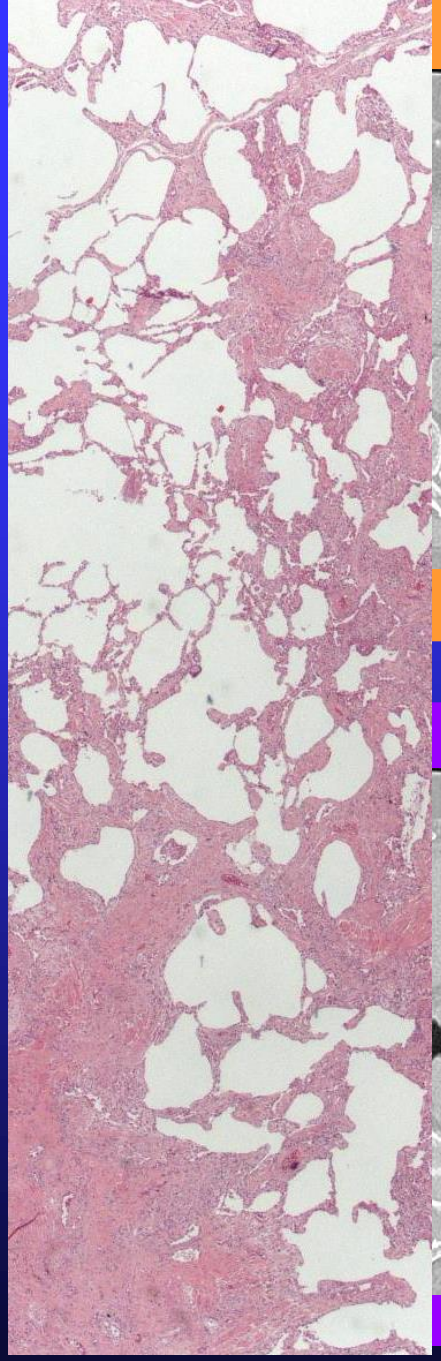
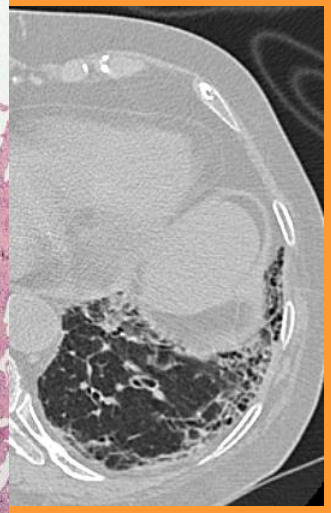
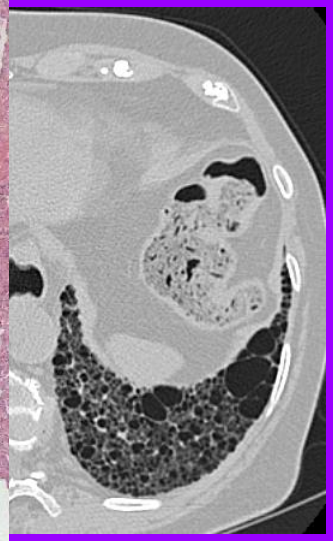
LE MALATTIE INTERSTIZIALI DEL POLMONE

Il punto di vista dell'internista: un approccio teorico-pratico

Il moderno approccio terapeutico (all'IPF)







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Cremona, 29 Maggio 2015

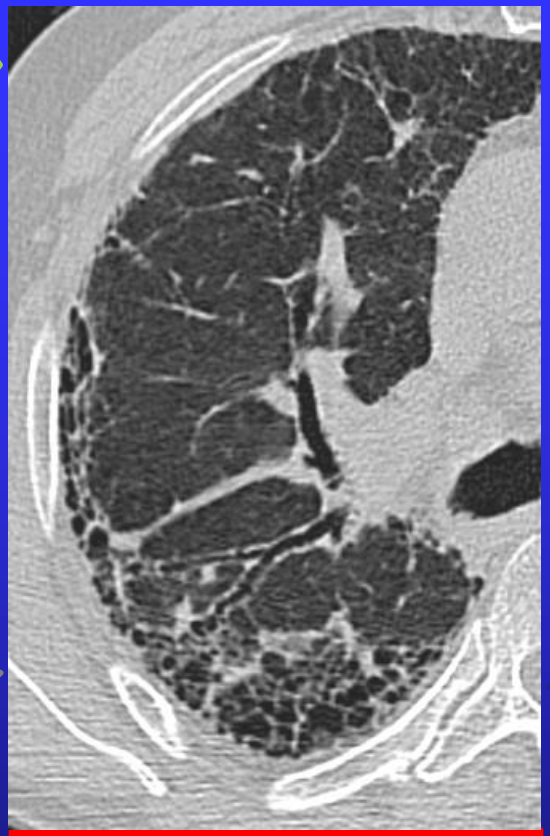
Disclosures

Fees for speaking and/or organising education: InterMune, Boehringer Ingelheim

Worldwide prevalence is estimate of at least 5 million people

Progressive deterioration is inevitable

Considerable inter- and intra patient variability



IPF

Lung transplantation is an option

A genetic disease?

Median survival historically is only ~3-5 years

A rare disease

Limited therapeutic options

Why IPF versus non-IPF is the key

The prevalence of IPF in Europe is ~ 120000 and an estimated 40000 new cases are diagnosed each year

- Prevalence in idiopathic disease: IPF 60% versus

The prevalence of IPF in Lombardy region in 2010 is 3600 patients and incidence is 450

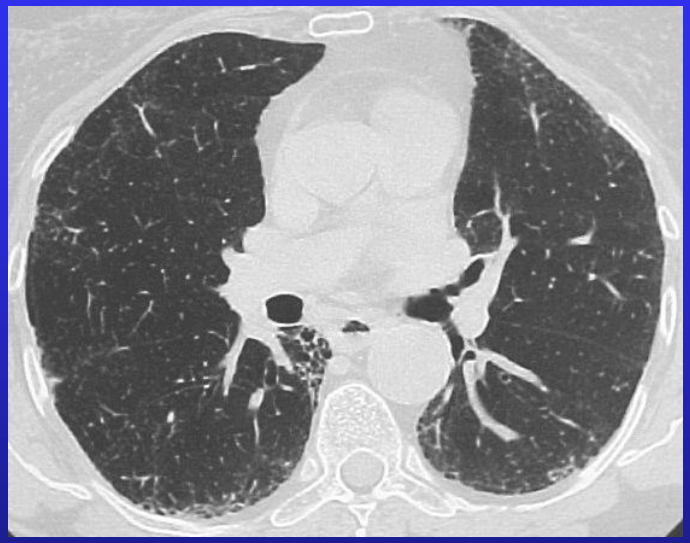
cancer

- Above all, broad disease mechanisms and related therapies: an epithelial fibrotic disorder versus various forms of immune dysregulation
- IPF is strongly associated with cigarette smoking and is predominantly a disease of ageing

UIP: progression of fibrosis on CT

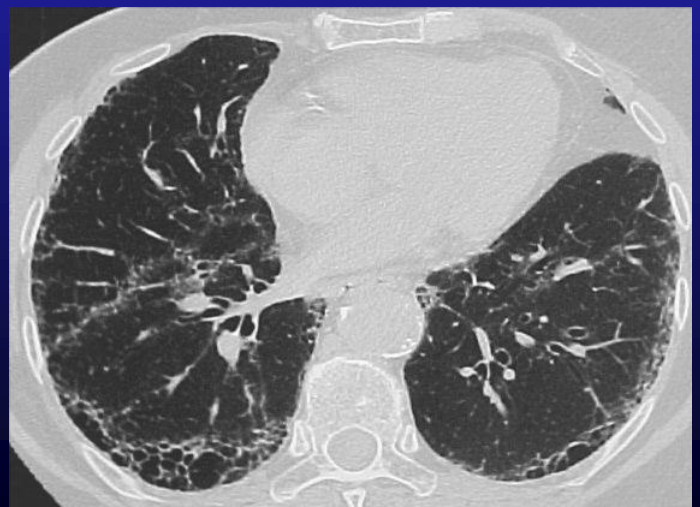
Early:

Reticular



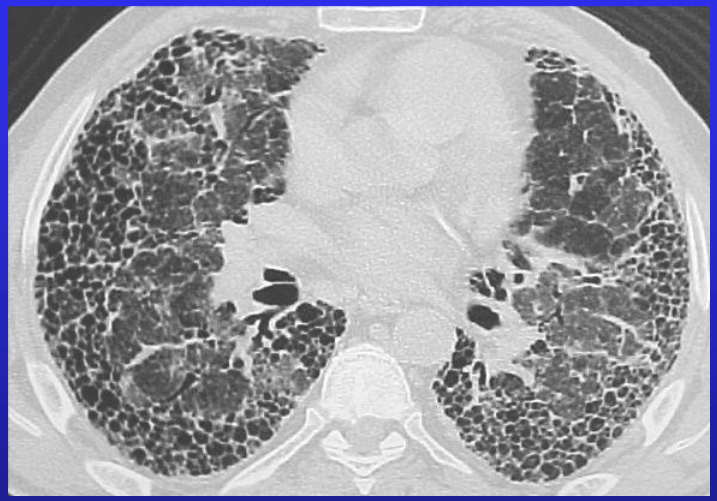
Midcourse:

Subpleural honeycombing

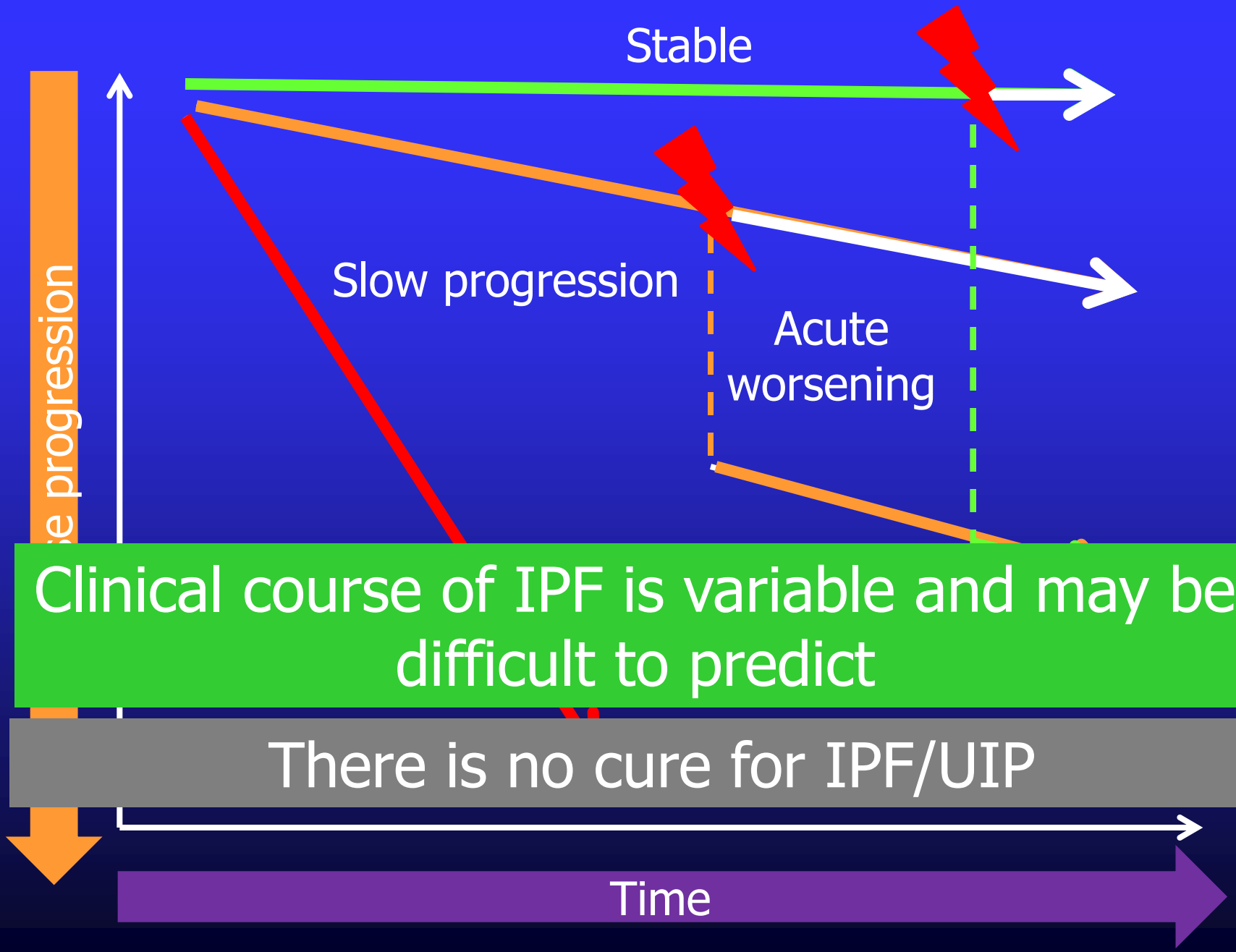


Late:

Diffuse honeycombing



Raghu, G et al. Am J Respir Crit Car Med 2011; 183; 788-824



Clinical course of IPF is variable and may be difficult to predict

There is no cure for IPF/UIP

Key IPF clinical trials

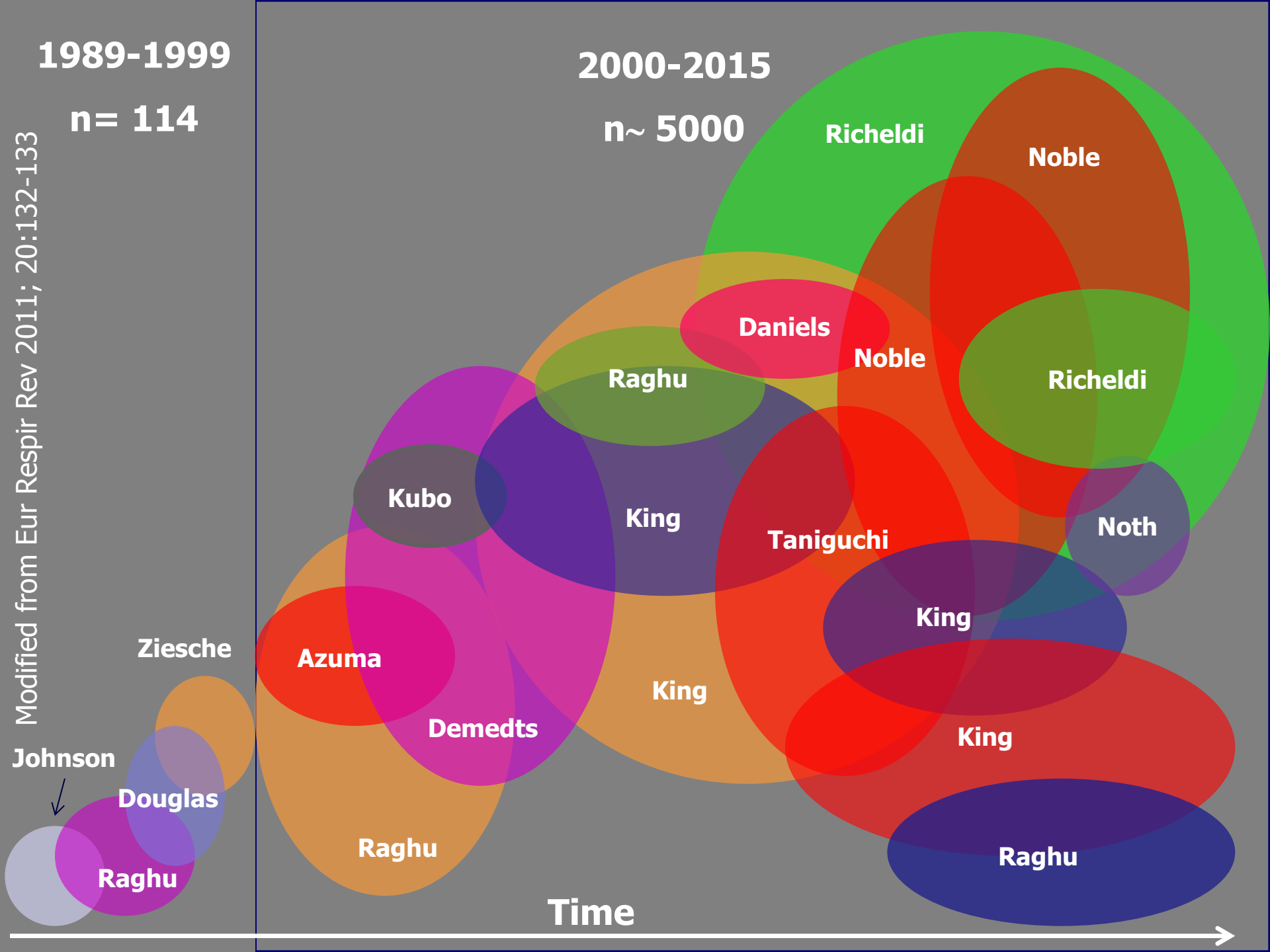
Year	Study	Agent	Reference
2004	GIPF-001	IFN-γ	Raghu G, *et al. NEJM* 2004.
2005	IFIGENIA	N-acetylcysteine	Demedts M, *et al. NEJM* 2005.
2008	BUILD-1	Bosentan	King TE Jr., *et al. AJRCCM* 2008.
2008	NCT00063869	Etanercept	Raghu G, *et al. AJRCCM* 2008.
2009	INSPIRE	IFN-γ	King TE Jr., *et al. Lancet* 2009.
2009	CAPACITY 1	Pirfenidone	Noble P, *et al. AJRCCM* 2009.
2009	CAPACITY 2	Pirfenidone	Noble P, *et al. AJRCCM* 2009.

Key IPF clinical trials

Year	Study	Agent	Reference
2010	STEP-IPF	sildenafil	*NEJM* 2010.
2010		imatinib	Daniels CE, *et al*. *AJRCCM* 2010.
2011	BUILD-3	Bosentan	King TE, *et al. AJRCCM* 2011.
2011	TOMORROW	BIBF1120	Richeldi L, *et al. NEJM* 2011.

In the period 1989–1999 a total of 114 patients were enrolled in four well conducted IPF studies, whereas the following decade (2000–2010) saw almost 3000 patients enrolled in 11 studies

Eur Respir Rev 2011;20: 132


1989-1999
n= 114
2000-2015
n~ 5000
Modified from Eur Respir Rev 2011; 20:132-133
Ziesche
Johnson
Douglas
Raghu
Azuma
Demedts
Raghu
Kubo
Raghu
King
King
Daniels
Noble
Taniguchi
Richeldi
Noble
Richeldi
Noth
King
King
Raghu
Time

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?

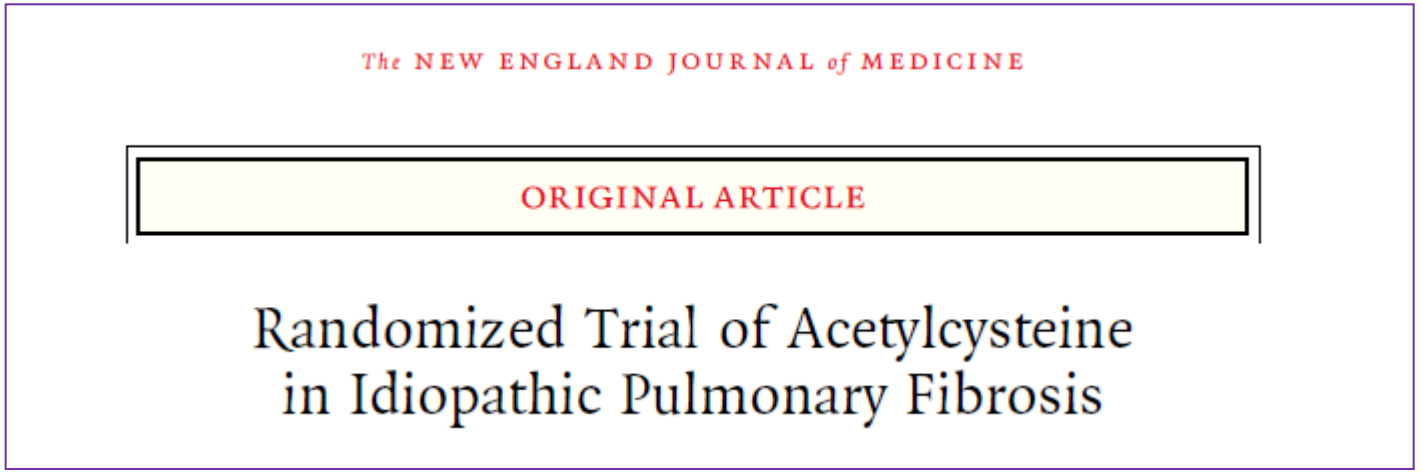
Cyclophosphamide

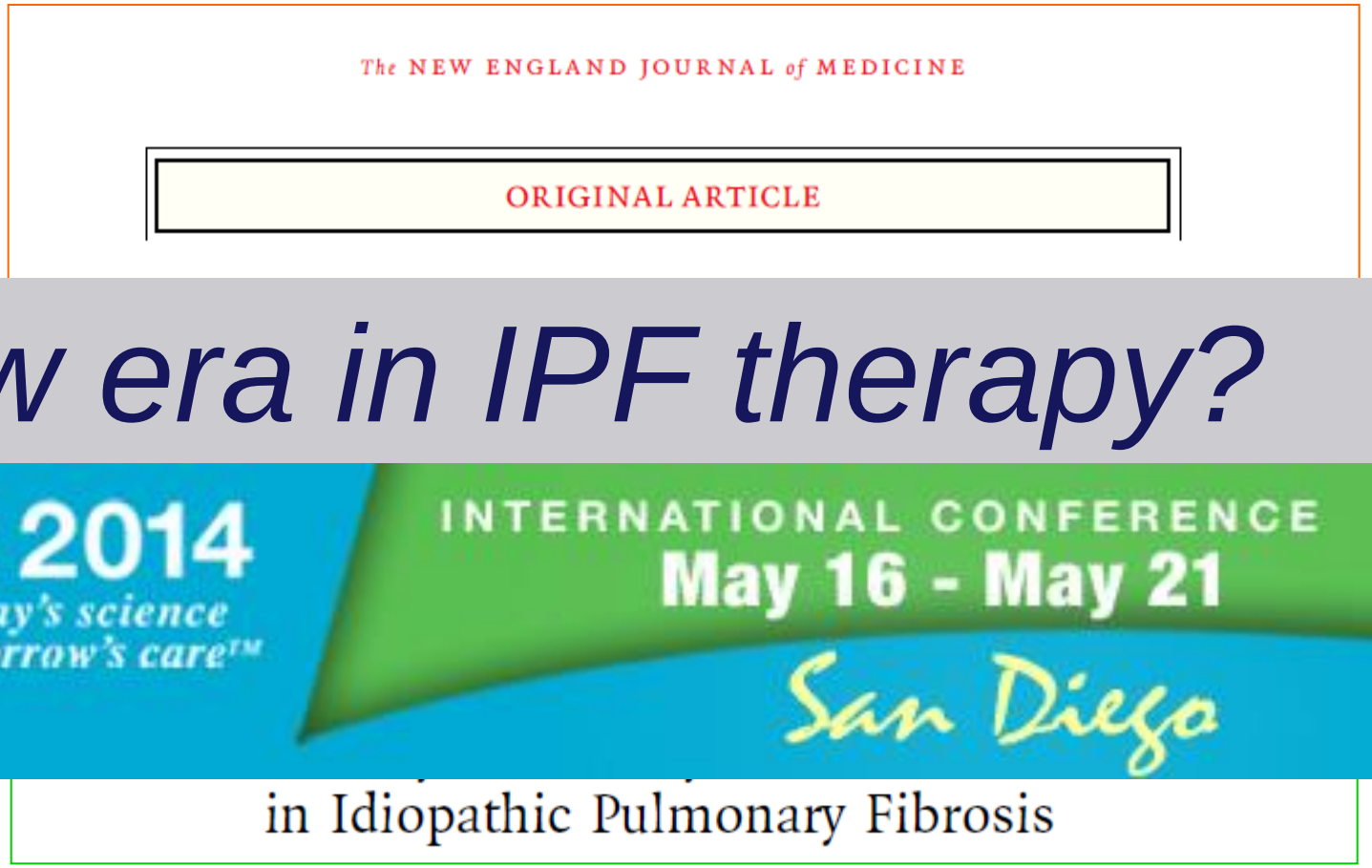
Pirfenidone

Ambrisentan
Sitaxestan

1950s **1990s** **2009** **2015**

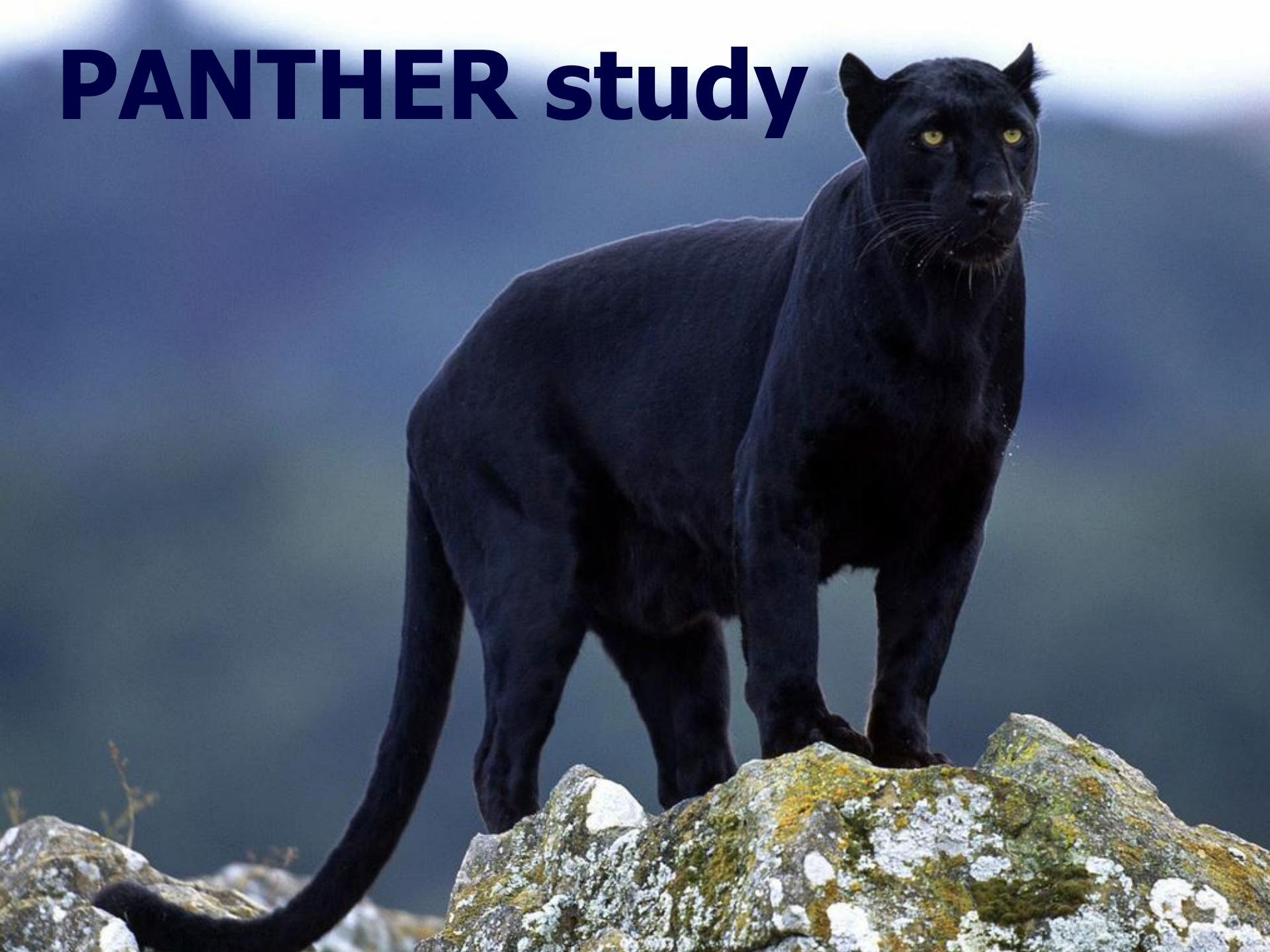
18 May 2014



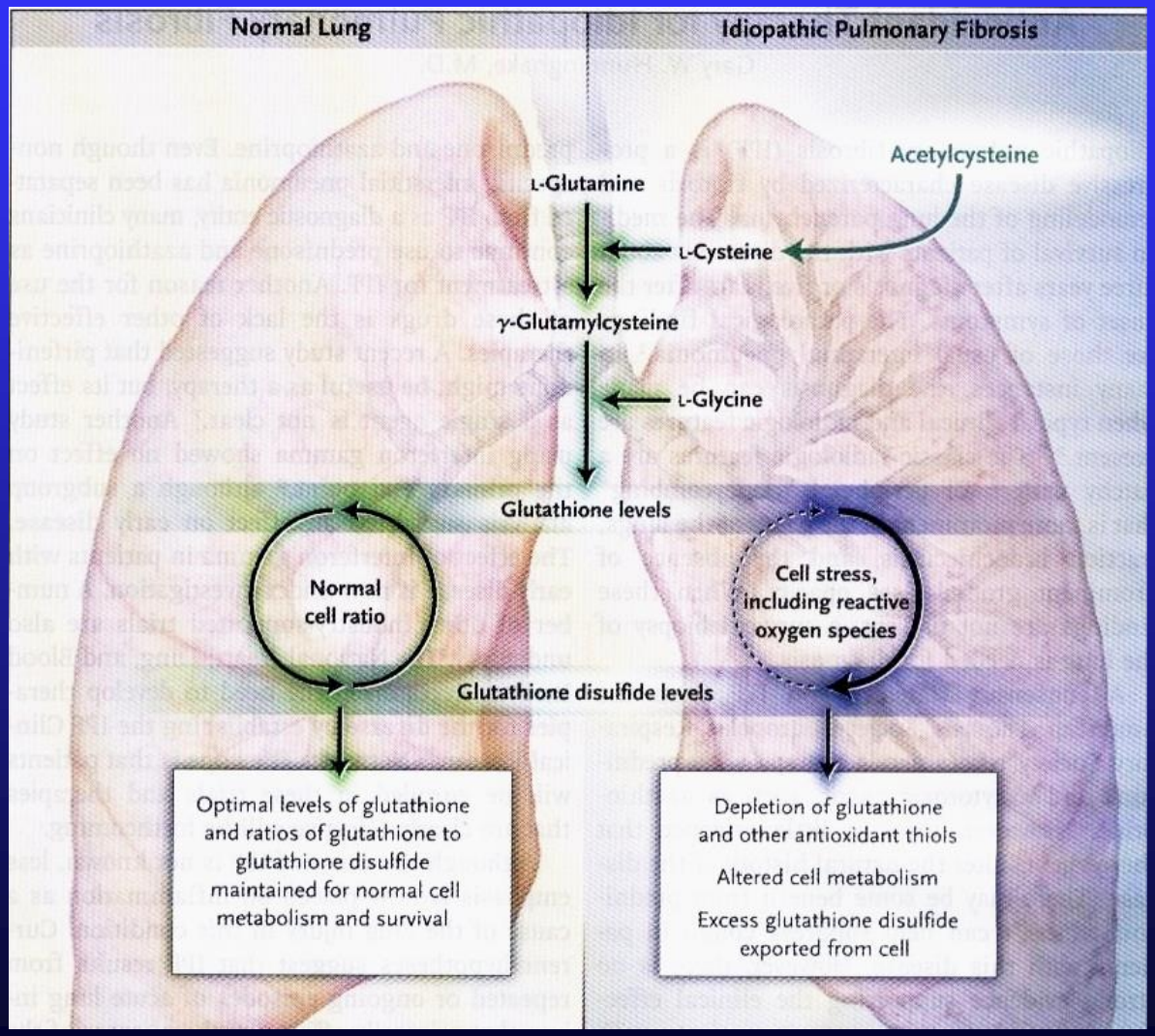


A new era in IPF therapy?

PANTHER study



High-Dose Acetylcysteine in Idiopathic Pulmonary Fibrosis
(IFIGENIA study)



N Engl J Med 2005; 353: 2229-42

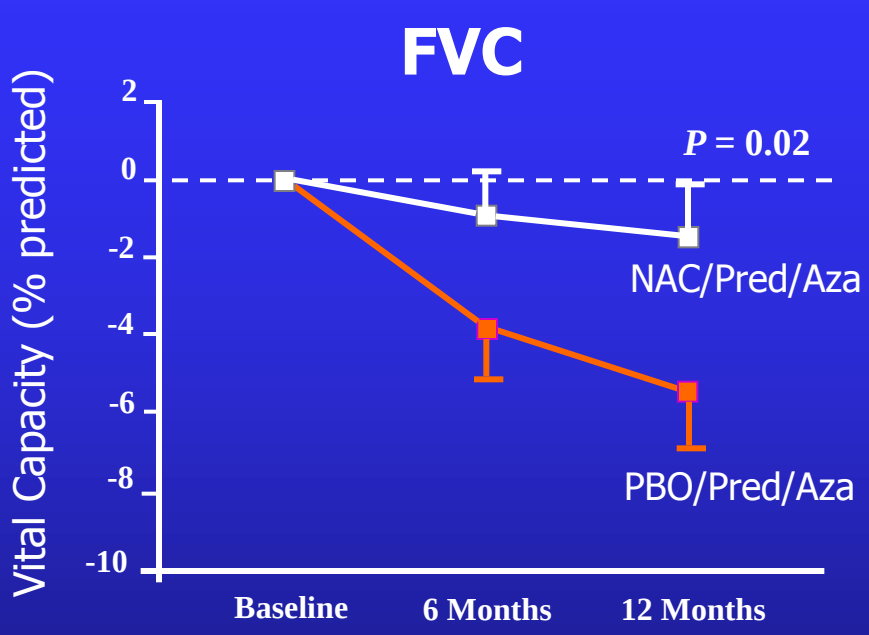
N-Acetylcysteine: IFIGENIA trial

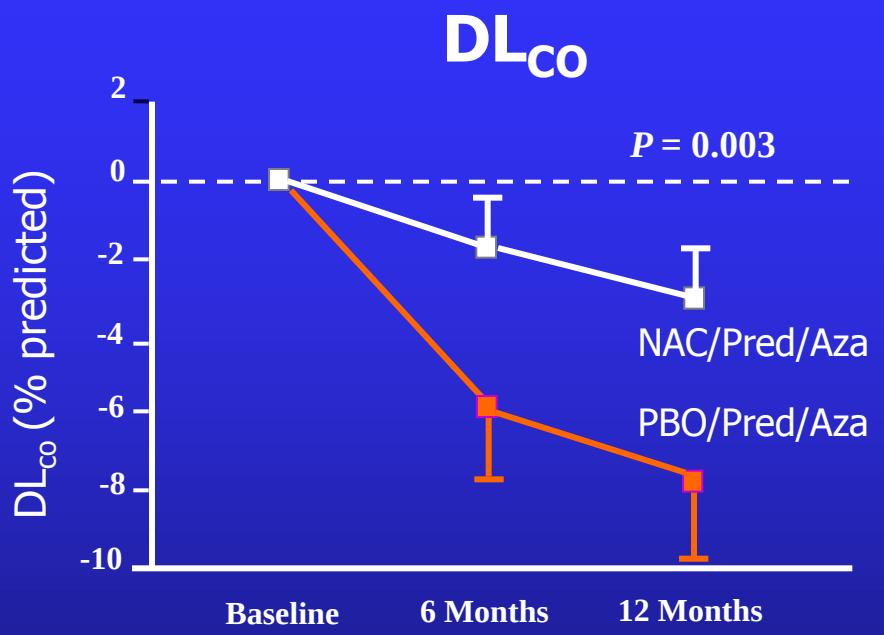
Classification	Variant of amino acid *L*-cysteine, precursor for glutathione
Trial Design	Multinational, double-blind, randomized
Primary Endpoint	Mean change from baseline of FVC and DL_{CO}
Secondary Endpoint	Survival
Treatment Arms	Active: NAC (600 mg TID) + Pred (0.5 mg/kg/d) + Aza (2 mg/kg/d) Control: Pred (0.5 mg/kg/d) + Aza (2 mg/kg/d)
Number of Patients	182 randomized
Treatment Duration	1 year, completed
Result	Primary endpoints met: NAC added to Pred/Aza preserved vital capacity and DL_{CO} better than Pred/Aza alone; No mortality difference

ATS/ERS 2000 recommended therapy

Demedts M, et al. *N Engl J Med.* 2005;353:2229-2242

IFIGENIA Study results





No. of Patients						
NAC/Pred/Aza	80	63	55	79	58	55
PBO/Pred/Aza	75	60	51	74	59	51

	Mortality, *P* = NS
NAC/Pred/Aza	7/80 (9%)
Placebo/Pred/Aza	8/75 (11%)

No mortality difference

Demedts M, et al. *N Engl J Med.* 2005;353:2229-2242

Prednisone/Azathioprine/NAC PANTHER Trial

Classification	Combination therapy
Mechanisms	Antiinflammatory, immunosuppression, antioxidant
Trial Design	Randomized, double blind, placebo controlled
Inclusion Criteria	FVC > 50% and DL_{CO} > 30%
Primary Endpoint	Change in FVC % predicted
Treatment Arms	Placebo vs Pred/Aza/NAC vs NAC
Number of Patients	236
Treatment Duration	52 weeks
Result	negative

Press Release, 21 october 2011

Commonly used three-drug regimen for idiopathic pulmonary fibrosis found harmful
NIH stops one treatment arm of trial; other two treatments to continue

The National Heart, Lung, and Blood Institute (NHLBI), part of the

The interim results from this study showed that compared to placebo,

This study, called PANTHER-IPF (Prednisone, Azathioprine, and N-acetylcysteine: A Study that Evaluates Response in Idiopathic Pulmonary Fibrosis) was designed and conducted by the Idiopathic Pulmonary Fibrosis Clinical Research Network, funded by the NHLBI. The PANTHER-

PANTHER-IPF was the first study in IPF comparing the effectiveness of this combined treatment to a placebo for all three drugs. Each participant had a one in three chance of being randomized to receive the triple drug regimen, NAC alone, or placebo for a period of up to 60 weeks.

Prednisone, Azathioprine and N-Acetylcysteine for pulmonary fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network

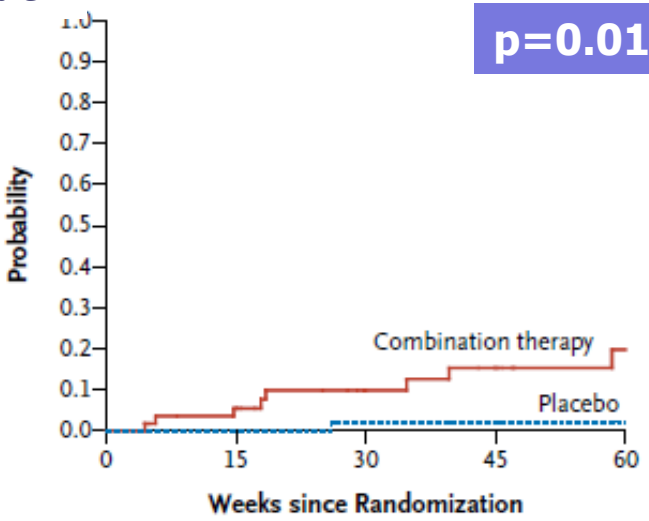
N Eng J Med 2012

Safety end point

End point	Combination therapy (n= 77)	Placebo (n= 78)	P value
Death – no. (%)			
From any cause	8(10)	1 (1)	0.01
From respiratory cause	7(9)	1 (1)	0.02
Hospitalization for any cause – no.(%)	23 (30)	7 (9)	<0.001
Acute exacerbation – no. (%)	5 (6)		0.03
Serious adverse events - no. (%)	24 (31)	8 (10)	0.001

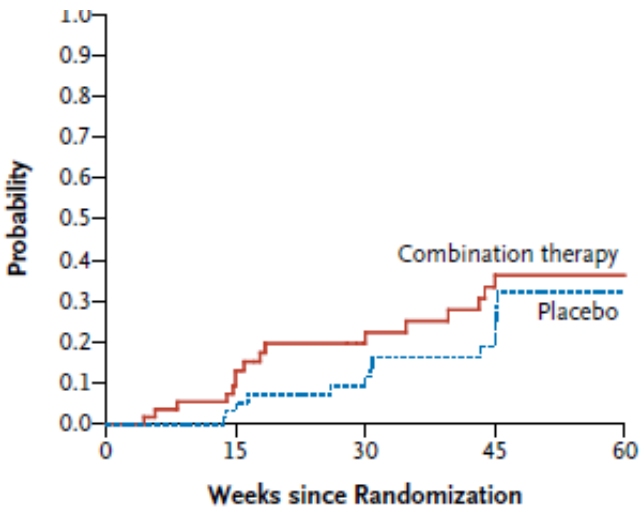
Time to death

p=0.01



No. at Risk					
Combination therapy	77	50	34	29	14
Placebo	78	57	44	31	17

Time to death or disease progression

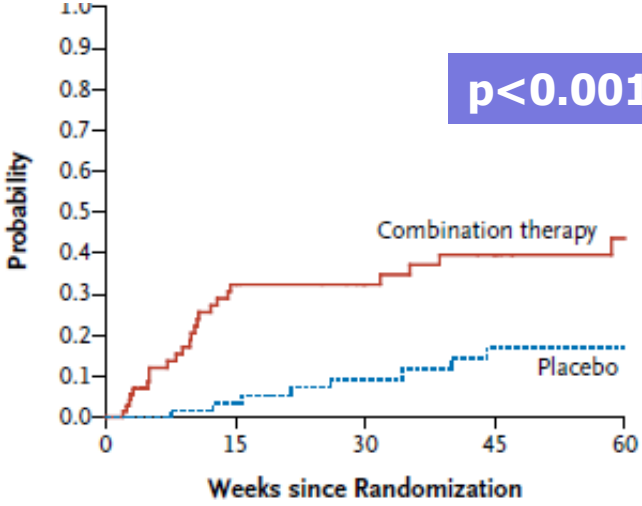


No. at Risk					
Combination therapy	77	46	29	22	12
Placebo	78	55	39	24	11

These findings provide evidence against the use of this combination in IPF patients

Time to death or hospitalization

p<0.001



No. at Risk					
Combination therapy	77	40	29	23	10
Placebo	78	55	42	26	16

N Eng J Med 2012

EDITORIAL

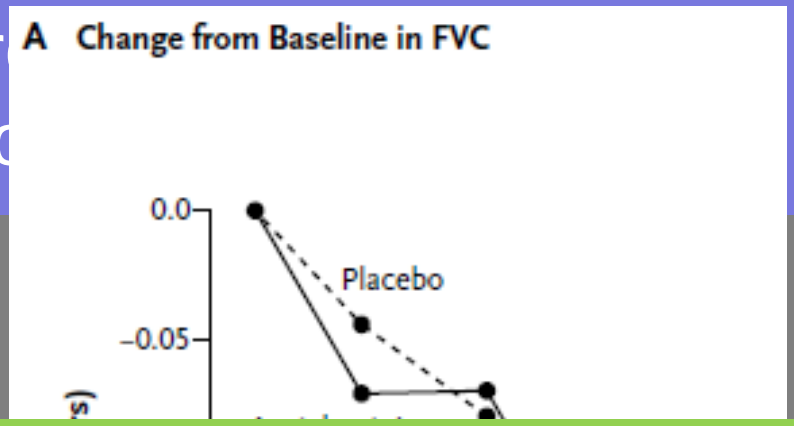
Triple therapy in idiopathic pulmonary fibrosis: an alarming press release

Wells AU et al. Eur Respir J 2012; 39:805

- most patients and physicians will decide against starting immunosuppressive therapy de novo in IPF
- Similarly, most patients and clinicians are likely to withdraw immunosuppressive therapy if disease is continuing to progress despite treatment

Randomized Trial of Acetylcysteine in Idiopathic Pulmonary Fibrosis

133 and 131 patients were enr
acetylcysteine and placebo gro

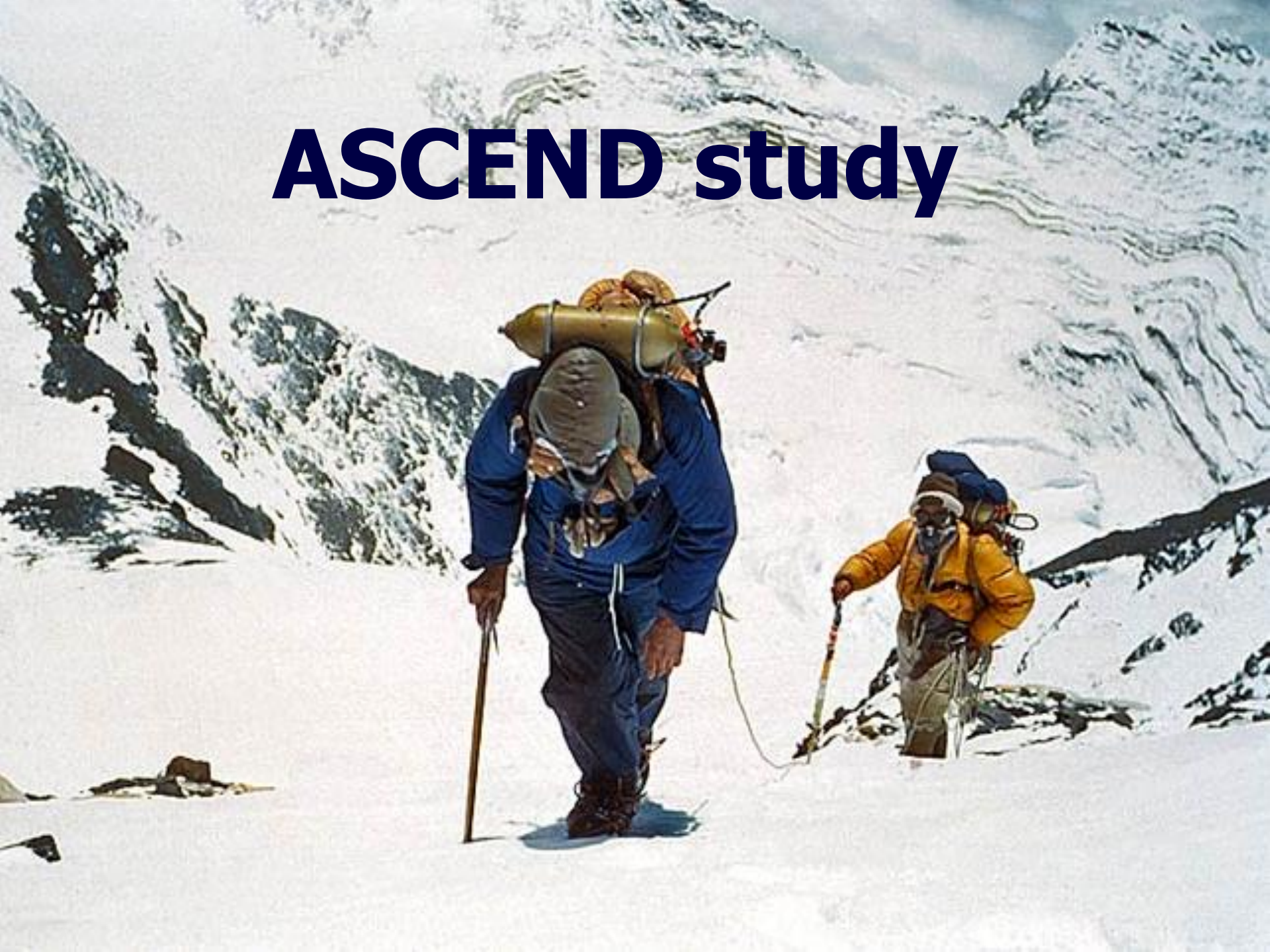


Inclusion criteria
35-85 age

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



Pirfenidone - Background

Pirfenidone is an oral ant
evaluated in **Phase 3 tria**

- **SP3** (Japan, N=275)[1]
  - ➢ Reduced the mean decline in VC at week 52 and improved progression-free survival time
- **CAPACITY** (Multinational, N=779)[2]

Pirfenidone was approved in Japan since 2008

On February 2011, EMA approved Pirfenidone for mild to moderate IPF
The approval authorized marketing in all 28 EU member states

On July 2013, AIFA approved Pirfenidone in Italy

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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

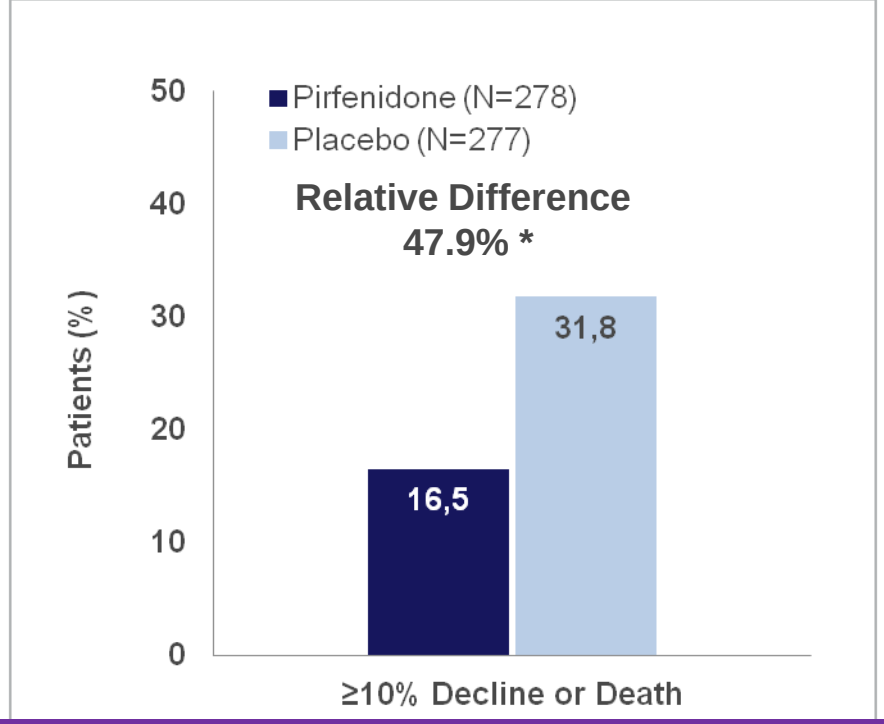
Inclusion criteria

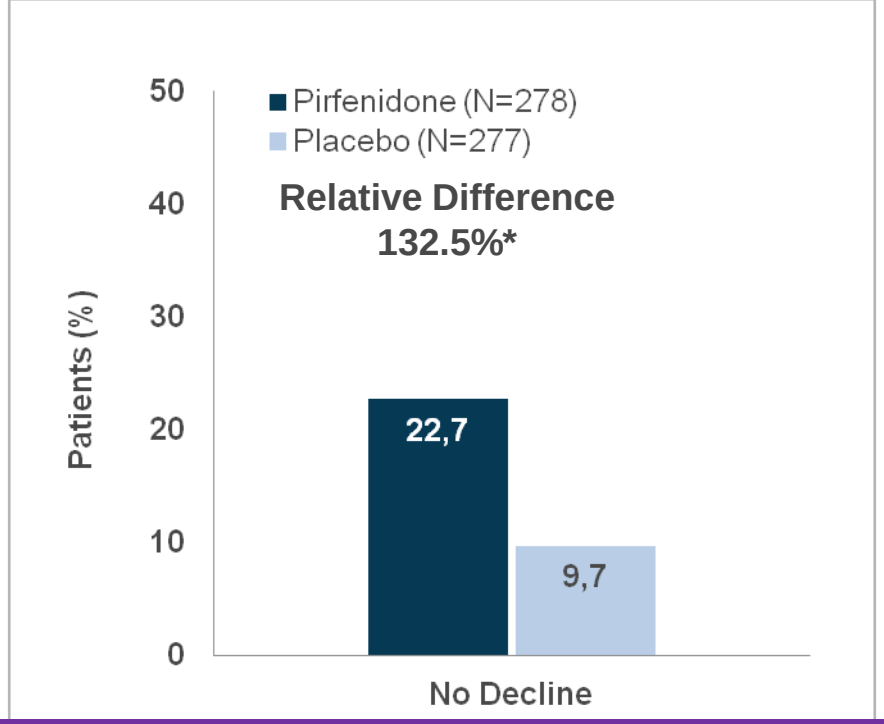
40-80 yr

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



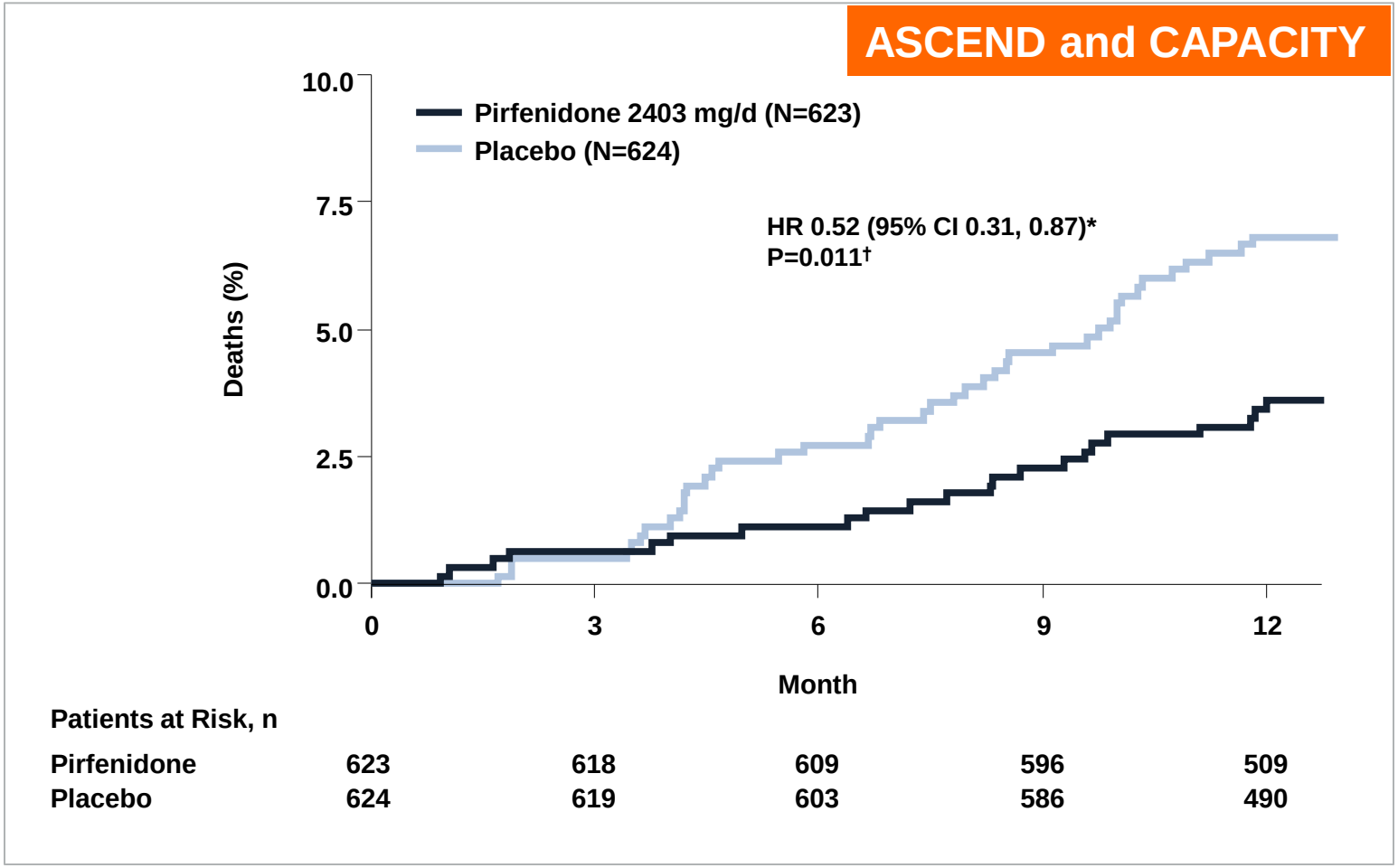


A total of 93.5% and 94.6% of patients completed the study in the pirfenidone and placebo groups, rispectively

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**

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

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

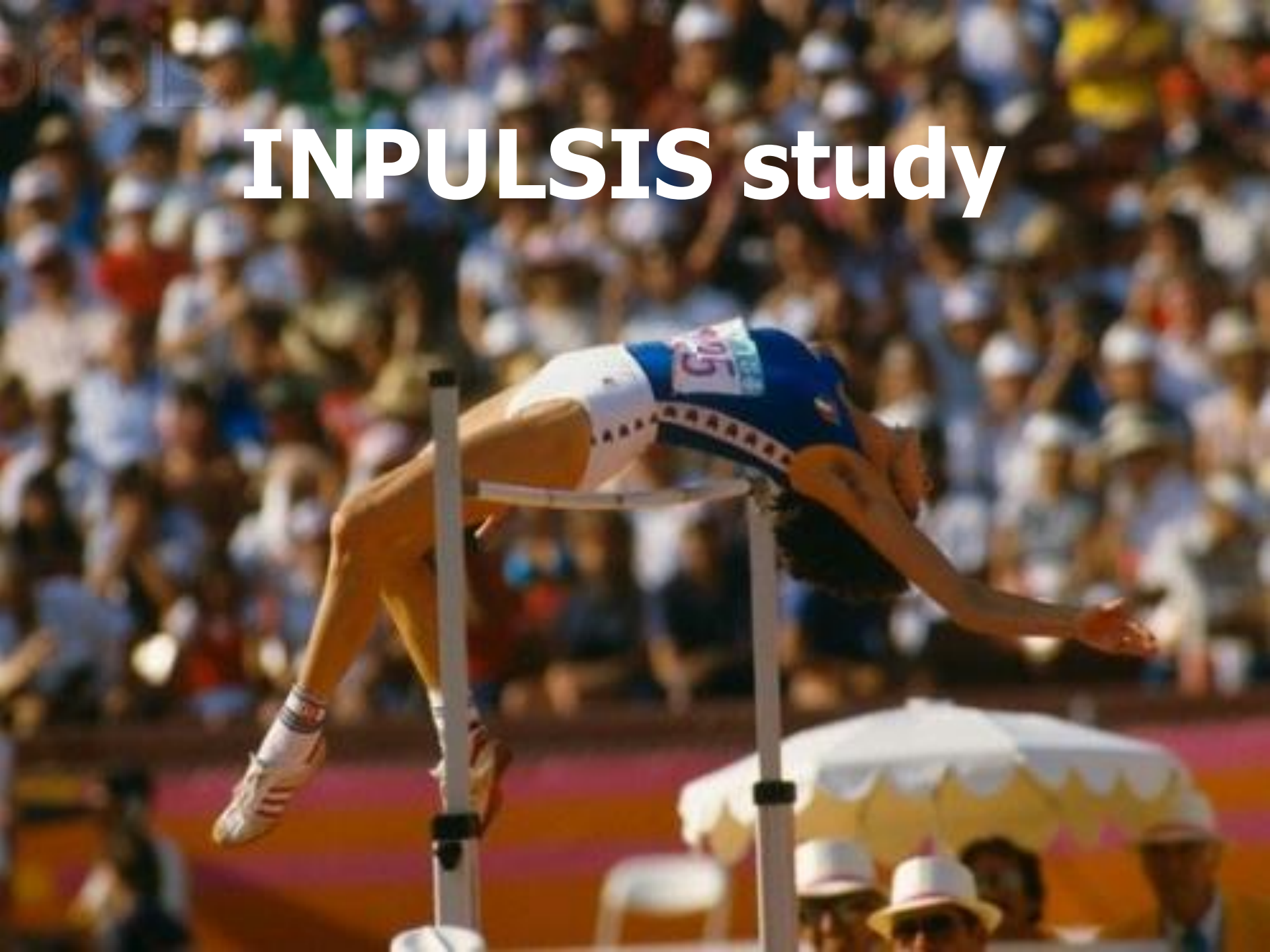
Treatment with pirfenidone for 52 weeks significantly reduced disease progression, as measured by

- 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

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

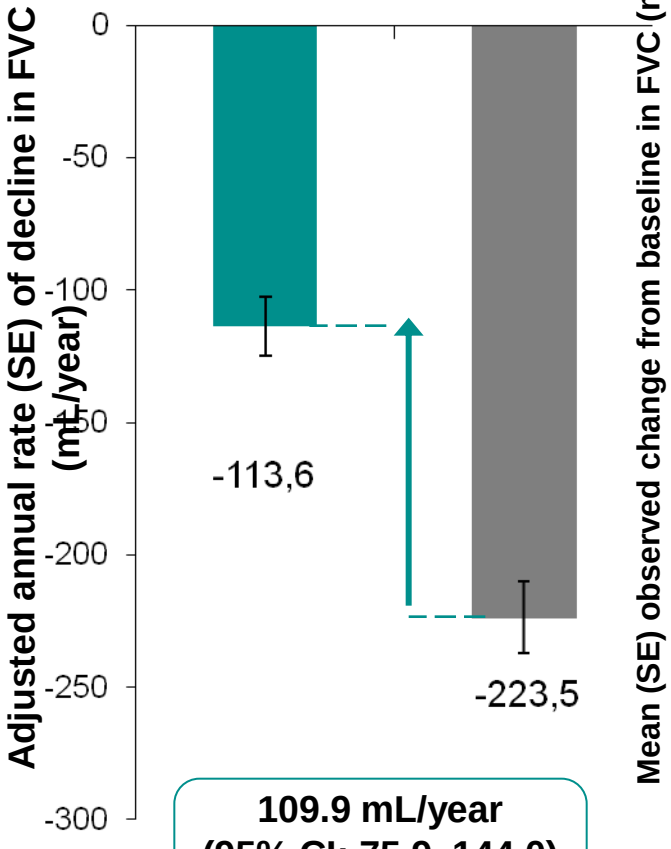
Age ≥40 years

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

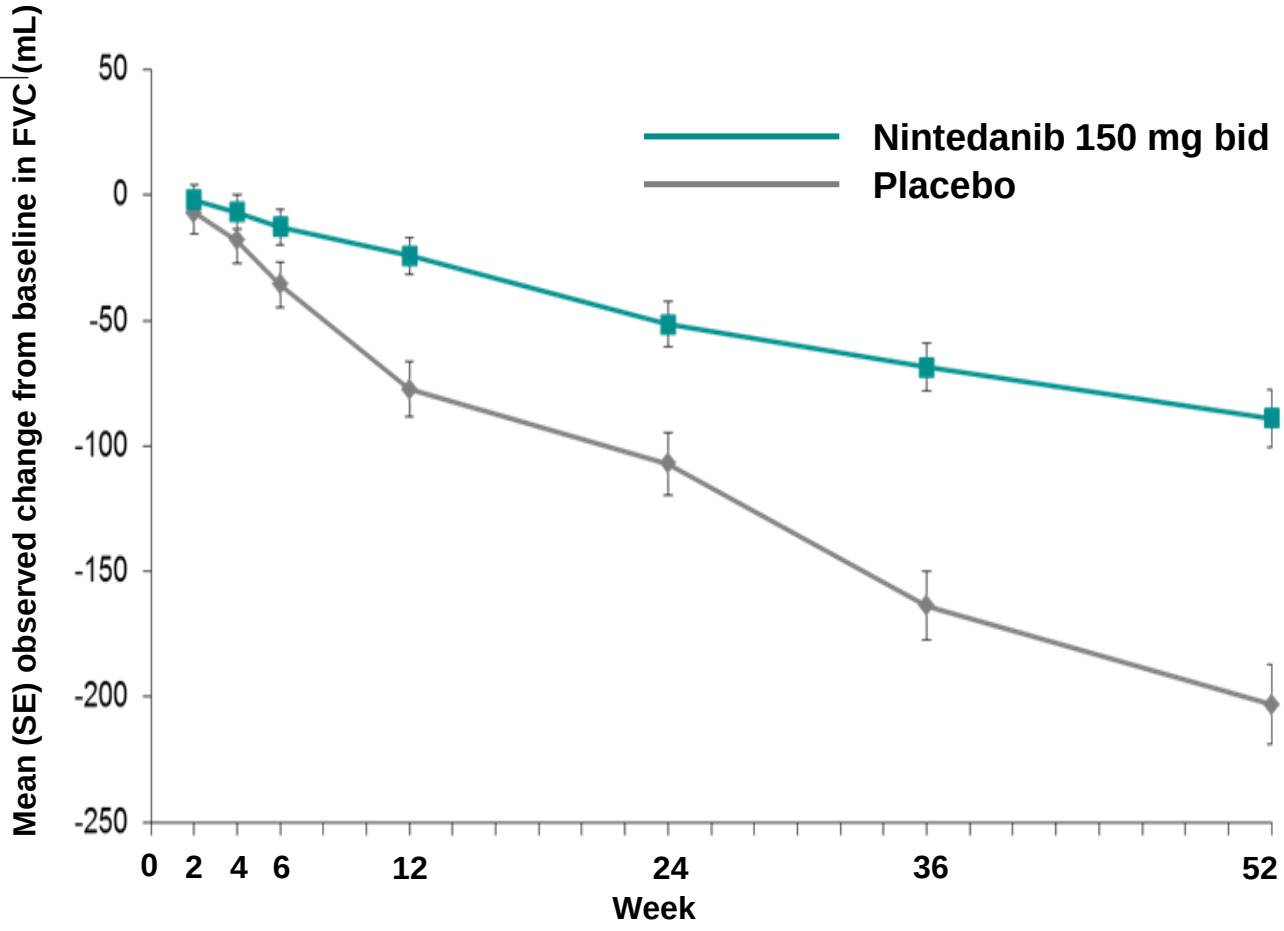
FVC ≥50% of predicted value; DL_{CO} 30–79% of predicted value

Primary efficacy endpoint in pooled data



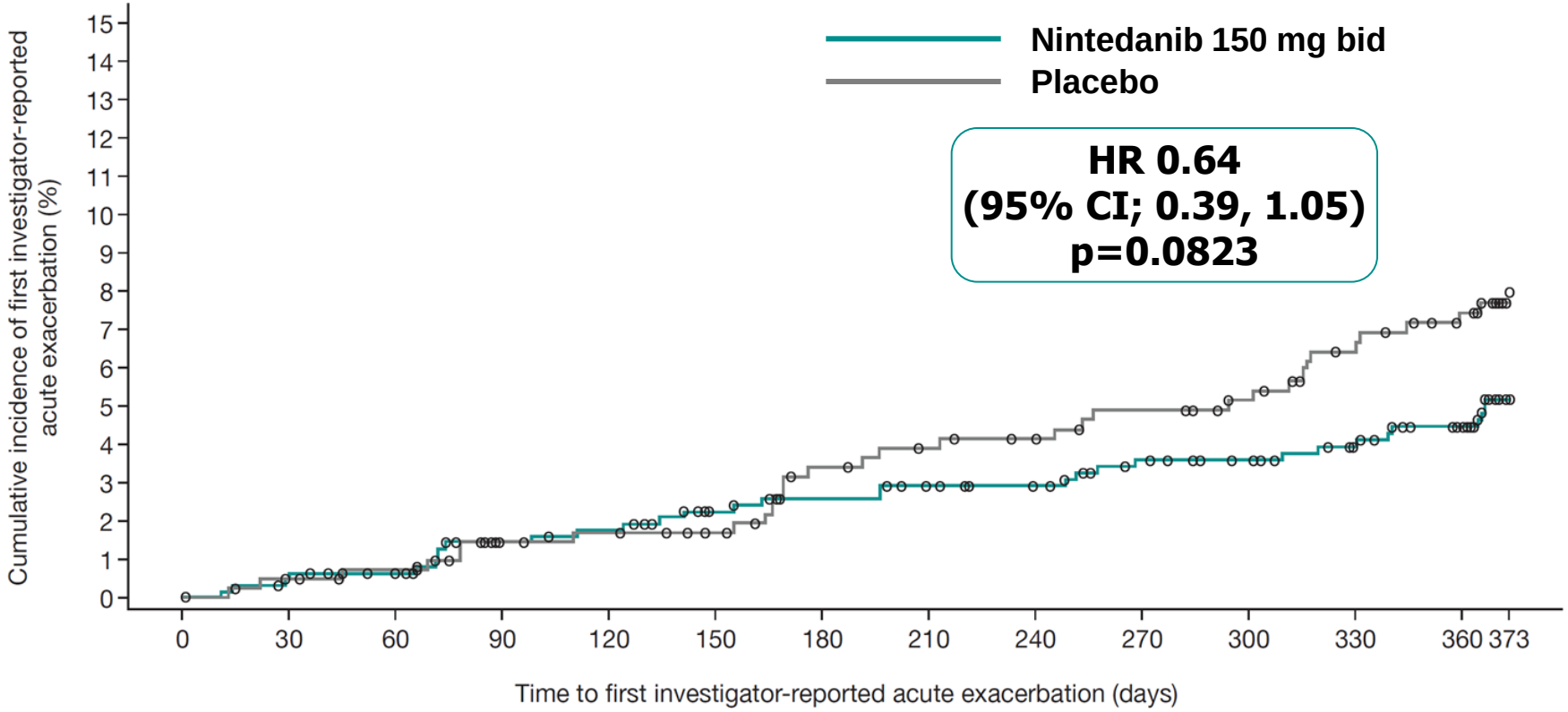
109.9 mL/year
(95% CI: 75.9, 144.0)
p<0.0001

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

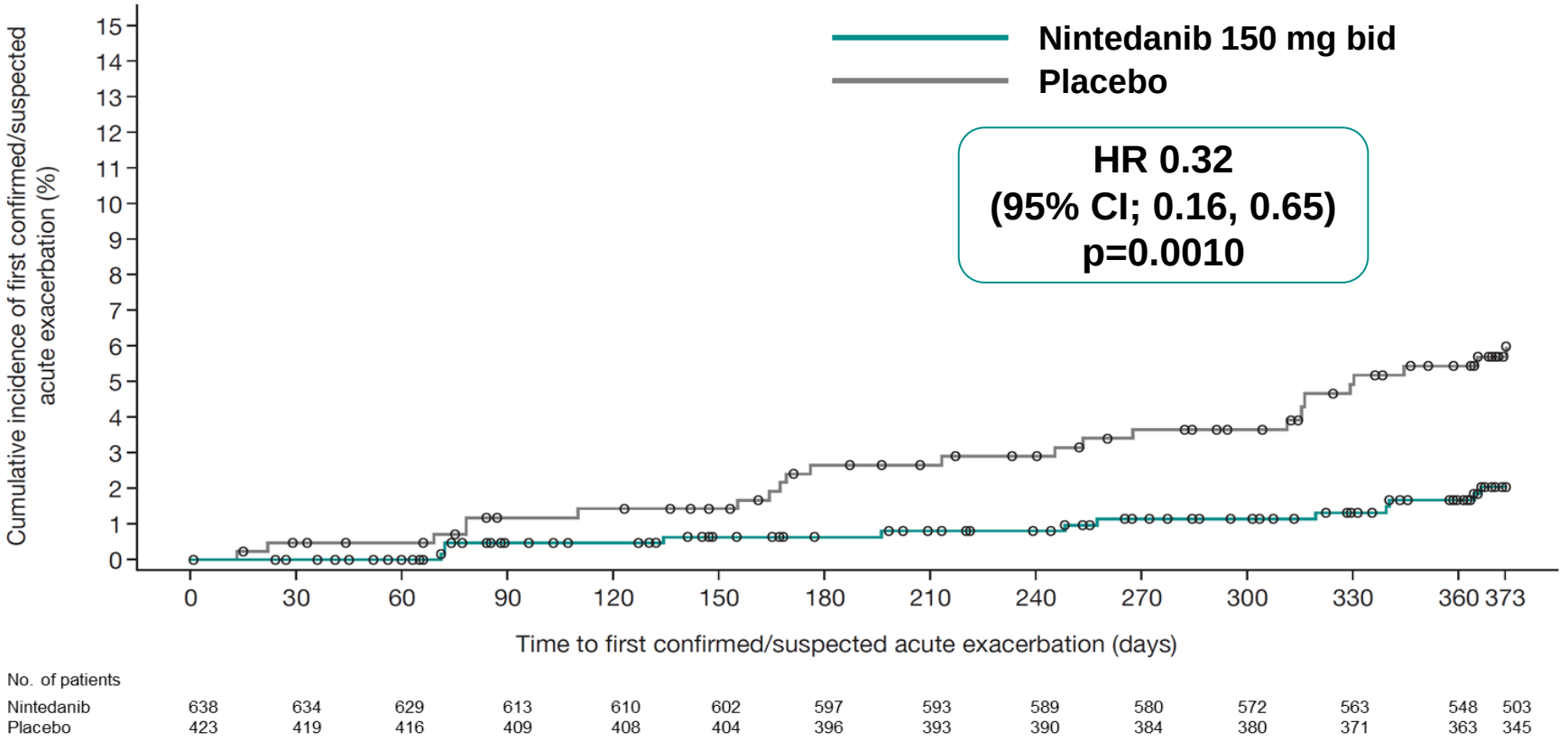
Nintedanib	638	632	627	609	605	595	589	584	580	570	562	553	537	492
Placebo	423	419	415	408	407	403	393	389	386	381	376	367	359	341

	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

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

Richeldi et al. N Eng J Med 2014

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

- FDA approved pirfenidone and nintedanib in october 2014
- EMA approved pirfenidone for the treatment of mild to moderate IPF in march 2011
- EMA approved nintedanib for the treatment of IPF in February 2015

*An **early** and **accurate** diagnosis of IPF is **critical**, particularly with the advent of novel specific treatments that may have the potential to reduce disease progression*

Timely diagnosis

Begin treatment early

Treat aggressively

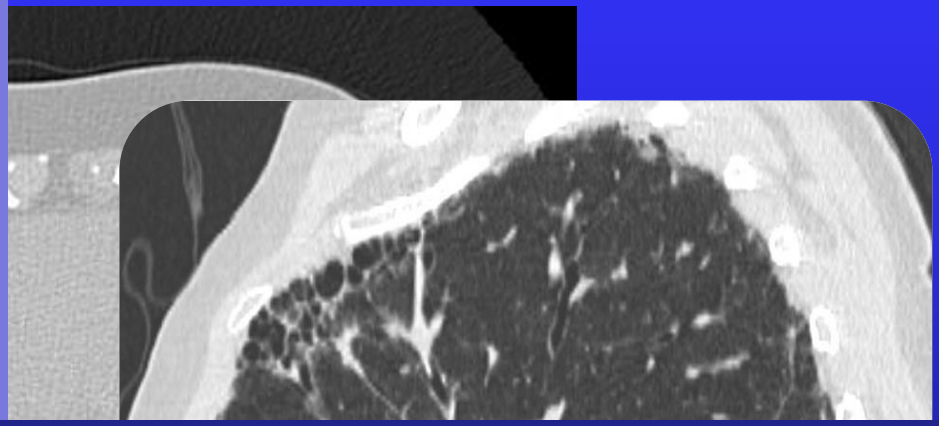
UIP pattern (all four):

Sub-pleural, basal predominance

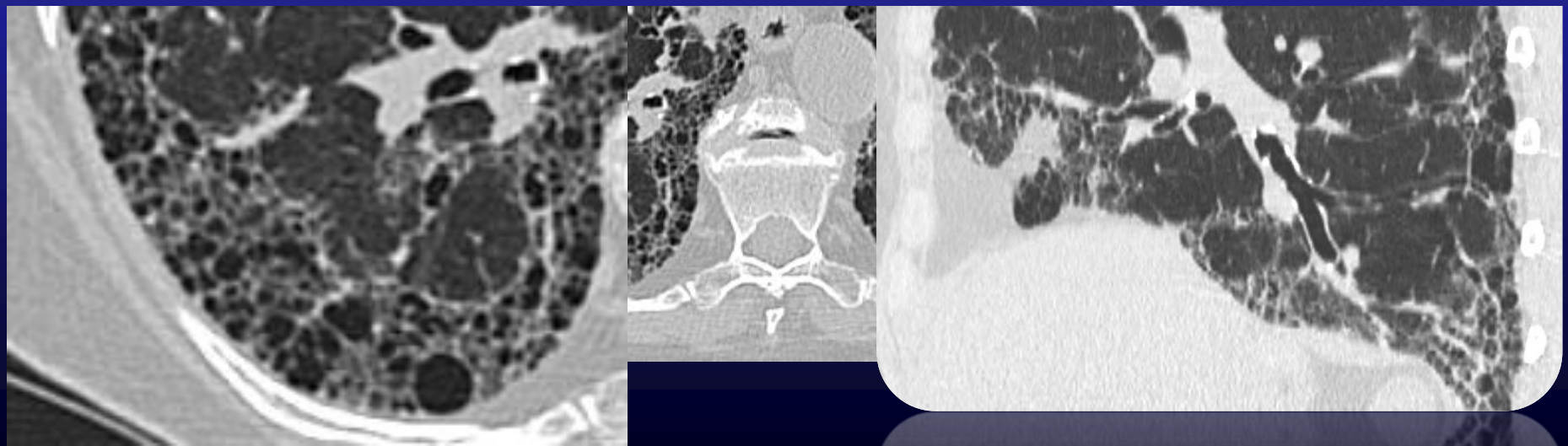
Reticular abnormality

Honeycombing with or without traction bronchiectasis

Absence of features listen as inconsistent with UIP



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



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

Menage comorbidities

Depression

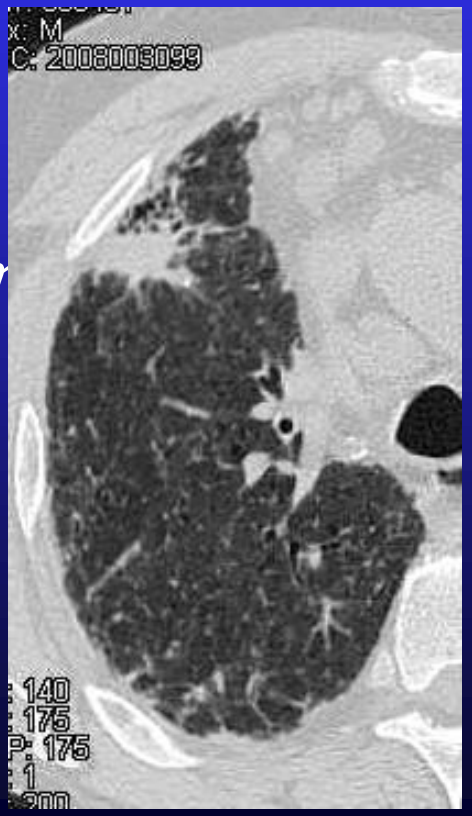
Sleep disorders

Cardiovascular diseases

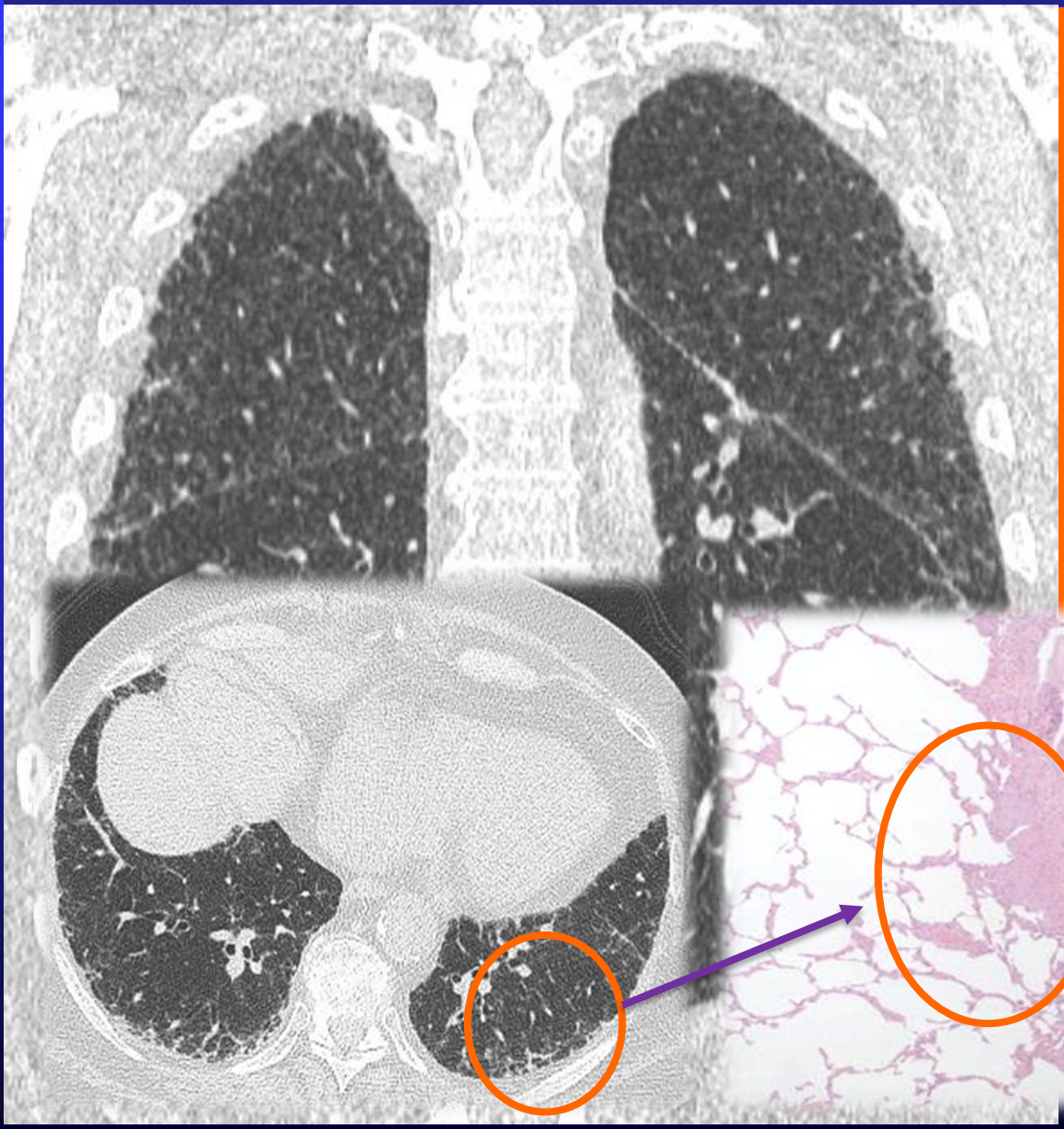
GERD 87% of patients; 47% with symptom

Emphysema

Lung cancer



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

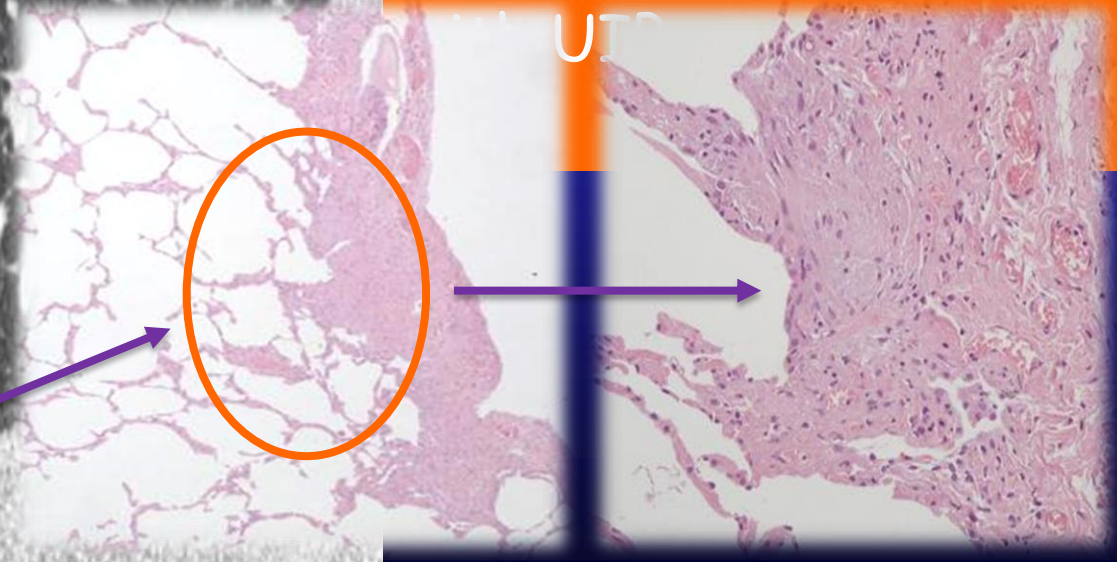


Possible UIP pattern (all three):

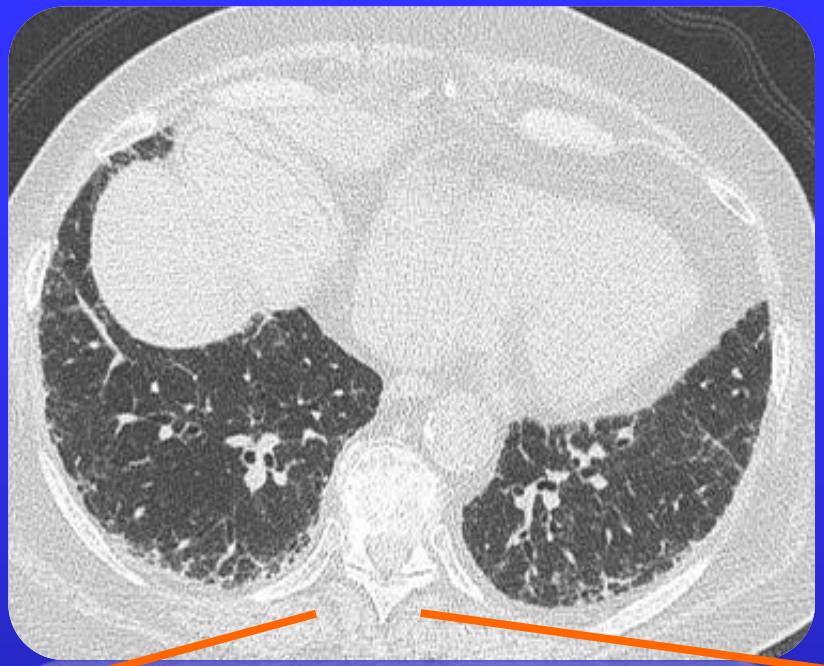
Subpleural, basal predominance

Reticular abnormality

Absence of features listen as inconsistent



Fell CD et al, AJRCCM 2010



Male gender
Current or former smoker
Older age (>70 yrs)
Low-inspiratory velcro rales
Neutrophils on BAL

Very high likelihood of IPF (PPV 95%)

Female gender
Younger age
Non smoker

Mid-inspiratory squeaks
Positive serologies
Lymphocytosis on BAL
Skin findings

More likely idiopathic or secondary NSIP

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

The problems is….

"Possible UIP" is the major current diagnostic problem in chronic fibrotic ILD:

- What's the treatment?
- What's the prognosis?
- What's the role of BAL evaluation?

If the distinction between IPF and alternative diagnoses remains in doubt after full evaluation, a period of treatment as for HP or NSIP is also a diagnostic test

Corticosteroids for over 60 yr: why? And why continue?

- NSIP cases
- Chronic HP was not well recognised

Chronic hypersensitivity pneumonitis in patients diagnosed with idiopathic pulmonary fibrosis: a prospective case-cohort study

Morell et al. Lancet Respir Med 2013; 1: 684

20 of the 46 (43%, 95% CI 29-58) patients with IPF according to 2011 guidelines had a subsequent diagnosis of chronic hypersensitivity pneumonitis

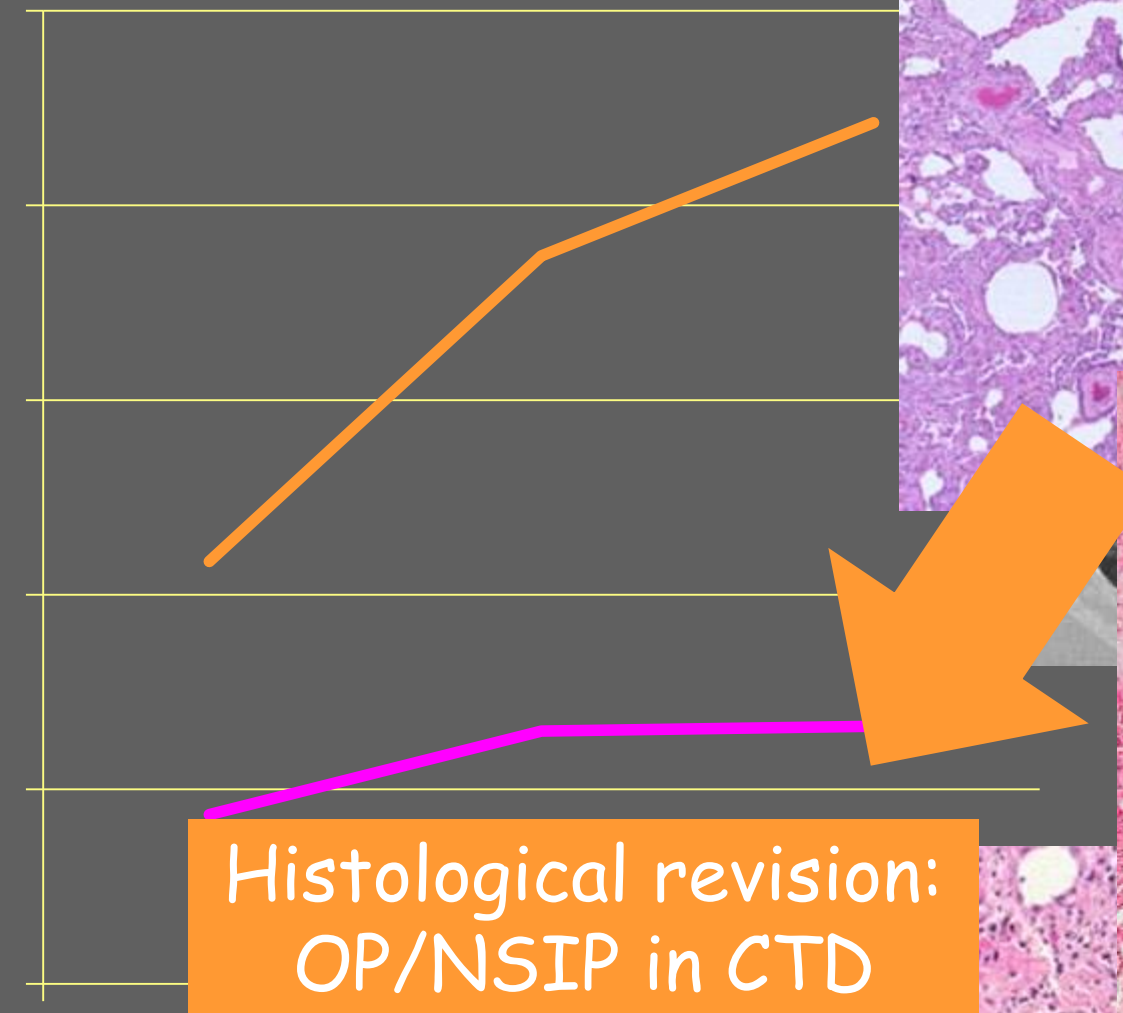
Almost half of patients diagnosed with IPF on the basis of 2011 criteria were subsequently diagnosed with chronic hypersensitivity pneumonitis, and most of these cases were attributed to exposure of occult avian antigens from commonly used feather bedding.

Corticosteroids for over 60 yr: why? And why continue?

- NSIP cases
- Chronic HP was not well recognised
- Lung involvement in CTD

We often are unsure of what we are treating

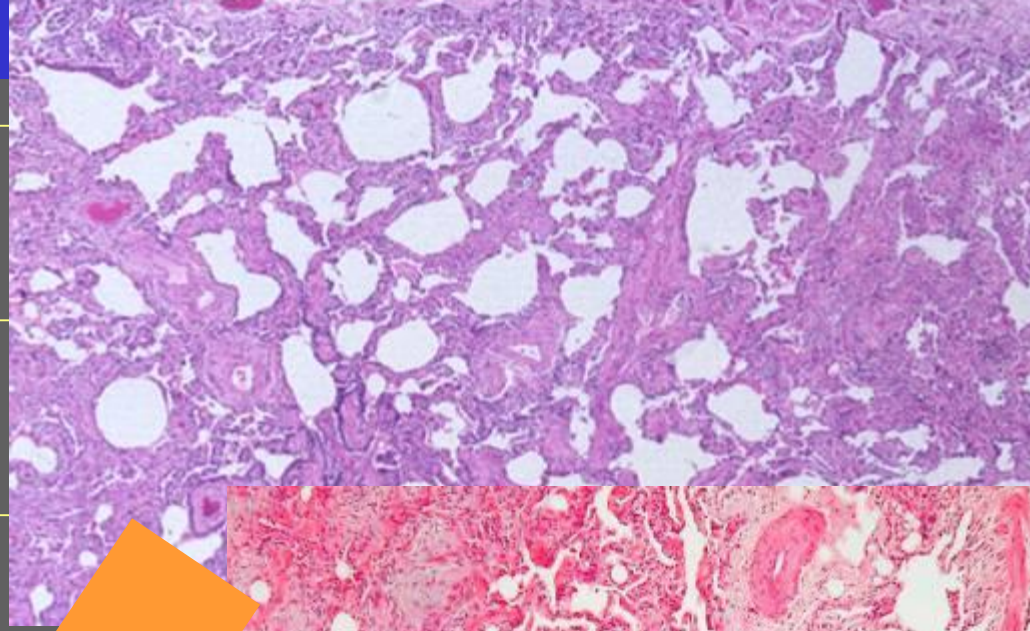
Woman. 44 yrs.

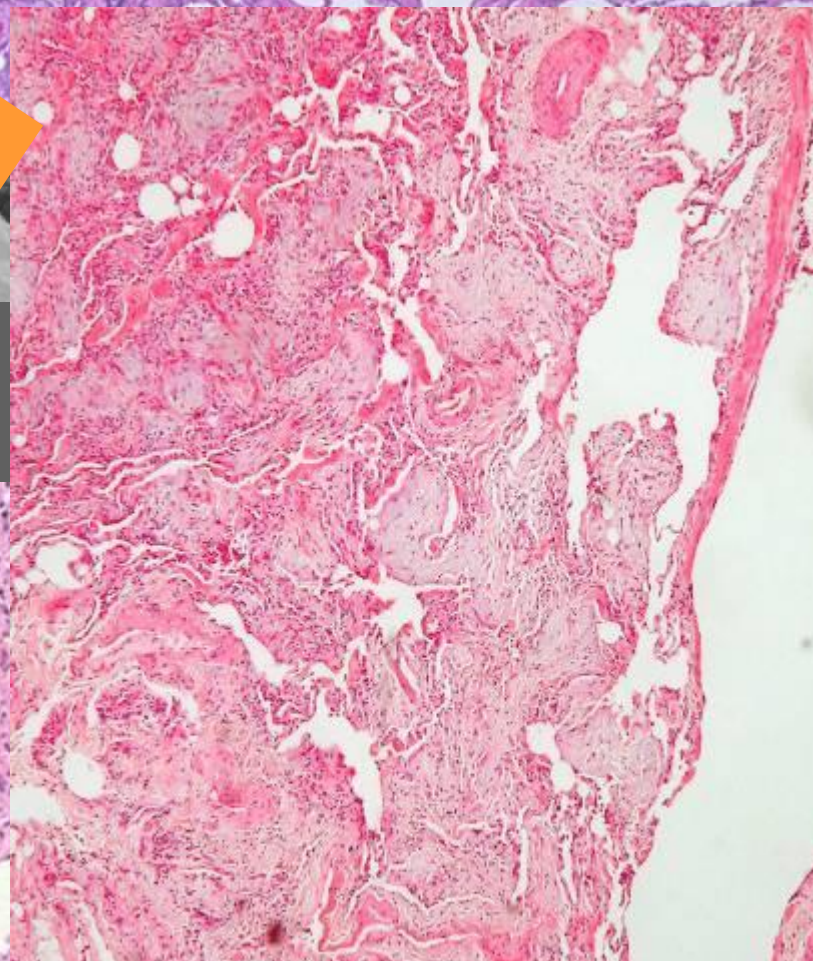


Histological revision:
OP/NSIP in CTD

Basale 6 months later 1 year

Therapy with s





Conclusions

- A new era in the IPF therapy is beginning
- We yet have not a cure for IPF but a therapy
- An early and accurate diagnosis of IPF is critical
- Many questions are still unanswered!