The Results Are In
Data from Recent Phase 3 Trials in IPF

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Disclosures

• I have financial relationships with the following organizations:
  – Research Grants and Contracts:
    Boehringer-Ingelheim, NIH/NHLBI
  – Consulting Contracts:
    AstraZeneca/MedImmune, Bayer, Biogen, FibroGen, Five Prime, Genoa, Gilead, Mesoblast, Moerae Matrix, Pfizer, Promedior, Prometic, Pulmatrix, Pulmonary Fibrosis Foundation, Roche/Genentech/InterMune
IPF Management

Risk stratify

- Symptom management
- Pulmonary rehabilitation
- Oxygen
- Co-morbidities/complications
- Lung transplant evaluation (if appropriate)

Pharmacological Therapy

- Enroll in a clinical trial (where available and appropriate)

Lung transplant (where available and appropriate)

IPF Treatment: 2010

RX

- Prednisone, azathioprine and acetylcysteine
- Warfarin

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- “Triple therapy”
  - Variant of historical approach of combined prednisone and immunomodulator (azathioprine or cyclophosphamide)

- Anticoagulation
  - Warfarin and LMWH
IPF Treatment: 2010

Acetylcysteine with prednisone and azathioprine

Warfarin

Demedts NEJM 2005;353:2229
Kubo Chest 2005;128:1475

Key Phase 3 Clinical Trials

CAPACITY I and II
ASCEND
PANTHER Part B

2011 2012 2013 2014

ACE-IPF PANTHER Part A INPULSIS I and II

CAPACITY

- Clinical Studies Assessing Pirfenidone in Idiopathic Pulmonary Fibrosis: Research or Efficacy and Safety Outcomes
  - Two parallel RCTs of pirfenidone vs. placebo
  - Conducted in 110 centers in 13 countries

Noble Lancet 2011;377:1760
CAPACITY

- Enrolled patients with FVC ≥ 50%, DLCO ≥ 35%
- Randomized to pirfenidone or placebo for 72 weeks (one study had a reduced dose arm)
- Primary endpoint: Change in FVC

Noble Lancet 2011;377:1760

<table>
<thead>
<tr>
<th>Baseline</th>
<th>CAPACITY I</th>
<th>CAPACITY II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pirfenidone  Placebo</td>
<td>Pirfenidone  Placebo</td>
</tr>
<tr>
<td>Age, years</td>
<td>66 66</td>
<td>67 67</td>
</tr>
<tr>
<td>Male sex</td>
<td>68% 74%</td>
<td>72% 72%</td>
</tr>
<tr>
<td>FVC</td>
<td>75% 76%</td>
<td>75% 73%</td>
</tr>
<tr>
<td>DLCO</td>
<td>46% 46%</td>
<td>48% 47%</td>
</tr>
<tr>
<td>6MWT distance</td>
<td>411 410</td>
<td>378 399</td>
</tr>
<tr>
<td>Supplemental O2</td>
<td>17% 14%</td>
<td>28% 28%</td>
</tr>
</tbody>
</table>

Noble Lancet 2011;377:1760
CAPACITY

- Individual trial data were discordant.

CAPACITY I

Relative difference = 35%
P value 0.001

CAPACITY II

Relative difference = 7%
P value 0.50

Noble Lancet 2011;377:1760

CAPACITY

- Overall data from both trials demonstrated a significant slowing of decline in FVC.

Noble Lancet 2011;377:1760
Pirfenidone approved in EU

InterMune Receives European Union Approval for Esbriet® (pirfenidone)
- First Approved Medicine for Idiopathic Pulmonary Fibrosis Patients in the EU -

BRISBANE, Calif., March 3, 2011 /PRNewswire/ -- InterMune, Inc. (Nasdaq: ITMN) today announced that the European Commission (EC) has granted marketing authorization for Esbriet® (pirfenidone). Esbriet is indicated in adults for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF), a progressive and fatal lung disease. The approval authorizes marketing of Esbriet in all 27 EU member states, and marks a significant turning point for the treatment of IPF patients in Europe. More than 100,000 patients suffer from IPF in the 10 nations that comprise the most-populated European countries; approximately 87,000 patients in the five largest countries of Germany, France, Spain, Italy and the United Kingdom.

IPF Treatment Update 2011

RX
• Prednisone, azathioprine and acetylcysteine
• Warfarin
• (Pirfenidone)

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ACE-IPF


ACE-IPF

• **Anticoagulation Effectiveness in IPF**
  
  — Designed and funded by the NIH IPFnet
  — Follow up to the Japanese anticoagulation trial

IPFnet AJRCCM 2012;186:88
ACE-IPF

- Enrolled 145 patients with IPF (no PFT exclusion)
- Randomized to warfarin or placebo for 48 weeks
- Primary endpoint: Time to death, hospitalization (non-elective), or disease progression (10% FVC decline)

IPF net AJRCCM 2012;186:88

ACE-IPF

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Warfarin (n=72)</th>
<th>Placebo (n=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>68</td>
<td>66</td>
</tr>
<tr>
<td>Male sex</td>
<td>67%</td>
<td>79%</td>
</tr>
<tr>
<td>FVC</td>
<td>59%</td>
<td>59%</td>
</tr>
<tr>
<td>DLCO</td>
<td>34%</td>
<td>34%</td>
</tr>
<tr>
<td>6MWT distance</td>
<td>289</td>
<td>280</td>
</tr>
<tr>
<td>Dyspnea (UCSD)</td>
<td>34</td>
<td>42</td>
</tr>
<tr>
<td>QOL (SGRQ)</td>
<td>46</td>
<td>50</td>
</tr>
</tbody>
</table>

IPFnet AJRCCM 2012;186:88
ACE-IPF

• Stopped early for increased mortality risk
  – 14 treatment vs. 3 placebo deaths
  – Excess deaths were mostly respiratory
  – No significant difference in primary endpoint (23 vs. 17 events), FVC or other secondary

IPFnet AJRCCM 2012;186:88

IPF Treatment Update 2012

RX

• Prednisone, azathioprine and acetylcysteine
• (Pirfenidone)

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PANTHER

IPFnet. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. NEJM 2012;366:1968

IPFnet. Randomized trial of acetylcysteine in idiopathic pulmonary fibrosis. NEJM 2014;370:2093

PANTHER

• Prednisone, Azathioprine and N-acetylcysteine: A Study That Evaluates Response in IPF

  – Designed and funded by the NIH IPFnet
  – Address the use of NAC alone and in combination with prednisone/azathioprine against true placebo
**PANTHER**

- Enrolled 341 patients with FVC ≥ 50%, DLCO ≥ 30%
- Randomized to NAC, NAC plus prednisone/azathioprine, or placebo for 60 weeks
- Primary endpoint: Change in FVC

*Stopped early*

**Baseline**

<table>
<thead>
<tr>
<th></th>
<th>NAC alone (n=133)</th>
<th>NAC + P/A (n=77)</th>
<th>Placebo (n=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>68</td>
<td>69</td>
<td>67</td>
</tr>
<tr>
<td>Male sex</td>
<td>74%</td>
<td>77%</td>
<td>67%</td>
</tr>
<tr>
<td>FVC</td>
<td>72%</td>
<td>69%</td>
<td>73%</td>
</tr>
<tr>
<td>DLCO</td>
<td>45%</td>
<td>42%</td>
<td>46%</td>
</tr>
<tr>
<td>6MWT distance</td>
<td>371</td>
<td>362</td>
<td>375</td>
</tr>
<tr>
<td>Dyspnea (UCSD)</td>
<td>26</td>
<td>30</td>
<td>27</td>
</tr>
<tr>
<td>QOL (SGRQ)</td>
<td>40</td>
<td>39</td>
<td>38</td>
</tr>
</tbody>
</table>

IPFnet NEJM 2012;366:1968 and IPFnet NEJM 2014;370:2093
**PANTHER Part A**

- NAC plus prednisone/azathioprine stopped early for evidence of harm

![Graph showing death or hospitalization probability over weeks since randomization.](IPFnet NEJM 2012;366:1968)

**PANTHER Part B**

- No difference in rate of FVC decline with NAC monotherapy
- Also no difference in:
  - Death
  - Acute exacerbation
  - Disease progression
  - Hospitalization
  - Dyspnea
  - 6MWT distance
  - Overall QOL

![Graph showing FVC changes over weeks.](IPFnet NEJM 2014;370:2093)
IPF Treatment Update 2012

RX

• (Pirfenidone)

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May 2014
### ASCEND

King et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. NEJM 2014;370:2083

### ASCEND

- **Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis**
  - Performed in response to an FDA request for an additional trial to support approval
  - Designed to enrich subjects for disease progression (as measured by change in FVC)

King. NEJM 2014;370:2083
ASCEND: Study design

- Enrolled 555 highly-selected patients with IPF
- Randomized to pirfenidone or placebo for 52 weeks
  - Primary endpoint: Change in FVC
  - Secondary endpoints: 50 meter decline in 6MWT; 20 point increase in UCSD dyspnea score; PFS (10% FVC decline, 50 meter 6MWT decline, or death); death (any cause and related to IPF)

King. NEJM 2014;370:2083

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ASCEND: Study design

- Enrolled 555 highly-selected patients with IPF

King. NEJM 2014;370:2083

- 1562 patients screened
- 64% screen failure rate
- 555 patients randomized

1087 were excluded
445 did not meet HRCT or lung biopsy criteria
200 had FVC <50% or >90%
171 had DLco <30% or >90%
152 had FV1/FVC ratio <0.80
130 had greater extent of emphysema than of fibrosis
ASCEND: Subjects

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Pirfenidone (n=278)</th>
<th>Placebo (n=277)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td>Male sex</td>
<td>80%</td>
<td>77%</td>
</tr>
<tr>
<td>FVC</td>
<td>68%</td>
<td>69%</td>
</tr>
<tr>
<td>DLCO</td>
<td>44%</td>
<td>44%</td>
</tr>
<tr>
<td>6MWT distance</td>
<td>415</td>
<td>421</td>
</tr>
<tr>
<td>Dyspnea (UCSD)</td>
<td>34</td>
<td>37</td>
</tr>
<tr>
<td>Definite UIP HRCT</td>
<td>96%</td>
<td>95%</td>
</tr>
</tbody>
</table>

King. NEJM 2014;370:2083

ASCEND: 1° Endpoint

*Relative difference = 45%  
P value < 0.001*

King. NEJM 2014;370:2083
**ASCEND: 1° Endpoint**

Decreased FVC or Death

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pirfenidone (N=278)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Placebo (N=277)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>13</td>
<td>26</td>
</tr>
</tbody>
</table>

10% or greater absolute decline

King. NEJM 2014;370:2083

**ASCEND: 2° Endpoints**

Decreased walk distance or death

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pirfenidone (N=278)</td>
<td>P=0.49</td>
</tr>
<tr>
<td>Placebo (N=277)</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>13</td>
<td>26</td>
</tr>
</tbody>
</table>

50 meter decline from baseline

Progression-free survival

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pirfenidone (N=278)</td>
<td>P&lt;0.04</td>
</tr>
<tr>
<td>Placebo (N=277)</td>
<td>P=0.94</td>
</tr>
<tr>
<td>13</td>
<td>26</td>
</tr>
</tbody>
</table>

10% FVC decline; 50 meter 6MWT decline; death

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pirfenidone (N=278)</td>
<td>100</td>
</tr>
<tr>
<td>Placebo (N=277)</td>
<td>100</td>
</tr>
</tbody>
</table>

Worsened dyspnea

<table>
<thead>
<tr>
<th></th>
<th>Pirfenidone</th>
<th>Placebo</th>
<th>HR (CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsened dyspnea</td>
<td>29.1%</td>
<td>36.1%</td>
<td>NP</td>
<td>0.16</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>4.0%</td>
<td>7.2%</td>
<td>0.55 (0.26, 1.15)</td>
<td>0.10</td>
</tr>
<tr>
<td>Death “related to IPF”</td>
<td>1.1%</td>
<td>2.5%</td>
<td>0.44 (0.11, 1.72)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

King. NEJM 2014;370:2083
ASCEND: Safety and tolerability

- No difference in SAEs (3x LFT increase 2.9% vs 0.7%)
- Treatment discontinuation in 14.4% vs 10.8%

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Pirfenidone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>36.0%</td>
<td>13.4%</td>
</tr>
<tr>
<td>Rash</td>
<td>28.1%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>17.6%</td>
<td>13.0%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>17.6%</td>
<td>6.1%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>15.8%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12.9%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Decrease in weight</td>
<td>12.6%</td>
<td>7.9%</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>11.9%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>11.2%</td>
<td>6.5%</td>
</tr>
</tbody>
</table>

King. NEJM 2014;370:2083

INPULSIS

Richeldi et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. NEJM 2014;370:2071
**INPULSIS**

- **INPULSIS I and II** (not an acronym)
  
  - Two identical RCTs designed to further develop nintedanib (an intracellular multiple tyrosine kinase inhibitor) after promising phase II results.

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**INPULSIS: Study design**

- Enrolled 1066 patients with IPF/likely IP
- Randomized (3:2) to nintedanib/placebo for 52 wks
  - Primary endpoint: Change in FVC
  - Secondary endpoints: time to acute exacerbation; quality of life (SGRQ); categorical change in FVC; death (any cause, respiratory)
INPULSIS: Study design

- Enrolled 1066 patients with IPF/likely IPF
  HRCT required A/B/C, A/C, or B/C for enrollment:
  - A. Definite honeycombing, basal/peripheral predominance
  - B. Reticulation and traction bronchiectasis
  - C. Atypical features are absent

<table>
<thead>
<tr>
<th>UIP Pattern (All Four Features)</th>
<th>Possible UIP Pattern (All Three Features)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Subpleural, basal predominance</td>
<td>• Subpleural, basal predominance</td>
</tr>
<tr>
<td>• Reticular abnormality</td>
<td>• Reticular abnormality</td>
</tr>
<tr>
<td>• Honeycombing with or without traction bronchiectasis</td>
<td>• Absence of features listed as inconsistent with UIP pattern (see third column)</td>
</tr>
<tr>
<td>• Absence of features listed as inconsistent with UIP pattern (see third column)</td>
<td></td>
</tr>
</tbody>
</table>

Richeldi Resp Med 2014;108:1023
Raghu. AJRCCM 2011;183:788

INPULSIS: Study design

- Enrolled 1066 patients with IPF/likely IPF
  HRCT required A/B/C, A/C, or B/C for enrollment:
  - A. Definite honeycombing, basal/peripheral predominance
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<td>• Reticular abnormality</td>
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<tr>
<td>• Absence of features listed as inconsistent with UIP pattern (see third column)</td>
<td></td>
</tr>
</tbody>
</table>

Richeldi Resp Med 2014;108:1023
Raghu. AJRCCM 2011;183:788
INPULSIS: Subjects

<table>
<thead>
<tr>
<th>Baseline</th>
<th>INPULSIS 1</th>
<th>INPULSIS II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nintedanib</td>
<td>Placebo</td>
</tr>
<tr>
<td>Age, years</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td>Male sex</td>
<td>81%</td>
<td>80%</td>
</tr>
<tr>
<td>FVC</td>
<td>80%</td>
<td>81%</td>
</tr>
<tr>
<td>DLCO</td>
<td>48%</td>
<td>48%</td>
</tr>
<tr>
<td>Oxygen saturation</td>
<td>96%</td>
<td>96%</td>
</tr>
<tr>
<td>SGRQ score</td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>

Richeldi NEJM 2014;370:2071

INPULSIS: 1° Endpoint

Relative difference = 52%
P value < 0.001

Relative difference = 45%
P value < 0.001

Richeldi NEJM 2014;370:2071
**INPULSIS: 1° Endpoint**

![Graph showing mean difference in FEV1 for Nintedanib and Placebo over weeks. Mean difference 109.9 (71.3, 148.6) P value < 0.001]

Richeldi NEJM 2014;370:2071

**INPULSIS: 2° Endpoints**

**Acute exacerbation**

<table>
<thead>
<tr>
<th>Days</th>
<th>Nintedanib</th>
<th>Placebo</th>
<th>Nintedanib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4.34</td>
<td>4.39</td>
<td>2.80 *</td>
<td>5.48</td>
</tr>
</tbody>
</table>

**Hazard ratio**

1.15 (0.54, 2.42) P value = 0.67

Any death

POOLED 5.5% 7.8%

Respiratory death

POOLED 3.8% 5.0%

*Statistically significant difference

Richeldi NEJM 2014;370:2071
INPULSIS: 2° Endpoints

Acute exacerbation

Hazard ratio 0.38 (0.19, 0.77)
P value = 0.005

INPULSIS II N P U L S I S

Nintedanib Placebo Nintedanib Placebo
Change in SGRQ 4.34 4.39 2.80 * 5.48
Any death POOLED 5.5% 7.8%
Respiratory death POOLED 3.8% 5.0%

INPULSIS: Safety and tolerability

- No difference in SAEs (3x LFT increase 5.1% vs 0.7%)
- Treatment discontinuation 23.7-25.2% vs 17.6-20.1%

Adverse event | Nintedanib | Placebo
--- | --- | ---
Diarrhea | 62%, 63% | 19%, 18%
Nausea | 23%, 26% | 6%, 7%
Decreased appetite | 8%, 13% | 7%, 5%
Vomiting | 13%, 10% | 2%, 3%
Weight loss | 8%, 11% | 6%, 1%
IPF Treatment Today

- Both therapies slow disease progression as measured by change in FVC over time.
  - Appear to have equal efficacy
  - Appear to have equal safety
  - Differing tolerability profiles

RX

- Nintedanib
- Pirfenidone

Harold Collard, MD
Questions

• How do I prescribe nintedanib or pirfenidone?
• Which drug should I start with?
• Should I treat patients with advanced IPF?
• Should I treat patients with suspected (but unconfirmed) IPF?
• What defines a treatment failure?
• Should these drugs be used in combination?

Thank you for your attention