UNIVERSITA di CATANIA – SCUOLA DI MEDICINA

DIPARTIMENTO DI MEDICINA CLINICA E SPERIMENTALE

“CENTRO di RIFERIMENTO REGIONALE per le MALATTIE RARE del POLMONE”

When to start and when to stop anti-fibrotic therapies?

Carlo Vancheri

Disclosures

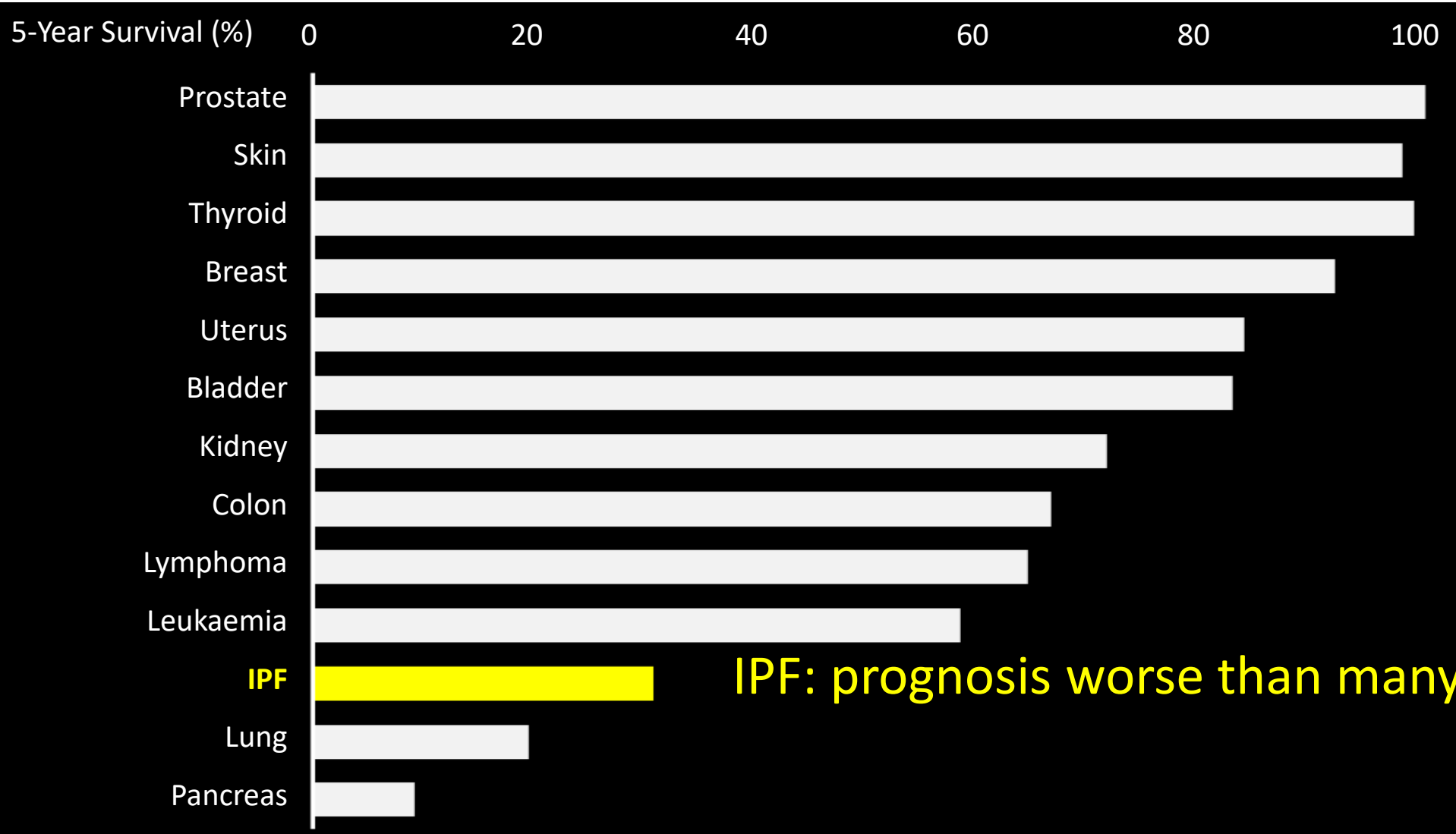
- Served on advisory committees of: InterMune-Roche and Boehringer Ingelheim
- Received lecture fees from: InterMune,Roche, Boehringer Ingelheim, Novartis, Chiesi, Menarini and Sanofi
- Non-governmental research support from: InterMune, Roche, Boehringer Ingelheim and Astra-Zeneca

When to start anti-fibrotic treatments?

Common sense would suggest as soon as diagnosis is made.

Idiopathic pulmonary fibrosis: a disease with similarities and links to cancer biology

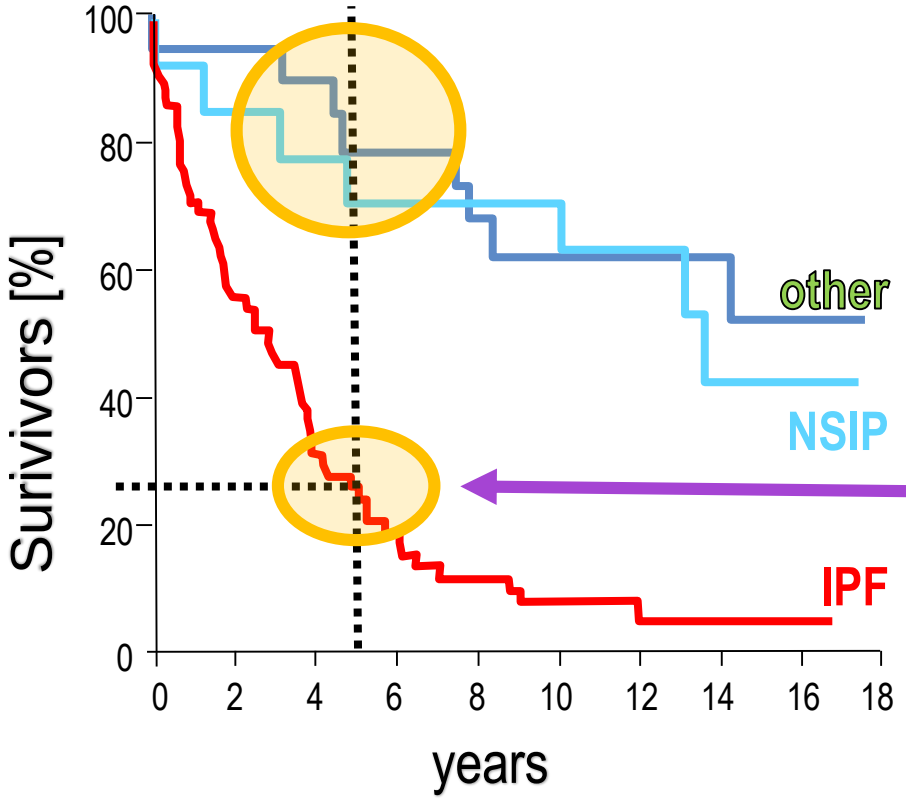
Vancheri et al, Eur Respir J 2010; 35: 496-504



IPF: prognosis worse than many cancers

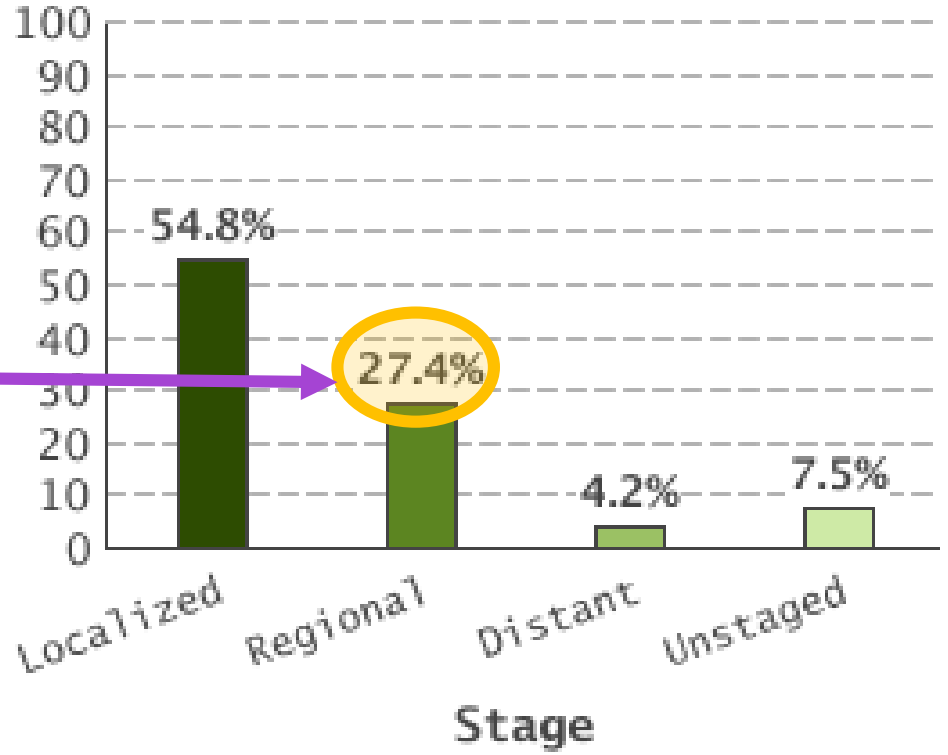
Until very recently the prognosis of IPF was comparable to that of non methastatic lung cancer

Survival of IPF vs NSIP ad others fibrosing idiopathic ILDs



Bjoraker JA et al.; *Am J Respir Crit Care Med.;* 1998;157

5 years survival rate Lung Cancer 2005-2011



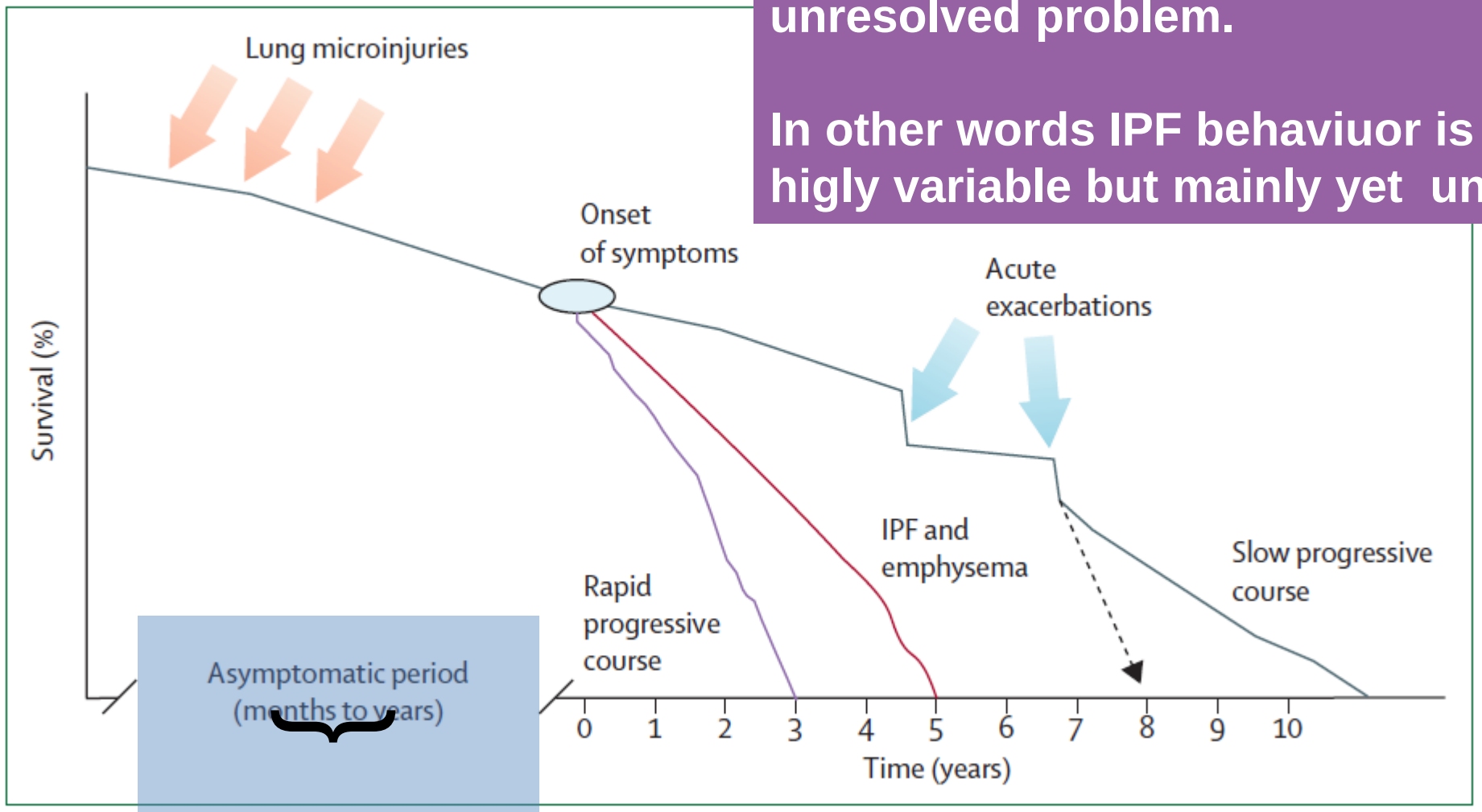
Surveillance, epidemiology and end-results program NTL Cancer Institute, USA

Strong rationale for an early treatment

Key words: heterogeneity, variability

Result : to identify progressors is today an unresolved problem.

In other words IPF behaviuor is not only higly variable but mainly yet unpredictable

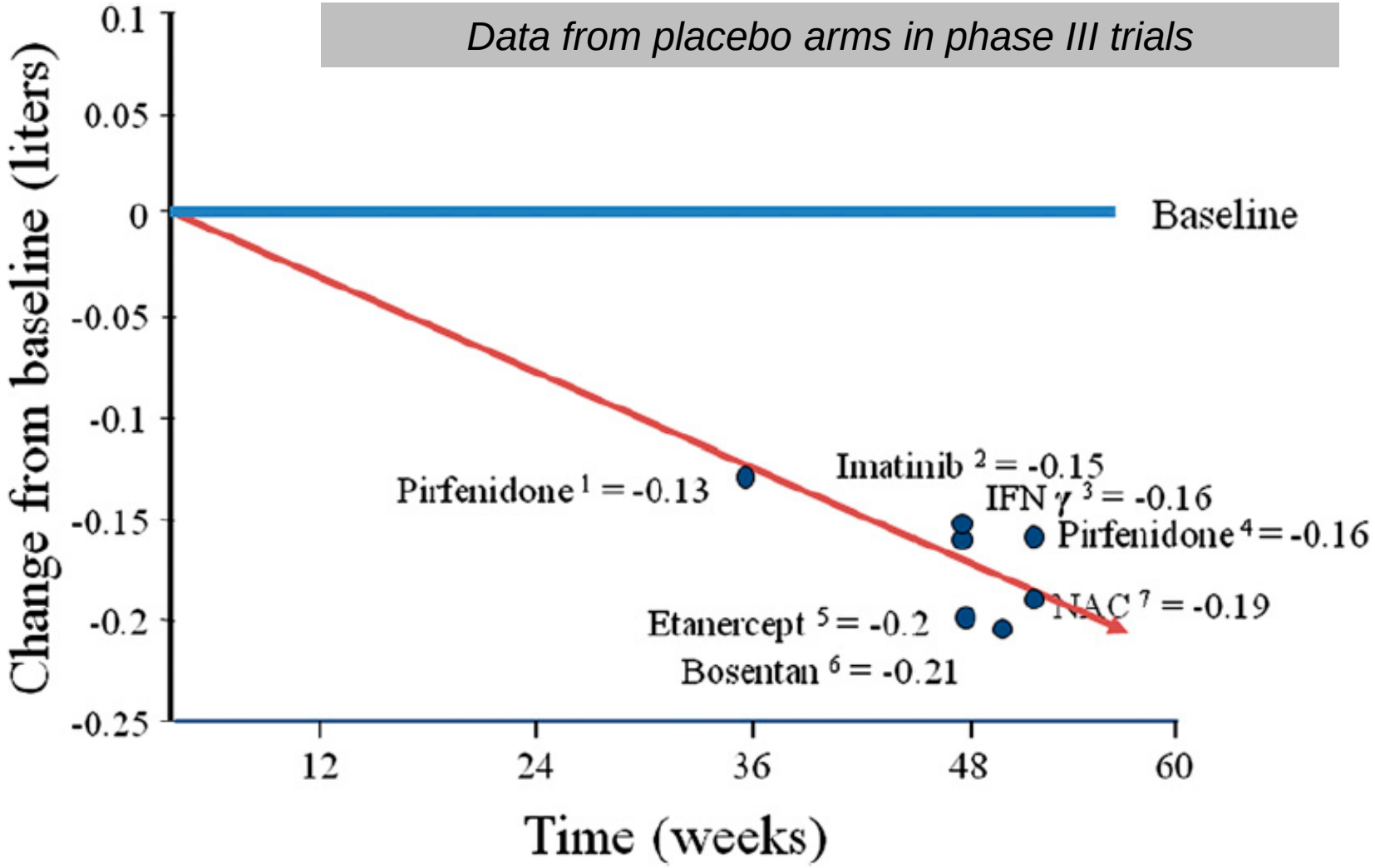


Duration ?

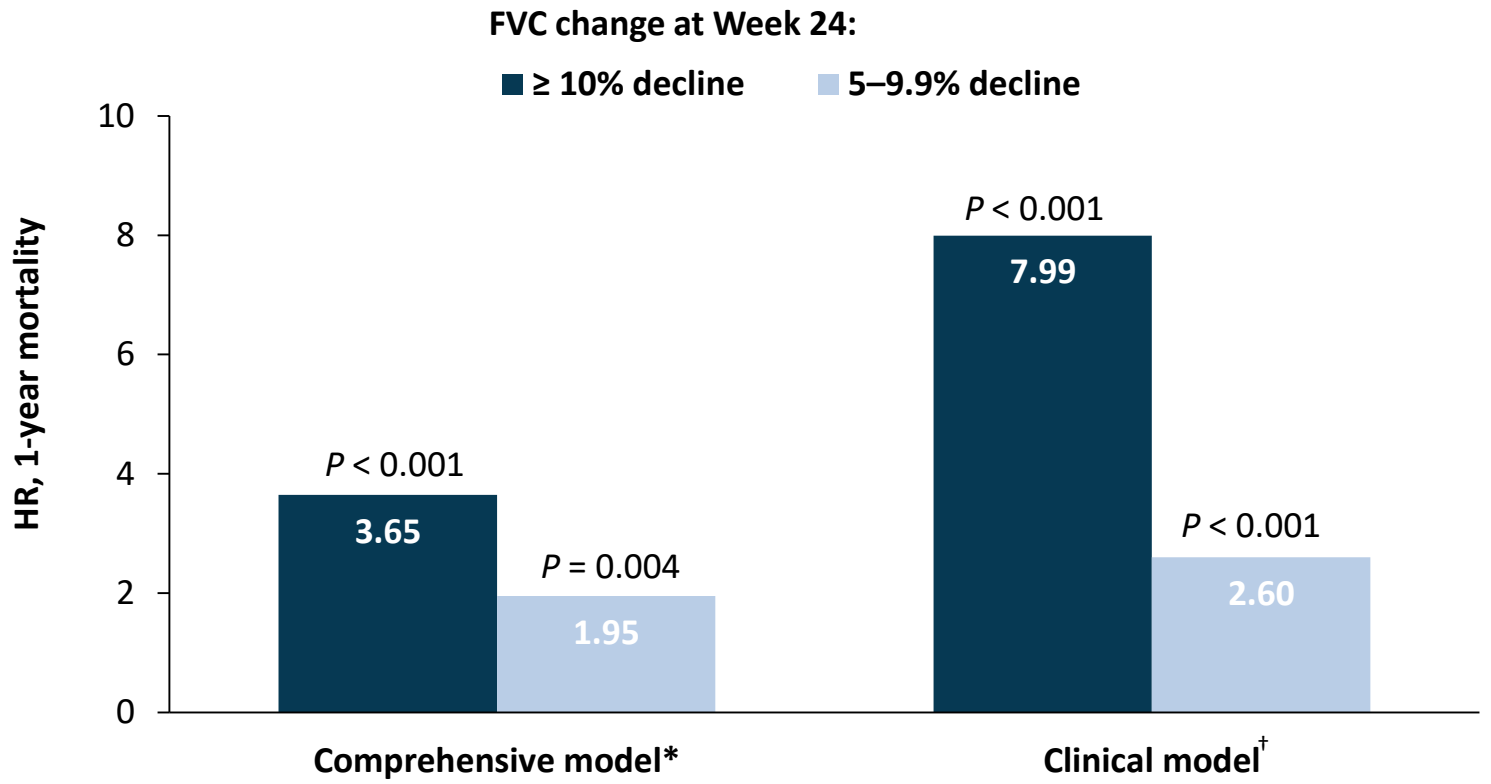
King et al, Lancet 378:1949, 2011

Progression even if not predictable is a real problem

since ALL patient are going to loose on average 200ml FVC/year



FVC: An independent predictor of mortality in IPF



Graphical elaboration of data text

* Adjusted for age, history of respiratory hospitalisation, %FVC, $\%DL_{CO}$, 24-week change in $\%DL_{CO}$, and 24-week change in SGRQ; † Adjusted for age, history of respiratory hospitalisation, %FVC. DL_{co}: carbon monoxide diffusing capacity; FVC: forced vital capacity; HR: hazard ratio; SGRQ: St George's respiratory Questionnaire.

1. du Bois RM et al. Am J Respir Crit Care Med 2011;184:459–466.

Four common sense reasons to start anti-fibrotic treatment as soon as diagnosis is made:

1. IPF prognosis is really bad (worse than many cancers and comparable to non-M lung cancer)
2. IPF behaviour is unpredictable
3. FVC tends to decline on average of 200 ml/year
4. Change in FVC is associated with increased mortality

In spite of common sense the question is still debated

When to start anti-fibrotic treatments?

Scientific evidence suggest as soon as diagnosis is made.

Six months change in FVC is associated with increased mortality in several studies

Flaherty et al AJRCCM 2003; 168: 530-8

HR et al AJRCCM 2003; 168: 538-42

Latsi et al AJRRCM 2003; 168: 510-1

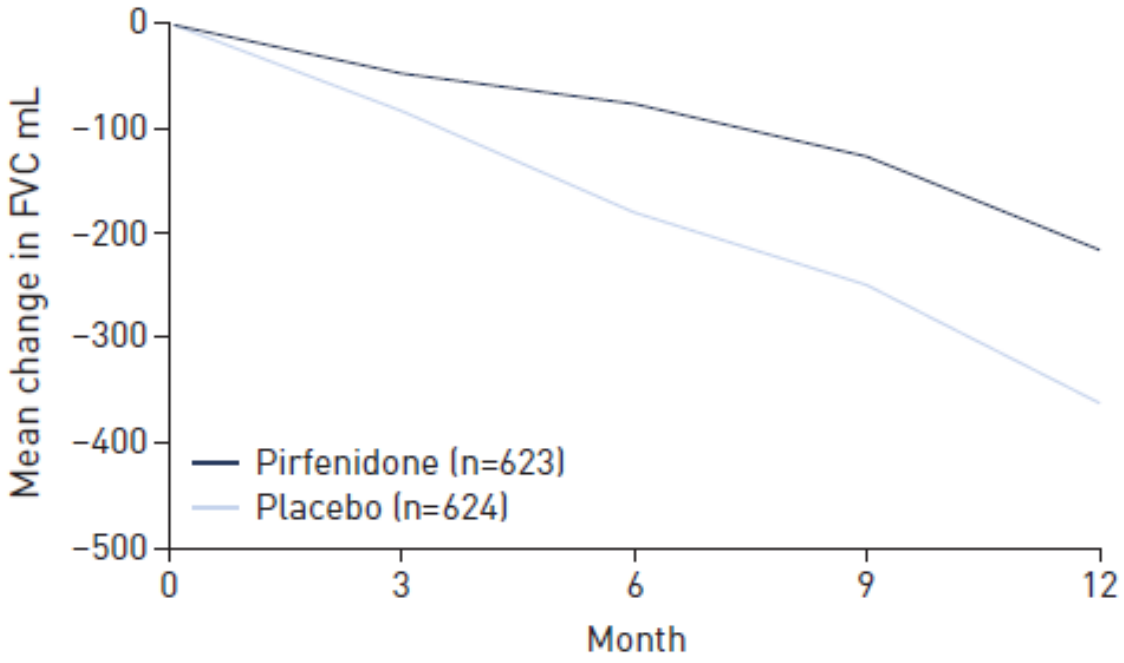
Zapala et al ERJ 2010; 35: 830-5

DuBois et al AJRCCM 2011; 184: 1382-9

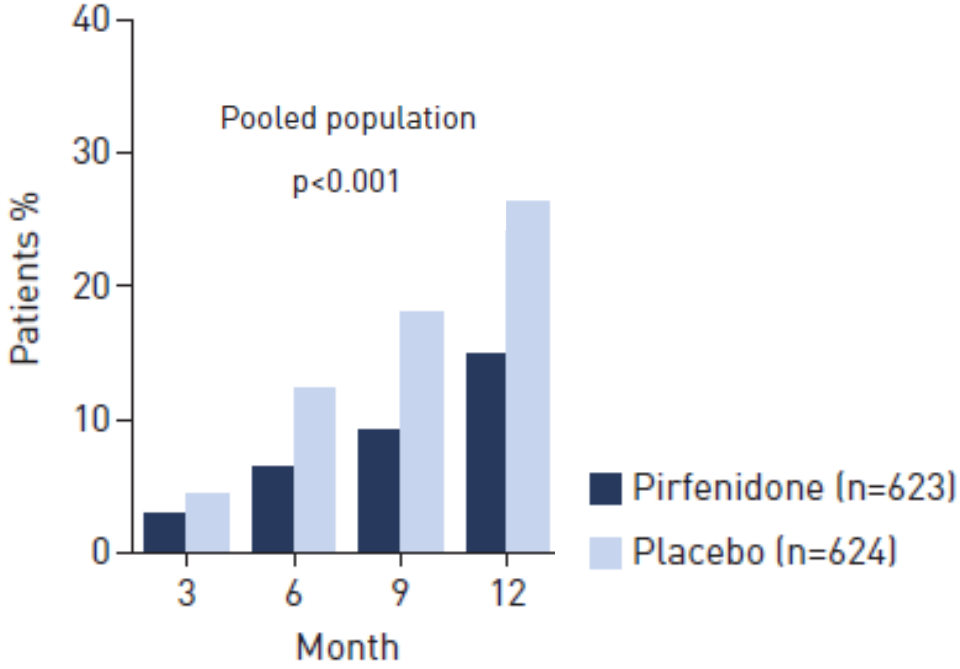
Richeldi et al Thorax 2012; 67: 407-11

Pirfenidone reduced the decline in FVC over 1 year in the pooled ASCEND + CAPACITY population

FVC decline (mL):



⩾10% FVC decline or death:



Conclusions

In the pooled population, pirfenidone reduced FVC decline and the composite endpoint of % predicted FVC decline ⩾10% or death over 1 year vs placebo

Rank ANCOVA: pirfenidone 2403 mg/day vs placebo
ANCOVA, analysis of covariance; FVC, forced vital capacity

Noble PW et al. Eur Respir J 2016;47:27-30

Nintedanib in patients with idiopathic pulmonary fibrosis: Combined evidence from the TOMORROW and INPULSIS® trials

Luca Richeldi [a, *], Vincent Cottin [b], Roland M. du Bois [c], Moisés Selman [d], Toshio Kimura [e], Zelie Bailes [f], Rozsa Schlenker-Herceg [g], Susanne Stowasser [e], Kevin K. Brown [h]

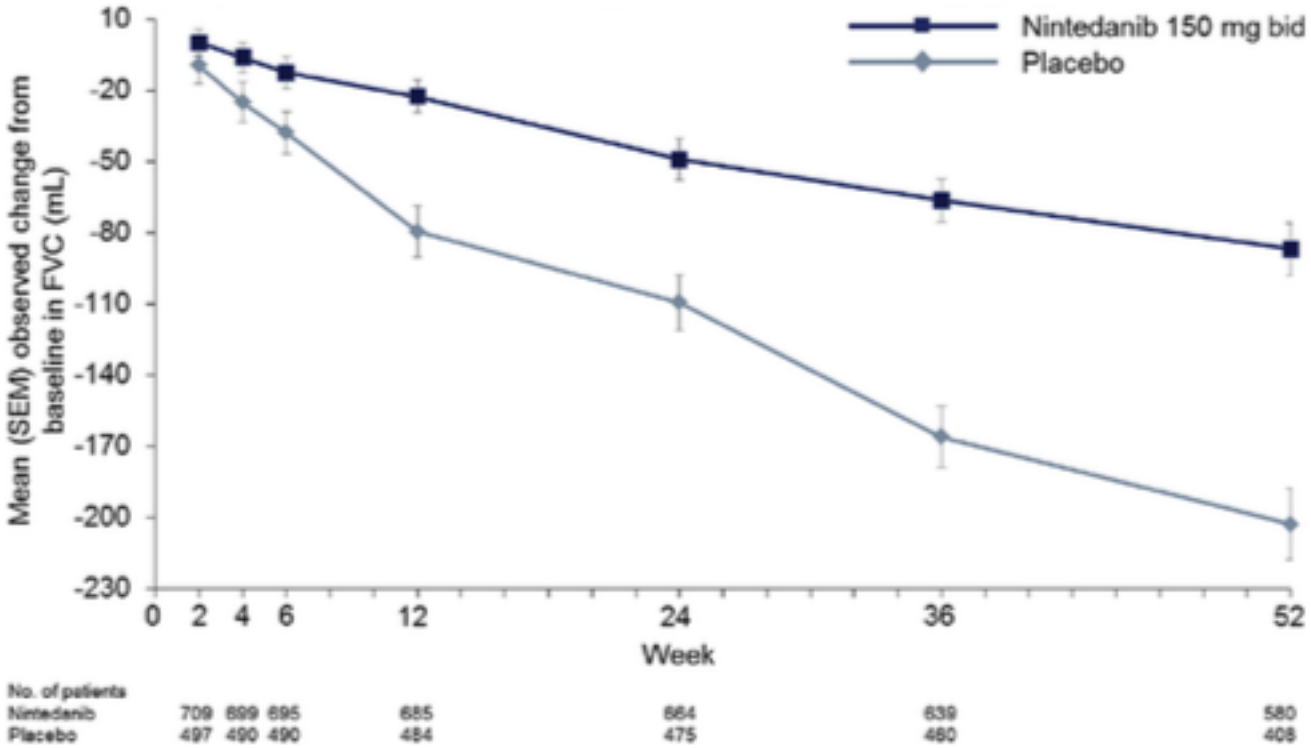
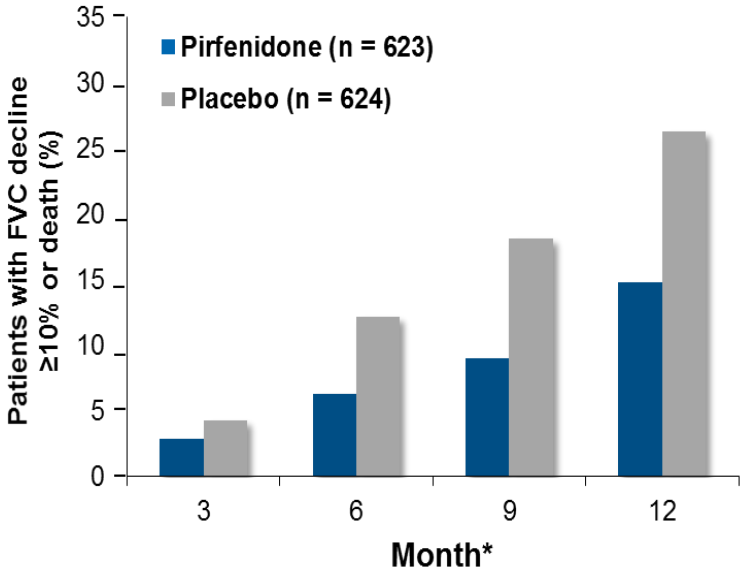


Fig. 2. Changes in FVC over time: pooled data from the TOMORROW and INPULSIS® trials.

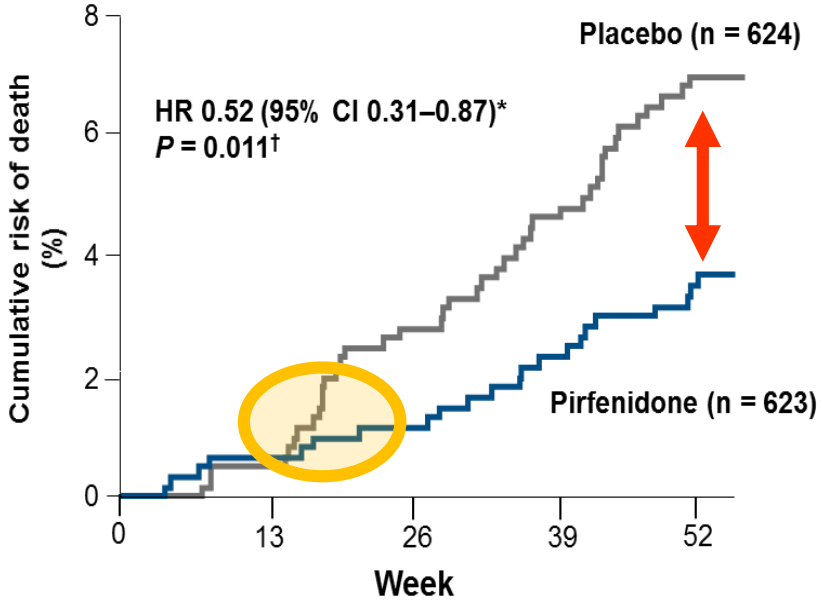
Summary of Key Clinical Endpoints in Pooled Analyses of Pirfenidone Phase 3 Trials (1247 patients)

FVC



Relative Difference, %	33.2	48.6	50.4	43.8
P Value	<0.0001	<0.0001	<0.0001	<0.0001

All-Cause Mortality



Conclusions

- Pirfenidone reduced the proportion of patients with a ≥ 10% decline in FVC or death by 44% at Week 52
- Pirfenidone reduced the risk of mortality by 48% at Week 52 compared with placebo (*P* = 0.01)

*Assessed at Weeks 12, 24, 36 and 48 in CAPACITY and Weeks 13, 26, 39 and 52 in ASCEND. Noble PW et al. Am J Respir Crit Care Med 2014; ATS meeting abstract A1423 (presented as a poster). FVC, forced vital capacity.

Nintedanib in patients with idiopathic pulmonary fibrosis: Combined evidence from the TOMORROW and INPULSIS® trials

Luca Richeldi [a, *], Vincent Cottin [b], Roland M. du Bois [c], Moisés Selman [d], Toshio Kimura [e], Zelie Bailes [f], Rozsa Schlenker-Herceg [g], Susanne Stowasser [e], Kevin K. Brown [h]

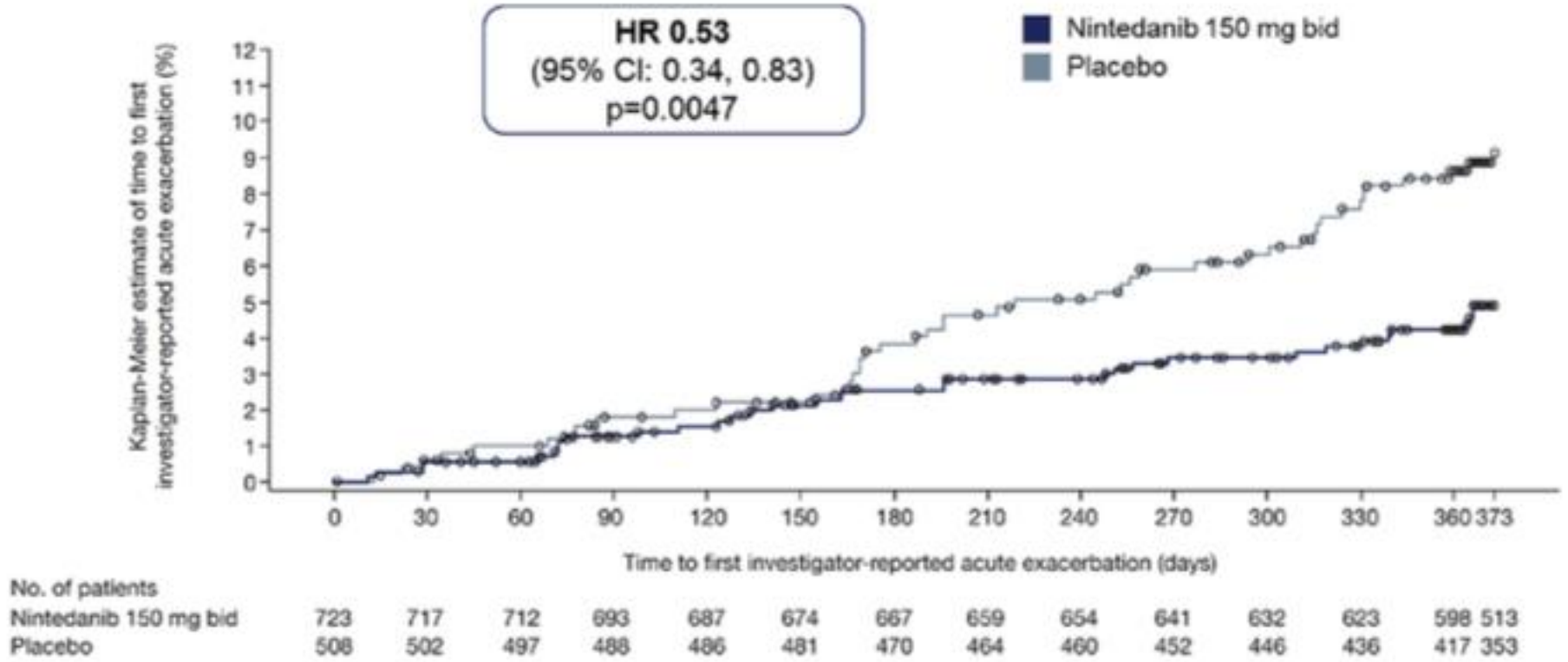
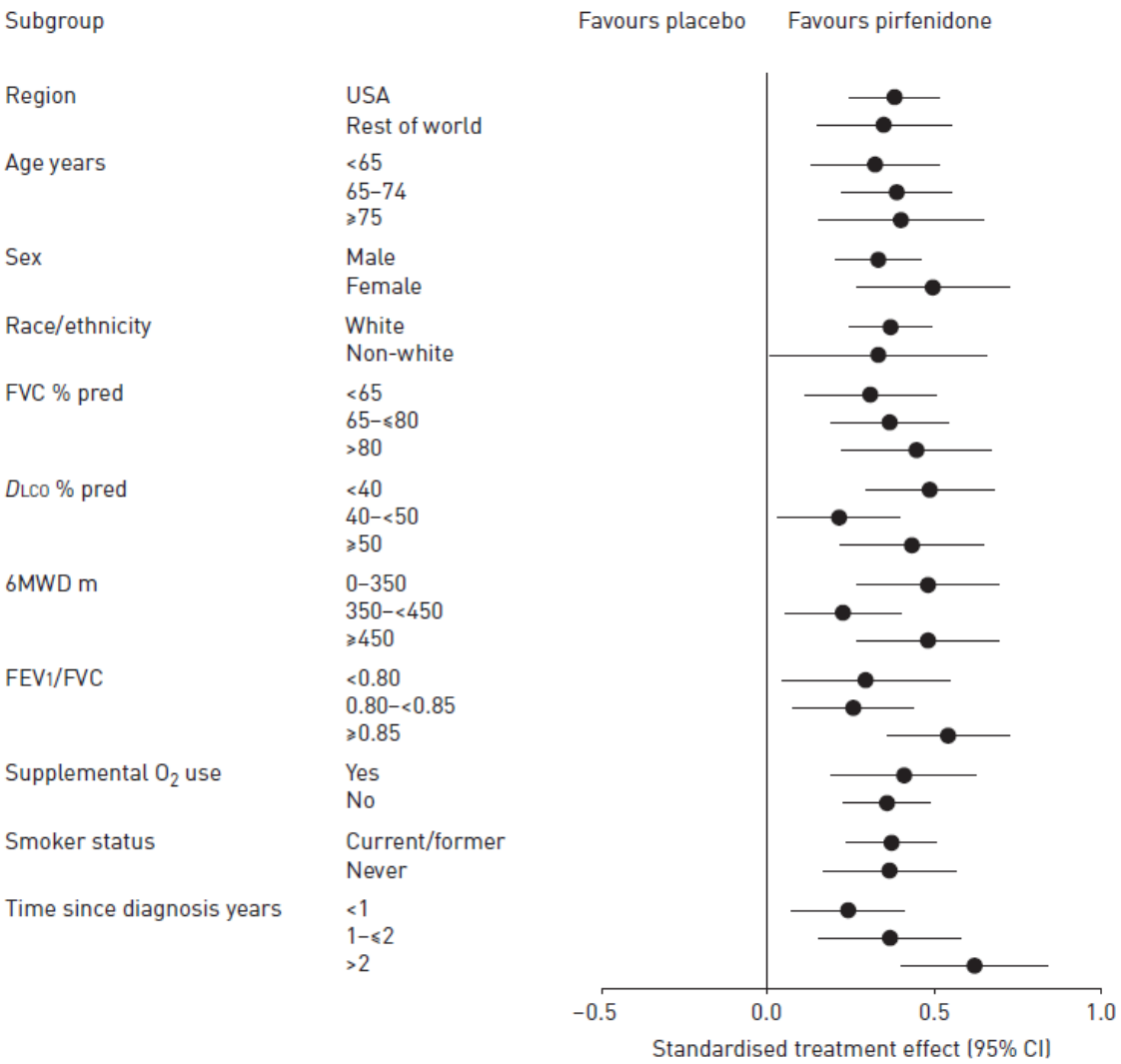


Fig. 3. Time to first investigator-reported acute exacerbation: pooled data from the TOMORROW and INPULSIS® trials.

The benefit of pirfenidone on FVC decline was observed in all patient subgroups



Conclusions

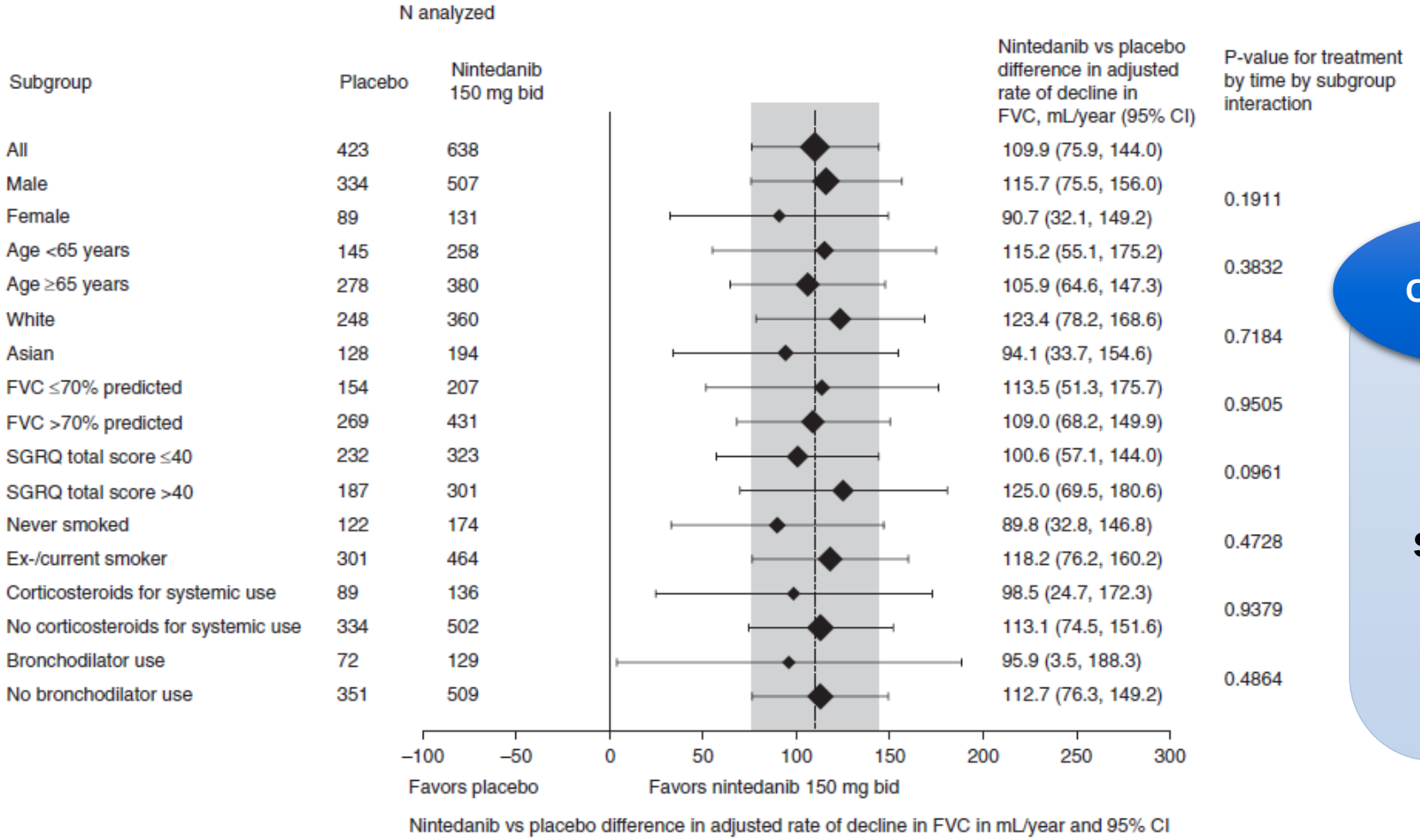
In the pooled population, pirfenidone reduced FVC decline in all patient subgroups

6MWD, 6-minute walk distance; CI, confidence interval; DLco, carbon monoxide diffusing capacity; FEV_1, forced expiratory volume in 1 second

Noble PW et al. Eur Respir J 2016;47:27-30

Nintedanib reduced FVC decline versus placebo consistently across a range of patient subgroups

Forest plot for the annual rate of decline in FVC (mL/year) by subgroup:



Based on a random coefficient regression with fixed effects for treatment, sex, age, height and random effect of patient-specific intercept and time. The vertical dashed line and shaded area show the point estimate and 95% CI for the overall pooled population.
SGRQ, St. George's Respiratory Questionnaire

Conclusions

Nintedanib reduced FVC decline in all patient subgroups including those with prior steroid or bronchodilator use

Costabel U et al. Am J Respir Crit Care Med 2016;193:178-185

In spite of these scientific evidence the question is still debated

Some physicians prefer not to treat patients with preserved lung volume.

Some patients prefer not to be treated because they have no clear symptoms

Efficacy of pirfenidone in patients with idiopathic pulmonary fibrosis with more preserved lung function

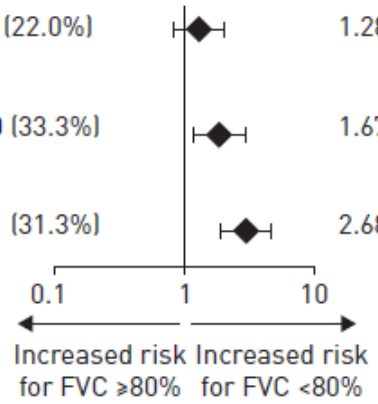
Carlo Albera[1], Ulrich Costabel[2], Elizabeth A. Fagan[3], Marilyn K. Glassberg[4], Eduard Gorina[3], Lisa Lancaster[5], David J. Lederer[6], Steven D. Nathan[7], Dominique Spirig[8] and Jeff J. Swigris[9]

Albera C et al. Eur Respir J 2016;48:843

Clinically significant disease progression occurred in patients with both more preserved and less preserved lung function at baseline

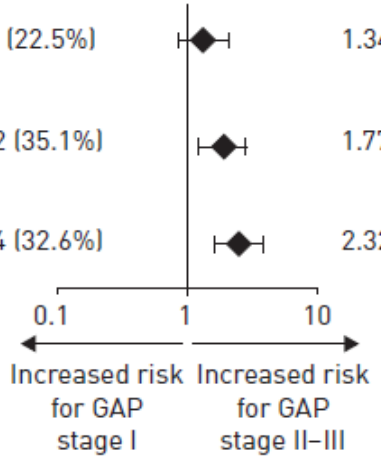
FVC ≥80% vs <80%

	FVC ≥80% event/total	FVC <80% event/total	Hazard ratio (95% CI)	Between-subgroup p-value
FVC decline ≥10% or death	30/168 (17.9%)	99/450 (22.0%)	1.28 (0.85–1.92)	0.2403
6MWD decline ≥50% m or death	36/168 (21.4%)	150/450 (33.3%)	1.67 (1.16–2.41)	0.0049
UCSD SOBQ total score change ≥20 points or death	22/169 (13.0%)	141/451 (31.3%)	2.68 (1.71–4.21)	<0.0001



GAP I vs GAP II/III

	GAP stage I event/total	GAP stage II–III event/total	Hazard ratio (95% CI)	Between-subgroup p-value
FVC decline ≥10% or death	42/234 (17.9%)	86/382 (22.5%)	1.34 (0.93–1.94)	0.1175
6MWD decline ≥50% m or death	51/234 (21.8%)	134/382 (35.1%)	1.77 (1.28–2.45)	0.0004
UCSD SOBQ total score change ≥20 points or death	38/234 (16.2%)	125/384 (32.6%)	2.32 (1.61–3.33)	<0.0001



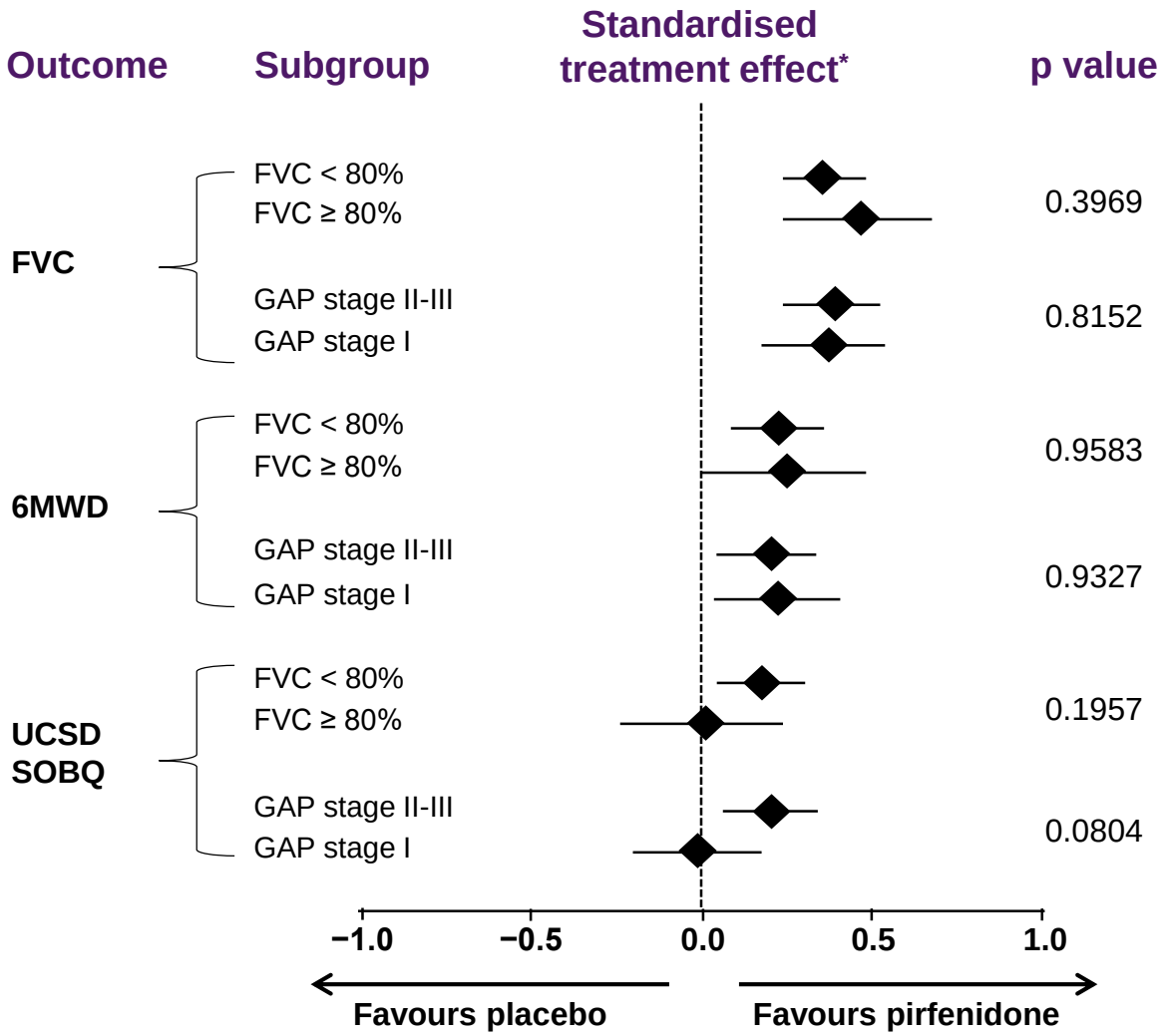
Patients n=1247
GAP, Gender, Age and Physiology; UCSD SOBQ, The University of California in San Diego Shortness of Breath Questionnaire

Conclusions

Patients with baseline FVC ≥80% or GAP stage I and patients with baseline FVC <80% or GAP stage II/III experienced clinically significant disease progression

Albera C et al. Eur Respir J 2016;48:843

Pirfenidone has a beneficial effect in patients with FVC ≥80% or GAP stage I



EVOLVING CONCEPT

Mild/moderate disease

↓

IPF with more preserved/ less preserved lung function

Conclusions

Pirfenidone had a similar effect in patients with FVC ≥80% vs <80% and GAP stage I vs II/III

Pirfenidone is efficaciuos in patients with more preserved lung function

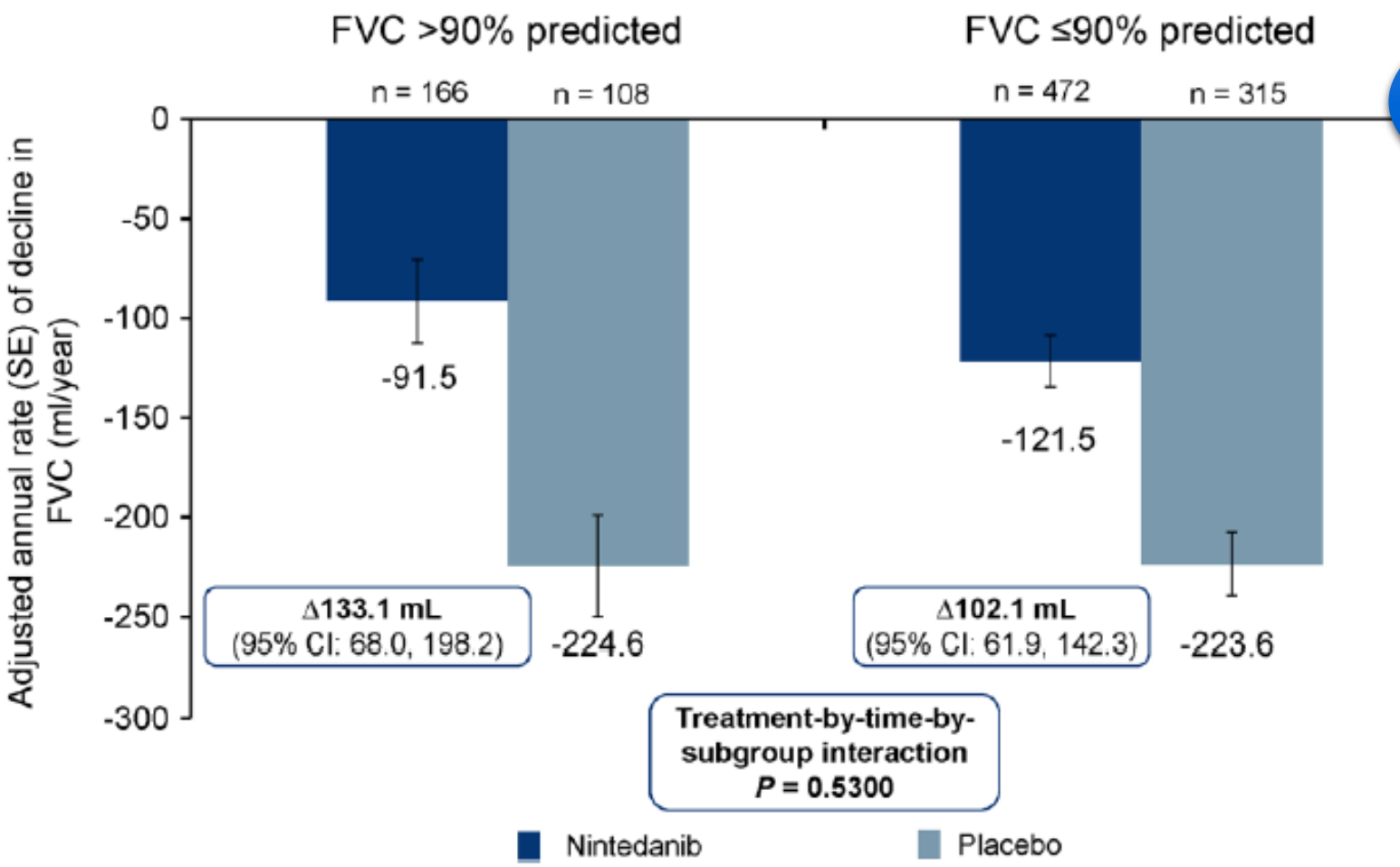
Patients n=1247

*For FVC and 6MWD: treatment difference = pirfenidone–placebo; for UCSD SOBQ, treatment difference = placebo–pirfenidone

Albera C et al. Eur Respir J 2016;48:843

Nintedanib provided similar benefits in patients with preserved (FVC >90%) and impaired (FVC ≤90%) lung volume

Adjusted annual rate (SE) of decline in FVC (mL/year)



Conclusions

Nintedanib had a similar effect on FVC decline in patients with FVC >90% and ≤90%

SE, standard error

Kolb M et al. Thorax 2016; Epub ahead of print

OPEN ACCESS

ORIGINAL ARTICLE

Nintedanib in patients with idiopathic pulmonary fibrosis and preserved lung volume

Martin Kolb,[1] Luca Richeldi,[2] Jürgen Behr,[3] Toby M Maher,[4,5] Wenbo Tang,[6] Susanne Stowasser,[7] Christoph Hallmann,[7] Roland M du Bois[8]

Key messages

What is the key question?

- Do patients with idiopathic pulmonary fibrosis (IPF) and preserved lung volume receive the same benefit from nintedanib as patients with more impaired lung volume?

What is the bottom line?

- Patients with IPF and FVC >90% predicted at baseline have the same rate of FVC decline and receive the same benefit from nintedanib as patients with more impaired lung volume.

Why read on?

- These data provide, for the first time, evidence in a significant subgroup of patients with preserved lung volume to support the concept of offering early treatment to patients with IPF.

Kolb M, *et al*. *Thorax* 2016;**0**:1–7. doi:10.1136/thoraxjnl-2016-208710

When anti-fibrotic treatment should be stopped?

It should be stopped if we have functional decline?

It should be stopped before lung transplantation?

It should be stopped before surgery?

OPEN ACCESS

ORIGINAL ARTICLE

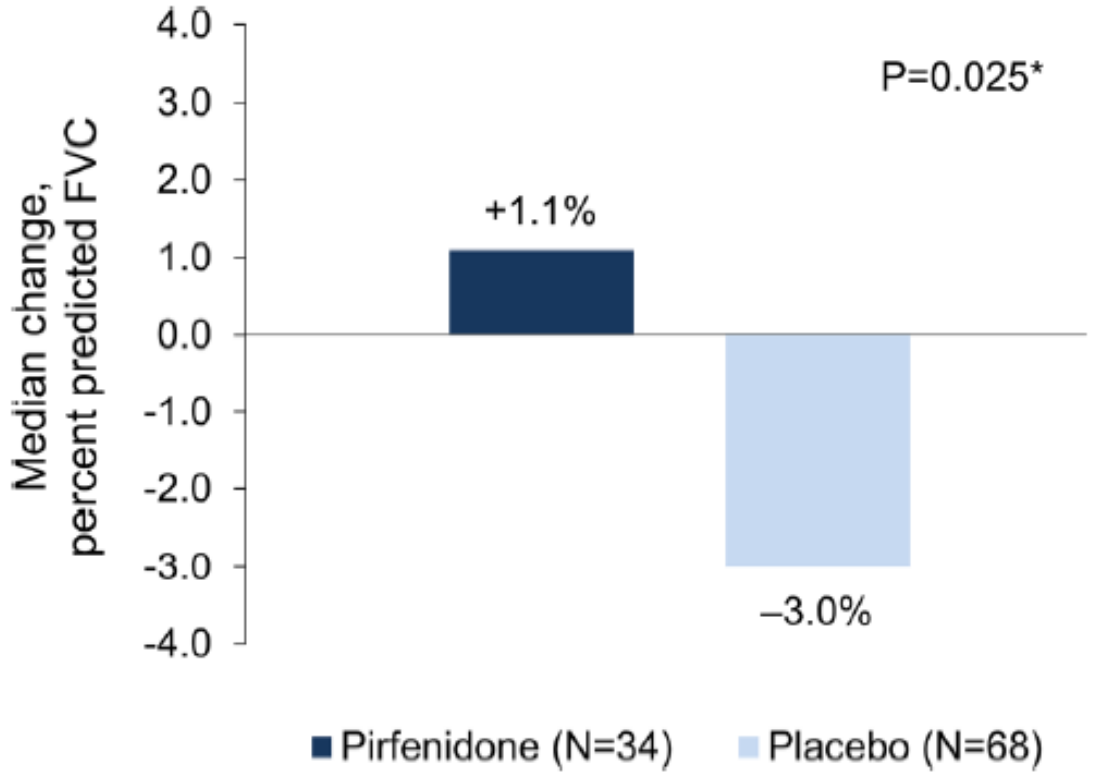
Effect of continued treatment with pirfenidone following clinically meaningful declines in forced vital capacity: analysis of data from three phase 3 trials in patients with idiopathic pulmonary fibrosis

Steven D Nathan,[1] Carlo Albera,[2] Williamson Z Bradford,[3] Ulrich Costabel,[4] Roland M du Bois,[5] Elizabeth A Fagan,[3] Robert S Fishman,[3] Ian Glaspole,[6] Marilyn K Glassberg,[7] Kenneth F Glasscock,[3] Talmadge E King Jr,[8] Lisa Lancaster,[9] David J Lederer,[10] Zhengning Lin,[3] Carlos A Pereira,[11] Jeffrey J Swigris,[12] Dominique Valeyre,[13] Paul W Noble,[14] Athol U Wells[15]

Nathan SD et al. Thorax 2016;71:429-435

Continued treatment with pirfenidone following a ≥10% decline in FVC improved outcomes for patients in the following 6 months

Median change in % predicted FVC during the 6-month period following an initial decline in FVC ≥10%



	Pirfenidone (N=34)	Placebo (N=68)	Relative difference (%)	p Value†
≥10% decline in FVC or death	2 (5.9%)	19 (27.9%)	–78.9	0.009
No further decline in FVC‡	20 (58.8%)	26 (38.2%)	53.8	0.059
Death	1 (2.9%)	14 (20.6%)	–85.7	0.018

Conclusions

Patients who have an initial decline in FVC ≥10% benefit from continued treatment with pirfenidone compared with placebo

*Rank analysis of covariance with ranked change from baseline as the outcome variable; study, treatment, and region as fixed effects; and ranked baseline FVC as a covariate. Deaths are ranked worst according to time until death

†Fisher's exact test

‡Either no decline or increase in FVC

Nathan SD et al. Thorax 2016;71:429-435

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

BMC Pulmonary Medicine

RESEARCH ARTICLE Open Access

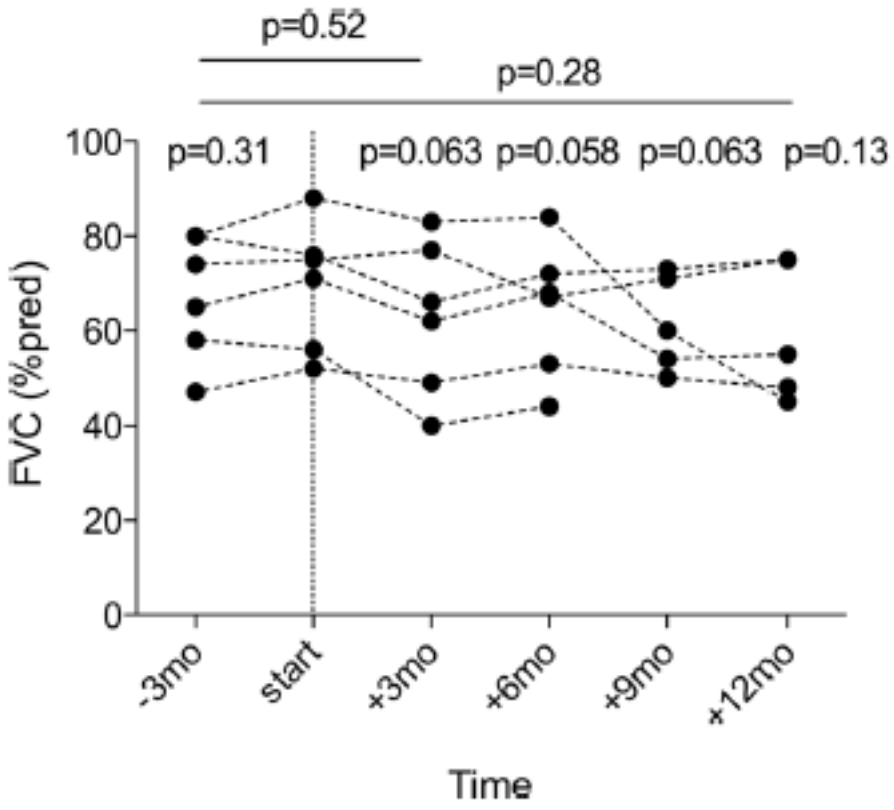
Safety and efficacy of bridging to lung transplantation with antifibrotic drugs in idiopathic pulmonary fibrosis: a case series

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*]

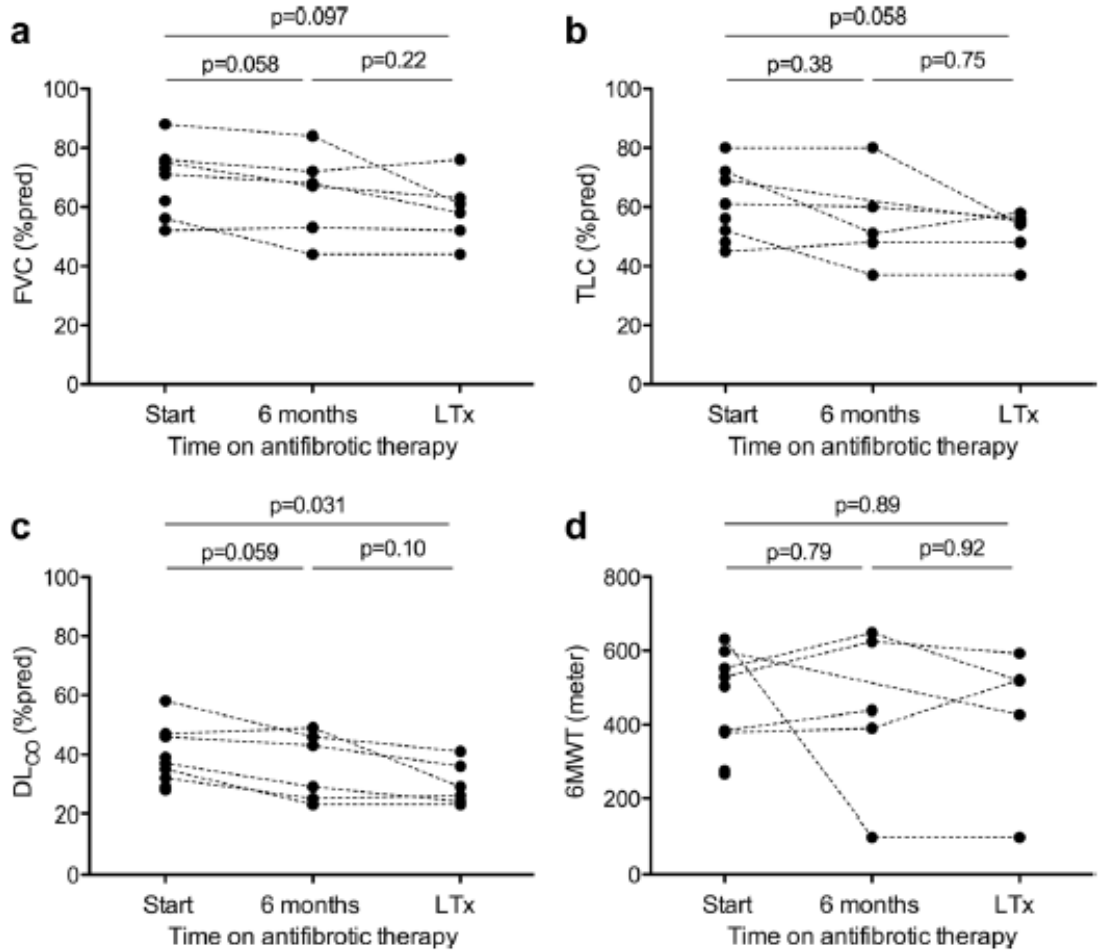
A total of 9 IPF patients were treated with antifibrotics and subsequently underwent LTx:

pirfenidone n = 7 (n = 2 study vs. n = 5 open-label treatment),
nintedanib n = 2 (n=2 study).

Forced Vital Capacity in IPF patients with at least 6 months antifibrotic therapy before transplantation



Pretransplant evolution of pulmonary function and functional exercise capacity following treatment with antifibrotic drugs



Delanote et al. BMC Pulmonary Medicine (2016) 16:156

In summary, antifibrotic drugs are showed to be safe in IPF patients undergoing LTx.

By attenuating disease progression while awaiting LTx, these antifibrotics may perhaps further help to reduce the number of IPF patients dying on the waiting list.

Antifibrotic therapy was continued until the day of transplant procedure.

All patients received the full, recommended dose (i.e. 801 mg tid for pirfenidone and 150 mg bid for nintedanib).

Post-operatively, no problems with bleeding or thoracic wound healing were observed

None of the patients developed chronic lung allograft dysfunction after a median follow-up of 19.8 (11.2–26.5) months; and **post-transplant survival was 100% after 1 year and 80% after 2 years.**

Antifibrotic drugs can probably be safely administered in IPF patients, possibly attenuating disease progression over time, while awaiting LTx.

Iwata et al. Respiratory Research (2016) 17:90
DOI 10.1186/s12931-016-0398-4

Respiratory Research

RESEARCH Open Access

A phase II trial evaluating the efficacy and safety of perioperative pirfenidone for prevention of acute exacerbation of idiopathic pulmonary fibrosis in lung cancer patients undergoing pulmonary resection: West Japan Oncology Group 6711 L (PEOPLE Study)

Takekazu Iwata[1], Ichiro Yoshino[1*], Shigetoshi Yoshida[1], Norihiko Ikeda[2], Masahiro Tsuboi[3], Yuji Asato[4], Nobuyuki Katakami[5], Kazuhiro Sakamoto[6], Yoshinori Yamashita[7], Jiro Okami[8], Tetsuya Mitsudomi[9], Motohiro Yamashita[10], Hiroshi Yokouchi[11], Kenichi Okubo[12], Morihito Okada[13], Mitsuhiro Takenoyama[14], Masayuki Chida[15], Keisuke Tomii[16], Motoki Matsuura[17], Arata Azuma[18], Tae Iwasawa[19], Kazuyoshi Kuwano[20], Shuji Sakai[21], Kenzo Hiroshima[22], Junya Fukuoka[23], Kenichi Yoshimura[24], Hirohito Tada[25], Kazuhiko Nakagawa[26], Yoichi Nakanishi[27] and West Japan Oncology Group

IPF is often accompanies lung cancer, and life-threatening acute exacerbation (AE) of IPF (AE-IPF) is reported to occur in 20 % of IPF patients who undergo lung cancer surgery.

A phase II study was conducted to evaluate whether perioperative pirfenidone treatment could reduce the incidence of postoperative AE-IPF patients with lung cancer.

Pirfenidone was orally administered to IPF patients who were candidates for lung cancer surgery at 600 mg/day for the first 2 weeks, followed by 1200 mg/day.

Surgery was performed after at least 2 weeks of 1200-mg/day administration.

The primary endpoint was non–AE-IPF rate during postoperative days 0–30, compared to the null value of 80 %, and the secondary endpoint was safety.

Iwata et al. Respiratory Research (2016) 17:90

Radiologic and pathologic diagnoses of IPF and AE-IPF were confirmed by an independent review committee..

AE-IPF did not occur in 37/39 patients (94.9 % [95 % confidential interval: 82.7–99.4 %, p = 0.01]) in the FAS, and in 38/39 patients (97.2 % [95 % confidential interval: 85.5–99.9 %, p = 0.004] in the PPS.
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Conclusions
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In conclusion, this single-arm phase II study revealed that perioperative pirfenidone treatment is **safe and promising for reducing AE-IPF after lung cancer surgery.**

These results encourage the planning of future confirmatory studies to compare pirfenidone to other treatments, such as nintedanib, for which the efficacy against progression of IPF has already been reported [

Now, let’s answer to Sergio’s questions

When anti-fibrotic treatment should be started?
- As soon as diagnosis is made, evidence show the treatments should be started even in patients with preserved lung function

When anti-fibrotic treatment should be stopped?
- Should not be stopped neither if a functional decline is evident nor in specific conditions like lung Tx and surgery for cancer.

However…the situation in real life it is different

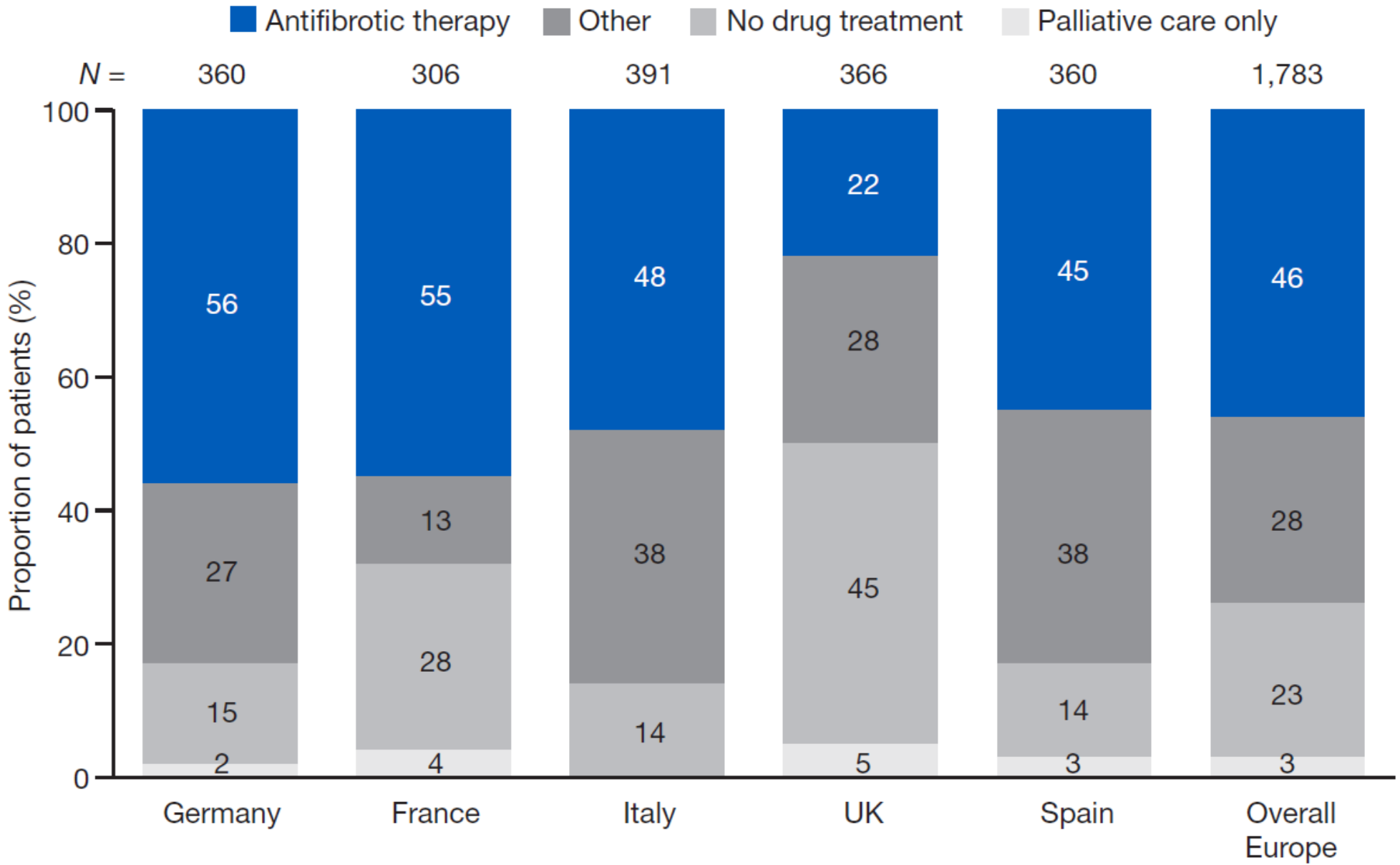
Unmet needs in the treatment of idiopathic pulmonary fibrosis—insights from patient chart review in five European countries

Toby M. Maher[1], Maria Molina-Molina[2], Anne-Marie Russell[1], Francesco Bonella[3], Stéphane Jouneau[4], Elena Ripamonti[5], Judit Axmann[6], Carlo Vancheri[7]

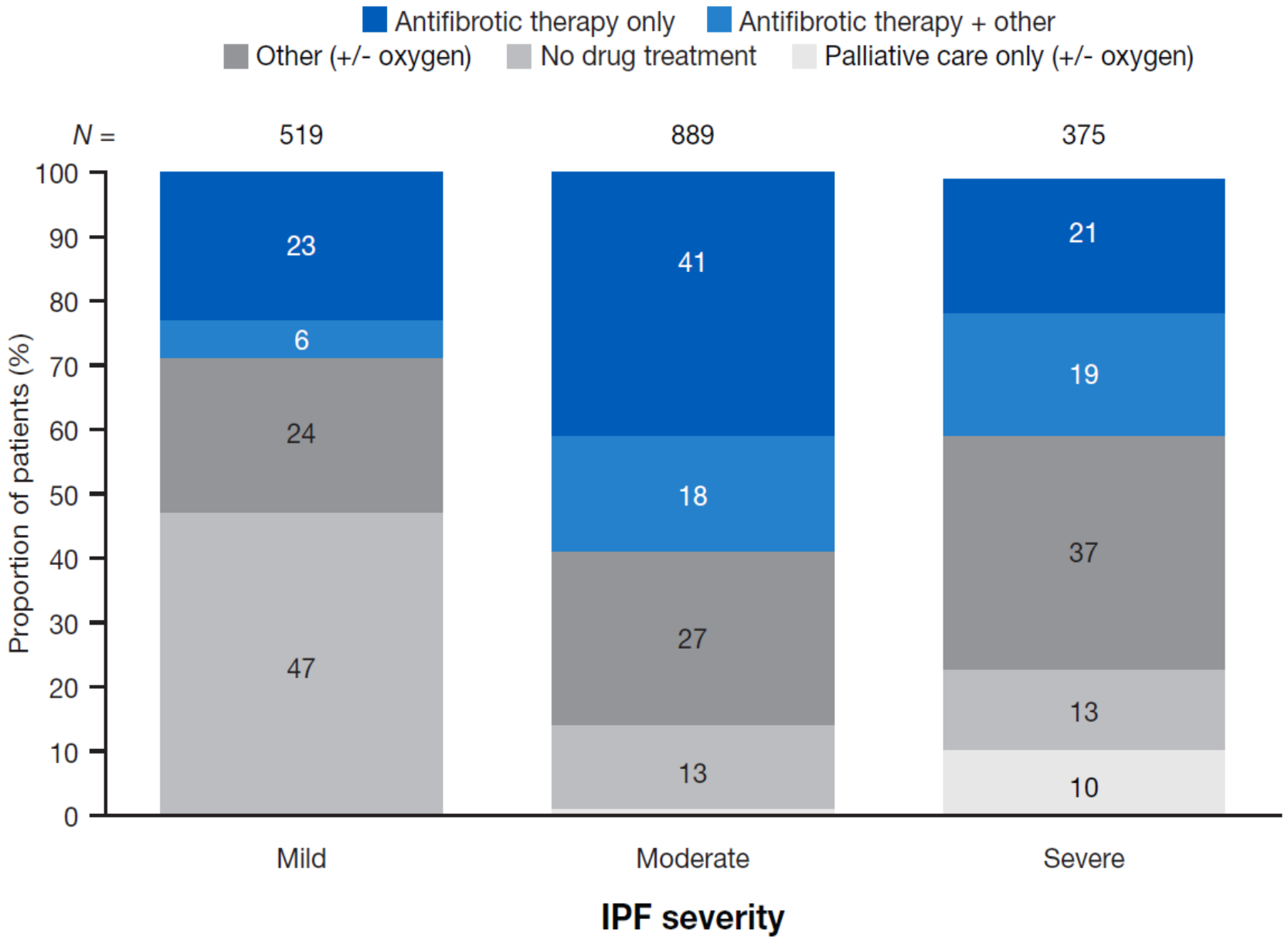
Sample size	# respondents W4	# patients charts W4
EU	**290**	**1.838**
DE	**60**	**360**
FR	**51**	**306**
IT	**70**	**420**
UK	**49**	**392**
ES	**60**	**360**
CANADA	**30**	**180**

(Submitted)

Proportion of patients that are treated or untreated across European countries



Overall proportion of treated and untreated patients based on current disease severity



Physicians less keen to use approved IPF drugs are strongly driven by symptoms when choosing not to prescribe any treatment

TOP 5 Physicians' **barriers to tx** based on their prescribing behaviour
(# of Approved Tx vs No Tx & Not Approved Tx patient charts)

★ Stat Sign Diff 99-95%

	Physicians with **Approved Tx <** No Tx & Not Approved Tx Patients	Physicians with **Approved Tx >** No Tx & Not Approved Tx Patients
1	**Lack or few symptoms** 34% ★	**Patient's refusal** 32% ★
2	**Good QoL** 24%	**Old age** 26%
3	**Stable disease** 21%	**Stable disease** 25%
4	**Patient's refusal** 19%	**Good QoL** 22%
5	**Old age** 15%	**Co-morbidities** 19% ★

Base: All Patient Charts – App < No 165 – App > No 68

In the EU, 54% of IPF patients are not receiving an approved IPF drug.

"WHO ARE THESE PATIENTS?"

"WHO ARE THEIR DOCTORS?"

UNIVERSITA di CATANIA – SCUOLA DI MEDICINA

DIPARTIMENTO DI MEDICINA CLINICA E SPERIMENTALE

“CENTRO di RIFERIMENTO REGIONALE per le MALATTIE RARE del POLMONE”

When to start and when to stop anti-fibrotic therapies?

Carlo Vancheri