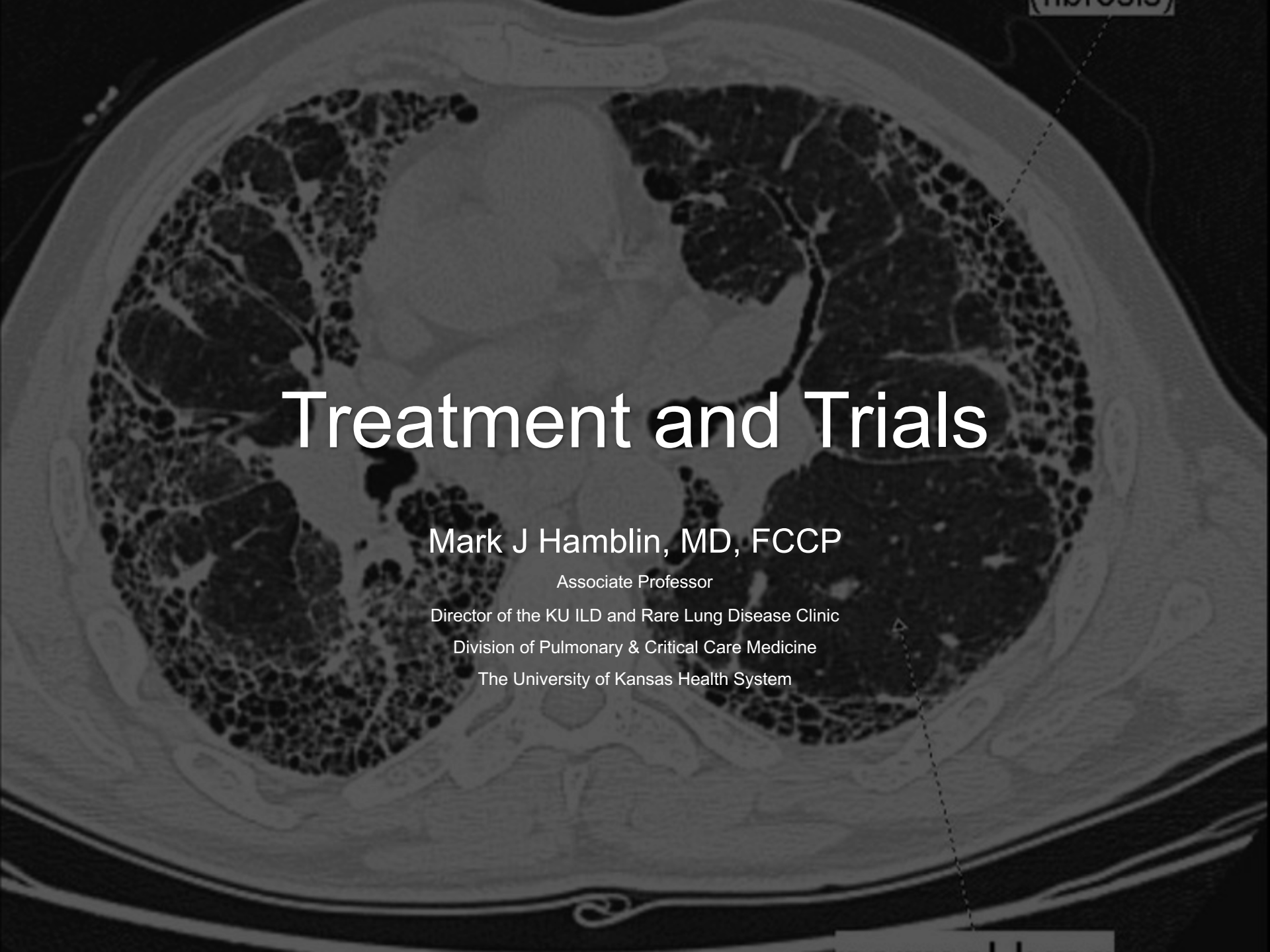


Treatment and Trials

Mark J Hamblin, MD, FCCP

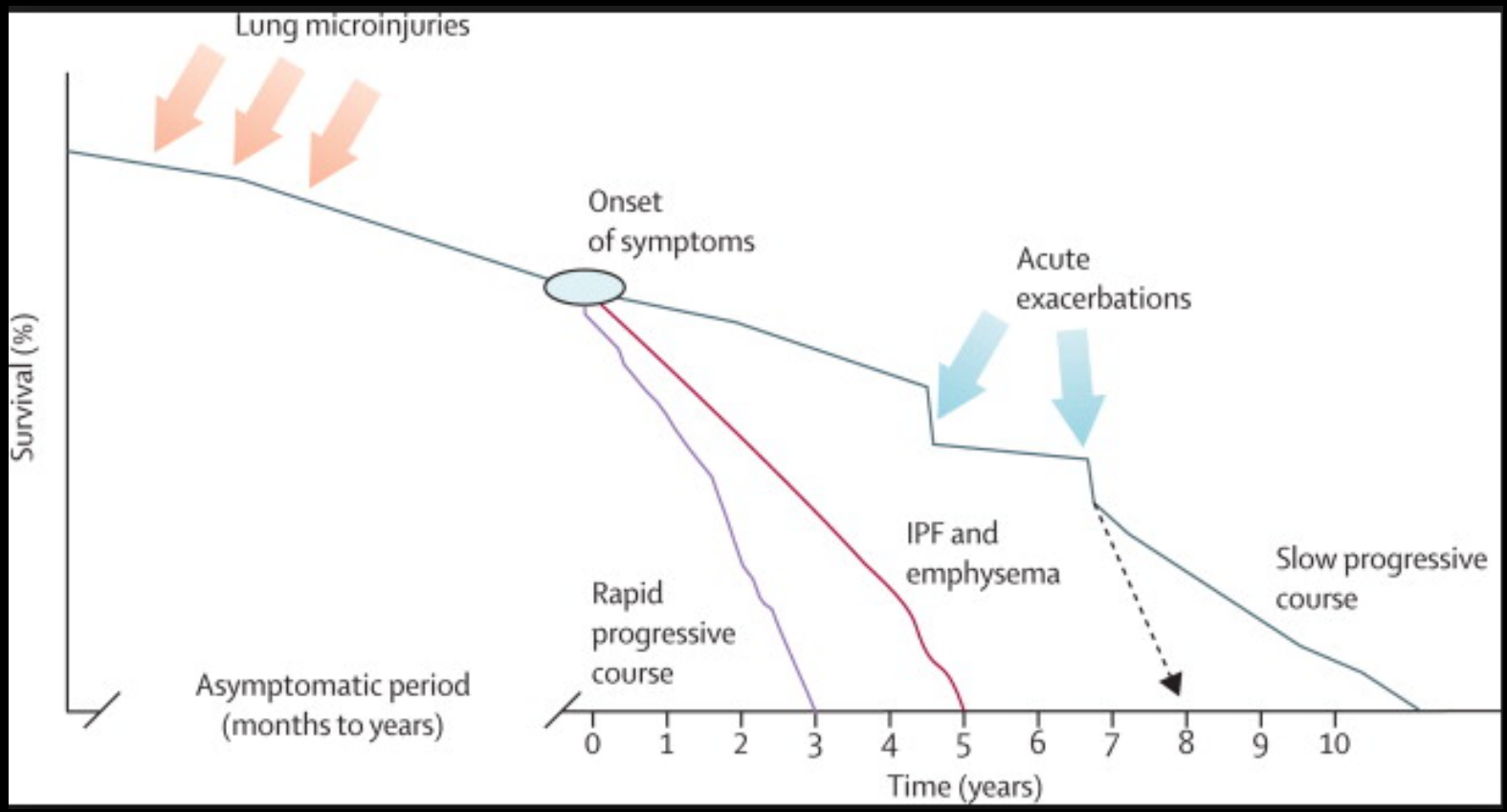
Associate Professor

Director of the KU ILD and Rare Lung Disease Clinic

Division of Pulmonary & Critical Care Medicine

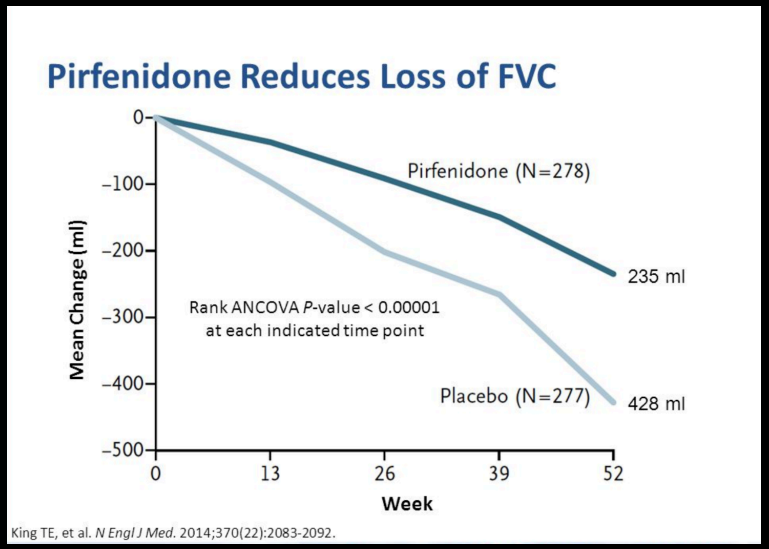
The University of Kansas Health System

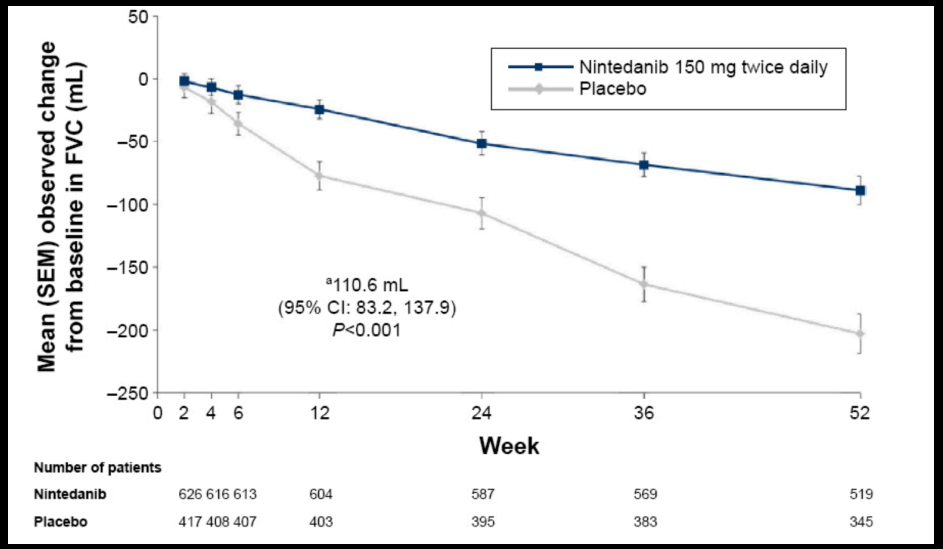
IPF: Natural History



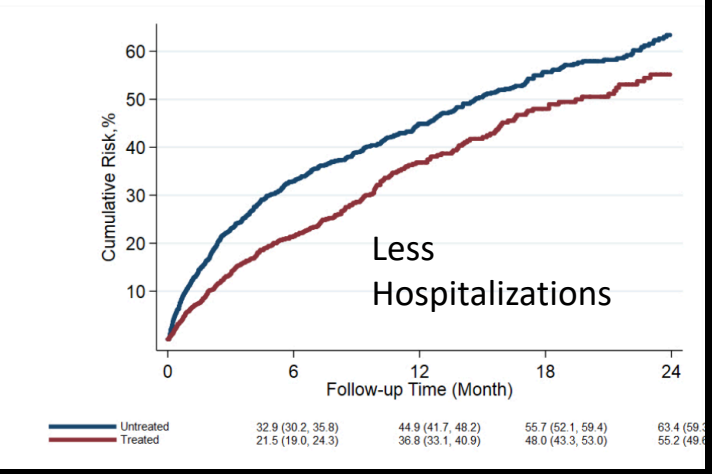
- Prior to the FDA approval of anti-fibrotic drugs, the life expectancy for IPF patients was estimated at 2-5 years with median survival about 27 months
- There can be wide variation as a result of underlying genetic defects, ongoing environmental insults, and triggers for acute exacerbations

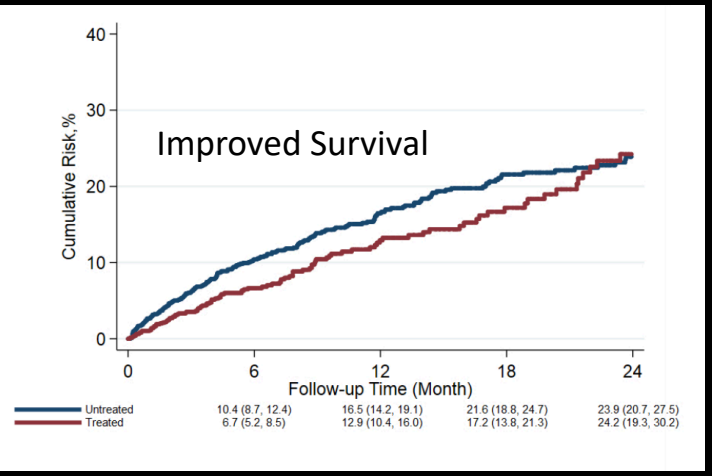
IPF: Anti-Fibrotic Therapy

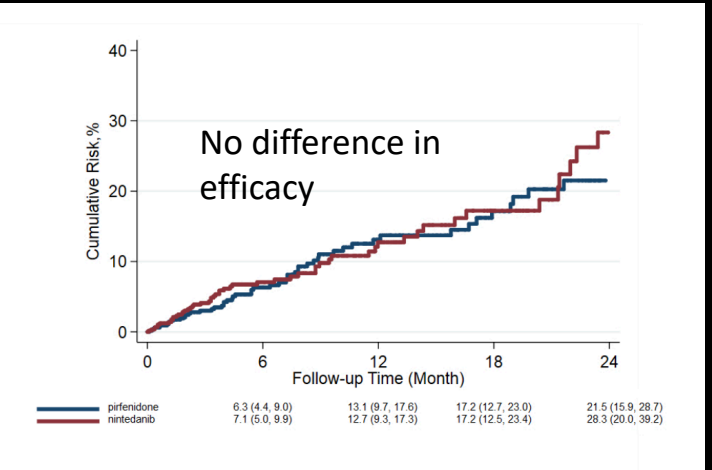




- Although they work through different mechanisms, Esbriet (pirfenidone) and OFEV (Nintedanib) both slow the rate of decline in FVC by ~50%
- Roughly 25% of patients discontinue therapy due to side effects





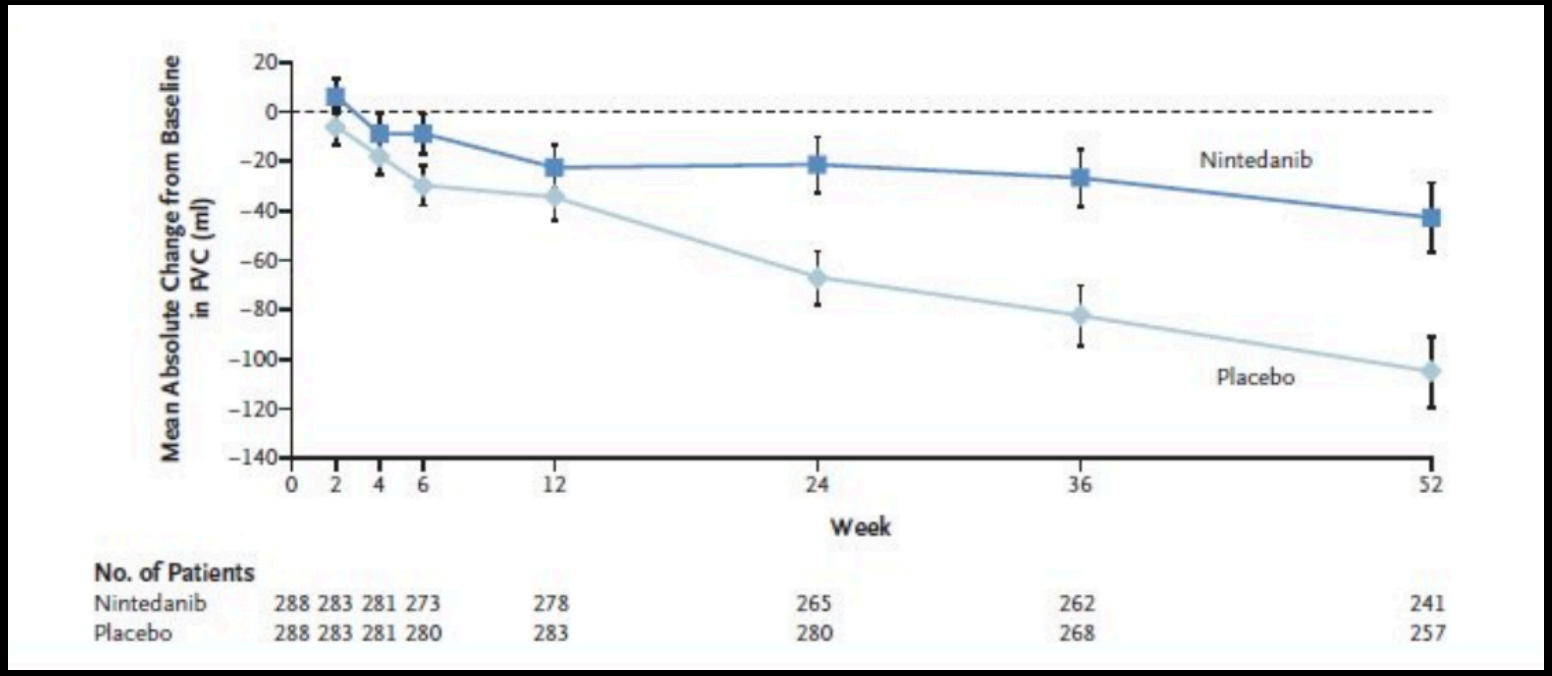


IPF: Anti-Fibrotic Therapy

- Patients on Anti-fibrotic therapy live about 2 years longer shifting the average survival with treatment to 4-7 years
- The two drugs are equally effective, and about 70% of people will show a good response to either drug. For others they may only respond to one, the other, or none. We don't have the technology readily available to tell who should be treated with what.
- Additionally, people don't necessarily feel better on the medications, and they have side effects much like chemotherapy drugs.

The Future for Non-IPF ILD?

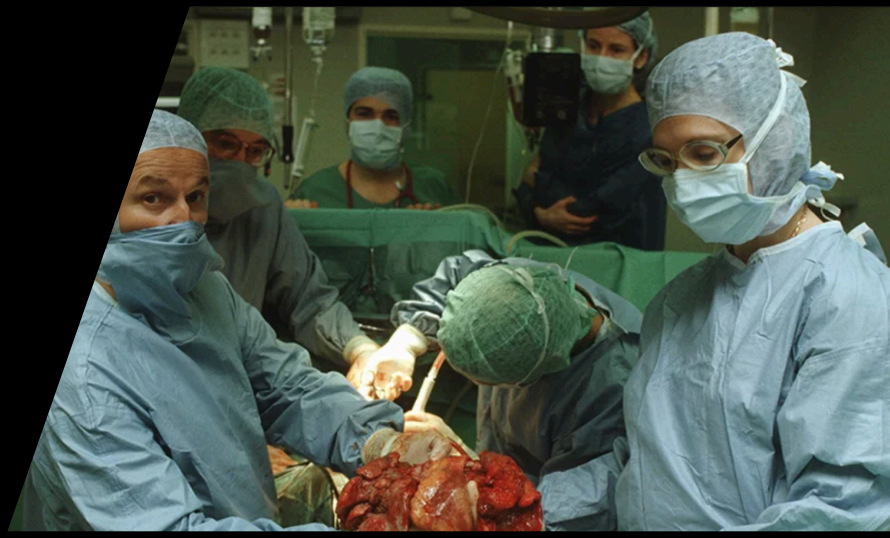
SENSCIS Study: Nintedanib for Scleroderma Associated Interstitial Lung Disease

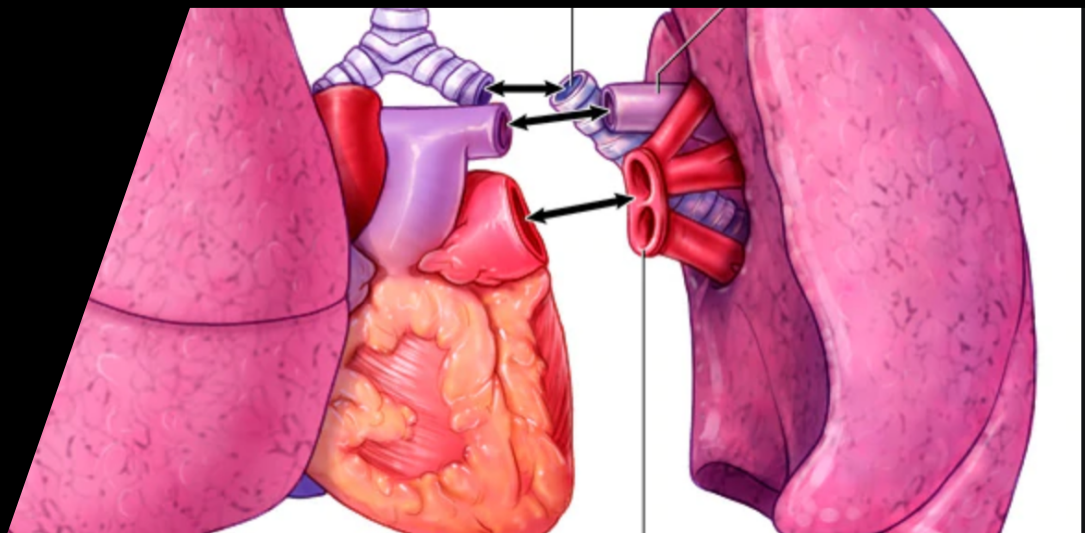


- OFEV is now a treatment option for scleroderma lung disease
- We anticipate OFEV will be a treatment option for any form of progressive fibrosis within the year.
- We will likely see the same for Esbriet in the future.

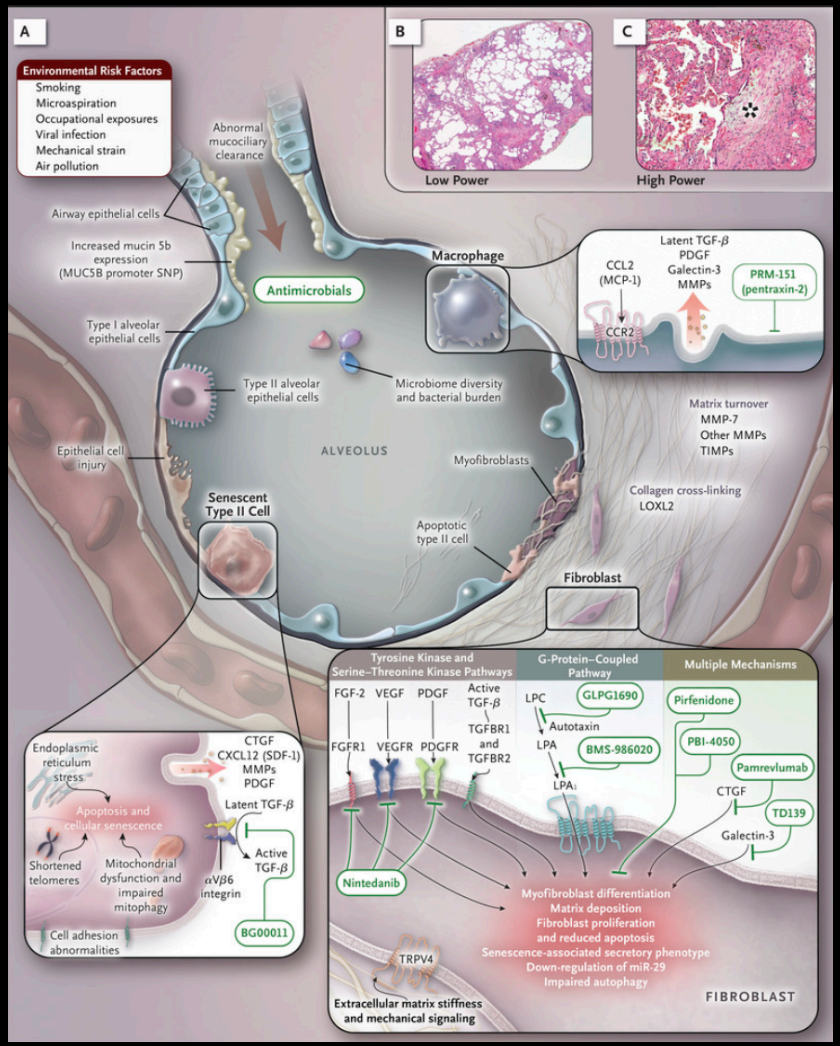
Lung Transplant

- Lung transplant is currently the only treatment option that can restore people back to health.
- This is not a miracle cure, as you do trade one set of problems for a new set of problems
- If chronic rejection occurs, you can be right back where you started within a few years





The Future for IPF and Beyond



Phase III Trials:

GLPG1690; Galapagos, Inc
Pemrevlumab; Fibrogen, Inc
PRM-151; Hoffman La Roche, Inc
PBI-4050; Prometic Life Sciences, Inc
PRECISIONS, NIH
Tyvaso, United Therapeutics

Phase IIB Trials:

TD139; Galecto Biotech, Inc
BMS-986020; Bristol Meyers Squibb, Inc

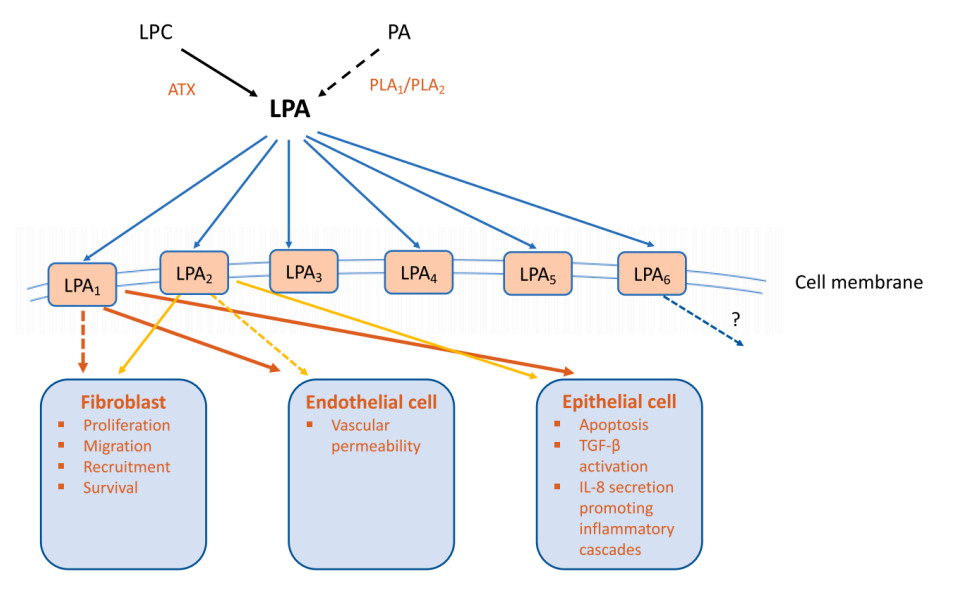
Phase IIA Trials:

ND-L02-s0201, Nitto Danko, Inc
TD-1058, Theravance, Inc
Saracitinab
BI1015550, Boehringer, Ingelheim
Nalbuphine, Trevi Therapeutics
Jaktinib, Suzhou Zelgen Biopharmaceuticals

Phase 1:

Saracitinab
Senolytics (Dasatinib and Quercetin)
jin-shui Huan-xian granule
ORIN 1001
GKT137831
PLN-74809
TRK-250, Toray Pharmaceuticals
VAY736, Novartis

LPA1 Inhibitors: Lysophosphatidic Acid 1 Receptor



- Autotaxin is a phospholipase that can convert phospholipids to lysophospholipids (LPA)
- Autotaxin is found to be high in areas of fibrosis
- LPAs signaling through a specific receptor – LPA1 promotes fibrosis

- Phospholipids are the main molecule of all our cell membranes
- We have phospholipid growth factors (PLGFs) that can pass through cell membranes activating small G proteins on the underside of the cell membrane activating downstream pathways that are involved in cell proliferation, cell invasion, apoptosis, and chronic inflammation

PMID: 32765123

Autotaxin-LPA1 Inhibitors:

Table 2 Autotaxin (ATX) and Lysophosphatidic Acid (LPA) receptor antagonists in clinical development

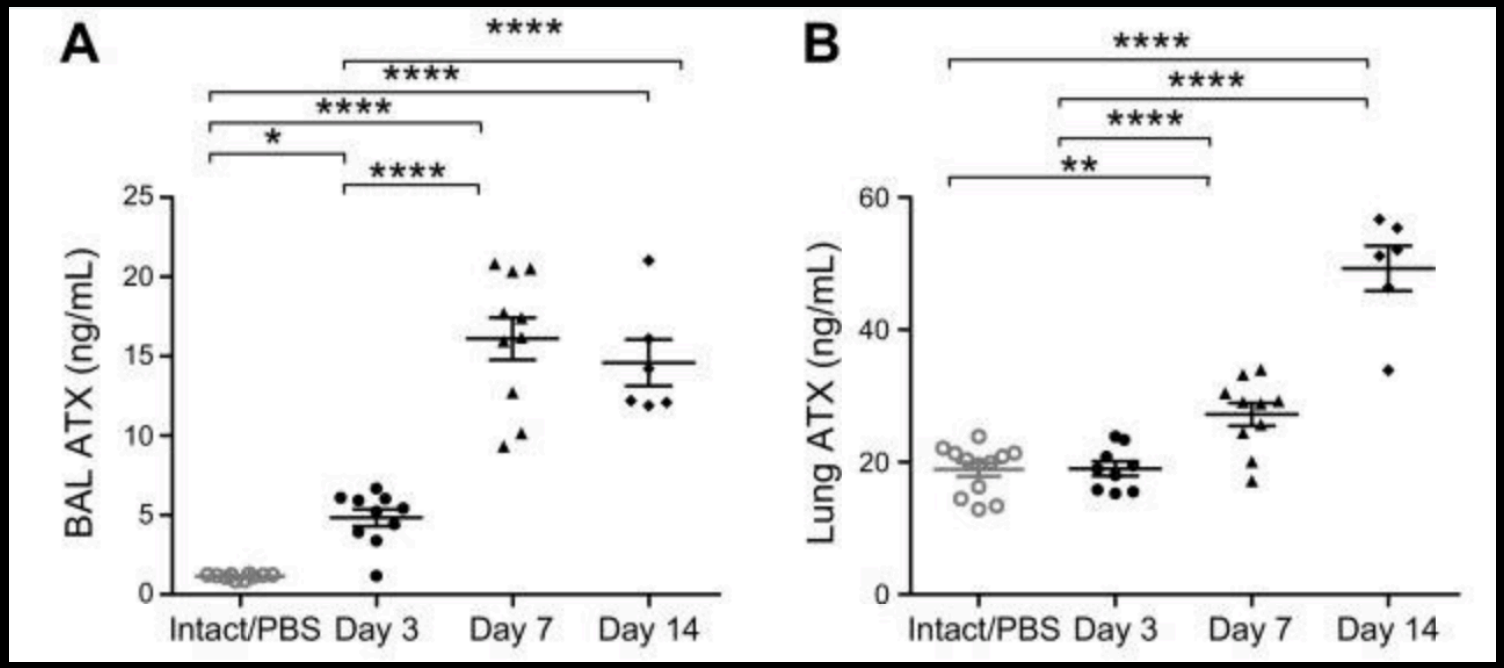
Name of Trial Drug	Company	Phase	Trial Number	Mechanism of Action	Disease
GLPG1690	Galapagos	3	NCT03711162 (ISABELA 1) NCT03733444 (ISABELA 2)	Autotaxin inhibitor	Idiopathic pulmonary fibrosis
BBT 877	Bridge Biotherapeutics Boehringer Ingelheim	1	NCT03830125	Autotaxin inhibitor	Pulmonary fibrosis
GLPG1690	Galapagos	2a	NCT03798366 NCT03976648	Autotaxin inhibitor	Systemic sclerosis: skin disease
SAR100842	Sanofi	2	NCT016551143	LPA_1 receptor antagonist	Systemic sclerosis
BMS-986,278*	Bristol-Myers Squibb	1	NCT03981094	LPA_1 receptor antagonist	Idiopathic pulmonary fibrosis
BMS 986,020	Bristol-Myers Squibb	2	NCT01766817	$LPAR_1$ receptor antagonist	Idiopathic pulmonary fibrosis

Note: *This agent has been voluntarily withdrawn from clinical development due to hepatobiliary toxicity.

- The Autotaxin-Lysophosphatidic (ATX-LPA) axis is important in the development of pulmonary fibrosis
- Activation of the ATX-LPA1 axis causes lung epithelial cells to die (apoptosis) promoting development of fibrosis
- Blocking this pathway attenuates both inflammation and fibrosis

PMID: 32765123

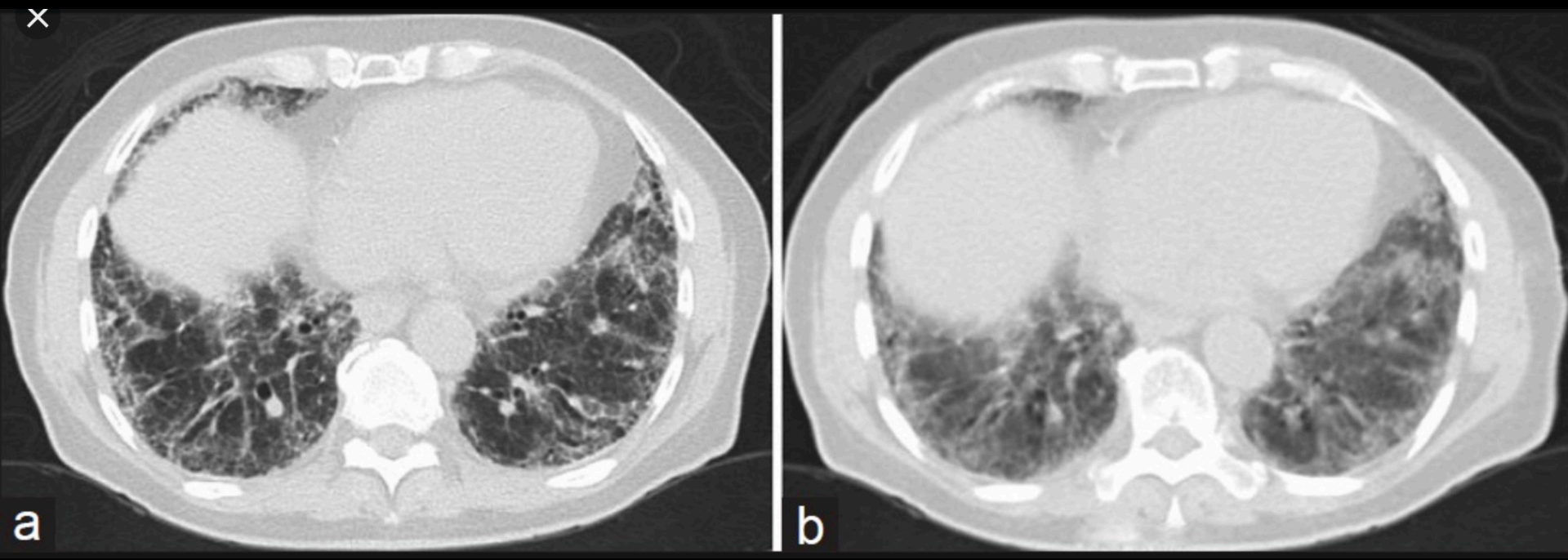
Autotaxin-Levels after lung injury



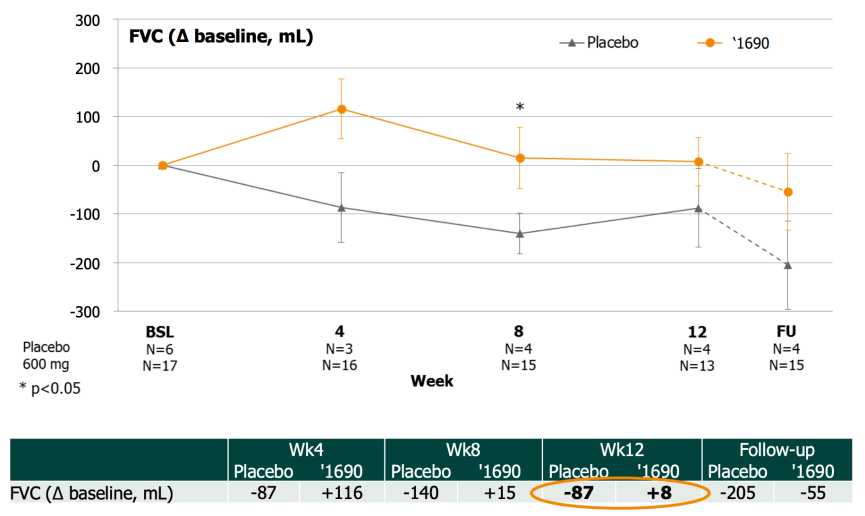
- 17 fold increase in autotaxin levels following administration of an exacerbating agent
- In this study they used an ATX inhibitor PAT-048, and while it reduced autotaxin it did not prevent the development of pulmonary fibrosis
- This suggests that blocking autotaxin alone may not be enough, as other things could signal through the LPA1 receptor to promote fibrosis

PMID: 27006447

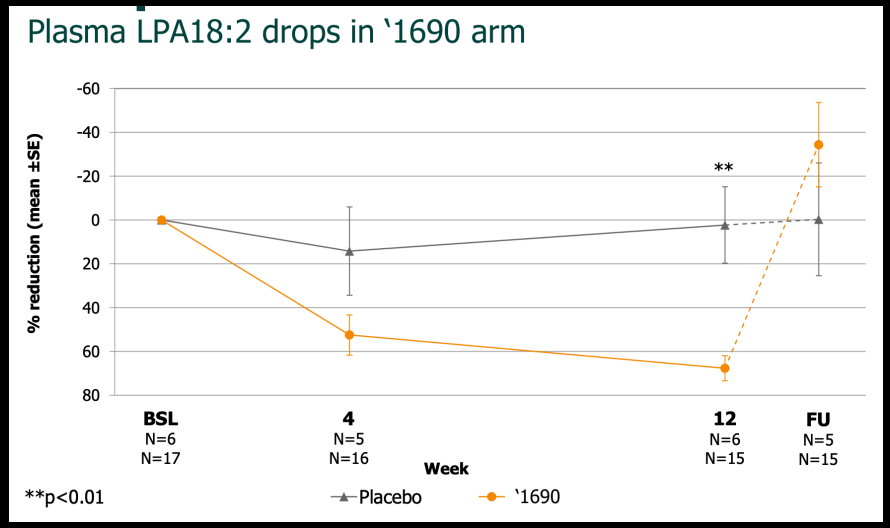
Acute Exacerbations



GLPG1690 in IPF



	Wk4		Wk8		Wk12		Follow-up	
	Placebo	'1690	Placebo	'1690	Placebo	'1690	Placebo	'1690
FVC (Δ baseline, mL)	-87	+116	-140	+15	**-87**	**+8**	-205	-55

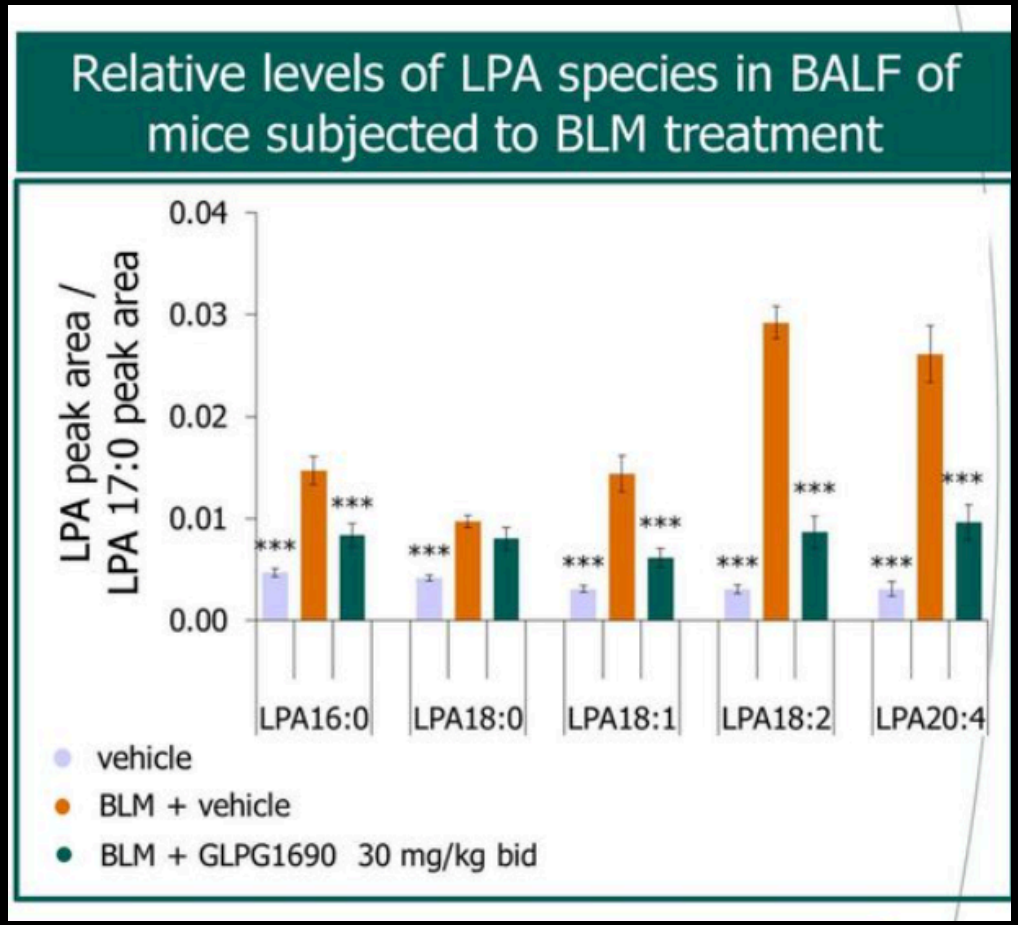


- GLPG1690 was the first Autotaxin Inhibitor in Clinical Trials for IPF
- The Phase 2A FLORA Trial
- Patients on treatment saw a 25 ml increase in FVC over 12 weeks
- Patients on placebo saw a -70 ml decrease in FVC over 12 weeks
- Results were promising and the FDA granted immediate movement to phase 3 studies

GLPG1690 in IPF
ISABELA I and 2: Phase 3

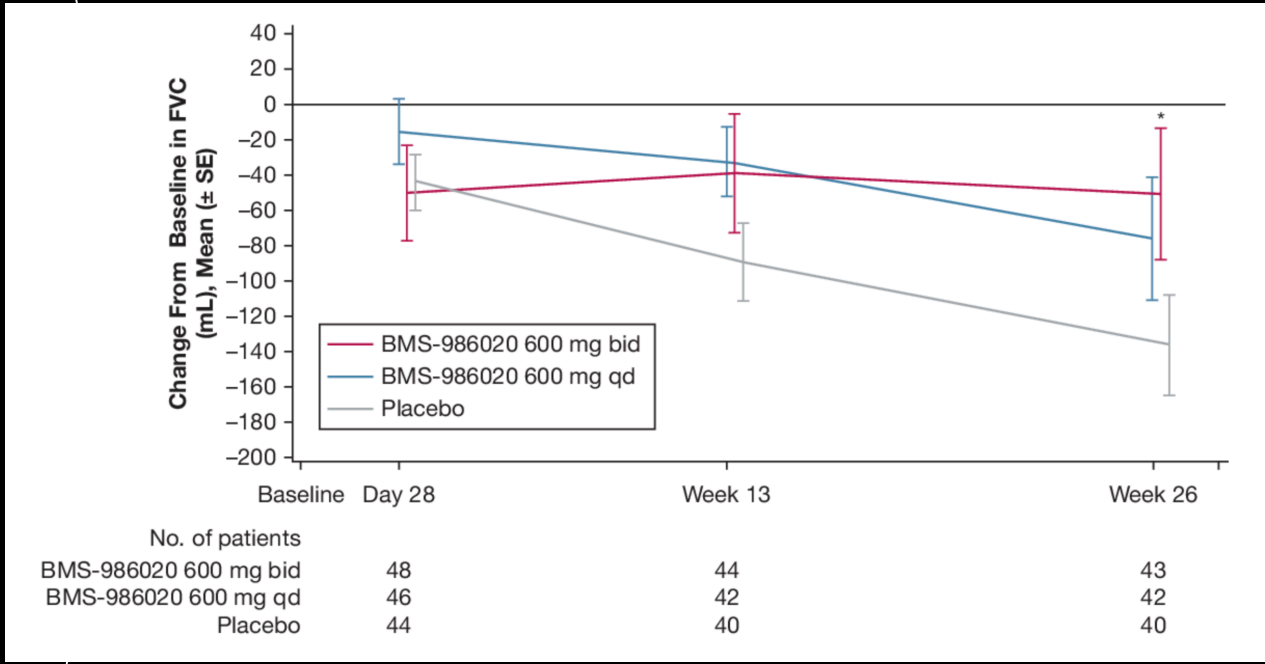
Key Inclusion Criteria:

- Patients 40-80
- Disease <5 years
- FVC >45%
- DLCO 30-79%
- HRCT with definite or probable UIP or lung biopsy consistent with IPF
- On stable dose of OFEV or Esbriet for 8 weeks if on background therapy
- No longer enrolling patients on Esbriet or OFEV



BMS-986020

- BMS-986020 was the first LPA1 Receptor Inhibitor in clinical trials
- Patients were randomized to placebo, low dose (600 mg daily) or high dose treatment (600 mg twice daily
- Normal age related decline in FVC is 30-70 ml over 1 year
- High dose patients lost 42 ml
- Low dose lost 106 ml
- Placebo lost 134 ml
- It was stopped early due to liver toxicity



CHEST 2018; 154(5):1061-1069

BMS-986278:

New formulation that eliminated the liver toxicity
Phase 2 Randomized Double Blind Placebo Controlled Trial

- 6 month randomized trial

Randomization to 1 of 3 arms

- Placebo
- Low Dose
- High Dose
- After 6 months everyone has option for open label extension

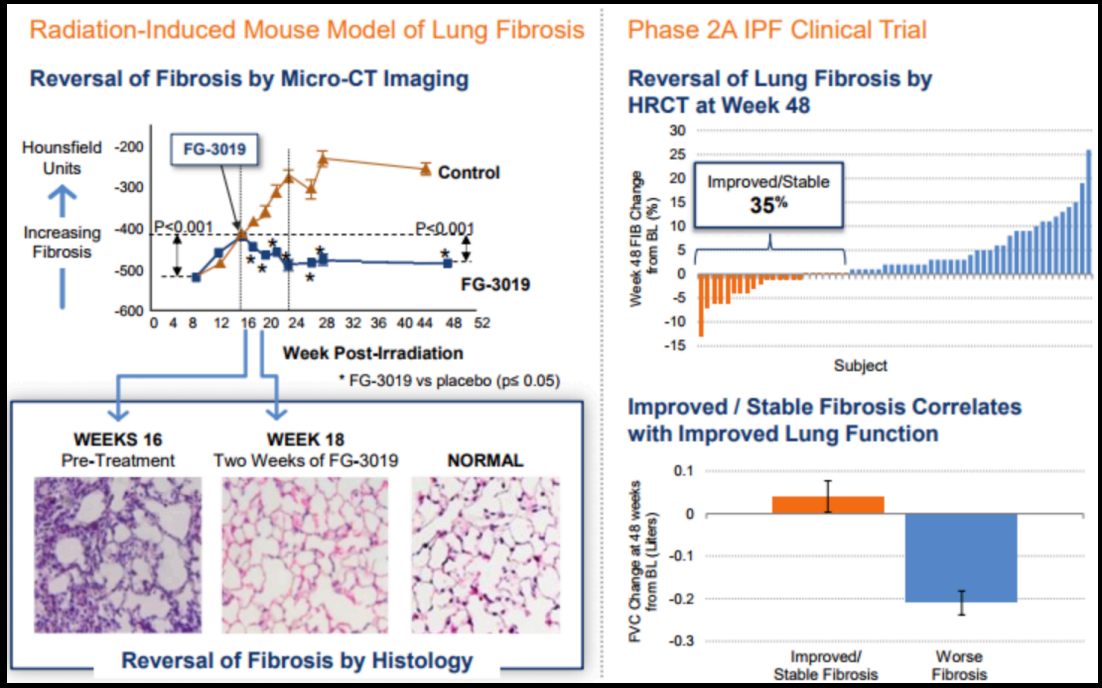
Side Effects from Phase 1
Low blood pressure
Headaches

Key Inclusion Criteria:

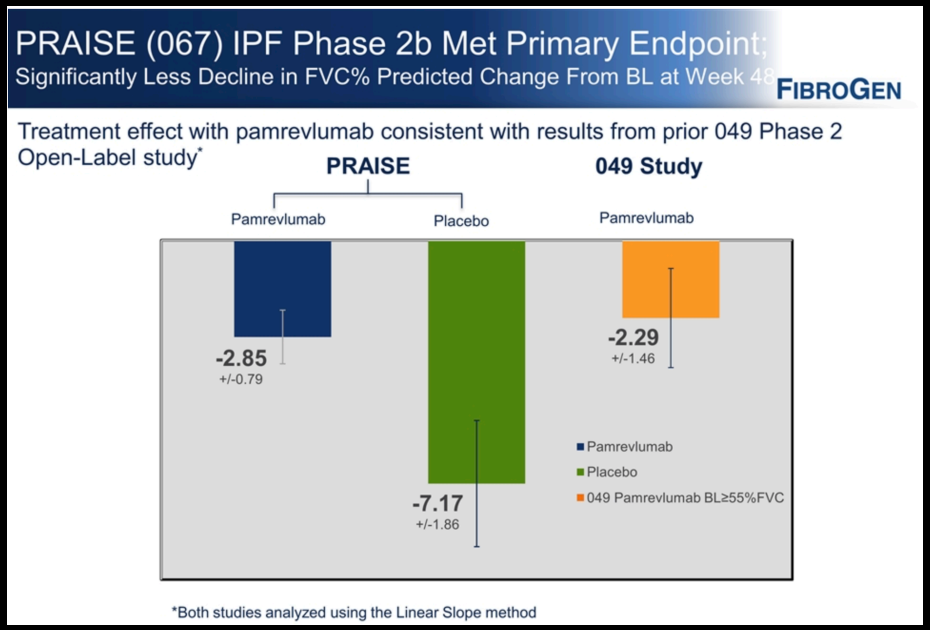
- Patients Age >40
- Disease duration <7 years
- FVC >45%
- DLCO >25%
- HRCT with definite or probable UIP or lung biopsy consistent with IPF
- On stable dose of OFEV or Esbriet for 8 weeks if on background therapy
- No history of cancer

Pemrevulmab
Fibrogen, Inc

- PRAISE: Phase 2B Results showed similar outcomes
- FVC decline in Phase 2A was -2.29%
- FVC decline in Phase 2B was -2.85% for Pemrevulmab vs -7.17% for placebo
- **By 48 weeks only 10% of patients on Pemrevulmab experienced a >10% decline vs 31% in placebo**



Pemrevulmab



- Study FG-3019-049: 2.29 % decline in FVC over 48 weeks
- Study FG-3019-067: 2.85 % decline in FVC over 48 weeks vs 7.17% in placebo

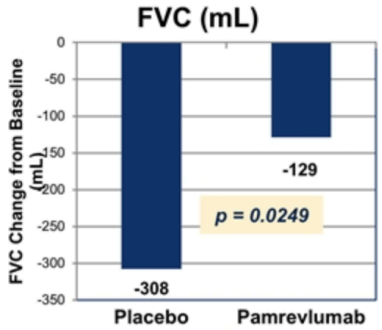
https://www.sec.gov/Archives/edgar/data/921299/000119312518004999/d521134dex991.htm

Pemrevulmab

PRAISE (067) IPF Phase 2b
Pamrevlumab Attenuated FVC Decline

FIBROGEN

Pamrevlumab significantly attenuated FVC decline from Baseline to Week 48.



	Pamrevlumab Ph 2 PRAISE Study (067)				Nintedanib INPULSIS Ph 3- 52 Weeks				Pirfenidone ASCEND Ph 3- 52 wks	
	ITT 48- week Result		Projected 52 wks		Study 32 (N=513)		Study 34 (N=548)		Linear Slope, N=555	
	Pamrevlumab	Placebo	Pamrevlumab	Placebo	Nintedanib	Placebo	Nintedanib	Placebo	Pirfenidone	Placebo
ΔFVC (mL)	-129	-308	-138	-332	-115	-240	-113.6	-207.3	-164	-280
LS mean diff	178		195		125		93.7		116	
p-value	0.0249		0.024		<0.001		<0.001		<0.001	
Relative difference	*57.9%*		*58.5%*		*52.1%*		*45.2%*		*41.4%*	
					Richeldi, NEJM 2014, 370: 22; 2071-2082				King, NEJM 2014; 370: 2083-92 Suppl	

48 Weeks	Subgroup Analysis (N=90)	
	Pamrevlumab	Placebo
ΔFVC (mL)	-143	-341
LS mean diff	198	
P-value	*0.0212*	

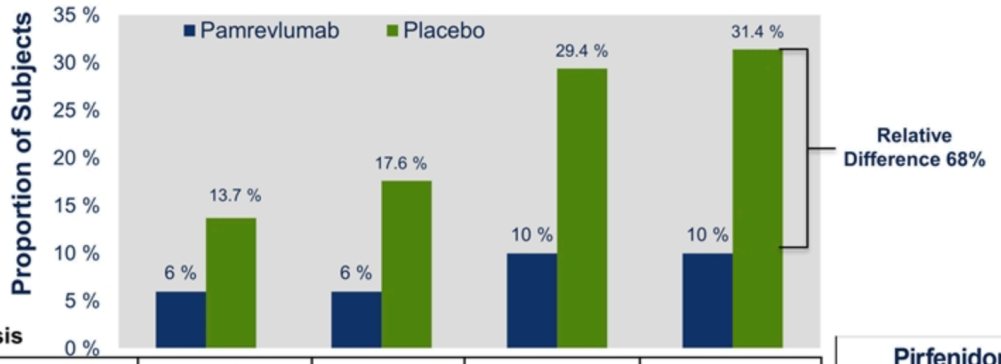
In separate studies, pamrevlumab has larger treatment difference from placebo than nintedanib and pirfenidone in preservation of FVC.

Pemrevulmab

PRAISE (067) IPF Phase 2b

Pamrevlumab Reduces The Proportion of Subjects with FVC % Predicted Decline ≥10% or Death

FIBROGEN



ITT Analysis

Visit (Weeks)	12w	24w	36w	48w
P-Value*	0.1235	0.0527	0.0172	0.0103
Pamrevlumab, n (%)	3 (6.0%)	3 (6.0%)	5 (10.0%)	5 (10.0%)
Placebo, n (%)	7 (13.7%)	9 (17.6%)	15 (29.4%)	16 (31.4%)
Difference (%)		-11.6%		- 21.4%
Relative Difference	-56%	-66%	-66%	-68%

PRAISE Subgroup Analysis of N=90		
	Treatment Δ48 wk	-24.7%
	p- value	*0.0076*

Pirfenidone Phase 3 ASCEND (52 Wks)	
P-Value	*<0.001*
pirfenidone	6.5%
Placebo	17.7%
Difference	-11.2%
Relative Difference	-43%

Both ITT and subgroup analyses of PRAISE show larger reduction in IPF progression (FVC % predicted decline >=10%) or death than pirfenidone in ASCEND (ph 3 study).

ZEPHYRUS:

Phase 3 Randomized Double Blind Placebo Controlled Trial

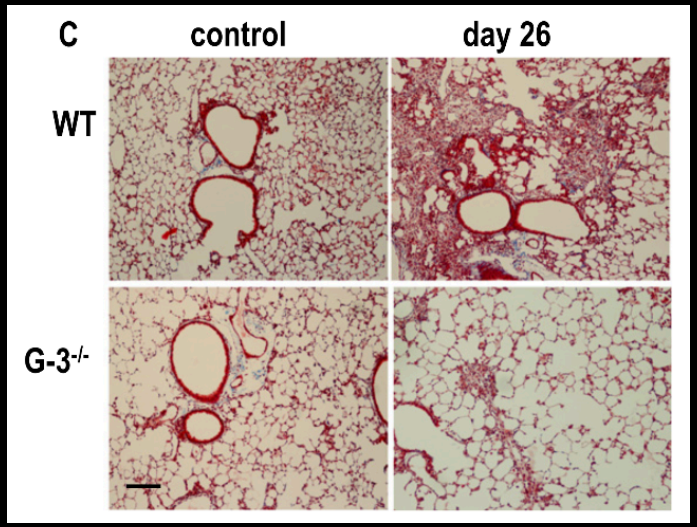
- 52 Week Study
- Randomization 1:1 drug to placebo
- IV Infusion every 3 weeks
- Everyone has option for open label extension
- Treatment with Esbriet or OFEV is not allowed

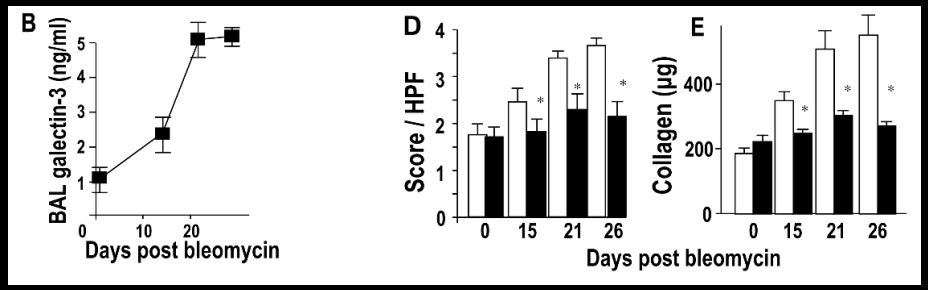
Key Inclusion Criteria:

- Patients Age 40-85
- Disease duration <7 years
- FVC 50-80%
- DLCO 30-90%
- >10% and <50% fibrosis on CT
- HRCT with definite or probable UIP or lung biopsy consistent with IPF
- No history of cancer

Galectin 3 Inhibitor: TD139

- Galectin-3 is a beta-galactoside binding lectin that is highly expressed in fibrotic tissue of diverse etiologies.
- Galectin 3 links the extracellular matrix with TGF-beta receptors promoting fibrosis
- Levels of Galectin 3 are high in pulmonary fibrosis and lung cancer
- **TD-139 blocked 80% of galectin 3**
- **First inhaled therapy**





GALACTIC-1:

Phase 2b Randomized Double Blind Placebo Controlled Trial

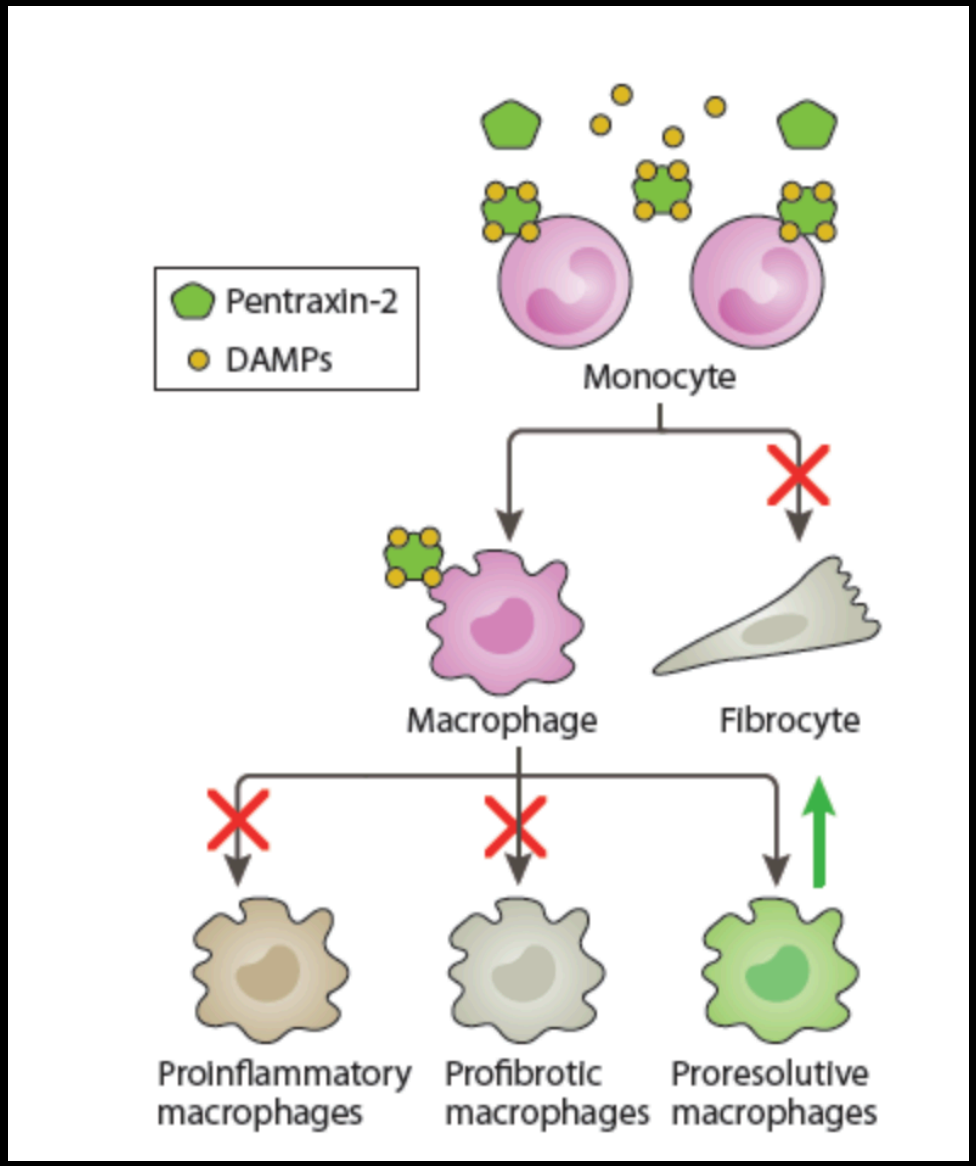
- 52 Week Study
- Randomization 2:1 drug to placebo
- Inhaled therapy
- Comparing 2 doses of TD-139 against placebo: 10 mg and 3 mg
- No open label extension
- No longer enrolling patients on treatment with Esbriet or OFEV

Key Inclusion Criteria:

- Patients Age >40
- Disease duration <4 years
- FVC >45%
- DLCO 30-79%
- HRCT with definite or probable UIP or lung biopsy consistent with IPF
- No history of cancer

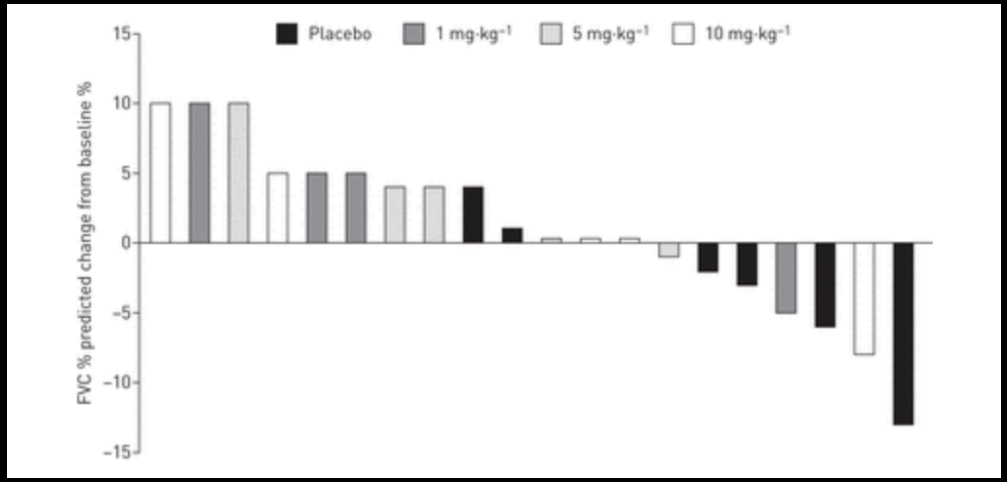
PRM-151

- Pentraxin 2 is a molecule that activates monocytes (a type of white blood cell) that is supposed to clean up scar tissue
- Patients with IPF on average have Pentraxin 2 levels 5 times lower than age matched controls without the disease
- PRM-151 is a synthetic form of Pentraxin 2 administered as an IV infusion every 4 weeks



PRM-151

- Phase 2A Study showed promising results
- All doses showed benefit: FVC improved ~2.4% over 8 weeks
- 6MWD improved 35 meters in the high dose group



	Placebo	PRM-151			
		1 mg·kg^{-1}	5 mg·kg^{-1}	10 mg·kg^{-1}	All doses
FVC % pred					
Baseline	63.2±16.7	82.4±15.5	80.0±7.8	72.8±14.3	78.8±12.5
Day 57 change from baseline	−1.5±3.3	2.4±4.6	2.8±3.0	1.8±5.3	2.4±4.0
6MWD m					
Baseline	458±73	457±157	470±101	439±63	456±109
Day 57 change from baseline	−11±51	−11±63	6±43	35±45	8±51

Eur Respir J 2016; 47: 889–897

PRM-151

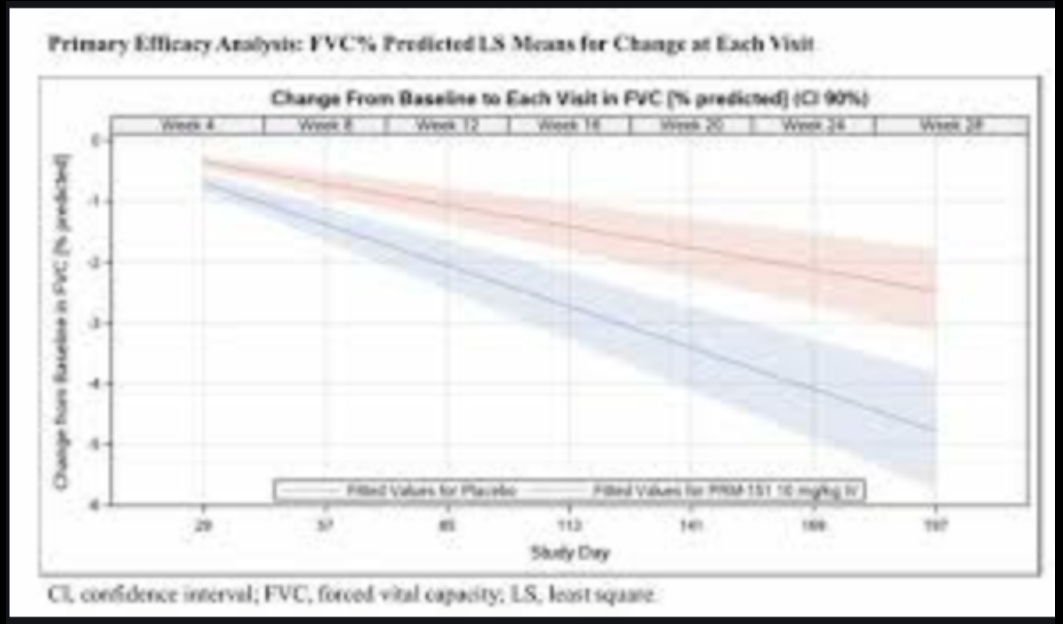
The Phase 2B study was a 6 month study in patients showing active decline in FVC despite Esbriet or OFEV

PRM-151

- FVC decline was 2.5%
- 6MWD decline -0.5 meters

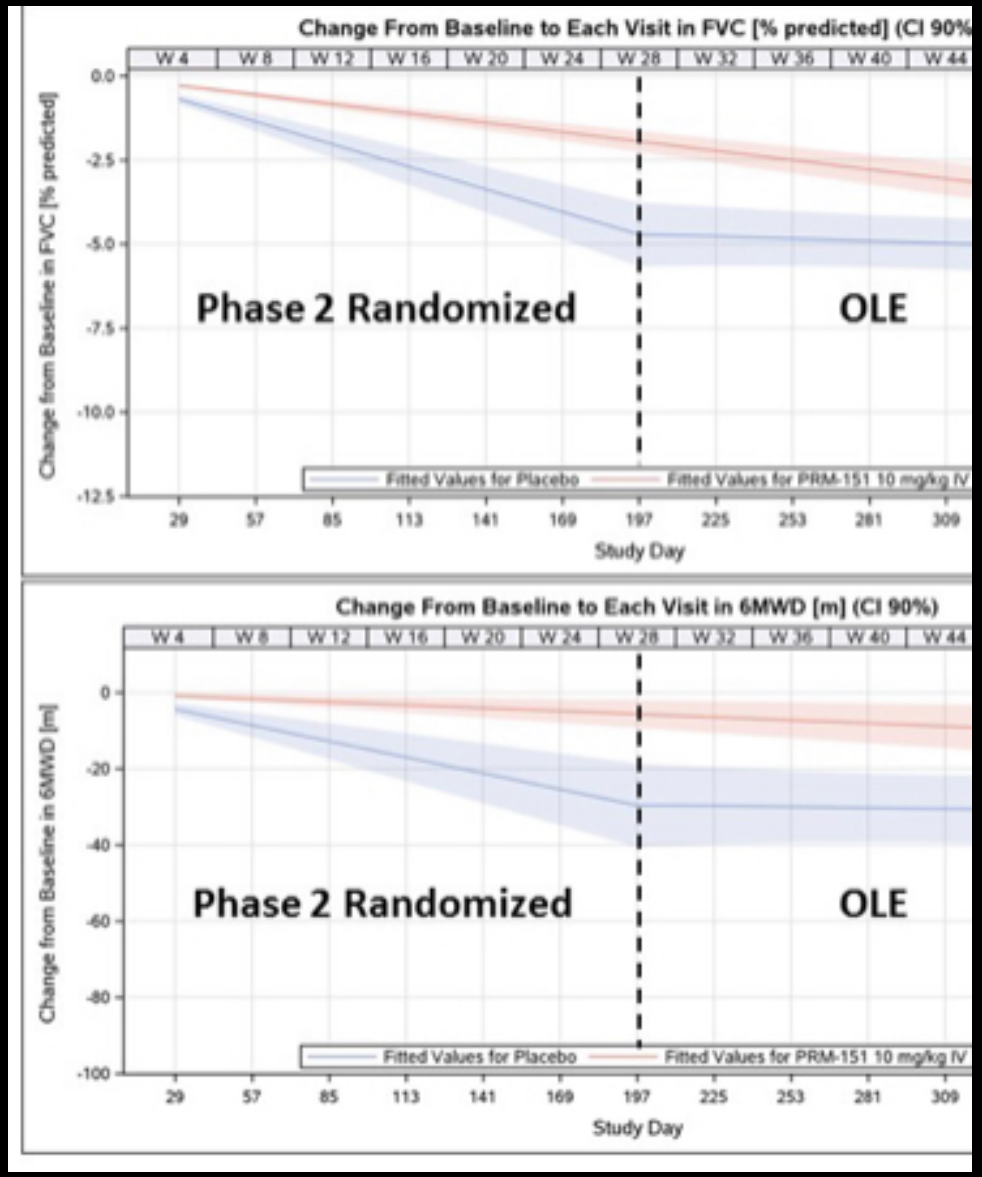
Placebo

- FVC decline was 4.8% on placebo
- 6MWD decline -31.8 meters



PRM-151

- For those continuing treatment
  - FVC decline was -3.6% per year
  - 6MWD -10.5 m
- For those rolling over to active drug
  - **FVC decline went from -8.7% per year to -0.9% per year on PRM-151**
  - **6MWD went from -54.9 m to -3.5 m**



STARSCAPE:

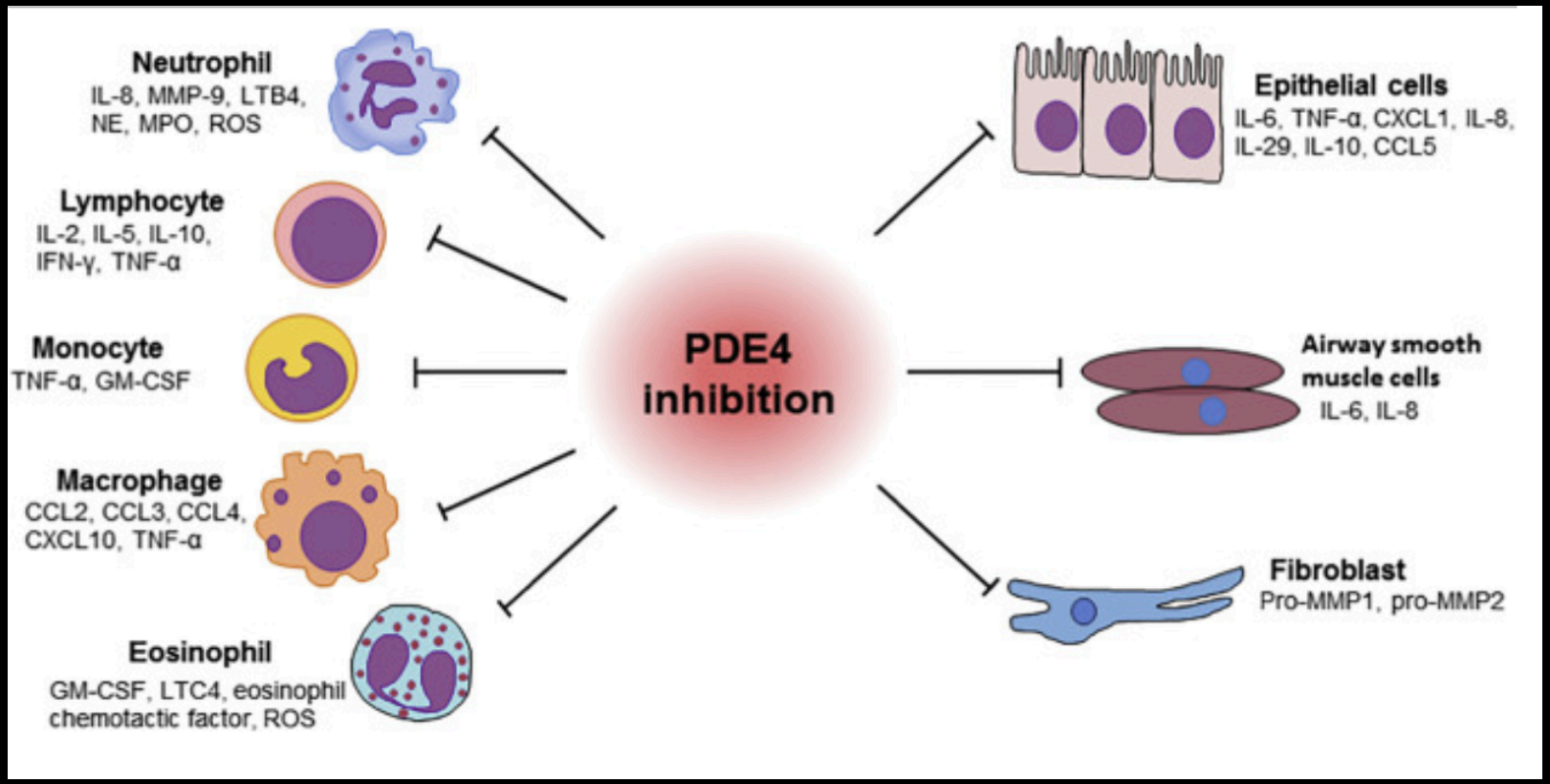
Phase 3 Randomized Double Blind Placebo Controlled Trial

- 52 Week Study
- Randomization 1:1 drug to placebo
- IV Infusion every 4 weeks
- Open label extension
- Allows treatment with Esbriet or OFEV
- Excluded if FVC is improving over 6 months prior to screening
- Excluded is SpO2 <89% on 6 L

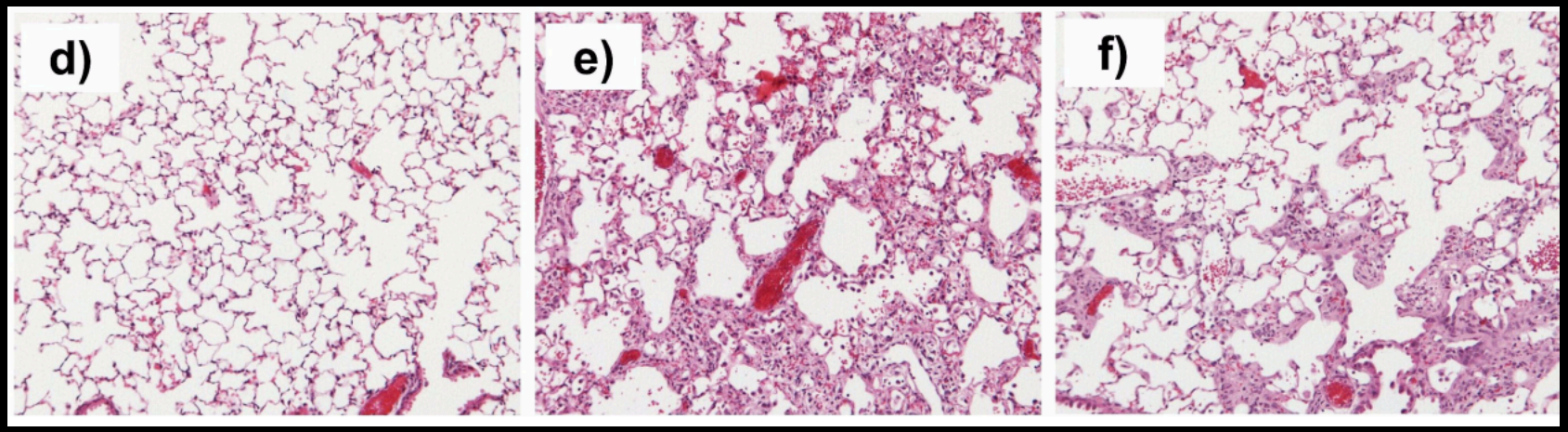
Key Inclusion Criteria:

- Patients Age 40-85
- Disease duration <4 years
- FVC >45%
- DLCO 30-90%
- HRCT with definite or probable UIP or lung biopsy consistent with IPF
- Minimum 6 minute walk distance (6MWD) of 150 meters with maximum use of 6 L/min at sea-level and up-to 8 L/min at altitude of supplemental oxygen while maintaining oxygen saturation of greater than or equal to (>/=)83%
- No history of cancer

Phosphodiesterase Inhibitors
PDE4 Inhibitor:



Phosphodiesterase Inhibitors PDE4D Inhibitor:



- Preclinical animal studies show anti-fibrotic effects of PDE4D inhibitors
- There are already phosphodiesterase inhibitors on the market for COPD/Chronic bronchitis and they are most effective for the chronic cough symptoms of chronic bronchitis
- I'm hopeful this will not only slow the progression of fibrosis, but will actually help the chronic cough symptoms in IPF

BMC Pulmonary Medicine 2010, 10:26

BI1015550

Phase 2A Randomized Double Blind Placebo Controlled Trial

- 12 Week Study
- Randomization 1:1 drug to placebo
- Twice daily tablet
- Allows treatment with Esbriet or OFEV

- There is specific cough sub-study

Key Inclusion Criteria:

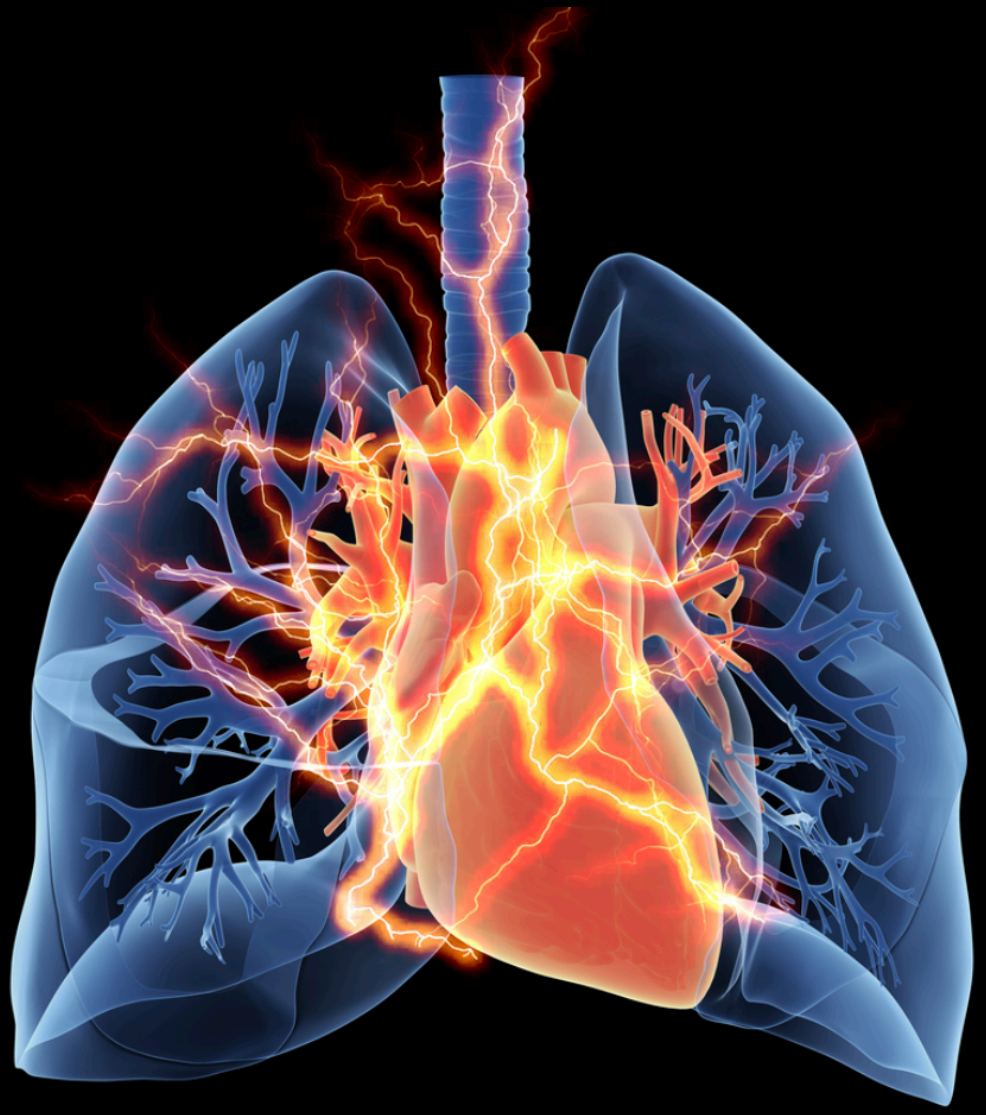
- Patients Age >40
- Disease duration: No limit
- FVC >45%
- DLCO 25-80%
- HRCT with definite or probable UIP or lung biopsy consistent with IPF
- No history of cancer

Pulmonary Hypertension in IPF

- A DLCO < 40% and need for supplemental oxygen are key risk factors for the presence of pulmonary hypertension in IPF. When both are present there is an 87% chance of underlying pulmonary hypertension.

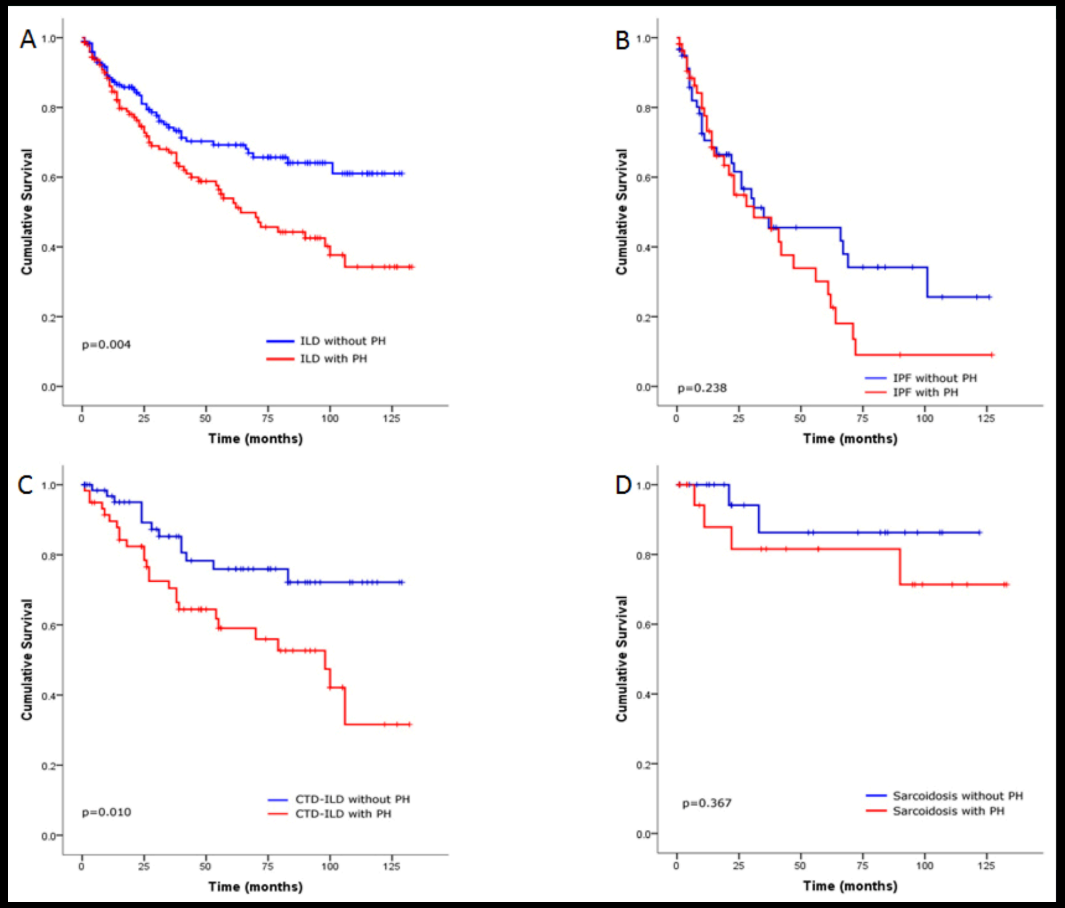
- Even when not present about 20% of patients will still have pulmonary hypertension

- Roughly 30% of patients who have a normal echocardiogram will actually have pulmonary hypertension when assessed by right heart catheterization



Pulmonary Hypertension in ILD

- The development of pulmonary hypertension in IPF is associated with increased shortness of breath, leg weakness, and increased mortality
- It's estimated that anywhere from 10-50% of patients with IPF have Pulmonary hypertension
- In the setting of Combined Pulmonary Fibrosis and Emphysema (CPFE), up to 70% of patients were found to have PH.

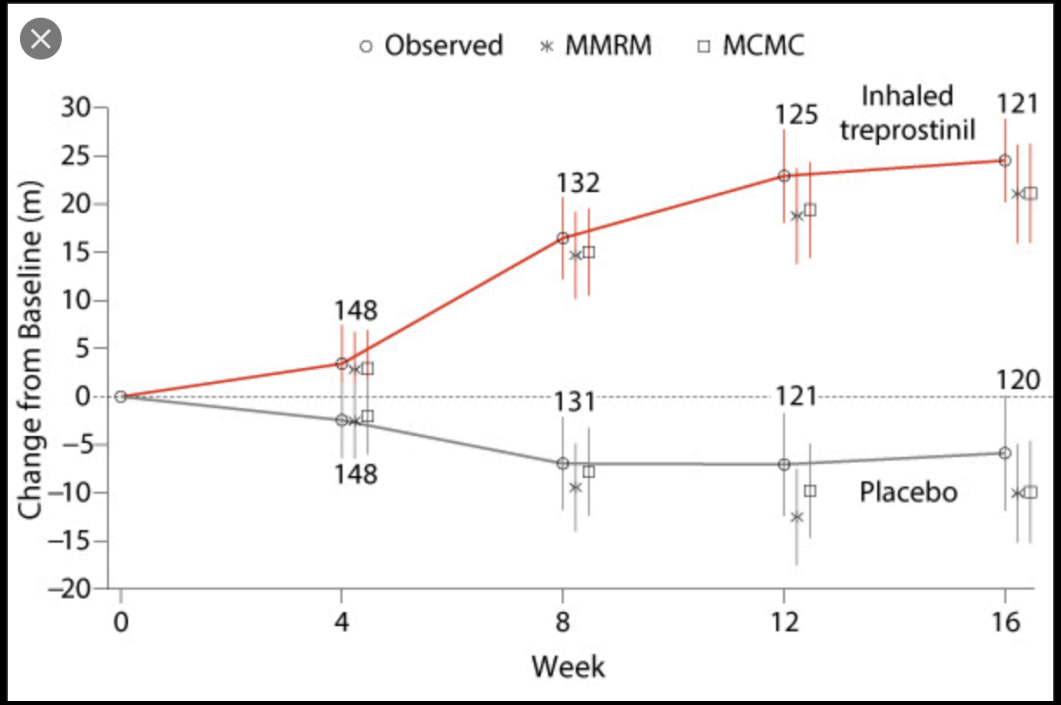


J. Clin. Med. **2020**, *9*(12), 3828

Tyvaso:
Inhaled Trepostinil

The INCREASE study was a 16 week study in patients with Interstitial Lung Disease with Pulmonary Hypertension

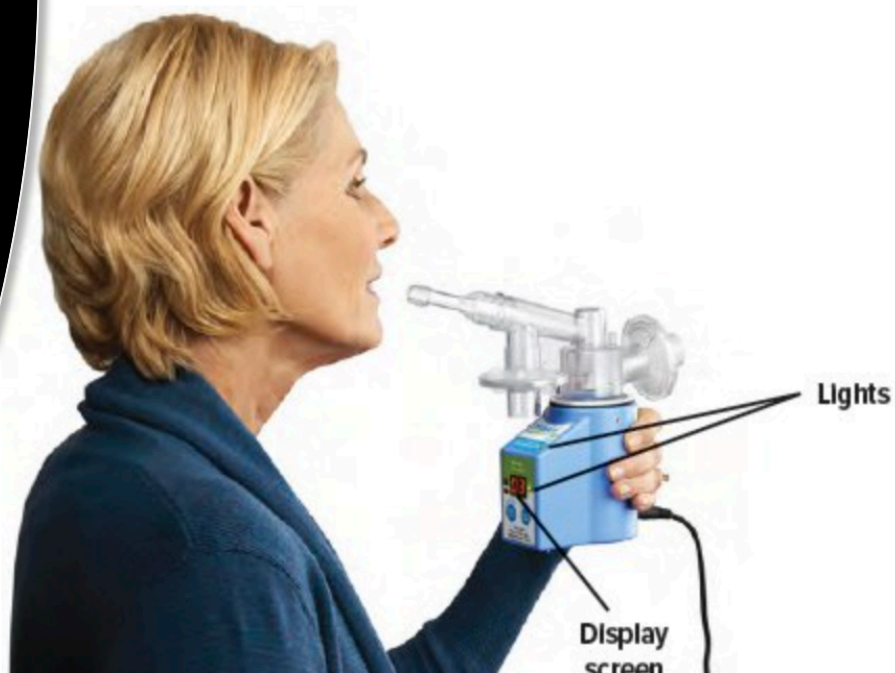
- Patients received up to 12 breaths four times daily
- Tyvaso group saw a 31.8 meter increase their 6 MWD
- Clinical Worsening occurred in 22.7% of treated patients vs 33.1% of placebo
- FVC improved as well



N Engl J Med 2021; 384:325-334

Tyvaso:
Inhaled Trepostinil

- The question is naturally, can Tyvaso delay or prevent the development of pulmonary hypertension
- Would it help maintain quality of life longer?
- Could it actually help combat the progression of fibrosis too?



TETON:

Phase 3 Randomized Double Blind Placebo Controlled Trial

- 52 Week Study
- Randomization 1:1 drug to placebo
- Inhaled Trepostinil
- Open label extension
- Allows treatment with Esbriet or OFEV
- Excluded is SpO2 <89% on 10 L
- Life expectancy <6 months

Key Inclusion Criteria:

- Patients Age 40-85
- Disease duration: No limit
- FVC 45-80%
- DLCO no criteria
- HRCT with definite or probable UIP or lung biopsy consistent with IPF
- No history of cancer

Summary Thoughts

- In the early 1980's, a child born with cystic fibrosis was not expected to live beyond their 20's
- There are many people with Cystic fibrosis who were in their 40's when they developed drugs that could actually cure the disease.
- They did not plan for retirement.

Summary Thoughts

- Things will change for IPF too.
- Unfortunately, only about 10% of eligible patients with IPF participate in clinical studies.
- Be the difference you want to see.