Under the aegis of

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI MEDICINA SPECIALISTICA, DIAGNOSTICA E SPERIMENTALE

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
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PULMONARY HYPERTENSION BOLOGNA 2014

a LANDSCAPE CHANGE from NEW TRIALS:
DRUG DEVELOPMENT, GUIDELINES,
DEBATES AND CLINICAL CASES

ROYAL HOTEL CARLTON - BOLOGNA - ITALY
NOVEMBER 28-29, 2014

DEBATE À TROIS: TREATMENT OPTIONS FOR PH DUE TO LUNG DISEASES

Clinical phenotypes and optimization of the general treatment options

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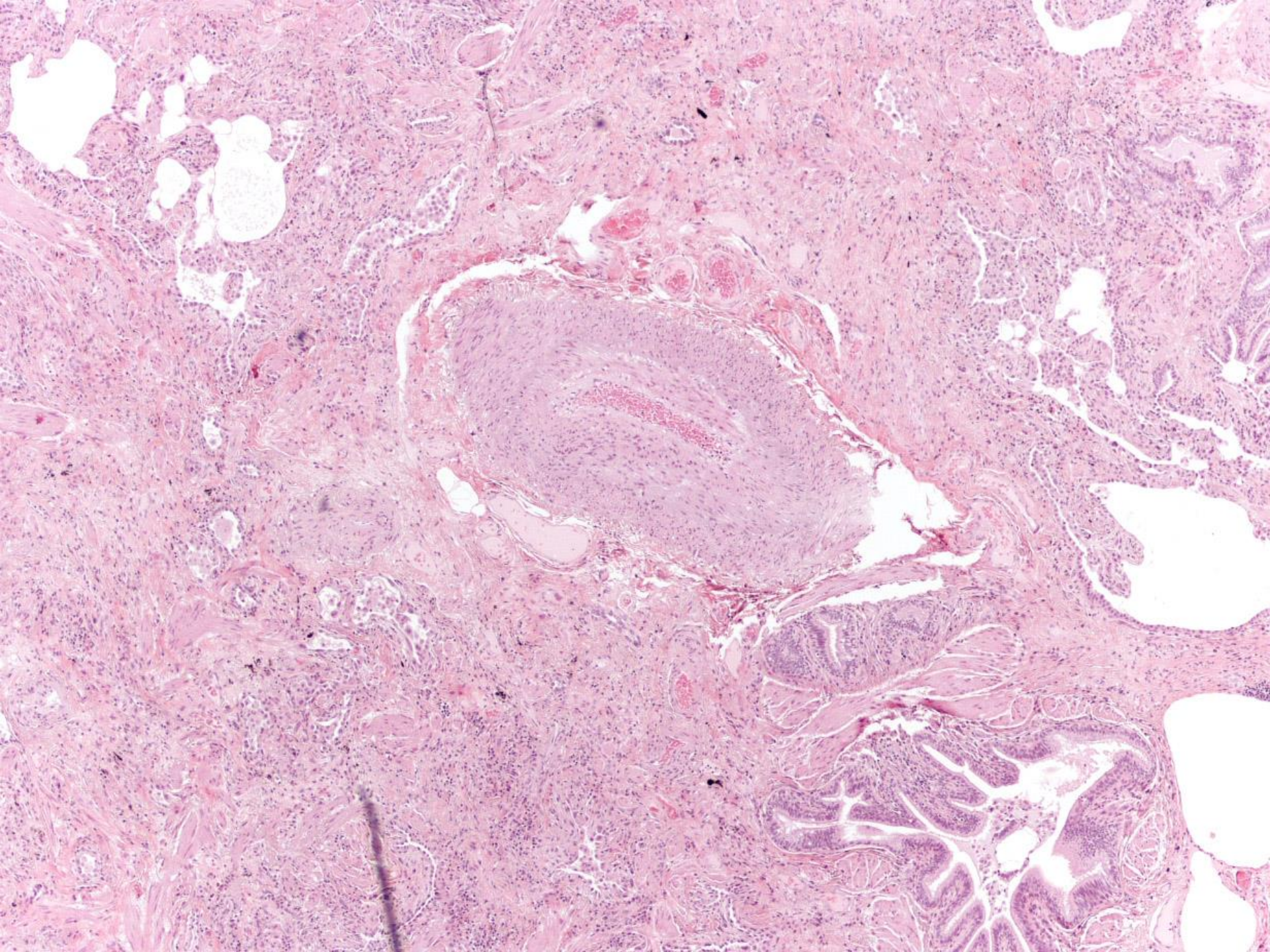
Disorders of the respiratory system and hypoxemia

- PH is generally mild or moderate (PAP < 30 mmHg), is not per se a predominant prognosis factor and not require specific therapeutic intervention (except oxygen therapy)
- Medial hypertrophy and mild intimal fibrosis



- The prevalence of PH in patients with ILD varies greatly as a function of the underlying disease and the diagnostic mode used to identify PH
- The most extensive data have been published in IPF

Author	Year	Patients	N	Diagnosis	Definition of PH	Prevalence, %
Leutche et al.	2004	IPF	28	RHC	mPAP>35 mmHg	21.4
Nadrous et al.	2005	IPF	88	Echo	sPAP>35 mmHg sPAP>50 mmHg	84 31
Hamada et al.	2007	IPF	70	RHC	mPAP>25 mmHg	8.1
Zisman et al.	2007	IPF	65	RHC	mPAP>25 mmHg	41.5
Patel et al.	2007	IPF	41	RHC	mPAP>25 mmHg +PCWP ≤15 mmHg	20
Shorr et al.	2007	IPF	2.5	RHC	mPAP>25 mmHg	46.1
Nathan et al.	2008	IPF	118	RHC	mPAP>25 mmHg	40.7
Song et al.	2009	IPF	131	Echo	sPAP>40 mmHg	25
Minai et al.	2009	IPF	148	RHC	mPAP>25mmHg mPAP>40mmHg	45.9 14.2
Kimura et al.	2012	IPF	101	RHC	mPAP > 20 mmHg	34,6

The incidence and prevalence of PH in IPF remain unclear, with widely varying estimates.

The differences reflect:

- varying patient populations
- varying underlying disease severity
- differing diagnostic modalities

Out-of-Proportion PH
Nice definitions 2013

COPD/IPF/CPFE **without PH** : mPAP <25mmHg

COPD/IPF/CPFE **with PH** mPAP >25mmHg;

COPD/IPF/CPFE **with severe** PH

mPAP >35mmHg or mPAP >25mmHg with low cardiac index (CI <2.0 l/min/m2)

Pulmonary hypertension in IPF

- Frequency
- Prognosis
- Diagnosis

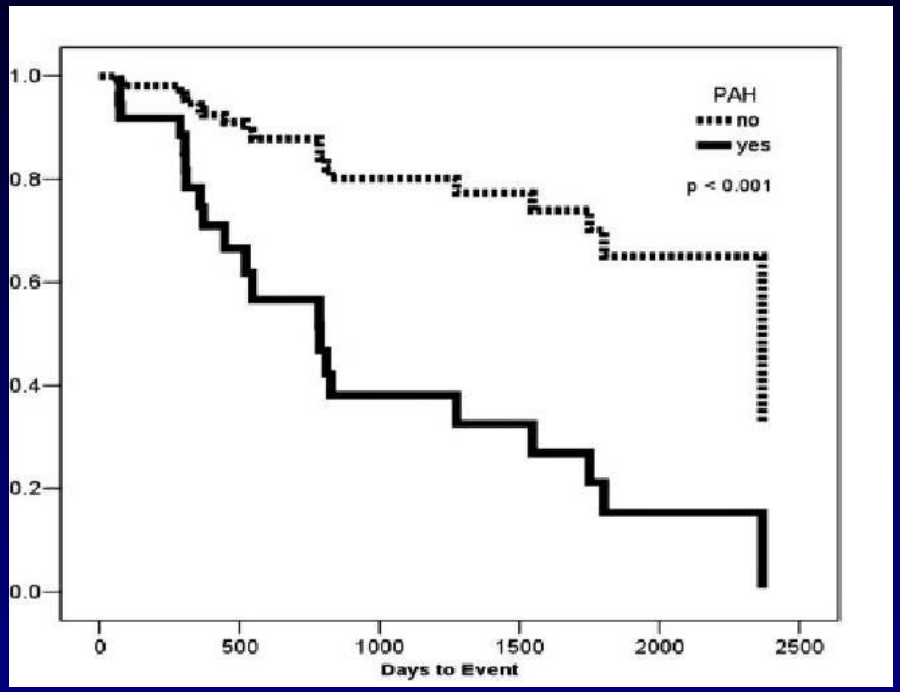
Does it affect the prognosis of IPF?

Pulmonary hypertension in IPF

88 patients with IPF	PASP 0-34 mmHg (n=14)	PASP 35-49 mmHg (n=47)	PASP >50 mmHg (n=27)
Median survival	4.8y	4.1y	0.7y
1 year survival	100%	79%	44%
3 year survival	64%	61%	32%

Nadrous et al Chest 2005: 128;616-7

Pulmonary hypertension in IPF



Variables	MAP ≤ 25 mmHg (n= 10)	MAP > 25 mmHg (n= 24)	P value
MPAP, mmHg	18.2 ± 3.6	29.8 ± 5.1	NA
6MWT distance, m	365.9 ± 81.8	143.5 ± 65.5	< 0.001
SpO2 nadir on 6MWT, %	88.0 ± 3.5	80.1 ± 3.7	< 0.001
Mortality rate, %	37.5	70.0	0.003

Lettieri CJ et al. Chest 2006, 129:746-52

Table 1 Demographic and clinical data of the study population (n = 66)

Parameters	No
Clinical parameters*	
Age (years)	57 (12)
Gender (F:M)	28:38
Smoking (pack years)	27 non-smokers, 31 ex-smokers, 7 current smokers, 1 unknown
Time from presentation (months)	33 (4–264)
WHO class	3 (1–4)
Working diagnosis (based on multidisciplinary consensus including lung biopsy when available)	IPF (n = 16) Idiopathic NSIP (n = 6) CTD-related fibrosis (n = 17) Sarcoidosis (n = 12) Other interstitial diseases (n = 15)
Biopsy diagnosis	n = 13 (20%)
Right heart catheter*	
mPAP (mm Hg)	33.6 (11.8)
mRAP (mm Hg)	5.9 (4.2)
mLAP (mm Hg)†	10.7 (5.1)
PVR (Wood units)	5.9 (4.3)
PVR index (Wood units/m²)	10.4 (7.1)
Cardiac output (l/min)	4.3 (1.2)
Cardiac index (l/min/m²)	2.3 (0.5)
Echocardiography	
RVSP (mm Hg, n = 48)	56 (24–102)
PAT (ms, n = 46)	100 (33–144)
Pulmonary function	
T_{LCO} % (n = 65)	29.6 (14.7)
K_{CO} % (n = 65)	52.0 (19.7)
TLC % (n = 61)	72.5 (20.2)
FEV_1 % (n = 62)	62.4 (23.3)
FVC % (n = 62)	67.9 (23.1)
Pao_2 (kPa, n = 61)	8.4 (2.2)
$Paco_2$ (kPa, n = 61)	5.0 (0.9)
CPI (n = 62)	56.9 (14.6)
6MWT (n = 42)	
End Spo_2 (%)	81.4 (8.4)
6MWT distance (m)	254.6 (128.1)

Pulmonary vascular resistance predicts early mortality in patients with diffuse fibrotic disease and suspected pulmonary hypertension

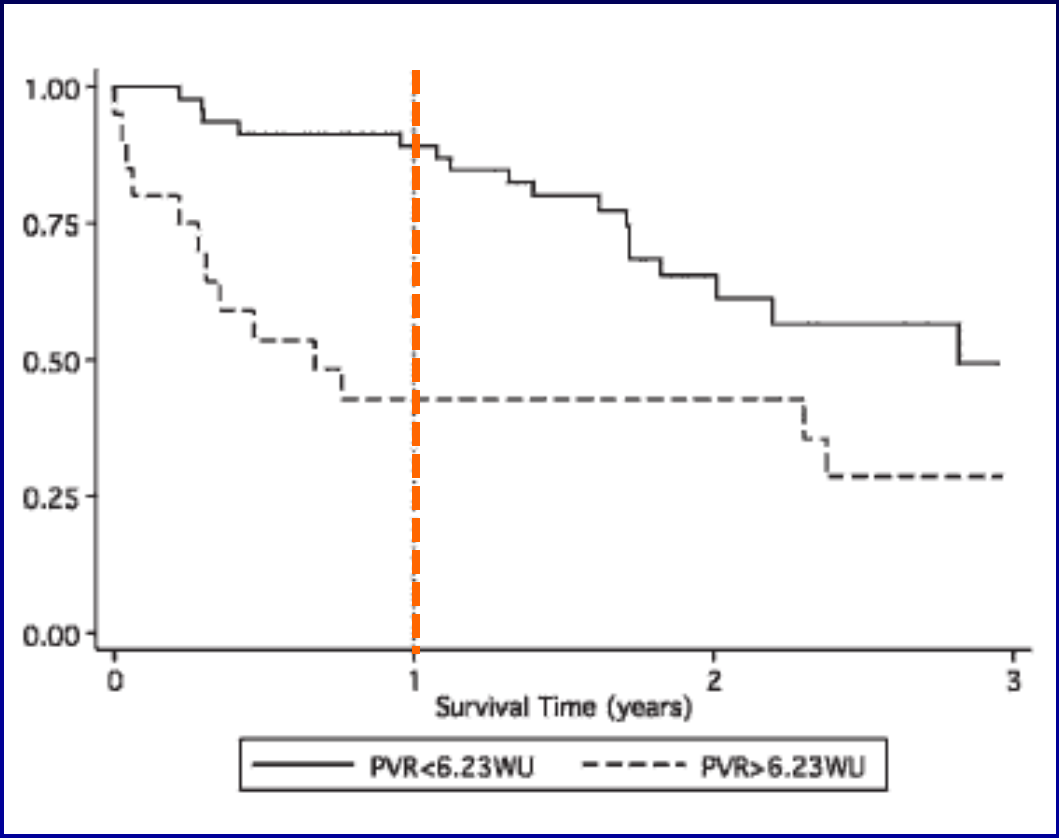
Corte TJ et al. Thorax 2009; 64: 883

Table 2 Comparison of patients dying within 12 months with those surviving at 12 months

	Death within 12 months	Survival at 12 months	p Value*
mPAP (mm Hg)	39.0 (14.1)	31.7 (10.4)	0.03
PVR (WU)	9.4 (5.8)	4.6 (2.8)	<0.001
PVR index (WU/m²)	16.4 (9.7)	8.5 (4.8)	<0.001
mLAP (mm Hg)	12.2 (6.4)	9.5 (5.0)	0.11
Cardiac output (l/min)	3.8 (1.3)	4.4 (1.1)	0.06
PAT (ms)	69.4 (21.2)	99.5 (28.1)	0.005
Pao_2 (kPa)	7.4 (1.4)	8.8 (2.3)	0.03

Pulmonary vascular resistance predicts early mortality in patients with diffuse fibrotic disease and suspected pulmonary hypertension

Corte TJ et al. Thorax 2009; 64: 883



In severe diffuse lung disease, raised PVR strongly predicts death within 1 year independent of disease severity or diagnosis of IPF.

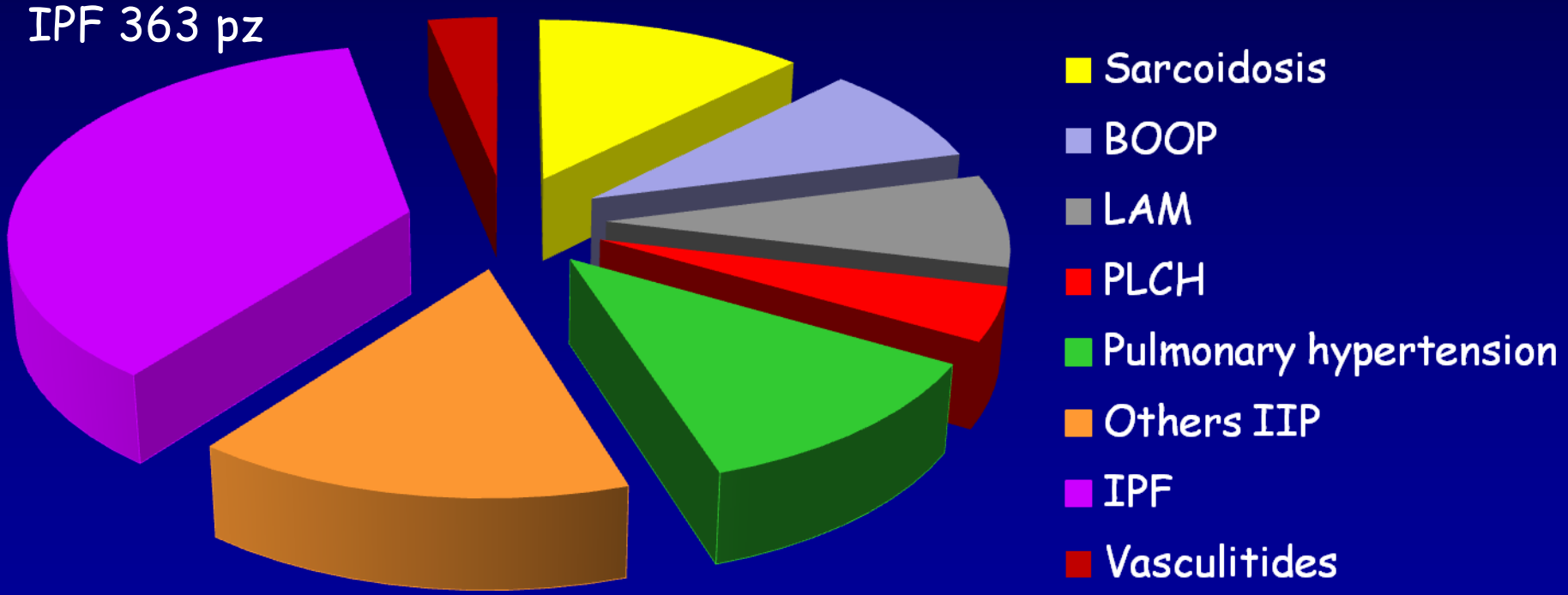
PVR is superior to other measurements at RHC and also to non-invasive tests (alone or in combination). These findings suggest that, in advanced lung disease, prognostic information that is only obtainable by RHC has important management implications

- The presence of PH in IPF is associated with higher mortality and its development contributes to the deterioration of IPF patients

Pulmonary rare diseases

Ospedale San Giuseppe Experience (2001- 2012)

Tot. 996 patients



RHC and 6MWD in IPF

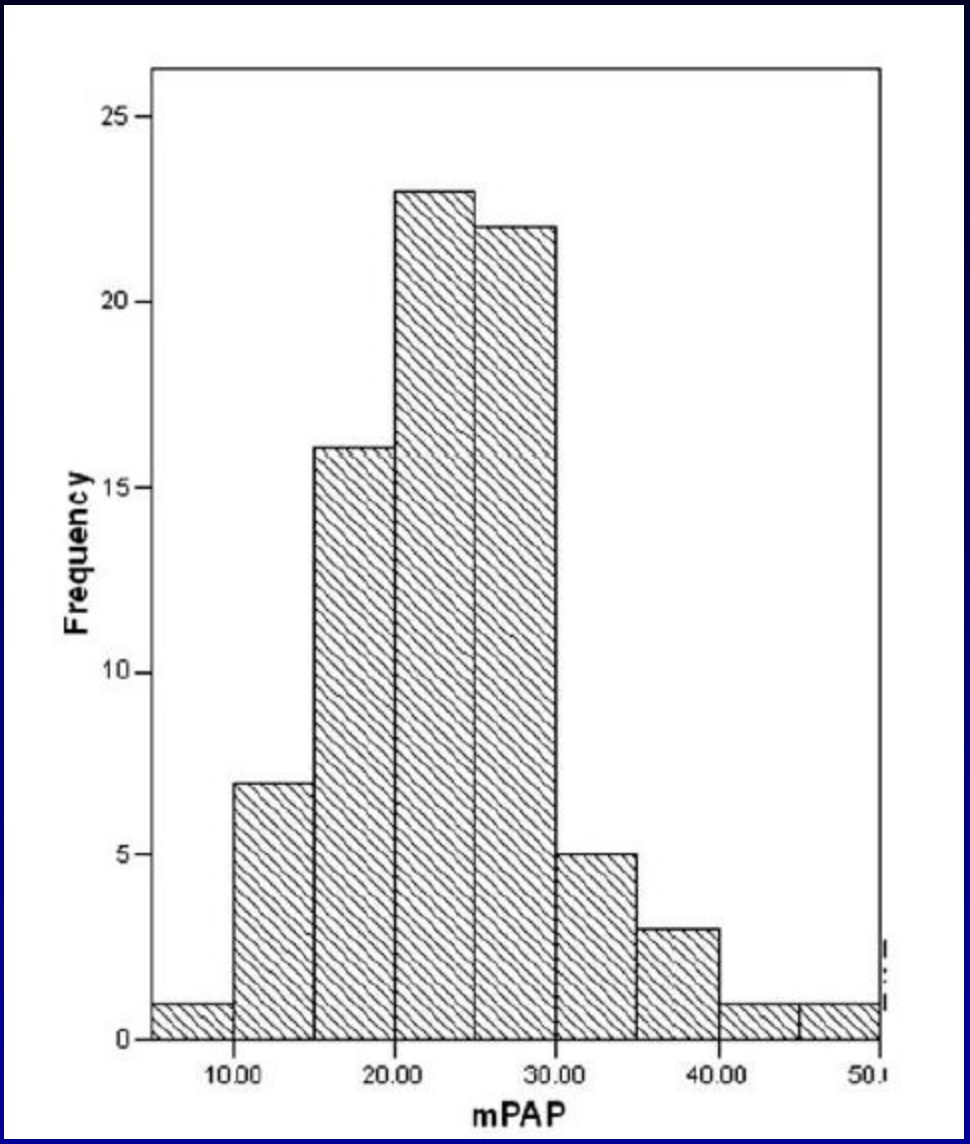
Variables	MAP ≤ 25 mmHg (n= 17)	MAP > 25 mmHg (n= 13)	MAP > 35 mmHg (n= 4)	P value
MPAP, mmHg	19.4 ± 3.6	32.4 ± 6	40,5 ± 2,6	NA
6MWT distance, m	222.0 ± 118.5	222.3 ± 118.5	203.7 ± 128.3	>0.1
FVC, %	51.6 ± 13.8*	63.8 ± 16*	56.0 ± 6.7	<0.05
FEV1, %	58.3 ± 16.3	65.8 ± 18.8	55.2 ± 3.7	>0.05
DLCO, %	31.4 ± 9.6	24.2 ± 13.0	29.0 ± 7.4	>0.05
CI, l/min/m2	3.4 ± 0.55*	2.9 ± 0.7*	2.8 ± 0.6	<0.05
PVR, wood units	3.5 ± 1.1*	6.9 ± 1.4*	10.3 ± 2.0	<0.05

Harari S. Sarcoidosis in press

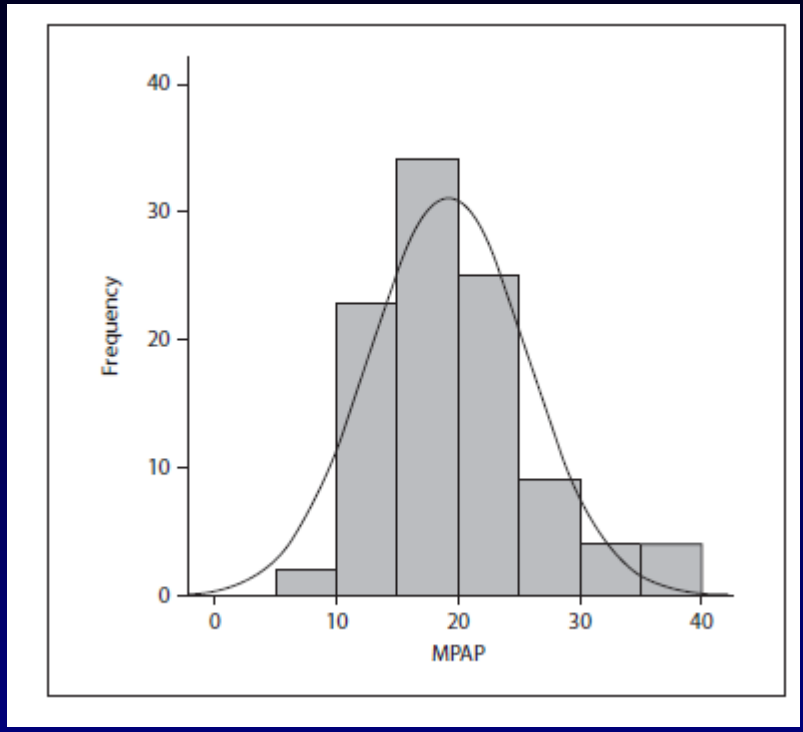
Our data suggest that meters walked during 6MWT are not statistically different in IPF patients with or without PH.

6MWD should not be used as surrogate end point in clinical study in IPF-PH pts.

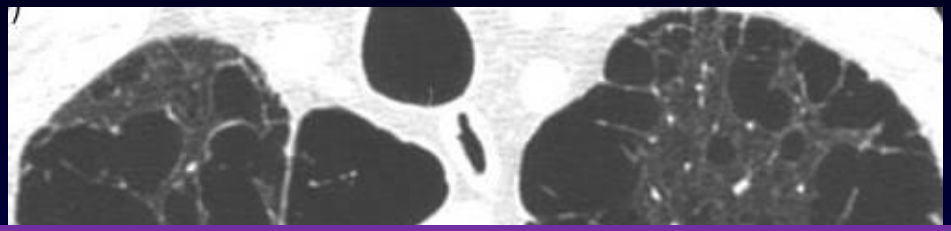
Harari S. Sarcoidosis in press



Lettieri CJ et al. Chest 2006, 129:746-52



Kimura M et al. Respiration 2012



Combined pulmonary fibrosis and emphysema (CPFE)

Definition: Presence on HRCT of the chest of both:

- emphysema of the upper lobes (areas of abnormally low attenuation with a very thin wall [< 1 cm] or no wall),
- opacities suggestive of fibrosis of the lung bases (reticular opacities, basal and subpleural predominance, traction bronchiectasis, possibly honeycombing, with no or little ground glass opacities or consolidation).

PH in CPFE

PH is frequent in patients with the CPFE syndrome, with 47% of patients with estimated systolic right ventricular pressure ≥45 mmHg at echocardiography.

The risk of developing pulmonary hypertension is much higher in CPFE than in IPF without emphysema

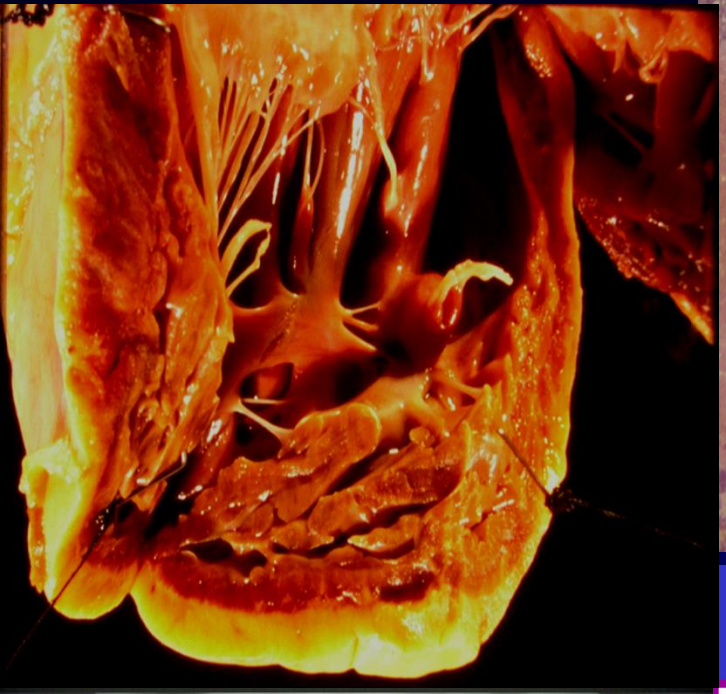
The prognosis of CPFE is worse than that of IPF without emphysema, an outcome determined by severe pulmonary hypertension and not only by the presence of associated emphysema

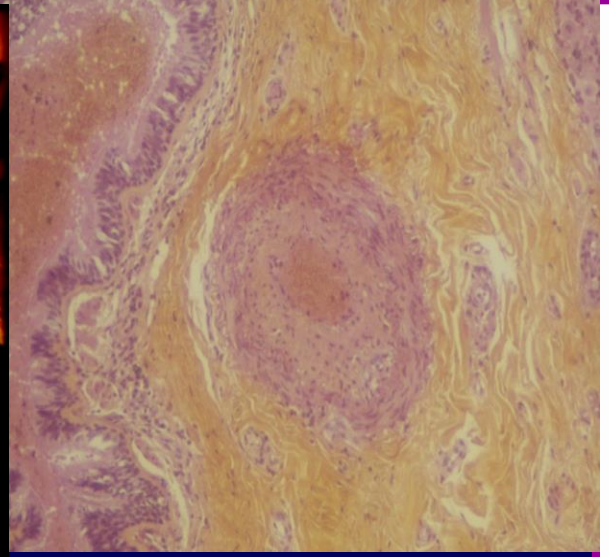
PH in patients with CPFE

Although the efficacy of drugs specifically indicated in pulmonary arterial hypertension has not been demonstrated in patients with pulmonary parenchymal disorders and associated out-of-proportion pulmonary hypertension, a large number of patients from were treated off-label on an individual basis, thereby providing some preliminary information on the efficacy and safety of pulmonary hypertension therapy in this condition.

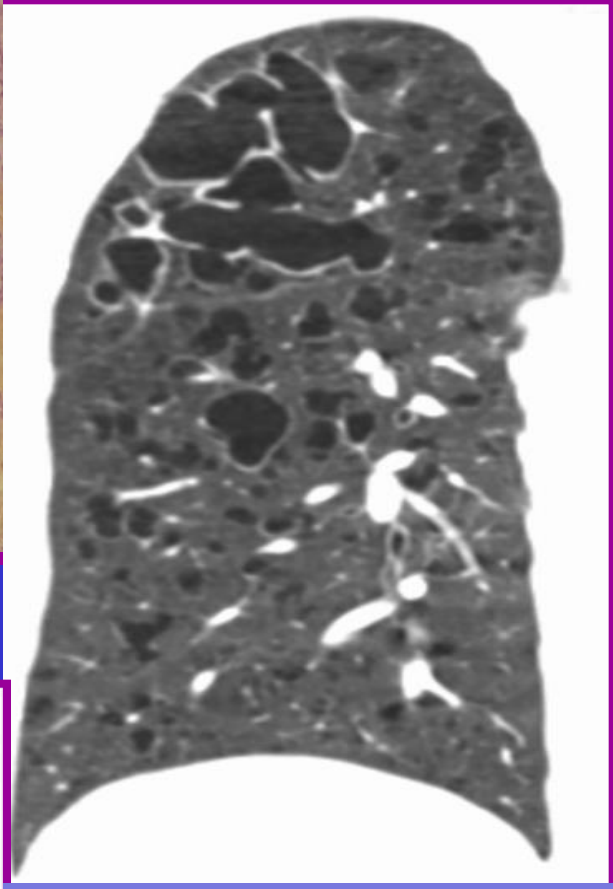
No significant effect of treatment was found on survival.

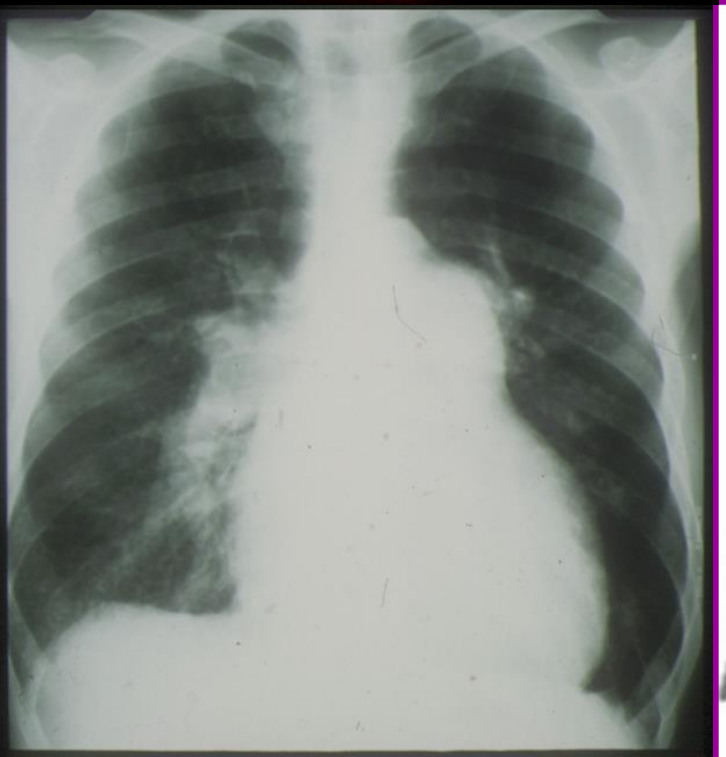
Cottin V et al Eur Respir J 2010; 35; 105

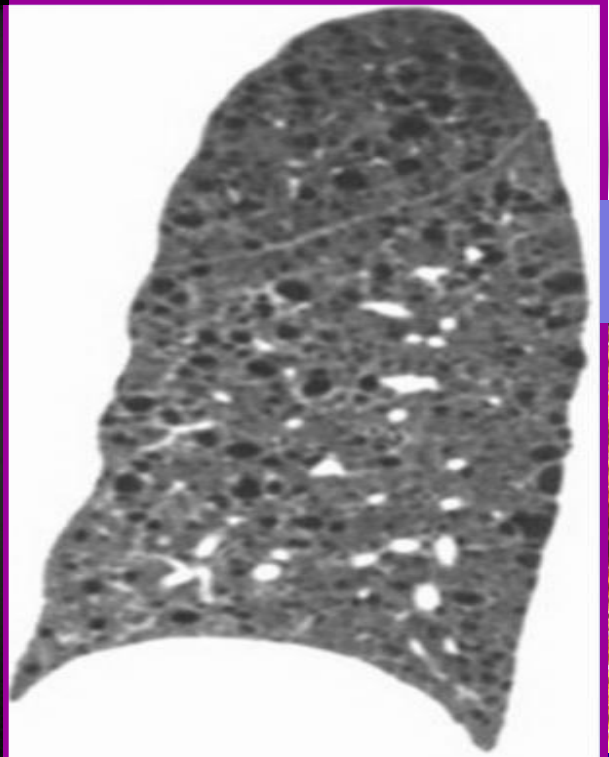




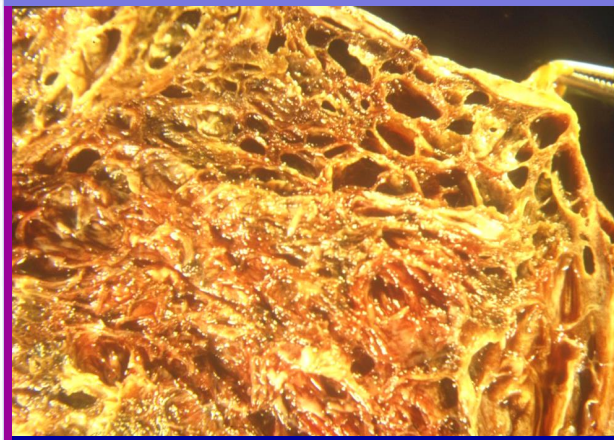
PLCH

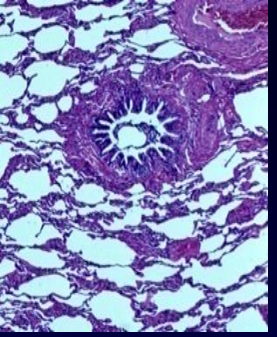






LAM



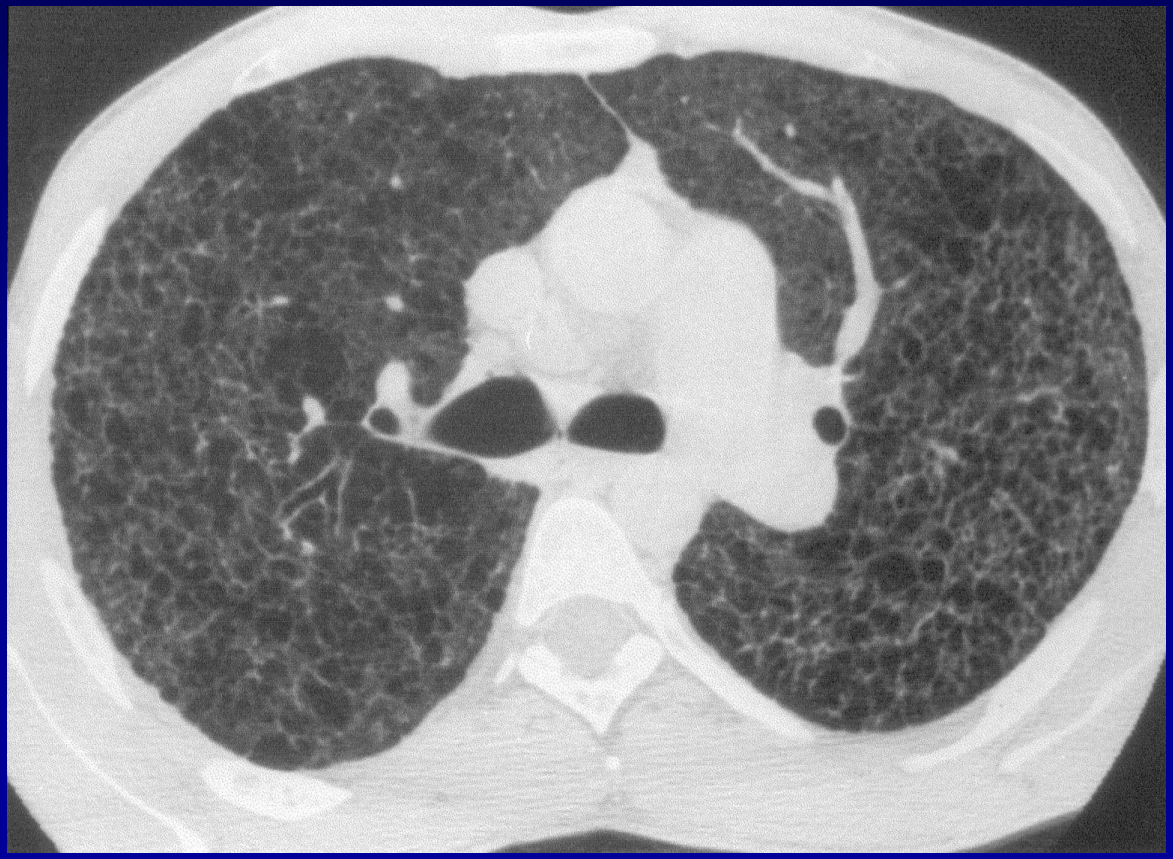


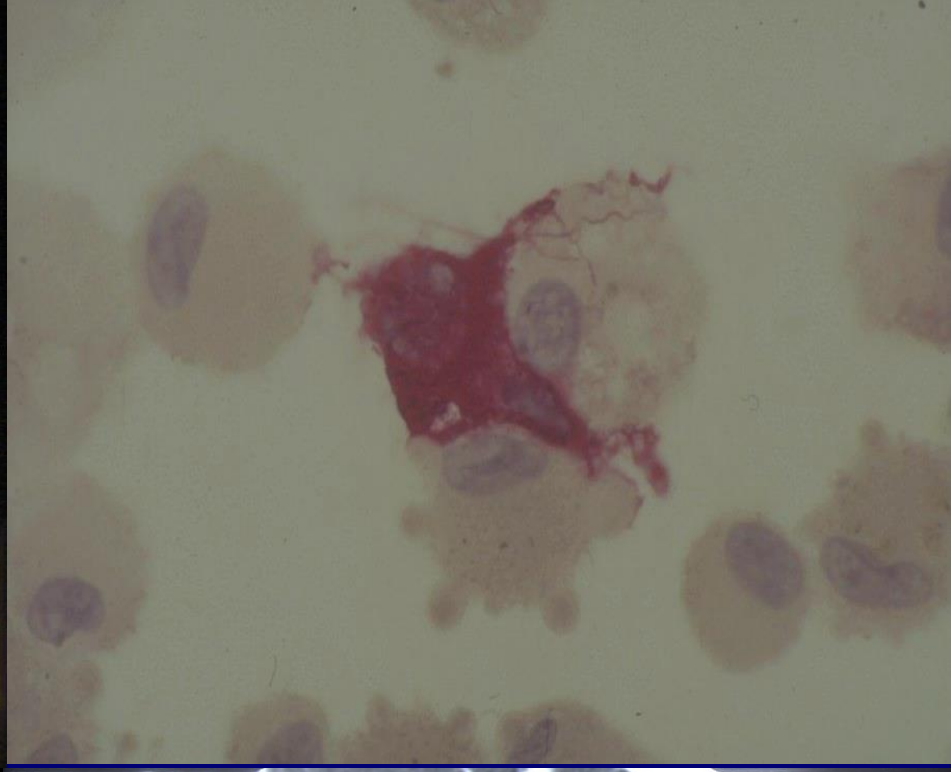
PULMONARY HYPERTENSION DIAGNOSTIC CLASSIFICATION

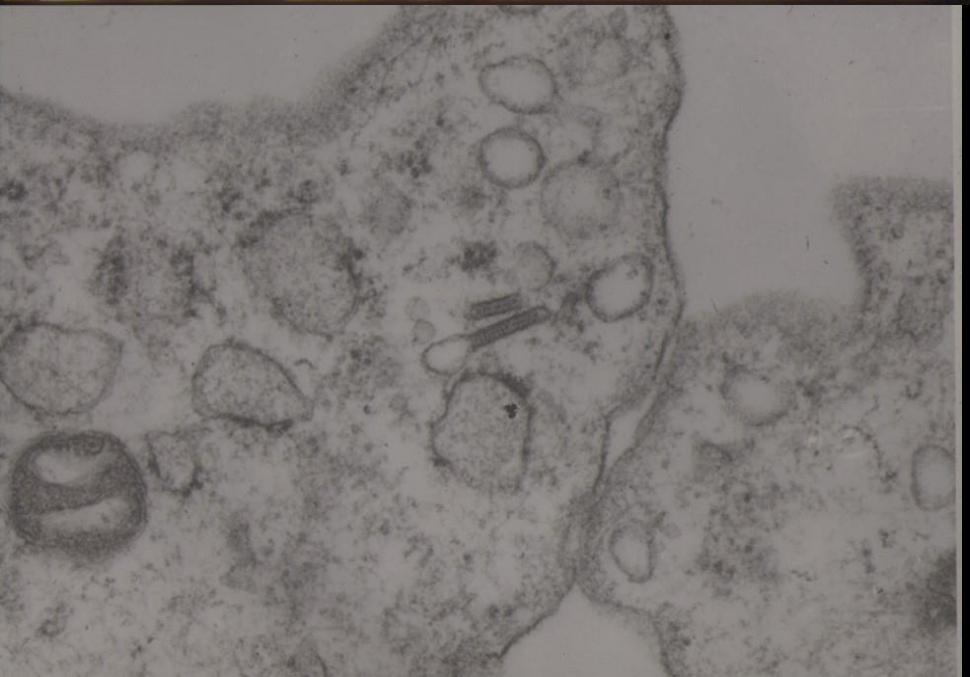
(updated 4th WSPAH-Dana Point 2008)

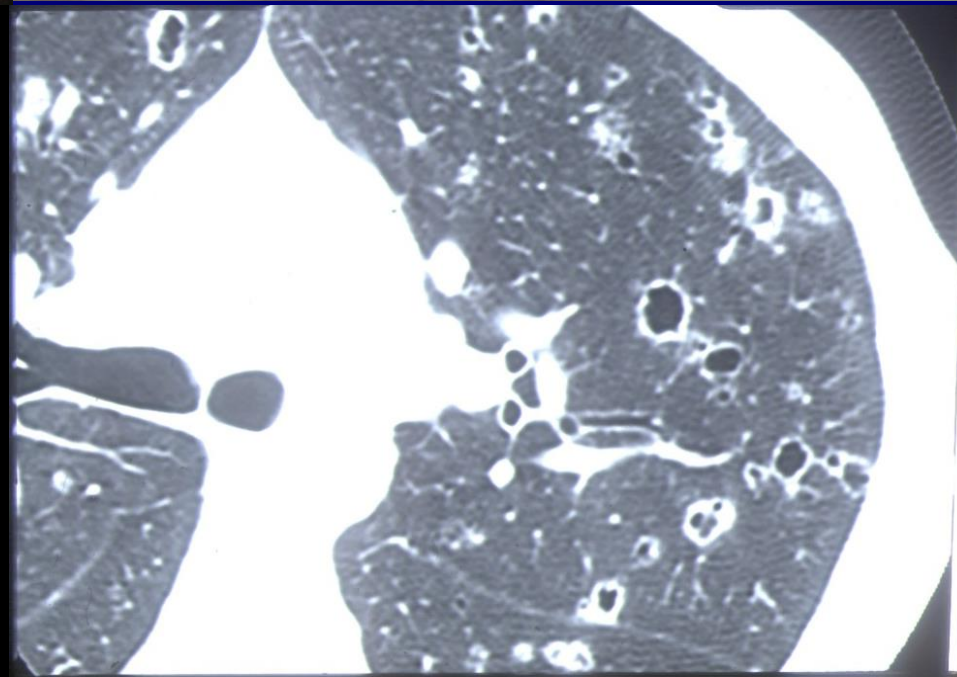
5. PH with unclear or multifactorial mechanisms

- Histiocitosis X









IS PULMONARY LCH A HYPERTENSIVE DISEASE?

18 LCH PATIENTS

FEV1	**42.8% ± 15.5 S.D.**
TLC	**99.9% ± 18.8 S.D.**
Tiffenau	**55.4% ± 13.9 S.D.**
PaO2	**57.7 ± 10.6 S.D.**
PAPm	**55.9 ± 12 S.D.**
C.I.	**2.77 ± 0.71 S.D.**
PVRi	**17.6 ± 6.5 S.D.**

Harari S., Simonneau G. Brenot F. et Coll.

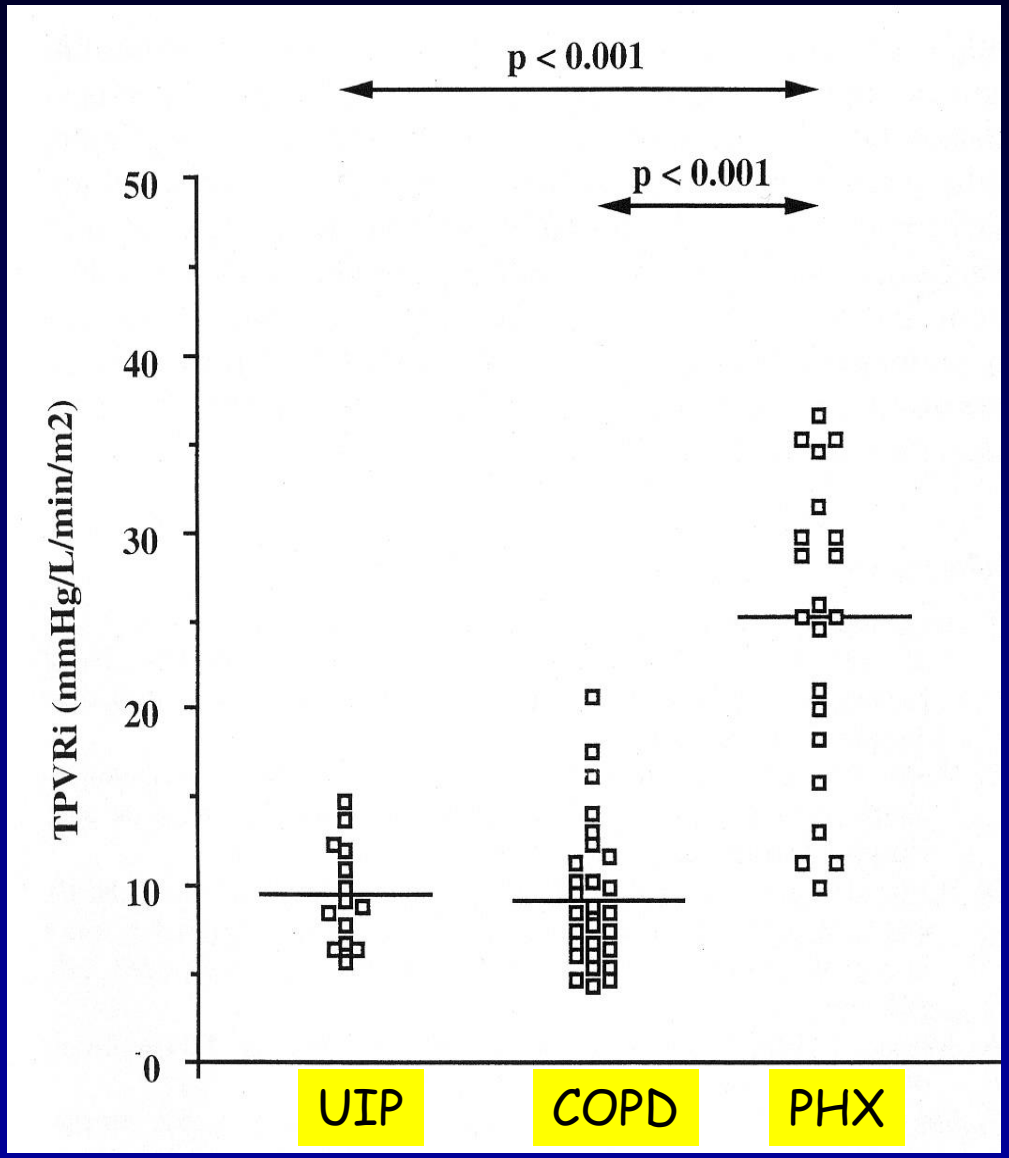
J Heart Lung Transplant 1997 Apr;16(4):460-463

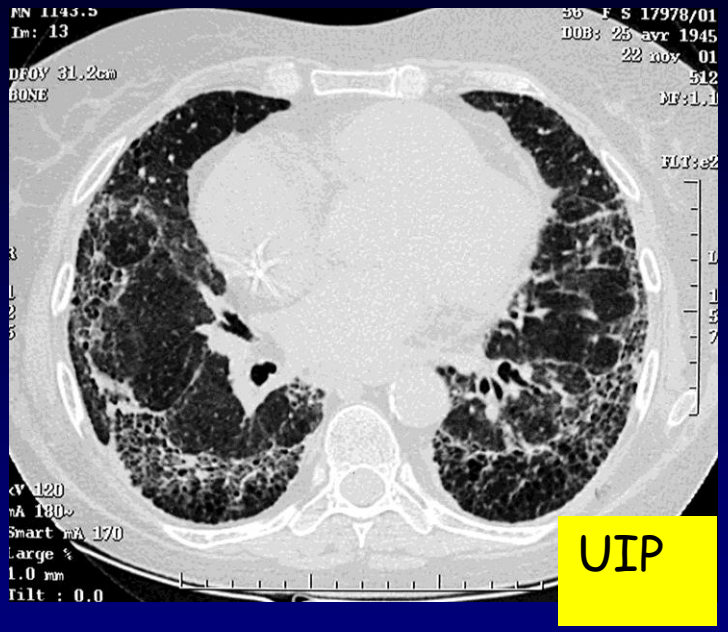
PULMONARY VASCULAR INVOLVEMENT IN HISTIOCYTOSIS X

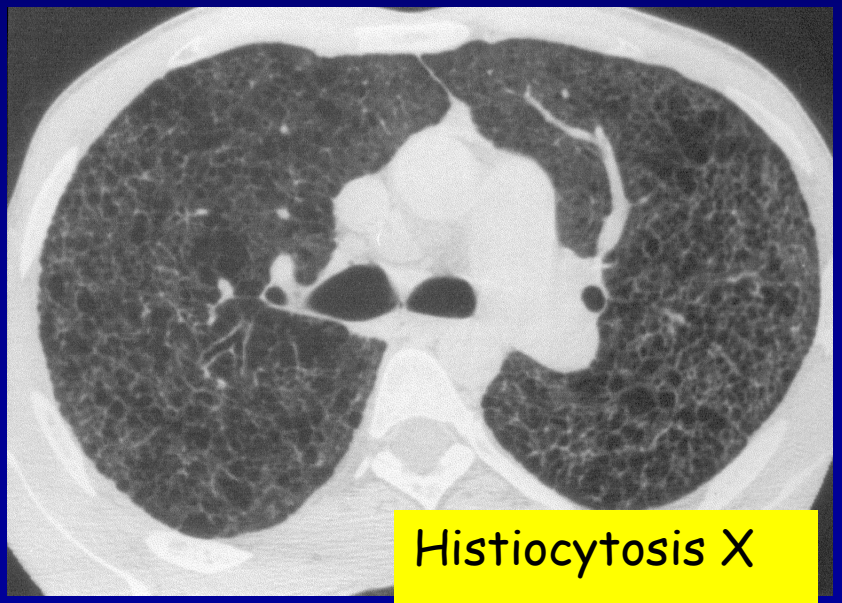
- 21 pts with advanced PLCH referred for LTx
- All of them had moderate-to-severe PH
- mPAP: 59 ± 4 mm Hg (range 36-74 mmHg)
- No correlation between mPAP and PFT
- Pathological findings (n = 12): intrinsic proliferative vasculopathy involving both small to medium-sized arteries and septal veins. VOD in 1/3 of pts

Fartoukh et al. Am J Respir Crit Care Med 2000; 161:216-23

PULMONARY VASCULAR INVOLVEMENT IN HISTIOCYTOSIS X



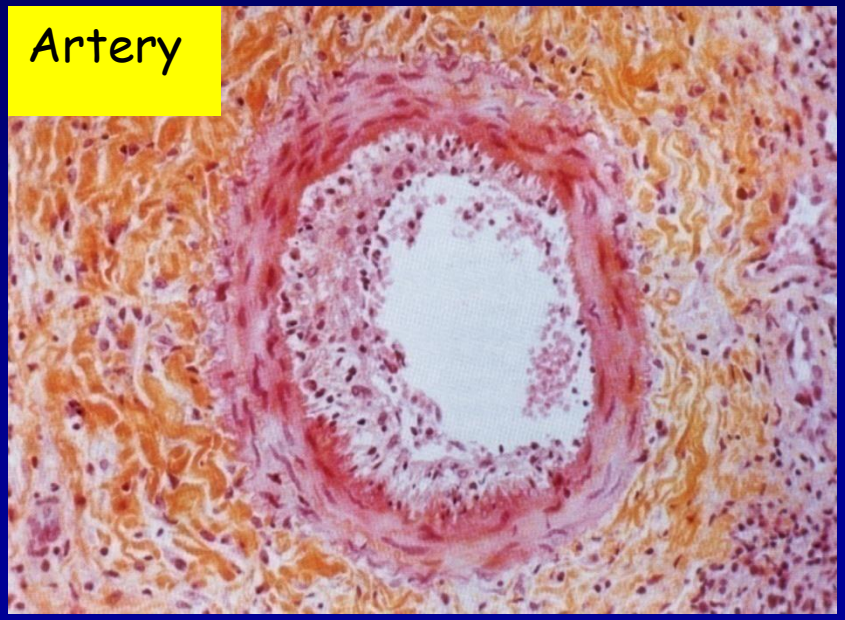


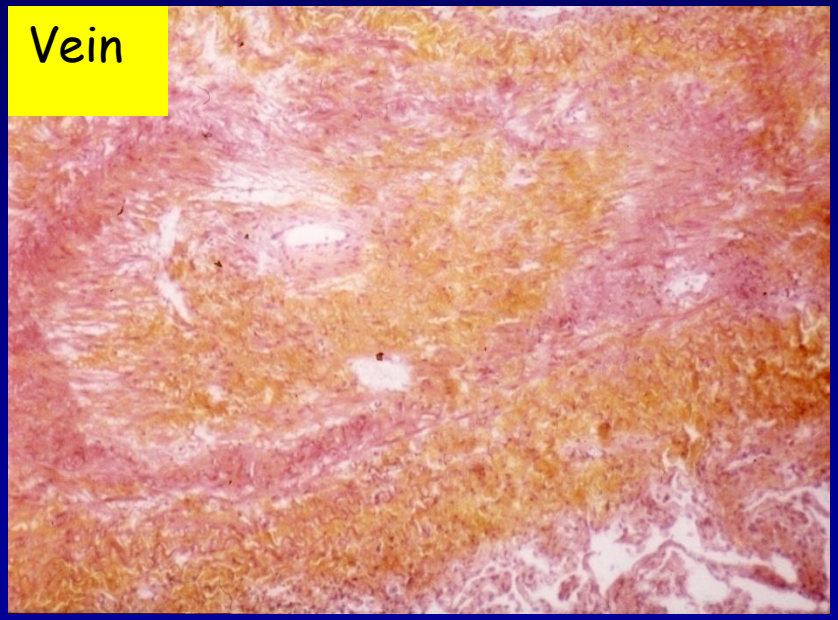


Fartoukh et al. Am J Respir Crit Care Med 2000; 161:216-23

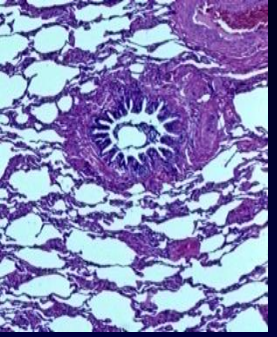
PULMONARY VASCULAR INVOLVEMENT IN HISTIOCYTOSIS X

- Pulmonary histiocytosis X = marked pulmonary vascular remodeling predominantly affecting pulmonary veins
- In patients with sequential histologies, this pulmonary vasculopathy was progressing with time (while parenchymal lesions were stable)
- A case of steroid-sensitive pulmonary hypertension has been reported (specific steroid-sensitive vasculopathy?)





Fartoukh et al. Am J Respir Crit Care Med 2000; 161:216-23
Harari S. et al. Chest 1997; 111: 1142-44
Benyounes et al. Chest 1996; 110:284-6

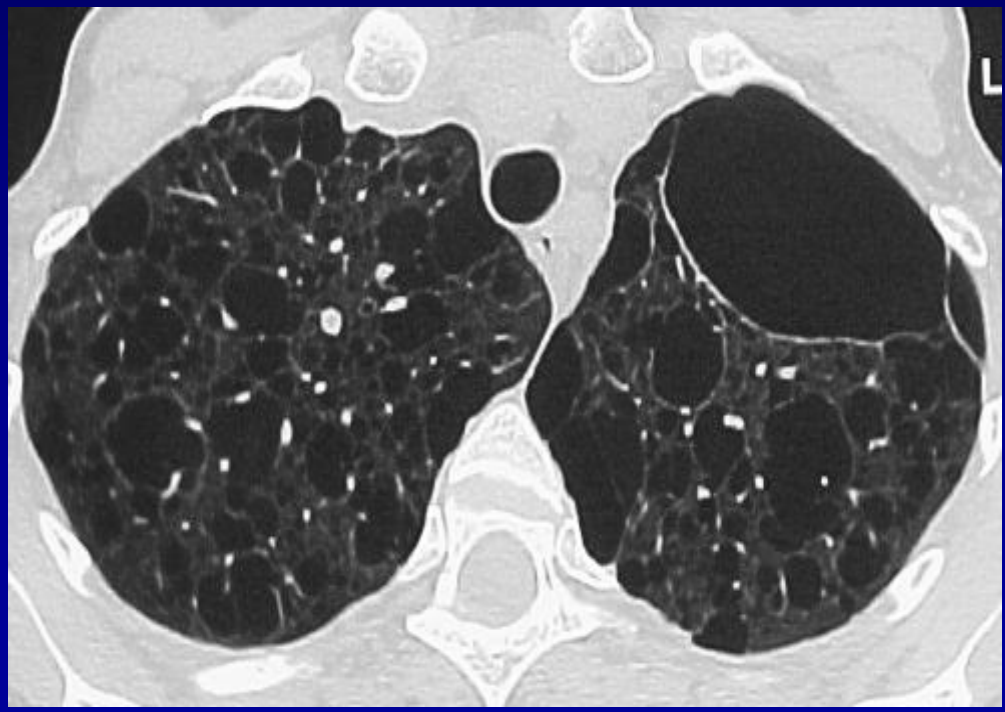


PULMONARY HYPERTENSION DIAGNOSTIC CLASSIFICATION

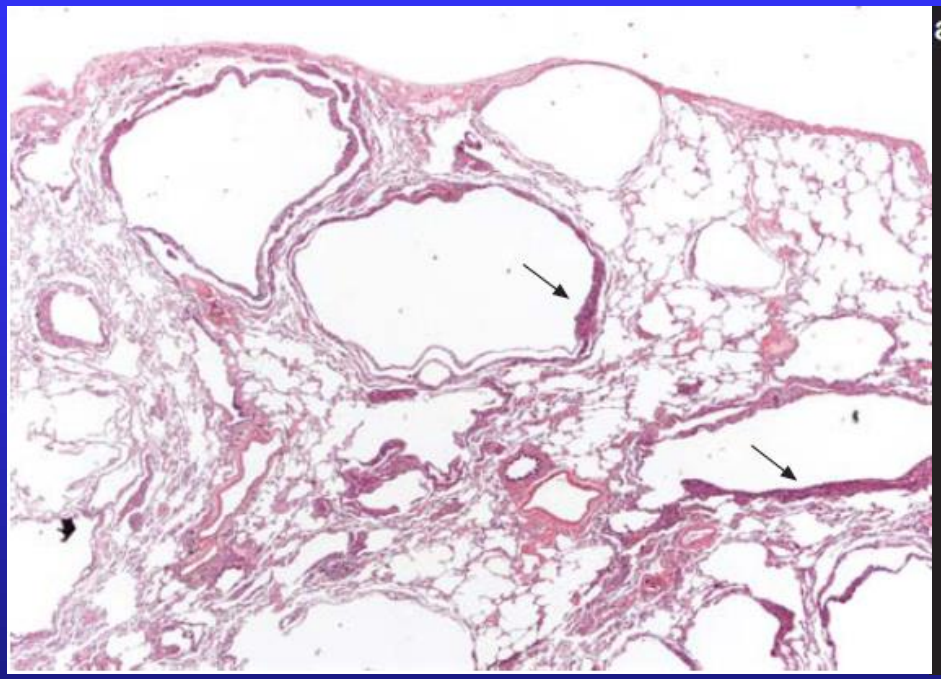
(updated 4th WSPAH-Dana Point 2008)

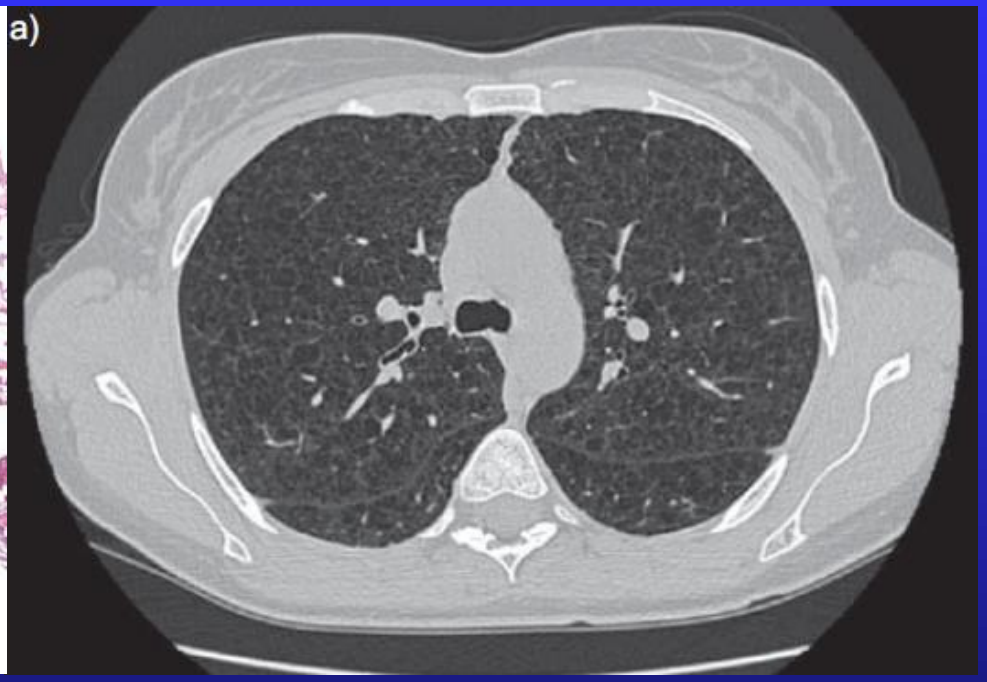
5. PH with unclear or multifactorial mechanisms

- Lymphangioleiomiomatosis

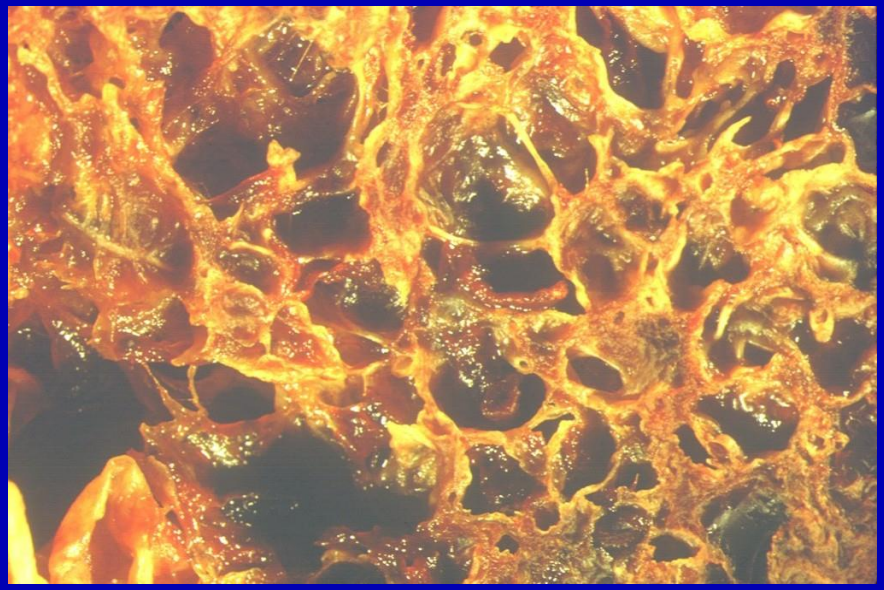


Lymphangioleiomyomatosis (LAM)



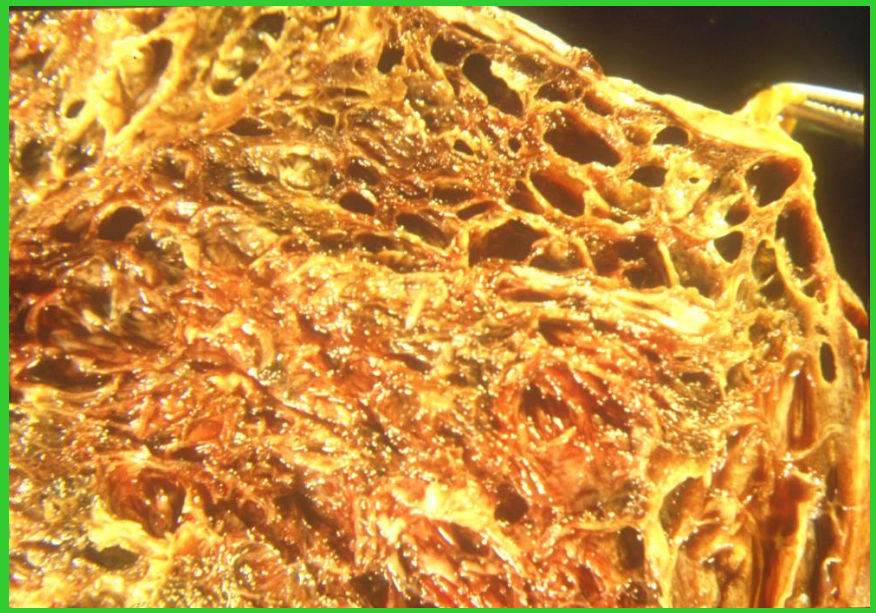


Lymphangioleiomyomatosis (LAM) is a rare multisystem disorder affecting predominantly young females in their reproductive years. It is characterised by progressive cystic destruction of the lung, lymphatic abnormalities and abdominal tumours(e.g. angiomyolipomas)



PLCH

LAM



Pulmonary Hypertension in Lymphangioleiomyomatosis: Characteristics in 20 patients

- This retrospective, multicenter study evaluated patients with LAM and pre-capillary PH by RHC
- Mean ± SD age: 49 ± 12 years and mean ± SD time interval between LAM and PH diagnosis of 9.2 ± 9.8 yrs
- All, except for one patient, were receiving supplemental oxygen
- Mean ± SD 6MWD: 340 m ± 84 m
- mPAP: 32 ± 6 mmHg
- mPAP > 35 mmHg in only 20% of cases
- Mean ± SD FEV1: 42 ± 25%; DLCO 29 ± 135

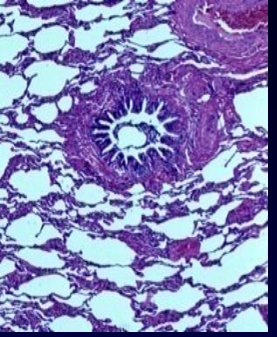
Cottin V et al. Eur Respir J 2012; 40: 630

Pulmonary Hypertension in Lymphangioleiomyomatosis: Characteristics in 20 patients

- In six patients who received oral PAH therapy , the PAP decreased from 33 ± 9 mmHg to 24 ± 10 mmHg

Pre-capillary PH of mild haemodynamic severity may occur in patients with LAM, even with mild pulmonary function impairment.
PAH therapy might improve the haemodynamics in PH associated with LAM.

Cottin V et al. Eur Respir J 2012; 40: 630

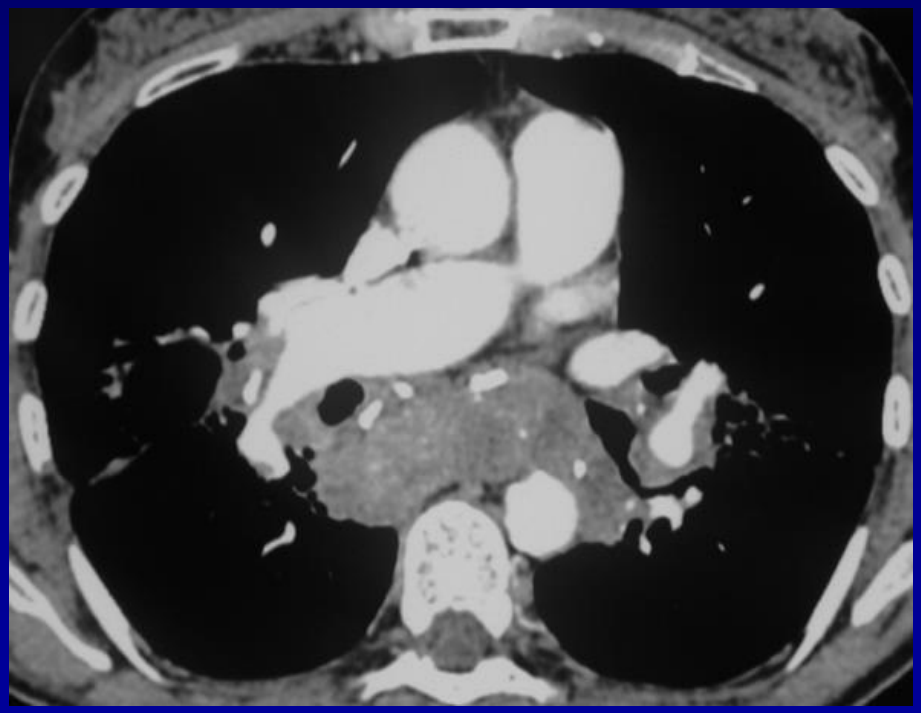


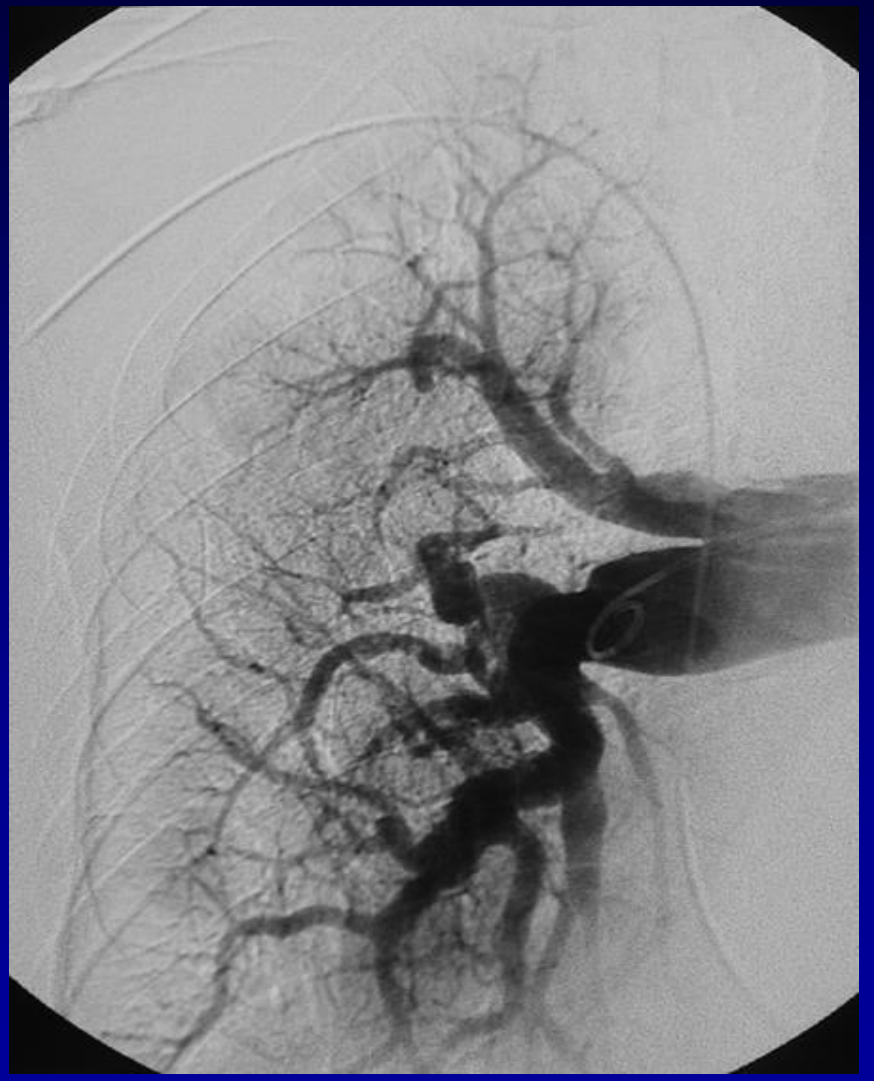
PULMONARY HYPERTENSION DIAGNOSTIC CLASSIFICATION

(updated 4th WSPAH-Dana Point 2008)

5. PH with unclear or multifactorial mechanisms

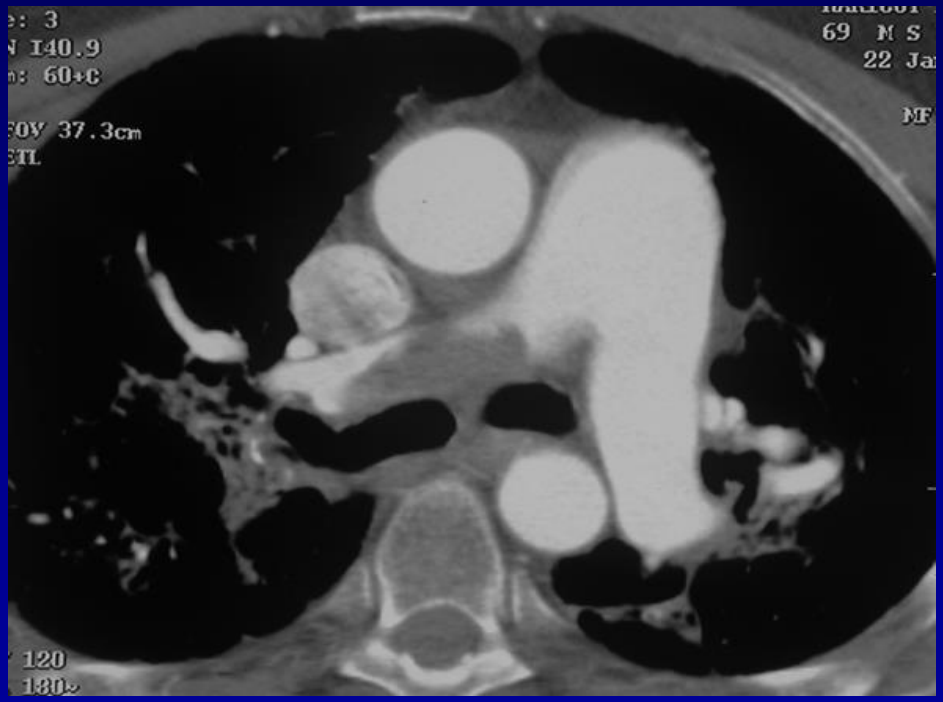
- Sarcoidosis

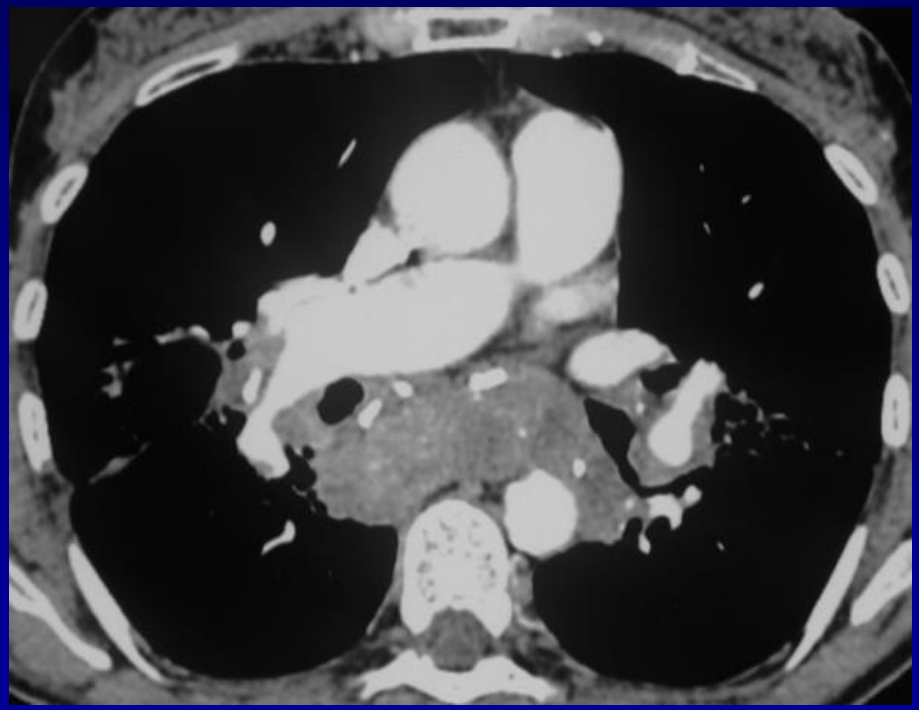




PULMONARY VASCULAR INVOLVEMENT IN SARCOIDOSIS

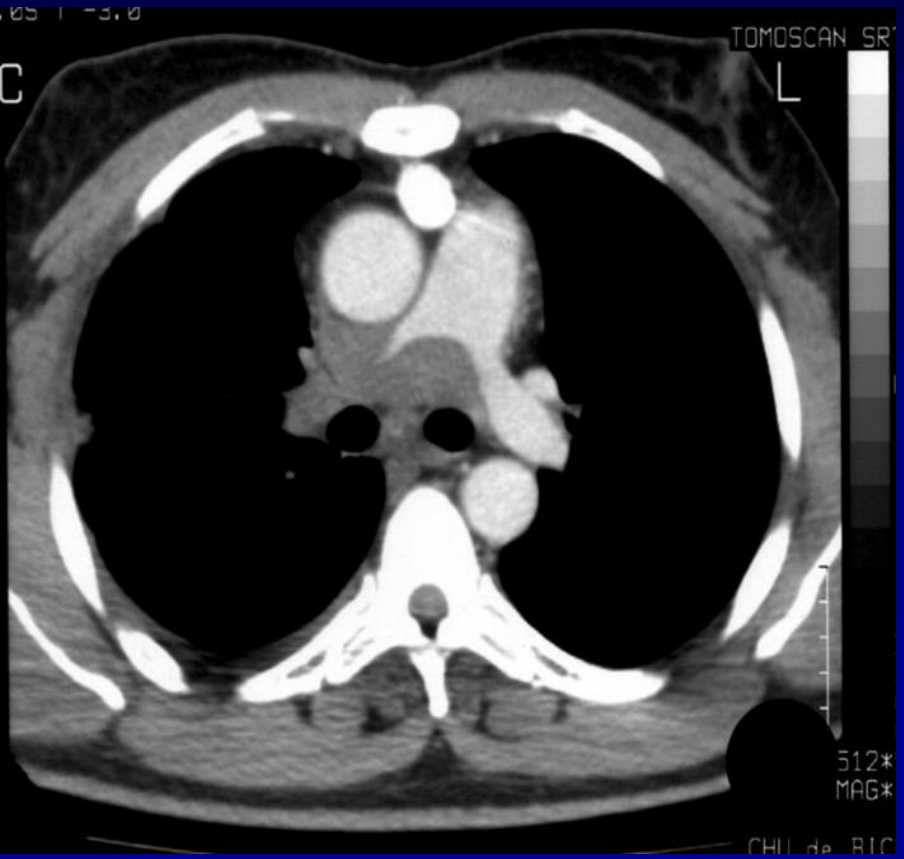
- Extrinsic compression of large pulmonary arteries by mediastinal or hilar adenopathies or fibrosis was detected in 4 out of 15 patients in stage IV

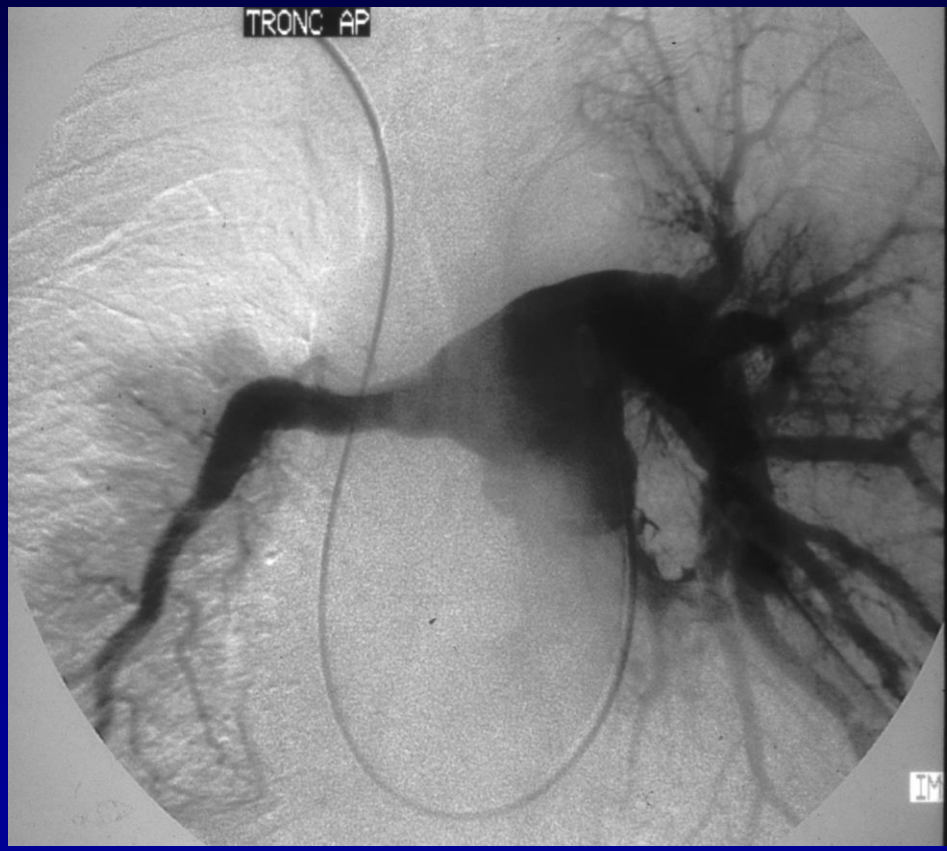




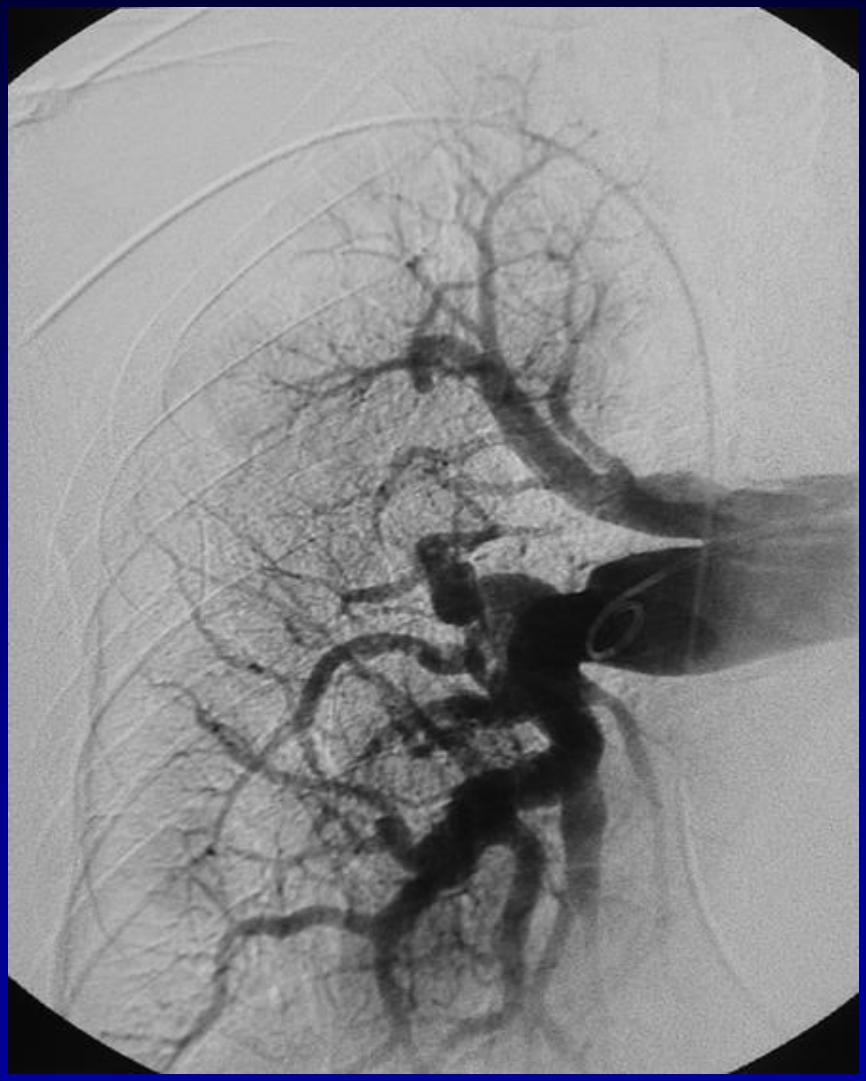
Nunes et al. Thorax 2006

FIBROSING MEDIASTINITIS IS A CAUSE OF PULMONARY HYPERTENSION IN SARCOIDOSIS





PULMONARY VASCULAR INVOLVEMENT IN SARCOIDOSIS



Pulmonary angiography

(9 patients)

➔ Vascular distorsion associated with extrinsic compression: n = 4 (stage IV in all the cases)

Nunes et al. Thorax 2006

PULMONARY VASCULAR INVOLVEMENT IN SARCOIDOSIS

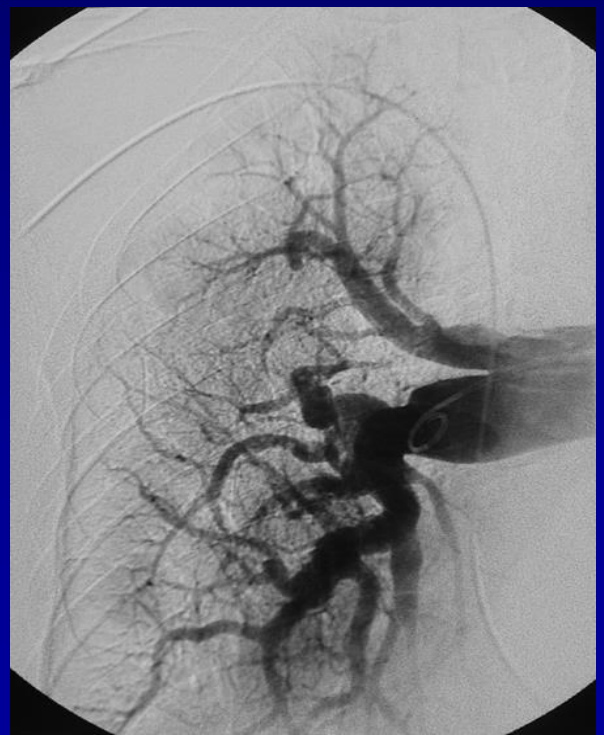
Precapillary pulmonary hypertension in the context of sarcoidosis may be due at least in part to:

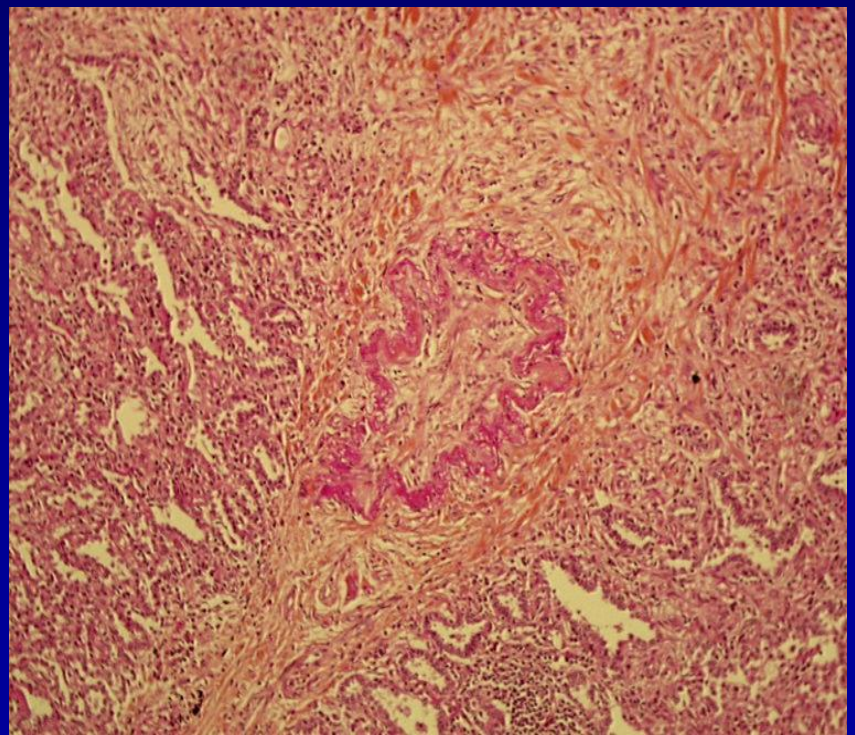
- ➔ Extrinsic compression of large pulmonary arteries by mediastinal or hilar adenopathies or fibrosis
- ➔ Destruction of the distal capillary bed by fibrotic process and resulting hypoxia (stage IV)
- ➔ Specific vasculitis, with infiltration of the walls of pulmonary arteries and/or veins by granulomas (steroid sensitive ?)

Nunes et al. Thorax 2006

PULMONARY VASCULAR INVOLVEMENT IN SARCOIDOSIS

- Pulmonary hypertension in sarcoidois occurs in two very different settings
- In the absence of pulmonary fibrosis, PH appears to be related to a specific vasculopathy and may be steroid-sensitive
- In case of pulmonary fibrosis, the mechanism of PH is complex, but certainly involves at least in part a specific vasculopathy as PH is out of proportion with alterations in lung fuction. In these patients, physicians have to consider lung transplantation sooner than they would have solely on the basis of lung function





Original research

Bosentan for Sarcoidosis-Associated Pulmonary Hypertension A Double-Blind Placebo Controlled Randomized Trial

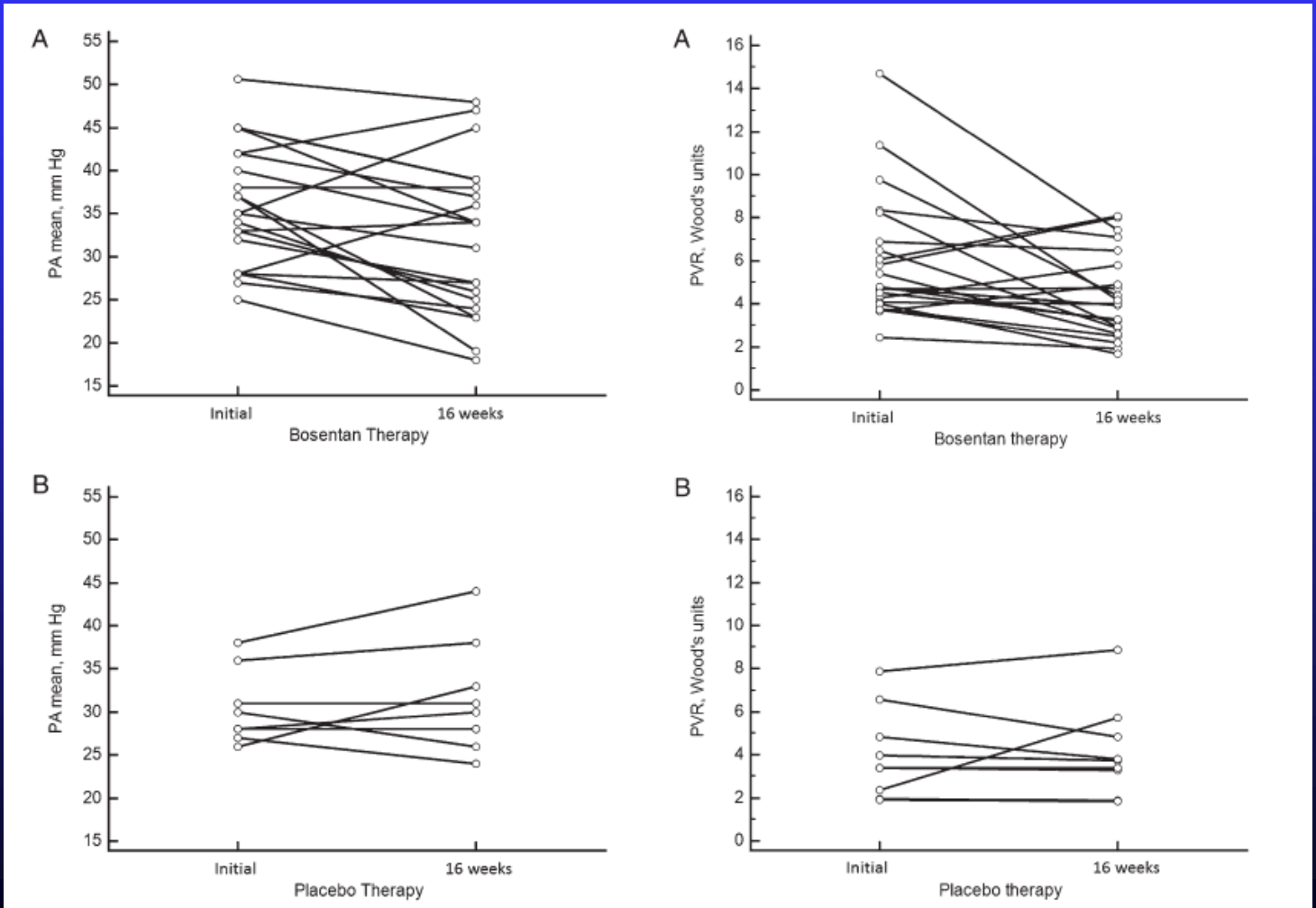
Baughman RP, et al. Chest 2014; 145; S10

In conclusion, we found that 16 weeks of bosentan therapy in patients with SAPH is associated with a significant improvement in PA mean pressure and PVR. The level of improvement was similar to that reported in other WHO groups treated with bosentan. The treatment was well tolerated. The effect of treatment over longer periods will require further investigation.

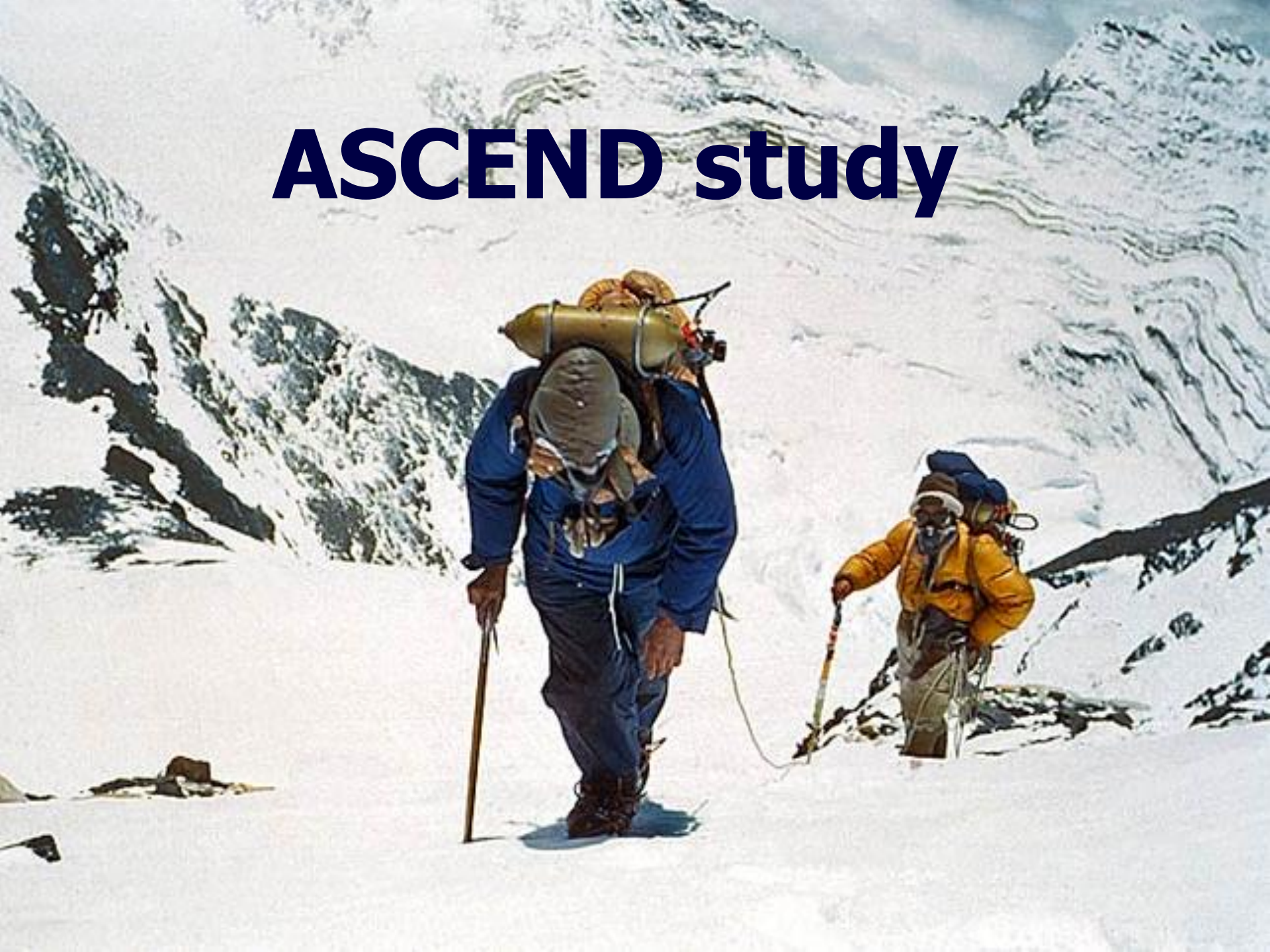
Original research

Bosentan for Sarcoidosis-Associated Pulmonary Hypertension A Double-Blind Placebo Controlled Randomized Trial

Baughman RP, et al. Chest 2014; 145; S10



ASCEND study



ASCEND Study Design
Eligibility

- Age: 40–80 years
- HRCT: Confident diagnosis of IPF
  - Definite UIP, or
  - Possible UIP, with confirmation on SLB
- FVC: ≥50% and ≤90% percent of predicted
- DL_{CO}: ≥30% and ≤90% percent of predicted
- FEV_1/FVC ratio: ≥0.80
- Centralized review: spirometry, HRCT, SLB, deaths

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

ASCEND Study Design
Primary Endpoint

- Percent of predicted FVC change from baseline to week 52
  - **Primary analysis:** Rank ANCOVA to test for differences in the distribution between groups
  - **Magnitude of effect**: Categorical analysis of 2 clinically important thresholds of change:
    - ≥10% decline in %FVC or death,
    - No %FVC decline

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

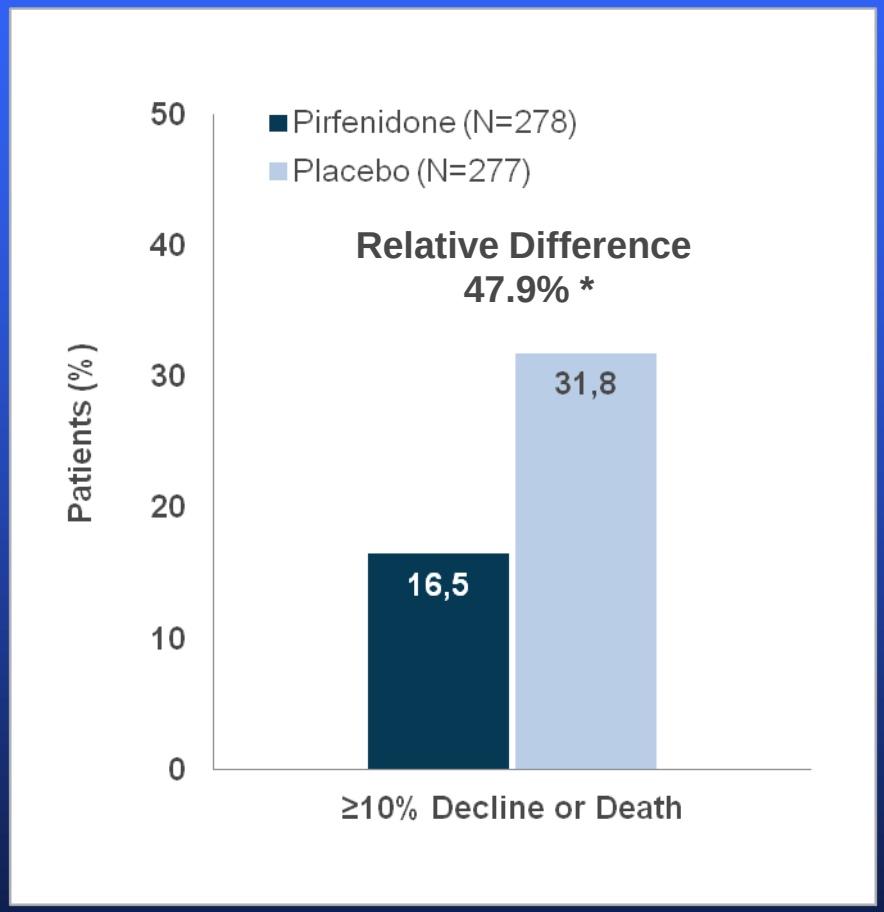
ASCEND Study Design
Key Secondary Efficacy Endpoints

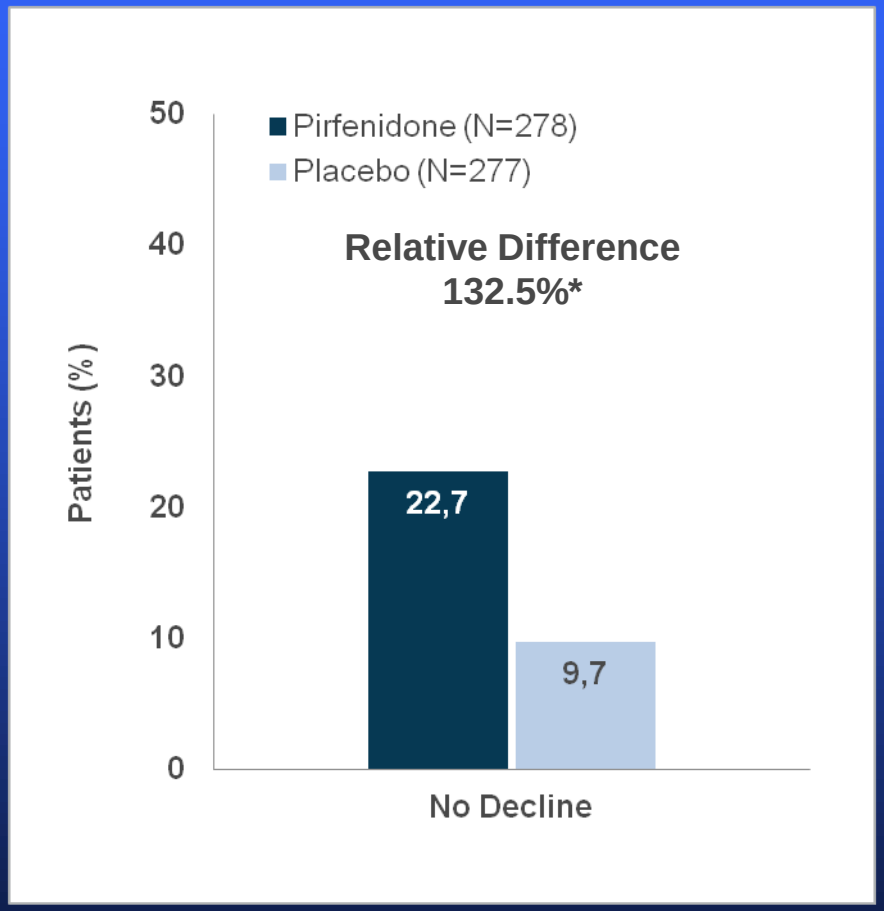
- Change in 6MWT distance (6MWD) from Baseline to Week 52
- Progression-free survival (PFS): defined as time to first occurrence of
  - Death;
  - Confirmed ≥10% decline in %FVC; or
  - Confirmed ≥50 m decline in 6MWD

* Tested for multiple comparisons using the Hochberg procedure

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

Primary Efficacy Analysis:
%FVC Change at week 52

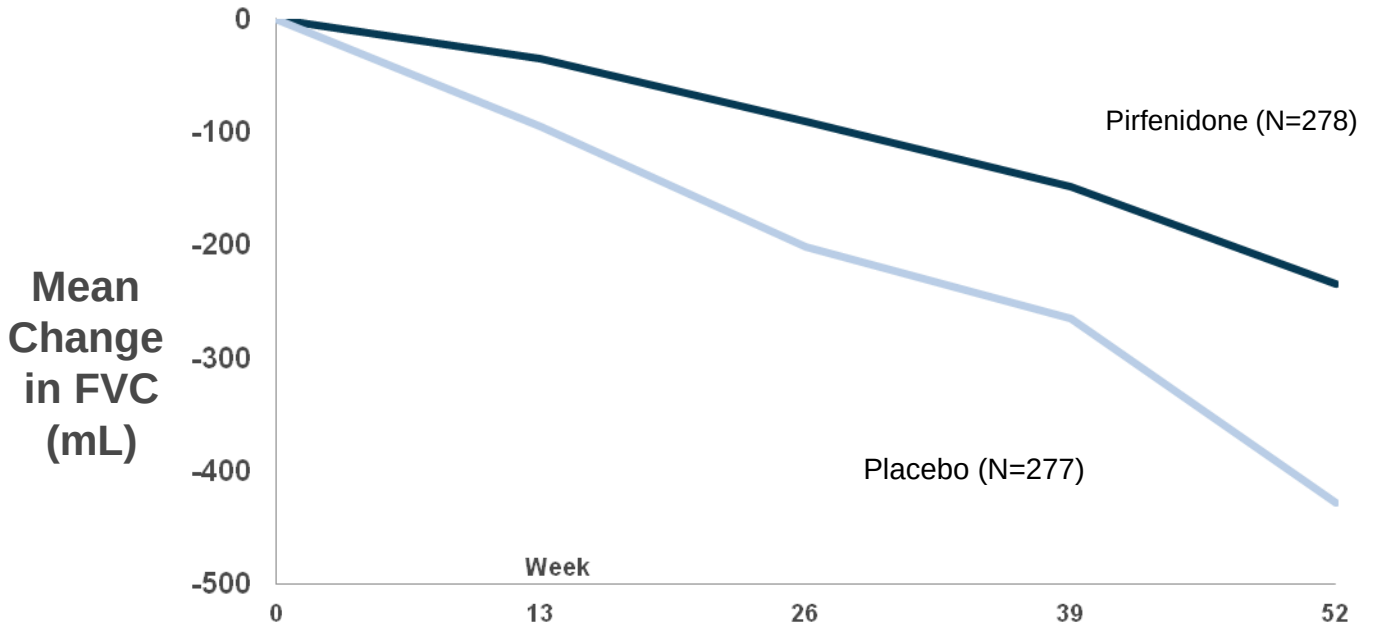




* Rank ANCOVA P-value <0.000001

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

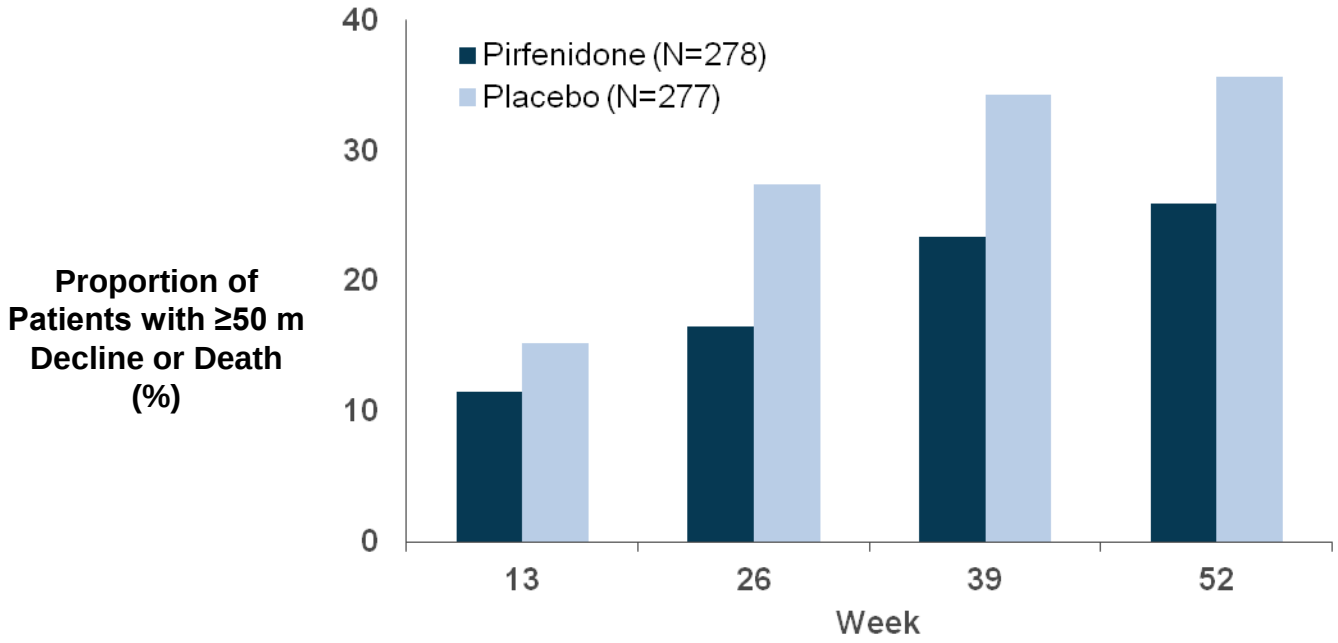
Supportive Analyses of the Primary Endpoint Treatment group difference of 193 mL at week 52 – 45% relative riduction in the mean change in FVC



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**

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

6-MWT: Significant between-group difference in the change from baseline to week 52

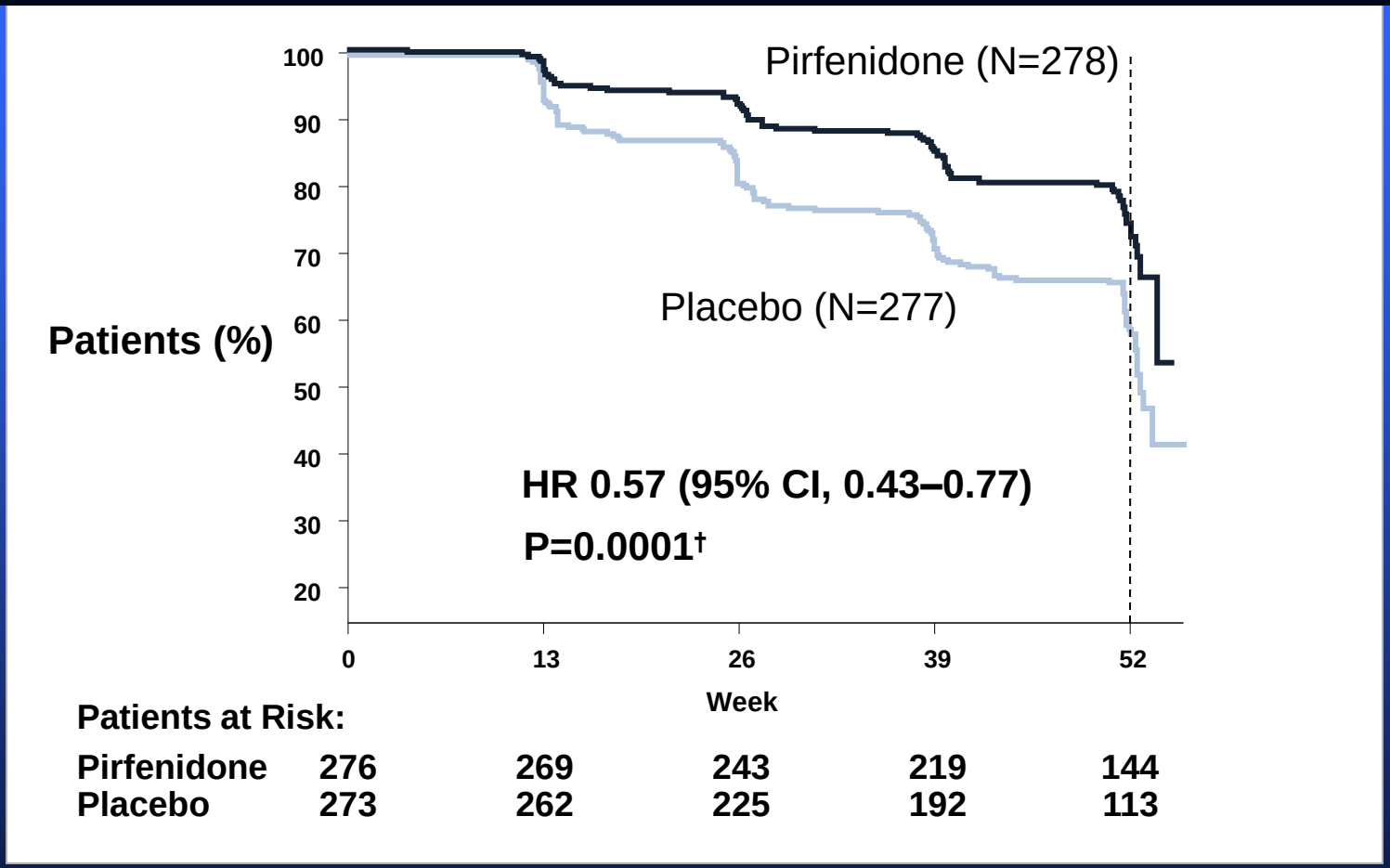


Absolute Difference	3.7%	10.9%	10.9%	9.8%
Relative Difference	24.1%	39.7%	31.8%	27.5%
Rank ANCOVA p-value*	0.401	0.119	0.041	0.036

* Tested for multiple comparisons using the Hochberg procedure

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

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



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

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

Pooled All-cause Mortality (week 52): Pirfenidone reduced risk of death by 48%

Patients	Pirfenidone	Placebo	HR (95% CI)‡	P-value §
ASCEND* (N=555)	11 (4.0%)	20 (7.2%)	0.55 (0.26–1.15)	0.105
CAPACITY† (N=692)	11 (3.2%)	22 (6.3%)	0.49 (0.24,1.01)	0.047
Pooled* (N=1247)	22 (3.5%)	42 (6.7%)	0.52 (0.31–0.87)	0.011

HR=hazard ratio; 95% CI=95% confidence interval
* Pre-specified secondary endpoint in ASCEND
† Exploratory analysis in CAPACITY
‡ Cox proportional hazards model
§ Log-rank test

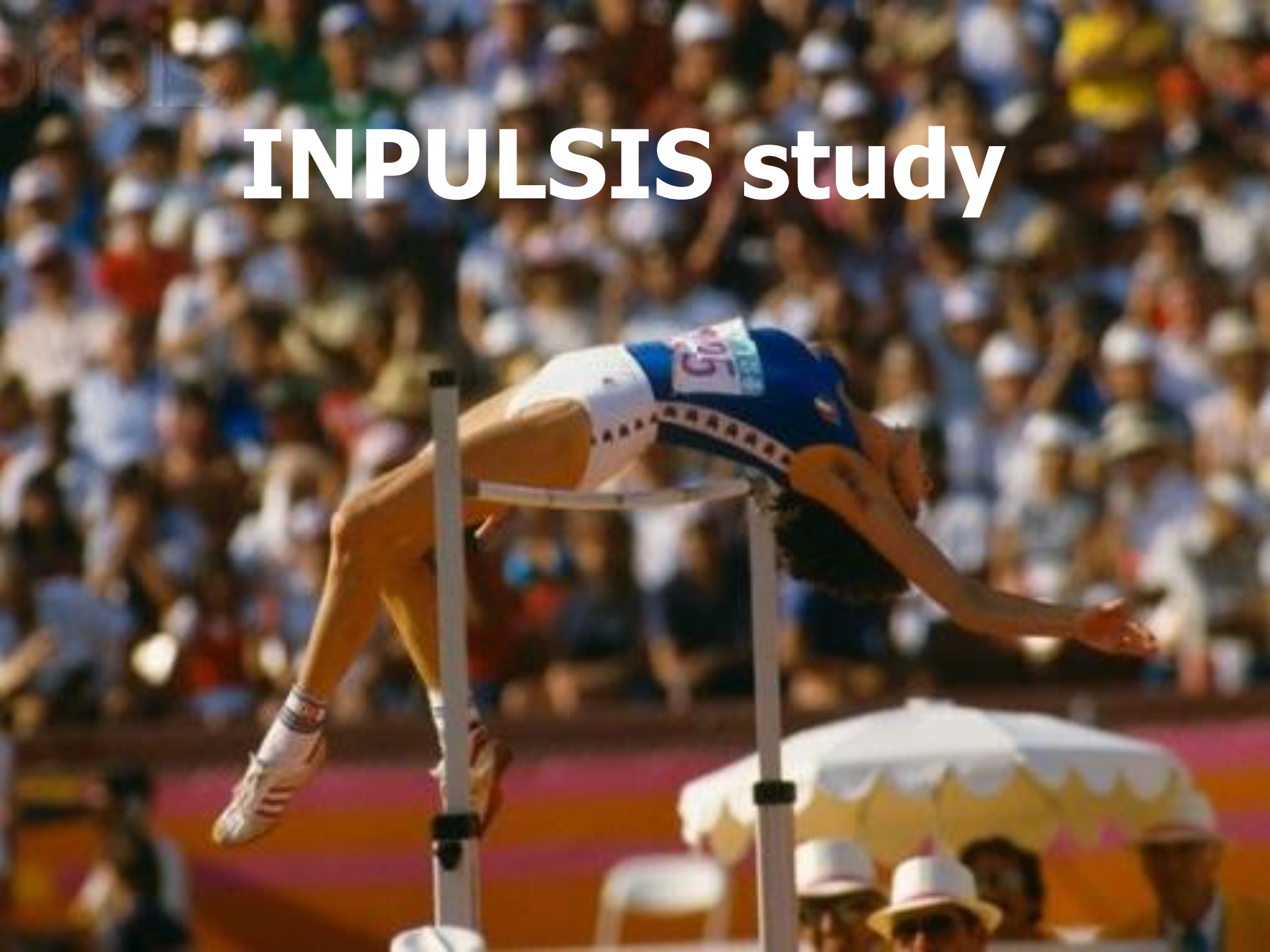
King TE et al. *N Engl J Med* 2014 May 18. doi:10.1056/NEJMoa1402582

ASCEND Study 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.

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

INPULSIS study



Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

NEJM 2014

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.

A total of 1066 patients were randomly assigned in a 3:2 ratio to receive nintedanib or placebo.

This article was published on May 18, 2014, at NEJM.org.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

- Age ≥40 years
- Diagnosis of IPF within 5 years of randomization
- Chest HRCT performed within 12 months of screening
- 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

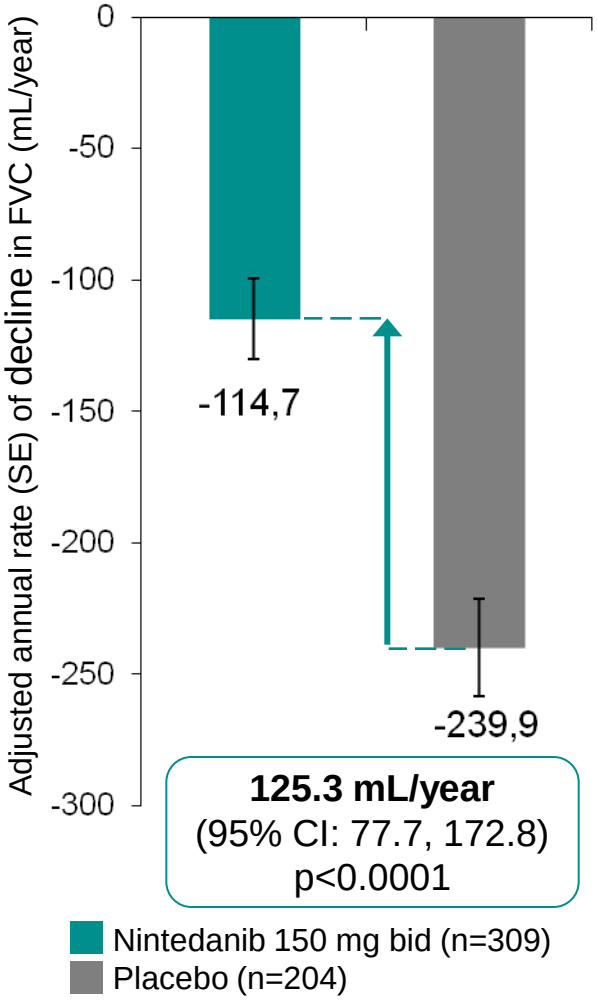
Primary endpoint

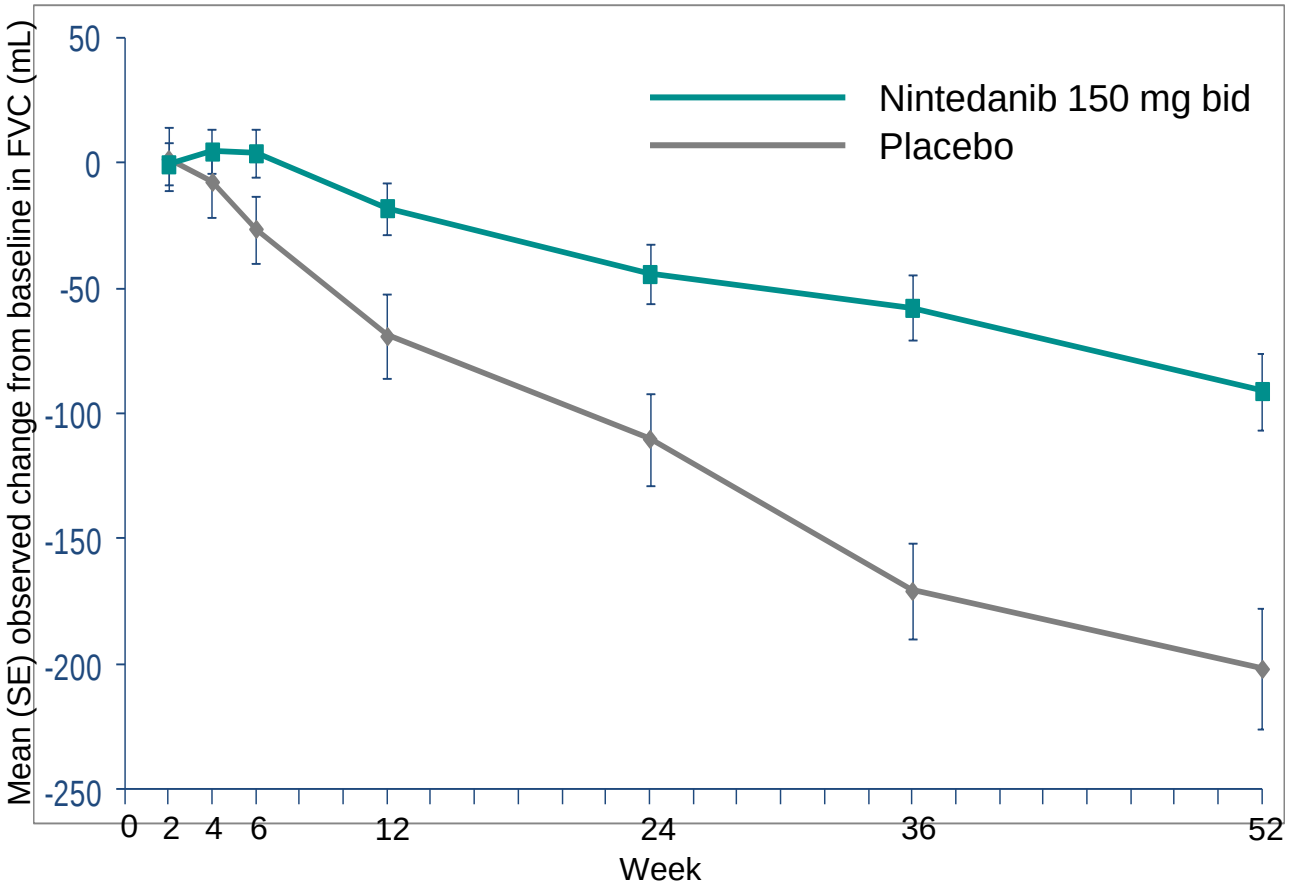
- Annual rate of decline in FVC (mL/year)

Key secondary endpoints

- Time to first acute exacerbation (investigator-reported) over 52 weeks
- Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score over 52 weeks

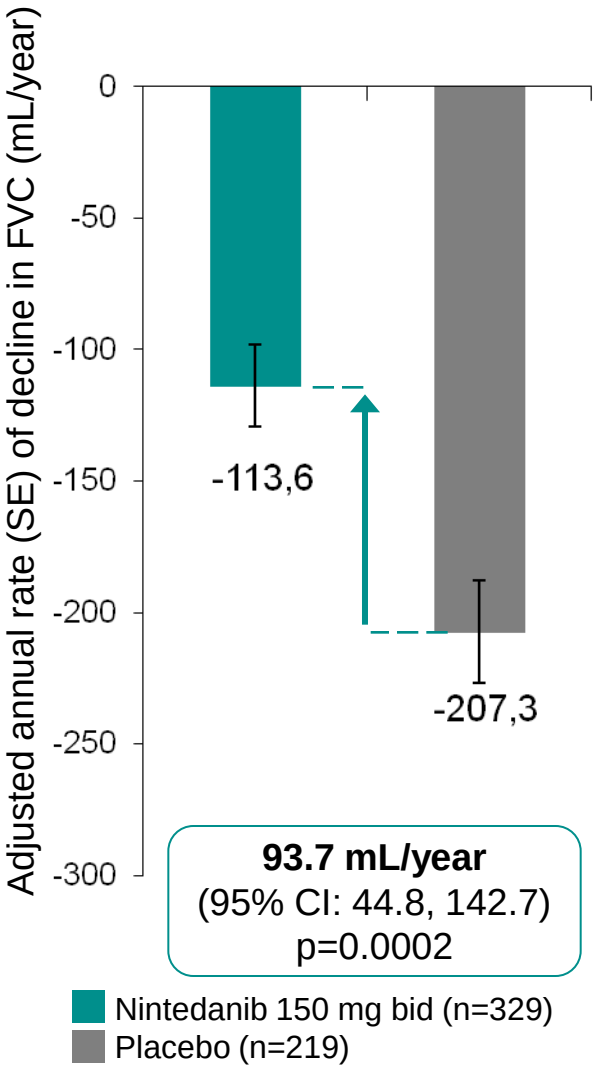
Primary efficacy endpoint in INPULSIS-1

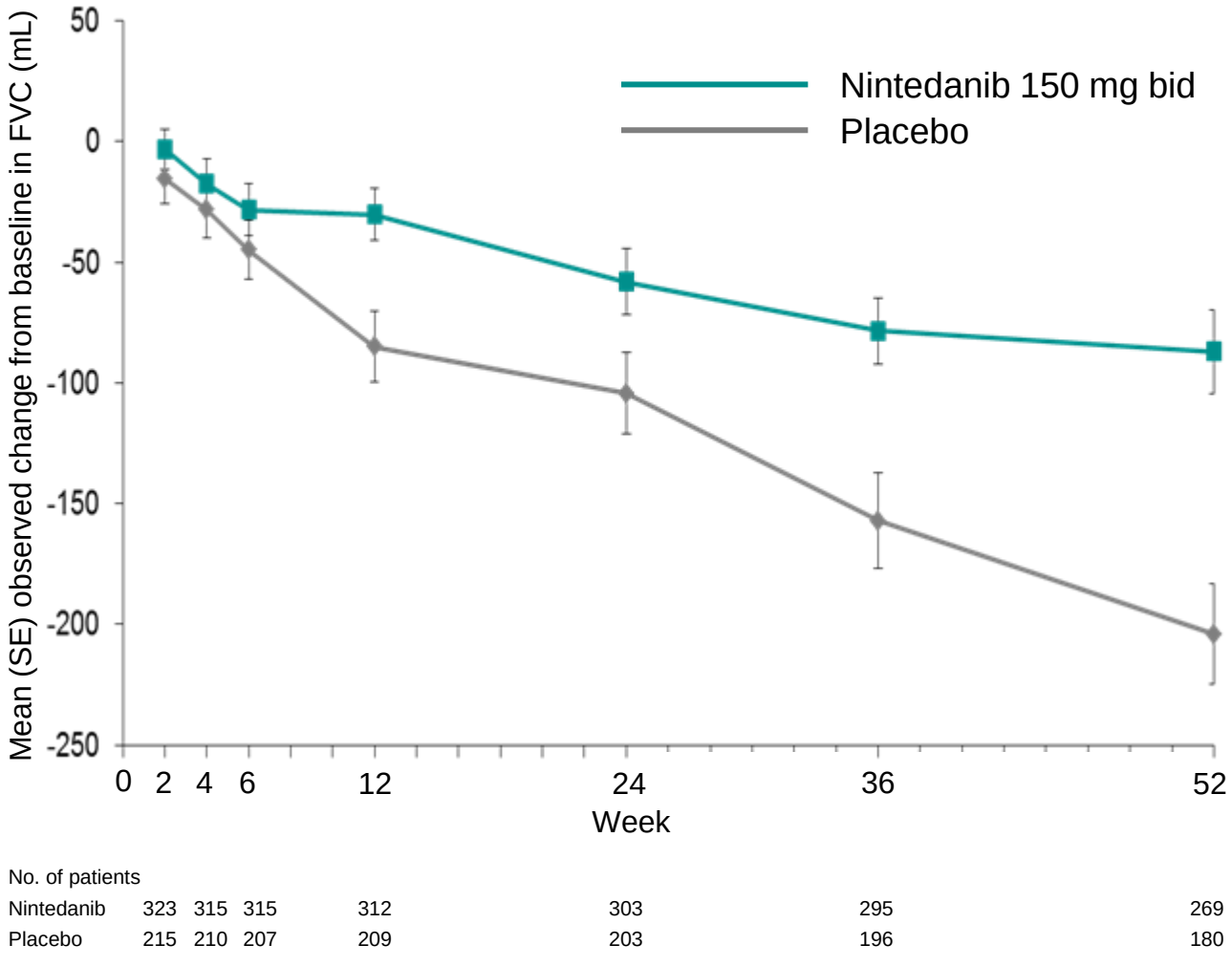




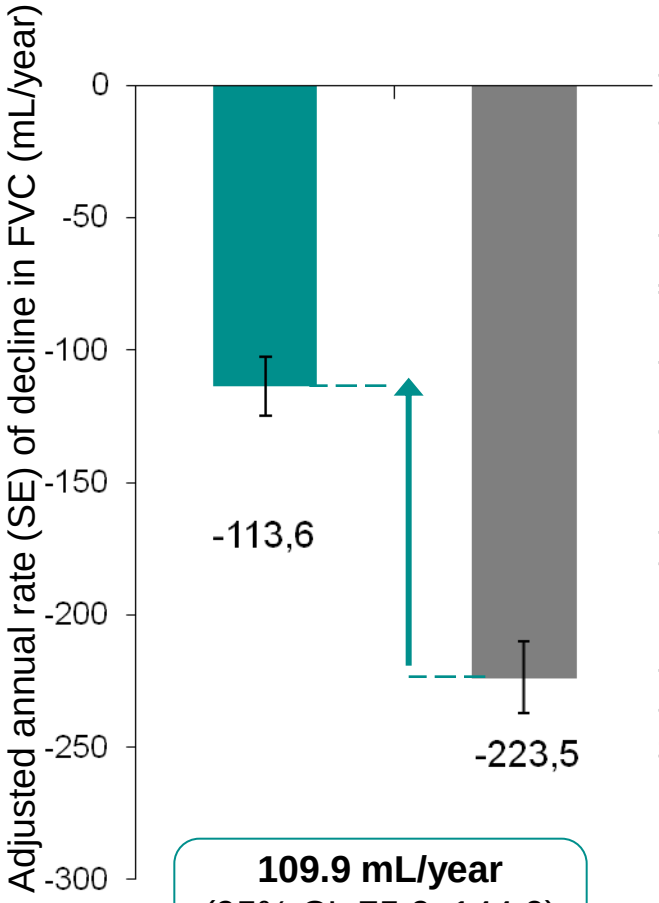
No. of patients							
Nintedanib	303	301	298	292	284	274	250
Placebo	202	198	200	194	192	187	165

Primary efficacy endpoint in INPULSIS-2



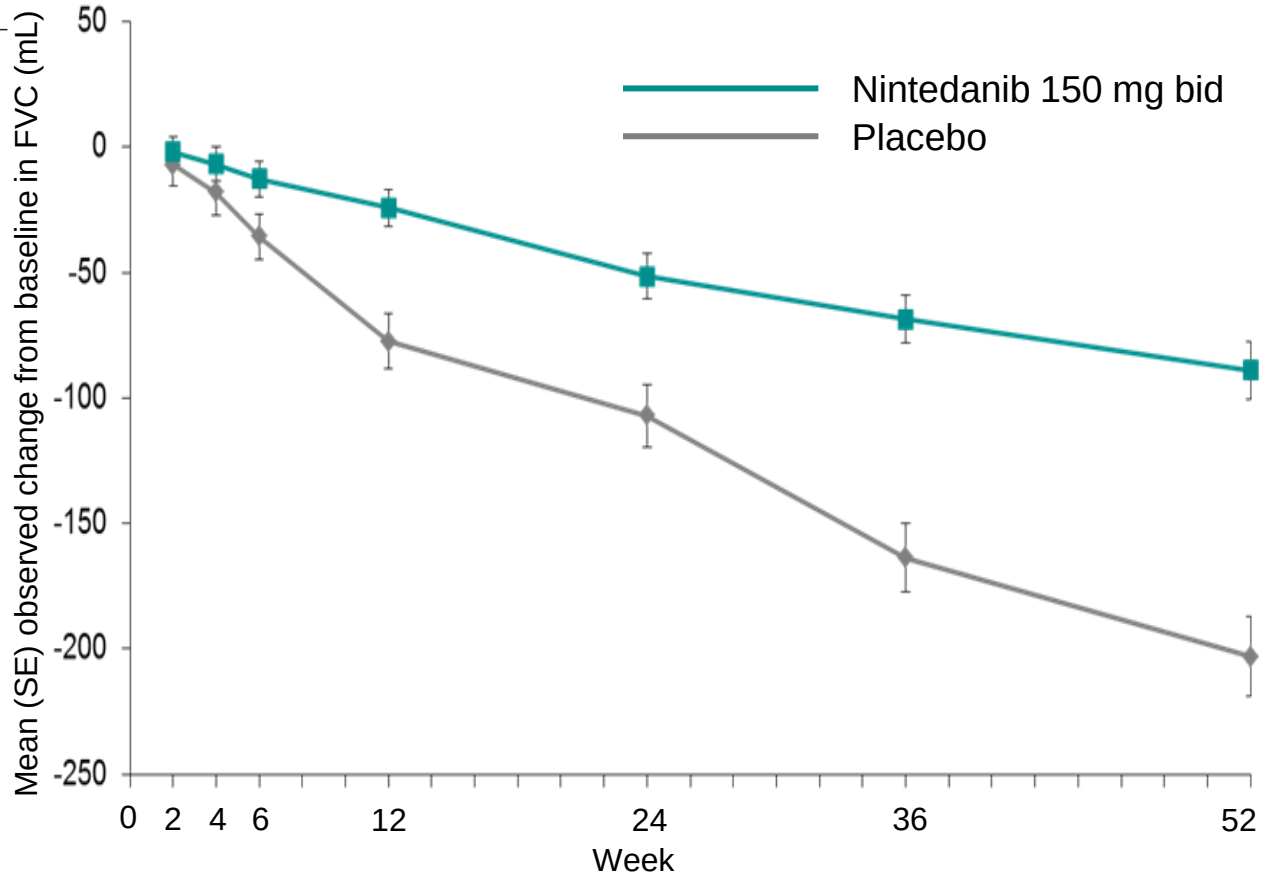


Primary efficacy endpoint in pooled data



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

MOST FREQUENT ADVERSE EVENTS*

	INPULSIS-1		INPULSIS-2	
No of patients (%)	**Nintedanib 150 mg bid (n=309)**	**Placebo (n=204)**	**Nintedanib 150 mg bid (n=329)**	**Placebo (n=219)**
Diarrhea	190 (61.5)	38 (18.6)	208 (63.2)	40 (18.3)
Nausea	70 (22.7)	12 (5.9)	86 (26.1)	16 (7.3)
Nasopharyngitis	39 (12.6)	34 (16.7)	48 (14.6)	34 (15.5)
Cough	47 (15.2)	26 (12.7)	38 (11.6)	31 (14.2)
Progression of IPF†	31 (10.0)	21 (10.3)	33 (10.0)	40 (18.3)
Bronchitis	36 (11.7)	28 (13.7)	31 (9.4)	17 (7.8)

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

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