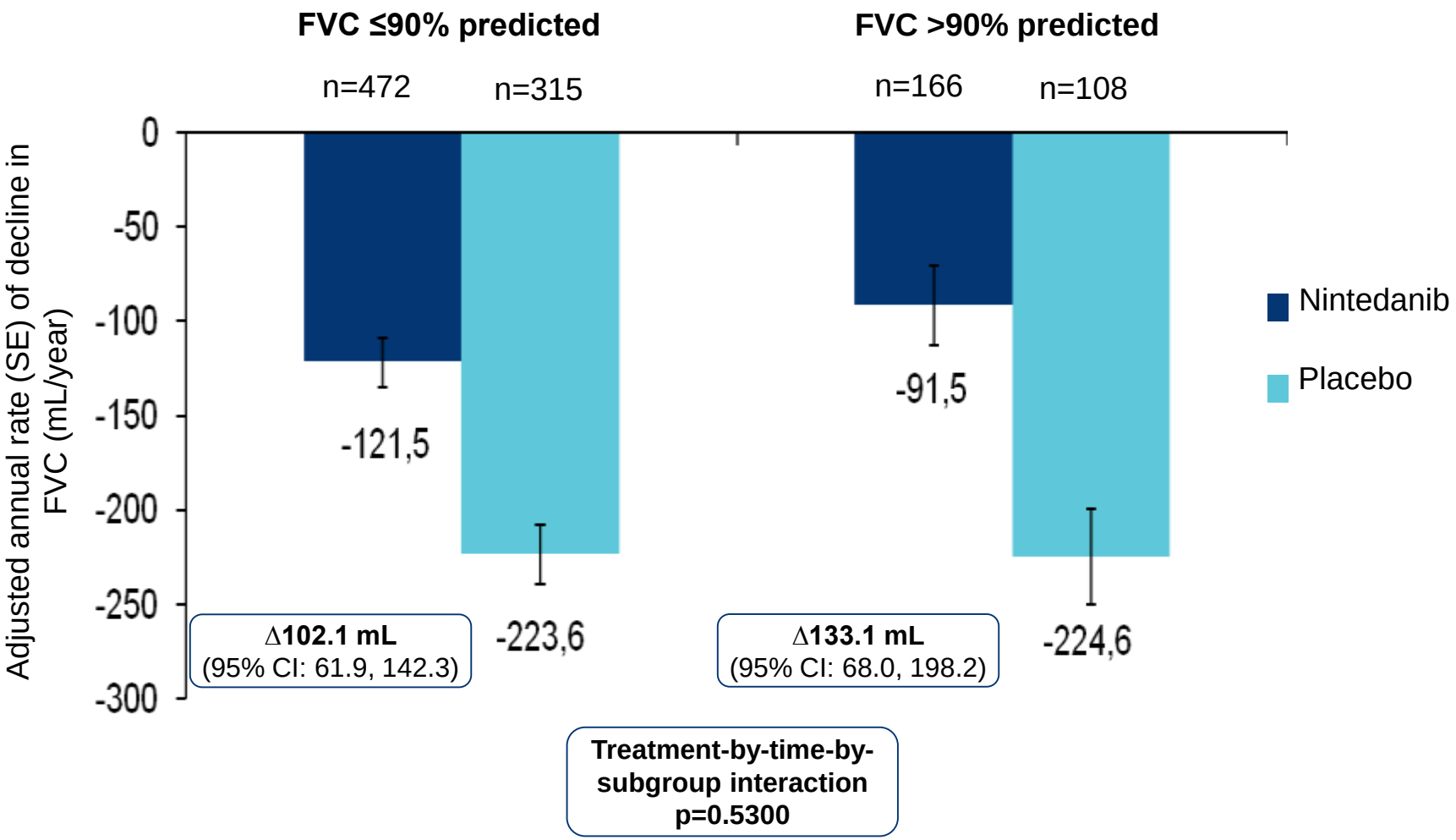
Nintedanib and pirfenidone slow disease progression in IPF



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

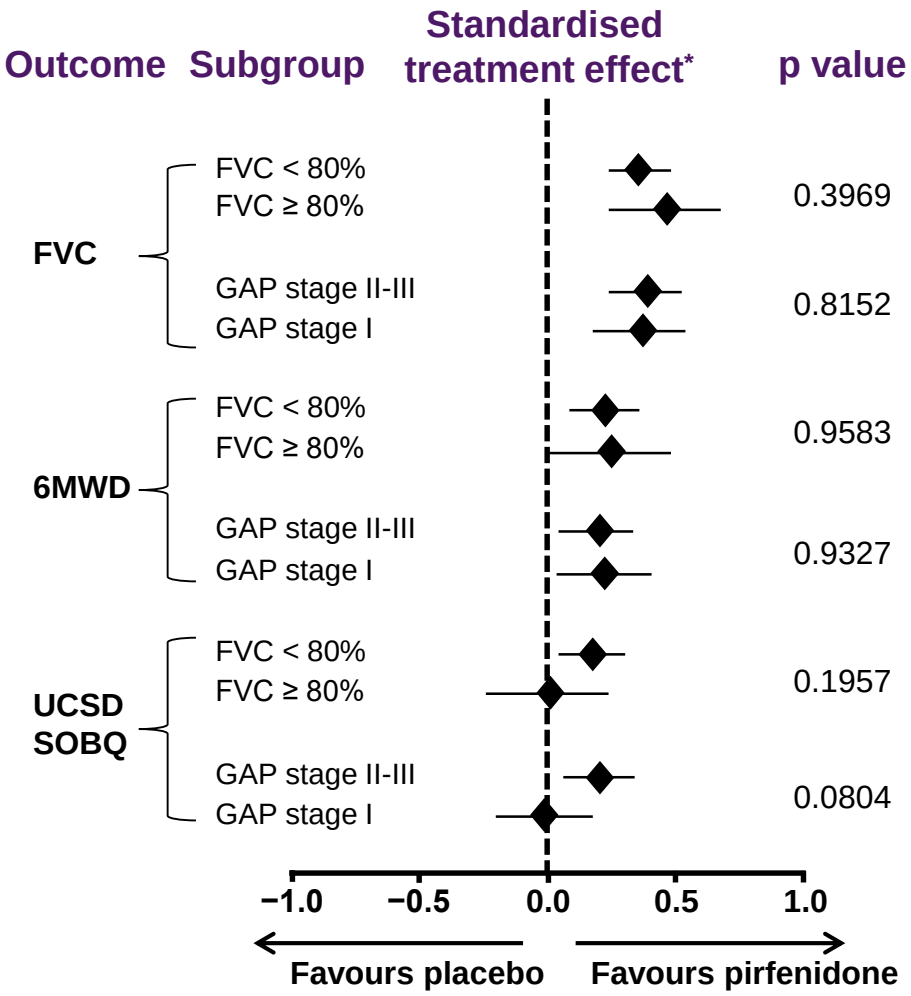
King TE Jr et al. N Engl J Med 2014;370:2083-92.

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

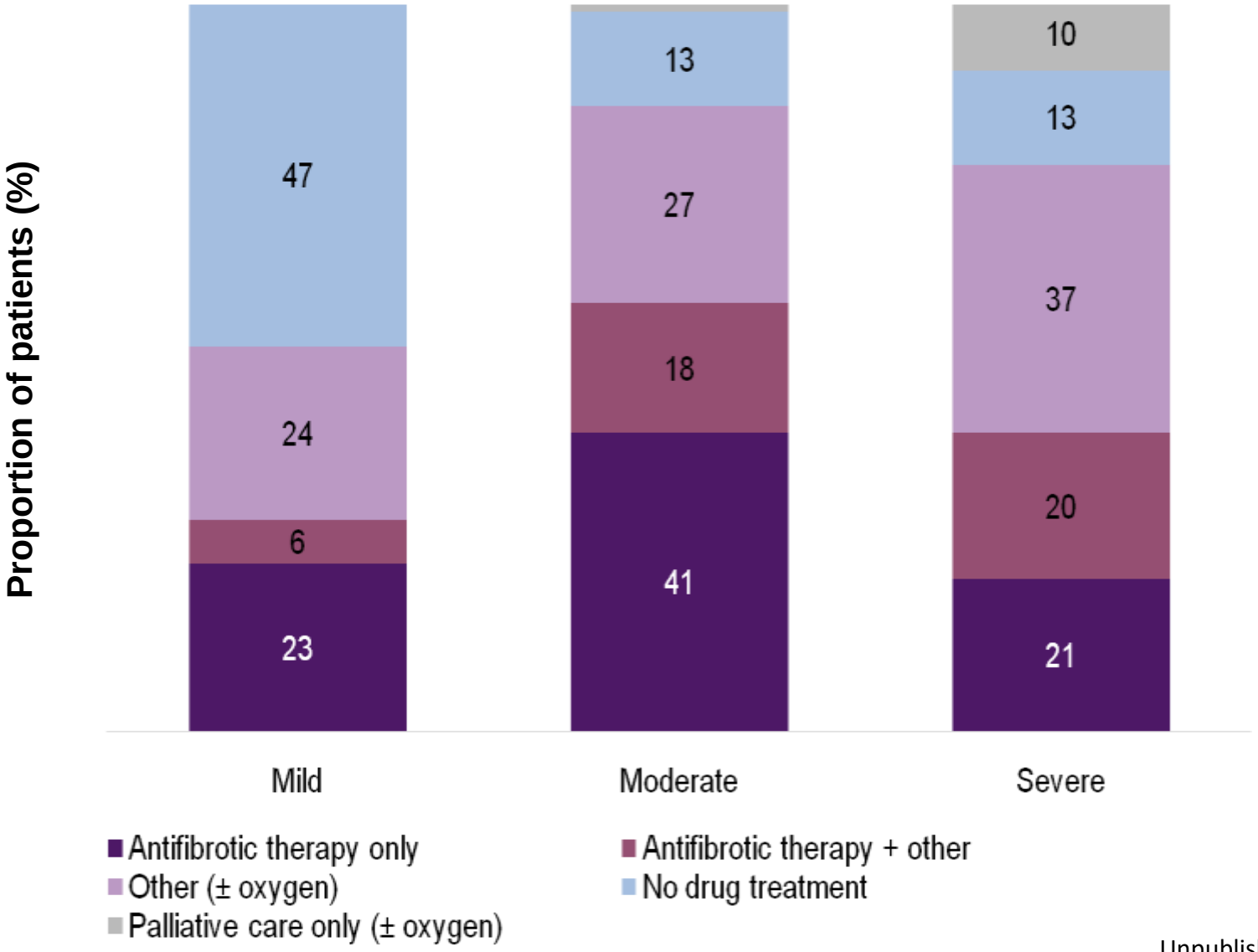
Pirfenidone is efficaciuos in patients with more preserved lung function

Patients n=1247

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

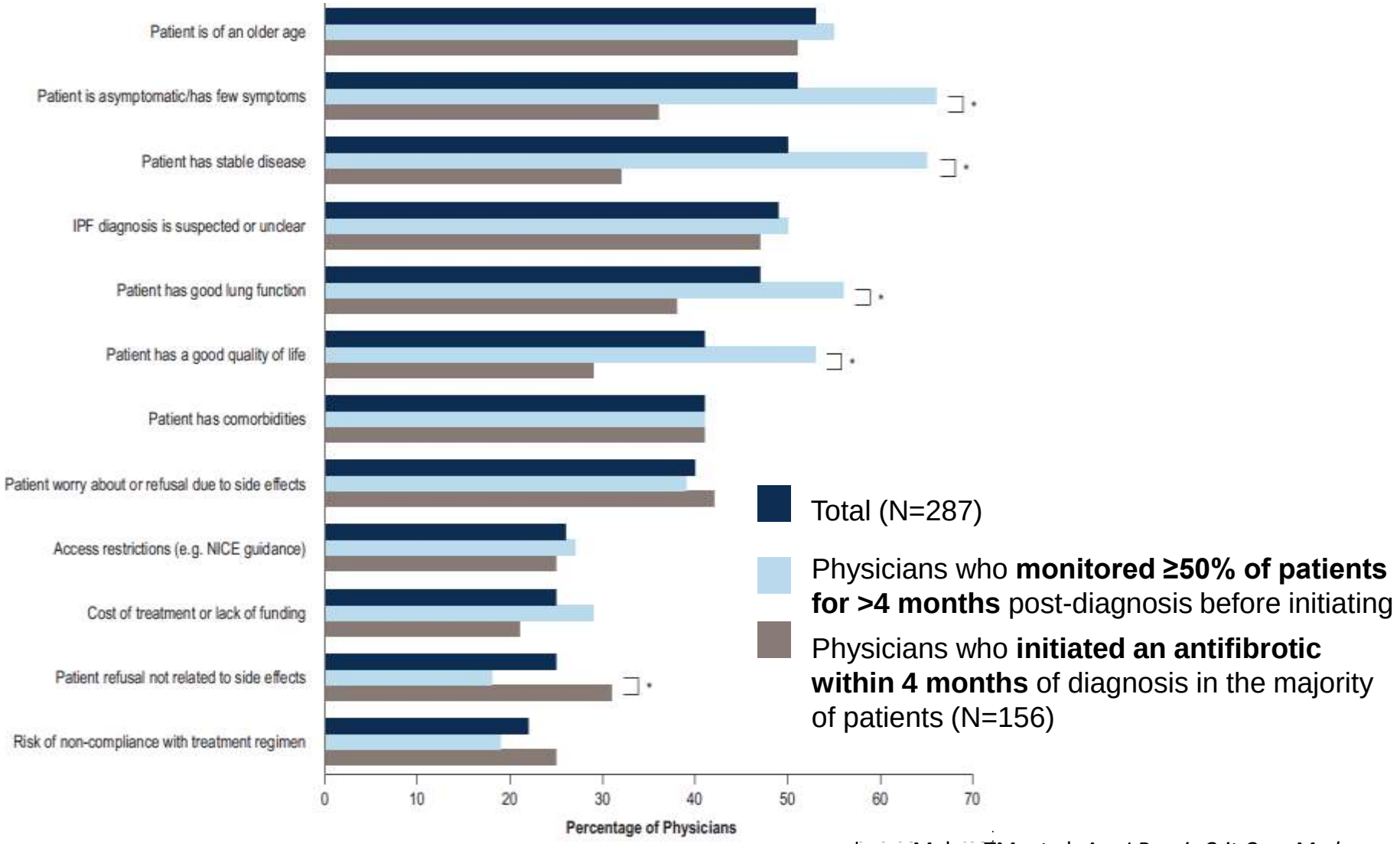
Albera C et al. Eur Respir J 2016;48:843

Patients with mild IPF are least likely to receive treatment



Unpublished data

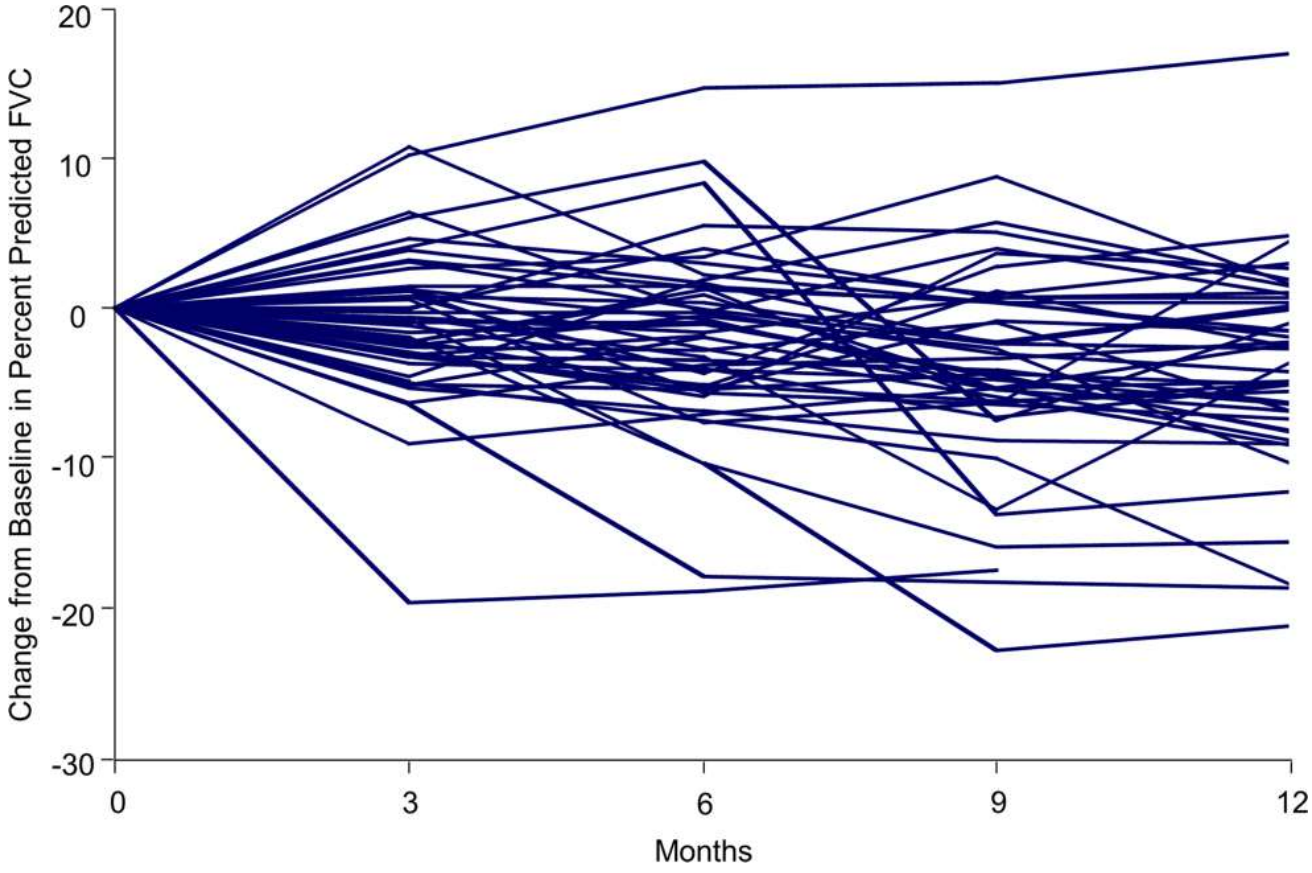
Reasons cited by physicians for not treating patients with mild IPF



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

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



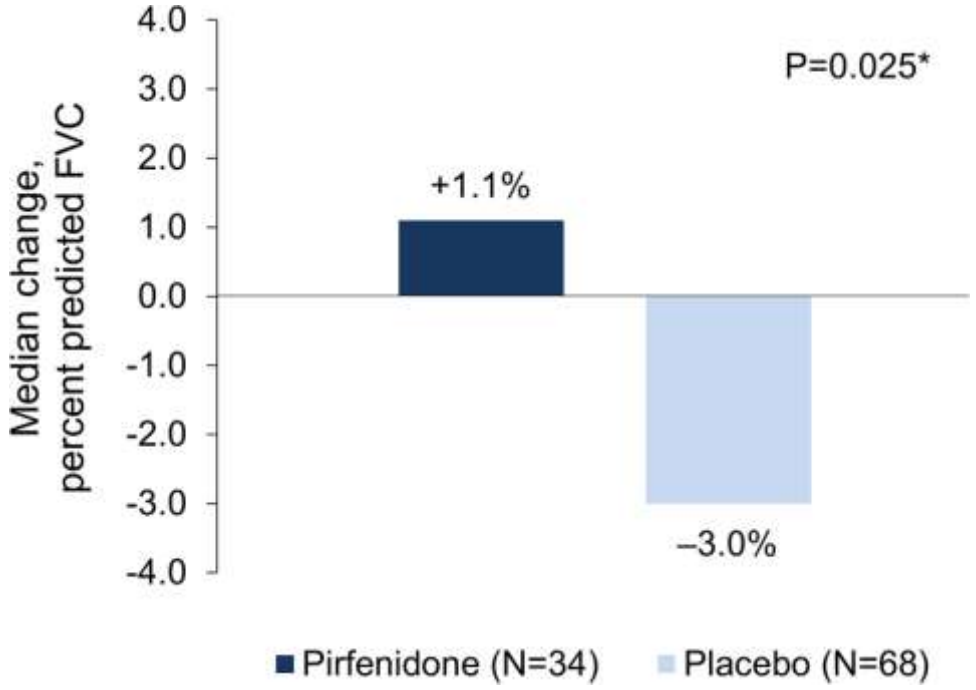
Spaghetti plot of in % predicted FVC*

*Randomly selected patients from the pooled placebo population from the CAPACITY and ASCEND studies (N=50)

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%

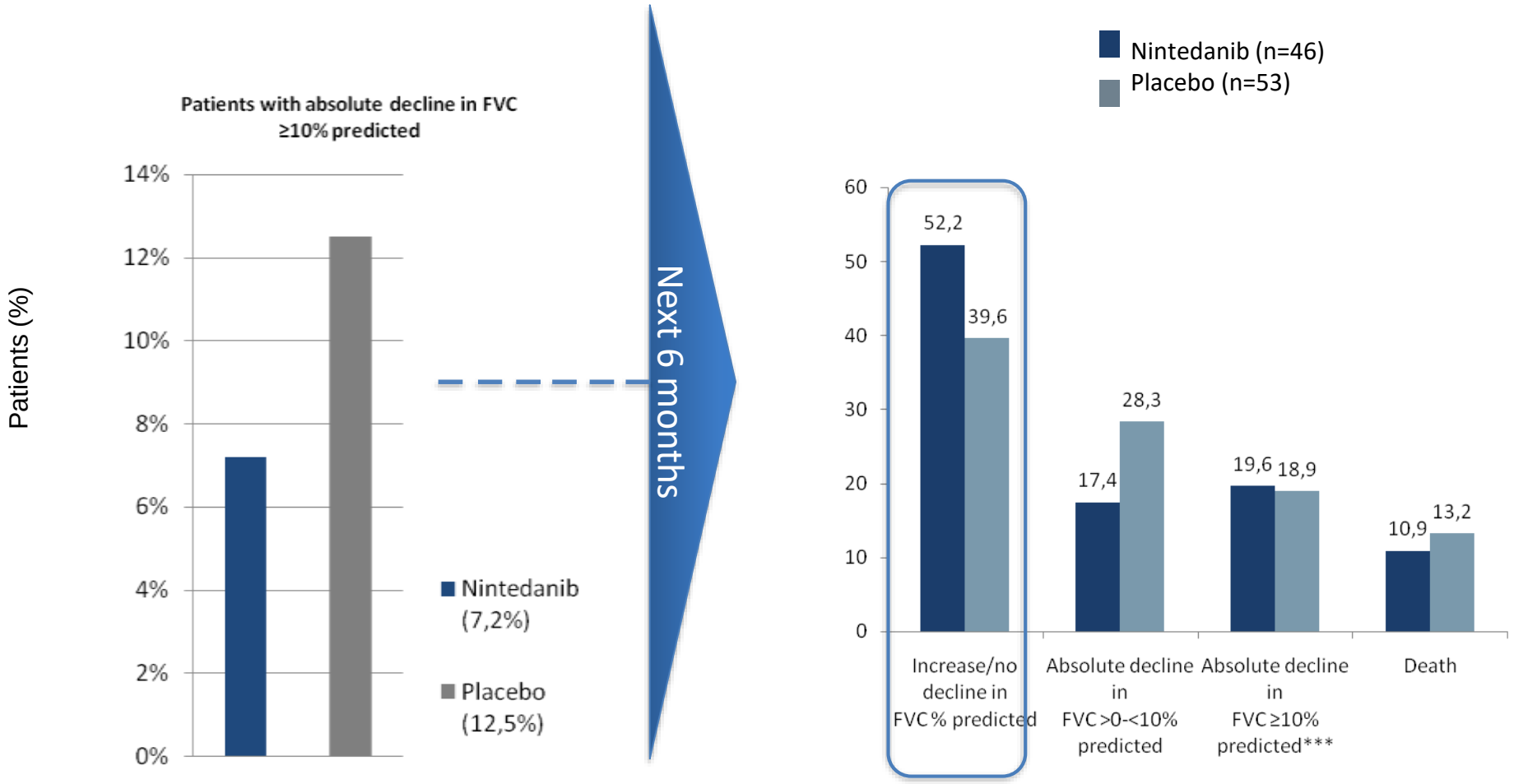
Effect of continued treatment with pirfenidone following clinically meaningful declines in forced vital capacity: analysis of data from three phase 3 trials in patients with idiopathic pulmonary fibrosis

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

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:

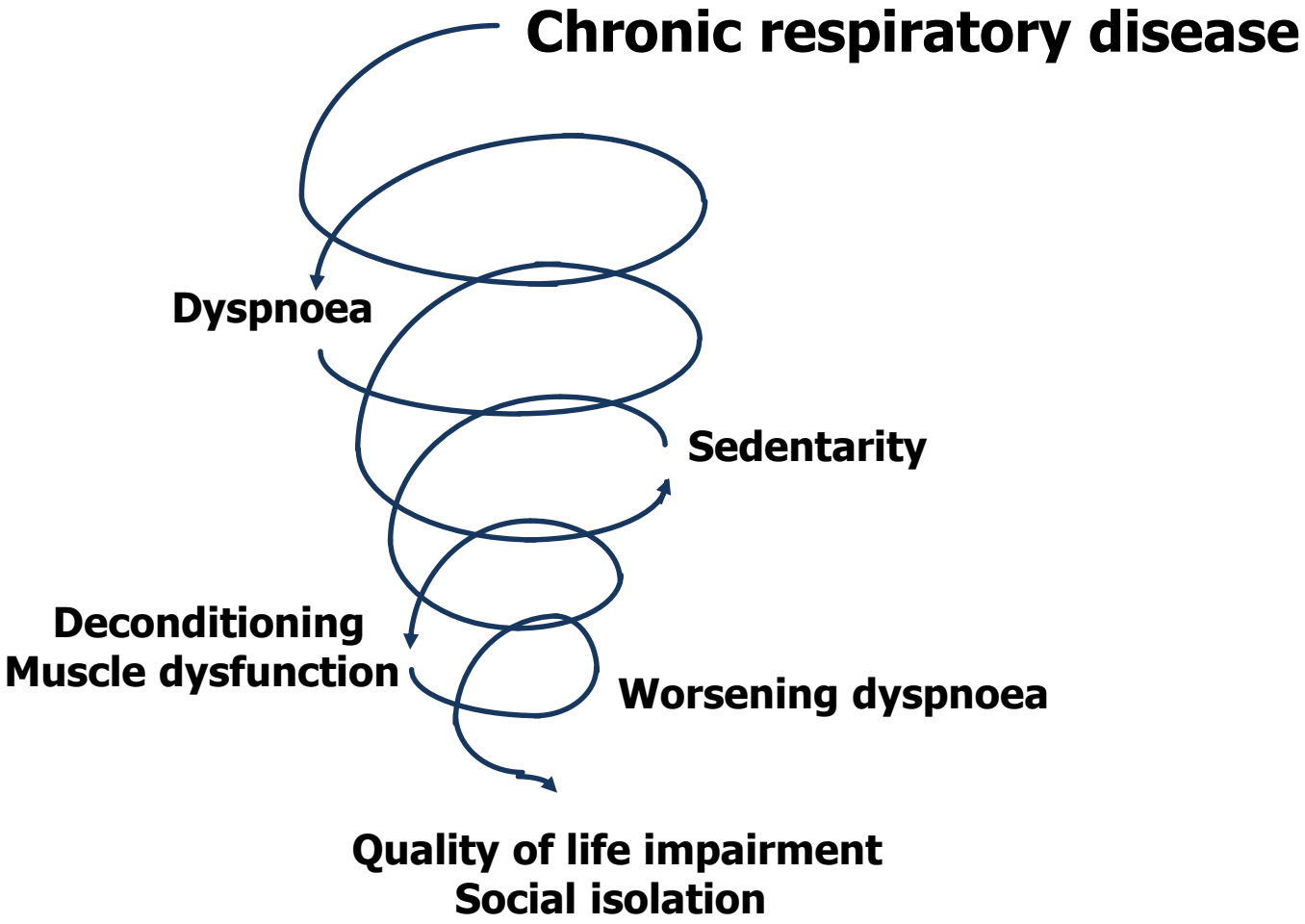
- Worsening of IPF (11.5%)
- Rash (2.2 %)
- Nausea (1.7%)
- Photosensititivity (0.5%)

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

Symptom-centred management
Pulmonary rehabilitation



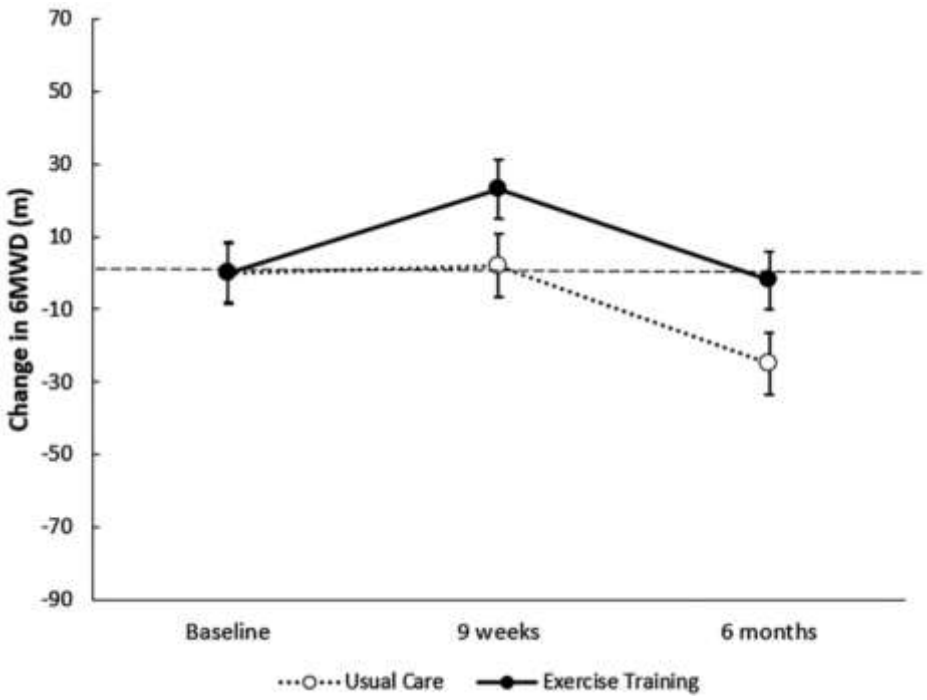
Vicious circle

Young A. *Ann Acad Med Singapore.* 1983;12:410–416

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

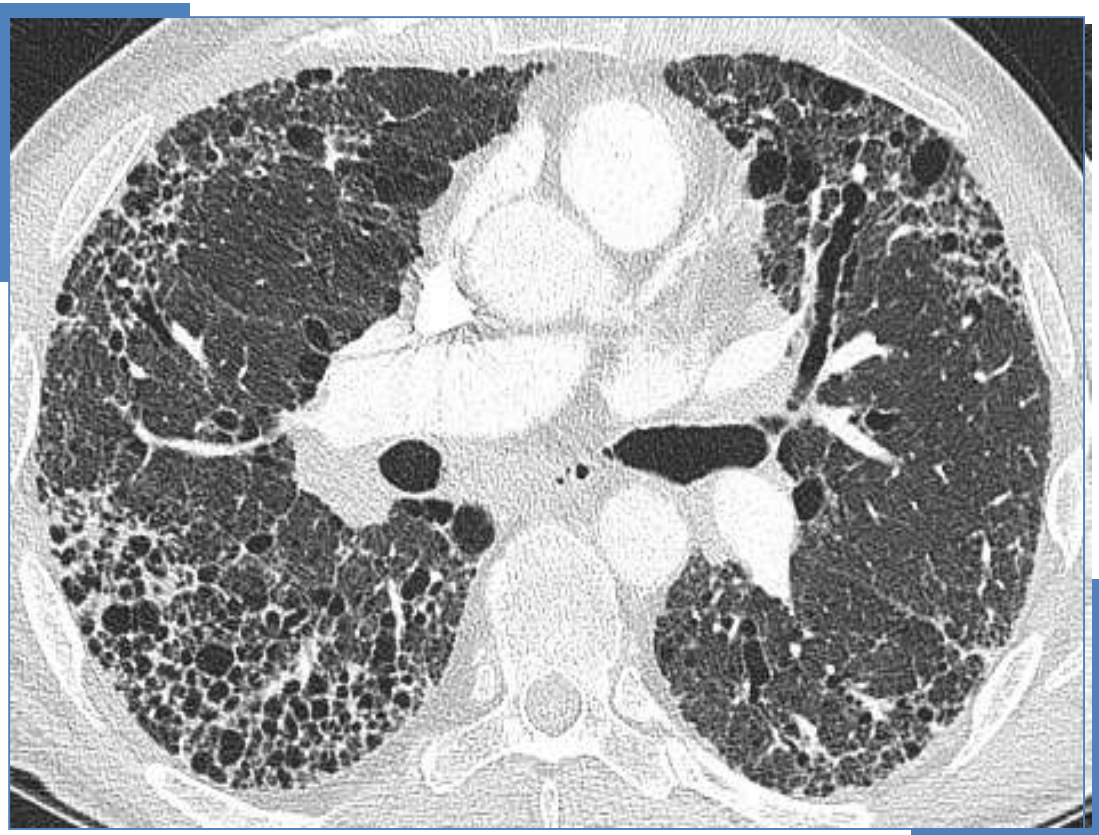


CTD-ILD, connective tissue disease-ILD; HRQoL, health-related quality of life

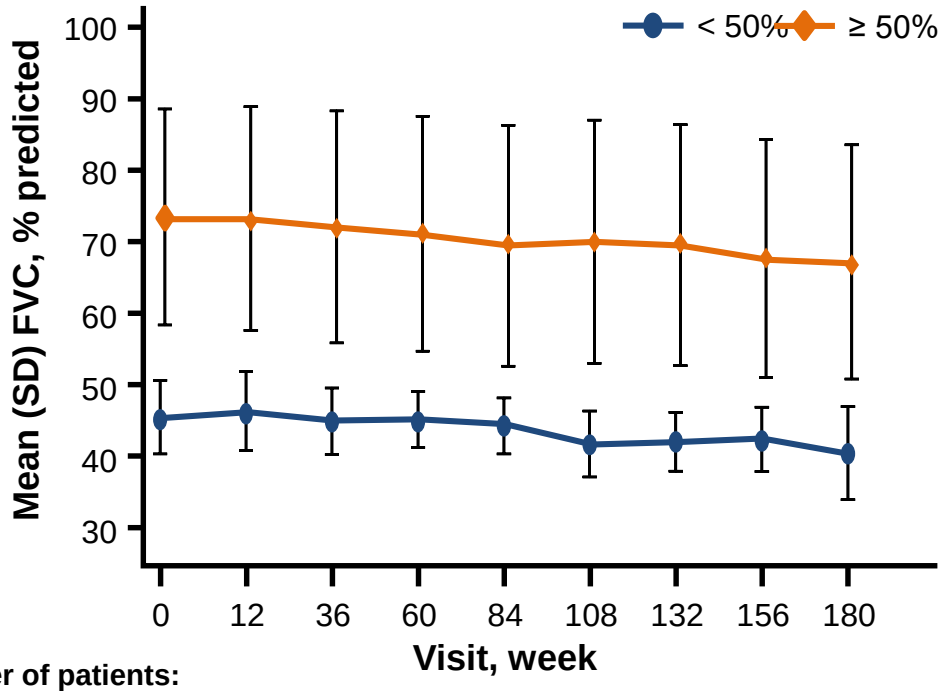
Dowman LM, et al. *Thorax.* 2017;72:610–619

Who to treat

IPF – the challenge



Rate of FVC decline was similar in patients with baseline FVC<50% vs ≥50%



Number of patients:

< 50%	54	47	38	30	25	21	17	15	13
≥ 50%	530	504	469	421	381	337	299	273	233

Patients with missing baseline are excluded. Patients with prior treatment (placebo, pirfenidone 1197 mg/day and 2403 mg/day in CAPACITY 004/006 are included)

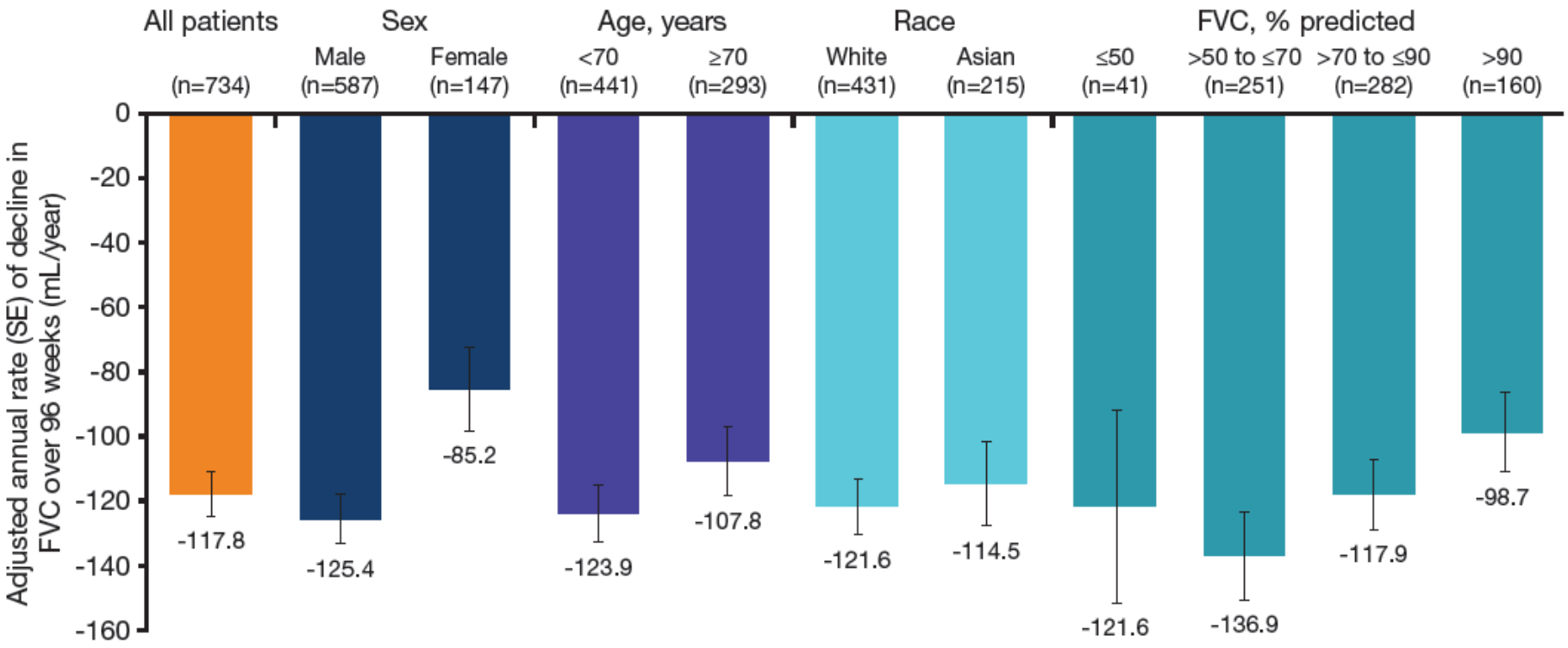
Conclusions

The rate of FVC decline was similar in patients with FVC <50% vs ≥50%

Pirfenidone is an acceptable treatment in patients with more severe lung function impairment

Costabel U et al. Presented at ERS 2016

Annual rate of decline in FVC over 96 weeks in subgroups by patient characteristics at start of INPULSIS®-ON



Kreuter et al. Presented at American Thoracic Society (ATS) International Conference, Washington, DC, USA, 19–24 May 2017

Eligibility criteria based on HRCT

- To qualify to enter the INPULSIS® trials in the absence of a surgical lung biopsy, criteria **A and B and C**; or A and C; or B and C had to be met:

A	Definite honeycomb lung destruction with basal and peripheral predominance
B	Presence of reticular abnormality and traction bronchiectasis consistent with fibrosis with basal and peripheral predominance
C	Atypical features are absent, specifically nodules and consolidation. Ground glass opacity, if present, is less extensive than reticular opacity pattern

- HRCT scans were assessed centrally by one expert radiologist

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Aim and methods

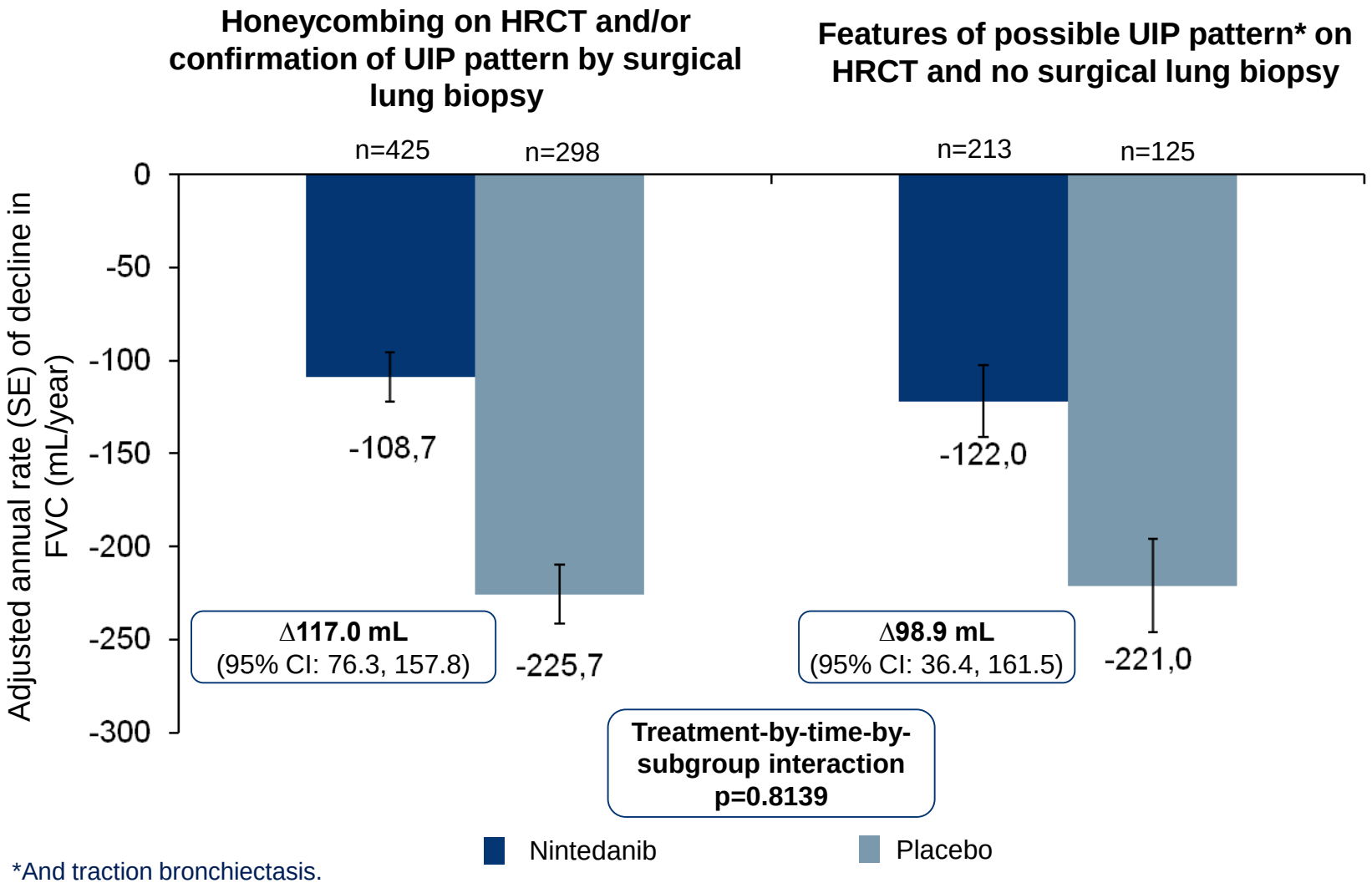
- **Aim**
  - To investigate the potential impact of HRCT diagnostic subgroups on the effect of nintedanib in patients with IPF
- **Methods**
  - *Post-hoc* subgroup analyses were conducted using pooled data from the two INPULSIS® trials in patients with:

Honeycombing on HRCT and/or confirmation of UIP pattern by surgical lung biopsy	versus	Features of possible UIP pattern* on HRCT and no surgical lung biopsy

  - Analyses were conducted on the primary and key secondary endpoints

*And traction bronchiectasis. Possible UIP comprises all three of the following features: subpleural, basal predominance; reticular abnormality; absence of features noted as inconsistent with UIP pattern [Raghu et al. Am J Respir Crit Care Med 2011;183:788–824].

Annual rate of decline in FVC



*And traction bronchiectasis.

Aim and methods

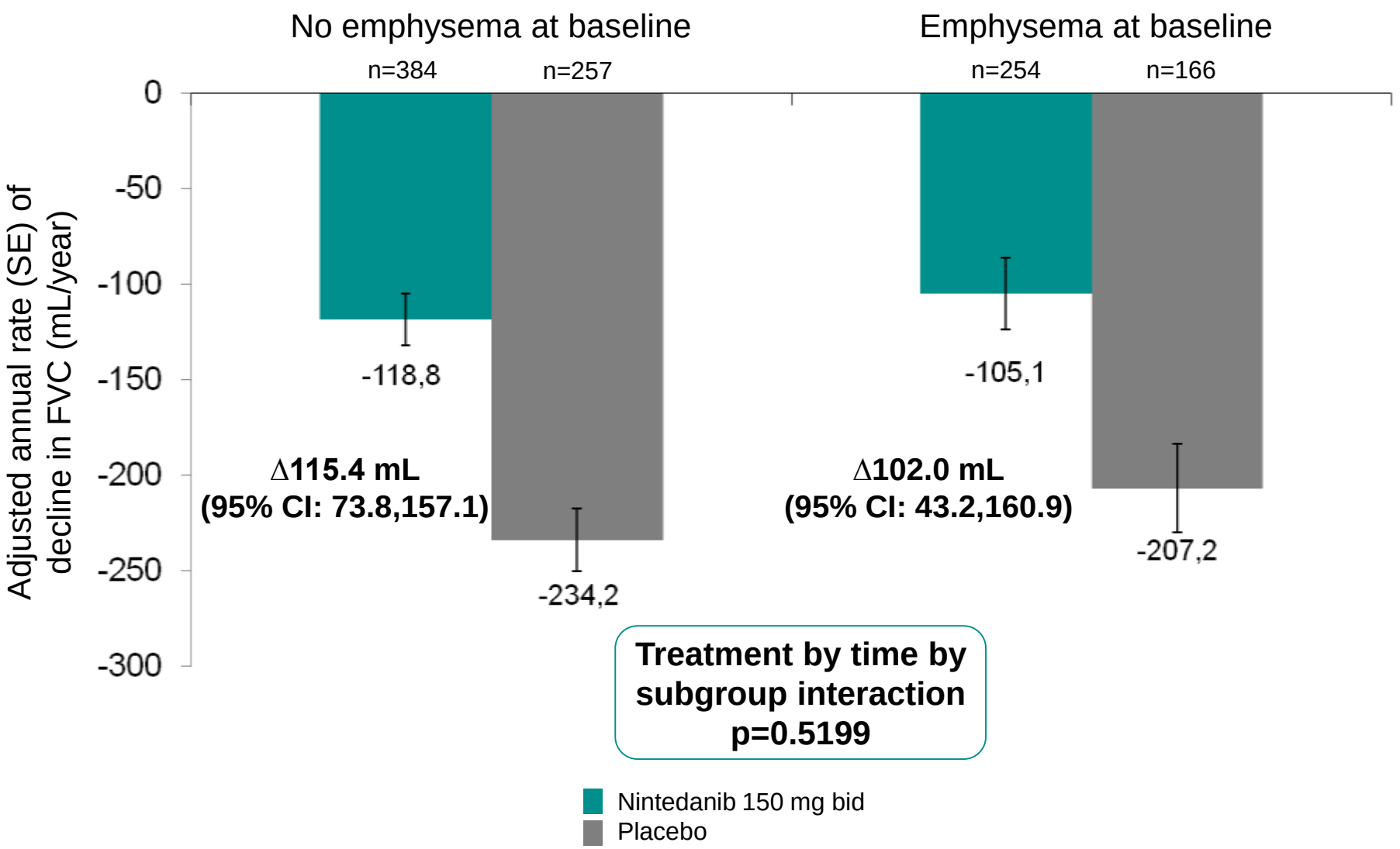
- Aim

- To investigate the potential impact of emphysema on the effect of nintedanib in patients with IPF

- Methods

- Presence of emphysema (yes/no) at baseline was determined by qualitative assessment of chest HRCT scans, centrally reviewed by a single radiologist
- *Post-hoc* subgroup analyses of patients with/without emphysema at baseline were conducted using pooled data from the two INPULSIS™ trials
- Subgroup analyses were conducted on the primary and key secondary endpoints

Annual rate of decline in FVC



Addressing ongoing challenges in pulmonary fibrosis in the era of antifibrotic treatment

- Confident diagnostic criteria
- When to initiate treatment
- Treatment of patients with advanced disease
- Combination treatment
- Disease progression
- Precision medicine
- Feasibility of drug development in rare diseases
- Other chronic fibrosing ILD

The initial differential diagnosis of ILD is difficult

- Overlapping clinical presentations occur among all ILD diagnoses
- No single chest imaging or pathologic pattern is unique to a specific diagnosis (e.g., a UIP chest imaging or pathologic pattern can be seen in IIP, CTD, HP and other exposure-related ILD)
- Significant discordance between clinical, chest imaging, and pathologic features often occurs (i.e., classic combination patterns are not universal)

Another perspective: classification according to disease behaviour

Clinical behaviour	Treatment goal	Monitoring strategy
Reversible and self-limited (e.g. many cases of RB-ILD)	Remove possible cause	Short-term (3- to 6- month) observation to confirm disease regression
Reversible disease with risk of progression (e.g. cellular NSIP and some fibrotic NSIP, DIP, COP)	Initially achieve response and then rationalise longer term therapy	Short-term observation to confirm treatment response. Long-term observation to ensure that gains are preserved
Stable with residual disease (e.g. some fibrotic NSIP)	Maintain status	Long-term observation to assess disease course
Progressive, irreversible disease with potential for stabilisation (e.g. some fibrotic NSIP)	Stabilise	Long-term observation to assess disease course
Progressive, irreversible disease despite therapy (e.g. IPF, some fibrotic NSIP)	Slow progression	Long-term observation to assess disease course and need for transplant or effective palliation

COP, cryptogenic organising pneumonia; DIP, desquamative interstitial pneumonia; RB-ILD, respiratory bronchiolitis-interstitial pneumonia. Travis WD et al. Am J Respir Crit Care Med 2013;188:733-48.

Progressive fibrosing ILD (PF-ILD)

Several patients with ILD develop a progressive fibrosing phenotype, characterised by self-sustaining fibrosis, deterioration in lung function, and worsening of symptoms and quality of life

Is there a distinct phenotype of patients with PF-ILD who might benefit from antifibrotic treatment similar to IPF?

Ongoing research in other fibrosing ILDs

Drug/patient population	Clinicaltrials.gov	Study design; sample size	Primary endpoint
Nintedanib			
SSc-ILD (SENSCIS™)	NCT02597933	Randomised, placebo-controlled; **n=520**	Rate of decline in FVC over 52 weeks
PF-ILD	NCT02999178	Randomised, placebo-controlled; **n=600**	Rate of decline in FVC over 52 weeks
Pirfenidone			
Chronic HP	NCT02496182	Randomised, placebo-controlled; n=60	Change in FVC at week 52
Progressive ILD associated with clinically amyopathic dermatomyositis	NCT02821689	Open-label, randomised, placebo-controlled; n=57	Survival 12 months from onset of ILD
LTx recipients with BOS grade 1-2	NCT02262299	Randomised, placebo-controlled; n=80	Change in FEV_1 at month 6
Fibrotic HP	NCT02958917	Randomised, placebo-controlled; n=40	Change in FVC at week 52
Unclassifiable PF-ILD	NCT03099187	Randomised, placebo-controlled; n=250	Rate of decline in FVC over 24 weeks
RA-ILD	NCT02808871	Randomised, placebo-controlled; n=270	PFS at week 52 (progression defined as FVC decline ≥10% predicted)
SSc-ILD (SLS III) - on top of MMF	NCT03221257	Randomised, placebo-controlled; n=150	Change in FVC %pred at 18 months

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: it is still a problem