RENCONTRES EN IMMUNOLOGIE & IMMUNOTHERAPIE PRATIQUES

Antifibrosants et pneumopathies interstitielles diffuses (PID) des connectivites

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16, rue Jean Rey - 75015 Paris

Sous l'égide de :

Je n’ai pas de liens d’intérêts avec le sujet traité

Intérêt financier	Nature du lien, industrie
Tobacco-industry and tobacco corporate affiliate related conflict of interest	**NO**
Grants/research support (to myself, my institution or department):	**NO**
Honoraria or consultation fees:	**NO**
Participation in a company sponsored bureau:	**NO**
Stock shareholder:	**NO**
Spouse/partner:	**NO**
Other support or other potential conflict of interest:	**Participation as PI to academic or industry sponsoring trials, using nintedanib or pirfenidone**

PID des connectivites

Prevalence and incidence of interstitial lung diseases in a multi-ethnic county of Greater Paris

Boris Duchemann[1,2], Isabella Annesi-Maesano[3], Camille Jacobe de Naurois[4], Shreosi Sanyal[3], Pierre-Yves Brillet[2,5], Michel Brauner[5], Marianne Kambouchner[6], Sophie Huynh[7], Jean Marc Naccache[8], Raphael Borie[9], Jacques Piquet[10], Arsène Mekinian[11], Jerôme Virally[7], Yurdagul Uzunhan[1,2], Jacques Cadranel[8], Bruno Crestani[9], Olivier Fain[11], Francois Lhote[12], Robin Dhote[13], Nathalie Saidenberg-Kermanac'h[14], Paul-André Rosental[15], Dominique Valeyre[1,2] and Hilario Nunes[1,2]

- Seine Saint Denis 2012 (n=1170), prevalence: 97.9/100‰; incidence: 19.4/100‰
- Excluding cardiovascular, infectious and tumoral causes

Duchemann B, Eur Respir J 2017, 50:1602419

PID des connectivites

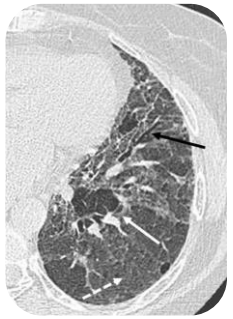
	Sclérodermie systémique[1]	Polyarthrite rhumatoïde[2]	Myopathies inflammatoires idiopathiques	Syndrome de Sjögren[6]	Connectivites mixtes	Lupus érythémateux disséminé
Prévalence CTD *(100‰)*	13-23	360	2-34	50	3	41
Fréquence PID	45%[9]	8%	15-78%	11-15%	54%	<10%
Facteurs de risque de survenue	• Origine afro-américaine[1] • Sexe masculin[1] • Forme cutanée diffuse[1] • Anti-Scl-70 +; Anti-Th/To +; Anti-PM-Scl +; Anti-Ro52 +[1] • Ulcères digitaux[1] • HTAP[1]	• Sexe masculin • Âge avancé • Fumeur • Taux élevé de Facteur Rhumatoïde • Anti-CCP	• Origine afro-américaine[3] • AAN[3] • Anti-histidyl-ARNt synthétase[3] • Expositions professionnelles[4] • Âge[5] • Arthralgies[5]; Fièvre[5]; CRP • Ac anti-Jo1[5] • Anti-MDA5	• Âge • Durée évolution maladie • Facteur Rhumatoïde • Anti-SSA • CRP		• Anti-SSA[7] • Évolution >10 ans[8] • Âge[8] • Fumeur[8]
Pattern	• **PINS +++** • **PIC+** • FEPP	• **PIC ++** • **PINS +** • FEPP	• **PINS ++** • **PINS-PO ++** • PO++	• **PINS ++** • Bronchiolite folliculaire/PIL++	• **PINS ++** • **PIC ++**	• HIA, shrinking lung • PINS, PIC connectivite associée
Pronostic	• **Survie à 10 ans: 40%** • Mortalité liée à la ScS - PID en cause dans 35% des cas	• **Survie médiane: 3 ans en cas de PIC** - Autres *pattern* : >3 ans	• Survie à 5 ans : 80%	• Risque de lymphome pulmonaire à cellules B • Risque d'amylose		

D'après "Connexion PID" 01/2021

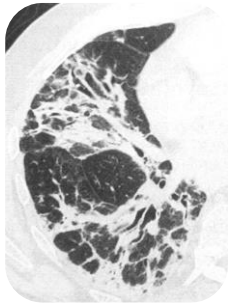
1. Perelas A, *et al.* Systemic sclerosis-associated interstitial lung disease. Lancet Respir Med 2020;8:304-20.
2. Shaw M, *et al.* Rheumatoid arthritis-associated lung disease. Eur Respir Rev 2015;24:1-16.
3. Chua F, *et al.* Idiopathic inflammatory myositis-associated interstitial lung disease: ethnicity differences and lung function trends in a British cohort. Rheumatol 2012;51:1870-76.
4. Labirua-Iturburu A, *et al.* Occupational exposure in patients with the antisynthetase syndrome. Clin Rheumatol 2014;33:221-25.
5. Zhang L, *et al.* Factors associated with interstitial lung disease in patients with polymyositis and dermatomyositis: a systematic review and meta-analysis. PLoS ONE 2016;11:e0155381
6. Gao H, *et al.* Prevalence, risk factors, and prognosis of interstitial lung disease in a large cohort of chinese primary Sjögren syndrome patients: a case-control study. Medicine (Baltimore) 2018;97:1-5.
7. Kokosi M, *et al.* Systemic Lupus erythematosus and antiphospholipid antibody syndrome. Clin Chest Med 2019;40:519-29.
8. Medlin J L, *et al.* Pulmonary manifestations in late versus early systemic lupus erythematosus: a systematic review and meta-analysis. Semin Arthr Rheum 2018; 48:198-204
9. Orphanet

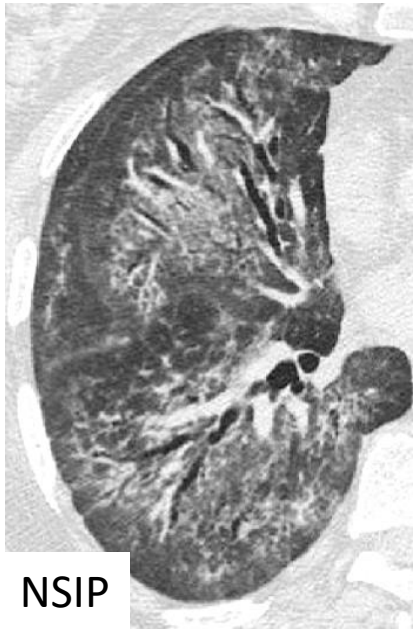
PIC, PINS et connectivites

PHS
RA
GS

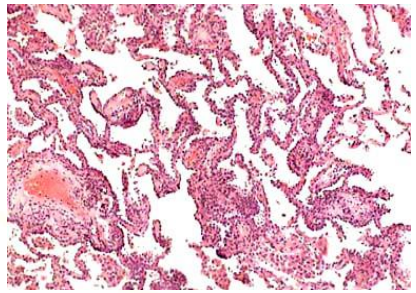


IIM
Anti-Jo1





NSIP

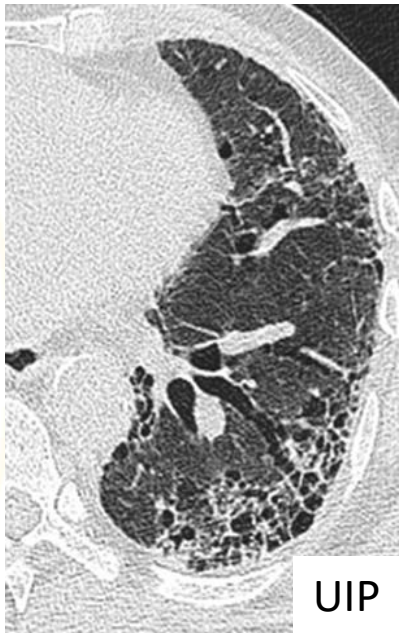


Auto-immunity

- Systemic scleroderma
- RA, Sjögren
- MCTD

NSIP :

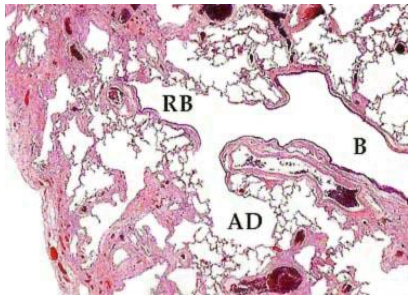
Non specific interstitial pneumonitis



UIP

RA
MCTD
ANCA

- Man
- >70 years old
- Smoker
- Clubbing
- “Velcro“ rales
- **IPF**

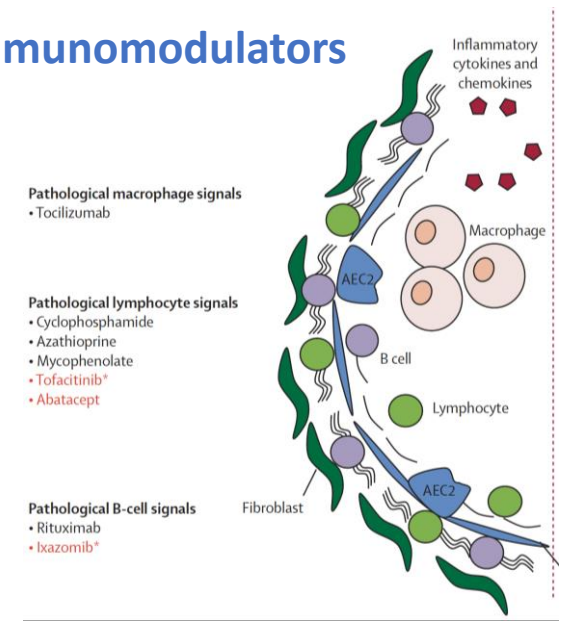


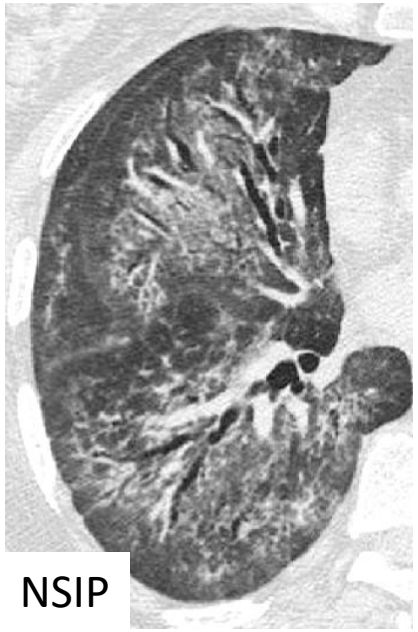
UIP :

Usual interstitial pneumonia

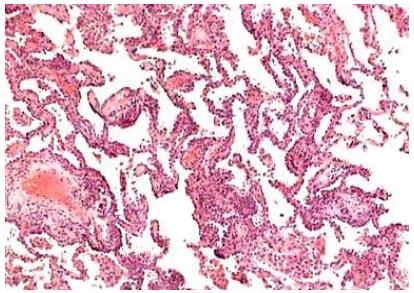
PIC, PINS et connectivites

Immunomodulators





NSIP



Auto-immunity

- Systemic scleroderma
- RA, Sjögren
- MCTD

NSIP :

Non specific interstitial pneumonitis

?

Johannson K, Lancet 2021, 398:1450

Effet protecteur du Méthotrexate dans PID de PR

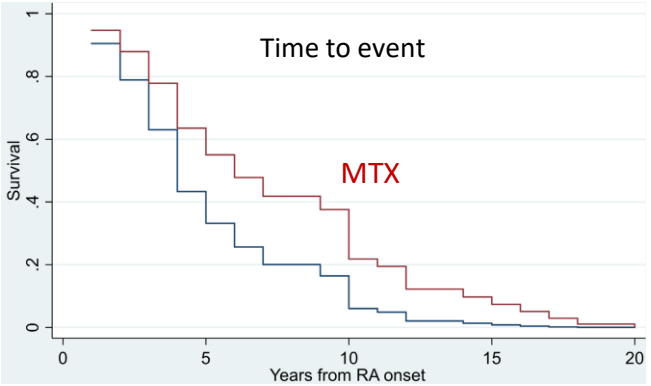
Protective effect of Methotrexate on RA-ILD

ERAN and ERAS cohorts, 92 ILD incident in 2721 RA; 1578 MTX exposed

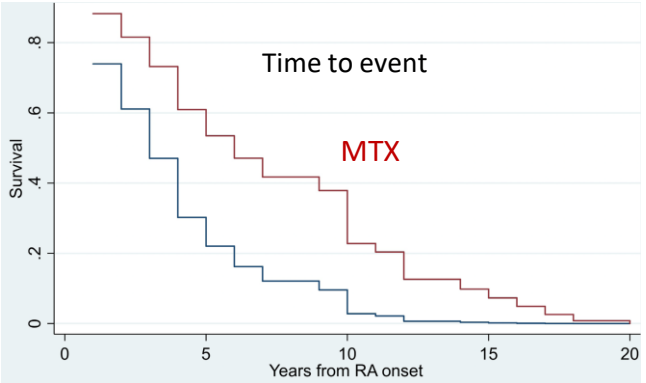
Table 3 Multivariate logistic analysis showing covariates independently associated with RA-ILD development

	Primary analysis, RA-ILD onset after any csDMARD exposure (n=67)	Wald test	Extended cohort, including RA-ILD onset prior to any csDMARD (n=92)	Wald test
	OR (95% CI)	P value	OR (95% CI)	P value
Methotrexate exposure	0.85 (0.49 to 1.49)	0.578	0.48 (0.3 to 0.79)	0.004
Age RA onset	1.04 (1.02 to 1.06)	<0.001	1.04 (1.02 to 1.06)	<0.001
Smoking, ever, baseline	2.21 (1.21 to 4.03)	0.01	1.91 (1.13 to 3.25)	0.016
Male gender	1.44 (0.83 to 2.48)	0.193	1.74 (1.05 to 2.86)	0.03
RF positive, baseline	2.02 (1.07 to 3.82)	0.029		n.s.
RA nodules, baseline		n.s.	2.19 (1.08 to 4.41)	0.029
Onset – OPD	1.04 (1.00 to 1.07)	0.027	1.03 (1.0 to 1.07)	0.04
Baseline major comorbidities*	0.62 (0.40 to 0.95)	0.027	0.67 (0.46 to 0.98)	0.037
Baseline ESR	-	n.s.	1.01 (1.0 to 1.02)	0.047

No ILD before exposure



ILD before exposure

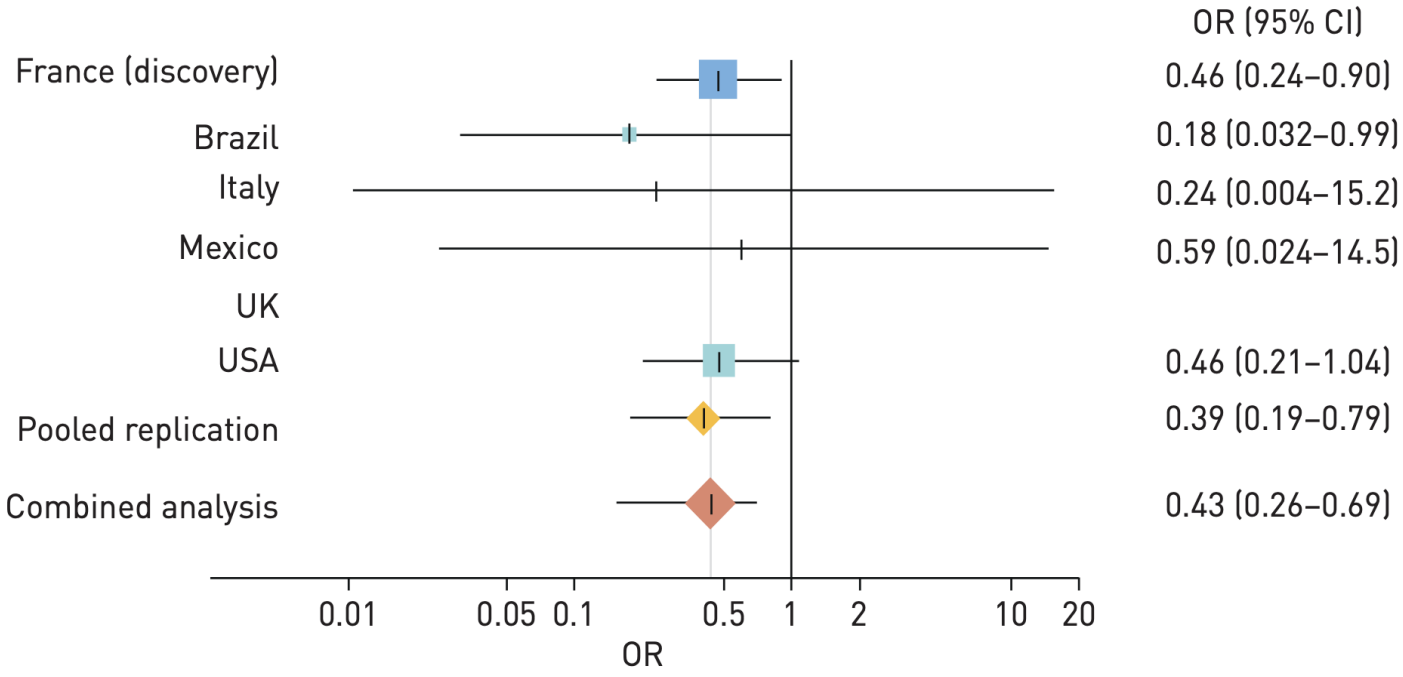


Kiely P, BMJ Open 2019, 9:028466

Effet protecteur du Méthotrexate dans PID de PR

Protective effect of Methotrexate on RA-ILD

Discovery and replication cohorts, 482 ILD-RA and 741 No-ILD-RA; 929 MTX exposed



(adjusted for age at RA onset, sex, smoking, other biologics used, MTX duration)

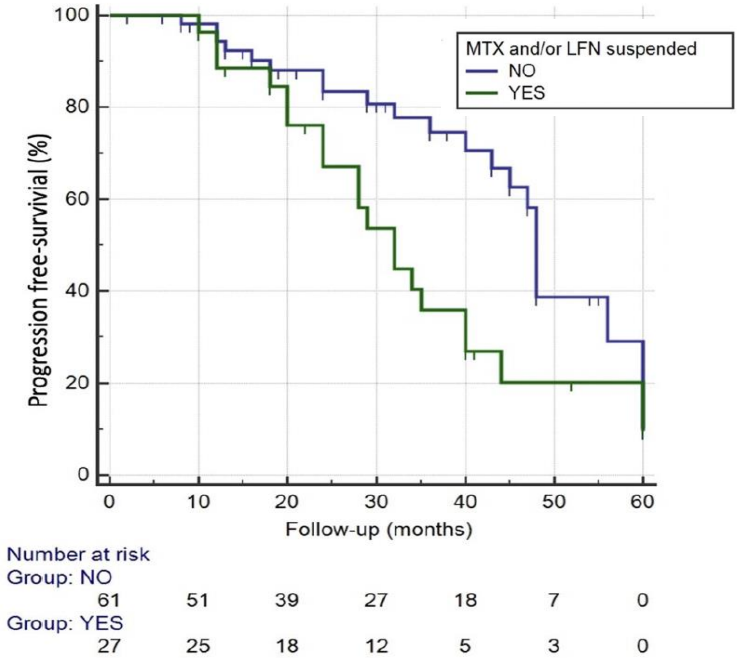
- ILD was also delayed in patients receiving MTX, from 4 to 11.4 years

OPEN

Diagnostic delay of associated interstitial lung disease increases mortality in rheumatoid arthritis

Esteban Cano-Jiménez[1✉], Tomás Vázquez Rodríguez[1], Irene Martín-Robles[1], Diego Castillo Villegas[2], Javier Juan García[3], Elena Bollo de Miguel[3], Alejandro Robles-Pérez[4], Marta Ferrer Galván[5], Cecilia Mouronte Roibas[6], Susana Herrera Lara[7], Guadalupe Bermudo[4], Marta García Moyano[8], Jose Antonio Rodríguez Portal[9], Jacobo Sellarés Torres[10], Javier Narváez[4] & María Molina-Molina[4]

ILD progression free survival



Juge PA, Eur Respir J 2021, 57:2000337; Cano-Jimenez E, Scientific Reports 2021, 11:9184

Immunomodulateurs et PID de connectivites

Proposed therapies for CTD-ILD, in general

Medication	Dose[b]	Disease
Prednisone	0.5-1 mg/kg/d up to 60 mg/d	SSc, RA, DM, PM, SS
Methylprednisolone	1 g/d IV for 3 d	Acute worsening CTD-ILD
Azathioprine	1-2 mg/kg/d	SSc, RA, DM, PM, SS
Cyclophosphamide	1-2 mg/kg/d po or 500-1,000 mg IV pulse every 4 wk	SSc, RA
Mycophenolate mofetil	1.0-1.5 g bid	SSc, RA, DM, PM
Tacrolimus	1 mg bid	DM, PM
Rituximab	375 mg/wk, 4 wks or 1 g at d1 and d15	SSc, RA, DM, PM, SS

Vij R, Chest 2012, 143:814

Cyclophosphamide et PID de

2006

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cyclophosphamide versus Placebo in Scleroderma Lung Disease

Donald P. Tashkin, M.D., Robert Elashoff, Ph.D., Philip J. Clements, M.D., M.P.H., Jonathan Goldin, M.D., Ph.D., Michael D. Roth, M.D., Daniel E. Furst, M.D., Edgar Arriola, Pharm.D., Richard Silver, M.D., Charlie Strange, M.D., Marcy Bolster, M.D., James R. Seibold, M.D., David J. Riley, M.D., Vivien M. Hsu, M.D., John Varga, M.D., Dean E. Schraufnagel, M.D., Arthur Th
Robert Simms, M.D., Robert Wise, M.D., Fredrick Wigley, M.D., E
Virginia Steen, M.D., Charles Read, M.D., Maureen Mayes, M.D
Kamal Mubarak, M.D., M. Kari Connolly, M.D., Jeffrey C
Mitchell Olman, M.D., Barri Fessler, M.D., Naomi Rot
and Mark Metersky, M.D., for the Scleroderma Lung Study

Yes!

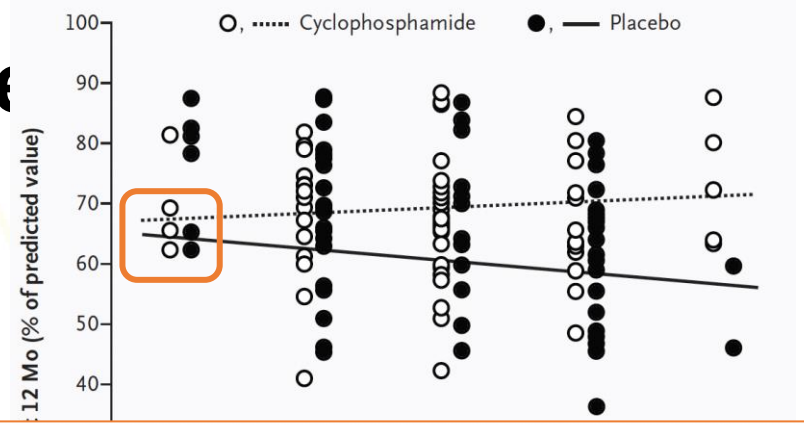
Effects of 1-Year Treatment with Cyclophosphamide on Outcomes at 2 Years in Scleroderma Lung Disease

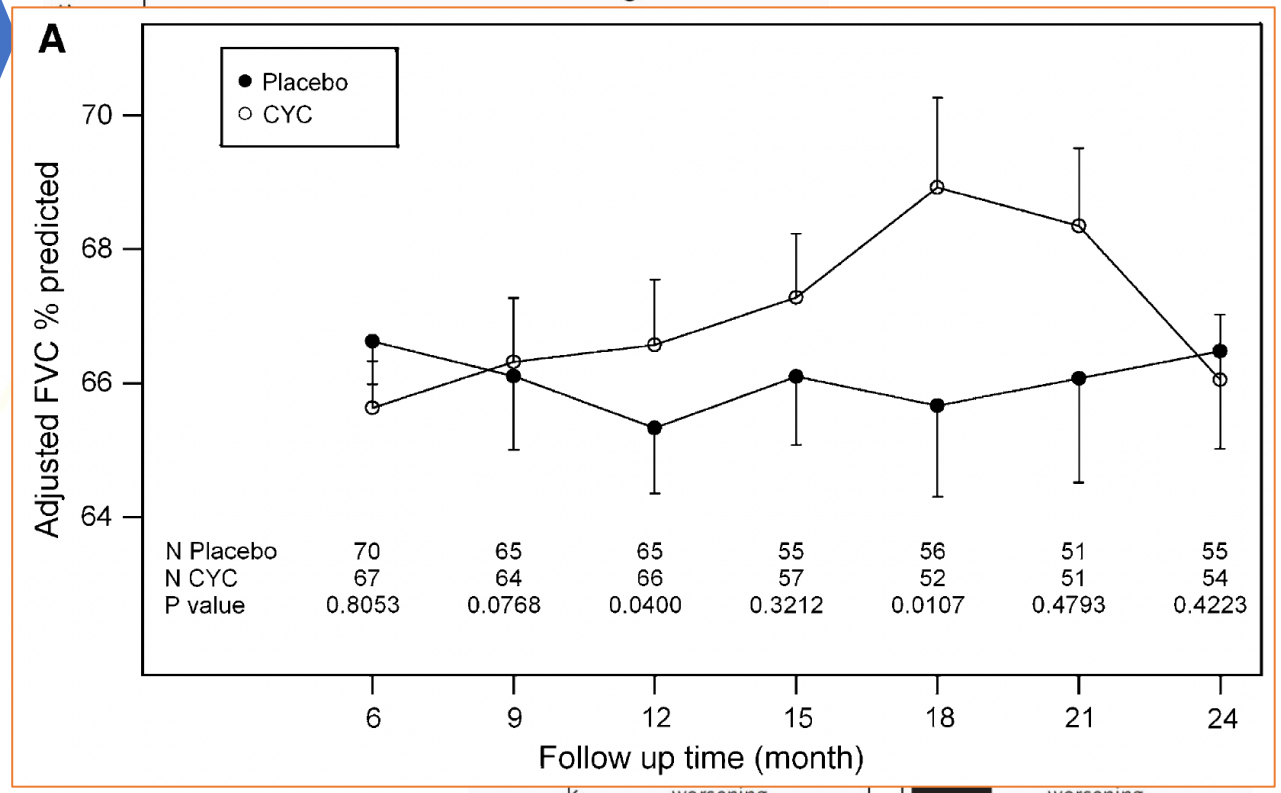
Donald P. Tashkin[1], Robert Elashoff[2], Philip J. Clements[1], Michael D. Roth[1], Daniel E. Furst[1], Richard M. Silver[3], Jonathan Goldin[4], Edgar Arriola[5], Charlie Strange[3], Marcy B. Bolster[2], James R. Seibold[6], David J. Riley[6], Vivien M. Hsu[6], John Varga[7], Dean Schraufnagel[7], Arthur Theodore[8], Robert Simms[8], Robert Wise[9], Fred Wigley[9], Barbara White[9], Virginia Steen[10], Charles Read[10], Maureen Mayes[11], Ed Parsley[11], Kamal Mubarak[12], M. Kari Connolly[13], Jeffrey Golden[13], Mitchell Olman[14], Barri Fessler[14], Naomi Rothfield[15], Mark Metersky[15], Dinesh Khanna[1], Ning Li[2], and Gang Li[2], for the Scleroderma Lung Study Research Group*

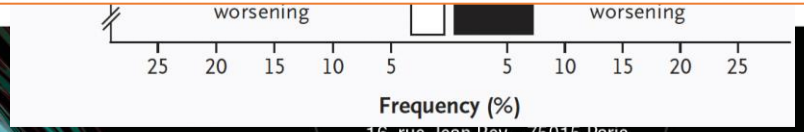
[1]Department of Medicine and [2]Department of Biomathematics, David Geffen School of Medicine, University of California, Los Angeles (UCLA), Los Angeles, California; [3]Department of Medicine, Medical University of South Carolina, Charleston, South Carolina; [4]Department of Radiological Sciences, David Geffen School of Medicine, UCLA, Los Angeles, California; [5]Pharmaceutical Services, UCLA Medical Center, Los Angeles, California; [6]Department of Medicine, University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical Sch
[7]Department of Medicine, University of Illinois Chicago, Chicago, Illinois; [8]Department of Medicine, Boston Unive
[9]Department of Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland; [10]Department of Medicine, Ge
Medicine, University of Texas Houston Medical School, Houston, Texas; [12]Department of M
Department of Medicine, University of California, San Francisco, San Francisco, California; [14]De
, Birmingham, Alabama; and [15]Department of Medicine, University of Connecticut Health C

2007

But?







Vij R, Chest 2012, 143:814

Mycophenolate et PID de Sclérodermie

ARTHRITIS & RHEUMATOLOGY
Vol. 00, No. 00, Month 2017, pp 00–00
DOI 10.1002/art.40114

2006-2016

Mycophenola
Systemic Sclerosis

An Analysis of

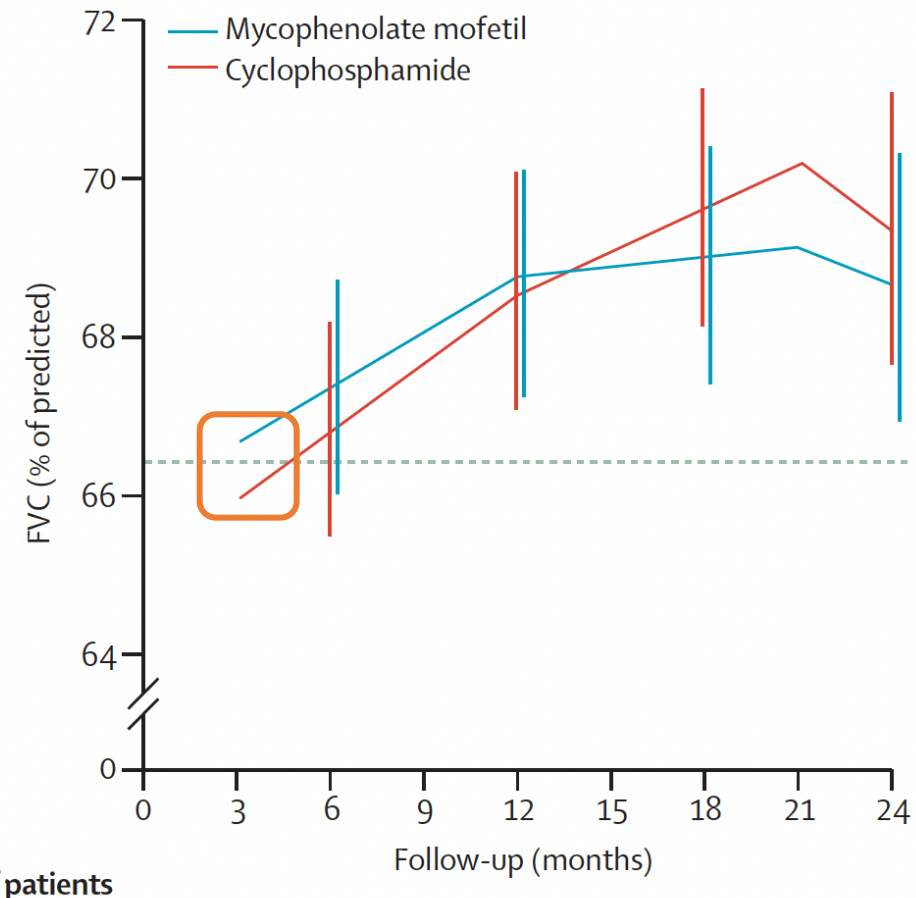
Elizabeth R. Volkmann,[1] Donald
Anna-Maria Hoffmann-Vold,
Daniel E

2017

Mycophenolate mofetil vers
scleroderma-related interstit
a randomised controlled, dou

Donald P Tashkin, Michael D Roth, Philip J Clements, Daniel E Furst,
Elizabeth R Volkmann, Suzanne Kafaja, Richard Silver, Virginia Steen
Sabiha Hussain, Shervin Assassi, Vivien M Hsu, Bela Patel, Kristine P
Jane Dematte, Monique E Hinchcliff, Aryeh Fischer, Jeffrey Swigris,
Dean E Schraufnagel, Mary Beth Scholand, Tracy Frech, Jerry A Molit
Chi-Hong Tseng, Robert M Elashoff, for the Sclerodema Lung Study

	Mycophenolate mofetil		Cyclophosphamide "oral"	
	Adverse events	Patients (n=69)	Adverse events	Patients (n=73)
Adverse events*				
Leucopenia†	5	4 (6%)	51	30 (41%)
Neutropenia	3	3 (4%)	7	5 (7%)
Anaemia	18	8 (12%)	26	13 (18%)
Thrombocytopenia	0	0	7	4 (6%)
Haematuria	3	3 (4%)	2	2 (3%)
Pneumonia	6	5 (7%)	4	4 (6%)
Serious adverse events‡				
Total	42	27 (39%)	36	22 (30%)
Related to treatment§	3	3 (4%)	8	7 (10%)
Related to underlying disease§	16	9 (13%)	16	13 (18%)
Due to other causes§¶	22	14 (20%)	11	6 (8%)
Unknown cause§	3	3 (4%)	3	3 (4%)
Death	..	5 (7%)	..	11 (15%)



Number of patients	0	3	6	9	12	15	18	21	24
Mycophenolate mofetil	69	64	60	54	59	51	49	47	53
Cyclophosphamide	72	62	56	51	51	44	46	40	51

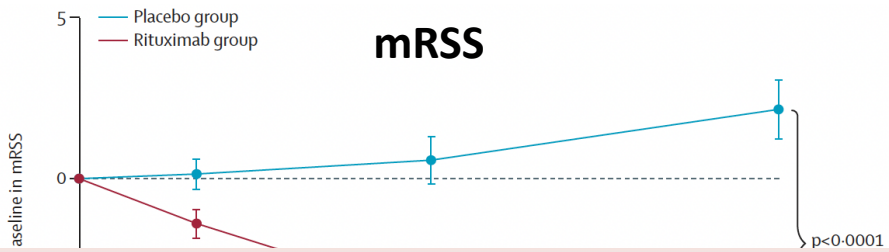
Vij R, Chest 2012, 143:814

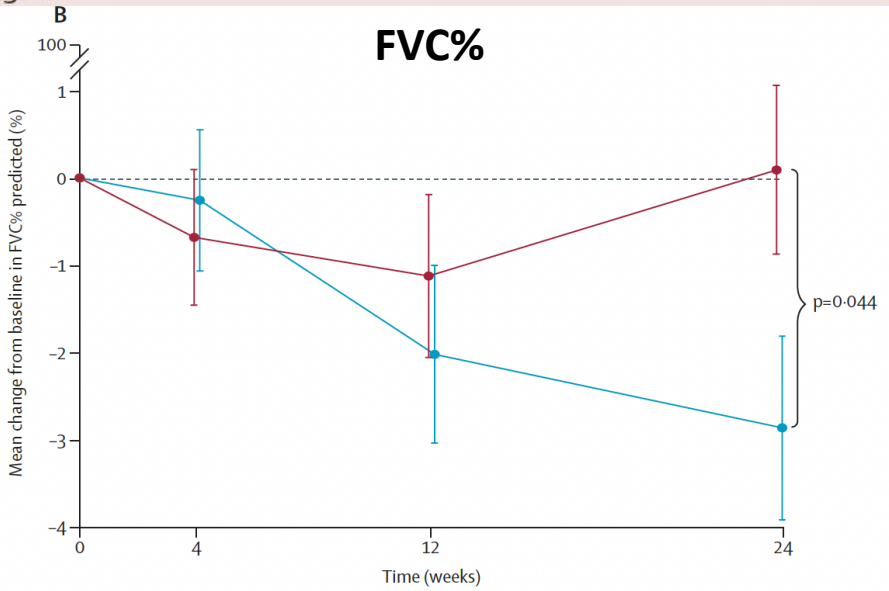
Rituximab et PID Sclérodermie

DESIRES Trial

Rituximab Dy1-8-15-21 vs Placebo; primary objective RSS
56 SSc among whom 48 with ILD

	Rituximab group (n=28)	Placebo group (n=26)
Sex		
Female	25 (89%)	24 (92%)
Male	3 (11%)	2 (8%)
Age, years	49·1 (14·4)	48·3 (9·2)
Diffuse cutaneous systemic sclerosis	23 (82%)	22 (85%)
Disease duration, months	58·5 (0–268)	52·0 (9–248)
mRSS	14·4 (3·7)	15·7 (5·5)
Interstitial lung disease present	25 (89%)	23 (88%)
FVC% predicted	87·9% (15·8)	89·4% (17·9)
%DLCO	84·1% (19·3)	80·6% (16·6)
Surfactant protein-D, ng/mL	151·3 (79·7)	166·8 (126·2)
KL-6, U/mL	678·1 (646·5)	874·4 (1066·1)
Area occupied with interstitial shadows, % of lung fields	13·64% (12·0)	15·39% (13·8)
Concomitant systemic corticosteroid use	15 (54%)	16 (62%)
Dose of systemic corticosteroid, mg/day	6·5 (2·4)	7·3 (2·6)
Previous immunosuppressants and biologics	13 (46%)	17 (65%)





- Trend in DLCO improvement
- Significant decrease in CT-ILD area
- No improvement in QoL scores

Ebata S, Lancet Rheumatol 2021,3:e489; Ebata S, Rheumatology 2022,Epub September

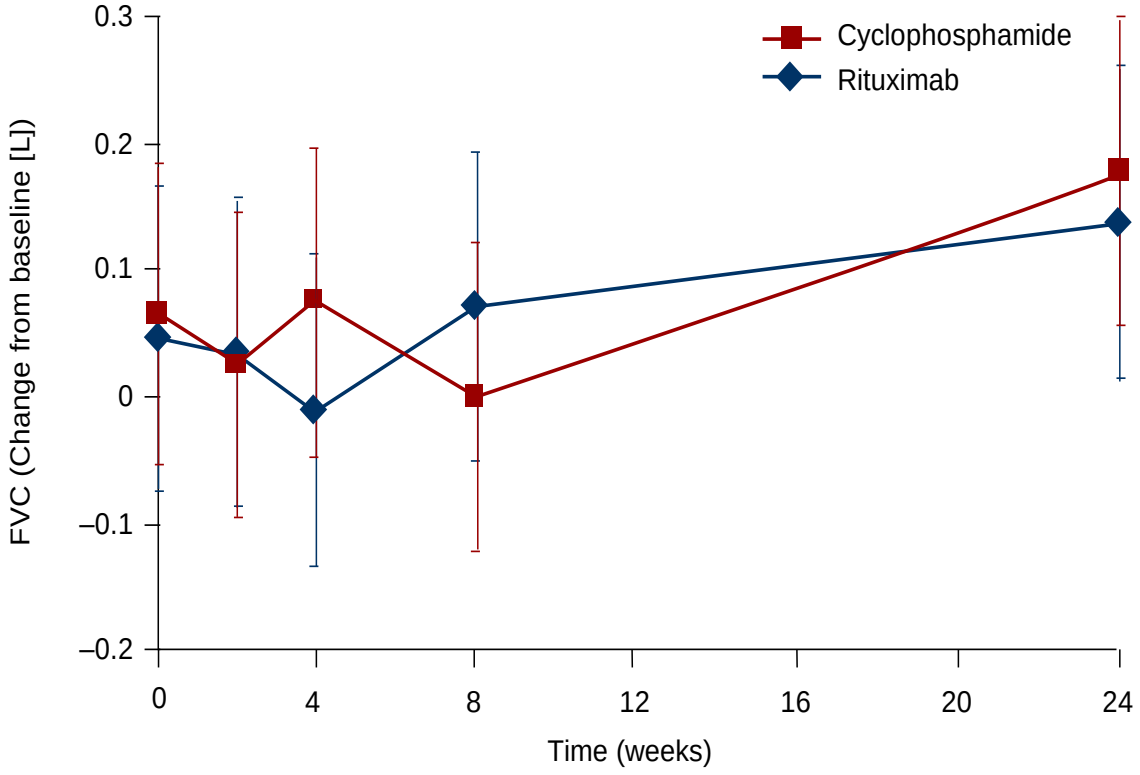
Rituximab et PID de Connectivites

RECITAL trial

Rituximab Dy1-Dy15 vs Cyclophosphamide, 6 months

- CTD-ILD with **"severe progressive?"** disease deserving use of Cyclophosphamide
- Systemic sclerosis (n=39); myositis (n=45); MCTD (n=17)

- Both improved FVC at 24 and 48 weeks
- Similar improvement in QoL
- Fewer adverse events with Rituximab
- **Effect by type of CTD?**



Saunders A, ATS 2022

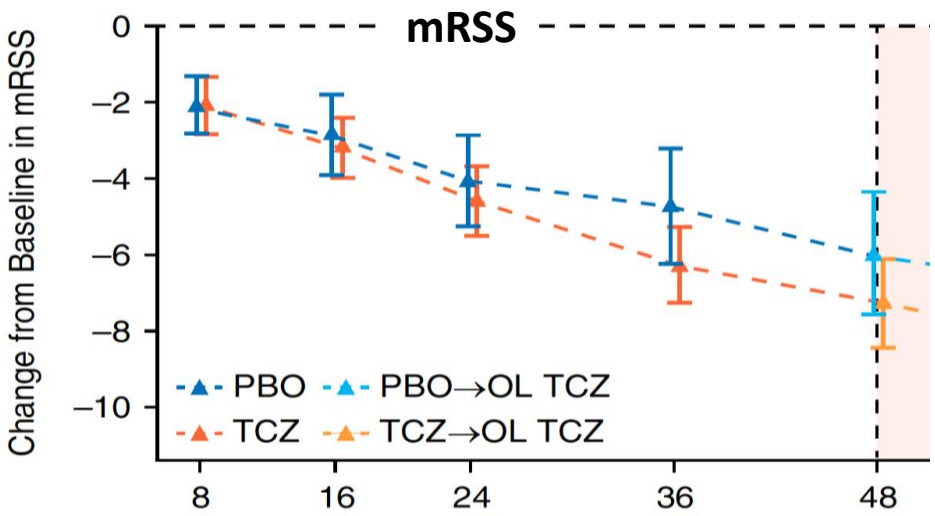
Tocilizumab et PID Sclérodermie

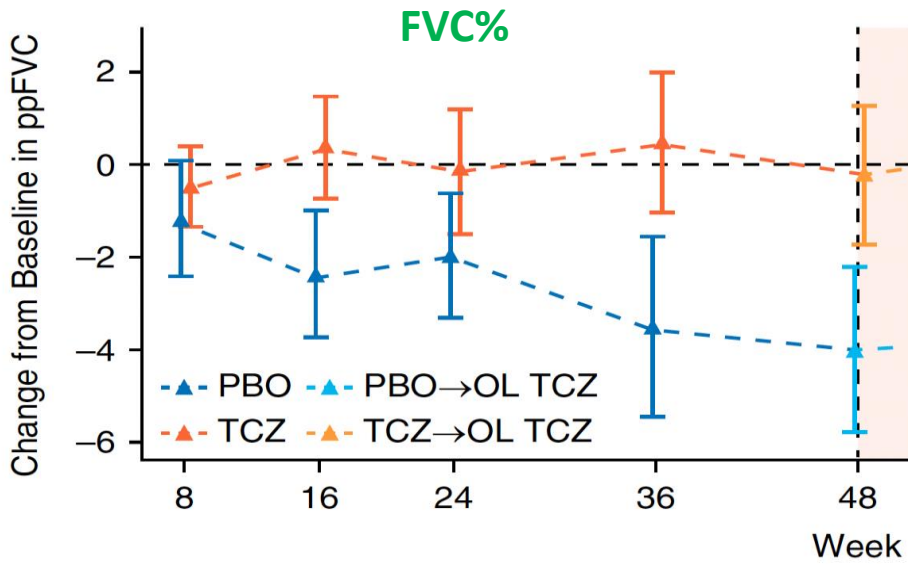
FocuSSced trial

Tocilizumab 162 mg weekly vs Placebo 48 weeks
Primary objective RSS

- 60 mo. duration or less
- >CRP, ESR, platelet
- Active disease
- Other treatments?

	Double Blind (Week 0–48)			
	All Patients		Patients with SSc-ILD	
	PBO (*N* = 106)	TCZ (*N* = 104)	PBO (*N* = 68)	TCZ (*N* = 68)
Females, *n* (%)	90 (84.9)	81 (77.9)	55 (80.9)	53 (77.9)
Age, yr	49.3 (12.6)	47.0 (12.2)	48.7 (13.3)	47.6 (12.5)
Duration of SSc, mo	23.1 (17.0)	22.2 (16.0)	22.6 (16.6)	23.0 (17.2)
Total mRSS (range, 0–51)	20.4 (7.0)	20.3 (6.7)	20.9 (7.2)	20.7 (6.8)
ppFVC	83.9 (15.0)	80.3 (14.4)	81.5 (14.9)	77.7 (13.9)
$ppDL_{CO}$ (normal, ⩾80%)	76.8 (18.6)	74.4 (19.2)	72.1 (16.9)	68.7 (16.8)
SSc-ILD, *n*/*N* (%), HRCT visual read	68/104 (65.4)	68/102 (66.7)	68/68 (100)	68/68 (100)





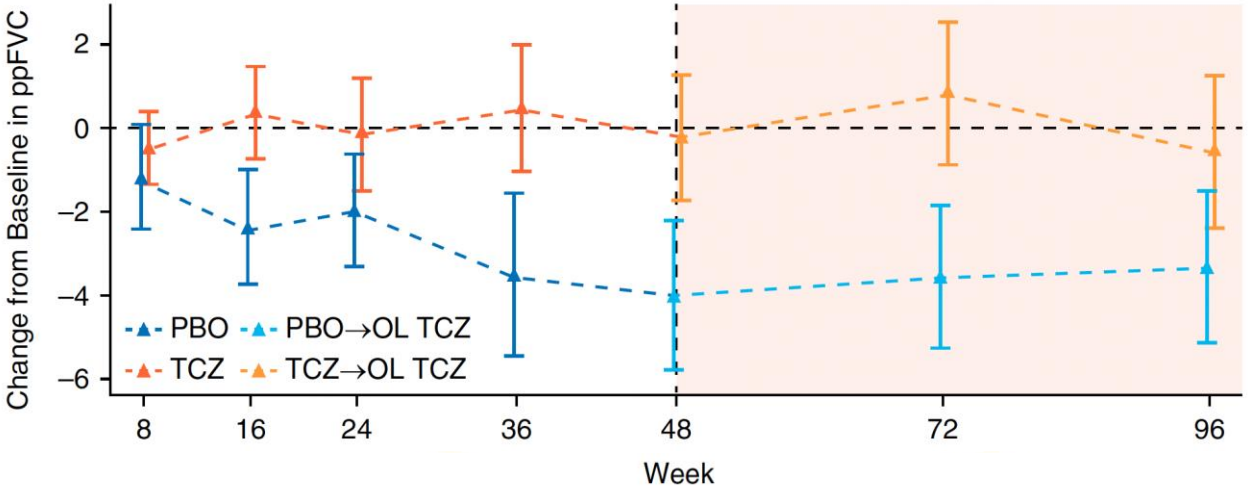
PBO, *n*	78	77	78	77	78
TCZ, *n*	82	83	79	81	82

Khanna D, Lancet Respir Med 2020, 8:963; Khanna D, Am J Respir Crit Care 2022, 205:674

Tocilizumab et PID Sclérodermie

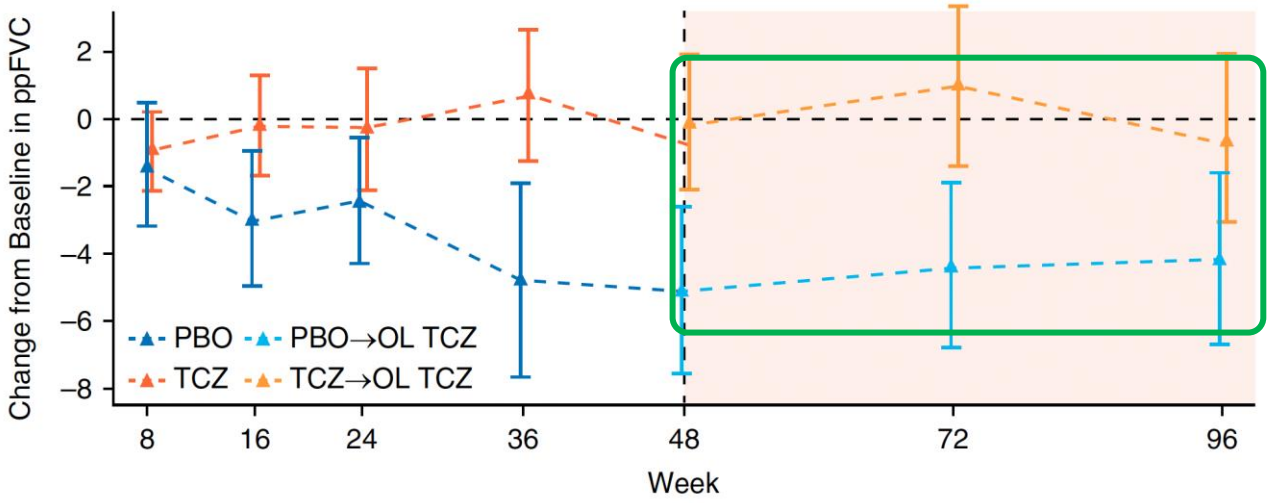
Open Label* (Week 48–96)			
All Patients		Patients with SSc-ILD	
PBO-TCZ (*N* = 89)	Continuous-TCZ (*N* = 92)	PBO-TCZ (*N* = 54)	Continuous-TCZ (*N* = 60)

Overall population



PBO, *n*	78	77	78	77	78	75	79
TCZ, *n*	82	83	79	81	82	80	84

ILD population

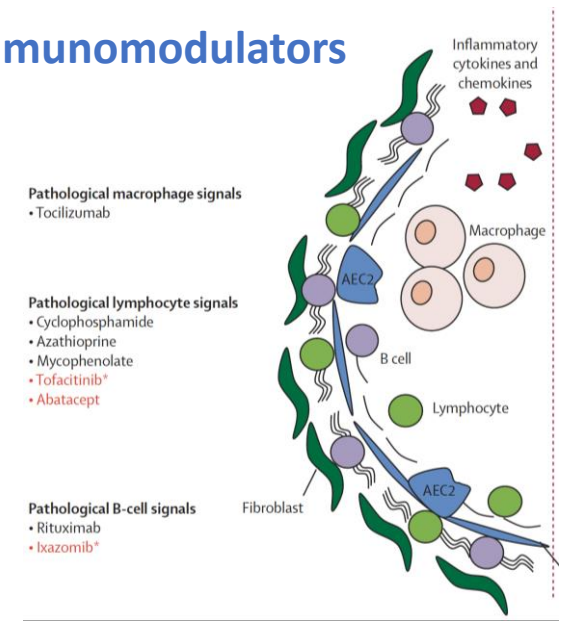


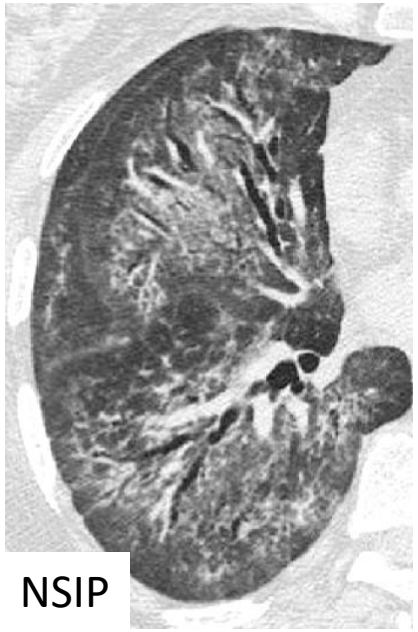
PBO, *n*	49	48	50	48	50	48	50
TCZ, *n*	53	53	51	52	53	50	54

Khanna D, Lancet Respir Med 2020, 8:963; Khanna D, Am J Respir Crit Care 2022, 205:674

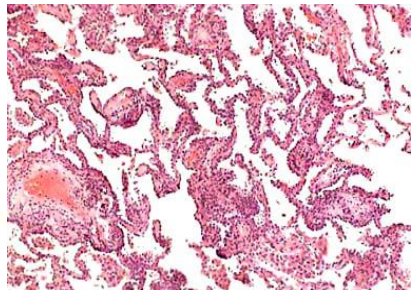
PIC, PINS et connectivites

Immunomodulators





NSIP



Auto-immunity

- Systemic scleroderma
- RA, Sjögren
- MCTD

NSIP :

Non specific interstitial pneumonitis

- **SSc-ILD**
  - Cyclophosphamide
  - Micophenolate
  - Rituximab?
  - Tocilizumab?
- **RA-ILD**
  - Methotrexate?
  - (Leflunomide; Abatacept*/anti-TNF**)
- **CTD-ILD**
  - Cyclophosphamide?
  - Rituximab?

*Johannson K, Lancet 2021, 398:1450; *Fernandez-Diaz C, Rheumatology 2020, 59:3906; **Holroyd C, Rheumatology 2019, 58:220*

PIC, PINS et connectivites

- preserve FVC decline (HR: 0.52)
- preserve DLCO decline
- reduction of risk of death (HR:0.70)
- reduction of risk of AE

Idiopathic pulmonary fibrosis

TREATMENT CONSIDERATIONS

PHARMACOLOGICAL
- Nintedanib
- Pirfenidone

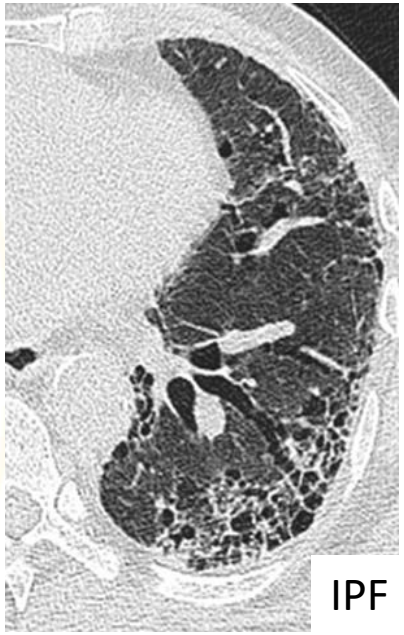
(FCV ≥50%/DLCO ≥30%)

NONPHARMACOLOGICAL
- Oxygen supplementation (if hypoxemic)
- Pulmonary rehabilitation

COMORBIDITIES
- Pulmonary hypertension
- Gastroesophageal reflux
- Obstructive sleep apnea
- Lung cancer

SYMPTOM CONTROL
- Palliative care

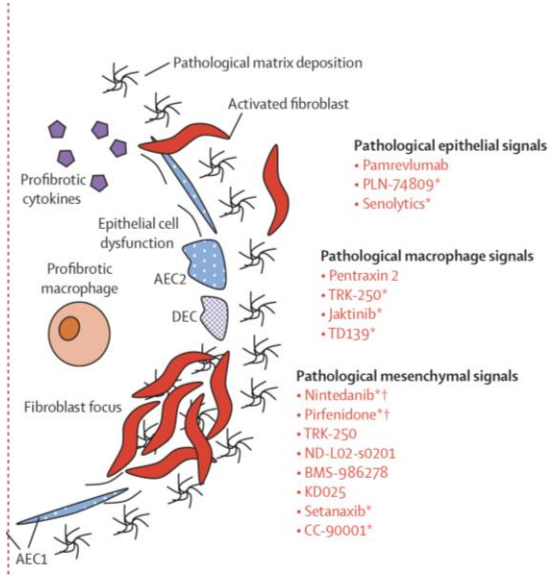
If increased risk of mortality, evaluate for lung transplantation at diagnosis

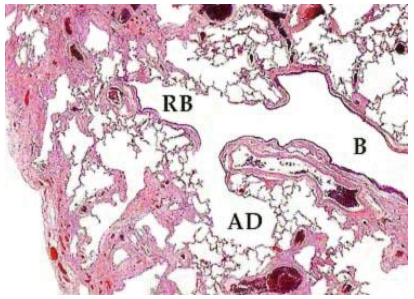


IPF

- Man
- >70 years old
- Smoker
- Clubbing
- “Velcro“ rales
- **IPF**

Fibromodulators





UIP :

Usual interstitial pneumonia

Johannson K, Lancet 2021, 398:1450; Raghu G, Am J Respir Crit Care 2022,e18

Pirfenidone et nintedanib pour la pratique

Tableau 12 Pirfénidone et nintédanib : synthèse pour la pratique.

	Pirfénidone[a]	Nintédanib[a]
Tolérance	Nausées, troubles digestifs Photosensibilité Fatigue, troubles du sommeil Amaigrissement	Diarrhée Nausées Amaigrissement
Dose recommandée	3 comprimés à 801 mg ou 9 comprimés à 267 mg/j en trois prises en cours de repas	2 gélules à 150 mg/j en cours de repas
Surveillance	Bilan hépatique (ex : avant traitement, puis tous les mois pendant 6 mois, puis tous les 6 mois).	Bilan hépatique (ex : avant traitement, puis tous les mois pendant 6 mois, puis tous les 6 mois).
Prescription	Pneumologue hospitalier Médicament d'exception	Pneumologue hospitalier Médicament d'exception
Interactions principales	Inhibiteurs du CYP1A2 : fluvoxamine (contre-indiquée), jus de pamplemousse, ciprofloxacine, amiodarone, propafénone Autres inhibiteurs du CYP : fluoxétine, paroxétine, chloramphénicol Inducteurs du CYP1A2 (ou autres CYP) : tabac, oméprazole[b], rifampicine	Inhibiteurs de la P-gp : kétoconazole, érythromycine, ciclosporine Inducteurs de la P-gp : rifampicine, carbamazépine, phénytoïne Pirfénidone
Contre-indications	Hypersensibilité/angiœdème à la pirfénidone Traitement par fluvoxamine Insuffisance hépatique ou rénale sévère Tabac fortement déconseillé Cirrhose Child-Pugh C Insuffisance rénale sévère (clairance de la créatinine < 30 ml/min) Prudence en cas de cirrhose Child-Pugh A ou B ou d'insuffisance rénale légère à modérée (clairance de la créatinine 30—50 ml/min)	Hypersensibilité au nintédanib ou au soja Éviter si traitement anticoagulant, traitement antiagrégant plaquettaire à forte posologie, risque hémorragique, ou cardiopathie ischémique Cirrhose Child-Pugh B ou C Insuffisance rénale sévère (clairance de la créatinine < 30 ml/min)
Résumé des caractéristiques du produit	https://www.ema.europa.eu/en/documents/product-information/esbriet-epar-product-information_fr.pdf	https://www.ema.europa.eu/en/documents/product-information/ofev-epar-product-information_fr.pdf

Cottin V, Recommandations pratiques Fibrose Pulmonaire idiopathique 2021

Progressive pulmonary fibrosis (PPF)

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*:

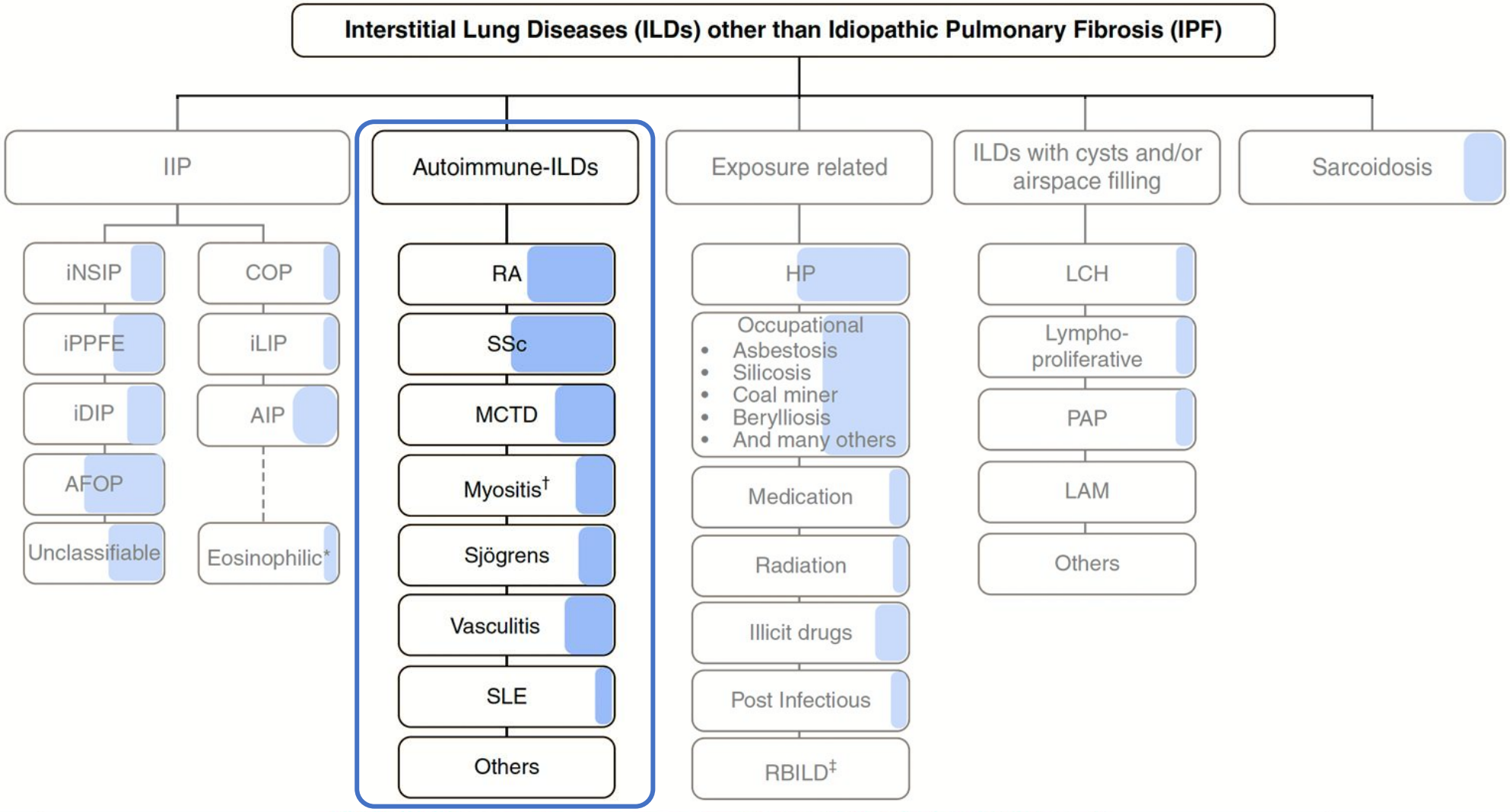
1 Worsening respiratory symptoms

2 Physiological evidence of disease progression (either of the following):
- a. Absolute decline in FVC ⩾5% predicted within 1 yr of follow-up (10% within 6 mo.)
- b. Absolute decline in D_{LCO} (corrected for Hb) ⩾10% predicted within 1 yr of follow-up (15% within 6 mo.)

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

Raghu G, Am J Respir Crit Care 2022,e18

Progressive pulmonary fibrosis (PPF)



Raghu G, Am J Respir Crit Care 2022,e18

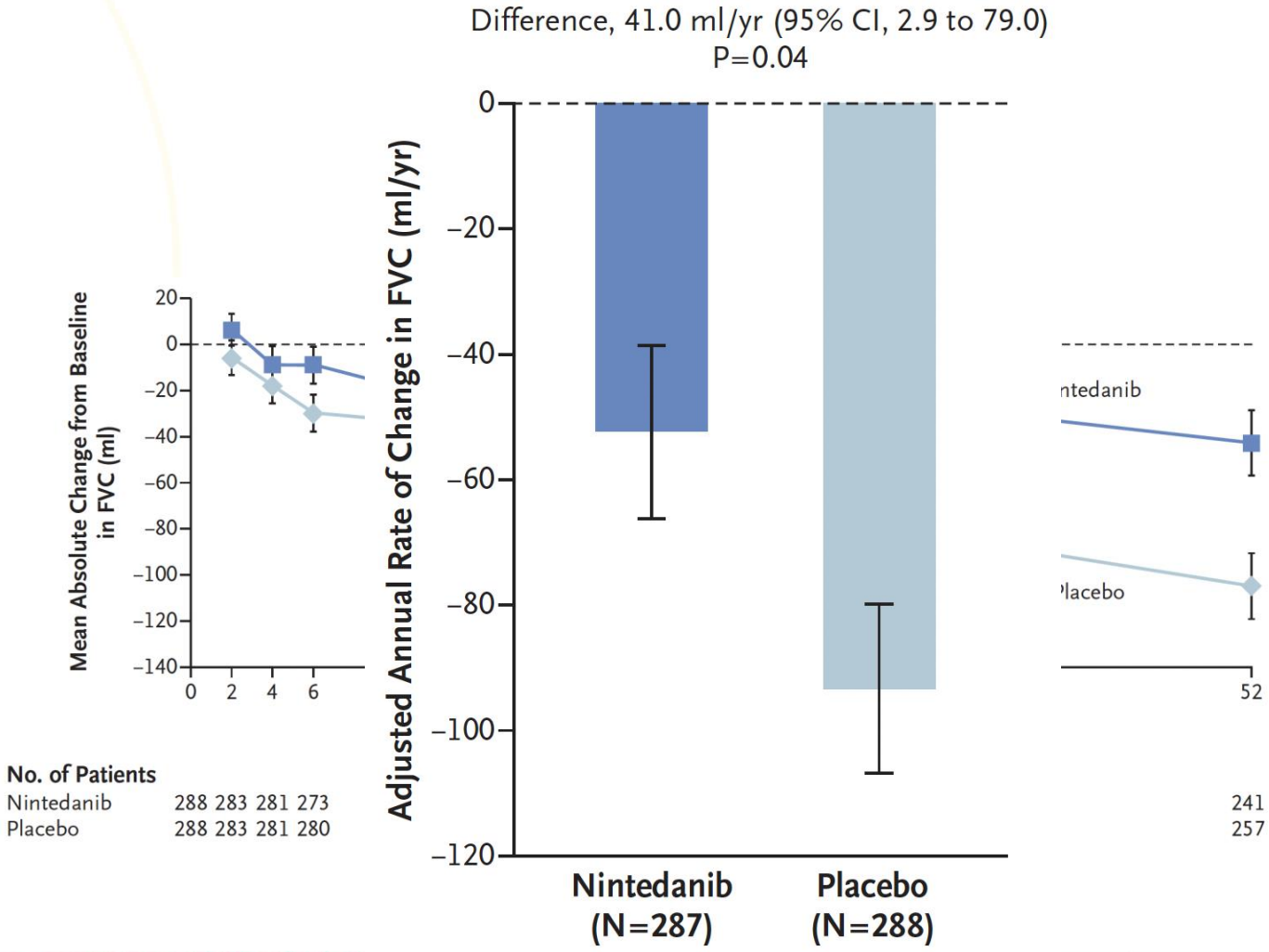
Nintedanib et PID Sclérodermie

SENCSIS Phase III trial

Nintedanib 150 mg twice daily vs Placebo 52 weeks
Primary objective FVC in SSc-ILD

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)



Distler O, N Engl J Med 2019, 380:2518

Nintedanib et PID Sclérodermie

SENCSIS Phase III trial

Nintedanib 150 mg twice daily vs Placebo 52 weeks
*Primary objective FVC in SSc-ILD, **impact of MMF***

	Patients taking mycophenolate at baseline		Patients not taking mycophenolate at baseline	
	Nintedanib (n=139)	Placebo (n=140)	Nintedanib (n=149)	Placebo (n=148)
Sex				
Female	102 (73%)	101 (72%)	119 (80%)	111 (75%)
Male	37 (27%)	39 (28%)	30 (20%)	37 (25%)
Age, years	52·6 (12·0)	51·5 (11·9)	56·5 (11·3)	55·1 (13·0)
Body-mass index, kg/m²	26·9 (5·0)	26·2 (5·5)	25·1 (4·5)	25·4 (4·8)
Race*				
White	112 (81%)	108 (77%)	89 (60%)	78 (53%)
Asian	9 (6%)	19 (14%)	53 (36%)	62 (42%)
Years since onset of first non-Raynaud's symptom	3·4 (0·9–6·9)	3·5 (1·0–7·0)	3·4 (0·3–7·1)	3·3 (0·4–7·2)
Extent of fibrotic ILD on high-resolution CT, %	37·9 (22·4)	35·8 (20·9)	35·8 (21·2)	34·7 (20·6)
FVC				
mL	2496 (724)	2581 (813)	2423 (748)	2503 (819)
% predicted	70·4 (15·6)	71·1 (16·5)	74·2 (17·7)	74·2 (16·6)
Diffusing capacity of the lung for carbon monoxide, % predicted†	50·8 (13·7)	52·6 (14·6)	54·8 (16·1)	53·8 (15·5)

	Patients taking mycophenolate at baseline		Patients not taking mycophenolate at baseline	
	Nintedanib (n=139)	Placebo (n=140)	Nintedanib (n=149)	Placebo (n=148)
Any adverse event*	136 (98%)	135 (96%)	147 (99%)	141 (95%)
Most frequent adverse events†				
Diarrhoea	106 (76%)	48 (34%)	112 (75%)	43 (29%)
Nausea	43 (31%)	23 (16%)	48 (32%)	16 (11%)
Skin ulcer	22 (16%)	23 (16%)	31 (21%)	27 (18%)
Vomiting	32 (23%)	17 (12%)	39 (26%)	13 (9%)
Cough	20 (14%)	33 (24%)	14 (9%)	19 (13%)
Nasopharyngitis	10 (7%)	22 (16%)	26 (17%)	27 (18%)
Upper respiratory tract infection	19 (14%)	25 (18%)	14 (9%)	10 (7%)
Abdominal pain	14 (10%)	6 (4%)	19 (13%)	15 (10%)
Fatigue	19 (14%)	14 (10%)	12 (8%)	6 (4%)
Headache	16 (12%)	15 (11%)	11 (7%)	9 (6%)
Urinary tract infection	16 (12%)	11 (8%)	8 (5%)	12 (8%)
Weight decreased	10 (7%)	4 (3%)	24 (16%)	8 (5%)
Decreased appetite	14 (10%)	10 (7%)	13 (9%)	2 (1%)
Severe adverse event	28 (20%)	18 (13%)	24 (16%)	18 (12%)
Serious adverse event	36 (26%)	22 (16%)	33 (22%)	40 (27%)
Fatal adverse event	3 (2%)	2 (1%)	2 (1%)	2 (1%)
Adverse event leading to treatment discontinuation	15 (11%)	9 (6%)	31 (21%)	16 (11%)

Distler O, N Engl J Med 2019, 380:2518; Highland K, Lancet Respir Med 2021, 9:96

MMF±Pirfenidone et PID Sclérodermie

Scleroderma Lung Study III (SLS III):

Combining the anti-fibrotic effects of Pirfenidone (PFD) with Mycophenolate (MMF) for treating Scleroderma-related Interstitial Lung Disease

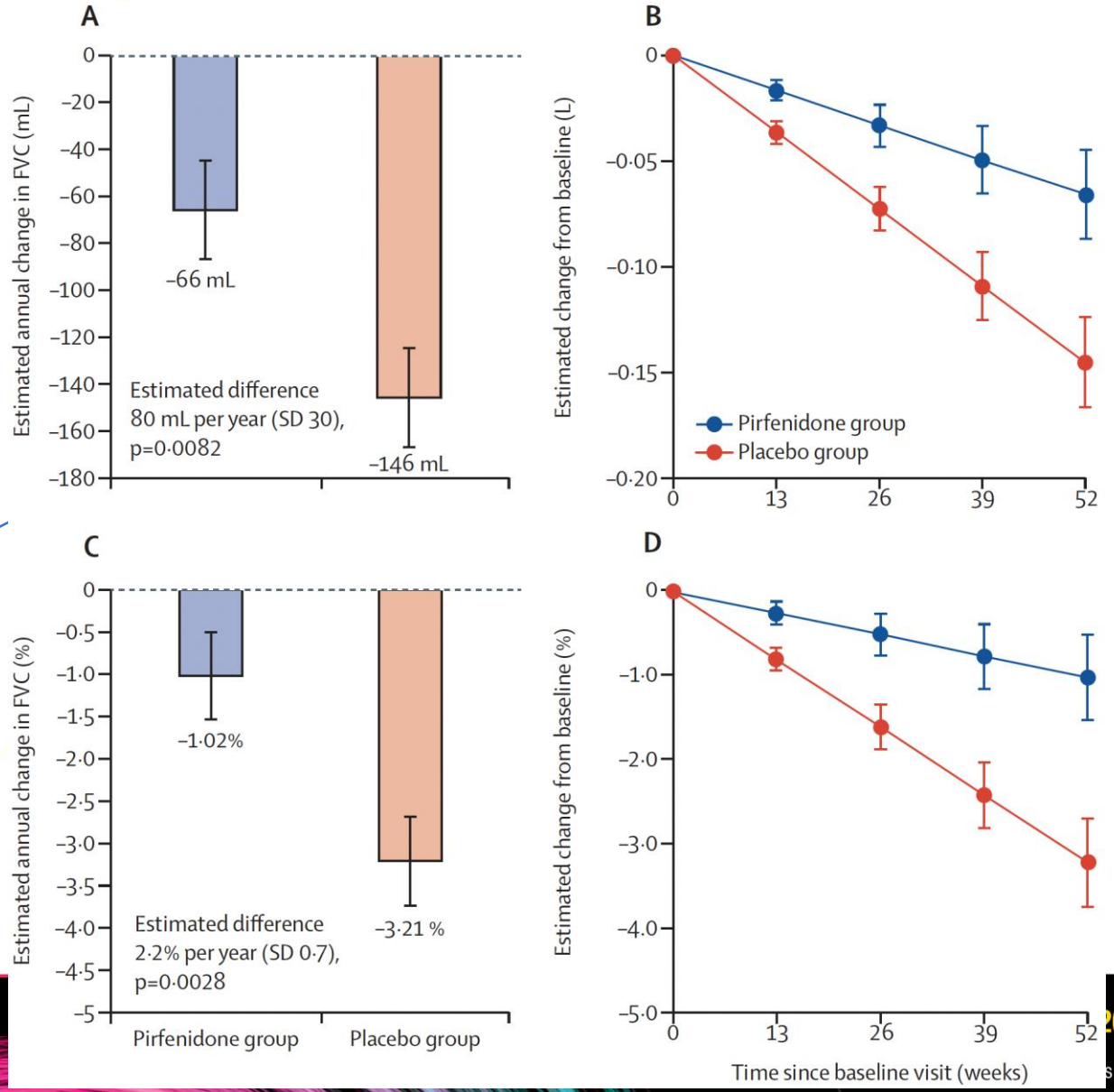
Pirfenidone et PID Polyarthrite rhumatoide

TRAIL-1 Phase II trial

Pirfenidone 801 mg tid vs Placebo 52 weeks

Primary objective FVC in RA-ILD

	Pirfenidone group (n=63)	Placebo group (n=60)
Age (years)	66·0 (61·0–74·0)	69·5 (63·5–74·5)
Sex		
Female	25 (40%)	21 (35%)
Male	38 (60%)	39 (65%)
Predominant HRCT pattern		
UIP	34 (54%)	47 (78%)
NSIP	9 (14%)	4 (7%)
LIP	0	3 (5%)
Indeterminate	20 (32%)	6 (10%)
DMARDs		
DMARD use	56 (89%)	50 (83%)
Pulmonary physiology		
Percent predicted FVC	69·4 (14·8)	70·4 (14·2)
FVC (L)	2·6 (0·8)	2·6 (0·8)
Percent predicted DLCO	50·0 (12·6)	47·6 (12·8)
DLCO (mL/min per mmHg)	12·0 (4·3)	10·9 (4·4)
HRCT		
CT extent of fibrosis	20·8 (9·8)	24·2 (11·8)



Solomon S, Lancet Respir Med 2022, Epub September

Pirfenidone et PID Polyarthrite rhumatoide

TRAIL-1 Phase II trial

Pirfenidone 801 mg tid vs Placebo 52 weeks

Primary objective FVC in RA-ILD

	Pirfenidone group* (n=62)	Placebo group (n=60)	p value
Treatment-emergent adverse events	62 (100%)	56 (94%)	0·039
Treatment-emergent serious adverse events	9 (15%)	8 (13%)	0·85
Treatment-emergent and treatment-related adverse events	27 (44%)	18 (30%)	0·12
Nausea	33 (53%)	11 (18%)	<0·0001
Fatigue	20 (32%)	12 (20%)	0·12
Diarrhoea	19 (31%)	16 (27%)	0·62
Anorexia	17 (27%)	6 (10%)	0·014
Gastro-oesophageal reflux	13 (21%)	6 (10%)	0·095
Vomiting	12 (19%)	4 (7%)	0·059

	Pirfenidone group* (n=62)	Placebo group (n=60)	p value
Treatment-emergent and treatment-related serious adverse events	1 (2%)	0	0·32
Adverse events leading to discontinuation of study drug	15 (24%)	6 (10%)	0·038
Treatment-emergent death or transplant	2 (3%)	4 (7%)	0·44
Treatment-emergent rheumatoid arthritis-associated interstitial lung disease-related mortality	1 (2%)	0	1

Solomon S, Lancet Respir Med 2022, Epub September

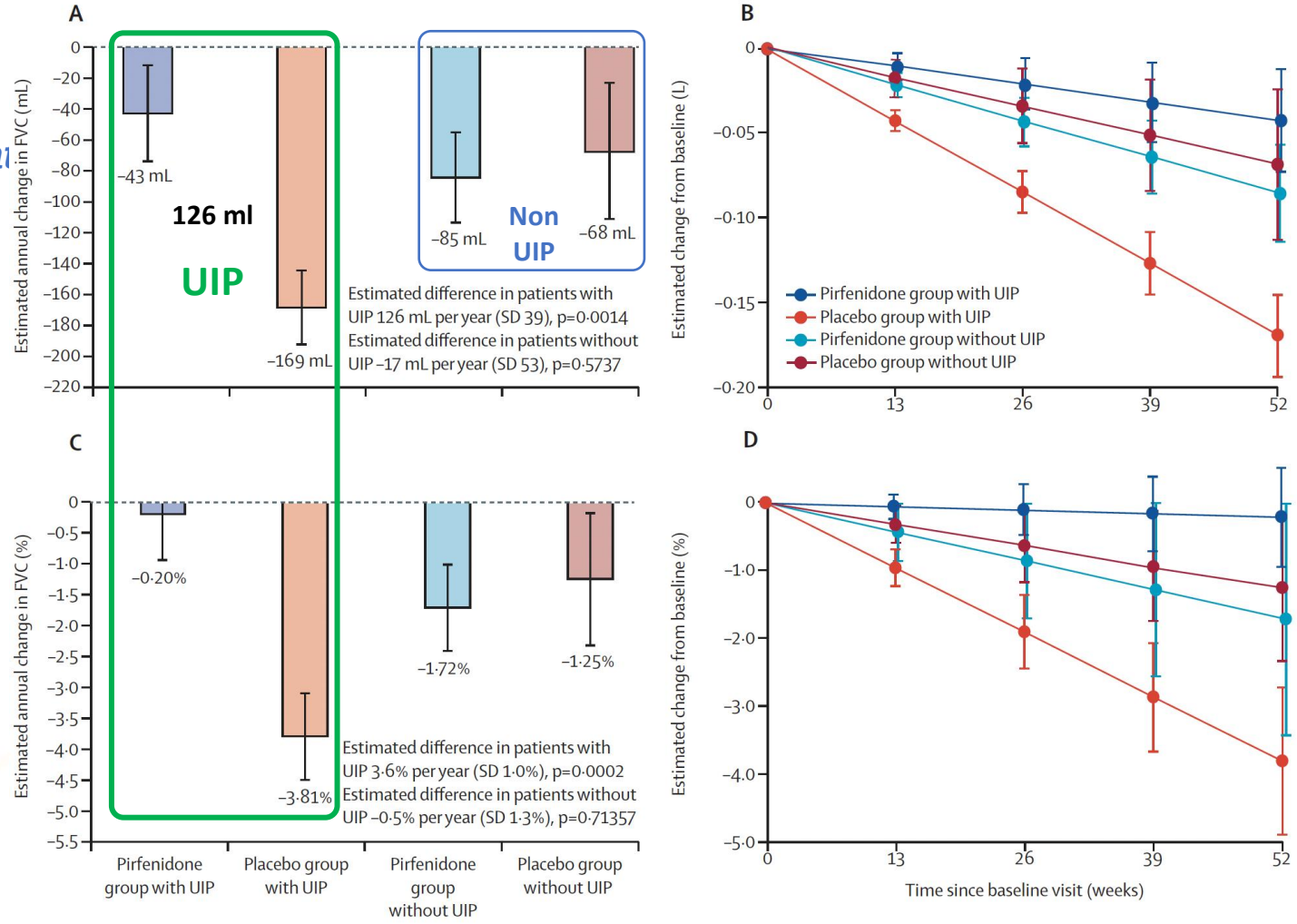
Pirfenidone et PID Polyarthrite rhumatoide

TRAIL-1 Phase II trial

Pirfenidone 801 mg tid vs Placebo 52 weeks

*Primary objective FVC in RA-ILD, **impact of UIP pat***

	Pirfenidone group (n=63)	Placebo group (n=60)
Age (years)	66·0 (61·0–74·0)	69·5 (63·5–74·5)
Sex		
Female	25 (40%)	21 (35%)
Male	38 (60%)	39 (65%)
Predominant HRCT pattern		
UIP	34 (54%)	47 (78%)
NSIP	9 (14%)	4 (7%)
LIP	0	3 (5%)
Indeterminate	20 (32%)	6 (10%)
DMARDs		
DMARD use	56 (89%)	50 (83%)
Pulmonary physiology		
Percent predicted FVC	69·4 (14·8)	70·4 (14·2)
FVC (L)	2·6 (0·8)	2·6 (0·8)
Percent predicted DLCO	50·0 (12·6)	47·6 (12·8)
DLCO (mL/min per mmHg)	12·0 (4·3)	10·9 (4·4)
HRCT		
CT extent of fibrosis	20·8 (9·8)	24·2 (11·8)



Solomon S, Lancet Respir Med 2022, Epub September

Nintedanib et PPF (±connectivites)

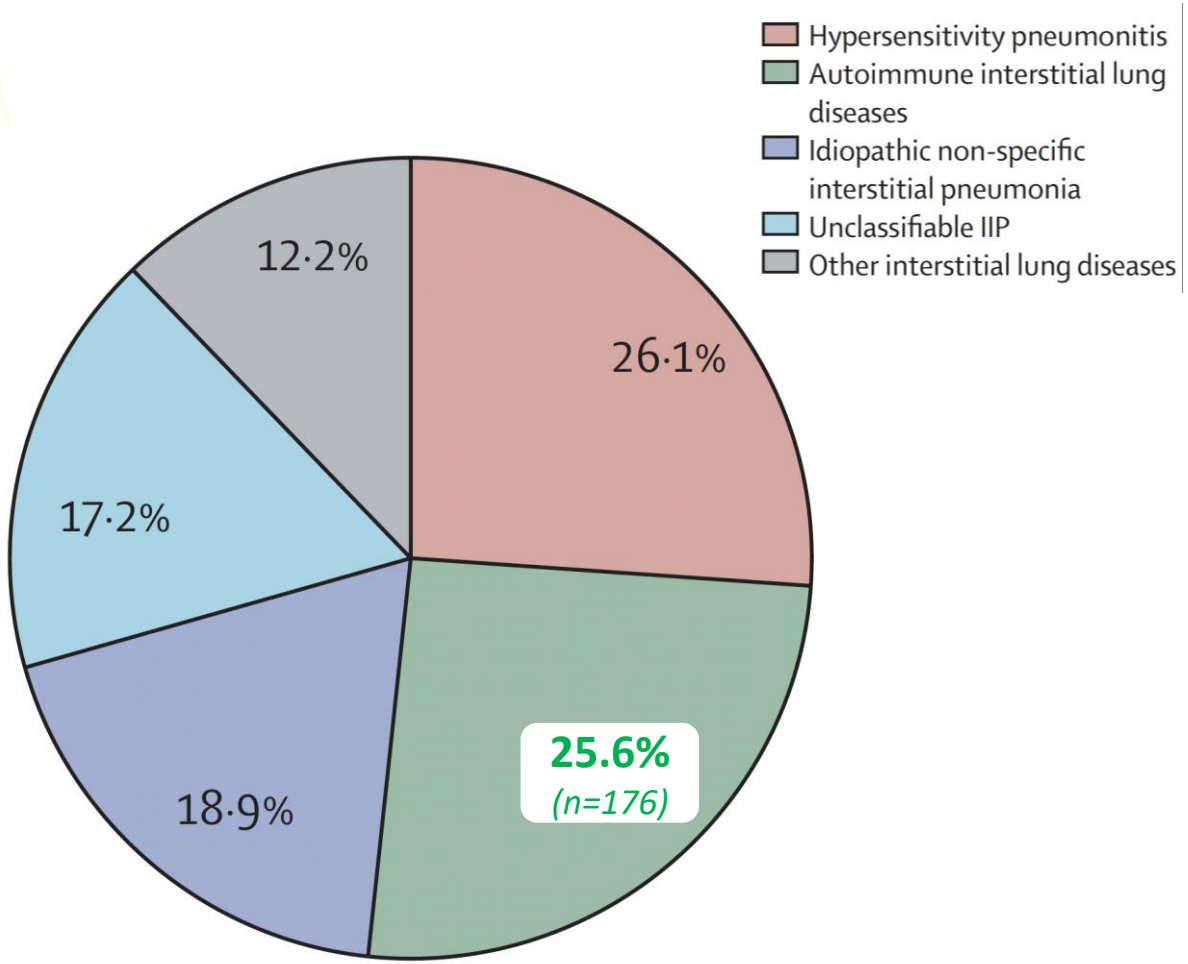
INBUILD Phase III trial

Nintedanib 150 mg twice daily vs Placebo 52 weeks

Primary objective FVC

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



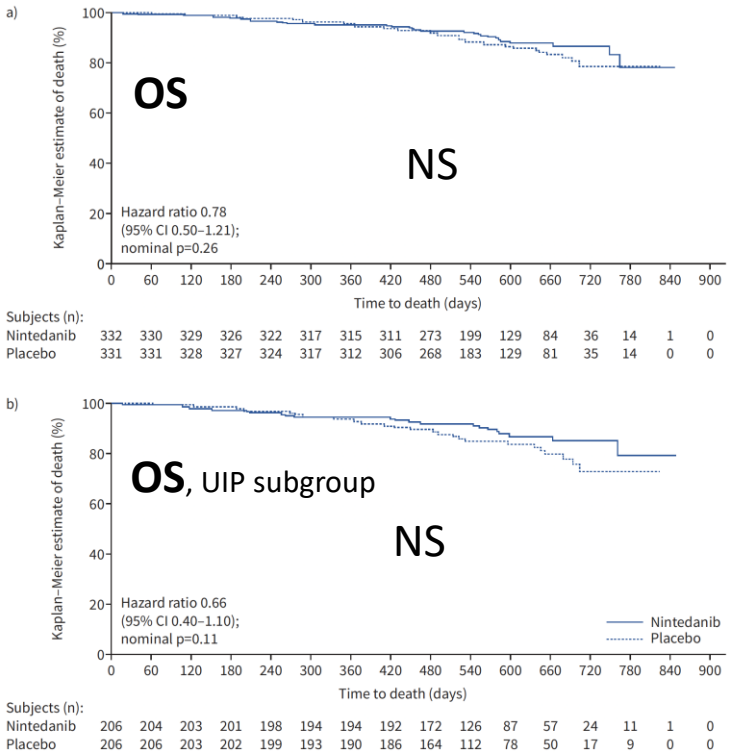
Flaherty KR, N Engl J Med 2019, 381:1718; Wells A, Lancet Respir Med 2020

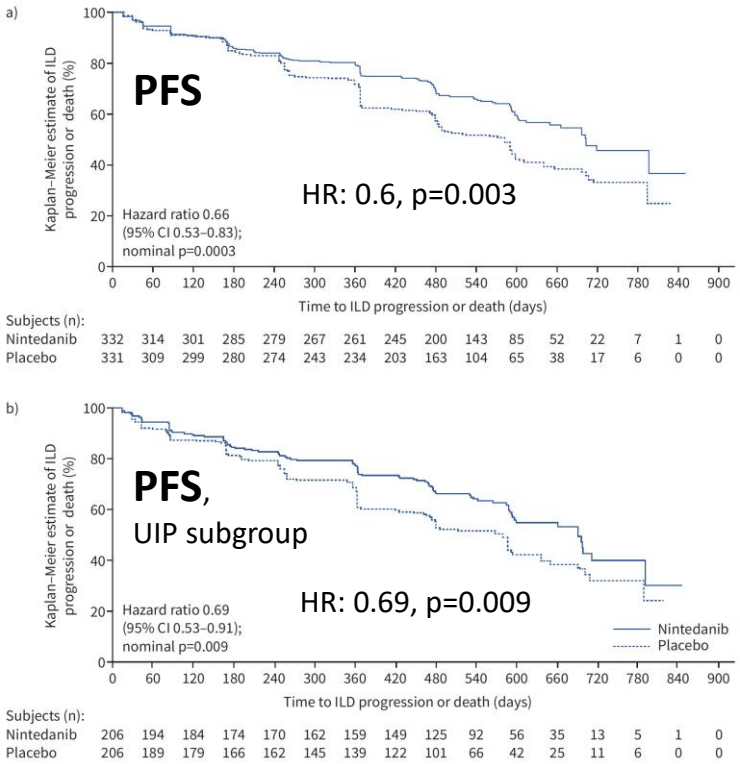
Nintedanib et PPF (±connectivites)

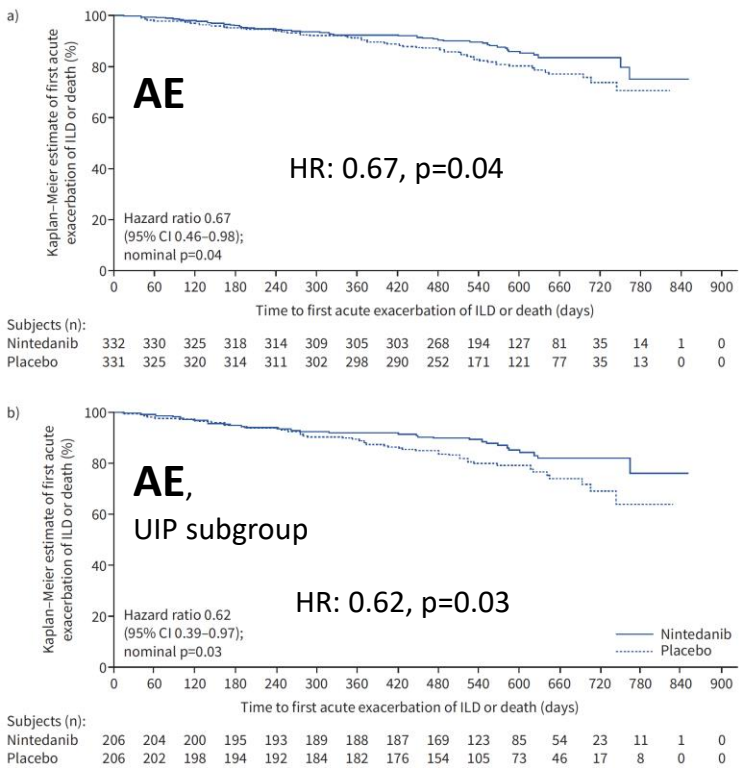
INBUILD Phase III trial

Nintedanib 150 mg twice daily vs Placebo 52 weeks

*Primary objective FVC, **secondary objectives***







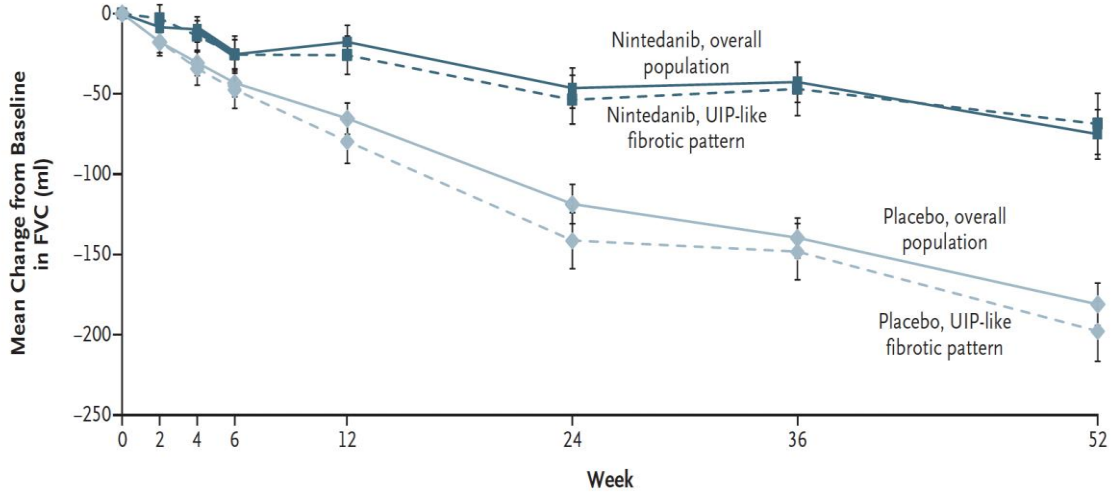
Flaherty KR, N Engl J Med 2019, 381:1718; Cottin V, Eur Respir J 2022, 59:2004538

Nintedanib et PPF (±connectivites)

INBUILD Phase III trial

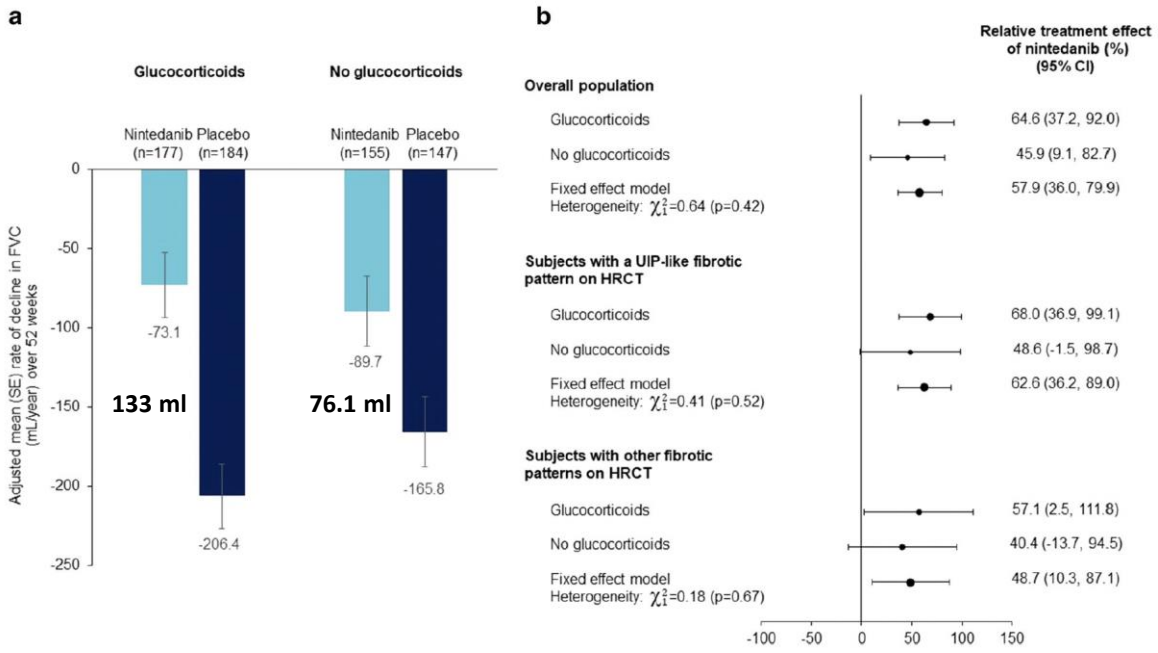
Nintedanib 150 mg twice daily vs Placebo 52 weeks

*Primary objective FVC, **impact of corticosteroids and UIP pattern***



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

Efficacy in by corticosteroids exposure and UIP pattern



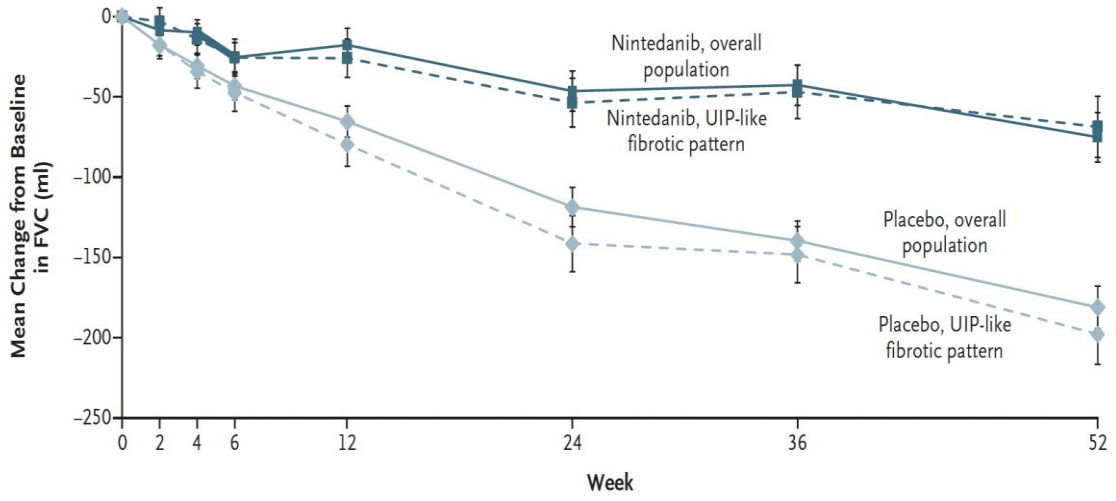
Flaherty KR, N Engl J Med 2019, 381:1718; Wells A, Lancet Respir Med 2020; Cottin V, Respiratory Research 2021, 22:84; Matteson E, Arthritis Rheum 2022, 74:1039

Nintedanib et PPF de connectivites

INBUILD Phase III trial

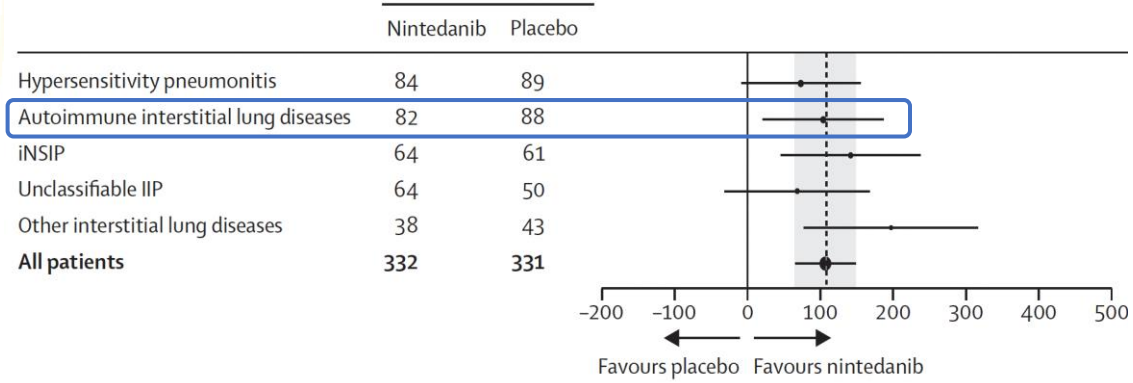
Nintedanib 150 mg twice daily vs Placebo 52 weeks

*Primary objective FVC, **impact of etiologies and UIP pattern***



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

Efficacy in CTD-PPF



Flaherty KR, N Engl J Med 2019, 381:1718; Wells A, Lancet Respir Med 2020

Nintedanib et PPF de connectivites

INBUILD Phase III trial

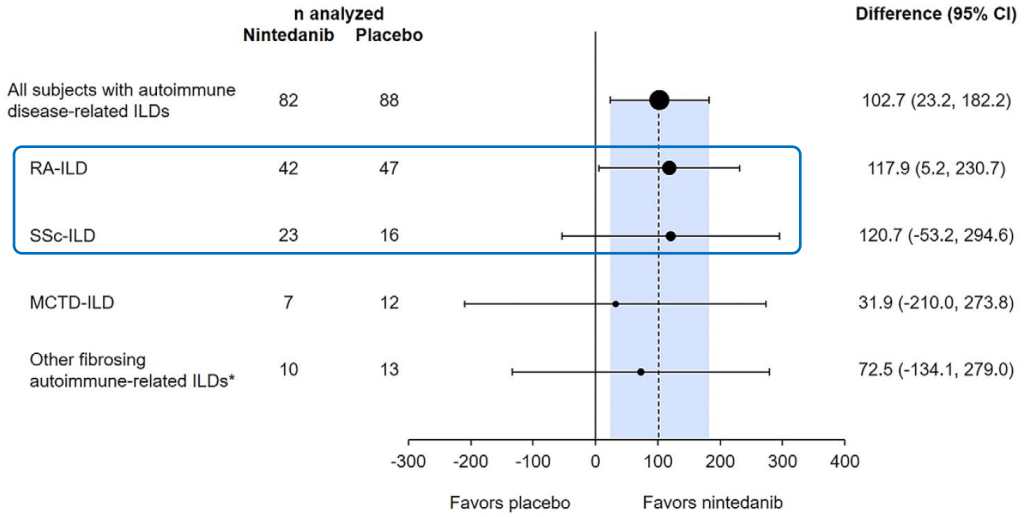
Nintedanib 150 mg twice daily vs Placebo 52 weeks

*Primary objective FVC, **impact of CTD subgroups and UIP pattern***

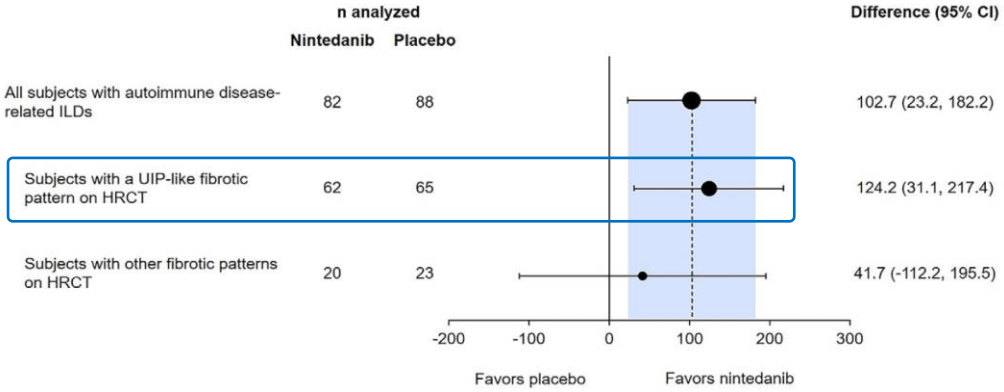
Table 1. Baseline characteristics of subjects with autoimmune disease–related ILDs in the INBU

	Nintedanib (n = 82)	Placebo (n = 88)
Female	47 (57.3)	43 (48.9)
Age, mean ± SD years	63.3 ± 10.0	65.1 ± 11.1
BMI, mean ± SD kg/m^2	26.7 ± 5.2	28.0 ± 4.9
Current or former smoker	40 (48.8)	45 (51.1)
ILD diagnosis		
RA-associated ILD	42 (51.2)	47 (53.4)
SSc-associated ILD	23 (28.0)	16 (18.2)
MCTD-associated ILD	7 (8.5)	12 (13.6)
Other autoimmune ILDs†	10 (12.2)	13 (14.8)
Time since diagnosis of ILD based on imaging, mean ± SD years	4.6 ± 4.4	4.0 ± 3.9
UIP-like fibrotic pattern on HRCT‡	62 (75.6)	65 (73.9)
FVC, mean ± SD ml	2,291 ± 722	2,366 ± 680
FVC%, mean ± SD	69.6 ± 15.1	72.1 ± 14.6
DLco%, mean ± SD§	44.9 ± 13.4	50.8 ± 16.0

Efficacy by CTD-PPF subgroups



Efficacy by CTD-PPF CT-scan patterns



Flaherty KR, N Engl J Med 2019, 381:1718; Wells A, Lancet Respir Med 2020; Cottin V, Respiratory Research 2021, 22:84; Matteson E, Arthritis Rheum 2022, 74:1039

Nintedanib et PPF de connectivites

INBUILD Phase III trial

Nintedanib 150 mg twice daily vs Placebo 52 weeks

*Primary objective FVC, **impact of associated DMARDs treatment***

Table 1. Baseline characteristics of subjects with autoimmune disease–related ILDs in the INBU

	Nintedanib (n = 82)	Placebo (n = 88)
Female	47 (57.3)	43 (48.9)
Age, mean ± SD years	63.3 ± 10.0	65.1 ± 11.1
BMI, mean ± SD kg/m^2	26.7 ± 5.2	28.0 ± 4.9
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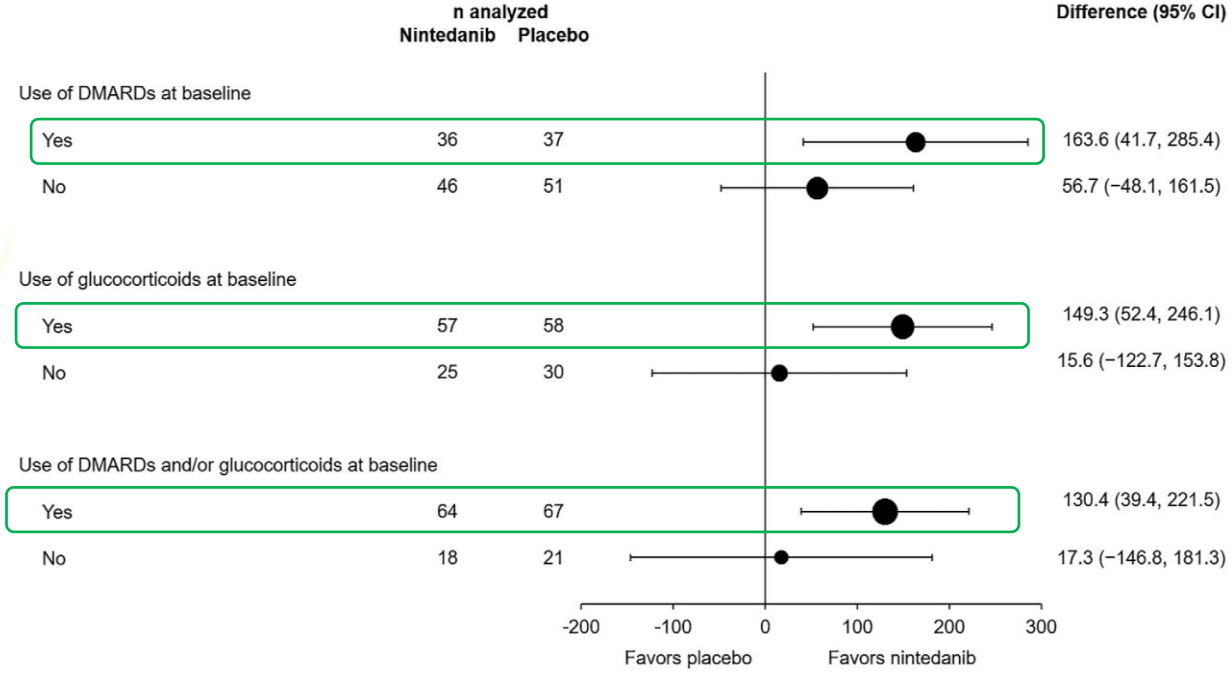
DLco%, mean ± SD§	44.9 ± 13.4	50.8 ± 16.0

Efficacy by corticosteroids ± DMARDS subgroups



Flaherty KR, N Engl J Med 2019, 381:1718; Wells A, Lancet Respir Med 2020; Cottin V, Respiratory Research 2021, 22:84; Matteson E, Arthritis Rheum 2022, 74:1039

Pirfenidone et PPF (±connectivites)

RELIEF Phase IIb trial

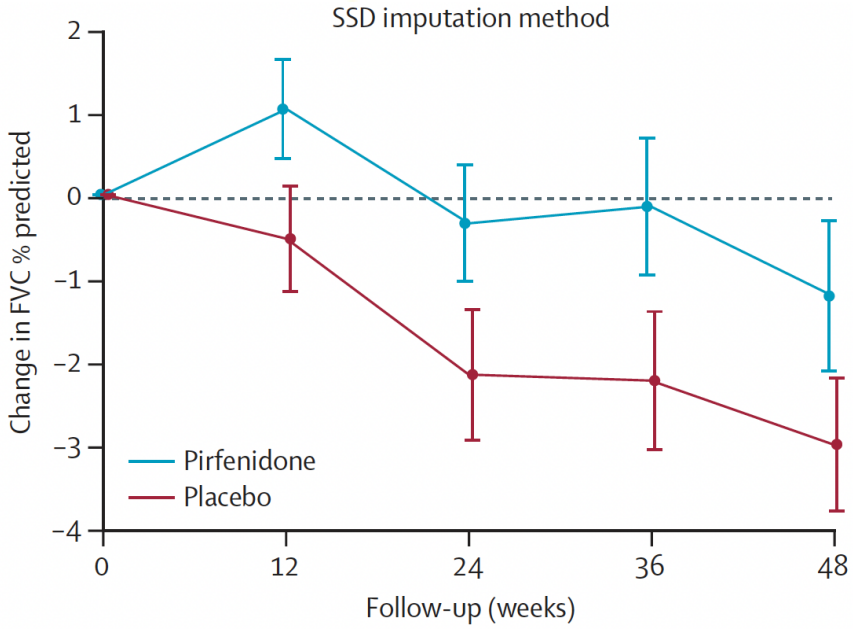
Pirfenidone 801 mg tid vs Placebo 52 weeks

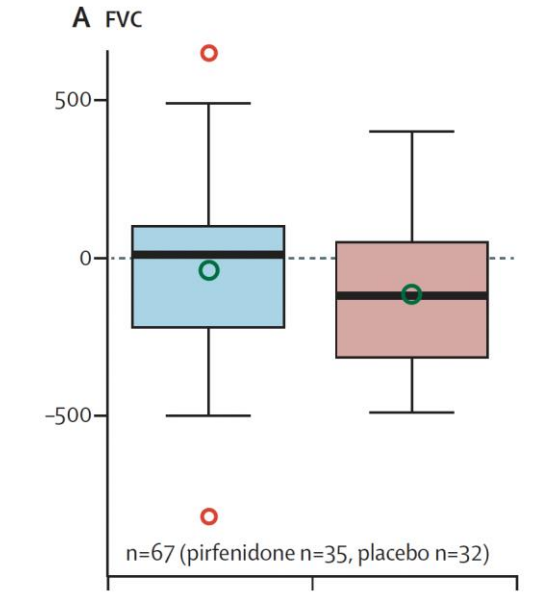
Primary objective FVC in PPF±CTD

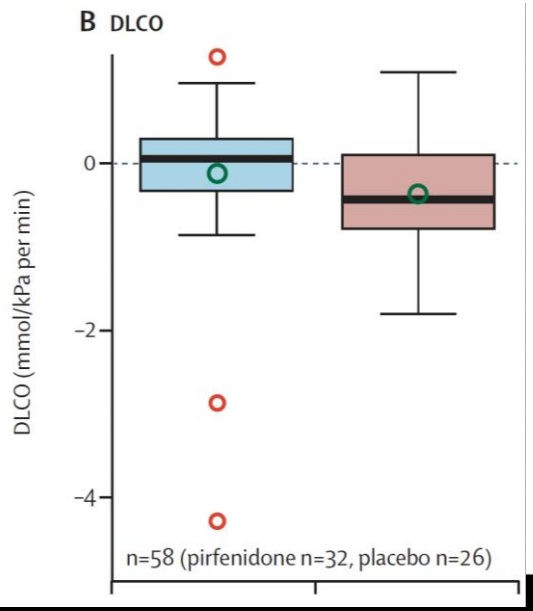
	Pirfenidone (n=64)	Placebo (n=63)
Age, years	63·2 (10·6)	63·5 (9·1)
Sex		
Men	43 (67%)	32 (51%)
Women	21 (33%)	31 (49%)
Supplemental O_2 at rest	14 (22%)	20 (32%)
Flow rate at rest, L/min	2·2 (0·9)*	2·3 (0·8)†
FVC, % predicted	62·6 (14·5)	62·2 (13·5)
FEV_1, % predicted	68·1 (15·4)	64·4 (14·3)
DLCO, % predicted	38·1 (14·1)	37·7 (14·2)
FEV_1/FVC ratio	86·7 (6·9)	83·8 (7·7)
6MWD, m	357·7 (99·2)	345·2 (110·0)
Any steroid or immunosuppressant therapy	47 (73%)	56 (89%)
Steroid monotherapy	17 (27%)	31 (49%)
Combination therapy with steroids	23 (36%)	22 (35%)
Azathioprine	11 (17%)	11 (18%)
Mycophenolate	7 (11%)	6 (10%)

Efficacy in 127 PPF among whom 37 PPF-CTD (29%)

Similar effect in all subgroups after asbestosis exclusion



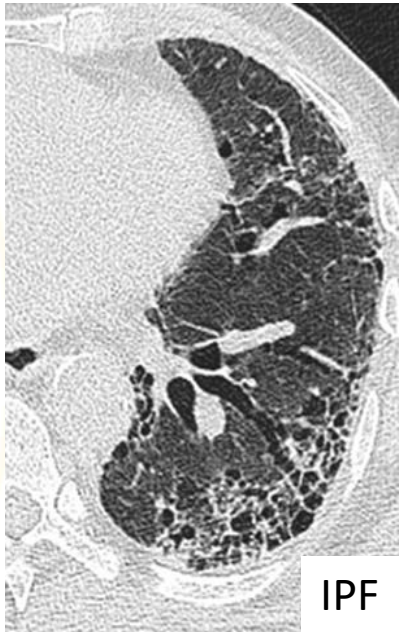




Behr, J Lancet Respir Med 2021, 9:476

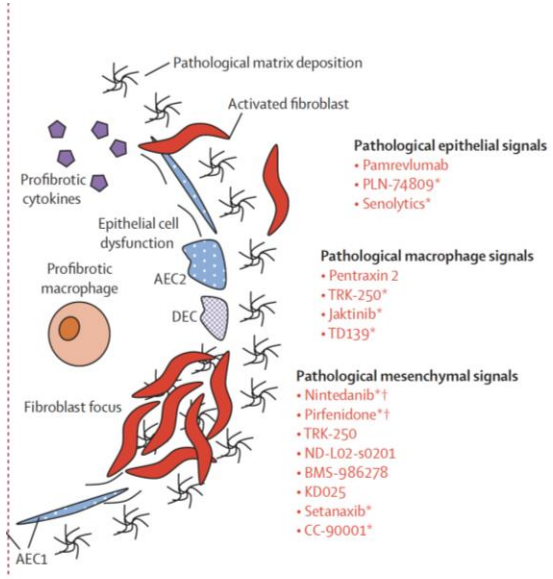
PIC, PINS et connectivites

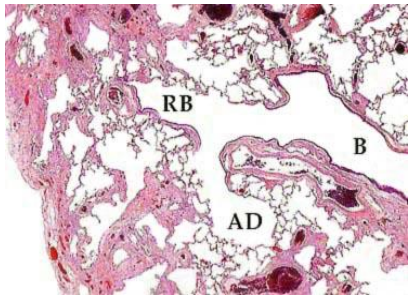
- **SSc-ILD**
  - **Nintedanib**
    ±MMF
  - (Pirfenidone±MMF?)
- **RA-ILD**
  - **Pirfenidone?**
    ±UIP pattern
    >toxicity
- **PPF**
  - **Nintedanib?**
    ± CTD
    ± UIP pattern
    ± SSc/RA
    ± Corticosteroids
    ± DMARDS
  - **Pirfenidone?**



IPF

Fibromodulators



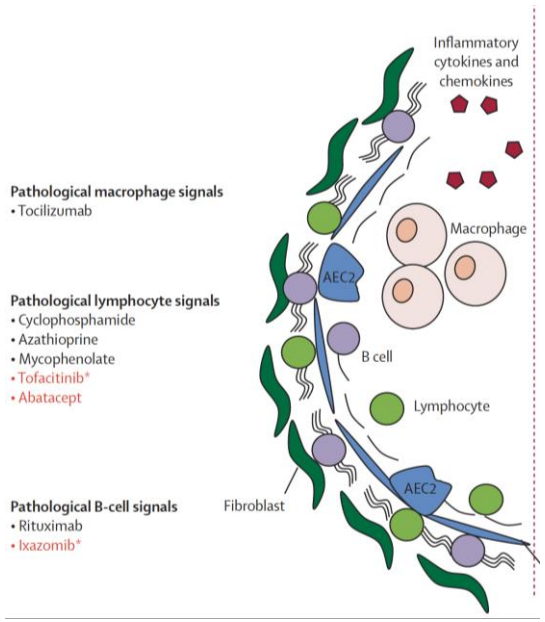


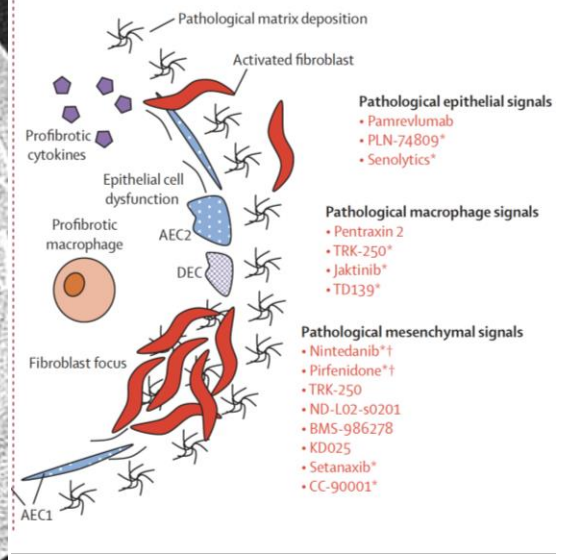
UIP :

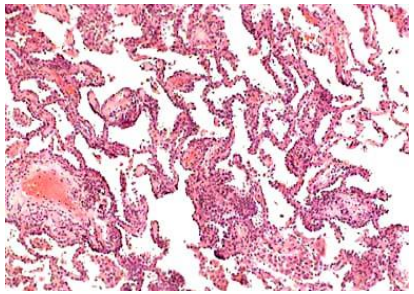
Usual interstitial pneumonia

Johannson K, Lancet 2021, 398:1450; Raghu G, Am J Respir Crit Care 2022,e18

PIC, PINS, PPR et connectivites

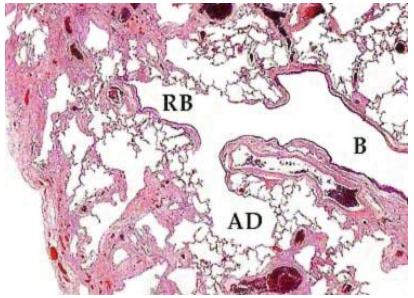






Immunomodulators? ⟷ **Fibromodulators?**

- Systemic scleroderma
- RA, Sjögren
- MCTD



NSIP :

Non specific interstitial pneumonitis

UIP :

Usual interstitial pneumonia

Points clefs: antifibrosants et PID des connectivites

- Diagnostic précoce des PID, pattern, étendue/sévérité, activité de la CTD
- IS et biothérapies semblent actives sur les PID: délais d'apparition (méthotrexate), prévention de la progression
  - Niveau de preuve variable en fonction des connectivites
  - Cyclophosphamide et MMF ont été évalués sur des PID plus sévères
  - Tociluzimab et Rituximab sur PID moins sévères
  - Effet "CTD" ou "pattern de PID" dépendant?
- Les antifibrosants ont été évalués sur des PID (déjà traitées?) stables ou progressives de CTD "récentes"
  - Plus de données avec le Nintedanib qu'avec la Pirfenidone : épargne 40 à 130 ml/an
  - Niveau de preuve variable en fonction des connectivites
  - Effet de l'association avec corticostéroïdes et MMF (et les autres?)
  - Rôle majeur du pattern UIP (ou PPF?)
- Y-a-t-il une place pour les antifibrosants en "front-line"
  - Toxicités; interactions +++

“My step by step questioning“

Q1

- Which connective tissue disorder? (RA, SSc, MCTD)
- **Perform baseline thoracic LD-CT; if ILD contact your favorite pulmonologist** and perform PFTs (FVC and DLCO)
- Respiratory symptoms/signs?

Q2

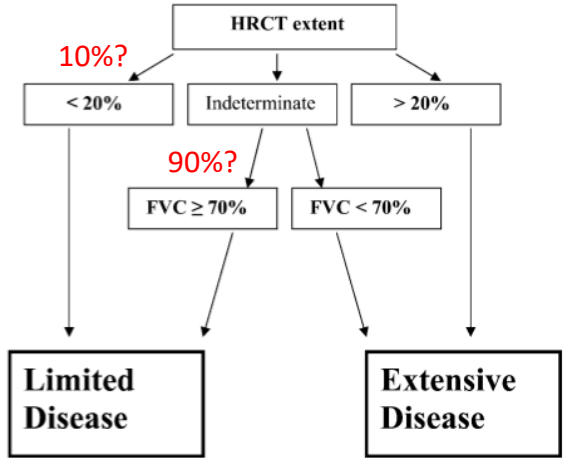
- CT scan pattern, UIP/fibrotic, extension vs OP, NSIP-COP
- FVC: >70%; 70-50%; <50%; DLCO: >80%; 80-30; <30%
- Pulmonary hypertension?
- Bronchoalveolar lavage?

Q3

- Smoking, recent onset
- Extra-thoracic disease activity
- Inflammatory markers? (CRP, ESR, platelets?); alveolitis (lymphocytes vs polymorphonuclears)

=

- **Begin your favorite treatment to obtain the best CTD control**
- **Methotrexate, MMF, rituximab, tocilizumab please your pulmonologist**
- Others, look at https://www.pneumotox.com/drug/index/



PNEUMOTOX ON LINE

“My step by step questioning“

Q4

- **ILD immediate indication to treat:** i) symptoms; ii) HRCT/FVC/DLCO; iii) PHT
- Multidiciplinary meeting
  - Cyclophosphamide or not? Corticosteroids or not? (< 20 mg if ScS or MCTD)
  - CTD **AND** ILD treatment? (MMF, rituximab, tocilizumab?)

Trials

Table 1
List of recruiting and not-yet recruiting randomized clinical trials on the medical treatment of connective tissue disease–interstitial lung diseases

Study Title	Condition	Status	Intervention	Sponsor
APRIL (AbatacePt in Rheumatoid Arthritis-ILD) NCT03084419	RA-ILD	Recruiting	Abatacept	Cambridge University Hospitals NHS Foundation Trust, United Kingdom
Effects of Tofacitinib vs Methotrexate on Rheumatoid Arthritis Interstitial Lung Disease NCT04311567	RA-ILD	Not yet recruiting	Tofacitinib	Vastra Gotaland Region (Göteborg University), Sweden
Pragmatic Clinical Trials in Scleroderma (PCTS) NCT03610217	SSc-ILD	Not yet recruiting	Rituximab or intravenous cyclophosphamide	University of West London, Ontario, Canada
Comparing and Combining Bortezomib and Mycophenolate in SSc Pulmonary Fibrosis NCT02370693	SSc-ILD	Recruiting	Bortezomib	Northwestern University, Illinois
Abatacept for the Treatment of Myositis-associated Interstitial Lung Disease NCT03215927	Antisynthetase syndrome	Recruiting	Abatacept	University of Pittsburgh, PA
Cyclophosphamide and Azathioprine vs Tacrolimus in Antisynthetase Syndrome-related Interstitial Lung Disease NCT03770663	Antisynthetase syndrome	Not yet recruiting	Cyclophosphamide and azathioprine vs tacrolimus	Assistance Publique - Hôpitaux de Paris, France
Evaluation of Efficacy and Safety of Rituximab With Mycophenolate Mofetil in Patients With Interstitial Lung Diseases NCT02990286	CTD-ILD/IPAF	Recruiting	Rituximab	University Hospital, Tours, France
Cyclosporine A in the Treatment of Interstitial Pneumonitis Associated With Sjogren’s Syndrome NCT02370550	pSS-ILD	Recruiting	Cyclosporine	Peking University, China

Kawano-Dourado L, Clin Chest Medicine 2021, 42:295

“My step by step questioning“

Q5

- **No immediate indication to treat**
  - Stop smoking, vaccination, rehabilitation, screen for environmental exposure
  - PFTs and DLCO every 3 to 4 months during 1 to 2 years?
- Then, every 6 to 12 months?

Q6

- If UIP pattern alone or PPF definition
- Multidiciplinary meeting
  - If uncontrolled “extra-thoracic“ CTD **AND** “PPF“: switch CTD treatment to MMF, rituximab, tocilizumab? **THEN?** add an antifibrotic drug
  - If PPF only: add antifibrotic drug (nintedanib>pirfenidone)

Trials

Q7

- If subacute/acute exacerbation…

Table 1
List of recruiting and not-yet recruiting randomized clinical trials on the medical treatment of connective tissue disease–interstitial lung diseases

Study Title	Condition	Status	Intervention	Sponsor
Phase II Study of Pirfenidone in Patients With RAILD (TRAIL1) NCT02808871	RA-ILD	Recruiting	Pirfenidone	Brigham and Women’s Hospital, United States
Efficacy and Safety of Pirfenidone in Patient With Systemic Sclerosis-associated Interstitial Lung Disease NCT03856853	SSc-ILD	Recruiting	Pirfenidone	Beijing Continent Pharmaceutical Co, Ltd, China
Scleroderma Lung Study III - Combining Pirfenidone With Mycophenolate NCT03221257	SSc-ILD	Recruiting	Pirfenidone	University of California, Los Angeles, CA
Efficacy and Safety of Pirfenidone in Patient With Dermatomyositis Interstitial Lung Disease (Dm-ILD) NCT03857854	DM-ILD	Recruiting	Pirfenidone	Beijing Continent Pharmaceutical Co, Ltd, China

Kawano-Dourado L, Clin Chest Medicine 2021, 42:295

Algorithme for the management of ScS-ILD

Diagnosis

ILD on HRCT

Disease Severity

Subclinical ILD

Disease does not impact how the patient feels or functions. No symptoms or impact on day-to-day functioning attributable to ILD
All variables should be met (including #1), but there are exceptions (e.g., severe extent of ILD on HRCT, without any other feature):

1. Minimal-to-mild extent of ILD on HRCT
2. FVC% or Dlco% predicted >Lower Limit of Normal
3. No clinically meaningful decline on repeat FVC or DLco

Clinical ILD

Disease impacts how the patient feels, functions, or survives. This includes symptoms or impact on day-to-day functioning attributable to ILD.
At least #1 variable should be met:

1. Mild-to-severe extent of ILD on HRCT
2. FVC% or Dlco% predicted <Lower Limit of Normal
3. Clinically meaningful decline on repeat FVC or DLco

Risk of Progression

Low Risk of Progressive ILD

High Risk of Progressive ILD

Burden of Disease

Early SSc with progressive skin disease and elevated acute phase reactants

Predominant lung involvement, absent active skin and musculoskeletal symptoms

Multi-organ involvement including skin and musculoskeletal symptoms

Management/ Treatment

Disease Monitoring

Frequent monitoring with symptom assessment, PFTs every 4-6 months, and serial hallwalk testing for the first 5 years

Repeat HRCT if indicated by symptoms, PFT abnormalities, and declining hallwalk testing

Consider pharmacologic treatment, based on individual patient factors

Immunomodulatory Therapy

Tocilizumab*

Mycophenolate Mofetil

Anti-Fibrotic Therapy

Nintedanib

or

Immunomodulatory Therapy

Mycophenolate Mofetil

Cyclophosphamide

Immunomodulatory Therapy

Mycophenolate Mofetil

Cyclophosphamide

Rituximab

Tocilizumab*

Escalation Therapy

Escalation Therapy

Hematopoietic Stem Cell Transplantation
Add Nintedanib
Change therapy to Cyclophosphamide/MMF
Add Rituximab if not initially used
Lung Transplant
Clinical trials

Roofeh D, Curr Opin Rheumatol 2021, 33:240

	Sclérodermie systémique[1]	Polyarthrite rhumatoïde[2]	Myopathies inflammatoires idiopathiques[4]	Syndrome de Sjögren	Connectivites mixtes[5]	Lupus érythémateux disséminé
Fréquence	40%	32%	16%	24%		
Facteurs de risque communs[3]	• PIC[3] • Progression rapide de la maladie[3] • Étendue des bronchectasies de traction au scanner[3] • Âge avancé[3]	• PIC • Progression rapide de la maladie • Étendue des bronchectasies de traction au scanner • Âge avancé	• PIC • Progression rapide de la maladie • Étendue des bronchectasies de traction au scanner • Âge avancé	• PIC • Progression rapide de la maladie • Étendue des bronchectasies de traction au scanner • Âge avancé	• PIC • Progression rapide de la maladie • Étendue des bronchectasies de traction au scanner • Âge avancé	• PIC • Progression rapide de la maladie • Étendue des bronchectasies de traction au scanner • Âge avancé
Facteurs de risque spécifiques	• Fumeur[1] • Etendue FP sur TDM >20%[1] • Sexe masculin[1] • Âge avancé au diagnostic[1] • Ulcères digitaux[1] • HTAP[1] • Arthite[1] • Fibrose cutanée progressive[1] • Atteinte rénale[1] • Fibrose myocardique[1] • Diamètre oesophagien augmenté[1] • CVF réduite >10%[1] • DLco réduite >15%[1]	• Fumeur • Etendue FP sur TDM >20% • Methotrexate	• Anti-Ro52 • Durée de la PID • Fièvre • Érythème périunguéal • Ulcères cutanés • Faiblesse musculaire • Emphysème sous-cutané ou médiastinal • Tumeur • Taux de lymphocytes • Taux de HDL • Taux de CRP • Taux de ferritine • Anti-Jo1 • Anti-MDA5		• Sexe masculin • Anti-Ro52 • Anti-RNP • Absence d'arthrite	

1. Perelas A, *et al*. Systemic sclerosis-associated interstitial lung disease. Lancet Respir Med 2020;8:304-20.
2. Shaw M, *et al*. Rheumatoid arthritis-associated lung disease. Eur Respir Rev 2015;24:1-16.
3. George PM, *et al*. Progressive fibrosing interstitial lung disease: clinical uncertainties, consensus recommendations, and research priorities. Lancet Respir Med 2020;8:925-34.
4. Li Y, *et al*. Predictors and mortality of rapidly progressive interstitial lung disease in patients with idiopathic inflammatory myopathy: a series of 474 patients. Front Med (Lausanne) 2020;7:1-9.
5. Reiseter S, *et al*. Progression and mortality of interstitial lung disease in mixed connective tissue disease: a long-term observational nationwide cohort study. Rheumatology (Oxford) 2018;57:255-62.

RIIP

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