대한 결핵및 호흡기학회
제 46차 Workshop

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Interstitial lung disease Year in review 2018

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Contents

- **Idiopathic pulmonary fibrosis (IPF)**
  - **Monitoring of IPF**
  - **Treatment of IPF: pirfenidone, nintedanib, and statin**
  - **Effect of atmospheric pollution on IPF**
- **Sarcoidosis**
- **Systemic sclerosis-related ILD (SSc-ILD)**
- **Guideline**
  - **LAM diagnosis and management**
- **Summary**

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- **Guideline**
  - **LAM diagnosis and management**
- **Summary**

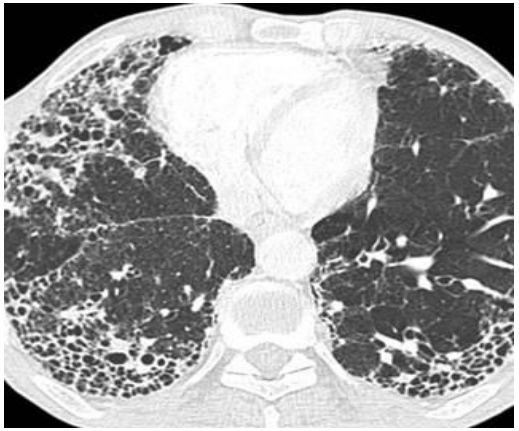
Idiopathic pulmonary fibrosis

- Chronic, progressive lung disease occurring primarily in older adults, with a median survival of 3–5 years from diagnosis

- Most common and severe form of idiopathic interstitial pneumonia

- Few treatment options
  - ✓Pirfenidone: approved in US in 2014
    covered by Korea National Health Insurance in 2015
  - ✓Nintedanib: approved in US in 2014
    not covered by KNHI yet

- 희귀난치성질환 산정특례 대상 (2009년)



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- **Guideline**
  - **LAM diagnosis and management**
- **Summary**

ORIGINAL ARTICLE

Effect of Emphysema Extent on Serial Lung Function in Patients with Idiopathic Pulmonary Fibrosis

Vincent Cottin[1,2], David M. Hansell[3], Nicola Sverzellati[4], Derek Weycker[5], Katerina M. Antoniou[6], Mark Atwood[5], Gerry Oster[5], Klaus-Uwe Kirchgaessler[7], Harold R. Collard[8], and Athol U. Wells[3]

[1]Department of Respiratory Medicine, National Reference Center for Rare Pulmonary Diseases, Louis Pradel Hospital, Lyon, France; [2]Université Claude Bernard, Lyon, France; [3]Interstitial Lung Disease Unit, Royal Brompton Hospital, London, United Kingdom; [4]Department of Surgical Sciences, Ospedale Maggiore di Parma, Parma, Italy; [5]Policy Analysis Inc., Brookline, Massachusetts; [6]Department of Thoracic Medicine, University of Crete, Heraklion, Greece; [7]Roche, Basel, Switzerland; and [8]Division of Pulmonary and Critical Care Medicine, University of California, San Francisco, San Francisco, California

Am J Respir Crit Care Med, 2017. 196(9): p. 1162-1171.

- Decline in FVC: widely used to identify disease progression
- Advantages of FVC
  - ✓Ease and reproducibility of measurement
  - ✓Serial decline in FVC for 6-12M: predicts earlier mortality
- Serial FVC change
  - →Preferred primary endpoint in IPF clinical trials
  - →2011 ATS/ERS IPF guideline: FVC - routine monitoring variable

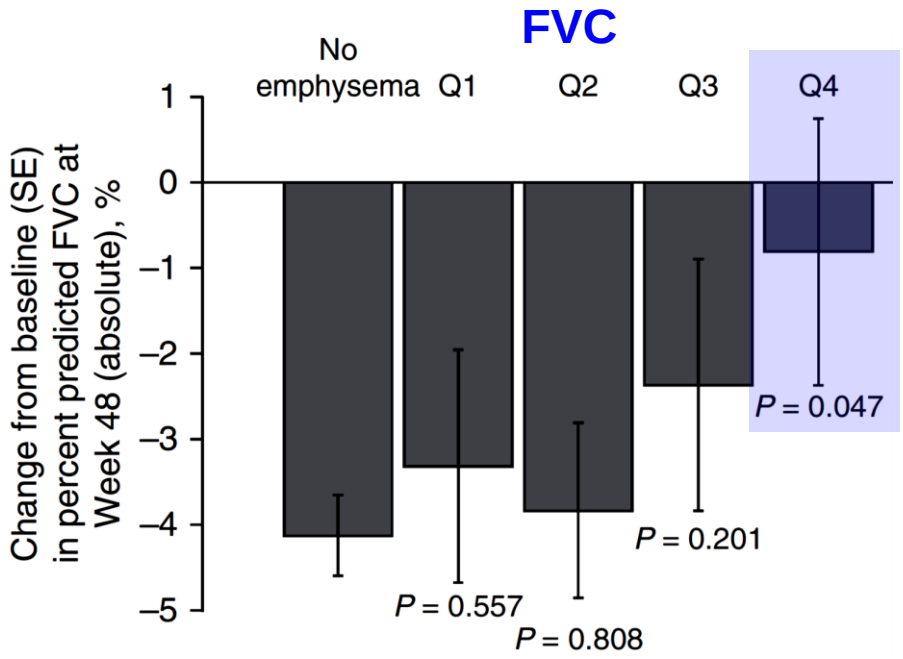
Impact of concurrent emphysema

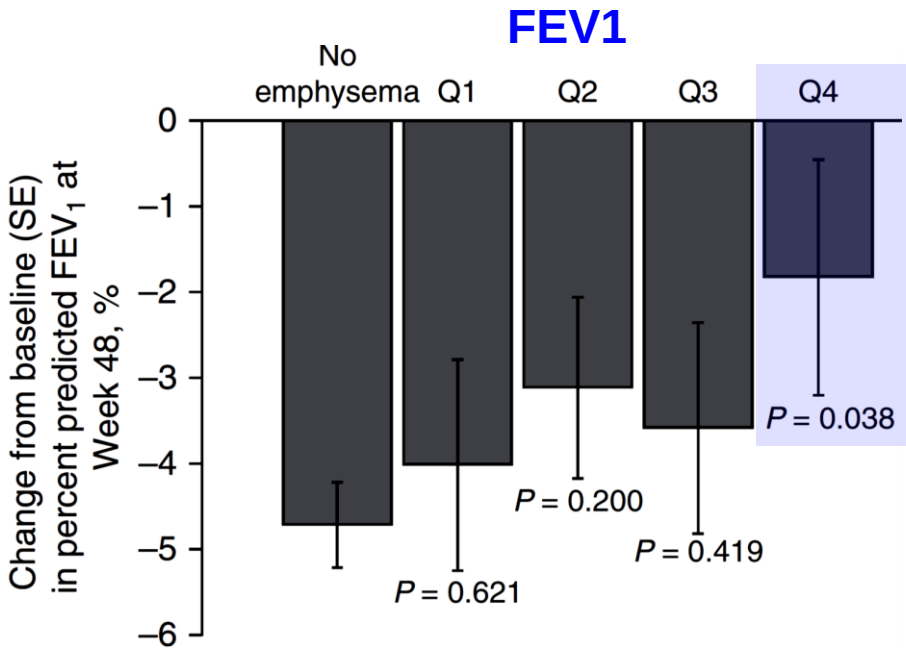
- Emphysema (+) in approximately 1/3 IPF patients
- Previous studies for the relationship btw emphysema extent and changes in lung function: mixed results
- Hypothesis
  - ✓Coexisting emphysema has a significant attenuating effect on serial FVC decline
  - →FVC for disease monitoring/primary endpoint in trials?
- Aim of the study
  - To characterize the relationship btw emphysema extent and changes in pulmonary function over time

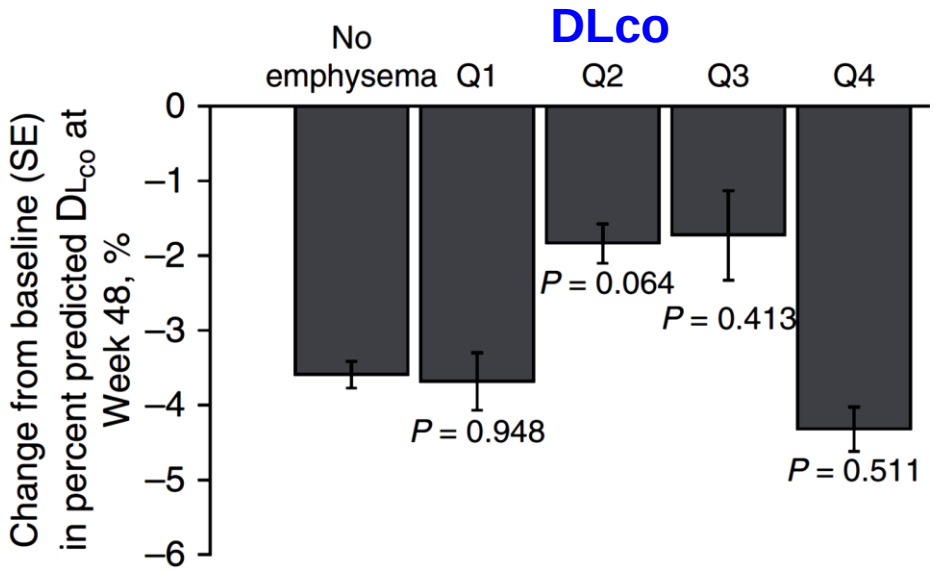
Methods

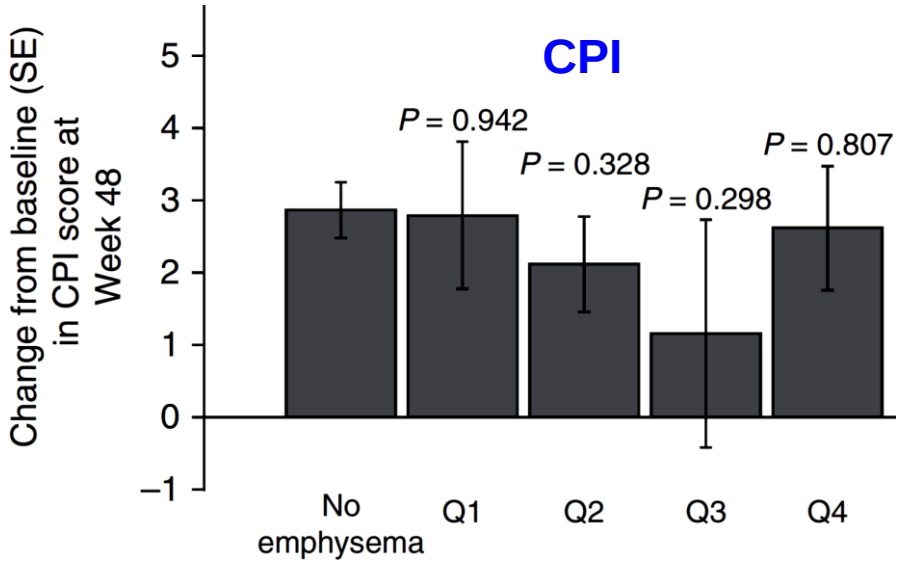
- *Post hoc* analysis
- Data from 2 phase III RCT of IFN-γ-1b in IPF (GIPF-001 and 007)
- Patients with Week 48 lung function data
- Eligibility for inclusion
  - GIPF-007
    - All patients with FEV1/FVC < 0.7 or > 0.9
    - Randomly selected patients with FEV1/FVC of 0.7–0.8 and 0.8–0.9
  - GIPF-001
    - All patients with FEV1/FVC < 0.8 or > 0.9
    - Randomly selected patients with FEV1/FVC of 0.8-0.9
- HRCT images reviewed

Disease endpoints by quartile of emphysema extent

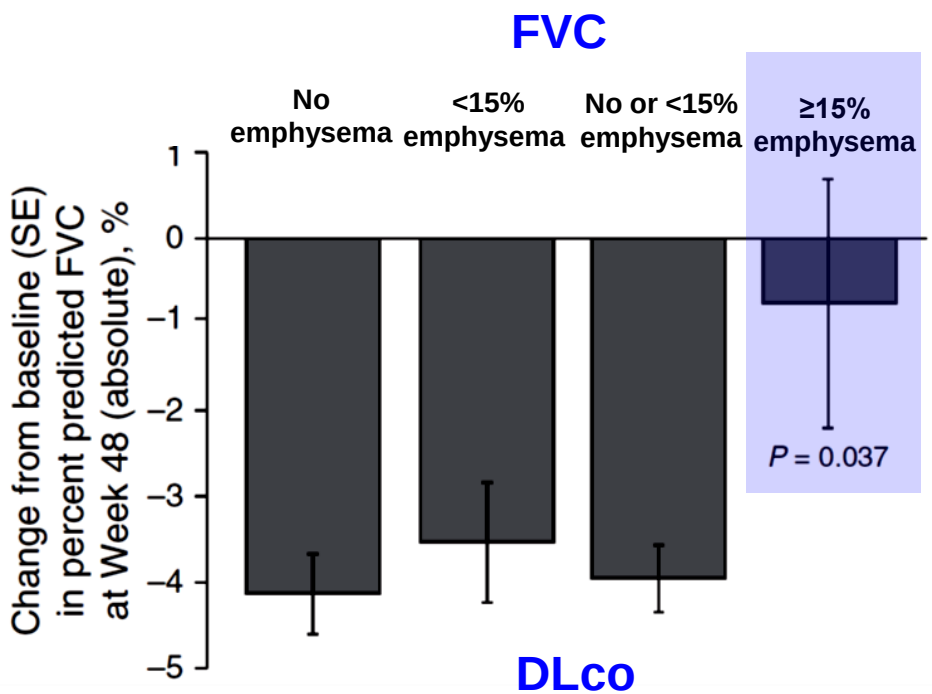


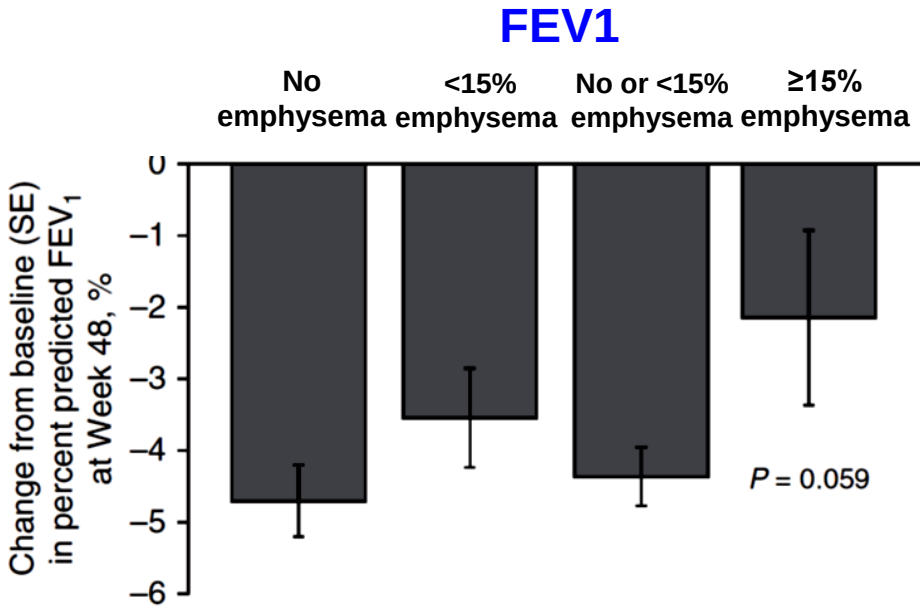


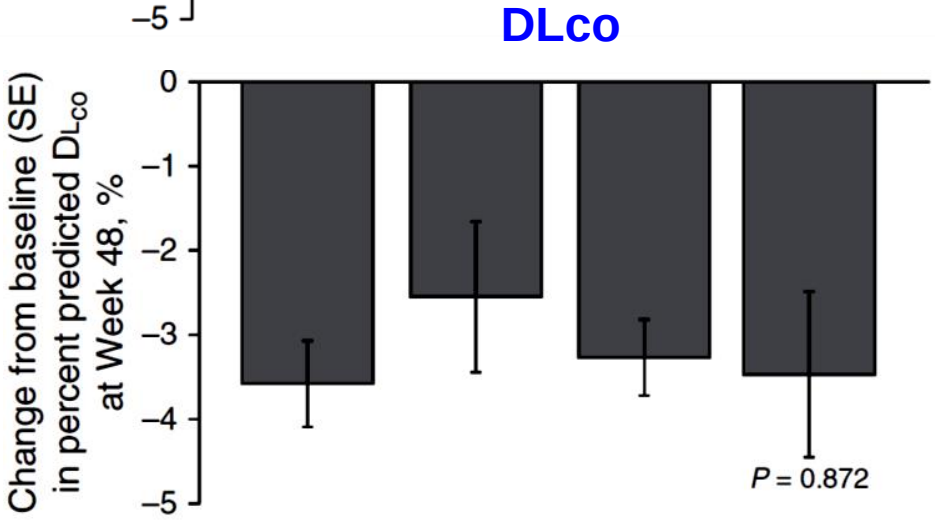


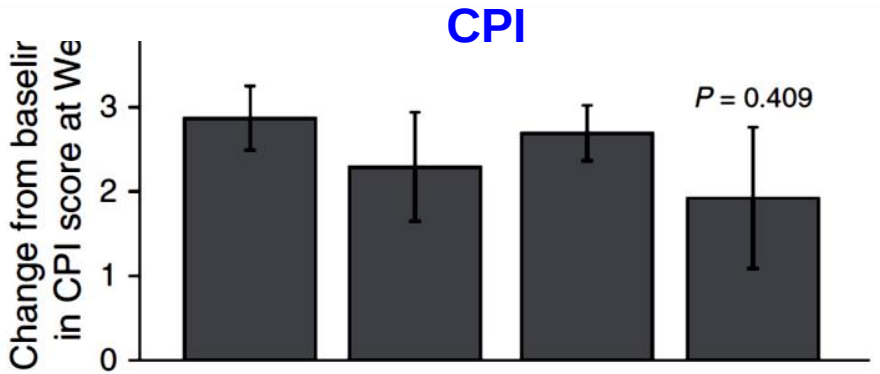


Endpoints by emphysema threshold

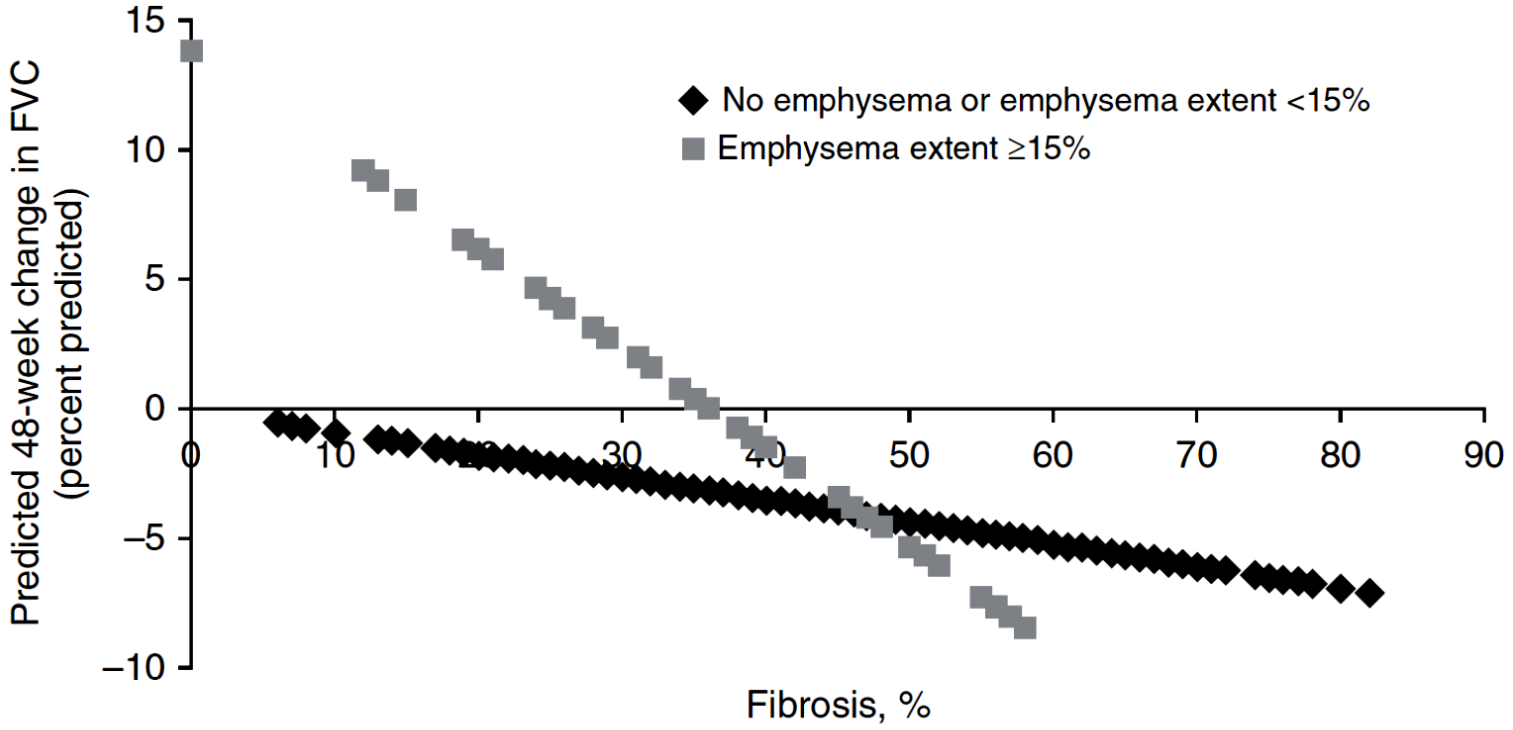








Predicted 48 week absolute change in % pred FVC by fibrosis extent



	Multivariate model		
Independent variables	**Estimate**	**95% CI**	***P* value**
Emphysema extent ≥15%	13.896	7.321, 20.470	< 0.001
Fibrosis extent	−0.086	−0.144, −0.028	0.004
Interaction	−0.297	−0.459, −0.136	< 0.001

Conclusion

- Emphysema extent ≥ 15% was associated with reduced FVC decline over 48 weeks compared with < 15% or no emphysema in patients with IPF
- In patients with combined IPF and emphysema, serial FVC measurements may not capture IPF progression
- Other endpoints (DLCO, CPI, etc.) should be considered in patients with combined IPF and emphysema

Contents

Pirfenidone

- A pyridone derivative
- Anti-fibrotic, anti-inflammatory, anti-oxidant
- CAPACITY1, CAPACITY2, ASCEND trial
- ASCEND trial (N Engl J Med 2014;370:2083–92)
  - ✓ FVC 50-90 % pred, DLCO 35-90% pred, FEV1/FVC≥ 0.8
  - ✓ Significantly reduced the change in FVC % pred from baseline
  - ✓ Significantly reduced number of patients with decreased FVC or death
- Pooled data analysis (ASCEND and CAPACITY trials) (ERJ 2016;47:243)
  - ✓ Better progression-free survival
  - ✓ Decreased all-cause mortality
  - ✓ Decreased IPF-related mortality
- Nausea and rash being the most frequent adverse events

Nintedanib

- A potent intracellular inhibitor of tyrosine kinases receptors (FGFR, PDGFR, VEGFR) involved in lung fibrosis

- INPULSIS-1, INPULSIS-2 trials (NEJM 2014;370:22)
  - ✓ FVC≥60% pred, DLCO 30-79% pred
  - ✓ Significantly reduced the annual rate of decline in FVC ($p<0.0001$)
  - ✓ Acute exacerbation was significantly reduced only in INPULSIS-2

- Pooled data analysis (INPULSIS-1, 2) (AJRCCM 2016;193:178)
  - Reduced annual rate of decline in FVC
  - Prolonged time to disease progression (HR 0.6, 95% CI: 0.49-0.74)
  - Prolonged time to first acute exacerbation (HR 0.64, 95% CI 0.39-1.05)

- Gastrointestinal adverse events, particularly diarrhea, were the most frequent adverse events

ORIGINAL ARTICLE

Pirfenidone Reduces Respiratory-related Hospitalizations in Idiopathic Pulmonary Fibrosis

Brett Ley[1], Jeffrey Swigris[2], Bann-mo Day[3], John L. Stauffer[3], Karina Raimundo[3], Willis Chou[3], and Harold R. Collard[1]

[1]Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, University of California, San Francisco, San Francisco, California; [2]Interstitial Lung Disease Program, Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, National Jewish Health, Denver, Colorado; and [3]Genentech, Inc., South San Francisco, California

Am J Respir Crit Care Med,2017. 196(6): p. 756-761.

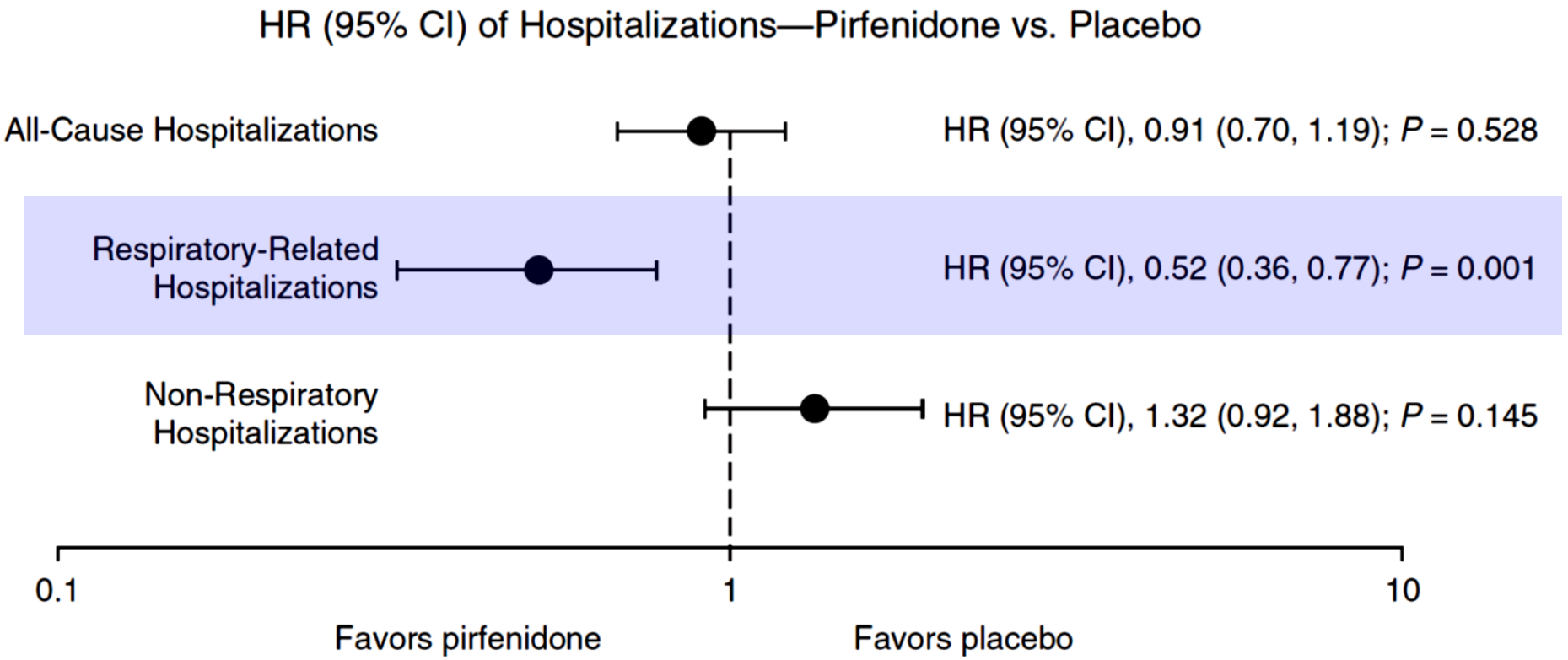
- Respiratory related hospitalization are associated with increased mortality and health care costs in IPF

- Aim of the study
  - ✓ To evaluate the 1-year risk of non-elective hospitalization (including all-cause, respiratory related, and non–respiratory related) and death after hospital admission among patients randomized to pirfenidone versus placebo

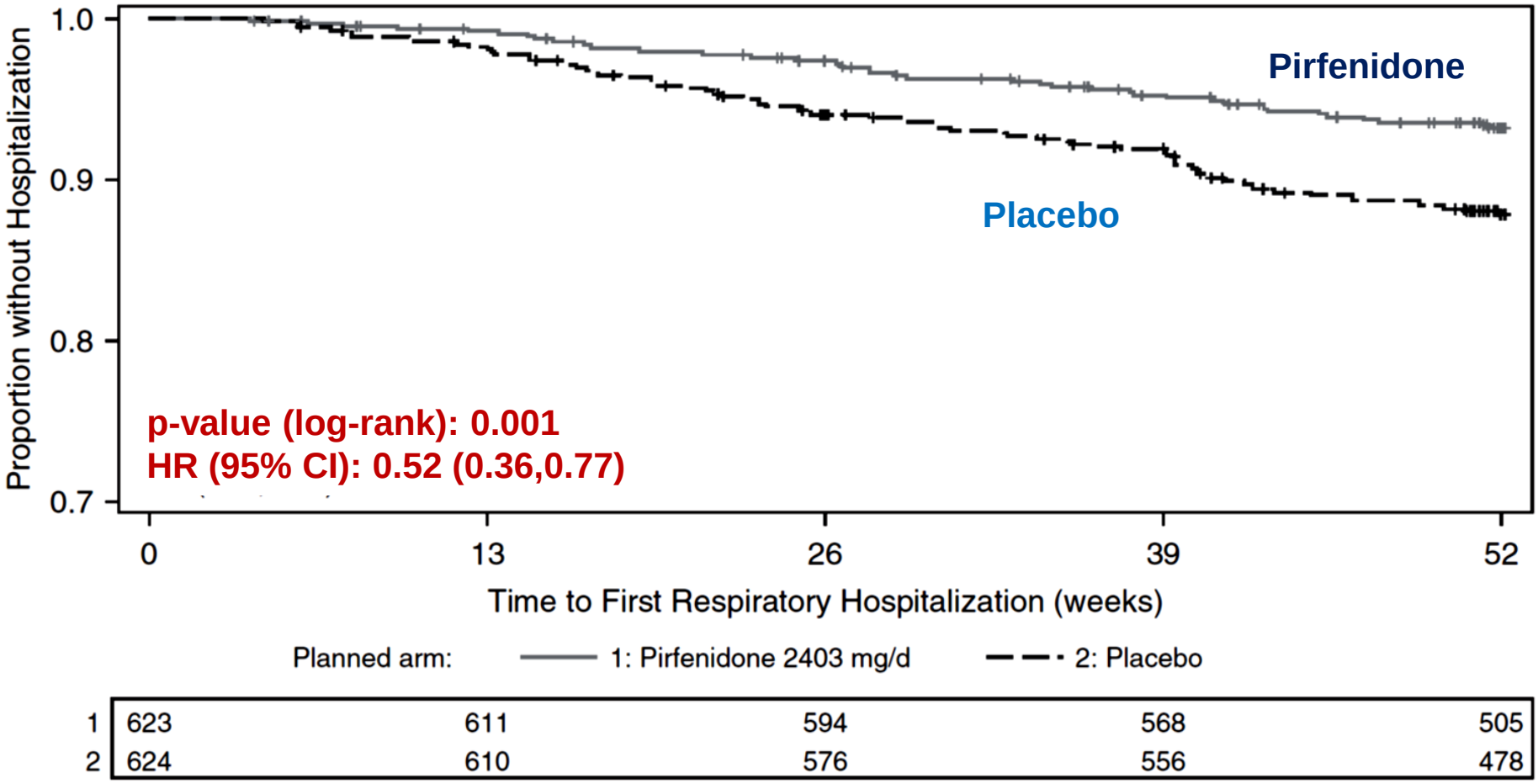
Methods

- *Post hoc* analysis
- Study population from 3 phase III RCT of pirfenidone (CAPACITY 004, 006, and ASCEND trial)
- CAPACITY (72 weeks)
  - ✓ FVC %pred ≥ 50%, DLco %pred ≥ 35%, 6MWT ≥ 150 m
  - ✓ Upper limits : FVC or DLco %pred ≤ 90%
  - ✓ Post BD FEV1/FVC ≥ 70%
- ASCEND (52 weeks)
  - ✓ FVC %pred ≥ 50%, DLco %pred≥ 30%, 6MWT ≥ 150 m
  - ✓ Upper limits : FVC and DLco %pred ≤ 90%
  - ✓ Post BD FEV1/FVC ≥ 80%
- Hospitalization
  - ✓ Prespecified secondary endpoint in CAPACITY
  - ✓ Recorded as serious adverse events in ASCEND

Risk of first non-elective hospitalization by type



Time to first non-elective respiratory-related hospitalization



1	623	611	594	568	505
2	624	610	576	556	478

Deaths after non-elective admission

	All-Cause Hospitalizations		Respiratory Hospitalizations		Nonrespiratory Hospitalizations	
	Pirfenidone (*n* = 106)	Placebo (*n* = 115)	Pirfenidone (*n* = 41)	Placebo (*n* = 74)	Pirfenidone (*n* = 70)	Placebo (*n* = 54)
Deaths, n (%)	18 (17)	37 (32)	11 (27)	34 (46)	8 (11)	9 (17)

	Hazard Ratio	95% Confidence Interval	*P* Value
All-cause hospitalization (n = 221*)			
Unadjusted	0.49	0.28–0.86	0.013
Adjusted for propensity score†	0.56	0.32–0.99	0.047
Respiratory-related hospitalization (n = 115*)			
Unadjusted	0.55	0.28–1.08	0.082
Adjusted for propensity score†	0.50	0.25–1.03	0.061
Non–respiratory-related hospitalization (n = 124*)			
Unadjusted	0.67	0.26–1.74	0.412
Adjusted for propensity score†	0.73	0.27–1.97	0.537

This association was no longer significant when we considered F/U to 72 weeks in the CAPACITY trials

Conclusion

- Pirfenidone reduces the risk of hospitalization for respiratory reasons

- The effect of pirfenidone on death after hospitalization is uncertain

ORIGINAL ARTICLE

Effect of Nintedanib in Subgroups of Idiopathic Pulmonary Fibrosis by Diagnostic Criteria

Ganesh Raghu[1], Athol U. Wells[2], Andrew G. Nicholson[2], Luca Richeldi[3], Kevin R. Flaherty[4], Florence Le Maulf[5], Susanne Stowasser[6], Rozsa Schlenker-Herceg[7], and David M. Hansell[2]

[1]Department of Medicine, University of Washington, Seattle, Washington; [2]Royal Brompton and Harefield NHS Foundation Trust and National Heart and Lung Institute, Imperial College, London, United Kingdom; [3]National Institute for Health Research Southampton Respiratory Biomedical Research Unit and Clinical and Experimental Sciences, University of Southampton, Southampton, United Kingdom; [4]University of Michigan Health System, Ann Arbor, Michigan; [5]Boehringer Ingelheim France S.A.S., Reims, France; [6]Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany; and [7]Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, Connecticut

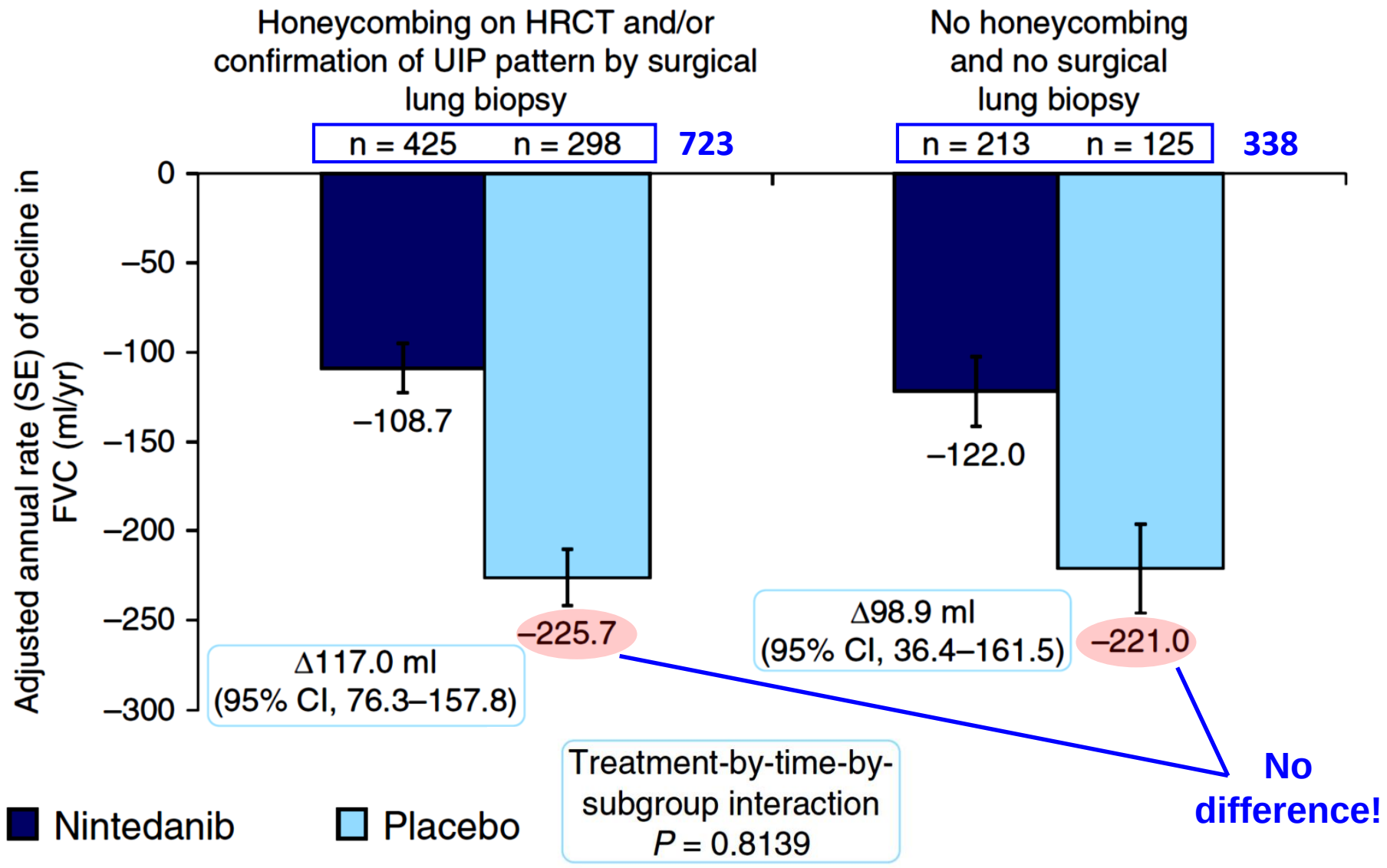
Am J Respir Crit Care Med, 2017. 195(1): p. 78-85.

- Diagnosis of IPF in 2011 ATS/ERS guideline
  - ✓ Exclusion of other known causes of ILD
  - ✓ UIP pattern on HRCT in patients without surgical lung biopsy
- UIP pattern
  - ✓ Subpleural basal predominance / Reticular abnormality
  - ✓ Honeycombing / Absence of features inconsistent with UIP
- Possible UIP or inconsistent of UIP pattern
  - ✓ Surgical lung biopsy is required to make a definitive diagnosis
- Aim of the study
  - ✓ To investigate the potential impact of diagnostic subgroups on the progression of IPF and the effect of nintedanib

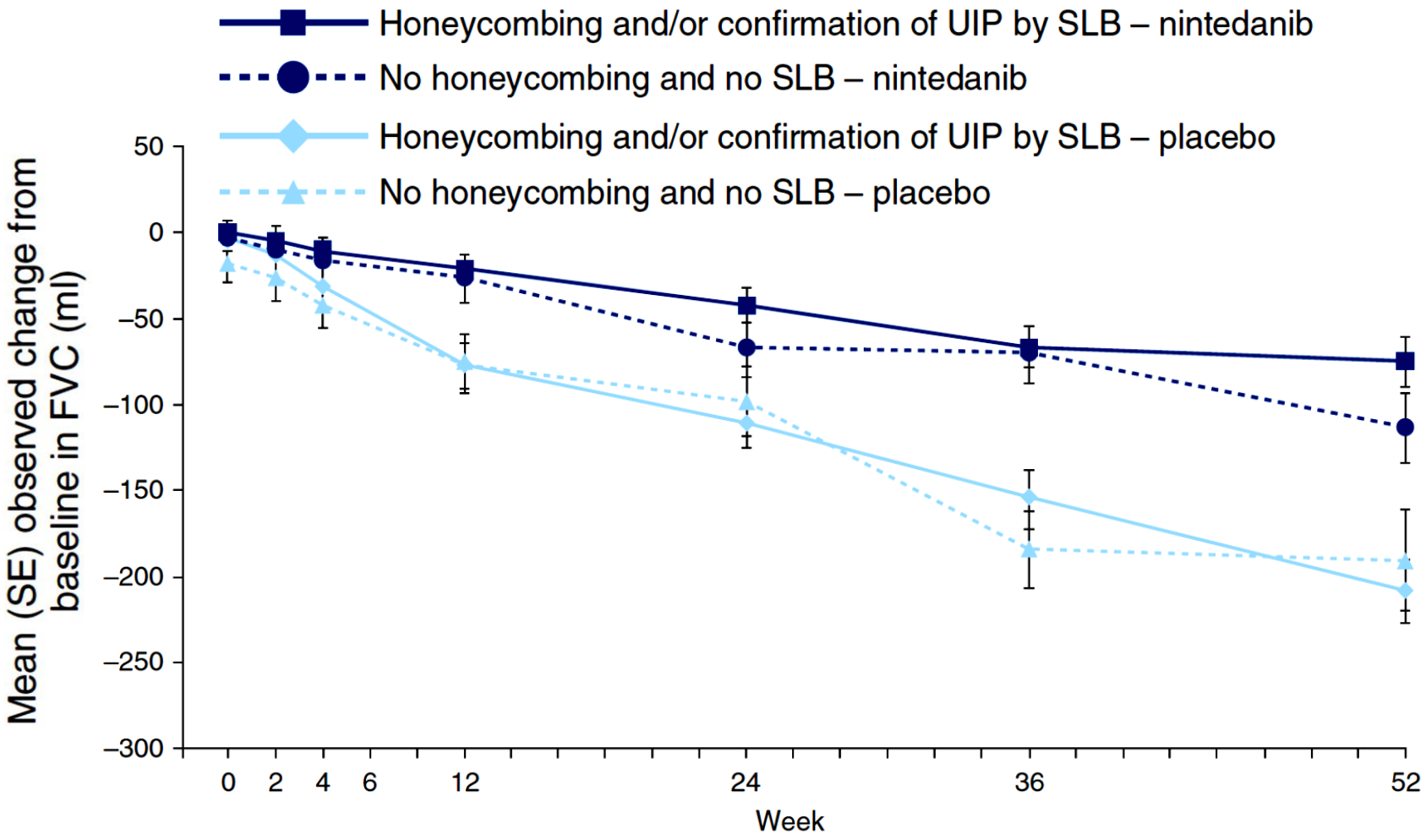
Methods

- Study population from 2 phase III RCT of nintedaib (INPULSIS-1, 2)
- Inclusion criteria of INPULSIS
  - ✓ A: honeycombing with basal/peripheral predominance
  - ✓ B: reticular abnormality and traction bronchiectasis
  - ✓ C: absence of atypical features
  - (A+B+C) or (A+C) or (B+C)
  - FVC ≥50% predicted (no upper threshold)
  - DLCO 30% - 79% predicted
  - FEV1/FVC ratio ≥0.7.
- *Post hoc* subgroup analysis
  - ✓ Patients with honeycombing on HRCT and/or UIP by surgical lung biopsy vs patients with possible UIP on HRCT without surgical lung biopsy

Annual decline rate in FVC by subgroup



Change from baseline in FVC over time by subgroup



Conclusion

- Patients who have possible UIP with traction bronchiectasis on HRCT have disease that progresses in a similar way and responds similarly to nintedanib, as do patients who have definite UIP on HRCT and/or confirmation of UIP by biopsy

OPEN ACCESS

ORIGINAL ARTICLE

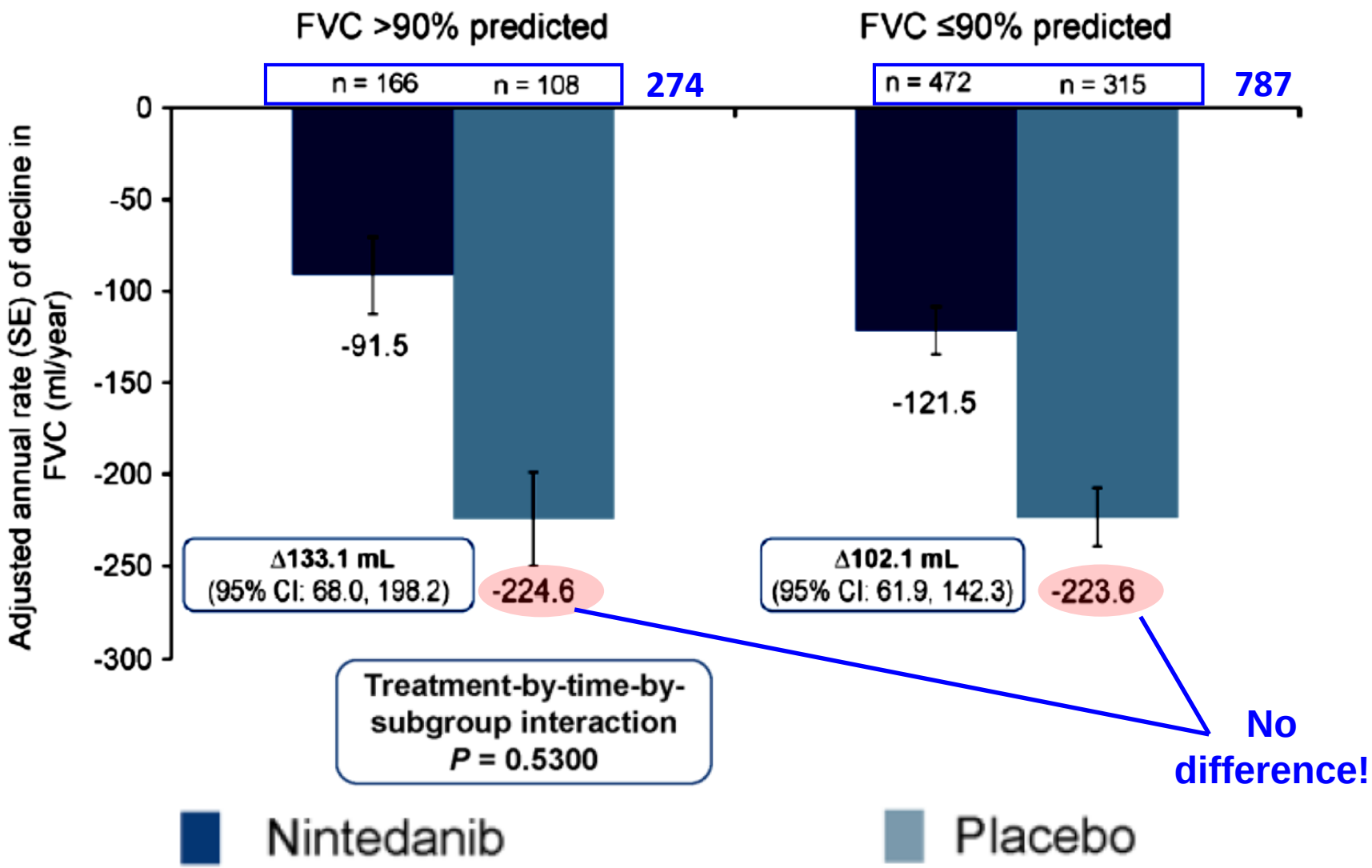
Nintedanib in patients with idiopathic pulmonary fibrosis and preserved lung volume

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]

Thorax, 2017. 72(4): p. 340-346.

- Clinical course of IPF is variable and difficult to predict
- No consensus regarding at which point therapy should be initiated or stopped
- INPULSIS trial : no upper limit on FVC% pred for inclusion
- Aim of the study: whether patients with IPF and preserved lung volume (FVC > 90% predicted) received the same benefit from nintedanib as patients with greater impairment in lung volume
- *Post hoc* subgroup analysis from 2 INPULSIS trials
  - ✓ Patients with baseline FVC >90% pred versus ≤90% pred

Adjusted annual rate of decline in FVC by subgroup



Conclusion

- The annual rate of decline in FVC was similar in placebo-treated patients with preserved lung volume (FVC >90% predicted) at baseline as in patients with greater impairment in lung volume

- Nintedanib slowed the decline in lung function independent of the degree of FVC impairment at baseline

- Against a ‘watch and wait’ approach & early intervention

ORIGINAL ARTICLE
INTERSTITIAL LUNG DISEASES

Acute exacerbations in the INPULSIS trials of nintedanib in idiopathic pulmonary fibrosis

Harold R. Collard[1], Luca Richeldi[2,3], Dong Soon Kim[4], Hiroyuki Taniguchi[5], Inga Tschoepe[6], Maurizio Luisetti[†7], Jesse Roman[8], Gregory Tino[9], Rozsa Schlenker-Herceg[10], Christoph Hallmann[11] and Roland M. du Bois[12]

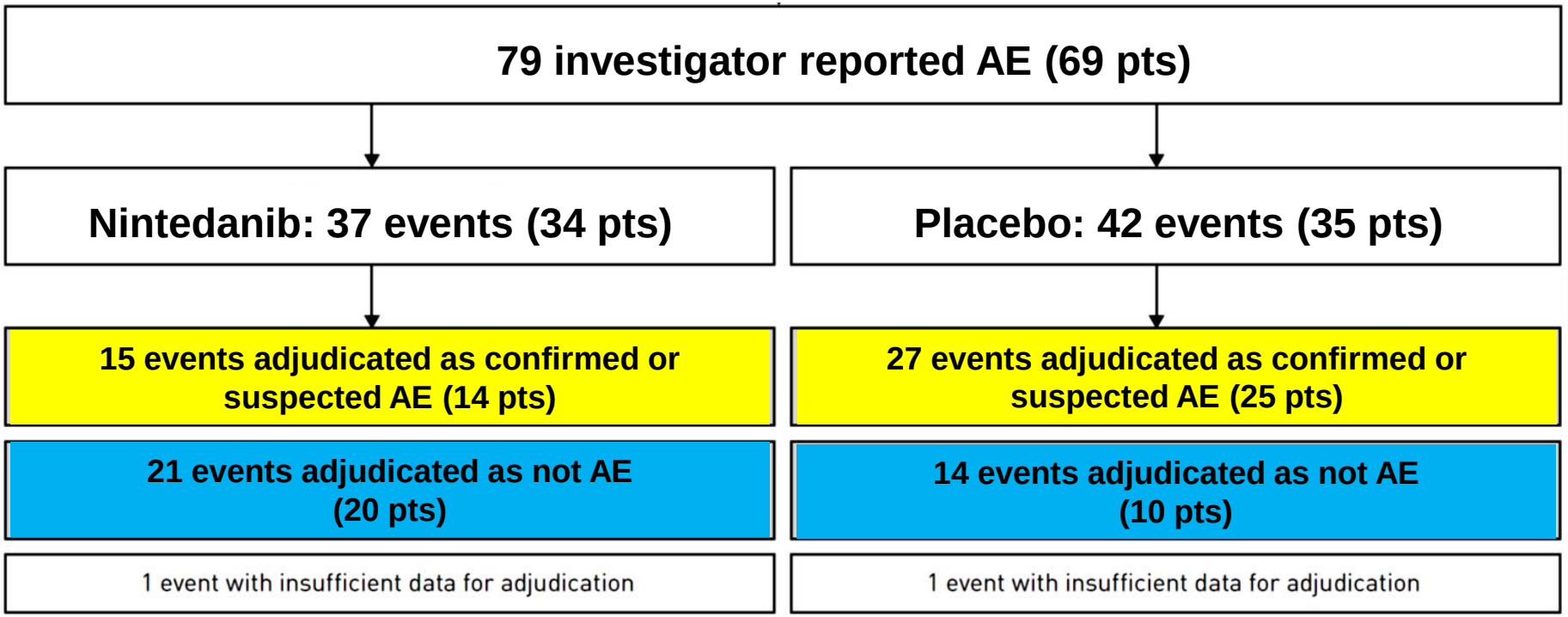
Eur Respir J, 2017. 49(5)

- Acute exacerbation (AE) defined in 2007
  - ✓ Acute deteriorations in symptoms associated with changes in radiographic appearance and the absence of an identifiable cause
  - ✓ Occur in approximately 5–10% of patients annually
  - ✓ Associated with high morbidity and high short term mortality
- Risk factor of AE
  - ✓ Low FVC, worse dyspnea, worse gas exchange, honeycombing, greater extent of disease on HRCT, GERD, elevated KL-6, air pollution
- Aim of the study
  - ✓ To further investigate the risk factors for AE of IPF
  - ✓ To explore the impact of nintedanib on risk and outcome of investigator-reported and confirmed/suspected AE

Methods

- Study population from 2 phase III RCT of nintedaib (INPULSIS-1, 2)
- *Post hoc* subgroup analysis
- Definition of AE (2007)
  - ✓ Unexplained worsening or development of dyspnea within 30 days
  - ✓ New diffuse pulmonary infiltrates on chest radiograph and/or HRCT
  - ✓ Possible causes of the acute worsening (infection, left heart failure, pulmonary embolism etc) excluded by routine clinical examination and microbiological studies
- Adjudication of AE
  - ✓ Investigator completed an Acute Exacerbation Questionnaire & documents
  - ✓ Adjudication committee: 3 experts in IPF who were not investigators in the INPULSIS trials, blinded to treatment allocation
  - → Confirmed AE / Suspected AE / Not an AE

Events included in the analyses



Incidence rates of investigator-reported AE
- Nintedanib group- 5.3/100 patient-years
- Placebo group- 8.2/100 patient-years

(risk ratio 0.65; 95% CI 0.40, 1.04; p=0.07).

Incidence rate of confirmed or suspected AE
- Nintedanib group - 2.2/100 patient-years
- Placebo group - 5.8/100 patient-years

(risk ratio 0.37; 95% CI 0.19, 0.72; p=0.003)

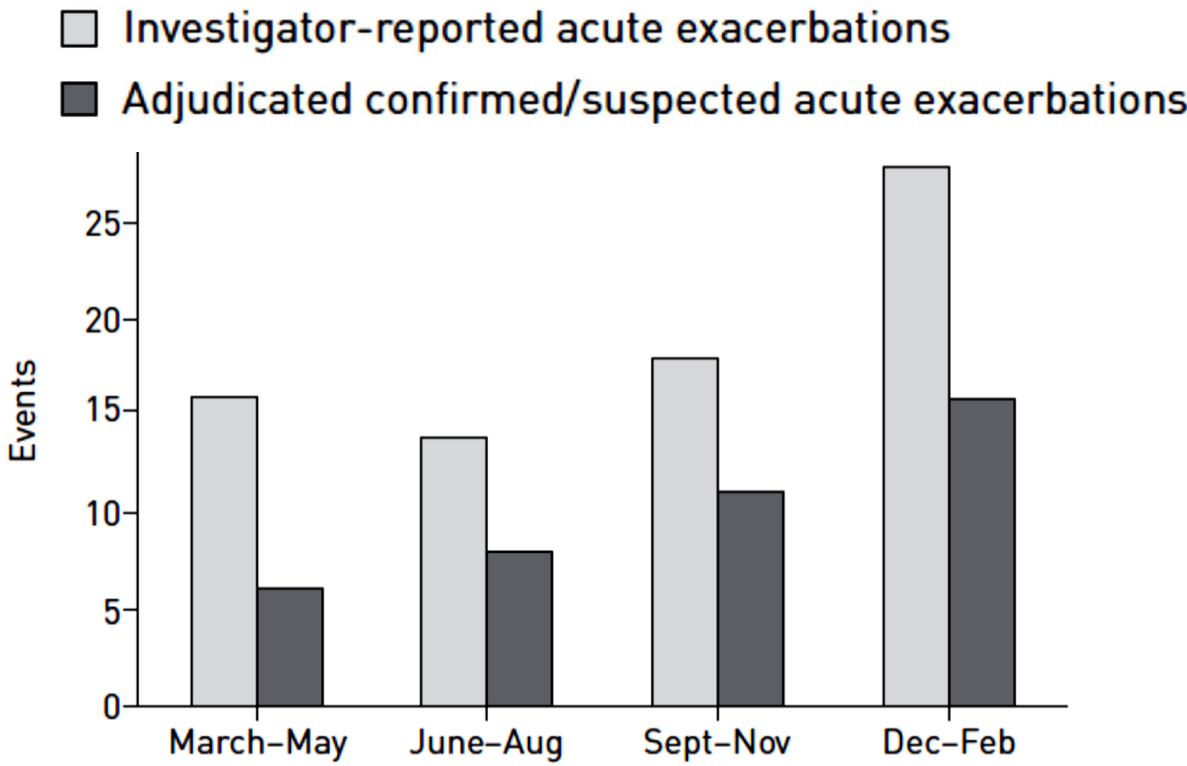
Risk prediction models for AE

	Risk factor analysis			Final model
	Model variable[#]	p-value[¶]	AIC[+]	HR (95% CI)[§]
Investigator-reported AE	FVC % predicted at baseline[f]	<0.0001	830.217	0.67 (0.55–0.80)
	Supplemental oxygen use at baseline	0.0018	824.565	2.47 (1.37–4.47)
	Antacid medication use at baseline	0.0873	823.706	1.50 (0.91–2.47)
	Randomisation to nintedanib	0.1150	823.271	0.66 (0.40–1.08)
Adjudicated confirmed or suspected AE	FVC % predicted at baseline	0.0006	483.723	0.67 (0.53–0.86)
	Randomisation to nintedanib	0.0010	475.169	0.33 (0.16–0.66)
	Antacid medication use at baseline	0.0676	473.938	1.78 (0.92–3.43)
	Former or current smoker	0.0938	472.805	2.13 (0.89–5.13)
	Supplemental oxygen use at baseline	0.1322	472.870	1.85 (0.80–4.29)

Mortality following AE

Mortality rate[¶]	Patients with investigator-reported acute exacerbations		Patients with events adjudicated as confirmed or suspected acute exacerbations[#]		Patients with all events adjudicated as not acute exacerbations[#]	
	Nintedanib (n=34)	Placebo (n=35)	Nintedanib (n=14)	Placebo (n=25)	Nintedanib (n=23)	Placebo (n=13)
30-day	7 (20.6)	14 (40.0)	3 (21.4)	9 (36.0)	4 (17.4)	5 (38.5)
90-day	10 (29.4)	15 (42.9)	5 (35.7)	12 (48.0)	6 (26.1)	7 (53.9)
180-day	12 (35.3)	20 (57.1)	6 (42.9)	15 (60.0)	7 (30.4)	7 (53.9)

Seasonality of AE



Conclusion

- Acute exacerbations of IPF assessed by local investigators were associated with poor outcomes, regardless of whether they were centrally confirmed or not
- Acute exacerbation of IPF is more common in patients with more physiologically advanced disease (lower FVC% pred)
- Treatment with nintedanib may reduce the risk of developing an acute exacerbation
- Nintedanib may improve post-acute exacerbation survival, but not statistically significant

ORIGINAL ARTICLE

Nintedanib with Add-on Pirfenidone in Idiopathic Pulmonary Fibrosis
Results of the INJOURNEY Trial

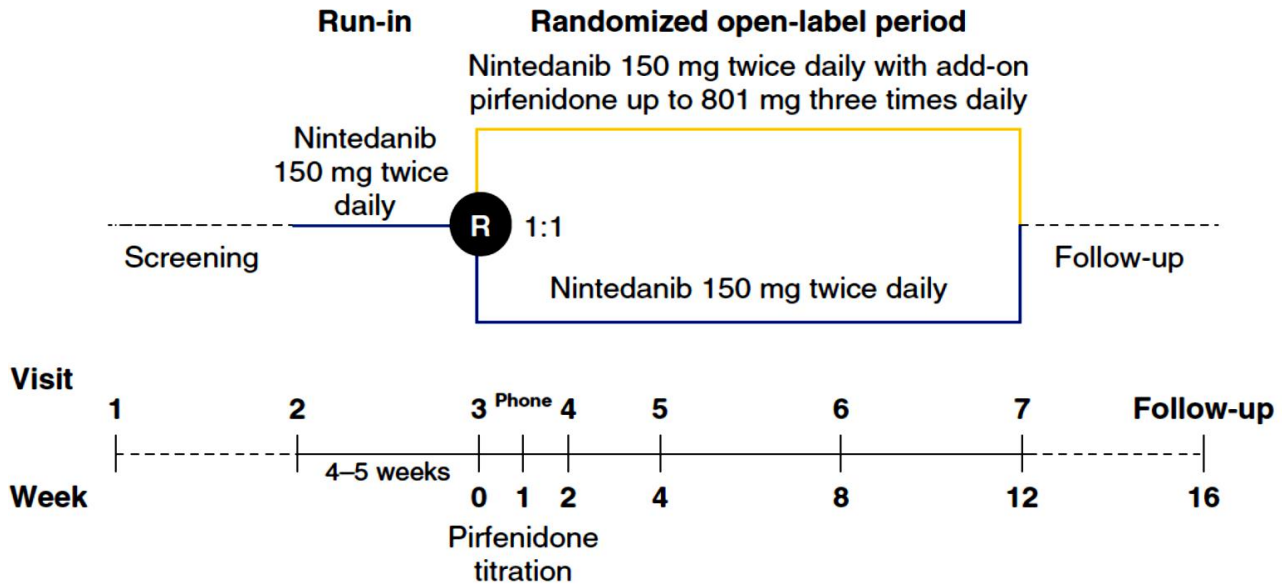
Carlo Vancheri[1], Michael Kreuter[2], Luca Richeldi[3], Christopher J. Ryerson[4], Dominique Valeyre[5], Jan C. Grutters[6,7], Sabrina Wiebe[8], Wibke Stansen[9], Manuel Quaresma[2,9], Susanne Stowasser[9], and Wim A. Wuyts[10]; on behalf of the INJOURNEY Trial Investigators

Am J Respir Crit Care Med, 2018. 197(3): p. 356-363.

- Pirfenidone and nintedanib
  - ✓ Reduce the rate of disease progression in IPF patients
  - ✓ No drugs stop disease progression yet
  - ✓ Thought to target different aspects of the fibrotic cascade
  - → Suggesting that therapy with both drugs may provide additive or even synergistic effects
- Aim of the study
  - ✓ To investigate safety, tolerability, and pharmacokinetic and exploratory efficacy endpoints in patients treated with nintedanib and add-on pirfenidone versus nintedanib alone

Methods

- Open-label, randomized trial of nintedanib with add-on pirfenidone compared with nintedanib alone in patients with IPF



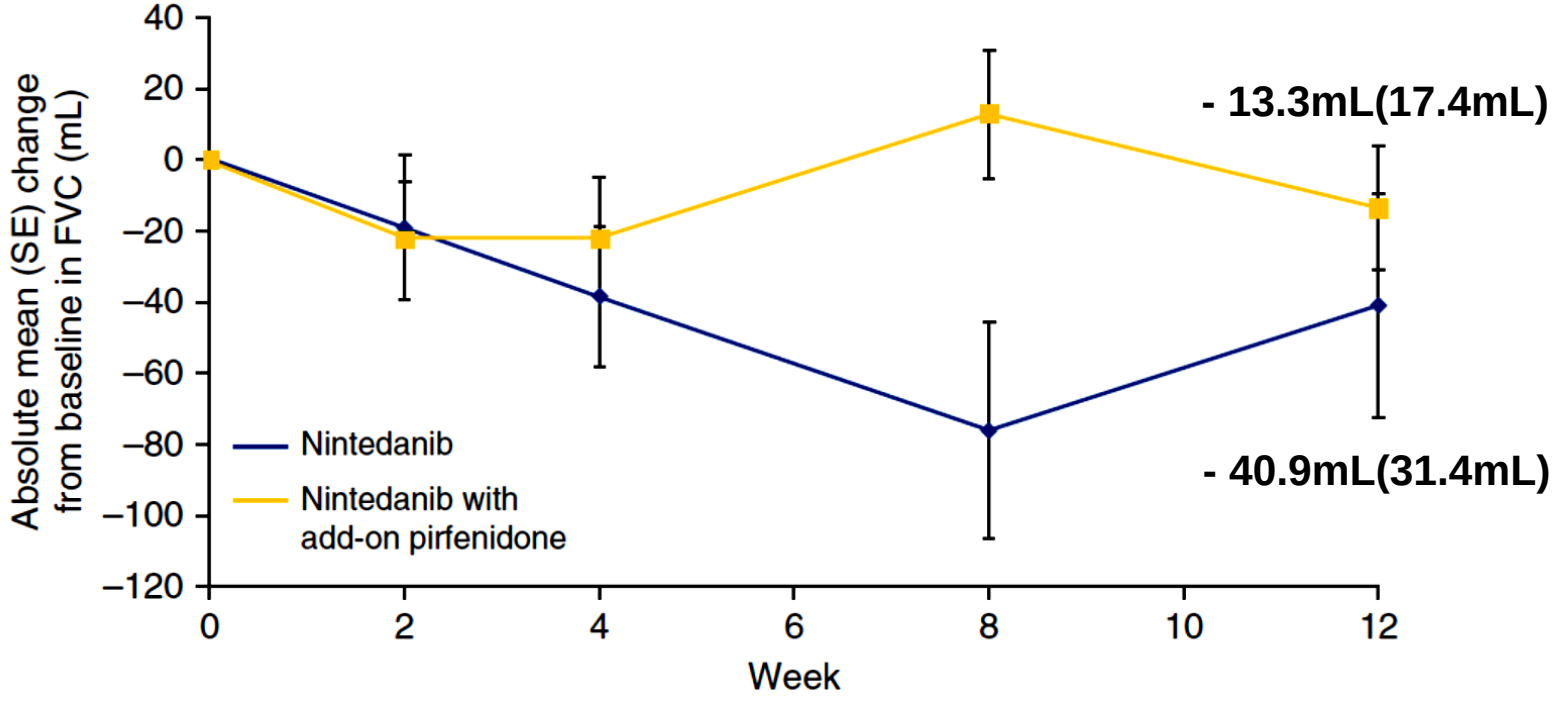
- Inclusion criteria : Age ≥ 40, FVC ≥ 50 % pred
- Exclusion criteria:
  - ✓ AST/ALT elevation, T.bil elevation
  - ✓ History of MI within 6 months, or unstable angina within 1M
  - ✓ Bleeding risk (anticoagulation or high dose antiplatelet therapy)
  - ✓ History thrombotic event within 12M
- **Primary endpoint: % of patients with on-treatment GI adverse events**

Adverse events

On-treatment GI adverse events - 37 (69.8%) in nintedanib with add-on pirfenidone group
27 (52.9%) in nintedanib alone group

	Nintedanib 150 mg Twice Daily with Add-on Pirfenidone (*n* = 53)	Nintedanib 150 mg Twice Daily (*n* = 51)
Any adverse events	47 (88.7)	45 (88.2)
Most frequent adverse events*		
Diarrhea	20 (37.7)	16 (31.4)
Nausea	22 (41.5)	6 (11.8)
Vomiting	15 (28.3)	6 (11.8)
Fatigue	10 (18.9)	6 (11.8)
Upper abdominal pain	7 (13.2)	4 (7.8)
Decreased appetite	6 (11.3)	5 (9.8)
Dyspnea	2 (3.8)	8 (15.7)
Headache	7 (13.2)	1 (2.0)
Any serious adverse events†	2 (3.8)	5 (9.8)
Any fatal adverse events	0	0
Maximum AST and/or ALT		
≥3× ULN	3 (5.7)	0
≥5× ULN	2 (3.8)	0
≥8× ULN	0	0
Maximum total bilirubin		
≥1.5× ULN	0	1 (2.0)
≥2× ULN	0	1 (2.0)
Maximum alkaline phosphatase		
≥1.5× ULN	1 (1.9)	0
≥2× ULN	0	0
Maximum γ-glutamyltransferase		
≥1× ULN	29 (54.7)	25 (49.0)
≥3× ULN	7 (13.2)	3 (5.9)
ALT and/or AST ≥3× ULN and bilirubin ≥2× ULN	0	0

Exploratory efficacy outcome: Absolute change from baseline in FVC



n					
Nintedanib	51	49	48	45	44
Nintedanib with add-on pirfenidone	53	52	50	50	48

Conclusion

- Treatment with nintedanib and add-on pirfenidone for 12 weeks had a manageable safety and tolerability profile

- Smaller numerical decline in FVC over 12 weeks in patients treated with nintedanib with addon pirfenidone than with nintedanib alone

OPEN ACCESS

ORIGINAL ARTICLE

Effect of statins on disease-related outcomes in patients with idiopathic pulmonary fibrosis

Michael Kreuter,[1,2] Francesco Bonella,[3] Toby M Maher,[4] Ulrich Costabel,[3] Paolo Spagnolo,[5] Derek Weycker,[6] Klaus-Uwe Kirchgaessler,[7] Martin Kolb[8]

Thorax 2017. 72(2): p. 148-153.[7]

- Cardiovascular (CV) comorbidities are common in IPF
- Medications are often required to treat patients with CV risk factors
- Statin
  - ✓Attenuate the decline in pulmonary function associated with normal ageing
  - ✓Development of ILD → controversial
  - ✓Effect on ILD → controversial (no effect vs reduced mortality)
- Aim of the study
  - ✓ To investigate the potential effects of statins in patients with IPF
  - ✓ To investigate the potential effects of statins on disease related outcomes in IPF

Methods

- *Post hoc* analysis of data from the placebo arms of 3 phase III RCT of pirfenidone in IPF (ASCEND, CAPACITY 1, 2)

- Exclusion criteria of the ASCEND, CAPACITY-1 and 2
  - ✓ History of unstable or deteriorating cardiac disease within previous 6 M
  - ✓ Active infection/ Active malignancy
  - ✓ COPD from ASCEND

- Outcomes evaluated
  - Disease progression / all-cause mortality / IPF-related mortality
  - Change from baseline in FVC, 6MWD
  - All-cause hospitalization and respiratory-related hospitalization
  - The composite outcomes of all-cause mortality or a ≥10% absolute decline in % pred FVC and all-cause mortality or a ≥50 m decline in 6MWD were prespecified outcomes in ASCEND

Baseline demographics

Parameter	Statin users (N=276)	Statin non-users (N=348)	p Value
Mean age, years (SD)	68.2 (7.0)	66.3 (7.8)	0.0014
Sex, n (%)			
Male	225 (81.5)	240 (69.0)	0.0004
Mean % predicted FVC (SD)	72.5 (14.0)	71.6 (13.3)	0.4297
Mean % predicted DLco* (SD)	45.4 (10.3)	45.7 (11.7)	0.7329
Mean 6MWD*, m (SD)	407.4 (89.8)	415.3 (97.6)	0.3028
Mean UCSD-SOBQ score* (SD)	34.3 (22.1)	35.4 (21.2)	0.5325
Medical history, n (%)			
Cardiovascular disease	127 (46.0)	53 (15.2)	<0.0001
Chronic renal failure	13 (4.7)	7 (2.0)	0.0573
COPD	14 (5.1)	8 (2.3)	0.0621
Cardiovascular risk factors, n (%)			
Hypercholesterolaemia	234 (84.8)	61 (17.5)	<0.0001
Smoker (current/former)	186 (67.4)	198 (56.9)	0.0074
Hypertension	183 (66.3)	157 (45.1)	<0.0001
Obesity†	125 (45.3)	140 (40.2)	0.2041
Diabetes	75 (27.2)	59 (17.0)	0.0020

simvastatin, 38.4%; atorvastatin, 34.8%; pravastatin, 9.8%; rosuvastatin, 9.4%; other, 7.6%

Multivariate analyses baseline statin users vs non-users

Outcome	HR	95% CI	p Value
Disease progression†	0.75	0.52 to 1.07	0.1135
Mortality			
All-cause	0.54	0.24 to 1.21	0.1369
IPF-related	0.36	0.14 to 0.95	0.0393
FVC			
Absolute decrease ≥10%	0.81	0.47 to 1.40	0.4533
Relative decrease ≥10%	0.90	0.59 to 1.38	0.6262
Absolute decrease ≥5%	0.97	0.68 to 1.40	0.8805
Relative decrease ≥5%	0.91	0.66 to 1.25	0.5548
Death or absolute FVC decrease ≥10%	0.71	0.48 to 1.07	0.1032
Death or 6MWD decrease ≥50 m	0.69	0.48 to 0.99	0.0465
Hospitalisation			
All-cause	0.58	0.35 to 0.94	0.0289
Respiratory-related‡	0.44	0.25 to 0.80	0.0063

Conclusion

- This post hoc analysis supports the hypothesis that statins may be beneficial in patients with IPF.

- Future studies should include prospective analyses of statin use in IPF and their potential use in combination with antifibrotic therapies.

Contents

- **Idiopathic pulmonary fibrosis (IPF)**
  - Monitoring of IPF
  - Treatment of IPF: pirfenidone, nintedanib, and statin
  - **Effect of atmospheric pollution on IPF**
- Sarcoidosis
- Systemic sclerosis-related ILD (SSc-ILD)
- Guideline
  - LAM diagnosis and management
- Summary

ORIGINAL ARTICLE

Role of atmospheric pollution on the natural history of idiopathic pulmonary fibrosis

Lucile Sesé,[1,2,3] Hilario Nunes,[2,3] Vincent Cottin,[4] Shreosi Sanyal,[1] Morgane Didier,[2,3] Zohra Carton,[2] Dominique Israel-Biet,[5] Bruno Crestani,[6] Jacques Cadranel,[7] Benoit Wallaert,[8] Abdellatif Tazi,[9] Bernard Maître,[10] Grégoire Prévot,[11] Sylvain Marchand-Adam,[12] Stéphanie Guillot-Dudoret,[13] Annelyse Nardi,[14] Sandra Dury,[15] Violaine Giraud,[16] Anne Gondouin,[17] Karine Juvin,[5] Raphael Borie,[6] Marie Wislez,[7] Dominique Valeyre,[2,3] Isabella Annesi-Maesano[1]

Thorax, 2018. 73(2): p. 145-150.

- The natural history of IPF has not been fully elucidated and remains unpredictable
- Air pollution: associated with poorly controlled asthma, altered lung function growth, increased incidence of COPD, AE COPD, respiratory-related mortality
- Significant association between AE and increased urban background levels of ozone and nitrogen dioxide close to the residential addresses in the previous 6 weeks in Korea (Eur Respir J 2014;43:1124–31)
- Aim of the study
  - ✓ To investigate the impact of major urban air pollutants, namely NO2, O3, PM10 and PM2.5 on AE, disease progression and death

Methods

- COFI (Cohorte Fibrose): a national multicenter prospective study on the natural history of IPF in France, December 2007 to December 2010, with 5-year follow-up
- Definition of AE: (1) worsening dyspnoea ≤1 month, (2) decrease in PaO2 >10 mm Hg compared with the results of the previous scheduled visit, (3) new opacities on HRCT (4) exclusion of other causes of worsening
- Definition of disease progression: (1) absolute decrease in FVC >10%pred or absolute decrease in DLco>15%pred compared with baseline values, (3) within >6 months and (3) exclusion of other causes of worsening.
- Air pollution data: French Regional Air Quality Agencies
  - Hourly concentrations of NO2, O3, PM10 and PM2.5 from rural and traffic ambient air monitoring stations, during the study period
  - Exposure period: 6 weeks preceding the date of AE, entire period form inclusion to the date of disease progression or death

Table 2 Short-term effect of air pollution on acute exacerbations

Exposure	Increase	HR (95% CI)	p Value
O_3	10 µg/m^3	1.47 (1.13 to 1.92)	0.005
NO_2	10 µg/m^3	0.92 (0.68 to 1.24)	0.584
PM_{10}	10 µg/m^3	0.80 (0.52 to 1.27)	0.347
$PM_{2.5}$	10 µg/m^3	1.29 (0.65 to 2.57)	0.463

Table 3 Association of cumulative air pollution exposure and disease progression

Exposure	Increase	HR (95% CI)	p Value
O_3	10 µg/m^3	1.06 (0.74 to 1.54)	0.72
NO_2	10 µg/m^3	1.09 (0.85 to 1.40)	0.52
PM_{10}	10 µg/m^3	1.03 (0.51 to 2.08)	0.92
$PM_{2.5}$	10 µg/m^3	1.89 (0.68 to 5.23)	0.22

Table 4 Association of cumulative air pollution exposure and mortality

Exposure	Increase	HR (95% CI)	p Value
O_3	10 µg/m^3	0.89 (0.66 to 1.18)	0.43
NO_2	10 µg/m^3	1.01 (0.79 to 1.29)	0.90
PM_{10}	10 µg/m^3	2.01 (1.07 to 3.77)	0.03
$PM_{2.5}$	10 µg/m^3	7.93 (2.93 to 21.33)	<0.001

Conclusion

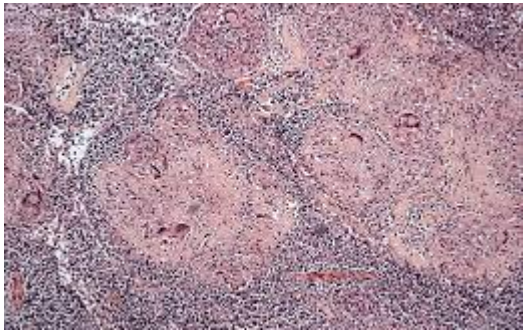
- Short-term exposure (6W) to increased levels of ozone is a risk factor for AE of IPF

- Long-term exposure to elevated levels of PM10 and PM2.5 is a risk factor for mortality in patients with IPF

Contents

Sarcoidosis

- A multisystem granulomatous disorder of unknown etiology
- Self limiting in most patients, but organ-threatening and life threatening in others
- Reported mortality rate: 1%-5%
- Rate of hospitalization and death from sarcoidosis has increased significantly during the past 30 years
- Sarcoidosis related mortality
  - ✓Respiratory failure: most common cause
  - ✓Neurologic and cardiac complications
- 희귀난치성질환 산정특례 대상



[Original Research **Diffuse Lung Disease**]

CHEST

Predictors of Mortality in Pulmonary Sarcoidosis

Gamze Kirkil, MD; Elyse E. Lower, MD; and Robert P. Baughman, MD

Chest, 2018. 153(1): p. 105-113

- Respiratory failure: most common cause of sarcoidosis-related death

- Prognostic factors for mortality and organ threatening disease
  - ✓ Older age
  - ✓ Presence of precapillary pul HTN
  - ✓ Impaired lung function (reduced VC)
  - ✓ Presence of pulmonary fibrosis

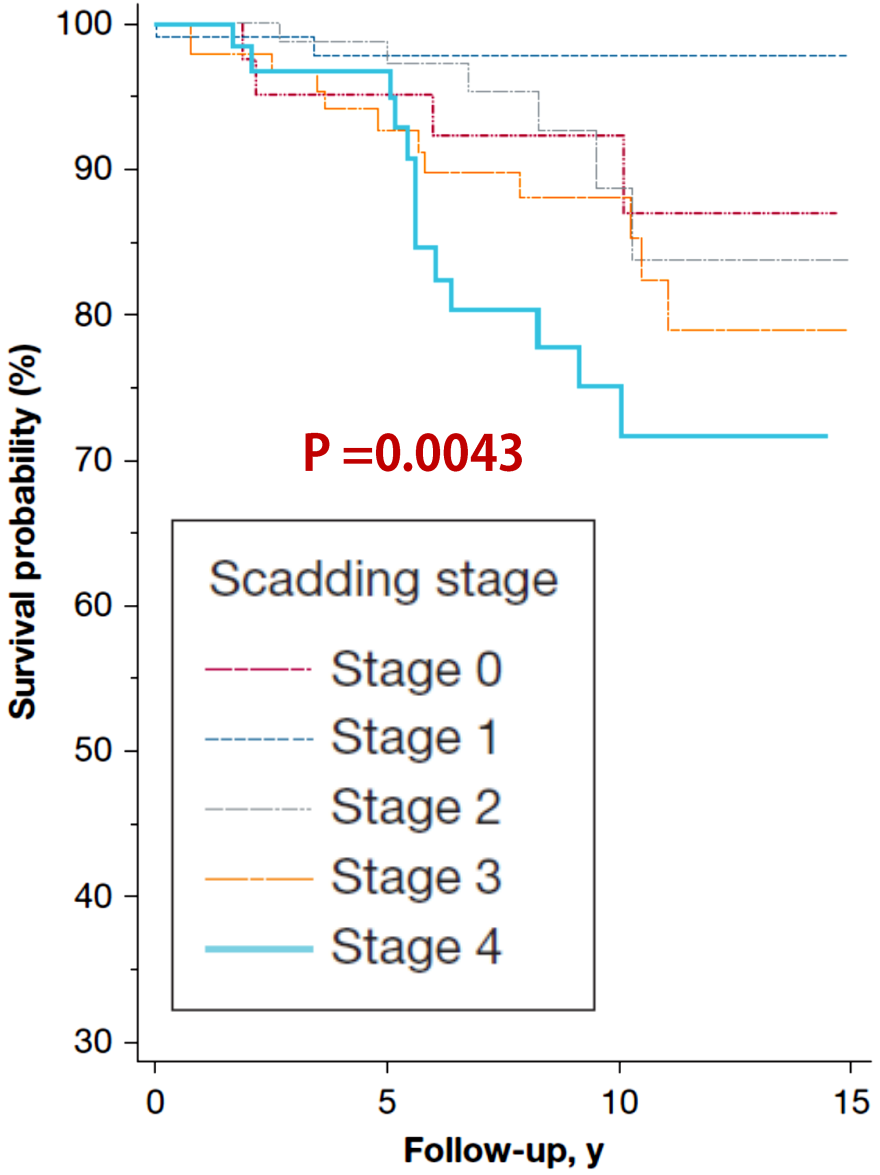
- Aim of the study
  - ✓ To assess the value of several factors in predicting respiratory death in pulmonary sarcoidosis in a large cohort of unselected patients with sarcoidosis

Methods

- Retrospective cohort study
- University of Cincinnati Sarcoidosis Clinic, between 2002 and 2008
- Minimum 8-year follow-up
- Variables
  - ✓ Age, sex, time of death, spirometry, DLCO, chest radiograph stage
  - ✓ Deaths: confirmed by using the National Death Index database and the Social Security Death Master File
  - ✓ Fibrotic extent on HRCT - minimal (< 20%) or moderate to severe (> 20%)
  - ✓ Presence of precapillary pul HTN
  - ✓ Gender-Age-Physiology (GAP) index / GAP stage were calculated
  - ✓ Walsh model criteria (CPI, HRCT fibrosis, HRCT estimate of pul HTN) for high vs low risk were calculated

overall mortality - 8%

Characteristic	Control Subjects (n = 414)	Died of Sarcoidosis (n = 38)	
Age, y	50 ± 9.9	54 ± 9.9[a]	
Race[b]			P=0.0139
White	292	19	
Black	117	19	
Asian	5	0	P=0.0178
Sex			
Female	289	24	
Male	125	14	
FEV_1, % predicted	81.0 ± 20.84	79.6 ± 20.17	
FVC, % predicted	83.1 ± 18.29	83.6 ± 16.95	
DLco, % predicted	75.3 ± 24.01	82.1 ± 21.76	
CPI	26 ± 18.0	21 ± 15.9	



Predictor of mortality by cox proportional hazard regression

Variable	Regression Coefficient b	SE	*P* Value	HR
Age	0.0471	0.0181	.009	ND
Fibrosis on HRCT scan > 20%	0.904	0.404	.026	2.80 (1.19-6.56)
Pulmonary hypertension	0.831	0.421	.048	8.96 (3.85-20.87)
Race (black vs white)	−0.505	0.342	.139	2.50 (1.28-4.88)
Walsh model, bad prognosis	0.627	0.394	.112	3.21 (1.61-6.4)
GAP stage 1 vs 2 or 3	0.575	0.541	.288	2.84 (1.00-8.01)

Conclusion

- Advanced age, extensive pulmonary fibrosis on HRCT, pulmonary hypertension were independent predictors of mortality

Contents

Mycophenolate Mofetil Versus Placebo for Systemic Sclerosis–Related Interstitial Lung Disease

An Analysis of Scleroderma Lung Studies I and II

Elizabeth R. Volkmann,[1] Donald P. Tashkin,[1] Ning Li,[1] Michael D. Roth,[1] Dinesh Khanna,[2] Anna-Maria Hoffmann-Vold,[3] Grace Kim,[1] Jonathan Goldin,[1] Philip J. Clements,[1] Daniel E. Furst,[1] and Robert M. Elashoff[1]

Arthritis Rheumatol, 2017. 69(7): p. 1451-1460.

- ILD accounts for the majority of deaths in patients with SSc
- Scleroderma Lung Study (SLS) **(N Engl J Med 2006;354:2655–66)**
  - ✓ Compare cyclophosphamide (CYC) with placebo
  - ✓ Favored CYC for FVC change, dyspnea, skin thickening, QOL etc
- Scleroderma Lung Study II (SLS II) study **(Lancet Respir Med 2016;4:708–19)**
  - ✓ Compare CYC (1Y) with MMF (2Ys) for SSc-ILD
  - ✓ Comparable efficacy in FVC change, and less adverse events with MMF
  - ✓ No placebo arm
- Aim of the study
  - ✓ To determine whether MMF improve FVC %pred over 2 ys compared with placebo
  - ✓ to compare secondary efficacy outcomes and the safety profiles

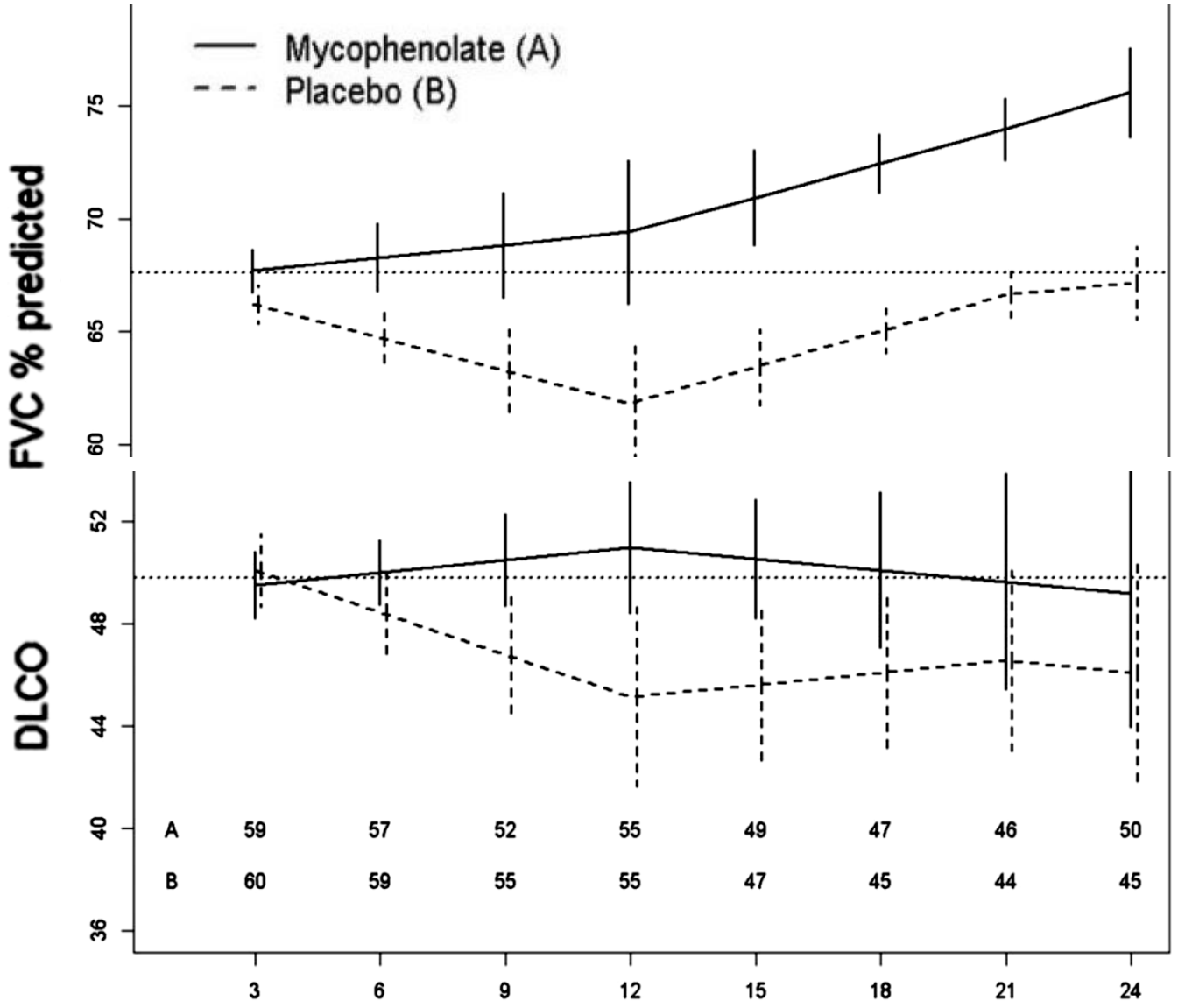
Methods

- All participants of the MMF arm of SLS II and the placebo arm of SLS I

- Common inclusion criteria of SLS I and SLS II
  - ✓ Age ≥18 years/ duration of disease ≤7 years
  - ✓ FVC 40–85% pred (SLS I) or 40–80% pred (SLS II)
  - ✓ DLCO ≥ 40% pred (or 30–39% pred if significant pulmonary HTN (-))
  - ✓ Evidence of any ground glass opacity on HRCT: “active” disease

- Primary outcome
  - ✓ FVC % pred

- Secondary outcomes
  - ✓ DLCO %pred
  - ✓ Transition Dyspnea Index (TDI)
  - ✓ modified Rodnan skin thickness score (MRSS)
  - ✓ Safety



- **Treatment with MMF was also associated with**
  - ✓ **Improved MRSS over 24 M (p < 0.0001)**
  - ✓ **Improvement in dyspnea compared as measured by the TDI (p = 0.0112)**

Conclusion

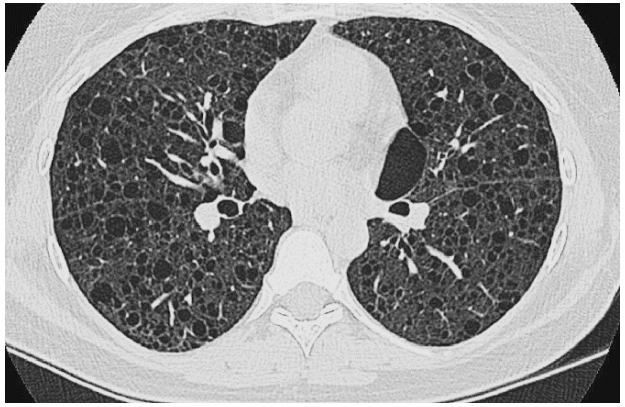
- Treatment with MMF is associated with improvements in the % predicted FVC, % predicted DLCO, TDI, and MRSS, compared with placebo in SSc-ILD

- The MMF treatment effect was greatest within the first 12 months but persisted throughout the 2-year trial

Contents

Lymphangioleiomyomatosis (LAM)

- Uncommon, progressive and often fatal lung disease of young women characterized by smooth muscle cell (LAM cell) infiltration and cystic destruction of lung tissue



- Medial survival: 8.5-29 years

- MILES trial (NEJM 2011;364:1595)
  - ✓Sirolimus: reduced decline in FEV1

    covered by National health insurance in Korea

- 희귀난치성질환 산정특례 대상

AMERICAN THORACIC SOCIETY DOCUMENTS

Official American Thoracic Society/Japanese Respiratory Society Clinical Practice Guidelines: Lymphangioleiomyomatosis Diagnosis and Management

Am J Respir Crit Care Med, 2016.194(6): p. 748

Context	Recommendation	Strength of Recommendation	Confidence in Estimates of Effect
Treatment with mTOR inhibitors YES	For patients with LAM with abnormal/declining lung function, we recommend treatment with sirolimus rather than observation.	Strong	Moderate
	For selected patients with LAM with problematic chylous effusions, we suggest treatment with sirolimus before invasive management.	Conditional	Very low
Treatment with doxycycline	We suggest NOT using doxycycline as treatment for LAM.	Conditional	Low
Treatment with hormonal therapy No	We suggest NOT using hormonal therapy as treatment for LAM. ("Hormonal therapy" includes the progestins, GnRH agonists, selective estrogen receptor modulators like tamoxifen, and oophorectomy.)	Conditional	Very low
VEGF-D as a diagnostic test YES	For patients whose CT scan shows cystic abnormalities characteristic of LAM but have no confirmatory clinical or extrapulmonary radiologic features of LAM, we recommend VEGF-D testing before consideration of proceeding to diagnostic lung biopsy. ("Confirmatory features of LAM" include tuberous sclerosis complex, angiomyolipomas, chylous pleural effusions or ascites, and cystic lymphangioleiomyomas.)	Strong	Moderate

AMERICAN THORACIC SOCIETY DOCUMENTS

Lymphangioleiomyomatosis Diagnosis and Management: High-Resolution Chest Computed Tomography, Transbronchial Lung Biopsy, and Pleural Disease Management

An Official American Thoracic Society/Japanese Respiratory Society Clinical Practice Guideline

Am J Respir Crit Care Med, 2017. 196(10): p. 1337-1348.

Context	Recommendation	Strength of Recommendation	Confidence in Estimates of Effect
HRCT as sole confirmatory feature for LAM diagnosis **No**	For patients who have cystic changes on HRCT of the chest that are characteristic of LAM, but have no additional confirmatory features of LAM (i.e., clinical, radiologic, or serologic), we suggest NOT using the HRCT features in isolation to make a clinical diagnosis of LAM.	Conditional	Low
Transbronchial lung biopsy for histopathological diagnosis of LAM **YES**	When a definitive diagnosis is required in patients who have parenchymal cysts on HRCT that are characteristic of LAM, but no additional confirmatory features of LAM (i.e., clinical, radiologic, or serologic), we suggest a diagnostic approach that includes transbronchial lung biopsy before a surgical lung biopsy.	Conditional	Very low
Pleurodesis after a sentinel pneumothorax to prevent recurrence **YES**	We suggest that patients with LAM be offered ipsilateral pleurodesis after their initial pneumothorax rather than waiting for a recurrent pneumothorax before intervening with a pleural symphysis procedure.	Conditional	Very low
Pleurodesis as a contraindication to future lung transplant **No**	We suggest that previous unilateral or bilateral pleural procedures (i.e., pleurodesis or pleurectomy) NOT be considered a contraindication to lung transplantation in patients with LAM.	Conditional	Very low

Contents

Summary

- **Idiopathic pulmonary fibrosis (IPF)**
  - Monitoring of IPF
    - ✓ Emphysema extent ≥ 15%: associated with reduced FVC decline
    - ✓ Serial FVC measurements may not capture IPF progression in CPFE patients
  - Treatment of IPF
    - ✓ Pirfenidone reduces the risk of respiratory related hospitalization
    - ✓ Patients with possible UIP on HRCT have similar disease progression and response to nintedanib as do patients with definite UIP on HRCT and/or confirmation of UIP by biopsy
    - ✓ Nintedanib slowed the decline in lung function independent of the degree of FVC impairment at baseline
    - ✓ Treatment with nintedanib may reduce the risk of developing an AE
    - ✓ Treatment with nintedanib and add-on pirfenidone for 12 weeks had a manageable safety and tolerability profile
    - ✓ Statins may be beneficial in patients with IPF.

Summary

- **Idiopathic pulmonary fibrosis (IPF)**
  - Effect of atmospheric pollution on IPF
    - ✓ Short-term exposure (6W) to increased levels of ozone is a risk factor for AE of IPF
    - ✓ Long-term exposure to elevated levels of PM10 and PM2.5 is a risk factor for mortality in patients with IPF

- **Sarcoidosis**
  - ✓ Advanced age, extensive pulmonary fibrosis on HRCT, pulmonary hypertension were independent predictors of mortality

Summary

- **Systemic sclerosis related ILD**
  - Treatment with MMF is associated with improvements in % pred FVC, % pred DLCO, TDI, and MRSS, compared with placebo
  - The MMF treatment effect was greatest within the first 12 months but persisted throughout the 2-year trial

- **Lymphangioleiomyomatosis (conditional recommendation)**
  - Don’t use HRCT as sole confirmatory features for LAM diagnosis
  - Use TBLB before a surgical lung biopsy
  - Offer patients pleurodesis after initial pneumothorax
  - Don’t consider pleurodesis as a contraindication to future lung TPL

Thank you for your attention