İdiyopatik Pulmoner Fibrozis (İPF)

Dr Dildar Duman
SBÜ Süreyyapaşa EAH

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.

İPF- Klinik bulgular

- En sık görülen semptomlar nefes darlığı ve öksürüktür.
- En sık 60 yaş üzeri, sigara içen erkek hastalarda görülür.
- Fizik muayenede hastaların yarısında çomak parmak saptanabilir.
- Hastaların tamamına yakınında oskultasyonda velkro raller duyulabilir

İPF- Patoloji

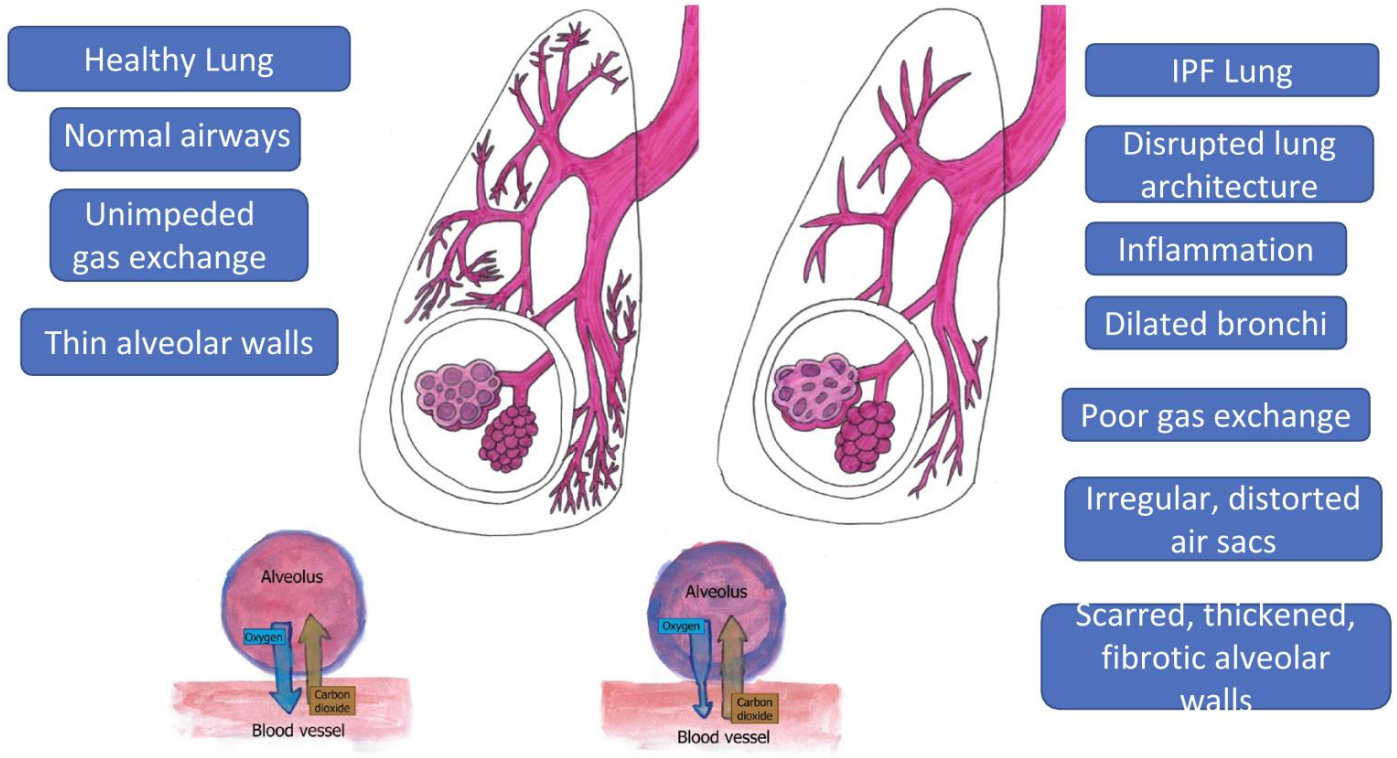
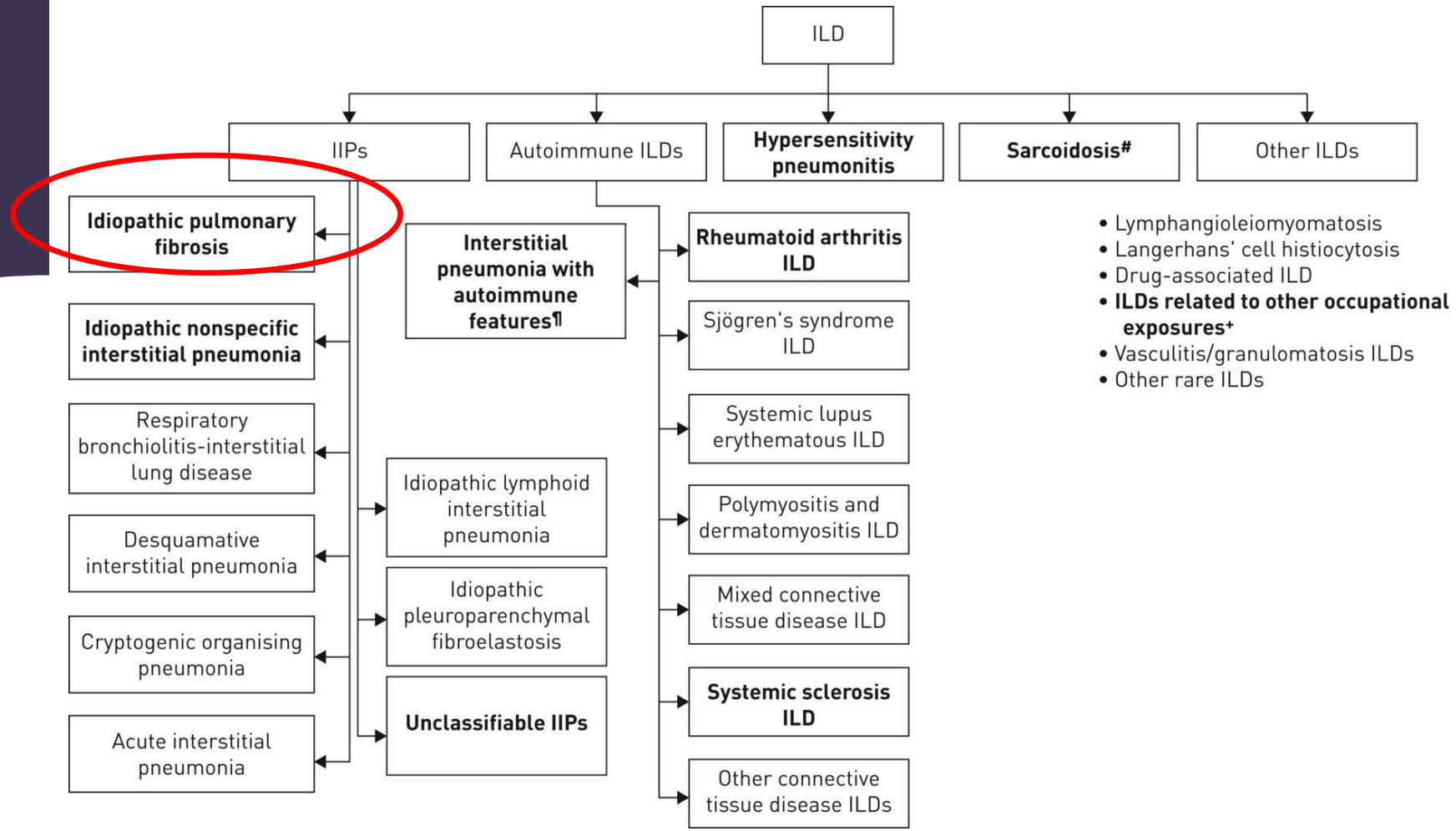


FIGURE 1 Comparison of healthy lung to idiopathic pulmonary fibrosis (IPF) lung. The healthy lung is characterized by unscarred airways with thin-walled alveoli and unimpeded gas exchange. Pathological features of the IPF lung include dilated bronchi, airway distortion, and thickened alveolar walls. Inflammation and fibrosis lead to impaired gas exchange within the alveoli

Clin Respir J. 2022;16:84–96.

İnterstisyel AC Hastalıkları

Sınıflandırma



İPF- PPF

ATS 2022

AMERICAN THORACIC SOCIETY DOCUMENTS

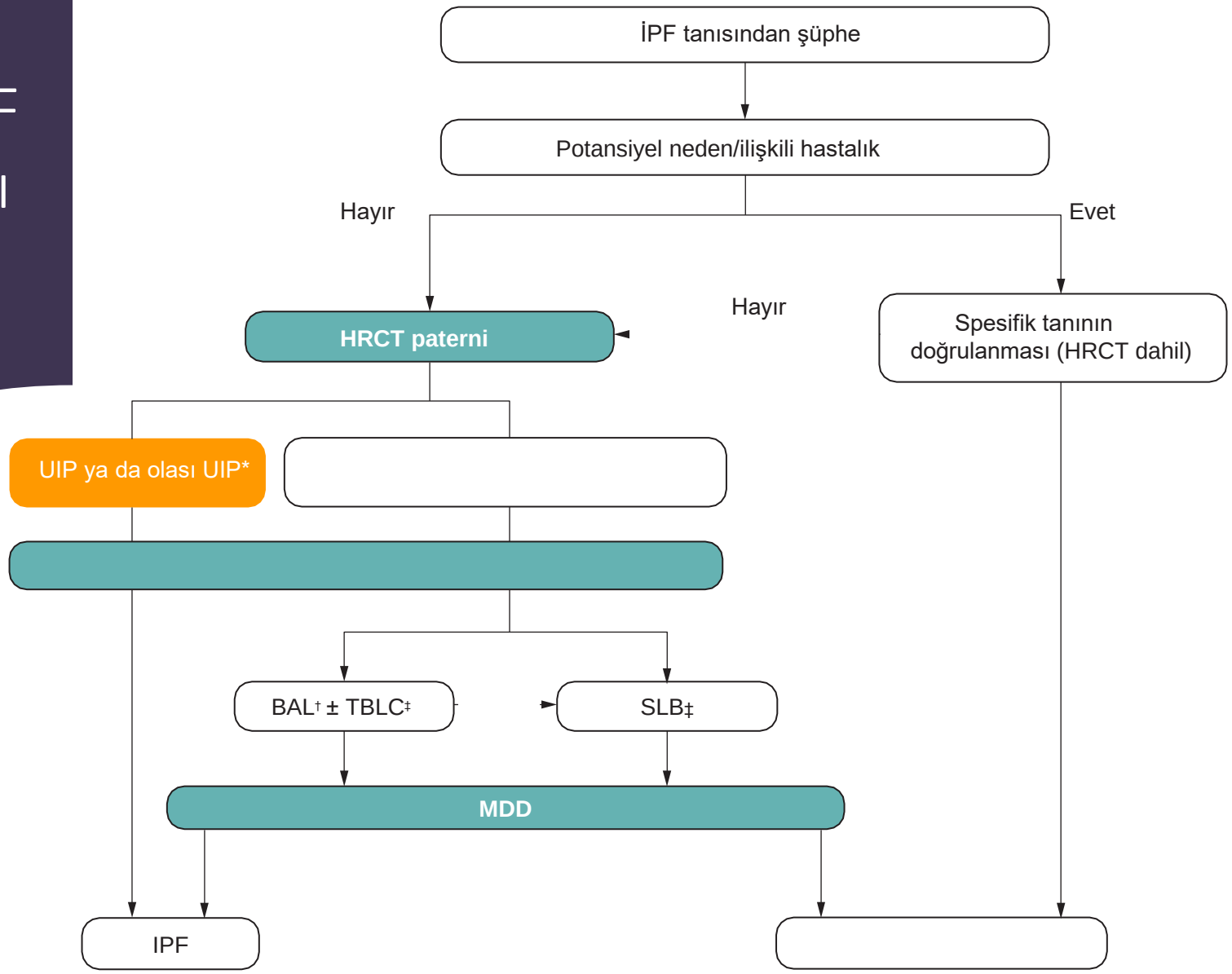
Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

Ganesh Raghu, Martine Remy-Jardin, Luca Richeldi, Carey C. Thomson, Yoshikazu Inoue, Takeshi Johkoh, Michael Kreuter, David A. Lynch, Toby M. Maher, Fernando J. Martinez, Maria Molina-Molina, Jeffrey L. Myers, Andrew G. Nicholson, Christopher J. Ryerson, Mary E. Strek, Lauren K. Troy, Marlies Wijsenbeek, Manoj J. Mammen, Tanzib Hossain, Brittany D. Bissell, Derrick D. Herman, Stephanie M. Hon, Fayez Kheir, Yet H. Khor, Madalina Macrea, Katerina M. Antoniou, Demosthenes Bouros, Ivette Buendia-Roldan, Fabian Caro, Bruno Crestani, Lawrence Ho, Julie Morisset, Amy L. Olson, Anna Podolanczuk, Venerino Poletti, Moisés Selman, Thomas Ewing, Stephen Jones, Shandra L. Knight, Marya Ghazipura, and Kevin C. Wilson; on behalf of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax

This official clinical practice guideline was approved by the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax February 2022

Güncel 2022 İPF Tanı Algoritması

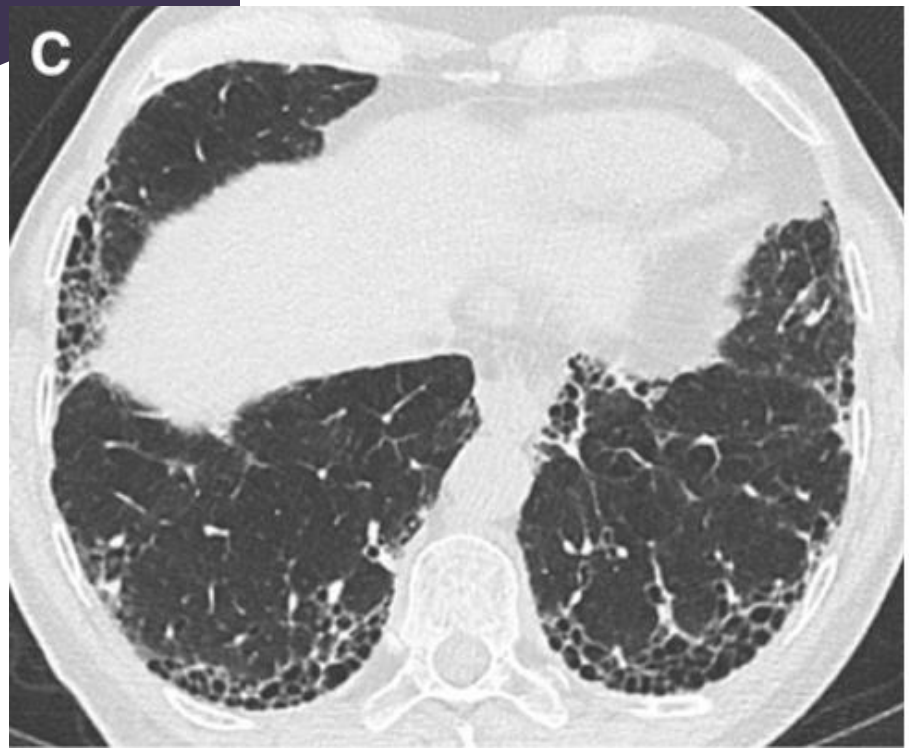


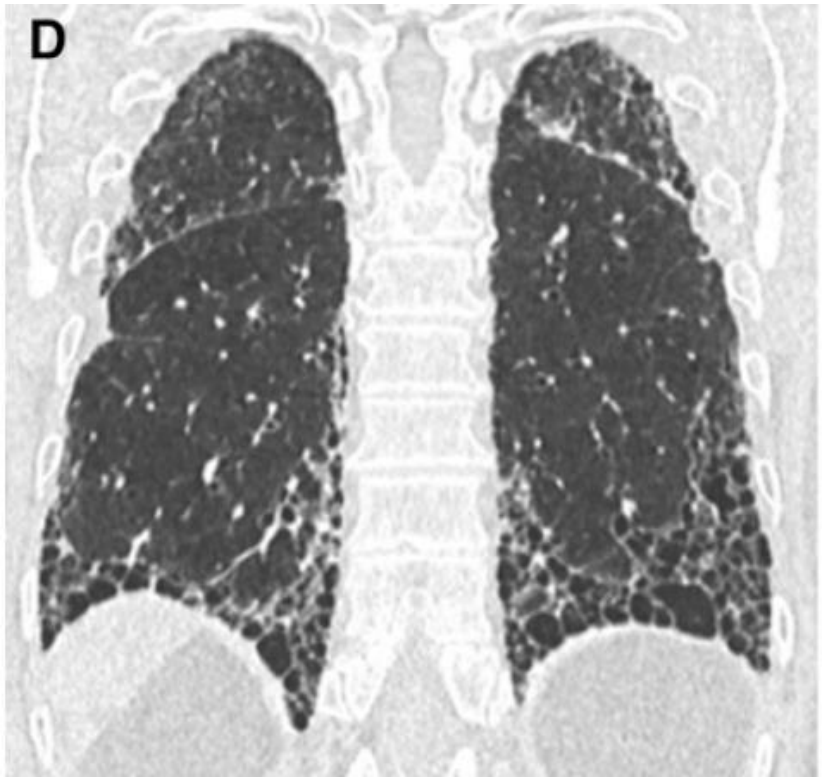
Raghu, Ganesh, et al. "Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline." American Journal of Respiratory and Critical Care Medicine 205.9 (2022): e18-e47.

	UİP paterni	Muhtemel UİP paterni	Belirsiz UİP paterni	CT bulguları Alternatif tanıyı düşündürüyor
UİP histolojisi ile uyum seviyesi	%90	%70-89	%51-69	<%50
Dağılım	*Subplevral ve bazal dominant *Sıklıkla heterojen (fibrozisin arasında normal akciğer alanları) *Bazen diffüz *Belki asimetrik olabilir	*Subplevral ve bazal dominant *Sıklıkla heterojen (retikülasyon ve traksiyon bronşetazisi/ bronşiolektazisi arasında normal akciğer alanları)	*Subplevral baskınlık olmadan diffüz dağılım	*Subplevral korunma ile peribronkovasküler baskın (NSİP düşün) *Perilenfatik baskın (sarkoidoz düşün) *Üst ve Orta akciğer tutulumu (fibrotik HSP, KDH-İAH, sarkoidoz) *Subplevral korunma (NSİP, sigara ilişkili İAH)
CT bulguları	*Traksiyon bronşektazisi/bronşiolektaz i ile birlikte veya birlikte olmadan balpeteği *İnterlobuler septalarda irregüler kalınlaşma *Sıklıkla retiküler patern ile süperpoze, hafif buzlu cam *Belki pulmoner osifikasyon olabilir	*Traksiyon bronşektazisi/bronşiolek tazi ile birlikte retiküler patern *Belki hafif buzlu cam *Subpelvral korunmanın olmaması	*Akciğer fibrozisinin CT bulguları spesifik bir etyolojiyi düşündürmüyor	*Akciğer bulguları -Kistler (LAM, PLHHx, LIP, DIP) -Mozaik atenuasyon veya üç-yoğunluk bulgusu (HSP) -Buzlu cam baskın (HSP, sigara ilişkili, ilaç, fibrozisin akut alevlenmesi) -Bol sentrilobuler nodüller (HSP veya sigara ilişkili) -Nodüller (Sarkoidoz) -Konsolidasyon (Organize pnömoni vs) *Mediastinal bulgular -Plevral plaklar (asbestozis)

İPF Radyoloji

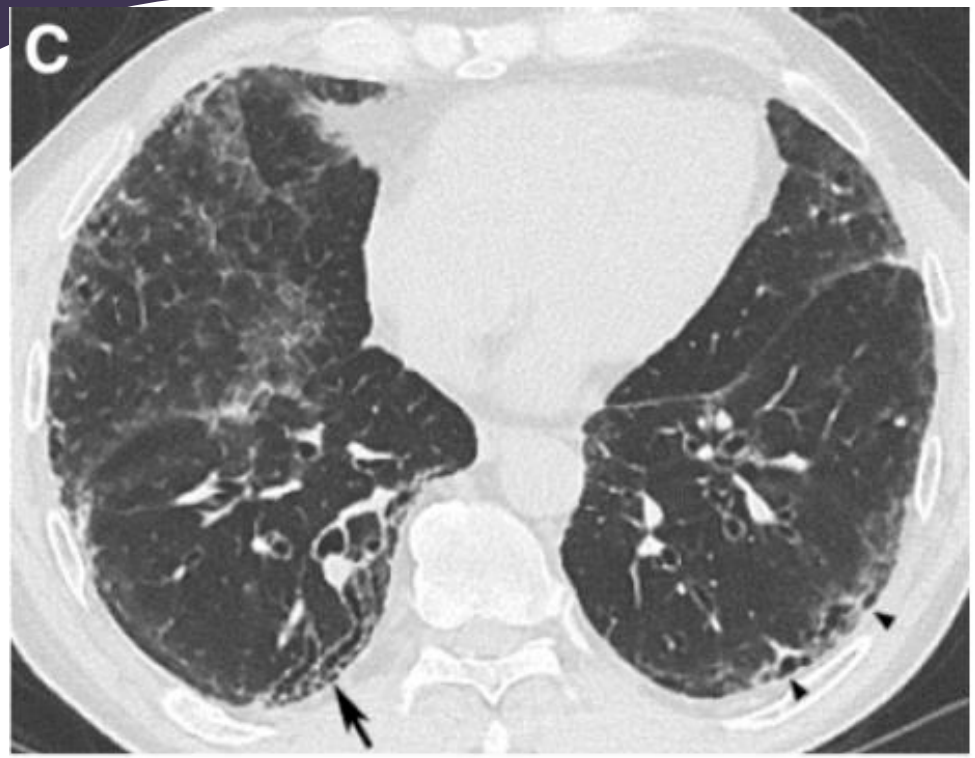
UIP

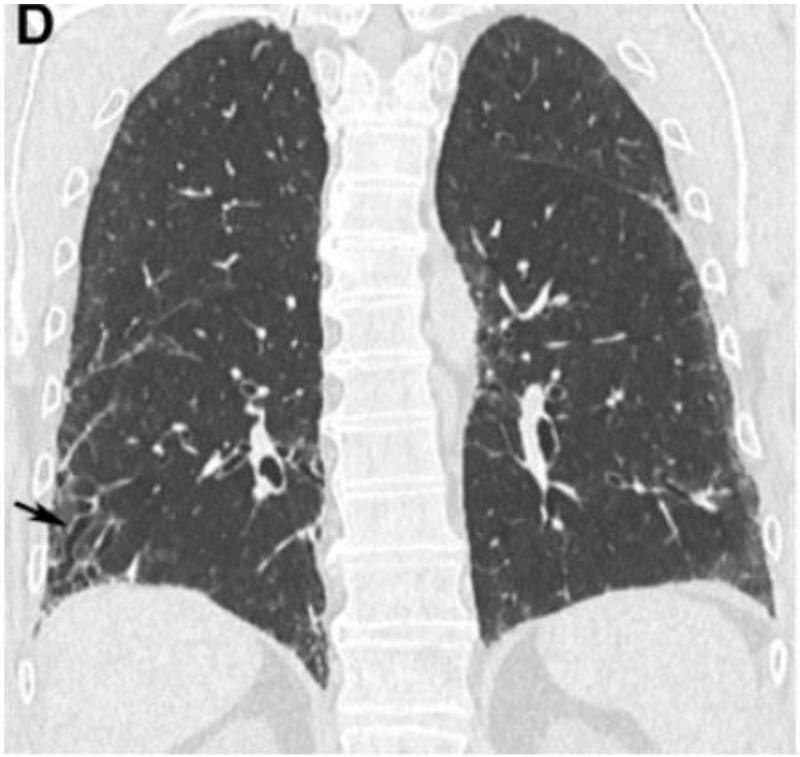




İPF Radyoloji

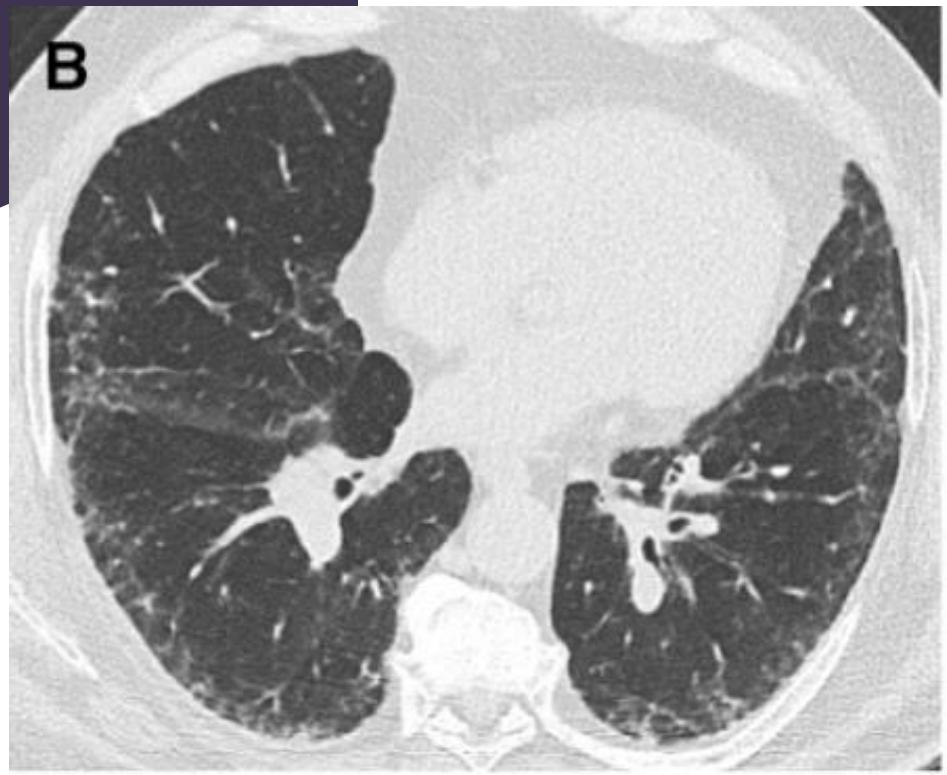
Olası UIP

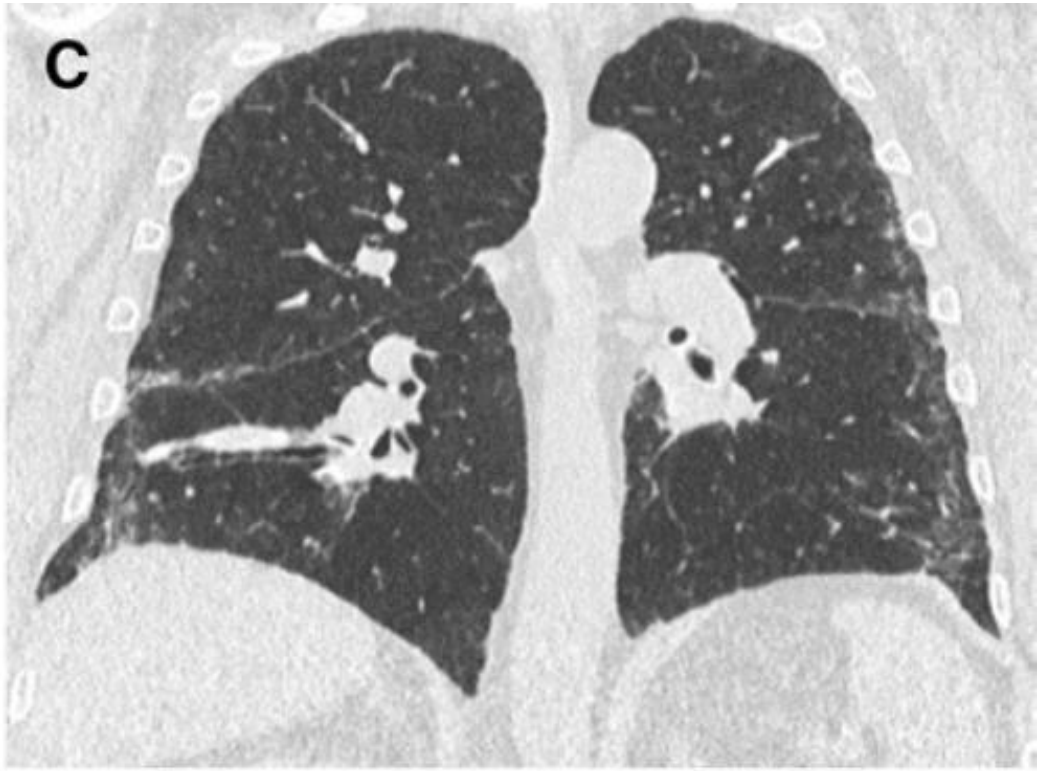




İPF Radyoloji

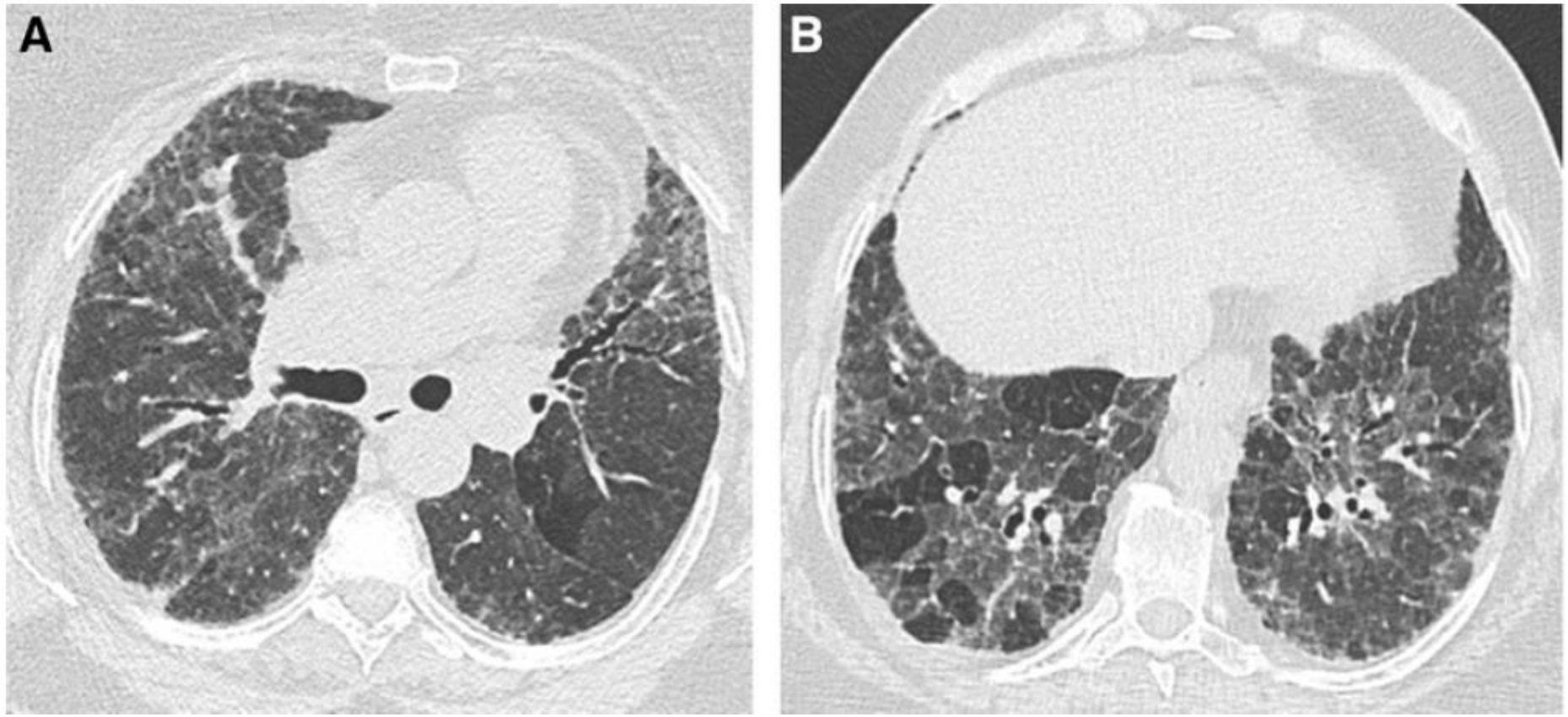
Belirsiz UIP





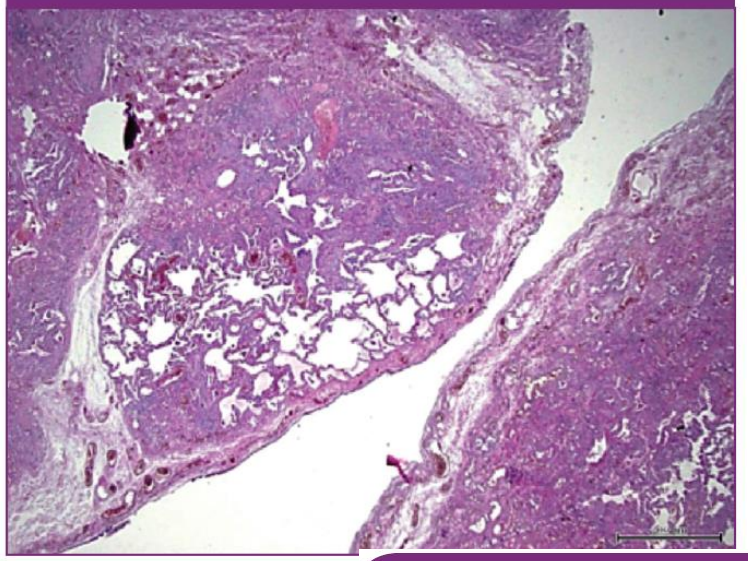
İPF Radyoloji

Alternatif Tanı

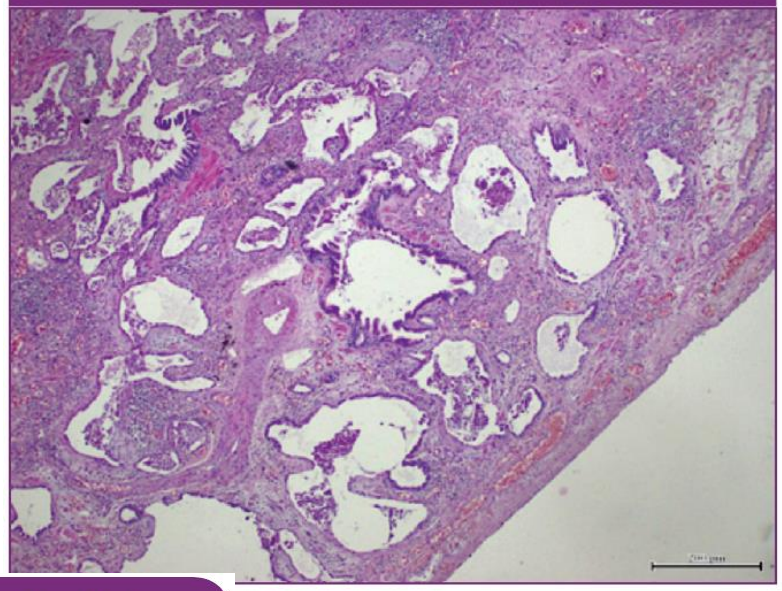


İPF Patoloji

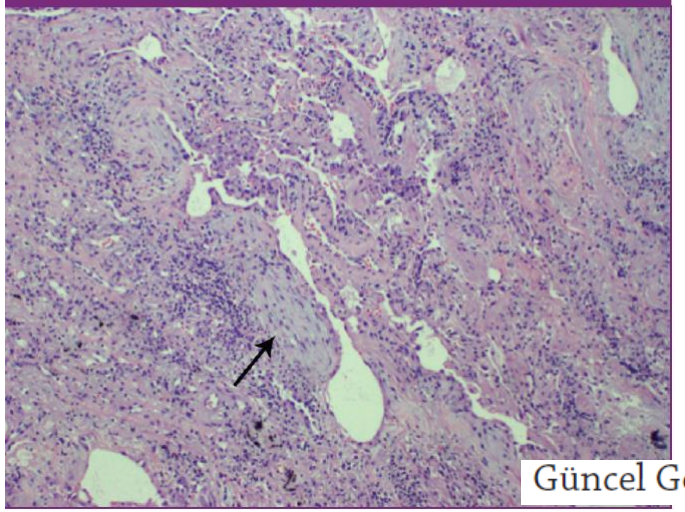
Resim 1. Mikroskobik küçük büyütme alanında subplevral ve paraseptal yamalı interstisyel fibrozis (H&E, x40).



Resim 2. Subplevral alanda fibrozisle çevrili çok sayıda bal peteği kistler (H&E, x40).



Resim 3. Alveolar epitel altında miksoid stromalı prolifere iğsi hücrelerden oluşan fibroblastik fokus(ok) (H&E, x 200).



Güncel Göğüs Hastalıkları Serisi 2017; 5 (2): 31-38

Güncel Radyolojik ve Histopatolojik İPF Tanı Tablosu

İPF şüphesi*		Histopatolojik patern†			
		UIP	Olası UIP	UIP açısından belirsiz sonuç ya da biyopsi yapılmamış	Alternatif tanı
HRCT paterni	UIP	İPF	İPF	İPF	İPF dışı tanı
	Olası UIP	İPF	İPF	İPF (Muhtemel)‡	İPF dışı tanı
	Belirsiz	İPF	İPF (Muhtemel)‡	Belirsiz§	İPF dışı tanı
	Alternatif tanı	İPF (Muhtemel)‡	Belirsiz§	İPF dışı tanı	İPF dışı tanı

Şekil referanstan uyarlanmıştır

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. Raghu, Ganesh, et al. "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 205.9 (2022): e18-e47.

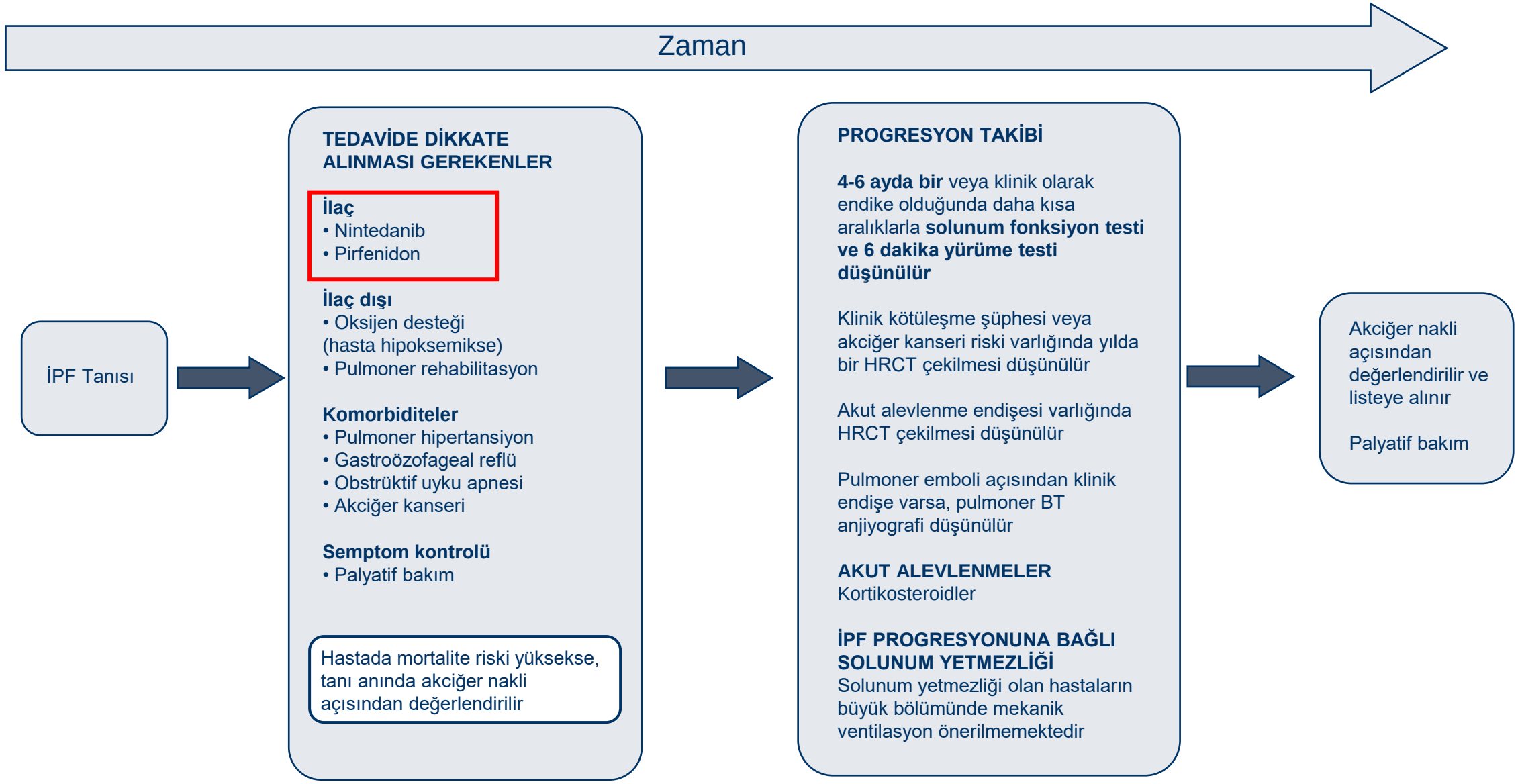
İPF Rehberdeki Değişiklikler

Radyolojik olarak olası UIP paterni bulunan hastalara, biyopsi yapılmadan multidisipliner tartışma yoluyla İPF tanısı konulması önerildi

Transbronşiyal akciğer **kriyobiyopsinin**, İPF'nin histopatolojik tanısında cerrahi akciğer biyopsisine alternatif olarak kullanılması **koşullu olarak önerildi**

Anti-asit ilaçların İPF'de akciğerin tedavisine yönelik **kullanımı aleyhinde öneri getirildi**

Raghu, Ganesh, et al. "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 205.9 (2022): e18-e47.


Zaman
İPF Tanısı
TEDAVİDE DİKKATE ALINMASI GEREKENLER
İlaç
• Nintedanib
• Pirfenidon
İlaç dışı
• Oksijen desteği (hasta hipoksemikse)
• Pulmoner rehabilitasyon
Komorbiditeler
• Pulmoner hipertansiyon
• Gastroözofageal reflü
• Obstrüktif uyku apnesi
• Akciğer kanseri
Semptom kontrolü
• Palyatif bakım
Hastada mortalite riski yüksekse, tanı anında akciğer nakli açısından değerlendirilir
PROGRESYON TAKİBİ
4-6 ayda bir veya klinik olarak endike olduğunda daha kısa aralıklarla solunum fonksiyon testi ve 6 dakika yürüme testi düşünülür
Klinik kötüleşme şüphesi veya akciğer kanseri riski varlığında yılda bir HRCT çekilmesi düşünülür
Akut alevlenme endişesi varlığında HRCT çekilmesi düşünülür
Pulmoner emboli açısından klinik endişe varsa, pulmoner BT anjiyografi düşünülür
AKUT ALEVLENMELER
Kortikosteroidler
İPF PROGRESYONUNA BAĞLI SOLUNUM YETMEZLİĞİ
Solunum yetmezliği olan hastaların büyük bölümünde mekanik ventilasyon önerilmemektedir
Akciğer nakli açısından değerlendirilir ve listeye alınır
Palyatif bakım

İPF Tedavi Algoritması

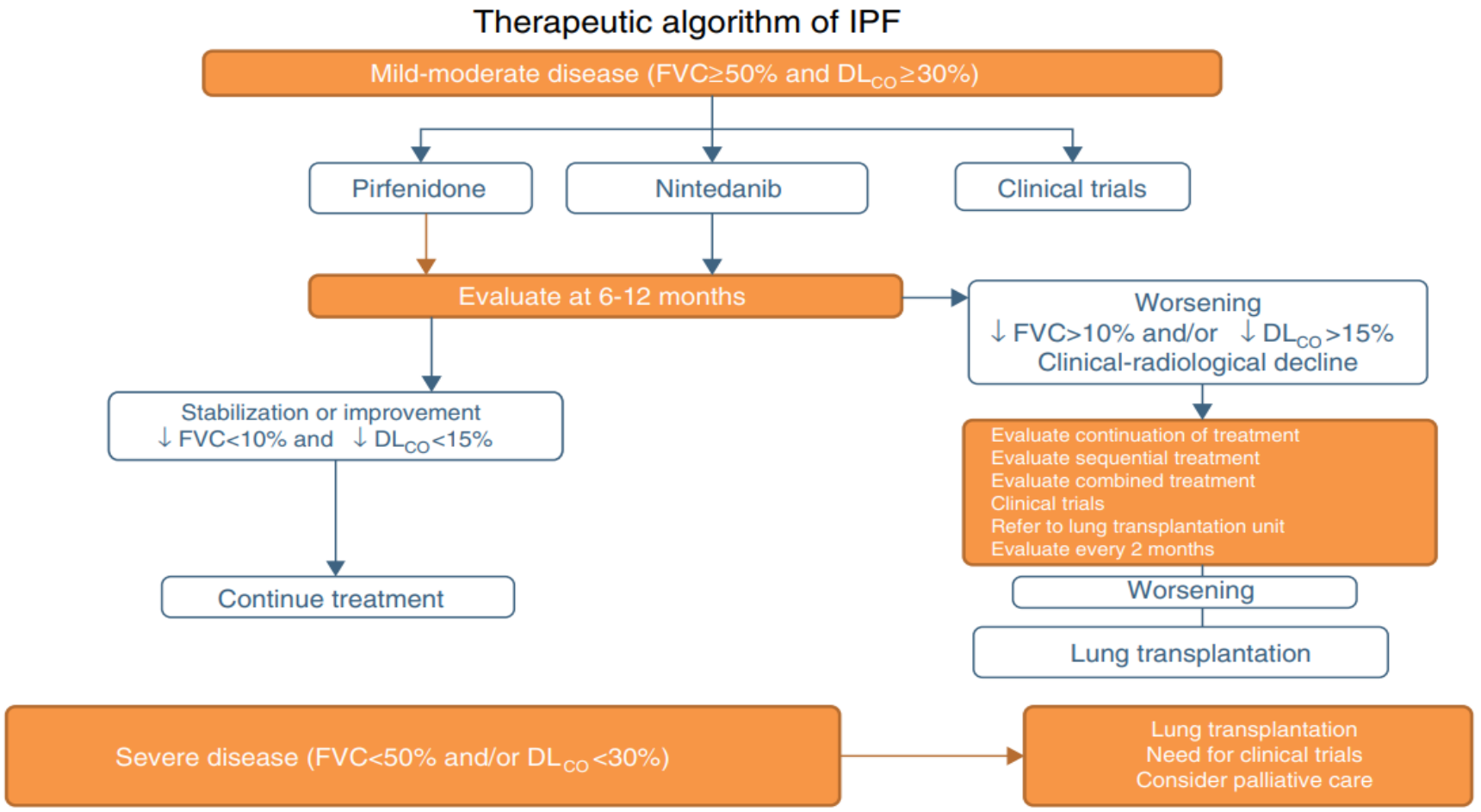


Fig. 1. IPF pharmacological treatment algorithm. FVC: forced vital capacity; DL_{CO}: carbon monoxide diffusing capacity.

Hangi hastalarda antifibrotik tedavi**

- FVC ≥ %50, DLCO ≥ %30 olan hafif ve orta düzeydeki olgular
- HRCT ve/veya akciğer biyopsisi ile (OİP) İPF tanısı konmuş
- Bağ dokusu belirteçleri negatif

İPF Tedavi Hedefleri

- İlaç seçimi neye göre yapılmalıdır?
- Etkinlikleri nasıldır?
- Semptomlarda iyileşme sağlar mı?
- Mortaliteyi azaltır mı?
- Komorbiditeler üzerine etkisi var mıdır?
- Yan etkilerin yönetimi nasıl olmalıdır ?

Nintedanib

- Nintedanib, pulmoner fibrozisin patogenezinde rol oynayan tirozin kinazların güçlü bir hücre içi inhibitörüdür.
- Bu tirozin kinazların, pulmoner fibrozisin patogenezinde yer alan hücre proliferasyonu, farklılaşması ve apoptoz dahil farklı yolaklarda kilit rol oynadığına inanılmaktadır.
- Nintedanib ayrıca anti-enflamatuvar ve antianjiyojenik aktiviteye sahiptir.
- TOMORROW VE INPULSIS çalışmalarında nintedanibin İPF hastalarında FVC düşüşünü yavaşlattığı, yaşam kalitesini düzeltiği ve İPF alevlenmelerini önlediği gösterilmiştir.

Nintedanib

INPULSIS

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

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 INPULSIS

FVC kaybını azaltır

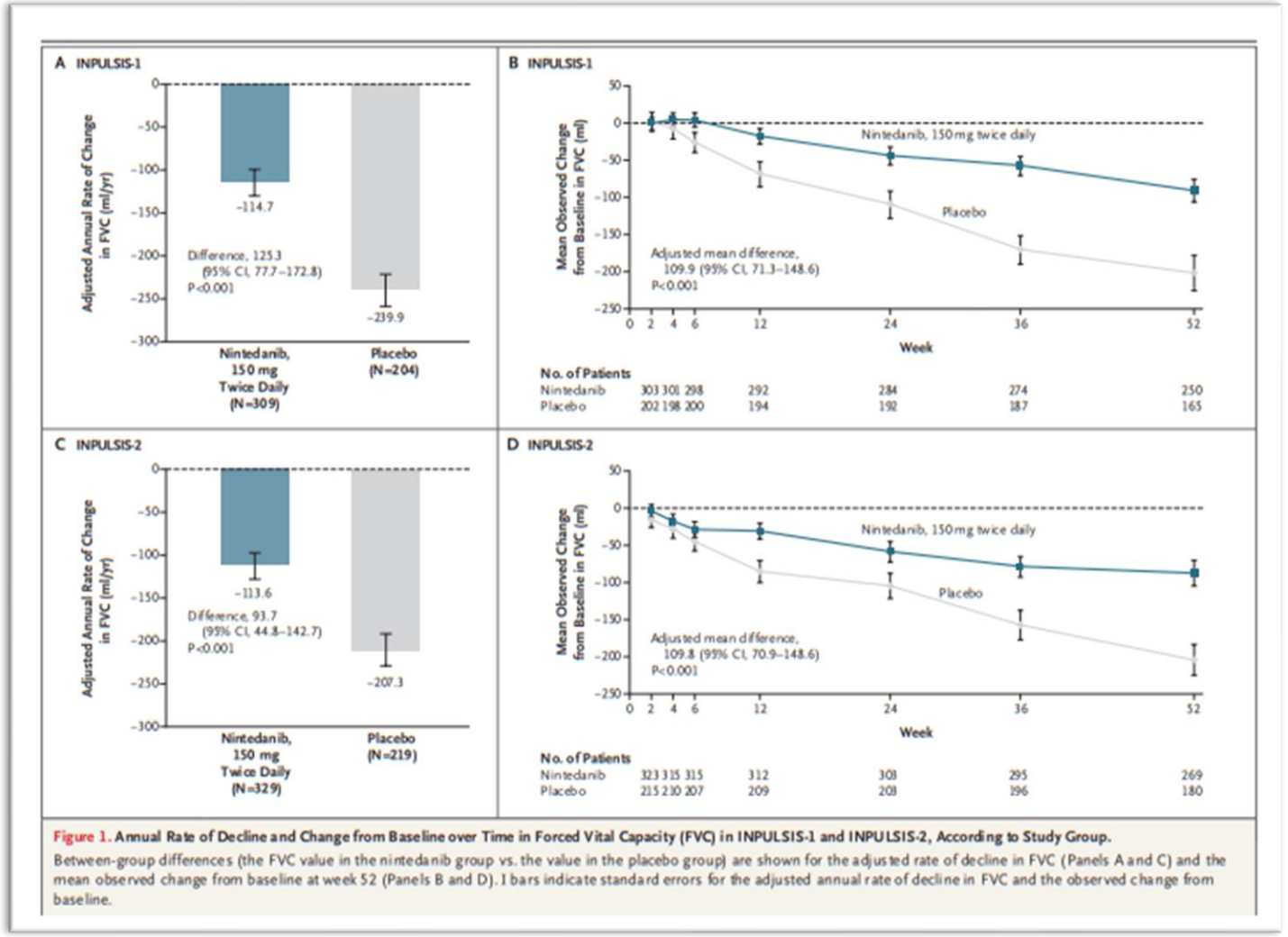


Figure 1. Annual Rate of Decline and Change from Baseline over Time in Forced Vital Capacity (FVC) in INPULSIS-1 and INPULSIS-2, According to Study Group.

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.

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 espresyonunu azaltır.

Fibroblast proliferasyonunu azaltır.

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

İPF hastalarında akciğer fonksiyonu, egzersiz toleransı ve progresyonsuz sağkalımı plaseboya göre iyileştirmiştir.

Pirfenidon ASCEND

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

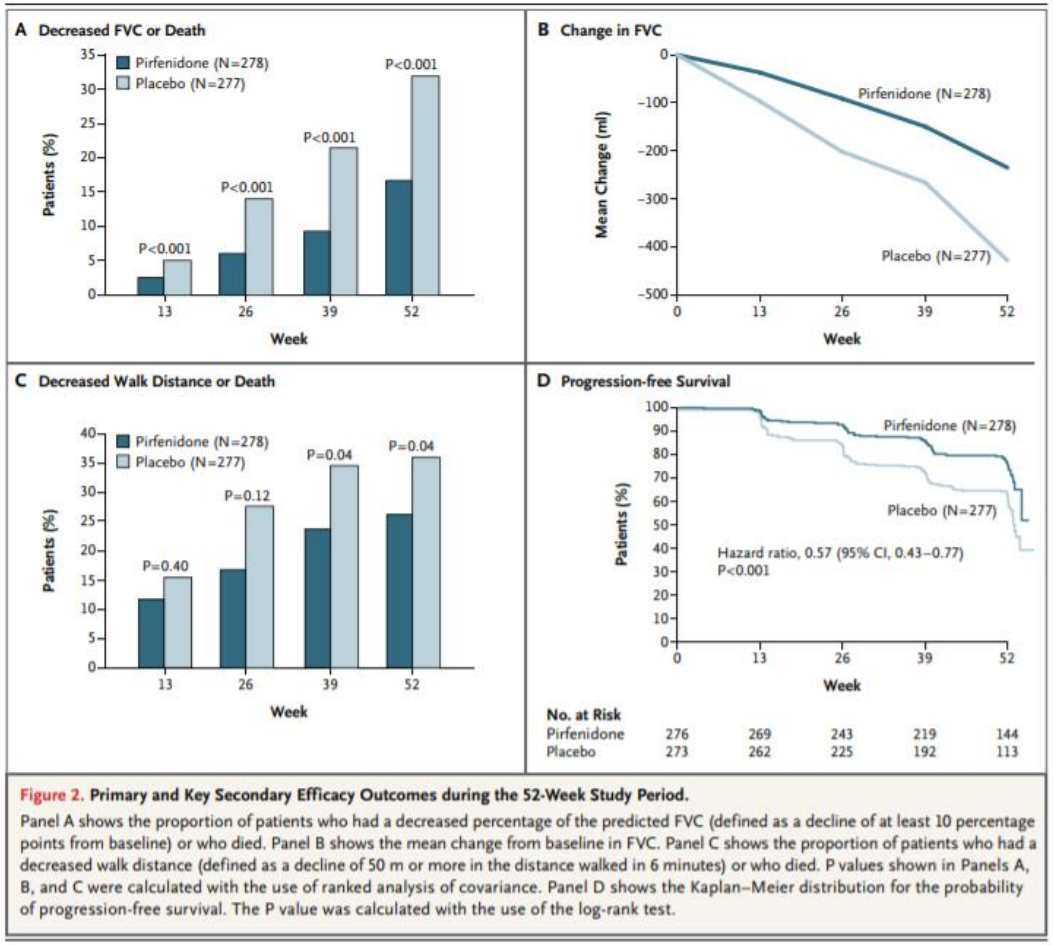


Figure 2. Primary and Key Secondary Efficacy Outcomes during the 52-Week Study Period.

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 improved progression-free survival (P<0.001). There was no significant between-group difference in dyspnea scores (P=0.16) or in rates of death from any cause (P=0.10) or from idiopathic pulmonary fibrosis (P=0.23). However, in a prespecified pooled analysis incorporating results from two previous phase 3 trials, the between-group difference favoring pirfenidone was significant for death 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.)

Pirfenidon İPF hastalık progresyonunu yavaşlatır

Pirfenidone for idiopathic pulmonary fibrosis: analysis of pooled data from three multinational phase 3 trials

Eur Respir J 2016; 47: 243–253 |

ABSTRACT Pirfenidone is an antifibrotic agent that has been evaluated in three multinational phase 3 trials in patients with idiopathic pulmonary fibrosis (IPF). We analysed pooled data from the multinational trials to obtain the most precise estimates of the magnitude of treatment effect on measures of disease progression.

All patients randomised to pirfenidone 2403 mg·day^{-1} or placebo in the CAPACITY or ASCEND studies were included in the analysis. Pooled analyses of outcomes at 1 year were based on the pre-specified end-points and analytic methods described in the ASCEND study protocol.

A total of 1247 patients were included in the analysis. At 1 year, pirfenidone reduced the proportion of patients with a ⩾10% decline in per cent predicted forced vital capacity or death by 43.8% (95% CI 29.3–55.4%) and increased the proportion of patients with no decline by 59.3% (95% CI 29.0–96.8%). A treatment benefit was also observed for progression-free survival, 6-min walk distance and dyspnoea. Gastrointestinal and skin-related adverse events were more common in the pirfenidone group, but rarely led to discontinuation.

Analysis of data from three phase 3 trials demonstrated that treatment with pirfenidone for 1 year resulted in clinically meaningful reductions in disease progression in patients with IPF.

Pirfenidon mu ?

Nintedanib mi?

Impact of novel antifibrotic therapy on patient outcomes in idiopathic pulmonary fibrosis: patient selection and perspectives

Table 1 Comparison of antifibrotic agents approved for the treatment of IPF

	Nintedanib	Pirfenidone
Efficacy	• Slower rate of decline in forced vital capacity over 1 year when compared with placebo • Reduction in acute exacerbations • Lower all-cause mortality at 1 year	• Slower rate of decline in forced vital capacity over 1 year when compared with placebo • Improved progression-free survival • Reduction in respiratory-related hospitalizations • Lower all-cause mortality at 1 year
Potential side effects	• Diarrhea • Weight loss • Elevated liver enzymes	• Nausea • Photosensitivity • Elevated liver enzymes
Dosing	• One capsule taken twice per day	• Three capsules taken three times per day
Contraindications	• No absolute contraindications • Not recommended in Child Pugh Class B or C hepatic impairment • Caution in patients with high cardiovascular risk or high risk for bleeding	• No absolute contraindications
Impact on quality of life	• Slower rate of decline in respiratory-specific quality of life as measured by St. George's Respiratory Questionnaire	• May slow the progression of worsening dyspnea

Abbreviation: IPF, idiopathic pulmonary fibrosis.

Patient Related Outcome Measures 2018:9

Pirfenidon ?

Nintedanib?

İlaç Seçimi

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

İPF ve öksürük

frontiers in Rehabilitation Sciences

Cough in Idiopathic Pulmonary Fibrosis

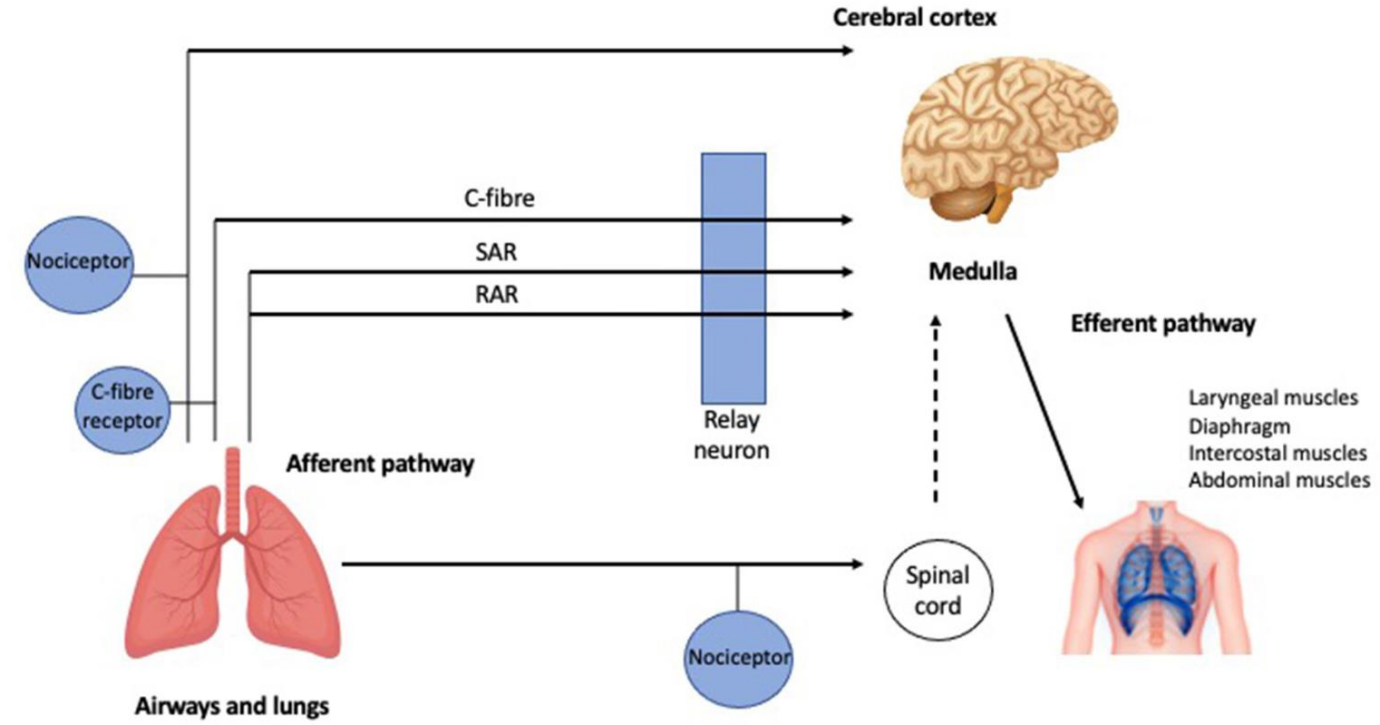


FIGURE 2 | The cough reflex. Schematic representation of the afferent and efferent pathways of the cough reflex (further detail in the text). RAR, Rapidly adapting receptors; SAR, slowly adapting stretch receptors [adapted from Mazzone (19) with permission from Elsevier].

İPF ve öksürük

Official Journal of the Asian Pacific Society of Respirology
Respirology

Cough predicts prognosis in idiopathic pulmonary fibrosis

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SUMMARY AT A GLANCE

Cough in IPF is common, and is more prevalent in never-smokers and patients with more advanced disease. Cough is an independent predictor of disease progression and may predict time to death or lung transplantation in IPF.

Nintedanib ile öksürük %52'den %21'e gerilemiştir

Respiration

Clinical Investigations

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

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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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Karger

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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%).

İPF ve dispne

Managing Dyspnea in Individuals With Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis is an unrelenting form of interstitial lung disease associated with a high symptom burden and reported low health-related quality of life. Clinicians have access to limited pharmacologic interventions to help slow the disease progression. Nonpharmacologic interventions are vital in managing dyspnea for these individuals, which is one of the most frequently reported factors that negatively impacts health-related quality of life. Common methods of symptom control include integration of pulmonary rehabilitation, supplemental oxygen, and interdisciplinary support, such as support groups, palliative care, and case conferences, into routine medical care. This literature review describes a multidisciplinary approach for managing dyspnea to improve health-related quality of life for those with idiopathic pulmonary fibrosis. Findings demonstrate that structured pulmonary rehabilitation programs, fast-track case conferences, and supplemental oxygen therapy are most effective. Further research is needed to demonstrate a clinically significant benefit of palliative care visits in the long term for these individuals.

İPF ilişkili mortalite oranları düşüyor (USA)

Mortality Trends of Idiopathic Pulmonary Fibrosis in the United States From 2004 Through 2017

RESEARCH QUESTION: What are the trends in IPF-related mortality rates in the United States from 2004 through 2017?

STUDY DESIGN AND METHODS: We used the Multiple Cause of Death Database available through the Centers for Disease Control and Prevention website, which contains data from all deceased US residents. IPF-related deaths were identified using International Classification of Diseases, 10th revision, codes. We examined annual trends in age-adjusted mortality rates stratified by age, sex, race, and state of residence. We also evaluated trends in place of death and underlying cause of death.

RESULTS: From 2004 through 2017, the age-adjusted mortality decreased by 4.1% in men (from 75.5 deaths/1,000,000 in 2004 to 72.4 deaths/1,000,000 in 2017) and by 13.4% in women (from 46.3 deaths/1,000,000 in 2004 to 40.1 deaths/1,000,000 in 2017). This overall decrease was driven mainly by a decline in IPF-related mortality in patients younger than 85 years. The decreasing trend also was noted in all races except White men, in whom the rate remained stable. The most common cause of death was pulmonary fibrosis. The percentage of deaths occurring in the inpatient setting and nursing homes decreased, whereas the percentage of deaths occurring at home and hospice increased.

INTERPRETATION: From 2004 through 2017, the IPF age-adjusted mortality rates decreased. This may be explained partly by a decline in smoking in the United States, but further research is needed to evaluate other environmental and genetic contributors.

CHEST 2021; 159(1):228-238

Antifibrotik tedavi tüm sebepli mortalite ve akut alevlenmeleri azaltır !!! (NEJM)

Impact of Antifibrotic Therapy on Mortality and Acute Exacerbation in Idiopathic Pulmonary Fibrosis

A Systematic Review and Meta-Analysis

RESEARCH QUESTION: Does antifibrotic treatment decrease risk of mortality and AE?

STUDY DESIGN AND METHODS: A comprehensive search of several databases, including Ovid MEDLINE(R), Ovid Embase, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus, was conducted. Studies were included if they were original articles comparing mortality or AE events in IPF patients with and without antifibrotic treatment. Relative risk (RR) with 95%CI was pooled using random-effects meta-analyses with inverse variance method, assessing two primary outcomes of all-cause mortality and AE risk.

RESULTS: A total of 12,956 patients across 26 studies (eight randomized controlled trials and 18 cohort studies) were included in the meta-analysis. Antifibrotic treatment was associated with decreased risk of all-cause mortality with a pooled RR of 0.55 (95% CI, 0.45-0.66) and I^2 of 82%. This effect was consistent across additional subgroup analyses, including stratification by study type, risk of bias, duration of follow-up, and antifibrotic subtype. Antifibrotic treatment also reduced the risk of AE, with a pooled RR of 0.63 (95% CI, 0.53-0.76), and I^2 of 0%. Effect on AE risk was consistent across subgroup analyses by study type and for nintedanib but not for pirfenidone.

INTERPRETATION: Antifibrotic treatment appears to reduce the risk of all-cause mortality and AE in IPF. Despite greater heterogeneity with pooled analysis, its effect was robust in subgroup analyses by study type, duration of follow-up, and antifibrotic subtype.

CHEST 2021; 160(5):1751-1763

İPF’de pirfenidon mortalite riskini 120 haftalık takipte azaltmıştır.

Effect of pirfenidone on mortality: pooled analyses and meta-analyses of clinical trials in idiopathic pulmonary fibrosis

Background: In clinical trials of idiopathic pulmonary fibrosis, rates of all-cause mortality are low. Thus prospective mortality trials are logistically very challenging, justifying the use of pooled analyses or meta-analyses. We did pooled analyses and meta-analyses of clinical trials of pirfenidone versus placebo to determine the effect of pirfenidone on mortality outcomes over 120 weeks.

Methods: We did a pooled analysis of the combined patient populations of the three global randomised phase 3 trials of pirfenidone versus placebo-Clinical Studies Assessing Pirfenidone in Idiopathic Pulmonary Fibrosis: Research of Efficacy and Safety Outcomes (CAPACITY 004 and 006; trial durations 72-120 weeks) and Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis (ASCEND 016; 52 weeks)-for all-cause mortality, treatment-emergent all-cause mortality, idiopathic-pulmonary-fibrosis-related mortality, and treatment-emergent idiopathic-pulmonary-fibrosis-related mortality at weeks 52, 72, and 120. We also did meta-analyses of these data and data from two Japanese trials of pirfenidone versus placebo-Shionogi Phase 2 (SP2) and Shionogi Phase 3 (SP3; trial durations 36-52 weeks).

Findings: At week 52, the relative risk of death for all four mortality outcomes was significantly lower in the pirfenidone group than in the placebo group in the pooled population (all-cause mortality hazard ratio [HR] 0·52 [95% CI 0·31-0·87; p=0·0107]; treatment-emergent all-cause mortality 0·45 [0·24-0·83; 0·0094]; idiopathic-pulmonary-fibrosis-related mortality 0·35 [0·17-0·72; 0·0029]; treatment-emergent idiopathic-pulmonary-fibrosis-related mortality 0·32 [0·14-0·76; 0·0061]). Consistent with the pooled analysis, meta-analyses for all-cause mortality at week 52 also showed a clinically relevant and significant risk reduction in the pirfenidone group compared with the placebo group. Over 120 weeks, we noted significant differences in the pooled analysis favouring pirfenidone therapy compared with placebo for treatment-emergent all-cause mortality (p=0·0420), idiopathic-pulmonary-fibrosis-related mortality (0·0237), and treatment-emergent idiopathic-pulmonary-fibrosis-related (0·0132) mortality; similar results were shown by meta-analyses.

Interpretation: Several analytic approaches demonstrated that pirfenidone therapy is associated with a reduction in the relative risk of mortality compared with placebo over 120 weeks.

Pirfenidon ila sağkalım ortalama 8.7 yıldır ve en iyi destek tedaviden 2.5 yıl fazladır

Predicting Life Expectancy for Pirfenidone in Idiopathic Pulmonary Fibrosis

Mark Fisher, MSc; Steven D. Nathan, MD; Christian Hill, BSc; Jade Marshall, MSc; Fred Dejonckheere, MD; Per-Olof Thuresson, MSc; and Toby M. Maher, MD

TABLE 4 Comparison of Survival in Patients Receiving Pirfenidone and BSC Using the Weibull Distribution

	Survival (Years)		
	Pirfenidone	BSC	Difference
Median	7.25	4.67	2.58
Mean (95% CI)	8.72 (7.65-10.15)	6.24 (5.38-7.18)	2.47 (1.26-4.17)

BSC = best supportive care; CI = confidence interval.

J Manag Care Spec Pharm. 2017;23(3-b):S17-S24.

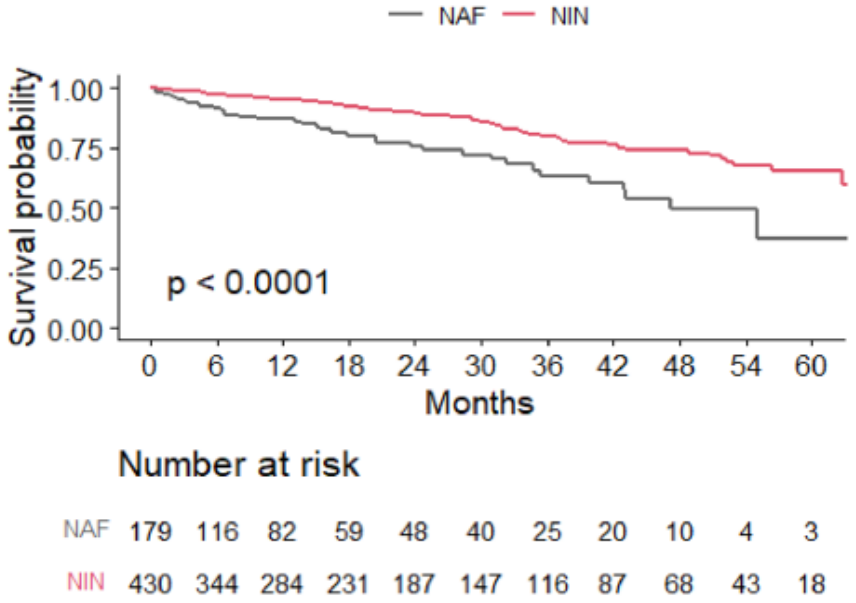
Nintedanib 5 yıllık mortalite riskini, antifibrotik almayan gruba göre %55 azaltmıştır.

Štefániková et al. BMC Pulmonary Medicine (2023) 23:154
https://doi.org/10.1186/s12890-023-02450-3

BMC Pulmonary Medicine

RESEARCH Open Access

The effect of nintedanib on lung functions and survival in idiopathic pulmonary fibrosis: real-life analysis of the Czech EMPIRE registry



Characteristic	Median of survival (months)	1-year survival (95% CI)	3-year survival (95% CI)	5-year survival (95% CI)
NAF	47	0.87 (0.81-0.93)	0.63 (0.53-0.76)	0.37 (0.19-0.71)
NIN	*NA*	0.95 (0.93-0.98)	0.80 (0.74-0.85)	0.65 (0.57-0.75)
HR (95% CI)[1] for NIN		0.45 (0.30-0.68), p<0.001		
Adj HR[2] for NIN		0.45 (0.29-0.69), p<0.001		

NIN – patients treated with nintedanib; NAF – patients with no-antifibrotic treatment
[1]HR = Hazard Ratio, CI = Confidence Interval
[2]Adj HR – Hazard ratio adjusted on sex, age and baseline FVC level

Fig. 1 Overall survival of patients with nintedanib (NIN) and with no-antifibrotic (NAF) treatment

Ortalama survi nintedanib grubunda 8.5 yıl iken, plasebo grubunda 3.3 yıldır

BMJ Open Respiratory Research

Safety and survival data in patients with idiopathic pulmonary fibrosis treated with nintedanib: pooled data from six clinical trials

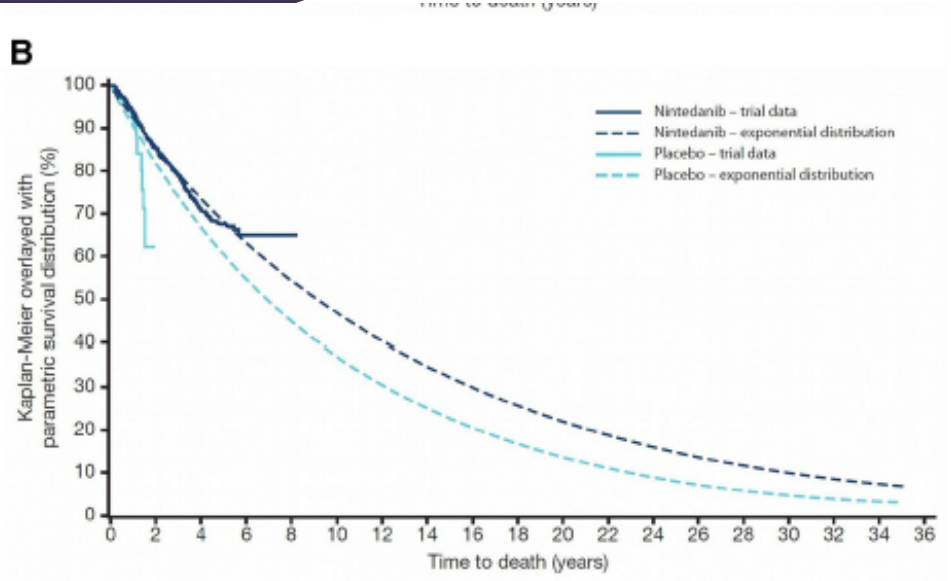


Figure 2 Estimated time to death using (A) the Weibull distribution and (B) exponential distribution.

nintedanib.

Modelling and extrapolation of survival data from the clinical trials included in this pooled analysis suggest that nintedanib extends life expectancy in patients with IPF. Median survival based on the better fitting statistical model (Weibull) was extended by approximately 5 years in patients treated with nintedanib compared with placebo. Clearly such extrapolations have limitations and should be interpreted with caution, but these data add to the growing body of evidence suggesting that antifibrotic therapies are associated with improved survival in patients with IPF.[6 12 23–26]

Strengths of these analyses include the use of a large and well-characterised cohort of patients participating in prospectively designed clinical trials and a maximum treatment duration of over 7 years. Limitations include

Nintedanib ile İPF de akut alevlenme riski %37 azalmıştır

Impact of Antifibrotic Therapy on Mortality and Acute Exacerbation in Idiopathic Pulmonary Fibrosis: A Systematic Review and Meta-Analysis

Abstract

Background: Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing interstitial lung disease associated with significant morbidity and mortality. Nintedanib and pirfenidone are two antifibrotic medications currently approved for slowing the rate of lung function decline in IPF, but data on treatment effect on mortality and risk of acute exacerbation (AE) remains limited or unknown.

Research question: Does antifibrotic treatment decrease risk of mortality and AE?

Study design and methods: A comprehensive search of several databases, including Ovid MEDLINE(R), Ovid Embase, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus, was conducted. Studies were included if they were original articles comparing mortality or AE events in IPF patients with and without antifibrotic treatment. Relative risk (RR) with 95%CI was pooled using random-effects meta-analyses with inverse variance method, assessing two primary outcomes of all-cause mortality and AE risk.

Results: A total of 12,956 patients across 26 studies (eight randomized controlled trials and 18 cohort studies) were included in the meta-analysis. Antifibrotic treatment was associated with decreased risk of all-cause mortality with a pooled RR of 0.55 (95% CI, 0.45-0.66) and I^2 of 82%. This effect was consistent across additional subgroup analyses, including stratification by study type, risk of bias, duration of follow-up, and antifibrotic subtype. Antifibrotic treatment also reduced the risk of AE, with a pooled RR of 0.63 (95% CI, 0.53-0.76), and I^2 of 0%. Effect on AE risk was consistent across subgroup analyses by study type and for nintedanib but not for pirfenidone.

Interpretation: Antifibrotic treatment appears to reduce the risk of all-cause mortality and AE in IPF. Despite greater heterogeneity with pooled analysis, its effect was robust in subgroup analyses by study type, duration of follow-up, and antifibrotic subtype.

Keywords: acute exacerbation; antifibrotic; idiopathic pulmonary fibrosis; mortality; nintedanib; pirfenidone.

Perioperatif Pirfenidon tedavisi postop AE-İPF için proflaktik etki gösterir.

Effect of Perioperative Pirfenidone Treatment in Lung Cancer Patients With Idiopathic Pulmonary Fibrosis

Background: Acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) is a life-threatening complication of lung cancer operation for patients with IPF, and no effective prophylaxis has ever been reported. In this study, we investigate the effect of perioperative treatment with an anti-IPF agent on reduction of the risk of developing AE-IPF.

Methods: A consecutive series of 50 lung cancer patients with IPF who underwent operations at our institution from October 2006 to October 2014 was retrospectively investigated. Since September 2009, pirfenidone was orally administered to patients from 4 weeks before operation to 4 weeks after operation. Thirty-one patients received the perioperative pirfenidone treatment (PPT), and their clinical outcome was retrospectively compared with that of 19 patients who did not receive PPT.

Results: No differences were found in age, smoking history, sex, vital capacity, KL-6, procedure, or risk score (10.5 ± 2.2 versus 11.2 ± 1.5) between the PPT and non-PPT groups. The incidence of AE-IPF for the PPT/non-PPT groups was 0.0%/10.5% within 30 postoperative days ($p = 0.07$) and 3.2%/21.1% within 90 postoperative days ($p = 0.04$), respectively. Logistic regression analysis showed a significant association between PPT and the incidence of AE-IPF within 30 ($p = 0.045$) and 90 ($p = 0.04$) postoperative days.

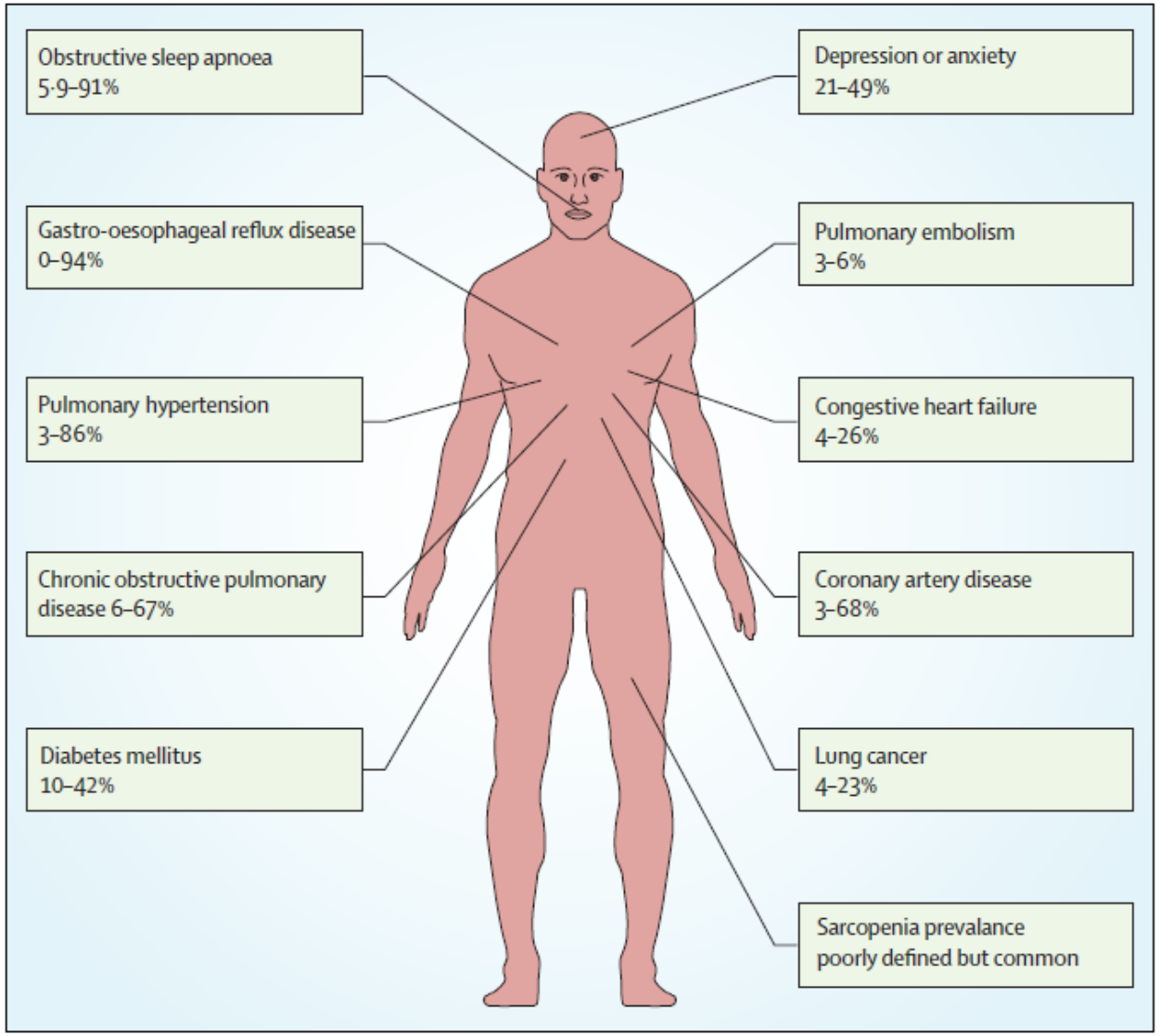
Conclusions: A prophylactic effect of PPT for postoperative AE-IPF in patients with lung cancer was suggested. Further confirmatory prospective studies should be considered for PPT.

Ann Thorac Surg
2016;102:1905–10

İPF

Komorbiditeler

Idiopathic pulmonary fibrosis: effects and optimal management of comorbidities



Lancet Respir Med 2016

İPF

Komorbiditeler

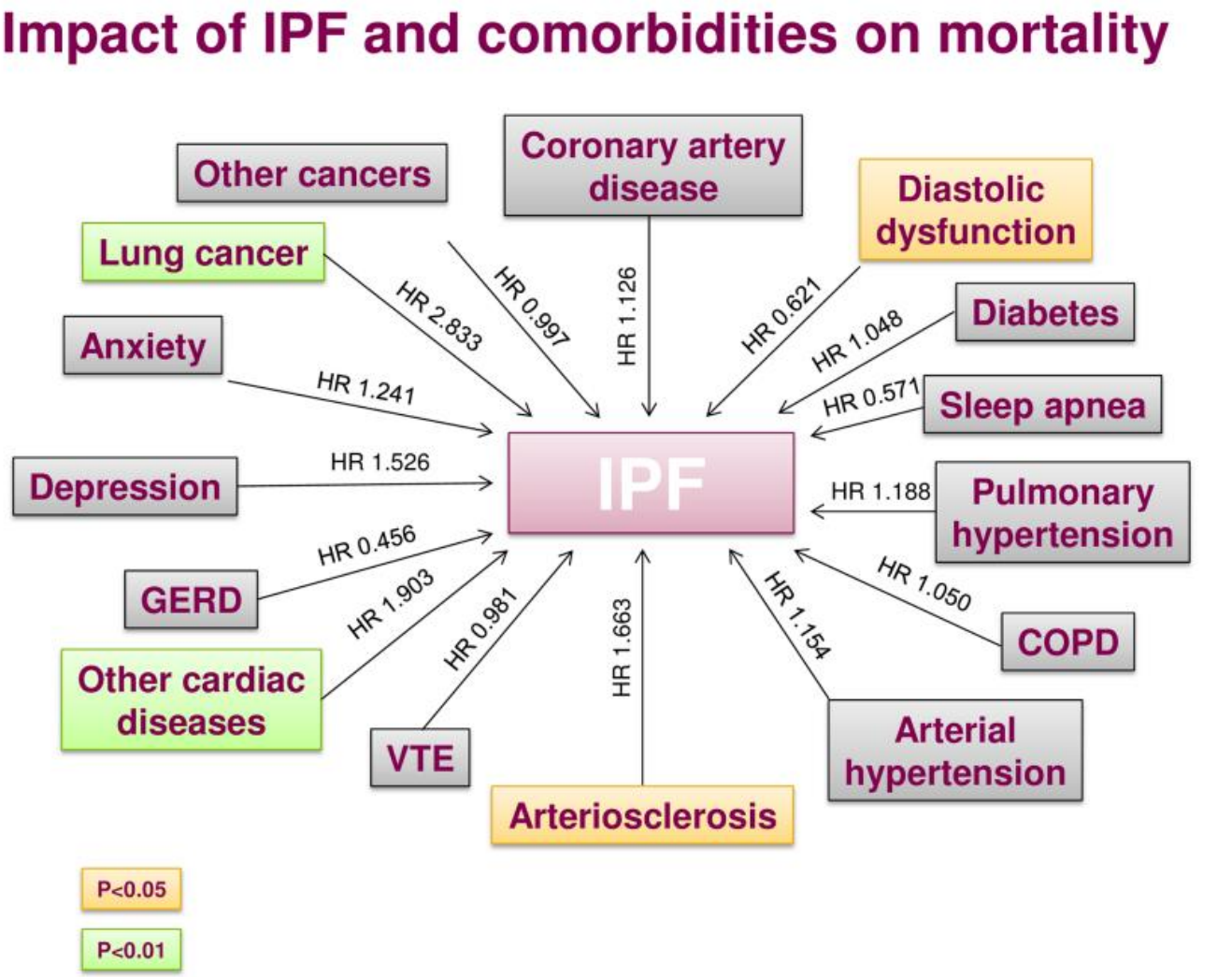


Fig 5. Impact of idiopathic pulmonary fibrosis and comorbidities on mortality. Hazard ratios (HR) have been determined using a predictive multivariate Cox proportional hazards regression model.

doi:10.1371/journal.pone.0151425.g005

İPF de pulmoner hipertaniyon gelişmesi mortalite ile kuvvetle ilişkli!!

International Journal of *Environmental Research and Public Health*

MDPI

Article

Mortality Associated with Idiopathic Pulmonary Fibrosis in Northeastern Italy, 2008–2020: A Multiple Cause of Death Analysis

Alessandro Marcon [1,*], Elena Schievano [2] and Ugo Fedeli [2]

Table 3. Proportion of death certificates mentioning selected complications/comorbidities and associations between IPF and these conditions.

Condition (ICD10)	Deaths with IPF (n = 2251)	Deaths without IPF (n = 555,681)	Odds Ratio (95% Confidence Interval)
Pulmonary hypertension (I27)	12.5%	0.8%	15.7 (13.8–17.9)
Congestive heart failure (I50.0)	2.5%	1.8%	1.5 (1.2–2.0)
Influenza, pneumonia (J09–J18)	15.3%	10.2%	1.6 (1.5–1.8)
Pulmonary embolism (I26.x)	2.8%	2.0%	1.4 (1.0–1.7)
COPD (J40–J44, J47)	12.9%	7.2%	1.8 (1.6–2.0)
Esophagitis/reflux (K20, K21)	0.3%	0.1%	2.9 (1.3–6.5)
Conditions causally related to pulmonary fibrosis (M05–M08, M32–M36, D86, J60–J65, J67, J70.1)	8.0%	0.8%	9.8 (8.3–11.5)

İPF- Ac ca

Original article

Reduced incidence of lung cancer in patients with idiopathic pulmonary fibrosis treated with pirfenidone

Table 4 – Outcome and causes of death.

	Pirfenidone	Non-pirfenidone
Alive	36 (43.4)	76 (42.7)
Dead	29 (34.9)	56 (31.5)
Causes of death		
Acute exacerbation	10 (34.5)	28 (50.0)
Respiratory failure	9 (31.0)	4 (7.1)
Infection	4 (13.8)	7 (12.5)
Lung cancer	1 (3.5)	9 (16.1)
Acute myocardial infarction	0	1 (1.8)
Other organs cancers	0	1 (1.8)
Gastrointestinal bleeding	0	1 (1.8)
Unknown	5 (17.2)	5 (8.9)
Transferred to other hospitals	18 (21.7)	46 (25.8)

Data are presented as n (%).

A B S T R A C T

Background: Idiopathic pulmonary fibrosis (IPF) is a disease with a worse prognosis than some types of cancer. In patients with IPF, lung cancer is critical because of the associated high mortality rate from its progression and fatal complications from anticancer treatments. Therefore, preventing lung cancer in patients with IPF is primordial. Pirfenidone is an anti-fibrotic agent that reduces the decline in forced vital capacity. This study aimed to assess the effect of pirfenidone in the development of lung cancer in patients with IPF.

Methods: Data from 261 patients with IPF with and without pirfenidone were retrospectively reviewed, and the incidence of lung cancer was analyzed.

Results: In the pirfenidone group, the incidence of lung cancer was significantly lower than in the non-pirfenidone group (2.4% *vs.* 22.0%, $P < 0.0001$). Multivariate Cox proportional hazards regression analysis demonstrated that pirfenidone decreased the risk of lung cancer (hazard ratio, 0.11; 95% confidence interval, 0.03 to 0.46; $P = 0.003$), whereas coexisting emphysema increased the incidence of lung cancer (hazard ratio, 3.22; 95% confidence interval, 1.35 to 7.70; $P = 0.009$).

Respir Investig. 2018 Jan;56(1):72–79.

Pirfenidon
Yan etkiler

BMJ Open Respiratory Research

Safety of pirfenidone in patients with idiopathic pulmonary fibrosis: integrated analysis of cumulative data from 5 clinical trials

Table 3 Treatment-emergent adverse events*

	Integrated population (N=1299)†	Phase 3 multinational trials‡ Pirfenidone (N=623)	Placebo (N=624
Duration of exposure, median (range), years	1.7 (>0, 9.9)	1.0 (>0, 2.3)	1.0 (>0, 2.3)
Treatment-emergent adverse event, %			
Nausea	37.6	36.1	15.5
Cough	35.1	27.8	29.2
Dyspnoea	30.9	16.9	20.2
Upper respiratory tract infection	30.6	26.8	25.3
Idiopathic pulmonary fibrosis	29.3	13.0	19.9
Fatigue	28.2	26.0	19.1
Diarrhoea	28.1	25.8	20.4
Rash	25.0	30.3	10.3
Bronchitis	23.8	14.1	15.4
Headache	21.6	22.0	19.2
Nasopharyngitis	21.3	16.7	17.9
Dizziness	21.2	18.0	11.4
Dyspepsia	18.4	18.5	6.9
Vomiting	15.9	13.3	6.3
Weight decreased	15.6	10.1	5.4
Back pain	15.4	10.4	10.4
Anorexia	15.2	13.0	5.0

*Occurring in ≥15% of patients in the cumulative clinical database.
†Includes two patients in study 002 with a diagnosis of "pulmonary fibrosis."
‡CAPACITY (studies 004 and 006) and ASCEND (study 016).

TEMEL MESAJLAR

Bu bulgular, pirfenidon tedavisi uygulanmış 1299 idiyopatik pulmoner fibrozis hastasından oluşan, iyi tanımlanmış, geniş bir kohorta ait güvenlilik sonlanımlarının kapsamlı bir analizini temsil etmektedir.

İleriye dönük olarak 9.9 yıl sürdürülen bu uzun dönemli izleme sırasında, pirfenidonun güvenli olduğu ve genellikle iyi tolere edildiği gösterilmiştir.

En yaygın advers olaylar gastrointestinal sistemle ve deriyle ilişkilidir ve bunlar genellikle hem hafif ya da orta şiddette hem de doz değişikliklerine yanıt veren olaylardır.

Tipik olarak tedavinin ilk 6 ayı içinde aminotransferaz değerlerinde gözlemlenen artışların genellikle geçici olduğu ve doz değişikliği ya da tedavinin kesilmesiyle klinik sekel bırakmadan yok olduğu belirlenmiştir.

Nintedanib
En sık yan etki: Diyare

Kalıcı tedavi bırakılması %3.5

Table 3. Adverse Events.

Event	INPULSIS-1		INPULSIS-2	
	Nintedanib (N=309)	Placebo (N=204)	Nintedanib (N=329)	Placebo (N=219)
	number of patients (percent)			
Any adverse event	298 (96.4)	181 (88.7)	311 (94.5)	198 (90.4)
Any adverse event, excluding progression of idiopathic pulmonary fibrosis*	296 (95.8)	179 (87.7)	311 (94.5)	197 (90.0)
Most frequent adverse events†				
Diarrhea	190 (61.5)	38 (18.6)	208 (63.2)	40 (18.3)
Nausea	70 (22.7)	12 (5.9)	86 (26.1)	16 (7.3)
Nasopharyngitis	39 (12.6)	34 (16.7)	48 (14.6)	34 (15.5)
Cough	47 (15.2)	26 (12.7)	38 (11.6)	31 (14.2)
Progression of idiopathic pulmonary fibrosis*	31 (10.0)	21 (10.3)	33 (10.0)	40 (18.3)
Bronchitis	36 (11.7)	28 (13.7)	31 (9.4)	17 (7.8)
Upper respiratory tract infection	28 (9.1)	18 (8.8)	30 (9.1)	24 (11.0)
Dyspnea	22 (7.1)	23 (11.3)	27 (8.2)	25 (11.4)
Decreased appetite	26 (8.4)	14 (6.9)	42 (12.8)	10 (4.6)
Vomiting	40 (12.9)	4 (2.0)	34 (10.3)	7 (3.2)
Weight loss	25 (8.1)	13 (6.4)	37 (11.2)	2 (0.9)
Severe adverse events‡	81 (26.2)	37 (18.1)	93 (28.3)	62 (28.3)
Serious adverse events‡	96 (31.1)	55 (27.0)	98 (29.8)	72 (32.9)
Fatal adverse events	12 (3.9)	10 (4.9)	25 (7.6)	21 (9.6)
Adverse events leading to treatment discontinuation§	65 (21.0)	22 (10.8)	58 (17.6)	33 (15.1)
Gastrointestinal disorders	26 (8.4)	3 (1.5)	21 (6.4)	2 (0.9)
Respiratory, thoracic, and mediastinal disorders	12 (3.9)	10 (4.9)	8 (2.4)	18 (8.2)
Investigation results¶	10 (3.2)	1 (0.5)	8 (2.4)	1 (0.5)
Cardiac disorders	5 (1.6)	4 (2.0)	2 (0.6)	3 (1.4)
General disorders and conditions involving site of study-drug administration‖	8 (2.6)	3 (1.5)	2 (0.6)	1 (0.5)

Nintedanib iyi tolere edilir ve yan etkileri birçok hastada yönetilebilir

BMJ Open Respiratory Research

Safety and survival data in patients with idiopathic pulmonary fibrosis treated with nintedanib: pooled data from six clinical trials

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ABSTRACT

Introduction Nintedanib slows disease progression in patients with idiopathic pulmonary fibrosis (IPF) by reducing the rate of decline in forced vital capacity, with an adverse event profile that is manageable for most patients. We used data from six clinical trials to characterise the safety and tolerability profile of nintedanib and to investigate its effects on survival.

Methods Data from patients treated with ≥1 dose of nintedanib 150 mg two times per day or placebo in the 52-week TOMORROW trial and/or its open-label extension; the two 52-week INPULSIS trials and/or their open-label extension, INPULSIS-ON; and a Phase IIIb trial with a placebo-controlled period of ≥6 months followed by open-label nintedanib were pooled. All adverse events, irrespective of causality, were included in descriptive

Key messages

- Is nintedanib therapy well tolerated in patients with idiopathic pulmonary fibrosis (IPF) and does it improve survival?
- Data from 1126 patients with IPF participating in prospective clinical trials showed that the adverse event profile of nintedanib was manageable for most patients; extrapolation of survival data suggested that nintedanib extends life expectancy.
- This is the largest data set on nintedanib to be published to date and the first analyses to estimate life expectancy in patients with IPF treated with nintedanib based on extrapolation of survival data from clinical trials.

KCFT ARTIŞI

- Tedavi öncesi AST, ALT ve bilirubin bakılmalı
- Tedavide 2., 4. haftalar, ayda bir ve daha sonra 3 ayda bir takip yapılmalıdır
- Semptom ve hiperbilirubinemi olmadan KCFT >3-≤5x ULN ise değerler normale dönünceye kadar doz azaltılabilir ya da tedaviye ara verilebilir
- ≤5x ULN ve hiperbilirubinemi eşlik ediyorsa veya veya KCFT >5x ULN ise tedavi tamamen bırakılmalıdır.

İZLEM

Hastalar her 12 ayda bir yeniden değerlendirilmelidir.

FVC’de ≥%10 düşme olmadığı her raporda belirtilmelidir.

FVC değerinde ≥%10 düşme olması ilaca yanıtsızlık olarak kabul edilir ve tedavi sonlandırılır.

İlaçlardan birine yanıtsızlık veya intolerans gelişmişse ilaçlar arasında geçiş yapılabilir.

Teşekkürler..