
# İPF: Tedavi Planı ve İzlem

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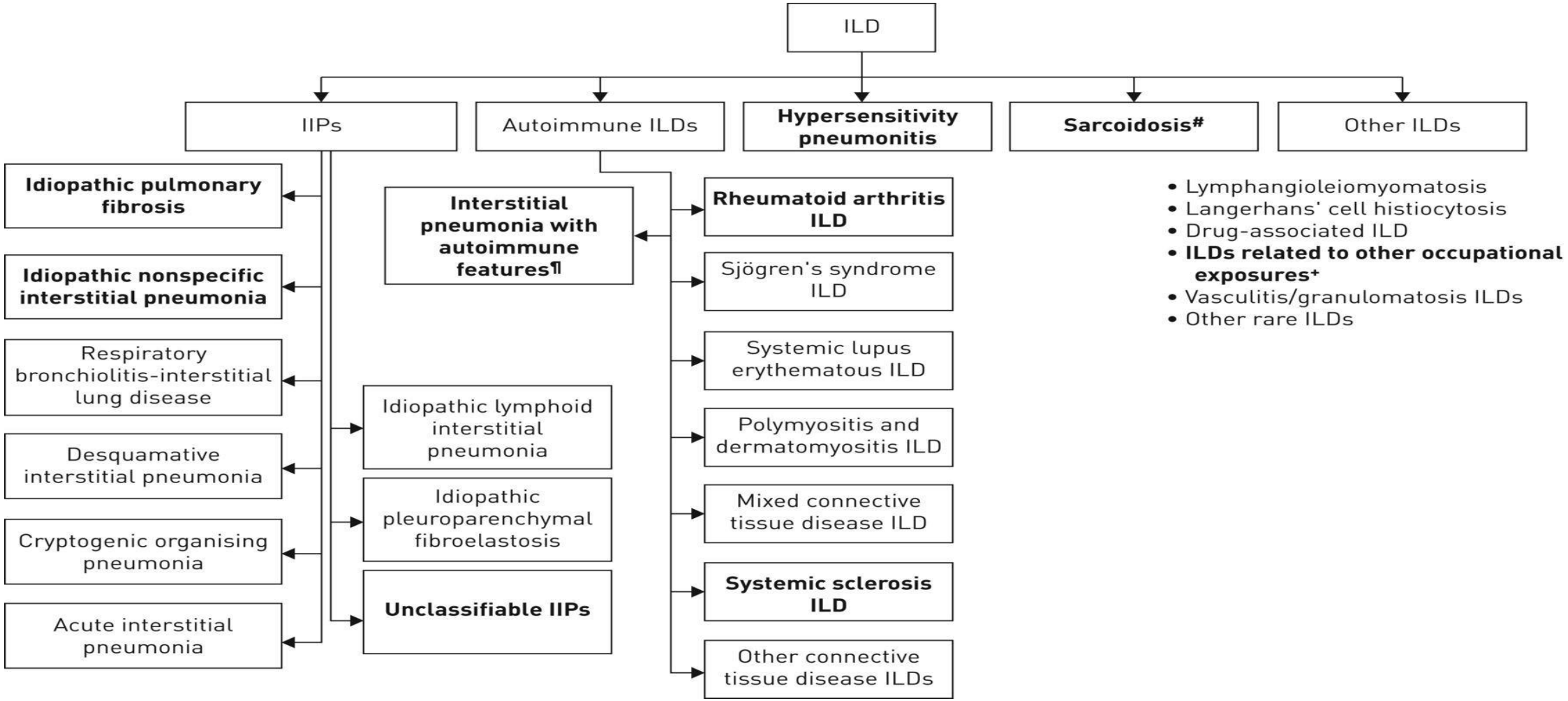
# İdiyopatik Pulmoner Fibrozis (İPF)

- İdiyopatik Pulmoner Fibrozis (İPF) sebebi bilinmeyen, daha çok ileri yaşlarda görülen, kronik, progresif seyreden, küratif tedavisi olmayan histopatolojik olarak olağan interstisyel pnömoni (OIP) paterni gösteren interstisyel akciğer hastalığıdır .

- İPF, mortalitesi ortalama 3-5 yıl ?? olup prognozu ve mortalitesi diğer interstisyel akciğer hastalıklarından ve birçok kanserden daha kötüdür.

# İAH Sınıflama



| | Morphologic patterns by Pathology and Imaging | Major clinical-radiologic-pathologic diagnoses | |
|---|---|---|---|
| | | **Secondary** | **Primary / Idiopathic** |
| **Interstitial patterns** | **Usual interstitial pneumonia (UIP)** | **Secondary UIP** (*e.g.*, CTD, HP, medications) | **Idiopathic pulmonary fibrosis** (Idiopathic UIP) |
| | **Nonspecific interstitial pneumonia (NSIP)** | **Secondary NSIP** (*e.g.*, CTD >>> HP, medications) | **Idiopathic NSIP** |
| | **Bronchiolocentric interstitial pneumonia (BIP)*** | **Secondary BIP** (*e.g.*, HP >>> CTD, aspiration, inhalational exposures, medications) | **Idiopathic BIP** *(provisional diagnosis*)* |
| | **Diffuse alveolar damage (DAD)** | **Secondary DAD** (multiple causes) | **Idiopathic DAD** (acute interstitial pneumonia) |
| | **Pleuroparenchymal fibroelastosis (PPFE)** | **Secondary PPFE** (*e.g.*, IPF, CTD, HP, medications, radiation, transplant [restrictive allograft syndrome, pulmonary infection [post-tuberculosis], occupational) | **Idiopathic PPFE** |
| | **Lymphoid interstitial pneumonia (LIP)** | **Secondary LIP** (*e.g.*, CTD, immune deficiency) | **Idiopathic LIP** |
| **Alveolar filling patterns** | **Organising pneumonia (OP)** | **Secondary OP** (*e.g.*, CTD, post-infectious, medications, aspiration) | **Cryptogenic OP** (Idiopathic OP) |
| | **Respiratory bronchiolitis-ILD (RB-ILD)** | **Secondary RB-ILD** (*e.g.*, smoking >>> CTD, medications, aspiration, hereditary) | **Idiopathic RB-ILD** |
| | **Alveolar macrophage pneumonia† (AMP)** | **Secondary AMP** (*e.g.*, smoking >>> CTD, medications, aspiration, hereditary | **Idiopathic AMP** |
| | **Rare alveolar filling disorders** | *e.g.*, **Acute and chronic eosinophilic pneumonia**, **pulmonary alveolar proteinosis, lipoid pneumonia** (See **Supplemental Table 1**) | |
| **Other** | **Combined pattern** | **Multiple combinations** (*e.g.*, NSIP + OP, UIP + PPFE) | |
| | **Unclassifiable pattern** | **Unclassifiable ILD** (multiple undefined patterns) | |

Ryerson *et al*, AJRCCM 2025.

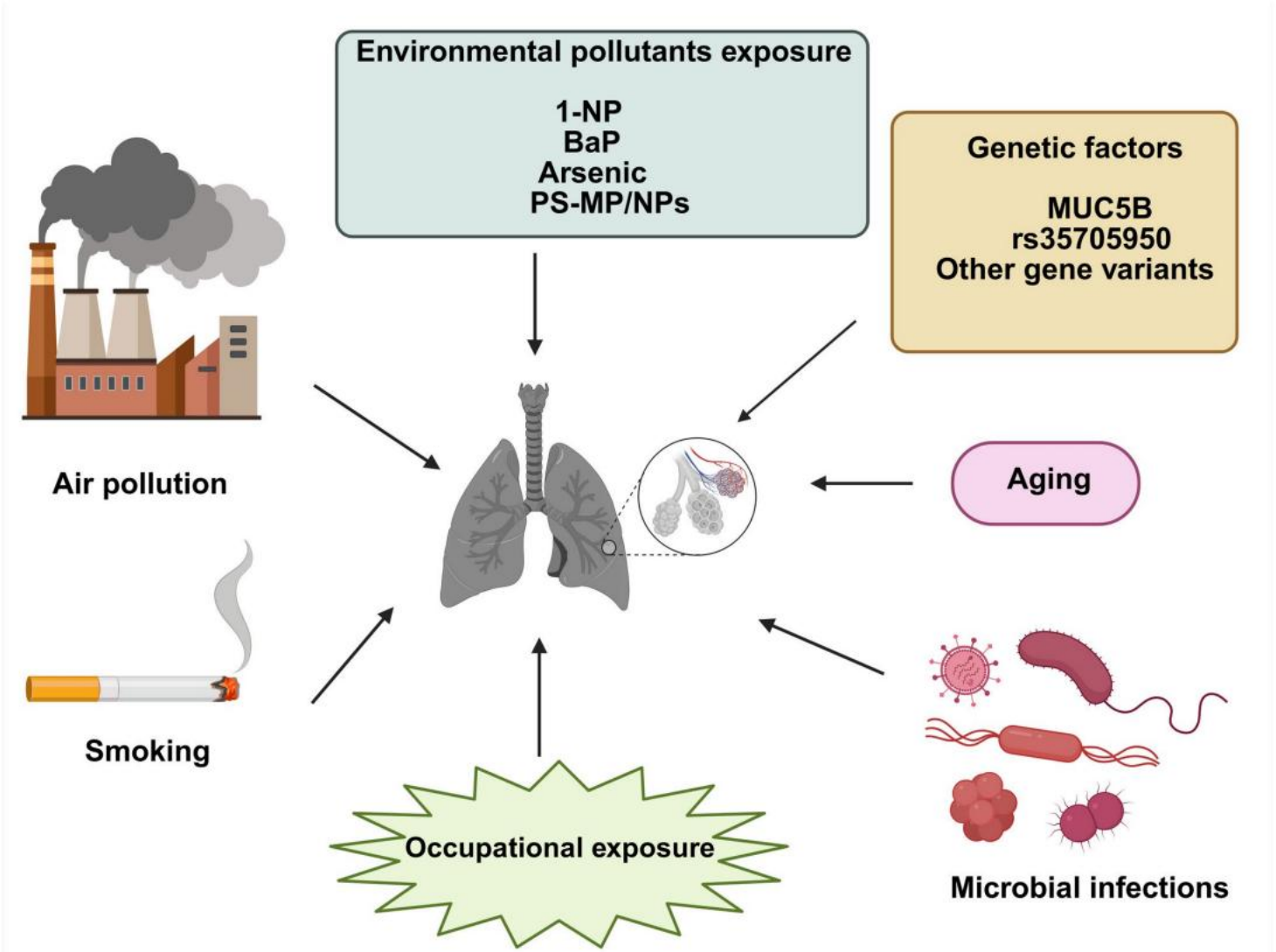
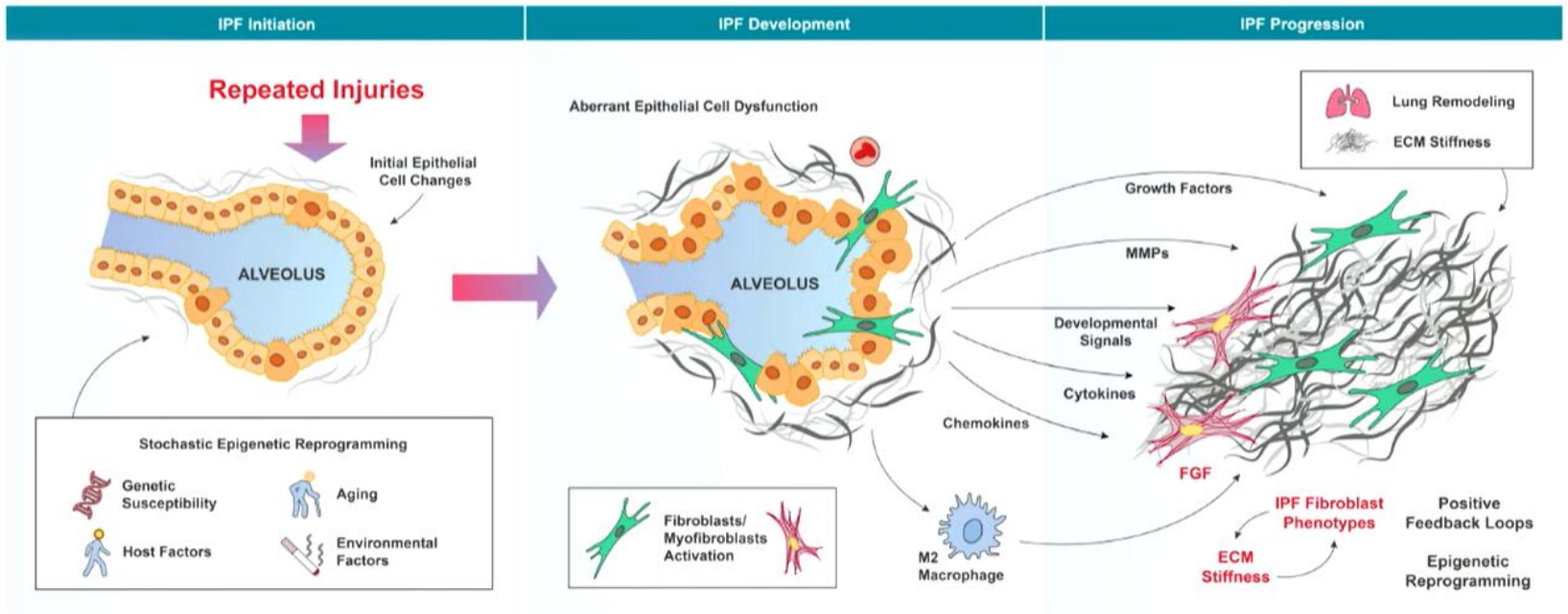



**Fig. 1** Schematic representation of PF potential risk factors. Diverse risk factors, including intrinsic factors (including genetic factors and aging), and extrinsic factors (including air pollution, smoking, occupational exposure, environmental pollutants exposure, and microbial infections) contribute to PF. Image Created in https://BioRender.com




A complex interplay of genetic and environmental risk factors, aging-associated processes, and epigenetic reprogramming causes IPF

ECM, extracellular matrix; FGF, fibroblast growth factor; IPF, idiopathic pulmonary fibrosis; MMPs, matrix metalloproteinases; TGFβ, transforming growth factor beta.

*Adapted from: Pardo A, Selman M. The interplay of the genetic architecture, aging, and environmental factors in the pathogenesis of idiopathic pulmonary fibrosis.* Am J Respir Cell Mol Biol 2021;64:163–172.

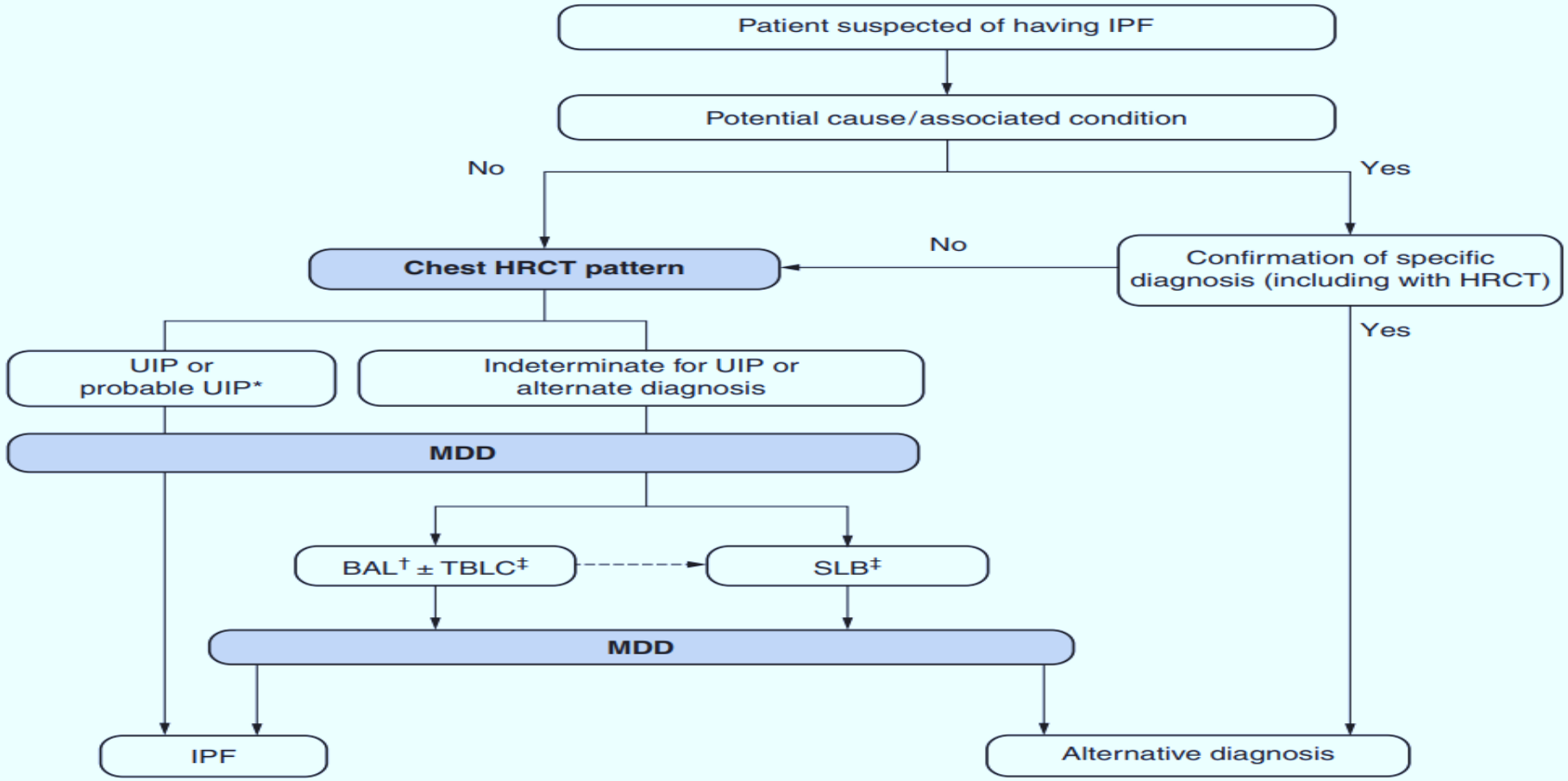
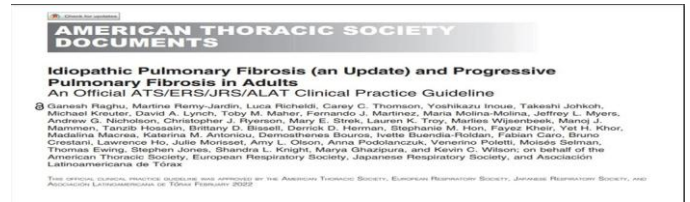



**Figure 10.** Diagnostic algorithm for idiopathic pulmonary fibrosis (IPF), developed using consensus by discussion. *Patients with a radiological pattern of probable usual interstitial pneumonia (UIP) can receive a diagnosis of IPF after multidisciplinary discussion (MDD) without confirmation by lung biopsy in the appropriate clinical setting (e.g., 60 yr old, male, smoker). BAL may be appropriate in some patients with a probable UIP pattern. †BAL may be performed before MDD in some patients evaluated in experienced centers. ‡Transbronchial lung cryobiopsy (TBLC) may be preferred to surgical lung biopsy (SLB) in centers with appropriate expertise and/or in some patient populations, as described in the text. A subsequent SLB may be justified in some patients with nondiagnostic findings on TBLC. Adapted from Reference 2. HRCT = high-resolution computed tomography.

**2022 İPF tanı algoritması**


AMERICAN THORACIC SOCIETY DOCUMENTS

Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults
An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

| IPF suspected* | | Histopathology pattern† | | | |
|---|---|---|---|---|---|
| | | UIP | Probable UIP | Indeterminate for UIP or biopsy not performed | Alternative diagnosis |
| HRCT pattern | UIP | IPF | IPF | IPF | Non-IPF dx |
| | Probable UIP | IPF | IPF | IPF (Likely)‡ | Non-IPF dx |
| | Indeterminate | IPF | IPF (Likely)‡ | Indeterminate§ | Non-IPF dx |
| | Alternative diagnosis | IPF (Likely)‡ | Indeterminate§ | Non-IPF dx | Non-IPF dx |

**Figure 9.** Idiopathic pulmonary fibrosis (IPF) diagnosis on the basis of high-resolution computed tomography (HRCT) and biopsy patterns, developed using consensus by discussion. *"Clinically suspected of having IPF" is defined as unexplained patterns of bilateral pulmonary fibrosis on chest radiography or chest computed tomography, bibasilar inspiratory crackles, and age > 60 years. Middle-aged adults (>40 and <60 yr old) can rarely present with otherwise similar clinical features, especially in patients with features suggesting familial pulmonary fibrosis. †Diagnostic confidence may need to be downgraded if histopathological assessment is based on transbronchial lung cryobiopsy given the smaller biopsy size and greater potential for sampling error compared with surgical lung biopsy. ‡IPF is the likely diagnosis when any of the following features are present: *1*) moderate to severe traction bronchiectasis and/or bronchiolectasis (defined as mild traction bronchiectasis and/or bronchiolectasis in four or more lobes, including the lingula as a lobe, or moderate to severe traction bronchiectasis in two or more lobes) in a man >50 years old or in a woman >60 yr old, *2*) extensive (>30%) reticulation on HRCT and age > 70 yr, *3*) increased neutrophils and/or absence of lymphocytosis in BAL fluid, and *4*) multidisciplinary discussion produces a confident diagnosis of IPF. §Indeterminate for IPF *1*) without an adequate biopsy remains indeterminate and *2*) with an adequate biopsy may be reclassified to a more specific diagnosis after multidisciplinary discussion and/or additional consultation. Adapted from Reference 2. dx = diagnosis; UIP = usual interstitial pneumonia.

## Assessment and treatment of ILD

- **Assess disease severity**
  - Pulmonary function testing
  - 6-min walk test
- **Exclude complications**
  - Echocardiogram
  - Overnight oximetry
  - Polysomnography

### Treatment based on ILD classification

**Idiopathic pulmonary fibrosis**
- Nintedanib
- Pirfenidone

**Systemic sclerosis ILD**
- Cyclophosphamide
- Mycophenolate mofetil
- Rituximab
- Nintedanib
- Tocilizumab

**Other ILD**
- Immunosuppression
- Antigen avoidance for hypersensitivity pneumonitis

**Progressive pulmonary fibrosis**
- Ninetdanib

### Treatment for disease complications

- Pulmonary rehabilitation
- Pulmonary hypertension: inhaled treprostinil
- Respiratory failure: oxygen
- End-stage disease: lung transplant
- Management of symptoms (eg, cough and breathlessness)

**JAMA | Review**

# Interstitial Lung Disease
## A Review

Toby M. Maher, MD, MSc, PhD

*JAMA*. doi:10.1001/jama.2024.3669
Published online April 22, 2024.

# İPF'de Tedavi

- Hastalığın seyri tahmin edilemez
- Küratif farmakolojik tedavisi henüz yok
- Anti-fibrotik ilaçlar hastalığın ilerlemesini yavaşlatıcı
- Tedavi verilmeyen hastalarda sağ kalım 2-3 yıl

# İPF'de Tedavi

**Medikal Tedavi**

**Destekleyici tedavi:**

- Oksijen
- Pulmoner rehabilitasyon (egzersiz toleransını artırabilir ve yaşam kalitesini iyileştirebilir)
- Aşı

**Akciğer nakli**

**Hasta Eğitimi ve Psikososyal Destek**

- Hasta ve ailesine hastalığın seyri ve tedavi seçenekleri hakkında bilgi verilmelidir.
- Psikolojik destek ve sosyal yardım hizmetleri ile yaşam kalitesine yönelik müdahaleler yapılabilir.

# İPF’de Medikal Tedavi

**Antifibrotik ilaçlar:**

- **Pirfenidon**
- **Nintedanib**

- Antifibrotik ilaçların hastalığın ilerlemesini yavaşlattığı, akut alevlenmelerin sıklığını azalttığı, mortalite riskini  azalttığı gösterilmiştir


1. Petnak T, Lertjitbanjong P, Thongprayoon C, Moua T. Impact of Antifibrotic Therapy on Mortality and Acute Exacerbation in Idiopathic Pulmonary Fibrosis: A Systematic Review and Meta-Analysis. Chest 2021; 160:1751.
2. Canestaro WJ, Forrester SH, Raghu G, et al. Drug Treatment of Idiopathic Pulmonary Fibrosis: Systematic Review and Network Meta-Analysis. Chest 2016; 149:756.

# Pirfenidon

Pirfenidon, İPF tedavisinde oral yoldan verilen bir piridin türevi ilaçtır.

Antiinflamatuar, antioksidan ve antifibrotik etkileri vardır.

Kollajen sentezini inhibe eder.

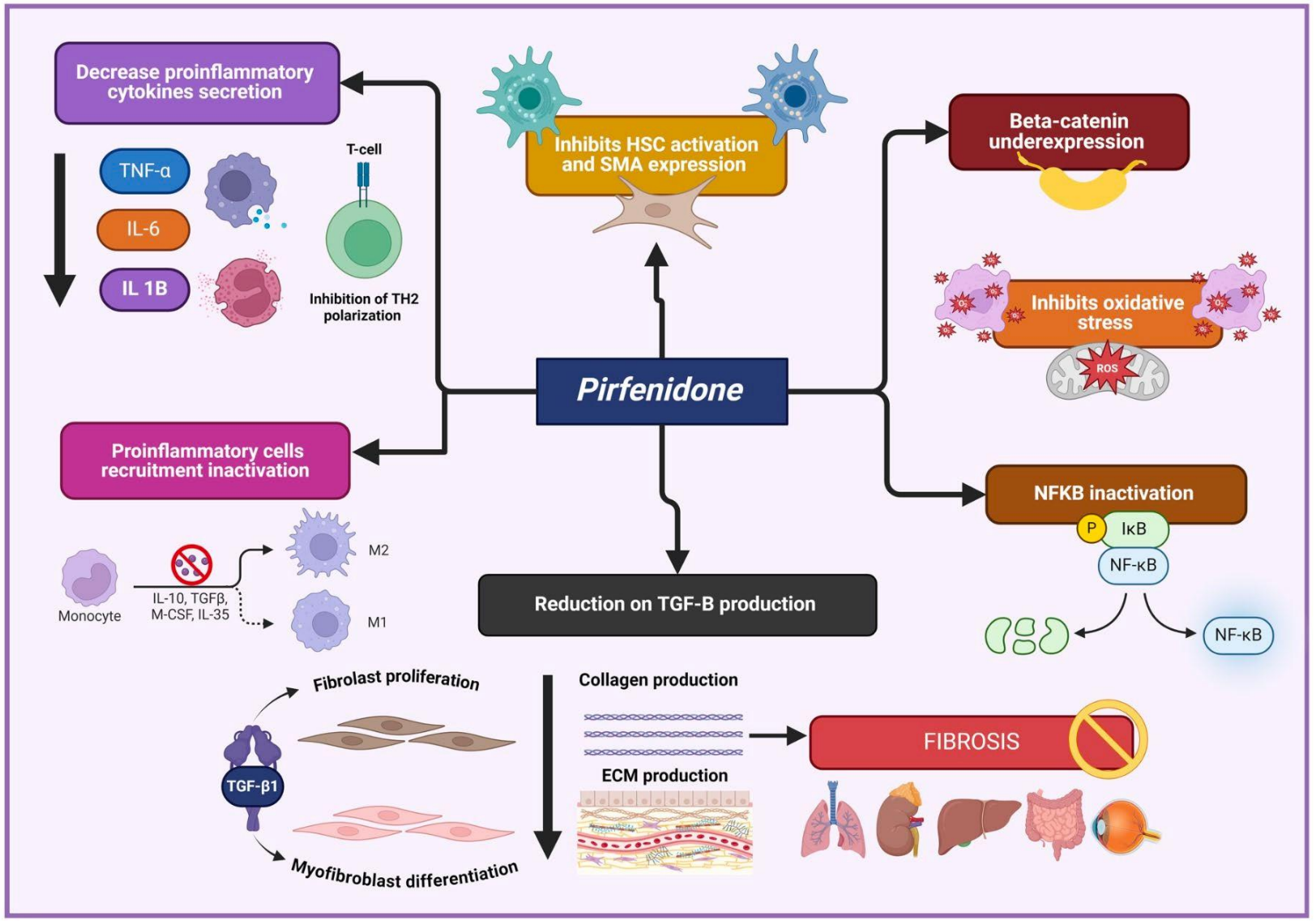
Transforming growth faktör (TGF)-β ve tümör nekroz faktörünün (TNF)-α expresyonunu azaltır.

Fibroblast proliferasyonunu azaltır.

CAPACİTY ve ASCEND çalışmalarında 2403 mg/gün pirfenidon, hastalığın ilerlemesini yavaşlatmıştır.

İPF hastalarında akciğer fonksiyonunu, egzersiz toleransını ve progresyonsuz sağkalımı plaseboya göre iyileştirmiştir.

# Pirfenidon etki mekanizması



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

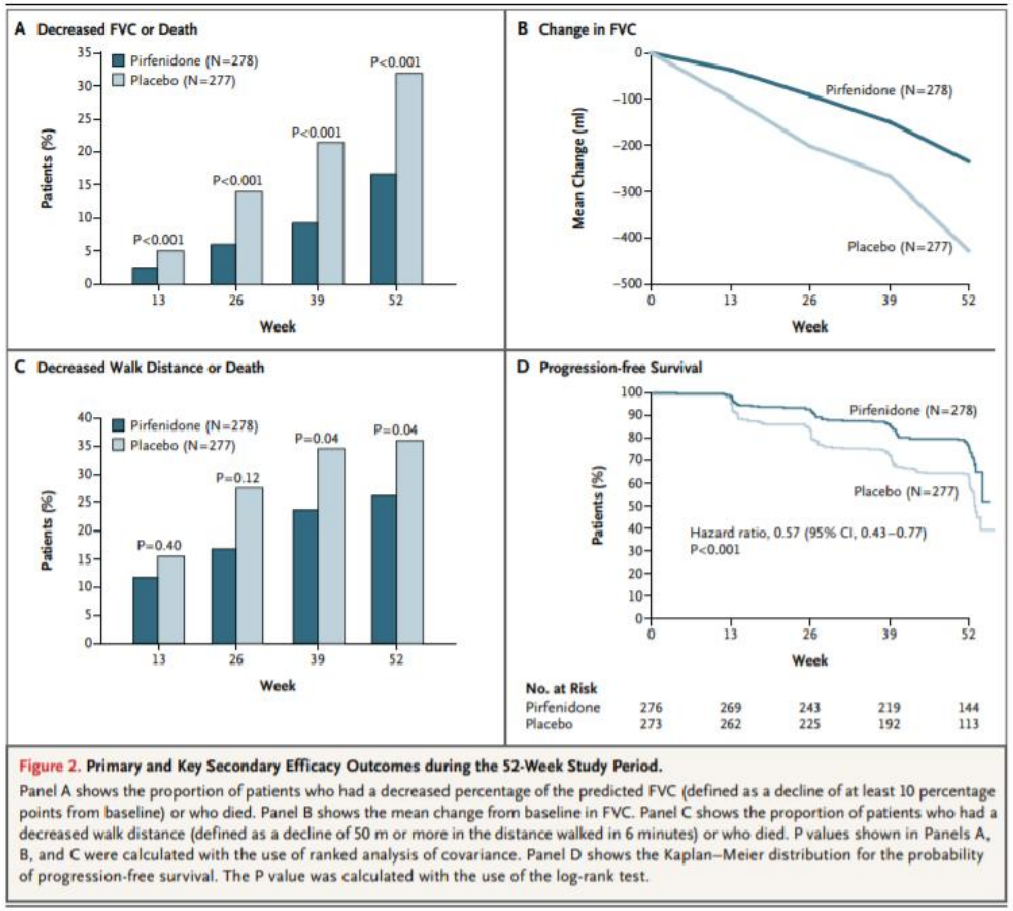



**Figure 2. Primary and Key Secondary Efficacy Outcomes during the 52-Week Study Period.**
Panel A shows the proportion of patients who had a decreased percentage of the predicted FVC (defined as a decline of at least 10 percentage points from baseline) or who died. Panel B shows the mean change from baseline in FVC. Panel C shows the proportion of patients who had a decreased walk distance (defined as a decline of 50 m or more in the distance walked in 6 minutes) or who died. P values shown in Panels A, B, and C were calculated with the use of ranked analysis of covariance. Panel D shows the Kaplan–Meier distribution for the probability of progression-free survival. The P value was calculated with the use of the log-rank test.


**BACKGROUND**

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

**METHODS**

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

**RESULTS**

In the pirfenidone group, as compared with the placebo group, there was a relative reduction of 47.9% in the proportion of patients who had an absolute decline of 10 percentage points or more in the percentage of the predicted FVC or who died; there was also a relative increase of 132.5% in the proportion of patients with no decline in FVC (P<0.001). Pirfenidone reduced the decline in the 6-minute walk distance (P=0.04) and im
significant between-group
from any cause (P=0.10) c
in a prespecified pooled a
trials, the between-group
from any cause (P=0.01) and from idiopathic pulmonary fibrosis (P=0.006). Gastrointestinal and skin-related adverse events were more common in the pirfenidone group than in the placebo group but rarely led to treatment discontinuation.

**CONCLUSIONS**

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


ASCEND çalışması: Hastalık progresyonunu, FVC'deki yıllık kaybı azalttığı, egzersiz toleransını ve sağkalımı artırdığı görülmüş.

# Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials

*Paul W Noble, Carlo Albera, Williamson Z Bradford, Ulrich Costabel, Marilyn K Glassberg, David Kardatzke, Talmadge E King Jr, Lisa Lancaster, Steven A Sahn, Javier Szwarcberg, Dominique Valeyre, Roland M du Bois, for the CAPACITY Study Group*

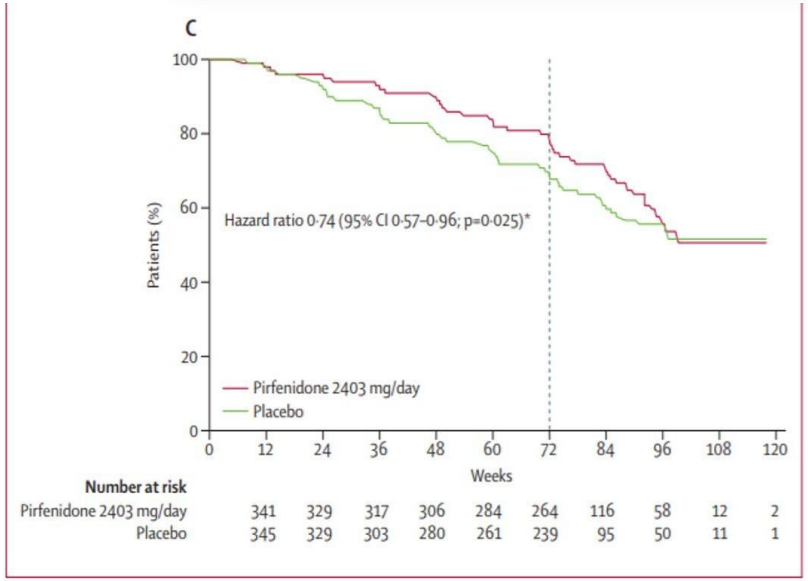



***Figure 3:*** **Kaplan-Meier distribution of progression-free survival time in study 004 (A), Study 006 (B), and the pooled population (C)**
*Pirfenidone 2403 mg/day versus placebo.

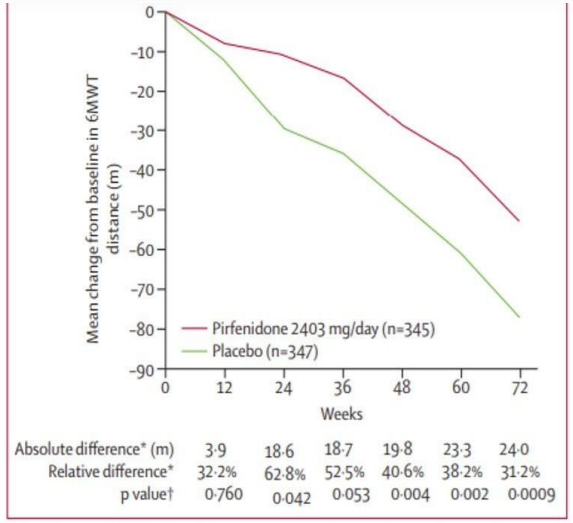
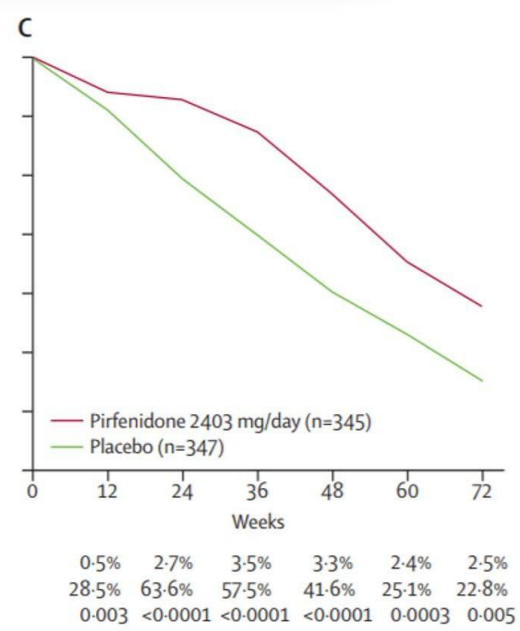



***Figure 4:*** **Mean change from baseline in 6-min walk test distance in the pooled patient population (studies 004 and 006)**
6MWT=6-min walk test. *Pirfenidone 2403 mg/day versus placebo. †Rank ANCOVA (pirfenidone 2403 mg/day *vs* placebo).



# Pirfenidon

- 200 mg, 400mg, 600 mg tablet
- 267 mg, 801 mg tablet
- 40mg/kg/gün, max doz 2400mg veya 2403 mg
- Tedaviye düşük dozla başlanır ve kademeli arttırılır (Haftalık aralarla 3. haftada maksimum doza çıkılır)
- Etkili minimum doz 1200 mg/gün
- İlk 6 ay aylık, sonrasında 3 aylık aralarla KCFT ve BFT takibi
- CrCl <30 mL/min ise pirfenidon kullanımına dikkat!. Doz azaltımı ? İlacın kesilmesi ?

# Pirfenidon

**Yan etkiler:**

- Gastrointestinal: Dispepsi, iştahsızlık, bulantı, kusma, diyare.
- Cilt: Döküntü, fotosensitivite.
- Nörolojik: Baş ağrısı, baş dönmesi
- Halsizlik
- Kilo kaybı
- Hiponatremi

# Pirfenidon

Kontrendikasyon:

- İlaca karşı aşırı duyarlılık
- Kreatin klirensi <30ml/min
- Ağır karaciğer yetmezliği olan hastalar (Child-Pugh Sınıf C)

# Pirfenidona bağlı GİS yan etkisi varsa:

- İlaçların yemekle birlikte alınması
- Proton pompa inhibitörü ve prokinetik ajanlar kullanılması
- Semptomlar devam ederse ilaç dozu azaltılır (3x1-3x2, 4x1-4x2), kademeli arttırılarak izlenir.
- Semptomlar devam ederse 1-2 hafta süre ile tedavi kesilebilir.

# Pirfenidon kullanımı sırasında karaciğer fonksiyonları bozulduğunda

- **Karaciğer hasarının semptom-bulguları ve bilirubin seviyesinde artış olmadan ALT-AST 3-5 kat arası artarsa (normal değerlerin üst sınırının)**

➢ Pirfenidon dozu azaltılmalı veya kesilmeli.

➢ Karaciğer toksisitesi ile ilişkili diğer ilaçlar kesilmeli.

➢ Diğer nedenler dışlanmalıdır

➢ Hasta yakından takip edilmelidir .

➢ Karaciğer fonksiyon testleri normal sınırlara geldiğinde hasta tolere edebiliyorsa önerilen günlük doza tekrar artırılabilir.

- KCFT 3-5 kat arası yükselmiş hastada

  ➢ Klinik semptom ve bulgular varsa

  ➢ Bilirubin yüksekliği varsa

tedavi kalıcı olarak sonlandırılmalı ve tekrar başlatılmamalıdır.

- KCFT > 5 kat yükselmişse

tedavi kalıcı olarak sonlandırılmalı ve tekrar başlatılmamalıdır.

# Pirfenidona bağlı fotosensitivite gelişirse;

- İlaca başlamadan önce bu yan etki hakkında hastalar uyarılmalı ve koruyucu önlemler alınması gerektiği söylenmeli
- Yine de fotosensitivite veya döküntü gelişirse;

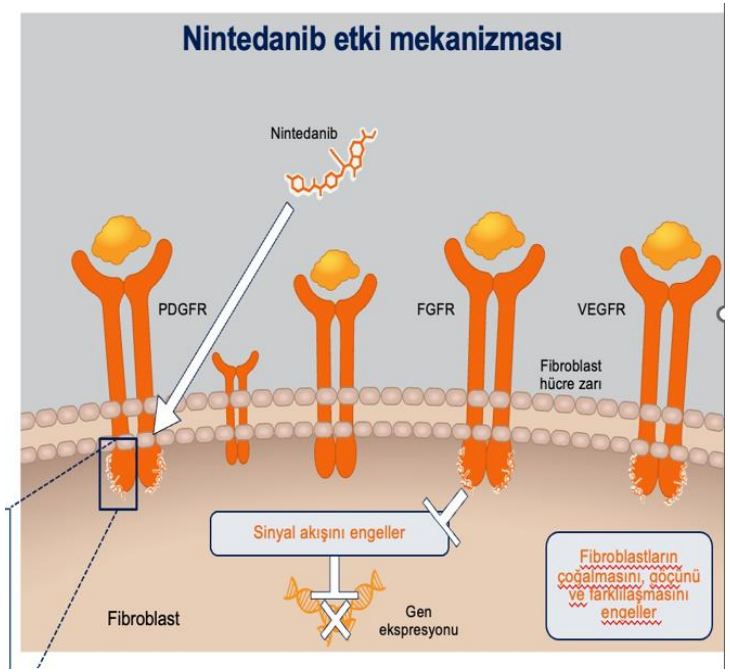
➢ Hafif ila orta derecede fotosensitivite reaksiyonu veya döküntü yaşayan hastalarda pirfenidonun dozu azaltılabilir (3x1 -4x1)

➢ Döküntü 7. gün sonunda devam ediyorsa tedaviye 2 hafta ara verilir ve doz yükseltme periyoduna göre önerilen günlük doza tekrar yükseltilebilir.

## Pirfenidona bağlı fotosensitivite gelişirse;

- Şiddetli derecede fotosensitivite reaksiyonu veya döküntü yaşayan hastalarda doza ara verilmeli ve dermatoloji konsültasyonu istenmelidir.
- Döküntü ortadan kalktıktan sonra pirfenidon tedavisi tekrar başlatılabilir ( titre edilerek) veya değiştirilebilir.
- Titrasyonda yeniden fotosensitivite ve döküntü gelişirse ilaç değişimi yapılmalıdır.

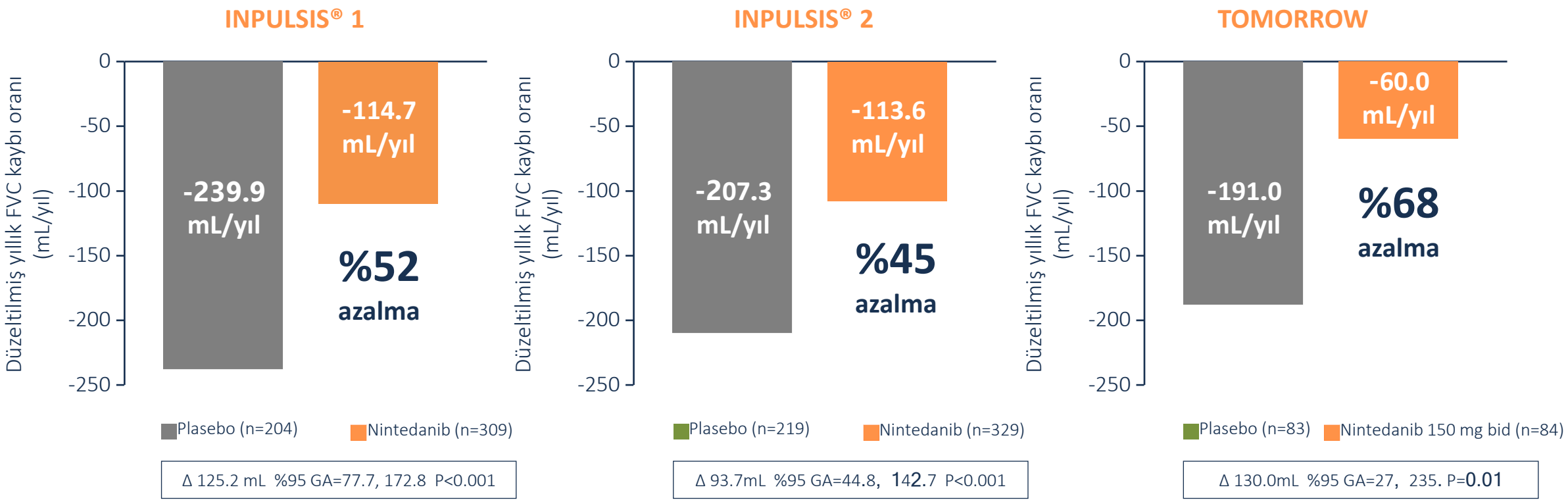
# Nintedanib




- Antifibrotik, anti-enflamatuar ve anti-anjiyogenik aktiviteye sahip birden fazla reseptörü hedef alan tirozin kinaz inhibitörüdür.
- Fibrojenik büyüme faktörlerinin **(PDGF, VEGF, FGF)** işlenmesine aracılık eden tirozin kinaz reseptörlerini bloke eder.
- Kinazların ATP bağlayan kısmına kompetetif bağlanarak, fibrotik doku remodeling patogenezinde rol alan intraselüler sinyalizasyon kaskadlarını bloke eder.
- Fibroblast proliferasyonu, migrasyonu, myofibroblast transformasyonu ve ECM sentezini inhibe eder

# Nintedanib ile Yıllık FVC Düşüşünde Anlamlı Azalma[1.-3]

## IPF'de hastalık progresyonunda tutarlı şekilde yavaşlama.




FVC, zorlu vital kapasite; GA, güven aralığı

Grafikler 1-3 numaralı referanstan uyarlanmıştır

**1**. Richeldi L, et al. N Engl J Med. 2014;370(22):2071-2082. **2.** Richeldi L, et al.N Engl J Med.2011;365(12):1079-1087. **3.** Richeldi L, et al. Respir Med. 2016 Apr;113:74-9.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 29, 2014 VOL. 370 NO. 22

# Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

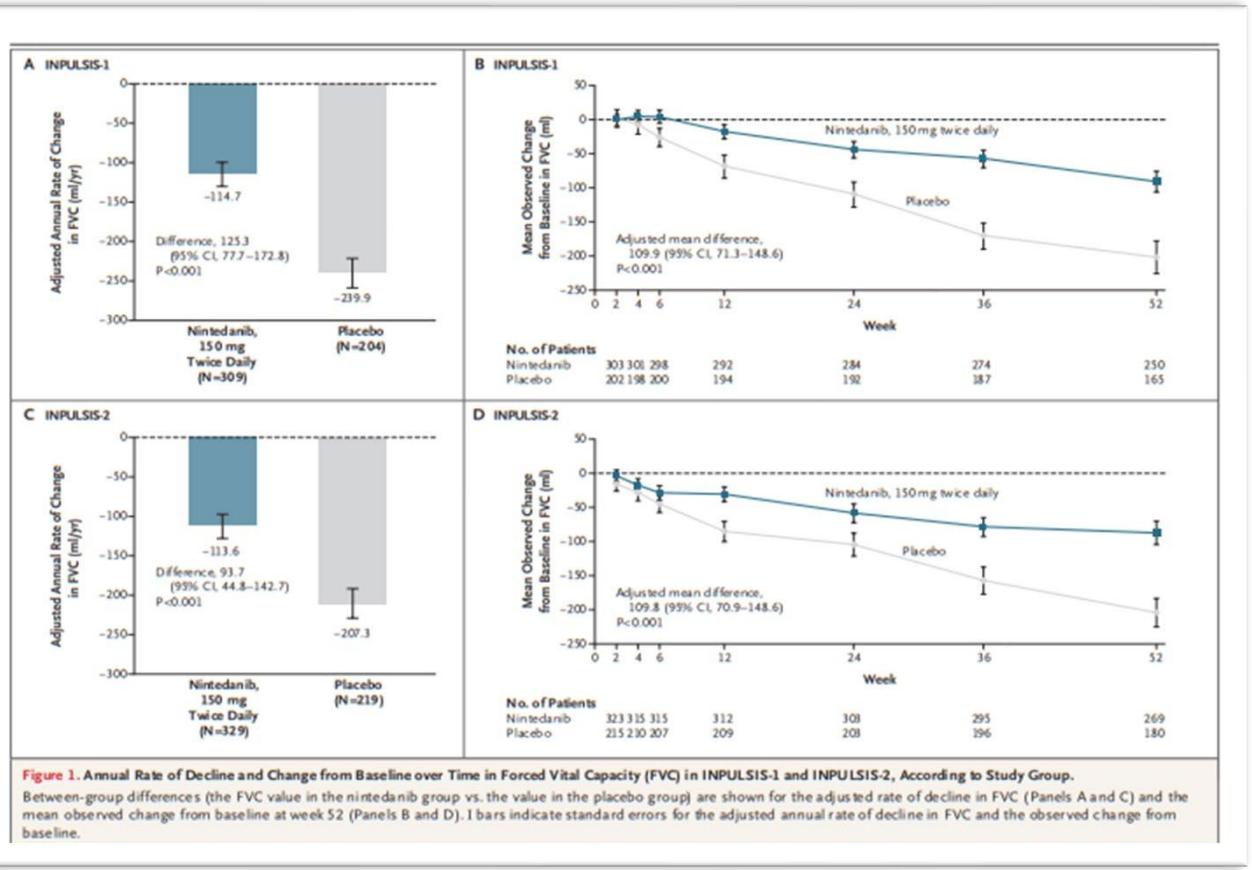



**Figure 1. Annual Rate of Decline and Change from Baseline over Time in Forced Vital Capacity (FVC) in INPULSIS-1 and INPULSIS-2, According to Study Group.**
Between-group differences (the FVC value in the nintedanib group vs. the value in the placebo group) are shown for the adjusted rate of decline in FVC (Panels A and C) and the mean observed change from baseline at week 52 (Panels B and D). I bars indicate standard errors for the adjusted annual rate of decline in FVC and the observed change from baseline.

## ABSTRACT

### BACKGROUND

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

### METHODS

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

### RESULTS

A total of 1066 patients were randomly assigned in a 3:2 ratio to receive nintedanib or placebo. The adjusted annual rate of change in FVC was –114.7 ml with nintedanib versus –239.9 ml with placebo (difference, 125.3 ml; 95% confidence interval [CI], 77.7 to 172.8; P<0.001) in INPULSIS-1 and –113.6 ml with nintedanib versus –207.3 ml with placebo (difference, 93.7 ml; 95% CI, 44.8 to 142.7; P<0.001) in INPULSIS-2. In INPULSIS-1, there was no significant difference between the nintedanib and placebo groups in the time to the first acute exacerbation (hazard ratio with nintedanib, 1.15; 95% CI, 0.54 to 2.42; P=0.67); in INPULSIS-2, there was a significant benefit with nintedanib versus placebo (hazard ratio, 0.38; 95% CI, 0.19 to 0.77; P=0.005). The most frequent adverse event in the nintedanib groups was diarrhea, with rates of 61.5% and 18.6% in the nintedanib and placebo groups, respectively, in INPULSIS-1 and 63.2% and 18.3% in the two groups, respectively, in INPULSIS-2.

### CONCLUSIONS

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

# Nintedanib

- 150 mg tablet , 2x1,300 mg/gün, PO

- KCFT ve BFT ilk üç ay ayda bir, sonrasında 3 ayda bir yapılır

# INPULSIS En Sık Advers Olaylar

| | Nintedanib (n=638) | Plasebo (n=423) |
|---|---|---|
| Diyare | 398 (62.4) | 78 (18.4) |
| Bulantı | 156 (24.5) | 28 (6.6) |
| Nazofarenjit | 87 (13.6) | 68 (16.1) |
| Öksürük | 85 (13.3) | 57 (13.5) |
| Kusma | 74 (11.6) | 11 (2.6) |
| İştahta azalma | 68 (10.7) | 24 (5.7) |
| Bronşit | 67 (10.5) | 45 (10.6) |
| IPF progresyonu* | 64 (10.0) | 61 (14.4) |
| Dispne | 49 (7.7) | 48 (11.3) |

Veriler hasta sayısı (%) şeklindedir. İki grupta da hastaların >%10'unda bildirilen advers olaylar gösterilmektedir. *Hastalık kötüleşmesi ve akut alevlenmeleri içeren 'IPF' MedDRA terimine tekabül etmektedir.

Tablo1 numaralı referanstan uyarlanmıştır

# Nintedanib

Kontrendikasyonlar:

- İlaca karşı aşırı duyarlılık
- GFR <30 ml/dk
- Orta derecede veya şiddetli karaciğer hasarı olan (Child-Pugh Sınıf B ve C)
- Kanama diyatezi olan, tam doz antikoagülan kullanımı
- Soya, yer fıstığı alerjisi

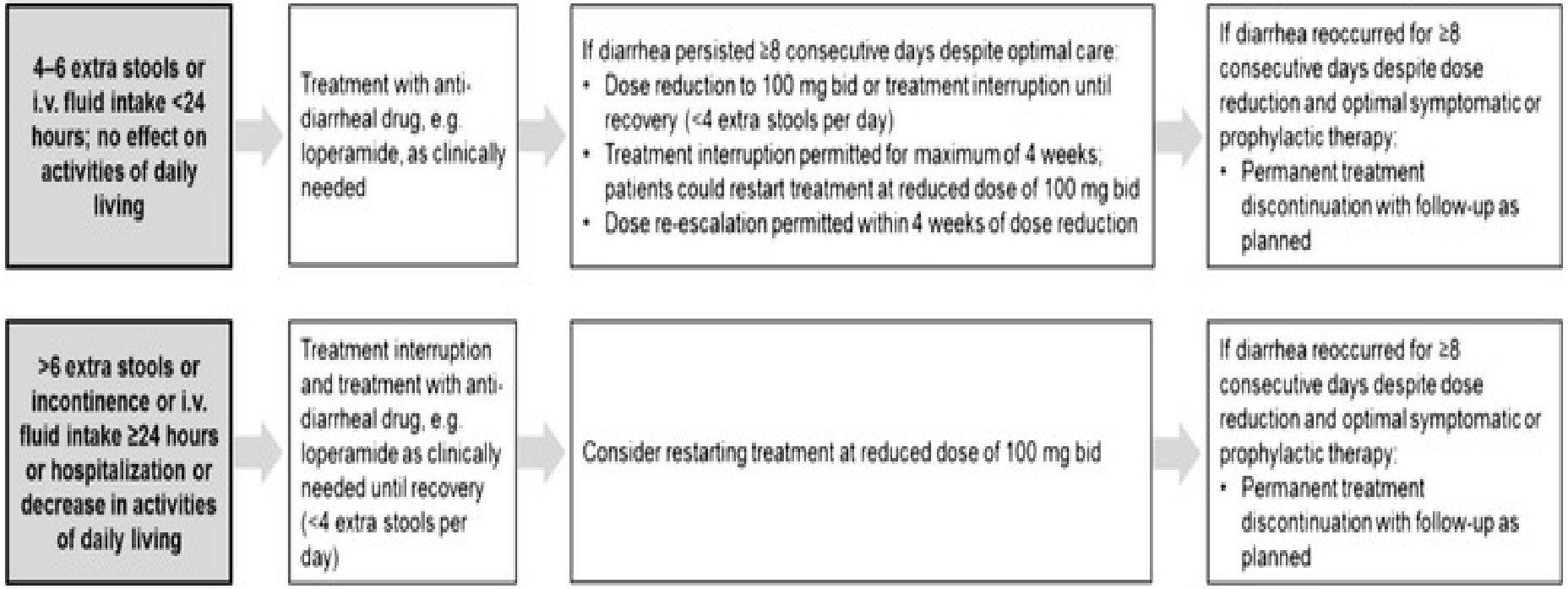
# Nintedanib başlanan hastada diyare gelişirse;

- Oral hidrasyon
- Loperamid 2x1 (4mg) başlanır, doz 8 tableti ( 16 mg) geçmemelidir.
- Eğer kontrol altına alınamazsa doz günde 2 kez 100 mg'a azaltılır.
- Kontrol edilemezse tedaviye ara verilebilir ( sonra 2x100 -2x150 mg ile başlanabilir)
- Yine kontrol edilemezse ilaç kesilir.

Respir Res. 2015; 16: 116.

Safety, tolerability and appropriate use of nintedanib in idiopathic pulmonary fibrosis

Tamera Corte, Francesco Bonella, Bruno Crestani, Maurits G. Demedts, Luca Richeldi, Carl Coeck, Katy Pelling, Manuel Quaresma, and Joseph A. Lasky




Algorithm for the management of diarrhea adverse events in the INPULSIS® trials. i.v., intravenous

# Nintedanib tedavisi sırasında KCFT yüksekliği

- Asemptomatik hastada AST–ALT değerleri normalin 3 katından daha fazla yükselirse doz azaltılabilir veya tedaviye ara verilebilir.
- Değerler normale döndüğünde doz 2x100 mg olarak başlatılır sonra doz arttırılabilir.
- KCFT değerlerindeki artışın diğer nedenleri araştırılmalıdır.
- KCFT değerlerinde artış klinik semptom ve bulgularla birlikteyse tedavi kesilmeli ve yeniden başlanmamalıdır.

Respir Res. 2015; 16: 116.

Safety, tolerability and appropriate use of nintedanib in idiopathic pulmonary fibrosis

Tamera Corte, Francesco Bonella, Bruno Crestani, Maurits G. Demedts, Luca Richeldi, Carl Coeck, Katy Pelling, Manuel Quaresma, and Joseph A. Lasky

| AST veya ALT Artışı | | |
|---|---|---|
| **ULN'nin 3 ila <5 katı düzeyine** | **ULN'nin 5 ila <8 katı düzeyine** | **ULN'nin ≥ 8 katı düzeyine veya ağır karaciğer hasarı belirtileri*** |
| **Doz 100 mg bid'e düşürülür VEYA nintedanib tedavisine ara verilir** | **Nintedanib tedavisine ara verilir** | **Nintedanib tedavisi kalıcı şekilde kesilir** |
| ALT, AST, AP, total bilirubin ve özonofiller dahil olmak üzere laboratuvar testleri 48-72 saat içinde ve klinik açıdan endike oldukça tekrarlanmalıdır | ALT, AST, AP, total bilirubin ve özonofiller dahil olmak üzere laboratuvar testleri 48-72 saat içinde ve klinik açıdan endike oldukça tekrarlanmalıdır | Rutin uygulamaya göre, laboratuvar testleri (örn. kimya, hematoloji, hepatit serolojisi, TSH, INR) ve abdominal ultrason dahil olmak üzere karaciğer hasarının ilave klinik değerlendirmeleri yapılmalıdır |
| ≥2 hafta sonra AST ve ALT <3x ULN düzeyine inerse:<br>• **Doz azaltıldıysa, 150 mg bid dozuna geri dönülür**<br>• **Tedaviye ara verildiyse, 100 mg bid dozunda tekrar başlanır**<br>• ≥8 hafta süresince (iki haftada bir) transaminazların takibine devam edilir<br>**≥2 hafta sonra AST veya ALT ≥3x ULN ise:**<br>Tedavi kalıcı şekilde kesilmeli ve hasta yakın gözlem altına alınmalıdır | 2 hafta veya daha uzun bir süre sonra AST ve ALT <3x ULN düzeyine inerse:<br>• **Tedaviye 100 mg bid dozunda tekrar başlanır**<br>• ≥8 hafta süresince (iki haftada bir) transaminazların takibine devam edilir<br>**≥2 hafta sonra AST veya ALT ≥3x ULN ise:**<br>Tedavi kalıcı şekilde kesilmeli ve hasta yakın gözlem altına alınmalıdır | |

# INPULSIS çalışmasında

- Tam doz antikoagülasyon tedavisi alan hastalar (örn., K vitamini antagonistleri, dabigatran, heparin, hirudin) veya yüksek doz antitrombositik tedavi alan hastalar çalışmaya dahil edilmemiştir
- Kanama advers olayları nintedanib alanlarda **(%10.3)** plasebo grubuna göre **(%7.8)** daha yüksek raporlanmıştır
- INPULSIS çalışmalarında ciddi kanama yaşayan hastaların oranı Nintedanib ve plasebo kollarında benzer olmuştur. (%1.3'e karşılık %1.4)

**Antikoagülasyon tedavisinin tam dozunu almakta olan hastalar dahil, kanama için risk taşıdığı bilinen hastalar yalnızca beklenen fayda, potansiyel riskten ağır basıyorsa nintedanib ile tedavi edilmeli****

**European Summary of Product Characteristics OFEV®, approved April 17, 2020. Available at www.ema.europa.eu/ [accessed February 2021]

## Inpulsis çalışmasında:

Plasebo ile karşılaştırıldığında nintedanib alan hastalarda daha fazla MI görülmüştür (% 1.6 ve %0.5)

- **Yüksek kardiyovasküler risk taşıyan hastalar (bilinen koroner arter hastalığı dahil) tedavi edilirken dikkatli olunmalıdır.****
- **Akut miyokard enfarktüsü belirti ve semptomları gelişen hastalarda tedaviye ara verilmesi düşünülmelidir.****

**European Summary of Product Characteristics OFEV®, approved April 17, 2020. Available at www.ema.europa.eu/ [accessed February 2021]

8 Avrupa ülkesinden 13 hekimin oluşturduğu bir multidisipliner uzman paneli, İPF hastalarında kombine antitrombotik ve Nintedanib kullanımına ilişkin önerilerini aşağıdaki tabloda özetlemiştir.

## Kombine antitrombotik ve Nintedanib tedavi önerileri

| Endikasyon | Antitrombotik tedavi | Nintedanib |
|---|---|---|
| **Aritmi** | | |
| $CHA_2DS\text{-}VASC \leq 1$ | YOK | **EVET** |
| $CHA_2DS\text{-}VASC \geq 2$ | 1: NOAC[1] ömür boyu | **EVET** |
| | 2: VKA[2, 3] ömür boyu | Dikkatle düşünülmelidir |
| **Anjina pektoris** | | |
| Stabil | ASA 75 mg/gün ömür boyu | **EVET** |
| Stabil + PCI[5] | ASA 75 mg/gün + klopidogrel 75 mg/gün 6 ay boyunca (3 ayı ikili) | Dikkatle düşünülmelidir |
| **Miyokard Enfarktüsü** | | |
| STEMI | 1. Fraksiyonlanmamış heparin[4]+ yüksek doz ASA + PCI[5] | Dikkatle düşünülmelidir |
| | 2. ASA 75 mg/day + klopidogrel 75 mg/gün | **EVET** |
| Non-STEMI | 1. Fondaparinaks[4]/LMWH[4] + yüksek doz ASA + yüksek doz klopidogrel | Dikkatle düşünülmelidir |
| | 2. ASA 75 mg/gün | **EVET** |

[1] Apiksaban, dabigatran, edoksaban ve rivaroksaban'ı içermektedir.
[2] İPF tedavisi için verilen VKA, mortalitede, hastaneye yatışlarda ve yan etkilerde artışla ilişkili bulunmuştur.
[3] Mekanik aort kapakçık için INR 2–3 ve mekanik mitral kapakçık için INR 2.5–3.5 olacak şekilde verilen tekli dozlar.
[4] Vücut ağırlığına göre tekli doz uygulaması
[5] Daha kısa süreli ikili antitrombin tedavisi verilmesini gerektiren bir stent. Örneğin bir Freedom stent™

*ASA, asetil salisilik asit; CHA2DS-VASC, CHADSVASC atriyal fibrilasyon risk skoru; NOAC, yeni nesil oral antikoagülanlar; PCI, perkutan koroner girişim; STEMI, ST-segment yükselmeli miyokard enfarktüsü; VKA, vitamin K antagonisti;*

Bendstrup, Elisabeth, et al. "Nintedanib in idiopathic pulmonary fibrosis: practi al management recommendations for potential adverse events." Respiration 97.2 (2019): 173-184.

EXPERT REVIEW OF RESPIRATORY MEDICINE
2019, VOL. 13, NO. 7, 601–614
https://doi.org/10.1080/17476348.2019.1627204

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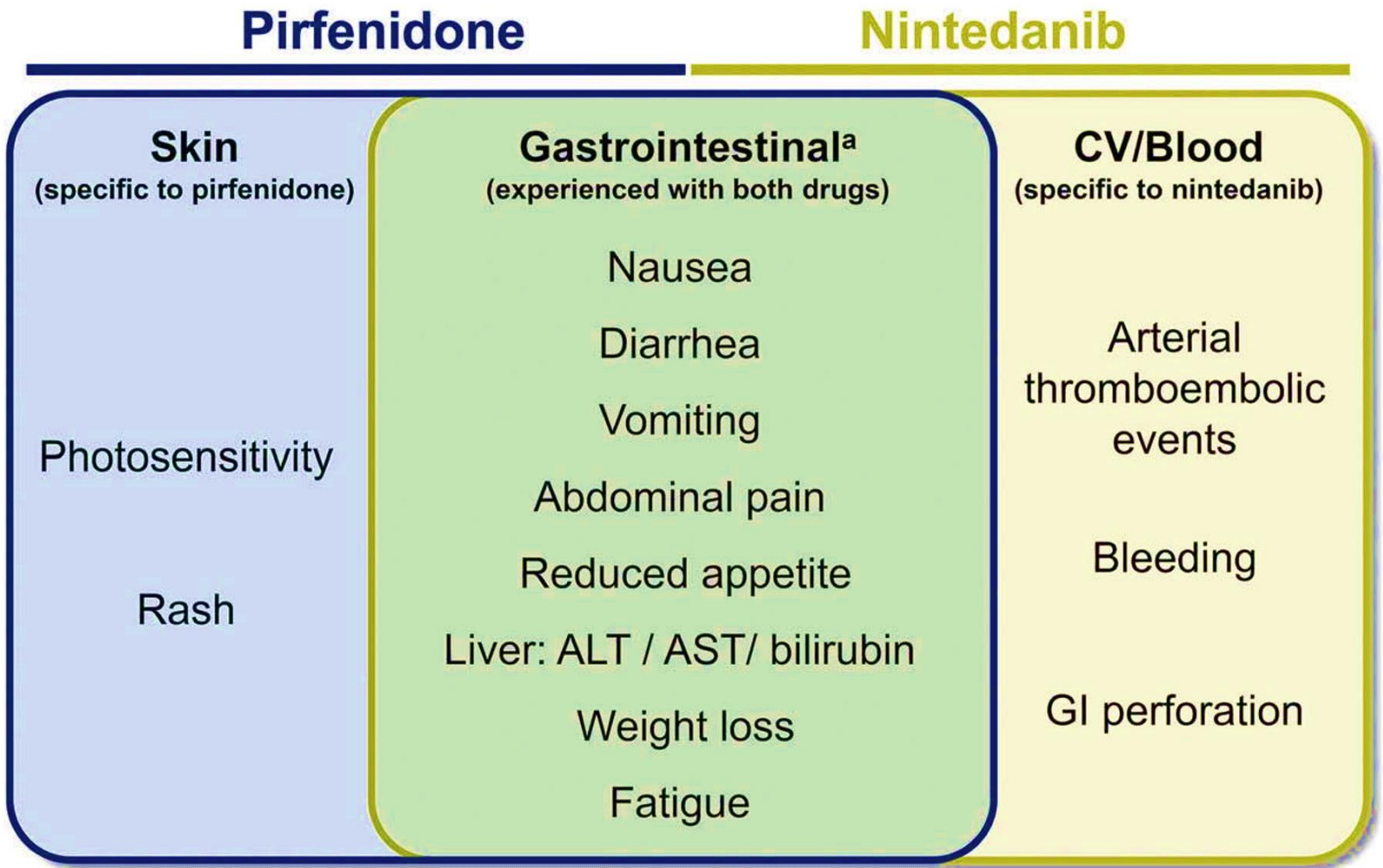
REVIEW



# A comprehensive and practical approach to the management of idiopathic pulmonary fibrosis

Onofre Moran-Mendoza[a], Rebecca Colman[b], Meena Kalluri[c], Czerysh Cabalteja[d] and Ingrid Harle[e]



Marijic et al. Respir Res (2021) 22:268
https://doi.org/10.1186/s12931-021-01857-y

Respiratory Research

RESEARCH Open Access

# Pirfenidone vs. nintedanib in patients with idiopathic pulmonary fibrosis: a retrospective cohort study

Pavo Marijic[1,2,3*], Larissa Schwarzkopf[1,2,4,5], Lars Schwettmann[1,6], Thomas Ruhnke[7], Franziska Trudzinski[8] and Michael Kreuter[8]

## Abstract

**Background:** Two antifibrotic drugs, pirfenidone and nintedanib, are licensed for the treatment of patients with idiopathic pulmonary fibrosis (IPF). However, there is neither evidence from prospective data nor a guideline recommendation, which drug should be preferred over the other. This study aimed to compare pirfenidone and nintedanib-treated patients regarding all-cause mortality, all-cause and respiratory-related hospitalizations, and overall as well as respiratory-related health care costs borne by the Statutory Health Insurance (SHI).

**Methods:** A retrospective cohort study with SHI data was performed, including IPF patients treated either with pirfenidone or nintedanib. Stabilized inverse probability of treatment weighting (IPTW) based on propensity scores was applied to adjust for observed covariates. Weighted Cox models were estimated to analyze mortality and hospitalization. Weighted cost differences with bootstrapped 95% confidence intervals (CI) were applied for cost analysis.

**Results:** We compared 840 patients treated with pirfenidone and 713 patients treated with nintedanib. Both groups were similar regarding two-year all-cause mortality (HR: 0.90 95% CI: 0.76; 1.07), one-year all cause (HR: 1.09, 95% CI: 0.95; 1.25) and respiratory-related hospitalization (HR: 0.89, 95% CI: 0.72; 1.08). No significant differences were observed regarding total (€− 807, 95% CI: €− 2977; €1220) and respiratory-related (€− 1282, 95% CI: €− 3423; €534) costs.

**Conclusion:** Our analyses suggest that the patient-related outcomes mortality, hospitalization, and costs do not differ between the two currently available antifibrotic drugs pirfenidone and nintedanib. Hence, the decision on treatment with pirfenidone versus treatment with nintedanib ought to be made case-by-case taking clinical characteristics, comorbidities, comedications, individual risk of side effects, and patients' preferences into account.

**Keywords:** Idiopathic pulmonary fibrosis, Mortality, Hospitalization, Health care costs, Administrative data, Drugs, Statutory health insurance

**Mortalite, hospitalizasyon sıklığı her iki ilaç grubunda benzer**

CHEST

# Comparison of Pirfenidone and Nintedanib

## Post Hoc Analysis of the CleanUP-IPF Study



**BACKGROUND:** Antifibrotics are effective in slowing FVC decline in idiopathic pulmonary fibrosis (IPF). However, whether antifibrotic type is differentially associated with FVC decline remains inconclusive.

**RESEARCH QUESTION:** Are there significant differences in 12-month FVC decline between pirfenidone and nintedanib?

**RESULTS:** Out of the 513 participants with IPF randomized in the CleanUP-IPF trial, 407 reported using pirfenidone (n = 264, 65%) or nintedanib (n = 143, 35%). The pirfenidone group had more participants with a history of coronary artery disease than the nintedanib group (34.1% vs 20.3%, respectively). Patients treated with nintedanib had a higher 12-month visit FVC than patients treated with pirfenidone (mean difference, 106 mL; 95% CI, 34-178). This difference was attenuated at the 24-month study visit. There were no significant differences in overall survival and nonelective respiratory hospitalization between the pirfenidone- and nintedanib-treated groups.

**INTERPRETATION:** Patients with IPF who used nintedanib had a slower 12-month FVC decline than pirfenidone in a post hoc analysis of a clinical trial. CHEST 2024; 165(5):1163-1173

**TABLE 2** ] Differences in FVC Between Nintedanib and Pirfenidone

| Visit | Mean FVC (95% CI), mL | | Mean Difference (95% CI) | *P* Value |
|---|---|---|---|---|
| | Nintedanib | Pirfenidone | | |
| Overall cohort | | | | |
| Baseline | 2,808 (2,800-2,819) | 2,806 (2,798-2,814) | 3 (−11 to 16) | .70 |
| 12 mo | 2,745 (2,687-2,804) | 2,640 (2,598-2,681) | 106 (34 to 178) | .004 |
| 24 mo | 2,471 (2,341-2,601) | 2,539 (2,451-2,627) | −68 (−225 to 89) | .39 |

## Take-home Points

**Study Question:** Are there differences in lung function trajectories by antifibrotic type in patients with idiopathic pulmonary fibrosis?

**Results:** Patients with idiopathic pulmonary fibrosis who reported to be using nintedanib had a slower 12-month decline in FVC than patients who used pirfenidone. There were no significant differences in survival and hospitalization.

**Interpretation:** Compared with patients who used pirfenidone, patients who used nintedanib had a slower decline in FVC over a period of 12 months.

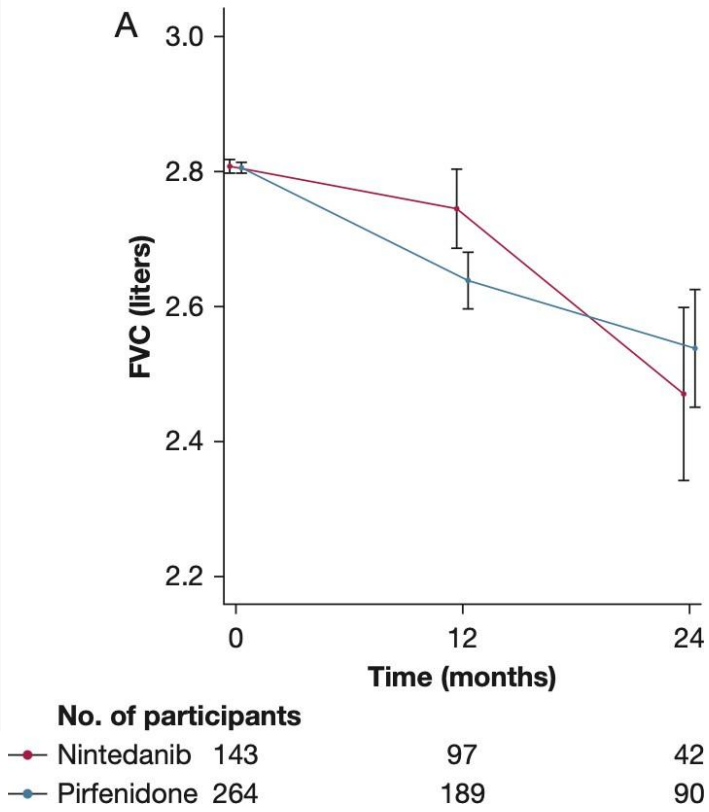
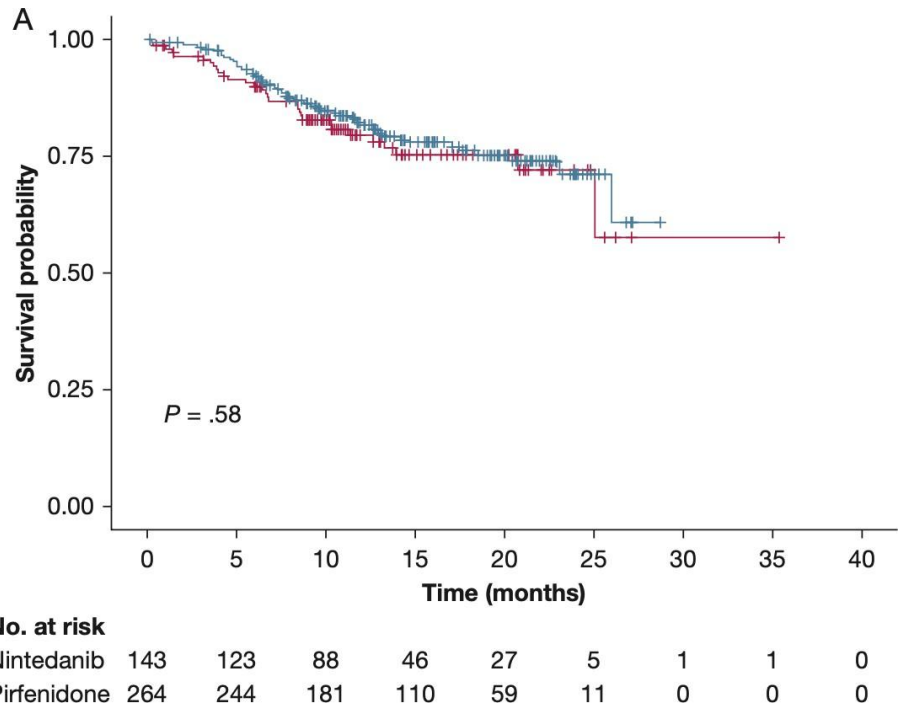
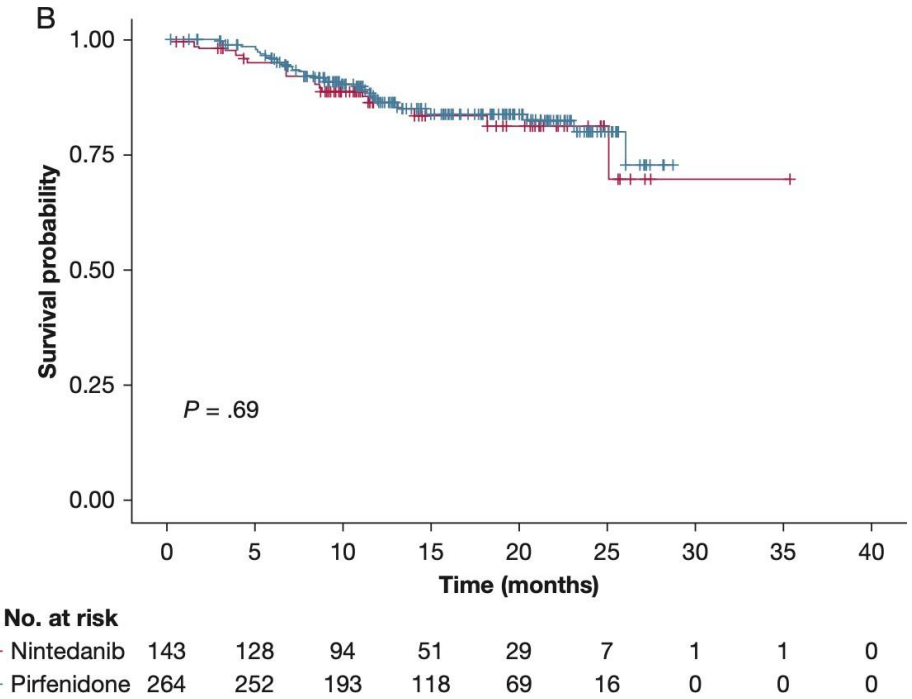


Figure 3 – *A, Time to composite outcome of death or nonelective respiratory hospitalization and (B) death by pirfenidone- and nintedanib-treated groups with log-rank*




Pirfenidon alan hastalarla karşılaştırıldığında; nintedanib grubunda 12 ay sonunda FVC'deki azalma daha yavaş bulunmuş, 24 ayın sonunda ise iki ilaç arasında anlamlı fark görülmemiş.

Sağkalım ve hospitalizasyon sıklığı her iki ilaç kolunda benzer bulunmuş.

CHEST 2024; 165(5):1163-1173

Meta-Analysis > Eur J Clin Pharmacol. 2024 Oct;80(10):1445-1460.
doi: 10.1007/s00228-024-03720-7. Epub 2024 Jul 4.

# Real-world safety and effectiveness of pirfenidone and nintedanib in the treatment of idiopathic pulmonary fibrosis: a systematic review and meta-analysis

**Conclusion:** The results of this study indicate that pirfenidone and nintedanib are both effective in slowing down the decline of lung function in IPF patients in real-world settings. The incidence of adverse events with pirfenidone is lower than that with nintedanib, but both are below the clinical trial data, and no new major adverse events have been observed. The discontinuation rates due to adverse reactions of the two drugs are consistent with clinical trial data, indicating good tolerability. However, the mortality rates and AE-IPF incidence rates of these two drugs in real-world settings are higher than those in previous clinical trials, with pirfenidone patients showing a higher mortality rate. Further large-sample studies are needed to investigate the risks of these drugs in these aspects. Additionally, we recommend that future real-world studies pay more attention to patients' subjective symptoms and conduct stratified analyses of the efficacy and safety of pirfenidone and nintedanib based on factors such as patients' baseline lung function, comorbidities, and age, in order to provide more personalized medication advice for IPF patients in clinical practice.

**Pirfenidon ve nintedanib İPF hastalarında FVC'deki azalmayı yavaşlatmada etkili**

**Advers olay insidansı her iki ilaçda da klinik çalışma verilerinin altında**

**İki ilaç da tolere edilebilir ve mortalite ve AE-İPF insidans oranları önceki klinik çalışmalara göre daha yüksek bulunmuş.**

**İPF tanılı hastalarda antifibrotik tedavi başlama kriterleri**

- HRCT ve/veya akciğer biyopsisi ile UİP paterni saptanan olgular
- FVC ≥ %50, DLCO ≥ %30 olan hafif ve orta düzeydeki olgular
- Bağ dokusu belirteçleri negatif olgular

- Tromboemboli veya kardiyovasküler hastalık öyküsü
- Antikoagülan kullanan
- Child Pugh sınıf B karaciğer yetmezliği
- Soya fasulyesi yer fıstığı alerjisi

→ **Pirfenidon**

- Güneşe fazla maruziyeti olan
- Cilt hastalığına yatkın ( özellikle güneş ışığına hassasiyeti olanlar)

→ **Nintedanib**

# İPF tedavi algoritması

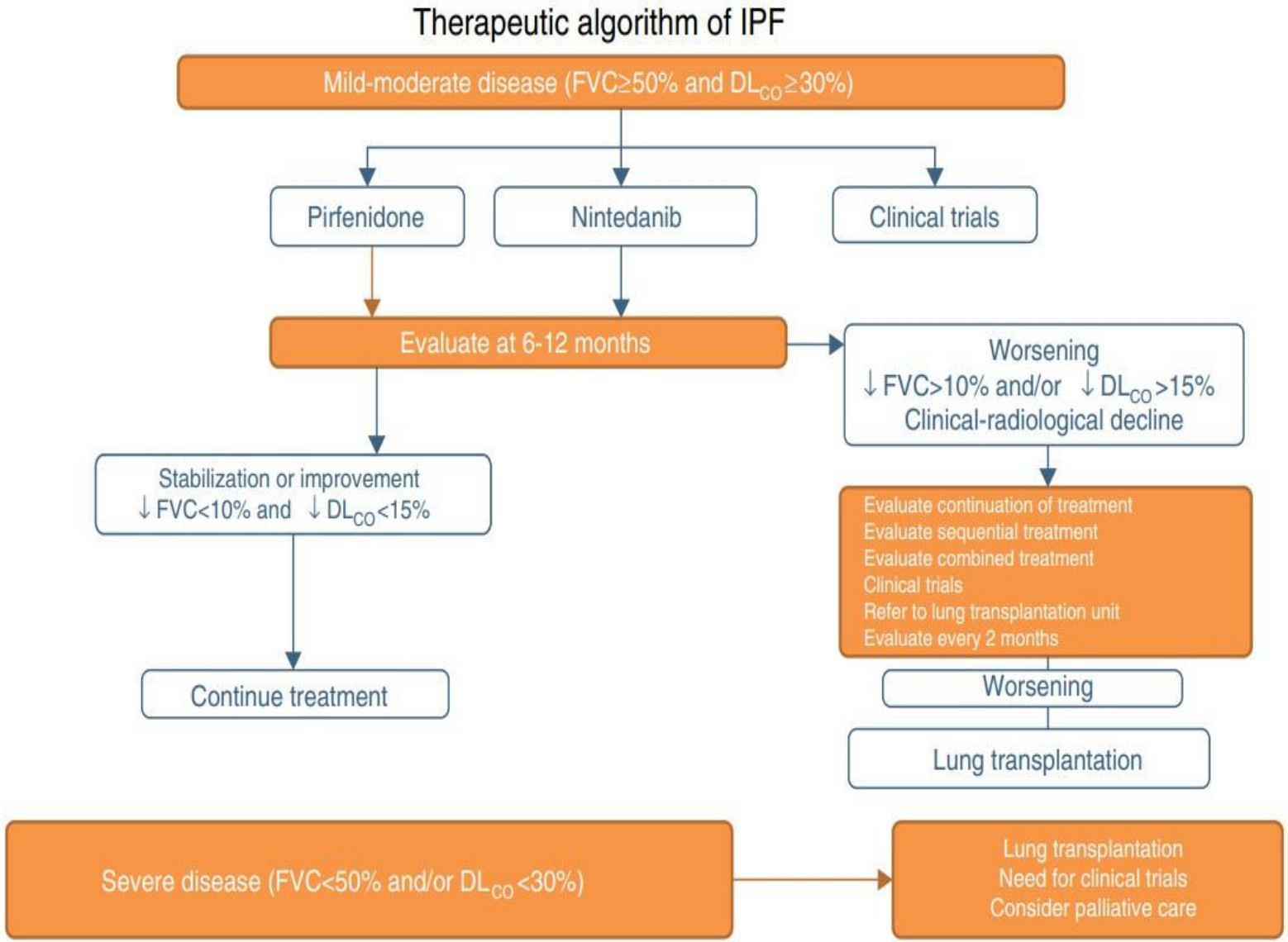



**Fig. 1.** IPF pharmacological treatment algorithm. FVC: forced vital capacity; $DL_{CO}$: carbon monoxide diffusing capacity.

# İzlem

- 4-6 ayda bir ( gereklilik halinde daha erken);
- Hastanın fonksiyonel durumu değerlendirilmelidir (**FVC**, DLCO, **6 DYT**, spO2)
- Hastalar ilaç devamı açısından 12 ayda bir değerlendirilmelidir.
- Bir önceki sağlık kurulu raporu değerine göre (ataklar dışında) FVC değerinin ≥ %10 düşme olması ilaca yanıtsızlık olarak kabul edilir ve tedavi sonlandırılır.
- İlaçlardan birine intolerans gelişmişse ilaçlar arasında geçiş yapılabilir.

# İPF’de Nonfarmakolojik Tedavi

- Sigaranın bıraktırılması
- USOT
- HFO ve NIMV
- Pulmoner rehabilitasyon
- Akciğer transplantasyonu
- Aşılama

# Uzun süreli oksijen tedavisi

- İstirahat hipoksemisi olan hastalara,
- Yalnızca efor esnasında hipoksemi olan hastalarda sağ kalımı iyileştirip iyileştirmediği bilinmemekle birlikte verilebilir


- Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011; 183: 788-824
- Cottin V, Crestani B, Valeyre D, et al. Diagnosis and management of idiopathic pulmonary fibrosis: French practical guidelines. Eur Respir Rev 2014; 23: 193–214. Hardinge M, Annandale J, Bourne S, et al. British Thoracic Society guidelines for home oxygen use in adults. Thorax 2015; 70: Suppl. 1, i1–i43.

**Tablo 2. Akciğer nakli için sevk ve listeleme için hastalığa özgü spesifik kriterler.***

| Akciğer Hastalığı | Yönlendirme zamanı | Listeleme zamanı |
|---|---|---|
| Kronik obstrüktif akciğer hastalığı (KOAH) | Maksimal tedaviye rağmen kötüleşme (ilaç, ek oksijen ve pulmoner rehabilitasyon dahil).<br>Hasta endoskopik veya cerrahi akciğer hacmini azaltma cerrahisi (LVRS) için uygun değil.<br>BODE indeksi 5-6.<br>$PaCO_2$ > 50 mmHg (veya 6.6kPa) ± $PaO_2$ < 60 mmHg (veya 8kPa).<br>$FEV_1$ < %25. | BODE indeksi ≥ 7 veya aşağıdakilerden en az biri:<br>• $FEV_1$ < %20 tahmin edildi.<br>• Bir önceki yıl boyunca üç şiddetli alevlenme.<br>• Akut hiperkapnik solunum yetmezliği olan en az bir şiddetli alevlenme.<br>• Orta ila şiddetli pulmoner hipertansiyon. |
| İnterstisyel akciğer hastalığı (İAH) | Histopatolojik veya radyografik değerlendirmede:<br>• Usual interstisyel pnömonit (UIP) veya<br>• Fibrozan nonspesifik interstisyel pnömonit (NSIP)<br>Akciğer fonksiyon bozukluğu:<br>• FVC < %80.<br>• DLCO < %40<br>Akciğer hastalığından kaynaklanan dispne veya fonksiyonel kısıtlılık.<br>Oksijen desteği gereksinimi.<br>İnflamatuar İAH için medikal tedaviye rağmen dispnede, oksijen ihtiyacında ve/veya akciğer fonksiyonlarında düzelme olmaması | • Altı aylık takipte FVC'de ≥ %10 düşüş .<br>• Altı aylık takipte DLCO'da ≥ %15 düşüş<br>• Altı dakika yürüme testi:<br>- Desatürasyon < %88 veya<br>- Yürüme mesafesi < 250 m, veya<br>- Altı aylık takipte yürüme mesafesindeki düşüş > 50 m<br>• Pulmoner hipertansiyon:<br>- Sağ kalp kateterizasyonunda veya<br>- Ekokardiyografide<br>• Hastane yatışı:<br>- Solunum yetmezliği ile veya<br>- Pnomotoraks ile veya<br>- Akut alevlenme ile |

# Acute Exacerbation of Idiopathic Pulmonary Fibrosis

## An International Working Group Report

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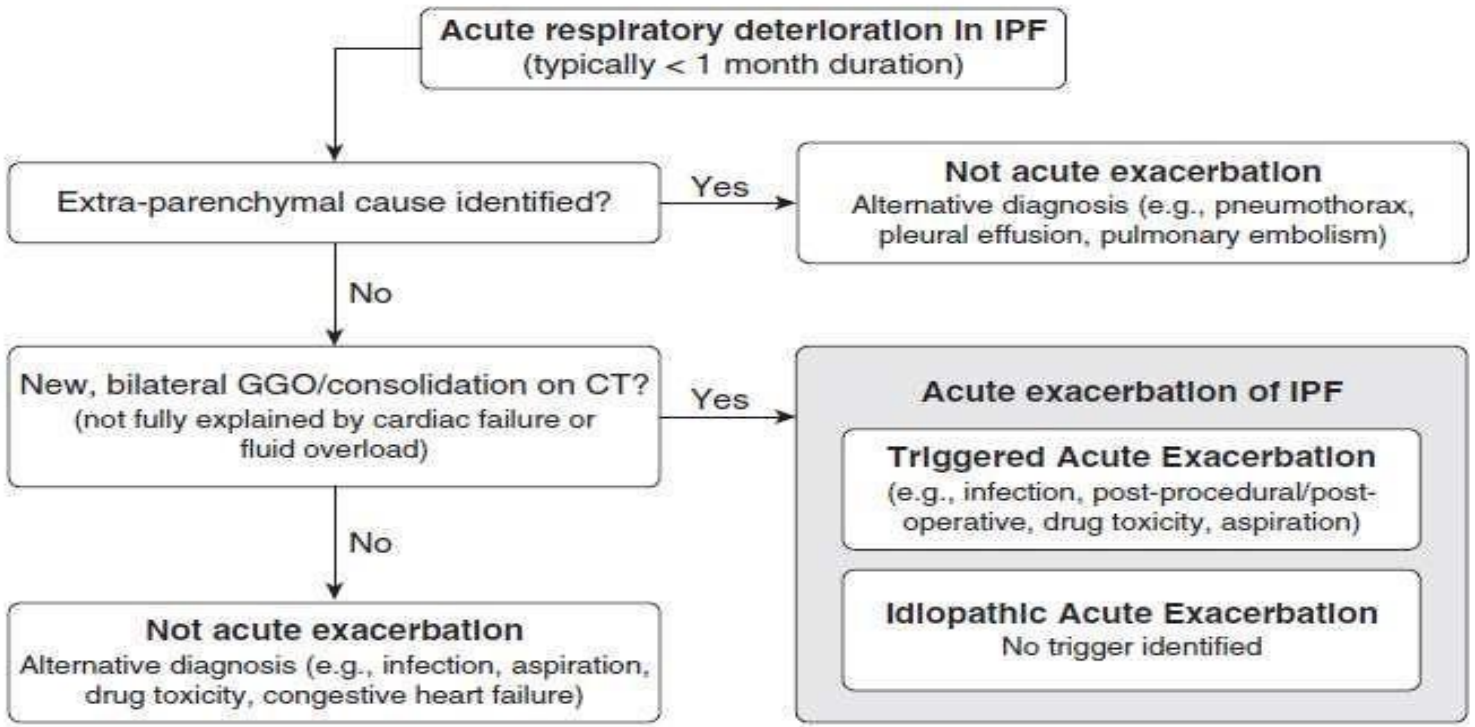
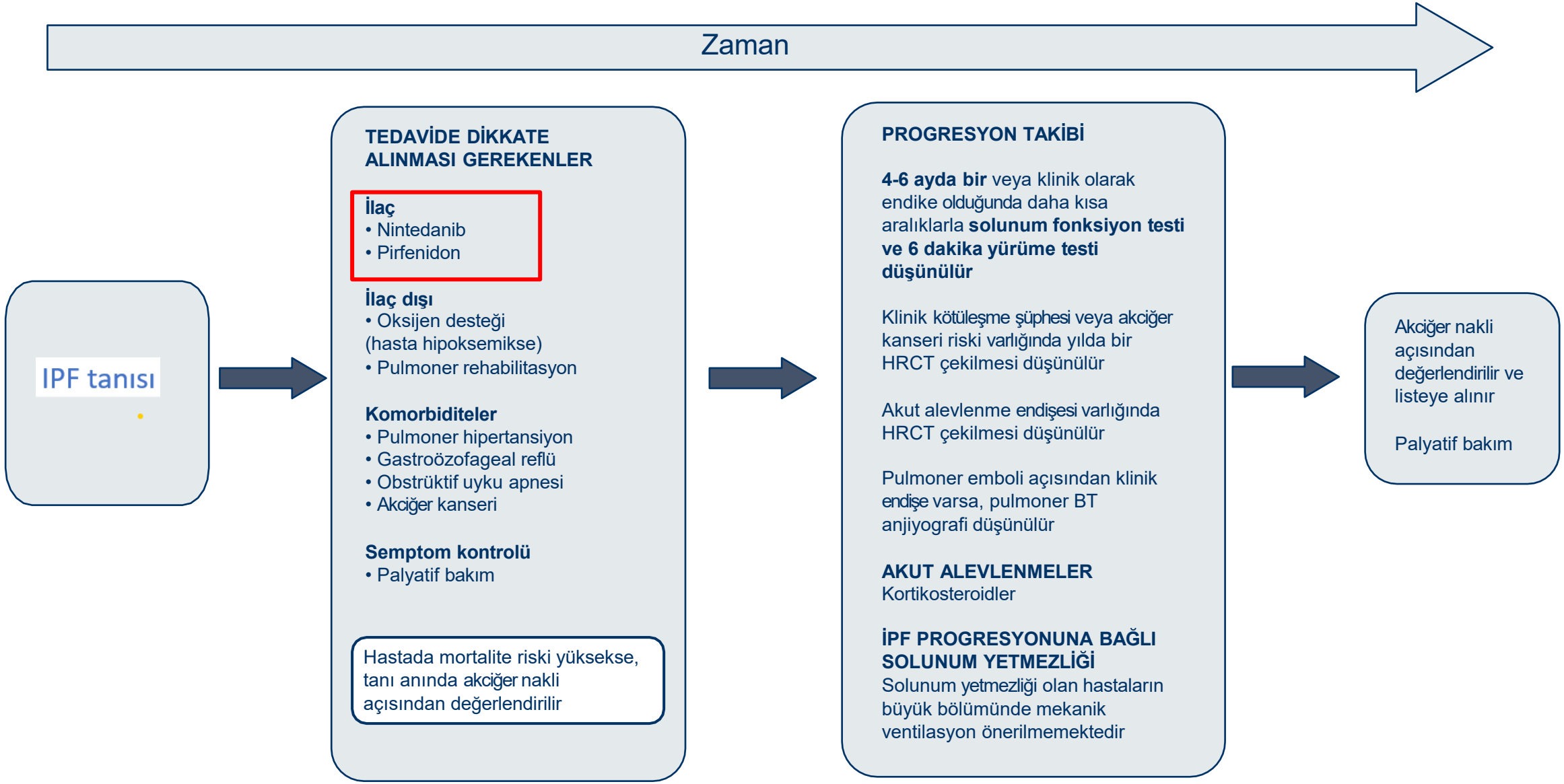


# AE-İPF Tedavi

- Kortikosteroid
- Oksijen ( Nazal kanül, maske, HFNC)
- Mekanik ventilasyon (NİMV-İMV?)
- Opioidler




Raghu G et all. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. American Journal of Respiratory and Critical Care Medicine Volume 205 Number 9 | May 1 2022

**Table 2** Summary of available therapies for PF based on scientific society guidelines

| Line of Treatment | Therapy | Mechanism of Action | Route of Administration | Key Recommendations (ATS/ERS/JRS/ALAT) |
|---|---|---|---|---|
| **First-line** | Pirfenidone | Antifibrotic; anti-inflammatory; modulates growth factors (TGF-β, PDGF); inhibits fibroblast proliferation and collagen synthesis, and antioxidant. | Oral | Conditional recommendation for use in PF. Recommended if lung capacity is 50–80% expected. |
| | Nintedanib | Tyrosine kinase inhibitor targeting PDGF, FGF, and VEGF receptors; inhibits fibroblast proliferation, migration, and differentiation. | Oral | Conditional recommendation for use in PF. Recommended if lung capacity is 50–80% expected. |
| **Supportive care (Throughout)** | Oxygen therapy | Supplemental oxygen to alleviate hypoxemia. | Inhalation | Recommended for patients with hypoxemia to improve breathing, exercise tolerance, and potentially reduce complications. |
| | Pulmonary rehabilitation | Exercise training; breathing techniques; education; nutritional and psychological support. | Program-based | Strongly recommended to improve exercise capacity, reduce breathlessness, and enhance overall well-being. |
| | Vaccinations (influenza, pneumococcal) | Prevention of respiratory infections. | Injection | Recommended to prevent exacerbations. |
| | Smoking cessation | Eliminating a major risk factor for lung disease. | Behavioral/Pharmacological | Strongly recommended for current smokers. |
| | Nutritional support & lifestyle | Maintaining a healthy diet; regular exercise within tolerance, and adequate rest. | Lifestyle modifications | Advised for managing symptoms and maintaining overall health. |
| **Later-Stage/ Severe Disease** | Lung transplantation | Surgical replacement of diseased lungs with healthy donor lungs. | Surgical | Potential option for selected patients with severe and progressive PF who meet specific criteria. Early referral for evaluation is recommended. |
| **Management of acute exacerbations** | Corticosteroids | Anti-inflammatory. | Oral/Intravenous | Recommended for treating acute worsening of symptoms. |

Abbreviations: AST, American Thoracic Society; ERS, European Respiratory Society; JRS, Japanese Respiratory Society; ALAT, Latin American Thoracic Association

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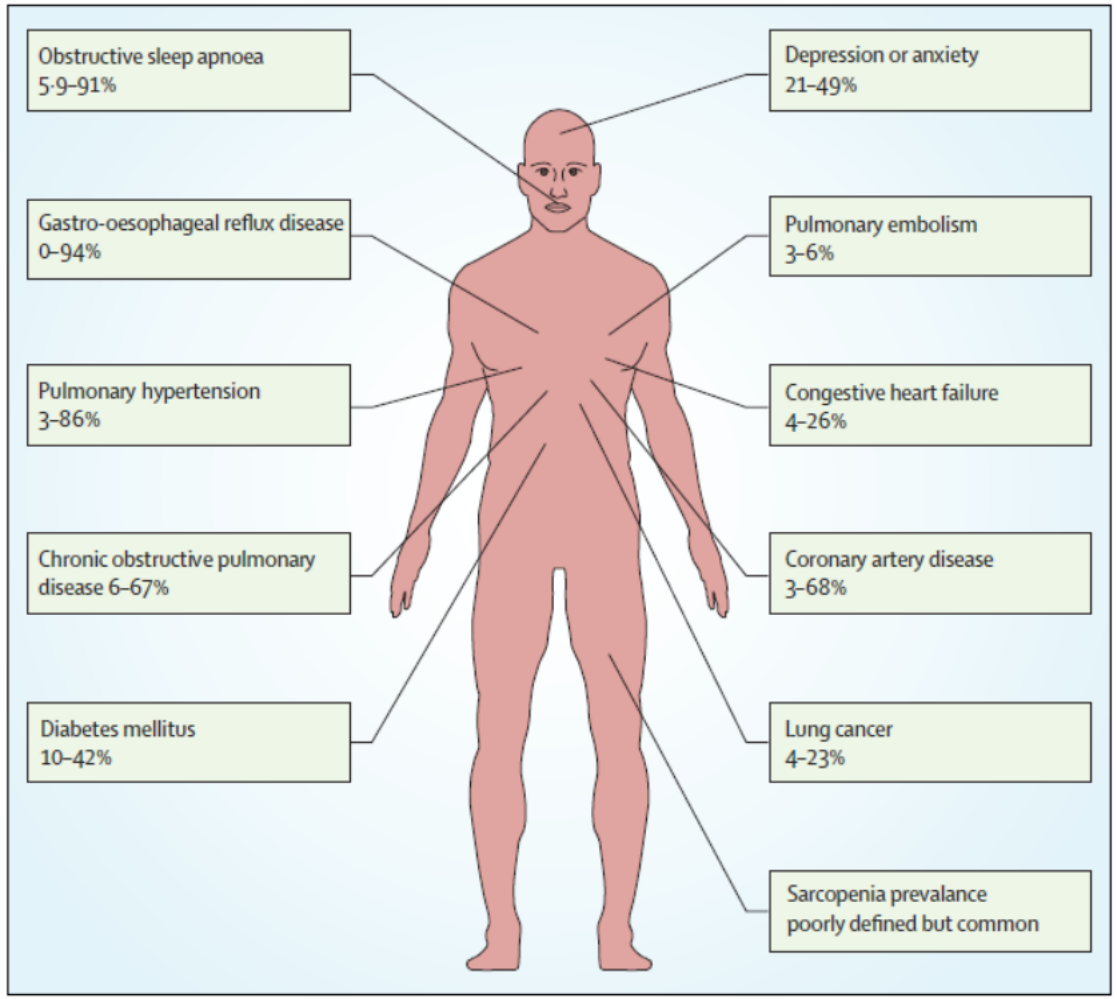
# İPF- Komorbiditeler



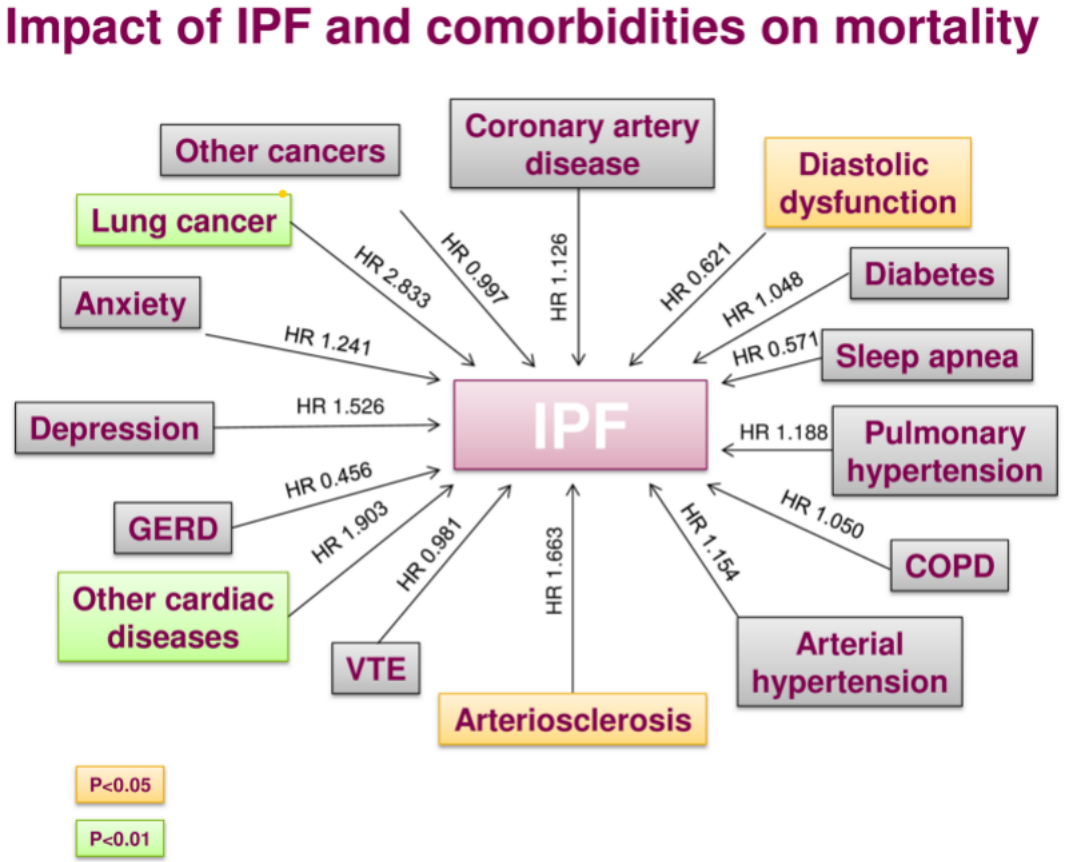




**Fig 5. Impact of idiopathic pulmonary fibrosis and comorbidities on mortality.** Hazard ratios (HR) have been determined using a predictive multivariate Cox proportional hazards regression model.

doi:10.1371/journal.pone.0151425.g005

Lee et al. BMC Pulmonary Medicine (2023) 23:54
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RESEARCH Open Access

# Epidemiology and comorbidities in idiopathic pulmonary fibrosis: a nationwide cohort study



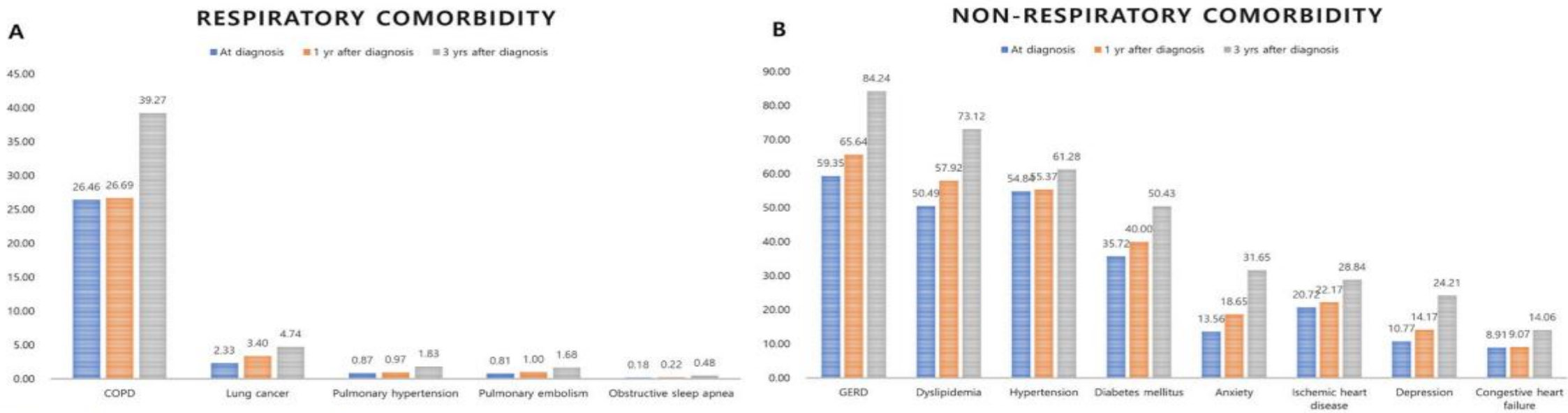
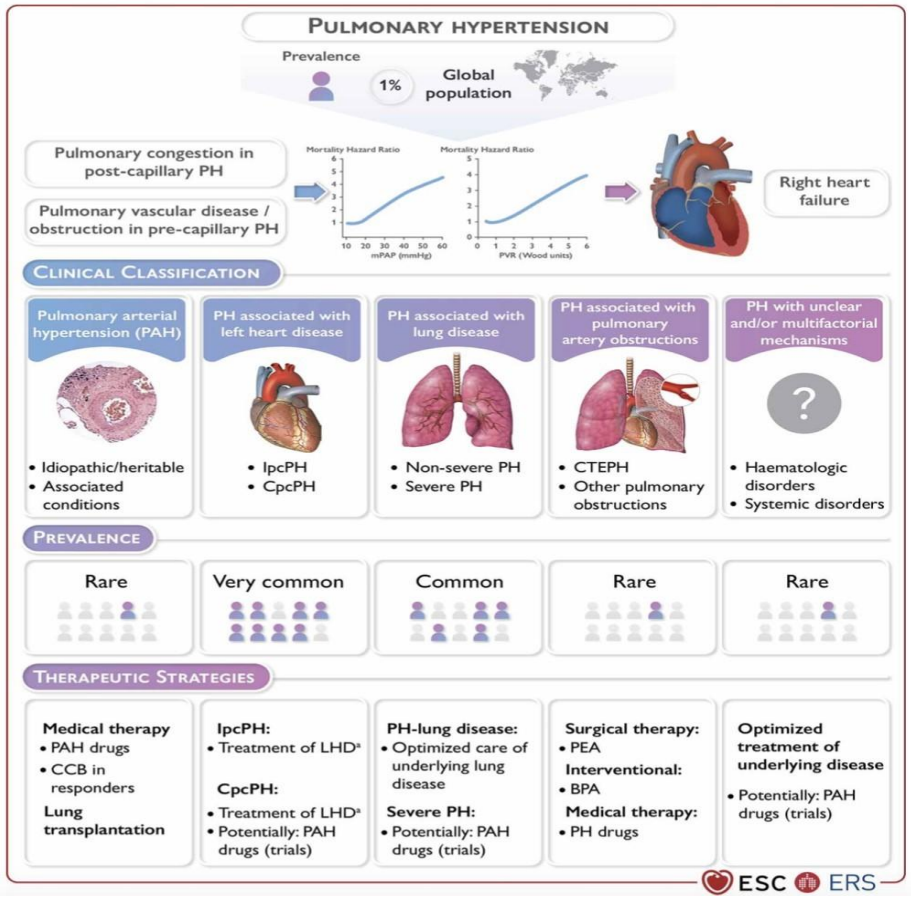
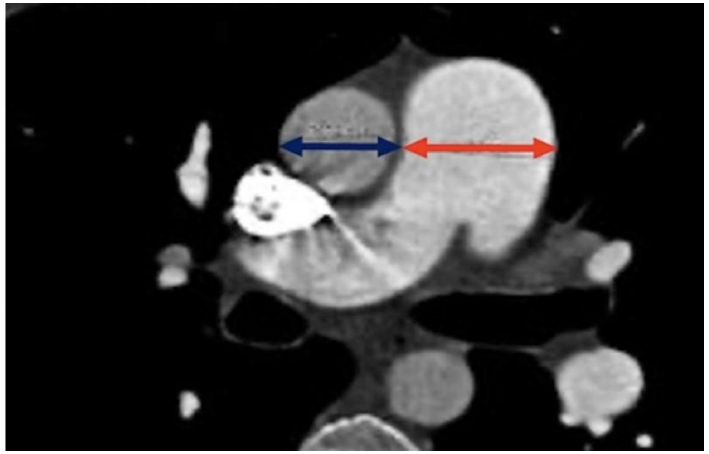



**Fig. 2** Prevalence of comorbidities in patients with idiopathic pulmonary fibrosis at the time of diagnosis (blue), 1 year after diagnosis (orange) and 3 years after diagnosis (grey). We presented the change of prevalence at three different time points of respiratory comorbidities (**A**) and non-respiratory comorbidities (**B**) Abbreviations: GERD, gastro-oesophageal reflux disease; COPD, chronic obstructive pulmonary disease

# İPF'DE Pulmoner Hipertansiyon

PA/aort çap > 1:1
PA>29 mm



## Treatment for disease complications

Pulmonary rehabilitation
Pulmonary hypertension: inhaled treprostinil
Respiratory failure: oxygen
End-stage disease: lung transplant
Management of symptoms (eg, cough and breathlessness)

ORIGINAL ARTICLE

# Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease

Aaron Waxman, M.D., Ph.D., Ricardo Restrepo-Jaramillo, M.D.,

**Table 2. Summary of Primary and Secondary End Points.***

| End Point | Inhaled Treprostinil (N=163) | Placebo (N=163) | Treatment Effect (95% CI) | P Value |
|---|---|---|---|---|
| **Primary end point** | | | | |
| Change in peak 6-minute walk distance from baseline to wk 16 — m† | 21.08±5.12 | −10.04±5.12 | 31.12±7.25 (16.85 to 45.39)‡ | <0.001 |
| **Secondary end points§** | | | | |
| Change in plasma concentration of NT-proBNP from baseline to wk 16¶ | | | | |
| Mean (±SD) change — pg/ml | −396.35±1904.90 | 1453.95±7296.20 | | |
| Median — pg/ml | −22.65 | 20.65 | | |
| Range — pg/ml | −11,433.0 to 5373.1 | −5483.3 to 87,148.3 | | |
| Ratio to baseline | 0.85±0.06 | 1.46±0.11 | 0.58±0.06 (0.47 to 0.72)‖ | <0.001 |
| Occurrence of clinical worsening — no. (%) | | | 0.61 (0.4 to 0.92)** | 0.04 |
| Any event | 37 (22.7) | 54 (33.1) | | |
| Hospitalization for cardiopulmonary indication | 18 (11.0) | 24 (14.7) | | |
| Decrease in 6-minute walk distance of >15% from baseline | 13 (8.0) | 26 (16.0) | | |
| Death from any cause | 4 (2.5) | 4 (2.5) | | |
| Lung transplantation | 2 (1.2) | 0 | | |
| Least-squares mean change in peak 6-minute walk distance from baseline to wk 12 — m† | 18.77±4.99 | −12.52±5.01 | 31.29±7.07 (17.37 to 45.21)‡ | <0.001 |
| Least-squares mean change in trough 6-minute walk distance from baseline to wk 15 — m | 9.3±5.5 | −12.7±5.5 | 21.99±7.7 (6.85 to 37.14)‡ | 0.005†† |

# Long-term inhaled treprostinil for pulmonary hypertension due to interstitial lung disease: INCREASE open-label extension study

Aaron Waxman [1], Ricardo Restrepo-Jaramillo [2], Thenappan Thenappan [3], Peter Engel [4], Abubakr Bajwa [5],

## Abstract

***Introduction*** The 16-week randomised, placebo-controlled INCREASE trial (RCT) met its primary end-point by improving 6-min walk distance (6MWD) in patients receiving inhaled treprostinil for pulmonary hypertension due to interstitial lung disease (PH-ILD). The open-label extension (OLE) evaluated long-term effects of inhaled treprostinil in PH-ILD.

***Methods*** Of 258 eligible patients, 242 enrolled in the INCREASE OLE and received inhaled treprostinil. Assessments included 6MWD, pulmonary function testing, N-terminal pro-brain natriuretic peptide (NT-proBNP), quality of life and adverse events. Hospitalisations, exacerbations of underlying lung disease and death were recorded.

***Results*** At INCREASE OLE baseline, patients had a median age of 70 years and a mean 6MWD of 274.2 m; 52.1% were male. For the overall population, the mean 6MWD at week 52 was 279.1 m and the mean change from INCREASE RCT baseline was 3.5 m (22.1 m for the prior inhaled treprostinil arm and −19.5 m for the prior placebo arm); the median NT-proBNP decreased from 389 $pg \cdot mL^{-1}$ at RCT baseline to 359 $pg \cdot mL^{-1}$ at week 64; and the absolute (% predicted) mean forced vital capacity change from RCT baseline to week 64 was 51 mL (2.8%). Patients who received inhaled treprostinil *versus* placebo in the RCT had a 31% lower relative risk of exacerbation of underlying lung disease in the OLE (hazard ratio 0.69 (95% CI 0.49–0.97); p=0.03). Adverse events leading to drug discontinuation occurred in 54 (22.3%) patients.

***Conclusions*** These results support the long-term safety and efficacy of inhaled treprostinil in patients with PH-ILD, and are consistent with the results observed in the INCREASE RCT.

## Introduction

Pulmonary hypertension (PH) frequently complicates the course of most fibrosing interstitial lung diseases (ILDs) [1]. Between 15% and 86% of patients with ILD may develop PH, which is then associated with further impaired exercise tolerance, decreased quality of life and a poor prognosis [2, 3]. Prior to March 2021, no therapies were approved for treating PH due to ILD (PH-ILD). Vasodilators used for pulmonary arterial hypertension (PAH) have been utilised off-label with mixed success, sometimes even causing harm [4, 5].

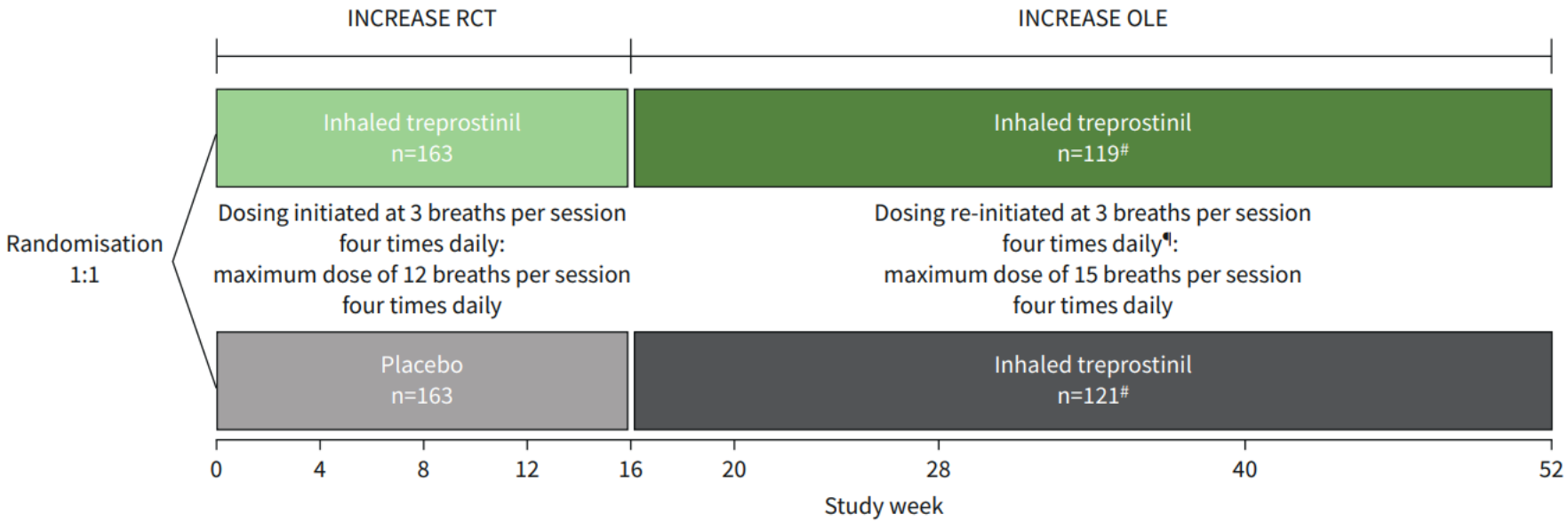



**FIGURE 1** Study schema: INCREASE randomised controlled trial (RCT) and open-label extension (OLE). #: two additional patients entered the OLE who were excluded from the RCT due to a labelling issue; ¶: patients receiving >3 breaths per session four times daily at week 16 of the RCT had their dose reduced to 3 breaths per session four times daily at the start of the OLE.

In conclusion, the INCREASE OLE demonstrated the safety of long-term inhaled treprostinil in patients with PH-ILD. No new safety signals were observed and the rate of cough decreased with a longer treatment duration. The safety profile was accompanied by maintained exercise capacity and increased FVC, despite challenges associated with the COVID-19 pandemic. Overall, these long-term results are consistent with the findings from the parent INCREASE study and lend further support to the study of the potential antifibrotic effects of inhaled treprostinil.

# İPF’li hastalarda akciğer kanseri gelişimi

- İPF'li hastalarda akciğer kanseri görülme sıklığı zamanla artar
- 1. yılda %3,
- 3,5. yılda %15,4
- 10. yılda %54,7.
- En sık görülen histolojik tümör tipi skuamöz hücreli karsinom
- Tümörlerin %81'i akciğer periferinde, %56'sı ise alt lobda yerleşir.
- Çoğunluğu (%70) fibrotik bölgede görülür.

- *Düşük doz BT ile yıllık akciğer kanseri taraması*

# İPF'de mortalite nedenleri

1. Solunum yetmezliği (%60)
2. Kardiyovasküler hastalık (%8.5)
3. Akciğer kanseri (%2.9)

Respiration

Clinical Investigations

Respiration
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# Nintedanib in IPF: Post hoc Analysis of the Italian FIBRONET Observational Study

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Christian Amici[g] Giovanna Crespi[h] Benedetta Campolo[h] Carlo Vancheri[i]
on behalf of the FIBRONET study group

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**Keywords**
Idiopathic pulmonary fibrosis · Nintedanib · Antifibrotic treatment · Observational study · Lung function

**Abstract**
***Background:*** The FIBRONET study was an observational study of patients with idiopathic pulmonary fibrosis (IPF) in Italy. ***Objectives:*** In this post hoc descriptive analysis, we describe changes in lung function, anxiety/depression, coughing, exacerbations, and adverse events (AEs) in patients receiving nintedanib treatment. ***Methods:*** Patients with IPF from 20 centers in Italy, aged ≥40 years who received nintedanib for ≥7 months, were followed up for 12 months from study enrollment, attending clinic visits every 3 months. Outcomes included change in forced vital capacity (FVC)% predicted from baseline to 12 months, anxiety/depression measured by the Hospital Anxiety and Depression Scale (HADS), and the proportion of patients with cough, AEs, and exacerbations. ***Results:*** In total, 52 patients received nintedanib (mean duration of 11.6 months). Ten patients had dose reductions from 150 mg to 100 mg twice daily, due to AEs. FVC% predicted was unchanged in the overall nintedanib population (78.7% at baseline; 79.8% at 12 months) and those with a reduced dose (77.7% at baseline; 81.0% at 12 months). HADS score was low at baseline and throughout the study. The proportion of patients with cough decreased from 50.0% to 21.2% over 12 months. Two patients experienced exacerbations, 2 patients discontinued treatment, and 27 (51.9%) reported AEs. The most common AE was diarrhea (34.6%). ***Conclusions:*** In patients with IPF who received nintedanib in the FIBRONET study, FVC% predicted was stable over 12 months, and the proportion of patients with cough decreased. The safety profile was consistent with the known safety profile for nintedanib in IPF.



Benedetta Campolo was an employee of Boehringer Ingelheim (Italy) at the time of this study.
Trial registration: This study was registered at clinicaltrials.gov; https://clinicaltrials.gov/ct2/show/NCT02803580.

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**Nintedanib ile öksürük %5'den %21'e gerilemiştir.**

Pirfenidon öksürüğü %34 azaltmıştır

# Effect of pirfenidone on cough in patients with idiopathic pulmonary fibrosis

Eur Respir J 2017; 50: 1701157

This international, multicentre, prospective, observational study at four sites (The Netherlands, Italy, France and UK) recruited patients between 2013 and 2016. Treatment-naïve IPF patients aged 40–85 years with a forced vital capacity (FVC) ⩾50% and corrected transfer factor of the lung for carbon monoxide ($T_{LCOc}$) ⩾30%, in whom pirfenidone therapy was about to be initiated according to regular practice, who had daily IPF-related cough for ⩾8 weeks with a cough score of ⩾40 mm on a 0–100 mm visual analogue scale (VAS), were eligible for the present study.

After 12 weeks of pirfenidone treatment, objective 24-h cough decreased by 34% (95% CI −48% to −15%) (table 1). An improvement in 24-h cough was observed in 20 out of 27 patients (74%). Sensitivity analysis showed similar results (data available on request). Subjective cough measures showed consistent improvements (table 1). No significant changes in disease-specific QoL and anxiety were found. Even at the earlier time point of 4 weeks, a smaller, but significant effect on cough counts was observed, with a 14% reduction in 24-h cough frequency (95% CI −22% to −6%; p=0.002). At this time point, improvements in cough were observed in 24 out of 35 patients (69%).

BMJ Open Respiratory Research

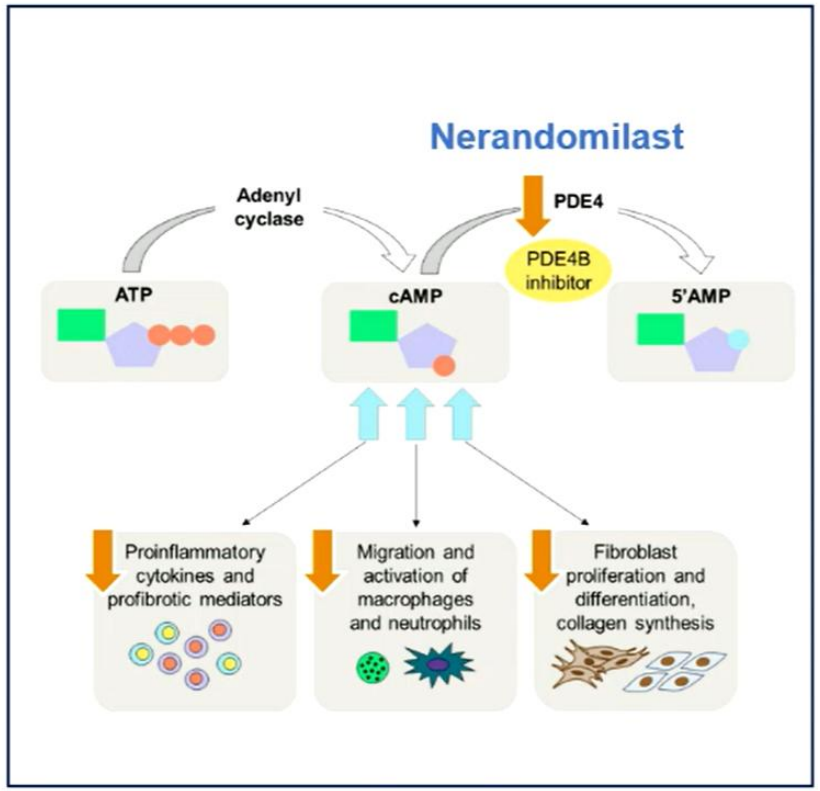
# Design of a phase III, double-blind, randomised, placebo-controlled trial of BI 1015550 in patients with idiopathic pulmonary fibrosis (FIBRONEER-IPF)

Luca Richeldi ,[1] Arata Azuma,[2,3] Vincent Cottin,[4] Michael Kreuter,[5,6] Toby M Maher ,[7,8] Fernando J Martinez,[9] Justin M Oldham,[10] Claudia Valenzuela ,[11] Maud Gordat,[12] Yi Liu,[13] Susanne Stowasser,[14] Donald F Zoz,[15] Marlies S Wijsenbeek[16]

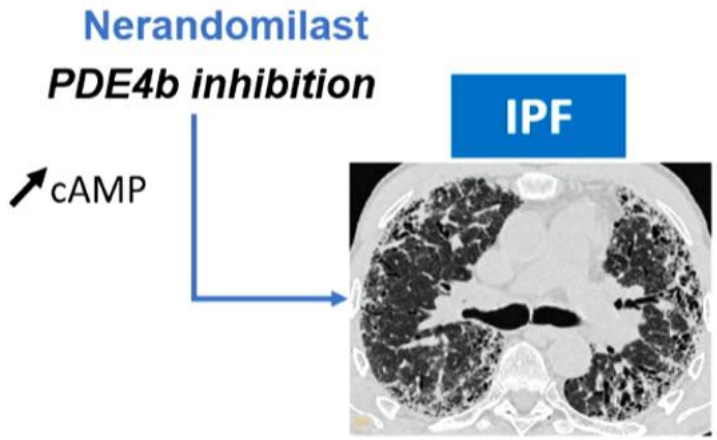
## CONCLUSIONS

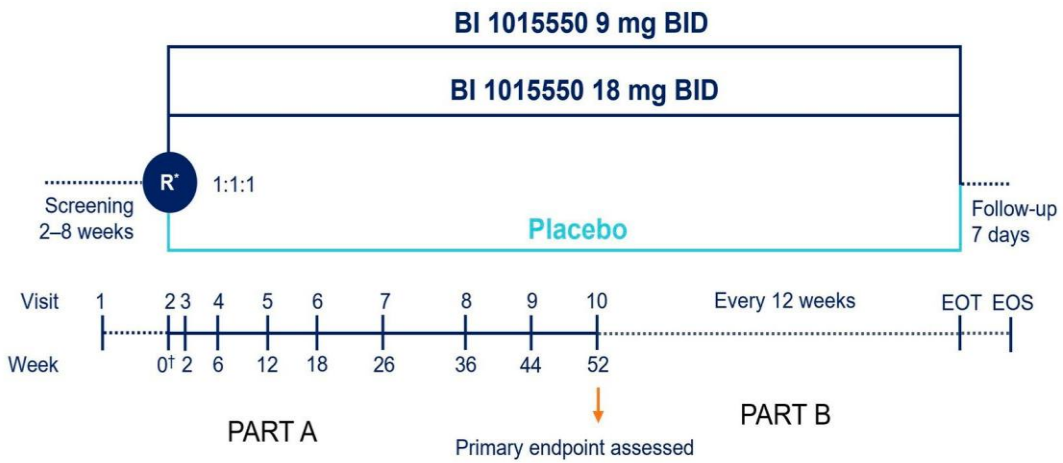
FIBRONEER-IPF is the first phase III trial of a preferential PDE4B inhibitor in patients with IPF. The results of this trial will increase our understanding of the safety and efficacy of BI 1015550 as a monotherapy or in combination with current antifibrotic standard of care in a larger and broader population of patients with IPF. These data will help to address an unmet need for new treatments for patients with IPF and potentially provide evidence for combination treatment in IPF.

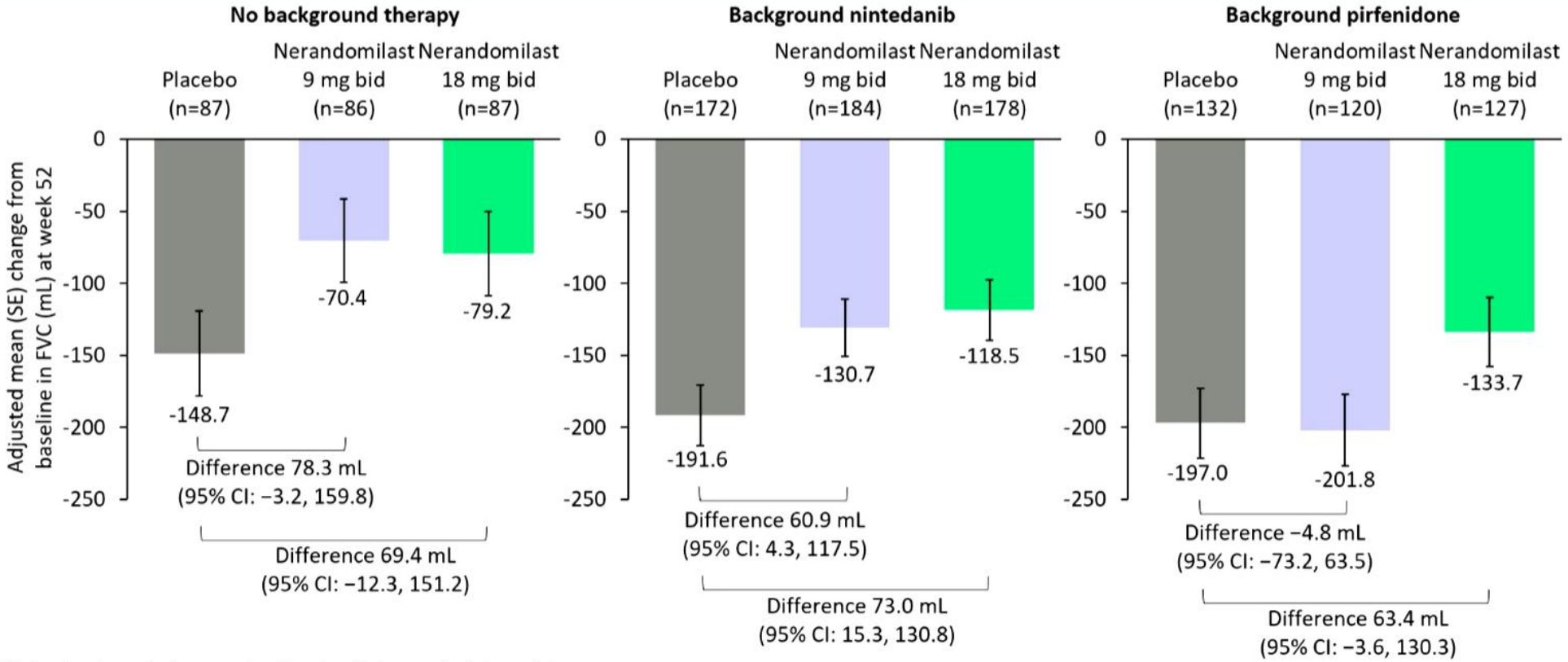
***Phosphodiesterase 4b***




Keith, Ther Adv Respir Dis 2025


Nerandomilast
PDE4b inhibition
cAMP
IPF


BI 1015550 9 mg BID
BI 1015550 18 mg BID
R*
1:1:1
Screening
2–8 weeks
Placebo
Follow-up
7 days
Visit 1 2 3 4 5 6 7 8 9 10 Every 12 weeks EOT EOS
Week 0† 2 6 12 18 26 36 44 52
PART A
Primary endpoint assessed
PART B




Missing data due to death were replaced based on 10th percentile of observed changes across treatment arms.

Richeldi L et al. N Engl J Med 2025;392:2193–2202.

These data support the use of nerandomilast in the treatment of IPF as monotherapy and in combination with currently approved treatments

Open Access Interstitial lung disease

BMJ Open Respiratory Research

# Study design and rationale for the TETON phase 3, randomised, controlled clinical trials of inhaled treprostinil in the treatment of idiopathic pulmonary fibrosis

Steven D Nathan,[1] Jurgen Behr,[2] Vincent Cottin,[3] Lisa Lancaster,[4] Peter Smith,[5]

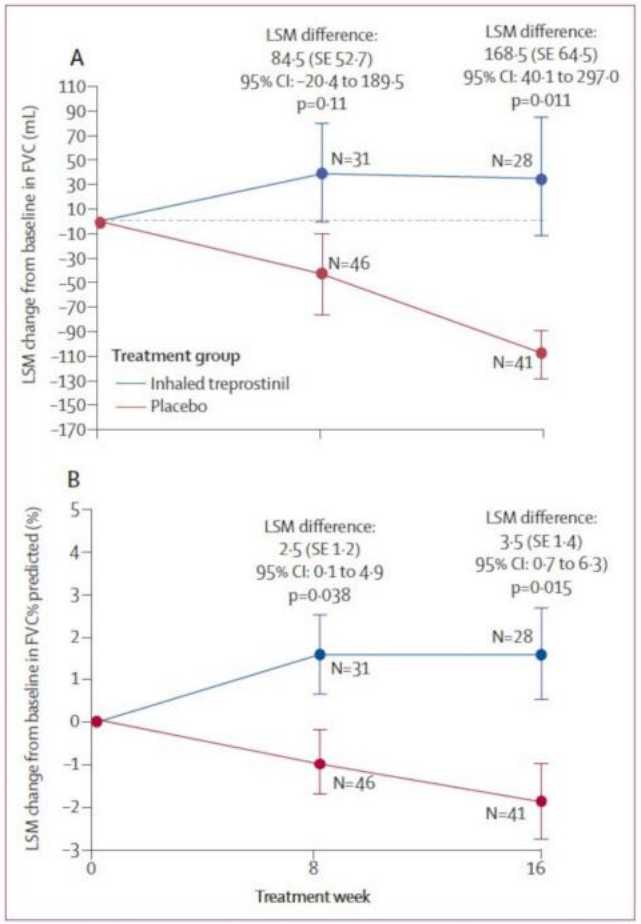
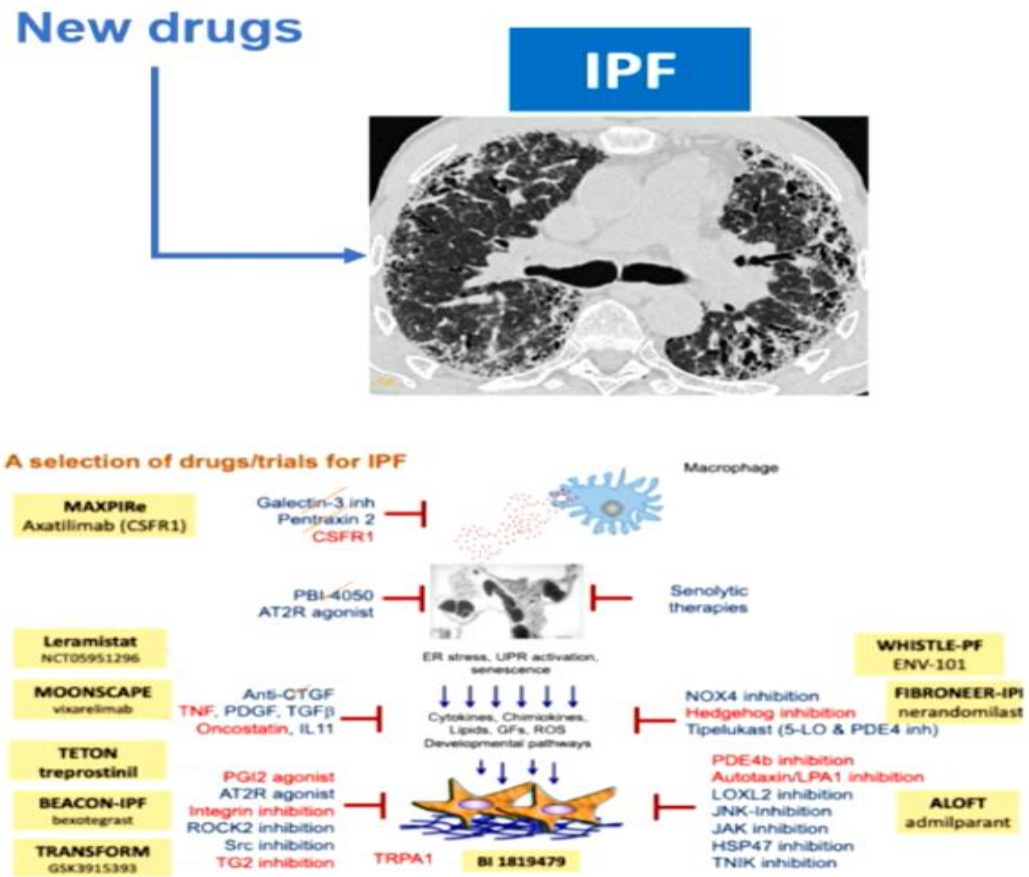



**Figure 1** Change in FVC at weeks 8 and 16 for patients with idiopathic pulmonary fibrosis in the increase study. FVC, forced vital capacity. LSM, least-squares mean




1: Raghu et al, AJRCCM 2024;

# AIR – an open-label, 36-week, clinical trial of buloxibutid – investigating the disease modifying potential of a novel angiotensin II type 2 receptor agonist in IPF

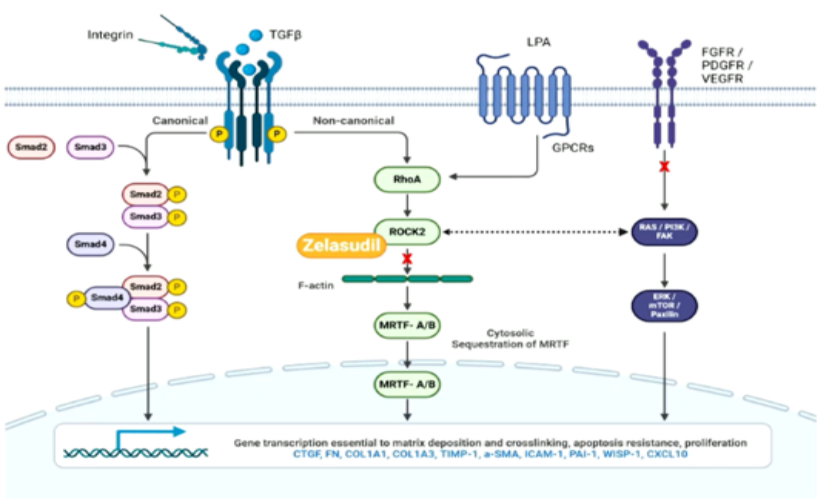
Cecilia Ganslandt | Philip Molyneaux | Anand Devaraj Show More

European Respiratory Journal 2024 64(suppl 68): OA2859; DOI: https://doi.org/10.1183/13993003.congress-2024.OA2859

# Zelasudil is a Best in Class, Potent, Selective ROCK2 Inhibitor

## Potential of selective ROCK2 inhibition

- ROCK sits at a nodal position in fibrotic signaling pathways
- Pan-ROCK inhibition shows robust anti-fibrotic activity in preclinical models
- Systemic pan-ROCK inhibition results in hypotension. This does not happen with selective ROCK2 inhibition
- ROCK2 inhibition alone is sufficient to drive anti-fibrotic efficacy in multiple preclinical fibrosis models




**Selective ROCK2 inhibitors hold great treatment potential in fibrotic disease**

ROCK: Rho-associated protein kinase

- IPF remains an area of high unmet need with limited therapeutic options
- ROCK sits at a nodal position in fibrotic signaling pathways
- Zelasudil is a best-in-class ROCK 2 inhibitor
- Zelasudil is well tolerated both with and without background antifibrotic therapy
- Pharmacokinetics in-line with predictions and Zelasudil can be combined with other antifibrotic therapies (nintedanib and pirfenidone)
- In this Phase 2a study, antifibrotic activity has been demonstrated which is supported by circulating biomarker data
- Further investigation in IPF / ILD is warranted

nature medicine

Article

https://doi.org/10.1038/s41591-025-03743-2

# A generative AI-discovered TNIK inhibitor for idiopathic pulmonary fibrosis: a randomized phase 2a trial

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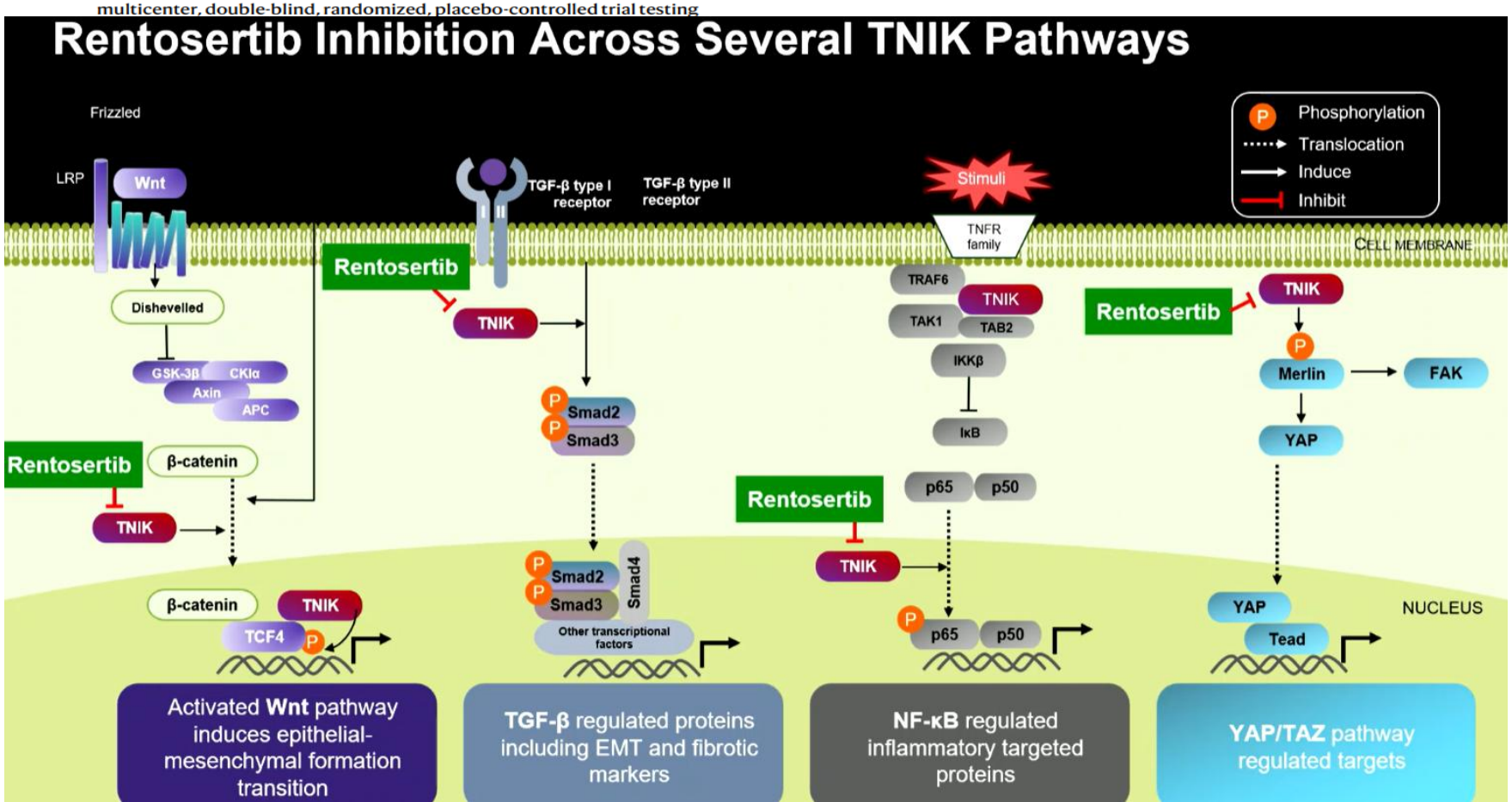
Check for updates

A list of authors and their affiliations appears at the end of the paper

Despite substantial progress in artificial intelligence (AI) for generative chemistry, few novel AI-discovered or AI-designed drugs have reached human clinical trials. Here we present the results of the first phase 2a multicenter, double-blind, randomized, placebo-controlled trial testing



# Emerging clinical-stage IPF therapeutics targeting pro-fibrotic signalling

| Anti-fibrotic mechanism (pathway) | Target | Agent (company) | Modality / route | Clinical stage & 2025 status |
|---|---|---|---|---|
| Pro-fibrotic signaling (GPCRs, kinases, growth factors, macrophage pathways) | | | | |
| **PDE4B inhibition (↑cAMP → anti-fibrotic/anti-inflammatory)** | PDE4B | Nerandomilast (BI 1015550) – Boehringer Ingelheim | Oral small molecule | Phase 3 positive in IPF & PPF (NCT05321069 NCT05321082) (FVC decline slowed); regulatory next steps underway |
| **LPA signaling blockade** | LPA1 | Admilparant (BMS-986278) – Bristol Myers Squibb NCT06003426 NCT06025578 | Oral small molecule | Phase 2 positive; Phase 3 ALOFT-IPF/PPF ongoing; (NCT06003426; NCT06025578) |
| **Rho/ROCK pathway inhibition** | ROCK2 | Zelasudil (RXC007) – Redx NCT05570058 | Oral small molecule | Phase 2a completed; advancing development; note prior US >28-day partial hold (NCT05570058) |
| **Wnt pathway kinase inhibition** | TNIK | INS018_055 (ISM001-055) – Insilico Medicine (AI-discovered target and drug) | Oral small molecule | Phase 2a positive topline (2024) (NCT05975983) |
| **Src kinase inhibition** | Src | Saracatinib (AZD0530) – AstraZeneca / NIH | Oral small molecule | STOP-IPF Ph1b/2a listed as Active, not recruiting on ClinicalTrials.gov (NCT04598919) |
| **Autotaxin (LPA synthesis) inhibition** | Autotaxin (ATX) | BBT-877 – Bridge Biotherapeutics | Oral small molecule | Phase 2 proof-of-concept in IPF: enrolment completed 2024; NCT05483907 |
| **CSF-1R blockade (anti–pro-fibrotic macrophage)** | CSF-1R | Axatilimab – Syndax | Monoclonal antibody | MAXPIRe Ph2 randomized 26-week IPF study: recruiting. (NCT06132256) |
| **Prostacyclin → cAMP signaling (anti-proliferative/anti-fibrotic)** | IP receptor (prostacyclin) | Treprostinil inhalation solution (Tyvaso®) – United Therapeutics | Inhaled | Phase 3 TETON-2 met primary endpoint (↑FVC); TETON-1 ongoing. (NCT04708782) |
| **Direct TGF-β1 gene silencing** | TGF-β1 mRNA | TRK-250 (BNC-1021) – Toray / BONAC | Inhaled siRNA | Phase 1 completed (safe/tolerated). (NCT03727802) |
| **Multi-target anti-angiogenic/anti-fibrotic TKI** | VEGFR / FGFR / PDGFR | Anlotinib – multiple sponsors | Oral small molecule | Phase 2/3 trials in IPF/PF-ILD (China). (NCT05828953) |
| **Wnt-associated matricellular protein neutralization** | WISP1 | MTX-463 – Mediar Therapeutics | Monoclonal antibody | Phase 2 WISPer-IPF initiated (2025). (NCT06967805) |
| **Inhaled pirfenidone (nebulized)** | Multiple | AP01 (inhaled pirfenidone) – Avalyn | Inhaled (nebulizer) | MIST Ph2b in PPF (includes IPF subsets): recruiting globally. (NCT06329401) |

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***Original Research***

# A Randomized, Double-Blinded, Placebo-Controlled, Dose-Escalation Phase 1 Study of Aerosolized Pirfenidone Delivered via the PARI Investigational eFlow Nebulizer in Volunteers and Patients with Idiopathic Pulmonary Fibrosis

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