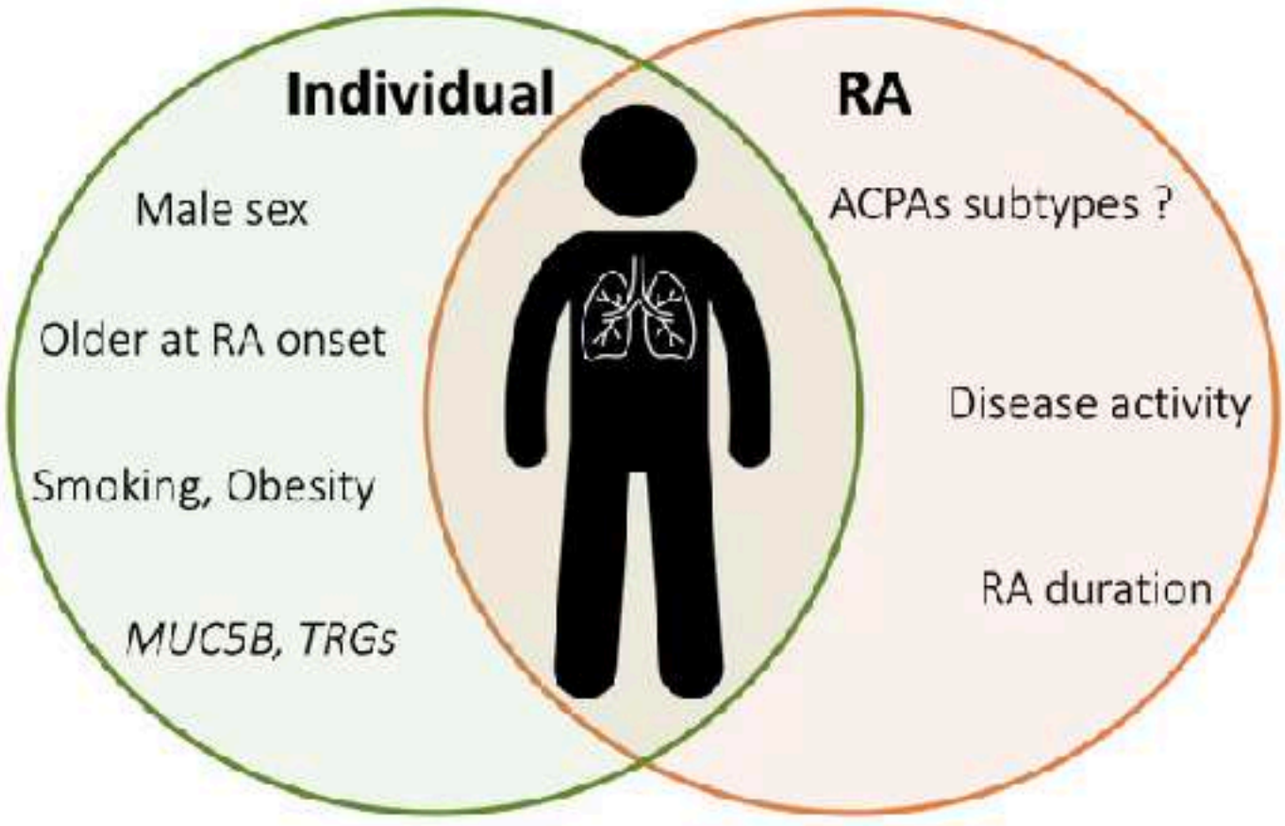
Main risk factors For RA-ILD



Identification of high-risk individuals in the context of screening

MUC5B & screening for RA-ILD

- ***MUC5B*** **($OR_{allelic}$ ~ 2.5)**
- **Age**

- **Prospective cohort** (Aurora, CO, USA)
- **184** patients with RA **without clinical diagnosis of ILD**
- Median RA disease duration of **8.5 years**
- Systematically assessed by **HRCT** : **21%** had ILD

Independent risk factors of asymptomatic RA-ILD

	OR (95%CI)	*P* - value
Age at inclusion	1.07 (1.03-1.11)	*< 0.001*
MUC5B $_{GT/TT}$	2.49 (1.01-6.12)	*0.047*

MUC5B & screening for RA-ILD

- ***MUC5B*** **($OR_{allelic}$ ~ 3.7)**
- **Male sex, Age**
- **RA disease activity**

- **Cross-sectional** study of a French **prospective cohort** (ESPOIR)
- **163** patients with RA **without respiratory symptoms**
- Median RA disease duration of **13.9 years** (IQR 13-14.1)
- Systematically assessed by **HRCT** : **19.1%** had ILD

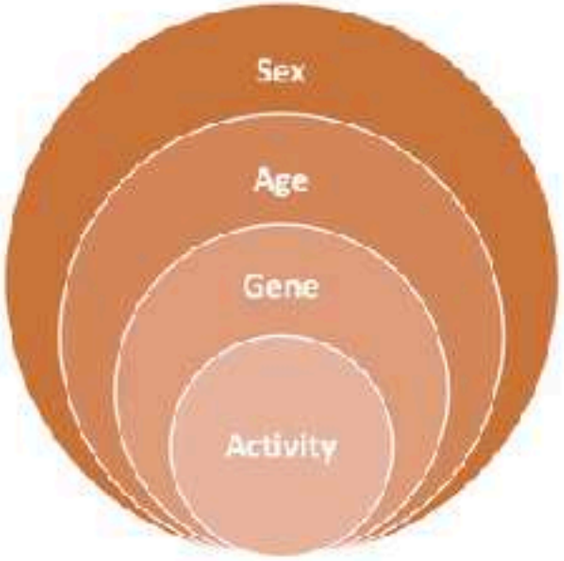
Independent risk factors of asymptomatic RA-ILD

	OR (95%CI)	*P* - value
Male Sex	3.93 (1.40-11.39)	*0.01*
Age at RA onset /Year	1.10 (1.04-1.16)	*< 0.001*
Mean DAS28 $_{ESR}$	2.03 (1.24-3.42)	*0.006*
MUC5B **$_{GT/TT}$**	3.74 (1.37-10.39)	*0.01*

Risk score for RA-ILD

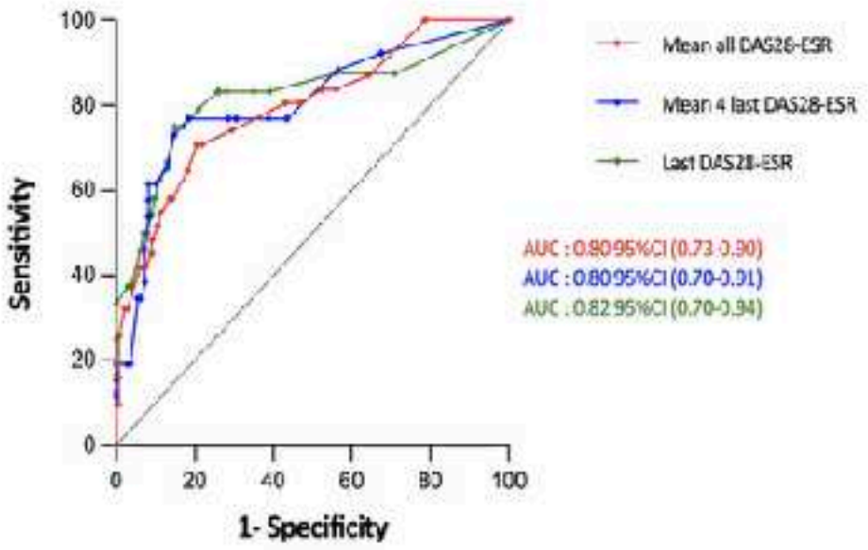
- **Validated** in an independent population
- Last **DAS28$_{ESR}$ is a reliable proxy of all DAS28$_{ESR}$**
- AUC = 0.82 and 0.78

Risk score for asymptomatic RA-ILD

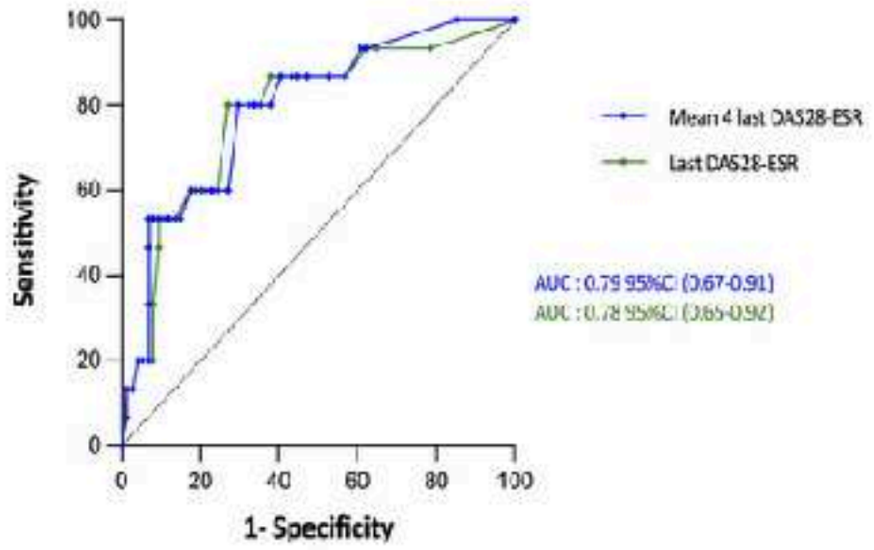


ROC curves

Discovery population



Replication population



Risk score for RA-ILD

- 4 variables risk score : **Se 0.75**, Sp 0.83, NPV 0.93
- 3 variables risk score : **Se 0.75**, Sp 0.69, NPV 0.92
- **Better performance when including *MUC5B***

		DAS28-ESR ≤ 2.9		DAS28-ESR]2.9 – 4.3]		DAS28-ESR > 4.3	
Age at RA onset (years)	*MUC5B* rs35705950 genotypes	Female	Male	Female	Male	Female	Male
Risk matrix of the model including *MUC5B* rs35705950							
≤ 49	GG	2.0 [0.3–5.7]	7.1 [1.0–18.6]	6.7 [1.2–16.5]	21.3 [3.2–50.3]	12.5 [2.0–29.7]	34.9 [5.9–71.4]
	GT/TT	6.7 [1.4–17.6]	21.3 [5.4–48.0]	20.3 [5.2–38.2]	48.9 [16.0–80.1]	33.5 [6.3–59.4]	65.4 [16.3–90.8]
]49 – 58]	GG	6.2 [1.5–15.6]	19.9 [4.5–41.6]	18.9 [5.9–30.6]	46.8 [15.0–71.7]	31.6 [8.3–57.1]	63.4 [18.1–87.5]
	GT/TT	18.9 [3.8–50.1]	46.8 [13.0–80.8]	45.2 [15.6–71.7]	75.6 [39–94.6]	62 [17.9–87.4]	86.0 [40.7–97.7]
> 58	GG	16.7 [5.0–39.1]	42.9 [20.6–72.0]	41.4 [15.0–69.5]	72.7 [35.6–92.3]	58.3 [25.1–84.8]	84.0 [48.3–97.2]
	GT/TT	41.4 [17.4–76.6]	72.7 [46.9–92.7]	71.4 [40.8–91.7]	90.4 [66.9–98.3]	83.1 [47.3–96.8]	94.9 [72.1–99.3]
Risk matrix of the model not including *MUC5B* rs35705950							
≤ 49		3.6 [0.8–7.1]	11.9 [3.3–24.7]	8.6 [2.3–17.6]	25.6 [7.2–53.7]	17.5 [4.0–40.4]	43.6 [9.7–81.8]
]49 – 58]		9.1 [2.2–20.3]	26.6 [8.8–53.5]	20.2 [7.9–35.8]	48.0 [21.7–73.8]	36.3 [10.1–66.2]	67.4 [22.0–91.5]
> 58		24.6 [8.0–51.2]	54.4 [26.8–79.3]	45.4 [20.2–71.9]	75.2 [45.2–93.7]	65.1 [35.3–91.1]	87.2 [59.1–98.3]

4-variables risk score

Simplified risk score without *MUC5B*

Juge PA et al. Arthritis Rheumatol. 2022.

Screening for RA-ILD

- **5 conditions**

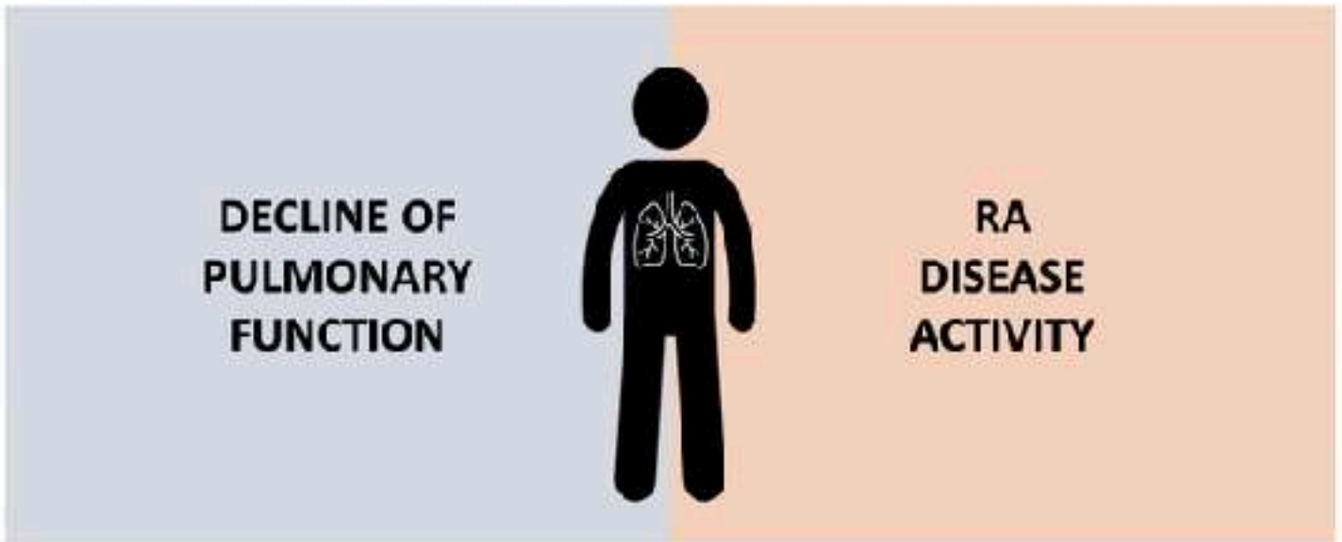
1. Frequent & potentially severe
2. Identification of high-risk individuals
3. Specific treatment available
4. Evidence of treatment benefit
5. Known indication for treatment

Screening programmes: a short guide. Increase effectiveness, maximize benefits and minimize harm. Copenhagen: WHO Regional Office for Europe; 2020

Is there a « specific treatment » for RA-ILD ?

2 main objectives

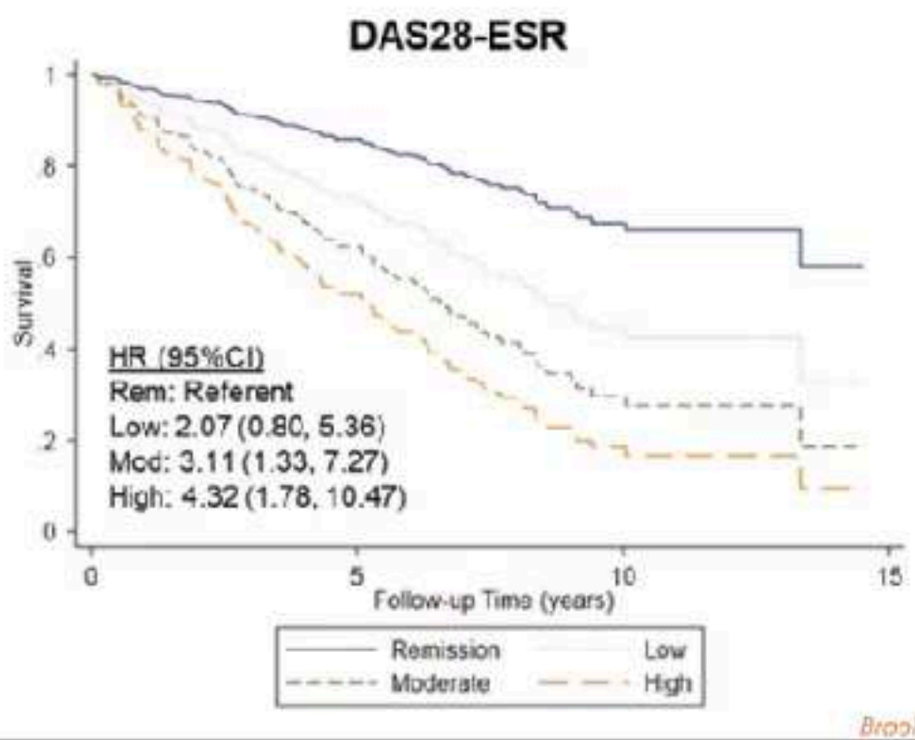
- **MD discussion is mandatory +++**

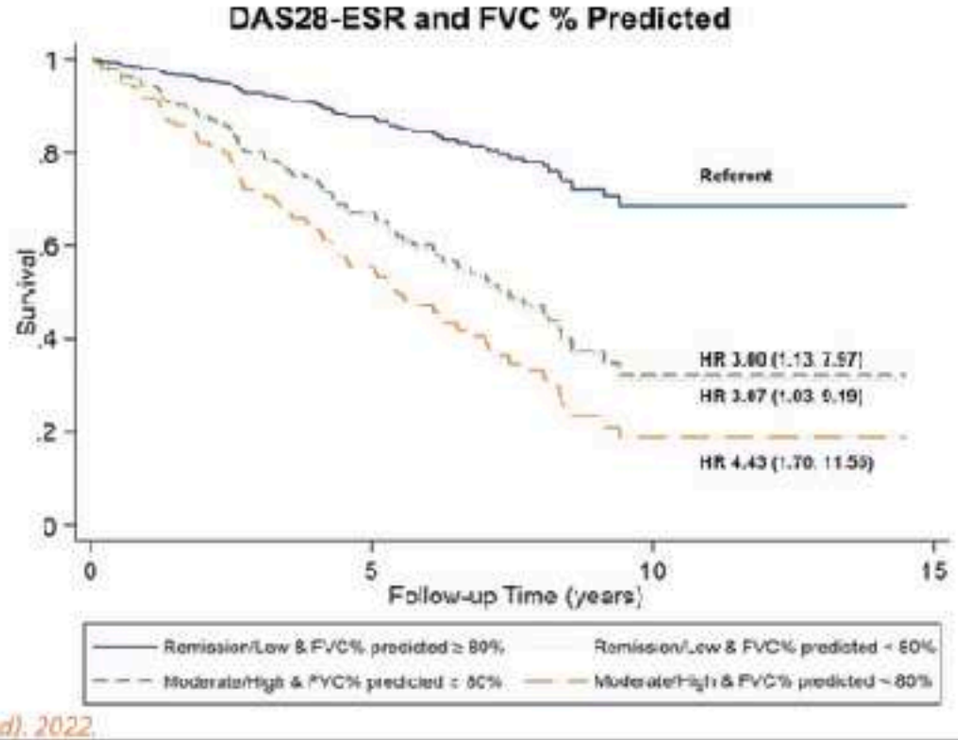


Additional arguments for controlling RA disease activity…

- **Is RA disease activity impacting ILD ?**

US veterans with RA-ILD prospective cohort, registry identification of RA-ILD, RA 1987 ACR criteria, n = 227 - 27.7% of deaths attributed to respiratory system



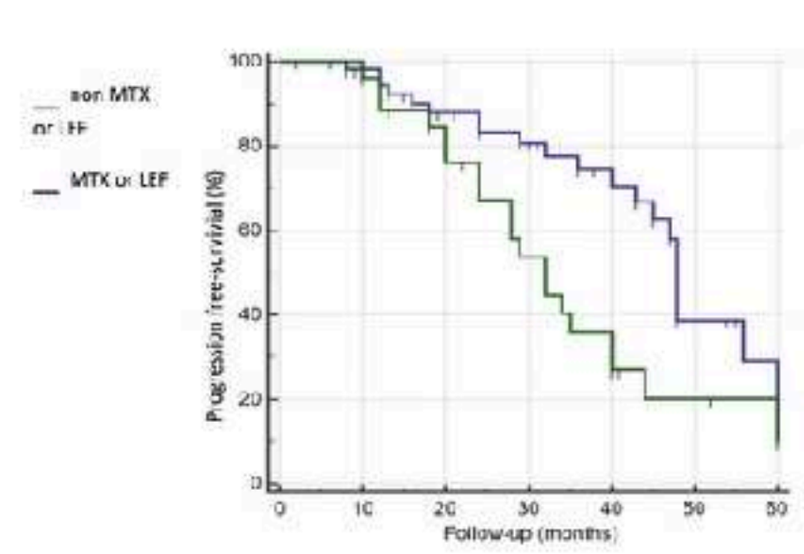


Brooks R et al. Rheumatology (Oxford). 2022.

Additional arguments for controlling RA disease activity…

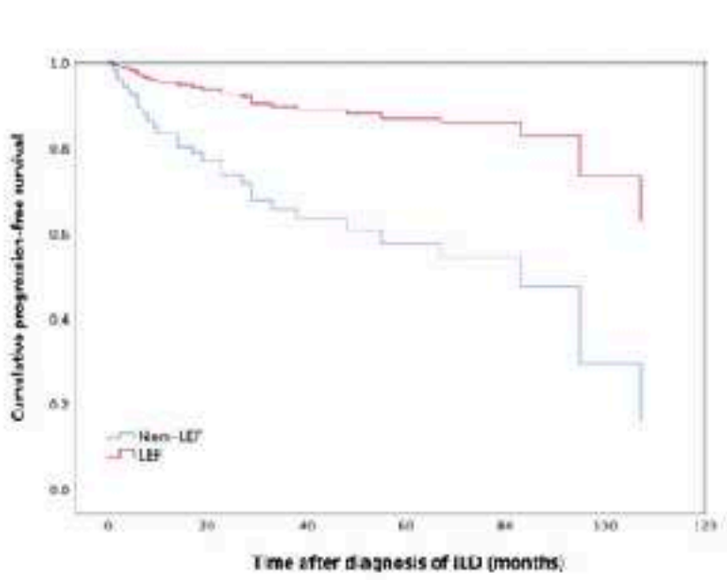
- **Withdrawal of DMARDs** : negative effect
- MTX : benefic effect (meta-analysis)
- **No RCT available**

Multicentric, cross-sectional study of consecutive patients, n= 106, Spain



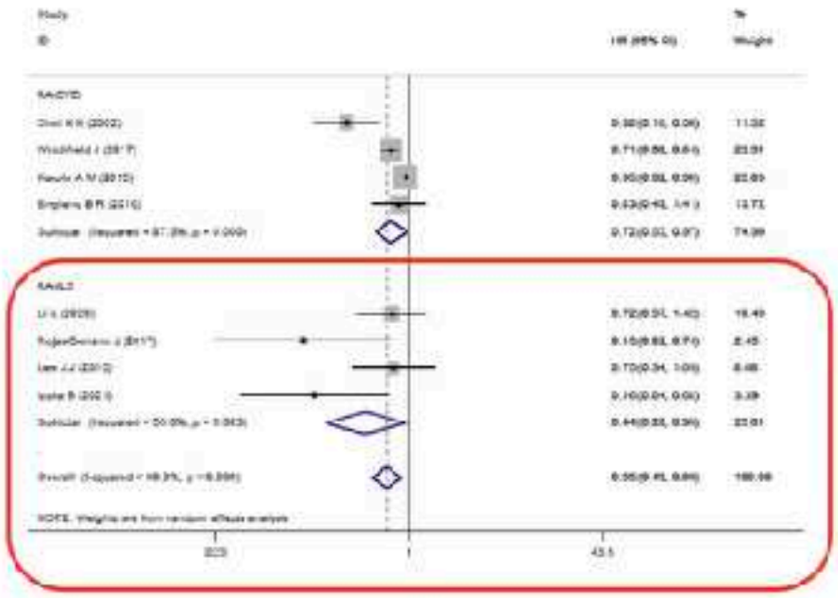
HR = 0.46 (0.24–0.88)

Monocentric, retrospective study, n= 75, Korea



HR = 0.25 (0.10–0.61)

MTX Meta-analysis - 15 studies

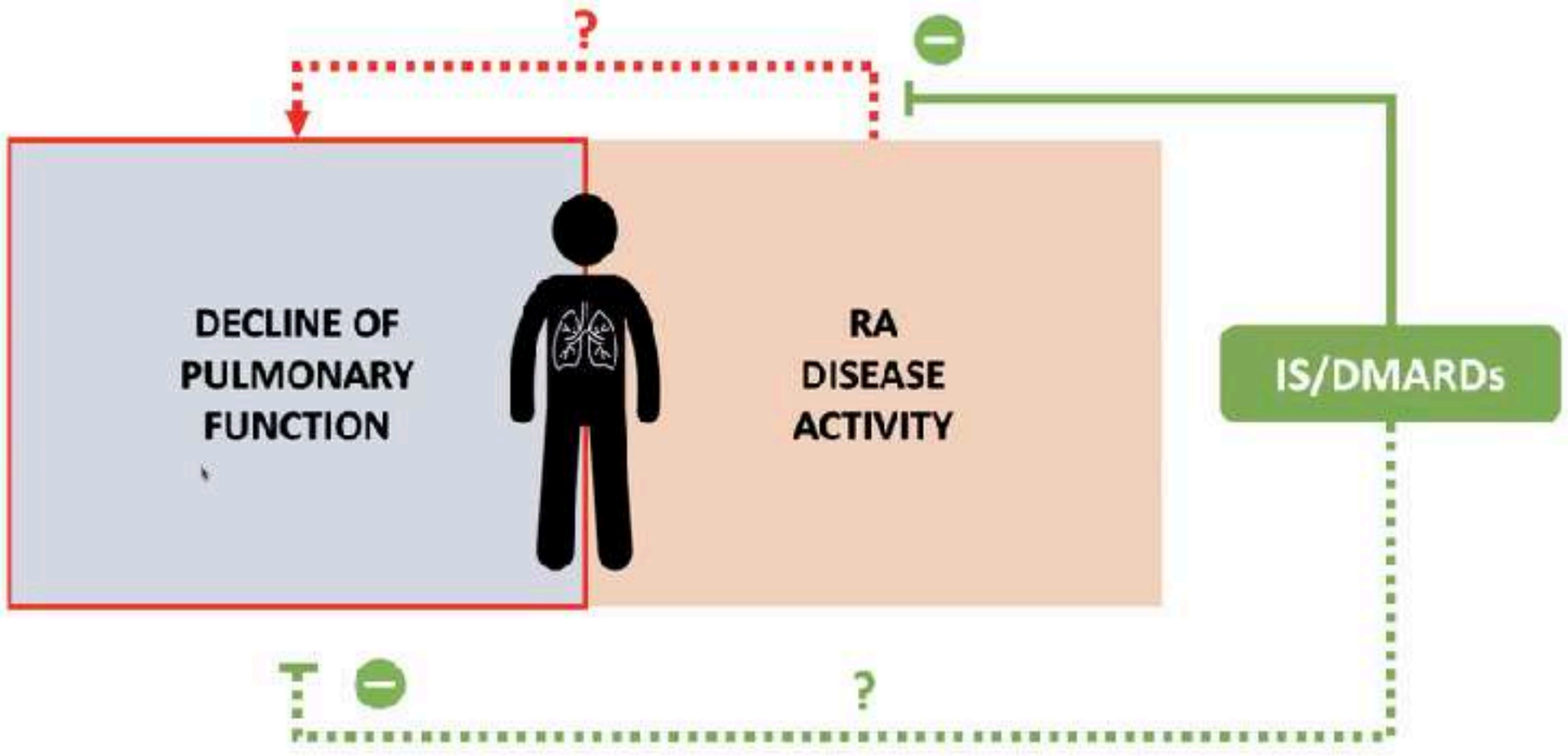


HR = 0.65 (0.49–0.86)

Rojas Serrano J Clin Rheumatol 2017 , Cano-Jimenez E et al. Sci Rep. 2021; Xu J et al. Semin Arthritis Rheum. 2022; Chen N et al. Semin Arthritis Rheum. 2022 , Chang SH et al. Rheumatology (Oxford). 2023.

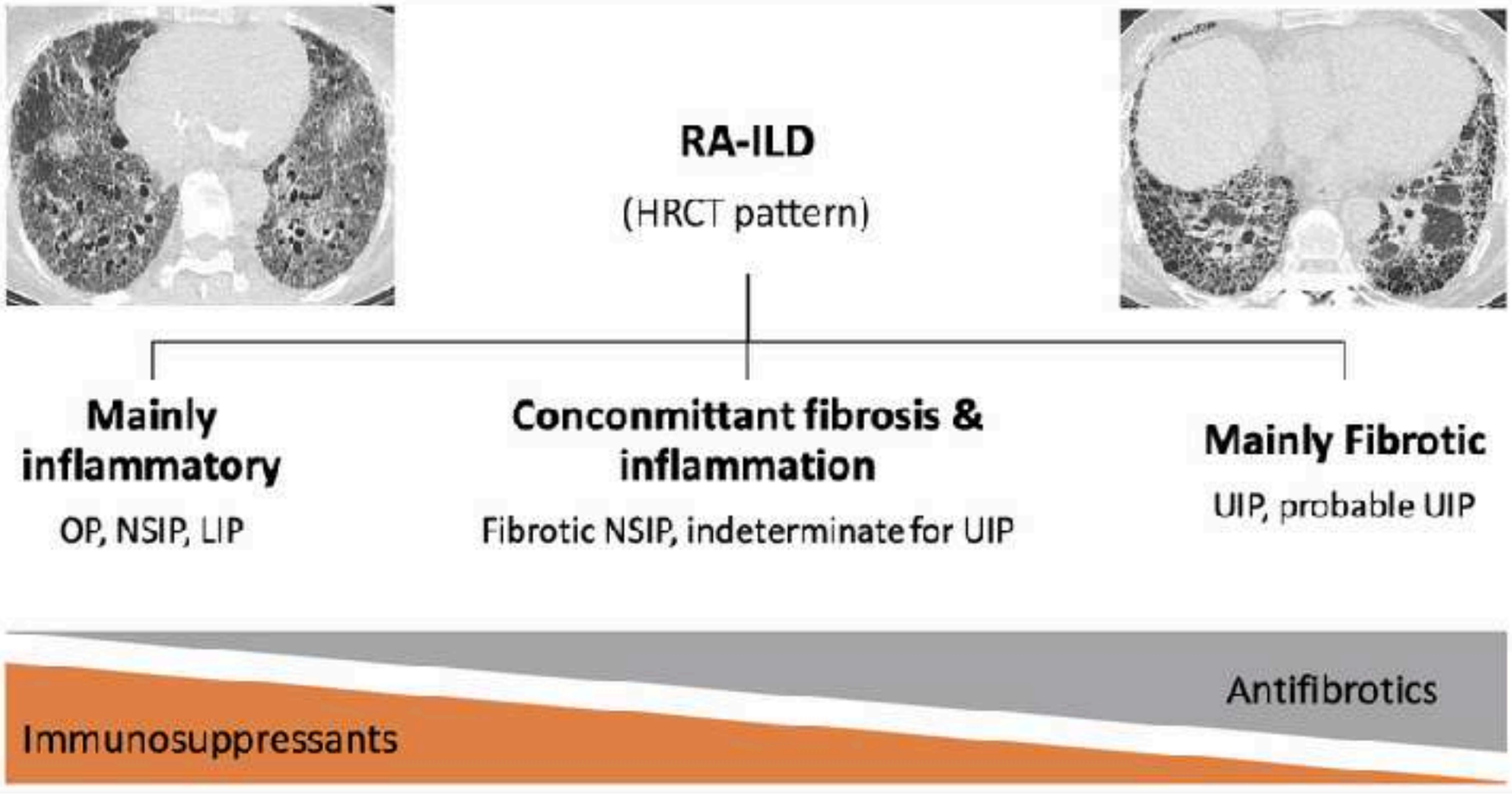
2 main objectives

- **Do IS/DMARDs directly impact ILD ?**



Strategy based on HRCT patterns ?

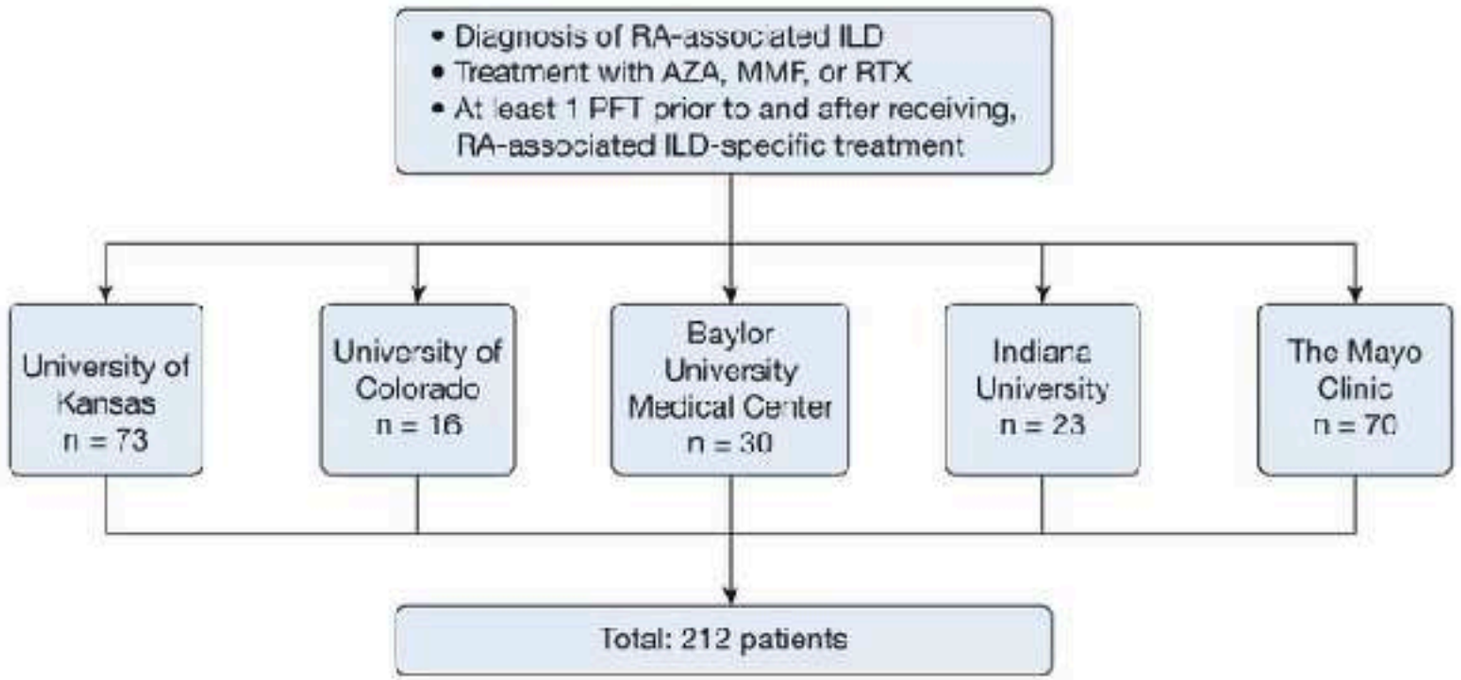
- **Current paradigm**



Do IS/DMARDs directly impact ILD ?

- **IS initiation for RA-ILD**
- IS = **RTX, MMF, AZA**
- RA-related ttt: 69 % DMARDs, 68% prednisone

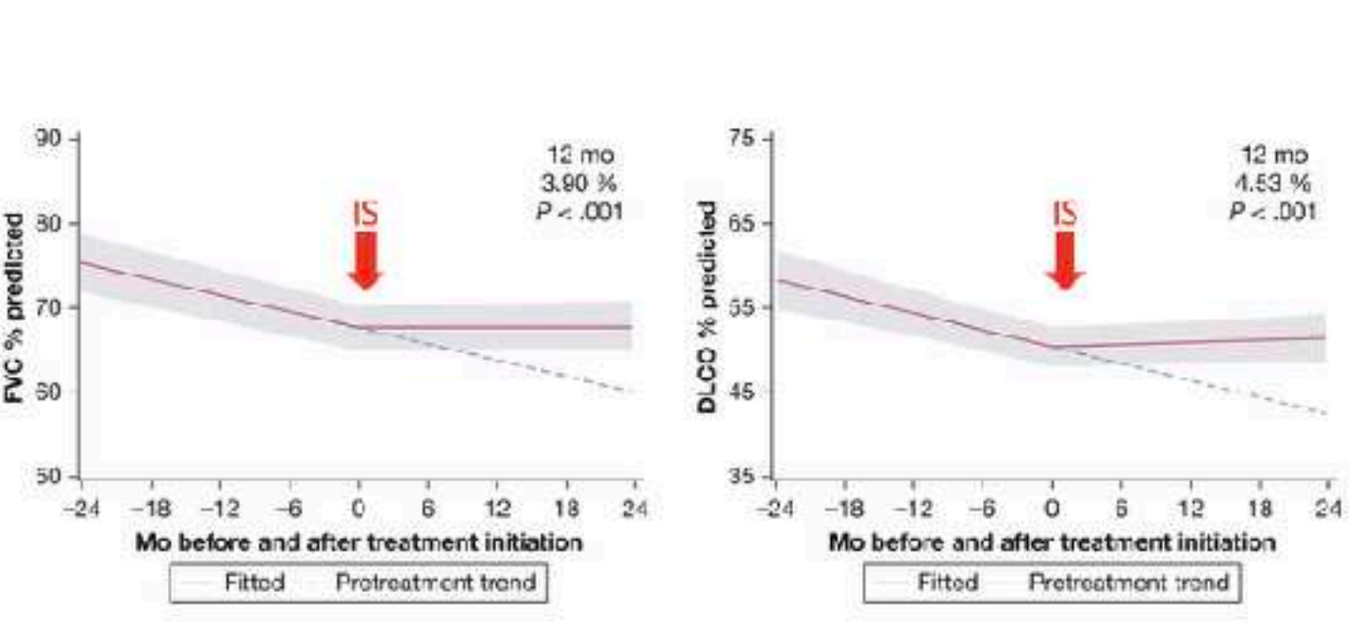
212 patients with RA-ILD, retrospective cohort, USA

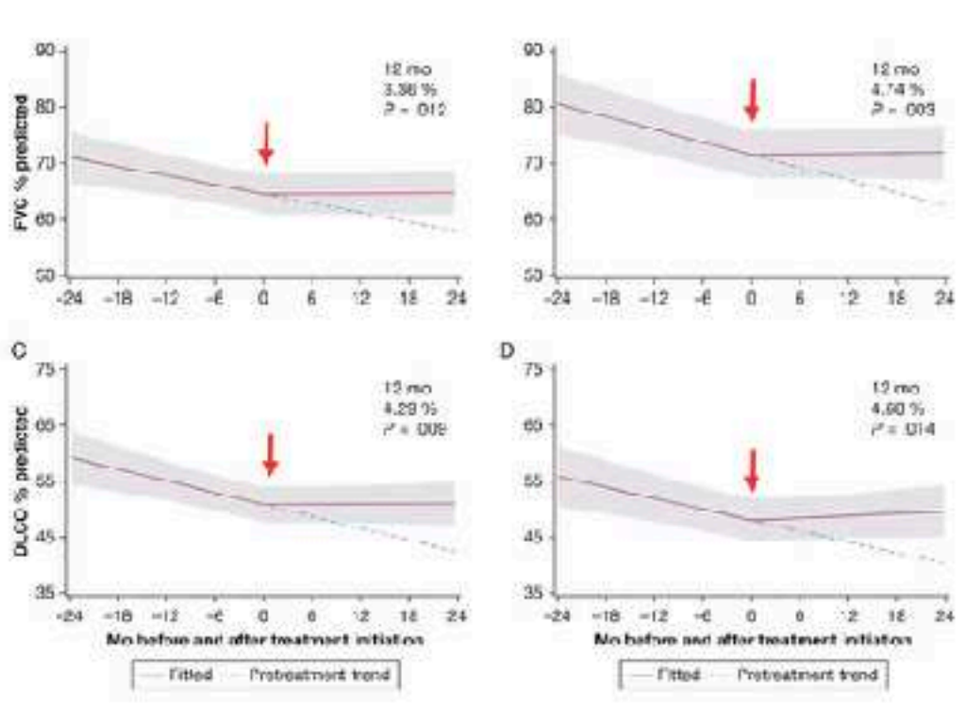


Do IS/DMARDs directly impact ILD ?

- **IS associated with an improved** trajectory in FVC and DLCO
- **Regardless of the HRCT pattern** (UIP = 40%)

212 patients with RA-ILD, retrospective cohort, USA





Matson SM et al. Chest. 2022.

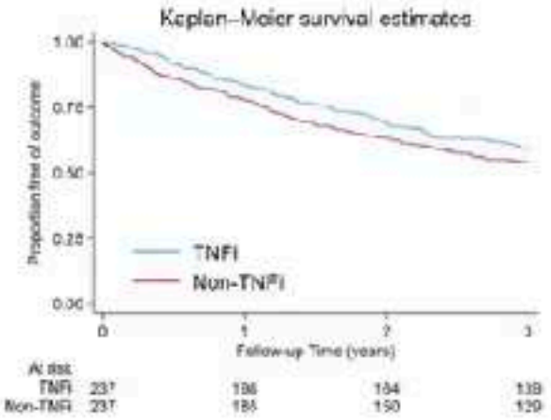
TNFi

- **Not associated** with increased **mortality**
- **Not associated** in **lung-related hospitalisation**

VARA cohort, emulated comparative trial : non-TNFi b/tsDMARDs (n=237) vs. TNFi in RA-ILD (n=237)

Results: Primary Outcome

3-year Composite: Death or respiratory hospitalization



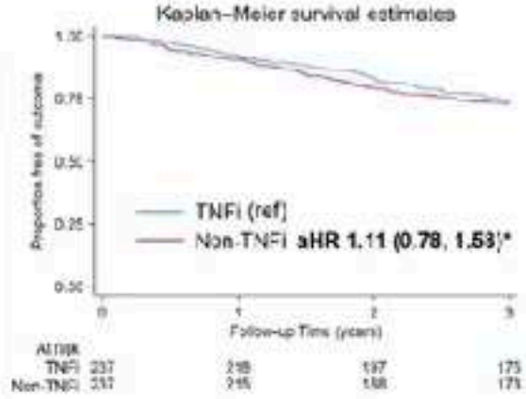
	Events	PY	IR (95% CI) /100PY
TNFi	96	550.6	17.3 (14.6, 21.7)
Non-TNFi/JAKi	109	508.4	21.2 (17.6, 25.7)

Non-TNFi/JAKi vs. TNFi:
aHR 1.21 (95% CI 0.92, 1.59)*

*Models adjusted for variables with Std Diff >0.1

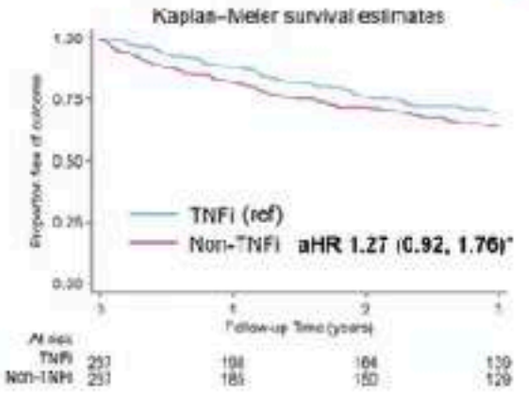
Results: Secondary Outcomes

Death (3-year)



36% of deaths respiratory-related
Respiratory-related death: aHR 1.36 (0.75, 2.46)

Respiratory hospitalization (3-year)

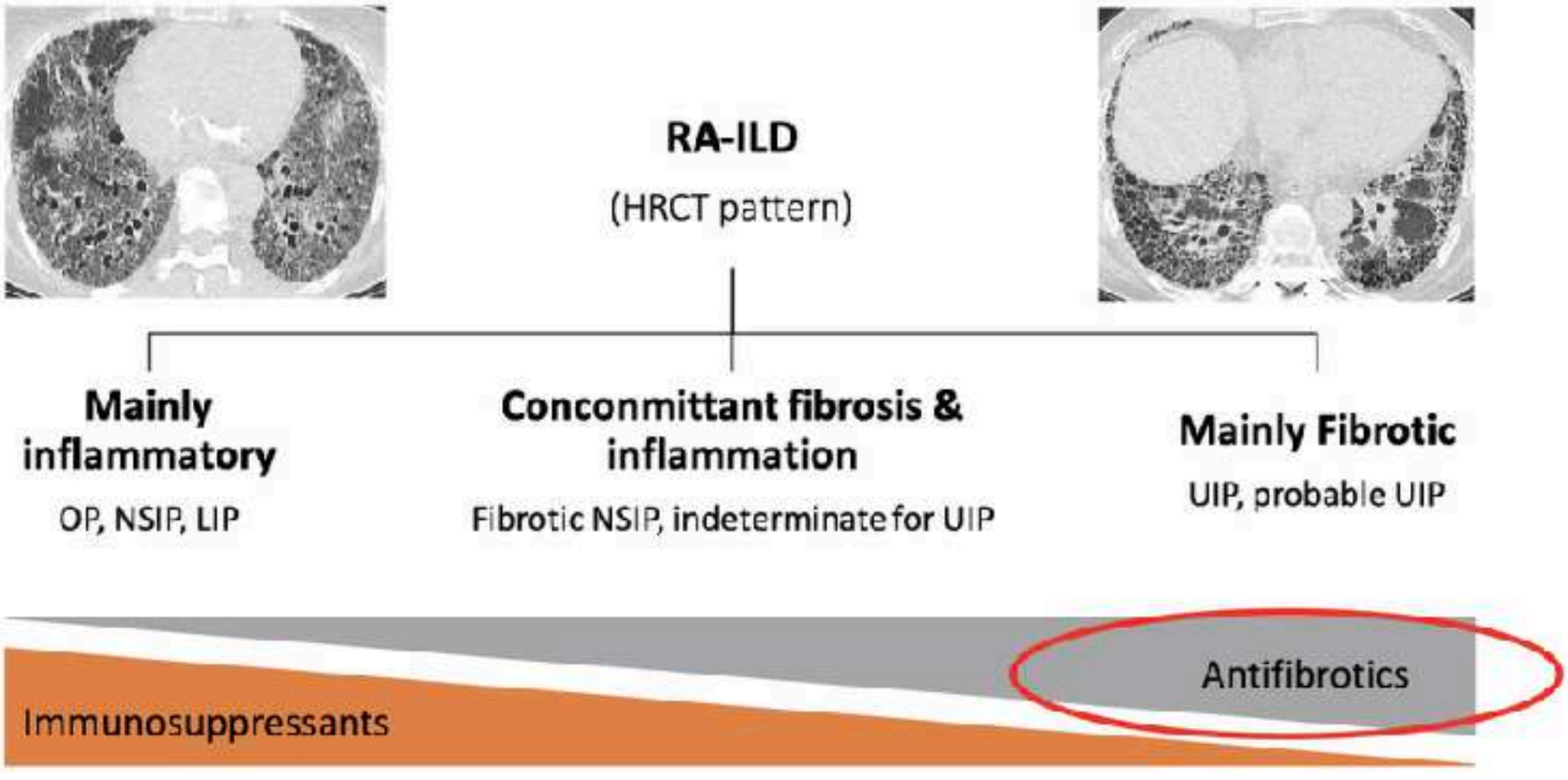


*Models adjusted for variables with Std Diff >0.1

England B et al. ACR Convergence 2023 abstr. # 1562

Antifibrotics ?

- **RCT available, but… low level of evidence !**



Nintedanib & RA-ILD

- *Post-hoc* analyses of the **INBUILD** study
- Non IPF progressive fibrotic ILD
- Including AI-ILD

INBUILD inclusion criteria

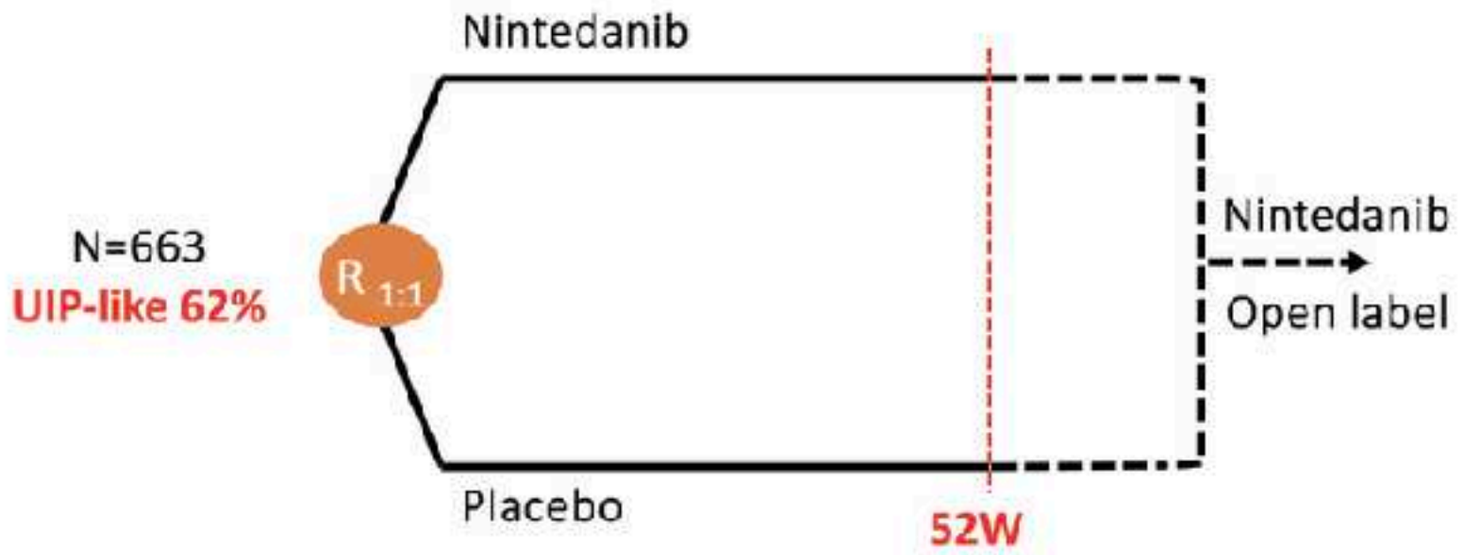
1 - Reticulations and traction bronchiectasis, wih or without honeycombing on HRCT with ≥ **10% extent**

2 - **Progressive fibrosis** in the last 24 months despite optimal Tt:

- ≥ 10% FVC decline
- 5-10% FVC decline and worsening respiratory symptoms and/or evidence of increasing fibrosis on HRCT
- Worsening of symptoms with increased fibrosis extent on chest imaging

3 - **FVC ≥ 45%**

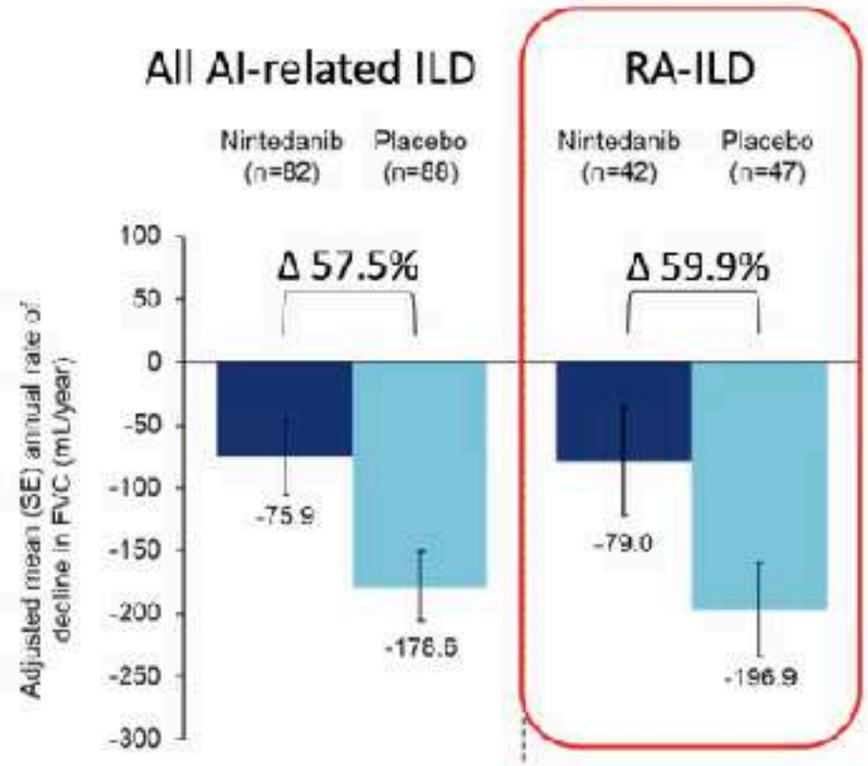
Primary endpoint : annual rate of decline in FVC (over 52 weeks)

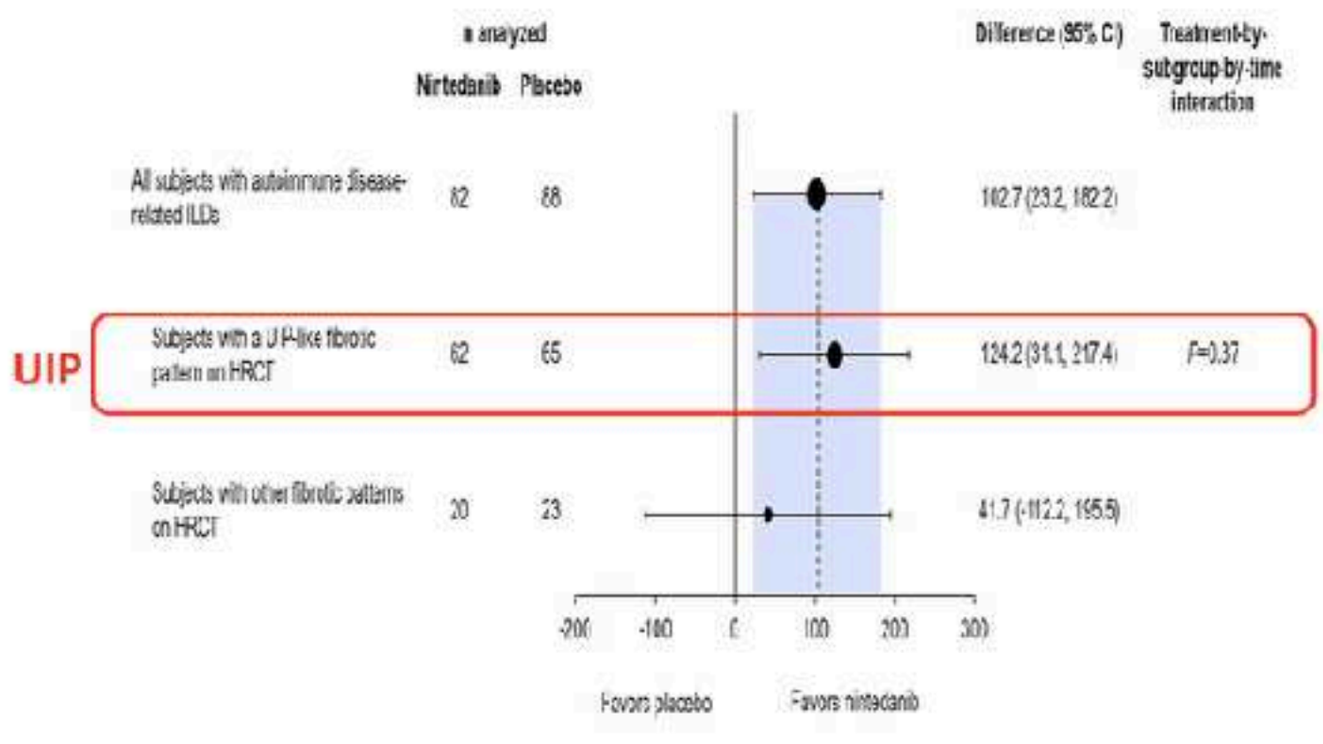


Nintedanib & RA-ILD

- Few number of patients with RA-ILD (n=89, 52.4%)
- Slowed rate of FVC decline in RA-ILD (*P = 0.041*)
- Effect numerically greater in AI-ILD with UIP

Annual rate of decline in FVC (ml/year) over 52 weeks



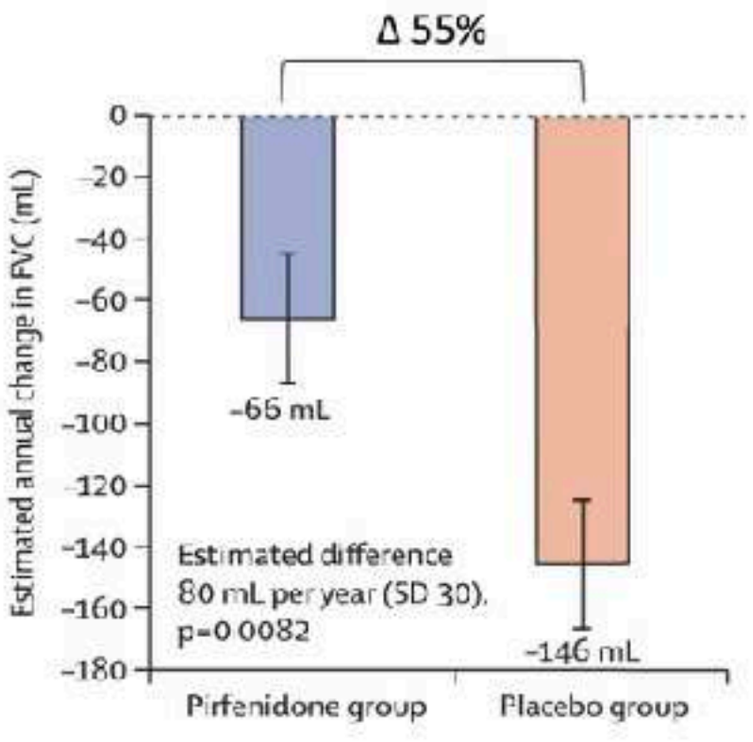


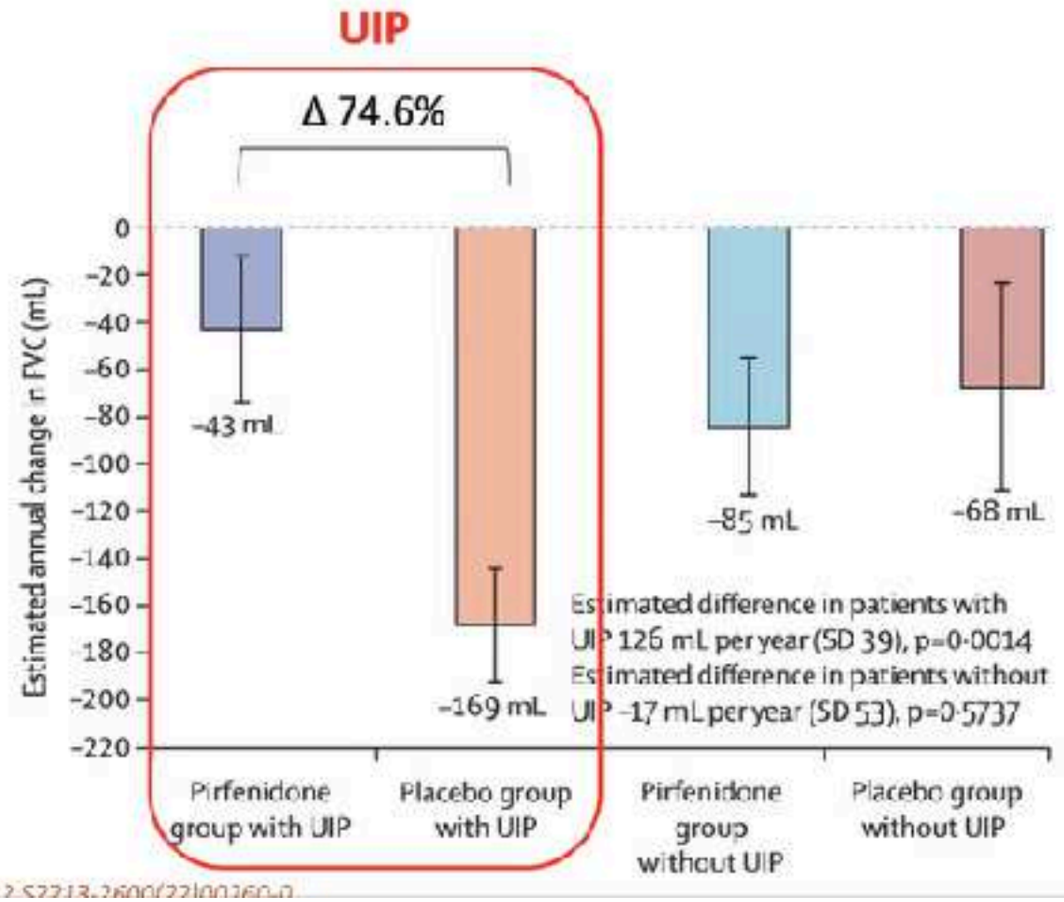
Adapted from: Matteson EL et al. Arthritis Rheumatol. 2022 Jun;74(6):1039-1047.

Pirfenidone & RA-ILD

- Primary endpoint not achieved
- Meeting the PEP of INBUILD (*P=0.0082*) !
- Effect restricted RA-UIP (*P=0.0014*) (*post-hoc*)

Annual rate of decline in FVC (ml/year) over 52 weeks

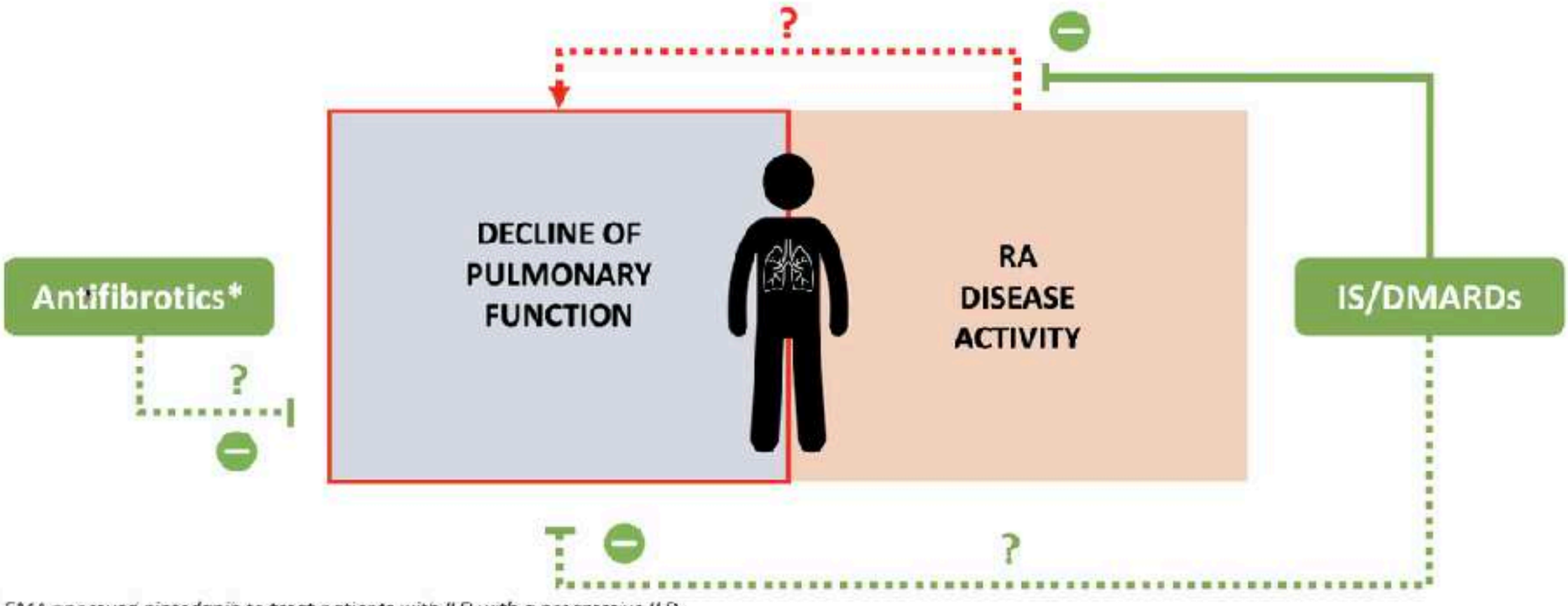




Adapted from: Solomon J et al. Lancet Respir Med. 2022 Sep 2:S2213-2600(22)00260-9

RA-ILD treatments

- MD discussion is mandatory +++
- Very low level of evidence



*FDA & EMA approved nintedanib to treat patients with ILD with a progressive ILD

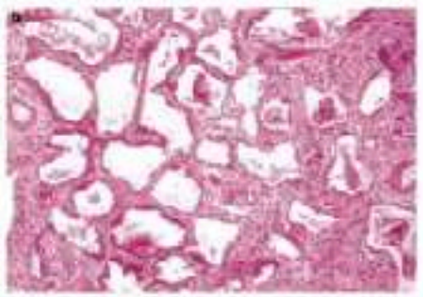
RA-ILD treatments

- **Inflammation is always associated with fibrosis**

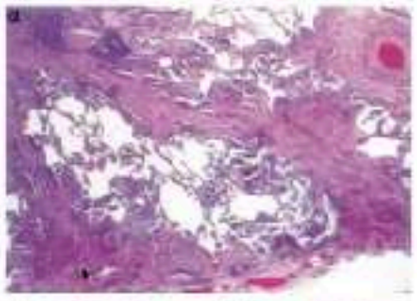
17 surgical lung biopsies (RA-ILD)

Major pattern	N	Additional minor component
Follicular bronchiolitis	6	NSIP, n=5
NSIP	7 (cellular 2, fibrotic 5)	Follicular bronchiolitis, n=5 OP, n=1
UIP	2	Follicular bronchiolitis, n=2
Respiratory bronchiolitis	1	
Mixed NSIP and respiratory bronchiolitis	1	

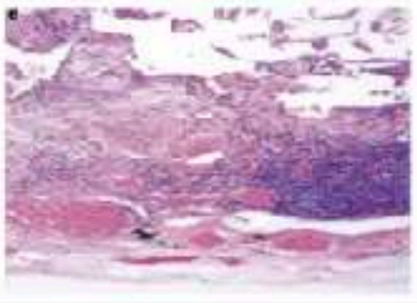
fNSIP



UIP



Fibroblastic foci
Lymphoid follicles

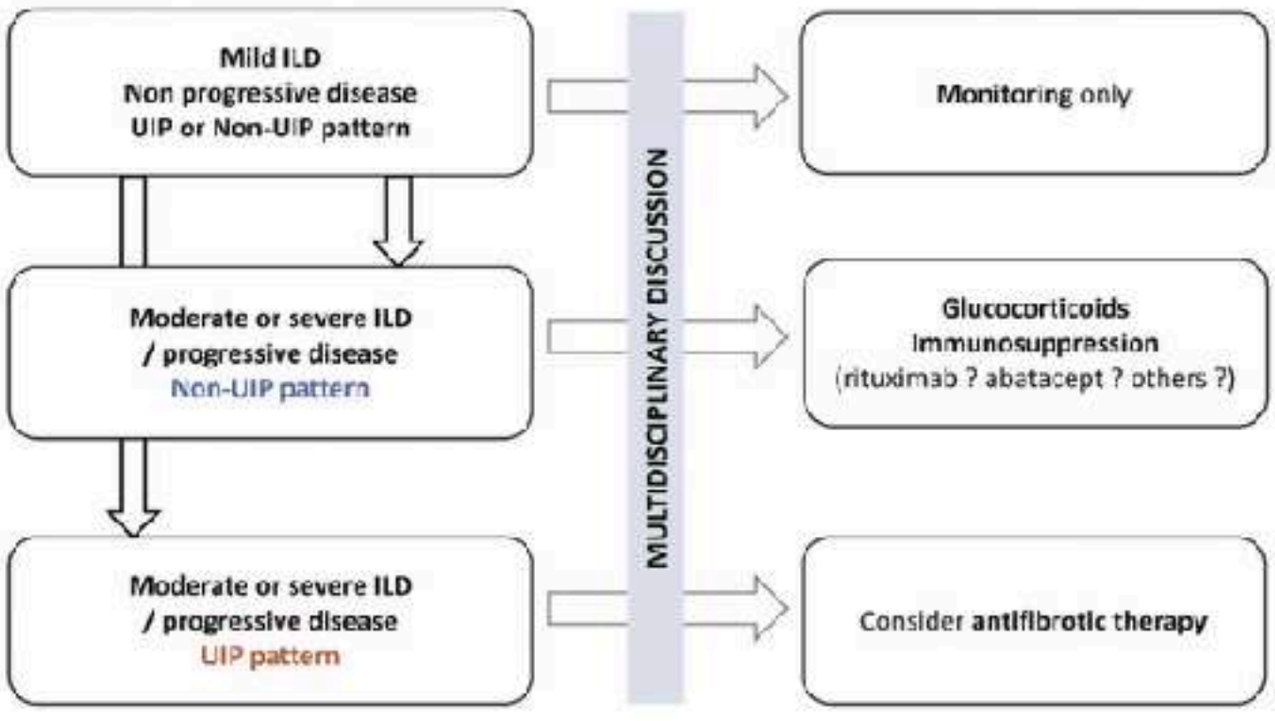


Jansey D et al. Histopathology 2004.

Indication(s) for « treating » RA-ILD ?

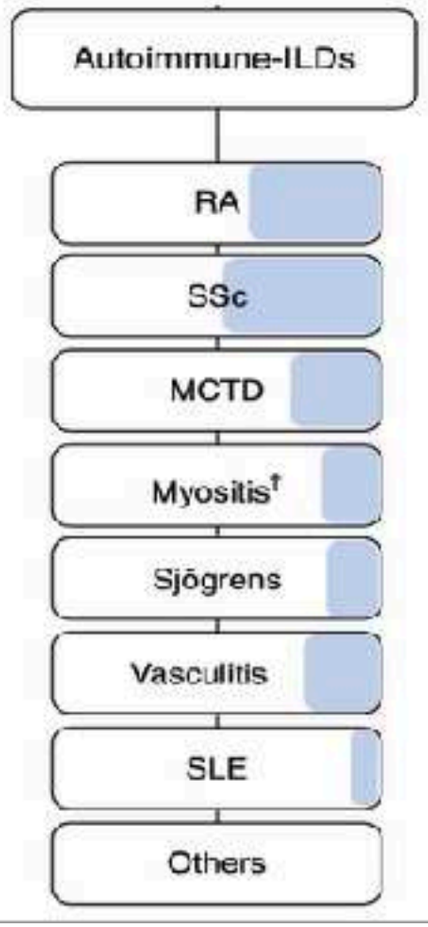
Indication for treatment initiation

- **No guideline +++**
- **PPF** would be relevant
- **Severe RA-ILD at baseline ?**



Indication for treatment initiation

- **PPF definition**



Definition of Progressive Pulmonary Fibrosis (PPF)

In a patient with ILD, **PPF** is defined as at least **2 of** the following **3 criteria occurring within the past year** with no alternative explanation*:

1 Worsening respiratory symptoms

2 Physiological evidence of disease progression (either of the following):

a. Absolute decline in FVC >5% predicted within 1 yr of follow-up
b. Absolute decline in DLCO (corrected for Hb) >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

Raghu G et al. AJRCCM 2022.

Should we screen for RA-ILD ?

Screening for RA-ILD

- **Probably too early to promote screening !**
- Identification of high-risk individuals for
  - RA-ILD
  - PPF **(additional criteria)**

1. Frequent & potentially severe ✓
2. Identification of high-risk individuals ✓
3. Specific treatment available ?
4. Evidence of treatment benefit ?
5. Known indication for treatment ✓

Unmet needs in RA-ILD

- **No dedicated guideline +++**

- Validated risk & prognosis scores are needed
- The best screening tool should be identified (HRCT, LUS, PFTs,…)
- Best temporality for screening remains to be determined
- Treatments; low level of evidence : RCT are needed

⚠ **Avoid asking GPT for advice…at least for RA-ILD screening**