

## **Συστηματική σκληροδερμία Συνδυαστική θεραπεία και εξατομικευμένη θεραπευτική προσέγγιση**

Δαούσης Δημήτρης

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Αντιπρόεδρος Ελληνικής Ρευματολογικής Εταιρείας (ΕΡΕ-ΕΠΕΡΕ)

# Σύγκρουση συμφερόντων

- Τιμητική αμοιβή για ομιλίες και συμμετοχή σε advisory boards από τις εταιρείες UCB, Pfizer, Novartis, BMS, MSD, Janssen, Abbvie, Lilly, Aenorasis, Boehringer, Astra Zeneca, GSK

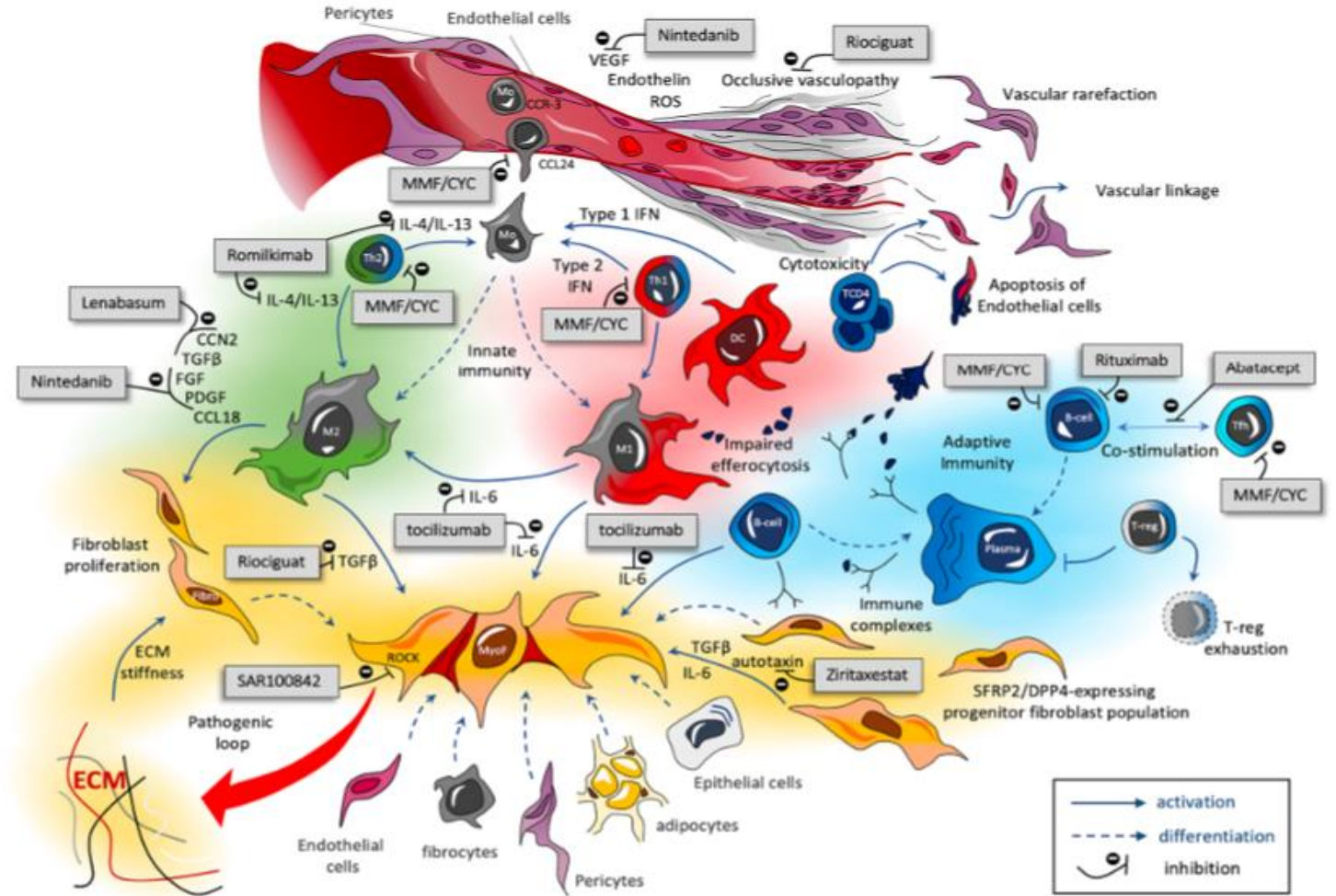
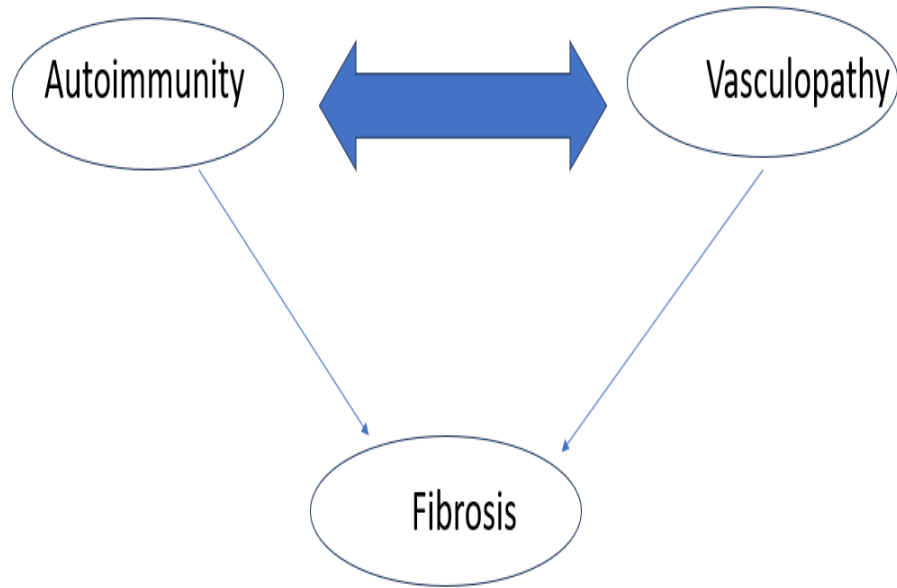
# ΘΕΡΑΠΕΙΑ

Διάμεση πνευμονοπάθεια-Τι εργαλεία διαθέτουμε....

- **Μυκοφαινολική μοφετίλη**
- Κυκλοφωσφαμίδη
- Nintedanib
- Rituximab-αντίσωμα έναντι Β λεμφοκυττάρων
- Αναστολέας της IL-6 (tocilizumab)
- Αυτόλογη μεταμόσχευση αρχέγονων αιμοποιητικών κυττάρων.

### Therapeutic Approaches to Systemic Sclerosis: Recent Approvals and Future Candidate Therapies

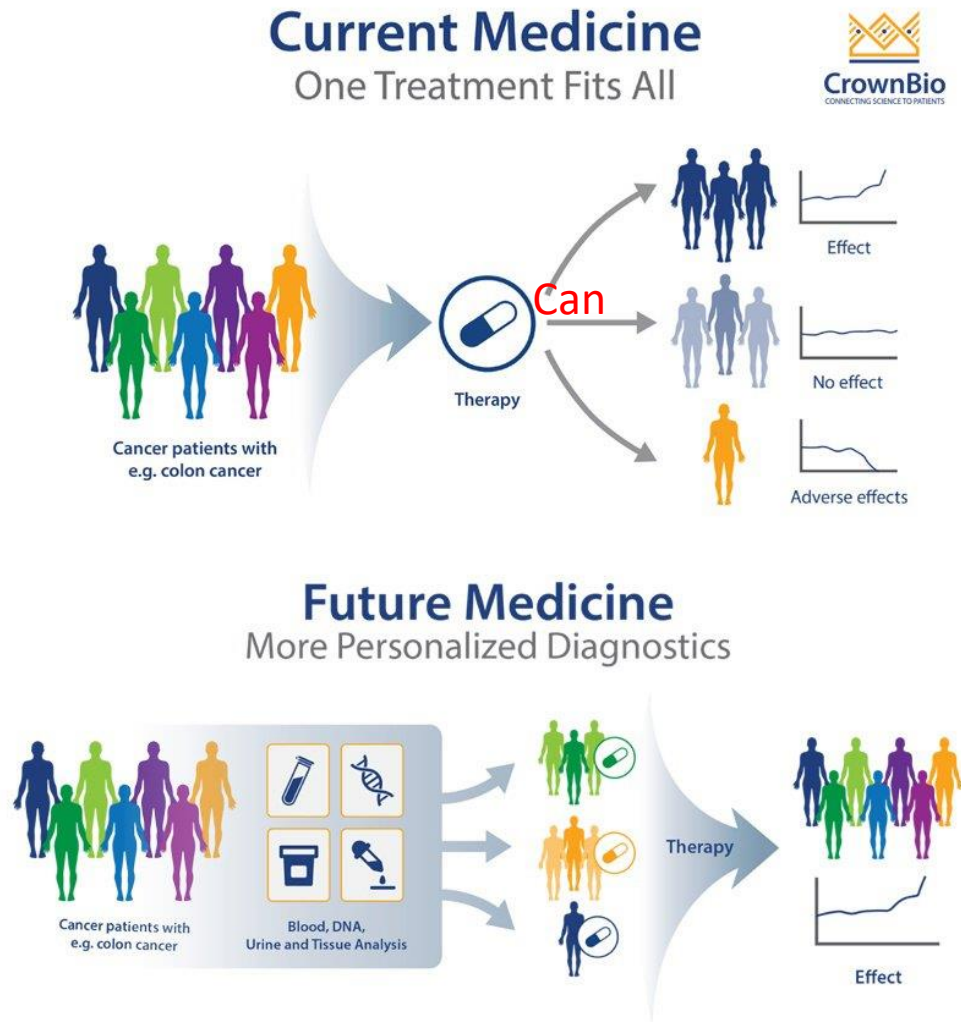
Alain Lescoat<sup>1,2,3,4</sup> · David Roofeh<sup>3,4</sup> · Masataka Kuwana<sup>5</sup> · Robert Lafyatis<sup>6</sup> · Yannick Allanore<sup>7,8,9</sup> · Dinesh Khanna<sup>3,4</sup>



# Θεραπευτικές στρατηγικές υπό εξέλιξη....

- Εξατομικευμένη ιατρική
- Συνδυαστική θεραπεία-Θεραπεία πολλαπλών στόχων

# Precision/Personalized medicine



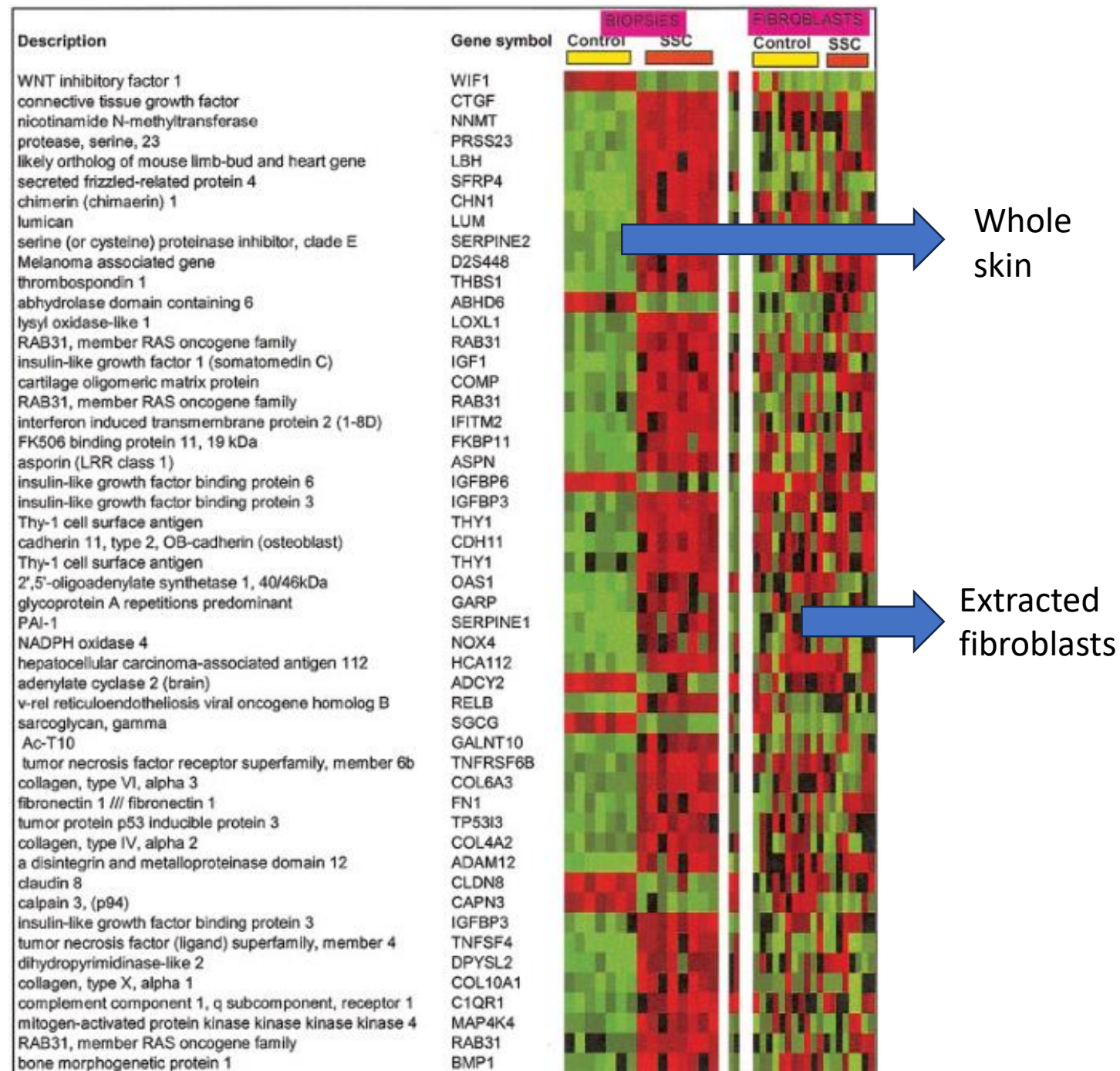
- Not all pts with a chronic disease have the “same disease”
- Use of biomarkers (soluble markers, histology, gene expression...) to identify patient subgroups that are more likely to respond to a specific treatment

# Can skin gene expression analysis help?

- Profound differences between scleroderma and normal skin

Gene Profiling of Scleroderma Skin Reveals Robust Signatures of Disease That Are Imperfectly Reflected in the Transcript Profiles of Explanted Fibroblasts

Humphrey Gardner,<sup>1</sup> Jeffrey R. Shearstone,<sup>1</sup> Raj Bandaru,<sup>1</sup> Tom Crowell,<sup>1</sup> Matthew Lynes,<sup>1</sup> Maria Trojanowska,<sup>2</sup> Jaspreet Pannu,<sup>2</sup> Edwin Smith,<sup>2</sup> Stefania Jablonska,<sup>3</sup> Maria Blaszczyk,<sup>3</sup> Filemon K. Tan,<sup>4</sup> and Maureen D. Mayes<sup>4</sup>



RESEARCH ARTICLE

# Experimentally-Derived Fibroblast Gene Signatures Identify Molecular Pathways Associated with Distinct Subsets of Systemic Sclerosis Patients in Three Independent Cohorts

Michael E. Johnson<sup>1</sup>, J. Matthew Mahoney<sup>1</sup>, Jaclyn Taroni<sup>1</sup>, Jennifer L. Sargent<sup>1</sup>, Eleni Marmarelis<sup>1</sup>, Ming-Ru Wu<sup>1</sup>, John Varga<sup>2</sup>, Monique E. Hinchcliff<sup>2</sup>, Michael L. Whitfield<sup>1\*</sup>



- Not all patients with SSc have the same skin gene expression

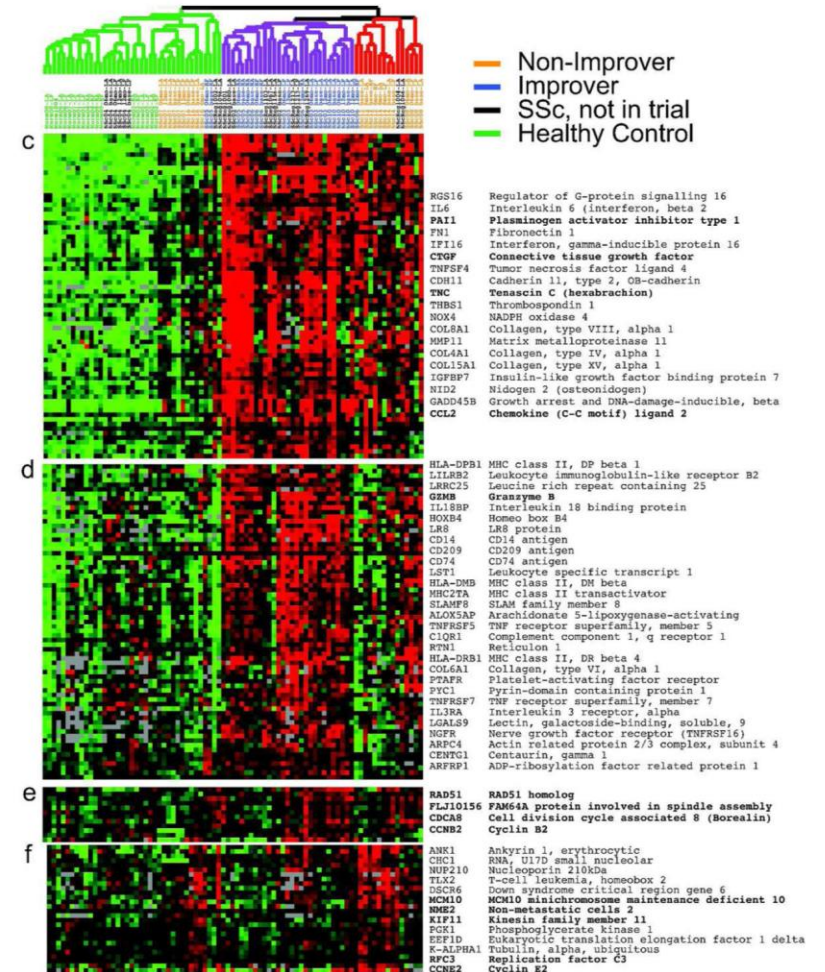


- 4 different signatures in scleroderma skin
  - Fibroproliferative
  - Inflammatory
  - Limited
  - Normal-like



## Molecular Signatures in Skin Associated with Clinical Improvement During Mycophenolate Treatment in Systemic Sclerosis

- Pts with the inflammatory signature respond better to MMF



## Peripheral blood gene expression profiling shows predictive significance for response to mycophenolate in systemic sclerosis-related interstitial lung disease

Shervin Assassi <sup>1</sup>, Elizabeth R Volkman <sup>2</sup>, W Jim Zheng,<sup>3</sup> Xuan Wang,<sup>4</sup> Holly Wilhalme,<sup>2</sup> Marka A Lyons,<sup>1</sup> Michael D Roth,<sup>2</sup> Donald P Tashkin<sup>2</sup>

**Table 5** Predictive significance of baseline annotated modular scores for improvement in FVC% (as a dichotomised variable) at 12 months in the MMF arm

| Module | Annotation               | OR   | 95% CI        | P value |
|--------|--------------------------|------|---------------|---------|
| M5.10  | Mitochondria/proteasome  | 3.68 | 1.09 to 12.44 | 0.0358  |
| M6.12  | Lymphoid lineage         | 3.63 | 1.21 to 10.89 | 0.0215  |
| M6.9   | Lymphoid lineage         | 2.9  | 1.16 to 7.26  | 0.0233  |
| M4.3   | Protein synthesis        | 2.23 | 1.05 to 4.71  | 0.0359  |
| M3.2   | Myeloid lineage          | 0.48 | 0.24 to 0.98  | 0.0444  |
| M4.13  | Inflammation             | 0.46 | 0.23 to 0.92  | 0.0277  |
| M5.7   | Myeloid lineage          | 0.4  | 0.17 to 0.92  | 0.0313  |
| M6.20  | Neutrophils/granulocytes | 0.36 | 0.16 to 0.8   | 0.0124  |
| M5.14  | Myeloid lineage          | 0.35 | 0.16 to 0.78  | 0.0105  |

FVC%, per cent predicted forced vital capacity; MMF, mycophenolate mofetil.

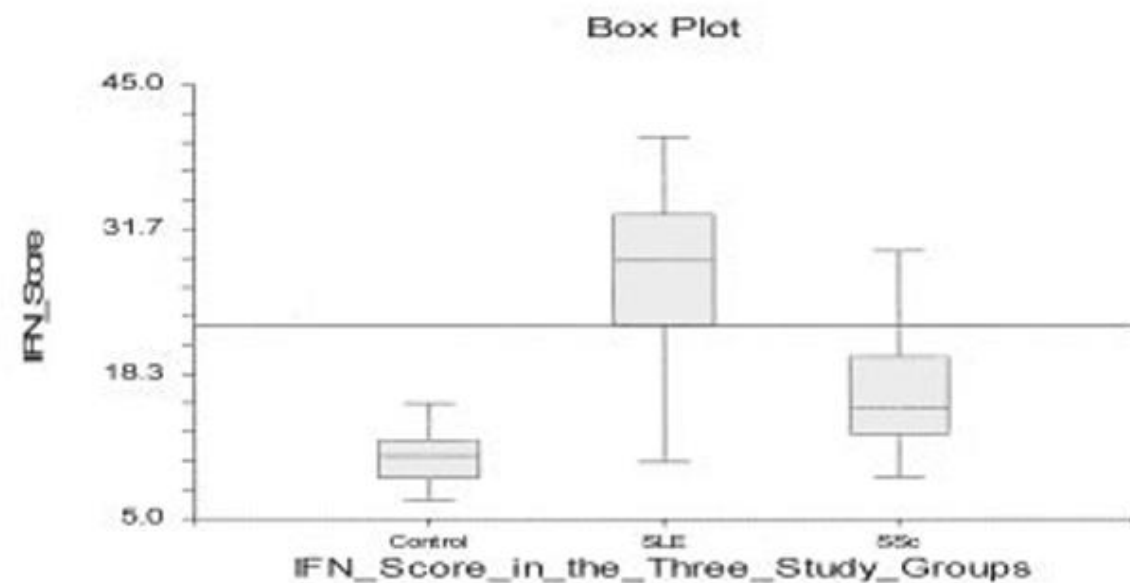
**Conclusion** Consistent with the primary mechanism of action of MMF on lymphocytes, patients with SSc-ILD with higher baseline lymphoid module scores had better FVC% course, while those with higher myeloid cell lineage activation score had poorer FVC% course on MMF.

# Systemic Sclerosis and Lupus

## Points in an Interferon-Mediated Continuum

Shervin Assassi,<sup>1</sup> Maureen D. Mayes,<sup>1</sup> Frank C. Arnett,<sup>1</sup> Pravitt Gourh,<sup>1</sup> Sandeep K. Agarwal,<sup>1</sup>  
Terry A. McNearney,<sup>2</sup> Damien Chaussabel,<sup>3</sup> Nancy Oommen,<sup>3</sup> Michael Fischbach,<sup>4</sup>  
Kairav R. Shah,<sup>1</sup> Julio Charles,<sup>1</sup> Virginia Pascual,<sup>3</sup> John D. Reveille,<sup>1</sup> and Filemon K. Tan<sup>1</sup>

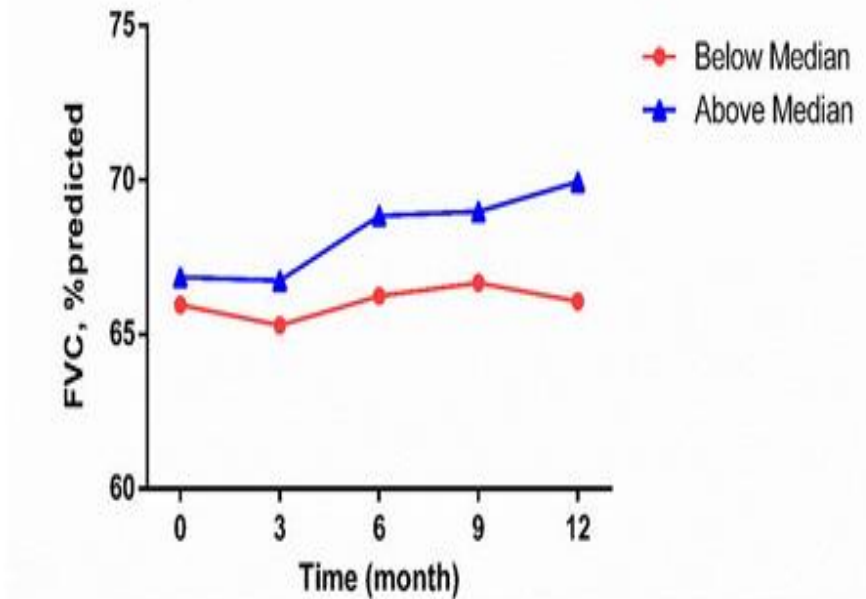
- Η «σφραγιδα της ιντερφερονης»  
υπαρχει και στο σκληροδερμα



## Predictive Significance of Serum Interferon Inducible Protein Score for Response to Treatment in Systemic Sclerosis Related Interstitial Lung Disease

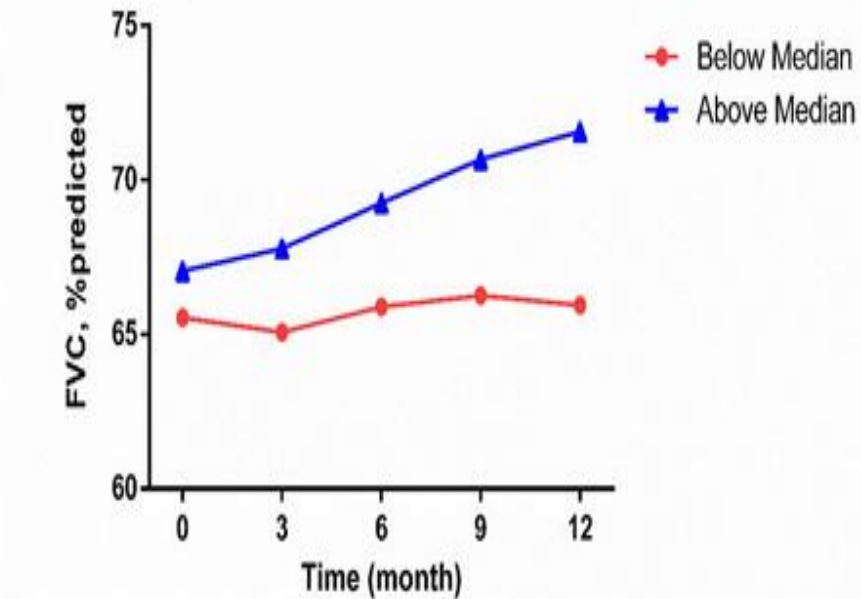
A

MMF arm, by median of IFN Inducible Protein Score

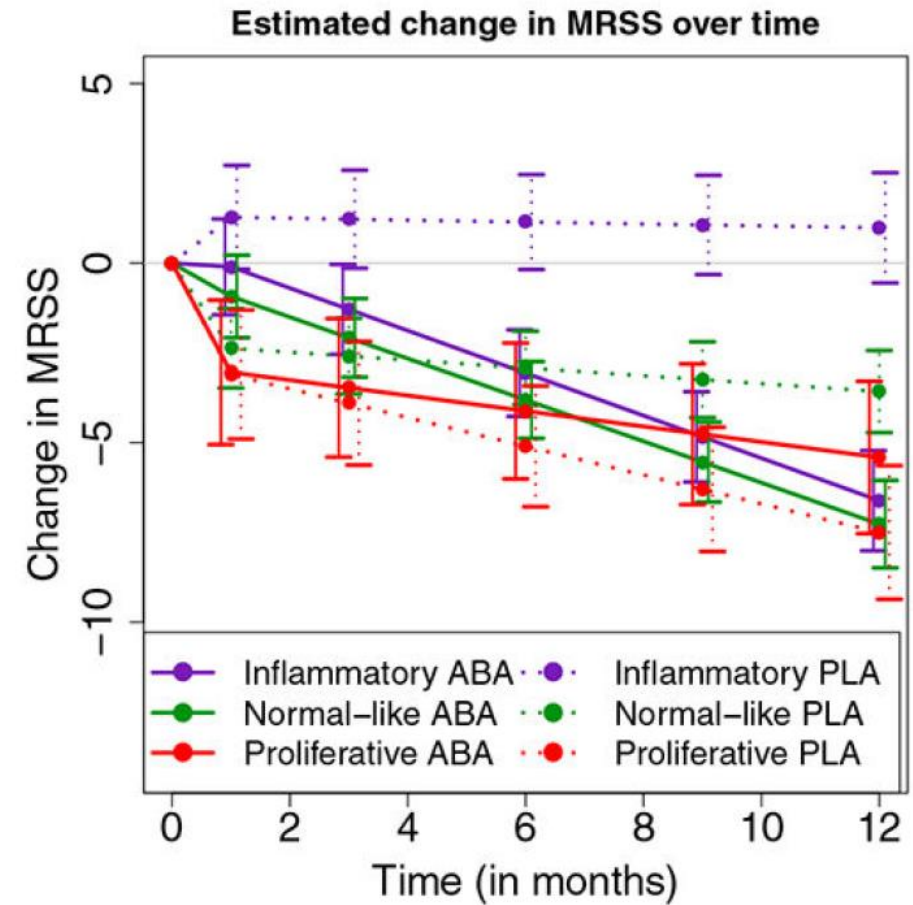
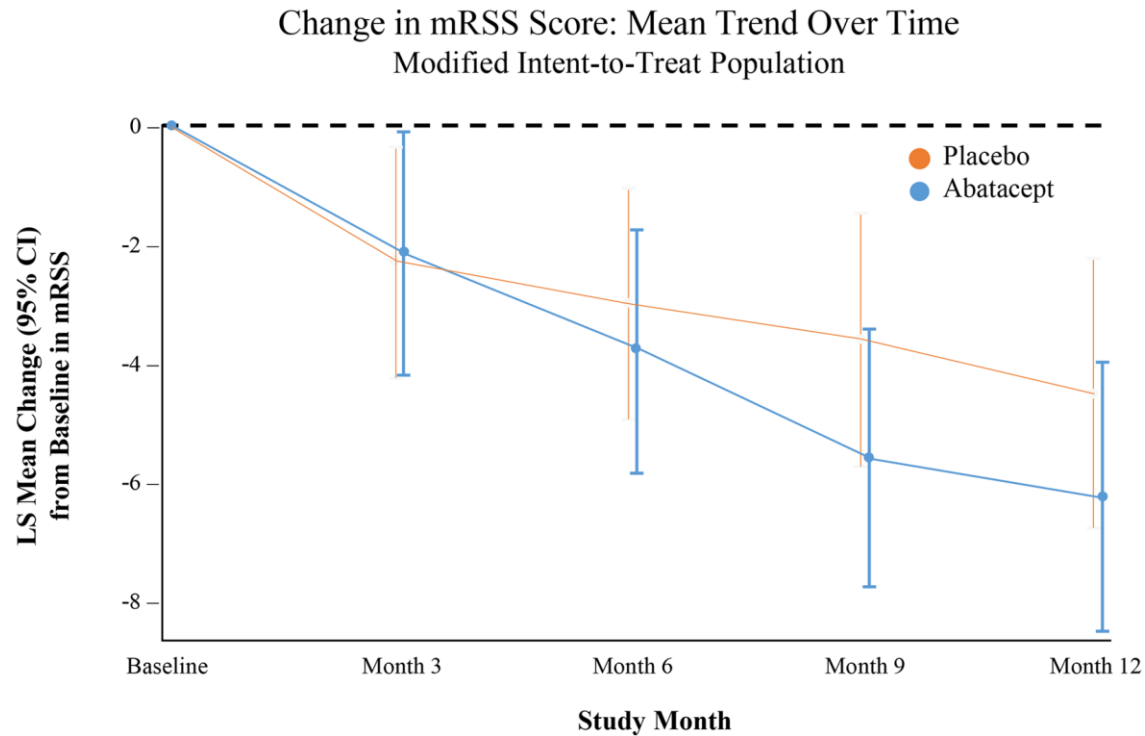


B

CYC arm, by median of IFN Inducible Protein Score



# Η ιστορία μιας «αποτυχημένης» κλινικής μελέτης.....



Published in final edited form as:  
*Arthritis Rheumatol.* 2020 January ; 72(1): 125–136. doi:10.1002/art.41055.

**Abatacept in Early Diffuse Cutaneous Systemic Sclerosis –  
Results of a Phase 2 Investigator-Initiated, Multicenter, Double-  
Blind Randomized Placebo-Controlled Trial**

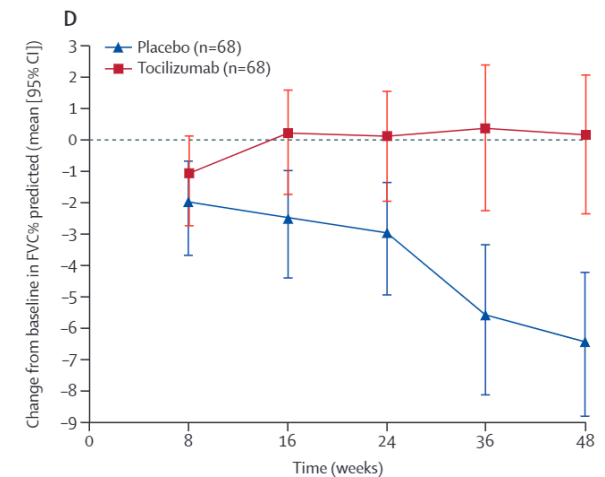
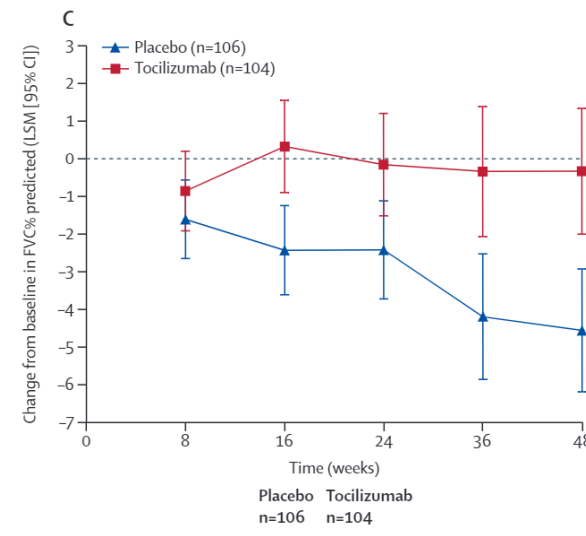
# Και η ιστορία μιας επιτυχημένης μελέτης....

- Κριτήριο εισόδου η παρουσία φλεγμονώδους απάντησης
- Θα είχε άραγε θετικά αποτελέσματα η μελέτη αν δεν ήταν «εμπλουτισμένη» με τέτοιους ασθενείς?

## 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†



# Θα μπορούσαν τα αυτοαντισώματα να βοηθήσουν?

Systemic sclerosis

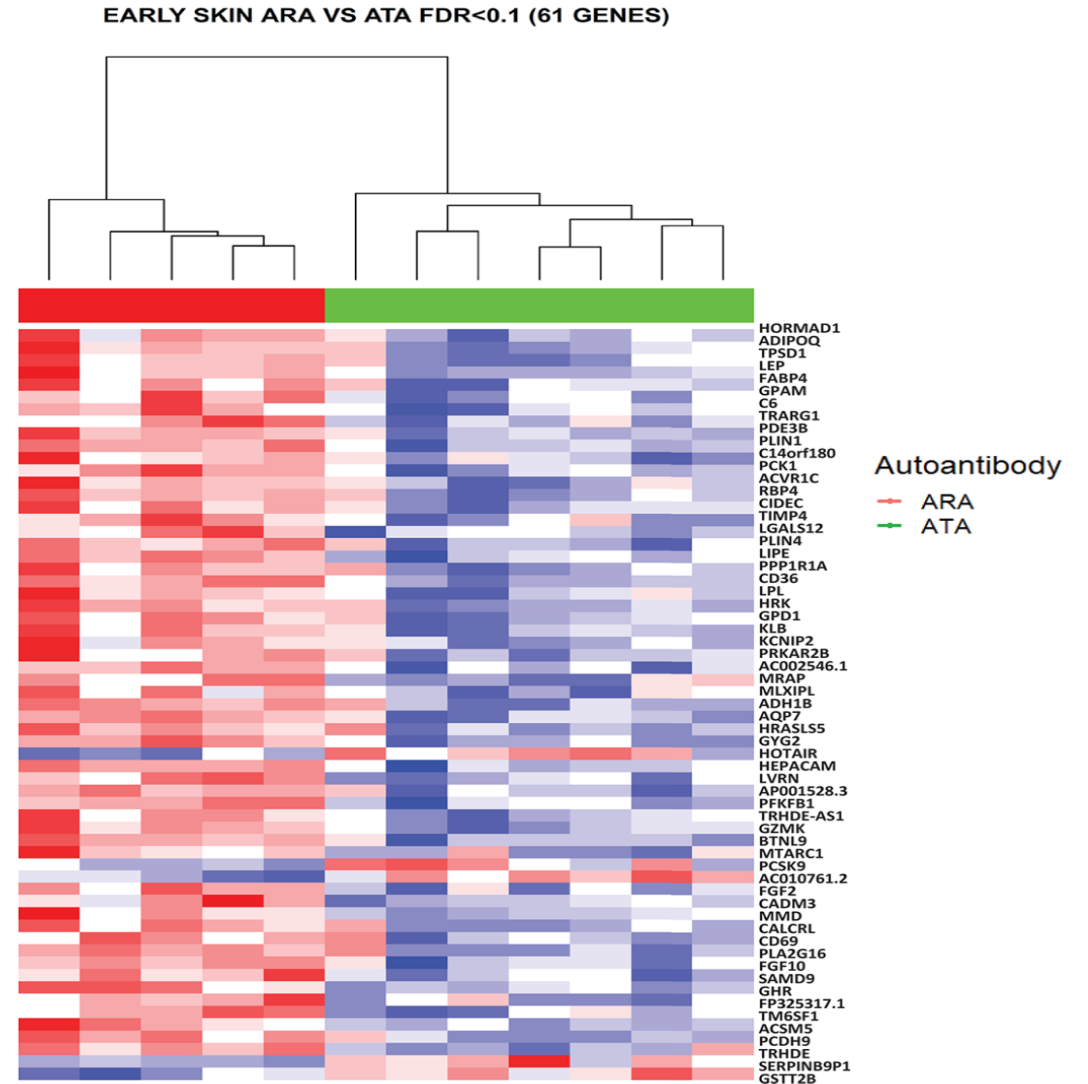
TRANSLATIONAL SCIENCE

## Molecular basis for clinical diversity between autoantibody subsets in diffuse cutaneous systemic sclerosis

Kristina Elizabeth Neergaard Clark <sup>1</sup>, Corrado Campochiaro,<sup>1</sup> Eszter Csomor,<sup>2</sup> Adam Taylor,<sup>2</sup> Katherine Nevin,<sup>2</sup> Nicholas Galwey,<sup>2</sup> Mary A Morse,<sup>2</sup> Jennifer Singh,<sup>2</sup> Yee Voan Teo,<sup>2</sup> Voon H Ong,<sup>1</sup> Emma Derrett-Smith,<sup>1</sup> Nicolas Wisniacki,<sup>2</sup> Shaun M Flint,<sup>2</sup> Christopher P Denton <sup>1</sup>

- Γνωστό από παλιά ότι καθορίζουν σε κάποιο βαθμό τον κλινικό φαινότυπο

C

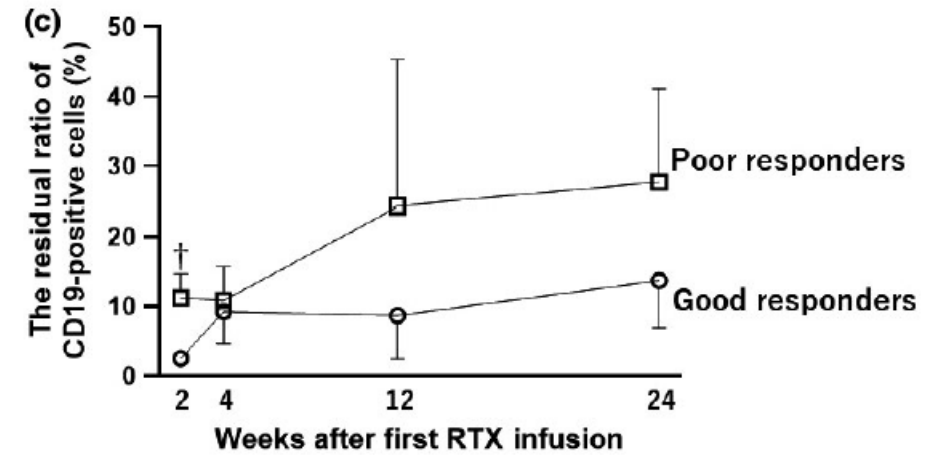
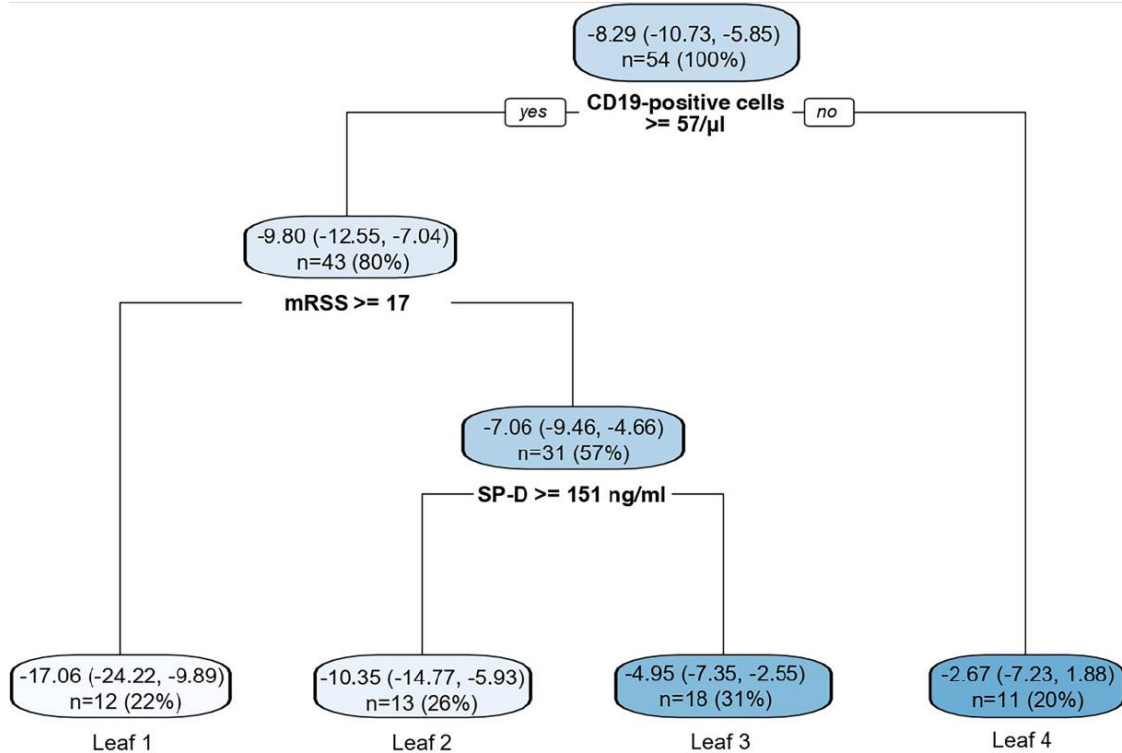


Original article

**Predictors of rituximab effect on modified Rodnan skin score in systemic sclerosis: a machine-learning analysis of the DesiReS trial**

Percentage of residual B cells after 2 weeks of rituximab treatment predicts the improvement of systemic sclerosis-associated interstitial lung disease

Satoshi Ebata<sup>1</sup> | Ayumi Yoshizaki<sup>1</sup> | Takemichi Fukasawa<sup>1</sup> | Asako Yoshizaki-Ogawa<sup>1</sup> | Yoshihide Asano<sup>1</sup> | Kosuke Kashiwabara<sup>2</sup> | Koji Oba<sup>3</sup> | Shinichi Sato<sup>1</sup>



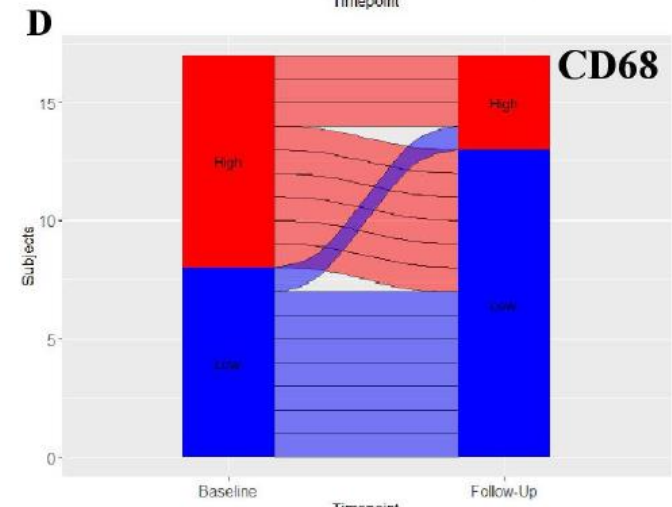
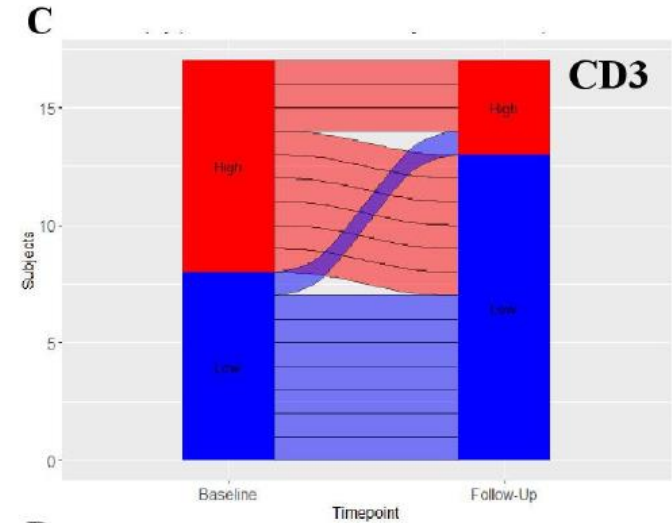
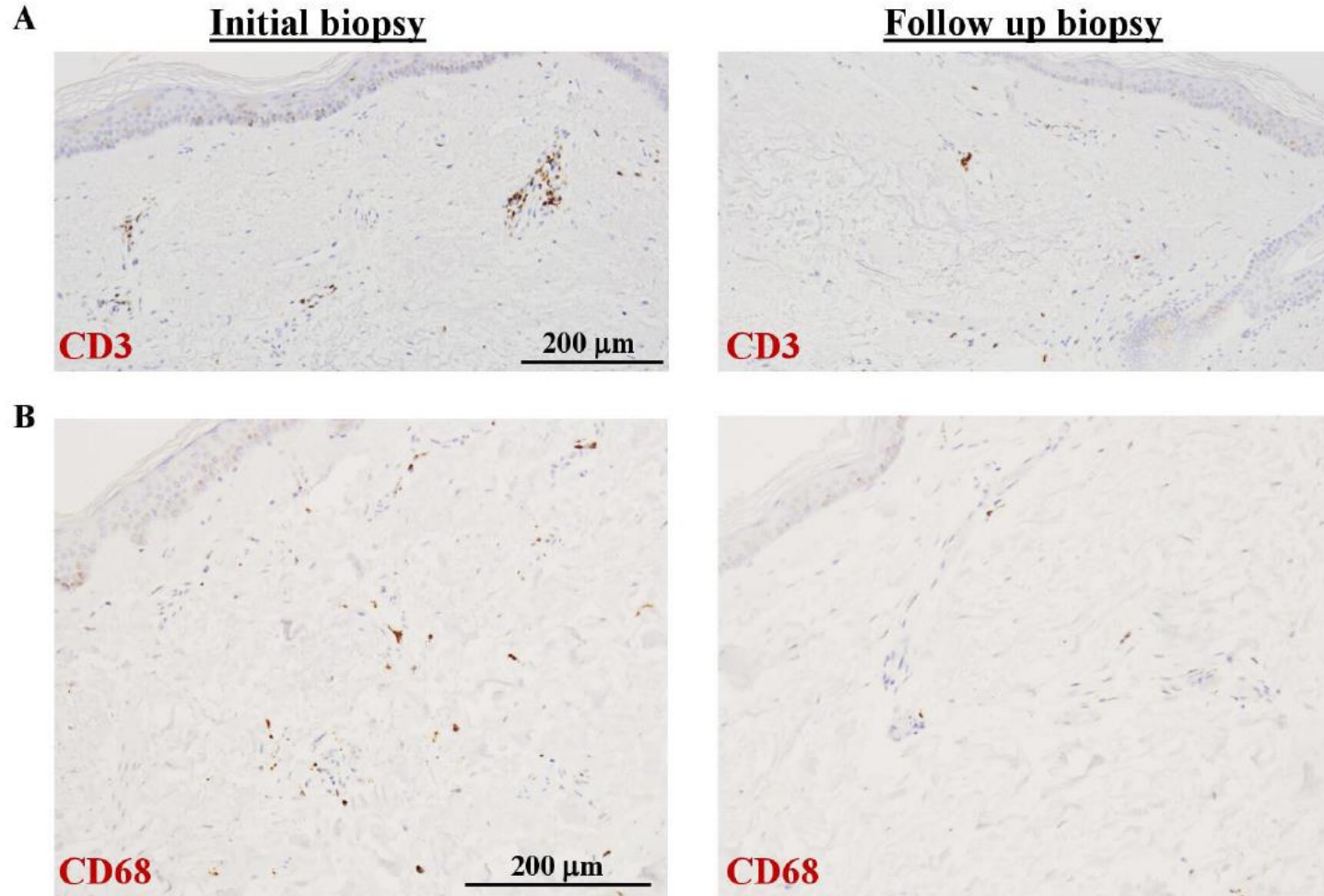


# Οι ανοσοτροποποιητικές θεραπείες έχουν νόημα στην αρχή της νόσου....

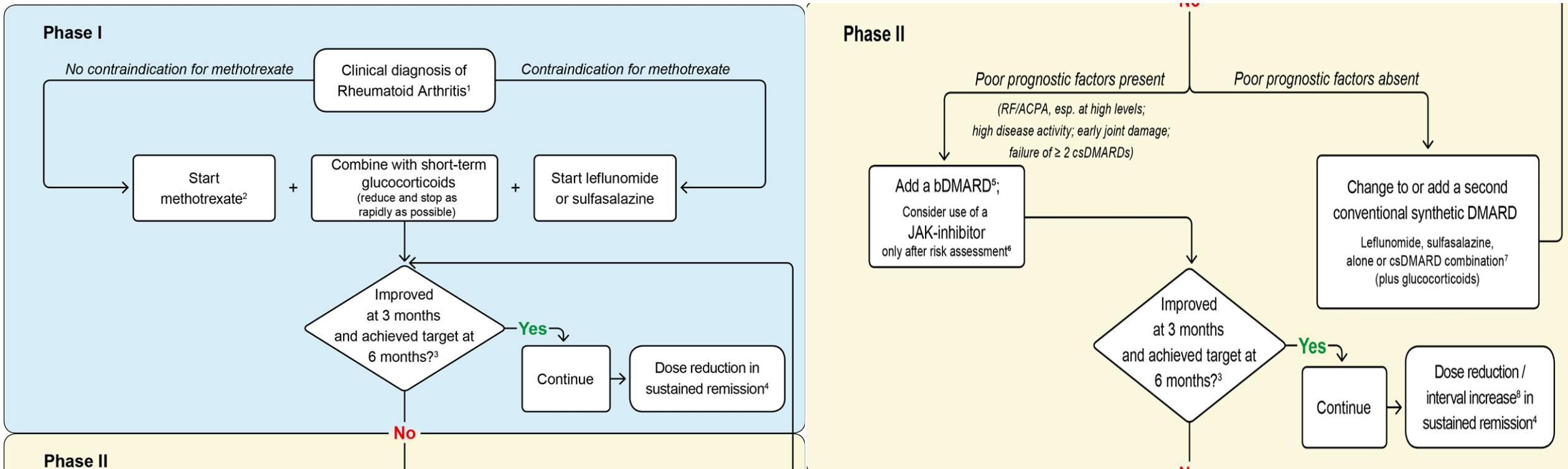
TRANSLATIONAL SCIENCE

Large-scale analysis of longitudinal skin gene expression in systemic sclerosis reveals relationships of immune cell and fibroblast activity with skin thickness and a trend towards normalisation over time

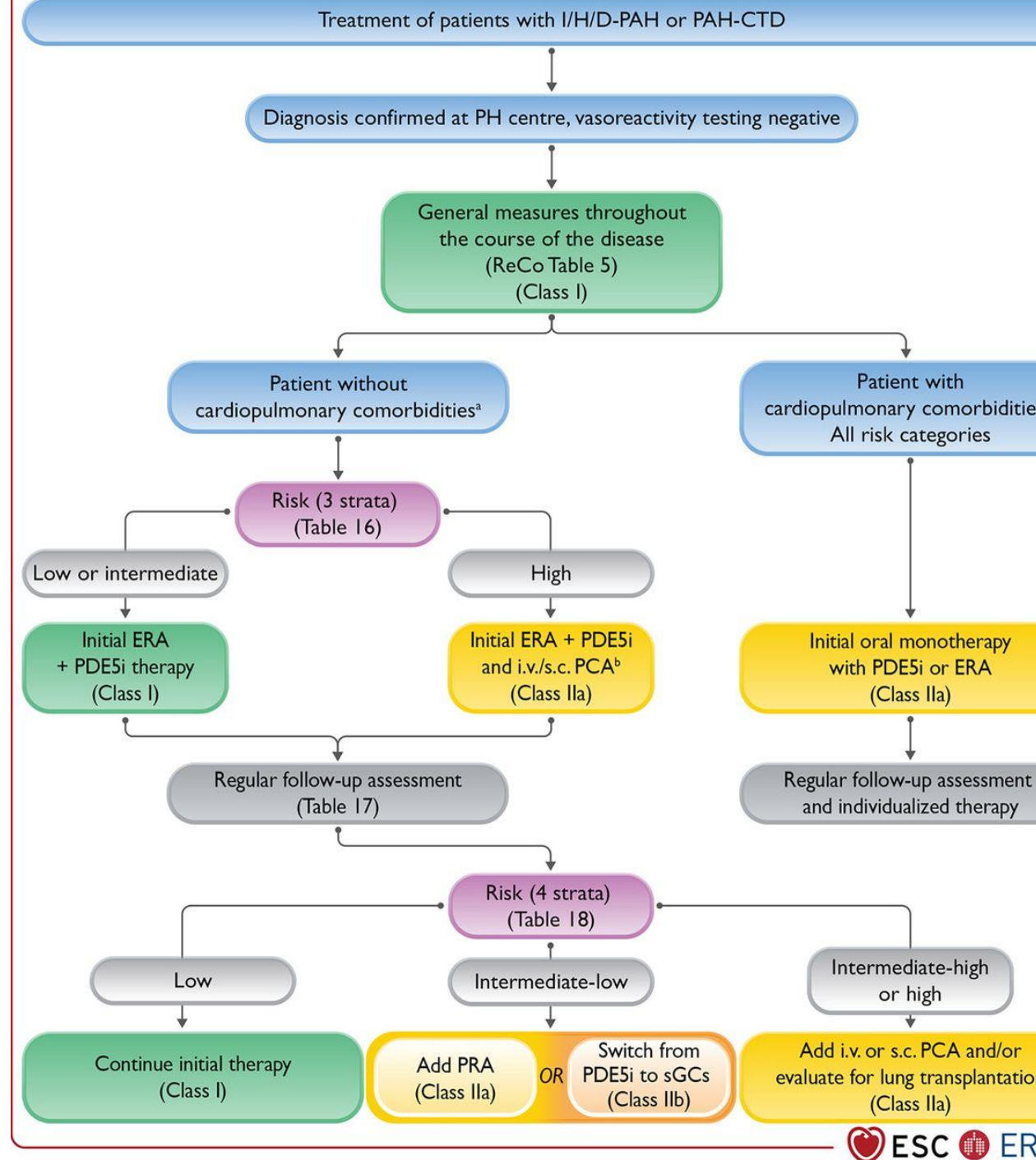
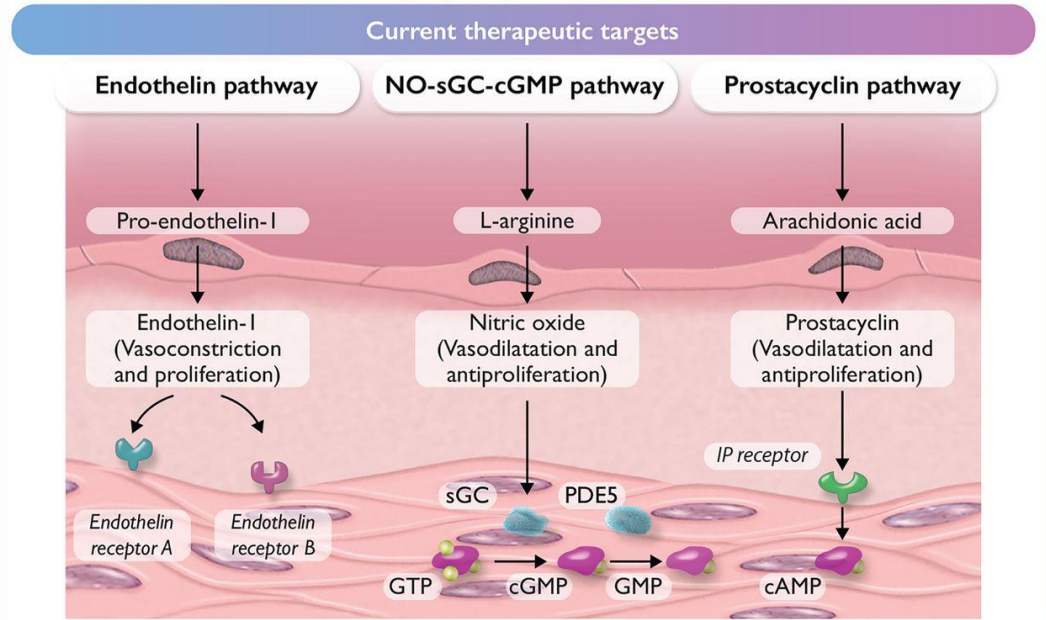
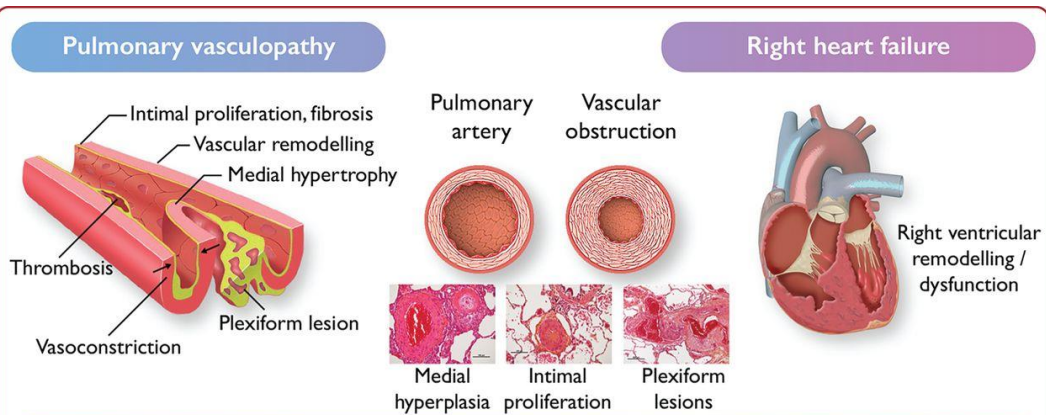
Brian Skaug <sup>1</sup>, Marka A Lyons, <sup>1</sup> William R Swindell, <sup>2</sup> Gloria A Salazar, <sup>1</sup> Minghua Wu <sup>1</sup>, Tuan M Tran, <sup>3</sup> Julio Charles, <sup>1</sup> Connor P Vershel, <sup>1</sup> Maureen D Mayes, <sup>1</sup> Shervin Assassi <sup>1</sup>



# Συνδυαστική Θεραπεία. Το παράδειγμα της ΡΑ



# Το παράδειγμα της ΠΑΥ



# Θεραπευτική αντιμετώπιση

MMF Πρώτη γραμμή θεραπείας

CYC?

RTX

Σημαντική προσβολή  
δέρματος/αρθρώσεων  
Εφιππεύοντα σύνδρομα

TCZ

Φλεγμονώδης απάντηση  
Πρωιμη νόσος

Nintedanib

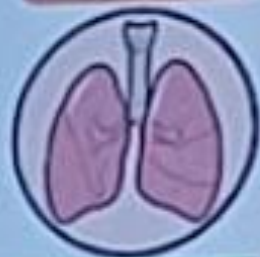
Προσβολή πνεύμονα



Επί αστοχία όλων των παραπάνω HSCT

# Systemic sclerosis

Interstitial lung disease

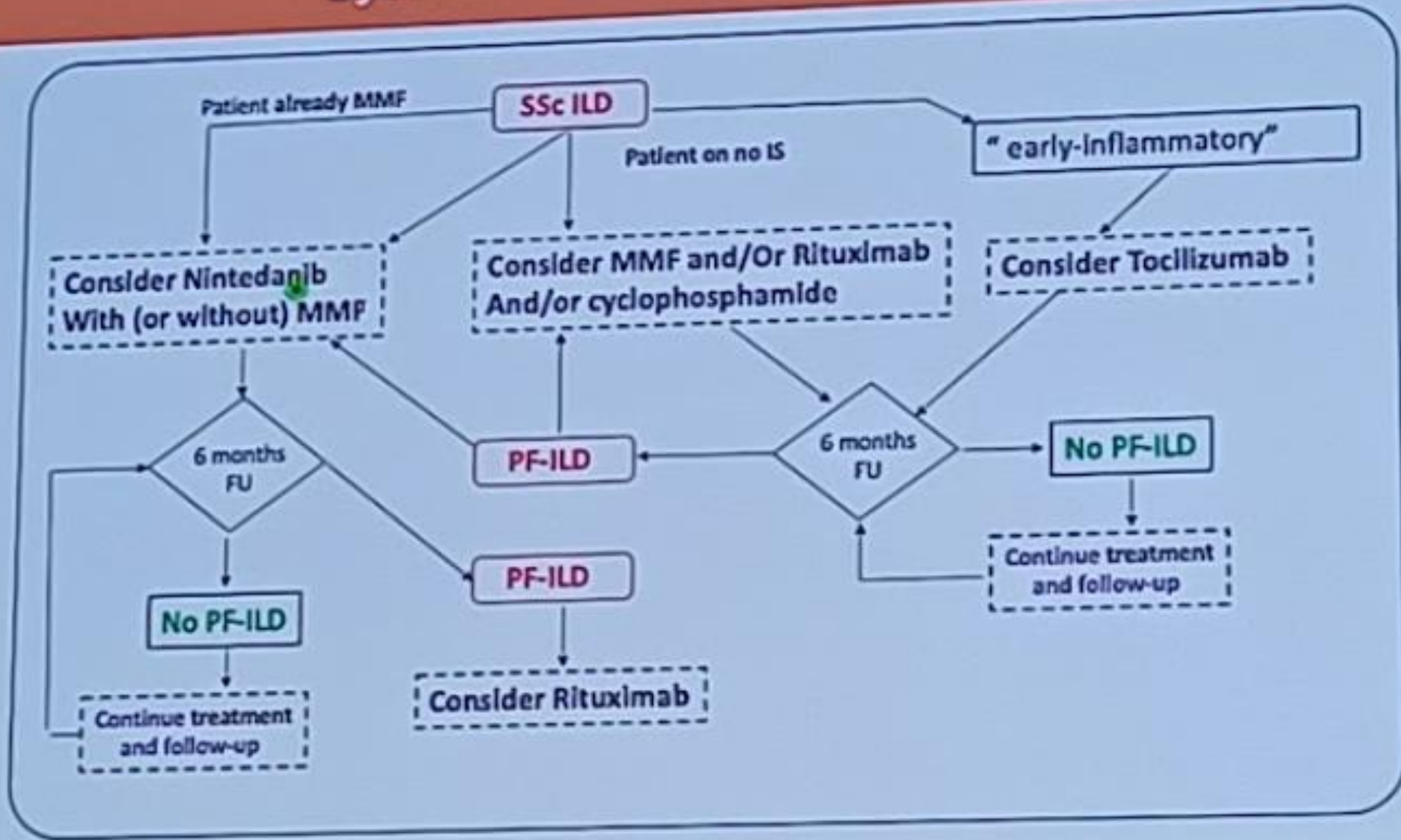


A  
 RTUX  
 MMF  
 CYC  
 NINTEDANIB

B  
 TCZ

C

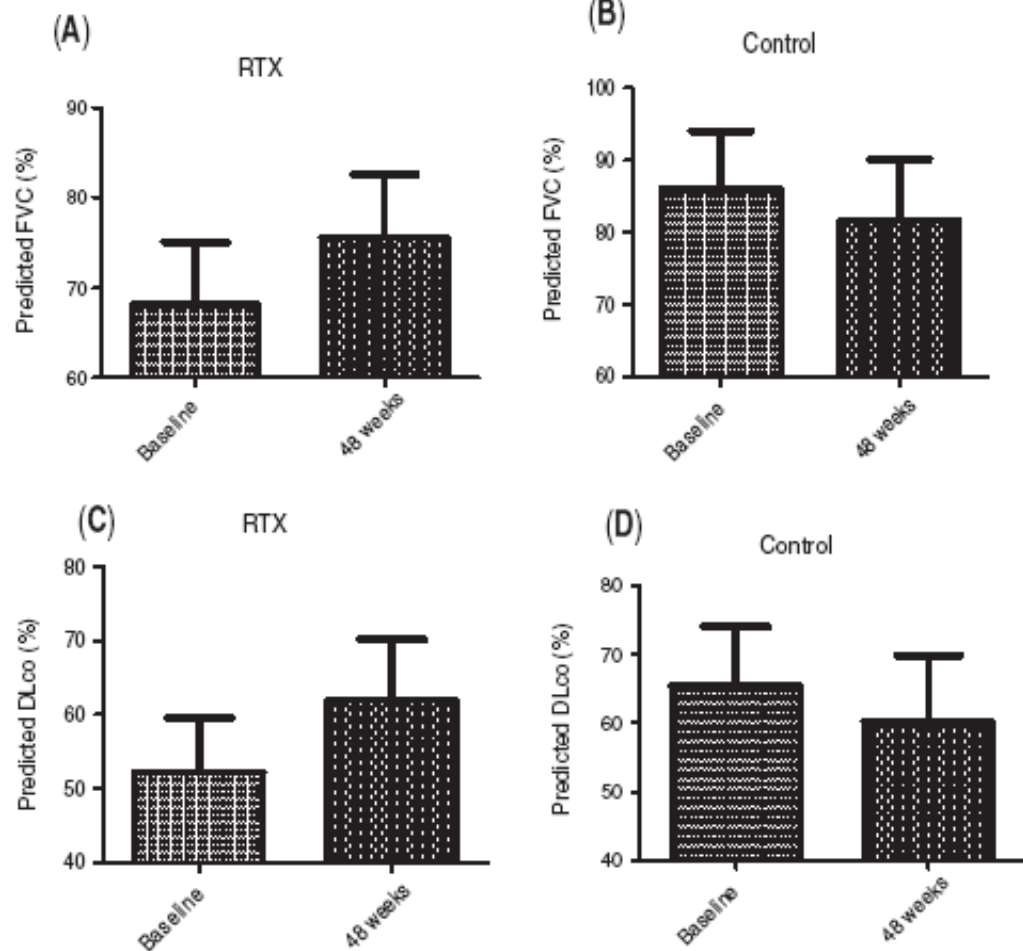
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# Rituximab

## Rituximab: a potential therapeutic advance in scleroderma

What is the evidence?



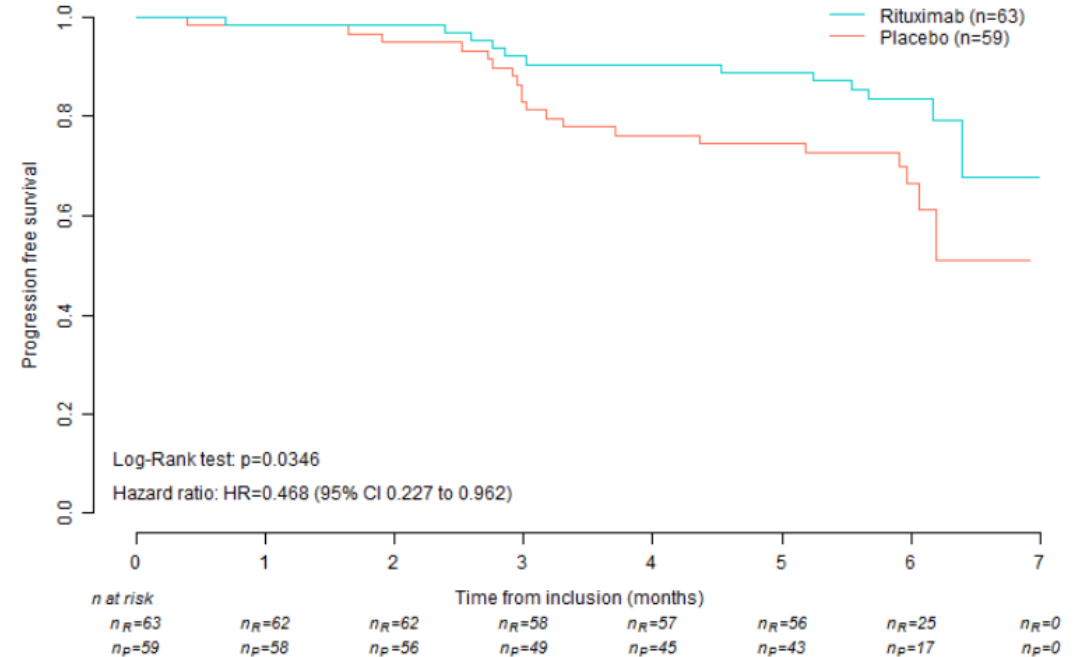
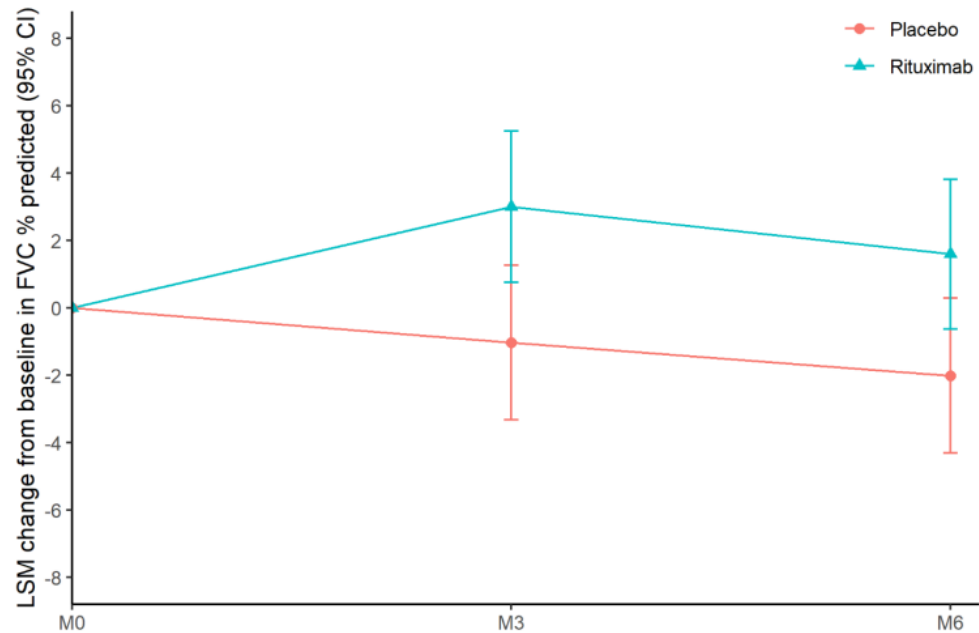
## Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study

Dimitrios Daoussis<sup>1\*</sup>, Stamatis-Nick C. Liossis<sup>1\*</sup>, Athanassios C. Tsamandas<sup>2</sup>, Christina Kalogeropoulou<sup>3</sup>, Alexandra Kazantzi<sup>3</sup>, Chaido Sirinian<sup>2</sup>, Maria Karampetsou<sup>1</sup>, Georgios Yiannopoulos<sup>1</sup> and Andrew P. Andonopoulos<sup>1</sup>

- Improvement of PFTs following 2 courses of therapy

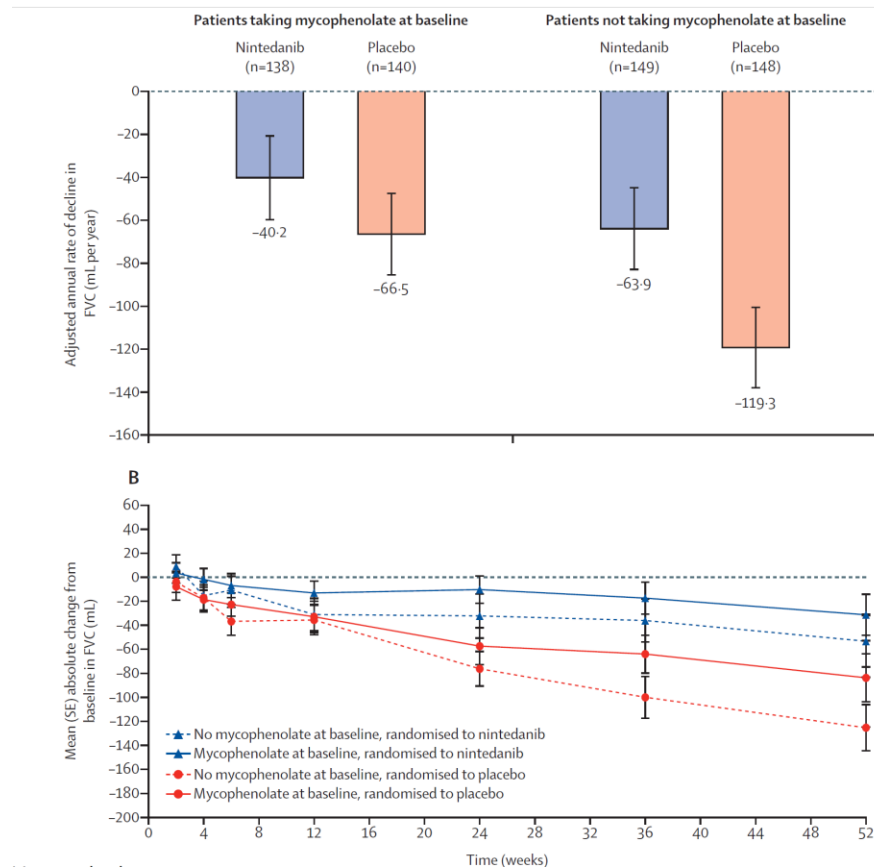
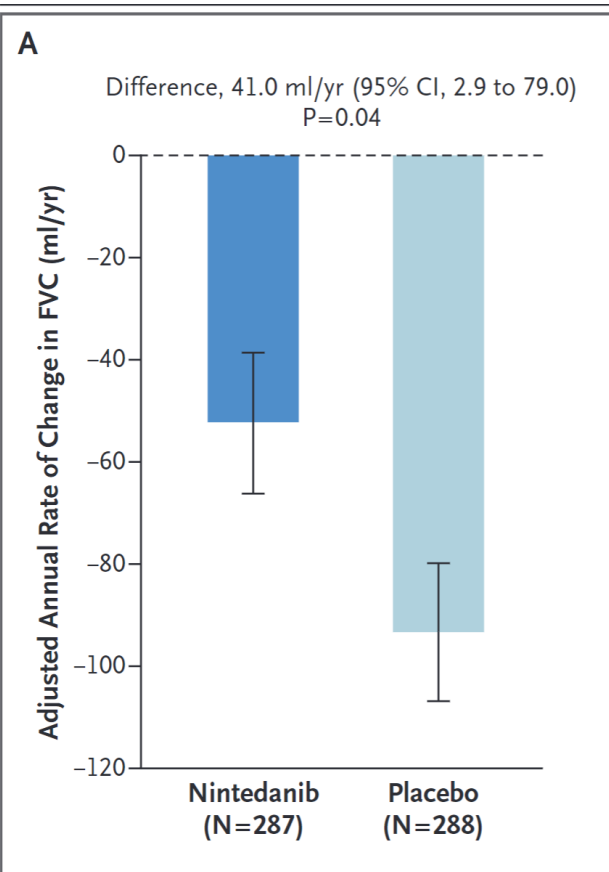
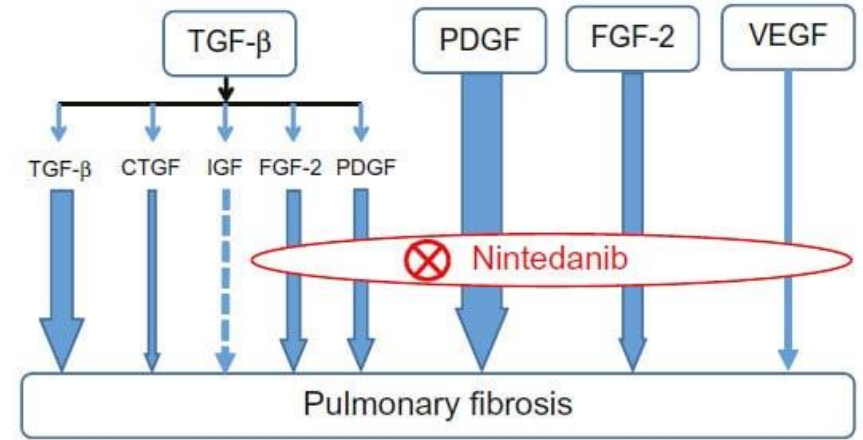
# MMF and RTX combination

Rituximab and mycophenolate mofetil combination in patients with interstitial lung disease (EVER-ILD): a double-blind, randomised, placebo-controlled trial



ORIGINAL ARTICLE

# Nintedanib for Systemic Sclerosis–Associated Interstitial Lung Disease

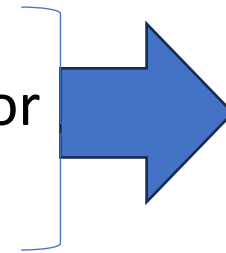


- Pts receiving MMF plus nintedanib had the best response

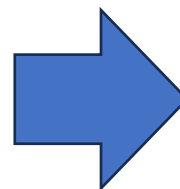


# Future directions....(personal view)

- MMF as the anchor drug
- Early use of combination treatment
- Precision medicine
- Pts with “inflammatory features” such as
  - “Inflammatory signature” in skin gene expression or
  - “lymphoid lineage” signature in PBMC gene expression or
  - Interferon signature
- Patients with fibrotic features
  - Lack of biomarkers....



RTX  
TCZ (early  
inflammatory  
phenotype)



Antifibrotic

- Early escalation to triple therapy (MMF+ RTX or TCZ + antifibrotic) in pts with aggressive disease

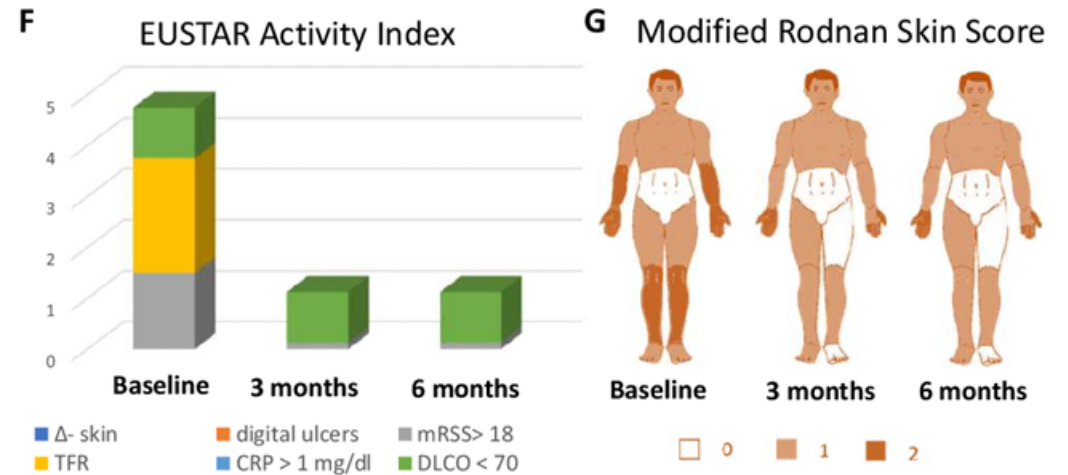
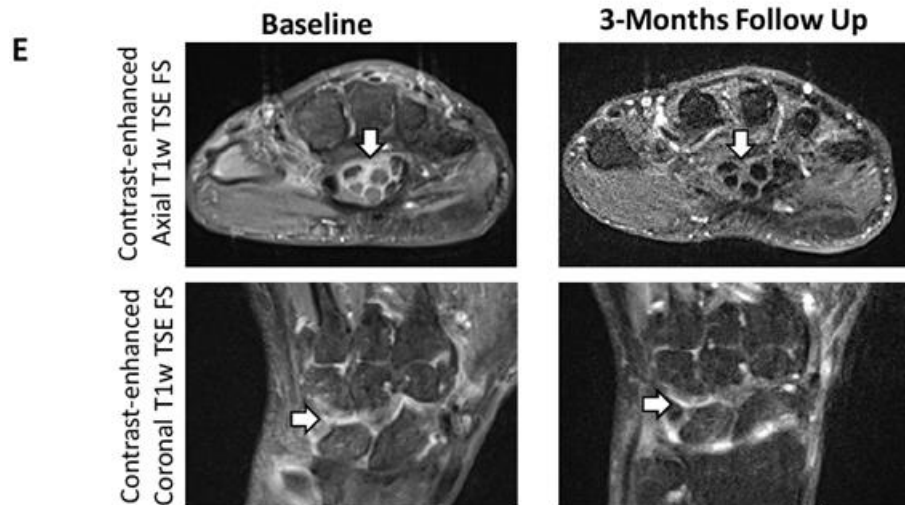
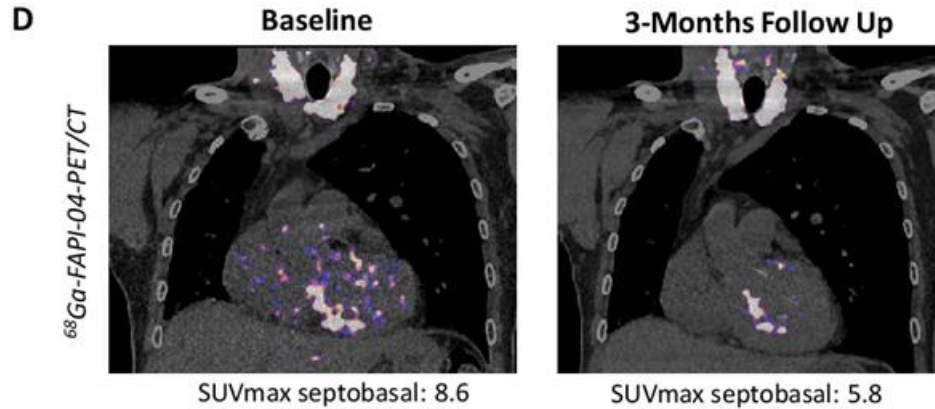


ευχαριστώ!

Email: [jimdaoussis@hotmail.com](mailto:jimdaoussis@hotmail.com)

# CAR-T cells

Treatment of a patient with severe systemic sclerosis (SSc) using CD19-targeted CAR T cells



**H**

|      | Baseline            | 3 months follow-up  | 6 months follow up  |
|------|---------------------|---------------------|---------------------|
| PFT  |                     |                     |                     |
| FVC  | 3,27 l (73% pred.)  | 3,45 l (77% pred.)  | 3,21 (72% pred.)    |
| DLCO | 49 mmol/(min*kPa)   | 52 mmol/(min*kPa)   | 59 mmol/(min*kPa)   |
| KCO  | 58 mmol/(min*kPa*l) | 68 mmol/(min*kPa*l) | 80 mmol/(min*kPa*l) |

**I**

|         | Baseline           | 6 months follow up |
|---------|--------------------|--------------------|
| TTE     |                    |                    |
| EF      | 55-60%             | 55-60%             |
| PASP    | 27 mmHg            | 20 mmHg            |
| RA area | 31 cm <sup>2</sup> | 17 cm <sup>2</sup> |

# Patient characteristics at baseline

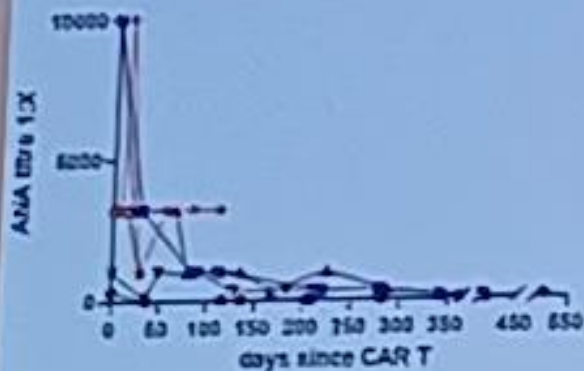
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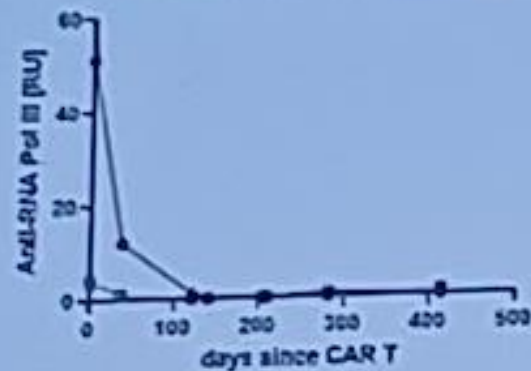
|                              | Patient 1 | Patient 2                             | Patient 3                        | Patient 4            | Patient 5  | Patient 6           |
|------------------------------|-----------|---------------------------------------|----------------------------------|----------------------|--|---------------------|
| <b>Demographics</b>          |           |                                       |                                  |                      |  |                     |
| Age (years)                  | 60        | 36                                    | 37                               | 47                   | 55   | 29                  |
| Sex (female/male)            | male      | male                                  | female                           | male                 | male   | female              |
| Disease duration (months)    | 23        | 30                                    | 15                               | 134                  | 42   | 47                  |
| EUSTAR activity index (0-10) | 4.75      | 9.00                                  | 5.25                             | 3.93                 | 7.75   | 4.00                |
| <b>Laboratory values</b>     |           |                                       |                                  |                      |  |                     |
| Baseline ANA (titre)         | 1:320     | 1:10,000                              | 1:10,000                         | 1:1000               | 1:3200   | 1:3200              |
| Baseline ENA profile         | RNAP-III  | Scl70                                 | Scl70                            | Scl70                | Scl70  | Scl70               |
| <b>Skin Involvement</b>      |           |                                       |                                  |                      |  |                     |
| mRSS (0-51)                  | 24        | 27                                    | 32                               | 17                   | 35   | 25                  |
| Tendon friction rubs         | √         | √                                     | -                                | -                    | -  | -                   |
| Digital ulcerations          | -         | √                                     | √                                | -                    | √  | -                   |
| <b>Lung Involvement</b>      |           |                                       |                                  |                      |  |                     |
|                              | √         | √                                     | √                                | √                    | √  | √                   |
| Pulmonary hypertension       | √         | -                                     | -                                | √                    | -  | -                   |
| <b>Heart Involvement</b>     |           |                                       |                                  |                      |  |                     |
|                              | √         | √                                     | -                                | -                    | √  | -                   |
| <b>Kidney Involvement</b>    |           |                                       |                                  |                      |  |                     |
| Renal crisis                 | -         | -                                     | √                                | -                    | -  | -                   |
| <b>Treatments</b>            |           |                                       |                                  |                      |  |                     |
| Failed treatment             | MMF, MTX  | MMF, Prednisolone, Hydroxychloroquine | MMF, MTX, Tocilizumab, Rituximab | MMF, Cyclophosphamid | MMF, MTX, Prednisolone, Rituximab, Cyclophosphamid | MMF, MTX, Rituximab |

# Antibody profile

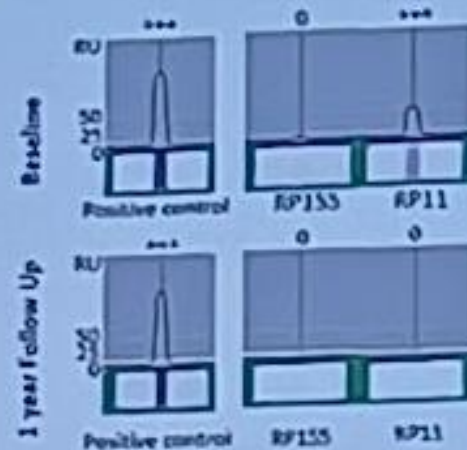
ANA titer



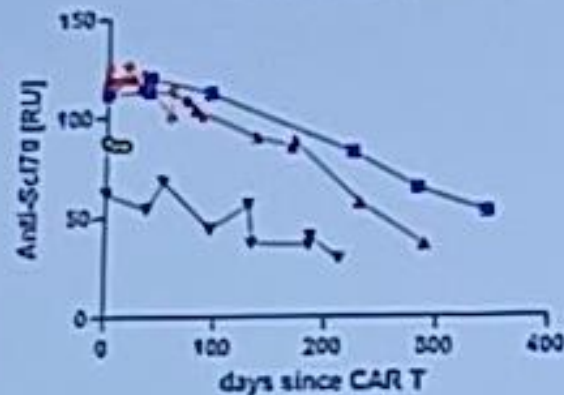
Anti-SNA polymerase III antibodies



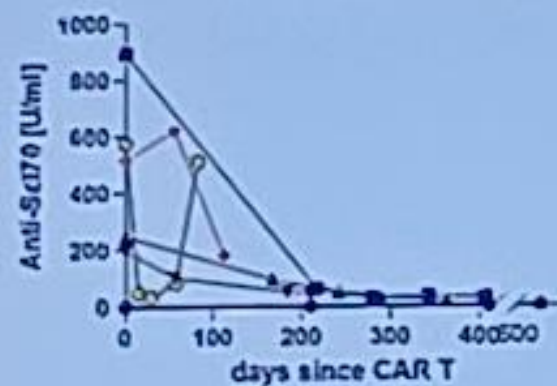
▲ patient 1: RP11  
● patient 1: RP155



Anti-Sci70 antibodies



Anti-Sci70 ELISA



▲ patient 1 ● patient 2 ▲ patient 3 ▲ patient 4 ▲ patient 5 ◆ patient 6

# Skin involvement and disease activity

Modified Rodnan Skin Score (mRSS)

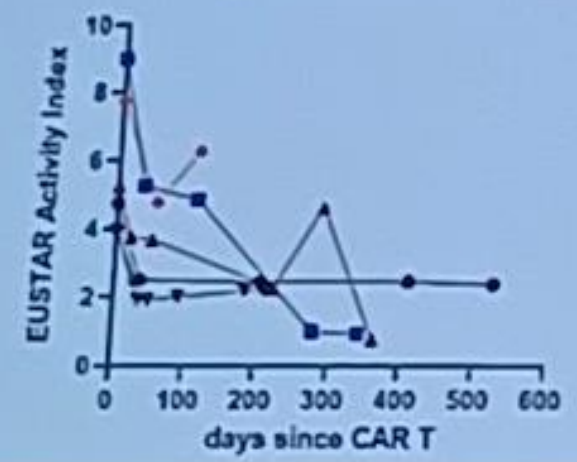


Digital ulcerations  
Patient 3

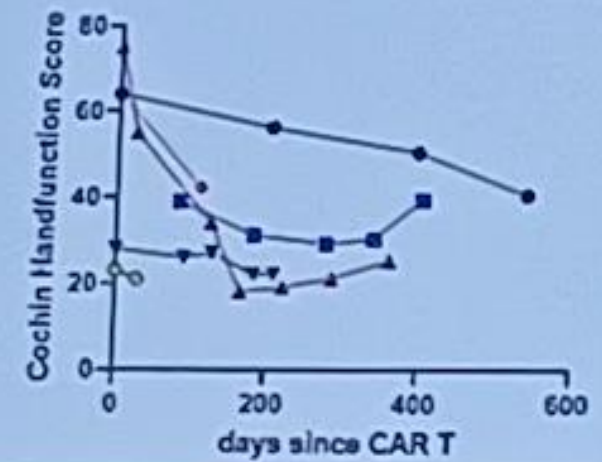


before CAR T therapy

EUSTAR Activity Index



Cochlin Hand Function Scale

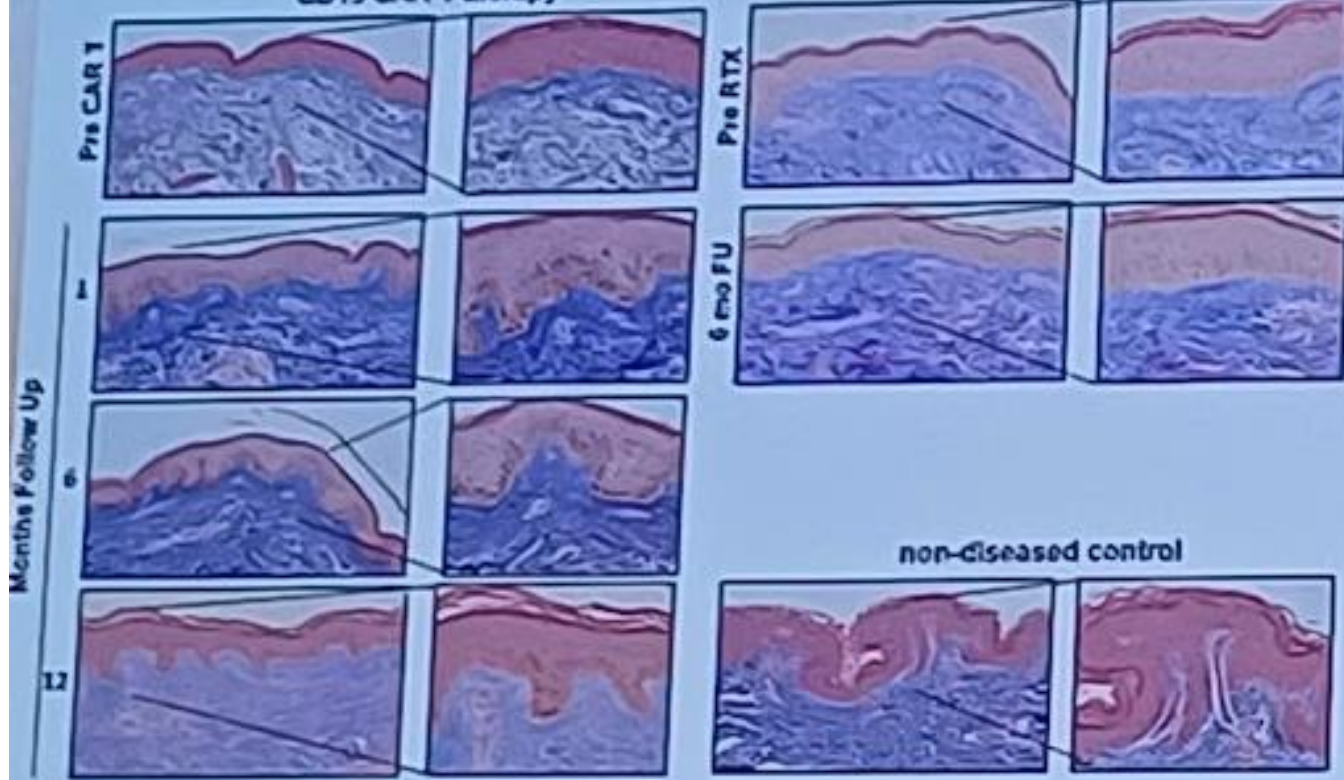


4 weeks after CAR T therapy

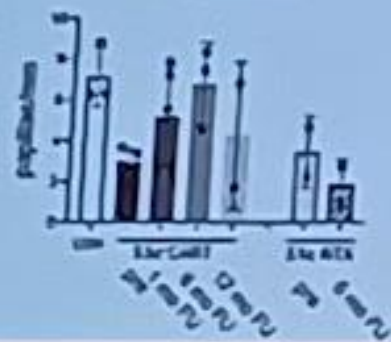
# Histological changes

## CD19 CAR T therapy

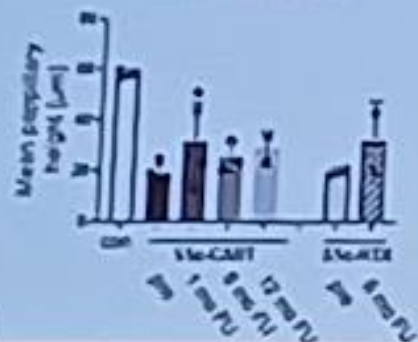
## Rituximab (RTX)



### Papillae/mm

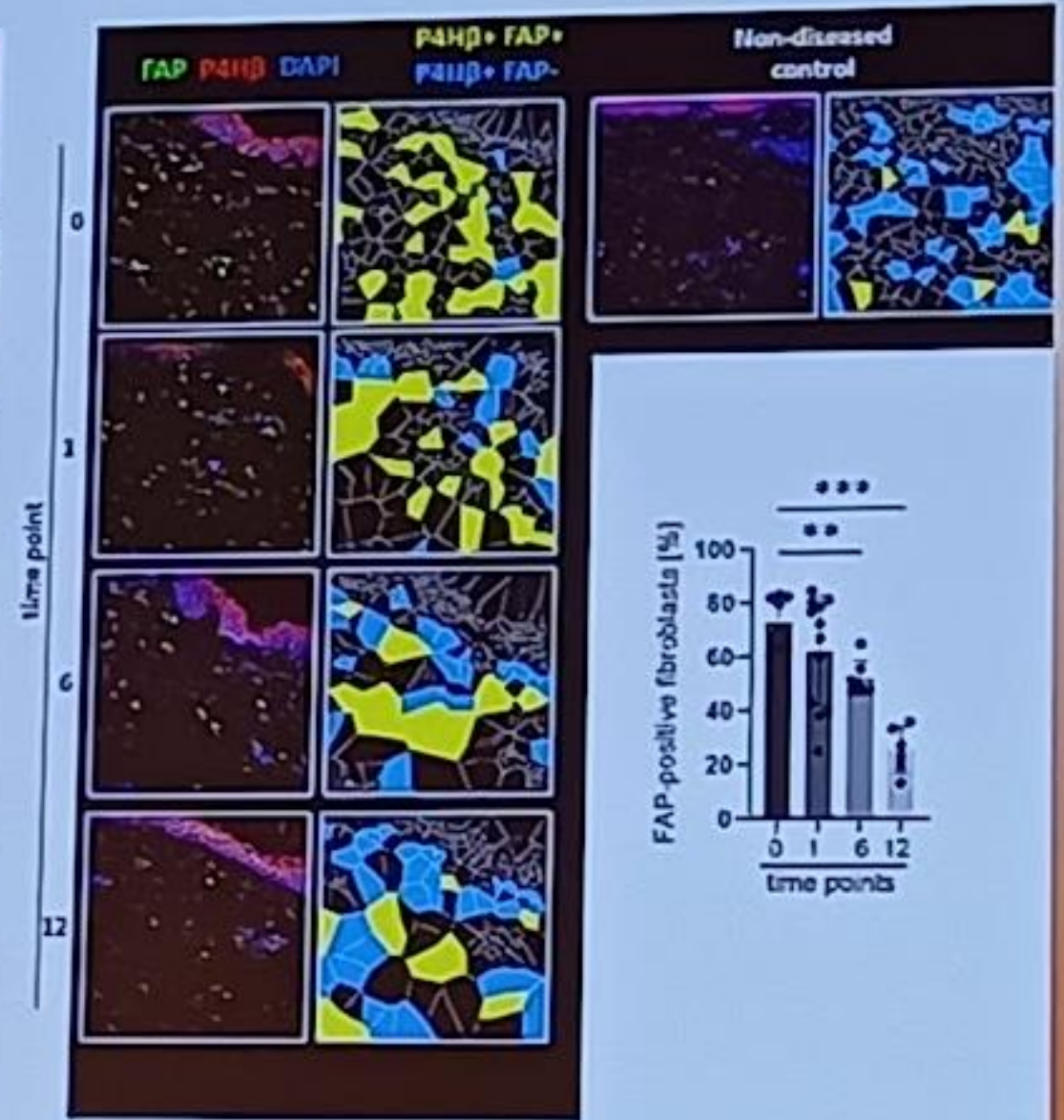


### Papillae height



**OC23:**  
Reticularized skin phenotype in SSc – potential mediators  
*Sara Chenguti Fakhouri et al*

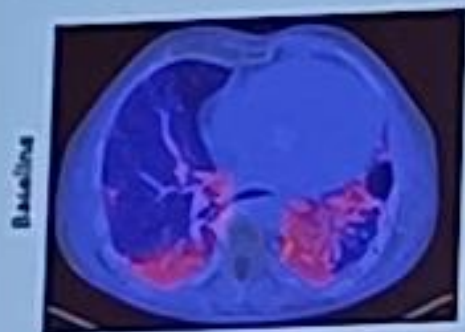
## Fibroblast activation protein



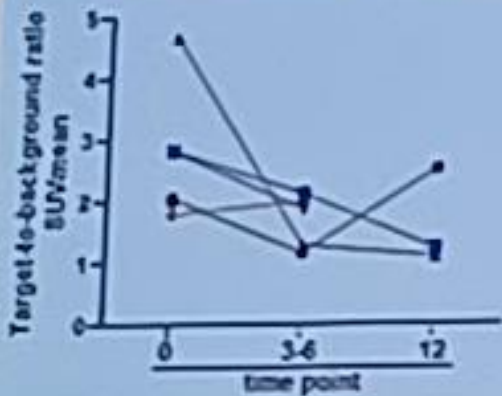
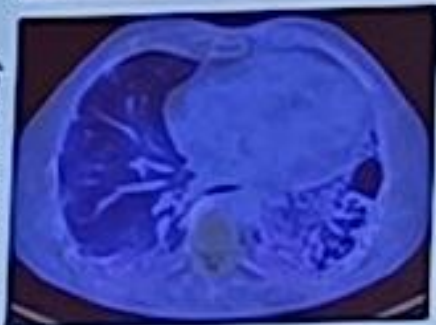


# Lung involvement

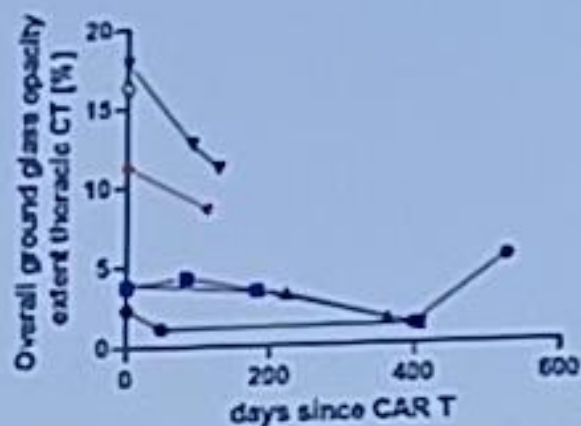
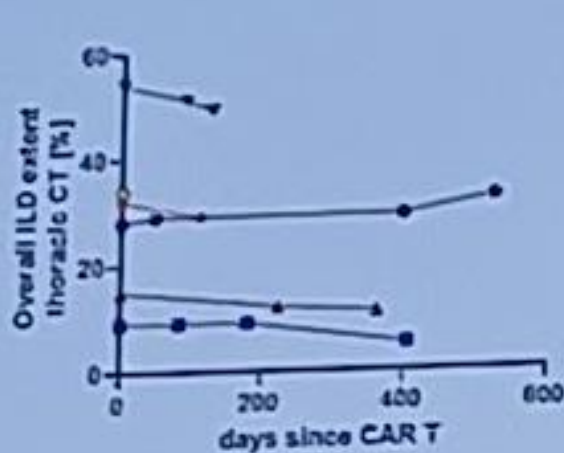
<sup>68</sup>Ga-FAPI-04-PET-CT



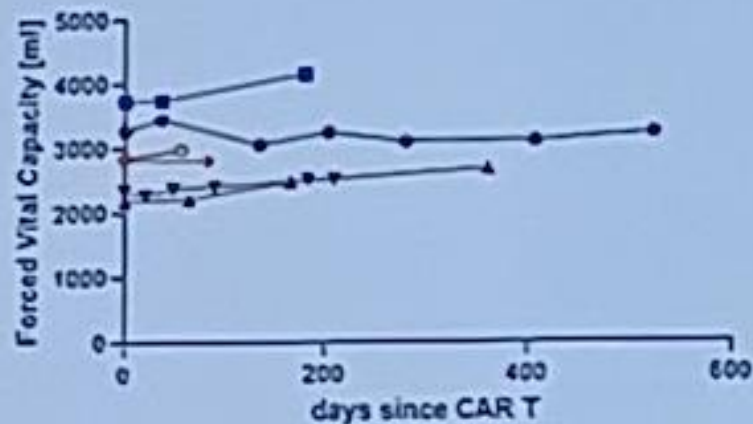
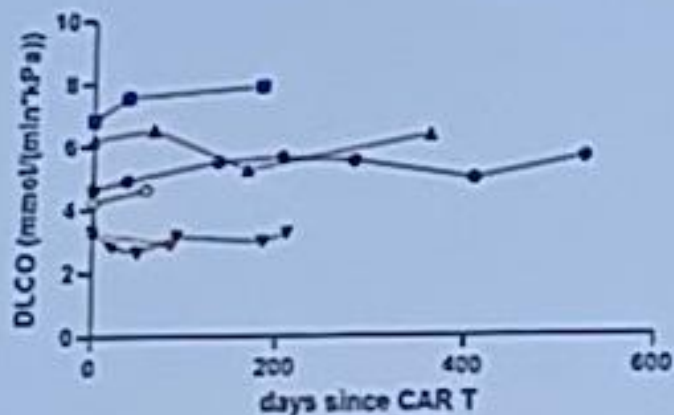
3 months follow up



Thoracic CT



Pulmonary function



◆ patient 1   
 ● patient 2   
 ▲ patient 3   
 ▼ patient 4   
 ◆ patient 5   
 ◇ patient 6

# Τι τρέχει σε κλινικές μελέτες.....

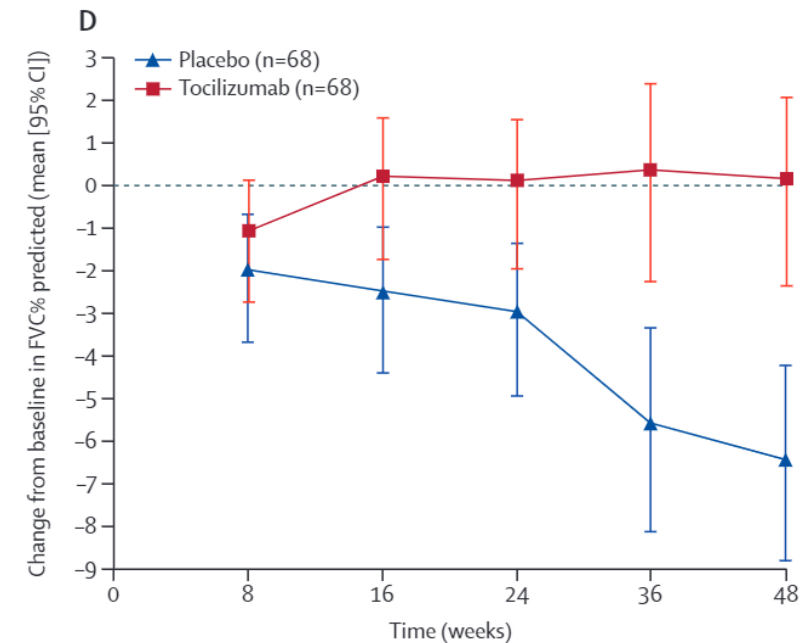
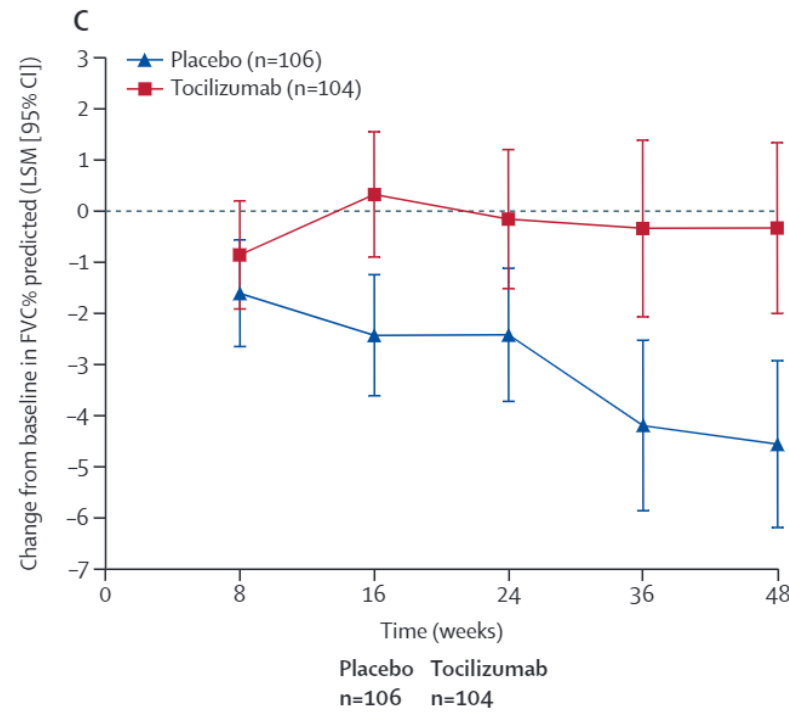
| Trial identifier | Intervention        | Mechanism of action   | Number of patients       | Primary end point      | Secondary end point   | Duration of study | Date of completion |
|------------------|---------------------|---|--------------------------|------------------------|---|-------------------|--------------------|
| NCT02370693      | Bortezomib          | Proteasome inhibitor  | 30 SSc-ILD               | AEs                    | mRSS and change in FVC                                      | 48 weeks          | Unpublished        |
| NCT04837131      | Ixazomib            | Oral proteasome inhibitor                                       | 12 SSc-ILD               | AEs                    | Change in mRSS, FVC, DL <sub>CO</sub> , TLC, dyspnoea index | 28 weeks          | April 2024         |
| NCT03198689      | Brentuximab vedotin | Anti-CD30 monoclonal antibody                                   | 11 dcSSc active          | mRSS                   | Change in FVC and DL <sub>CO</sub>                          | 48 weeks          | February 2023      |
| NCT04948554      | ACE-1334            | TGFβ1 and TGFβ3 inhibitor                                       | 210 SSc with/without ILD | AEs                    | Pharmacokinetics, pharmacodynamics of ACE-1334              | 48 weeks          | May 2028           |
| NCT05270668      | PRA023              | anti-TL1A monoclonal antibody                                   | 100 SSc-ILD              | AEs, FVC annual change | Change in HRCT, ACR, CRISS                                  | 50 weeks          | June 2024          |
| NCT05177471      | Ruxolitinib         | JAK inhibitor   | 20 SSc-ILD               | Change in FVC          | Change in DL <sub>CO</sub> , skin fibrosis                  | 12 months         | July 2022          |
| NCT05925803      | Anifrolumab         | Type I interferon receptor inhibiting IgG1k monoclonal antibody | 306 SSc                  | CRISS-25               | Change in mRSS, FVC, DL <sub>CO</sub> , HRTC                | 52 weeks          | December 2027      |
| NCT05878717      | Belimumab           | B cell-activating factor monoclonal antibody                    | 300 SSc-ILD              | Absolute change of FVC | Change in mRSS, DL <sub>CO</sub> , FACIT                    | 52 weeks          | February 2027      |
| NCT05085444      | CAR T cell therapy  | CD19/BCMA CAR T cell therapy                                    | 9 refractory SSc         | AEs, TEAEs             | Progression-free survival, overall survival                 | 90 days/2 years   | October 2024       |
| NCT05321082      | BI 1015550          | Phosphodiesterase 4B  | 1,041 progressive        | Absolute               | Change in DL <sub>CO</sub>                                  | 52 weeks          | November 2024      |

# 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†

- Δοκιμάστηκε μόνο σε ασθενής με φλεγμονώδη απάντηση
- Καθυστερεί την εξέλιξη της πνευμονικής νόσου
- Δεν έπιασε το καταληκτικό σημείο στο δέρμα



## Autologous Hematopoietic Stem Cell Transplantation vs Intravenous Pulse Cyclophosphamide in Diffuse Cutaneous Systemic Sclerosis

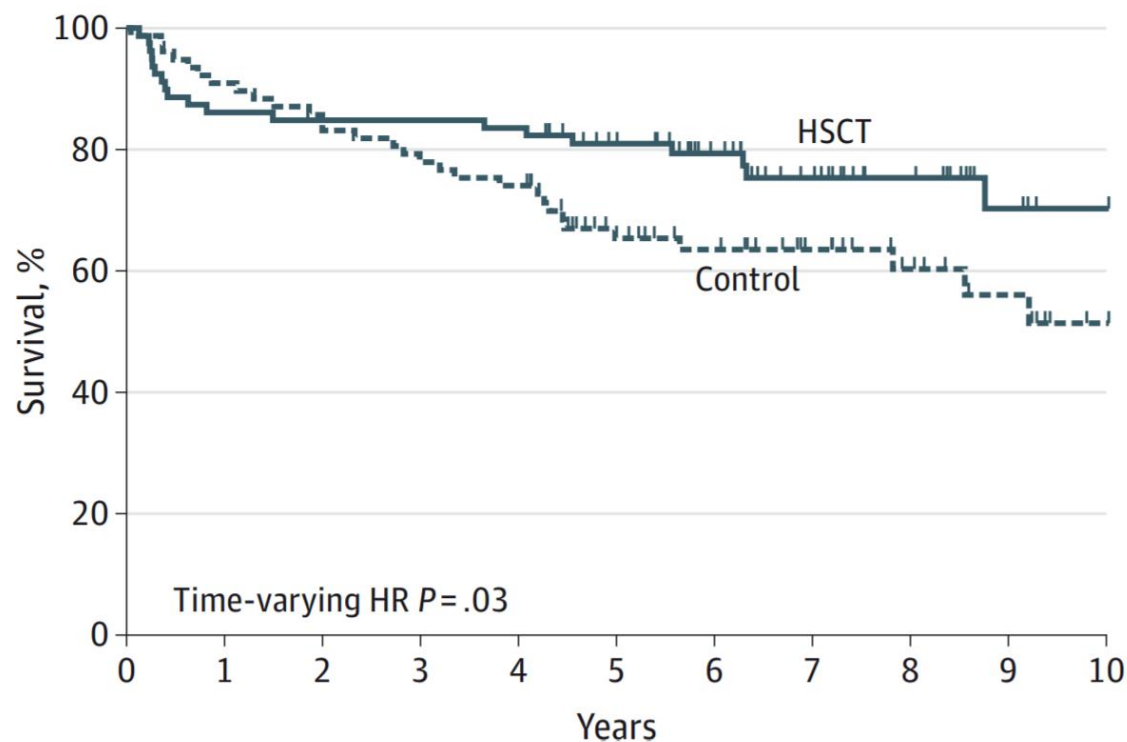
A Randomized Clinical Trial

Jacob M. van Laar, MD, PhD<sup>1</sup>; Dominique Farge, MD, PhD<sup>2</sup>; Jacob K. Sont, PhD<sup>3</sup>; [et al](#)

## Αυτόλογη μεταμόσχευση αρχέγονων αιμοποιητικών κυττάρων

- Ένδειξη μόνο σε ασθενείς με πολύ σοβαρή/εξελισσόμενη νόσο καθώς η διαδικασία σχετίζεται με υψηλή νοσηρότητα-θνητότητα. Μακροχρόνια, αυξάνεται η επιβίωση

**B** Overall survival



| No. at risk | 0  | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 |
|-------------|----|----|----|----|----|----|----|----|----|----|----|
| HSCT        | 79 | 68 | 67 | 67 | 66 | 55 | 43 | 32 | 23 | 14 | 11 |
| Control     | 77 | 70 | 64 | 60 | 57 | 40 | 34 | 25 | 18 | 12 | 6  |

# Θεραπευτικές επιλογές-CYC

## Scleroderma Lung Study I. Η πρώτη μελέτη που απέδειξε την αποτελεσματικότητα της ανοσοκαταστολής

**Table 2. Change in Values from Baseline to Month 12.\***

| Characteristic   | Baseline Value | Value at 12 Mo | Difference  |
|--|----------------|----------------|-------------|
| <b>Cyclophosphamide group</b>                          |                |                |             |
| FVC (% of predicted)                                   | 67.6±1.3       | 66.6±1.7       | -1.0±0.92†  |
| Total lung capacity (% of predicted)                   | 70.4±2.1       | 70.5±1.8       | -0.3±1.82†  |
| DLCO (% of predicted)                                  | 47.2±1.6       | 42.8±1.7       | -4.2±1.16   |
| Score on Mahler Dyspnea Index                          |                |                |             |
| According to baseline instrument                       | 5.6±0.22       |                |             |
| According to transitional dyspnea index (focal score)† |                | 1.4±0.23       |             |
| Cough (%)  | 72.5           | 66.2           |             |
| Score for HAQ disability index                         | 0.94±0.077     | 0.84±0.08      | -0.11±0.05† |
| SF-36 score  |                |                |             |
| Physical component                                     | 33.0±1.3       | 33.8±1.3       | 0.7±1.0     |
| Mental component                                       | 48.7±1.2       | 51.8±1.3       | 2.9±1.5     |
| Skin-thickness score                                   |                |                |             |
| Diffuse  | 15.5±1.3       | 11.9±1.3       | -3.6±0.8†   |
| Limited  | 6.1±3.6        | 5.0±4.3        | -0.8±2.4    |
| <b>Placebo group</b>                                   |                |                |             |
| FVC (% of predicted)                                   | 68.3±1.5       | 65.6±1.6       | -2.6±0.9    |
| Total lung capacity (% of predicted)                   | 67.9±1.9       | 64.7±1.9       | -2.8±1.2    |
| DLCO (% of predicted)                                  | 47.9±1.7       | 44.3±2.1       | -3.5±1.0    |
| Score on Mahler Dyspnea Index                          |                |                |             |
| According to baseline instrument                       | 5.6±0.42       |                |             |
| According to transitional dyspnea index (focal score)‡ |                | -1.5±0.43      |             |
| Cough (%)  | 55.9           | 67.2           |             |
| Score for HAQ disability index                         | 0.70±0.09      | 0.86±0.10      | 0.16±0.06   |
| SF-36 score  |                |                |             |
| Physical component                                     | 35.1±1.4       | 33.2±1.4       | -1.9±1.2    |
| Mental component                                       | 50.8±1.4       | 50.9±1.5       | 0.1±1.5     |
| Skin-thickness score                                   |                |                |             |
| Diffuse  | 20.2±9.3       | 19.1±11.2      | -1.7±6.9    |
| Limited  | 5.5±3.4        | 5.7±4.2        | 0.2±3.3     |

-1%

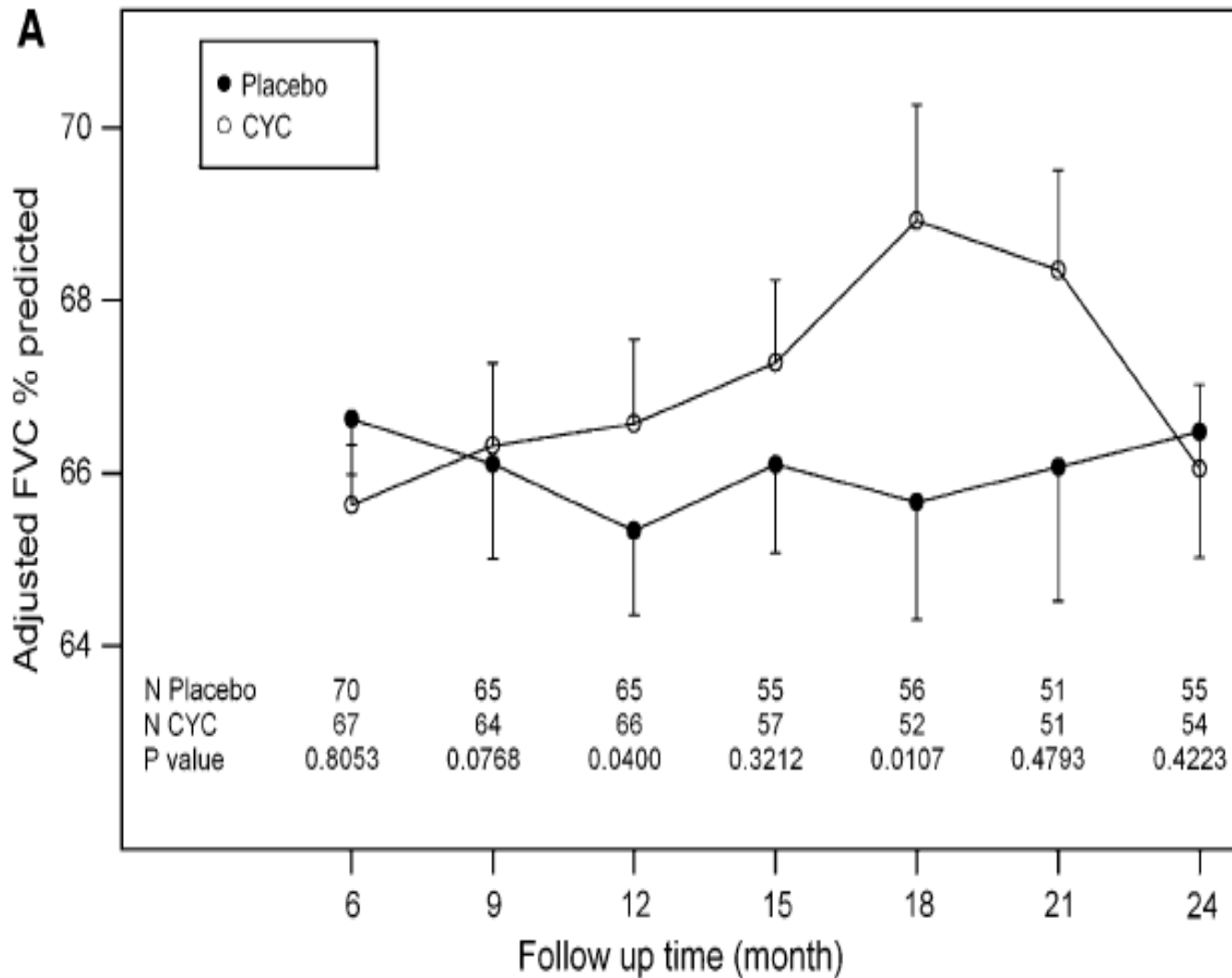
-2.6%

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

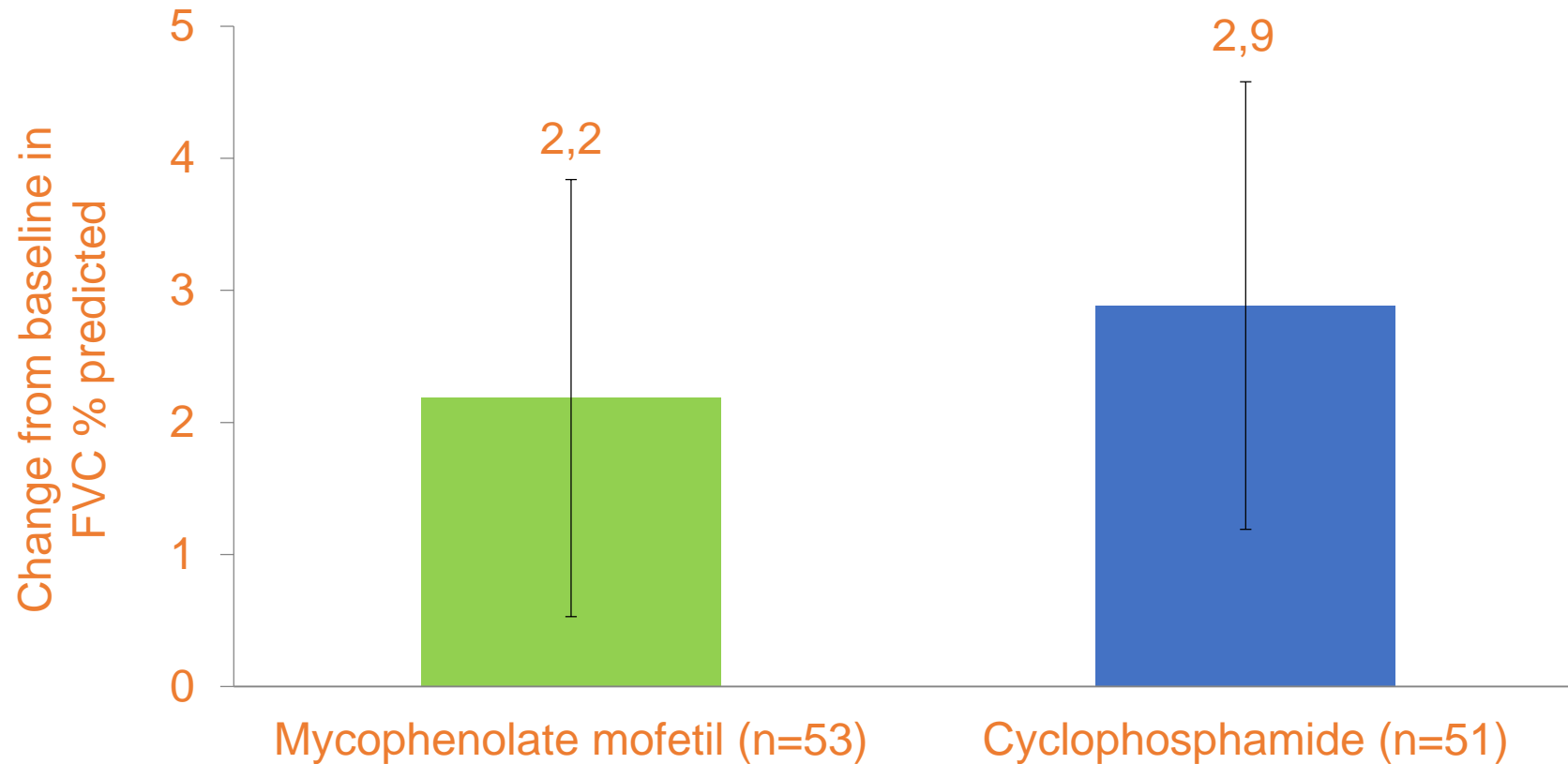
Cyclophosphamide versus Placebo  
in Scleroderma Lung Disease

**Effects of 1-Year Treatment with Cyclophosphamide on Outcomes at 2 Years in Scleroderma Lung Disease**



- Η ευεργετική δράση της CYC διατηρείται για λίγους μήνες μετά την διακοπή της θεραπείας

# Scleroderma Lung Study II: Το MMF ισάξιο της CYC



Data are mean  $\pm$  95% CI.

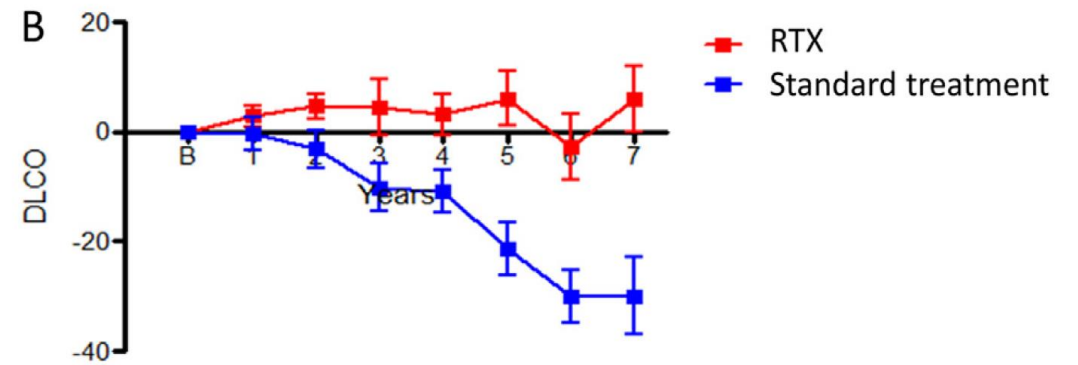
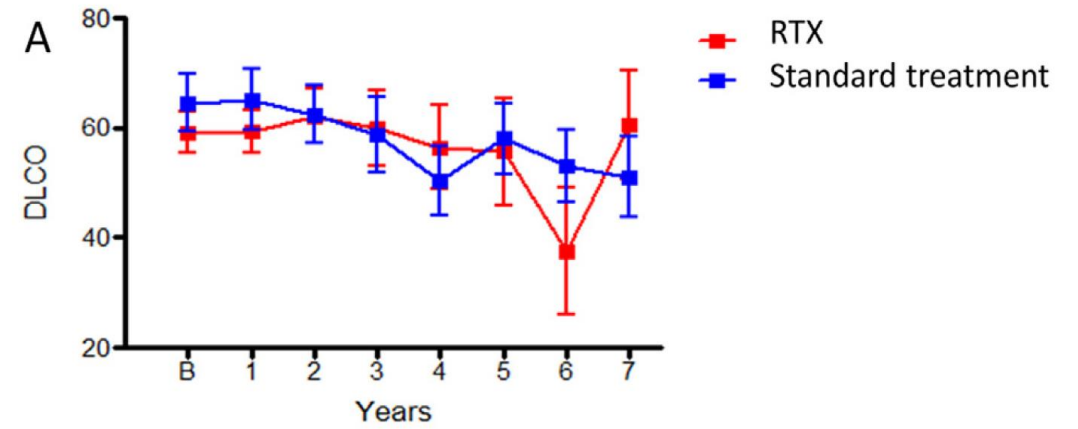
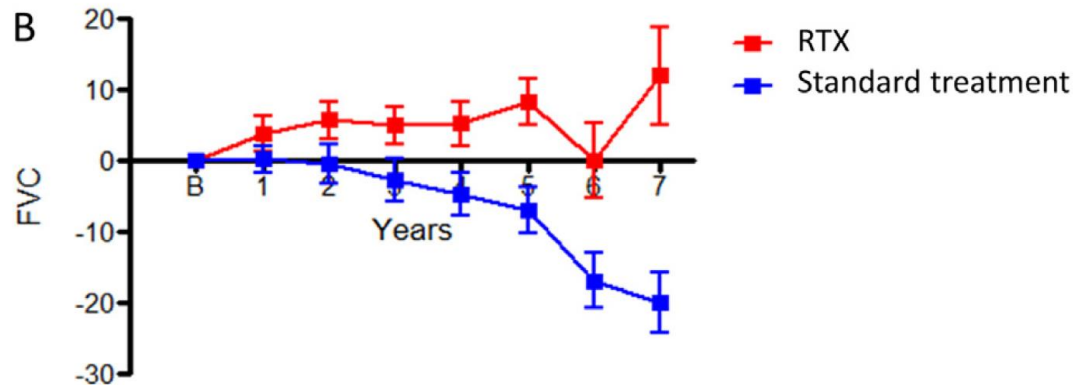
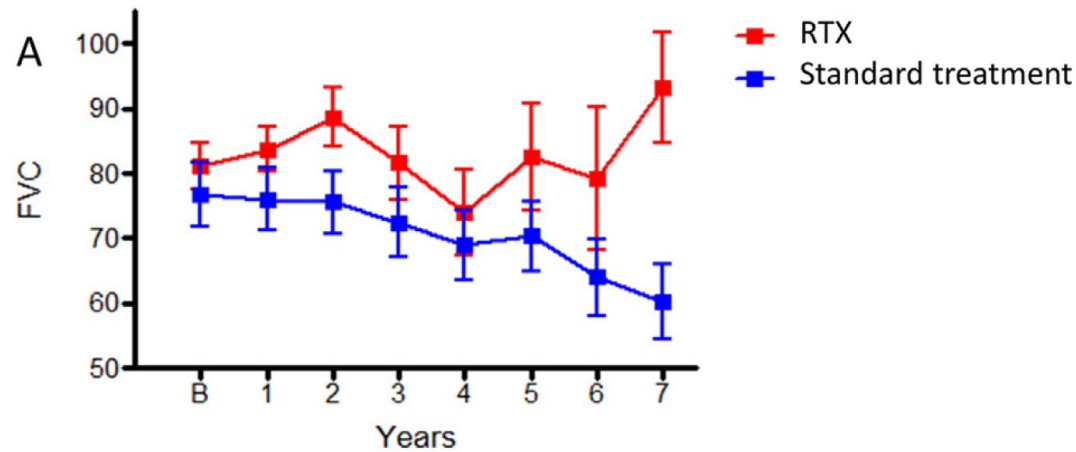
$p=0.56$  for mycophenolate mofetil versus cyclophosphamide.

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

# Rituximab

A multicenter, open-label, comparative study of B-cell depletion therapy with Rituximab for systemic sclerosis-associated interstitial lung disease<sup>☆</sup>

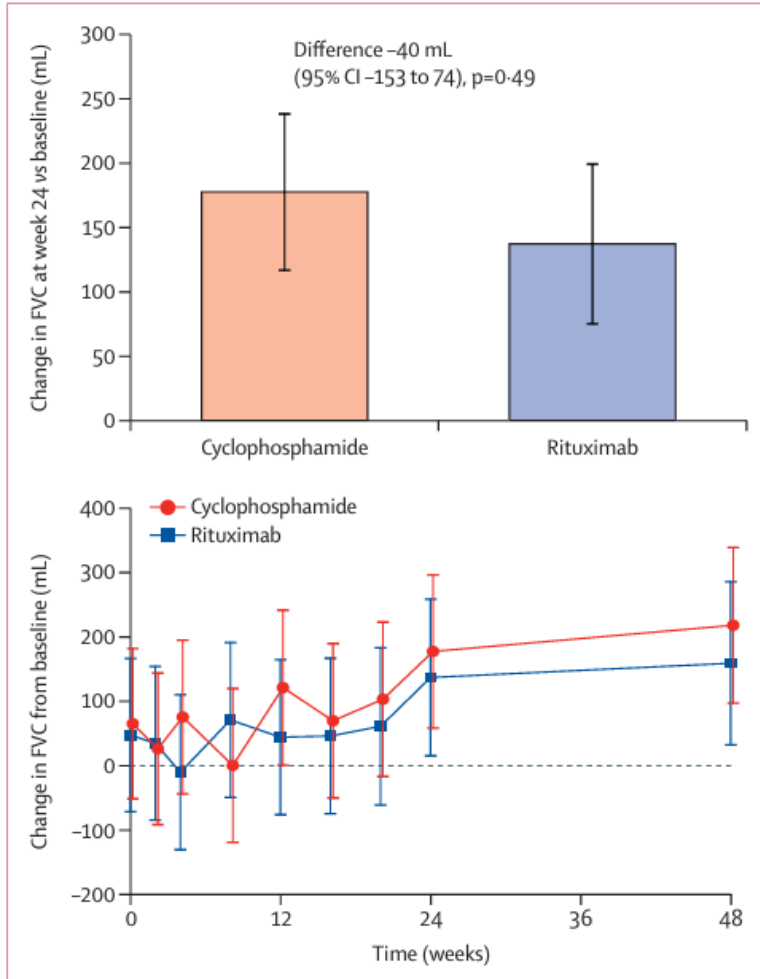
Dimitrios Daoussis, MD<sup>a,\*</sup>, Konstantinos Melissaropoulos, MD<sup>a,1</sup>, Georgios Sakellariopoulos<sup>c</sup>, Ioannis Antonopoulos, MD<sup>a</sup>, Theodora E. Markatseli, MD<sup>b</sup>, Theodora Simopoulou, MD<sup>c</sup>, Panagiotis Georgiou, MD<sup>d</sup>, Andrew P. Andonopoulos, MD<sup>a</sup>, Alexandros A. Drosos, MD<sup>b</sup>, Lazaros Sakkas, MD, DM, PhD(UK), FRCP(UK)<sup>c</sup>, Stamatis-Nick Liossis, MD<sup>a</sup>





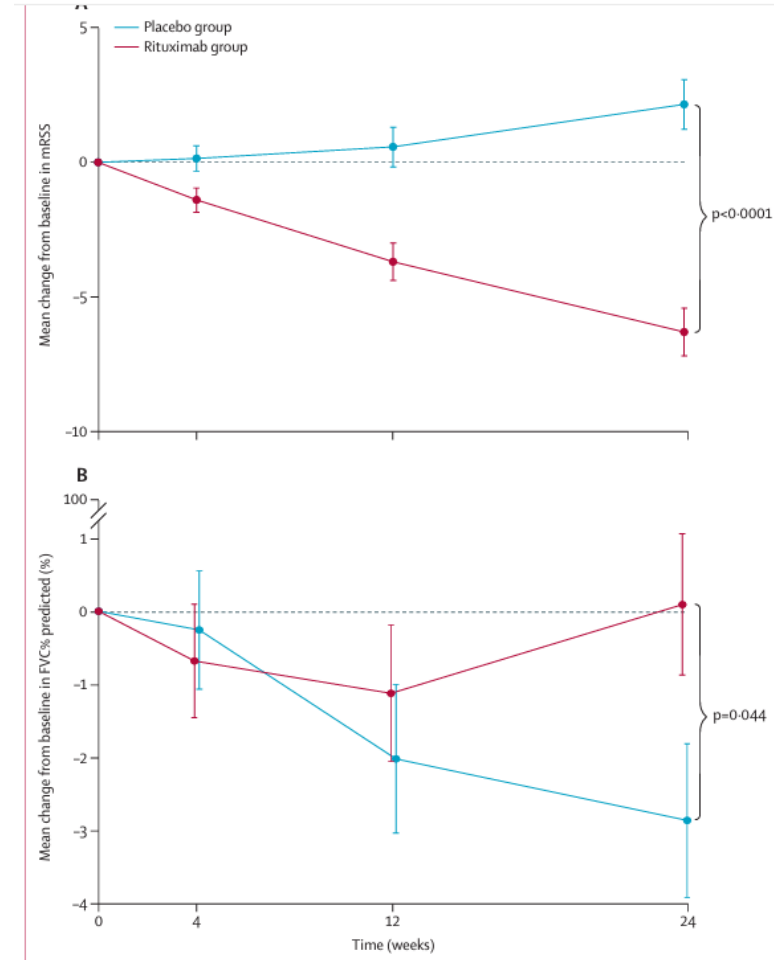
# Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): a double-blind, double-dummy, randomised, controlled, phase 2b trial

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\*



# Safety and efficacy of rituximab in systemic sclerosis (DESIREs): a double-blind, investigator-initiated, randomised, placebo-controlled trial

Satoshi Ebata\*, Ayumi Yoshizaki\*, Koji Oba, Kosuke Kashiwabara, Keiko Ueda, Yukari Uemura, Takeyuki Watadani, Takemichi Fukasawa, Shunsuke Miura, Asako Yoshizaki-Ogawa, Yoshihide Asano, Naoko Okiyama, Masanari Kodera, Minoru Hasegawa, Shinichi Sato\*



# RTX and nintedanib

**RMD  
Open**Rheumatic &  
Musculoskeletal  
Diseases

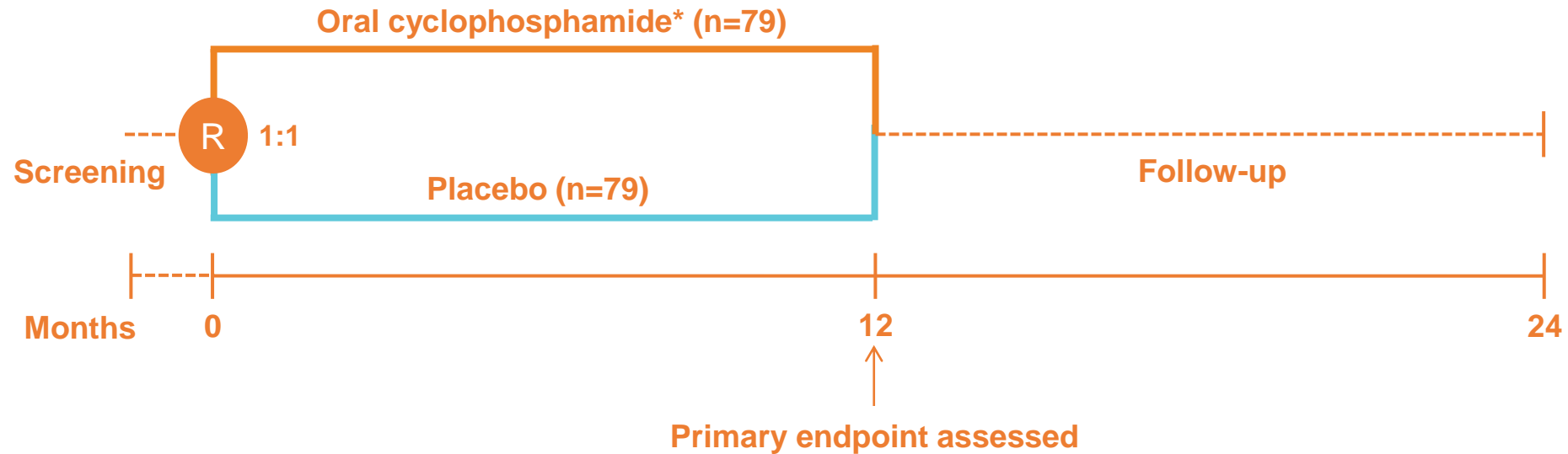
ORIGINAL RESEARCH

**Real-life efficacy and safety of nintedanib in systemic sclerosis-interstitial lung disease: data from an Italian multicentre study**

|                              |             |
|------------------------------|-------------|
| Concurrent therapies         | 77 patients |
| Corticosteroids, n (%)       | 71 (92)     |
| Mycophenolate mofetil, n (%) | 63 (81)     |
| Methotrexate, n (%)          | 2 (3)       |
| Cyclophosphamide, n (%)      | 0 (0)       |
| Azathioprine, n (%)          | 2 (3)       |
| Tocilizumab, n (%)           | 5 (6)       |
| Rituximab, n (%)             | 18 (23)     |

# Scleroderma Lung Study I. Η πρώτη μελέτη που απέδειξε την αποτελεσματικότητα της ανοσοκαταστολής

- Randomised, double-blind, placebo-controlled trial of cyclophosphamide in patients with symptomatic SSc-ILD



- Primary endpoint: change in FVC % predicted at month 12

\*Cyclophosphamide was initiated at a dose of 1 mg/kg/day and increased to a maximum of 2 mg/kg/day.

1. Tashkin DP, et al. N Engl J Med 2006;354;2655-66.

# Θεραπευτικές επιλογές-CYC

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| SF-36 score  |                |                |             |
| Physical component                                     | 33.0±1.3       | 33.8±1.3       | 0.7±1.0     |
| Mental component                                       | 48.7±1.2       | 51.8±1.3       | 2.9±1.5     |
| Skin-thickness score                                   |                |                |             |
| Diffuse  | 21.7±10.1      | 15.9±11.0      | -5.3±7.4    |
| Limited  | 6.1±3.6        | 5.0±4.3        | -0.8±2.4    |
| <b>Placebo group</b>                                   |                |                |             |
| FVC (% of predicted)                                   | 68.3±1.5       | 65.6±1.6       | -2.6±0.9    |
| Total lung capacity (% of predicted)                   | 67.9±1.9       | 64.7±1.9       | -2.8±1.2    |
| DLCO (% of predicted)                                  | 47.9±1.7       | 44.3±2.1       | -3.5±1.0    |
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-1%

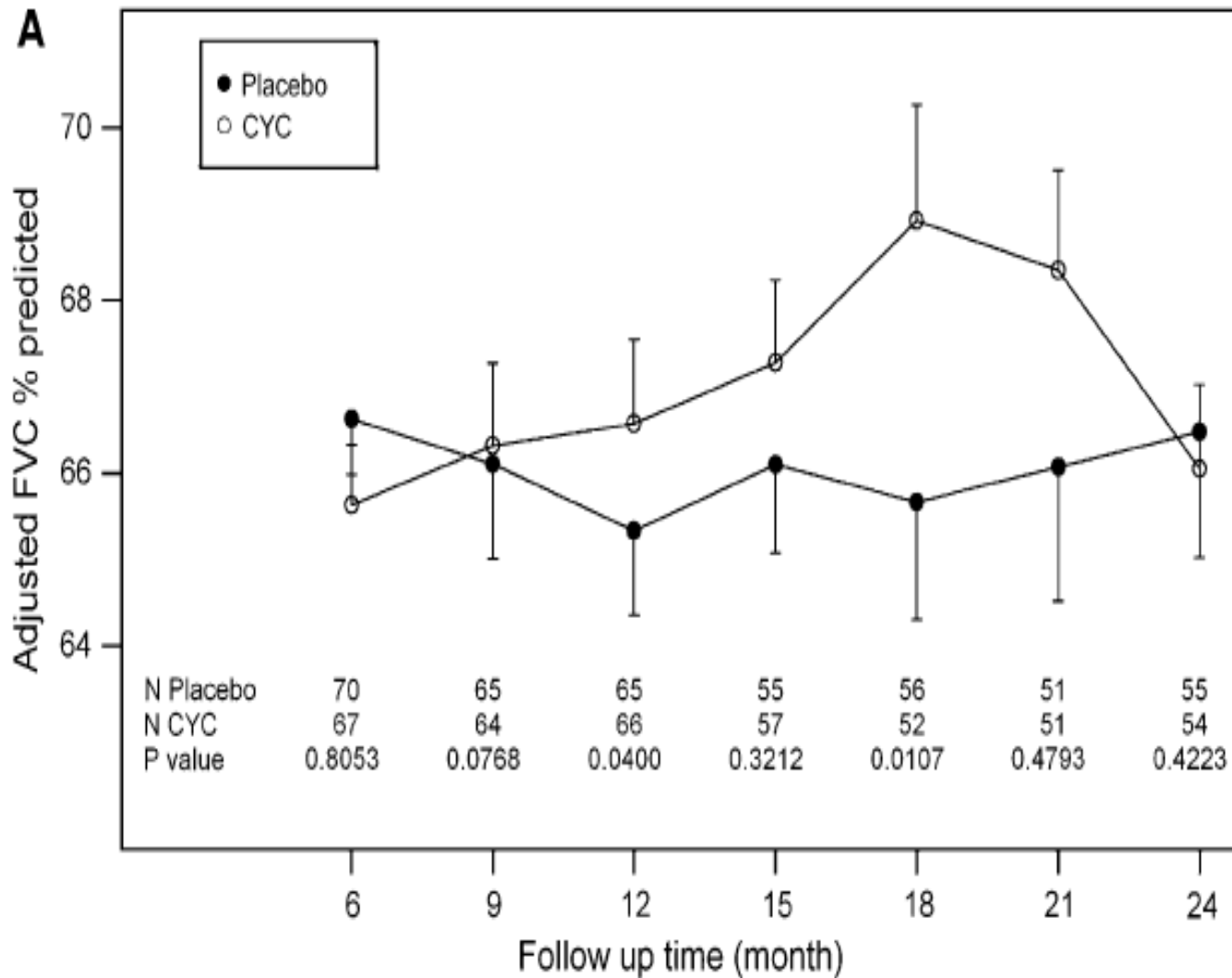
-2.6%

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cyclophosphamide versus Placebo  
in Scleroderma Lung Disease

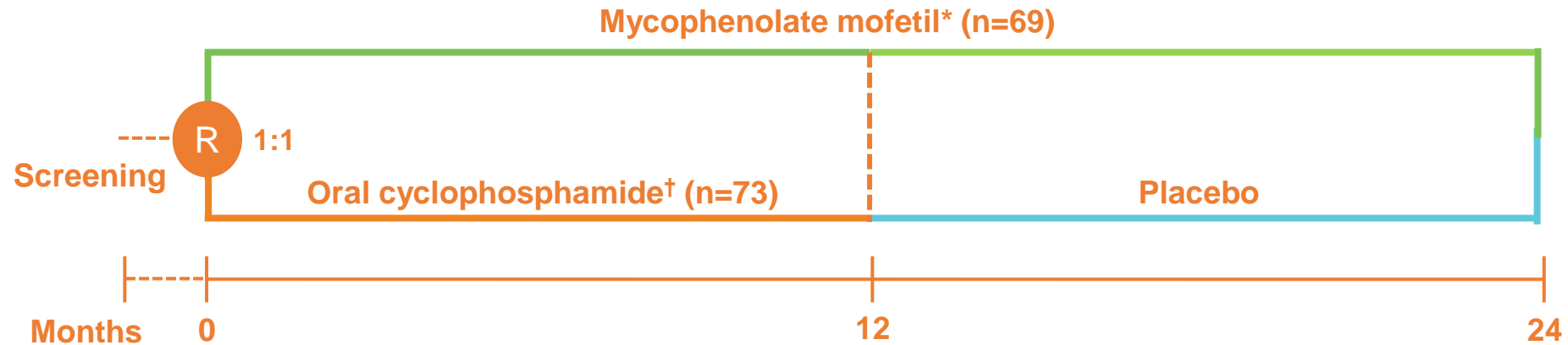
**Effects of 1-Year Treatment with Cyclophosphamide on Outcomes at 2 Years in Scleroderma Lung Disease**



- Η ευεργετική δράση της CYC διατηρείται για λίγους μήνες μετά την διακοπή της θεραπείας

# Scleroderma Lung Study II: Design

- Randomised, double-blind, trial of mycophenolate mofetil versus cyclophosphamide in patients with symptomatic SSc-ILD



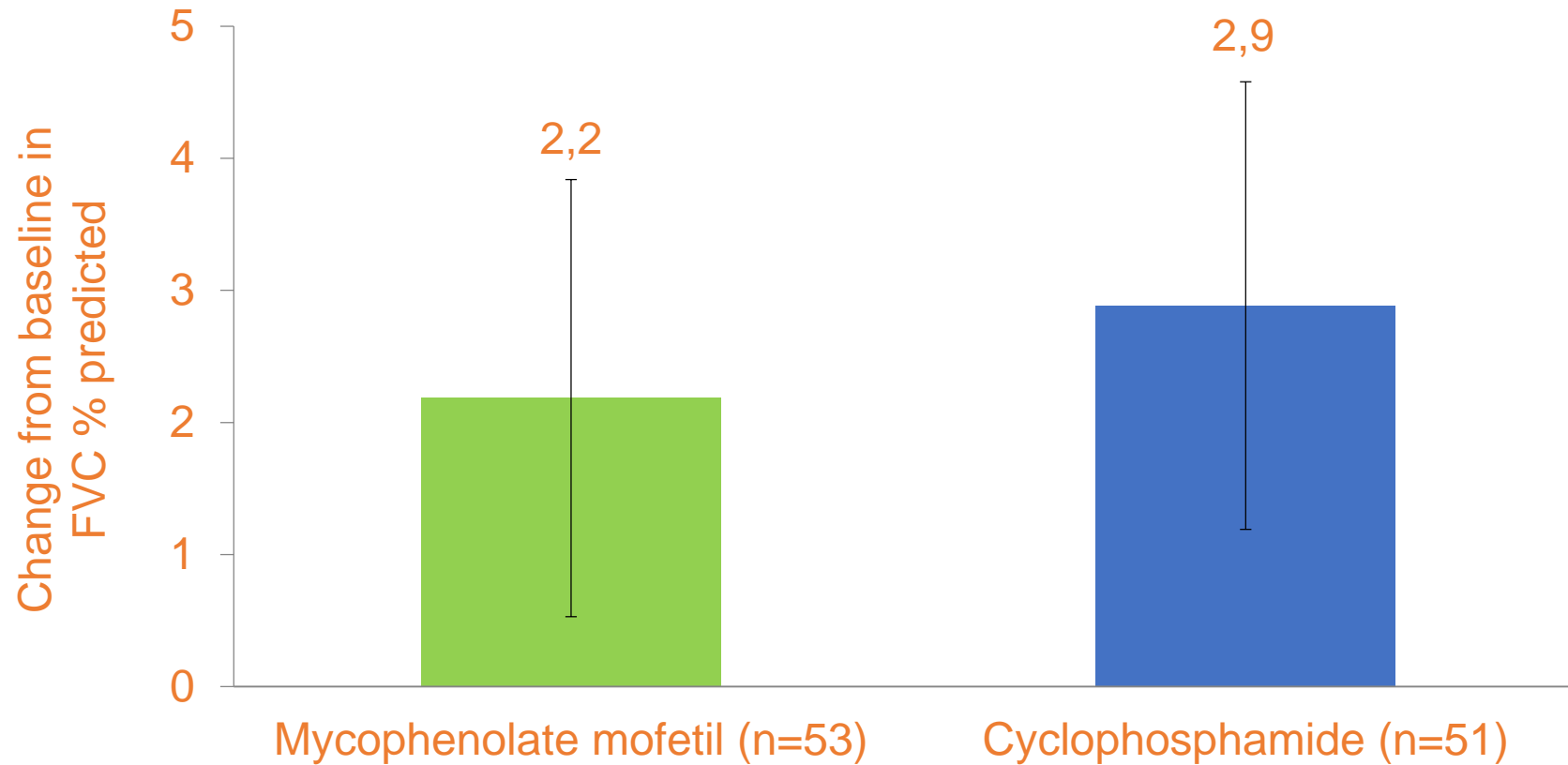
- Primary endpoint: change in FVC % predicted at month 24

\*Mycophenolate mofetil was initiated at 500 mg bid and increased to a maximum of 1500 mg bid.

<sup>†</sup>Cyclophosphamide was initiated at 50-150 mg/kg/day and increased to 1.8-2.3 mg/kg/day.

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

# Scleroderma Lung Study II: Change from baseline in FVC % predicted at month 24 (primary endpoint)



Data are mean  $\pm$  95% CI.

$p=0.56$  for mycophenolate mofetil versus cyclophosphamide.

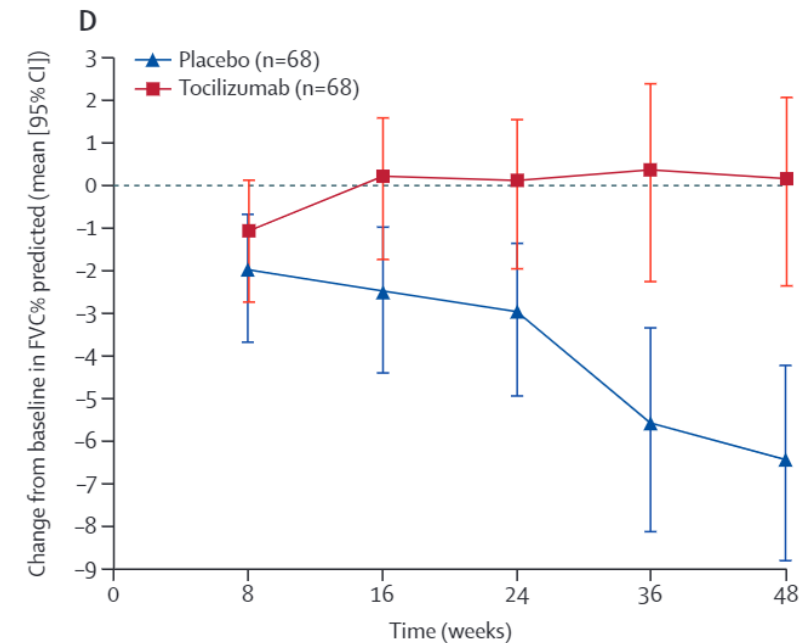
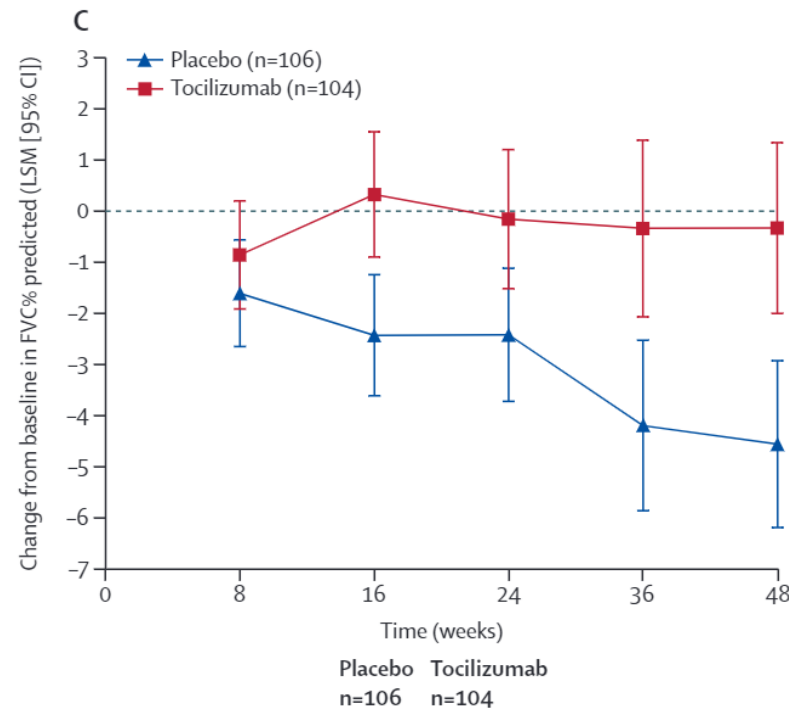
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# Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial



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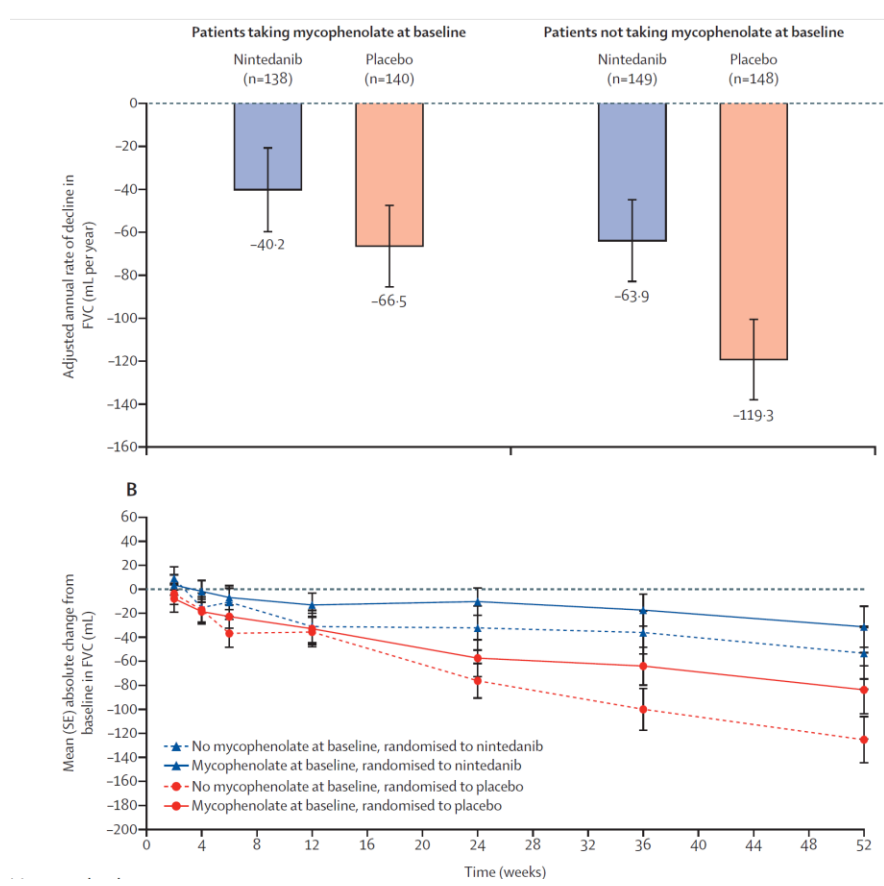
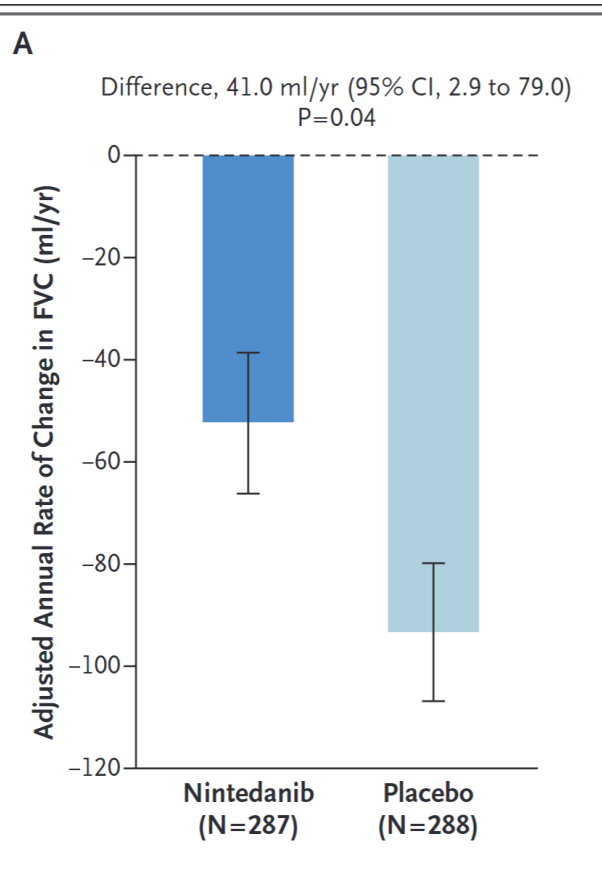
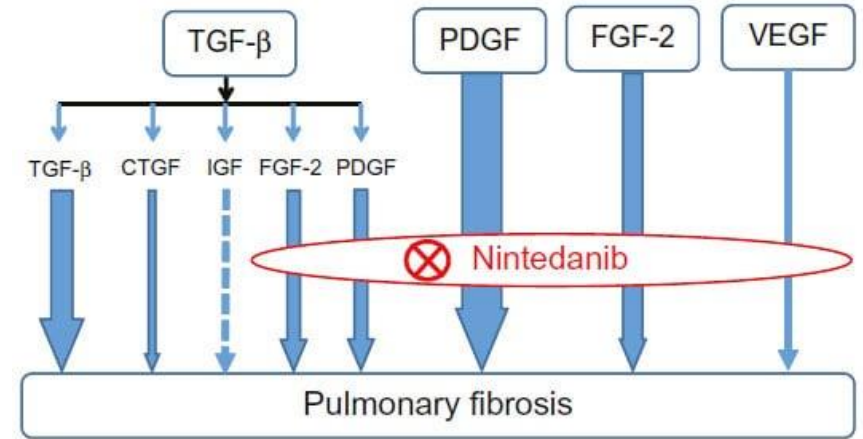
- Δοκιμάστηκε μόνο σε ασθενής με φλεγμονώδη απάντηση
- Καθυστερεί την εξέλιξη της πνευμονικής νόσου
- Δεν έπιασε το καταληκτικό σημείο στο δέρμα





ORIGINAL ARTICLE

# Nintedanib for Systemic Sclerosis–Associated Interstitial Lung Disease



- Συνεργική δράση με το MMF
- Δεν δρα σε άλλα όργανα

## Autologous Hematopoietic Stem Cell Transplantation vs Intravenous Pulse Cyclophosphamide in Diffuse Cutaneous Systemic Sclerosis

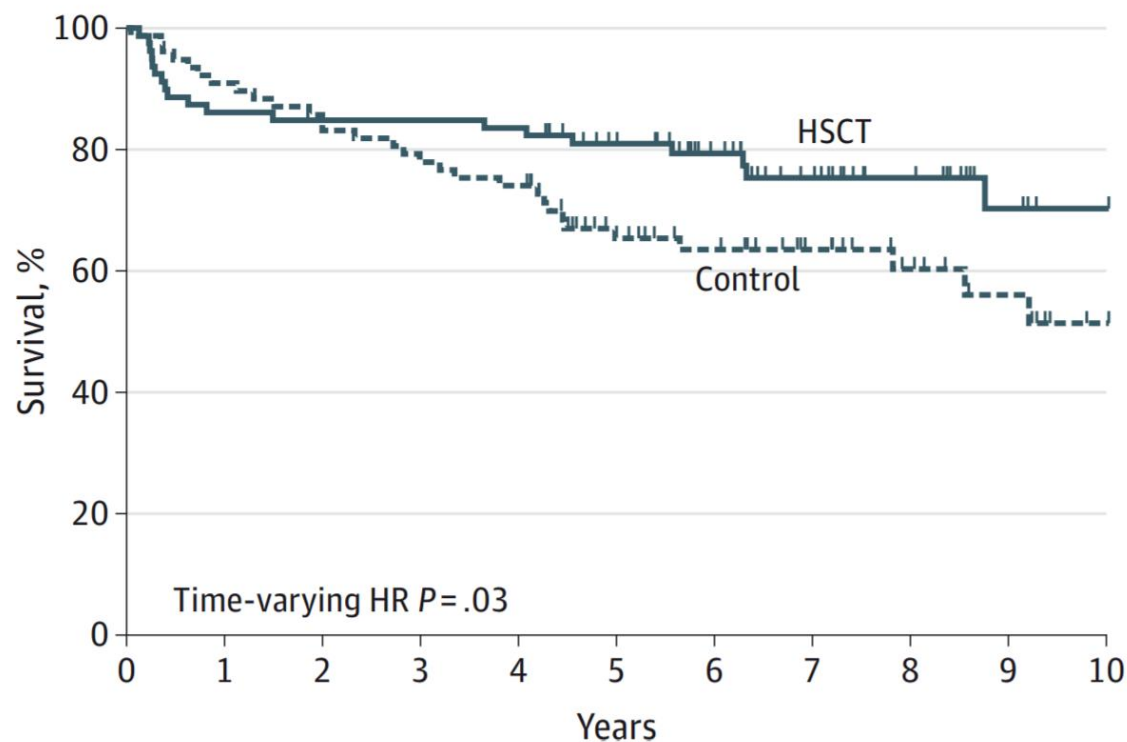
A Randomized Clinical Trial

Jacob M. van Laar, MD, PhD<sup>1</sup>; Dominique Farge, MD, PhD<sup>2</sup>; Jacob K. Sont, PhD<sup>3</sup>; [et al](#)

## Αυτόλογη μεταμόσχευση αρχέγονων αιμοποιητικών κυττάρων

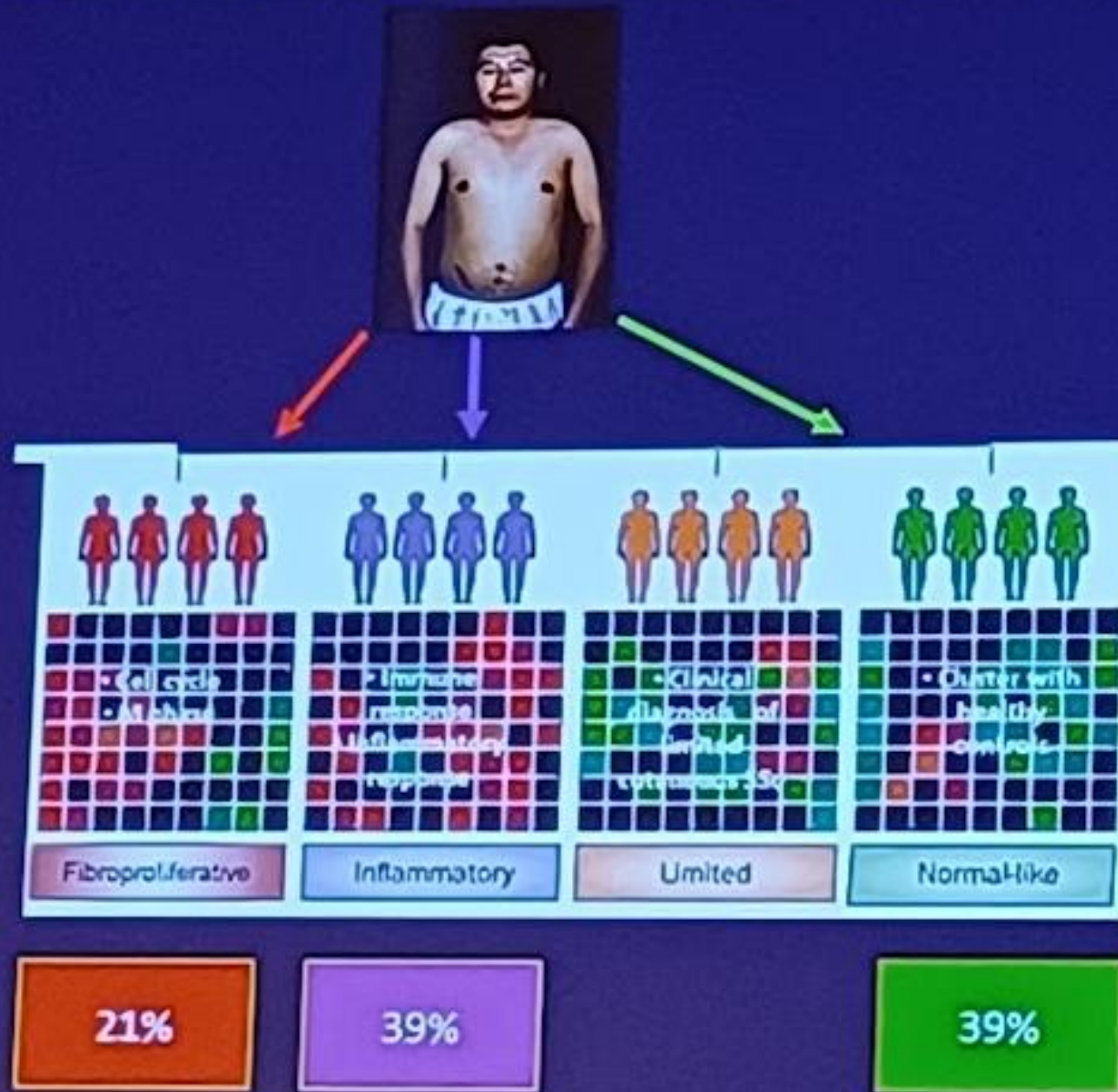
- Ένδειξη μόνο σε ασθενείς με πολύ σοβαρή/εξελισσόμενη νόσο καθώς η διαδικασία σχετίζεται με υψηλή νοσηρότητα-θνητότητα. Μακροχρόνια, αυξάνεται η επιβίωση

**B** Overall survival



| No. at risk | 0  | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 |
|-------------|----|----|----|----|----|----|----|----|----|----|----|
| HSCT        | 79 | 68 | 67 | 67 | 66 | 55 | 43 | 32 | 23 | 14 | 11 |
| Control     | 77 | 70 | 64 | 60 | 57 | 40 | 34 | 25 | 18 | 12 | 6  |

# Classification based on Gene Expression



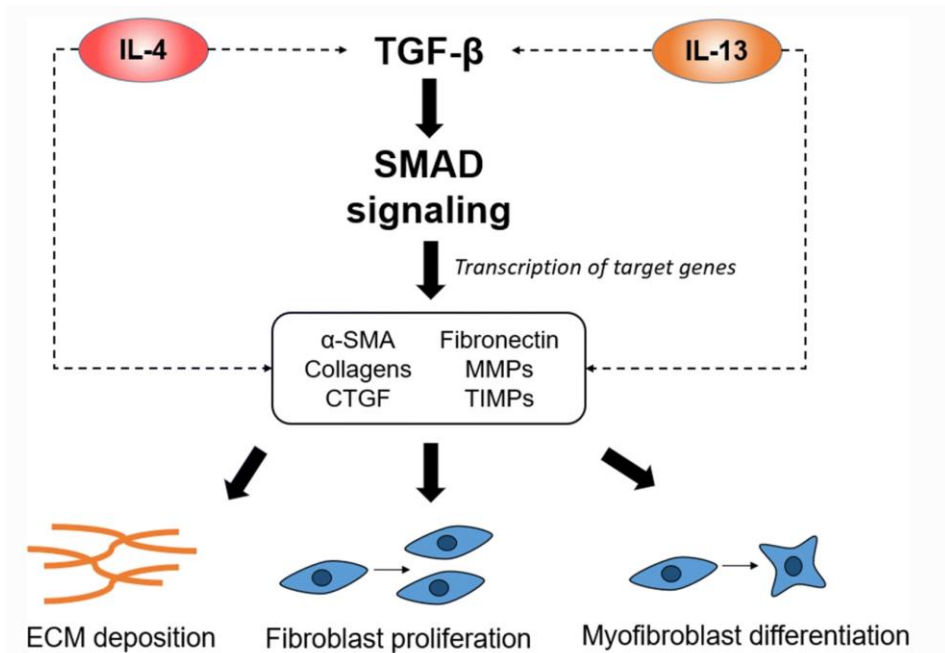
# Myeloablation followed by autologous stem cell transplantation normalises systemic sclerosis molecular signatures

Shervin Assasi,<sup>1</sup> Xuan Wang,<sup>2</sup> Guocai Chen,<sup>3</sup> Ellen Goldmuntz,<sup>4</sup> Lynette Keyes-Elstein,<sup>5</sup> Jun Ying,<sup>1</sup> Paul K Wallace,<sup>6</sup> Jacob Turner,<sup>7</sup> W Jim Zheng,<sup>3</sup> Virginia Pascual,<sup>8</sup> John Varga,<sup>9</sup> Monique E Hinchcliff,<sup>10</sup> Chiara Bellocchi,<sup>1</sup> Peter McSweeney,<sup>11</sup> Daniel E Furst,<sup>12,13</sup> Richard A Nash,<sup>11</sup> Leslie J Crofford,<sup>14</sup> Beverly Welch,<sup>4</sup> Ashley Pinckney,<sup>15</sup> Maureen D Mayes,<sup>1</sup> Keith M Sullivan<sup>16</sup>

**Results** At the baseline visit, interferon (IFN) and neutrophil transcript modules were upregulated and the cytotoxic/NK module was downregulated in SSc compared with unaffected controls. A paired comparison

# Τι νεότερο στην θεραπευτική... Στοχεύοντας κυτταροκίνες με προινωτική δράση...

- Οι IL-4 και IL-13 είναι ενδιαφέροντες θεραπευτικοί στόχοι



## Systemic sclerosis

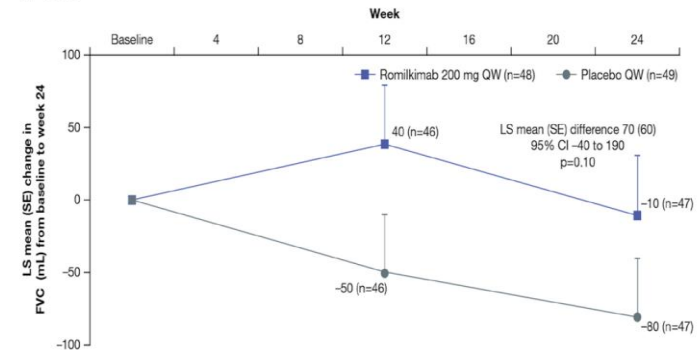


OPEN ACCESS

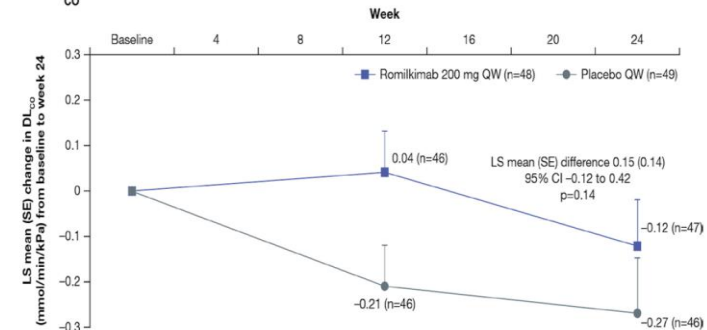
CLINICAL SCIENCE

A randomised, double-blind, placebo-controlled, 24-week, phase II, proof-of-concept study of romilkimab (SAR156597) in early diffuse cutaneous systemic sclerosis

### A FVC



### B DL<sub>CO</sub>



# Το παράδειγμα του ΣΕΛ

Clinical and epidemiological research



EXTENDED REPORT

Prospective observational single-centre cohort study to evaluate the effectiveness of treating lupus nephritis with rituximab and mycophenolate mofetil but no oral steroids

Marie B Condon,<sup>1</sup> Damien Ashby,<sup>1</sup> Ruth J Pepper,<sup>1</sup> H Terence Cook,<sup>1,2</sup> Jeremy B Levy,<sup>1</sup> Megan Griffith,<sup>1</sup> Tom D Cairns,<sup>1</sup> Liz Lightstone<sup>1,2,3</sup>

