Con il patrocinio di

Associazione Italiana Pneumologi Ospedalieri

Ospedale San Giuseppe
MultiMedica S.p.A.

PNEUMOLOGIA 2016

Milano, 16 – 18 giugno 2016 · Centro Congressi Palazzo delle Stelline

PNEUMOLOGIA 2016

Milano, 16 – 18 giugno 2016 · Centro Congressi Palazzo delle Stelline

I nuovi approcci terapeutici alla fibrosi polmonare idiopatica

Sergio Harari
U.O. di Pneumologia e Terapia Semi Intensiva
Servizio di Fisiopatologia Respiratoria ed Emodinamica Polmonare
Osp. San Giuseppe - MultiMedica, Milano

Conflict of interests disclosures

Actelion

Boehringer Ingelheim

InterMune

Roche

Anamnesi

- Amedeo B., maschio, 75 anni, ex-fumatore da 30 anni (20 sigarette/die per 20 anni), non intolleranze farmacologiche note
- Avvocato, non esposizioni
- Dislipidemia
- Ipertensione arteriosa sistemica
- DMNID noto da circa 5 anni
- Episodio di FAP a giugno 2009

Anamnesi

Sintomatico per tosse secca e dispnea presente da diversi mesi

Gennaio 2009: quadro Rx torace di interstiziopatia

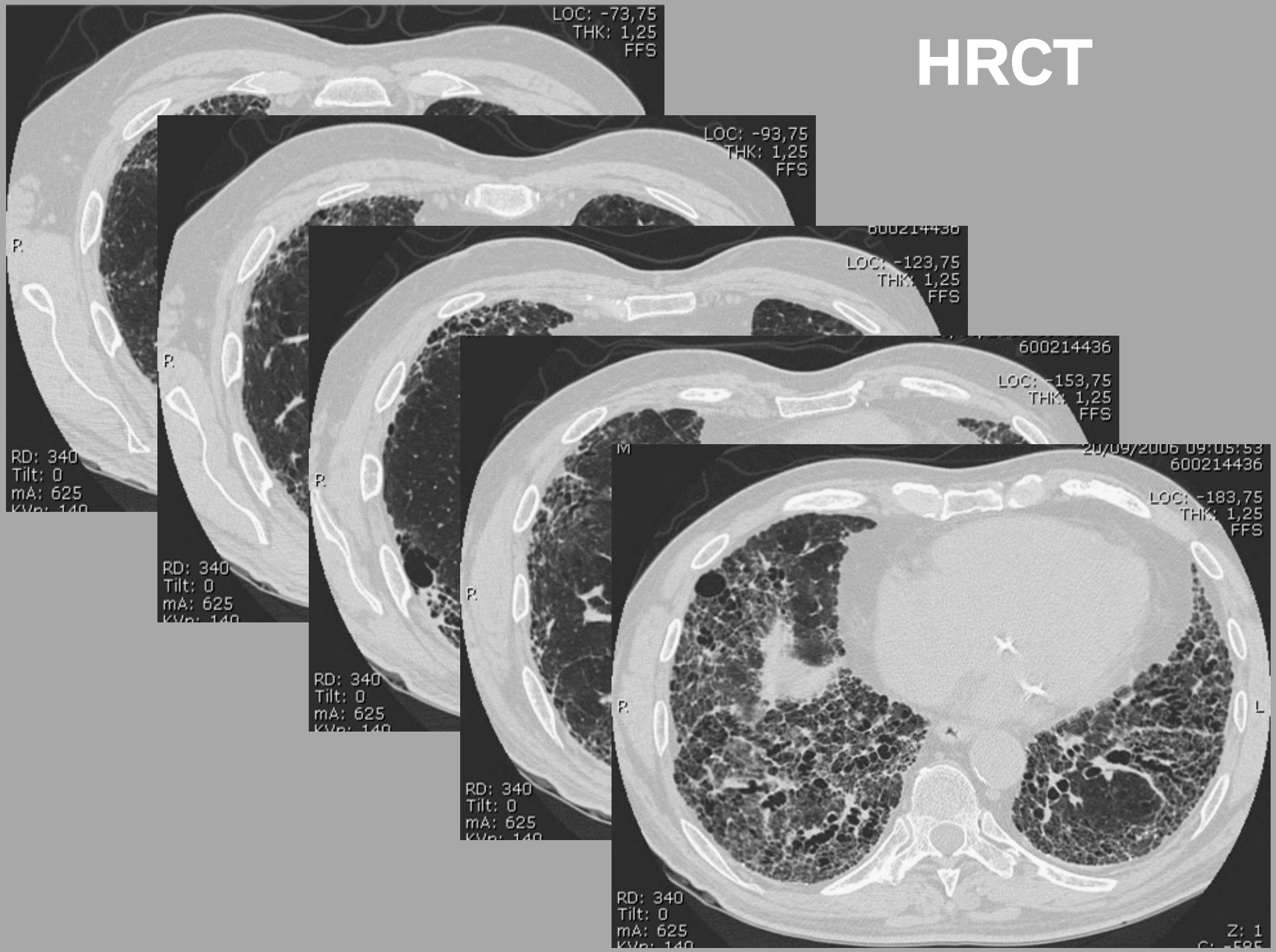
Autoimmunità: negativa

Esame obiettivo

Buone condizioni generali; eupnoico a riposo

PA 130/70, FC 86R, Sat.O2 in AA 95%

EOT: MV presente su tutto l'ambito con rantoli crepitanti "a velcro distaccato" ai campi polmonari medio-inferiori bilateralmente


HRCT
LOC: -73,75
THK: 1,25
FFS
LOC: -93,75
THK: 1,25
FFS
LOC: -123,75
THK: 1,25
FFS
600214436
LOC: -153,75
THK: 1,25
FFS
600214436
LOC: -183,75
THK: 1,25
FFS
RD: 340
Tilt: 0
mA: 625
P.
L.
M
Z: 1

Il paziente viene sottoposto ad esame broncoscopico con BAL: Macrofagi 65%, Linfociti 15%, Neutrofili 20%

Dal 2009 al 2011 il paziente è già stato trattato con steroidi a scalare e quindi con steroidi + azatioprina, quest’ultima sospesa per rialzo delle transaminasi

EGA in AA: PaO2 73.2 mmHg, PaCO2 36.7 mmHg, pH 7.43, Sat.O2 95.2%

PFR: FVC 2.10L 63%, FEV1 1.76L 70%, FEV1/FVC 84%, DLCO 9.1 40%

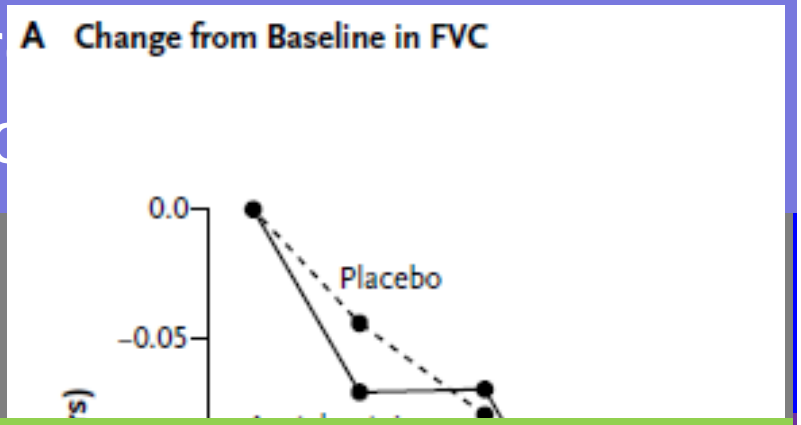
6MWT: presenza di desaturazione senza indicazione ad O2-terapia (percorre 300 m, Sat.O2 iniziale 96% e finale 89%)

Quali sono attualmente le opzioni terapeutiche da proporre a questo paziente?

Inclusion	PANTHER	INPULSIS	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

Randomized Trial of Acetylcysteine in Idiopathic Pulmonary Fibrosis

133 and 131 patients were enr
acetylcysteine and placebo gr



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

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

Patients, n (%)	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 Population* (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

- FDA approved pirfenidone and nintedanib in october 2014
- EMA approved pirfenidone for the treatment of mild to moderate IPF in march 2011
- AIFA approved pirfenidone for the treatment of IPF in June 2013
- EMA approved nintedanib for the treatment of IPF in February 2015
- AIFA approved nintedanib for the treatment of IPF in April 2016

*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

Which drug do I choose?

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

FVC ≥ 50% and DLCO ≥ 30%

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

Pirfenidone

- Patients assessment before treatment
- Posology and method of administration
- Adverse events

Precaution of use

- Liver function tests (ALT, AST and bilirubin) should be conducted prior to the initiation of treatment
- At monthly intervals for the first 6 months: AST, ALT and bilirubin
- Every 3 months thereafter

Posology

Days 1 to 7: one capsule, three times a day (801 mg/day)

Days 8 to 14: two capsules three times a day (1602 mg/day)

Days 15 onward: three capsules, three times a day (2403 mg/day)

With food!!

Dose adjustment for safe use

Gastrointestinal events: pt should be reminded to take the medicinal product with food. Pirfenidone may be reduced to 1-2 capsules 2-3 times/day

Photosensitivity reaction or rash: pt should be reminder to use a sun block daily and to avoid sun exposure

Pirfenidone's safety profile

- Generally well tolerated, a minority of patients discontinue therapy due to gastrointestinal and skin-related adverse events (AEs)
- Pirfenidone's safety profile has been evaluated in a well-defined cohort of about 1300 patients exposed to treatment for up to 9.9 years (long-term safety pooling)
- These events were generally mild to moderate in intensity, reversible, and with minimal clinical consequence
- GI and skin-related AEs have a tendency to occur early in the course of treatment and decrease over time

GI adverse events

Take pirfenidone during or after a meal.

In addition:

- take each of the three capsules separately throughout the meal, rather than simultaneously
- a longer initial dosing titration scheme—for example, starting with one capsule three times a day and titrating up to the full dose (three capsules three times a day) over a period of 4 weeks instead of 2 weeks
- Dose reductions may be helpful
- If AEs still persist despite dose reduction, temporary treatment discontinuation until symptoms become tolerable (typically 1–2 weeks) should be considered

GI adverse events

- Use of prokinetic agents such as domperidone and metoclopramide may help mitigate treatment-related GI AEs
- Use of proton pump inhibitors may also be helpful for managing GI side-effects in pirfenidone-treated patients with IPF

Skin-related adverse events

- Avoiding exposure to direct sunlight (including sunlamps), use of sunscreen active against both UVA and UVB, use of protective clothing, and avoid other medical products known to cause photosensitivity

- In cases of mild to moderate photosensitivity reaction or rash that does not spontaneously resolve, the dose may be reduced to one capsule (267 mg) three times a day for 7 days, or until symptom resolution.

Skin-related adverse events

- Patients experiencing a severe photosensitivity event (erythema and edema with exudation, erosions, cracked or scarred skin, possible dehydration) of sun-exposed skin (i.e., a non-allergic reaction), should be instructed to seek medical advice on dose adjustments and temporary discontinuation, until the skin reaction normalizes

- Use of topical treatments for burns (e.g., silver sulfadiazine or potent steroids) immediately after the appearance of skin lesions may help attenuate reactions and improve associated symptoms.

Dose adjustment for safe use

Hepatic function: >3 to ≤ 5 AST/ALT confounding medicinal products should be discontinued, other causes excluded and the patient monitored closely. If clinically appropriate, the dose of pirfenidone should be reduced or interrupted

AST/ALT ≤ 5 with symptoms or hyperbilirubinaemia or AST/ALT > 5, pirfenidone should be discontinued and the patient should not be rechallenged

Others side effects

Dizziness, fatigue, weight loss

Interactions

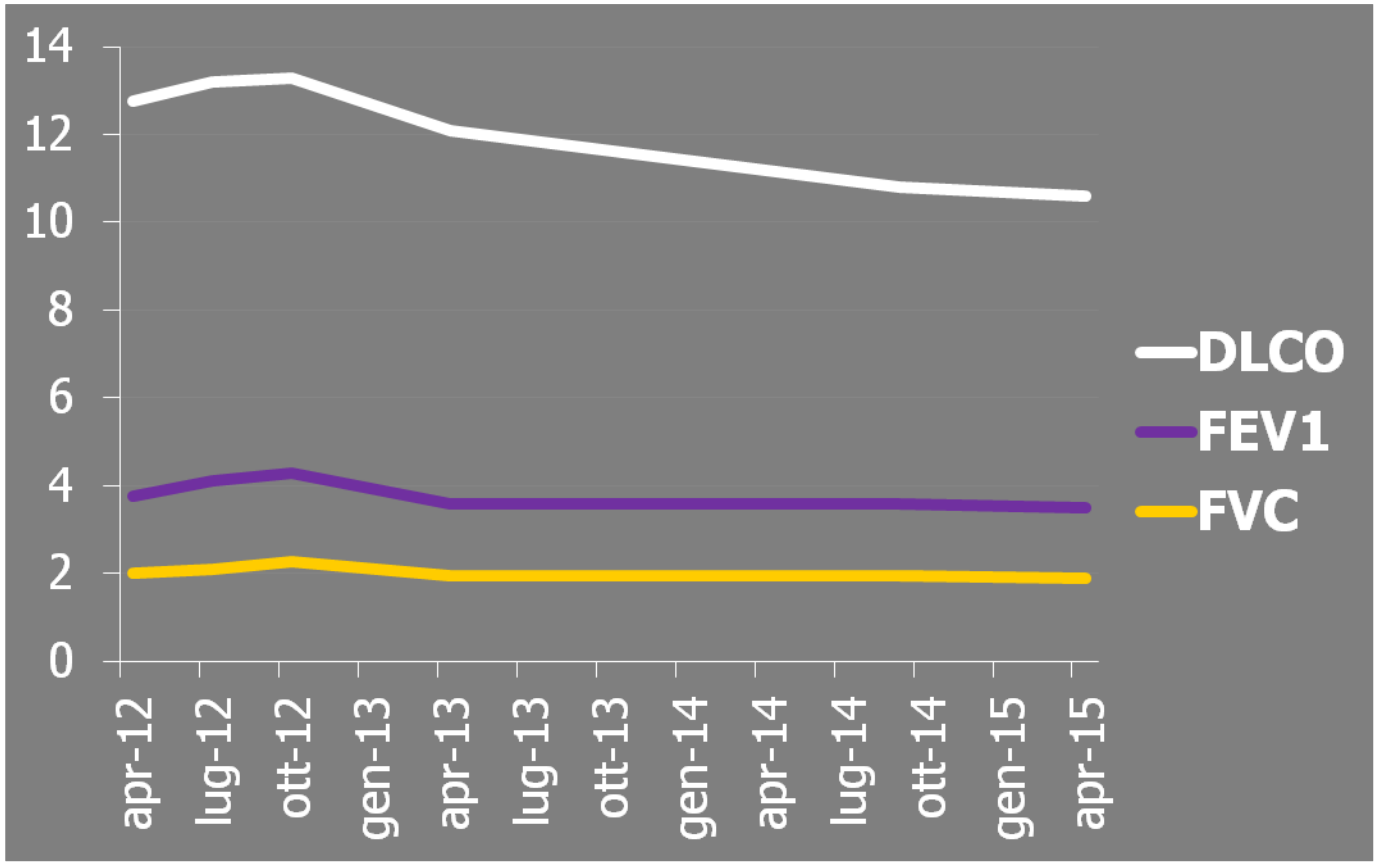
Pirfenidone should be used with caution in patients treated with moderate or strong inhibitors of CYP1A2 (e.g. ciprofloxacin, amiodarone, propafenone)

In the case of moderate inducers of CYP1A2 (e.g. omeprazole), concomitant use may theoretically result in a lowering of pirfenidone plasma levels

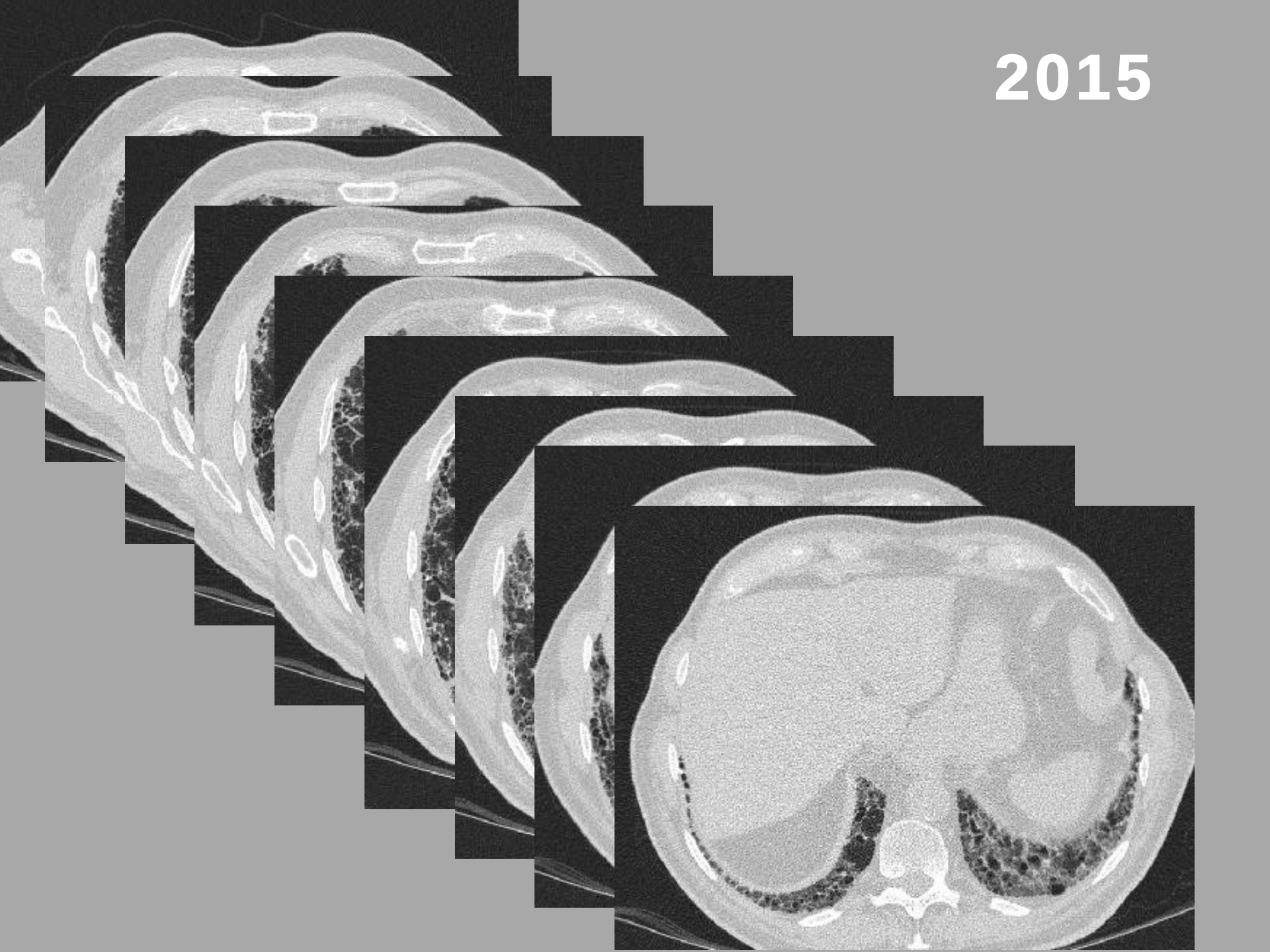
Per tornare al nostro paziente.....

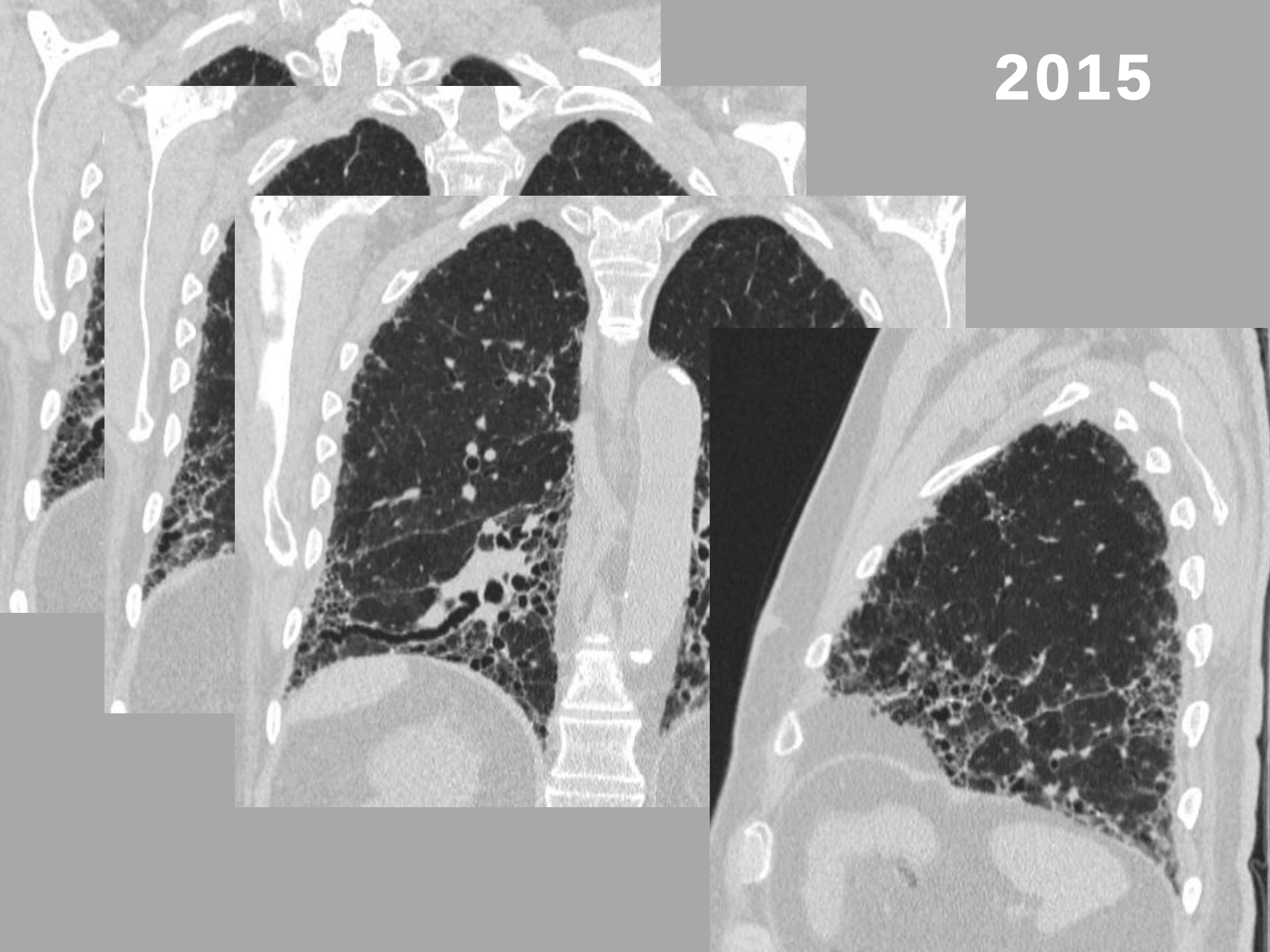
Il paziente partecipa a protocollo sperimentale con nintedanib e poi prosegue la terapia in “open label”

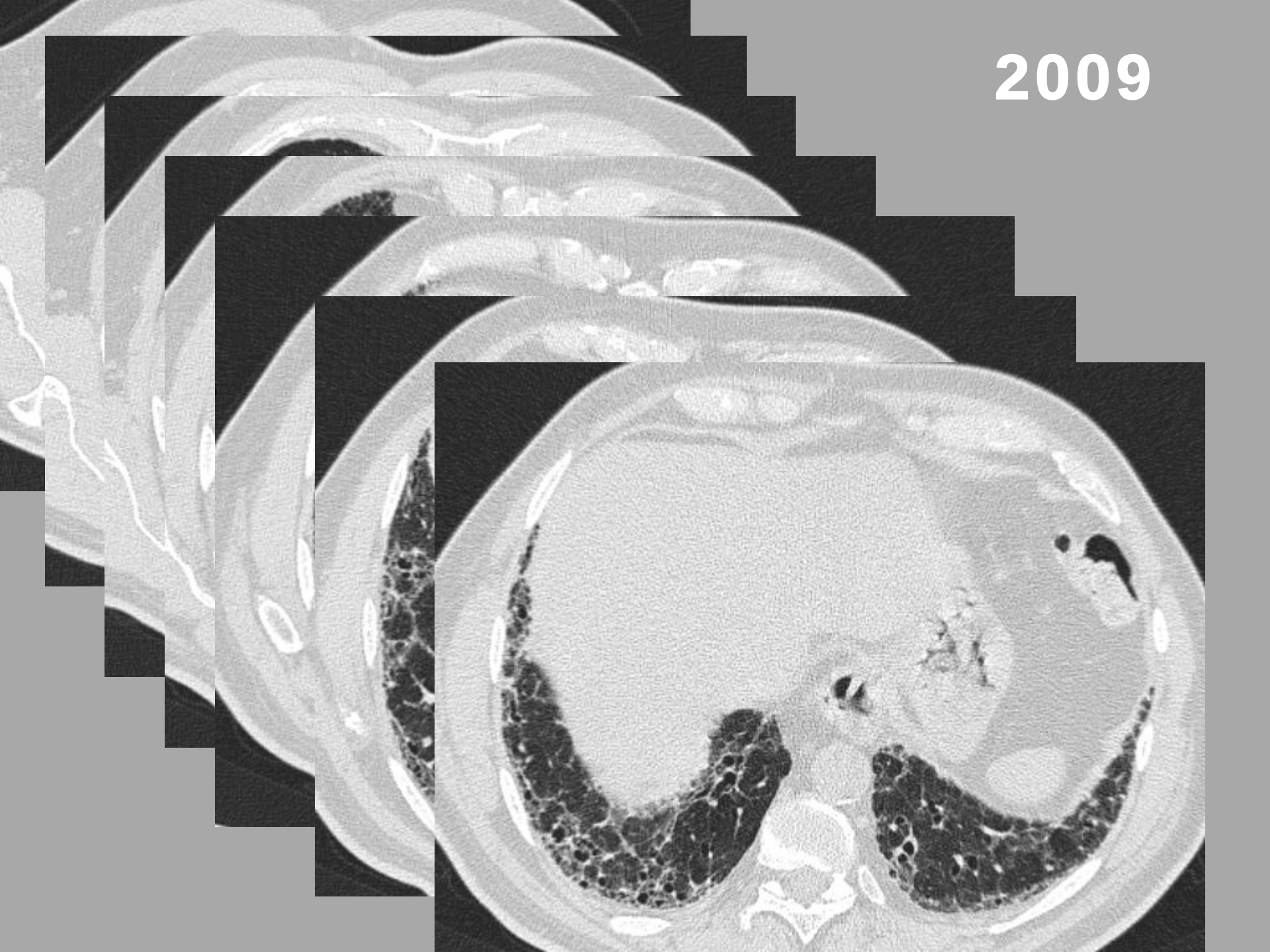
Nintedanib



	4/ 2012	4/ 2013	4/ 2014	4/ 2015
FVC	2L 65%	1.95L 63%	1.96L 63%	1.89L 60%
FEV1	1.75L 73%	1.65L 70%	1.64L 70%	1.60L 68%
FEV1/SVC	85%	85%	84%	85%
DLCO	9 43%	8.5 39%	7.2 33%	7.1 33%


2015


2015


2009

Nintedanib

Recently nintedanib was approved by AIFA, before it was available though an open label compassionate use program for patients with IPF

GI adverse events of nintedanib

Take nintedanib with food (150 mg bid)

- Diarrhea is the most frequent gastrointestinal event
- Treat diarrhea at first signs with adequate hydration and antidiarrheal medication (e.g., loperamide), and consider treatment interruption if diarrhea continues
- Dose reductions may be helpful
- For nausea or vomiting that persists despite appropriate supportive care including anti-emetic therapy, dose reduction or treatment interruption may be required

Others adverse events of nintedanib

- Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia.
- Based on the mechanism of action (VEGFR inhibition), nintedanib may increase the risk of bleeding. Use nintedanib in patients with known risk of bleeding only if the anticipated benefit outweighs the potential risk.

Others adverse events of nintedanib

Conduct liver function tests (ALT, AST, and bilirubin) prior to treatment with nintedanib, monthly for 3 months, and every 3 months thereafter, and as clinically indicated.

Dosage modifications, interruption, or discontinuation may be necessary for liver enzyme elevations.

Our experience with open label compassionate use programm with nintedanib

Today, nintedanib has been discontinued in 10 patients (7 for diarrhea, 1 for liver enzymes increase and 2 for progression of IPF). 8 patients died: 7 for progression of disease and 1 for lung cancer after 2-3 months of therapy

Patients with severe IPF

First patients enrolled on February 2015

4 patients previously were treated with pirfenidone, stopped for adverse event (rush)

1 patient stopped pirfenidone for age (> 80 years) after commercialization

GAP index and stage at baseline

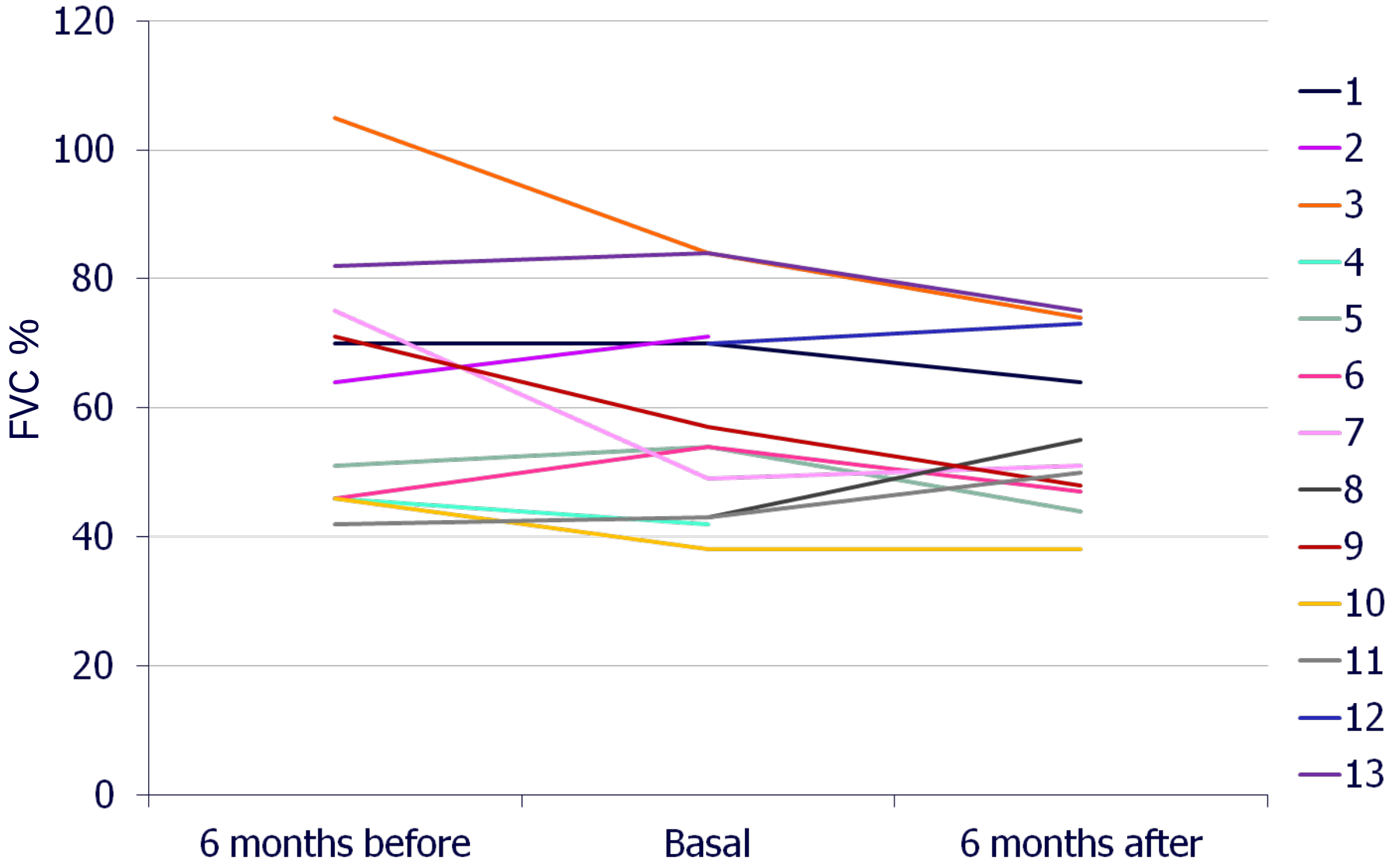
	Predictor	N (%)
G - Gender	Female	6 (17.7)
	Male	28 (82.3)
A – Age	<=60	2 (5.9)
	61-65	4 (11.8)
	65+	28 (82.3)
P - Physiology	**FVC %**	
	>=0.75	8 (23.5)
	0.50-0.75	14 (41.2)
	<0.50	12 (35.3)
	DLCO %	
	>0.55	1 (2.9)
	0.36-0.55	8 (23.5)
	<=0.35	13 (38.2)
	No performed	12 (35.3)

	Predictor	N (%)	Median, (Min-Max)
GAP index			5.8 (2-8)
Stage	I (GAP index 0-3)	4 (11.8)	
	II (GAP index 4-5)	11 (32.3)	
	III (GAP index 6-8)	19 (55.9)	

Severe disease

Our experience with open label compassionate use programm with nintedanib

- 13 patients with 6 months follow-up, 11 male
- Basal mean FVC 58.4% (38-84, min – max) Mean FVC at 6 months 56.3% (38-75, min – max)
- Only 4 patients performed DLCO

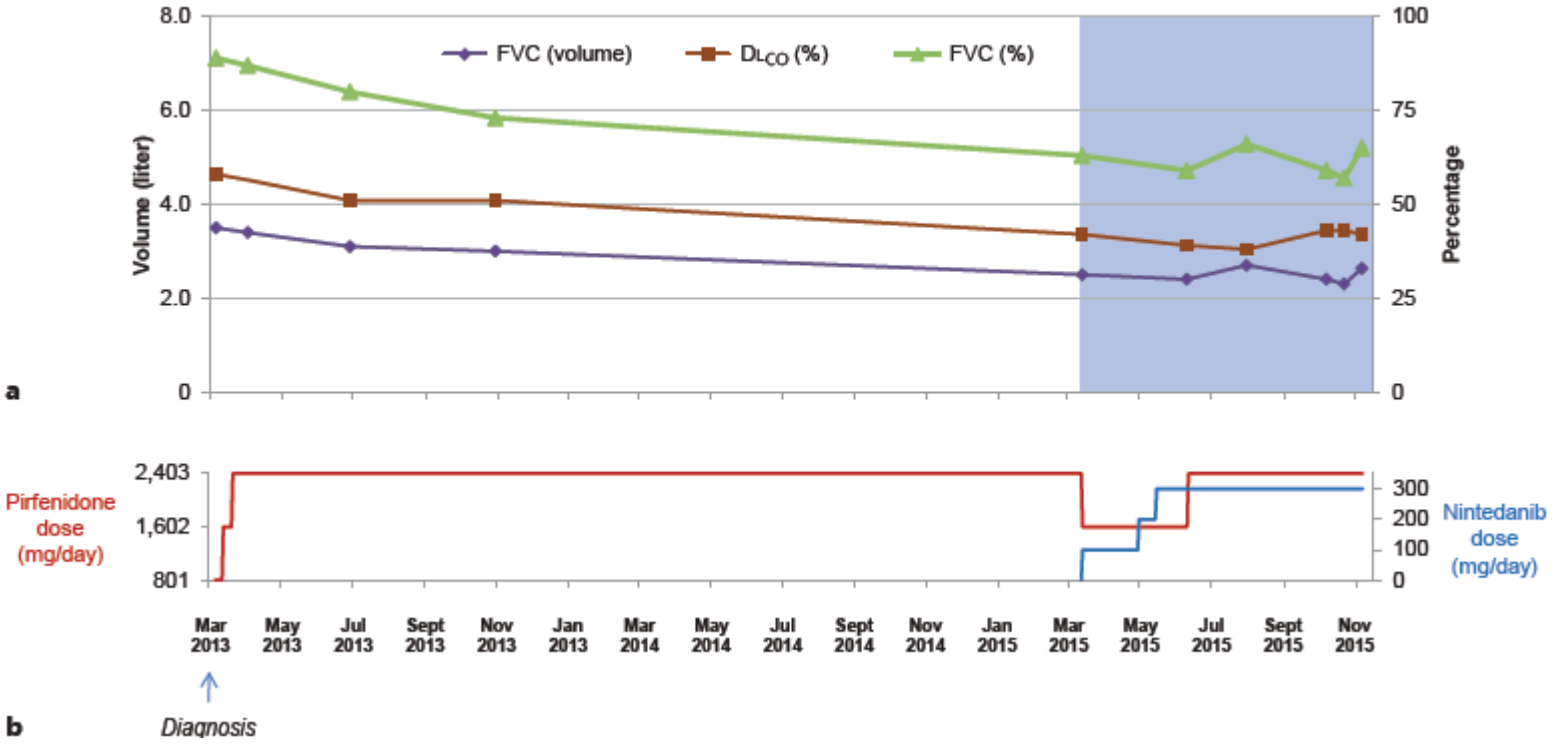


Mean FVC% 6 months before: 63.4%, basal FVC%: 58.4, FVC% 6 months after: FVC 56.3

After 6 months with nintedanib therapy we observed FVC decrease $\geq$ 10% in 4 patients and stable FVC in 9 patients

Successful Concomitant Therapy with Pirfenidone and Nintedanib in Idiopathic Pulmonary Fibrosis: A Case Report

Hagmeyer L et al. Respirology 2016



Novel Insight

Concomitant treatment with pirfenidone and nintedanib appears to be a feasible treatment option and may show a substantial benefit in patients not responding to anti-fibrotic monotherapy with pirfenidone.

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

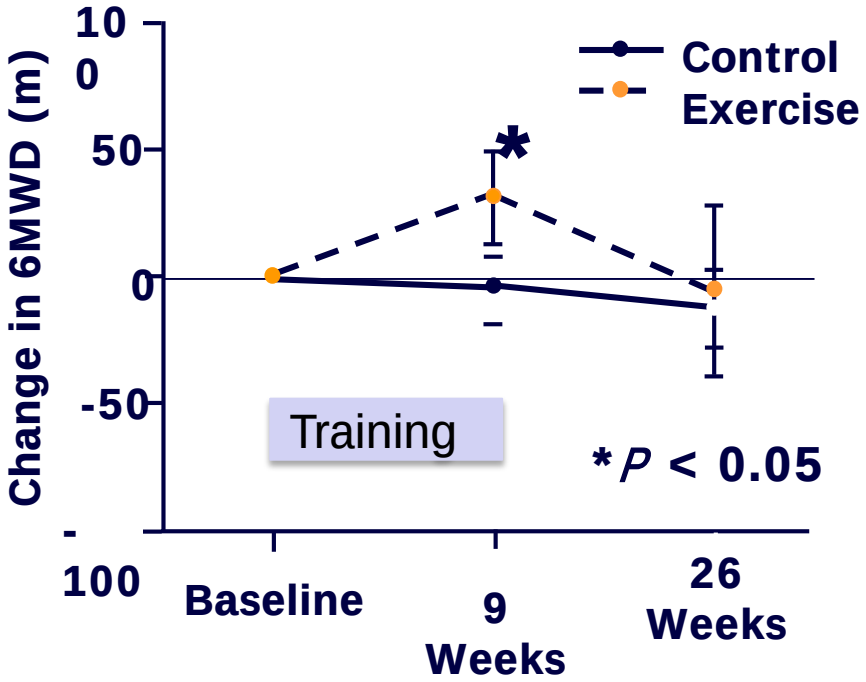
These goals should be reached with a minimum of side effects from treatment

Pulmonary rehabilitation studies in IPF

Author	Citation	Dyspnea	QOL	6MWD	Other
Swigris et al.	Respir Care 2011	Trend	Trend	61.6m	Fatigue Anxiety Depression
Salhi et al.	Chest 2010	-	-	79m	-
Ferreira et al.	Chest 2009	Better	-	56m	-
Kozu et al.	Respiration 2011	Better	Same	16m	Force ADL
Holland et al.	Thorax 2008	Better	Energy	25.1m	VO_2
Nishiyama et al.	Respirology 2008	Same	Better	46m	-

*** Statistically significant**

Exercise training effect on 6MWD



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

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

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

What’s new in IPF management?

Panorama study

Introduction

- The 2015 ATS/ERS guidelines made a conditional recommendation against NAC in IPF, **but no recommendation was made with regard to NAC with antifibrotics**
- A German real-world observational study (N = 63) found that adverse events (AEs) and discontinuations were more common with combined therapy (pirfenidone, oral NAC and/or corticosteroids) than with pirfenidone alone[6]

Behr J et al. Lancet Respir Med 2016

Objective

- The aim of the PANORAMA study was **to evaluate the safety and tolerability of oral NAC 600 mg three times a day (TID) + pirfenidone compared with placebo + pirfenidone over 24 weeks in patients with IPF**

- Exploratory **efficacy endpoints** were also investigated

Behr J et al. Lancet Respir Med 2016

Conclusions

- The PANORAMA study findings suggest that the addition of NAC to pirfenidone does not significantly alter the tolerability of pirfenidone, although photosensitivity should be closely monitored

- The exploratory efficacy endpoints suggest that NAC is unlikely to have a beneficial role in IPF when combined with pirfenidone, and it is possible that the combination is harmful

Behr J et al. Lancet Respir Med 2016

Anticoagulant use in IPF

Medically indicated anticoagulant (AC) use in IPF

Rationale and objective

- The summary of the evidence suggests that ACs given specifically for the treatment of IPF may be associated with negative outcomes
- Therefore, the updated IPF treatment guidelines strongly recommend against the use of ACs for the treatment of IPF
- ACs continue to be used in patients with IPF in clinical practice; therefore, it is important to clearly understand the impact of ACs in these patients

The aim of this post hoc analysis was to investigate the effect of ACs prescribed for non-IPF medical indications on mortality, disease progression and other outcomes in patients with IPF

AC use in patients with IPF
Baseline characteristics

- The study population consisted of all patients randomized to placebo in the pirfenidone Phase III trials (CAPACITY [004/006], ASCEND [016])
  - 624 patients were included in the post hoc analyses, of whom 32 patients (5.1%) received ACs at baseline

Characteristic	Baseline AC arm (N = 32)	Non-AC arm (N = 592)	P value
Age, mean (SD), years	71.1 (6.8)	66.9 (7.5)	0.0025
Male, n (%)	24 (75.0)	441 (74.5)	0.9489
Percent predicted FVC, mean (SD)	70.0 (11.7)	72.1 (13.7)	0.3996
Percent predicted DL_{CO}, mean (SD)	43.3 (8.4)	45.7 (11.2)	0.1290
6MWD, mean (SD), m	368.2 (109.4)	414.1 (92.9)	0.0080
UCSD SOBQ score, mean (SD)	38.2 (23.8)	34.7 (21.5)	0.3697

Unadjusted 1-year risk of study outcomes stratified by baseline AC use

Outcome	Baseline AC (N = 32)	Non-AC (N = 592)	P value
Disease progression composite outcome,* n (%)	14 (43.8)	231 (39.0)	0.5936
All-cause mortality	5 (15.6)	27 (4.6)	0.0390
FVC decrease ≥ 10%	3 (9.4)	61 (10.3)	0.8660
6MWD decrease ≥ 50 m	6 (18.8)	143 (24.2)	0.4848
All-cause mortality, n (%)	5 (15.6)	37 (6.3)	0.0057
IPF-related mortality, n (%)	5 (15.6)	23 (3.9)†	0.0018
Observed % predicted FVC change from baseline on the visit prior to death, mean (SD)	−4.2 (5.96)	−14.6 (7.68)	
Time to mortality,‡ weeks	25.6 (9.78)	30.8 (14.57)	
FVC change, n (%)			
Absolute decrease ≥ 10%	6 (18.8)	107 (8.1)	0.9230
Relative decrease ≥ 10%	11 (34.4)	174 (29.4)	0.5477
Observed % predicted FVC change, mean (SD)	−6.0 (6.4)§	−65.2 (6.9)§	0.5274
6MWD decrease ≥ 50 m, n (%)	8 (25.0)	158 (26.7)	0.8332
All-cause hospitalization, n (%)	7 (21.9)	112 (18.9)	0.6784

***Only the first disease progression event was counted for each patient.**
†Causes of non-IPF–related death were: cardiac arrest, acute corpulmonale, hemorrhagic stroke, central nervous system metastases, myocardial infarction and small-cell lung cancer (2.7% each); unknown cause (8.1%).
‡Time to death from trial initiation.
§n = 26 and n = 523 for the AC and non-AC groups, respectively.

Unfavorable effects of ACs on survival in IPF

Conclusions

- This post-hoc analysis suggested that the use of ACs may have unfavorable effects in IPF
- This finding may be due to a harmful effect of ACs in IPF or an increased risk of death due to comorbidities in patients treated with ACs
- Future research should investigate whether this unfavorable effect is due to ACs or the indicating comorbidities and explore the possibility of a class effect with vitamin K antagonists versus other ACs

Statin use in IPF

Background

- Cardiovascular comorbidities and risk factors are common in IPF
  - Many patients are prescribed HMG-CoA reductase inhibitors (statins) to lower cholesterol and reduce the risk of cardiovascular events
- The potential for additional benefits of statins in pulmonary disease has previously been investigated in COPD
- Data are conflicting regarding the possible effects of statins in patients with IPF

Kreuter M et al. ATS 2016

Objective

To evaluate the effect of statins on mortality, lung function, and hospitalization in patients with IPF

Kreuter M et al. ATS 2016

Results

Baseline characteristics

Parameter	Statin users (N = 276)	Statin non-users (N = 348)
Age, mean (SD), y	68.2 (7.0)	66.3 (7.8)
Male, n (%)	225 (81.5)	240 (69.0)
FVC, mean (SD), % predicted	72.5 (14.0)	71.6 (13.3)
DLco, mean (SD), % predicted*	45.4 (10.3)	45.7 (11.7)
6MWD, mean (SD), m*	407.4 (89.8)	415.3 (97.6)

Statin users were older than non-users ($P = 0.001$), and a greater proportion were male ($P < 0.001$)

Kreuter M et al. ATS 2016

Results

Baseline characteristics

Medical history, n (%)	Statin users (N = 276)	Statin non-users (N = 348)
Cardiovascular disease	127 (46.0)	53 (15.2)
Cardiovascular risk factors		
Hypercholesterolemia	234 (84.8)	61 (17.5)
Smoker	186 (67.4)	198 (56.9)
Hypertension	183 (66.3)	157 (45.1)
Obesity	125 (45.3)	140 (40.2)
Diabetes	75 (27.2)	59 (17.0)
Statin		
Simvastatin	106 (38.4)	–
Atorvastatin	96 (34.8)	–
Pravastatin	27 (9.8)	–
Rosuvastatin	26 (9.4)	–
Other*	21 (7.6)	–

Statin users had a higher prevalence of cardiovascular disease ($P < 0.0001$) and cardiovascular risk factors, including hypertension, smoking, diabetes, and hypercholesterolemia (all $P < 0.01$) versus non-users

Kreuter M et al. ATS 2016

*** Lovastatin, fluvastatin or pitavastatin.**

Results

Multivariate analyses

Outcome (baseline statin use: yes vs no)	Multivariate analyses (statin users versus non-users)		
	Multivariate hazard ratio	95% CI	P value
Disease progression	0.75	0.52–1.07	0.1135
All-cause mortality	0.54	0.24–1.21	0.1369
IPF-related mortality	0.36	0.14–0.95	**0.0393**
Death or absolute FVC decrease ≥ 10%	0.71	0.48–1.07	0.1032
Death or 6MWD decrease ≥ 50 m	0.69	0.48–0.99	**0.0465**
FVC decrease ≥ 10% (absolute)	0.81	0.47–1.40	0.4533
FVC decrease ≥ 10% (relative)	0.90	0.59–1.38	0.6262
All-cause hospitalization	0.58	0.35–0.94	**0.0289**
Respiratory-related hospitalization	0.44	0.25–0.80	**0.0063**

Hazard ratios were calculated adjusting for age, gender, smoking status, lung function, exercise tolerance, dyspnea, and cardiovascular risk factors

Kreuter M et al. ATS 2016

Conclusions

This post-hoc analysis supports the hypothesis that the use of statins may be beneficial in patients with IPF

In multivariate analyses, statin use was associated with a reduced risk of:

- Death or a decrease ≥ 50 m in 6MWD
- IPF-related mortality
- All-cause hospitalization
- Respiratory-related hospitalization

Prospective trials are required to validate these findings and investigate the potential use of statins in combination with anti-fibrotic therapies

Kreuter M et al. ATS 2016

There is still a role for steroids in IPF?

In INSIGH-IPF registry the rate of steroid use was high despite the fact that international guidelines discourage this.

Reasons are speculative, but may include treatment of dry cough, previous exacerbations or difficulty in tapering off therapy.

A similar pattern in the use of steroids has been described in the RCTs and in a survey of French pulmonologists

We often are unsure of what we are treating

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

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!