Pulmonary complications in CTD

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Disclosure

- ER has received speaker/advisory board fees from Boehringer Ingelheim, F. Hoffmann-La Roche and Mundipharma

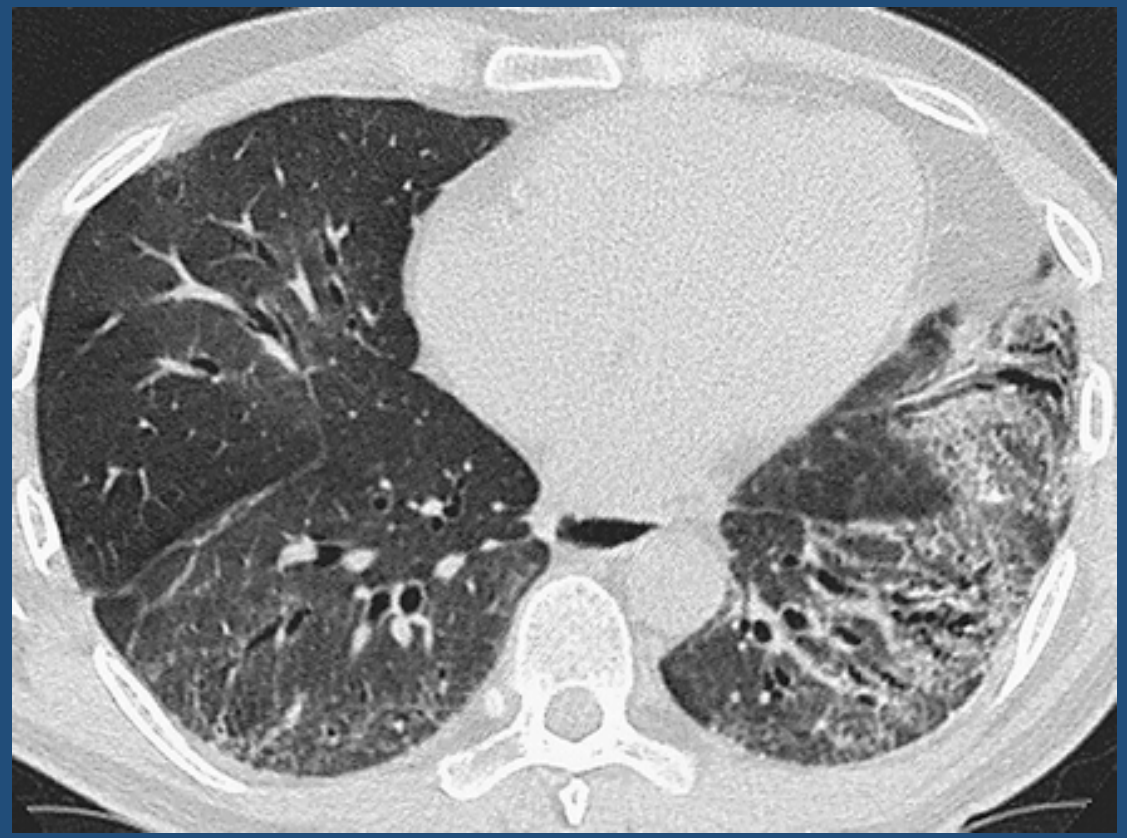
- ILD patterns in the three main CTDs
  - Scleroderma (SSc)
  - Rheumatoid arthritis (RA)
  - Idiopathic inflammatory myositis/anti-synthetase syndrome (IIMs)

- Prognosis estimation and management

CTD, connective tissue disease; ILD, interstitial lung disease

SSc-ILD

- Occurs in most patients with SSc
- Variable severity, ~30% have clinically significant disease
- Main cause of death
- By far most common morphological pattern is NSIP



NSIP, non-specific interstitial pneumonitis; SSc-ILD, interstitial lung disease associated with systemic sclerosis

Solomon JJ et al. *Eur Resp Rev* 2013;22:6–19;
Steen VD and Medsger TA. *Ann Rheum Dis* 2007;66:940–944;
Desai SR et al. *Radiology* 2004;232:560–567

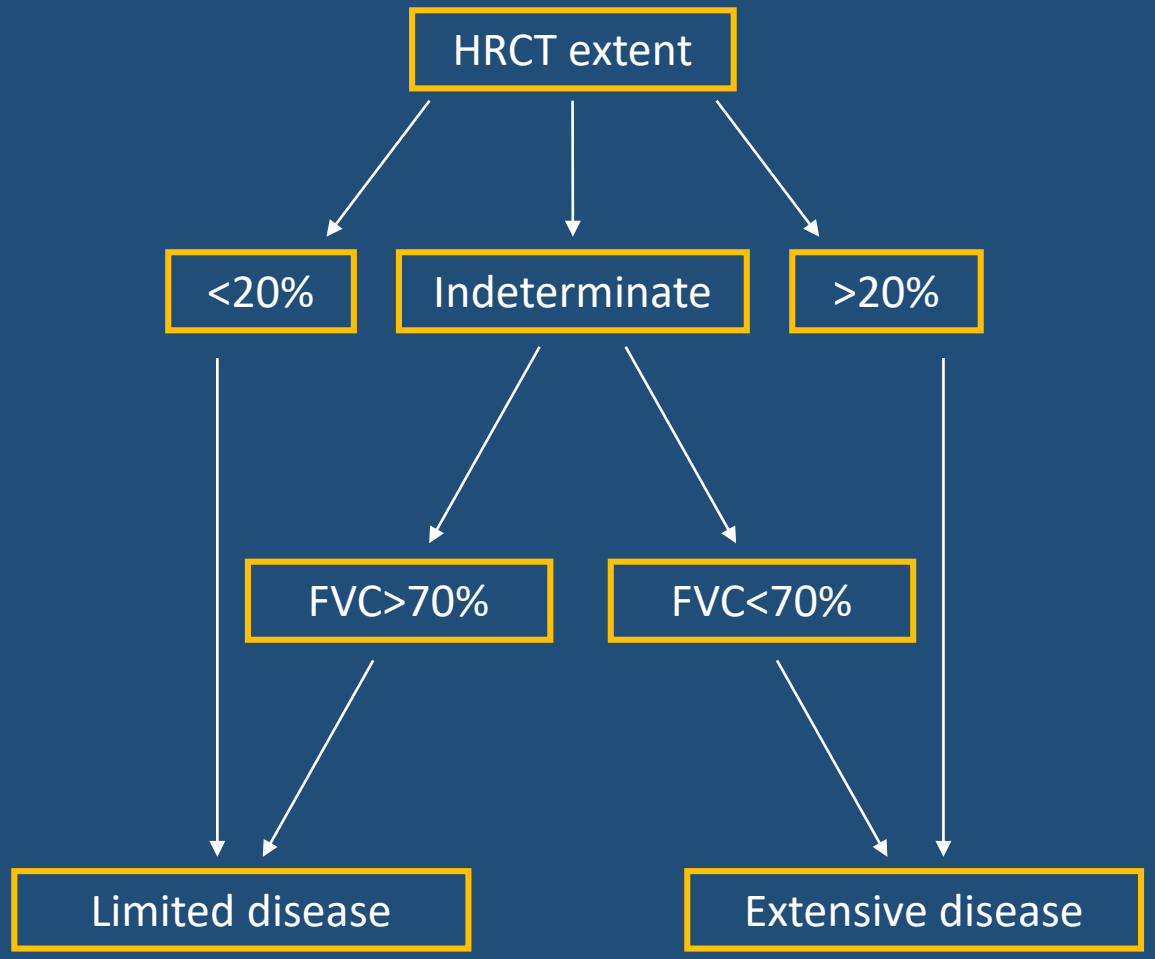
Poor performance of lung function to assess presence and severity of ILD

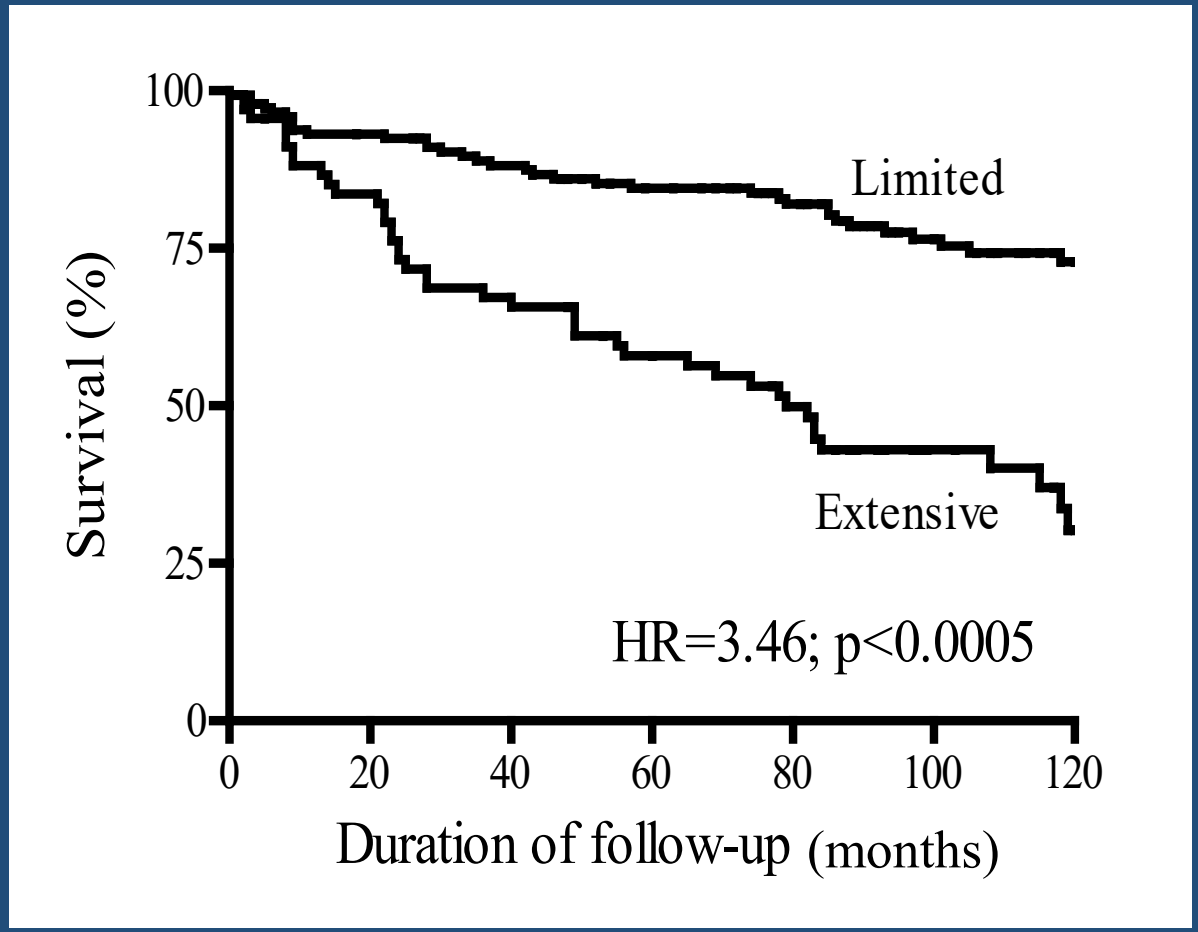
- FVC: Risk of missing significant ILD or overestimating
- DLco: Affected also by pulmonary vasculature

HRCT extent more informative

DLco, carbon monoxide diffusing capacity; FVC, forced vital capacity; HRCT, high-resolution computed tomography

Simple staging system to assess risk of progression in SSc-ILD





HR, hazard ratio

Goh NS, et al. *Am J Respir Crit Care Med.* 2008;177:1248–1254

Other predictors of progression in SSc-ILD

- Autoantibodies:
  - Risk: Scl-70, Th/To, U3RNP -Protective: ACA (but associated with PH)
- Early disease: First 4 years since diagnosis
- Short-term lung function worsening:
  - Decline in FVC ≥10% or composite FVC decline 5-9% + decline DLco ≥15% at 1 and 2 years predicts survival in extensive disease
  - Decline in DLco ≥15% or decline KCO ≥10% were predictive of mortality in the limited group, and in group overall

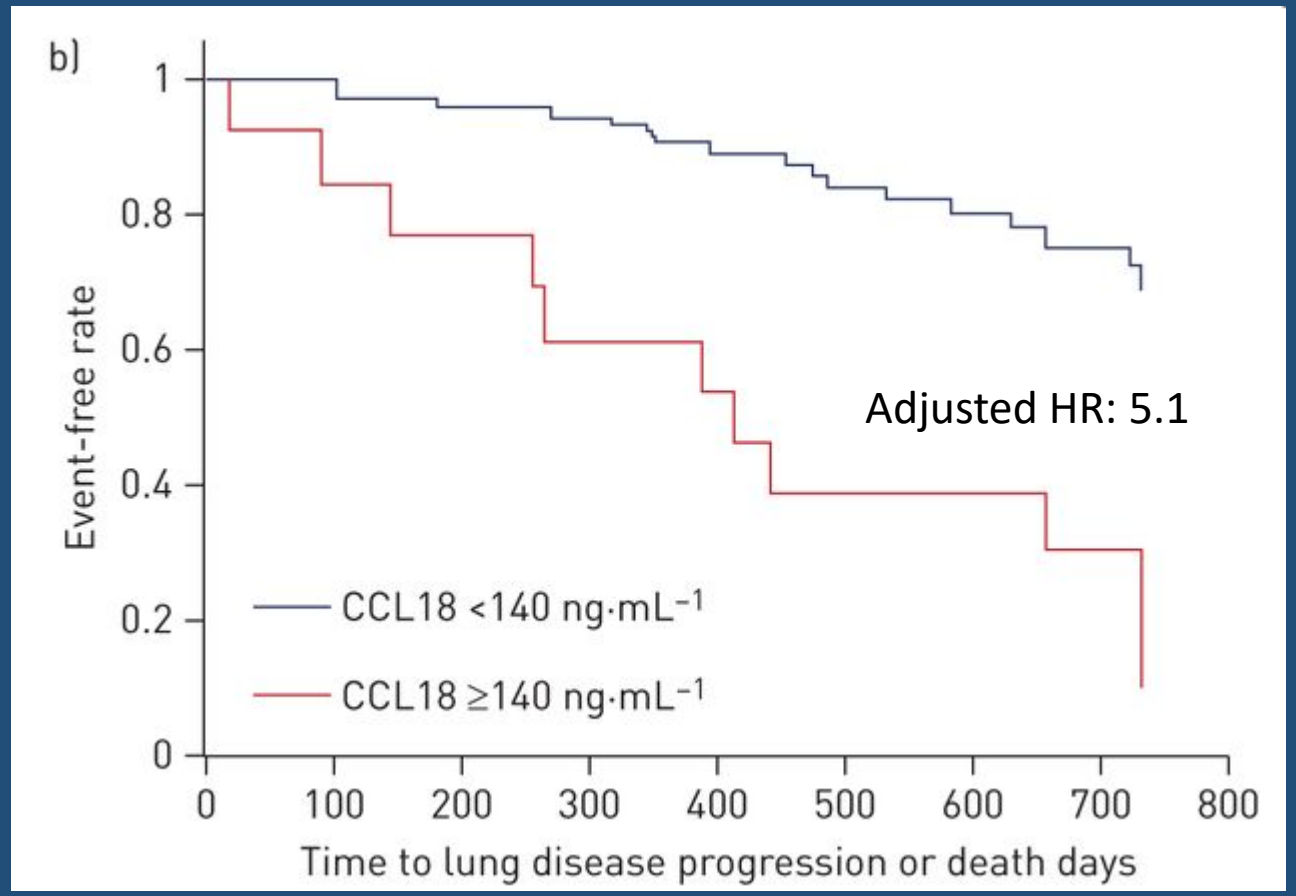
ACA, anti-centromere antibody; PH, pulmonary hypertension

Silver KC and Silver RM. *Rheum Dis Clin North Am.* 2015 Aug;41:439–57;
Steen V. *Ann Rheum Dis.* 2003 Feb;62:97–9;
Steen VD, et al. *Arthriris Rheum* 1994;37:1283–1289;
Goh NS, et al. *Arthritis Rheumatol*. 2017;69:1670–1678

Serum CCL18 is predictive for lung disease progression and mortality in systemic sclerosis

Jonas Schupp, Mike Becker, Jeannine Günther, Joachim Müller-Quernheim, Gabriela Riemekasten, Antje Prasse

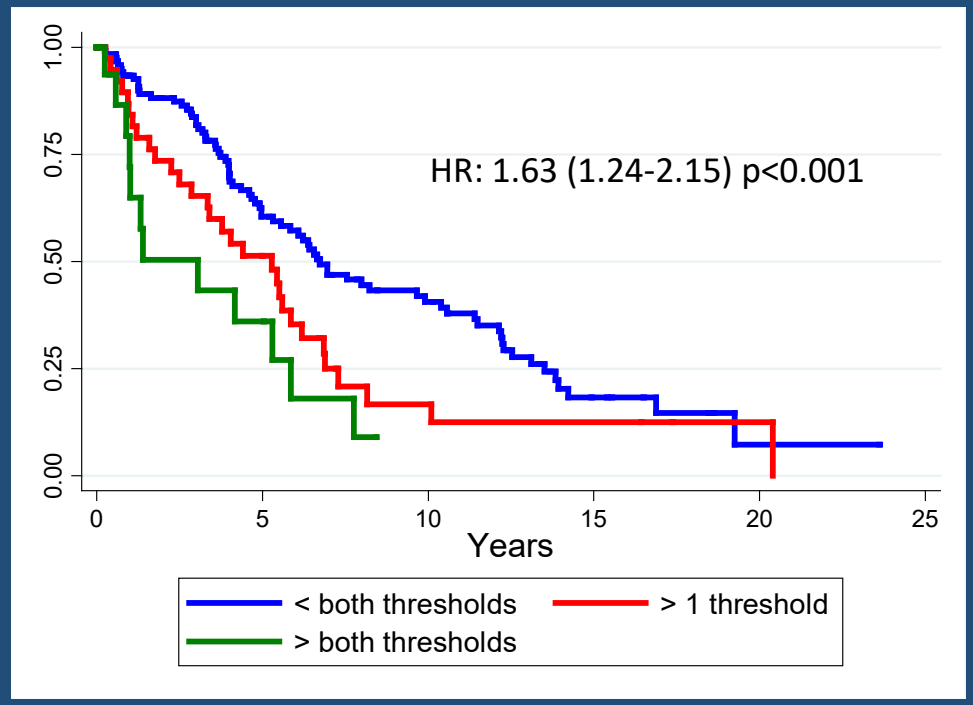
European Respiratory Journal 2014 43: 1530-1532; **DOI:** 10.1183/09031936.00131713



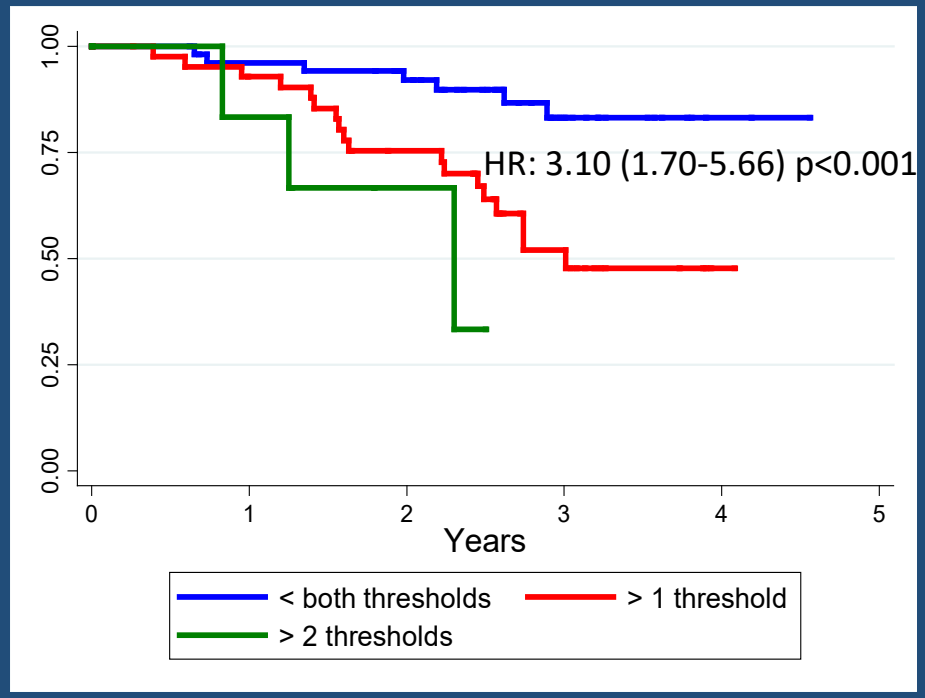
Progression free survival according to serum CCL18 in patients with SSc-ILD

Epithelial serum biomarkers in SSc-ILD predictive to time to decline in DLCO>15%

CYFRA 21_1 ≥3.37 ng/ml and/or serum KL-6 >1472 U/ml



Retrospective cohort
n=189



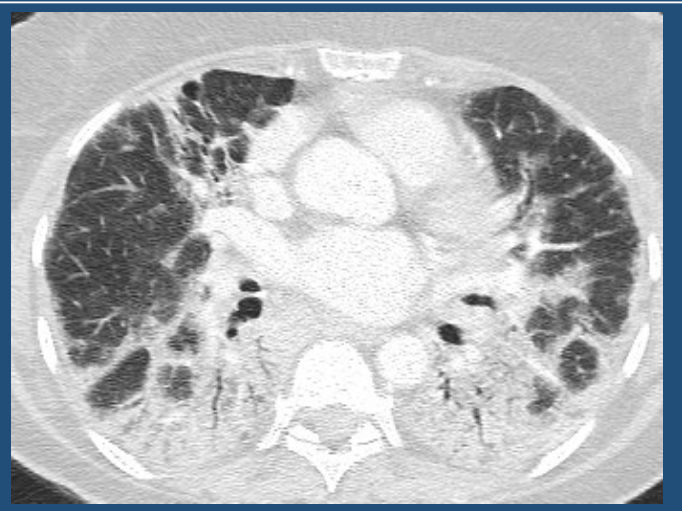
Prospective cohort
n=118

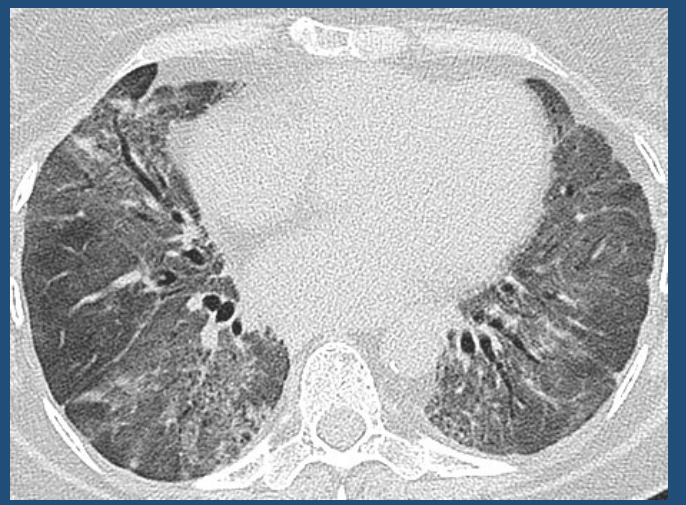
ARTHRITIS RESEARCH UK

Stock et al. Submitted to Arthritis and Rheumatism

ILD in idiopathic inflammatory myositis/ anti-synthetase syndrome

- NSIP/OP pattern
  - Often subacute course over months
  - Can improve markedly with treatment
  - Iv MP 1gr x 3 followed by tapering oral prednisone and MMF or iv cyclo/rituximab if severe/rapidly progressive
  - Overall can have good prognosis, but long-term maintenance immunosuppression needed





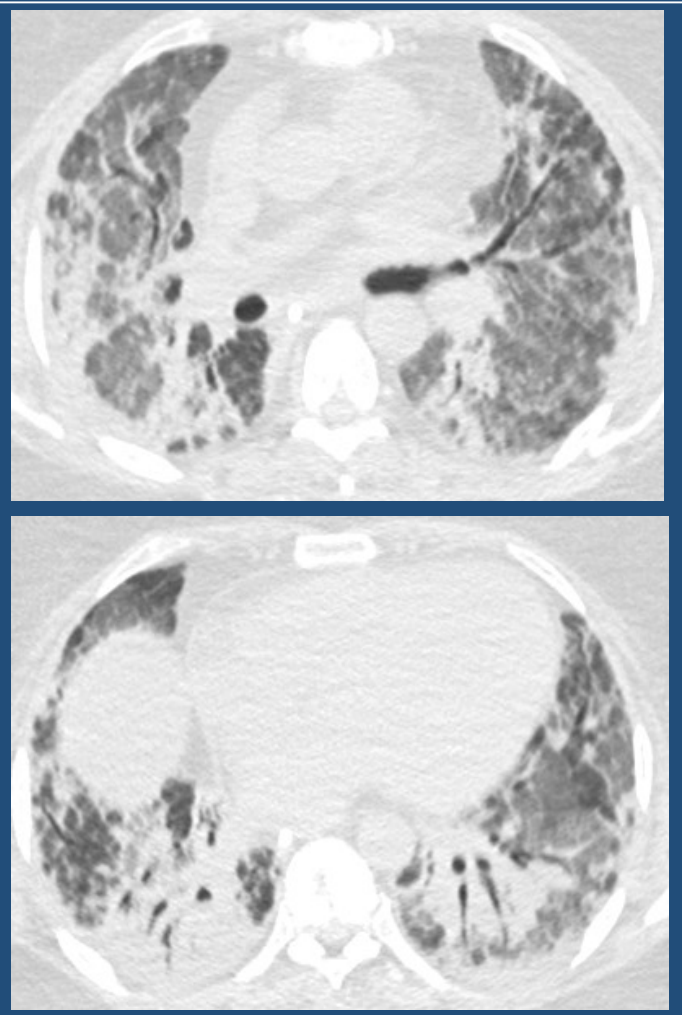
After six weeks

MMF, mycophenolate mofetil; OP, organizing pneumonia

Kouranos et al Curr Opin Pulm Med. 2018 Sep;24(5):453-460.

ILD in idiopathic inflammatory myositis/ anti-synthetase syndrome or MDA5+

- OP/DAD pattern
  - Acute/subacute presentation
  - Rapid progression over days/weeks to respiratory failure
  - Prognosis uncertain; vigorous combination immunosuppression needed, once infection excluded



DAD, diffuse alveolar damage

Kouranos et al Curr Opin Pulm Med. 2018 Sep;24(5):453-460.

Rheumatoid arthritis (RA)-ILD

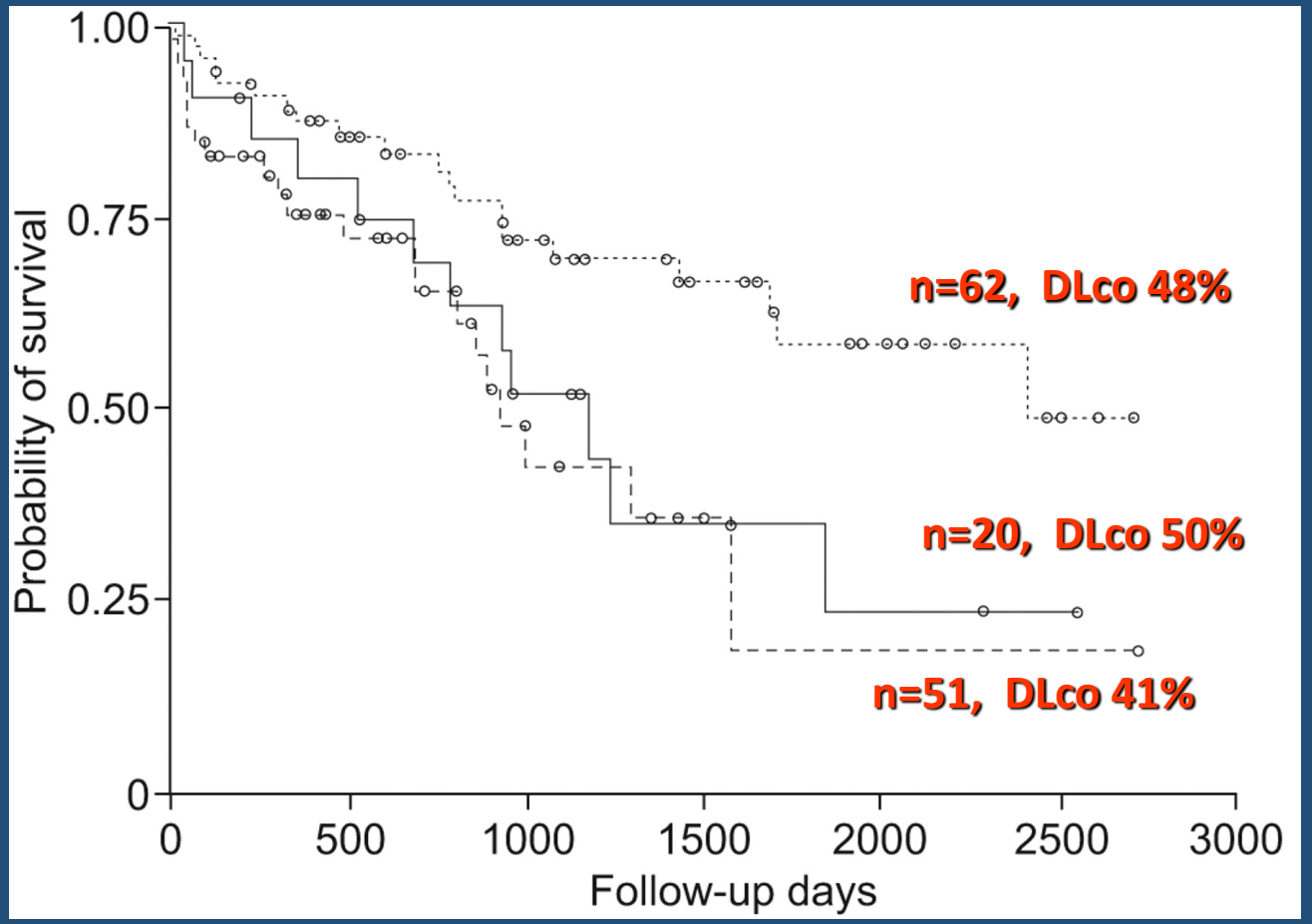
- Histologically, a UIP pattern is at least as frequent as NSIP

- On CT, a definite UIP pattern is present in less than half of patients

UIP, usual interstitial pneumonitis

Kim DS. *Curr Opin Pulm Med*. 2006;12:346–353; Kim EJ, et al. *Eur Respir J.* 2010;35:1322–1328

RA-UIP vs RA non-UIP based on CT appearances



RA non-UIP: 6.6 years

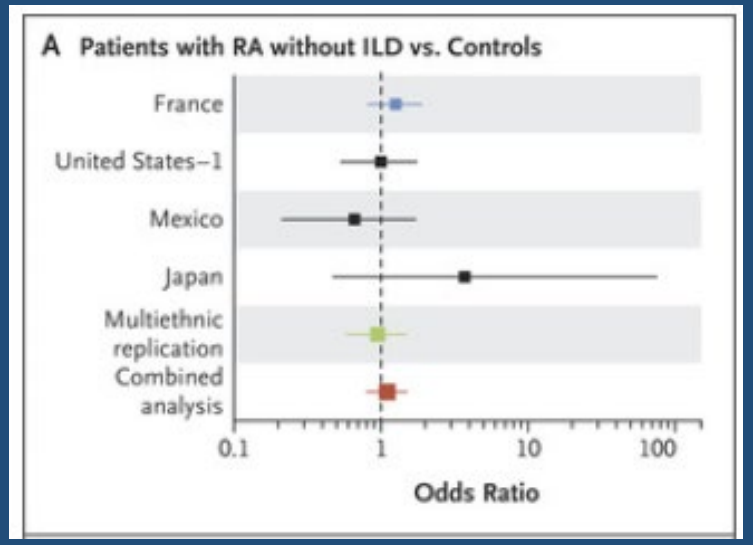
RA-UIP: 3.2 years

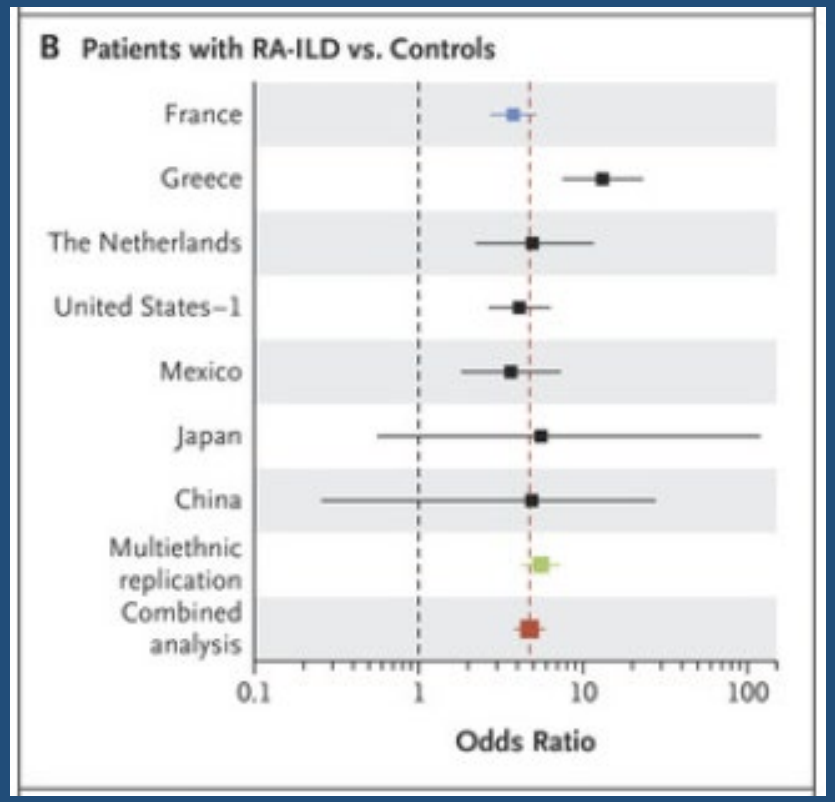
IPF: 2.6 years

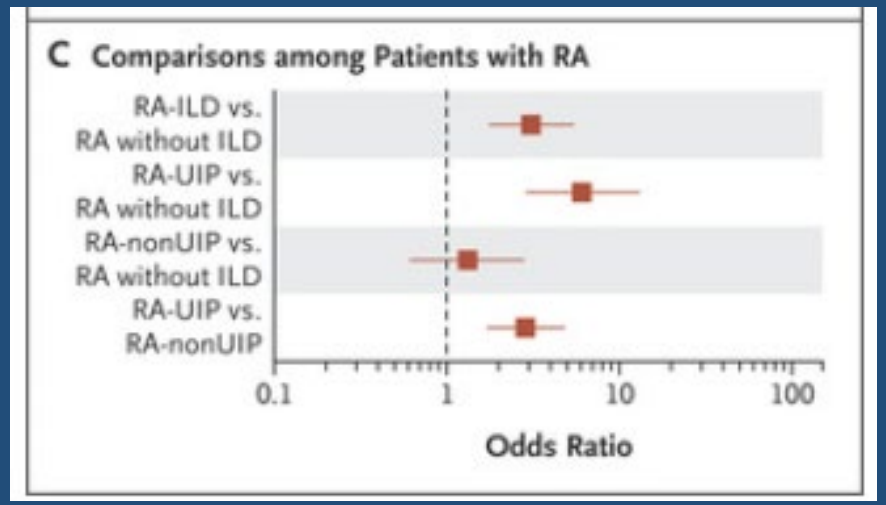
Kim EJ, et al. *Eur Respir J.* 2010;35:1322–1328

MUC5B Promoter Variant and Rheumatoid Arthritis with Interstitial Lung Disease

Pierre-Antoine Juge, M.D., Joyce S. Lee, M.D., Esther Ebstein, M.D., Hiroshi Furukawa, M.D., Ph.D., Evgenia Dobrinskikh, Ph.D., Steven Gazal, Ph.D., Caroline Kannengiesser, Pharm.D., Ph.D., Sébastien Ottaviani, M.D., Shomi Oka, Ph.D., Shigeto Tohma, M.D., Naoyuki Tsuchiya, M.D., Ph.D., Jorge Rojas-Serrano, M.D., Ph.D., et al.







NEJM December 6, 2018

Retrospective review of 84 patients with RA-UIP

- Median follow up: 33 months
- 41% received immunosuppression due to severe or worsening lung function; of these, half improved or stabilised
- Age, FVC and change DLco at 6 months predicted mortality
- Prognosis of RA-UIP was better than IPF even after matching for age, sex, initial FVC % and history of smoking (53 vs 41 months, p=0.015)

Song JW, et al. *Sarcoidosis Vasc Diffuse Lung Dis.* 2013;30:103–112

Randomised placebo-controlled clinical trials completed so far only in SSc-ILD

- SLS I: Oral cyclophosphamide vs placebo for one year:
  - FVC change at 12 months – difference greater in more extensive ILD at baseline

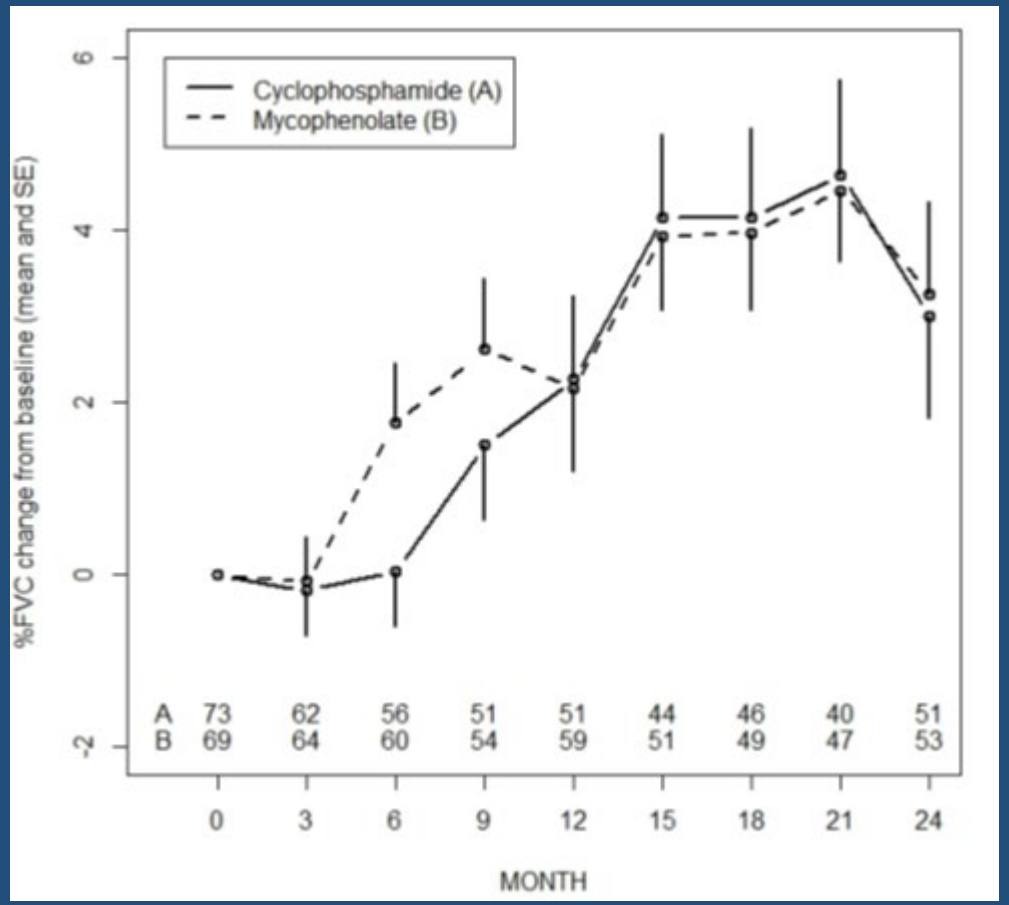
- SLS II: 2 years of MMF vs 1 year cyclophosphamide + 1 year placebo:
  - Both treatments associated with increases vs baseline in FVC and dyspnoea

Please note that MMF is not approved for the treatment of SSc-ILD

Tashkin DP, et al. *N Engl J Med.* 2006;354:2655–2666; Tashkin DP, et al. *Lancet Respir Med.* 2016;4:708–719

Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial

*Donald P Tashkin, Michael D Roth, Philip J Clements, Daniel E Furst, Dinesh Khanna, Eric C Kleerup, Jonathan Goldin, Edgar Arriola, Elizabeth R Volkmann, Suzanne Kafaja, Richard Silver, Virginia Steen, Charlie Strange, Robert Wise, Fredrick Wigley, Maureen Mayes, David J Riley, Sabiha Hussain, Shervin Assassi, Vivien M Hsu, Bela Patel, Kristine Phillips, Fernando Martinez, Jeffrey Golden, M Kari Connolly, John Varga, Jane Dematte, Monique E Hinchcliff, Aryeh Fischer, Jeffrey Swigris, Richard Meehan, Arthur Theodore, Robert Simms, Suncica Volkov, Dean E Schraufnagel, Mary Beth Scholand, Tracy Frech, Jerry A Molitor, Kristin Highland, Charles A Read, Marvin J Fritzler, Grace Hyun J Kim, Chi-Hong Tseng, Robert M Elashoff, for the Sclerodema Lung Study II Investigators**



- Both groups had significant increases vs baseline FVC at 12, 18 and 24 months
- Both groups had significant improvements in dyspnoea and in skin scores
- Less reduction in DLCO and KCO in MMF vs cyclo arms
- MMF better tolerated, fewer pts stopping prematurely

Tashkin DP, et al. *Lancet Respir Med.* 2016;4:708–719

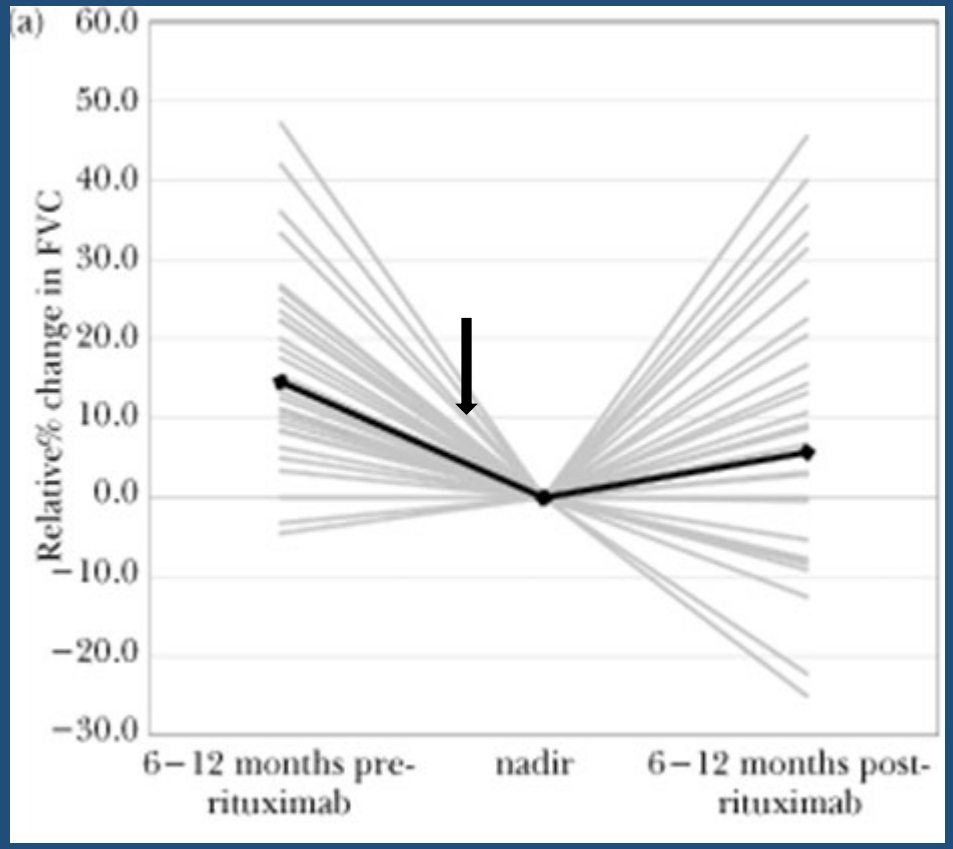
Unmet clinical need in ILD-CTD: severe unresponsive disease

Rituximab as rescue therapy

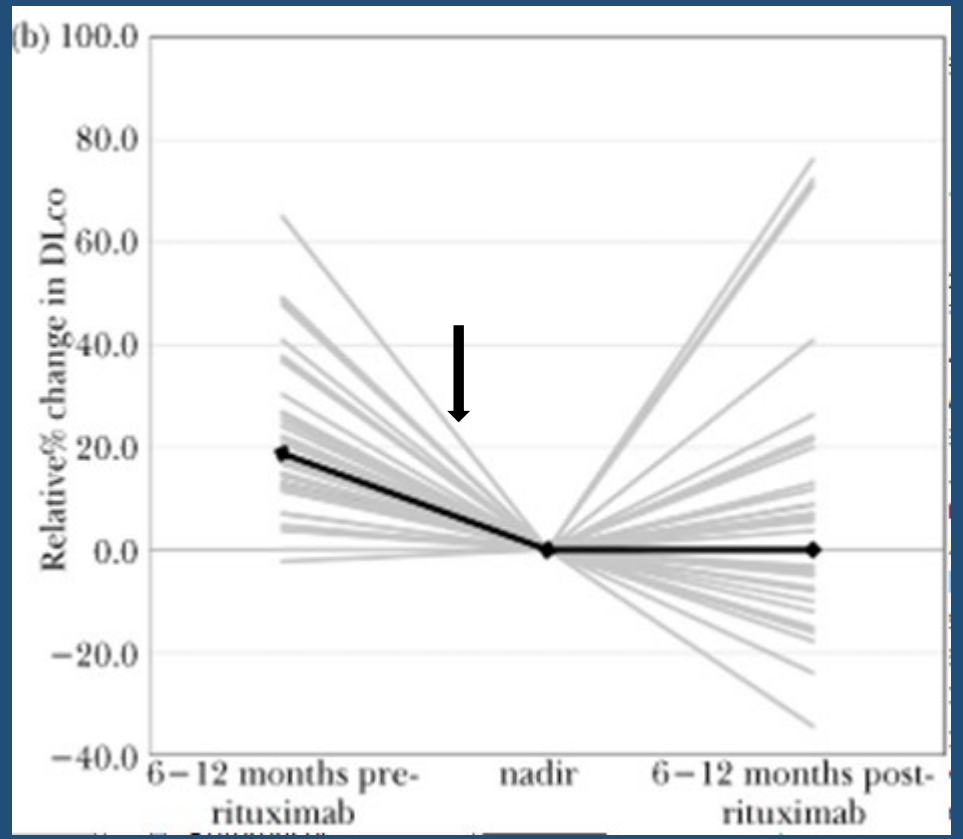
ORIGINAL ARTICLE

Rituximab in severe, treatment-refractory interstitial lung disease

GREGORY J. KEIR,[1,2] TOBY M. MAHER,[1] DAMIEN MING,[1] REZA ABDULLAH,[1] ANGELO de LAURETIS,[3] M. WICKREMASINGHE,[4] ANDREW G. NICHOLSON,[1] DAVID M. HANSELL,[1] ATHOL U. WELLS[1] AND ELISABETTA A. RENZONI[1]



FVC pre- and post-rituximab



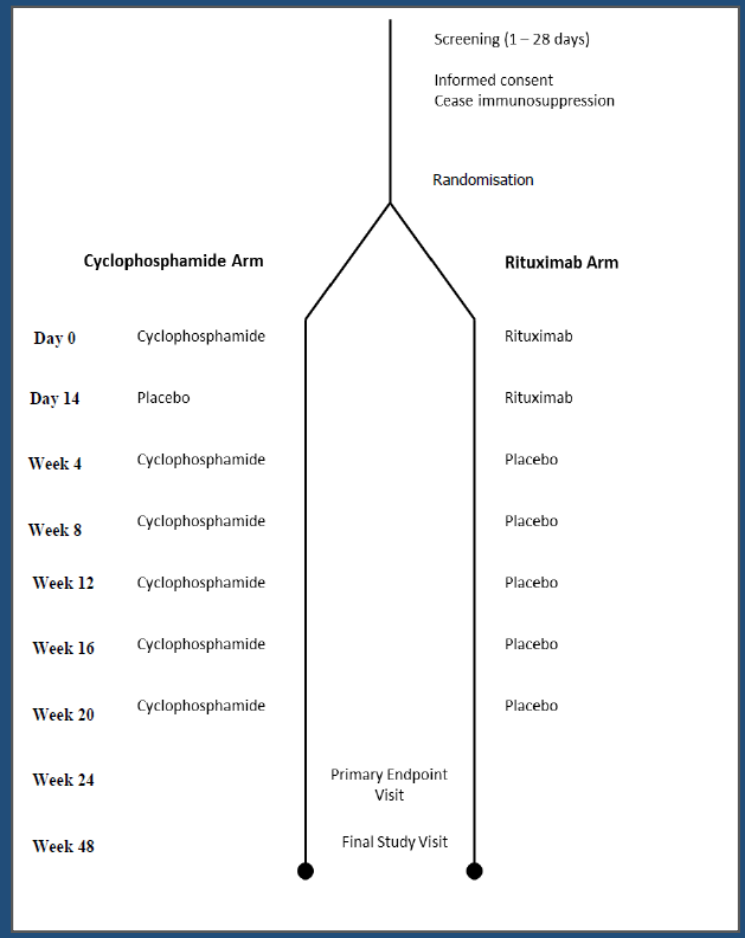
DLco pre- and post-rituximab

Please note that rituximab is not approved for the treatment of severe, treatment-refractory ILD

Keir GJ, et al. *Respirology*. 2014;19:353–359

RECITAL trial:

- Rituximab (1 gr x2) vs iv cyclophosphamide (monthly for six months) in CTD-ILD (*NCT01862926*)
  - Systemic sclerosis
  - Mixed connective tissue disease
  - Idiopathic inflammatory myositis
- Primary outcome: FVC change at twelve months
- Recruitment target: 116 pts



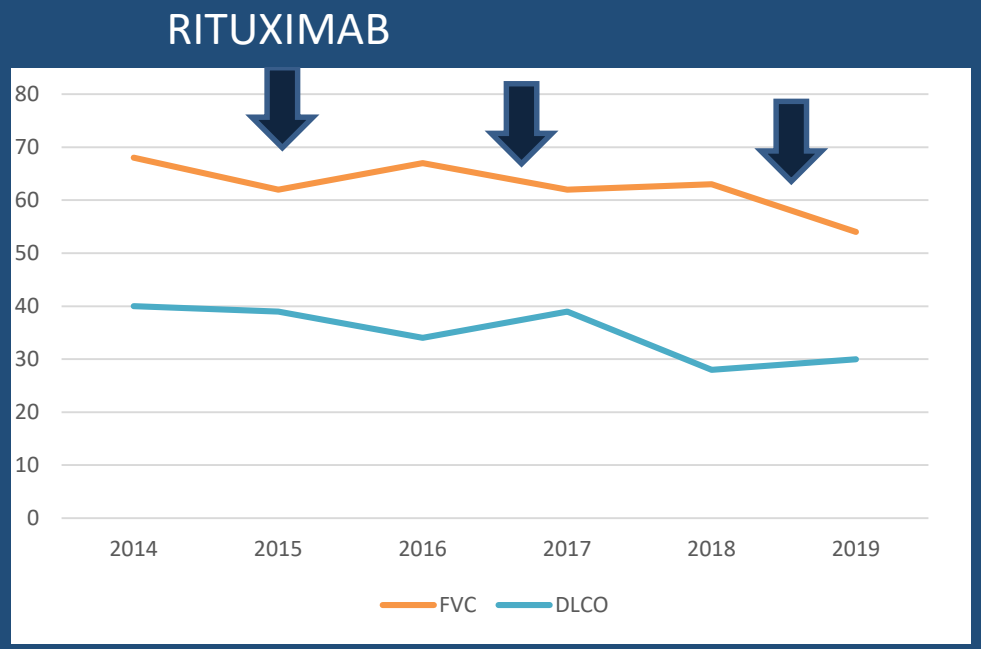
Saunders P et al Trials. 2017 Jun 15;18(1):275.

- Majority of patients with progressive CTD-ILD can expect to stabilise on immunosuppression

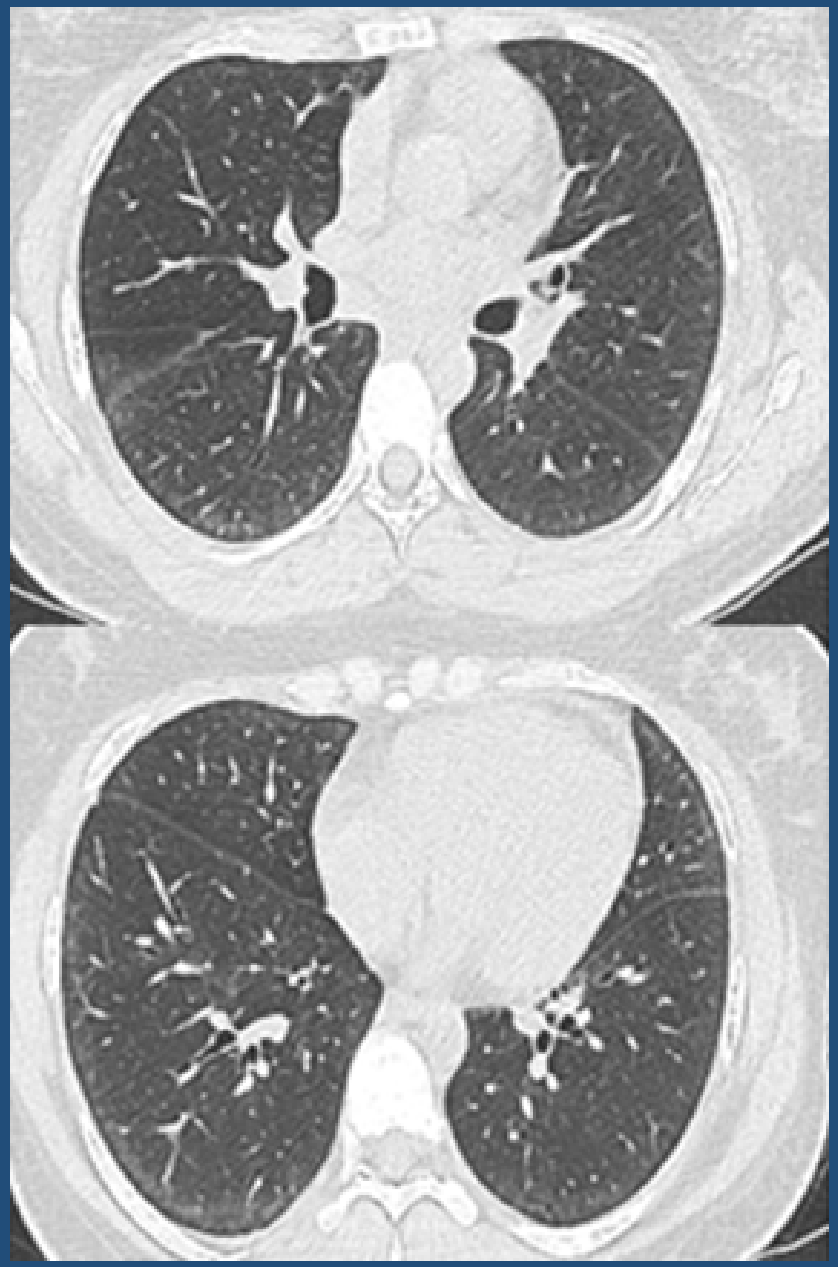
- However, in a minority, disease course is progressive, despite intensive immunosuppression. Unmet need.

Ms MJ

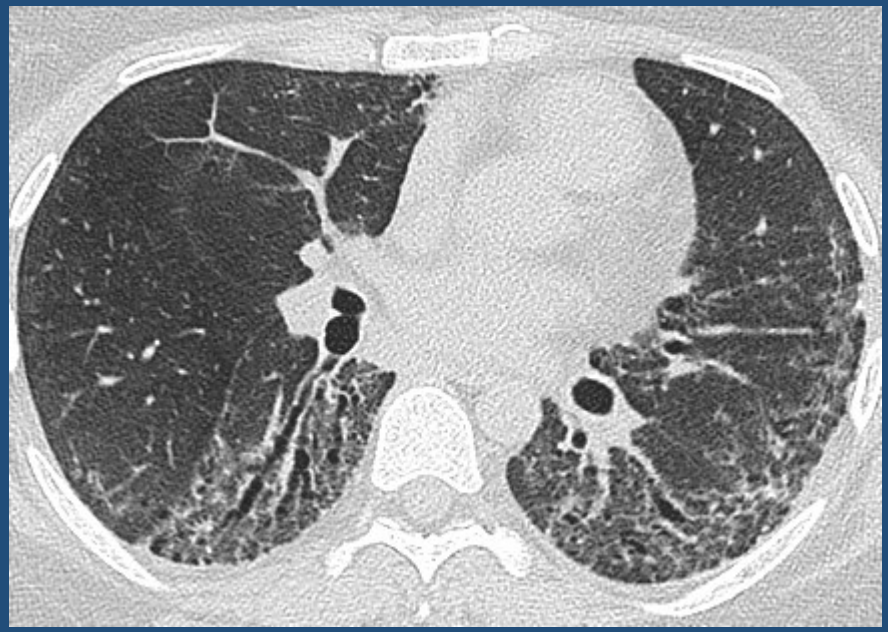
- 30 yr old woman with Scl70+ diffuse cutaneous SSc
- Despite subtle changes on HRCT, presents with significantly impaired DLCO of 40%. FVC of 70%
- Starts low dose pred and MMF 1.5 gr bd, but ongoing subtle decline
- Rituximab added

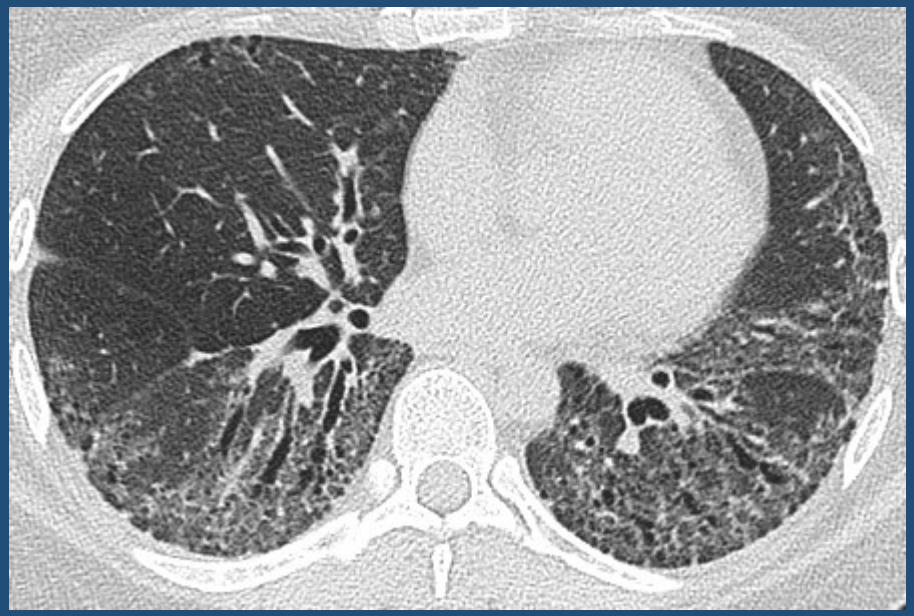


2013



2018





Trials of antifibrotic agents in CTD-ILDs

SSc-ILD

- Phase 2 LOTUSS Study: Pirfenidone +/- MMF
- NCT03221257 (SLS III): Phase 2 study combining MMF with pirfenidone vs placebo for 18 months
  - Recruitment to start in October 2017
  - 150 patients target enrolment; estimated end May 2021
- NCT02597933: Phase 3 study of nintedanib vs placebo (background MMF permitted stable dose)
  - 520 patients target enrolment
  - Primary outcome: annual rate of FVC decline
  - Estimated completion: December 2018

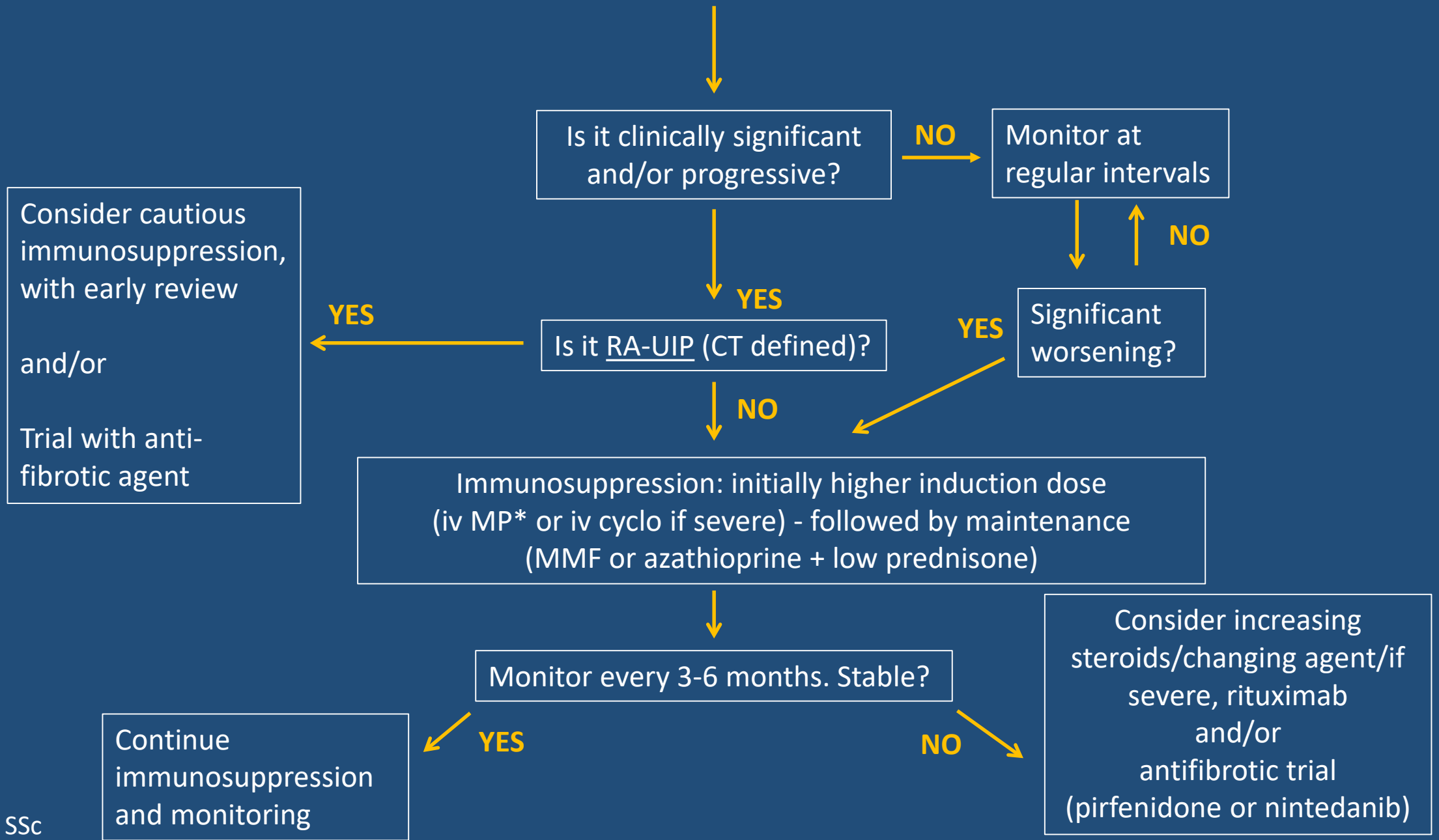
RA-ILD

- NCT02808871: Phase 2 study of pirfenidone vs placebo
  - Primary outcome: Incidence of FVC ≥10% or death within 52 weeks
  - 270 patients target enrolment; estimated completion: January 2021
  - Allows stable dose (at least 3 months) of immunosuppression or biologics prescribed for rheumatoid arthritis
- NCT02999178: Phase 3 study of nintedanib vs placebo in progressive, non-IPF lung fibrosis
  - MMF or azathioprine not allowed within four weeks of visit 2

MTX, methotrexate
Please note that pirfenidone±MMF is not approved for the treatment of SSc-ILD
Nintedanib is not approved for the treatment of SSc-ILD
Pirfenidone is not approved for the treatment of RA-ILD
Nintedanib is not approved for the treatment of progressive, non-IPF lung fibrosis

Khanna D, et al. *J Rheumatol.* 2016;43:1672–1679

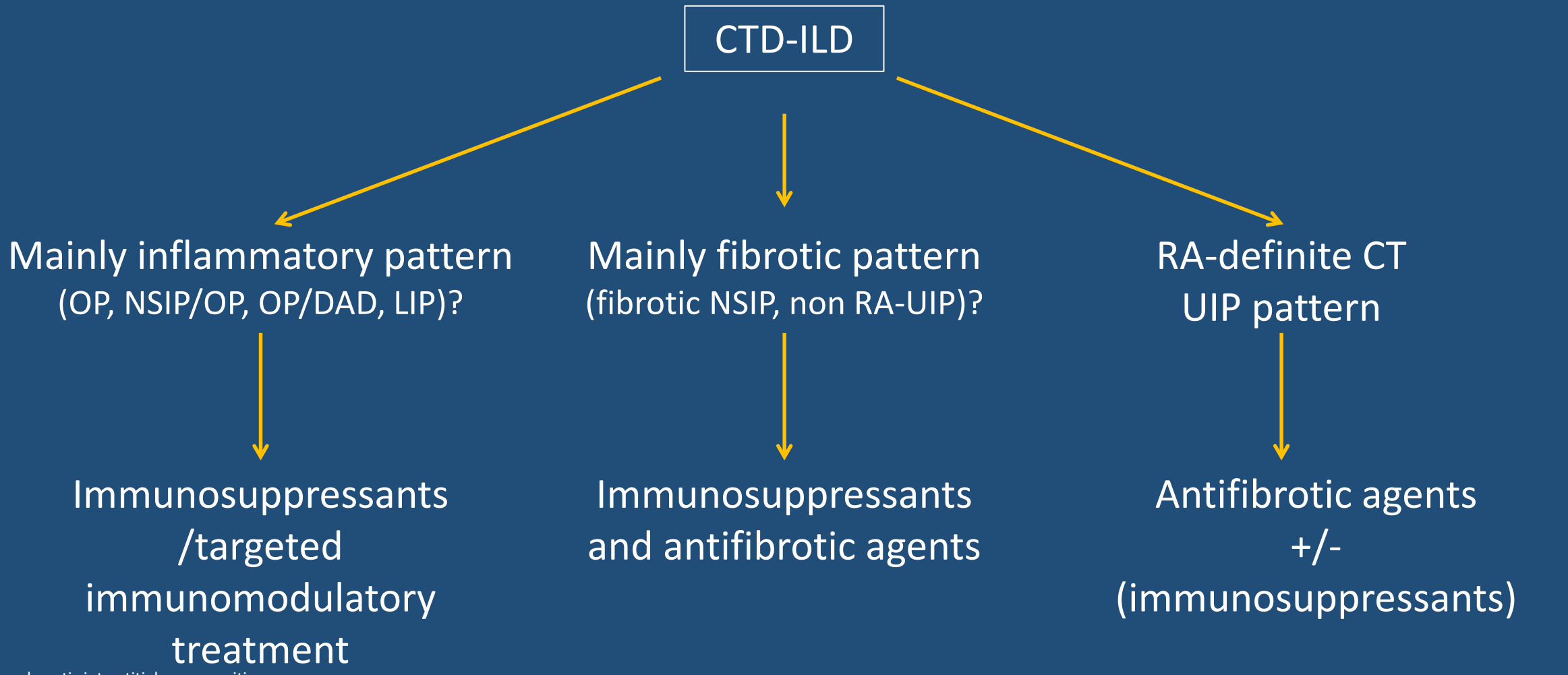
CTD-ILD: Current approach



*Not in SSc

Kouranos et al Curr Opin Pulm Med. 2018 Sep;24(5):453-460.

Possible future approach

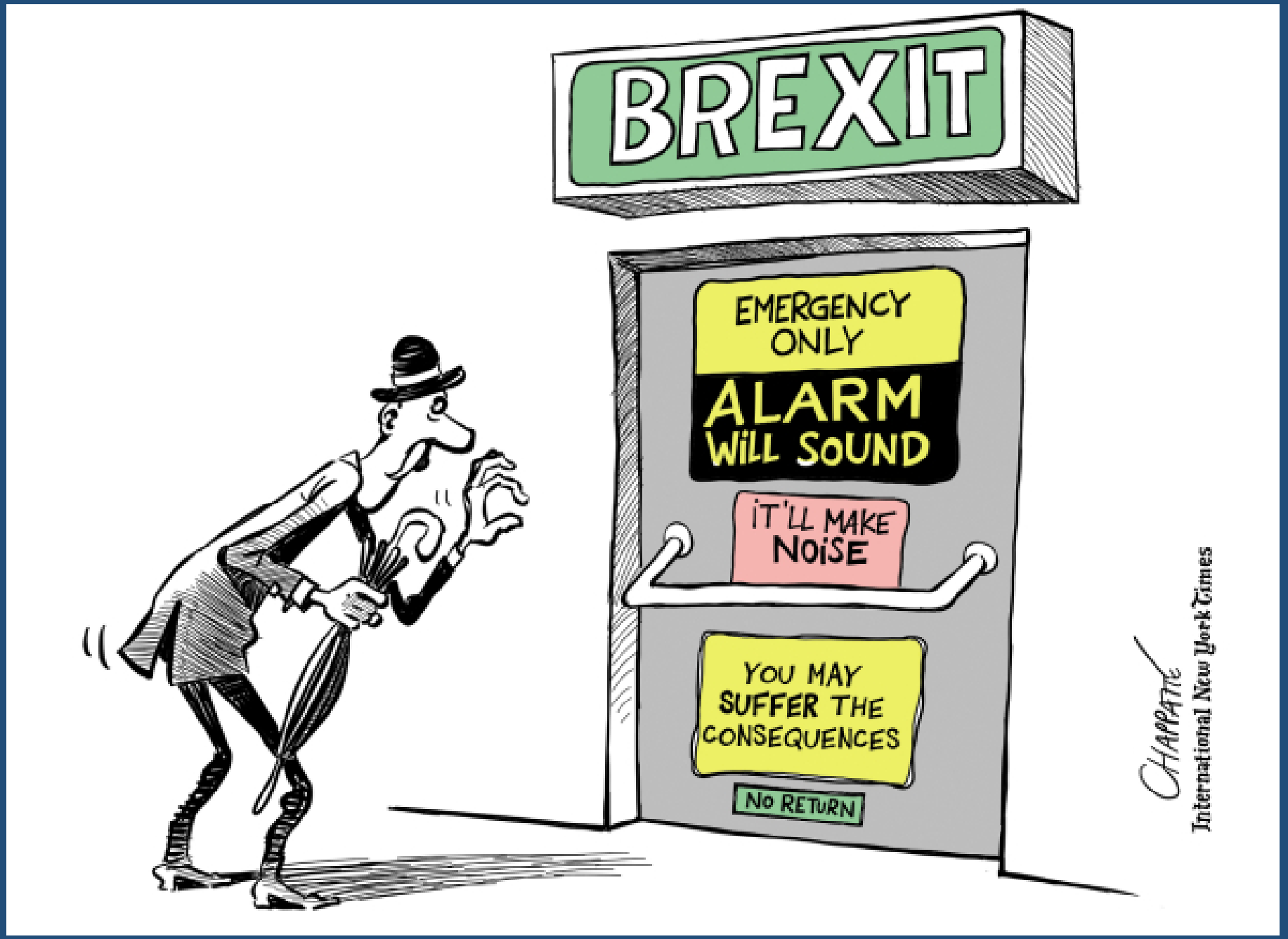


LIP, Lymphocytic interstitial pneumonitis

Kouranos et al Curr Opin Pulm Med. 2018 Sep;24(5):453-460.

In conclusion....

- In CTD-ILD, the majority of patients will stabilise/improve on immunosuppression ; RA-UIP (CT defined) may be an exception
- Minority of CTD-ILD experience progression despite intensive immunosuppression
- Genetic / molecular markers to refine prognosis and treatment options; subgroups with differential response to targeted treatments likely
- Place of anti-fibrotic agents in CTD-ILDs with progressive lung fibrosis to be determined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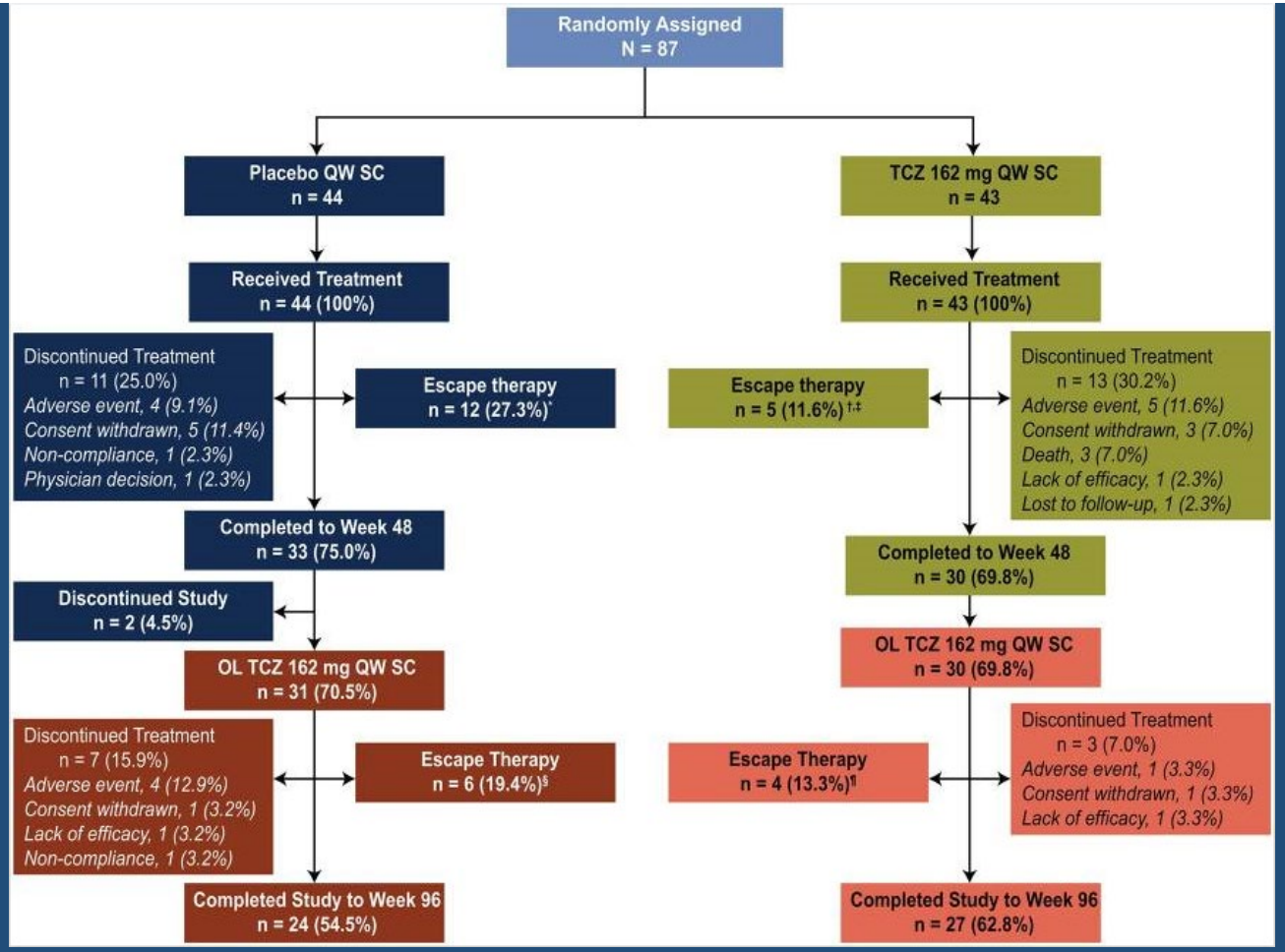
ALARM WILL SOUND
IT'LL MAKE NOISE
YOU MAY SUFFER THE CONSEQUENCES
NO RETURN
CHAPPATTE
International New York Times

OPEN ACCESS

EXTENDED REPORT

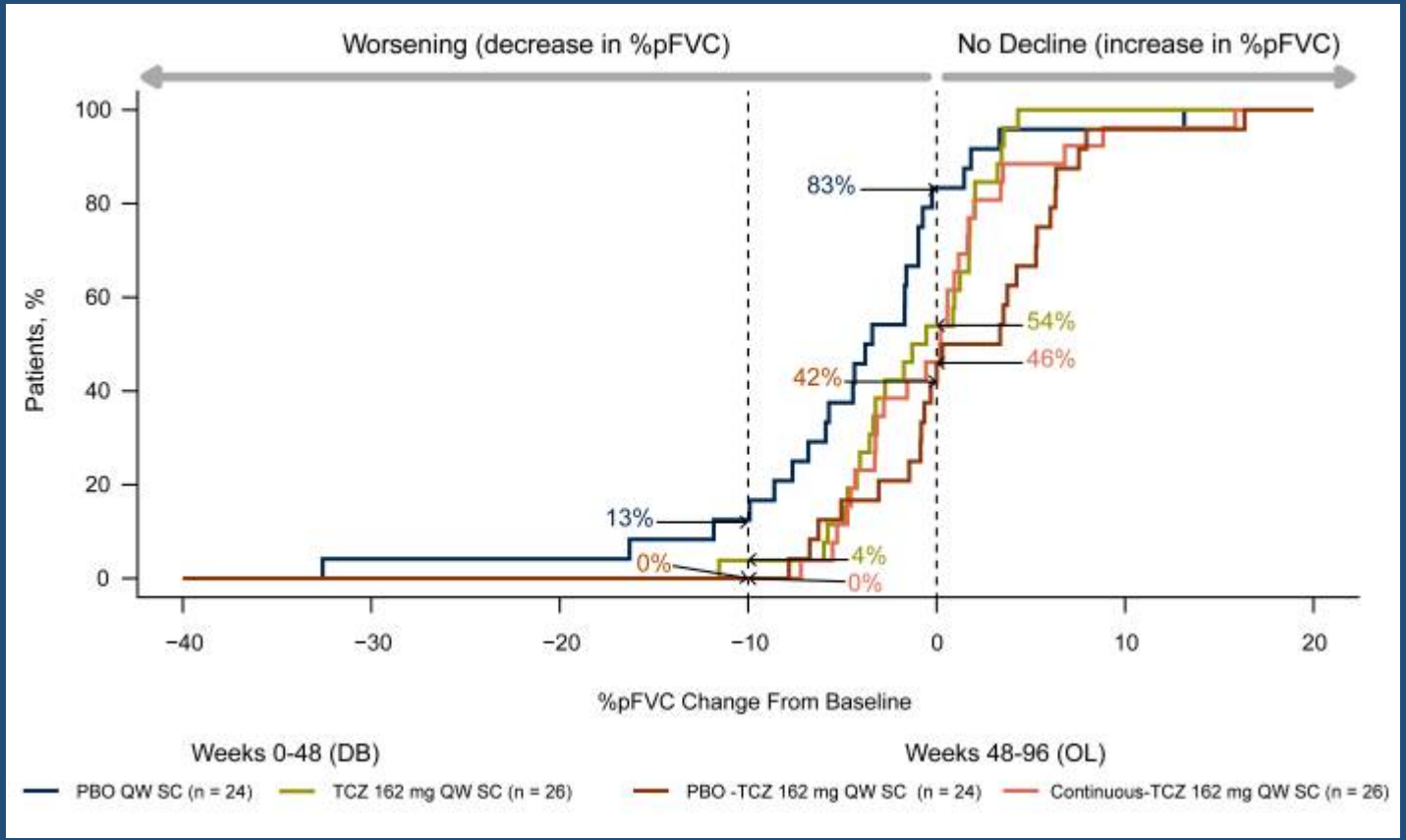
Safety and efficacy of subcutaneous tocilizumab in systemic sclerosis: results from the open-label period of a phase II randomised controlled trial (faSScinate)

Dinesh Khanna,[1] Christopher P Denton,[2] Celia J F Lin,[3] Jacob M van Laar,[4] Tracy M Frech,[5] Marina E Anderson,[6] Murray Baron,[7] Lorinda Chung,[8] Gerhard Fierlbeck,[9] Santhanam Lakshminarayanan,[10] Yannick Allanore,[11] Janet E Pope,[12] Gabriela Riemekasten,[13] Virginia Steen,[14] Ulf Müller-Ladner,[15] Helen Spotswood,[16] Laura Burke,[16] Jeffrey Siegel,[3] Angelika Jahreis,[3] Daniel E Furst[17]



Ann Rheum Dis. 2018 Feb;77(2):212-220.

Exploratory analysis on FVC change (secondary outcome)



Ann Rheum Dis. 2018 Feb;77(2):212-220.