Real world experiences in the treatment of IPF

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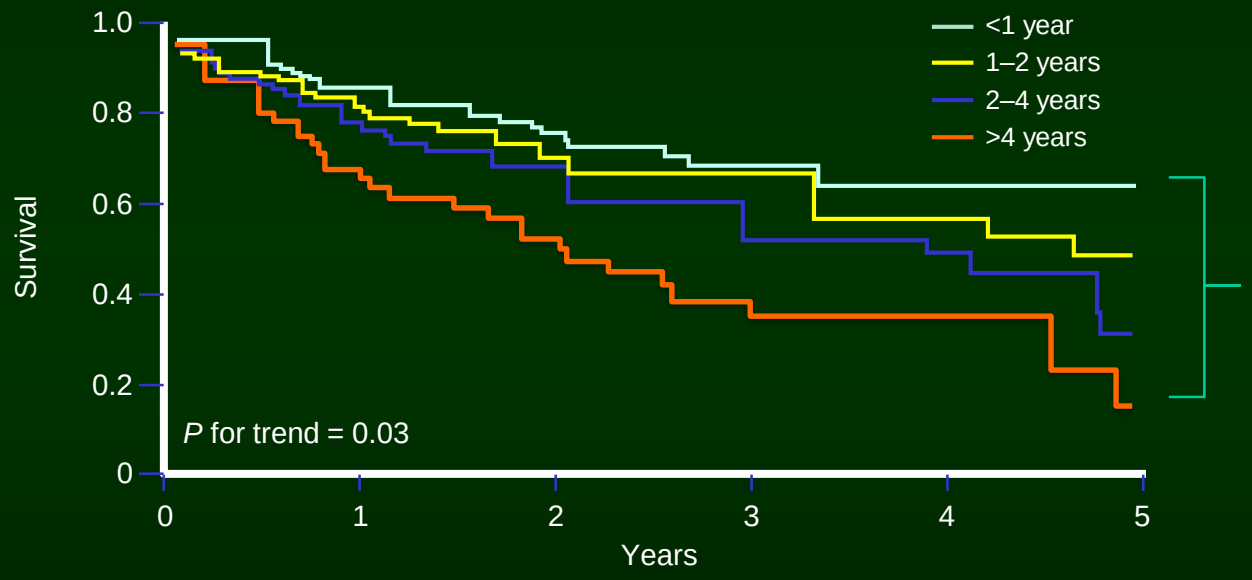
Delays in the referral of patients to tertiary care centers contribute to poor patient prognosis

Mortality risk is higher with longer referral delays, regardless of disease severity[1]



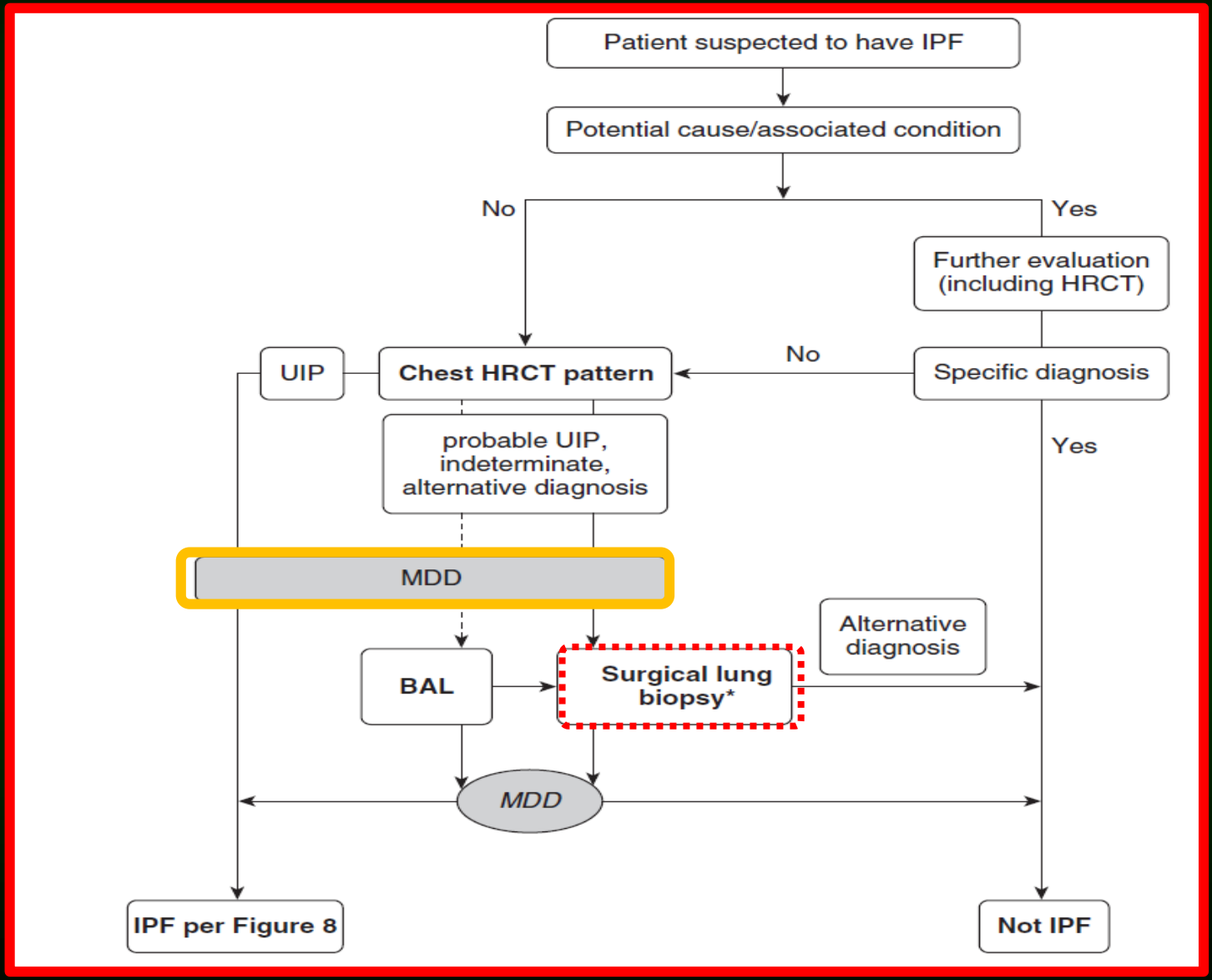
Delays likely lead to a poorer prognosis:

- **Irreversible lung changes have already occurred[2]**
- **Possible misdiagnosis and use of inappropriate therapies[3]**

Survival rate is 3.4 times higher when patients are referred for tertiary care evaluation within 1 year of symptom onset versus 4 years[1]

1. Lamas DJ *et al. Am J Respir Crit Care Med* 2011;184:842–847
2. Molina-Molina M *et al. Exp Rev Resp Med* 2018;12:537–539
3. Cosgrove GP *et al. BMC Pulm Med* 2018;18:9

2018 Diagnosis of IPF
An official ATS/ERS/JRS/ALAT clinical practice guideline



- Surgical lung biopsy is not indicated in patients at high risk for intra-, peri-, or postoperative complications (e.g., severe hypoxemia at rest and/or severe pulmonary hypertension with a diffusion capacity less than 25% after correction for hematocrit).
- Surgical lung biopsy may be unnecessary in some familial cases.
- The panel has no recommendation for or against conventional transbronchial biopsyand/or cryobiopsy; however, if performed, histopathology may be sufficient in selected patients.

Am J Respir Crit Care Med Vol 198, Iss 5, pp e44–e68, Sep 1, 2018

Fleischner Society White Paper :

Pathways to a confident working multidisciplinary diagnosis of IPF

When can one make a confident diagnosis of IPF without biopsy?

- ✓ Clinical context of IPF*, with CT pattern of typical or probable UIP

When is a diagnostic biopsy necessary to make a confident diagnosis of IPF?

- ✓ Clinical context of IPF* with CT pattern either indeterminate or suggestive of an alternative diagnosis
- ✓ Clinical context indeterminate for IPF† with any CT pattern

When is multidisciplinary diagnosis necessary in the context of suspected IPF?

- ✓ When the clinical context or the CT pattern, or both, are indeterminate; the outcome of multidisciplinary discussion will be a decision whether to perform an additional clinical evaluation, bronchoalveolar lavage, or diagnostic biopsy, or some combination of these procedures
- ✓ After biopsy, to integrate the clinical, imaging, and histological features
- ✓ To re-review patients in whom the longitudinal course of disease is discordant with the previously established multidisciplinary diagnosis
- ✓ When diagnostic tissue is not available, to consider a working diagnosis of IPF

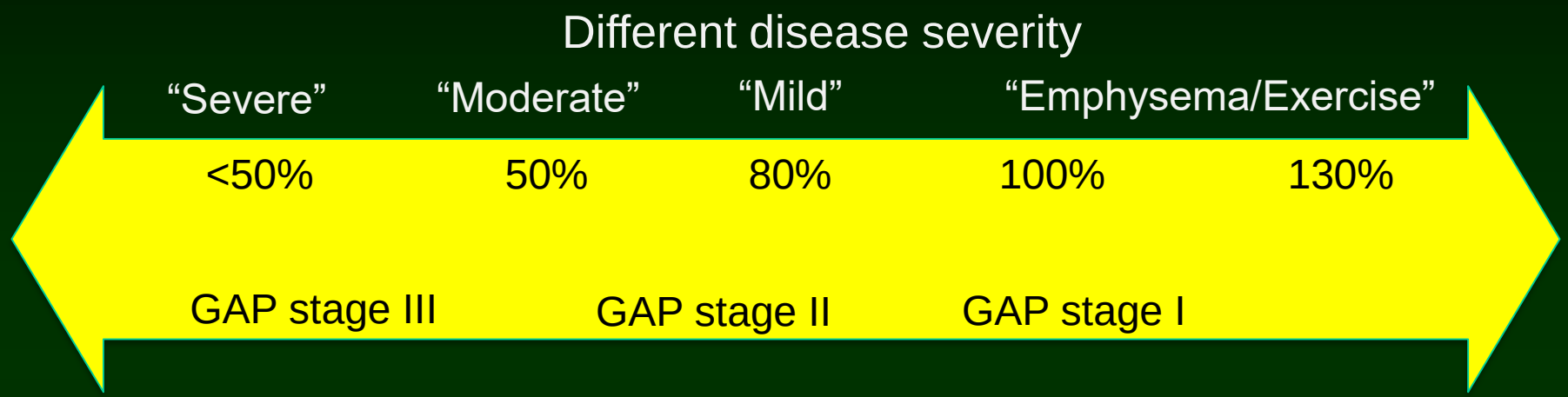
What should be done when diagnostic tissue is not available?

- ✓ Multidisciplinary diagnosis with consideration of the patient's age, sex, smoking status, findings on bronchoalveolar lavage, and longitudinal disease behaviour
- ✓ In this context, a working diagnosis of IPF can be made in the presence of a progressive fibrosing interstitial pneumonia, and in the absence of an alternative explanation; the level of diagnostic confidence of such a working diagnosis should be recorded, and the diagnosis should be reviewed at regular intervals, since it might change over time

*Clinical context of IPF includes all of the following: older than 60 years, absence of clinically significant environmental or medication exposure, no evidence of connective tissue disease.
†Clinical context indeterminate for IPF includes any of the following: aged 60 years or younger, potentially significant environmental or medication exposure, or evidence of connective tissue disease.

Lancet Respir Med 2017

Broad range of IPF patient types



HRCT pattern w/wo definite finding

Comorbidities (GERD, emphysema, PH, others)

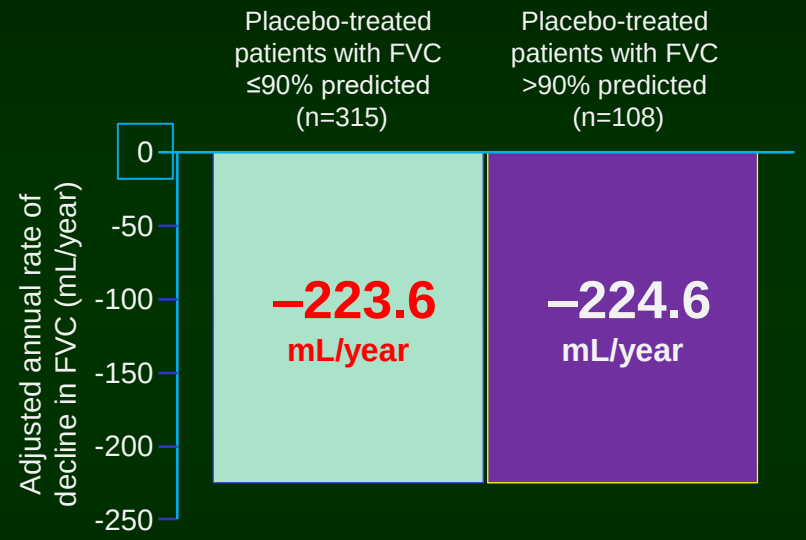
Biomarker

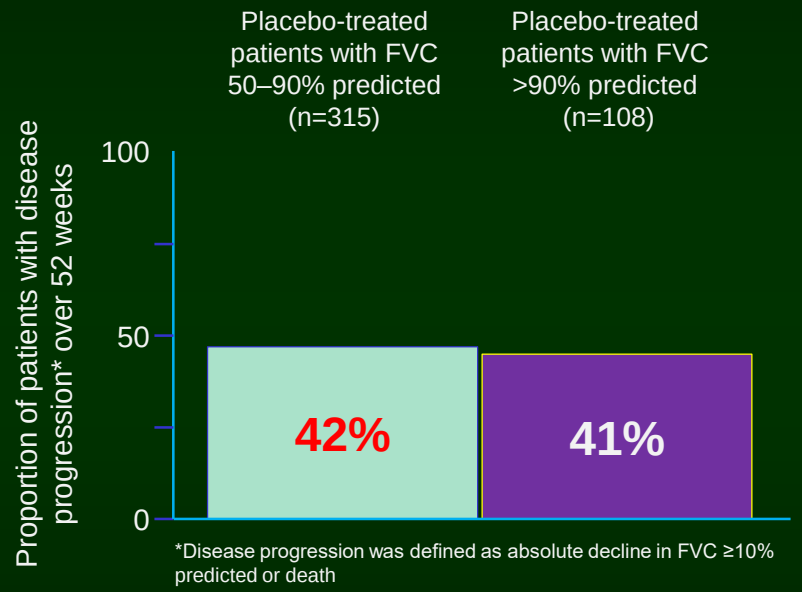
Concomitant medicine

Optimal management of IPF

- When?
- How?
- Which one?

Patients with IPF with preserved lung function have a high risk of disease progression

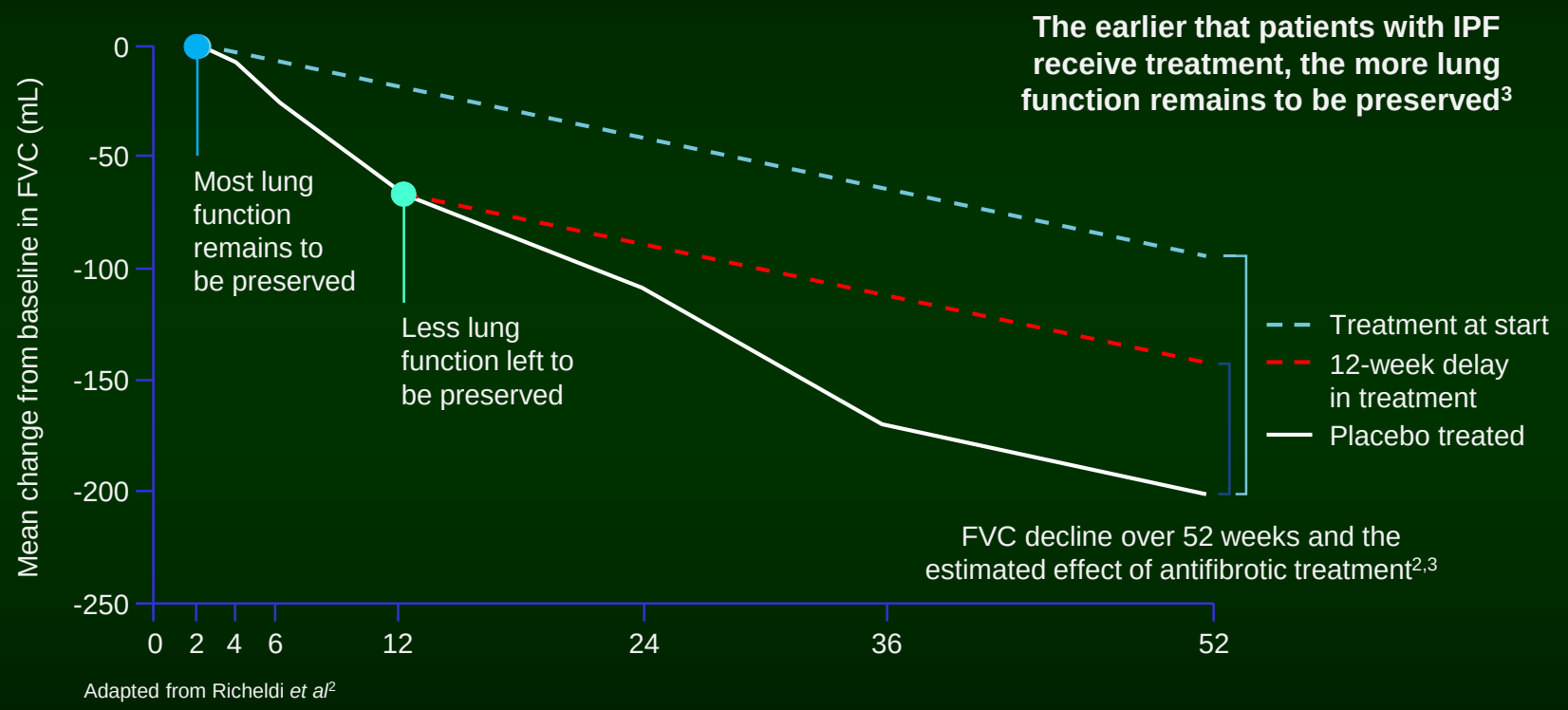




Patients with IPF with preserved lung function (FVC >90% predicted) have the same rate of FVC decline as patients with more impaired lung function[1]

1. Kolb M *et al. Thorax* 2017;72:340–346

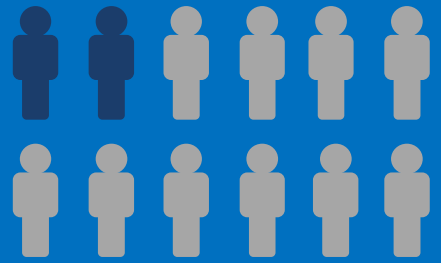
Early intervention could help to preserve lung function before it is lost irredeemably



1. Richeldi L *et al. N Engl J Med* 2014;370:2071–2082
2. Kolb M *et al. Thorax* 2017;72:340–346

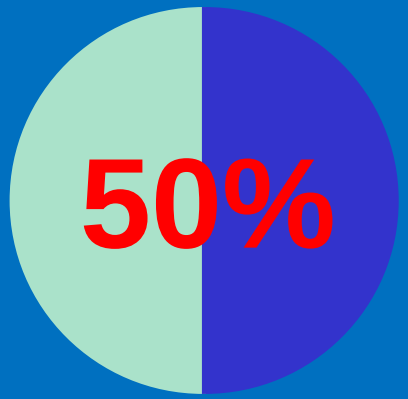
Acute exacerbations can occur in all patients with IPF

Physicians report acute exacerbations in the past year in **16% of patients with IPF and mild lung function impairment**[1]



Median survival in patients with IPF after an acute IPF exacerbation is **~3–4 months**[2]

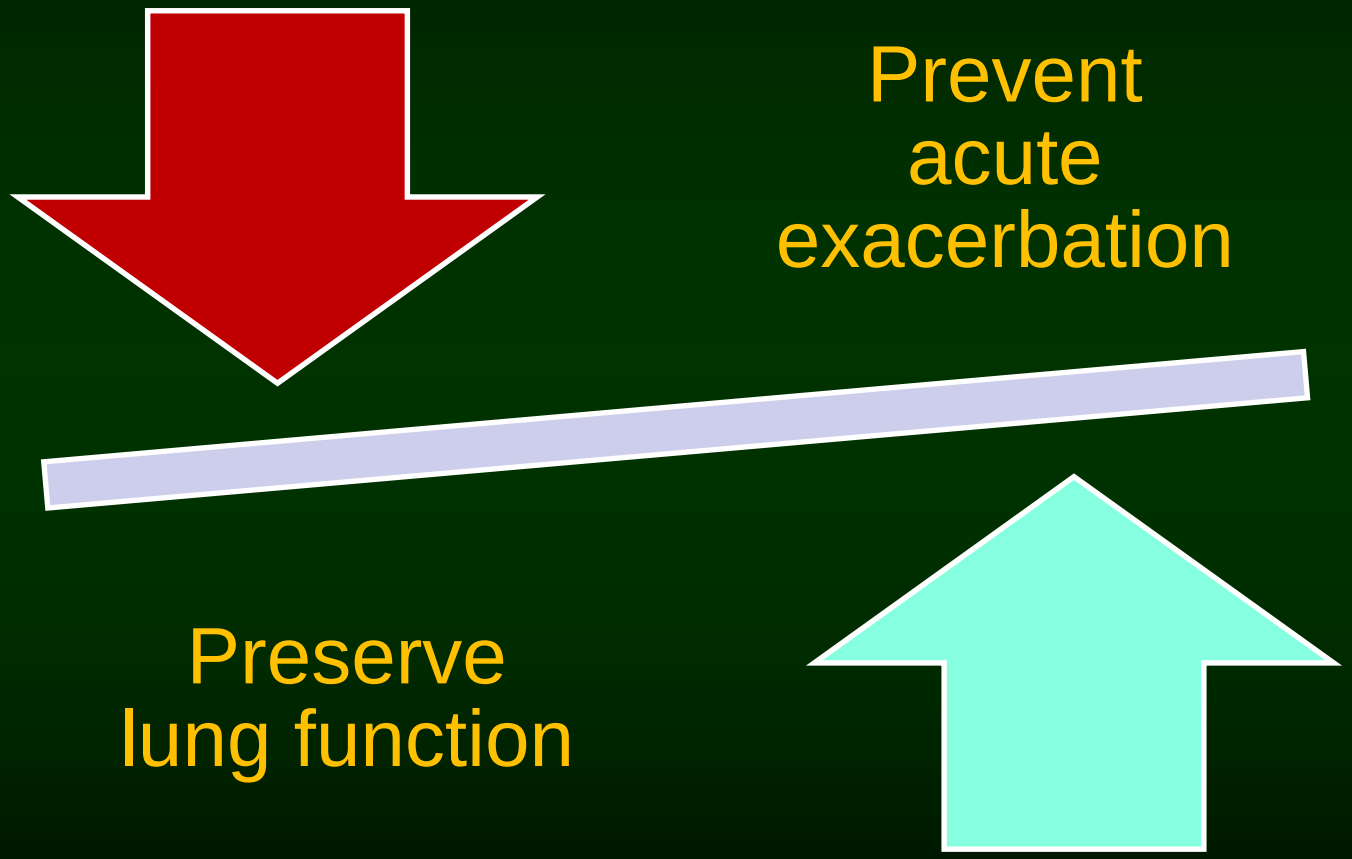
50% of patients hospitalized for an acute IPF exacerbation **die during hospitalization**[3]



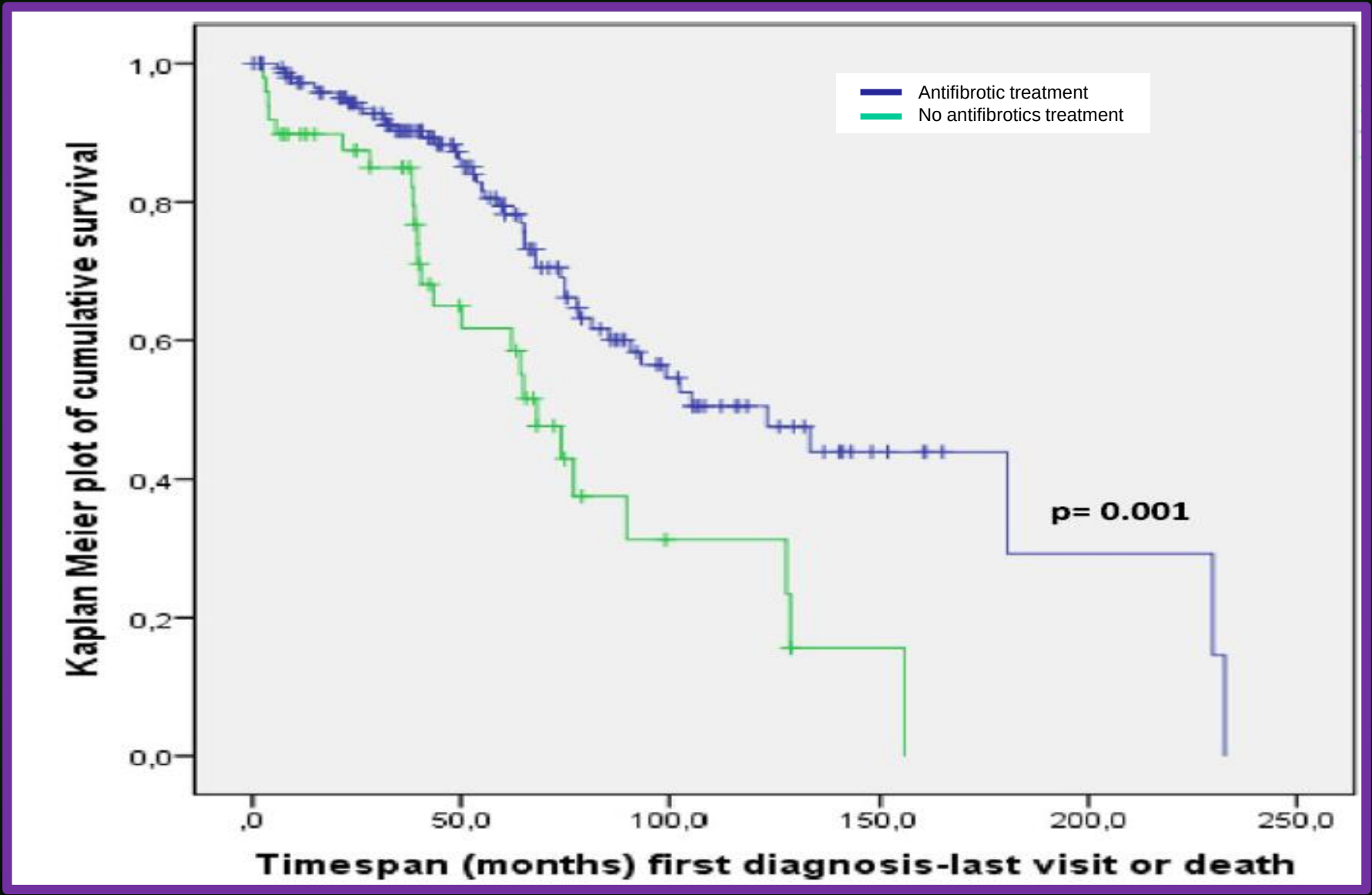
Low or worsening FVC is a risk factor for acute exacerbations, although they can occur in all patients.[3,4] Theoretically, preservation of FVC could reduce the risk of acute exacerbations

1. Maher TM *et al. BMC Pulm Med* 2017;17:124; 2. Collard HR *et al. Am J Respir Crit Care Med* 2016;194:265–275;
3. Song JW *et al. Eur Respir J* 2011;37:356–363; 4. Costabel U *et al. Am J Respir Crit Care Med* 2016;193:178–185

Key components of slowing disease progression



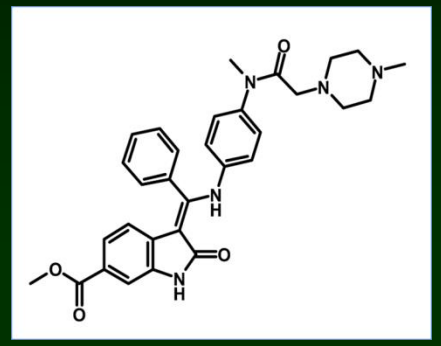
Early intervention improves the survival rate of IPF



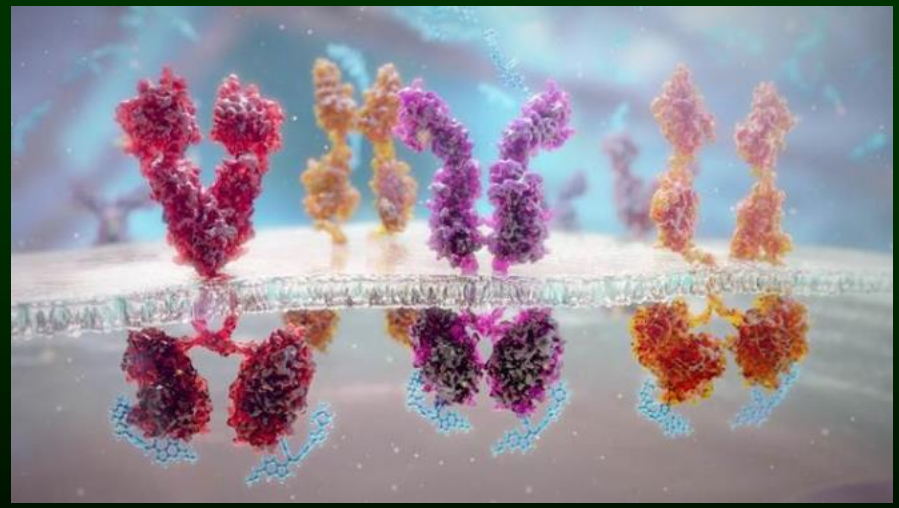
Respiratory Research 2018;19:141
European registry for idiopathic pulmonary fibrosis (eurIPFreg)

Nintedanib:
A potent intracellular tyrosine kinase inhibitor

- Nintedanib targets the vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) receptors



- Nintedanib acts by blocking the intracellular ATP binding site of the receptors and with it activation and signaling



Hilberg F, *et al. Cancer* Res 2008;68:4774–4782; Wollin L, *et al.* J *Pharmacol Exp Ther* 2014;349:209–220.

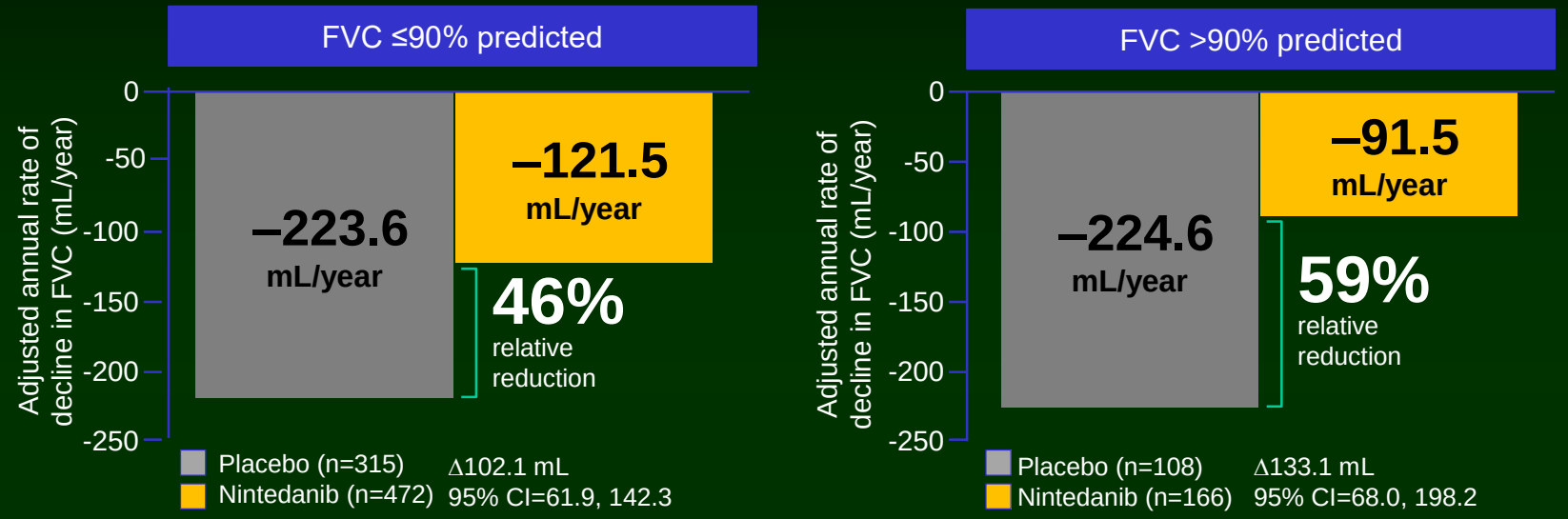
Anti-fibrotic, anti-inflammatory and vascular remodeling effects of nintedanib

- Nintedanib has anti-fibrotic, anti-inflammatory and vascular remodelling effects in non-clinical models of SSc and ILD that suggest it may be effective as a treatment for SSc-ILD

Anti-fibrotic[1–5]	Anti-inflammatory[1-3, 5 -8]	Vascular remodelling[3,8]
• Profibrotic mediators ↓ • Fibroblast proliferation and migration ↓ • Fibroblast differentiation ↓ • Myofibroblasts in skin and lung ↓ • Secretion of extracellular matrix ↓ • Lung and skin fibrosis in animal models ↓	• Interferon-γ ↓ • Interleukins 1β, 2, 4, 5, 6, 10, 12p70 and 13↓ • TGF-β ↓ • Polarisation of M2 macrophages ↓ • Neutrophils ↓ • Lymphocytes ↓ • Inflammation and granuloma in animal models ↓	• Vascular smooth muscle cells ↓ • Microvascular endothelial cells apoptosis ↓ • Vessel wall thickness ↓ • Occluded vessels ↓ • Capillary loss ↓ • Distorted microvascular architecture in lungs ↓

1. Wollin L, et al. Eur Respir J 2015;45:1434–45. 2. Huang J, et al. Ann Rheum Dis 2016;75:883–90.
3. Huang J, et al. Ann Rheum Dis 2017;76:1941-48. 4. Wollin L, et al. Eur Respir J 2017;PA903.
5. Wollin L et al. Am J Respir Crit Care Med 2017;195:A2450. 6. Tandon K, et al. Am J Respir Crit Care Med 2017;195:A2397.
7. Wollin L, et al. J Pharmacol Exp Ther 2014;349:209-220. 8. Ackermann M, et al. Angiogenesis 2017;20:359-372.

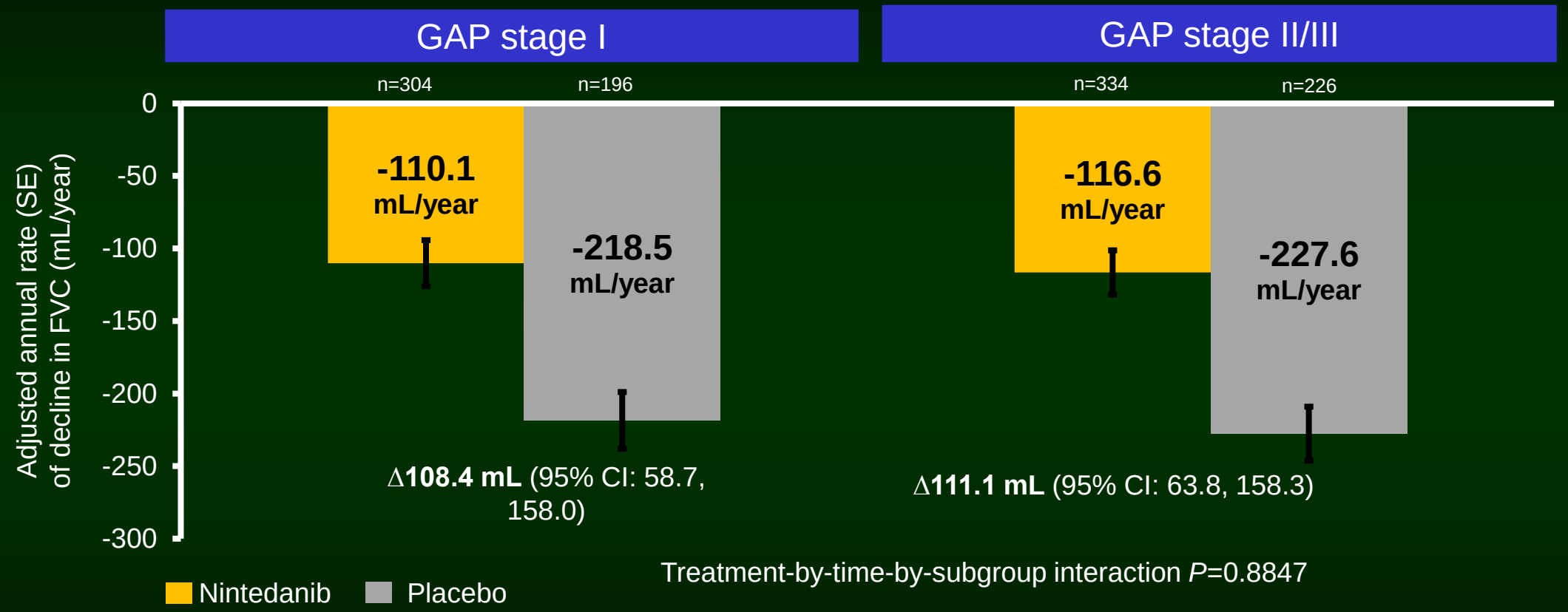
Nintedanib demonstrated a beneficial effect in patients with minimally impaired lung function at baseline



Placebo-treated patients with FVC >90% predicted at baseline experienced an annual rate of FVC decline similar to patients with FVC ≤90% predicted at baseline[1]

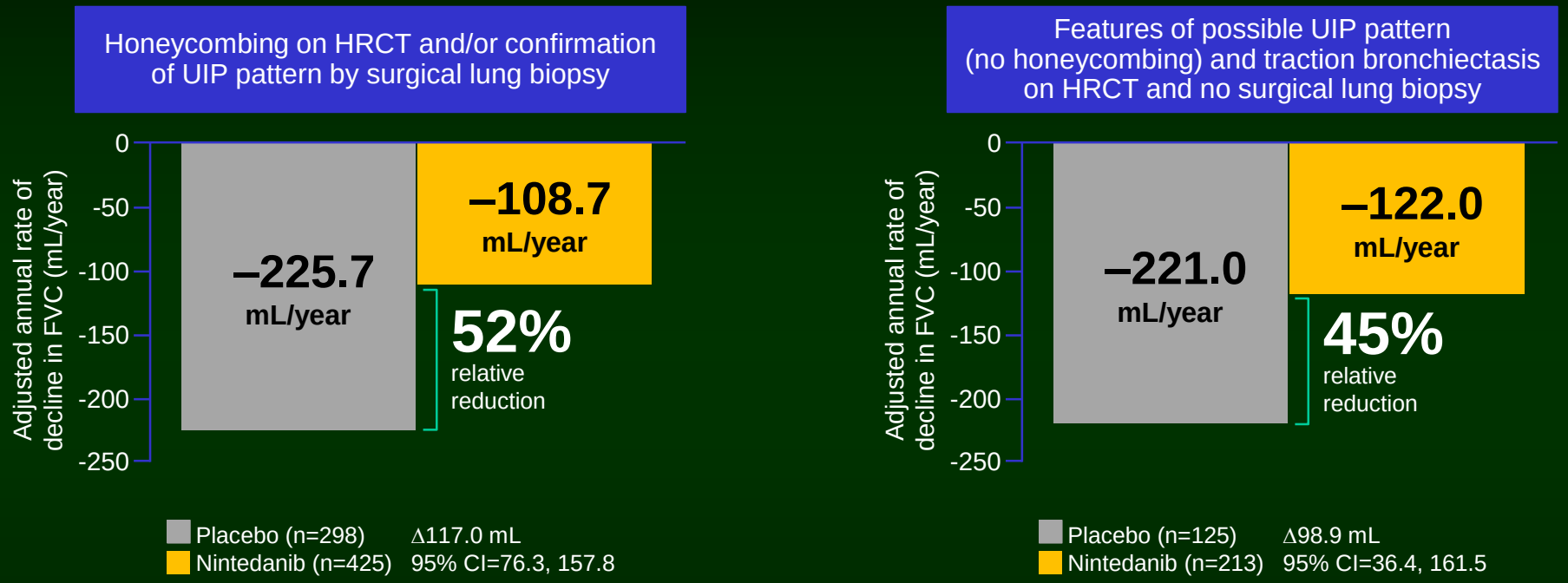
1. Kolb M *et al. Thorax* 2017;72:340–346

Nintedanib reduced the annual rate of decline in FVC by 50% irrespective of GAP stage at baseline



Ryerson CJ *et al.* *ERJ Open Res* 2019; 5: 00127-2018

Patients with IPF benefit from nintedanib when HRCT shows possible UIP

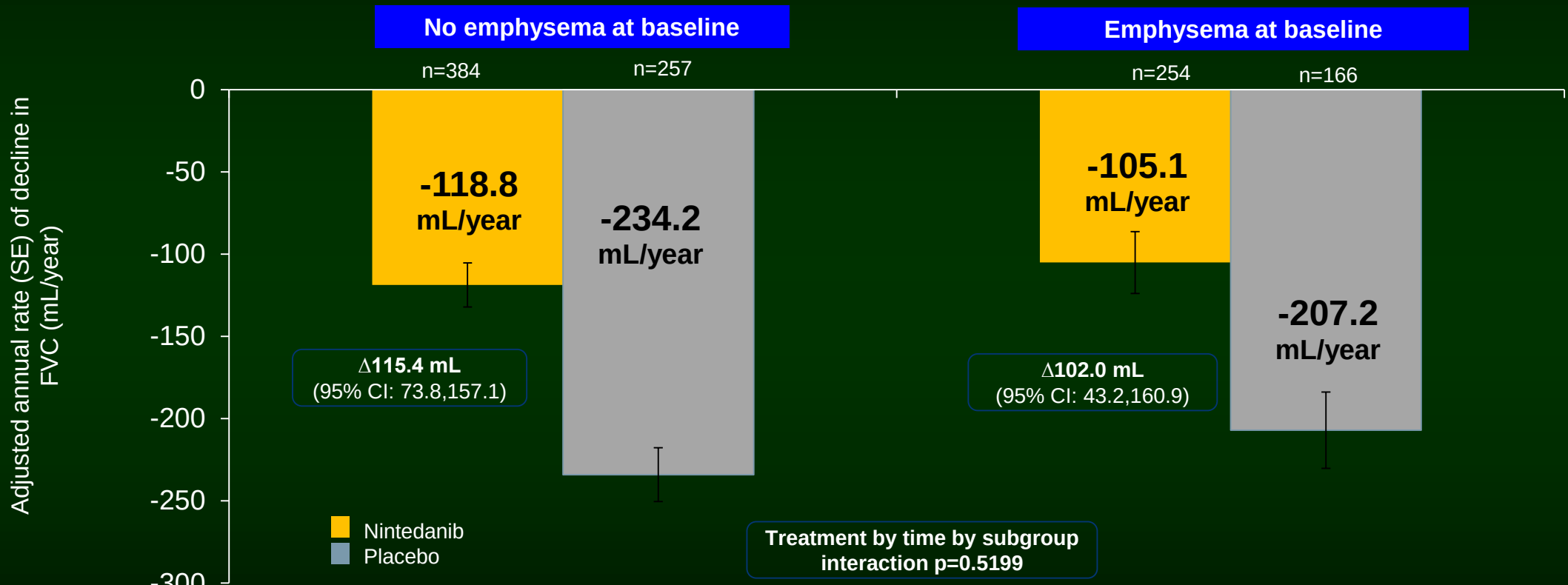


Placebo-treated patients with evidence of honeycombing on HRCT experienced an annual rate of FVC decline similar to patients without evidence of honeycombing on HRCT

Raghu G *et al. Am J Respir Crit Care Med* 2017;195:78–85

Nintedanib is effective for IPF patients with/without emphysema

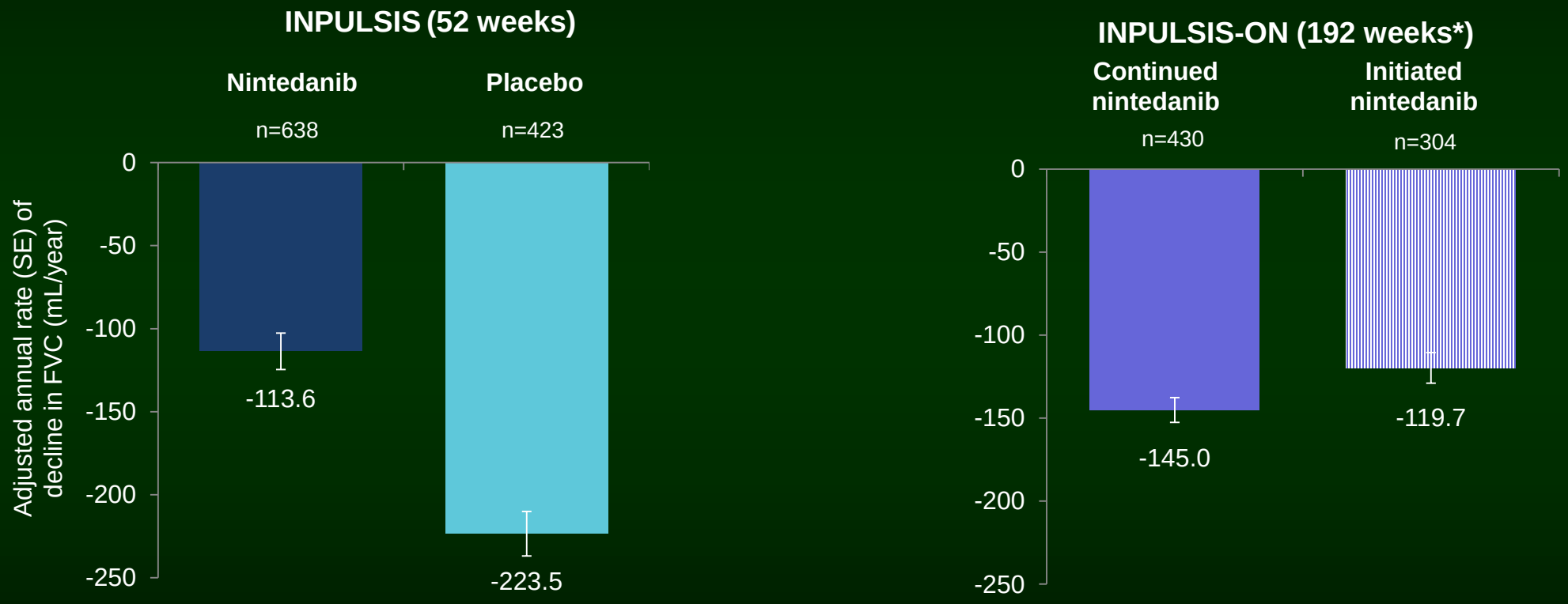
Annual rate of decline in FVC in subgroups by absence/presence of emphysema at baseline:



Cottin V, Azuma A, Raghu G, *et al*. Therapeutic effects of nintedanib are not influenced by emphysema in the INPULSIS trials. *Eur Respir J* 2019; in press

Long term efficacy of Nintedanib on slowing FVC decline INPULSIS and INPULSIS-ON:

Annual rate of decline in FVC beyond 4 years



*Time point reached by last patient in INPULSIS-ON who was still receiving nintedanib when BI stopped the trial.

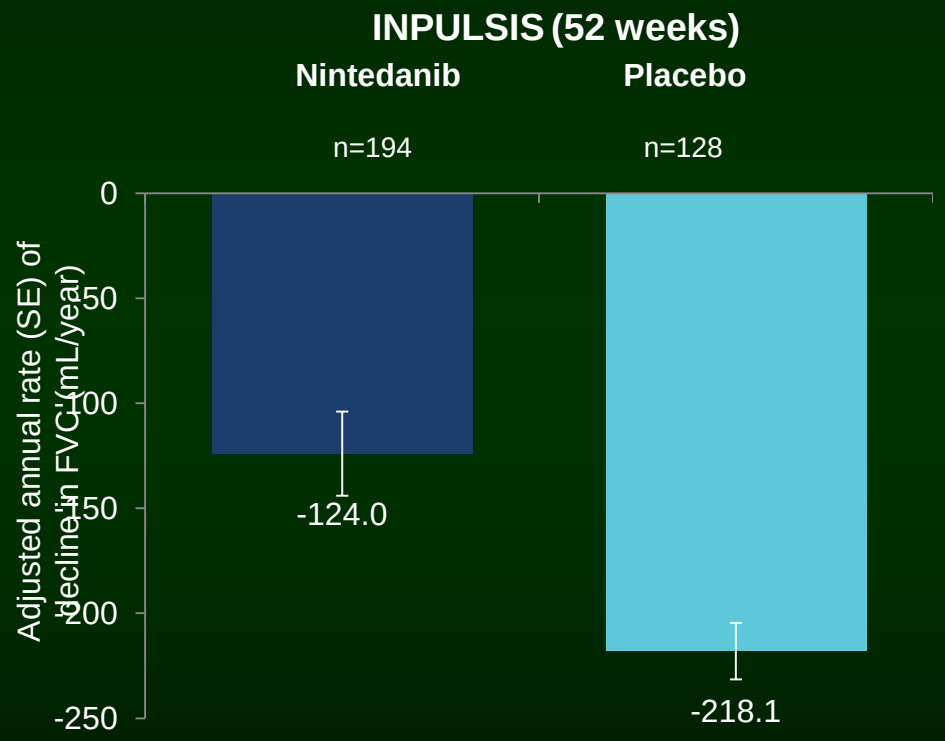
Crestani B *et al. Lancet Respir Med* 2019;7:60-68.

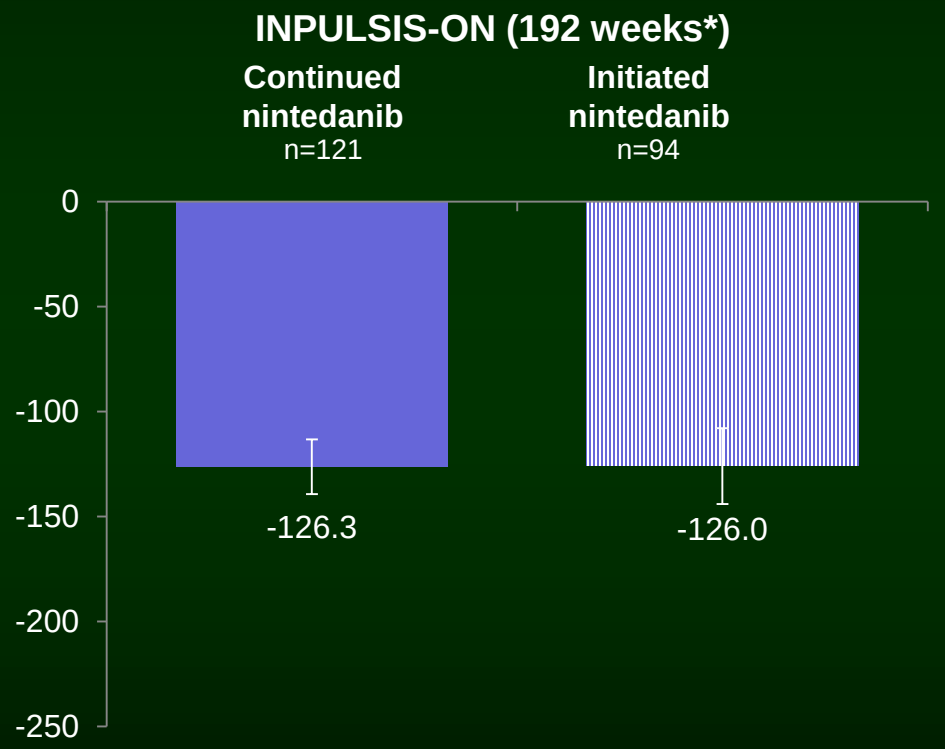
Asia subgroup result-

Long term efficacy of Nintedanib on slowing FVC decline

INPULSIS and INPULSIS-ON:

Annual rate of decline in FVC beyond 4 years

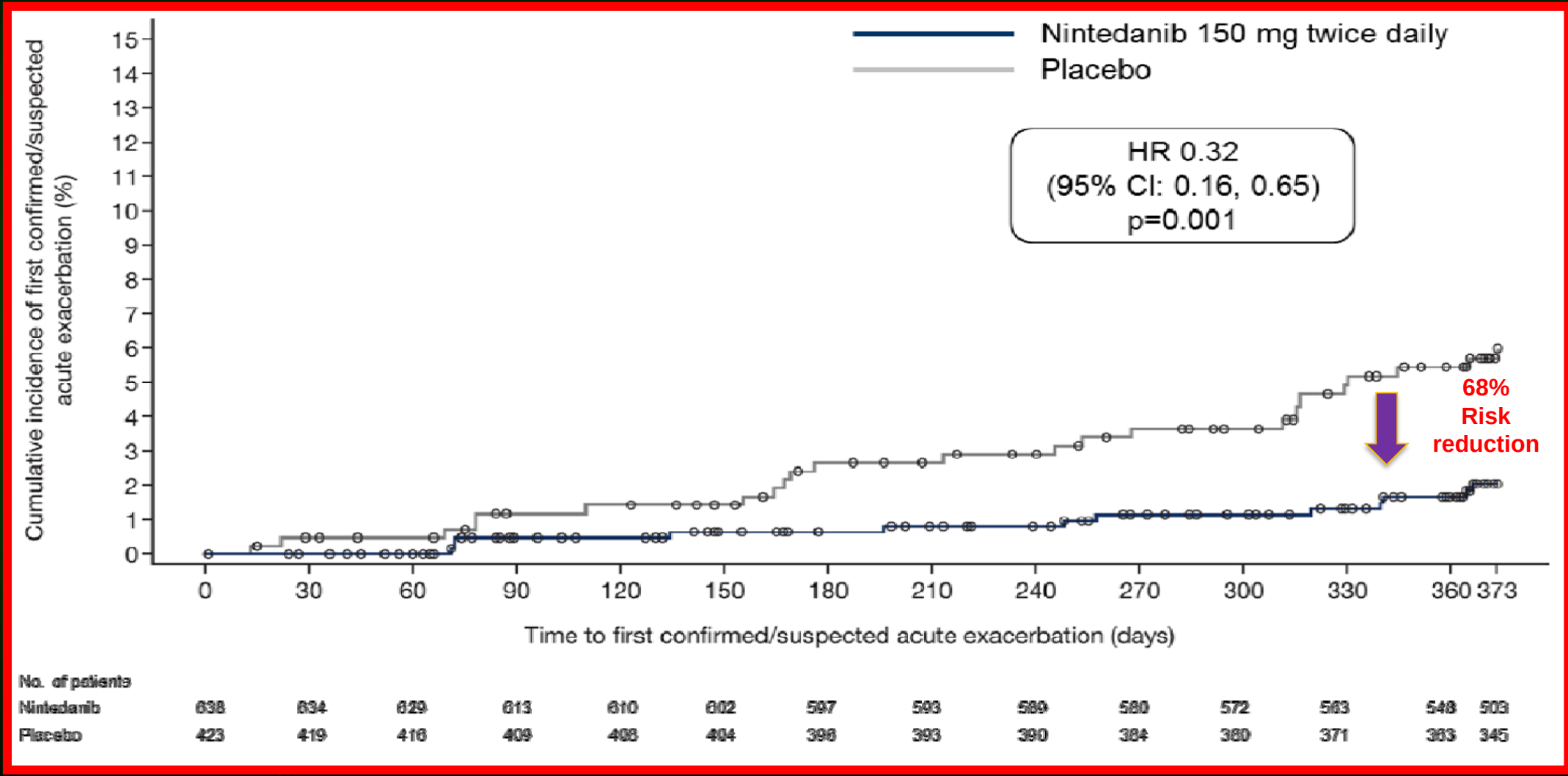




*Time point reached by last patient in INPULSIS-ON who was still receiving nintedanib when BI stopped the trial.

JW Song *et al*. *Respirology* (2019)

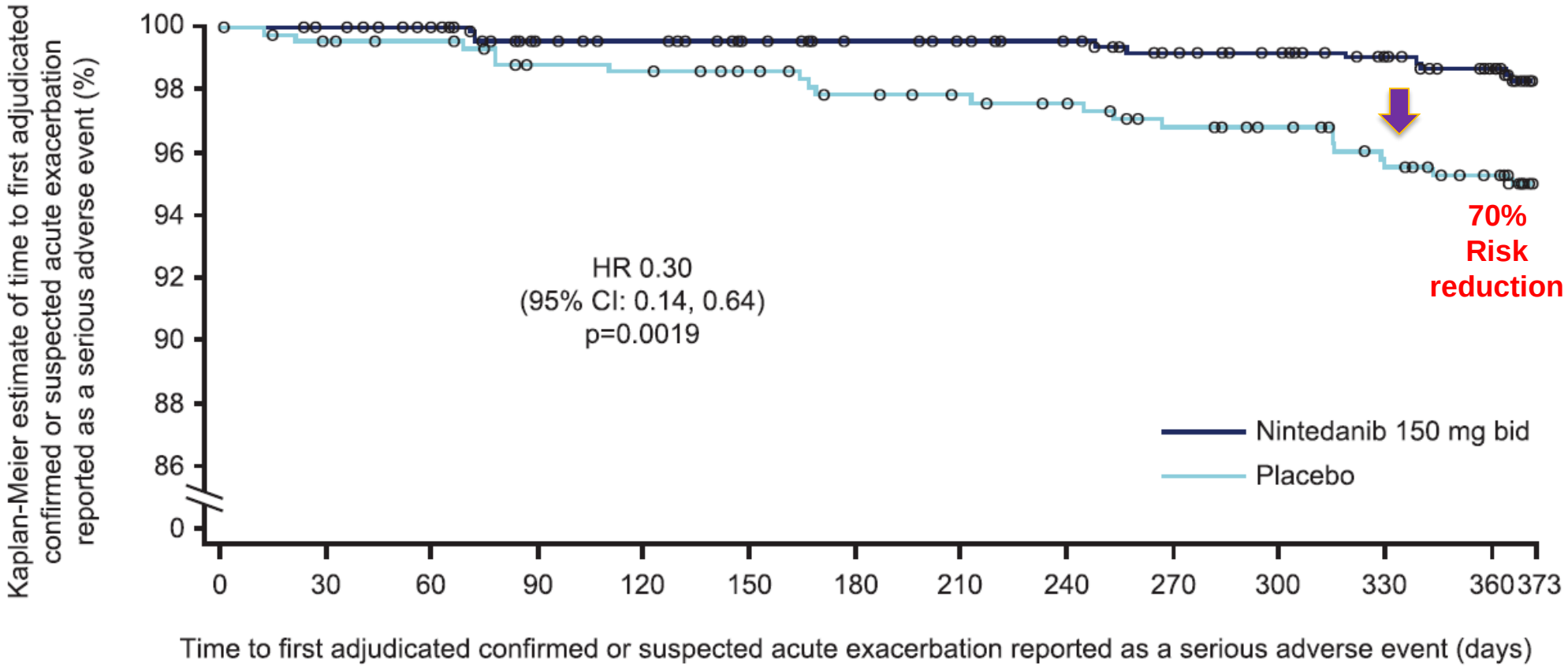
Nintedanib significantly reduced the risk of "Time to first acute exacerbation" by 68%



Richeldi *et al*, *NEJM* 2014

Nintedanib significantly reduced the severity of AE:

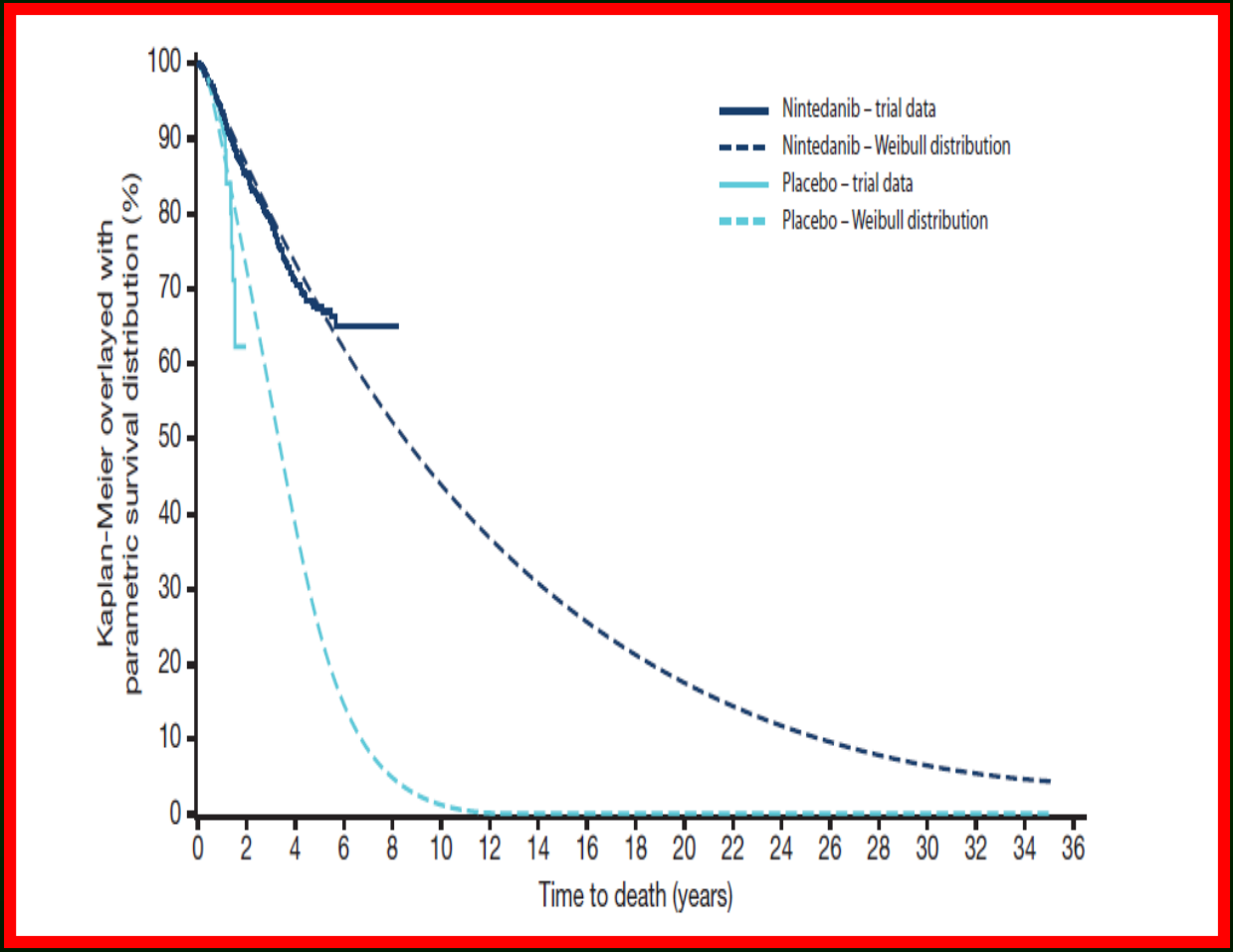
Reducing acute exacerbations reported as serious adverse events



No. at risk													
Nintedanib 150 mg bid	638	634	629	613	610	603	598	595	591	582	574	564	549 504
Placebo	423	419	416	409	408	404	398	395	392	385	381	373	364 346

Kreuter *et al. Respiratory Research* (2019) 20:71

Estimated time to death using the Weibull distribution: Additional 7.9 years life time in Nintedanib group

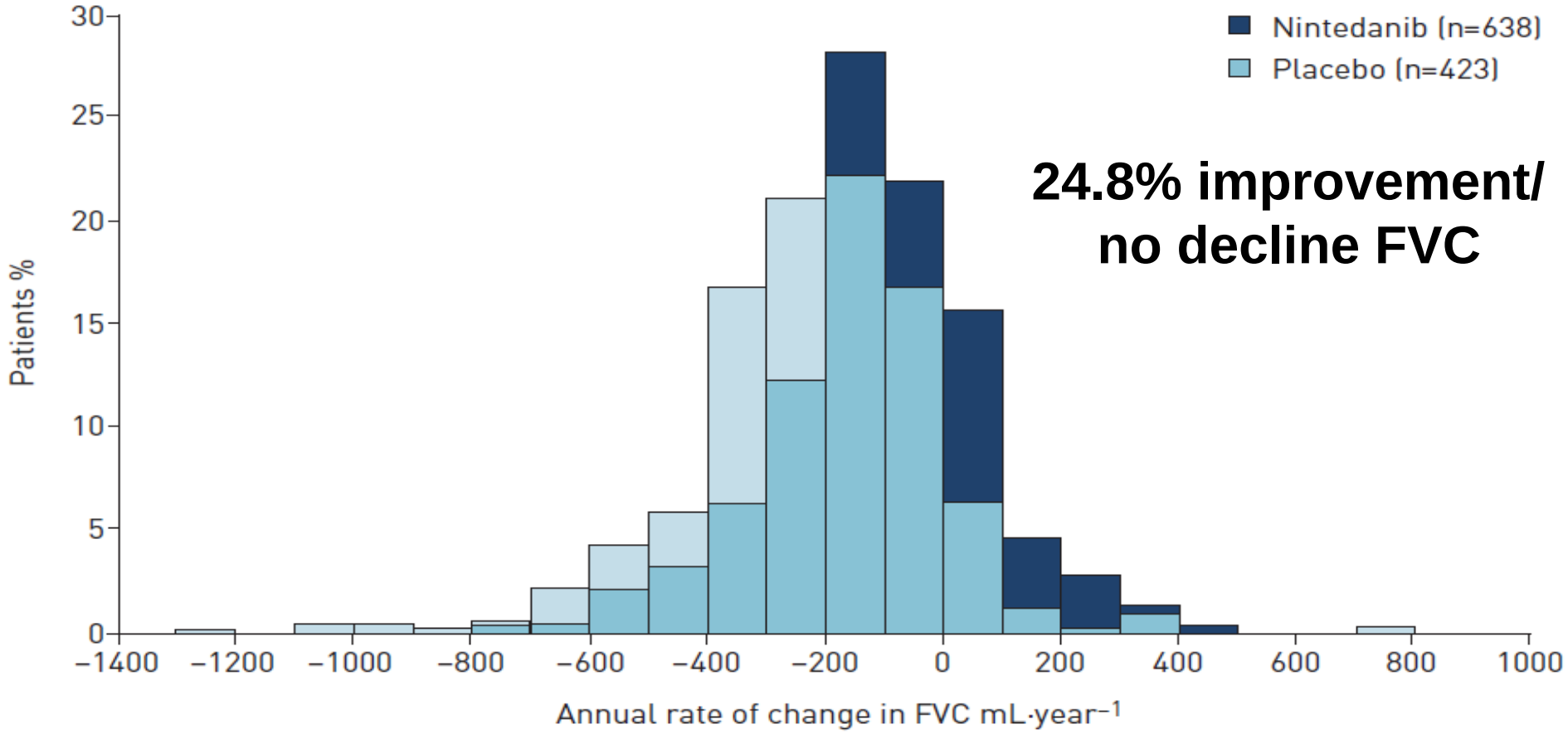


- Mean (95% CI) survival was estimated as **11.6 (9.6, 14.1) years in nintedanib-treated** patients and 3.7 (2.5, 5.4) years in placebo-treated patients
- **Median survival was estimated as 8.5 years in nintedanib-treated patients** and 3.3 years in placebo-treated patients

Data presented at the American Thoracic Society International Conference, San Diego, CA, USA, 18–23 May 2018 [Lancaster et al]

Real World Experiences in IPF Registration Studies

Stability or improvement in forced vital capacity with nintedanib in patients with IPF



Eur Respir J. 2018 Aug 2;52(2). pii: 1702593

TABLE 4 Univariate Cox regression analysis for mortality

Variable	Patients	HR (95% CI)	p-value
Age per year	453	1.03 (1.01–1.05)	**0.001**
Female *versus* male	453	1.04 (0.78–1.39)	0.794
BMI per kg·m^{-2}	355	0.98 (0.95–1.02)	0.353
Ex/current smoker *versus* never-smoker	438	1.17 (0.88–1.57)	0.284
*D*LCO per % predicted	367	0.96 (0.95–0.97)	**<0.0001**
FVC per % predicted	407	0.98 (0.97–0.99)	**<0.0001**
GAP stage	370	1.71 (1.24–2.36)	**0.0010**
>6 months antifibrotic treatment	453	0.67 (0.46–0.98)	**0.037**

HR: hazard ratio; BMI: body mass index; *D*LCO: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity. Bold indicates statistically significant p-values.

FinnishIPF registry patients.

Time years

Long-term overall survival and progression-free survival in idiopathic pulmonary fibrosis treated by pirfenidone or nintedanib or their switch: real-world data from the EMPIRE registry

Martina Vašáková,[1] Martina Šterclová,[1] Nesrin Mogulkoc,[2] Katarzyna Lewandowska,[3] Veronika Müller,[4] Marta Hájková,[5] Dragana Jovanovic,[6] Jasna Tekavec-Trkanjec,[7] Mordechai Kramer,[8] Michael Studnicka,[9] Natalia Stoeva,[10] Simona Littnerová,[11] Karel Hejduk,[11] Ladislav Dušek[11]

[1]Department of Respiratory Diseases of the First Faculty of Medicine Charles University, Thomayer Hospital, Prague, Czech Republic; [2]Department of Pulmonary Medicine, Ege University Medical School, Izmir, Turkey; [3]Department of Pulmonary Diseases, Institute of Tuberculosis and Lung Diseases, Warsaw, Poland; [4]Department of Pulmonology, Semmelweis University, Budapest, Hungary; [5]Clinic of Pneumology and Phthisiology, University Hospital Bratislava, Bratislava, Slovakia; [6]University Hospital of Pulmonology, Clinical Center of Serbia, Belgrade, Serbia; [7]Pulmonary Department, University Hospital Dubrava, Zagreb, Croatia; [8]Institute of Pulmonary Medicine, Rabin Medical Center, Petah Tikva, Israel; [9]Department of Pneumology, Paracelsus Medical University, SALK, Salzburg, Austria; [10]Pulmonary Department, Acibadem City Clinic Tokuda Hospital, Sofia, Bulgaria; [11]Institute of Biostatistics and Analyses of the Faculty of Medicine, Masaryk University, Brno, Czech Republic

ERS

INTERNATIONAL CONGRESS 2019

MADRID Spain, 28 September – 2 October

About EMPIRE

AIMs

- To compare OS and PFS in patients from **the European Multipartner IPF registry** (EMPIRE; http://empire.registry.cz/) treated with either pirfenidone or nintedanib, or who switched from nintedanib to pirfenidone, or vice versa, or who received other or no treatment.

Patient characteristics

- A total of 2745 patient with IPF for the EMPRIE registry were included and assigned to groups on the basis of antifibrotic treatment received.
  - female: 29.5%; male: 70.5%
  - mean diagnosed age: 66.5 years
- For patients who switched between treatments, the median duration of first therapy was 8.05 months and median time to starting the second therapy was 0.25 months.
- There was no significant difference in baseline characteristics between patients who switched due to adverse effects (AEs) and those who switched due to lack of treatment effect.

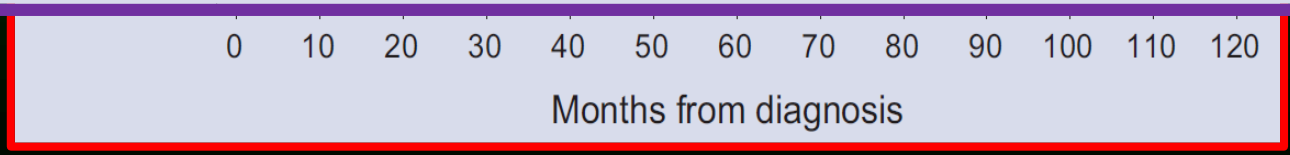
Long term survival

- Median OS was longer in the nintedanib group and in patients who switched treatment, compared with patients on pirfenidone (P=0.003) or those who received other treatment (P<0.001).
- Median PFS was similar in the nintedanib group vs the pirfenidone group(P=0.200) and longer in patients who switched treatment vs those who received other treatment (P<0.001).

A. OS

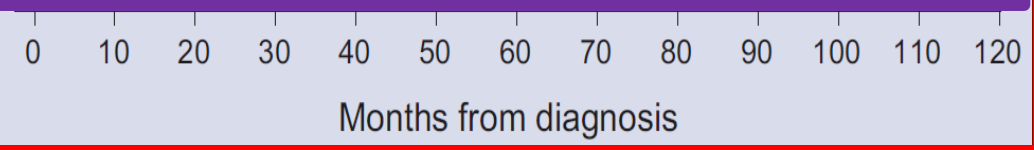
	Median survival (months)	1-year survival (95% CI)	5-year survival (95% CI)	10-year survival (95% CI)
Pirfenidone	38.7	0.872 (0.831–0.904)	0.311 (0.251–0.372)	0.105 (0.060–0.163)
Nintedanib	56.3	0.912 (0.867–0.943)	0.430 (0.314–0.540)	0.197 (0.097–0.323)
Switch	71.9	0.961 (0.884–0.987)	0.540 (0.382–0.674)	0.347 (0.171–0.530)
Other treatment	21.4	0.688 (0.633–0.737)	0.138 (0.101–0.180)	0.023 (0.011–0.042)

[a]Long-term survival according to TL_{CO} % at diagnosis. [b]Progression defined as death, transplant or progression (TL_{CO} or FVC decline).

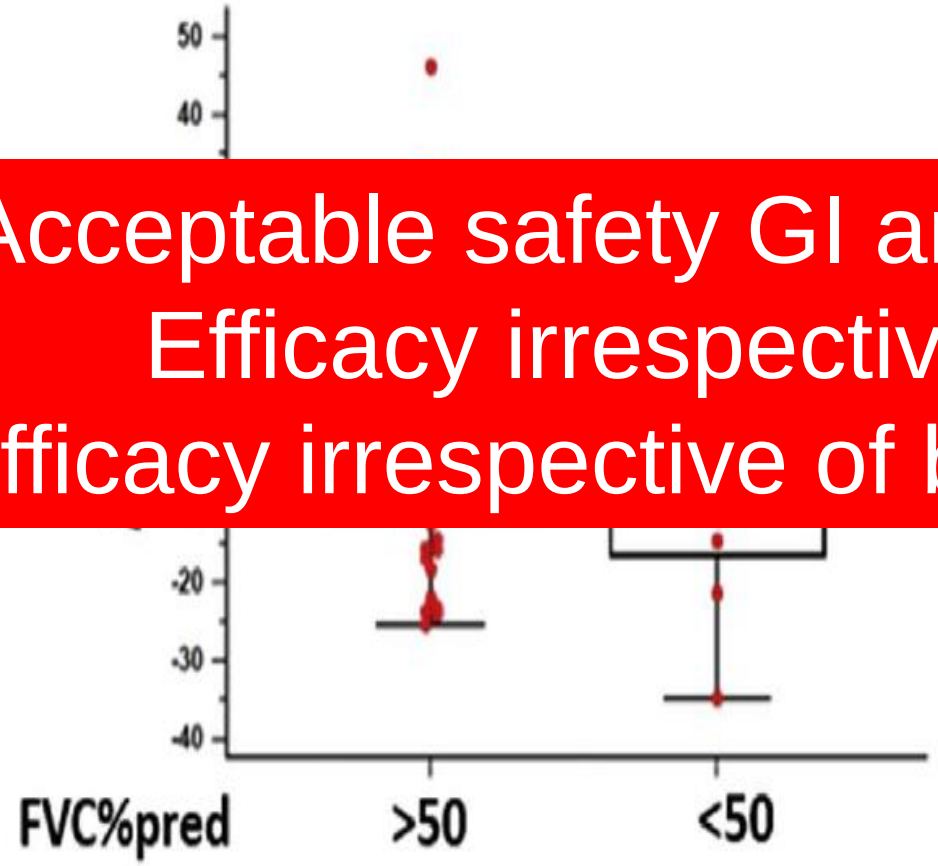


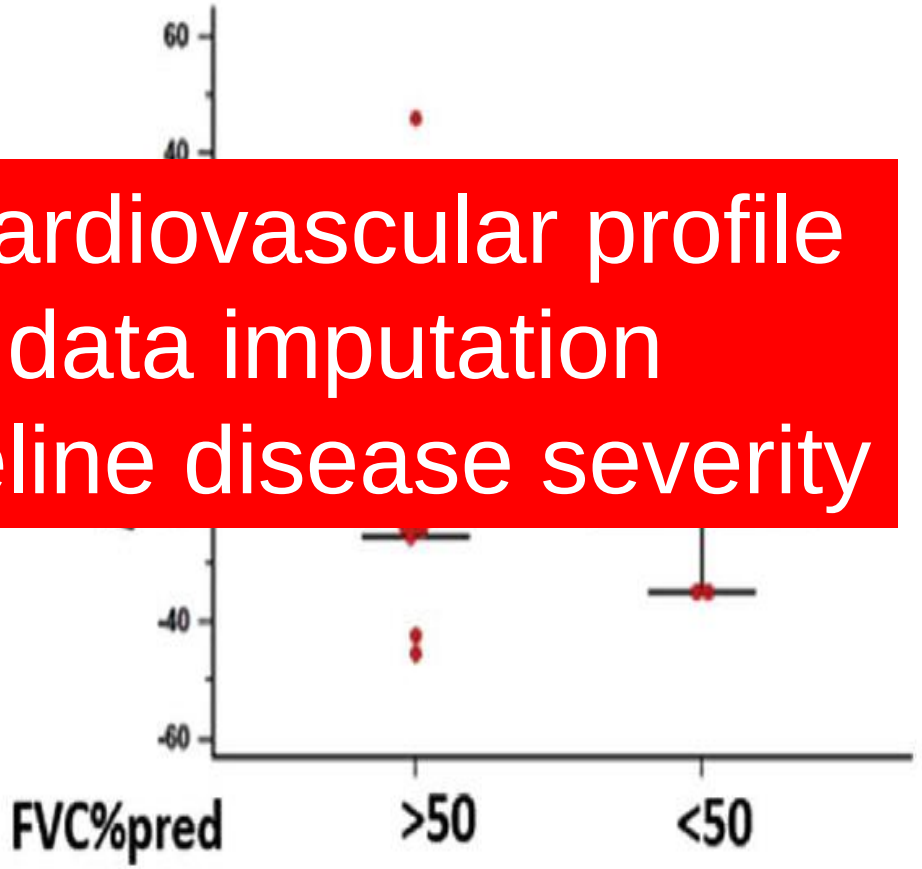
B. PFS

	Median survival (months)	1-year survival (95% CI)	5-year survival (95% CI)	10-year survival (95% CI)
Pirfenidone	20.5	0.673 (0.621–0.719)	0.173 (0.133–0.217)	0.040 (0.018–0.076)
Nintedanib	22.9	0.669 (0.609–0.723)	0.232 (0.162–0.310)	0.055 (0.021–0.112)
Switch	30.4	0.789 (0.683–0.863)	0.333 (0.210–0.460)	0.084 (0.010–0.268)
Other treatment	17.3	0.617 (0.561–0.669)	0.094 (0.066–0.129)	0.008 (0.003–0.020)



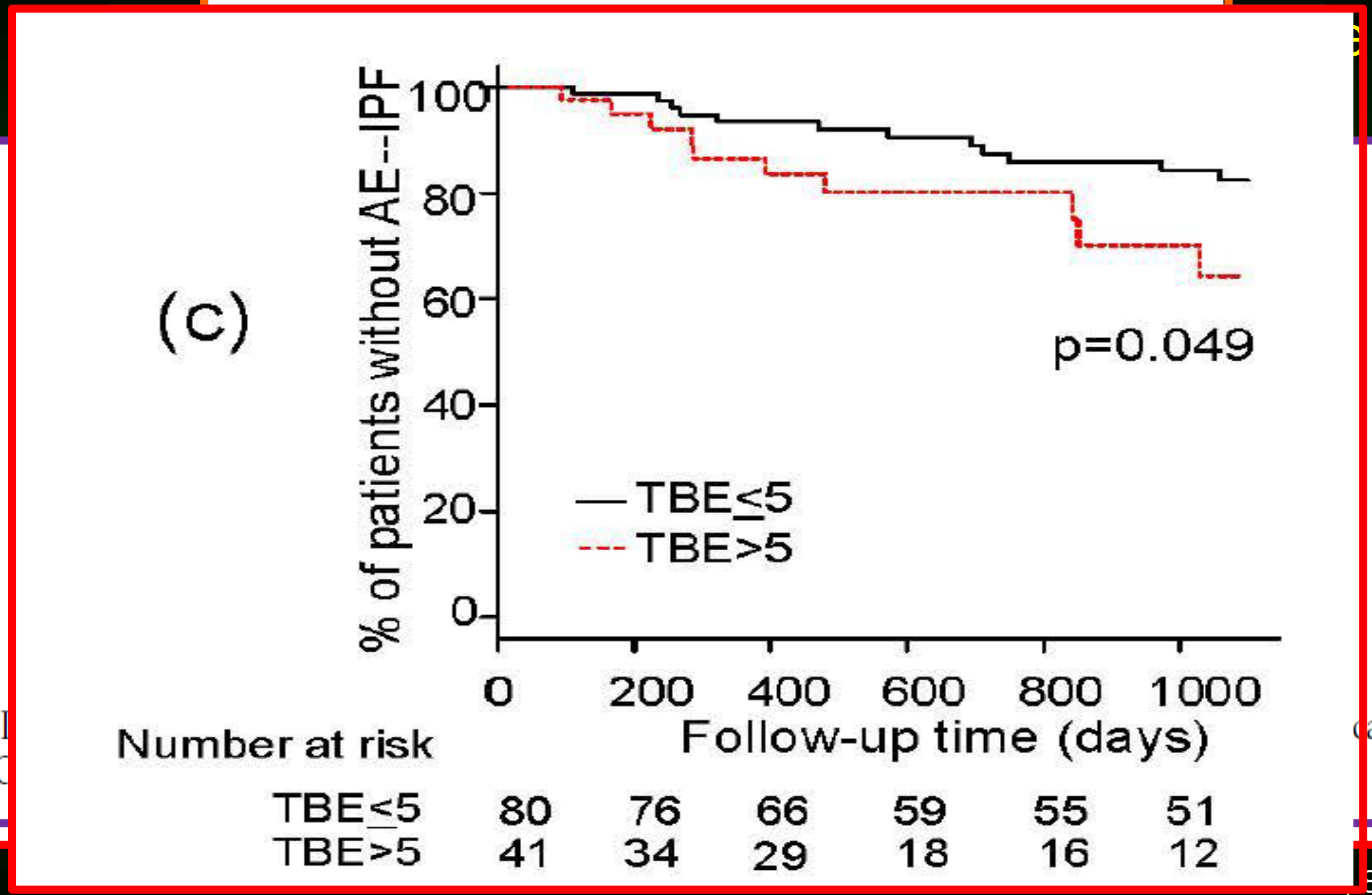
Safety and efficacy of Nintedanib in idiopathic pulmonary





Acceptable safety GI and cardiovascular profile
Efficacy irrespective of data imputation
Efficacy irrespective of baseline disease severity

Pulmonary Pharmacology & Therapeutics 49 (2018) 61–66


(c)
% of patients without AE--IPF
100
80
60
40
20
0
p=0.049
TBE≤5
TBE>5
0
200
400
600
800
1000
Follow-up time (days)
Number at risk
TBE≤5 80 76 66 59 55 51
TBE>5 41 34 29 18 16 12

Post-marketing observational study (All-Case Surveillance) of Ofev Capsules in patients with Idiopathic Pulmonary Fibrosis (IPF) in Japan (2nd interim report)

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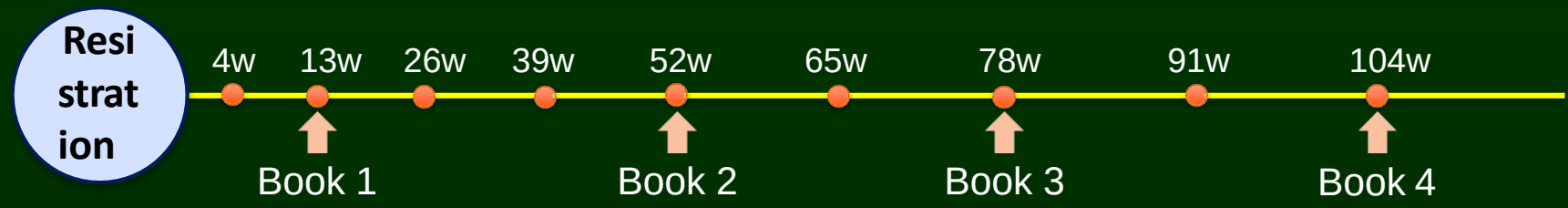
Study design and outcomes

Objective: To evaluate safety and effectiveness of Nintedanib under a Japanese real world setting.

Method: This study started from 31st August, 2015 with all patients who administered Nintedanib. Observation period was 104 weeks (24 months) after initiation of Nintedanib treatment, or until discontinuation of the treatment.

IPF patients **Nintedanib 100 mg or 150 mg，i.b.d.**



Study method：all-case surveillance
Planned population：1000 (safety analysis set)
Study period：104 weeks (2 years)
Evaluation period (plan)：Aug 2015 – Jun 2020
Primary endpoint (safety): incidence of treatment-related adverse events (number and percent)
Secondary endpoint (effectiveness): Absolute change from baseline in FVC at Week 104

IPF，Idiopathic Pulmonary Fibrosis ； FVC，Forced Vital Capacity

Baseline

Background	Safety set (N=4,098)
Age mean ± SD/median	71.7± 8.0 /73.0
men， N (%)	3,174 (77.5)
Body weight mean± SD （N=3893）	59.5 ±12.5
BMI, kg/m^2, mean ± SD (N=3,874)	22.9 ± 3.9
BSA, m^2, mean ± SD (N=3,874)	1.6 ± 0.2
Current smoker + with history of smoking, N (%)	2,894 (70.6)
FVC at baseline, mean mL ± SD (N=3,590)	2,113.5± 715.5
%FVC at baseline, mean %FVC ± SD (N=3,327)	69.7± 41.3
<70%	1,845 (45.0)
≥70%	1,482 (36.2)
unknown	771 (18.8)

- The background of the patients registered in this study were in consistent with those generally observed in IPF patients (men, elderly and history of smoking)
- Mean %FVC（69.7%）at baseline was lower than INPULSIS ®study（81.8%）[1]

BMI，body mass index；BSA， body surface area ；IPF，Idiopathic Pulmonary Fibrosis ；FVC，forced vital capacity；SD, standard deviation

[1] Azuma A et al. Nintedanib in Japanese patients with idiopathic pulmonary fibrosis:A subgroup analysis of the INPULSIS® randomized trials. Respirology. 2017;22:750–7.

Baseline (continued)

Background	Safety set (N=4,098)
Concomitant diagnosis, N (%)	3,167 (77.3)
pulmonary cancer	222 (5.4)
COPD	299 (7.3)
GERD	444 (10.8)
Previous medication for IPF, N (%)	919 (22.4)
corticosteroid	153 (3.7)
pirfenidone	729 (17.8)
immunosuppressant	78 (1.9)
Co-medication for IPF at baseline, N (%)	1,397 (34.1)
corticosteroid	1013 (24.7)
pirfenidone	218 (5.3)
immunosuppressant	222 (5.4)

- 77% of safety aalysis set (n=4,098) had comorbidities.

COPD, chronic obstructive pulmonary disease; GERD, gastrooesophageal reflux disease; IPF，Idiopathic Pulmonary Fibrosis

Exposure to Nintedanib

Criteria		Safety set (N=4,098)
Exposure duration, days, mean ± SD (N=4,098)/median treatment period		226.1 ± 200/123.0
Initial dose, N (%)		
150 mg b.i.d		3,503 (85.5)
Reduction from 150 mg b.i.d to 100 mg b.i.d		1,025 (29.3)
100 mg b.i.d		515 (12.6)
Increase from 100 mg b.i.d to150 mg b.i.d		94 (18.3)
Others, unknown		80 (2.0)
Time to first dose reduction, days, mean± SD (N= 1,135)		105.3± 115.2
Dose discontinuation, N (%)		1,945 (47.5)
Time to dose discontinuation, days, mean± SD (N= 1,945)		155.2± 155.3
Reasons for discontinuation, N (%)	Adverse event*	1,346 (32.9)
	Insufficient effectiveness	150 (3.7)
	Improved	13 (0.3)
	Lost to follow up, other, missing	436 (10.6)

*include acute exacerbation, n=156 (3.8%) b.i.d；twice a day administration

Incidence of AE

Terms	Safety set (N=4,098) n (%)
AEs ≥5%*	
Diarrhoea	1182 (28.8%)
Hepatic function abnormal	582 (14.3)
Nausea	218 (5.3)
IPF*	513 (12.5)
Decreased appetite	394 (9.6)
Liver disorder	307 (7.5)
Serious AEs ≥1%*	
IPF*	453 (11.1)
Pneumonia bacterial	75 (1.8)
Pneumothorax	74 (1.8)
Pneumonia	71 (1.7)
Malignant neoplasm progression	42 (1.0)

- The most frequently reported AE was diarrhoea (28.8%)

Classified according to MedDRA ver. 21.0, * IPF, Idiopathic pulmonary fibrosis

Priority survey items and actions taken safety set (N=4,098)

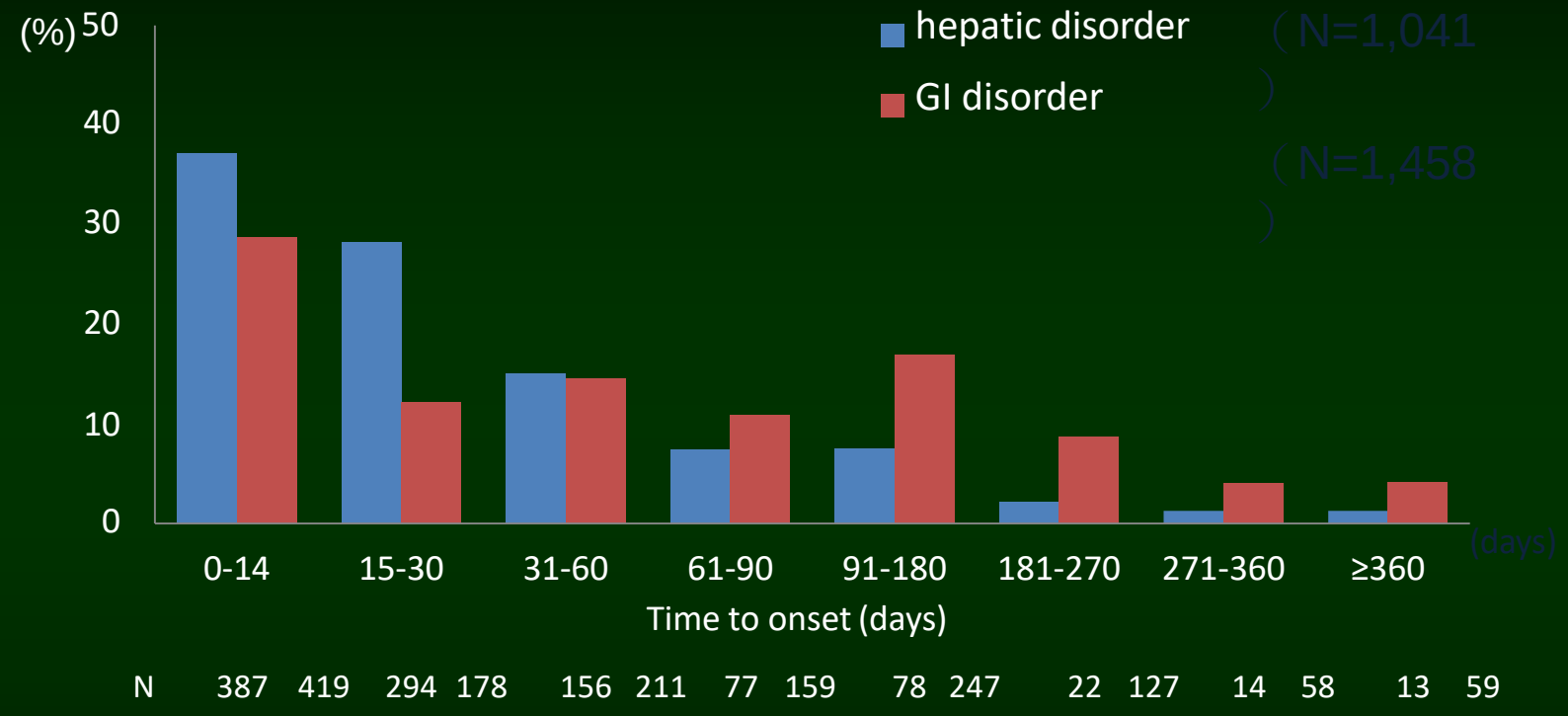
Priority survey items			Actions					
	N	Median time to onset, (days)	Continued	Dose decreased	Temporary discontinued	Permanently discontinued	Occurred after termination	Unknown
GI symptoms including diarrhoea and nausea	1,458	49	746	317	123	254	0	2
Hepatic function disorder†	1,041	20	334	233	238	222	4	0
Interstitial pneumonia††	60	58	10	0	2	35	5	1
Bleeding	36	56.5	10	2	7	12	1	2
Thromboembolism	8	127.5	2	0	0	6	0	0
Gastrointestinal perforation	4	149.5	0	0	0	4	0	0

Classified according to MedDRA ver. 21.0

†The Standardised MedDRA Queries (SMQ) were searched and evaluated for cases with “Liver related investigations, signs and symptoms (Broad)”, “hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (Narrow)”, “cholestasis and jaundice of hepatic origin (Narrow)” and “hepatitis, non-infectious (Narrow)”.

††The Standardised MedDRA Queries (SMQ) were searched and evaluated for cases with “Interstitial lung disease (Broad) ”

ADR Time to onset of hepatic and gastrointestinal disorders (including diarrhoea and nausea)



- Hepatic disorders expressed in 25% of safety set (1041/4098). More than half of them (65.4%) were reported within 30 days after the initiation of the treatment. Median duration by the time of the onset was 20 days.
- Gastrointestinal disorders expressed in 35.6% of safety set (1458 /4098). 40.9% of them were reported within 30 days after the initiation of the treatment. Median duration by the time of the onset was 49 days.

†The Standardised MedDRA Queries (SMQ) were searched and evaluated for cases with “Liver related investigations, signs and symptoms (Broad)”, “hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (Narrow)”, “cholestasis and jaundice of hepatic origin (Narrow)” and “hepatitis, non-infectious (Narrow)”.

Incidence of investigator reported acute exacerbation of IPF over 104 week

All	%FVC at baseline		IIPs severity grade			
	<70%	≥70%	I	II	III	IV
N=2026	N=963	N=936	N=496	N=89	N=423	N=491
7.5%	8.5%	5.8%	4.4	4.5	5.2	12.0

Effectiveness set (N=2026) %FVC at baseline Missing N=127
IIPs severity grade Missing N=193, Unknown N=334

- Patients who experienced ≥1 acute exacerbation of IPF (defined by investigators) over 104 week were 7.5%(152/ 2,026) in overall effectiveness set.
- Among IIPSs severity grade, the highest incidence of acute exacerbation were reported in the patients with grade IV (12.0%)

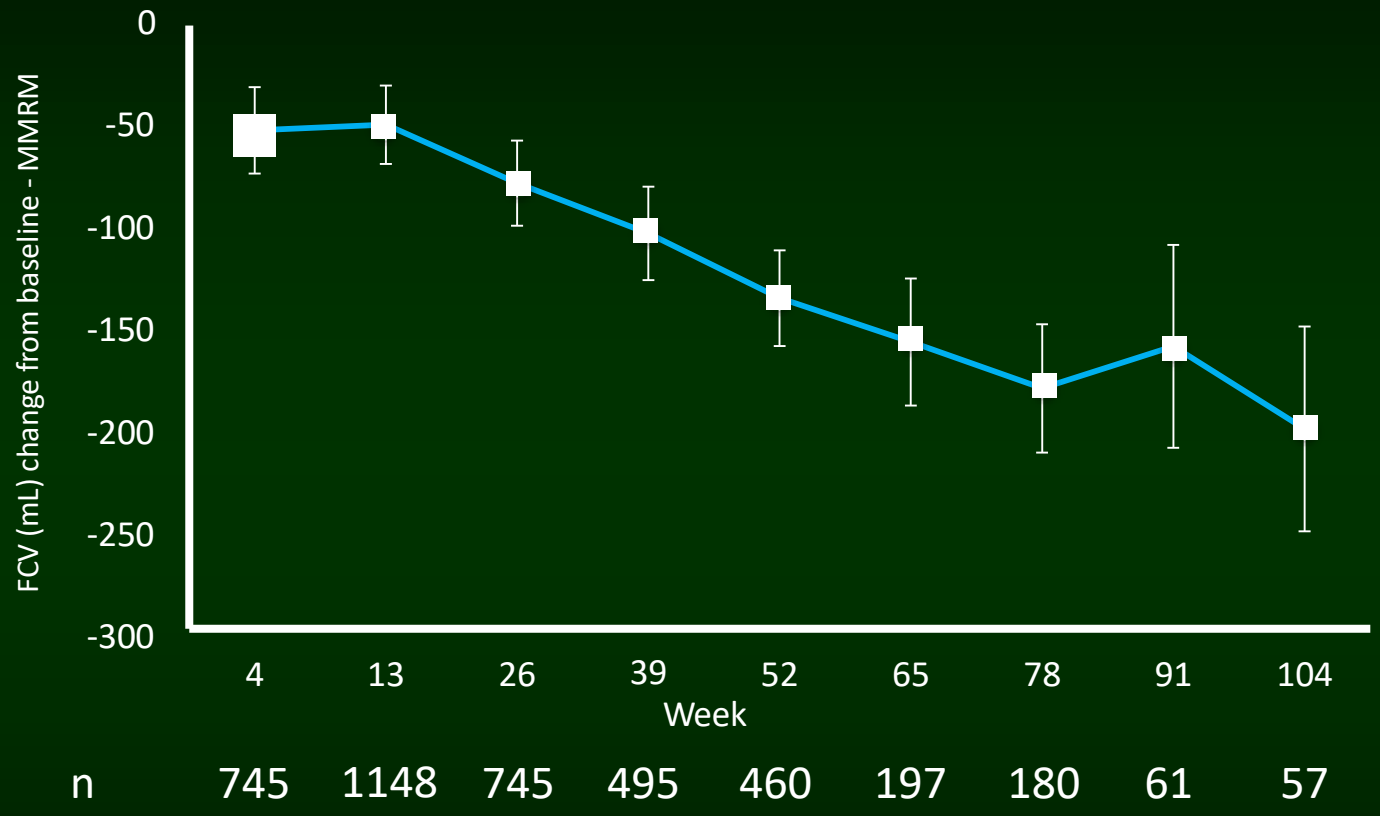
FVC, forced vital capacity; [1]The Japanese Respiratory Society, Committee for the IPF Guidelines; Guidelines for the diagnosis and treatment of IPF・2004

Nintedanib and Pirfenidone : result from the individual PMS result

	OFEV	PIRESPA
	Nintedanib *	Pirfenidone #
Patient with ≥ 1 acute exacerbation, n (%)	152/2026 (7.5%)	179/1332 (12.8%)
Mortality	581/4091 (14.2%)	306/1371 (22.3%)

* Result in 104 weeks (2019 JRS presentation)
# Result in 52 weeks (Respiratory investigation 53_2015_232–241)

Adjusted absolute change from baseline in FVC



- Adjusted absolute mean change from baseline to week 52 in FVC was –135.6 mL (95%CI: -159.4, -111.8)

FVC, forced vital capacity; MMRM Mixed Model for Repeated Measure

Non-Interventional study (NIS) Collecting Experiences For IPF in Taiwan (NICEFIT)

Recruitment Plan

total :100 人

10 Centers

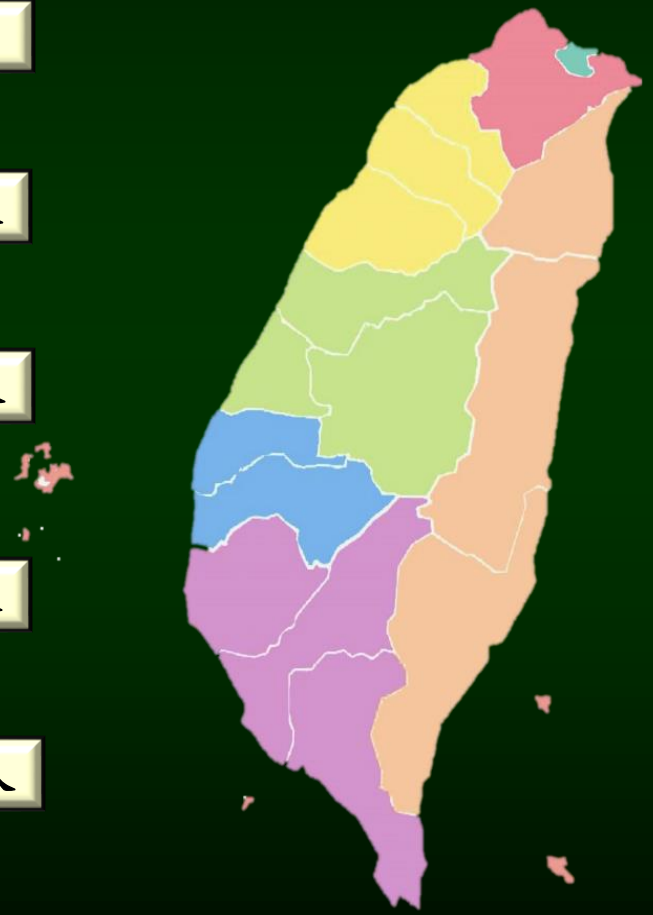
06. 台中榮總醫院 PI 許正園 醫師 — 10人

07. 中國附醫 PI 杭良文 醫師 — 10 人

08. 彰基醫院 PI 林慶雄 醫師 — 10 人

09. 高雄附醫 PI 許超群 醫師 — 10 人

10. 高雄長庚醫院 PI 方文豐 醫師 — 10 人



01. 臺大醫院 PI 王鶴健 醫師 — 10人

02. 台北榮總醫院 PI 彭殿王 醫師 — 10 人

03. 三軍總醫院 PI 簡志峯醫師 — 10 人

04. 林口長庚醫院 PI 高國晉 醫師 — 10 人

05. 亞東醫院 PI 鄭世隆 醫師 — 10 人

Study Timeline

Protocol overview

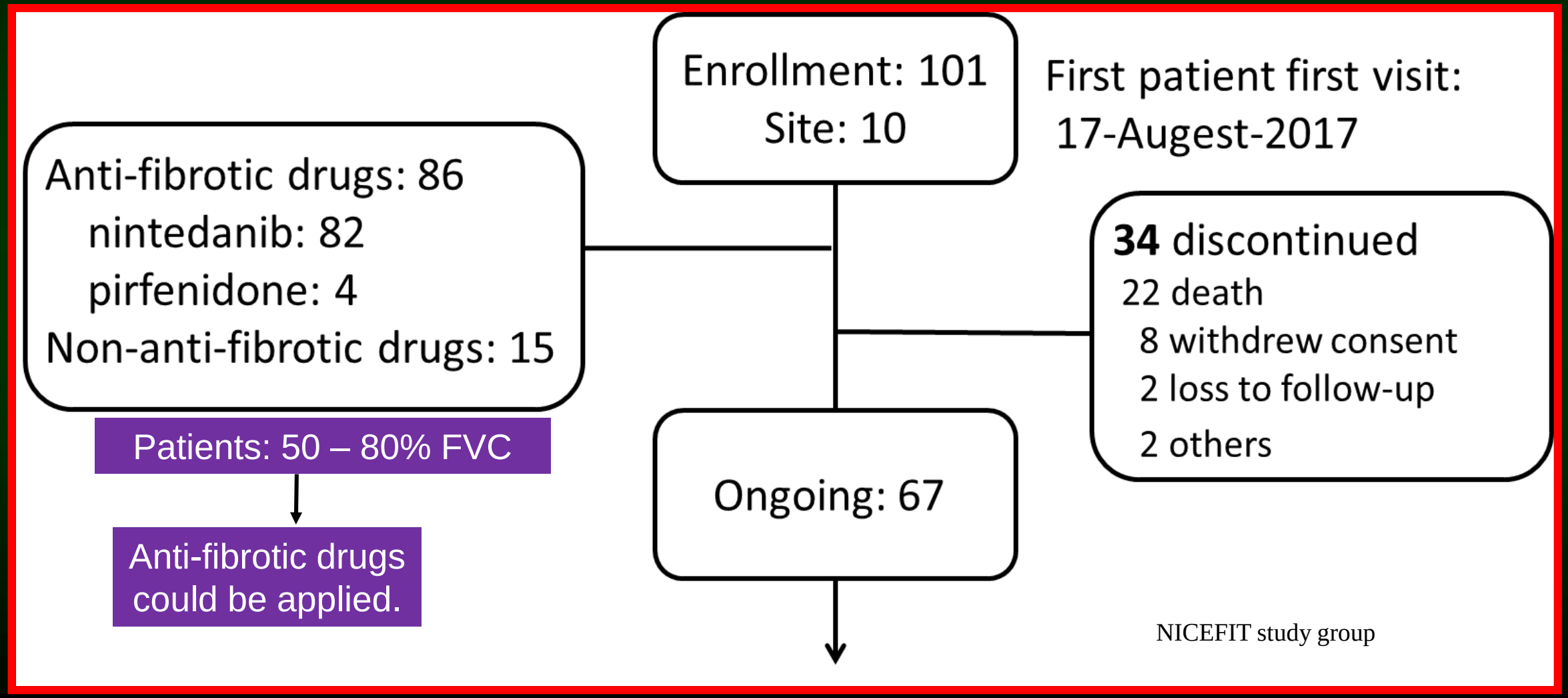
Study design

- It was a non-interventional study to collect data from IPF patients according to clinical practice in 10 medical centers Taiwan.
- Time points of data collection: baseline, Week 4, and Week 16/death or withdrawal

Inclusion	Exclusion
• Newly diagnosed IPF within 6 months based on IPF guideline	• Lung transplantation expected within next 6 months • Inclusion in ongoing clinical trials

Clinical results from this study

- Patient disposition (Until 6-Aug-2019)



Clinical results from this study

- Demographics (1/5)

Characteristics	Anti-fibrotic drugs N = 86	Non-anti-fibrotic drugs N = 15
Age (years)		
mean ± SD	74.7 ± 9.06	73.9 ± 9.87
Gender (%)		
male	81.4	93.3
Smoking history (%)		
former/current smoker	54.7	60.0
never smoker	45.3	40.0
HRCT pattern (%)		
definite UIP	70.9	73.3
possible UIP	23.3	20.0
OSA risk by STOP-Bang scoring (%)		
low	16.3	33.3
medium	61.6	53.3
high	22.1	13.3

Clinical results from this study

- Demographics (2/5)

Characteristics	Anti-fibrotic drugs N = 86	Non-anti-fibrotic drugs N = 15
FVC (L)		
mean ± SD	2.0 ± 0.59	2.8 ± 0.58
FVC, predicted (%)		
mean ± SD	69.2 ± 13.85	96.6 ± 11.26
DL_{CO} (L)		
mean ± SD	7.4 ± 3.94	6.8 ± 4.50
DL_{CO}, predicted (%)		
mean ± SD	43.7 ± 17.47	59.8 ± 17.84

Demographics (3/5)

Characteristics	Anti-fibrotic drugs N = 86	Non-anti-fibrotic drugs N = 15
Cardio and cerebrovascular comorbidities		
Arterial Hypertension	48.8 %	40.0 %
Coronary Artery Disease (CAD)	20.9 %	6.7%
Pulmonary Hypertension (PH)	7 %	0 %
Respiratory comorbidities		
COPD	34.9 %	33.3 %
Obstructive Sleep Apnea (according to STOP-Bang Scoring Model at baseline)	18.6 %	6.7 %
Emphysema(radiologic)	16.3 %	40 %
asthma	5.8 %	0 %
Acute exacerbation of IPF	2.3 %	0 %

Clinical results from this study

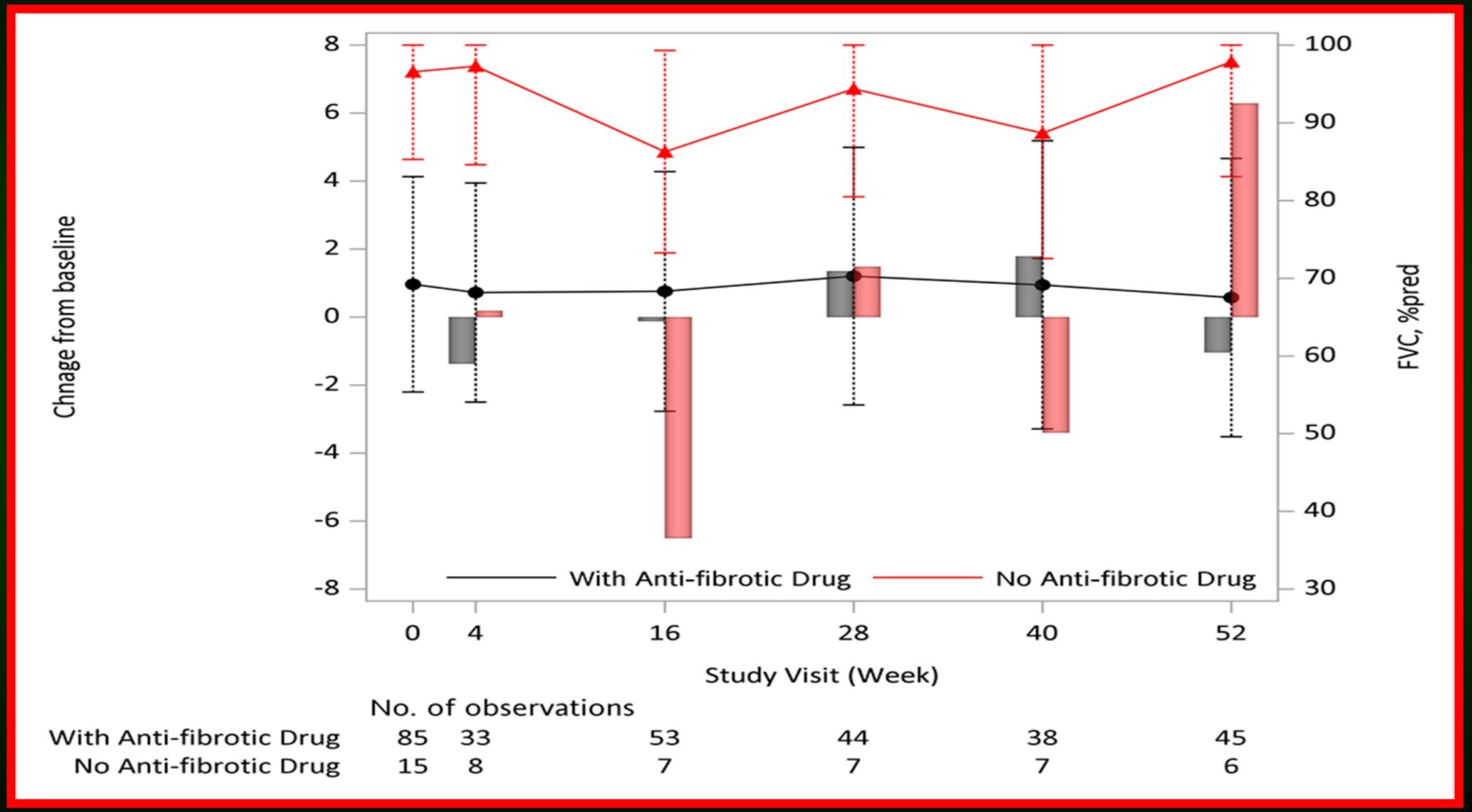
- Demographics (4/5)

Characteristics	Anti-fibrotic drugs N = 86	Non-anti-fibrotic drugs N = 15
Gastrointestinal comorbidities		
GERN	26.7 %	20 %
Gastric ulcer	14 %	0 %
Metabolic		
T2/T1 Diabetes Mellitus	24.4 %	6.7 %
Hyperlipidemia	18.6 %	6.8 %
Neoplasm (Cancer)		
Colorectal	4.7 %	0 %
Prostate	2.3 %	0 %
Lung	1.2 %	0 %

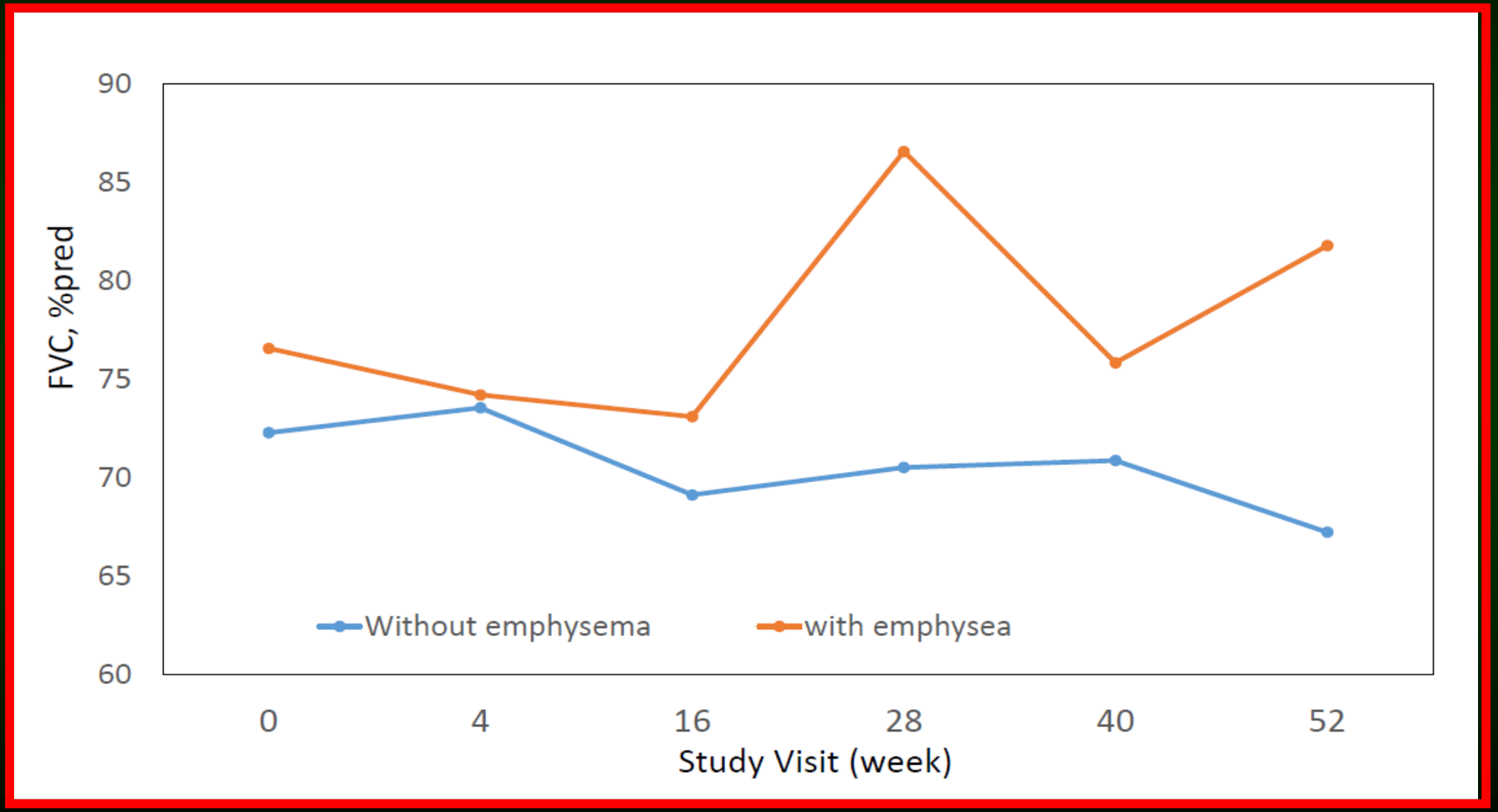
Demographics (5/5)

Medication (%)	N = 101 (%)
Anti-fibrotic drugs	
Nintedanib	77 (76.2)
Pirfenidone	4 (4.0)
Switch	5 (5.0)
None	15 (14.9)
Daily Dose of Nintedanib (mg)	
150	10 (12.3)
300	71 (87.7)
Daily Dose of Pirfenidone (mg)	
600	7 (77.8)
1200	2 (22.2)
Concomitant Medication	
Respiratory	67.4
Hypertension	22.1
CVD/cerebral artery occlusion	17.4
Diabetes mellitus	14.0

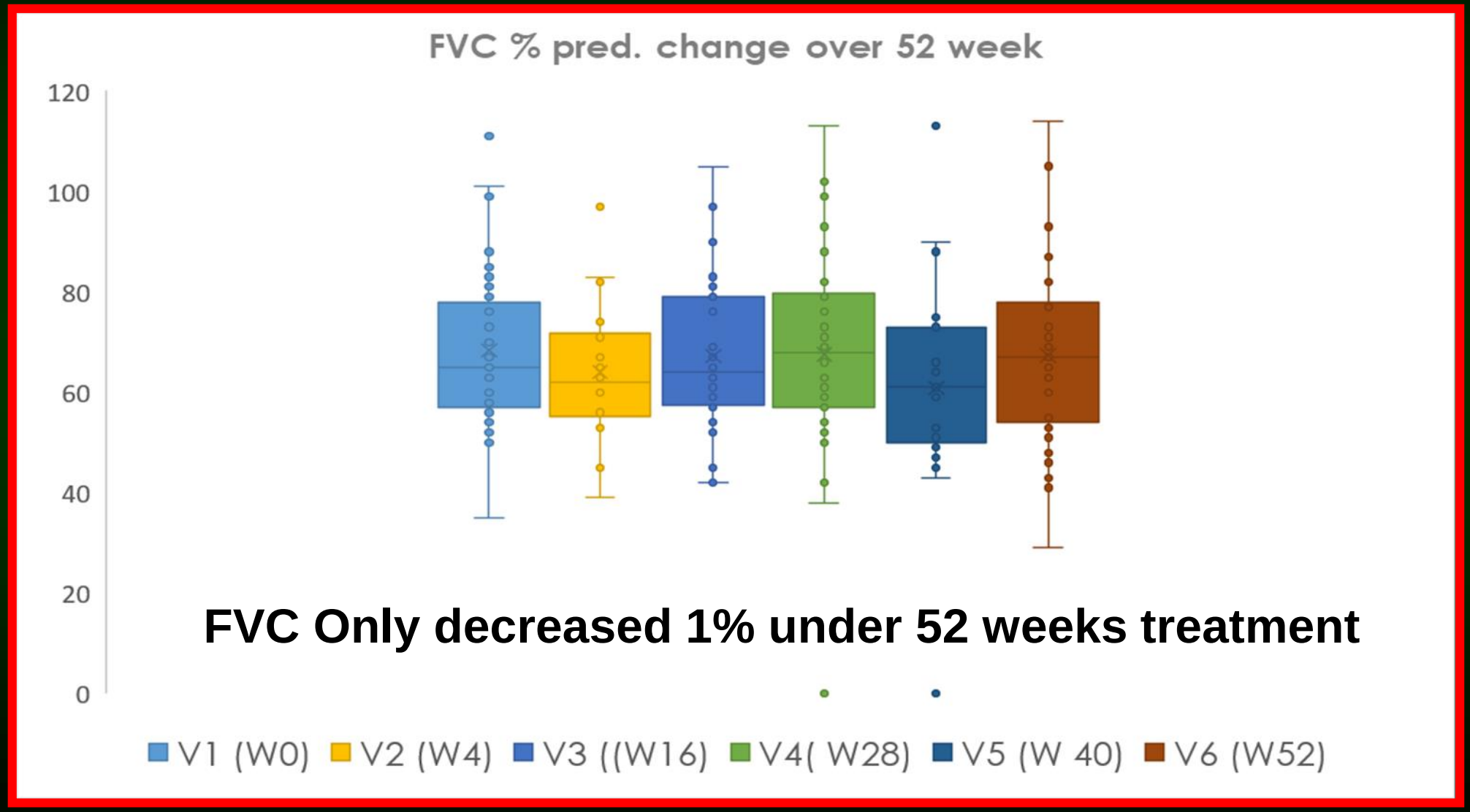
FVC change over 52 weeks



FVC% of patients with/without emphysema (radiologic)



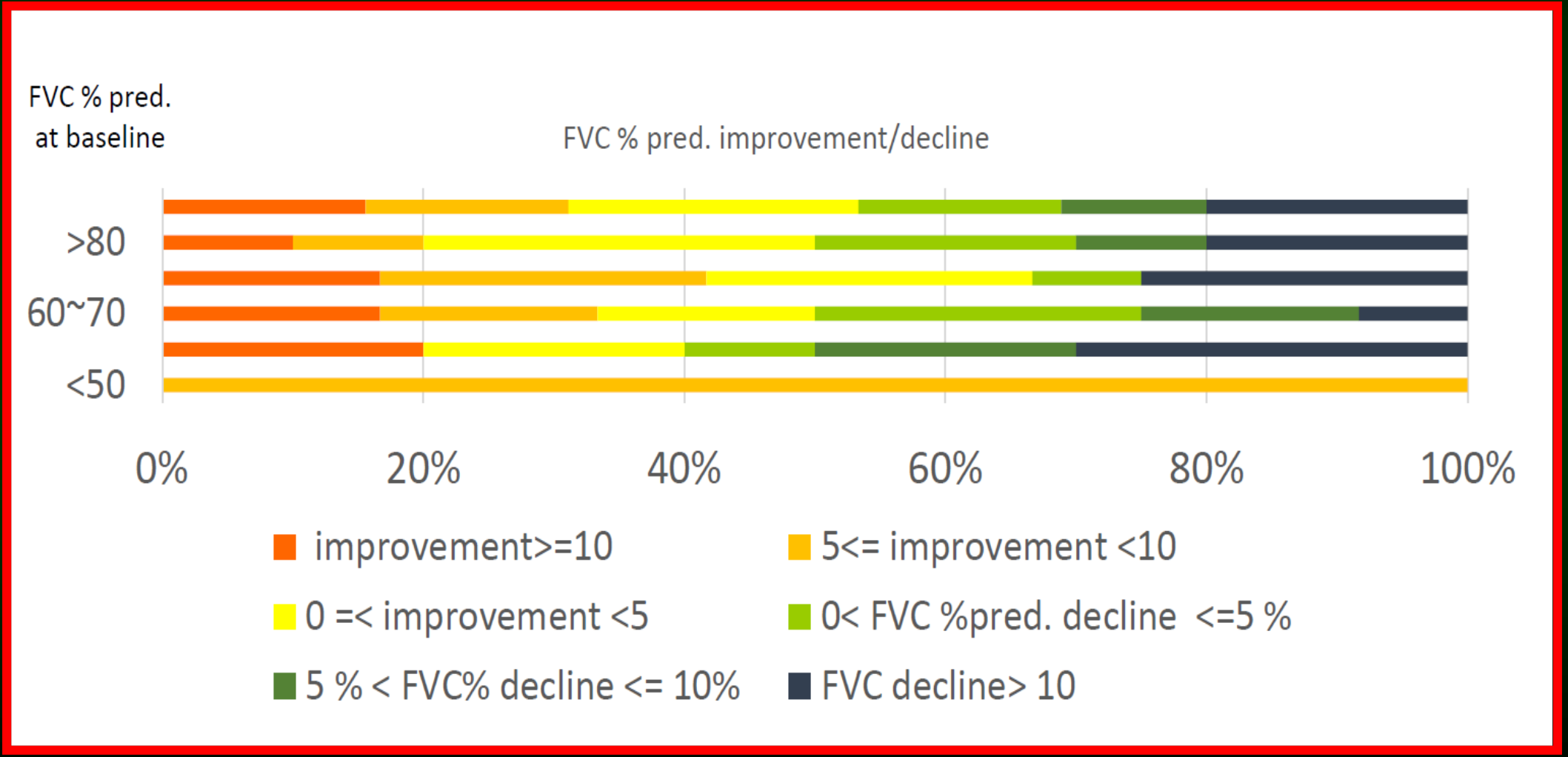
FVC% pred. change over 52 week in antifibrotics group



FVC Only decreased 1% under 52 weeks treatment

Lung function improvement/decline snapshot in treatment group

>50% patients lung function improvement after treatment

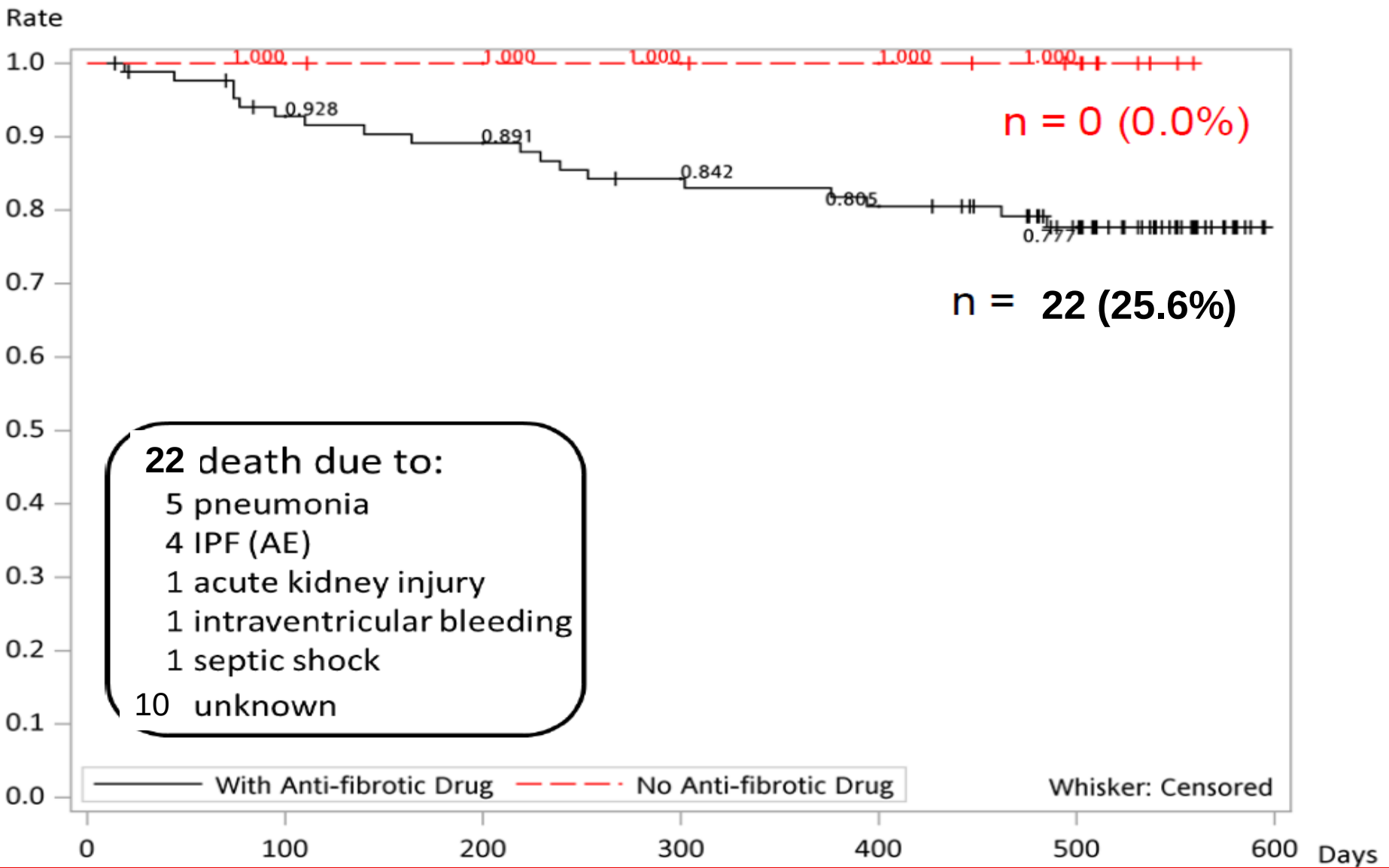


The Rate of acute exacerbation

Characteristics	With Anti-fibrotic Drug N = 86	No Anti-fibrotic Drug N = 15
Patient with ≥ 1 acute exacerbation		
	13 (15.1%)	3 (20.0%)
Survival Time, days (95% CI)		
25%	NA (350.0, NA)	NA (96.00, NA)
50%	NA (NA, NA)	NA (178.0, NA)
75%	NA (NA, NA)	NA (NA, NA)
Time to first acute exacerbation, days		
Number	84	14
Mean ± Std	393.4 ± 203.51	388.3 ± 179.64
Median	495.5	498.0
Range	(6.0, 595.0)	(96.0, 551.0)
95% C.I.	(349.2, 437.5)	(284.6, 492.0)

Overall survival

Overall survival (1 year follow up)



NICEFIT: Summary

1. According to the interim report of NICEFIT, anti-fibrotic drugs are effective in slowing disease progression under the routine practice in Taiwan.
2. Based on the FVC data, IPF patients with better lung function have high percentage with emphysema component (CPFE).
3. The incidence of adverse effects occurring in Taiwanese patients with Nintedanib therapy is similar to those patients in Japan. (PMS study)

- Diarrhea: ~ 27% vs. ~ 28.8% (Taiwan vs. Japan)
- Liver disorder: ~ 11.6% vs. ~ 14.3% (Taiwan vs. Japan)
- A.E: ~ 15.1% vs. ~ 7.5% (Taiwan vs. Japan)
- Mortality: ~ 25.6% vs. ~ 14.2% (Taiwan vs. Japan)

4. Lung function improvement ~ 10ml vs. ~ 135ml (Taiwan vs. Japan)

Take Home Message

- Prompt treatment of IPF is critical to preserving individuals' lung function, reducing the risk of acute exacerbations and improving outcomes
- Pulmonologists may be reluctant to initiate antifibrotic therapy in individuals with IPF whose lung function appears to be stable
- Have an obligation to explain to patients that their disease is progressive and that therapies are available that slow progression but that cannot reverse fibrosis or improve breathlessness once progression has occurred
- Physicians also have a key role to play in helping patients manage side-effects of antifibrotic therapies through education and dose adjustment, thus enabling them to gain the advantages of long-term treatment
- Real world experiences for IPF treatment are exciting, still have challenges in the future.

Thanks for Your Attention !