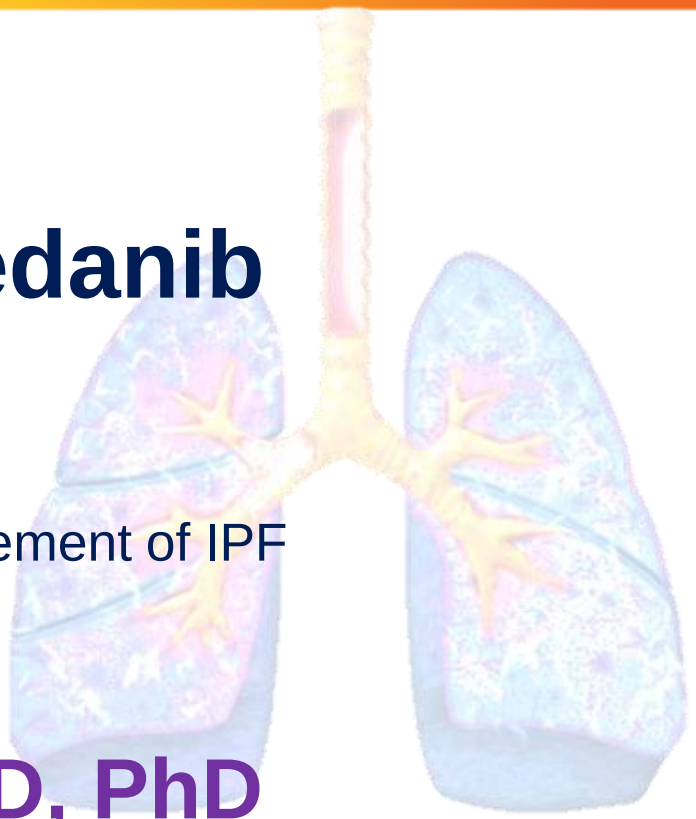
An update of Nintedanib in ATS 2019

Moving forward to optimal management of IPF



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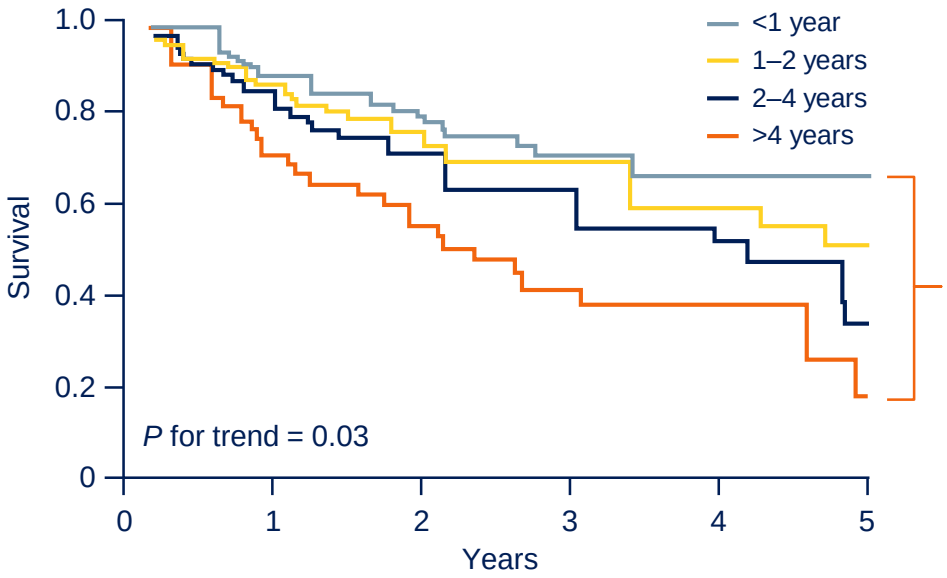
Division for Pulmonary Medicine,

Center of Clinical Trial & Evidence-Based Medicine

Far Eastern Memorial Hospital

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]



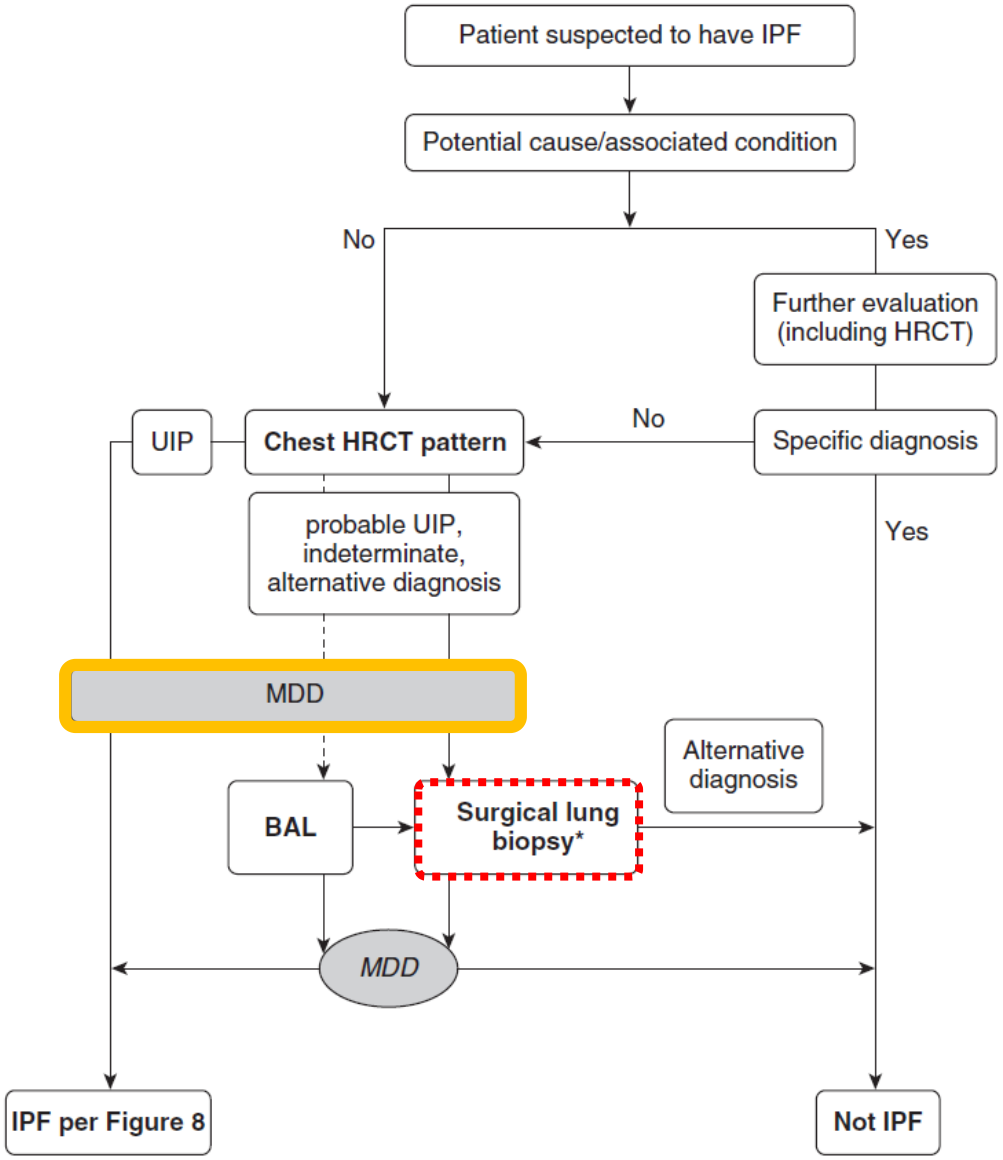
Delays likely lead to a poorer prognosis:

- **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.

Idiopathic pulmonary fibrosis diagnosis based upon HRCT and biopsy patterns

IPF suspected*		Histopathology pattern			
		UIP	Probable UIP	Indeterminate for UIP	Alternative diagnosis
HRCT pattern	UIP	IPF	IPF	IPF	Non-IPF dx
	Probable UIP	IPF	IPF	IPF (Likely)**	Non-IPF dx
	Indeterminate	IPF	IPF (Likely)**	Indeterminate***	Non-IPF dx
	Alternative diagnosis	IPF (Likely)** /non-IPF dx	Non-IPF dx	Non-IPF dx	Non-IPF dx

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

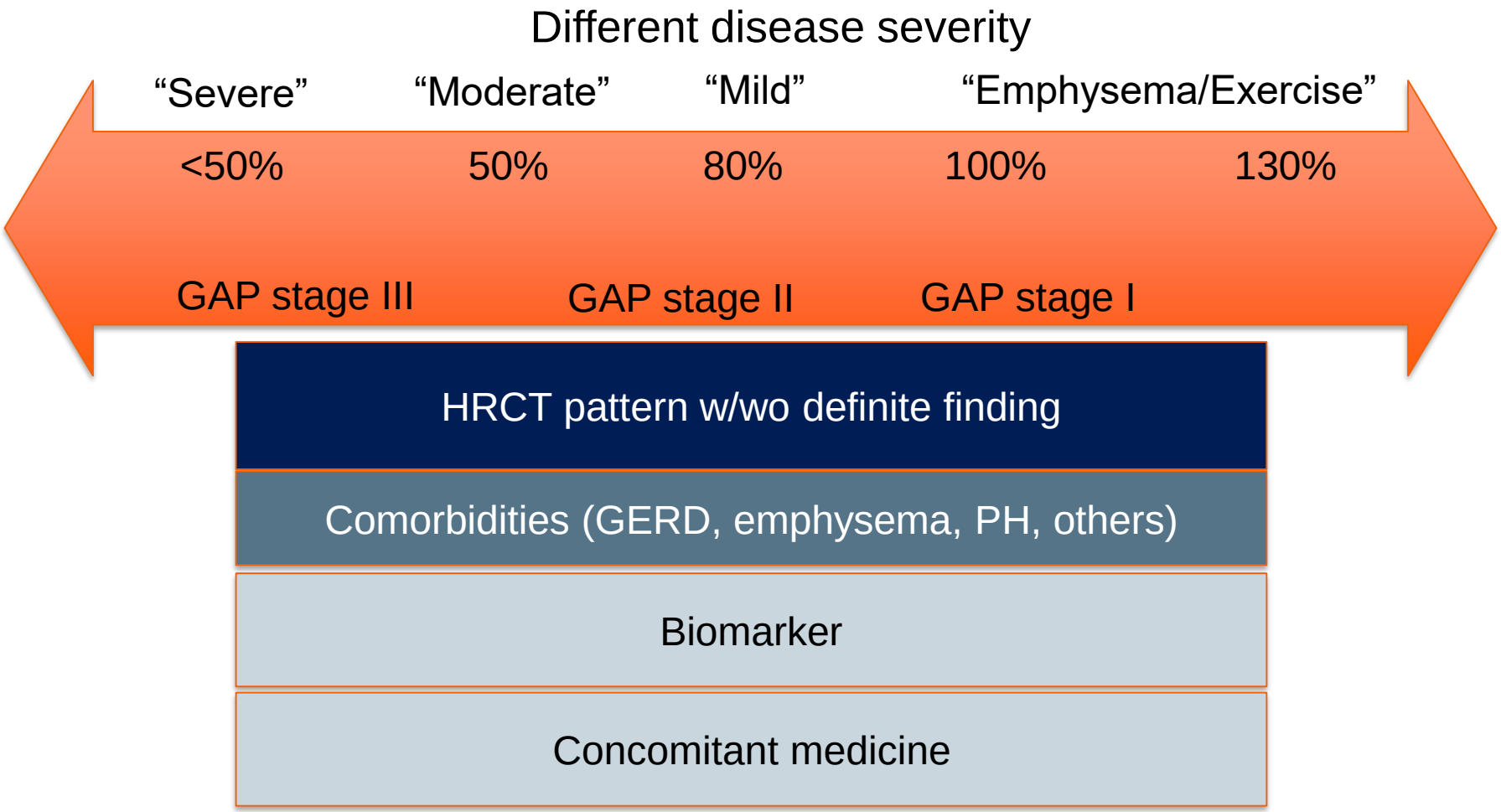
What should be done when diagnostic tissue is not available?

- ✓ 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



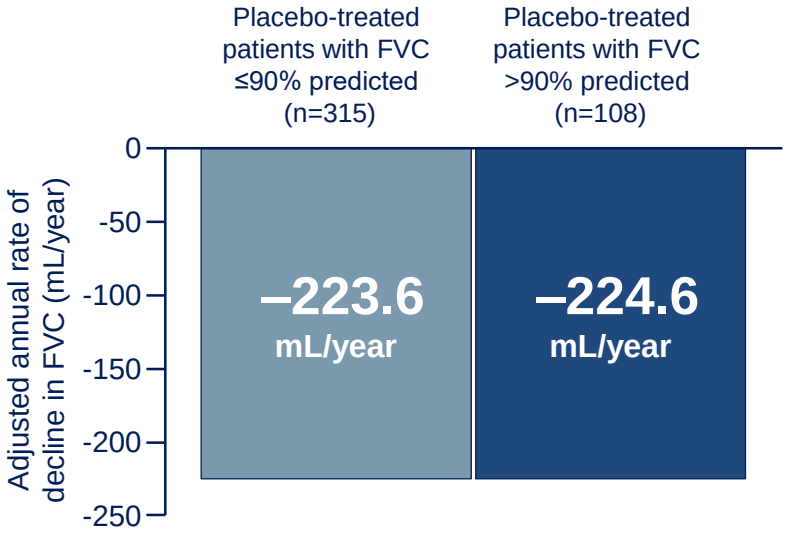
Optimal management of IPF

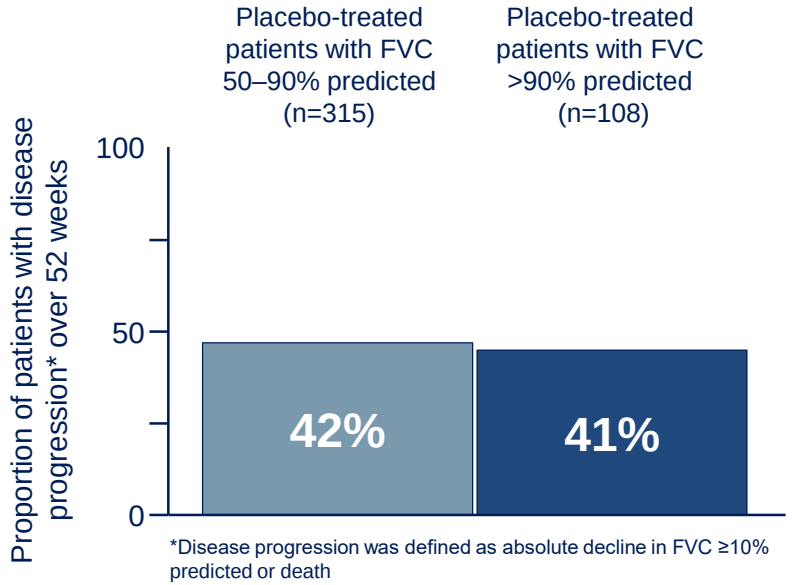
When?

How?

Which one?

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

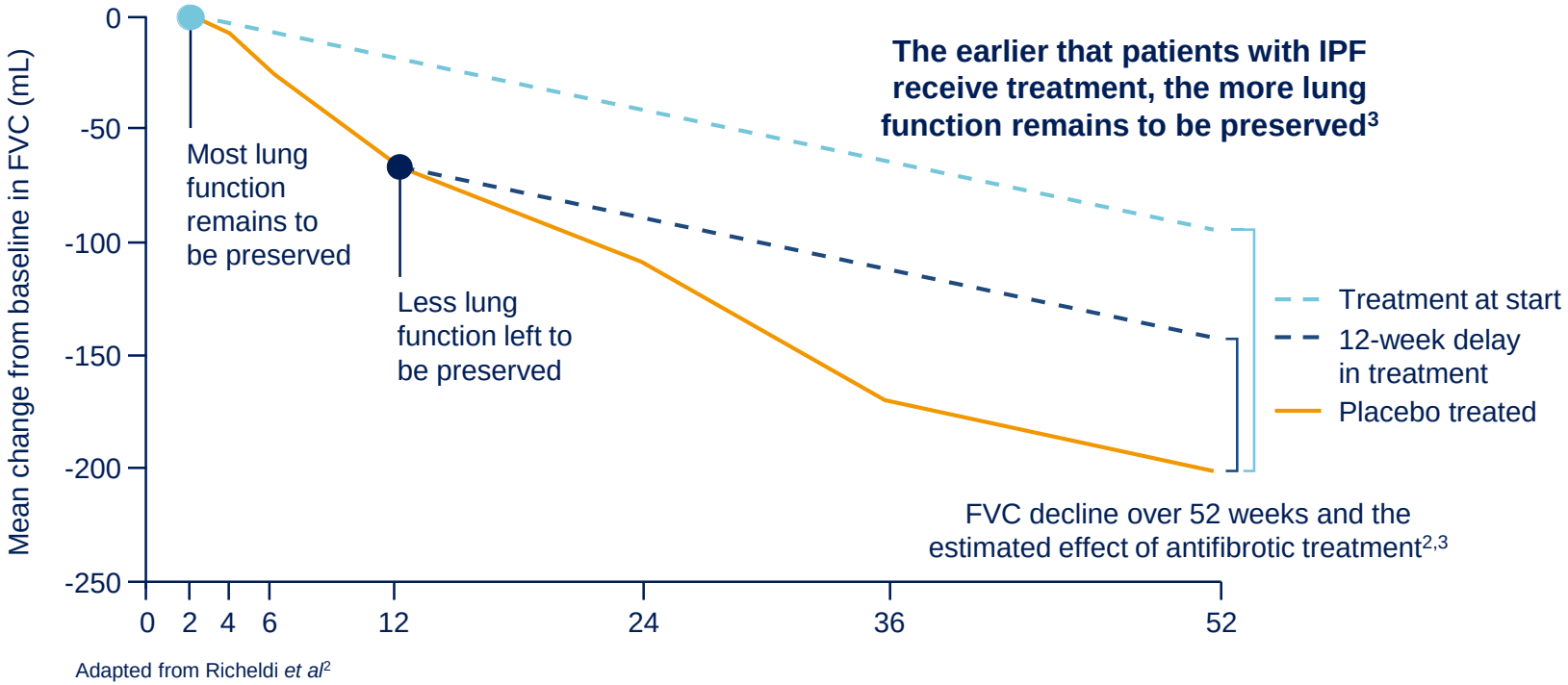




Patients with IPF with preserved lung function (FVC >90% predicted) have the same rate of FVC decline as patients with more impaired lung function[1]

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

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



Adapted from Richeldi *et al*[2]

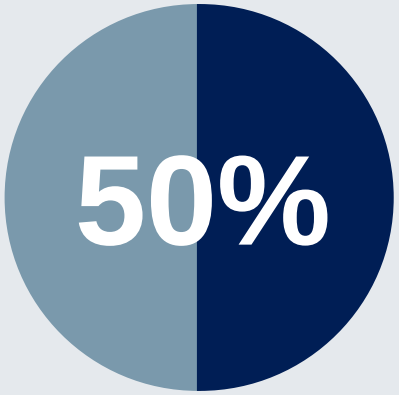
1. Richeldi L *et al. N Engl J Med* 2014;370:2071–2082
2. Kolb M *et al. Thorax* 2017;72:340–346

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]

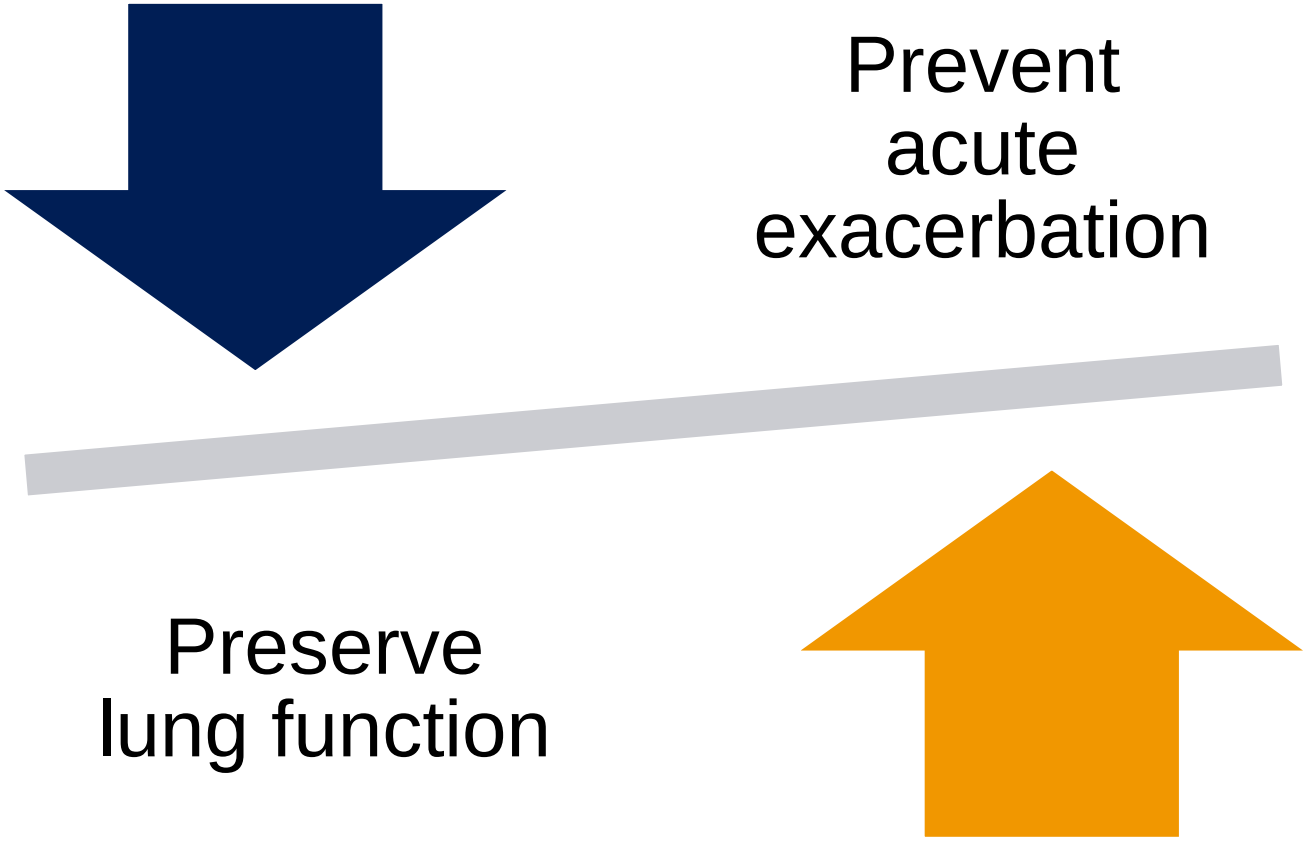
50% of patients hospitalized for an acute IPF exacerbation **die during hospitalization**[3]



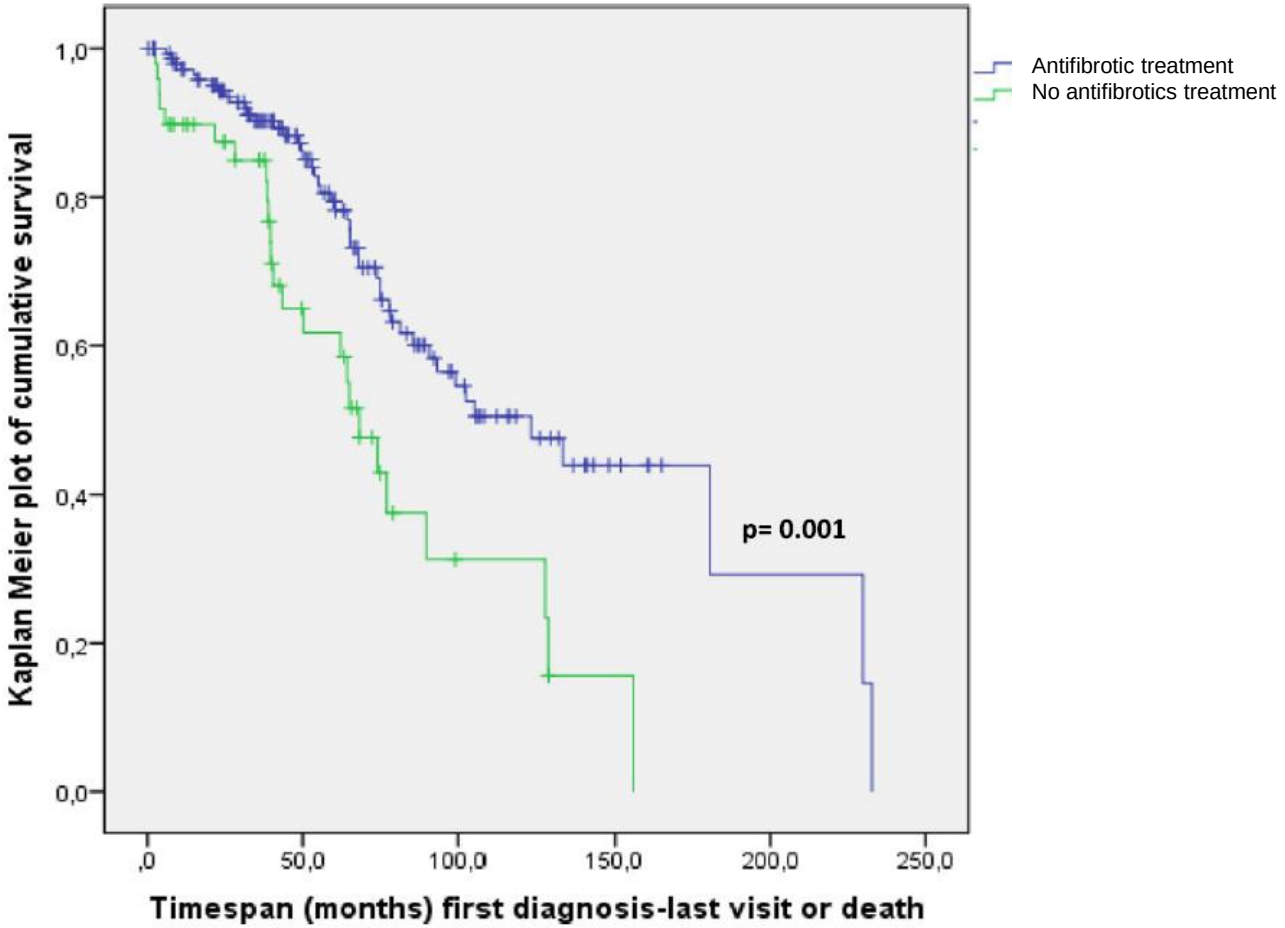
Low or worsening FVC is a risk factor for acute exacerbations, although they can occur in all patients.[3,4] Theoretically, preservation of FVC could reduce the risk of acute exacerbations

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



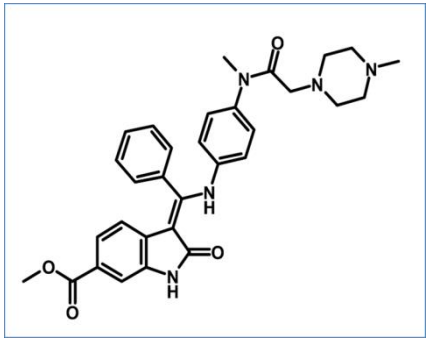
Early intervention improves the survival rate of IPF

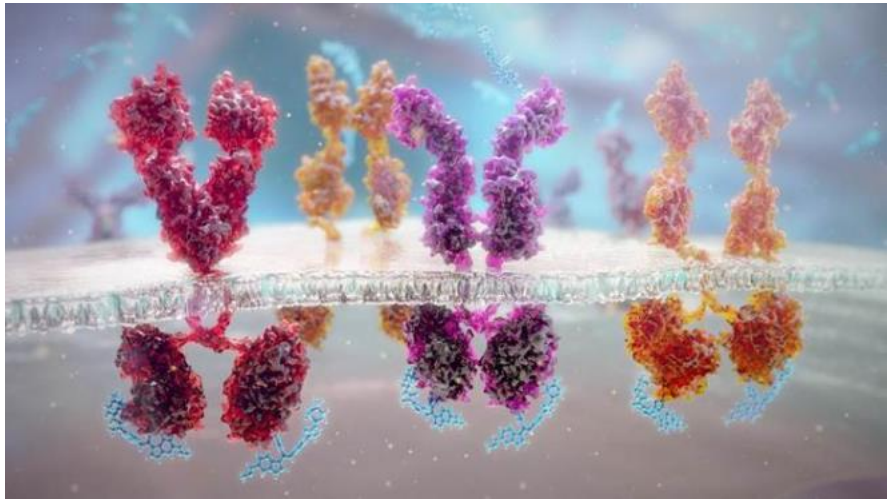


Respiratory Research 2018;19:141
European registry for idiopathic pulmonary fibrosis (eurIPFreg)

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.

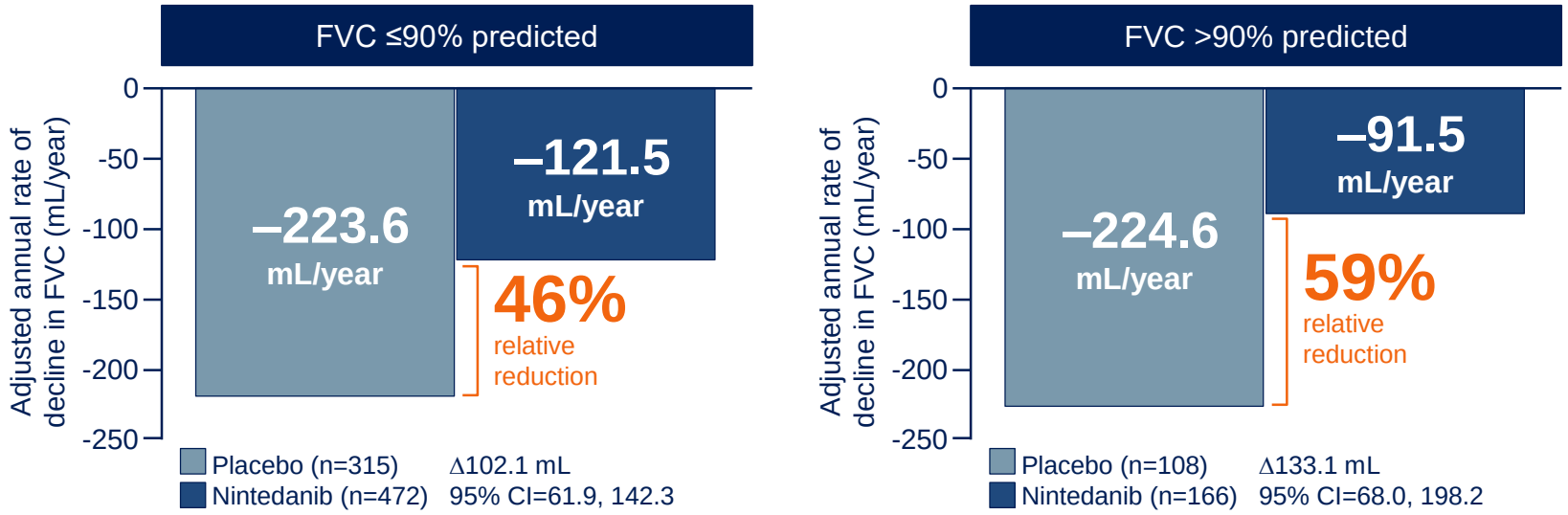
Anti-fibrotic, anti-inflammatory and vascular remodeling effects of nintedanib

- 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

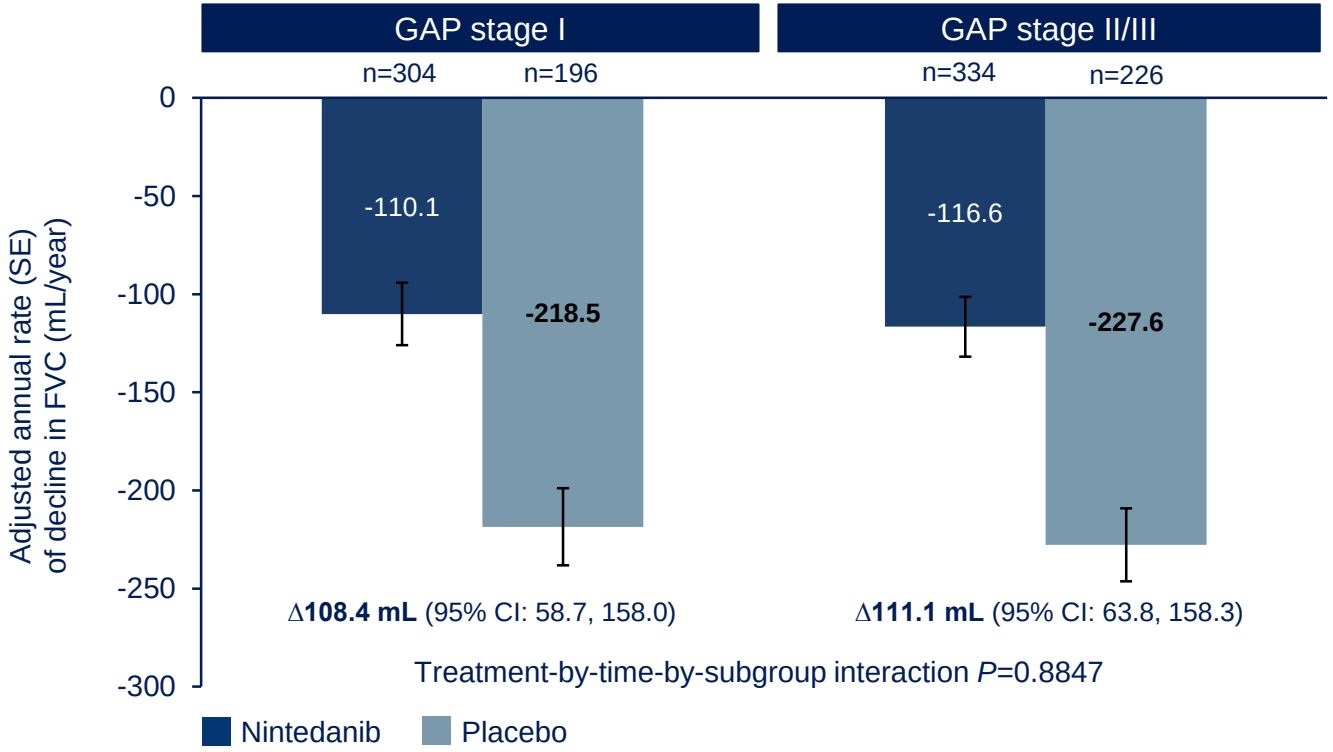


Placebo-treated patients with FVC >90% predicted at baseline experienced an annual rate of FVC decline similar to patients with FVC ≤90% predicted at baseline[1]

Figures reproduced from Thorax, Kolb M et al, Vol. 72, pp340-346, ©2017 with permission from BMJ Publishing Group Ltd

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

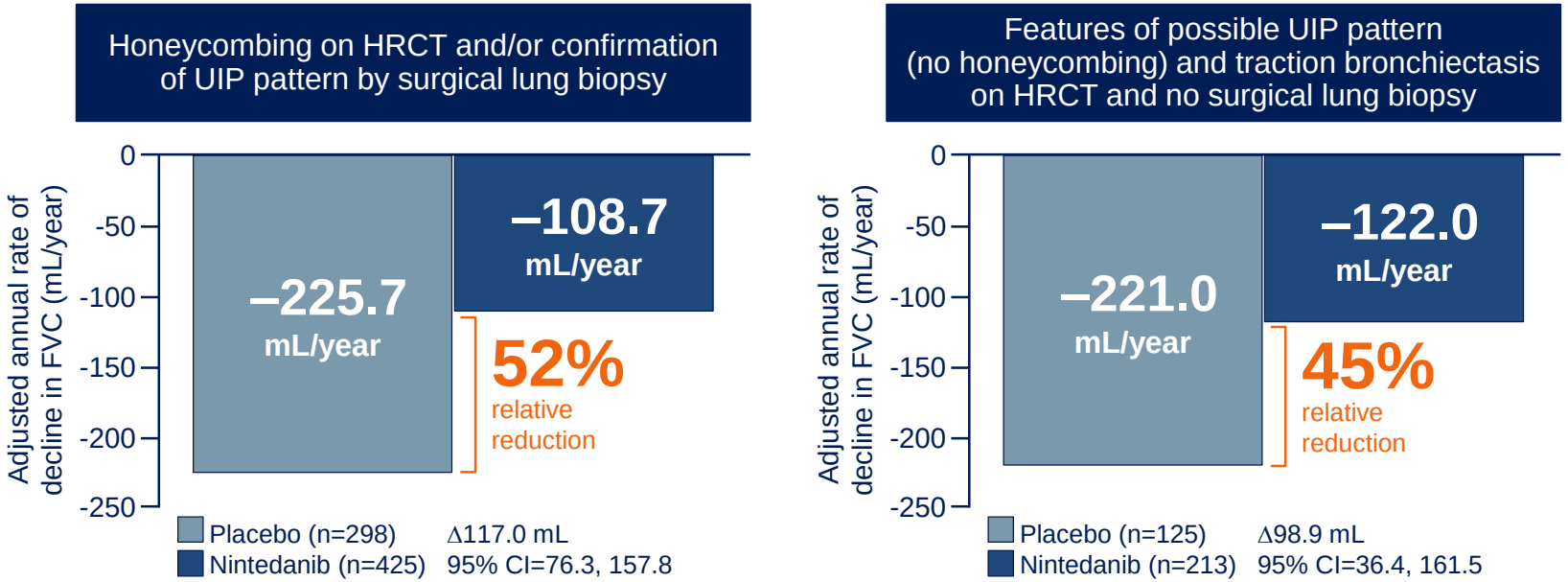
Nintedanib reduced the annual rate of decline in FVC by 50% irrespective of GAP stage at baseline



SE, standard error

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

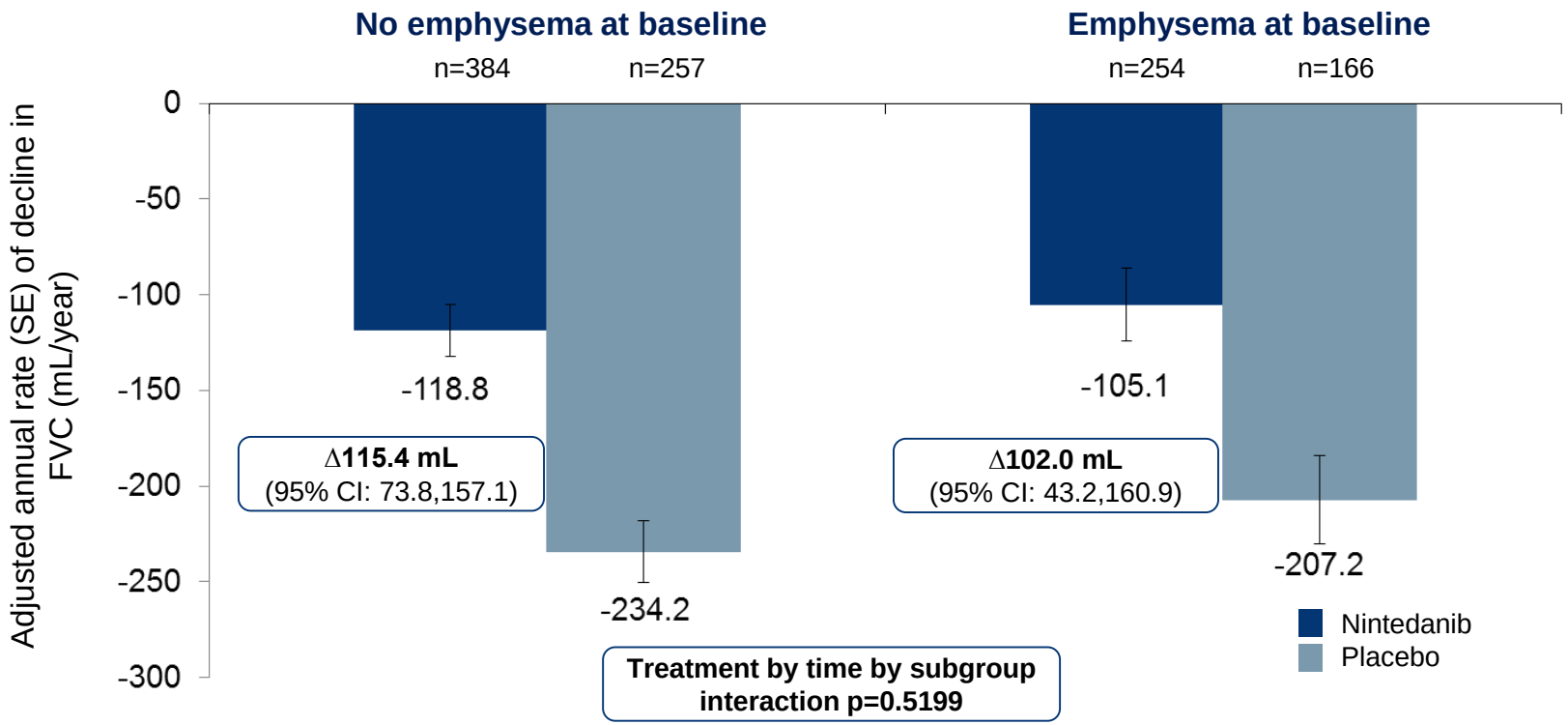
Patients with IPF benefit from nintedanib when HRCT shows possible UIP



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

Nintedanib is effective for IPF patients with/without emphysema

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



Slides presented at ICLAF, Mont Tremblant, Canada, 20–24 September 2014.

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

Nintedanib showed more stability or improvement in FVC in INPULSIS

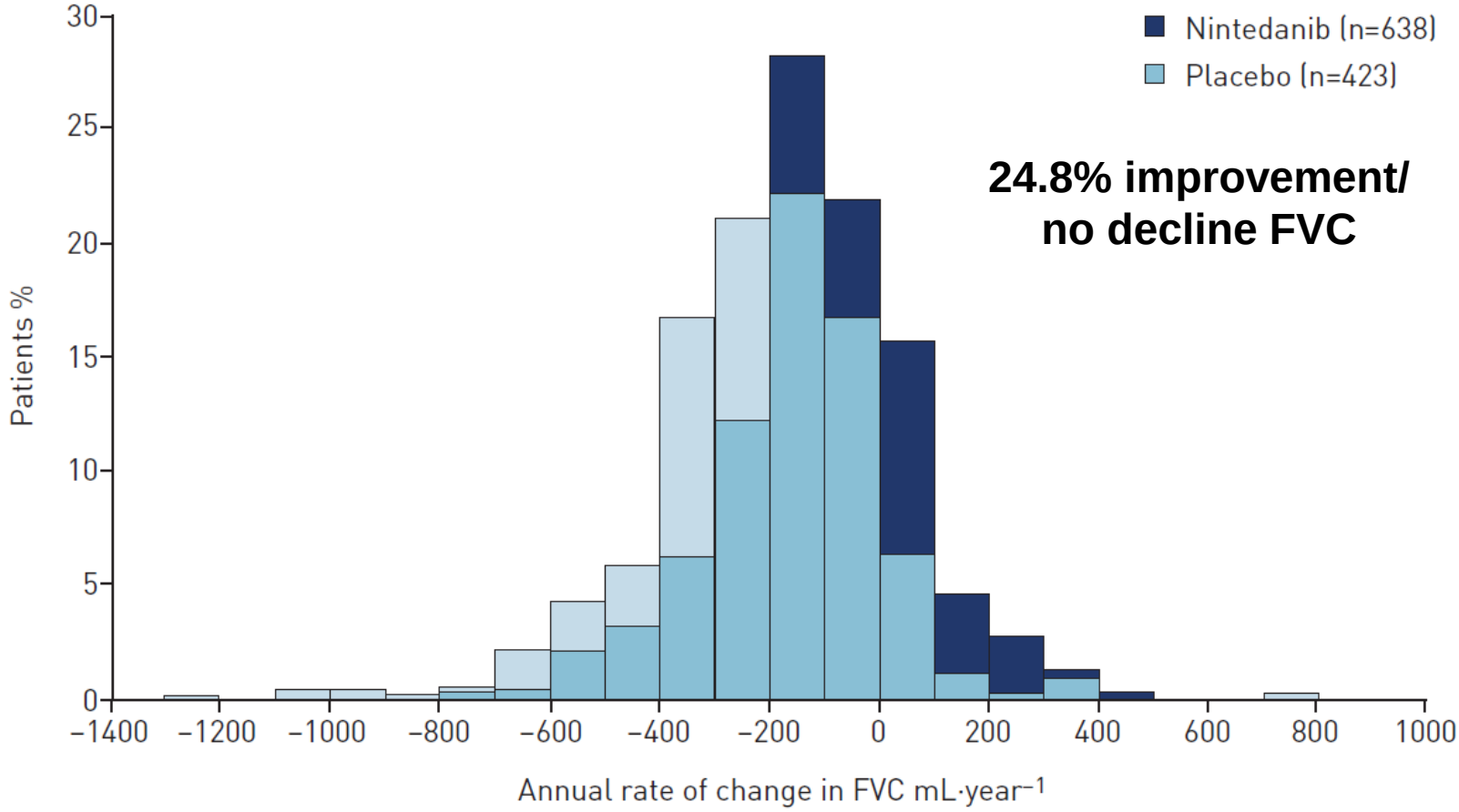
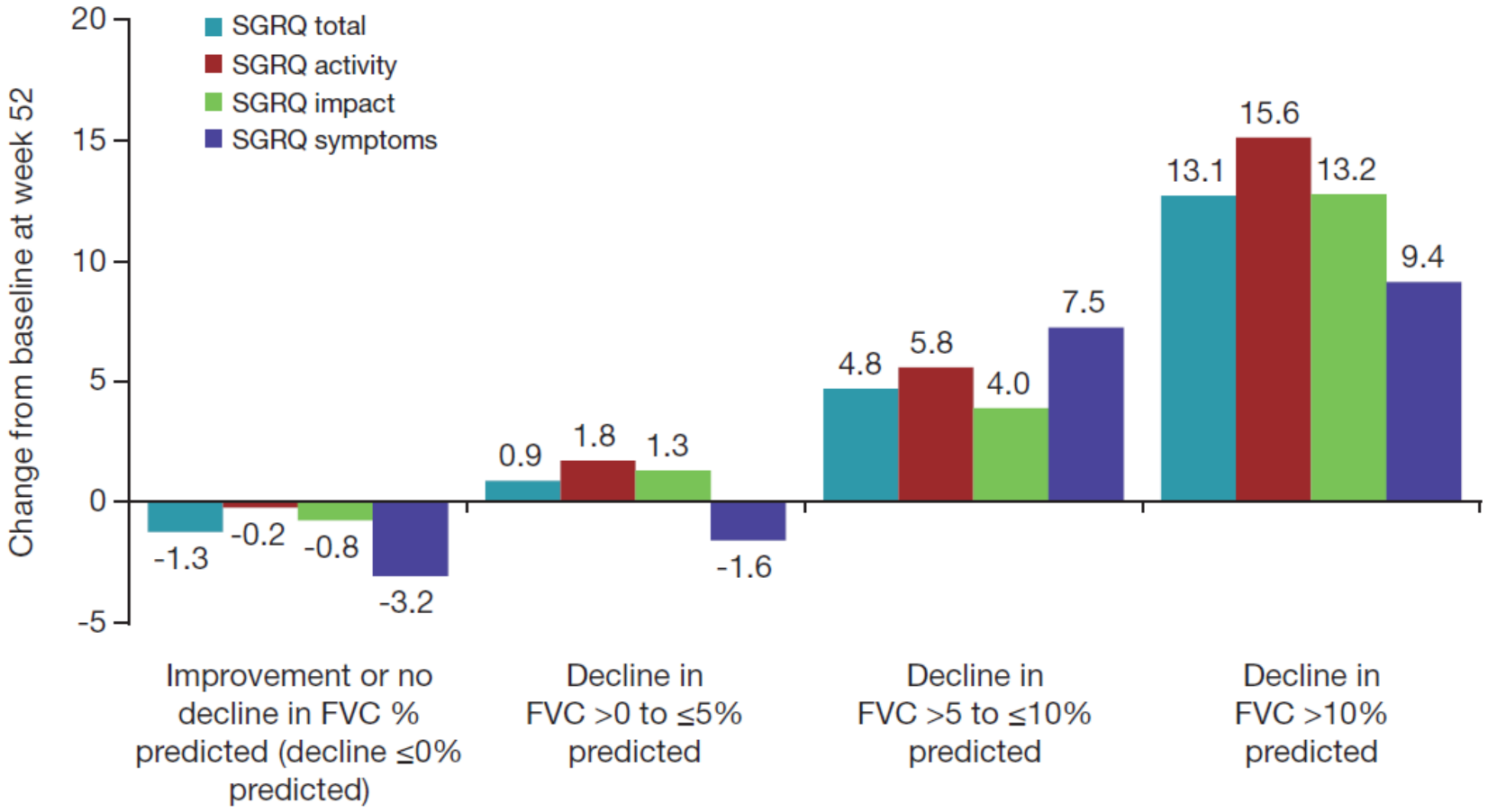


FIGURE 1 Annual rate of change in forced vital capacity (FVC) in the INPULSIS® trials.

Eur Respir J 2018; 52: 1702593

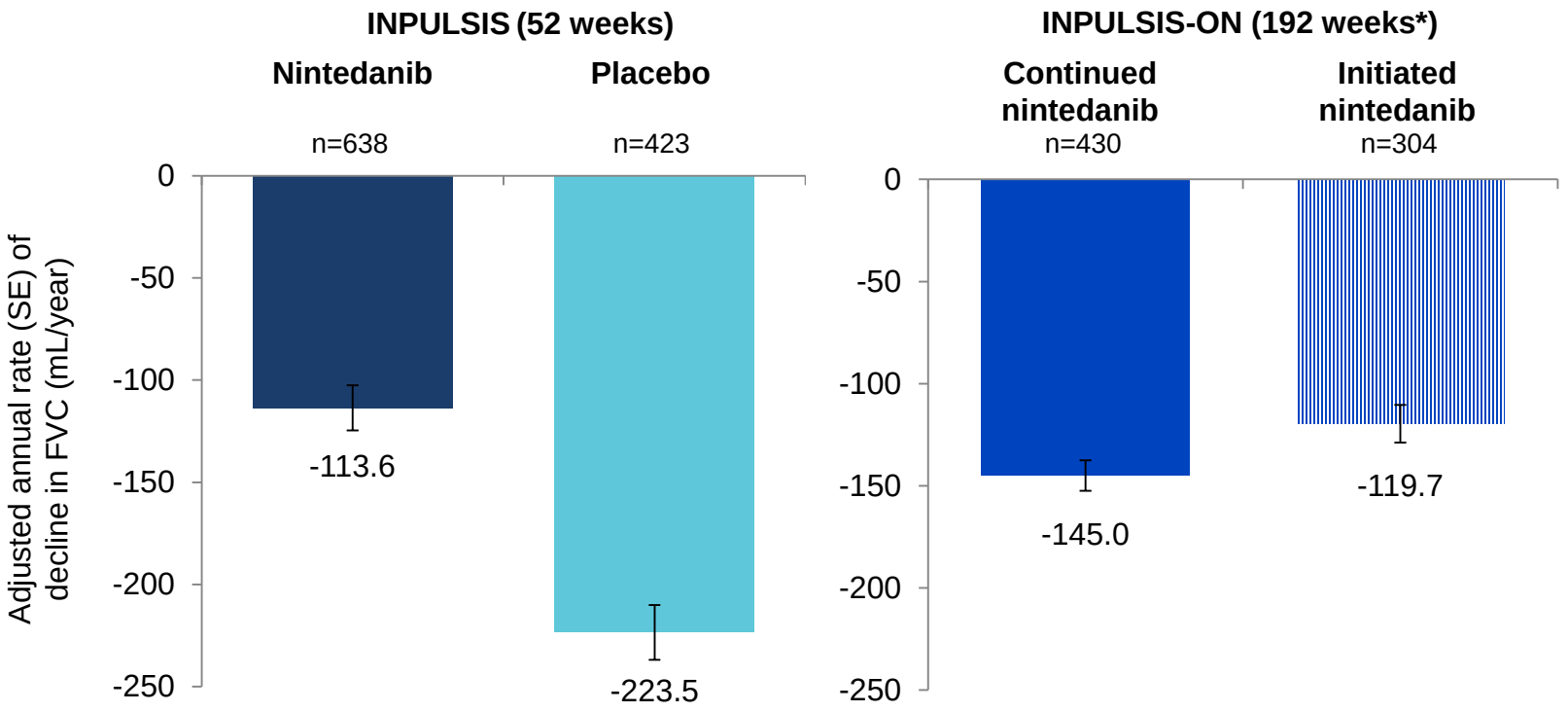
Changes from baseline in SGRQ scores at week 52 by changes in FVC % predicted at week 52



Kreuter et al presented at the American Thoracic Society International Conference 2019

Long term efficacy of Nintedanib on slowing FVC decline

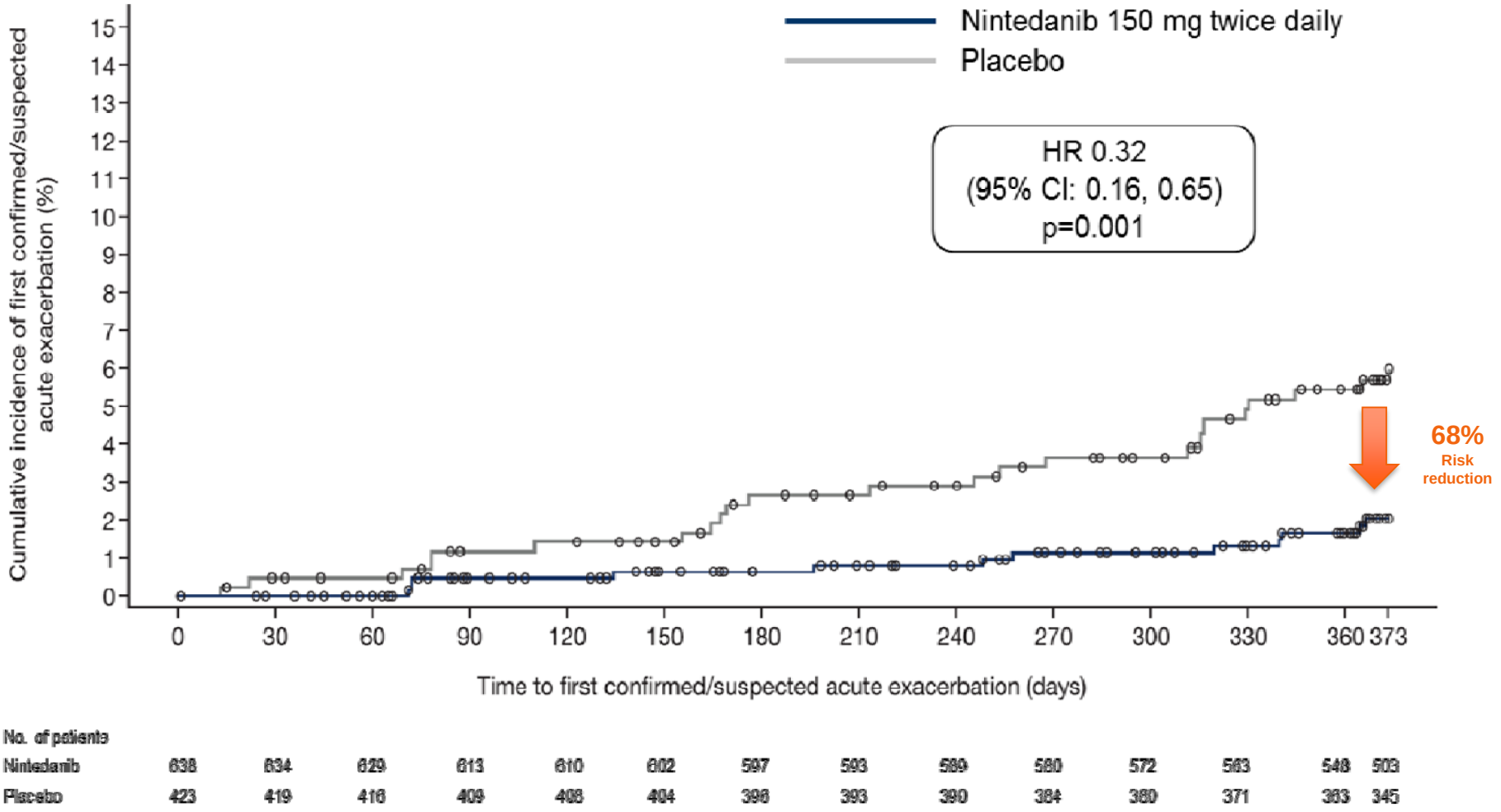
INPULSIS and INPULSIS-ON: Annual rate of decline in FVC beyond 4 years



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

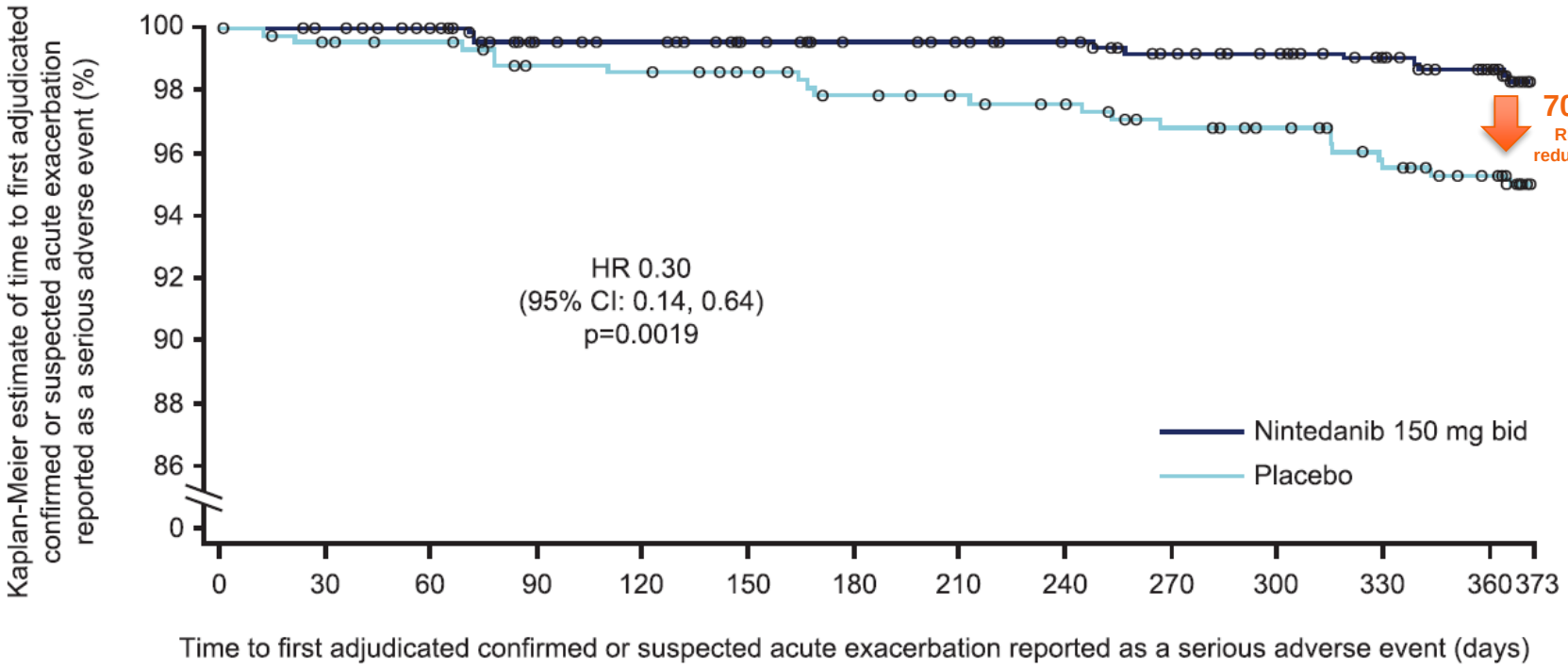
Crestani B et al. Lancet Respir Med 2019;7:60-68.

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



Richeldi *et al*, *NEJM* 2014

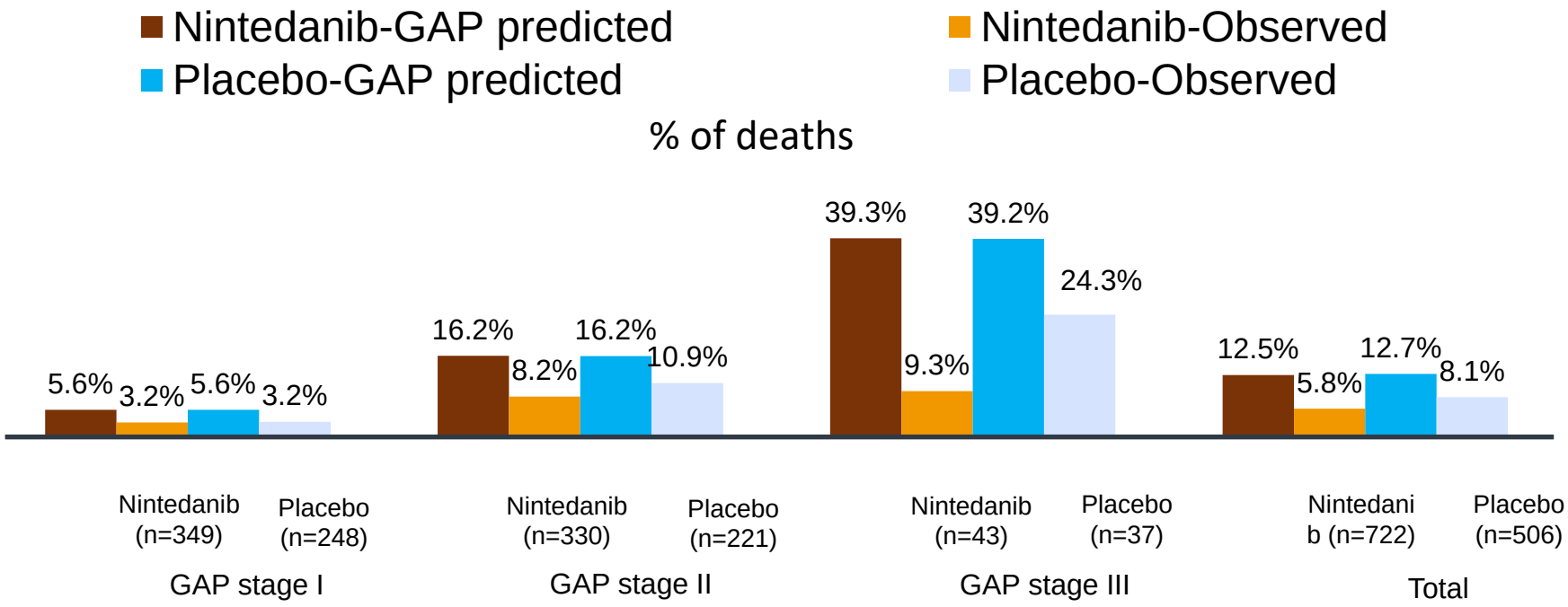
Nintedanib significantly reduced the severity of AE:
Reducing acute exacerbations reported as serious adverse events



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

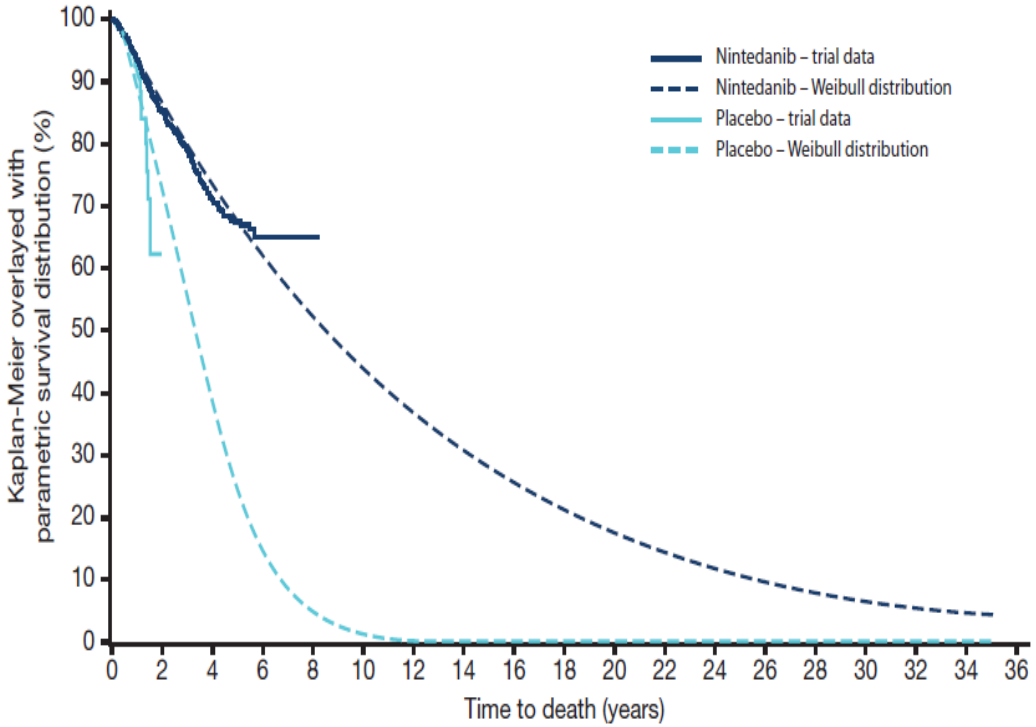
Kreuter et al. Respiratory Research (2019) 20:71

TOMORROW and INPULSIS: Predicted deaths based on GAP stage at baseline vs observed deaths by treatment



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

Estimated time to death using the Weibull distribution: Nintedanib provides more 7.9 years lifetime vs. placebo 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**

Lancaster L, *et al*. *BMJ Open Resp Res* 2019;**6**:e000397

The INMARK® study

Key results presented in ATS 2019

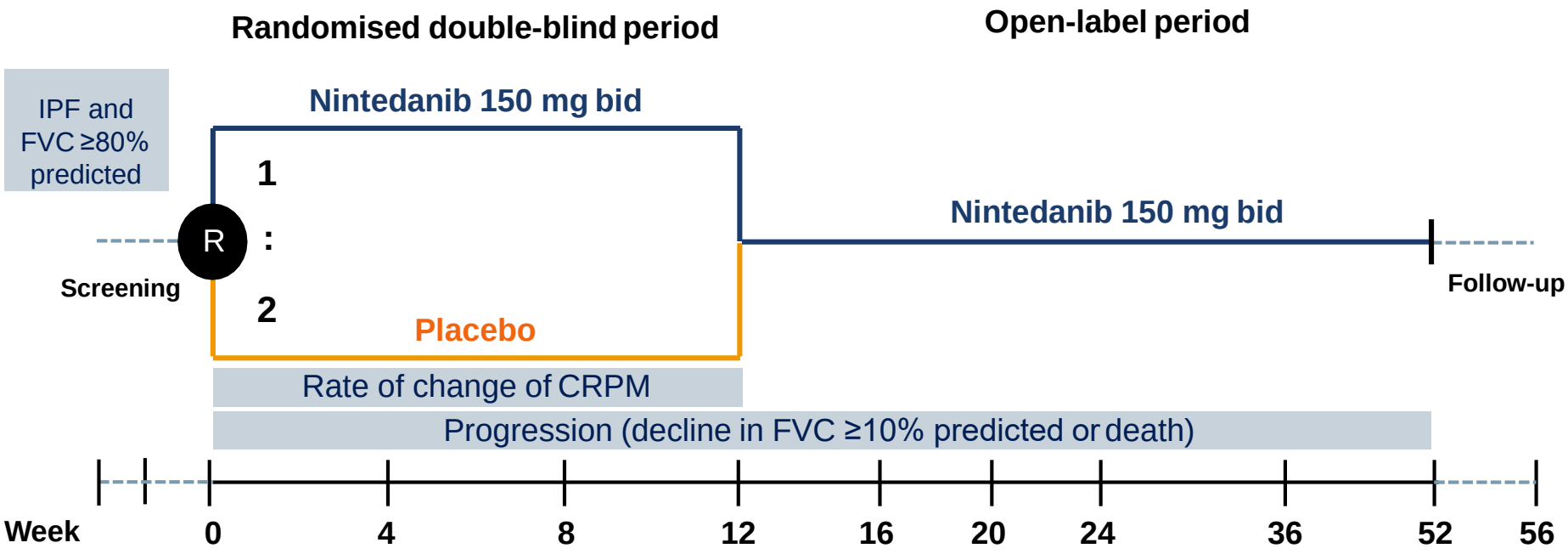
Key objectives of INMARK

- The objectives of the INMARK trial were to:
  - Evaluate the effect of nintedanib on the rate of change in CRPM
  - Further investigate CRPM as a prognostic marker in IPF
  - Assess whether nintedanib affects the association between changes in CRPM and disease progression

INMARK was the first clinical trial to investigate the predictive value of neoepitopes in patients with IPF treated with antifibrotic therapy

Maher TM et al. BMJ Open Respir Res 2018;5:e000325.

Trial design



R, randomisation. Treatment interruptions and dose reductions to 100 mg bid were recommended to manage adverse events.

Endpoints

Primary endpoint

- Rate of change (slope) in CRPM (ng/mL/month) from baseline to week 12

Key secondary endpoint

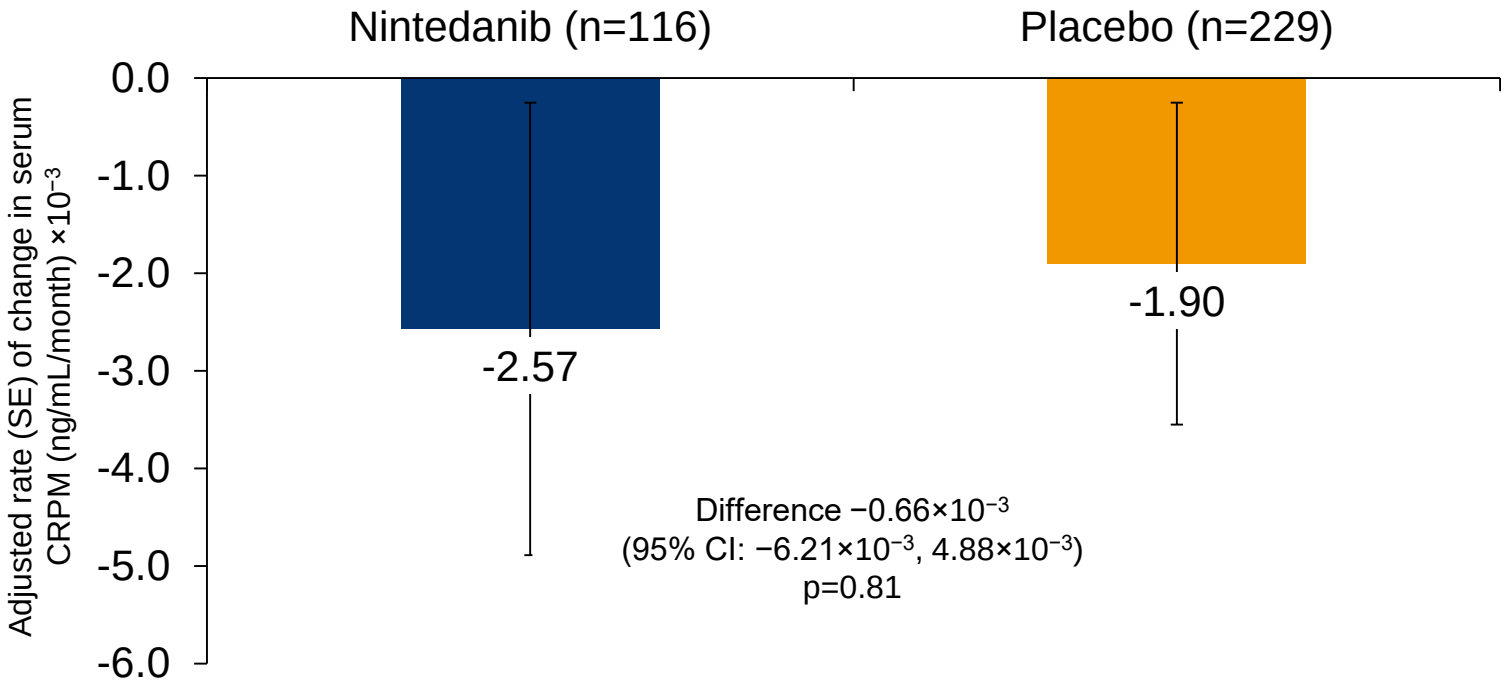
- Proportion of subjects who had an absolute decline in FVC ≥10% predicted or who died over 52 weeks

Exploratory endpoint

- Change in C-reactive protein (which is degraded to form CRPM)

Analyses were conducted in subjects who received ≥1 dose of study medication. CRPM, c-reactive protein (CRP) degraded by MMP-1/8.

Rate of change in CRPM from baseline to week 12 (primary endpoint)



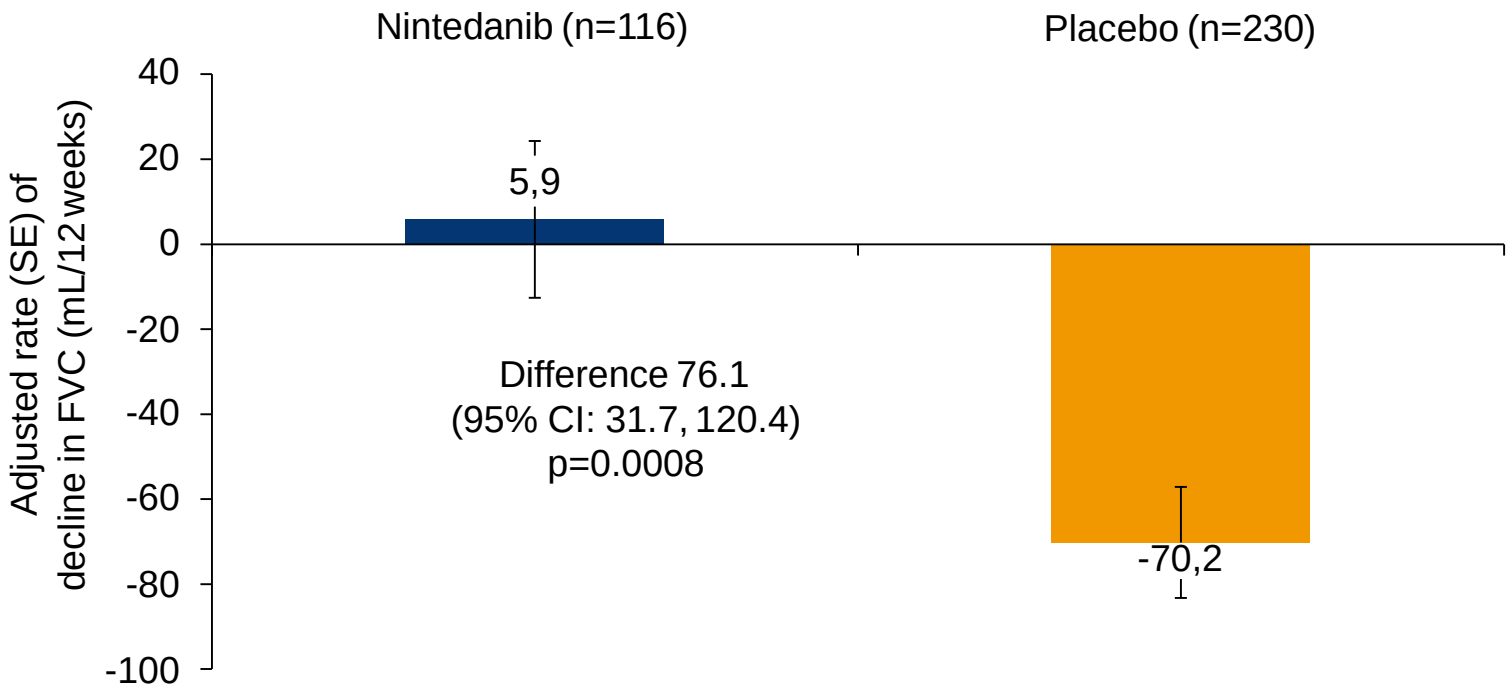
Rate of change in CRPM (ng/mL/month) was based on log10 transformed values. CRPM, c-reactive protein degraded by MMP-1/8.

Disease severity in patients in INMARK vs PROFILE and INPULSIS

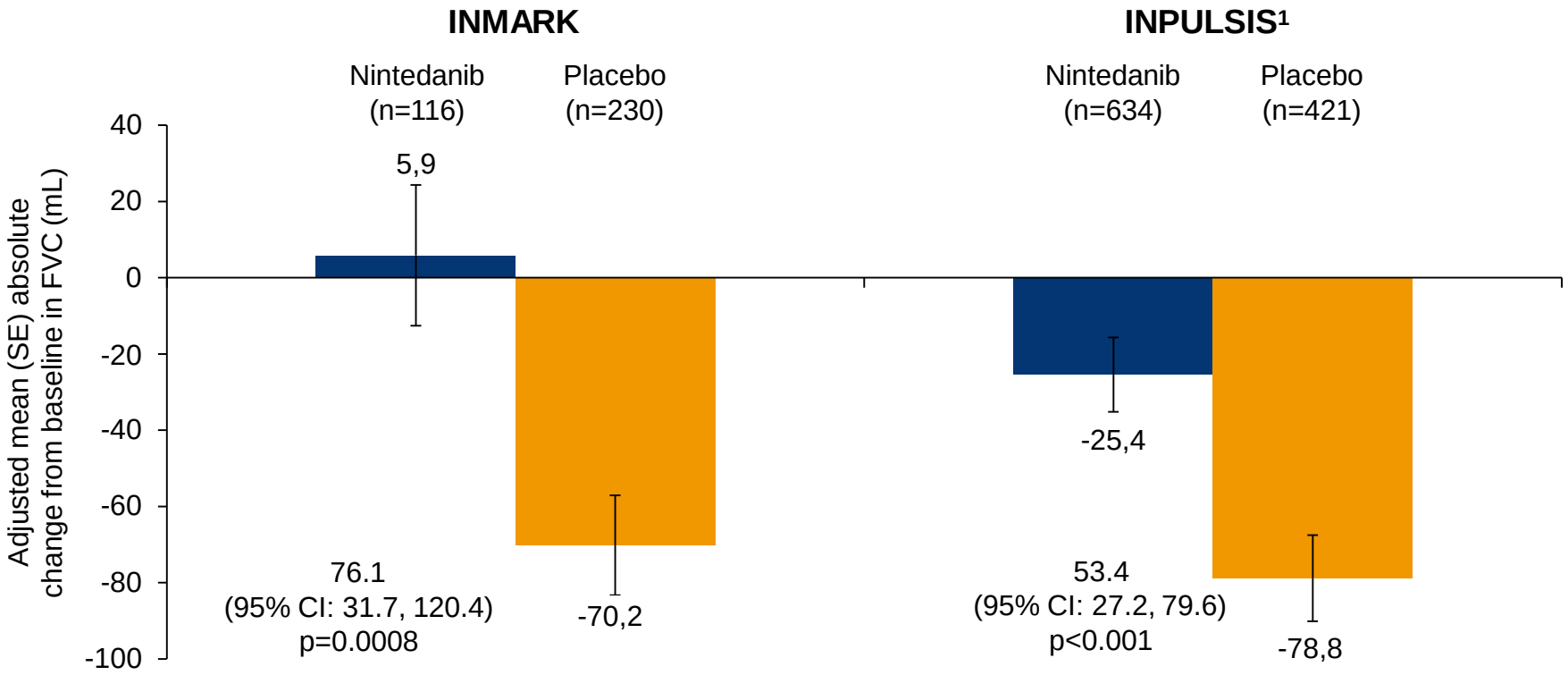
	INMARK		PROFILE[1]	INPULSIS[2]	
	Nintedanib (n=116)	Placebo (n=230)	All (n=184)	Nintedanib (n=638)	Placebo (n=423)
FVC % predicted, mean (SD)	96.6 (15.2)	98.0 (12.6)	77.5 (19.2)	79.7 (17.6)	79.3 (18.2)
DLco % predicted, mean (SD)*	60.9 (16.6)	65.5 (21.2)	42.8 (15.2)	47.4 (13.5)	47.0 (13.4)

*DLco data were not available for all patients. 1. Jenkins RG et al. Lancet Respir Med 2015;3:462–72; 2. Richeldi L et al. N Engl J Med 2014;370:2071–82.

Rate of change in FVC (mL) over 12 weeks



Absolute change from baseline in FVC (mL) at week 12 in INPULSIS and INMARK



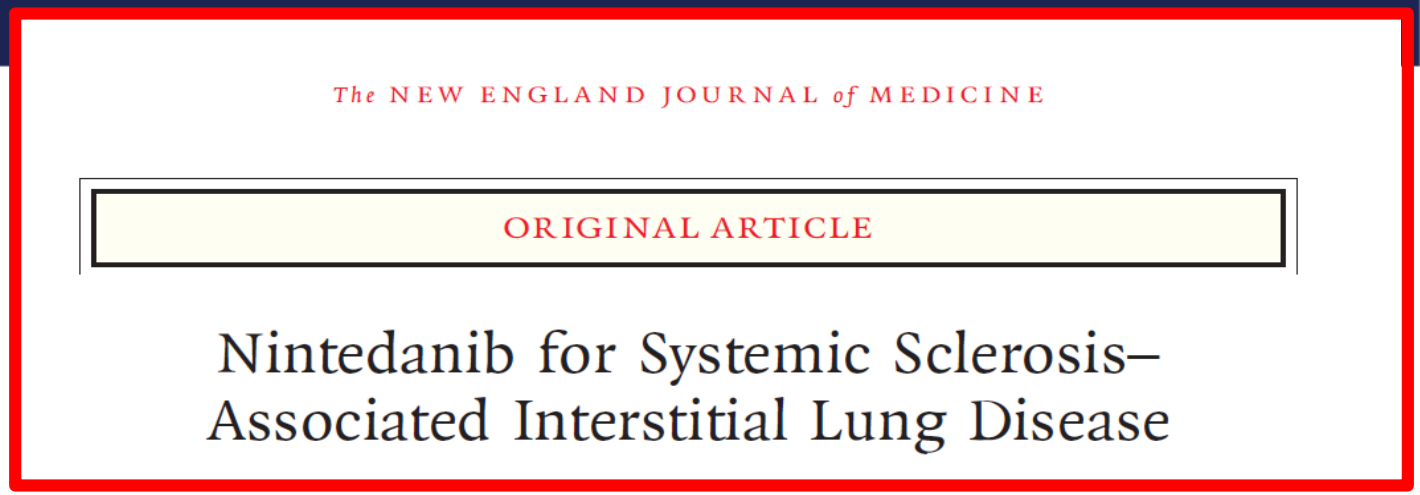
1. Richeldi L et al. N Engl J Med 2014;370:2071–82.

Summary of INMKAR

- In the INMARK trial in subjects with IPF and preserved lung volume:
  - In patients with very well preserved lung function at baseline (mean FVC: >97% predicted)
  - Treatment with nintedanib for 12 weeks did not affect the rate of change in biomarkers indicative of ECM turnover compared with placebo
  - Over 12 weeks, nintedanib was associated with a lower rate of decline in FVC compared with placebo
  - The rate of decline in FVC over 52 weeks in subjects treated with nintedanib was consistent with that observed in other trials
  - In subjects who received placebo for 12 weeks, rising levels of CRPM over 12 weeks were associated with disease progression over 52 weeks
    - Treatment with nintedanib did not have a significant effect on this association
  - The adverse event profile of nintedanib was consistent with that observed in previous studies
- Further analyses of biomarkers reflective of epithelial damage, inflammation and ECM turnover are ongoing

The SENSCIS® trial

Key results presented in 2019 ATS



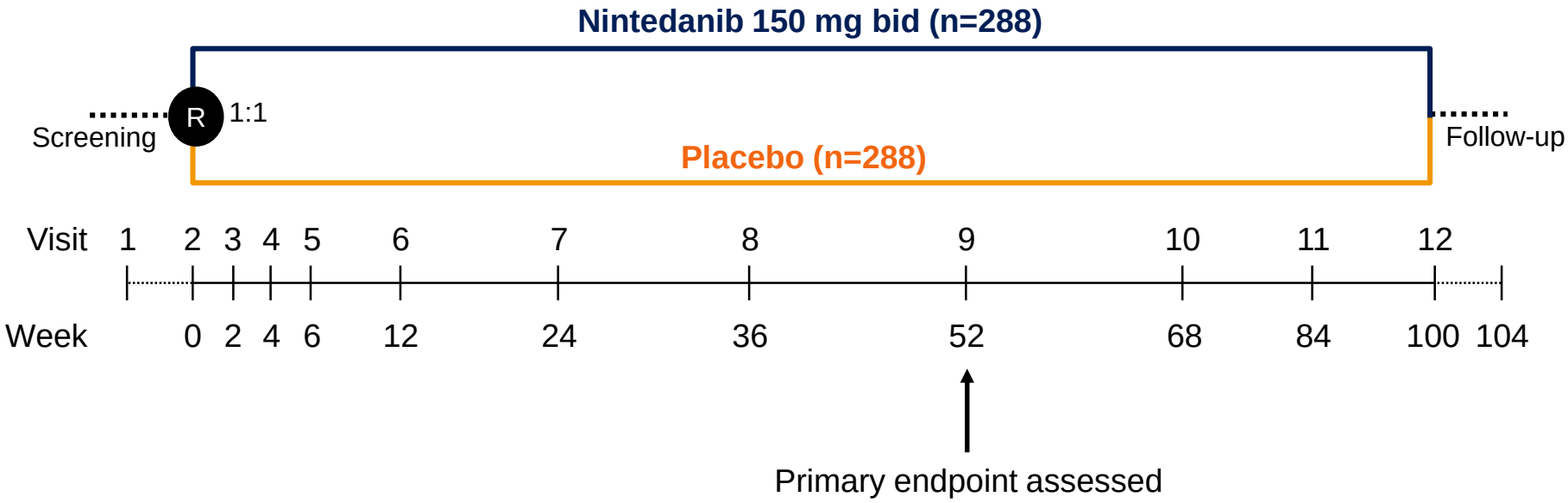
N Engl J Med. 2019 May 20

Scientific rationale for performing the SENSCIS® trial

Systemic sclerosis	• Orphan disease of unknown aetiology • Heterogenous disease • Multiple organ fibrosis
SSc-ILD	• A leading cause of SSc-related death[1] • High unmet medical need – no approved treatments • Mechanisms of lung fibrosis show similarities with IPF[2,3]
Nintedanib	• Antifibrotic efficacy proven in patients with IPF[4] • Pre-clinical evidence for efficacy in models of SSc and SSc-ILD[5,6]

1. Elhai M, et al. Ann Rheum Dis 2017;76:1897-1905; 2. Hsu E, et al. Arthritis Rheum 2011;63:783–94; 3. Lam AP, et al. Am J Respir Cell Mol Biol 2011;45:915–22; 4. Richeldi L, et al. N Engl J Med 2014;370:2071-82; 5. Huang J, et al. Ann Rheum Dis 2016;75:883-90; 6. Huang J, et al. Ann Rheum Dis 2017;76:1941-48.

SENSCIS: Trial design



Randomised patients were stratified by anti-topoisomerase antibody (ATA) status (positive or negative). Patients remained on blinded treatment until the last patient had reached week 52 but for no longer than 100 weeks.

bid, twice daily; R, randomisation.

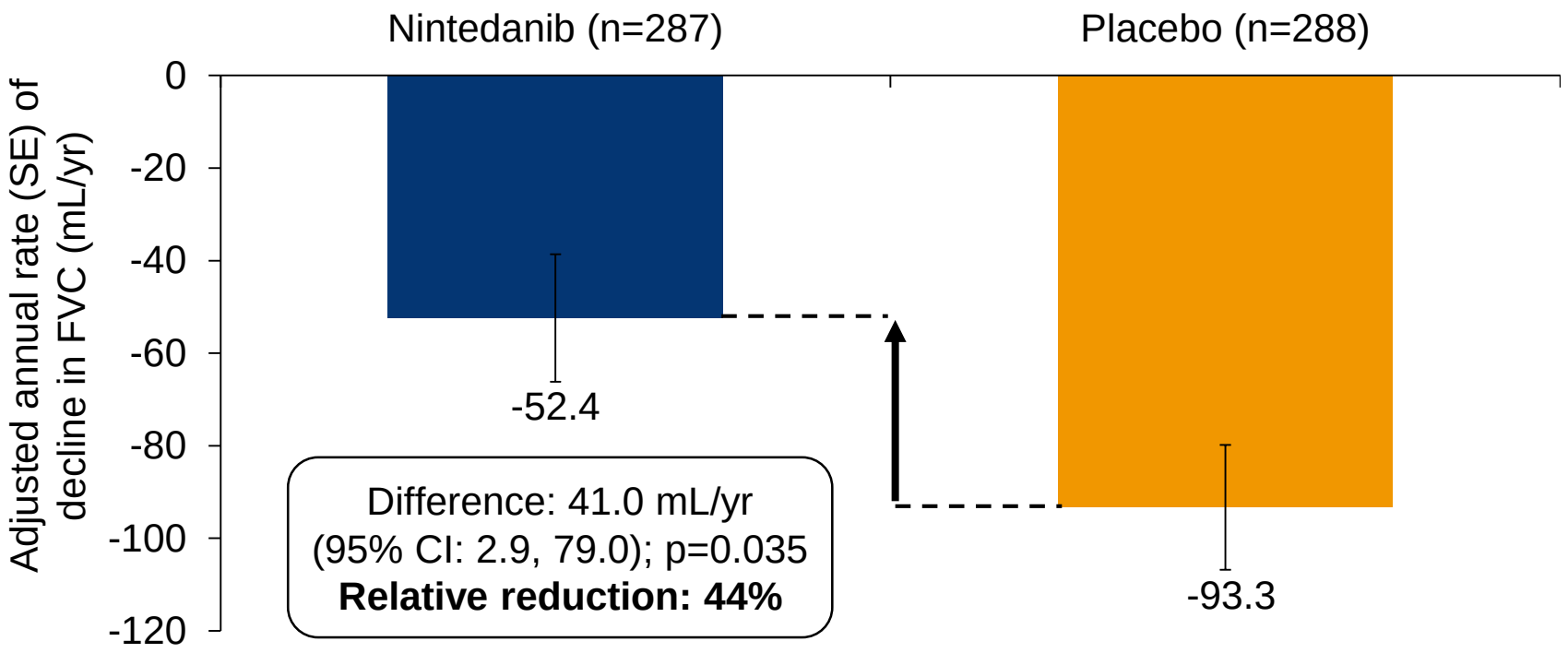
SENSCIS: Key inclusion criteria

- Age ≥18 years
- SSc (based on 2013 ACR/EULAR criteria[1]) with disease onset (first non-Raynaud symptom) <7 years from screening
- ILD based on chest HRCT performed within 12 months of screening with ≥10% extent of fibrosis of the lungs (confirmed by central assessment)
- FVC ≥40% predicted
- DL_{CO} 30–89% predicted

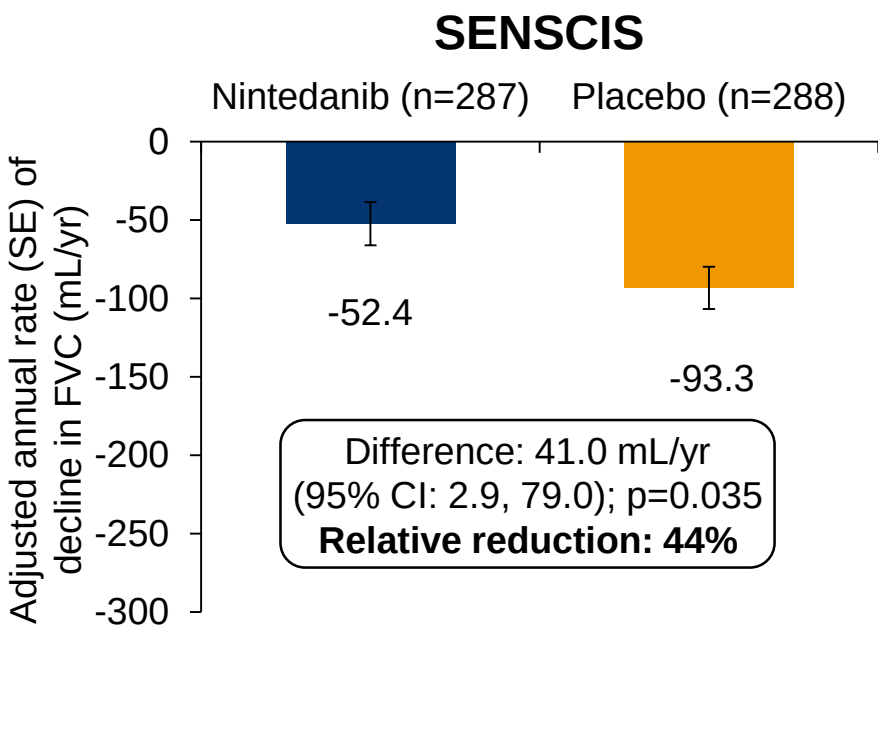
ACR/EULAR, American College of Rheumatology/ European League Against Rheumatism; DL_{CO}, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution computed tomography.

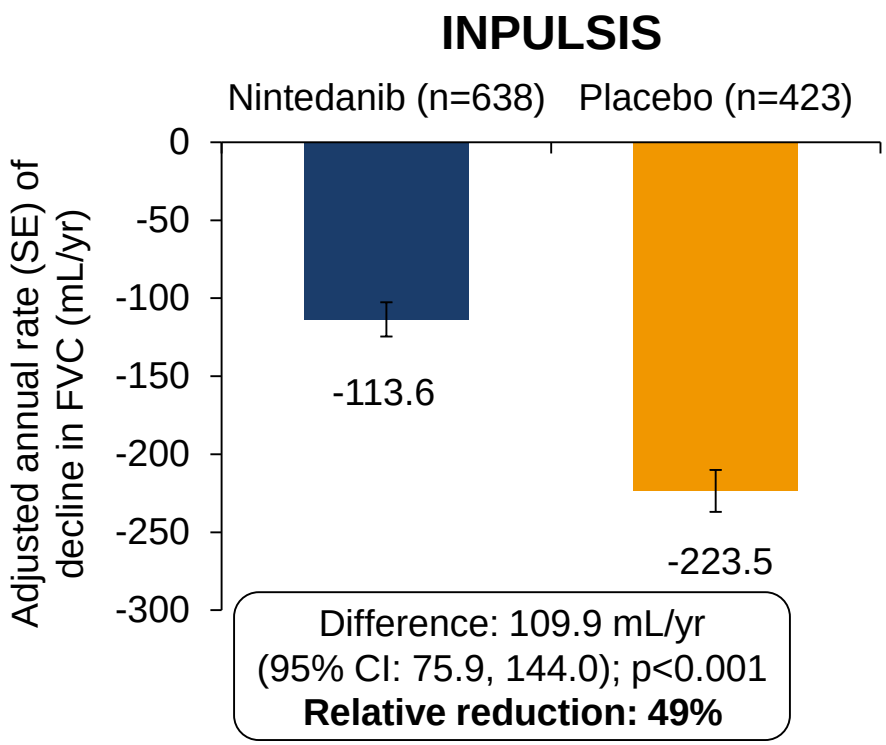
1. van den Hoogen F, et al. Arthritis Rheum 2013;65:2737–47.

Primary endpoint
Annual rate of decline in FVC (mL/yr) over 52 weeks

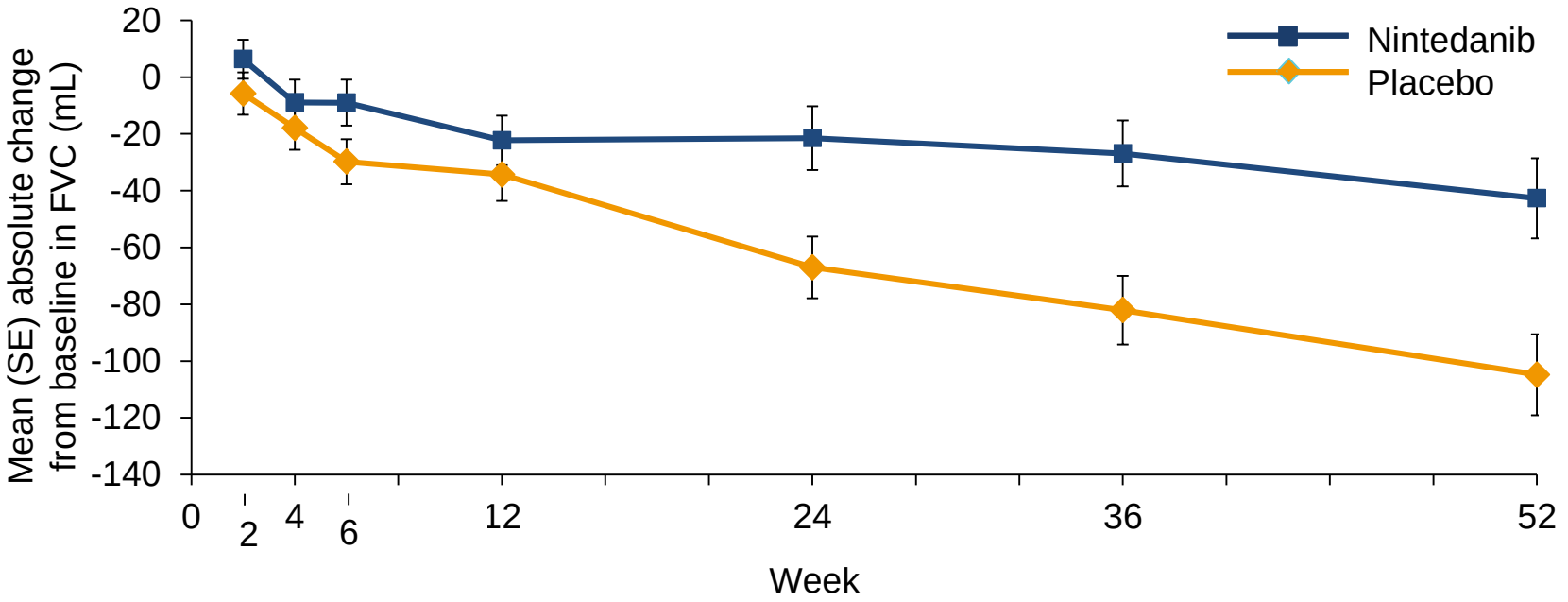


SENSCIS and INPULSIS: Annual rate of decline in FVC (mL/yr)





SENSCI: Change from baseline in FVC (mL) over 52 weeks

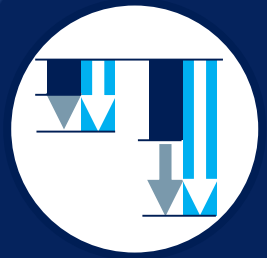


No. of patients								
Nintedanib	288	283	281	273	278	265	262	241
Placebo	288	283	281	280	283	280	268	257

Nintedanib demonstrated similar efficacy on reducing FVC decline in SENSCIS and INPULSIS

Progression of ILD was slower in patients with SSc-ILD than IPF

Annual rate of decline in FVC in placebo group:
SENSCIS: -93.3 mL/year
INPULSIS: -223.5 mL/year



Nintedanib almost halved the annual rate of decline in FVC both in patients with SSc-ILD and IPF:

Relative reduction in annual rate of FVC decline:
SENSCIS: 44%
INPULSIS: 49%

Summary:
Nintedanib in a broad range of IPF

OFEV® slows disease progression with **a 50% reduction in FVC decline in a broad range of IPF patient types**

OFEV® sustains long-term efficacy and safety beyond **4 years**

Only OFEV® **significantly reduces the risk of AE-IPF by 68 %** in the **pooled INPULSIS result**

Side effects can be effectively managed in most patients

Only one capsule twice daily ensuring ease of dosing

Nintedanib: Aim to slow the progression of pulmonary fibrosis across all diseases associated ILD