IV Forum di Pneumologia Interventistica

Bologna 5- 6 Giugno 2015

IPF : Dalla Diagnosi alla Terapia

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Conflict of interests disclosures

Actelion

Boehringer Ingelheim

InterMune

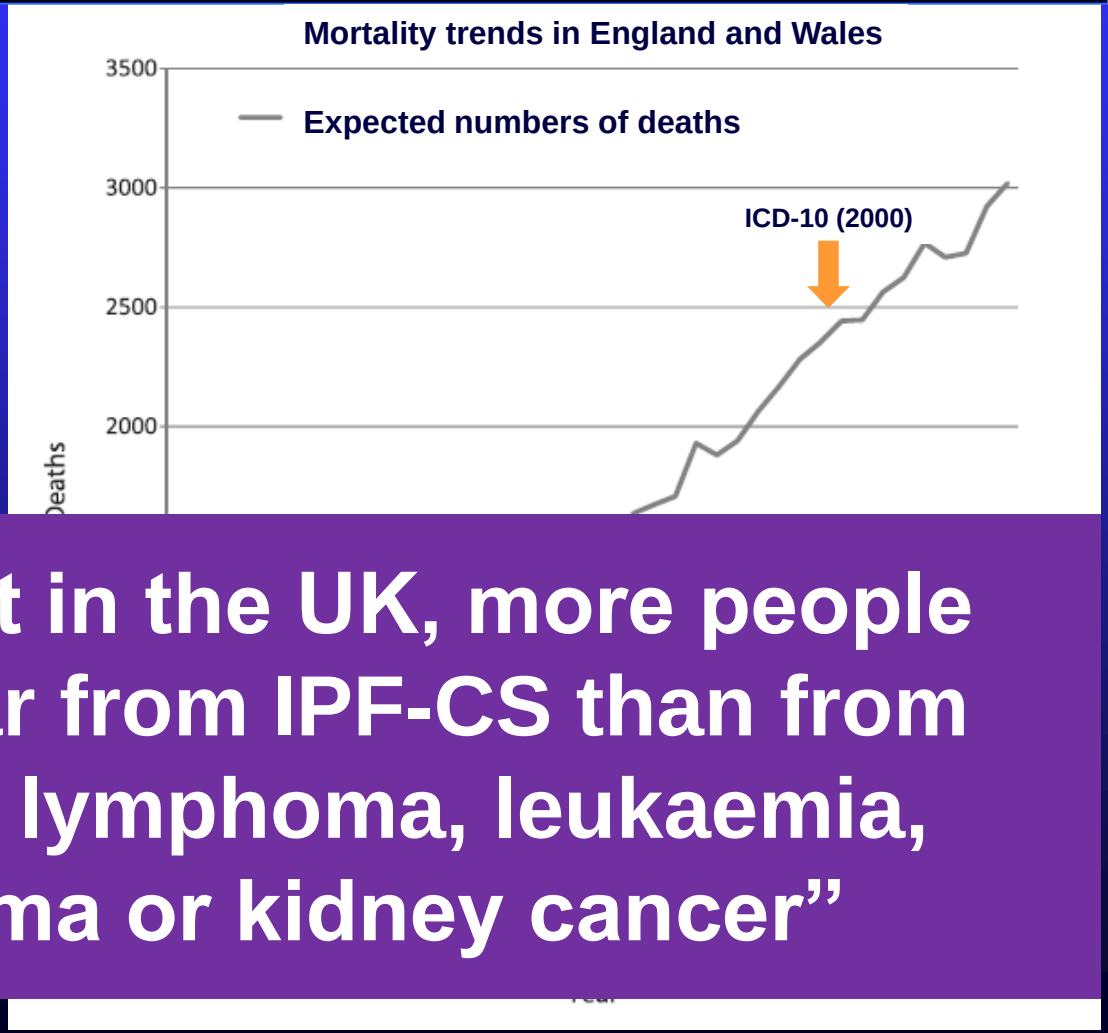
Roche

Diagnosis	Frequency	
Idiopathic Interstitial pneumonias		40%
Idiopathic pulmonary fibrosis	55%	
Non specific interstitial pneumonia	25%	
Respiratory bronchiolitis-ILD and desquamative interstitial pneumonia	15%	
Cryptogenic organizing pneumonia	3%	
Acute interstitial pneumonia	<1%	
Occupational and environmental		26%
Sarcoidosis		10%
Connective tissue diseases		9%
Drug and radiation		1%
Pulmonary hemorrhage		1%
Others		13%

The rising incidence of idiopathic pulmonary fibrosis in UK

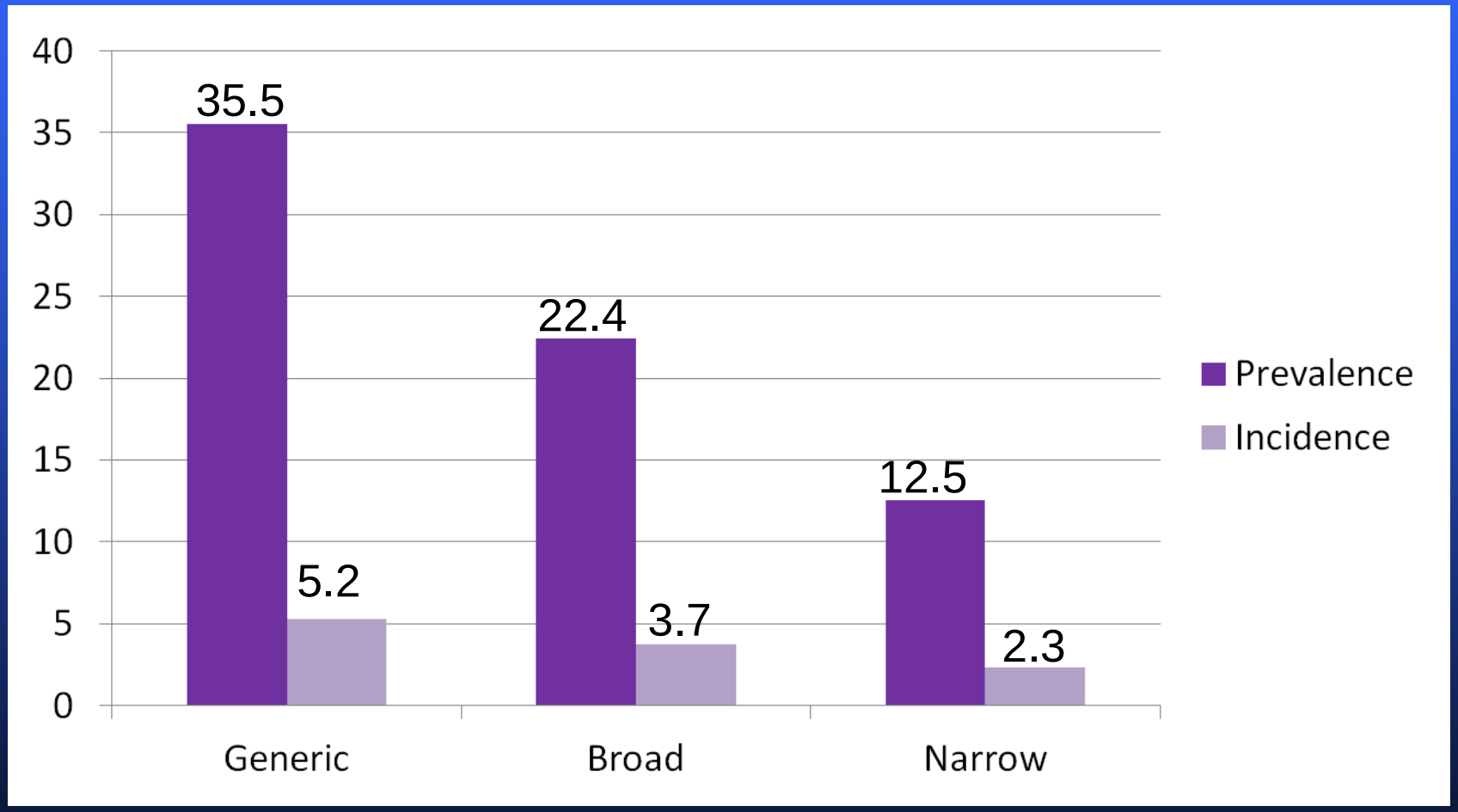
Navaratnam V et al. Thorax 2011;66:462

- 15000 people in the UK have a diagnosis of IPF-CS
- each year, 5000 new cases of IPF
- each year, 5000



"This means that in the UK, more people will die each year from IPF-CS than from ovarian cancer, lymphoma, leukaemia, mesothelioma or kidney cancer"

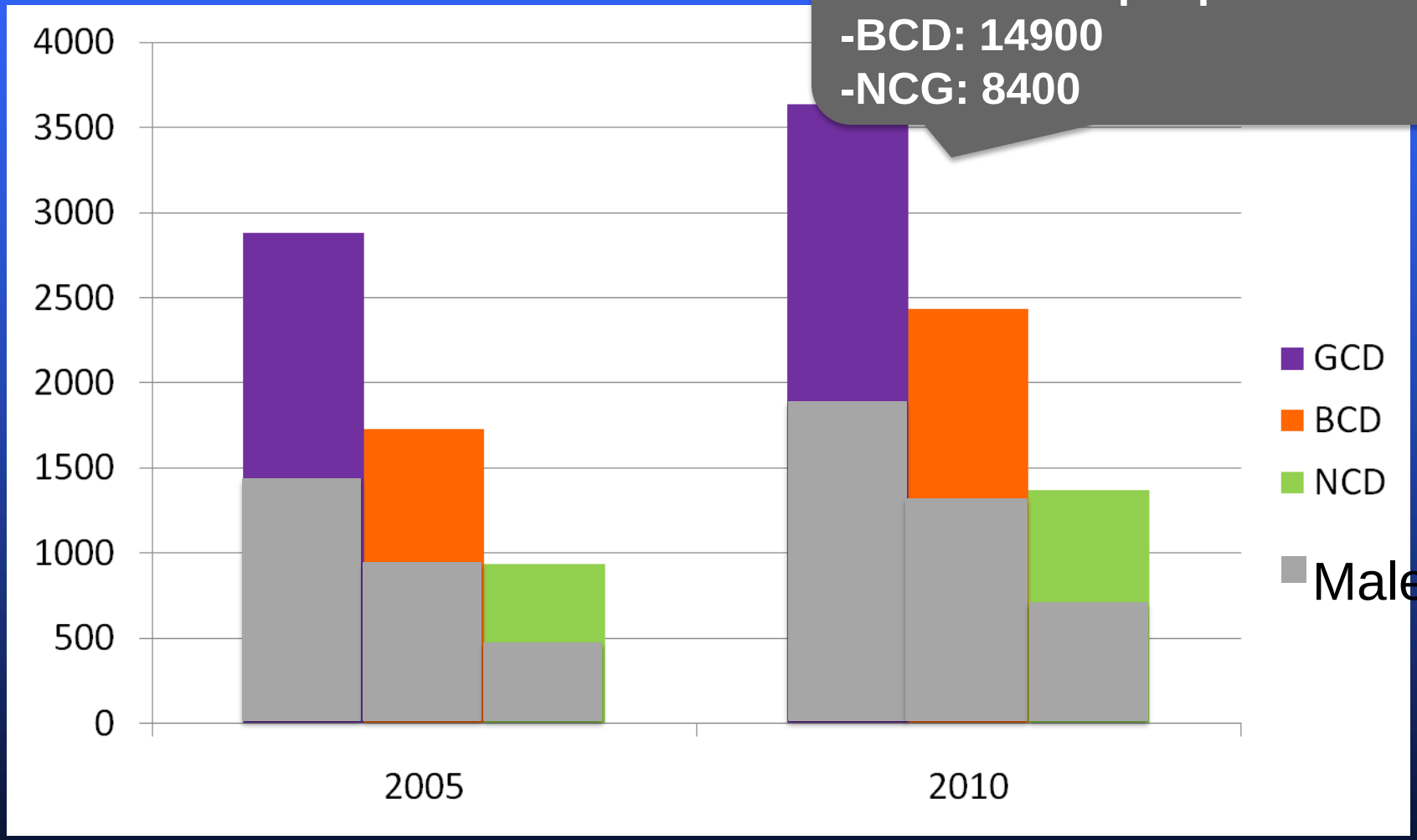
Prevalence and incidence rate *(x100,000 person-years) according to the three case definitions, during the period 2005-2010 in Lombardy*

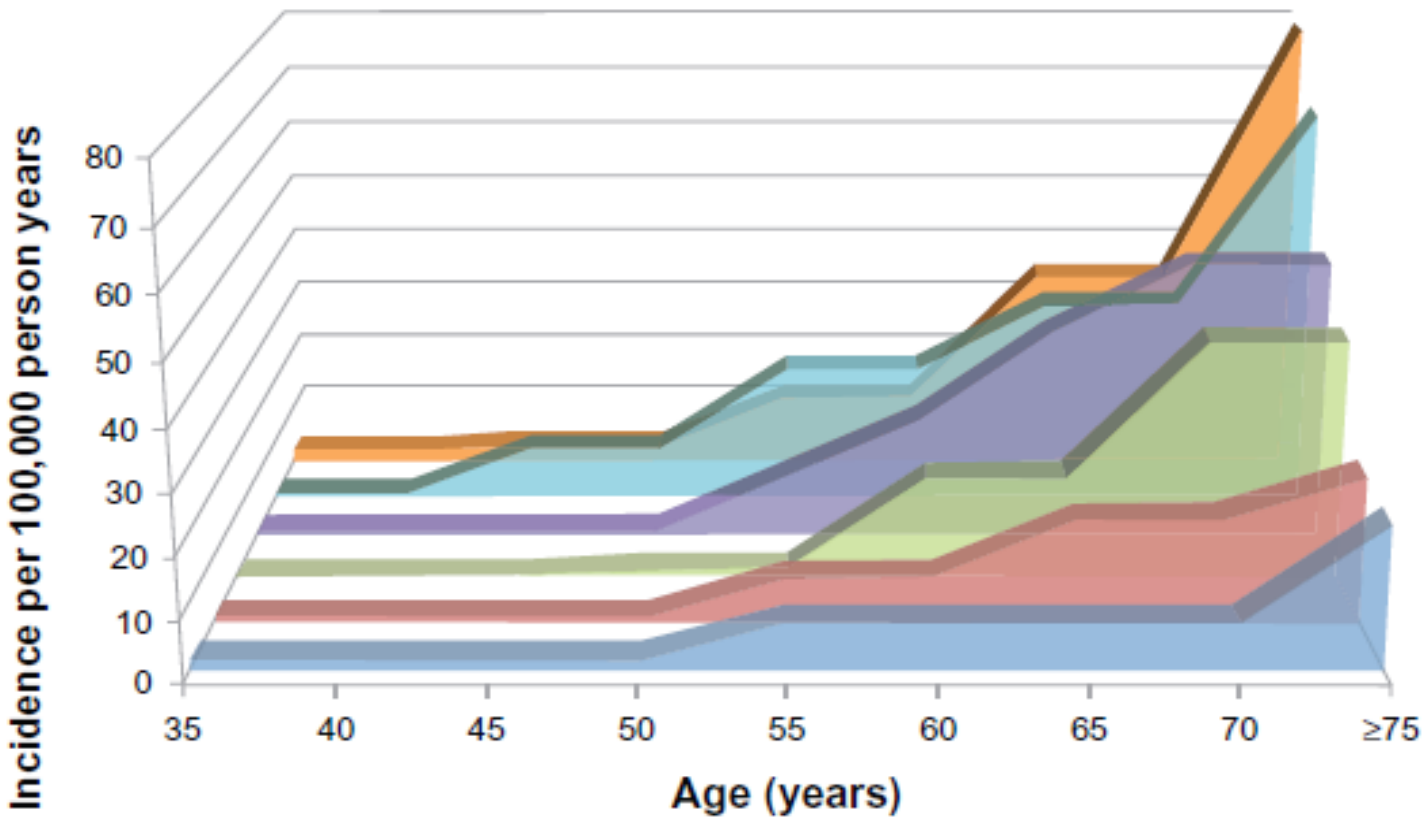


Case definition

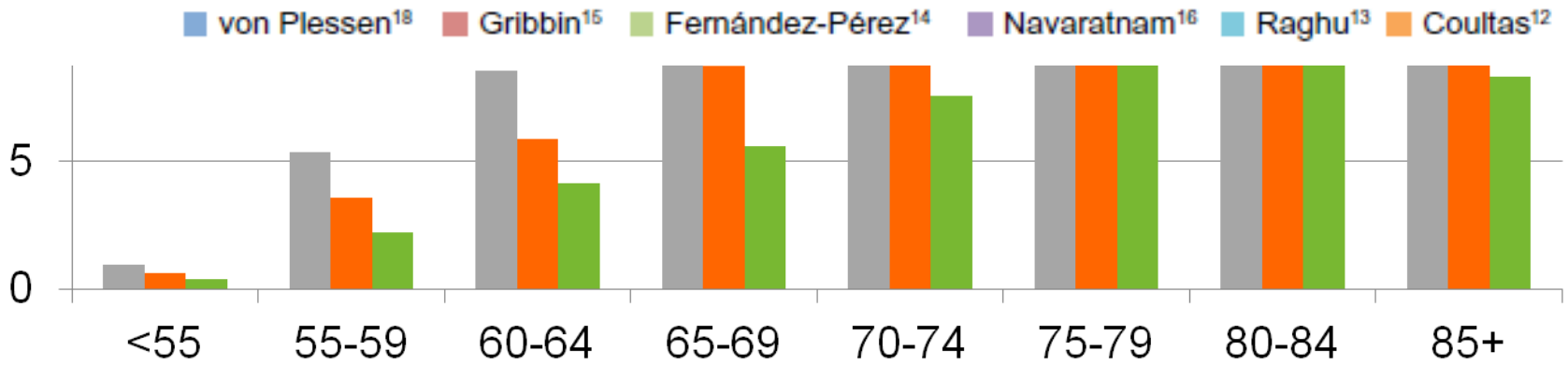
Increase of prevalence - Lombardy

In Italy:
-GCD: 22300 people with IPF
-BCD: 14900
-NCG: 8400




Incidence per 100,000 person years
80
70
60
50
40
30
20
10
0
35
40
45
50
55
60
65
70
≥75
Age (years)

GCD
BCD
NCD


von Plessen[18]
Gribbin[15]
Fernández-Pérez[14]
Navaratnam[16]
Raghu[13]
Coultas[12]
5
0
<55
55-59
60-64
65-69
70-74
75-79
80-84
85+

New definition of IPF

- IPF is a specific form of ***progressive*** fibrosing interstitial pneumonia
- Unknown cause
- Occurring in older adults
- Limited to the lungs
- Associated with a histological ***and/or radiological*** pattern of usual interstitial pneumonia (UIP)

Am J Respir Crit Care Med 2011; 183: 788-824

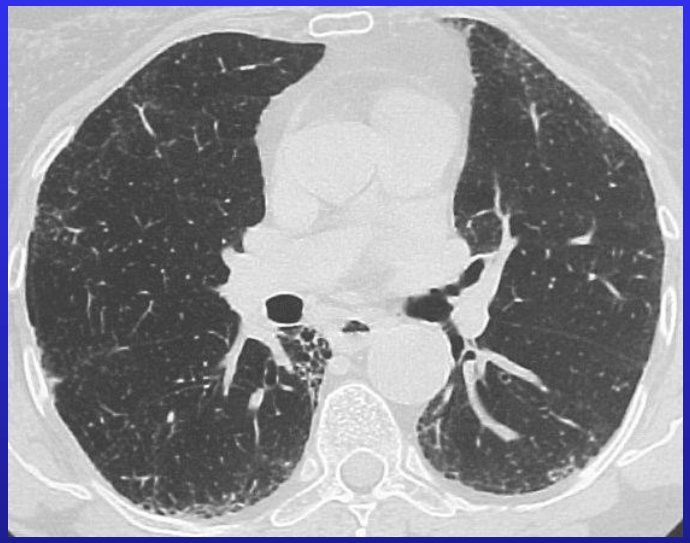
Importance of early diagnosis of IPF

- Begin evaluation for lung transplant earlier
- Allows for earlier referral and enrollment in clinical trials (which are generally limited to patients with mild to moderate disease)
- Emerging evidence regarding response to therapy
- Exclude other more treatable diseases

UIP: progression of fibrosis on CT

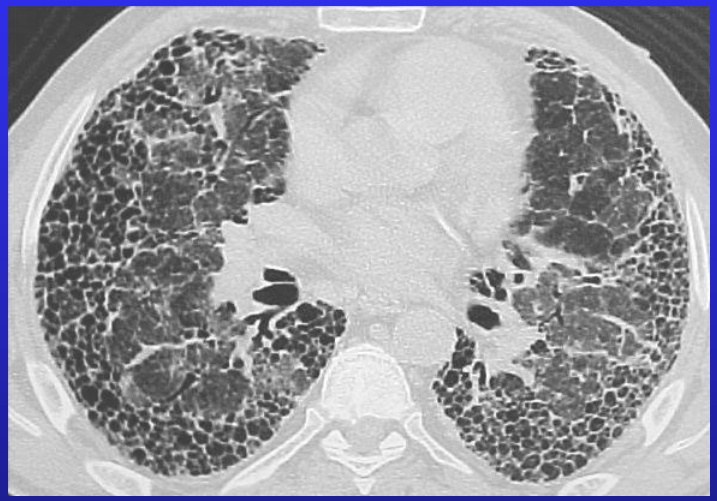
Early:

Reticular



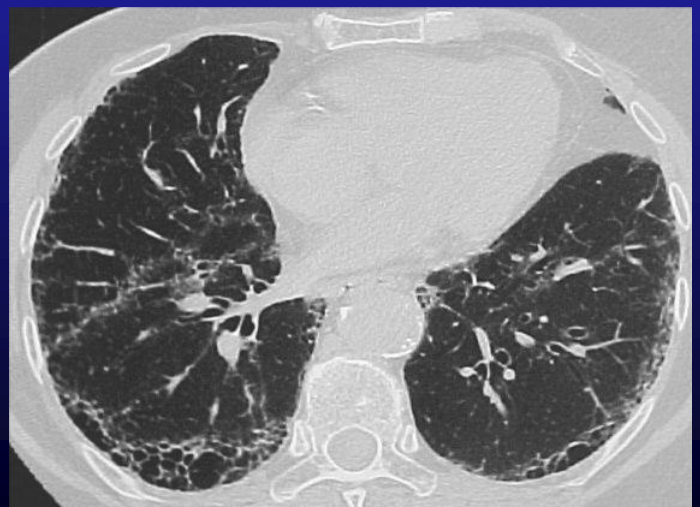
Late:

Diffuse honeycombing



Midcourse:

Subpleural honeycombing



Don't stop with "pulmonary fibrosis"

- Reason for a specific diagnosis:
  - many forms are treatable
  - treatments depend on diagnosis
  - prognosis varies
  - clinical trial eligibility requirements

In idiopathic interstitial pneumonia, diagnosis is prognosis

American Thoracic Society Documents

An official American Thoracic Society/European Respiratory Society Statement: Update of the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias

Travis TW et al. Am J Respir Crit Care Med 2013; 188: 733

Major IIPs are distinguished from rare IIPs and unclassifiable cases

Chronic fibrosing IIP

Smoking-related IIP

Acute/subacute IIP

NSIP is now accepted as a distinct clinical entity

rstitial pneumonias
idiopathic pulmonary fibrosis
c interstitial pneumonia
itis-interstitial lung disease
itial pneumonia
ng pneumonia
Acute interstitial pneumonias
Rare idiopathic interstitial pneumonia
Idiopathic pleuro-parenchymal fibroelastosis
Idiopathic lymphoid interstitial pneumonia
Unclassifiable idiopathic interstitial pneumonias

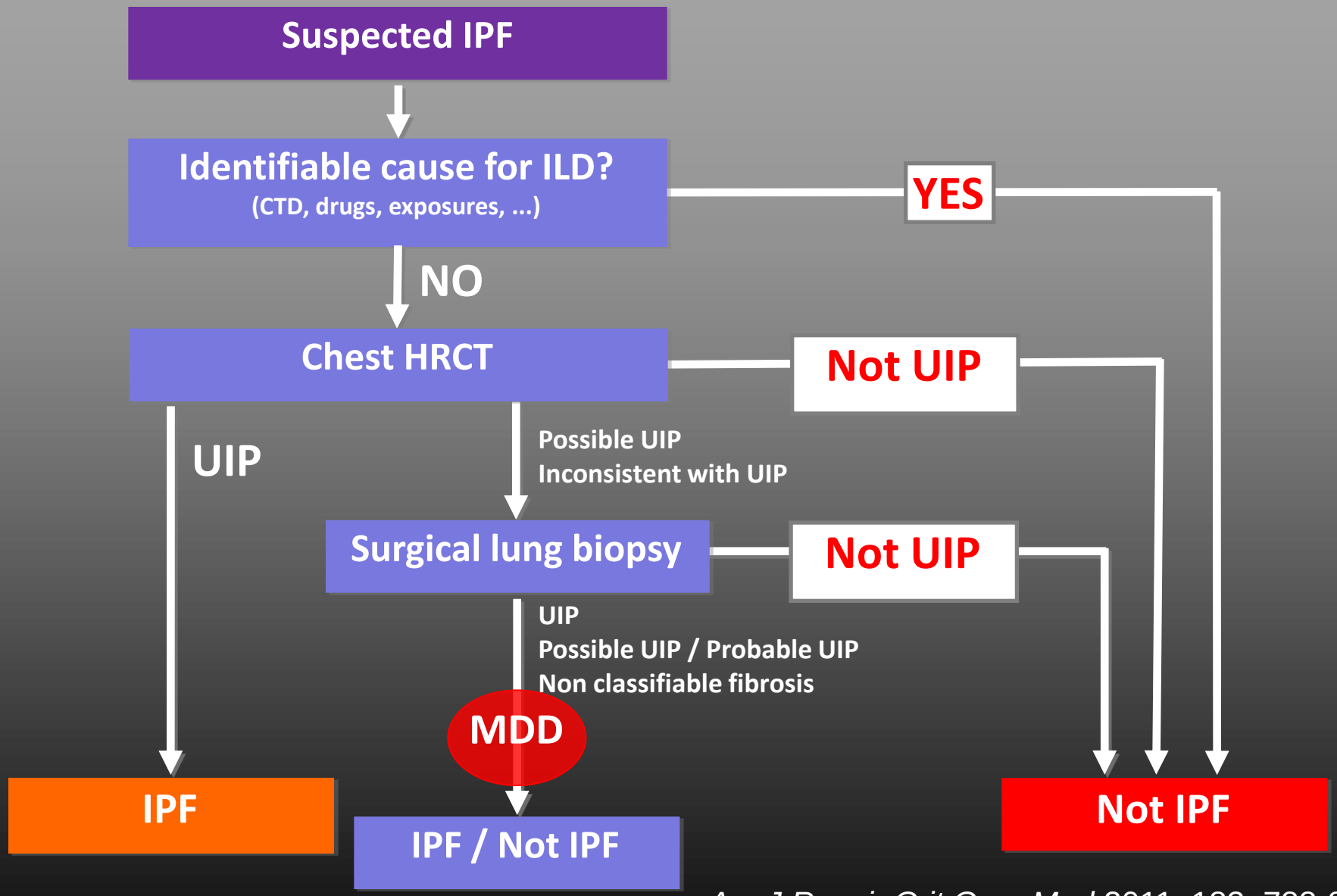
Typical exam is non-specific

Dry bi-basilar crackles most common finding

Inspiratory high-pitched squeaks can be seen with bronchiolitis

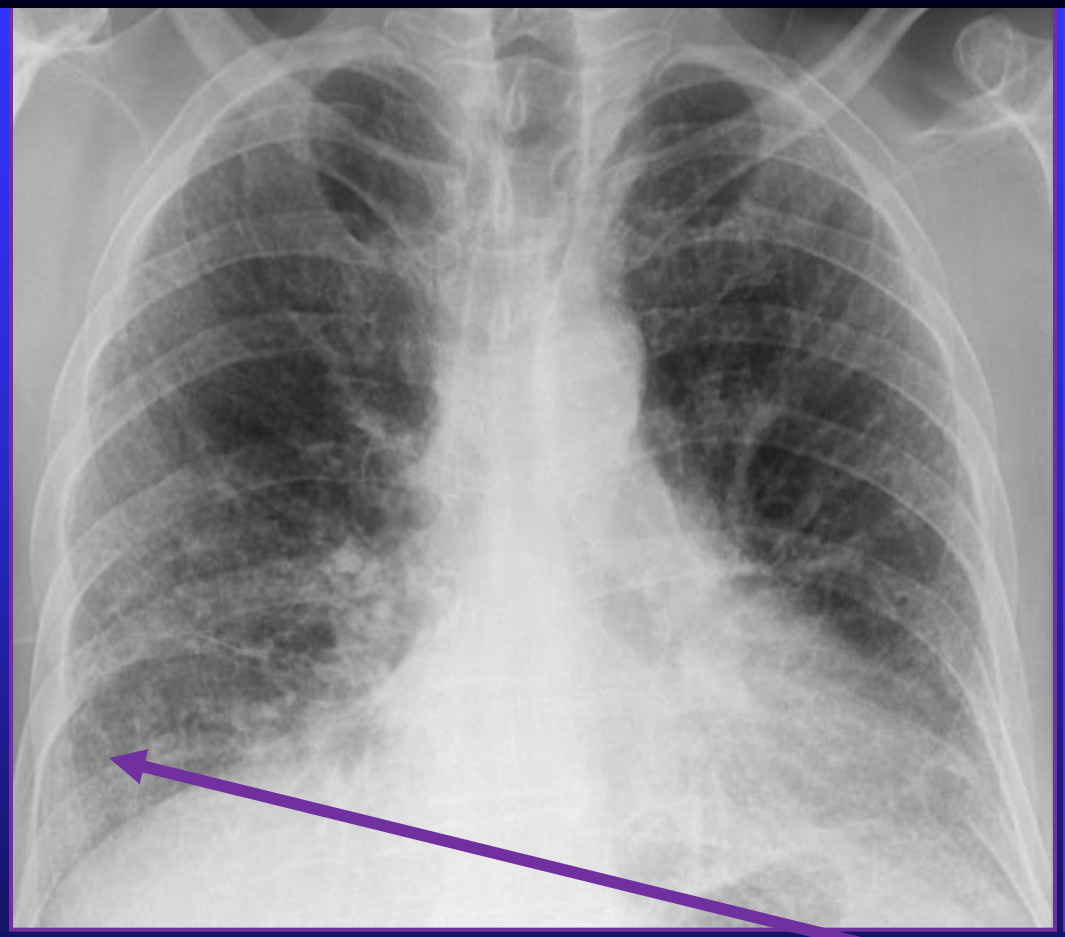
Skin, joint, or muscle findings should prompt evaluation for an underlying rheumatologic disorder

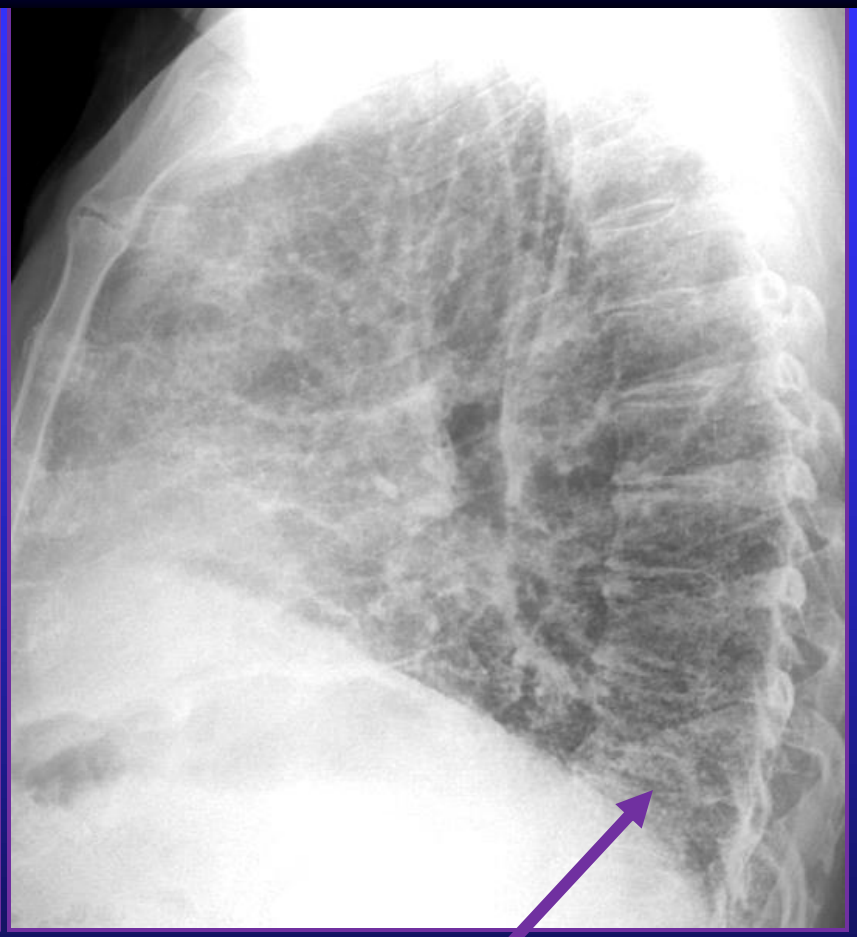
Diagnostic algorithm for IPF



Am J Respir Crit Care Med 2011; 183: 788-824

Chest radiograph in IPF



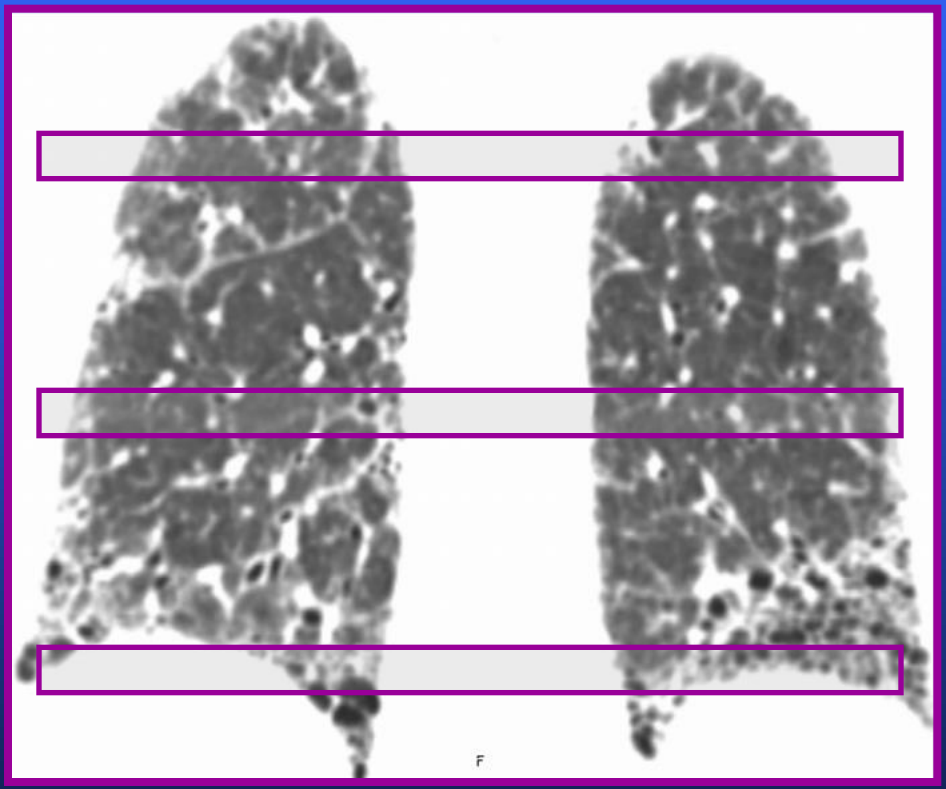


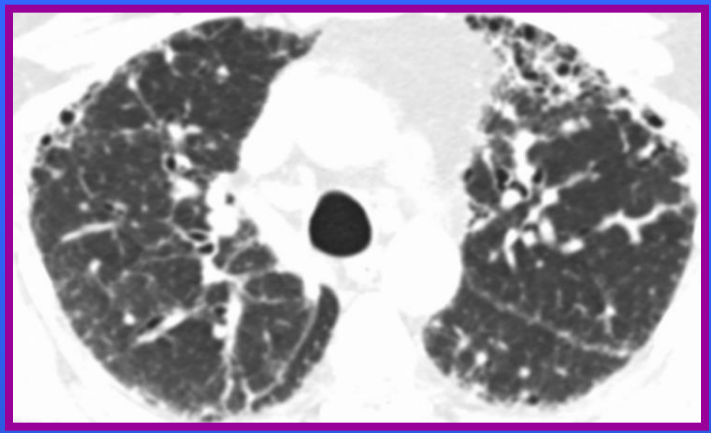
Reduced lung volume

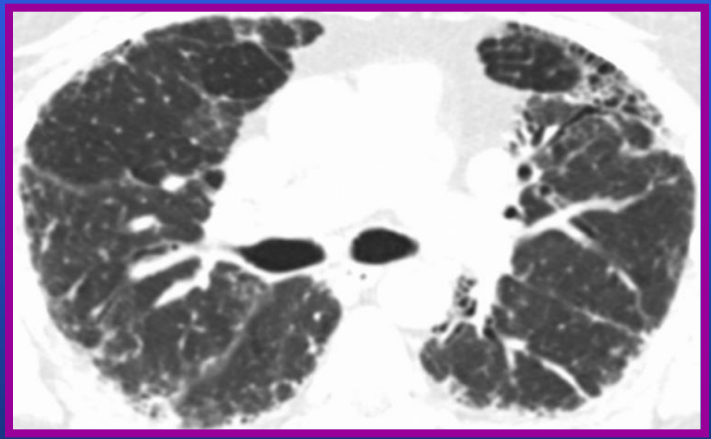
Basal and peripheral reticulation

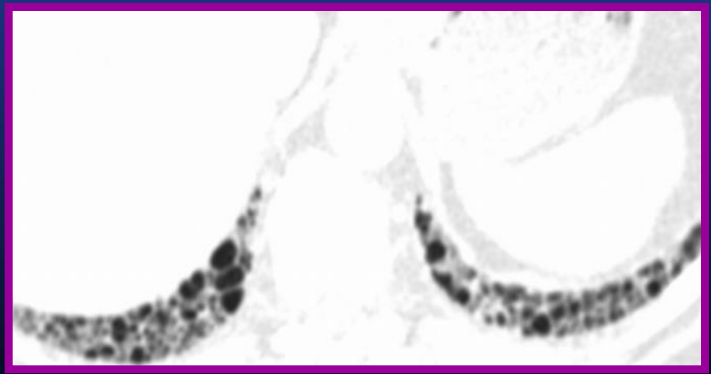
A normal chest x-ray does not exclude IPF

HRCT

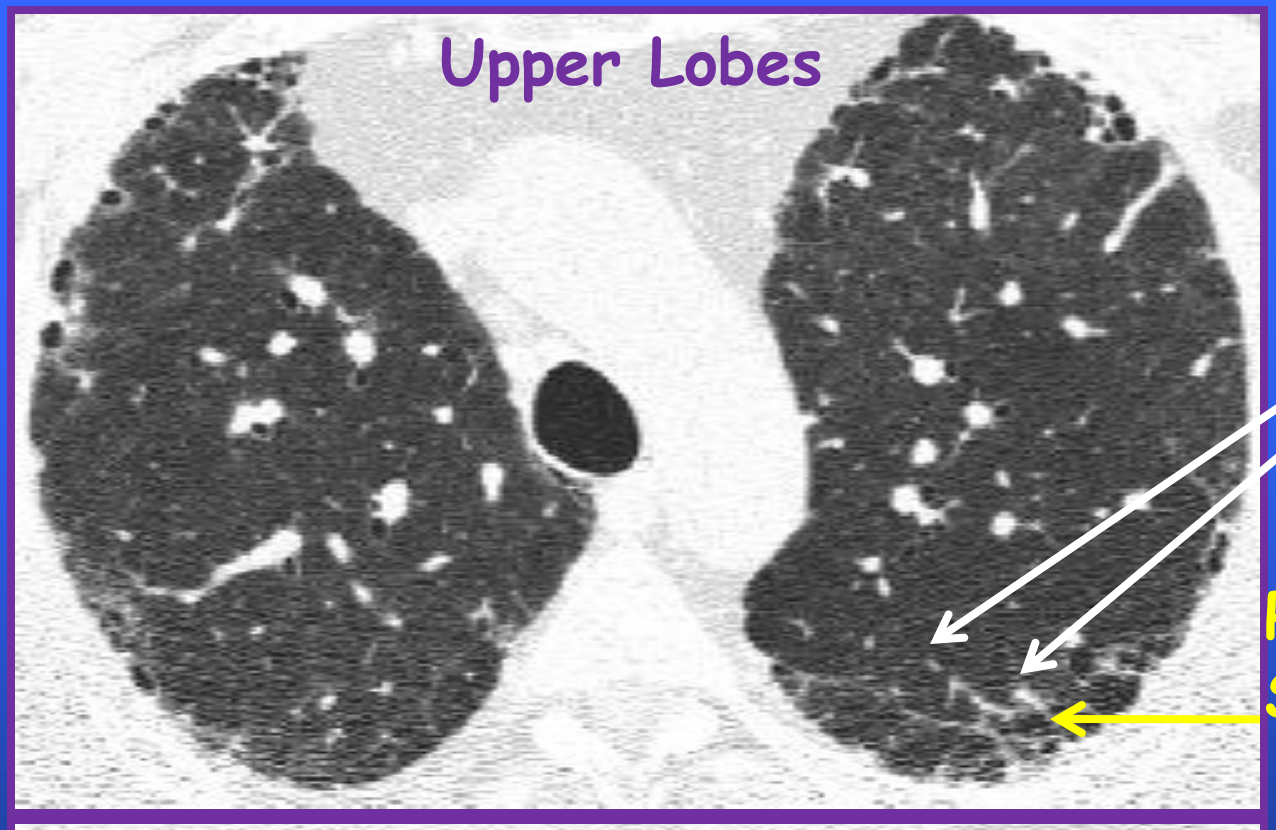








UIP



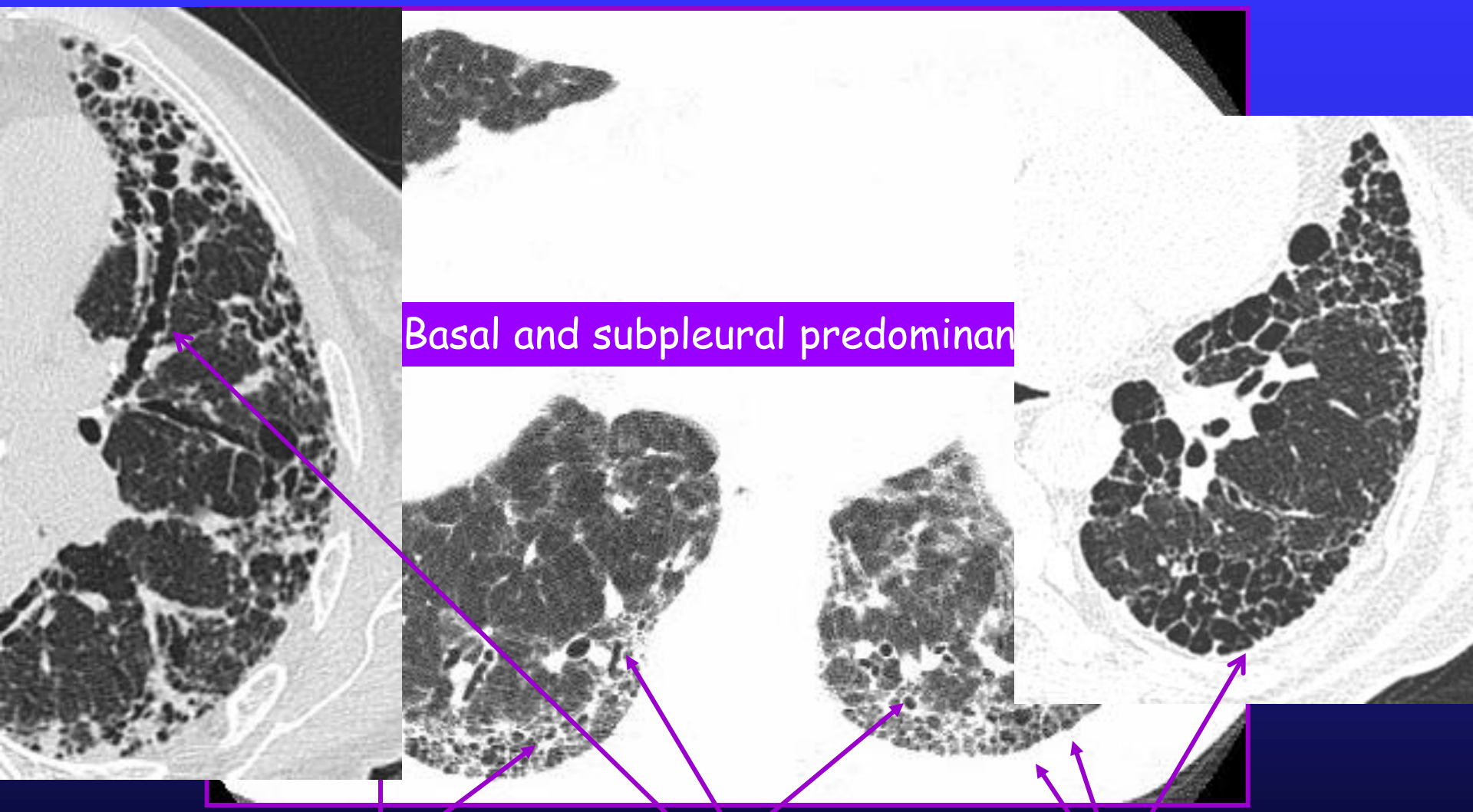
Irregular lines

Peripheral/ Sub-pleural

Honeycomb

Lower Lobe Predominant

Classic IPF HRCT

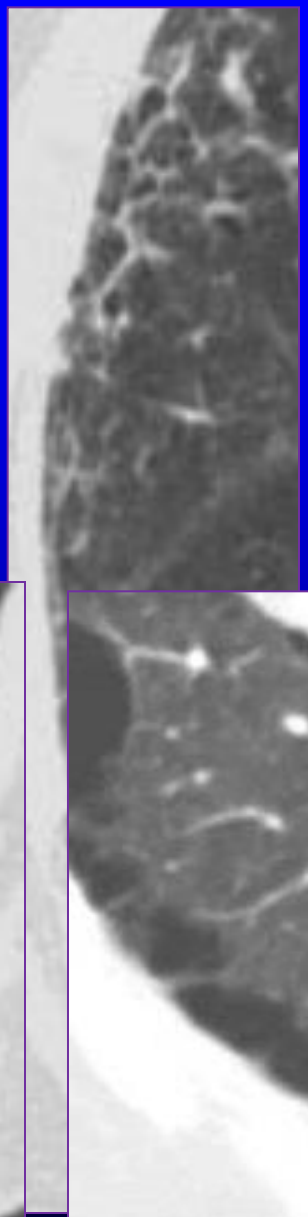


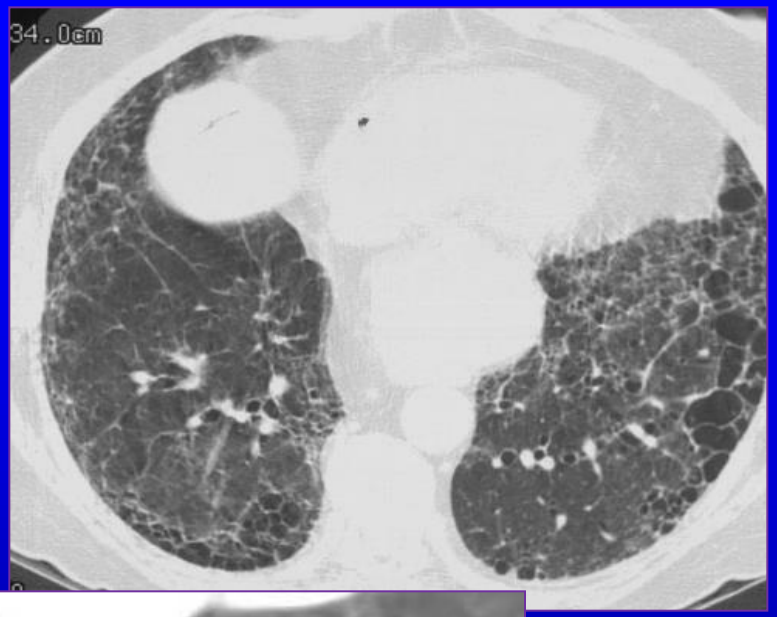
HRCT

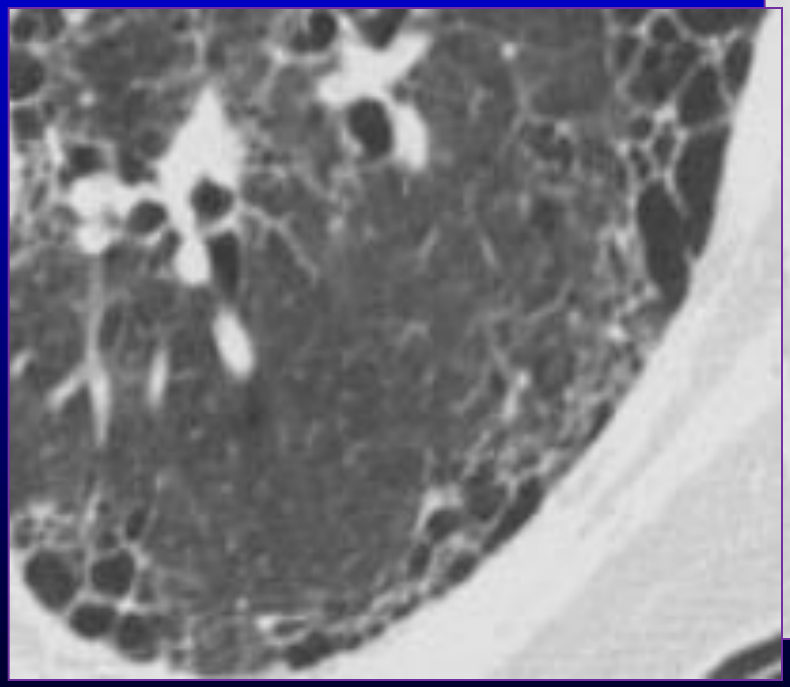
<u>features of fibrosis</u>,

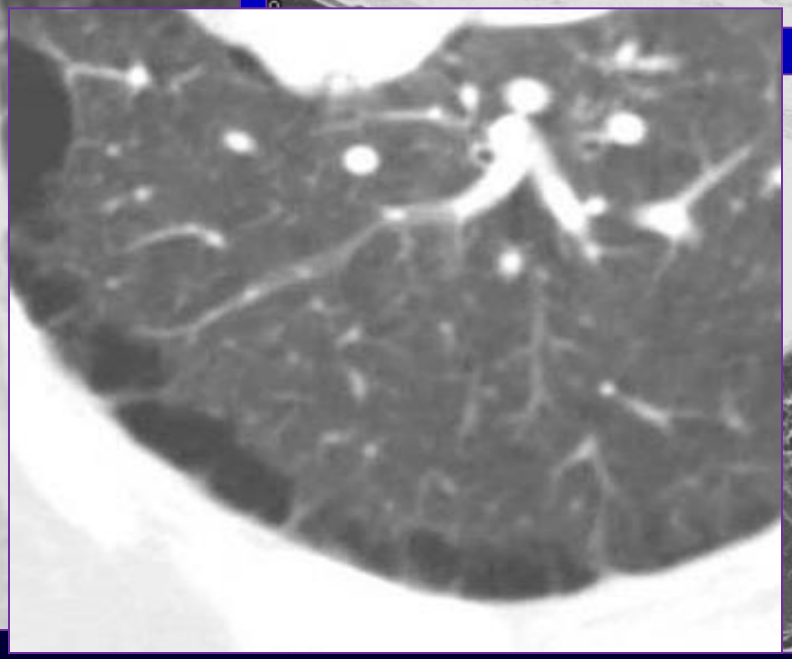
Intra-lobular and inter-lobular septal thickening, walled cysts representing honeycombing,

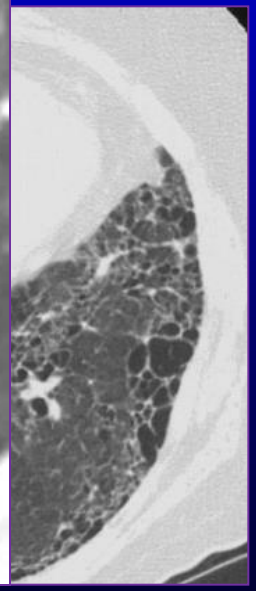
may be associated traction bronchiectasis









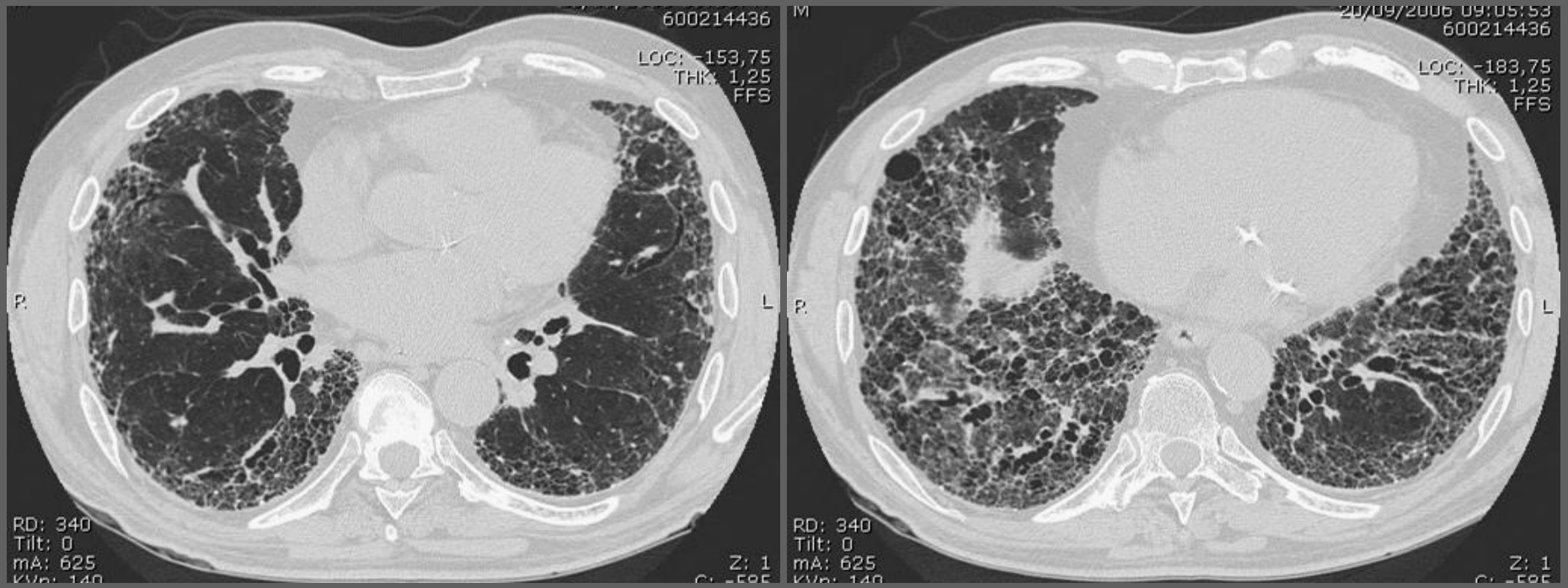


“The diagnosis of IPF *requires*:

a) exclusion of other known causes of interstitial lung disease

a) the presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy

a) specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy”

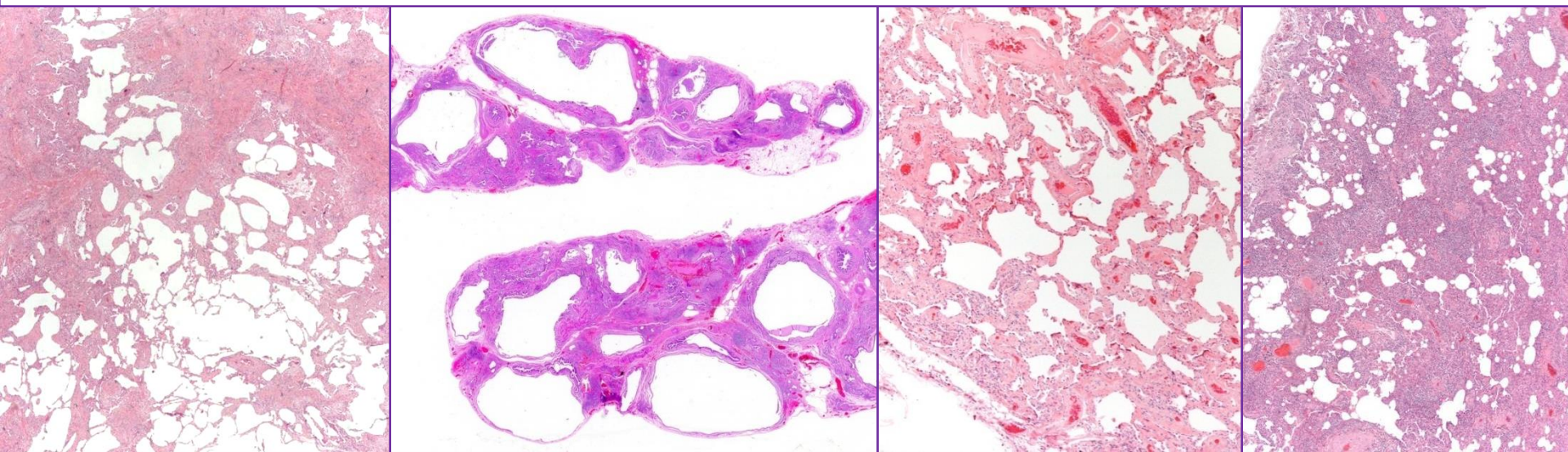


***Am J Respir Crit Care Med* 2011; 183: 788-824**

Am J Respir Crit Care Med 2011; 183: 788-824

TABLE 5. HISTOPATHOLOGICAL CRITERIA FOR UIP PATTERN

UIP Pattern (All Four Criteria)	Probable UIP Pattern	Possible UIP Pattern (All Three Criteria)	Not UIP Pattern (Any of the Six Criteria)
• Evidence of marked fibrosis/ architectural distortion, ± honeycombing in a predominantly subpleural/ paraseptal distribution • Presence of patchy involvement of lung parenchyma by fibrosis • Presence of fibroblast foci • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)	• Evidence of marked fibrosis / architectural distortion, ± honeycombing • Absence of either patchy involvement or fibroblastic foci, but not both • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (*see* fourth column) OR • Honeycomb changes only‡	• Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation • Absence of other criteria for UIP (*see* UIP PATTERN column) • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (*see* fourth column)	• Hyaline membranes* • Organizing pneumonia*† • Granulomas† • Marked interstitial inflammatory cell infiltrate away from honeycombing • Predominant airway centered changes • Other features suggestive of an alternate diagnosis



HRCT Pattern	Surgical Lung Biopsy Pattern *(when performed)*	Diagnosis of IPF?
UIP	UIP Probable UIP Possible UIP Non-classifiable fibrosis	YES
	Not UIP	No
Possible UIP	UIP Probable UIP	YES
	Possible UIP Non-classifiable fibrosis	*Probable*
	Not UIP	No
Inconsistent with UIP	UIP	*Possible*
	Probable UIP Possible UIP Non-classifiable fibrosis Not UIP	No

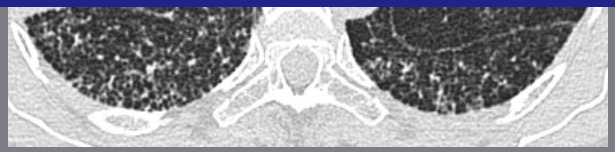
Am J Respir Crit Care Med 2011; 183: 788-824

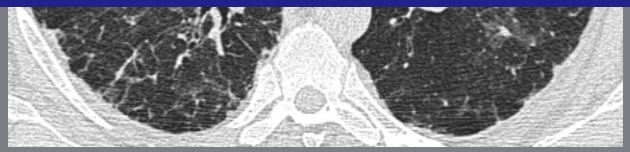
Am J Respir Crit Care Med 2011; 183: 788-824

Inconsistent with UIP pattern (any of the seven):

- Upper or mid-lung predominance
- Peribronchovascular predominance
- Extensive groud glass abnormality (extent > reticular abnormality)
- Profuse micronodules (bilateral, predominantly upper lobes)
- Discrete cysts (multiple, bilateral, away from areas of honeycombing)
- Diffuse mosaic attenuation/air-trapping (bilateral, in three or more lobes)
- Consolidation in bronchopulmonary segment(s)/lobe(s)

***Am J Respir Crit Care Med* 2011; 183: 788-824**

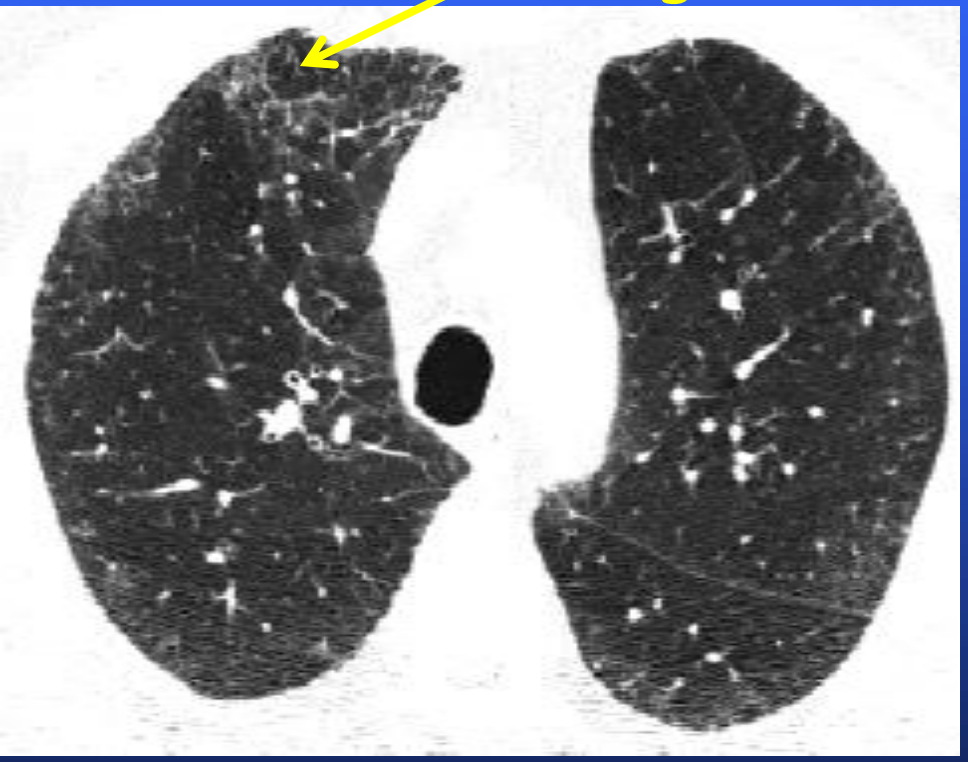


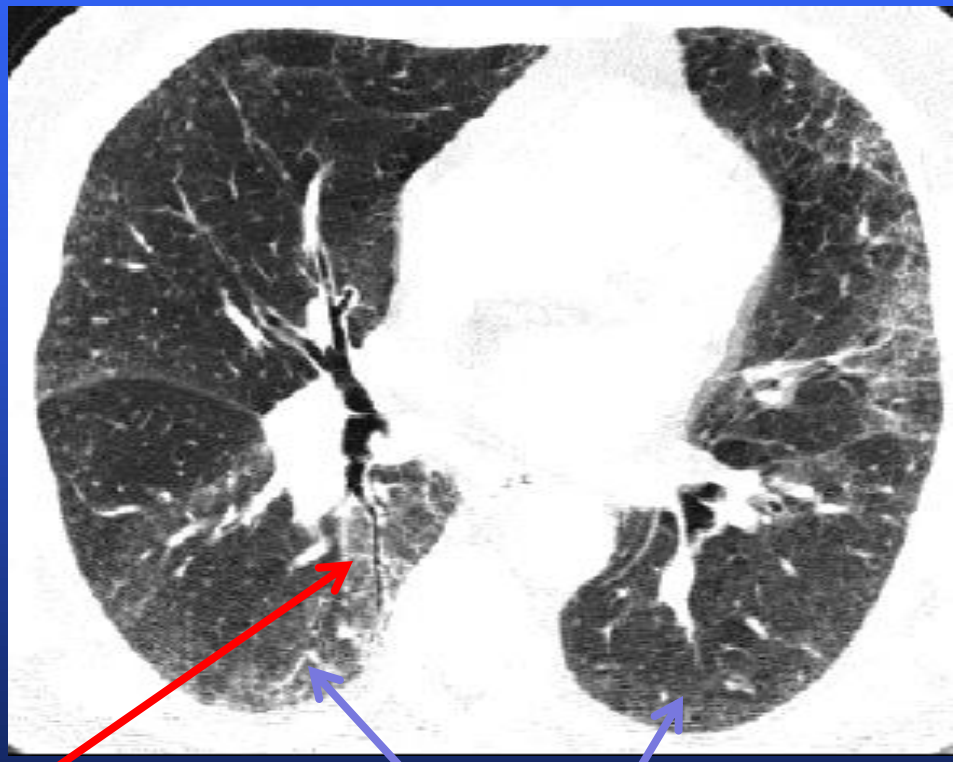


HRCT e Polmone

Non Specific Interstitial Pneumonia

Irregular lines





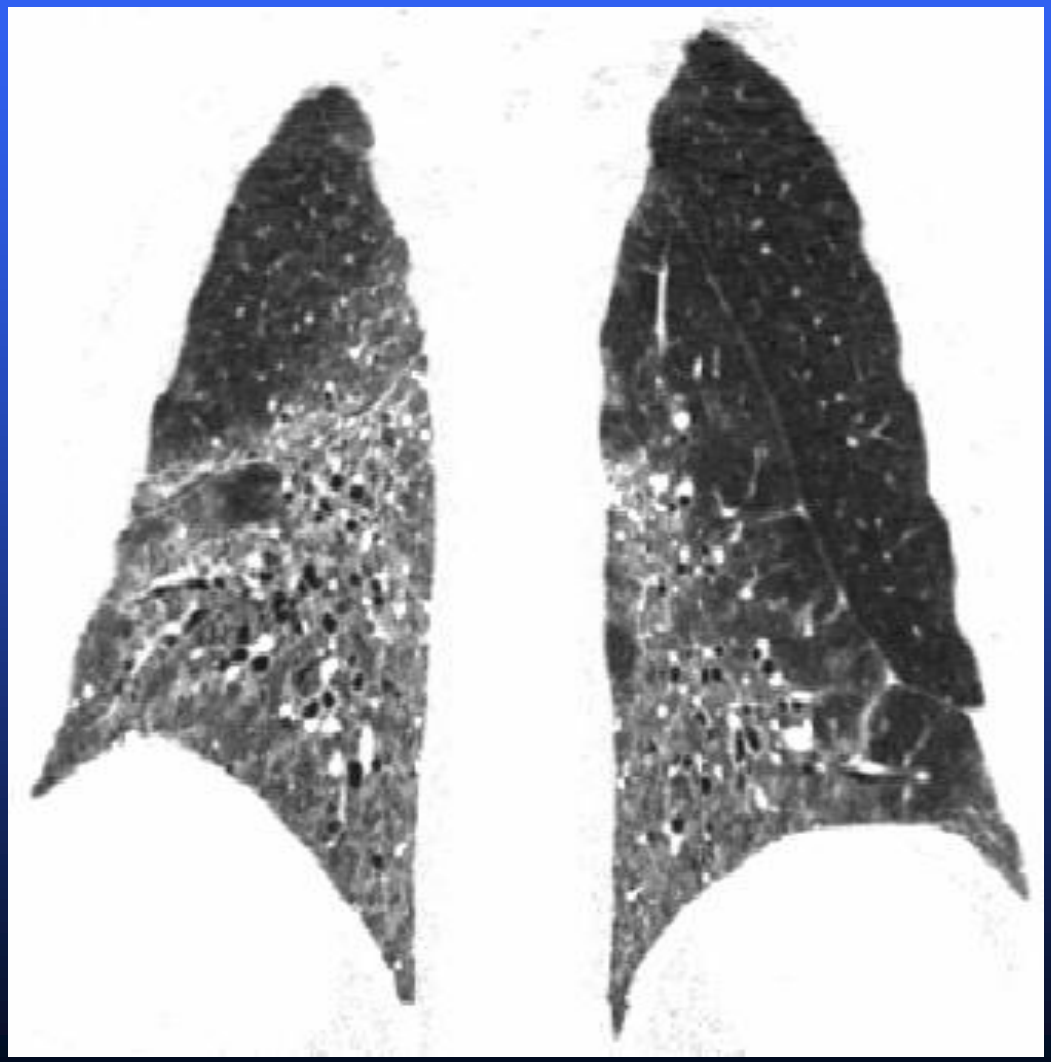
Peripheral/
Lower Lobes
distribution

Traction bronchiectasis

Ground glass

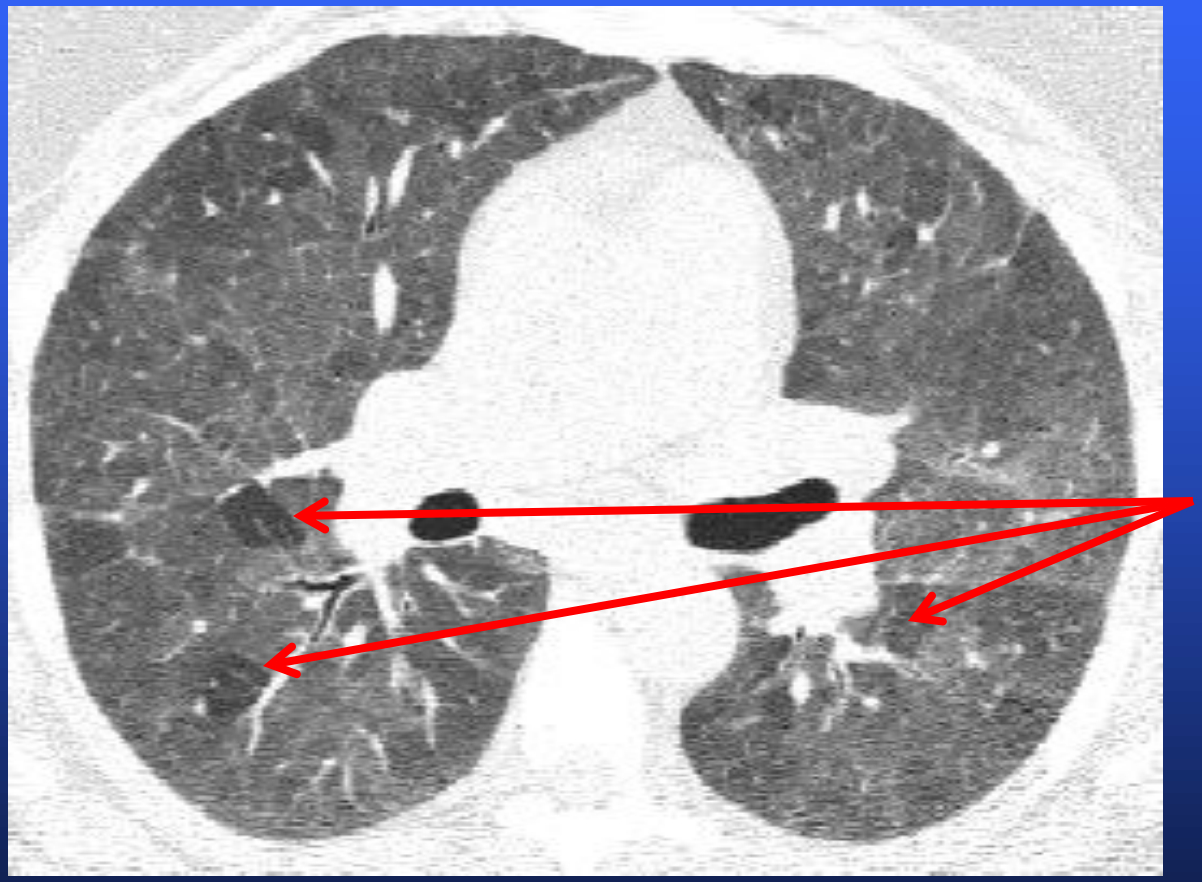
HRCT e Polmone

Non Specific Interstitial Pneumonia



HRCT e Polmone

Hypersensitivity Pneumonitis



Mosaic

- Ground glass
- air-trapping

**Note: if chronic, fibrosis can mimic UIP, but is usually patchy and less sub-pleural and lower lung in distribution

Chronic hypersensitivity pneumonitis: differentiation from UIP and NSIP using thin-section CT

Silva C. Radiology 2008; 246: 288

HRCT findings allow confident distinction of chronic HP from IPF and NSIP approximately 50% of the time

Diagnosis of HP at CT prompts a thorough clinical history to determine inciting antigens and removal of

IIPs are frequently confused with HP, and vice versa, except when the exposure is readily apparent
A detailed search for potential exposure in patients with these findings is essential, including consideration of specific circulating IgG antibodies, but up to 30% of subjects with histological HP have no identifiable exposure

Reason for being unclassifiable

Reasons	•Examples
No biopsy performed or biopsy non-contributory (unclassifiable clinical/radiological condition)	• Biopsy non proposed (stable or mild disease with biopsy risk outweighing benefit) •Contraindication to biopsy •Biopsy suggested but refused by patient •Inadequate biopsy sample
Overlapping histological features (unclassifiable histology)	•NSIP/UIP overlap •HP/UIP overlap, etc.
Major discrepancy (unclassifiable clinical/radiological/ pathological condition)	•Stable disease, but UIP on histology

10-20% of ILD patients remain unclassified after multidisciplinary evaluation

Usefulness of BAL in diagnosis of IPF: Conclusions

Should BAL cellular analysis be performed in the diagnostic evaluation of suspected IPF?

The most important application of BAL is in the exclusion of chonic HP; prominent lymphocitosis (>40%) should suggest the diagnosis

Recommendation: BAL cellular analysis should not be performed in the diagnostic evaluation of IPF in the majority of patients, but may be appropriate in a minority (weak recommendation, low-quality evidence)

Am J Respir Crit Care Med 2011; 183: 788-824

What's the problem?

- It is not uncommon for pulmonologist to find patients with IP who are supposed to have a systemic autoimmune disease
- Within current classification schemes, many of these patients are labeled as idiopathic by default
- Despite the recognition that IP may be the *forme fruste* presentation of CTD, current classification criteria do not allow a CTD designation for ILD alone

Why is important to discover an occult CTD?

- For disease prognosis
- For appropriate therapeutic approach
- For a search of additional system involvement or underlying malignancy
- For specific complications
- Is lung biopsy indicated?

Conclusions

- The early recognition of IPF starts with a high level of clinical suspicion
- The approach to the diagnosis of IPF requires a multi-disciplinary effort (pulmonologist, radiologist, and pathologist)
- Differentiating IPF from other ILDs can direct the management and predict the prognosis of these patients

Conclusions

- It is important to look for additional minor/minimal abnormalities (clinical, radiological, histological) that may help in diagnosis of occult CTD or chronic HP
- IPF can be diagnosed on HRCT in the majority of cases but a crucial sub-group have very atypical HRCT appearances
- Early diagnosis of IPF allows early treatment approaches and prompt referral for LTx

18 May 2014

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Randomized Trial of Acetylcysteine in Idiopathic Pulmonary Fibrosis

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

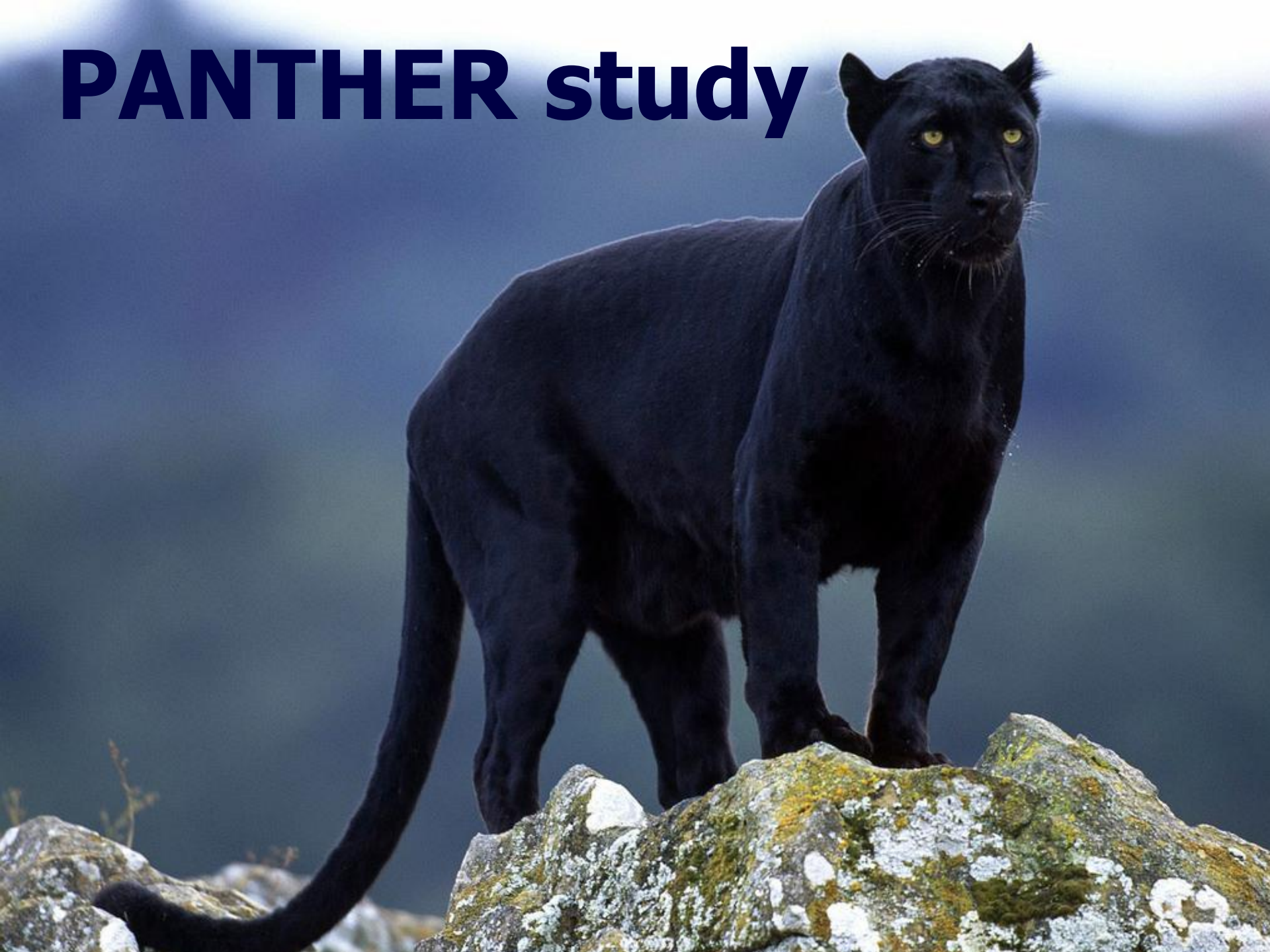
A new era in IPF therapy?

ATS 2014
Where today's science meets tomorrow's care™

INTERNATIONAL CONFERENCE
May 16 - May 21
San Diego

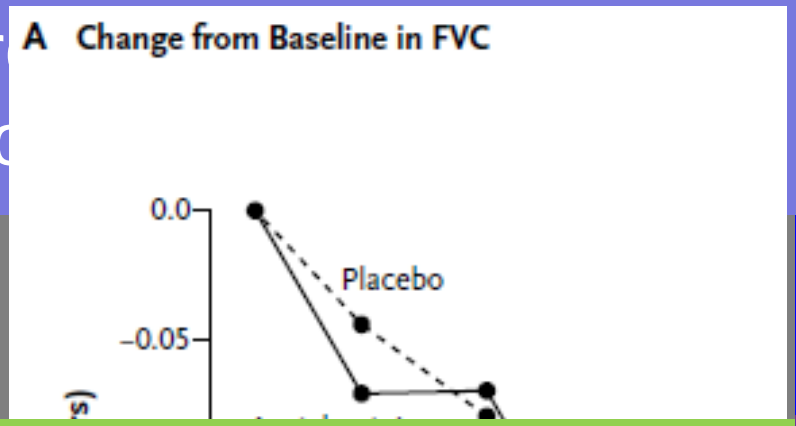
in Idiopathic Pulmonary Fibrosis

PANTHER study



Randomized Trial of Acetylcysteine in Idiopathic Pulmonary Fibrosis

133 and 131 patients were enr
acetylcysteine and placebo gro

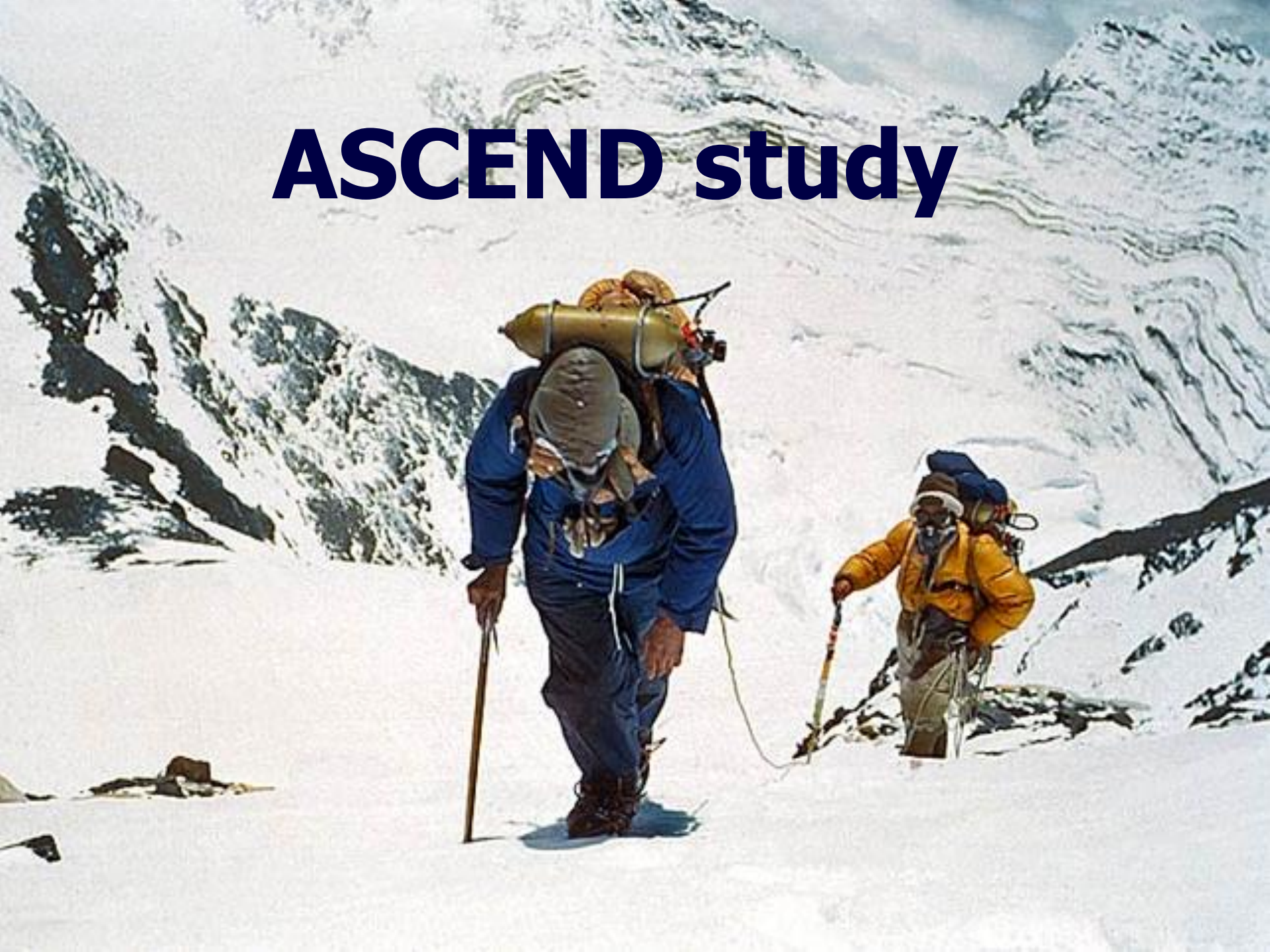


Inclusion criteria
35-85 age

Adverse events: cardiac disorders occurred in 9 of 133 patients (6.8%) in the acetylcysteine group and in 2 of 131 patients (1.5%) in the placebo group (P = 0.03)

respect to the preservation of FVC in patients with IPF with mild to-moderate impairment in lung function

ASCEND study



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

In this phase 3 study, 555 patients with IPF was randomly assigned to receive either oral pirfenidone (2403 mg per day) or placebo for 52 weeks

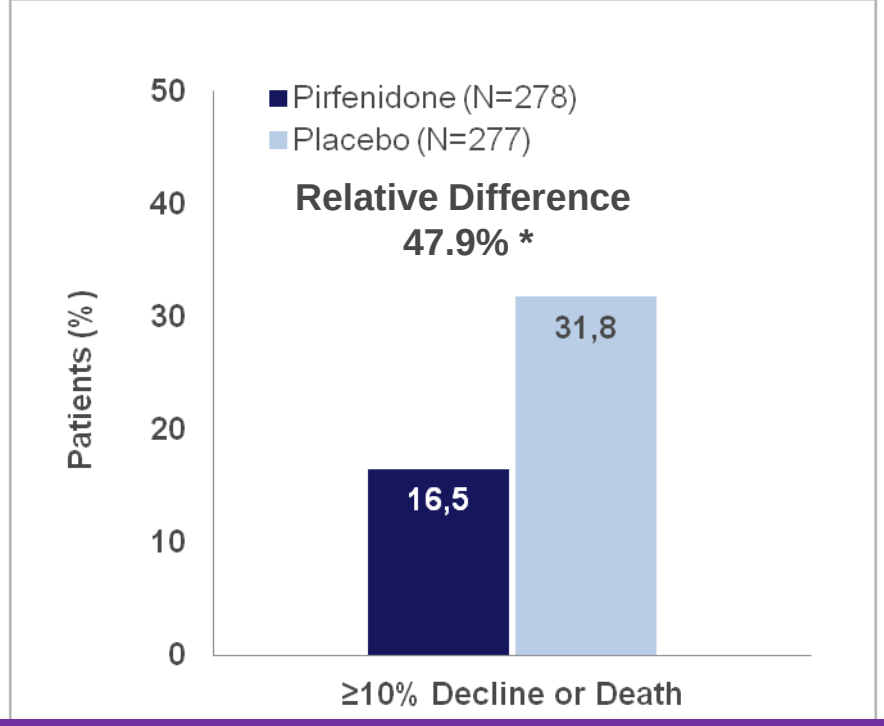
Inclusion criteria

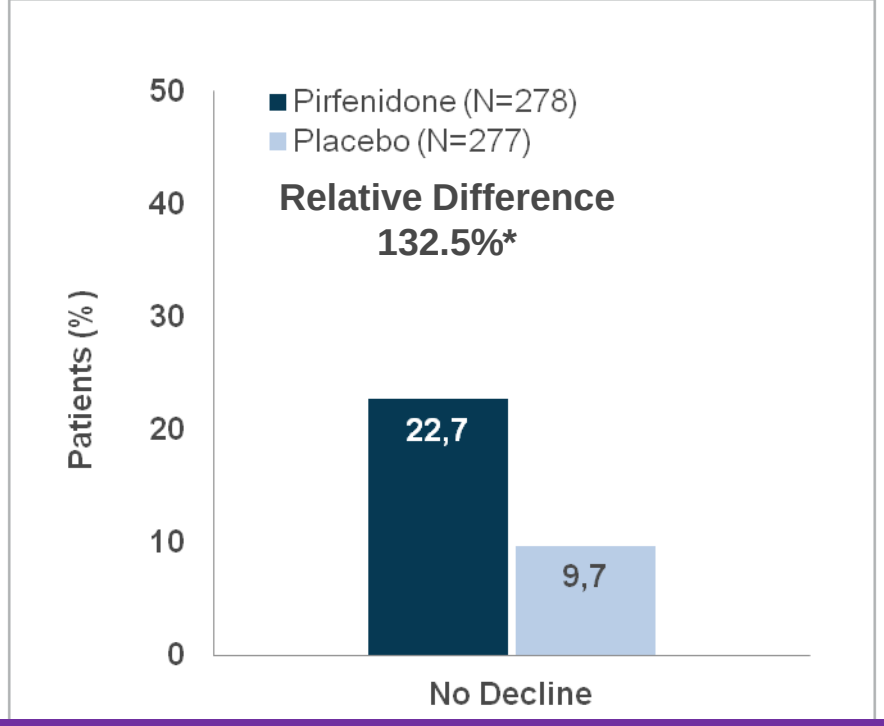
40-80 yr

Diagnosis of definite or probable IPF per the ATS 2011 guidelines up to 48 months before randomization

%FVC≥50% and ≤90% at screening

%DLCO≥30% and ≤90% at screening

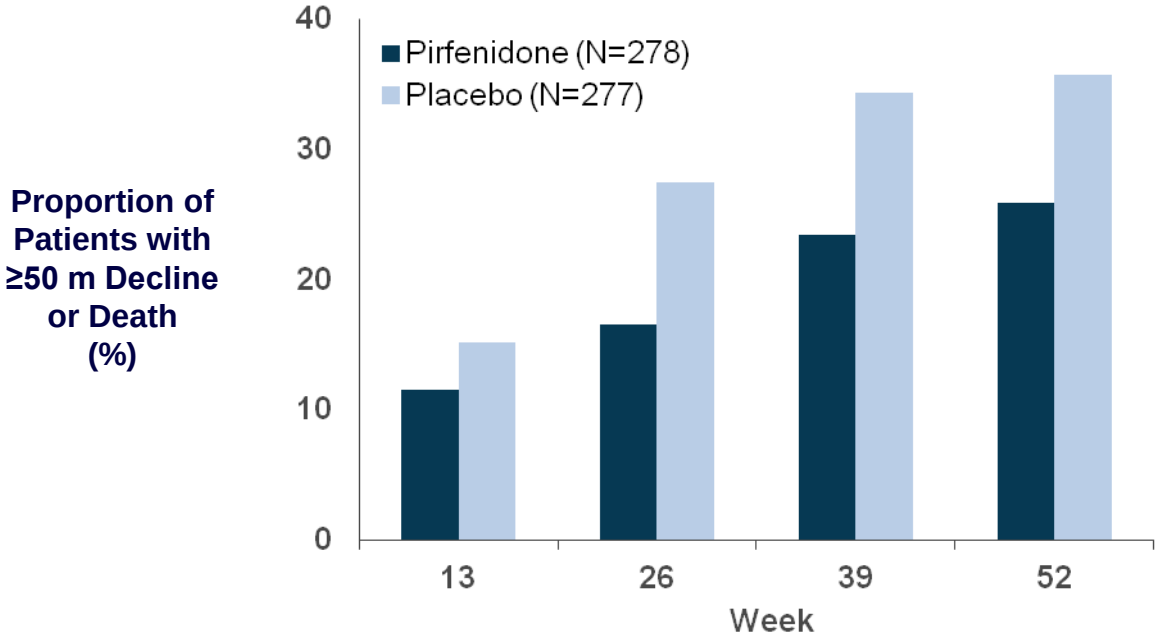




A total of 93.5% and 94.6% of patients completed the study in the pirfenidone and placebo groups, rispectively

The percentage of patients discontinuing treatment due to and adverse event was 14.4% in the pirfenidone group and 10.8% in the placebo group

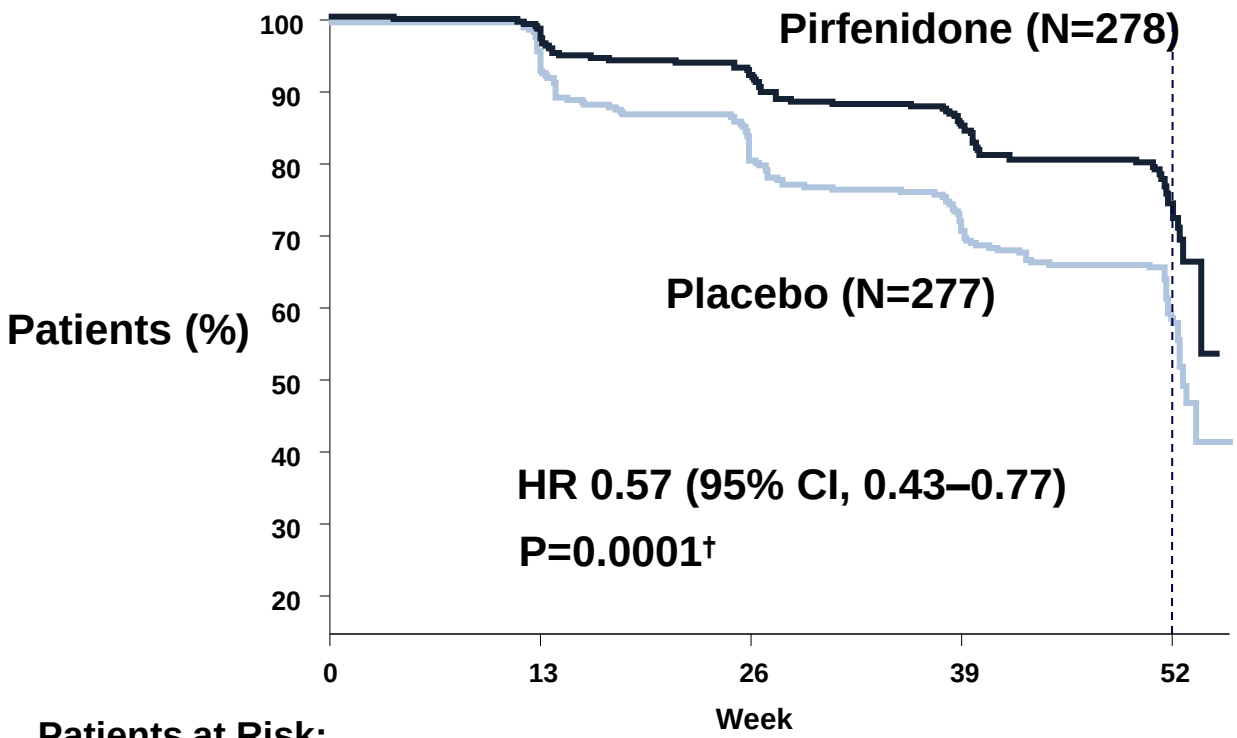
Absolute difference	**59.6 mL**	**111.0 mL**	**116.7 mL**	**192.8 mL**
Relative difference	**62.5%**	**54.9%**	**43.9%**	**45.1%**
Rank ANCOVA P-value	**<0.000001**	**<0.000001**	**0.000002**	**<0.000001**



Absolute Difference	3.7%	10.9%	10.9%	9.8%
Relative Difference	24.1%	39.7%	31.8%	27.5%
Rank ANCOVA p-value*	0.401	0.119	0.041	0.036

6-Minute Walk Distance: Significant between-group difference in the change from baseline to week 52

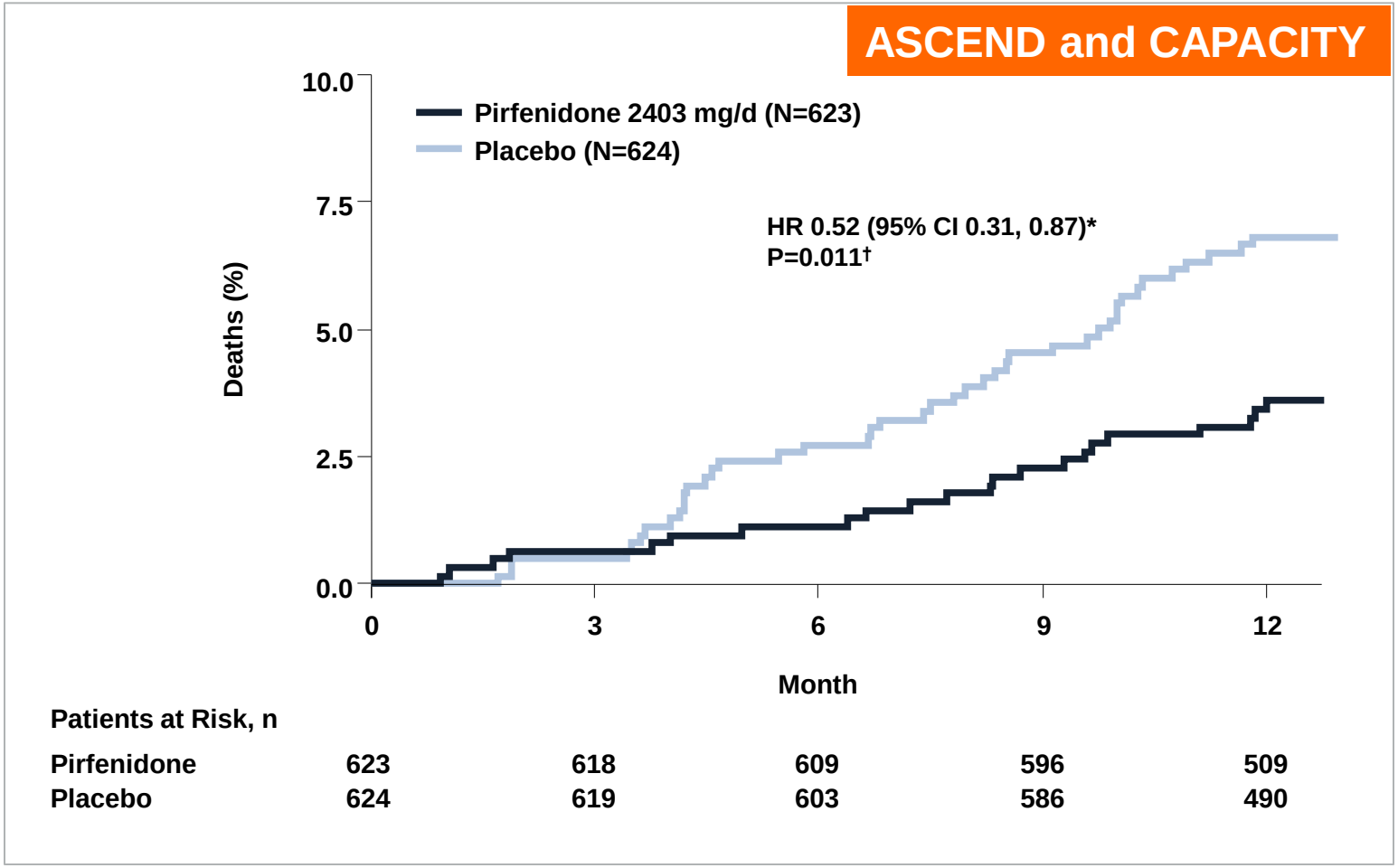
Progression-free Survival (PFS)* : Pirfenidone reduced the risk of disease progression or death by 43%



Patients at Risk:					
Pirfenidone	276	269	243	219	144
Placebo	273	262	225	192	113

*** Time to death or disease progression (confirmed ≥10% decline in FVC or confirmed ≥50 m decline in 6MWD)**
† Log-rank test

Pooled All-cause Mortality (Week 52): Treatment group curves diverge early and continue separating throughout the study period



* Cox proportional hazards model)
† Log-rank test

King TE et al. *N Engl J Med* 2014 May 18. doi:10.1056/NEJMoa1402582

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

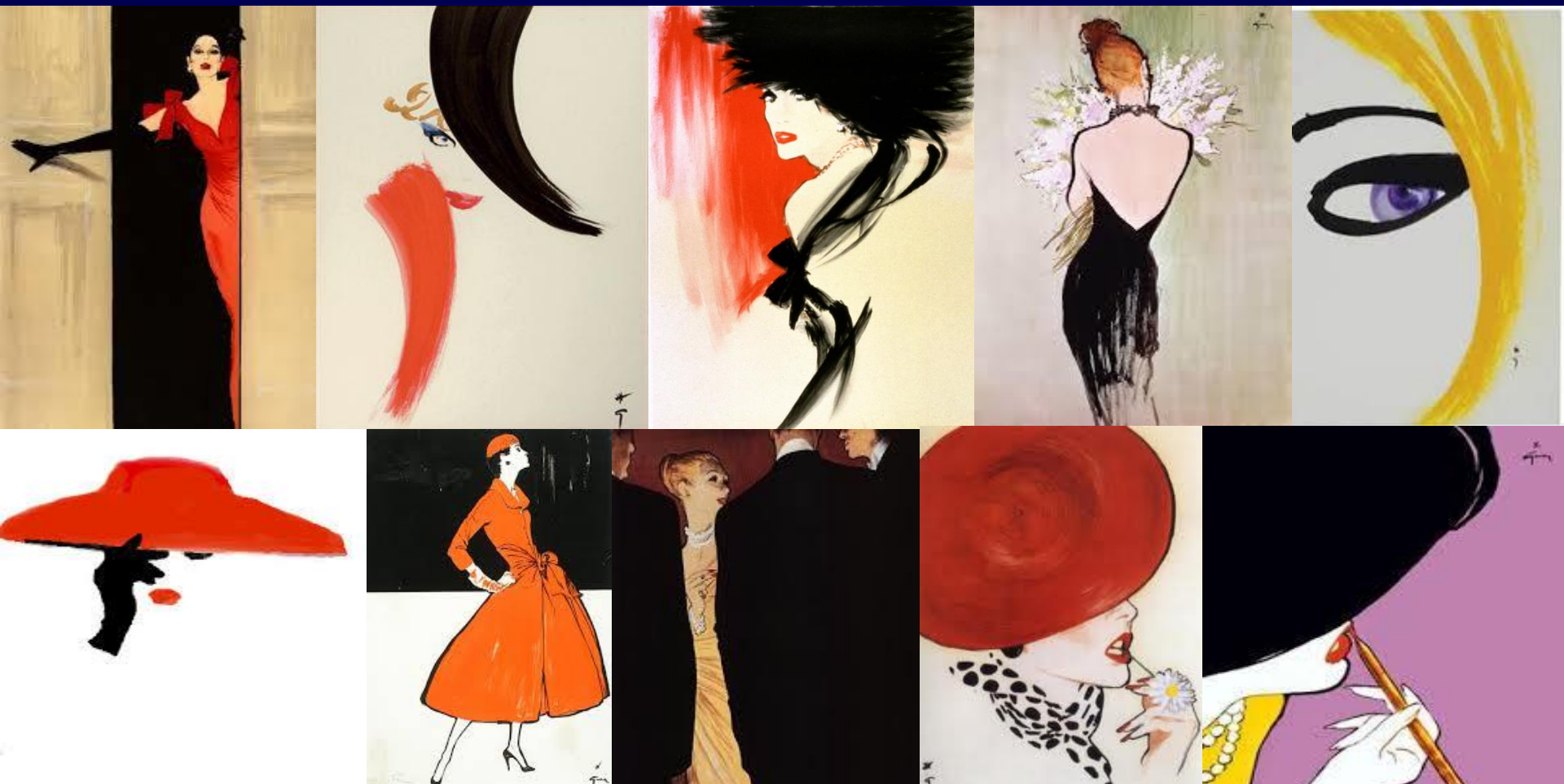
Treatment with pirfenidone for 52 weeks significantly reduced disease progression, as measured by

- Changes in % predicted FVC ($p<0.000001$)
- Changes in 6-minute walk distance ($p=0.036$)
- Progression-free survival ($p<0.001$)

Treatment with pirfenidone reduced all-cause mortality and treatment emergent IPF-related mortality in pooled analyses at week 52

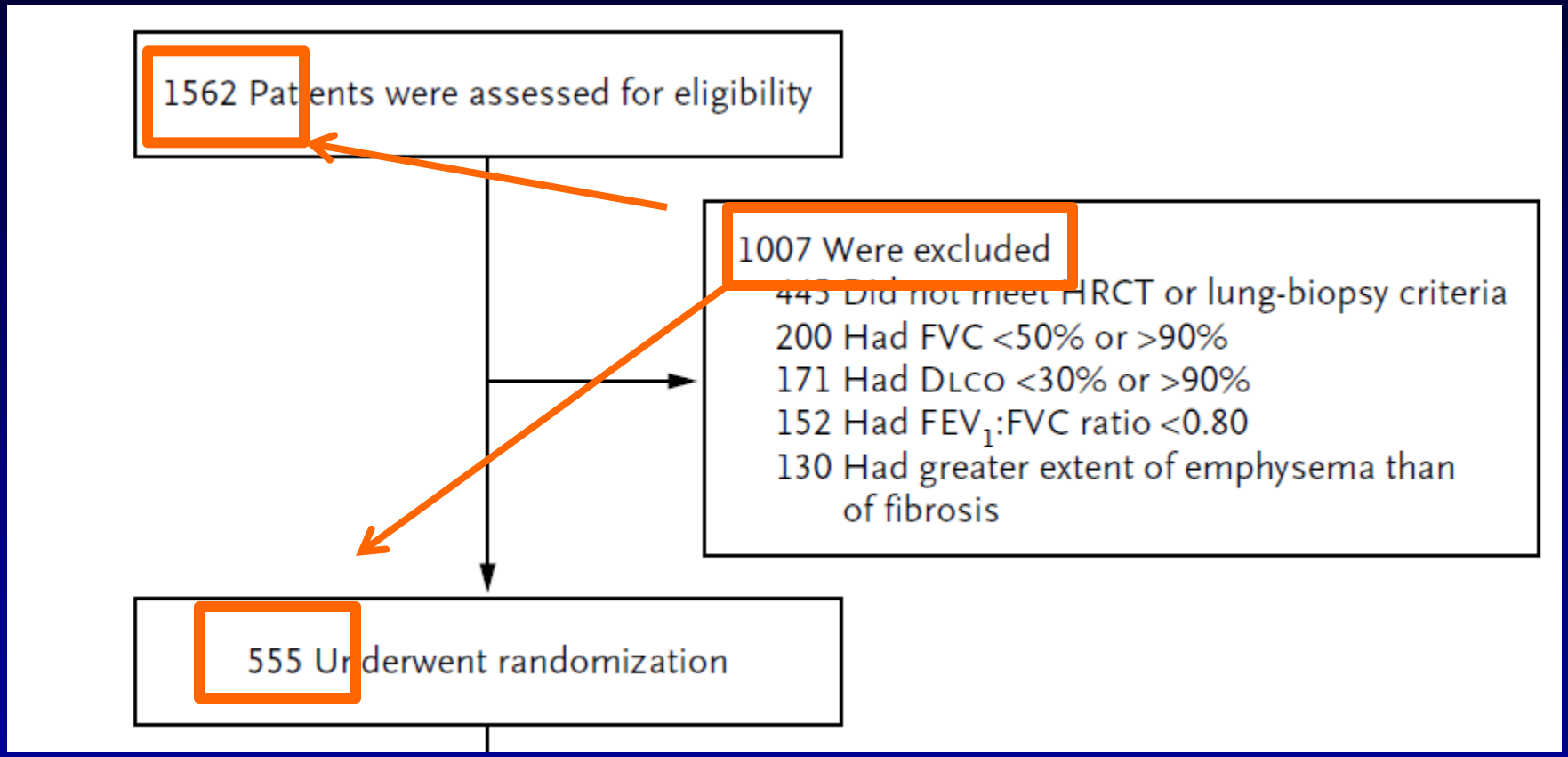
Pirfenidone was generally safe and well tolerated

..but real life is not a clinical trial…



- 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%

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

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

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

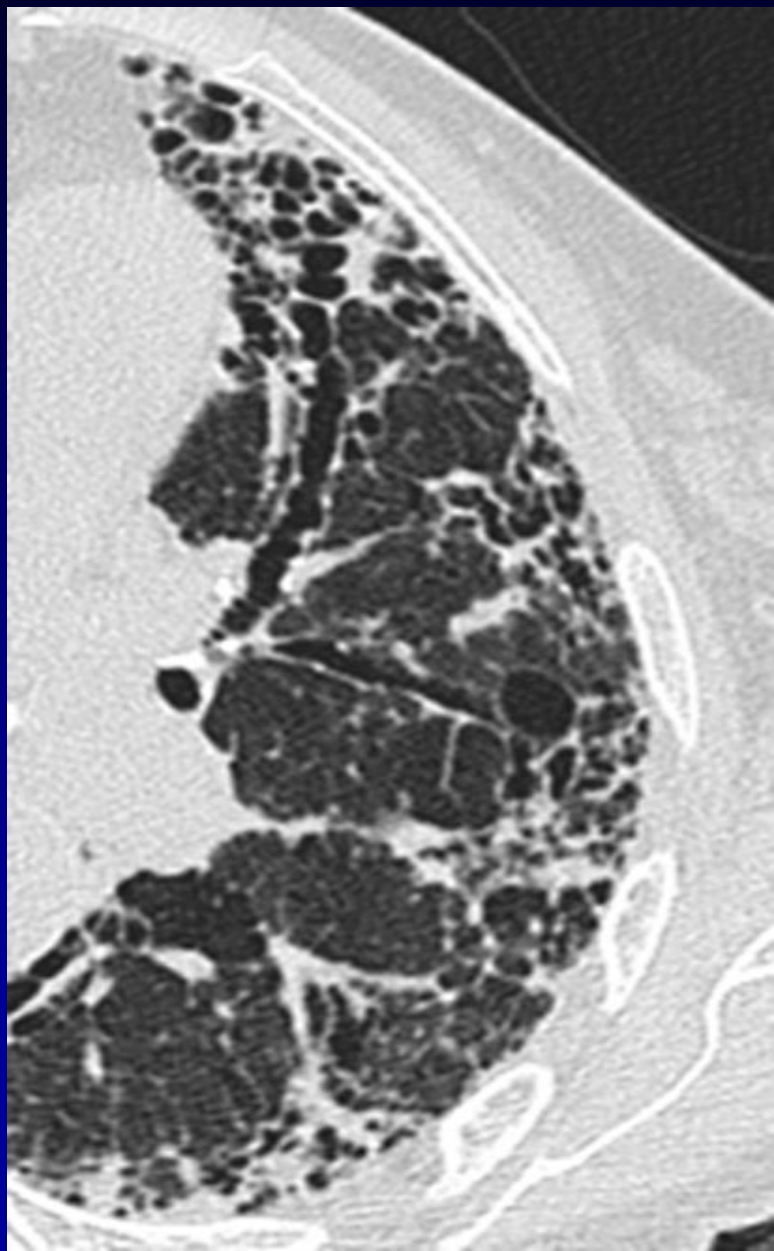
Respir Med. 2015 Apr 25.(15) 121-3

Design of the study

- Observational, multicentric, nation-wide, retrospective study about the progression of functional parameters in IPF patients before and after therapy with Pirfenidone
- Population:
  - Diagnosis: confirmed by HRCT UIP pattern and/or surgical lung biopsy (according to 2011 IPF guidelines);
  - Mild/moderate and severe stage disease, according to guidelines classification;
  - Availability of functional follow-up data at least 6 months before and 6 months after the start of Pirfenidone therapy

Aim

To evaluate the impact of Pirfenidone therapy (PT) on disease progression in a real life cohort of patients with IPF



Matherials and Methods

Study population: 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 PT;

Exclusion criteria: not availability of functional follow-up data at least 12 months before and at least 12 months after starting PT;

Matherials and Methods

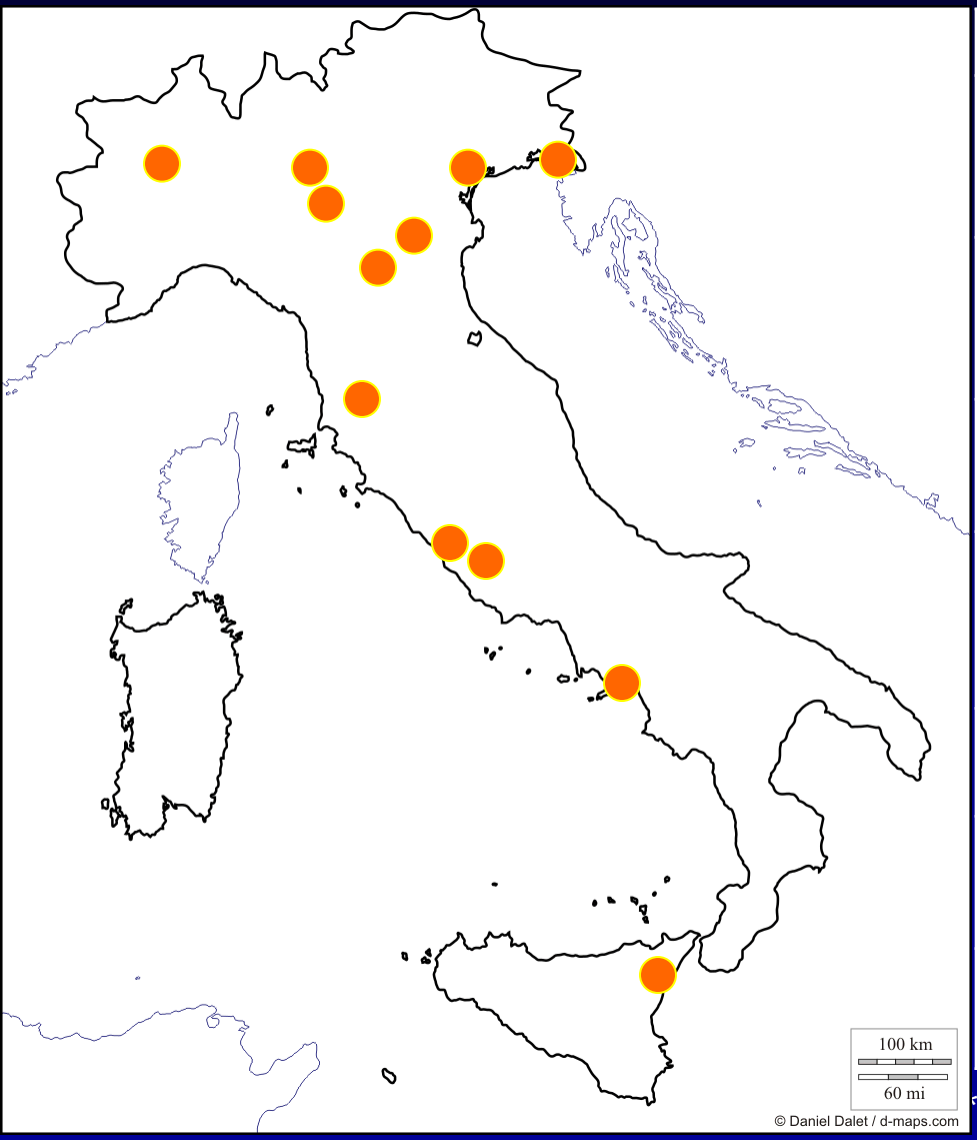
Study design:

- 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;
- Baseline conditions for each period can be defined using functional evaluation at the beginning of each period, i.e. 12 months before the initiation of the therapy and at the initiation itself.

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
- Data have been analyzed using a regression statistical model built using available data points

Table 1. 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

Table 2. 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

Table 3. 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

Table 4a. 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

Table 4b. Changes in 6MWT. All patients (N=128)

Parameter	Time	Mean* (95% CI)	% change**	Difference in % change	p-value***
Distance w/o O2	1-yr before	452 (423, 481)	-	-	
	baseline	433 (411, 454)	- 4.4%	-	
	1-yr after	421 (393, 450)	- 2.6%	1.8%	0.661
Distance w O2	1-yr before	403 (340, 466)	-	-	
	baseline	358 (331, 386)	-11.1%	-	
	1-yr after	362 (330, 394)	1.0%	12.1%	0.28

* 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;

Table 5a. 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

Table 6a. 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

Table 6b. 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:

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

→In general population:

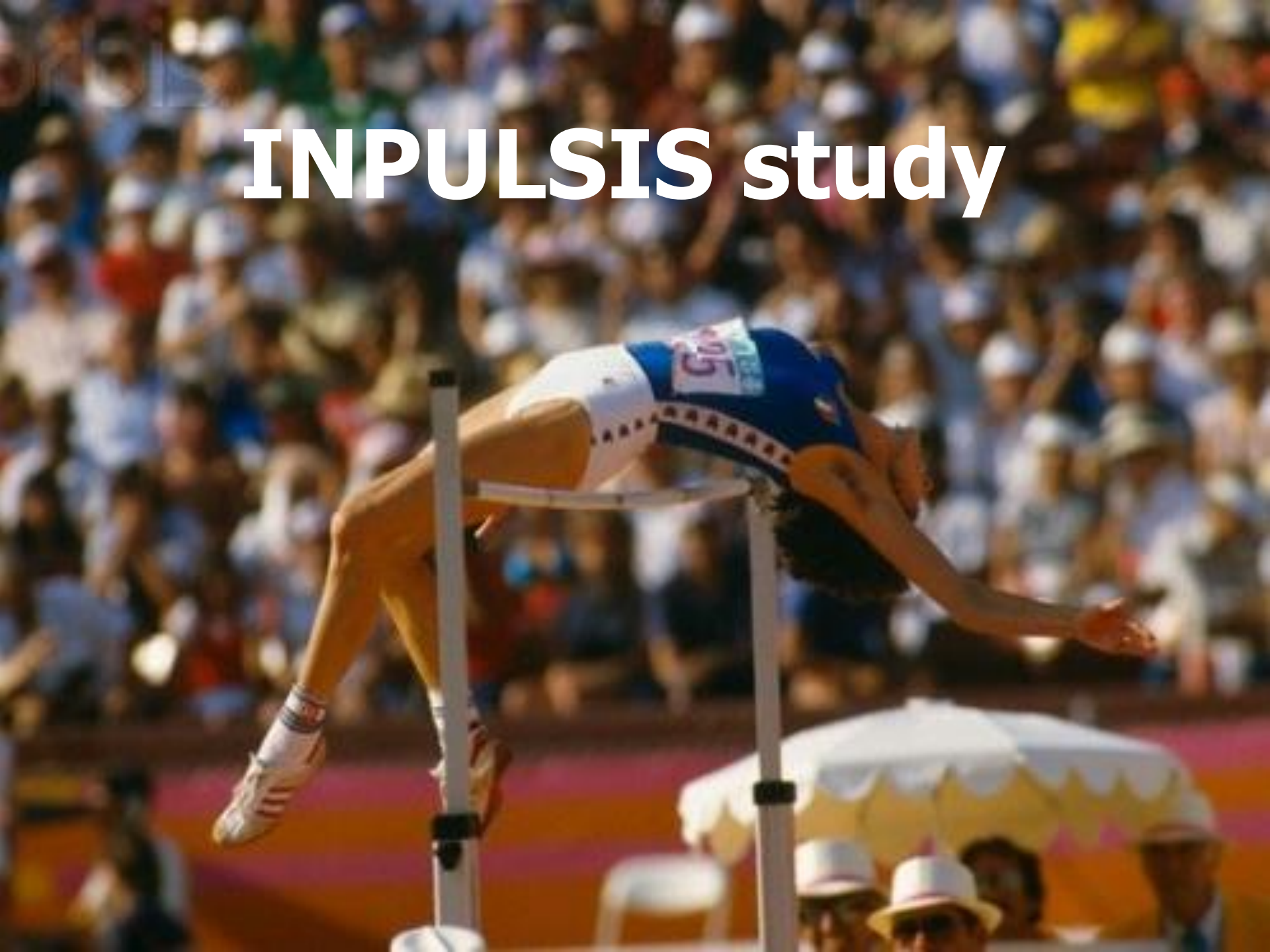
- The drug reduces the slope of decrease of FVC% (p= 0,065);

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

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

This important findings need further investigations

INPULSIS study



Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

Nintedanib (formerly known as BIBF 1120) is an intracellular inhibitor that targets multiple tyrosine kinases.

Two replicate 52-week, randomized, double-blind, phase 3 trials (INPULSIS-1 and INPULSIS-2) was conducted to evaluate the efficacy and safety of 150 mg of nintedanib twice daily as compared with placebo in patients with IPF

Inclusion criteria

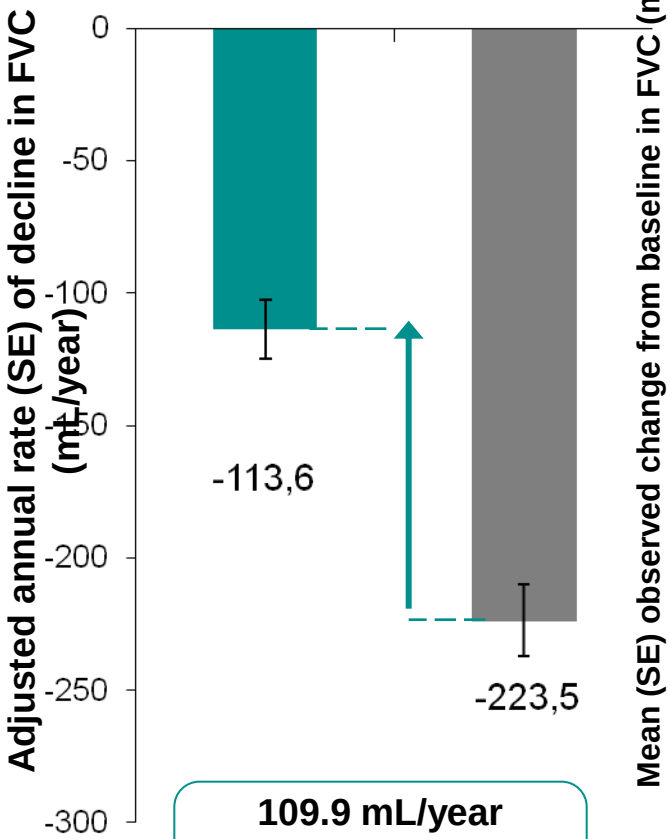
Age ≥40 years

Diagnosis of IPF within 5 years of randomization

HRCT pattern, and, if available, surgical lung biopsy pattern, consistent with diagnosis of IPF, as assessed centrally by one expert radiologist and one expert pathologist

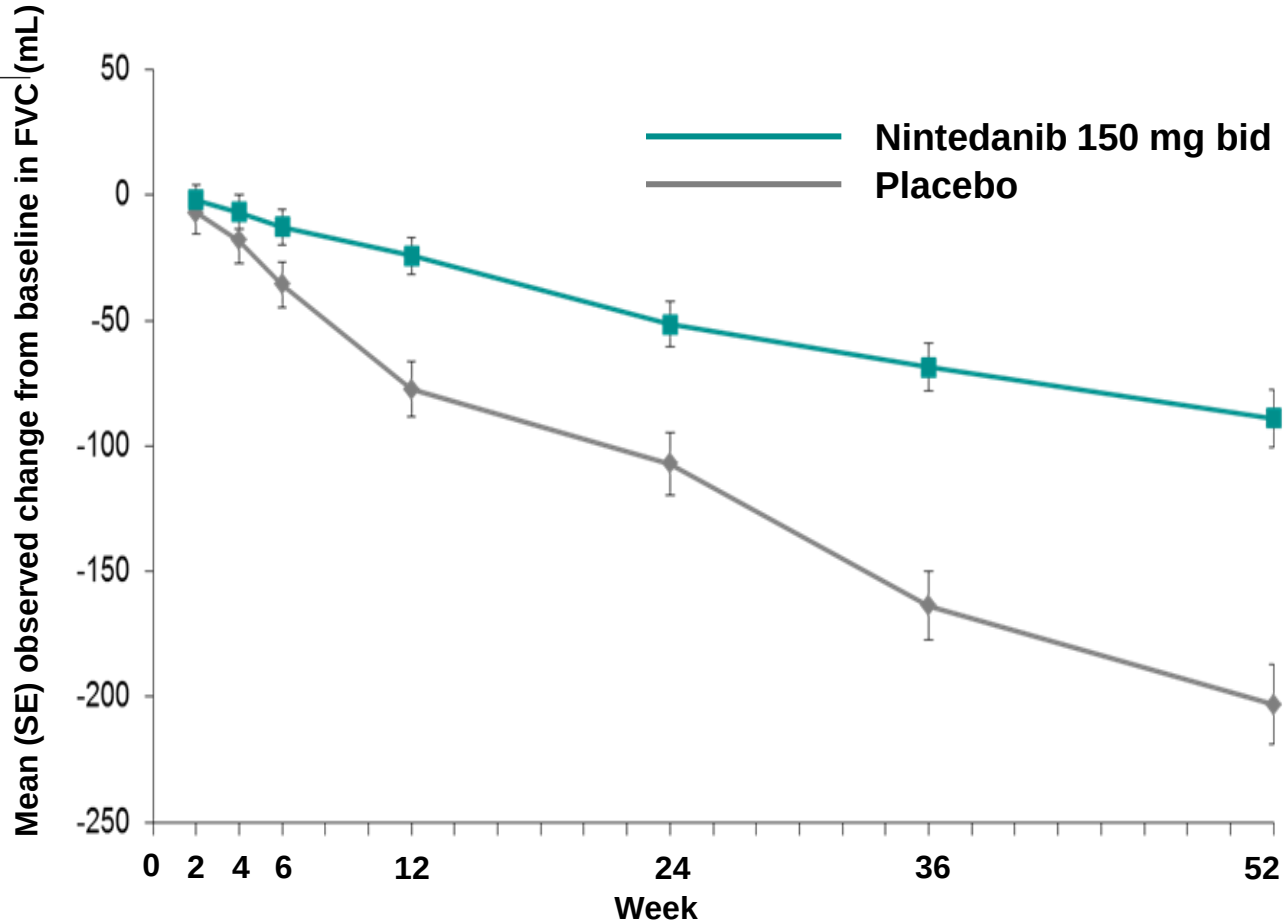
FVC ≥50% of predicted value; DL_{CO} 30–79% of predicted value

Primary efficacy endpoint in pooled data



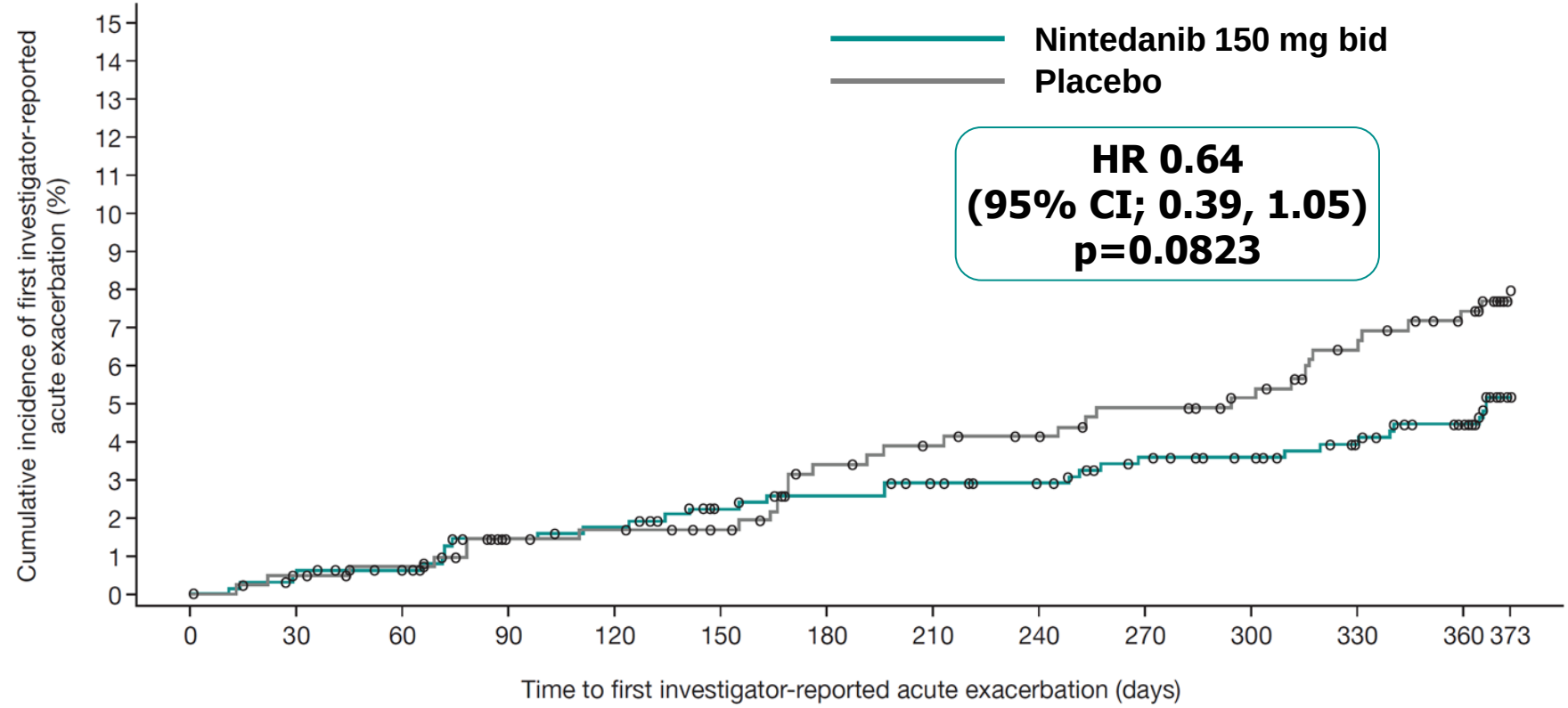
109.9 mL/year
(95% CI: 75.9, 144.0)
p<0.0001

Nintedanib 150 mg bid (n=638)
Placebo (n=423)



No. of patients							
Nintedanib	626	616	613	604	587	569	519
Placebo	417	408	407	403	395	383	345

Time to first acute exacerbation (investigator-reported) in pooled data



No. of patients

Nintedanib	638	632	627	609	605	595	589	584	580	570	562	553	537	492
Placebo	423	419	415	408	407	403	393	389	386	381	376	367	359	341

	Nintedanib 150 mg bid (n=638)	Placebo (n=423)
Patients with ≥1 acute exacerbation, n (%)	31 (4.9)	32 (7.6)

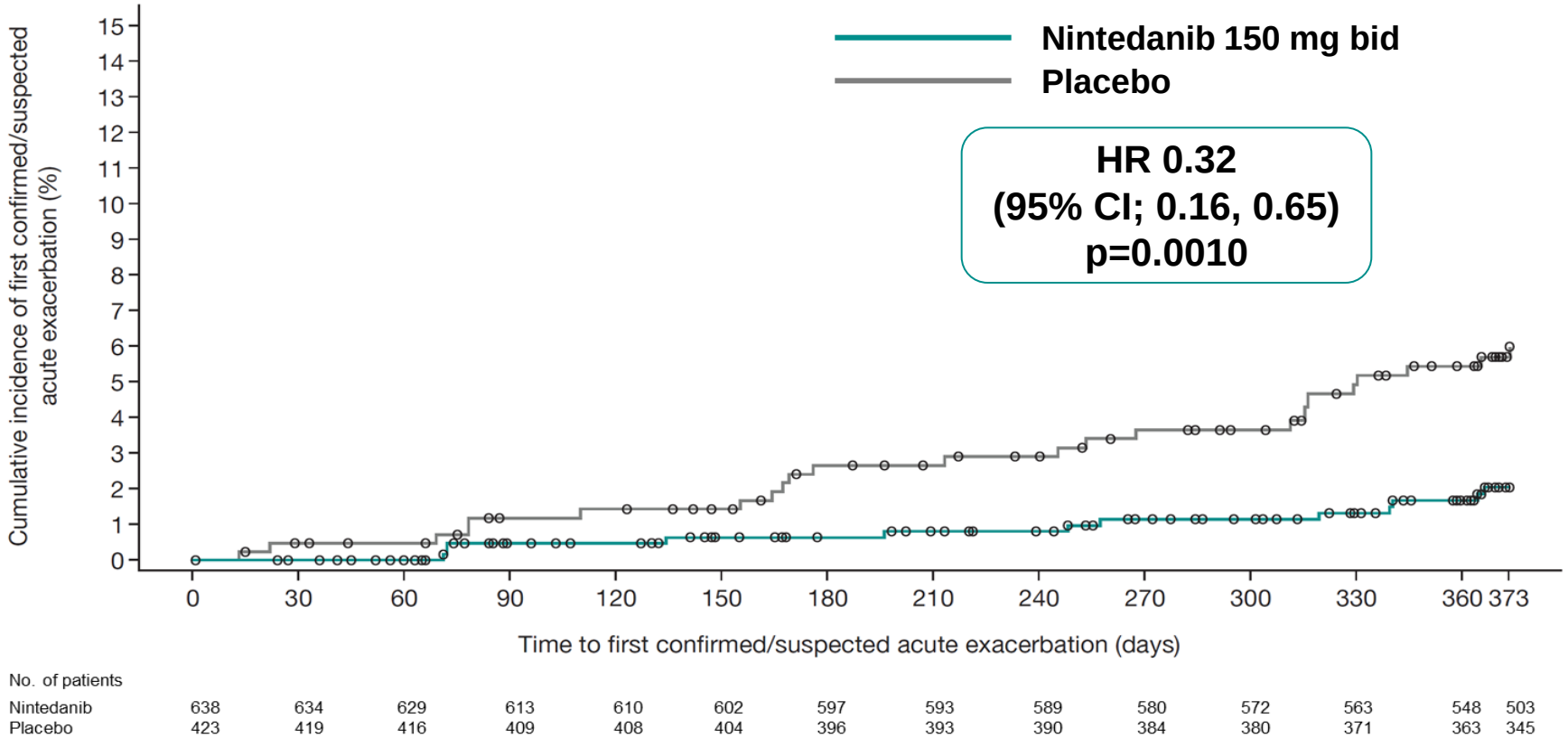
Adjudication of acute exacerbations

- The adjudication committee categorized the investigator-reported acute exacerbations according to pre-specified criteria[1]:
  - Confirmed acute exacerbation
  - Suspected acute exacerbation
  - Not an acute exacerbation

- The adjudication committee was blinded to treatment allocation and events were adjudicated before database lock and data unblinding

1. Collard HR, et al. Am J Respir Crit Care Med 2007;176:636–643

Time to first confirmed or suspected acute exacerbation per adjudication (prespecified sensitivity analysis of pooled data)



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

Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

In patients with IPF nintedanib reduced the decline in FVC, which is consistent with a slowing of disease progression; nintedanib was frequently associated with diarrhea, which led to discontinuation of the study medication in less than 5% of patients

Inclusion	PANTHER	IMPULSIS	ASCEND
Drug	NAC (1800 mg/day) vs placebo	Nintedanib 150 mg twice a day vs placebo	Pirfenidone (2403 mg/day vs placebo
Randomization	1:1	3:2	1:1
Patients Number	264	1066	555
Age	35-85	≥ 40	40-80
PFTs	FVC ≥50% and DLCO≥30%	FVC ≥50% and DLCO≥30%	FVC ≥50% and DLCO≥30%
Time	60 weeks	52 weeks	52 weeks
Primary endpoint	Change in %FVC	Annual decline in FVC (mL)	Change in %FVC
Secondary endpoint	Time to disease progression, death, acute exacerbations, 6MWT	Time to first acute exacerbation, SGRQ	Change in 6MWD, PFS, dyspnea score

ASCEND

94% of patients completed the study

The pirfenidone group had a greater annual decline in the mean FVC (-235 ml) than did the placebo groups of both of the INPULSIS studies (-205 ml). The mean decline in FVC in placebo group was 428 mL

INPULSIS

In both trials, a higher proportion of patients in the nintedanib groups than in the placebo groups had elevated levels of liver enzymes

Myocardial infarction was reported in 10 treated patients and in 2 in the placebo group

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	?	?

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

The goals of effective IPF management

Acute exacerbations: major cause of death
Ventilation: 3 months mortality rate is 94%
→ not ventilate patients with AE of IPF
→ Ventilation may be appropriate in patient with other comorbidities

Pulmonary Rehab.
Oxygen
Vaccination

ew approaches needed??

- Prevent and treat exacerbations
- Prevent disease progression
- Reduce mortality

Experimental therapy in a RCT

Pirfenidone: mild/moderate IPF
Nintedanib

Lung Transplantation

These goals should be reached with a minimum of side effects from treatment

Conclusions

- A new era in the IPF therapy is started
- An early and accurate diagnosis of IPF is critical
- Antifibrotic drugs slow the progression of the disease
- Larger data are today available on Pirfenidone: the drug reduce mortality and work also in real life
- Nintenabid is newer but is a very interesting drug also for its mechanism of action