

# KATRD 심포지엄 증례

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- Case 1 : 한 달 전부터 시작된 기침, 호흡곤란으로 내원한 환자
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# 증례 #1

- **Case 1 : 한 달 전부터 시작된 기침, 호흡곤란으로 내원한 환자**
- Case 2 : 30년 전 수술적 폐생검 후 간질성 폐질환 진단, 이후 추적 중단된 상태에서 한 달 전부터 갑자기 악화된 호흡곤란을 주소로 내원한 환자

**Chief complaint)** Cough and dyspnea, mMRC 3

**Present illness)**

한 달 전부터 시작된 기침으로 local clinic 에서 약 복용하던 중 진행하는 호흡곤란으로 입원, antibiotics 및 systemic steroid 1mg/kg 2주간 사용하며 dyspnea 는 호전되었으나, desaturation 반복 되며 further evaluation 위해 전원 문의 후 ER referred (O2 demand 2L/min via nasal prong)

# Past medical history

**Past medical history)** DM, dyslipidemia

**Social history)**

**Smoking:** Never smoker

**Alcohol:** non-alcoholic

**Occupation:** 주부

**Family history)** 어머니 – 폐암

# Review of system

cough / sputum / rhinorrhea / dyspnea (+/+/-/+)

Morning stiffness (-)

Malar rash (+) 이전부터 잦은 facial flushing

Photosensitivity (+)

Oral ulcer (-) Genital ulcer (-)

Sicca Sx. (+) : dry eye(-), dry mouth(+) 입이 너무 마른다

Raynaud's Ph.(+) - 한겨울에 손끝이 저린다. 양손 끝 붉어진 소견, 손끝이 딱딱해졌다.

Hair loss (-) Arthralgia (-) Back pain (-)

# Physical examination

**Vital sign)** 126/72 mmHg – 96/min – 20/min - 37 °C

**General)** alert, Skin rash on face, hands

**Chest)** inspiratory crackle, BLLF

## **Extremities)**

Palmar erythema (+)

Salt and pepper appearance, both arms (+)

Mild skin eruption, both limbs

# Initial laboratory results

CBC : WBC 12960/mm<sup>3</sup>, Hb 13.5 mg/dL, PLT 379,000/mm<sup>3</sup>

AST/ALT : 14/18 U/L

BUN/Cr : 15.5 mg/dL / 0.50 mg/dL

CRP : 1.3 mg/dL

Procalcitonin <0.04 ng/mL

ABGA (O<sub>2</sub> 2L/min) : pH 7.390, pCO<sub>2</sub> 40.9 mmHg, pO<sub>2</sub> 61.5 mmHg, HCO<sub>3</sub> 24.2 mmol/L, Sat 94%

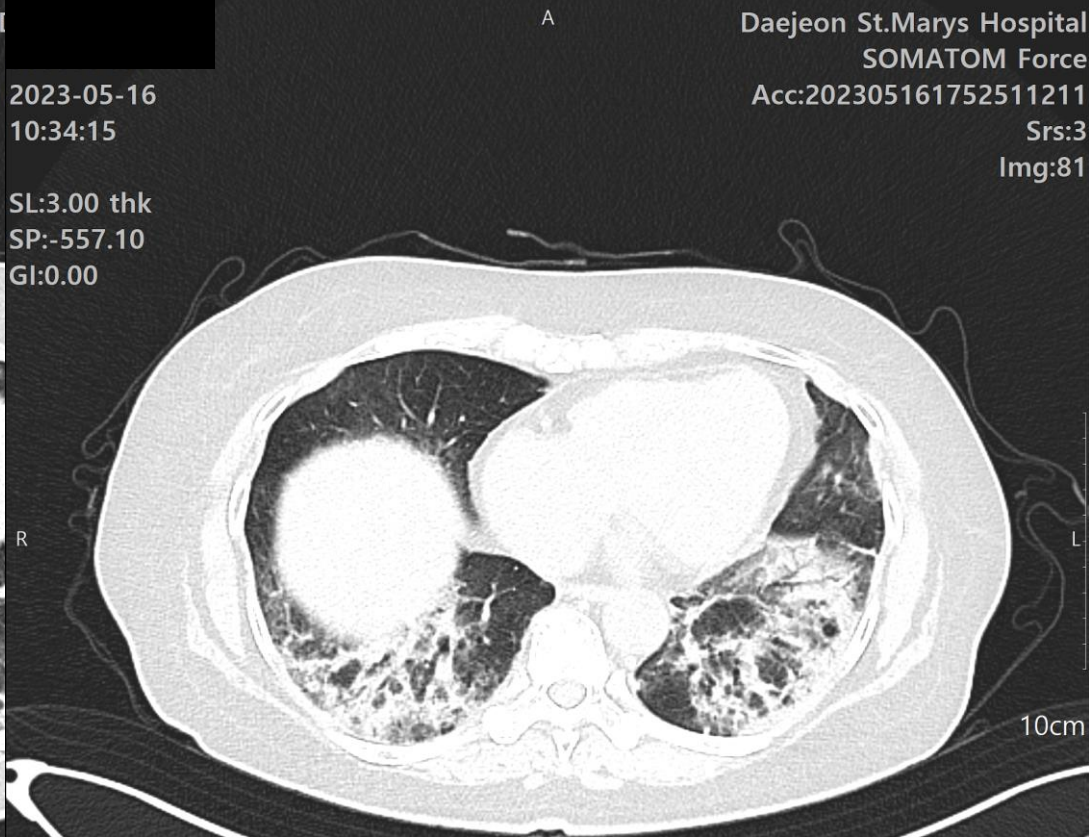
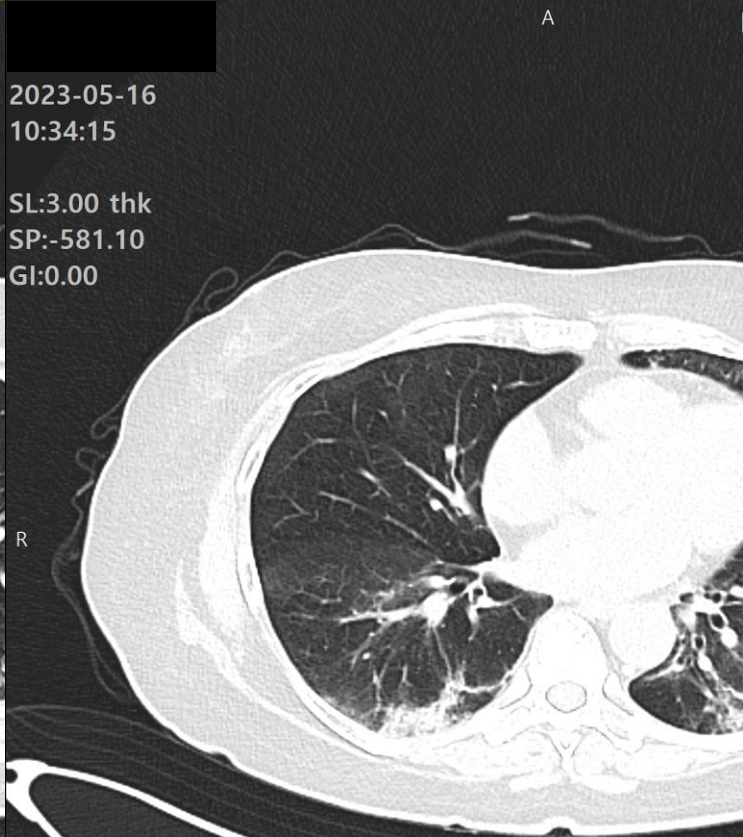
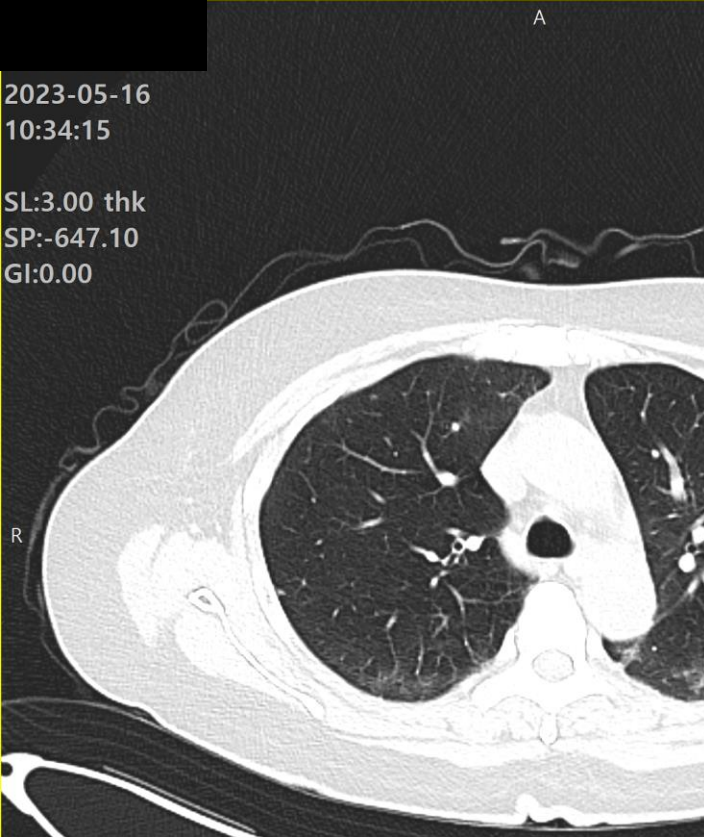
Troponin T: 0.009 ng/mL, CK-MB : 0.3 ng/mL

NT-ProBNP: 67.9 pg/mL

D-dimer : 0.27 mg/L

KL-6 : 1362.4 U/mL

# Initial Chest CT



# Special laboratory results

ANA : positive, cytoplasmic, nuclear, 1:160

Anti-SS-A 52 : 3+

RA factor : 6.1

Anti-CCP Ab : negative

C3/C4 : 135 / 29.6 mg/dL

IgG/A/M : 850 / 274 / 193 mg/dL

ANCA : negative

# Special examination

## Spirometry

FVC 1.91 L (57%)

FEV<sub>1</sub> 1.54 L (58%)

FEV<sub>1</sub>/FVC ratio 0.81

TLC 2.88 L (58%)

DLCO 48%

## Sono Salivary gland

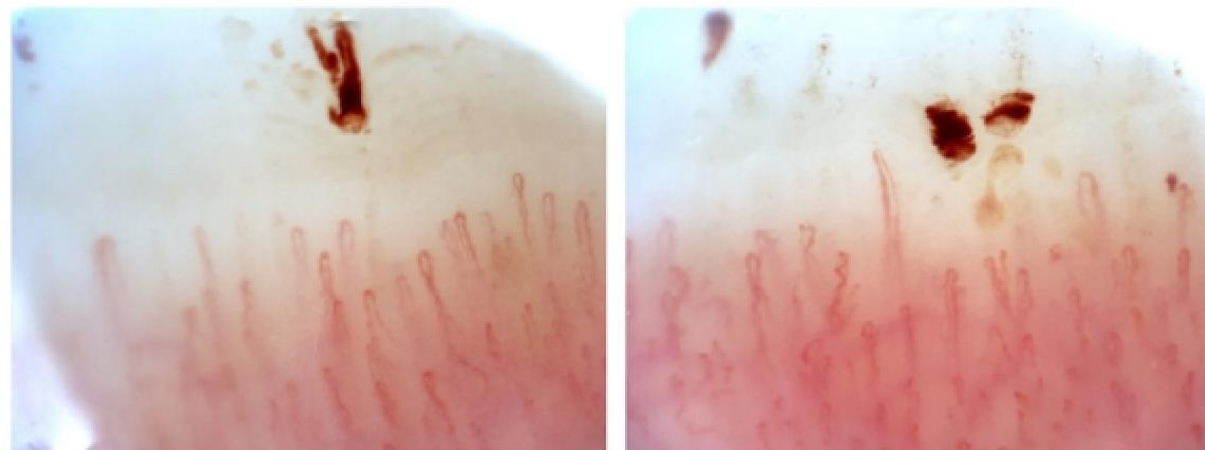
Submandibular gland, both, Grade 1

→ Suspicious for Sjogren's syndrome

## Salivary flow test

- Unstimulated saliva : 0.01 ml/5min  
→ **0.002mL/min** (normal :  $\geq 0.1-0.3$  mL/min)
- Stimulated saliva : 4 ml/5min  
→ 0.8 mL/min (normal :  $\geq 0.5-1.0$  mL/min)

## Nailfold capillary microscope



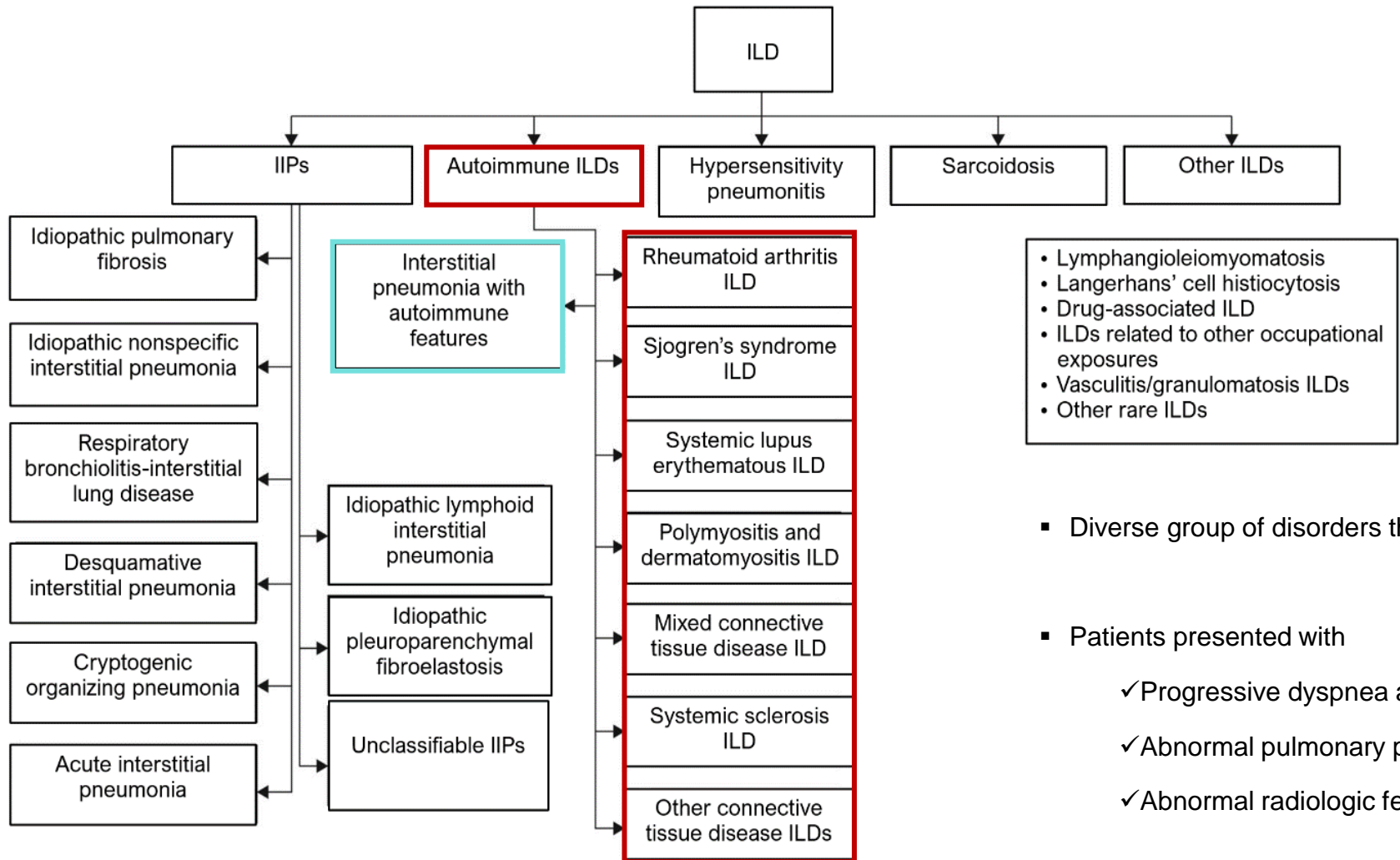
# Assessment

**Diagnosis)** Sjogren-associated ILD : OP pattern

## **Therapeutic plan)**

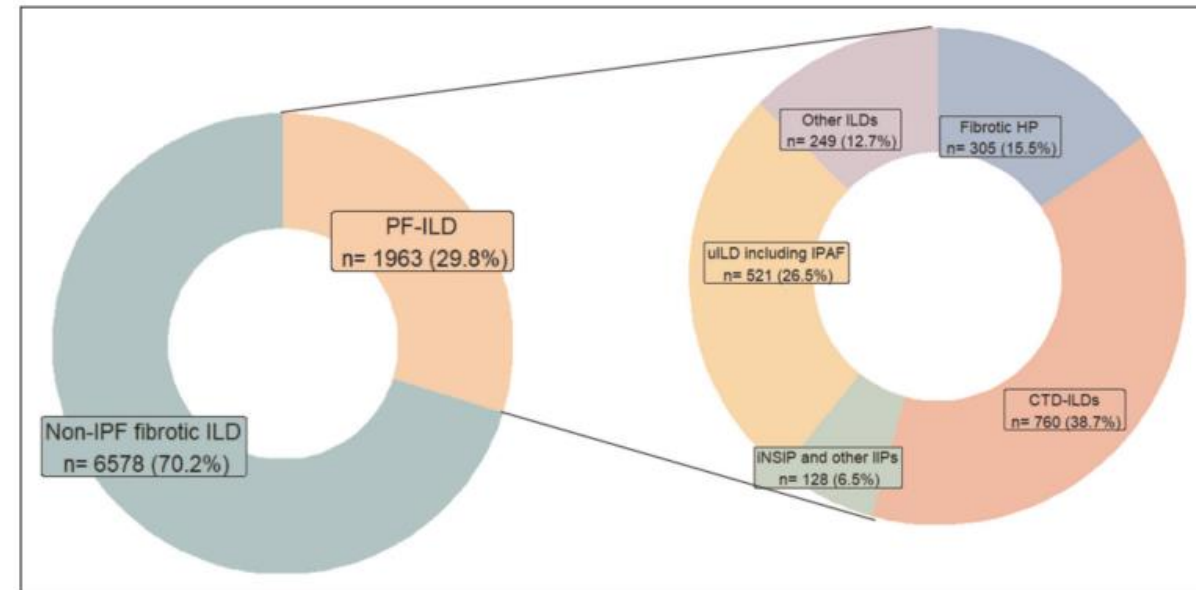
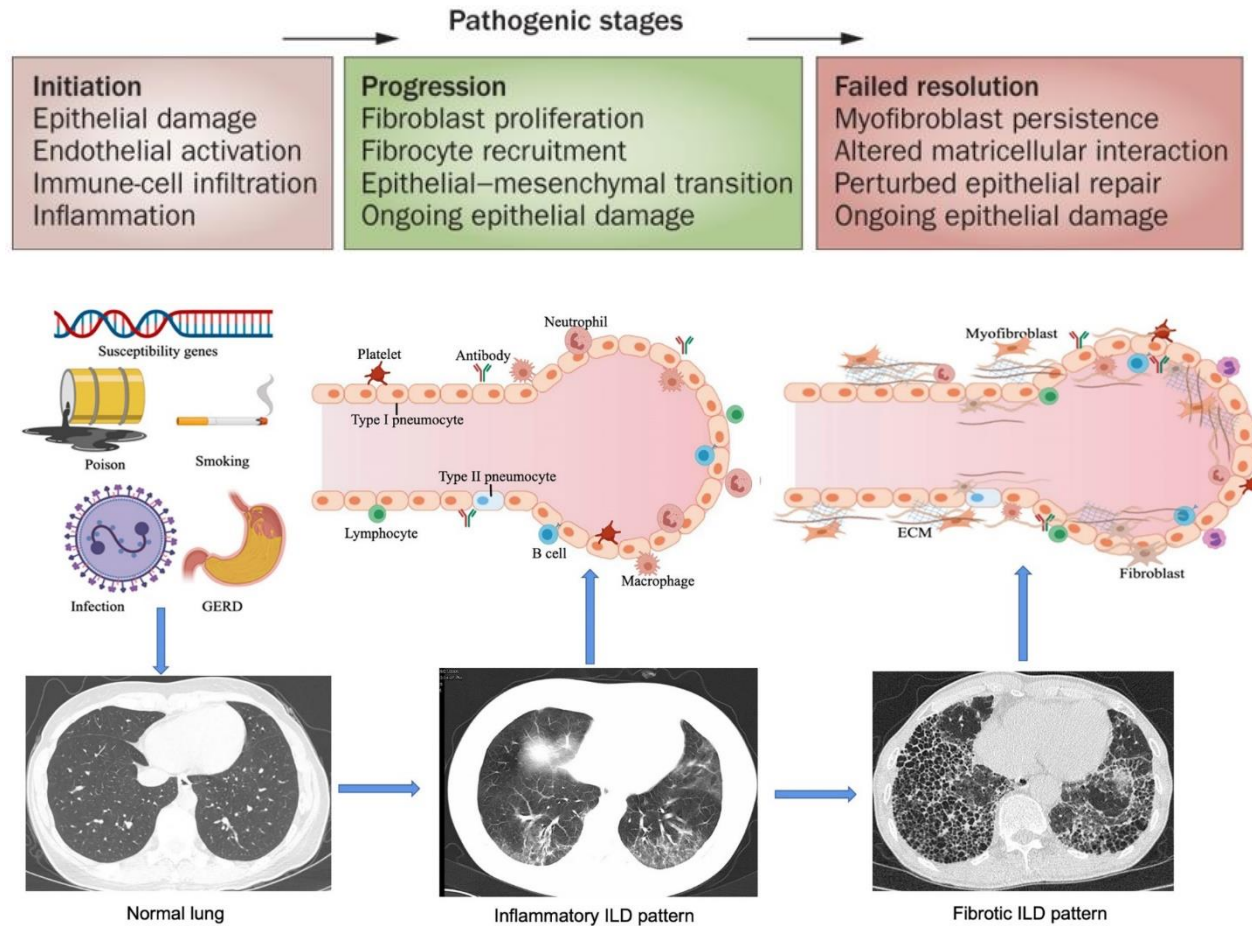
- ✓ Systemic steroid tapering slowly
- ✓ Azathioprine add on

# Interstitial Lung Disease (ILD)

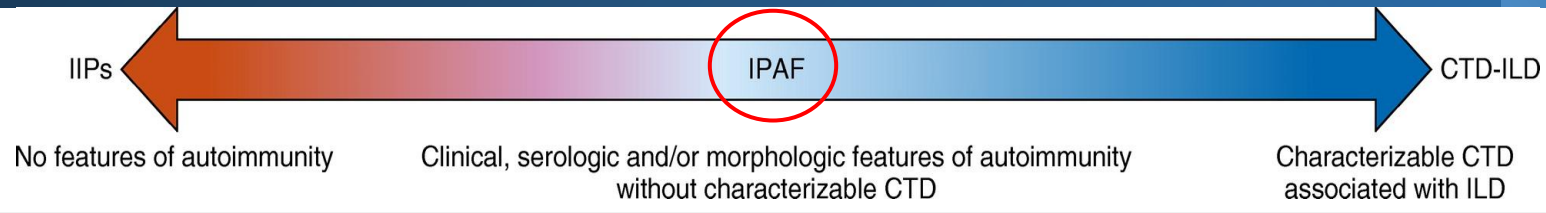


- Diverse group of disorders that involve the distal pulmonary parenchyma
- Patients presented with
  - ✓ Progressive dyspnea and cough
  - ✓ Abnormal pulmonary physiology
  - ✓ Abnormal radiologic features on CXR and/or HRCT

# Autoimmune disease associated ILD



# Classification criteria



1. Presence of an interstitial pneumonia by HRCT or SLB *and*
2. Exclusion of alternative etiologies *and*
3. Does not meet criteria for a defined CTD *and*
4. At least one feature from at least two of the following domains:

## A. Clinical domain

1. Distal digital fissuring (i.e., “mechanic hands”)
2. Distal digital tip ulceration
3. Inflammatory arthritis *or* polyarticular morning joint stiffness  $\geq 60$  min
4. Palmar telangiectasia
5. Raynaud phenomenon
6. Unexplained digital edema
7. Unexplained fixed rash on the digital extensor surfaces (Gottron sign)

## B. Serologic domain

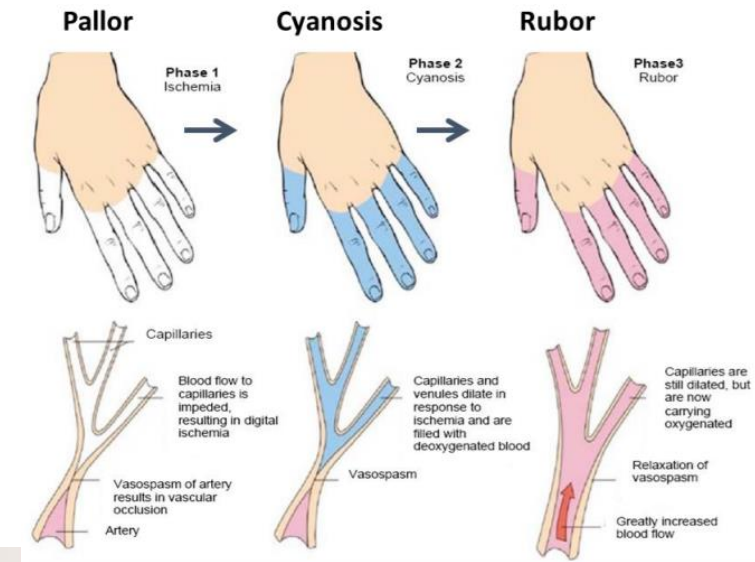
1. ANA  $\geq 1:320$  titer, diffuse, speckled, homogeneous patterns *or*
  - a. ANA nucleolar pattern (any titer) *or*
  - b. ANA centromere pattern (any titer)
2. Rheumatoid factor  $\geq 2 \times$  upper limit of normal
3. Anti-CCP
4. Anti-dsDNA
5. Anti-Ro (SS-A)
6. Anti-La (SS-B)
7. Anti-ribonucleoprotein
8. Anti-Smith
9. Anti-topoisomerase (Scl-70)
10. Anti-tRNA synthetase (e.g., Jo-1, PL-7, PL-12; others are: EJ, OJ, KS, Zo, tRS)
11. Anti-PM-Scl
12. Anti-MDA-5

## C. Morphologic domain

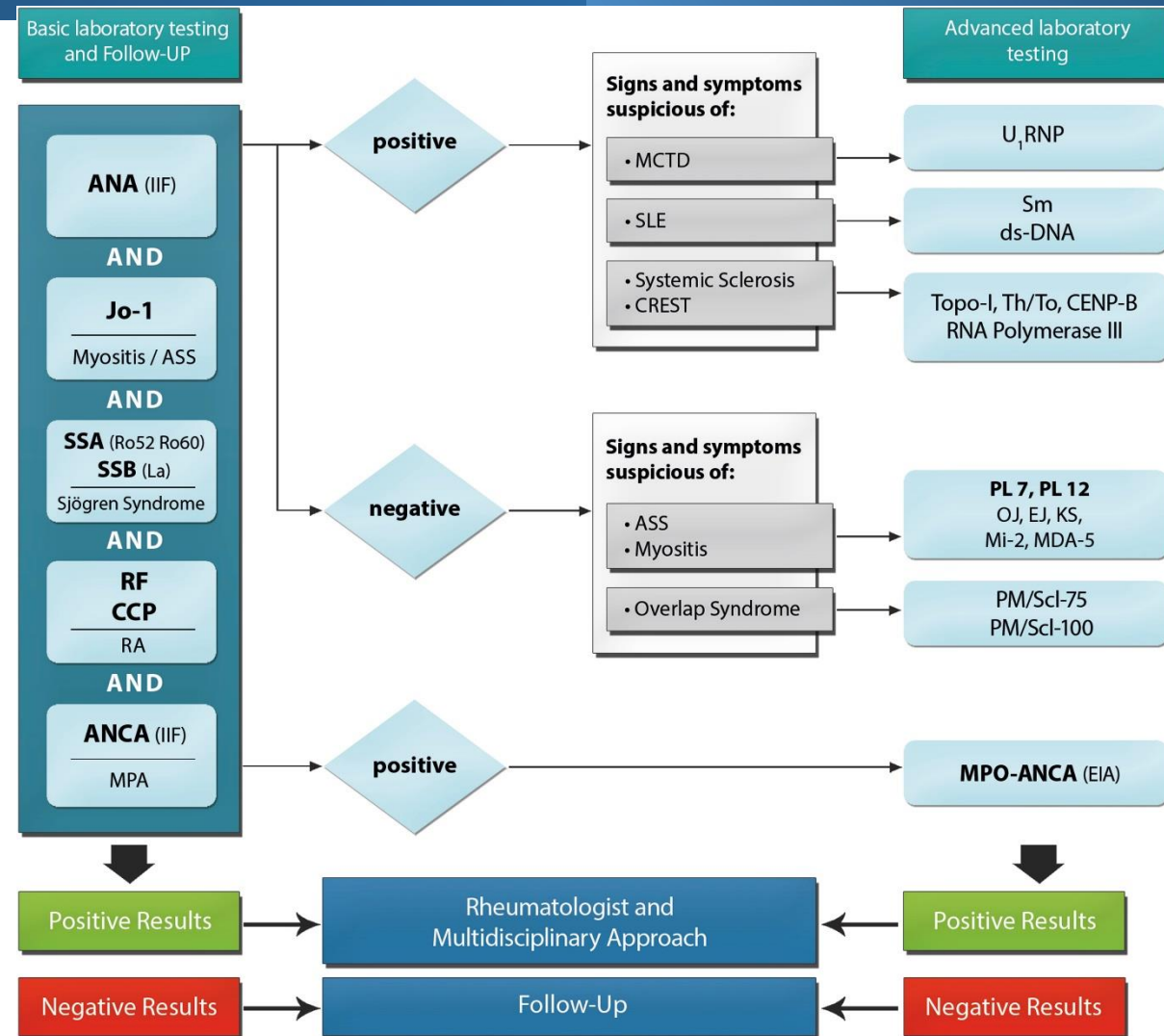
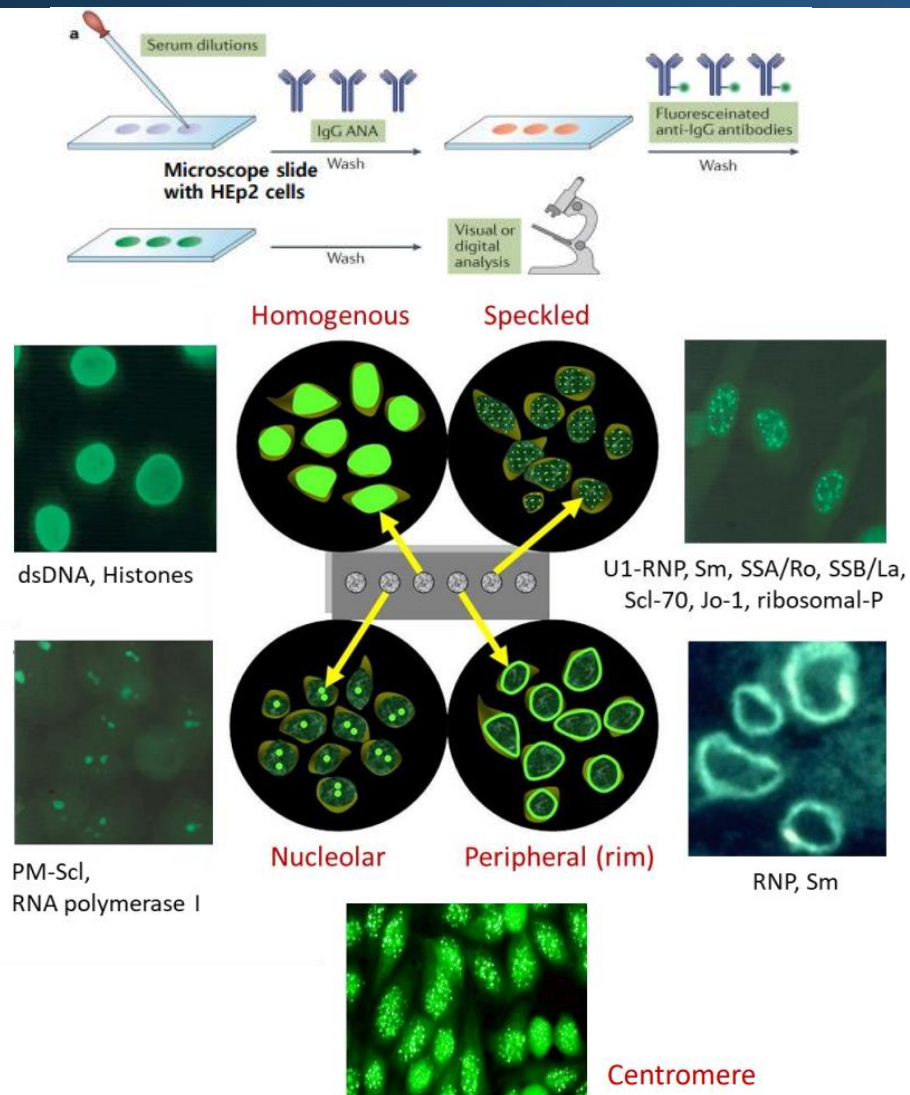
1. Suggestive radiology patterns by HRCT:
  - a. NSIP
  - b. OP
  - c. NSIP with OP overlap
  - d. LIP
2. Histopathology patterns or features by surgical lung biopsy:
  - a. NSIP
  - b. OP
  - c. NSIP with OP overlap
  - d. LIP
  - e. Interstitial lymphoid aggregates with germinal centers
  - f. Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)
3. Multicompartment involvement (in addition to interstitial pneumonia):
  - a. Unexplained pleural effusion or thickening
  - b. Unexplained pericardial effusion or thickening
  - c. Unexplained intrinsic airways disease\* (by PFT, imaging or pathology)
  - d. Unexplained pulmonary vasculopathy

- 1) ILD on CT
- 2) 다른 원인 배제
- 3) CTD 진단기준에는 만족하지 못함
- 4) 2개 이상의 domain 에 해당
  - (a) 임상적
  - (b) 혈청학적
  - (c) 형태학적

# (1) Clinical domain



# (2) Serologic domain: FANA (fluorescent ANA)



### (3) Morphologic domain : radiologic & histologic pattern of CTD-ILD

	Type of connective tissue disease					
	SSc	RA	SS	MCTD	PM/DM	SLE
CTD prevalence	26 <sup>a</sup>	0.5%–2% of the general population [14]	3% in > age of 50 years	3.8 <sup>a</sup>	Unknown	15%–50 <sup>a</sup>
Clinical ILD <sup>b</sup>	≤ 45% [21] <sup>c</sup>	7.7% [22] <sup>d</sup>	11%–15% [23] <sup>e</sup> [24] <sup>f</sup>	54% [25] <sup>g</sup>	15%–78% [21,26-28] <sup>h</sup>	11% [29] <sup>i</sup>
HRCT abnormality	70%–90% [21]	19% [31]	75% of asymptomatic patients [33]	52%–85% [20,32]	23%–61% [3,27]	≤ 30% [21]
Common ILD type	NSIP UIP	UIP NSIP OP, DIP	NSIP LIP, OP, UIP, DIP	NSIP	NSIP OP, UIP, DAD, LIP	NSIP LIP, OP, UIP AIP, DIP
ILD-cause mortality	Unknown	10%–20% [42]	5-Year survival: 84% [49]	Unknown	From subclinical to rapidly progressive and fatal [61]	50% [63]

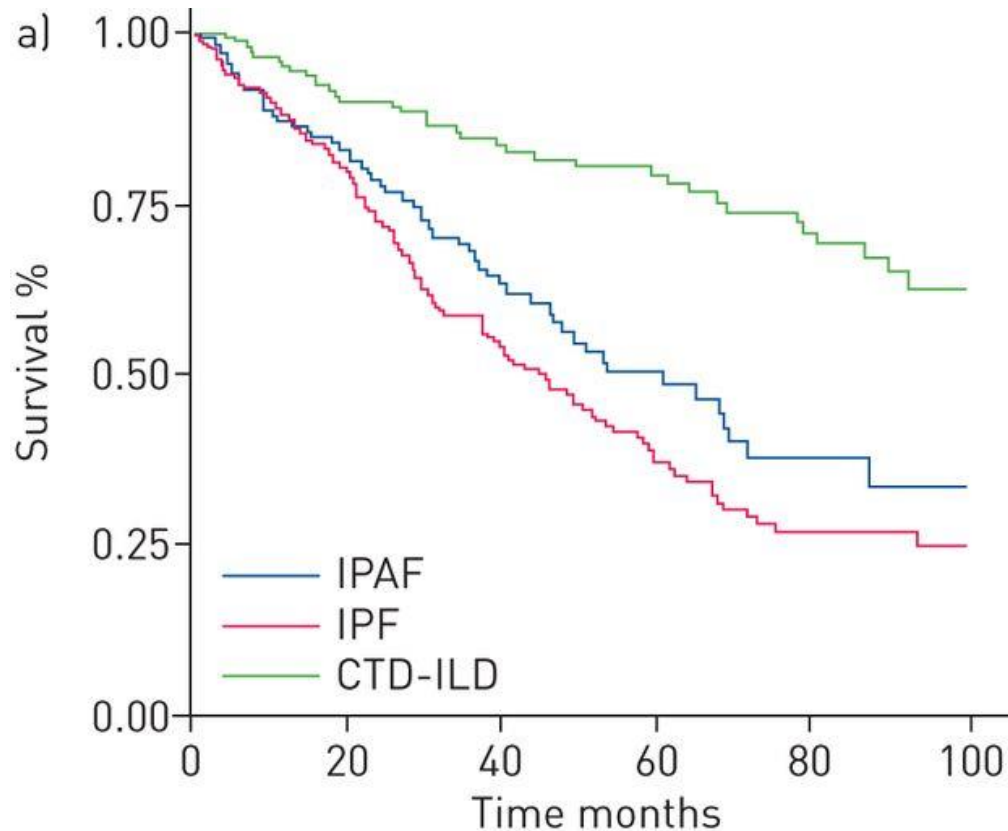
**Table 1** | The relative prevalence of histological patterns in IIP in CTDs

Lung pattern	IIP	Rheumatoid arthritis	Systemic sclerosis	SLE	Polymyositis-dermatomyositis	Sjögren syndrome
Usual interstitial pneumonia	+++	++	+	+	+	±
Nonspecific interstitial pneumonia	++	++	+++	++	++	++
Desquamative interstitial pneumonia and/or RB-ILD	+	±	±	±	±	±
Organizing pneumonia	++	+	±	±	++	±
Lymphocytic interstitial pneumonia	±	±	±	±	±	++
Pleuroparenchymal fibroelastosis	±	?	?	?	?	?
Diffuse alveolar damage	+	+	±	+	+	±

# DDx of CTD-ILD from IIP: Why important ?

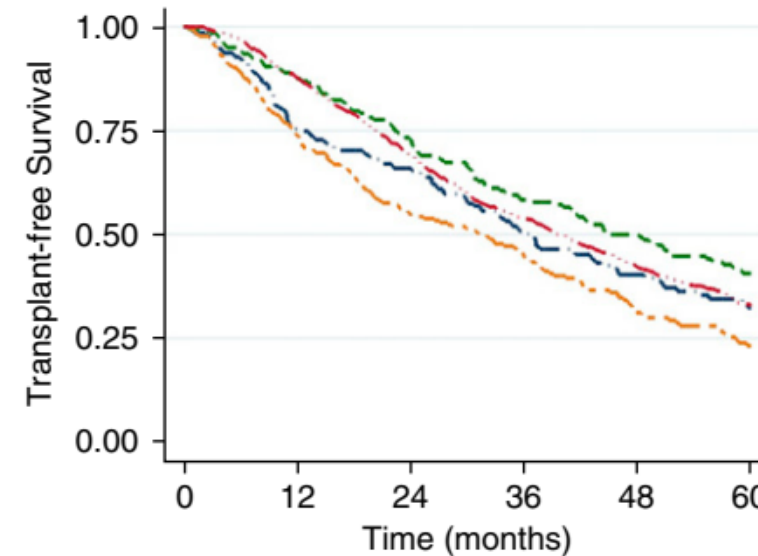
## - Prognostic perspective

- In RA, 10-20% ILD precedes articular disease
- No correlation with severity



828 U.S cohort & 513 UK ILD cohort

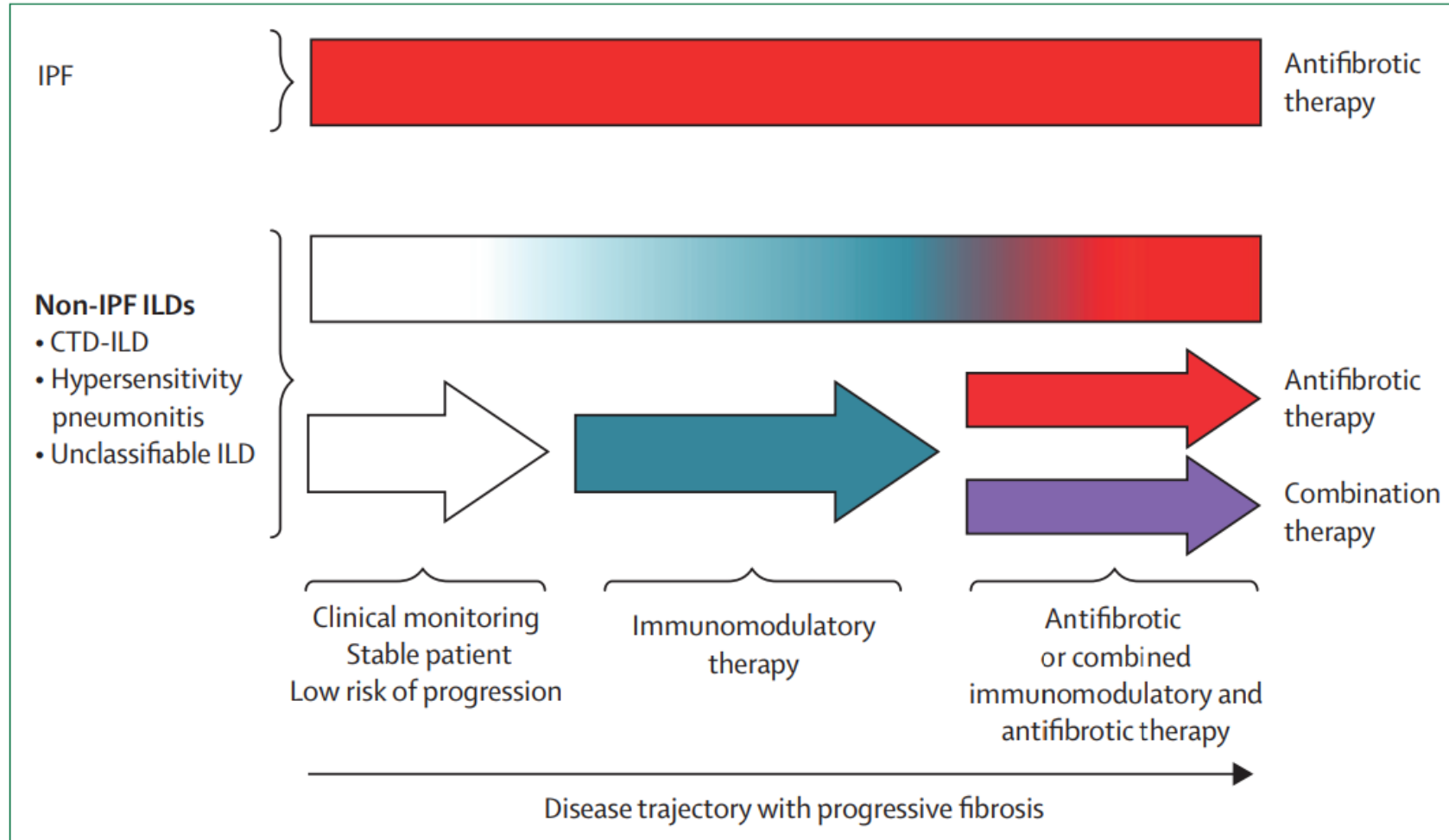
PPF defined by >10% relative FVC decline



at risk	0	12	24	36	48	60	HR (95% CI)
fHP210	150	121	81	55	31		1.11 (0.91-1.36)
CTD204	172	135	103	79	56		0.84 (0.68-1.03)
IIP226	161	116	82	52	34		1.40 (1.16-1.68)
IPF740	639	490	368	262	178		

# DDx of CTD-ILD from IIP: Why important ?

- therapeutic perspective



# Treatment for SARD-ILD

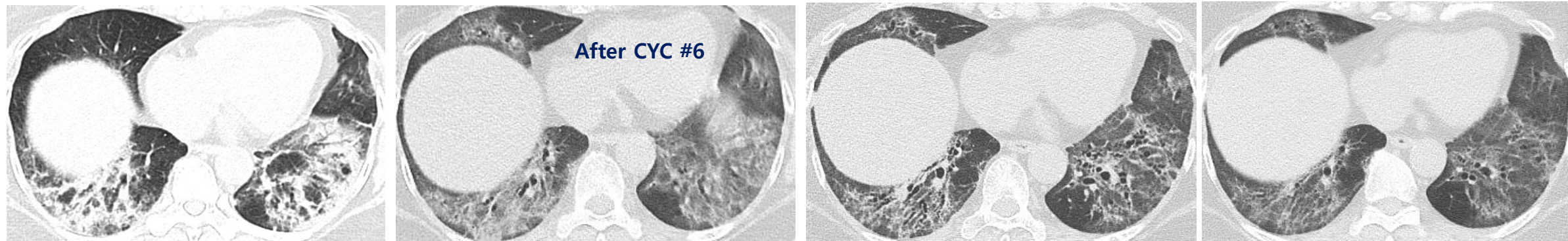
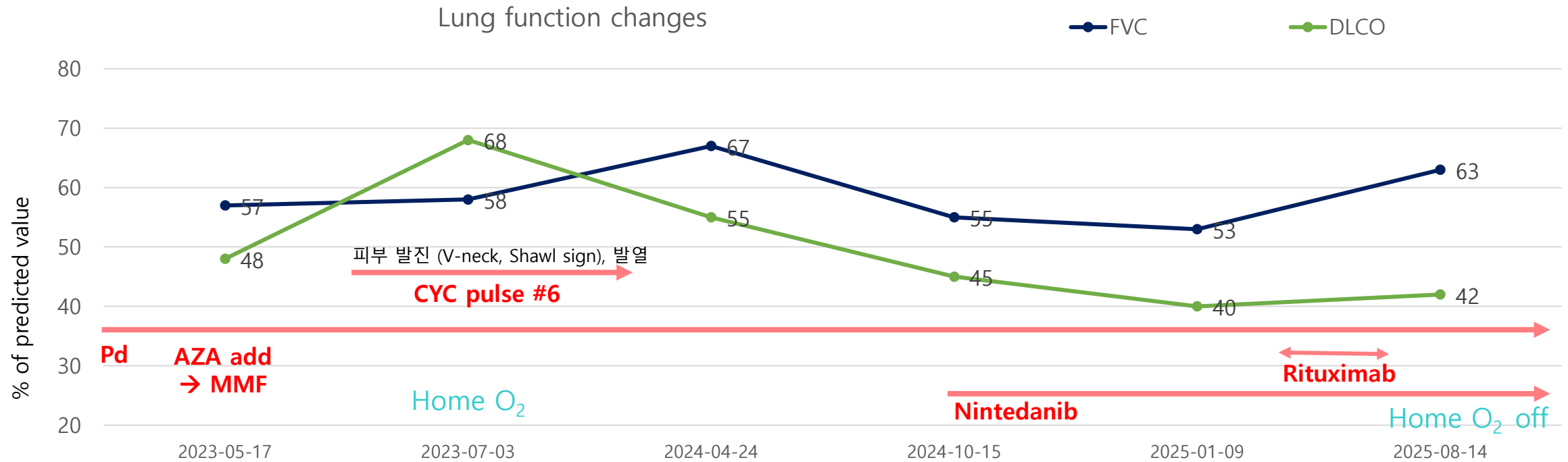
ACR/CHEST guideline (July 2024)

## Initial treatment options for the treatment of SARD associated ILD

	Systemic Sclerosis	Myositis	MCTD	Rheumatoid Arthritis	Sjögren's
<b>Preferred First-line ILD therapy</b>	Mycophenolate <sup>†</sup> Tocilizumab Rituximab	Mycophenolate <sup>†</sup> Azathioprine Rituximab CNI	Mycophenolate <sup>†</sup> Azathioprine Rituximab	Mycophenolate <sup>†</sup> Azathioprine Rituximab	Mycophenolate <sup>†</sup> Azathioprine Rituximab
<b>Additional options</b>	Cyclophosphamide Nintedanib Azathioprine	JAKi Cyclophosphamide	Tocilizumab Cyclophosphamide	Cyclophosphamide	Cyclophosphamide
<b>+ Glucocorticoids</b>	<b>Strong recommendation against GCs</b>	Short-term GCs*	Short-term GCs*	Short-term GCs*	Short-term GCs*

■ Strong recommendation *against*     ■ Conditional recommendation

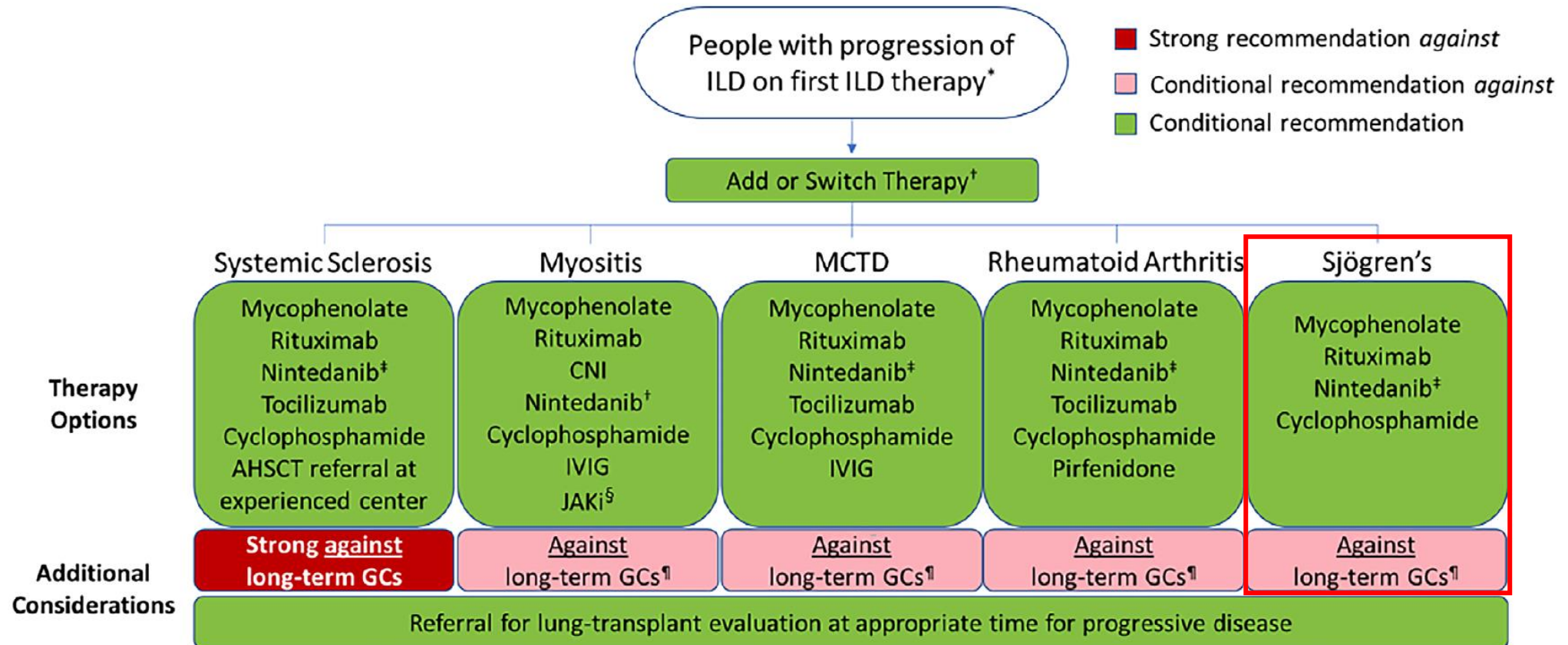
# Clinical course



# Treatment for SARD-ILD

ACR/CHEST guideline (July 2024)

Management of SARD-ILD with **progression** of ILD despite first ILD therapy

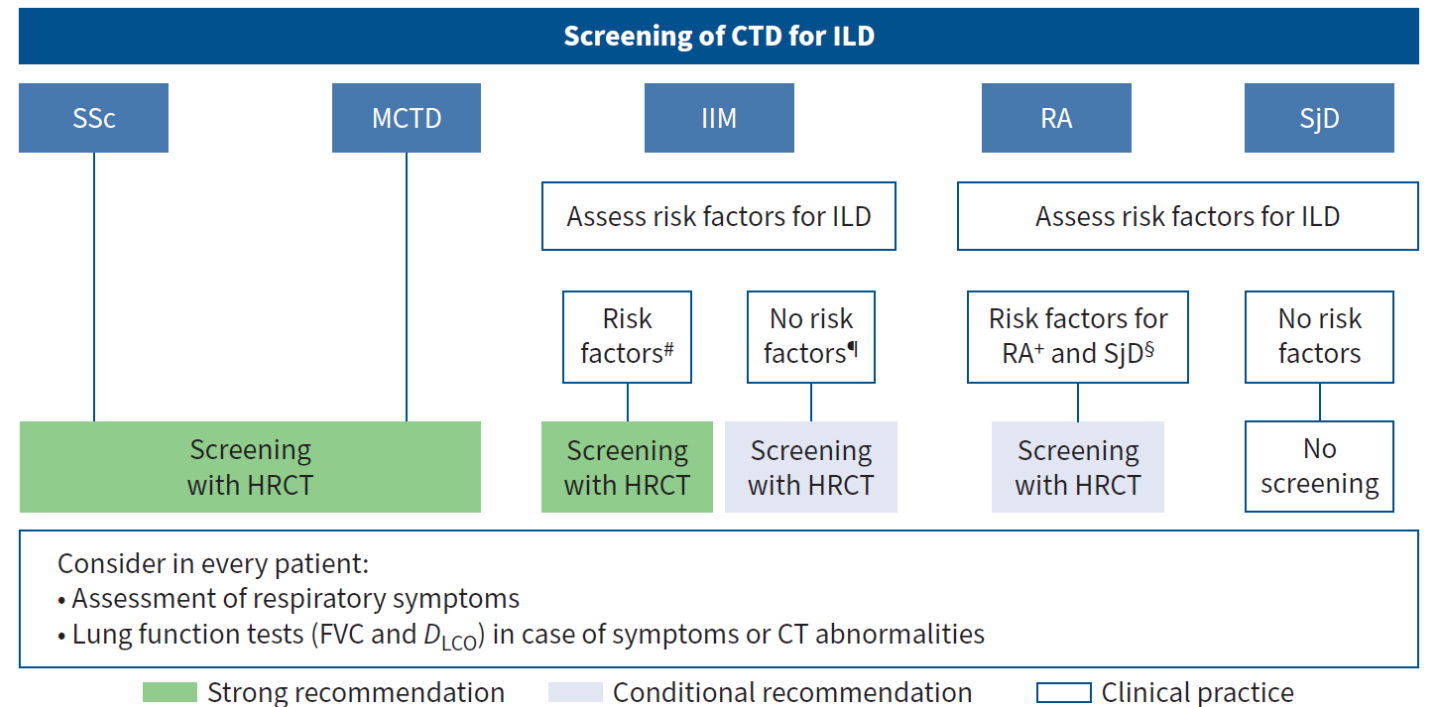
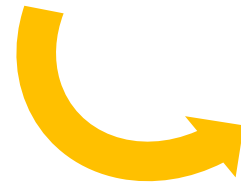


# Screening for ILD in CTD

## ERS/EULAR guideline (Sep, 2025)

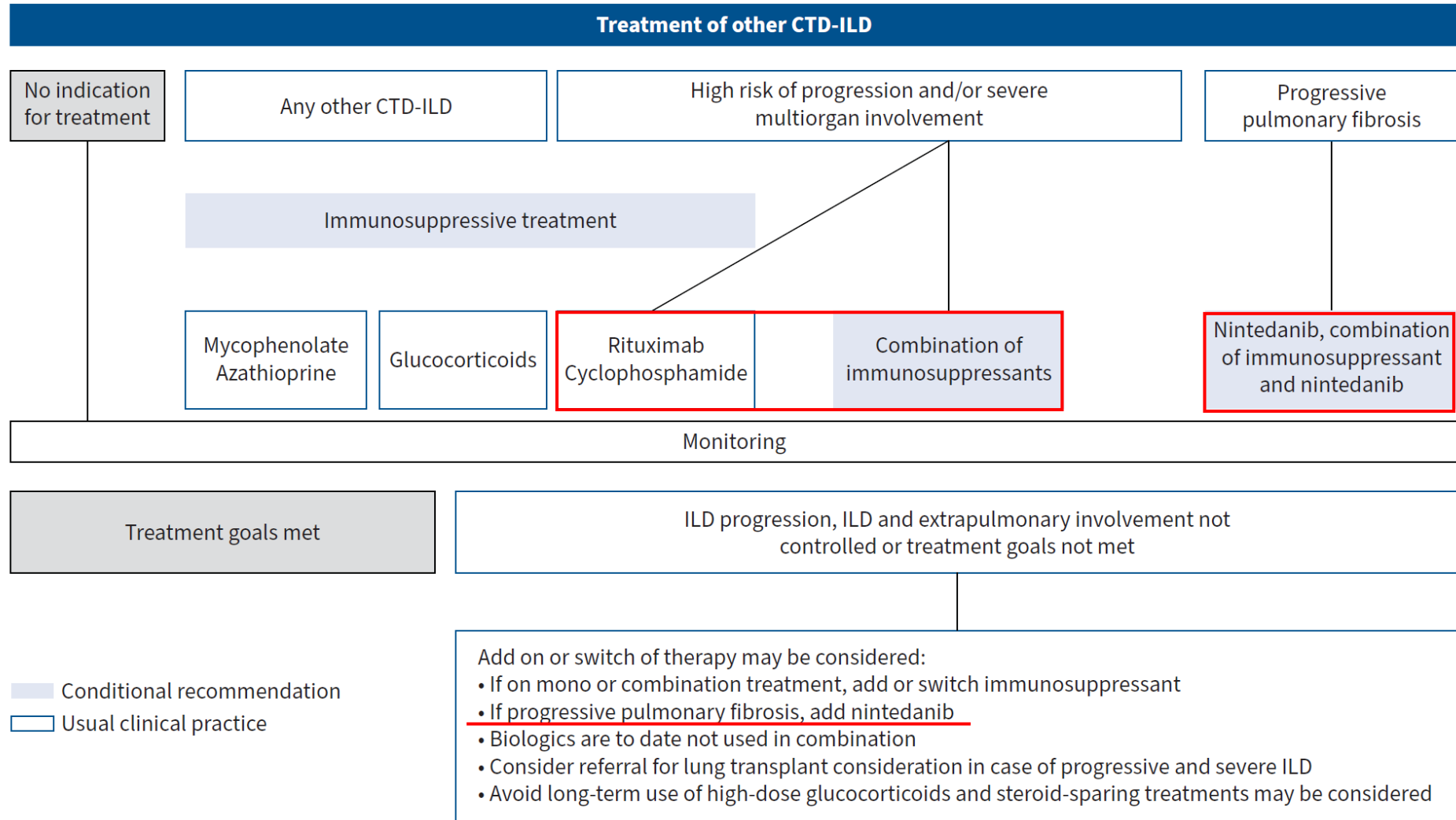
**TABLE 3** Risk factors in patients with connective tissue disease and rheumatoid arthritis (RA) defining an at-risk patient population that should be screened for interstitial lung disease

	SSc	RA	IIM	SjD
<b>Demographics</b>	<ul style="list-style-type: none"> <li>Longer disease duration</li> </ul>	<ul style="list-style-type: none"> <li>Older age</li> <li>Male sex</li> <li>Smoking</li> </ul>	<ul style="list-style-type: none"> <li>Older age</li> </ul>	<ul style="list-style-type: none"> <li>Older age</li> <li>Male sex</li> </ul>
<b>Circulating markers</b>	<ul style="list-style-type: none"> <li>Increased KL-6</li> <li>Presence of ATA-I</li> </ul>	<ul style="list-style-type: none"> <li>Increased ESR</li> <li>Presence of anti-CCP, RF</li> </ul>	<ul style="list-style-type: none"> <li>Increased CRP, ESR</li> <li>Presence of anti-Jo1, anti-MDA-5, anti-Ro52</li> </ul>	<ul style="list-style-type: none"> <li>Increased CRP</li> <li>Presence of anti-Ro52</li> </ul>
<b>Extrapulmonary involvement</b>	<ul style="list-style-type: none"> <li>Diffuse cutaneous SSc</li> <li>Higher mRSS</li> </ul>	<ul style="list-style-type: none"> <li>Higher articular disease activity</li> </ul>	<ul style="list-style-type: none"> <li>Anti-synthetase syndrome</li> <li>Clinical amyopathic dermatomyositis</li> <li>Skin involvement<sup>#</sup></li> <li>Arthritis/arthritis</li> </ul>	<ul style="list-style-type: none"> <li>Presence of extrapulmonary involvement</li> </ul>



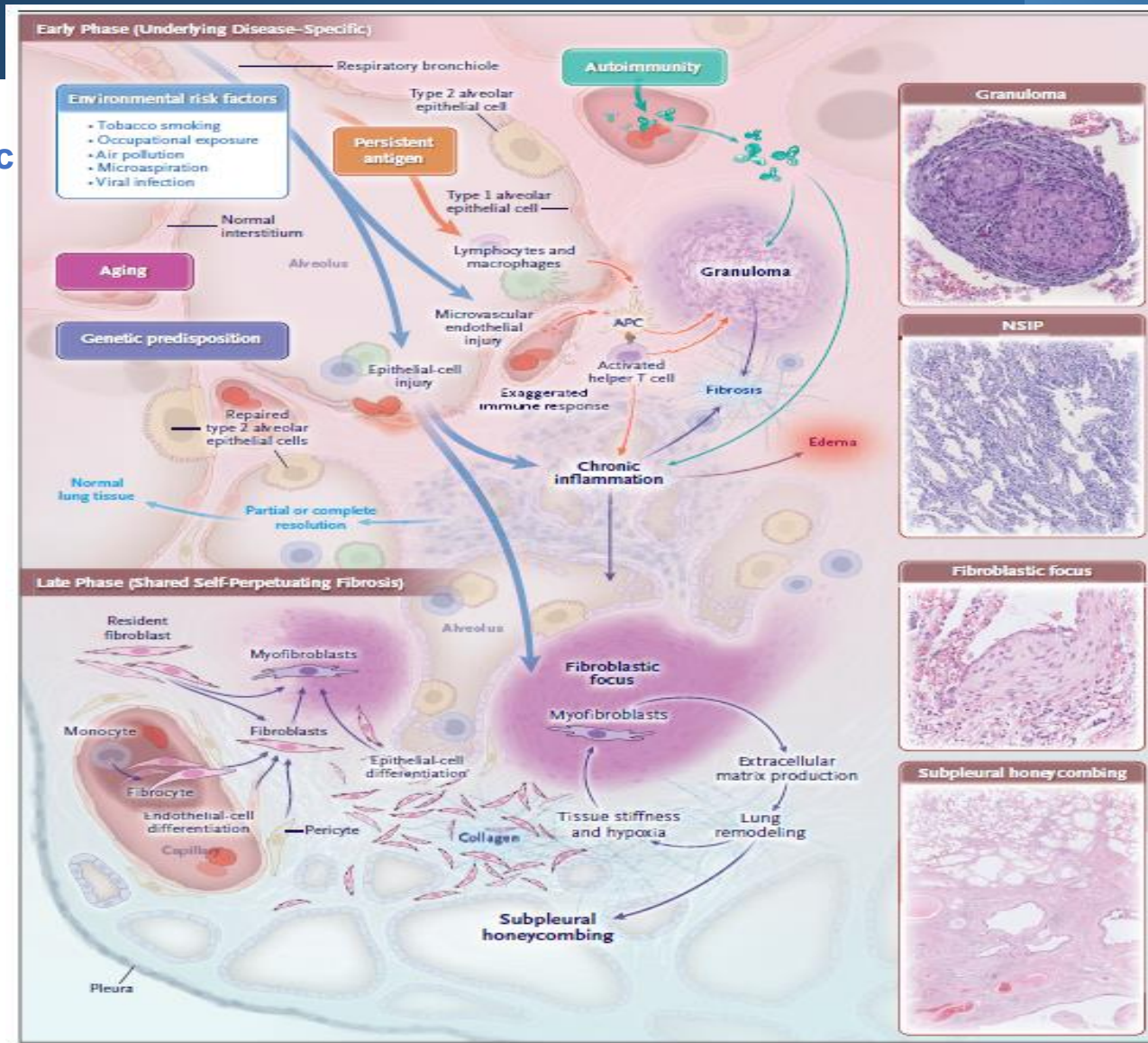
# Treatment for other CTD-ILD

ERS/EULAR guideline (Sep, 2025)



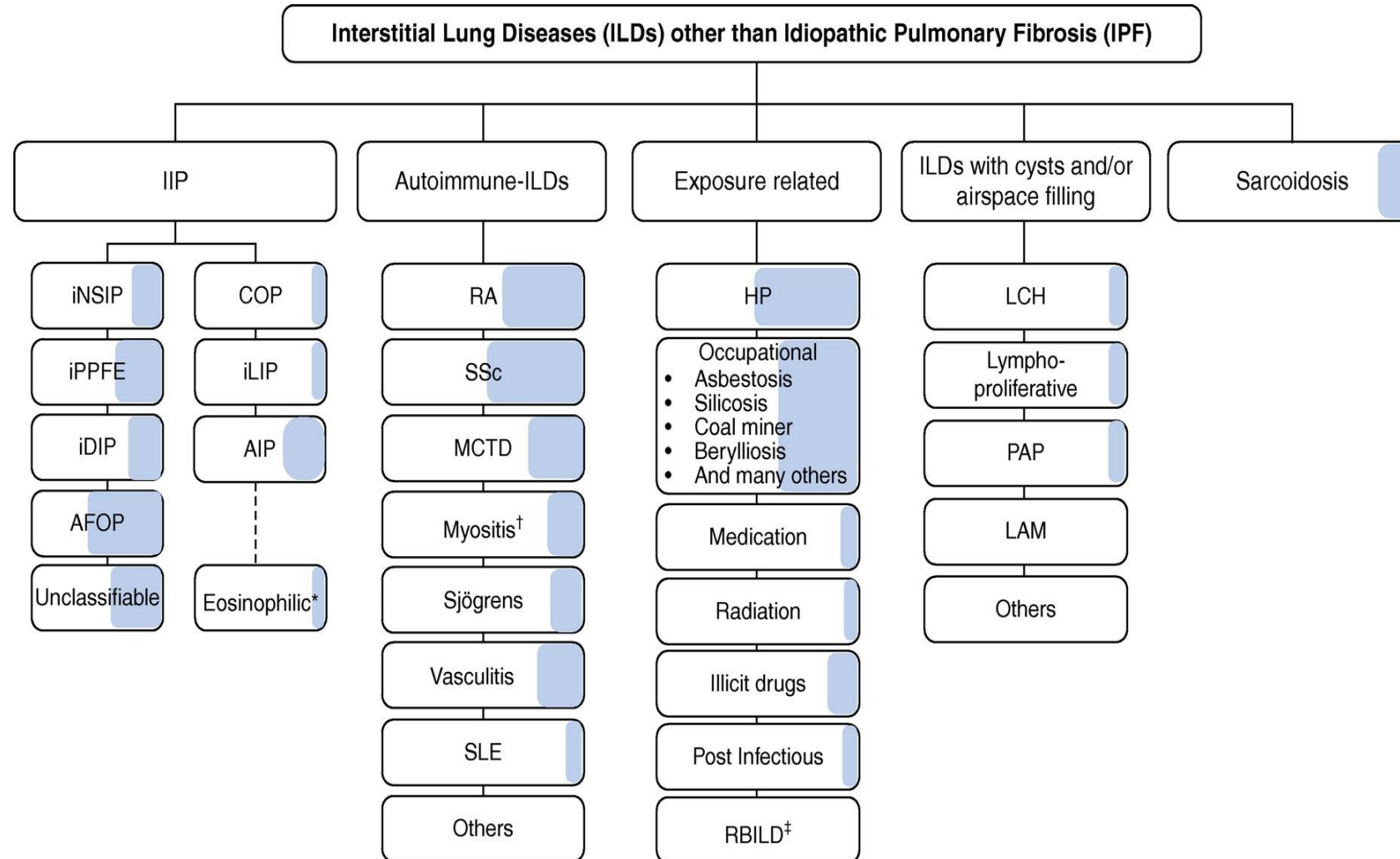
# Pathogenesis of self-perpetuation of pulmonary fibrosis

Early phase  
: Underlying disease-specific

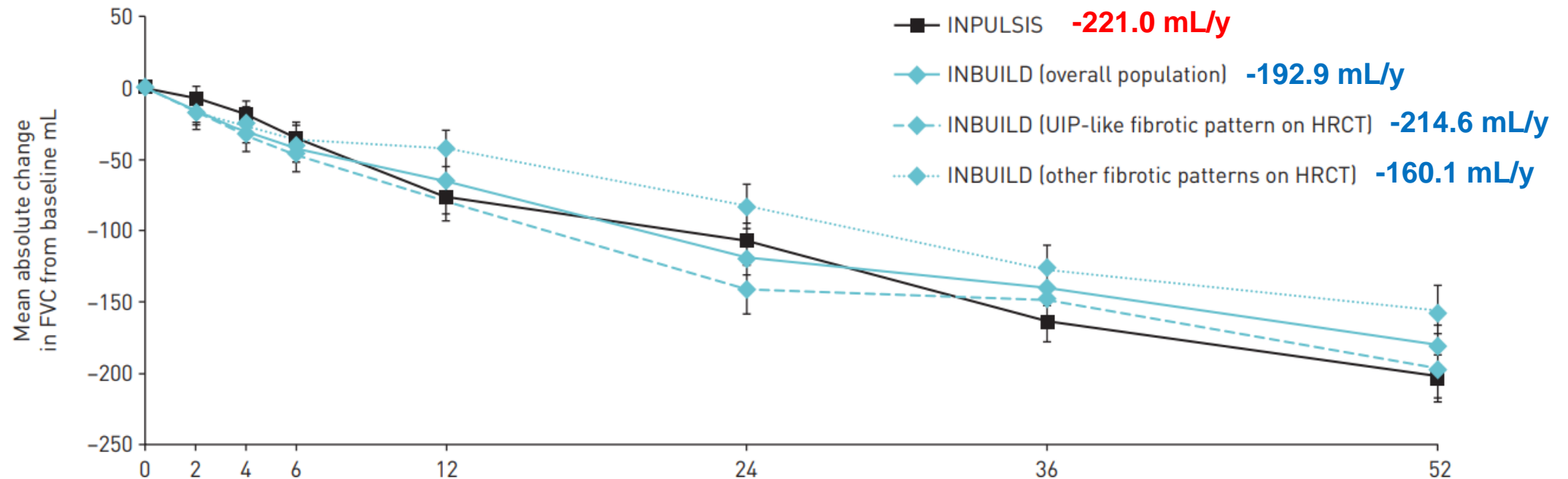


Late phase  
: shared self-perpetuating fibrosis

# ILDs manifesting progressive pulmonary fibrosis (PPF)



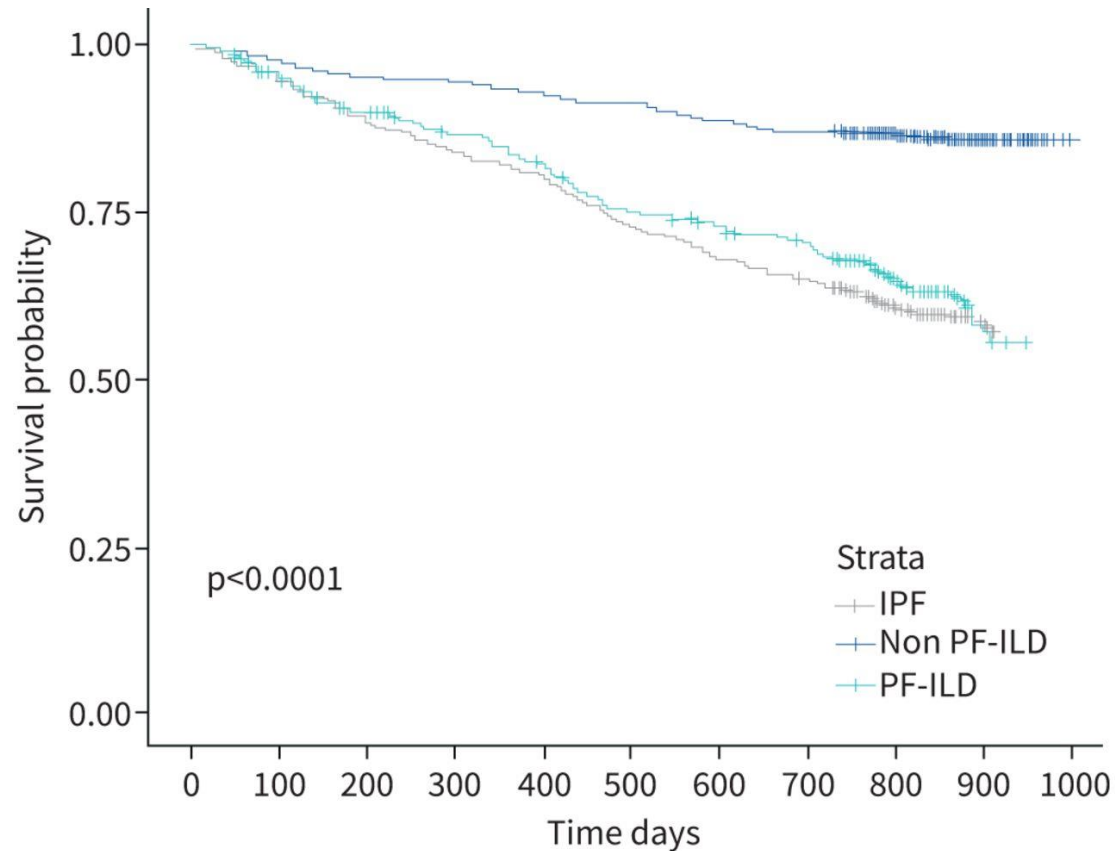
# Natural course of PPF – Lung function



Number of subjects	Week							
	0	2	4	6	12	24	36	52
INPULSIS	417	408	407		403	395	383	345
INBUILD (overall population)	325	326	325		320	311	296	274
INBUILD (UIP-like fibrotic pattern)	202	202	201		197	190	176	162
INBUILD (other fibrotic patterns)	123	124	124		123	121	120	112

# Natural course of PPF – Mortality

PF-ILD in UK (9 centres): 14.5% (253 out of 1,749) by *INBUILD* criteria  
: cHP (33.2%), uILD (17.3%), CTD-ILD (16.6%), others (14.2%)



- **Mortality of PF-ILD**

- HR, 3.32 (95% CI, 2.53 – 4.37)

- compared to non-progressive ILD

- **HR 1.06** (95% CI, 0.84-1.35)

- compared to IPF**

# International guidelines ATS/ERS/JRS/ALAT (2022)

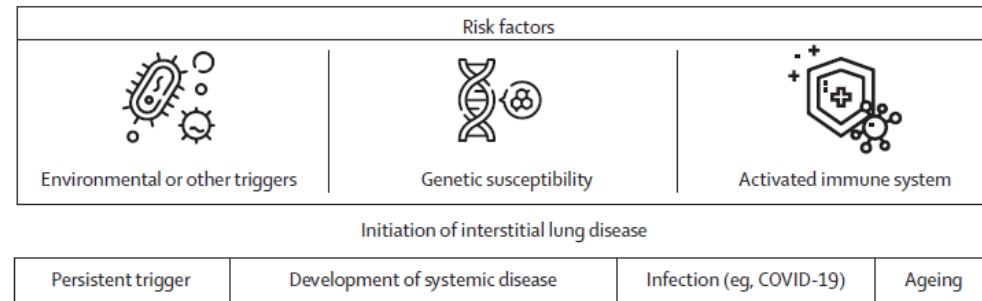
## “Progressive pulmonary fibrosis (PPF)”

### Definition of PPF

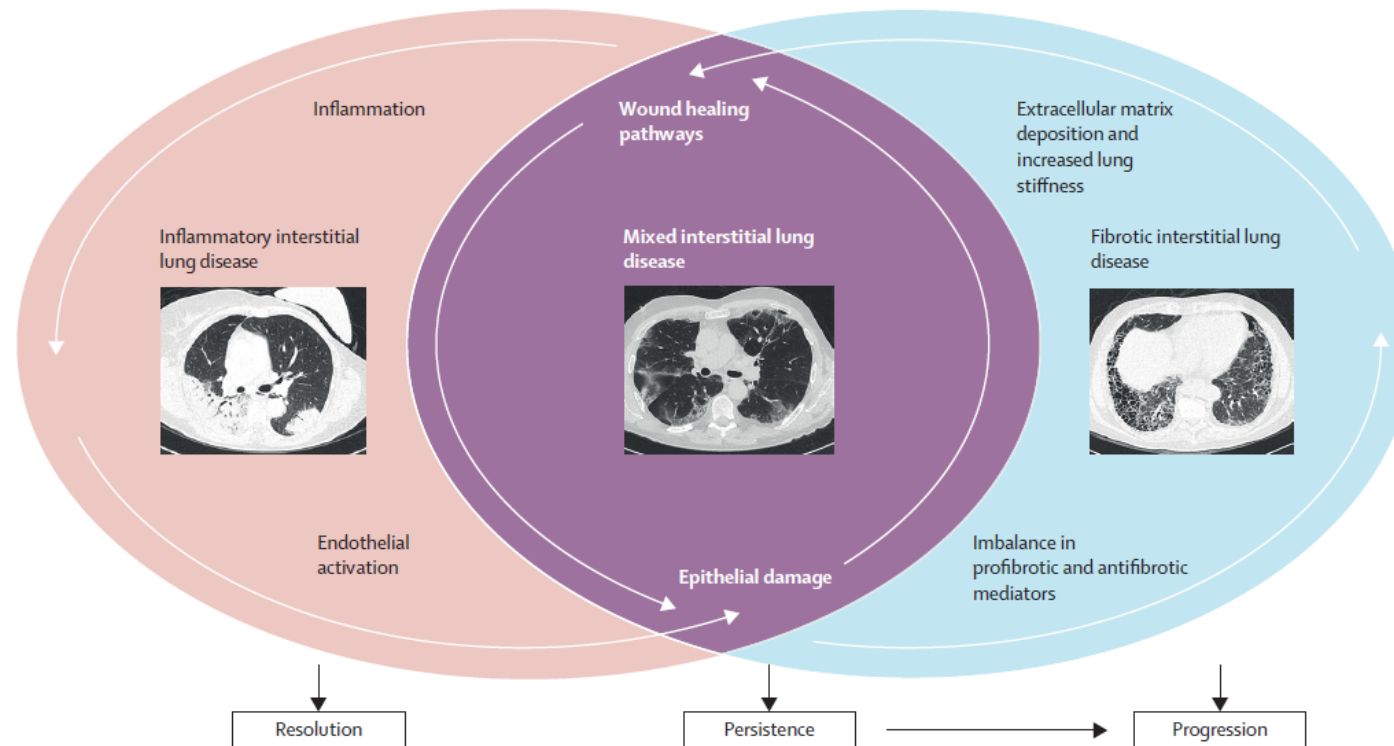
In a patient with ILD of known or unknown etiology other than IPF who has radiological evidence of pulmonary fibrosis, PPF is defined as **at least two of the following three criteria occurring within the past year** with no alternative explanation\*:

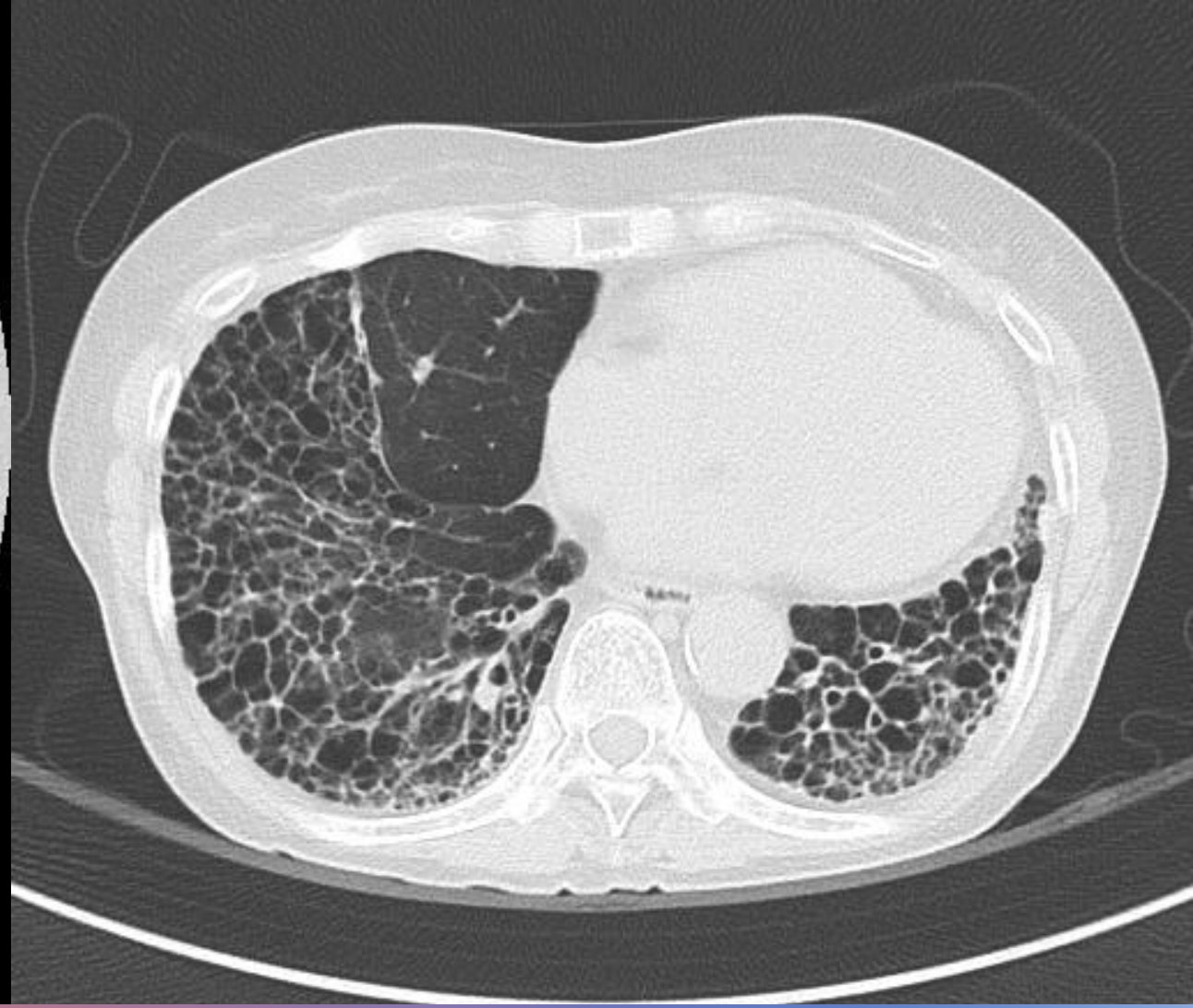
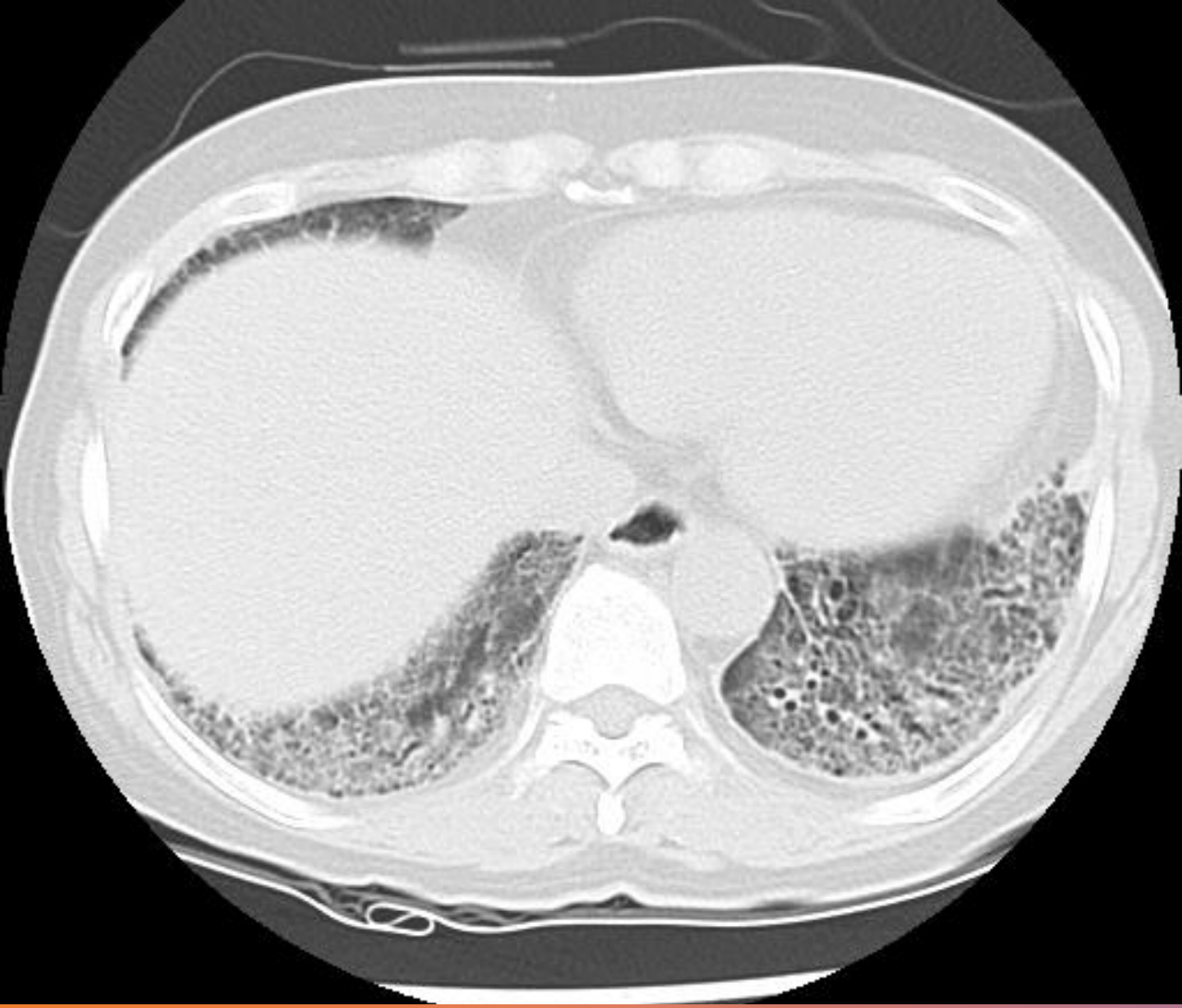
- 1 **Worsening respiratory symptoms**
- 2 **Physiological evidence** of disease progression (either of the following):
  - a. Absolute decline in **FVC  $\geq 5\%$  predicted** within 1 yr of follow-up
  - b. Absolute decline in **DL<sub>CO</sub> (corrected for Hb)  $\geq 10\%$  predicted** within 1 yr of follow-up
- 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

# Different phenotype -Inflammation vs. Fibrosis



Inflammation  
ex) Autoimmune disease





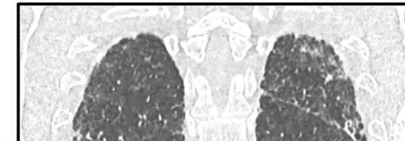
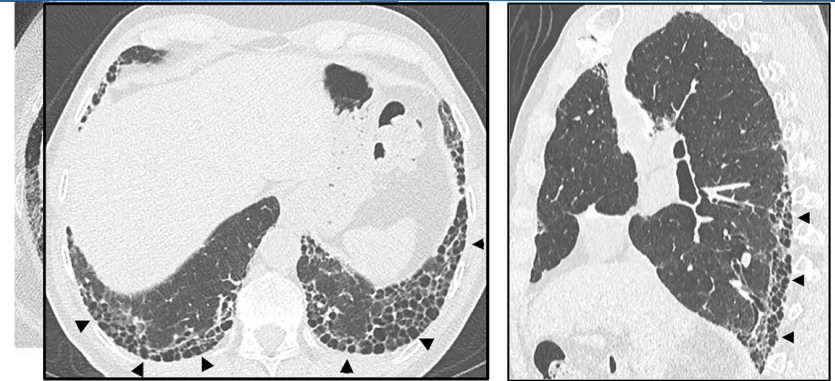
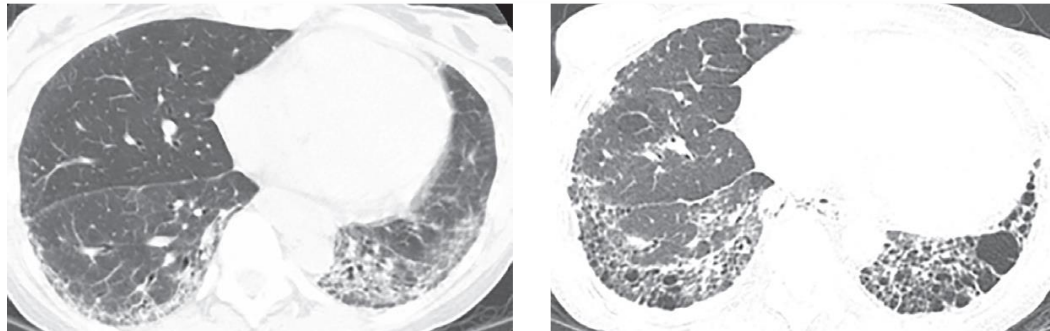
Are Symptom and Physiologic Decline Enough to Define PPF?

# Radiologic criteria for PPF

## Definition of PPF

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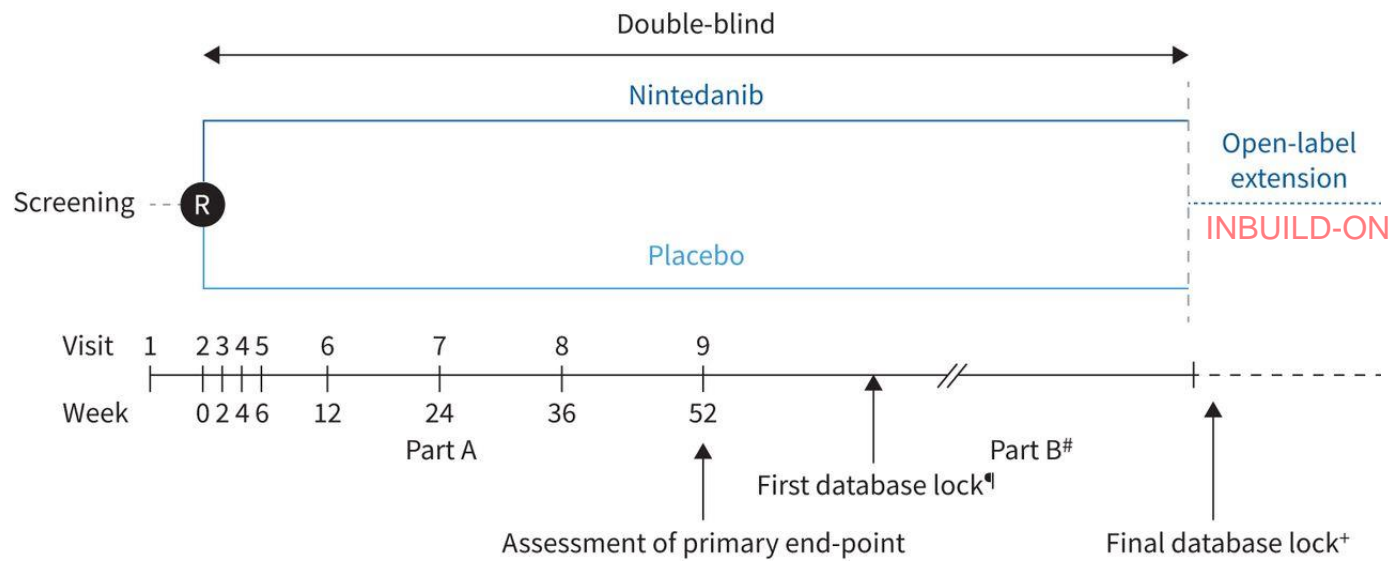
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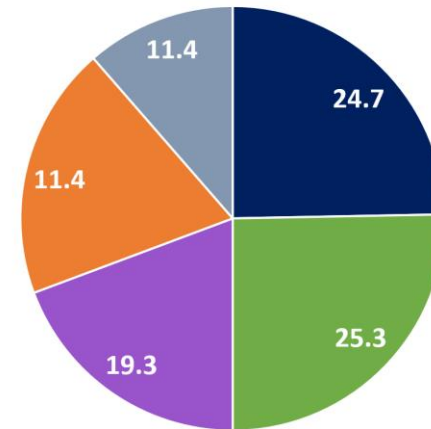
# Nintedanib in PPF

663 patients with PF-ILD (**non IPF ILD**) in 15 countries

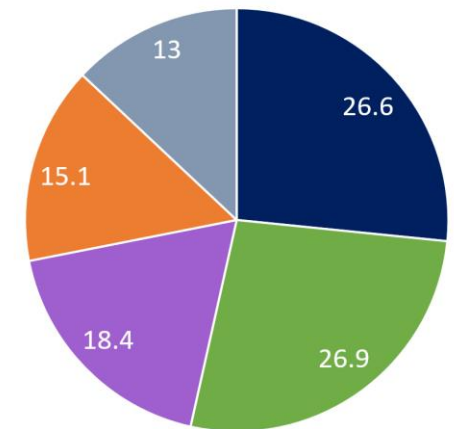
## INBUILD trial design



Nintedanib (n=332)

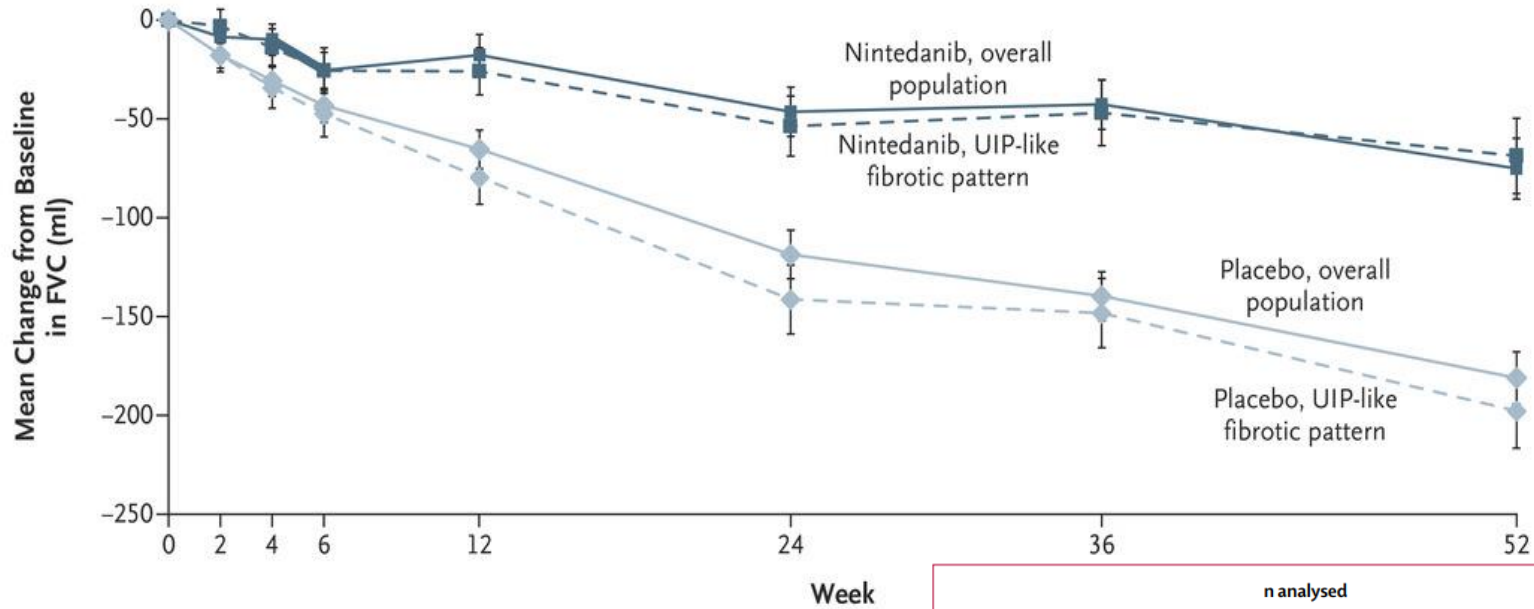


Placebo (n=331)



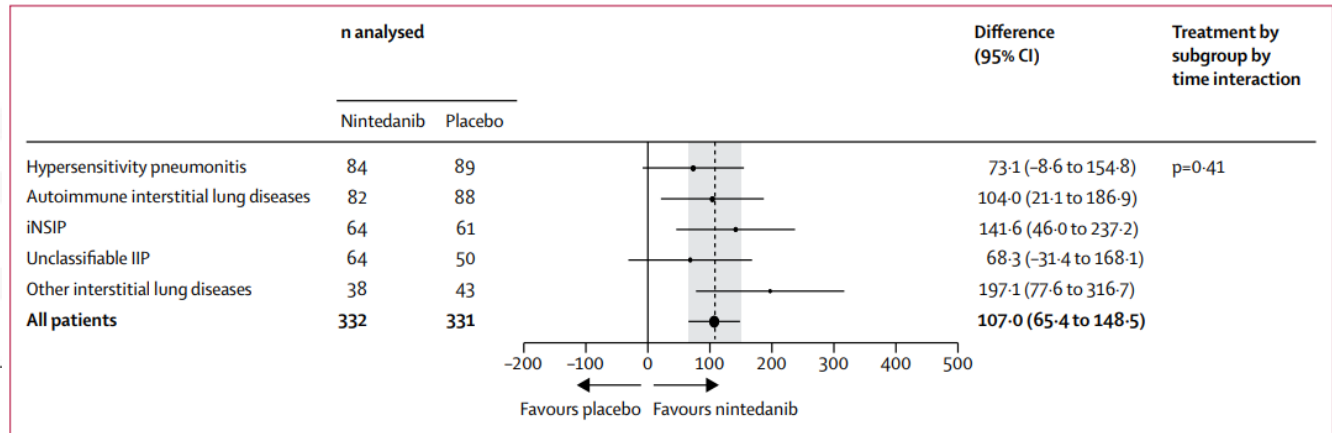
- Autoimmune ILDs
- HP
- Unclassifiable IIP
- Idiopathic NSIP
- Other ILDs

# Nintedanib slowed the rate of lung function decline

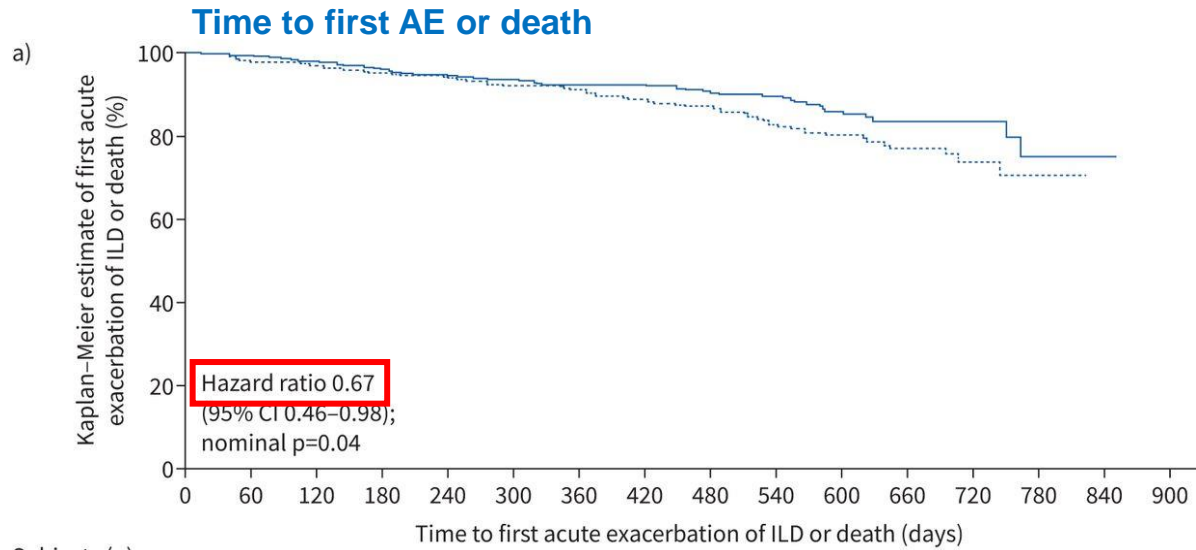


## No. of Patients

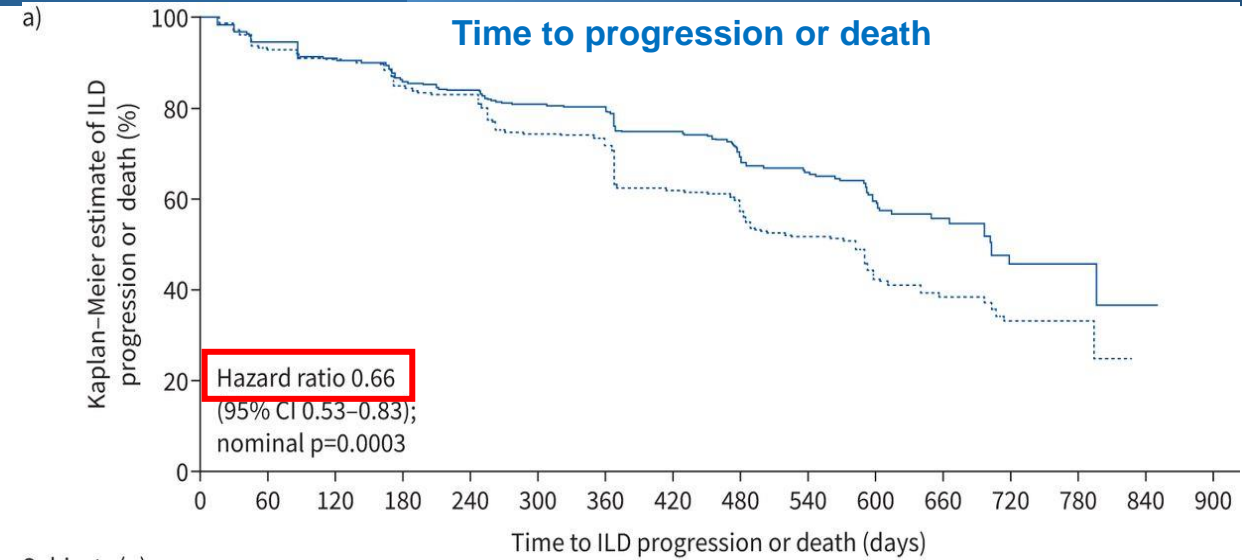
	0	2	4	6	12	24	36	52
<b>Overall population</b>								
Nintedanib	332	326	320	322	314	298		
Placebo	331	325	326	325	320	311		
<b>Patients with UIP-like fibrotic pattern</b>								
Nintedanib	206	203	200	199	193	180		
Placebo	206	202	202	201	197	190		



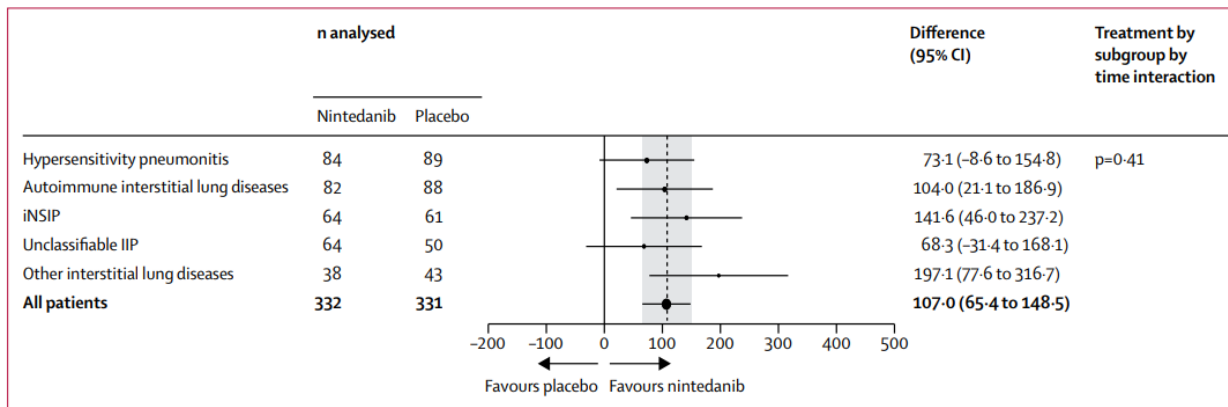
# Nintedanib reduced mortality



Subjects (n):	0	60	120	180	240	300	360	420	480	540	600	660	720	780	840	900
Nintedanib	332	330	325	318	314	309	305	303	268	194	127	81	35	14	1	0
Placebo	331	325	320	314	311	302	298	290	252	171	121	77	35	13	0	0



Subjects (n):	0	60	120	180	240	300	360	420	480	540	600	660	720	780	840	900
Nintedanib	332	314	301	285	279	267	261	245	200	143	85	52	22	7	1	0
Placebo	331	309	299	280	274	243	234	203	163	104	65	38	17	6	0	0



# Nintedanib in Korea

구 분	세부인정기준 및 방법
[229]  Nintedanib 경구제 (품명 : 오펜브연질캡슐 100밀리그램, 150밀리그램)	<p>허가사항 범위 내에서 아래와 같은 기준으로 투여 시 요양급여를 인정하며, 동 인정기준 이외에는 약값 전액을 환자가 부담토록 함.</p> <p style="text-align: center;">- 아 래 -</p> <p>○ 진행성 표현형을 나타내는 만성 섬유성 간질성 폐질환</p> <p>1. 투여대상</p> <p>고해상 흉부전산화단층촬영(HRCT)으로 확인된 만성 섬유성 간질성 폐질환 환자로서 다음 조건을 모두 만족하는 경우 (단, 특별성폐섬유증은 제외함.)</p> <p style="text-align: center;">- 다 음 -</p> <p>1) Predicted forced vital capacity(FVC) 45% 이상</p> <p>2) Predicted carbon monoxide diffusing capacity(DLco) 30% 이상이고 80% 미만</p> <p>3) 기존치료(스테로이드, 면역억제제 등)에도 불구하고 최근 24개월 이내 가), 나), 다) 중 하나 이상이 확인된 경우</p> <p>가) relative decline in predicted FVC(%)가 10% 이상</p> <p>나) <math>5\% \leq \text{relative decline in predicted FVC}(\%) &lt; 10\%</math> 이면서, 호흡기 증상의 악화</p> <p>다) <math>5\% \leq \text{relative decline in predicted FVC}(\%) &lt; 10\%</math> 이면서, HRCT에서의 섬유화 진행</p> <p>2. 평가방법</p> <p>치료 시작 후 12개월마다 평가(HRCT 및 폐기능검사)를 하여야 함.</p>

## 2025.05 ~ PF-ILD 에서 Nintedanib 급여화

구 분	세부인정기준 및 방법
	<p>3. 투여 중지기준</p> <p>반응평가를 실시하여 질병 진행(12개월 이내 Predicted FVC가 10% 이상 절대적 감소(absolute decline)하면서 HRCT 악화 소견)이 확인되는 경우 투여를 중단함.</p>

# 증례 #2

- Case 1 : 한 달 전부터 시작된 기침, 호흡곤란으로 내원한 환자
- **Case 2 : 30년 전 수술적 폐생검 후 간질성 폐질환 진단, 이후 추적 중단된 상태에서 한 달 전부터 갑자기 악화된 호흡곤란을 주소로 내원한 환자**

# F/75

2025-12-01 dyspnea 로 ER visit

**Chief complaint)** dyspnea, mMRC 3

**Present illness)**

1997 – 2019 년까지 호흡기내과 ILD 로 추적하던 분, 이후 follow-up loss 로 일상생활에 무리없이 지내시던 중, 1개월 전 허리 통증으로 injection 시술 후부터 점차 dyspnea 악화되었다고 함

# Past medical history

## Past medical history)

1997년 구차트 스캔: CT multifocal consolidation 으로 입원, Open lung biopsy 시행, organizing pneumonia 로 결과 보고, 이후 annual CT FU 하던 중 2019 년부터 추적 종료되며 폐에 대한 진료는 loss 된 상태로 지냄

## Social history)

**Smoking:** Never smoker

**Alcohol:** non-alcoholic

**Occupation:** 국어 교사, 이후 전업 주부

**Family history)** denied

# Review of system

Cough – sputum –

Dyspnea (+), mMRC 3, 1개월 전 발생, 점차 악화

관절 부종 (-) 관절통(-) 근 위약 (-)

입 마름 (+) 눈 마름(+)

피부 발진 (-)

레이노 (-)

# Physical examination

**Vital sign)** 151/93 mmHg-101/min-20/min-36.7°C, SpO2 82% at ambient air → O2 4L/min apply

**General)** alert, Skin rash (-)

**Chest)** inspiratory crackle, BLLF

## **Extremities)**

Digit deformity +/-

both leg pitting edema +/-



# Initial laboratory results

CBC : 8390 – 14.9 – 200k, ANC 5340

AST/ALT 29/23

BUN/Cr 12 / 0.62

CRP 0.62

ABGA (O2 2L/min) : pH 7.456, pCO2 29 mmHg, pO2 61 mmHg, HCO3 20 mmol/L, Sat 93%

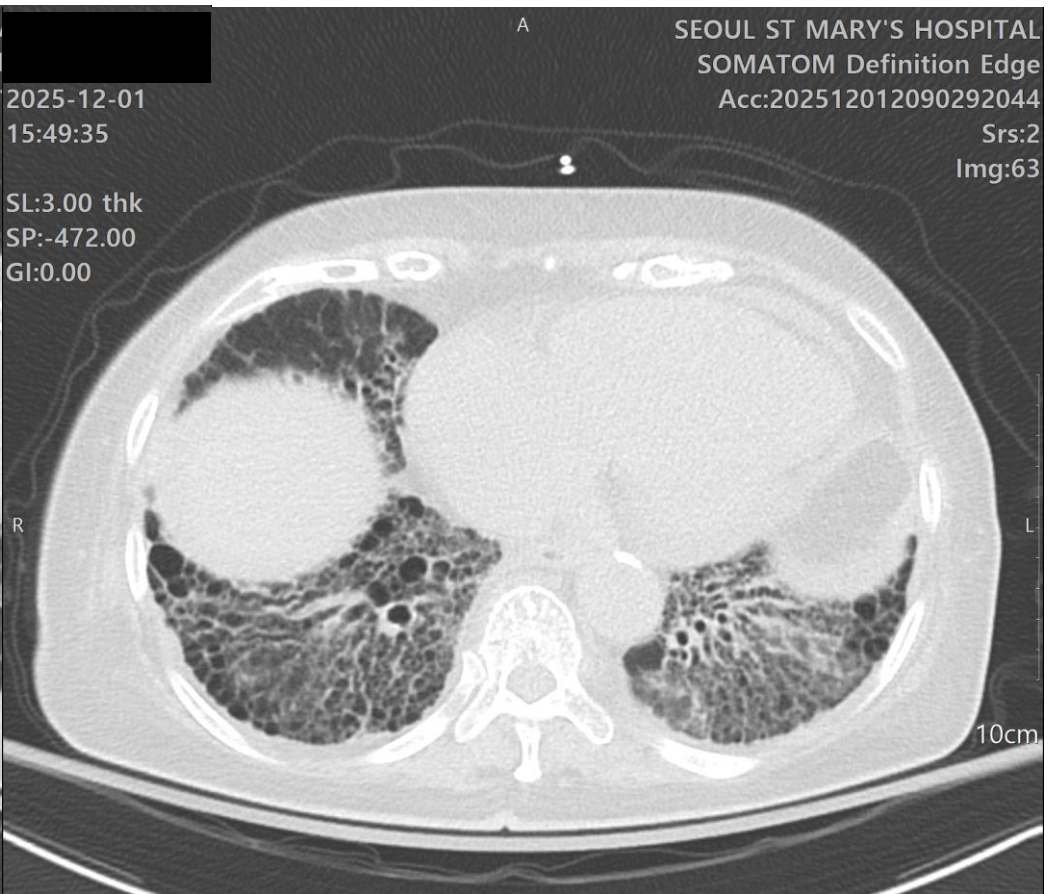
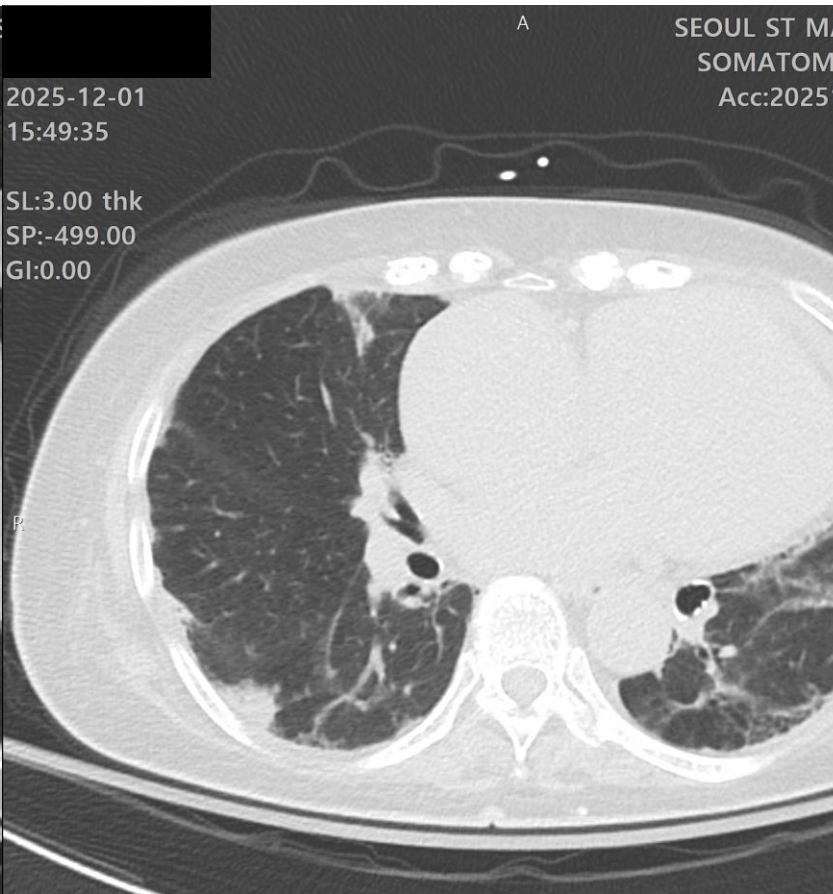
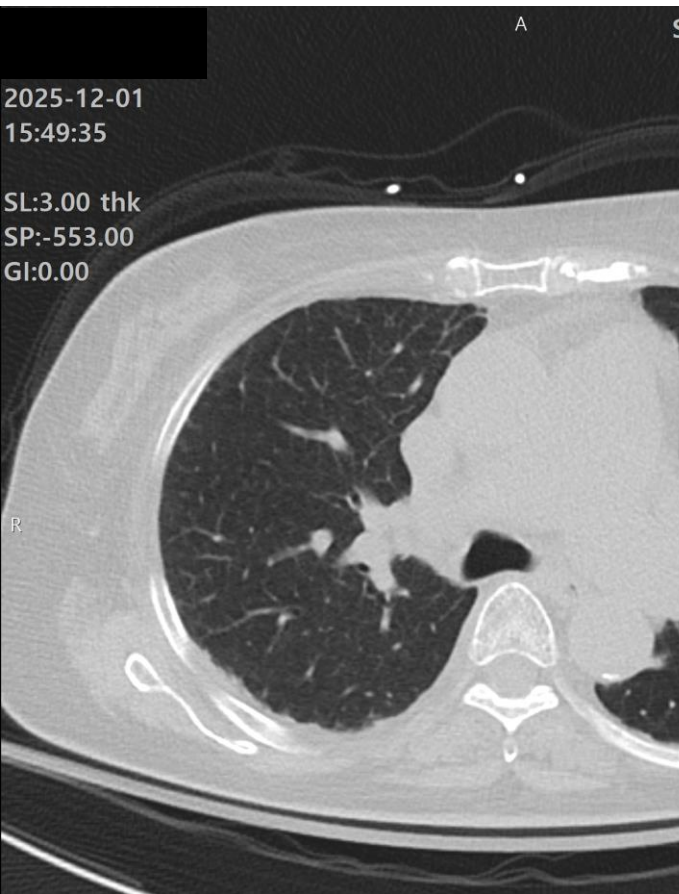
Troponin T: 0.015 ng/mL, CK-MB : 0.27 ng/mL

NT-ProBNP 4065 pg/mL

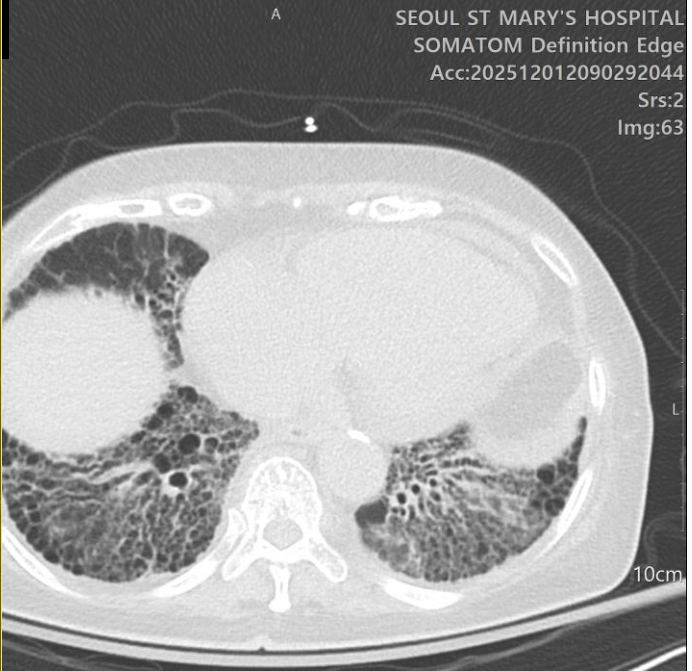
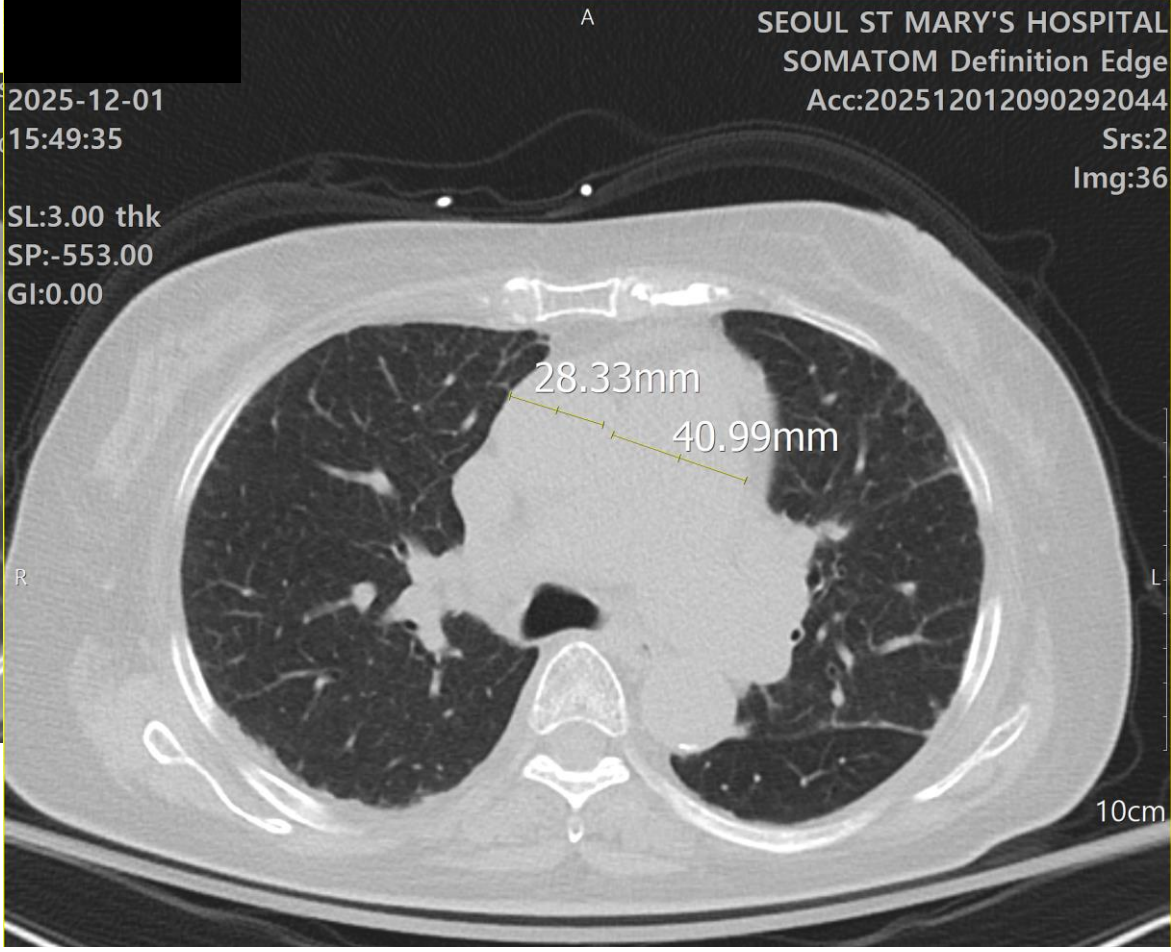
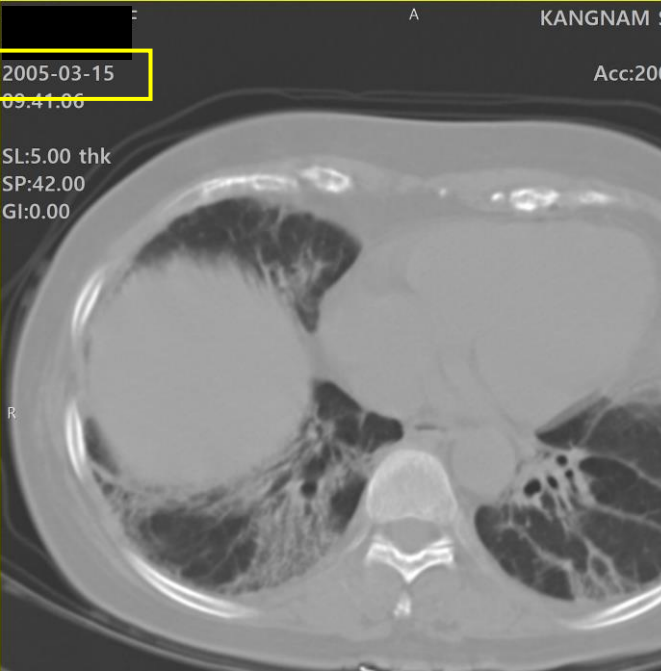
D-dimer : 0.85

KL-6 : 177 U/mL

# Initial Chest CT



# Comparison with old CT



# Special laboratory results

ANA : positive, cytoplasmic, nuclear, 1:320

Anti-SS-A 52 : 3+

Anti-Jo1 : 3+

RA factor : 7.8

Anti-CCP Ab : negative

C3/C4 : 99 / 17.6 mg/dL

IgG/A/M : 1723 / 294 / 138 mg/dL

ANCA : negative

# Special examination

## Spirometry

FVC 1.73 L (66%)

FEV<sub>1</sub> 1.28 L (68%)

FEV<sub>1</sub>/FVC ratio 0.74

TLC 3.31 L (79%)

DLCO 26%

## Sono Salivary gland

Parotid gland, both, Grade 1

Submandibular gland, both, Grade 2

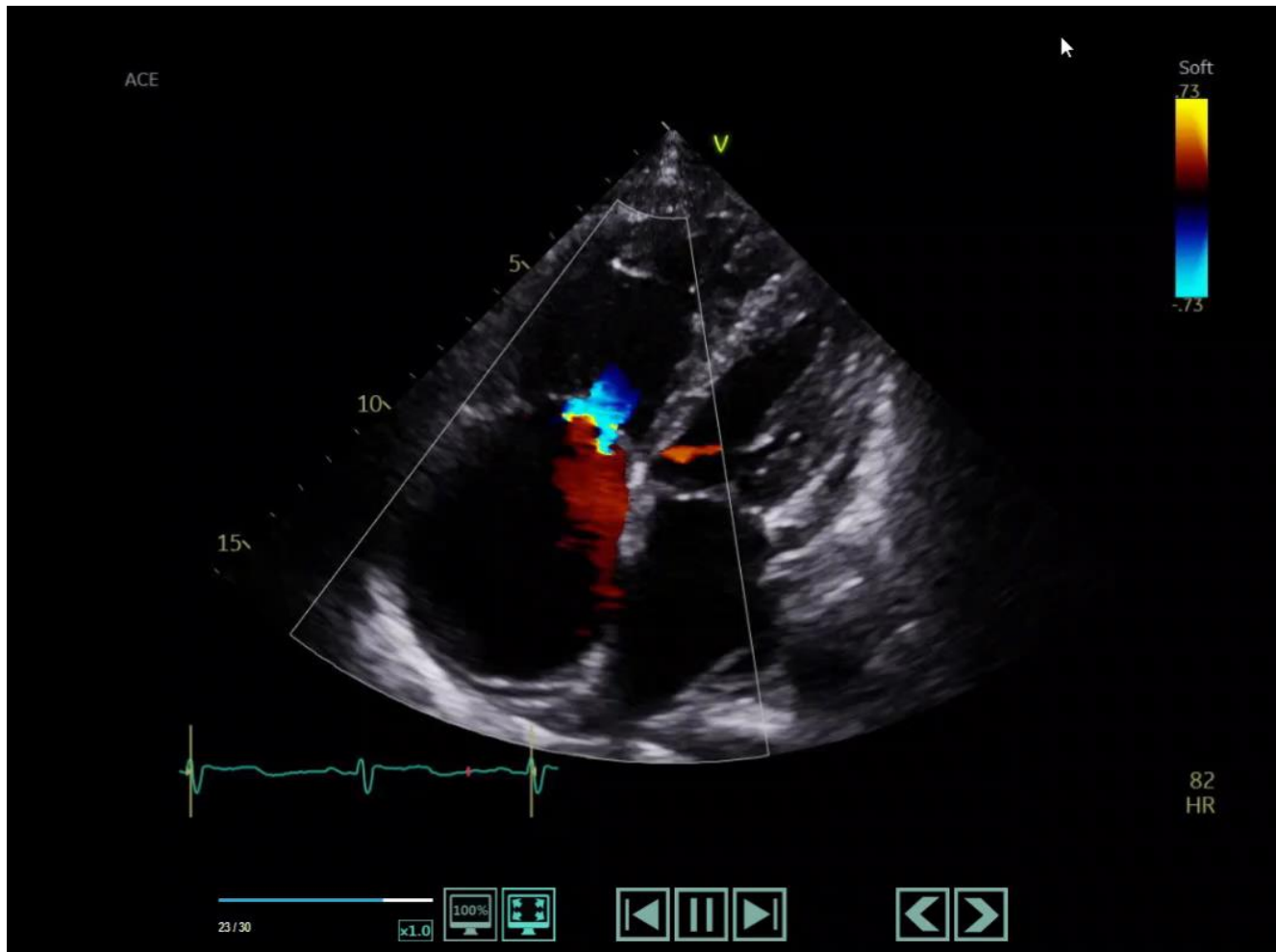
→ Consistent with Sjogren's syndrome

## Salivary flow test

- Unstimulated saliva : 0.01 ml/5min  
→ **0.106 mL/min** (normal : ≥ 0.1–0.3 mL/min)

→ *Suggestive of primary Sjogren's syndrome*

# Echocardiography



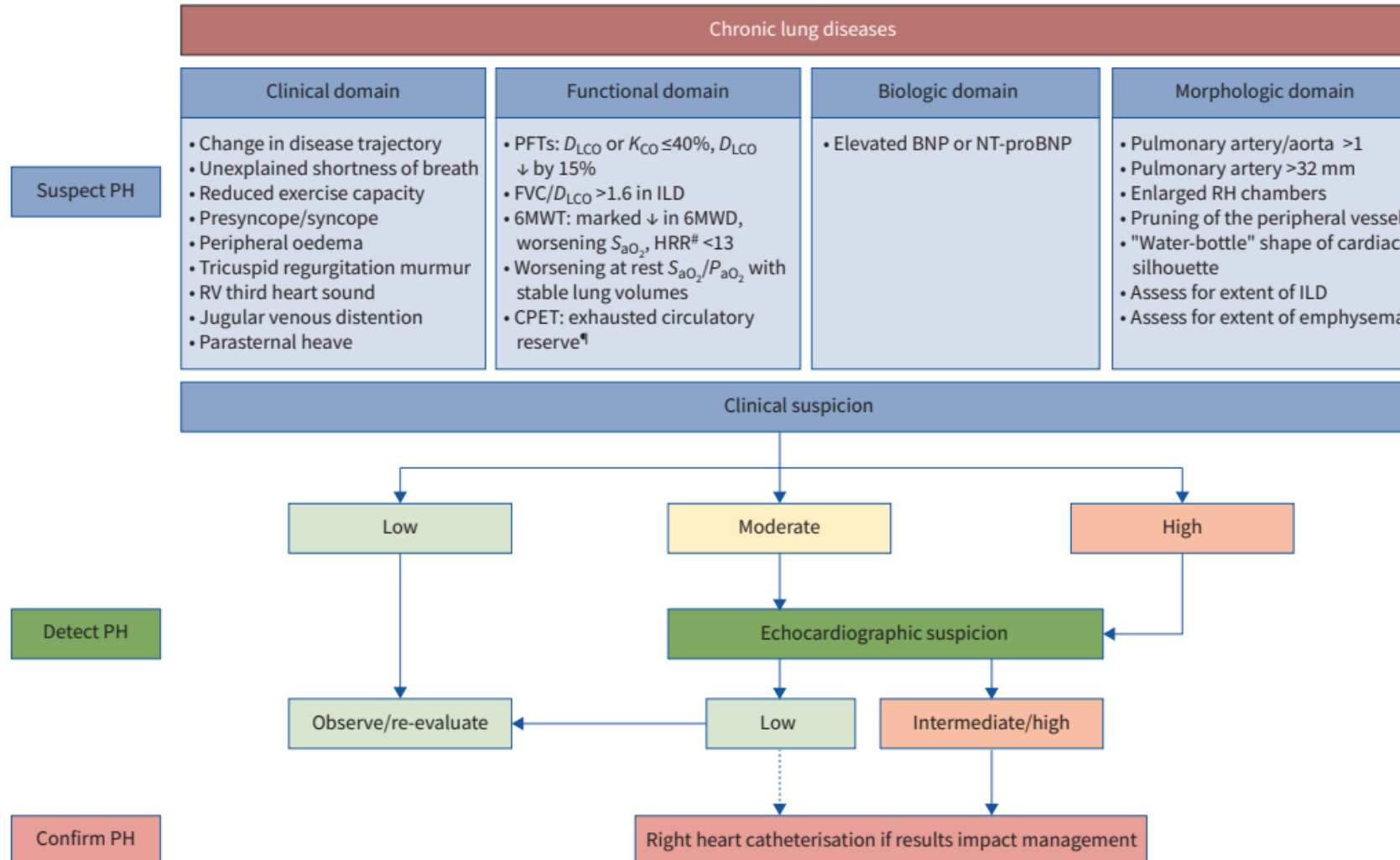
## Echocardiography

1. severe PH (TR Vmax 3.9 m/s, RVSP = 76mmHg),  
**maybe underlying Lung disease**
2. RV dilatation with mild RV dysfunction
3. RA dilatation
4. scanty pericardial effusion

→ Evidence of PTE excluded on Chest CT

→ PH due to lung disease ? RHC is not necessary ?

# Diagnostic algorithm for PH in chronic lung disease



# Rt heart catheterization (RHC)

- Gold standard to confirm PH
- Inconclusive echoCG findings in case with a high level of suspicion and potential therapeutic implications.



In patients with lung disease and suspected PH, it is recommended to optimize treatment of the underlying lung disease and, where indicated, hypoxaemia, sleep-disordered breathing, and/or alveolar hypoventilation

I

C

In patients with lung disease and suspected PH, RHC is recommended if the results are expected to aid management decisions

I

C

# RHC results

성별 : 여

신장 : 151 cm

체중 : 51 kg

체표면적(BSA) : 1.45 m<sup>2</sup>

검사시행일 : 2025-12-04

## 검사정보

정맥접근위치 : Rt. JV

산소공급 : 3 l/min

심박수 (Heart Rate) : 82 BPM

우심방압 평균 (RA Pressure) : 6 mmHg

## 폐동맥압

폐동맥압 수축기 (sPAP) : 61 mmHg

폐동맥압 이완기 (dPAP) : 26 mmHg

폐동맥압 평균 (meanPAP) : 36 mmHg

폐동맥 쇄기압 평균 (meanPAWP) : 10 mmHg

폐순환 평균 압력차 (TPG) : 26 mmHg

폐순환 이완기 압력차 (DPG) : 16 mmHg

대동맥 수축기압 (sBP) : 148 mmHg

대동맥 이완기압 (dBP) : 76 mmHg

대동맥 평균압 (mBP) : 107 mmHg

심박출량 (Cardiac Output) : 2.3 l/min

심박출량지수 (Cardiac Output Index) : 1.6 l/min/m<sup>2</sup>

폐혈관저항 (PVR), WU : 11.3

체혈관저항 (SVR), WU : 42.6

저항비 (PVR/SVR) : 3.76

동맥혈 산소포화도 (Art O<sub>2</sub> Sat) : 100 %

혼합정맥 산소포화도 (Ven O<sub>2</sub> Sat) : 66.7 %

헤모글로빈 (Hb) : 13.4 g/dl

## 검사후 결론

(RVSP : 62mmHg)

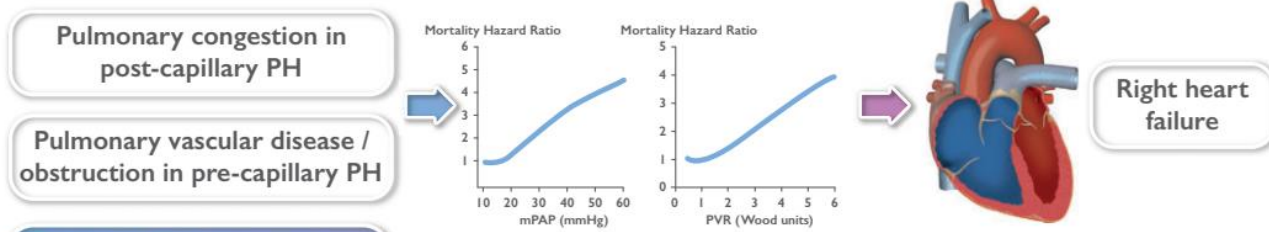
precapillary PH

PH d/t chronic lung disease ?

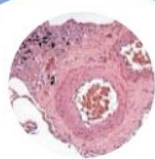




Treat underlying lung disease ?

# Classification of PH

2022 ESC/ERS Guidelines



## CLINICAL CLASSIFICATION

<p><b>Pulmonary arterial hypertension (PAH)</b></p>  <ul style="list-style-type: none"> <li>• Idiopathic/heritable</li> <li>• Associated conditions</li> </ul>	<p><b>PH associated with left heart disease</b></p>  <ul style="list-style-type: none"> <li>• IpcPH</li> <li>• CpcPH</li> </ul>	<p><b>PH associated with lung disease</b></p>  <ul style="list-style-type: none"> <li>• Non-severe PH</li> <li>• Severe PH</li> </ul>	<p><b>PH associated with pulmonary artery obstructions</b></p>  <ul style="list-style-type: none"> <li>• CTEPH</li> <li>• Other pulmonary obstructions</li> </ul>	<p><b>PH with unclear and/or multifactorial mechanisms</b></p>  <ul style="list-style-type: none"> <li>• Haematological disorders</li> <li>• Systemic disorders</li> </ul>
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## THERAPEUTIC STRATEGIES

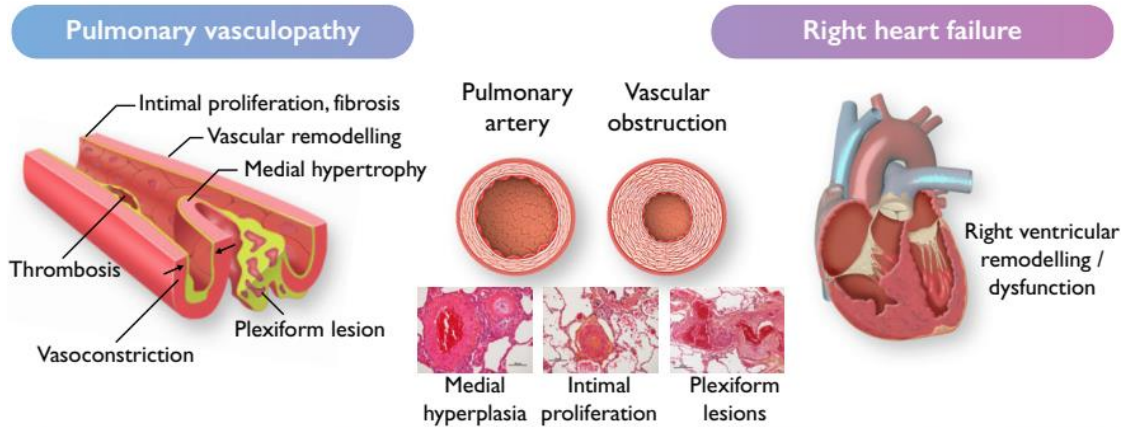
<p><b>Medical therapy</b></p> <ul style="list-style-type: none"> <li>• PAH drugs</li> <li>• CCB in responders</li> </ul> <p><b>Lung transplantation</b></p>	<p><b>IpcPH:</b></p> <ul style="list-style-type: none"> <li>• Treatment of LHD<sup>a</sup></li> </ul> <p><b>CpcPH:</b></p> <ul style="list-style-type: none"> <li>• Treatment of LHD<sup>a</sup></li> <li>• Potentially: PAH drugs (trials)</li> </ul>	<p><b>PH-lung disease:</b></p> <ul style="list-style-type: none"> <li>• Optimized care of underlying lung disease</li> </ul> <p><b>Severe PH:</b></p> <ul style="list-style-type: none"> <li>• Potentially: PAH drugs (trials)</li> </ul>	<p><b>Surgical therapy:</b></p> <ul style="list-style-type: none"> <li>• PEA</li> </ul> <p><b>Interventional:</b></p> <ul style="list-style-type: none"> <li>• BPA</li> </ul> <p><b>Medical therapy:</b></p> <ul style="list-style-type: none"> <li>• PH drugs</li> </ul>	<p><b>Optimized treatment of underlying disease</b></p> <ul style="list-style-type: none"> <li>• Potentially: PAH drugs (trials)</li> </ul>
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**Group 1 (PAH)**

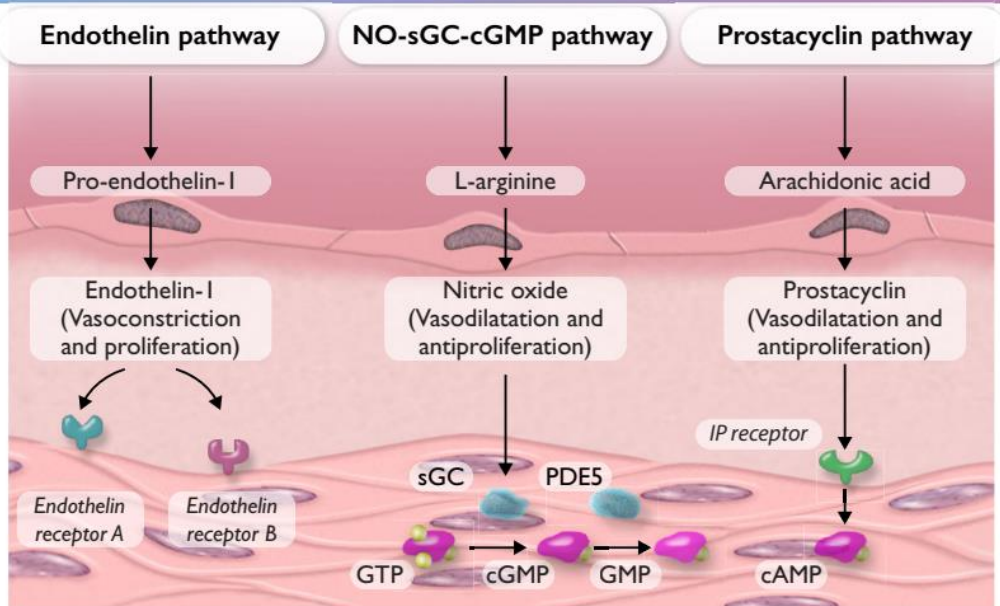
VS

**Group 3 (PH associated with lung disease)**

# Pathophysiology and current therapeutic targets of PAH (Group 1)



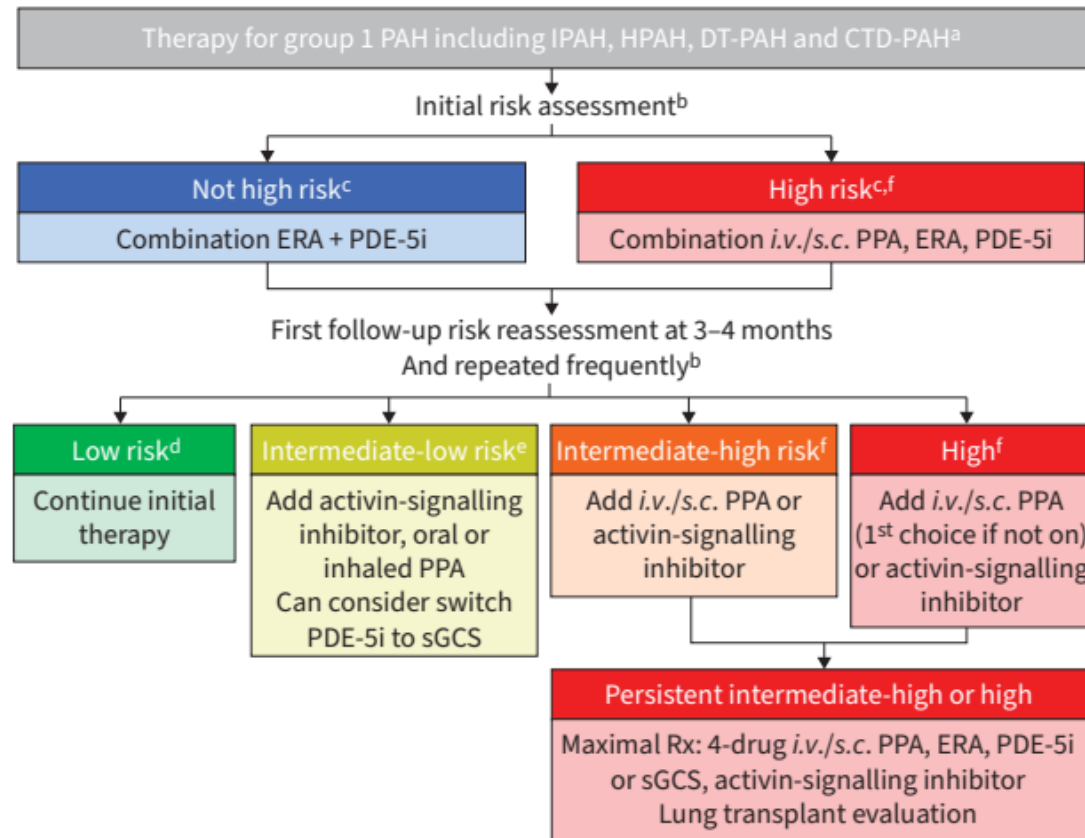
## Current therapeutic targets



Endothelin receptor antagonists (oral administration)		
Ambrisentan	5 mg o.d.	10 mg o.d.
Bosentan	62.5 mg b.i.d.	125 mg b.i.d.
Macitentan	10 mg o.d.	10 mg o.d.
Phosphodiesterase 5 inhibitors (oral administration)		
Sildenafil	20 mg t.i.d.	20 mg t.i.d. <sup>c</sup>
Tadalafil	20 or 40 mg o.d.	40 mg o.d.
Prostacyclin analogues (oral administration)		
Beraprost sodium	20 µg t.i.d.	Maximum tolerated dose up to 40 µg t.i.d.
Beraprost extended release	60 µg b.i.d.	Maximum tolerated dose up to 180 µg b.i.d.
Treprostinil	0.25 mg b.i.d. or 0.125 mg t.i.d.	Maximum tolerated dose
Prostacyclin receptor agonist (oral administration)		
Selexipag	200 µg b.i.d.	Maximum tolerated dose up to 1600 µg b.i.d.

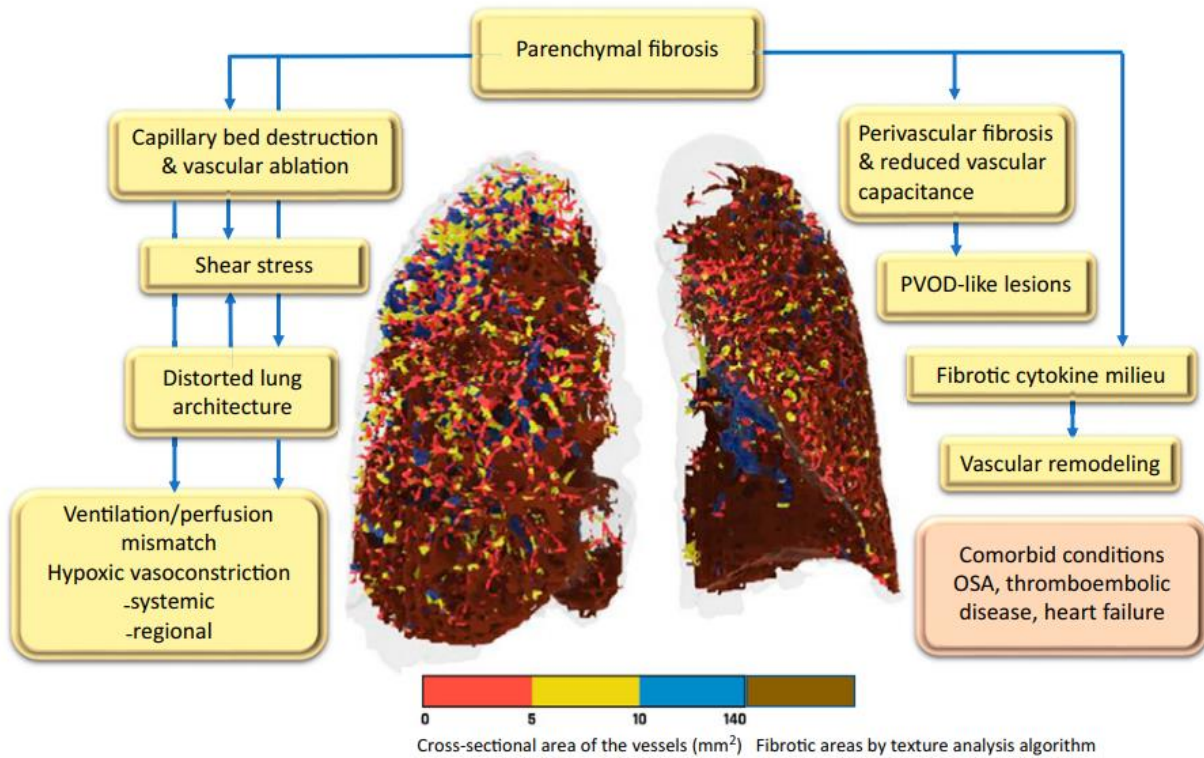
Soluble guanylate cyclase stimulator (oral administration)		
Riociguat <sup>d</sup>	1 mg t.i.d.	2.5 mg t.i.d.
Prostacyclin analogues (inhaled administration)		
Iloprost <sup>e</sup>	2.5 µg 6–9 times per day	5.0 µg 6–9 times per day
Treprostinil <sup>e</sup>	18 µg 4 times per day	54–72 µg 4 times per day
Prostacyclin analogues (i.v. or s.c. administration)		
Epoprostenol i.v.	2 ng/kg/min	Determined by tolerability and effectiveness; typical dose range at 1 year is 16–30 ng/kg/min, with wide individual variability
Treprostinil s.c. or i.v.	1.25 ng/kg/min	Determined by tolerability and effectiveness; typical dose range at 1 year is 25–60 ng/kg/min, with wide individual variability

# Management of PAH

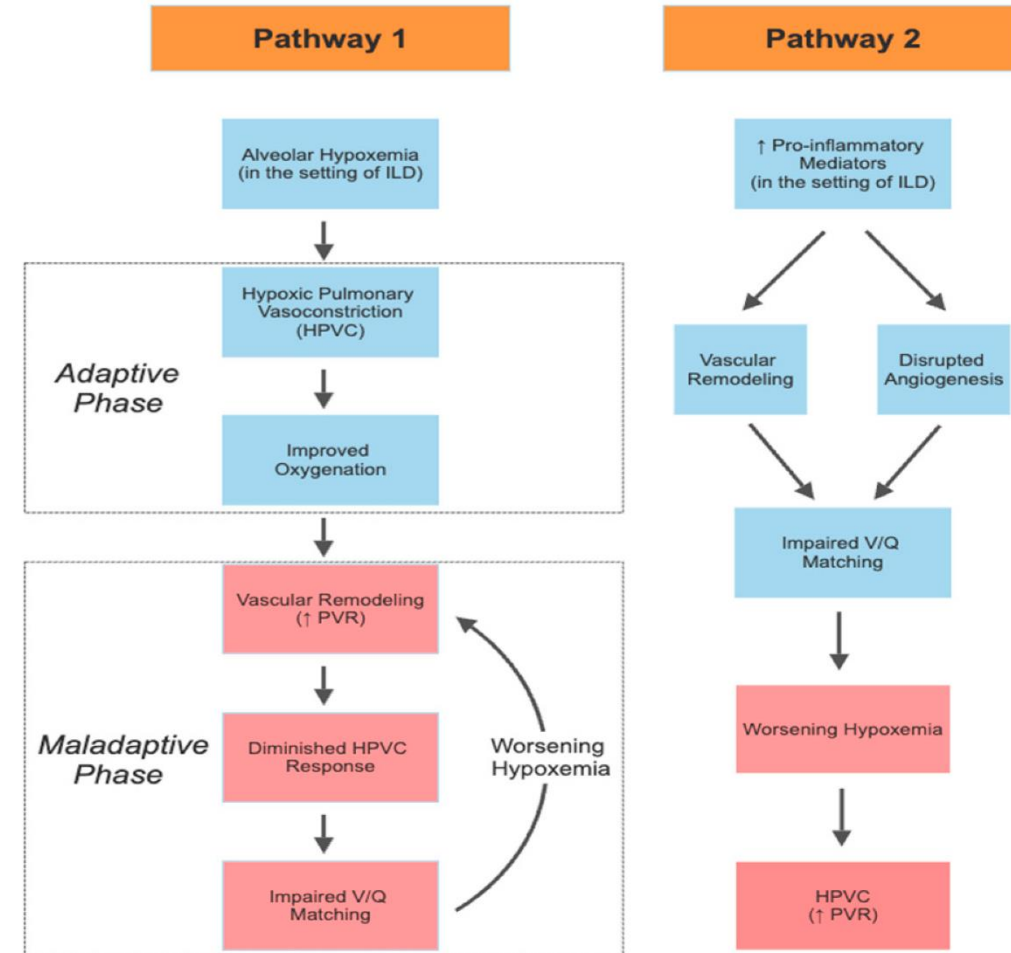


- Treatment algorithm key points
- The treatment algorithm is intended for patients with confirmed group 1 PAH (phenotypically clear-cut, including **mPAP  $\geq 25$  mmHg and PVR  $> 3$  Wood Units** and no significant response on acute vasoreactivity testing). See text for treatment in PAH with complex phenotypes.
  - Risk assessment** should be performed at baseline, within 3–4 months and periodically thereafter, and using FC, 6MWD and natriuretic peptides as a part of a validated risk calculator. Haemodynamics, RV imaging and other measures should be used to supplement risk assessment.
  - Initial triple therapy** with an *i.v./s.c.* PPA is recommended in high-risk patients and may be considered in non-high risk with severe haemodynamics and/or poor RV function.
  - Most **low-risk patients** at follow-up should continue initial therapy.
  - Clinical trials with oral and inhaled treprostinil included **only patients on monotherapy**, while studies of selexipag and sotarcept included patients on combination therapy.
  - Transplant referral** should be considered for select high-risk patients at diagnosis, and for intermediate-high and high-risk patients at first or subsequent follow-up.

# Pathogenic factors associated with the development of PH in ILD



PVOD = pulmonary veno-occlusive disease



# Studies of ILD & PH a/w ILD with PH medications

## ILD/IIP/IPF trials

KOLB, 2018 [170]	IPF	RCT	274	Nintedanib +sildenafil (n=137)	Primary end-point of change in SGRQ was not met	
BEHR, 2021 [171]	IPF	RCT	177	Pirfenidone +sildenafil (n=88)	No difference in disease progression (composite end-point)	Composite end-point of decline in 6MWD and hospitalisation or all-cause mortality
NATHAN, 2020 [172]	Fibrotic ILD	RCT	45	iNO (n=23)	Improvement in moderate to vigorous and overall activity	Patients on supplemental oxygen
Bellerophon Pulse Technologies [173]	Fibrotic ILD	RCT	145	iNO (n=73)	Did not improve moderate to vigorous activity	Patients on supplemental oxygen

## PH associated with ILD/ IIP/IPF trials

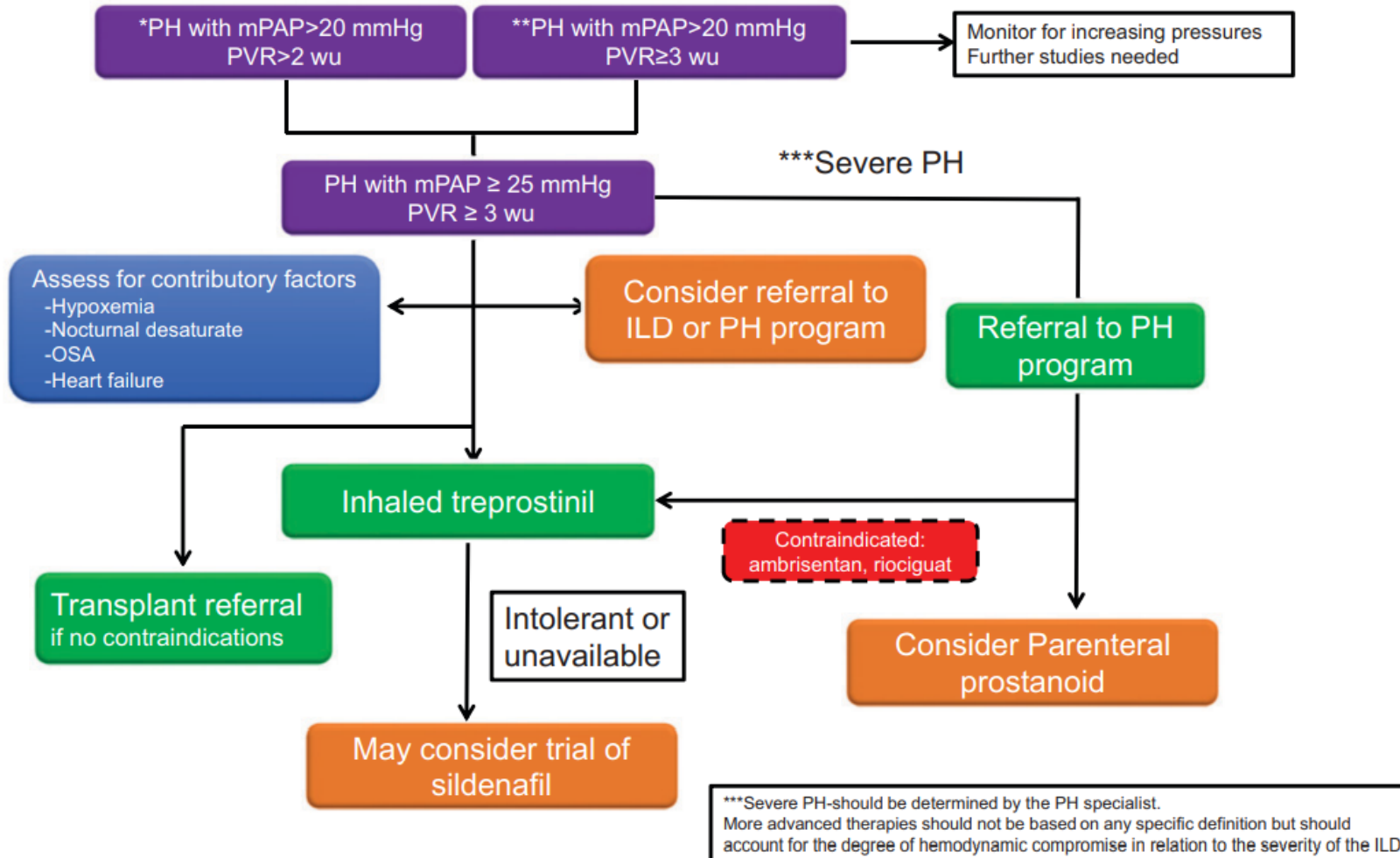
FARIA-URBINA, 2018 [174]	ILD-PH	Retrospective	22	Treprostinil (inhaled) (n=22)	Improvement in FC and 6MWD No change in resting oxygen requirements	
NATHAN, 2019 [62]	IIP-PH	RCT	147	Riociguat (n=73)	Terminated early for unfavourable risk/benefit profile	<i>Post hoc</i> analysis of CT scans suggested that advanced CPFE phenotype with emphysema >> fibrosis may have contributed to the negative signal [87]
WAXMAN, 2021 [61]	ILD-PH	RCT	326	Treprostinil (inhaled) (n=163)	Improved 6MWD, NT-proBNP, clinical worsening and FVC	
DAWES, 2023 [175]	ILD-PH	Retrospective	60	PDE-5i (n=50) ERAs (n=10)	Patients treated with sildenafil showed longer survival	No effect on V/Q' matching

# Recommendations for PH associated with lung disease



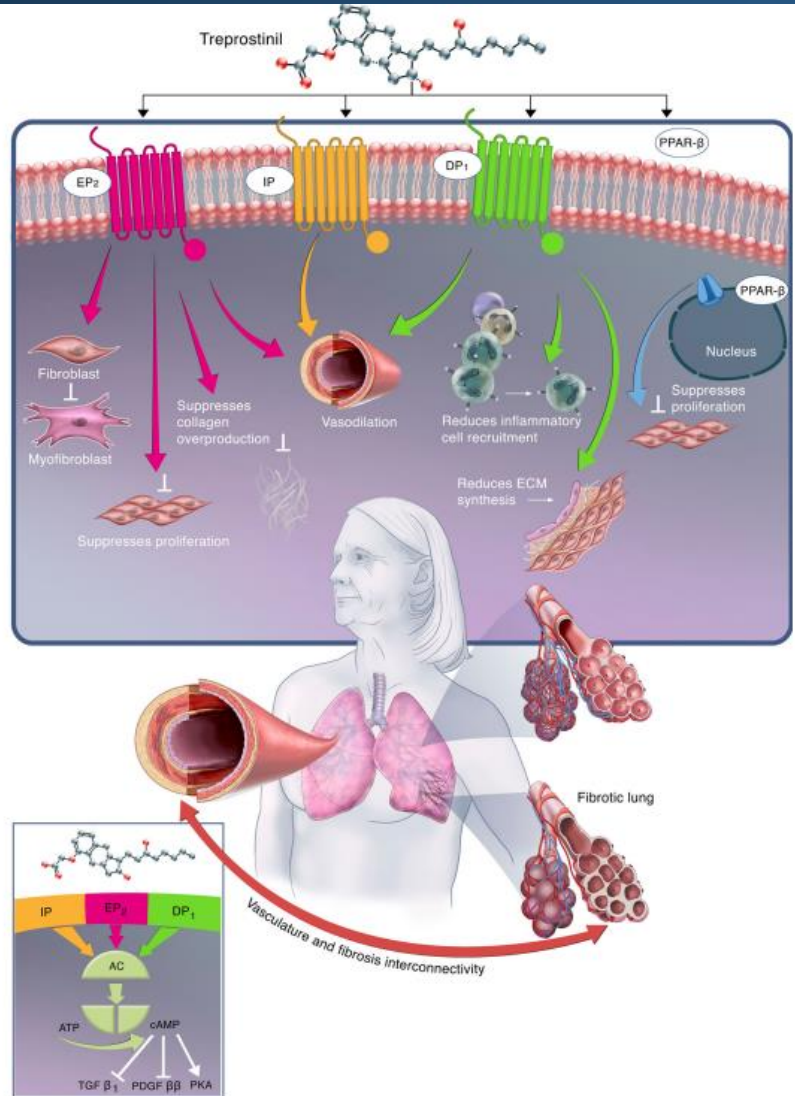
In patients with lung disease and severe PH, an individualized approach to treatment is recommended			<b>I</b>	<b>C</b>
It is recommended to refer eligible patients with lung disease and PH for LTx evaluation			<b>I</b>	<b>C</b>
<u>Inhaled treprostinil</u> may be considered in patients with PH associated with ILD <sup>734</sup>			<b>IIb</b>	<b>B</b>
The use of <u>ambrisentan</u> is not recommended in patients with PH associated with IPF <sup>740</sup> ✘			<b>III</b>	<b>B</b>
The use of <u>riociguat</u> is not recommended in patients with PH associated with IIP <sup>181</sup> ✘			<b>III</b>	<b>B</b>
The use of PAH medication is not recommended in patients with lung disease and non-severe PH <sup>e</sup>			<b>III</b>	<b>C</b>
<u>PDE5is</u> may be considered in patients with severe PH associated with ILD (individual decision-making in PH centres)	Very low	Conditional	<b>IIb</b>	<b>C</b>
The use of PDE5is in patients with ILD and non-severe PH is not recommended	Very low	Conditional	<b>III</b>	<b>C</b>

# Management algorithm in ILD-PH patients



# inhaled Treprostinil

TETON trial



## Mechanism of action

1. Activation of prostaglandin E type 2 (EP2), prostacyclin receptor (IP), prostaglandin D type 1 (DP1) receptor

→ *Vasodilation*

→ Inhibits fibroblast to myofibroblast differentiation

→ Suppresses *fibroblast proliferation*

→ Suppresses *collagen overproduction*

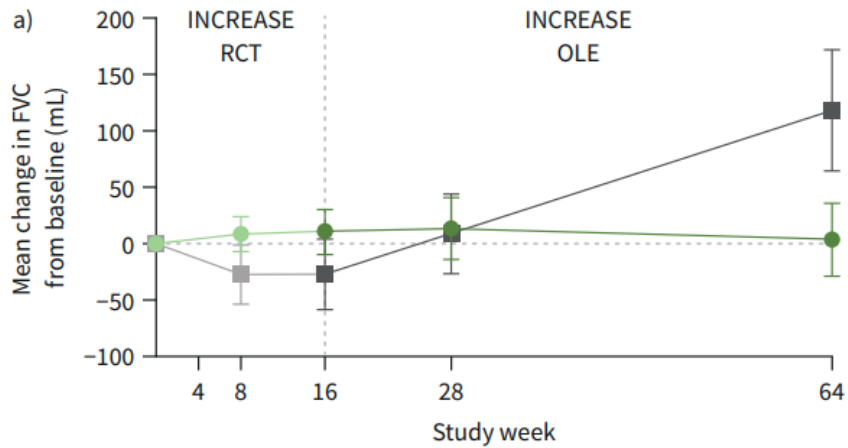
→ Reduces *inflammatory cell recruitment* & reduces *ECM synthesis*

2. Activation of the nuclear receptor, peroxisome proliferator-activated receptor b (PPAR-β)

→ Suppresses *fibroblast proliferation*

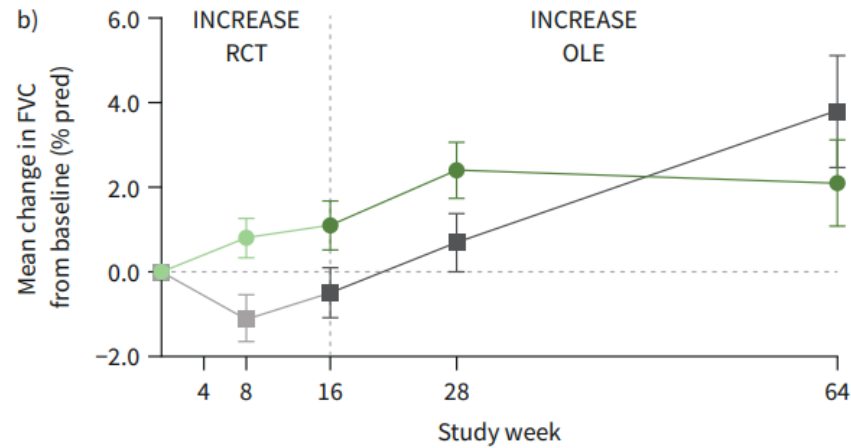
# inhaled Treprostinil in ILD with PH

## INCREASE study



Inhaled treprostinil in RCT (n):	162	141	129	100	46
Placebo in RCT (n):	161	140	124	97	67

● Inhaled treprostinil  
● Inhaled treprostinil in RCT → inhaled treprostinil in OLE



Inhaled treprostinil in RCT (n):	162	141	129	100	46
Placebo in RCT (n):	161	140	124	97	67

■ Placebo  
■ Placebo in RCT → inhaled treprostinil in OLE

**TETON 1** : IPF 598명,  
USA, Canada

**TETON 2** : IPF 597명,  
Asian-pacific, Europe, Latin America

**TETON-PPF**: 698명, non-IPF PPF

# Framework for management of patients with ILD-associated PH

PH associated with fibrotic ILDs		
Treatment of underlying ILD and hypoxaemia Referral of potentially eligible patients for lung transplantation Pulmonary rehabilitation, supportive care, symptom management		
Clinical trial enrolment Individualised management		
Favours no PH therapy	Domains	Favours PH therapy
Relevant comorbidities	Clinical domain	Worsening symptoms due to PH Underlying CTD
PVR 2–3 WU and mPAP 20–25 mmHg	Haemodynamics	PVR $\geq$ 4 WU and mPAP $\geq$ 25 mmHg
Severe restrictive ventilatory defect FEV <sub>1</sub> /FVC <0.7	Functional domain	Mild-to-moderate restrictive ventilatory defect Vascular limitation to exercise
Normal BNP/NT-proBNP	Biological domain	Elevated BNP/NT-proBNP
Extensive fibrotic ILD on CT Emphysema extent >15%	Morphological domain	Non-severe fibrotic ILD on CT
Significant drug interactions	Other considerations	Drug approval and reimbursement <sup>#</sup>
Fibrosis		Vasculopathy
Serial re-assessment for progression		

# Assessment

## Diagnosis)

#1. Sjogren-associated ILD : OP pattern → fibrotic progression over 30 years

#2. progressive dyspnea (onset 1MA)

- d/t Pulmonary hypertension : type 1 + 3 (not solely type 3)

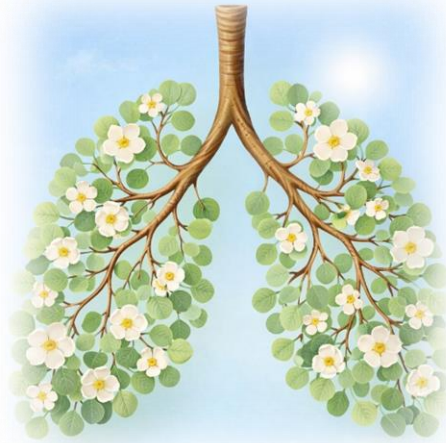
## Therapeutic plan)

✓ Steroid tapering & MMF add on

✓ Opsumit 10mg qd start → Sildenafil add on

# Take home message

- Regular follow up of non-IPF ILDs for progression to PPF
- Timely antifibrotic therapy for PPF
- Differential diagnosis of other cause when dyspnea worsen in fibrosing ILD but not PPF
- PH in ILD



**Thank you for your attention**