The ILD Intel: What's New, What's Next

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Update of the International Multidisciplinary Classification of the Interstitial Pneumonias: An ERS/ATS Statement

Christopher J. Ryerson, Ayodeji Adegunsoye, Sara Piciucchi, Lida P. Hariri, Yet H. Khor, Marlies S. Wijsenbeek, Athol U. Wells, Amita Sharma, Wendy A. Cooper, Katerina Antoniou, Raphael Borie, Aurelie Fabre, Yoshikazu Inoue, Kerri Johannson, Takeshi Johkoh, Leticia Kawana-Dourado, Ella Kazerooni, Toby M. Maher, Philip L. Molyneaux, Raymond Protti, Claudia Ravaglia, Elisabetta A. Renzoni, Ryoko Saito-Koyama, Nicola Sverzellati, Simon L. F. Walsh, Paul Wolters, Soo-Ryum Yang, William Travis, Andrew G Nicholson

ERJ 2025

2002 & 2013 classifications

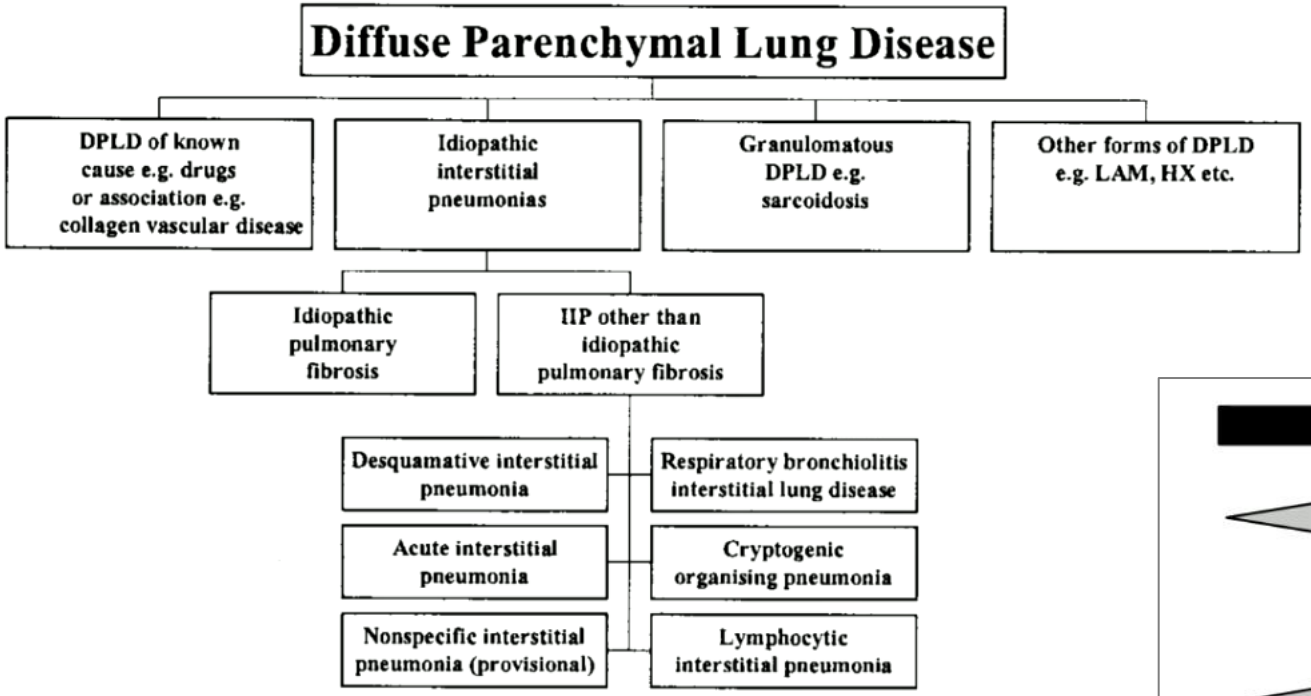
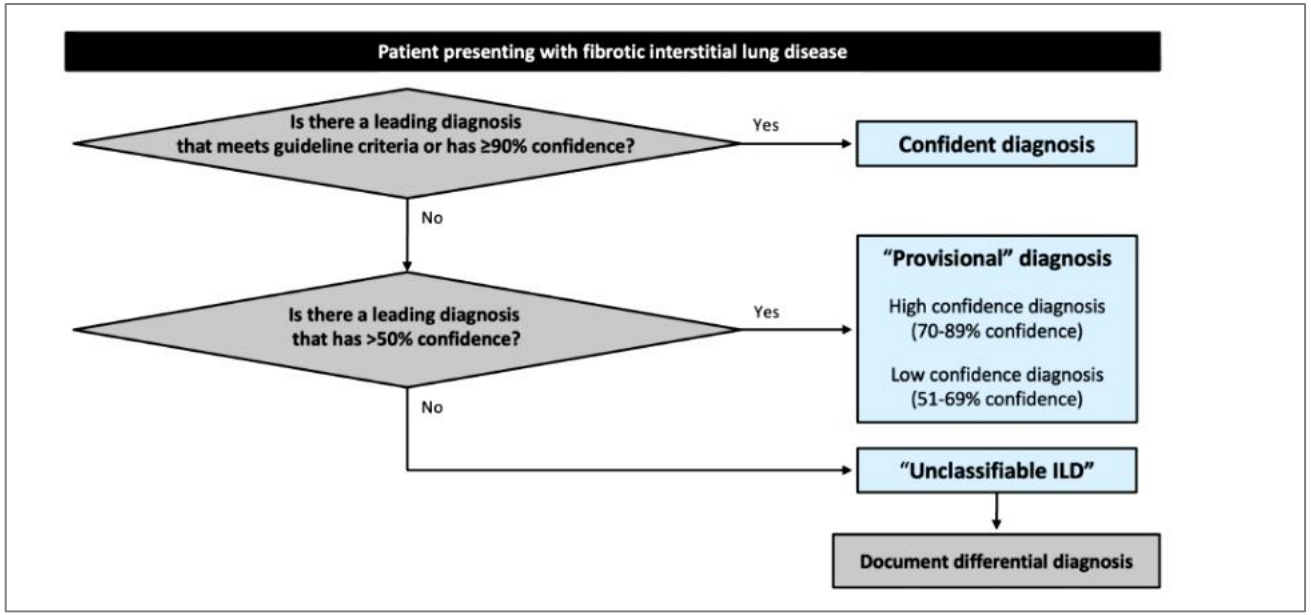


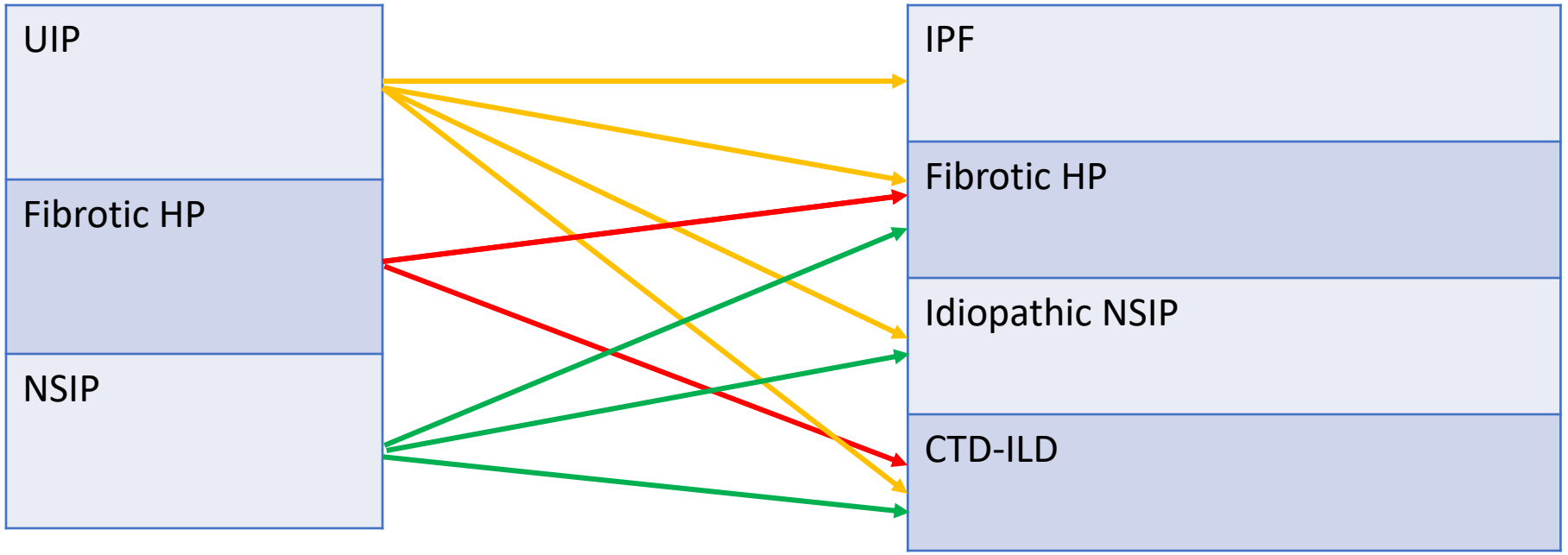
TABLE 3. IDIOPATHIC INTERSTITIAL PNEUMONIAS: CLASSIFICATION ACCORDING TO DISEASE BEHAVIOR*

Clinical Behavior	Treatment Goal	Monitoring Strategy
Reversible and self-limited (e.g., many cases of RB-ILD)	Remove possible cause	Short-term (3- to 6-mo) observation to confirm disease regression
Reversible disease with risk of progression (e.g., cellular NSIP and some fibrotic NSIP, DIP, COP)	Initially achieve response and then rationalize longer term therapy	Short-term observation to confirm treatment response. Long-term observation to ensure that gains are preserved
Stable with residual disease (e.g., some fibrotic NSIP)	Maintain status	Long-term observation to assess disease course
Progressive, irreversible disease with potential for stabilization (e.g., some fibrotic NSIP)	Stabilize	Long-term observation to assess disease course
Progressive, irreversible disease despite therapy (e.g., IPF, some fibrotic NSIP)	Slow progression	Long-term observation to assess disease course and need for transplant or effective palliation



Pattern
Imaging and/or histology

MDT diagnosis

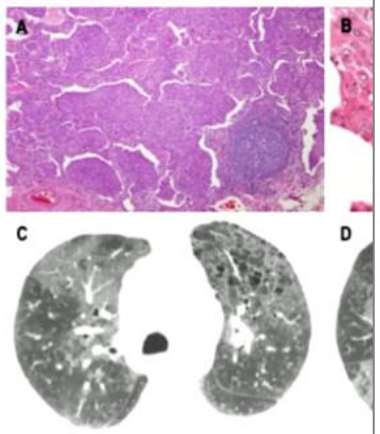


Morphologic patterns by Pathology and Imaging	Major clinical-radiologic-pathologic diagnoses	
	Secondary	Primary / Idiopathic
Usual interstitial pneumonia (UIP)	**Secondary UIP** (*e.g.*, CTD, HP, medications)	**Idiopathic pulmonary fibrosis** (Idiopathic UIP)
Nonspecific interstitial pneumonia (NSIP)	**Secondary NSIP** (*e.g.*, CTD >>> HP, medications)	**Idiopathic NSIP**
Bronchiolocentric interstitial pneumonia (BIP)*	**Secondary BIP** (*e.g.*, HP >>> CTD, aspiration, inhalational exposures, medications)	**Idiopathic BIP** *(provisional diagnosis*)*
Diffuse alveolar damage (DAD)	**Secondary DAD** (multiple causes)	**Idiopathic DAD** (acute interstitial pneumonia)
Pleuroparenchymal fibroelastosis (PPFE)	**Secondary PPFE** (*e.g.*, IPF, CTD, HP, medications, radiation, transplant [restrictive allograft syndrome, pulmonary infection [post-tuberculosis], occupational)	**Idiopathic PPFE**
Lymphoid interstitial pneumonia (LIP)	**Secondary LIP** (*e.g.*, CTD, immune deficiency)	**Idiopathic LIP**
Organising pneumonia (OP)	**Secondary OP** (*e.g.*, CTD, post-infectious, medications, aspiration)	**Cryptogenic OP** (Idiopathic OP)
Respiratory bronchiolitis-ILD (RB-ILD)	**Secondary RB-ILD** (*e.g.*, smoking >>> CTD, medications, aspiration, hereditary)	**Idiopathic RB-ILD**
Alveolar macrophage pneumonia† (AMP)	**Secondary AMP** (*e.g.*, smoking >>> CTD, medications, aspiration, hereditary	**Idiopathic AMP**
Rare alveolar filling disorders	*e.g.*, **Acute and chronic eosinophilic pneumonia, pulmonary alveolar proteinosis, lipoid pneumonia** (See **Supplemental Table 1**)	
Combined pattern	**Multiple combinations** (*e.g.*, NSIP + OP, UIP + PPFE)	
Unclassifiable pattern	**Unclassifiable ILD** (multiple undefined patterns)	

Changes in terminology

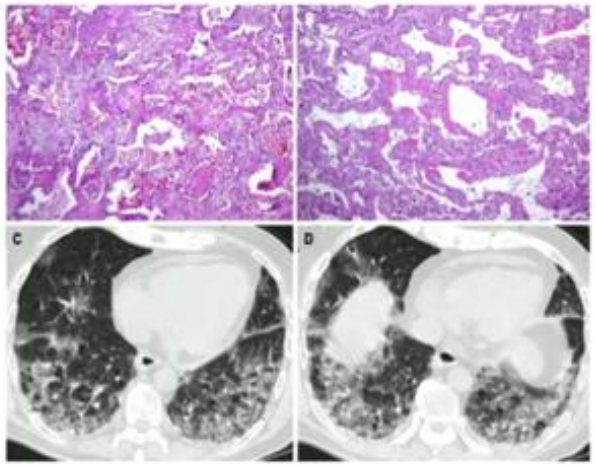
Alveolar macrophage pneumonia - replaces "desquamative interstitial pneumonia"

"AMP replaces DIP as the term used to describe excessive widespread accumulation of macrophages within alveoli. Most cases of AMP are
causes, including surfactant-p



Idiopathic diffuse alveolar damage - replaces "acute interstitial pneumonia"

"DAD is the cardinal histological pattern in ARDS and is caused by a variety of infections, drugs, inhalational injuries, CTDs (especially inflammatory myopathy), and other lung insults. Most cases of acute exacerbation of IP are characterised by a DAD pattern. Idiopathic DAD was previously referred to as acute interstitial pneumonia (AIP); however, AIP is an imprecise term since other IPs can present acutely."



Lung biopsy of organising DAD (**A**) shows alveolar walls diffusely thickened by loose organising connective tissue with less conspicuous hyaline membranes than seen in exudative (acute) DAD. Lung biopsy of exudative DAD (**B**) shows alveolar walls diffusely thickened by prominent hyaline membranes and edema with mild organising connective tissue. Axial chest CT of DAD (**C** and **D**) shows bilateral confluent areas of ground glass attenuation. Subtle distortion is visible in the subpleural regions, mainly in the left lower lobe.

Bronchiolocentric interstitial pneumonia - evolves from "typical HP pattern"

"BIP is recognised as a major interstitial pattern seen on lung biopsy with corresponding features on chest imaging. The 2013 document included bronchiolocentric patterns of IP as a rare histologic pattern that might be of value; however, such cases were excluded from the category of idiopathic IP as the published data were insufficient to justify formal recognition as an idiopathic entity at that time. Expansion of this classification beyond idiopathic entities mandates integration of HP and other bronchiolocentric interstitial disorders."

Bronchiolocentric interstitial pneumonia - evolves from "typical HP pattern"

"BIP" has been introduced as the overarching term to describe an airway-centred pathologic and/or radiologic pattern observable in HP and other IPs, such as CTD-ILD, aspiration, and drug-induced ILD. Incorporation of BIP as a pattern in this document better recognises the 3 main fibrosing patterns of interstitial pneumonia (UIP, NSIP, and BIP), and is akin to UIP serving as the pattern seen in IPF and other diagnoses in which distinct terms are used to refer to pattern and multidisciplinary diagnosis. To provide further consistency with the other patterns of IP, we propose that "HP" no longer be used to describe a pattern seen on chest imaging or lung biopsy, and that the term "HP" instead be reserved for the multidisciplinary diagnosis of HP. It is important to highlight that specific disease features seen on radiology and pathology in the setting of a BIP pattern can suggest a high confidence for HP even in the absence of a clear exposure."

Critically important notes:

- Most of the relevant literature is derived from "HP" literature that has described a "typical HP pattern"
- Many patients referred to as "cryptogenic HP" (or similar) may now be considered "idiopathic BIP"
- Patients with a BIP pattern require a comprehensive evaluation for exposures (as well as for CTD)

	Morphologic patterns by Pathology and Imaging	Major clinical-radiologic-pathologic diagnoses	
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Interstitial patterns	**Usual interstitial pneumonia (UIP)**	**Secondary UIP** (*e.g.*, CTD, HP, medications)	**Idiopathic pulmonary fibrosis** (Idiopathic UIP)
	Nonspecific interstitial pneumonia (NSIP)	**Secondary NSIP** (*e.g.*, CTD >>> HP, medications)	**Idiopathic NSIP**
	Bronchiolocentric interstitial pneumonia (BIP)*	**Secondary BIP** (*e.g.*, HP >>> CTD, aspiration, inhalational exposures, medications)	**Idiopathic BIP** *(provisional diagnosis*)*
	Diffuse alveolar damage (DAD)	**Secondary DAD** (multiple causes)	**Idiopathic DAD** (acute interstitial pneumonia)
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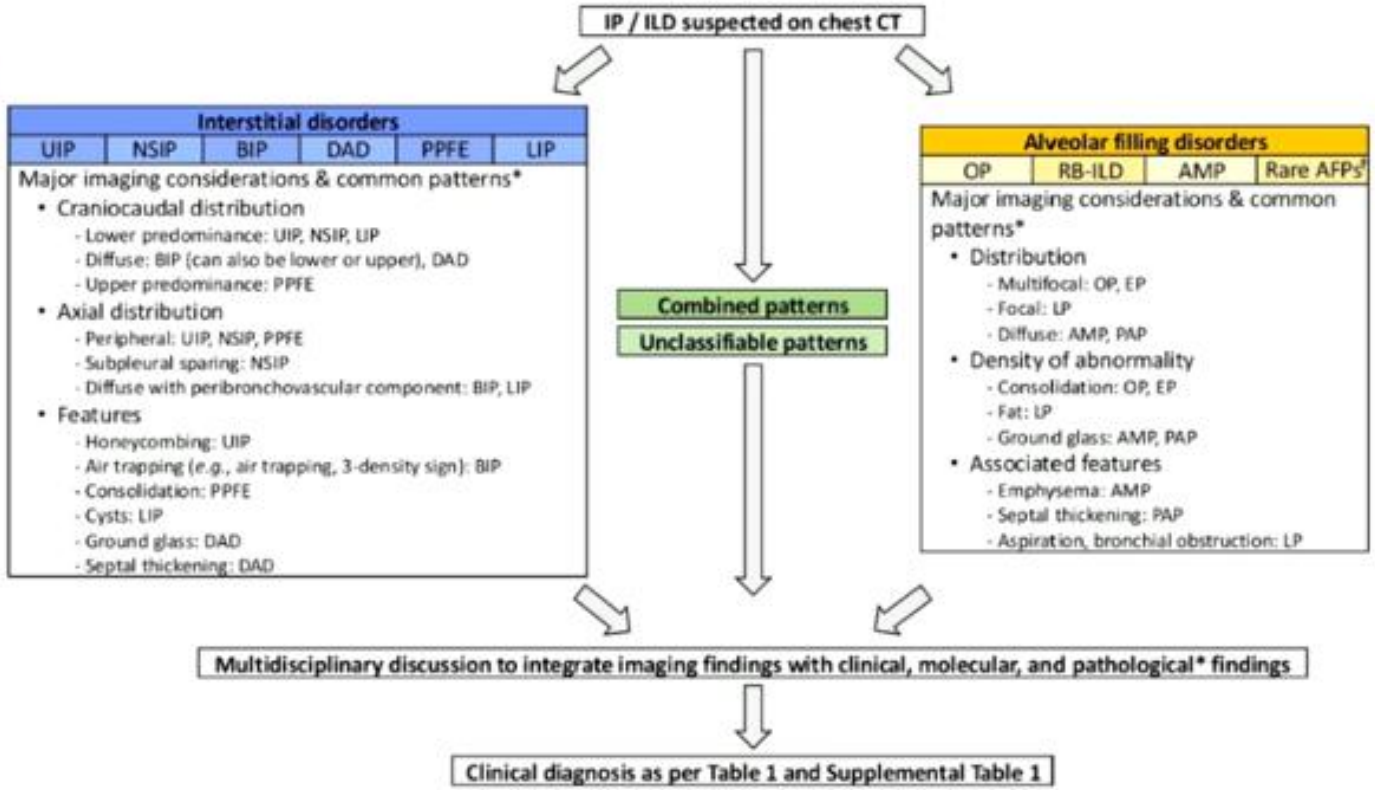
	Respiratory bronchiolitis-ILD (RB-ILD)	**Secondary RB-ILD** (*e.g.*, smoking >>> CTD, medications, aspiration, hereditary)	**Idiopathic RB-ILD**
	Alveolar macrophage pneumonia† (AMP)	**Secondary AMP** (*e.g.*, smoking >>> CTD, medications, aspiration, hereditary	**Idiopathic AMP**
	Rare alveolar filling disorders	*e.g.*, **Acute and chronic eosinophilic pneumonia**, **pulmonary alveolar proteinosis, lipoid pneumonia** (See **Supplemental Table 1**)	
Other	**Combined pattern**	**Multiple combinations** (*e.g.*, NSIP + OP, UIP + PPFE)	
	Unclassifiable pattern	**Unclassifiable ILD** (multiple undefined patterns)	

MDT approach

1. Predominantly “interstitial” or “pneumonia”? Or “other”?
2. What’s the morphological pattern?
3. Are there secondary causes?



Updated classification

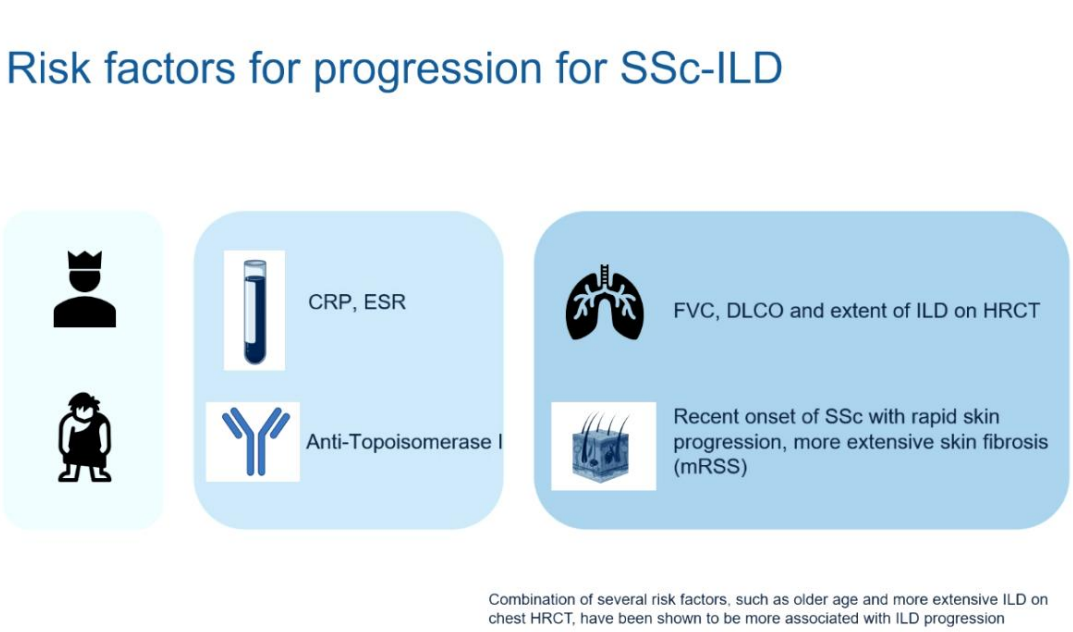
- Not only idiopathic entities
- Updated terminology
- Rational subcategorization
- Describes molecular advances

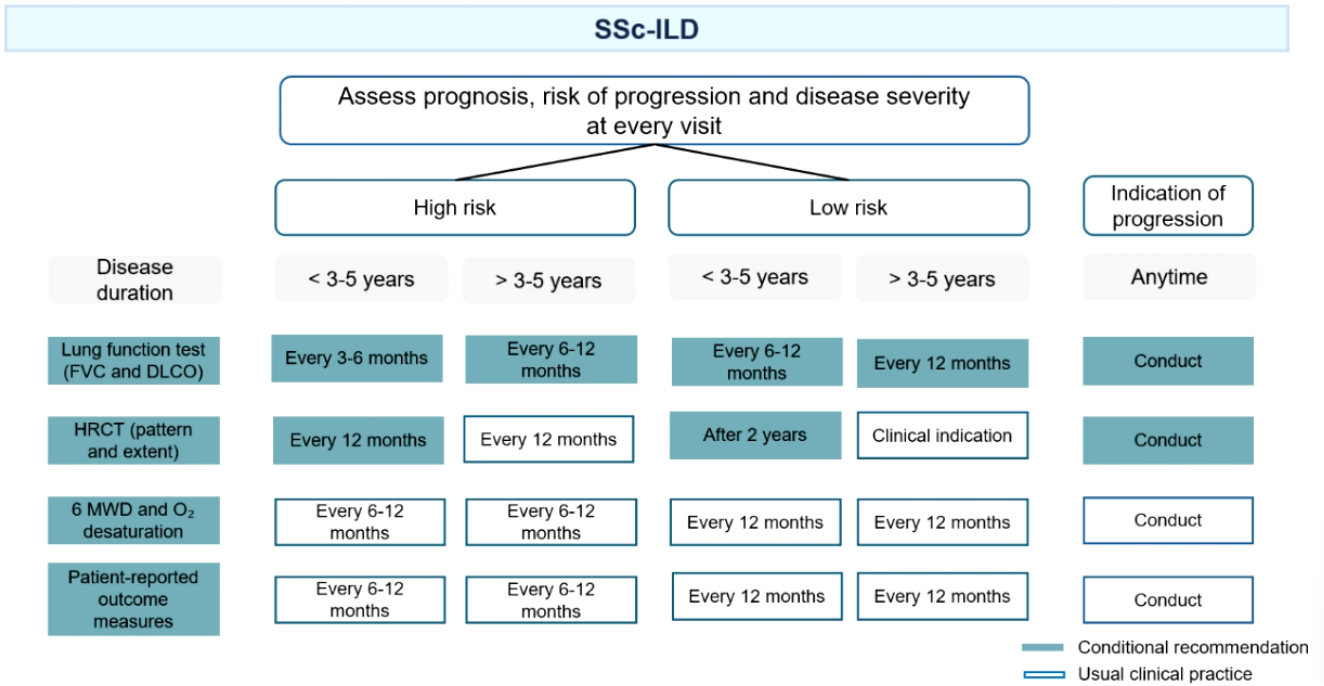
Biomarker	Pathophysiology	Clinical Accessibility	Clinical value		
			Diagnostic	Prognostic	Therapeutic
Genetic					
MUC5B *rs35705950*	Risk allele linked to increased pulmonary fibrosis susceptibility but slower progression rate	Variably accessible	Unclear	Unclear	Unclear
Telomere-related genes (*TERT, TERC, RTEL1, PARN, DKC1, NAF1, ZCCHC8*)	Telomere-related gene variants linked to increased PF risk and rapid disease progression	Variably accessible	Potential value	Potential value	Unclear
Surfactant-related genes (*SFTPC, SFTPA1 SFTPA2*)	SRG variants linked to increased pulmonary fibrosis risk and to lung cancer	Variably accessible	Potential value	Unclear	Unclear
Other gene loci (ind. *DSP, KIF15,* & *HLA-DRB1*)	Polymorphisms in these genes linked to increased pulmonary fibrosis risk	Variably accessible	Unclear	Unclear	Unclear
Short telomeres / Telomeropathies					
Leukocyte telomere length	Leukocyte telomere length attrition associated with increased ILD susceptibility and rapid progression rate	Variably accessible	Potential value	Potential value	Emerging value in guiding post-lung transplant & ILD pharmacotherapy
Short telomere syndromes (ind. dyskeratosis congenita, Hoyeraal–Hreidarsson syndrome)	Clinical manifestation often at younger age, show Mendelian inheritance, have multiorgan involvement.	Accessible	Potential value	Unclear	Unclear
Transcriptomic RNA signatures					
Lung biopsy-based Envisia® Genomic Classifier	Integrates gene expression profiling with machine learning algorithms to recognise the genomic signature of a UIP pattern	Accessible in North America & Europe	Strengthens UIP diagnosis but clinical utility unproven	Unclear	Unclear
Peripheral blood-based 52-gene RNA signature	Specific set of 52 genes whose combined expression pattern is indicative of IPF	Unclear	Unclear	Unclear	Unclear
Serum/Plasma-based antibody panels					
Autoimmune serology (ind. ANA, dsDNA, anti-Sm, ACA, anti-Scl-70, anti-RNA polymerase III, anti-Jo-1, anti-MDA5, RF, anti-CCP, SS-A, SS-B, anti-RNP, ANCA, anti-U1 RNP, anti-PL-12, & anti-PL-7, anti-GM-CSF)	Identify the presence of discrete autoantibodies that target protein, nuclear or other cellular components which aid the diagnosis of specific autoimmune diseases.	Accessible	Strengthens diagnosis of specific subtypes of CTD-ILD	Potential value	May guide choice of therapy.
Hypersensitivity pneumonitis	Serum IgG testing against HP-associated antigens. Suboptimal sensitivity and specificity.	Accessible	Positive test may support HP exposure	Unclear	Unclear
Other serum- / plasma-based protein markers					
Proteomics / Specific proteins (ind. MMP7, CCL18, SP-D, CA-125, CA19-9, KL-6, MMP-1, MMP-8, TGF-β, & PDGF)	Tissue-derived glycoproteins, enzymes, and protein signatures linked to various pulmonary processes including innate immunity, tissue remodeling, extracellular matrix turnover, and fibrosis.	Variably accessible	Unclear	Unclear	Unclear
Inflammatory / immunologic markers (CRP, ESR)	Acute-phase protein and proinflammatory markers that play pivotal roles in immune, autoimmune, and inflammatory disorders.	Globally accessible	Positive markers may support specific IP diagnoses	Extent of positivity may predict outcomes (e.g., CRP)	May guide therapeutic response.

ERS/EULAR clinical practice guidelines for connective tissue disease associated interstitial lung disease

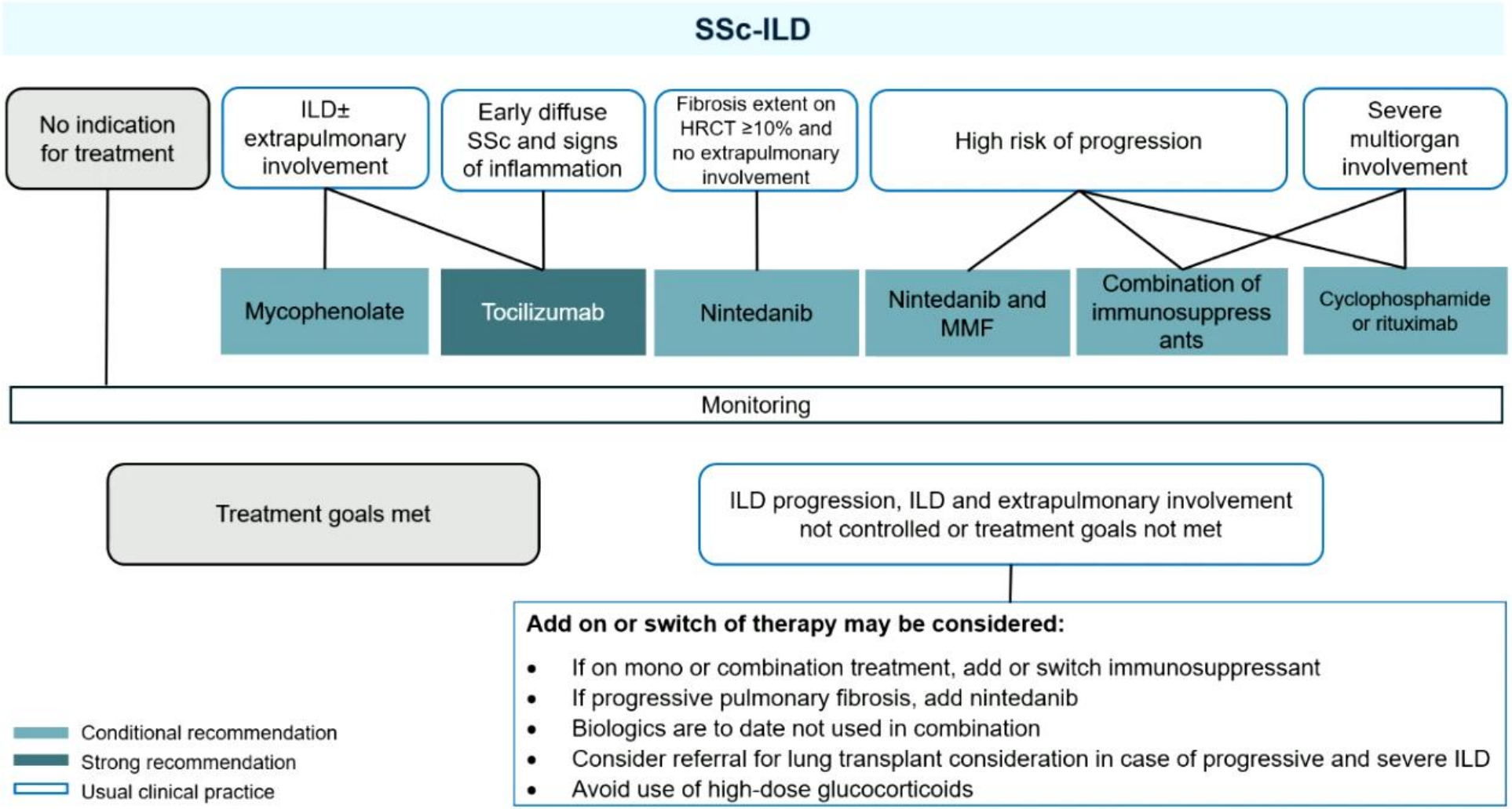
Katerina M. Antoniou, Oliver Distler, Ana-Maria Gheorghiu, Catharina C. Moor, Jens Vikse, Nikoleta Bizymi, Ilaria Galetti, Graham Brown*, Elena Bargagli, Yannick Allanore Tamera J. Corte, Philippe Dieudé, Vincent Cottin, Benjamin A. Fisher, Aurelie Fabre, Jon T. Giles, Michael Kreuter, Ingrid E. Lundberg, Venerino Poletti, Britta Maurer, Elisabetta A. Renzoni, Ulf Müller-Ladner, Mary E. Strek, Nicola Sverzellati, Paul Studenic, Jibril Mohammed, Blin Nagavci, Tanja Stamm, Thomy Tonia, Bruno Crestani, Anna-Maria Hoffmann-Vold

SSc-ILD: risk factors & monitoring



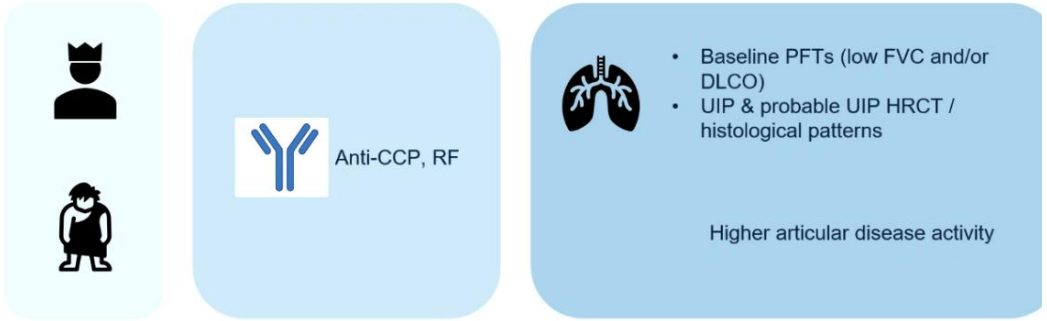


Treatment


SSc-ILD
No indication for treatment
ILD± extrapulmonary involvement
Early diffuse SSc and signs of inflammation
Fibrosis extent on HRCT ≥10% and no extrapulmonary involvement
High risk of progression
Severe multiorgan involvement
Mycophenolate
Tocilizumab
Nintedanib
Nintedanib and MMF
Combination of immunosuppressants
Cyclophosphamide or rituximab
Monitoring
Treatment goals met
ILD progression, ILD and extrapulmonary involvement not controlled or treatment goals not met
Add on or switch of therapy may be considered:
If on mono or combination treatment, add or switch immunosuppressant
If progressive pulmonary fibrosis, add nintedanib
Biologics are to date not used in combination
Consider referral for lung transplant consideration in case of progressive and severe ILD
Avoid use of high-dose glucocorticoids
Conditional recommendation
Strong recommendation
Usual clinical practice

RA-ILD: risk factors & monitoring

Risk factors for progression for RA-ILD



Combination of several risk factors, such as older age and more extensive ILD or chest HRCT, have been shown to be more associated with ILD progression

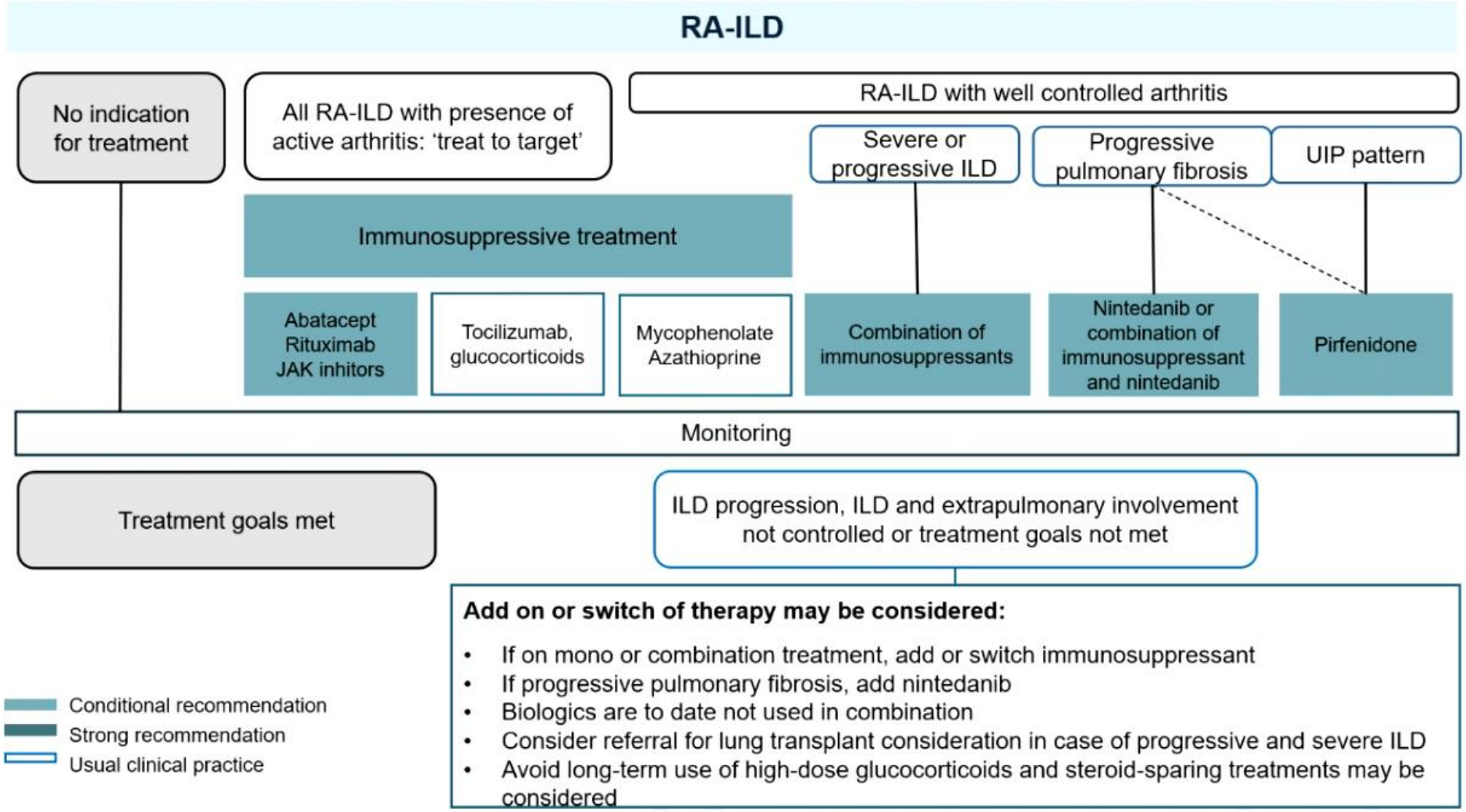
RA-ILD

Assess prognosis, risk of progression and disease severity at every visit

	High risk		Low risk		Indication of progression
Disease duration	< 1-2 years	> 2 years	< 1-2 years	> 2 years	Anytime
Lung function test (FVC and DLCO)	Every 3-6 months	Every 6-12 months	Every 6-12 months	Every 12 months	Conduct
HRCT (pattern and extent)	Every 12 months	Every 12 months	After 2 years	Clinical indication	Conduct
6 MWD and O_2 desaturation	Every 6-12 months	Every 6-12 months	Every 12 months	Every 12 months	Conduct
Patient-reported outcome measures	Every 6-12 months	Every 6-12 months	Every 12 months	Every 12 months	Conduct

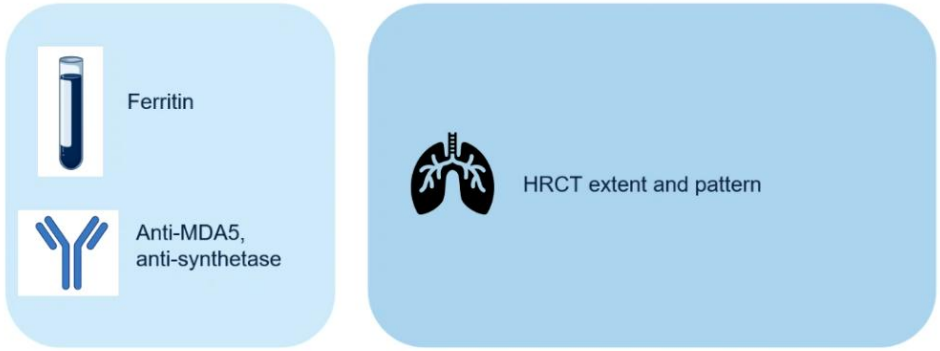
Conditional recommendation
Usual clinical practice

Treatment

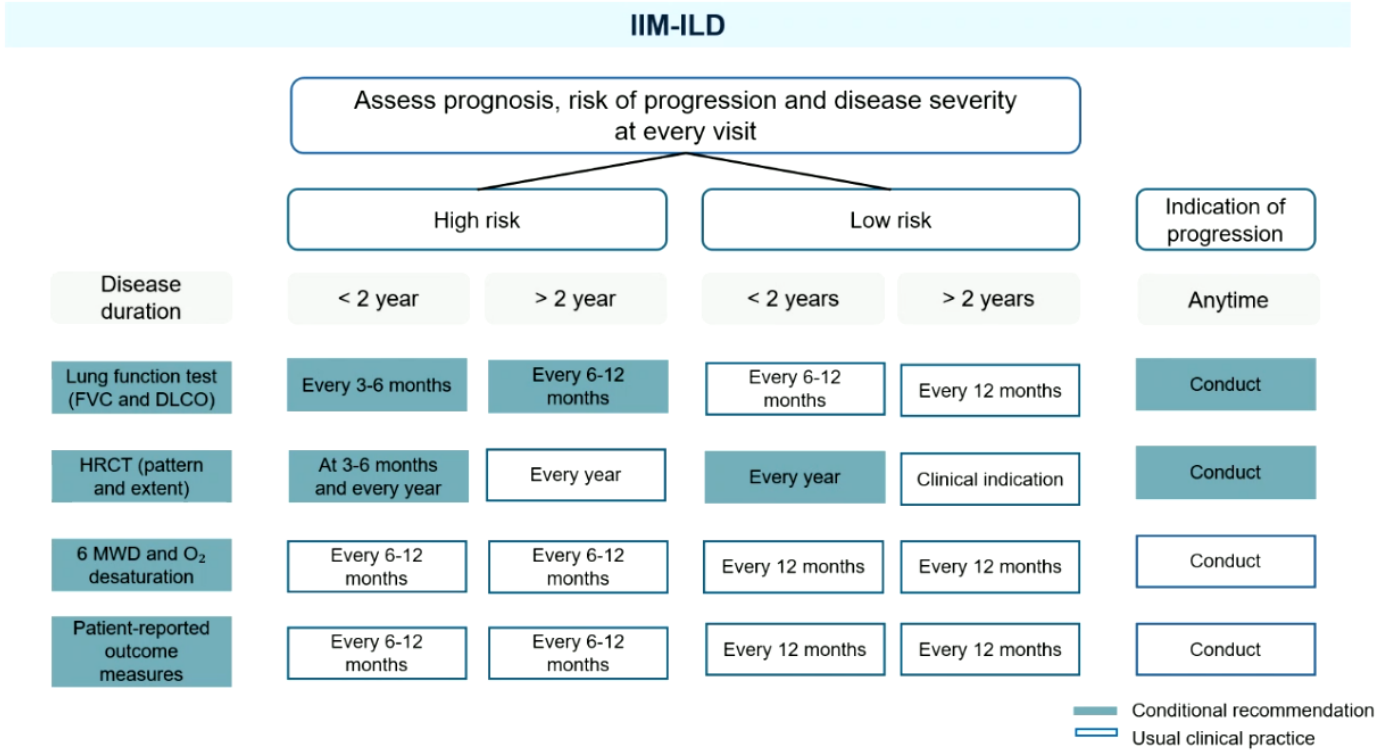

RA-ILD
No indication for treatment
All RA-ILD with presence of active arthritis: 'treat to target'
RA-ILD with well controlled arthritis
Severe or progressive ILD
Progressive pulmonary fibrosis
UIP pattern
Immunosuppressive treatment
Abatacept
Rituximab
JAK inhitors
Tocilizumab, glucocorticoids
Mycophenolate
Azathioprine
Combination of immunosuppressants
Nintedanib or combination of immunosuppressant and nintedanib
Pirfenidone
Monitoring
Treatment goals met
ILD progression, ILD and extrapulmonary involvement not controlled or treatment goals not met
Add on or switch of therapy may be considered:
• If on mono or combination treatment, add or switch immunosuppressant
• If progressive pulmonary fibrosis, add nintedanib
• Biologics are to date not used in combination
• Consider referral for lung transplant consideration in case of progressive and severe ILD
• Avoid long-term use of high-dose glucocorticoids and steroid-sparing treatments may be considered
Conditional recommendation
Strong recommendation
Usual clinical practice

IIM-ILD: risk factors & monitoring

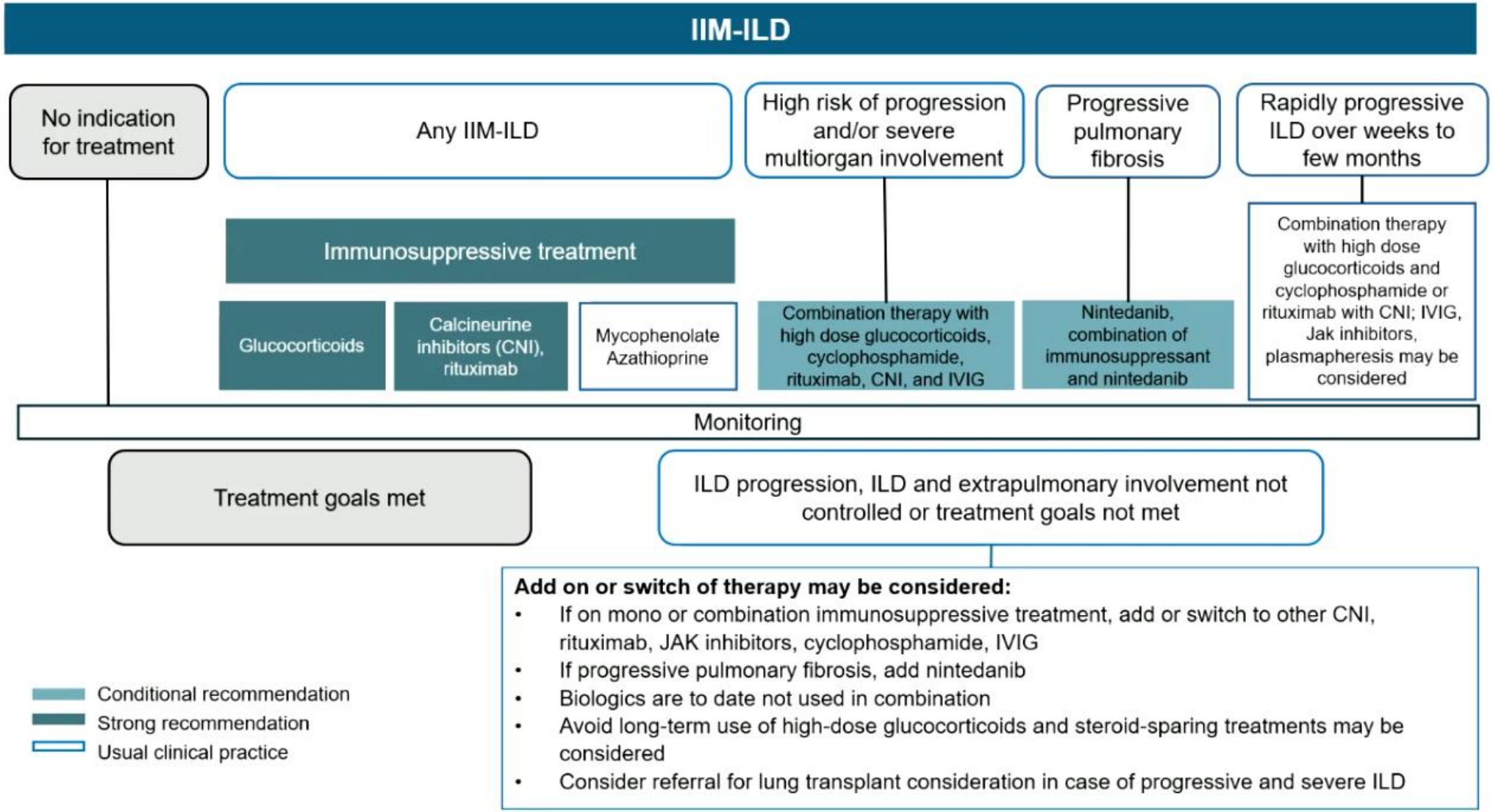
Risk factors for progression for IIM-ILD



Risk factors for poor outcome in MDA-5 positive IIM-ILD patients: extent of ILD on HRCT, higher ferritin levels, KL-6, older age, low P[A-a]O2



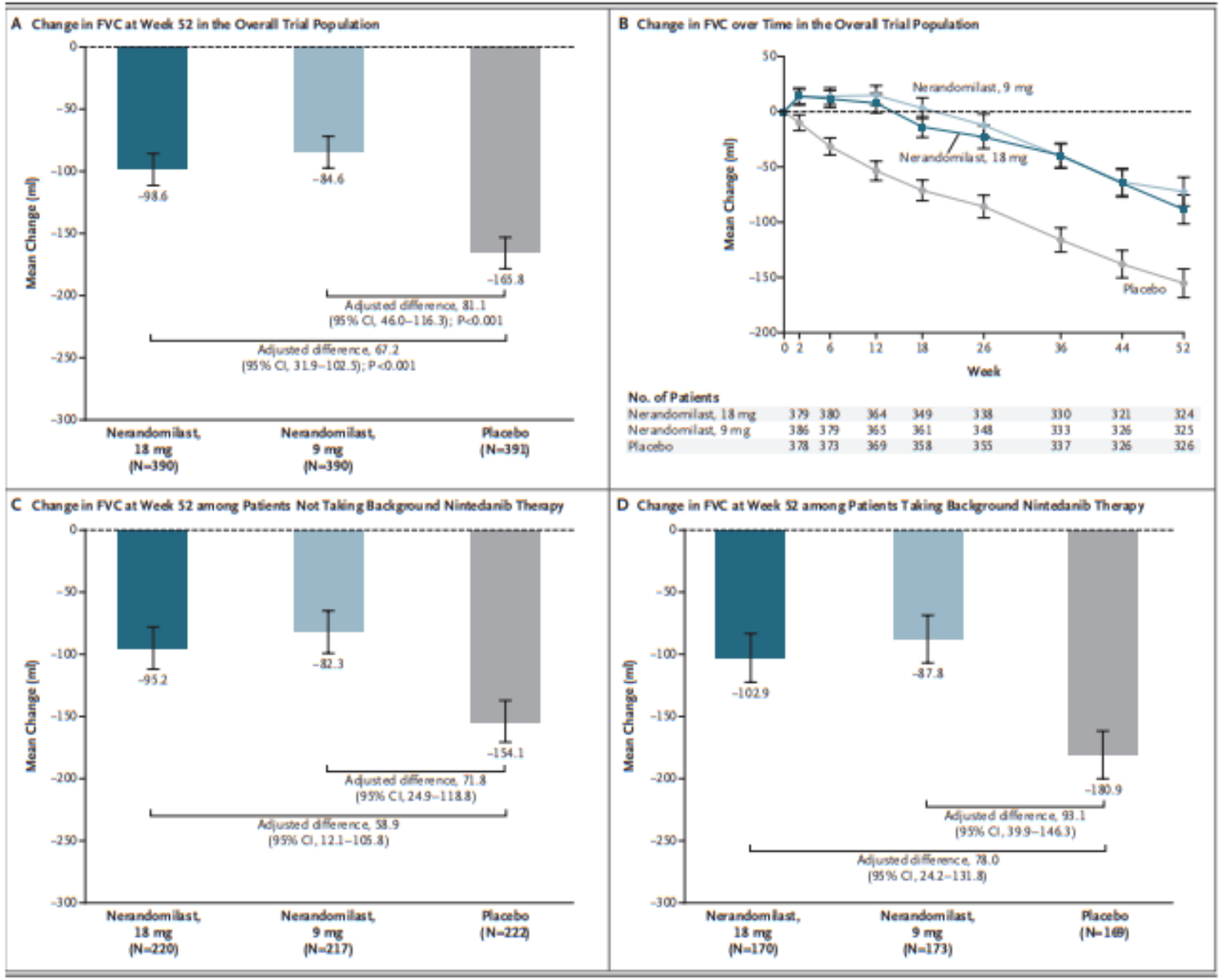
Treatment


IIM-ILD
No indication for treatment
Any IIM-ILD
High risk of progression and/or severe multiorgan involvement
Progressive pulmonary fibrosis
Rapidly progressive ILD over weeks to few months
Immunosuppressive treatment
Glucocorticoids
Calcineurine inhibitors (CNI), rituximab
Mycophenolate Azathioprine
Combination therapy with high dose glucocorticoids, cyclophosphamide, rituximab, CNI, and IVIG
Nintedanib, combination of immunosuppressant and nintedanib
Combination therapy with high dose glucocorticoids and cyclophosphamide or rituximab with CNI; IVIG, Jak inhibitors, plasmapheresis may be considered
Monitoring
Treatment goals met
ILD progression, ILD and extrapulmonary involvement not controlled or treatment goals not met
Add on or switch of therapy may be considered:
• If on mono or combination immunosuppressive treatment, add or switch to other CNI, rituximab, JAK inhibitors, cyclophosphamide, IVIG
• If progressive pulmonary fibrosis, add nintedanib
• Biologics are to date not used in combination
• Avoid long-term use of high-dose glucocorticoids and steroid-sparing treatments may be considered
• Consider referral for lung transplant consideration in case of progressive and severe ILD
Conditional recommendation
Strong recommendation
Usual clinical practice

ORIGINAL ARTICLE

Nerandomilast in Patients with Progressive Pulmonary Fibrosis

Toby M. Maher, M.D.,[1,2] Shervin Assassi, M.D.,[3] Arata Azuma, M.D.,[4,5] Vincent Cottin, M.D.,[6] Anna-Maria Hoffmann-Vold, M.D.,[7,8] Michael Kreuter, M.D.,[9,10] Justin M. Oldham, M.D.,[11] Luca Richeldi, M.D.,[12] Claudia Valenzuela, M.D.,[13] Marlies S. Wijsenbeek, M.D.,[14] Emmanuelle Clerisme-Beaty, M.D.,[15] Carl Coeck, M.D.,[16] Hui Gu, Ph.D.,[17] Ivana Ritter, M.D.,[15] Arno Schlosser, M.Sc.,[18] Susanne Stowasser, M.D.,[15] Florian Voss, Ph.D.,[19] Gerrit Weimann, M.D.,[15] Donald F. Zoz, M.D.,[20] and Fernando J. Martinez, M.D.,[21] for the FIBRONEER-ILD Trial Investigators*

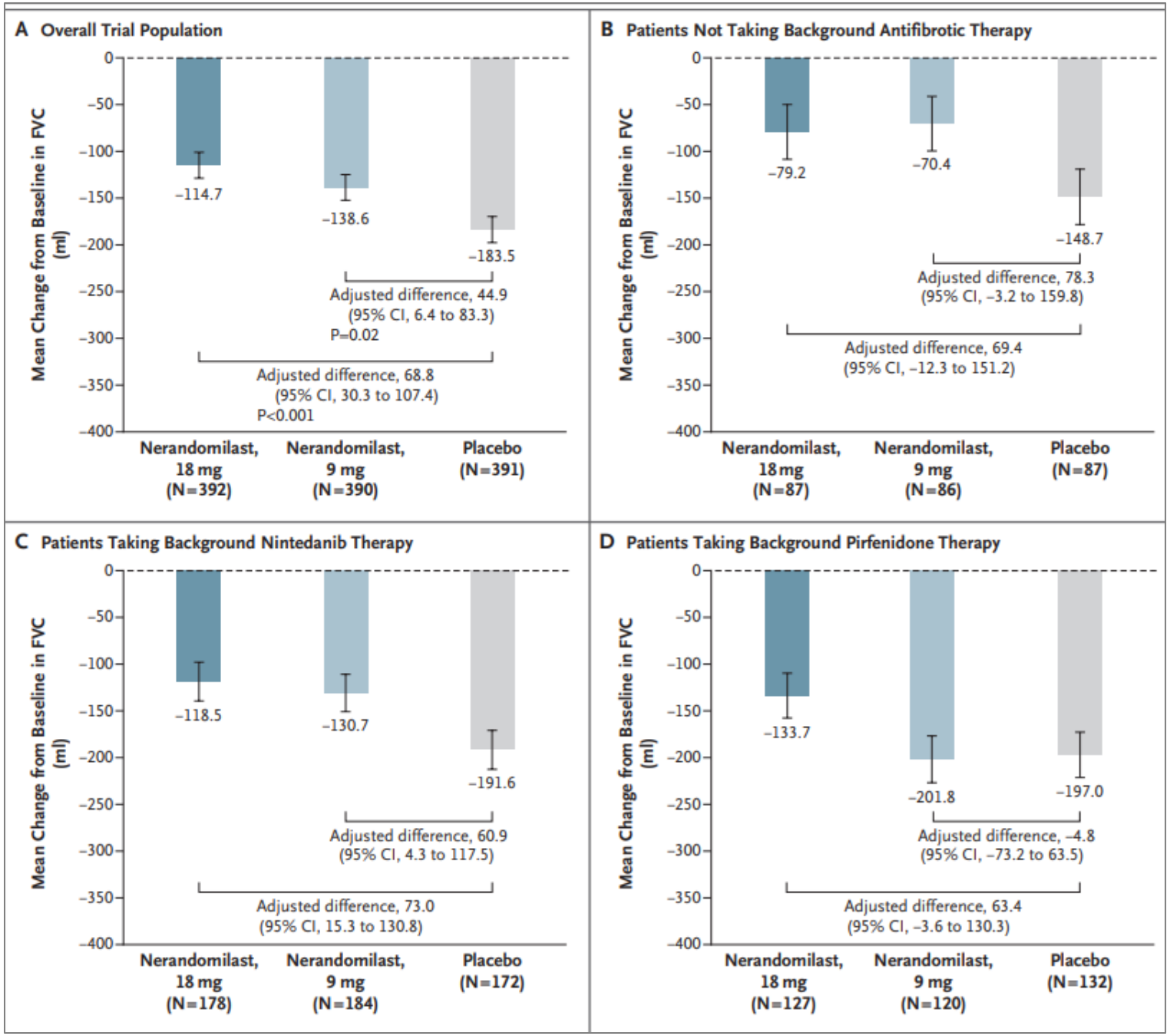


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nerandomilast in Patients with Idiopathic Pulmonary Fibrosis

Luca Richeldi, M.D.,[1] Arata Azuma, M.D.,[2,3] Vincent Cottin, M.D.,[4] Michael Kreuter, M.D.,[5,6] Toby M. Maher, M.D.,[7,8] Fernando J. Martinez, M.D.,[9] Justin M. Oldham, M.D.,[10] Claudia Valenzuela, M.D.,[11] Emmanuelle Clerisme-Beaty, M.D.,[12] Maud Gordat, M.Sc.,[13] Daniel Wachtlin, M.Sc.,[14] Yi Liu, Ph.D.,[15] Christina Schlecker, M.D.,[16] Susanne Stowasser, M.D.,[12] Donald F. Zoz, M.D.,[17] and Marlies S. Wijsenbeek, M.D.,[18] for the FIBRONEER-IPF Trial Investigators*



Inhaled Treprostinil in IPF

Preliminary Baseline Data from the TETON Phase 3 Clinical Trials of Inhaled Treprostinil in the Treatment of Idiopathic Pulmonary Fibrosis

S.D. Nathan[1]; J. Behr[2]; V. Cottin[3]; P. Smith[4]; Y. Rao[4]; N. Breytenbach[4]; H. Bell[4]; L. Peterson[4]; K. Flaherty[5]

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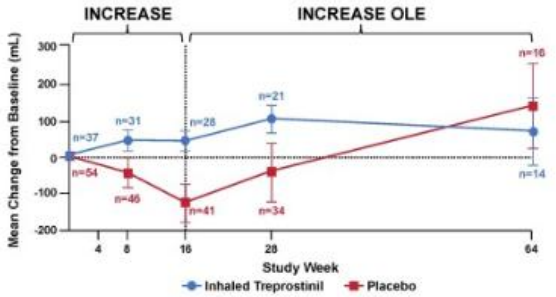
BACKGROUND

- Idiopathic pulmonary fibrosis (IPF) is a serious, chronic, progressive, fibrosing interstitial pneumonia with no known cause typically occurring in patients above 50 years of age.[1] It is characterized by progressive fibrosis and a radiological pattern known as usual interstitial pneumonia.[2] IPF greatly impacts quality of life and eventually leads to premature death from respiratory failure.
- In a post-hoc analysis of the landmark INCREASE study (NCT02630316) in patients with interstitial lung disease and associated pulmonary hypertension, inhaled treprostinil demonstrated placebo-corrected improvements in forced vital capacity (FVC) and reduced exacerbations of underlying lung disease.[3,4] In participants with IPF, between-treatment differences of 84.5 mL and 168.5 mL were observed in absolute FVC at Weeks 8 (p=0.11) and 16 (p=0.011), respectively.
- Sustained improvements in FVC were also observed in the open-label extension study (INCREASE OLE, NCT02633293) for patients previously assigned to inhaled treprostinil. Improvement in FVC was observed when patients previously assigned to placebo switched over to inhaled treprostinil at Week 16 in the open-label extension (Figure 1)[5].
- These results, combined with preclinical evidence of treprostinil's antifibrotic activity, support its investigation in the treatment of IPF and led to the initiation of the TETON program (TETON-1/RIN-PF-301, NCT04708782; TETON-2/RIN-PF-303, NCT05255991).

Figure 1. Change from Baseline in Absolute FVC for IPF Participants Enrolled in INCREASE and INCREASE OLE[5]



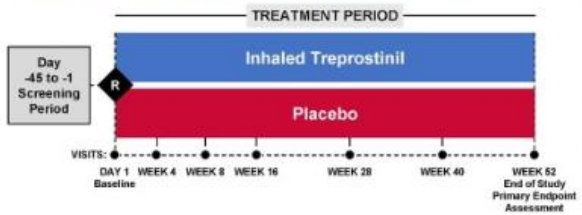
OBJECTIVES/ENDPOINTS

- The primary objective of the TETON-1 and TETON-2 studies is to evaluate the safety and efficacy of inhaled treprostinil in patients with IPF. The primary efficacy endpoint is change in absolute FVC at Week 52. Secondary efficacy endpoints include time to clinical worsening (first event of death, respiratory hospitalization, or ≥10% decline in % predicted FVC), time to first acute exacerbation of IPF, overall survival, change in % predicted FVC, and change in the King's Brief Interstitial Lung Disease Questionnaire at Week 52.

METHODS

- The TETON program consists of two replicate, 52-week, randomized, double-blind, placebo-controlled, Phase 3 studies, enrolling a total of 1195 participants.
- Eligible patients must have a diagnosis of IPF confirmed by central imaging review, along with an FVC ≥45% predicted. Stable background use of pirfenidone or nintedanib is allowed.
- The studies consist of a Screening Period of up to 45 days and a 52-week Treatment Period. During the Treatment Period, 6 visits to the clinic are required at Weeks 4, 8, 16, 28, 40, and 52 (Figure 2).
- Safety parameters include adverse events, hospitalizations, oxygenation, and laboratory parameters.
- All participants initiate inhaled treprostinil (6 mcg/breath) or placebo at a dose of 3 breaths (18 mcg) administered 4 times daily (QID; during waking hours) and titrate to a target dosing regimen of 12 breaths (72 mcg) QID.
- Patients who complete Week 52 on study drug are eligible to enter an open-label extension study (TETON OLE/RIN-PF-302, NCT04905693).

Figure 2. Study Design of Studies TETON-1 and TETON-2



RESULTS (Data presented through 10 July 2025)

- Enrollment in the TETON studies is complete. Sites are in 18 countries globally (Figure 3). As of 10 July 2025, 598 and 597 participants have been enrolled in TETON-1 and TETON-2, respectively.
- Most participants are male (79%) with a mean age of 72 (TETON-2) to 73 years (TETON-1), and approximately 4 years since IPF diagnosis. Participants in TETON-1 had mean baseline FVC of 2724 mL and mean % predicted FVC of 75%. Participants in TETON-2 had mean baseline FVC of 2696 mL and mean % predicted FVC of 77%. In both studies, mean % predicted lung diffusion capacity (DLCO) at baseline was 49%. In TETON-1 and TETON-2, approximately the same percentage of participants were on nintedanib (46% and 36%, respectively) and pirfenidone (32% and 39%, respectively) background therapy (Table 1).
- Comparison of the baseline demographics for the TETON studies (Table 1) with the PH-IPF Population in the landmark INCREASE study (Table 2), which served as the basis for initiation of the TETON program, suggests that patients with IPF alone have higher FVC, higher DLCO, and lower supplemental oxygen use than participants with concomitant PH.

RESULTS (cont.)

Table 1. Baseline Demographics: TETON-1 and TETON-2

	TETON-1 (N = 598)	TETON-2 (N = 593)
Age at Study Entry (years), mean (SD)	73.0 (6.6)	71.7 (7.3)
Female / Male	22.7% / 77.3%	19.9% / 80.1%
Time Since IPF Diagnosis (years), mean (SD)	3.585 (3.031)	3.880 (2.824)
Ethnicity		
Hispanic or Latino	5.0%	26.8%
Not Hispanic or Latino	92.8%	68.3%
Not Reported	1.3%	3.2%
Unknown	0.8%	1.7%
Race		
White	90.6%	83.8%
Asian	4.3%	11.8%
American Indian or Alaska Native	0.5%	0
Black or African American	1.7%	0.2%
Native Hawaiian/Pacific Islander	0.2%	0.2%
Multiple	0.8%	0.2%
Unknown	1.8%	3.9%
FVC (L), mean (SD)	2.72 (0.77)	2.70 (0.74)
Percent Predicted FVC (%), mean (SD)	74.71 (17.22)	76.76 (17.52)
Percent Predicted DLCO (%), mean (SD)	49.24 (18.45)	48.54 (19.38)
FEV_1/FVC Ratio, mean (SD)	0.804 (0.059)	0.810 (0.058)
Use of Supplemental Oxygen		
No	80.3%	87.0%
Yes	19.7%	13.0%
OSA Treatment		
Positive Airway Pressure Device	22.4%	8.8%
Oral Appliance	0.7%	0
Other	1.0%	0.3%
Background Therapy		
Nintedanib	45.8%	36.1%
Pirfenidone	31.6%	39.3%
No background therapy	22.6%	24.6%

Abbreviations: DLCO, lung diffusion capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; OSA, obstructive sleep apnea; SD, standard deviation

Figure 3. TETON Program Country Selection

RESULTS (cont.)

Table 2. Baseline Demographics: INCREASE PH-IPF Population

Age at Study Entry (years), mean (SD)	70.8 (9.1)
Female / Male	34% / 66%
Ethnicity (%)	
Hispanic or Latino	11%
Not Hispanic or Latino	89%
Race (%)	
White	83%
Black	11%
Asian	4%
Native Hawaiian/Pacific Islander	2%
FVC (mL), mean (SD)	2192.1 (724.6)
Percent Predicted FVC (%), mean (SD)	60.8 (17.7)
Percent Predicted DLCO (%), mean (SD)	29.1 (11.5)
Use of Supplemental Oxygen	
No	26%
Yes	74%
Background Therapy	
Nintedanib	21%
Pirfenidone	33%
No background therapy	47%

Abbreviations: DLCO, lung diffusion capacity; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; PH, pulmonary hypertension; SD, standard deviation

CONCLUSIONS

The prospectively designed TETON Phase 3 clinical trials aim to explore inhaled treprostinil for the treatment of IPF and may offer a much-needed inhaled treatment option for this vulnerable patient population.

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1. Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of idiopathic pulmonary fibrosis: An official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2018;198(5):e44-e68. 2. Cottin V, Hirani NA, Hotchkin DL, et al. Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. *Eur Respir Rev*. 2018;27(150):180076. 3. Waxman AB, Restrepo-Jaramillo R, Thenappan T, et al. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. *N Engl J Med*. 2021;384(4):325-334. 4. Nathan SD, Waxman A, Rajagopal S, et al. Inhaled Treprostinil and forced vital capacity in patients with interstitial lung disease and associated pulmonary hypertension: a post-hoc analysis of the INCREASE study. *Lancet Respir Med*. 2021;9(11):1266-1274. 5. Waxman AB, Restrepo-Jaramillo R, Thenappan T, et al. Long-term inhaled treprostinil for PH-ILD: INCREASE open-label extension study. *Eur Respir J* 2023; in press (https://doi.org/10.1183/13993003.02414-2022).

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Presented at ERS 2025 | Amsterdam, Netherlands | September 27-October 1, 2025
Disclosure: These studies are sponsored by United Therapeutics Corporation.

United Therapeutics

Inhaled Treprostinil in PPF

ELEVATE IPF phase 2b open-label extension demonstrates durable efficacy of deupirfenidone

Compared to Placebo and Pirfenidone in IP
ELEVATE Part A Resu

Argyrios E. Tzouvelekis, M.D., Ph.D.; Respiratory Medicine, University of Patras, PATRAS, Greece; Mark J. Hamblin, M.D.; Internal Medicine, University of Kansas Medical Center, Kansas City, KS, USA; Won-Il Choi, M.D., Ph.D.; Dept. of Internal Medicine, Hanyang University, Myongji Hospital, Goyang-si, Republic of Korea; Amy Hajari Case, M.D.; Pulmonary, Critical Care, and Sleep, Piedmont Healthcare, Atlanta, GG, USA; Ioannis P. Tomos, M.D., Ph.D.; 5th Pulmonary Medicine Department, Sotiria Chest Diseases Hospital, Athens, Greece; Jessica E. Shore, R.N, Ph.D. Pulmonary Fibrosis Foundation, Chicago, IL, USA; Miguel A. Bergna, M.D.; Research, CEMER, Florida, Vicente López, Argentina; David Golod, Ph.D.; PureTech Health, Boston, MA, USA; Eric Elenko, Ph.D.; PureTech Health, Boston, MA, USA; Yanqiong Zhang, Ph.D.; PureTech Health, Boston, MA, USA; Camilla S. Graham, M.D., M.P.H.; PureTech Health, Boston, MA, USA; Jin Woo Song, M.D., Ph.D.; Pulmonary and Critical Care Medicine, Asan Medical Center, Seoul, Republic of Korea; Tejaswini Kulkarni, M.D., M.P.H.; Medicine, University of Alabama at Birmingham, Birmingham, AL, USA; Toby M. Maher, M.D. Ph.D.; Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; National Heart and Lung Institute, Imperial College, London, UK and the ELEVATE IPF Investigators

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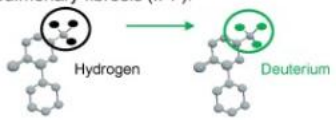

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- Determine the longer-term effect of deupirfenidone on lung function in patients with idiopathic pulmonary fibrosis (IPF).
- Assess change in forced vital capacity (FVC) over 52 weeks using an integrated analysis of deupirfenidone data from a 26-week, randomized, double-blind Phase 2b study (Part A) and the first 26 weeks of an open-label extension (Part B).
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Figure 1. Study Design - 170 of 187 Participants Who Completed Part A Enrolled in Part B, Open-label Extension (OLE)

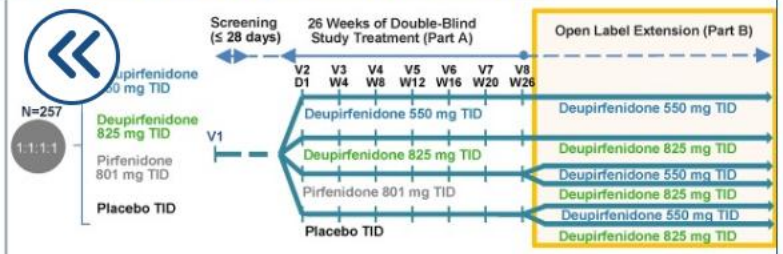
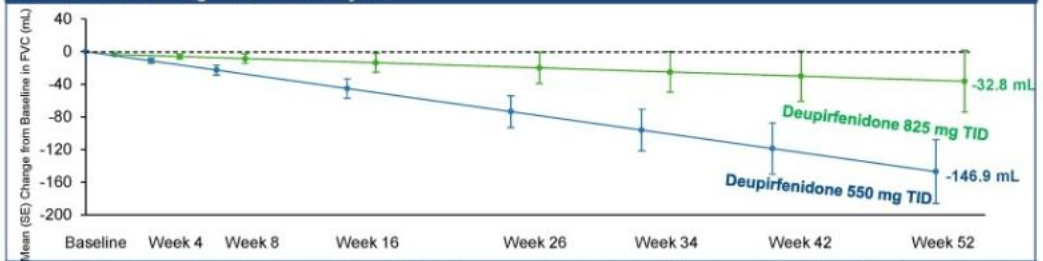


Table 1. Characteristics of the Randomized Patients at Baseline According to Treatment Arm

	Placebo TID (N=65)	Pirfenidone 801 mg TID (N=63)	Deupirfenidone 550 mg TID (N=65)	Deupirfenidone 825 mg TID (N=64)
Mean Age	71.7	71.0	70.9	70.0
Percent Male	72.3%	74.6%	70.8%	67.2%
Percent White/Caucasian	58.5%	66.7%	61.5%	65.6%
Prior nintedanib use <6 months, n (%)	1 (1.5)	2 (3.2)	3 (4.6)	3 (4.7)
Years of IPF diagnosis (mean, SD)	1.4 (1.75)	1.8 (2.50)	1.8 (2.42)	2.1 (2.30)
Baseline FVC (ml)	2550.5	2682.6		2659.2 (871.70)

Figure 3. Adjusted Mean (SE) Change from Baseline in FVC Over Time – Part A + Part B Mixed Model Regression Analysis



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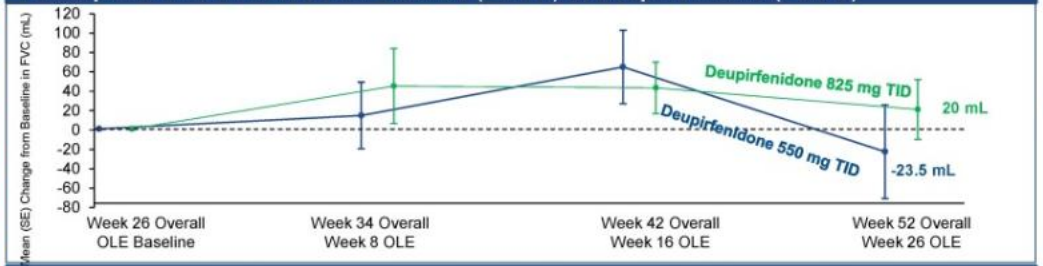

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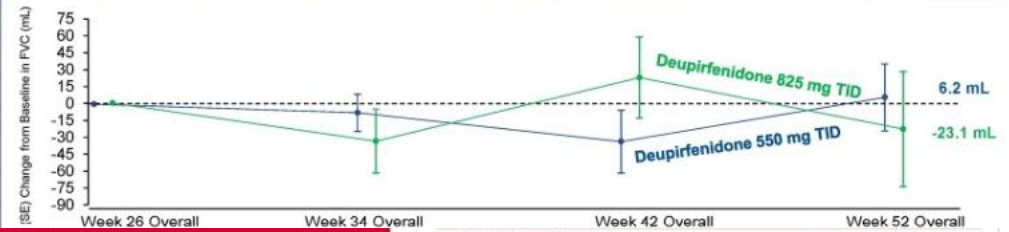

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SOC/PT	Deupirfenidone 550 mg TID (N=83) n (%)	Deupirfenidone 825 mg TID (N=87) n (%)
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Summary of Most Common (≥10% in Any Treatment Group) TEAEs by PT		
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Upper Respiratory Infections	14 (16.9)	15 (17.2)
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CONCLUSIONS

- Initial open-label extension data suggest the FVC change for deupirfenidone 825 mg TID is durable out to at least 52 weeks (FVC -32.8 mL) and approached the level of lung function decline expected in healthy older adults (Luoto, 2019).
- Patients who switched from placebo or pirfenidone in Part A to deupirfenidone in Part B (OLE) demonstrated stable lung function decline over 26 weeks.
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ACKNOWLEDGEMENTS

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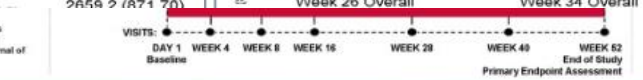

No background therapy	43.2%

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* = Results for the ongoing placebo-controlled blinded study are presented for participants overall.

4. Kolb M, Orfanos SE, Lambers C, et al. The antifibrotic effects of inhaled treprostinil: an emerging option for ILD. *Adv Ther.* 2022;39:3881-3895. 5. Waxman AB, Restrepo-Jaramillo R, Thenappan T, et al. Long-term inhaled treprostinil for PH-ILD: INCREASE open-label extension study. *Eur Respir J* 2023; in press (https://doi.org/10.1183/13993003.02414-2022).

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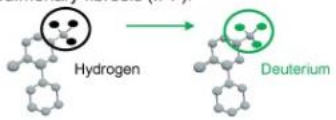

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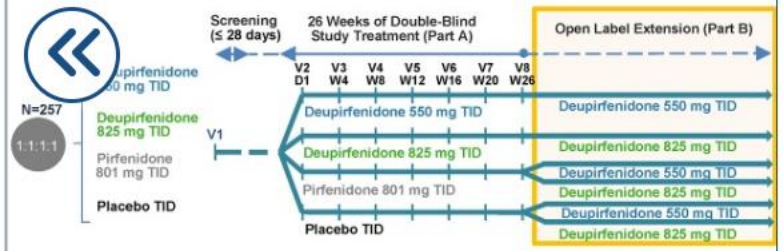

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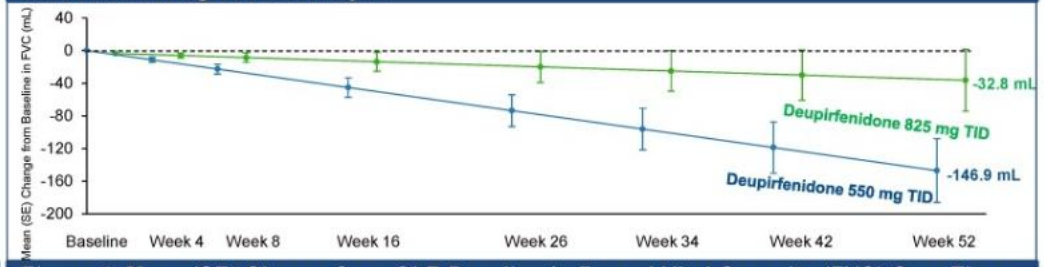

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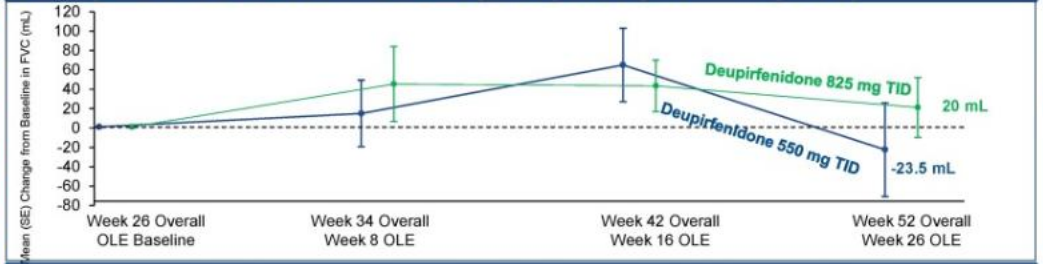

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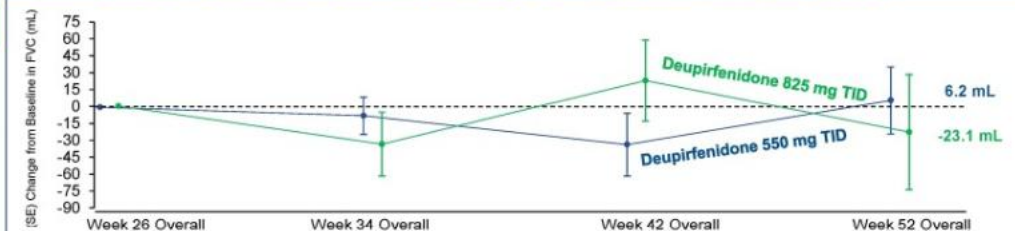

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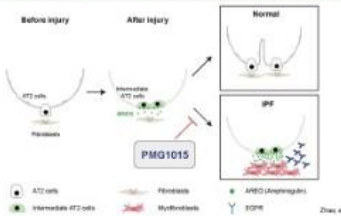
PMG1015 demonstrates well-tolerated safety and favorable FVC changes after 12 weeks of treatment in IPF patients

Toby M. Maher[1], Huaping Dai[2], Chen Wang[2], Huilan Zhang[3], Qun Luo[4], Jinfu Xu[5], Jiuwu Bai[5], Mengshu Cao[6], Feng Li[7], Jing Geng[2], Muhunthan Thillai[8], Simon Walsh[8], Kiril Kirov[8], Rui Zhao[9], Nan Tang[9]

1. Keck School of Medicine of USC - Los Angeles, USA 2. China-Japan Friendship Hospital, Beijing, China 3. Tongji Hospital, Huazhong University of Sciences and Technology, Wuhan, China 4. The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China
5. Shanghai Pulmonary Hospital, Shanghai, China 6. Nanjing Drum Tower Hospital, Nanjing, China 7. Shanghai Chest Hospital, Shanghai, China 8. Qureight Ltd - Cambridge, United Kingdom 9. Pulmongene Ltd, Beijing, China

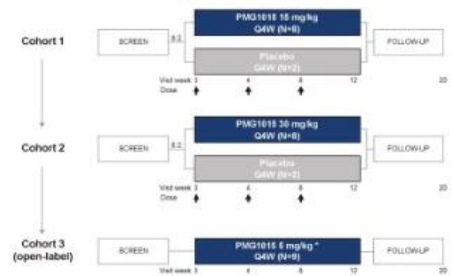
PMG1015 is a mAb against Amphiregulin (AREG), a newly discovered key driver of lung fibrosis

- Idiopathic Pulmonary Fibrosis (IPF) is a relentlessly progressive and fatal disease. Currently approved drugs have modest efficacy, tolerability challenges, frequent oral dosing, and risk of drug-drug interactions.
- PMG1015 has demonstrated very favorable safety and immunogenicity and robust PK in both preclinical and clinical studies.
- AREG directly binds epidermal growth factor receptor (EGFR), activating downstream signaling and promoting fibroblast cell proliferation and transdifferentiation into myofibroblasts.
- Serum AREG levels are dramatically elevated and highly prognostic for poor clinical outcomes in patients with IPF and Progressive Pulmonary Fibrosis (PPF).[1,2]



A Phase 1b Randomized, Double-Blind, Multicenter, Placebo-controlled Trial in IPF Patients

Phase 1b Trial Design



* Original Cohort 3 40 mg/kg dose reduced to 0 mg/kg based on emerging favorable nonclinical efficacy data and translational study findings.

Endpoints

- **Primary:** Safety, Tolerability
- **Secondary:** PK, Immunogenicity
- **Exploratory:** Target engagement, Circulating biomarkers, Lung function, HRCT biomarkers

All inferential statistical analyses were exploratory. *P* values are presented nominally and should be interpreted with caution.

Baseline Characteristics

Baseline characteristics were generally balanced across study groups

A total of 29 IPF patients were randomized into 3 cohorts to receive PMG1015 or Placebo.

Characteristic	Placebo (N=4)	PMG1015			
		All Treatment (N=22)	5 mg/kg (N=7)	15 mg/kg (N=7)	30 mg/kg (N=8)
Male, n (%)	3 (75.0)	20 (100)	6 (100)	7 (100)	7 (100)
Age, mean (SD) years	69.5 (12.3)	64.5 (9.4)	64.0 (9.1)	61.4 (11.6)	68.1 (8.7)
Body weight, mean (SD) kg	71.4 (21.3)	69.1 (10.6)	72.6 (10.0)	69.4 (13.9)	64.9 (8.1)
Time since IPF Dx, mean (SD) mo	8.6 (7.4)	5.3 (13.1)	5.0 (11.0)	1.3 (0.8)	9.5 (20.2)
HRCT UIP, n (%)	3 (75.0)	16 (72.0)	7 (77.8)	5 (62.5)	6 (75.0)
%FVC, mean (SD)	81.6 (23.2)	78.4 (16.1)	76.2 (12.2)	75.3 (15.6)	83.9 (20.5)
%DLCO, mean (SD)	66.4 (5.0)	52.4 (14.2)	54.1 (14.1)	42.8 (5.9)	59.2 (15.7)
GAP stage, n (%) GAP I GAP II	4 (100) 0 (0)	13 (52.0) 12 (48.0)	4 (44.4) 5 (55.6)	3 (37.5) 5 (62.5)	6 (75.0) 2 (25.0)
Previous antifibrotic treatment (pirfenidone, nintedanib), n (%)	0 (0)	7 (28.0)	2 (22.2)	3 (37.5)	2 (25.0)

GAP = staging tool; HRCT = high-resolution computed tomography; UIP = usual interstitial pneumonia; FVC = forced vital capacity; DLCO = diffusion capacity of the lung for carbon monoxide; GAP = gender, age, physiology; SD = standard deviation.

Adverse Events and Immunogenicity

PMG1015 was safe and well tolerated in IPF patients across all doses

- Incidence of TEAEs was low and comparable between PMG1015 and Placebo groups.
- Most common TEAEs were upper respiratory tract infection and hyperlipidaemia.

PMG1015 showed clean immunogenicity with no anti-drug antibodies across all dose levels

AEs, n (%) of participants	Placebo (N=4)	PMG1015			
		All Treatment (N=22)	5 mg/kg (N=7)	15 mg/kg (N=7)	30 mg/kg (N=8)
TEAEs	3 (75.0)	20 (90.9)	7 (77.8)	7 (87.5)	6 (75.0)
BAEs	0	3 (12.0)	1 (11.1)[a]	0	2 (25.0)[a]
Grade 3 TEAEs	0	3 (12.0)	1 (11.1)[a]	0	2 (25.0)[a]
Grade 4 TEAEs	0	0	0	0	0
Deaths	0	1 (4.0)	0	0	1 (12.5)
TEAEs leading to termination of study drug	0	0	0	0	0
TEAEs leading to study withdrawal	0	1 (4.0)	0	0	1 (12.5)
TEAEs related to study drug	2 (50.0)	11 (44.0)	2 (22.2)	6 (75.0)	3 (37.5)
SAEs, Grade 3 TEAEs, deaths,TEAEs leading to study withdrawal related to study drug	0	0	0	0	0
ADA	0	0	0	0	0

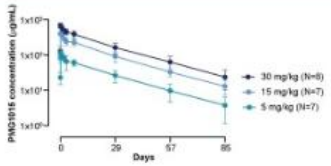
TEAE = treatment-emergent adverse event; SAE = serious adverse event; ADA = anti-drug antibodies.
a) Acute upper respiratory tract infection (Coronavirus positive) b) Bacterial pneumonia (Influenza virus positive, H1 Like subtype) (n=1 c) Bacterial pneumonia (Influenza virus positive)

Most common TEAEs (n ≥ 10% in Placebo or All Treatment):

TEAEs, n (%)	Placebo (N=4)	PMG1015			
		All Treatment (N=22)	5 mg/kg (N=7)	15 mg/kg (N=7)	30 mg/kg (N=8)
Upper respiratory tract infection	0	3 (12.0)	1 (11.1)	1 (12.5)	1 (12.5)
Hyperlipidaemia	0	3 (12.0)	1 (11.1)	2 (25.0)	0
Chest discomfort	1 (25)	1 (4.0)	0	1 (12.5)	0
Muscle strength abnormal	1 (25)	0	0	0	0
Eosinophil count increased	1 (25)	0	0	0	0
Dacryoadenitis acquired	1 (25)	0	0	0	0
Supraventricular extrasystoles	1 (25)	0	0	0	0
Myalgia	1 (25)	0	0	0	0
Synovial cyst	1 (25)	0	0	0	0

Pharmacokinetics

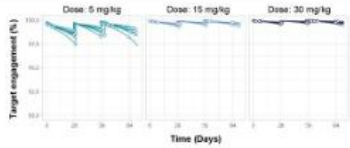
After the third IV infusion, PMG1015 showed linear and dose-proportional PK profiles



Target Engagement

Efficient binding of PMG1015 to human AREG established in IPF patients

- 1 month after the 3rd infusion, average drug-to-target molar ratios ~1000 fold across different cohorts
- ~ 98% of target occupancy was achieved across all three dose groups.
- Levels of circulating OPN, downstream of AREG signaling, were reduced 7.83% at week 12 by PMG1015.



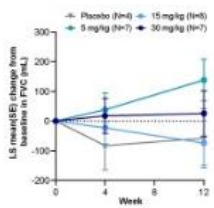
A PK-PD model was used to simulate target engagement, defined as the ratio of bound target to total target.

Lung Function Change from Baseline at Week 12

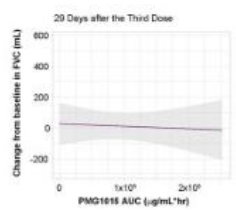
Improved FVC at week 12 observed in PMG1015 group

- At week 12, FVC improved by a mean of 97.5 mL in PMG1015 group corrected for Placebo.
- FVC increased in 45% of patients in PMG1015 group, versus 0% in Placebo group.

FVC change: No dose response

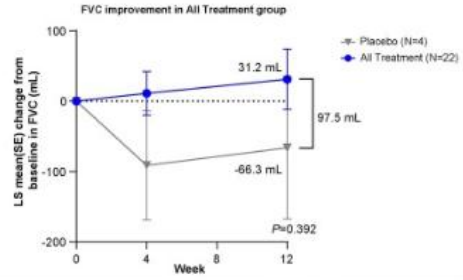


FVC change: No exposure response



Based on high level of target engagement and lack of dose response and exposure response, exploratory efficacy analyses focus on the All Treatment and Placebo groups.

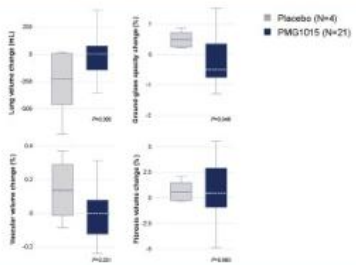
FVC improvement in All Treatment group



- **Placebo-corrected All Treatment group differences in TLC (+172 mL) and %DLco (+1.48%) at week 12 favored PMG1015 over Placebo**

HRCT Change from Baseline at Week 12

- **Placebo-corrected estimate of lung volume improved 229.9 mL in PMG1015 group**
- **Favorable effects on ground-glass opacity and vascular volume**



Conclusions:

- **PMG1015 was safe and well tolerated**
  - Incidence of TEAEs was low and similar between PMG1015 and Placebo
- **PK was linear and dose proportional and no anti-drug antibodies were observed**
- **Robust target engagement (> 98%) was observed across all dose levels**
- **FVC mean change from baseline at week 12 improved 31.2 mL in PMG1015 group, representing a 97.5 mL Placebo-corrected treatment effect**
  - Changes in TLC and HRCT lung volume also suggest favorable treatment effects
- **HRCT biomarker changes generally favored PMG1015, including a reduction in ground glass opacities**

These encouraging Phase 1b results support the conduct of a larger and longer-duration trial in patients with IPF to confirm safety and efficacy.

Several drugs on the horizon

- Monotherapy or combination therapy
- If ongoing decline, switch or add another drug?
- Further reduction in FVC decline compared to monotherapy?
- Synergy or overlapping toxicities?
- Increased cost

Predictive Power of the e-Lung Weighted Reticulovascular Score for Mortality in Progressive Pulmonary Fibrosis

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1. University of Chicago, Chicago, IL, United States, 2. Brainomix Limited. Oxford, OX2 0JJ, United Kingdom.

Background

- The care of patients with interstitial lung disease (ILD) is challenging with high rates of disease progression occurring in many cases.
- Progressive pulmonary fibrosis (PPF) is frequent and drives mortality in ILD.
- Current diagnostic classification criteria do not uniformly predict mortality risk.
- The e-Lung (Brainomix, Oxford, UK) weighted reticulovascular score (WRVS), an imaging biomarker of pulmonary fibrosis, offers prognostic value.
- We aimed to determine the predictive value of WRVS for mortality in patients with ILD and its prognostic benefit when combined with established clinical predictors.

Methods

- We retrospectively evaluated ILD patients at University of Chicago (IRB#17-1617), and assessed WRVS on baseline HRCT, defining high-risk WRVS as ≥20%. PPF was classified per ATS clinical, physiological and radiological criteria. Univariate and multivariable Cox regression assessed WRVS, GAP-ILD score, and PPF as mortality predictors. Harrell's c-statistic evaluated the impact of WRVS on model performance.

Figure 1. Automated Imaging Biomarkers of Fibrosis Progression Using e-Lung

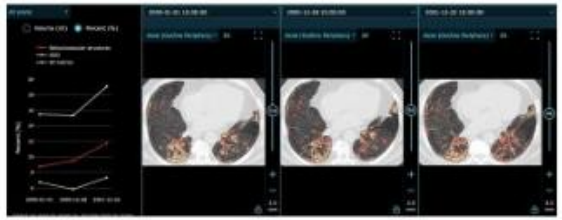
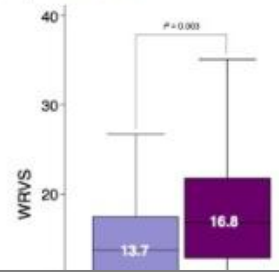


Figure 2. Baseline Weighted Reticulovascular Score (WRVS) Stratified by PPF Status. Boxplots show higher baseline WRVS in PPF compared to non-PPF (median 16.8 vs 13.7; *P* = 0.003).



Results

Table 1. Baseline Clinical Characteristics by PPF Status (UChicago Cohort, N=272)

Variable	No PPF (n=122)	PPF (n=150)	P-value
Age, years (mean ± SD)	61.4 ± 11.7	63.6 ± 10.3	0.10
Male sex, n (%)	53 (51)	70 (49)	0.80
White race, n (%)	67 (64)	107 (75)	0.37
Ever smoker, n (%)	58 (56)	82 (58)	0.71
Pack-years (mean ± SD)	19.7 ± 22.9	22.9 ± 21.8	0.33
FVC % predicted (mean)	68.4 ± 19.7	66.8 ± 18.0	0.50
DLCO % predicted (mean)	56.5 ± 19.9	53.8 ± 22.4	0.32
Immunosuppressive therapy, n (%)	41 (35)	70 (48)	**0.03**
Antifibrotic therapy, n (%)	13 (11)	16 (11)	0.98
ILD subtype, n (%)			0.20
– IPF	36 (30)	41 (27)	
– IPAF	18 (15)	32 (21)	
– CTD-ILD	38 (31)	38 (25)	
– Fibrotic HP	15 (12)	28 (19)	
– Unclassifiable	15 (12)	11 (7)	
Median follow-up, months	65.1	47.8	**0.04**

Figure 3. Weighted Reticulovascular Score (WRVS) Trajectories and Prognostic Value in PPF. (A) Longitudinal WRVS trajectories with 95% confidence intervals stratified by PPF status. PPF WRVS starting score was 3.97 points higher than non-PPF (P < 0.001). Annual WRVS increase: PPF 0.16 (95% CI −0.19 to 0.50) vs non-PPF 0.17 (95% CI 0.01 to 0.31). **(B)** Kaplan–Meier survival by baseline CT WRVS score showing high WRVS scores were associated with increased mortality (P < 0.001) in all subjects; and **(C)** in non-IPF PPF subjects (P < 0.001).

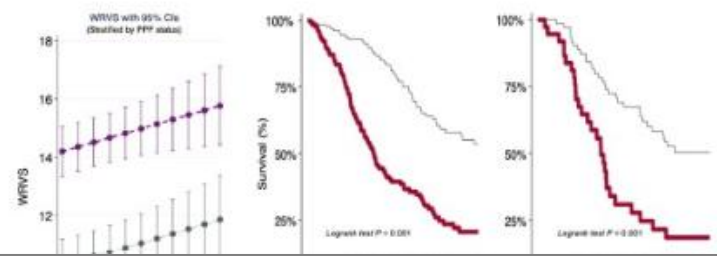


Figure 4. Improvement in Harrell's c-statistic for Mortality Prediction (*P*<0.001)

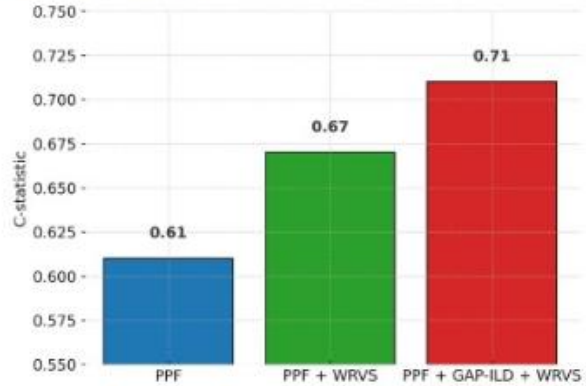


Table 3. Predictors of Mortality Risk in Subjects with Progressive Pulmonary Fibrosis (PPF)

Variable	HR	95% CI	*P*-value
Univariate analyses			
High-risk WRVS	2.90	2.11 - 3.98	< 0.001
GAP-ILD score	1.43	1.28 - 1.59	< 0.001
PPF status	2.10	1.50 - 2.94	< 0.001
Multivariable analyses			
High-risk WRVS	1.87	1.32 – 2.66	< 0.001

- *adjusted for sex, age, FVC, diffusing capacity of the lungs for carbon monoxide, ILD subtype, immunosuppressive therapy, and PPF status*

Conclusions

- **WRVS is a robust, independent predictor of mortality in ILD.**
- **Adds value when combined with PPF and GAP-ILD.**
- **Supports personalized ILD care and trial stratification.**

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Longitudinal Changes in Quantitative Imaging Biomarkers are Associated with Increased Risk of Mortality in Connective Tissue Disease-Related Interstitial Lung Disease

Qureight.

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OPEN SOURCE IMAGING CONSORTIUM against Interstitial Lung Disease

Objectives

Connective tissue disease-associated interstitial lung disease (CTD-ILD) encompasses a broad spectrum of fibrotic lung disorders linked to autoimmune conditions. Prognosis is highly variable and difficult to predict. While pulmonary function tests (PFTs) are standard for monitoring, they lack spatial resolution and are insensitive to regional structural change.

High-resolution CT (HRCT) is increasingly central to both clinical care and trial design in ILD. Quantitative CT (qCT) techniques — particularly those powered by deep learning — offer reproducible, objective biomarkers for cohort enrichment, risk stratification, and treatment monitoring. These tools are particularly relevant in CTD-ILD, where disease often affects multiple anatomical compartments, including airways, vessels, and parenchyma.

Qureight has developed a suite of deep learning models capable of segmenting and quantifying multiple lung compartments from HRCT, including airway volume, pulmonary vessel volume, fibrosis, and ground-glass opacification. These multi-compartment qCT tools are ideally suited to CTD-ILD, which rarely conforms to a single-compartment pattern. Despite this potential, qCT remains underused in CTD-ILD, and longitudinal studies linking structural change to outcome are scarce. This study applies the full Qureight pipeline to a large real-world cohort to evaluate associations between structural metrics and survival.

Methods

A total of 528 connective tissue disease-associated interstitial lung disease (CTD-ILD) patients were identified from which 68 patients had paired baseline and follow-up high-resolution CT (HRCT) scans suitable for quantitative analysis. Patients were obtained from a Global ILD Imaging Biorepository, The Open-Source Imaging Consortium (OSIC)

Imaging biomarkers were extracted using Qureight's proprietary deep learning-based quantitative CT (qCT) pipeline, which provides volumetric measurements of fibrosis, ground-glass opacification (GGO), pulmonary vessel volume, and airway volume (Figure 1). All volumes were expressed as a percentage of total lung volume. Clinical data included percent predicted forced vital capacity (%ppFVC) and all-cause mortality.

Two clinical outcomes were analysed: all-cause mortality and progressive disease, defined as ≥10% relative decline in %ppFVC or death within 12 months. Cox proportional hazards models were constructed for each qCT feature, incorporating both baseline values and 3-month interval changes, and were adjusted for baseline %ppFVC. Optimal cut points were derived for each feature to stratify patients. Harrell's concordance index (C-index) was used to evaluate model performance. Kaplan-Meier survival curves and stratified threshold analyses were used to visualise outcome separation.

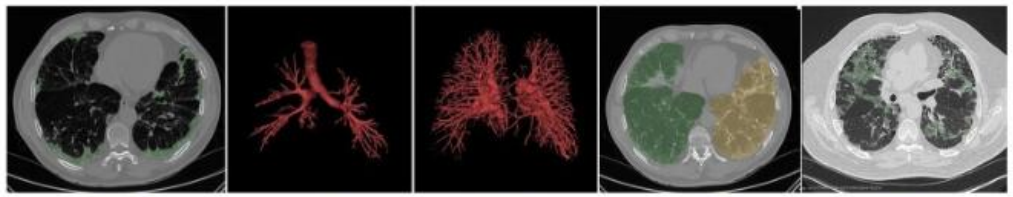

Figure 1. Quantitative CT-derived imaging biomarkers in CTD-ILD. Panel A: Fibr8, quantifying the volume of fibrotic parenchyma. Panel B: Air8, measuring central and peripheral airway volume. Panel C: Vascul8, quantifying total pulmonary vascular volume. Panel D: Lung8

Results

Underlying CTD diagnoses by subtype is shown in Table 1. Baseline associations between qCT biomarkers and mortality are shown in Table. 2.

Among the 68 patients with longitudinal imaging, adjusting for baseline %ppFVC, both baseline and 3-month interval change in fibrosis extent were significantly associated with increased risk of mortality (baseline HR: 1.07, p<0.0001, 95% CI: 1.03–1.10; 3-month change HR: 1.28, p=0.02, 95% CI: 1.04–1.58; C-index: 0.80). Similarly, baseline and 3-month change in pulmonary vascular volume were associated with mortality (baseline HR: 4.84, p=0.01, 95% CI: 1.46–15.97; 3-month change HR: 1.12, p=0.007, 95% CI: 1.03–1.23; C-index: 0.73) (Table 3)

Change in airway volume over 3 months was also a significant predictor of mortality (HR: 1.02, p<0.0001, 95% CI: 1.01–1.03; C-index: 0.76). A 1% increase in fibrosis extent over 3 months conferred a 1.6-fold increased risk of progressive disease (defined as ≥10% decline in FVC or death within 12 months). However, 3-month changes in airway or pulmonary vascular volume were not significantly associated with progression risk.

Variable (n=528)	N
Rheumatoid Arthritis-ILD	79
Systemic Sclerosis-ILD	184
Polymyositis/Dermatomyositis	65
Mixed Connective Tissue Disease	44
Systemic Lupus Erythematosus	22
Non-specific CTD	134

Table 1. CTD diagnosis by subtype

Results

Variable (n=528)	HR	95%CI	p-value
Fibr8® (fibrosis extent %)	1.02	1.01-1.04	<0.0001
Air8® (Airway volume %)	3.80	2.24-6.45	<0.0001
Vascul8® (Vascular volume %)	2.29	1.69-3.11	<0.0001
Glass8® (GGO extent %)	1.02	1.00-1.05	0.046
Lung8® (Total lung volume)	0.99	0.99-1.00	0.055

Table 2. Univariate associations between qCT biomarkers and mortality

Variable (n=68)	HR	95%CI	p-value
Fibr8®	1.07	1.03-1.10	<0.0001
Fibr8® 3-month change	1.28	1.03-1.23	0.007
Vascul8®	4.84	1.46-15.97	0.01
Vascul8® 3-month change	1.12	1.03-1.23	0.007

Table 3. Multivariate associations between baseline qCT and 3-month change in qCT biomarkers and mortality

Conclusion

1. Short-term longitudinal changes in quantitative CT biomarkers — particularly fibrosis extent and pulmonary vascular volume — are independently associated with increased mortality risk in CTD-ILD.
2. These findings highlight the value of deep learning-based, multi-compartment qCT analysis as a powerful tool for early risk stratification.
3. The ability to detect meaningful structural progression within three months suggests that qCT may play a critical role in future trial design, enabling cohort enrichment, early surrogate endpoint assessment, and personalised treatment strategies in this heterogeneous patient population.

Home monitoring

Longitudinal home monitoring in interstitial lung disease: report on 12-month data capture

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[1]Peter Gorer Department of Immunobiology, King's College London, UK, [2]Guy's and St Thomas' NHS Trust, UK, [3]patientMpower, Ireland, [4]Royal Devon University Healthcare NHS Trust, UK, [5]Exeter Patients in Collaboration (EPIC) for Pulmonary Fibrosis Research, University of Exeter, UK, [6]Action for Pulmonary Fibrosis, UK, [7]School of Health Sciences, University of Birmingham, UK, *Joint lead authors

Home Monitoring Programme

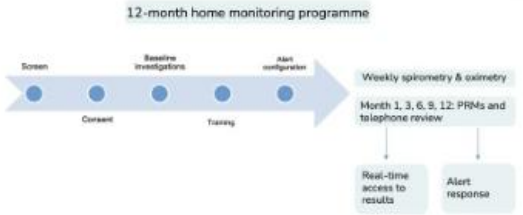


Figure 1. 12-month remote monitoring programme

Patients were asked to record one acceptable spirometry and resting pulse oximetry measurement weekly and patient reported measures (PRMs) 3-monthly. Clinicians had access to the results in real-time and reviewed alerts, set to each individual's baseline. Remote clinician review involved assessing measurements, quality, trends, change from baseline and contributing factors leading to clinical intervention.

Rationale

Long-term home monitoring and remote clinician review offers an alternative approach for patients with interstitial lung disease (ILD). It may:

- enable early identification of clinically significant respiratory deterioration and acute exacerbations,
- improve timely access to treatments at the patient's home,
- and enhance quality-of-life (QoL).

The impact of continuously monitoring home spirometry, oxygen saturation and health-related quality-of-life (HQoL) is not well understood. Understanding the relationships between these measurements may improve early identification of clinical change.

Aims

To explore the relationships between home forced vital capacity (FVC), pulse oximetry and patient-reported measures (PRMs), including symptoms and HQoL scores.

Methods

Patients from ILD specialised services in the UK were enrolled in a home monitoring programme. This is demonstrated in figure 1.

A retrospective comparative analysis of a 12-month home monitoring programme was undertaken. HQoL scores (EQ-5D-5L) were compared with home FVC and oxygen saturation measurements, modified Medical Research Council dyspnoea scale (mMRC), cough severity visual analogue scale (VAS), generalised anxiety disorder-7 (GAD-7) and patient health questionnaire-9 (PHQ-9) at baseline and 3-monthly intervals.

Results

186 patients were enrolled in the home monitoring programme between March 2022 and January 2023. 10 patients did not initiate home monitoring due to withdrawn consent, anxiety and difficulties with technology during training. 147 patients completed PRMs at least once at baseline and/or 3-monthly intervals.

Strongly negative correlations were observed between EQ-5D-5L and mMRC, GAD-7 and PHQ-9 and between mMRC and predicted home FVC and oxygen saturations.

Positive correlations were observed between mMRC and cough severity VAS, GAD-7 and PHQ-9. This is demonstrated in table 1.

Results

		EQ-5D-5L	FVC % predicted	Oximetry	MMRC	Cough severity VAS	GAD-7	PHQ-9
EQ-5D-5L	Correlation coefficient	1.000	0.282**	0.239**	**-0.723****	-0.284**	**-0.560****	**-0.743****
	Sig (2-tailed)		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	N	461	362	402	169	223	220	221
FVC % predicted	Correlation coefficient	0.282**	1.000	0.310**	**-0.501****	-0.280**	-0.049	-0.167*
	Sig (2-tailed)	<0.001		<0.001	<0.001	<0.001	0.511	0.025
	N	362	362	322	135	181	179	179
Oximetry	Correlation coefficient	0.239**	0.310**	1.000	**-0.303****	-0.177*	-0.087	-0.185*
	Sig (2-tailed)	<0.001	<0.001		<0.001	0.014	0.233	0.011
	N	402	322	402	153	193	190	191
mMRC	Correlation coefficient	**-0.723****	**-0.501****	**-0.303****	1.000	**0.316****	**0.447****	**0.592****
	Sig (2-tailed)	<0.001	<0.001	<0.001		0.002	<0.001	<0.001
	N	169	135	153	169	95	91	91
Cough severity VAS	Correlation coefficient	-0.284**	-0.280**	-0.177*	**0.316****	1.000	0.205**	0.363**
	Sig (2-tailed)	<0.001	<0.001	0.014	0.002		0.002	<0.001
	N	223	181	193	95	223	219	218
GAD-7	Correlation coefficient	**-0.560****	-0.049	-0.087	**0.447****	0.205**	1.000	0.723**
	Sig (2-tailed)	<0.001	0.511	0.233	<0.001	0.002		<0.001
	N	220	179	190	91	219	220	217
PHQ-9	Correlation coefficient	**-0.743****	-0.167*	-0.185*	**0.592****	0.363**	0.723**	1.000
	Sig (2-tailed)	<0.001	0.025	0.011	<0.001	<0.001	<0.001	
	N	221	179	191	91	218	217	221

Table 1. Spearman's rank correlation coefficients

Strongly negative correlations were observed between EQ-5D-5L and MMRC, GAD-7 and PHQ-9 and between mMRC and predicted home FVC and oxygen saturations. Positive correlations were observed between mMRC and cough severity VAS, GAD-7 and PHQ-9. **Correlation is significant at the 0.01 level (2-tailed) *Correlation is significant at the 0.05 level (2-tailed)

Conclusion

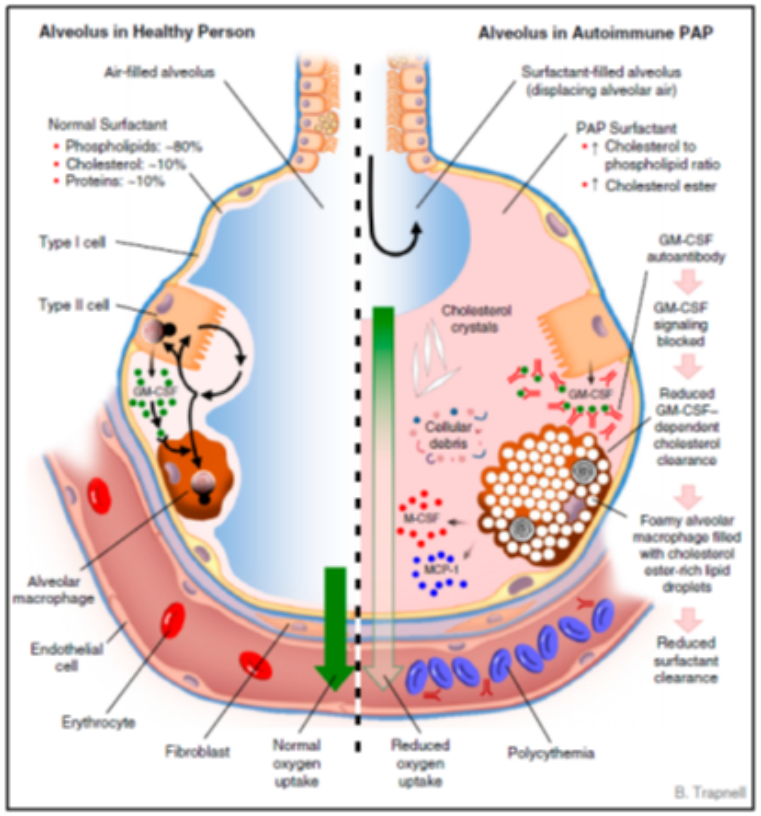
Home monitoring with a combination of spirometry, pulse oximetry and PRMs can enable the identification of clinical change. Optimising the choice and frequency of PRMs is a step closer to personalising care for patients with ILD. Further statistical analysis of these measurements and resulting clinician interventions and applying machine learning to assess whether these measurements can predict acute exacerbations is recommended.



European Respiratory Society guidelines for the diagnosis and management of pulmonary alveolar proteinosis

Cormac McCarthy [1,24], Francesco Bonella [2,24], Marissa O'Callaghan[1], Clairelyne Dupin [3], Tiago Alfaro [4], Markus Fally [5], Raphael Borie [3], Ilaria Campo [6], Vincent Cottin [7], Aurelie Fabre [8], Matthias Griese [9], Alice Hadchouel [10], Stephane Jouneau [11], Maria Kokosi[12], Effrosyni Manali[13], Helmut Prosch [14], Bruce C. Trapnell[15], Marcel Veltkamp[16,17], Tisha Wang[18], Ingrid Toews[19], Alexander G. Mathioudakis [20,21,25] and Elisabeth Bendstrup [22,23,25]

Pulmonary Alveolar Proteinosis (PAP)

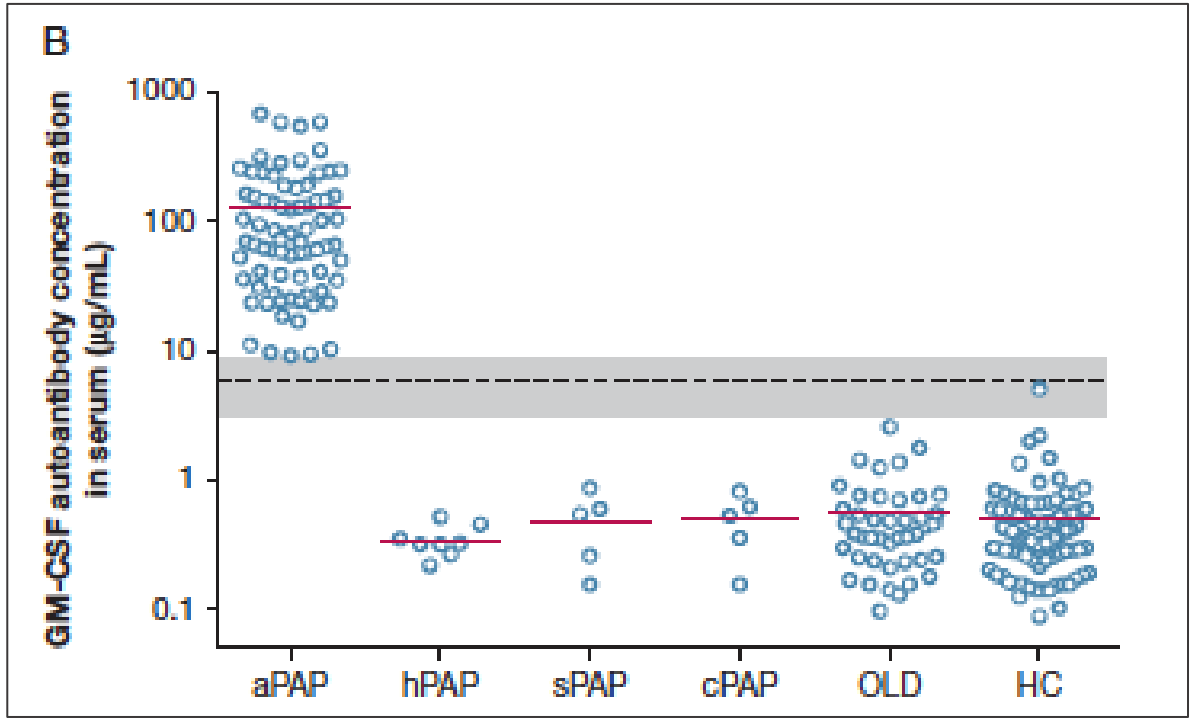


Maintenance of surfactant as a thin layer on the alveolar surface (that is, surfactant homeostasis) is tightly regulated by

1) **balanced production in type II alveolar epithelial cells,**
2) **secretion into the alveolar space, and**
3) **clearance by either recycling or catabolism in type II alveolar epithelial cells or uptake and clearance by alveolar macrophages**

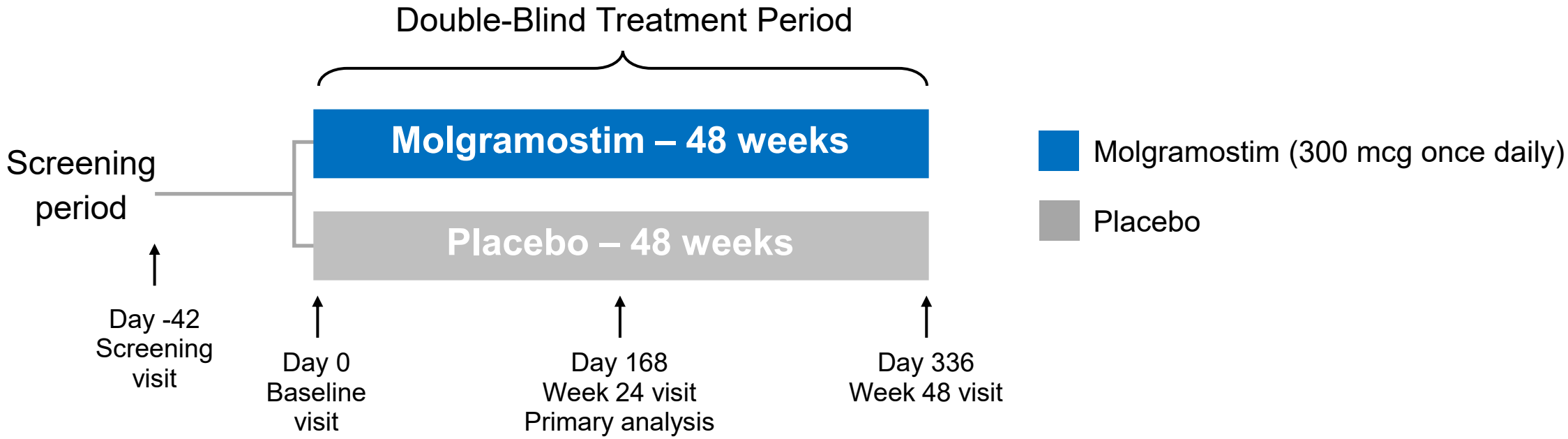
In healthy alveoli, pulmonary GM-CSF stimulates the survival, proliferation, differentiation, and functions of alveolar macrophages

Anti-GM-CSF antibodies



Kitamura T, et al. Am J Respir Crit Care Med. 2000
Uchida K, et al. J Immunol Methods. 2014
McCormack C, et al. Chest. 2018

IMPALA-2 clinical trial study design



Primary Endpoint

- Gas Transfer: $DL_{CO\%}$ at 24 weeks

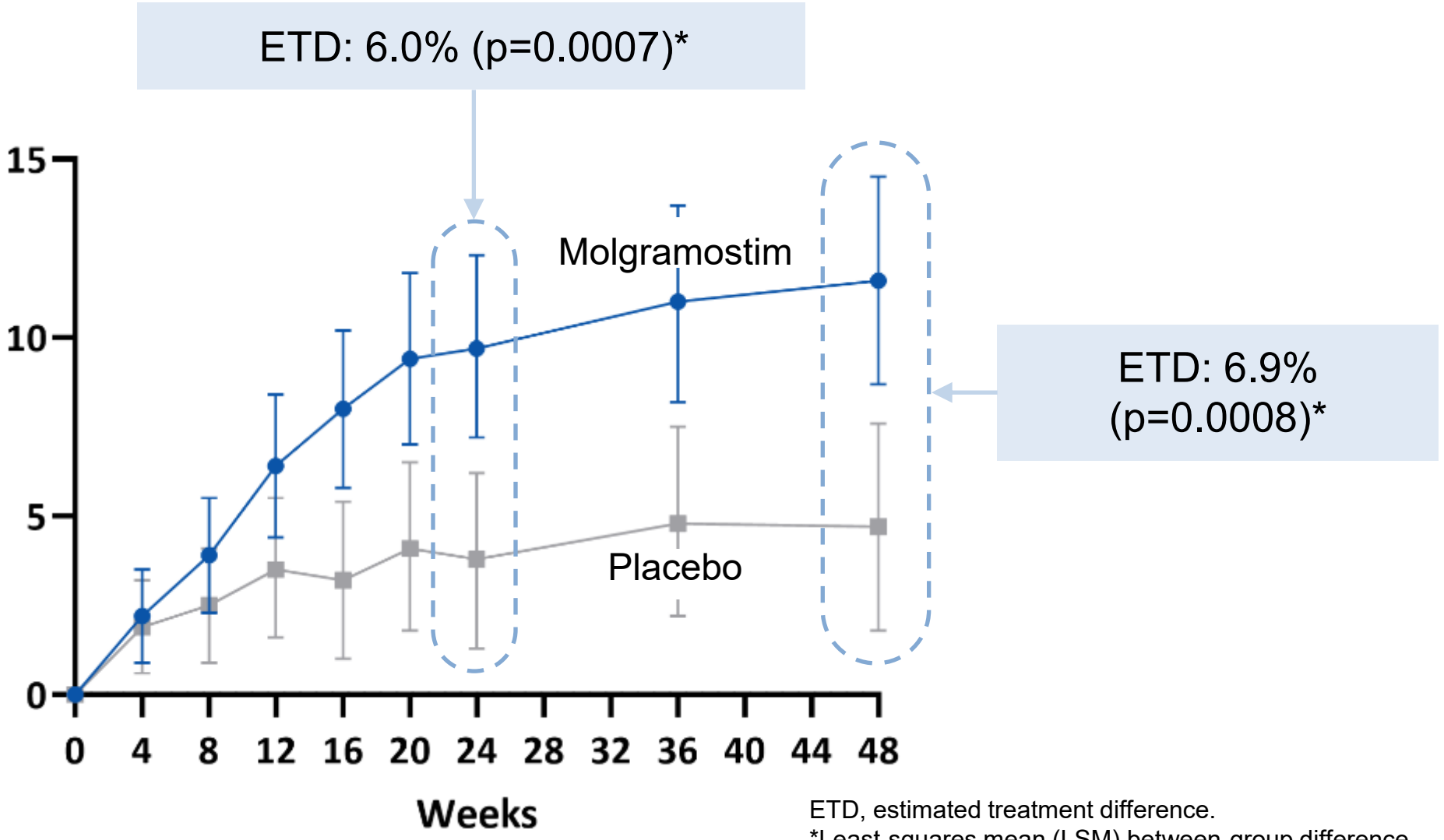
Key Secondary Endpoints

- $DL_{CO\%}$ at 48 weeks
- SGRQ Total Score at 24 and 48 weeks
- SGRQ Activity Score at 24 and 48 weeks
- Exercise capacity test using treadmill at 24 and 48 weeks

SGRQ, Saint George's Respiratory Questionnaire

IMPALA-2 primary endpoint: Change in $DL_{CO\%}$ at 24 Weeks

Molgramostim improves pulmonary gas exchange



ETD, estimated treatment difference.
*Least-squares mean (LSM) between-group difference.

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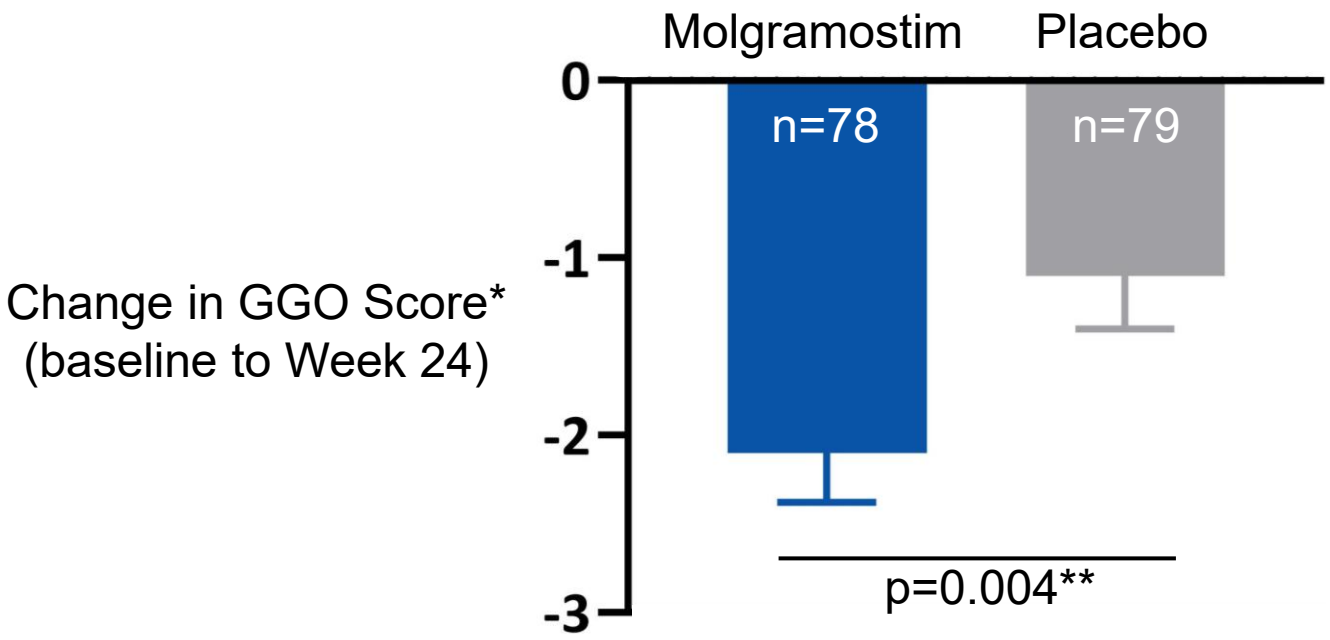
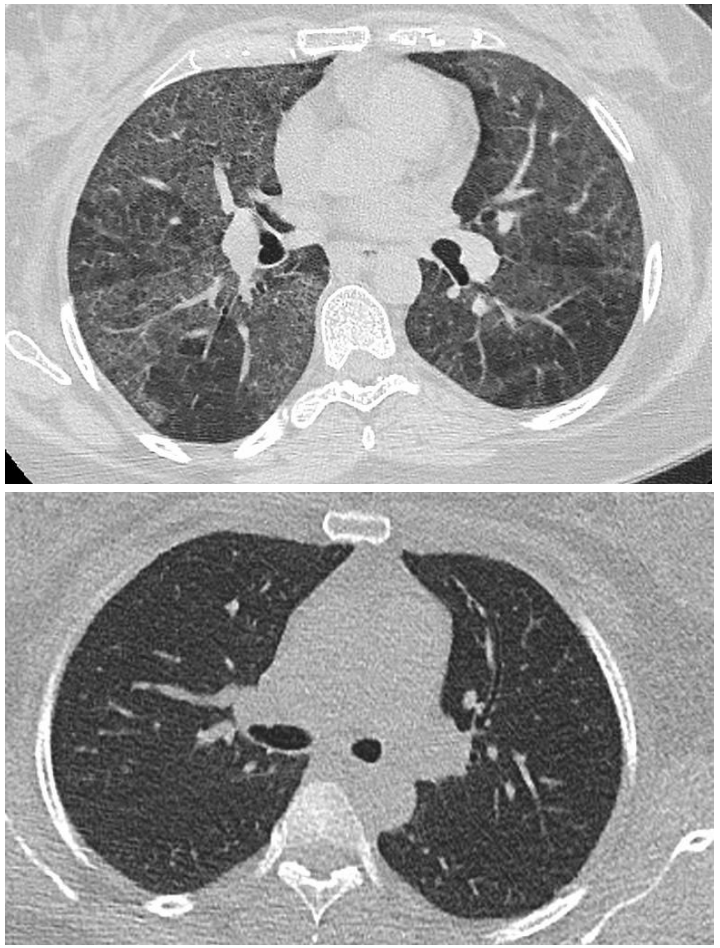
IMPALA-2 exploratory endpoint: Change in ground-glass opacification (GGO) score at 24 and 48 Weeks

Molgramostim reduces pulmonary surfactant burden



Representative 'Responder'



Baseline

Week 24

Interpretation: Results support primary endpoint

*mean ± SEM (range 0-15; higher=worse).
**p-value based on post hoc analysis. GGO, ground-glass opacity.

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IMPALA-2 adverse events during the blinded-treatment period

Molgramostim is well tolerated

Adverse events (AEs) in >10% of patients in any treatment arm during the double-blind treatment period

Treatment-Emergent Adverse Event	Molgramostim n=81 n (%)	Placebo n=83 n (%)
Most common		
COVID-19	18 (22)	8 (10)
Cough	17 (21)	18 (22)
Pyrexia	11 (14)	9 (11)
Nasopharyngitis	11 (14)	7 (8)
Arthralgia	9 (11)	7 (8)
Headache	9 (11)	7 (8)
Diarrhea	9 (11)	2 (2)
Alveolar proteinosis	4 (5)	12 (14)

- **97% of patients completed the double-blind treatment period**
  - Participation in open-label treatment period: 100% of double-blind treatment period completers
- **Low discontinuations in double-blind treatment period: 3%**
- **No deaths in either group**

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What the future holds

New Therapeutic Agents & Drug Targets

Precision Medicine, Biomarkers, and Diagnostics

- **Genetic and epigenetic profiling** to understand different disease subtypes
- **Blood biomarkers** for early diagnosis, disease activity, disease behaviour and response to therapy
- **Advances in imaging**: better CT-based quantification, and AI/deep learning to improve detection and classification.
- **New diagnostic techniques**: transbronchial lung cryobiopsy, robotic bronchoscopy

Clinical Trial Design / Platforms

- **Platform/adaptive trials** are being developed (e.g. REMAP-ILD) to test multiple interventions more efficiently

Non-Pharmacological / Symptom Management

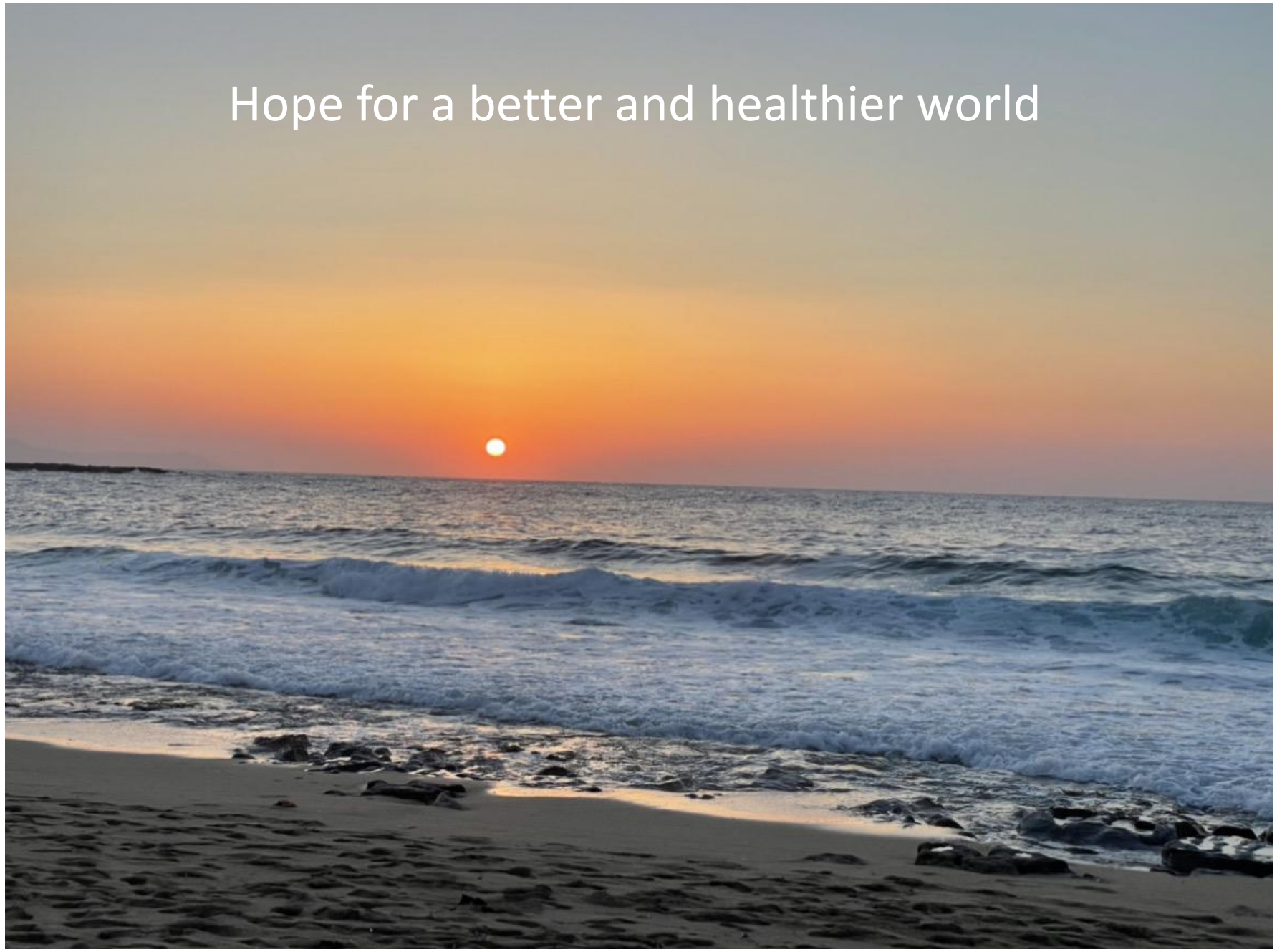
- **Better tools for home monitoring** (e.g. handheld spirometry)
- **Addressing quality of life**: cough, breathlessness, fatigue, etc. Some trials are specifically addressing cough or symptom burden.

Comorbidities and Complications

- **Pulmonary hypertension in ILD (PH-ILD):** new therapies (e.g. inhaled tyrosine kinase inhibitors like Seralutinib) are emerging
- **ILD and lung cancer**
- Understanding **interstitial lung abnormalities (ILA)**

Mechanistic Understanding

- Better understanding of what drives fibrosis
- Identifying triggers of disease progression, acute exacerbations, and environmental/genetic interactions


Hope for a better and healthier world