Rheumatoid arthritis-associated ILD: The latest data on treatment advances

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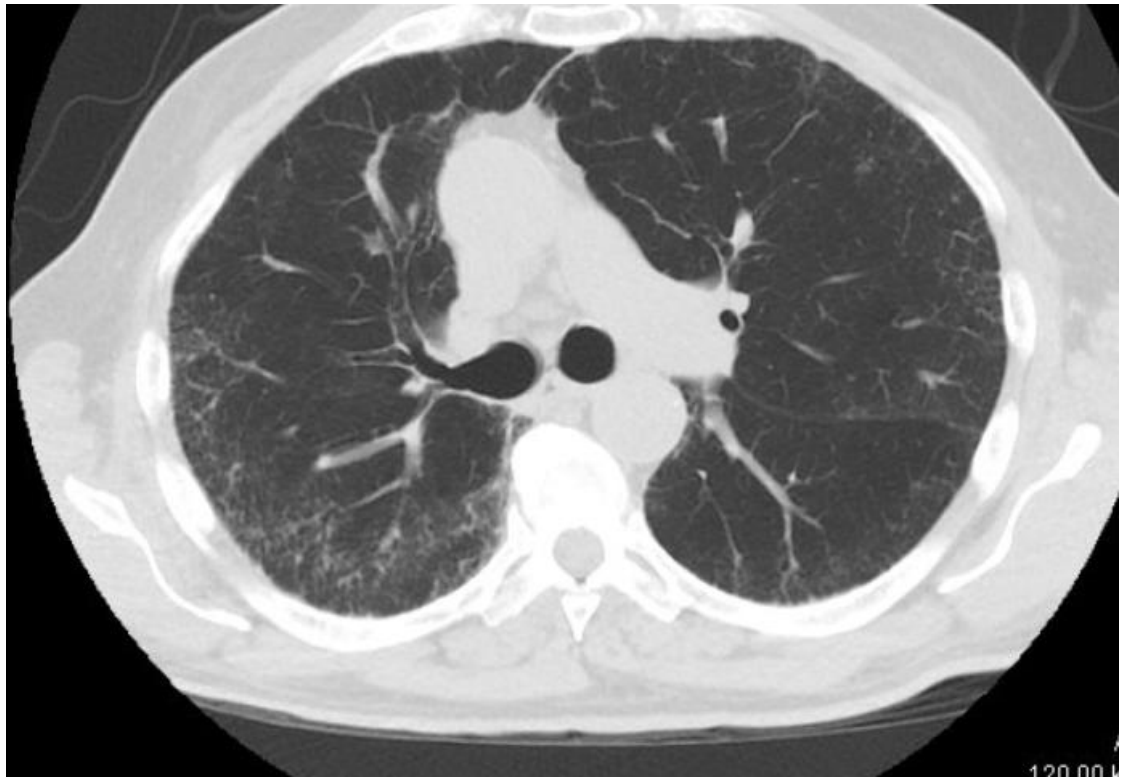
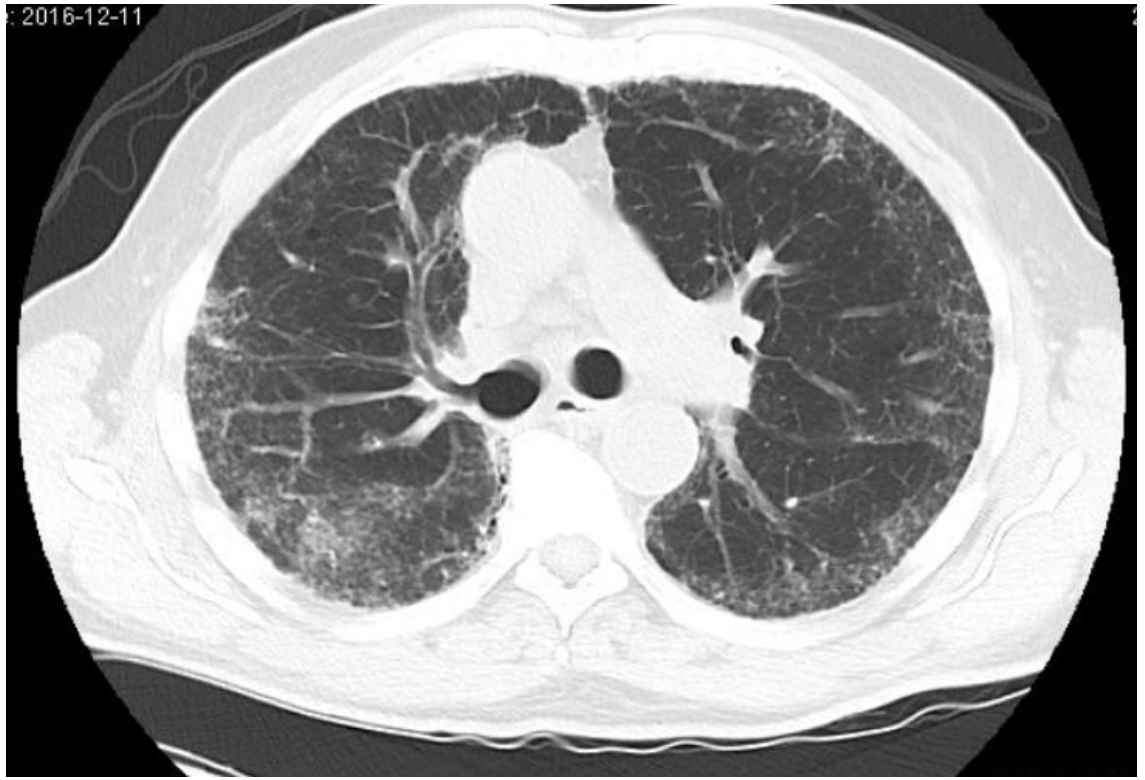
Disclosures

- Advisory board: Boehringer Ingelheim
- Authorship Fees: UpToDate, Dynamed
- Paid consultation: Vicore, Merck
- PI on clinical trials: Boehringer Ingelheim, Vicore

73 M with long-standing seropositive RA





Joint pain minimal on prednisone 5 daily, hydroxychloroquine

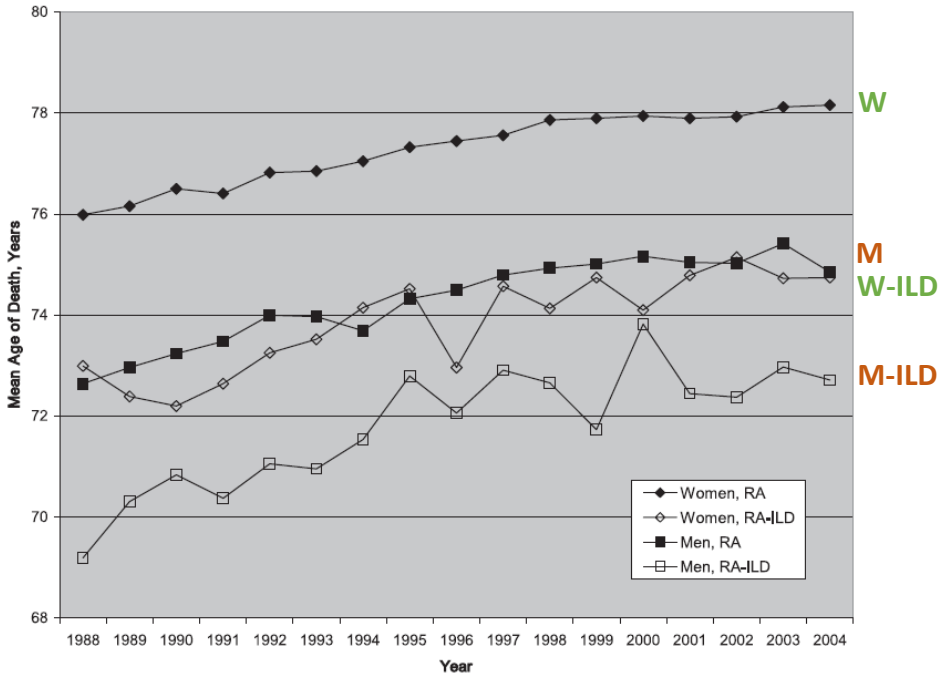
ILD is common in patients with RA

- Reported prevalence of clinically significant RA ranges from 2-15%
- Incidentally found in up to 50% of autopsy cases
- ILD precedes the diagnosis of RA in at least 14% of patients
- ILD develops within the first year of RA diagnosis in 33% of patients

Koduri et al. *Rheumatology (Oxford).* 2010;49(8):1483-9.
Bongartz et al. *Arthritis Rheum.* 2010;62(6):1583-91.
Hyldgaard et al. *Ann Rheum Dis*. 2017;76(10):1700-6.
Raimundo et al. *J Rheumatol.* 2019;46(4):360-9.

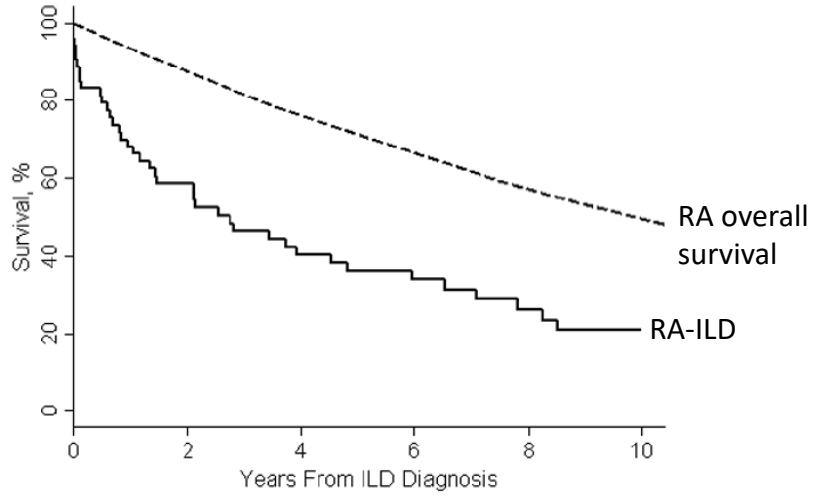
ILD is associated with death in RA

- Natl Ctr Health Stats 1988-2004
- ILD was the leading cause of death (35.3%)
- "RA complications" second leading cause (35%)



Olson et al. *Am J Respir Crit Care.* Med Vol 183. pp 372–378, 2011

- 582 pts with RA, 603 pts without RA followed a mean of 16.4 /19.3 yrs
- 7.7% developed ILD, with a lower median survival than expected (2.6 vs 9.9 yrs)
- ILD HR for death 2.86



Bongartz et al. *Arthritis Rheum*. 2010 June ; 62(6): 1583–1591.

Risk Factors for developing ILD and ILD *progression* in RA

- Advanced age
- Male sex
- RA duration
- Smoking history
- Disease severity
- HLA allele variants
- Elevated antibody titers: RF, CCP

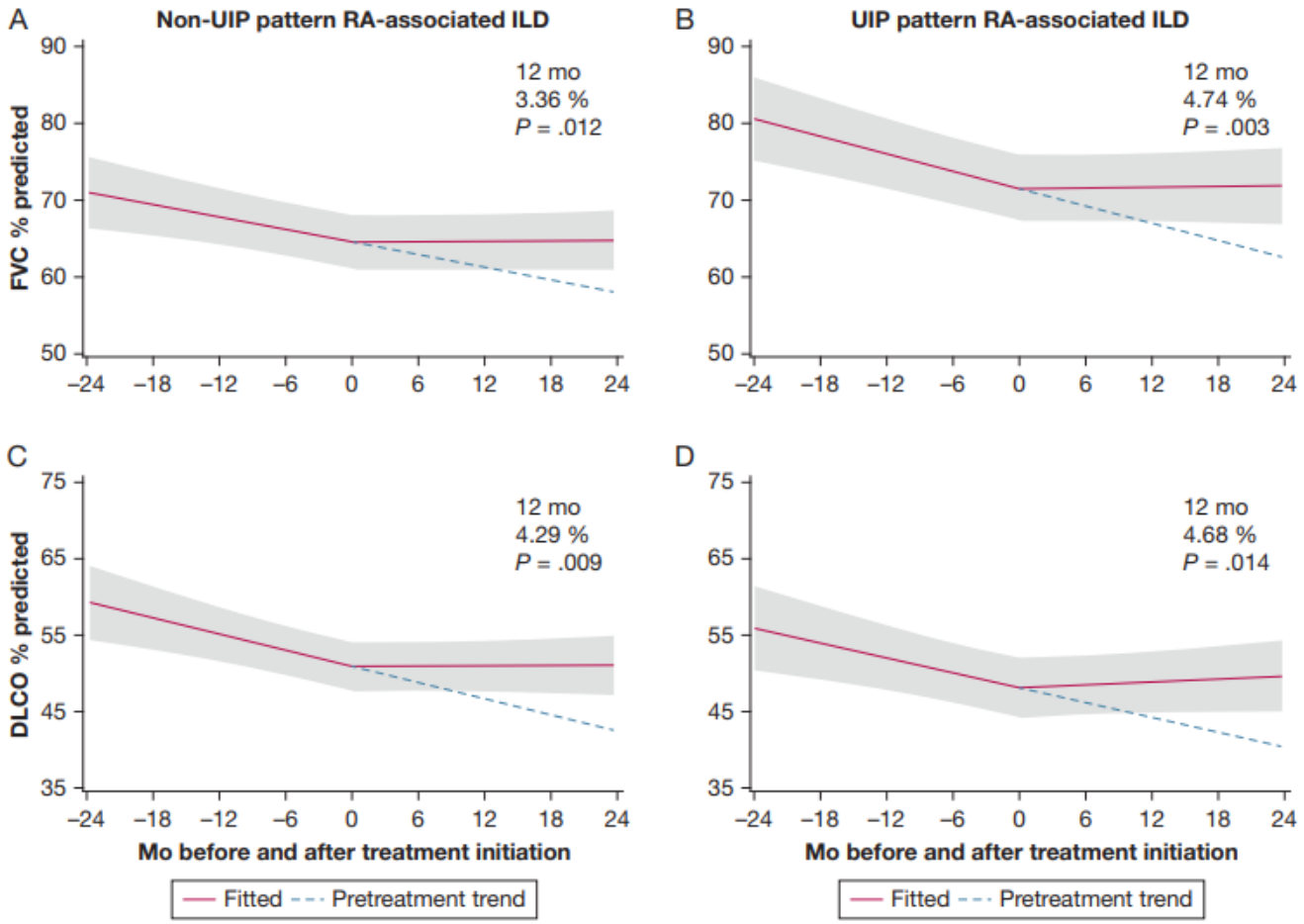
Kur-Zalewska et al. *PLOS ONE* April 16, 2021.
Hallowell and Horton. *Drugs* (2014) 74:443–450.

Immunosuppression can be useful in RA-ILD, regardless of the radiographic pattern

- Retrospective study of 212 patients
- 92 AZA; 77 MMF; 43 RTX
- No difference between treatment groups

Concurrent therapy

Prednisone	67.9%
HCQ	26.4%
Leflunomide	13.7%
Methotrexate	11.8%
Infliximab	7.1%
Sulfasalazine	6.1%
Etanercept	5.7%
Abatacept	4.7%
Adalimumab	3.8%
Tofacitinib	1.9%



Matson et al. *Chest.* 2023; 163(4):861-869

Rituximab for RA-ILD

- 20 studies
- 1619 patients with RA-ILD who received RTX
- F/u ranged from 6-38 months
- Concurrent therapy was common or not reported

Based on PFTs (11 studies), mean proportion of disease progression was 14.5% (95% CI, 7.6% - 25.8%)

Based on CT imaged (6 studies), mean proportion of disease progression was 19.5% (95% CI, 8.1% - 40%)

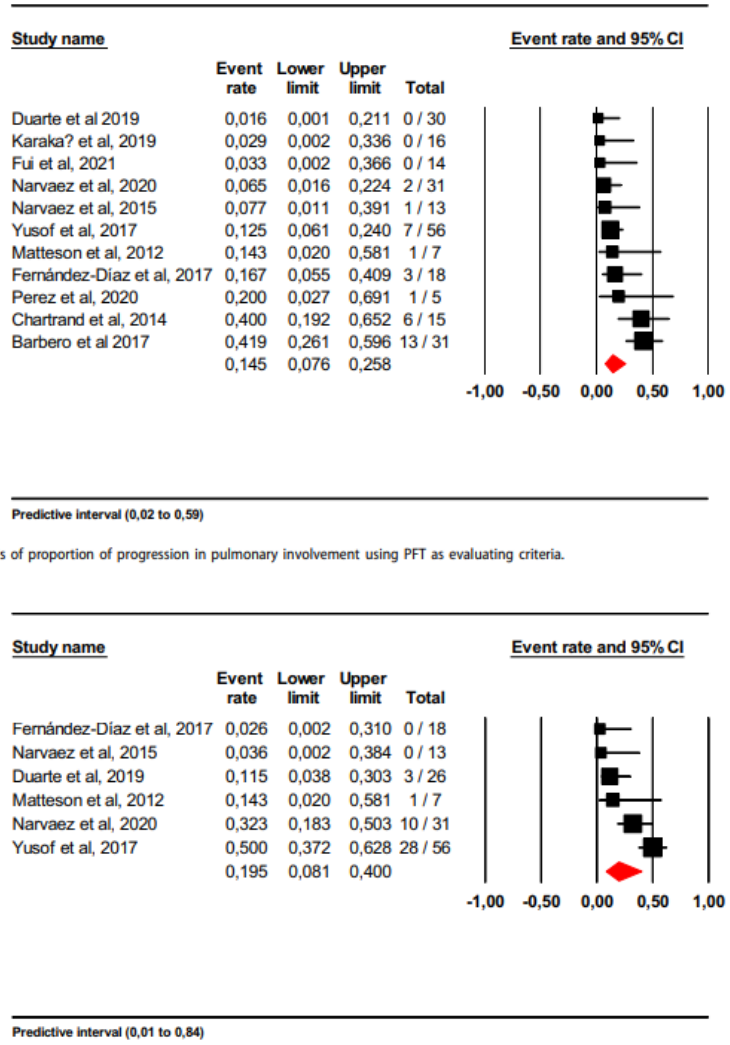


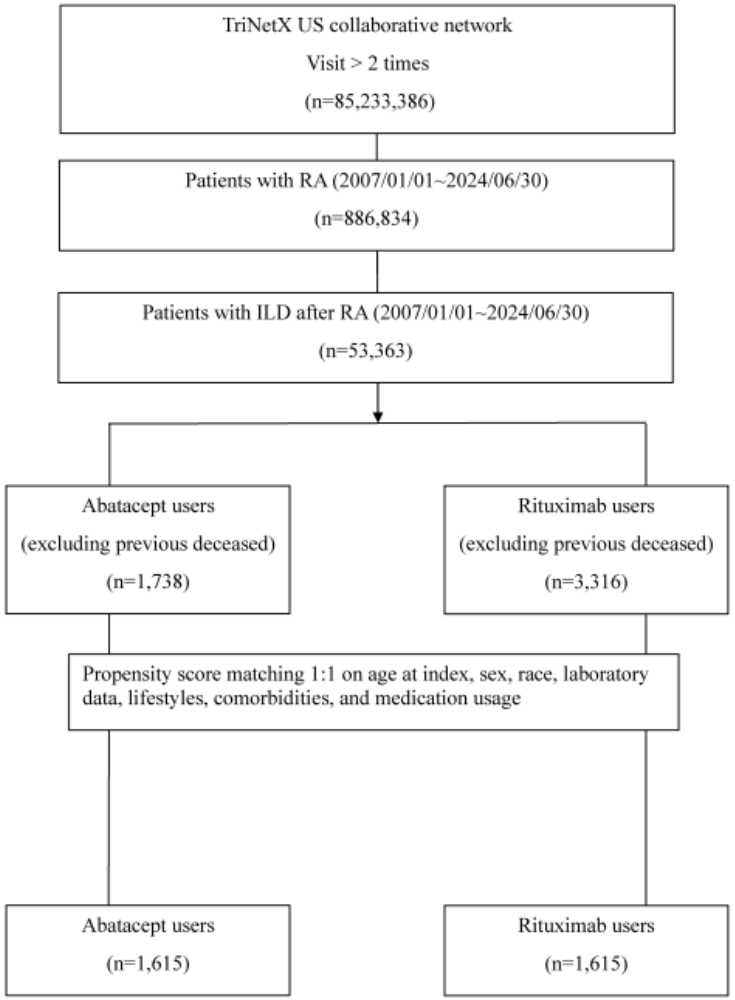
Figure 2. Meta-analysis of proportion of progression in pulmonary involvement using PFT as evaluating criteria.

Abatacept is associated with lower mortality than RTX in patients with RA-ILD

- Emulated target trial design
- TriNetX database
- Propensity score matching

- Reduced risk of mechanical ventilation

ABA vs RTX:
(HR, 0.698; 95% CI, 0.521–0.934)



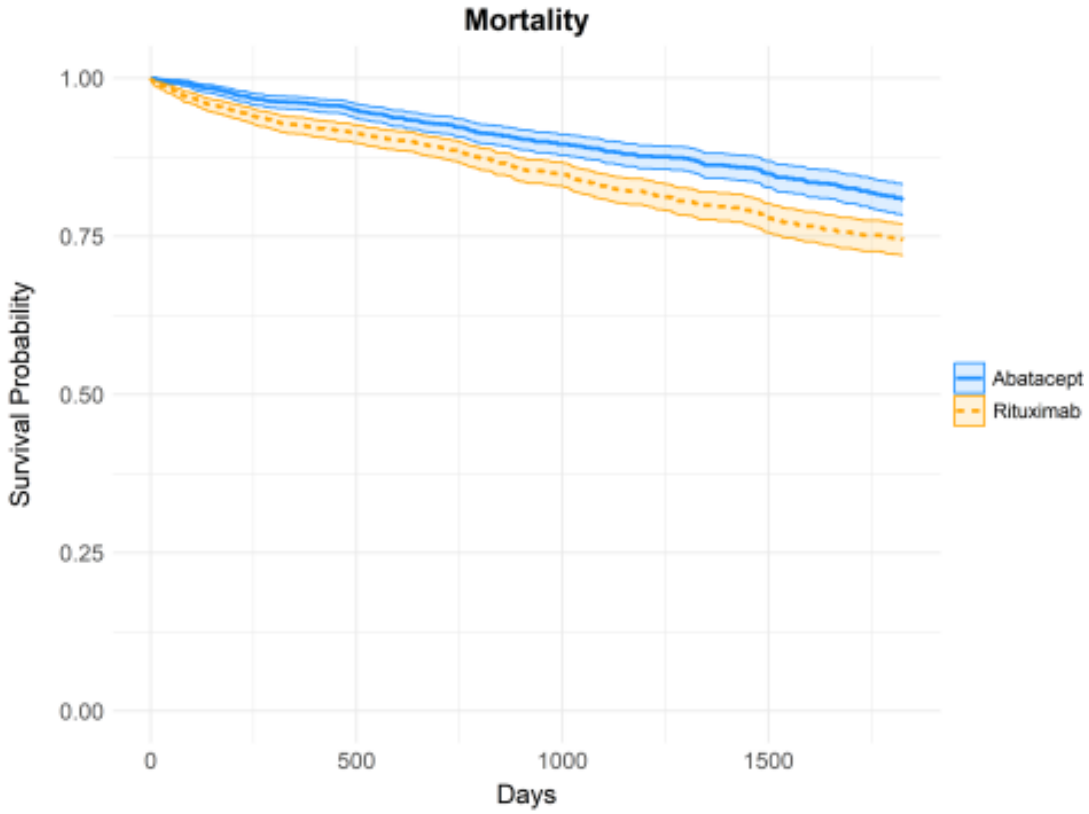
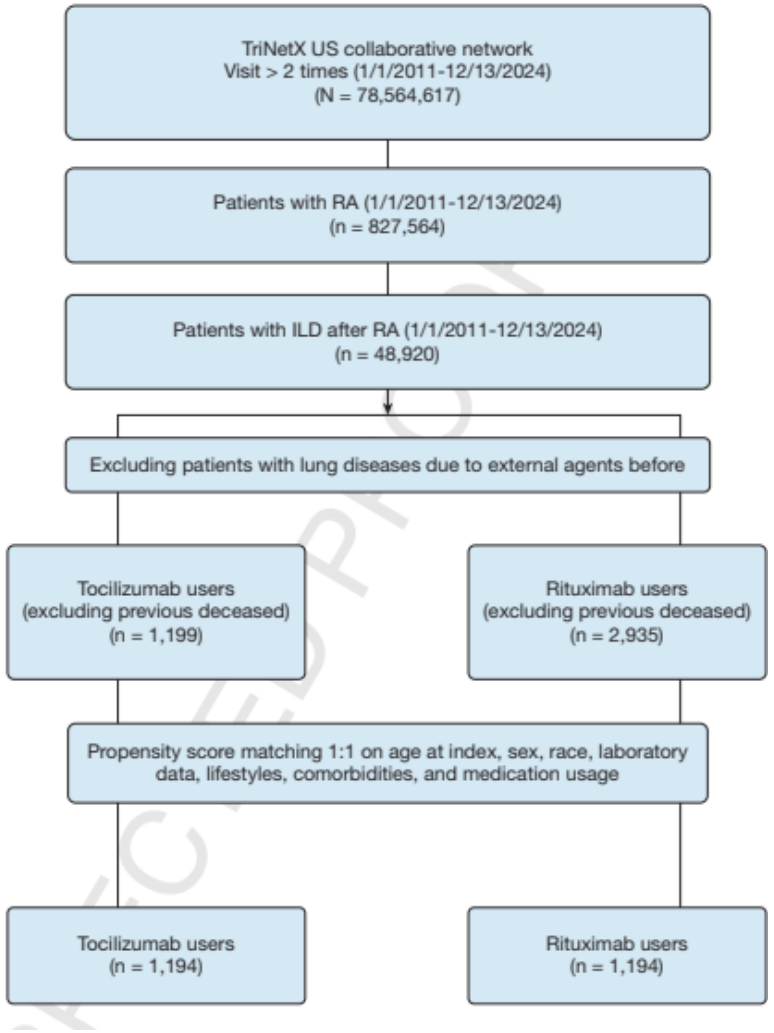


Figure 2. Kaplan–Meier Plots for all-cause mortality.

HR, 0.689; 95% CI, 0.581–0.818

Comparing Tocilizumab and Rituximab in RA-ILD



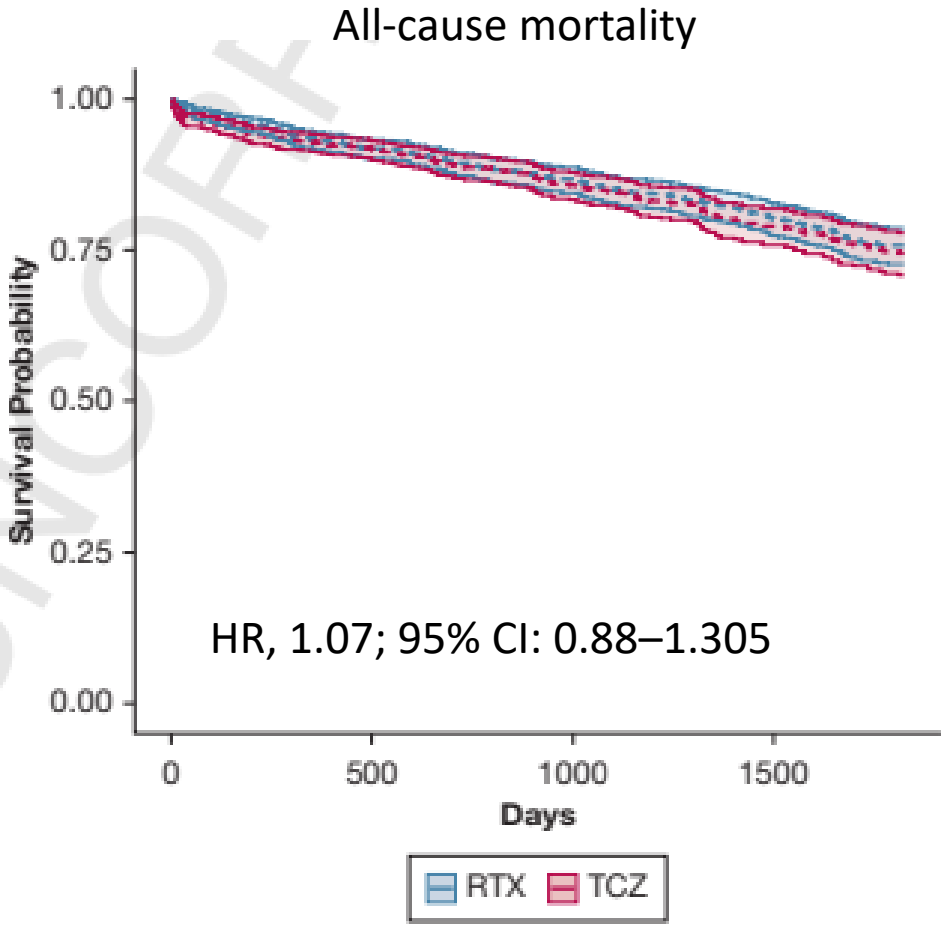
- Emulated target trial design

TABLE 1] *(Continued)*

Variable	Prior to PSM			Following PSM[a]		
	TCZ Cohort (n = 1,199)	RTX Cohort (n = 2,934)	SMD	TCZ Cohort (n = 1,194)	RTX Cohort (n = 1,194)	SMD
Systemic sclerosis (scleroderma)	153 (12.8)	327 (11.1)	0.050	150 (12.6)	143 (12.0)	0.018
Sjögren's syndrome	99 (8.3)	348 (11.9)	0.120	98 (8.2)	86 (7.2)	0.038
Medications						
Corticosteroids for systemic use	927 (77.3)	2371 (80.8)	0.086	923 (77.3)	900 (75.4)	0.045
Methotrexate	267 (22.3)	565 (19.3)	0.074	267 (22.4)	274 (22.9)	0.014
Sulfasalazine	90 (7.5)	167 (5.7)	0.073	89 (7.5)	95 (8.0)	0.019
Mycophenolate mofetil	170 (14.2)	706 (24.1)	0.253	169 (14.2)	173 (14.5)	0.010
Mycophenolic acid	38 (3.2)	158 (5.4)	0.110	38 (3.2)	41 (3.4)	0.014
Cyclosporine	49 (4.1)	91 (3.1)	0.053	49 (4.1)	40 (3.4)	0.040
Azathioprine	63 (5.3)	367 (12.5)	0.257	63 (5.3)	57 (4.8)	0.023
Leflunomide	163 (13.6)	240 (8.2)	0.174	161 (13.5)	162 (13.6)	0.002
Hydroxychloroquine	279 (23.3)	746 (25.4)	0.050	277 (23.2)	268 (22.4)	0.018
Sildenafil	57 (4.8)	133 (4.5)	0.010	56 (4.7)	40 (3.4)	0.068
Tadalafil	29 (2.4)	53 (1.8)	0.043	28 (2.3)	20 (1.7)	0.048
Epoprostenol	10 (0.8)	24 (0.8)	0.002	10 (0.8)	0 (0.0)	0.130
Treprostinil	10 (0.8)	15 (0.5)	0.039	10 (0.8)	10 (0.8)	0
Selexipag	10 (0.8)	10 (0.3)	0.065	10 (0.8)	10 (0.8)	0
Iloprost	10 (0.8)	0 (0.0)	0.130	0 (0.0)	0 (0.0)	NA
Antihypertensive agents for PAH	19 (1.6)	58 (2.0)	0.030	18 (1.5)	13 (1.1)	0.037

Wu et al. *Chest* 2025 *in press*.

Comparing Tocilizumab and Rituximab in RA-ILD



In patients with elevated baseline **inflammatory markers**, Toci had worse outcomes

Ventilation:
(HR, 1.936; 95% CI, 1.125-3.331)

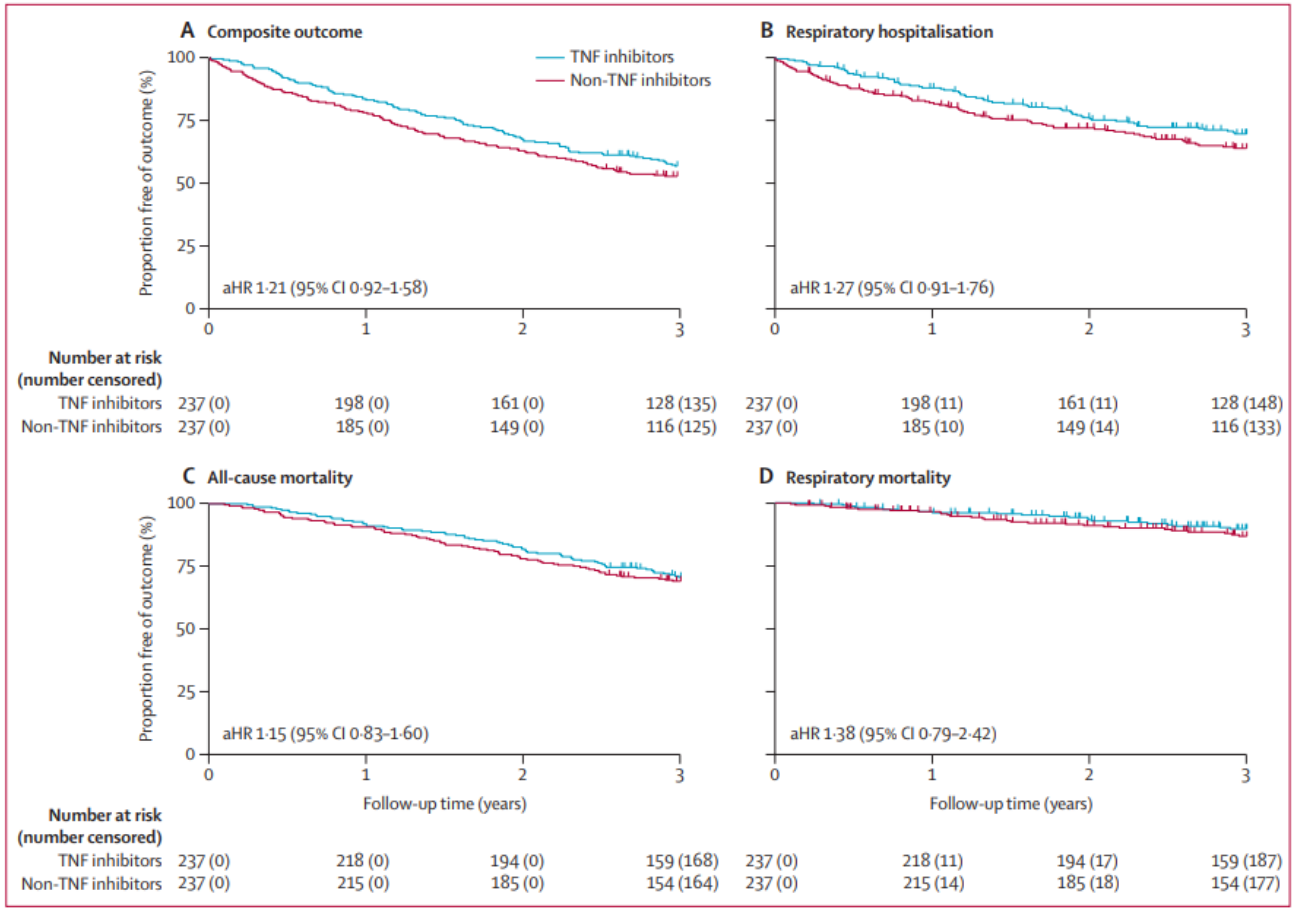
All-cause mortality:
(HR, 1.403; 95% CI: 1.013-1.942)

Wu et al. *Chest* 2025 *in press*.

TNF inhibitors are *not* associated with worse outcomes in RA-ILD

- Retrospective, active-comparator, observational cohort
- US Dept of Veteran Affairs EHR records
- No previous ILD-directed therapies
- Propensity score matching for the following: demographics, health care use, comorbidities, RA severity factors, ILD severity factors

- 237 TNF inhibitor patients matched with 237 non-TNF inhibitor patients
- 92% male
- No difference in respiratory hospitalization, all cause mortality, respiratory mortality



IVIG as adjunct therapy for RA-ILD

- Prospective pilot study of RA-ILD patients over 52 wks
- 40 received standard care
  (prednisone 40 mg/d with taper to 10 mg + MTX)
- 40 received standard care + IVIG
- Propensity score matching in a 1:1 ratio:
  (age, sex, FVC, severity of ILD, ESR)

Characteristic	Control group ($n=30$)	Immunoglobulin group ($n=30$)	p
CAT score (mean ± SD)			
Pre-	22.7 ± 2.6	21.8 ± 3.0	.43
Post-	19.1 ± 3.3	17.7 ± 3.4	.03
p	.01	<.001	
Distance of 6MWD (mean ± SD)			
Pre-	265.6 ± 42.4	266.5 ± 46.7	.93
Post-	332.3 ± 55.1	364.4 ± 54.3	.04
p	.02	<.001	
FVC (mean ± SD)			
Pre-	58.7 ± 11.5	57.3 ± 13.1	.85
Post-	66.6 ± 11.2	78.8 ± 12.6	.05
p	.05	.01	
HRCT score (mean ± SD)			
Pre-	9.2 ± 2.5	9.5 ± 1.9	.56
Post-	7.6 ± 1.6	6.0 ± 1.5	.04
p	.04	.01	
ESR (mean ± SD)			
Pre-	39.2 ± 14.6	38.4 ± 13.8	.85
Post-	14.1 ± 6.2	7.4 ± 3.3	.045
p	.01	<.001	

Shen et al. *Int J Rheum Dis.* 2023;26:1745–1750.

Pirfenidone for (RA-ILD) TRAIL1

- Phase 2 RCT at 34 centers
- Failed to meet its recruitment goal due to COVID
- 123 patients randomized (goal 270)
- Primary composite endpoint
  (10% FVC decline or death) not met

- Pirfenidone associated with slower estimated annual rate of FVC decline (–66 *vs* –146; p=0·0082)

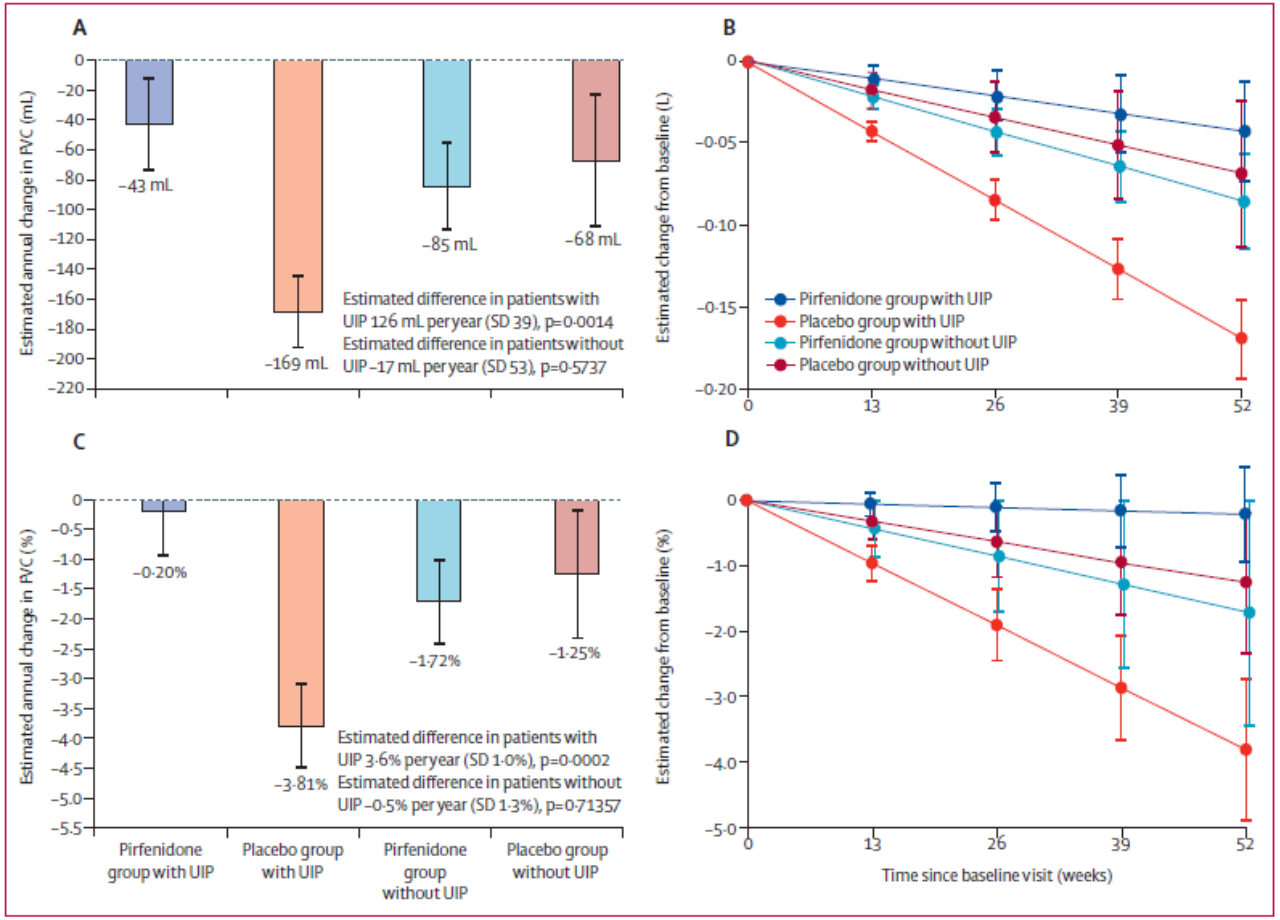
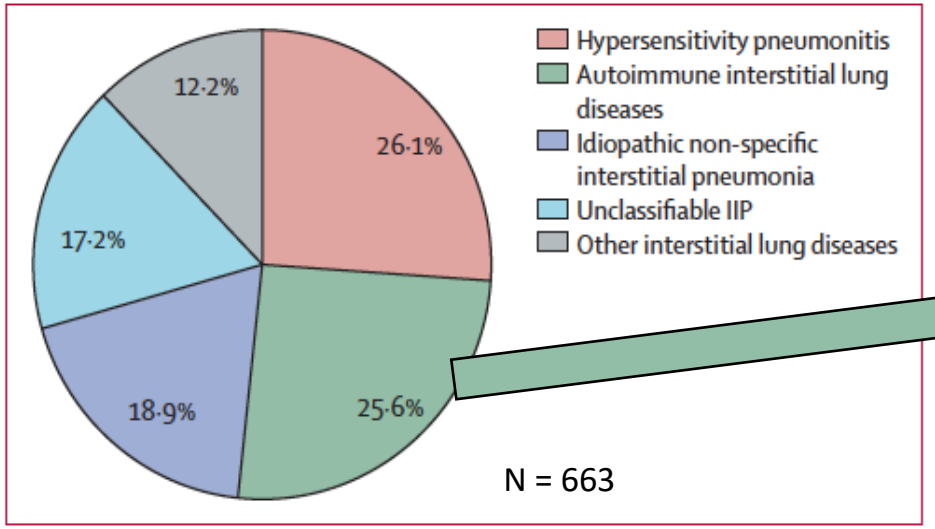


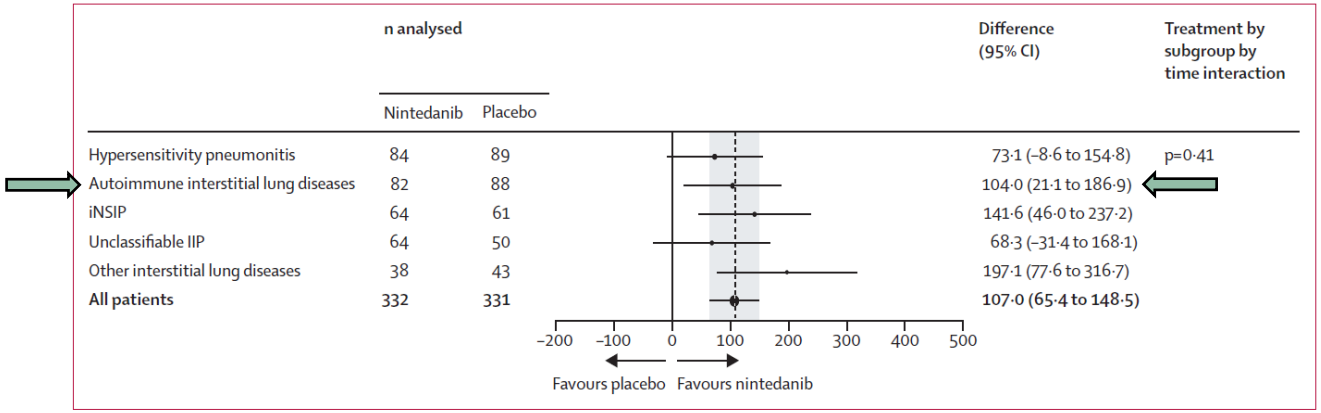
***Figure 3*: Estimated change in FVC and percent predicted FVC by high-resolution CT pattern**
(A) Estimated annual change in FVC (mL). (B) Estimated change in FVC (L) from baseline. (C) Estimated annual change in percent predicted FVC (%). (D) Estimated annual change in percent predicted FVC (%) from baseline. Error bars are SE. FVC=forced vital capacity. UIP=usual interstitial pneumonia.

Solomon et al. *Lancet Respir Med* 2023; 11: 87–96

The INBUILD trial (Nintedanib) included patients with RA-ILD



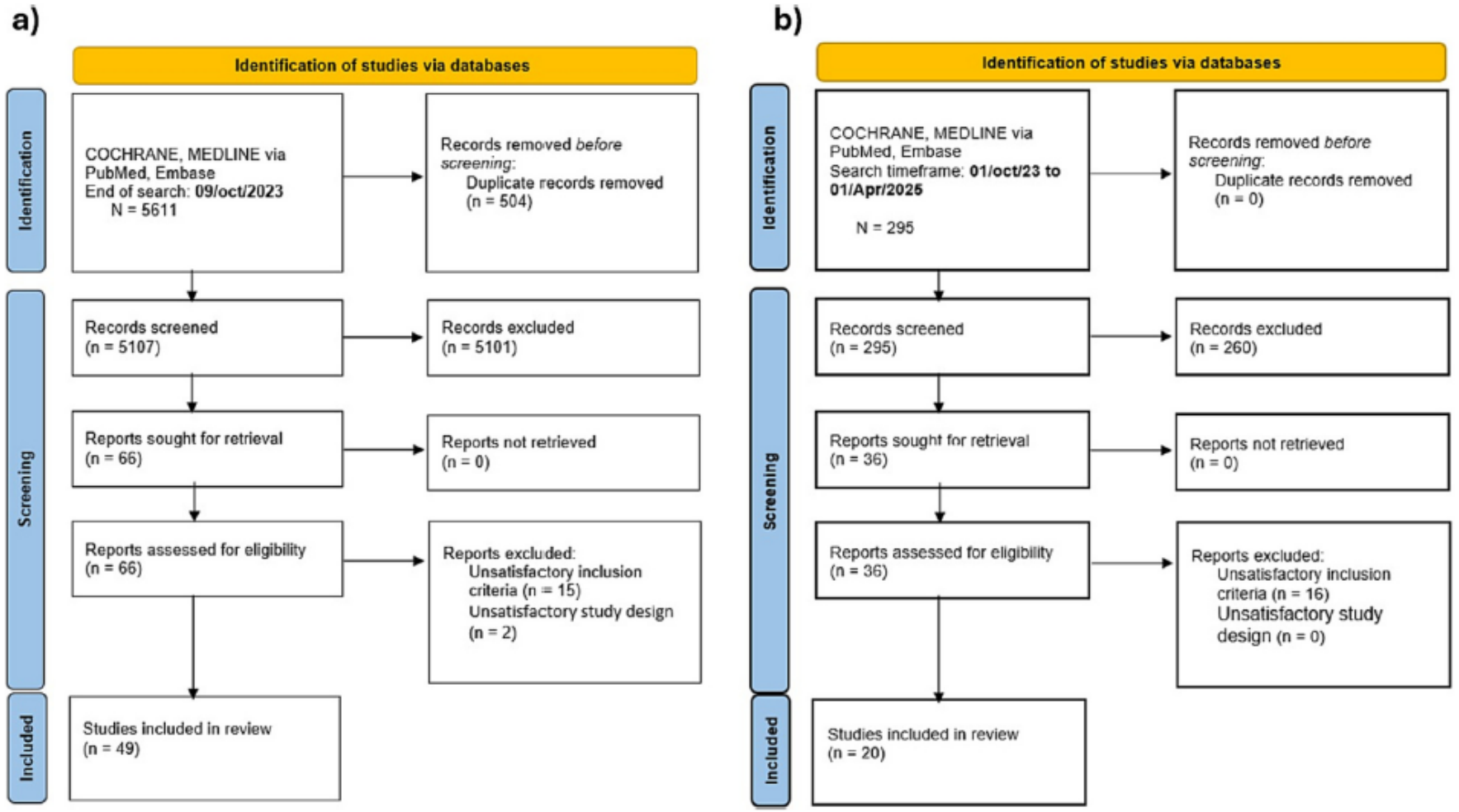
Subgroup analysis of 25.6% (170) autoimmune patients:
--13.4% of patients had RA-ILD
--Difference in FVC decline vs placebo: 104 mL/year

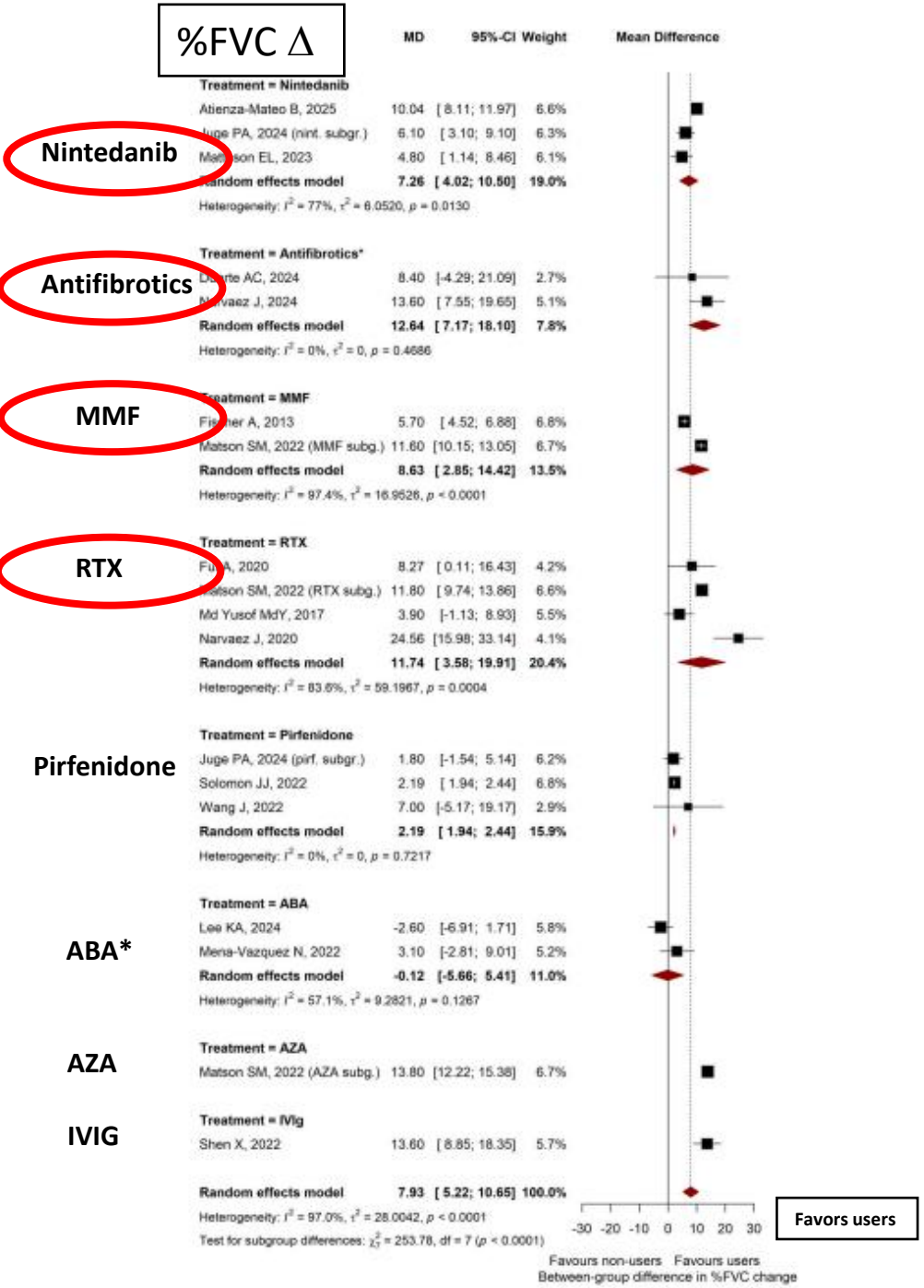


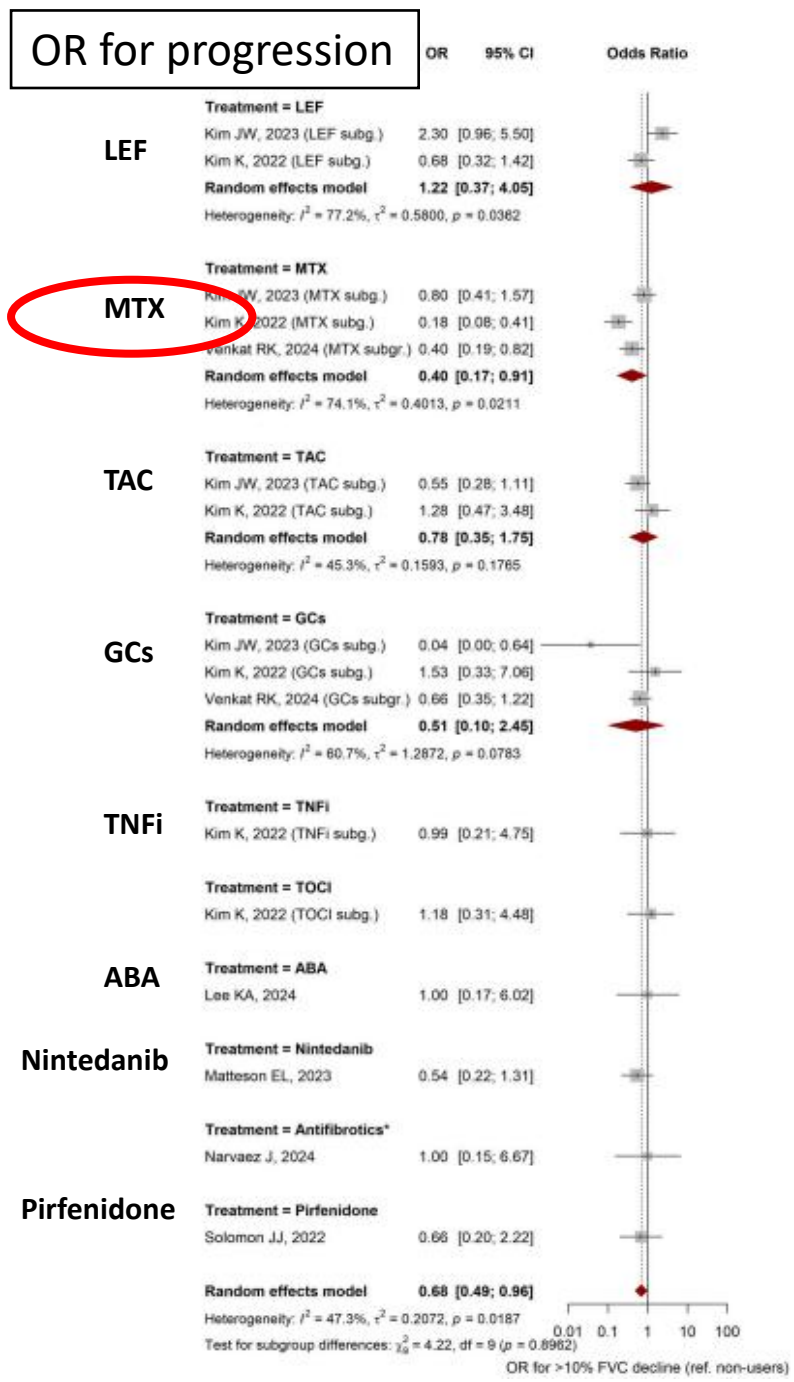
Meta-analysis to inform the Italian Society of Rheumatology on RA-ILD treatment

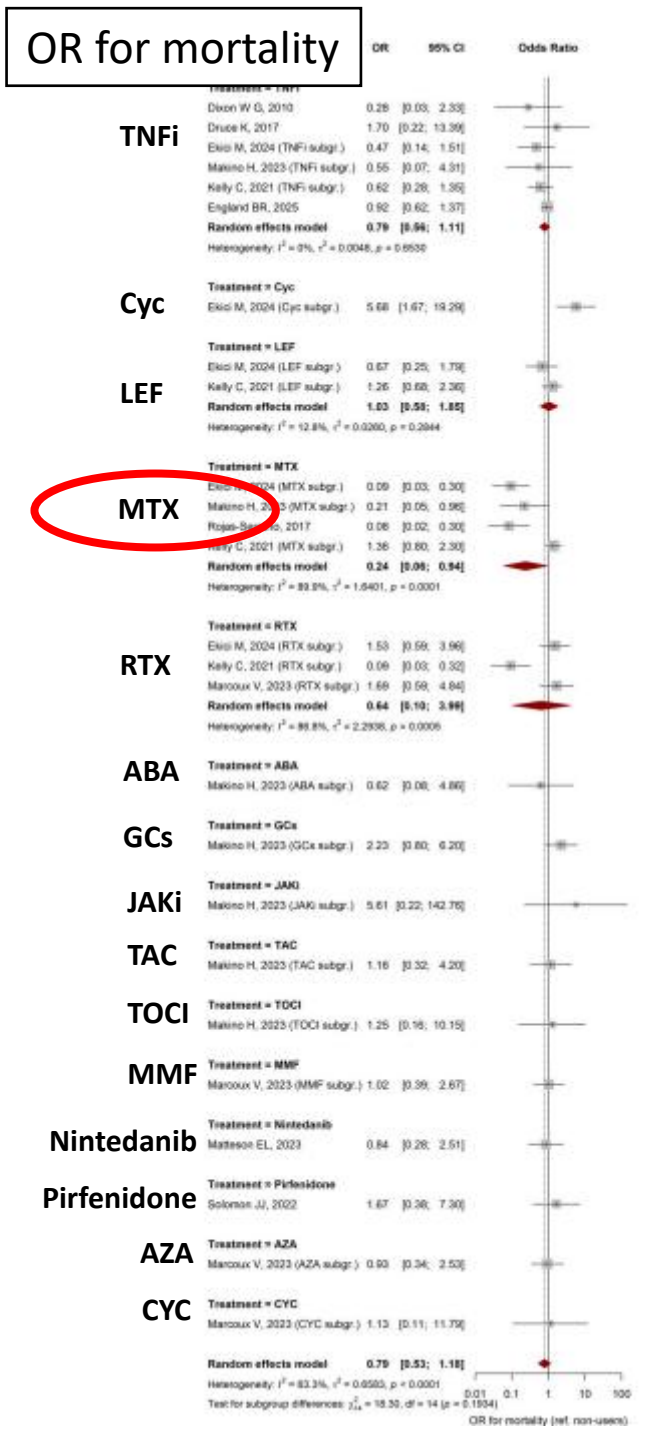
- 69 studies
- 7879 RA-ILD patients

- RCTs, cohort studies, case series




%FVC Δ
MD
95%-CI
Weight
Mean Difference
Nintedanib
Antifibrotics
MMF
RTX
Pirfenidone
ABA*
AZA
IVIG
Treatment = Nintedanib
Atienza-Mateo B, 2025 10.04 [8.11; 11.97] 6.6%
Juge PA, 2024 (nint. subgr.) 6.10 [3.10; 9.10] 6.3%
Matteson EL, 2023 4.80 [1.14; 8.46] 6.1%
Random effects model 7.26 [4.02; 10.50] 19.0%
Heterogeneity: I^2 = 77%, τ^2 = 6.0520, p = 0.0130
Treatment = Antifibrotics*
Duarte AC, 2024 8.40 [-4.29; 21.09] 2.7%
Narvaez J, 2024 13.60 [7.55; 19.65] 5.1%
Random effects model 12.64 [7.17; 18.10] 7.8%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.4686
Treatment = MMF
Fischer A, 2013 5.70 [4.52; 6.88] 6.8%
Matson SM, 2022 (MMF subg.) 11.60 [10.15; 13.05] 6.7%
Random effects model 8.63 [2.85; 14.42] 13.5%
Heterogeneity: I^2 = 97.4%, τ^2 = 16.9526, p < 0.0001
Treatment = RTX
Fu A, 2020 8.27 [0.11; 16.43] 4.2%
Matson SM, 2022 (RTX subg.) 11.80 [9.74; 13.86] 6.6%
Md Yusof MdY, 2017 3.90 [-1.13; 8.93] 5.5%
Narvaez J, 2020 24.56 [15.98; 33.14] 4.1%
Random effects model 11.74 [3.58; 19.91] 20.4%
Heterogeneity: I^2 = 83.6%, τ^2 = 59.1967, p = 0.0004
Treatment = Pirfenidone
Juge PA, 2024 (pirf. subgr.) 1.80 [-1.54; 5.14] 6.2%
Solomon JJ, 2022 2.19 [1.94; 2.44] 6.8%
Wang J, 2022 7.00 [-5.17; 19.17] 2.9%
Random effects model 2.19 [1.94; 2.44] 15.9%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.7217
Treatment = ABA
Lee KA, 2024 -2.60 [-6.91; 1.71] 5.8%
Mena-Vazquez N, 2022 3.10 [-2.81; 9.01] 5.2%
Random effects model -0.12 [-5.66; 5.41] 11.0%
Heterogeneity: I^2 = 57.1%, τ^2 = 9.2821, p = 0.1267
Treatment = AZA
Matson SM, 2022 (AZA subg.) 13.80 [12.22; 15.38] 6.7%
Treatment = IVIg
Shen X, 2022 13.60 [8.85; 18.35] 5.7%
Random effects model 7.93 [5.22; 10.65] 100.0%
Heterogeneity: I^2 = 97.0%, τ^2 = 28.0042, p < 0.0001
Test for subgroup differences: χ^2_7 = 253.78, df = 7 (p < 0.0001)
-30 -20 -10 0 10 20 30
Favours non-users Favours users
Between-group difference in %FVC change
Favors users


OR for progression
OR
95% CI
Odds Ratio
LEF
MTX
TAC
GCs
TNFi
ABA
Nintedanib
Pirfenidone
Treatment = LEF
Kim JW, 2023 (LEF subg.) 2.30 [0.96; 5.50]
Kim K, 2022 (LEF subg.) 0.68 [0.32; 1.42]
Random effects model 1.22 [0.37; 4.05]
Heterogeneity: I^2 = 77.2%, τ^2 = 0.5800, p = 0.0362
Treatment = MTX
Kim JW, 2023 (MTX subg.) 0.80 [0.41; 1.57]
Kim K, 2022 (MTX subg.) 0.18 [0.08; 0.41]
Venkat RK, 2024 (MTX subgr.) 0.40 [0.19; 0.82]
Random effects model 0.40 [0.17; 0.91]
Heterogeneity: I^2 = 74.1%, τ^2 = 0.4013, p = 0.0211
Treatment = TAC
Kim JW, 2023 (TAC subg.) 0.55 [0.28; 1.11]
Kim K, 2022 (TAC subg.) 1.28 [0.47; 3.48]
Random effects model 0.78 [0.35; 1.75]
Heterogeneity: I^2 = 45.3%, τ^2 = 0.1593, p = 0.1765
Treatment = GCs
Kim JW, 2023 (GCs subg.) 0.04 [0.00; 0.64]
Kim K, 2022 (GCs subg.) 1.53 [0.33; 7.06]
Venkat RK, 2024 (GCs subgr.) 0.66 [0.35; 1.22]
Random effects model 0.51 [0.10; 2.45]
Heterogeneity: I^2 = 60.7%, τ^2 = 1.2872, p = 0.0783
Treatment = TNFi
Kim K, 2022 (TNFi subg.) 0.99 [0.21; 4.75]
Treatment = TOCI
Kim K, 2022 (TOCI subg.) 1.18 [0.31; 4.48]
Treatment = ABA
Lee KA, 2024 1.00 [0.17; 6.02]
Treatment = Nintedanib
Matteson EL, 2023 0.54 [0.22; 1.31]
Treatment = Antifibrotics*
Narvaez J, 2024 1.00 [0.15; 6.67]
Treatment = Pirfenidone
Solomon JJ, 2022 0.66 [0.20; 2.22]
Random effects model 0.68 [0.49; 0.96]
Heterogeneity: I^2 = 47.3%, τ^2 = 0.2072, p = 0.0187
Test for subgroup differences: χ^2_9 = 4.22, df = 9 (p = 0.8962)
0.01 0.1 1 10 100
OR for >10% FVC decline (ref. non-users)

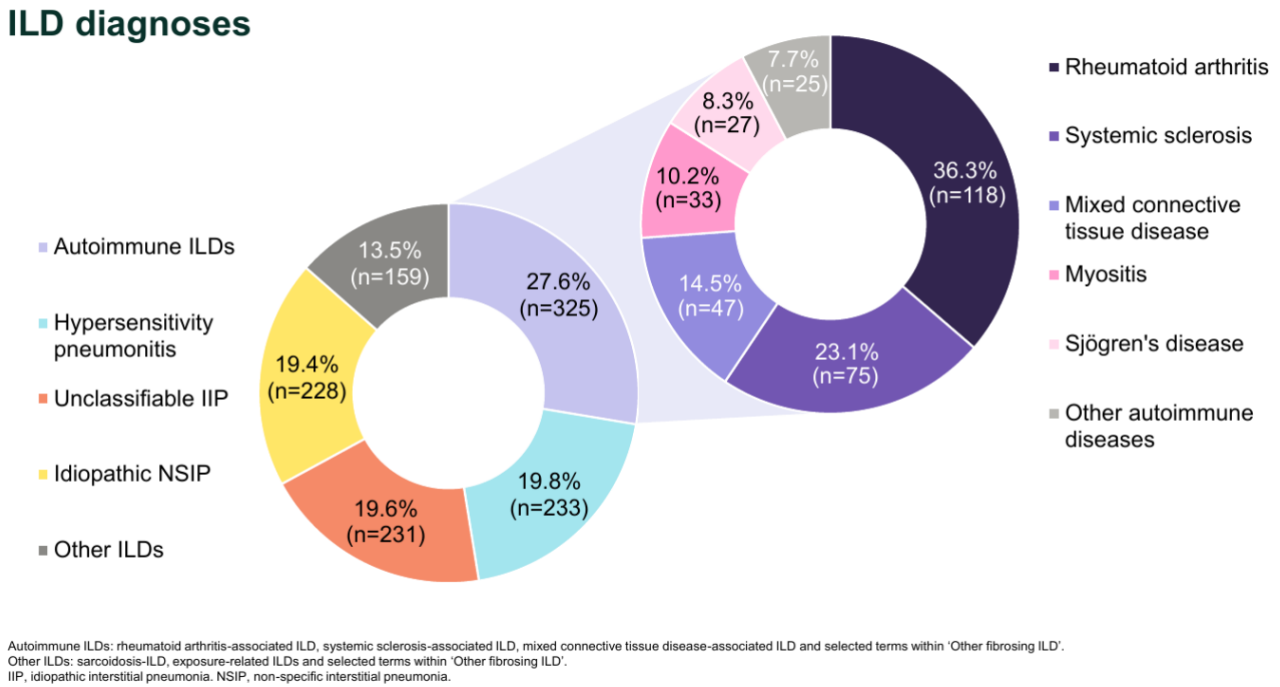

OR for mortality
OR
95% CI
Odds Ratio
TNFi
Cyc
LEF
MTX
RTX
ABA
GCs
JAKi
TAC
TOCI
MMF
Nintedanib
Pirfenidone
AZA
CYC
Dixon W G, 2010 0.28 [0.03; 2.33]
Druce K, 2017 1.70 [0.22; 13.39]
Ekici M, 2024 (TNFi subgr.) 0.47 [0.14; 1.51]
Makino H, 2023 (TNFi subgr.) 0.55 [0.07; 4.31]
Kelly C, 2021 (TNFi subgr.) 0.62 [0.28; 1.35]
England BR, 2025 0.92 [0.62; 1.37]
Random effects model 0.79 [0.56; 1.11]
Ekici M, 2024 (Cyc subgr.) 5.68 [1.67; 19.29]
Ekici M, 2024 (LEF subgr.) 0.67 [0.25; 1.79]
Kelly C, 2021 (LEF subgr.) 1.26 [0.68; 2.36]
Random effects model 1.03 [0.58; 1.85]
Ekici M, 2024 (MTX subgr.) 0.09 [0.03; 0.30]
Makino H, 2023 (MTX subgr.) 0.21 [0.05; 0.96]
Rojas-Serrano, 2017 0.08 [0.02; 0.30]
Kelly C, 2021 (MTX subgr.) 1.36 [0.80; 2.30]
Random effects model 0.24 [0.06; 0.94]
Ekici M, 2024 (RTX subgr.) 1.53 [0.59; 3.96]
Kelly C, 2021 (RTX subgr.) 0.09 [0.03; 0.32]
Marcoux V, 2023 (RTX subgr.) 1.69 [0.59; 4.84]
Random effects model 0.64 [0.10; 3.99]
Makino H, 2023 (ABA subgr.) 0.62 [0.08; 4.86]
Makino H, 2023 (GCs subgr.) 2.23 [0.80; 6.20]
Makino H, 2023 (JAKi subgr.) 5.61 [0.22; 142.76]
Makino H, 2023 (TAC subgr.) 1.16 [0.32; 4.20]
Makino H, 2023 (TOCI subgr.) 1.25 [0.16; 10.15]
Marcoux V, 2023 (MMF subgr.) 1.02 [0.39; 2.67]
Matteson EL, 2023 0.84 [0.28; 2.51]
Solomon JJ, 2022 1.67 [0.38; 7.30]
Marcoux V, 2023 (AZA subgr.) 0.93 [0.34; 2.53]
Marcoux V, 2023 (CYC subgr.) 1.13 [0.11; 11.75]
Random effects model 0.79 [0.53; 1.18]
0.01 0.1 1 10 100
OR for mortality (ref. non-users)

The FIBRONEER-ILD trial (Nerandomilast) included patients with RA-ILD

- Phase 3, double-blind, placebo-controlled
- 403 sites in 44 countries
- Non-IPF but at least 10% fibrosis on CT
- FVC > 45%; DLCO ≥ 25%
- Progression in last 24 months (at least one):
  - -- FVC relative decline ≥ 10%
  - -- FVC relative decline 5-9% + worsening symptoms
  - -- FVC relative decline 5-9% + worsening fibrosis on CT
  - -- Worsening dyspnea + worsening fibrosis on CT

- Randomized 1:1:1
  (Nerandomilast 18 mg : Nerandomilast 9 mg : Placebo)
- Primary endpoint: Absolute change from baseline in FVC

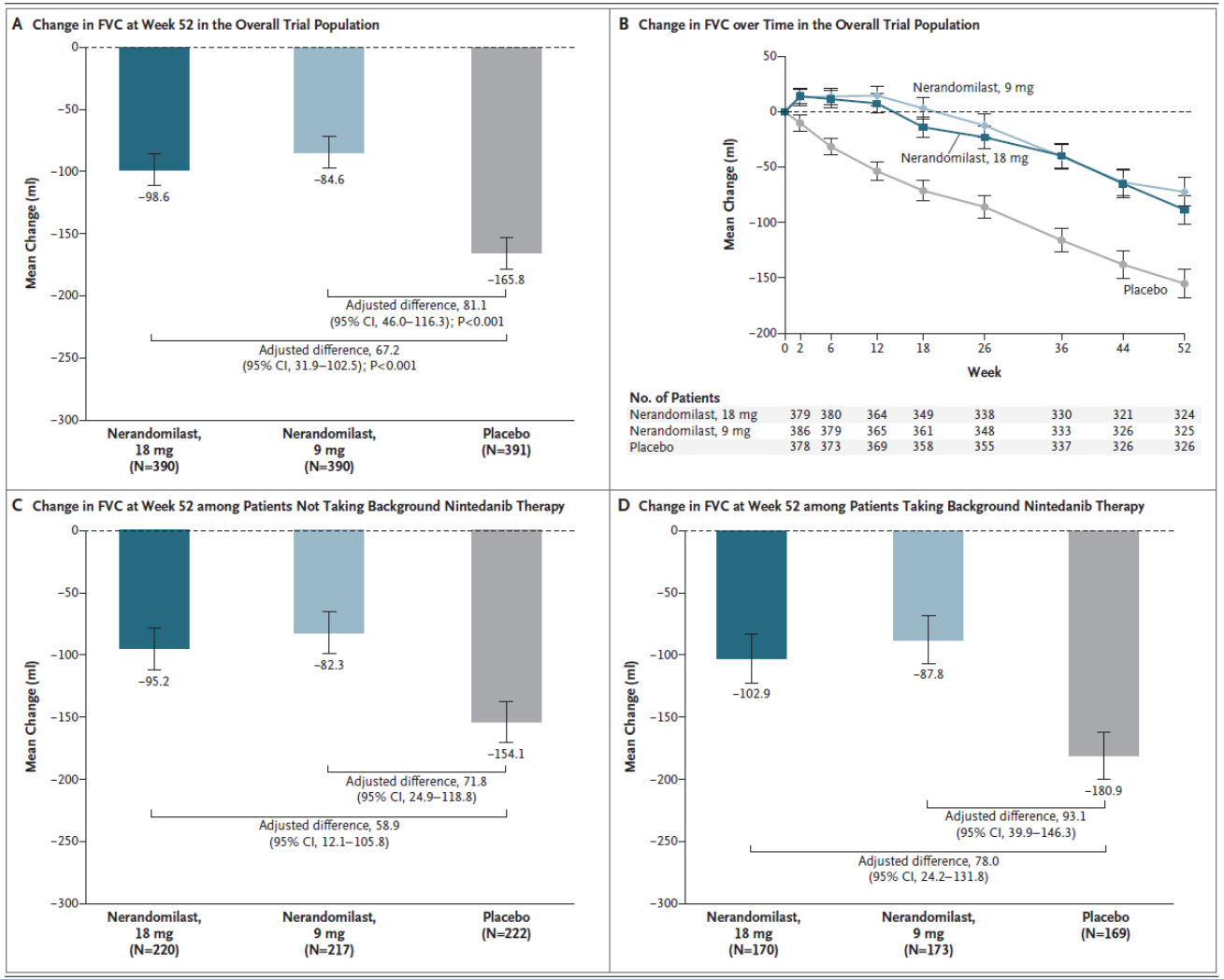
- 1176 patients randomized; 43.5% on background therapy



Autoimmune ILDs: rheumatoid arthritis-associated ILD, systemic sclerosis-associated ILD, mixed connective tissue disease-associated ILD and selected terms within 'Other fibrosing ILD'.
Other ILDs: sarcoidosis-ILD, exposure-related ILDs and selected terms within 'Other fibrosing ILD'.
IIP, idiopathic interstitial pneumonia. NSIP, non-specific interstitial pneumonia.

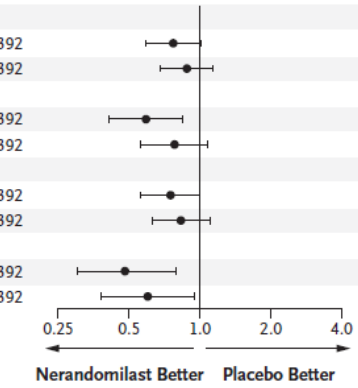
Maher et al. *N Engl J Med.* 2025 Jun 12;392(22):2203-14.
Graphic complements of Boehringer Ingelheim

Nerandomilast slows FVC decline and reduces mortality in non-IPF pulmonary fibrosis



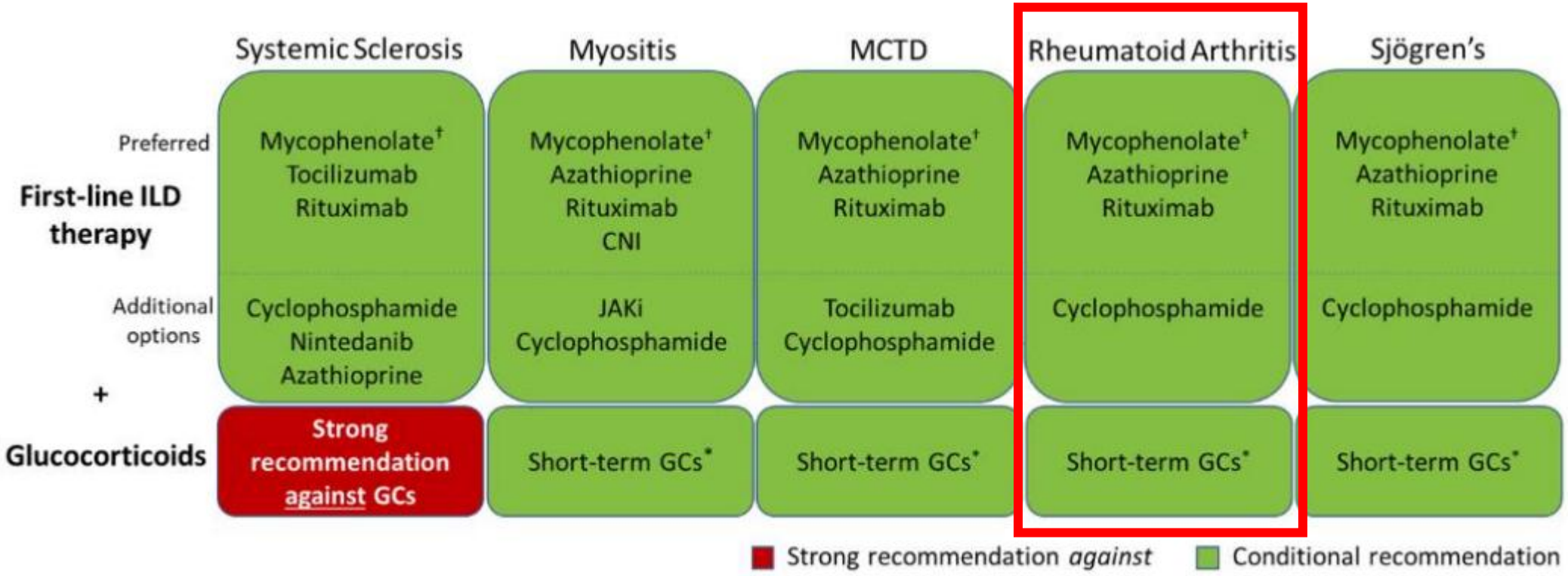
B Analyses of Key Secondary End Point and Related Secondary End Points up to First Database Lock

End Point	Nerandomilast	Placebo	Hazard Ratio (95% CI)	P Value
	no. with event/no. of patients			
Key secondary end point				
Nerandomilast, 18 mg	95/391	122/392	0.77 (0.59–1.01)	0.06
Nerandomilast, 9 mg	110/393	122/392	0.88 (0.68–1.14)	0.34
Acute exacerbation of ILD or death				
Nerandomilast, 18 mg	48/391	83/392	0.59 (0.41–0.84)	
Nerandomilast, 9 mg	65/393	83/392	0.78 (0.56–1.08)	
Hospitalization for respiratory cause or death				
Nerandomilast, 18 mg	84/391	110/392	0.75 (0.56–1.00)	
Nerandomilast, 9 mg	97/393	110/392	0.83 (0.63–1.10)	
Death				
Nerandomilast, 18 mg	24/391	50/392	0.48 (0.30–0.79)	
Nerandomilast, 9 mg	33/393	50/392	0.60 (0.38–0.95)	



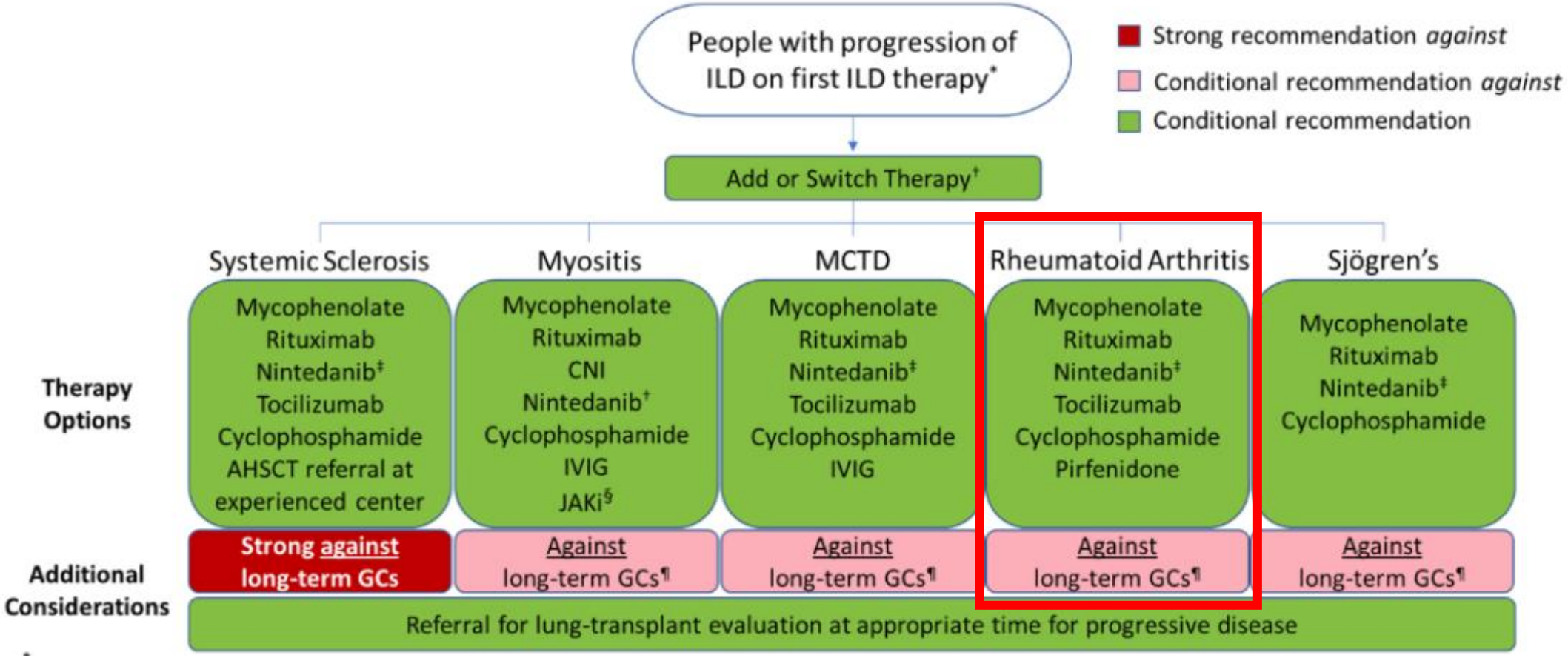
Maher et al. *N Engl J Med.* 2025 Jun 12;392(22):2203-14.

First-line therapy for SARD-ILD (ACR)



- "For people with SARD-ILD, we conditionally recommend against leflunomide, methotrexate, TNFi, and abatacept as first-line ILD treatment options."

Therapy for progressive SARD-ILD (ACR)



Summary

- ILD is common in RA and associated with morbidity and mortality
- Patients with RA-ILD may benefit from immunosuppression that targets the lungs
- Data supporting the use of a particular immunosuppressant agent is lacking
- Patients with a fibrotic phenotype may benefit from the addition of an anti-fibrotic agent