7TH

INTERNATIONAL MEETING ON PULMONARY RARE DISEASES AND ORPHAN DRUGS

PROGRAM

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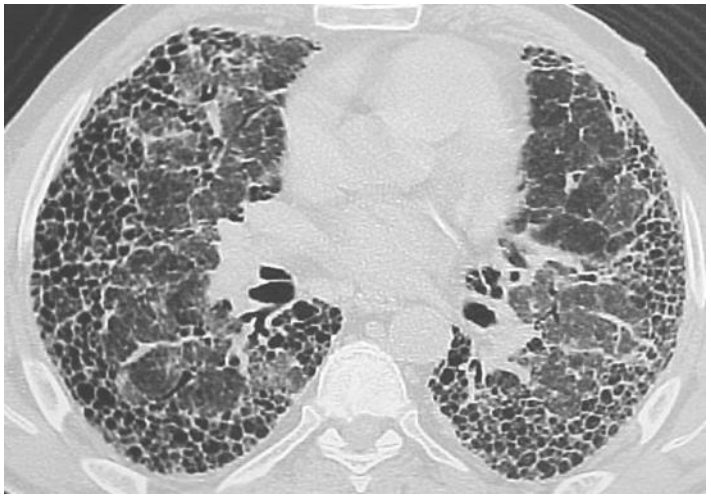
Severe IPF: What to do ?



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Conflict of interests disclosures

Actelion

Boehringer Ingelheim

Roche

How to treat severe IPF?

Are pirfenidone and nintedanib indicated also in these patients?

- The patient populations in clinical trials are not representative of the whole IPF population
- Few patients in RCT 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 RCT than in clinical practice
- Screening failure in randomized trials is usually relevant

Pirfenidone

RECAP Study Background and rationale

- Data from controlled clinical studies on patients with more severe lung function impairment are very limited
- Patients with IPF who had %FVC < 50% or $\%DL_{CO}$ < 35% at screening were excluded from the pirfenidone Phase III CAPACITY trials
  - Inclusion criteria for CAPACITY (004/006)[1]:
    - %FVC ≥ 50%
    - $\%DL_{CO}$ ≥ 35%
    - Either %FVC or $\%DL_{CO}$ ≤ 90%

$\%DL_{CO}$, percent predicted diffusing capacity for carbon monoxide; %FVC, percent predicted forced vital capacity; IPF, idiopathic pulmonary fibrosis.

1. Noble PW, et al. *Lancet.* 2011;377:1760-1769;

Study objective

- To assess the efficacy and safety of pirfenidone in patients with more severe lung function impairment (%FVC < 50% and/or %DL_{CO} < 35%) in the open-label extension study of the pirfenidone Phase III trials (RECAP [012])
  - RECAP was conducted between September 2008 and June 2015 in 1058 patients with IPF who completed ASCEND or CAPACITY

Study design

- Patient population
  - Patients in CAPACITY were randomized to receive placebo or pirfenidone; patients who enrolled in RECAP then received open-label pirfenidone 2403 mg/day
  - Patients from ASCEND were not included due to lack of FVC follow-up data

- Outcomes assessed during the subsequent 180-week follow up:
  - FVC decline from baseline
  - Adverse events

* Only patients missing both FVC and DL_{CO} values were excluded.

Costabel U. et al. ERS 2016

Patient categorization by lung function impairment at entry into RECAP

– Patients were categorized according to baseline %FVC and $\%DL_{CO}$:

More Severe Lung Function Impairment*		
%FVC		$\%DL_{CO}$
< 50%	AND/OR	< 35%
< 50%	AND	Not available
Not available	AND	< 35%

Less Severe Lung Function Impairment*		
%FVC		$\%DL_{CO}$
≥ 50%	AND	≥ 35%
≥ 50%	AND	Not available
Not available	AND	≥ 35%

Costabel U. et al. ERS 2016

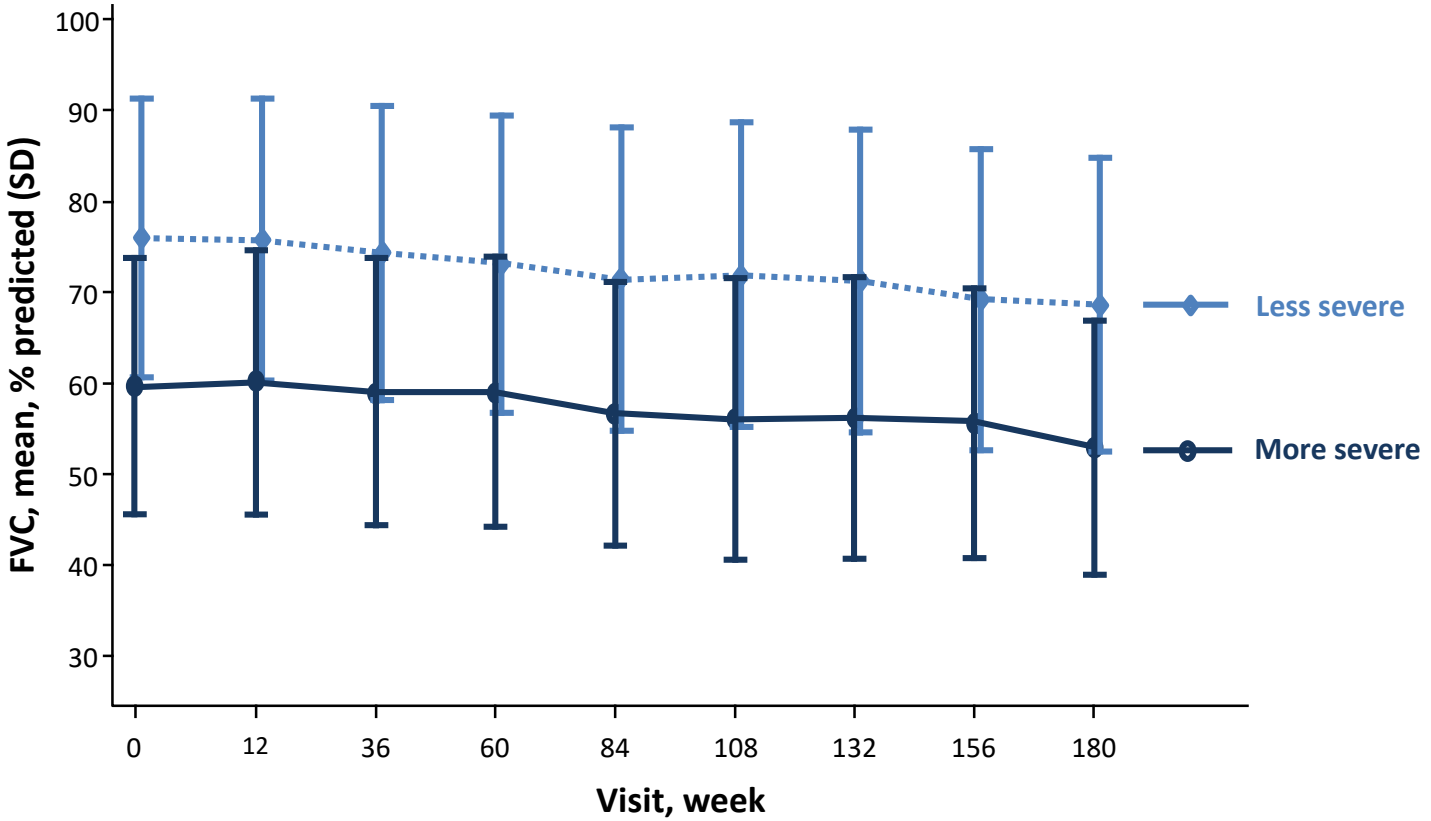
Demographics and baseline characteristics at entry into RECAP

Characteristic	More Severe Lung Function Impairment (n = 187)		Less Severe Lung Function Impairment (n = 409)	
	Treatment Prior to RECAP			
	Pirfenidone* (n = 100)	Placebo (n = 87)	Pirfenidone* (n = 225)	Placebo (n = 184)
Age, median, years	69.0	69.0	68.0	69.0
Male, %	72.0	78.2	70.7	70.7
White, %	98.0	100	97.8	96.7
FVC, mean, % predicted	61.0†	58.4	76.0	76.1
$DL_{CO,}$ mean, % predicted	29.5	28.8	46.7	47.4

* "More severe": 2403 mg/day, n = 84; 1197 mg/day, n = 16; "Less severe": 2403 mg/day, n = 173; 1197 mg/day, n = 52.
† n = 61.
Baseline is defined as the last available assessment prior to first dose.

Costabel U. et al. ERS 2016

Course of mean FVC over time by severity of lung function impairment at baseline in RECAP



Number of patients*									
Less severe	400	392	376	343	318	287	258	237	208
More severe	184	170	142	117	97	80	67	60	46

* Patients with missing baseline values were excluded.

Costabel U. et al. ERS 2016

Annual rate of decline in FVC and by treatment during RECAP

Parameter	More Severe Lung Function Impairment (n = 187)		Less Severe Lung Function Impairment (n = 409)	
	Treatment Prior to RECAP			
	Pirfenidone (n = 100)	Placebo (n = 87)	Pirfenidone (n = 225)	Placebo (n = 184)
Baseline FVC, mean, % predicted	61.0	58.4	76.0	76.1
Annual rate of decline (180 weeks) in RECAP, % FVC (SE)	3.79 (0.40)	3.35 (0.43)	3.85 (0.24)	3.85 (0.27)

Costabel U. et al. ERS 2016

Adverse events during RECAP

Preferred Term, n (%)	More Severe Lung Function Impairment (n = 187)	Less Severe Lung Function Impairment (n = 409)
Nausea	56 (29.9)	154 (37.7)
Diarrhea	44 (23.5)	123 (30.1)
Rash	40 (21.4)	106 (25.9)
Vomiting	26 (13.9)	66 (16.1)
Photosensitivity	16 (8.6)	42 (10.3)

- Both patient groups exhibited a similar safety profile

* All related terms grouped to nausea, rash, diarrhea, vomiting and photosensitivity.

Costabel U. et al. ERS 2016

Reasons for treatment discontinuation during RECAP

Reason, n (%)	More Severe Lung Function Impairment (n = 187)		Less Severe Lung Function Impairment (n = 409)	
	Treatment Prior to RECAP			
	Pirfenidone (n = 100)	Placebo (n = 87)	Pirfenidone (n = 225)	Placebo (n = 184)
All discontinuations	**70 (70.0)**	**64 (73.6)**	**93 (41.3)**	**84 (45.7)**
Adverse event	40 (40.0)	41 (47.1)	53 (23.6)	57 (31.0)
Death	**12 (12.0)**	**8 (9.2)**	**6 (2.7)**	**7 (3.8)**
Lung transplantation	7 (7.0)	5 (5.7)	13 (5.8)	1 (0.5)
Withdrawal by patient	7 (7.0)	9 (10.3)	20 (8.9)	15 (8.2)
Physician decision	4 (4.0)	1 (1.1)	1 (0.4)	2 (1.1)
Other	0	0	0	2 (1.1)

Costabel U. et al. ERS 2016

Limitations

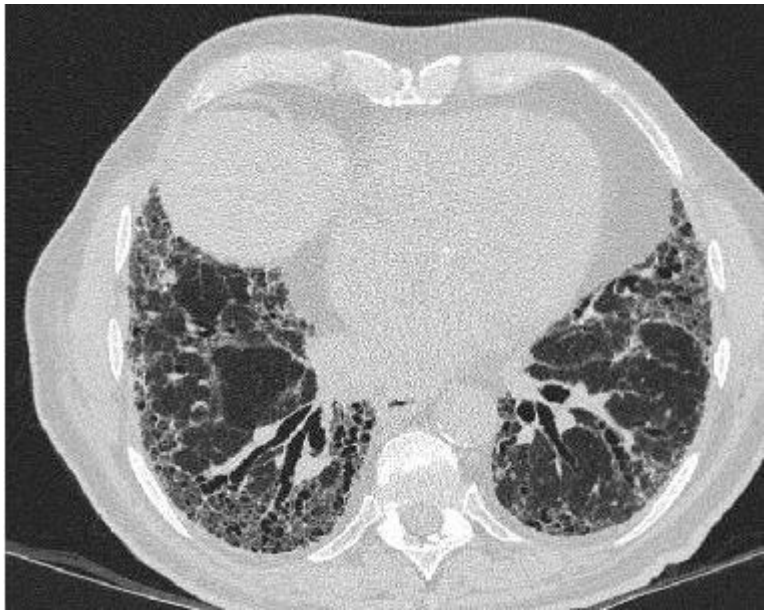
- Number of patients in the more severe subgroup is limited
- All data analyses are post hoc exploratory
- Pts were well selected as enrolled from randomized clinical trials

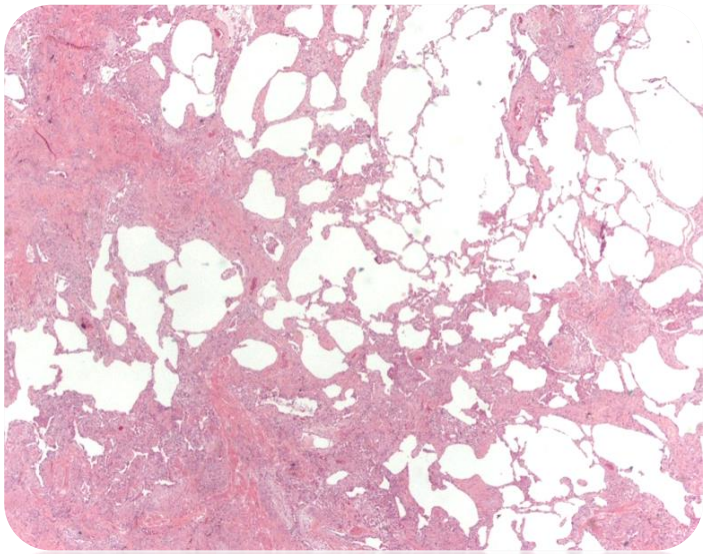
Conclusions

- Long-term treatment with pirfenidone resulted in similar rates of decline in patients with more severe lung function impairment and those with less severe lung function impairment
- Safety profiles were comparable between the 2 patient populations
- These data suggest that pirfenidone could be an acceptable treatment also in patients **with more severe** lung function impairment

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

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;

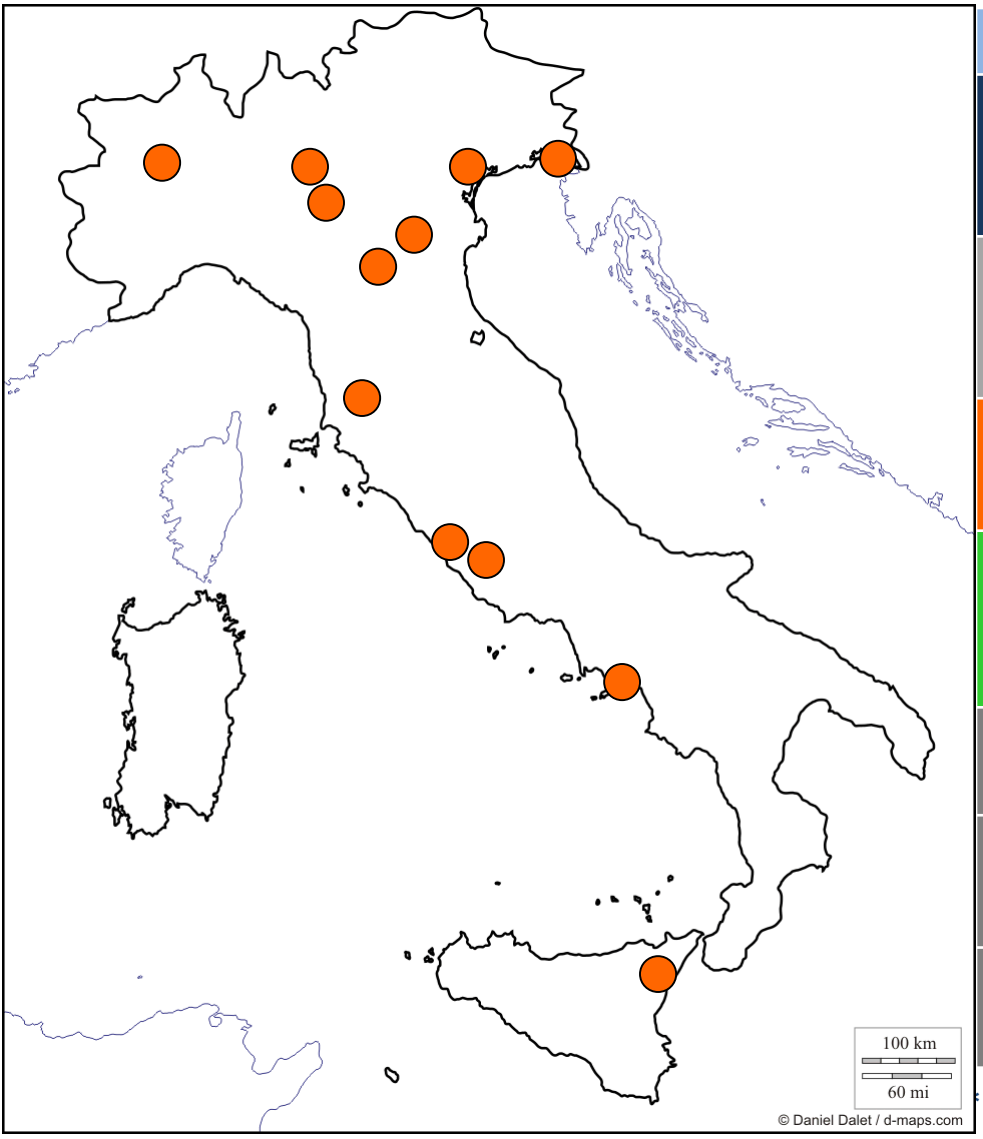
Exclusion criteria: not availability of functional follow-up data at least 12 months before and at least 12 months after starting PT;

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.

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)
Steroids	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)

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

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)	

21/ 128 pts had a FVC < 50% and/or a Dlco < 35%

8 Pts were in GAP 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;

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;

FVC% measured one year before pirfenidone therapy (1-yr before), at the time of treatment entry (baseline), and one year after therapy initiation (1-yr after) in patients stratified by severity in the year before treatment.

		GRUPPO 1 (FVC%<50% and/or DLCO<=35%) N=21				GRUPPO 2 N=107			
Parameter	**Time**	**Mean* (95% CI)**	**Change (%)**	**Difference in change (%)**	**p-value§**	**Mean* (95% CI)**	**Change (%)**	**Difference in change (%)**	**p-value§**
FVC (% of predicted)	1-yr before	72 (63, 81)	-	-		82 (78, 86)	-	-	
	baseline	68 (60, 75)	-5.5%**	-		77 (74, 80)	-6.1%**	-	
	1-yr after	65 (56, 73)	-4.4%***	1.1%	0.689	76 (72, 79)	-1.2%***	4.9%	0.066
		p-value for homogeneity of difference in % changes between strata:				*0.739*			

*Based on predicted values at 1-yr before, at baseline and at 1-yr after therapy initiation, as estimated from a linear mixed model

** % change during pre-treatment period: (baseline - 1yr before)/(1yr before)

*** % change during follow-up period: (1yr after -baseline)/(baseline)

§Based on the null hypothesis that % change over pre-treatment period = % change over follow-up period

Conclusions

In this real life national experience:

→ pirfenidone 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);
- No significant difference were detected in the slope of decline of FVC in more severe (21) and less severe (107)pts.

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

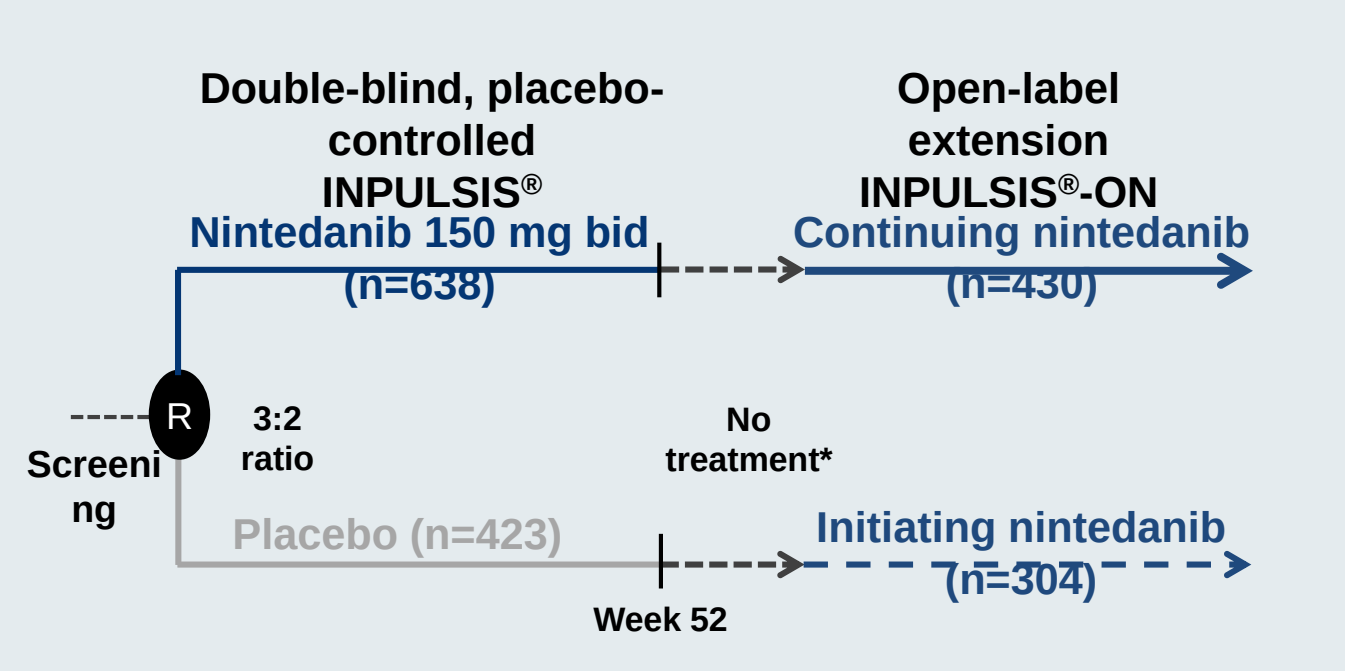
- The pirfenidone effect is more evident in moderate-severe patients;

This important findings need further investigations

Harari S. et al. Respir Med 2015 109; 904

Nintedanib

INPULSIS® and INPULSIS®-ON: trial designs



- 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

Wuyts WA, et al. Lung 2016

Aim and methods

Aim

- Patients with forced vital capacity (FVC) ≤50% predicted were not eligible to participate in the INPULSIS® trials, but could participate in INPULSIS®-ON if this threshold was reached during the INPULSIS® trials
- We assessed the efficacy and safety of nintedanib in INPULSIS®-ON in patients who started this open-label extension trial with FVC ≤50% and >50% predicted

Methods

- The first patient was enrolled into INPULSIS®-ON in July 2012. The interim database lock for this analysis was in November 2014
- A *post-hoc* subgroup analysis of patients with FVC ≤50% and >50% predicted at the start of INPULSIS®-ON was conducted
- Efficacy and safety analyses in INPULSIS®-ON were descriptive

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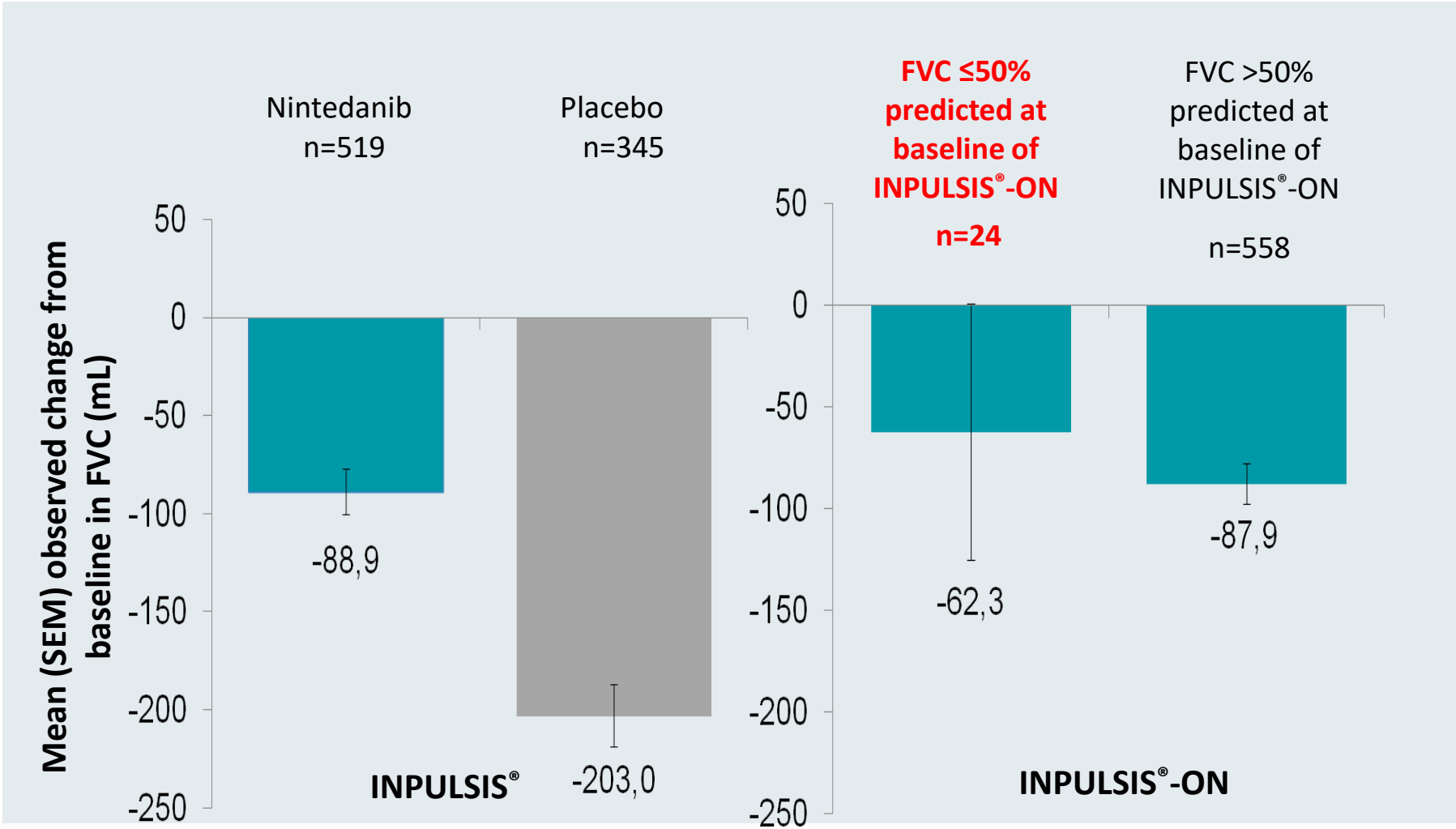
Change in FVC from baseline to week 52 of INPULSIS® and from baseline to week 48 of INPULSIS®-ON



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Adverse events in INPULSIS® and INPULSIS®-ON

	INPULSIS®		INPULSIS®-ON	
	Nintedanib (n=638)	Placebo (n=423)	FVC ≤50% predicted (n=41)	FVC >50% predicted (n=690)
Adverse event(s)	609 (95.5)	379 (89.6)	41 (100.0)	649 (94.1)
Severe adverse event(s)	174 (27.3)	99 (23.4)	**21 (51.2)**	**210 (30.4)**
Adverse event(s) leading to drug discontinuation	123 (19.3)	55 (13.0)	**17 (41.5)**	**155 (22.5)**
Serious adverse event(s)	194 (30.4)	127 (30.0)	**26 (63.4)**	**271 (39.3)**
Most frequent serious adverse events*				
Progression of IPF†	42 (6.6)	39 (9.2)	7 (17.1)	68 (9.9)
Dyspnea	3 (0.5)	6 (1.4)	5 (12.2)	20 (2.9)
Fatal adverse event(s)	37 (5.8)	31 (7.3)	9 (22.0)	66 (9.6)

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 hospitalization, was related to a congenital anomaly or birth defect, or was deemed serious for any other reason.
*Adverse events defined by MedDRA preferred terms reported in ≥10% of patients in any group.
†MedDRA term 'IPF', which included disease worsening and IPF exacerbations.

Wuyts WA, et al. Lung 2016

Most frequent adverse events leading to drug discontinuation in INPULSIS® and INPULSIS®-ON

	INPULSIS®		INPULSIS®-ON	
	Nintedanib (n=638)	Placebo (n=423)	FVC ≤50% predicted (n=41)	FVC >50% predicted (n=690)
Diarrhea	28 (4.4)	1 (0.2)	2 (4.9)	37 (5.4)
Progression of IPF*	13 (2.0)	21 (5.0)	**7 (17.1)**	**37 (5.4)**
Nausea	13 (2.0)	0 (0.0)	1 (2.4)	5 (0.7)
Fatigue	1 (0.2)	1 (0.2)	1 (2.4)	1 (0.1)
Weight decreased	6 (0.9)	1 (0.2)	1 (2.4)	6 (0.9)
Decreased appetite	9 (1.4)	1 (0.2)	0 (0.0)	3 (0.4)

*Corresponds to MedDRA term 'IPF', which included disease worsening and IPF exacerbations. Adverse events that led to permanent treatment discontinuation in ≥1% of patients in the nintedanib or placebo group in INPULSIS® and/or in the overall patient population in INPULSIS®-ON.

Wuyts WA, et al. Lung 2016

Conclusions

- In an interim analysis of the INPULSIS®-ON trial:
  - Decline in FVC in patients with FVC ≤50% and >50% predicted at the start of INPULSIS®-ON was similar to that in patients treated with nintedanib in INPULSIS®
  - Results suggest a similar benefit of nintedanib on disease progression in patients with FVC ≤50% and >50% predicted
  - In general, the adverse event profile was comparable between the subgroups, with no new signals identified; however, adverse events indicating underlying rapid disease progression, including fatal adverse events, were more frequent in the subgroup of patients with FVC ≤50% predicted at the start of INPULSIS®-ON
  - These data should be interpreted with caution as the analyses were exploratory and the number of patients with baseline FVC ≤50% predicted was **very** small

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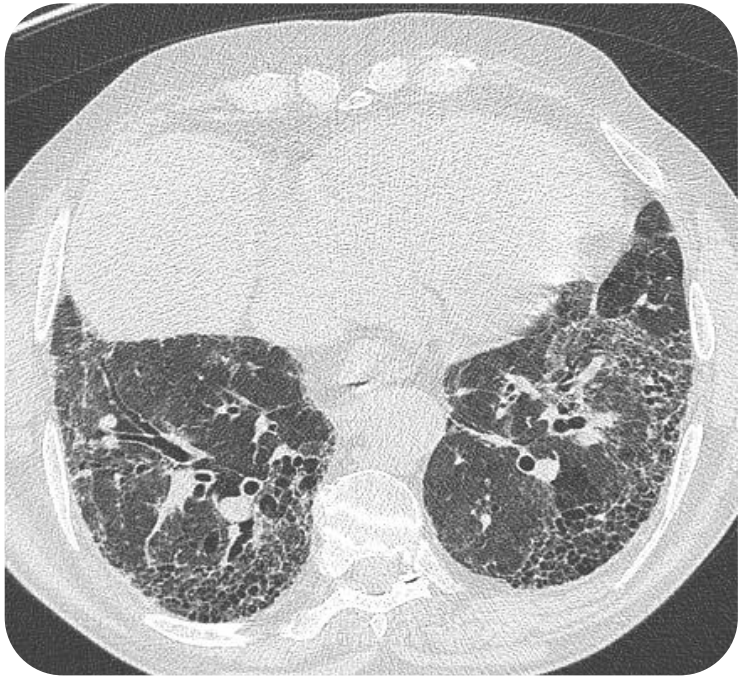
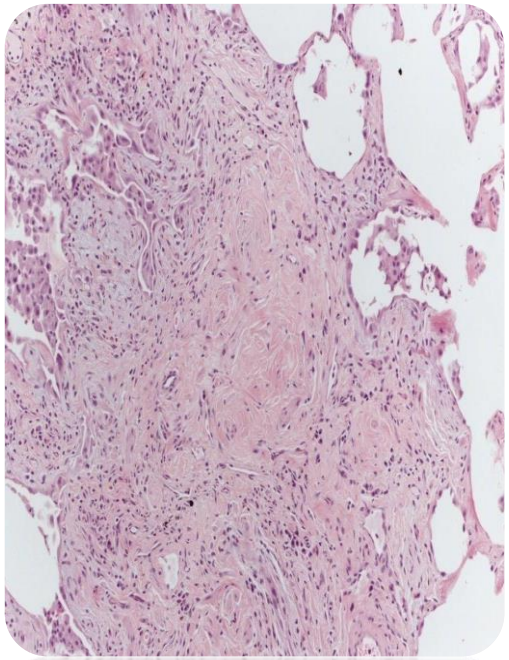
A real life multicenter national study on the use of nintedanib in moderate to severe IPF patients

Harari S, Caminati A, Poletti V, Confalonieri M, Gasparini S, Lacedonia D, Luppi F, Pesci A, Sebastiani A, Spagnolo P, Vancheri C, Balestro E, Bonifazi M, Cerri S, De Giacomi F, Della Porta R, Foschino Barbaro MP, Fui A, Pasquinelli P, Rosso R, Specchia C, Tomassetti S, Rottoli P.

in preparation





Matherials and Methods

Study design: we conducted a national, retrospective, unsponsored, observational study of patients with IPF treated with nintedanib

Inclusion criteria:

- Diagnosis (definite or probable) of IPF (according to 2011 IPF guidelines);
- Severe stage of disease (FVC ≤50% and/or DLCO ≤35%, at baseline)
- Availability of functional follow-up data at least 6 (± 2) months before, at the starting therapy point and at least 6 (± 2) months after starting therapy;

Exclusion criteria: not availability of functional follow-updata at least 6 months before and at least 6 months after starting therapy;

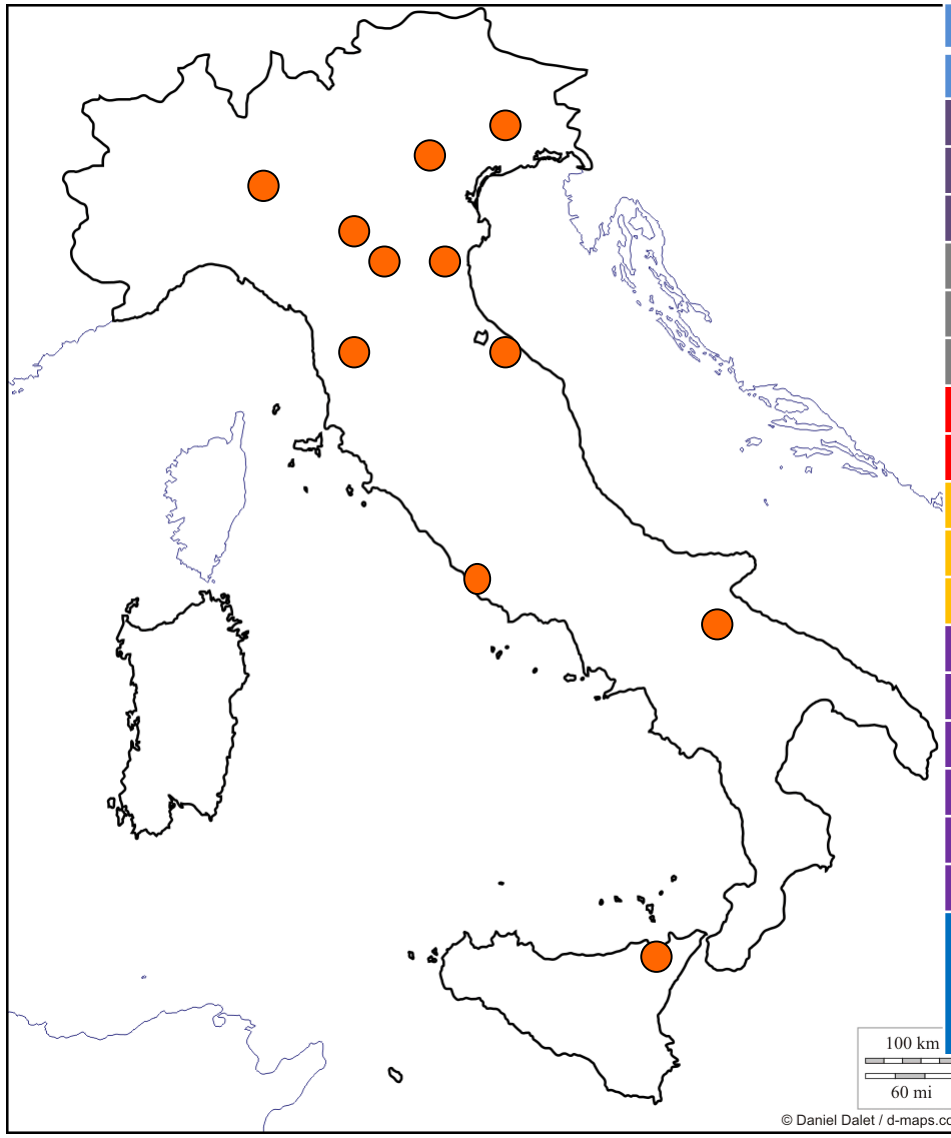
Matherials and Methods

- Primary End-point:
  - Evaluation of the slope of decline of FVC% 6-months before and 6-months after starting nintedanib;

- Secondary End-points:
  - Distance walked on 6MWT; DLCO change

Differences between post and pre-treatment changes of lung function parameters have been tested using Wilcoxon signed-rank test. In addition, the correlation between differences in changes between post and pre-treatment was evaluated using Spearman's correlation coefficient.

Table 1. Patients' characteristics at baseline – first nintedanib prescription (N=41)



Gender	Female	N 7 (17 %)
	Male	34 (83)
Age (years)*	55-64	7 (17)
	65-74	20 (49)
	75+	14 (34)
Smoking status	Ex-smoker	28 (68)
	Non smoker	11 (27)
	Smoker	2 (5)
Histological diagnosis	No	35 (85)
	Yes	6 (15)
Clinical/Radiological diagnosis	Definite UIP	26 (63)
	Probable UIP	13 (32)
	Possible UIP	2 (5)
Steroids	No	17 (41)
	Yes	24 (59)
Pirfenidone	No	34 (82.9)
	Yes	7 (17.1)
N-Acetylcysteine	No	36 (88)
	Yes	5 (12)
Time from diagnosis (months) **	0-5	11 (27)
	6-11	12 (29)
	>12	18 (44)

* mean age 70 years ± SD 8 years

** mean time from diagnosis 20 months ± SD 28 months

PFTs 6 months before, at baseline (first prescription nintedanib) and 6 months after

Parameter	N	Time	Mean (SD)	Changes (95%CI)	difference in changes (SD)	p-value
FVC	39	pre	2.05(0.58)	-	-	
	39	baseline	1.99(0.54)	-0.07(-0.15;0.02)	-	
	39	post	1.87(0.58)	-0.12(-0.20;-0.04)	-0.06(0.36)	0.22
FVC %	41	pre	61.83(15.25)	-		
	41	baseline	60.63(14.57)	-1.20(-3.78;1.39)		
	41	post	58.00(17.77)	-2.63(-5.21;-0.06)	-1.44(12.36)	0.34
DLCO %	26	pre	32.73(8.56)	-		
	26	baseline	26.54(5.70)	-6.19(-9.26;-3.12)		
	26	post	29.23(12.08)	2.69(-1.54;6.93)	8.88(15.30)	0.004
DLCO	22	pre	5.48(3.25)	-		
	22	baseline	4.50(2.77)	-0.98(-1.60;-0.37)		
	22	post	5.03(3.64)	0.53(-0.47;1.53)	1.51(3.46)	0.03
FEV1	37	pre	1.72(0.45)	-		
	37	baseline	1.70(0.46)	-0.02(-0.10;0.05)		
	37	post	1.60(0.44)	-0.11(-0.18;-0.03)	-0.08(0.38)	0.15
FEV1%	39	pre	67.62(16.02)	-		
	39	baseline	66.67(15.62)	-0.95(-4.43;2.53)		
	39	post	63.62(17.66)	-3.05(-5.64;-0.46)	-2.10(15.62)	0.37
TLC	15	pre	3.85(1.13)	-		
	15	baseline	3.78(1.03)	-0.07(-0.34;0.20)		
	15	post	3.73(1.01)	-0.05(-0.48;0.38)	-0.02(1.07)	1
TLC%	17	pre	59.06(13.73)	-		
	17	baseline	58.71(13.46)	-0.35(-4.34;3.64)		
	17	post	57.65(13.16)	-1.06(-6.60;4.48)	-0.71(15.74)	0.83

FVC/DLCO ratio

Pulmonary Hypertension and Pulmonary Function Testing in Idiopathic Pulmonary Fibrosis

Nathan SD et al. Chest 2007

"…In patients with diffuse systemic sclerosis, the FVC/DLCO has been demonstrated to be predictive of PH.

A FVC%/Dlco% ratio > 1.5 was associated with a nearly twofold-increased risk of PH in IPF patients; however, a DLCO < 30% was also associated with a similar increased risk of PH

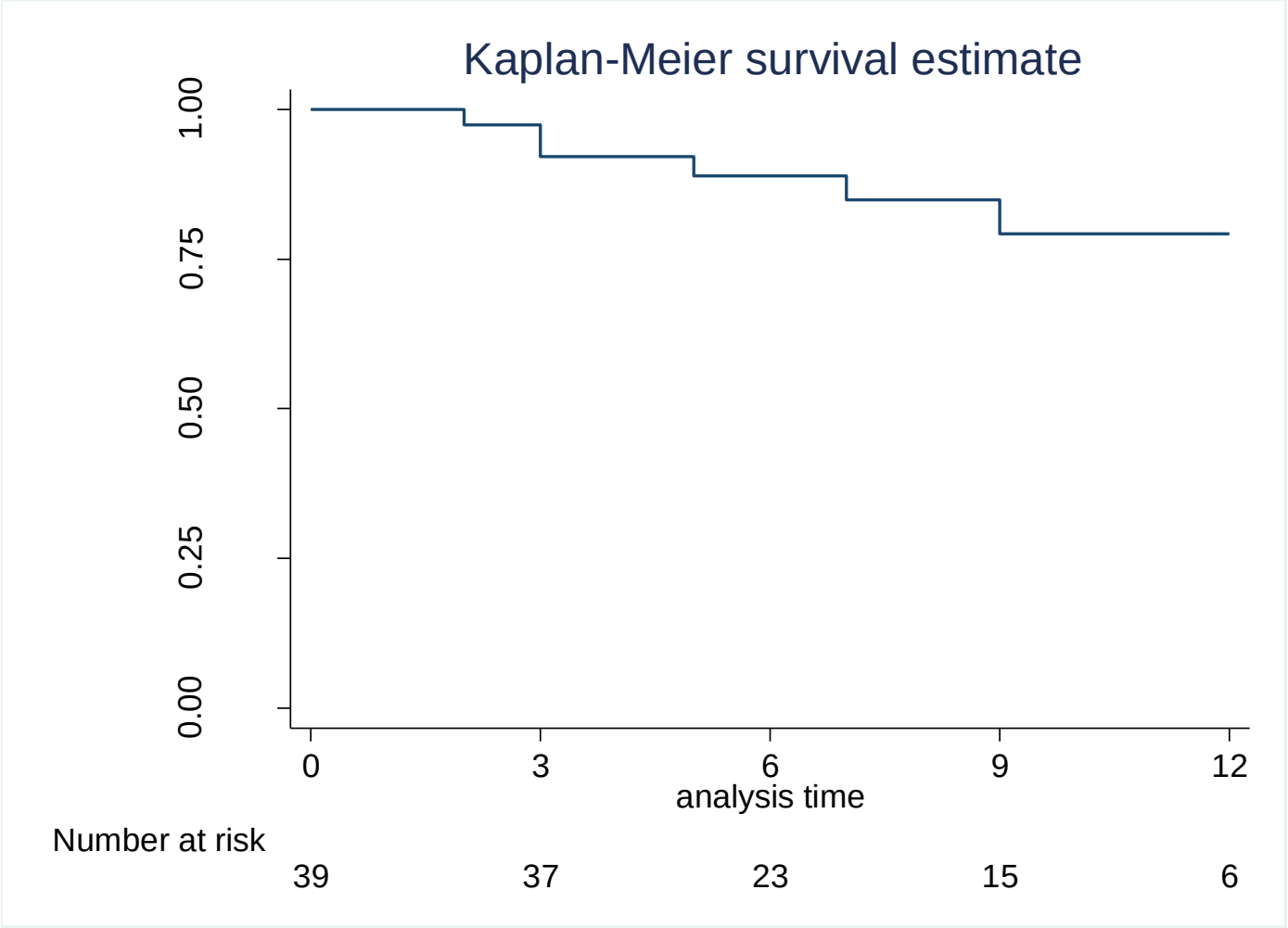
Utility of FVC/DLCO ratio to stratify the risk of mortality in unselected subjects with pulmonary hypertension

Lacedonia D et al Intern Emerg Med 2016

"…This is one of the first reports on FVC%/DLCO% as a prognostic marker for PH and mortality in an unselected population of consecutive outpatients with suspected PH…"

FVC%/DlCO% ratio

Parameter	N	Time	Mean (SD)	Changes (95%CI)	difference in changes(SD)	p-value
FVC%/DLCO%	26	pre	2.17 (0.79)	-	-	
	26	baseline	2.60 (0.97)	0.43 (0.20;0.66)	-	
	26	post	2.87 (2.42)	0.27(-0.55;1.10)	0.15(2.29)	**0.7332**



Survival at 3 moths **0.92** [95% CI: 0.78 - 0.97]
Survival at 6 months **0.89** [95% CI: 0.73 - 0.96]
Survival at 12 months **0.79** [95% CI: 0.58 - 0.91]

The near future

A phase IIb, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of sildenafil added to pirfenidone in patients with advanced idiopathic pulmonary fibrosis and intermediate or high probability of group 3 pulmonary hypertension

Study design Pirfenidone + Sildenafil

Phase 2 study

Patients between 40 and 80 ys

Diagnosis of IPF by the investigator for at least 3 months prior to screening (2011 guidelines)

Advanced IPF (defined as measurable DLCO $\leq$ 40% and intermediate or high probability of group 3 PH)

Participants will receive pirfenidone along with placebo matched to sildenafil for 52 weeks

Primary outcome: percentage of participants with disease progression, as determined by decline in 6MWT distance $\geq$15% from baseline, respiratory related non elective hospitalization or death from any cause

Efficacy and Safety of Nintedanib when co-administered with Sildenafil in Idiopathic Pulmonary Fibrosis patients with advanced lung function impairment

Study design Nintedanib + Sildenafil

Phase 3 study

Patients $\geq$ 40 yrs
Clinical diagnosis of IPF within the last 6 years (2011 guidelines)
DLCO $\leq$ 35%
Participants will receive nintedanib plus placebo or sildenafil
For 24 weeks

Primary outcome: change from baseline in SGRQ at week 12

Rationale

- PH is common in patients with IPF, and its prevalence increases with disease severity
- PH is a major contributor to morbidity and mortality in patients with advanced IPF, and it has an adverse impact on survival
- There are currently no approved therapies for PH secondary to lung disease (Group 3 PH), including PH secondary to IPF
- Phase II and III clinical trials in IPF, including pirfenidone and nintedanib trials have generally excluded patients with advanced disease and/or PH
- Patients with PH secondary to advanced IPF therefore represent a group with a high unmet medical need

Rationale

STEP-IPF: RCT, sildenafil studied in 180 patients with advanced IPF (DLCO< 35%), failed to meet its primary endpoint of ≥20% improvement in 6MWD; some secondary endpoints such as DLCO, dyspnoea, SaO2 and QoL achieved statistical significance

•Patients with RV systolic dysfunction (n = 119) treated with sildenafil experienced a 99 m lower decline in 6MWD and improved QoL compared with those who received placebo

Table 3—*Contrast Tests Comparing Effect of Sildenafil vs Placebo in Subjects With and Without RVH and RVSD on Change in 6MWD at 12 Wk*

Subgroup	Estimate for Difference in 6MWD Between Treatment Groups[a], m	95% CI		*P* Value for Contrast Test[a]	*P* Value for Interaction[b]
Sildenafil with no RVH vs placebo with no RVH	19.1	−18.1	56.4	.31	.28
Sildenafil with RVH vs placebo with RVH	78.5	−24.1	181.0	.13	
Sildenafil with no RVSD vs placebo with no RVSD	10.0	−27.9	47.8	.60	.04
Sildenafil with RVSD vs placebo with RVSD	99.3	22.3	176.2	.01	

Conclusions

Today, therapy of severe IPF is a challenge and an early diagnosis is mandatory

Preliminary data show that pirfenidone and nintedanib are active also in severe IPF

More data on real life and more severe pts are needed

Conclusions

The comprehensive care of patients with severe IPF remains essential, which includes management of comorbidities and physical debility 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 programs, palliative care and end-of-life support