4ο ΔΙΑΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΠΡΟΓΡΑΜΜΑ ΕΚΠΑΙΔΕΥΣΗΣ ΣΤΗ ΡΕΥΜΑΤΟΛΟΓΙΑ 2022-24

“Θεραπεία διάμεσης πνευμονικής νόσου στη συστηματική σκληροδερμία”

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Ρευματολόγος – Επ. Συνεργάτης

Μονάδα Ρευματολογίας & Κλινικής Ανοσολογίας

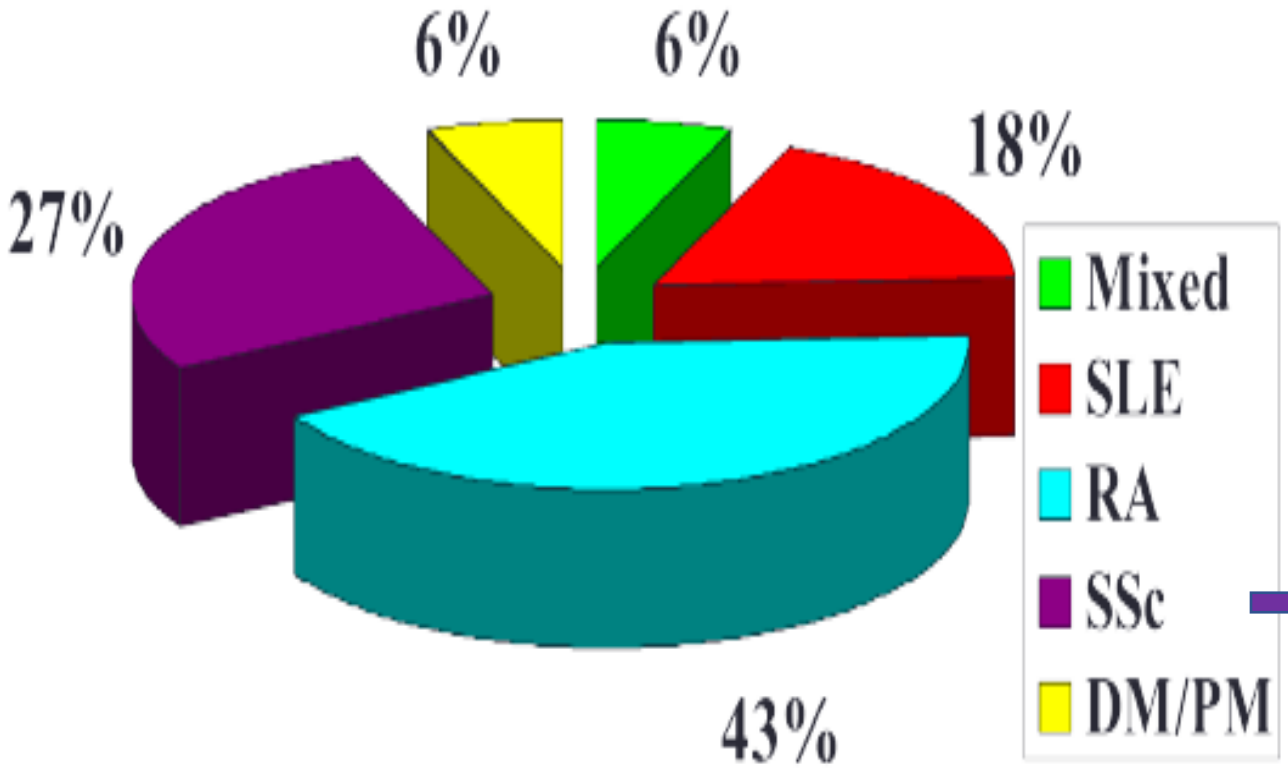
Δ’ Παν/κη Παθολογική Κλινική – Π.Γ.Ν. «Αττικόν»

Δήλωση σύγκρουσης συμφερόντων:

- Ο ομιλητής έχει λάβει την τελευταία διετία αμοιβή για διαλέξεις και υποστήριξη για συμμετοχή σε συνέδρια από τις εταιρείες : UCB, Genesis, Aenorasis, Abbvie, MSD, ELPEN, Pfizer, Boehringer-Ingelheim

- **Καμία σχετική με τη συγκεκριμένη παρουσίαση**

Εισαγωγή: CTD-ILDs



Life-time Prevalence of ILD ≲ 65%[1]

Am J Respir Crit Care Med 1994; 150:967-72

[1]Khanna D., et al., Arthritis and Rheumatology 2022, 74 (1), pp.13-27

Ποιοί ασθενείς με SScl έχουν αυξημένο κίνδυνο για ILD?

Συστηματική Σκληροδερμία

↑Επιπολασμός ILD

Screening για ILD σε όλους[3]

- Διάχυτη σκληροδερμία[1,2]
- Anti-Scl70[1]
  - Anti-Th/To, anti-NOR90, Anti-U3 RNP, Anti-U11/U12 RNP, anti-Pm-Scl[2]
- Άρρεν φύλο (RR=1.24)[1,2]
- Αφρο – καραιβική εθνική καταγωγή[1,2]

- **HRCT (gold standard)**

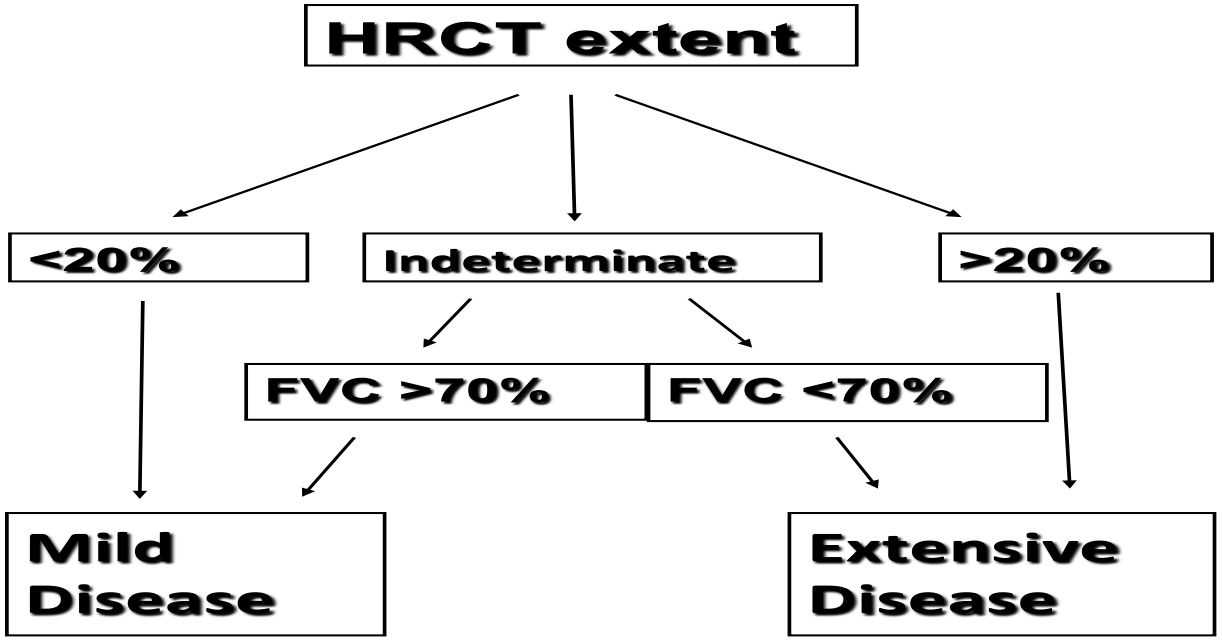
+ Assessment of disease severity:

1) PFTs
   NB: FVC<80% → sensitivity = 63%
   Combination FVC or DLco <80% → sensitivity 85%
2) 6MWT
3) Echo

[1]Distler O et al Eur Respir J 2020;55:1902026
[2]Perelas A et al Lancet Resp Med 2020
[3]Khanna D., et al., Arthritis and Rheumatology 2022, 74 (1), pp.13-27

Ποιοί ασθενείς με SScl έχουν αυξημένο κίνδυνο για PF-ILD?

Α) Ασθενής με σοβαρή- εκτεταμένη νόσο



- **Επιδημιολογικά:**
  - Άρρεν φύλο
  - Μεγάλη ηλικία
  - Αφρο – καραϊβική καταγωγή
- **Κλινικά:**
  - **Διάχυτη σκληροδερμία**
  - **Αρθρίτιδα**
- **Εργαστηριακά:**
  - **Anti-Scl70**
  - Anti-Th/To, anti-NOR90, Anti-U11/U12, anti-Pm-Scl[2]
  - **ΤΚΕ/CRP ↑**

Β) Ασθενής με εξελισσόμενη νόσο (> 2 από 3 κριτήρια προοδευτικής ίνωσης)

- FVC ≤ 5% ή/και DLCO ≤ 10%
- Επιδείνωση δύσπνοιας/βήχα
- Απεικονιστική επιδείνωση

Distler O et al Eur Respir J 2020;55:1902026
Perelas A et al Lancet Resp Med 2020
Khanna D., et al., Arthritis and Rheumatology 2022, 74 (1), pp.13-27
Goh NS. Am J Respir Crit Care Med. 2008
American Journal of Respiratory and Critical Care Medicine Volume 205 Number 9 | May 1 2022

Θεραπευτικές επιλογές

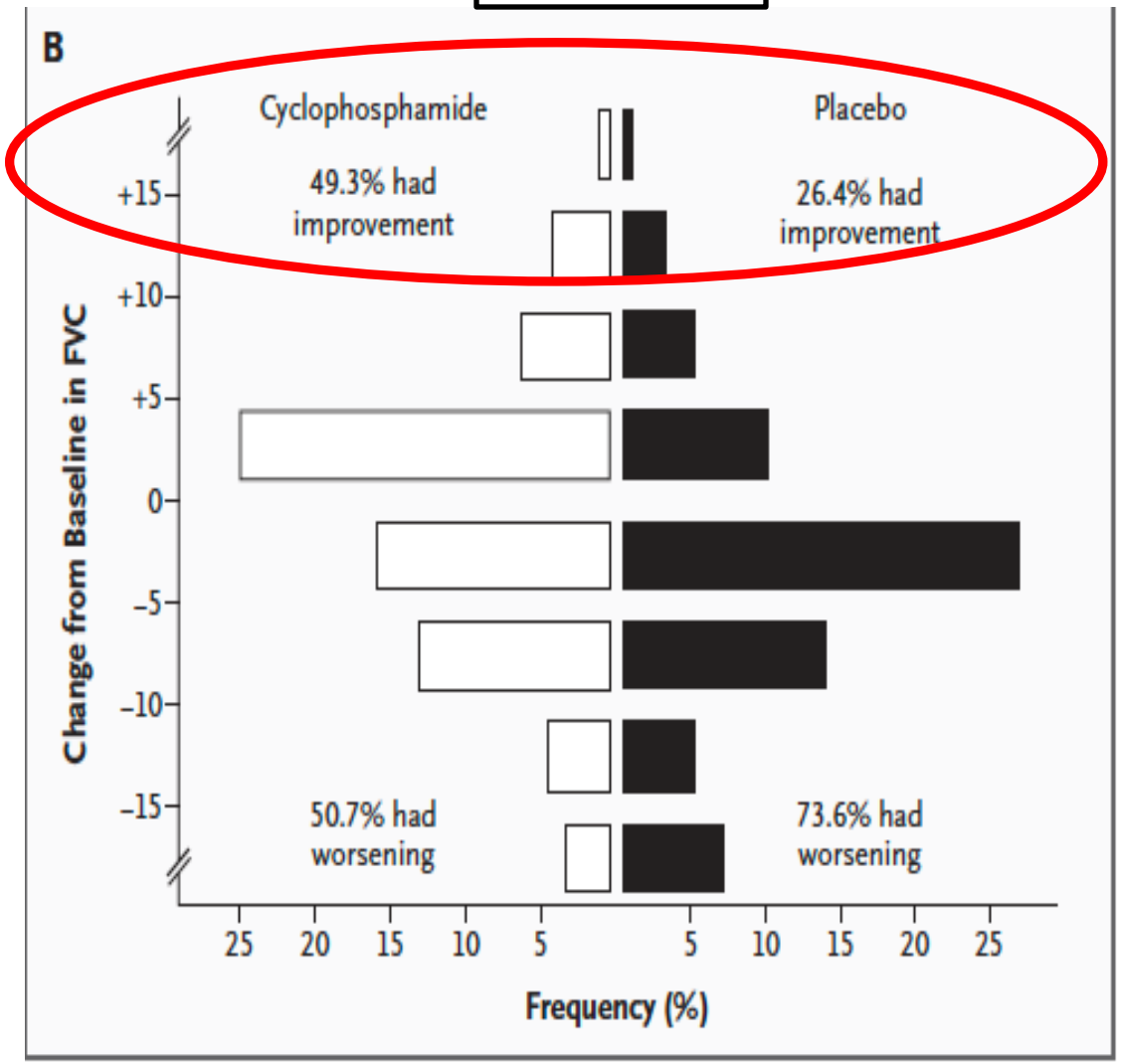
- **Ανοσοτροποιητικά φάρμακα**
- **Αντι-ινωτικά φάρμακα**
- **Μη φαρμακευτικές παρεμβάσεις**

‘Put your patients where the data is….’?

O.Distler ACR convergence 2021

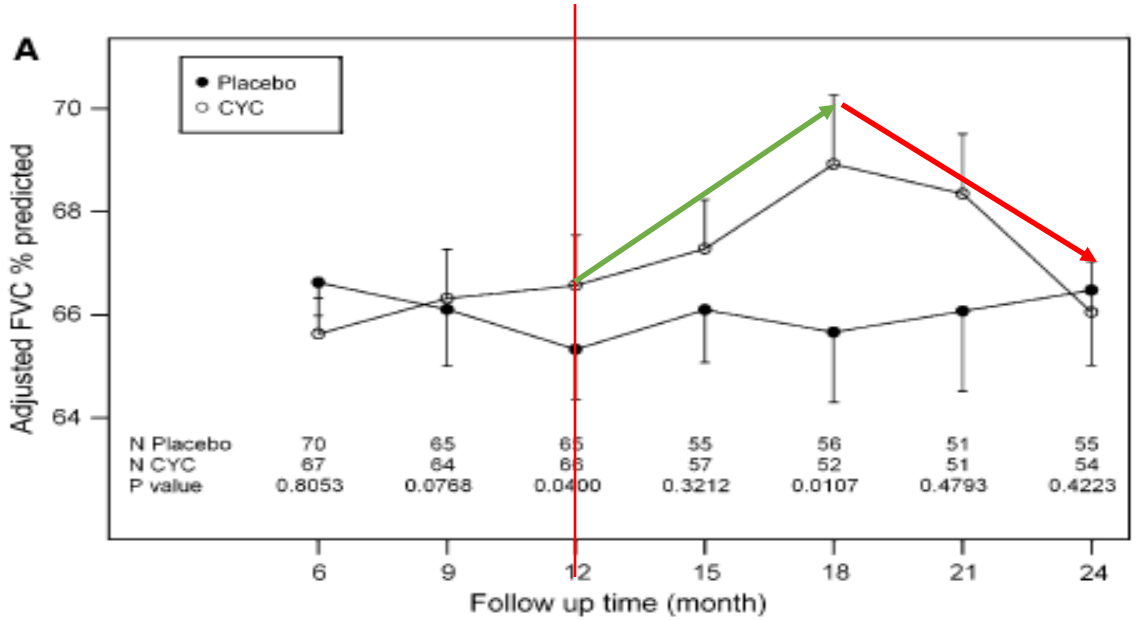
SLS I: oral CY vs PBO

158pts (1:1)



Patients' phenotype:

- *Disease duration <7yr*
- *Diffuse SScl 60%*
- *FVC = 45-85% and DLCO>30%*
- ***Pre <10mg/d (no DMARDs)***

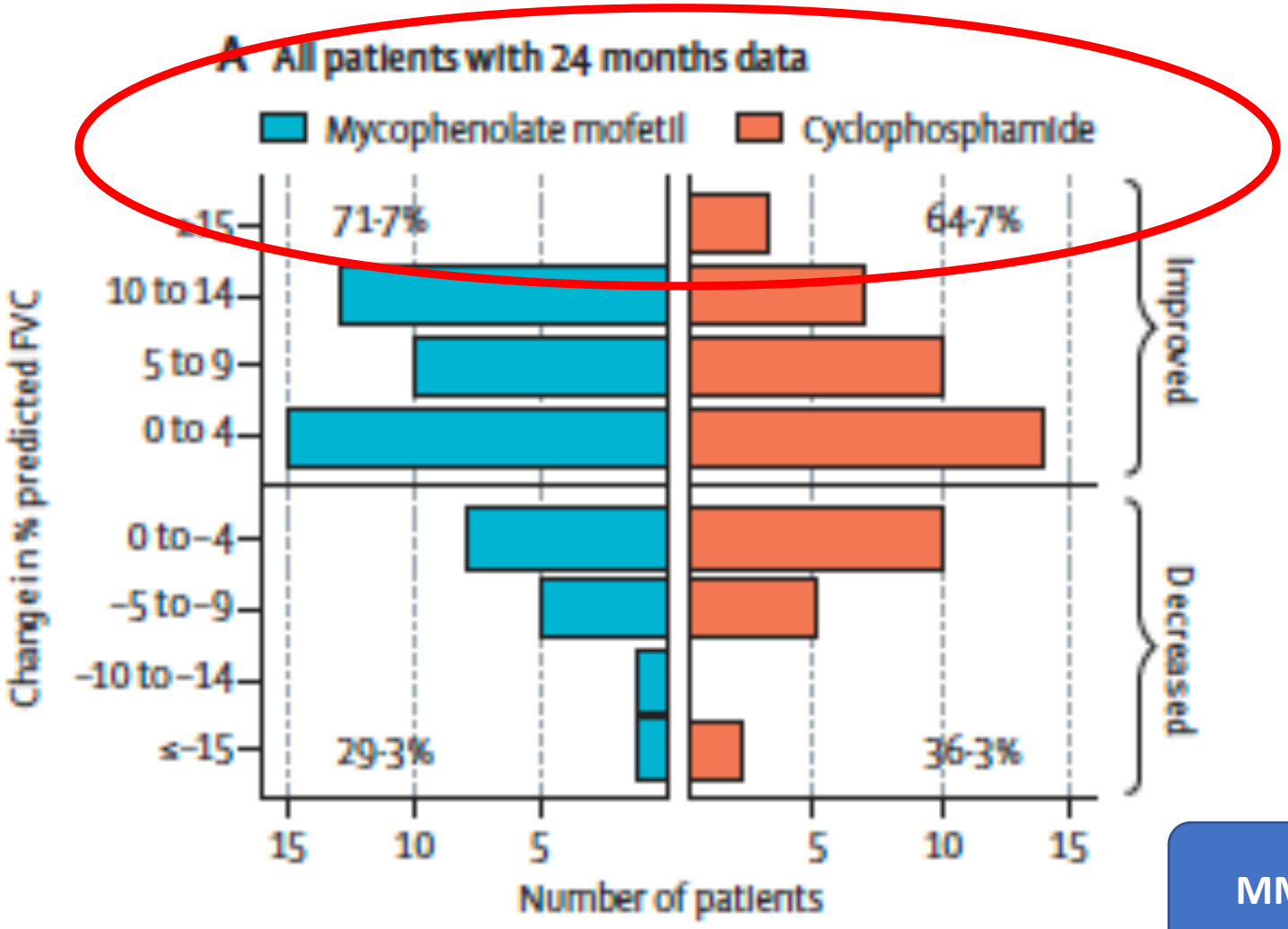


CY: Αποτελεσματική αλλά όχι «μακράς πνοής» θεραπεία

Tashkin DP, et al. N Engl J Med. 2006;354:25.

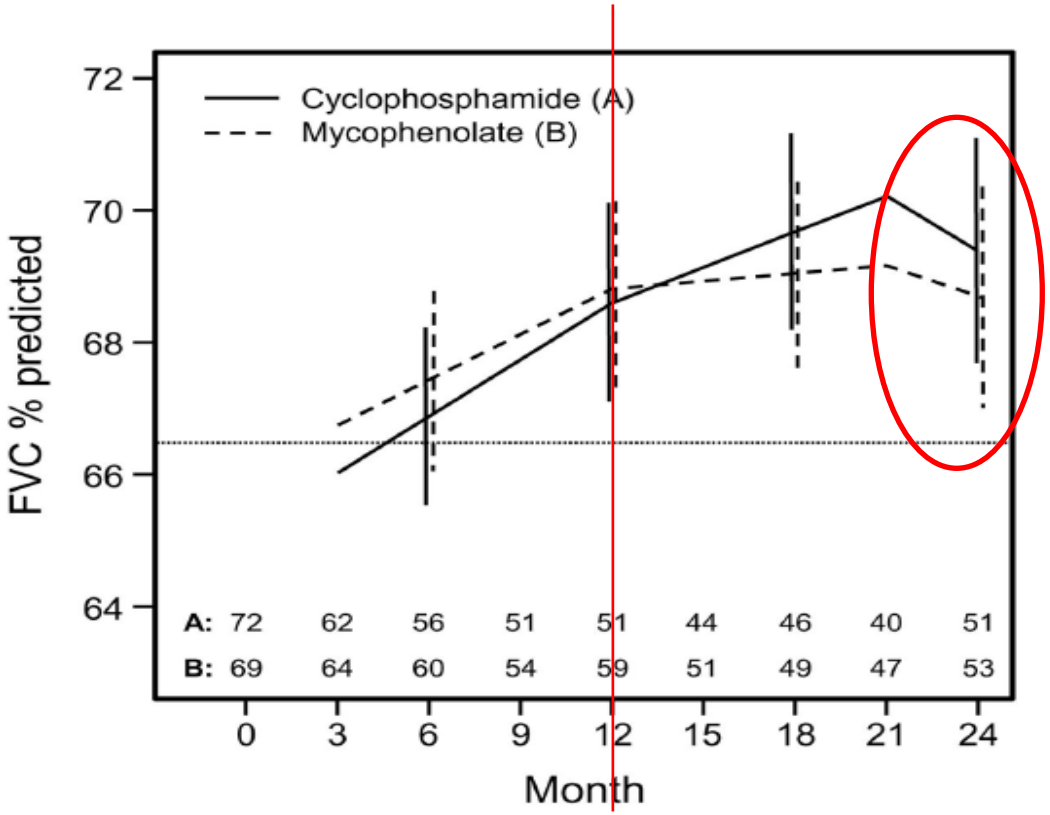
SLS II: CY vs MMF

126pts (1:1)



Patients' phenotype:

- *Disease duration <7yr*
- *Diffuse SScl 60%*
- *FVC = 45-80% and DLCO>30%*
- ***Pre <10mg/d (no DMARDs)***



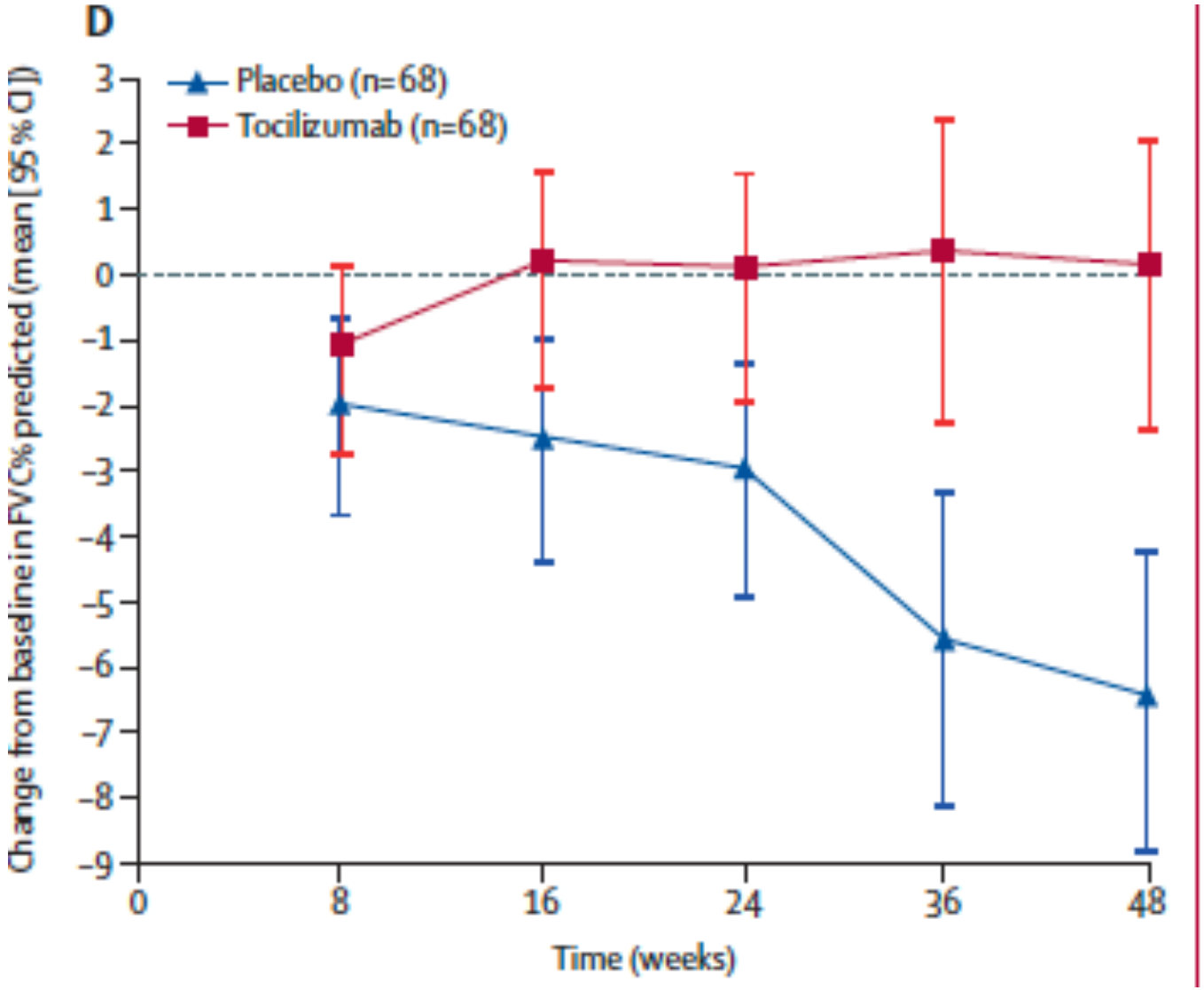
MMF: σχεδόν εφάμιλλη με CY αλλά «μακράς πνοής»

Tashkin DP, et al. Lancet Respir Med. 2016;4:708–19.

FocuSSced trial: TCZ vs PBO

Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial

Dinesh Khanna, Celia J F Lin, Daniel E Furst, Jonathan Goldin, Grace Kim, Masataka Kuwana, Yannick Allanore, Marco Matucci-Cerinic, Oliver Distler, Yoshihito Shima, Jacob M van Laar, Helen Spotswood, Bridget Wagner, Jeffrey Siegel, Angelika Jahreis*, Christopher P Denton*, for the focuSSced investigators†



Patients' phenotype:

- *Disease duration* ***<5yr***
- ***Diffuse*** *SScl*
- ***Scl 70(+) and/or high CRP/ESR***
- *136/210 με ILD at diagnosis*

ΔFVC = 6.2%

TCZ: Αποτελεσματικό σε SScl-ILD **ειδικά** σε ασθενείς με **πρώιμη νόσο και κακούς προγνωστικούς δείκτες!**

Safety and Efficacy of Rituximab for Systemic Sclerosis: a Double-Blind, Parallel-Group Comparison, Investigators Initiated Confirmatory Randomized Clinical Trial (DESIRES study)

RTX in SSc?

- Background: RTX effective in skin and lung involvement in open-label and case series

- **RCT 1:1 RTX vs placebo 24wks(Japan pts=56):**
  - Inclusion:
    - MRSS>/= 10
    - Pre</=10mg/d
    - IS stopped 4wks before
  - Exclusion:
    - FVC<60%
    - PH
    - CY past 2yrs

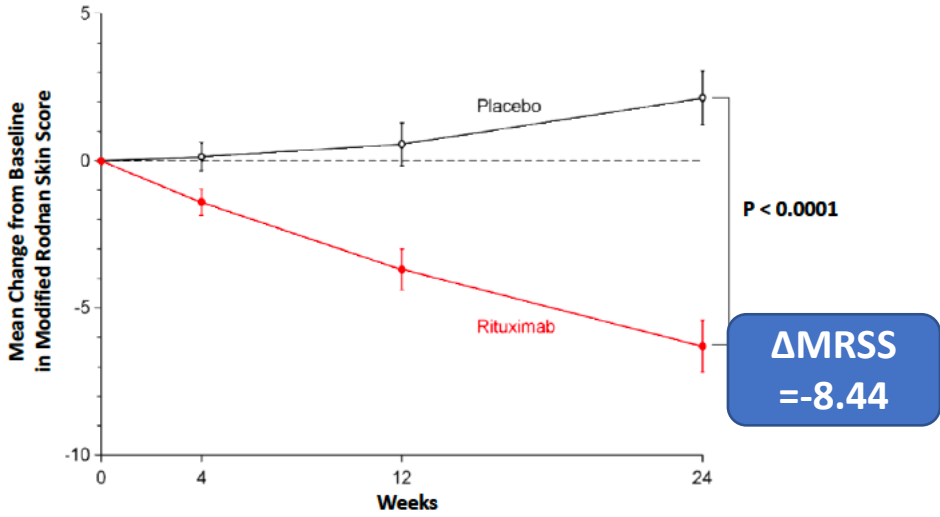
1ary endpoint: ΔMRSS

2ary endpoints:

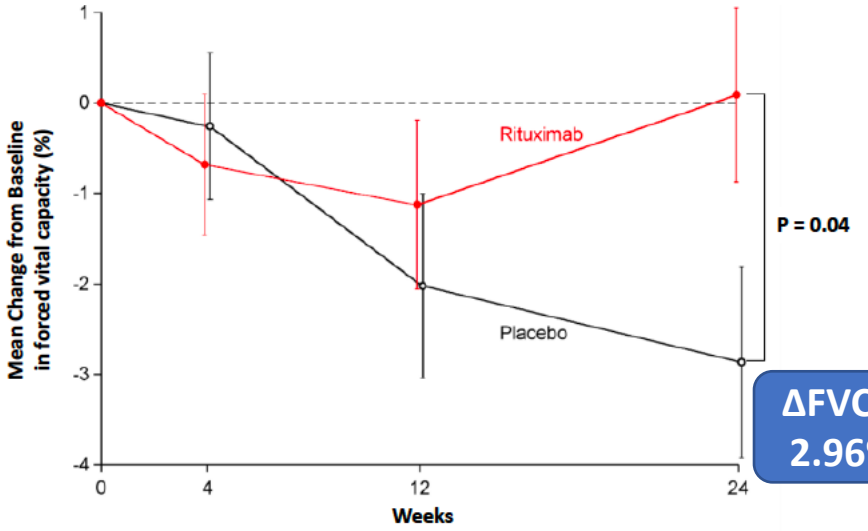
- **ΔFVC**
- ΔDLCO
- Δ CT abnormalities (% lung fields)
- SEs

Patients' phenotype:

- *Disease duration 4-5yr*
- *Diffuse >80%*
- *Scl 70(+) 50%*
- *MRSS =14-15*
- *PFTs >80%*



ΔMRSS =-8.44



ΔFVC = 2.96%

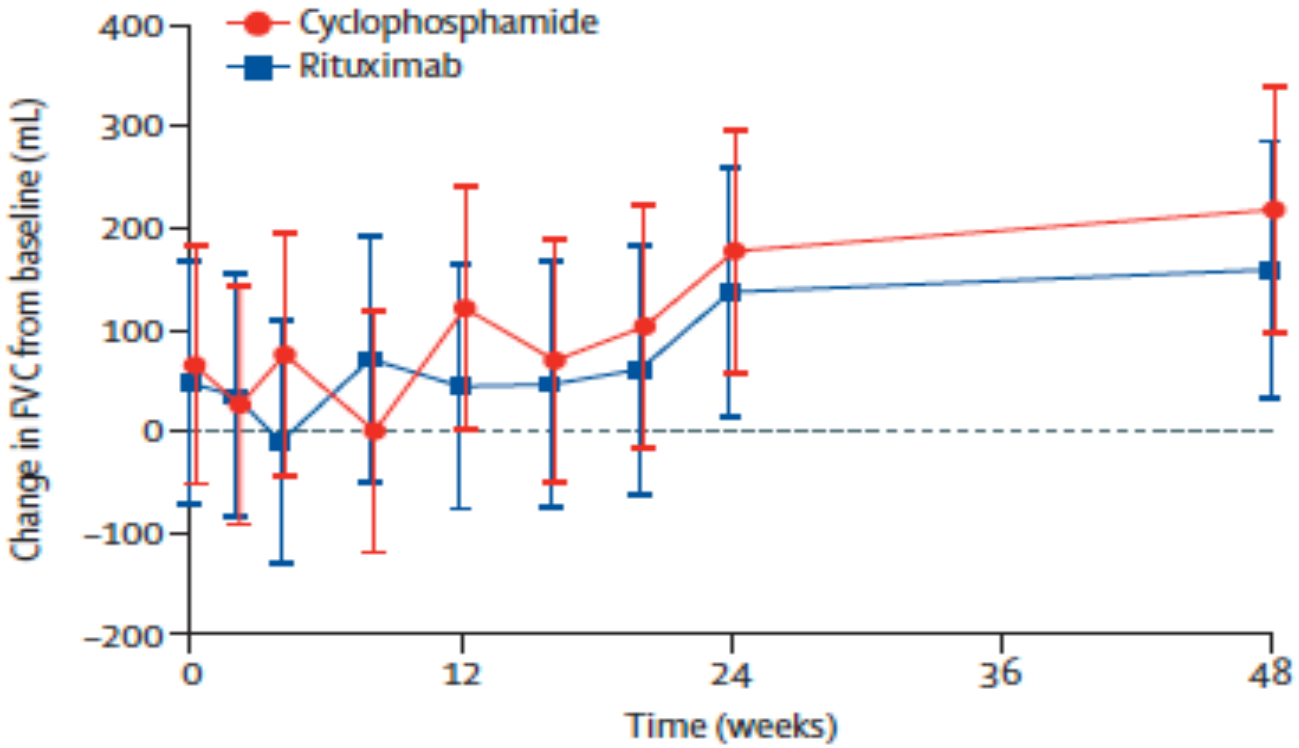
Japan-FDA approval of RTX in SScl

No new SEs

Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): a double-blind, double-dummy, randomised, controlled, phase 2b trial

*Toby M Maher, Veronica A Tudor, Peter Saunders, Michael A Gibbons, Sophie V Fletcher, Christopher P Denton, Rachel K Hoyles, Helen Parfrey, Elisabetta A Renzoni, Maria Kokosi, Athol U Wells, Deborah Ashby, Matyas Szigeti, Philip L Molyneaux, on behalf of the RECITAL Investigators**

Connective tissue disease type		
Idiopathic inflammatory myositis	22 (46%)	22 (45%)
Systemic sclerosis	19 (40%)	18 (37%)
Mixed connective tissue disease	7 (15%)	9 (18%)



RTX not superior but with ↓ **SEs and ↓CS vs CY**

Maher T. et al., Lancet Respir Med 2022

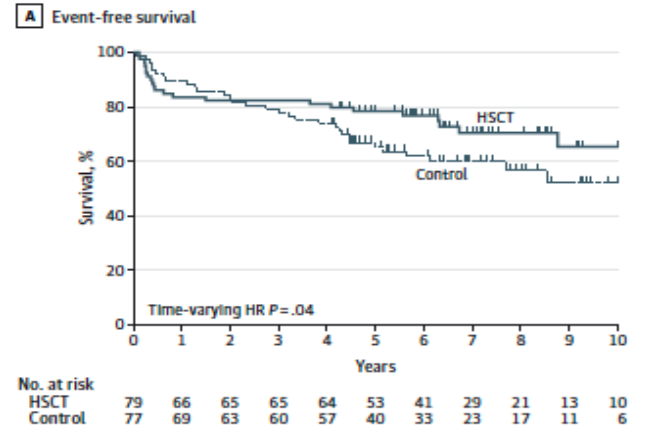
AHSCT in SSc?

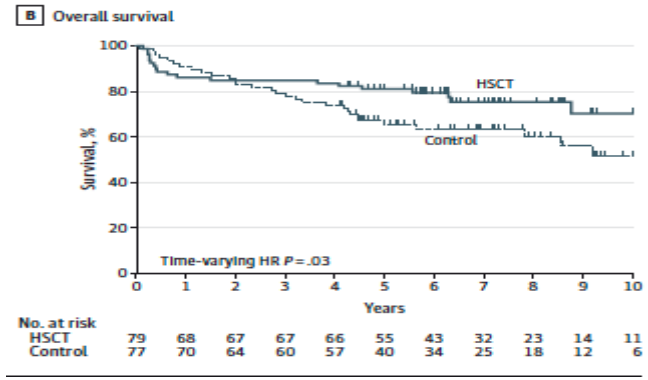
- 2 RCTs

***AHSCT improves long-term survival and event-free survival** at the cost of higher 1yr treatment-related toxicity*
CAREFUL PATIENT SELECTION!

ASTIS trial JAMA 2014

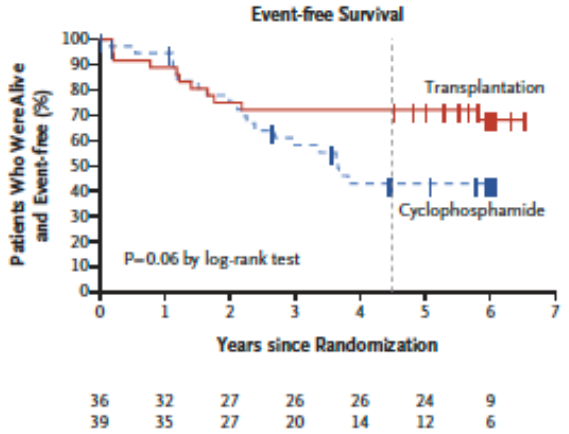
156 pts AHSCT (ATG + CY) vs ivCY
- Disease duration <4yr
- MRSS>15
- Involvement of heart, lungs, kidneys (noPH)

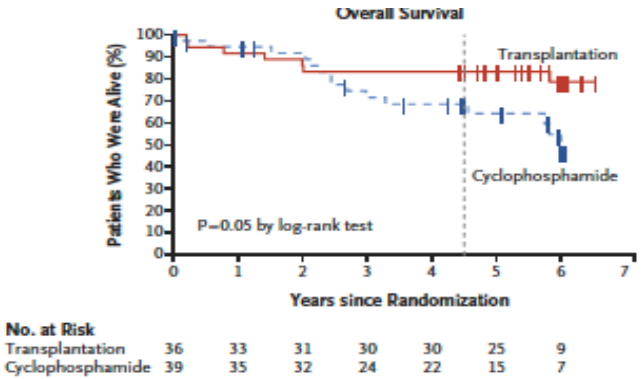




At 2 yr FU:
FVC (+9·1%; p=0·004) and TLC (+ 6·4%; p=0·02) not DLCO in AHSCT group

SCOT trial NEJM 2018





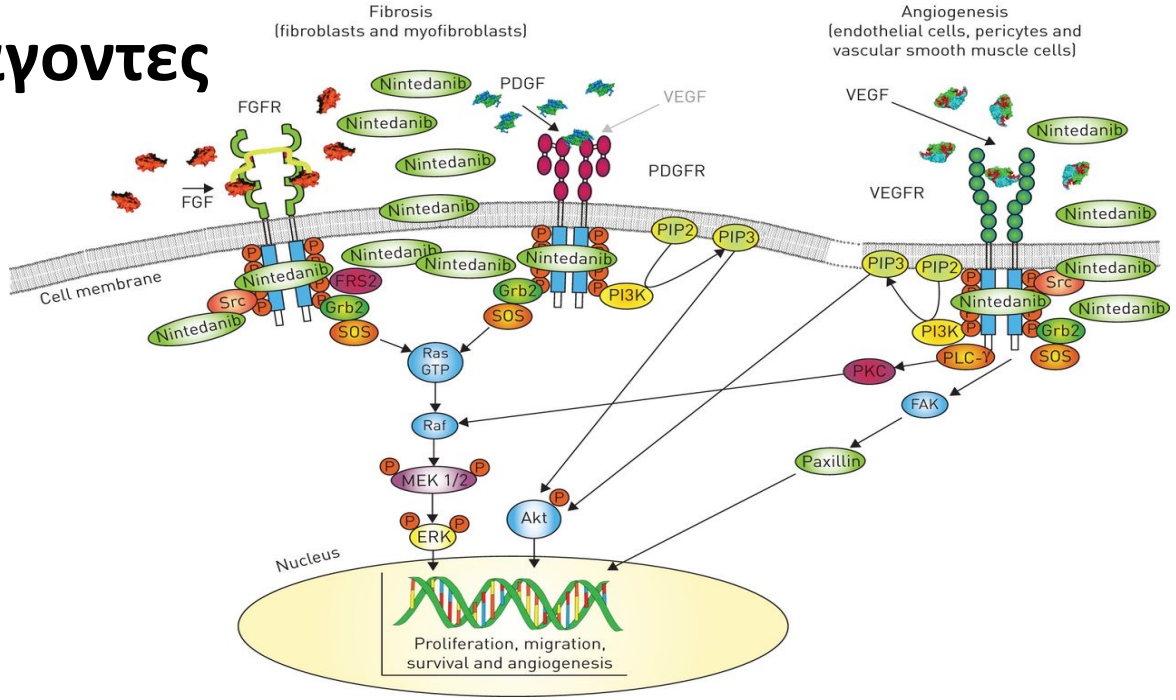
75pts AHSCT (TBI+ATG + CY) vs ivCY
- Disease duration <5yr
- Active ILD PFTs <75% but>40-45% or scleroderma kidney dis
- noPH, no CHF, no CKD <3b

At 4+yr FU:
- **More complications** from therapy **BUT**
- **More likely improved or stabilised PFTs and fewer episodes of respiratory failure**

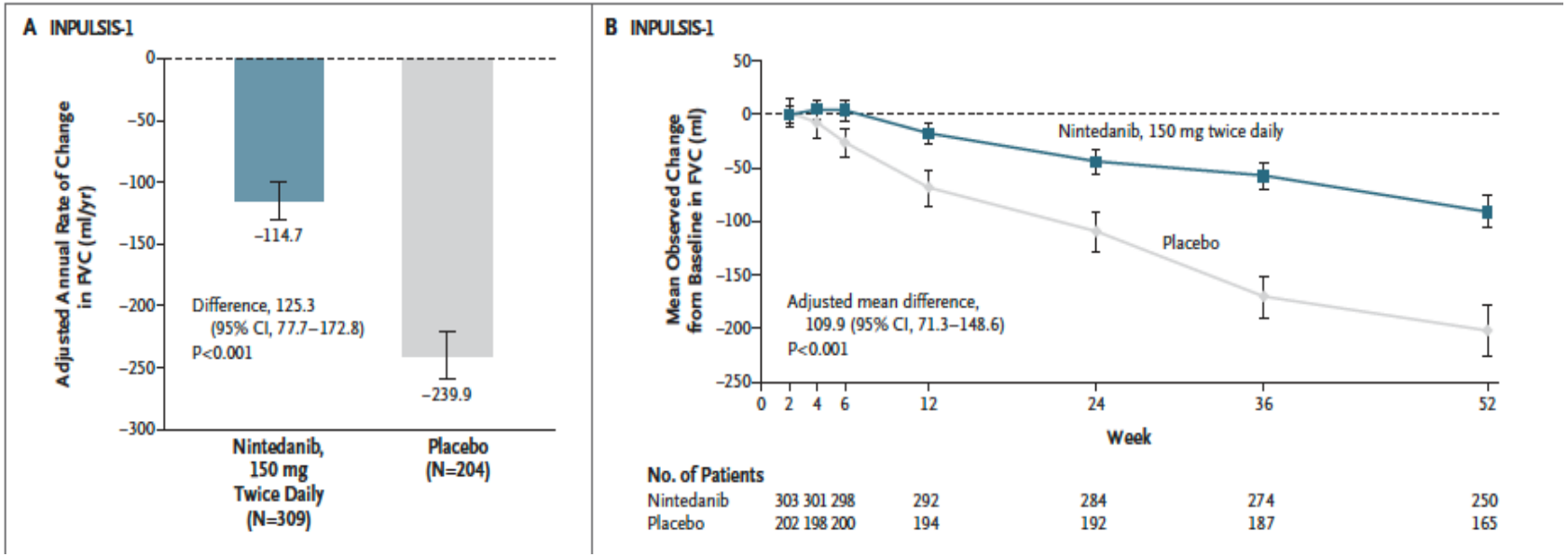
Μια «νέα» επιλογή: Αντι-ινωτικοί παράγοντες

Nintedanib

- **Ενδοκυτταρικός αναστολέας Tyr κινάσης** → ❌ ενδοκυττάρια σηματοδότηση από FGFR, PGFR, VEGFR → ↓ ενεργοποίηση, πολλαπλασιασμό και μετατροπή (σε μυοινοβλάστες) των ινοβλαστών και την αγγειογένεση → **↓ Ίνωση**



- **Εγκεκριμένο στην IPF**



Lutz Wollin et al. Eur Respir J 2015
Richeldi L et al., NEJM 2014

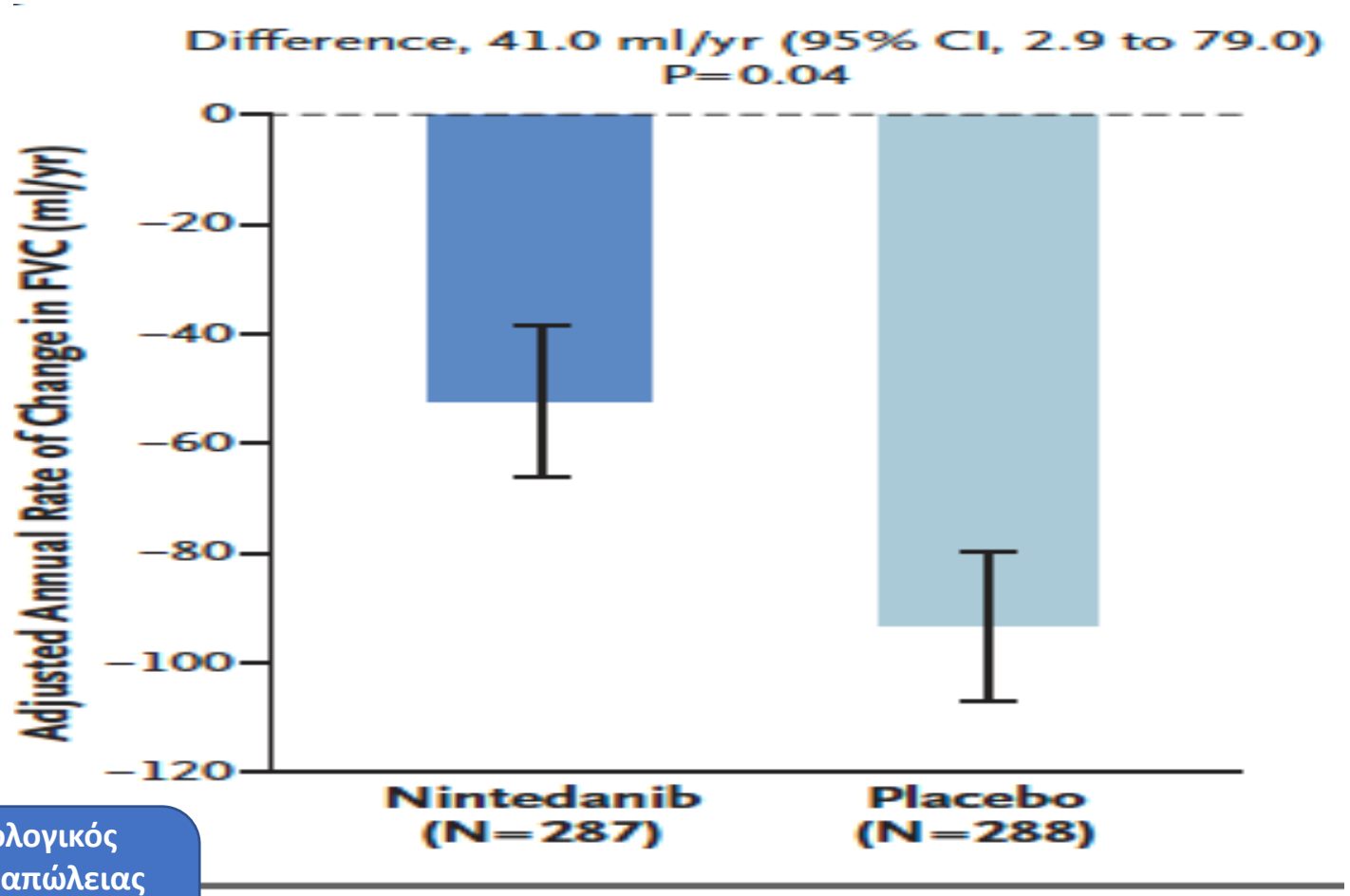
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nintedanib for Systemic Sclerosis–Associated Interstitial Lung Disease

Oliver Distler, M.D., Kristin B. Highland, M.D., Martina Gahlemann, M.D., Arata Azuma, M.D., Aryeh Fischer, M.D., Maureen D. Mayes, M.D., Ganesh Raghu, M.D., Wiebke Sauter, Ph.D., Mannaig Girard, M.Sc., Margarida Alves, M.D., Emmanuelle Clerisme-Beaty, M.D., Susanne Stowasser, M.D., Kay Tetzlaff, M.D., Masataka Kuwana, M.D., and Toby M. Maher, M.D., for the SENSCIS Trial Investigators*

SENSCIS trial: Nintedanib vs PBO



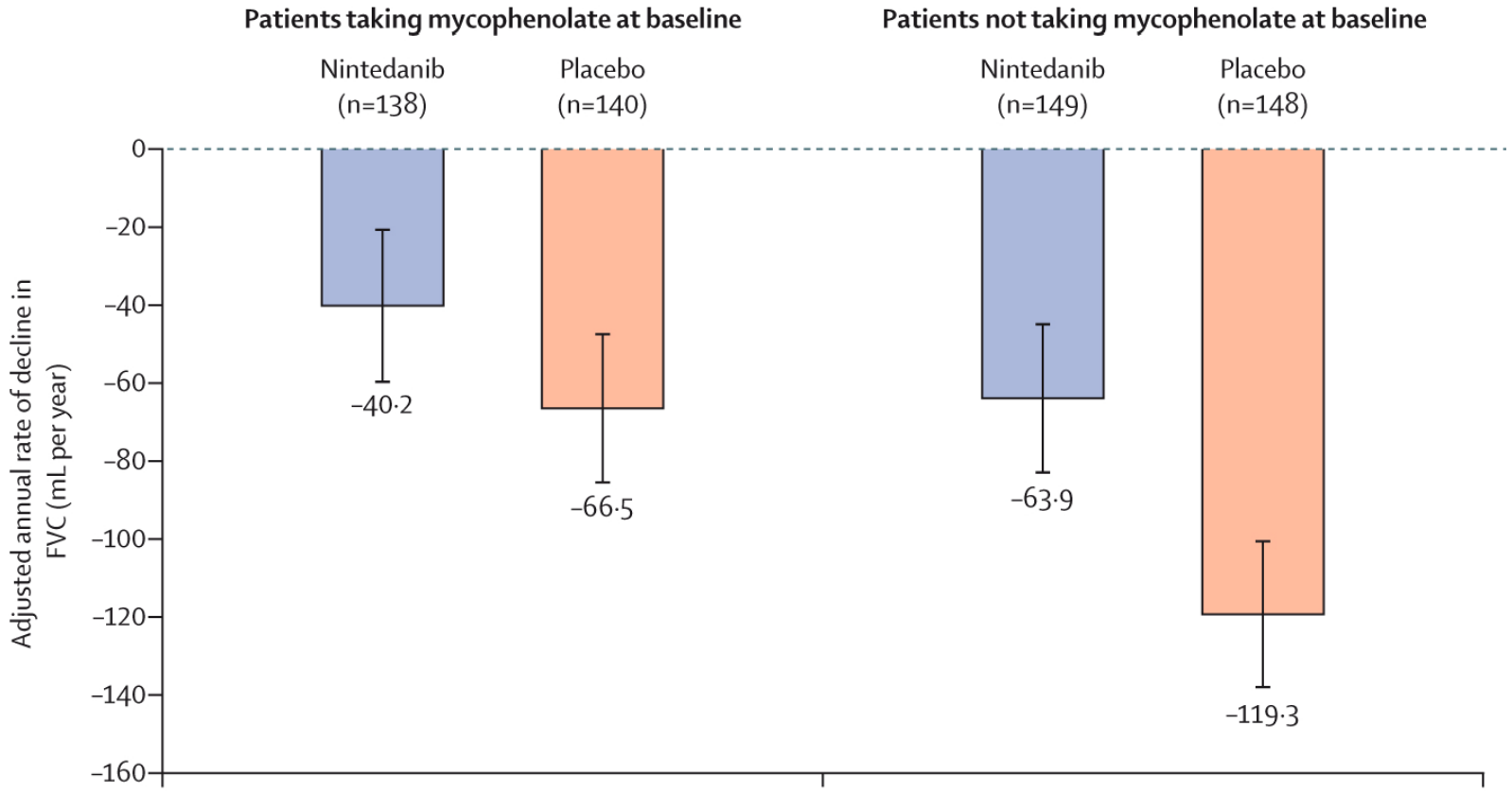
Patients' phenotype:

- *Disease duration 0.3-7yr*
- *Diffuse SScl = Limited SScl*
- Scl 70(+) 60%
- MMF = 50%

Φυσιολογικός ρυθμός απώλειας FVC μετά τα 25 έτη = 25-30mL/yr (Eur Respir J 2012)

Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSCIS trial

Kristin B Highland, Oliver Distler*, Masataka Kuwana, Yannick Allanore, Shervin Assassi, Arata Azuma, Arnaud Bourdin, Christopher P Denton, Jörg H W Distler, Anna Maria Hoffmann-Vold, Dinesh Khanna, Maureen D Mayes, Ganesh Raghu, Madelon C Vonk, Martina Gahlemann, Emmanuelle Clerisme-Beaty, Mannaig Girard, Susanne Stowasser, Donald Zoz, Toby M Maher, on behalf of the SENSCIS trial investigators†*



Συνεργικό αποτέλεσμα MMF + Nintedanib?

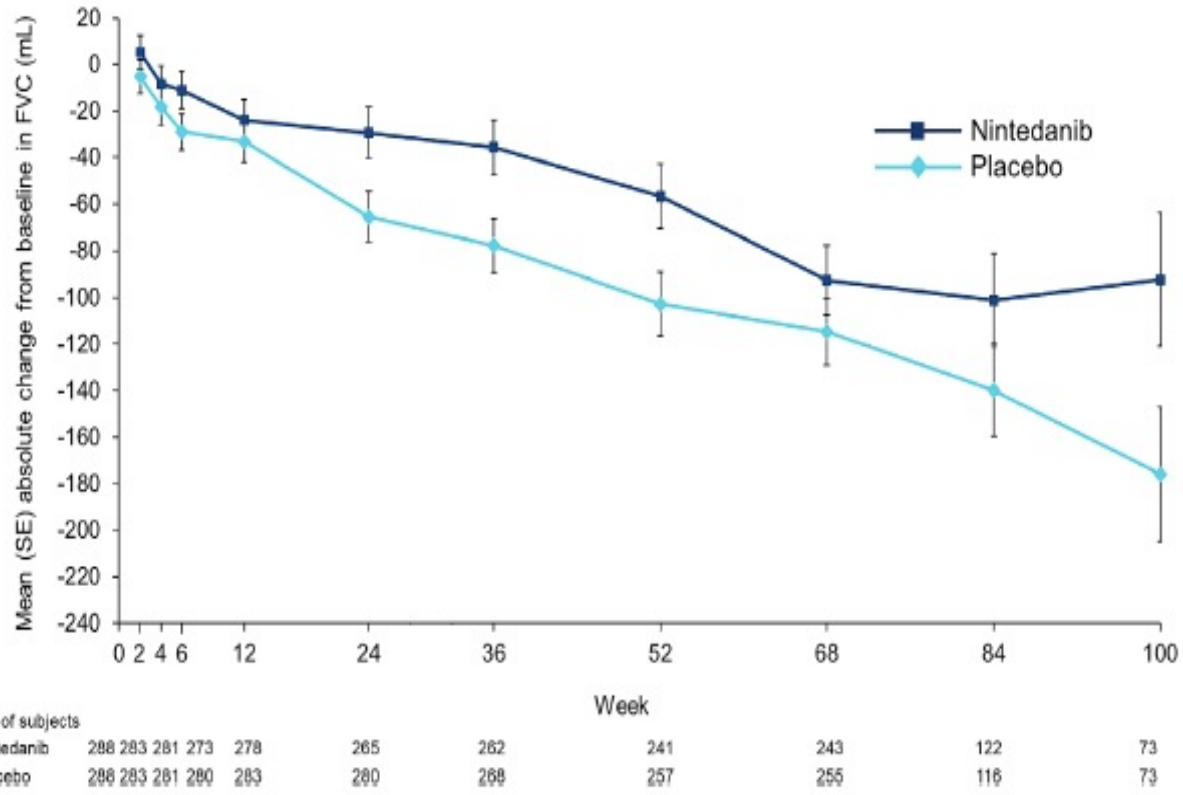
Highland K., et al., The Lancet Respiratory Medicine, 2021, 9 (1), pp.96-106

ACR Open Rheumatology
Vol. 4, No. 10, October 2022, pp 837–844
DOI 10.1002/acr2.11483

American College of Rheumatology
Empowering Rheumatology Professionals

Effect of Nintedanib on Progression of Systemic Sclerosis-Associated Interstitial Lung Disease Over 100 Weeks: Data From a Randomized Controlled Trial

2 χρόνια



OPEN ACCESS

CLINICAL SCIENCE

Continued treatment with nintedanib in patients with systemic sclerosis-associated interstitial lung disease: data from SENSCIS-ON

Yannick Allanore [1], Madelon C Vonk [2], Oliver Distler [3], Arata Azuma,[4] Maureen D Mayes,[5] Martina Gahlemann,[6] Alexandra James,[7] Veronika Kohlbrenner,[8] Margarida Alves,[9] Dinesh Khanna [10], Kristin B Highland,[11] on behalf of the SENSCIS-ON trial investigators

3ος χρόνος

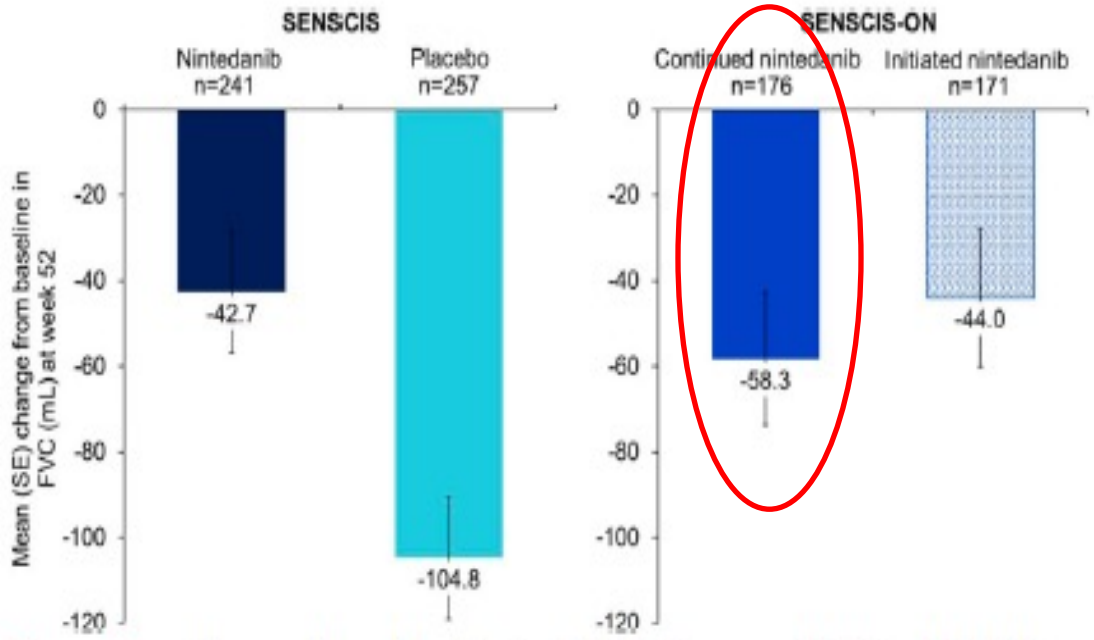


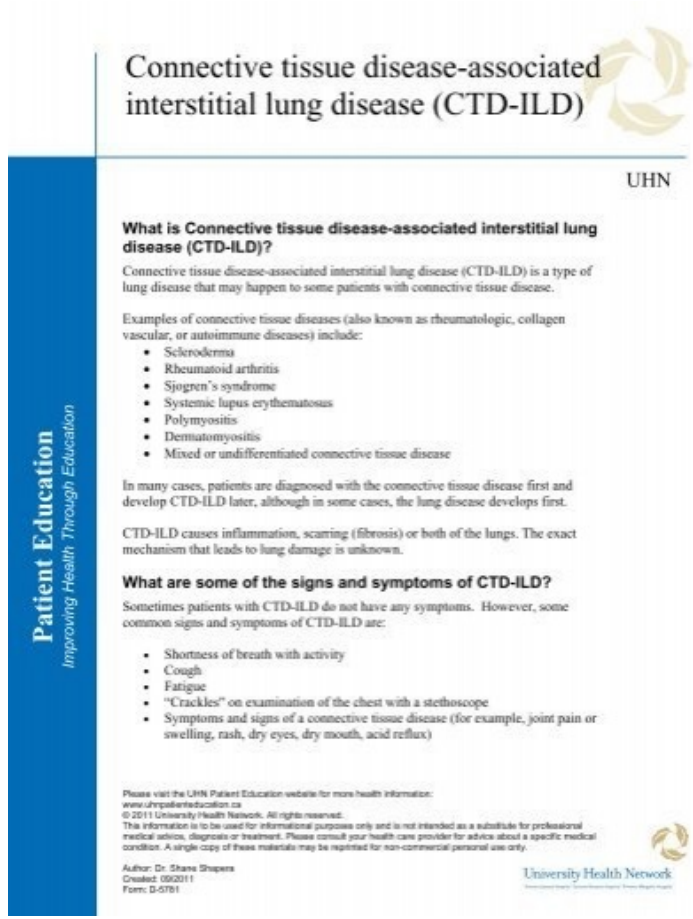
Figure 2 Change from baseline in FVC (mL) at week 52 in SENSCIS and SENSCIS-ON. Changes were based on data from patients with available data at baseline and at week 52. FVC, forced vital capacity.

Assassi S, et al. ACR Open Rheumatology Oct 2022

Allanore Y, et al. Ann Rheum Dis 2022;81:1722–1729

Μη Φαρμακευτικές Παρεμβάσεις

- Patient education
- Vaccinations (COVID-19, flu, pneumococcal etc)
- Pulmonary rehabilitation
- LTOT (if spO2<88% or desaturation on 6MWT)
- Manage GERD and other comorbidities



Connective tissue disease-associated interstitial lung disease (CTD-ILD)

UHN

Patient Education
Improving Health Through Education

What is Connective tissue disease-associated interstitial lung disease (CTD-ILD)?

Connective tissue disease-associated interstitial lung disease (CTD-ILD) is a type of lung disease that may happen to some patients with connective tissue disease.

Examples of connective tissue diseases (also known as rheumatologic, collagen vascular, or autoimmune diseases) include:

- Scleroderma
- Rheumatoid arthritis
- Sjogren's syndrome
- Systemic lupus erythematosus
- Polymyositis
- Dermatomyositis
- Mixed or undifferentiated connective tissue disease

In many cases, patients are diagnosed with the connective tissue disease first and develop CTD-ILD later, although in some cases, the lung disease develops first.

CTD-ILD causes inflammation, scarring (fibrosis) or both of the lungs. The exact mechanism that leads to lung damage is unknown.

What are some of the signs and symptoms of CTD-ILD?

Sometimes patients with CTD-ILD do not have any symptoms. However, some common signs and symptoms of CTD-ILD are:

- Shortness of breath with activity
- Cough
- Fatigue
- "Crackles" on examination of the chest with a stethoscope
- Symptoms and signs of a connective tissue disease (for example, joint pain or swelling, rash, dry eyes, dry mouth, acid reflux)

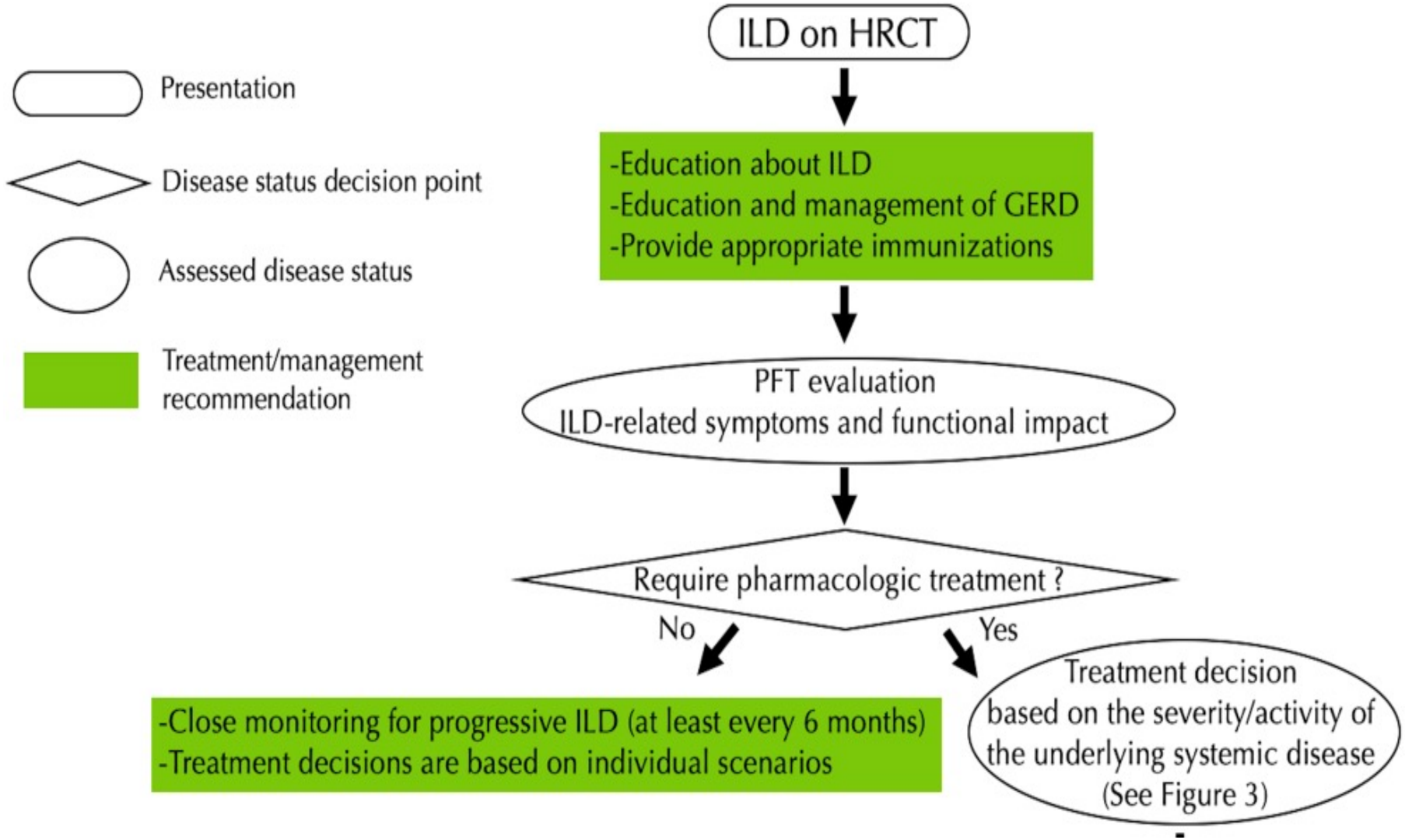
Please visit the UHN Patient Education website for more health information:
www.uhnpatienteducation.ca

Author: Dr. Shane Shapera
Created: 09/2011
Form: D-5781

University Health Network

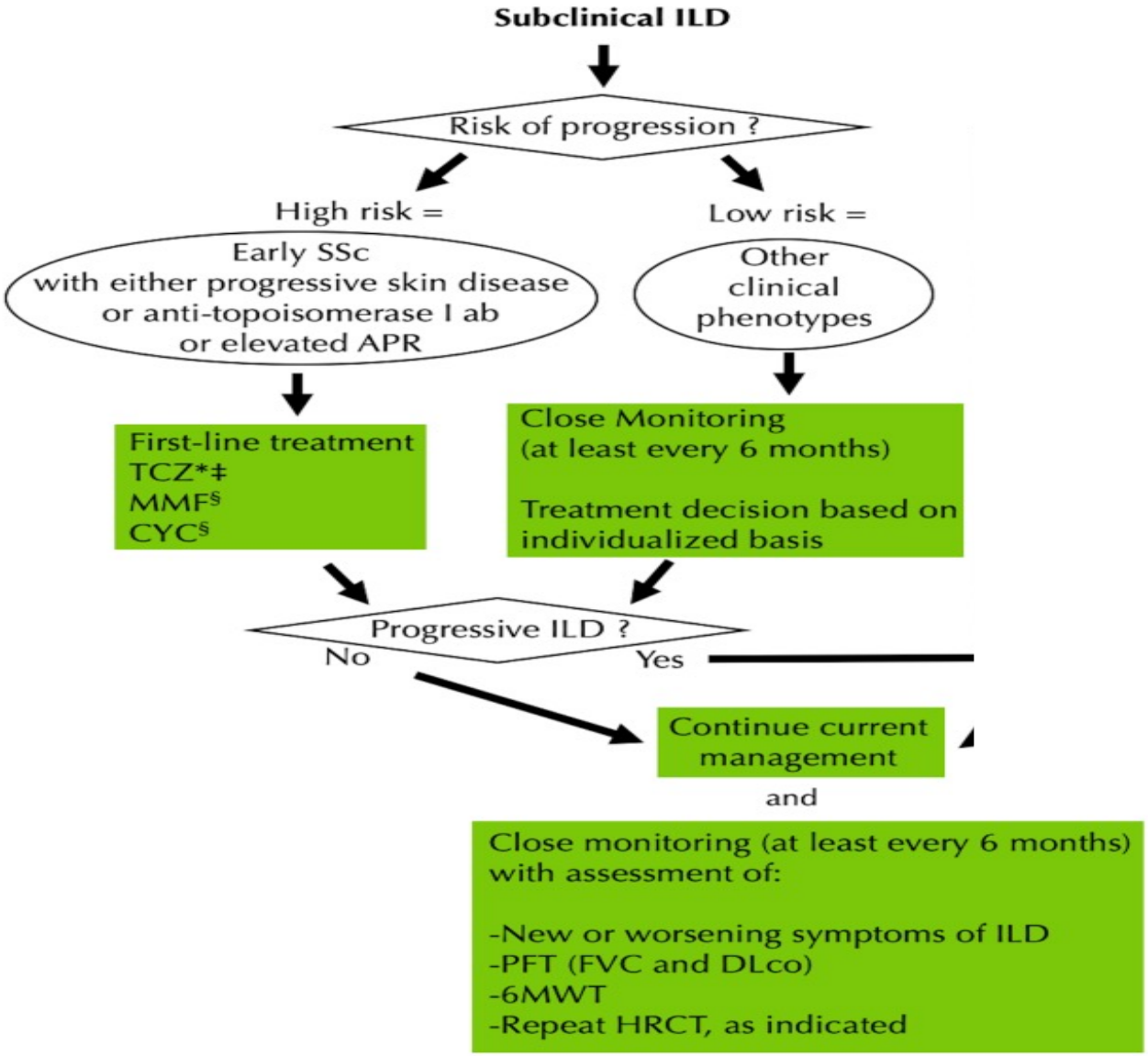
Khanna D., et al., Arthritis and Rheumatology 2022, 74 (1), pp.13-27

Θεραπευτικός Αλγόριθμος: SScl-ILD



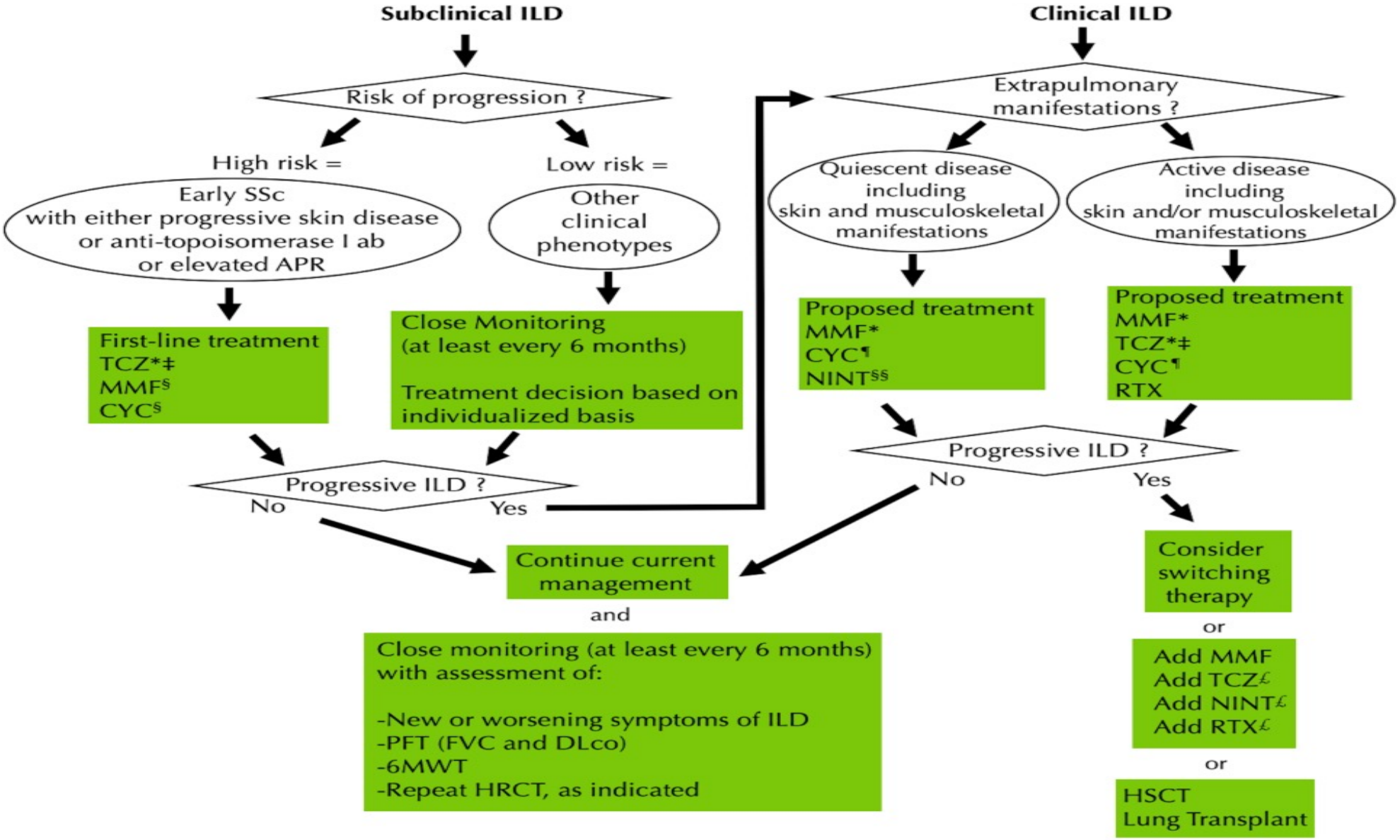
Khanna D., et al., Arthritis and Rheumatology 2022, 74 (1), pp.13-27

Θεραπευτικός Αλγόριθμος: SScI-ILD



Khanna D., et al., Arthritis and Rheumatology 2022, 74 (1), pp.13-27

Θεραπευτικός Αλγόριθμος: SScI-ILD



Khanna D., et al., Arthritis and Rheumatology 2022, 74 (1), pp.13-27

SScl-ILD –Παρακολούθηση

ΜΗΝ χάνετε χρόνο!
1. **Πρώιμη έναρξη θεραπείας**
2. **Τακτική Αξιολόγηση (3-4 mo)**
3. **Τροποποίηση της αγωγής**

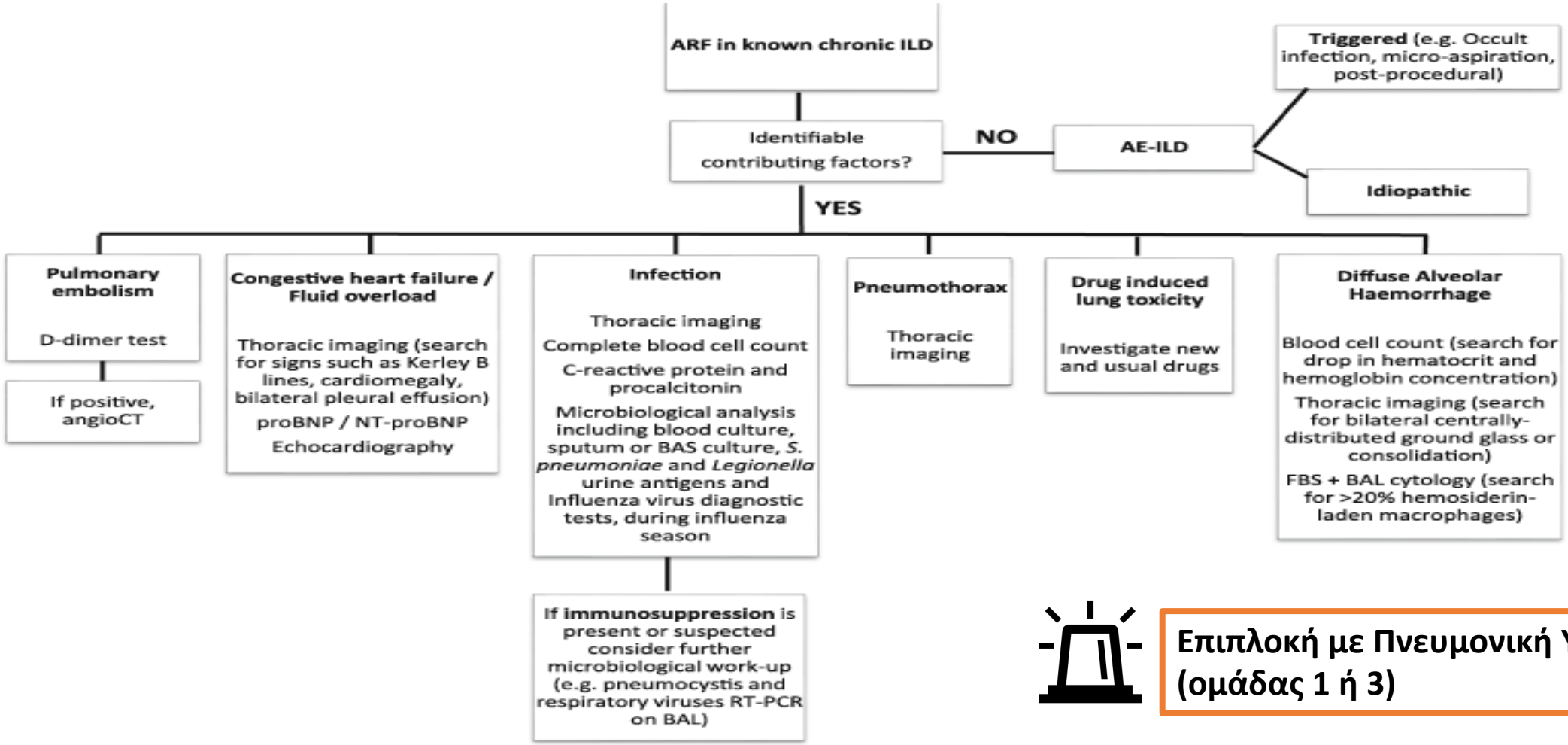
1. **Σπιρομέτρηση- Διάχυση**
   - **Ευαίσθητο** τεστ για follow-up
   - Συχνότητα ανά **3**-6 μήνες ανάλογα την περίπτωση
   - Κλινικά σημαντική επιδείνωση:
     - **FVC ≤ 5% ή/και DLCO ≤ 10% εντός έτους[1,2]**

2. **HRCT**
   - Συνήθως επί κλινικής επιδείνωσης
   - Συχνότητα ανά >12 μήνες

3. **Άλλες δοκιμασίες** (π.χ. 6MWT, ABG, **Echo**)

[1]Khanna D et al. J Rheumatol 2015
[2] Goh NS et al, Arthritis&Rheumatol 2017

Οξεία Αναπνευστική Επιδείνωση κατά το follow-up



Επιπλοκή με Πνευμονική Υπέρταση (ομάδας 1 ή 3)

Faverio et al. BMC Pulmonary Medicine (2018)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease

PH λόγω ILD – INCREASE study

- RCT με 326 ασθενείς με PH ομάδας 3 λόγω ILD (22.1% CTD-ILD) → inh Treprostenil vs PBO

- **Αποτελέσματα:**
  - **Βελτίωση 6MWD στους 4 μήνες (p<0.01)**
  - Μείωση NT-proBNP (p<0.01)
  - **Μείωση 39% στην κλινική επιδείνωση (p =0.04)**
  - **Μείωση στον κίνδυνο έξαρσης υποκείμενης ILD (43 [26.4%] vs.63 [38.7%]; P = 0.02)**
  - **Παρόμοια επίπτωση SAEs**

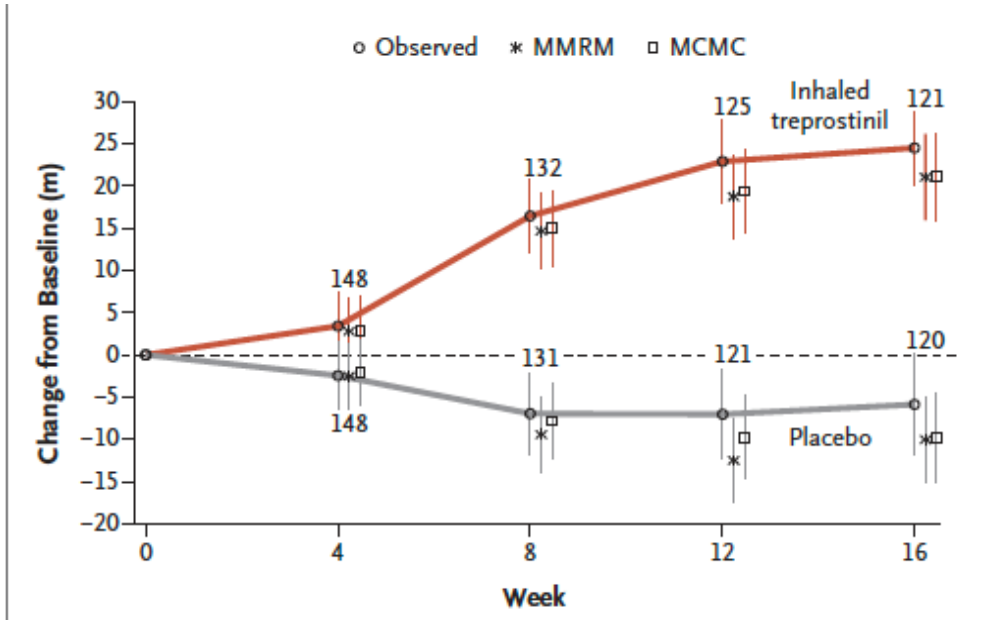
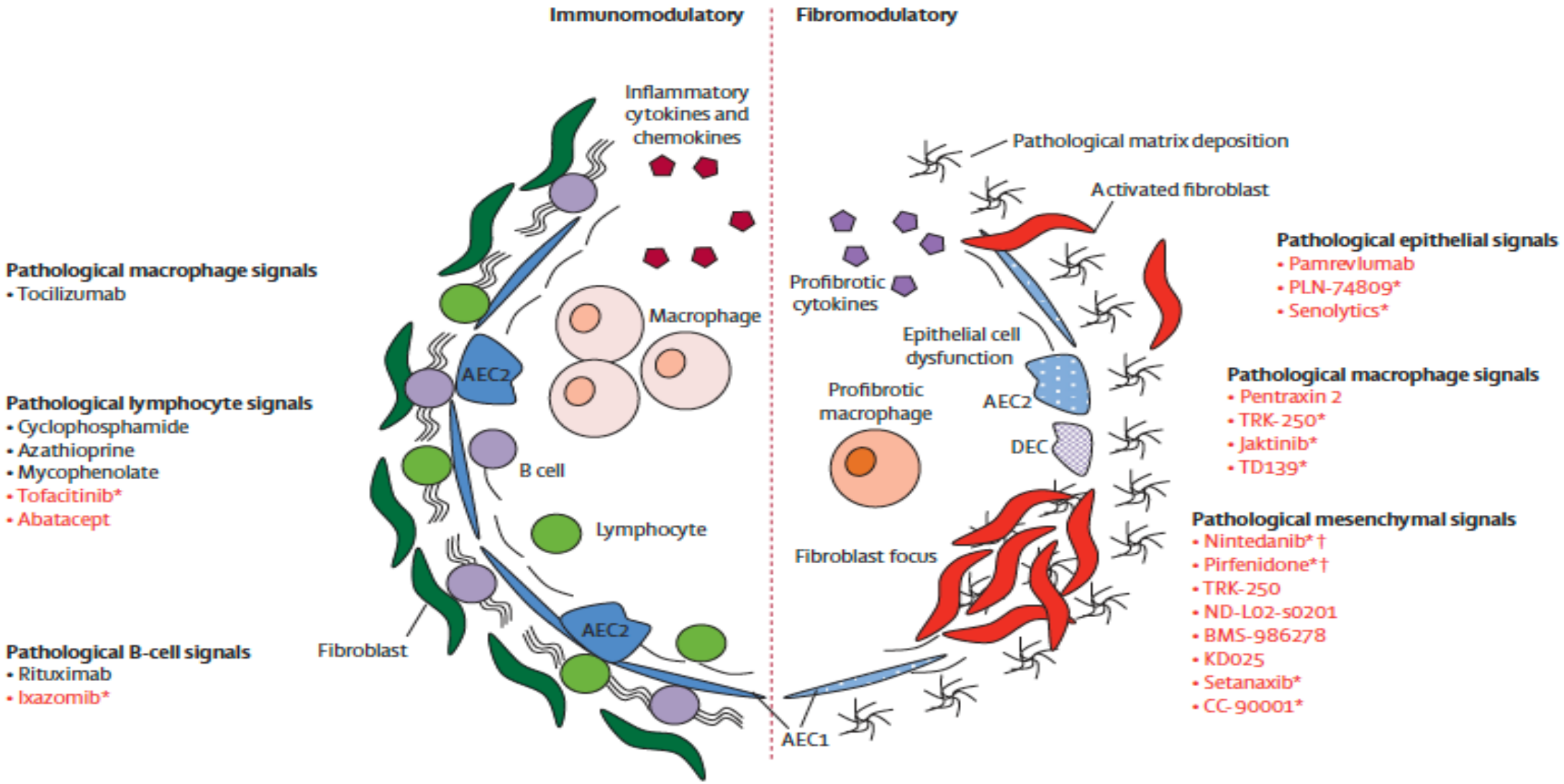


Figure 2. Mean Change from Baseline in Peak 6-Minute Walk Distance through Week 16.

Εισπνεόμενη Τρεπροστενίλη φαίνεται αποτελεσματική στην κατηγορία ασθενών με PH ομάδας 3

Waxman A et al. N Eng J Med 2021; 384:4

Νέοι θεραπευτικοί στόχοι?



Kerri A Johannson et al, The Lancet Respiratory Medicine Series 2021

SLS III: MMF + Pirferidone vs MMF +PBO

ABSTRACT NUMBER: 0520

Combination Therapy of Mycophenolate Mofetil and Pirfenidone vs. Mycophenolate Alone: Results from the Scleroderma Lung Study III

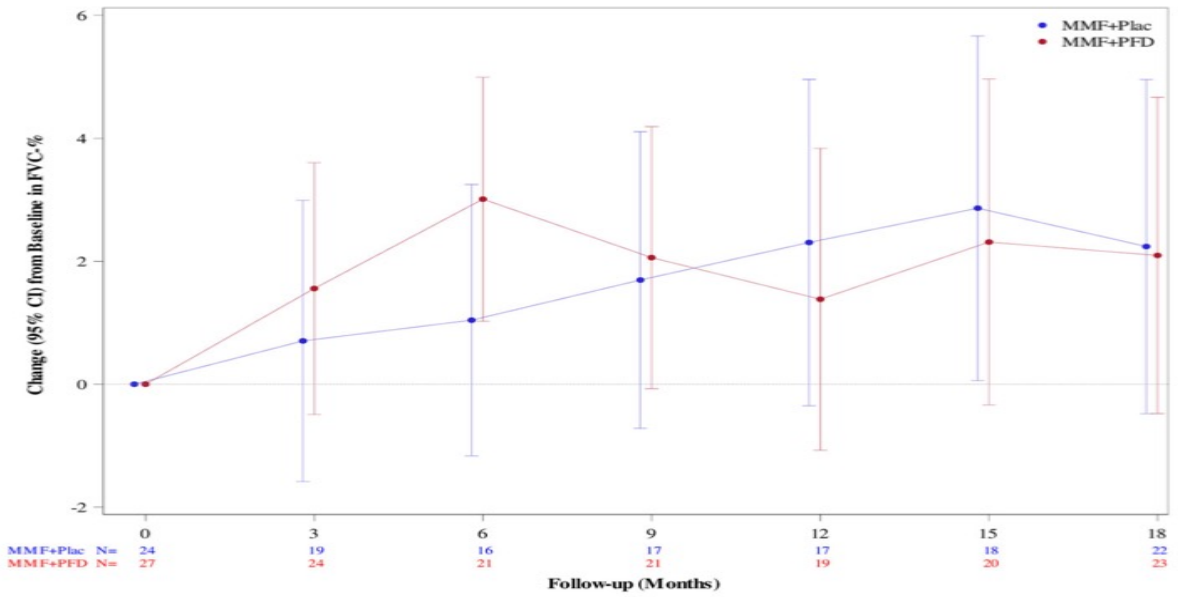
Dinesh Khanna[1], Cathie Spino[2], Elana Bernstein[3], Jonathan Goldin[4], Donald Tashkin[4], Michael roth[4] and On Behalf of SLS III Investigators[2], [1]Division of Rheumatology, Department of Internal Medicine, Scleroderma Program, University of Michigan, Ann Arbor, MI, [2]University of Michigan, Ann Arbor, MI, [3]Columbia University, New York, NY, [4]University of California Los Angeles, Los Angeles, CA

Meeting: ACR Convergence 2022

Keywords: clinical trial, interstitial lung disease, Systemic sclerosis

51 randomized -*Recruitment was prematurely stopped due to COVID-19 and the impact of prior drug treatment on eligibility*

Fig 1: Change in FVC% over 18 months. Estimates are based on a linear mixed effects model, adjusting for prior MMF exposure and baseline FVC%.

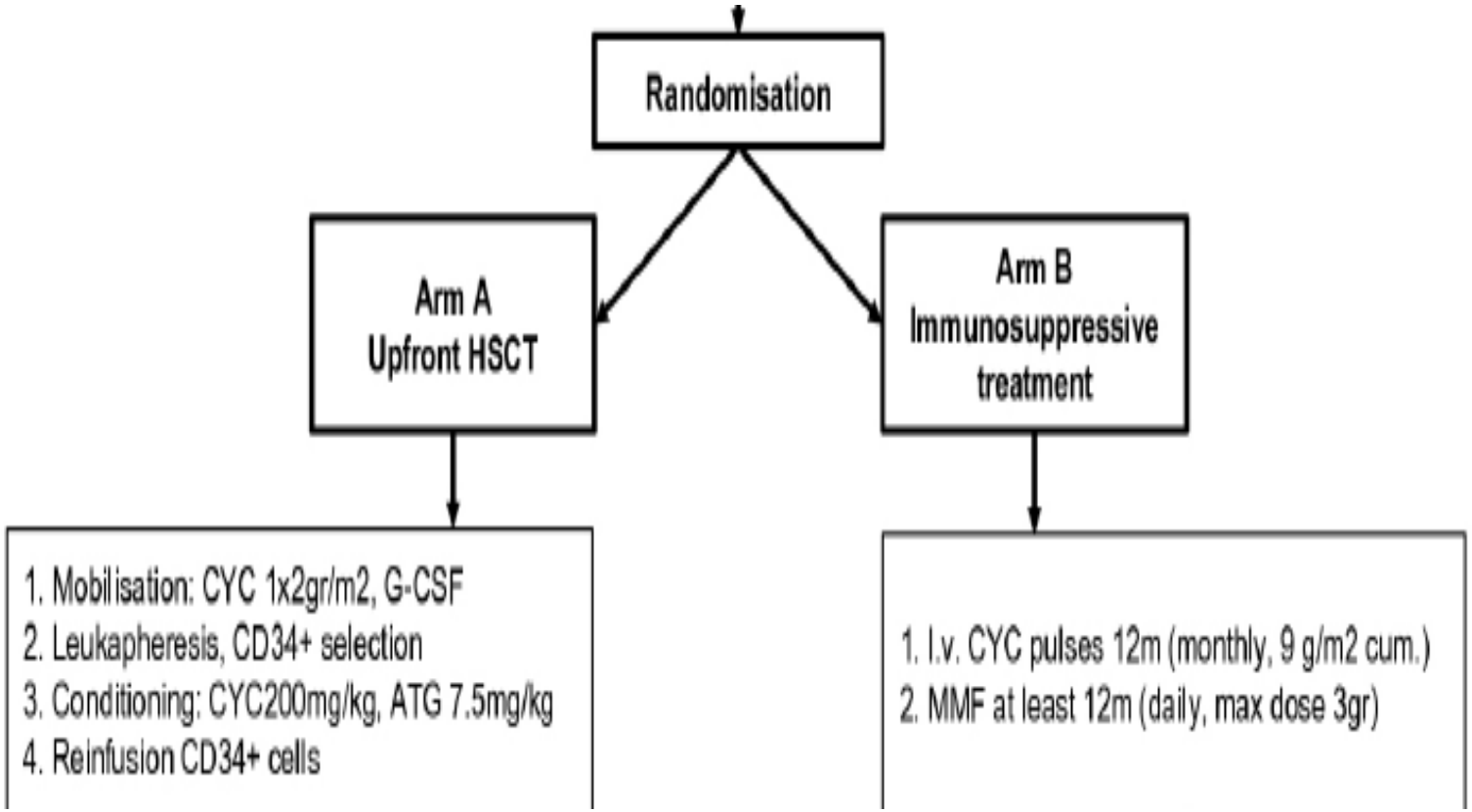


Conclusions:

- Upfront combination therapy (MMF+PFD) more rapid improvement in the FVC% (0-6 mo) but with a similar overall improvement over 18 mo
- Changes in HRCT outcomes and patient-reported outcomes tended to favor MMF+PFD

BMJ Open

A randomised, open-label trial to assess the optimal treatment strategy in early diffuse cutaneous systemic sclerosis: the UPSIDE study protocol



Spierings J, et al. BMJ Open 2021;

Συμπεράσματα

- **Απαραίτητη συνεργασία** με Πνευμονολόγο, Ακτινολόγο.

- **Screening σε όλους τους ασθενείς με SScl**

- **Εξατομικευμένη** θεραπευτική προσέγγιση:

  - **Ανοσοτροποιητικά:** ισχυρά δεδομένα για **MMF, CY, RTX, TCZ**

  - **Αντι-ινωτικά – Nintedanib: πρώιμη χορήγηση σε όλους τους ασθενείς** ειδικά με προοδευτικό φαινότυπο

- Αναμένονται σημαντικές δημοσιεύσεις στο εγγύς μέλλον (νέα φάρμακα, συνδυαστική θεραπεία κα)

Ευχαριστώ για την προσοχή σας!