Progresivna plućna fibroza

Prof dr Bakir Mehić

Specijalistički seminar „Bolesti plućnog intersticijuma“

Sarajevo, 07.12.2024.

Opća bolnica „Prim dr Abdulah Nakaš“

Terminology in *Progressive* Fibrosis

- Progressive fibrotic phenotype
- Progressive fibrotic interstitial lung disease (PF-ILD)
- **Progressive pulmonary fibrosis (PPF)**

- *PPF (despite optimal management)?*

Progressive pulmonary fibrosis: an expert group consensus statement

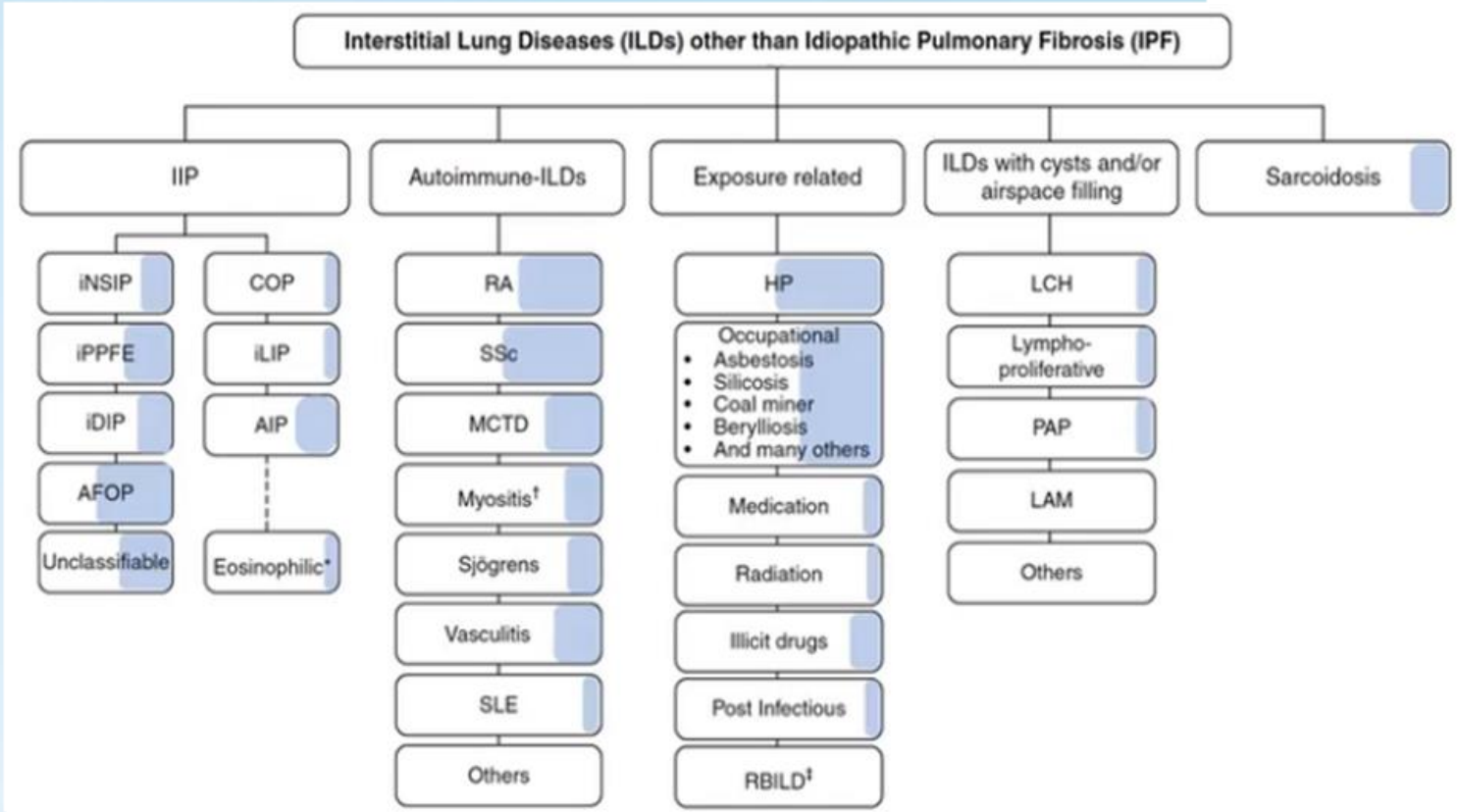
Sujeet K. Rajan, Vincent Cottin, Raja Dhar, Sonye Danoff, Kevin R. Flaherty, Kevin K. Brown, Anant Mohan, Elizabeth Renzoni, Murali Mohan, Zarir Udwadia, Padmanabha Shenoy, David Currow, Anand Devraj, Bhavin Jankharia, Ritu Kulshrestha, Steve Jones, Claudia Ravaglia, Silvia Quadrelli, Rajam Iyer, Sahajal Dhooria, Martin Kolb, and Athol U. Wells

Raghu, G *et al. Am. J. Respir. Crit. Care Med.* 9, e18-e47 (2022), PMID: 35486072.

Rajan, SK *et al. Eur. Respir. J.* 3, doi:10.1183/13993003.03187-2021 (2023), PMID: 36517177.

Etiologies of Progressive Pulmonary Fibrosis

Approximately 18–32% of non-IPF ILDs progress despite initial treatment within 61–80 months



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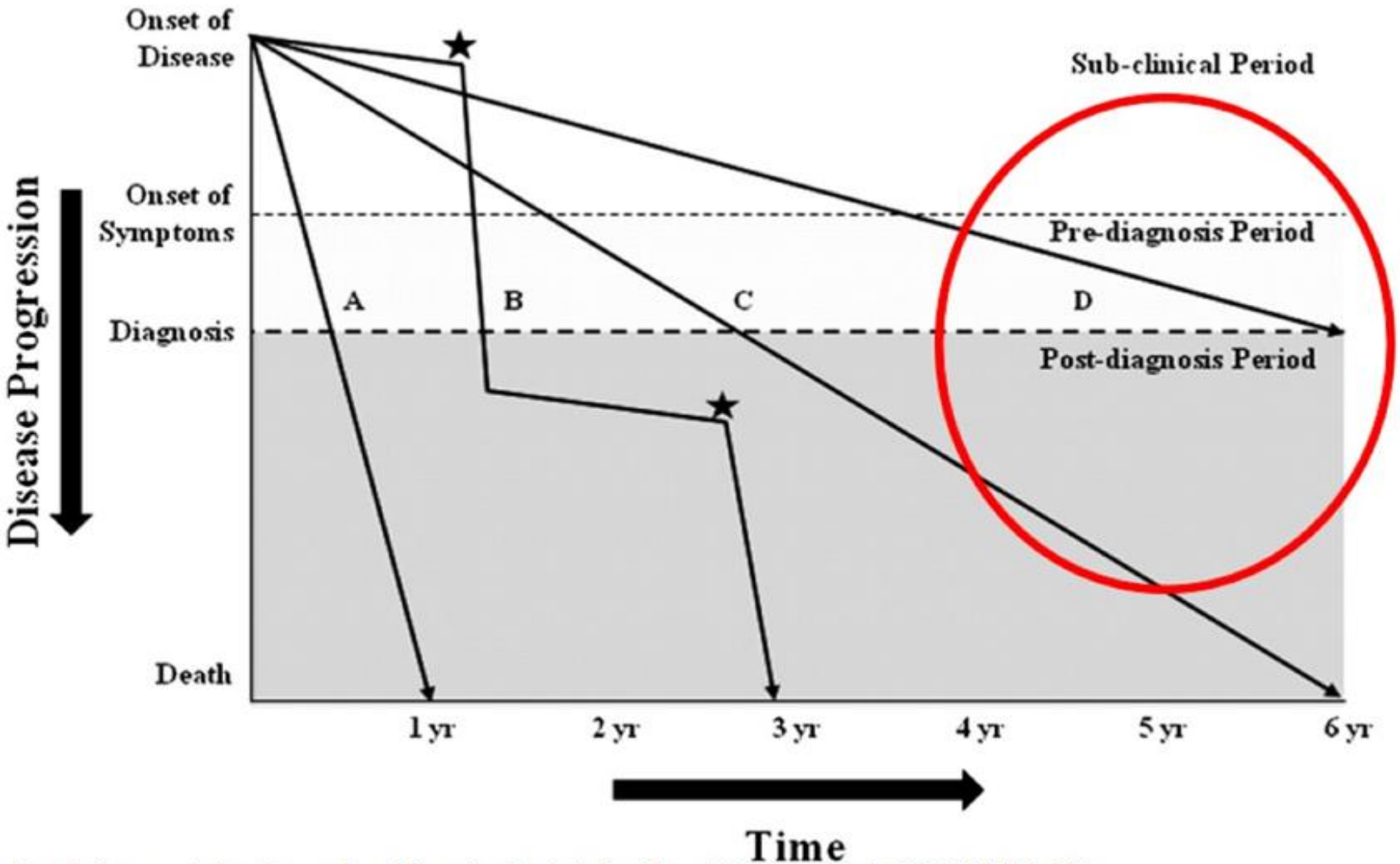
Longitudinal change

Non-IPF Can Have Slow Progression



In some patients, progression is slow

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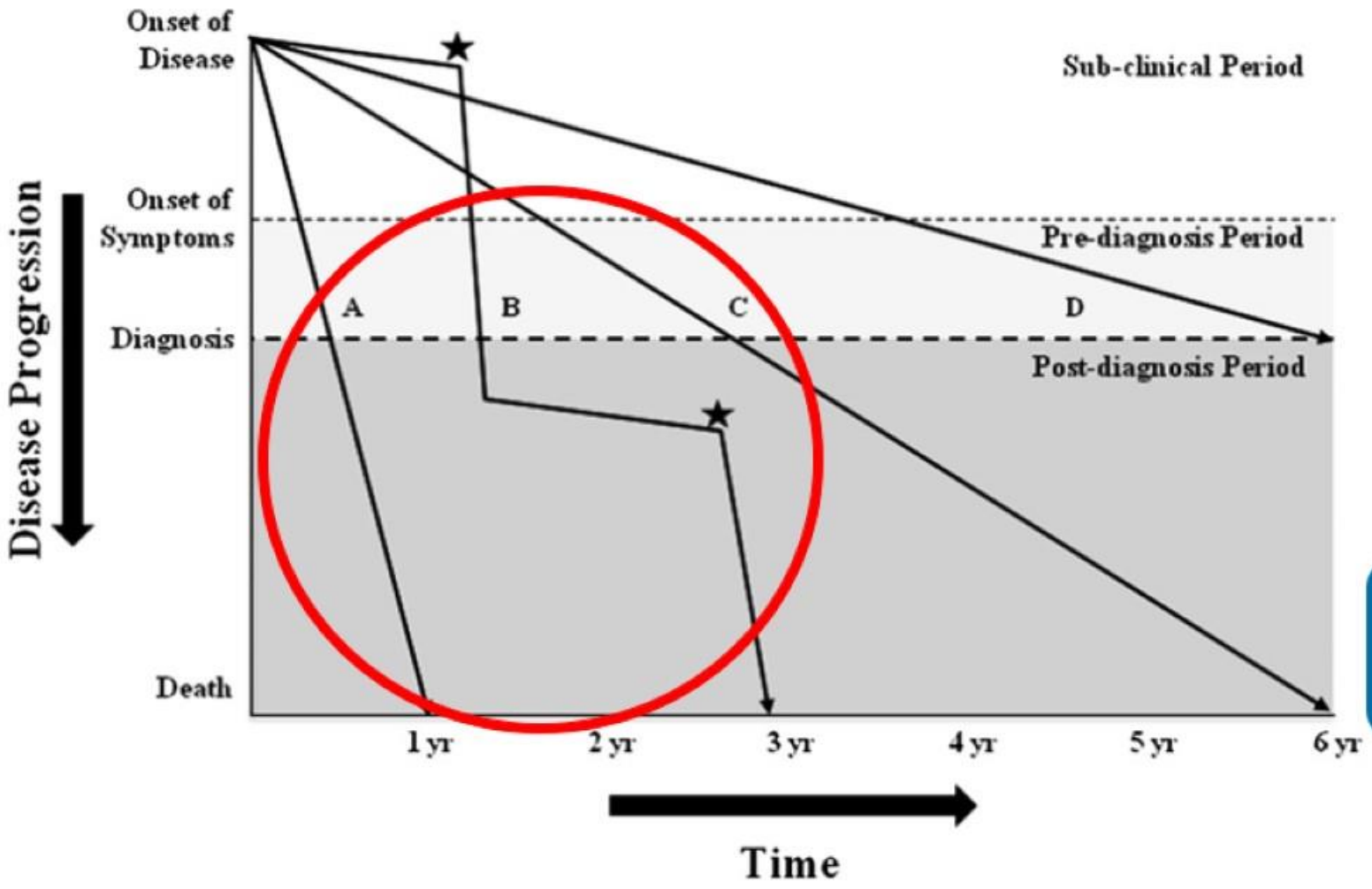
Longitudinal Change

Non-IPF Can Have Rapid Progression



Faktori koji su povezani sa kraćim vremenom preživljavanja zbog PPF uključuju: dob, pušački staž, niži indeks tjelesne mase (BMI), ozbiljnije fiziološko oštećenje, veću radiološku proširenost bolesti i razvoj drugih komplikacija ili stanja, posebno plućne hipertenzije, emfizema i raka pluća

In other patients, progression can be very fast

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PPF Definicija

Kod bolesnika s ILD poznate ili nepoznate etiologije (osim IPF), koji imaju radiološke dokaze plućne fibroze, **PPF se definira kao najmanje dva od sljedeća tri kriterija** koja su se pojavila u protekloj godini bez alternativnog objašnjenja:

1. **Pogoršanje respiratornih simptoma**
2. **Dokaz progresije bolesti u plućnim funkcijama** (kao slijedeće)
    a. apsolutno smanjenje in FVC ≥5% unutar jedne godine dana praćenja
        (npr. pacijent prelazi s predviđenih od 60% na 55% FVC FVC)
    b. apsolutno smanjenje DLCO ≥10% unutar jedne godine dana praćenja
3. **Radiološki dokaz progresije bolesti** (kao slijedeće)
    a. porast opsega ili ozbiljnosti trakcionih bronhiektazija i bronhioloektazija
    b. nove ground-glass opacifikacije sa trakcionim bronhiektazijama
    c. nove fine retikulacije
    d. porast opsega i porast grubosti ranijih retikularnih abnormaliteta
    e. novo ili povećanje postojećeg saća
    f. povećanje gubitka lobarnog volumena

Monitoring Disease Progression

Is the ILD Progressing?

Definition of PPF

In a patient with ILD of known or unknown etiology other than IPF who has radiological evidence of pulmonary fibrosis, PPF is defined as at least two of the following three criteria occurring within the past year with no alternative explanation*:

1	Worsening respiratory symptoms	Every 3 months
2	Physiological evidence of disease progression (either of the following): a. Absolute decline in FVC ≥5% predicted within 1 yr of follow-up b. Absolute decline in D_{LCO} (corrected for Hb) ≥10% predicted within 1 yr of follow-up	Every 3-6 months
3	Radiological evidence of disease progression (one or more of the following): a. Increased extent or severity of traction bronchiectasis and bronchiolectasis b. New ground-glass opacity with traction bronchiectasis c. New fine reticulation d. Increased extent or increased coarseness of reticular abnormality e. New or increased honeycombing f. Increased lobar volume loss	Every 12 months or as needed

Raghu G, et al. *Am J Crit Care Resp Med*. 2022;205:e18-e47.

Routine Monitoring of Patients With PF-ILDs (Non-IPF)

Proposed criteria that may be used in clinical practice to assess disease progression in fibrotic interstitial lung diseases

Symptoms and patient-reported outcomes	Change in symptoms Change in everyday life exercise capacity Questionnaires on shortness of breath, cough, and/or quality of life

<u>Pacijenti se prezentiraju sa:</u>

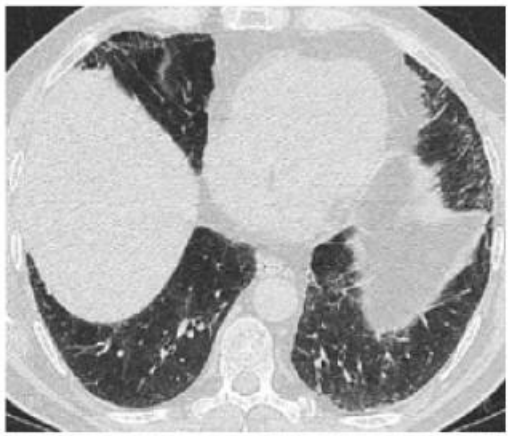
- Dispnoom na napor,
- Kašljem,
- Zamorom koji ne odgovara uloženom naporu

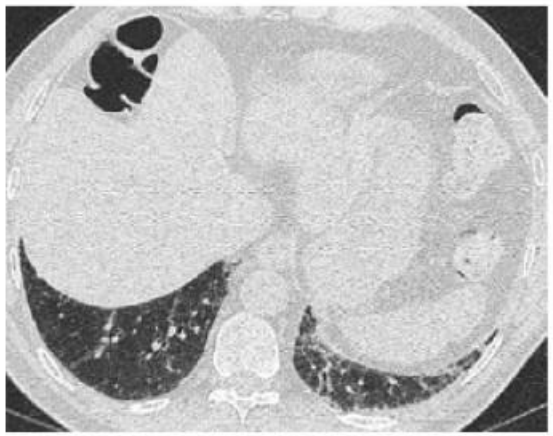
Fizikalnim pregledom se nađu:

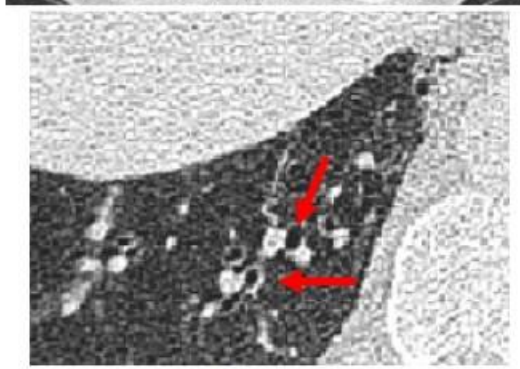
- Fina auskultatorna pucketanja,
- Inspiratorno škripanje
- Naglašen II ton nad pulmonalnim ušćem, desnostrano odizanje zida gr. koša, desnostrani galop,
- Batičasti prsti,
- Sinovitis, sklerodaktilija
- Osip

Serum biomarkers	None validated Not yet applicable in clinical practice

Traction Bronchiectasis







Right lung
First CT

Right lung
1 year later

Airway dilatation (arrows) increases as fibrosis progresses

Fibrosis occurring in the lower lobes is associated with traction bronchiectasis

Traction bronchiectasis is a valuable measure of disease progression because **it's in a linear relationship with disease worsening**

Images courtesy of Dr Joseph Jacob.

Milliron B, et al. *Radiographics*. 2015;35:1011-1030; Jacob J, et al. *Thorax*. 2020;75:648-654.

Summary of Radiographic Patterns

UIP

- RA (NSIP can occur)
- SSc (less common than NSIP)

NSIP

- SSc
- MCTD
- Myositis
- Sjogren's
- SLE

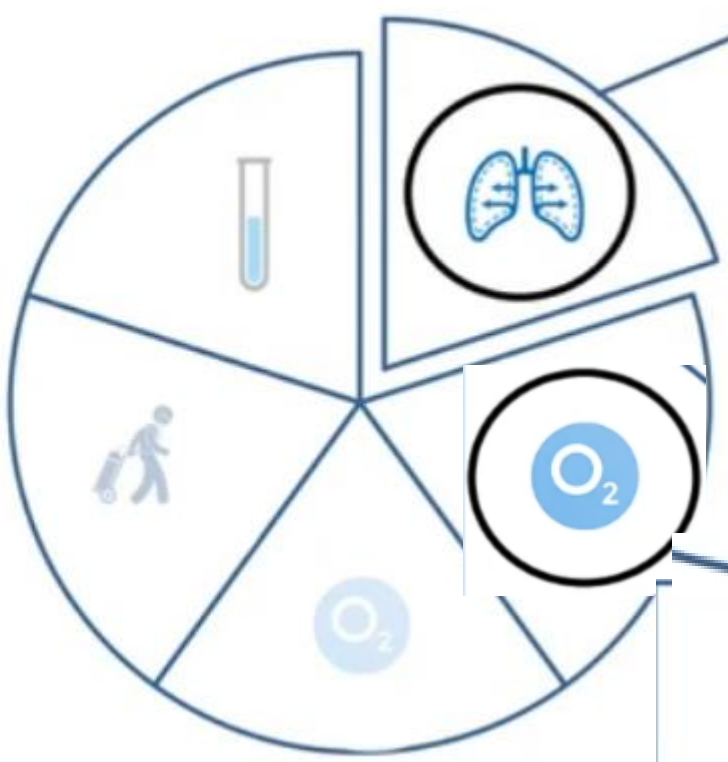
OP

- Myositis
- RA

LIP

- Sjogren's

Plućne funkcije i kapacitet za napor



Pulmonary Function Testing

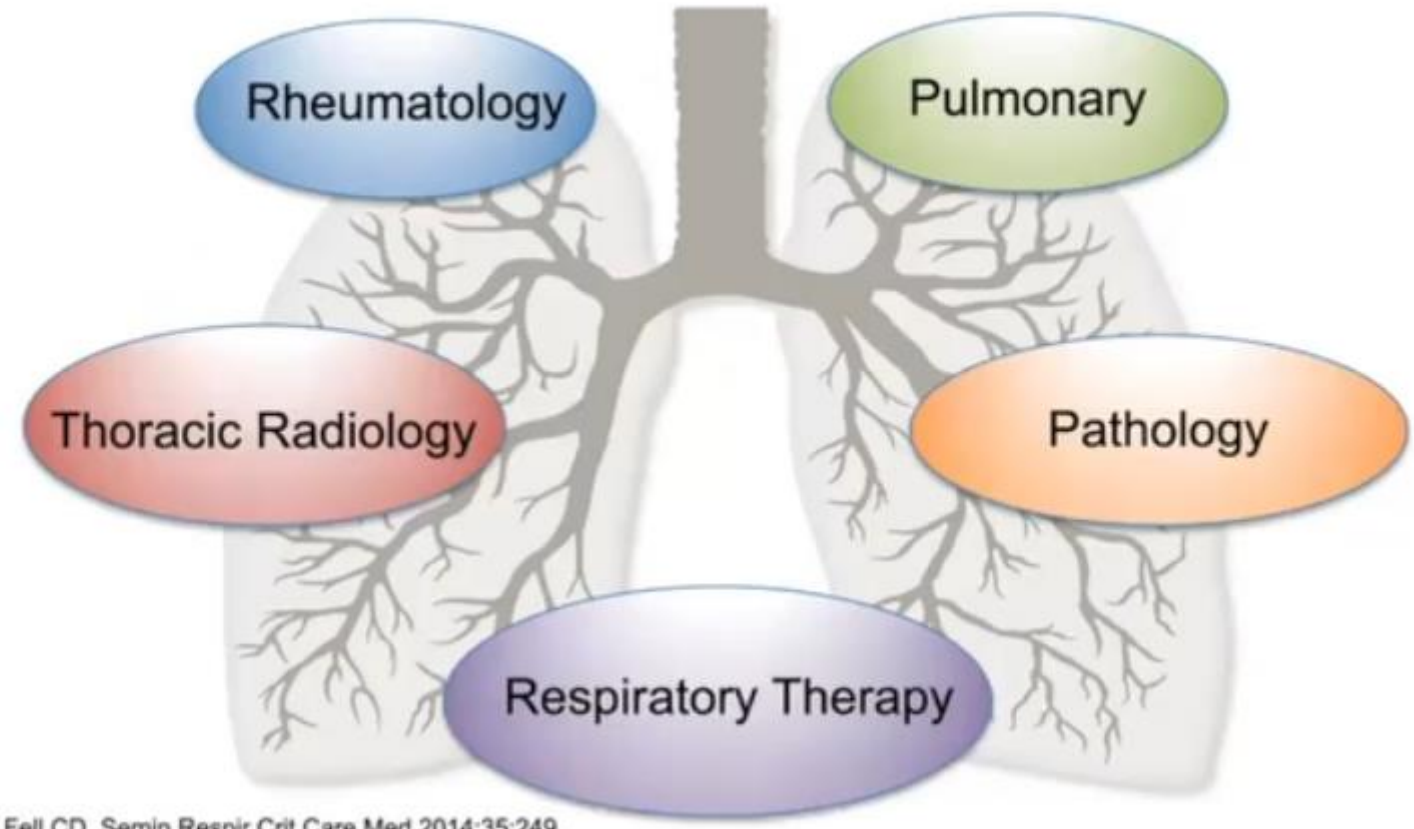
Restrictive physiology
- FVC
- DLCO
- TLC

Oxygen Desaturation with 6MWT

Exercise capacity	Absolute change in 6MWT distance Change in oxygen saturation nadir during 6MWT Change in maximal exercise capacity

MANAGEMENT OF PPF

Multi-Disciplinary Team (MDT)[1]



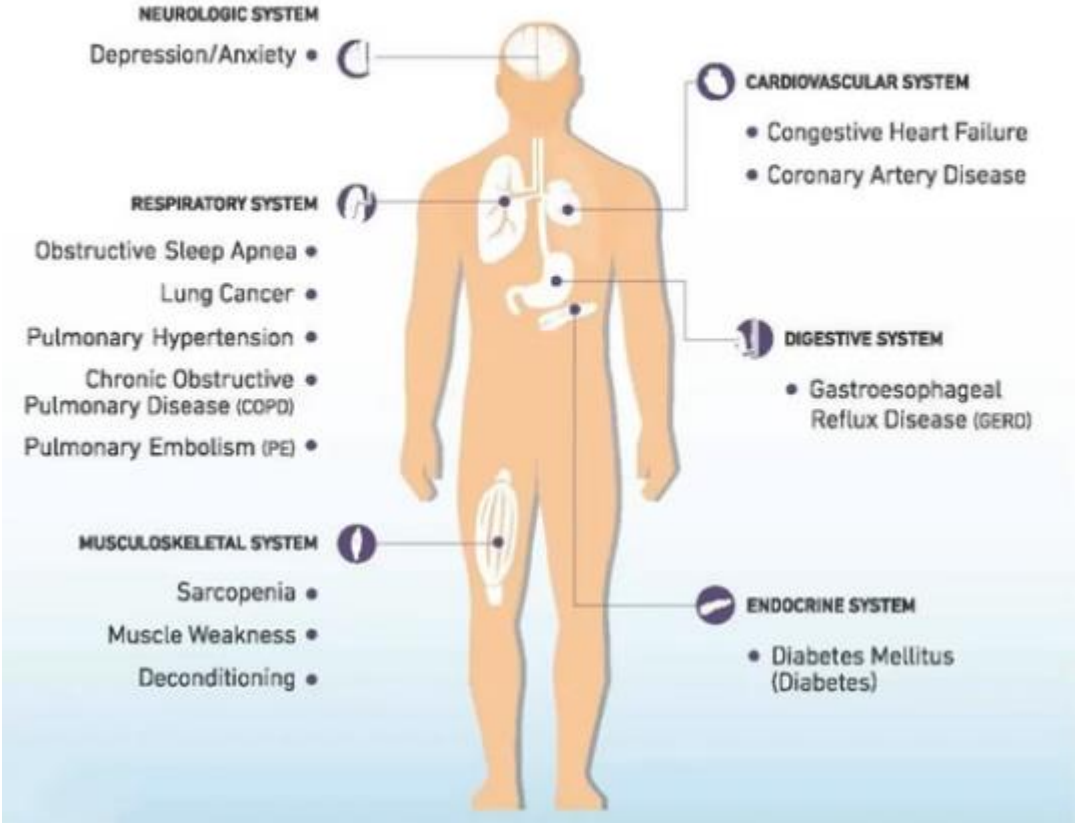
1. Mitto S, Fell CD. Semin Respir Crit Care Med 2014;35:249.

Need for supportive care	Initiation of ambulatory oxygen therapy at exercise Initiation of supplemental oxygen therapy at rest or change in flow of oxygen

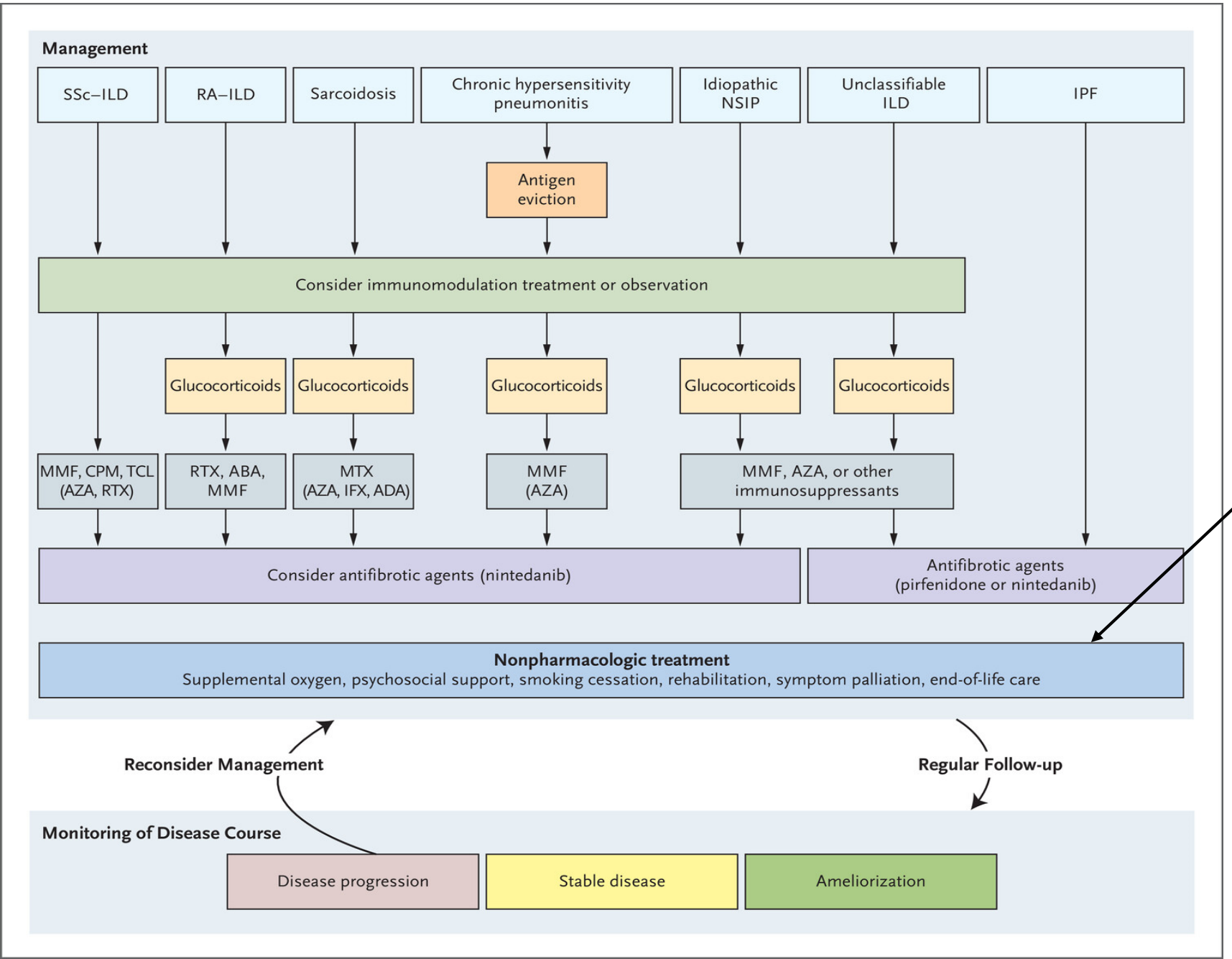
Treatment Approach in PPF

Anti-fibrotics should not be considered first-line therapy.

COMORBIDITIES



Algorithm for the Management of Progressive Fibrotic Phenotype



Osim u slučaju IPF terapija prve linije je imunomodulatorna terapija.

Pacijentima s idiopatskom plućnom fibrozom (IPF), antifibrotičke lijekove treba ponuditi prilikom postavljanja dijagnoze.

U zavisnosti od osnovnog stanja, antifibrotska terapija se razmatra u slučajevima progresije bolesti uprkos odgovarajućoj terapiji prve linije.

Nefarmakološko liječenje treba uzeti u obzir tokom cijelog toka bolesti.

Akutne egzacerbacije plućne fibroze takođe predstavljaju progresiju bolesti.

Legenda

ABA - abatacept, ADA - adalimumab, AZA - azatioprin, CPM - ciklofosfamid, IFX - infliksimab, MMF - mikofenolat mofetil, MTX - metotreksat, RA–ILD reumatoidni artritis i ILD, RTX - rituksimab, TCL - tocisilumab

Conventional and biological immunomodulators and approved antifibrotic therapy are used to treat CTD-ILDs

Conventional immunomodulators

- Corticosteroids
- AZA
- CYC
- MMF
- Cyclosporine
- Tacrolimus

Biological immunomodulators

- Rituximab
- Tocilizumab
- Abatacept

Approved antifibrotic therapy

- Nintedanib[7]

- In the US only, tocilizumab is licensed for slowing the rate of decline in pulmonary function in adult patients with SSc-ILD[8]
- Although not approved treatments, other immunomodulatory therapies are also frequently used to treat SSc-ILD and other CTD-ILDs in clinical practice*

Nintedanib je oralni intracelularni inhibitor tirozin kinaze. Blokira stanične signalne puteve uključene u napredovanje fibroze. Dnevna doza je 150 mg dva puta dnevno.

Recent data from clinical trials, and the emergence of approved treatment options for some patient subsets, may lead to a shift in the treatment paradigm for CTD-ILDs

*Corticosteroids, AZA, CYC, MMF and abatacept are not licensed for the treatment of SSc-ILD and other CTD-ILDs. Rituximab is licensed for the treatment of SSc in Japan only

AZA, azathioprine; CTD-ILD, connective tissue disease-associated interstitial lung disease; CYC, cyclophosphamide; MMF, mycophenolate mofetil; SSc-ILD, systemic sclerosis-associated interstitial lung disease; US, United States

1. Castelino FV, Varga, *J. Arthritis Res Ther* 2010;12:213; 2. Gutsche M *et al. Curr Respir Care Rep* 2012;1:224–32; 3. Vij R, Strek ME. *Chest* 2013;143:814–24; 4. Vacchi C *et al. J Clin Med* 2020;9:407; 5. Oliveira RP *et al. Pulmonology* 2020;doi:10.1016/j.pulmoe.2020.01.004; 6. Iqbal K, Kelly C. *Ther Adv Musculoskeletal Dis* 2015;7:247–67; 7. Nintedanib Summary of Product Characteristics. Available at: www.ema.europa.eu (accessed February 2023); 8. Tocilizumab Prescribing Information. Available at: https://www.fda.gov/Drugs (accessed February 2023)

Mehanizam djelovanja

Nintedanib je mala molekula, koja se kompetitivno veže na mjesto za adenozin-trifosfat (ATP) na:

- α i ß receptore faktora rasta koji potiču od trombocita (engl. *platelet-derived growth factor receptor*, PDGFR)
- receptor fibroblastnog faktora rasta (engl. *fibroblast growth factor receptor*, FGFR 1-3) i VEGFR 1-3
- kinaze: Lck (limfocit-specifična protein-tirozin-kinaza), Lyn (tirozin-protein-kinaza lyn), Src (protoonkogen protein-tirozin-kinaza src) i CSF1R (receptor faktora 1 stimulacije kolonija)

te blokira unutarstanične signalne kaskade tirozin-kinaze za koje je dokazano da su uključene u patogenezu remodeliranja fibroznog tkiva u intersticijskoj bolesti pluća.

Efikasnost i sigurnost Nintedaniba u Idiopatskoj plućnoj fibrozi

Dva ponovljena 52-sedmična, randomizirana, dvostruko slijepa ispitivanja faze 3 (INPULSIS-1 i INPULSIS-2) radi procjene efikasnosti i sigurnosti 150 mg nintedaniba dva puta dnevno u poređenju s placebom kod pacijenata s **progredirajućom idiopatskom plućnom fibrozom (IPF)**. Primarni cilj bio je godišnja stopa gubitka forsiranog vitalnog kapaciteta (FVC).

Study Overview

- In this randomized, placebo-controlled trial, treatment with nintedanib, an intracellular inhibitor of multiple tyrosine kinases, led to a reduced rate of loss of forced vital capacity in patients with idiopathic pulmonary fibrosis.

The NEW ENGLAND JOURNAL of MEDICINE

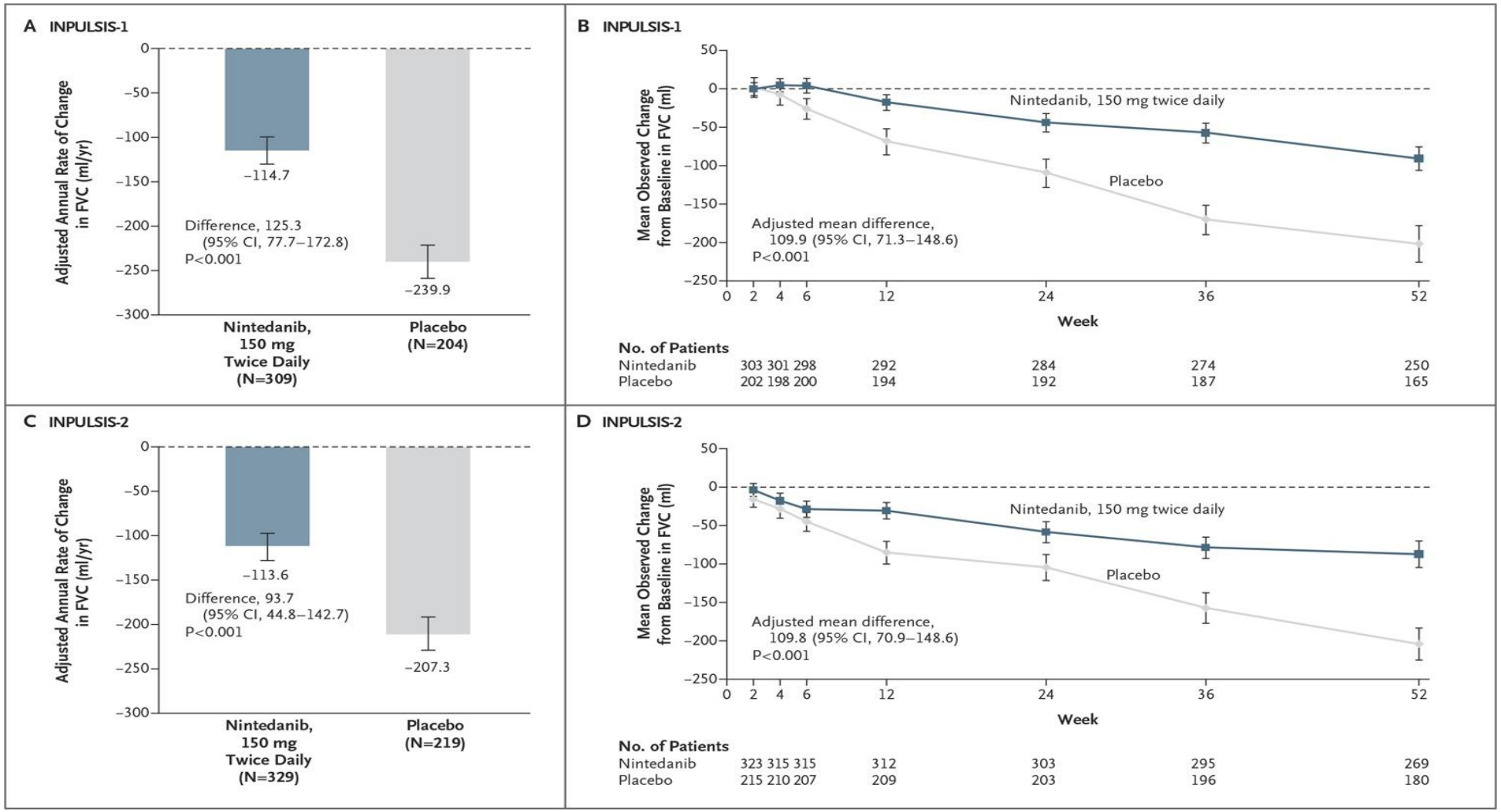
Osnovne karakteristike pacijenata u INPULSIS-1 i INPULSIS-2

Table 1. Baseline Characteristics of Patients in INPULSIS-1 and INPULSIS-2.*

Characteristic	INPULSIS-1		INPULSIS-2	
	Nintedanib (N=309)	Placebo (N=204)	Nintedanib (N=329)	Placebo (N=219)
Male sex — no. (%)	251 (81.2)	163 (79.9)	256 (77.8)	171 (78.1)
Age — yr	66.9±8.4	66.9±8.2	66.4±7.9	67.1±7.5
Weight — kg	82.0±16.8	81.2±16.3	76.6±15.9	76.3±16.5
Body-mass index†	28.6±4.5	28.1±4.6	27.6±4.6	27.2±4.5
Smoking status — no. (%)				
Never smoked	71 (23.0)	51 (25.0)	103 (31.3)	71 (32.4)
Former smoker	217 (70.2)	144 (70.6)	218 (66.3)	139 (63.5)
Current smoker	21 (6.8)	9 (4.4)	8 (2.4)	9 (4.1)
Time since diagnosis of idiopathic pulmonary fibrosis	1.7±1.4	1.6±1.4	1.6±1.3	1.6±1.3
Specimen from surgical lung biopsy available — no. (%)	60 (19.4)	33 (16.2)	84 (25.5)	52 (23.7)
Systemic corticosteroid therapy — no. (%)‡	68 (22.0)	43 (21.1)	68 (20.7)	46 (21.0)
FVC				
Mean — ml	2757±735	2845±820	2673±776	2619±787
Median — ml	2700	2721	2615	2591
Percentage of predicted value	79.5±17.0	80.5±17.3	80.0±18.1	78.1±19.0
FEV_1:FVC (%)	81.5±5.4	80.8±6.1	81.8±6.3	82.4±5.7
DLCO				
mmol/min/kPa	4.0±1.2	4.0±1.1	3.8±1.2	3.7±1.3
Percentage of predicted value§	47.8±12.3	47.5±11.7	47.0±14.5	46.4±14.8
SpO_2 — %	95.9±2.0	95.9±1.9	95.8±2.6	95.7±2.1
Total SGRQ score¶	39.6±17.6	39.8±18.5	39.5±20.5	39.4±18.7

* Plus–minus values are means ±SD. FEV_1 denotes forced expiratory volume in 1 second, FVC forced vital capacity, and SpO_2 oxygen saturation of peripheral blood.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Prednisone at a dose of no more than 15 mg per day or the equivalent was permitted if the dose had been stable for at least 8 weeks before screening.
§ The percentage of the predicted value for the diffusion capacity of the lung for carbon monoxide (DLCO) was calculated with the use of the equation described by the European Community for Steel and Coal in Cotes et al.[18] In INPULSIS-2, data were available for 218 patients in the placebo group.
¶ In INPULSIS-1, the total score on the St. George's Respiratory Questionnaire (SGRQ) was available for 298 patients in the nintedanib group and 202 patients in the placebo group; in INPULSIS-2, the total SGRQ score was available for 326 patients in the nintedanib group and 217 patients in the placebo group. The total score ranges from 0 to 100, with higher scores indicating worse health-related quality of life.

Godišnja stopa pada i promjene u odnosu na početnu vrijednost u FVC tokom vremena u INPULSIS-1 i INPULSIS-2, prema studijskoj grupi



Kod pacijenata sa idiopatskom plućnom fibrozom, nintedanib je **smanjio pad FVC**, što je pratilo usporavanje progresije bolesti; nintedanib je često bio povezan s dijarejom, što je dovelo do prekida liječenja ispitivanim lijekom kod manje od 5% pacijenata.

Neželjeni efekti terapije

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)

* Progression of idiopathic pulmonary fibrosis was defined in accordance with the definition of idiopathic pulmonary fibrosis in the *Medical Dictionary for Regulatory Activities,* version 16.1, which includes disease worsening and exacerbations of idiopathic pulmonary fibrosis.
† The most frequent adverse events were defined as those with an incidence of more than 10% in any study group.
‡ A severe adverse event was related to intensity and was defined as an event that was incapacitating or that caused an inability to work or to perform usual activities. A serious adverse event was defined as any adverse event that resulted in death, was immediately life-threatening, resulted in persistent or clinically significant disability or incapacity, required or prolonged hospitalization, was related to a congenital anomaly or birth defect, or was deemed serious for any other reason.
§ Adverse events leading to study-drug discontinuation were reported when they occurred in 2% or more of patients in any study group and are listed according to system organ class. The analysis included adverse events with an onset after administration of the first dose of study medication and up to 28 days after administration of the last dose.
¶ Investigation results refer to the results of clinical laboratory tests, radiologic tests, physical examination, and physiologic tests.
‖ These events include disorders or conditions that involve several body systems or sites, including chest pain, fatigue, asthenia, and general deterioration of physical health.

Testove jetrene funkcije (transaminaza) treba pratiti mjesečno tokom prva 3 mjeseca, a zatim svaka 3-4 mjeseca tokom liječenja. Porast transaminaza 3 X iznad gornje granice ref. vrijednosti vodi ka smanjenju doze na 100 mg 2 X dnevno ili prekidu doziranja;

cca 20% pojedinaca ostaje bez lijeka zbog nepodnošljivih nuspojava.

Nintedanib za intersticijalnu bolest pluća udruženu sa progredir. sistemskom sklerozom

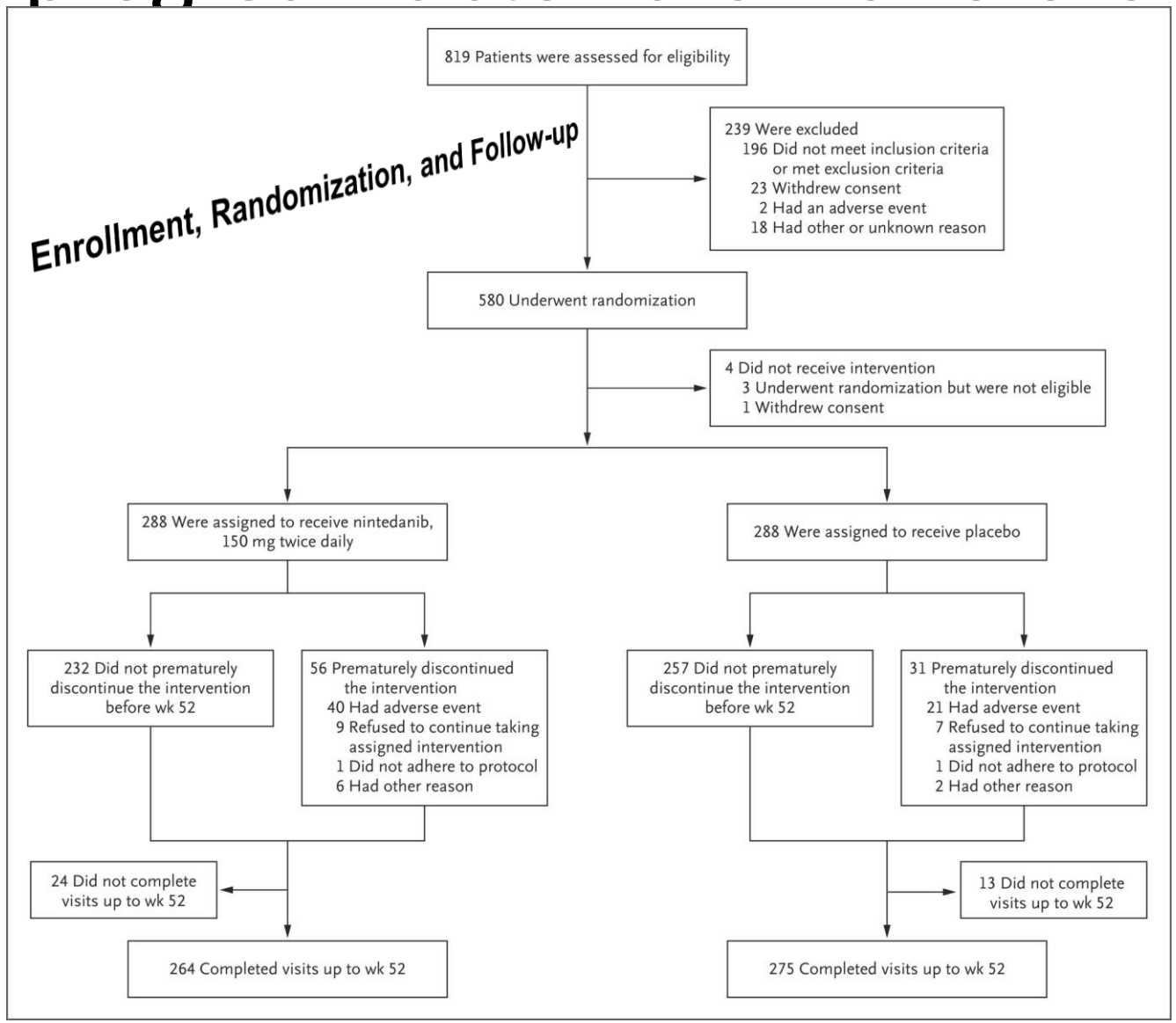


Table 1. Baseline Characteristics of the Patients.*

Characteristic	Nintedanib (N=288)	Placebo (N=288)
Female sex — no. (%)	221 (76.7)	212 (73.6)
Age — yr	54.6±11.8	53.4±12.6
Diffuse cutaneous systemic sclerosis — no. (%)	153 (53.1)	146 (50.7)
Years since the onset of the first non-Raynaud's symptom		
Median	3.4	3.5
Range	0.3–7.1	0.4–7.2
Extent of fibrosis of the lungs on high-resolution CT — %	36.8±21.8	35.2±20.7
FVC — ml	2459±736	2541±816
FVC — % of predicted value	72.4±16.8	72.7±16.6
DL_{CO} — % of predicted value†	52.9±15.1	53.2±15.1
Antitopoisomerase antibody positive — no. (%)‡	173 (60.1)	177 (61.5)
Modified Rodnan skin score§	11.3±9.2	10.9±8.8
Patients with diffuse cutaneous systemic sclerosis	17.0±8.7	16.3±8.9
Patients with limited cutaneous systemic sclerosis	4.9±4.2	5.4±4.1
Total score on the SGRQ¶	40.7±20.2	39.4±20.9
Score on the HAQ-DI‖	0.65±0.70	0.55±0.58
Scaled score on the FACIT-Dyspnea questionnaire**	47.01±9.64	45.67±9.90
Receiving mycophenolate — no. (%)	139 (48.3)	140 (48.6)
Receiving methotrexate — no. (%)	23 (8.0)	15 (5.2)

* Plus–minus values are means ±SD. Data on some variables were not available for all patients. A larger table of baseline characteristics is included in section G in the Supplementary Appendix. CT denotes computed tomography, DL_{CO} diffusion capacity of the lungs for carbon monoxide, FACIT Functional Assessment of Chronic Illness Therapy, FVC forced vital capacity, HAQ-DI Health Assessment Questionnaire–Disability Index, and SGRQ St. George's Respiratory Questionnaire.

† The DL_{CO} value was corrected for the hemoglobin level. DL_{CO} values were available for 285 patients in the nintedanib group and 284 patients in the placebo group.

‡ Historical information on antitopoisomerase antibody status was used, or, if this information was not available to the trial sites, it was provided by a central laboratory.

§ The modified Rodnan skin score is used to evaluate a patient's skin thickness through palpation of 17 areas; scores range from 0 to 3 for each area (to give a maximum score of 51), with higher scores indicating worse skin fibrosis. Scores were available for 288 patients in the nintedanib group and 286 patients in the placebo group. Among the patients with diffuse cutaneous systemic sclerosis, scores were available for 153 of those in the nintedanib group and for 144 of those in the placebo group. Among the patients with limited cutaneous systemic sclerosis, scores were available for 135 of those in nintedanib group and for 142 of those in placebo group.

¶ Total scores on the SGRQ range from 0 to 100, with higher scores indicating worse health-related quality of life. Scores were available for 282 patients in the nintedanib group and 283 patients in the placebo group.

‖ Scores on the HAQ-DI range from 0 to 3, with higher scores indicating worse disability. Scores were available for 283 patients in the nintedanib group and 281 patients in the placebo group.

** Scaled scores on the FACIT-Dyspnea questionnaire range from 27.7 to 75.9, with higher scores indicating worse dyspnea. Scores were available for 283 patients in the nintedanib group and 285 patients in the placebo group.

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Smanjenje forsiranog vitalnog kapaciteta u slučaju sistemske skleroze

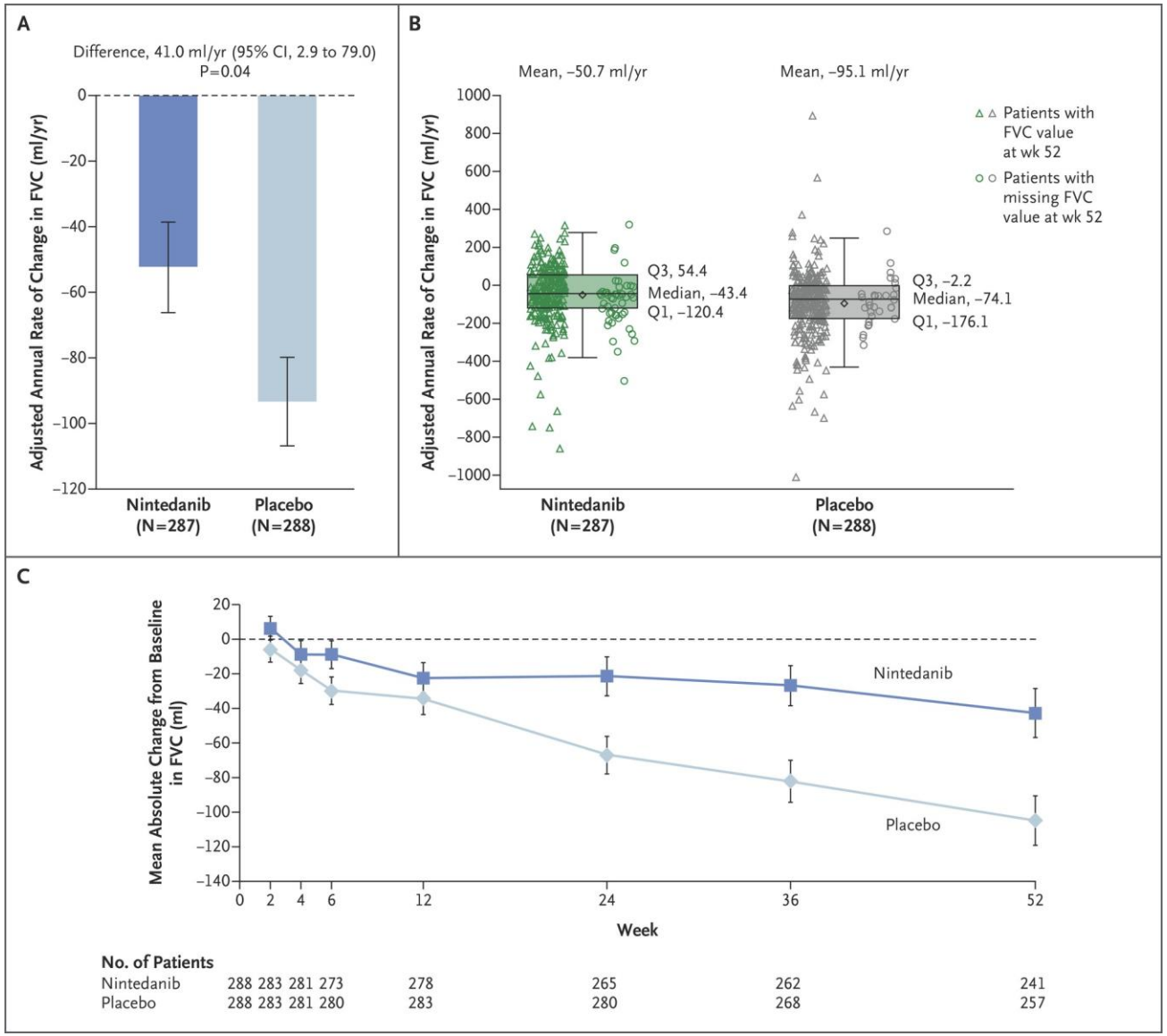

Table 3. Adverse Events.*

Event	Nintedanib (N=288)	Placebo (N=288)
	no. of patients (%)	
Any adverse event	283 (98.3)	276 (95.8)
Most common adverse events†		
Diarrhea	218 (75.7)	91 (31.6)
Nausea	91 (31.6)	39 (13.5)
Skin ulcer	53 (18.4)	50 (17.4)
Vomiting	71 (24.7)	30 (10.4)
Cough	34 (11.8)	52 (18.1)
Nasopharyngitis	36 (12.5)	49 (17.0)
Upper respiratory tract infection	33 (11.5)	35 (12.2)
Abdominal pain	33 (11.5)	21 (7.3)
Fatigue	31 (10.8)	20 (6.9)
Weight decrease	34 (11.8)	12 (4.2)
Severe adverse event‡	52 (18.1)	36 (12.5)
Serious adverse event§	69 (24.0)	62 (21.5)
Fatal adverse event	5 (1.7)	4 (1.4)
Adverse event leading to discontinuation of the intervention	46 (16.0)	25 (8.7)

* Adverse events, as reported over 52 weeks plus a 28-day post-treatment period, were coded according to the preferred terms in the *Medical Dictionary of Regulatory Activities*. Data are shown for the patients who had at least one such adverse event.
† The most common adverse events were those that were reported in more than 10% of the patients in either trial group.
‡ A severe adverse event was defined as an event that was incapacitating or that caused an inability to work or to perform usual activities.
§ A serious adverse event was defined as an event that resulted in death, was life-threatening, resulted in hospitalization or prolongation of hospitalization, resulted in persistent or clinically significant disability or incapacity, was a congenital anomaly or birth defect, or was deemed to be serious for any other reason.

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Nintedanib u progresivnim fibroznim intersticijskim plućnim bolestima

Osnovne kliničke dijagnoze ILD-a u skupinama uključenim u ispitivanje bile su:
- hipersenzitivni pneumonitis (26,1%),
- autoimuni ILD (25,6%),
- idiopatska nespecifična intersticijska upala pluća (18,9%),
- neklasificirana idiopatska intersticijska upala pluća (17,2%) i
ostale ILD (12,2%).

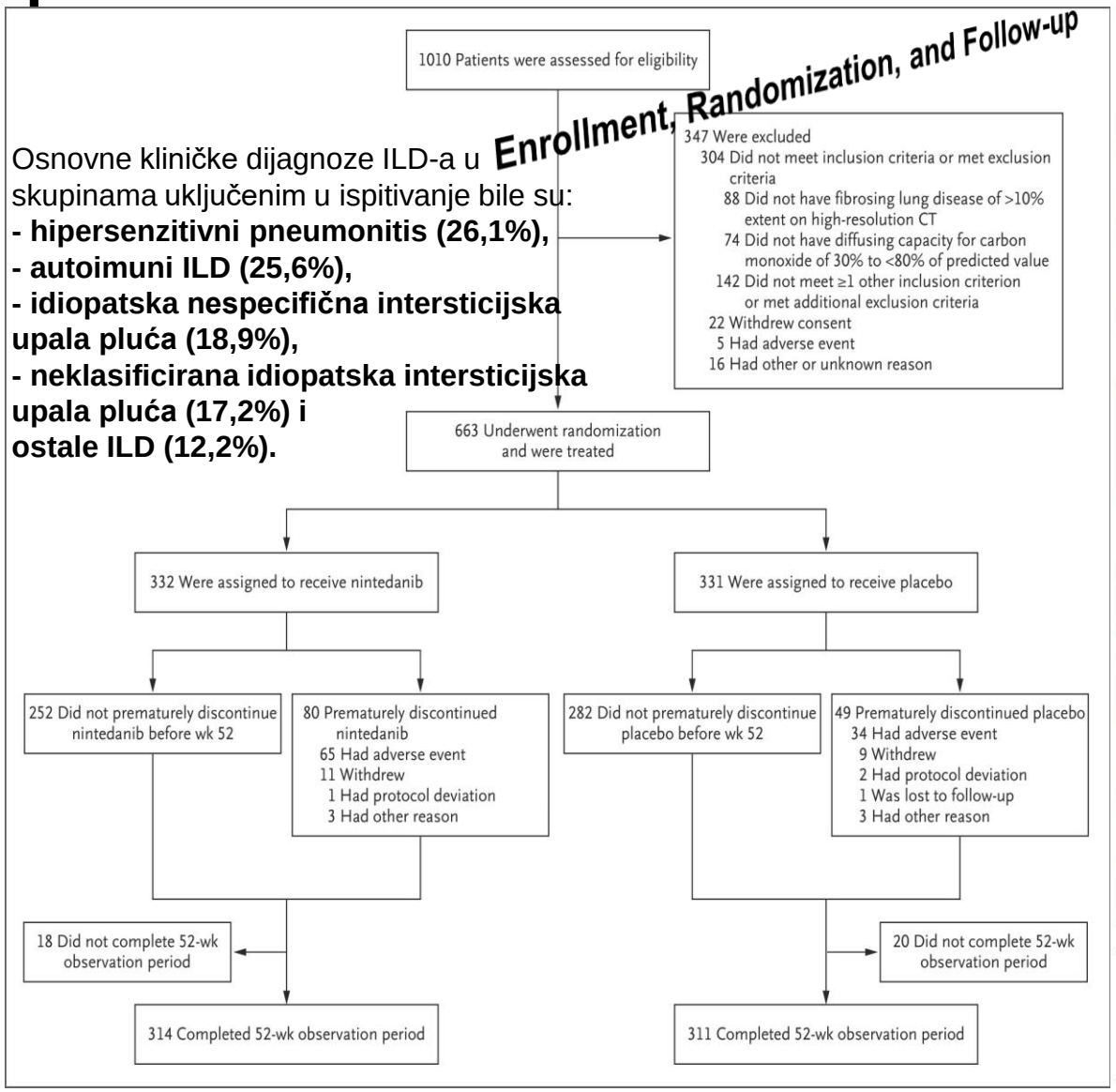

Table 1. Characteristics of the Overall Population at Baseline.*

Characteristic	Nintedanib (N=332)	Placebo (N=331)
Male sex — no. (%)	179 (53.9)	177 (53.5)
Age — yr	65.2±9.7	66.3±9.8
Former or current smoker — no. (%)	169 (50.9)	169 (51.1)
UIP-like fibrotic pattern on high-resolution CT — no. (%)	206 (62.0)	206 (62.2)
Criteria for disease progression in previous 24 mo — no. (%)		
Relative decline in FVC of ≥10% of predicted value	160 (48.2)	172 (52.0)
Relative decline in FVC of 5% to <10% of predicted value plus worsening of respiratory symptoms or increased extent of fibrosis on high-resolution CT	110 (33.1)	97 (29.3)
Worsening of respiratory symptoms and increased extent of fibrosis on high-resolution CT	62 (18.7)	61 (18.4)
FVC		
Mean value — ml	2340±740	2321±728
Percent of predicted value	68.7±16.0	69.3±15.2
Diffusing capacity for carbon monoxide†		
Mean value — mmol/min/kPa	3.5±1.2	3.7±1.3
Percent of predicted value	44.4±11.9	47.9±15.0
Total score on K-BILD questionnaire‡	52.5±11.0	52.3±9.8

* Plus–minus values are means ±SD. FVC denotes forced vital capacity, and UIP usual interstitial pneumonia.
† The values for diffusing capacity for carbon monoxide were corrected for the hemoglobin level.
‡ Scores on the King's Brief Interstitial Lung Disease (K-BILD) questionnaire range from 0 to 100, with higher scores representing better health status.

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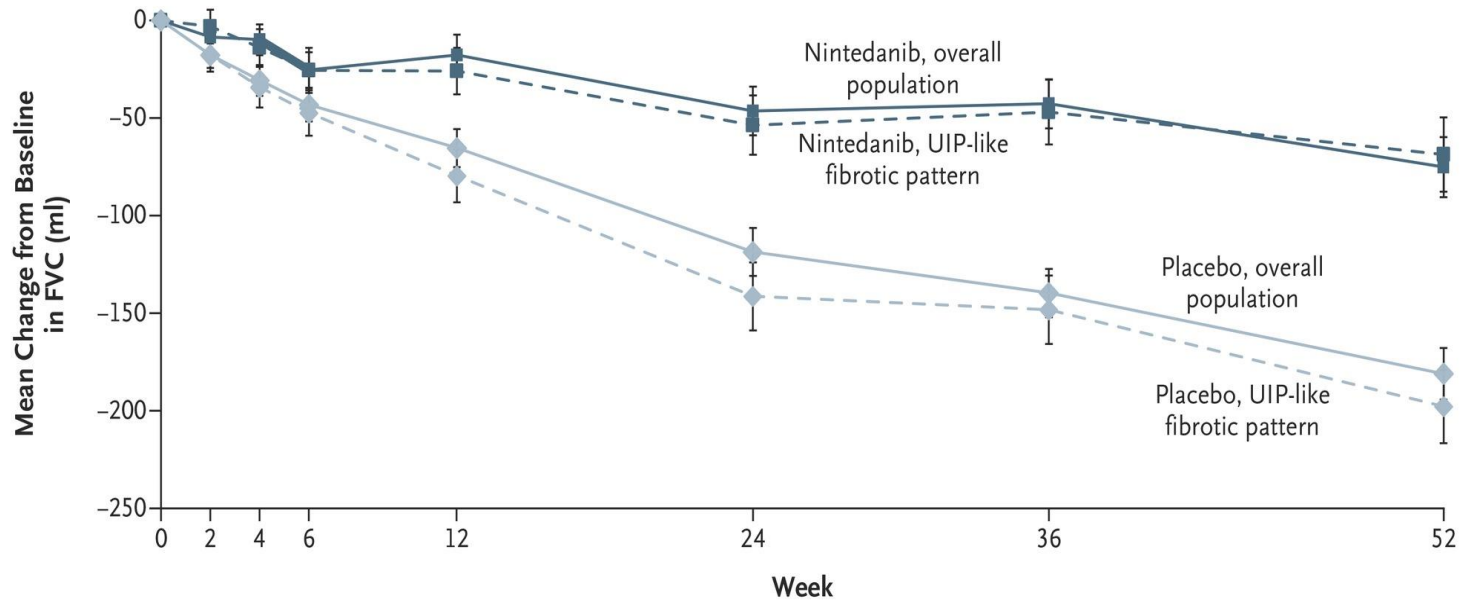
Smanjenje forsiranog vitalnog kapaciteta u odnosu na početnu vrijednost (FVC)



No. of Patients								
Overall population								
Nintedanib	332	326	320	322	314	298	285	265
Placebo	331	325	326	325	320	311	296	274
Patients with UIP-like fibrotic pattern								
Nintedanib	206	203	200	199	193	180	171	160
Placebo	206	202	202	201	197	190	176	162

End Point	Nintedanib (N=332)	Placebo (N=331)	Difference (95% CI)
Primary end point			
Rate of decline in the FVC at 52 wk — ml/yr†			
Overall population	−80.8±15.1	−187.8±14.8	107.0 (65.4 to 148.5)‡
Patients with a UIP-like fibrotic pattern	−82.9±20.8	−211.1±20.5	128.2 (70.8 to 185.6)‡
Patients with other fibrotic patterns	−79.0±21.6	−154.2±21.2	75.3 (15.5 to 135.0)§
Main secondary end points			

Kod pacijenata sa progresivnim fibrozirajućim intersticijskim bolestima pluća, godišnja stopa pada FVC bila je **značajno niža** među pacijentima koji su primali nintedanib nego među onima koji su primali placebo. Dijareja je bila česta nuspojava.

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Pirfenidon – mehanizam djelovanja

Pirfenidon inhibira TGF-β1-indukovanu diferencijaciju ljudskih fibroblasta pluća u miofibroblaste, sprječavajući na taj način višak sinteze kolagena i proizvodnju ekstracelularnog matriksa. Pored tog ima antiinflamatorni i antioksidativni efekat.

Pirfenidon u bolesnika s idiopatskom plućnom fibrozom (CAPACITY): dvije randomizirane studije

Dva istovremena ispitivanja (004 i 006)

pacijenti (u dobi od 40-80 godina) s idiopatskom plućnom fibrozom nasumično su raspoređeni na oralni pirfenidon ili placebo u toku najmanje 72 sedmice u 110 centara u Australiji, Evropi i Sjevernoj Americi.

U studiji 004, pacijenti su dodijeljeni u omjeru 2:1:2 na pirfenidon 2403 mg/dan, pirfenidon 1197 mg/dan ili placebo.

U studiji 006, pacijenti su raspoređeni u omjeru 1:1 na pirfenidon 2403 mg/dan ili placebo.

Dobiveni rezultati pokazuju da pirfenidon ima povoljan profil koristi i rizika i predstavlja odgovarajuću opciju liječenja za bolesnike s idiopatskom plućnom fibrozom.

AMERICAN THORACIC SOCIETY
DOCUMENTS

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

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

Evidence-based Recommendations for Treatment of PPF, Other than IPF

Pirfenidone. ***We recommend further research into the efficacy, effectiveness, and safety of pirfenidone in both 1) non-IPF ILD manifesting PPF in general and 2) specific types of non-IPF ILD manifesting PPF.***