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Idiopathic Pulmonary Fibrosis : Current Management and Future Perspectives

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Contents

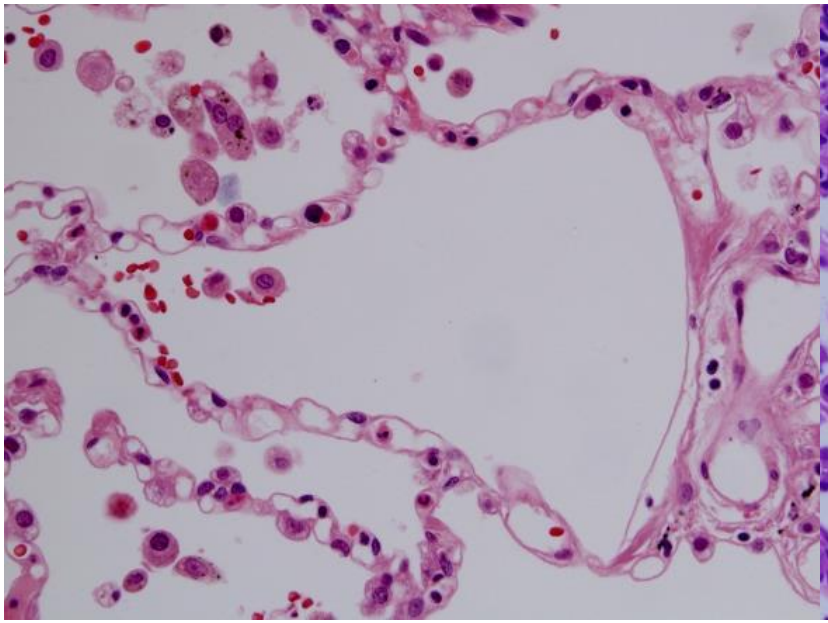
- Introduction
- Pharmacological treatment
  - ✓ Disease modifier - antifibrotics
  - ✓ Symptom control
- Non-pharmacological treatment
- Summary

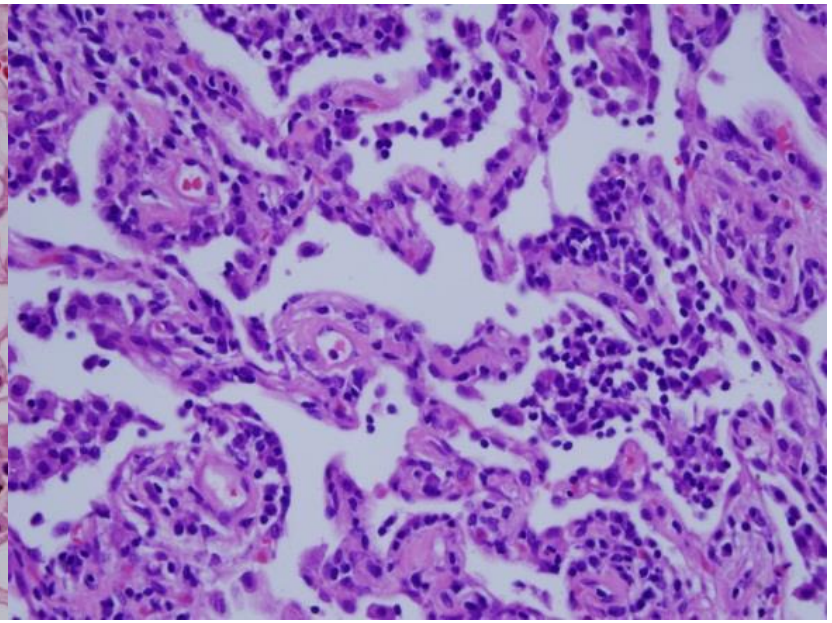
Contents

Interstitial lung disease

- A large number of conditions involving
  - Parenchyma of the lung- the alveoli
  - Alveolar epithelium
  - Capillary endothelium
  - Spaces between these structures, as well as the perivascular and lymphatic tissues

→ except malignant disease and infection



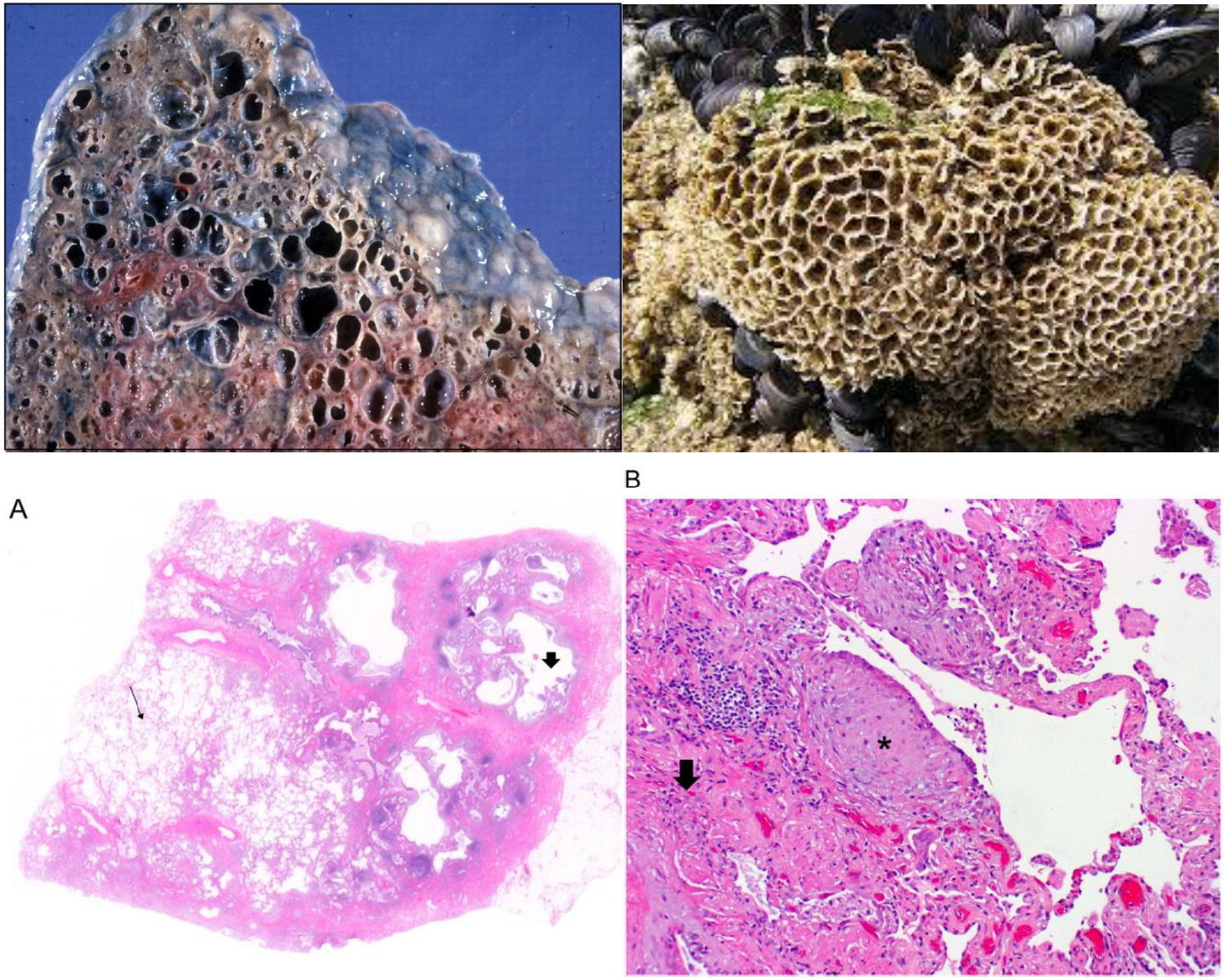


Idiopathic pulmonary fibrosis

- Most common form of idiopathic interstitial pneumonias
- A specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause
- Limited to the lungs, and associated with the histopathologic and/or radiologic pattern of UIP
- Incidence and prevalence
  - 2006-2012 US Incidence: 14.6 cases per 100,000 persons/year
    Prevalence : 125.2 cases per 100,000 population
- Risk factors: smoking, occupational exposure

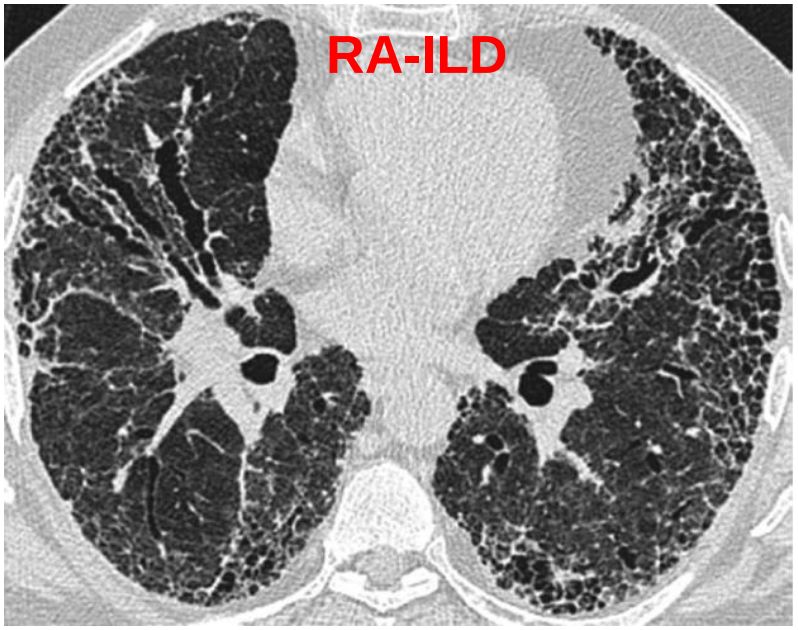
Clinical Handbook of Interstitial Lung disease, 2018

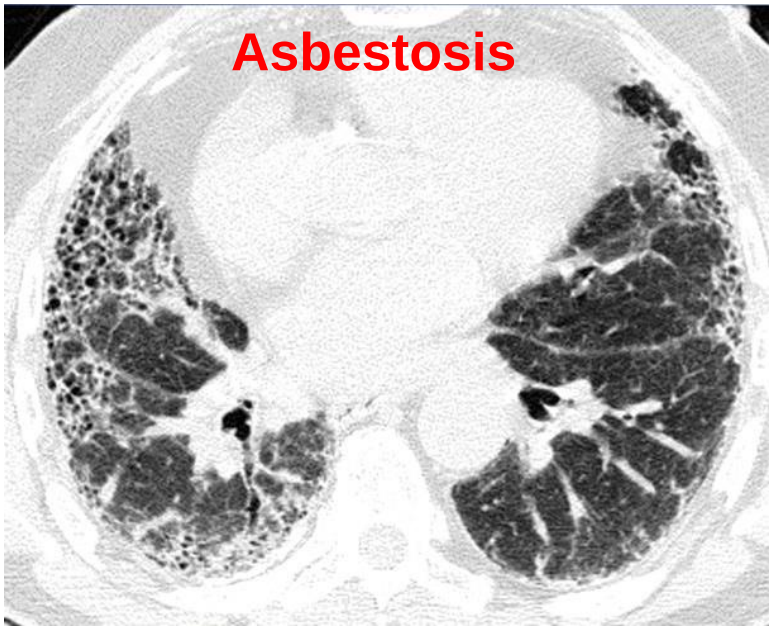
Histopathology of UIP pattern

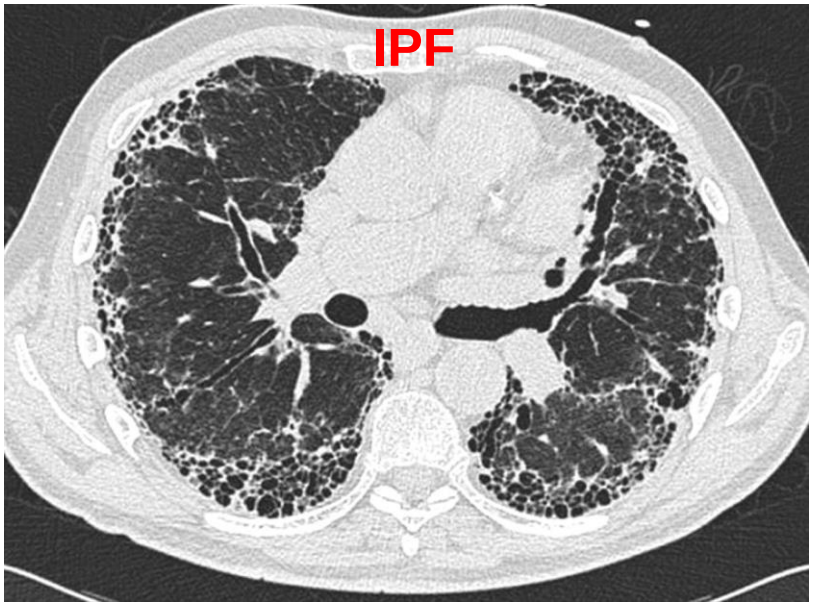


Am J Respir Crit Care Med. 2011;183(6):788-824

UIP pattern in HRCTs of different diseases







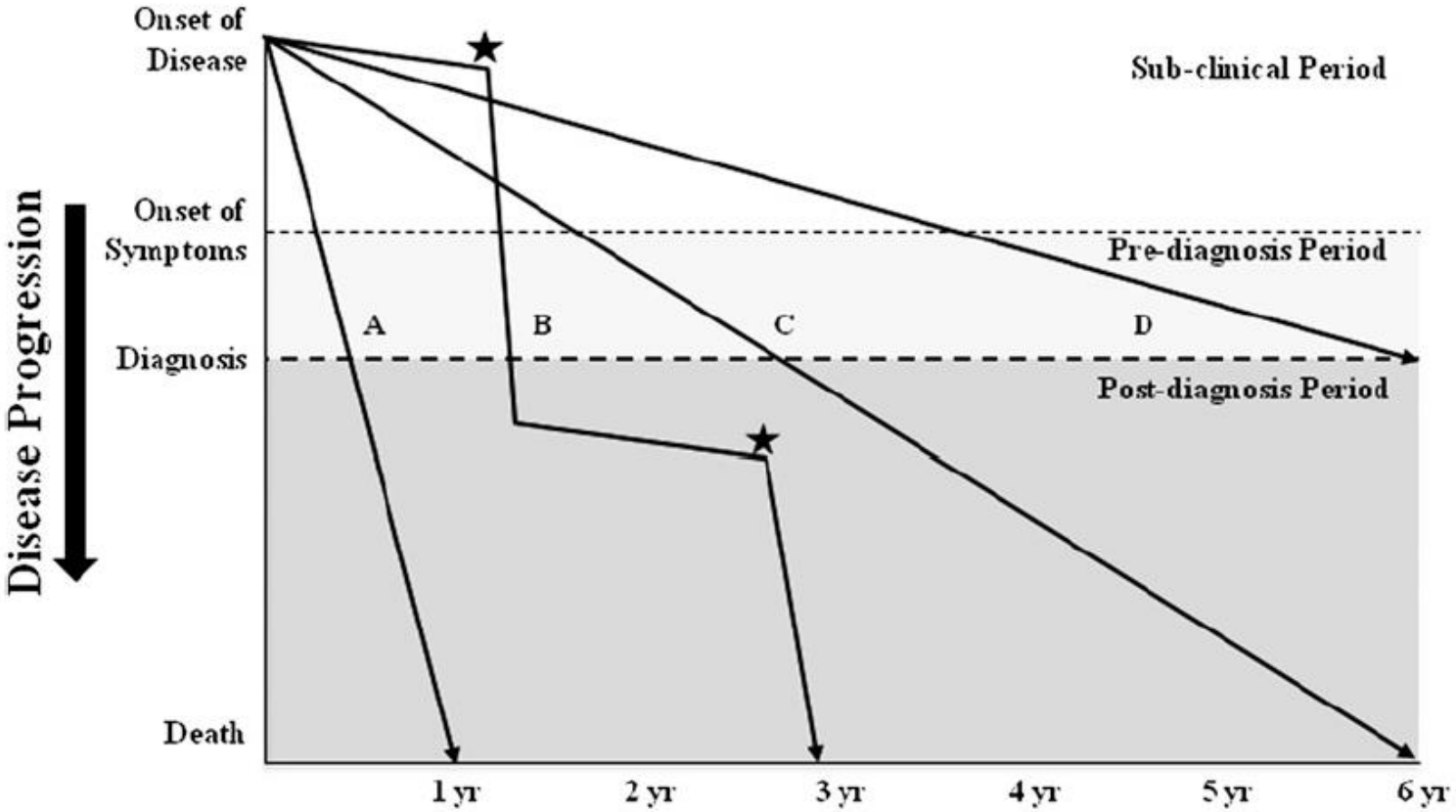
- Differential diagnosis of UIP pattern

  ✓ CTD - ILD (esp. RA)
  ✓ Chronic hypersensitivity pneumonitis
  ✓ Amiodarone pulmonary toxicity
  ✓ Asbestosis
  ✓ (Fibrosing NSIP → UIP pattern)

UIP ≠ Idiopathic pulmonary fibrosis!

Clinical presentation of IPF

- Male > female, older age (typically over the age of 50)
- Insidious onset of symptoms: DOE, cough
- Heterogeneous disease course
- Poor prognosis: previously, median survival of 2-3 years after dx



Ley B. et al. AJRCCM 2011

Contents

Drugs used for patients with IPF

1) Drugs for slowing the progression of IPF

→ Antifibrotics

- Pirfenidone, nintedanib
- New drugs

2) Drugs for symptom control

→ Cough, dyspnea

Drugs used for patients with IPF

1) Drugs for slowing the progression of IPF

→ Antifibrotics

- Pirfenidone, nintedanib
- New drugs

2) Drugs for symptom control

→ Cough, dyspnea

Guideline for treatment of IPF

Agent	2011 Guideline	2015 Guideline
New and revised recommendations		
Anticoagulation (warfarin)	Conditional recommendation against use‡	Strong recommendation against use*
Combination prednisone + azathioprine + *N*-acetylcysteine	Conditional recommendation against use†	Strong recommendation against use†
Selective endothelin receptor antagonist (ambrisentan)	Not addressed	Strong recommendation against use†
Imatinib, a tyrosine kinase inhibitor with one target	Not addressed	Strong recommendation against use*
Nintedanib, a tyrosine kinase inhibitor with multiple targets	Not addressed	Conditional recommendation for use*
Pirfenidone	Conditional recommendation against use†	Conditional recommendation for use*
Dual endothelin receptor antagonists (macitentan, bosentan)	Strong recommendation against use*	Conditional recommendation against use†
Phosphodiesterase-5 inhibitor (Sildenafil)	Not addressed	Conditional recommendation against use*
Unchanged recommendations		
Antiacid therapy	Conditional recommendation for use‡	Conditional recommendation for use‡
N-acetylcysteine monotherapy	Conditional recommendation against use†	Conditional recommendation against use†
Antipulmonary hypertension therapy for idiopathic pulmonary fibrosis-associated pulmonary hypertension	Conditional recommendation against use‡	Reassessment of the previous recommendation was deferred
Lung transplantation: single vs. bilateral lung transplantation	Not addressed	Formulation of a recommendation for single vs. bilateral lung transplantation was deferred

2011

Pharmacological Therapies

The committee did not find sufficient evidence to support the use of any specific pharmacologic therapy for patients with IPF.

2015

The recommendation *for* the use of the following agents for the treatment of IPF is conditional:

Nintedanib, Pirfenidone

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

Talmadge E. K
Socorro Ca
Ian Glaspole, M.B., B.
Peter M. Hopkin
David J. Lederer,
Steven A. Sahn,
and Paul

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 29, 2014 VOL. 370 NO. 22

Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

Luca Riche
Kevin K.
David M. H
Andrew G. N
Michèle
Rc

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

A New Hope for Idiopathic Pulmonary Fibrosis

Gary M. Hunninghake, M.D., M.P.H.

Pirfenidone

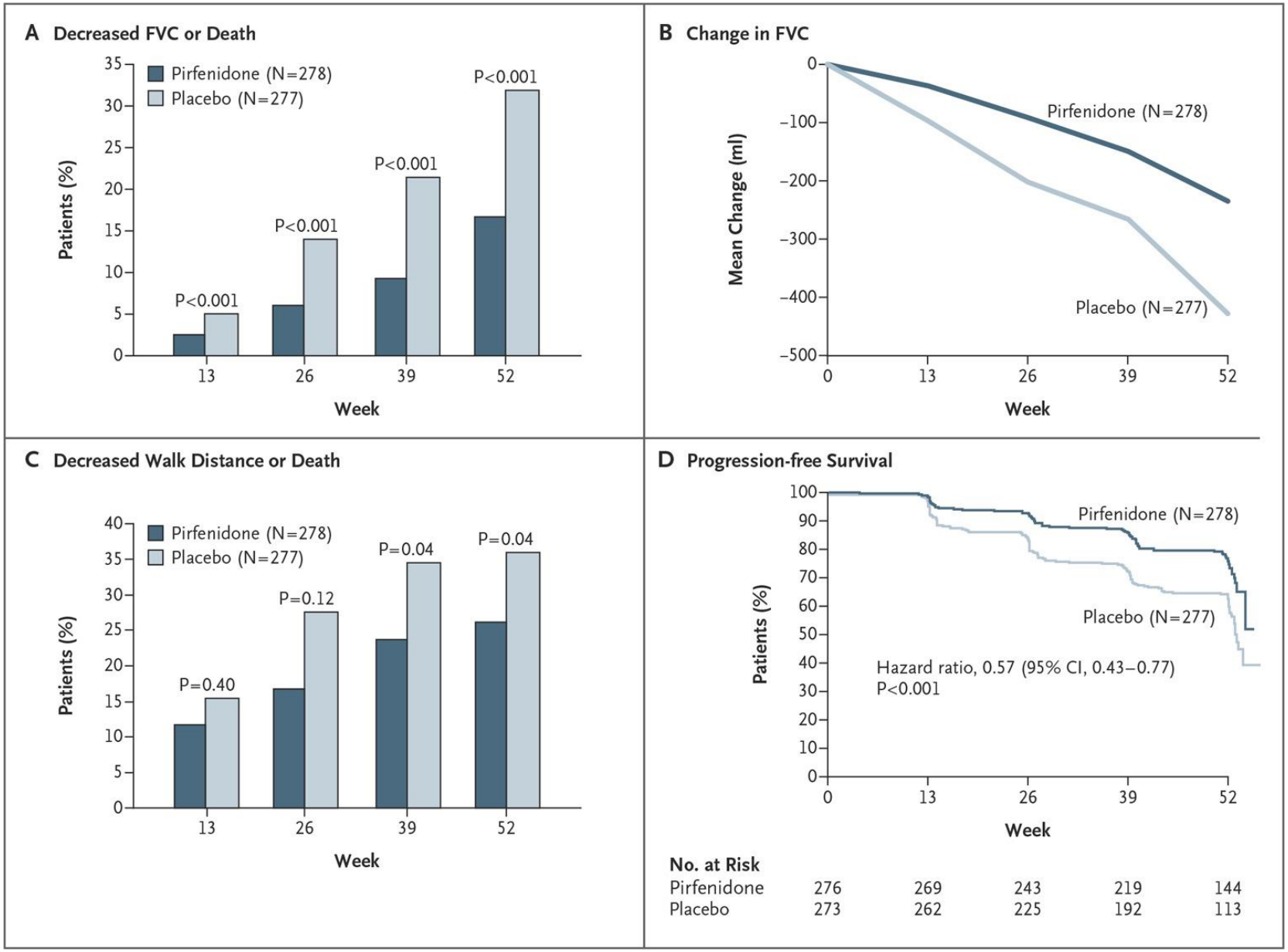
- Antifibrotic, anti-inflammatory, antioxidant effects

- 4 phase III RCTs
  - ✓ Japan: 275patients, 52 wks → Approved in Japan
    - primary endpoint: FVC decline
    - 1800mg group (-0.09 L) vs Placebo (-0.16 L) p=0.0416
  - ✓ CAPACITY trial (004/006): 435/344 patients, 72 wks → Approved in Europe (2011)
    - primary endpoint: change in % predicted FVC
    - 004 only met the primary endpoint
    - → 2403mg group (−8·0%) vs placebo (−12·4%) p =0.001
  - ✓ ASCEND trial: 555 patients, 52 weeks → Approved in U.S (2014)
    - primary endpoint: change in FVC or death
    - Reduction of 47.9% in the proportion of patients who had an absolute decline of ≥10% in the % of the predicted FVC or who died (p<0.001)
    - Deduction of 43% of relative risk of death or disease progression (p<0.001)

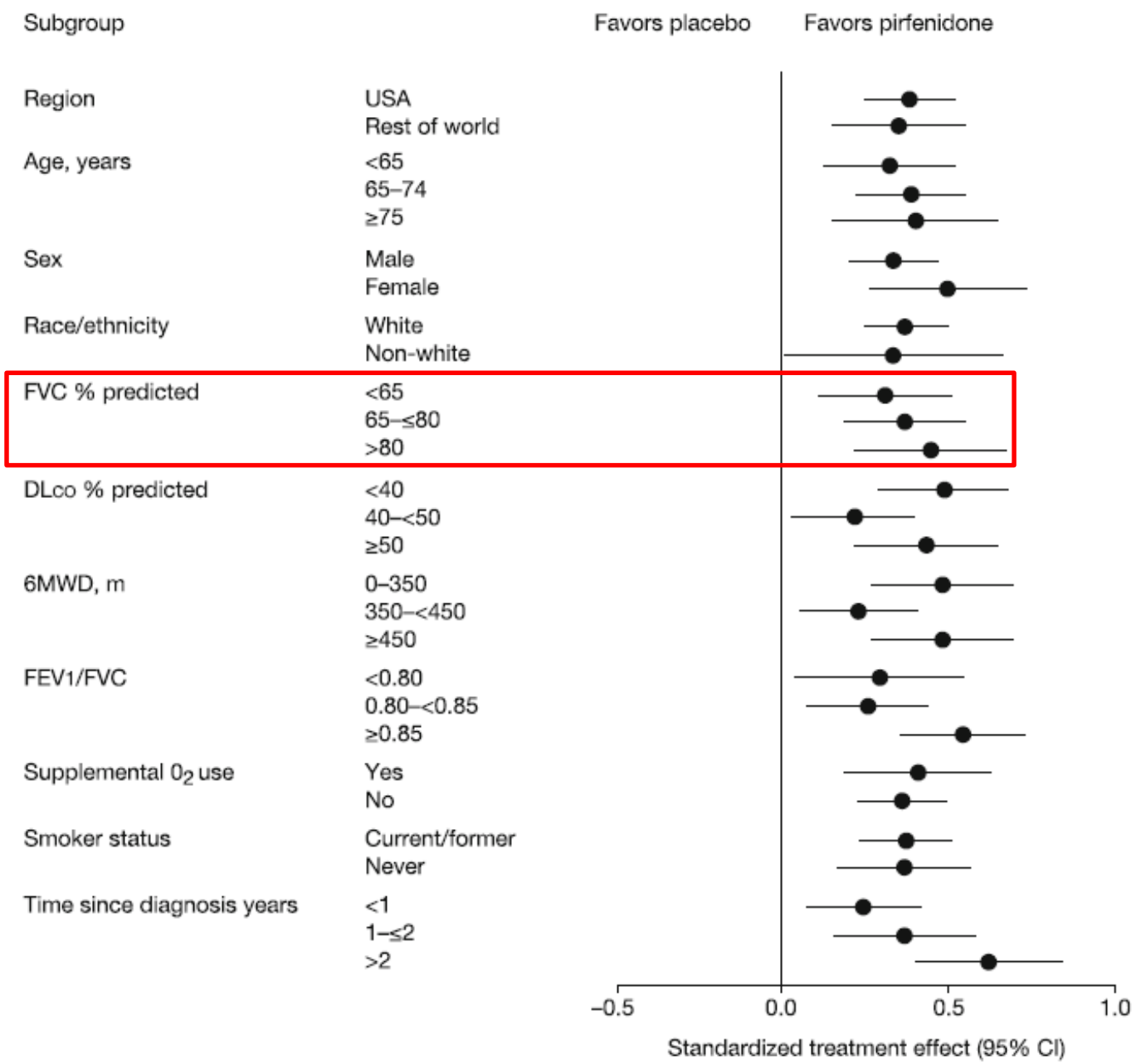
  → Pooled analysis : reduced the risk of death at 1Y by 48% (p<0.01)
  lowered the risk of respiratory-related hospitalization (p=0.001)
  slowed the worsening of dyspnea in patients with GAP II/III or FVC <80%

- RECAP trial: observational study - long term safety and efficacy

Primary and key secondary outcomes



Pooled data from 3 RCTs



Side effect of pirfenidone in RCTs

Side Effect	CAPACITY 004/006 Trials[5]		ASCEND Trial[6]	
	Pirfenidone (n=345)	Placebo (n=347)	Pirfenidone (n= 278)	Placebo (n=277)
Nausea	125 (36%)	60 (17%)	100 (36%)	37 (13.4%)
Dyspepsia	66 (19%)	26 (7%)	49 (17.6%)	17 (6.1%)
Dizziness	63 (18%)	35 (10%)	49 (17.6%)	36 (13%)
Vomiting	47 (14%)	15 (4%)	36 (12.9%)	24 (8.7%)
Rash/photosensitivity	153 (44%)	46 (14%)	78 (28.1%)	24 (8.7%)
Anorexia	37 (11%)	13 (4%)	44 (15.8%)	18 (6.5%)
Arthralgia	36 (10%)	24 (7%)	–	–
Weight reduction	28 (8%)	12 (3%)	35 (12.6%)	22 (7.9%)
Insomnia	34 (10%)	23 (7%)	31 (11.2%)	18 (6.5%)
Cough	–	–	70 (25.2%)	82 (29.6%)

Drug, Healthcare and Patient Safety 2020:12

Side effect of pirfenidone in Korean patients

FVC<50% predicted or
DLCO <35% predicted

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
Cough	21 (9.6)	2 (5.1)	19 (10.6)	0.383
Pneumonia	19 (8.7)	6 (15.4)	13 (7.2)	0.117
Dyspnea	18 (8.2)	7 (18.0)	11 (6.1)	0.023
Progression of IPF[a]	16 (7.3)	6 (15.4)	10 (5.6)	0.044
Productive cough	15 (6.9)	4 (10.3)	11 (6.1)	0.314
Constipation	13 (5.9)	3 (7.7)	10 (5.6)	0.707
Fatigue	11 (5.0)	4 (10.3)	7 (3.9)	0.111
Asthenia	10 (4.6)	1 (2.6)	9 (5.0)	1.000
Dizziness	10 (4.6)	1 (2.6)	10 (5.6)	0.694
Upper respiratory tract infection	9 (4.1)	0 (0.0)	9 (5.0)	0.367
Dyspepsia	8 (3.7)	2 (5.1)	6 (3.3)	0.635
Diarrhea	8 (3.7)	2 (5.1)	6 (3.3)	0.635
Abnormal liver function test	8 (3.7)	1 (2.6)	7 (3.9)	1.000

Reasons for discontinuation in Korean patients

Reasons for discontinuation	Total	Advanced	Non-advanced	*p* value
Total patients, *n*	219	39	180	
Discontinued patients	119 (54.3)	29 (74.4)	90 (50.0)	0.006
Adverse event	50 (22.8)	8 (20.5)	42 (23.3)	0.704
Decreased appetite	10 (4.6)	1 (2.6)	9 (5.0)	1.000
Photosensitivity reaction	9 (4.1)	1 (2.6)	8 (4.4)	1.000
Rash	6 (2.7)	0 (0.0)	6 (3.3)	0.594
Cough	4 (1.8)	0 (0.0)	4 (2.2)	1.000
Dyspnea	4 (1.8)	1 (2.6)	3 (1.7)	0.546
Epigastric discomfort	4 (1.8)	1 (2.6)	3 (1.7)	0.546
Nausea	4 (1.8)	0 (0.0)	4 (2.2)	1.000
Pneumonia	4 (1.8)	0 (0.0)	4 (2.2)	1.000
Abdominal pain	2 (0.9)	0 (0.0)	2 (1.1)	1.000
Dizziness	2 (0.9)	0 (0.0)	2 (1.1)	1.000
Myocardial infarction	2 (0.9)	1 (2.6)	1 (0.6)	0.325
Pruritus	2 (0.9)	0 (0.0)	2 (1.1)	1.000
Pyrexia	2 (0.9)	1 (2.6)	1 (0.6)	0.325

Adv Ther (2020) 37:2303–2316

Pirfenidone in Korea

- 현재 국내에서 보험으로 처방 가능
- 급여기준

FVC ≥ 50%
And
DLCo ≥ 35%
And
6MWT ≥ 150m

1) FVC≤ 90% or DLCO ≤ 80%

2) FVC > 90% and DLCO > 80%
인 경우 아래 중 두가지 이상 해당
가) 연간 FVC 10% 또는 200ml 이상 감소
나) 임상증상 악화
다) 흉부영상 악화 소견

Management of side effect

- Dose titration
  - ✓ 200mg tablet x 3/day → 400mg x 3/day → 600mg x 3/day
  - ✓ 부작용에 따라 약물 중단 또는 감량
- GI intolerance
  - 식사 중 또는 식사 직후에 약물 복용
  - Prokinetics, antacid
- Skin rash
  - ✓ Antihistamine, topical steroid
- Photosensitivity
  - ✓ Sunscreen (SPF-50), hat, long sleeves, if severe → steroid or siler sulfadiazine

Management of side effect

- If AST and ALT elevations are >3 to ⩽5 ULN without symptoms or hyperbilirubinaemia, reduce the dose or interrupt until values return to normal

- If AST and ALT elevations are >3 to ⩽5 ULN and accompanied by hyperbilirubinaemia, permanently discontinue pirfenidone

- If AST or ALT are >5 ULN, permanently discontinue pirfenidone

Nintedanib (Ofev)

- An intracellular inhibitor of multiple tyrosine kinase receptors including VEGFR, FGFR, and PDGFR

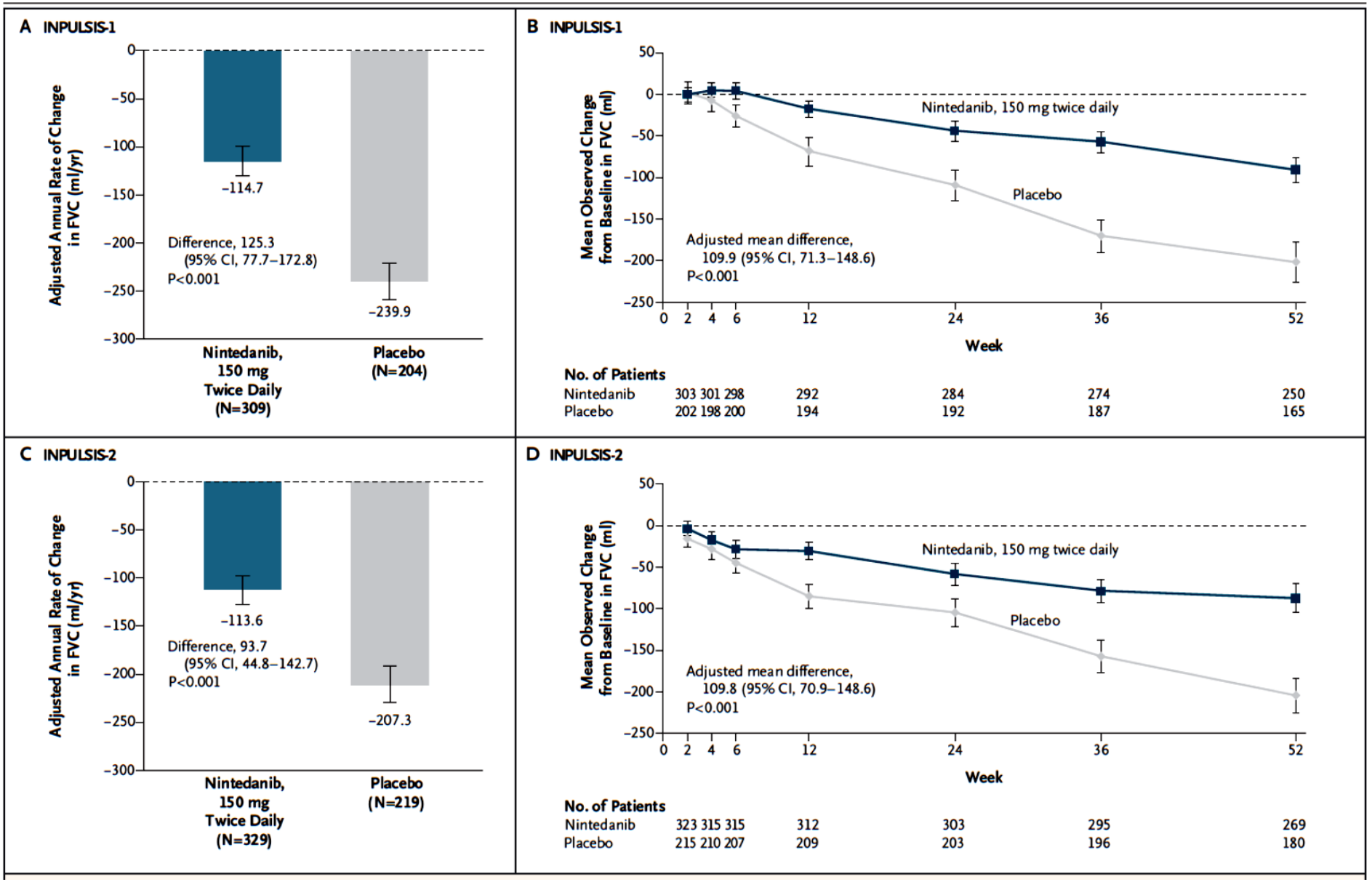
- Originally developed an anti-angiogenetic anti-cancer agent

- 3 RCTs
  - ✓ TOMORROW trial: phase II
  - ✓ INPULSIS I/II trial: phase III (52wks)
    - Primary endpoint: Adjusted annual rate of change in FVC
    - Nintedanib (-114.7 ml) vs placebo (-239.9 ml) 95% CI = 77.7–172.8

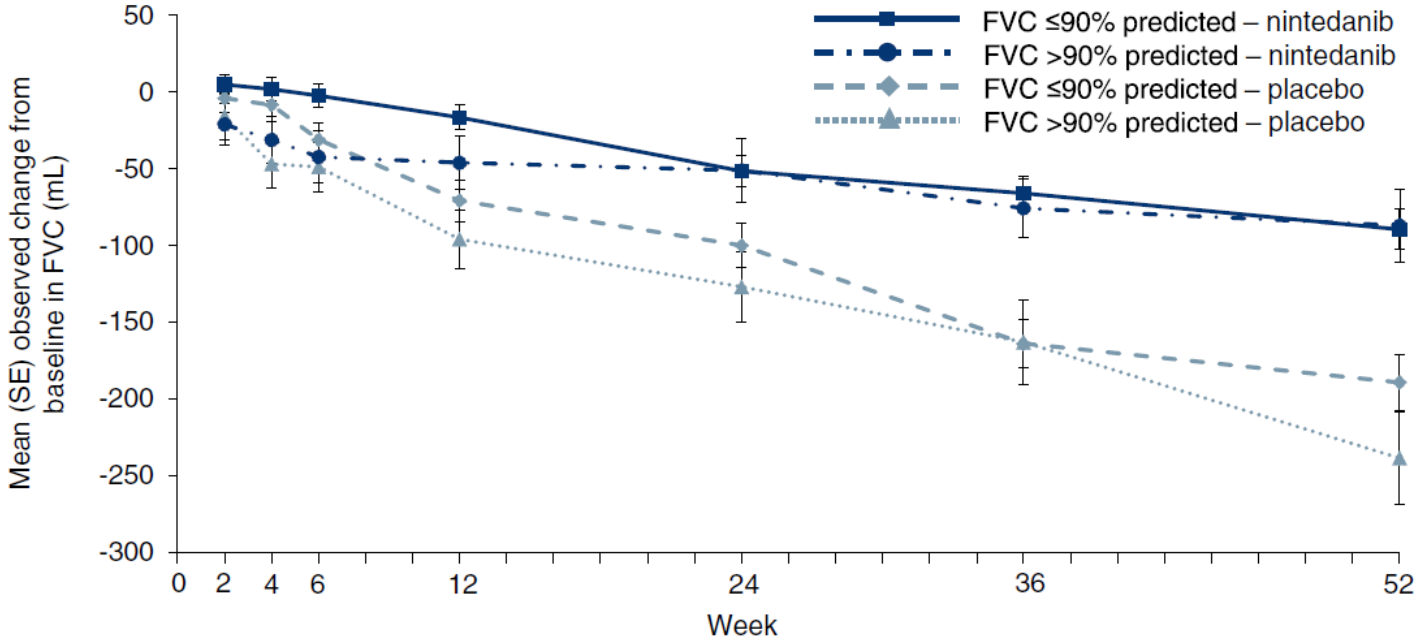
  ➔ *Post-hoc* analysis: reduction in the risk of on-treatment mortality
  reduction of 47% in the time of the first AE (p = 0.0047)

- INPULSIS-ON trial: long term safety and efficacy

INPULSIS

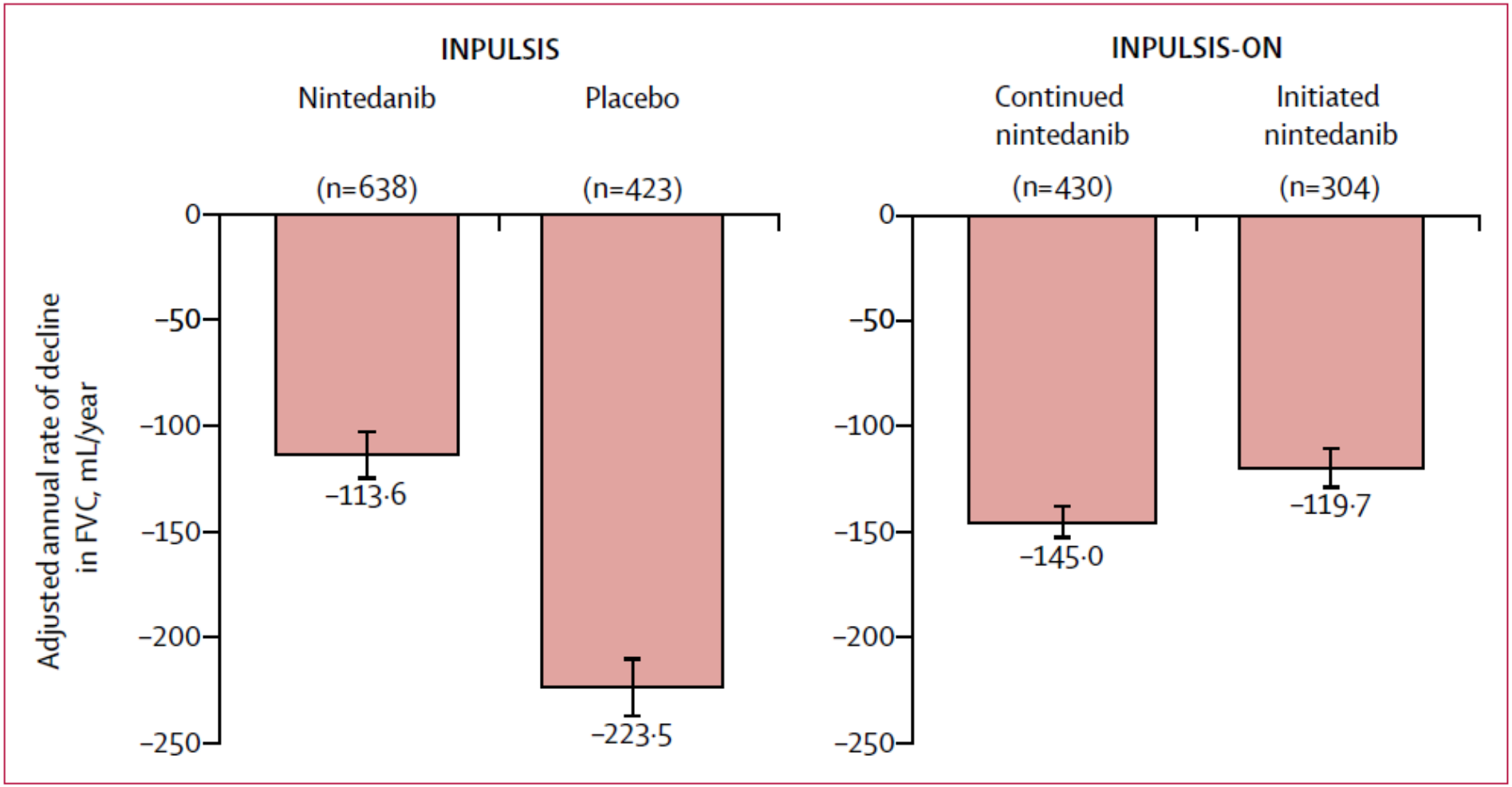

A INPULSIS-1
Adjusted Annual Rate of Change in FVC (ml/yr)
0
−50
−100
−150
−200
−250
−300
−114.7
−239.9
Difference, 125.3
(95% CI, 77.7–172.8)
P<0.001
Nintedanib, 150 mg Twice Daily (N=309)
Placebo (N=204)
B INPULSIS-1
Mean Observed Change from Baseline in FVC (ml)
50
0
−50
−100
−150
−200
−250
Nintedanib, 150 mg twice daily
Placebo
Adjusted mean difference,
109.9 (95% CI, 71.3–148.6)
P<0.001
0 2 4 6 12 24 36 52
Week
No. of Patients
Nintedanib 303 301 298 292 284 274 250
Placebo 202 198 200 194 192 187 165
C INPULSIS-2
Adjusted Annual Rate of Change in FVC (ml/yr)
0
−50
−100
−150
−200
−250
−300
−113.6
−207.3
Difference, 93.7
(95% CI, 44.8–142.7)
P<0.001
Nintedanib, 150 mg Twice Daily (N=329)
Placebo (N=219)
D INPULSIS-2
Mean Observed Change from Baseline in FVC (ml)
50
0
−50
−100
−150
−200
−250
Nintedanib, 150 mg twice daily
Placebo
Adjusted mean difference,
109.8 (95% CI, 70.9–148.6)
P<0.001
0 2 4 6 12 24 36 52
Week
No. of Patients
Nintedanib 323 315 315 312 303 295 269
Placebo 215 210 207 209 203 196 180

INPULSIS



n							
FVC ≤90% predicted – nintedanib	463	455	455	445	436	423	383
FVC >90% predicted – nintedanib	163	161	158	159	151	146	136
FVC ≤90% predicted – placebo	309	305	300	299	292	281	249
FVC >90% predicted – placebo	108	103	107	104	103	102	96

INPULSIS-ON


INPULSIS
Nintedanib
Placebo
(n=638)
(n=423)
INPULSIS-ON
Continued nintedanib
Initiated nintedanib
(n=430)
(n=304)
Adjusted annual rate of decline in FVC, mL/year
0
−50
−100
−150
−200
−250
−113·6
−223·5
−145·0
−119·7

Side effect of Nintedanib

Event	INPULSIS-1		INPULSIS-2	
	Nintedanib (N = 309)	Placebo (N = 204)	Nintedanib (N = 329)	Placebo (N = 219)
	number of patients (percent)			
Most frequent adverse events†				
Diarrhea	190 (61.5)	38 (18.6)	208 (63.2)	40 (18.3)
Nausea	70 (22.7)	12 (5.9)	86 (26.1)	16 (7.3)
Nasopharyngitis	39 (12.6)	34 (16.7)	48 (14.6)	34 (15.5)
Cough	47 (15.2)	26 (12.7)	38 (11.6)	31 (14.2)
Progression of idiopathic pulmonary fibrosis*	31 (10.0)	21 (10.3)	33 (10.0)	40 (18.3)
Bronchitis	36 (11.7)	28 (13.7)	31 (9.4)	17 (7.8)
Upper respiratory tract infection	28 (9.1)	18 (8.8)	30 (9.1)	24 (11.0)
Dyspnea	22 (7.1)	23 (11.3)	27 (8.2)	25 (11.4)
Decreased appetite	26 (8.4)	14 (6.9)	42 (12.8)	10 (4.6)
Vomiting	40 (12.9)	4 (2.0)	34 (10.3)	7 (3.2)
Weight loss	25 (8.1)	13 (6.4)	37 (11.2)	2 (0.9)
Adverse events leading to treatment discontinuation§	65 (21.0)	22 (10.8)	58 (17.6)	33 (15.1)
Gastrointestinal disorders	26 (8.4)	3 (1.5)	21 (6.4)	2 (0.9)
Respiratory, thoracic, and mediastinal disorders	12 (3.9)	10 (4.9)	8 (2.4)	18 (8.2)
Investigation results¶	10 (3.2)	1 (0.5)	8 (2.4)	1 (0.5)
Cardiac disorders	5 (1.6)	4 (2.0)	2 (0.6)	3 (1.4)
General disorders and conditions involving site of study-drug administration‖	8 (2.6)	3 (1.5)	2 (0.6)	1 (0.5)

N Engl J Med 2014;370:2071-82.

Nintedanib in Korea

- 현재 국내에서 보험으로 처방 불가능

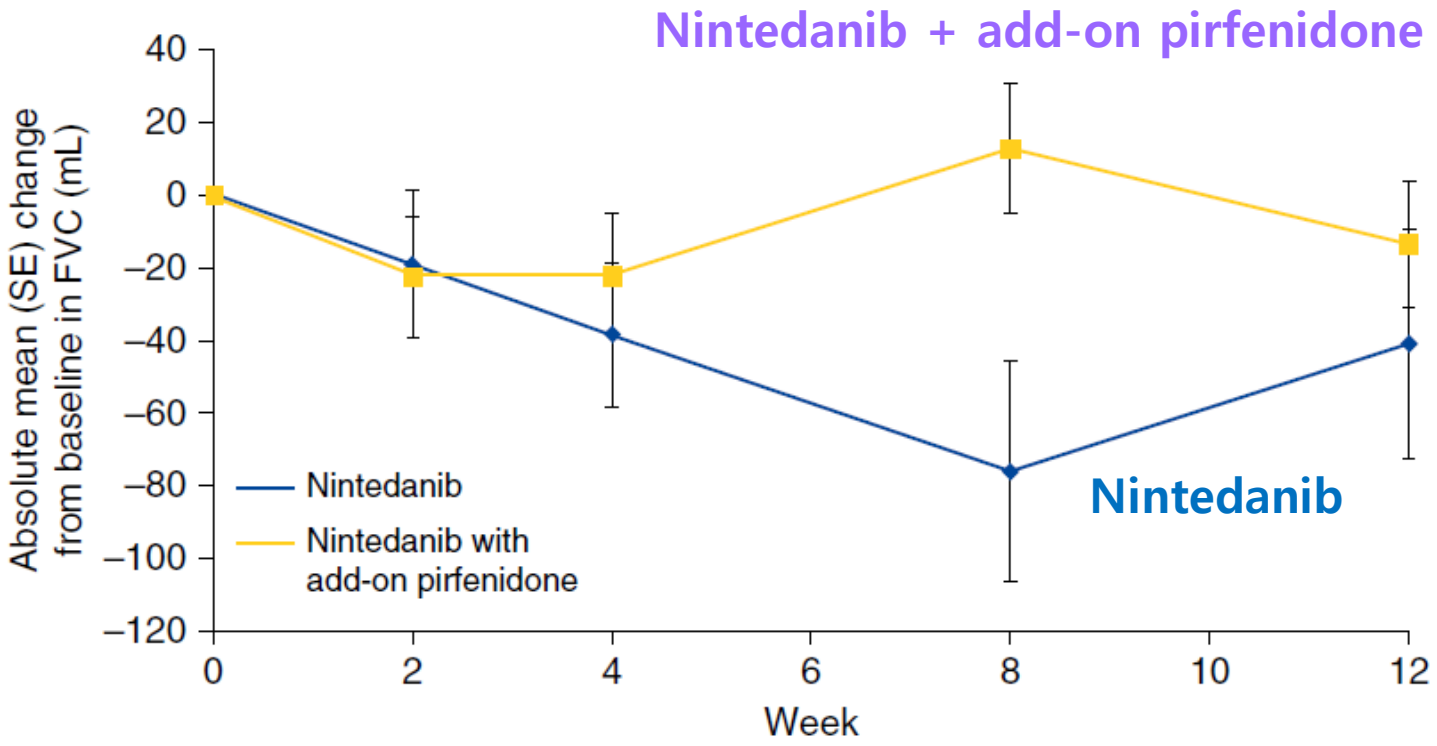
- 약제비 지원 제도

구분	기초생활수급자 차상위계층 환자	일반 환자
150mg 60 capsule (30days) - 약 300만원	1,400,000 지원	1,000,000 지원
100mg 60 capsule (30days) - 약 150만원	700,000 지원	500,000 지원

- 흔한 부작용 - 설사
  - ✓ Loperamide
  - ✓ 용량 조절 (150mg → 100mg)

Combination of antifibrotics

- INJOURNEY trial: open-label, randomized, phase IV, 12 weeks



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

FVC values from seven patients assigned to the week 12 time-point came from measurements made after week 12; the latest measurement was performed on day 96 and 1 day after the last dose of randomized treatment

AJRCCM, 2018:197 (3); 356–363

Combination of antifibrotics

- INJOURNEY trial: open-label, randomized, 12 weeks

	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

AJRCCM, 2018:197 (3); 356–363

Combination of antifibrotics

- INJOURNEY trial: open-label, randomized, 12 weeks

	Nintedanib 150 mg Twice Daily with Add-on Pirfenidone (*n* = 53)	Nintedanib 150 mg Twice Daily (*n* = 51)
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

AJRCCM, 2018:197 (3); 356–363

Combination of antifibrotics

	Patients with at least one TEAE[¶]	Patients with at least one TEAE related to pirfenidone only[+]	Patients with at least one TEAE related to nintedanib only[+]	Patients with at least one TEAE related to both pirfenidone and nintedanib[+]
TEAEs occurring in ⩾5% of patients				
⩾1 TEAE	88 (99)			
⩾1 treatment-related TEAE	74 (83)	15 (17)	67 (75)	26 (29)
Diarrhoea	44 (49)	2 (2)	38 (43)	5 (6)
Nausea	41 (46)	3 (3)	31 (35)	12 (14)
Vomiting	21 (24)	1 (1)	16 (18)	7 (8)
Decreased appetite	14 (16)	2 (2)	7 (8)	5 (6)
Fatigue	11 (12)	0	8 (9)	3 (3)
Dyspepsia	8 (9)	1 (1)	6 (7)	1 (1)
Headache	8 (9)	0	7 (8)	1 (1)
Weight decreased	6 (7)	1 (1)	3 (3)	2 (2)
Photosensitivity or rash TEAEs	7 (8)	4 (5)	2 (2)	1 (1)
Abdominal pain upper	5 (6)	1 (1)	2 (2)	2 (2)
Dizziness	5 (6)	0	4 (5)	1 (1)
TEAEs leading to discontinuation				
⩾1 TEAE	13 (15)			
⩾1 treatment-related TEAE	11 (12)	0	10 (11)	1 (1)
Nausea	4 (5)	0	3 (3)	1 (1)
Diarrhoea	4 (5)	0	3 (3)	1 (1)
Fatigue	2 (2)	0	2 (2)	0
Weight decreased	2 (2)	0	2 (2)	0
Deep vein thrombosis	1 (1)	0	1 (1)	0
Epigastric discomfort	1 (1)	0	1 (1)	0
Malaise	1 (1)	0	1 (1)	0
Migraine	1 (1)	0	1 (1)	0
Vomiting	1 (1)	0	1 (1)	0

Eur Respir J 2018; 52: 1800230

Timing of treatment initiation

The earlier the better?

Watch and wait ?

Timing of treatment initiation

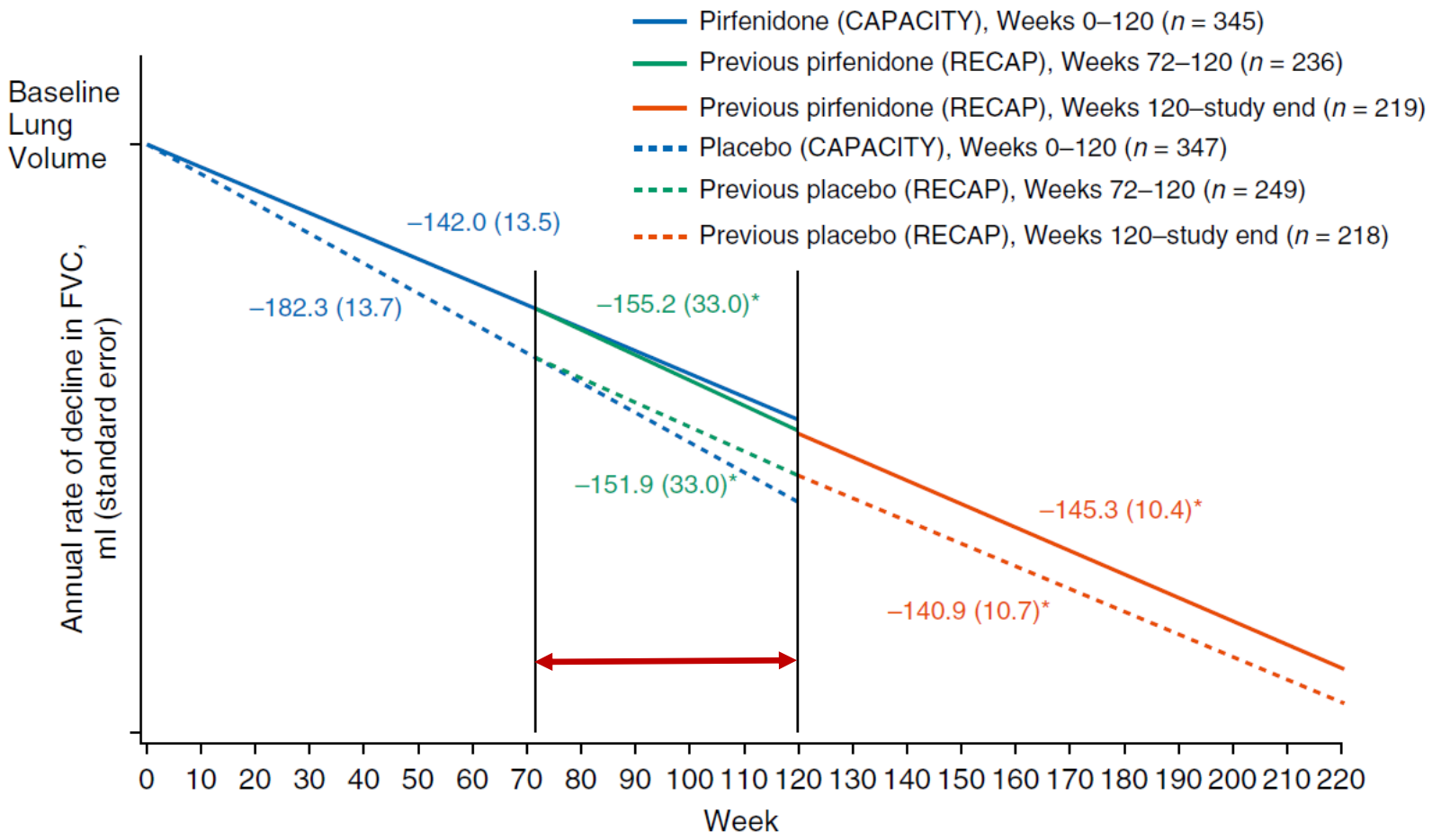
- 2015 ATS/ERS/JRS/ALAT IPF treatment guidelines
  ➔ No recommendations regarding timing of treatment initiation

- German guidelines
  ➔ Antifibrotic therapy should be recommended to symptomatic patients at time of diagnosis

- Swiss position paper
  ➔ Proposing treatment to patients with IPF when diagnosis is made, especially for patients who have experienced disease progression

- French guidelines
  ➔ Treating patients with IPF when the patient is diagnosed

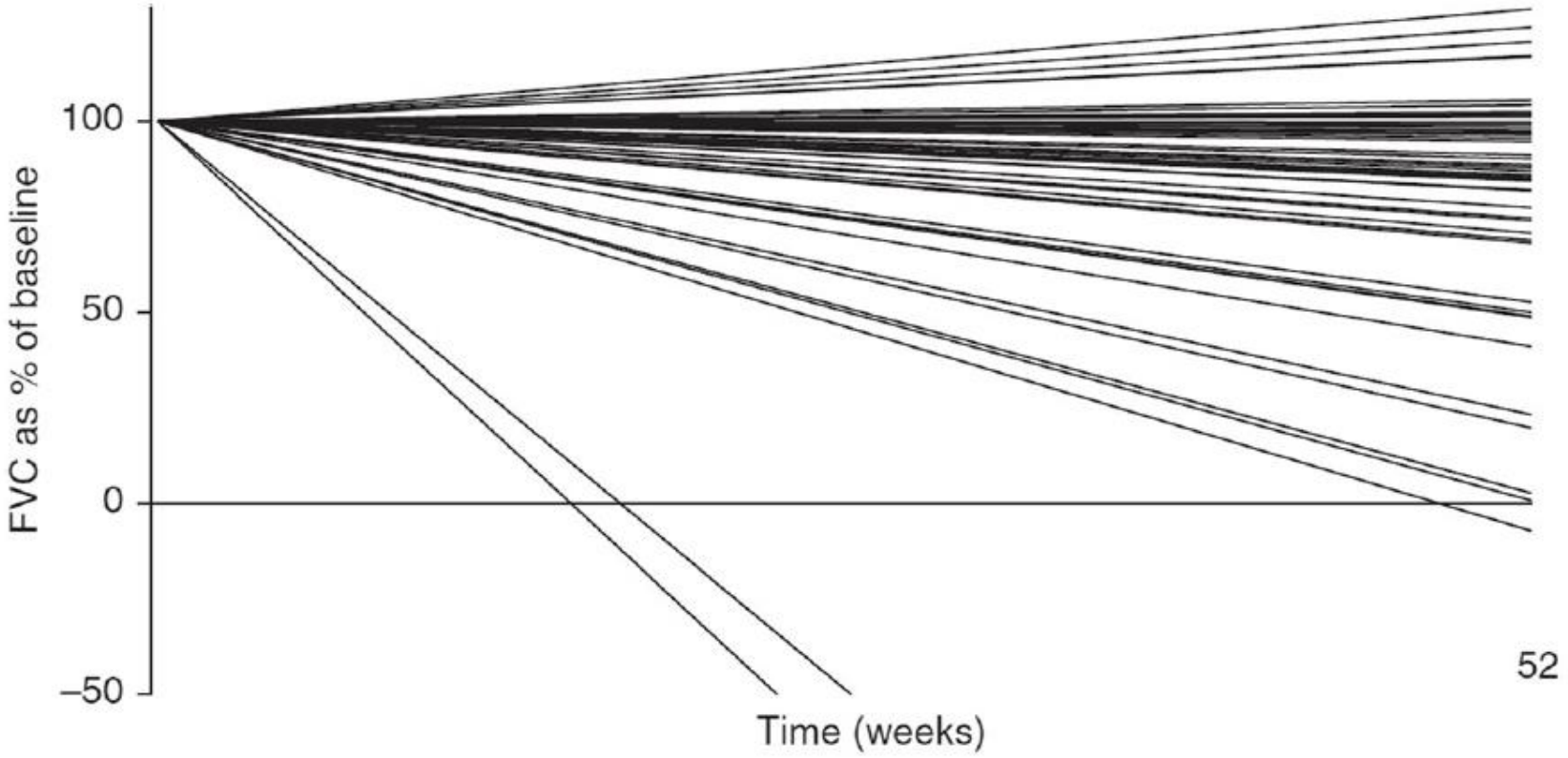
The earlier the better



CAPACITY→ RECAP

AnnalsATS 2019:16 (7)

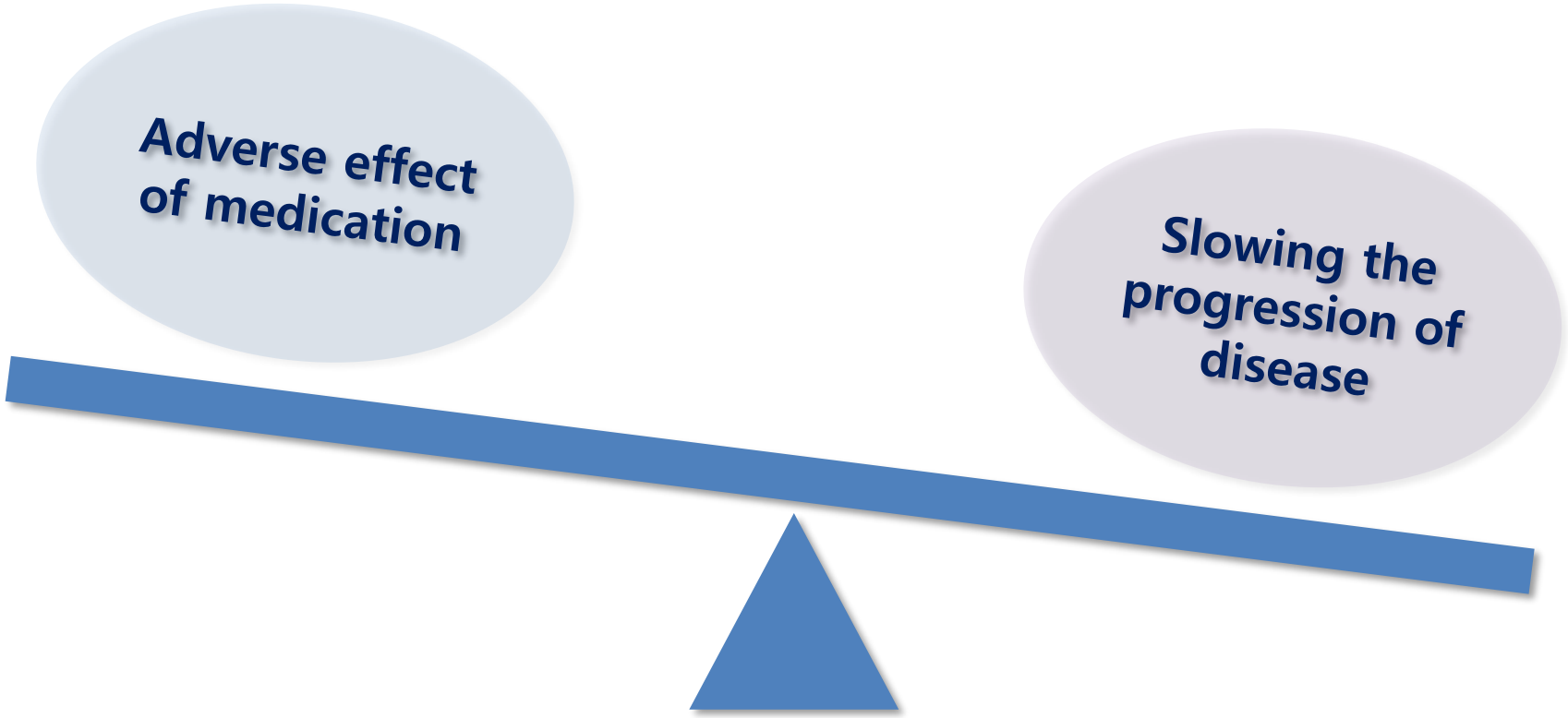
Watch and wait



8% of patients showing stability in FVC over 1 year

Am J Respir Crit Care Med. 2016;194:989–97

Benefit vs Risk of Treatment



Drugs used for patients with IPF

1) Drugs for slowing the progression of IPF

→ Antifibrotics

- Pirfenidone, nintedanib
- New drugs

2) Drugs for symptom control

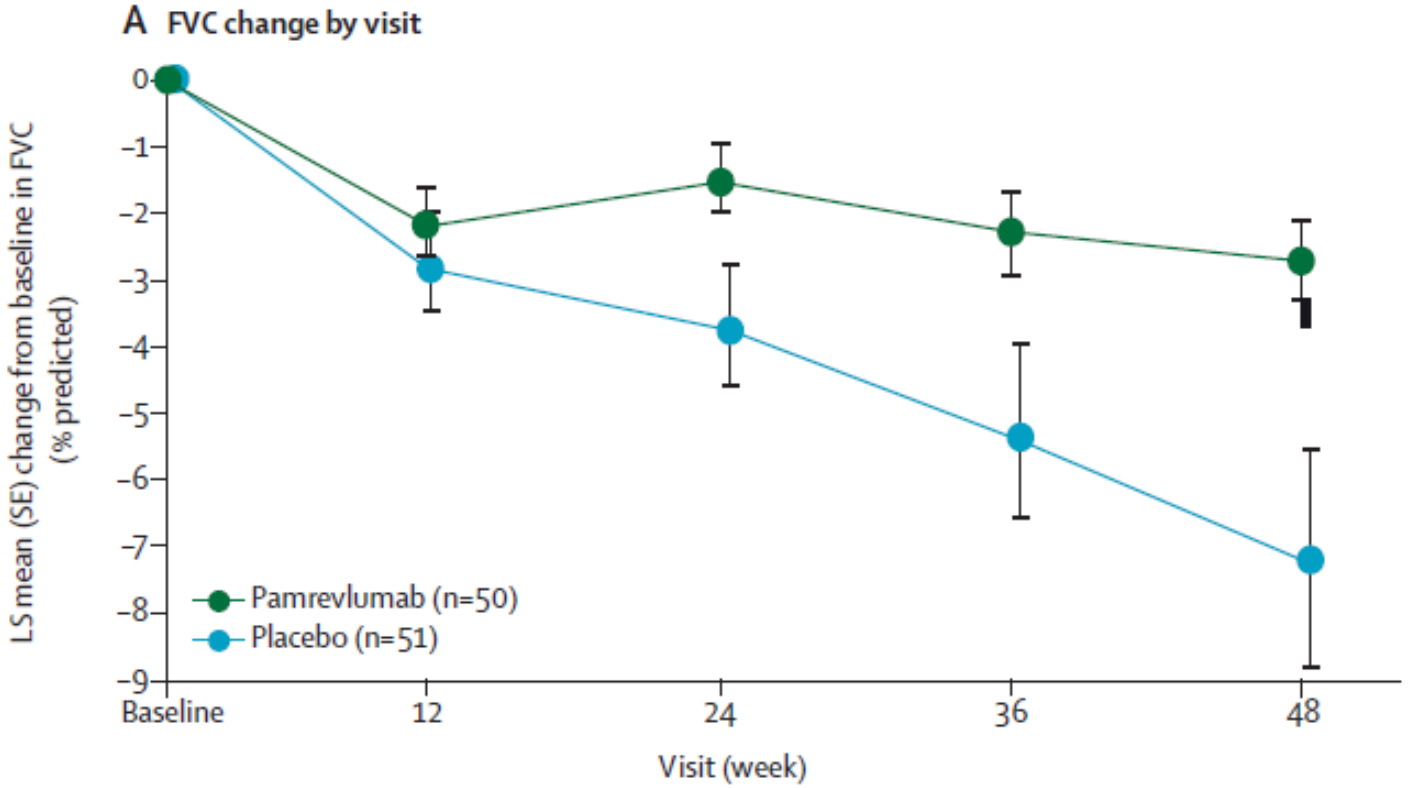
→ Cough, dyspnea

New potential drugs

Study drug	Mechanism of action	Clinical trial identifier (NCT)	Study description	Primary outcome measures	Phase of development	Treatment duration
PRM-151	Recombinant form of human SAP	NCT02550873	Randomized, double-blind, placebo controlled	Change from baseline in Forced Vital Capacity (FVC) [% Predicted]	II	28 weeks
Tipelukast	Leukotriene antagonists	NCT02503657	Randomized, double-blind, placebo controlled	Change from baseline of Forced Vital Capacity (FVC) at 26 weeks	II	26 weeks
BG00011	Anti-Integrin antibody	NCT03573505	Randomized, double-blind, placebo-controlled	Yearly rate of change in Forced (Expiratory) Vital Capacity (FVC)	II	52 weeks
Pamrevlumab (FG-3019)	Anti-connective tissue growth factor antibody	NCT01890265	Randomized, double-blind, placebo-controlled	Change from baseline in FVC (percent of predicted value) at week 48	II	48 weeks
PBI-4050	Anti-connective tissue growth factor antibody	NCT02538536	Open-label, single arm, exploratory, observational study	Number of subjects with abnormal laboratory values and/or adverse events that are related to treatment	II	20 weeks
KD025	Selective inhibitor of ROCK2	NCT02688647	Randomized, phase 2, open-label	Change in Forced Vital Capacity (FVC) in baseline to 24 weeks	II	24 weeks
CC-90001	Kinase inhibitor targeting JNKs	NCT03142191	Randomized, double-blind, placebo-controlled	Percentage point change in % predicted Forced vital capacity (FVC)	II	24 weeks
GLPG1690	Autotaxin-LPA inhibitor	NCT02738801	Randomized, double-blind, parallel group, placebo-controlled	Safety, Tolerability, Pharmacokinetic and Pharmacodynamic Properties of GLPG1690	II	12 weeks
Omipalisib/ GSK2126458	Inhibitor of PI3K pathway	NCT01725139	Randomized, double-blind, placebo-controlled	To explore a number of doses of GSK2126458 for engagement of pharmacology after short term dosing	I	7 to 10 days
Sirolimus	mTOR inhibitor	NCT01462006	Double-blind placebo-controlled pilot study	Change in peripheral blood concentration of CXCR4+ fibrocytes; number of subjects with drug side-effects	NA	22 weeks
Rituximab	Antibody targeting CD20	NCT01969409	Randomized, double-blind, placebo-controlled	Titers of anti-HEp-2 autoantibodies, by indirect immunofluorescence assays (IFA) over 9 months	II	36 weeks
Co-trimoxazole or Doxycycline	Antimicrobial drugs	NCT02759120	Randomized, un-blinded, phase III	Time to first non-elective, respiratory hospitalization or all-cause mortality	III	9 months

Presse Med 49 (2020) 104025

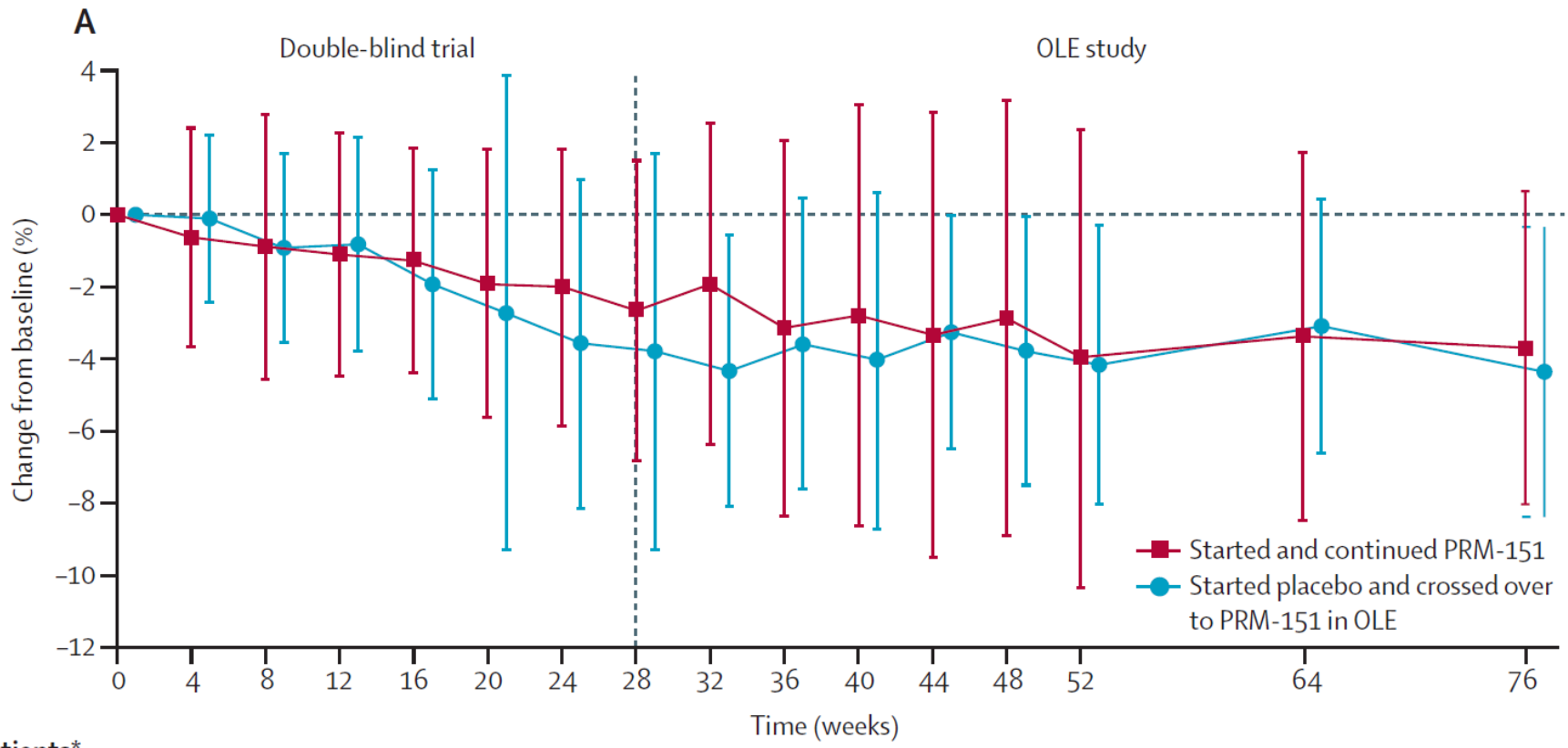
PRAISE: phase 2 of pamrevlumab



Pamrevlumab	−2·2 (0·6)	−1·5 (0·5)	−2·3 (0·7)	−2·7 (0·6)
Placebo	−2·8 (0·8)	−3·8 (0·9)	−5·3 (1·3)	−7·2 (1·7)
Absolute difference	0·6 (0·9)	2·3 (1·1)	3·0 (1·5)	4·5 (1·8)
95% CI	(−1·3 to 2·5)	(0·1 to 4·4)	(0·1 to 6·0)	(0·9 to 8·0)
Relative difference	22·2%	59·8%	57·0%	62·4%
p value	0·51	0·042	0·044	0·014

Lancet Respir Med 2020; 8: 25–33

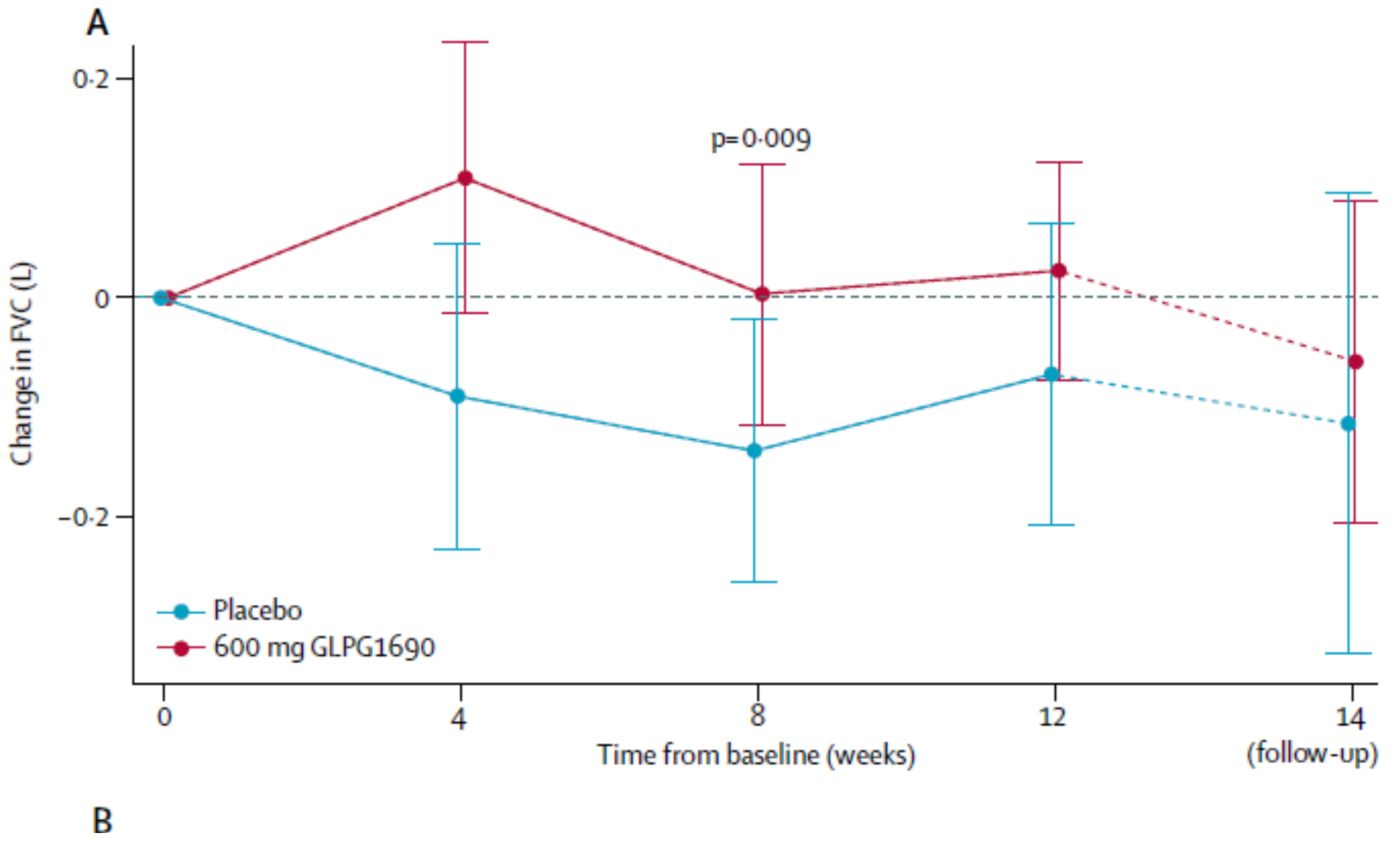
Long-term treatment with PRM-151



Number of patients*																
Continued PRM-151 in OLE	77	69	67	67	68	70	70	67	65	65	67	65	65	60	53	52
Crossed over to PRM-151 in OLE	39	35	36	38	37	37	36	35	28	33	32	34	33	29	27	26

Lancet Respir Med 2019; 7: 657–64

FLORA: phase 2a of GLPG1690



Lancet Respir Med 2018

Contents

- Introduction
- **Pharmacological treatment**
  - ✓ Disease modifier - antifibrotics
  - ✓ **Symptom control**
- Non-pharmacological treatment
- Summary

Treatment of cough

- Rule out other conditions causing cough
  - ✓ ex GERD, ACEI, etc

- Conventional antitussive therapies
  - ✓ cough syrups, dextromethorphan, codeine, etc

Treatment of cough

Randomized controlled trials	Omeprazole (2019, n=45)	• 39% reduction in geometric mean cough frequency per hour	• Single center study • 16% of screened patients included • No effect on cough-related QoL and reflux scores • Possibly increased LRT infections
	Inhaled PA101 (2017, n=24)	• Multicenter trial • 31% reduction in daytime cough frequency	• Phase II trial • 2 weeks study
	Thalidomide (2012, n=23)	• Improvement of cough-related QoL and cough severity scores	• Single center study • 20% of screened patients included • High incidence of adverse events • Potential severe side-effects • No objective cough measure
Cohort studies	Pirfenidone (2017, n=43)	• Multicenter trial • 34% reduction of 24 hour cough frequency • Improvement of cough-related QoL and cough severity scores	• No control group • Only patients with severe cough included
	Omeprazole or Lansoprazole + Ranitidine (2014, n=18)	• Decrease in acid reflux • Objective cough and acid reflux measure used	• No control group • Single center study • No change in cough frequency • No subjective cough measure • Non-acid reflux present in 72% of patients
	Interferon-α (2011, n=6)	• Cough-related QoL improved in 5 patients	• Single center study • Small sample size • No objective cough measure
	Prednisolone (2003, n=6)	• Reduction in cough reflex sensitivity to capsaicin • Improvement in cough severity score	• Single center pilot study • Small sample size • No objective cough measure • High dose steroids are associated with worse outcomes in IPF

Curr Opin Support Palliat Care 2019, 13:000–000

PAciFy Cough trial

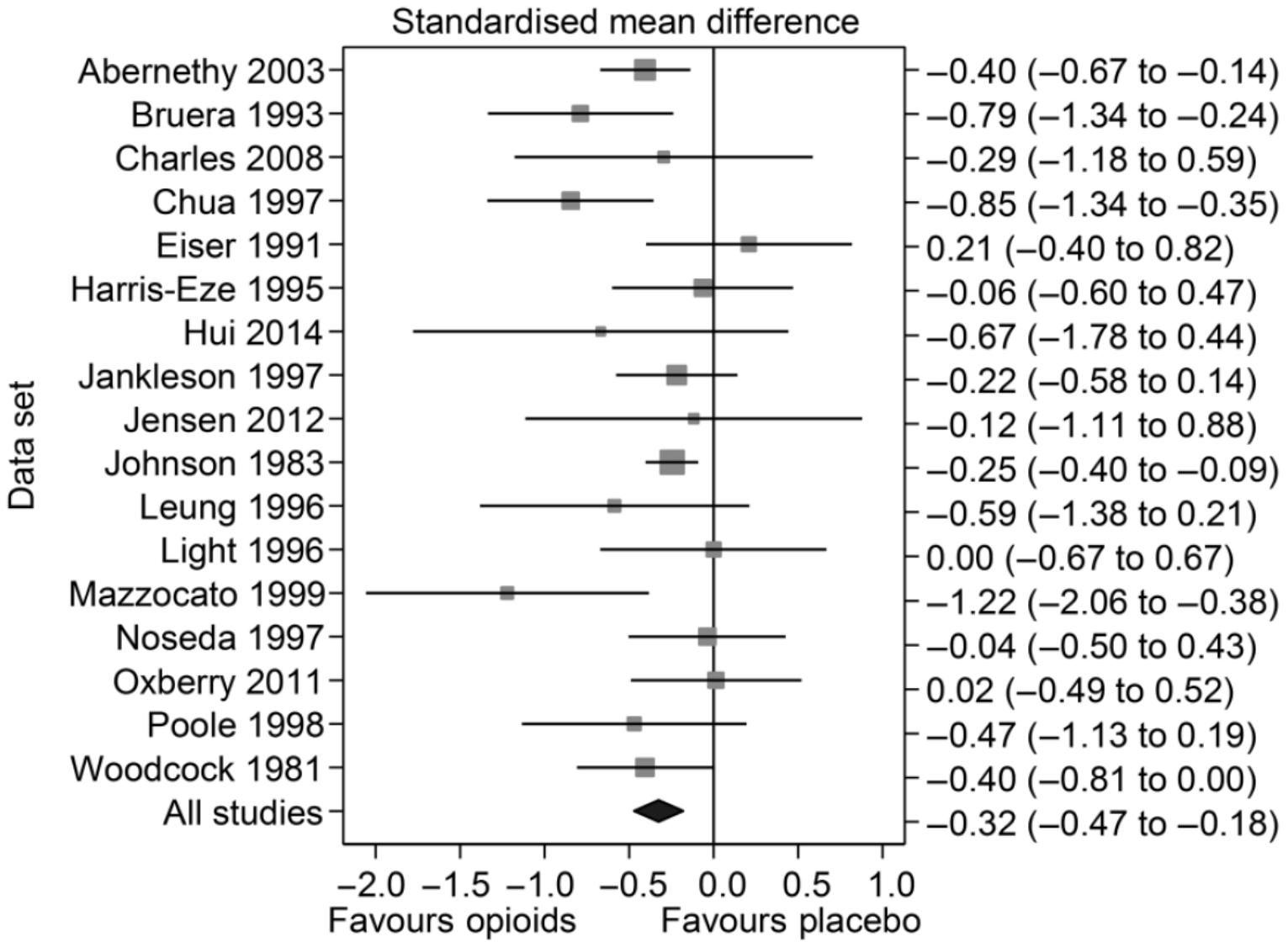
- A Multicenter, Double Blind, Placebo Controlled, Crossover Trial of Morphine Sulfate for the Treatment of Pulmonary Fibrosis Cough

- Drug: Morphine Sulfate
  - ✓ 5mg table x 2 per day for 14 days

- Patients will then crossover after a 7 day wash out period

- Primary outcome
  - ✓ The percent change in daytime cough frequency (coughs per hour)

Meta-analysis of opioid for breathlessness



Ekström M, Bajwah S, Bland J M, et al. Thorax 2018;73:88–90.

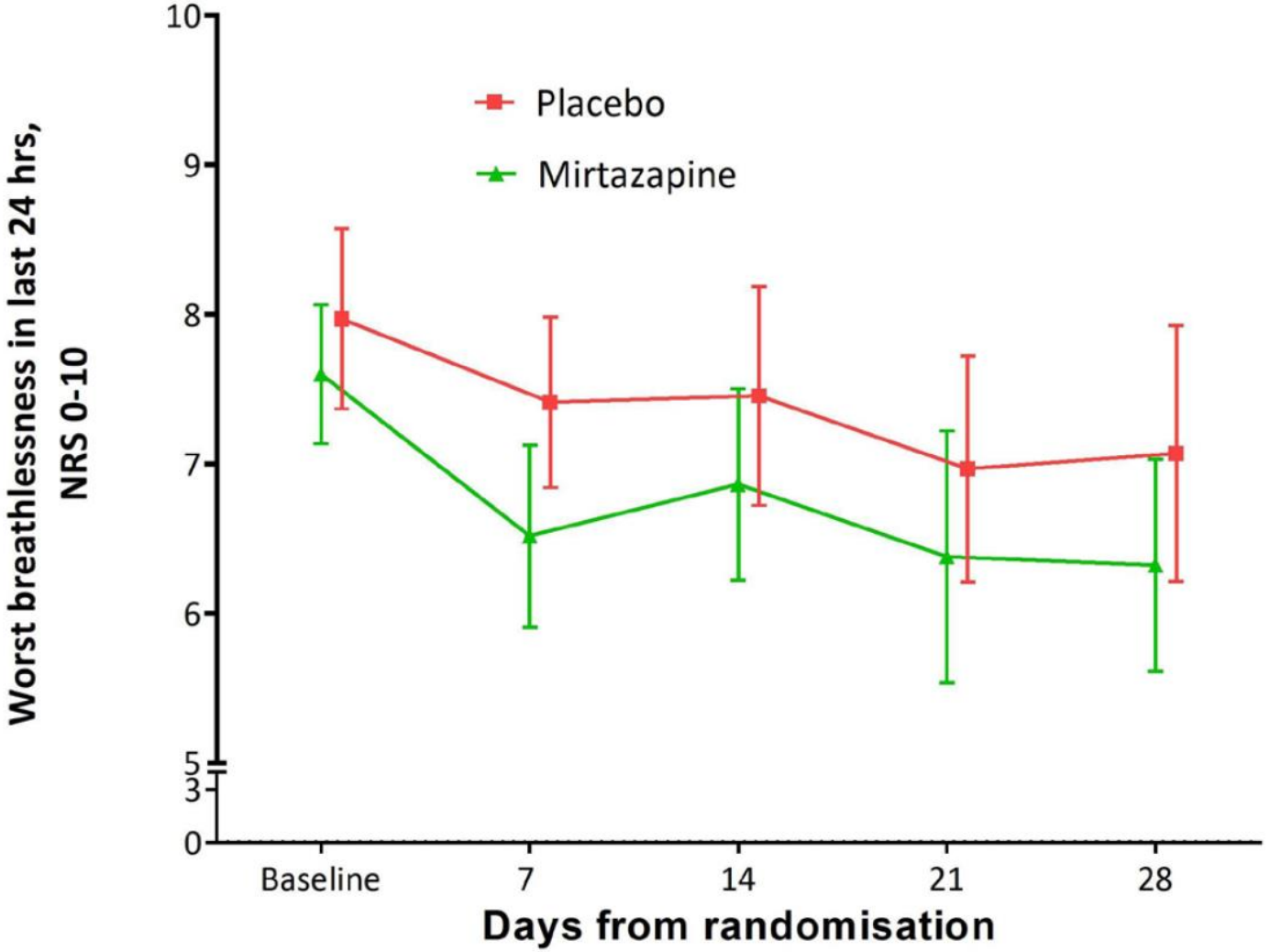
Selective serotonin reuptake inhibitors (SSRI)

- Well tolerated antidepressants
  - Sertraline: 4 weeks RCT – negative
  - Mirtazapine
    - ✓an antagonist at α2-adrenergic, H1, 5HT2A/C and 5HT3 receptors, resulting in serotonin, norepinephrine and dopamine release

BETTER-B feasibility trial

- Inclusion
  - COPD, ILD, cancer or chronic heart failure
  - mMRC score of 3 or 4 despite optimal treatment of underlying disease(s)
  - prognosis of ≥2 months
- Oral mirtazapine (15 mg/day) or placebo for 28 days
- Primary endpoint: number of patients recruited across three hospitals over 12 months, with a target of 60

Higginson IJ, et al. Thorax 2020;75:176–179.



Mean (95% CI data) at each time point					
Placebo	8.0 (7.4-8.6)	7.4 (6.8-8.0)	7.5 (6.7-8.2)	7.0 (6.2-7.7)	7.1 (6.2-7.9)
Mirtazapine	7.6 (7.1-8.1)	6.5 (5.9-7.1)	6.9 (6.2-7.5)	6.4 (5.5-7.2)	6.3 (5.6-7.0)

Higginson IJ, et al. Thorax 2020;75:176–179.

Contents

Oxygen therapy

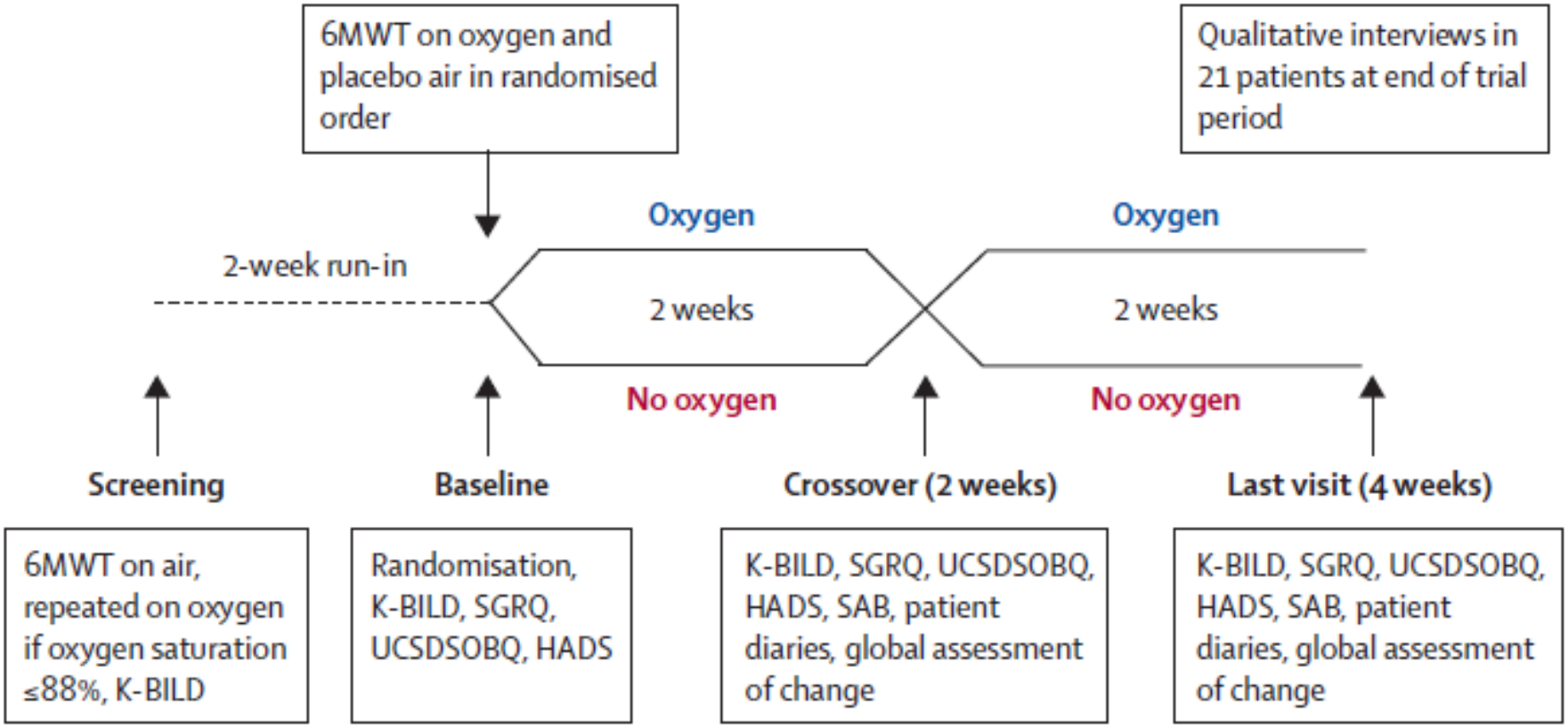
- 2011 ATS guideline
  - Prompt initiation of supplemental oxygen in patients with clinically significant resting hypoxemia

- 2015 BTS guidelines
  - Ambulatory oxygen should not be routinely offered to patients who are not hypoxic at rest
  - the possible benefit of ambulatory oxygen for individual patients with severe exertional breathlessness

AmbOx trial

prospective, open-label, mixed-method, crossover randomised controlled trial

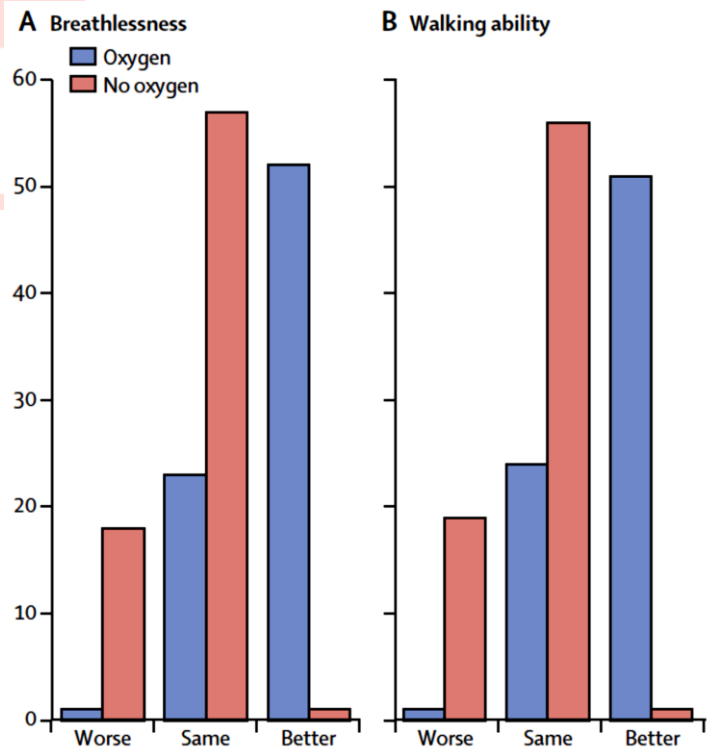
- ✓ Patients with fibrotic interstitial lung disease
- ✓ not hypoxic at rest but hypoxic on 6MWT



Lancet Respir Med 2018; 6: 759–70

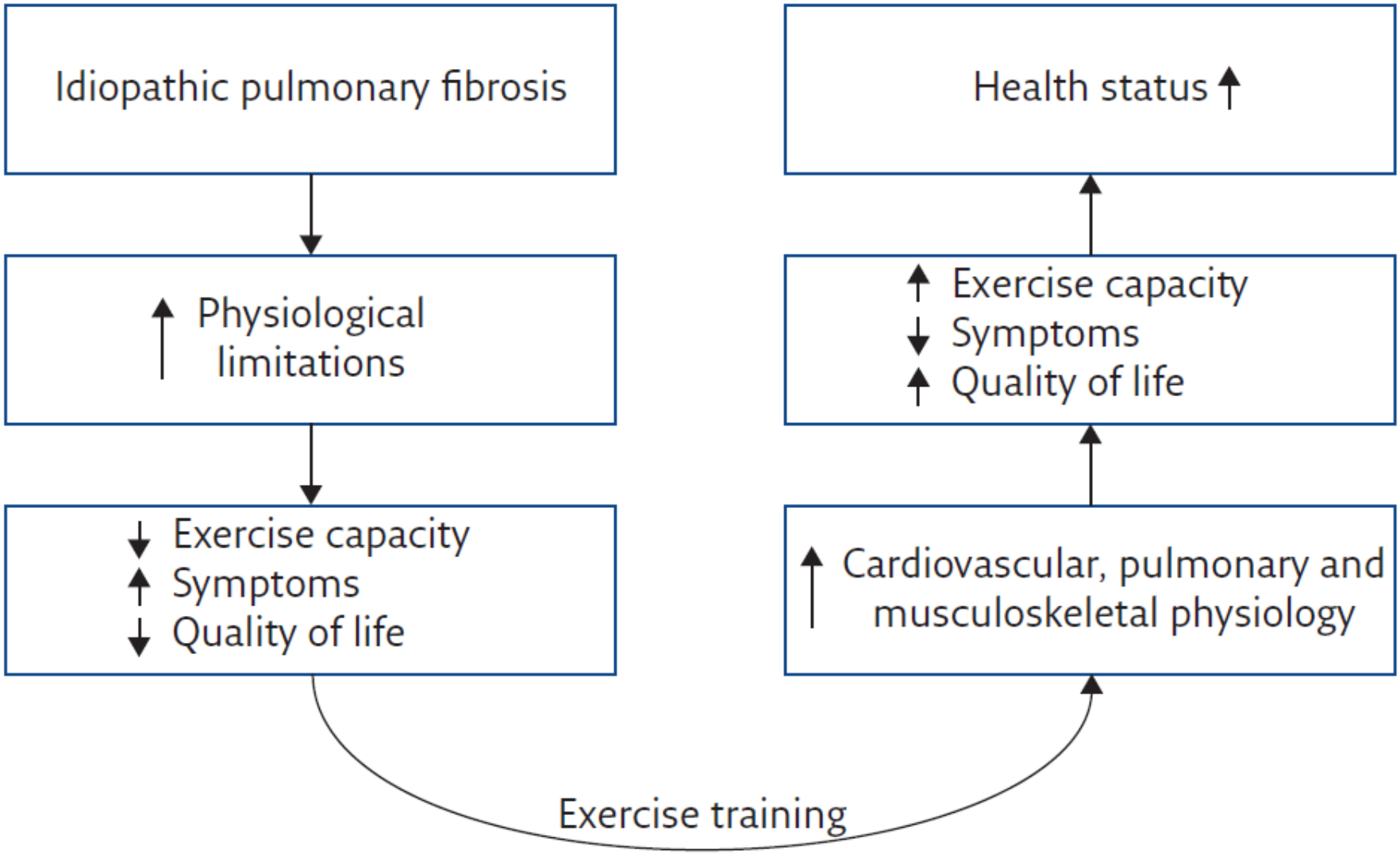
AmbOx trial

	Oxygen	No oxygen	Mean between-treatment difference (95% CI)	p value
K-BILD* (n=74)				
Total	55·5 (13·8)	51·8 (13·6)	3·7 (1·8 to 5·6)	<0·0001
Breathlessness and activities	44·4 (22·6)	35·8 (20·4)	8·6 (4·7 to 12·5)	<0·0001
Chest symptoms	65·5 (25·2)	57·9 (29·2)	7·6 (1·9 to 13·2)	0·009
Psychological symptoms	55·2 (19·6)	52·8 (19·6)	2·4 (−0·6 to 5·5)	0·12
UCSDSOBQ† (n=72)	41·0 (30·5)	49·1 (34·1)	−8·0 (−12·4 to −3·6)	<0·0001
SGRQ† (n=72)				
Total	48·7 (25·3)	52·4 (25·0)	−3·6 (−6·7 to −0·6)	0·018
Activity	61·5 (27·3)	68·9 (25·2)	−7·5 (−12·4 to −2·5)	0·003
Symptoms	53·3 (30·7)	54·9 (31·9)	−1·7 (−6·6 to 3·3)	0·51
Impact	39·7 (28·6)	41·8 (28·8)	−2·1 (−5·6 to 1·3)	0·22
Hospital Anxiety and Depression Scale‡ (n=70)				
Anxiety score ≥8	16 (23%)	18 (26%)	0·60 (0·14 to 2·50)§	0·47
Depression score ≥8	10 (14%)	18 (26%)	0·14 (0·02 to 1·16)§	0·14



Lancet Respir Med 2018; 6: 759–70

Rehabilitation

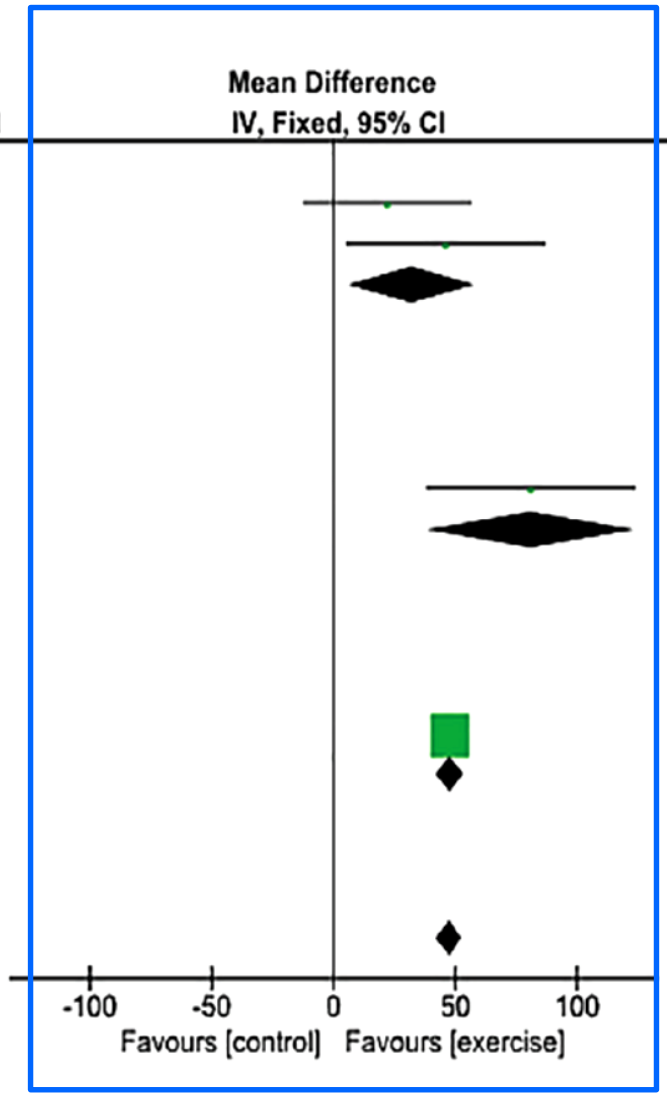


Breathe 2016; 12: 130–138.

Change in 6-minute walk distance

Exercise vs Control

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 Aerobic exercise								
Holland et al. 2012	43	56	25	21	58	19	2.3%	22.00 [-12.09, 56.09]
Nishiyama et al. 2008	42	50.8	13	-4	57.7	15	1.7%	46.00 [5.81, 86.19]
Subtotal (95% CI)			38			34	4.0%	32.04 [6.05, 58.04]
Heterogeneity: Chi² = 0.80, df = 1 (P = 0.37); I² = 0%								
Test for overall effect: Z = 2.42 (P = 0.02)								
1.1.2 Aerobic exercise + breathing exercise								
Vainshelboim et al. 2014	70.4	77	15	-10.6	35.4	17	1.5%	81.00 [38.56, 123.44]
Subtotal (95% CI)			15			17	1.5%	81.00 [38.56, 123.44]
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.74 (P = 0.0002)								
1.1.3 Aerobic exercise + inspiratory muscle training exercise								
Arizono et al, 2014	26.7	5.8	24	-21	12.1	24	94.5%	47.70 [42.33, 53.07]
Subtotal (95% CI)			24			24	94.5%	47.70 [42.33, 53.07]
Heterogeneity: Not applicable								
Test for overall effect: Z = 17.42 (P < 0.00001)								
Total (95% CI)			77			75	100.0%	47.57 [42.35, 52.79]
Heterogeneity: Chi² = 4.55, df = 3 (P = 0.21); I² = 34%								
Test for overall effect: Z = 17.87 (P < 0.00001)								
Test for subgroup differences: Chi² = 3.76, df = 2 (P = 0.15), I² = 46.7%								

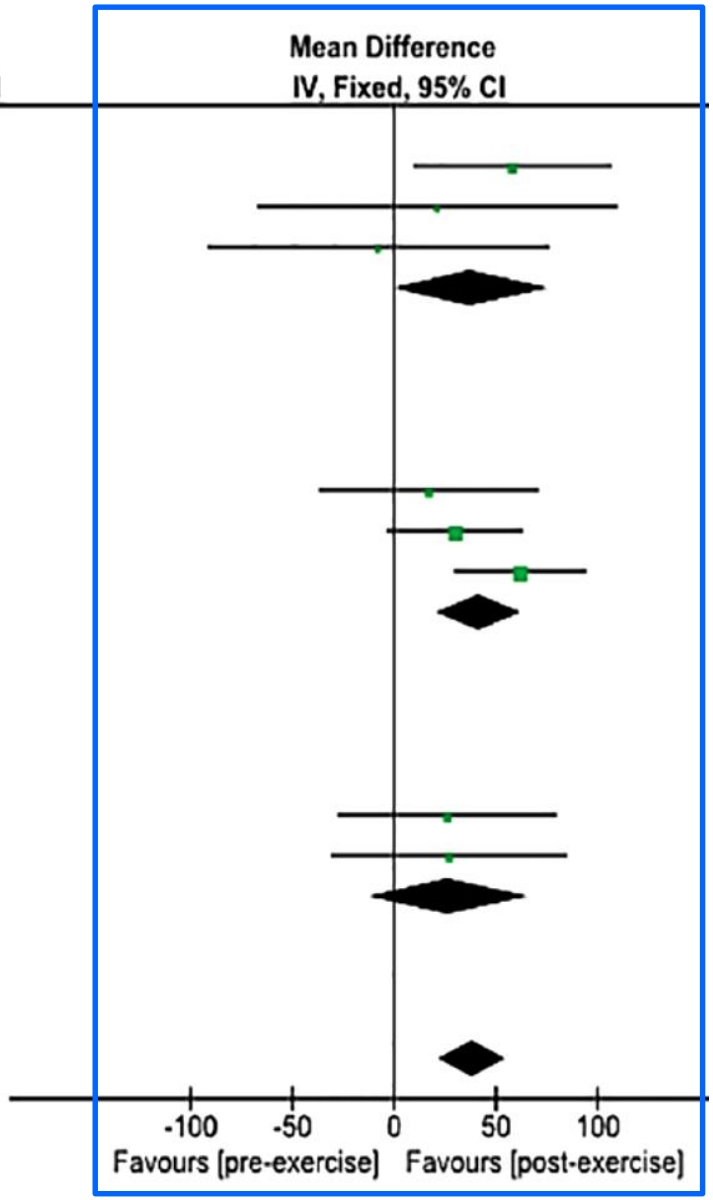


J Thorac Dis 2020;12(3):1041-1055.

Change in 6-minute walk distance

Pre versus Post exercise training

Study or Subgroup	Post-exercise Mean	SD	Total	Pre-exercise Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 Aerobic exercise								
Fontoura et al. 2018	442	100	31	384	92	31	12.0%	58.00 [10.17, 105.83]
Holland et al. 2012	391	185	25	370	127	25	3.5%	21.00 [-66.96, 108.96]
Rammaert et al. 2011	375	101	13	383	115	13	4.0%	-8.00 [-91.20, 75.20]
Subtotal (95% CI)			69			69	19.5%	37.86 [0.35, 75.37]
Heterogeneity: Chi² = 1.99, df = 2 (P = 0.37); I² = 0%								
Test for overall effect: Z = 1.98 (P = 0.05)								
1.1.2 Aerobic exercise + breathing exercise								
Kozu et al. 2011	340	122	36	323	109	36	9.6%	17.00 [-36.44, 70.44]
Rifaat et al. 2014	312	64	30	282	65	30	25.7%	30.00 [-2.64, 62.64]
Swigris et al. 2011	338	50	14	276	34	14	27.3%	62.00 [30.33, 93.67]
Subtotal (95% CI)			80			80	62.6%	41.97 [21.05, 62.88]
Heterogeneity: Chi² = 2.89, df = 2 (P = 0.24); I² = 31%								
Test for overall effect: Z = 3.93 (P < 0.0001)								
1.1.3 Aerobic exercise + inspiratory muscle training exercise								
Arizono et al. 2014	504	97	24	478	91	24	9.7%	26.00 [-27.21, 79.21]
Arizono et al. 2017	504	100	22	477	94	22	8.3%	27.00 [-30.35, 84.35]
Subtotal (95% CI)			46			46	18.0%	26.46 [-12.54, 65.47]
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%								
Test for overall effect: Z = 1.33 (P = 0.18)								
Total (95% CI)			195			195	100.0%	38.38 [21.83, 54.92]
Heterogeneity: Chi² = 5.35, df = 7 (P = 0.62); I² = 0%								
Test for overall effect: Z = 4.55 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.47, df = 2 (P = 0.79), I² = 0%								

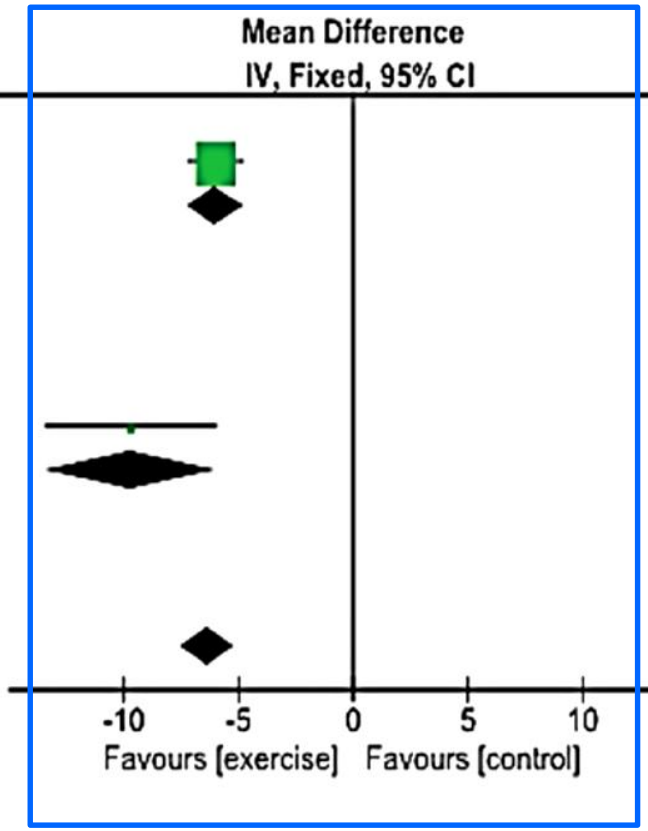


J Thorac Dis 2020;12(3):1041-1055.

Change in St. George's Respiratory Questionnaire

Exercise vs Control

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 Aerobic exercise								
Nishiyama et al. 2008	-2.9	1.1	13	3.1	2	15	90.9%	-6.00 [-7.18, -4.82]
Subtotal (95% CI)			**13**			**15**	**90.9%**	**-6.00 [-7.18, -4.82]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 10.00 (P < 0.00001)								
1.1.2 Aerobic exercise + breathing exercise								
Vainshelboim et al. 2014	-6.9	6.5	15	2.8	3.6	17	9.1%	-9.70 [-13.41, -5.99]
Subtotal (95% CI)			**15**			**17**	**9.1%**	**-9.70 [-13.41, -5.99]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.13 (P < 0.00001)								
Total (95% CI)			**28**			**32**	**100.0%**	**-6.34 [-7.46, -5.22]**
Heterogeneity: Chi² = 3.48, df = 1 (P = 0.06); I² = 71%								
Test for overall effect: Z = 11.09 (P < 0.00001)								
Test for subgroup differences: Chi² = 3.48, df = 1 (P = 0.06), I² = 71.2%								

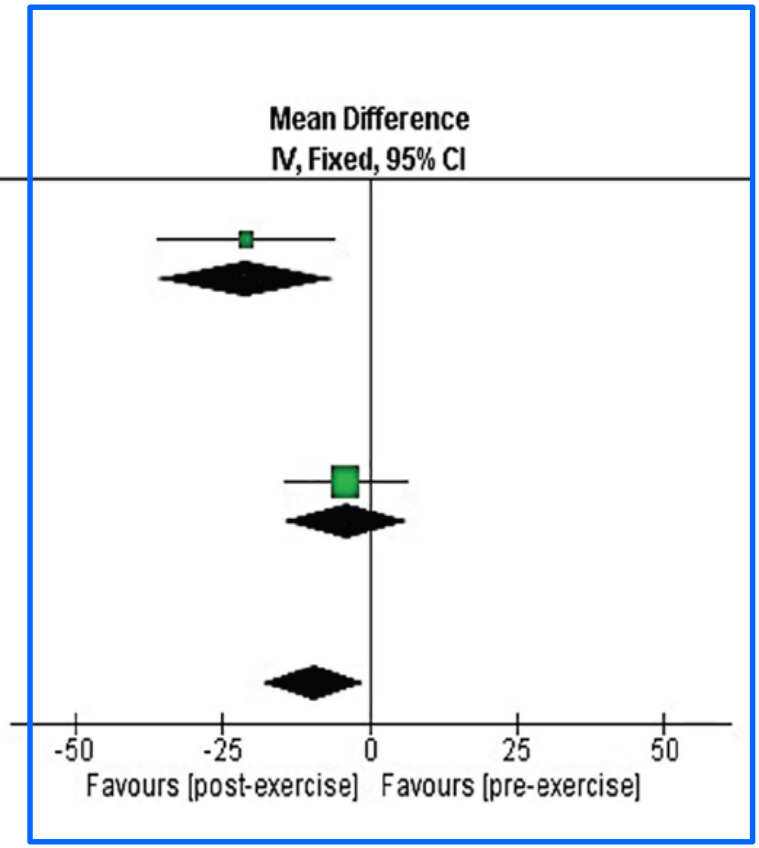


J Thorac Dis 2020;12(3):1041-1055.

Change in St. George's Respiratory Questionnaire

Pre versus Post exercise training

Study or Subgroup	Pre-exercise Mean	SD	Total	Post-exercise Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
3.1.2 Aerobic exercise + breathing exercise								
Rifaat et al. 2014	33	37	30	54	20	30	32.1%	-21.00 [-36.05, -5.95]
Subtotal (95% CI)			**30**			**30**	**32.1%**	**-21.00 [-36.05, -5.95]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.73 (P = 0.006)								
3.1.3 Aerobic exercise + inspiratory muscle training exercise								
Arizono et al. 2017	45	18	22	49	17	22	67.9%	-4.00 [-14.35, 6.35]
Subtotal (95% CI)			**22**			**22**	**67.9%**	**-4.00 [-14.35, 6.35]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.76 (P = 0.45)								
Total (95% CI)			**52**			**52**	**100.0%**	**-9.46 [-17.98, -0.93]**
Heterogeneity: Chi² = 3.33, df = 1 (P = 0.07); I² = 70%								
Test for overall effect: Z = 2.17 (P = 0.03)								
Test for subgroup differences: Chi² = 3.33, df = 1 (P = 0.07), I² = 70.0%								



J Thorac Dis 2020;12(3):1041-1055.

Suggested single supervised exercise session

Exercise component	Type	Time	Intensity
Warm-up	Calisthenics Breathing exercises Balance exercise	8–10 min	Low to moderate
Aerobic exercise	Walking	(5–10 min walking and 1 min rest)×3=18–33 min	80–90% of average walking speed on 6MWT
	Cycling	(3–5 min cycling and 1 min rest)×3=12–18 min	60–80% of peak work rate
Resistance exercises	Wall push-ups Chair squats Dumbbells shoulder press Supported one-hand rowing with dumbbell Dumbbells biceps curl Dumbbells arm extension Supported one-leg step-up Abdominal curl-ups	For each exercise 1–3 sets of 10–15 repetitions with 30–60 s rest after the set	4–6 on Borg CR 10 scale
Flexibility exercises	Seated single leg hamstring stretch Standing quadriceps stretch, Chest stretch Overhead reach stretch Cat stretch	For each exercise 1–2 repetitions of 15–30 s stretch	Muscle discomfort without severe pain

Breathe 2016; 12: 130–138.

Palliative care for patients with respiratory disease

Intervention	Predominant cycle of the BTF model	Evidence strength	Evidence origin	Practical comment
Pulmonary rehabilitation	Functioning	++++	Cochrane [47]	Patient may lack confidence and need one-to-one support or breathlessness service first.
Hand-held fan	Breathing	+++	[48, 49]	Evidence suggests this reduces breathlessness recovery time, supports exercise, increases self-efficacy. No important adverse effects, use in all patients, giving advice on how/why used.
Cognitive behavioural therapy	Thinking	++	[9, 50]	May require specialist psychological support.
Breathing techniques	Breathing	++	[9]	Need to be personalised, specialist respiratory physiotherapy advice required.
Inspiratory muscle training	Breathing	++	[9]	Needs to be personalised, specialist respiratory physiotherapy advice required.
Pedometer	Functioning	++	[9]	Pedometer training, *e.g.* as used by CBIS, increasing activity by 5% weekly from baseline.
Mindfulness-based stress reduction	Thinking	++	[9]	Requires 8-week course in standard evaluated form. Needs formal teaching even in abbreviated form.
Relaxation	Breathing	++	[9]	Various techniques, needs to be personalised.
Walking aids	Functioning	++	[51]	Should be standard assessment for every breathless individual, also possibly affects thinking *via* confidence.
Positioning	Breathing	+	[9]	Best position for individual may not fit standard ideas.
Acupuncture	Breathing?	+	[9]	Needs specialist training.

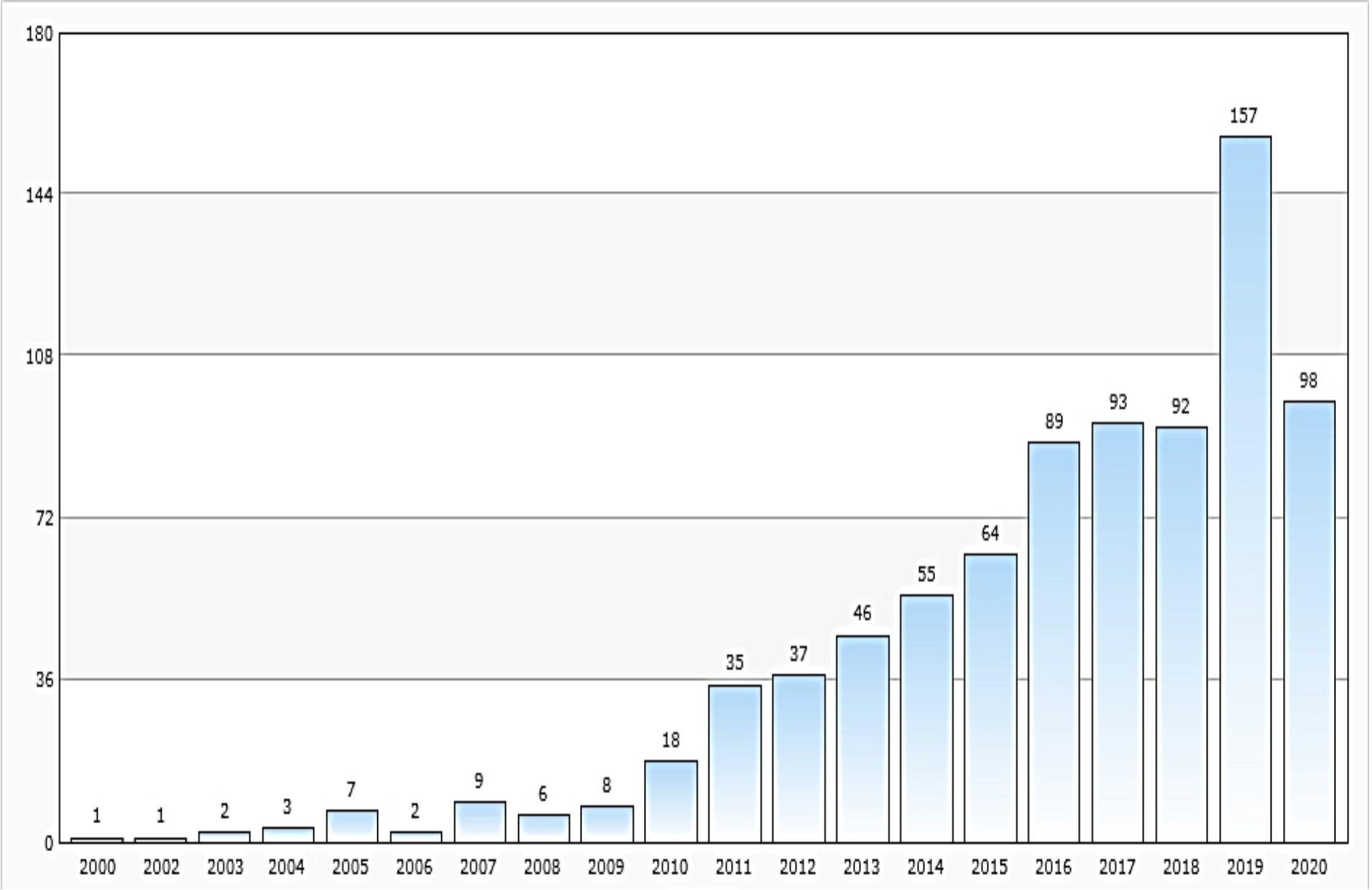
Breathe 2019; 15: 198–215.

Lung transplantation

KONOS 폐응급도 등록 서식

□ 응급도 0	- 입원한 환자로 다음 한 가지 이상 해당하는 경우 □ 호흡부전증으로 인공호흡기(Intubation ventilator)를 부착 중인 환자 □ 체외막형 심폐기를 가동 중인 환자
□ 응급도 1	(60일마다 재등록하며 검사결과는 검사시점과 상관없이 인정한다.) - 다음 한가지 이상 해당하여야 한다: 1) 산소 투여 없이 측정한 동맥혈 가스 검사상 PaO_2 〈55 mmHg 2) 평균 폐동맥혈압 〉 65 mmHg, 또는 평균 우심방 혈압 〉 15 mmHg 3) Cardiac index 〈2 L/min/m^2인 경우 4) 동맥혈검사상 PCO2 ≥80 mmHg인 경우 5) 입원환자 중 고유량비강캐뉼라 high-flow nasal cannula 30 L FiO_2 ≥0.6로 2주 이상 유지중인 경우(유지 중에만 인정)

Lung transplantation in Korea – KONOS database



Lung transplantation in Korea

Parameter	N = 69 (%)
Age, mean (SD), y	55.7 (10.09), range 28 −73
Male:female	46:23
Cause of lung transplantation, No. (%)	
Idiopathic pulmonary fibrosis	35 (50.7)
Connective tissue disease-related ILD	9 (13.0)
Acute respiratory distress syndrome	8 (11.5)
COPD (emphysema)	5 (7.2)
BOS after HSCT	3 (4.3)
Idiopathic pulmonary arterial hypertension	3 (4.3)
Other fibrosis	2 (2.9)
Lymphangioleiomyomatosis	1 (1.4)
Bronchiectasis	1 (1.4)
Other	2 (2.9)
Emergency status	
0	24 (34.5)
1	38 (55.1)
2	5 (7.2)
3	2 (2.9)

Transplantation Proceedings, 50, 2759e2763 (2018) 2759.

Stem cell treatment in IPF

- Mesenchymal stem cell
  - ✓ Non-haematopoietic, multipotent stromal cells having the ability to differentiate into tissue derived from a single germ layer
  - ✓ Have anti-inflammatory effects, migratory properties and immunoprivilege
  - ✓ Several animal models have suggested that MSCs can ameliorate inflammation and reduce the degree of fibrosis

Human studies of MSC therapy in IPF

	Cell type	Delivery and dose	Safety results	Efficacy results
J Transl Med. (2013) 11:171. (phase Ib)	autologous adipose derived stromal cells-stromal vascular fraction	Endobronchial, 0.5 × 10^6 cells/kg bwt in 10cc; 3 dosages over 3 months	No difference in AEs compared with placebo. No ectopic tissue formation	Cell-treated patients did not deteriorate in both functional parameters and indicators of QoL
Respirology (2014) 19:1013–8. (phase Ib)	Allogeneic placental MSCs	IV, 1 & 2 × 10^6cells/kg; one dose	Minor and transient acute AEs	Stable lung function. No evidence of worsening fibrosis
Chest (2017) 151:971–81 (phase I) AETHER study	Allogeneic BM-MSC	IV, one dose: 20 × 10^6 (*n* = 3) 100 × 10^6 (*n* = 3) 200 × 10^6 cells (*n* = 3)	No treatment-emergent serious AEs. Two non-treatment related deaths due to progression of IPF	3.0% decline in % pred FVC and 5.4% decline in % pred DLCO
Clin Respir J. (2018). Longitudinal study	autologous adipose derived stromal cells-stromal vascular fraction	Endobronchial, 0.5 × 10^6 cells/kg of Bwt in 10cc; 3 dosages over 3 months	No difference in AEs compared with placebo. No ectopic tissue formation	Median overall progression-free survival 26 months. Median overall survival 32 months. All patients alive for at least 2 years after first Administration

Transplantation Proceedings, 50, 2759e2763 (2018) 2759.

Contents

Summary

- **Drugs for slowing the progression of IPF**
  - Pirfenidone (Anorexia, GI intolerance, skin reaction)
  - Nintedanib (Diarrhea, LFT abnormality)

    ✓ Decreased mortality & acute exacerbation

    ✓ Similar effects in patients with early/advanced IPF

    ✓ Importance of management of side effect and dose titration

  - Ongoing clinical trials for new drugs

Summary

- **Drugs for symptom control**
  - ✓ Antitussive, PPI (?)
  - ✓ Studying drugs: Inhaled PA101, morphine, mirtazapine

- **Non-pharmacological management**
  - Rehabilitation
  - Oxygen therapy
  - Lung transplantation
  - MSC therapy

Thank you for your attention