Updates in Interstitial Lung Disease

Making Strides in Accurate Diagnosis and Optimized Treatment

An Industry-Organized Symposium at the ATS 2018 International Conference
A non-CME educational program sponsored by PVI, PeerView Institute for Medical Education, open to all ATS 2018 International Conference attendees.
Improving Early Recognition and Accurate Diagnosis of Idiopathic Pulmonary Fibrosis and Other Interstitial Lung Diseases

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Vice-Chairman of Medicine for Diversity and Innovation
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Sylvester Comprehensive Cancer Center
Miami, Florida
IPF: A Fatal Disease

IPF: A Fatal Disease

Progression of IPF

Normal Progressive destruction of lung architecture

5-year survival rate from diagnosis = 20 to 40% Age of onset : 2/3 over age 60

Images courtesy of Dr. Glassberg.
Diffuse Parenchymal Lung Diseases (DPLD)\(^1\)

- DPLD of known etiology (HP, drugs, collagen-vascular)
- Idiopathic interstitial pneumonia (IIP)
- Granulomatous DPLDs (sarcoidosis)
- Other forms of DPLD (eosinophilic pneumonia, LM, HX, etc)

**Chronic fibrosing**
- IPF
- NSIP

**Smoking related**
- RBILD
- DIP

**Acute/subacute**
- AIP
- COP

**Very rare IIPs**
- Idiopathic lymphocytic interstitial pneumonia (LIP)
- Idiopathic pleuroparenchymal fibroelastosis (PPFE)

Five-Year Survival of IPF Is Worse than Most Cancers

Diffuse Parenchymal Lung Diseases (DPLD)¹


DPLD of known etiology (HP, drugs, collagen-vascular)

- Idiopathic interstitial pneumonia (IIP)
- Granulomatous DPLDs (sarcoidosis)
- Other forms of DPLD (eosinophilic pneumonia, LM, HX, etc)

Question 1: Is DPLD possible?

Question 2: Is it idiopathic?

Question 3: Is it idiopathic UIP?

Very rare IIPs
- Idiopathic lymphocytic interstitial pneumonia (LIP)
- Idiopathic pleuroparenchymal fibroelastosis (PPFE)
IPF Diagnosis: Current Approach¹

Attempt to Elicit an Exposure That Might Cause ILD
Differential Diagnosis of ILD

Collagen Vascular Disease/Autoimmune
- Antisynthetase syndrome (Jo-1, PL-7, PL-12, EJ, OJ, SRP, Mi-2, Ku), also MDA-5
- Rheumatoid arthritis (higher proportion of UIP)
- SLE (greater prevalence of ILD than appreciated in the literature)
- Systemic sclerosis (diffuse more associated with ILD; limited more with PAH)
- Mixed connective tissue disease
- Sjogren’s
- Vasculitidies: granulomatous polyangiitis

Interstitial Pneumonia with Autoimmune Features (IPAF)
Differential Diagnosis of ILD (Cont’d)

**Idiopathic**
- IPF
- NSIP
- COP/BOOP
- AIP (Hamman-Rich Syndrome)
- RBILD
- DIP

**Environmental**
- Hypersensitivity pneumonitis (avian, molds, isocyonates, other organic dusts)
- Pneumoconioses (silicosis, asbestosis, berylliosis, coal miner’s lung disease)

**Medications**
- TNF-alpha inhibitors
- Chemotherapy drugs: bleomycin, busulfan, etc
- Amiodarone; methotrexate; sirolimus/everolimus
- NSAIDS, antibiotics (eosinophilic)

**Other**
- Eosinophilic pneumonia: idiopathic, parasitic
- Sarcoidosis
- Lymphangioleiomyomatosis (LAM)
- Pulmonary langerhans cell histiocytosis
- Chronic aspiration
- Lymphangitic carcinomatosis
- Pulmonary alveolar proteinosis
IPF Becomes Increasingly Likely as the Age of the Patient Increases\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, in years</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>2</td>
</tr>
<tr>
<td>≥60</td>
<td>3</td>
</tr>
<tr>
<td>Male sex</td>
<td>1</td>
</tr>
<tr>
<td>Possible UIP + total traction bronchiectasis score ≥4</td>
<td>6</td>
</tr>
<tr>
<td>Total score possible</td>
<td>10</td>
</tr>
</tbody>
</table>

IPF Becomes Increasingly Likely as the Age of the Patient Increases (Cont’d)¹,²

A Possible Approach to CTD Evaluation

History
- Joint pain, stiffness, or swelling
- Skin thickening or tightening
- Rash in sun-exposed areas
- Dryness of the eyes or mouth
- Raynaud’s
- Heartburn/regurgitation
- Family history of CTD

Physical Exam
- Joints
- Skin
- Hands

Clinical suspicion of ILD

Standard investigation
- History, physical exam (with detailed rheumatologic assessment), HRCT, lung function testing, 6MWT, echo ± biopsy

Antibody testing
- Core tests: ANA, ENA (including anti-Scl70, SSA/Ro, SSB/La, RNP, Sm, Jo-1), rheumatoid factor and anti-CCP, anti-dsDNA
- Additional/desirable autoantibodies: sclerodema associated (anti-Th/To, RNA polymerase, PM/Scl) and extended myositis panel (anti t-RNA synthetase, including PL-7, PL-12; Mi-2; SRP; CADM140/MDA5)

Multidisciplinary meeting

Consensus diagnosis
- CTD-ILD
- IPAF
- IIP

Continual reassessment and surveillance for secondary causes of ILD
IPF vs CT ILD Survival in Two Cohorts\textsuperscript{1,2}

Jim, a 75-Year-Old Man, Presents with a Three-Year History of Progressive Dyspnea and Cough

<table>
<thead>
<tr>
<th>Patient Medical History</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Severe knee osteoarthritis, 10 years</td>
</tr>
<tr>
<td>• Recurrent bronchitis, 5 years; diagnosed with asthma</td>
</tr>
<tr>
<td>• HTN</td>
</tr>
<tr>
<td>• Former smoker (40 pack-years); stopped 8 years ago</td>
</tr>
<tr>
<td>• Retired warehouse supervisor</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Current Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Acetaminophen</td>
</tr>
<tr>
<td>• Albuterol MDI</td>
</tr>
<tr>
<td>• Amlodipine</td>
</tr>
<tr>
<td>• Naproxen</td>
</tr>
<tr>
<td>• Vitamin C, Ca, and Mg</td>
</tr>
</tbody>
</table>
# Jim’s Workup

## PFT Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forced vital capacity (FVC)</td>
<td>3.17 L</td>
<td>81 percent</td>
</tr>
<tr>
<td>Forced expiratory volume in one second (FEV1)</td>
<td>2.48 L</td>
<td>82 percent</td>
</tr>
<tr>
<td>Forced expiratory volume in one second/forced vital capacity ratio (FEV1/FVC)</td>
<td>78 percent</td>
<td></td>
</tr>
<tr>
<td>Diffusing capacity of the lungs for carbon monoxide (DLCO)</td>
<td>11.34</td>
<td>51 percent</td>
</tr>
</tbody>
</table>

## Physical Examination Notes

- Father died of MI
- Bibasilar crackles
- Normal sinus rhythm
- Afebrile
- BP 126/82 mmHg
## PFT Results

<table>
<thead>
<tr>
<th>Test</th>
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<td>51%</td>
</tr>
</tbody>
</table>
IPF Diagnosis: Current Approach

Suspected ILD

Identifiable Causes for ILD? No

HRCT

Possible UIP/Inconsistent with UIP

Surgical Lung Biopsy

MDD

IPF

IPF/not IPF

Not UIP

Not IPF

IPF Diagnosis: Current Approach (Cont’d)¹

Jim’s Axial HRCT
Jim’s Coronal/Sagittal HRCT
ATS Guidelines for UIP

Definite UIP

- Subpleural basilar predominant fibrosis
- Reticulations
- Honeycombing
- Absence of features that would suggest an alternative diagnosis
ATS Guidelines for UIP

Possible UIP

- **Subpleural** basilar predominant fibrosis
- **Reticulations**
- **Honeycombing**
- Absence of features that would suggest an alternative diagnosis
NSIP: HRCT

- Basal predominance
- Peribronchovascular/subpleural sparing
- Confluent pattern
- Volume loss
- Ground glass
- Reticular
- Traction bronchiectasis
- ± consolidation
- Rare honeycombing

CHP: CT Features

- Upper-, mid-, or lower-lung predominance
- Clues to diagnosis
  - Centrilobular nodules
  - Mosaic attenuation

Image courtesy of Dr. David A. Lynch.
Inspiration Expiration

Images courtesy of Dr. David A. Lynch.
Diagnosis of IPF

• No alternative cause of ILD (eg, environmental exposures, CTD, drug toxicity)
• Usual interstitial pneumonitis (UIP) pattern on HRCT
  – Surgical lung biopsy not necessary
• Possible UIP pattern on HRCT with UIP on surgical lung biopsy (SLB)

## Fleischer: HRCT Criteria for UIP Pattern Are Evolving

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Typical UIP</th>
<th>Probable UIP</th>
<th>Indeterminate UIP</th>
<th>Non-IPF Pattern</th>
</tr>
</thead>
</table>
| • Basal (occasionally diffuse)  
  • Subpleural  
  • Often heterogeneous | • Subpleural  
  • Basal predominant  
  • Often heterogeneous | • Variable or diffuse | • Upper- or mid-lung  
  • Peribronchovascular  
  • Subpleural sparing |
| Features | • Honeycombing  
  • Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis\(^a\)  
  • Absence of alternative features | • Reticular with peripheral traction bronchiectasis or bronchiolectasis\(^a\)  
  • No honeycombing  
  • Absence of alternative features | • Fibrosis with some inconspicuous non-UIP features | Any of the following  
  • Predominant consolidation  
  • Extensive ground glass opacity  
  • Extensive mosaicism  
  • Diffuse nodules or cysts |

\(^a\) Reticular pattern is superimposed on ground glass opacity, and in these cases it is usually fibrotic. Pure ground glass opacity, however, would be against the diagnosis of UIP or IPF and would suggest acute exacerbation, hypersensitivity pneumonitis, or other conditions.

Conclusions

• Recognize signs and symptoms of IPF
  – Progressive exertional dyspnea
  – Chronic cough
  – Inspiratory crackles
  – Finger clubbing
• Obtain high-resolution CT scan of the chest
• Refer to specialty center
• Educate patient about diagnosis and treatment options
Optimizing an Individualized Approach to IPF Therapy

Lisa H. Lancaster, MD
Medical Director Interstitial Lung Disease and Idiopathic Pulmonary Fibrosis Program
Associate Professor of Medicine, Division of Allergy, Pulmonary, and Critical Care Medicine
Vanderbilt University Medical Center
Nashville, Tennessee
George: 81-Year-Old Caucasian Male with Shortness of Breath with Exertion

- Mild cough
- Minimal AM clear sputum
- No hemoptysis, wheezing, or chest pain
- ADLs are not limited
- Plays golf three days a week with friends
- No infectious signs or symptoms
- Good appetite and stable weight
George’s History

No signs or symptoms of autoimmune disease
• ANA 1:160, sed rate 17

Exposure history
• Insurance sales
• Gardening
• No asbestos exposure

No drug toxicity

Pets: one dog, no birds
<table>
<thead>
<tr>
<th>Condition</th>
<th>Status and Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive sleep apnea</td>
<td>Treated with CPAP</td>
</tr>
<tr>
<td>GERD</td>
<td>Controlled with daily esomeprazole</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
</tr>
<tr>
<td>Seasonal allergic rhinitis</td>
<td></td>
</tr>
</tbody>
</table>
Comorbidities in IPF

Gastroesophageal Reflux

Around 90 percent of IPF patients have GER

But only half are symptomatic

12 of 19 IPF patients receiving PPIs during 24-hour pH probe monitoring had abnormal acid exposure

Standard doses of PPIs may not suppress acid reflux fully in IPF patients

GER Therapy Is Associated with Longer Survival in IPF

Risk Factors for OSA\textsuperscript{1,2}

- Obesity (BMI $\geq 30$ kg/m$^2$)
- Type 2 diabetes mellitus
- Nocturnal dysrhythmias
- CAD
- CHF
- Atrial fibrillation
- Pulmonary hypertension
- High-risk driving populations (~10 percent—OSA)
- Preoperative for bariatric surgery (~10 percent—OSA)
- GERD
- Hypertension

OSA Symptoms

- Witnessed apneas, snoring
- Gasping/choking at night
- Excessive sleepiness not explained by other factors
- Nonrefreshing sleep
- Sleep fragmentation
- Nocturia
- Morning headaches
- Decreased libido
- Decreased concentration, memory loss
- Irritability

Reduced Lung Volumes Can Increase the Thickness of the Lateral Pharyngeal Walls

- Abdominal fat mass and recumbent posture decrease lung volume
- Reduced lung volume decrease the “tracheal tug”
OSA Is Common in IPF

50 subjects with IPF

Sleep apnea evaluation
- Epworth Sleepiness Scale (ESS)
- Sleep apnea scale of sleep disorders questionnaire (SA-SDQ)

Nocturnal polysomnogram

88 percent had OSA

Treatment of OSA in IPF Is Associated with Improved Survival\(^1\)

Compliance with PAP Therapy Is Associated with Extended Survival from the Time of Diagnosis of OSA

\[ \text{HR} = 2.9 \ (95\% \text{ CI, 1.0-8.4}) \]
\[ P = .05 \]

Number Deceased (Number Remaining in Analysis)

\begin{align*}
\text{Compliant} & \quad 0 \ (26) & 0 \ (26) & 0 \ (26) & 0 \ (26) & 0 \ (22) & 4 \ (17) & 4 \ (13) \\
\text{Noncompliant} & \quad 0 \ (13) & 0 \ (13) & 2 \ (11) & 3 \ (10) & 4 \ (7) & 6 \ (4) & 7 \ (2)
\end{align*}

Oxygenation During Sleep in IPF\textsuperscript{1,2}

Kolilekas L et al

- 31 patients with newly diagnosed untreated IPF
  - Sleep $O_2$ desaturation exceeded desaturation with maximal exercise
  - Lowest SpO$_2$ was directly related to survival

Lee RN et al

- Saturation was lower during sleep than exercise; $P < .01$
- Desaturation was greater in those with AHI >5

George: 82-Year-Old Caucasian Male with Shortness of Breath with Exertion

**Social History**
- Never smoker but some passive smoke exposure
- One to two drinks per week
- No history of illicit drug use
- Hobbies: golf, church activities

**Family History**
- Aunt with lymphoma
- Niece with leukemia
- No family history of pulmonary fibrosis

**Medications**
- Levothyroxine
- Amitryptyline
- Simvastatin
- Omeprazole
- MVI
Physical Exam

Vital signs: P78, 134/70, R16, afebrile, BMI 30.1

ENT-grade III airway: no lymphadenopathy, no JVD

Lungs: faint bibasilar Velcro crackles

CV-RRR with no audible murmur

GI: soft, nontender, pos bs x 4, no masses

Ext: no edema, no clubbing, no rashes
Diagnostic Testing

Nondiagnostic bronchoscopy

6MWT
- Distance: 1,450 feet
- SpO₂ nadir: 91 percent

Pulmonary function testing
- FEV₁/FVC ratio: 77
- FVC: 3.26L (75 percent)
- FEV₁: 2.53L (81 percent)
- TLC: 6.16L (75 percent)
- DLCO: 12.70 (51 percent)
Nintedanib Efficacy: Change in FVC (TOMORROW and INPULSIS Trials)\textsuperscript{1}

\[ \Delta = 111 \text{ mL/year} \]

\[ P < .0001 \]

Pirfenidone Efficacy: Change in FVC (ASCEND, CAPACITY 1, and CAPACITY 2)\(^1\)

<table>
<thead>
<tr>
<th>Absolute difference, mL</th>
<th>36</th>
<th>104</th>
<th>123</th>
<th>148</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative difference, percent</td>
<td>43.5</td>
<td>57.3</td>
<td>49.1</td>
<td>40.7</td>
</tr>
<tr>
<td>Rank ANCORA, (P)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

\(\Delta = 148\text{ mL} \quad P < .001\)

George’s Treatment

He chose an FDA-approved therapy

<table>
<thead>
<tr>
<th>Treatment Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Monitor for infections and O₂ need</td>
</tr>
<tr>
<td>• Keep vaccinations up to date</td>
</tr>
<tr>
<td>• Pulmonary rehabilitation</td>
</tr>
<tr>
<td>• Continue CPAP</td>
</tr>
<tr>
<td>• PPI and GERD precautions</td>
</tr>
<tr>
<td>• Weight loss</td>
</tr>
<tr>
<td>• Treat other comorbidities: CAD</td>
</tr>
<tr>
<td>• Continue education regarding disease state, IPF therapies, and clinical trials</td>
</tr>
</tbody>
</table>
Issues in the Elderly When Considering IPF Therapies¹

- Underweight or active weight loss
- Bedbound, poor quality of life, or in hospice
- Severely hypoxic with severe reductions in pulmonary function testing or high-flow O₂ need
- Survival less than one year
- Severe medical disease with limited life expectancy or poor quality of life because of diseases other than IPF
- Complicated medication regimens
- Drug interactions or compounded side effects from other medications

Comorbidities

- Coronary artery disease/peripheral vascular disease/clotting diseases
- Risk of thrombosis with VEGF inhibition
  - Risk of bleeding
- Hypothyroidism
- Acute or chronic kidney disease
- Liver disease

Close Monitoring Required on Therapy

- Liver enzymes are monitored for the first three to six months, depending on the therapy chosen then every three months afterward.

- Follow GI symptoms, weight, and appetite.

- Assess fatigue:
  - Rule out sleep apnea, anemia, and thyroid disease.

- Monitor concomitant medications to avoid drug interactions at each three-month visit:
  - Ask patients to call with any new medications or changes.
George’s Treatment

IPF progresses slowly
- FVC at 12 months is 62 percent
- FVC at 24 months is 54 percent
Outcomes After Six Months of Pirfenidone Treatment: FVC Decline >10 Percent

<table>
<thead>
<tr>
<th></th>
<th>Pirfenidone, n (Percent) (n = 34)</th>
<th>Placebo, n (Percent) (n = 68)</th>
<th>Δ, Percent</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥10 percent decline in FVC or death</td>
<td>2 (5.9)</td>
<td>19 (28)</td>
<td>-79</td>
<td>.009</td>
</tr>
<tr>
<td>No further decline in FVC</td>
<td>20 (59)</td>
<td>26 (38)</td>
<td>+54</td>
<td>.059</td>
</tr>
<tr>
<td>Death</td>
<td>1 (2.9)</td>
<td>14 (21)</td>
<td>-86</td>
<td>.018</td>
</tr>
</tbody>
</table>

Outcomes on Nintedanib Following Decline in Lung Function

The effect of nintedanib slowing disease progression, observed in INPULSIS, was maintained over two years.

George’s Treatment

IPF progresses slowly
• FVC at 12 months is 62 percent
• FVC at 24 months is 54 percent

HRCT shows progression

IPF therapy was continued despite progression
Key Aspects of Management

- Thorough evaluation to confirm the diagnosis
- Patient participation in treatment plan
- Consider referral to an IPF center
IPF and Other ILDs
At the Crossroads of Current Clinical Challenges and Emerging Therapeutic Strategies

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Inova Fairfax Hospital
Professor of Medicine
Virginia Commonwealth University-Inova Fairfax Campus
Falls Church, Virginia

PeerView Live
IPF and Other ILDs
At the Crossroads of Current Clinical Challenges and Emerging Therapeutic Strategies
Meeting at the Crossroads

Pathobiology

Biomarkers

Diagnosis

Therapeutics
IPF and Other ILDs

At the Crossroads of Current Clinical Challenges and Emerging Therapeutic Strategies
Biomarkers—It’s a Zoo!

- CA-125
- uPA
- CC16
- PAI-1
- MDSC
- CCL18
- IL-12
- MDSC
- uPA
- MMP3
- IL-12
- MUC5B
- BlyS
- Nepsin-A
- IL-6
- MUC5B
- IL-10
- Telomeres
- LOXL2

- Periostin
- HSP-70
- PBM gene exp
- IL-6
- YKL-40
- MMP-7
- CXCL-13
- Sputum cell count
- MMP-10

- Leptin
- MDSC
- IGFBP
- PBM
- IL-12
- Periostin
- MMP-10

- M2BP
- KL-6
- VEGF
- SP-D
- MDSC
- MMP-7
- CCL18
- MDSC
- IL-10

- Tregs
- cCK-18
- RDW
- SP-A
- Thrombomodulin
- PAI-1
- Thrombomodulin
- IL-10
- IL-12
- MMP-1

- Endothelial cells
- KLF-6
- CA19-9
- CA-125
- Periostin
- Telomeres
- Telomeres
- YKL-40

- MUC1
Biomarkers in the Diagnosis of IPF: Use in Combination May IncreaseAccuracy

Biomarkers in the Prognostication of IPF: Use in Combination May Increase Accuracy

The Future of IPF Diagnosis: From MDD to 4D
The Future of IPF Diagnosis: From MDD to 4D (Cont’d)
IPF and Other ILDs
At the Crossroads of Current Clinical Challenges and *Emerging Therapeutic Strategies*
What of Combination Therapy?
Combining Pirfenidone and Nintedanib: Ongoing Studies in Patients with IPF

Roche¹
(NCT02598193)

- N = 80 patients stable on pirfenidone
- Nintedanib added
- Safety/tolerability
- 24 weeks

Bi²
(NCT02579603)

- N = 100 patients
- Nintedanib ± pirfenidone
- Safety/tolerability/PK
- 12 weeks

✓ Enrollment has been completed for both studies

INJOURNEY Study Design: Nintedanib with Add-On Pirfenidone

Primary endpoint is the percentage of patients with on-treatment GI adverse events from baseline to week 12.

# INJOURNEY Study Results: Nintedanib with Add-On Pirfenidone

Nintedanib 150 mg BID with Add-On Pirfenidone, n (percent) (n = 53)  
Nintedanib 150 mg BID, n (percent) (n = 51)

<table>
<thead>
<tr>
<th>Event</th>
<th>Nintedanib 150 mg BID with Add-On Pirfenidone</th>
<th>Nintedanib 150 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE(s)</td>
<td>47 (88.7)</td>
<td>45 (88.2)</td>
</tr>
<tr>
<td><strong>Most frequent AEs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20 (37.7)</td>
<td>16 (31.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>22 (41.5)</td>
<td>6 (11.8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15 (28.3)</td>
<td>6 (11.8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (18.9)</td>
<td>6 (11.8)</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>7 (13.2)</td>
<td>4 (7.8)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>6 (11.3)</td>
<td>5 (9.8)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2 (3.8)</td>
<td>8 (15.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (13.2)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Any SAE(s)</td>
<td>2 (3.8)</td>
<td>5 (9.8)</td>
</tr>
<tr>
<td>Any fatal AE(s)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

INJOURNEY Study Results:
Nintedanib with Add-On Pirfenidone (Cont’d)\(^1\)

![Graph showing the change in absolute mean (SE) from baseline in FVC, mL over weeks.

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>Week 0</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
<th>Week 8</th>
<th>Week 10</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nintedanib</td>
<td>51</td>
<td>49</td>
<td>48</td>
<td>45</td>
<td>45</td>
<td>44</td>
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</tr>
<tr>
<td>Nintedanib with add-on pirfenidone</td>
<td>53</td>
<td>52</td>
<td>50</td>
<td>50</td>
<td>48</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

# IPF Studies Ongoing or Closed to Enrollment

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Mechanism/Target</th>
<th>Phase</th>
<th>Trial Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lebrikizumab</td>
<td>Anti–IL-13</td>
<td>2</td>
<td>Ongoing</td>
</tr>
<tr>
<td>PRM-151</td>
<td>Pentraxin-2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Laparoscopic antireflux surgery</td>
<td>Gastroesophageal reflux</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>KD025</td>
<td>ROCK inhibitor</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Co-trimoxazole or Doxycycline</td>
<td>Antibacterial</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>TD139</td>
<td>Galectin-3 inhibitor</td>
<td>1b/2a</td>
<td></td>
</tr>
<tr>
<td>Autologous mesenchymal stem cells</td>
<td>Immunomodulation</td>
<td>1</td>
<td>Completed</td>
</tr>
<tr>
<td>Vismodegib</td>
<td>Hedgehog pathway inhibitor</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pamrevlumab</td>
<td>Anti-CTGF (FG-3019)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>PBI-4050</td>
<td>Anti-fibrotic</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>SAR156597</td>
<td>Anti–IL-4, anti–IL-13</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>BMS-986020</td>
<td>LPA antagonist</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

WRAP-IPF: Phase 2 Trial of Laparoscopic Anti-Reflux Surgery in IPF

- Adjusted rate of change in FVC over 48 weeks was -0.05 liters (95% CI, -0.15, 0.05) with surgery compared with nonsurgery arm -0.13 liters (95% CI, -0.23, -0.02)

FLORA Trial: Phase 2a Trial of an Autotaxin Inhibitor (GLPG1690) in IPF

- Mean FVC remained similar to or greater than baseline values (25 mL [95% CI, -75 to 124] with GLPG1690 compared with placebo -70 mL [95% CI, -208 to 68]

Efficacy and Safety of Recombinant Human Pentraxin-2 (PRM0151) in IPF

- Mean FVC from baseline to week 28 was -2.5 (95% CI, -3.3 to -1.7; P = .0014) for PRM-151 compared with -4.8 (95% CI, -5.9 to -3.6) for placebo

Study Design: Many Moving Parts to Get It Right!

- A drug that works and is well tolerated
- The right dose, frequency, and route of administration
- The right patient population that is likely to be retained
- Disease stage, phenotype
- The right duration, the right endpoint(s)
Clinical Trial Design

- Clinical trials endpoints
- How to enrich
  - Precision clinical trials
- Which patient groups?
- Combination trials
Possible Components for Endpoints

- Which instrument (SGRQ, SGRQ-I, ATAQ, UCSD SOB)?
- Patient centered
- Requires further validation as endpoint
  - ΔPRO

- Well validated
- Does not capture full scope of drug effects
  - FVC

- Mean change or categorical (30-50 m)
- Δ distance or desaturation
- Δ pulse rate recovery
- Δ borg
  - Δ6MWT

Possible Components for Endpoints in IPF Studies

- Respiratory or all-cause?
- Different thresholds for hospitalization
- Remote hospitalizations problematic
- Patients refusing hospitalization
- Should it be “need for” hospitalization?
  - Hospitalization

- All-cause or respiratory-related?
  - Death

- Not all patients are candidates
- Regional, national, international differences in listing criteria, donor availability, wait times, and severity of disease at time of transplantation
  - Lung Transplantation

Can We Enrich Clinical Trials with More Severe Patients?

CAPACITY and ASCEND: outcomes of patients with severe disease (FVC <50 percent and/or DLco <35 percent predicted)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Patients with Severe Lung Function Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pirfenidone (n = 90)</td>
</tr>
<tr>
<td>≥10 percent absolute FVC decline or mortality</td>
<td>19 (21.1 percent)</td>
</tr>
<tr>
<td></td>
<td>P = .0006</td>
</tr>
<tr>
<td>Respiratory hospitalization or all-cause mortality</td>
<td>12 (13.3 percent)</td>
</tr>
<tr>
<td></td>
<td>P = .022</td>
</tr>
<tr>
<td>≥10 percent absolute FVC decline or respiratory hospitalization or all-cause mortality</td>
<td>25 (27.8 percent)</td>
</tr>
<tr>
<td></td>
<td>P = .0018</td>
</tr>
</tbody>
</table>
Incidence and Sequence of Multiple Events at 12 Months in Patients Treated with Pirfenidone vs Placebo

A lower proportion of patients who received pirfenidone had greater than one event compared with those who received placebo (17.0 percent vs 30.1 percent; \( P < .0001 \))

Pirfenidone \((n = 623)\)
- 106 patients with >1 event

Placebo \((n = 624)\)
- 188 patients with >1 event

A lower proportion of patients who received pirfenidone had greater than one event compared with those who received placebo (17.0 percent vs 30.1 percent; \( P < .0001 \))
Meeting at the Crossroads: from Pathobiology to Effective/Precision Medications

Pathobiology

Diagnosis

Biomarkers

Not so fast!

Maybe!
Simtuzumab Mechanism of Action\(^1\)

Efficacy of Simtuzumab vs Placebo in Patients with IPF (Cont’d)¹

Efficacy of Simtuzumab vs Placebo in Patients with IPF (Cont’d)\textsuperscript{1}

Number at Risk, events

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
<th>24</th>
<th>27</th>
<th>30</th>
<th>33</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simtuzumab (&gt;75th percentile)</td>
<td>68</td>
<td>61</td>
<td>51</td>
<td>34</td>
<td>15</td>
<td>10</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Placebo (&gt;75th percentile)</td>
<td>71</td>
<td>62</td>
<td>50</td>
<td>31</td>
<td>25</td>
<td>21</td>
<td>17</td>
<td>13</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Simtuzumab (&lt;75th percentile)</td>
<td>204</td>
<td>184</td>
<td>162</td>
<td>111</td>
<td>83</td>
<td>63</td>
<td>51</td>
<td>40</td>
<td>32</td>
<td>11</td>
<td>11</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Placebo (&lt;75th percentile)</td>
<td>201</td>
<td>182</td>
<td>152</td>
<td>108</td>
<td>72</td>
<td>56</td>
<td>41</td>
<td>31</td>
<td>16</td>
<td>7</td>
<td>1</td>
<td>0</td>
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</tr>
</tbody>
</table>

Pamrevlumab (FGCL-3019-067) MOA$^{1-3}$

CTGF plays a central role in tissue remodeling and fibrosis$^{2,3}$

Pathophysiologic insult

Hypertension

CTGF

Myofibroblast differentiation

Myofibroblast activation

ECM deposition/remodeling

Cell motility

Cell adhesion

Tissue remodeling

Fibrosis

Pamrevlumab: Ph2 in IPF Study Design\textsuperscript{1,2}

- Ph2 double-blind, placebo-controlled study in mild to moderate IPF
- FG-3019 dosed as
  - Monotherapy vs placebo: 103 subjects dosed for 45 weeks
  - Add-on to SOC (pirfenidone and nintedanib): sub-study, 60 subjects dosed for 21 weeks

## Key Eligibility Criteria

- Age 40 to 80 years
- Diagnosis of IPF by current international guidelines
- History of IPF of five years duration or less
- Evidence of $\geq 10\,\%$ to $<50\,\%$ parenchymal fibrosis (reticulation) and $<25\,\%$ honeycombing within the whole lung
- FVC percent of predicted value $\geq 55\,\%$ at screening
- DLCO $\geq 30\,\%$

## Primary Endpoint

- Change from baseline in FVC percent predicted to week 48

## Key Secondary Endpoints

- Change in pulmonary fibrosis score (qtHRCT) at week 24, week 48
- Change from baseline in HRQoL
- Time to progression of IPF (all cause death); $\geq 10\,\%$ decline in FVC

---

Change in FVC from baseline to week 48 was assessed.


- Absolute FVC difference = 178 mL
- Relative difference = 58 percent

\[ P = .0249 \]

- FVC percent predicted difference = 4.3
- Relative difference = 60 percent

\[ P = .0331 \]
Pamrevlumab: Safety

- Pamrevlumab was well tolerated
- Reported adverse events were balanced between study arms
- All the treatment-emergent adverse events were balanced
  - 96 percent to 98 percent, respectively, from pamrevlumab to placebo
- Serious AEs leading to treatment discontinuation
  - Pamrevlumab = 3, placebo = 7
  - Deaths: 51 percent reduction relative to placebo

---

Role of Microbiome in the Development, Pathogenesis, and Exacerbations of IPF

- Bacterial infection has only been indirectly implicated in IPF progression and mortality

- *Streptococcus, Staphylococcus, Veillonella, Neisseria, Haemophilus, Proteobacteria, Stenotrophomonas,* and *Campylobacter* increased risk of disease progression

- Correlation does not imply causality between bacterial burden and IPF pathogenesis
Role of Bacteria in the Pathogenesis and Progression of IPF


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\[ P < .05 \text{ high versus low, hazard ratio 0.21.} \]

Change in the Respiratory Microbiome During IPF Acute Exacerbations

Treating IPF with the Addition of Co-Trimoxazole: A Randomized Controlled Trial

Ongoing Studies with Cotrimoxazole

**CleanUP IPF**
- NHLBI-funded “large simple” trial
- IPF: “all comers”
- Intervention: co-trimoxazole (or doxycycline)
- Control: standard of care
- Primary outcome: time to respiratory hospitalization or death
- Currently open to enrollment

**EME-TIPAC**
- NIHR (UK) trial
- IPF
- Intervention: co-trimoxazole
- Control: placebo
- Primary outcome: time to death (all causes), lung transplant, or first non-elective hospital admission
- Currently open to enrollment

---

**Allogeneic MSC Therapy**

**AETHER Trial (NCT02013700)**

- Allogeneic human mesenchymal stem cells
- Phase 1
  - Nine subjects with mild to moderate IPF
  - Dose-escalating trial
- Safety and tolerability

- No treatment-emergent SAEs were reported; two nontreatment-related deaths occurred because of progression of IPF (disease worsening and/or acute exacerbation)
- By 60 weeks post infusion, there was a 3.0 percent mean decline in percent predicted FVC and 5.4 percent mean decline in percent predicted diffusing capacity of the lungs for carbon monoxide

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What About ILDs Other than IPF?
Nintedanib Clinical Trials in ILDs

A study of nintedanib for lymphangioleiomyomatosis (LAM)\(^1\)
- Recruiting participants for open label, phase 2 trial

Efficacy and safety of nintedanib in patients with progressive fibrosing interstitial lung disease (PF-ILD)\(^2\)
- Recruiting participants for double-blind, randomized, placebo-controlled phase 3 trial

SENSCIS (Safety and Efficacy of Nintedanib in Systemic SClerosIS) study\(^3\)
- Recruiting patients with scleroderma-related lung fibrosis for double-blind, randomized, placebo-controlled phase 3 trial

Pirfenidone Clinical Trials in ILDs

Safety and tolerability of pirfenidone in participants with systemic sclerosis-related interstitial lung disease (SSc-ILD) (LOTUSS)¹

- Open label, phase 2 trial is completed

Phase 2 study of pirfenidone in patients with RA-ILD²

- Recruiting participants for randomized, placebo-controlled phase 2 study

Study of efficacy and safety of pirfenidone in patients with fibrotic HP study³

- Recruiting participants for randomized, placebo-controlled trial

A study of pirfenidone in patients with unclassifiable progressive fibrosing ILD⁴

- Recruiting participants for double-blind, randomized, placebo-controlled phase 2 trial

Conclusions

• IPF is a complex, heterogeneous disease

• Multiple pathways
  – Some good, some bad; time and place dependent

• Will gene profiling and biomarkers lead the way to more accurate classification and precision therapies?

• Greater understanding of pathogenesis will lead to more therapies

• More therapies may lead to greater understanding of pathogenesis