Air Metting Italia 2015 – Roma 25-26 Giugno 2015

La Terapia dell'IPF con Pirfenidone

Le conferme dalla pratica clinica: dati di "real life"

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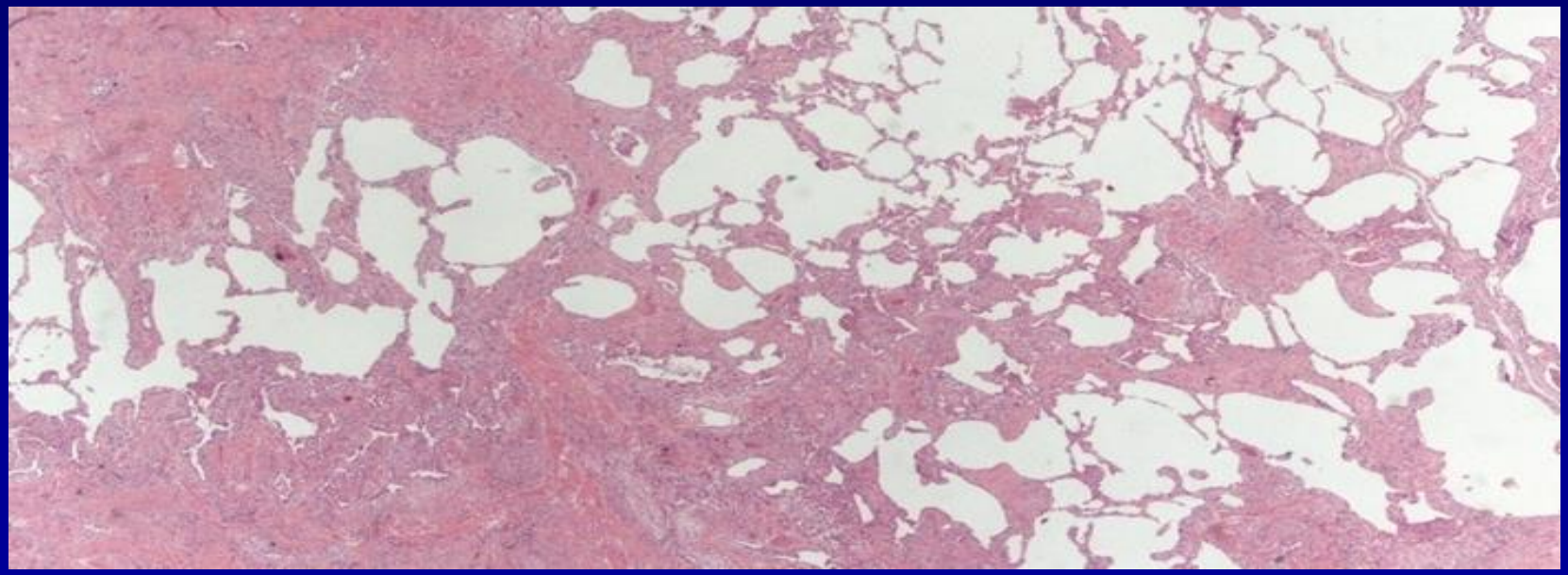
IPF : Where we are today

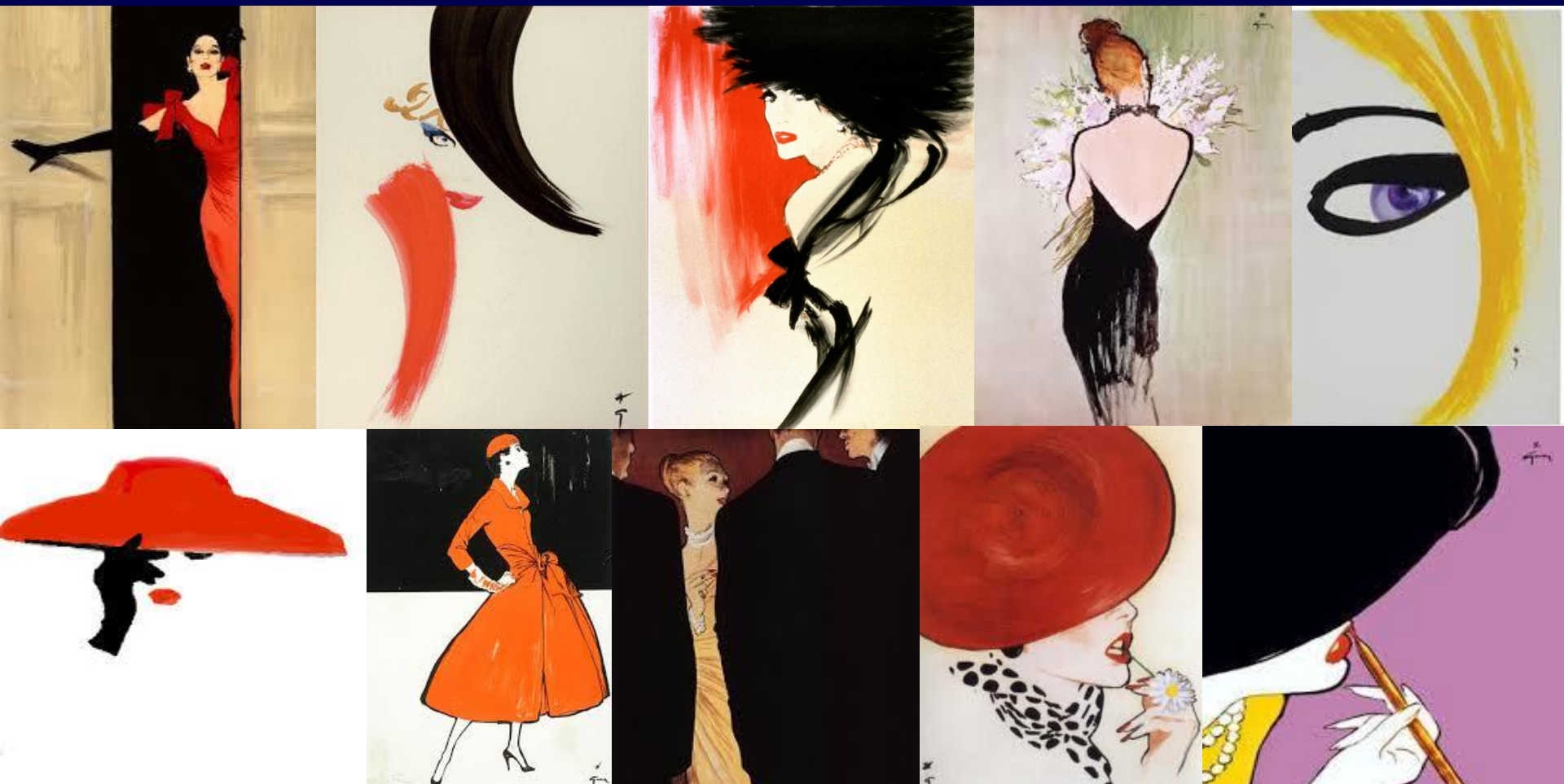
- It is clear that treatment decisions and the clinical management of patients with IPF should be based primarily on the findings of randomized controlled trials, and also, to a certain extent, on expert opinion
- Randomized clinical trials have increased our knowledge in several aspects of IPF
- Many promising compounds for IPF treatment have not shown efficacy when evaluated in phase II and III clinical trials

Results of clinical research

The recent positive results of the pirfenidone and nintedanib phase III trials demonstrate that agents targeting the biologic processes that drive fibrosis can reduce the progression of IPF

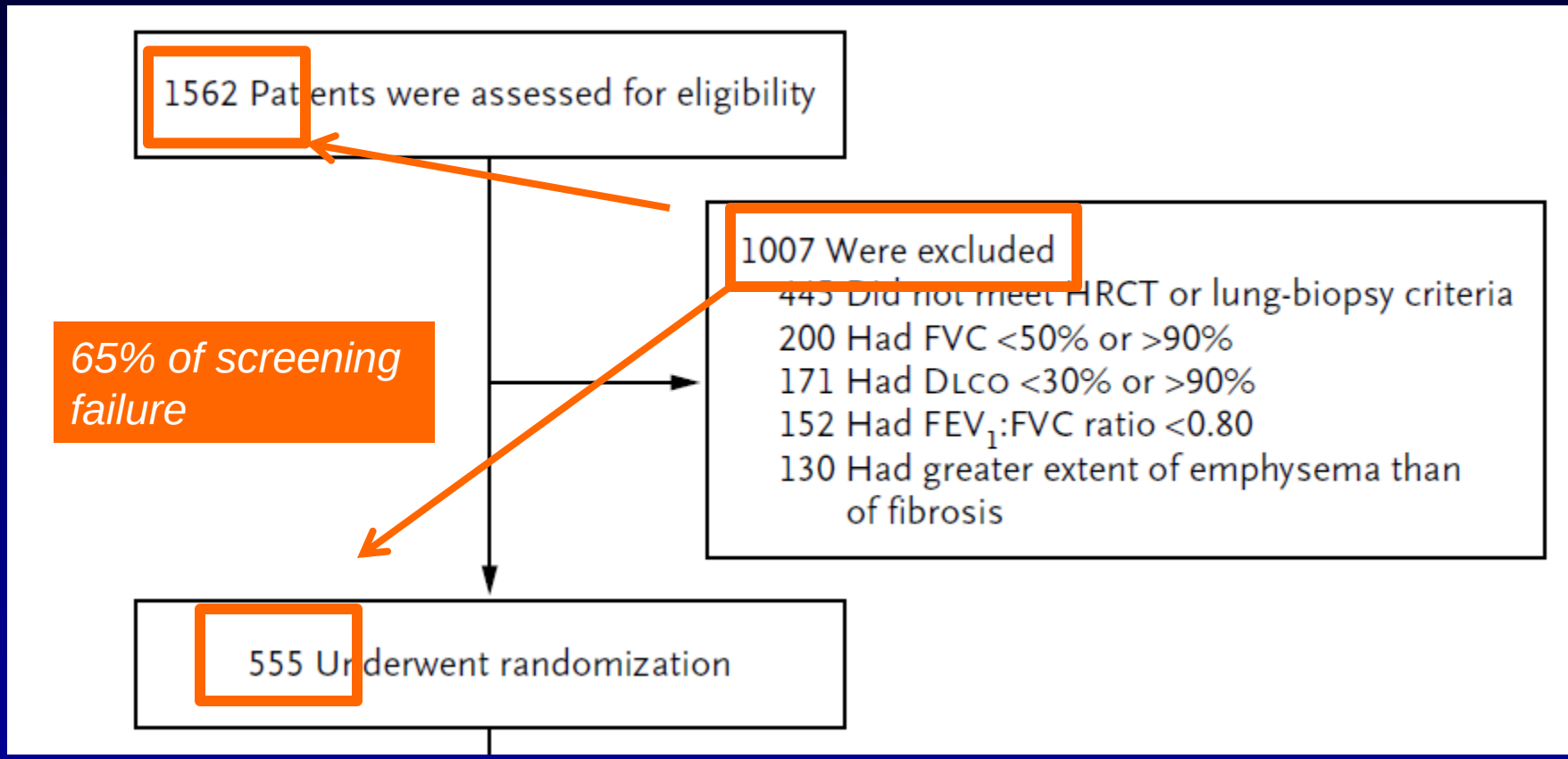


..but real life is not a clinical trial…



- 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

Mortality rates were significantly lower in trials excluding severe disease compared to those including all disease severities

There were significantly higher rates of infection in those studies permitting the use of low-dose corticosteroids versus those not allowing use of any immunosuppressants.

Atkins CP et al. Respir Med 2014; 108: 376

Controlled clinical trial results vs real world observations

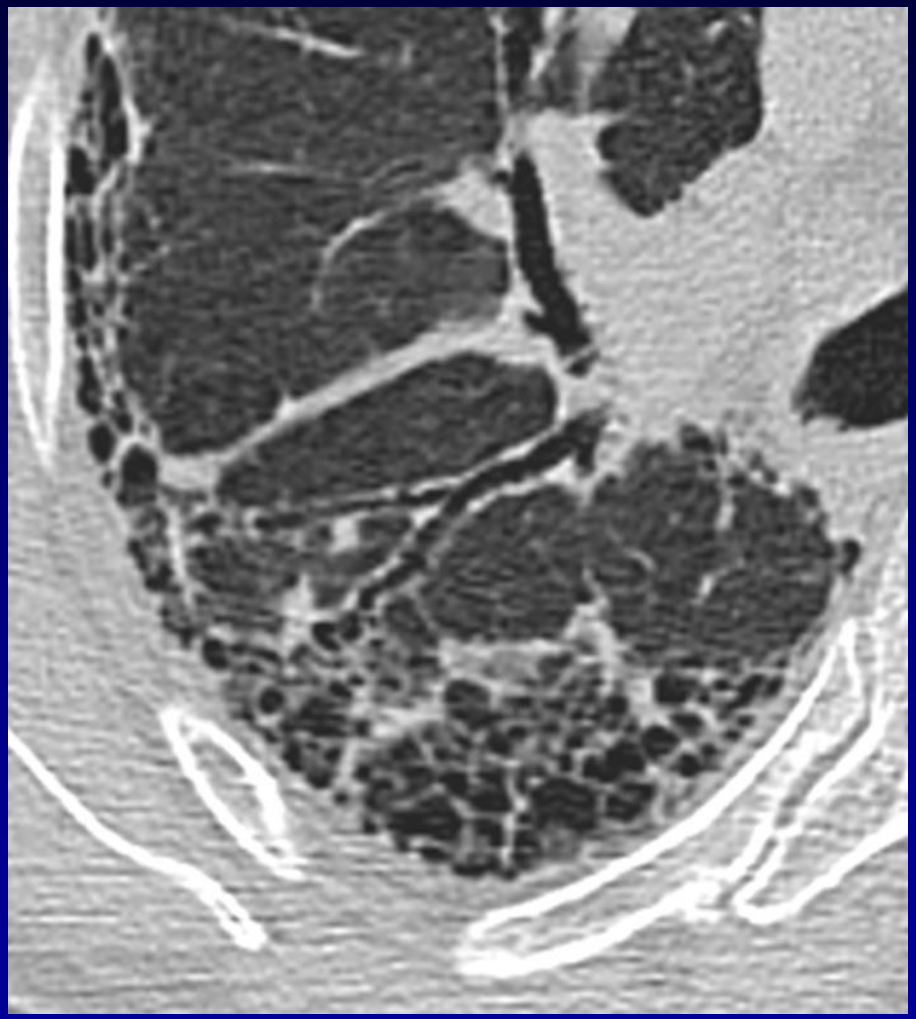
Will the treatment work in the real world? That's the issue often raised by the favorable outcome of a formal clinical trial

It's so important that special terminology has been developed for it: "the gap between efficacy and effectiveness" - ***efficacy*** meaning proof in a carefully controlled trial, and ***effectiveness*** meaning success in the circumstances of everyday life

The approved drugs in IPF therapy

- Pirfenidone is the first agent approved for the treatment of patients with mild-to-moderate IPF in the European Union in 2011
- Pirfenidone is also approved in Japan (from 2008), Canada, India, China, South Korea and Argentina
- FDA required an additional study (the ASCEND study) and approved pirfenidone for IPF therapy in USA in October 2014 together with nintedanib
- EMA approved nintedanib for treatment of IPF in January 2015

Following European approval, pirfenidone has been introduced into clinical practice for the treatment of patients with mild-to-moderate IPF and there is increasing interest about the efficacy and tolerability of pirfenidone in the real-world setting



RECAP...“almost a real life” study…

RECAP is a long-term, open-label extension study evaluating the safety of continued therapy with pirfenidone in patients who completed CAPACITY trials

603 patients (mean age 68.3 years, 72% male, mean 2.6 years since IPF diagnosis) were originally enrolled in RECAP study.

Data from patients initially randomised to pirfenidone 2403 mg/day in CAPACITY studies and subsequently included in RECAP had a follow-up time of almost 5 years (240 weeks) and demonstrated that 50% of patients who originally received pirfenidone in the CAPACITY studies were still alive and remained on treatment at almost 4 years (week 192) and 40% at week 240

Long-term treatment with pirfenidone had a favourable safety profile and was generally well tolerated for up to 4.9 years of therapy

Costabel U. et al. Eur Respir J 2011; 38: Suppl 55, 3s
Kreuter M. Eur Respir Rev 2014; 23: 111

PASSPORT is a post-authorisation safety registry required by the European Medicine Agency

Up to 140 EU sites involved.

Safety data are recorded at routine clinic visits for 2 years

Pirfenidone Post-authorisation Safety Registry (Passport)–interim Analysis of IPF Treatment

Maher TM, Cottin V, Skoeld M, Tomassetti S, Azuma A, Giot C, Hamza S, Koschel D

Results Data from 530 patients enrolled by 68 sites in 7 countries are included. Age was 69 ± 8.8 years (mean ± SD);

Of 311 patients with ADRs, 85 discontinued due to ADR and 41 discontinued for other reasons

Conclusion PASSPORT ADRs are comparable to those in clinical trials of pirfenidone in IPF. No new safety issues emerged. Dose adjustment may influence long-term tolerability of pirfenidone.

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

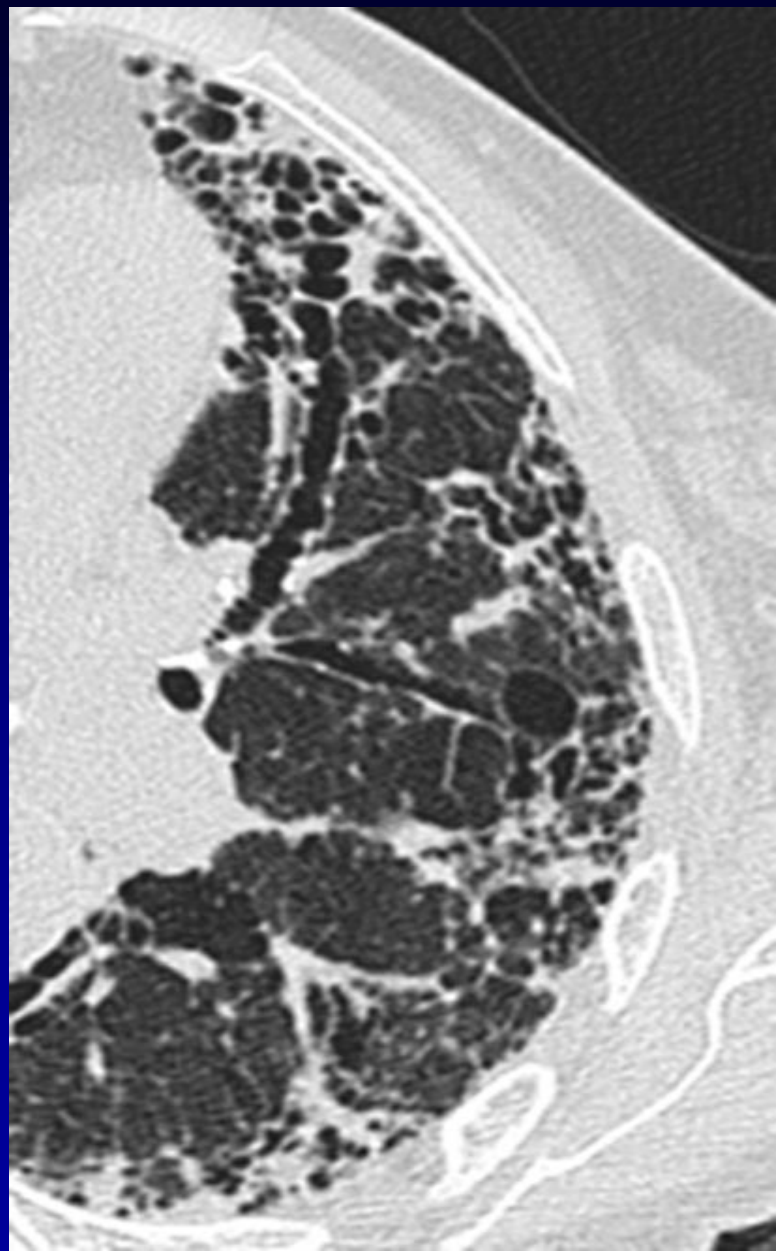
Respir Med. 2015 Apr 25.(15) 121-3

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

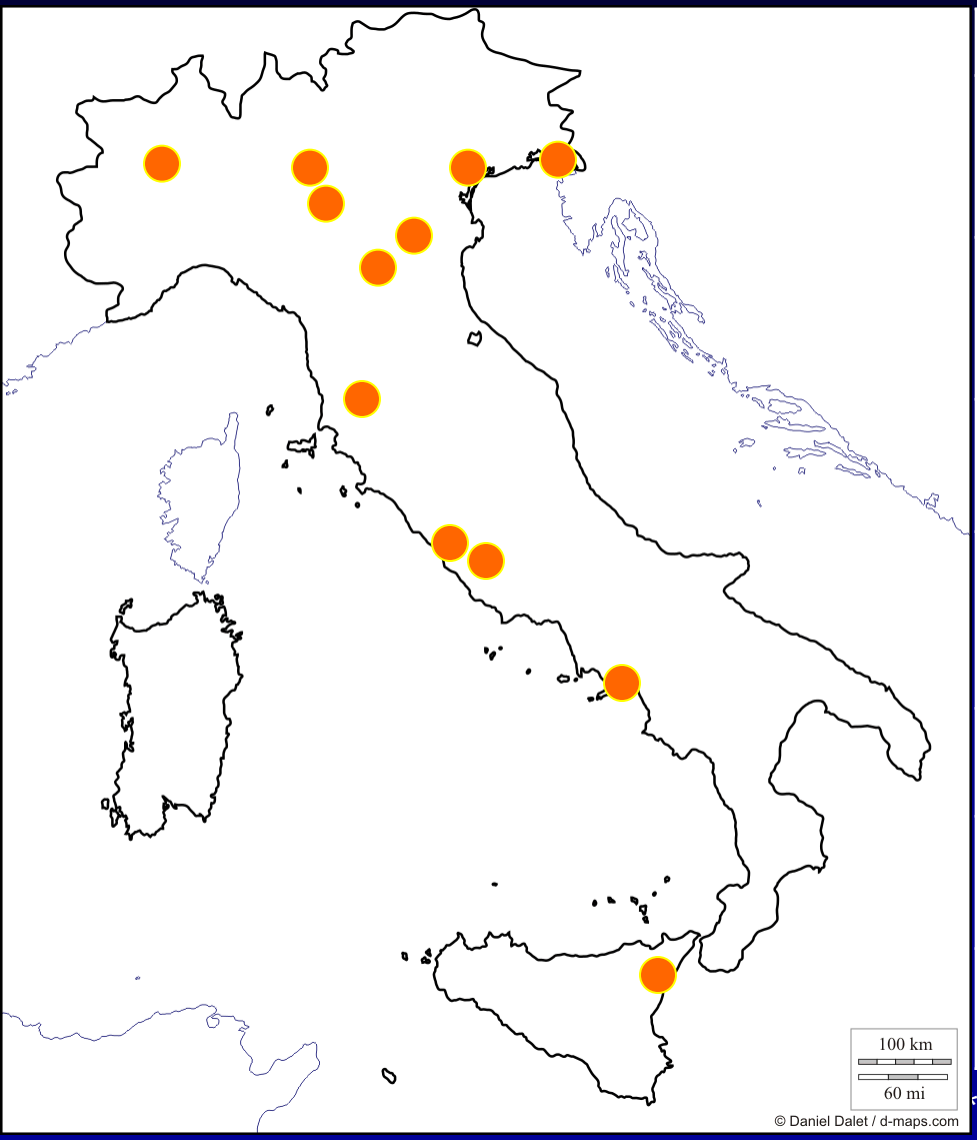
Study design:

- 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);

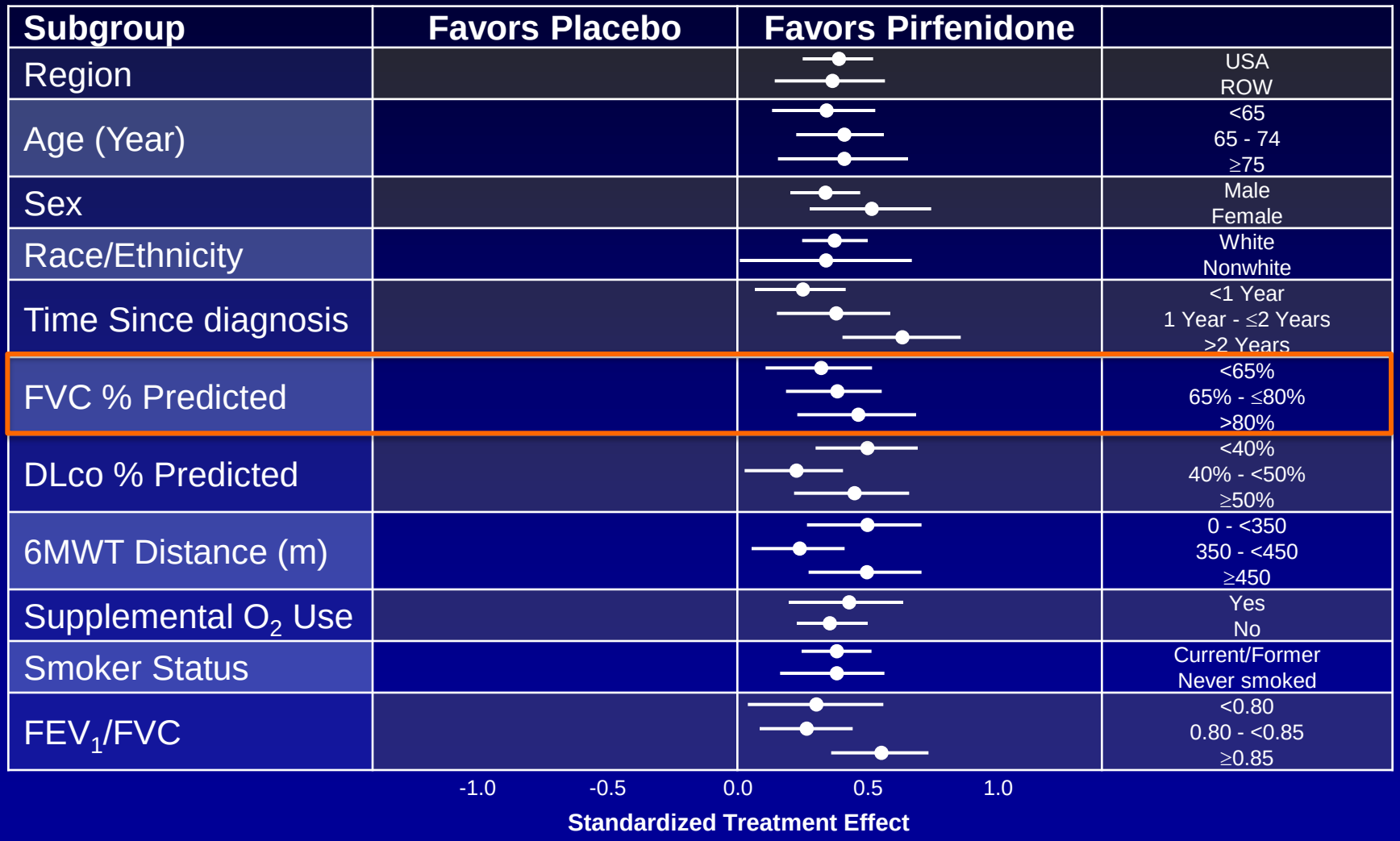
→ Splitting the whole population in two groups according to FVC% (>0,75 or <0,75 at baseline) and GAP index:

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

This important findings need further investigations

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

Treatment effect observed across subgroups:
%FVC change at 1 year in the pooled ASCEND and CAPACITY population*†



* Rank ANCOVA Model With Standardized Effects; † Statistical test for interaction provides no evidence that treatment effect is different at different levels of any of the covariates, except time since IPF diagnosis (p=0.034)

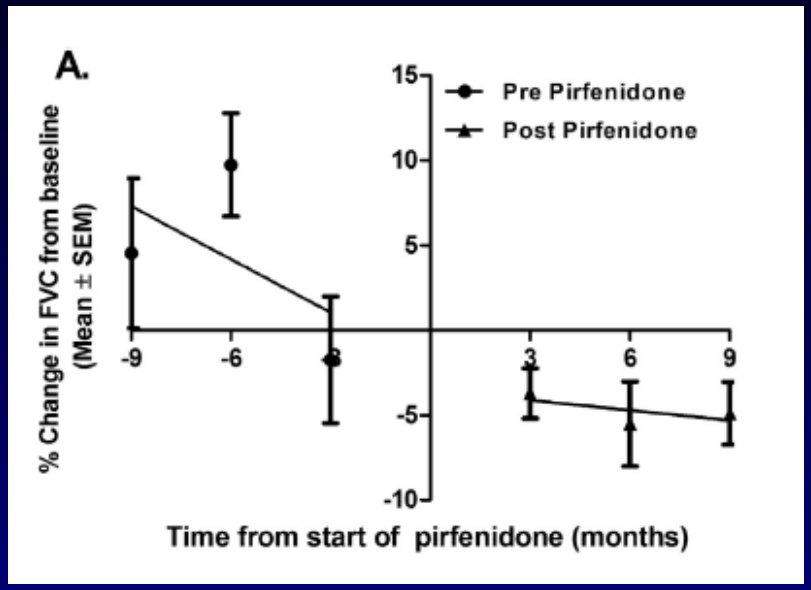
TE. King ERS 2014

Others real life experiences

Real word experiences: pirfenidone is well tolerated in patients with idiopathic pulmonary fibrosis

Chaudhuri N et al. Respir Med 2014; 108: 224

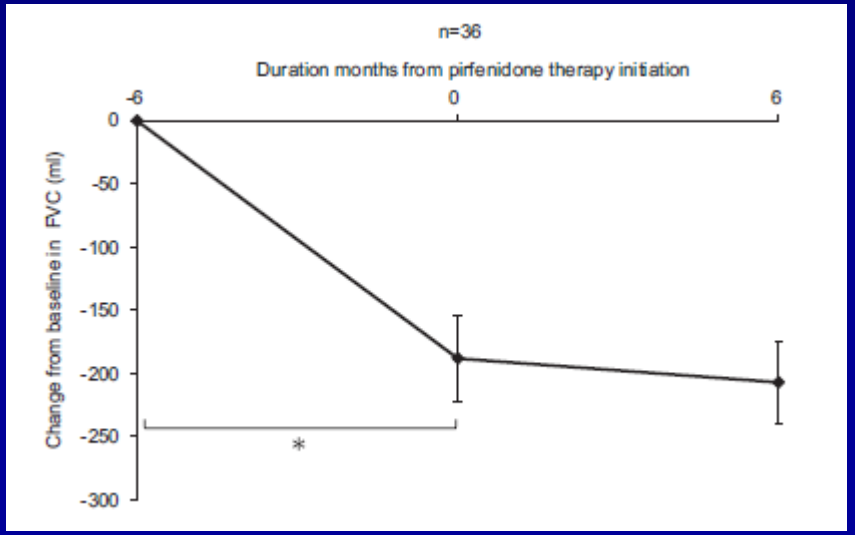
- Single centre observational study of patients involved in NPP
- Retrospective analysis, **40 pts**
- During the first 6 months of pirfenidone therapy 15% of patients discontinued treatment due to adverse events



Safety and efficacy of pirfenidone in idiopathic pulmonary fibrosis in clinical practice

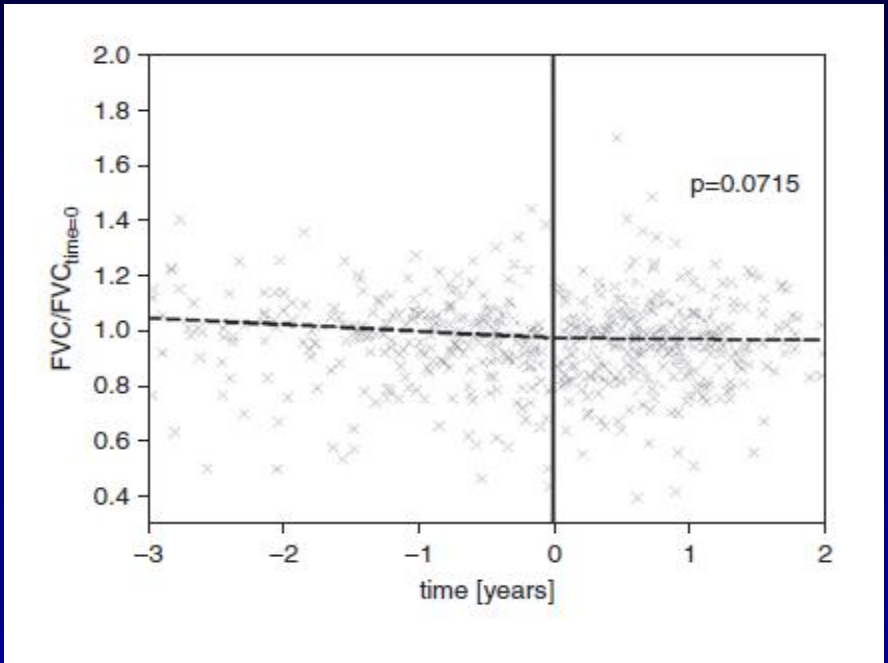
Okuda R et al. Respir Med 2013; 107: 1431

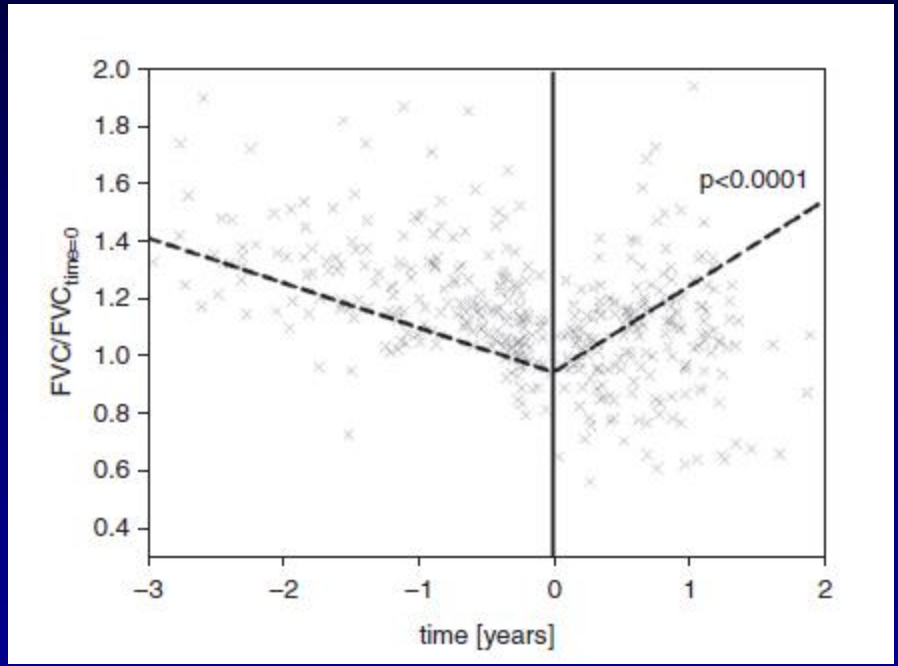
- Single centre observational study
- Retrospective analysis, **76 pts**
- Pirfenidone was well tolerated and had beneficial effects in patients with mild-to-severe and/or progressive disease



Intraindividual response to treatment with pirfenidone in idiopathic pulmonary fibrosis

Loeh B et al. Am J Respir Crit Care Med 2015; 191: 110





- Two patients cohorts in German and Italy
- Retrospective analysis, **197 pts**
- **R**esponse to pirfenidone in this “real-life” patient cohorts is favorable in the patient population as a whole, but most pronounced in those patients with the greatest decline in FVC evident before treatment.

Conclusions

- A new era in the IPF therapy is now started
- An early and accurate diagnosis of IPF is critical
- Pirfenidone slow the progression of the disease
- Larger data are today available on Pirfenidone and confirm that the drug work also in real life setting
- A possible use of Pirfenidone in more severe patients should be investigated