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MEDICINA RESPIRATORIA IN ETA' GERIATRICA

IPF severa: cosa fare?

PNEUMOROMA
Verifiche ed aggiornamenti in Pneumologia

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Sergio Harari
U.O. di Pneumologia
UTIR Servizio di Fisiopatologia
Respiratoria e Emodinamica Polmonare
Ospedale S. Giuseppe MultiMedica
Milano

Conflict of interests disclosures

Actelion

Boehringer Ingelheim

InterMune

Roche

IPF: Where we are today

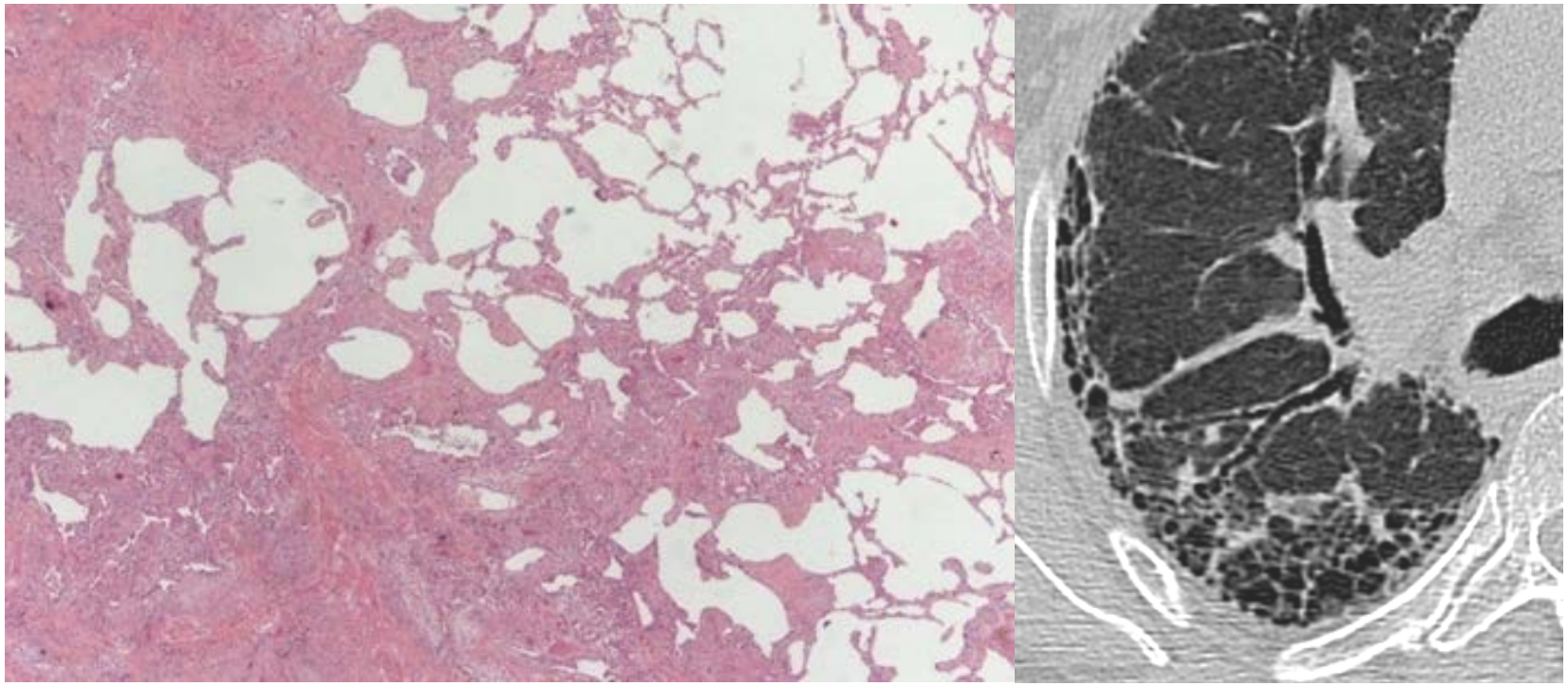
- It is clear that treatment decisions and the clinical management of patients with IPF should be based primarily on the findings of randomized controlled trials, and also, to a certain extent, on expert opinion

- 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 clinical 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

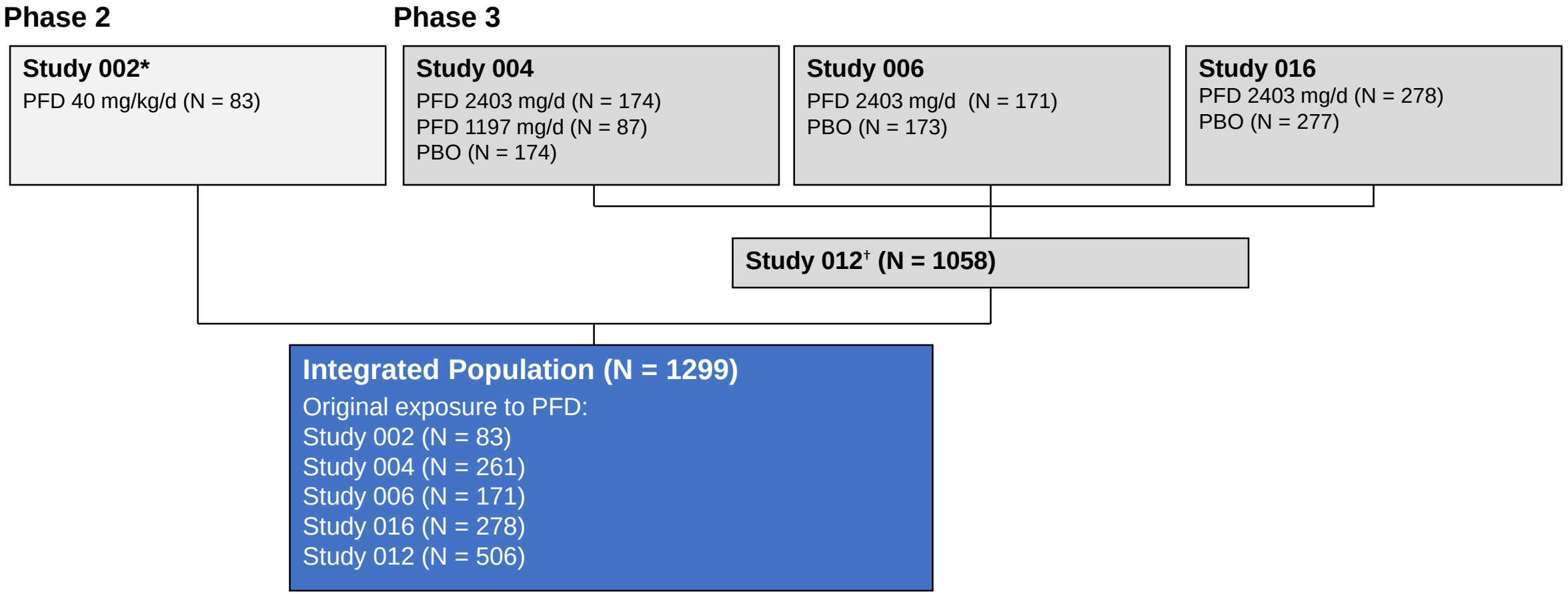
How to treat severe IPF?

Are pirfenidone and nintedanib indicated also in these patients?

Pirfenidone

Results

Study profile



* Study 002 participants received a daily dose of up to 3600 mg/d with an actual mean daily dose that ranged from 770 to 3600 mg/d.
† 506 patients initially received placebo and rolled over to receive pirfenidone.
PBO, placebo; PFD, pirfenidone.

Lancaster et al. BMJ Open Resp.Res.2016 Jan 12;3(1)

Results

Demographics and Baseline Characteristics

Characteristic*†	Integrated Population (N = 1299)	Phase 3 Trials[1,2]	
		Pirfenidone (N = 623)	Placebo (N = 624)
Age, years	68 (42-88)	68 (45-80)	68 (40-80)
Male, n %	968 (74.5)	463 (74.3)	465 (74.5)
Caucasian, n %	1229 (94.6)	592 (95.0)	590 (94.6)
FVC, % predicted, n (%)	69.1 (22-127)	71.1 (46-123)	69.8 (47-138)
< 50% predicted, n (%)	97 (7.5)	13 (2.1)	8 (1.3)
DL_{CO}, % predicted	43.3 (10-81)	44.0 (25-81)	44.3 (21-170)
< 35% predicted, n (%)	210 (16.2)	92 (14.8)	90 (14.4)
< 30% predicted, n (%)	79 (6.1)	19 (3.0)	16 (2.6)
Diagnosis			
IPF, n (%)	1297 (99.8)	623 (100)	624 (100)
Secondary pulmonary fibrosis, n (%)‡	2 (0.2)	0	0
Supplemental oxygen, n (%)	375 (28.9)	155 (24.9)	150 (24.0)
Time since diagnosis, years	1.9 (> 0-10)	1.1 (> 0-5)	1.1 (> 0-4)

* Values are expressed as the median (range) unless otherwise indicated.
† Measured at the time of first dose of study drug.
‡ Study 002.

1. King TE, et al. N Engl J Med. 2014; 370:2083-2092.
2. Noble PW, et al. Lancet. 2011;377:1760-1769.

DL_{CO}, diffusing capacity for carbon monoxide; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis.

Lancaster et al. BMJ Open Resp.Res.2016 Jan 12;3(1)

Conclusions

- These findings represent a comprehensive analysis of safety outcomes in a large and well-defined cohort of 1299 patients with IPF treated with pirfenidone
  - During this long-term, prospective follow-up of up to 9.9 years, pirfenidone was safe and generally well tolerated
- Gastrointestinal and skin-related events were among the most common adverse events
  - These adverse events were generally mild-to-moderate in severity and responsive to dose modification
- Elevations of aminotransferases typically occurred within the first 6 months of treatment
  - These elevations were generally transient, reversible with dose modification or discontinuation and without clinical sequelae

Lancaster et al. BMJ Open Resp.Res.2016 Jan 12;3(1)

RECAP Study Background and rationale

- 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%
- Data from controlled clinical studies on patients with more severe lung function impairment are limited[2]

$\%DL_{CO}$, 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; 2. Wuyts W, et al. *Lung.* 2016. (Epub ahead of print).

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.

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%

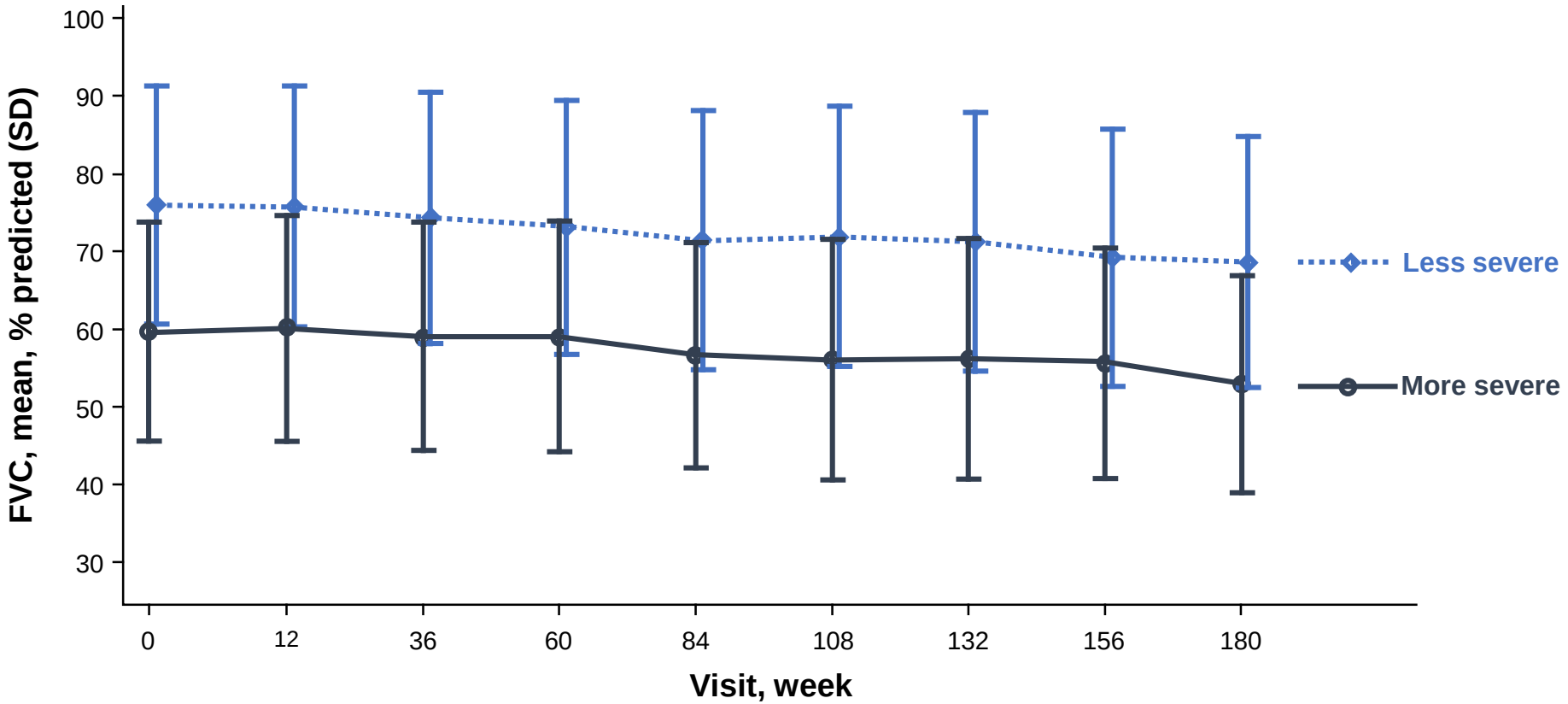
Less Severe Lung Function Impairment*		
%FVC		$\%DL_{CO}$
≥ 50%	AND	≥ 35%
≥ 50%	AND	Not available
Not available	AND	≥ 35%

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.

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.

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)

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.

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)

Limitations

- Number of patients in the more severe subgroup is small
- All data analyses are post hoc exploratory

Conclusions

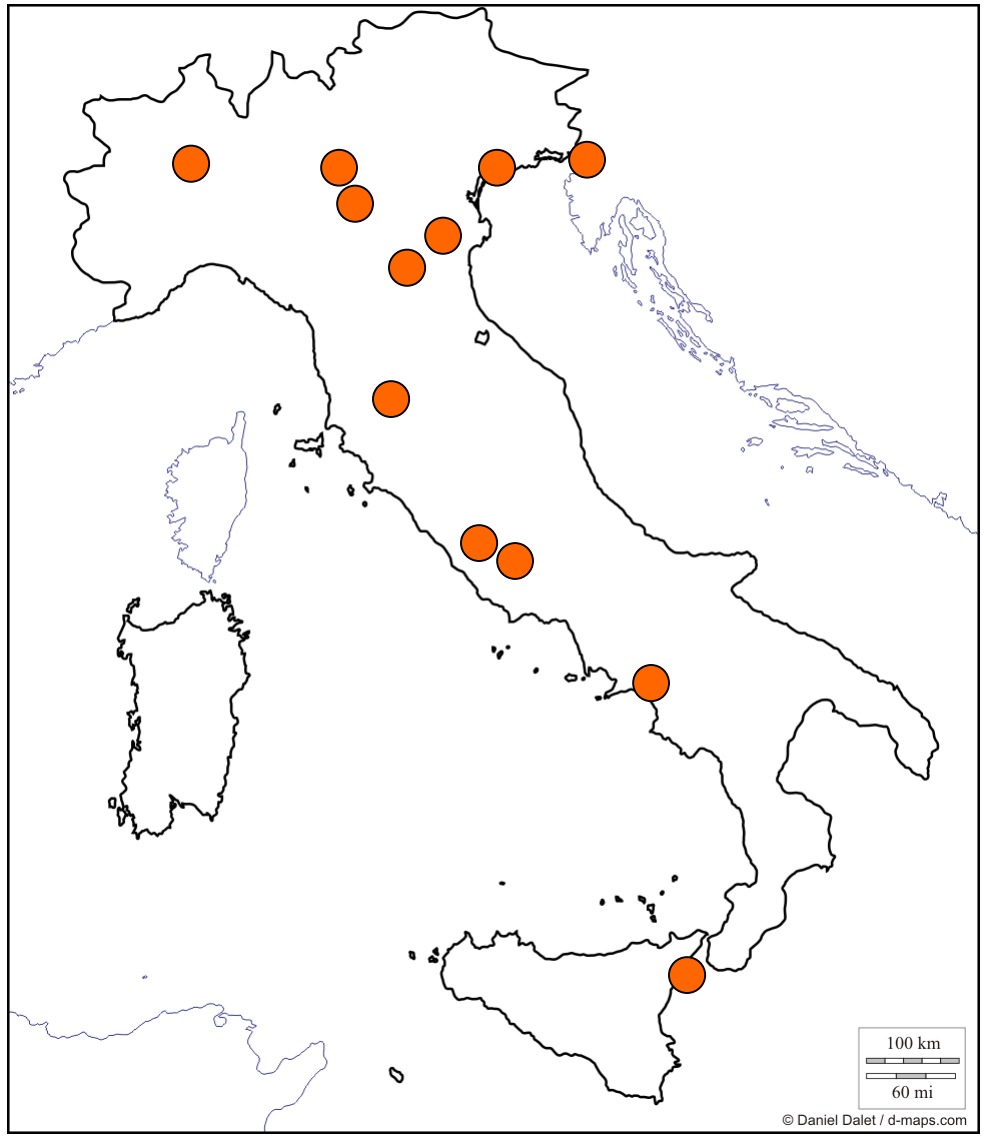
- Long-term treatment with pirfenidone resulted in similar rates of decline in patients with more severe lung function impairment and those with less severe lung function impairment
- Safety profiles were comparable between the 2 patient populations
- These data suggest that pirfenidone is an acceptable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

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)

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)	

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

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;

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

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;

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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;

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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

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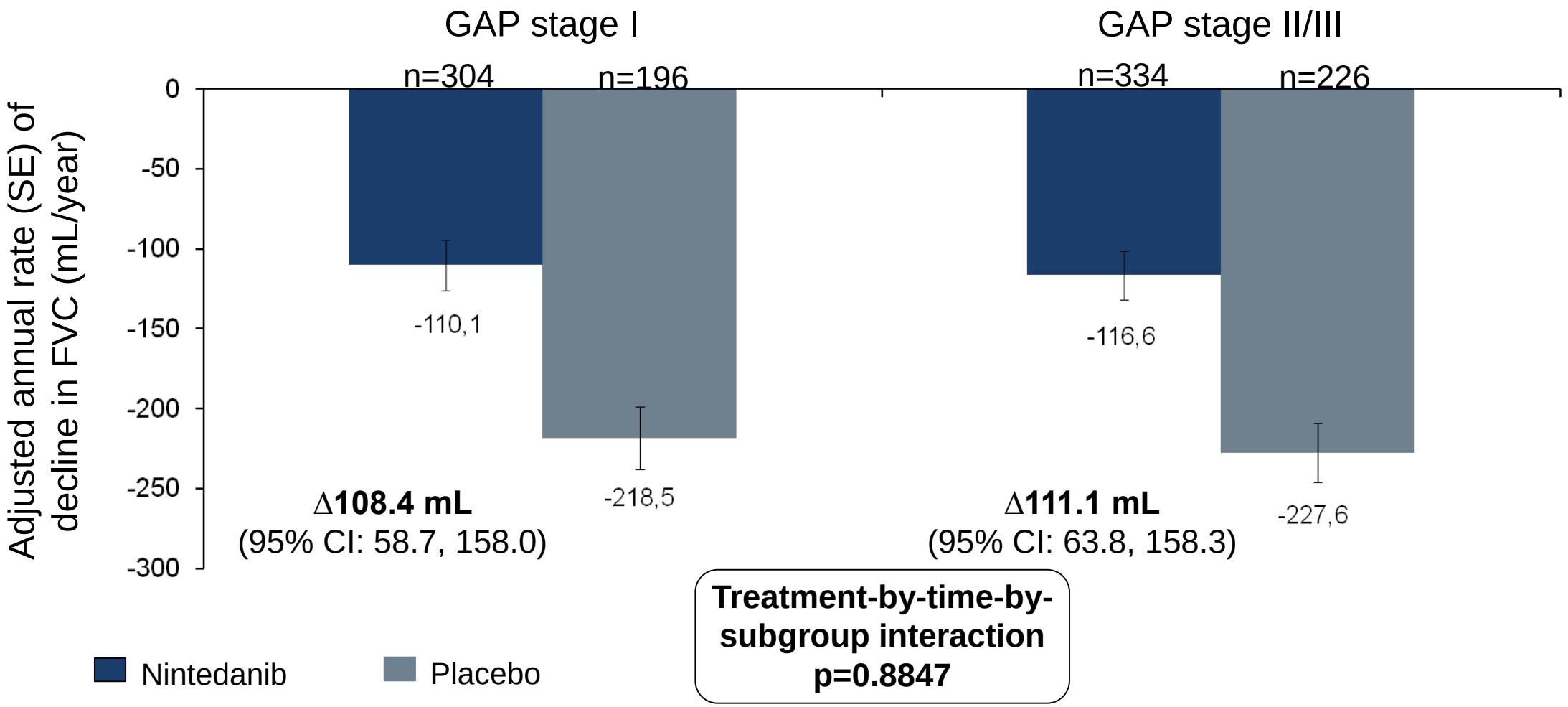
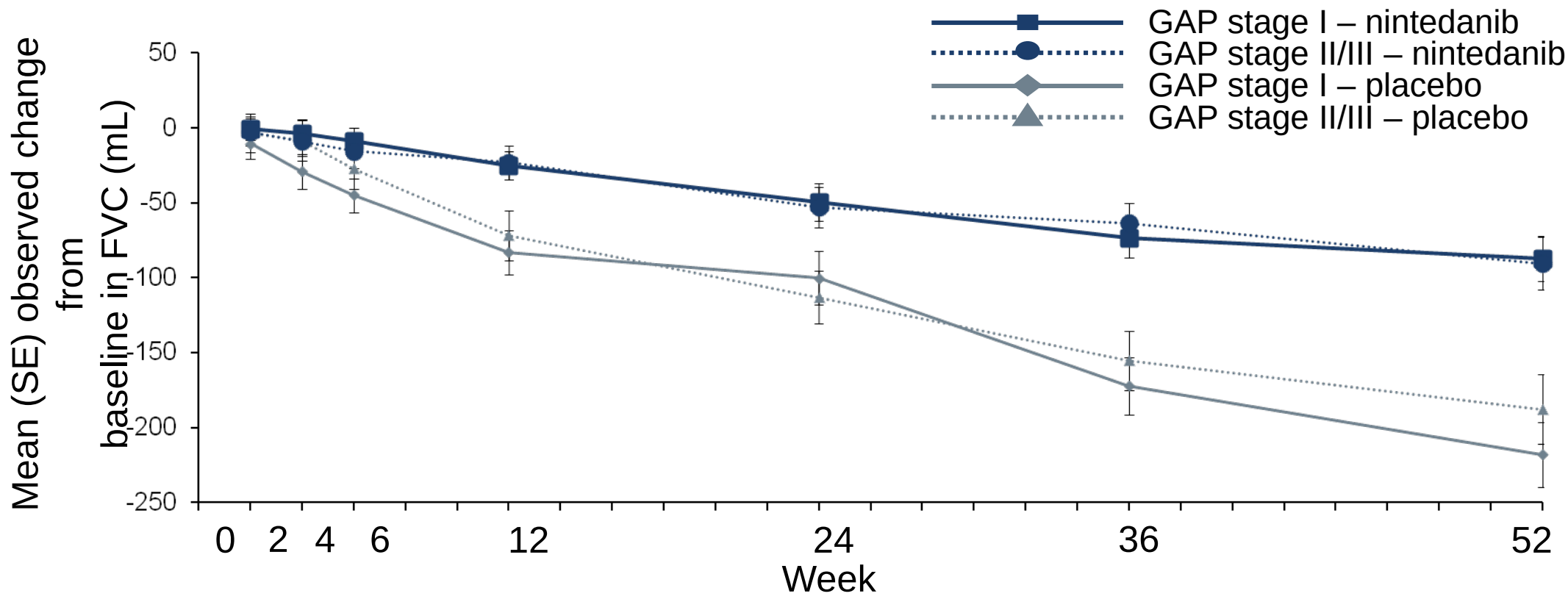
Nintedanib

Annual rate of decline in FVC by GAP stage at baseline in INPULSIS trials



Mean observed change from baseline in FVC by subgroup in INPULSIS trials



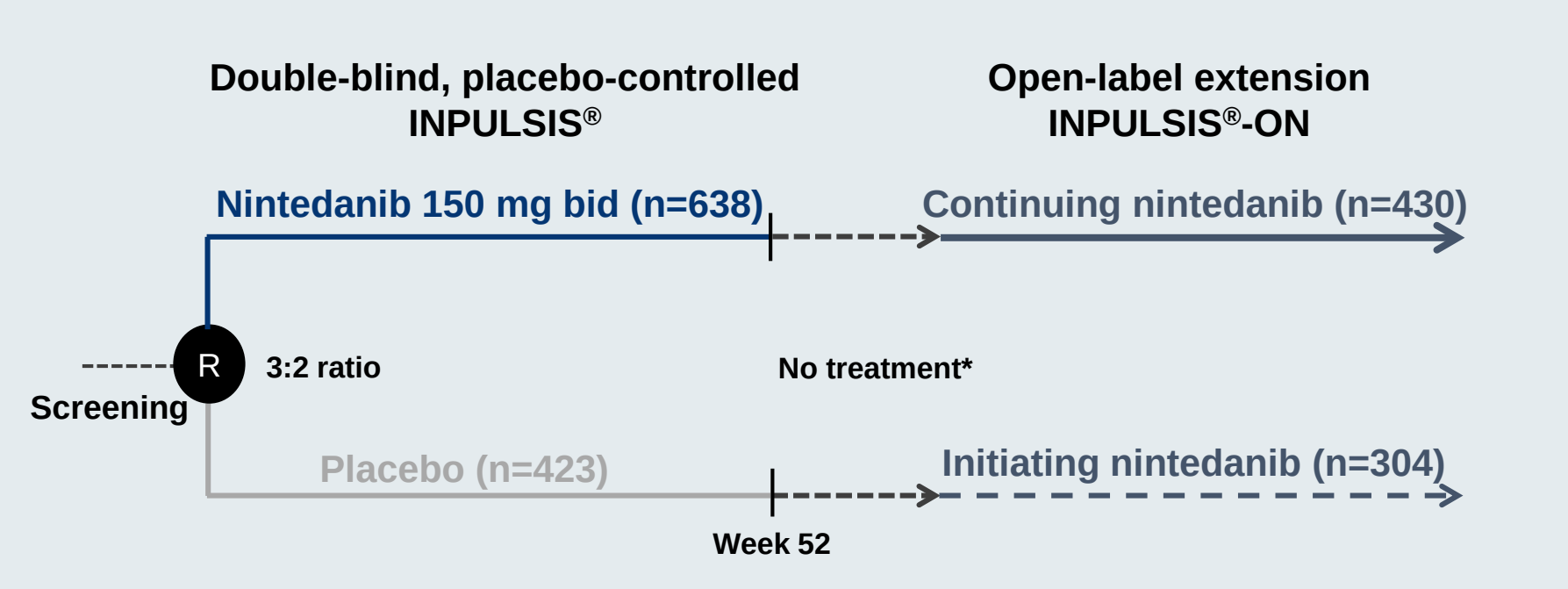
No. of patients							
GAP stage I – nintedanib	297	292	291	290	282	280	259
GAP stage II/III – nintedanib	329	324	322	314	305	289	260
GAP stage I – placebo	196	192	193	192	189	184	172
GAP stage II/III – placebo	220	215	213	210	206	198	172

Conclusions

- Patients at GAP stage I and GAP stage II/III who were treated with placebo showed a similar degree of disease progression, as measured by annual rate of decline in FVC; nintedanib slowed the decline in lung function in patients with IPF independent of GAP stage at baseline.

- A greater proportion of patients at GAP stage II/III at baseline had an acute exacerbation compared with patients at GAP stage I; there was no significant difference between subgroups in the treatment effect of nintedanib on acute exacerbations.

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

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

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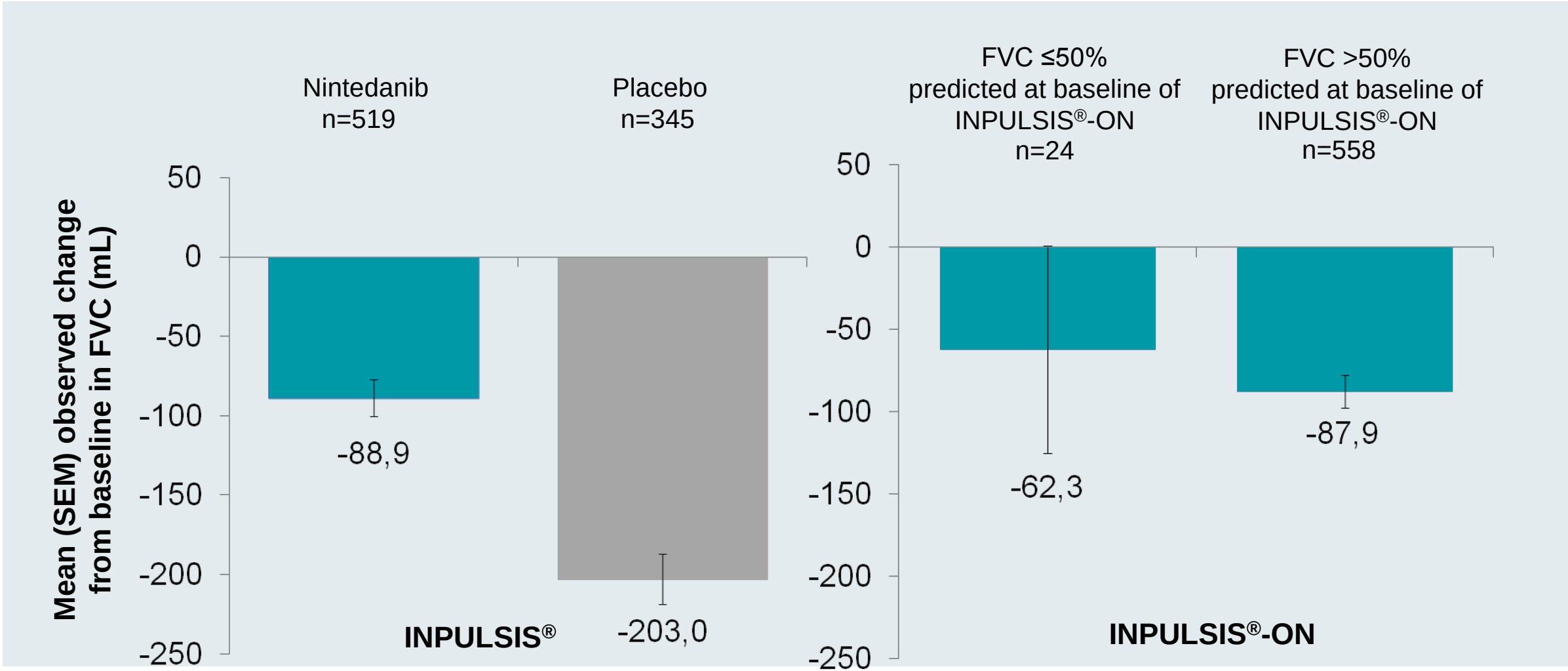
Change in FVC from baseline to week 52 of INPULSIS® and from baseline to week 48 of INPULSIS®-ON



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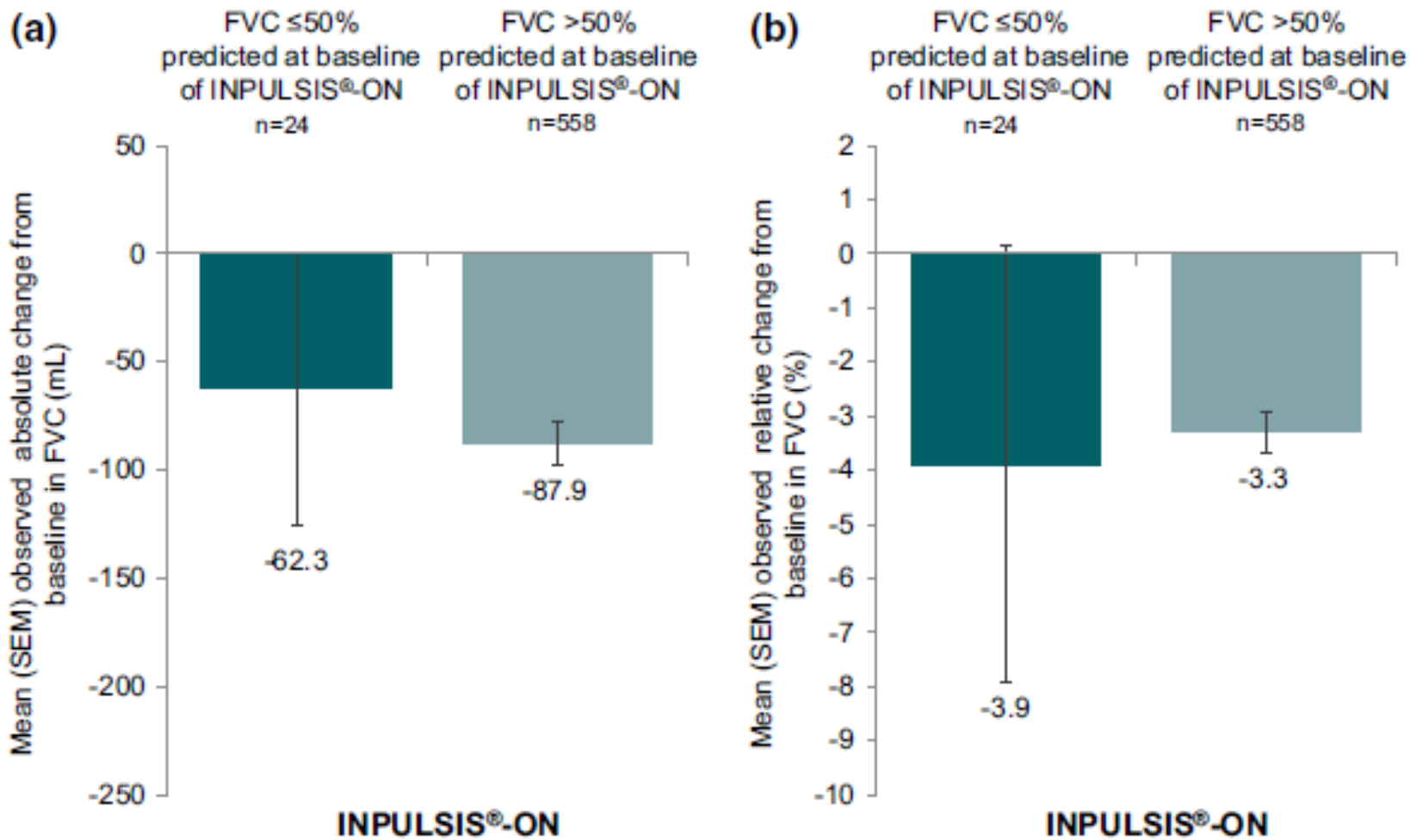
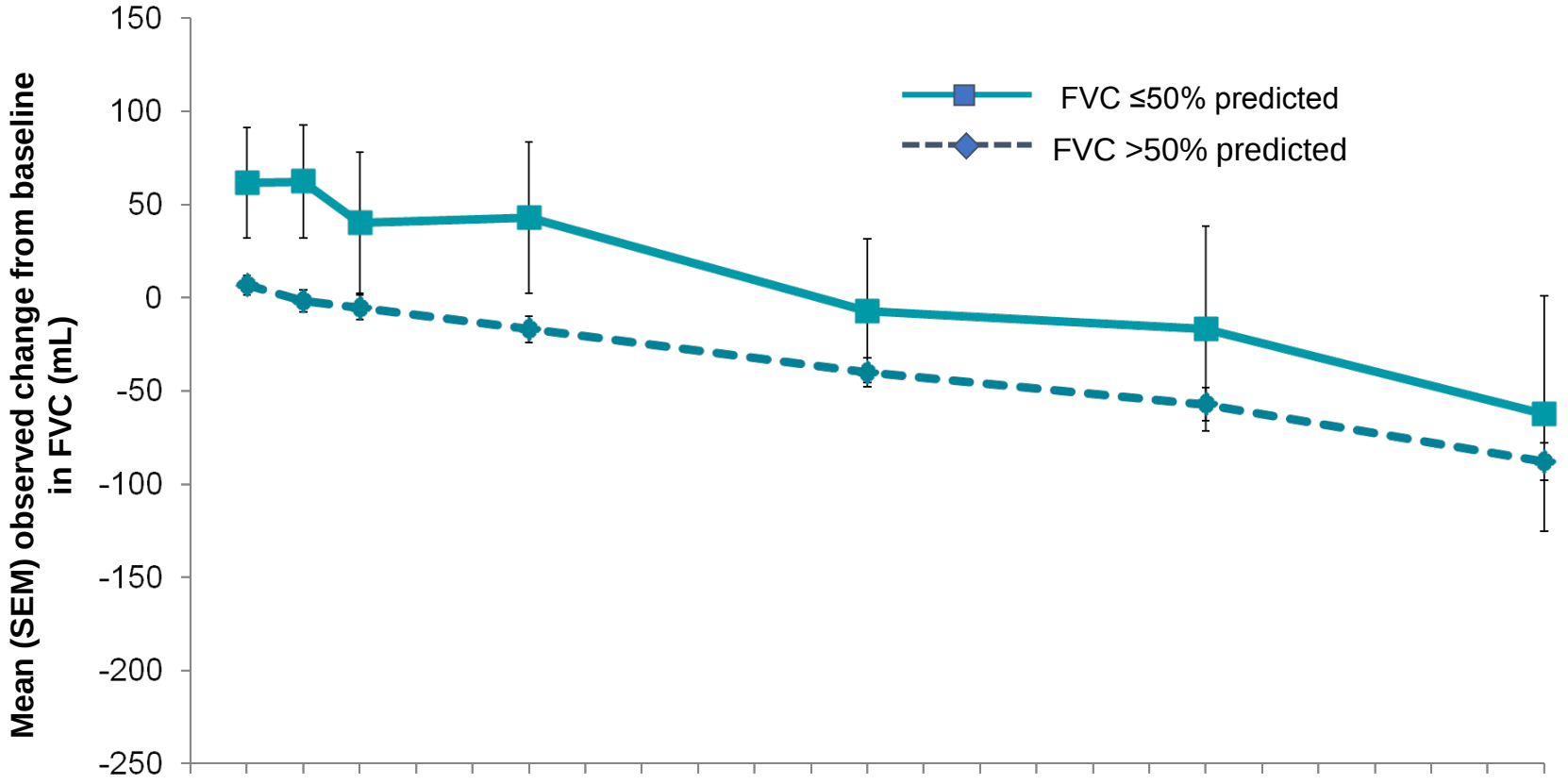

(a)
FVC ≤50% predicted at baseline of INPULSIS®-ON
n=24
FVC >50% predicted at baseline of INPULSIS®-ON
n=558
Mean (SEM) observed absolute change from baseline in FVC (mL)
50
0
-50
-100
-150
-200
-250
-62.3
-87.9
INPULSIS®-ON
(b)
FVC ≤50% predicted at baseline of INPULSIS®-ON
n=24
FVC >50% predicted at baseline of INPULSIS®-ON
n=558
Mean (SEM) observed relative change from baseline in FVC (%)
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
-9
-10
-3.9
-3.3
INPULSIS®-ON

Change from baseline in FVC over time in INPULSIS®-ON by FVC % predicted at baseline of INPULSIS®-ON



No. of patients							
FVC ≤50% predicted	35	35	32	29	29	23	24
FVC >50% predicted	674	663	660	659	626	600	558

Wuyts WA, et al. Lung 2016

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 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	398 (62.4)	78 (18.4)	19 (46.3)	446 (64.6)
Nausea	156 (24.5)	28 (6.6)	7 (17.1)	111 (16.1)
Cough	85 (13.3)	57 (13.5)	7 (17.1)	114 (16.5)
Nasopharyngitis	87 (13.6)	68 (16.1)	3 (7.3)	100 (14.5)
Bronchitis	67 (10.5)	45 (10.6)	4 (9.8)	97 (14.1)
Dyspnea	49 (7.7)	48 (11.3)	10 (24.4)	88 (12.8)
Progression of IPF*	64 (10.0)	61 (14.4)	14 (34.1)	104 (15.1)
Weight decreased	62 (9.7)	15 (3.5)	7 (17.1)	36 (11.8)

*Corresponds to MedDRA term 'IPF', which included disease worsening and IPF exacerbations.
Adverse events reported in >12% of patients in either treatment group in INPULSIS® or in the overall patient population in INPULSIS®-ON.

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 small

Wuyts WA, et al. Lung 2016

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

PARTECIPANTS: Ancona, Catania, Foggia, Forlì, Milano, Modena, Monza, Padova, S.Camillo-Forlanini, Siena, Trieste

Matherials and Methods

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

Inclusion criteria:

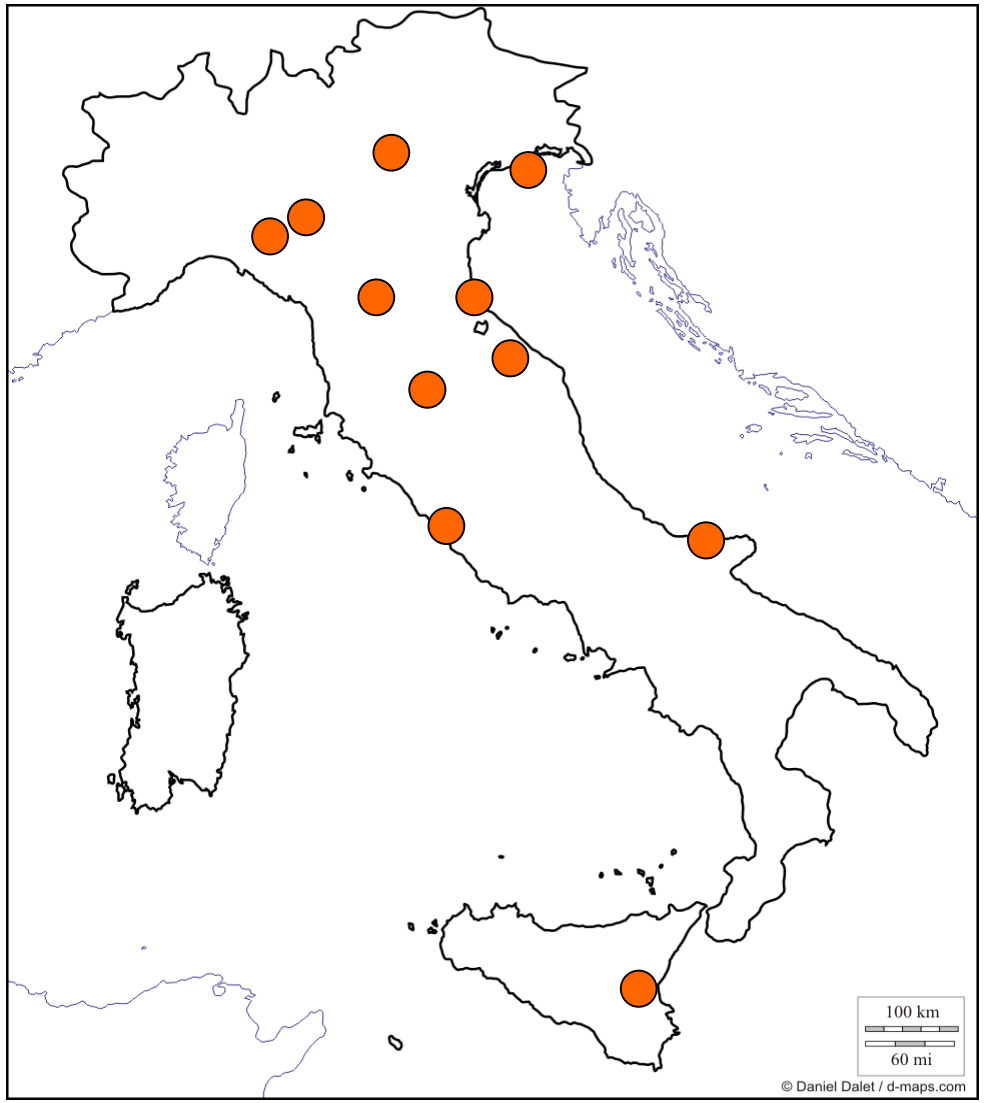
- Diagnosis (definite or probable) of IPF confirmed by HRCT UIP pattern and/or surgical lung biopsy (according to 2011 IPF guidelines);
- Severe stage of disease (FVC <50% e/o DLCO <35%, at baseline) ;
- Availability of functional follow-up data at least 6 months before, at the starting therapy point and at least 6 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 NT;
- 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 nintedanib prescription (N=41)



Gender	**Female**	**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)
Cortisone	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)

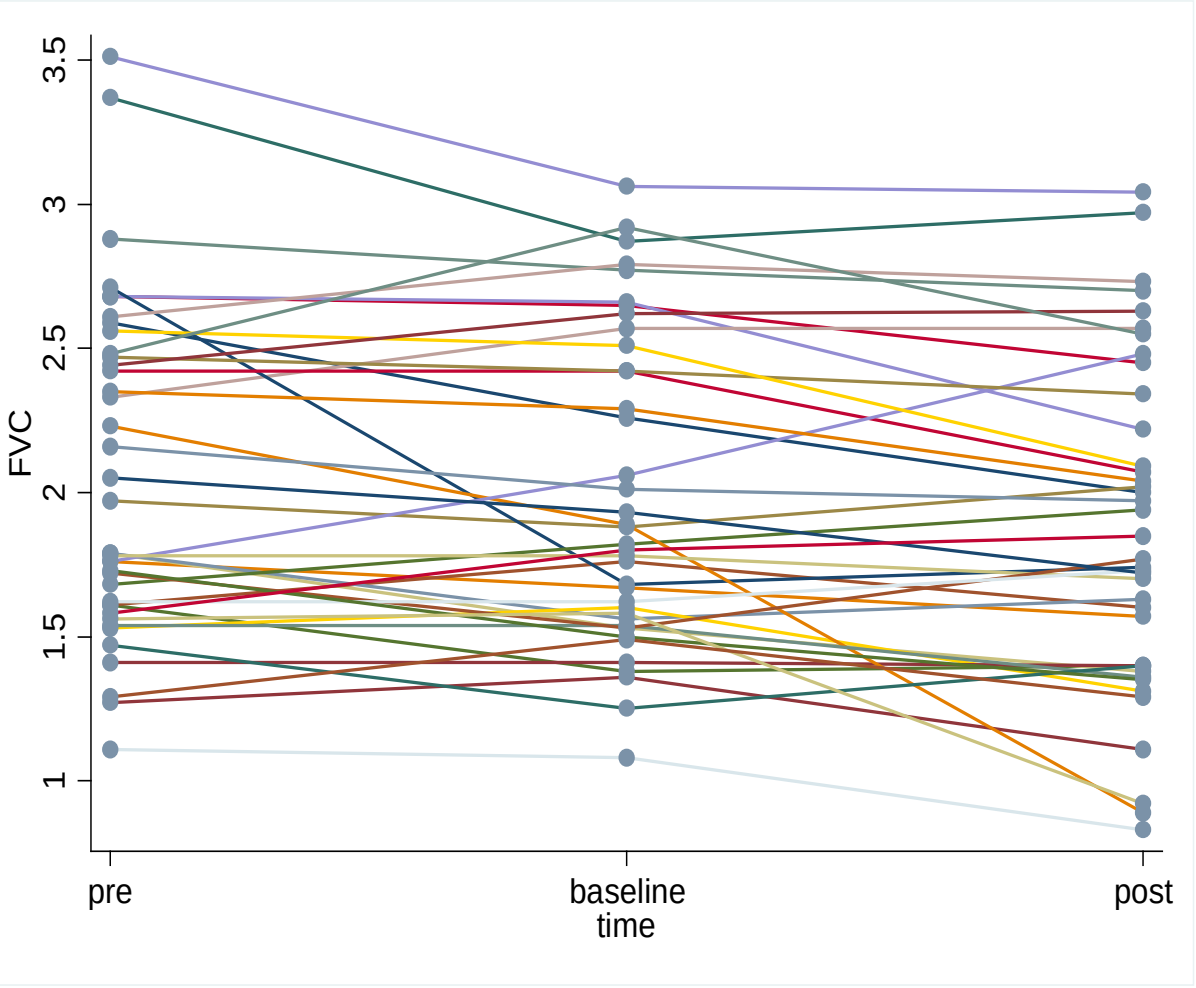
* mean age 70 years ± SD 8 years

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

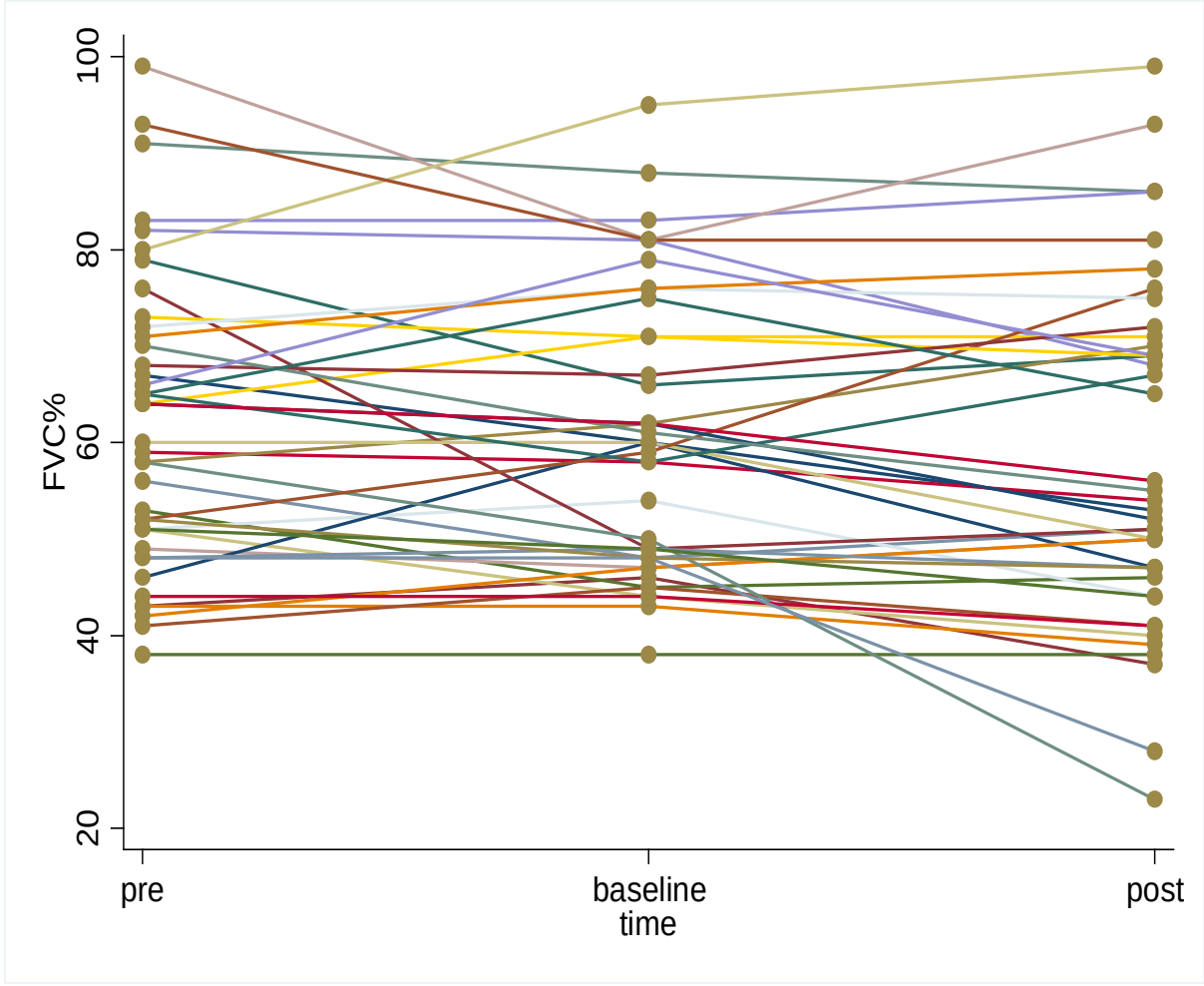
Table 2. PFTs 6 months before, at baseline (first prescription nintedanib) and 6 months after

Parameter	N	Time	Mean (SD)	Changes (95%CI)	difference in changes	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	0.3433
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	0.4602
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	0.0066
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	0.1930
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)	-2.5	0.4058
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	0.9470
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	0.8557
TLCO	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	0.0533

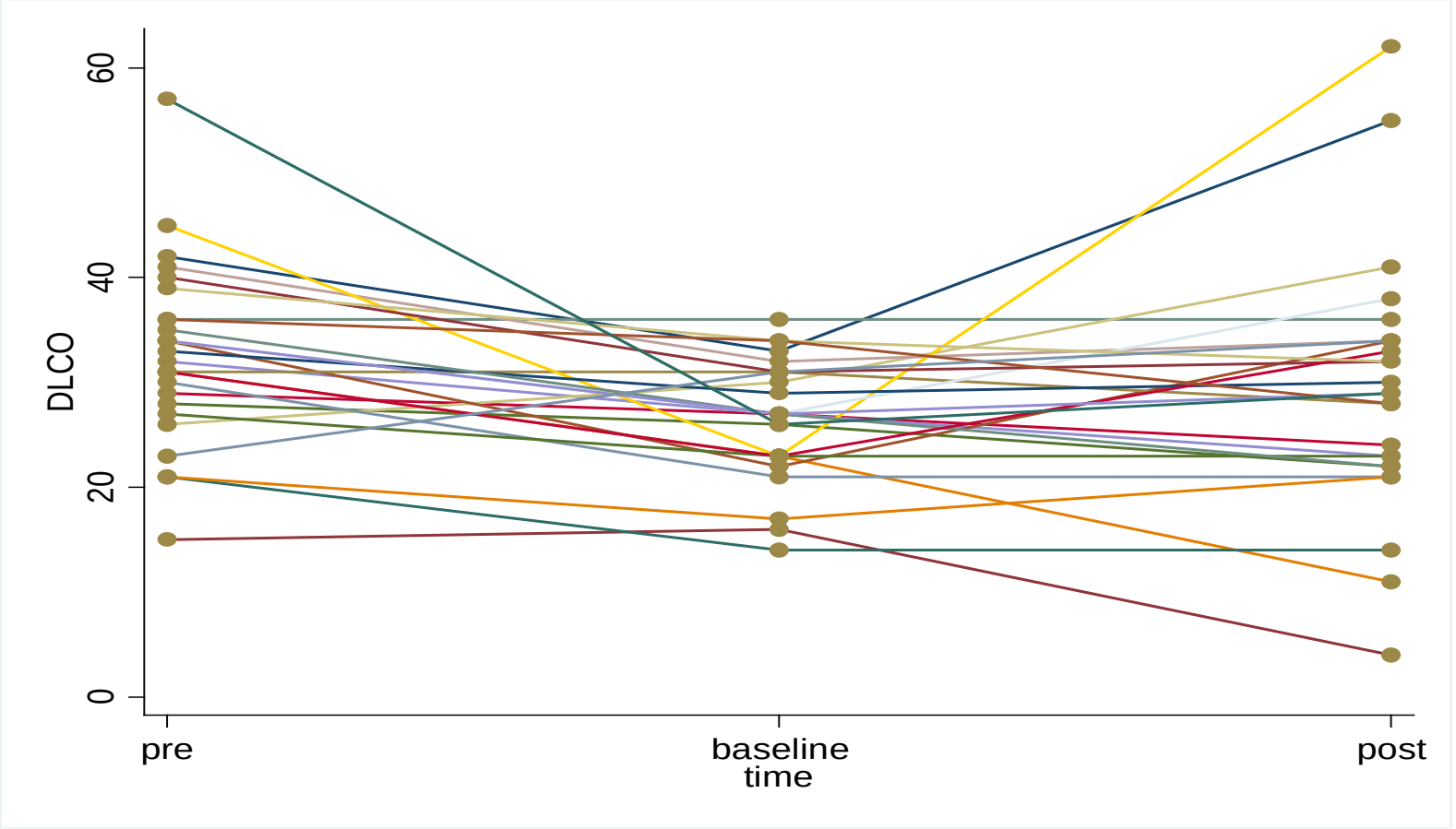
ΔFVC as assolute value



ΔFVC as percent of the predicted value



Δ DLCO pre, at baseline and post 6 months (N=26)



Trapianto polmonare e IPF

Tutti I potenziali candidati al trapianto di polmone devono essere inviati ad una valutazione trapianto

QUANDO → Al momento della diagnosi di IPF.

L'invio precoce ad un centro di esperienza nella gestione delle *patologie restrittive* e del *trapianto* **MIGLIORA** il risultato terapeutico a lungo termine


REVIEW

Idiopathic pulmonary fibrosis: Early detection and referral

Justin M. Oldham*, Imre Noth

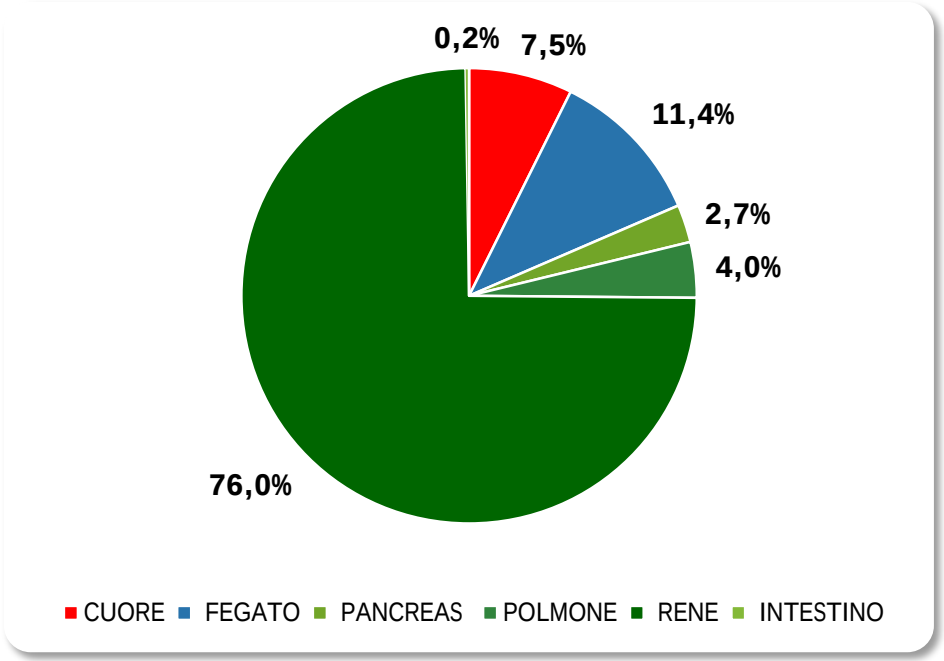
Respiratory Medicine (2014) 108, 819–829

Liste di Attesa al 31 Dicembre 2015

PAZIENTI in lista d'attesa in ITALIA al 31/12/2015 :

9070

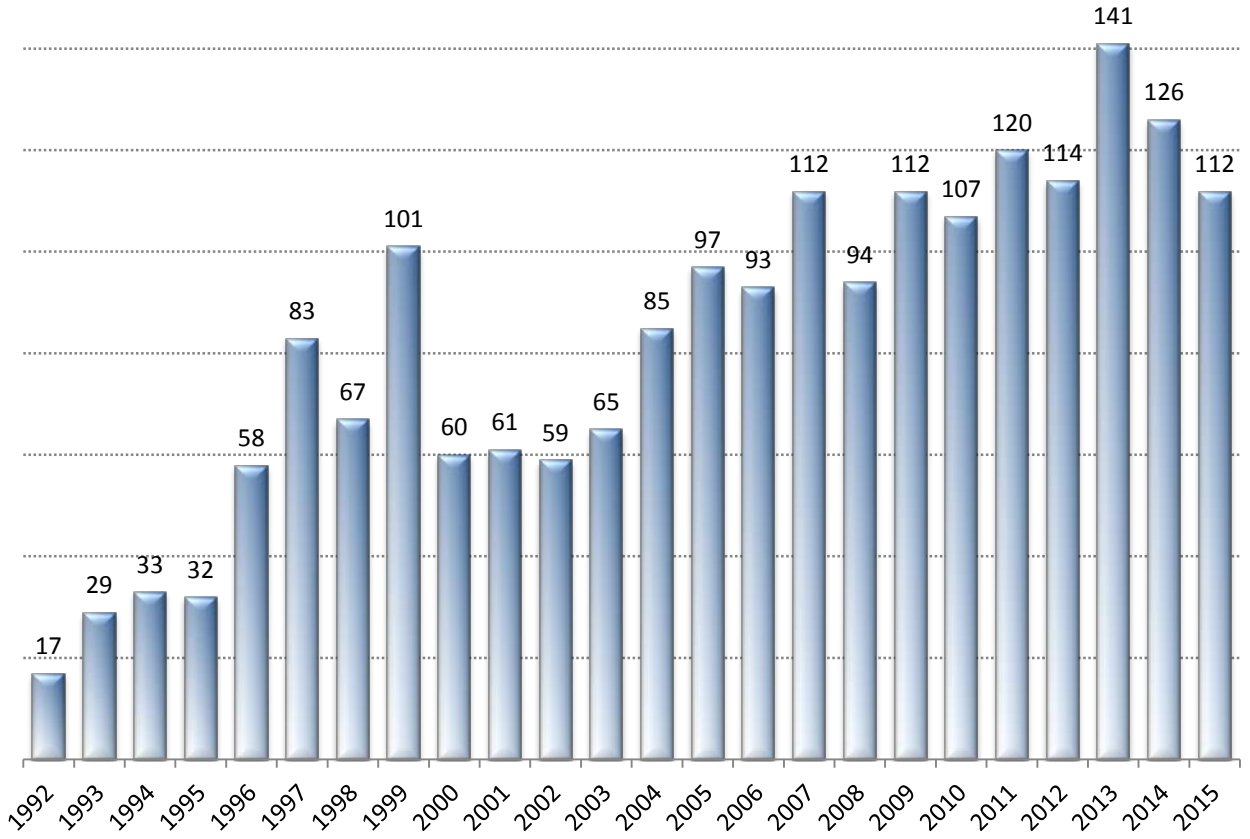
Rene	6765**
Fegato	1072
Cuore	731
Polmone	**383**
Pancreas	248
Intestino	20



*** Iscrizioni rene***
8433, per il rene ogni paziente può avere più di una iscrizione

Trapianti di POLMONE – Anni 1992-2015*

Incluse tutte le combinazioni



Fonte dati: Report CRT

**** Dati definitivi al 31 Dicembre 2015***

Delanote *et al. BMC Pulmonary Medicine* (2016) 16:156
DOI 10.1186/s12890-016-0308-z

BMC Pulmonary Medicine

RESEARCH ARTICLE Open Access

Safety and efficacy of bridging to lung transplantation with antifibrotic drugs in idiopathic pulmonary fibrosis: a case series

Isabelle Delanote[1], Wim A. Wuyts[1,2], Jonas Yserbyt[1], Eric K. Verbeken[3], Geert M. Verleden[1,2] and Robin Vos[1,2*]

A total of 9 IPF patients were treated with antifibrotics and subsequently underwent LTx: pirfenidone $n = 7$ ($n = 2$ study vs. $n = 5$ open-label treatment), nintedanib $n = 2$ (both in study). All patients, but one, underwent bilateral

No serious side effects were noted during antifibrotic therapy. However, significant weight loss occurred, which is most likely due to drug-induced anorexia or possibly due to respiratory cachexia in end-stage lung disease. Post-operatively, no problems with bleeding or thoracic wound healing were observed. One patient, treated with nintedanib; and three patients who had received pirfenidone developed, mostly mild and uneventful, anastomic airway complications. Intervention for anastomotic stenosis was needed for one case, which only occurred late-onset after prior fungal infection. Overall, it is unlikely that any of these anastomotic problems were directly related to prior antifibrotic treatment given the time of onset/clinical context of anastomotic complications, comparable anasto-

Guidelines for Referral and Listing for Trasnplantation in patients with IPF

Orens JB et al. J Heart Lung Transplant 2006; 25: 745

Guidelines	Description
For referral	Histologic or radiographic evidence of UIP irrespectively of vital capacity
	Histologic evidence of fibrotic NSIP
For listing	**Histologic or radiographic evidence of UIP and any of the following: DLCO of < 39% predicted; ≥ 10% decrement in FVC during 6 mo of follow-up; decrease in pulse oximetry below 88% during a 6MWT; and honeycombing seen on HRCT scan (fibrosis score > 2)**
	Histologic evidence of NSIP and any of following: DLCO < 35% predicted; and ≥ 10% decrement in FVC or 15% decrease in DLCO during 6 mo of follow-up

The goals of effective IPF management

- Relieve symptoms
- Improve exercise tolerance
- Improve health status
- Prevent and treat complications
- Prevent and treat exacerbations
- Prevent disease progression
- Reduce mortality

- Pulmonary Rehab.
- Oxygen

New approaches needed??

Experimental therapy in a RCT

Lung Transplantation

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

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

The comprehensive care of patients with severe IPF remains essential, which includes management of comorbidities and physical debility and timely referral for lung transplantation

Conclusions

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