Antifibrotic therapies in early IPF

ILD School
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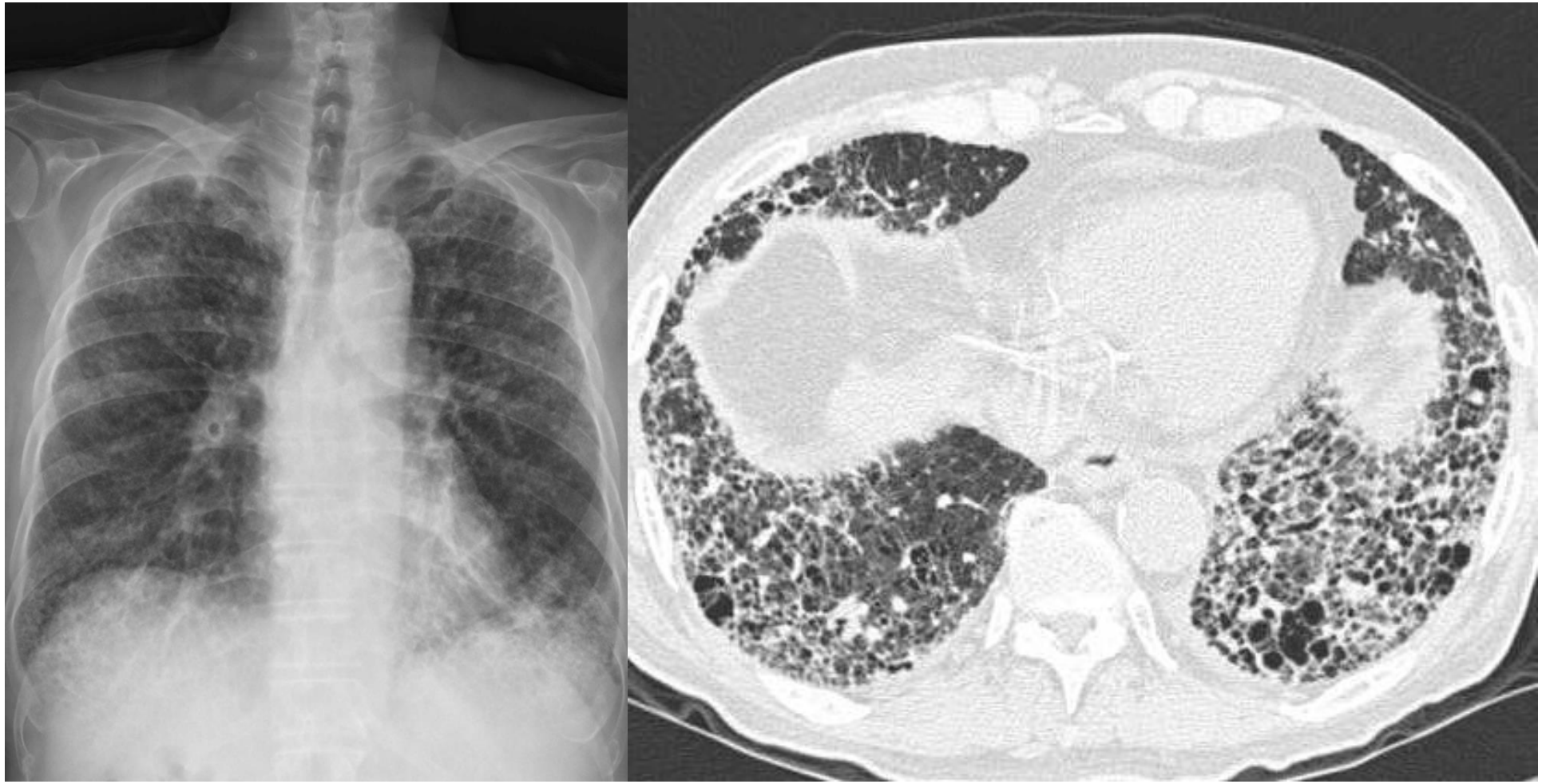
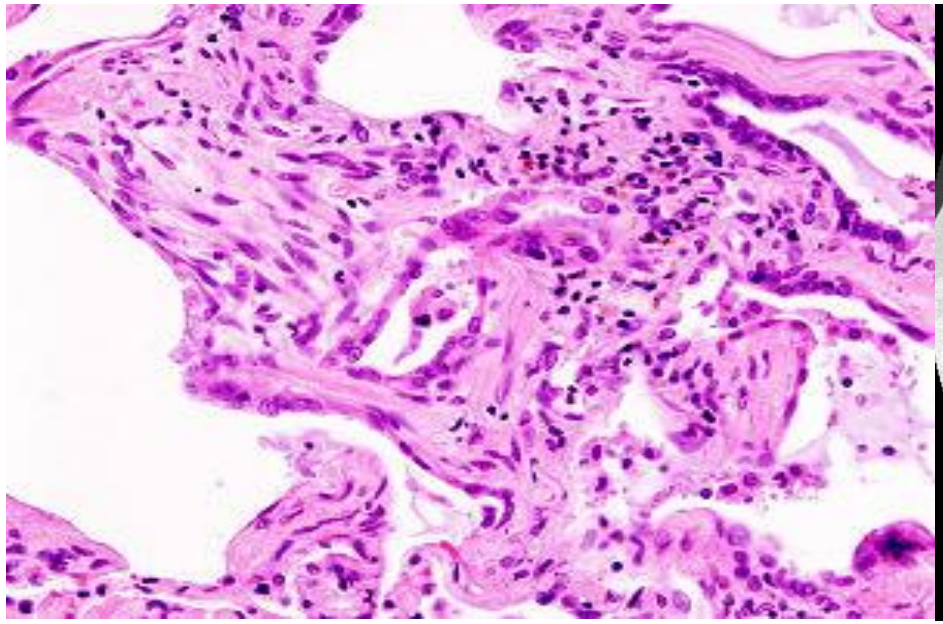
박종선
2021.6.5

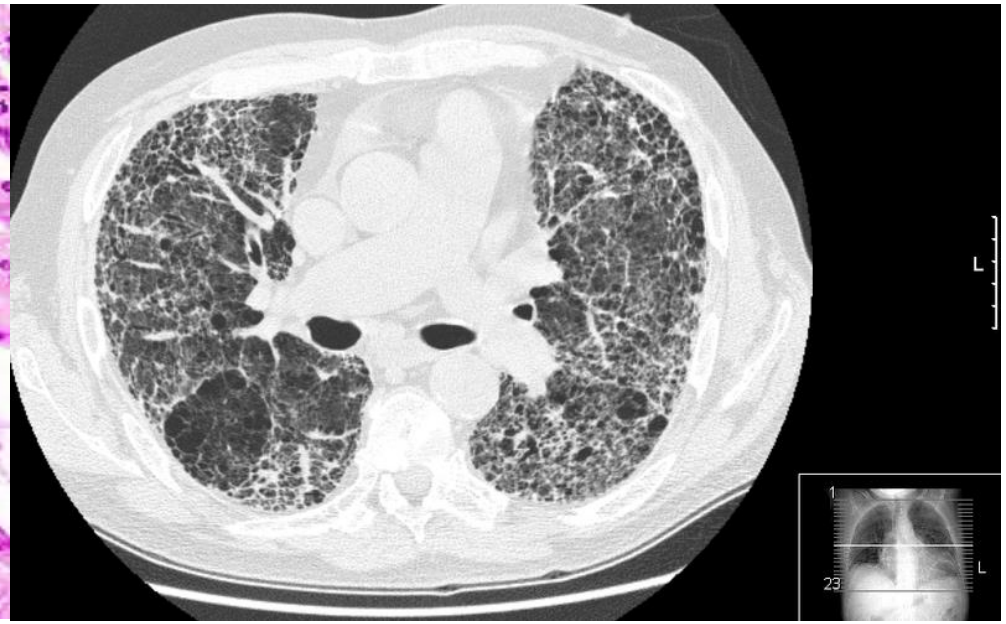
Patients with IPF



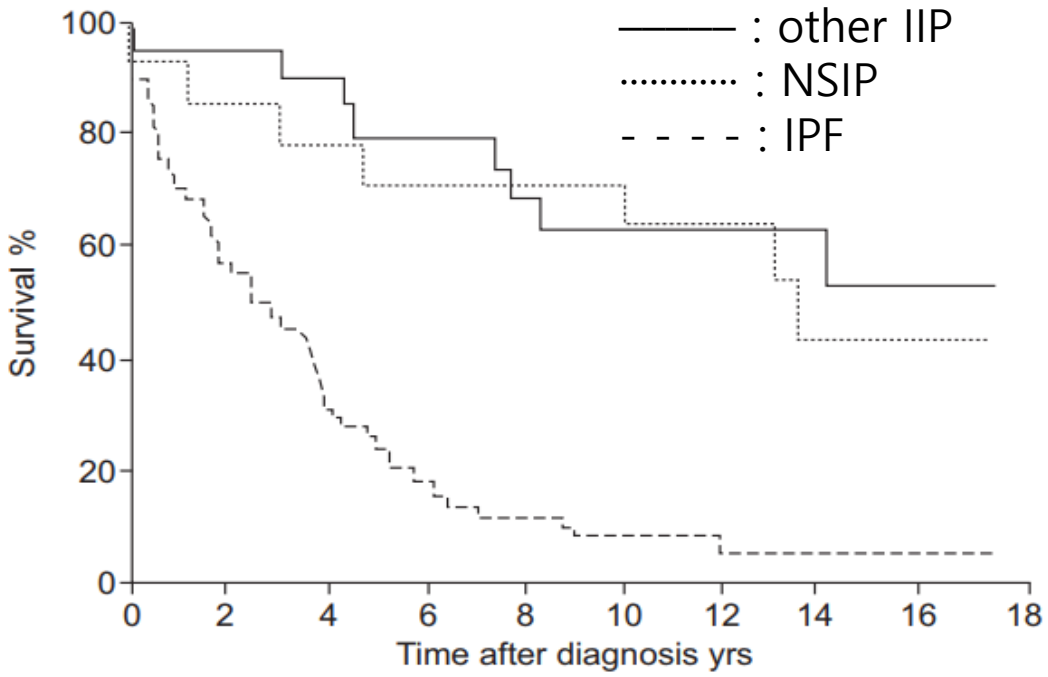
Idiopathic Pulmonary Fibrosis

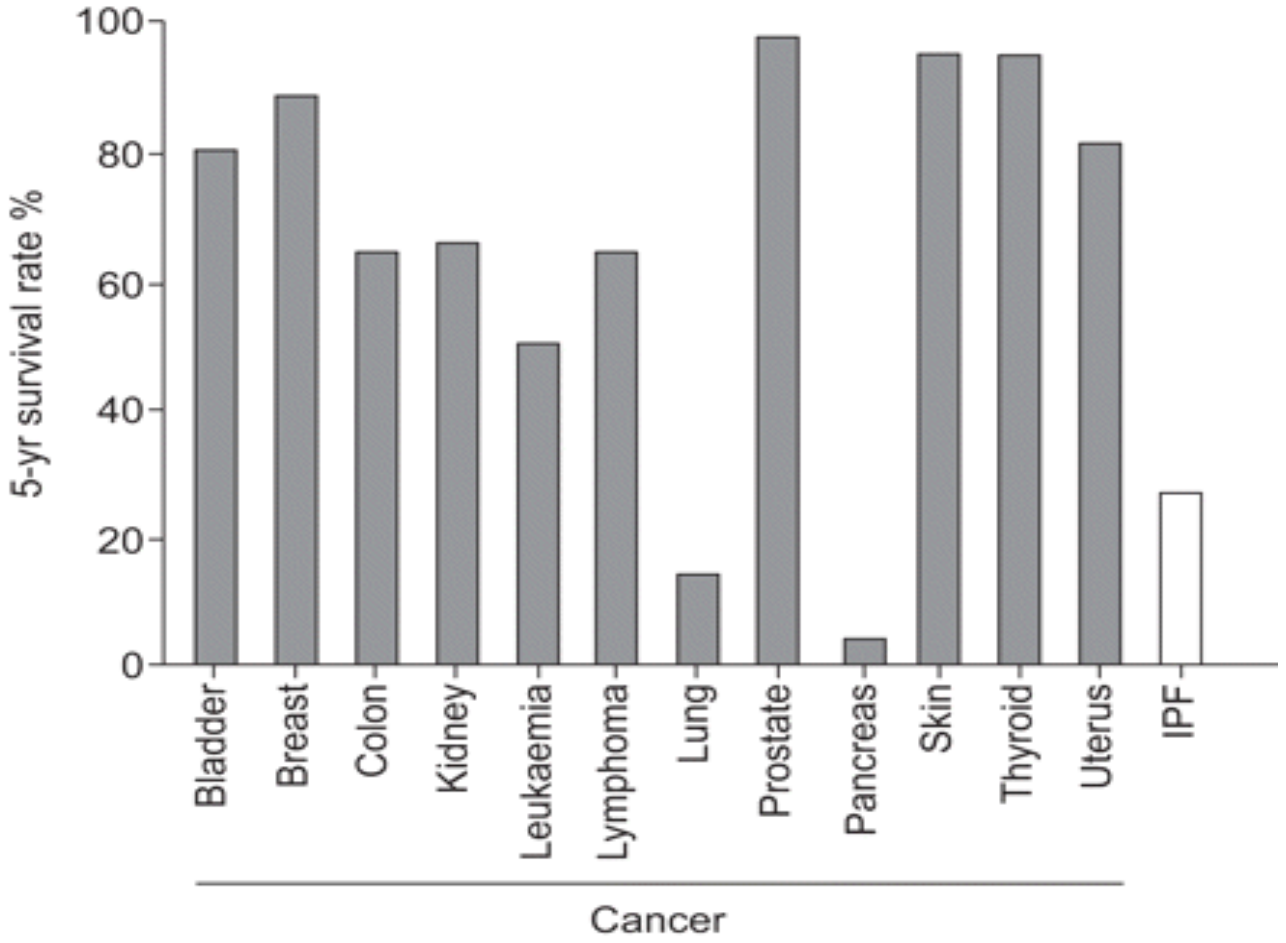
- Chronic, Progressive fibrosis
- Ultimately fatal nature
- Median survival: 3~ 5 years





Poor prognosis of IPF





Torrisi SE, et al. Eur Respir Rev. 2017;26(145).
du Bois RM. et al. Eur Respir Rev. 2012;21(124):141-6.
Olson AL et al. Am J Respir Crit Care Med 2007; 176: 277–284

Survival of Korean IPF patients

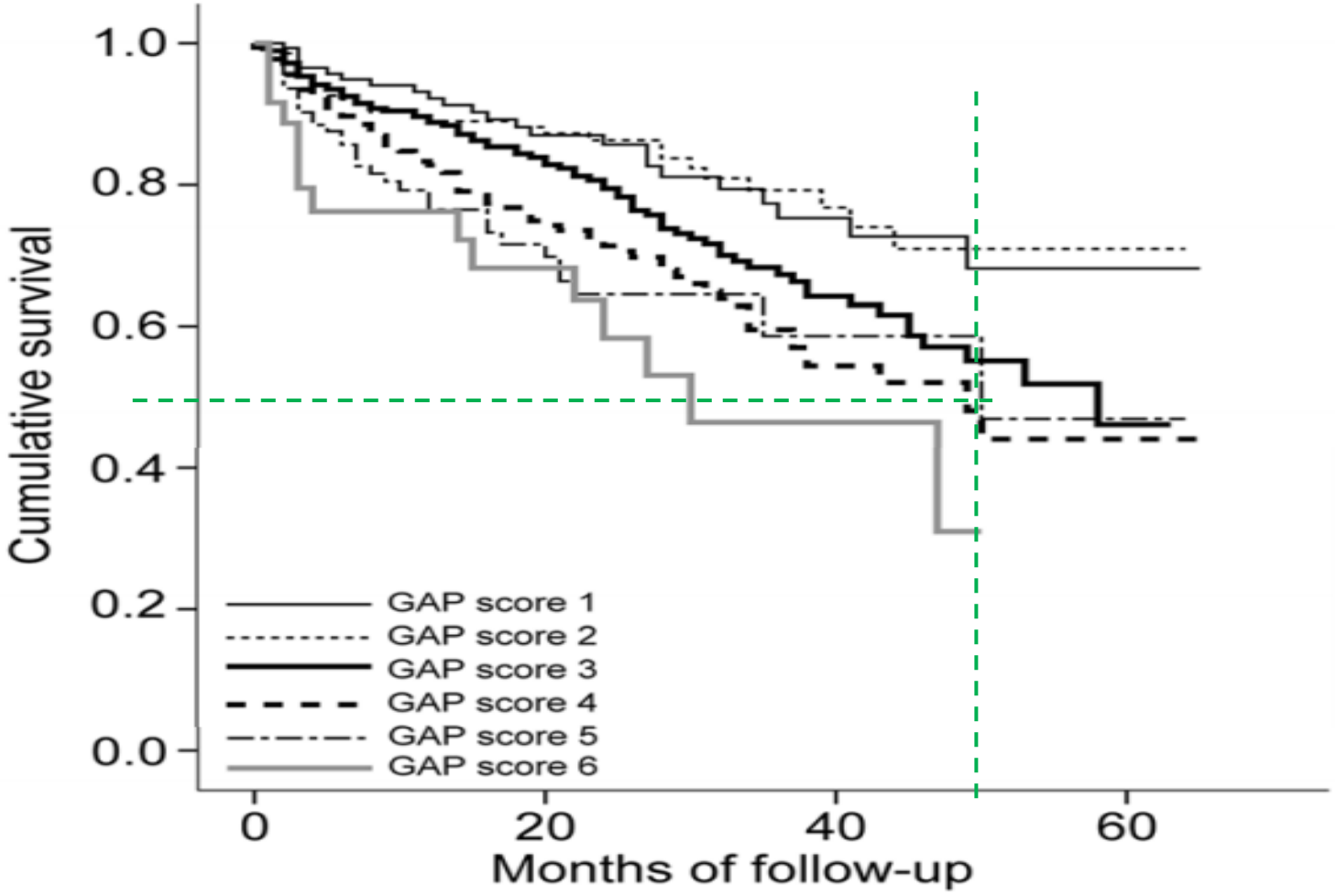


TABLE 2. The GAP Index and Staging System[29]

	Predictor		Points
G	Gender		
	Female		0
	Male		1
A	Age, y		
	≤60		0
	61-65		1
	>65		2
P	Physiology		
	FVC, % predicted		
	>75		0
	50-75		1
	<50		2
	DLCO, % predicted		
	>55		0
	36-55		1
	≤35		2
	Cannot perform		3
	Total Possible Points		8
Stage	I	II	III
Points	0-3	4-5	6-8
Mortality			
1-y	5.6	16.2	39.2
2-y	10.9	29.9	62.1
3-y	16.3	42.1	76.8

Lee SH, et al. Respir Res. 2016;17(1):131.

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Pirfenidone

FDA News Release

FDA approves Esbriet to treat idiopathic pulmonary fibrosis

For Immediate Release October 15, 2014

Release

The U.S. Food and Drug Administration today approved Esbriet (pirfeni
the treatment of idiopathic pulmonary fibrosis (IPF).

Idiopathic pulmonary fibrosis is a condition in which the lungs become
progressively scarred over time. As a result, patients with IPF experienc
shortness of breath, cough, and have difficulty participating in everyday
activities. Current treatments for IPF include oxygen therapy, pulmonary
rehabilitation, and lung transplant.

"Esbriet provides a new treatment option for patients with idiopathic pulr
fibrosis, a serious, chronic lung disease," said Curtis J. Rosebraugh, M.
director of the Office of Drug Evaluation II in the FDA's Center for Drug
and Research. "We continue to help advance medication therapies by a
products that treat conditions that impact public health."

The FDA granted Esbriet fast track, priority review, orphan product, and
breakthrough designations. Esbriet is being approved ahead of the proc
prescription drug user fee goal date of Nov. 23, 2014, the date the ager
scheduled to complete the review of the drug application.

Esbriet acts on multiple pathways that may be involved in the scarring o
tissue. Its safety and effectiveness were established in three clinical trial
patients with IPF. The decline in forced vital capacity – the amount of ai

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Nintedanib

FDA News Release

FDA approves Ofev to treat idiopathic pulmonary fibrosis

For Immediate Release October 15, 2014

Release

The U.S. Food and Drug Administration today approved Ofev (nintedanib) for the treatment of idiopathic pulmonary fibrosis (IPF).

Idiopathic pulmonary fibrosis is a condition in which the lungs become progressively scarred over time. As a result, patients with IPF experience shortness of breath, cough, and have difficulty participating in everyday physical activities. Current treatments for IPF include oxygen therapy, pulmonary rehabilitation, and lung transplant.

"Today's Ofev approval expands the available treatment options for patients with idiopathic pulmonary fibrosis, a serious, chronic condition," said Mary H. Parks, M.D., deputy director of the Office of Drug Evaluation II in the FDA's Center for Drug Evaluation and Research. "Providing health care professionals and patients with additional treatment options helps enable appropriate care decisions based on a patient's need."

The FDA granted Ofev fast track, priority review, orphan product, and breakthrough designations. Ofev is being approved ahead of the product's prescription drug user fee goal date of Jan. 2, 2015, the date the agency was scheduled to complete the review of the drug application.

Approved antifibrotic therapies for IPF

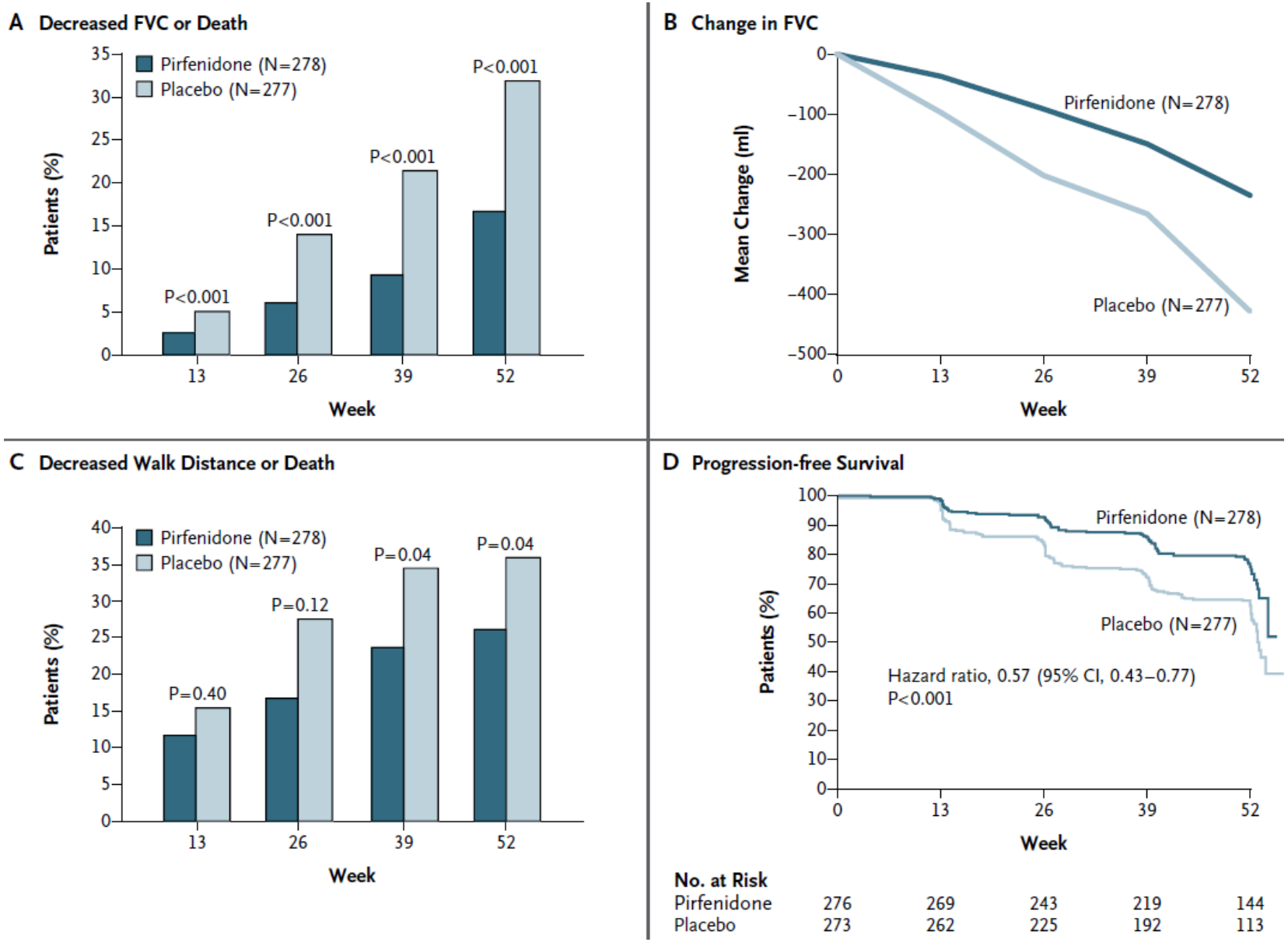
Pirfenidone

- FDA approval 2014
- Anti-fibrotics properties
- Orally administered, 801mg three times daily
- In Korea/Japan, 600mg tid
- Nausea, rash/photosensitivity, dyspepsia, anorexia

Nintedanib

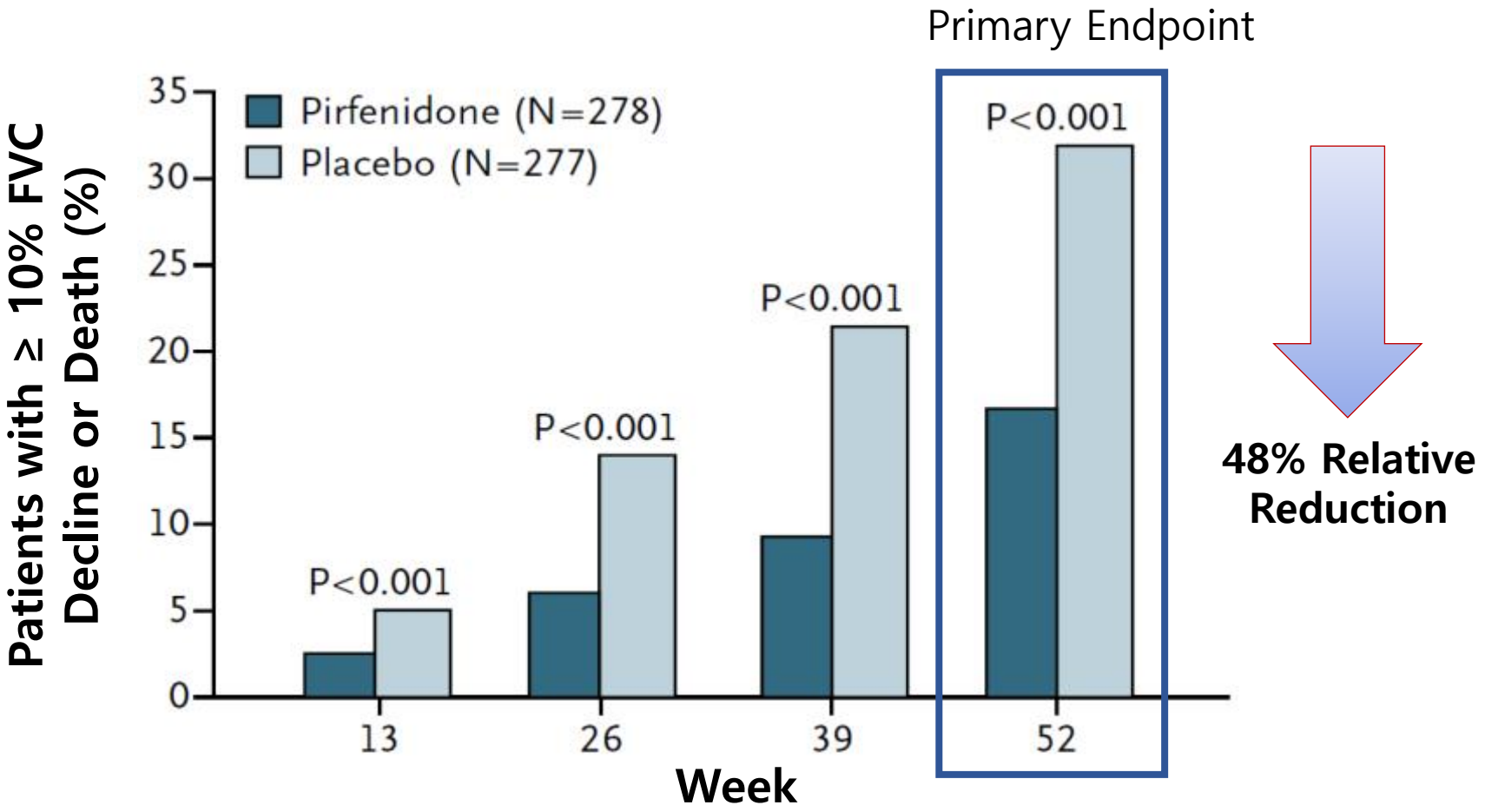
- FDA approval 2014
- Tyrosin kinase inhibitor
- Orally administered, 150mg two times daily
- Diarrhea, nausea

Pirfenidone, ASCEND trial



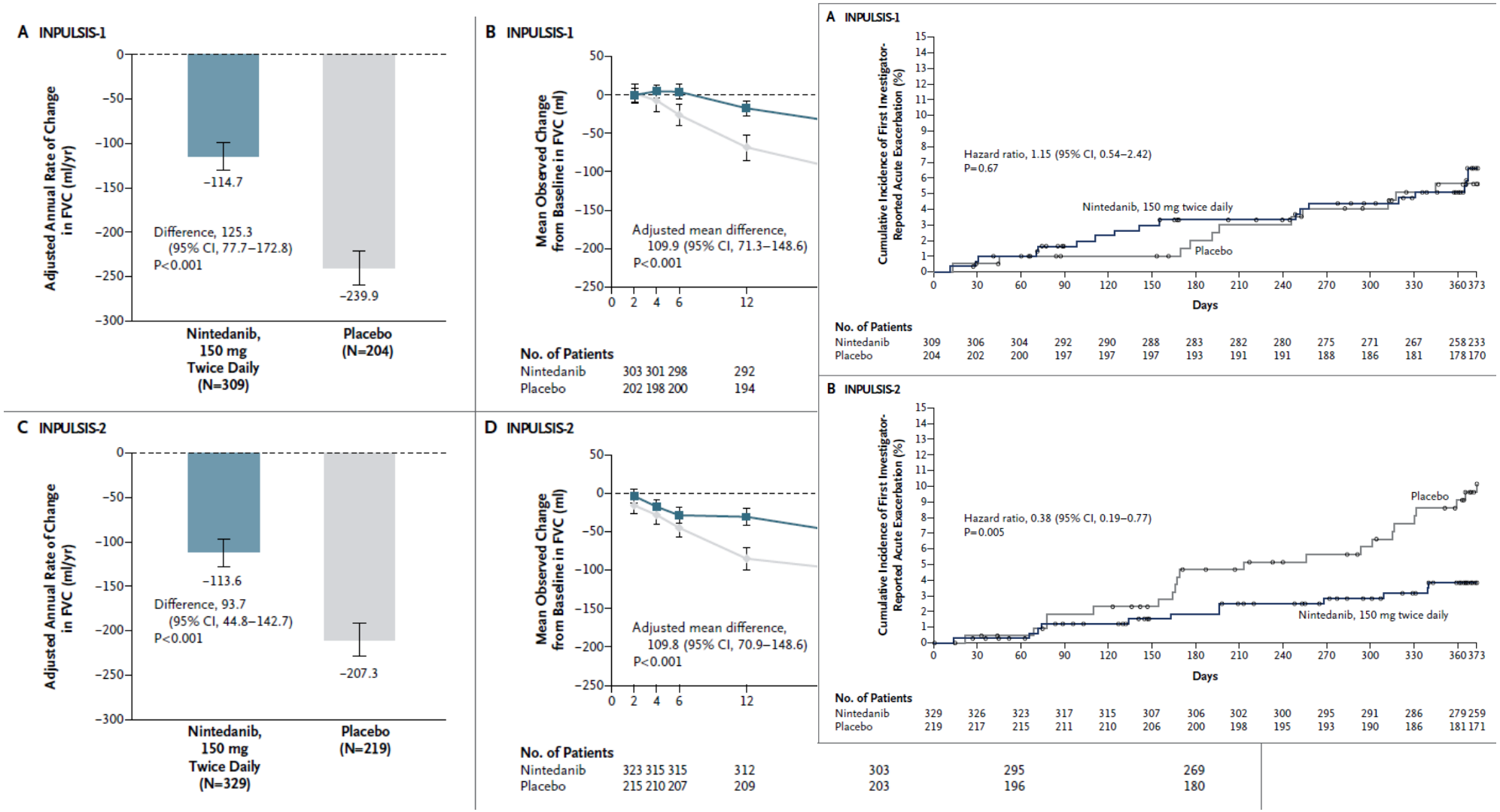
N Engl J Med 2014;370:2083-92

Pirfenidone decreased disease progression



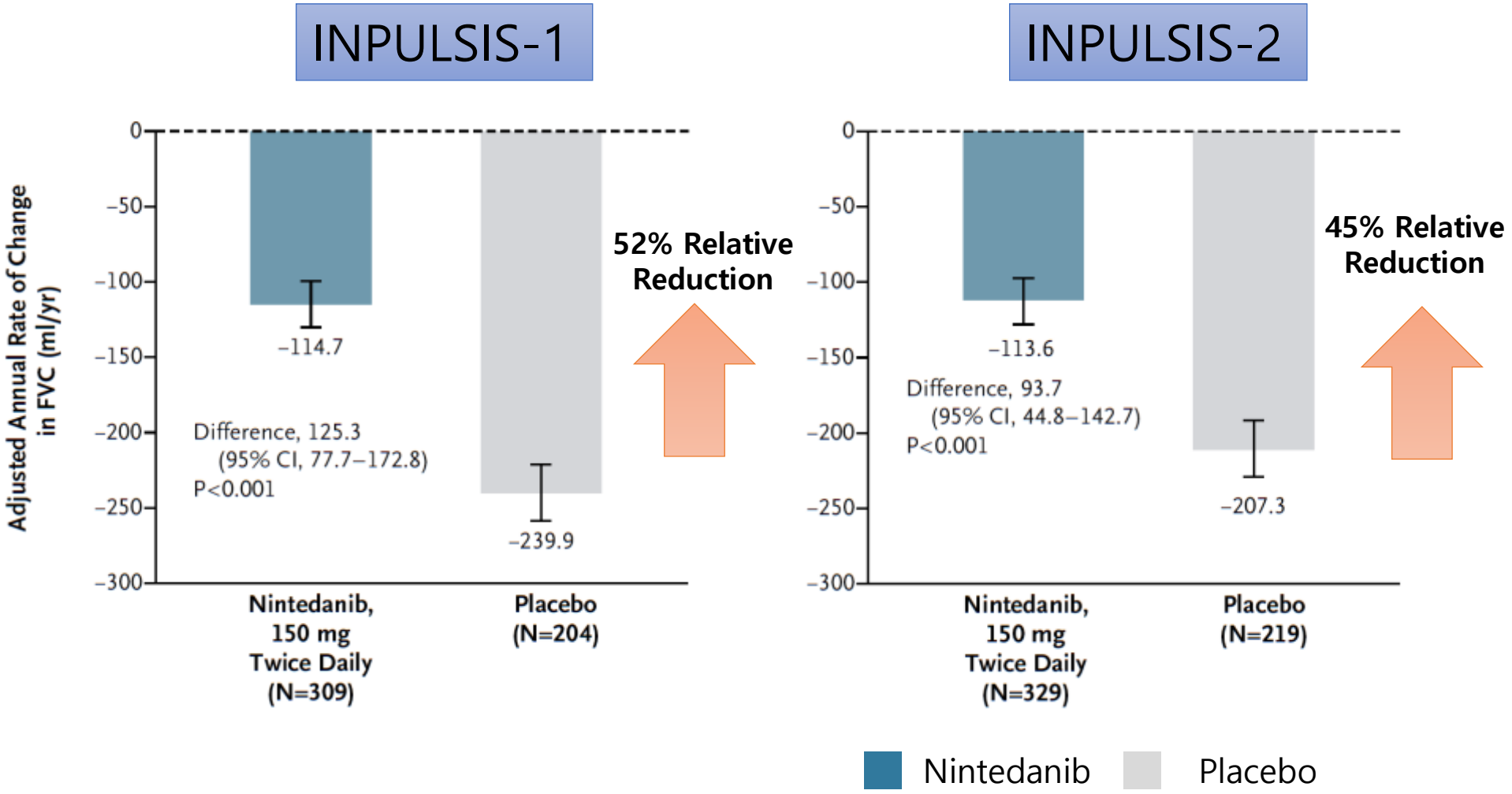
King TE, et al. *N Engl J Med.* 2014;370(22):2083

Nintedanib, INPULSIS trial



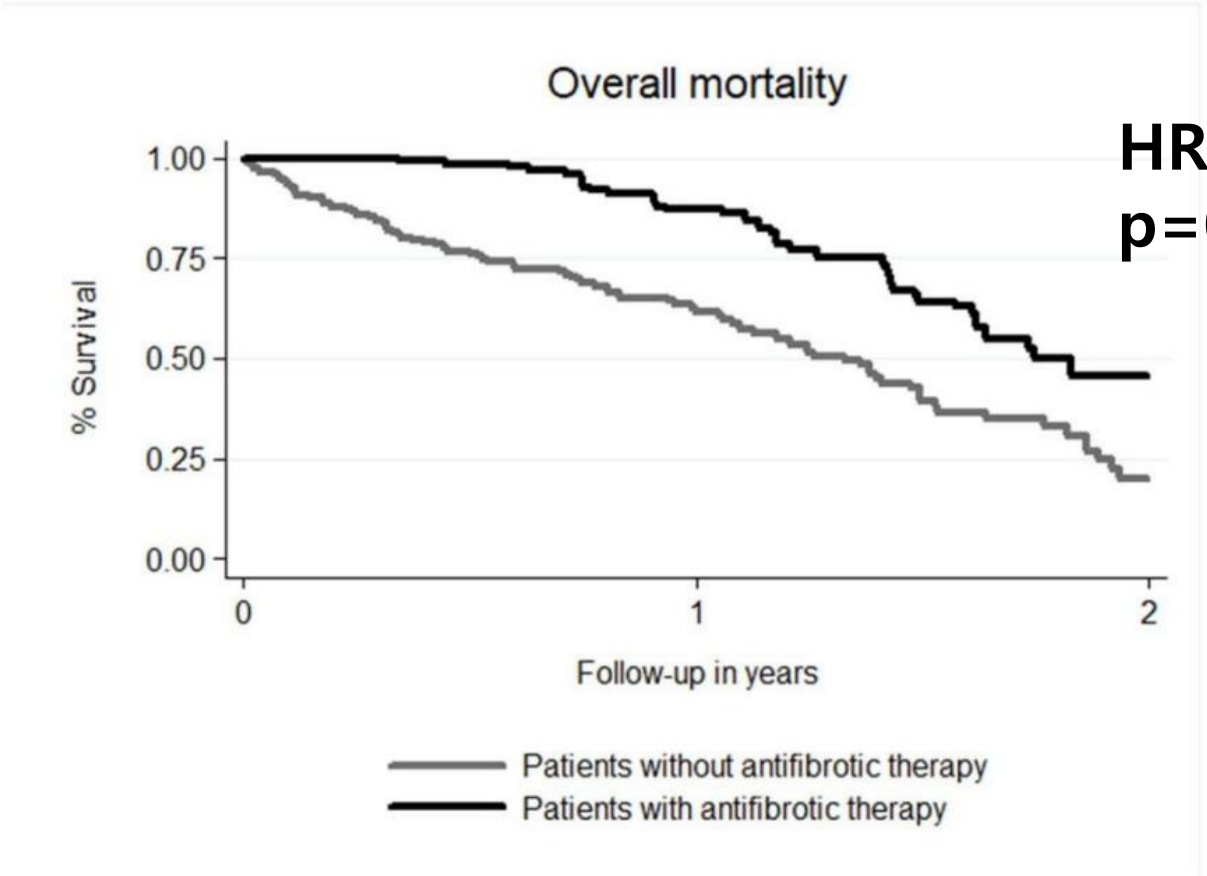
Luca Richeldi et al. N Engl J Med 2014;370:2071-82

Nintedanib decreased annual rate of change of FVC



Richeldi L, et al. N Engl J Med. 2014;370(22):2071

Antifibrotics improve survival in IPF

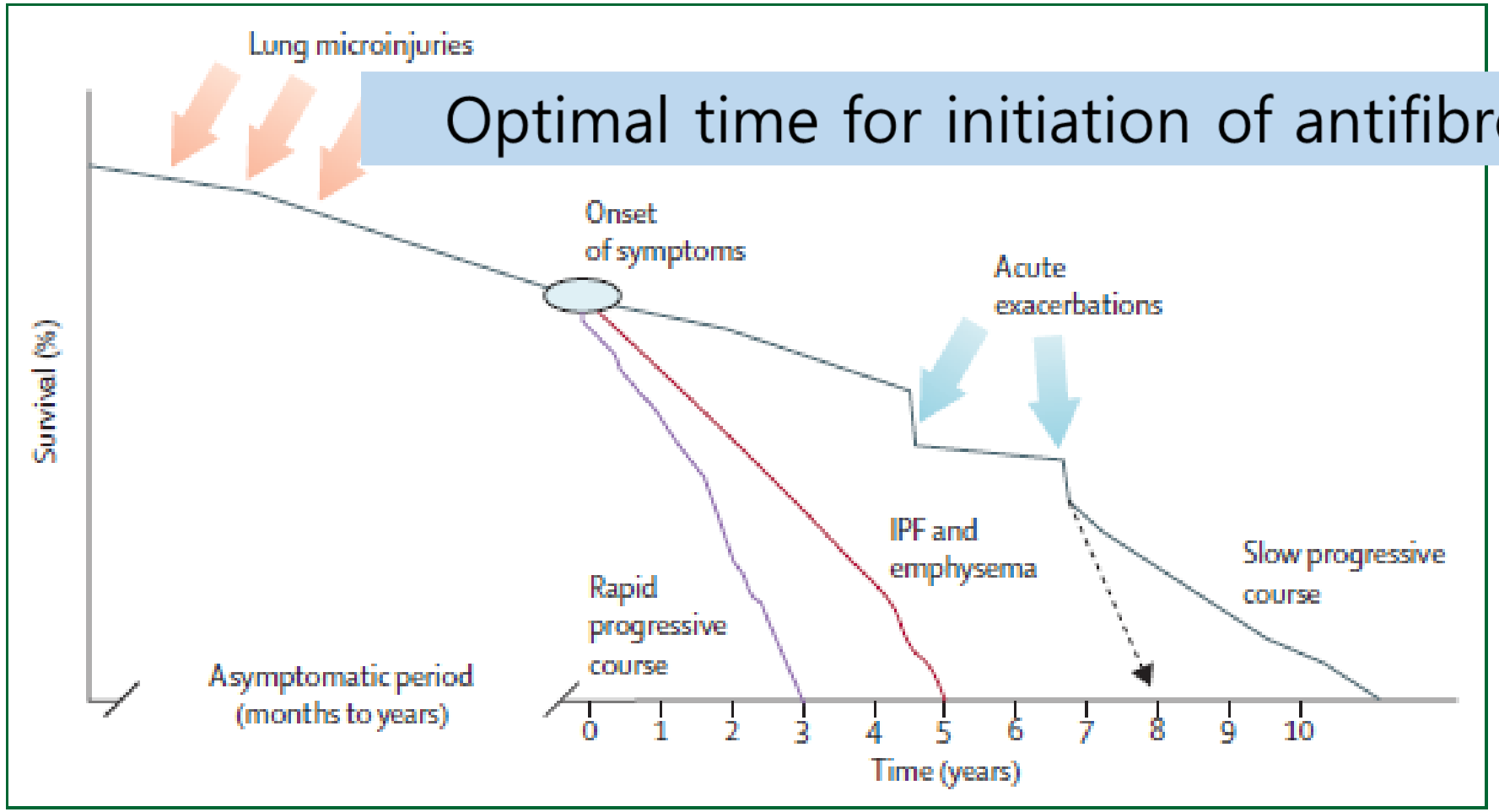


HR = 0.63, 95%CI: 0.45-0.87
p=0.005

Number of patients at risk			
With antifibrotic therapy	281	129	57
No antifibrotic therapy	252	139	93

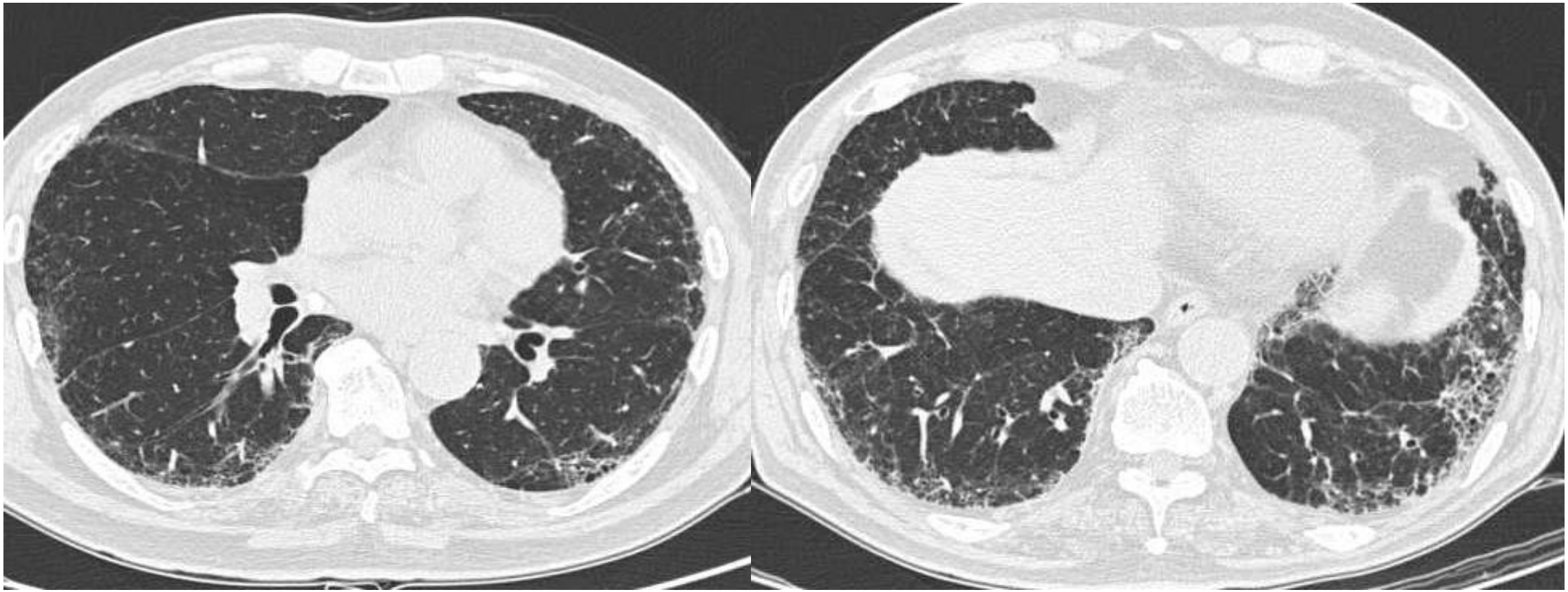
Eur Resp J 2020

Clinical course of IPF



Talmadge E King Jr. et al. Lancet 2011

Early IPF



Importance of early treatment in IPF

- Poor prognosis of IPF
- Progressive decline of FVC in IPF
- Variable, unpredictable clinical course of IPF
  - Acute exacerbation
  - Postoperative ARDS

Enroll criteria of antifibrotics clinical trial

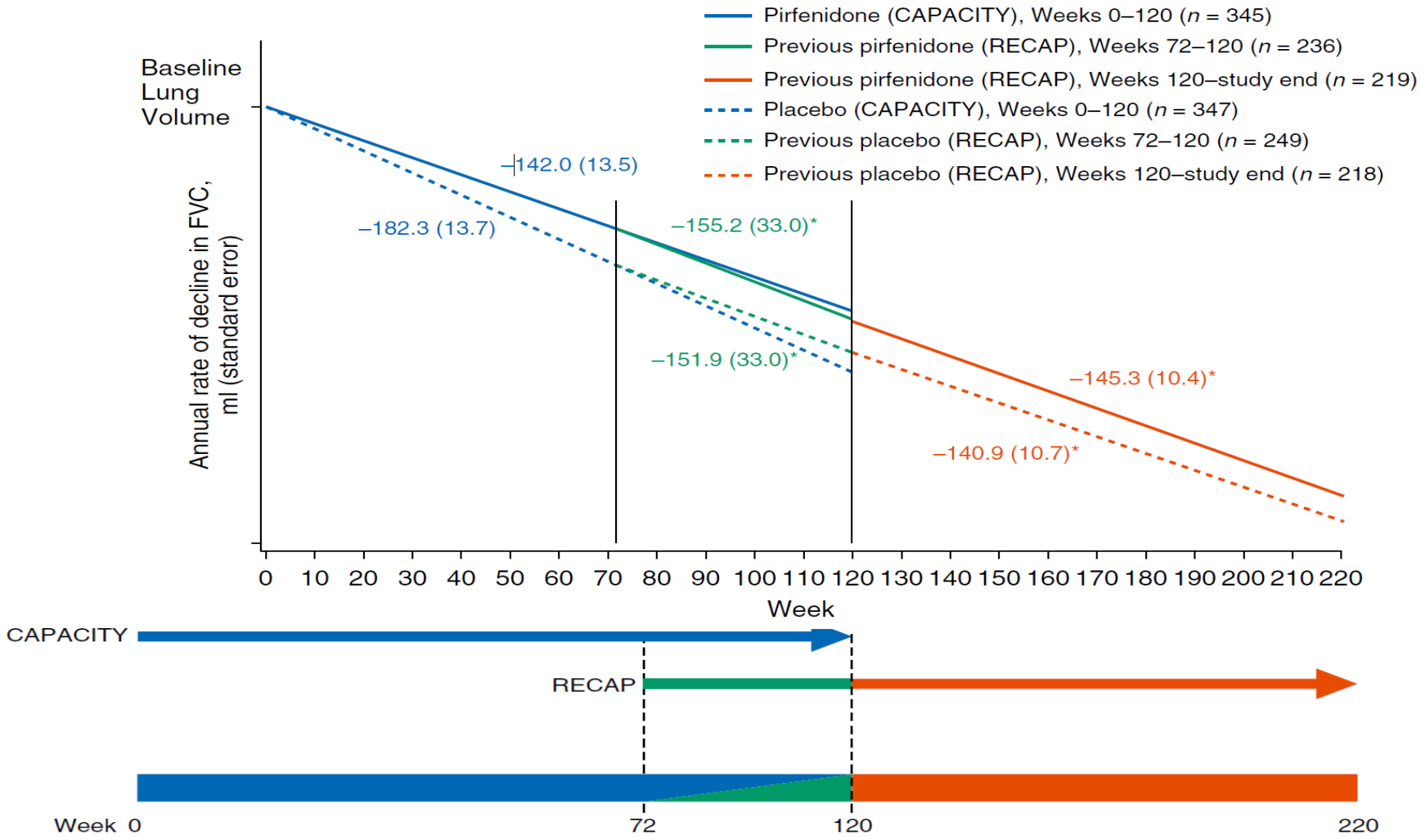
CAPACITY/ASCEND

- 50% ≤ FVC % pred ≤ 90%
- 30% ≤ DLCO % pred ≤ 90%
- FEV1/FVC ≥ 0.8
- 6MWD ≥ 150m

INPULSIS

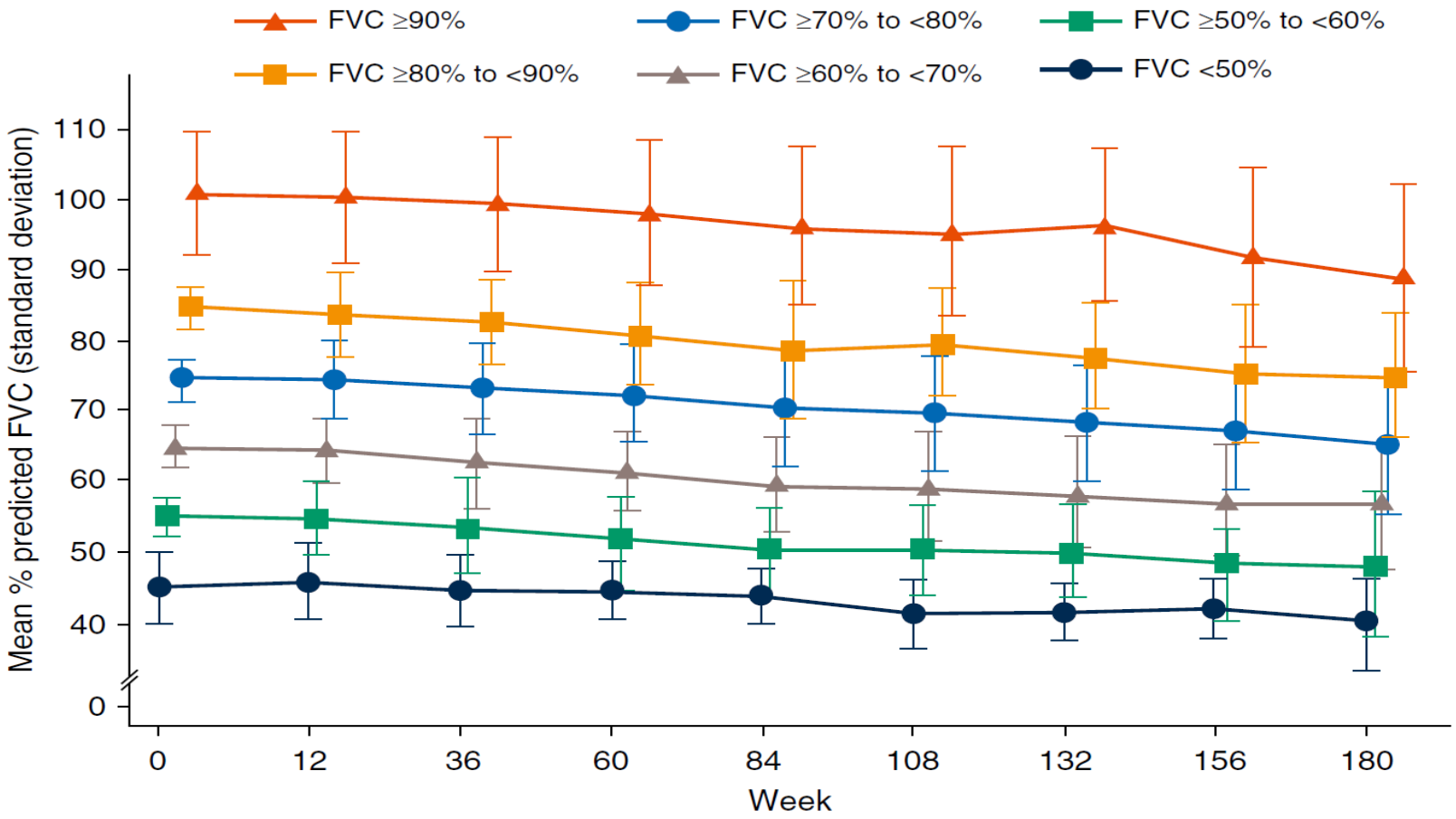
- FVC % predict ≥ 50%, no upper limit
- 30% ≤ DLCO % pred < 79%

Annual rate of lung function decline in CAPACITY and RECAP



TM Maher, et al. Ann Am Thorac Soc. 2019 Jul; 16(7): 927–930.

Rate of lung function decline in RECAP trial

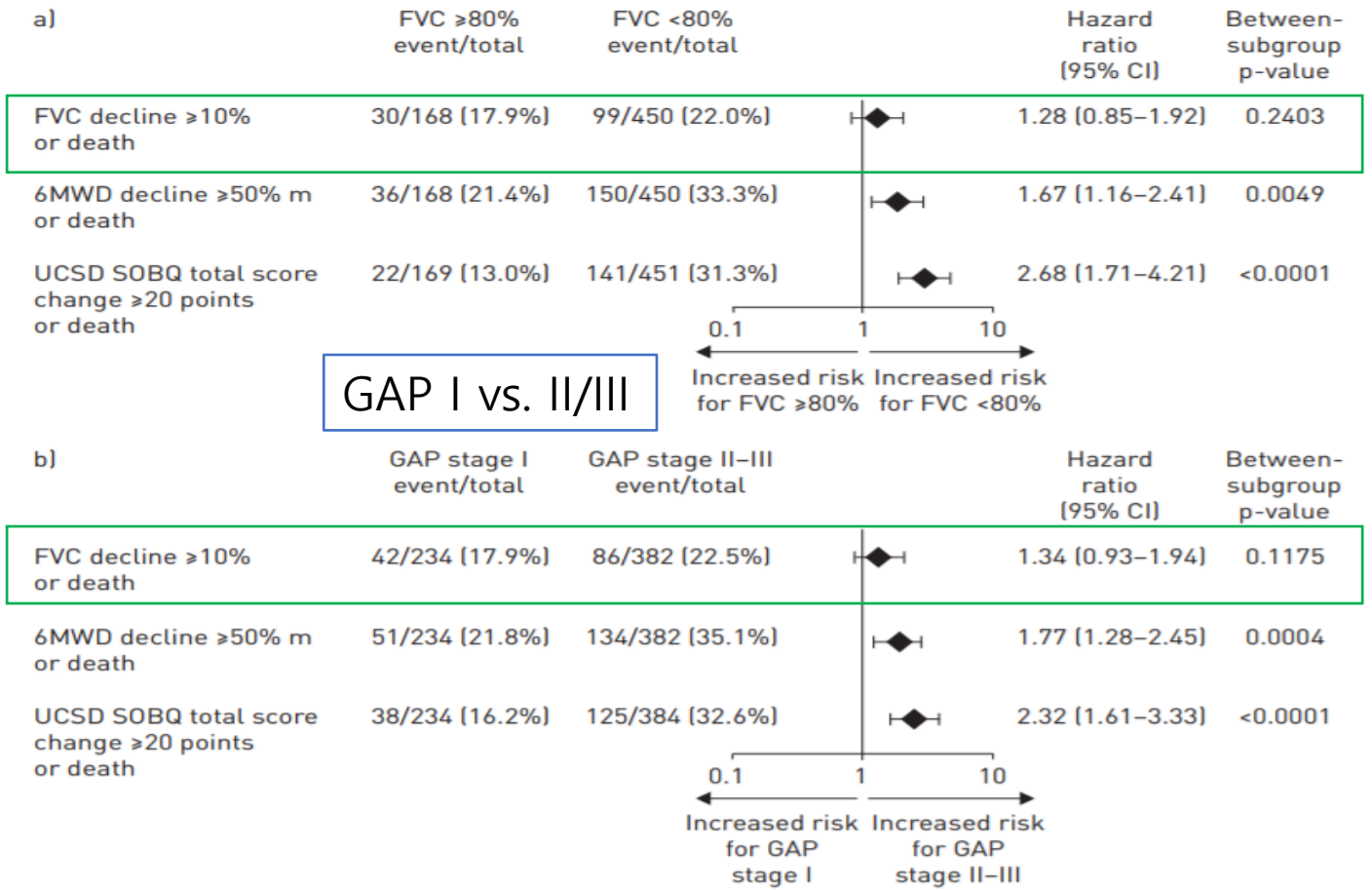


*

TM Maher, et al. Ann Am Thorac Soc. 2019 Jul; 16(7): 927–930.

Effect of pirfenidone : mild vs. moderate disease

FVC ≥ 80% vs. < 80%

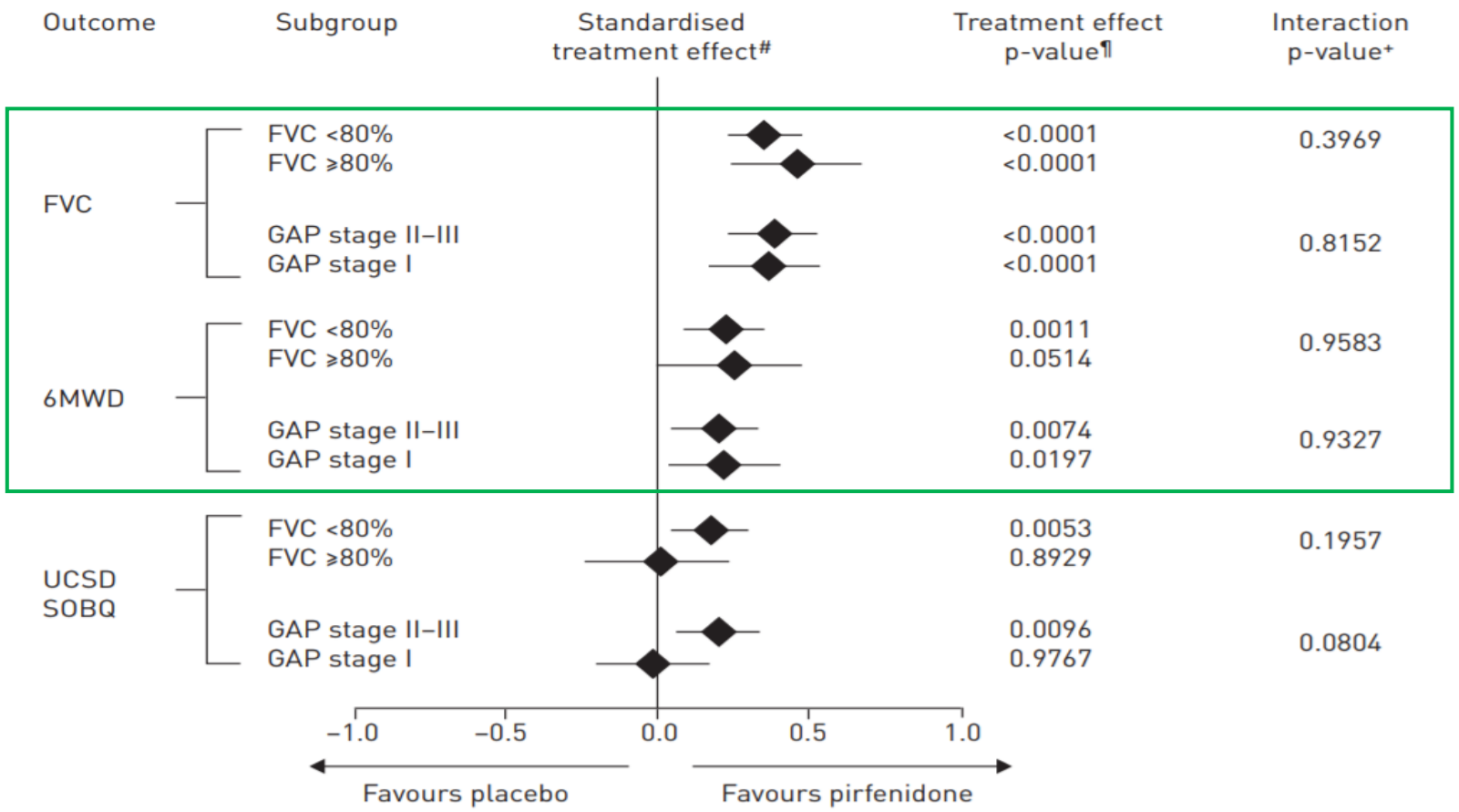


GAP I vs. II/III

No significant differences were found in terms of progression between patients with more preserved versus less preserved lung function.

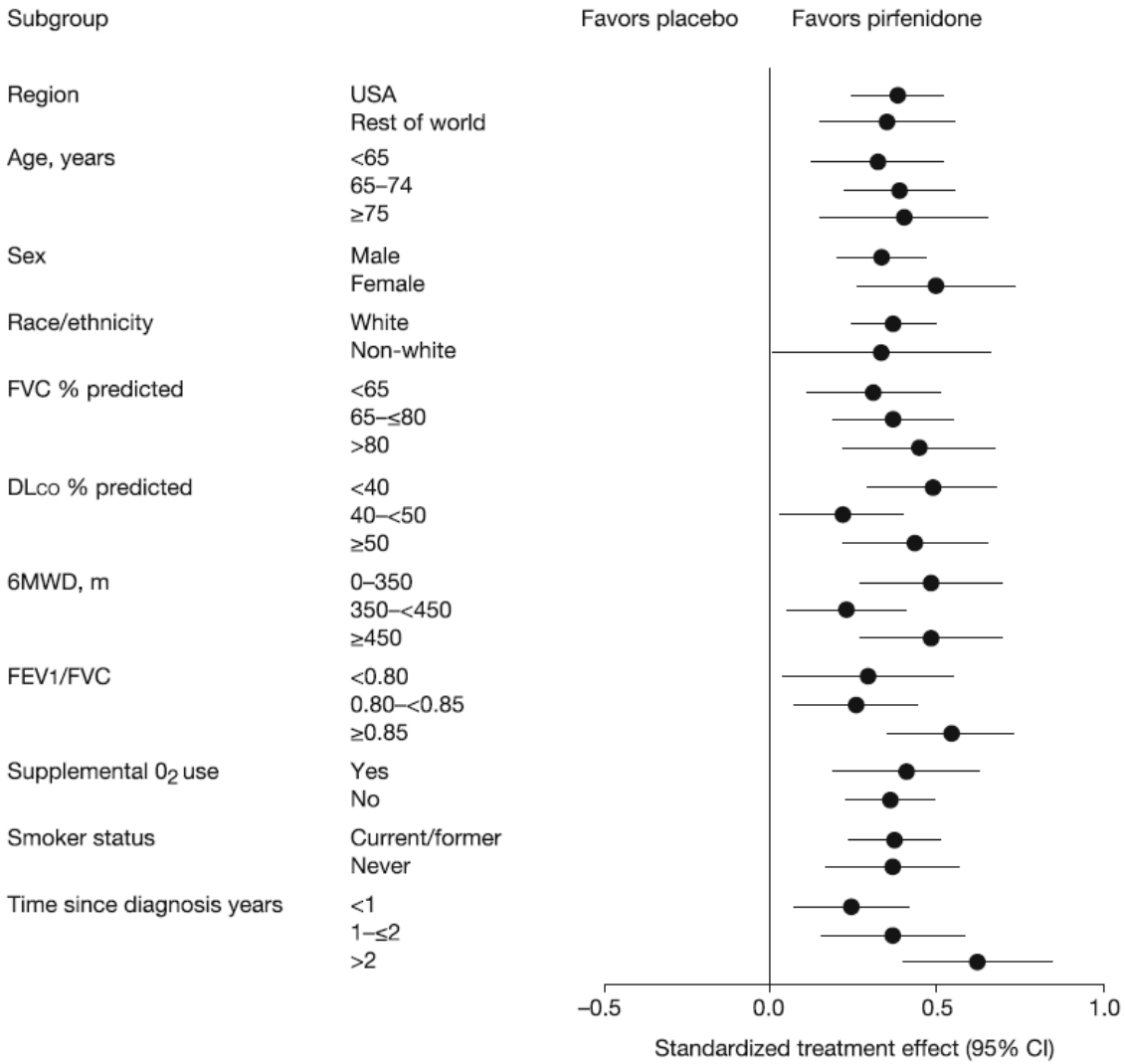
Albera C, et al. Eur Respir J. 2016;48(3):843-51.

Effect of pirfenidone : mild vs. moderate disease



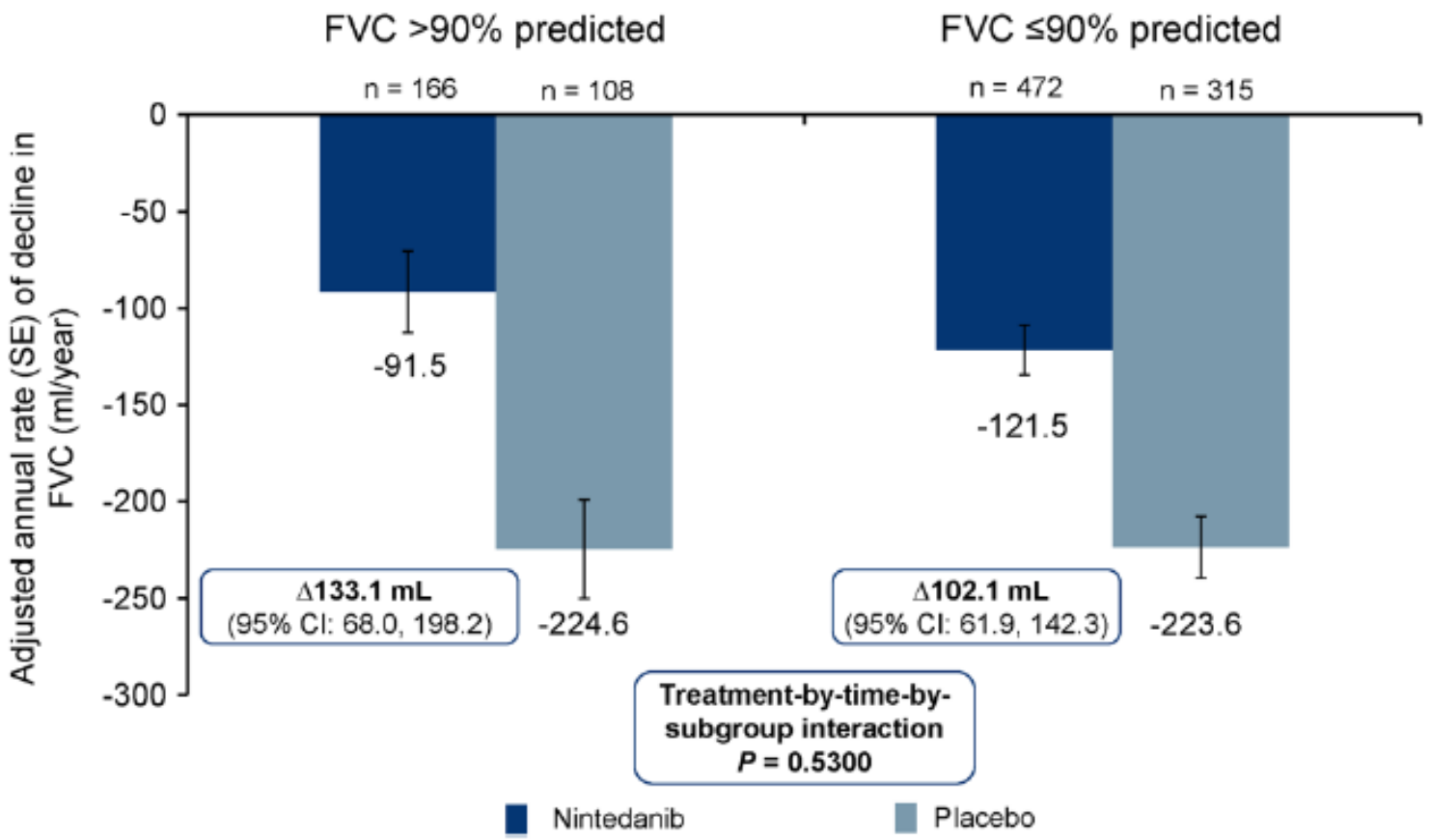
Albera C, et al. Eur Respir J. 2016;48(3):843-51.

Effect of pirfenidone



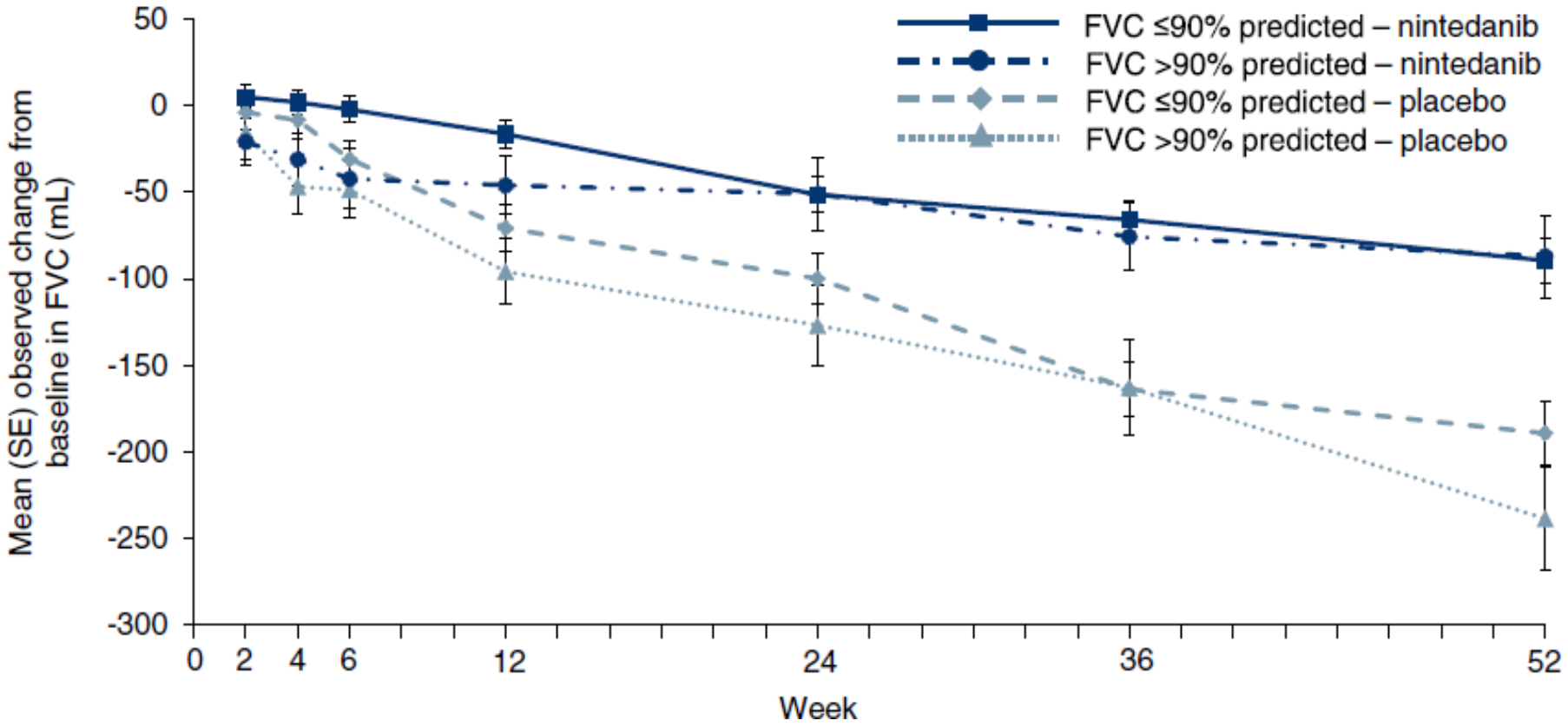
Eur Respir J 2016, 47 (1) 243–253

Effect of nintedanib: FVC > 90% vs. FVC ≤ 90%



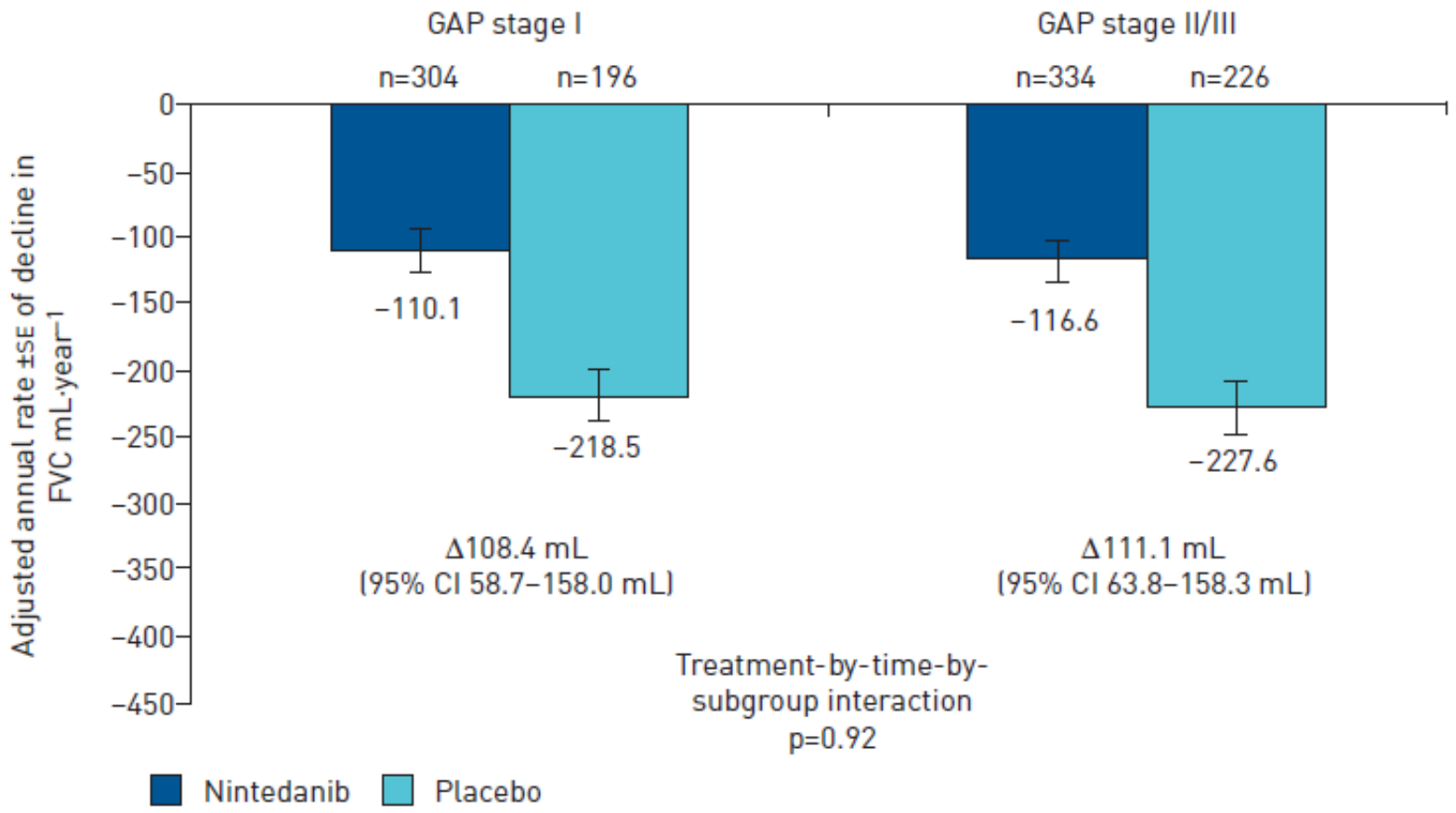
Kolb M et al. Thorax 2017;72:340–346

Effect of nintedanib: FVC > 90% vs. ≤ 90%



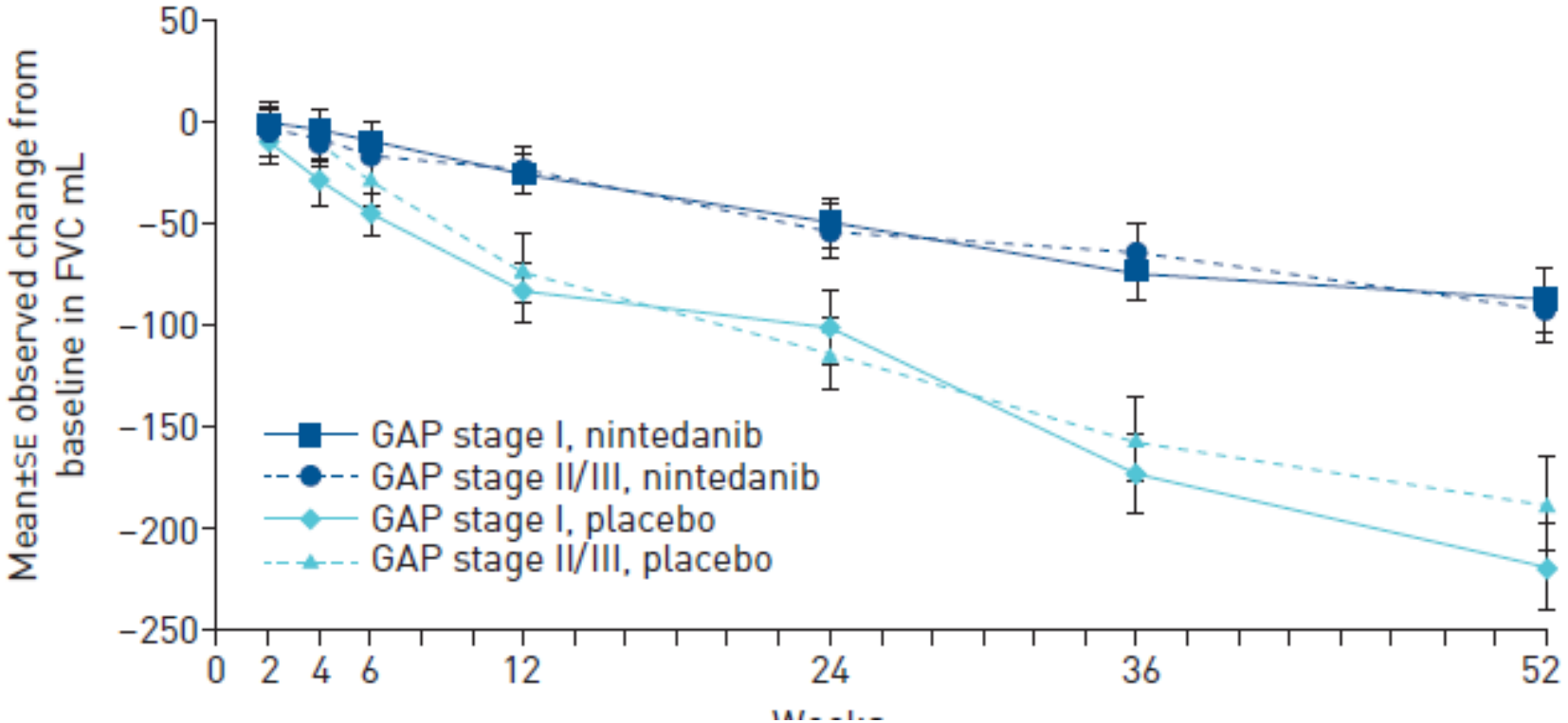
Kolb M et al. Thorax 2017;72:340–346

Effect of nintedanib by GAP stage



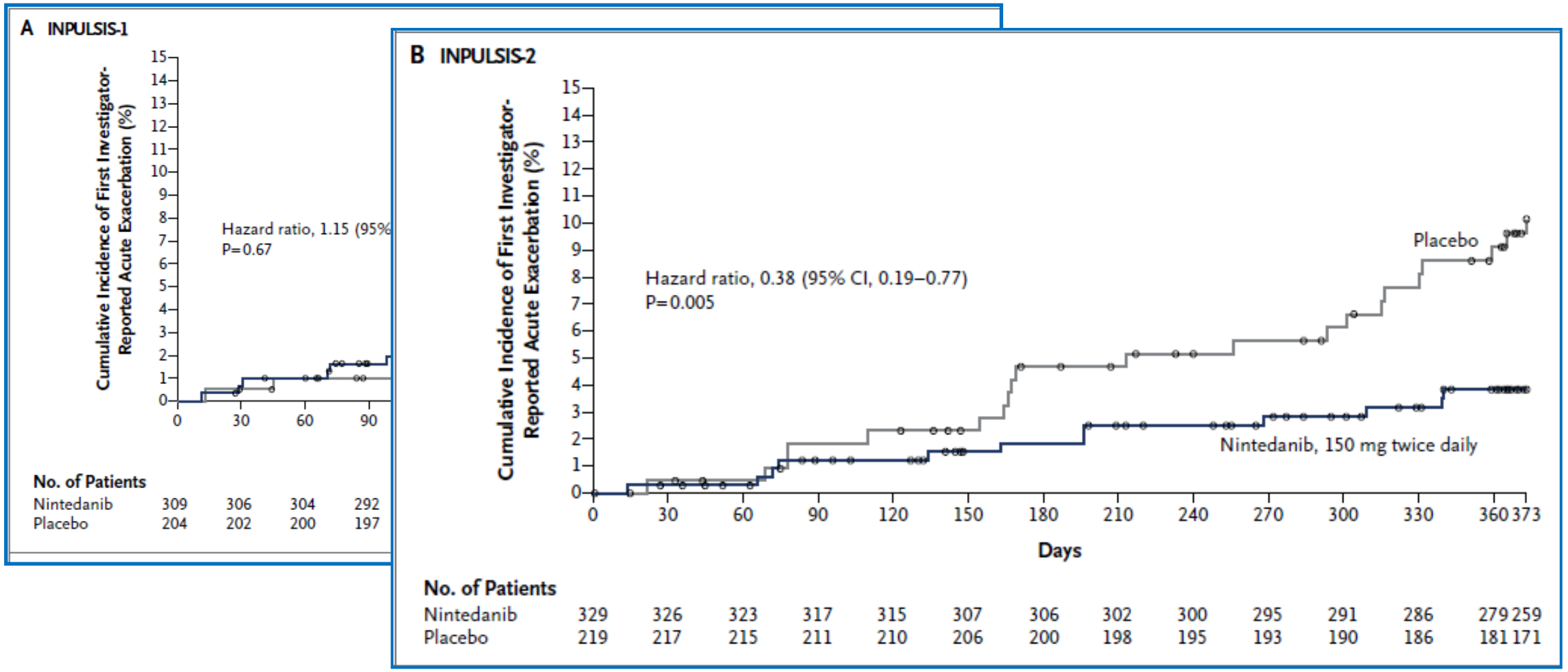
Ryerson C et al, ERJ Open Res 2019; 5: 00127-2018

Effect of nintedanib by GAP stage



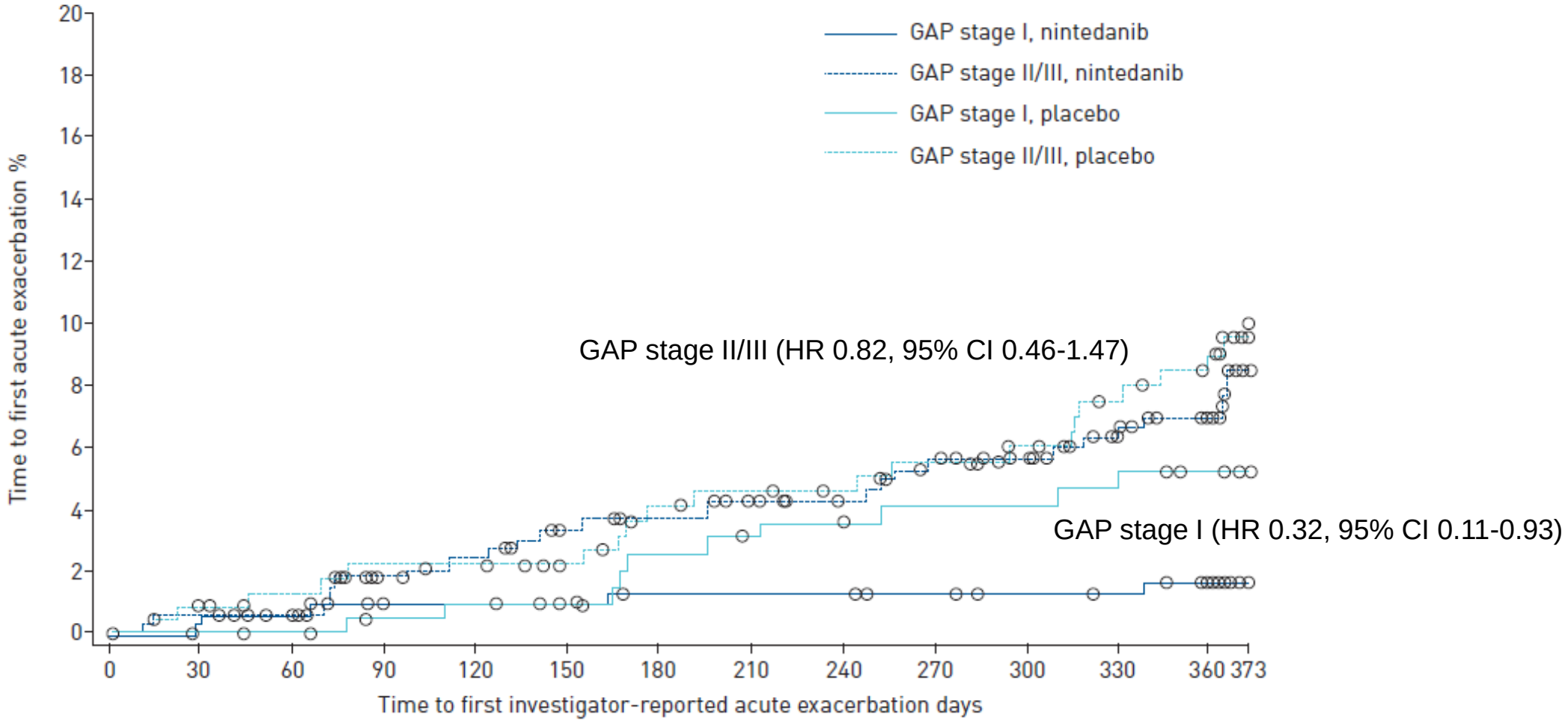
Ryerson C et al, ERJ Open Res 2019; 5: 00127-2018

Nintedanib: decrease rate of acute exacerbation



Luca Richeldi et al. N Engl J Med 2014;370:2071-82

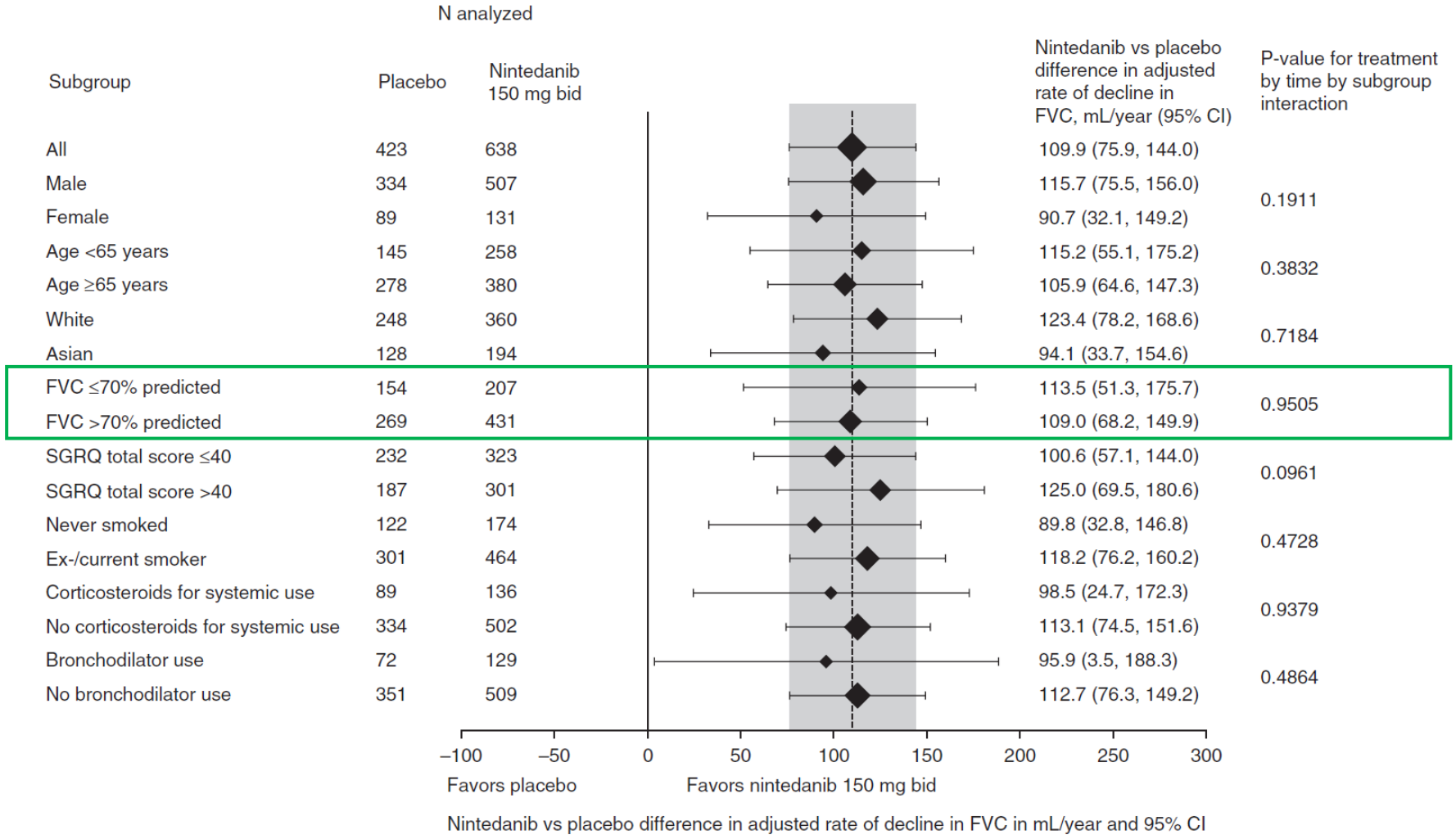
Time to first acute exacerbation by GAP stage



*Treatment-by-subgroup interaction was not significant (p=0.14)

Ryerson C et al, ERJ Open Res 2019; 5: 00127-2018

Effect of nintedanib by subgroups



Am J Respir Crit Care Med:2016:193;178–185

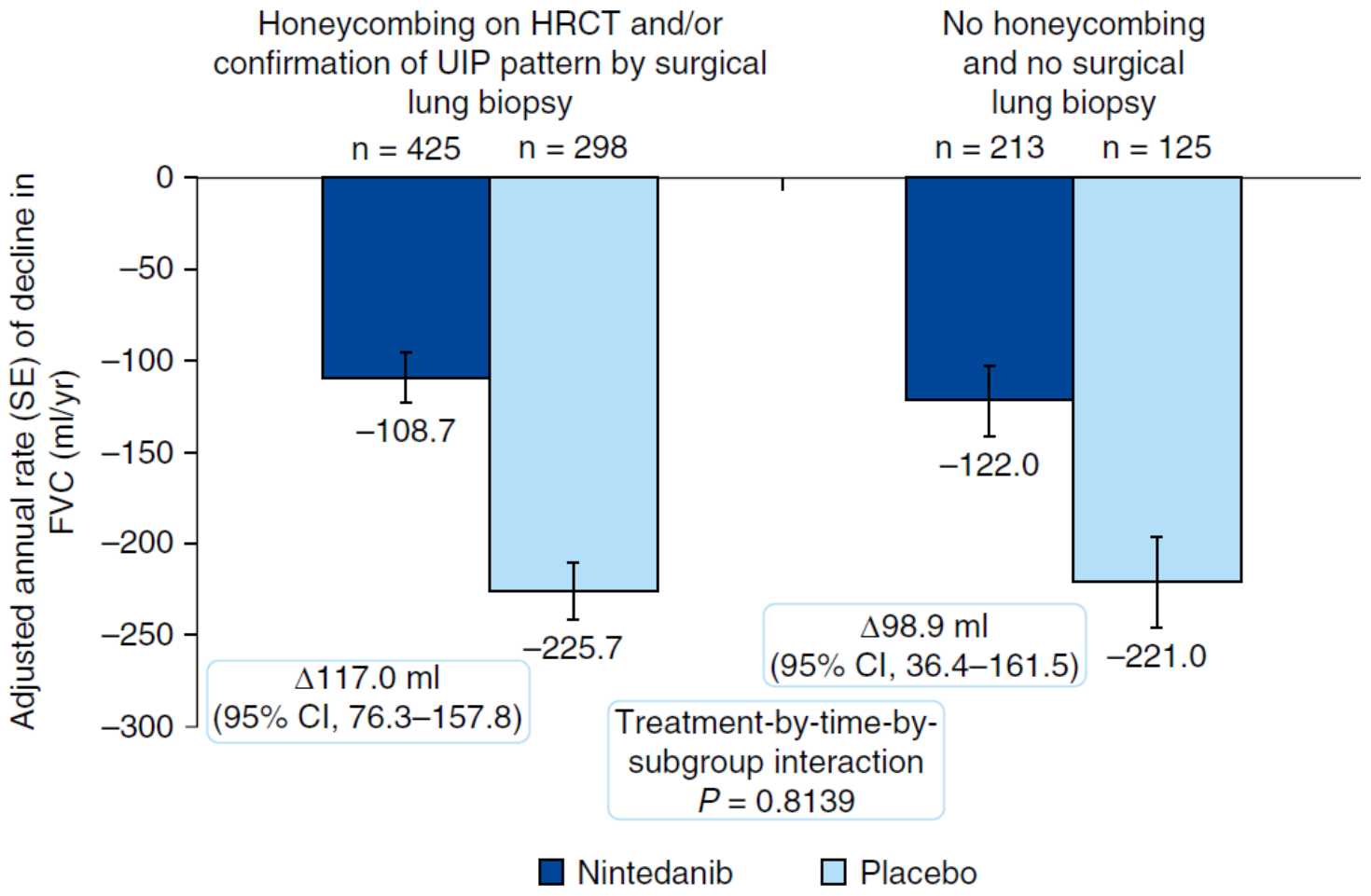
Definition of early IPF

- Definition?
  - Usually defined by FVC
  - IPF with preserved lung function

- Preclinical IPF
- Subclinical IPF
- Asymptomatic IPF
- IPF without honeycombing..

- Interstitial lung abnormality (ILA)

Effect of nintedanib in IPF without honeycombing



Raghu et al. Am J Respir Crit Care Med 2017:195(1) :78–85

Pirfenidone 보험 기준

1) Predicted FVC 90% 이하이거나 Predicted DLco 80% 이하

2) Predicted FVC 90% 초과하면서 Predicted DLco 80% 초과한 환자 중 아래 두 가지 이상에 해당되는 경우

가) 폐기능 저하: 연간 Predicted FVC 감소량이 10% 이상 이거나 연간 Predicted FVC 200ml 이상 감소

나) 임상증상 악화

다) 흉부영상 악화 소견

Pirfenidone

- Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone)
- Regulate TGF-β & TNF-α
- Inhibit fibroblast proliferation & collagen synthesis

- Pirespa (Japan) 200 → 400 → 600mg (3T) tid, 2주 간격으로 증량
- Fybro, Piresko (Korea), 200, 400, 600mg 1T
- Esbriet (US, Europe) 267mg → 801mg (3T) tid

Adverse events of pirfenidone

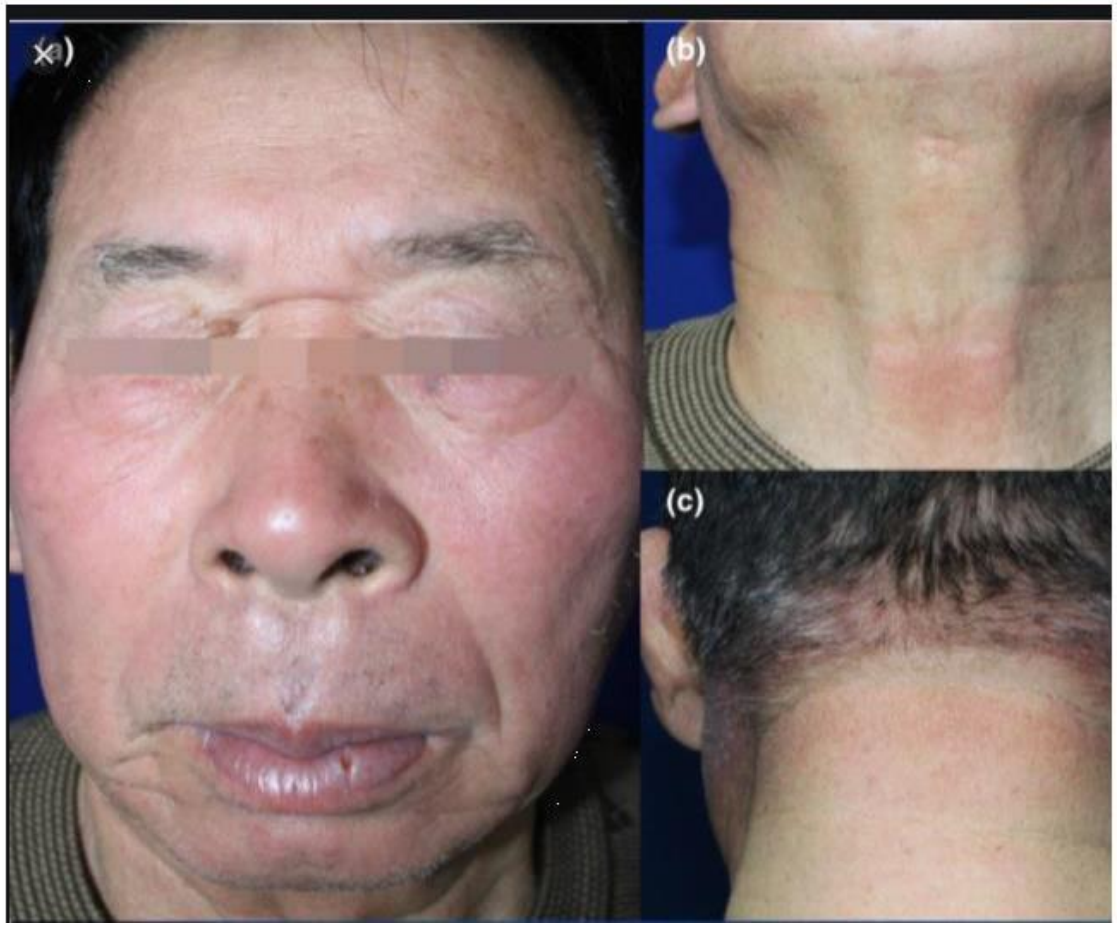
- Post-Marketing Surveillance Study in Korean IPF Patients

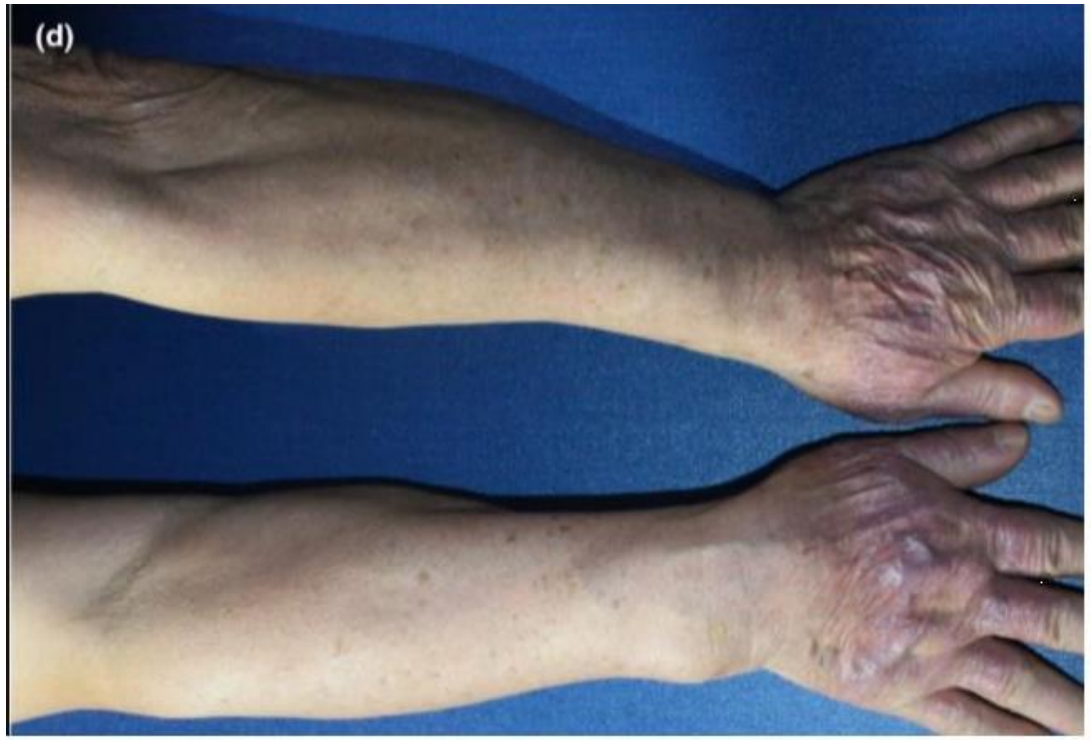
Table 2 Adverse events (frequency at least 3%) in the advanced and non-advanced IPF groups

Characteristic	Total	Advanced	Non-advanced	*p* value
Patients, *n*	219	39	180	
Adverse events	189 (86.3)	36 (92.3)	153 (85.0)	0.229
Decreased appetite	71 (32.4)	13 (33.3)	58 (32.2)	0.893
Photosensitivity reaction	30 (13.7)	6 (15.4)	24 (13.3)	0.736
Rash	25 (11.4)	2 (5.1)	23 (12.8)	0.266
Nausea	24 (11.0)	6 (15.4)	18 (10.0)	0.394
Pruritus	24 (11.0)	1 (2.6)	23 (12.8)	0.087
Epigastric discomfort	22 (10.1)	4 (10.3)	18 (10.0)	1.000

Chung MP et al, Adv Ther (2020) 37:2303–2316

Photosensitivity of pirfenidone





Park MY et al, Photodermatol Photoimmunol Photomed 2017; 33: 209–212

Management of pirfenidone adverse events

- Increase dose gradually
- Take with meals
- Use sunscreen
- Use PPI or GI motility drugs

Nintedanib

- Intracellular inhibitor that targets multiple tyrosine kinases, including the VEGF, FGF, and PDGF receptors

- 용법
  - 150mg bid or 100mg bid

- 부작용
  - 설사 → loperamide로 조절
  - 간기능 이상

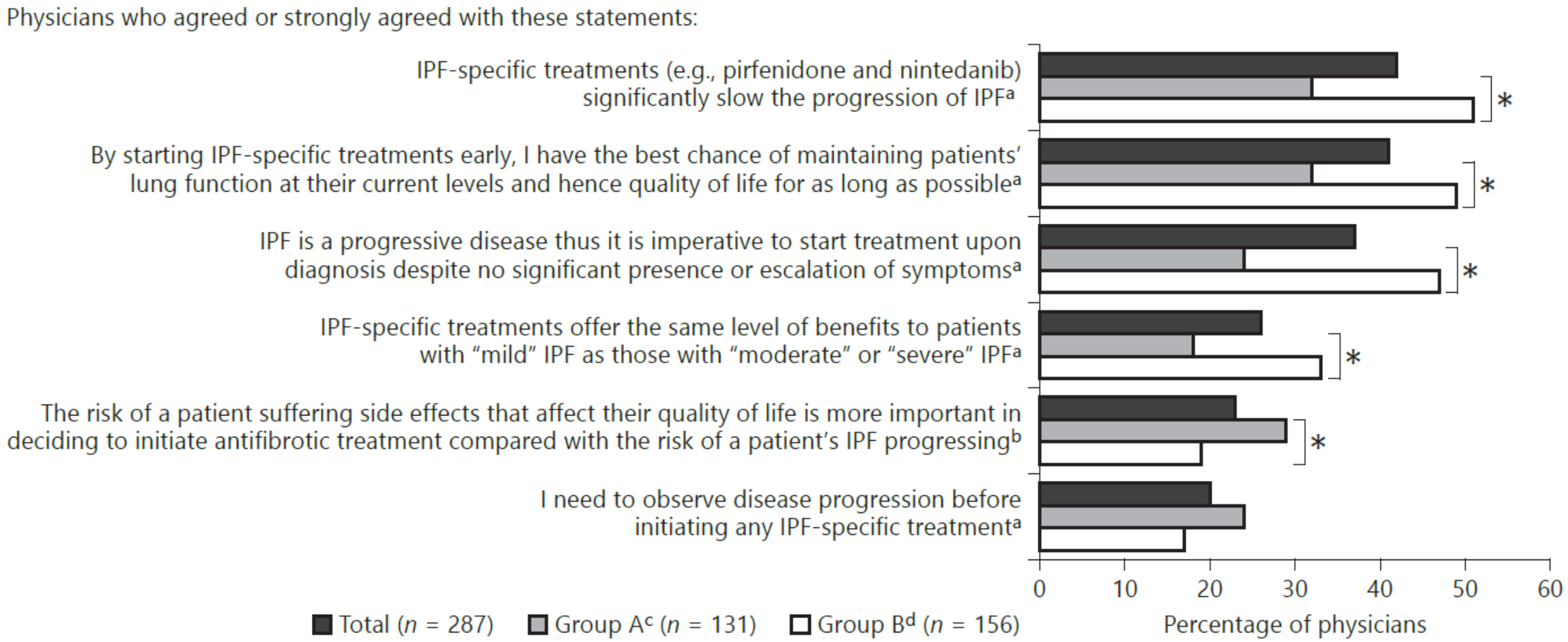
- 보험기준: 비급여, 혈액암 협회 지원

Problems and obstacles to earlier treatment

- Overdiagnosis, Overtreatment
- Physician’s perception: “mild” or “stable” disease does not warrant therapy
- A lack of confidence in the diagnosis of IPF
- Access/reimbursement issues, cost of therapy
- Concerns over the adverse effects of antifibrotic drugs

Maher et al, Respiratory Research (2019) 20:205

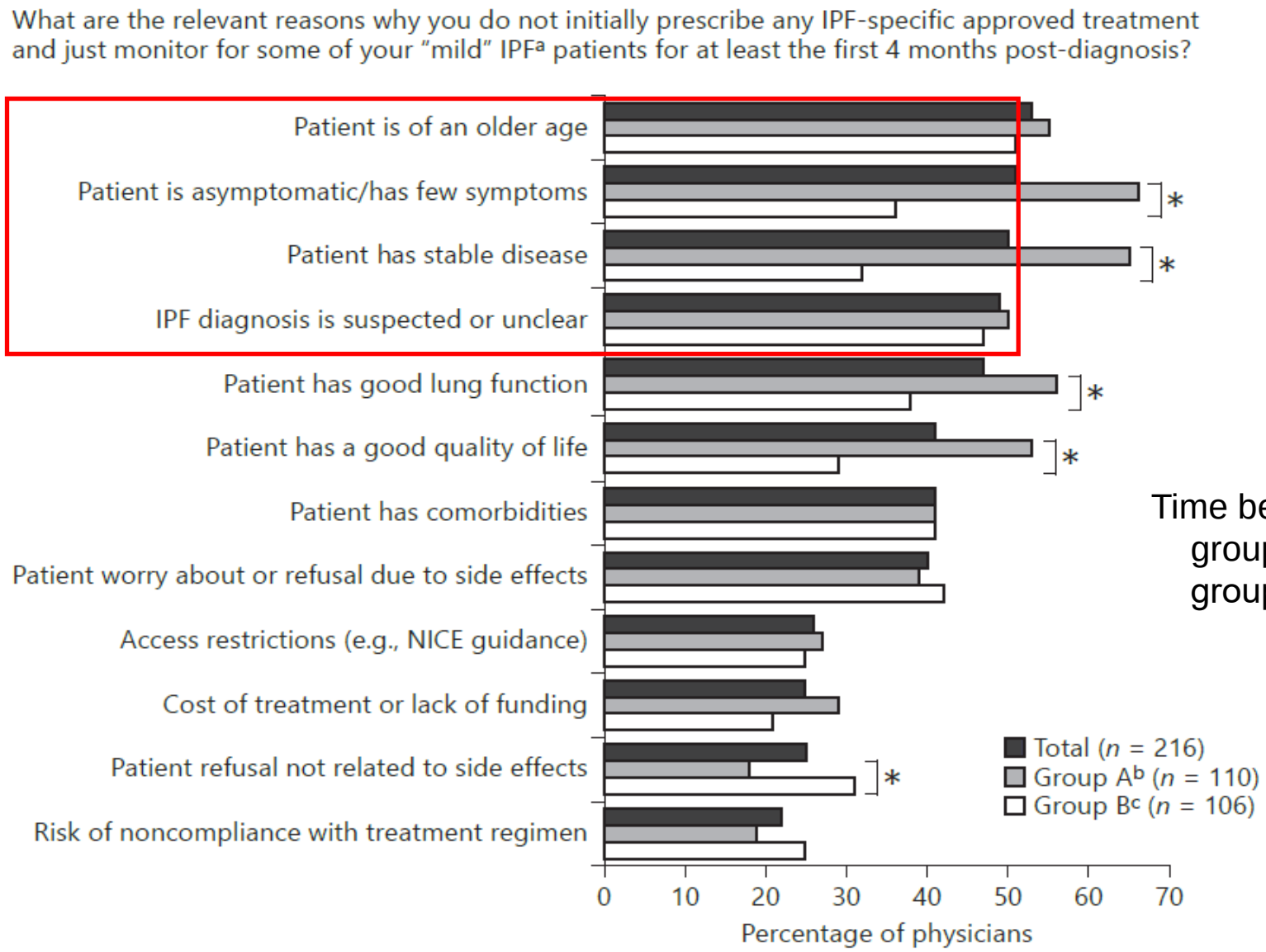
Physicians' attitudes to early treatment of IPF



Time between diagnosis & treatment initiation
group A: > 4 months, group B: ≤ 4 months

Maher et al, Respiration 2018;96:514–524

Reasons for not prescribing antifibrotics in mild IPF



Time between diagnosis & treatment initiation
- group A, > 4 months
- group B, ≤ 4 months

Maher et al, Respiration 2018;96:514–524

Potential candidates for early treatment

- Patients with genetic risk factors
  - *MUC5B* polymorphism
  - Telomere-related gene mutation, short telomere length
- Familial IPF
- Patients with high level of serum KL-6 or increasing KL-6 level

Future directions

- Find biomarker or predictors for disease progression
- Reduce side effects of current antifibrotics
- Development of new drugs with less side effect

Summary and Conclusions

- IPF is a progressive, fatal disease.
- Lung function decreases consistently even in the early stage of IPF.
- Antifibrotic treatment is also beneficial in early IPF.
- Patient-physician communication is needed before the treatment initiation of early IPF.