Anti-fibrotics or Immunosuppressants in CTD-PF (or both)

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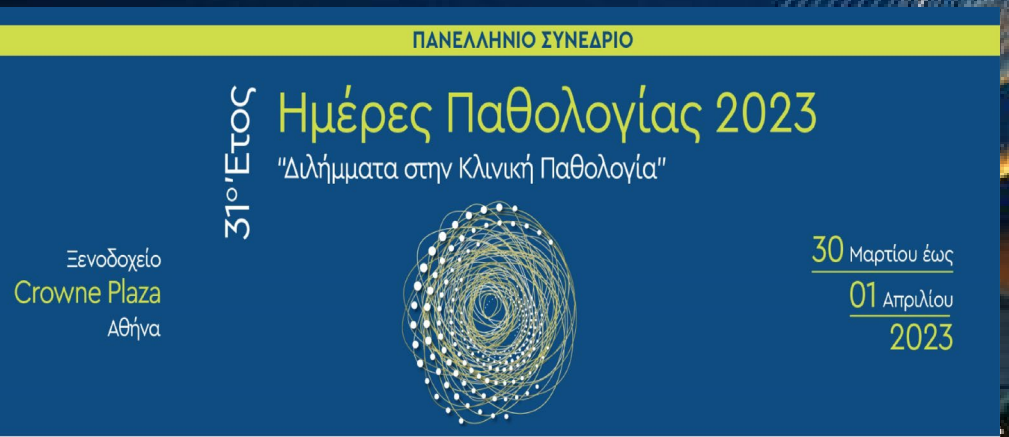

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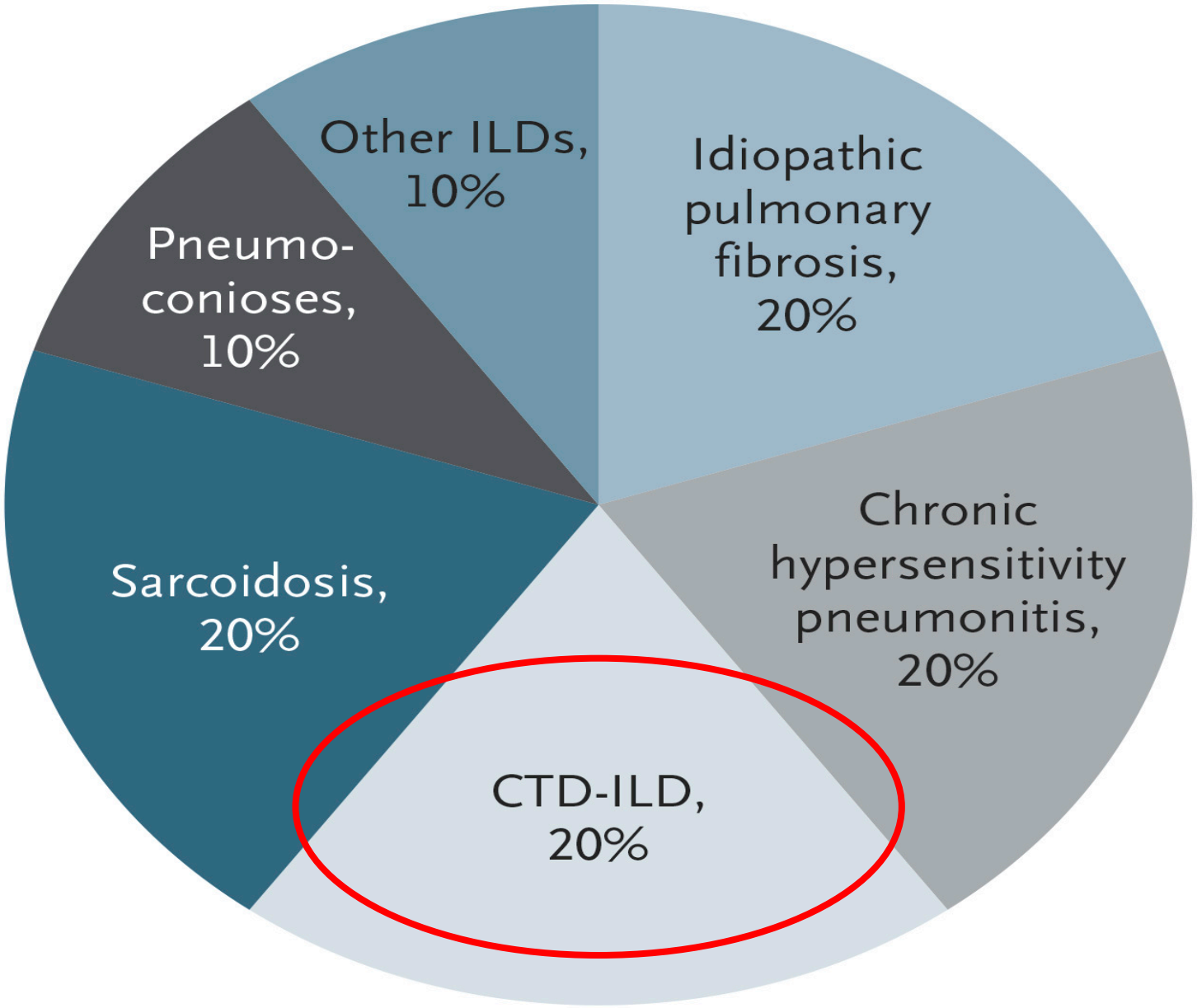
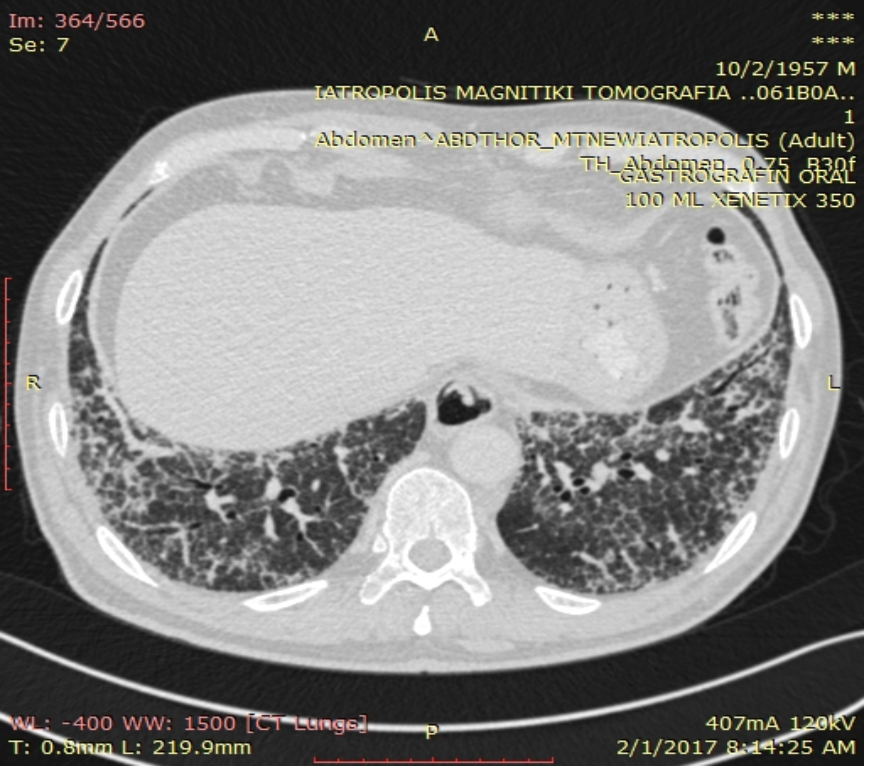
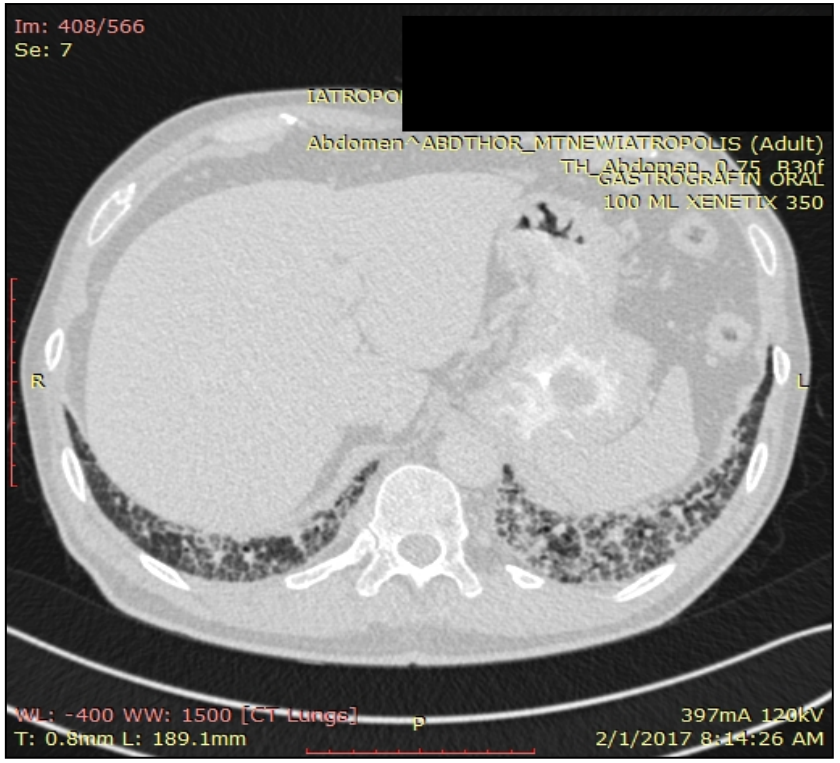
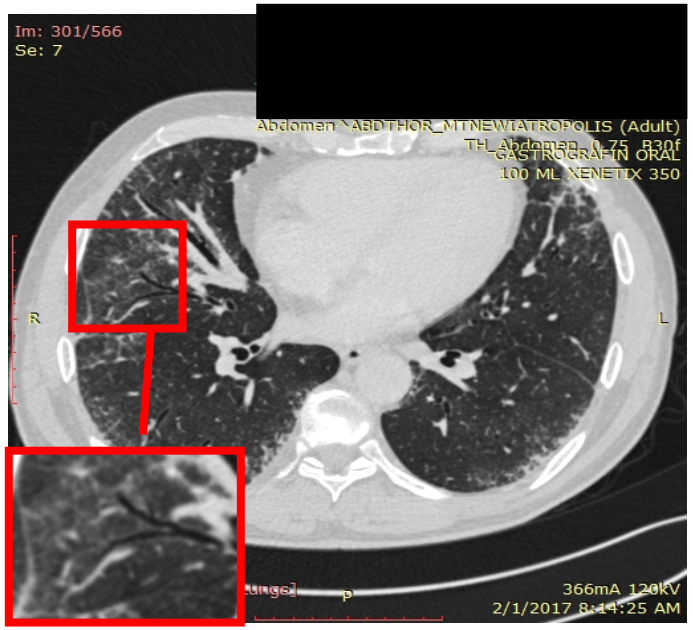
Estimated Relative Distribution of Specific ILDs in the US



NEJM 2018

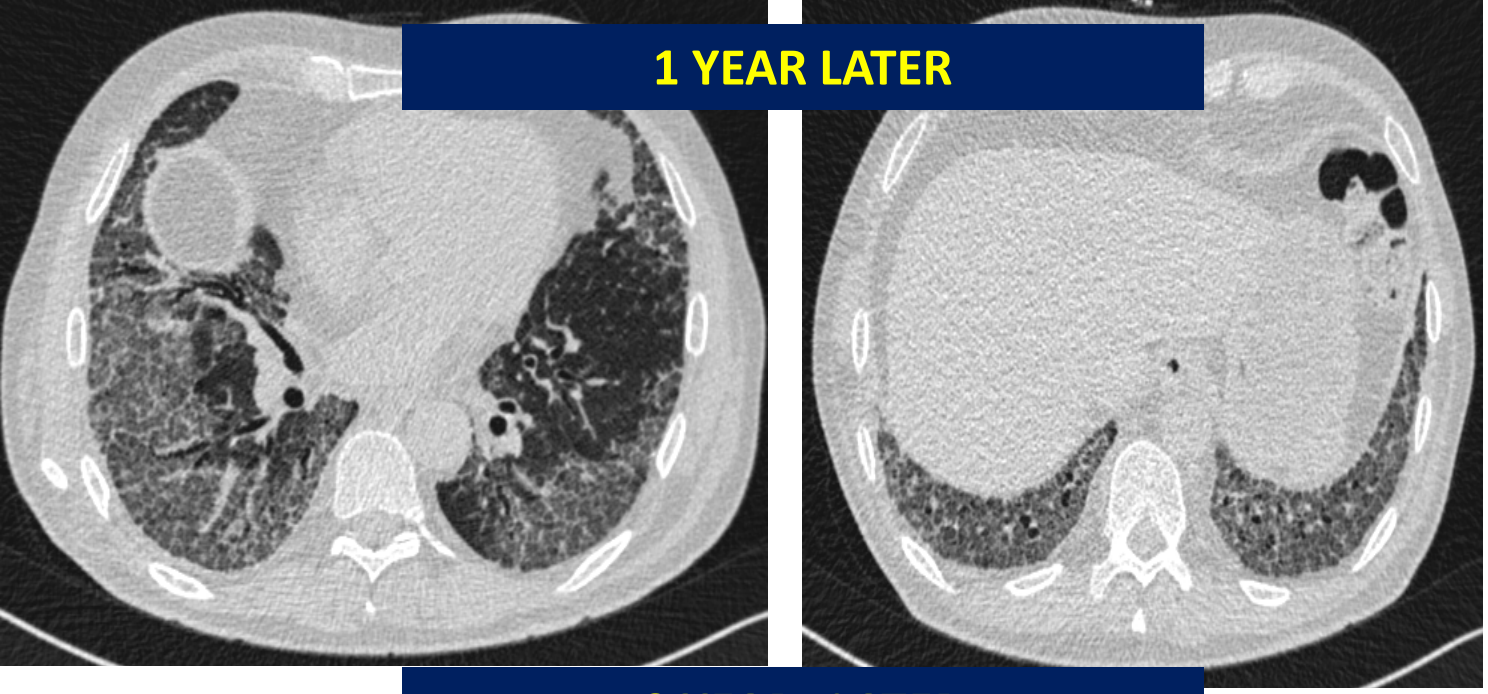




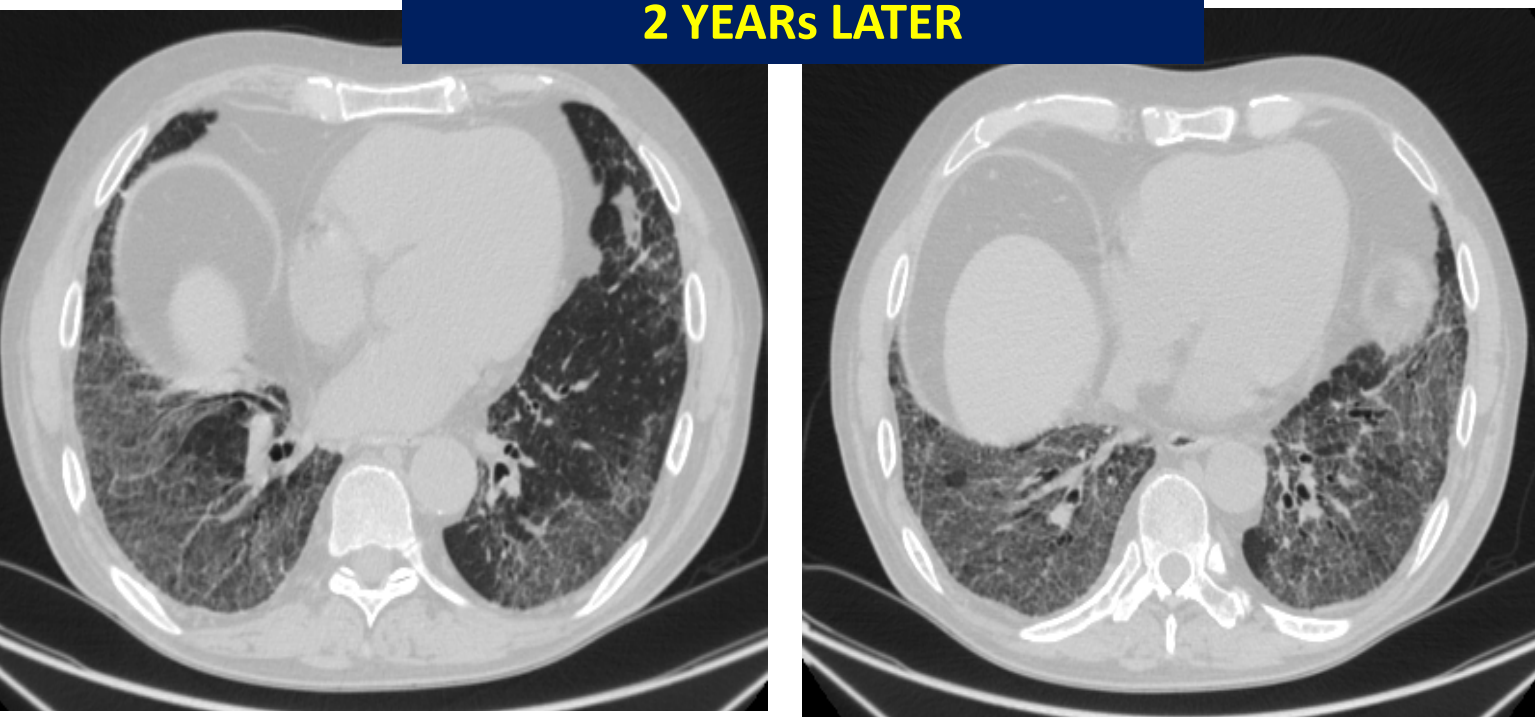


BAL: 37%L, (-) AFB, (-) fungi
ANA: 1/640, anti-SCL70+, RF: (-)
RVSP: 25 mmHg, 6MWD: 410 m,
SaO2: 98% – 94%
FVC: 72%, FEV1/FVC: 85, TLC:63%,
DLCO: 68%
Commenced on Rituximab plus MMF

60 yrs old female, ex-smoker, history of hypercalciuria, hashimoto,
Non-productive cough, DOE (II/IV) last 6 mo, low-grade fever last 3 days – family doctor – moxifloxacin (WBCs: 17450, CRP: 3.4)- Raynaud, no arthralgia-myalgia

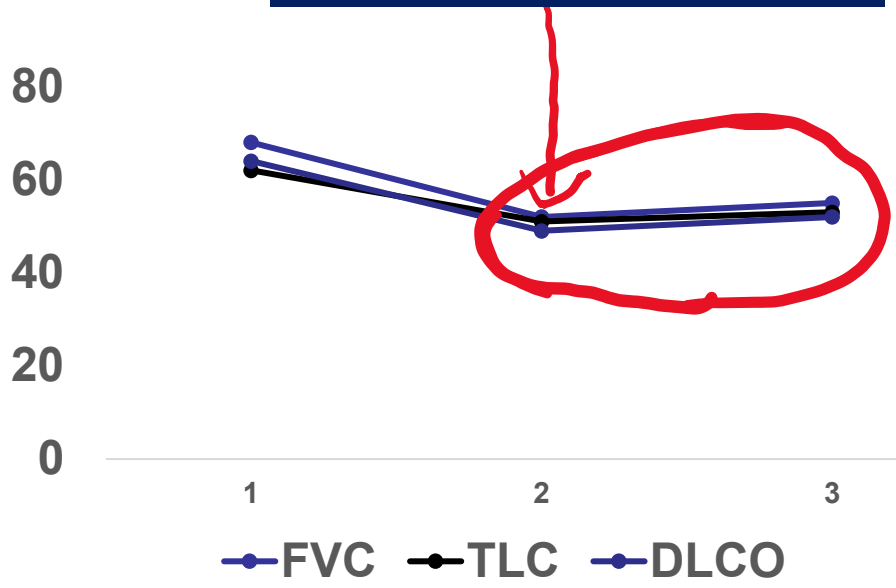


1 YEAR LATER

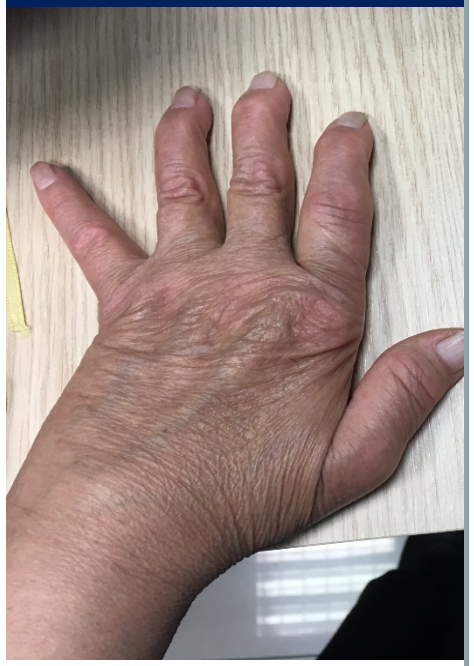


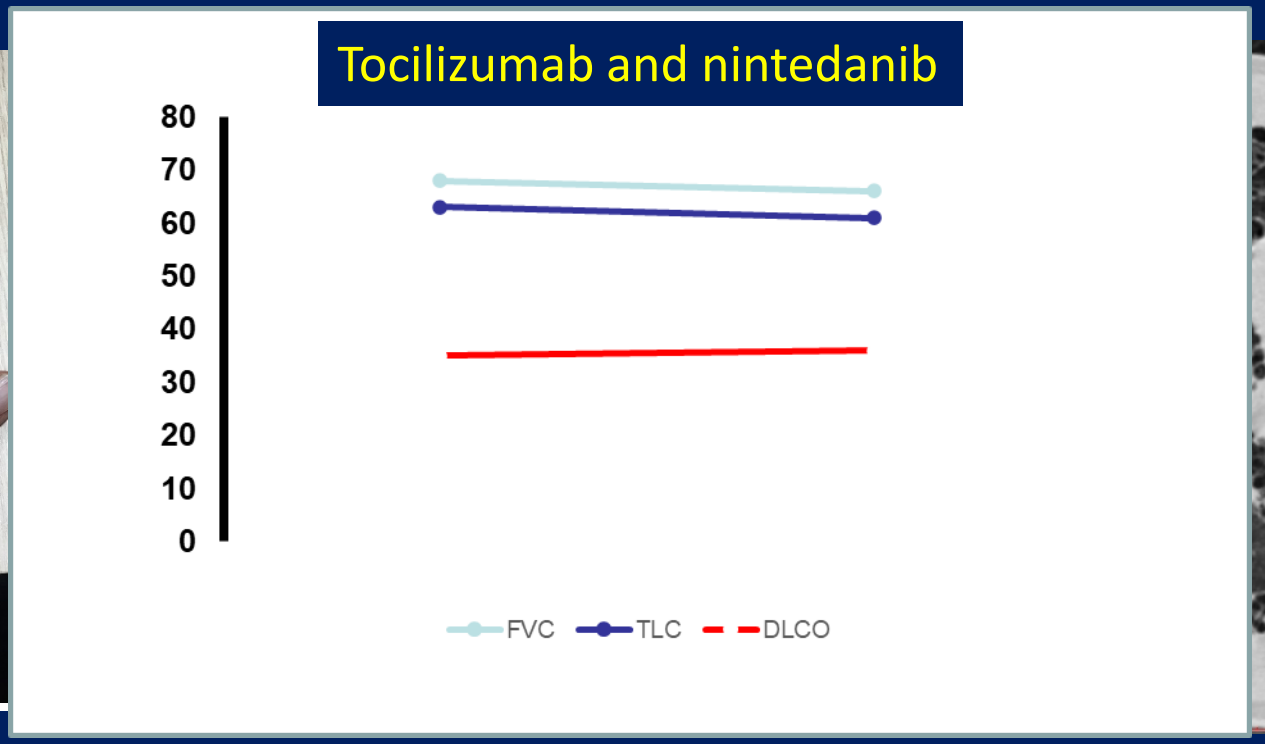
2 YEARs LATER

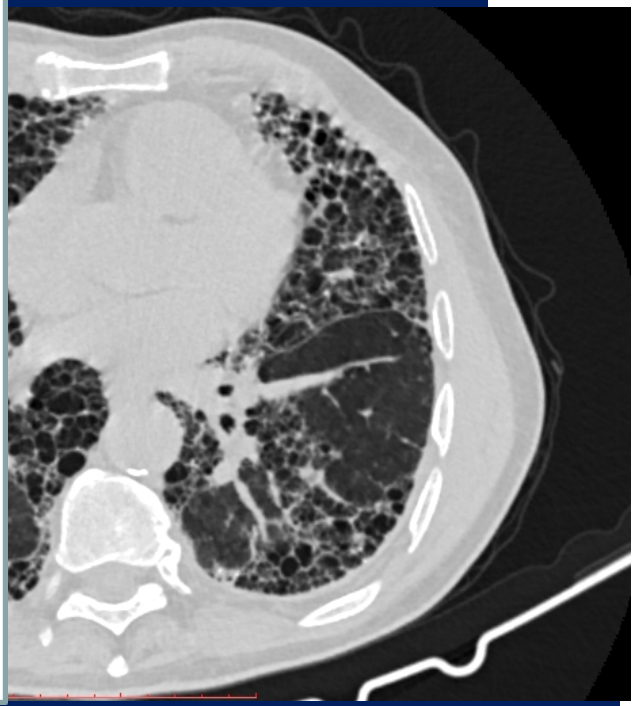
NINTEDANIB+MMF
(STOP RTX)



72-yr old, female, non-smoker, dry cough+DOE (mMRC II/IV) the past 9 months –
Morning stiffness, arthralgia past 3 years
Coronary Heart disease, arterial hypertension, hyperlipidemia
Velcro type crackles +

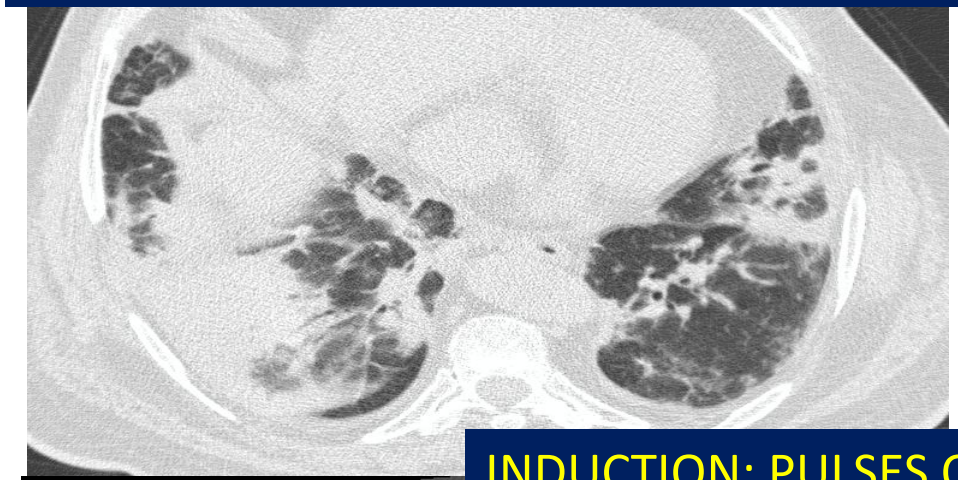


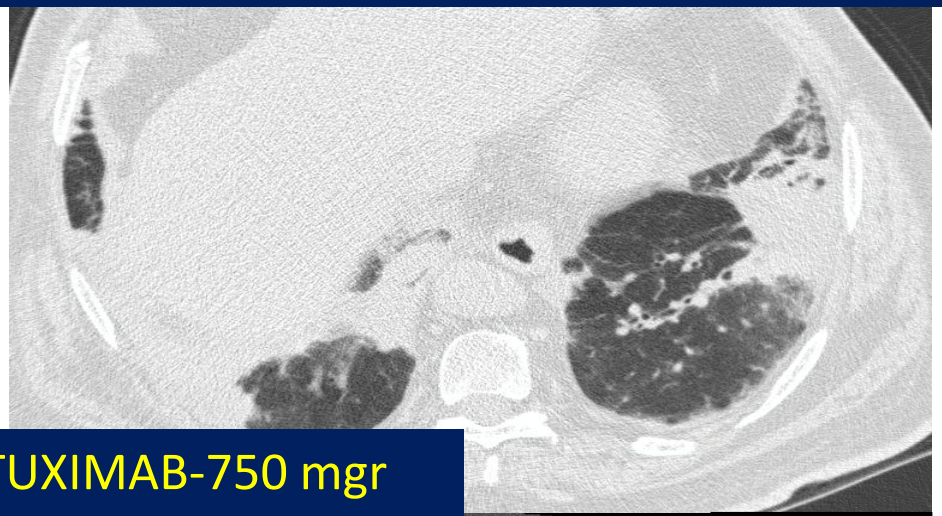




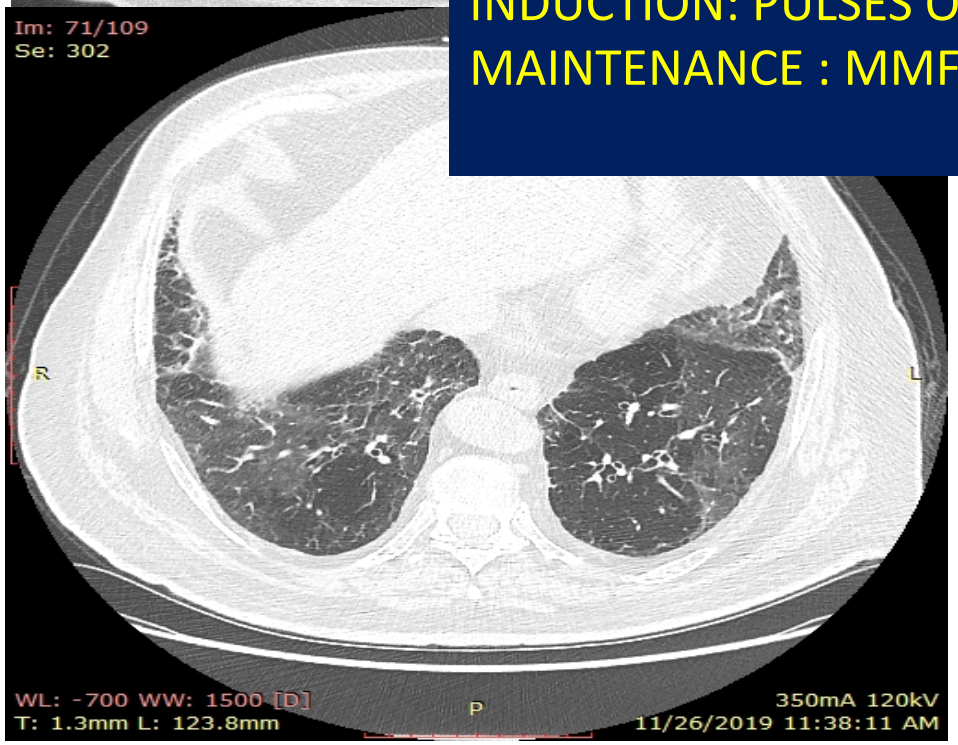
BAL: 28%L,N:13% (-) AFB, (-) fungi,
FVC: 68%, TIF: 73, TLC: 63%, DLCO: 35% (used to be 56% 12 mo ago) under MTX-PZN)
RVSP: 35 mmHg, Serology: ANA: 1/160, RF: 165U/ml, anti-CCPs: 18 (3x)

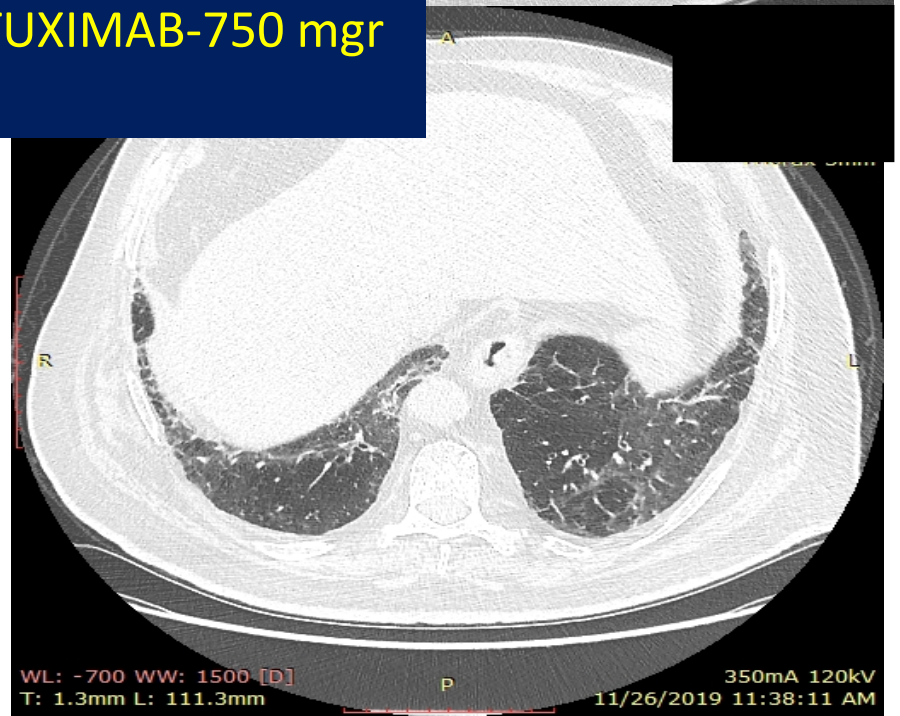
47 yrs old female, non-smoker, DOE (II/IV), dry cough-mild fever-recurrent RTIs past 9 months treated with BDs-antibiotics-NO MYALGIA-history unremarkable – Velcro type crackles +



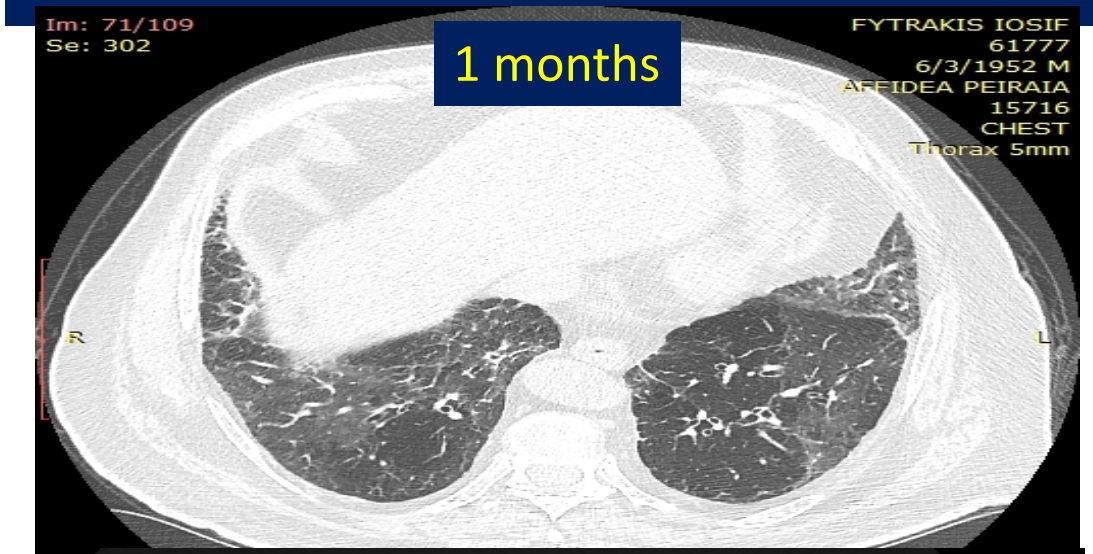


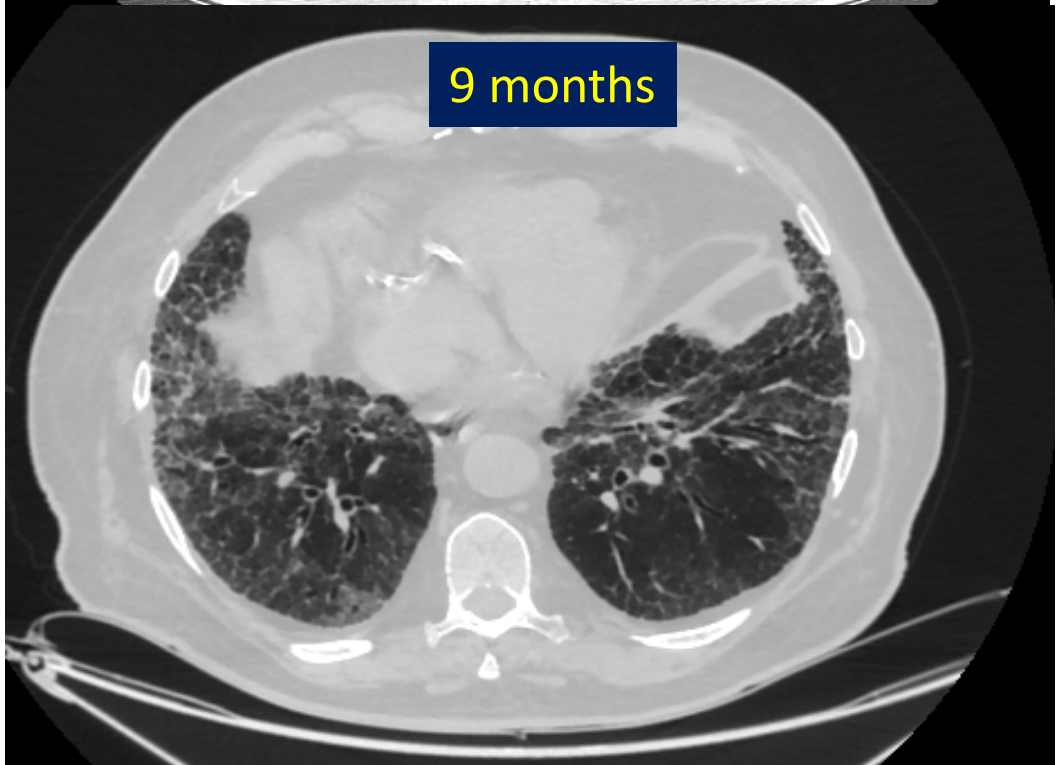
INDUCTION: PULSES OF CS+RITUXIMAB-750 mgr
MAINTENANCE : MMF -2gr + RITUXIMAB-750 mgr





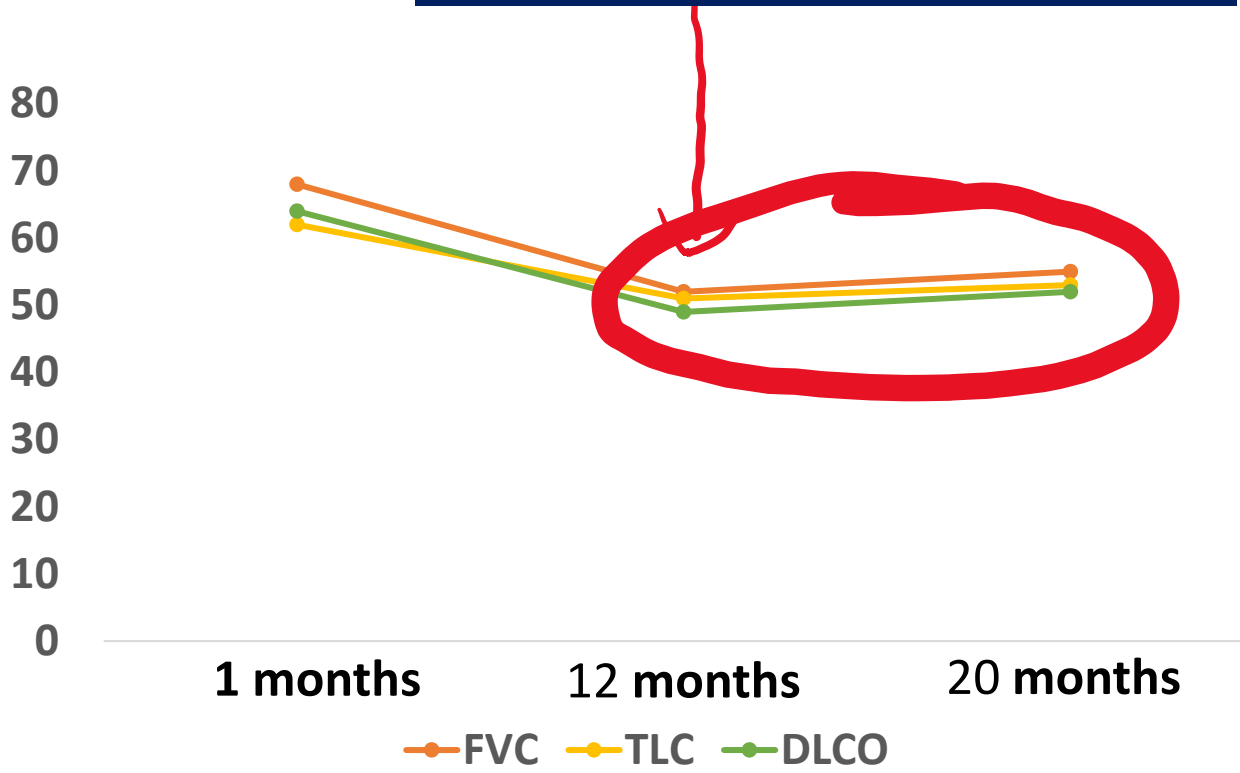
HRCT





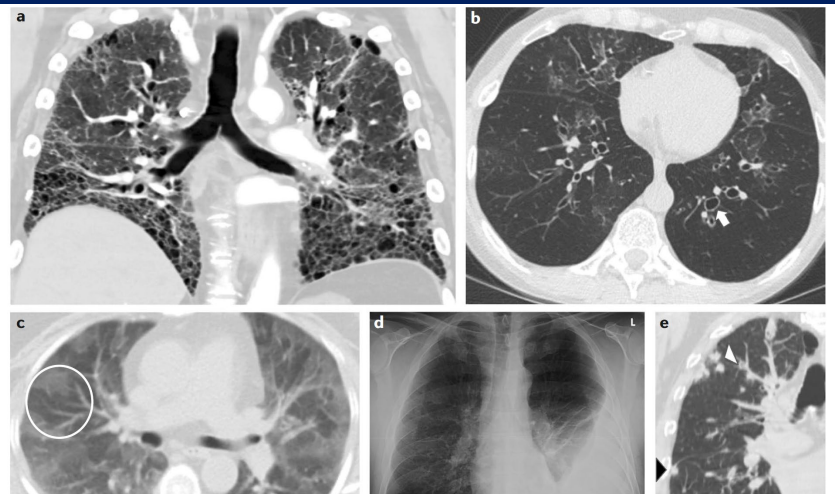
PFTs

STOP RTX
MMF 2gr + NINTEDANIB 150mg bid



What we have learned so far?

L1: Screen patients with symptoms – Be aware



Interstitial lung disease in connective tissue disorders

Aryeh Fischer, Roland du Bois Lancet Vol 380 August 18, 2012

	ILD	Airways	Pleural	Vascular	DAH
Systemic sclerosis	+++	–	–	+++	–
Rheumatoid arthritis	++	++	++	+	–
Primary Sjogren's syndrome	++	++	+	+	–
Mixed CTD	++	+	+	++	–
Polymyositis/ dermatomyositis	+++	–	–	+	–
Systemic lupus erythematosus	+	+	+++	+	++

The signs show prevalence of each manifestation (–=no prevalence; +=low prevalence; ++=medium prevalence; +++=high prevalence). ILD=interstitial lung disease. DAH=diffuse alveolar haemorrhage. CTD=connective tissue disease.

Table 1: CTDs and common pulmonary manifestations

Tzouvelekis et al. Frontiers in Medicine 2019

Respiratory involvement in autoimmune diseases

- Pleomorphic Involvement

MAIN DIFFERENTIAL DIAGNOSES

- Direct pulmonary involvement
- Indirect
  - ✓ Drug induced respiratory involvement?
  - ✓ Infection-Immunocompromise?
  - ✓ Comorbidities? (PH-COPD-Lung cancer)
- 10-15% of cases ILD precedes CTD diagnosis!

Airway involvement in autoimmune diseases

	Rheumatoid arthritis	SLE	DM/PM	Sjögren´s
Bronchitis	++			+
Bronchiectasis	++			±
Follicular bronchiolitis	±			±
Oblit. bronchiolitis	+	±	±	
BOOP/OP	++	±	++	±

Shaw et al. Eur Respir Rev 2015

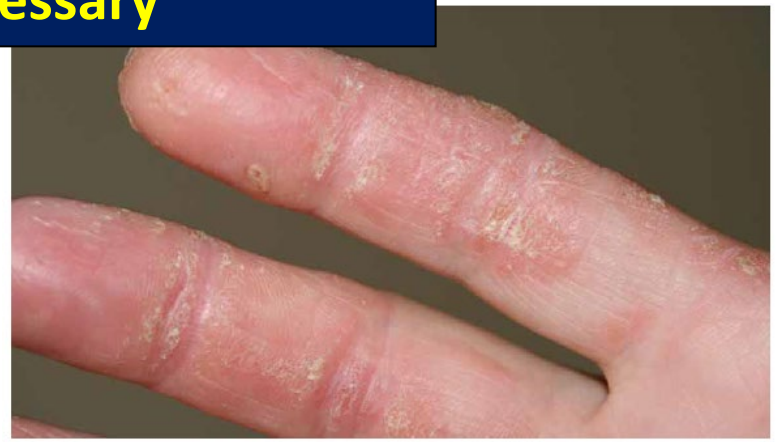
Sometimes you have to search deeper….

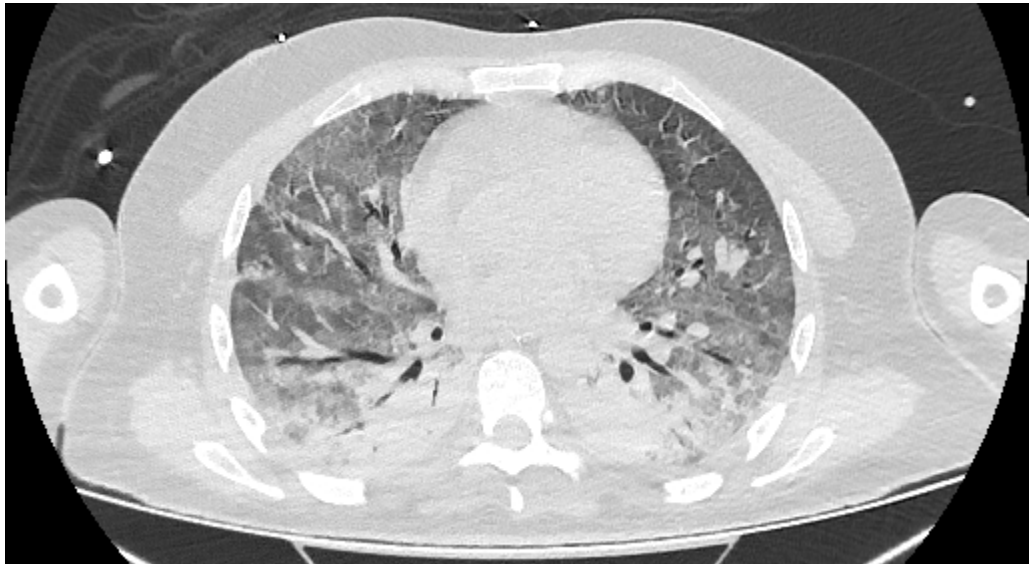
- ANA
- Anti-CCPs
- RF
- p, c ANCA
- ENA panel

1. *Scl-70*
2. *SSA-Ro*
3. *SSB-La*
4. *Jo-1*
5. *RNP*
6. *Sm*

Myositis panel maybe necessary

- Mi-2a
- Mi-2b
- TIF1-Y
- MDA5
- NXP2
- SAE-1
- Ku
- PM Scl-100
- PM-Scl-75
- Jo-1
- SRP
- PL-7
- PL-12
- EJ
- OJ
- Ro-52



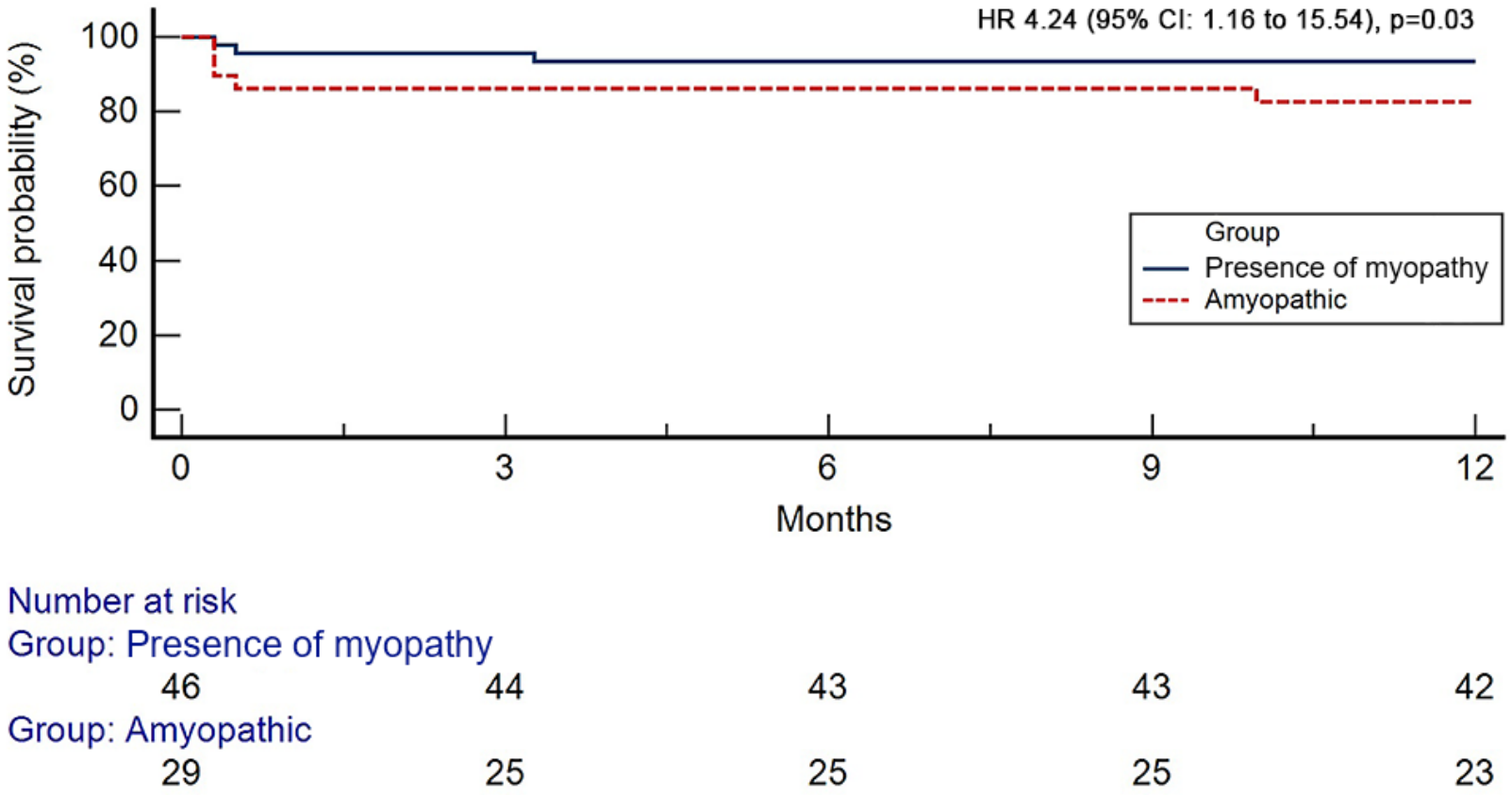


75 patients with myositis-associated ILD

4 centers – 2 countries (Greece-France)

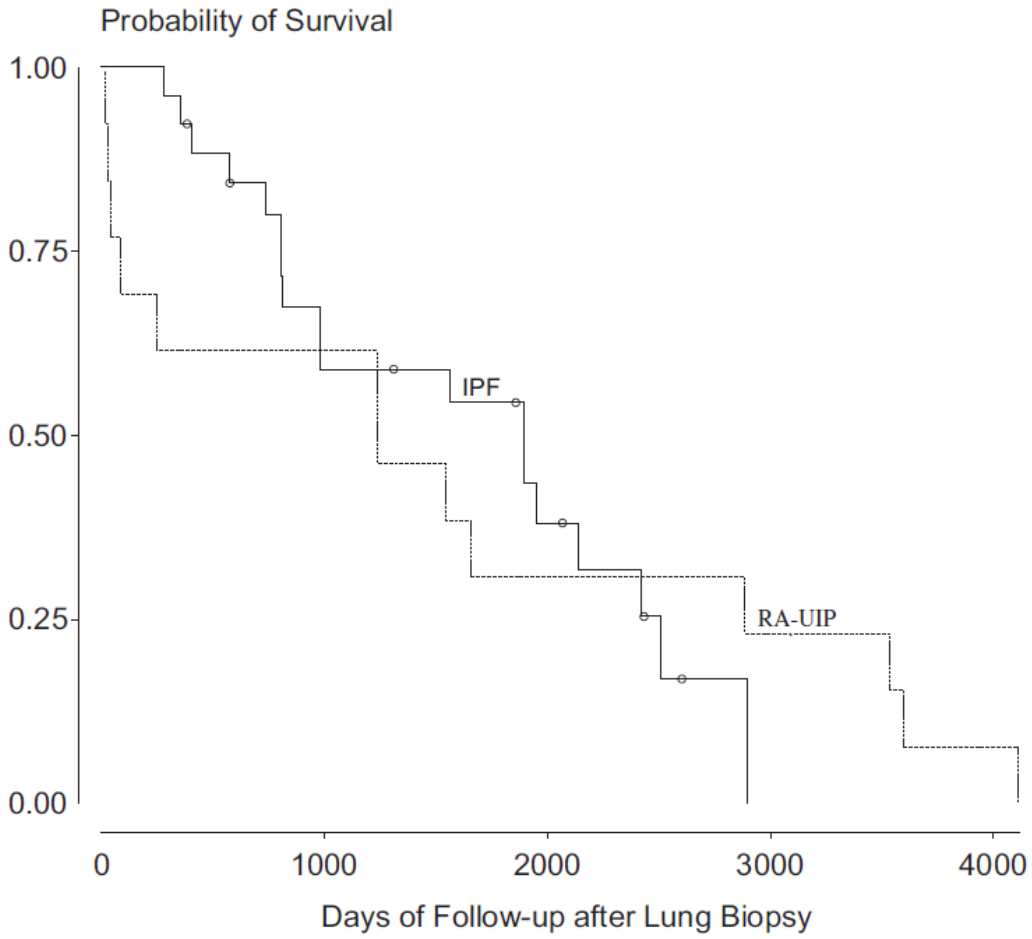
Amyopathic 4 times worse prognosis
Poor Clinical suspicion

Karampitsakos T et al- submitted

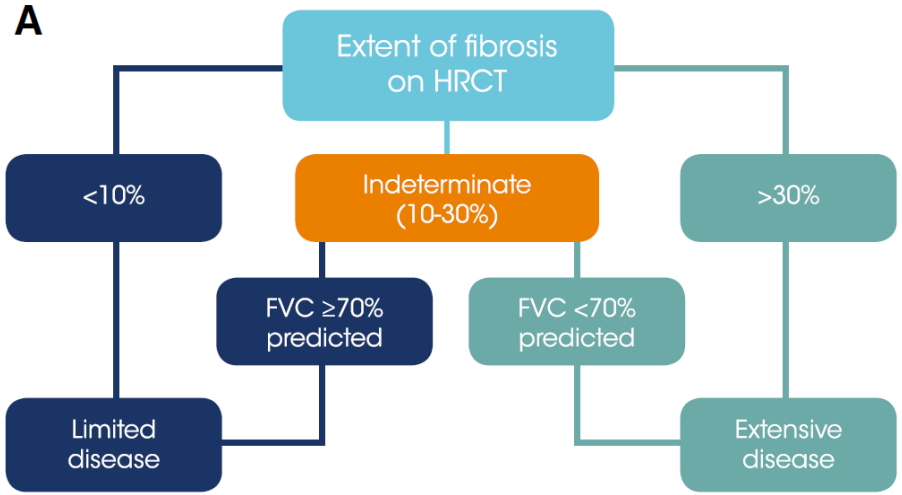


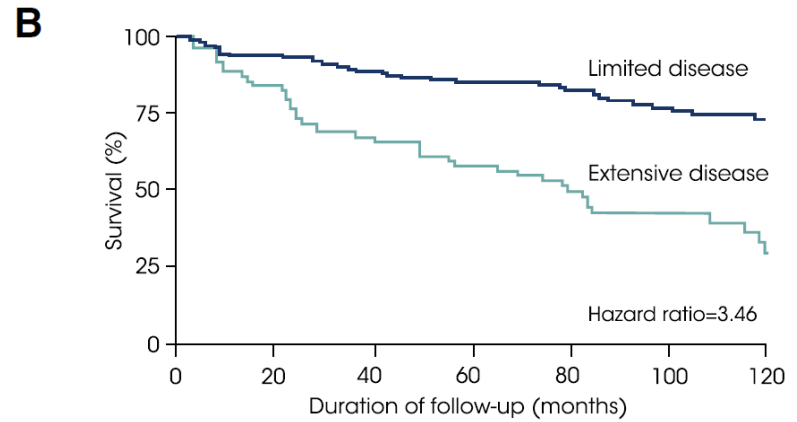
L3: Identify who will progress?

UIP pattern



Extensive disease – Low baseline PFTs

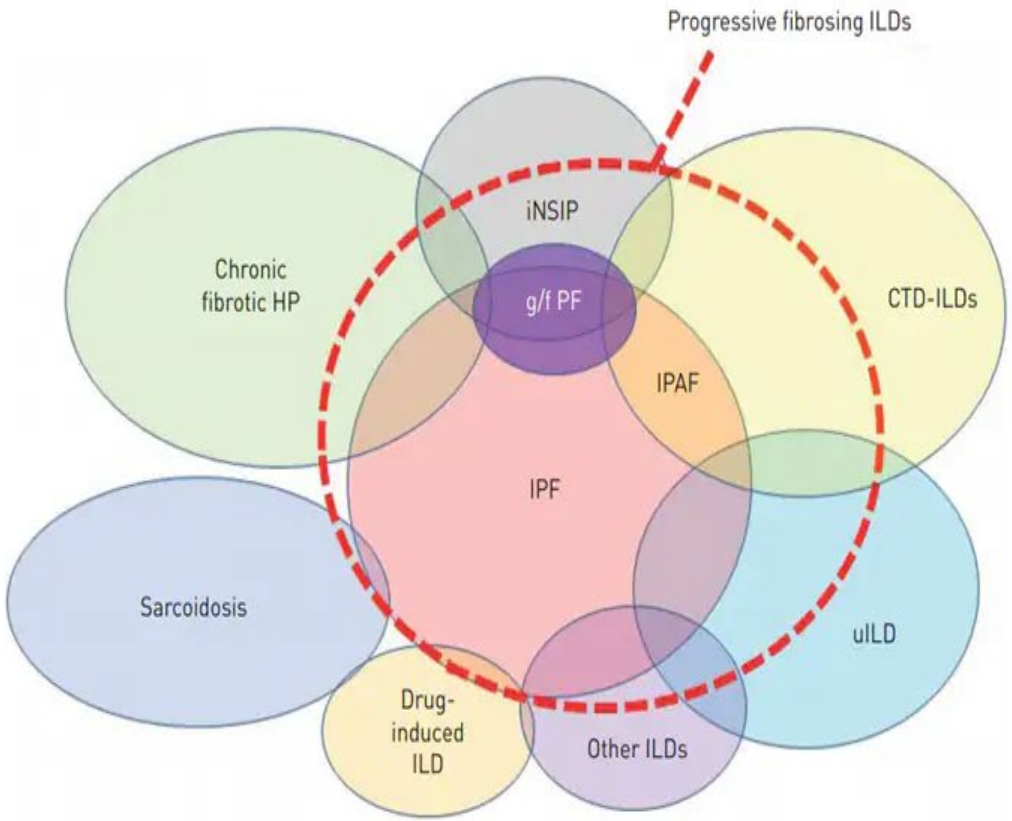




Introducing the term of “progressive” disease

Interstitial Lung Disease

ILDs That May Be Associated With Progressive Fibrosing Phenotype

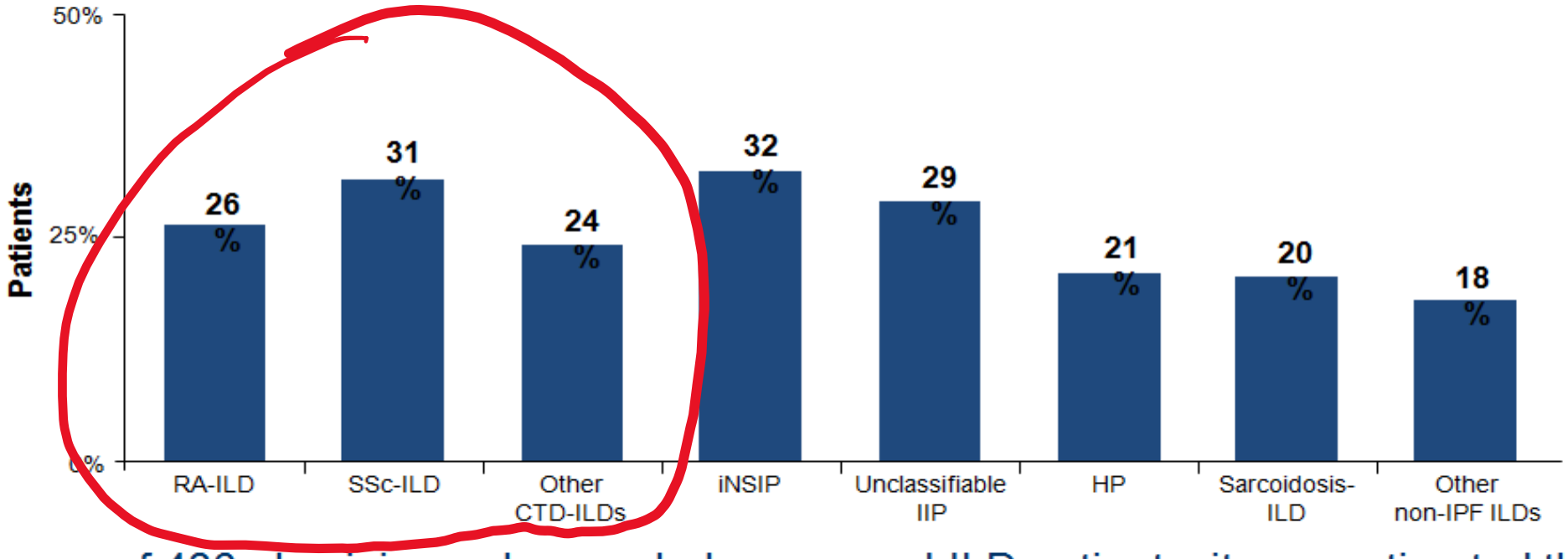


Besides IPF, a number of other fibrotic ILDs exist

Despite appropriate management, a proportion of patients with these diseases will experience disease worsening called progressive fibrosing (PF)-ILD

Treatment of progressive fibrosing interstitial lung diseases: a milestone in the management of interstitial lung diseases, Cottin V et. al European Respiratory Journal 2019 28: 190109.; DOI: 10.1183/16000617.0109-2019

Up to one-third of patients with ILDs, including CTD-ILD, develop progressive fibrosing disease



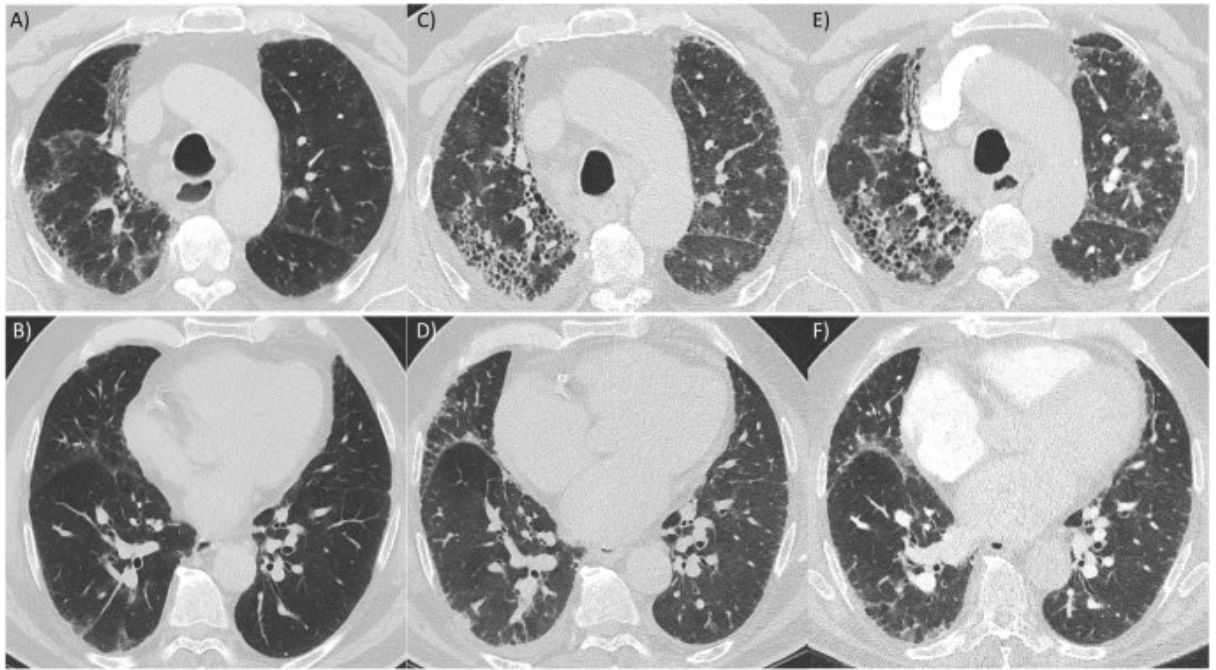
From a survey of 486 physicians who regularly managed ILD patients, it was estimated that 18–32% of patients diagnosed with non-IPF ILD develop progressive fibrosis[1]

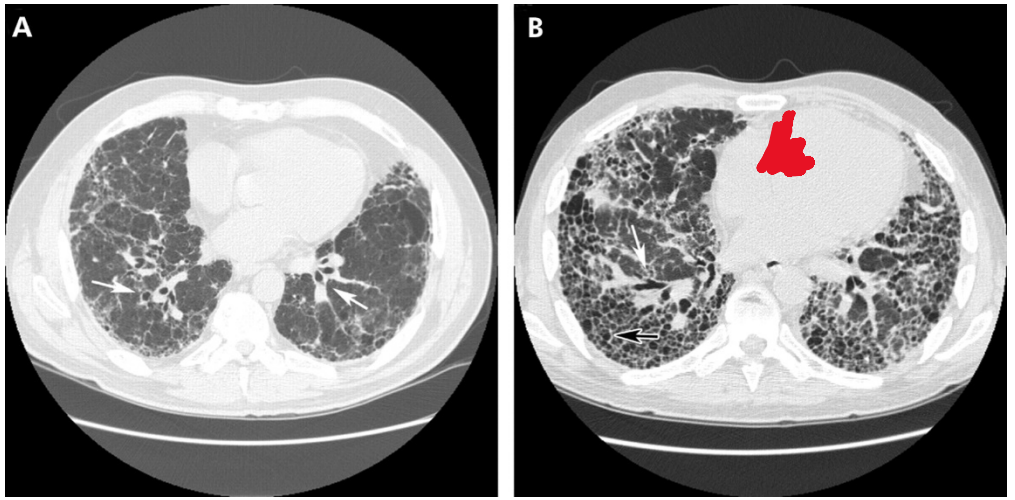
1. Wijsenbeek M *et al*. ATS 2018 International Conference. San Diego, USA, May 18–23, 2018; abstract A1678

Definition of Progressive Pulmonary Fibrosis

The presence of at least two of the following three criteria:

1. No alternative explanation for the worsening of respiratory symptoms
2. Physiological evidence of disease progression, *(Absolute decline in the FVC ≥5% pred OR DLco (corrected for Hb) ≥10% within one year of FU).*
3. Radiological evidence of disease progression



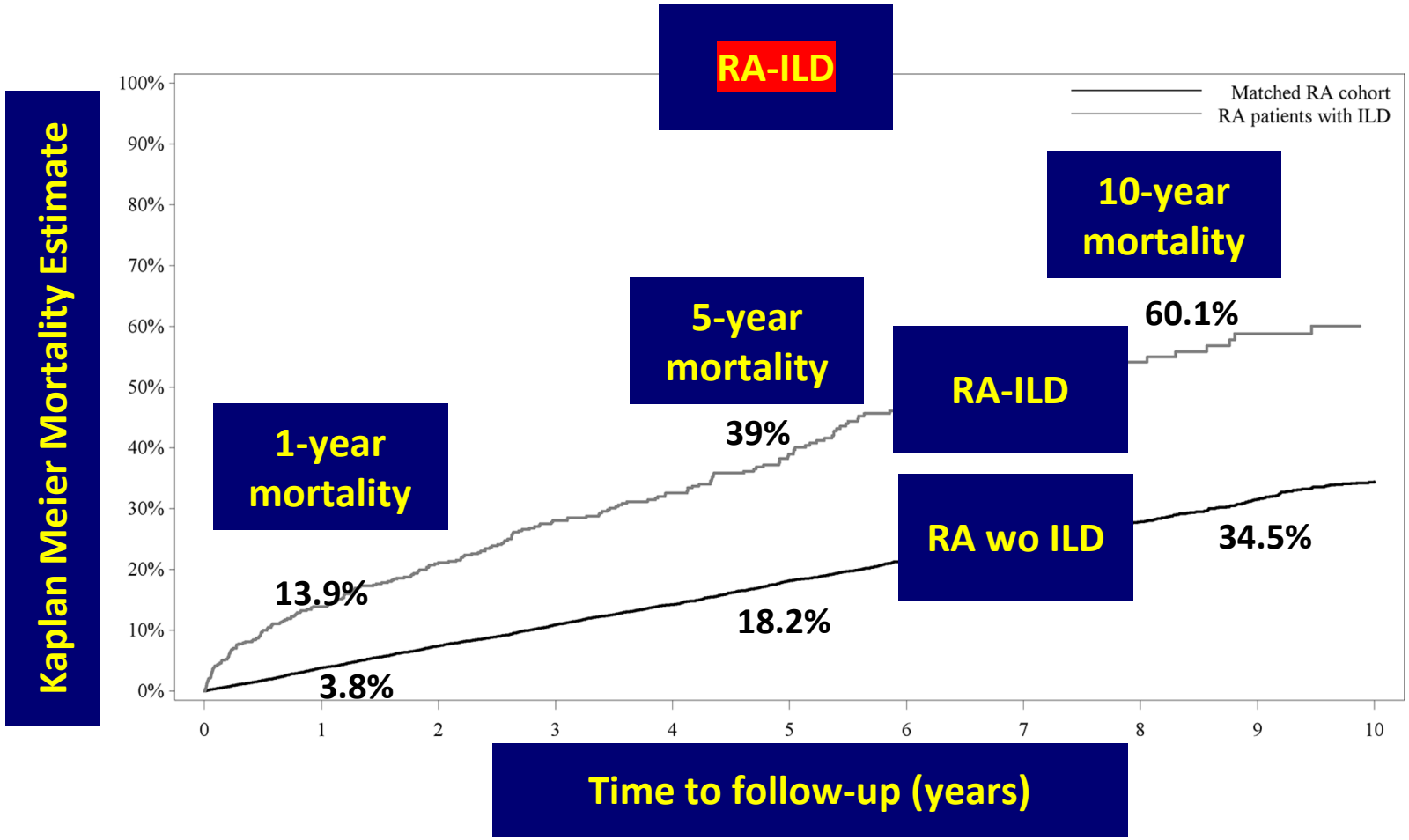


Radiological evidence of disease progression *(one or more of the following):*

1. Increased traction bronchiectasis and bronchiolectasis,
2. New ground glass opacity with traction bronchiectasis,
3. New fine reticulation,
4. Increased coarseness of reticular abnormality,
5. New or increased honeycombing,
6. Increased lobar volume loss.

Is ILD essential in autoimmune diseases?

- **YES!!!!! – MAJOR CAUSE OF DEATH**



Hyldgaard et al. Ann Rheum Dis 2017

Renal Crisis

Scleroderma renal crisis
Diagnosis and management

Internist Academy 2019

By Pauline Martins

Epidemiology

- 5% of systemic sclerosis
- From 100 to 200 cases par million inhabitants
- Overall survival : 65% at 5-years

Risk factors

- Diffuse cutaneous SSc
- Rapidly progressive disease
- Evoluti
- Peric
- Rece
- Posit polyr
- Gluc

Steen VD, An
Mouthon, Clin
PNDS Sclérod

Diagnosis

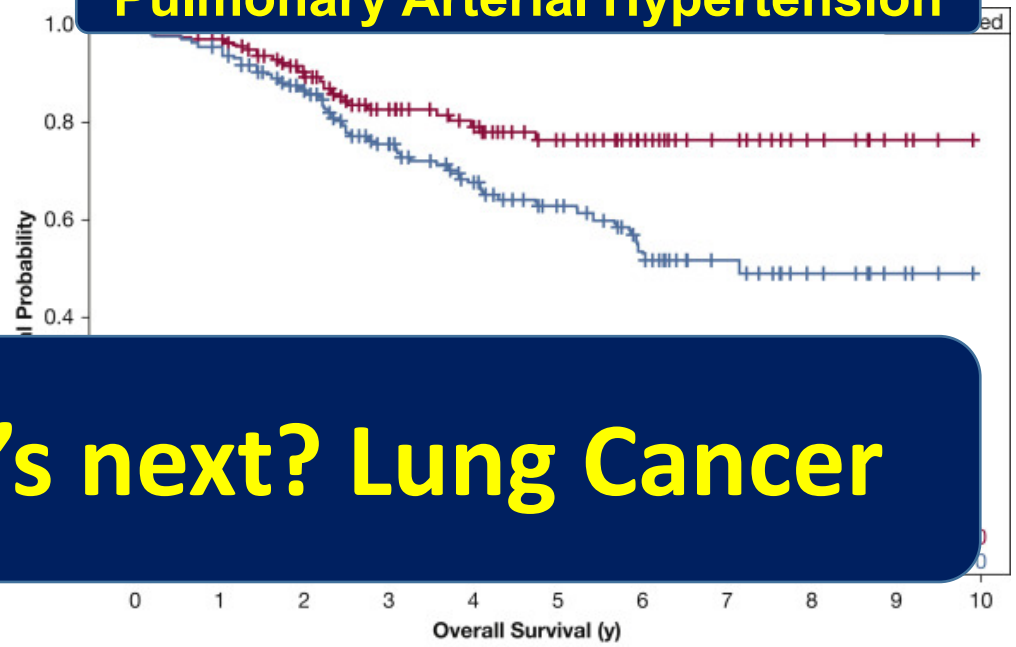
- *De novo* arterial hypertension of normotensive form +++
- Proteinuria ≥2 +
- Hematuria ≥2 +
- Thrombocytopenia <100 G/L
- Hemolysis
- Increased serum creatinin >50%
- Signs of thrombotic microangiopathy

Therapeutic management

- Angiotensin-converting enzyme inhibitors +++
- If needed to control blood pressure: IV nicardipin/urapidil
- Avoid diuretics and β-blockers
- Discuss dialysis with nephrologist
- Renal transplantation : to discuss after 2 years of dialysis (possible late recovery)

Major cause of death in SCL

Pulmonary Arterial Hypertension

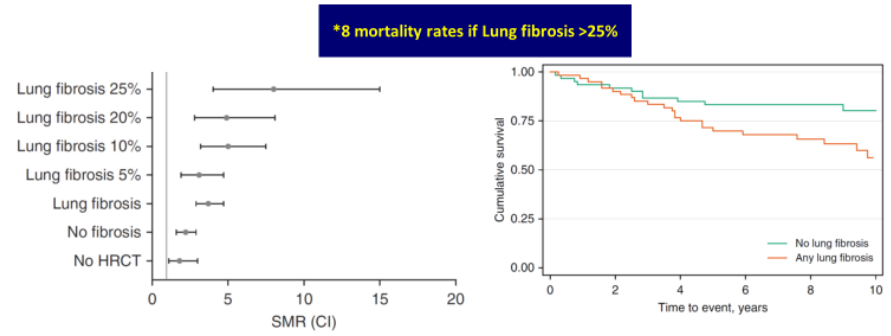


Following anti-fibrotics – what's next? Lung Cancer

42% of deaths-1972
6% of deaths - 2022

Internet address: www.atsjournals.org

Tracking Impact of Interstitial Lung Disease in Systemic Sclerosis in a Complete Nationwide Cohort



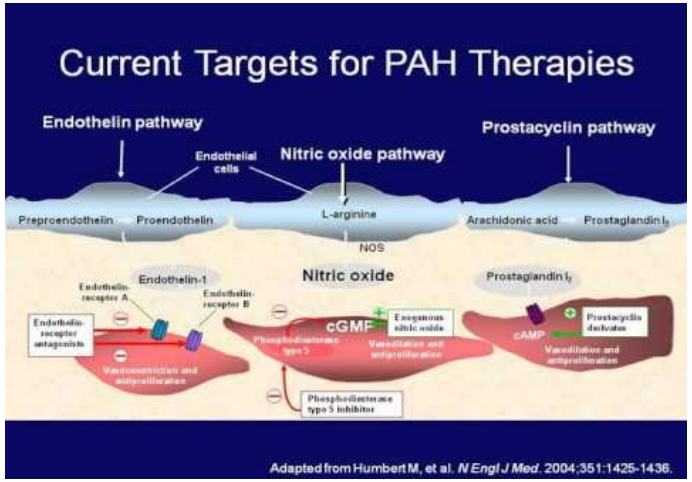
25% of deaths-2012
15% of deaths - 2022

fatal[3]. Since the introduction of angiotensin-converting enzyme (ACE) inhibitors, survival has greatly improved and the 1-year mortality rate decreased from 85% to 24%[4]. However, despite aggressive antihypertensive therapy, 5-year survival with SRC is only 65%[5,6,7,8]. In addition, exposure to certain drugs, particularly corticosteroids (CS), represents an additional risk factor for SRC[9,10].

The Journal of Rheumatology 2014; 41:6;

6% of deaths-1972
42% of deaths - 2022

No treatment??



Lumping rather than splitting

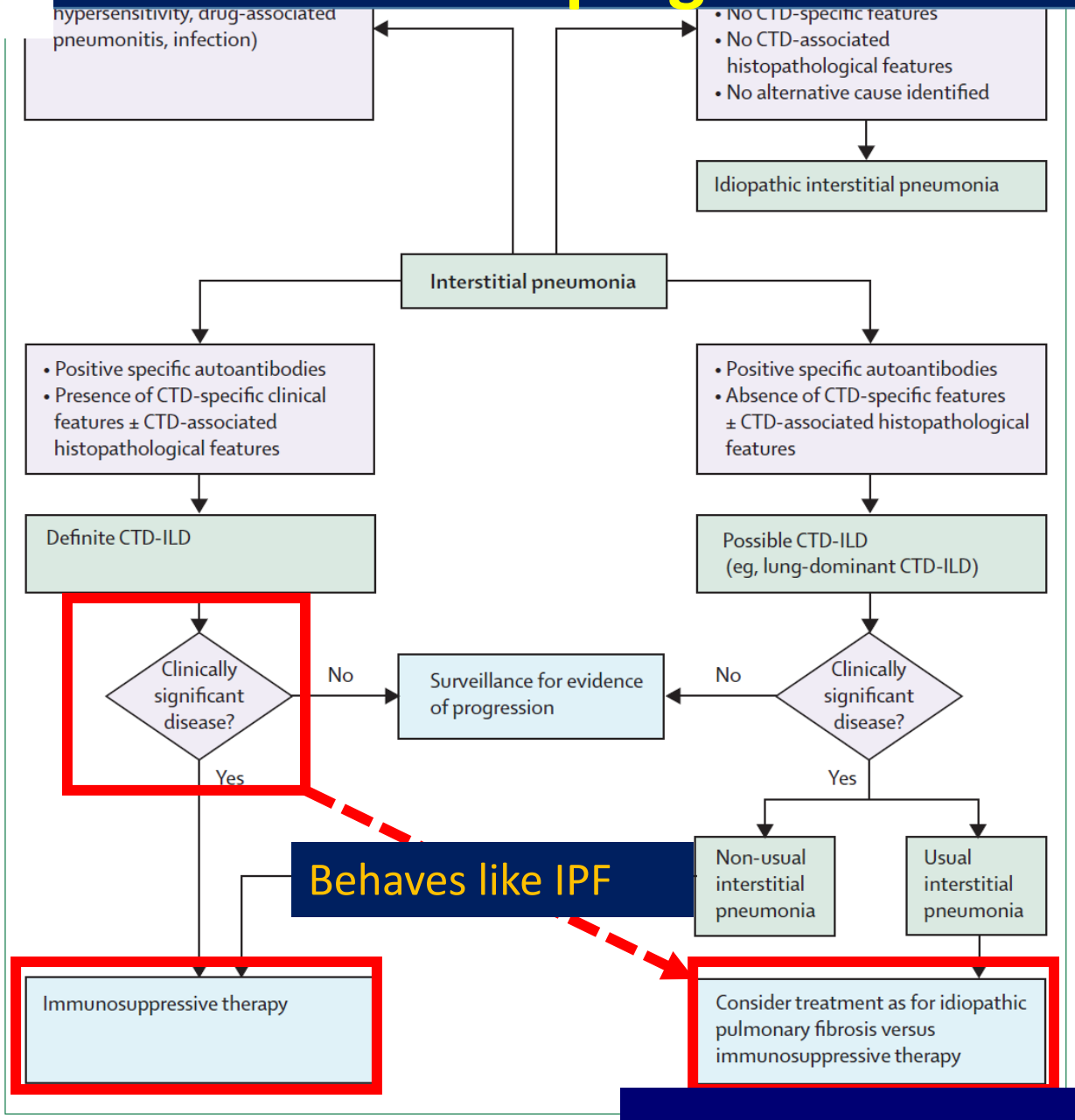
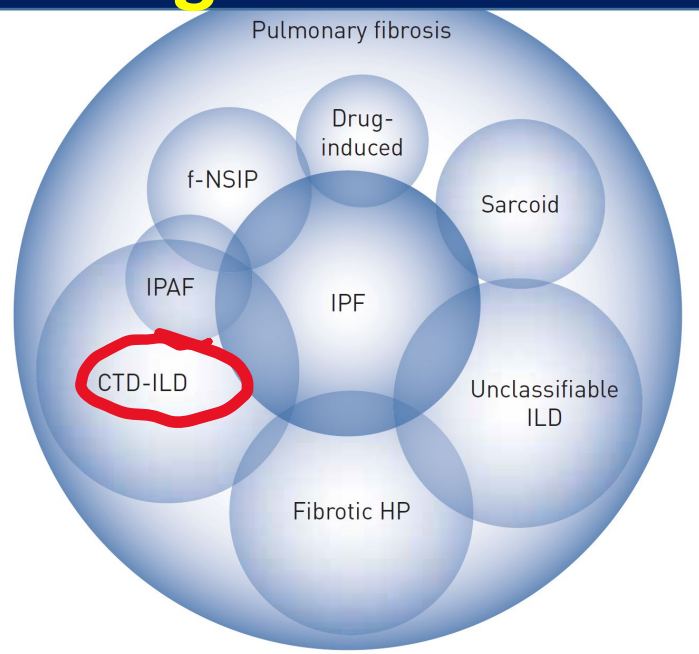


Figure 1: Management schema for interstitial pneumonia in CTD

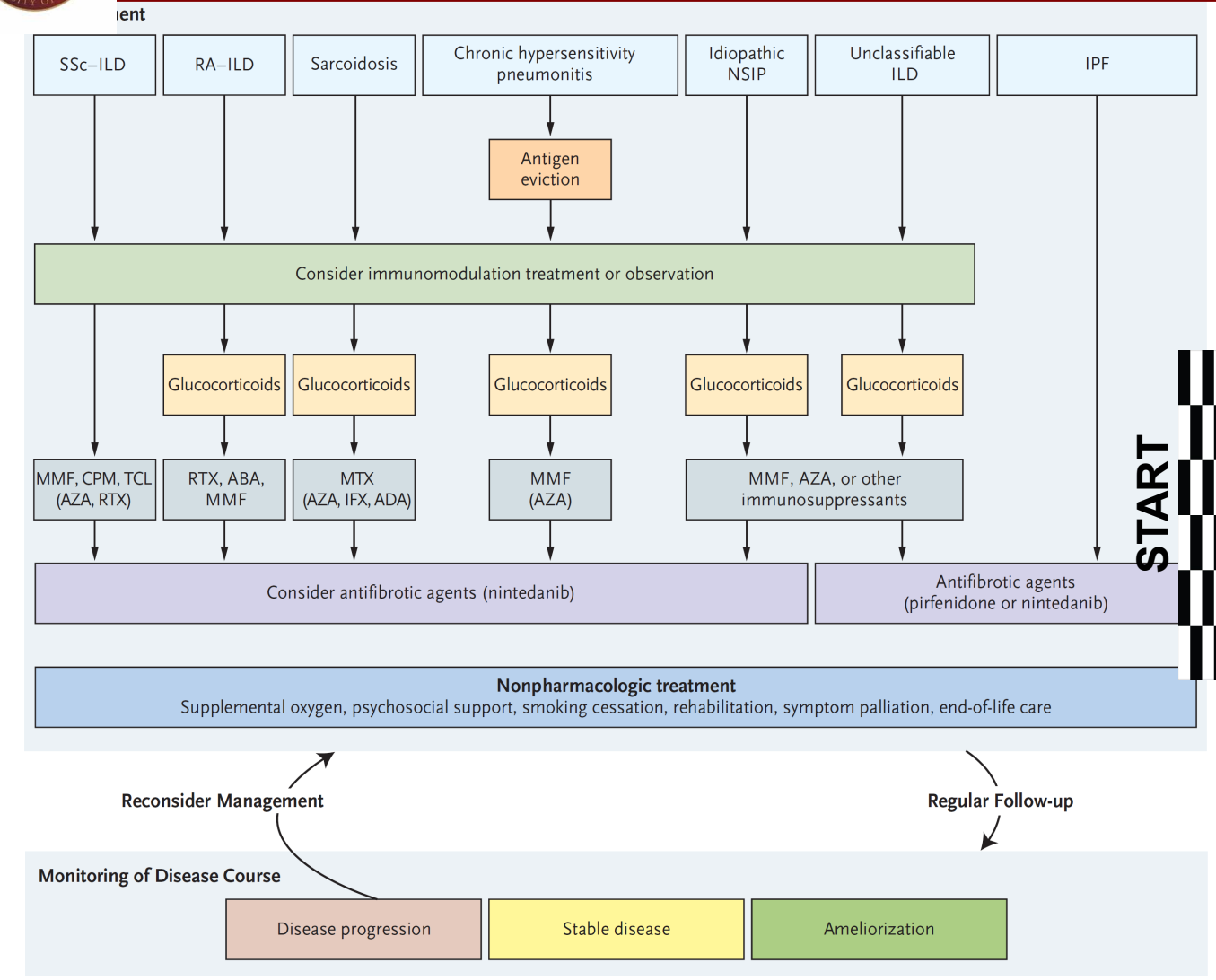
Fischer et al. Lancet 2012

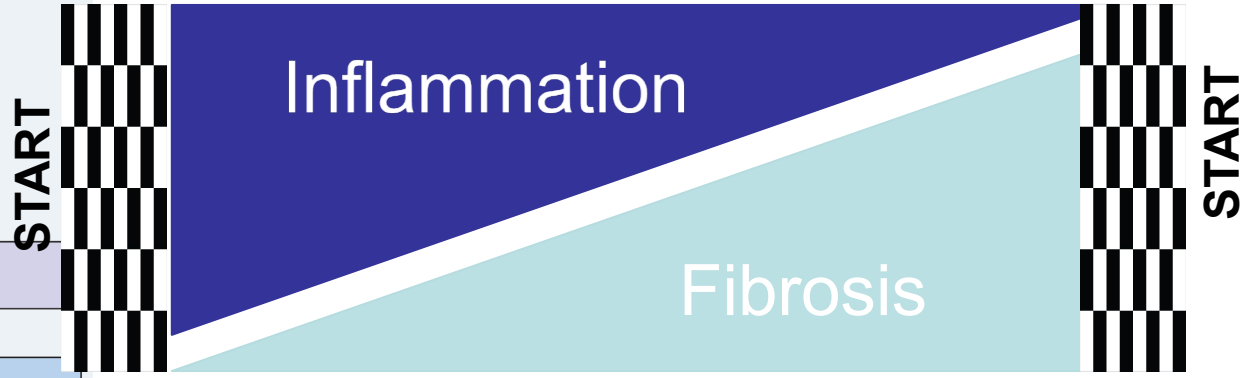


RA-ILD. Given the shared genetic background between idiopathic pulmonary fibrosis and RA-ILD in general and RA-ILD with a UIP or possible UIP pattern in particular, we would propose that drugs that are known to be effective in treating patients with idiopathic pulmonary fibrosis be evaluated in the treatment of RA-ILD.[41,42]

This article was published on October 20, 2018, at NEJM.org.

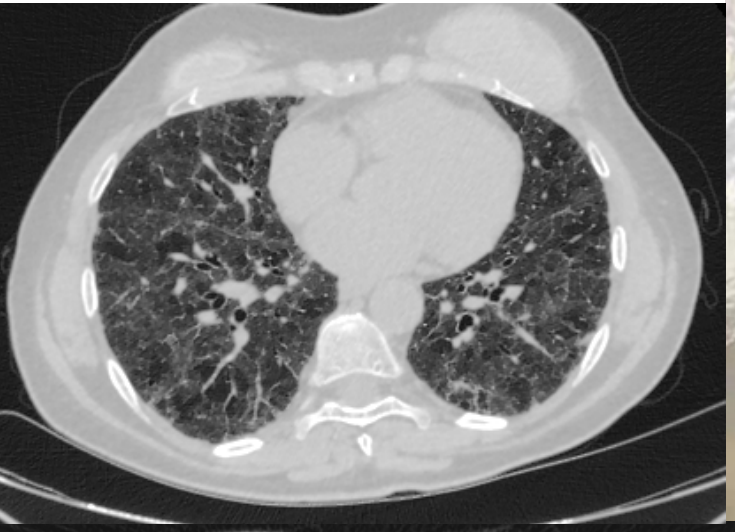
L3: Identify whether inflammation drives fibrosis

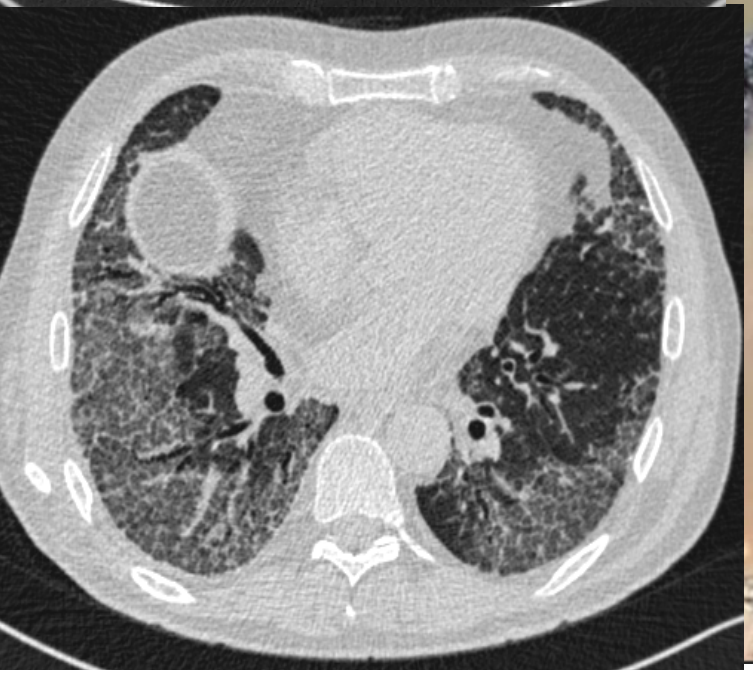


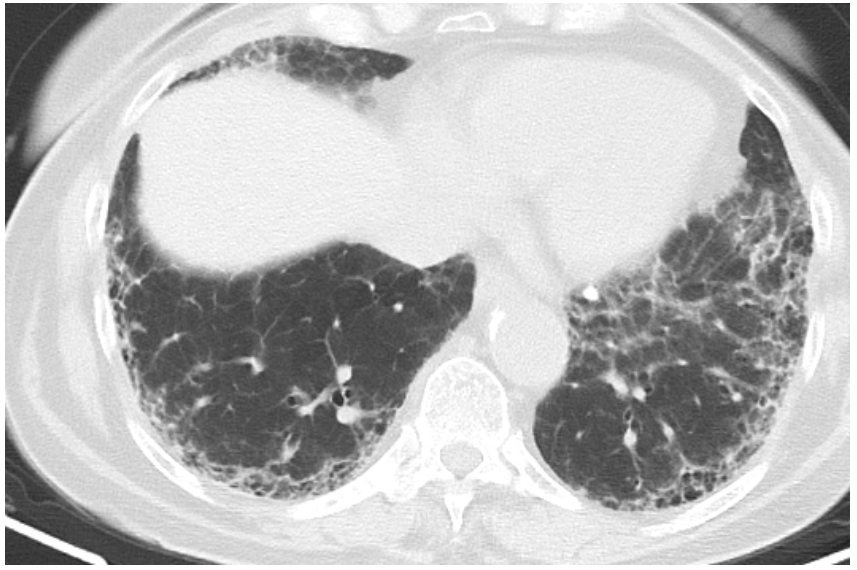


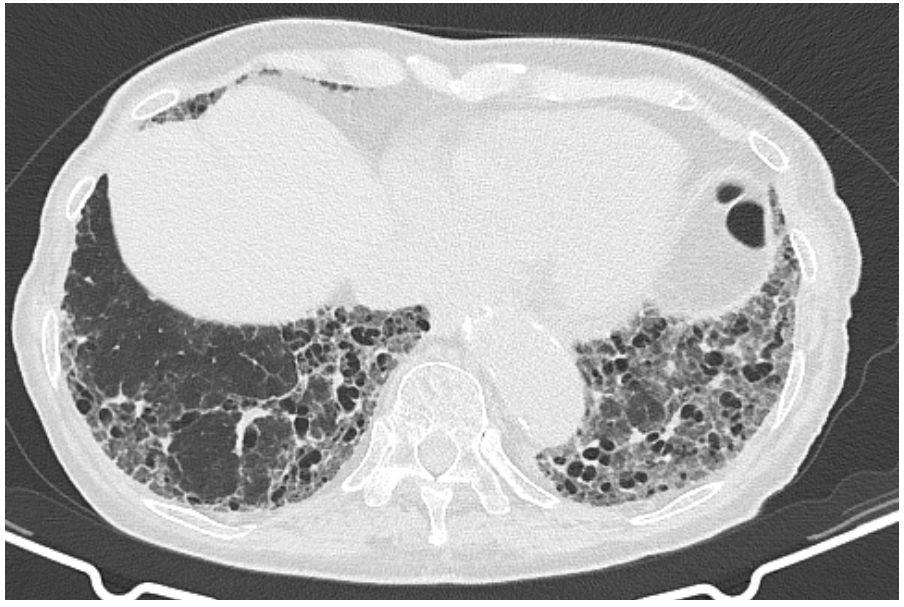
Sometimes the answer is not that simple

Who will respond to immunomodulation?



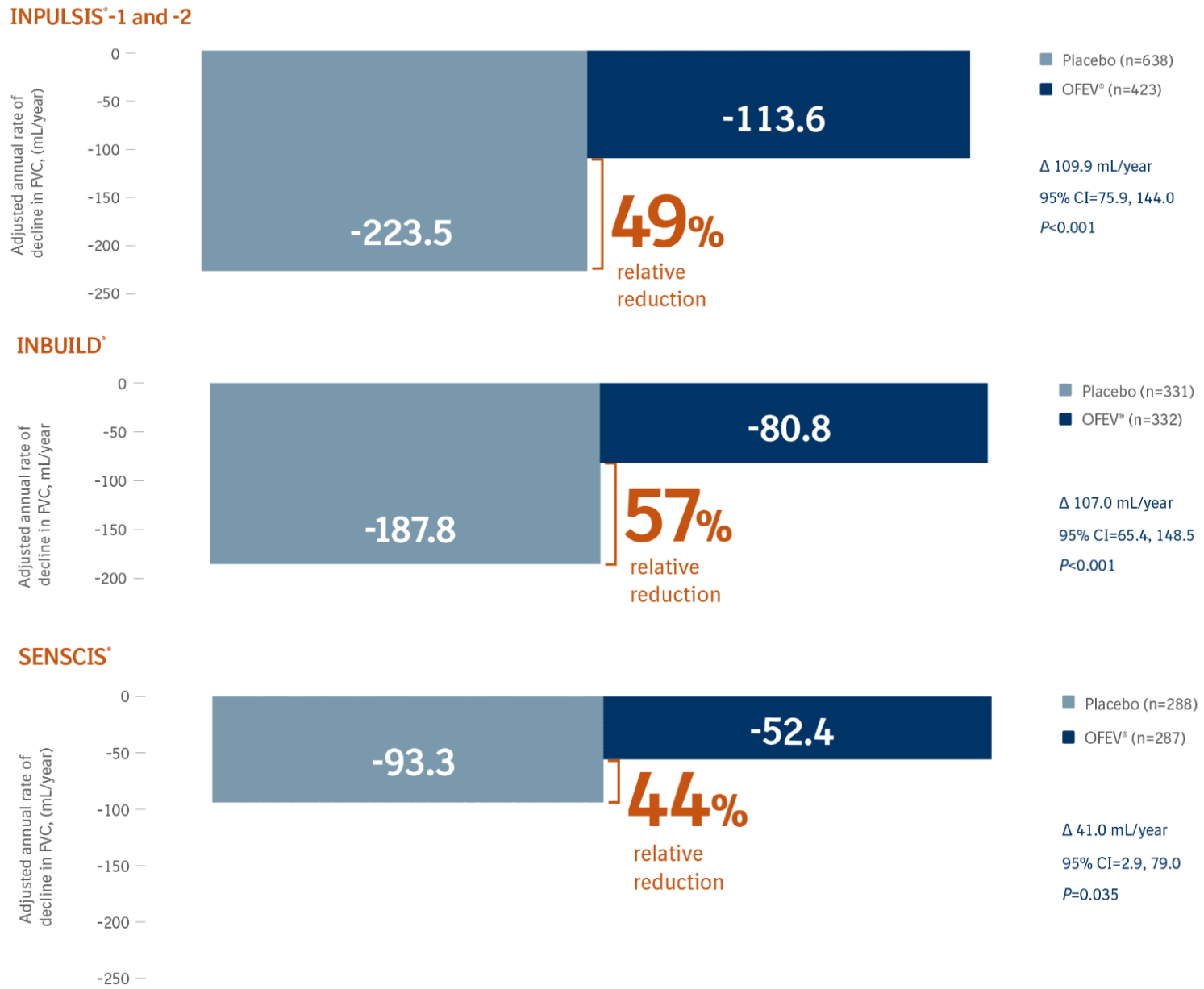






What options do we have?

Nintedanib efficacy across PF-ILDs



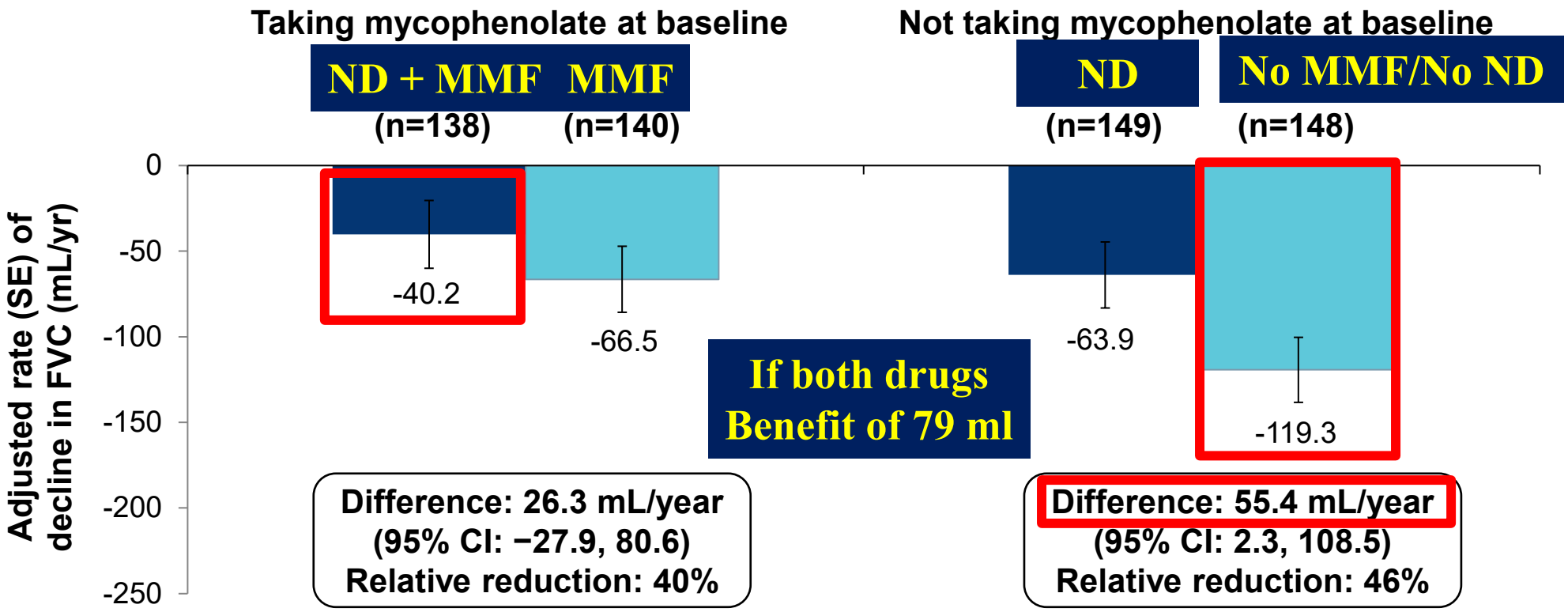
IPF, n=1016

PF-ILDs, n=663

SCL-ILD, n=580

Nintedanib is a Rheumatology Friendly Drug

Anti-fibrotics plus Immunomodulation…Synergy



Treatment-by-time-by-subgroup interaction p=0.452

June 27, 2019
N Engl J Med 2019; 380:2518-2528
DOI: 10.1056/NEJMoa1903076

ORIGINAL ARTICLE

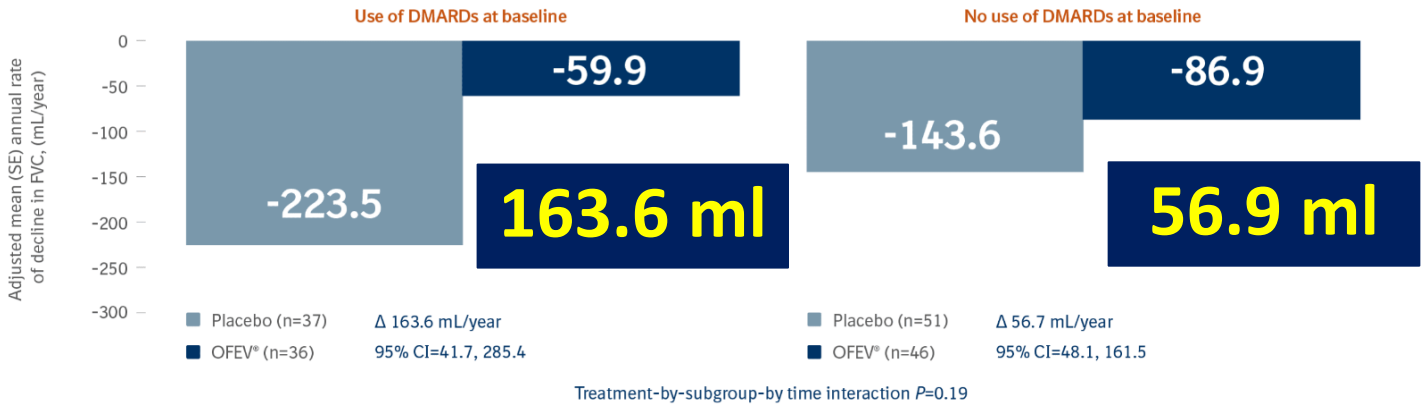
The NEW ENGLAND JOURNAL of MEDICINE

Nintedanib in Progressive Fibrosing Interstitial Lung Diseases

Kevin R. Flaherty, M.D., Athol U. Wells, M.D., Vincent Cottin, M.D., Anand Devaraj, M.D., Simon L.F. Walsh, M.D., Yoshikazu Inoue, M.D., Luca Richeldi, M.D., Martin Kolb, M.D., Kay Tetzlaff, M.D., Susanne Stowasser, M.D., Carl Coeck, M.D., Emmanuelle Clerisme-Beaty, M.D., et al., for the INBUILD Trial Investigators*

Post hoc analysis

DMARDs and no DMARDs at baseline



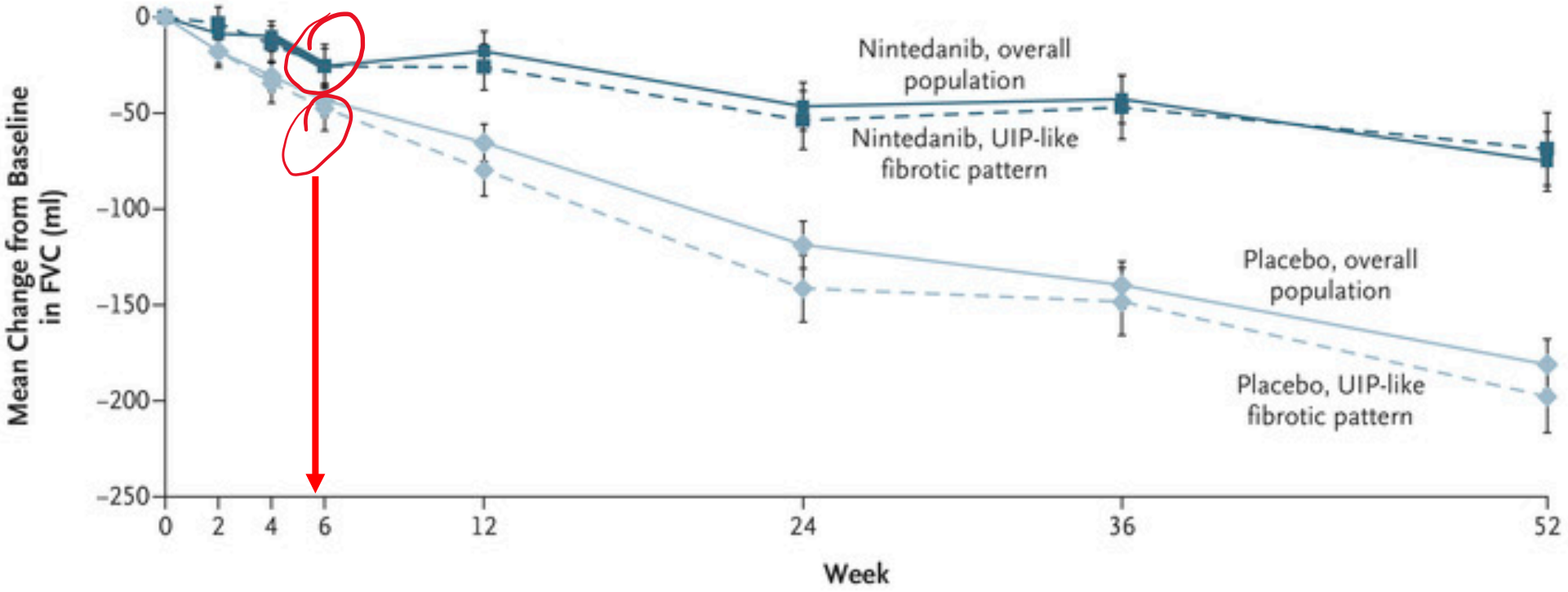
Treatment-by-subgroup-by time interaction *P*=0.19

	N analysed Placebo	N analysed OFEV®	Favors placebo / Favors OFEV® (-400, -200, 0, 200, 400)	Adjusted difference (95% CI)	*P* value
Overall population	331	332		107.0 (65.4,148.5)	*P*<0.001
UIP-like fibrotic pattern	206	206		128.2 (70.81, 185.59)	*P*<0.001
Other fibrotic patterns	125	126		75.3 (15.54, 135.01)	*P*<0.014

FVC	≤70% predicted	193	196		91.7 (37.4, 146.0)	*P*<0.37
	>70% predicted	138	136		130.0 (66.2, 193.7)	
Underlying ILD diagnosis in groups	Hypersensitivity pneumonitis	89	84		73.1 (-8.6, 154.8)	*P*<0.41
	CTD-ILDs	88	82		104.0 (21.1, 186.9)	
	INSIP	61	64		141.6 (46.0, 237.2)	
	Unclassifiable IIP	50	64		68.3 (-31.4, 168.1)	
	Other fibrosing ILDs	43	38		197.1 (77.6, 316.7)	

INBUILD (PF-ILD) study – Functional effects at WK 6

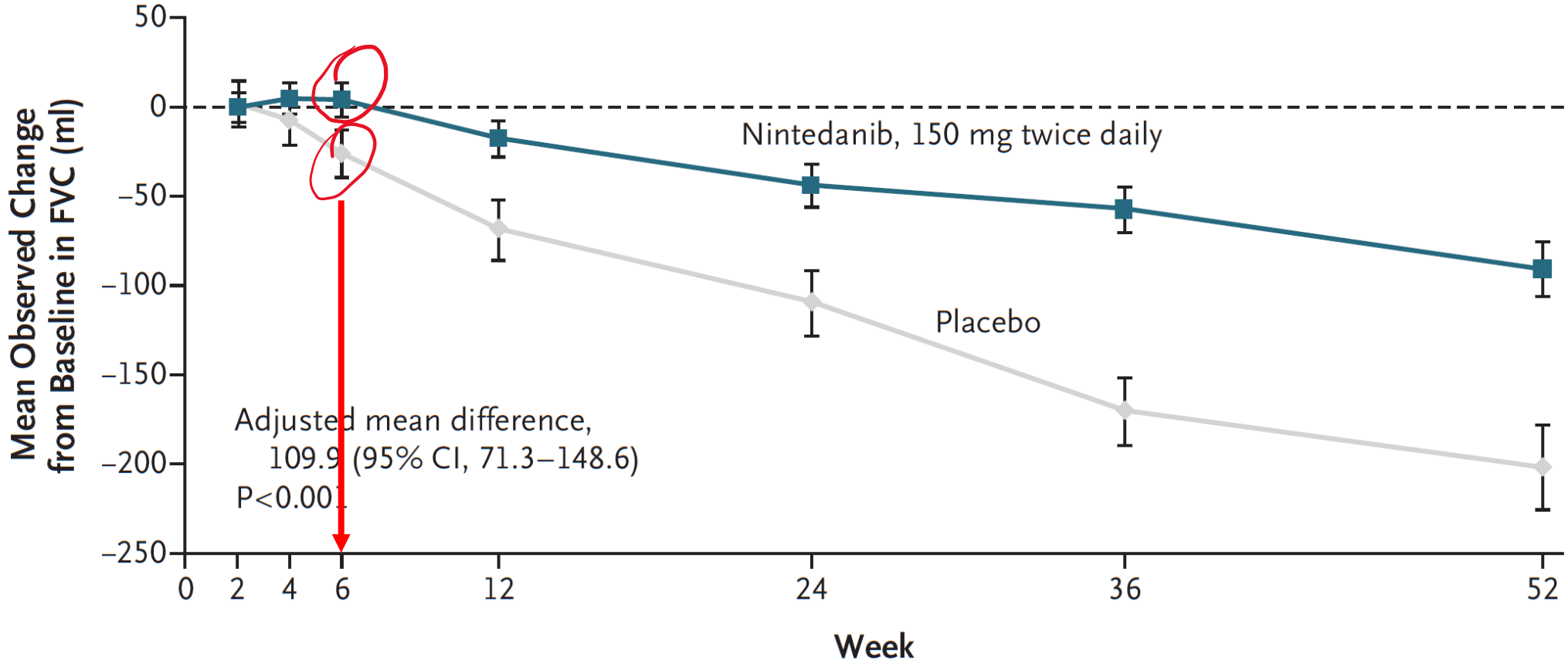
Nintedanib exerts anti-inflammatory properties



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

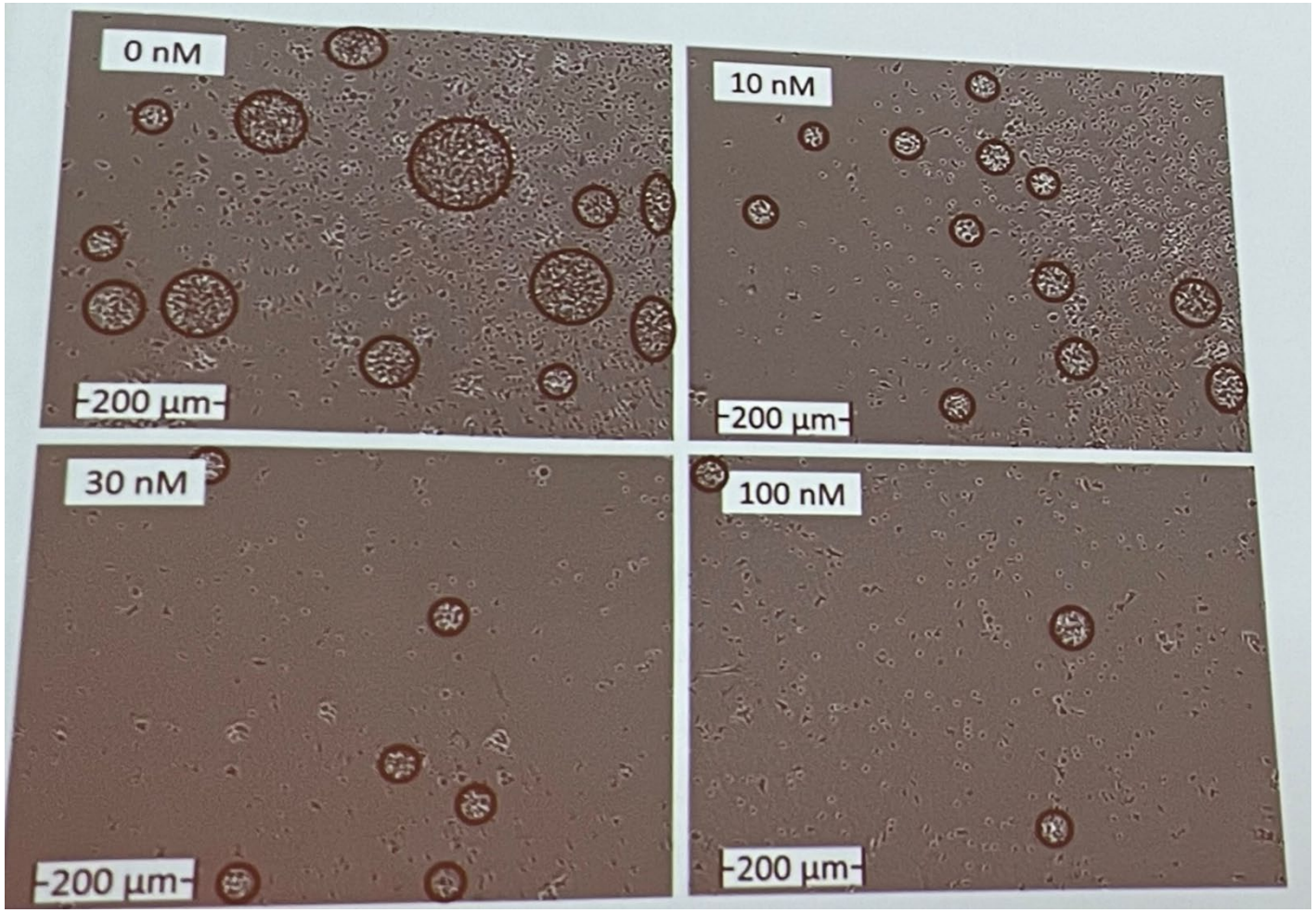
INPULSIS (IPF) study – Functional effects at WK 6

Nintedanib exerts anti-inflammatory properties



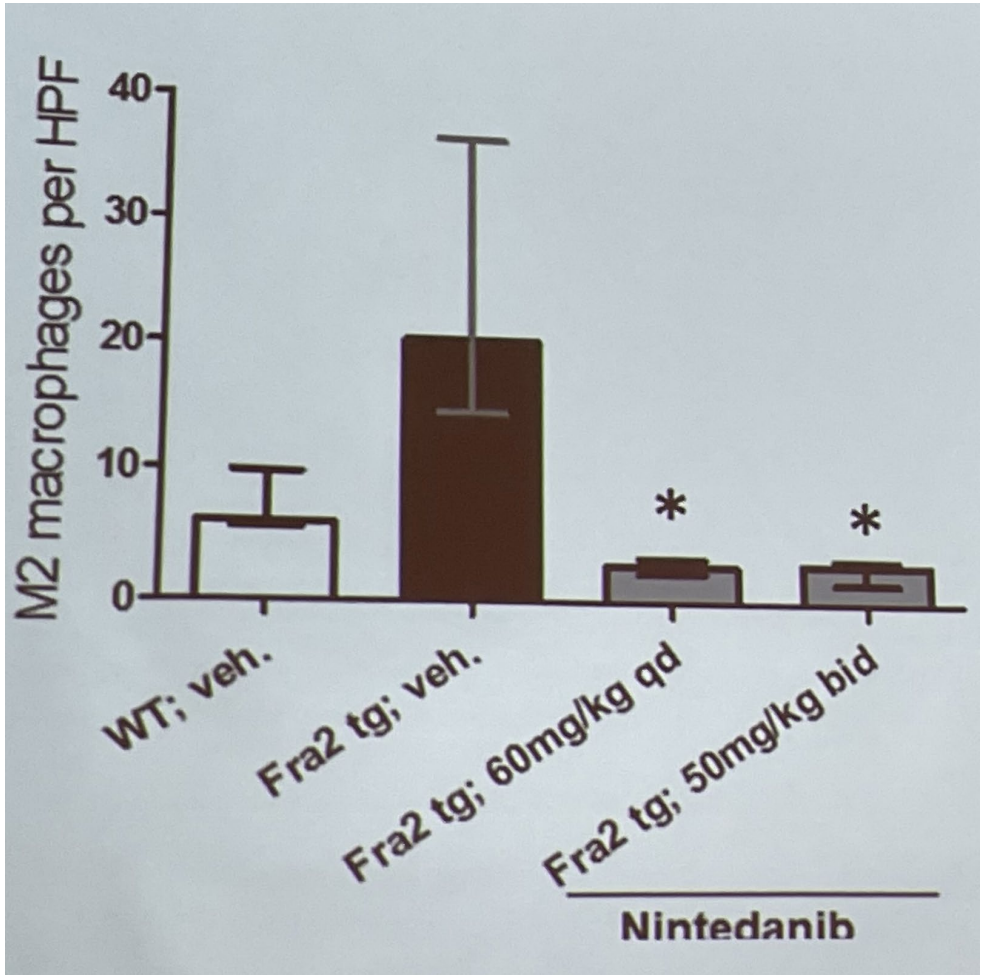
No. of Patients					
Nintedanib	303 301 298	292	284	274	250
Placebo	202 198 200	194	192	187	165

Nintedanib dampens T – cell activity



Ubieta et al. Drug Design, Development and Therapy 2021

Nintedanib prevents M2 polarization



ICLAF 2022 – Unpublished data

Nintedanib suppresses citrullination enzymes in RA-ILD experimental models

Suppression of epithelial abnormalities by nintedanib in induced-rheumatoid arthritis-associated interstitial lung disease mouse model

Received: 5 July 2021
Accepted: 19 Aug 2021

Yoko Miura [1], Hirotsugu Ohkubo [2], Akio Niimi [2] and Satoshi Kanazawa [1]

[1]Department of Neurodevelopmental Disorder Genetics, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan.
[2]Department of Respiratory Medicine, Allergy and Clinical Immunology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan.

We examined the characteristics of a novel induced RA-ILD (iRA-ILD) mouse model and the effects of nintedanib on the model.

D1CC×D1BC mice are highly susceptible to arthritogenic antigens, such as bovine type II collagen, resulting in severe inflammatory arthritis. ILD develops after joint inflammation is alleviated. Serum surfactant protein D levels were monitored as an ILD marker. Nintedanib was orally administered to iRA-ILD mice for 2 months.

The iRA-ILD model showed similar symptoms to those in patients with RA-ILD. The histopathological features of pulmonary disorder resembled nonspecific interstitial pneumonia, but with metaplastic epithelium. Histopathological analysis revealed that in addition to reducing fibrosis, nintedanib suppressed M2 macrophage polarisation and hyperplasia of Type 2 alveolar epithelial cells. The metaplastic epithelium acquired invasiveness because of the expression of E-cadherin, MMP7, *Tgf*-β, *Col1a1*, *Padi2* and *Padi4*. Moreover, citrullinated peptides were detected in these invasive epithelial cells as well as in the bronchiolar epithelium. Administration of nintedanib reduced the expression of Pad4 and citrullinated peptides and eliminated invasive epithelial cells.

The broad inhibitory effects of nintedanib on tyrosine kinases may contribute to the overall improvement in RA-ILD, including epithelial abnormalities associated with progressive lung fibrosis.

The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements

Anna-Maria Hoffmann-Vold, Toby M Maher*, Edward E Philpot, Ali Ashrafzadeh, Rafic Barake, Simone Barsotti, Cosimo Bruni, Paolo Carducci Patricia E Carreira, Ivan Castellví, Francesco Del Galdo, Jörg H W Distler, Ivan Foeldvari, Paolo Fraticelli, Peter M George, Bridget Griffiths, Alfredo Guillén-Del-Castillo, Abdul Monem Hamid, Rudolf Horváth, Michael Hughes, Michael Kreuter, Florentine Moazedi-Fuerst, Jacek Olas, Suman Paul, Cinzia Rotondo, Manuel Rubio-Rivas, Andrei Seferian, Michal Tomčík, Yurdagül Uzunhan, Ulrich A Walker, Ewa Więsik-Szewczyk, Oliver Distler*

***Lancet Rheumatol* 2020**

Published **Online**

January 14, 2020

Pharmacological therapy
Mycophenolate mofetil
Cyclophosphamide
Nintedanib

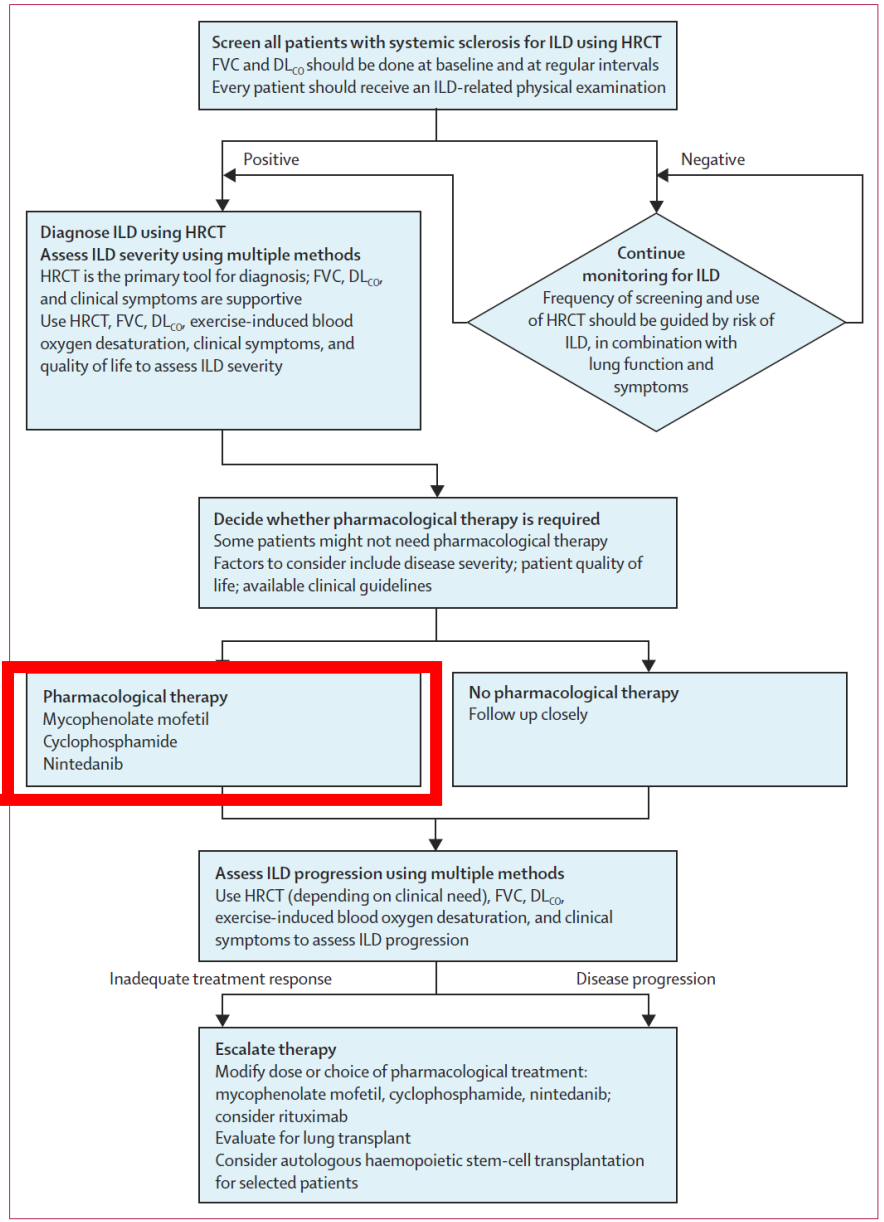


Figure 2: **Clinical management algorithm for systemic sclerosis-associated ILD**

Guideline

2023 American College of Rheumatology (ACR) Guideline for the Screening, Monitoring, and Treatment of Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Disease

The ACR is developing a new clinical practice guideline for clinicians who care for people with systemic autoimmune rheumatic disease who are at risk for or have been diagnosed with interstitial lung disease (ILD) (final publication of guideline anticipated autumn 2023).

- Response to Public Comments
- Public Comments
- Project Plan
- Disclosure Summary

Safety, tolerability, and efficacy of pirfenidone in patients with rheumatoid arthritis-associated interstitial lung disease: a randomised, double-blind, placebo-controlled, phase 2 study

TRAIL study

N=231

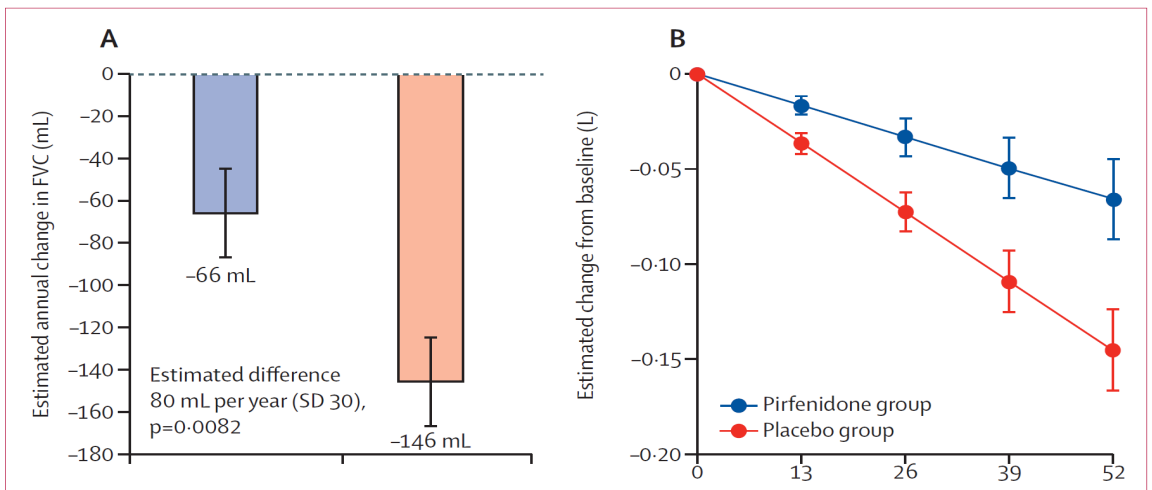
Design: RCT to receive pirfenidone or placebo

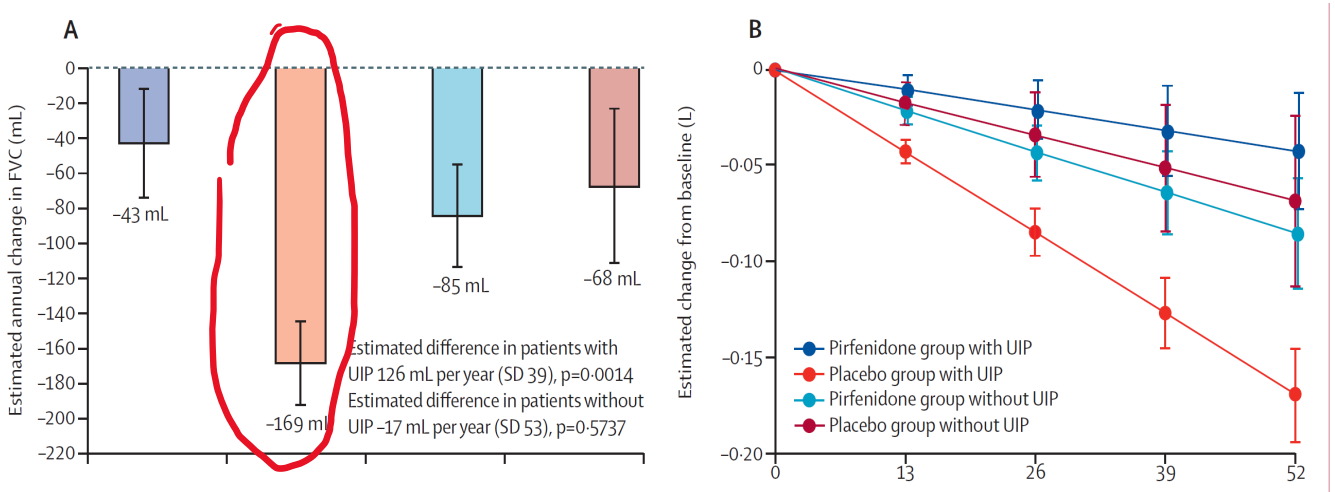
Joshua J Solomon, Sonye K Danoff,* Felix A Woodhead,* Shelley Hurwitz, Rie Maurer, Ian Glaspole, Paul F Dellaripa, Bibek Gooptu, Robert Vassallo, P Gerard Cox, Kevin R Flaherty, Huzaifa I Adamali, Michael A Gibbons, Lauren Troy, Ian A Forrest, Joseph A Lasky, Lisa G Spencer, Jeffrey Golden, Mary Beth Scholand, Nazia Chaudhuri, Mark A Perrella, David A Lynch, Daniel C Chambers, Martin Kolb, Cathie Spino, Ganesh Raghu,*† Hilary J Goldberg,*† Ivan O Rosas,*† for the TRAIL1 Network Investigators‡*

Lancet Respir Med 2022

Published Online
September 5, 2022
https://doi.org/10.1016/S2213-2600(22)00260-0

Results: Primary end-point -Negative– Incidence of patients with FVC decline>10%
Pirfenidone resulted in 80 ml annual FVC benefit and 123 ml in UIP pattern





Tocilizumab improves FVC in SSc-ILD

Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial

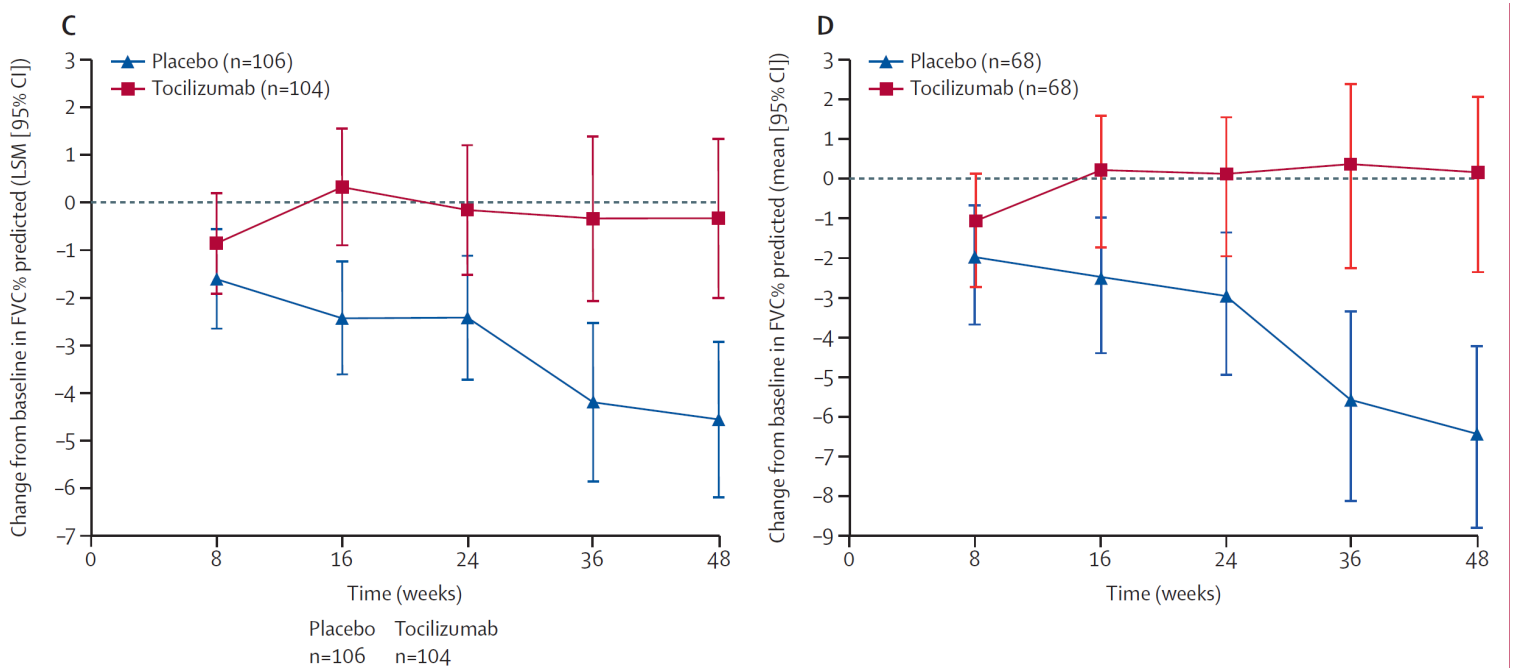
Dinesh Khanna, Celia J F Lin, Daniel E Furst, Jonathan Goldin, Grace Kim, Masataka Kuwana, Yannick Allanore, Marco Matucci-Cerinic, Oliver Distler, Yoshihito Shima, Jacob M van Laar, Helen Spotswood, Bridget Wagner, Jeffrey Siegel, Angelika Jahreis, Christopher P Denton*, for the focuSSced investigators†*

Lancet Respir Med 2020

Published Online
August 28, 2020

210 patients, mostly inflammatory component-NSIP

Interpretation The primary skin fibrosis endpoint was not met. Findings for the secondary endpoint of FVC% predicted indicate that tocilizumab might preserve lung function in people with early SSc-ILD and elevated acute-phase reactants. Safety was consistent with the known profile of tocilizumab.

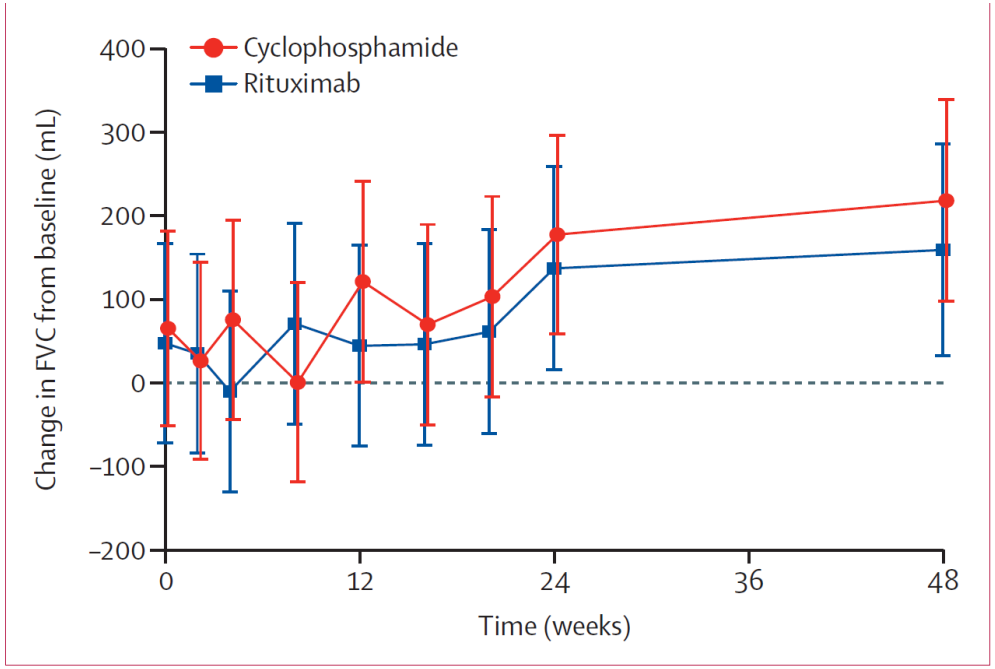


Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): a double-blind, double-dummy, randomised, controlled, phase 2b trial

*Toby M Maher, Veronica A Tudor, Peter Saunders, Michael A Gibbons, Sophie V Fletcher, Christopher P Denton, Rachel K Hoyles, Helen Parfrey, Elisabetta A Renzoni, Maria Kokosi, Athol U Wells, Deborah Ashby, Matyas Szigeti, Philip L Molyneaux, on behalf of the RECITAL Investigators**

Lancet Respir Med 2023; 11: 45–54

Published Online November 11, 2022 https://doi.org/10.1016/S2213-2600(22)00359-9



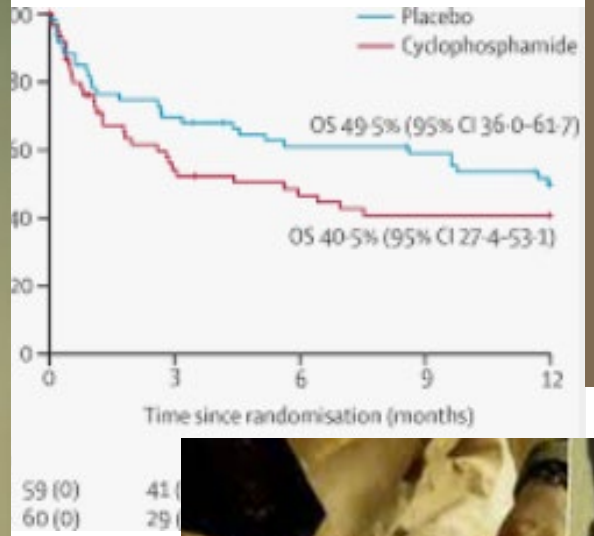
- ✓ **101 CTD-ILDs patients**
- ✓ **Mainly inflammatory (NSIP/OP) patterns**
- ✓ **68% females**
- ✓ **Mean FVC: 73%, DLCO: 40%**
- ✓ **99 ml gain in FVC – RTX=CYCLO**
- ✓ **10 m gain in 6MWD – RTX= CYCLO**
- ✓ **Fewer adverse events and OCS exposure in RTX**

Connective tissue disease type		
Idiopathic inflammatory myositis	22 (46%)	22 (45%)
Systemic sclerosis	19 (40%)	18 (37%)
Mixed connective tissue disease	7 (15%)	9 (18%)
Years since onset of connective tissue disease	4·8 (6·2)	4·5 (7·6)

THE LANCET
Respiratory Medicine

ARTICLES | VOLUME 10, ISSUE 1, P26-34, JANUARY 01, 2022

AZA/CYCLO/HIGH OCS BLACK LABEL FOR IPF!!!!



What's in the box?

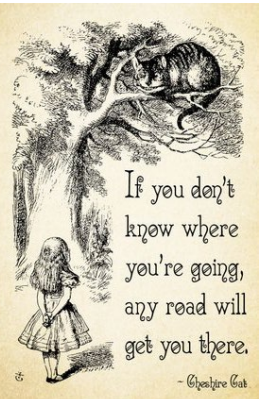
patients were a ned
and 119 patients (62 [52%] with severe IPF) received at least om
were included in the intention-to-treat analysis. The 3-montl
cyclophosphamide compared with 31% (18/59) in the placeb

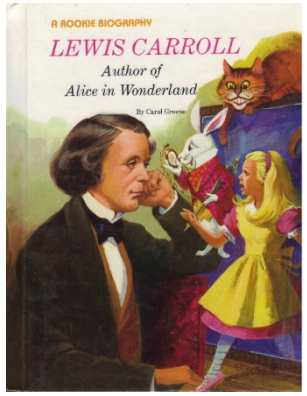
Interpretation

In patients with acute exacerbation of IPF, adding intravenous cyclophosphamide pulses to glucocorticoids increased 3-month mortality. These findings provide evidence against the use of intravenous cyclophosphamide in such patients.

Take home messages

- Nintedanib can be efficiently combined with immunomodulatory agents
- Need to early identify progression
- Need to identify whether inflammation drives fibrosis
- Need to identify reversible – treatable - features





2024

ICLAF

GREECE

SAVE THE DATE

BRIDGES OF PULMONOLOGY 2023

Organized by:

INSTITUTE OF RESEARCH AND EDUCATION OF RESPIRATORY DISEASES

DEPARTMENT OF RESPIRATORY MEDICINE UNIVERSITY OF PATRAS, GREECE

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City of Patras, Greece

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