INSYNC

EUSTAR

SCTC
Scleroderma Clinical Trials Consortium

Red de Enfermedades Inflamatorias (REI)
RICORS (RD21/0002)

NUEVOS AVANCES EN REUMATOLOGÍA E IMPLICACIONES TERAPÉUTICAS
2ª edición

European Reference Network
for rare or low prevalence complex diseases
Network Connective Tissue and Musculoskeletal Diseases (ERN ReCONNET)
Member University Hospital 12 de Octubre — Spain

unidad de EAS12
Enfermedades Autoinmunes Sistémicas

Antifibróticos en esclerosis sistémica: ¿existe alguna esperanza?

Patricia E Carreira

Servicio de Reumatología, Hospital Universitario 12 de Octubre

H12 Investiga
JUNTOS CONSTRUIMOS, JUNTOS AVANZAMOS

Hospital Universitario 12 de Octubre
SaludMadrid
Comunidad de Madrid

i+12
Instituto de Investigación Hospital 12 de Octubre

Conflicto de intereses

- Asesorías y conferencias: Actelion, Lilly, VivaCell, Emerald Health Pharmaceuticals, Gesynta Pharma, Boehringer Ingelheim, Abbie, Sanofi Genzyme, Mitsubishi Tanabe

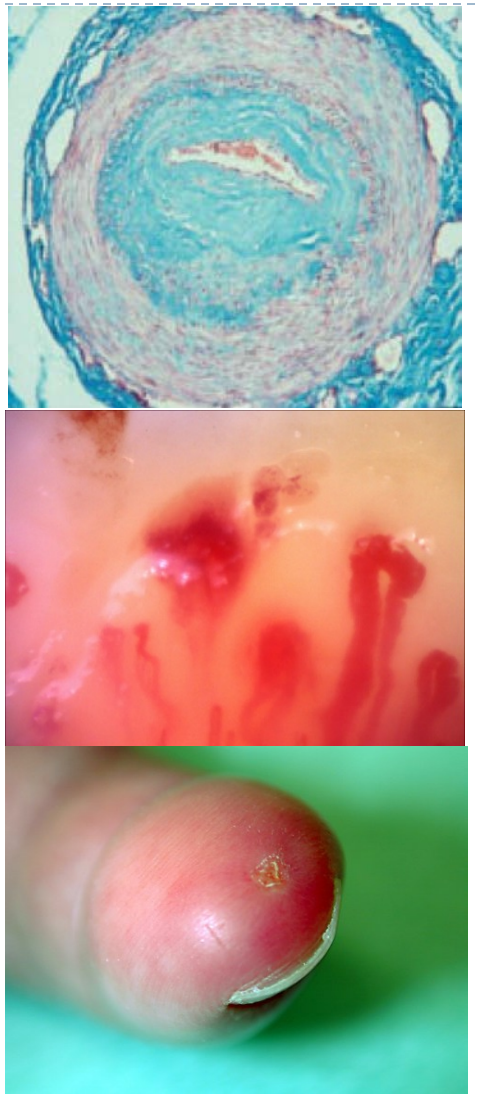
- Ensayos clínicos: Inventiva, BMS, Roche, Bayer, Merck Sorono, Boehringer Ingelheim, Iltoo, Corbus, Emerald Health Pharmaceuticals, Galapagos, Idorsia, Mitsubishi Tanabe, Certa, Prometheus, Pfizer, Alexion, Horizon, Argenx, Genentech

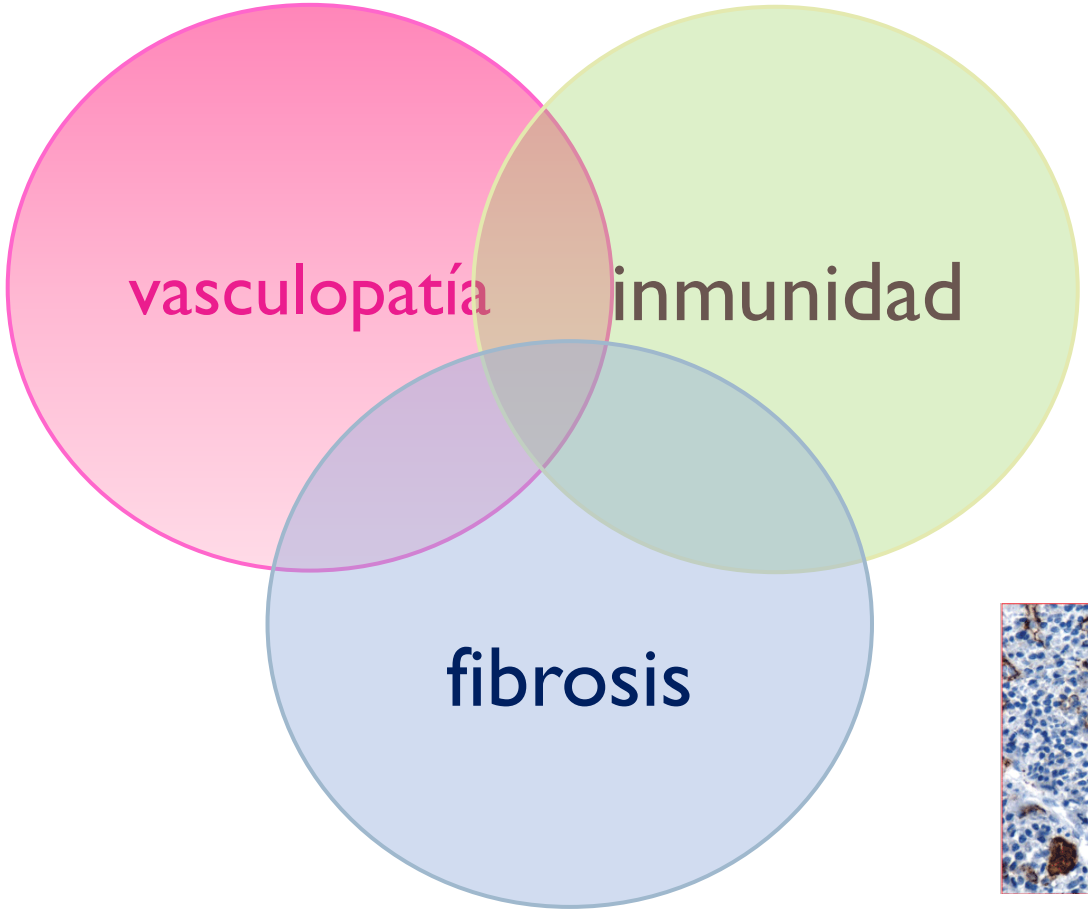
Se comentan indicaciones/dosis/pautas fuera de las aprobadas en Ficha Técnica AEMPS

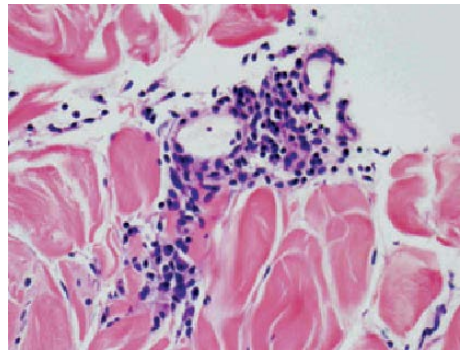
agenda

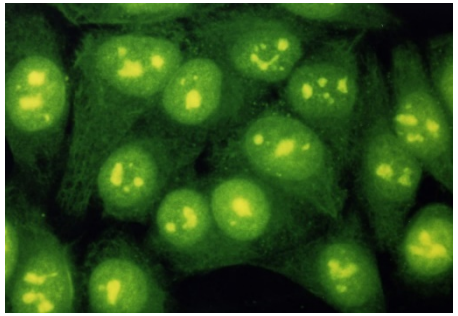
- Fisiopatología (muy breve) de la fibrosis
- Antifibróticos con evidencia en la esclerosis sistémica y otras enfermedades reumáticas: NINTEDANIB y PIRFENIDONA
- Evidencias con otros fármacos (antifibróticos?)
- Fármacos para el futuro
- Conclusiones

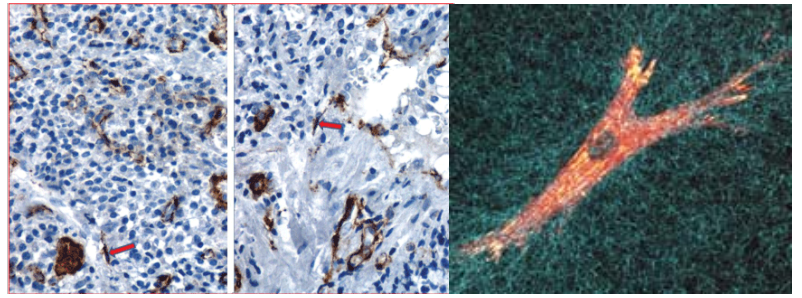
Fisiopatología de la esclerosis sistémica

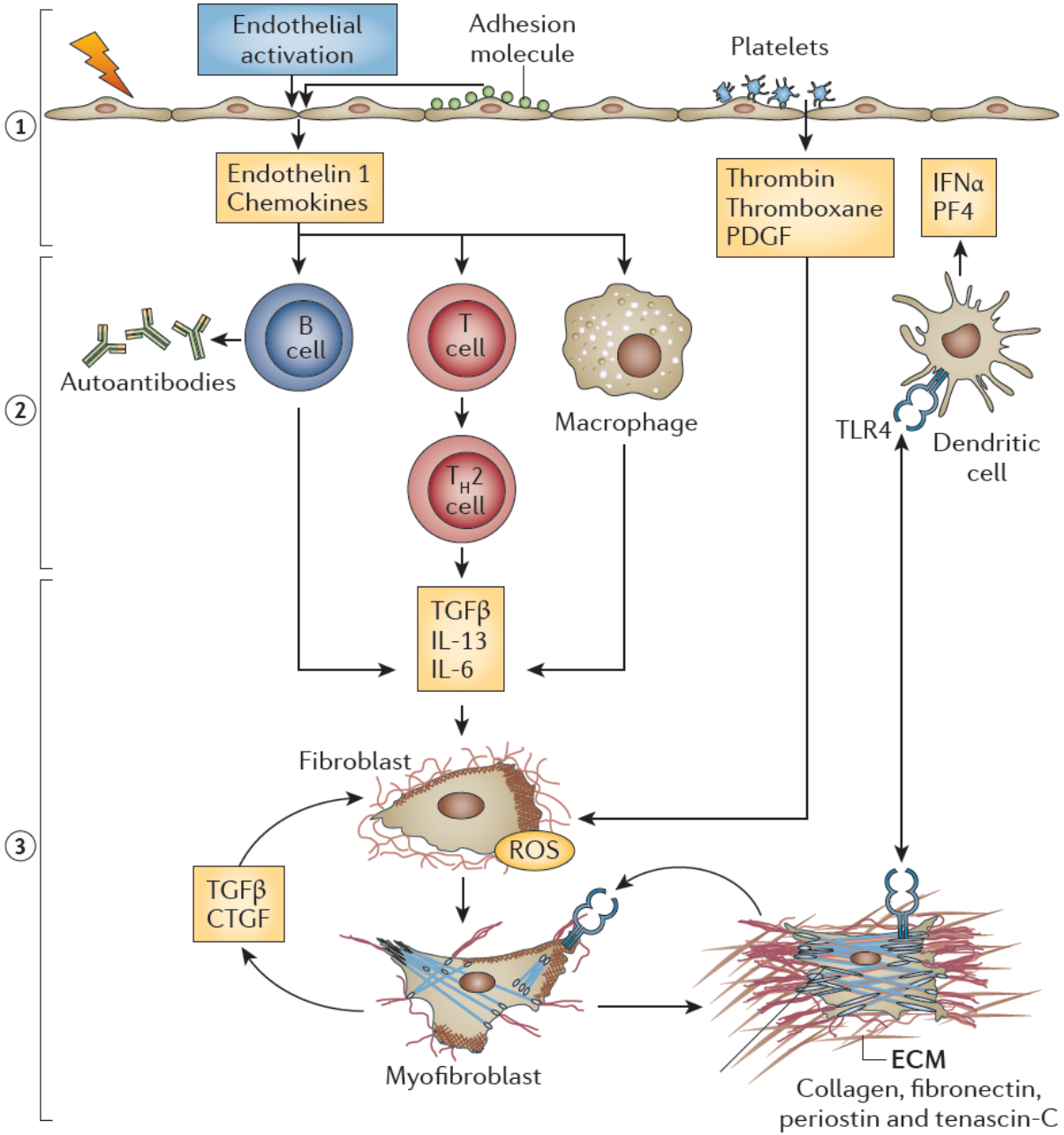


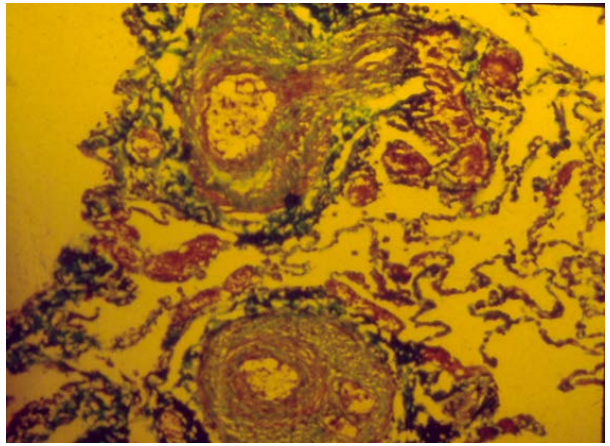


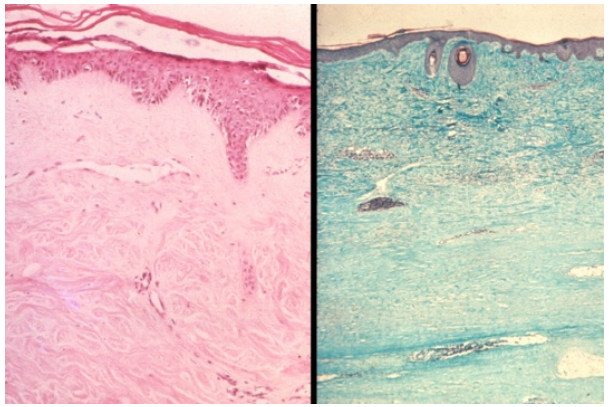


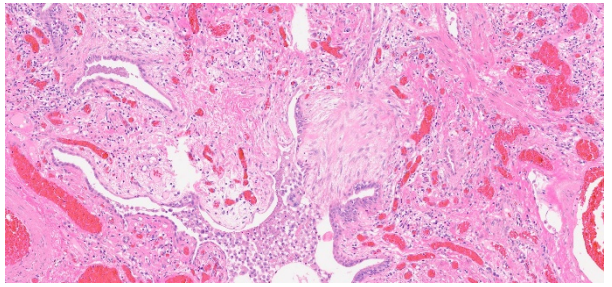


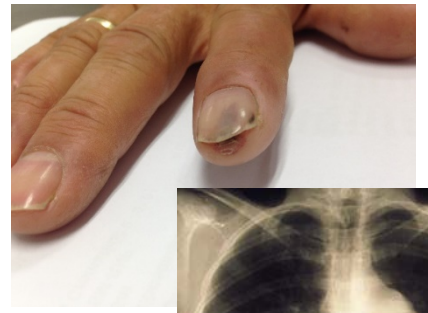


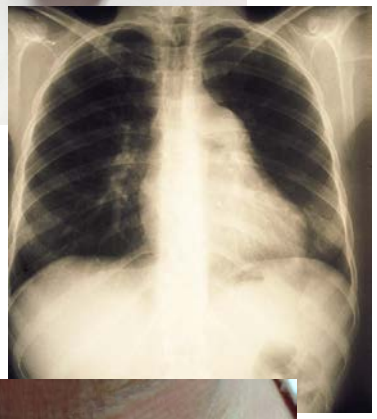

Endothelial activation
Adhesion molecule
Platelets
1
Endothelin 1
Chemokines
Thrombin
Thromboxane
PDGF
IFNα
PF4
2
B cell
Autoantibodies
T cell
Macrophage
TLR4
Dendritic cell
T_H2 cell
TGFβ
IL-13
IL-6
3
Fibroblast
ROS
TGFβ
CTGF
Myofibroblast
ECM
Collagen, fibronectin, periostin and tenascin-C

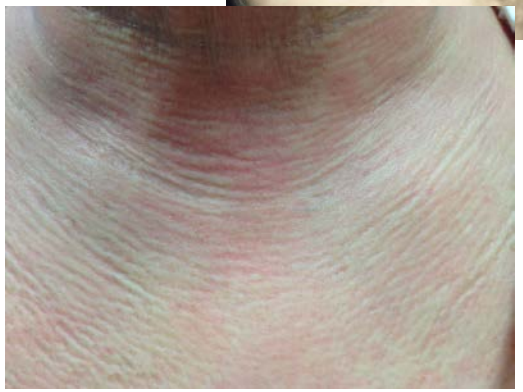


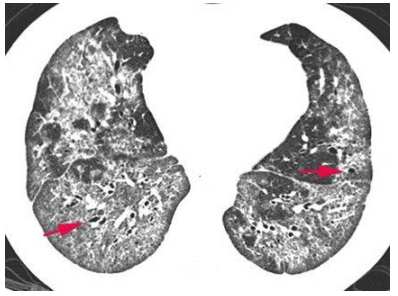


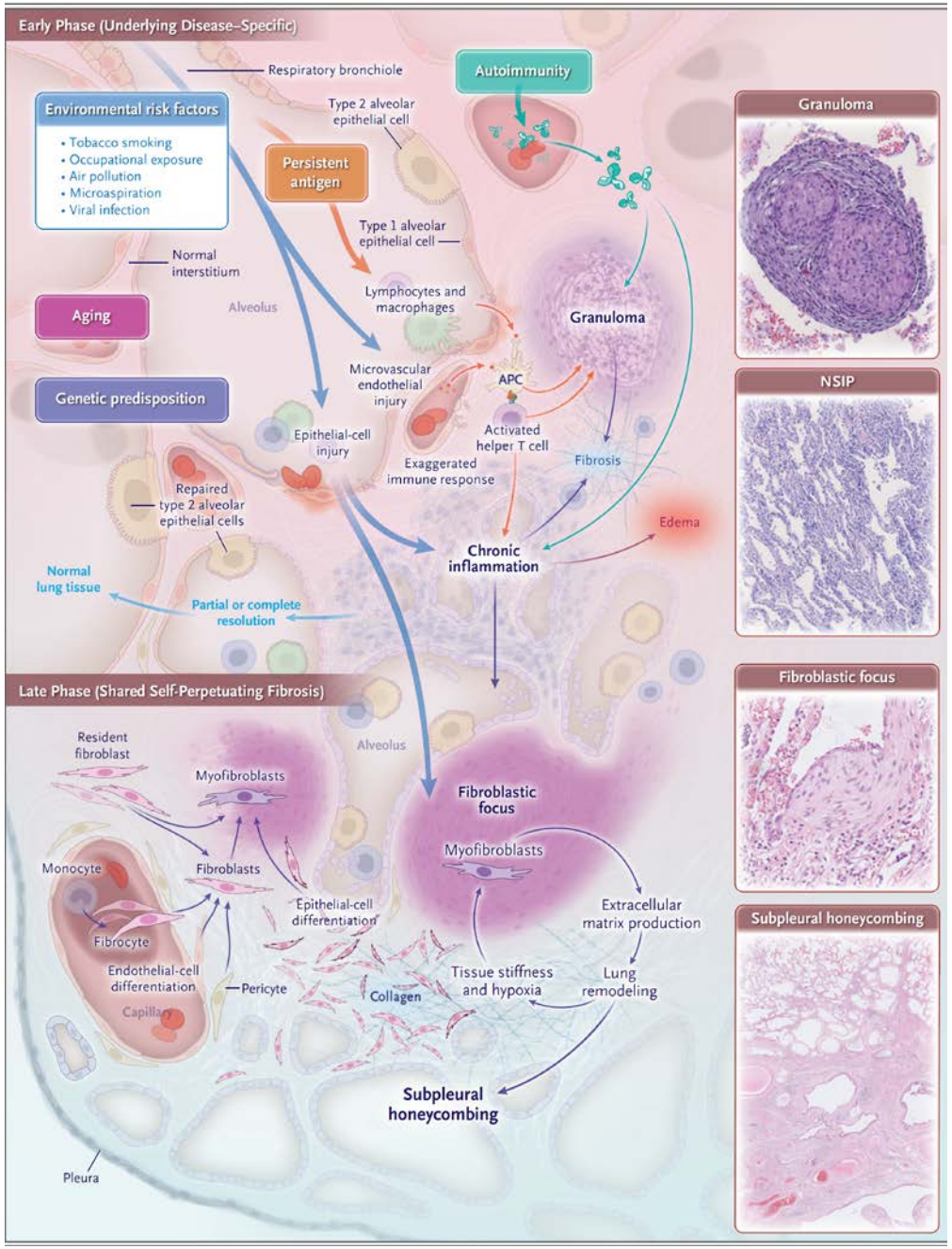












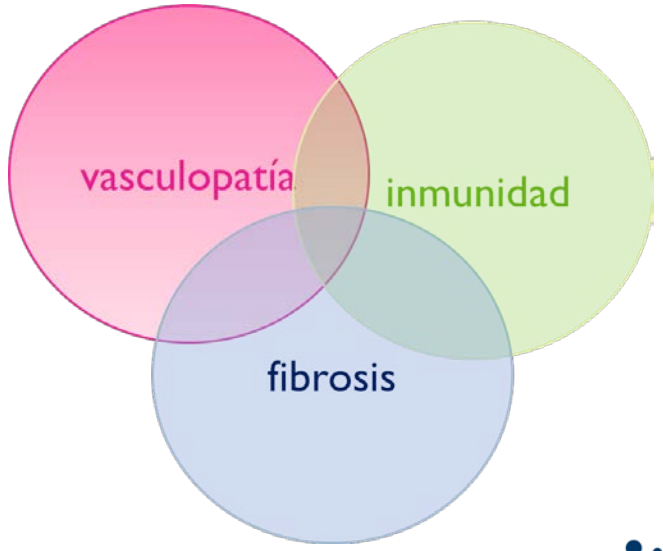
I

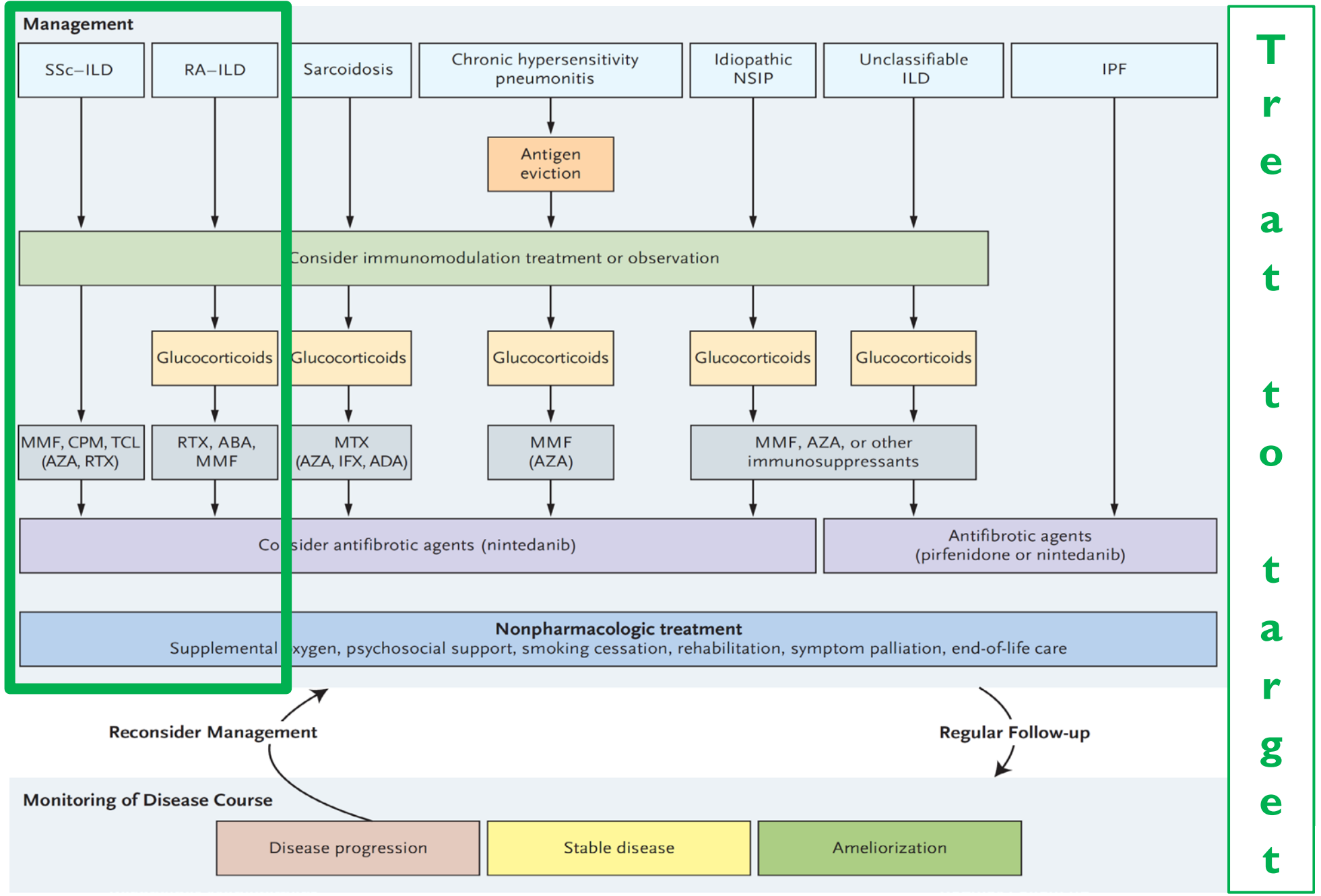
2

N ENGL J MED 383;10 NEJM.ORG SEPTEMBER 3, 2020

Spectrum of Fibrotic Lung Diseases

Marlies Wijsenbeek, M.D., and Vincent Cottin, M.D.

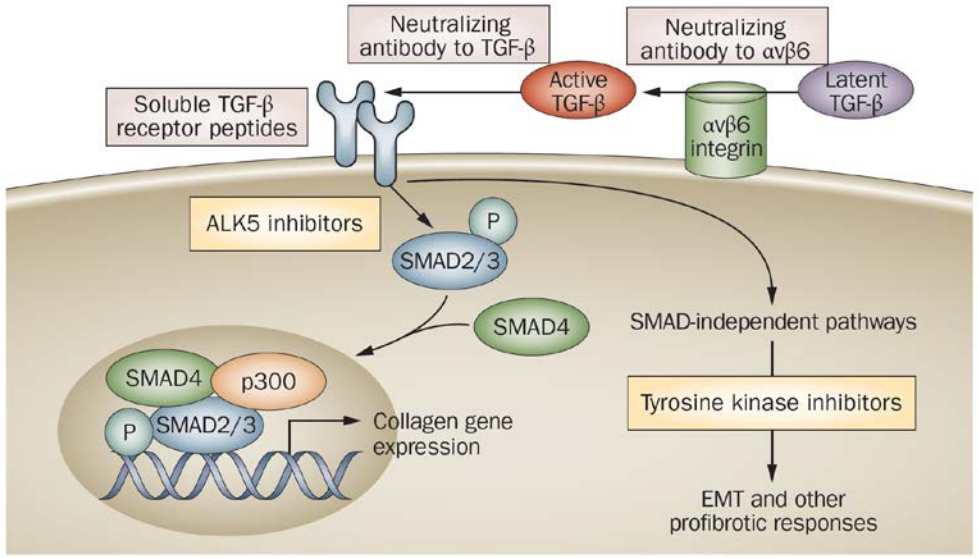



Management
SSc–ILD
RA–ILD
Sarcoidosis
Chronic hypersensitivity pneumonitis
Idiopathic NSIP
Unclassifiable ILD
IPF
Antigen eviction
Consider immunomodulation treatment or observation
Glucocorticoids
Glucocorticoids
Glucocorticoids
Glucocorticoids
Glucocorticoids
MMF, CPM, TCL (AZA, RTX)
RTX, ABA, MMF
MTX (AZA, IFX, ADA)
MMF (AZA)
MMF, AZA, or other immunosuppressants
Consider antifibrotic agents (nintedanib)
Antifibrotic agents (pirfenidone or nintedanib)
Nonpharmacologic treatment
Supplemental oxygen, psychosocial support, smoking cessation, rehabilitation, symptom palliation, end-of-life care
Reconsider Management
Regular Follow-up
Monitoring of Disease Course
Disease progression
Stable disease
Ameliorization
Treat to target

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*

N Engl J Med 2019;380:2518-28.



CRITERIOS DE INCLUSIÓN

- < 7 años de evolución
- EPI >10% en TACar
- FVC > 40%
- DLCO: 30-89%
- Prednisona ≤ 10 mg/d
- Metotrexate
- Micofenolato

CRITERIOS DE EXCLUSIÓN

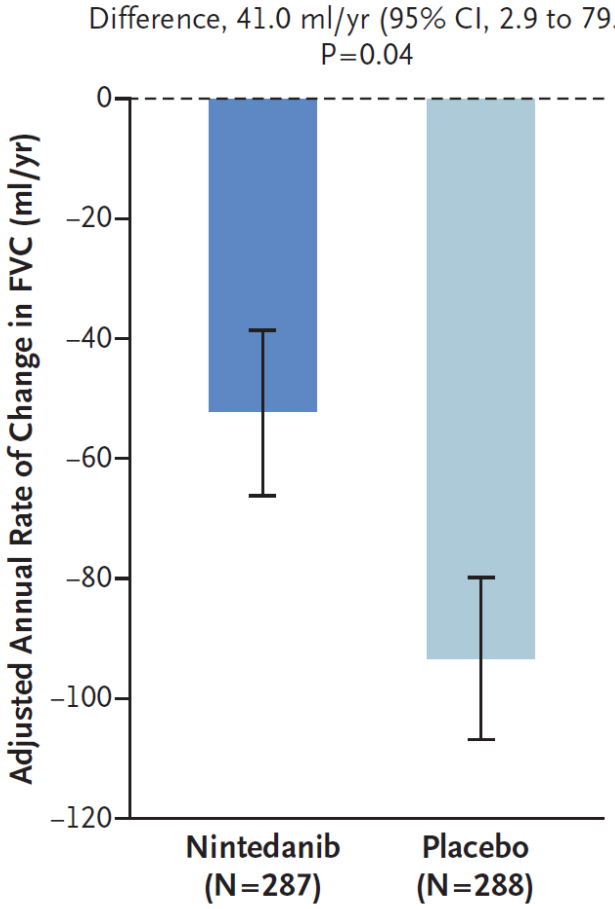
- HAP que requiere tratamiento vasodilatador
- Fracaso VD
- Índice cardiaco ≤ 2 l/min/m^2

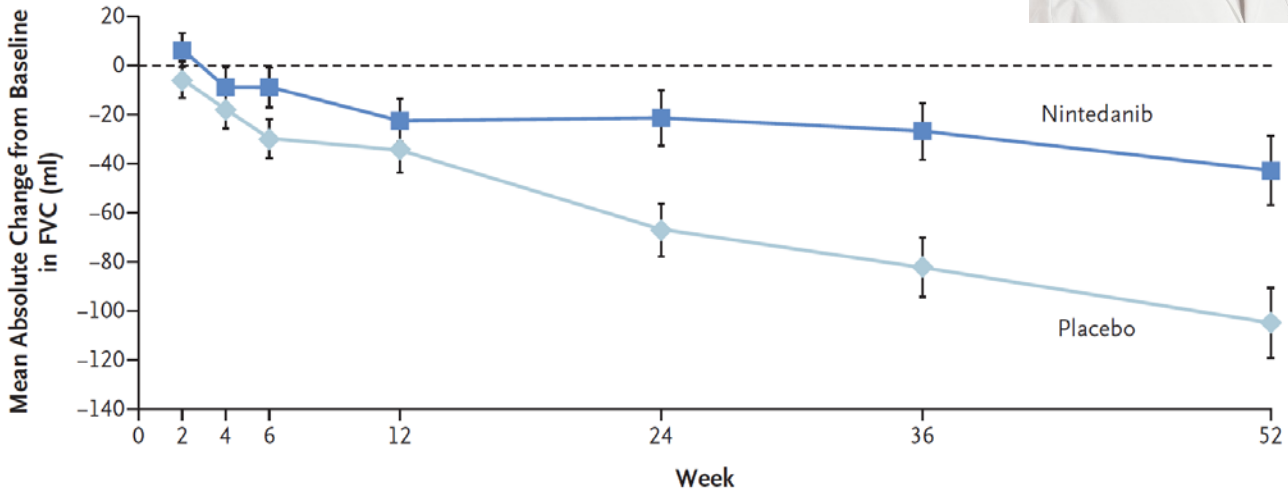
Nintedanib for Systemic Sclerosis–Associated Interstitial Lung Disease

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*

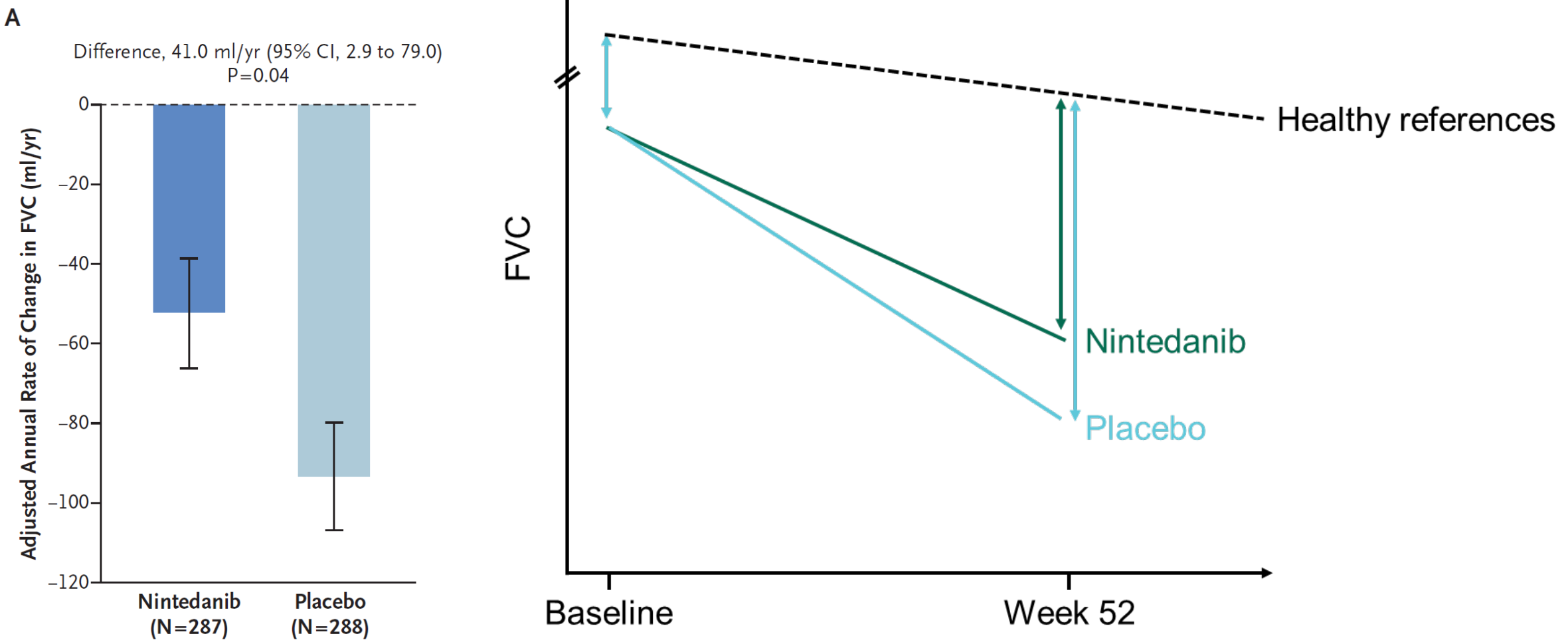
N Engl J Med 2019;380:2518-28.

Estudio SENSCIS



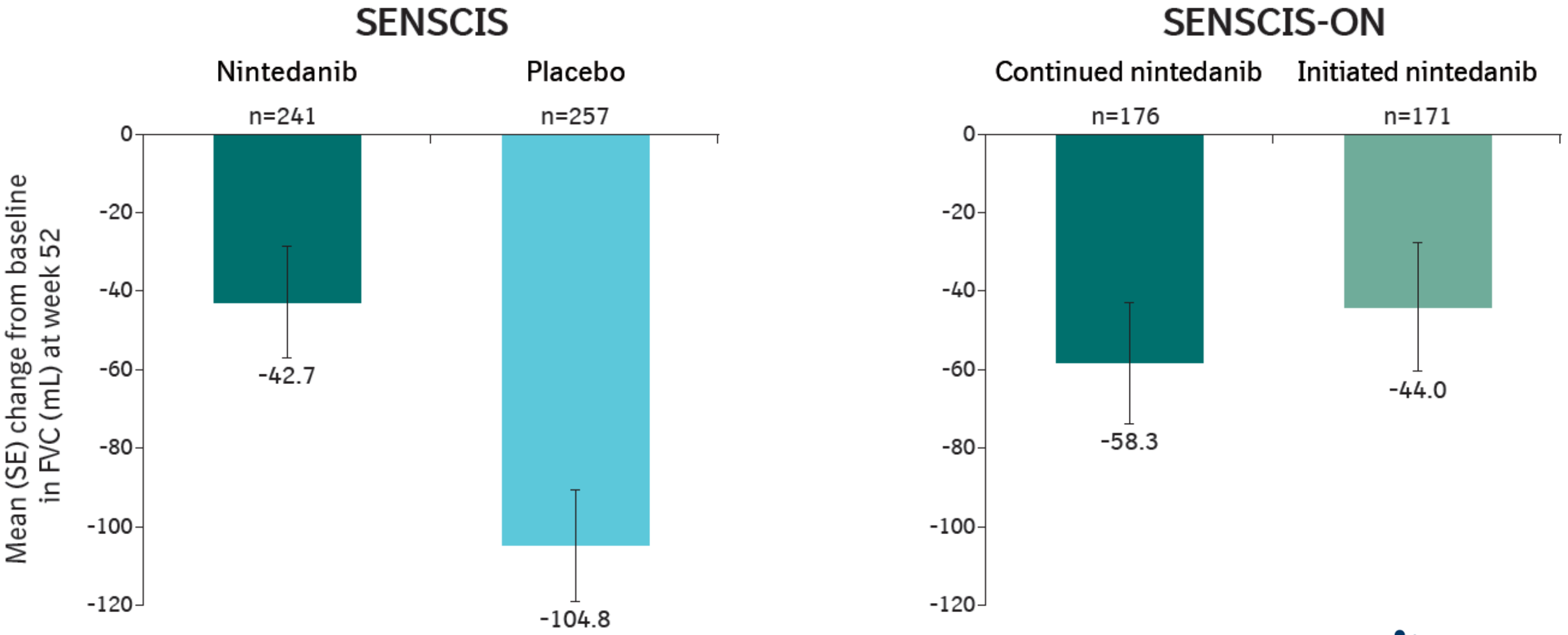


No. of Patients							
Nintedanib	288	283	281	273	278	265	262	24
Placebo	288	283	281	280	283	280	268	25

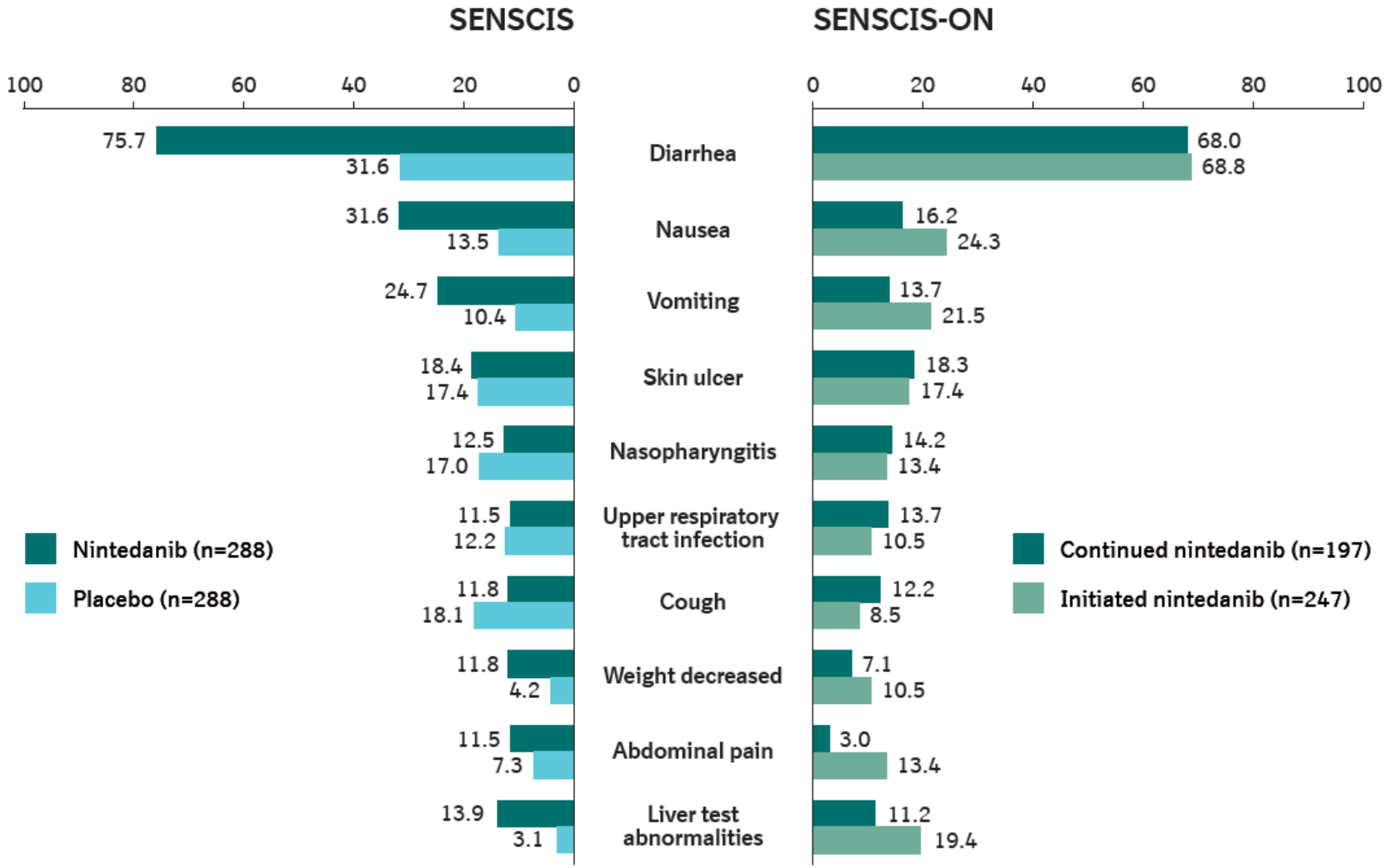

A
Difference, 41.0 ml/yr (95% CI, 2.9 to 79.0)
P=0.04
Adjusted Annual Rate of Change in FVC (ml/yr)
0
−20
−40
−60
−80
−100
−120
Nintedanib (N=287)
Placebo (N=288)
FVC
Healthy references
Nintedanib
Placebo
Baseline
Week 52

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

Ann Rheum Dis 2022;**81**:1722–1729.



Nintedanib: efectos adversos



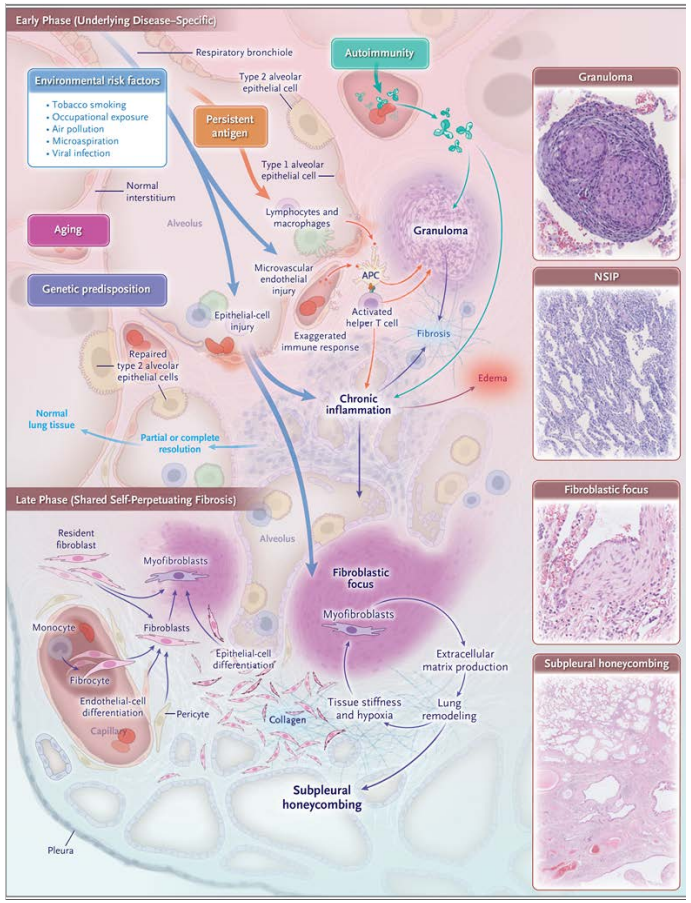
Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSCIS trial

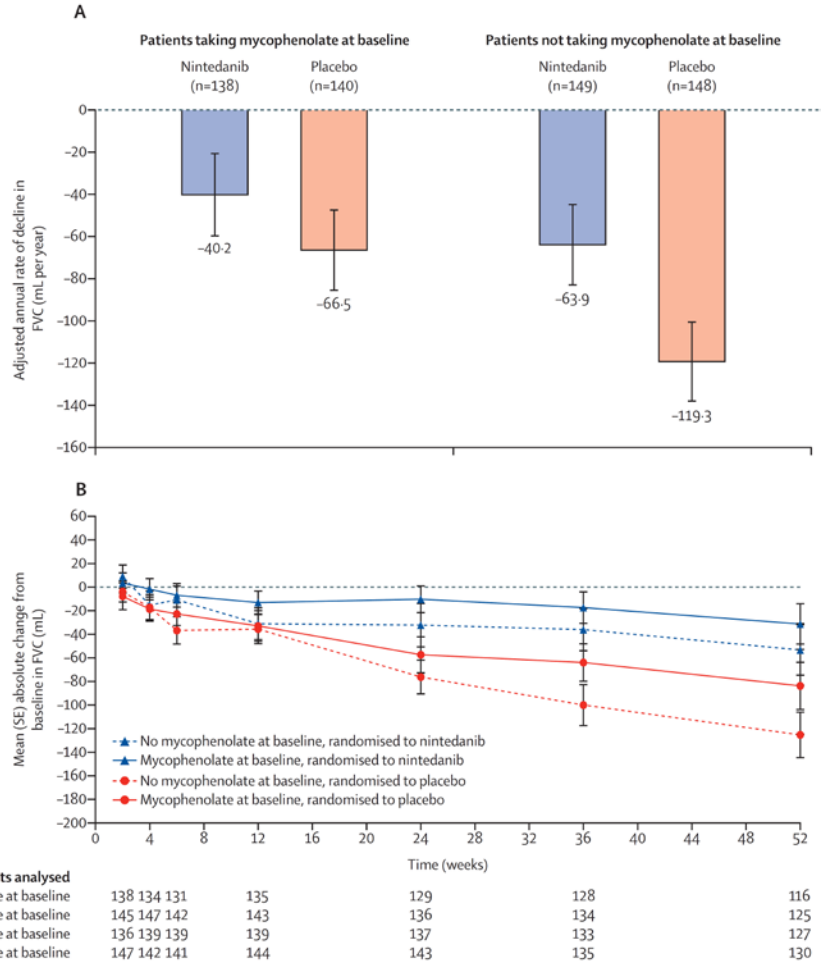
Lancet Respir Med 2021; 9: 96–106

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†*

1

2

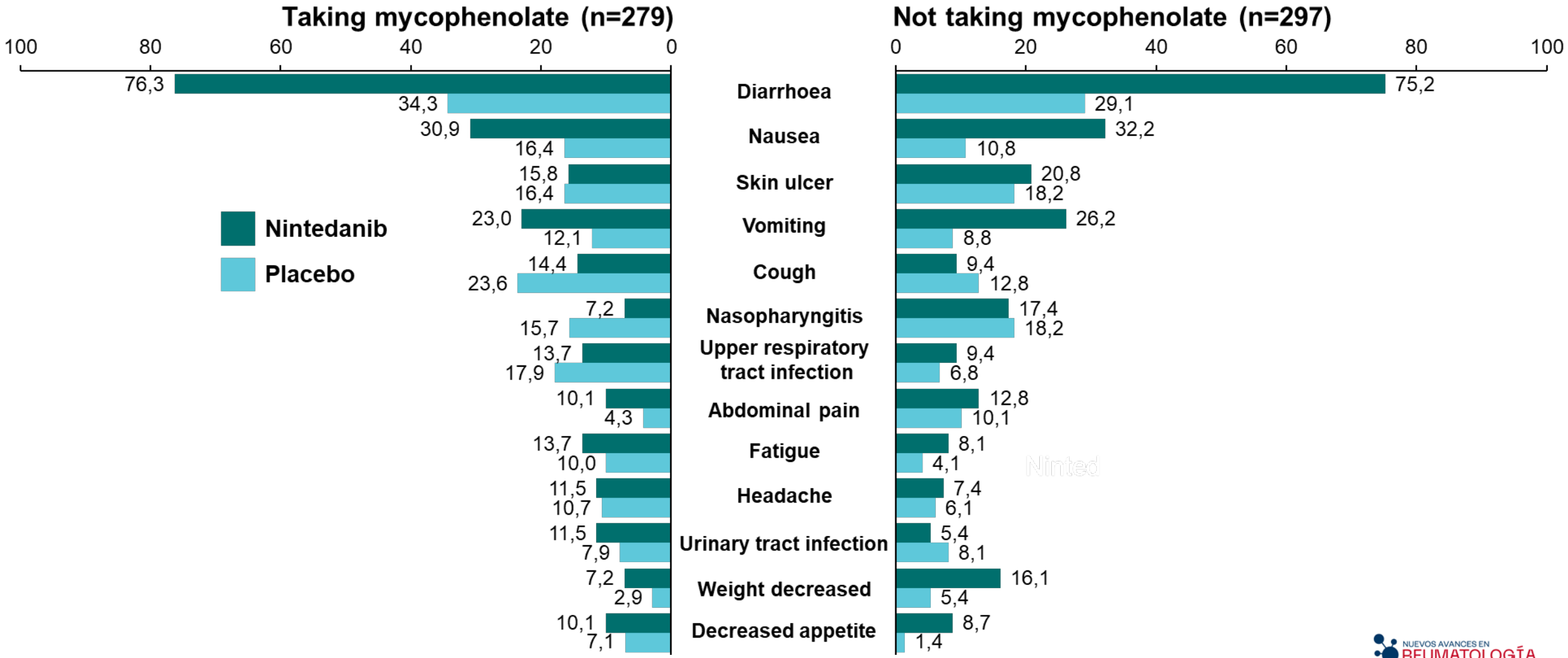




Number of participants analysed

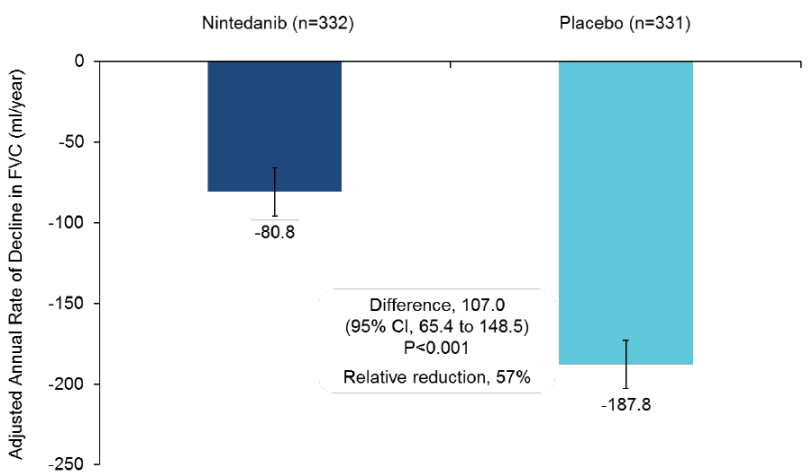
Nintedanib group, mycophenolate at baseline	138	134	131	135	129	128	116
Nintedanib group, no mycophenolate at baseline	145	147	142	143	136	134	125
Placebo group, mycophenolate at baseline	136	139	139	139	137	133	127
Placebo group, no mycophenolate at baseline	147	142	141	144	143	135	130

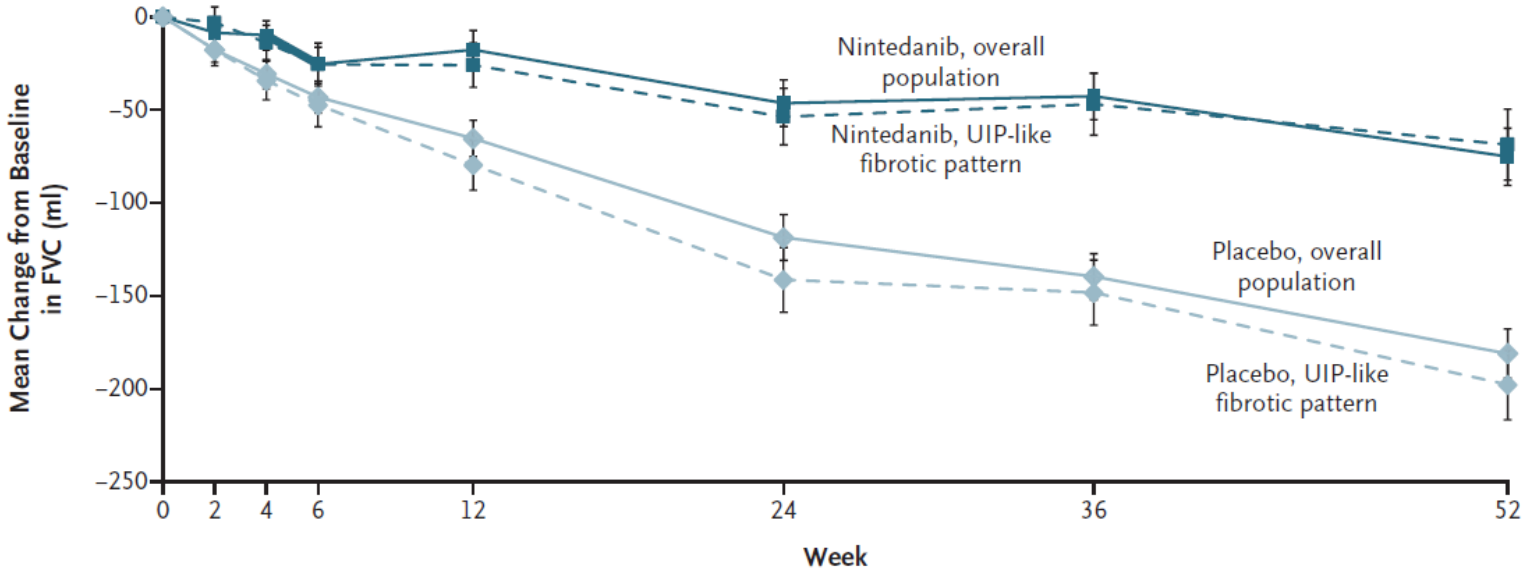
Nintedanib: efectos adversos



Nintedanib in Progressive Fibrosing Interstitial Lung Diseases

N Engl J Med 2019;381:1718-27.





Estudio INBUILD

Fibrosis progresiva:

- ↓ FVC% ≥ 10% en 24 meses preinclusión
- ↓ FVC% 5-10% + empeoramiento síntomas o ↑ extensión TCAR
- empeoramiento síntomas + ↑ extensión TCAR

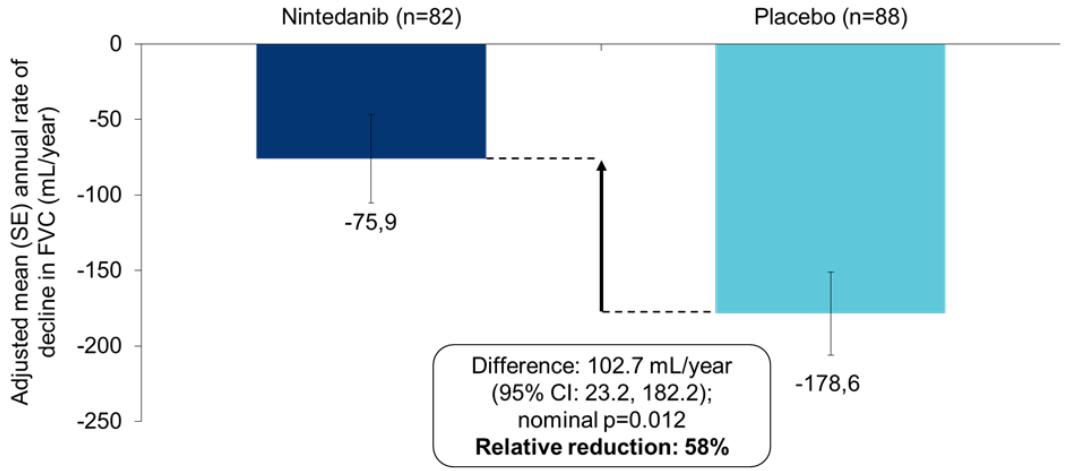
Nintedanib in Patients With Autoimmune Disease–Related Progressive Fibrosing Interstitial Lung Diseases: Subgroup Analysis of the INBUILD Trial

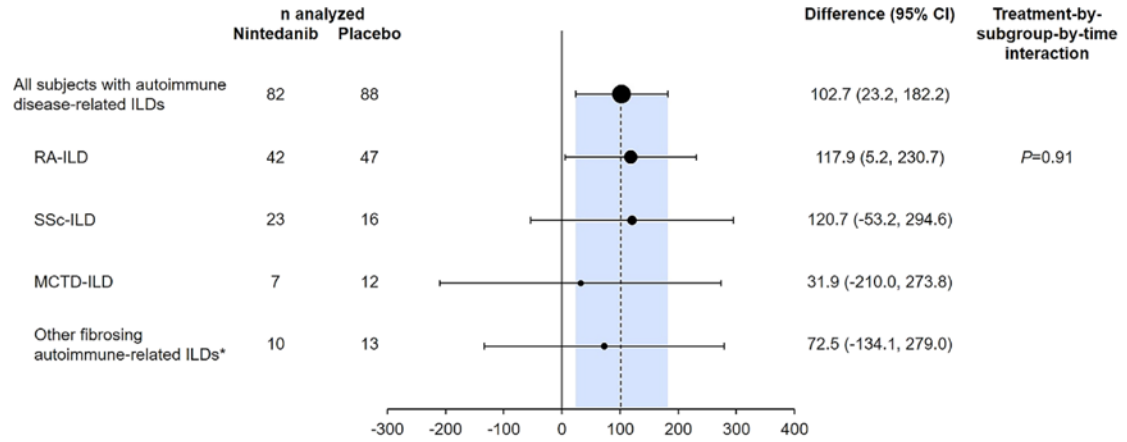
Arthritis & Rheumatology
Vol. 74, No. 6, June 2022, pp 1039–1047

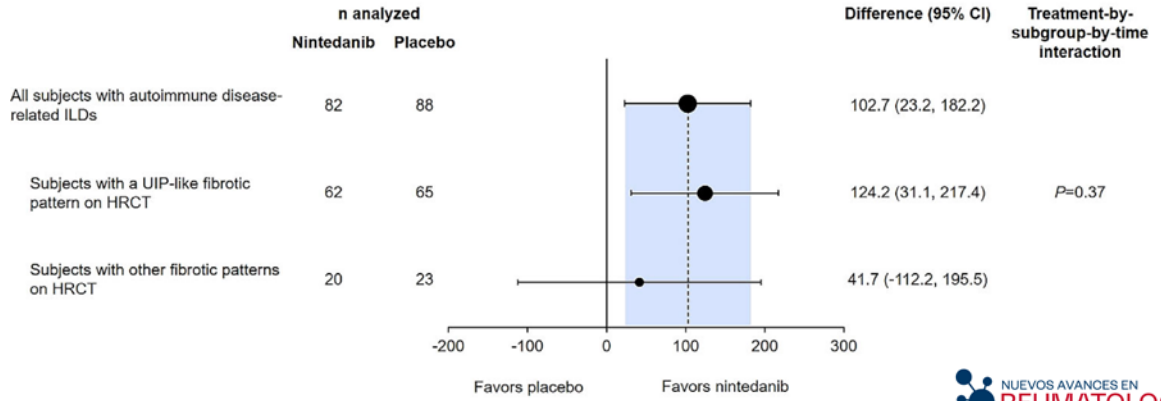
	Nintedanib (n=332)	Placebo (n=331)
Hypersensitivity pneumonitis	84 (25.3)	89 (26.9)
Autoimmune ILDs	82 (24.7)	88 (26.6)
Rheumatoid arthritis-associated ILD	42 (12.7)	47 (14.2)
Systemic sclerosis-associated ILD	23 (6.9)	16 (4.8)
Mixed connective tissue disease-associated ILD	7 (2.1)	12 (3.6)
Other autoimmune ILDs	10 (3.0)	13 (3.9)
Idiopathic non-specific interstitial pneumonia	64 (19.3)	61 (18.4)
Unclassifiable idiopathic interstitial pneumonia	64 (19.3)	50 (15.1)
Other ILDs*	38 (11.4)	43 (13.0)

Data are no (%) of patients.

Rate of decline in FVC over 52 weeks in patients with autoimmune disease-related ILDs







Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults

Am J Respir Crit Care Med Vol 205, Iss 9, pp e18–e47, May 1, 2022

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

agencia española de medicamentos y productos sanitarios

PPF guideline criteria[2]

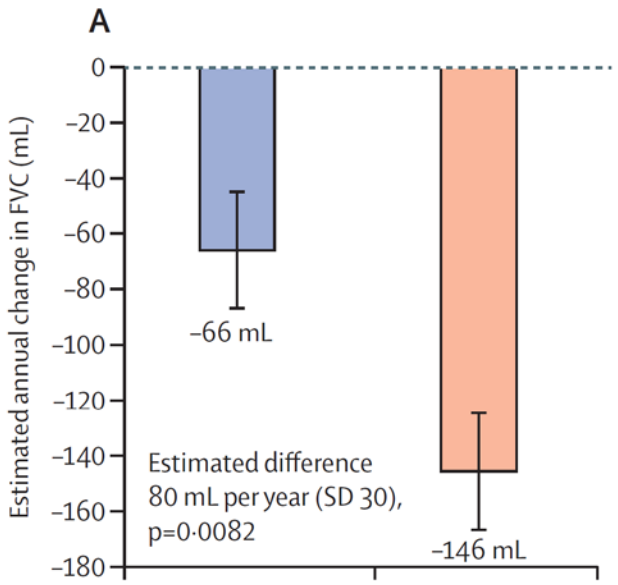
Clinical, physiological and radiological criteria to identify PPF (**≥2 of the following occurring within the past year**, with no alternative explanation):

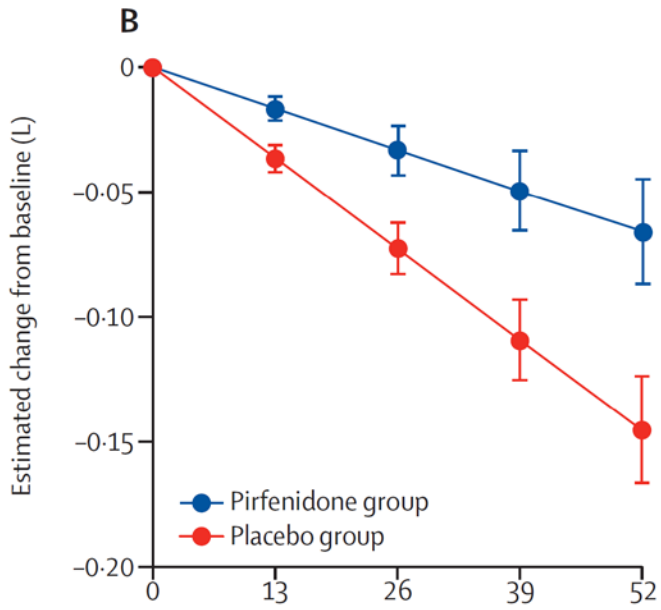
- Worsening respiratory symptoms
- Physiological evidence of disease progression
  - Absolute decline in FVC ≥5% predicted within 1 year of follow-up
  - Absolute decline in DL_{CO} ≥10% (corrected for Hb) predicted within 1 year of follow-up
- Radiological evidence of disease progression

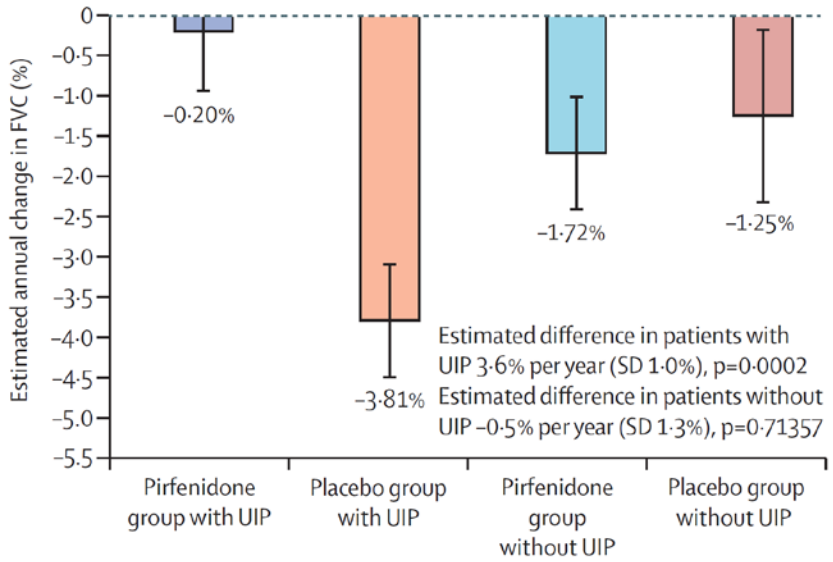
Safety, tolerability, and efficacy of pirfenidone in patients with rheumatoid arthritis-associated interstitial lung disease: a randomised, double-blind, placebo-controlled, phase 2 study

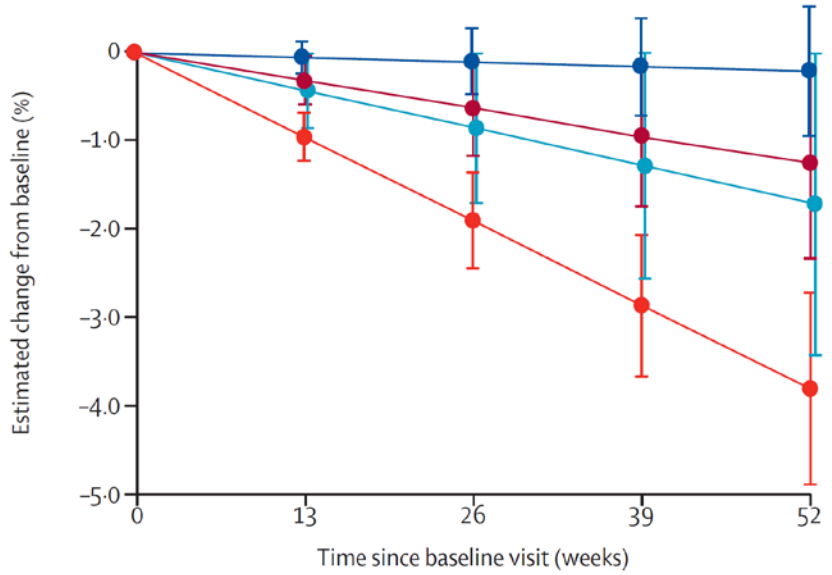
Lancet Respir Med 2022

	Pirfenidone group (n=63)	Placebo group (n=60)	p value
Primary endpoint			
Decline in percent predicted FVC by 10% or more or death	7 (11%)	9 (15%)	0·48



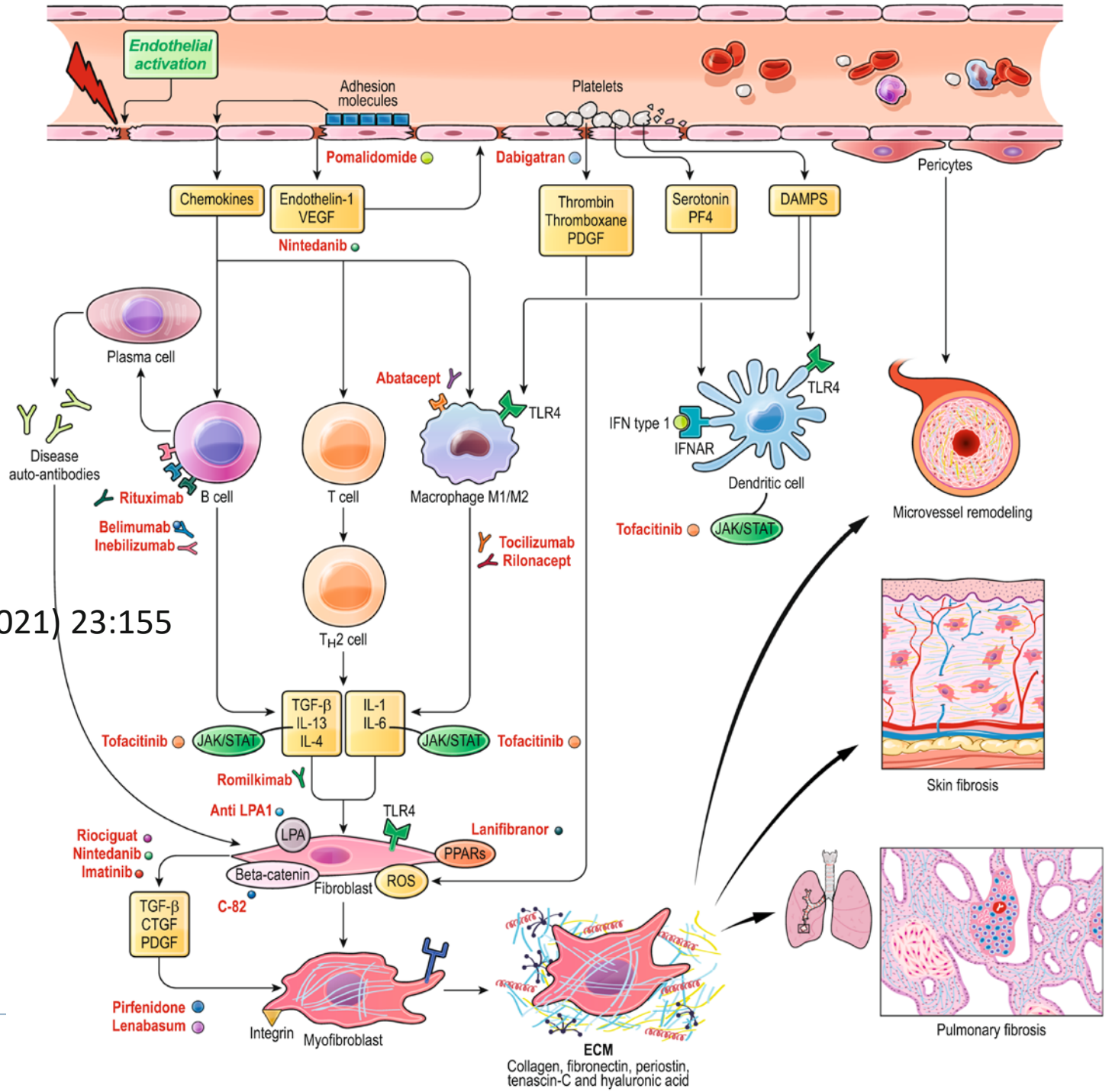




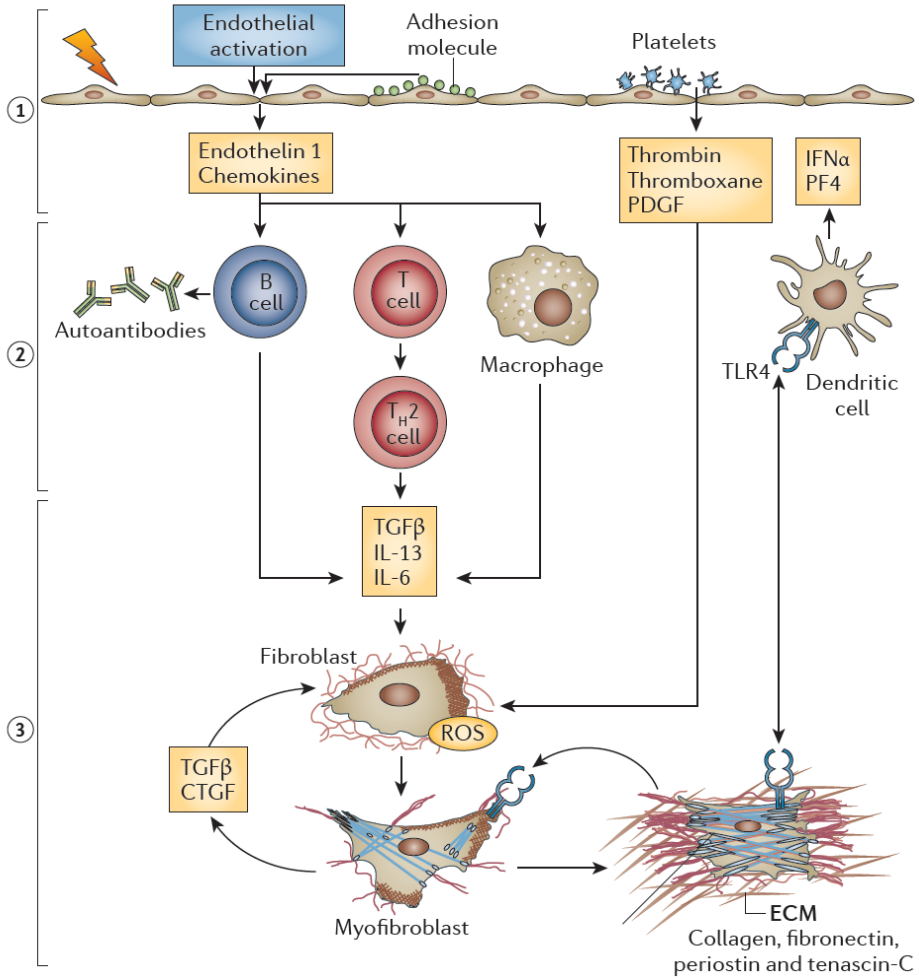


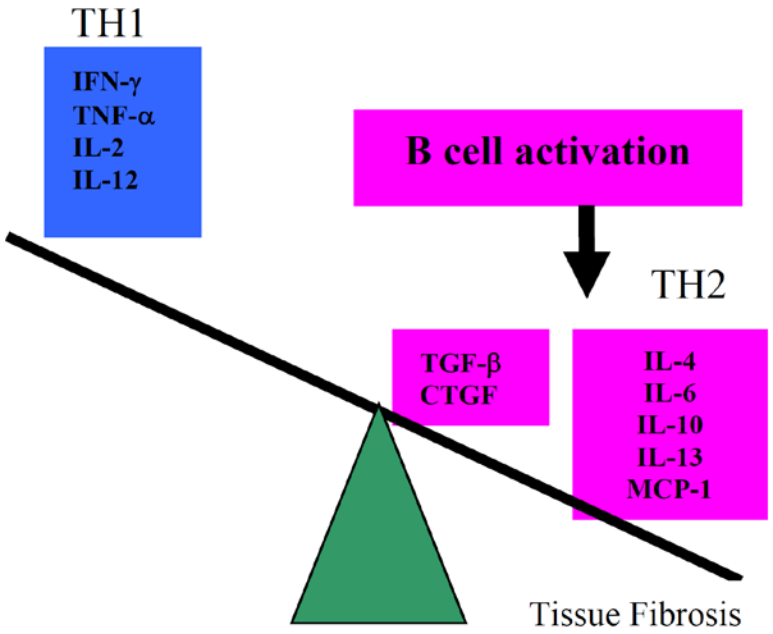
Pirfenidone group with UIP
Placebo group with UIP
Pirfenidone group without UIP
Placebo group without UIP

Arthritis Research & Therapy (2021) 23:155



Células B en esclerosis sistémica





Células B en esclerosis sistémica

Intravenous cyclophosphamide *vs* rituximab for the treatment of early diffuse scleroderma lung disease: open label, randomized, controlled trial

Geetabali Sircar[1], Rudra Prosad Goswami[1], Dipankar Sircar[2], Alakendu Ghosh[1] and Parasar Ghosh[1]

Rheumatology 2018;57:2106–2113

Parameter	Rituximab ($n=30$)			CYC ($n=30$)			Difference at 6 months	*P*-value
	Baseline, mean (S.D.)	6 months, mean (S.D.)	*P*-value	Baseline, mean (S.D.)	6 months, mean (S.D.)	*P*-value	Mean (95% CI)	
Forced vital capacity, %	61.30 (11.28)	67.52 (13.59)	0.002[a]	59.25 (12.96)	58.06 (11.23)	0.496[a]	9.46 (3.01 to 15.90)*	0.003[b]
Forced vital capacity, l	1.51 (0.45)	1.65 (0.47)	<0.001	1.42 (0.49)	1.42 (0.46)	0.356	0.23 (−0.013 to 0.47)**	0.091[b]
Modified Rodnan skin score at baseline	21.77 (9.86)	12.10 (10.14)	<0.001	23.83 (9.28)	18.33 (7.69)	<0.001	−6.23 (−10.88, −1.58)***	0.001[b]
Medsgers severity scale	8.33 (3.04)	4.67 (2.35)	<0.001	9.60 (2.44)	5.96 (2.81)	<0.001	−1.30 (−2.64, 0.04)[#]	0.036[b]
6-min walking test, m	359.63 (65.95)	409.60 (69.29)	<0.001	335.90 (89.30)	349.14 (99.75)	0.428	60.46 (16.07, 104.84)****	0.001[b]
Pulmonary hypertension present (%)	4 (13)	5 (16)		5 (16)	5 (16)		[##]	

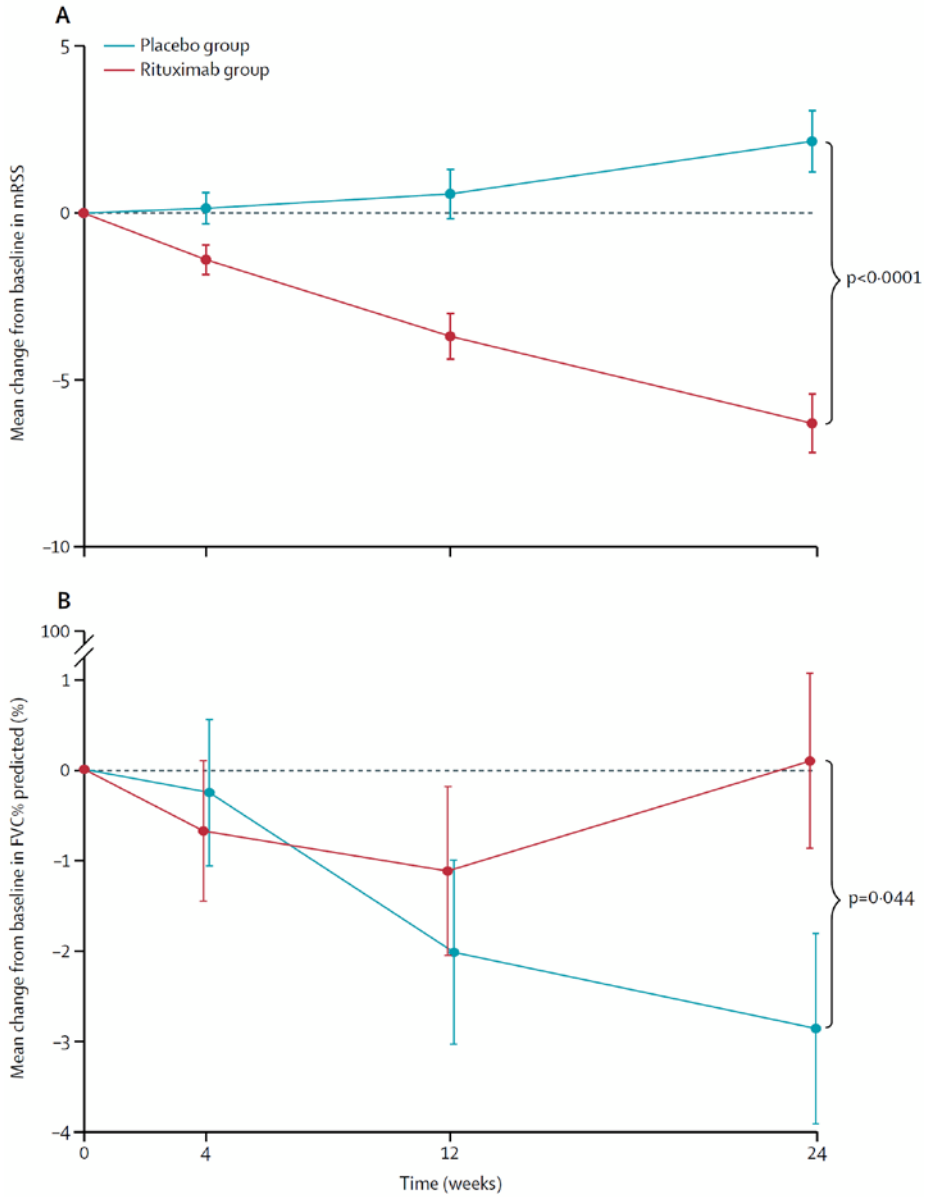
Rheumatology key messages

- Interstitial lung disease is an important cause of morbidity and mortality in SSc.
- Rituximab is an effective treatment of interstitial lung disease in early SSc, with improvement in skin and lung function.
- The adverse event profile of rituximab is superior to cyclophosphamide.

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

Lancet Rheumatol 2021; 3: e489–97

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**



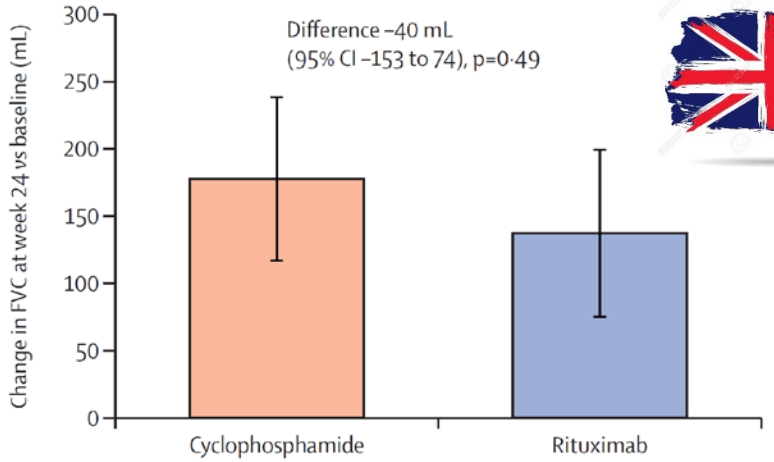
	Rituximab group (n=28)	Placebo group (n=26)
Sex		
Female	25 (89%)	24 (92%)
Male	3 (11%)	2 (8%)
Age, years	49·1 (14·4)	48·3 (9·2)
Diffuse cutaneous systemic sclerosis	23 (82%)	22 (85%)
Disease duration, months	58·5 (0–268)	52·0 (9–248)
mRSS	14·4 (3·7)	15·7 (5·5)
Interstitial lung disease present	25 (89%)	23 (88%)
FVC% predicted	87·9% (15·8)	89·4% (17·9)

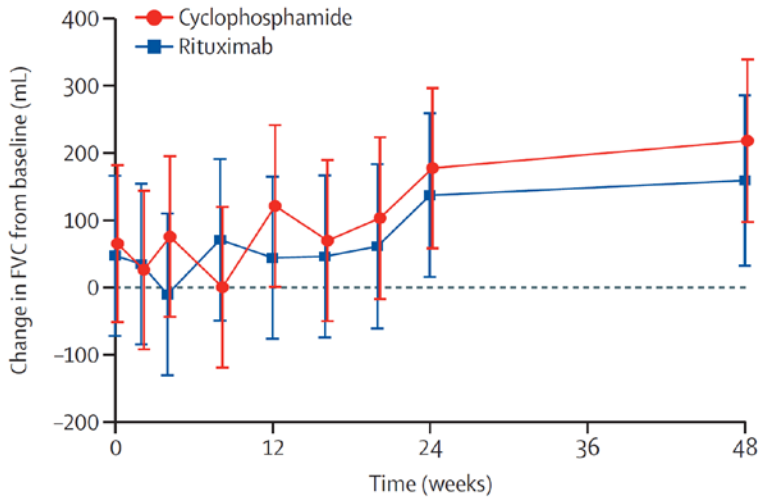
Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): a double-blind, double-dummy, randomised, controlled, phase 2b trial

Lancet Respir Med 2022

*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**

44 miopatías
37 esclerodermia
16 EMTC





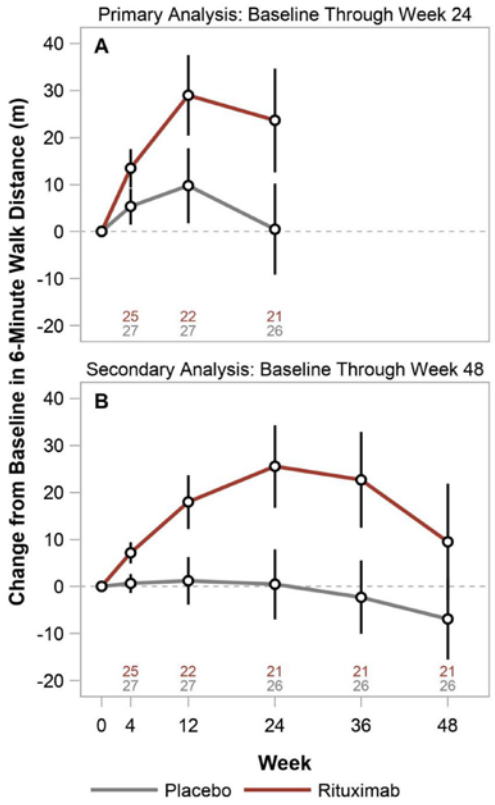
	Cyclophosphamide group (n=50)	Rituximab group (n=51)
All events	646	445
Blood and lymphatic system disorders	3 (<1%)	0
Cardiac disorders	10 (2%)	6 (1%)
Ear and labyrinth disorders	2 (<1%)	1 (<1%)
Eye disorders	16 (2%)	9 (2%)
Gastrointestinal disorders	170 (26%)	71 (16%)
General disorders and administration site conditions	91 (14%)	52 (12%)
Hepatobiliary disorders	1 (<1%)	1 (<1%)
Immune system disorders	0	2 (<1%)
Infections and infestations	50 (8%)	46 (10%)
Injury, poisoning, and procedural complications	8 (1%)	5 (1%)
Investigations	11 (2%)	8 (2%)
Metabolism and nutrition disorders	5 (1%)	3 (1%)
Musculoskeletal and connective tissue disorders	44 (7%)	40 (9%)
Nervous system disorders	72 (11%)	35 (8%)
Psychiatric disorders	9 (1%)	10 (2%)
Renal and urinary disorders	8 (1%)	1 (<1%)
Reproductive system and breast disorders	5 (1%)	4 (1%)
Respiratory, thoracic, and mediastinal disorders	94 (15%)	101 (23%)
Skin and subcutaneous tissue disorders	38 (6%)	32 (7%)
Surgical and medical procedures	1 (<1%)	0
Vascular disorders	7 (1%)	16 (4%)

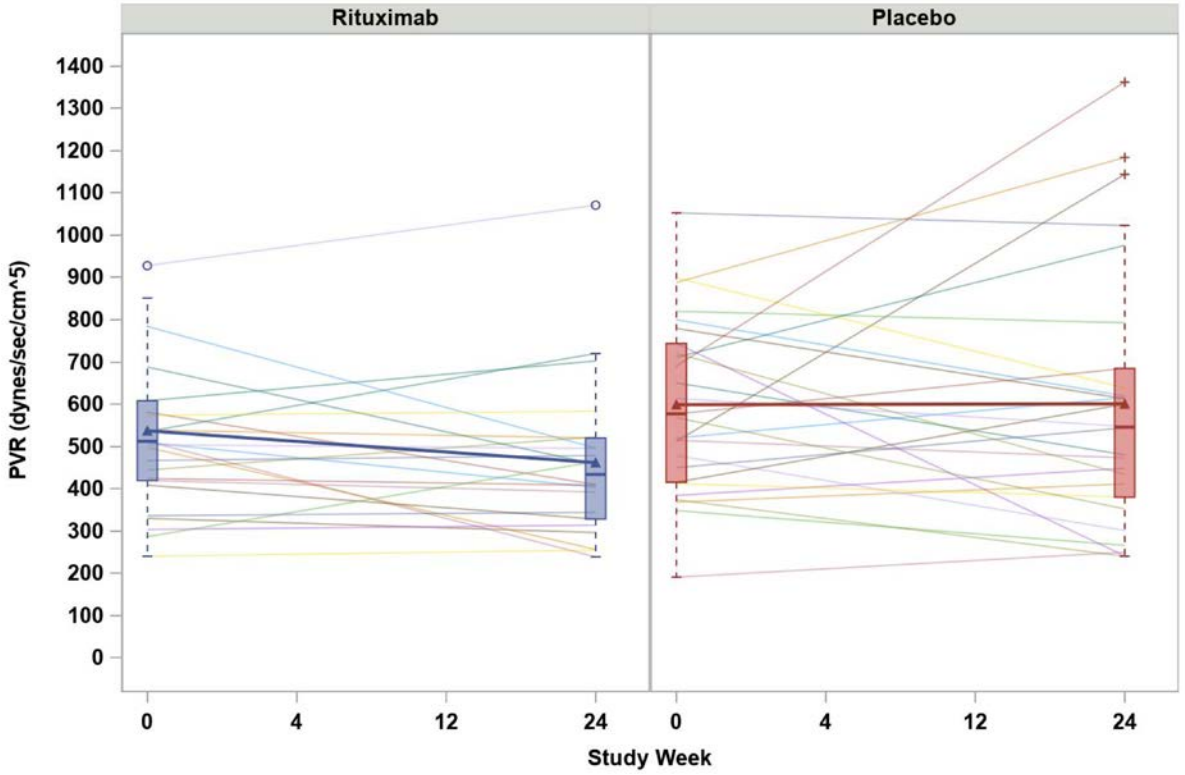
Data are number of events (% of total events reported per cohort).

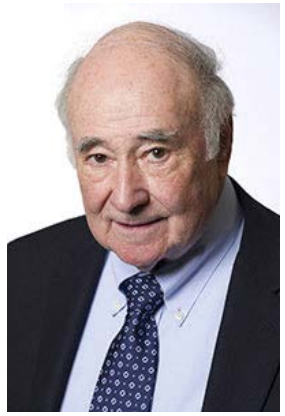
Safety and Efficacy of B-Cell Depletion with Rituximab for the Treatment of Systemic Sclerosis–associated Pulmonary Arterial Hypertension

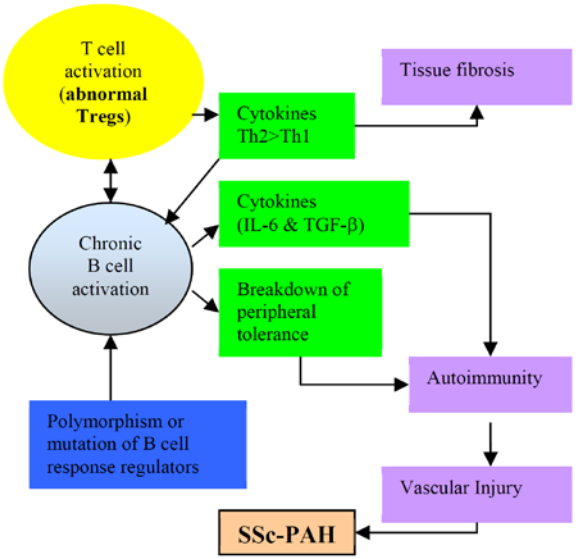
Am J Respir Crit Care Med Vol 204, Iss 2, pp 209–221, Jul 15, 2021

A Multicenter, Double-Blind, Randomized, Placebo-controlled Trial



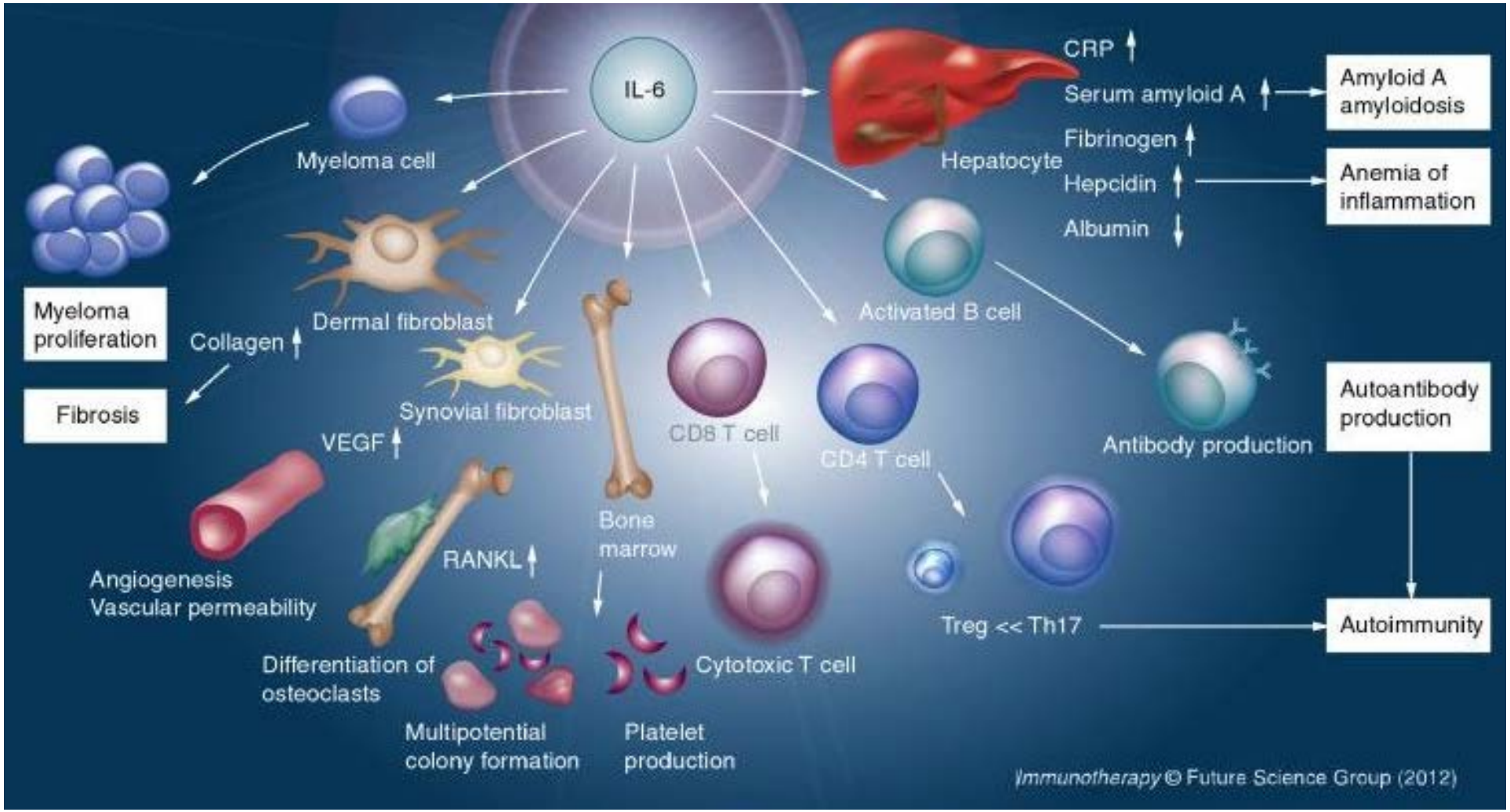






57 pacientes con esclerodermia e hipertensión arterial pulmonar (< 5 a)

IL-6 y fibrosis

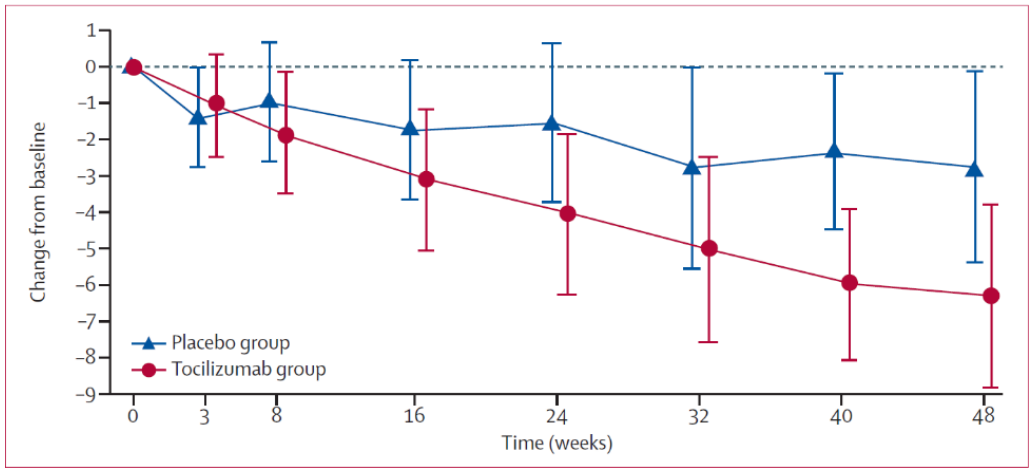


Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial

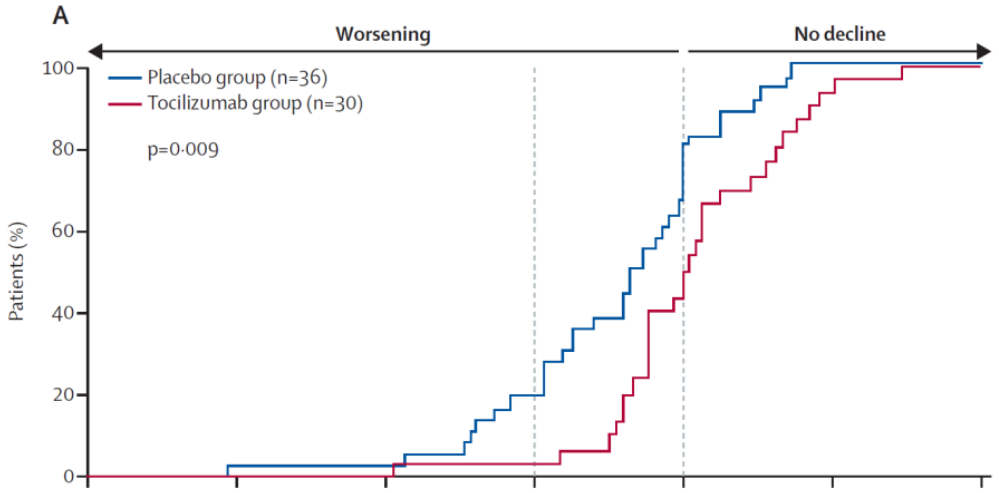
Lancet 2016; 387: 2630–40

Dinesh Khanna, Christopher P Denton, Angelika Jahreis, Jacob M van Laar, Tracy M Frech, Marina E Anderson, Murray Baron, Lorinda Chung, Gerhard Fierlbeck, Santhanam Lakshminarayanan, Yannick Allanore, Janet E Pope, Gabriela Riemekasten, Virginia Steen, Ulf Müller-Ladner, Robert Lafyatis, Giuseppina Stifano, Helen Spotswood, Haiyin Chen-Harris, Sebastian Dziadek, Alyssa Morimoto, Thierry Sornasse, Jeffrey Siegel, Daniel E Furst

Piel (mRSS)



Pulmón (FVC)

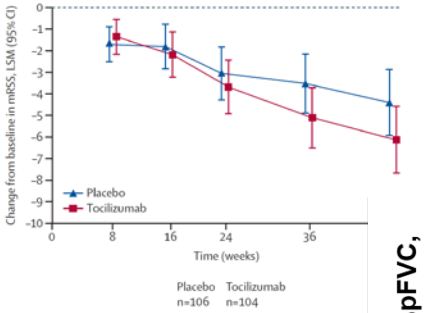


	Placebo (n=43)	Tocilizumab (n=44)
%pFVC	82 (13)§	80 (14)
%pDLCO (Hb corr)	74 (21)‡	73 (19)§

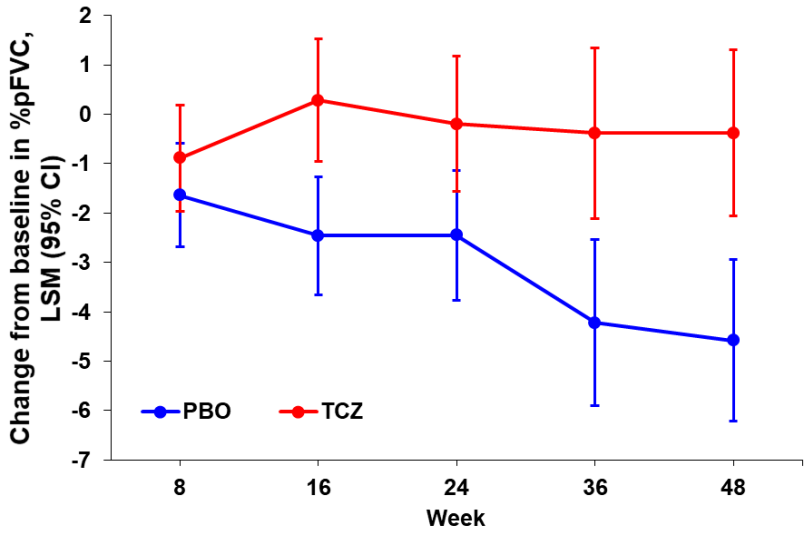
Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial

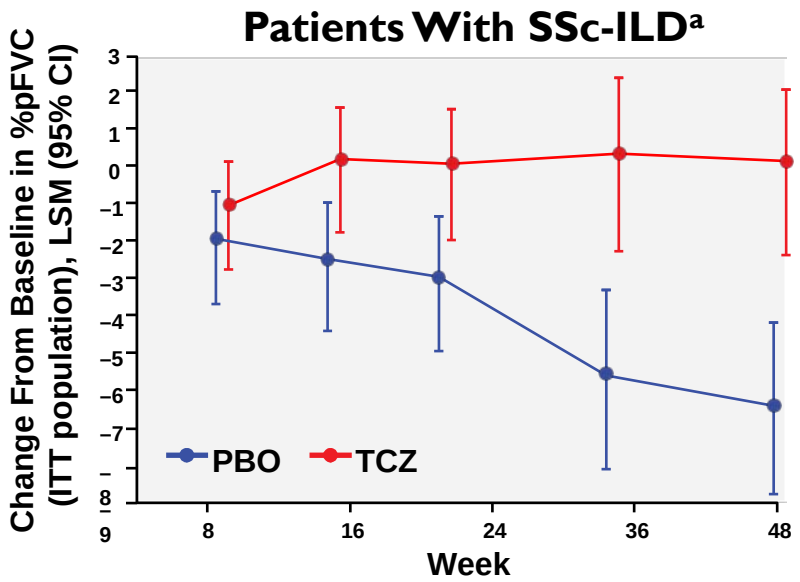
Lancet Respir Med 2020; 8: 963–74

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†*



210 pacientes: 104 tocilizumab; 106 placebo





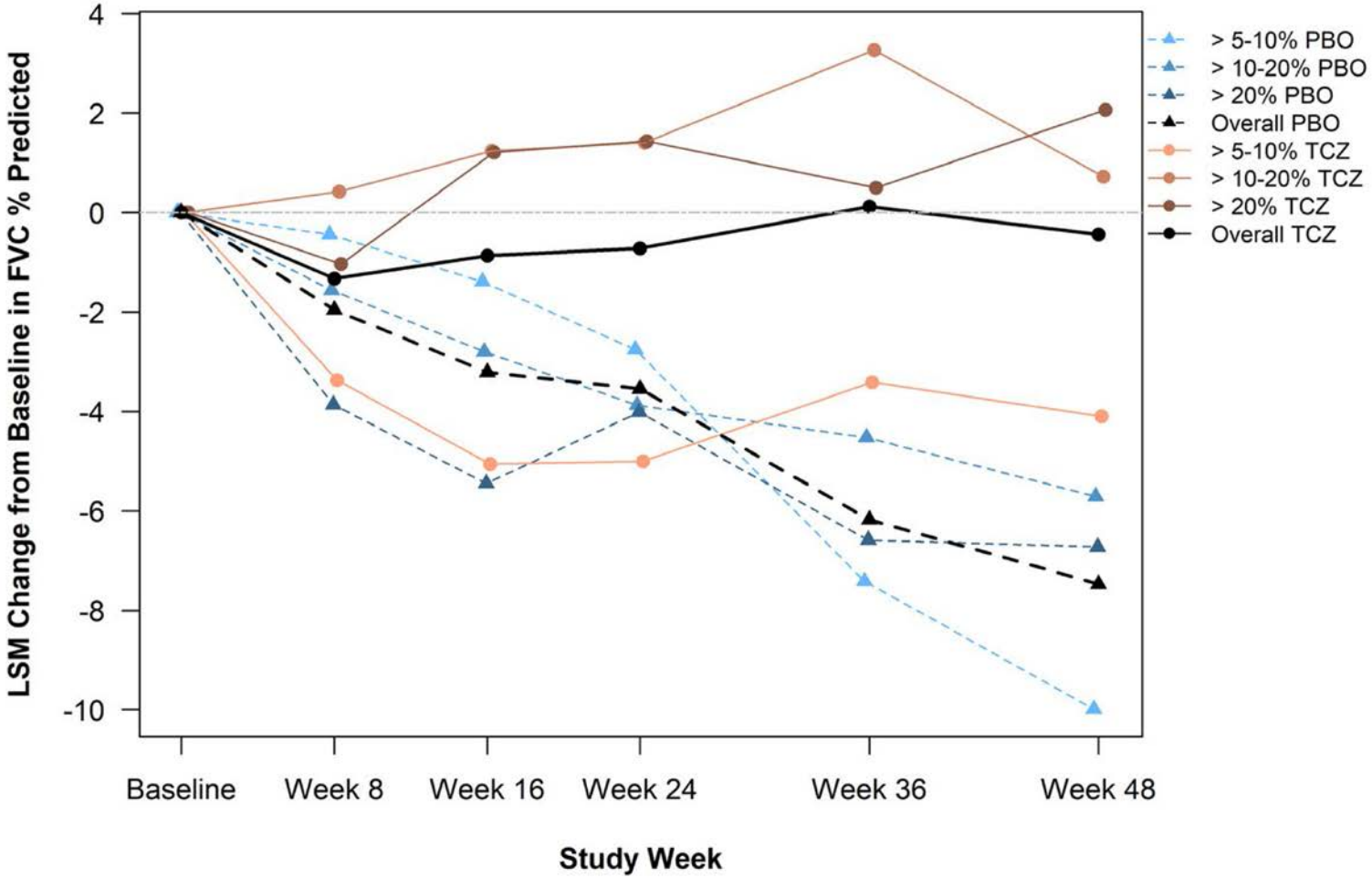
%pFVC	PBO n=106	TCZ n=104	Difference (95% CI) Nominal *p* Value
LSM change from baseline at week 48	-4.6	-0.4	4.2 (2.0, 6.4) *p*=0.0002
Absolute change in FVC, mL	-190	-24	167 (83, 250) *p*=0.0001

%pFVC	PBO n=63	TCZ n=67	Difference (95% CI) Nominal *p* Value
LSM change from baseline at week 48	-6.5	-0.1	6.4 (3.3, 9.4) *p*<0.0001
Absolute change in FVC, mL	-257	-20	238 (119, 357) *p*=0.0001

Tocilizumab Prevents Progression of Early Systemic Sclerosis–Associated Interstitial Lung Disease

Arthritis & Rheumatology
Vol. 73, No. 7, July 2021, pp 1301–1310

David Roofeh,[1] Celia J. F. Lin,[2] Jonathan Goldin,[3] Grace Hyun Kim,[3] Daniel E. Furst,[4] Christopher P. Denton,[5] Suiyuan Huang,[1] and Dinesh Khanna,[1] on behalf of the focuSSced Investigators



Genentech
A Member of the Roche Group

SCLERODERMA NEWS

Home About Scleroderma Treatments

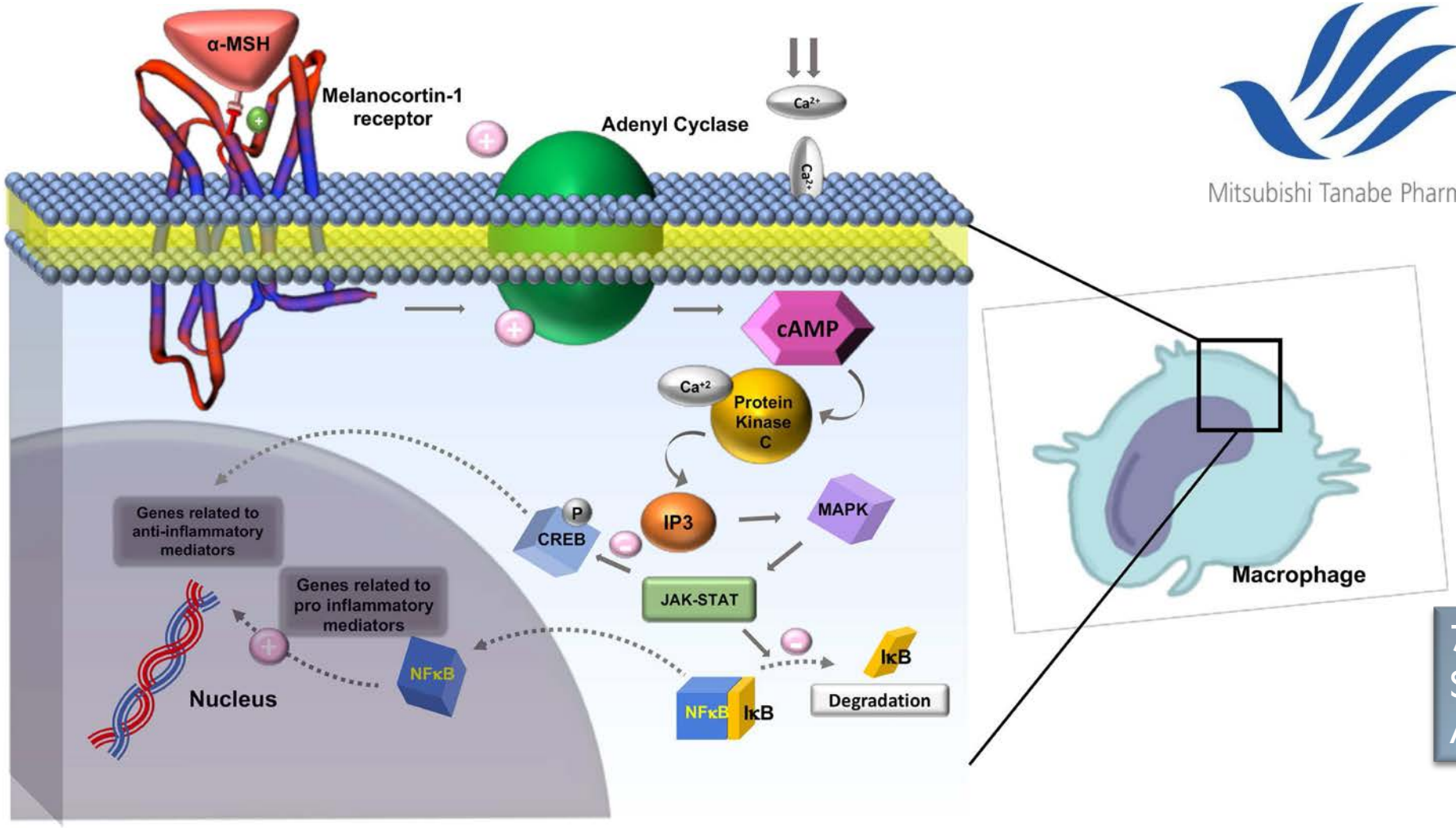
News > FDA Approves Actemra to Treat Adults With SSc-ILD

FDA Approves Actemra to Treat Adults With SSc-ILD

by *Steve Bryson PhD* | March 8, 2021

SHARE THIS ARTICLE:

MT-7117 (dersimelagon)
Agonista del receptor 1 de la melanocortina

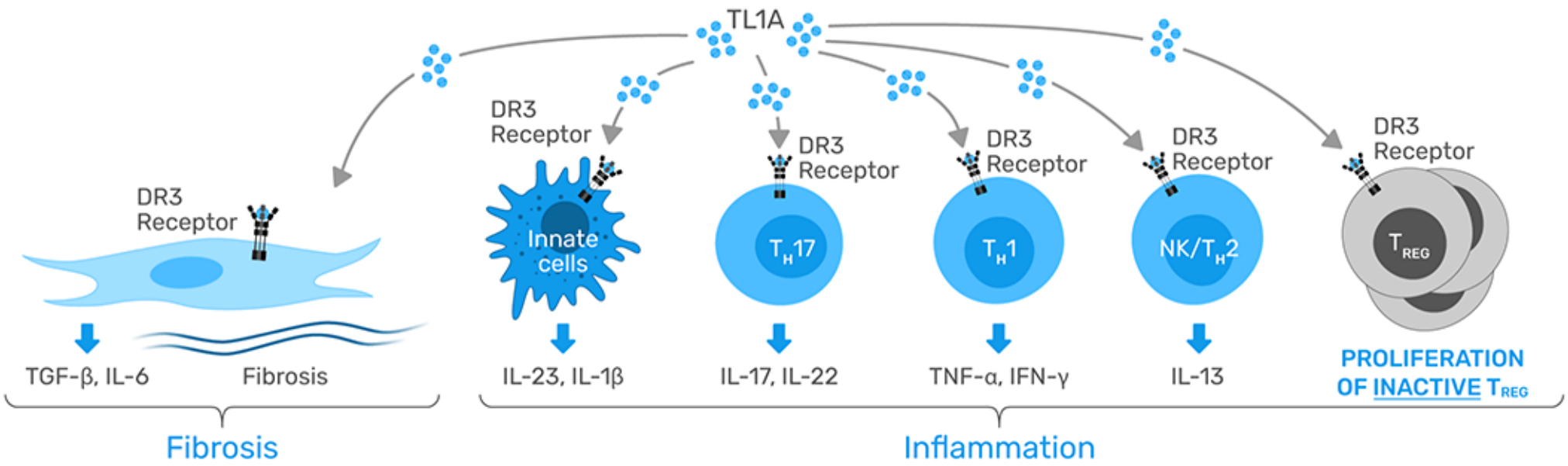


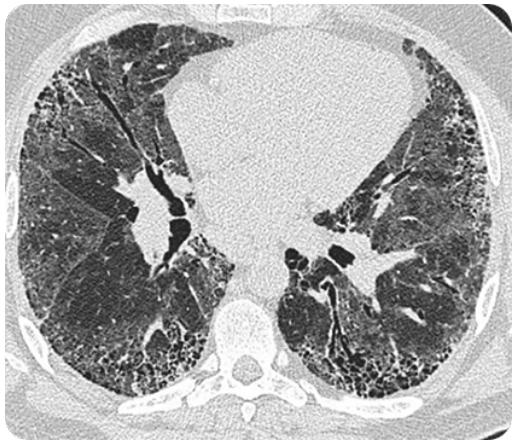
Mitsubishi Tanabe Pharma

72 pacientes
SSc difusa, <5 años
ACR-CRISS

ClinicalTrials.gov Identifier: NCT04440592

Anti-TL1A en EPID-SSc

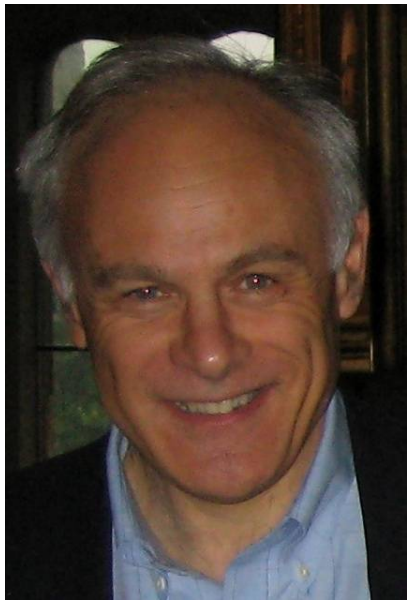


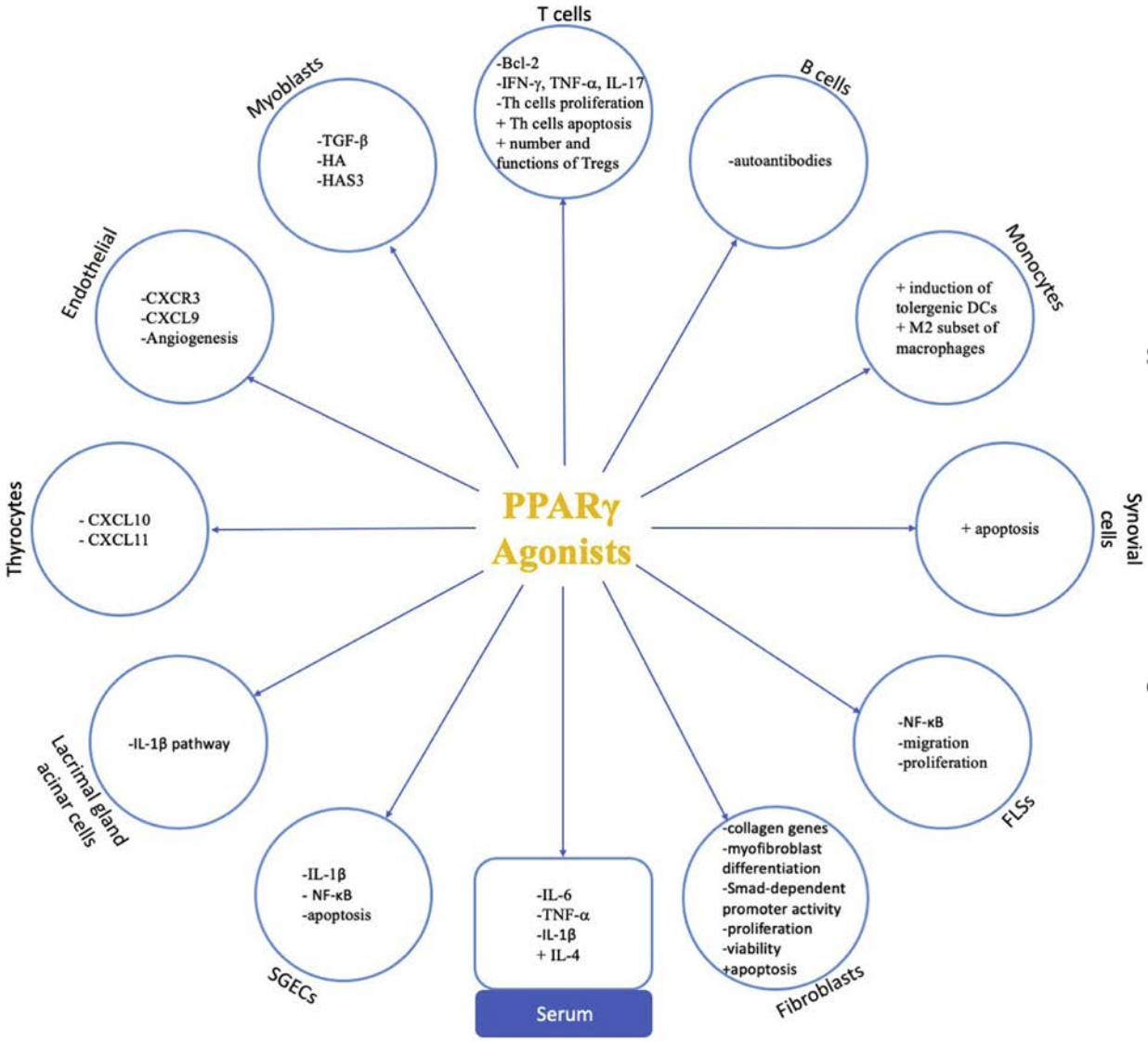


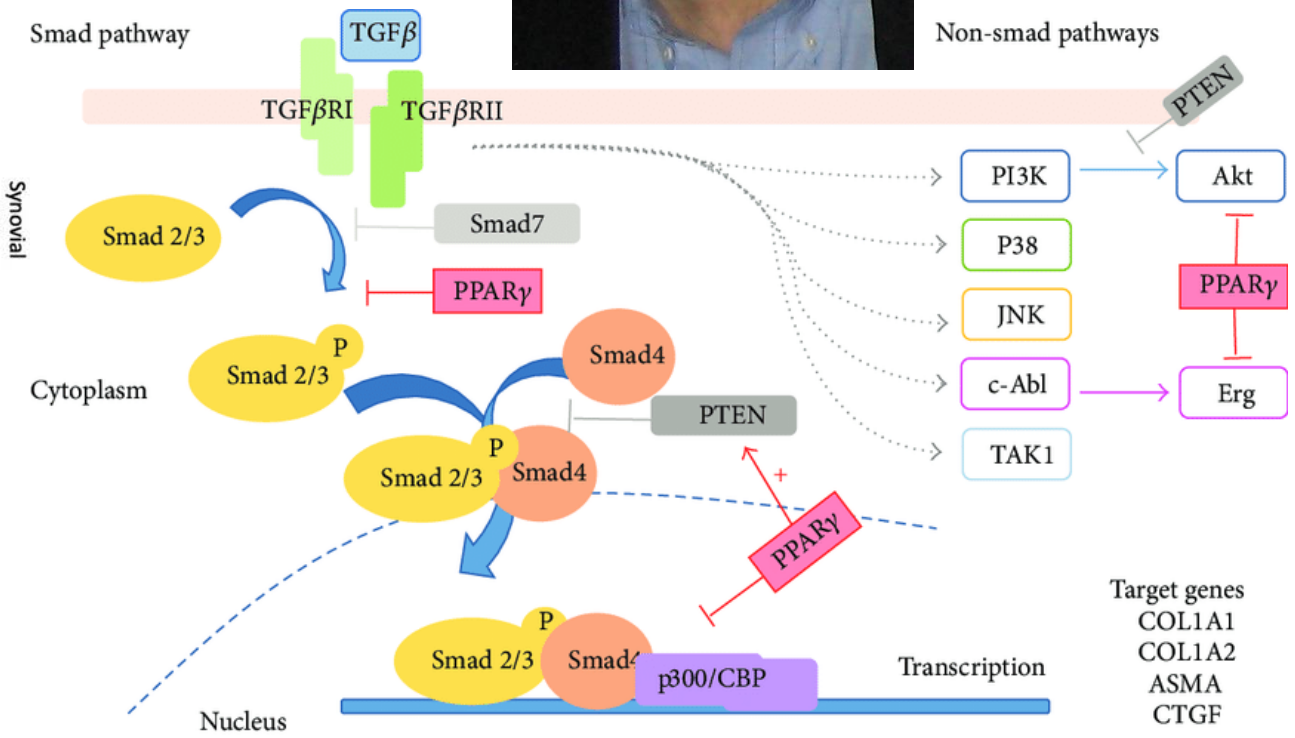
Prometheus Biosciences

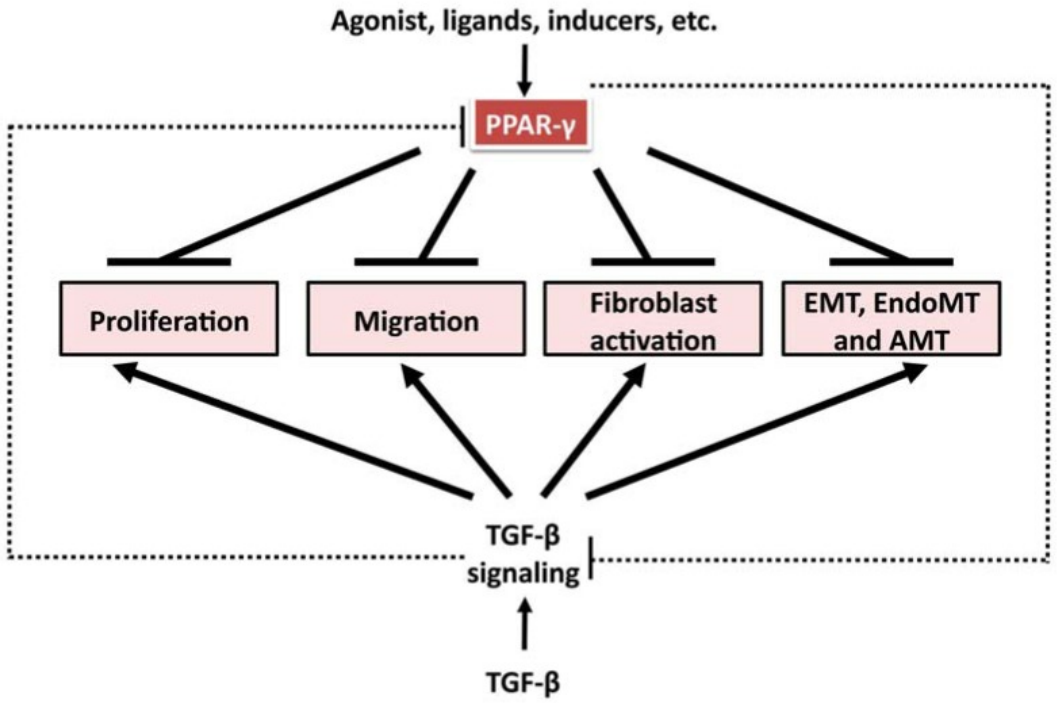
AGONISTAS DE PPAR-GAMMA

(Peroxisome proliferator-activated receptor gamma)









PPARγ agonistas

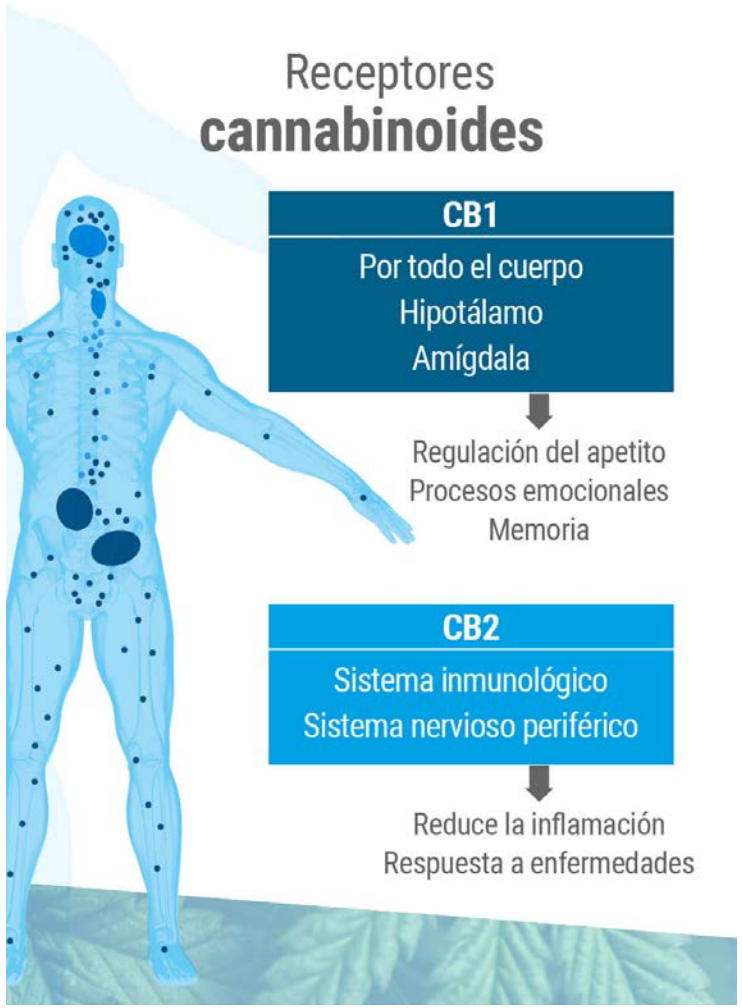
Lanifibranor (iva 337)

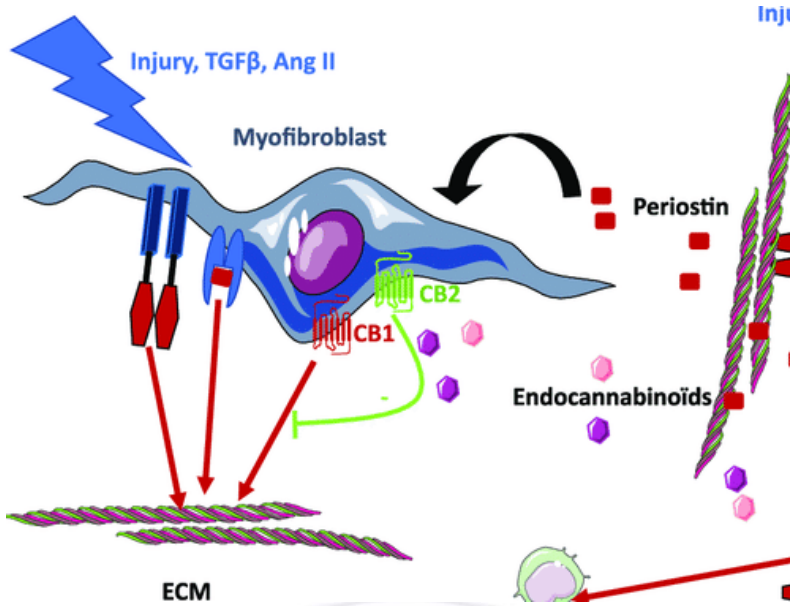
	800mg lanifibranor	1200mg lanifibranor	Placebo
Number of patients	49	48	48
Mean baseline mRSS (SD[1])	18.2 (3.8)	17.8 (3.9)	17.1 (-3.7)
Mean absolute change of mRSS from baseline to week 48 (SD[3])	-3.7 (4.2)	-4.3 (5.0)	-4.9 (4.6)

- Decision to discontinue further developments in the treatment of Systemic Sclerosis ("SSc")

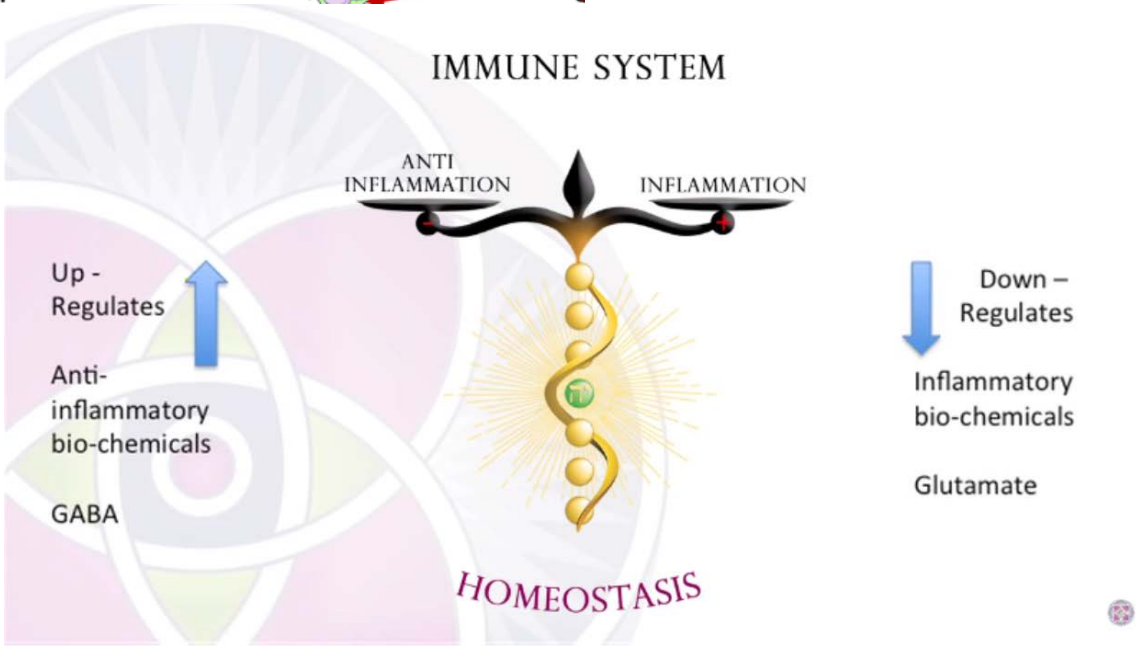
ClinicalTrials.gov Identifier: NCT0250364

cannabinoides





Raphael Mechoulam

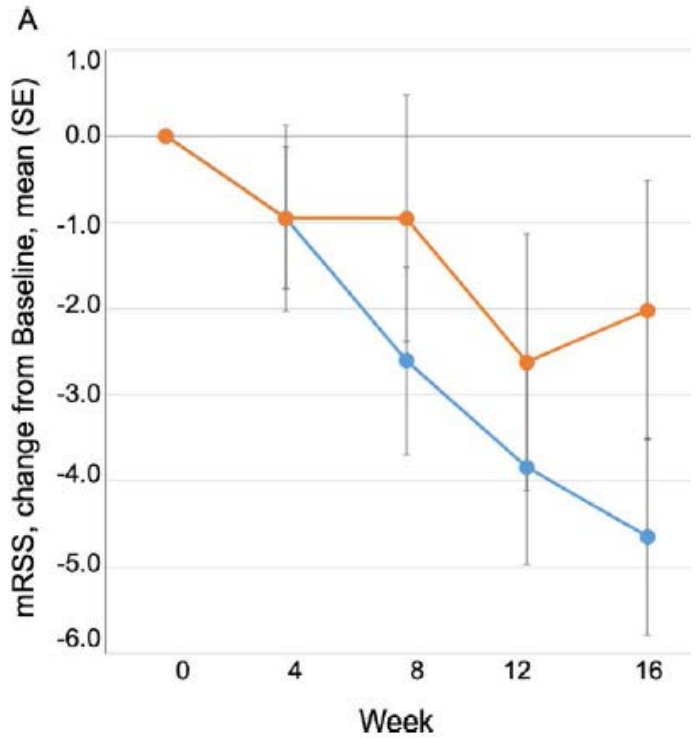


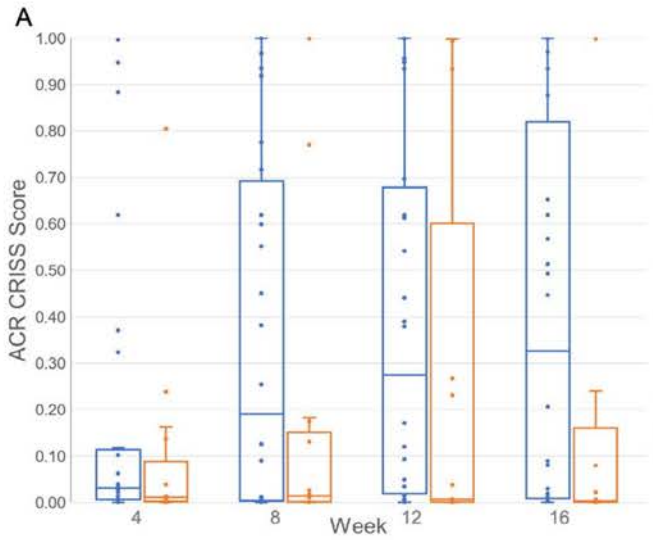
Safety and Efficacy of Lenabasum in a Phase II, Randomized, Placebo-Controlled Trial in Adults With Systemic Sclerosis

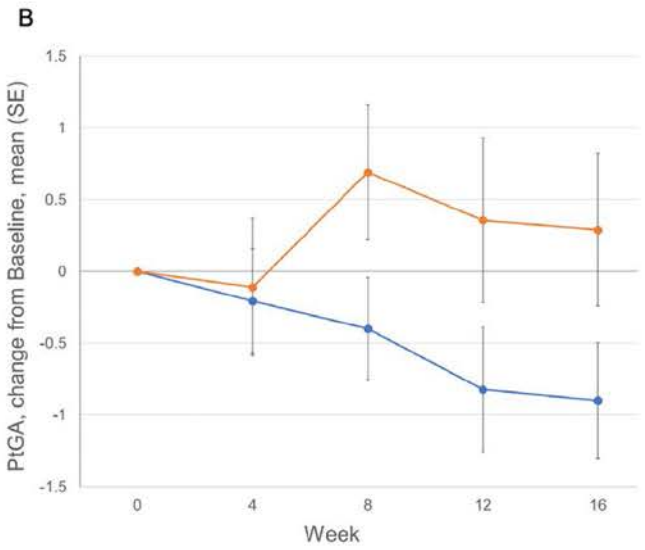
Robert Spiera,[1] Laura Hummers,[2] Lorinda Chung,[3] Tracy M. Frech,[4] Robyn Domsic,[5] Vivien Hsu,[6] Daniel E. Furst,[7] Jessica Gordon,[1] Maureen Mayes,[8] Robert Simms,[9] Robert Lafyatis,[5] Viktor Martyanov,[10] Tammara Wood,[10] Michael L. Whitfield,[10] Scott Constantine,[11] Elizabeth Lee,[11] Nancy Dgetluck,[11] and Barbara White[11]

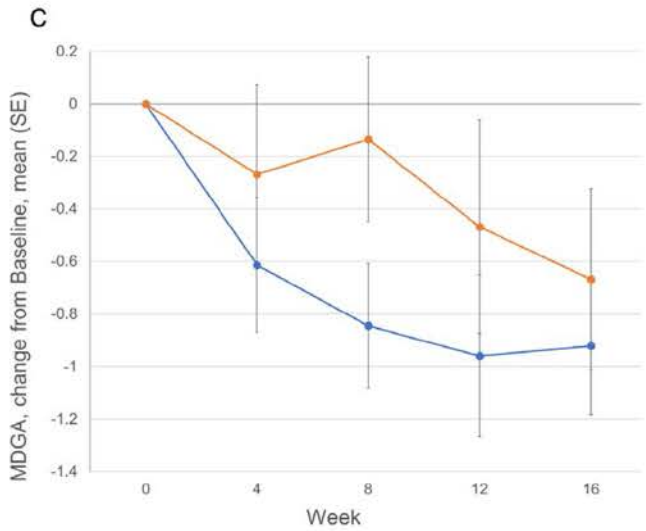
Arthritis & Rheumatology
Vol. 72, No. 8, August 2020, pp 1350–1360

Lenabasum 27 pacientes
Placebo 15 pacientes









Índice CRISS (Composite Response Index for clinical trials in Systemic Sclerosis)

- ✓ Índice compuesto, de mejoría desde el inicio
- ✓ Algoritmo exponencial, ponderado

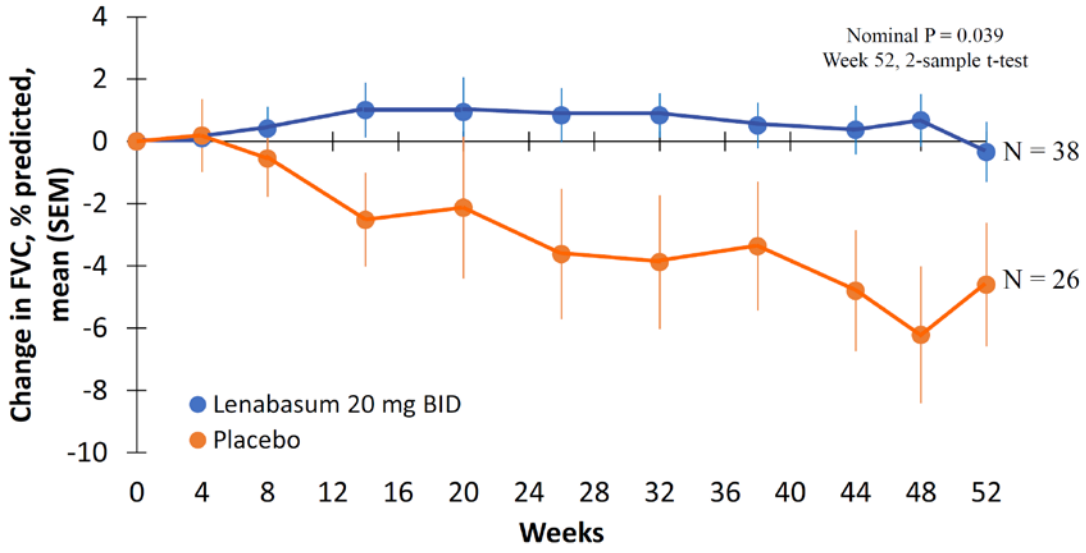
- ✓ ETAPA 1: Empeoramiento o nueva aparición de afectación grave puntúa "0". Específicamente:
  - ✓ Nueva crisis renal
  - ✓ Disminución FVC ≥15% y/o nueva EPID
  - ✓ Nueva disfunción VI (FEVI ≤ 45%)
  - ✓ Nueva HAP confirmada por cateterismo

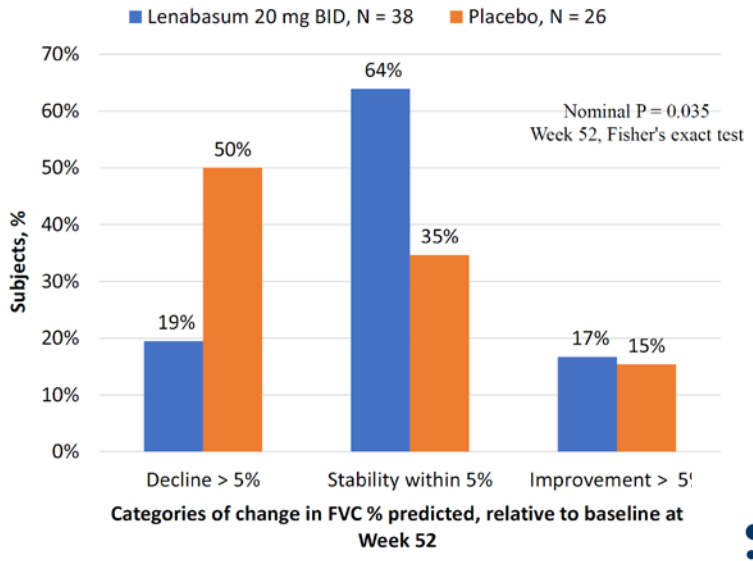
- ✓ ETAPA 2: Para los pacientes que no son "0" en la etapa 1, se calcula la probabilidad de mejoría mediante una ecuación compleja, que incluye los siguientes parámetros:
  - ✓ Cambio en el mRSS (piel)
  - ✓ Cambio en la FVC (pulmón)
  - ✓ Cambio en la evaluación global del médico
  - ✓ Cambio en la evaluación global del paciente
  - ✓ Cambio en el HAQ

RESOLVE-1, a Phase 3 Trial of Lenabasum, a CB2 Agonist, for the Treatment of Diffuse Cutaneous Systemic Sclerosis

ClinicalTrials.gov Identifier: NCT03398837

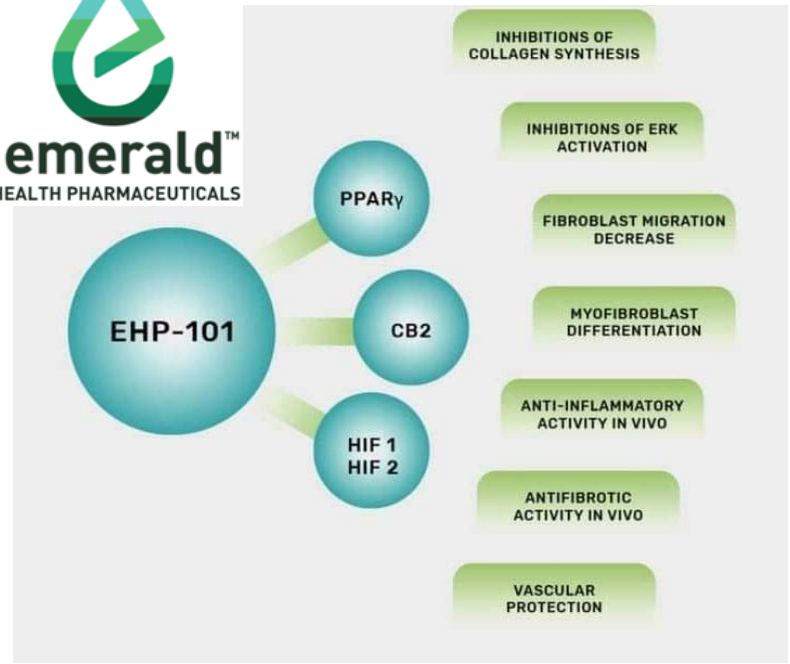
Outcome	Lenabasum 20 mg BID N = 100	Lenabasum 5 mg BID N = 113	Placebo BID N = 115
Primary			
ACR CRISS Step 1 = 0	n = 1, 1 ILD	N = 4, 1 CHF, 3 ILD	N = 4, 1 renal crisis, 3 ILD
ACR CRISS score, median (IQR)	0.8880 (0.9360)	0.8270 (0.9180)	0.8870 (0.0710, 0.9990)
P-value - Ranked Score, MMRM	0.4972	0.3486	
Secondary			
Change in mRSS, mean (SD)	-6.7 (6.59)	-7.1 (6.24)	-9.1 (7.72)
Change in HAQ-DI, mean (SD)	-0.133 (0.4363)	-0.060 (0.3917)	-0.127 (0.4677)
Change in FVC, %, L, mean (SD)	-1.602 (6.9106)	-2.248 (6.2099)	-0.993 (8.6840)

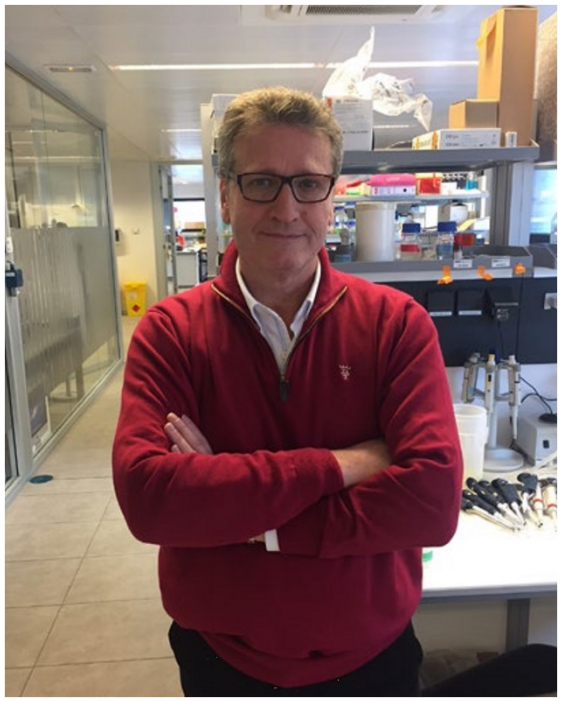




VCE 004.8 / EHP-101

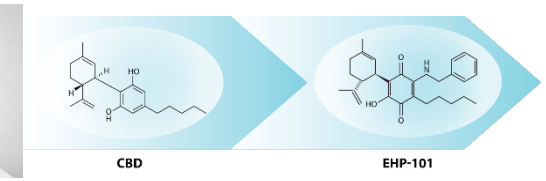
emerald™ HEALTH PHARMACEUTICALS



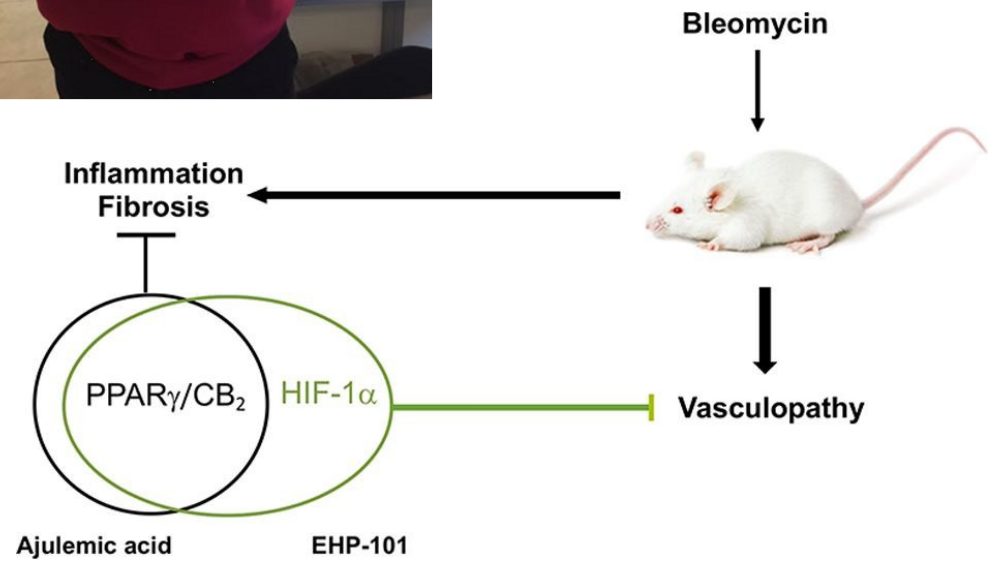


VIVACELL Biotechnology España

UNIVERSIDAD D CÓRDOBA

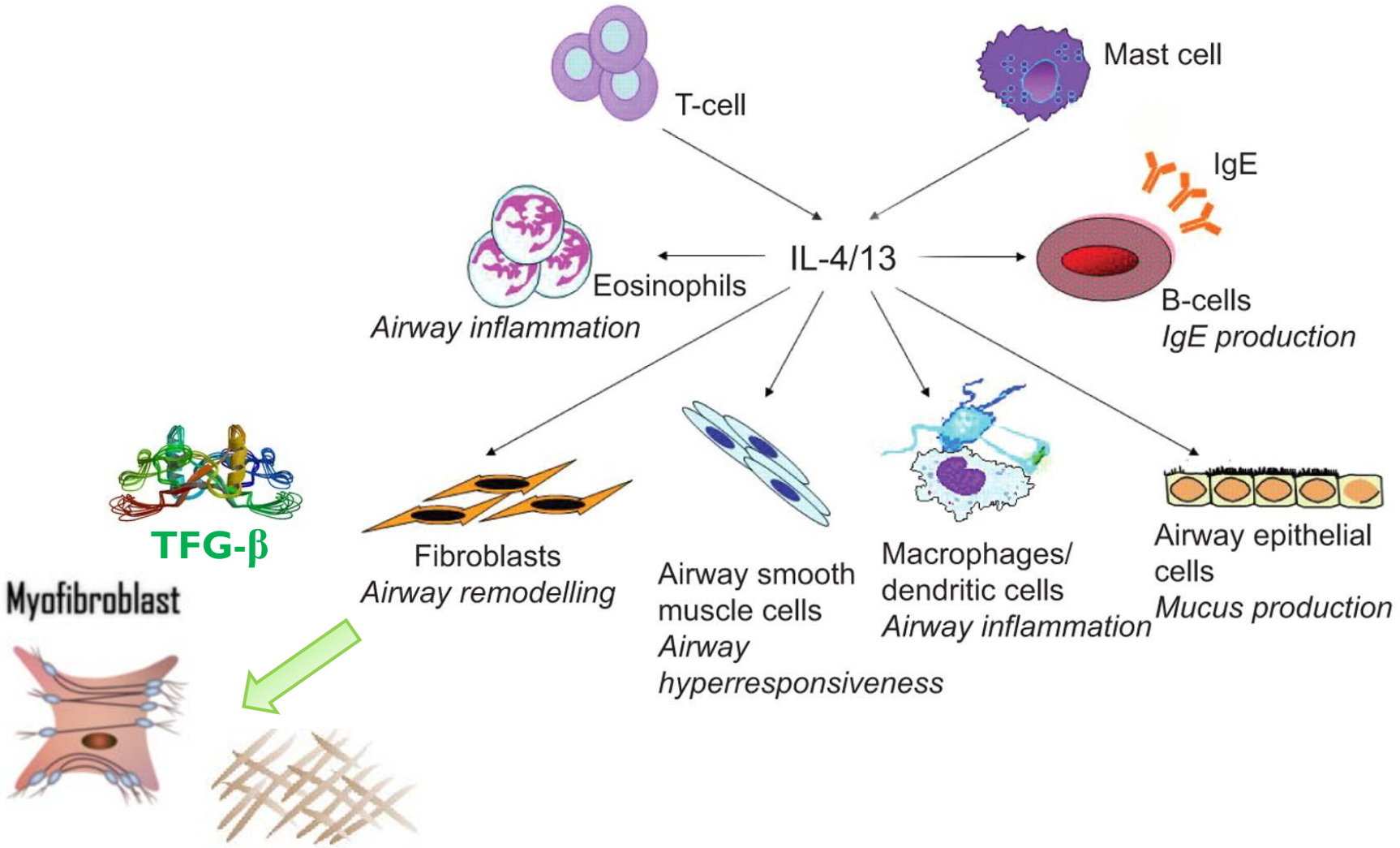


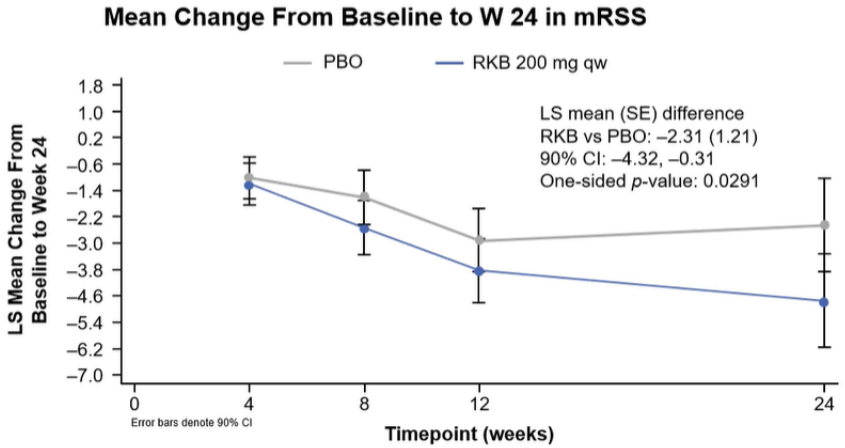
Product Candidate	Indication	Proof-of-concept	Formulation	Preclinical	Phase I
EHP-101	Multiple sclerosis				
	Scleroderma	Orphan designation granted, US and EU			



ClinicalTrials.gov Identifier: NCT04166552

IL-4 / 13 en fibrosis



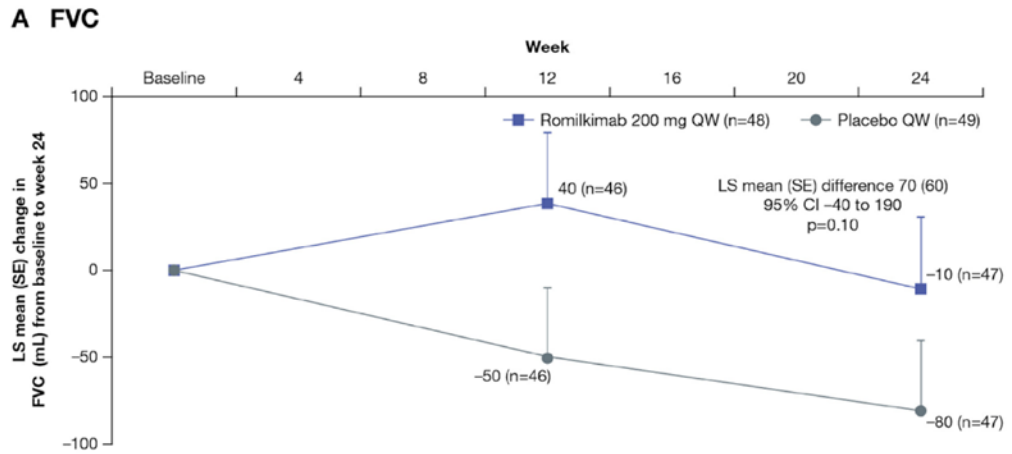


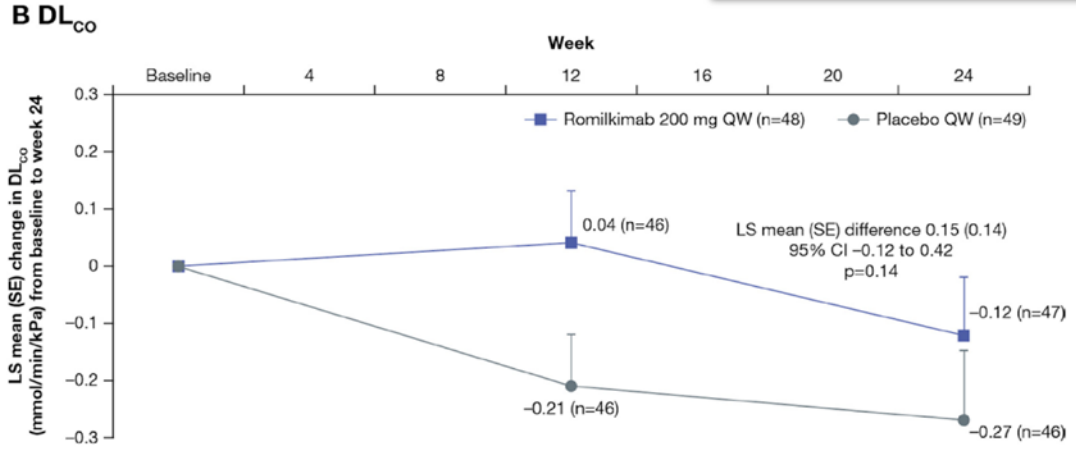
A randomised, double-blind, placebo-controlled, 24-week, phase II, proof-of-concept study of romilkimab (SAR156597) in early diffuse cutaneous systemic sclerosis

Ann Rheum Dis 2020;

Yannick Allanore ,[1] Peter Wung,[2] Christina Soubrane,[3] Corinne Esperet,[3] Frederic Marrache,[4] Raphael Bejuit,[5] Amel Lahmar,[6] Dinesh Khanna ,[7] Christopher P Denton ,[8] On behalf of the Investigators

47 pacientes romilkimab
47 pacientes placebo

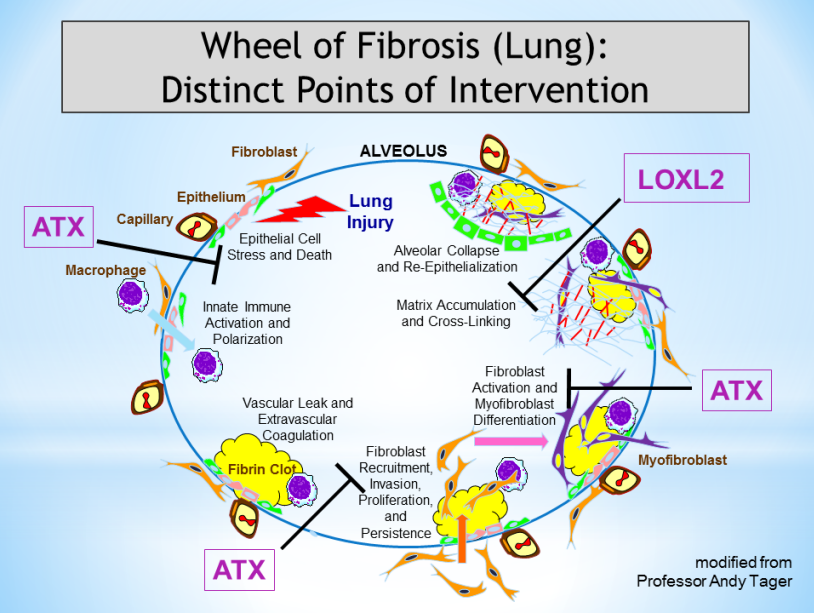




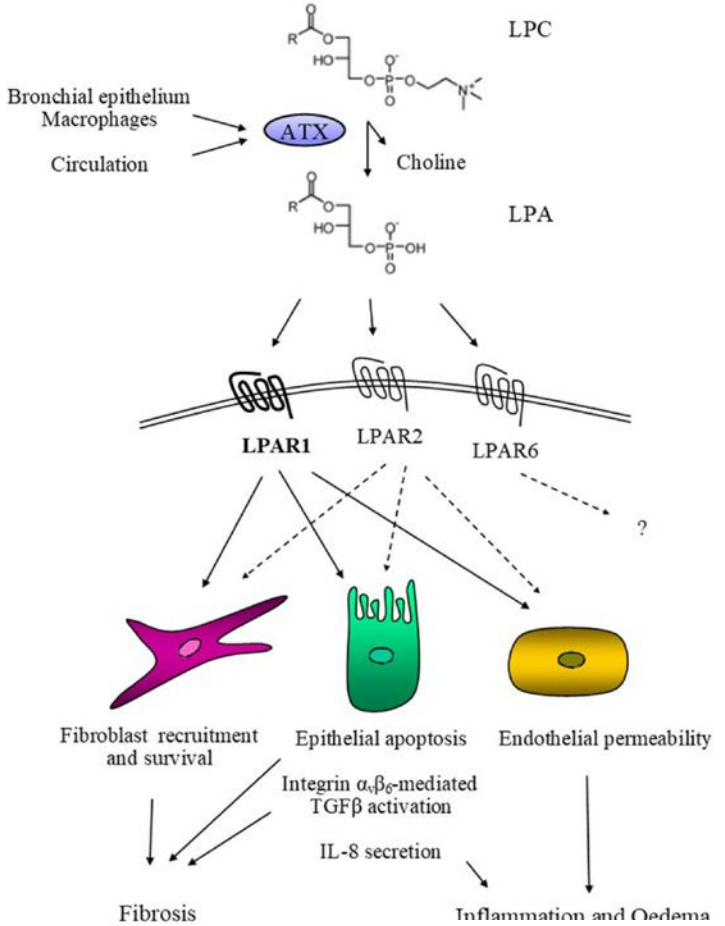
Baseline FVC (% predicted)		
Mean (SD)	89.5 (15.8)	96.1 (17.4)
Median (range)	91.9 (48–127)	97.3 (54–127)
Baseline DL_{CO} (% haemoglobin corrected)		
Mean (SD)	66.5 (14.6)	72.4 (14.2)
Median (range)	67.3 (38–102)	72.7 (39–102)

SANOFI

Autotaxina en la fibrosis pulmonar



- ✓ Pfizer
- ✓ Mitsubishi Tanabe Pharma
- ✓ Shionogi & Co
- ✓ Biogen
- ✓ Hoffmann-La Roche
- ✓ Novartis
- ✓ Galapagos
- ✓ PharmAkea
- ✓ ONO Pharmaceuticals
- ✓ Janssen Biotech



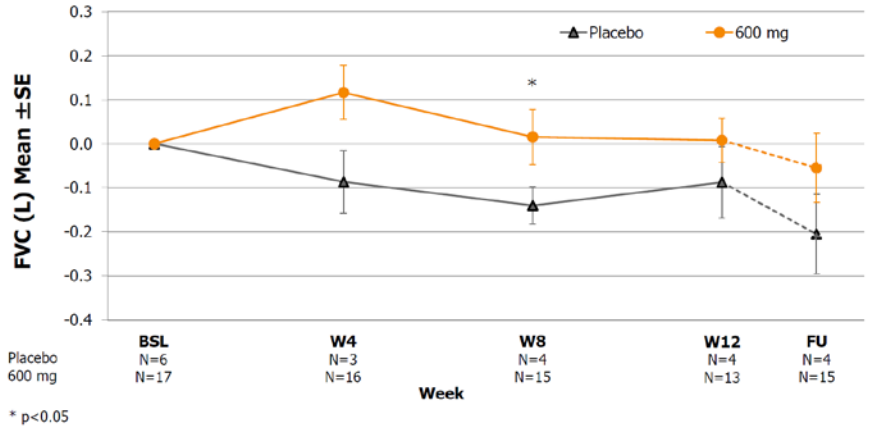
Safety, tolerability, pharmacokinetics, and pharmacodynamics of GLPG1690, a novel autotaxin inhibitor, to treat idiopathic pulmonary fibrosis (FLORA): a phase 2a randomised placebo-controlled trial

Toby M Maher, Ellen M van der Aar, Olivier Van de Steen, Lisa Allamassey, Julie Desrivot, Sonia Dupont, Liesbeth Fagard, Paul Ford, Ann Fieuw, Wim Wuyts

Lancet Respir Med 2018; 6: 627–35

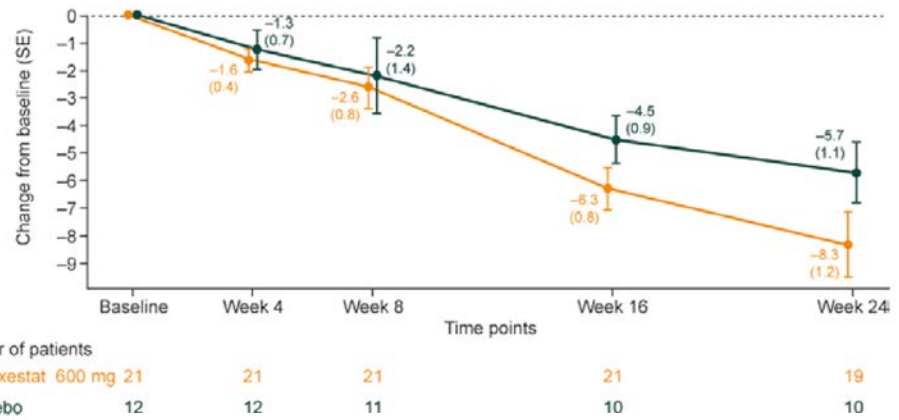
Galápagos

FLORA



	Wk4		Wk8		Wk12		Follow-up	
	Placebo	'1690	Placebo	'1690	Placebo	'1690	Placebo	'1690
FVC (Δ baseline, mL)	-87	+116	-140	+15	**-87**	**+8**	-205	-55

NOVESA



ClinicalTrials.gov Identifier: NCT03976648

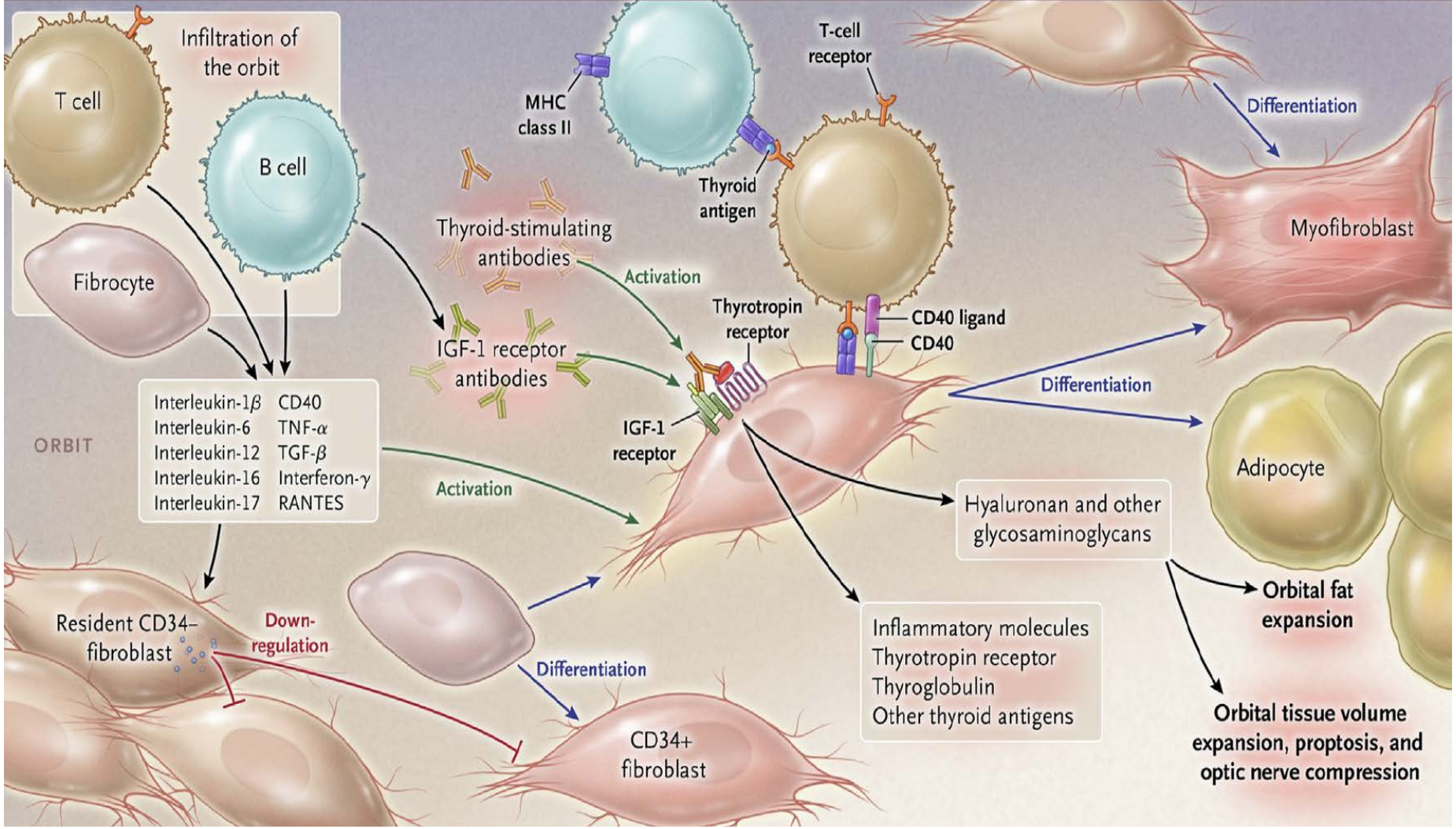
GILEAD
Creating Possible

Galápagos

ISABELA

Galapagos and Gilead discontinue ISABELA Phase 3 trials in IPF

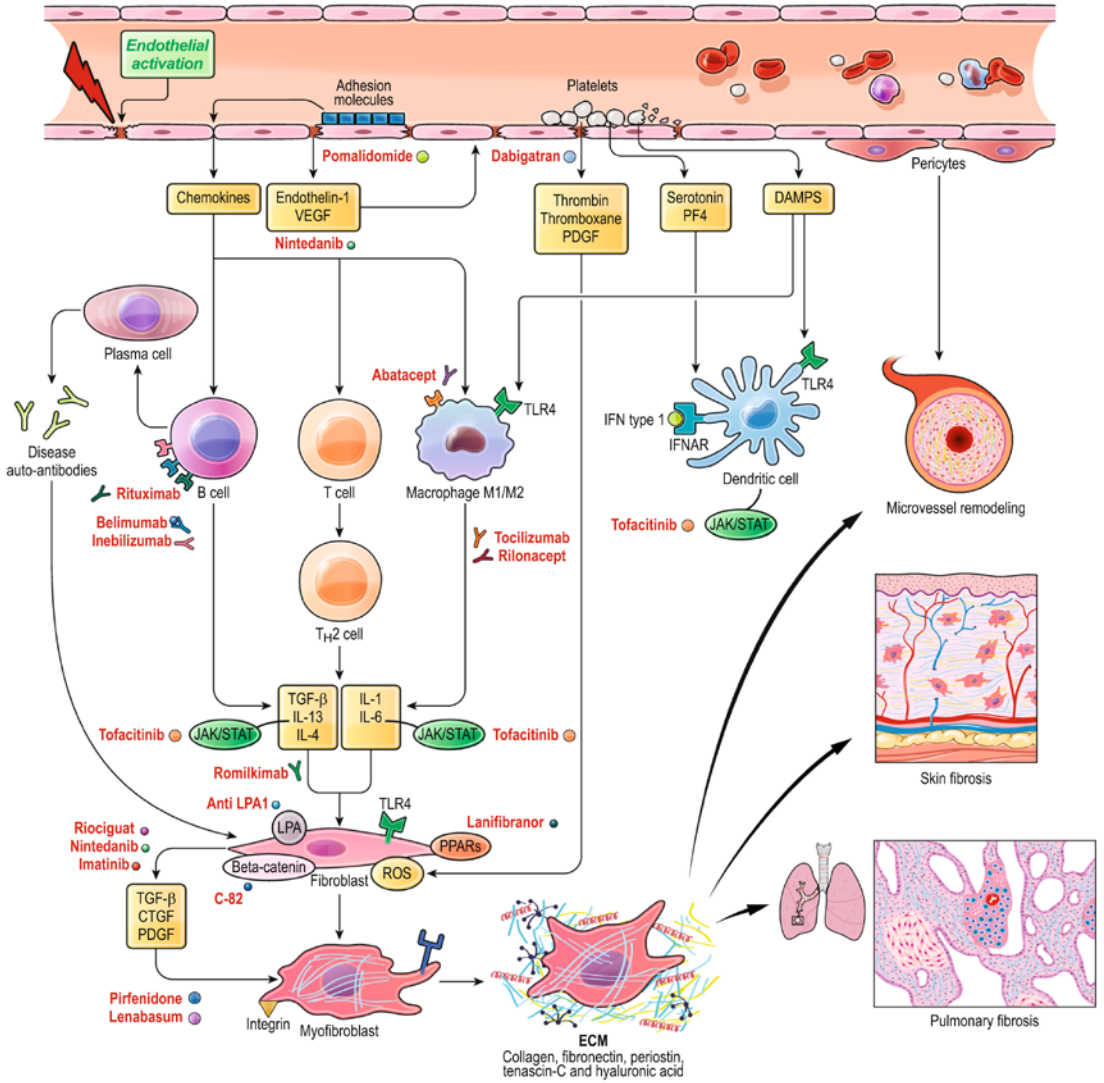
Foster City, CA and Mechelen, Belgium, 10 February 2021, 15.00 CET; regulated informa



Medicine / Candidate	Pre-clinical	Phase 1	Phase 2	Phase 3	Phase 3b/4
TEPEZZA® (*teprotumumab-trbw*) Diffuse Cutaneous Systemic Sclerosis					

HORIZON

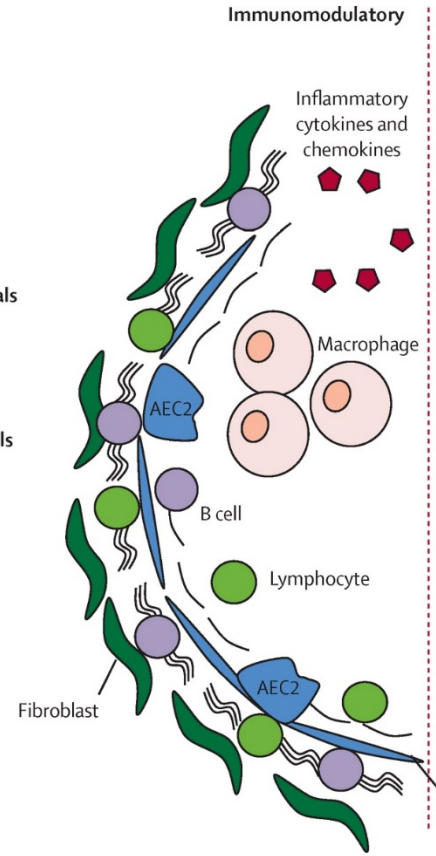
Nuevas terapias en esclerosis sistémica

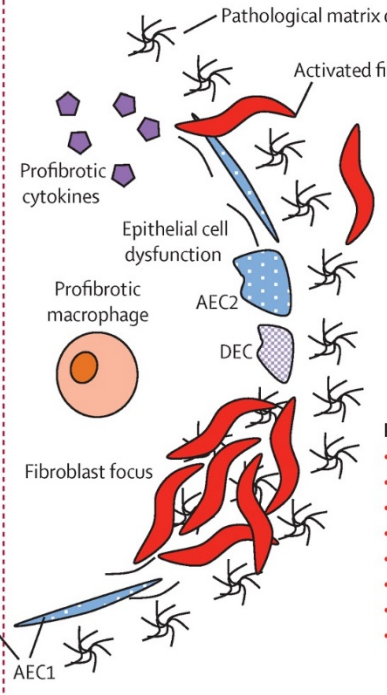


Pathological macrophage signals
- Tocilizumab

Pathological lymphocyte signals
- Cyclophosphamide
- Azathioprine
- Mycophenolate
- Tofacitinib*
- Abatacept

Pathological B-cell signals
- Rituximab
- Ixazomib*





Pathological epithelial signals
- Pamrevlumab
- PLN-74809*
- Senolytics*

Pathological macrophage signals
- Pentraxin 2
- TRK-250*
- Jaktinib*
- TD139*

Pathological mesenchymal signals
- Nintedanib*†
- Pirfenidone*†
- TRK-250
- ND-L02-s0201
- BMS-986278
- KD025
- Setanaxib*
- CC-90001*

conclusiones

- Los antifibróticos han llegado para quedarse (en la esclerosis sistémica y en otras enfermedades con fibrosis: AR, miopatías, etc)
- Es muy posible que los antifibróticos se utilicen asociados a tratamientos inmunosupresores / antiinflamatorios de forma habitual
- Al igual que ocurre en otras enfermedades inflamatorias y autoinmunes crónicas, es probable que el tratamiento precoz (con inmunosupresores y antifibróticos combinados) sea capaz de modificar el curso de la enfermedad

¿cual es el futuro en la modificación de la enfermedad en esclerodermia?

Patricia E Carreira
servicio de reumatología
hospital universitario 12 de Octubre, Madrid

Zaragoza, mayo 2012

Tratamiento modificador de la enfermedad en la esclerodermia

inmunosupresor + Anti-fibrótico

- ✓Ciclofosfamida
- ✓Micofenolato
- ✓Derivados de talidomida?
- ✓....

- ✓Inhibidor de quinasa
- ✓Inhibidores de otras moléculas post TGF-β
- ✓Mecanismos epigenéticos?
- ✓....

Zaragoza, Congreso SER, mayo 2012


gracias
INSYNC
EUSTAR
SCTC
Scleroderma
Clinical Trials Consortium
Red de Enfermedades
Inflamatorias (REI)
RICORS (RD21/0002)
European
Reference
Network
for rare or low prevalence
complex diseases
Network
Connective Tissue and
Musculoskeletal Diseases
(ERN ReCONNET)
Member
University Hospital 12
de Octubre — Spain
unidad de
EAS12
Enfermedades Autoinmunes Sistémicas
i+12
Instituto de Investigación
Hospital 12 de Octubre
H12 Investiga
JUNTOS CONSTRUIMOS, JUNTOS AVANZAMOS
Hospital Universitario
12 de Octubre
SaludMadrid
Comunidad de Madrid