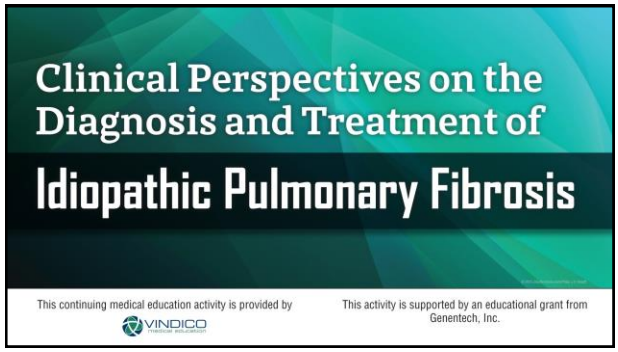
Activity presentations are considered intellectual property.

- These slides may not be published or posted online without permission from Vindico Medical Education (cme@vindicoCME.com).
- Please be respectful of this request so we may continue to provide you with presentation materials.



The Appointment: Patient Perspective

- Wait time
  - 2-3 months
- Travel to IPF center
  - Up to 11-hour drive
  - Most too sick or hypoxic to fly
  - Park and walk into office or medical center
- Time for testing and appointment
  - Pulmonary function test, 6-minute walk test
  - Plan to spend the day
- Anxiety and fear
  - Uncertain expectations for the plan of the day
  - Uncertain expectations of prognosis and recommendations

Causes of an Interstitial Radiologic Pattern

- Infections
  - Fungal (pneumocystis, coccidio, crypto, histo)
  - Atypical bacteria
  - Viral
- Occupational / Environmental toxins
  - Hypersensitivity pneumonitis
  - Asbestos
  - Silica
  - beryllium
- Drug induced
  - www.pneumotox.com
- Radiation induced
- Malignancy
  - Lymphangitic carcinomatosis
  - BAC
- Connective tissue disease / autoimmune
  - RA
  - Scleroderma
  - PM/DM
  - Mixed connective tissue disease
  - SLE
  - Sjögren's
  - Inflammatory bowel disease
- Vasculitis
  - MPA
- Idiopathic
  - IIP
  - COP
  - Sarcoidosis
  - LAM / LCH / TS / DKC
  - Genetic

Most Challenging Mimickers of IPF

- Fibrosing nonspecific interstitial pneumonitis
- Chronic hypersensitivity pneumonitis
- Connective tissue disease ILD

History

- Obtain a complete history!
  - Environmental exposures
  - Work history
  - Animal exposures / Organic exposures
  - Medications / Substance use
  - GERD / dysphagia / aspiration
  - Sleep history
  - Full review of symptoms
    - Thorough rheumatologic review of symptoms

Environmental History

- Jobs?
  - Protective gear?
- Spouse's jobs?
- Pets?
- Hot tubs / humidifiers / AC?
- Water damage / standing water?

Smoking Association

- Smokers
  - Pulmonary LCH
  - DIP / RBILD
  - IPF
- Never smokers
  - HP
  - Sarcoidosis

Schwarz MI, et al. Interstitial Lung Disease, 5th edition

Symptoms/Signs

- Hemoptysis
  - DAH
  - LAM
  - TS
  - PVOD / PCH
  - Mitral valve disease
  - Granulomatous vasculitis
- Wheezing
  - Chronic eosinophilic pneumonia
  - Bronchiolitis
  - Lymphangitic carcinomatosis
- Chest pain
  - Pleurisy – connective tissue disease
  - Substernal discomfort – sarcoidosis
- Extrapulmonary
  - Connective tissue disease
  - Inflammatory bowel disease
- Pneumothorax
  - Pulmonary LCH / TS
  - LAM
  - Neurofibromatosis

Schwarz MI, et al. Interstitial Lung Disease, 5th edition

Assess for Comorbidities of IPF

- Gastroesophageal reflux disease
- Obstructive sleep apnea
- Pulmonary arterial hypertension
- Cardiac disease

Physical Exam

- Velcro crackles
- RV lift / augmented P2 / right-sided gallop
- Extra pulmonary signs
- Signs of autoimmune disease
- Clubbing

Laboratory

- Hepatic function
  - Cirrhosis?
- Renal function
  - Connective tissue disease? Vasculitis?
- Bone marrow function
  - MDS? DKC?
- UA
  - Vasculitis?
- Cardiac
  - ECG, echo, BNP
- Serologies
  - ANA, RF, anti-ccp, anti scl 70, CPK, anti Jo, anti ds-DNA, anti-extractable nuclear ag (anti-Sm, Anti-ribonucleoprotein), ANCA
- Pulmonary Function Tests
  - Spirometry, lung volumes, DLCO

Pulmonary Function Testing

- Restriction
- Reduction in diffusing capacity
- May see preserved lung volumes when emphysema is present

Walk Studies

- Assist with determination of oxygen needs and disease progression
  - 6-minute walk study
    - Desats to 88% or less is correlated with a median survival of 3.21 years
  - Exertional walk study

High-resolution Computed Tomography Criteria for UIP Pattern

UIP Pattern (All Four Features)	Possible UIP Pattern (All Three Features)	Inconsistent with UIP Pattern (any of the Seven Features)
■ Subpleural, basal predominance	■ Subpleural, basal predominance	■ Upper or mid-lung predominance
■ Reticular abnormality	■ Reticular abnormality	■ Peribronchovascular predominance
■ Honeycombing with or without traction bronchiectasis	■ Absence of features listed as inconsistent with UIP pattern (see third column)	■ Extensive ground glass abnormality (extent >reticular abnormality)
■ Absence of features listed as inconsistent with UP		■ Profuse micronodules (bilateral, predominantly upper lobes)
		■ Discrete cysts (multiple, bilateral, away from areas of honeycombing)
		■ Diffuse mosaic attenuation / air-trapping (bilateral in three or more lobes)
		■ Consolidation in bronchopulmonary segment(s) / lobe(s)

Raghu G, et al. *Am J Respir Crit Care Med*. 2011;183(6):788-824.

Difficult Discussions

- 2 new FDA approved drugs
- Limited clinical trials
  - Some with a placebo group / some with background therapy
- Supportive care
  - Oxygen
  - Vaccinations
  - Treat Comorbidities
    - Diagnose and treat obstructive sleep apnea
    - Diagnose and treat gastroesophageal reflux
    - Consider treatment of PAH
  - Pulmonary rehab
    - Must have moderate restriction and reduction in DLCO to meet insurance criteria
    - Few programs
    - Under reimbursed
  - Maximize treatment of other causes of shortness of breath
    - Cardiac disease
    - Anemia

Difficult Discussions: Oxygen

- Visual reminder of patient's disease and weakness
- Complicates daily activities
- Durable medical company (DME) limitations
  - Cheaper cumbersome rolling tanks
  - Access to high flow regulators is limited
  - Supply of oxygen may be limited due to limited reimbursement
- Difficult to adjust oxygen from another room
- Complicates travel and limits flights
- DMEs have limited knowledge of the difference in IPF / ILD patients O2 needs versus those of emphysema patients

Difficult Discussions

- Lung transplantation
  - Generally up to age 65
  - No other major organ disease
  - Timing of transplant listing
- Palliative care / hospice
  - Symptom management
  - Home needs and family support
  - Home nursing support

Difficult Discussions for Patients

- Do I tell my family?
  - "I don't want them to worry."
- How do I tell my family?
- How do I explain this disease to my family?
- I don't want to be treated like an invalid.
- How do I discuss end of life decisions with my wife and children?
- How do I create a will and a living will?

Classification of ILDs

- Etiology
  - Infection
  - Occupational / environmental exposures
  - Drug induced
  - Radiation induced
  - Connective tissue disease / vasculitis
  - Idiopathic
  - Malignancy
- Timing of presentation
  - Acute
  - Subacute
  - Chronic
- Pattern of Infiltrates
- Age at presentation

Diagnostic Considerations

- Younger (20-50 yo)
  - Sarcoidosis
  - Connective tissue disease
  - LAM
  - Pulmonary LCH
  - Familial IPF
  - Hermansky Pudlak
  - Gaucher's
- Gender
  - Female
    - Premenopausal
      - LAM
      - Tuberous sclerosis
    - Connective tissue disease
      - RAILD is more common in men
  - Male
    - Pneumoconiosis

Schwarz MI, et al. Interstitial Lung Disease, 5th edition

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Talmadge E. King, Jr., M.D., Williamson Z. Bradford, M.D., Ph.D., Socorro Castro-Bernardini, M.D., Elizabeth A. Fagan, M.D., Ian Glaspole, M.B., B.S., Ph.D., Marilyn K. Glassberg, M.D., Eduard Gorina, M.D., Peter M. Hopkins, M.D., David Kardatzke, Ph.D., Lisa Lancaster, M.D., David J. Lederer, M.D., Steven D. Nathan, M.D., Carlos A. Pereira, M.D., Steven A. Sahn, M.D., Robert Sussman, M.D., Jeffrey J. Swigris, D.O., and Paul W. Noble, M.D., for the ASCEND Study Group*

King TE, et al. *N Engl J Med.* 2014;370:2083-2092.

BACKGROUND

In two of three phase 3 trials, pirfenidone, an oral antifibrotic therapy, reduced disease progression, as measured by the decline in forced vital capacity (FVC) or vital capacity, in patients with idiopathic pulmonary fibrosis; in the third trial, this end point was not achieved. We sought to confirm the beneficial effect of pirfenidone on disease progression in such patients.

METHODS

In this phase 3 study, we randomly assigned 555 patients with idiopathic pulmonary fibrosis to receive either oral pirfenidone (2403 mg per day) or placebo for 52 weeks. The primary end point was the change in FVC or death at week 52. Secondary end points were the 6-minute walk distance, progression-free survival, dyspnea, and death from any cause or from idiopathic pulmonary fibrosis.

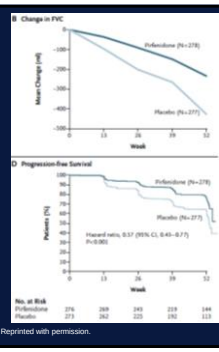
RESULTS

In the pirfenidone group, as compared with the placebo group, there was a relative reduction of 47.9% in the proportion of patients who had an absolute decline of 10 percentage points or more in the percentage of the predicted FVC or who died; there was also a relative increase of 132.5% in the proportion of patients with no decline in FVC (P<0.001). Pirfenidone reduced the decline in the 6-minute walk distance (P=0.04) and improved progression-free survival (P<0.001). There was no significant between-group difference in dyspnea scores (P=0.16) or in rates of death from any cause (P=0.38) or from idiopathic pulmonary fibrosis (P=0.23). However, in a prespecified pooled analysis incorporating results from two previous phase 3

CONCLUSIONS

Pirfenidone, as compared with placebo, reduced disease progression, as reflected by lung function, exercise tolerance, and progression-free survival, in patients with idiopathic pulmonary fibrosis. Treatment was associated with an acceptable side-effect profile and fewer deaths. (Funded by InterMune; ASCEND ClinicalTrials.gov number, NCT01366209.)

King TE, et al. *N Engl J Med.* 2014;370:2083-2092.



King TE, et al. *N Engl J Med.* 2014;370:2083-2092. Reprinted with permission.

Pirfenidone: Effects on Mortality

Mortality in the ASCEND and CAPACITY Trials.*

Variable	Pirfenidone	Placebo	Hazard Ratio (95% CI)†	*P* Value‡
ASCEND trial				
No. of patients	278	277		
Death – No. (%)				
From any cause	11 (4.0)	20 (7.2)	0.55 (0.26-1.15)	0.10
Related to idiopathic pulmonary fibrosis§	3 (1.1)	7 (2.5)	0.44 (0.11-1.72)	0.23
Pooled data from ASCEND and CAPACITY trials				
No. of patients	623	624		
Death – No. (%)				
From any cause	22 (3.5)	42 (6.7)	0.52 (0.31 – 0.87)	0.01
Related to idiopathic pulmonary fibrosis§	7 (1.1)	22 (3.5)	0.32 (0.14 – 0.76)	0.006

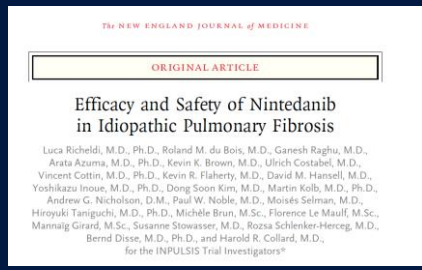
*Data from the two CAPACITY studies were censored at 1 year to standardize the follow-up for the three studies.
†Hazard ratios are for the pirfenidone group, as compared with the placebo group. And were calculated with the use of the Cox proportional-hazards model.
‡*P* values were calculated with the use of the log-rank test.
§ Death related to idiopathic pulmonary fibrosis was defined as death that occurred during the period from randomization to 28 days after the last does of the study drug. This category was evaluated in a blinded fashion by an independent mortality-assessment committee in the ASCEND trial and by clinical investigators in the CAPACITY trials.

King TE, et al. *N Engl J Med.* 2014;370:2083-2092.

Adverse Events

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)

King TE, et al. *N Engl J Med.* 2014;370:2083-2092.


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

Luca Richeldi, M.D., Ph.D., Roland M. du Bois, M.D., Ganesh Raghu, M.D., Arata Azuma, M.D., Ph.D., Kevin K. Brown, M.D., Ulrich Costabel, M.D., Vincent Cottin, M.D., Ph.D., Kevin R. Flaherty, M.D., David M. Hansell, M.D., Yoshikazu Inoue, M.D., Ph.D., Dong Soon Kim, M.D., Martin Kolb, M.D., Ph.D., Andrew G. Nicholson, D.M., Paul W. Noble, M.D., Moisés Selman, M.D., Hiroyuki Taniguchi, M.D., Ph.D., Michèle Brun, M.Sc., Florence Le Maulf, M.Sc., Mannaig Girard, M.Sc., Susanne Stowasser, M.D., Rozsa Schlenker-Herceg, M.D., Bernd Disse, M.D., Ph.D., and Harold R. Collard, M.D., for the INPULSIS Trial Investigators*

Richeldi L, et al. *N Engl J Med.* 2014;370:2071-2082.

BACKGROUND

Nintedanib (formerly known as BIBF 1120) is an intracellular inhibitor that targets multiple tyrosine kinases. A phase 2 trial suggested that treatment with 150 mg of nintedanib twice daily reduced lung-function decline and acute exacerbations in patients with idiopathic pulmonary fibrosis.

METHODS

We conducted two replicate 52-week, randomized, double-blind, phase 3 trials (INPULSIS-1 and INPULSIS-2) to evaluate the efficacy and safety of 150 mg of nintedanib twice daily as compared with placebo in patients with idiopathic pulmonary fibrosis. The primary end point was the annual rate of decline in forced vital capacity (FVC). Key secondary end points were the time to the first acute exacerbation and the change from baseline in the total score on the St. George's Respiratory Questionnaire, both assessed over a 52-week period.

RESULTS

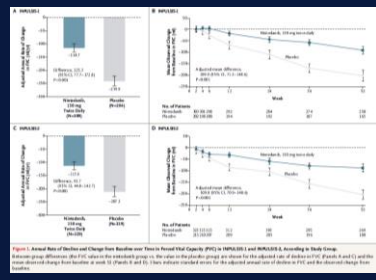
A total of 1066 patients were randomly assigned in a 3:2 ratio to receive nintedanib or placebo. The adjusted annual rate of change in FVC was −114.7 ml with nintedanib versus −239.9 ml with placebo (difference, 125.3 ml; 95% confidence interval [CI], 77.7 to 172.8; P<0.001) in INPULSIS-1 and −113.6 ml with nintedanib versus −207.3 ml with placebo (difference, 93.7 ml per year; 95% CI, 44.8 to 142.7; P<0.001) in INPULSIS-2. In INPULSIS-1, there was no significant difference between the nintedanib and placebo groups in the time to the first acute exacerbation (hazard ratio with

CONCLUSIONS

In patients with idiopathic pulmonary fibrosis, nintedanib reduced the decline in FVC, which is consistent with a slowing of disease progression; nintedanib was frequently associated with diarrhea, which led to discontinuation of the study medication in less than 5% of patients. (Funded by Boehringer Ingelheim; INPULSIS-1 and INPULSIS-2 ClinicalTrials.gov numbers, NCT01335464 and NCT01335477.)

Richeldi L, et al. *N Engl J Med.* 2014;370:2071-2082.

INPULSIS Studies



Richeldi L, et al. *N Engl J Med.* 2014;370:2071-2082. Reprinted with permission.

Adverse Events

Event	INPULSIS-1		INPULSIS-2	
	Nintedanib (N=309)	Placebo (N=204)	Nintedanib (N=329)	Placebo (N=219)
	number of patients (percent)			
Any adverse event	298 (96.4)	181 (88.7)	311 (94.5)	198 (90.4)
Any adverse event, including progression of idiopathic pulmonary fibrosis	296 (95.8)	179 (87.7)	311 (94.5)	197 (90.0)
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)
Severe adverse events	81 (26.2)	37 (18.1)	93 (28.3)	62 (28.3)
Serious adverse events	96 (31.1)	55 (27.0)	98 (29.8)	72 (32.9)
Fatal adverse events	12 (3.9)	10 (4.9)	25 (7.6)	21 (9.6)
Adverse events leading to treatment discontinuation	65 (21.0)	22 (10.8)	58 (17.6)	33 (15.1)
Gastrointestinal disorders	26 (8.4)	3 (1.50	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)

Richeldi L, et al. *N Engl J Med.* 2014;370:2071-2082.

Key Inclusionary Criteria

ASCEND (Pirfenidone)

- Diagnosis per ATS/ERS guidelines (adjudicated)
- Symptoms >12 months
- Diagnosis 6-48 months
- Age 40-80*
- FVC 50%-90%
- FEV1 / FVC ≥ 80%*
- DLco 30%-90%*
- 6MWT ≥ 150 meters

N=13 inclusion criteria

INPULSIS (Nintedanib)

- Diagnosis per ATS/ERS guidelines (adjudicated)
- Diagnosis within 5 years*
- Age ≥ 40
- FVC ≥ 50%
- DLCO 30-79%

N=7 inclusion criteria

*=notable differences

Key Exclusionary Criteria

ASCEND (Pirfenidone)

- Cigarette smoking within 3 months
- Other known cause for ILD
- Expected to receive LTx within a year
- Significant, cardiac, liver, or kidney* disease
- h/o asthma or COPD / +BD response
- Con Meds
  - Steroids, cytotoxic agents, and other agents with previous proposed use for IPF

N=26 exclusion criteria

INPULSIS (Nintedanib)

- FEV1 / FVC<70%*
- Expected to receive LTx within a year
- Bleeding risk*
- Thrombotic risk*
- Major surgery planned*
- Significant cardiac or liver disease
- Con Meds
  - cytotoxic agents, NAC*, prednisone >15 mg/day*

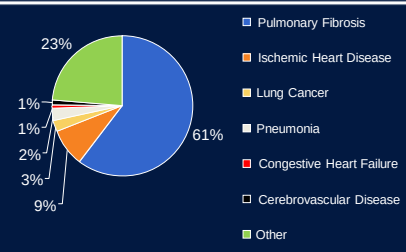
N=19 exclusion criteria

*=notable differences

Current Phase 2 Trials for IPF Next-generation Therapy?

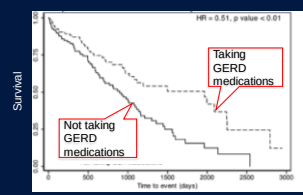
Trial	Target	N	Primary Endpoint
Co-trimoxazole (Ph 3)	Pneumocystis jirovecii	56	Change in FVC or respir. Hospitalization
FG-3019	Anti-CTGF	90	Change in FVC from baseline
Rituximab	CD-20	58	Titers of anti-HEp-2 autoantibodies
Simtuzumab	Anti-LOXL2	500	PFS
GC-1008	TGF-β	25	Safety, tolerability, PK
QAX576	Anti-IL-13	40	Safety, tolerability, FVC
Tralokinumab	Anti-IL-13	302	Change in FVC from baseline
STX-100	αvβ6	32	Adverse events
BMS-986020	LPA Receptor	300	Rate of change in FVC

Cause of Death in Patients with PF



Olson AL. *Am J Respir Crit Care Med.* 2007;176:277-284.

GERD Treatment and Survival



Lee JS, et al. *Am J Respir Crit Care Med.* 2011;184:1390-1394.

IPF Management Checklist

- Risk factor reduction
- Patient education
  - Advocacy group involvement
- Focus on comorbidities
  - Mental health needs
  - GERD, OSA, CAD, PH, VTE, etc.
- Supplemental oxygen
- Age-appropriate vaccinations
- Discussion about available medical therapies
- Pulmonary rehabilitation
- Clinical trials
- Lung transplant evaluation
- Address end of life issues: palliative and hospice care