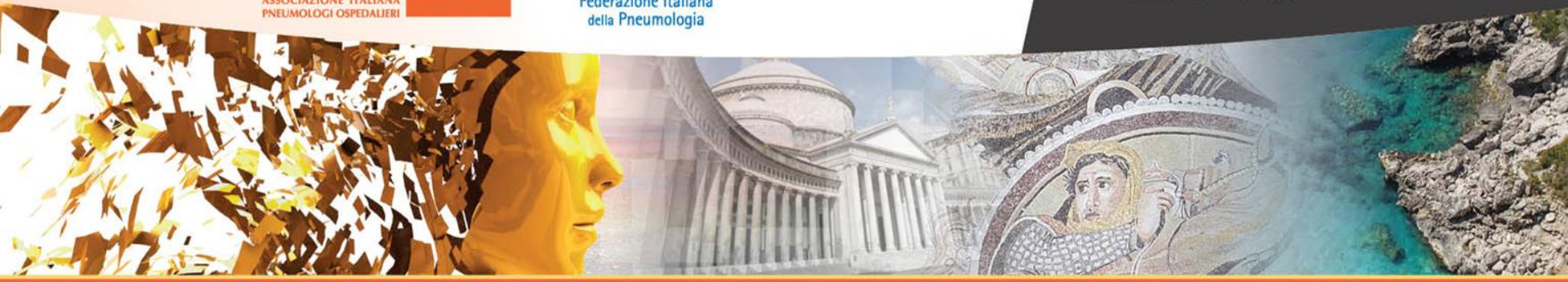
Qualità e Sostenibilità:
le sfide per la Pneumologia

XLIII AIPO CONGRESSO NAZIONALE
ASSOCIAZIONE ITALIANA PNEUMOLOGI OSPEDALIERI

FIP Federazione Italiana della Pneumologia

NAPOLI
Mostra d'Oltremare
11-14 Novembre
2015



Sergio Harari
UO di Pneumologia UTIR Servizio di Fisiopatologia
Respiratoria e Emodinamica Polmonare
Ospedale San Giuseppe MultiMedica Milano

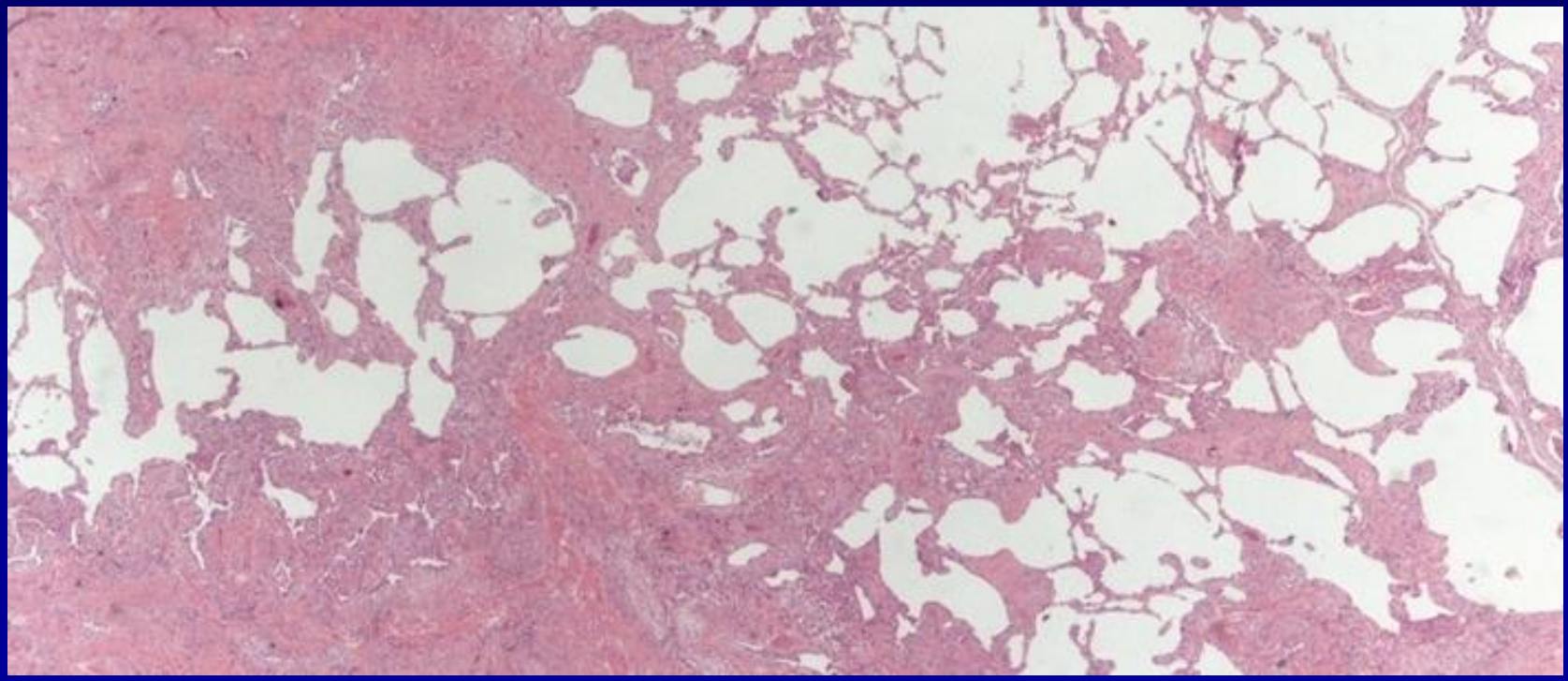
Trials clinici e real life, esperienze a confornto

IPF : Where we are today

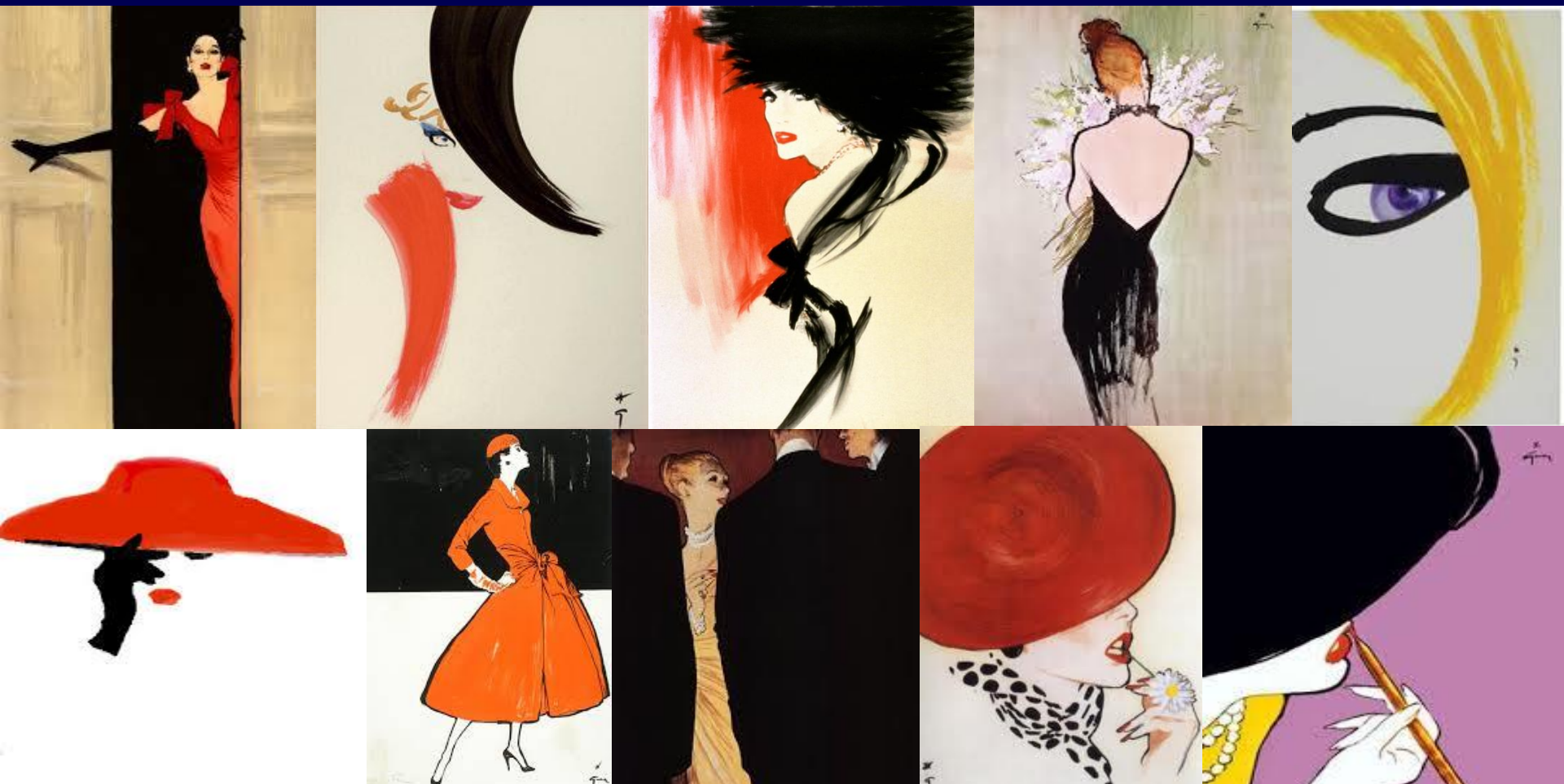
- It is clear that treatment decisions and the clinical management of patients with IPF should be based primarily on the findings of randomized controlled trials, and also, to a certain extent, on expert opinion
- Randomized clinical trials have increased our knowledge in several aspects of IPF
- Many 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

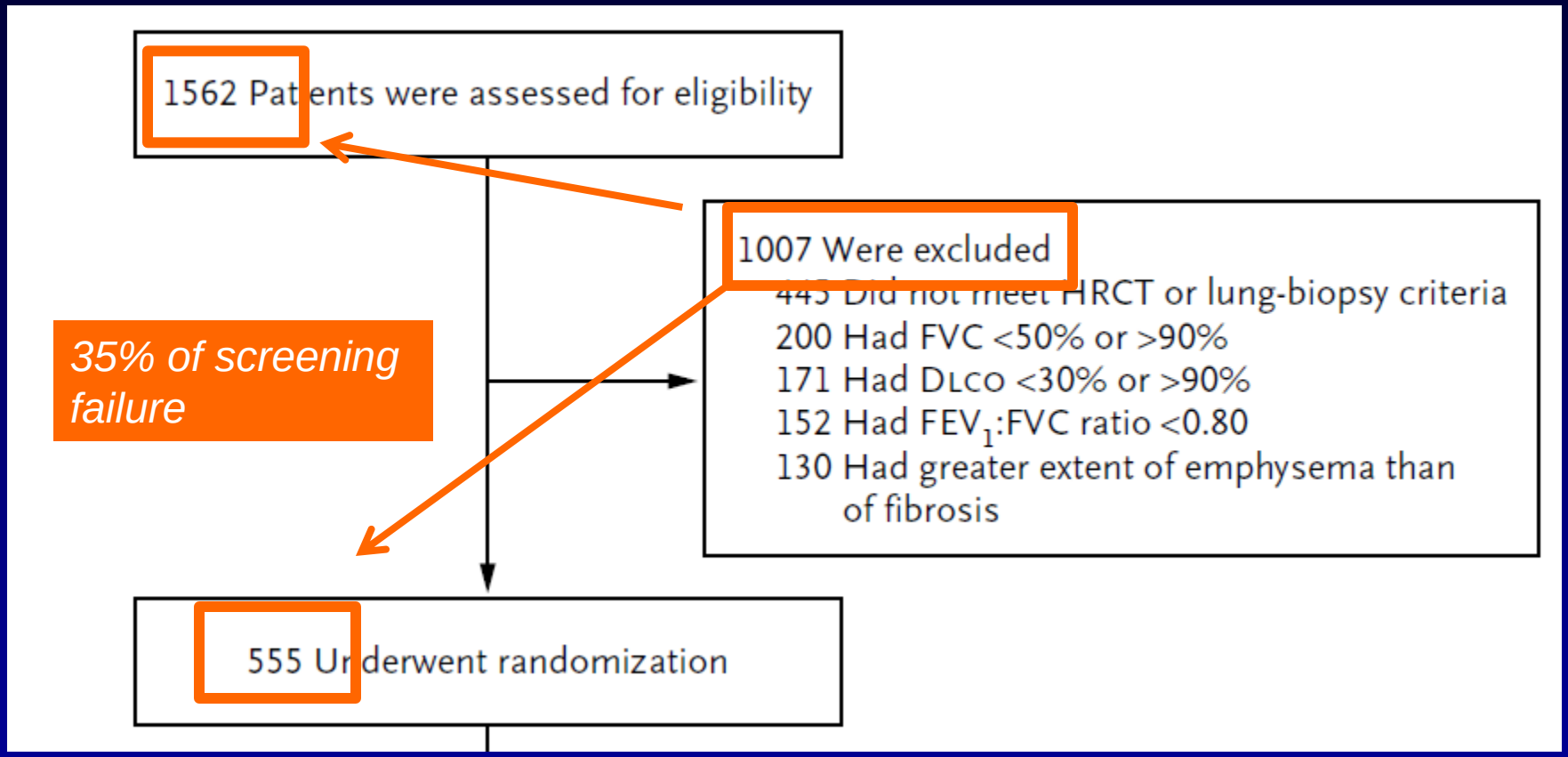


..but real life is not a clinical trial…



- 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	108/625 (14.2)

IPF patients in this prospective real-life large registry (625 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 2015

Controlled clinical trial results vs real world observations

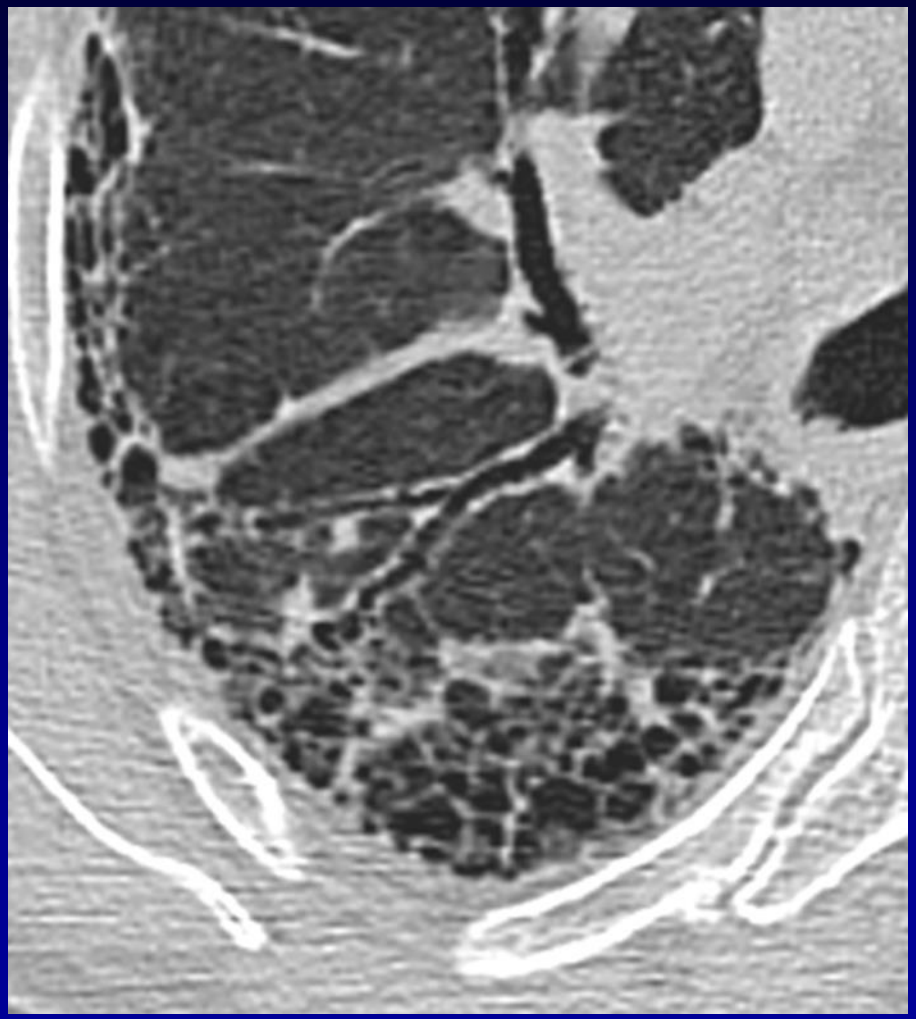
Will the treatment work in the real world? That's the issue often raised by the favorable outcome of a formal clinical trial

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

Study name	Patients	Type of study	Patients characteristics	Median time of treatment	Efficacy outcome	Adverse events GI	Adverse events Skin	Treatment discontinuation due to adverse events
RECAP	603	Ongoing open-label, long-term, follow-up extension study	The baseline characteristics of patients were similar to those in the CAPACITY study in terms of FVC % predicted, DLCO % predicted Age: 68.3	163.3 weeks (provisional)	FVC and survival outcome were similar to those in the CAPACITY pirfenidone group	Nausea in 30% of cases	Rush in 13.3% of cases	65.8% 45%
PASSPORT	530	Ongoing, post-authorisation safety registry Prospective, observational, long-term registry with a follow-up period of 2 years	Age: 69 ±8.8 years Baseline FVC (% pred): 64.5±16.6	5.5 months (provisional)	The longer term safety profile of pirfenidone appears to be consistent with those seen in the clinical trials	Nausea in 15.7% of cases	Rush in 7.5% and photosensitivity reaction in 4.2%	16%
INSIGHT-IPF	502	Multicentre, non interventional study (registry)	Age: 68.7 ±9.4 years Baseline FVC (% pred): 67±18.2	Start on November 2012	Prospectively assess the characteristics, diagnostic procedures, treatment patterns, quality of life, long-term outcome 44.2% of patients were treated with pirfenidone	-	-	-

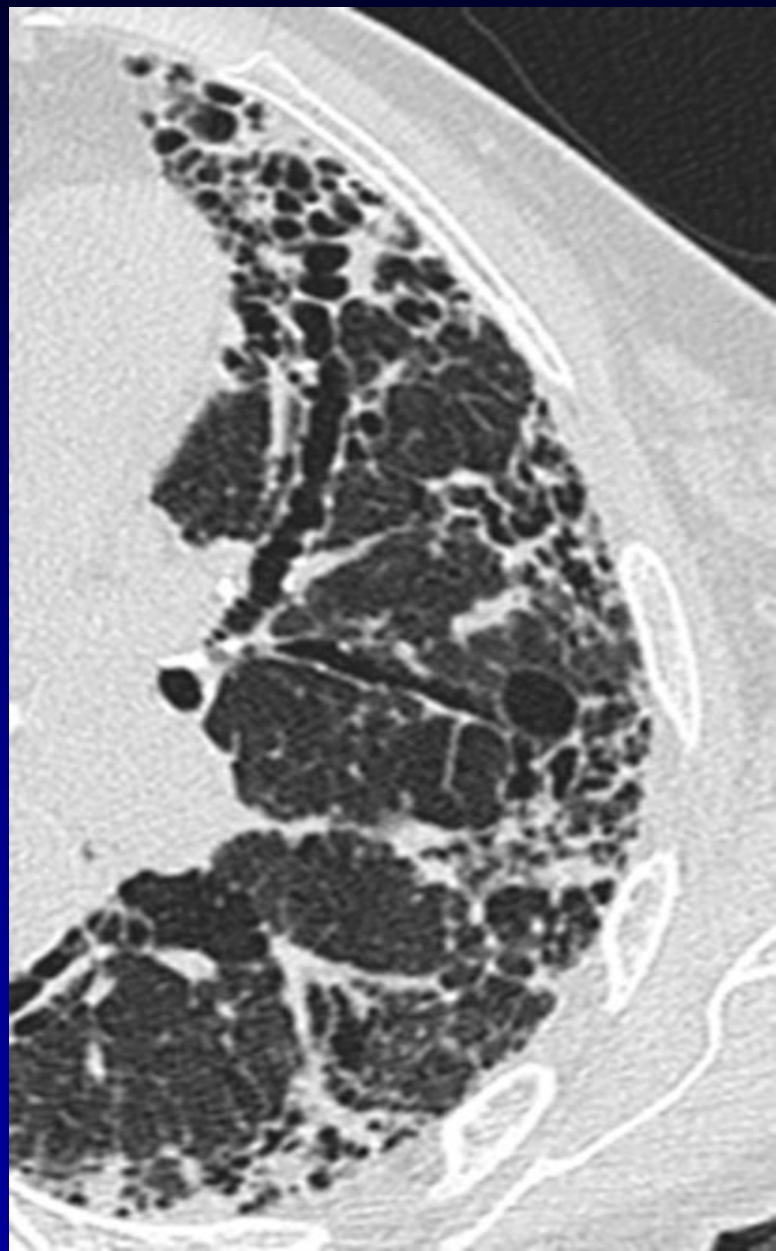
Efficacy of Pirfenidone for Idiopathic Pulmonary Fibrosis: an Italian real life study

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

Respir Med. 2015 Jul;109(7):904-1

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

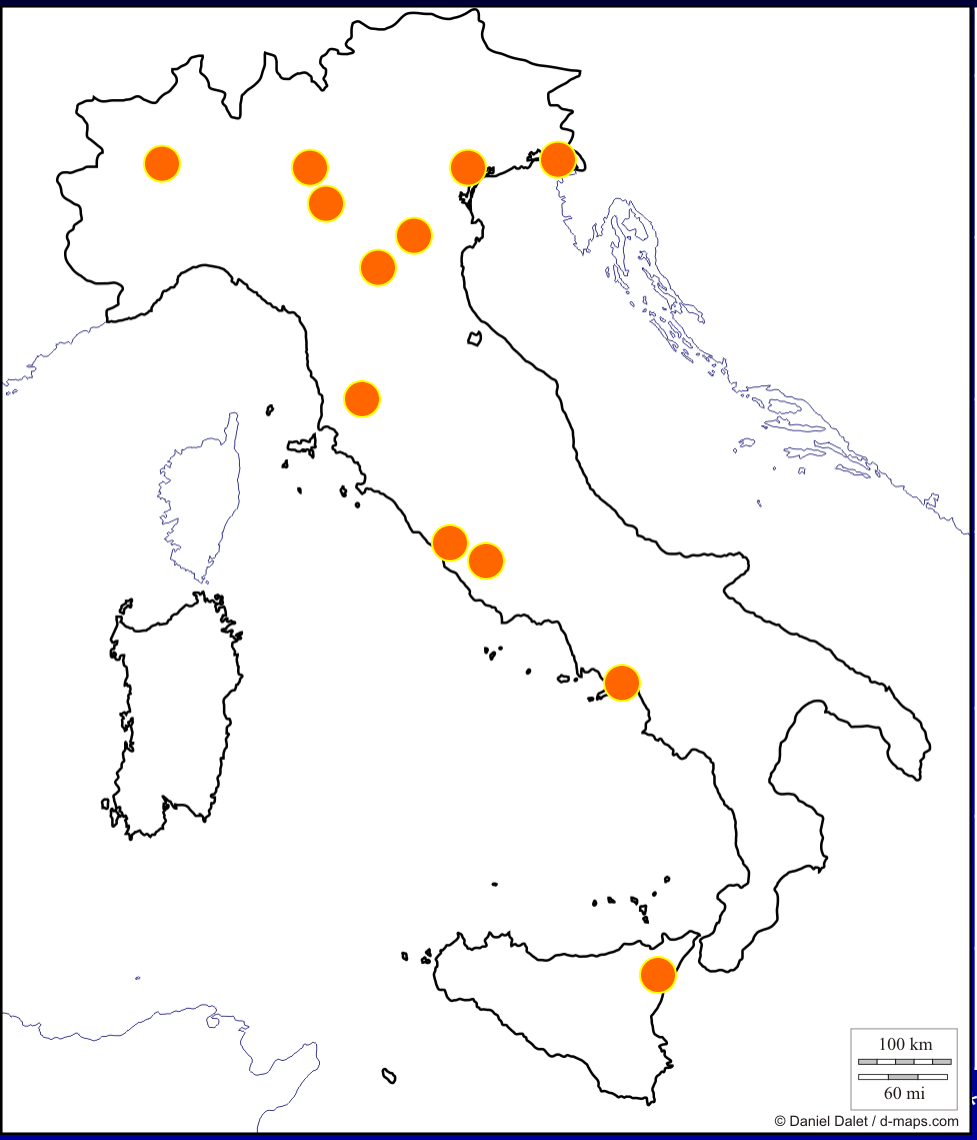
Study design:

- 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:

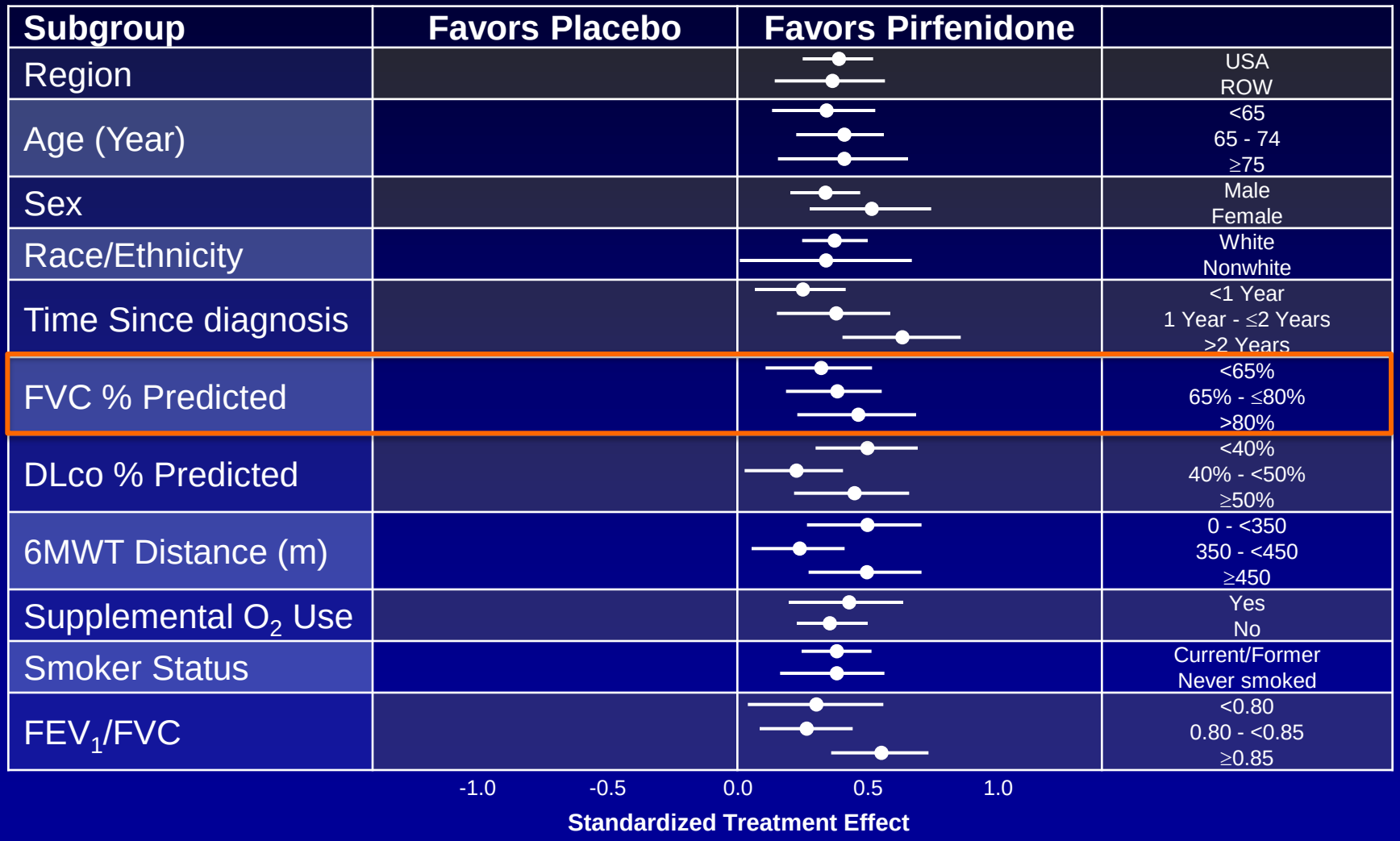
- The drug reduces the slope of decrease of FVC% (p= 0,065);

→ 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

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

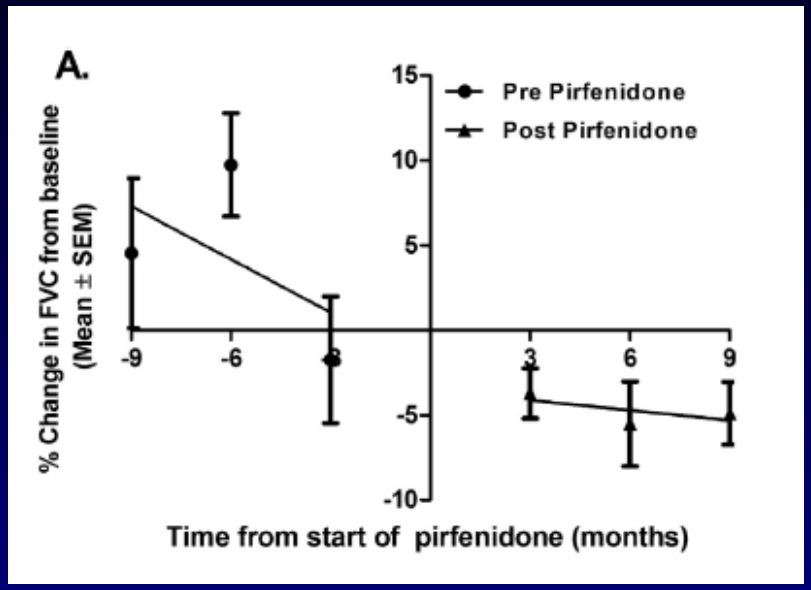
Others real life experiences

Harari S. and Caminati A. ERR 2015; 24: 420-27

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

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

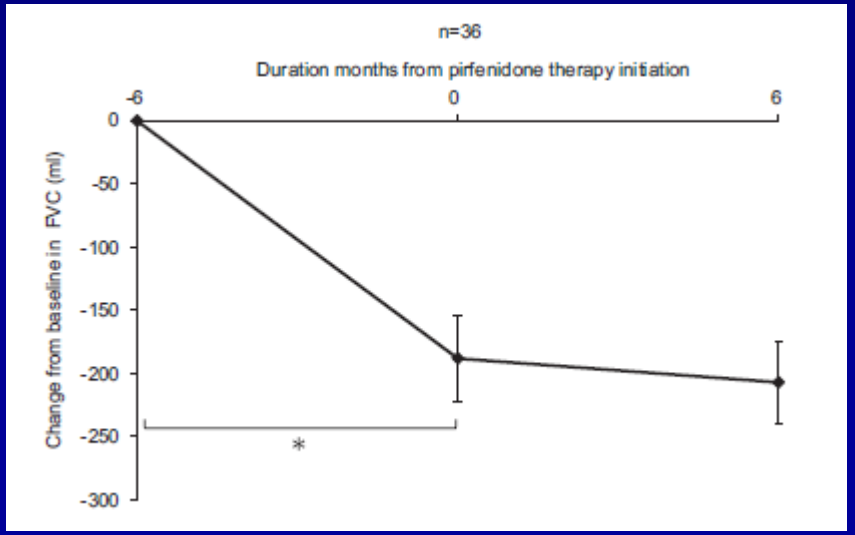
- Single centre observational study of patients involved in NPP
- Retrospective analysis, **40 pts**
- During the first 6 months of pirfenidone therapy 15% of patients discontinued treatment due to adverse events



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

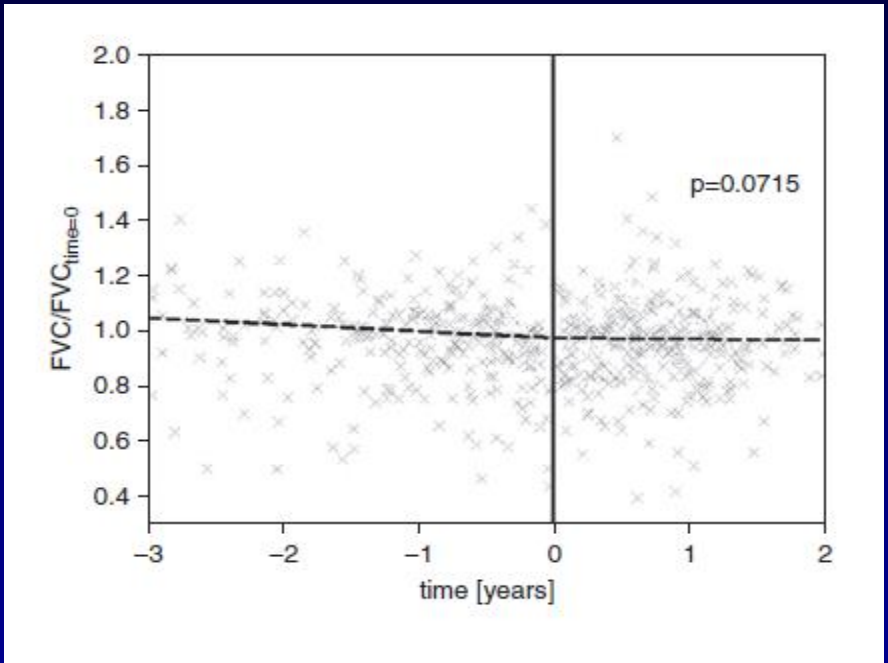
Okuda R et al. Respir Med 2013; 107: 1431

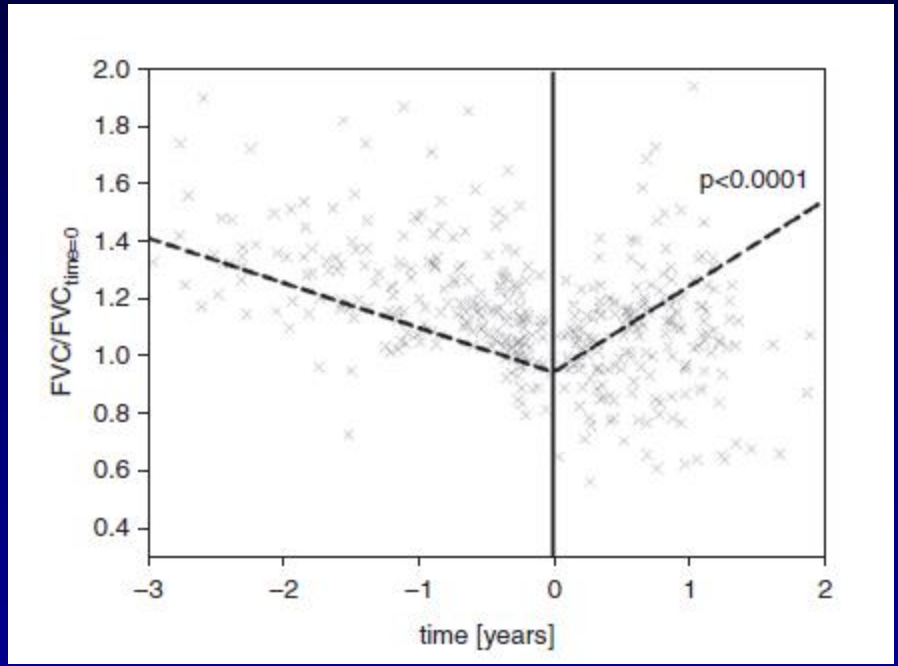
- Single centre observational study
- Retrospective analysis, **76 pts**
- Pirfenidone was well tolerated and had beneficial effects in patients with mild-to-severe and/or progressive disease



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.

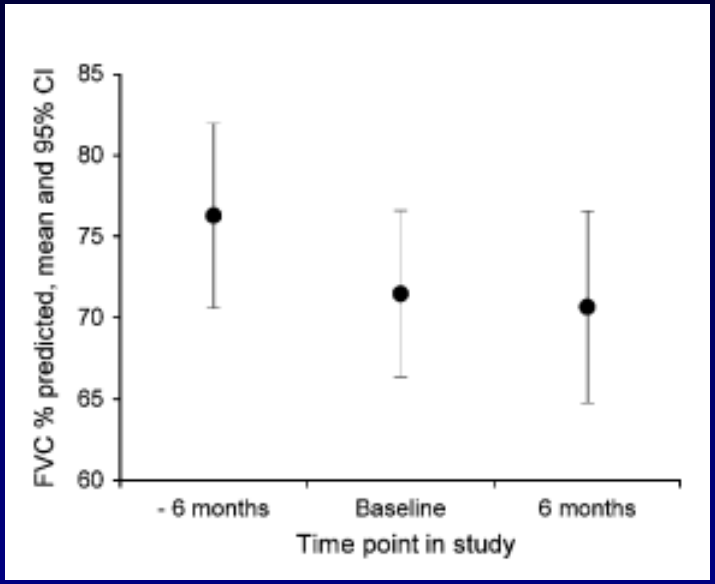
Early Experience of Pirfenidone in Daily Clinical Practice in Belgium and The Netherlands: a Retrospective Cohort Analysis

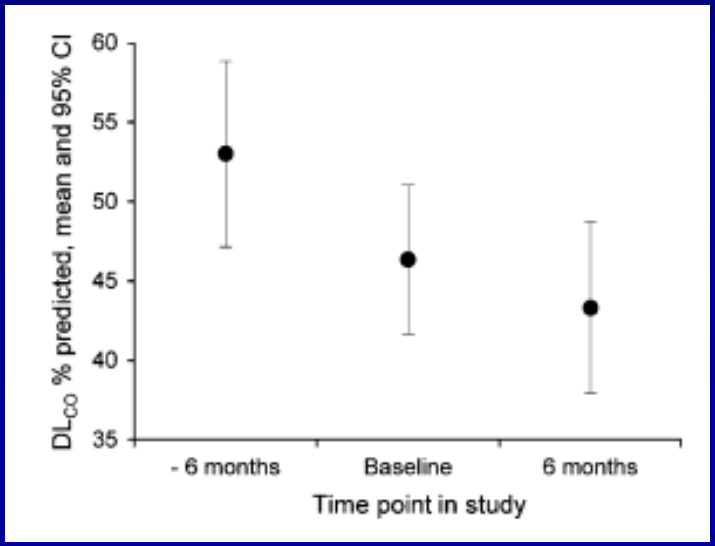
Wuyts WA et al. Adv Ther 2015; 32: 691

Clinical records of patients diagnosed with mild-to-moderate IPF and receiving pirfenidone treatment across three centers in Belgium and the Netherlands between April 2011 and October 2013 were retrospectively Collected.

63 patients enrolled.

In this clinical practice cohort, pirfenidone showed effectiveness and safety profiles consistent with those seen in the Phase III clinical study ASCEND
These results highlight the challenges and Benefits associated with pirfenidone treatment In clinical practice.

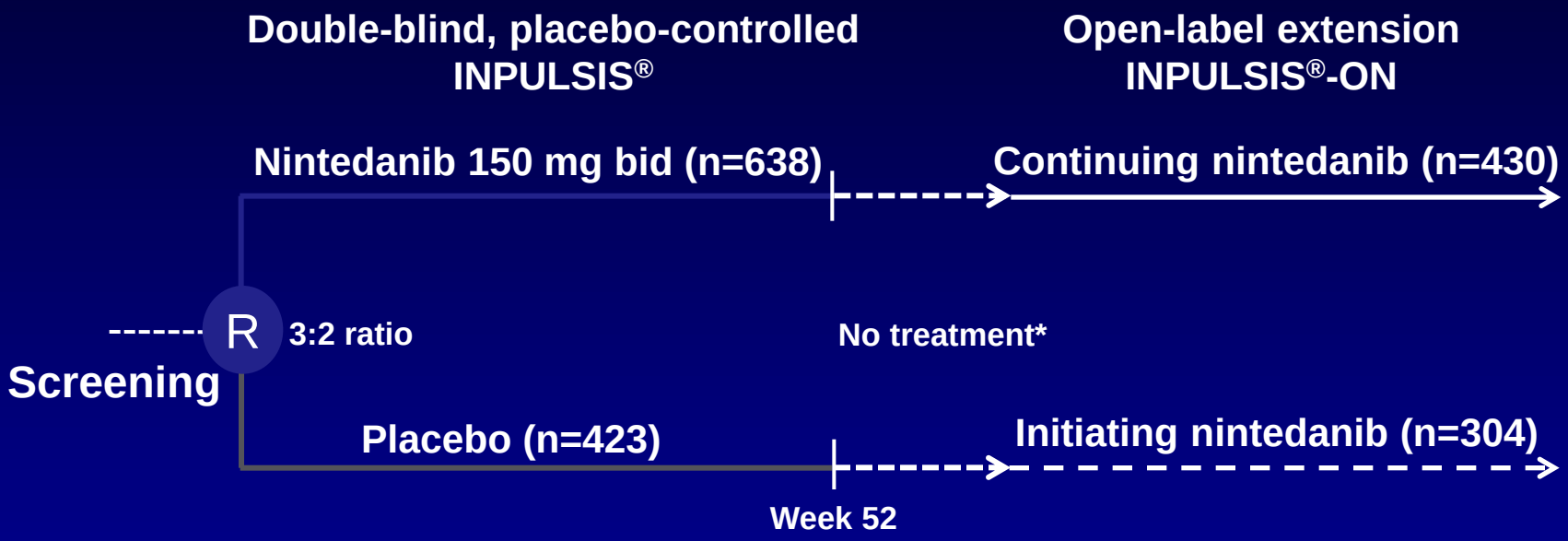




The new entry.....

Interim analysis of nintedanib in an open-label extension of the INPULSIS® trials (INPULSIS®-ON)

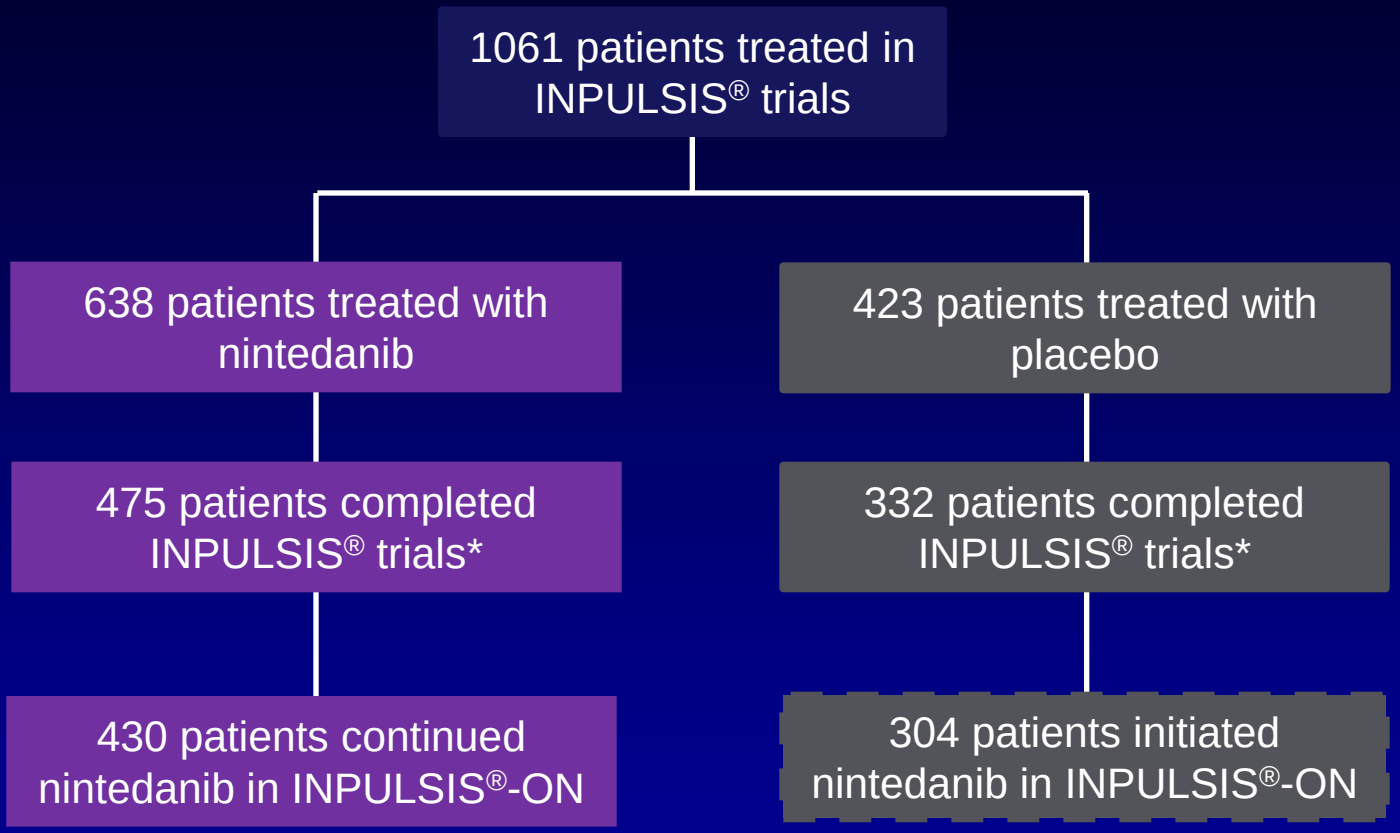
Interim analysis of nintedanib in an open-label extension of the INPULSIS trials (INPULSIS-ON)



- Patients who completed the 52-week treatment period and follow-up visit 4 weeks later in an INPULSIS® trial were eligible to enter INPULSIS®-ON
- Dose reduction to 100 mg bid or treatment interruption was allowed to manage adverse events; dose re-escalation to 150 mg bid was permitted

*Per protocol, the off-treatment period between INPULSIS® and INPULSIS®-ON could be between 4 and 12 weeks.

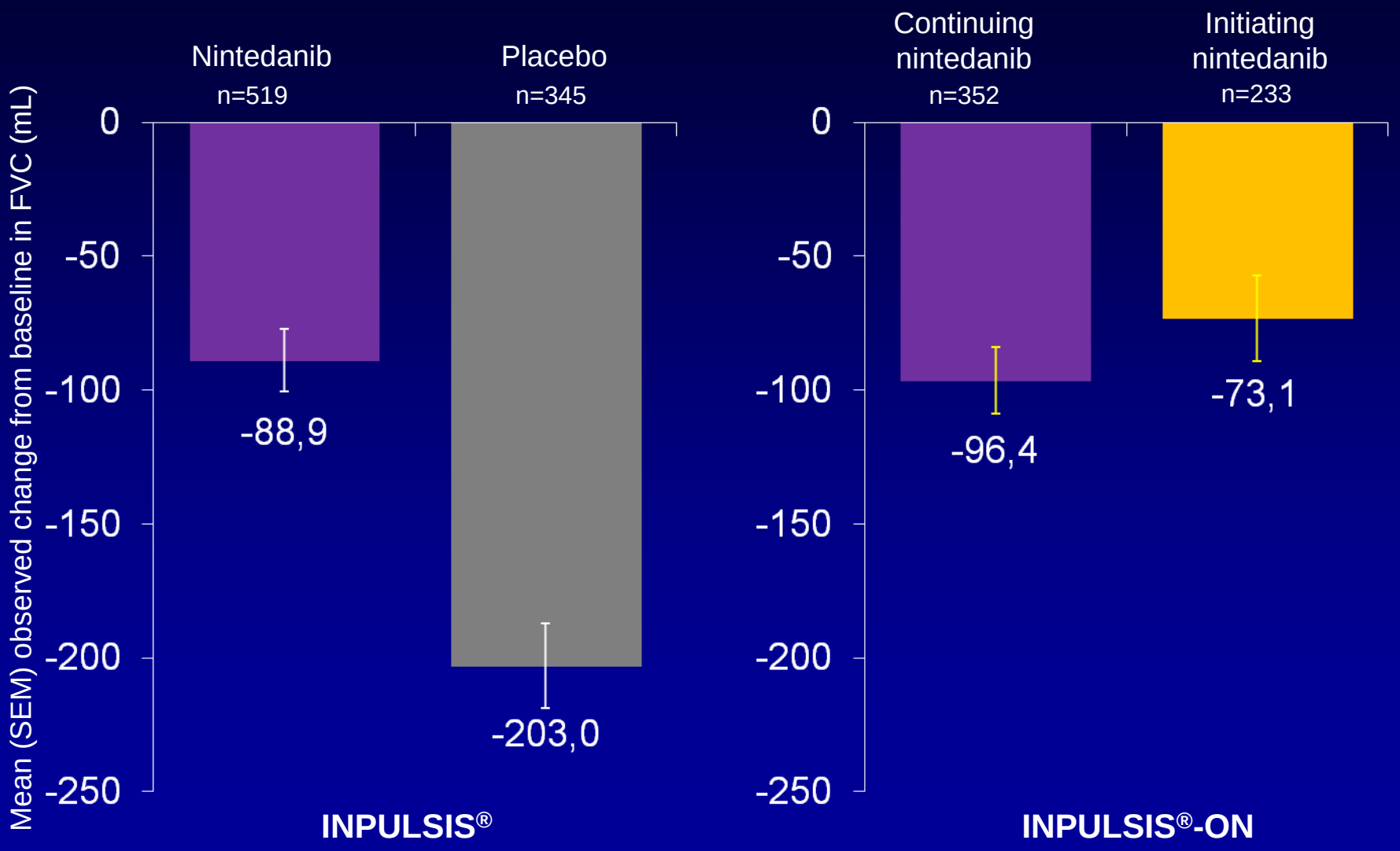
Patient disposition in INPULSIS® and INPULSIS®-ON



91% of eligible patients were treated in INPULSIS®-ON

*Did not prematurely discontinue trial medication and completed planned observation time.

Change from baseline in FVC at week 52 in INPULSIS® and at week 48 in INPULSIS®-ON



Adverse events

N (%)	INPULSIS®		INPULSIS®-ON	
	Nintedanib (n=638)	Placebo (n=423)	Continuing nintedanib (n=430)	Initiating nintedanib (n=304)
Exposure, months, mean (SD)	**10.3 (3.4)**	**10.8 (2.8)**	**17.2 (6.6)**	**16.0 (7.3)**
Adverse event(s)	609 (95.5)	379 (89.6)	399 (92.8)	294 (96.7)
Severe adverse event(s)	174 (27.3)	99 (23.4)	130 (30.2)	104 (34.2)
Adverse event(s) leading to drug discontinuation	123 (19.3)	55 (13.0)	86 (20.0)	87 (28.6)
Serious adverse event(s)	194 (30.4)	127 (30.0)	180 (41.9)	120 (39.5)
Fatal adverse event(s)	37 (5.8)	31 (7.3)	45 (10.5)	30 (9.9)

A severe adverse event was defined as an event that was incapacitating or that caused an inability to work or to perform usual activities. A serious adverse event was defined as an event that resulted in death, was immediately life-threatening, resulted in persistent or clinically significant disability or incapacity, required or prolonged hospitalisation, was related to a congenital anomaly or birth defect, or was deemed serious for any other reason.

Most frequent adverse events

N (%)	INPULSIS®		INPULSIS®-ON	
	Nintedanib (n=638)	Placebo (n=423)	Continuing nintedanib (n=430)	Initiating nintedanib (n=304)
Exposure, months, mean (SD)	**10.3 (3.4)**	**10.8 (2.8)**	**17.2 (6.6)**	**16.0 (7.3)**
Diarrhoea	398 (62.4)	78 (18.4)	272 (63.3)	195 (64.1)
Cough	85 (13.3)	57 (13.5)	76 (17.7)	46 (15.1)
Nausea	156 (24.5)	28 (6.6)	61 (14.2)	58 (19.1)
Progression of IPF*	64 (10.0)	61 (14.4)	72 (16.7)	46 (15.1)
Nasopharyngitis	87 (13.6)	68 (16.1)	60 (14.0)	43 (14.1)
Bronchitis	67 (10.5)	45 (10.6)	66 (15.3)	36 (11.8)
Dyspnoea	49 (7.7)	48 (11.3)	59 (13.7)	39 (12.8)
Weight decreased	62 (9.7)	15 (3.5)	36 (8.4)	48 (15.8)
Decreased appetite	68 (10.7)	24 (5.7)	32 (7.4)	45 (14.8)
Upper respiratory tract infection	58 (9.1)	42 (9.9)	48 (11.2)	26 (8.6)
Vomiting	74 (11.6)	11 (2.6)	41 (9.5)	27 (8.9)

Adverse events reported in >10% of patients in any treatment group in INPULSIS® or INPULSIS®-ON.
*Corresponds to MedDRA term ‘IPF’, which included disease worsening and IPF exacerbations.

Conclusions

- An interim analysis of the INPULSIS®-ON trial confirmed the long-term efficacy and safety of nintedanib in patients with IPF:
  - The decline in FVC in patients continuing or initiating nintedanib in INPULSIS®-ON was similar to the decline in FVC with nintedanib in INPULSIS®
  - This suggests that the treatment effect of nintedanib on slowing disease progression persists for 2 years
  - Long-term nintedanib treatment (up to 40 months) had a manageable safety and tolerability profile, with no new safety signals identified

Recently nintedanib 150 mg twice daily in patients with IPF has been approved in UE and an open label compassionate program started in Italy

Our experience with open label compassionate use programm with nintedanib

- 32 patients enrolled, 27 male

Drug discontinued in 3 patients (2 for diarrhea, 1 for liver enzymes increase). 3 patients died: 2 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

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

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

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.

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.

GAP index and stage at baseline

	Predictor	N (%)
G - Gender	Female	5 (15.6)
	Male	27 (84.4)
A – Age	<=60	2 (6.25)
	61-65	4 (12.5)
	65+	26 (81.25)
P - Physiology	**FVC %**	
	>=0.75	8 (25)
	0.50-0.75	13 (41)
	<0.50	11 (34)
	DLCO %	
	>0.55	1 (3.1)
	0.36-0.55	7 (21.9)
	<=0.35	13 (40.6)
	No performed	11 (34.4)

	Predictor	N (%)	Median, (Min-Max)
GAP index			5.5 (2-8)
Stage	I (GAP index 0-3)	4 (12.5)	
	II (GAP index 4-5)	10 (31.2)	
	III (GAP index 6-8)	18 (56.3)	

Severe disease

Echocardiographic evaluation:

Cut-off 50 mmHg:

PAPS $<$ 50 mmHg in 24 patients

PAPs $\geq$ 50 mmHg in 8 patients

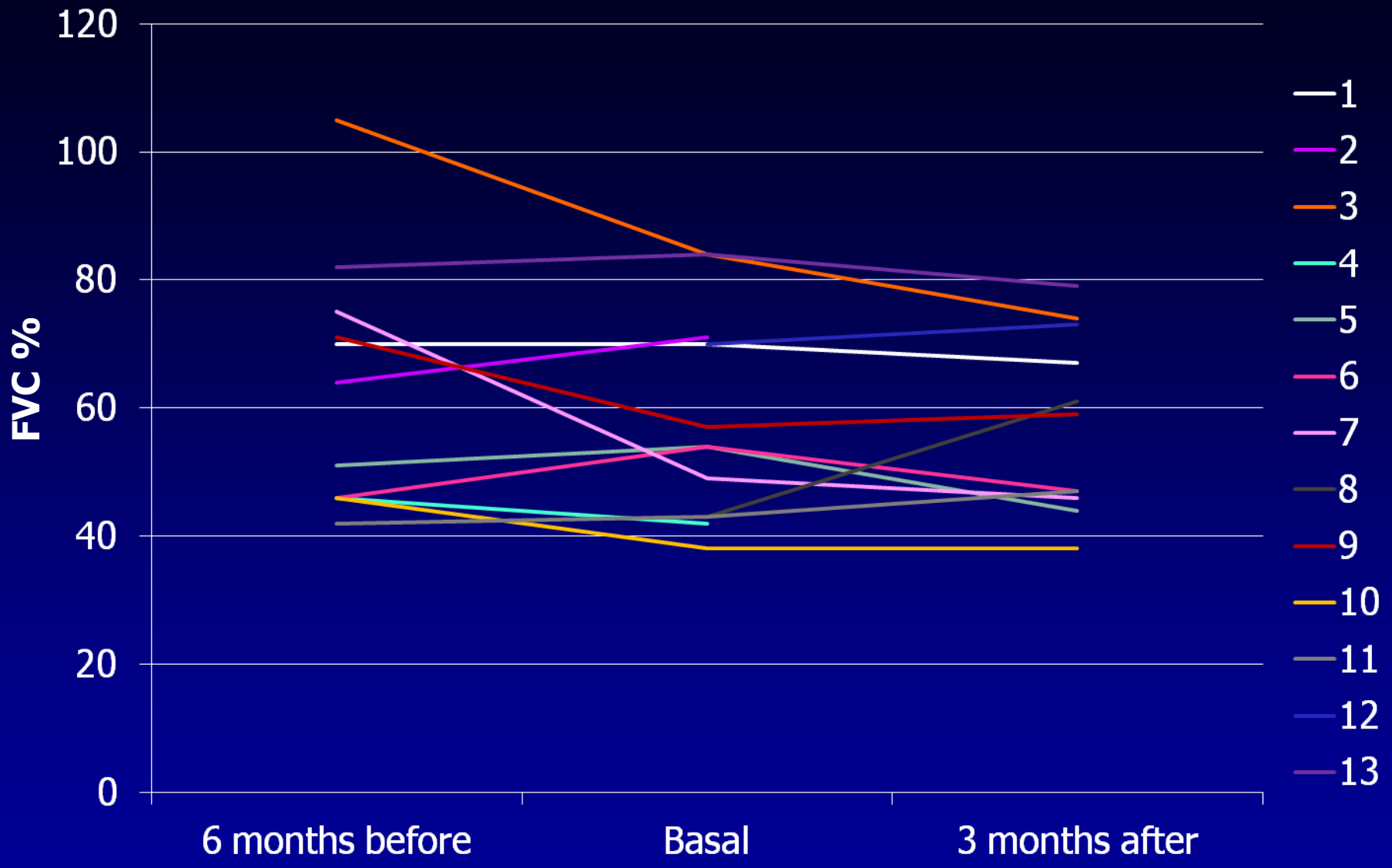
Cut-off 35 mmHg:

PAPS < 35 mmHg in 14 patients

PAPS $\geq$ 35 mmHg in 18 patients

Our experience with open label compassionate use programm with nintedanib

- 13 patients with 3 months follow-up, 11 male
- Basal mean FVC 58.4% (38-84, min – max) Mean FVC at 3 months 57.7% (38-79, min – max)
- Only 4 patients performed DLCO
- Only 4 patients with 6 months follow-up



Mean FVC% 6 months before: 63.4%, basal FVC%: 58.4, FVC% 3 months after: FVC 57.7

After 3 months with nintedanib therapy we observed FVC decrease $\geq$ 10% in 4 patients and stable FVC in 9 patients

Neither pirfenidone nor nintedanib is a cure for IPF

Therefore, the comprehensive care of patients with IPF remains essential, which includes careful risk prediction, management of comorbidities and physical debility, monitoring for disease progression, and timely referral for lung transplantation.

There is the need for further research into interventions to help alleviate or control symptoms of this debilitating condition, in particular pulmonary rehabilitation programmes, palliative care and end-of-life support

It is also critical that we continue to encourage patients with IPF to participate in clinical trials of new drug agents that will undoubtedly add benefit to these initial therapies.

Patients with IPF continue to await a cure for their disease, and the unmet medical needs remains high.

With the emergence of novel and effective therapy for patients with IPF, it is clear that IPF care will evolve significantly over the next few years.