

# Essences From ERS Congress 2021

**COBEL DAROU**



# Biomarker discovery, development, and implementation in interstitial lung diseases

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Essences From  
ERS Congress 2021

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ERS Congress 2021

**How can we discover novel biomarkers?**

***'Omics vs targeted discovery***

**What needs to be done to develop biomarkers for clinical use?**

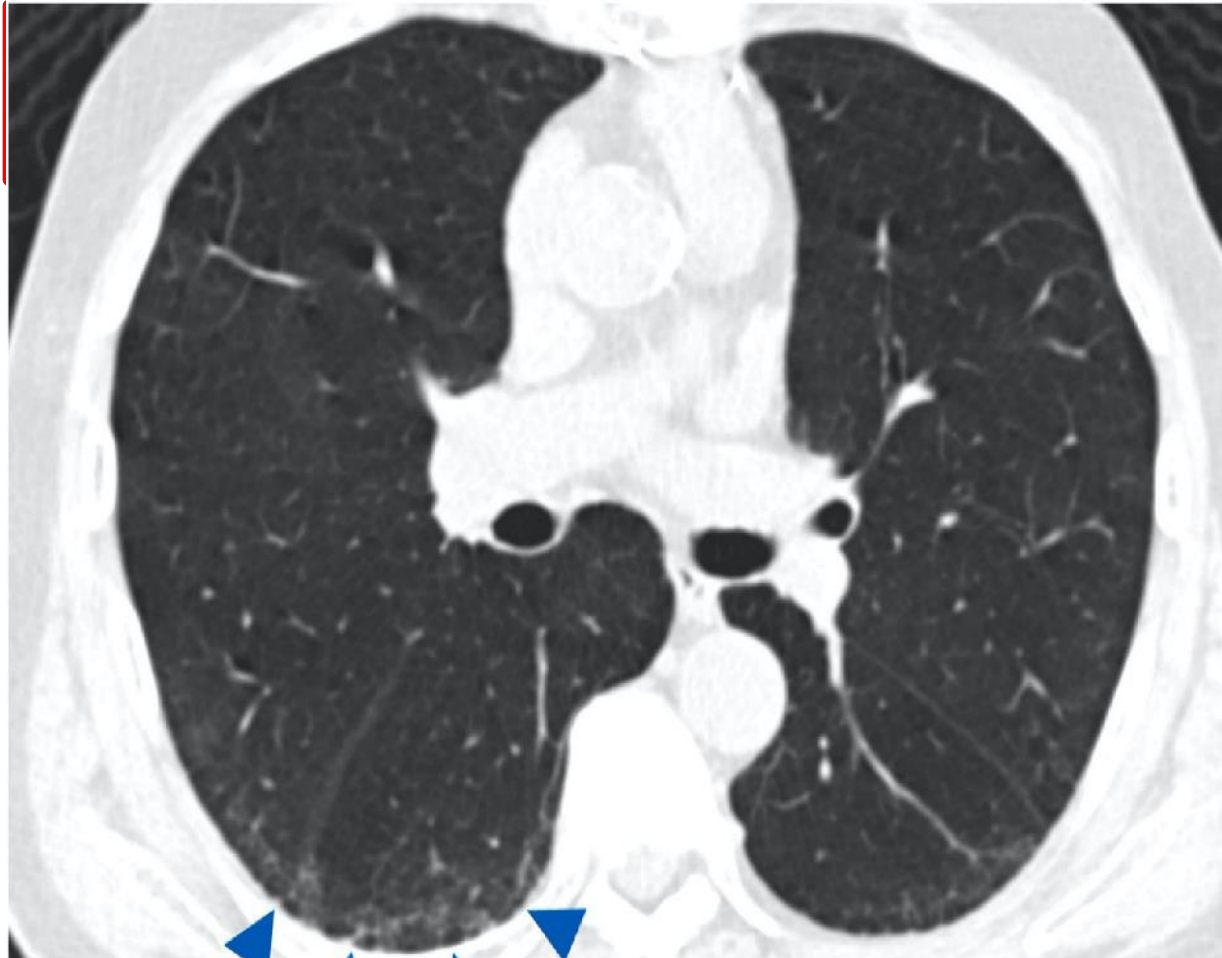
***(Generalizable) Standardize assays that replicate across cohorts***

**How can we integrate biomarkers into clinical practice?**

***Understand their role in different situations and demonstrate utility***

***Diagnostic, Prognostic, Endotypic, Theranostic***

# Diagnostic



# Prognostic

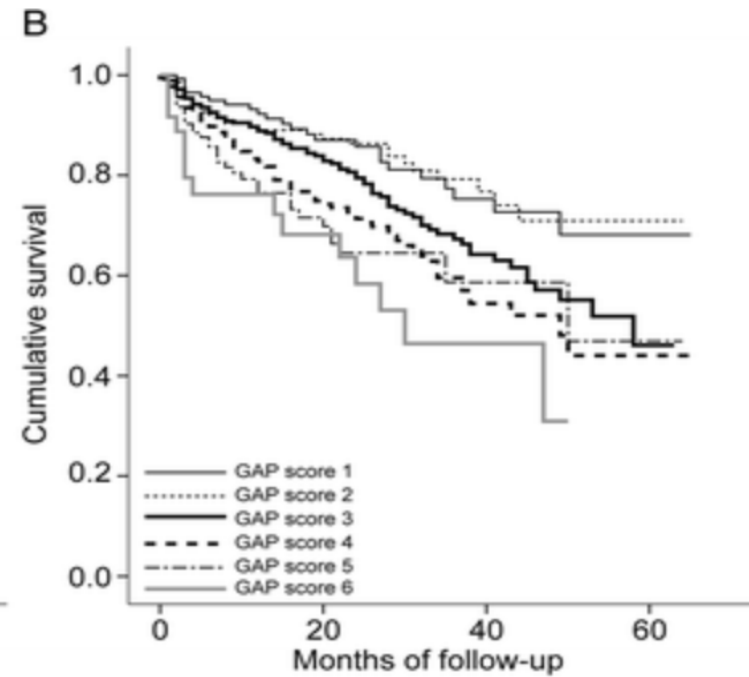
**Gender (Sex)**

**Age**

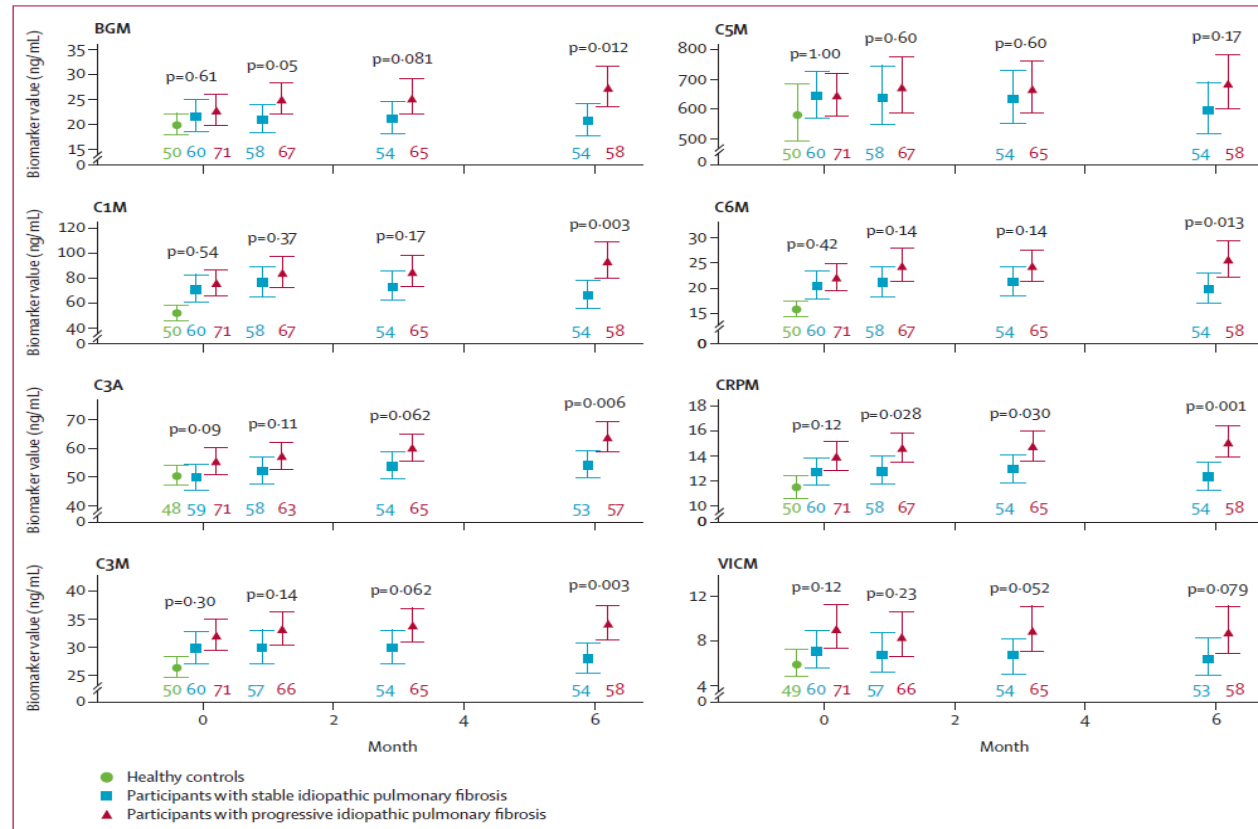
**Physiology**

FVC

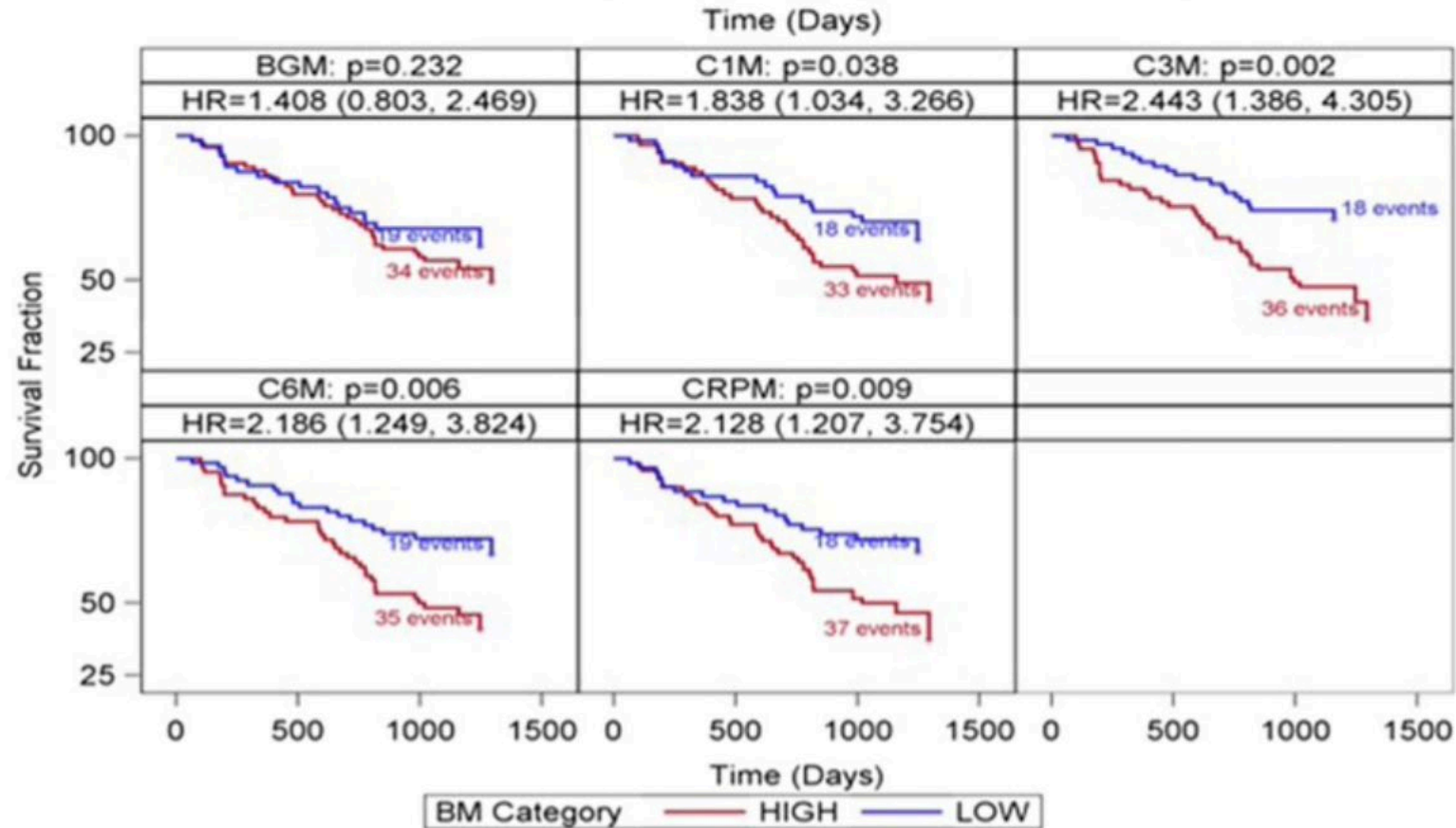
DLco



# Matrix derived markers distinguish progressive from stable IPF

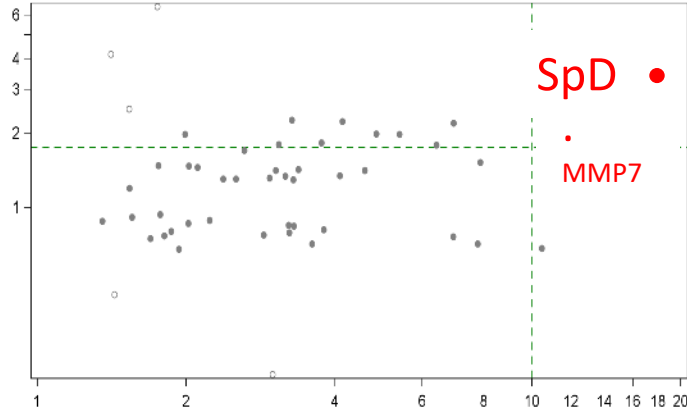


# Patients with rising C1M, C3M, C6M and CRPM have increased risk of mortality

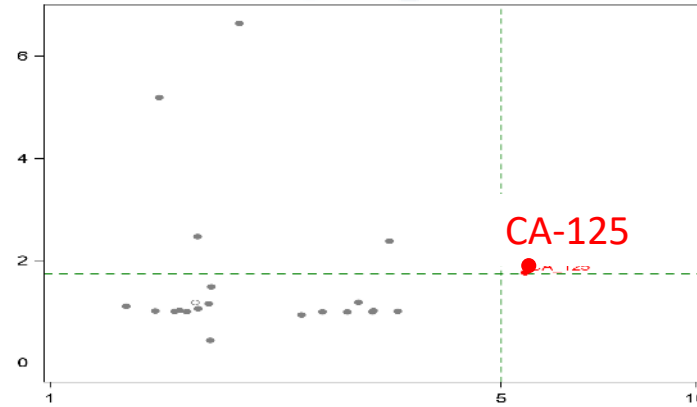


# Unbiased Proteomic Analysis Identified Four Candidate Biomarkers for Assessment in IPF

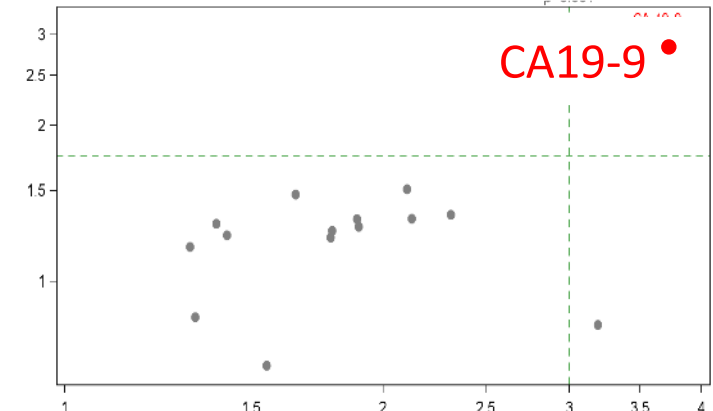
Disease versus Healthy



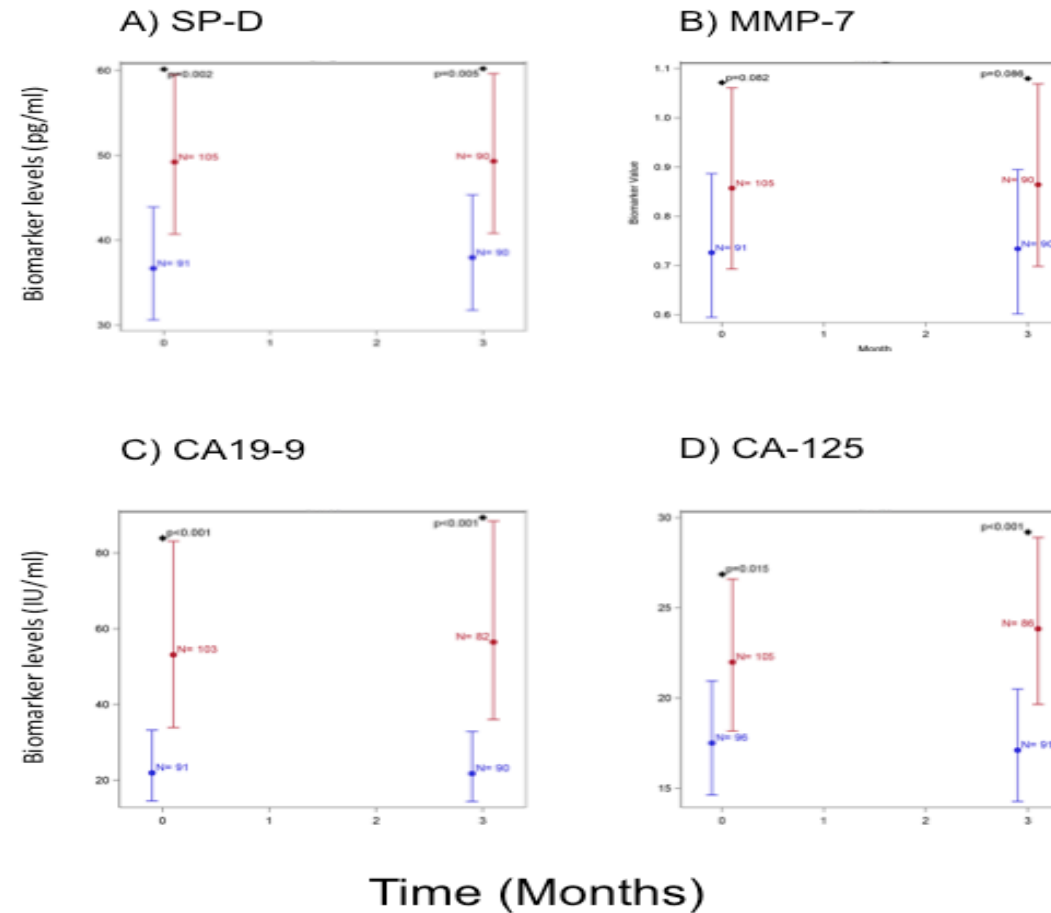
Rising levels and Mortality



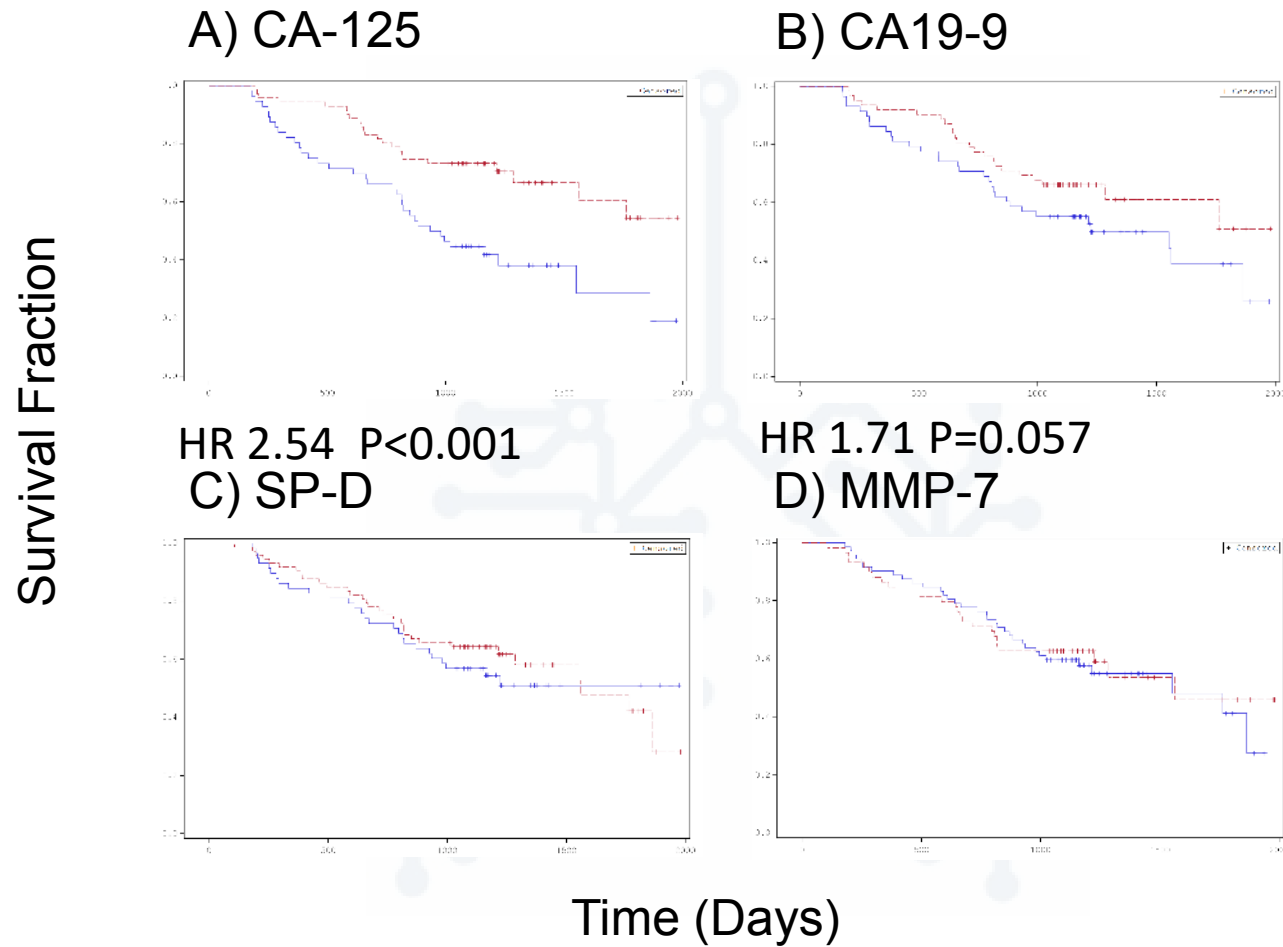
Progression versus Stable



# Replication Analysis Confirms SpD, CA19-9 and CA-125 Identify Patients with progressive Disease



# Rising Levels of CA-125 Predicts Increased Mortality

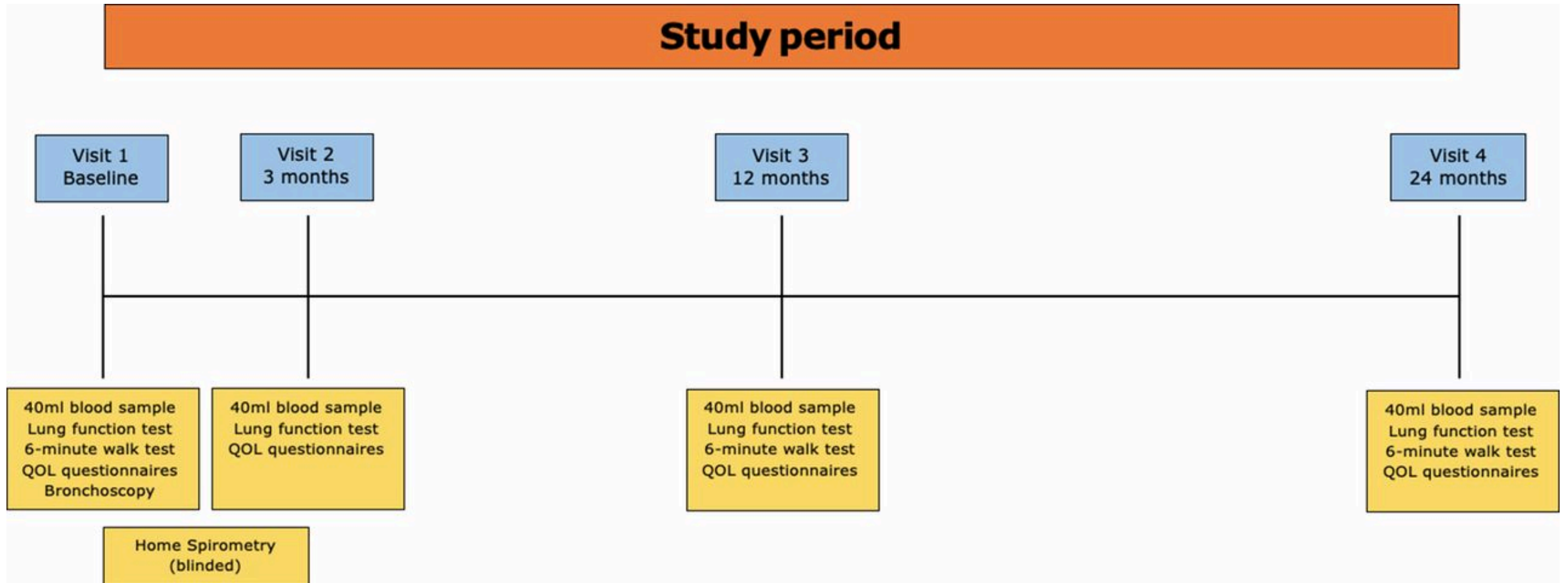


BMJ Open  
Respiratory  
Research

## The Its Not JUST Idiopathic pulmonary fibrosis Study (INJUSTIS): description of the protocol for a multicentre prospective observational cohort study identifying biomarkers of progressive fibrotic lung disease

Fasihul Khan,<sup>1</sup> Iain Stewart,<sup>2</sup> Lucy Howard,<sup>3</sup> Tricia M McKeever,<sup>2</sup> Steve Jones,<sup>4</sup> Glenn Hearson,<sup>5</sup> Rebecca Braybrooke,<sup>3</sup> Colin Edwards,<sup>6</sup> Gisli Jenkins,<sup>1</sup> Gauri Saini<sup>1</sup>

**Figure 1** Legend – participant flow through the study

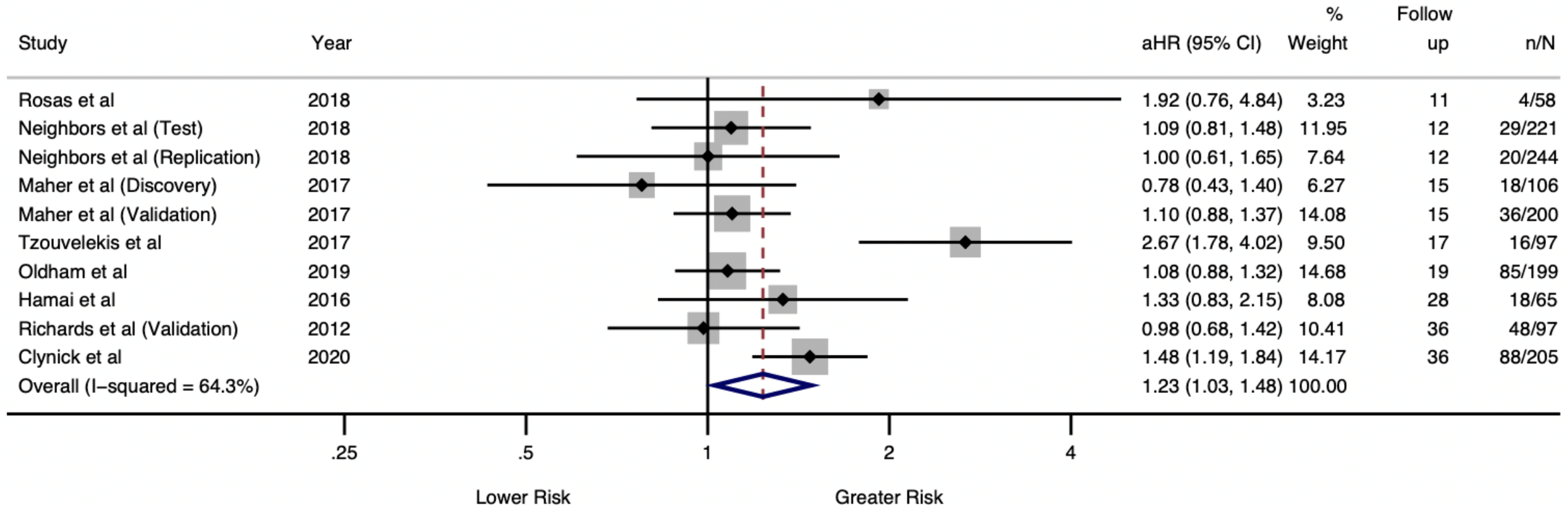


# Replication is central for successful development of biomarkers

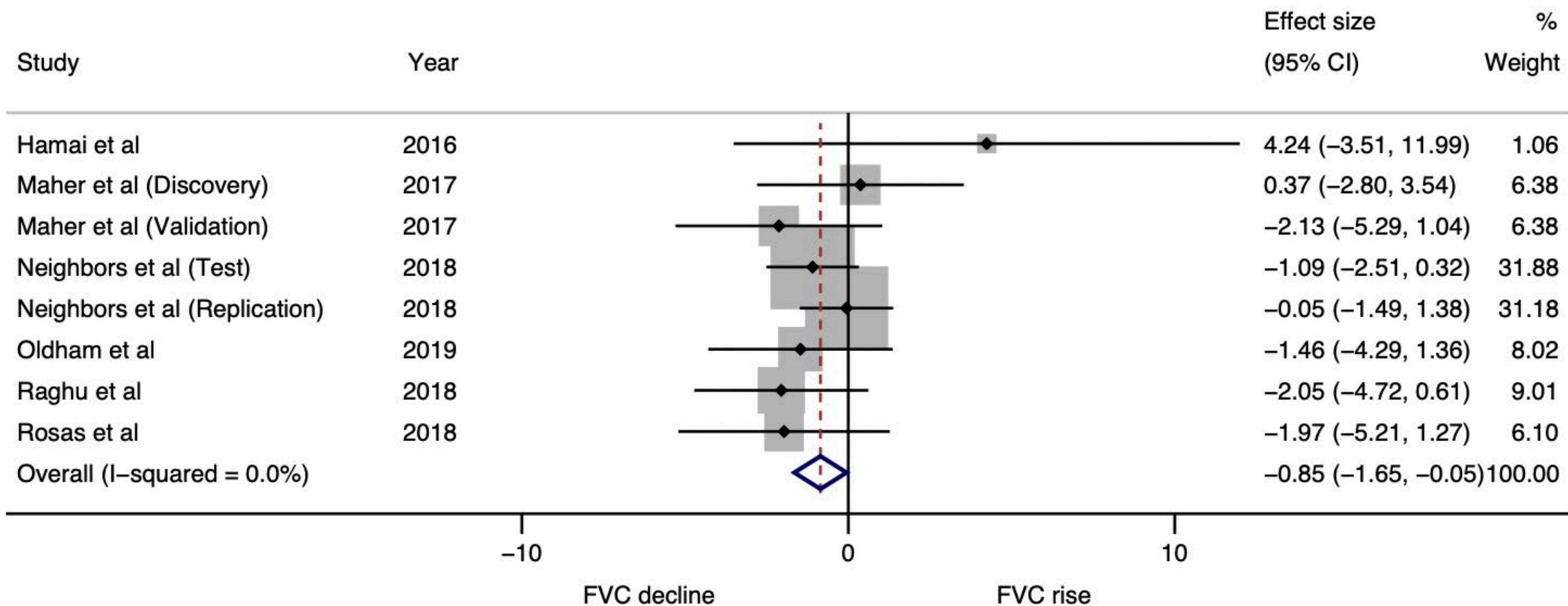
Biomarker	Mortality	Change in biomarkers predicting mortality	Disease progression	Change in biomarkers predicting disease progression	FVC change	Change in biomarkers predicting FVC change
SP-A		-		-		-
SP-D						-
KL-6		-				-
CA-125					-	-
CA19-9					-	-
LOXL2		-		-	-	-
Periostin		-		-		-
CCL-18		-		-		-
CXCL-13		-		-		-
IL-8				-	-	-
YKL-40		-		-		-
ICAM-1				-	-	-
IGFBP-2	-		-	-	-	-

# MMP7 predicts increased risk of mortality

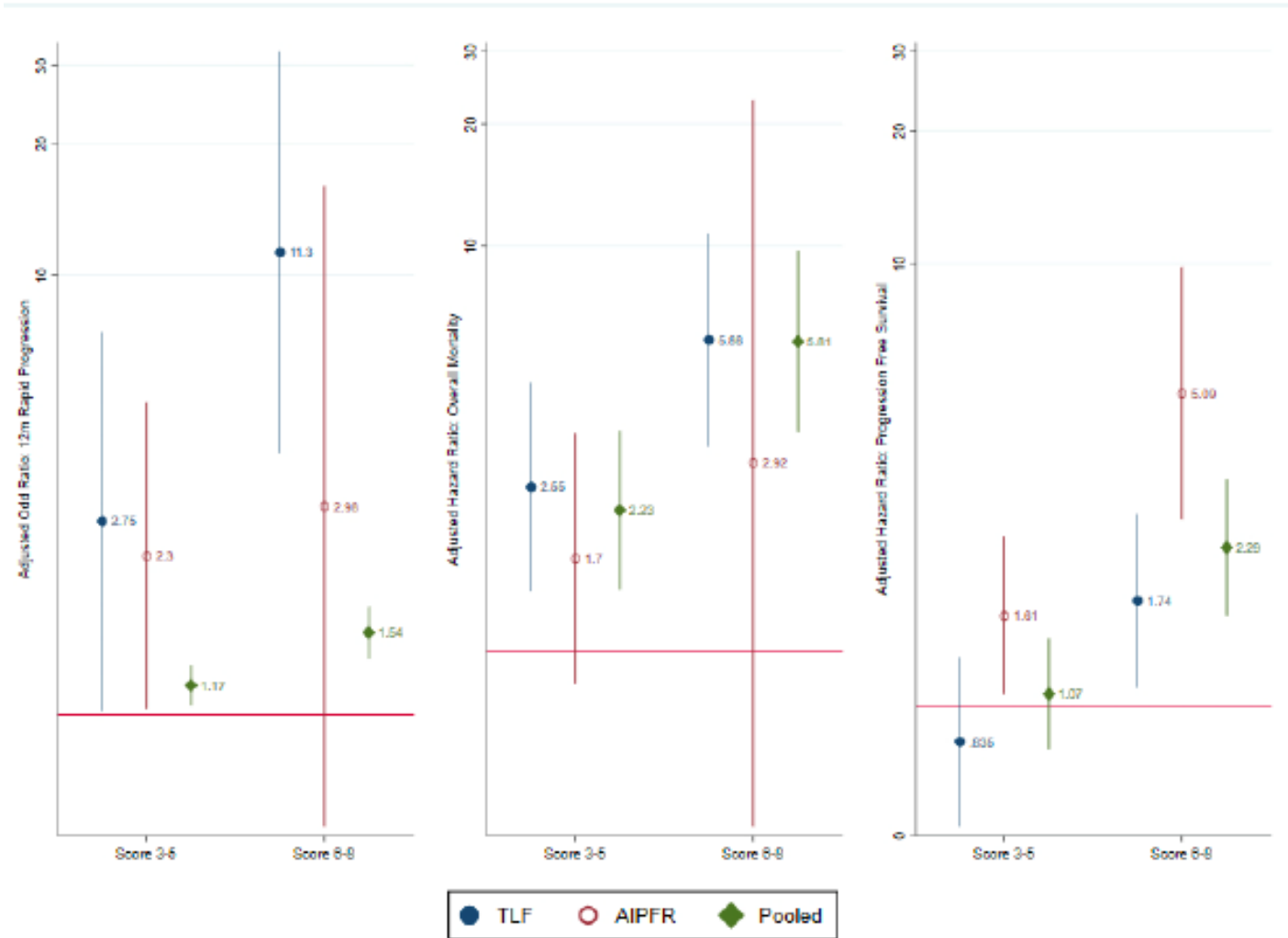
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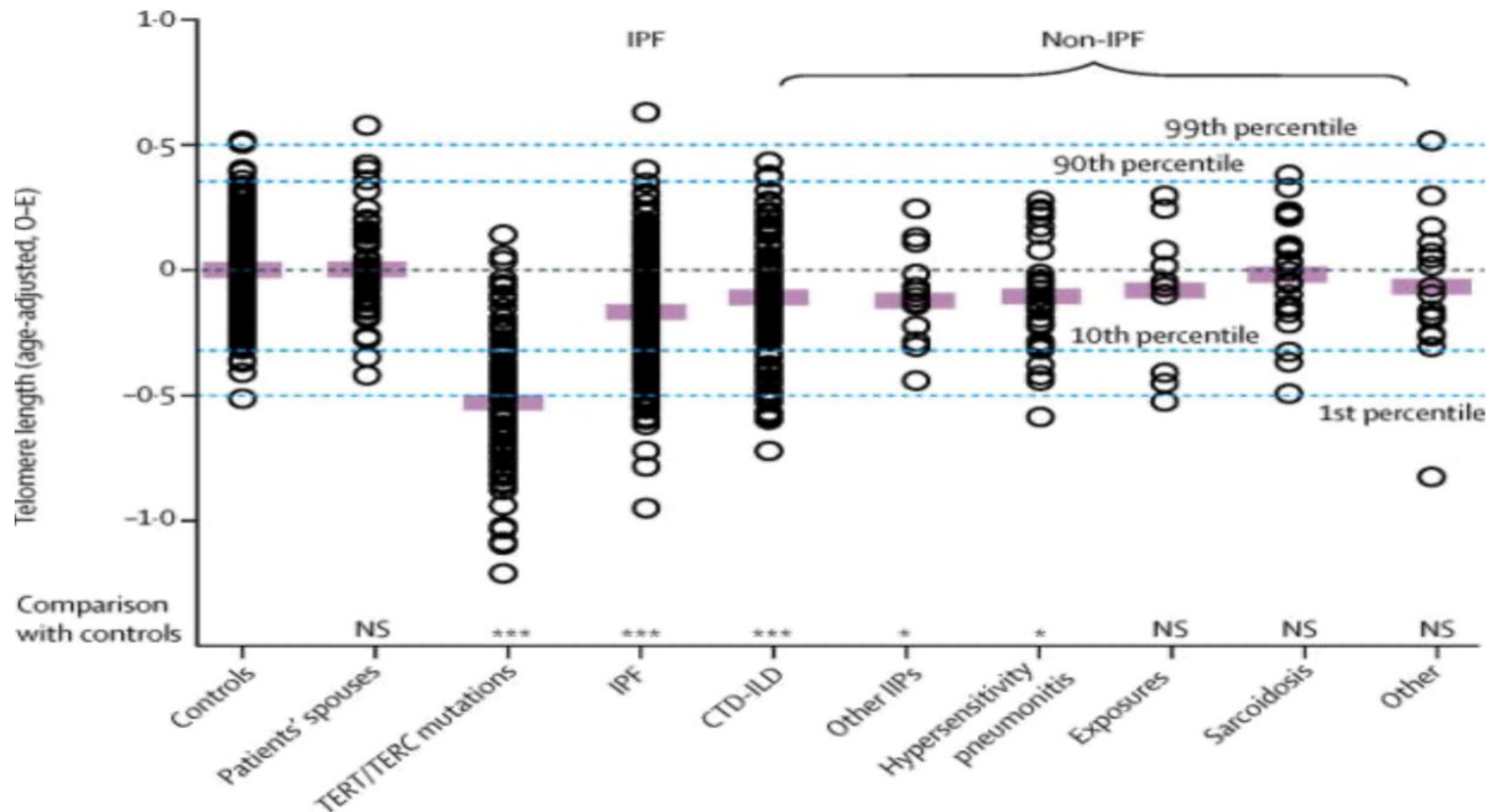
# Increased MMP7 is associated with reduced FVC at 12 months



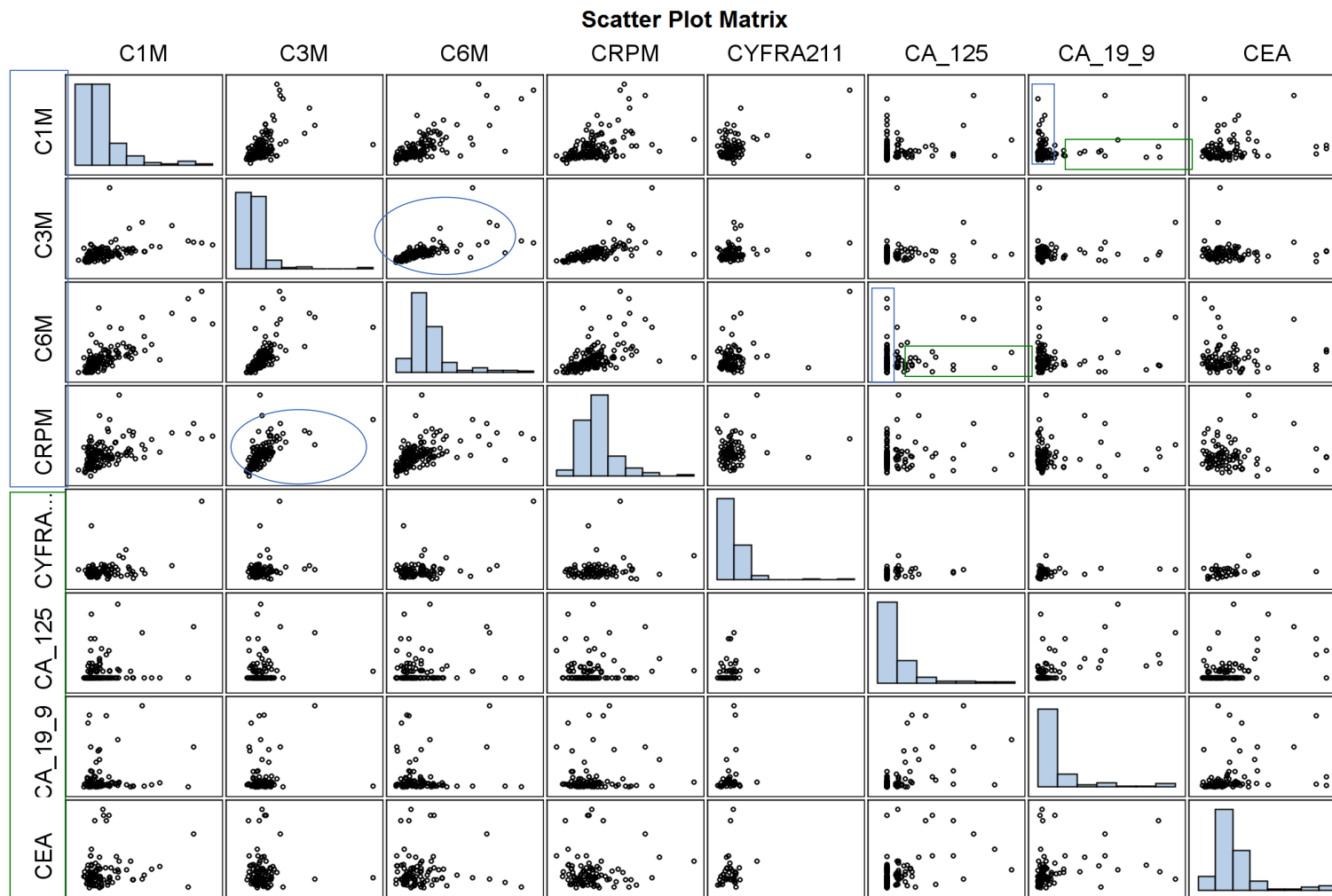
# Patients with a higher biomarker score have increased risk of disease progression and death.



# Endotypic

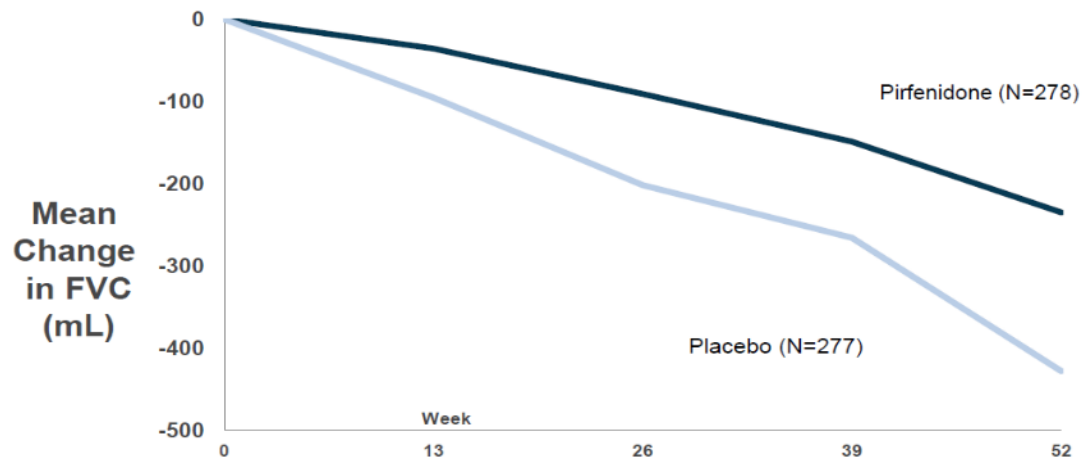


# Endotypic



# Theranostic

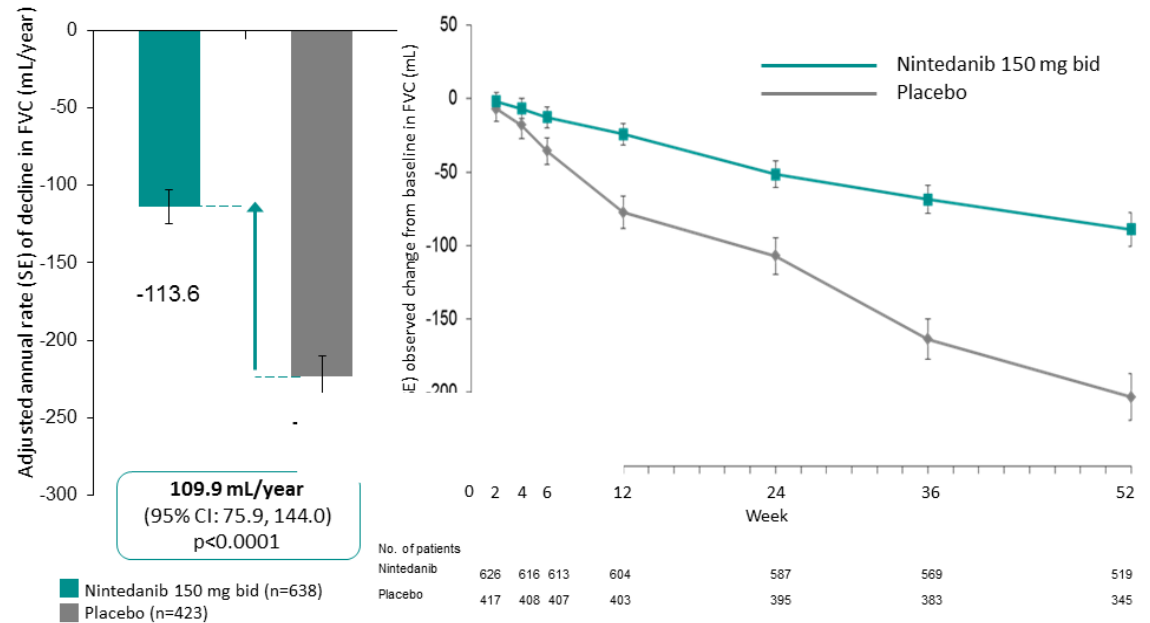
## Pirfenidone



Absolute difference	59.6 mL	111.0 mL	116.7 mL	192.8 mL
Relative difference	62.5%	54.9%	43.9%	45.1%
Rank ANCOVA P-value	<0.000001	<0.000001	0.000002	<0.000001

King et al NEJM 2014

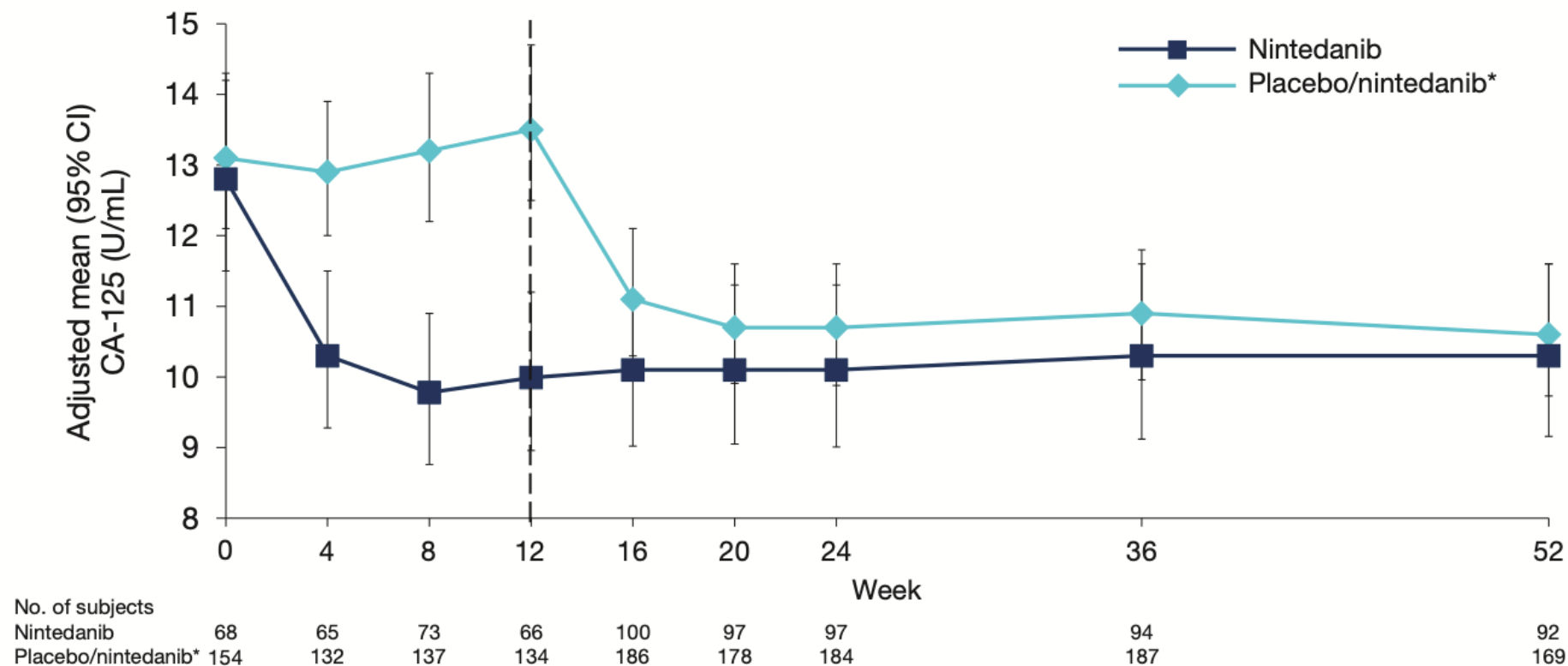
## Nintedanib



Richeldi et al NEJM 2014

# Nintedanib reduces CA-125 levels in the INMARK study

**Figure 2. CA-125 over 52 weeks**



\*Subjects received placebo (blinded) for 12 weeks followed by nintedanib (open-label) for 40 weeks.

- **CT remains the 'gold standard' diagnostic biomarker for established disease but serum biomarkers may help in early or complex cases.**
- **MMP7 either alone or in a panel of different biomarkers adds granularity to baseline prognostic assessment.**
- **Nordic and epithelial biomarkers identify different disease compartments and may be useful as endotypic biomarkers**
- **CA-125 is a standardised assay and may have value as a theranostic biomarker.**

# Conclusion

**MMP7 and CA-125 are almost ready for 'prime time' use in the management of IPF.**



# Treatment of Fibrotic Interstitial Lung Disease: Current Approach and Future Directions

Presented by M.A Saba  
Assistant Professor Kashan University of Medical Sciences

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# Aims / Learning objectives

1. Know Immunomodulatory & Anti-fibrotic Drugs to Treat Fibrotic ILD
2. Understand Evolving Treatment Concepts for Fibrotic ILD
3. Appreciate Importance of Comprehensive Patient Care

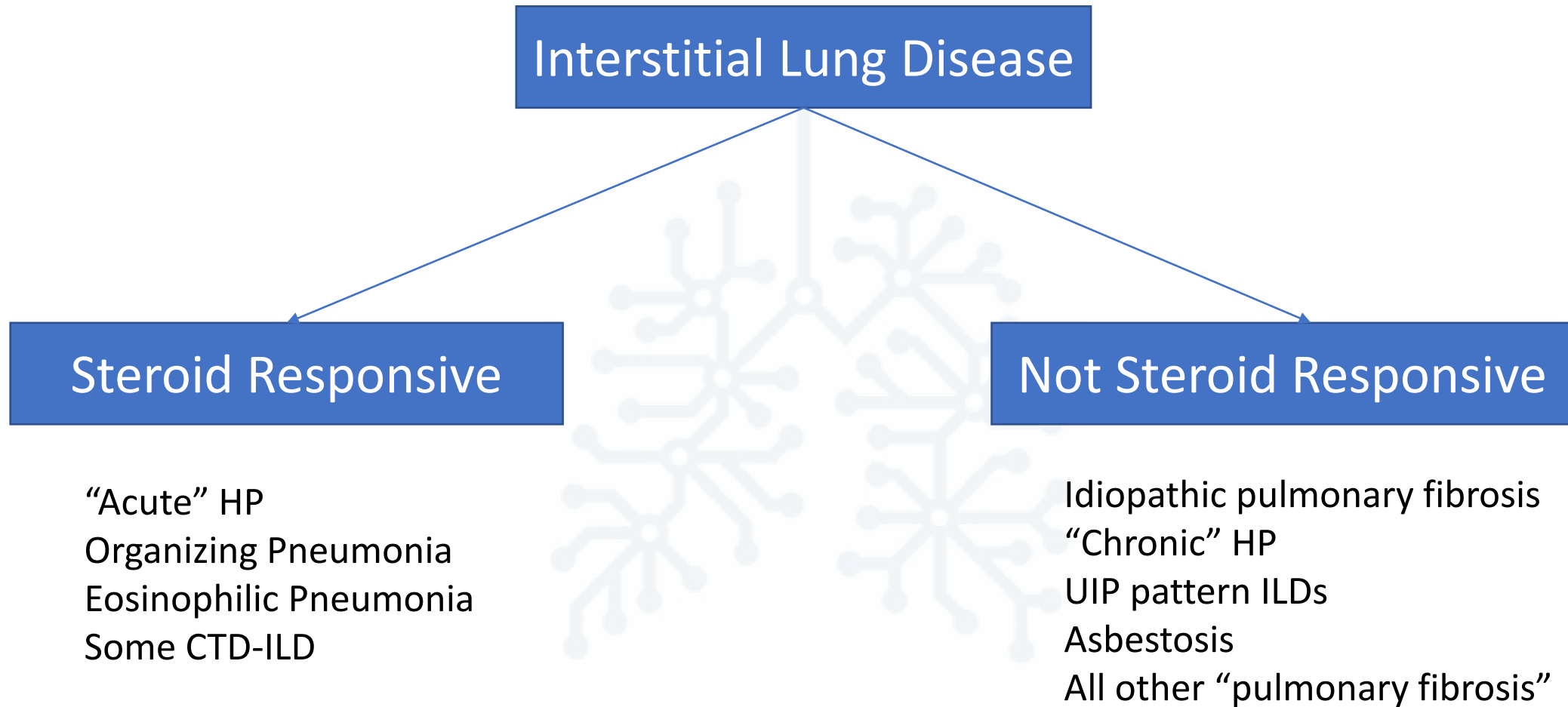
# Fibrotic Interstitial Lung Diseases

- **Idiopathic Pulmonary Fibrosis**
- **Connective Tissue Disease Associated – ILD (CTD-ILD)**
- **Fibrotic Hypersensitivity Pneumonitis (HP)**
- **Unclassifiable ILD**
- **Fibrotic Idiopathic Interstitial Pneumonias (IIPs)**
- **Exposure-related ILDs (eg. asbestosis, drug/radiation)**

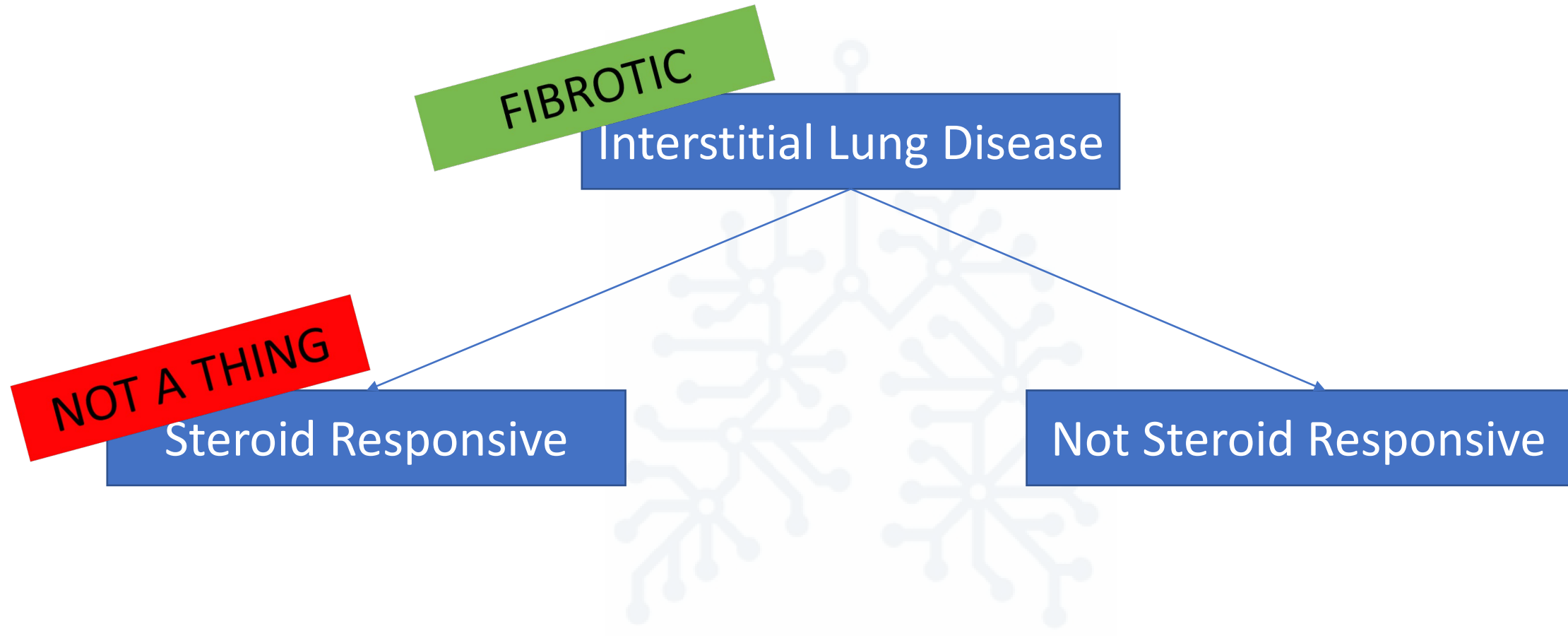
# Historical treatment approach



# Historical treatment approach

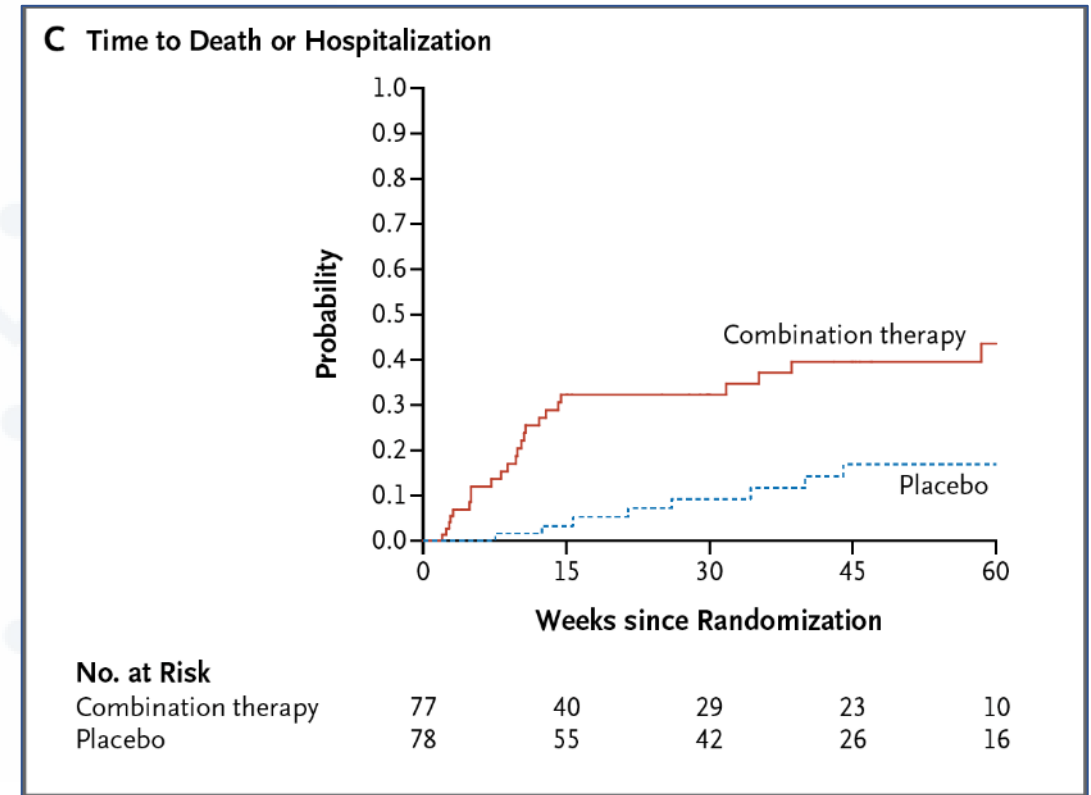
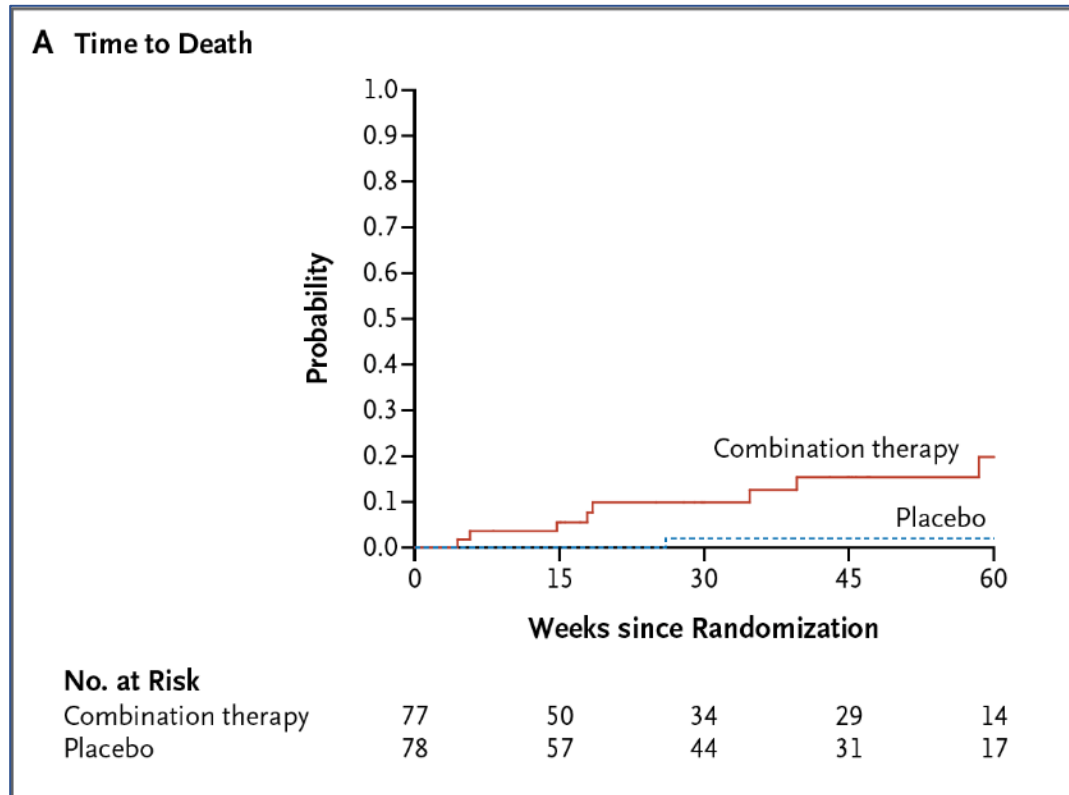


# Historical treatment approach

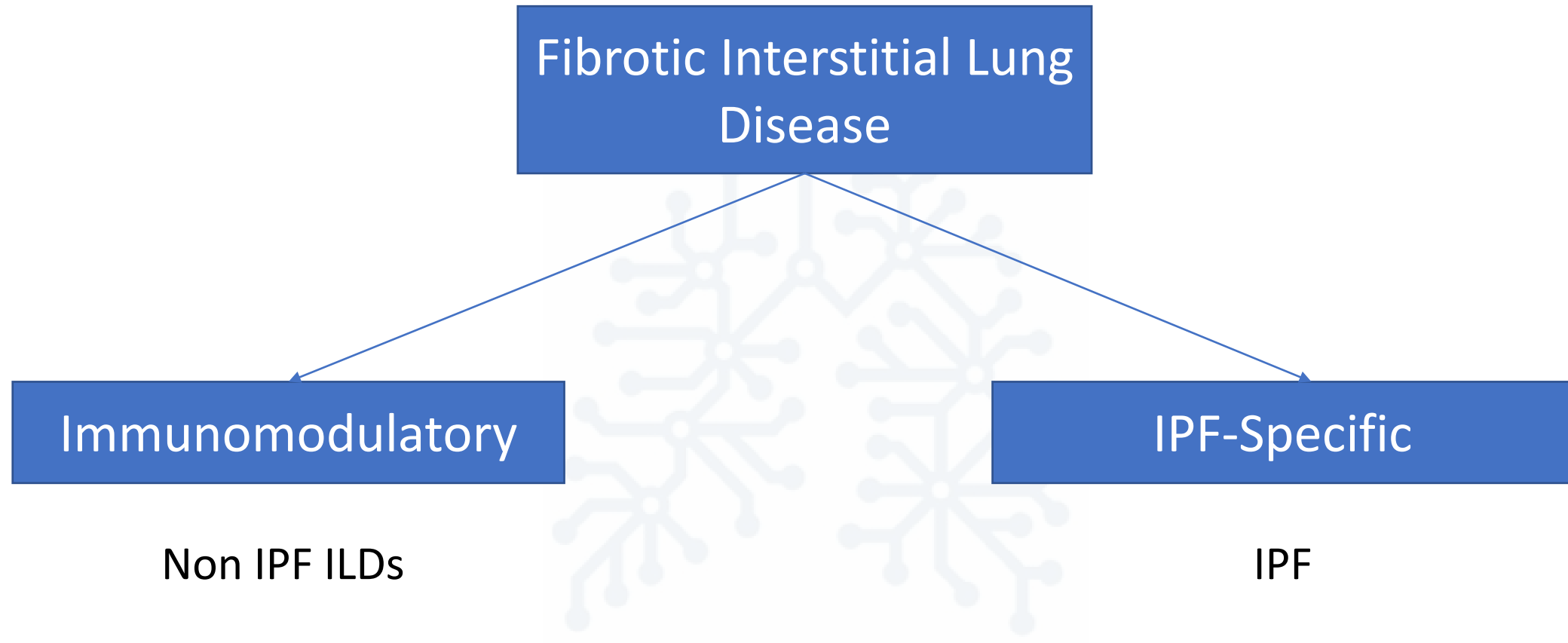


# PANTHER Trial in IPF

Combined Prednisone, AZA, N-acetylcysteine in patients with IPF



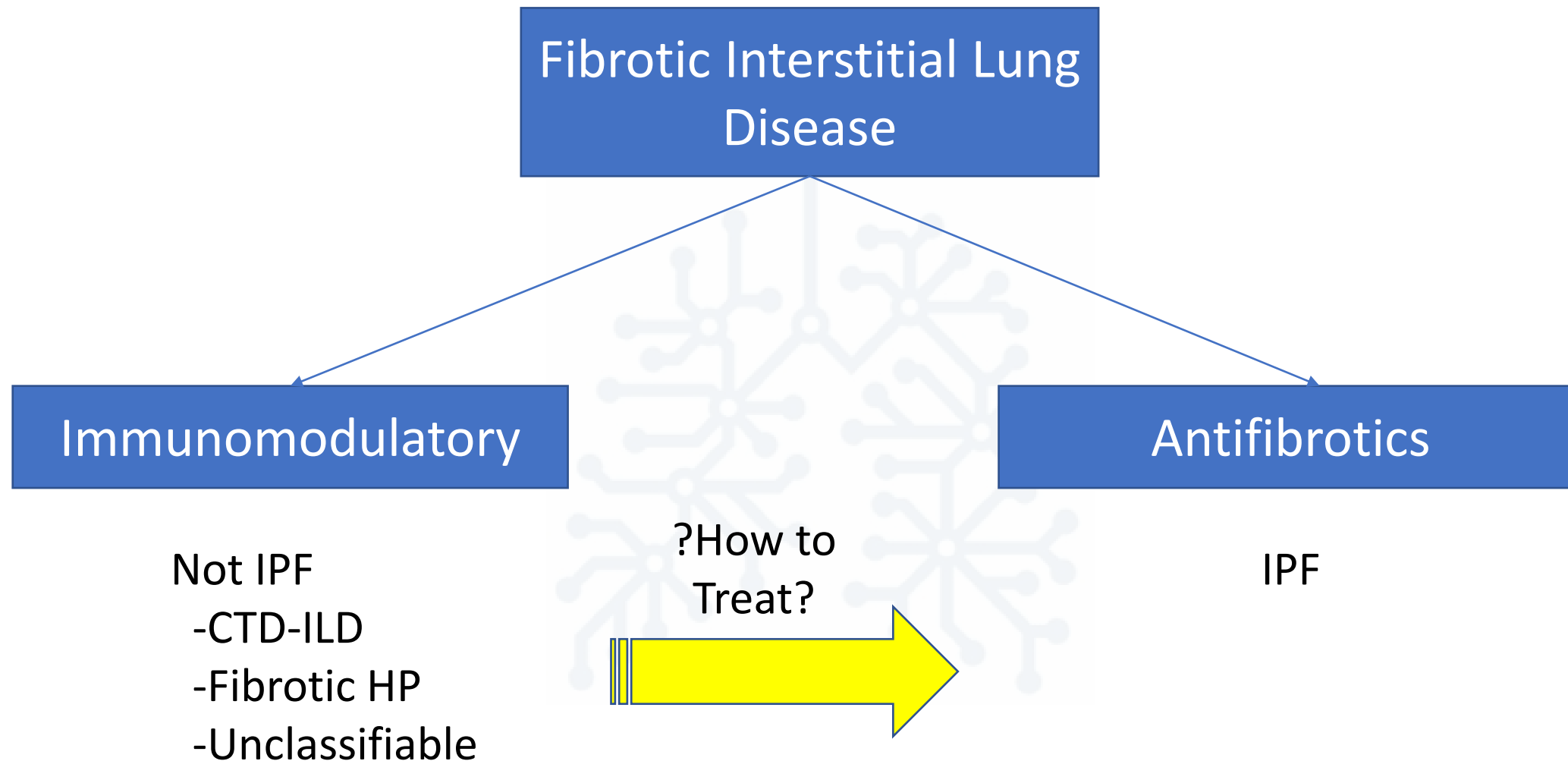
# Subsequent treatment approach



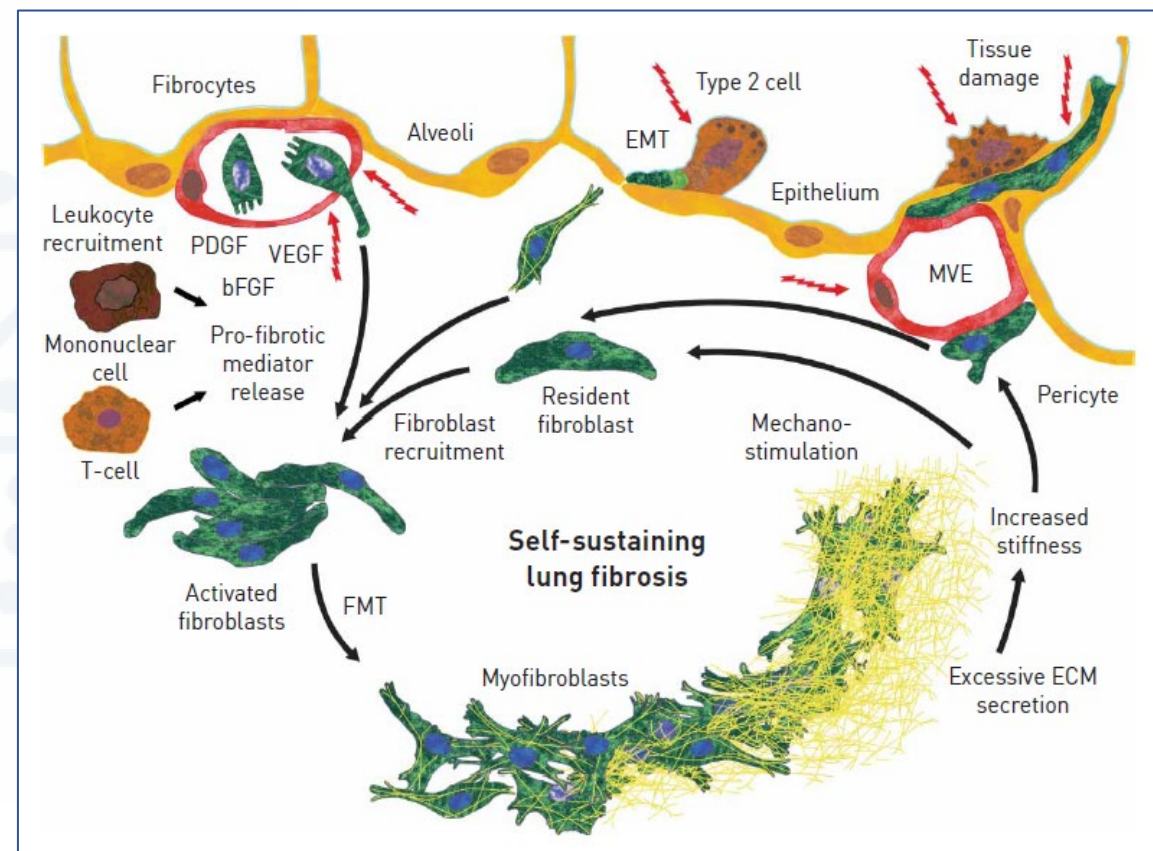
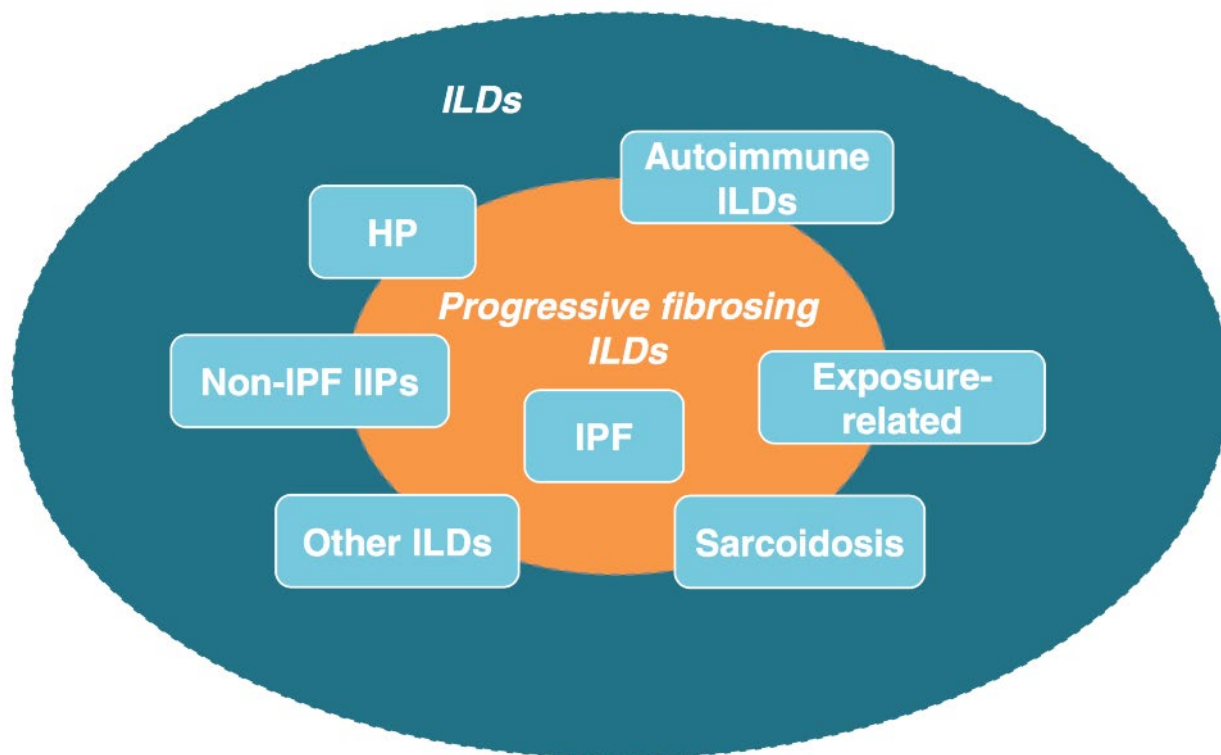
# Evidence for Immunomodulatory Drugs

	Anecdotal	Case Series	Randomized Trials
Corticosteroids	++	+	--
Azathioprine	+	CTD-ILD, FHP	--
Mycophenolate mofetil	+	CTD-ILD, FHP	SSc-ILD
Cyclophosphamide	+	CTD-ILD	SSc-ILD
Rituximab	+	CTD-ILD, FHP	--
Tocilizumab	+	CTD-ILD	SSc-ILD

# Subsequent treatment approach

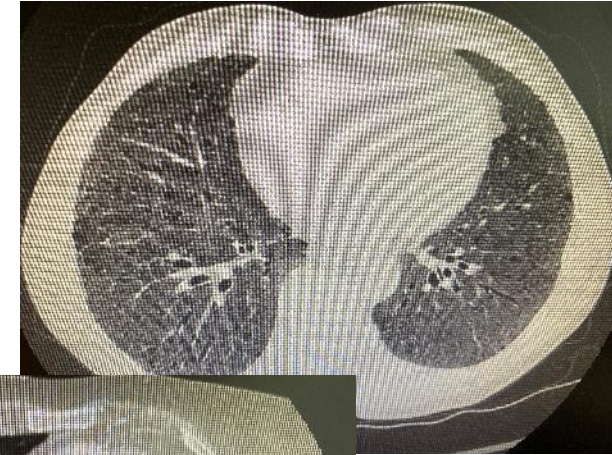


# Progressive Fibrosing ILDs



# Progressive Fibrosing ILD (PF-ILD)

- Not a diagnosis
- Clinical Phenotype
- Fibrotic ILD, progressing despite therapy
- ?How to treat?

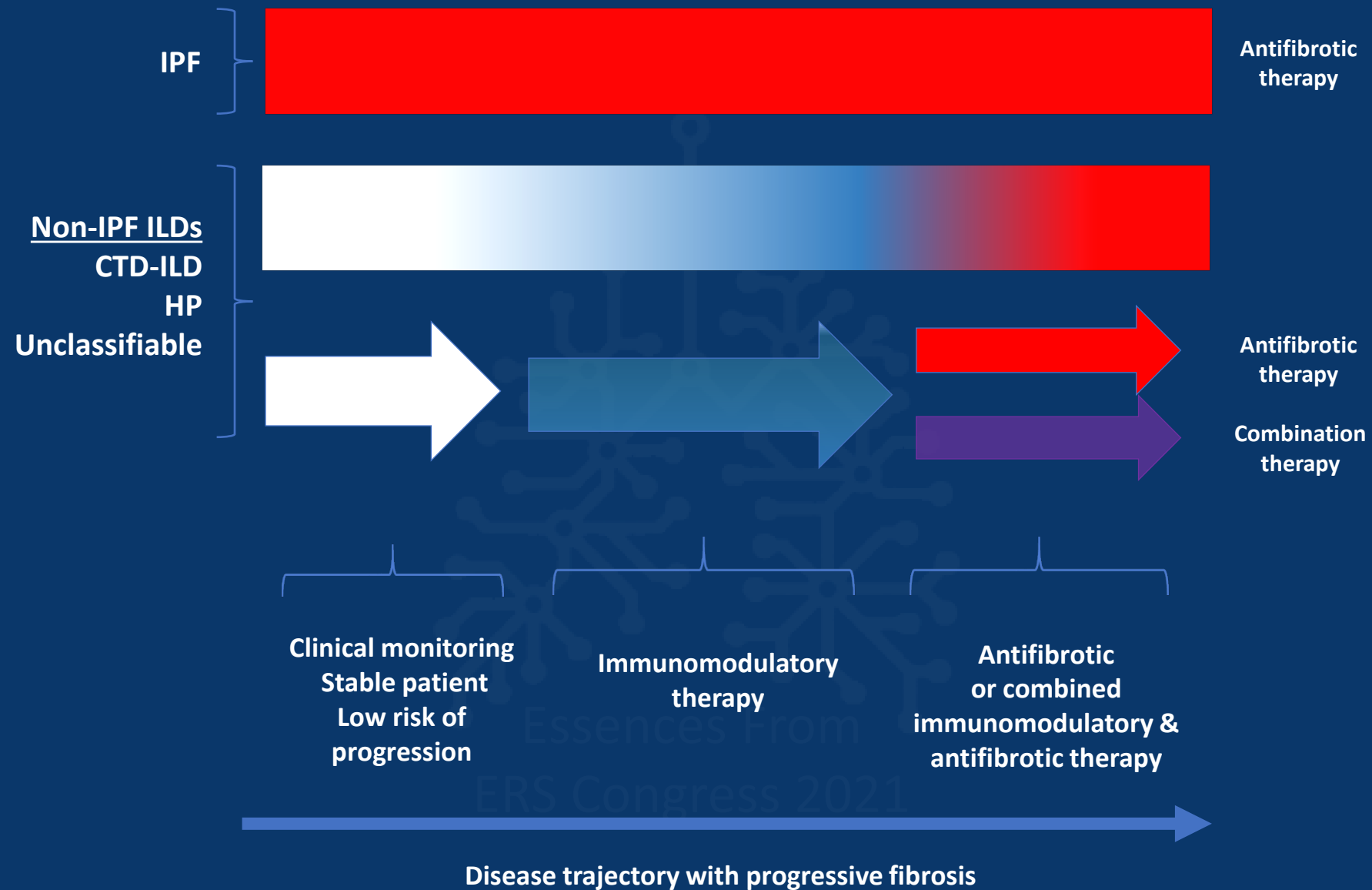


# Antifibrotics for non-IPF ILDs

Trial, year	Population	Design	Primary outcome	Primary effect measure	Progressive phenotype criteria	Comments
Distler et al. <i>NEJM</i> , 2019	576 patients with systemic sclerosis associated ILD	Nintedanib 150mg twice daily vs. placebo x 52 weeks	Annual rate of FVC decline at 52 weeks	Nintedanib - 52.4mL/year vs. placebo -93.3mL/year Difference of 41mL/year (95%CI 2.9 to 79.0)	N/A	Findings consistent when stratified by baseline MMF use
Flaherty et al. <i>NEJM</i> , 2019	663 patients with non-IPF progressive fibrosing ILD	Nintedanib 150mg twice daily vs. placebo x 52 weeks	Annual rate of decline in FVC at 52 weeks	Nintedanib -80.8mL/year vs. placebo -187.8mL/ year Difference of 107mL/year (95%CI 65.4 to 148.5)	Presence of at least one of the following within 2 years before screening: relative FVC decline of $\geq 10\%$ predicted; relative FVC decline of 5% to $< 10\%$ of predicted and worsening respiratory symptoms or increased fibrosis on HRCT; worsening respiratory symptoms and increased fibrosis on HRCT	Findings consistent when stratified by HRCT pattern (UIP vs non-UIP)
Maier et al. <i>Lancet Resp Med</i> , 2020	253 patients with progressive fibrosing unclassifiable ILD	Pirfenidone 801mg three times daily versus placebo X 48 weeks	Mean change in FVC% predicted at 24 weeks, measured by daily home spirometry	Median change pirfenidone -87.7mL vs. placebo -157.1mL	Decline in FVC of $> 5\%$ or significant symptomatic worsening; extent of fibrosis $> 10\%$ on HRCT	Secondary outcome (lab-based spirometry) treatment difference 95.3mL pirfenidone vs. placebo (95%CI 35.9 to 154.6)
Behr et al. <i>Lancet Resp Med</i> , 2021	127 patients with non-IPF progressive fibrosing ILD	Pirfenidone 801mg three times daily versus placebo X 48 weeks	Absolute change in FVC% predicted at 48 weeks	Mean difference pirfenidone vs placebo 1.69% (95%CI -0.65 to 4.03)	Progressive disease documented by at least 3 PFTs obtained 6–24 months before enrolment, demonstrating an annual % predicted FVC decline of $\geq 5\%$	Trial terminated prematurely. Multiple statistical approaches presented.

# Key Clinical Trials for Fibrotic ILD

- **Nintedanib slows FVC decline in SSc-ILD (SENSCIS)**
- **Nintedanib slows FVC decline in PF-ILD (INBUILD)**
- **Pirfenidone slows FVC decline in Unclassifiable PF-ILD**
- **Pirfenidone slows FVC decline in PF-ILD (RELIEF)**
- ❖ **Treprostinil improves 6MWD and FVC in ILD with group 3 PH**
- ❖ **Tocilizumab slows FVC decline in SSc-ILD**



# Areas of Discovery: Fibrotic ILD

- **Molecular phenotyping**
  - diagnosis
  - disease behaviour
  - theragnostics
- **Genetic variants**
- **Markers of telomere dysfunction**



# Novel Therapeutics: IPF

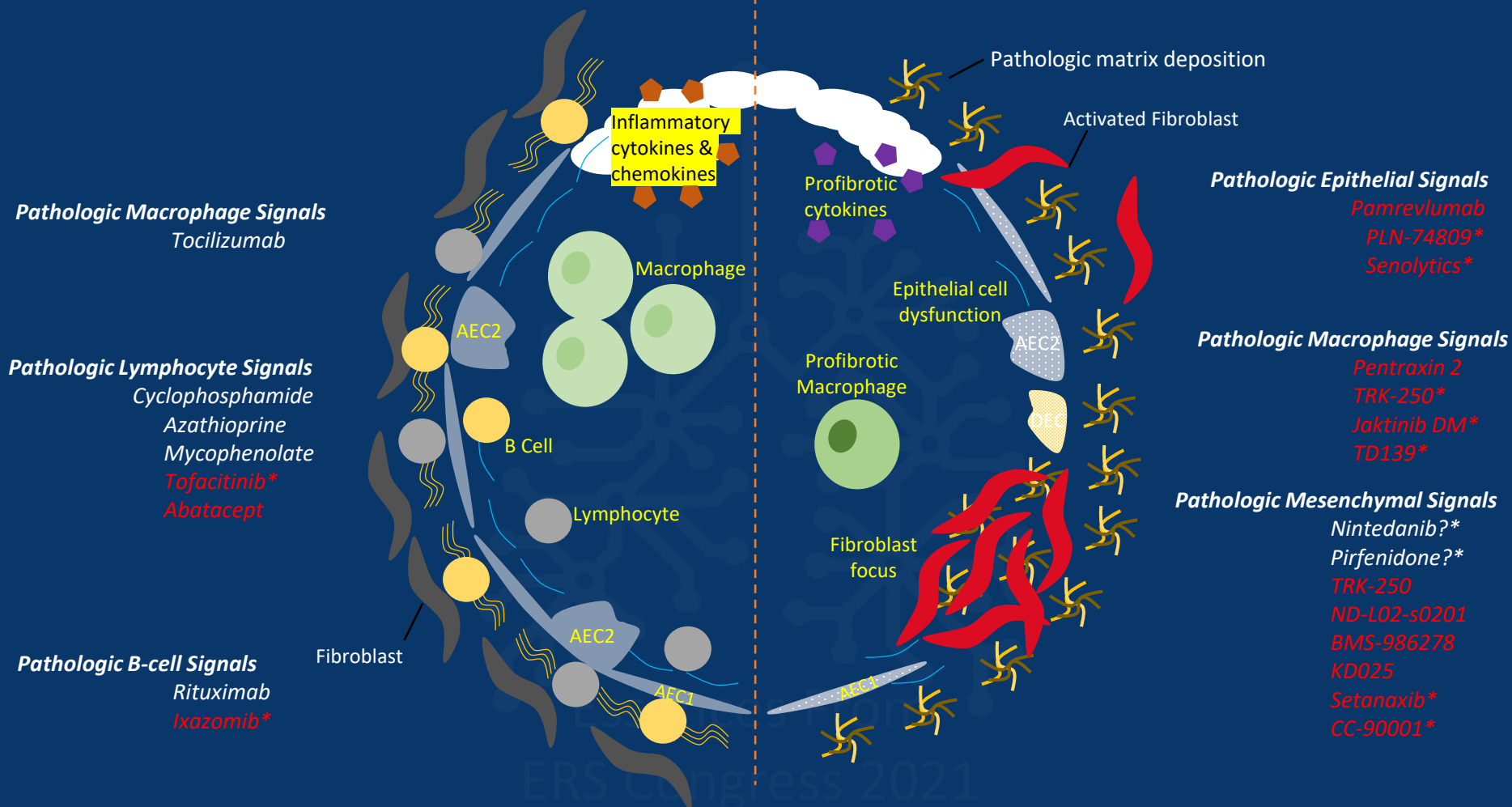
Therapy	Mechanism of action	Primary Outcome	Status	Clinical Trial identifier
<b>IPF (Phase I)</b>				
Autologous lung stem cells*	Immunomodulatory, and anti-proliferative	Number of patients with AEs and serious AEs; FVC change from baseline to week 48	Recruiting	NCT04262167 NCT02745184
DWN12088**	Prolyl-tRNA synthetase inhibitor	Pharmacokinetics and drug-drug interactions with currently approved antifibrotics	Recruiting	NCT03711162 NCT04888715
TD-1058***	Mechanism undefined	Number and severity of treatment emergent AEs	Recruiting	NCT04589260
TRK-250***	TGF-β1 suppression	Incidence and severity of AEs up to 7 days after last dose	Recruiting	NCT03727802
<b>IPF (Phase II)</b>				
BMS-986278**	LPA antagonist	Rate of change in percent predicted FVC (baseline to week 26)	Recruiting	NCT04308681
C21**	Angiotensin receptor agonist	Nature and frequency of AEs occurring over the trial period	Recruiting	NCT04533022
CC-90001**	Selective JNK inhibitor	Change in percentage predicted FVC from baseline to week 24	Recruiting	NCT03142191
GKT137831 (Setanaxib)**	NOX1 and NOX4 inhibitor	Surrogate biomarker of oxidative stress by mass spectrometry from baseline to week 24	Recruiting	NCT03865927
GLPG1205**	GPR84 antagonist	Change in FVC from baseline to week 26	Completed	NCT03725852
Jaktinib DM**	JAK -1, 2, and 3 Inhibitor	Change in FVC from baseline to week 24	Recruiting	NCT04312594
KD025 (SLx-2119)**	ROCK2 inhibitor	Change in FVC from baseline to week 24; number of subjects experiencing AEs	Active, not recruiting	NCT02688647
MN-001 (tipelukast)**	Leukotriene receptor antagonist, PDE-3, 4 inhibitor	Mean change in FVC from baseline to Week 26	Recruiting	NCT02503657
ND-L02-s0201 (BMS-986263)**	HSP47 inhibitor	Number with treatment-related AEs (baseline to week 24)	Recruiting	NCT03538301
PLN-74809**	Dual selective αVβ1/αVβ6 inhibitor	Number of study participants with treatment-related AEs and laboratory abnormalities	Recruiting	NCT04396756
Saracatinib**	Highly selective Src tyrosine kinase family inhibitor	Safety, tolerability, pharmacodynamics, pharmacokinetics, efficacy (as measured by change in FVC, baseline to week 24)	Recruiting	NCT04598919
TD139***	Galectin-3 inhibitor	Rate of FVC decline (mL) from baseline to week 52	Recruiting	NCT03832946
VAY736 (ianalumab)****	IgG1 monoclonal antibody against BAFF receptor	Change from baseline to week 48 in FVC	Recruiting	NCT03287414
<b>IPF (Phase III)</b>				
GLPG1690 (zirixestat)**	Autotaxin inhibitor	Rate of decline in FVC (baseline to week 52)	Completed	NCT03733444 NCT03711162
Morphine Sulfate**	Opiate receptor agonist	Percent change in daytime cough frequency (coughs per hour) from baseline to Day 14	Recruiting	NCT04429516
Pamrevlumab (FG-3019)*	Fully human monoclonal antibody against CTGF	Change in FVC from baseline to week 52, proportion with disease progression (death, or ≥10% decline in absolute FVC percentage predicted; baseline to week 52)	Recruiting	NCT03955146 NCT04419558
rhPTX-2/PRM-151*	TGF-β1 modulator	Absolute change in FVC (mL) from baseline to week 52; Incidence and severity of AEs;	Completed	NCT04552899 NCT04594707

# Novel Therapeutics: non-IPF ILDs

Therapy	Mechanism of action	Primary Outcome	Status	Clinical Trial identifier
<b>CHP (Phase III)</b>				
Pirfenidone in CHP**	May inhibit fibroblast proliferation	Change in FVC from baseline to week 52	Completed	NCT02958917
<b>RA-ILD (Phase II)</b>				
Abatacept	Inhibits T-cell activation	Change in FVC from baseline to week 24	Recruiting	NCT03084419
Pirfenidone**	May inhibit fibroblast proliferation	FVC decline of $\geq 10\%$ or death over 52 weeks	Recruiting	NCT02808871
<b>RA-ILD (Phase IV)</b>				
Tofacitinib vs. Methotrexate	Inhibits janus kinase	Change in total score of HRCT pulmonary abnormalities at 24 weeks	Recruiting	NCT04311567
<b>ASS-ILD (Phase III)</b>				
Cyclophosphamide and Azathioprine	Destroys proliferating B- and T- lymphoid cells.	Time from treatment initiation to first ASS-ILD related event	Recruiting	NCT03770663
<b>SSc-ILD (Phase II)</b>				
Pirfenidone**	May inhibit fibroblast proliferation	Change in FVC from baseline to 18 months	Active, not recruiting	NCT03221257
Ixazomib	Proteasome inhibitor	Number of participants with $\geq 1$ treatment-emergent adverse event at 7 months.	Recruiting	NCT04837131
<b>SSc-ILD (Phase III)</b>				
Rituximab vs. cyclophosphamide*^	B-cell depleting agent	Absolute change in FVC over 48 weeks	Completed	NCT01862926

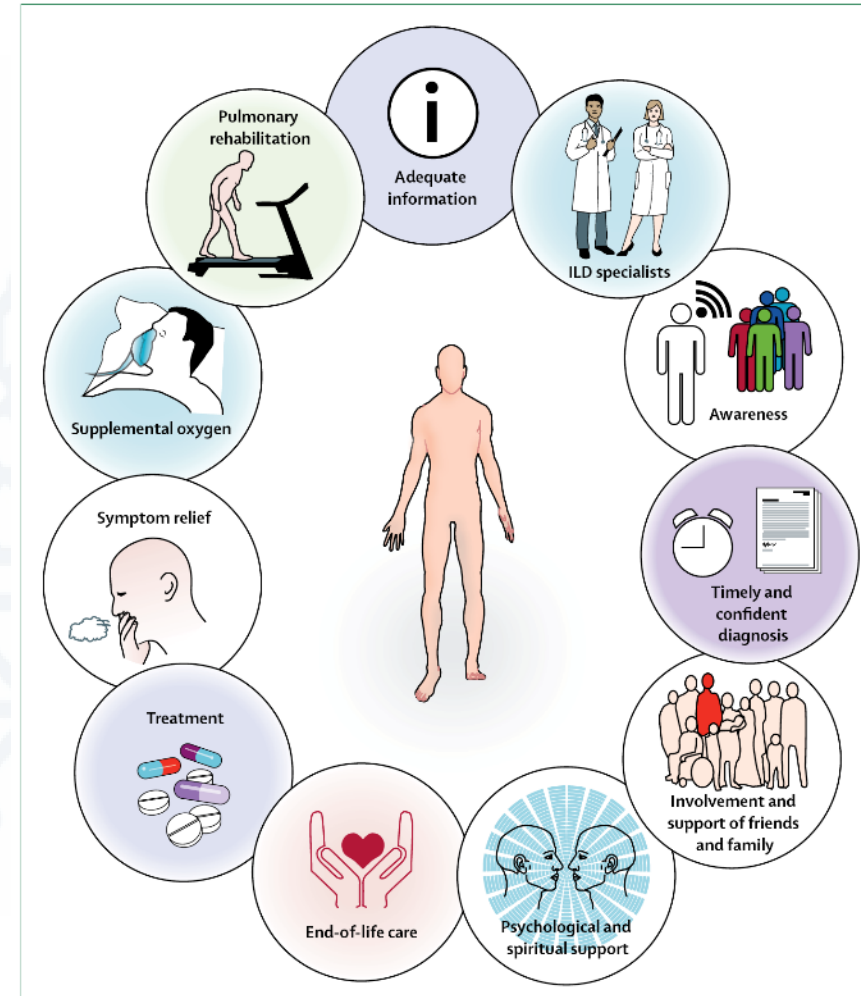
## Immunomodulatory

## Fibro-modulatory



# Comprehensive Care

- Pulmonary rehabilitation
- Supplemental oxygen
- Lung transplantation
- Infection prevention
- Education and support
- Symptom management
- Palliative care



# List of references

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# Thank You

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