RIIP

Les sclérodermies systémiques: traiter autrement en 2021 ?

Yannick Allanore
Hôpital Cochin, Paris

28 et **29** SEPTEMBRE 2021

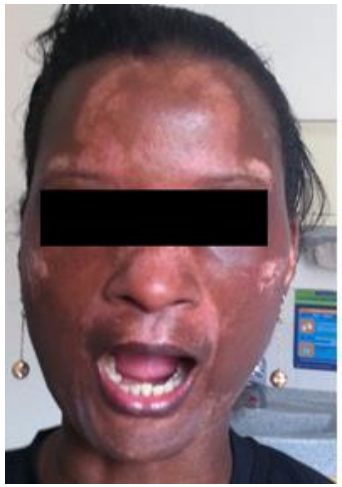
UIC-P - Espaces Congrès - 16, rue Jean Rey - 75015 Paris

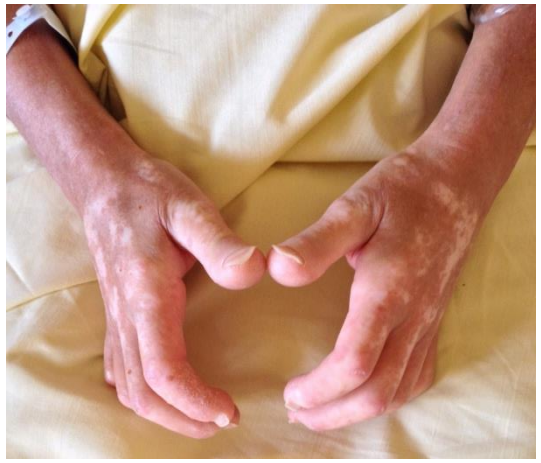
image Fotolia

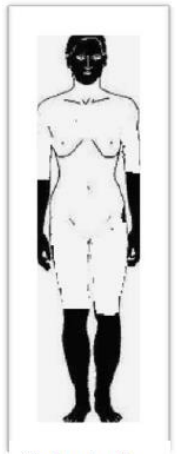
Sous l'égide de :

Les sclérodermies systémiques (SSc)

Fibrose systémique

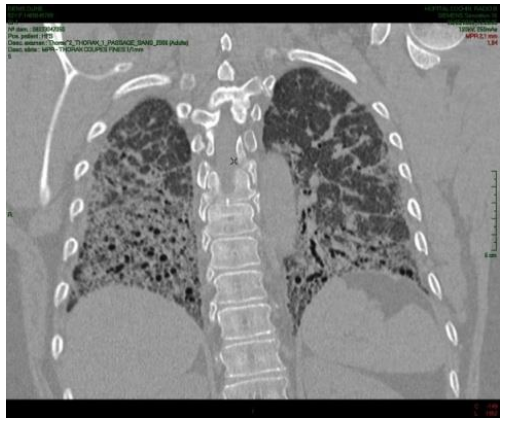




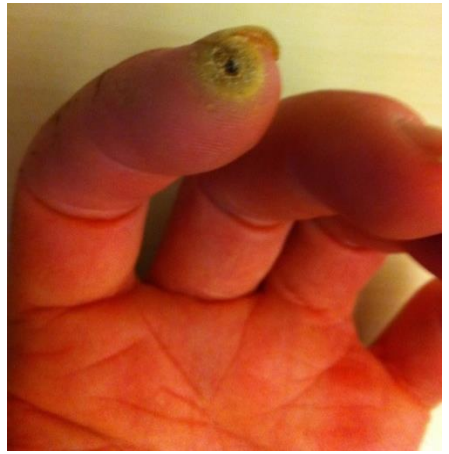


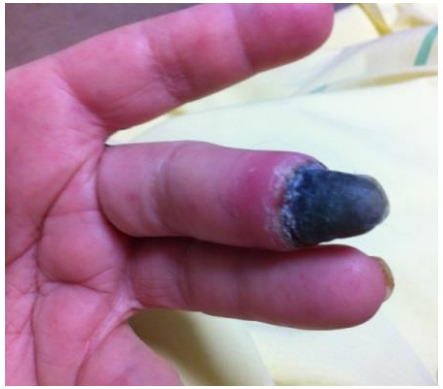
ScS cutanée limitée

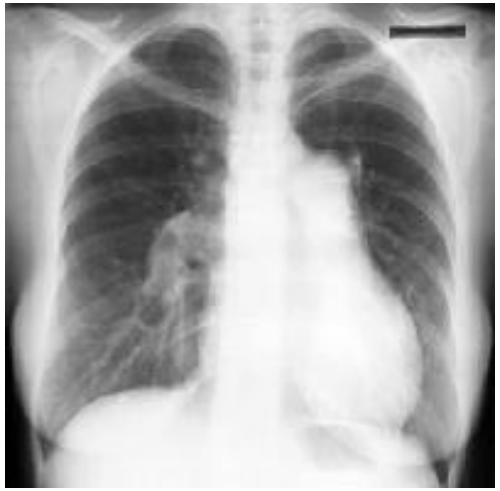
ScS cutanée diffuse



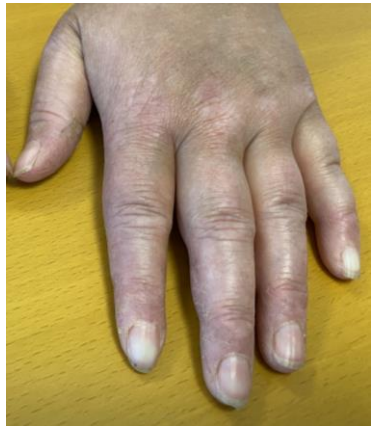
Micro-angiopathie généralisée

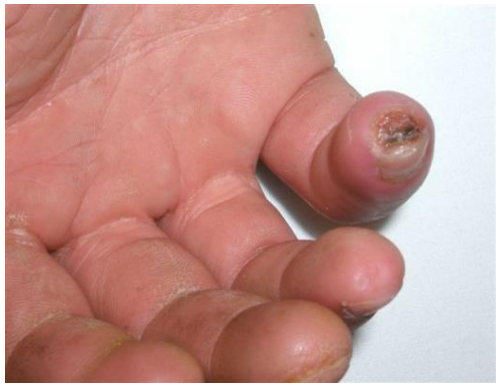


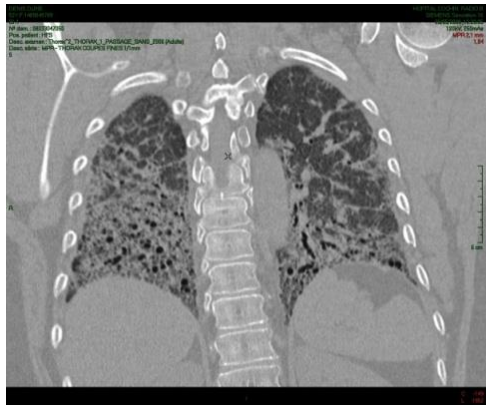




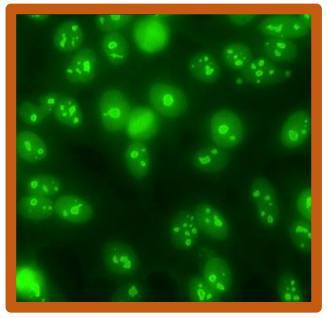
Histoire naturelle

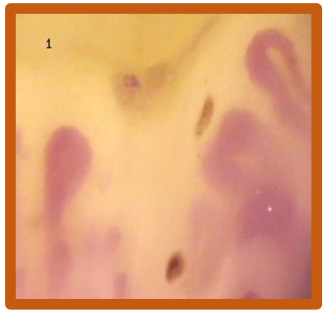


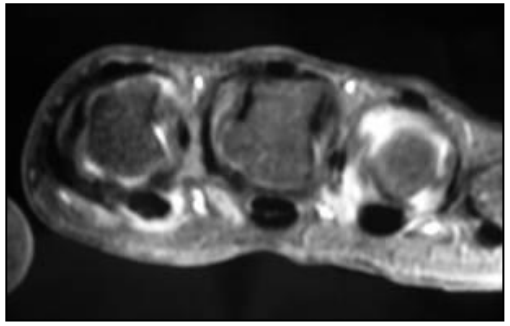


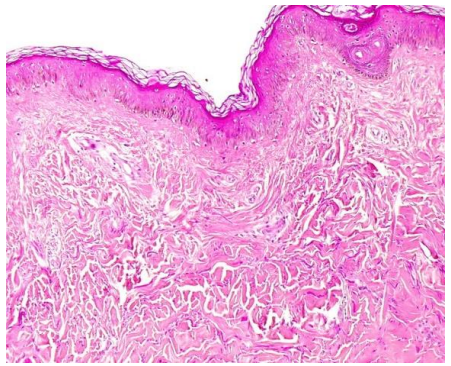


UCTD → Early SSc → SSc → Advanced stage

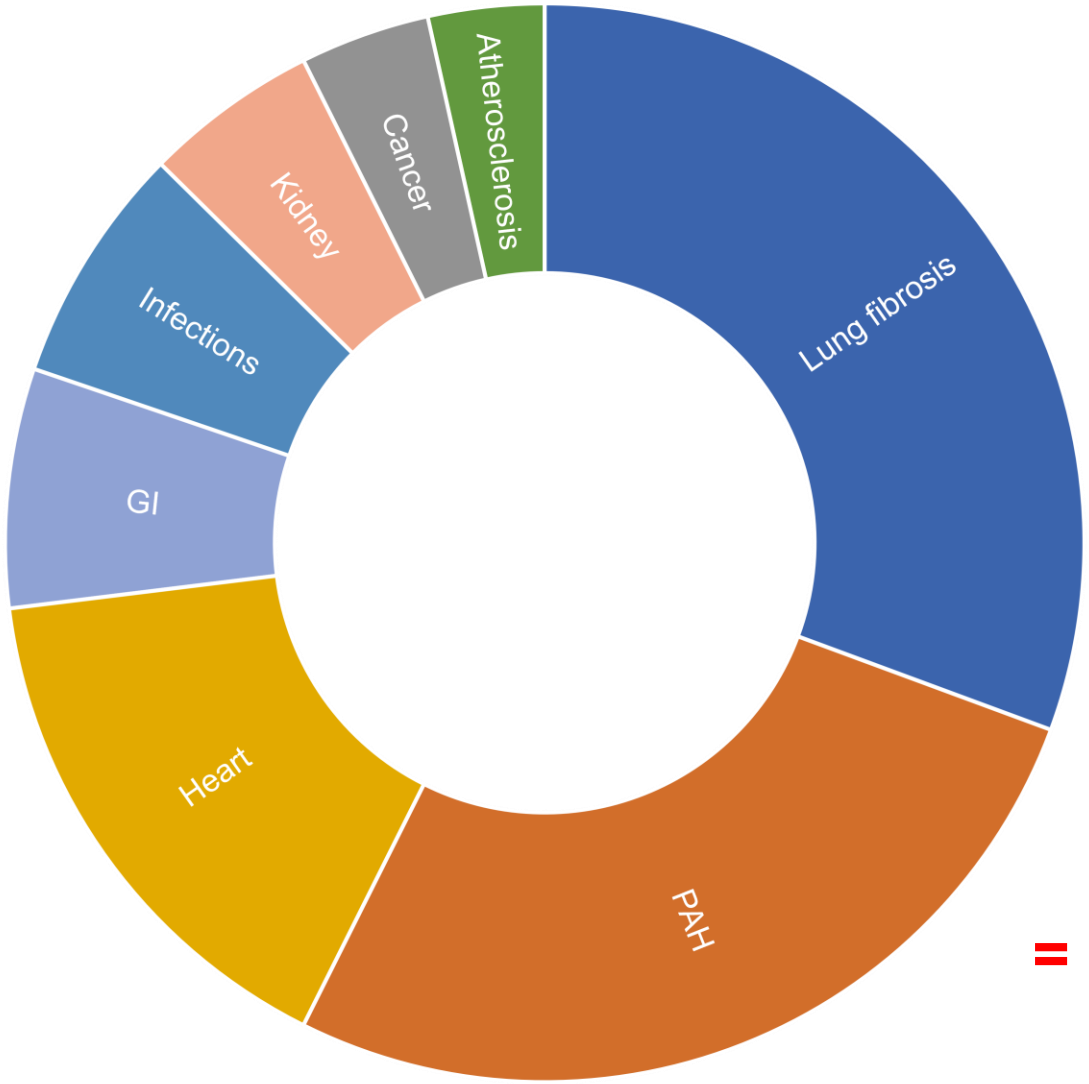








Causes de décès: liées à la maladies

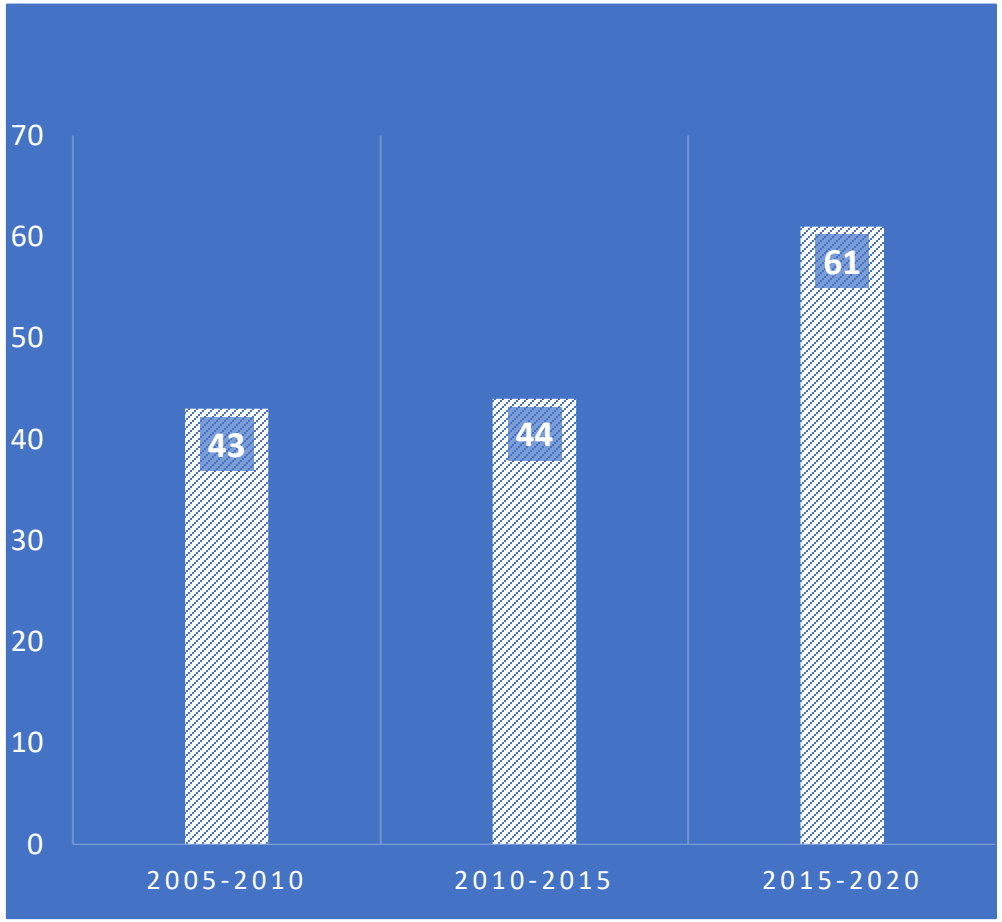


= 30%

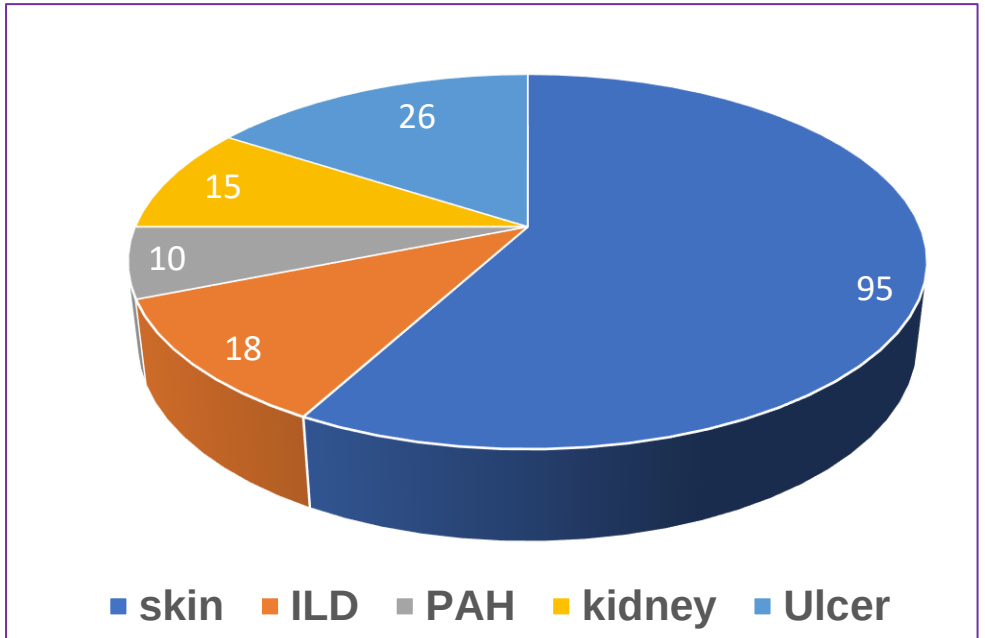
= 26%

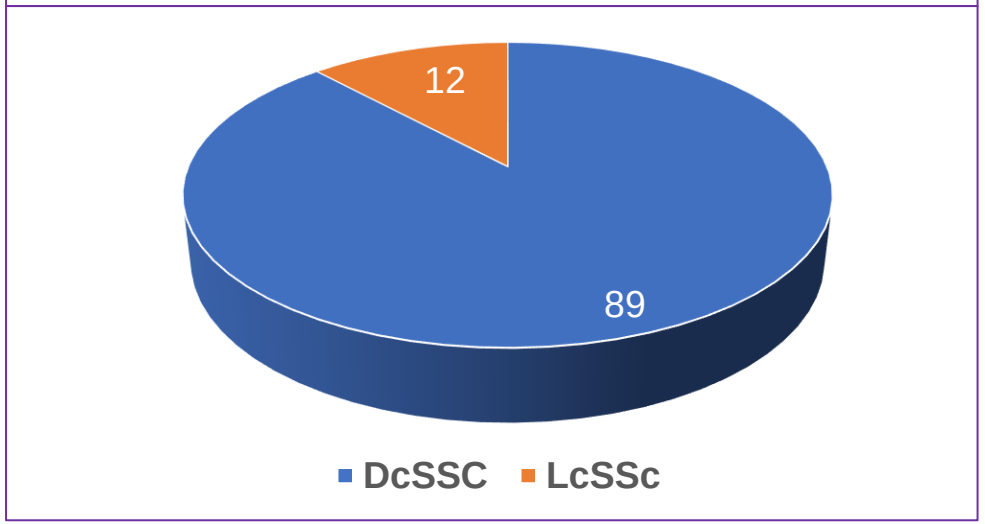
Elhai et al. Ann Rheum Dis. 2017;76:1897-1905

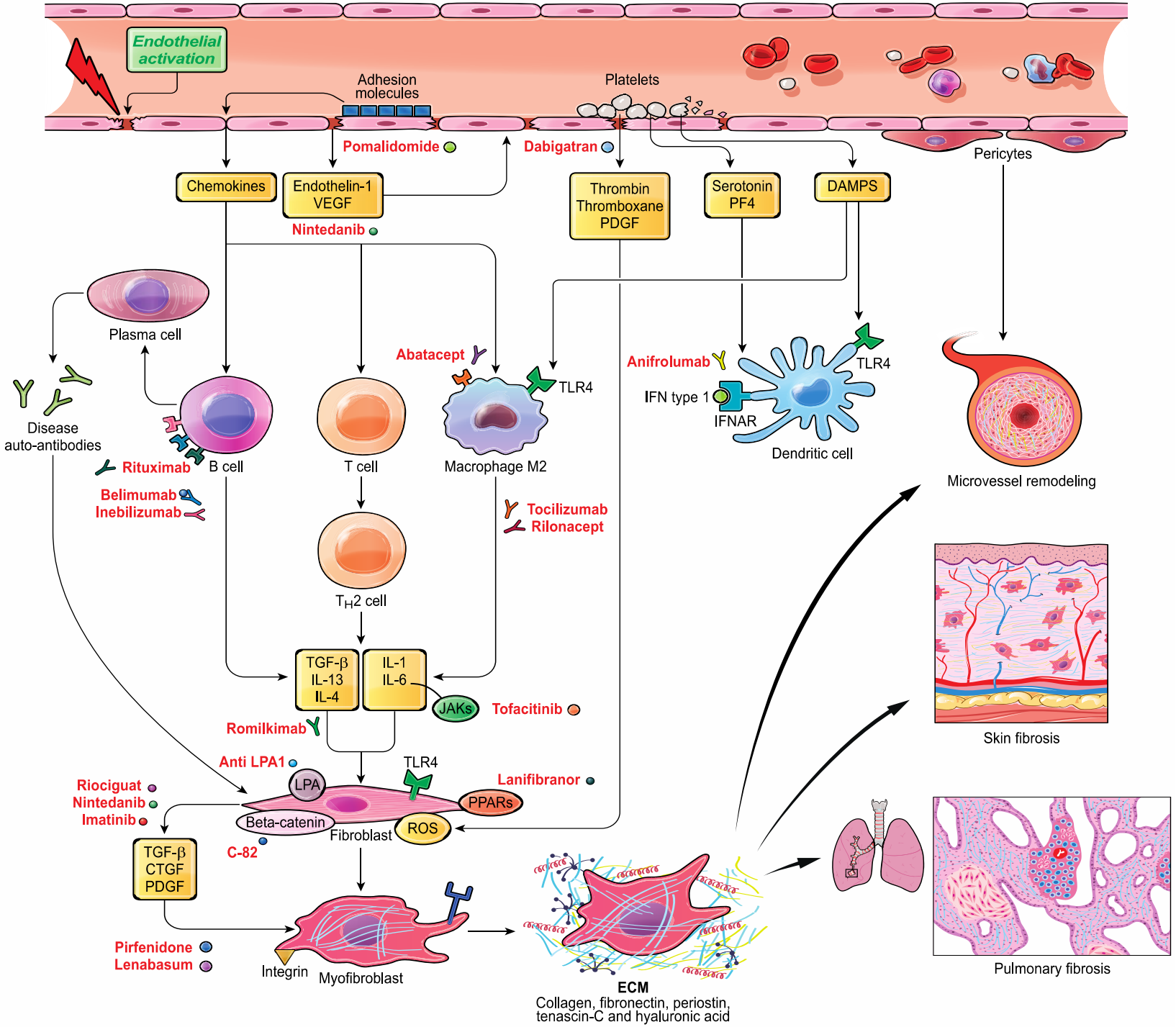
Essais thérapeutiques



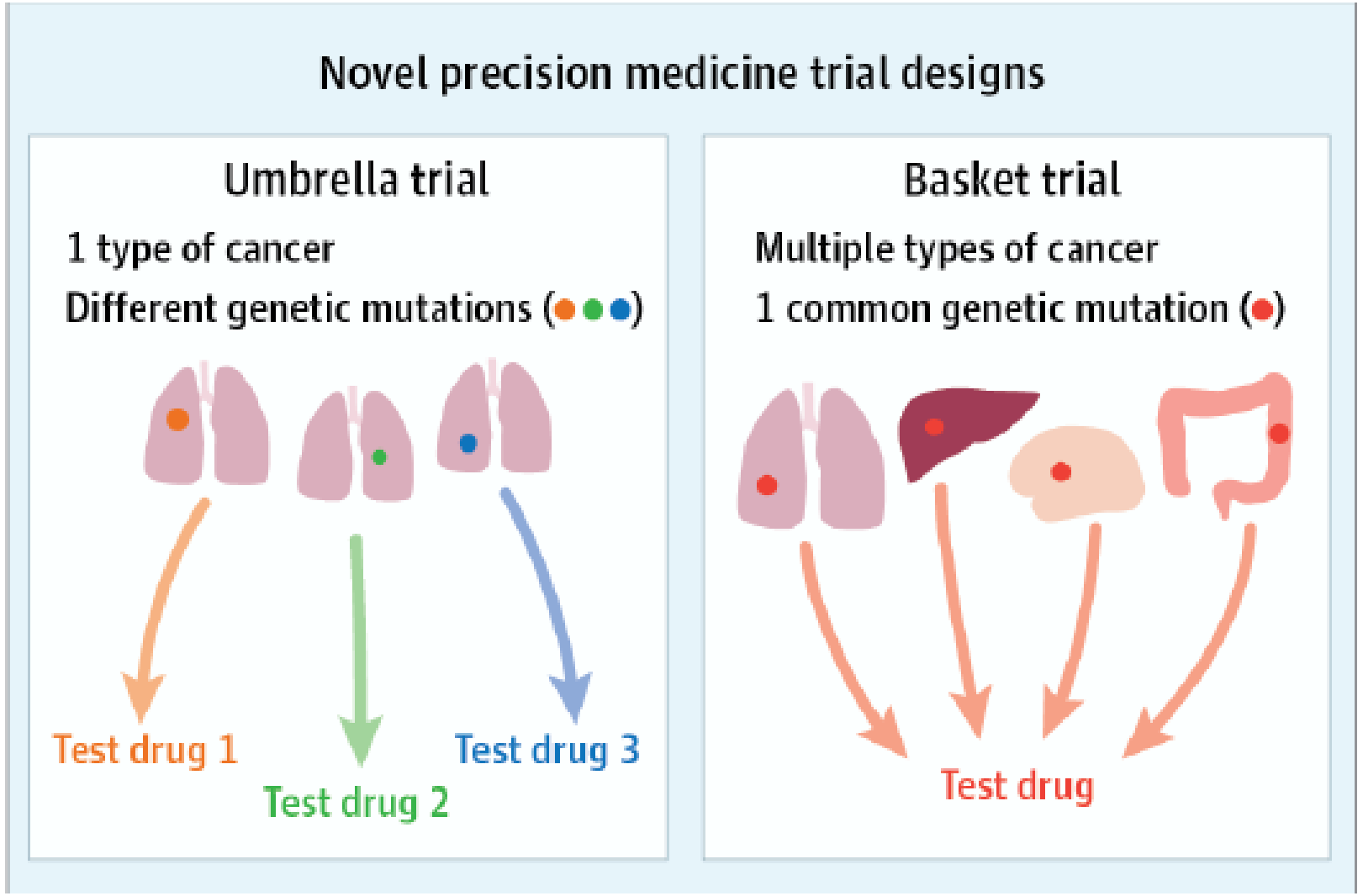
Changes with time of numbers of phase 2/3 RCT
Clinical trial gov



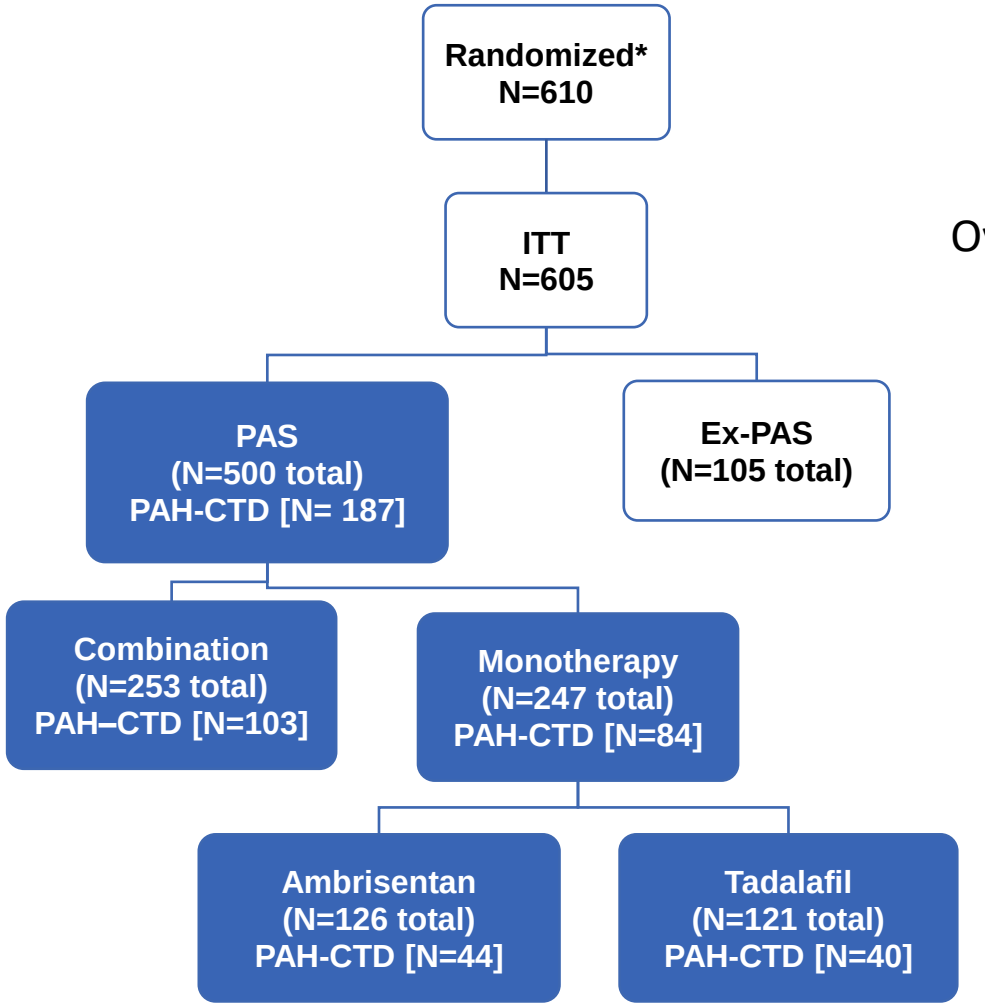


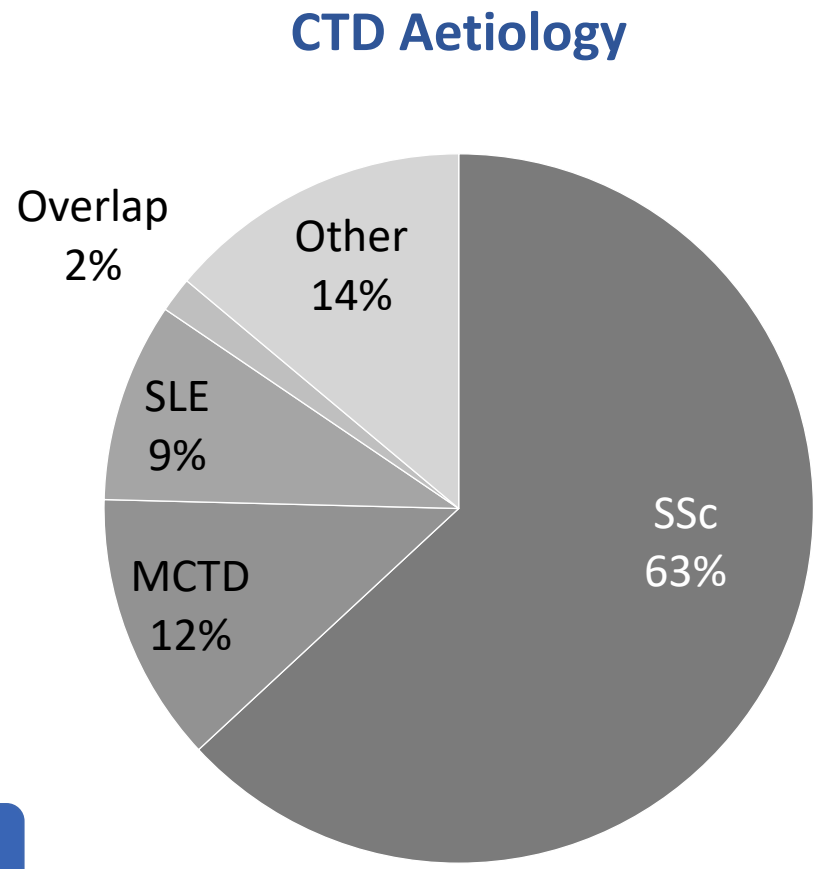

Endothelial activation
Adhesion molecules
Platelets
Pomalidomide
Dabigatran
Pericytes
Chemokines
Endothelin-1
VEGF
Nintedanib
Thrombin
Thromboxane
PDGF
Serotonin
PF4
DAMPS
Plasma cell
Abatacept
TLR4
Anifrolumab
IFN type 1
IFNAR
Disease auto-antibodies
Rituximab
B cell
T cell
Macrophage M2
Dendritic cell
Microvessel remodeling
Belimumab
Inebilizumab
Tocilizumab
Rilonacept
TH2 cell
TGF-β
IL-13
IL-4
IL-1
IL-6
JAKs
Tofacitinib
Romilkimab
Anti LPA1
LPA
TLR4
Lanifibranor
Riociguat
Nintedanib
Imatinib
PPARs
Beta-catenin
Fibroblast
ROS
C-82
TGF-β
CTGF
PDGF
Skin fibrosis
Pirfenidone
Lenabasum
Integrin
Myofibroblast
ECM
Collagen, fibronectin, periostin, tenascin-C and hyaluronic acid
Pulmonary fibrosis

Nouveaux design des essais thérapeutiques



HTAP étude AMBITION: combinaison d'emblée

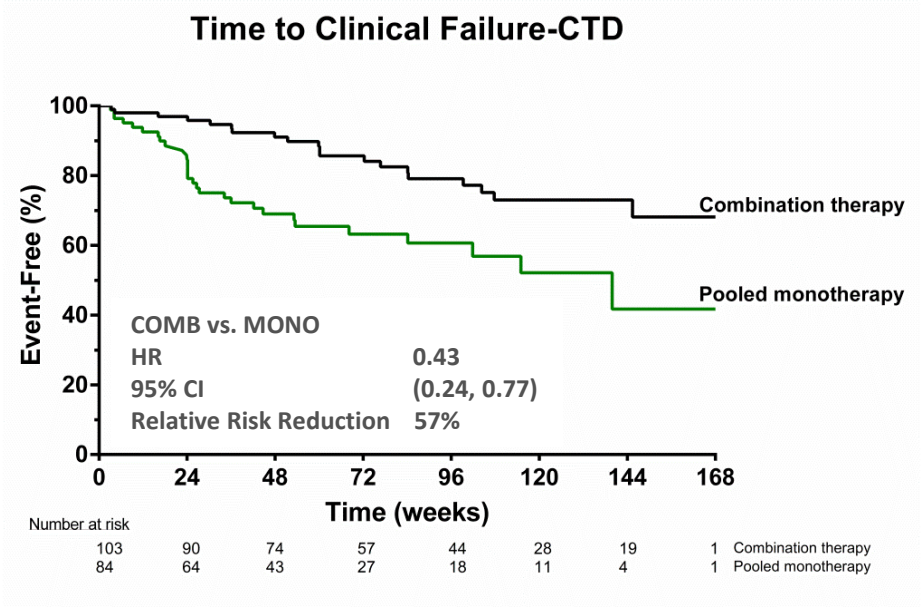


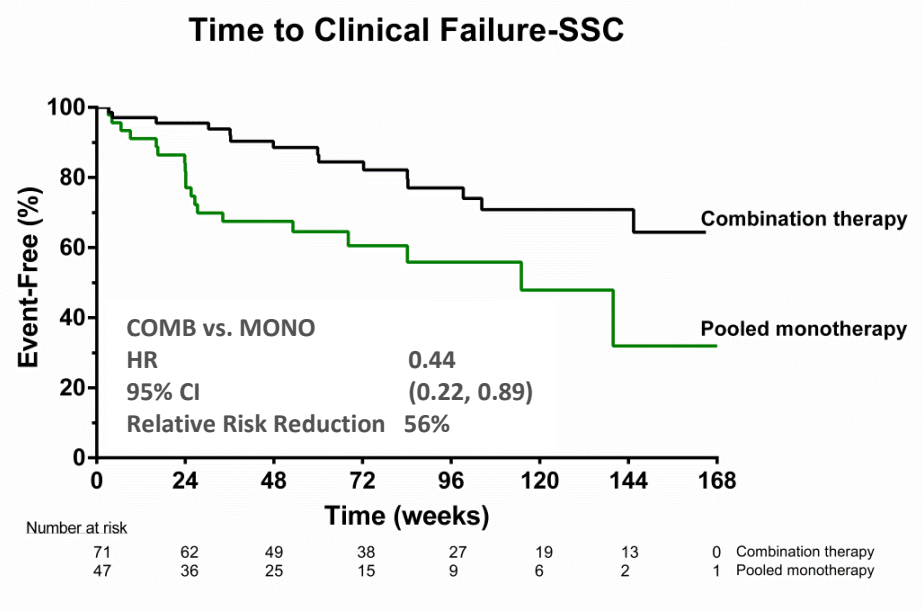


*5 subjects randomized did not receive study drug

Galie et al. N Engl J Med.;373(9):834-44

Time to first adjudicated clinical failure CTD-PAH and SSc-PAH subgroups





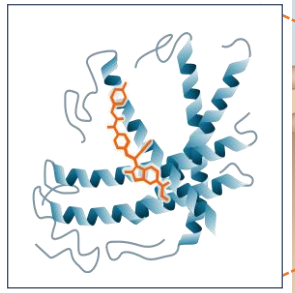
First adjudicated TTCF event by type	COMB (n=103)	MONO (n=84)
Number of subjects with first event, n (%)	20 (19%)	30 (36%)
Death	4 (4%)	2 (2%)
Hospitalisation for worsening PAH	5 (5%)	13 (15%)
Disease progression	5 (5%)	7 (8%)
Unsatisfactory long term clinical response	6 (6%)	8 (10%)

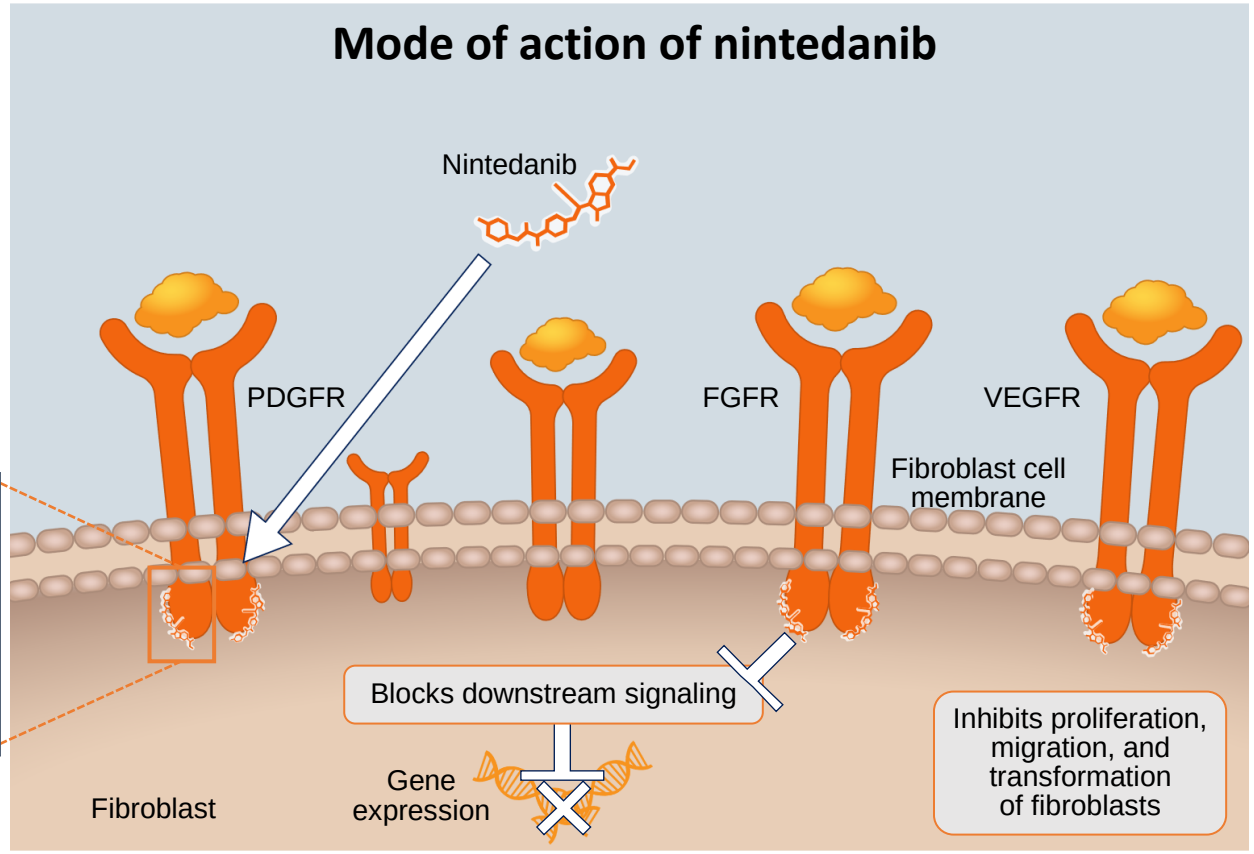
First adjudicated TTCF event by type	COMB (n=71)	MONO (n=47)
Number of subjects with first event, n (%)	15 (21%)	19 (40%)
Death	2 (3%)	2 (4%)
Hospitalisation for worsening PAH	4 (6%)	5 (11%)
Disease progression	4 (6%)	5 (11%)
Unsatisfactory long term clinical response	5 (7%)	7 (15%)

Coghlan et al. Ann Rheum Dis. 2017;76:1219-1227

Nintedanib is a tyrosine kinase inhibitor

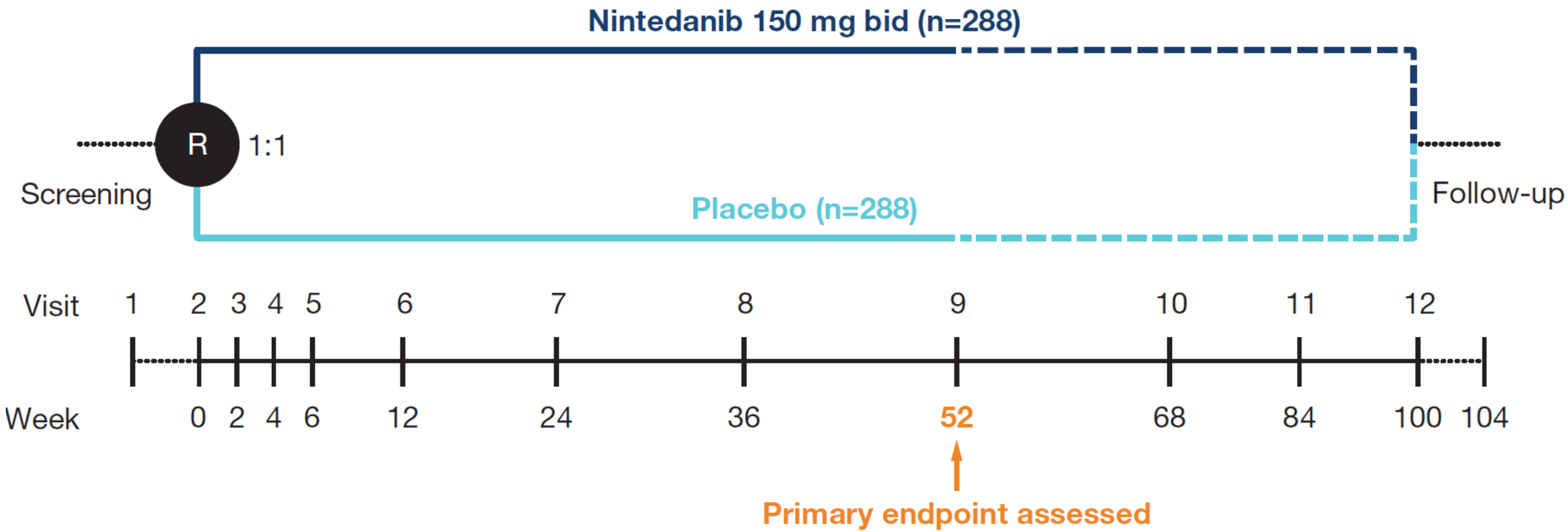
- Nintedanib is a small-molecule tyrosine kinase inhibitor
- Nintedanib binds to the receptors of tyrosine kinases involved in pathological pathways active in ILD
- Nintedanib blocks the downstream signaling pathways of cells that contribute to lung fibrosis
- Nintedanib also has anti-inflammatory and anti-angiogenic activity





Nintedanib Summary of Product Characteristics. Available at: http://www.ema.europa.eu [accessed October 2020]

Trial design: SENSCIS



- **Patients remained on blinded treatment until the last patient had reached week 52 but for no longer than 100 weeks**

Randomized patients were stratified by anti-topoisomerase antibody (ATA) status (positive or negative). Dose reductions from 150 mg bid to 100 mg bid and treatment interruptions were permitted to manage adverse events.
bid, twice daily; R, randomization.

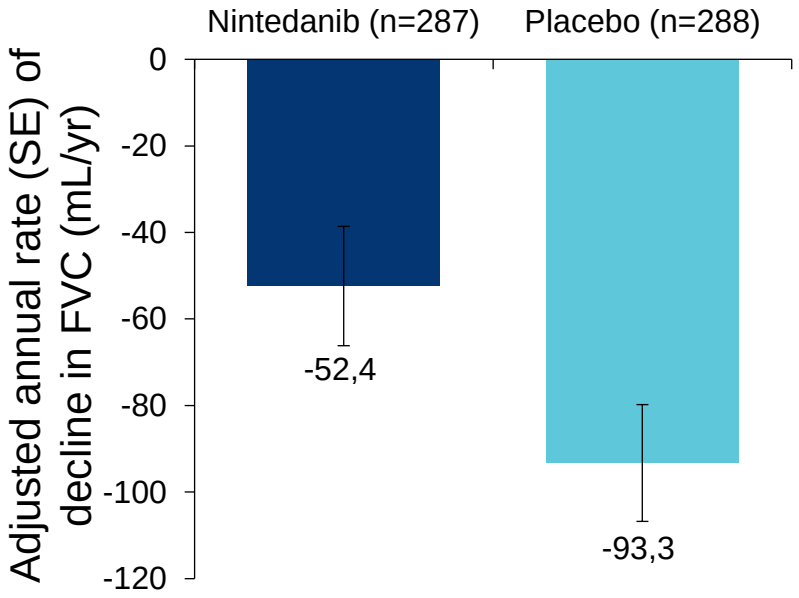
Distler et al. N Engl J Med 2019; 380:2518-2528

Key eligibility criteria

- Key inclusion criteria
  - SSc with first non-Raynaud symptom <7 years from screening
  - ≥10% fibrosis of the lungs, confirmed by central assessment of an HRCT scan performed ≤12 months before screening
  - FVC ≥40% predicted
  - DLco 30–89% predicted
- Key exclusion criteria
  - Significant pulmonary hypertension*
  - >3 digital ulcers or history of severe digital necrosis requiring hospitalization
- Background treatment permitted:
  - Prednisone ≤10 mg/day or equivalent
  - Stable mycophenolate or methotrexate for ≥6 months prior to randomization

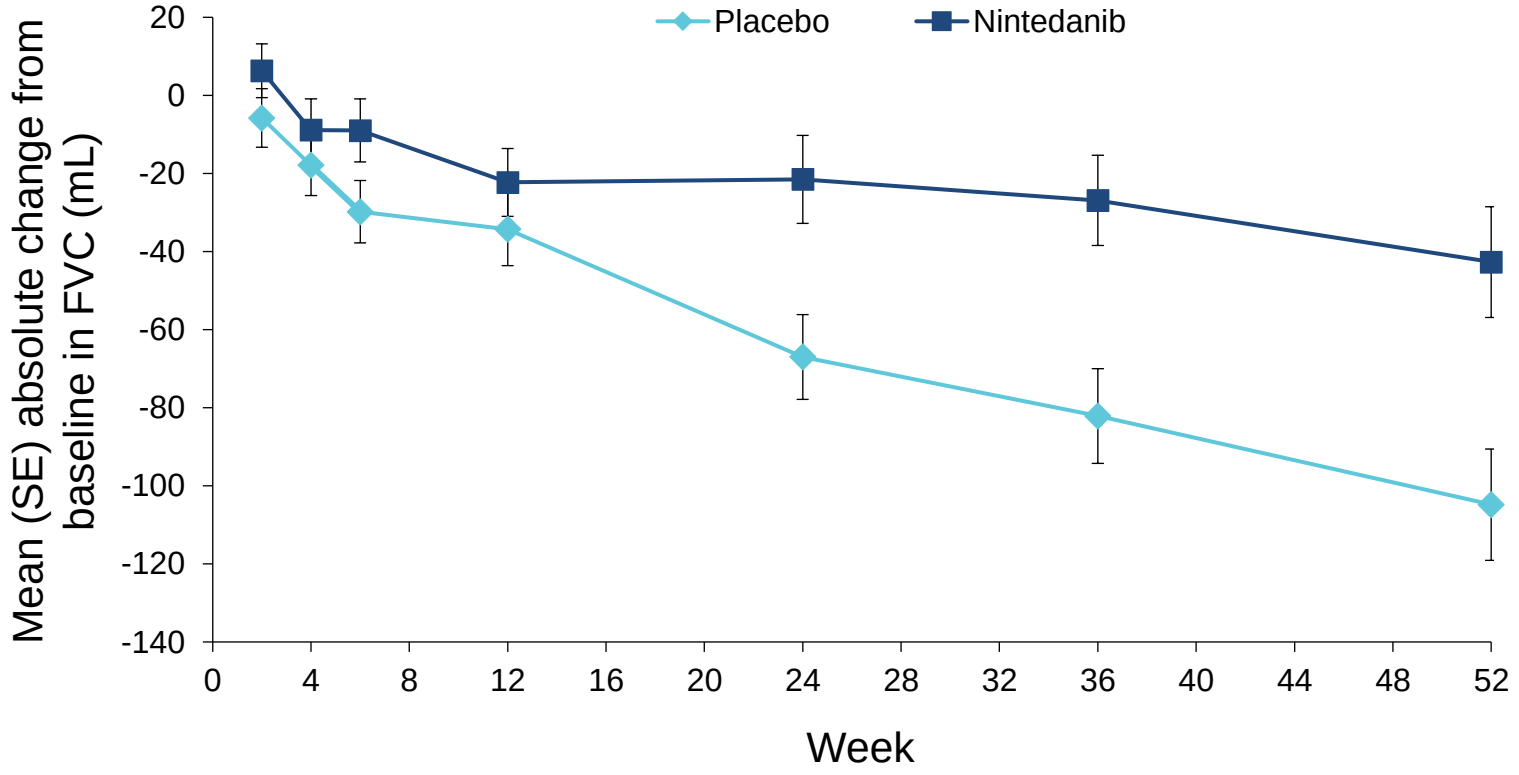
Primary outcome: decline in FVC over 52 weeks

Annual rate of decline in FVC (mL/yr) (primary endpoint)



Difference: 41.0 mL/yr
(95% CI: 2.9, 79.0); p=0.04
Relative reduction: 44%

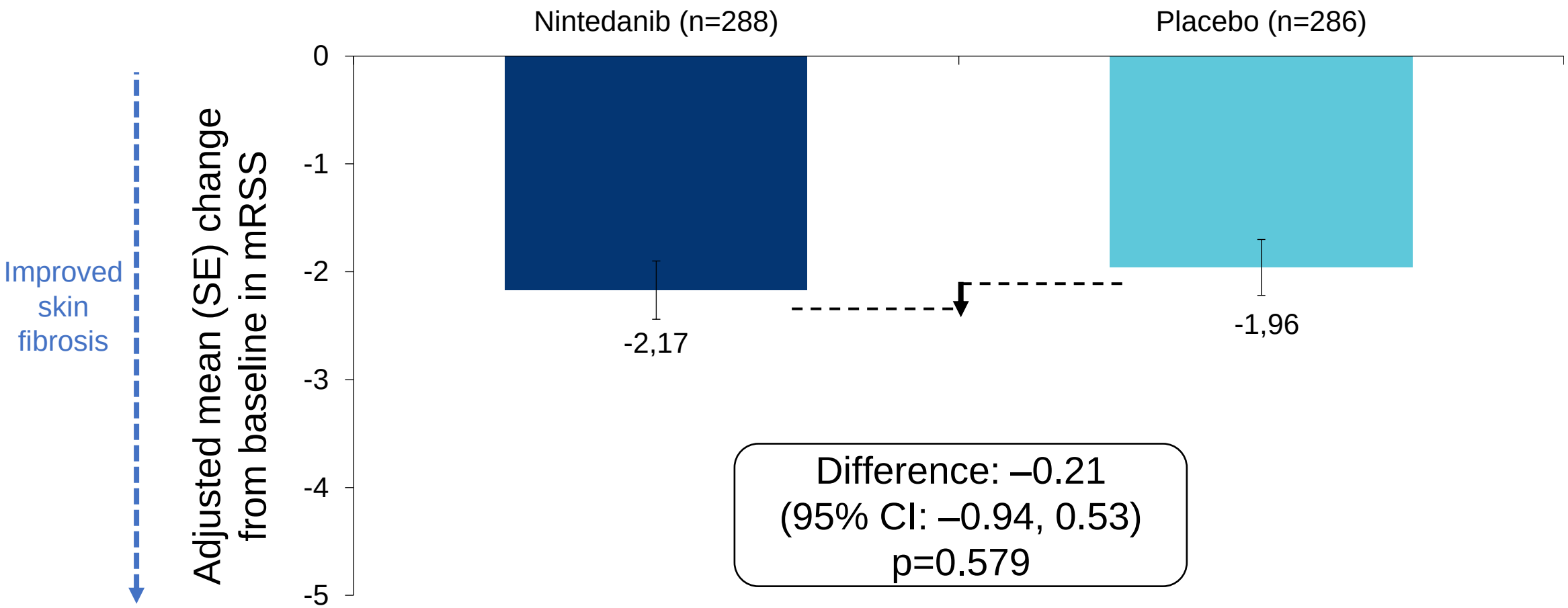
Change from baseline in FVC (mL) over 52 weeks



No. of patients													
Nintedanib	288	283	281	273		278		265		262			241
Placebo	288	283	281	280		283		280		268			257

Primary endpoint analyzed using random coefficient regression model (with random slopes and intercepts) including ATA status, age, height, gender and baseline FVC (mL) as covariates

Absolute change from baseline in mRSS at week 52



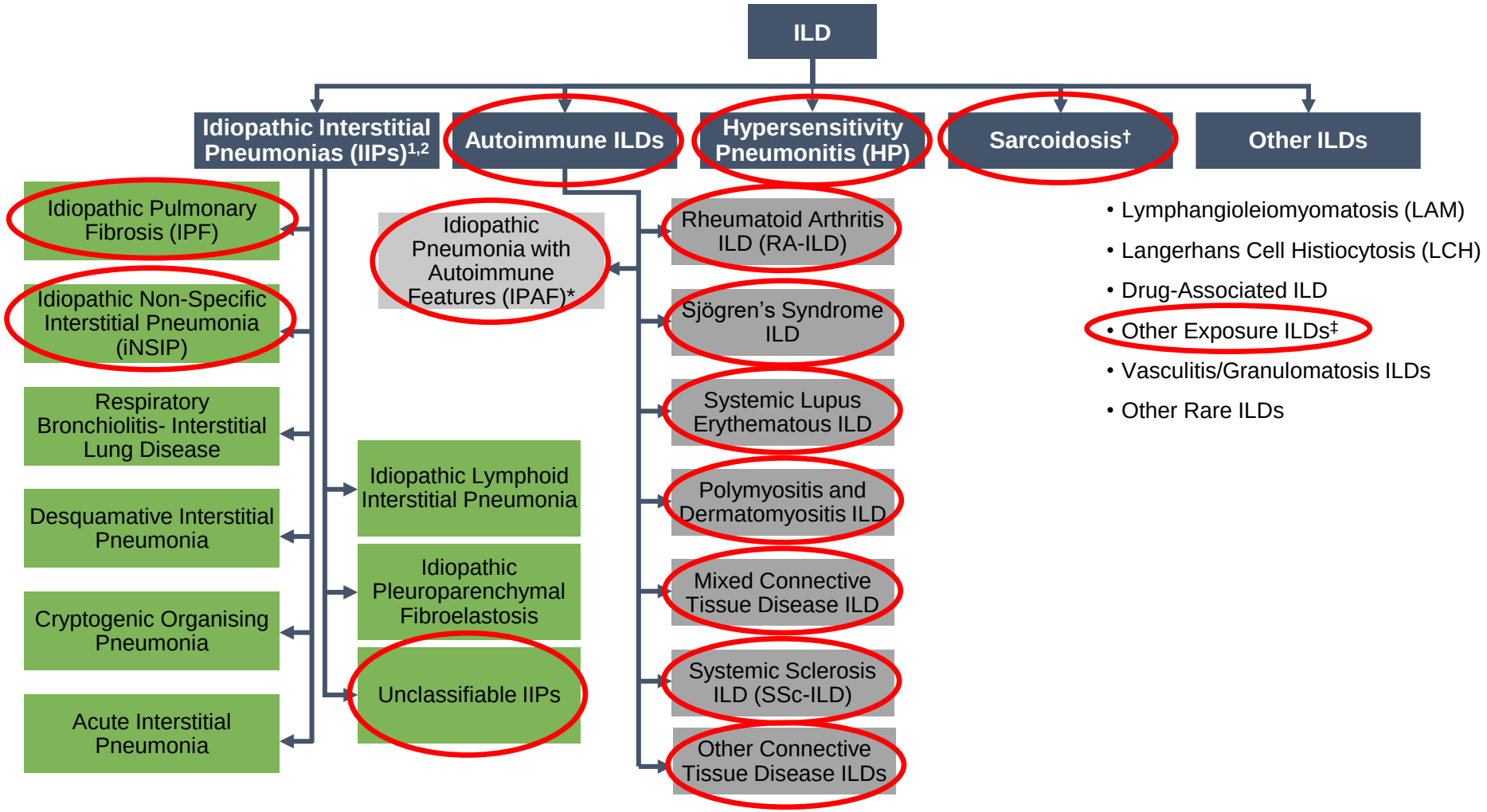
Restricted maximum likelihood-based repeated measures analysis including treatment, ATA status, visit, and treatment-by-visit interaction as fixed effects and baseline-by-visit interaction as a fixed covariate

Most frequent adverse events

	Nintedanib (n=288)	Placebo (n=288)
Diarrhea	**218 (75.7)**	**91 (31.6)**
Nausea	**91 (31.6)**	**39 (13.5)**
Vomiting	**71 (24.7)**	**30 (10.4)**
Skin ulcer	53 (18.4)	50 (17.4)
Cough	34 (11.8)	52 (18.1)
Nasopharyngitis	36 (12.5)	49 (17.0)
Upper respiratory tract infection	33 (11.5)	35 (12.2)
Abdominal pain	33 (11.5)	21 (7.3)
Fatigue	31 (10.8)	20 (6.9)
Weight decreased	34 (11.8)	12 (4.2)

Adverse events reported over 52 weeks plus 28-day post-treatment period in >10% of patients in either treatment group.
Data are n (%) of patients with ≥1 such adverse event coded based on MedDRA preferred terms.

Phenotype de fibrose progressive



*Not an established clinical diagnosis. †Stage IV sarcoidosis only. ‡e.g. asbestosis, silicosis.

Nintedanib in progressive fibrosing phenotype

- Physician-diagnosed ILD other than IPF
- Features of diffuse fibrosing lung disease (reticular abnormality with traction bronchiectasis, with or without honeycombing) of >10% extent on HRCT, confirmed by central review
- FVC ≥45% predicted
- DLco ≥30%–<80% predicted

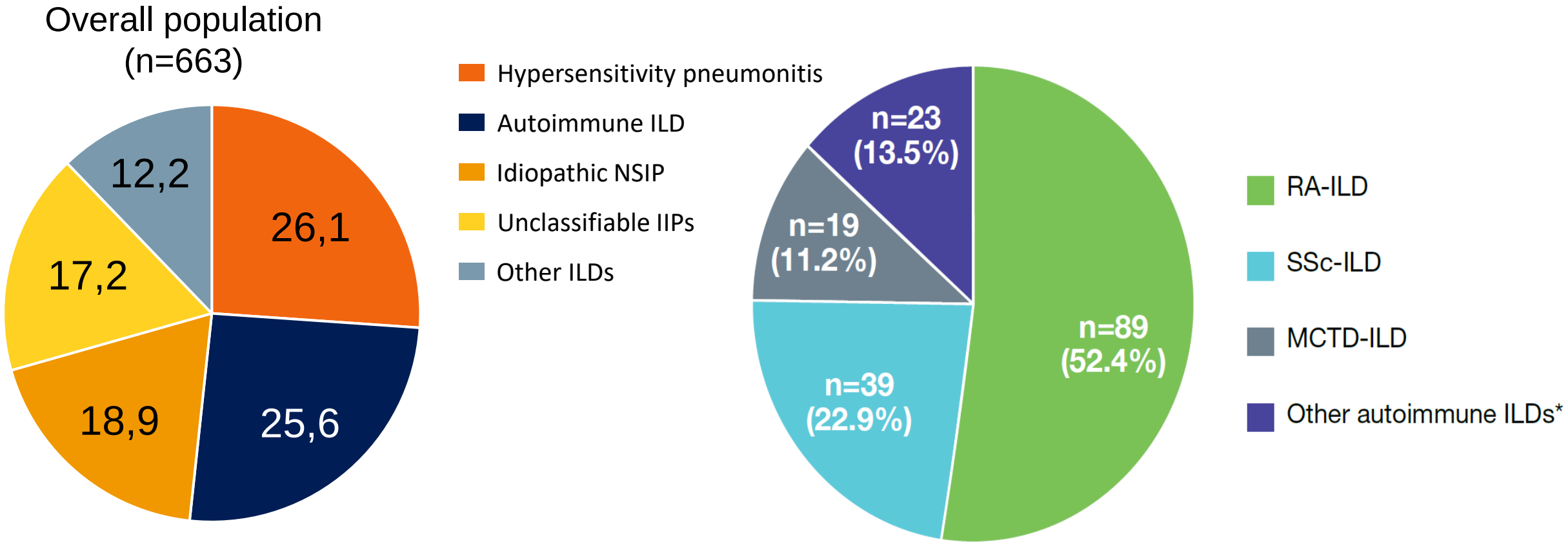
Patients were required to meet ≥1 of the following criteria for progression in the 24 months before screening:

- **Relative decline in FVC ≥10% predicted**
- **Relative decline in FVC ≥5–<10% predicted and worsened respiratory symptoms**
- **Relative decline in FVC ≥5–<10% predicted and increased extent of fibrosis on HRCT**
- **Worsened respiratory symptoms and increased extent of fibrosis on HRCT**

Immunosuppressants not allowed at baseline

Flaherty KR, et al. N Engl J Med 2019; DOI: 10.1056/NEJMoa1908681.

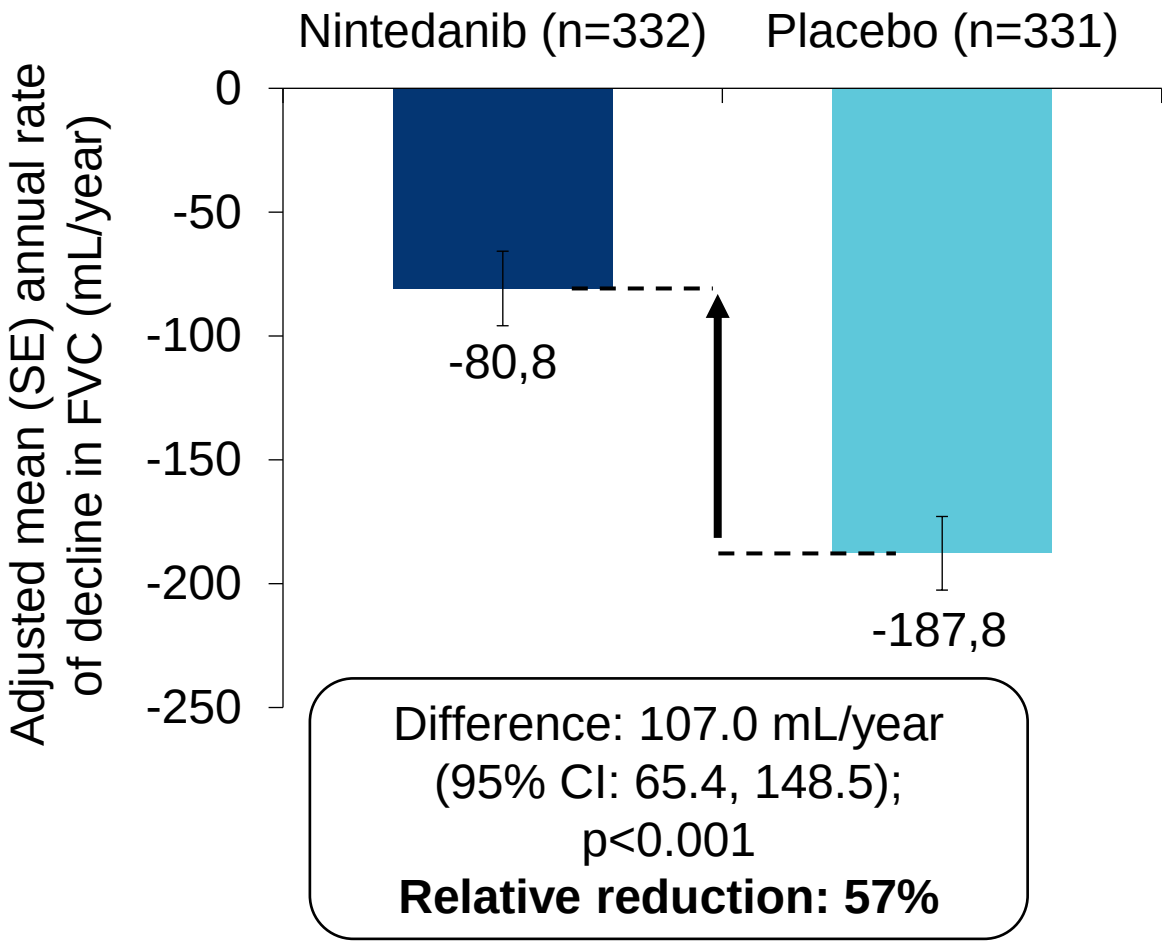
INBUILD: Clinical ILD diagnoses



Data are % of patients. *Included rheumatoid arthritis-associated ILD, systemic sclerosis-associated ILD, mixed connective tissue disease-ILD, and selected other terms in “Other fibrosing ILDs”. †Included sarcoidosis, exposure-related ILDs and selected other terms in “Other fibrosing ILDs”. IIP, idiopathic interstitial pneumonia.
Flaherty KR, et al. N Engl J Med 2019; DOI: 10.1056/NEJMoa1908681.

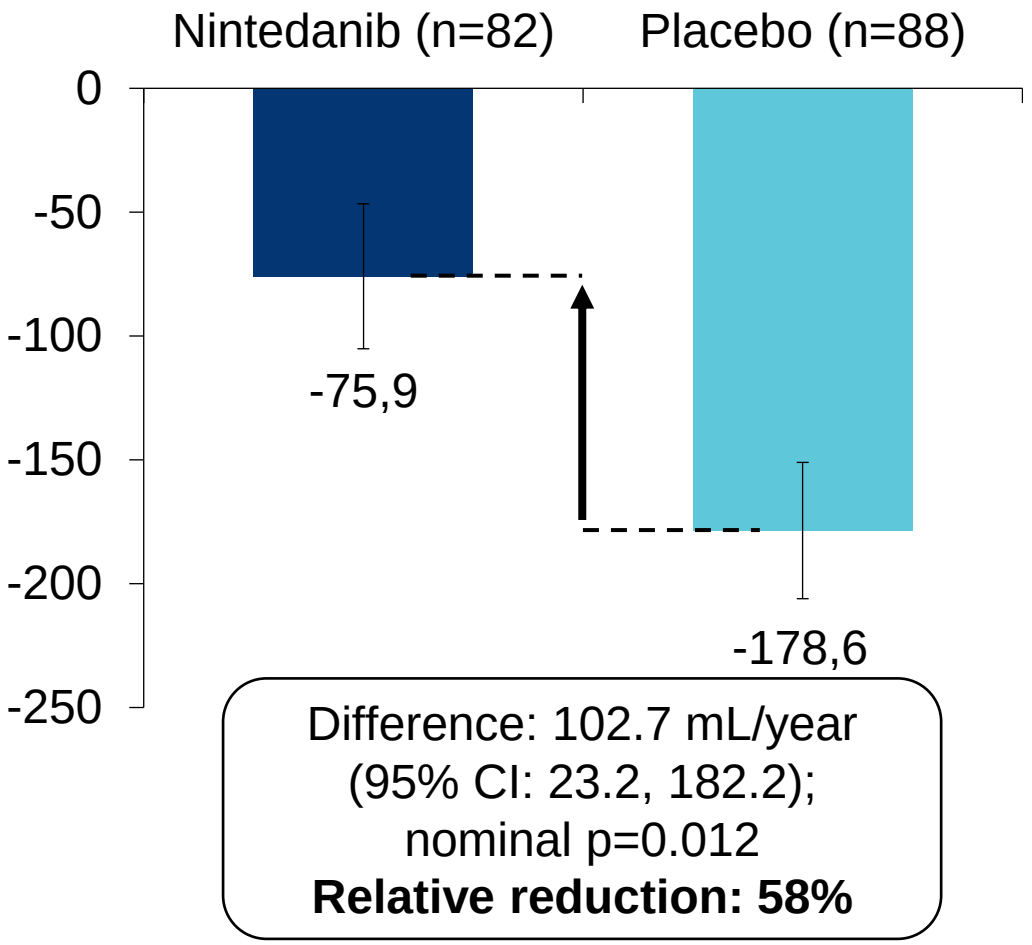
Sub-group analyses: Annual rate of decline in FVC over 52 weeks

Overall population



Flaherty KR et al. N Engl J Med 2019;381:1718–27.

Subjects with autoimmune disease-related ILDs



Matteson EL et al. Arthritis Rheumatol 2019; 71 (suppl 10).

Matteson EL et al. Effect of nintedanib on progression of interstitial lung disease (ILD) in patients with autoimmune disease-related ILDs: further data from the INBUILD trial. Oral presentation developed for Annual European Congress of Rheumatology, 2020.

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

Key inclusion/exclusion criteria:

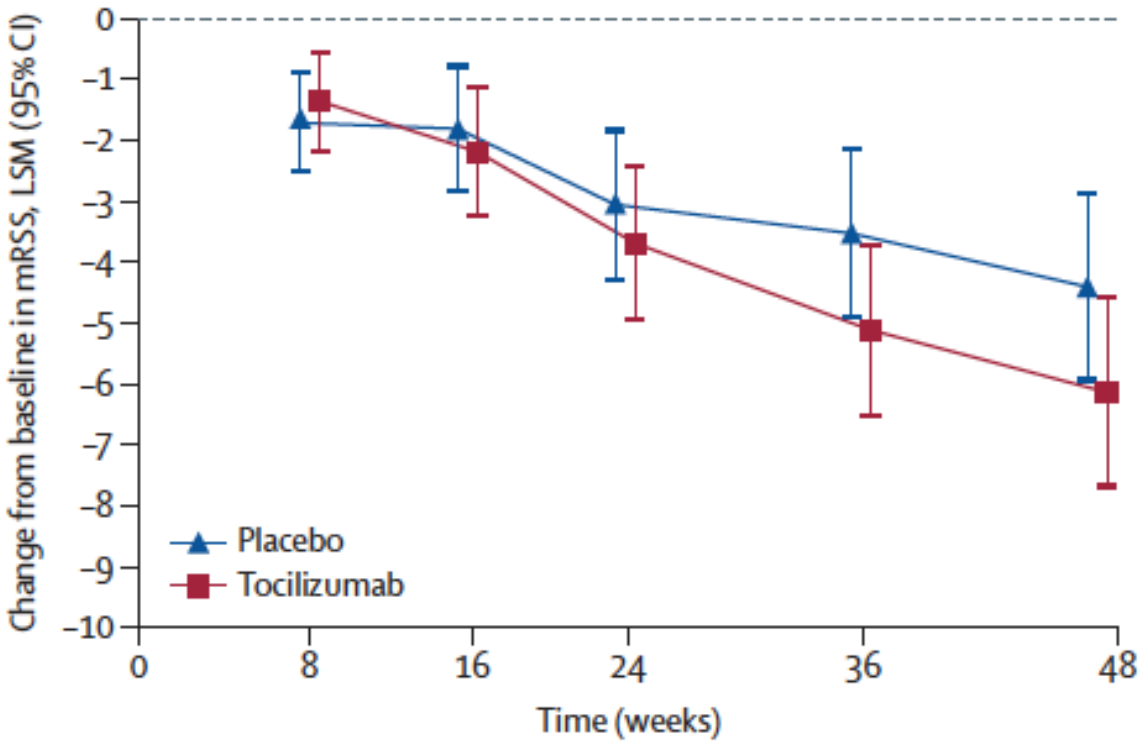
- *SSc per ACR/EULAR criteria and ≤60 months from first non-Raynaud's symptom*
- *mRSS 10-35 units*
- *Active disease*
- *At least one of these:*

CRP ≥6 mg/L; ESR ≥28 mm/h; platelet count ≥330×10^9/L

- *No other rheumatic autoimmune disease*
- *Other background immunomodulatory therapies not allowed*

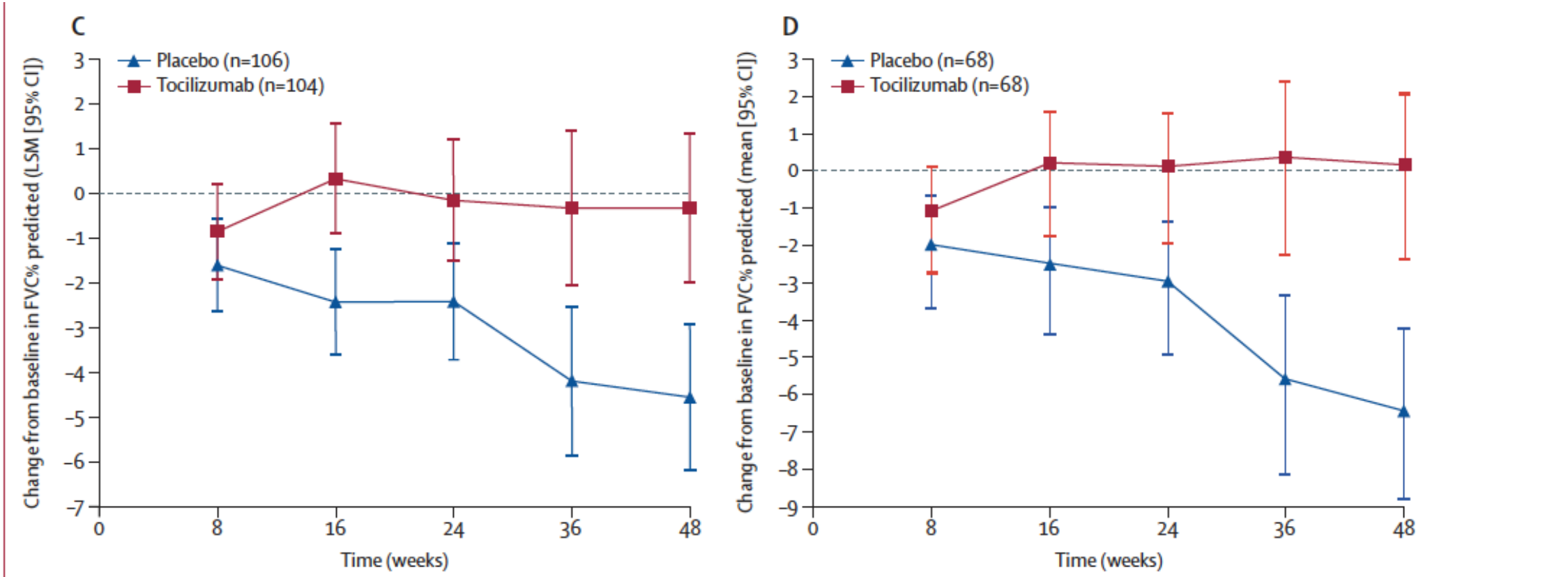
Khanna et al. Lancet Respir Med . 2020;S2213-2600(20)30318-0

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



	Placebo n=106	Tocilizumab n=104	
LSM change from baseline at week 48 (primary outcome)	−4·4	−6·1	−1·7 (95% CI −3·8 to 0·3); p=0·10
LSM change from baseline at week 24 (exploratory outcome)	−3·1	−3·7	−0·6 (95% CI −2·3 to 1·0); nominal p=0·45

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

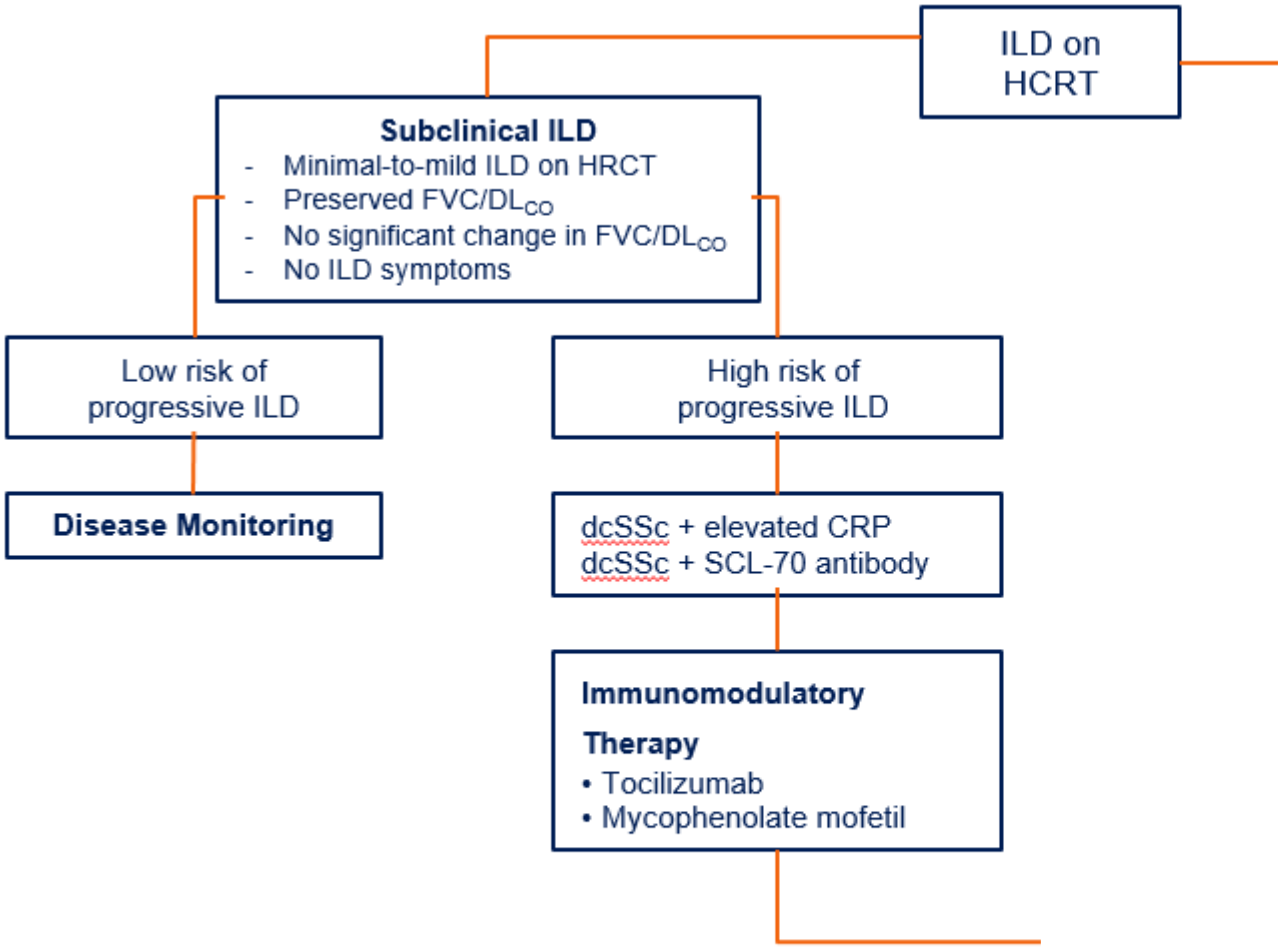


%pFVC	PBO n=106	TCZ n=104	Difference (95% CI); nominal *p* value
LSM change from BL at week 48	-4.6	-0.4	4.2 (2.0, 6.4); *p* = 0.0002
Absolute change in FVC, mL	-190	-24	167 (83, 250); *p* = 0.0001

%pFVC	PBO n=63	TCZ n=67	Difference (95% CI); nominal *p* value
LSM change from BL 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

Treatment algorithm of SSc-ILD

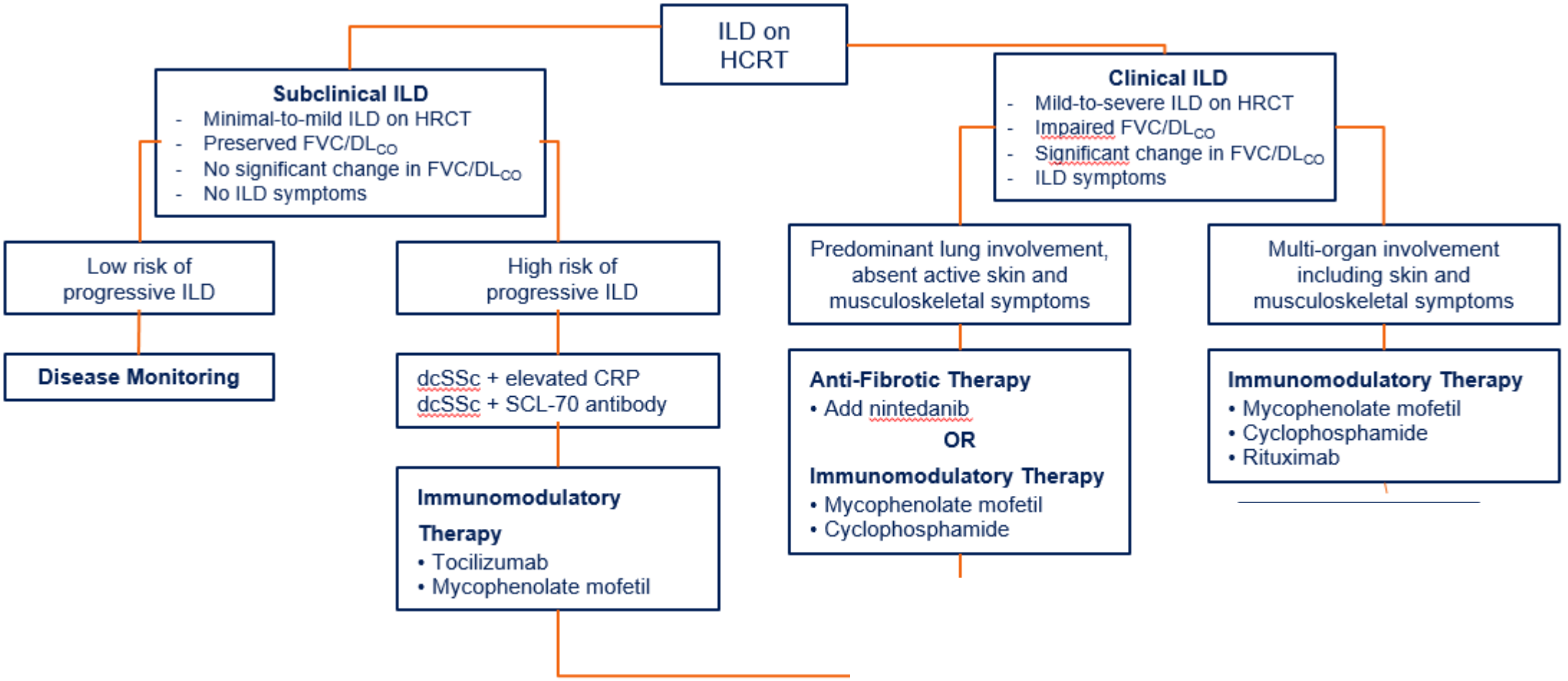
Evidence-based expert opinion



Roofeh D et al. J Scleroderma Relat Disord 2020;5(2S):61-71

Treatment algorithm of SSc-ILD

Evidence-based expert opinion



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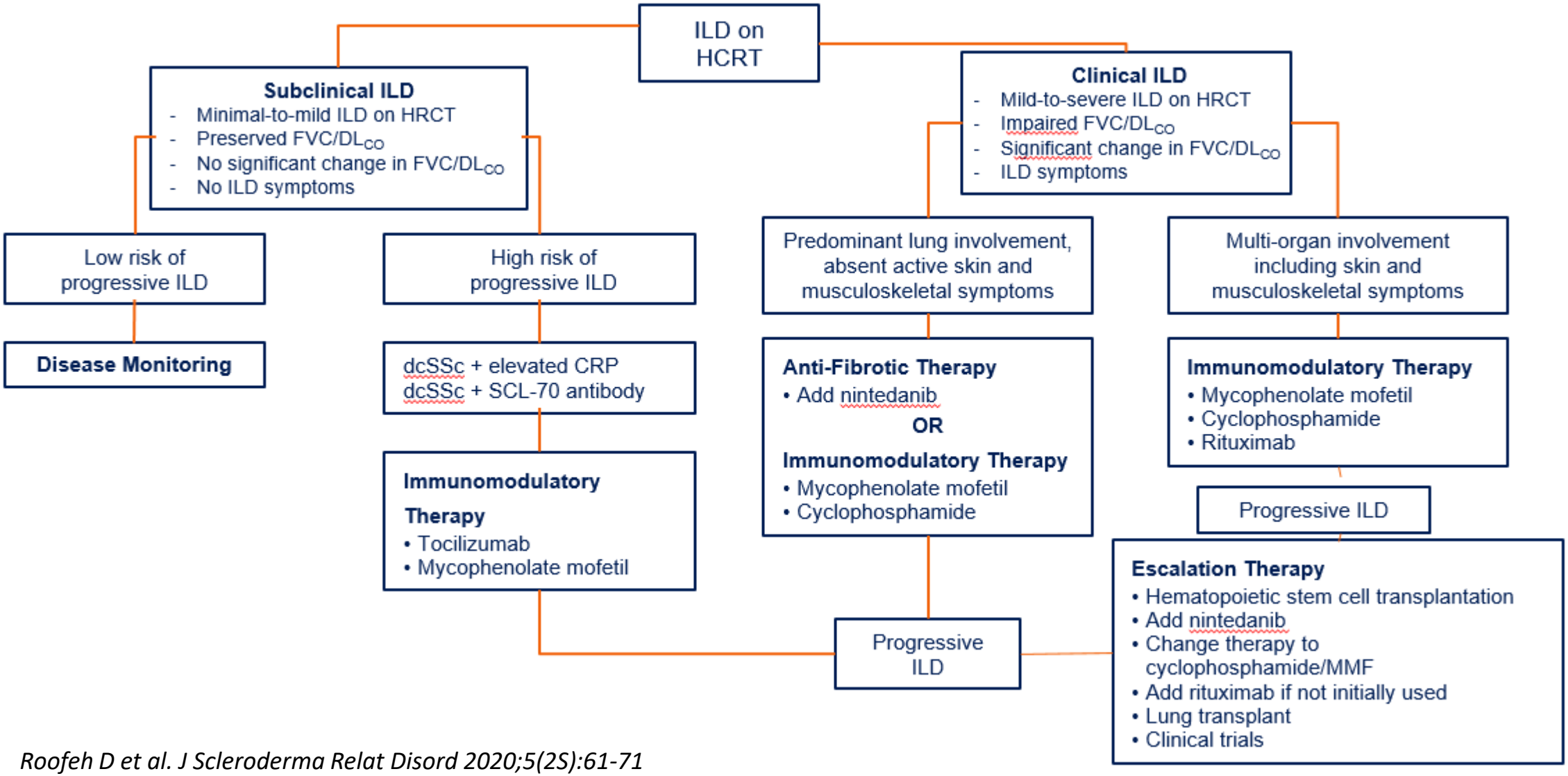
Treatment algorithm of SSc-ILD

Evidence-based expert opinion



Roofeh D et al. J Scleroderma Relat Disord 2020;5(2S):61-71

SSc traiter autrement en 2021

- ✓**Identification précoce des malades**
- ✓**Progrès dans les facteurs pronostiques**
- ✓**Concept de prévention de progression**
- ✓**Combinaisons de traitements a développer**
- ✓**Perspective de *disease modifying drug***