IPF의 치료와 부작용 관리

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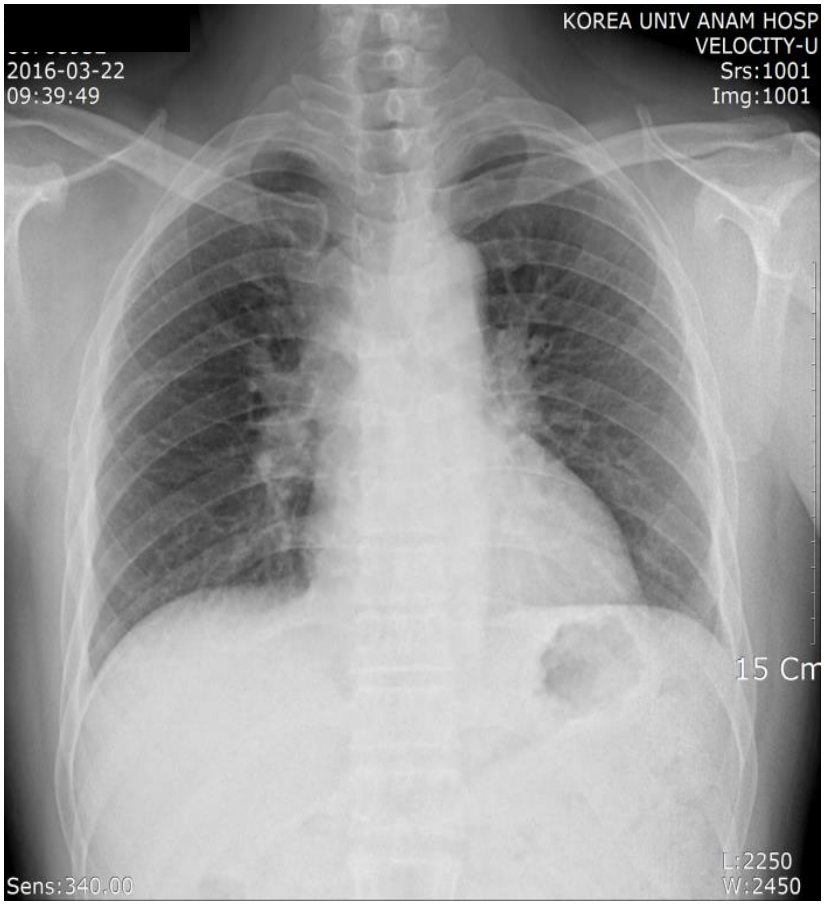
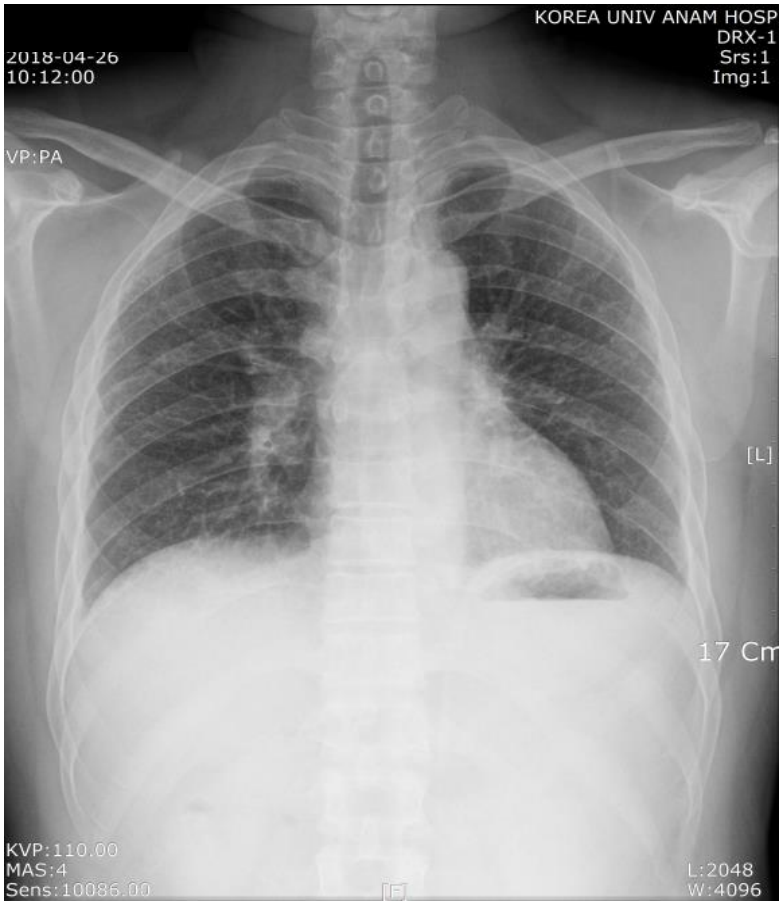
Case 1

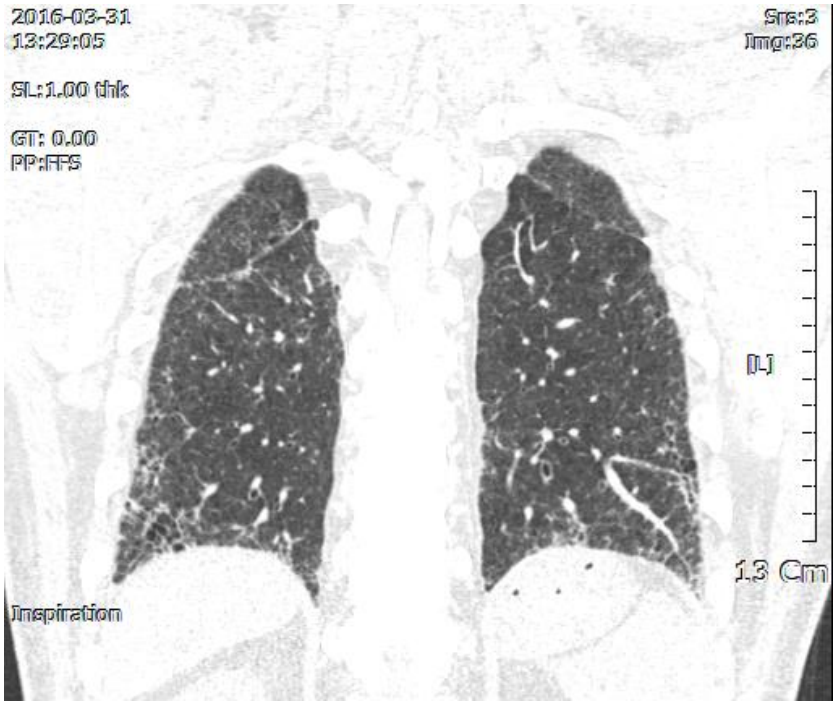
- M/ 62
- PI : 2016년 3월, 호흡곤란 없이 3-4개월 지속되는 기침, 가래로
  내원하여 cIPF 진단 후 대증 치료만 하던 중
  점차 호흡곤란 발생하여 2년 만에 다시 외래 내원
- 한약방
- ex smoker : 10년 전 중단
- PHx : DM/HTN/TBc/hepatitis(-/+/-/-), 협심증(+)

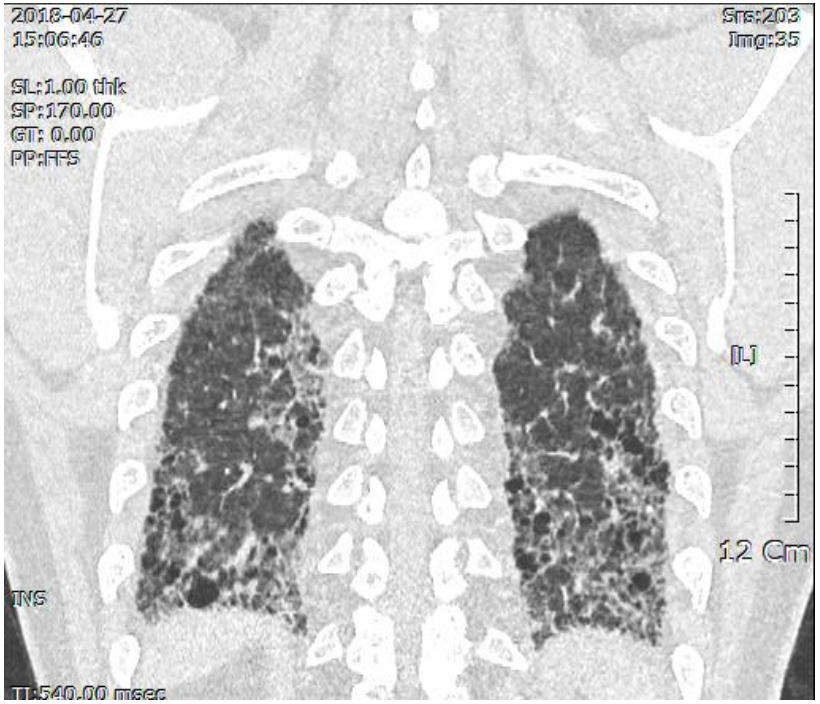
CXR (2016.3 & 2018. 4)





HR CT (2016. 3& 2018.4)





- Dx: cIPF

- Plan : pirfenidone start + PPI
  (2018. 8.17~)

Progress

2018.8

Weight(kg): 74.0
Race: Asian
Physician: 이상엽

		Ref	Pre	% Ref	Post	% Ref	%Chg
Spirometry							
FVC	Liters	4.15	1.77	43			
FEV1	Liters	3.00	1.28	43			
FEV1/FVC	%	75	72				
FEF25-75%	L/sec	2.70	0.84	31			
IsoFEF25-75	L/sec	2.70	0.84	31			
PEF	L/sec	6.97	5				
FET100%	Sec			8			
FIF50%	L/sec			2			
Lung Volumes							
TLC	Liters	5.79	2				
VC	Liters	3.59	1				
IC	Liters	2.43	0				
FRC PL	Liters	3.25	1				
ERV	Liters	1.22	0				
RV	Liters	2.24	1				
RV/TLC	%	38					
Diffusing Capacity							
DLCO	mL/mmHg/min	19.9					
DL Adj	mL/mmHg/min	19.9					
DLCO/VA	mL/mHg/min/L	4.04	4				
DL/VA Adj	mL/mHg/min/L		4				
VA	Liters		2				
IVC	Liters		1				

2019.8

Weight(kg): 71.0
Race:
Physician: 이은주

		Ref	Pre	% Ref	Post	% Ref	%Chg
Spirometry							
FVC	Liters	4.11	1.61	39	1.44	35	-10
FEV1	Liters	2.97	1.20	40	1.22	41	2
FEV1/FVC	%	75	74		85		
FEF25-75%	L/sec	2.66	0.86	33	1.48	56	71
IsoFEF25-75	L/sec	2.66	0.86	33	1.10	42	28
PEF	L/sec	6.94	4.20	61	3.68	53	-12
					3.10		-38
					2.06		14

2020.7

Weight(kg): 67.0
Race: Asian
Physician: 이은주

		Ref	Pre	% Ref	Post	% Ref	%Chg	
Spirometry								
FVC	Liters	4.06	1.54	38	1.34	33	-13	45
FEV1	Liters	2.94	1.26	43	1.12	38	-11	47
FEV1/FVC	%	75	82		84			28
FEF25-75%	L/sec	2.61	1.23	47	1.59	61	30	59
IsoFEF25-75	L/sec	2.61	1.23	47	0.90	34	-27	82
PEF	L/sec	6.90	4.69	68	3.94	57	-16	41
FET100%	Sec		3.70		3.66		-1	
FIF50%	L/sec		2.18		1.40		-36	
Lung Volumes								47
TLC	Liters	5.79	2.60	45				47
VC	Liters	3.54	1.54	43				100
IC	Liters	2.40	0.58	24				
FRC PL	Liters	3.26	2.02	62				
ERV	Liters	1.20	0.74	62				
RV	Liters	2.29	1.06	47				
RV/TLC	%	39	41					
Diffusing Capacity								
DLCO	mL/mmHg/min	19.4	5.1	26				
DL Adj	mL/mmHg/min	19.4	5.1	26				
DLCO/VA	mL/mHg/min/L	3.98	2.82	71				
DL/VA Adj	mL/mHg/min/L		2.82					
VA	Liters		1.81					
IVC	Liters		1.01					

날짜	내용
2012년 7월 31일	식품의약품안전처 피레스파정 허가
2014년 10월 14일	일동제약에서 피레스파정 보험등재신청
2015년 4월 9일	제5차 약제급여평가위원회 평가(비급여)
2015년 5월 22일	재평가신청(위험분담제 신청)
2015년 7월 9일	제7차 약제급여평가위원회 재평가(급여;위험분담적용)
2015년 8월 7일	위험분담제 적용약제로 건정심 보고
2015년 9월 30일	약가 협상 진행(환급형) 결과 5750원으로 협의
2015년 10월 2일	제18차 건강보험정책심의위원회 통과
2015년 10월 3일	위험분담제 환급형으로 급여 적용

2019.01.03

[메디칼업저버 양영구 기자] 일동제약(대표 윤웅섭)은 이달부터 특발성 폐섬유증 치료제 피레스파에 대한 급여 기준이 확대된다고 3일 밝혔다.

기존 피레스파 처방은 고해상 흉부 전산화 단층 촬영(HRCT) 또는 수술적 폐조직 생검(surgical lung biopsy)으로 확진된 특발성 폐섬유증 환자 중 경증 및 중등도 환자로서, 노력성 폐활량(forced vital capacity, FVC) 예측치 50% 이상, 일산화탄소 확산 능력(carbon monoxide diffusing capacity, DLco) 예측치 35% 이상이면서 6분 보행검사 시 150m 이상 걷기가 가능한 경우에만 건강보험 급여가 인정됐다.

하지만 개정된 보험급여 기준에 따르면 FVC 및 DLco과 관련한 인정 기준이 완화됐고, 6분 보행검사도 요건에서 제외돼 FVC 예측치 90% 이하이거나 DLco 예측치 80% 이하의 특발성 폐섬유증 환자이면 피레스파 처방에 대한 건강보험 급여가 가능하다.

특히 전과 달리 FVC 예측치 50% 미만, Dlco 예측치 35% 미만인 중증 특발성 폐섬유증 환자의 경우에도 건강보험 급여 약제로 피레스파 처방이 가능해졌다.

또 FVC 예측치 90% 초과 및 DLco 예측치 80% 초과 환자 중에서 ▲폐 기능 저하(연간 FVC 예측치 감소량 10% 이상 또는 연간 FVC 예측치 200ml 이상 감소 시) ▲임상증상 악화 ▲흉부영상 악화 소견 중 2가지 이상에 해당되는 경우에도 건강보험 혜택을 받을 수 있다.

Case 2

- M/ 70
- CC: rash
- PI : 2012년 CT 이상 소견으로 cIPF 진단 후
  2015년 11월부터 pirfenidone 시작하신 분으로
  2016년 2월 얼굴 및 목, 손등에 rash c itching sense 발생하여
  sunscreening 에 대한 교육 하며 약 감량 없이 호전 중
  2016년 6월 초 팔까지 rash 다시 발생.
  pirfenidone 잠시 중단 후 피부 병변 호전 되어
  저용량으로 6월 중순에 다시 시작 하였으나 바로
  rash 재발하여 중단.

Case 3

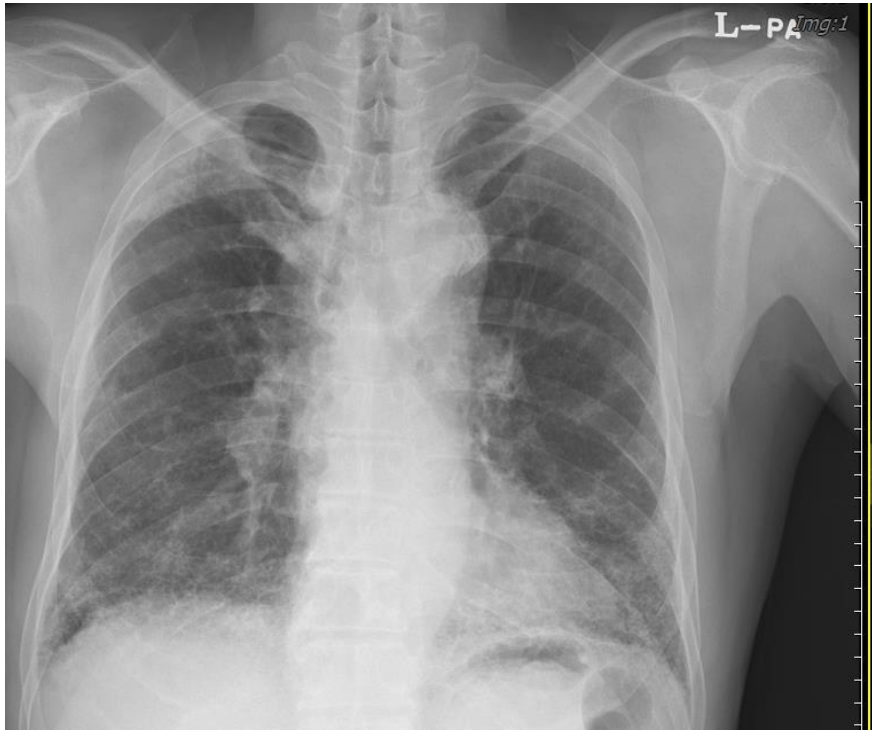
- M/ 67
- CC: CT 이상
- PI : 5년 전부터 기침, 가래, mMRC 2 정도의 호흡곤란이 있었으나 특별한 w/u 없이 지내시던 중 타원에서 시행한 흉부 CT 이상으로 내원
- 본교 공대 교수(정년퇴임하심)
- ex smoker : 25년 전 중단
- PHx : DM/HTN/TBc/hepatitis(-/+/-/-)

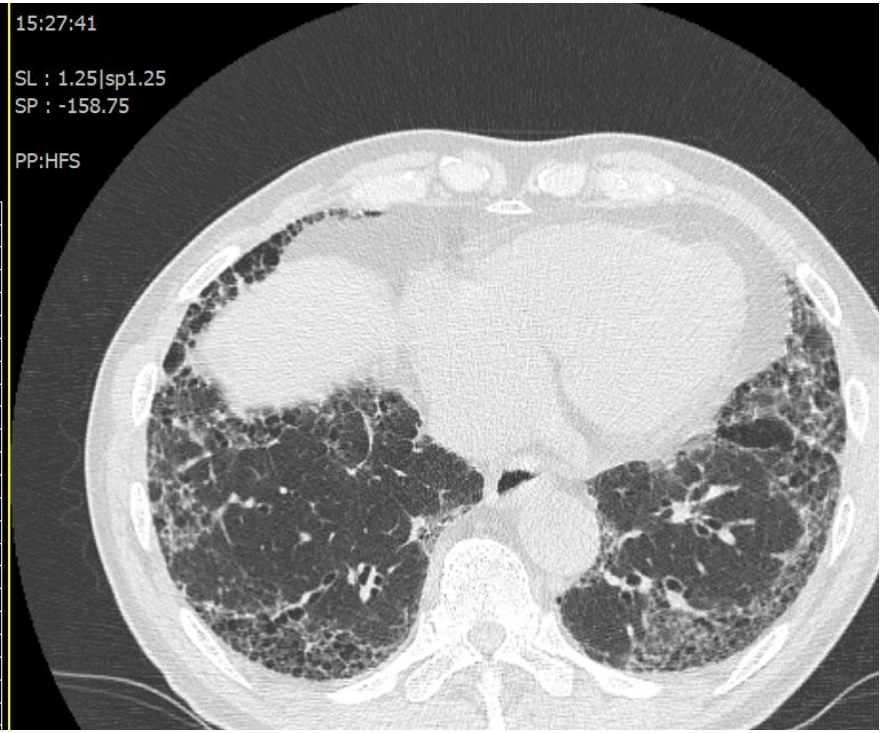
PFT (20. 2.19)

Weight(kg): 70.0
Race: Asian
Physician: 이은주

		Ref	Pre	% Ref	Post	% Ref	%Chg
Spirometry							
FVC	Liters	4.80	2.63	55	2.59	54	-2
FEV1	Liters	3.48	2.20	63	2.21	64	1
FEV1/FVC	%	72	84		86		
FEF25-75%	L/sec	2.74	2.80	102	3.38	123	21
IsoFEF25-75	L/sec	2.74	2.80	102	3.31	121	18
PEF	L/sec	8.11	11.75	145	10.04	124	-15
FET100%	Sec		6.36		6.84		8
FIF50%	L/sec		4.24		3.68		-13
Lung Volumes							
TLC	Liters	6.91	3.85	56			
VC	Liters	4.28	2.63	61			
IC	Liters	2.91	1.37	47			
FRC PL	Liters	3.62	2.48	69			
ERV	Liters	1.46	1.25	86			
RV	Liters	2.53	1.22	48			
RV/TLC	%	40	32				
Diffusing Capacity							
DLCO	mL/mmHg/min	23.7	9.7	41			
DL Adj	mL/mmHg/min	23.7	9.7	41			
DLCO/VA	mL/mHg/min/L	3.61	2.95	82			
DL/VA Adj	mL/mHg/min/L		2.95				
VA	Liters		3.28				
IVC	Liters		2.35				

CXR, CHEST CT





Progress

- Pirfenidone
  : 2020.2.19 시작
  → 2020.5월 햇빛에 노출되는 팔 위주로 (골프) rash 발생
  → sunscreening (긴옷, 모자, 선블럭) 에 대한 교육 다시 시행
  → CXR에서 약간의 악화 소견 및 피부 병변 호전 없음
  → 2020.6월까지만 복용

- Nintedanib
  : 2020.7.1일부터 시작
  피부 병변은 호전
  2020.10.21일 설사 발생하여 지사제 시작함
  식사양의 변화는 없으나 2kg의 체중 감량 있었다 함

Definition

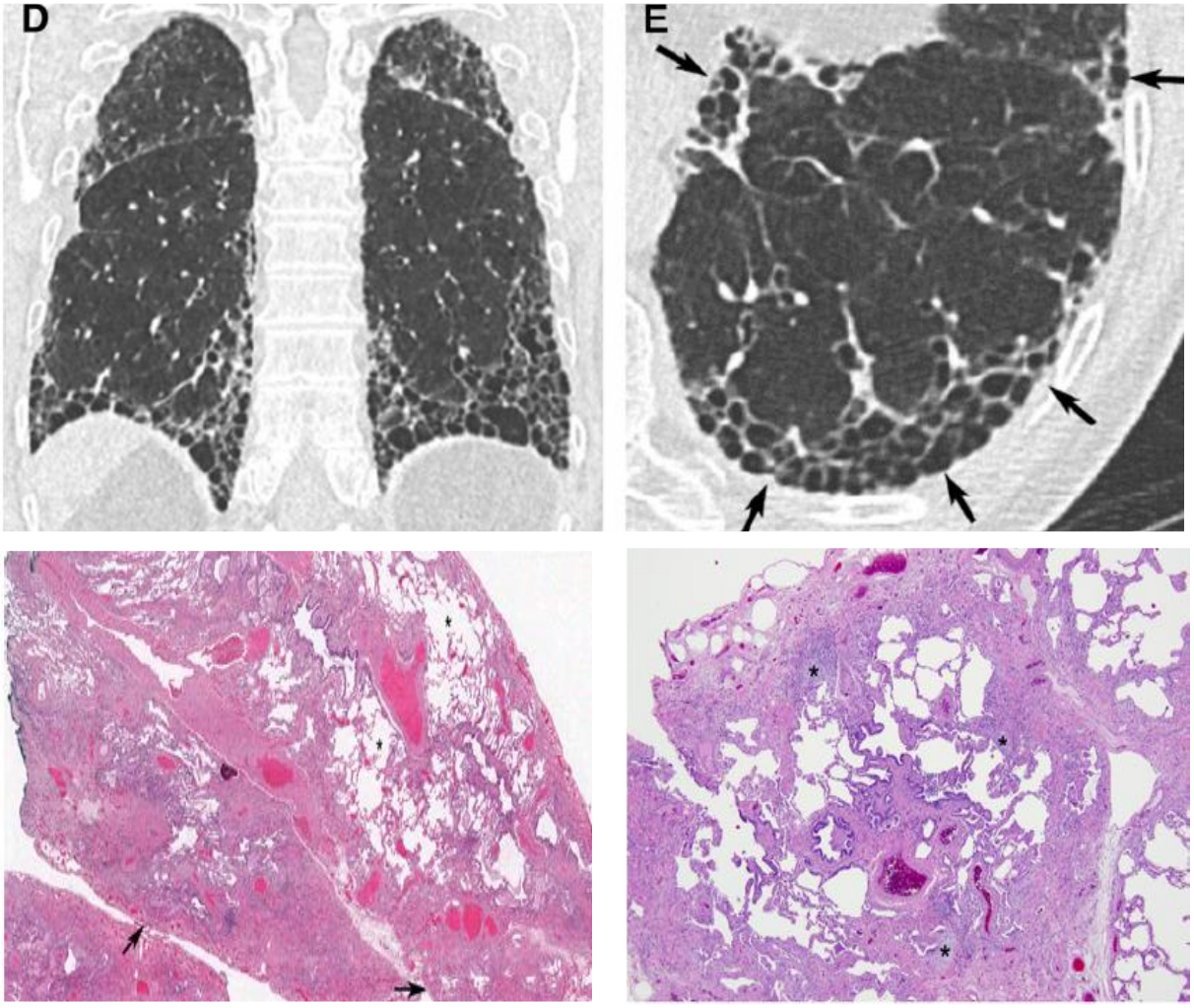
- Definition

  : a specific form of chronic, progressive
  fibrosing interstitial pneumonia of unknown cause,
  occupying primarily in older adults,
  limited to the lungs,
  and associated with the histopathologic and/ or radiologic
  pattern of UIP

  exclusion of other forms of idiopathic interstitial pneumonia
  & ILD associated with environmental exposure, medication,
  or systemic disease

Am J Respir Crit Care Med 2011;183: 788-824

Diagnosis



Am J Respir Crit Care Med 2018;198: e44-e68

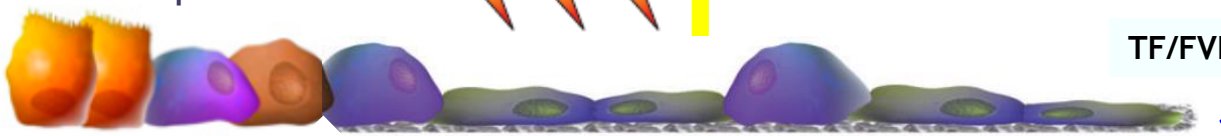
Telomere shortening
Increased oxidative stress
Epigenetic deregulation
Deregulation of embryological pathways

Ageing-related susceptible lung

Apoptosis → Caveolin-1 & RAGE ↓

ROS(reactive oxygen species)
Viral infection?
ER stress

Alveolar epithelium



TF/FVIIa/FX

FXa

Matrix metalloproteinases imbalance

Wound clot

Angiogenesis, vascular remodeling

Thrombin

Prothrombin

TGF-β1

Fibroblast

Pericytes & mesothelial cells & endothelial cells

TGF-β1

High mechanical stress
TGF- β 1
Matrix proteins

TGF-β1, PDGF, TNF-α, endothelin-1

Vasculature

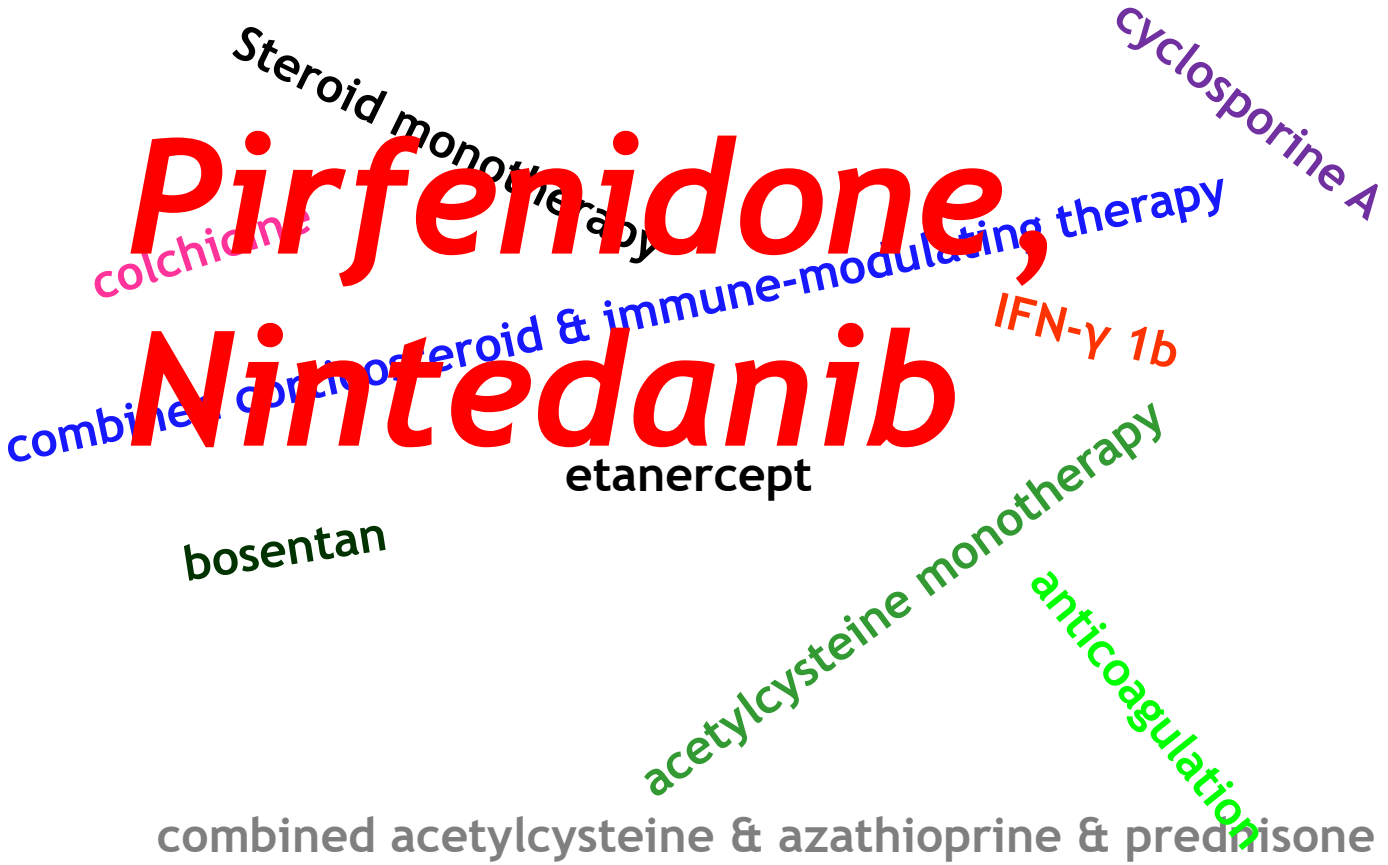
Fibrocytes

CXCR4/CXCL12
MMP 8

Myofibroblast

Exaggerated ECM accumulation → Progressive lung remodeling → Honeycomb changes

Treatment

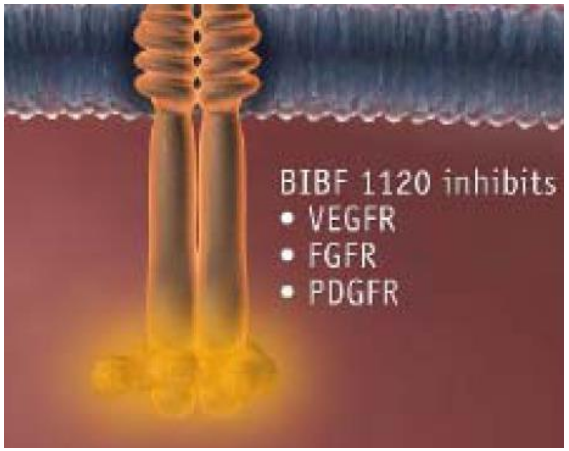


Am J Respir Crit Care Med 2011;183: 788-824


Risk
Benefit

Nintedanib

- Intracellular inhibitor of TKI (VEGFR, FGFR, PDGFR)
- Inhibit fibroblast proliferation, migration and differentiation
- Anti-fibrotic, anti-inflammatory, anti-angiogenetic activity

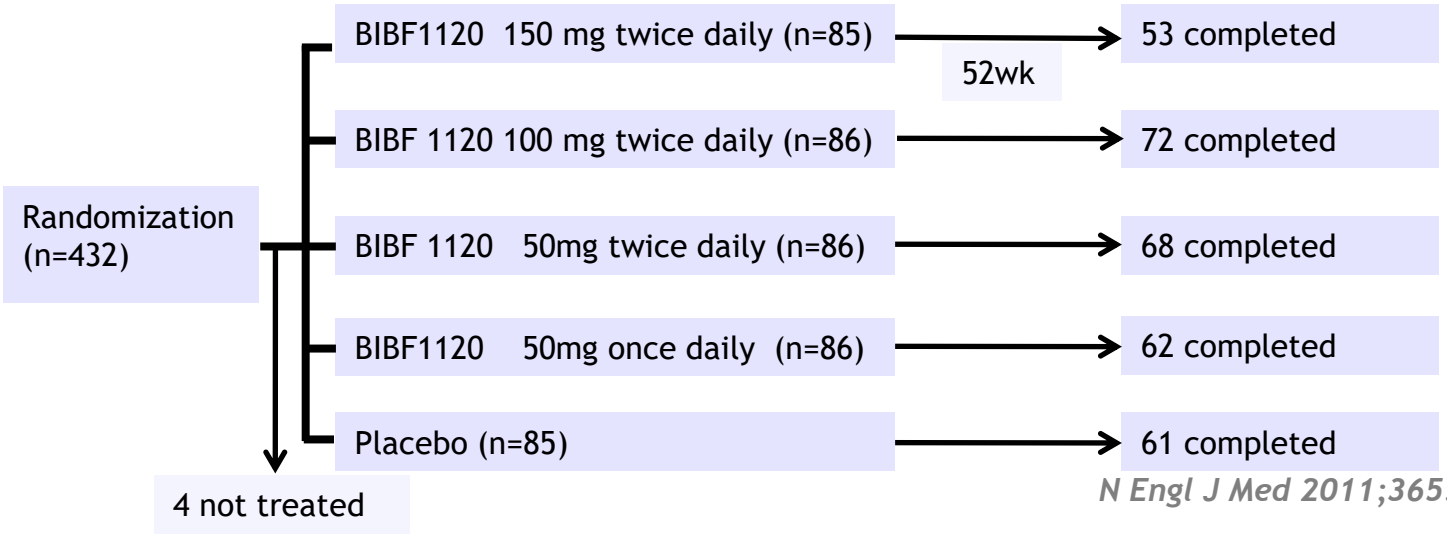


Semin Respir Crit Care Med 2016;37:368-377

TOMORROW :Nintedanib

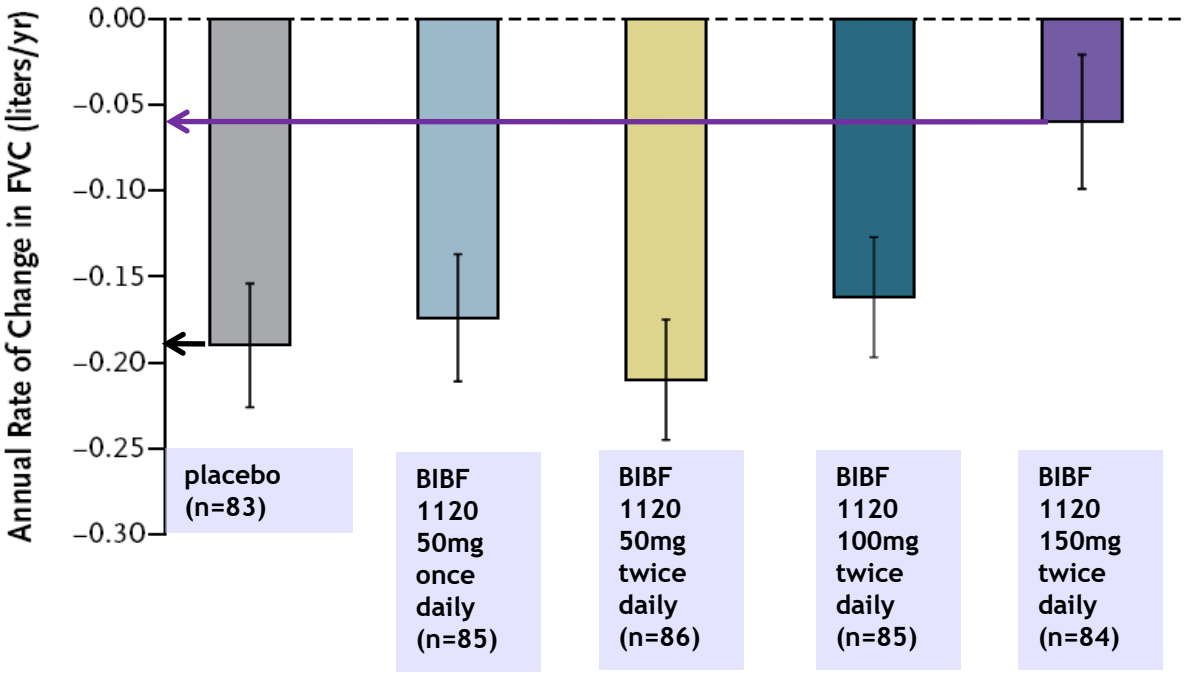
- 92 centers, 2007.9~2010.6, 428 pts
- Double blind, RCT, phase 2
- IPF: age ≥ 40 yrs , FVC≥50%, 30%≤ DL_{CO} <80%

  Dx≤ 5yr
- Primary outcome: annual rate of decline in FVC (12m)



N Engl J Med 2011;365:1079-1087

TOMORROW :Nintedanib



- Fewer AEs, preserved QoL

  FVC decline ≥ 10% or 200ml ↓ , Δ SpO_2&TLC ↓
- More GI Sx, more frequent elevations in liver enzyme

N Engl J Med 2011;365:1079-1087

INPULSIS :Nintedanib

- 205 centers, 2011.5~2012.

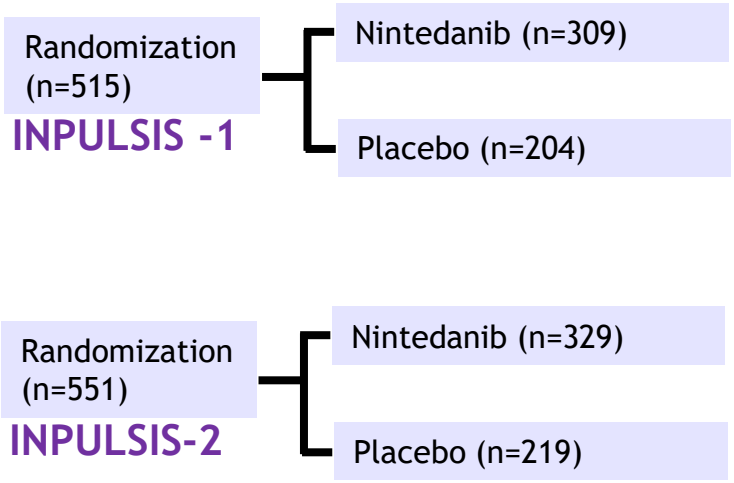
  Double blind, RCT, phase 3, 1,066 pts

- IPF: age ≥ 40 yrs

  FVC ≥ 50%, 30% ≤ DL_{CO}<80%

  Dx ≤ 5yr

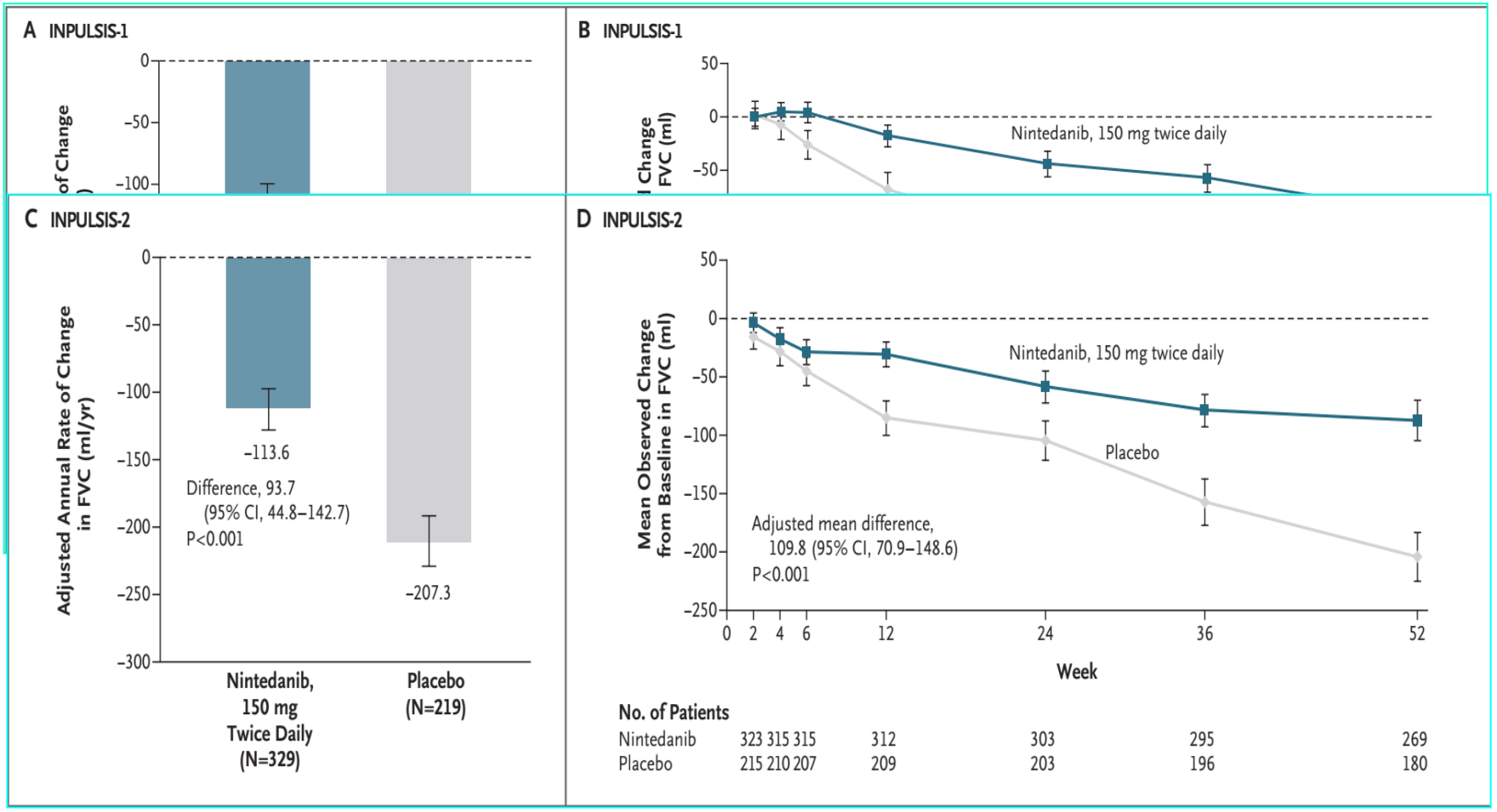
  CT: UIP or probable UIP



- Primary outcome: annual rate of decline in FVC (52wk)

N Engl J Med 2014;370:2071-2082

INPULSIS :Nintedanib



N Engl J Med 2014;370:2071-2082

INPULSIS :Nintedanib

- Acute Exacerbation

  INPULSIS -1 : No difference

  INPULSIS -2 : Significant increase in time to first AE

- S/Ex : Diarrhea (M/C, 60%), N (25%),
  decreased appetite(10%),
  MI (1.6 % vs 0.5% in INPULSIS-1
  1.5% vs. 0.5% in INPULSIS-2)

Financial Toxicity !!!

N Engl J Med 2014;370:2071-2082

INPULSIS-ON :Nintedanib

- Open-label nintedanib in the extension trial (from INPULSIS) median 44.7 m

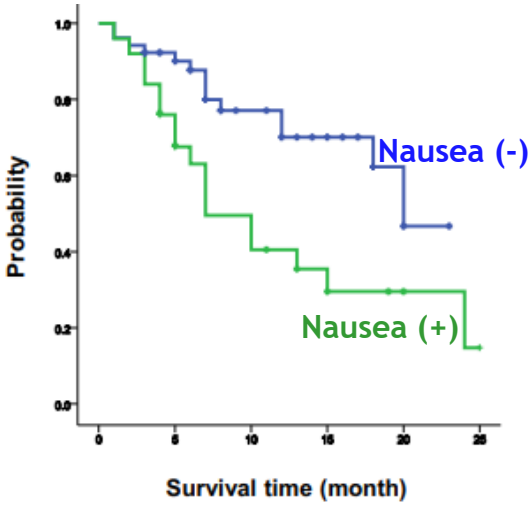
	INPULSIS				INPULSIS-ON			
	Nintedanib (n=638)		Placebo (n=423)		Continued nintedanib (n=430)		Initiated nintedanib (n=304)	
	Number of events	Event rate (per 100 patient exposure-years)	Number of events	Event rate (per 100 patient exposure-years)	Number of events	Event rate (per 100 patient exposure-years)	Number of events	Event rate (per 100 patient exposure-years)
Major adverse cardiovascular events	26	4·4	11	2·7	40	3·6	17	2·4
Myocardial infarction (broad scope)	18	3·0	5	1·2	14	1·3	5	0·7
Myocardial infarction (narrow scope)	11	1·8	2	0·5	13	1·2	4	0·6
Bleeding	94	15·8	42	10·2	93	8·4	48	6·7

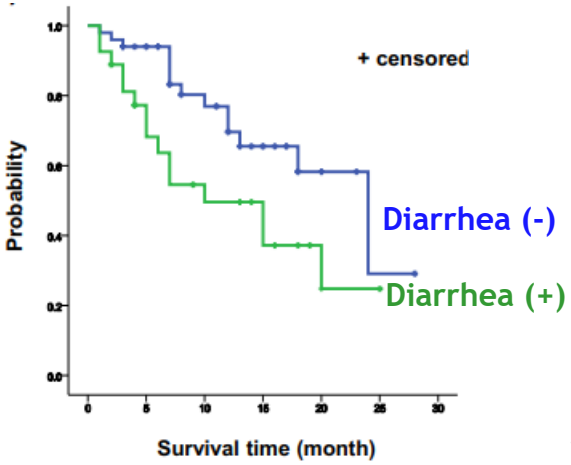
Lancet Respir Med 2019;7:60-68

GI S/Ex :Nintedanib

- Retrospective study, 2015.10-2018. 3, Japan, 77 pts
- Nausea(25/77, 32.5%), Diarrhea(27/77, 35.1 %)
- Risk factor for Nausea: poor PS, low BMI, full dose
- Risk factor for Diarrhea: low BMI
- Optimal Cut-off value for BMI was 21.6

→ AUC was 0.872 for Nausea, 0.668 for Diarrhea





Scientific Reports 2019;9:12062

Management for S/Ex :Nintedanib -1

- Diarrhea
  - loperamide 2mg--> can be increased up to 2mg or 4mg QID
    can be added codein phosphate → GI specialist
  - reducing dose 150 → 100mg bid
  - dose can be titrated back up to the optimal dose
- Nausea
  - consider prokinetics such as metoclopramide or ondansetron
  - reducing dose 150→ 100mg
- Hepatic side effects
  - reversible with dose reduction or short Tx interruption
  - not studied in pt with Child-Pugh B/C hepatic impairment

Respiration 2019;97:173-184

Management for S/Ex :Nintedanib -2

	INPULSIS[1] Nintedanib (n = 638)	INPULSIS[1] Placebo (n = 423)	INPULSIS-ON[2] (n = 430)	Post-marketing[3] (n = 6,758)
Major adverse cardiac events	3.9	2.7	3.1	2.9
Myocardial infarction[4]	1.7	0.5	0.7	1.0
Bleeding[5]	11.8	8.3	7.1	11.9

- Arrhythmia, Valve dz, VTE
  - NOAC (OK) vs VKA (consider c caution)
- Angina –Stable c ASA mono(OK)
  Stable+ PCI (ASA+ clopidogrel for 6 m)
  (consider c caution)
- MI – ASA (±clopidogrel)(OK)
  Heparin+high dose ASA+PCI/clopidogrel (consider c caution)
- Stroke- ASA/Clopidogrel (OK)

Respiration 2019;97:173-184

Management for S/Ex :Nintedanib -3

- Before & after OP/lung transplantation
  - For minor elective OP, Tx should not be interrupted.
  - For major elective OP(abd OP), Tx should be stopped 2-3 days prior to OP, this recommendation is based on 5 half-lives.
  - All non-elective Emergency OP should be undertaken as soon as possible without delay.
  - Following OP, Tx should be resumed as soon as the pt is able to eat food, since nintedanib Tx on an empty stomach is like to lead to an increased risk of side effects.
  - For transplant pts, ideally, maintain pts on nintedanib while they are on the transplant waiting list to help preserve existing lung function & to prevent acute exacerbations. *Respiration 2019;97:173-184*

Pirfenidone

- Anti-fibrotic effect

  - inhibit human lung fibroblast proliferation

    decrease collagen matrix formation in response to TGF-β

    decrease lung hydroxyproline content & histologic severity of fibrosis

- Anti-oxidant effect

  - decrease myeloperoxidase & superoxide dismutase

- Anti-inflammatory

  - suppress TNF-α

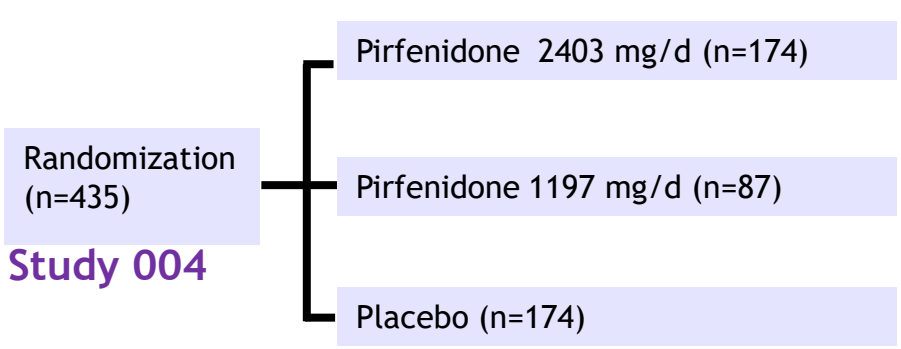
Semin Respir Crit Care Med 2016;37:368-377
Front Med 2018;5: 148

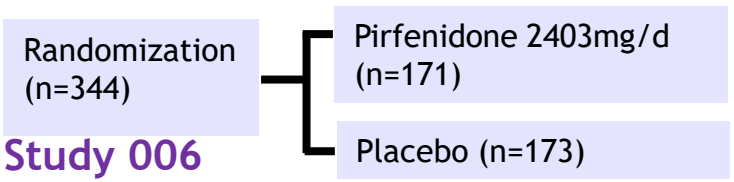
CAPACITY: Pirfenidone (004 & 006)

- 110 centers, 2006.4~2008.11
- Double blind, RCT, 435 pts in 004, 344 pts in 006
- IPF: 40-80 yrs & Dx within 48 months

  50% ≤ FVC ≤ 90%, 35% ≤ DL_{CO}≤ 90%, 6MWT distance ≥150m
- Primary outcome: ΔFVC % at 72 weeks

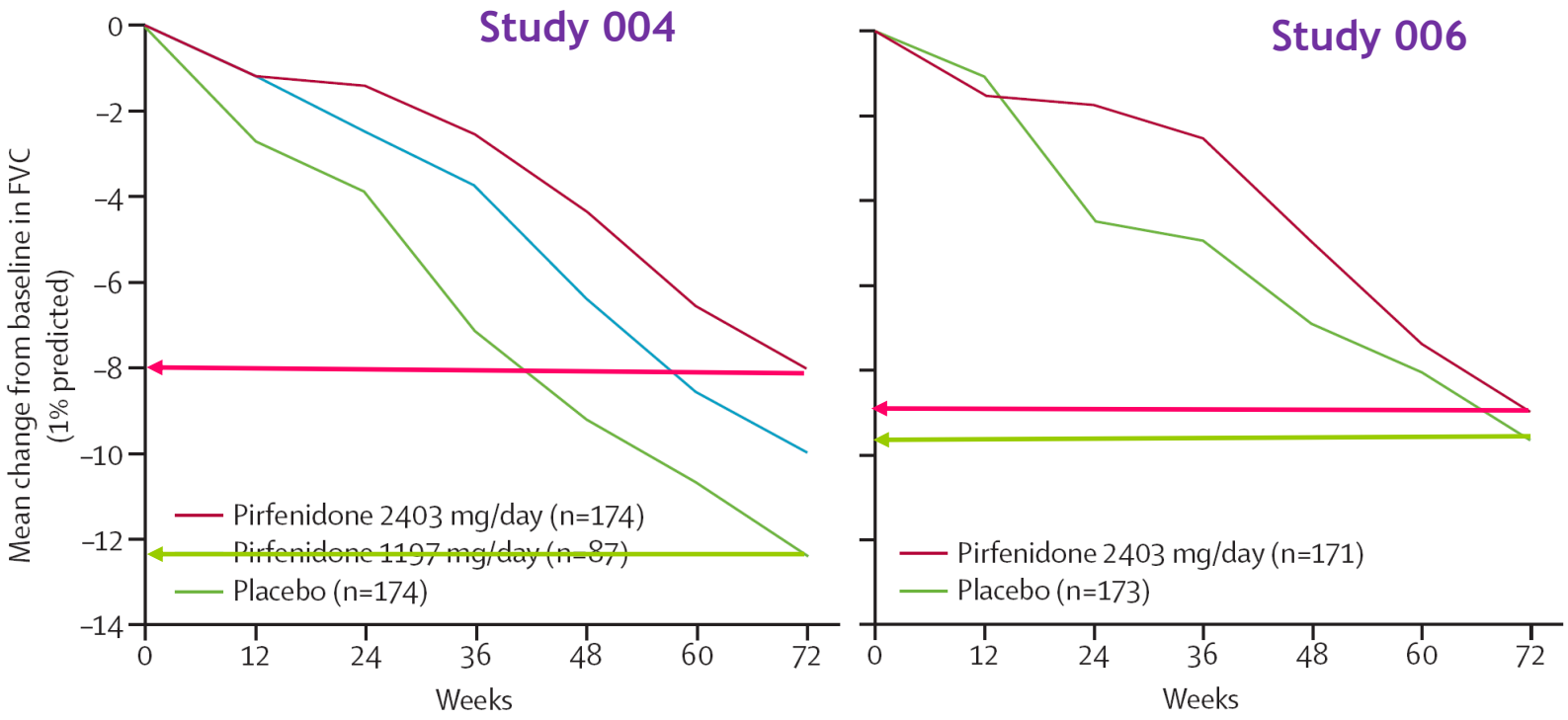
  secondary outcome: categorical FVC, progression-free survival, worsening IPF, dyspnea, 6MWD, SpO_2, fibrosis (HR CT), DL_{CO}%





Lancet 2011;3774:1760-1769

CAPACITY: Pirfenidone (004 & 006)

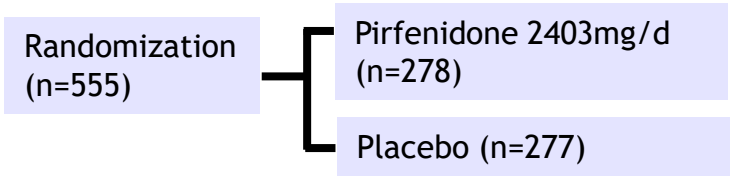


- Fewer overall deaths and fewer deaths related to IPF

Lancet 2011;3774:1760-1769

ASCEND: Pirfenidone

- 127 centers, 2011.7~2013.1
- Double blind, RCT, 555 pts



- IPF: 40-80 yrs

  50% ≤ FVC ≤ 90%, 30% ≤ DL_{CO}≤ 90%, 6MWT distance ≥150m

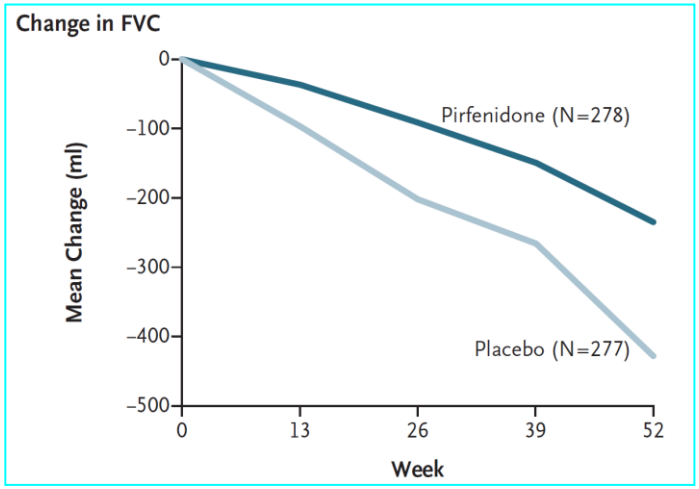
  fibrosis>emphysema, FEV_1/FVC ≥0.8, 6m ≤ Dx ≤ 48 m,

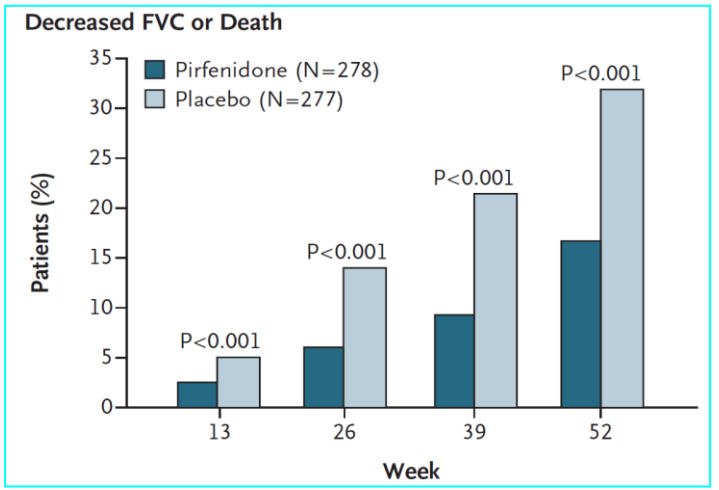
  Sx duration ≥ 12m

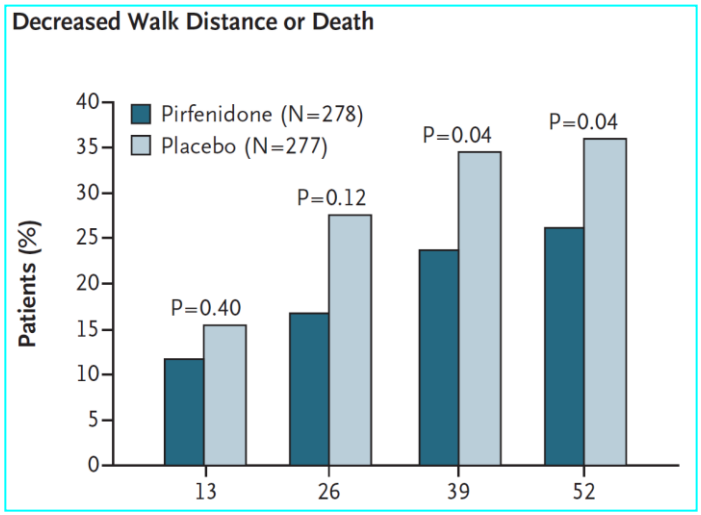
- Primary outcome: ΔFVC % at 52 wk

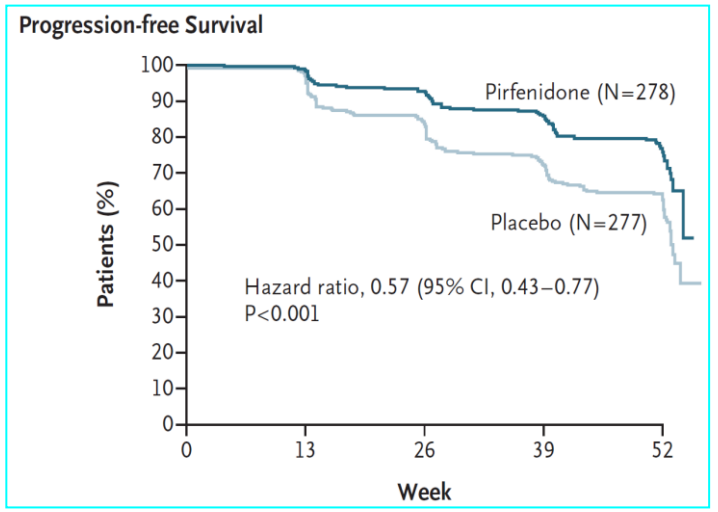
N Engl J Med 2014;370: 2083-92

ASCEND: Pirfenidone









N Engl J Med 2014;370: 2083-92

ASCEND: Pirfenidone

Mortality in the ASCEND and CAPACITY Trials				
Variable	Pirfenidone	Placebo	Hazard Ratio	P value
ASCEND				
No. of pts	278	277		
Death-no (%) From any cause Related to IPF	 11(4.0) 3(1.1)	 20(7.2) 7(2.5)	 0.55(0.26-1.15) 0.44(0.11-1.72)	 0.10 0.23
Pooled data from ASCEND & CAPACITY trials				
No. of pts	623	624		
Death-no (%) From any cause Related to IPF	 22(3.5) 7(1.1)	 42(6.7) 22(3.5)	 0.52(0.31-0.87) 0.32(0.14-0.76)	 0.01 0.006

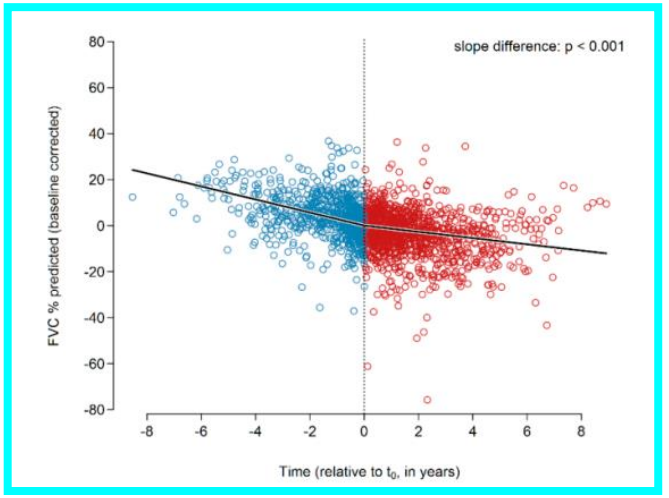
N Engl J Med 2014;370: 2083-92

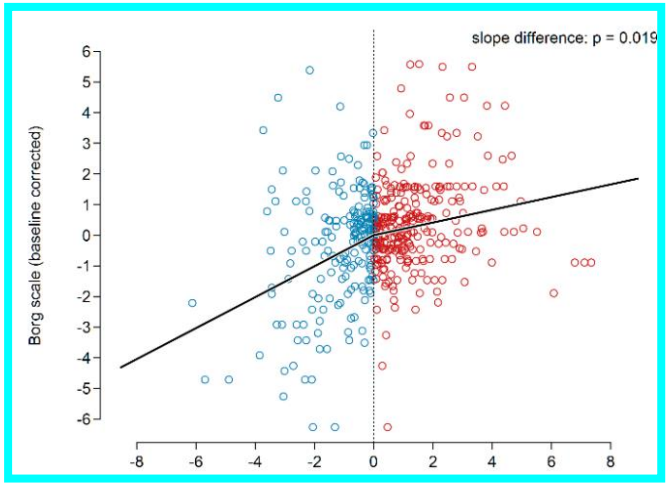
European IPF registry: Pirfenidone

- 2009.11~2018.5, 122 pts

Table 1. Clinical characteristics and baseline lung function in IPF patients at t_0.

Parameters at t_0	Pirfenidone Study Cohort
Patients in the analysis (n)	122
Male (%)	73.2
BMI (mean value ± SD (kg/m^2))	28.3 ± 4.56
Age at t_0 (mean value ± SD (years))	67.2 ± 10.3
Current smokers/previous smokers/never smoked (%)	4.1%/ 64.8%/31.1%
Pack years (mean value ± SD)	28.0 ± 21.0
GAP Stage I/II/III (% of the whole cohort)	21.1%/41.5%/21.1% (16.3% were missing values)
VC (% pred.; mean value ± SD)	64.5 ± 17.5
FVC (% pred.; mean value ± SD)	63.0 ± 18.3
DLco (% pred.; mean value ± SD)	42.4 ± 20.4
pO_2 (mm Hg) at rest (mean value ± SD)	67.6 ± 72.4
pCO_2 (mm Hg) at rest (mean value ± SD)	33.5 ± 44.9

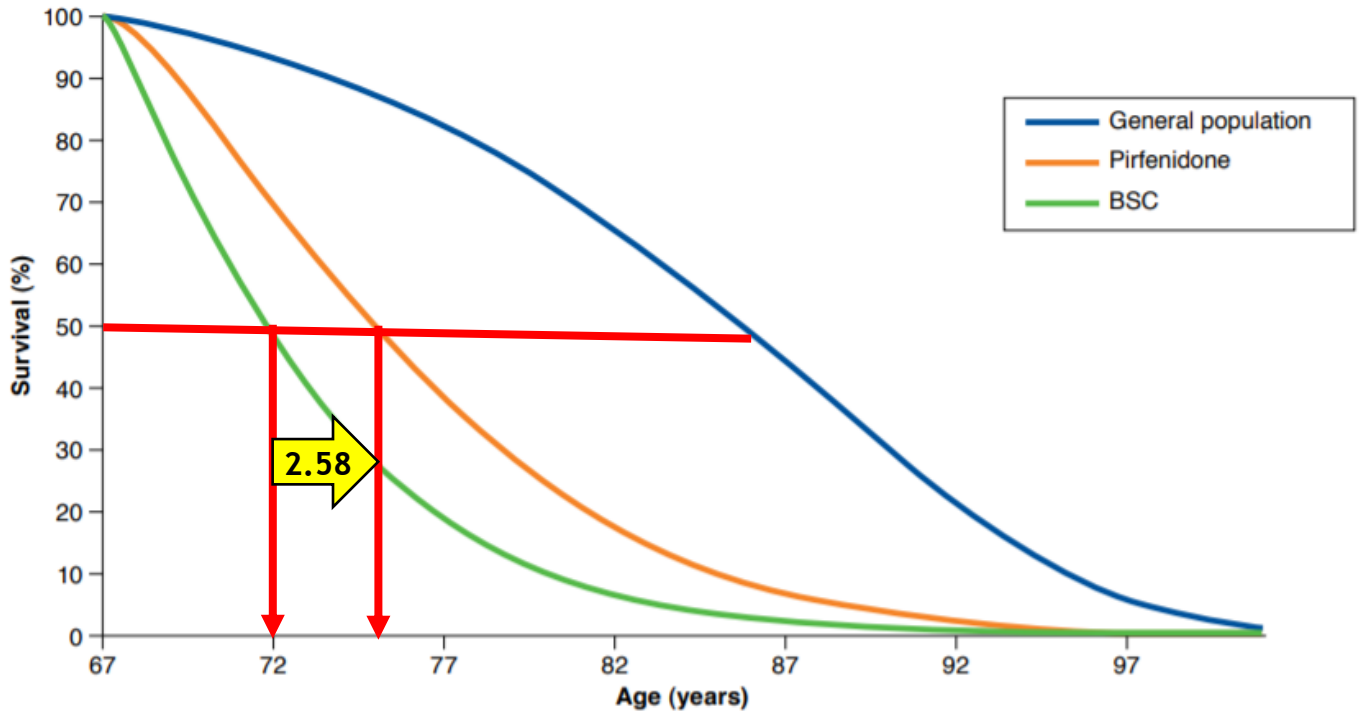




J Clin Med 2020; 3763

Predicting life expectancy: Pirfenidone

FIGURE 2 Survival with Pirfenidone and BSC in Patients with IPF Versus Survival in a Matched Population from the United Kingdom

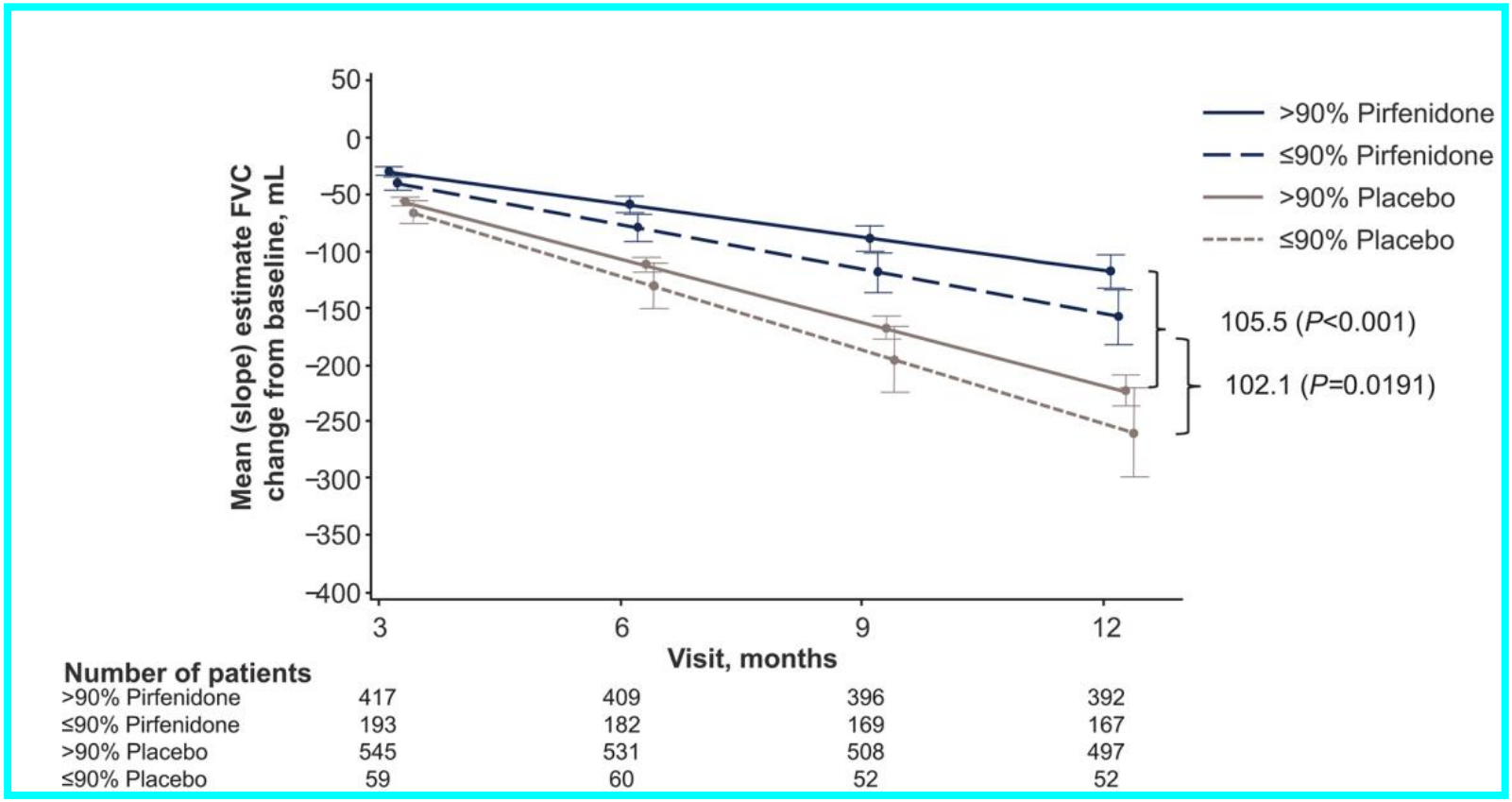


BSC = best supportive care; IPF = idiopathic pulmonary fibrosis.

J Manage Care Spec Pharm 2017;23: s17-s24

Impact of dose intensity: Pirfenidone

- CAPACITY + ASCEND (n=1247), post-hoc analysis



Number of patients				
>90% Pirfenidone	417	409	396	392
≤90% Pirfenidone	193	182	169	167
>90% Placebo	545	531	508	497
≤90% Placebo	59	60	52	52

BMJ Open Resp Res 2018; 5:e000323

Impact of dose intensity: Pirfenidone

- Retrospective cohort, 2012.7-2018.3, 338 pt, Korea

All patients	Value
Duration of total pirfenidone treatment, mo	16.1 ± 9.0

Table 4. Comparison of FVC and DL_{CO} decline rate before and after treatment according to the dose of pirfenidone

Parameter	Time	Standard dose (n = 32)			Non-standard dose (n = 82[a] or 75[b])		
		Mean	95% CI	*p* value	Mean	95% CI	*p* value
Δ F…	…	…	…		…	…	

Parameter	Time	1,200–1,600 mg dose (n = 53[a] or 48[b])			< 1,200 mg dose (n = 29[a] or 27[b])		
		Mean	95% CI	*p* value	Mean	95% CI	*p* value
Δ FVC/year (%)[c] (n = 82)	Pre-treatment	−5.64	−7.99 to −3.29		−3.95	−7.03 to −0.87	
	Post-treatment	−0.43	−1.63 to 0.76		−3.86	−5.36 to −2.37	
	Difference	5.21		< 0.001	0.09		0.931
p value for homogeneity of difference in parameter between two groups: < 0.001							
Δ DL_{CO}/year (%)[c] (n = 75)	Pre-treatment	−6.80	−10.77 to −2.83		−9.23	−13.64 to −4.82	
	Post-treatment	−2.02	−3.47 to −0.56		−4.86	−6.95 to −2.77	
	Difference	4.78		< 0.001	4.37		0.001
p value for homogeneity of difference in parameters between two groups: 0.798							

Pa… treatment, mo

KJIM 2022; 37:366-376

Adverse Event	Pirfenidone (N = 278)	Placebo (N = 277)
	no. of patients (%)	
Cough	70 (25.2)	82 (29.6)
Nausea	100 (36.0)	37 (13.4)
Headache	72 (25.9)	64 (23.1)
Diarrhea	62 (22.3)	60 (21.7)
Upper respiratory tract infection	61 (21.9)	56 (20.2)
Fatigue	58 (20.9)	48 (17.3)
Rash	78 (28.1)	24 (8.7)
Dyspnea	41 (14.7)	49 (17.7)
Dizziness	49 (17.6)	36 (13.0)
Idiopathic pulmonary fibrosis†	26 (9.4)	50 (18.1)
Bronchitis	39 (14.0)	36 (13.0)
Constipation	32 (11.5)	38 (13.7)
Back pain	30 (10.8)	37 (13.4)
Dyspepsia	49 (17.6)	17 (6.1)
Nasopharyngitis	33 (11.9)	30 (10.8)
Anorexia	44 (15.8)	18 (6.5)
Vomiting	36 (12.9)	24 (8.7)
Decrease in weight	35 (12.6)	22 (7.9)
Gastroesophageal reflux	33 (11.9)	18 (6.5)
Insomnia	31 (11.2)	18 (6.5)

N Engl J Med 2014;370: 2083-92

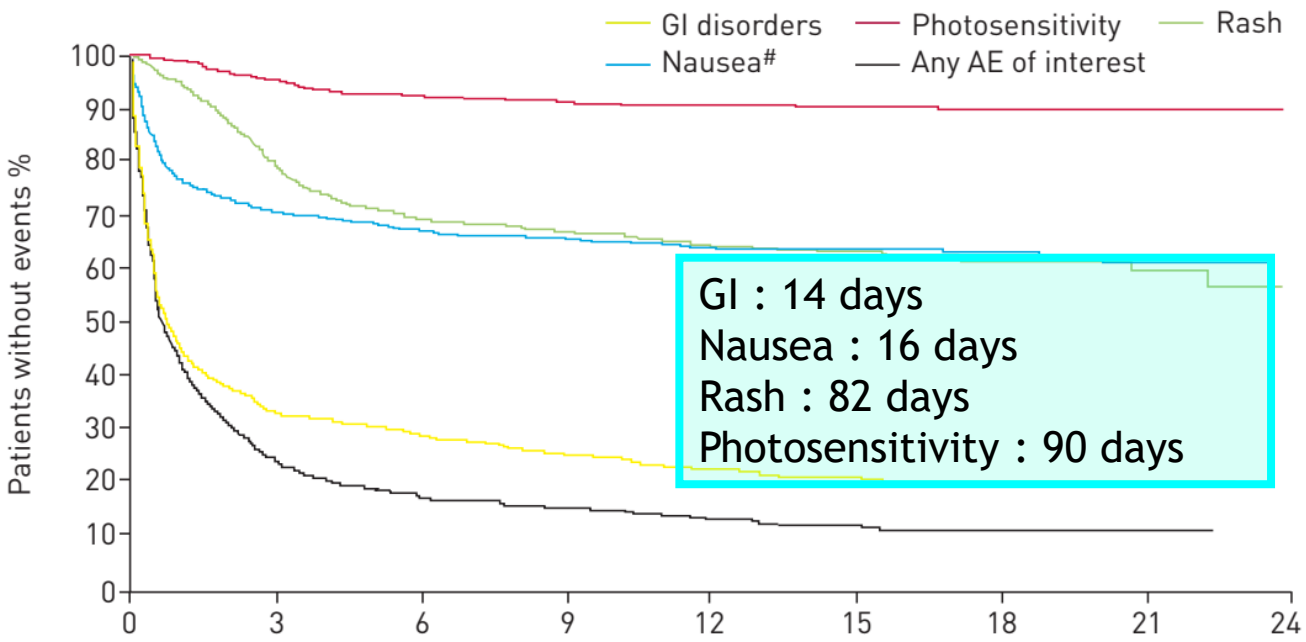
PASSPORT: Pirfenidone

- 99 clinics across Europe
- prospective, observational study, 1009 pts
- Median exposure: 442 days

	Total events	Patients with event
Any ADRSI	1577	693 (68.7)
Gastrointestinal symptoms	591	386 (38.3)
Photosensitivity and skin rashes	388	293 (29.0)
Fatigue	257	244 (24.2)
Weight loss	173	162 (16.1)
Dizziness	79	72 (7.1)
Abnormal LFTs	54	36 (3.6)
Angioedema	10	9 (0.9)
Specific cardiac events	9	7 (0.7)
Falls	6	6 (0.6)
Blood dyscrasias	4	4 (0.4)
Severe skin infections	4	4 (0.4)
Drug interactions (including smoking)	2	2 (0.2)
Increased platelet count	0	0 (0.0)

ERJ Open Res 2018;4: 00084-2018

Time to 1st occurrence (pirfenidone)



GI : 14 days
Nausea : 16 days
Rash : 82 days
Photosensitivity : 90 days

Patients at risk n									
GI disorders	623	199	166	139	86	64	25	12	0
Photosensitivity	623	574	530	499	343	258	118	66	6
Rash	623	478	395	366	244	176	81	36	5
Nausea#	623	427	385	361	248	188	87	43	4
Any AE of interest	623	143	100	87	56	38	12	5	0

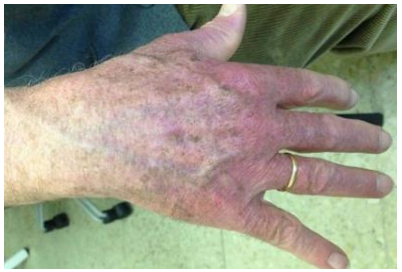
Eur Respir Rev 2017;26:170057

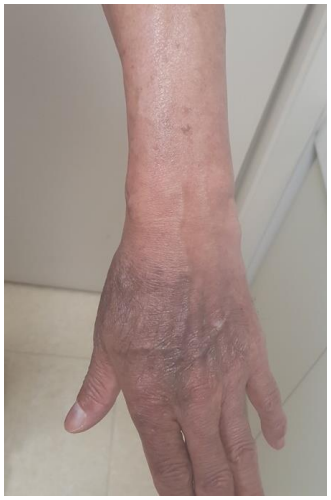
Skin S/Ex: Pirfenidone

- Erythematous or phototoxic burn-like skin rash

- It differs from an allergic type of eruption, which affect all parts of the skin including areas not exposed to sunlight.

- Mechanism
  - phototoxic
    related to ability
      to absorb both UV B/A
    proportional to
      light exposure & drug concentration

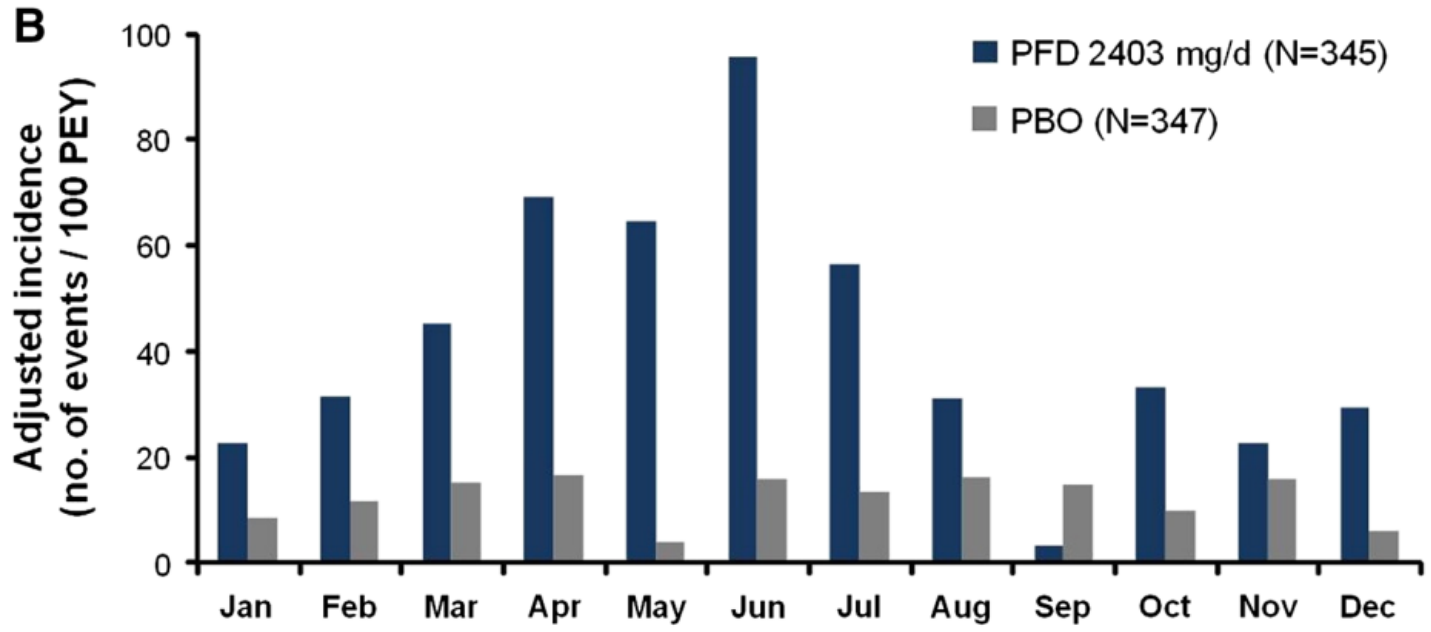




Adv Ther 2014;31: 375-391

Skin S/Ex: Pirfenidone

- CAPACITY study



Adv Ther 2014;31:375-391

Skin S/Ex: Pirfenidone

- Sun exposure should be avoided for a few hrs following pirfenidone intake.

- Protect skin with appropriate clothing
  (hat, sunglasses, long-sleeve shirts, trouser, and gloves)
  Re-apply a broad-spectrum sunscreen frequently

- In case of rashes, pirfenidone should be reduced.
  If rashes still persist after 7 days, it should be discontinued for 15 days and may be slowly re-introduced once Sx have resolved.
  If allergic rex, it should be permanently discontinued.

Adv Ther 2014;31: 375-391

PMS study in KOREA (pirfenidone)

- prospective, nationwide observational study, 219 pts
- 2014-2017

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

Characteristic	Total	Advanced		
Patients, *n*	219	39		
Adverse events	189 (86.3)	36 (92.3)		
Decreased appetite	71 (32.4)	13 (33.3)		
Photosensitivity reaction	30 (13.7)	6 (15.4)		
Rash	25 (11.4)	2 (5.1)		
Nausea	24 (11.0)	6 (15.4)		
Pruritus	24 (11.0)	1 (2.6)		
Epigastric discomfort	22 (10.1)	4 (10.3)		
Cough	21 (9.6)	2 (5.1)		
Pneumonia	19 (8.7)	6 (15.4)		
Dyspnea	18 (8.2)	7 (18.0)		
Progression of IPF[a]	16 (7.3)	6 (15.4)		
Productive cough	15 (6.9)	4 (10.3)		
Constipation	13 (5.9)	3 (7.7)		
Fatigue	11 (5.0)	4 (10.3)		
Asthenia	10 (4.6)	1 (2.6)		
Dizziness	10 (4.6)	1 (2.6)		
Upper respiratory tract infection	9 (4.1)	0 (0.0)		
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

Table 3 Reasons for premature discontinuation of the treatment in the advanced and non-advanced IPF groups

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

Adv Ther 2020;37: 2303-2316

GI S/Ex: Pirfenidone

- Randomized, open-label, single-dose (3x267 mg capsules),
  4 way crossover study,
  16 healthy subjects aged between 50 and 79 yrs

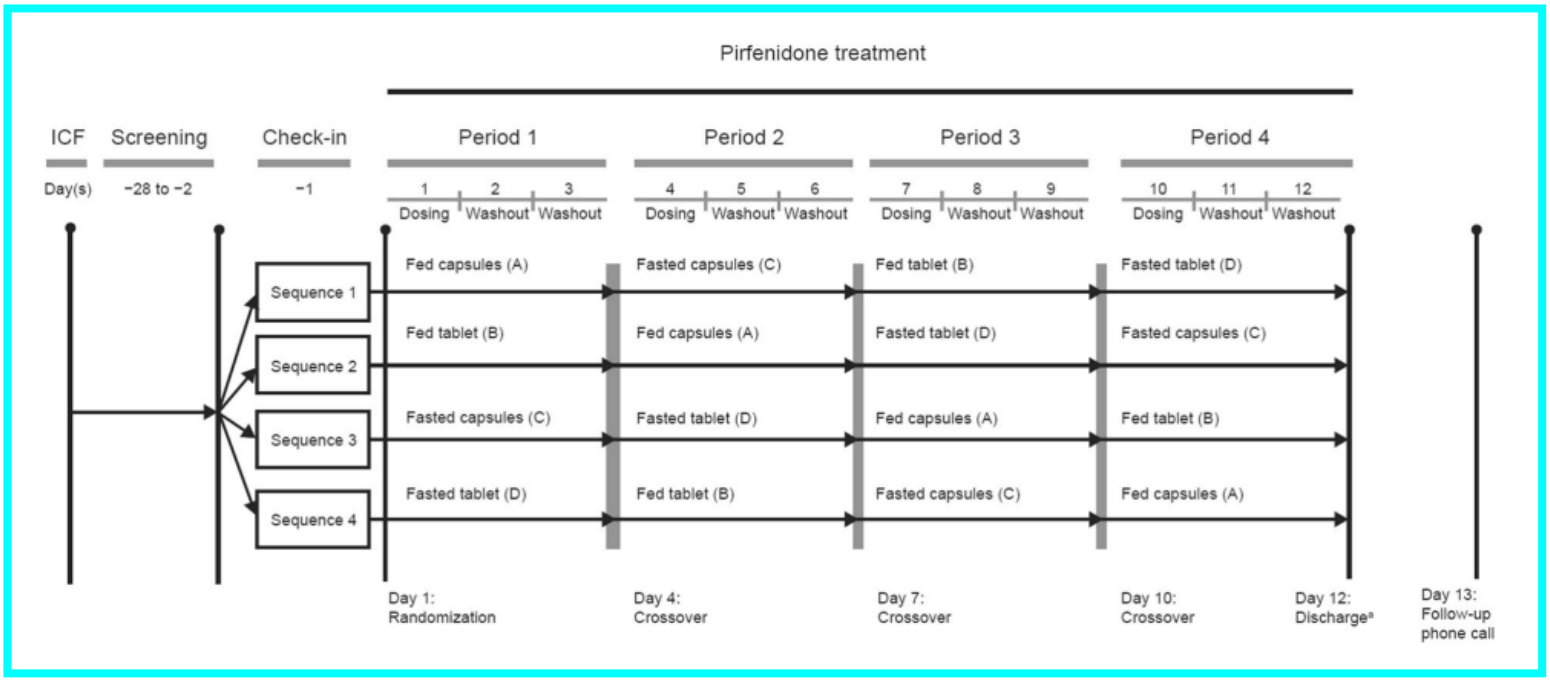
Treatment block	Statistic	CL_f/F^a (L/h)	V_{ss}/F^a (L)	$t_{½}$ (h)	$t_{½abs}$ (h)	$AUC_{0-\infty}$ (mg h/L)	C_{max} (µg/mL)	T_{max} (h)
A, fasted	Mean (SD)	11.8 (3.28)	40.4 (5.95)	2.88 (1.03)	0.572 (0.670)	69.7 (20.5)	15.7 (4.80)	
	Median (25th–75th)	11.3 (9.21–14.2)	40.5 (36.2–43.5)	2.54 (2.17–3.40)	0.375 (0.246–0.556)	69.7 (53.6–82.7)	15.4 (13.3–18.7)	0.50 (0.50–1.0)

Adverse event	Independent variables	Odds ratio (95% CI)	*P*-value
CNS	Fed state	0.15 (0.040–0.56)	0.005
GI	Female sex	510 (14–19000)	<0.001
	Pirfenidone C_{max}	1.4 (1.1–1.7)	0.001

Pulm Pharmacol Ther 2009;22:279-285

GI S/Ex: Pirfenidone

- Phase 1, open-label, randomized, 4 Tx crossover
  801mg single dose vs. 267mg X 3 capsules
  fasted vs. fed (≈800-1000kcal, fat≥50%)
  healthy adult volunteers (18-55 yr)



Adv Ther 2017;34:2071-2082

GI S/Ex: Pirfenidone

PK parameter	Geometric mean (CV%)			
	Fed state (n = 43)		Fasted state (n = 42)	
	3 × 267-mg capsules	1 × 801-mg tablet	3 × 267-mg capsules	1 × 801-mg tablet
C_{max} (ng/mL)	6560 (25.5)	7640 (27.9)	12,500 (27.9)	12,600 (32.8)
AUC_{0-t} (ng h/mL)	39,500 (36.6)	40,600 (35.0)	49,500 (34.5)	49,200 (35.1)
$AUC_{0-\infty}$ (ng h/mL)	39,800 (37.0)	40,900 (35.5)	49,700 (34.9)	49,400 (35.5)
t_{max} (h)[a]	3.00 (0.50, 6.00)	2.05 (1.00, 6.00)	0.75 (0.25, 2.00)	1.00 (0.25, 3.00)
$t_{1/2}$ (h)	2.75 (0.585)	2.74 (0.579)	2.77 (0.589)	2.77 (0.571)

- Slight higher Cmax & shorter median tmax c tablet compared with capsules in fed state

Adv Ther 2017;34:2071-2082

LOTUSS: Pirfenidone

- 18 sites(Canada, Italy, USA), 63 SSc ILD pts
- Randomized, open-label, phase II study
- 2013.10-2014.9

TEAE*	Pirfenidone, 2403 mg/day		
	2-week Titration Group, n = 32	4-week Titration Group, n = 31	Total, n = 63
At least 1 TEAE	31 (96.9)	30 (96.8)	61 (96.8)
Maximal intensity of TEAE**			
Mild***	7 (21.9)	12 (38.7)	19 (30.2)
Moderate	15 (46.9)	15 (48.4)	30 (47.6)
Severe***	9 (28.1)	3 (9.7)	12 (19.0)
Life-threatening	0	0	0
Relationship of TEAE to study treatment†‡			
Not related	3 (9.4)	2 (6.5)	5 (7.9)
Possibly related	7 (21.9)	6 (19.4)	13 (20.6)
Related	21 (65.6)	22 (71.0)	43 (68.3)
At least 1 TE SAE	3 (9.4)	0	3 (4.8)
At least 1 treatment-related TE SAE††	1 (3.1)	0	1 (1.6)
Discontinuation of study treatment due to TEAE***	5 (15.6)	1 (3.2)	6 (9.5)

3T tid

J Rheumatol 2016;43: 1672-1679

GI S/Ex: Pirfenidone

- Pirfenidone should be taken individually, over the course of a meal.
- If nausea is experienced in the morning, the morning dose may be delayed or reduced.
- Temporary Tx interruptions should be considered if Sxs do not resolve following dose reduction.

  Following dose interruption, it could be re-introduced c a slower re-escalation scheme to the full dose.
- All Tx-related decisions should be made following discussion c pt & the aim of balancing QoL/Efficacy benefits.

Adv Ther 2014;31: 375-391

How to manage S/E: Pirfenidone

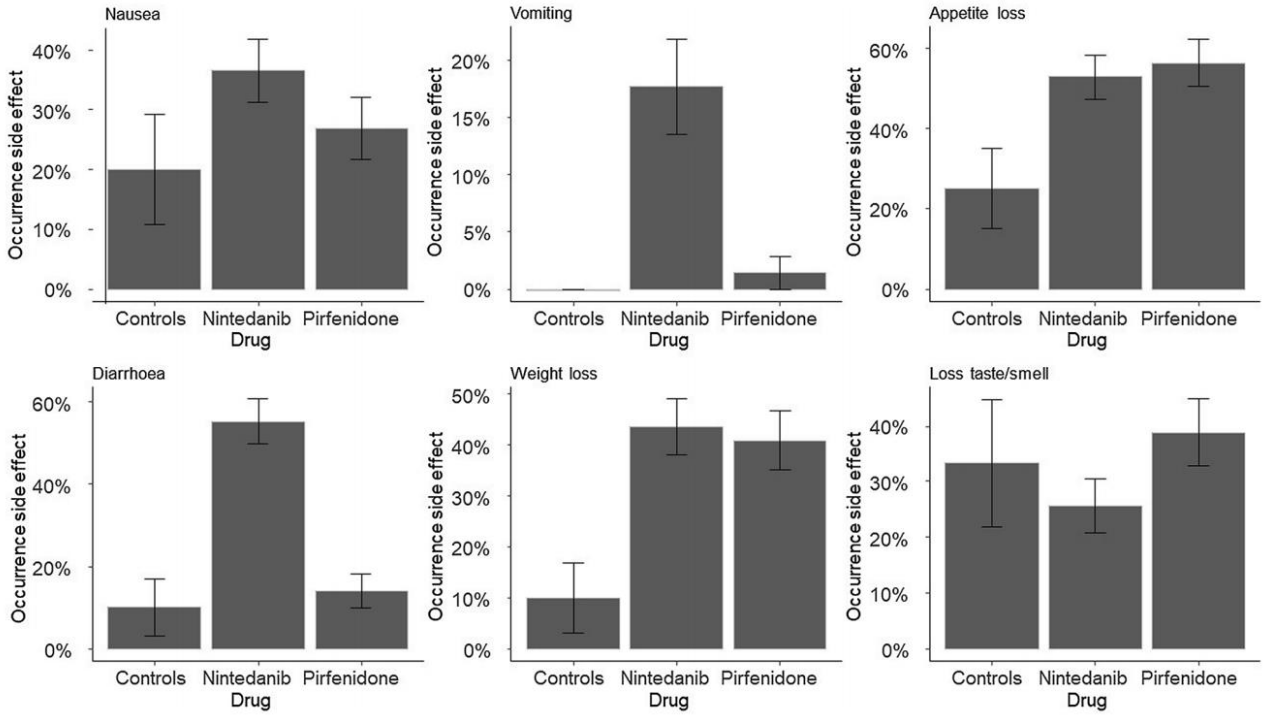
Pirfenidone-related AEs	Prevention	Management
General	Slower titration schedule	Dose reductions/interruptions
GI	Taking pirfenidone c a substantial meal (full dose at the end of meal or during a meal)	Dose reductions/interruptions with a slow titration back to full dose Reducing the morning dose if N at that time of day PPIs, Prokinetic agents
Skin	Skin protection c clothing/sunscreen Avoid sun exposure fro a few hrs after pirfenidone Frequent application of sunscreen	Severe phototoxicity: steroid, silver sulfadiazine Dose reductions for a rash Discontinuation if an allergic rex or recurred rash
Liver	Perform AST/ALT, bil before Tx Monitor at monthly intervals for first 6 months and then q 3 months	1) AST/ALT: 3~5 x ULN s Sx /hyperbil → reduce or interrupt 2) AST/ALT : 3~5 x ULN c Sx/hyperbil AST/ALT >5x ULN → discontinue permanently
Drug interactions	For CYP1A2 Inhibitors (fluvoxamine, enoxacin/ ciprofloxacin (750mg BID), pirfenidone should be reduced.	

ERJ Open Res 2017;26: 170057
Drug, Healthcare and Patient Safety 2020; 12: 85-94

Pirfenidone vs. Nintedanib (GI S/Ex)

- Web-based anonymous survey, 2018. 6-2018.10, Netherland

  176 IPF (pirfenidone (n=71), nintedanib (n=85) no Tx(n=20))



Lung 2019;197: 551-558

Pirfenidone vs. Nintedanib (S/Ex)

- Retrospective study, 2011.1 6-2020.1, France

  pirfenidone (n=115) vs nintedanib (n= 61)

Crude incidence of ADRs cases: organ systems and antifibrotic drugs.

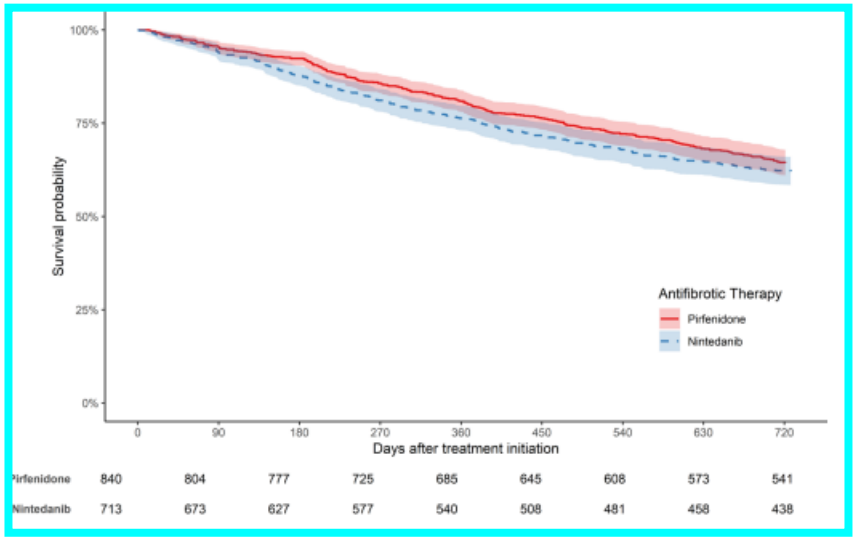
	Gastrointestinal		Cardiovascular		Hepatic		Skin	
	Pirfenidone	Nintedanib	Pirfenidone	Nintedanib	Pirfenidone	Nintedanib	Pirfenidone	Nintedanib
Number of ADR case[a]	37	34	9	3	4	4	26	1
% Serious (n)	18.9 (7)	11.7 (4)	66.7 (6)	100.0 (3)	25.0 (1)	0.0 (0)	23.1 (6)	0.0 (0)
Person-years	75.9	27.2	78.1	30.2	75.8	31.3	77.2	31.3
Crude incidence per 100 person-years	48.8	124.8	11.5	9.9	5.3	12.8	33.7	3.2
95% CI	33.1–64.5	82.9–166.8	4.0–19.1	0–21.2	0.1–10.5	0.3–25.3	20.7–46.7	0–9.5

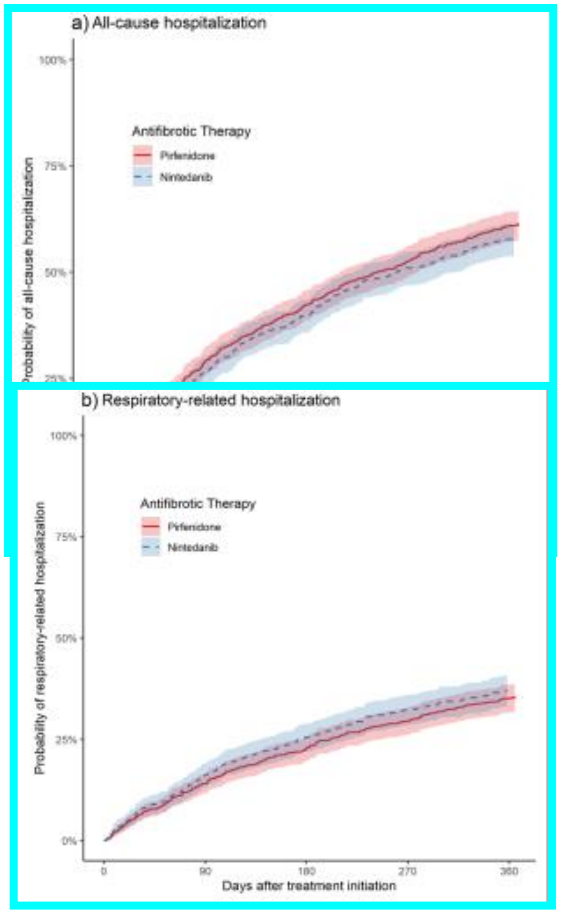
Pulmonary Pharmacology & Therapeutics 2022;76: 102149

Pirfenidone vs. Nintedanib (Efficacy)

- Retrospective cohort, 2013.1-2018.12, Germany

  pirfenidone (n=840) vs nintedanib (n=713)





Respir Res 2021;22: 268

Summary

- Pt education, AE prevention & management with prophylactic therapy

- If AEs occur and Sxs did not resolve
  : dose adjustment until Sxs are resolved

- If AEs persist
  : temporary therapy interruption

- Once Sxs have resolved or become tolerable
  : slow re-escalation back to full dose as tolerated

- All Tx-related decisions should be made following discussion c pt & the aim of balancing QoL/Efficacy benefits.

Thank You For Attention