

# AJMC®

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### 2024 YEAR IN REVIEW

### IDIOPATHIC PULMONARY FIBROSIS

This publication captures a year of impactful news, insights, and updates on idiopathic pulmonary fibrosis (IPF), a serious chronic disease characterized by fibrous tissue formation in the interstitium of the lungs. IPF carries a poor prognosis as dyspnea worsens with declining lung function, and median survival is just 3 to 5 years after diagnosis. Existing antifibrotic therapies have helped some patients, but experts are hopeful that novel treatment pathways and earlier diagnosis can help more patients begin treatment with an agent that is tolerable and efficacious. These articles and interviews describe the most important happenings in the IPF landscape in 2024.

## Advancing Care for IPF: Evaluating Current Treatments and Emerging Therapies for Improved Patient Outcomes

### What Is IPF?

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive lung disease characterized by the formation of fibrous tissue in the interstitium of the lungs.<sup>1</sup> Although the exact cause of IPF remains unclear, current knowledge suggests that the pathogenesis of IPF involves repeated or chronic injury to the lung epithelium, which triggers the activation and differentiation of fibroblasts and myofibroblasts.<sup>2</sup> The persistent myofibroblast activity leads to excessive extracellular matrix deposition and abnormal lung repair processes, resulting in the formation of scar tissue, distortion of alveolar architecture, and, ultimately, permanent loss of lung function.<sup>2</sup> IPF presents as a progressive worsening of dyspnea as

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lung function deteriorates, leading to a poor prognosis.<sup>3</sup> The estimated median survival for individuals with IPF is 3 to 5 years after diagnosis.<sup>4</sup> Respiratory hospitalizations are associated with significantly reduced survival, with only approximately 50% of patients surviving 2 years following their first respiratory-related hospitalization.<sup>5</sup>

**Impact of Disease**

**Population Impact**

IPF affects approximately 3 million individuals globally and 130,000 individuals in the US.<sup>6</sup> The disease predominantly affects older adults, particularly those aged 60 to 70 years, with a higher prevalence among men.<sup>1,7</sup> Although the exact etiology of IPF is unknown, risk factors include a history of smoking, gastroesophageal reflux disease (GERD), chronic viral infections, hepatitis, and family history of interstitial lung disease (ILD).<sup>1</sup> Multiple comorbidities are associated with IPF, including pulmonary hypertension, pulmonary embolism, lung cancer, coronary artery disease, and obstructive sleep apnea.<sup>7</sup> These comorbid conditions often arise long before an IPF diagnosis is made and contribute significantly to the clinical impact.<sup>7</sup>

**Economic Impact**

Between June 2014 and April 2016 in the US, the Idiopathic Pulmonary Fibrosis Prospective Outcomes (IPF-PRO) Registry, a prospective, observational, multicenter study, enrolled 300 participants with IPF to assess hospital-related resource use and costs, expressed in 2016 US\$.<sup>7</sup> The study results showed that 34% of patients had at least 1 hospital encounter during the first year of follow-up, for a total of 158 hospital encounters.<sup>7</sup> Of the patients who were hospitalized, 71% initially were admitted to the emergency department; 69% of those were subsequently admitted to inpatient care, and 19% of the patients hospitalized were treated in the intensive care unit.<sup>7</sup> Patients who received a lung transplant had significantly longer hospital stays than those who did not. Specifically,

these patients had more than 4 times the duration of hospital stay (17.9 vs 4.0 days), nearly 15 times the length of intensive care unit stay (7.3 vs 0.5 days), and approximately 20 times higher cost per hospital stay (\$254,417 vs \$13,795).<sup>7</sup>

**Diagnostic Challenges**

IPF is a diagnosis of exclusion, which may result in delays in diagnosis and treatment initiation.<sup>5</sup> Before IPF can be considered, other causes of ILD must be ruled out, leading to many patients initially being diagnosed with conditions such as heart failure or chronic obstructive pulmonary disease (COPD).<sup>8</sup> On average, the time from initial respiratory-related hospitalization to an IPF diagnosis is 2.2 years.<sup>5</sup> According to the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, Latin American Thoracic Society (ATS/ERS/JRS/ALAT) 2018 guidelines, adults with newly detected ILD of unknown origin should be assessed for IPF if they exhibit unexplained bilateral fibrosis on chest radiographs or CT scans, have bibasilar inspiratory crackles, and are older than 60 years.<sup>1</sup> Early diagnosis of IPF is crucial because a delay in initiating care is associated with a higher risk of death from IPF, regardless of disease severity.<sup>9</sup> The hallmark of IPF is the presence of usual interstitial pneumonia patterns, which are best identified through high-resolution CT (HRCT) scans.<sup>1</sup> HRCT is the gold standard for chest evaluation and is essential for accurate diagnosis of IPF.<sup>1</sup>

**Disease Management**

**Guideline Recommendations in Managing IPF**

The ATS/ERS/JRS/ALAT 2022 treatment guidelines for IPF include both pharmacologic and nonpharmacologic approaches. Antifibrotics nintedanib (Ofev) and pirfenidone (Esbriet) are recommended, along with nonpharmacologic options such as oxygen supplementation for hypoxemic patients and pulmonary rehabilitation.<sup>3</sup> The ATS/ERS/JRS/ALAT guidelines also advise that

patients with IPF should be thoroughly evaluated and treated for comorbidities, including pulmonary hypertension and GERD.<sup>3</sup> Involving patients in palliative care also can be beneficial for managing symptoms.<sup>3</sup>

### Obstacles in Managing IPF

Despite the development of IPF treatments, results of studies based on US registry data show that just 58% to 70% of patients with IPF are treated with antifibrotic medications.<sup>10</sup> This low treatment rate is largely due to a “watch and wait” approach that physicians commonly practice for patients with mild to moderate disease.<sup>10</sup> Additional challenges in IPF treatment include significant guideline variations among countries on the use of antifibrotics in mild to moderate disease.<sup>10</sup> Until 2023, United Kingdom guidelines recommended antifibrotic medications only in patients with a forced vital capacity (FVC) between 50% and 80%, despite knowing there were beneficial effects seen at higher FVC values.<sup>10,11</sup> The greatest predictors of mortality in patients with IPF are acute exacerbations of IPF (AE-IPF) and FVC decline greater than 15%.<sup>12</sup>

### Unmet Needs in IPF Treatment

Although nintedanib and pirfenidone are effective in slowing FVC decline, a 2024 systematic review and meta-analysis looked at real-world data across 74 studies with 23,119 participants and found higher rates of AE-IPF and mortality for both drugs in real-world settings compared with clinical trials.<sup>13</sup> During clinical trials, these medications were also associated with adverse effects such as gastrointestinal issues and skin rashes, which were major factors in patient discontinuation.<sup>10,14,15</sup> These discontinuation rates are also reflected in real-world data, which indicate that 10% to 20% of patients stop treatment due to adverse effects.<sup>10</sup> High rates of AE-IPF, mortality, and adverse effect–related treatment discontinuation highlight the critical need for new antifibrotic therapies that improve disease prognosis and treatment tolerability, enabling better long-term adherence and improved patient outcomes in IPF management.

### Potential for PDE4 Inhibitors in IPF Treatment

Phosphodiesterase 4 (PDE4) inhibitors are used for COPD to reduce exacerbations; however, none has yet been approved for IPF.<sup>16,17</sup> PDE4 enzymes mediate the breakdown of cyclic adenosine monophosphate (cAMP) and are highly expressed in cells that regulate immune inflammatory responses and tissue remodeling.<sup>18,19</sup> Inhibiting PDE4 results in elevated levels of cAMP, thereby producing its antifibrotic effects.<sup>19</sup> PDE4 inhibition has been identified as a potential mechanism for the treatment of pulmonary fibrosis. However, the clinical use is often limited by dose-dependent adverse effects, particularly nausea and vomiting.<sup>18,20,21</sup> There are 4 PDE4 subtypes (PDE4A, PDE4B,

PDE4C, and PDE4D) with varied functions and tissue expression throughout the body. Vomiting is thought to be associated with the inhibition of the PDE4D subtype.<sup>21,22</sup> Preferential inhibition of PDE4B is being investigated for the treatment of patients with IPF because it may retain its anti-inflammatory and antifibrotic properties while avoiding certain use-limiting adverse effects.<sup>18,21</sup>

### Conclusion

IPF is a progressive and fatal lung disease characterized by the scarring of lung tissue, leading to worsening respiratory function and significant morbidity. Its impact on patients is profound, including high health care costs, poor prognosis, and limited treatment options. Despite these challenges, recent clinical trial data offer hope by showcasing emerging therapies that may slow disease progression and improve patient outcomes. These advancements highlight the potential for new, more effective treatments, reinforcing the need for continued research and integration of novel therapies to address the unmet needs of patients with IPF and reduce the disease's burden on health care systems. ●

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## FIBRONEER-IPF Trial of Nerandomilast Meets Primary End Point

In a significant breakthrough for the treatment of patients with idiopathic pulmonary fibrosis (IPF), Boehringer Ingelheim announced that its investigational drug nerandomilast (BI 1015550) has successfully met the primary end point in the pivotal phase 3 FIBRONEER-IPF trial (NCT05321069).<sup>1</sup>

The main end point in the study was lung function based on absolute change from baseline in forced vital capacity (FVC) at week 52 vs placebo. The achievement marks the first such success in a decade, signaling a potential new treatment option for a condition that has limited pharmaceutical interventions.

“After 52 weeks, patients taking either dose of nerandomilast had better performance on the FVC test compared with those taking placebo.”

“This announcement is not just a milestone for us at Boehringer Ingelheim but a beacon of hope for the 3 million people worldwide... with idiopathic pulmonary fibrosis,” Ioannis Sapountzis, PhD, corporate senior vice president and global head of therapeutic areas at Boehringer Ingelheim, posted to LinkedIn.<sup>2</sup> “IPF is considered a rare disease, yet the burden on the individual and those around them is far from small. Through our growing understanding of the condition, we are able to streamline our research with the aim of fulfilling the unmet needs of those living with IPF.”

Based on the positive trial results, Boehringer Ingelheim plans to submit a new drug application for nerandomilast to the FDA and other global regulators.<sup>1</sup> The company is also conducting a second phase 3 study on progressive pulmonary fibrosis, FIBRONEER-ILD (NCT05321082).

Currently, IPF treatment options are limited to nintedanib (Ofev) and pirfenidone (Esbriet), both of which can slow disease progression. Nerandomilast, which inhibits the enzyme phosphodiesterase 4B (PDE4B), is poised to offer a novel mechanism of action that could outperform existing therapies. Boehringer Ingelheim’s decision to advance this drug into the phase 3 trial, which was launched in 2022, is a key step toward addressing the unmet needs of patients with IPF, many of whom experience significant declines in lung function over time.

The FIBRONEER-IPF trial included 1177 participants with IPF from more than 30 countries. They were divided into 3 groups, with participants taking a twice-daily dose of nerandomilast 9 mg, nerandomilast 18 mg, or placebo. The primary end point was absolute change in FVC—a key measure of lung function—from baseline to week 52.

After 52 weeks, patients taking either dose of nerandomilast had better performance on the FVC test compared with those taking placebo. This positive result meant the trial met its primary end point, although specific data on lung function improvement, including FVC scores, have yet to be released. Boehringer Ingelheim said it is holding back full data on efficacy and safety until the first half of 2025. Despite the limited release of data, nerandomilast’s potential to improve lung function and slow disease progression more effectively than current therapies is generating excitement.

“This is the first IPF phase 3 trial in a decade to meet its primary end point,” Sapountzis said in a news release.<sup>1</sup> “Today’s announcement represents the next step in our long history in the research of this disease. IPF has a high unmet need for patients, and we are continuously fostering our research activities to develop more options for one of the most common interstitial lung diseases.”

Although nerandomilast has not yet been approved for use, it received an FDA breakthrough therapy designation for IPF in

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February 2022.<sup>3</sup> Its efficacy, safety, and tolerability were initially assessed in a phase 2 trial that measured lung function over 12 weeks in 147 patients with IPF.

The FIBRONEER-IPF study's scope goes beyond lung function improvement.<sup>1</sup> Secondary end points include time to hospitalization or death, but Boehringer Ingelheim has yet to disclose these results. The trial also enrolled patients both on and off stable therapy with nintedanib or pirfenidone, raising questions about how nerandomilast performs as a monotherapy vs in combination with existing drugs. ●

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## Exploring Nerandomilast's Value in the Complex IPF Treatment Landscape

Idiopathic pulmonary fibrosis (IPF) remains a challenging and progressive disease with significant unmet needs and high mortality rates, despite the availability of 2 approved antifibrotic treatments. In this interview, Martin Kolb, MD, PhD, professor of medicine at McMaster University in Hamilton, Ontario, delves into the complexities of IPF treatment and explores how nerandomilast, a new phosphodiesterase 4B (PDE4B) inhibitor, could offer a valuable treatment alternative by targeting different pathways involved in disease progression.

According to Kolb, "By adding blockage of a different pathway to the ones that we currently block, we might achieve, hopefully, a more profound impact on disease progression."

Kolb also is a pulmonary physician and director of research at the Firestone Institute for Respiratory Health at St Joseph's Healthcare and the Jack Gaudie Boehringer Ingelheim Chair in Interstitial Lung Disease.

### What are some of the challenges and unmet needs in treating IPF?

**KOLB:** IPF is by definition a progressive disease, and the untreated mortality rate is about 40% to 50%. Now we have 2 antifibrotic drugs available that have clearly had an impact on many people, but not all. On average, there are still quite a few people who either don't tolerate the drugs or they just partially respond or they don't respond at all—that's why the overall survival rate is still way worse than what we'd like to see. There is a big need to get drugs that help on top of existing drugs, and drugs that are alternatives to the ones that we have because they are not tolerated or they don't work.

### How does nerandomilast differ from current antifibrotic treatments, and what are some advantages of its mechanism of action?

**KOLB:** It's a PDE4B inhibitor, and I'll emphasize a few differences. One is that we have worked with PDE4 inhibitors for a while for

other diseases, and that means there is a pretty solid understanding of the safety of this drug class. PDE4B is something that is less expressed in the intestinal system, which means things like diarrhea are probably less of a problem [with] this PDE4B [than the other] PDE4 inhibitors.

It affects 2 elements in wound healing. The first one is fibrosis; it interferes with fibroblast proliferation and scar formation driven by fibroblasts. The other part is that it also has a built-in anti-inflammatory effect. We know that although IPF is not the prototypical inflammatory disease, there is still some kind of immune activation going on, and it would certainly be a little bit different [from] other antifibrotic drugs that primarily focus on the fibrosis only. It's still mainly an antifibrotic drug from the concept that we pursue here, but it has a few added elements that could become beneficial, particularly for diseases that have a concomitant inflammatory component, such as progressive pulmonary fibrosis.

### Why is it challenging to treat IPF with a single drug, and how might nerandomilast contribute to the treatment of patients with this disease?

**KOLB:** It's a complex disease, and 1 drug will never hit it all. There are different components, and they are active at different times in an individual patient's journey; they are different in the different spaces of the lungs. You may have areas that have one biology more active, and other areas a different one, so it's unlikely that 1 single drug will ever have a profound impact on all patients because it's such a kind of multifaceted biology.

I wouldn't necessarily say that nerandomilast and the pathway that's targeted is better than the others—we'll have to find out with the clinical trials—but it certainly is different from the others, and that's why it is valuable, similar to other approaches currently, because it's not a biology that is currently catered to by pirfenidone [Esbriet] or nintedanib [Ofev]. It's different, and

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that makes it valuable, and...by adding blockage of a different pathway to the ones that we currently block, we might achieve, hopefully, a more profound impact on disease progression.

### **With the promising signs shown by PDE4B inhibitors in treating patients with IPF, what are your hopes for the future of IPF treatment?**

**KOLB:** The future will probably mean that we will have combination therapies for most patients. Maybe not all of them—there are people who are stable on just 1 drug now—but most people will probably need some kind of combination. If it's a combination of 1 or 2 or 3 drugs, or even more, that's to be [seen]. It's not unusual for complex disorders to have combination therapies, so we will be getting there, too, for IPF and other pulmonary fibrosis types. If it's nerandomilast or others, that will be [seen].

Nerandomilast is probably the next one where we will get big news, so we'll see if it's good news for the patients. But it's a very well-done, big clinical trial with a large number of patients, and it will give us an answer. And it will give us not an indeterminate answer: It will show us whether it works or it doesn't work, and that's important. Of course, we all hope for good outcomes here regardless....

“ Any drug that is successful would reduce, overall, the non-drug-related costs of this disease. So, yes, these new drugs are all expensive.... But if you keep a patient alive for longer, you will have savings on other fronts. ”

### **Once you've confirmed an IPF diagnosis, how do you approach the conversation about starting treatment, and what factors do you consider when determining the best next steps for the patient?**

**KOLB:** Dealing with cancer, everyone knows what that means. You know a neighbor, a family member, a relative of someone else who has had cancer, and you know this is not good. People may know that certain cancers are worse than others, but any cancer, we'll say, that's not good. For IPF, people wouldn't [necessarily] know that, so you need to really take some time to explain what that is. Explain it in layman's terms, because it's a complicated disease, even for professionals, to understand.

It's not anything that happens at the first visit or the second visit; we're talking about a disease that is progressive over a period of a couple of years. You can take your time over a few

months until the patient knows better what's happening and understands it better. You don't have to start these drugs at the first visit. You want people to be on the drugs for years to come, so take the time because *it takes time*. A patient has to learn that.

It's like buying insurance. I always say that no one likes to pay for insurance because it's costly, but if you need it, you want to have it. So you pay now for something that might happen in the future, and for these drugs, you basically invest in a drug's resources and [adverse] effects from a patient's perspective to prevent worsening in the future. You want to affect something that is not there yet.

It's different from other things. When you go to the doctor and have a phlegmy cough and fever, you get an antibiotic, and it makes you feel better after a few days. Patients' expectations from visiting a doctor are usually, “They give me something that makes me better,” and in IPF or ILD [interstitial lung disease] at large, we don't make you feel better. We just give you a certain promise to make it less bad in the future. As complicated as I describe it now, this is something that you always have to explain to the patient repeatedly, and that's, as I said, not an easy conversation; it takes time.

### **What kind of outcomes can be changed based on early intervention for patients with IPF? What evidence supports the clinical harm of delaying PDE4B therapy following standard antifibrotic treatments?**

**KOLB:** My answer is usually just knowing that not everyone responds.... Knowing that not everyone progresses, that's true as well. But at the time you make a diagnosis of IPF, you essentially give the patient the diagnosis of a disease that you know has a 50% mortality rate [at] 5 years. This is the same impactful diagnosis that you would give a patient with a cancer diagnosis. I always say, “Once you give this diagnosis, on average, statistically, this patient will die within 5 years with a 50% likelihood.” And that's how you should think about it.

You would not wait [to manage] a cancer once it's diagnosed. You would say, “I have to take the best possible chances to stop this cancer from killing that patient in 5 years.” Cancer, for one, is more in the minds of people and they understand what it means, so for IPF you still need to educate people.

If you see a lot of patients with IPF, you will see the sad truth that these numbers are real. I mean, it's not a random number. Yes, I see patients as well who are still alive after 15 or 20 years, and of course, those are lucky people and it's great to see them. So no one really knows, and obviously, no patient is just a statistical number. But you don't know at the time of making the diagnosis [whether] a patient will progress or will be stable over time. That's how I approach it, and that's why I always offer the drugs at the time of diagnosis. This is not an easy discussion to have with a patient.

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## How do you see the introduction of nerandomilast affecting the economic burden of IPF on health care systems and payers, since managing IPF is extremely costly?

**KOLB:** Any drug that is successful would reduce, overall, the non-drug-related costs of this disease. So, yes, these new drugs are all expensive. Any new drug for a rare condition is expensive.... And they are, of course, not neglectable costs. But if you keep a patient alive for longer, you will have savings on other fronts.

I don't think that [lung] transplant is, per se, a big driver for society in terms of cost. It's very big for an individual, but for society at large, it's not as big. But things like unscheduled

admissions to emergency [departments], they are super costly. When a patient with IPF goes to the emergency [department] because of progression, that will easily cost \$20,000 to \$25,000, depending on where this happens.... If you can stop this disease, you will have a good impact on society as well with eventual cost savings, but those are numbers that we don't see in the health care system.

There are people [who] analyze health economic costs and whether the cost is worth it from a societal perspective, but if a drug like nerandomilast or any other would be successful in stopping the disease, I'm sure that will be a big benefit not only for the people who are affected but also for society at large. ●

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## Early Intervention and Targeted Strategies Would Improve Disparities, Survival in Patients With IPF

Two posters presented at the CHEST 2024 Annual Meeting aimed to improve outcomes among patients with idiopathic pulmonary fibrosis (IPF) by explaining the underlying socioeconomic and clinical risk factors.

### Impact of Socioeconomic Disparities on Inpatient Outcomes in Patients With IPF

Approximately 30,000 to 40,000 new IPF cases are diagnosed annually, and as of 2022, nearly 100,000 Americans have the disease.<sup>1</sup> Consequently, the first poster analyzed how inpatient admissions of patients with IPF are divided by median income and insurance; it also explored pneumonia and respiratory failure rates within the population.

Through a retrospective cohort analysis of the 2020 National Inpatient Sample database, researchers grouped all adult patients with IPF according to the estimated median household income quartiles (EMHIQ) of residents in the patient's zip code. Quartiles Q1 through Q4 contained patients with an EMHIQ of less than \$50,000; \$50,000 to \$65,000; \$65,000 to \$86,000; and above \$86,000, respectively.<sup>1</sup>

The researchers also compared the expected primary payer (EPP; insurance type) and rates of respiratory failure, mortality, and pneumonia across the different quartile groups. Within the database, they identified 5440 patients with IPF, with a mean (SD) age of 73.4 (10.8) years. The median length of stay of those admitted with IPF was 5 days (IQR, 3-9).

When grouped by EMHIQ, 24.2%, 27.6%, 24.5%, and 23.7% of patients were distributed in the Q1, Q2, Q3, and Q4 groups, respectively. As for EPP, 78.3% of patients had Medicare, 13% had private insurance, and 5.4% had Medicaid. The researchers

determined that the EPP most prevalent in Q1 was Medicare (74.8%), followed by private insurance (12.8%) and Medicaid (7.8%). In comparison, a higher proportion of patients in Q4 had Medicare (81.4%) and private insurance (13.4%), whereas a lower amount had Medicaid (3.0%).

Additionally, when comparing pneumonia rates leading to acute exacerbations among the different quartile groups, they found an increased rate of pneumonia in Q1 when compared with Q4 (Q1, 29.4%; Q2, 28.2%; Q3, 25.8%; Q4, 24.9%). However, there were no significant differences in the rates of respiratory failure or mortality.

The researchers noted that these findings suggest a potential association between socioeconomic status and susceptibility to certain IPF complications. Consequently, they stated that addressing socioeconomic determinants is "imperative" for the timely identification of factors causing acute exacerbations of IPF, such as pneumonia, and the implementation of early intervention strategies.

"Further research is warranted to explore the underlying mechanisms driving these disparities and to develop targeted interventions to reduce health inequities in the IPF population," the authors concluded.

### Predictors of Long-Term Survival in Patients With IPF

Building on the socioeconomic factors affecting IPF complications, the second poster took a clinical approach, using the Idiopathic Pulmonary Fibrosis Prospective Outcomes (IPF-PRO) Registry to identify characteristics predictive of long-term survival in patients with IPF.<sup>2</sup> Patients diagnosed with IPF at the enrolling

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center within the past 6 months were included in the registry, which enrolled patients at 46 sites across the US between June 2014 and October 2018.

Therefore, the researchers followed patients prospectively, with follow-up data collected until death, lung transplant, or withdrawal from the registry, for up to 5 years. Also, they used a Classification and Regression Tree (CART) to identify predictors of shorter ( $\leq 5$  years) vs longer ( $> 5$  years) survival following registry enrollment; the CART algorithm makes predictions based on relationships in the data. They considered the impact of various variables on survival, such as age, IPF symptoms, and antifibrotic drug use.

The study population consisted of 819 patients, 278 of whom survived for more than 5 years after registry enrollment. The researchers identified the top 4 predictors that patients would survive more than 5 years: oxygen use, predicted forced vital capacity percentage (FVC %), body mass index (BMI), and age.

They noted that patients on oxygen had a 12% probability of surviving more than 5 years. However, a patient not on oxygen with a predicted FVC % of less than 65.2 had a 24% probability of surviving more than 5 years.

Overall, the researchers discovered that patients were more likely to survive beyond 5 years if they were younger than 81.5 years, not on oxygen, and had either an FVC % predicted

of 76.6 or greater or an FVC % predicted between 65.2 and 76.6 combined with a BMI of 32.7 or higher. In these groups, 61% and 77% of patients, respectively, survived for more than 5 years.

Lastly, the optimism-corrected area under the curve of the final CART was 0.73, with a 0.69 accuracy, indicating that it accurately predicted shorter rather than longer survival in 69% of patients.

“Discussion with patients with IPF around prognosis should reflect that IPF has a variable course and that some patients will survive for more than 5 years,” the authors concluded. “Variables known at diagnosis can aid these decisions.”

Overall, both posters emphasize the importance of early identification and intervention in patients with IPF, highlighting how socioeconomic disparities affect complications and how clinical variables predict long-term survival. Consequently, the authors of both posters called for targeted strategies to improve patient outcomes. ●

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## Overcoming Failures: Lessons From IPF Clinical Trials in the Past Year

**D**uring the European Respiratory Society Congress 2024, Luca Richeldi, MD, PhD, a professor of respiratory medicine at Catholic University of the Sacred Heart in Rome, Italy, presented a thought-provoking analysis on the failures of idiopathic pulmonary fibrosis (IPF) clinical trials.<sup>1</sup> His insights provide crucial lessons for the future of IPF research, emphasizing the need to learn from past setbacks to improve future trial designs.

Richeldi began by addressing a fundamental question: “Do we know if a negative randomized controlled trial is always a failure?”

He noted that not all negative trials are without merit, citing a landmark 2012 study that, despite its initial negative results, had a profound impact on clinical practice and has since been cited more than 1300 times.<sup>2</sup>

Over the past decade, there has been an increase in phase 2 and phase 3 trials for IPF, with more than 8500 patients enrolled overall.<sup>1</sup> However, there were 3 major phase 3 trials published in the past year that encountered challenges, offering valuable lessons in Richeldi’s eyes. The studies investigated ziritaxestat, zinpentraxin alfa, and pamrevlumab.<sup>3-5</sup>

The phase 2a trial of ziritaxestat included 23 patients with IPF who received just 12 weeks of treatment. The results showed statistically significant improvements in forced vital capacity (FVC) from baseline.<sup>3</sup> However, in the phase 3 trial involving 1300 patients over 52 weeks, the study was terminated early due to a lack of efficacy and a signal of harm, specifically increased mortality. Phase 2 results also appeared encouraging for zinpentraxin alfa, demonstrating significantly slowed disease progression.<sup>4</sup> However, phase 3 results again failed to replicate these findings as the patient cohort multiplied by 6 and the study period extended to 52 weeks.

Third time’s a charm, right? Once again, monoclonal antibody pamrevlumab showed a statistically significant reduction in FVC in a phase 2 trial with less than 400 patients but failed to produce similar results in a larger phase 3 trial, partly due to the concurrent use of antifibrotic therapies, which was not permitted in phase 2.<sup>5</sup>

So what do these studies have in common? First is the small sample sizes in phase 2 trials.<sup>1</sup> Having a smaller cohort can lead to overestimations of efficacy and does not always translate well



to larger phase 3 studies. The short study duration in phase 2 trials can fail to capture the long-term effects of treatments, again leading to optimistic results that may not hold up in longer-term studies.

As seen with the pamrevlumab trials, the presence of outliers can skew results, particularly if not adequately accounted for in the statistical analysis. Richeldi highlighted the challenge of distinguishing between true biological phenomena and statistical anomalies. Additionally, the use of concurrent therapies in phase 3 trials that were not present in phase 2 can confound results.

To address these issues, Richeldi proposed 3 key strategies to improve future trial design and execution. He advocated for adaptive trial designs that incorporate interim analyses and allow for adjustments based on emerging data. This approach can help identify issues early, leading investigators to adapt the study protocol accordingly. He also recommended adopting more rigorous statistical methods to handle outliers and missing data. This includes sensitivity analyses to assess the impact of removing outliers and better imputation methods for missing data.

Finally, he highlighted the importance of focusing on patient-relevant outcomes, such as quality of life and survival,

rather than solely relying on FVC changes. Of the 12 active and recruiting phase 2 studies of IPF he mentioned, only 2 had cough as a primary end point rather than FVC. According to Richeldi, this shift could provide a more comprehensive understanding of a treatment's impact on patients' quality of life.

"I think that we can do better," Richeldi concluded. "We did a lot, and hopefully we'll be learning from our mistakes and will do better in the future." ●

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## Oxygen Therapy for Fibrosing ILD Is Tied to Higher Costs and Mortality Rates

Patients with fibrosing interstitial lung disease (ILD) who initiate supplemental oxygen therapy face significantly higher mortality rates and health care costs than those who do not receive this treatment.

These findings were presented at the American Thoracic Society 2024 International Conference and published in the *American Journal of Respiratory and Critical Care Medicine*.<sup>1</sup>

Researchers used data from the Optum Market Clarity database from October 2015 to June 2022. The study included 24,680 patients who started oxygen therapy (exposed cohort) and a matched cohort of 24,680 patients who did not (unexposed cohort) and evaluated the clinical and economic impacts of supplemental oxygen therapy among these patients with newly diagnosed fibrosing ILD. The mean age of the participants was 68.9 years and 50.9% were men, according to the researchers.

Key findings indicated the exposed cohort had notably higher all-cause health care resource utilization across all categories than the unexposed cohort. Regarding hospitalization, the exposed group had more visits (0.09 vs 0.05 per patient per month [PPPM]) and longer stays (1.24 vs 0.55 days PPPM) than the unexposed group.

This increase in resource utilization translated to an 82% higher total all-cause health care cost for the exposed cohort,

with a mean (SD) cost of \$8812 (\$27,142) PPPM compared with \$4847 (\$9983) for the unexposed group. When looking at the medical cost breakdown among the treatment group, this total came from hospitalization (\$4655), ambulatory office and outpatient visits (\$1519), emergency department visits (\$340), and other medical costs (\$1385); the remaining \$913 came from pharmacy costs.

Looking specifically at fibrosing ILD-related health care costs, these PPPM numbers dropped but were still higher for the patients who received supplemental oxygen therapy. The mean (SD) total medical and pharmacy PPPM costs for the exposed group were 3 times the amount for the unexposed group at \$4378 (\$22,468) and \$1455 (\$6822), respectively. Hospitalization made up almost the entire total cost at \$3912 for the exposed cohort, and again this cost was much lower for those who did not receive oxygen therapy (\$1235). Fibrosing ILD-related health care resource utilization was also lower across the board, still with more (0.06 vs 0.02 PPPM) and longer (0.98 vs 0.37 days PPPM) hospital stays for those receiving oxygen therapy.

The study also highlighted a significant disparity in mortality rates. The censor-adjusted data showed that 54% of patients who received supplemental oxygen therapy died during the

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follow-up period, compared with 39% who did not receive the treatment ( $P < .001$ ). This suggests a considerable increase in the risk of death associated with the initiation of supplemental oxygen therapy.

The study's authors concluded that although supplemental oxygen therapy is a common treatment for patients with fibrosing ILD, it is associated with a higher economic burden and increased mortality.

"The study findings indicate that patients diagnosed with fibrosing ILD who initiated O<sub>2</sub> therapy bear a higher incremental economic burden and increased all-cause mortality compared [with] patients who did not yet initiate O<sub>2</sub> therapy," the authors wrote. "These findings suggest that future therapies reducing the need for O<sub>2</sub> therapy could potentially improve clinical outcomes and alleviate the economic burden among patients with fibrosing ILD."

Patients with ILD often require supplemental oxygen due to hypoxemia, with estimates suggesting that up to 40% may need it, including high-flow support, according to a narrative review published in the *Annals of the American Thoracic Society*

in 2023.<sup>2</sup> Despite its widespread use, there is limited evidence on the clinical benefits of oxygen therapy in ILD, with most guidelines based on older chronic obstructive pulmonary disease studies. Although oxygen can enhance quality of life and exercise capacity for some patients with ILD, it also introduces new challenges and costs.

The review authors also noted that current reimbursement policies as of publication provide minimal support for high-flow oxygen, potentially limiting access for some patients.<sup>2</sup> Given the scant evidence and financial implications, the authors recommended a patient-focused approach for prescribing supplemental oxygen in ILD, noting that further research is needed to better understand its impact. ●

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## New Findings Highlight the Impact of Lung Function Decline in IPF, PPF

Two study abstracts presented at the European Respiratory Society (ERS) Congress 2024 gave an update on current research into idiopathic pulmonary fibrosis (IPF) and progressive pulmonary fibrosis (PPF), highlighting the impact of these diseases on lung function and patient outcomes.

Results of the studies, which analyzed the decline in forced vital capacity (FVC) and its relationship to mortality risk, underscored the importance of understanding disease progression and the potential benefits of treatment with nintedanib.

“Taken together, these abstracts highlighted the burden of lung function decline in both IPF and PPF and identified the associated mortality risks.”

### FVC Decline in Patients With IPF and PPF

Claudia Valenzuela, MD, pulmonologist at the Hospital Universitario de La Princesa in Madrid, Spain, presented the first abstract at the ERS Congress.<sup>1</sup> Its researchers looked at baseline FVC and its decline in individuals with IPF from the

phase 3 INPULSIS trials (NCT01335464, NCT01335477) and those with PPF from the phase 3 INBUILD trial (NCT02999178) and compared these with hypothetical healthy references. Values for these healthy references were developed using equations published by the ERS Global Function Initiative.

These trials previously demonstrated that nintedanib (Ofev) reduced the rate of FVC decline by 49% in 1 year for those with IPF and by 57% for those with PPF compared with placebo. The newest comparison allowed researchers to quantify the physiological impact of IPF and PPF, illustrating how much these diseases accelerate lung function decline compared with individuals without either condition.

The researchers found that patients with IPF and PPF had substantially impaired lung function compared with their healthy counterparts when matched for age, sex, race, and height.

In the INPULSIS trials, patients with IPF treated with nintedanib had a mean baseline FVC of 2714 mL, whereas their healthy references had a much higher baseline FVC of 3597 mL. Similarly, in the INBUILD trial, patients in the nintedanib group had a baseline FVC of 2340 mL compared with 3411 mL in healthy individuals. Both trials also saw much lower baseline FVCs for patients receiving placebo than their healthy references.

Additionally, over 52 weeks of treatment, the rate of FVC decline in the placebo groups was 7 times greater than in the

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healthy reference group. In the nintedanib groups, the decline was only 3 to 4 times greater than in healthy individuals.

“This analysis demonstrates the physiological impact of IPF and PPF and supports the clinical relevance of the reduction in FVC decline seen with nintedanib,” Valenzuela said during her presentation.

### **Lung Function Decline Tied to Increased Mortality Risk in IPF**

The second abstract<sup>2</sup> was presented by Divya Patel, DO, MBA, director of clinical development and medical affairs at Boehringer Ingelheim and adjunct associate professor of medicine at the University of Florida in Gainesville.

This study focused on the relationship between changes in lung function and mortality risk in patients with IPF, with data pulled from the Idiopathic Pulmonary Fibrosis Prospective Outcomes (IPF-PRO) Registry, a real-world cohort of more than 1000 patients enrolled at 46 sites across the US. The study used a joint model to estimate FVC and diffusing capacity of the lungs for carbon monoxide (DLCO) as percentages predicted for each day of follow-up, allowing for an in-depth analysis of how changes in lung function influence patient prognosis.

Even small relative declines in lung function had a significant impact on mortality risk or the likelihood of lung transplant, according to the study results. Median relative changes in FVC and DLCO over 12 months were -3.3% and -11.2%, respectively, and for each threshold of decline examined—2%, 5%, or 10% for

FVC and 15% for DLCO—the researchers observed a corresponding increase in the risk of death or lung transplant.

“Generally, for thresholds of FVC decline, the risk was similar for an absolute or relative decline,” Patel noted. “But for thresholds of DLCO decline, the risk was greater for relative than for an absolute decline.”

These findings support the value of closely monitoring lung function in patients with IPF; early detection of even minor declines could have crucial prognostic value.

Taken together, these abstracts highlighted the burden of lung function decline in both IPF and PPF and identified the associated mortality risks, with these findings emphasizing the clinical relevance of treatments such as nintedanib in mitigating disease progression. By comparing FVC decline in these patients with healthy individuals, the results presented at ERS Congress 2024 contribute to a growing body of evidence supporting more proactive and tailored treatment approaches for fibrosing lung diseases. ●

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