Session 3: Clinical Updates in Idiopathic Pulmonary Fibrosis

Learning Objectives

1. Describe the epidemiology and pathophysiology of Idiopathic Pulmonary Fibrosis (IPF) and the importance of early diagnosis
2. Review the diagnosis and management of IPF as recommended in the 2011 ATS/ERS guidelines
3. Evaluate the emerging data in IPF treatment options and the impact this information has on management approaches for existing and newly diagnosed patients with IPF

Faculty

Kevin R. Flaherty, MD, MS
Professor, Department of Internal Medicine
Medical Director, Idiopathic Pulmonary Fibrosis Foundation Clinical Care Site
Ann Arbor, Michigan

Dr Kevin Flaherty, is a professor of medicine in the department of internal medicine and the medical director of the Idiopathic Pulmonary Fibrosis Foundation clinical care site at the University of Michigan Health System, Ann Arbor. Dr Flaherty has also been appointed chairman of the steering committee of the Pulmonary Fibrosis Foundation (PFF) Care Center Network (CCN) and patient registry, a national collaborative formed to improve the understanding and treatment of interstitial lung diseases. Dr Flaherty received MD at the Indiana University School of Medicine, and completed his fellowship in pulmonary & critical care medicine at the, University of Michigan, Ann Arbor. He also completed a MS degree at the University Of Michigan School Of Public Health. Dr Flaherty is board certified in adult pulmonary and critical care medicine by the American Board of Internal Medicine. His research interests include the identification and utilization of predictors of diagnosis, response to therapy, and survival in patients with interstitial lung disease.

Fernando J. Martinez, MD, MS
Executive Vice Chairman
Gladys and Roland Harriman Professor of Medicine
Joan and Sanford I. Weill Department of Medicine
Weill Cornell Medical College
New York-Presbyterian Hospital/Weill Cornell Medical Center
New York, New York

Dr Fernando Martinez is the executive vice chair of medicine at Weill Cornell Medical College, and New York-Presbyterian Hospital/Weill Cornell Medical Center. He is also the Gladys and Roland Harriman professor of medicine, Joan and Sanford I, Weill department of medicine, at Weill Cornell Medical College. He received his BS and MD at the University of Florida, completed an internal medicine residency at Beth Israel Hospital/Harvard Medical School, and a pulmonary and critical care medicine fellowship at Boston University. He also completed a MS degree in biostatistics and clinical study design from the University of Michigan School Of Public Health, Ann Arbor, Michigan. Dr Martinez is board certified in internal medicine, pulmonary medicine, and critical care medicine by the American Board of Internal Medicine. He has authored more than 241 peer reviewed manuscripts, 32 review articles in addition to 32 book chapters, and is nationally and internationally recognized for his seminal studies in the phenotypic and functional classification, and clinical interventions in COPD and interstitial lung disease.
**Faculty Financial Disclosure Statements**
The presenting faculty reported the following:

Dr Flaherty consults for Boehringer Ingelheim, Medimmune, Gilead, Intermune, Veracyte, Roche, Bristol Meyers Squibb, Immuneworks and Roche.

Dr Martinez is on the advisory committee and/or consults for Amgen, Bayer, Boehringer Ingelheim, CSA Medical, Genentech, GSK, Ikaria, Janssens, Johnson & Johnson, Pearl, Pfizer, Roche and Veracyte; on the steering committee for Bayer, Forest, Gilead, GSK, Janssens, Nycomed/Takeda and Promedior; DSMB for Stromedix and GSK; receives book royalties from UpToDate; speaks for Nycomed/Takeda; and participates in CME programs for CME Incite, Miller, NACE, Paradigm and Peer Voice.

**Education Partner Financial Disclosure Statement**
The content collaborator at Clark Medical Writing reported the following:
Margaret V. Clark, MS, RN, RRT – NPS is the medical writer and editor for this program. She has nothing relevant to disclose.

**Acronym List**

<table>
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<tr>
<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>6-MWD</td>
<td>6 min Walk Distance</td>
</tr>
<tr>
<td>ALAT</td>
<td>Latin American Thoracic Association</td>
</tr>
<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
</tr>
<tr>
<td>BOOP</td>
<td>Bronchiolitis Obliterans Organizing Pneumonia</td>
</tr>
<tr>
<td>COP</td>
<td>Cryptogenic Organizing Pneumonia</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>DLco</td>
<td>Diffusion Capacity for Carbon Monoxide</td>
</tr>
<tr>
<td>DPLD</td>
<td>Diffuse Parenchymal Lung Disease</td>
</tr>
<tr>
<td>ERS</td>
<td>European Respiratory Society</td>
</tr>
<tr>
<td>FEV1</td>
<td>Forced Expiratory Volume in 1 Second</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced Vital Capacity</td>
</tr>
<tr>
<td>FEV1/FVC ratio</td>
<td>Forced Expiratory Volume in 1 Second/ Forc</td>
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SESSION 3
10:30 – 11:45 am
Clinical Updates in Idiopathic Pulmonary Fibrosis

SPEAKERS
Kevin Flaherty, MD
Fernando Martinez, MD, MS

Presenter Disclosure Information
The following relationships exist related to this presentation:
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- Review the diagnosis and management of IPF as recommended in the 2011 ATS/ERS guidelines
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Interstitial Lung Diseases - Difficulties
- Diverse group of disorders (130+)
- Similar symptoms, physiology, radiology
- Difficult nomenclature
- Limited, often toxic, treatments
Idiopathic Pulmonary Fibrosis

A specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, and limited to the lungs.

It is characterized by progressive worsening of dyspnea and lung function and is associated with a poor prognosis.

Diffuse Parenchymal Lung Disease (DPLD)

- Idiopathic pulmonary fibrosis
- All other forms of idiopathic pulmonary fibrosis
- Desquamative interstitial pneumonia
- Acute interstitial pneumonia
- Non-specific interstitial pneumonia (provisional)
- Allergic alveolitis
- Granulomatous interstitial pneumonia
- Respiratory bronchiolitis interstitial lung disease
- Other forms of DPLD, eg, LAM, HFr, etc

Exacerbations of IPF are not infrequent

461 patients with IPF (269 biopsy proven)
- 163 Respiratory Deteriorations requiring hospitalization
  - Focal x-ray lesion (pneumothorax, pneumonia) 14%
  - Diffuse in 86%
  - Exacerbation in 55%
  - Infection 31% (opportunistic in 57%)
  - Heart Failure (3%)

Exacerbations of IPF: 58 (14.2%), 97 (23%), 124 (29%), 134 (31.4%)

<table>
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<tr>
<th>Predictor</th>
<th>Points</th>
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<tr>
<td>Female</td>
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<tr>
<td>Age &lt; 60y</td>
<td>1</td>
</tr>
<tr>
<td>Age 61-65</td>
<td>2</td>
</tr>
<tr>
<td>Age &gt; 65</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary Function</td>
<td></td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>6</td>
</tr>
<tr>
<td>DLCO, % predicted</td>
<td>8</td>
</tr>
<tr>
<td>DLco, % predicted</td>
<td>8</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>5</td>
</tr>
</tbody>
</table>

Total Points: 8

Mortality: 4.8, 9.4, 16.3, 39.2

Acute Exacerbation | Respiratory Deterioration

<table>
<thead>
<tr>
<th>Year</th>
<th>Acute Exacerbation</th>
<th>Respiratory Deterioration</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>58 (14.2%)</td>
<td>97 (23%)</td>
</tr>
<tr>
<td>2</td>
<td>73 (18.8%)</td>
<td>124 (29.2%)</td>
</tr>
<tr>
<td>3</td>
<td>75 (20.7%)</td>
<td>134 (31.4%)</td>
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</table>
Learning Objectives

- Describe the epidemiology and pathophysiology of Idiopathic Pulmonary Fibrosis (IPF) and the importance of early diagnosis
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2011 ATS/ERS Diagnostic Criteria for IPF

Exclusion of known causes of Intestinal Lung Disease (ILD)*

AND

Usual Interstitial Pneumonia (UIP) pattern on High-Resolution Computed Tomography (HRCT) without surgical biopsy OR

Definite/possible UIP pattern on HRCT with a surgical lung biopsy showing definite/probable UIP

*also known as diffuse parenchymal lung disease, DPLD

An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-Based Guidelines for Diagnosis and Management

The 2011 ATS/ERS Diagnostic Criteria for IPF are based on a panel of experts from various organizations. The criteria include the exclusion of known causes of ILD, and the presence of typical HRCT features of UIP in the absence of surgical biopsy. This approach is intended to improve the accuracy of the diagnosis of IPF and to ensure that patients are treated appropriately.
Diagnostic Algorithm for IPF

1. Suspected IPF
2. Identifiable causes for ILD?
   - Yes
   - No
   - Possible UIP
     - Inconsistent w/ UIP
     - Surgical Lung Biopsy
   - UIP
     - Probable UIP
     - Non-classifiable fibrosis
   - Multidisciplinary Discussion (MDD)

   IPF/Not IPF

Diagnostic “Tools”

Clinical History & Physical, PFT, Lab

1. Raise suspicion that ILD is present
2. Identify a cause of the disease
   a. Infection
   b. Systemic Disorders
   c. Exposures (inhaled or oral)
   d. Idiopathic

UIP Associated With Collagen Vascular Disease (CVD) Is Associated With Improved Prognosis and is not considered idiopathic pulmonary fibrosis

P = 0.005

Pulmonary Function Testing

- Pulmonary Mechanics – FEV₁, FVC, FEV₁/FVC
  - Obstructive Lung Disease → Decreased FEV₁/FVC ratio
  - Restrictive Lung Disease → Normal/Increased FEV₁/FVC ratio
  - Muscle weakness → Normal/Increased FEV₁/FVC ratio
  - Percent predicted grades severity of FEV₁ and FVC
- Lung Volumes
  - True measure of size of lung
  - Total lung capacity (TLC), residual volume (RV)
- Diffusion capacity for carbon monoxide (DLCO)
  - Decreased in many diseases such as emphysema, interstitial lung diseases, pulmonary vascular disease, pulmonary emboli

Diagnostic Algorithm for IPF

1. Suspected IPF
2. Identifiable causes for ILD?
   - Yes
   - No
   - Possible UIP
     - Inconsistent w/ UIP
     - Surgical Lung Biopsy
   - UIP
     - Probable UIP
     - Non-classifiable fibrosis
   - Multidisciplinary Discussion (MDD)

   IPF/Not IPF

Diagnostic “Tools”

Radiographic CXR, HRCT

HRCT Features
- Ground glass attenuation
- Honeycombing/cysts
- Lines/Reticular thickening
- Consolidation
- Nodules
- Decreased lung attenuation

HRCT Distribution
- Upper
- Lower
- Central
- Peripheral
- Diffuse/Bilateral
**High Resolution Computed Tomography**

Allows detailed evaluation of the lung parenchyma
Optimal for interstitial lung disease, infection, emphysema, bronchiectasis

Technique
- Does NOT use contrast
  - Thin collimation with approximately 1mm slice thickness
  - Reconstruction with specific Windows
  - Inspiration, Expiration, and prone images
  - Regular CT or PE CT for everything else

**Diagnostic Algorithm for IPF**

**Usual Interstitial Pneumonia Pattern:**

- Marked fibrosis/architectural distortion +/- honeycombing, predominantly subpleural/paraseptal
- Patchy Fibrosis
- Fibroblastic Foci
- Absence of features to suggest alternative diagnosis

**Putting the Pattern in Context**

**Interstitial Lung Disease Diagnostic Team**

Communication among multidisciplinary team is essential to an accurate diagnosis
Multidisciplinary Approach

Multidisciplinary interactions improve diagnostic agreement and confidence

<table>
<thead>
<tr>
<th>Step</th>
<th>Assessment Method</th>
<th>Information Provided</th>
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<tbody>
<tr>
<td>1</td>
<td>Individual</td>
<td>HRCT</td>
</tr>
<tr>
<td>2</td>
<td>Individual</td>
<td>HRCT, clinical data</td>
</tr>
<tr>
<td>3</td>
<td>Group</td>
<td>HRCT, clinical data</td>
</tr>
<tr>
<td>4</td>
<td>Group</td>
<td>HRCT, clinical data, ILD</td>
</tr>
<tr>
<td>5</td>
<td>Consensus</td>
<td>HRCT, clinical data, ILD</td>
</tr>
</tbody>
</table>

Diagnostic Algorithm for IPF

Back to our 63 year old male presents with progressive dyspnea and cough for four years

PMH/SH/FL
- Osteoarthritis
- Meds
  - Aspirin, multivitamin
  - Remote smoker (10 pack years); stopped 20 years earlier
  - Works as counselor
  - FH of diabetes

PE:
- Bi-basilar rales
- Normal CV, abdomen, neuro exam

2011 Guidelines on Management of IPF

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Strong For</th>
<th>Weak For</th>
<th>Weak Against</th>
<th>Strong Against</th>
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<tbody>
<tr>
<td>Corticosteroids</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Colchicine</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon γ 1b</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Bosentan</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-acetylcysteine/Pirfenidone</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAC/Aspirin/Peptidomimetics</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAC</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Lung transpl.
  - Initial                | X          |          |              |                |
| Lung transpl.
  - Transplant            | X          |          |              |                |

Three Recent IPF Clinical Trials

American Thoracic Society 2014

- **PANTHER**  N-acetylcysteine (NAC)
- **ASCEND**  pirfenidone
- **INPULSIS**  nintedanib (BIBF1120)

**PANTHER**  
N-acetylcysteine (NAC)
**PANTHER 2012 Interim Results**

<table>
<thead>
<tr>
<th>Primary</th>
<th>Triple Therapy</th>
<th>Placebo</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>FVC (liters)</td>
<td>-0.24</td>
<td>-0.23</td>
<td>0.85</td>
</tr>
</tbody>
</table>

- Triple therapy has no benefit for FVC
- Increased risk of death

**Time to Death**

Kaplan–Meier Analysis

HR 9.26
(95% CI 1.16–74.1)

P = 0.01

**PANTHER 2012 Adverse Events**

- Triple therapy has higher incidence of adverse events than placebo

**ASCEND Study Design**

- Inclusion Criteria:
  - Age 40-80
  - Confirmed IPF
  - 50 - 90% FVC pred
  - 30 - 90% DLCO pred
  - FEV/FVC ≥ 0.80
  - 6-MWD ≥ 150 m

- Endpoints:
  - 52 Weeks
  - Δ FVC or death
  - 6-MWD
  - PFS
  - Dyspnea
  - Death

- 555 Patients

**ASCEND Adverse Events**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Pirfenidone (%) (N = 278)</th>
<th>Placebo (%) (N = 277)</th>
<th>Δ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>36</td>
<td>15.4</td>
<td>22.6</td>
</tr>
<tr>
<td>Rash</td>
<td>28.1</td>
<td>8.7</td>
<td>19.4</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>17.6</td>
<td>6.1</td>
<td>11.5</td>
</tr>
<tr>
<td>Anorexia</td>
<td>16.8</td>
<td>6.5</td>
<td>9.3</td>
</tr>
<tr>
<td>GERD</td>
<td>11.9</td>
<td>6.5</td>
<td>5.4</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>12.6</td>
<td>7.9</td>
<td>4.7</td>
</tr>
<tr>
<td>Insomnia</td>
<td>11.2</td>
<td>6.5</td>
<td>4.7</td>
</tr>
<tr>
<td>Dizziness</td>
<td>17.6</td>
<td>13</td>
<td>4.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12.9</td>
<td>8.7</td>
<td>4.2</td>
</tr>
<tr>
<td>Cough</td>
<td>14.7</td>
<td>17.7</td>
<td>3</td>
</tr>
<tr>
<td>IPF</td>
<td>9.4</td>
<td>18.1</td>
<td>-8.7</td>
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</table>

**ASCEND Pirfenidone**

- Δ FVC or death
- PFS
- Dyspnea
- Death
INPULSIS
Nintedanib

INPULSIS-1 and INPULSIS-2 Study Design

Inclusion Criteria
- Age ≥ 40
- IPF ≤ 5 y
- ≥ 50% FVC pred
- 30 - 79% DLCO pred
- HRCT within 1y

Endpoints
- 52 Weeks
- Nintedanib 300 mg Daily
- Time to first AE
- Δ FVC
- Δ SGRQ

1066 Patients

AE – Acute Exacerbation
SGRQ – St. George’s Respiratory Questionnaire

Common Nintedanib Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>INPULSIS-1</th>
<th></th>
<th>INPULSIS-2</th>
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<tbody>
<tr>
<td></td>
<td>Nintedanib</td>
<td>Placebo</td>
<td>Nintedanib</td>
<td>Placebo</td>
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<tr>
<td>Any (%)</td>
<td>96</td>
<td>89</td>
<td>94</td>
<td>90</td>
</tr>
<tr>
<td>Diarrhea (%)</td>
<td>62</td>
<td>19</td>
<td>63</td>
<td>18</td>
</tr>
<tr>
<td>Nausea (%)</td>
<td>23</td>
<td>6</td>
<td>26</td>
<td>7</td>
</tr>
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</table>

Back to our 63 year old male presents with progressive dyspnea and cough for four years

PMH/SH/FL
- Osteoarthritis
- Meds
  - Aspirin, multivitamin
  - Remote smoker (10 pack years); stopped 20 years earlier
  - Works as counselor
  - FH of diabetes
PE:
- Bi-basilar rales
- Normal CV, abdomen, neuro exam

Back to our 63 year old male presents with progressive dyspnea and cough for four years

ONGOING CLINICAL TRIALS IN IPF*

<table>
<thead>
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<th>Product</th>
<th>Company/Sponsor</th>
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<tr>
<td>SX-A106</td>
<td>Biogen/IdeCred</td>
<td>Anti-A ε integrin MoAb</td>
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<tr>
<td>CC-513</td>
<td>Celgene</td>
<td>JAK2 inhibitor</td>
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<td>AMG-287</td>
<td>Amgen</td>
<td>Monoclonal IgG</td>
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<td>RS-993202</td>
<td>Bristol-Myers Squibb</td>
<td>LPA1 receptor antagonist</td>
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<td>ASS-3229</td>
<td>Asahi-Arakawa</td>
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<td>Genentech</td>
<td>ILOX2</td>
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<td>FibroGen</td>
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<td>Geno Life Science</td>
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<td>PRRS-151</td>
<td>Promeza</td>
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<td>GSK-2216458</td>
<td>GSK</td>
<td>mTOR/P3K</td>
<td>POC</td>
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*List likely incomplete
EARLY REFERRAL for SPECIALTY CARE

Why refer early to an ILD Center?

- Diagnostic expertise
  - Standardized assessment
  - Confirmation of diagnosis
- Management expertise
  - Oxygen prescription
  - Pulmonary rehabilitation
  - Attention to obesity and sarcopenia/frailty
  - Potential enrollment in a clinical trial
  - Transplant evaluation


Lung Transplantation for IPF: 2014 Referral Guidelines

- Histopathologic or radiographic evidence of usual interstitial pneumonitis (UIP)
- Abnormal lung function: FVC < 80% predicted or DLCO < 40% predicted
- Any dyspnea or functional limitation attributable to lung disease
- Any oxygen requirement, even if only during exertion


IPF - Summary

- A form of chronic, progressive fibrosing interstitial pneumonia of unknown cause
- Occurs primarily in older adults and is limited to the lungs
- Diagnostic process is centered on:
  - Excluding systemic diseases or exposures
  - Identifying a pattern of UIP on HRCT or Surgical lung biopsy
- Standard immunosuppressive therapy is no longer felt to be indicated
- Pirfenidone and nintedanib recently approved to treat IPF