



THE CATHOLIC UNIVERSITY OF KOREA
CATHOLIC MEDICAL CENTER

Systemic sclerosis associated ILD

(SSc-ILD)

: Where do we stand?

서울성모병원 호흡기내과
이종민



- 72/F
- Underlying disease (-)
- Never smoker
- 한 달 전부터 시작된 호흡곤란
- 타병원에서 R/O Cryptogenic organizing pneumonia 진단 하에 Prednisolone 40mg 사용 중 내원

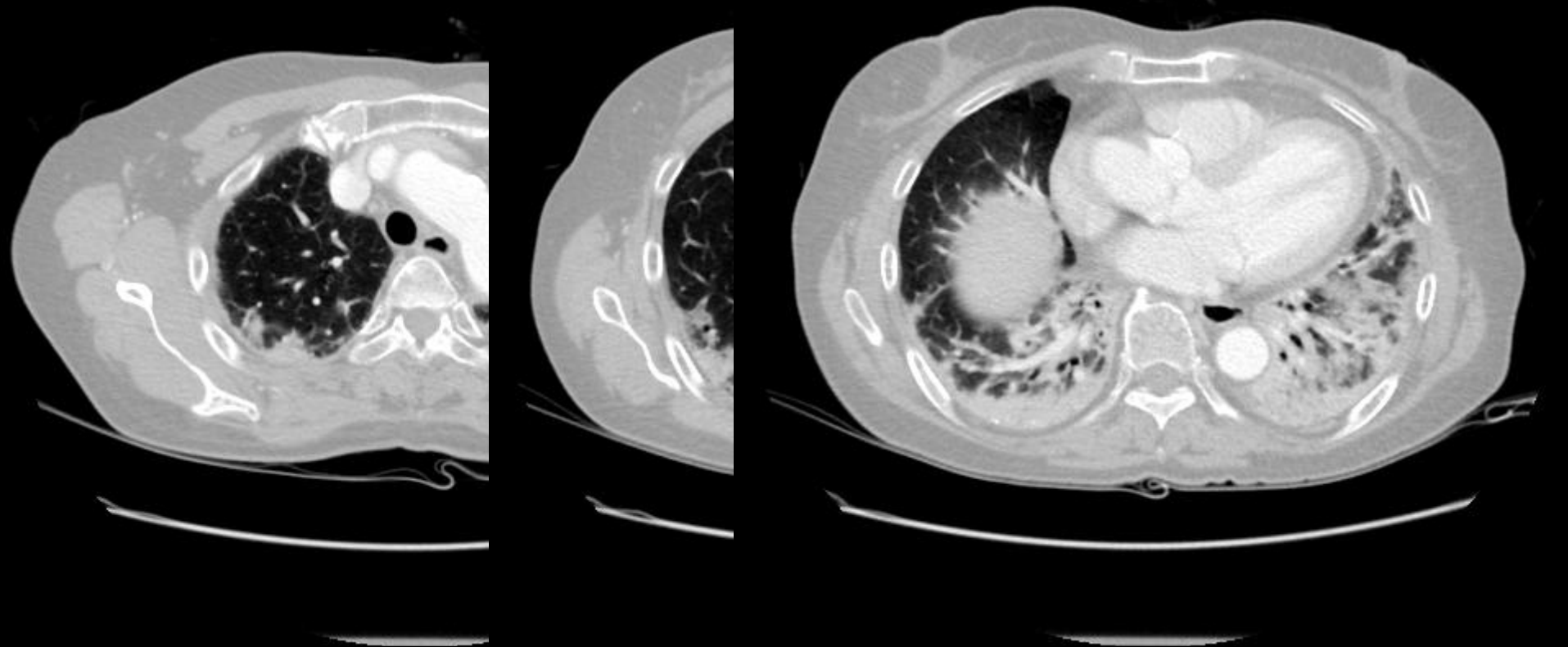


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• Chest CT



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• PFT

- **FVC 1.31 L (52%)**
- **FEV1 1.14 L (63%)**
- **FEV1/FVC 87%**
- **TLC 2.35 L (60%)**
- **DLCO 9.2 mL/mmHg/min (66%)**



진단명 : RA, SLE, SSc, SS, MCTD, UCTD, 기타()
Raynaud's phenomenon()

Findings : Giant capillary (no / a few / many)
Avascular area(no / some /extensive)
Preservation of capillary distribution (well preserved / mod / severe loss)
Hemorrhage (no / a few / frequent)

Conclusion: Short, branched capillaries, loss of capillaries



L3



R3





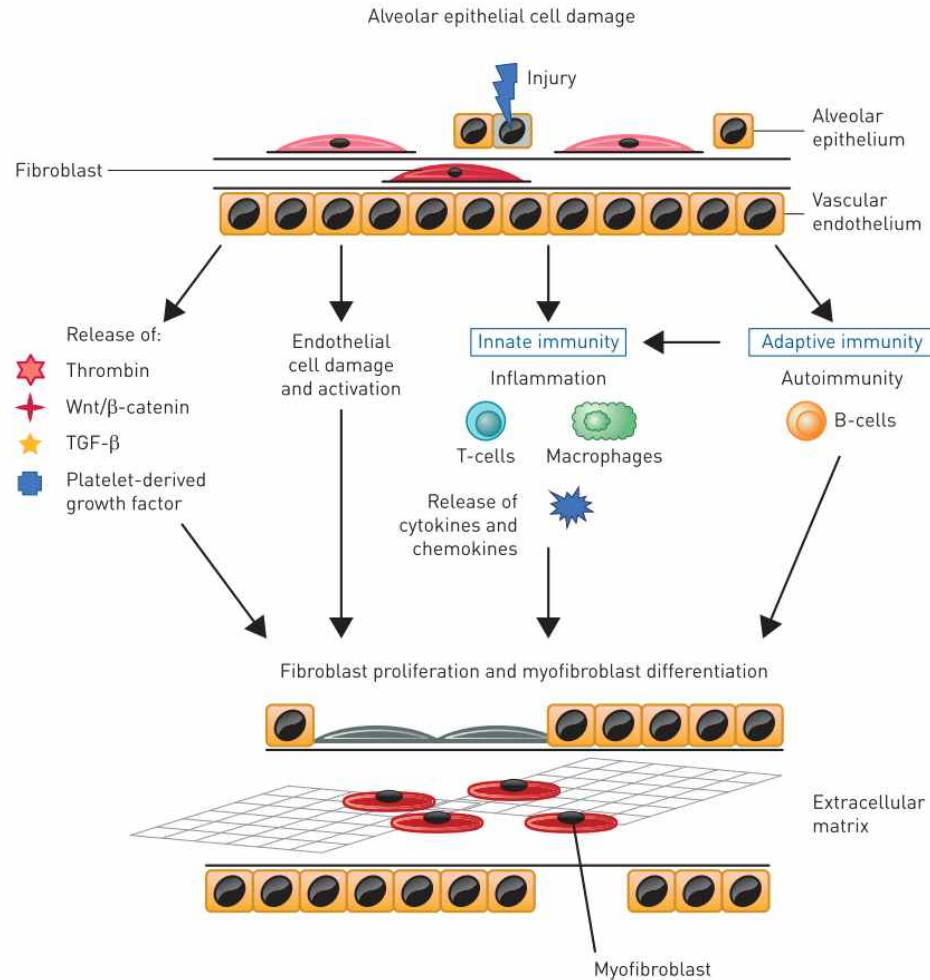
- **Lab**

- Rheumatoid factor (-)
- Anti-CCP (-)
- **ANA 1:160 (Centromere type)**
- **Anti Centromere Ab (+, > 8.0)**

Criteria for the classification of SSc	Score
Skin thickening of the fingers of both hands extending proximally to the MCP joints	9
Telangiectasia	2
Abnormal nailfold capillaries	2
Pulmonary arterial hypertension or interstitial lung disease, or both	2
Raynaud's phenomenon	3
Skin thickening of the fingers (only count highest score)	
Puffy fingers	2
Sclerodactyly of the fingers	4
Fingertip lesions (only count highest score)	
Digital tip ulcers	2
Fingertip pitting scars	3
Scleroderma-related autoantibodies (anticentromere, anti-topoisomerase 1, or anti-RNA polymerase 3)	3



• Pathophysiology of SSc related ILD





Tissue injury

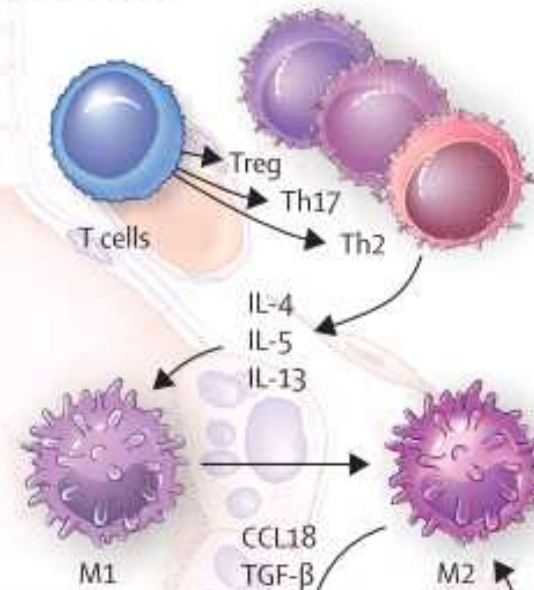
- Genetic predisposition
- Gastro-oesophageal reflux
- Oxidative stress
- Environmental stimuli
 - Organic solvents
 - Silica
 - Viruses

Endothelin 1
chemokines
tissue factor

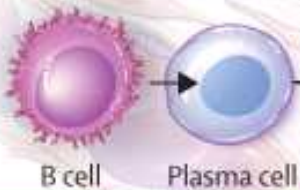
Vascular injury

- Endothelial cell injury
- Tissue hypoxia
- Ineffective angiogenesis

Inflammation



Autoimmunity



Auto-ABs

IL-6

Fibrosis

Fibrocytes recruited and resident fibroblasts activated → Myofibroblasts express α SMA and produce collagen

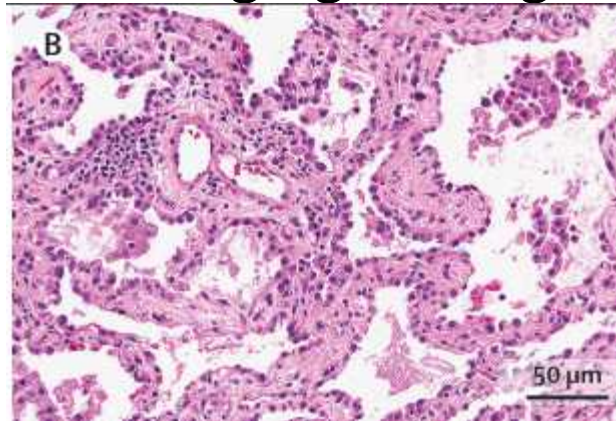


- **CT pattern of SSc-ILD**
 - **NSIP pattern: most common (> 80%)**
 - Peripheral GGO with apical – basal gradient
 - Subpleural sparing
 - **Definite UIP pattern < 10%**
 - **Esophageal dilatation**
 - **Pulmonary hypertension related changes**
 - Pulmonary artery enlargement
 - Right ventricular dilation

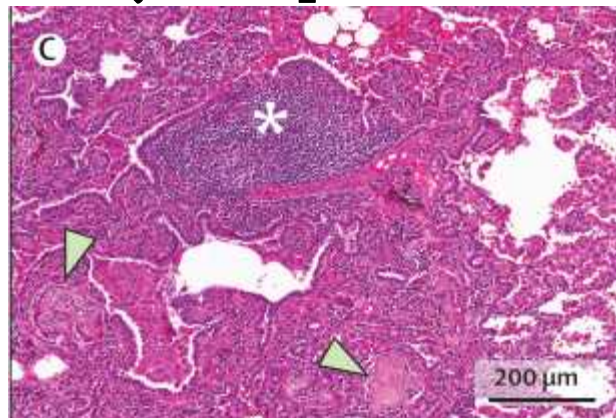


• Histopathology of SSc-ILD

- Usually reflects the imaging findings (NSIP pattern)



- Bronchitis secondary to aspiration





- **Treatment indication of SSc-ILD**
 - **Extensive disease**
 - Disease extent > 20% on HRCT
 - FVC < 70% predicted
 - **Limited disease with progression risk factor (+)**
 - Disease extent < 20% and FVC > 70% predicted
 - Factors related with progression
 - Early disease (< 12 – 24 months)
 - Anti-topoisomerase I Ab (+) / High IL-6 level
 - **Ongoing disease progression**



• Treatment options for SSc-ILD

- Immunosuppressive therapies
 - Mycophenolate mofetil, cyclophosphamide, azathioprine, steroids
- Biological therapies
 - Rituximab, (tocilizumab, bortezomib, brentuximab, tofacitinib ...)
- Antifibrotic therapies
 - Nintedanib, pirfenidone
- Autologous stem cell transplantation, Lung transplantation



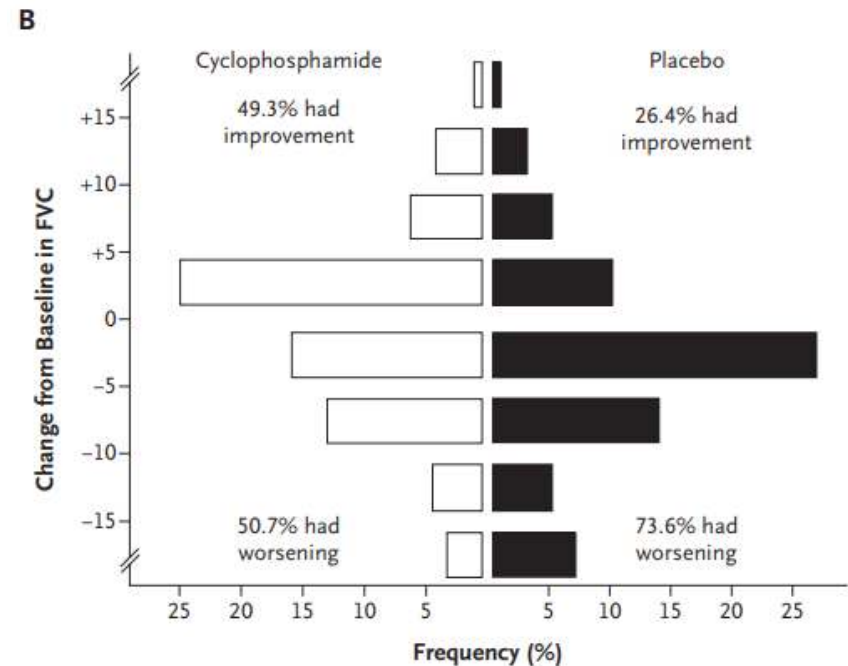
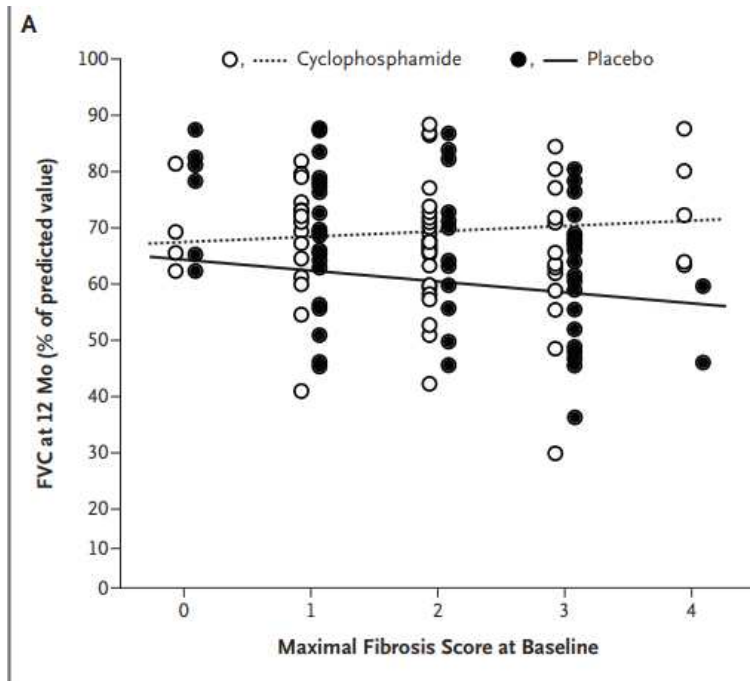
- **Initiating therapy**
 - Cyclophosphamide (CYC)
 - Mycophenolate mofetil (MMF)
 - Corticosteroids / Azathioprine
 - Nintedanib

- **Maintenance therapy**
 - CYC / MMF
 - Nintedanib

- **Refractory disease**
 - Rituximab / ASCT / Lung transplantation



- Scleroderma Lung Study (SLS I)
 - Cyclophosphamide (CYC) vs. Placebo



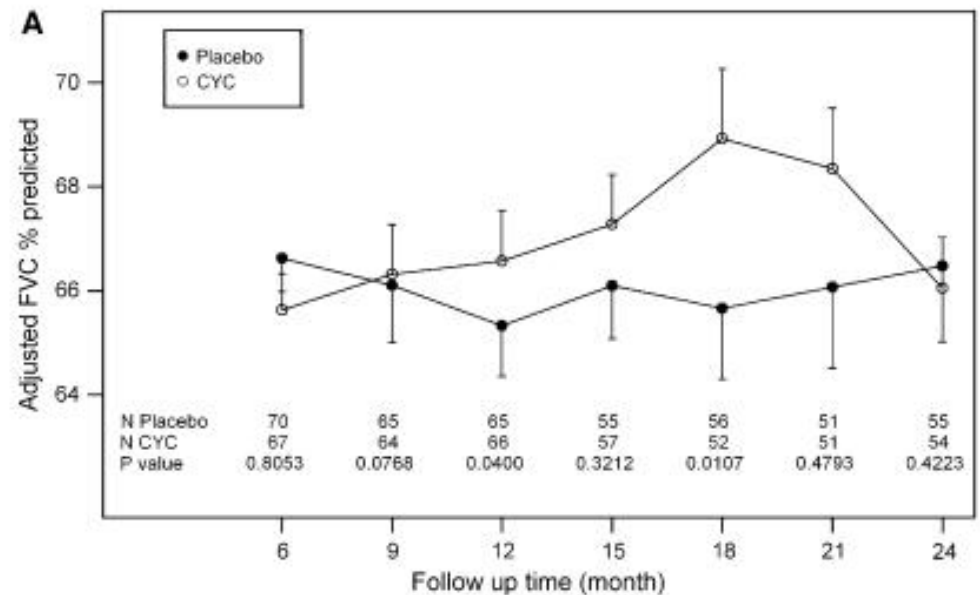


• Scleroderma Lung Study (SLS I)

• CYC vs. Placebo

Table 3. Adverse Events and Serious Adverse Events.*

Event	Cyclophosphamide Group		Placebo Group	
	Year 1	Year 2	Year 1	Year 2
	<i>number of patients</i>			
Adverse event				
Hematuria	9	1	3	2
Leukopenia†	19	0	0	0
Neutropenia†	7	0	0	0
Anemia	2	2	0	1
Pneumonia	5	1	1	0
Serious adverse event‡				
Probably related to treatment	2	4	0	0
Possibly related to treatment	3	4	2	5
Not related to treatment	15	19	14	17
Total	20	27	16	22
Death	2	4	3	3

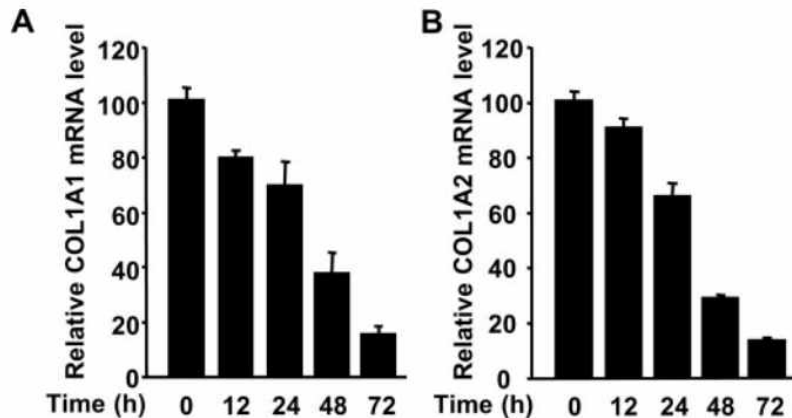




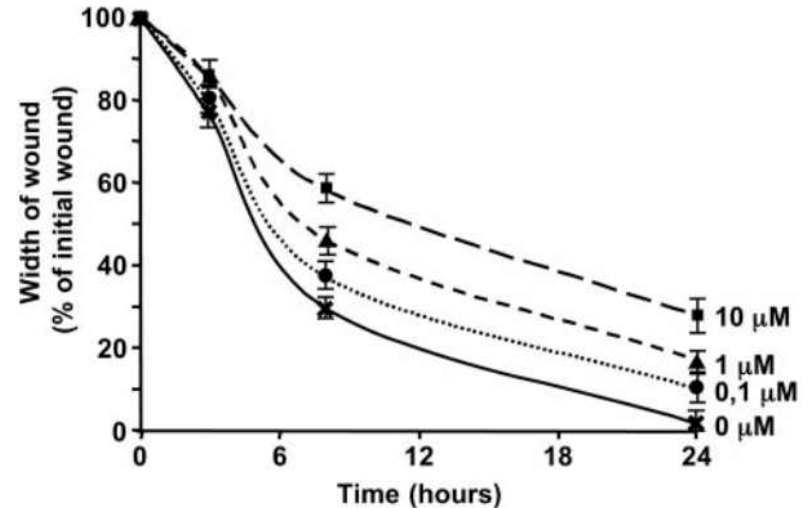
• Scleroderma Lung Study (SLS II)

• MMF

- Prevents T and B cell proliferation
- Antifibrotic actions



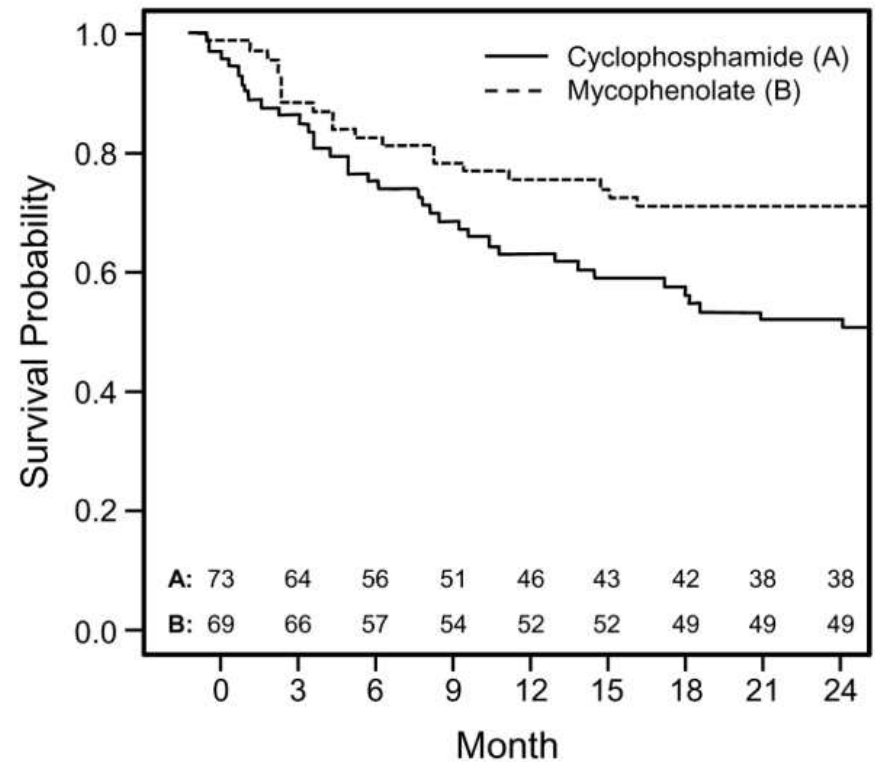
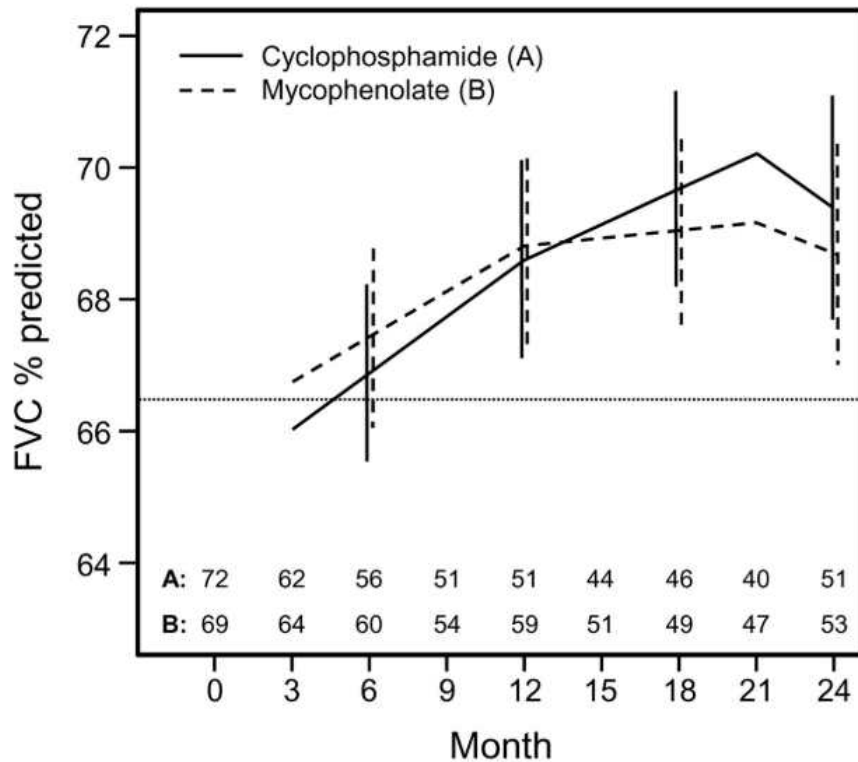
B





• Scleroderma Lung Study (SLS II)

- MMF (1.5g BID for 2 years) vs. CYC (2mg/kg/day for 1 year)





• Glucocorticoids & Azathioprine

• Glucocorticoids

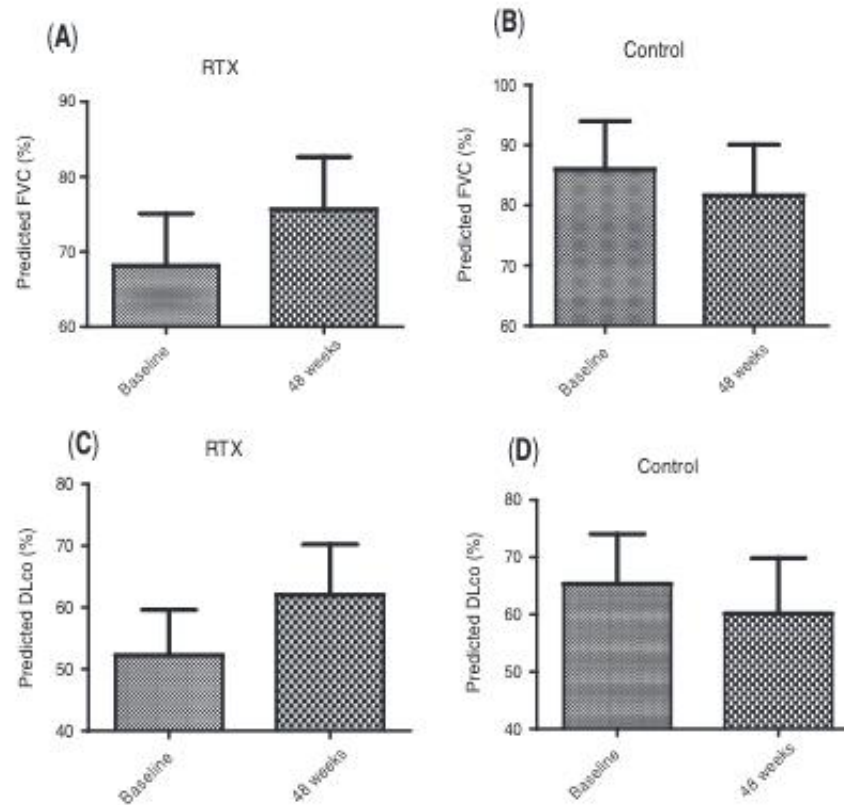
- Unclear role in SSc-ILD
- Risk of scleroderma renal crisis ($> 15\text{mg/day}$)

• Azathioprine

- Alternative initial therapy (Intolerable for CYC / MMF)
- Low dose steroids + Azathioprine



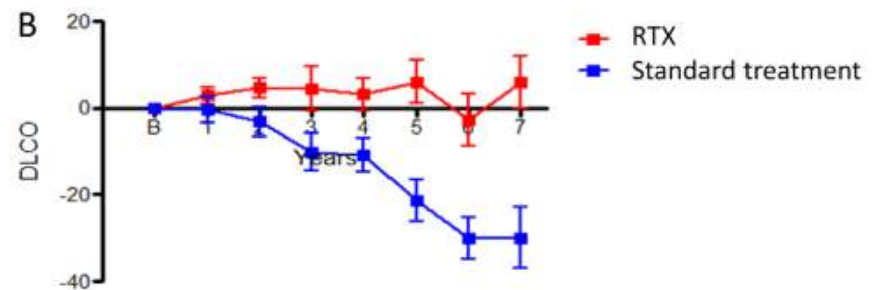
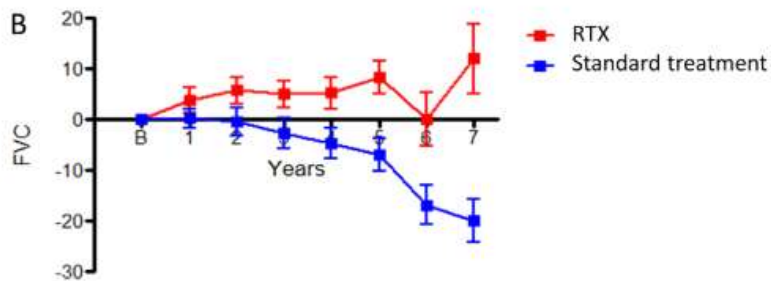
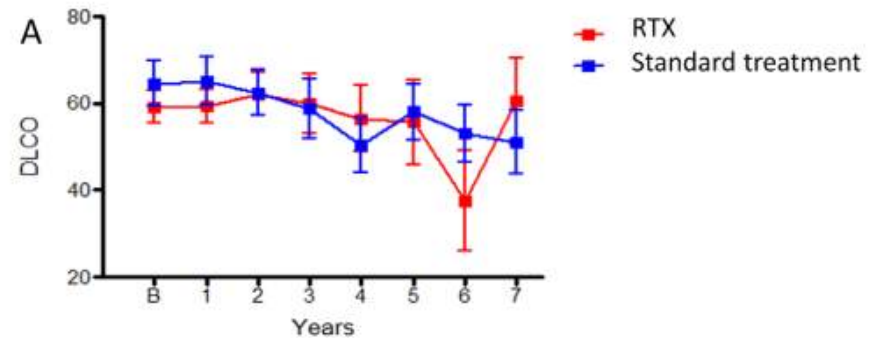
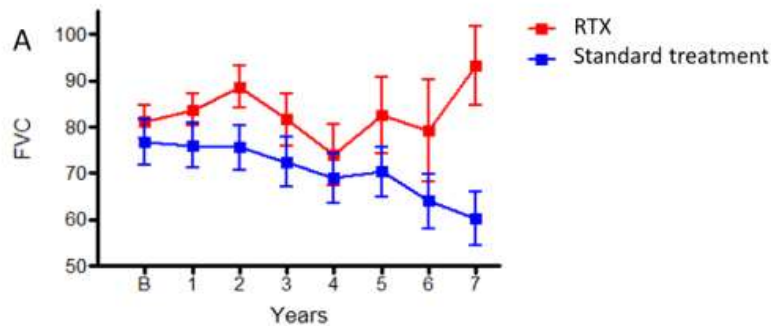
- **Biologic therapy**
 - Rituximab: anti-CD20 monoclonal antibody



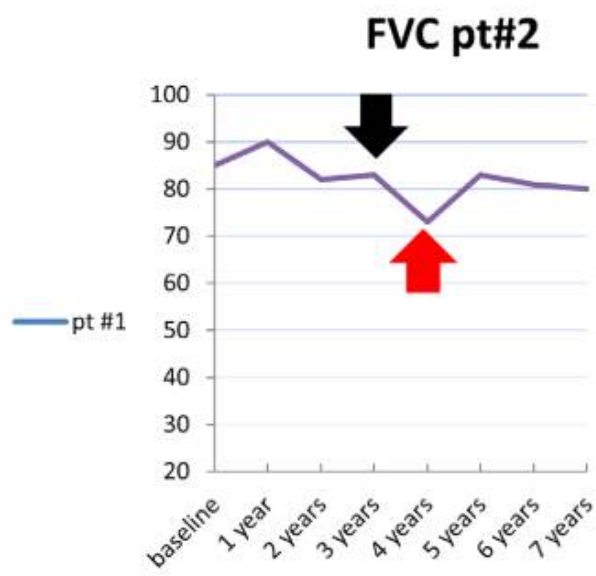


- Biologic therapy
 - Rituximab: anti-CD20 monoclonal antibody

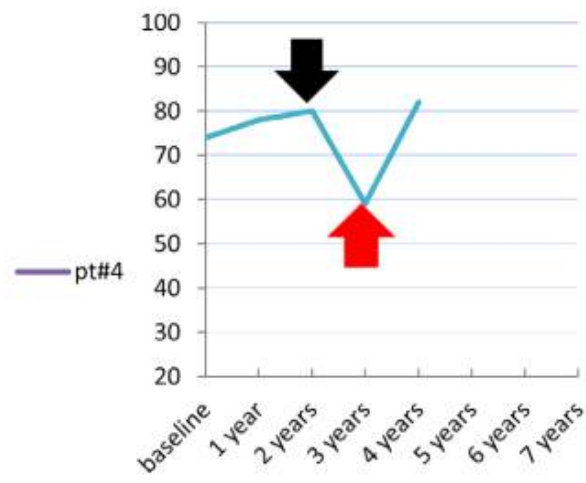
N = 51



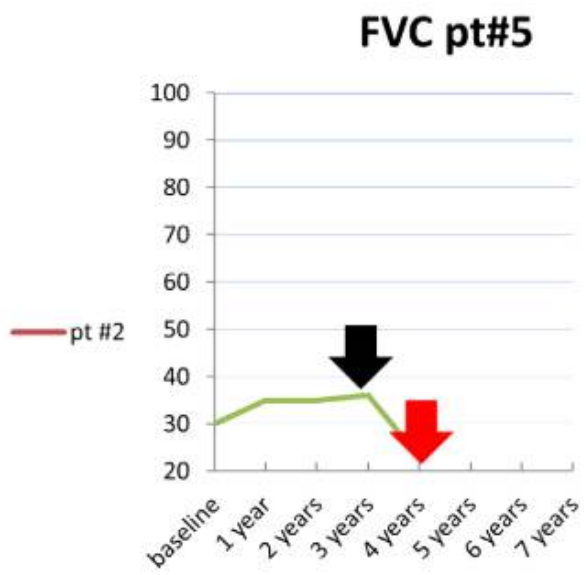
#1



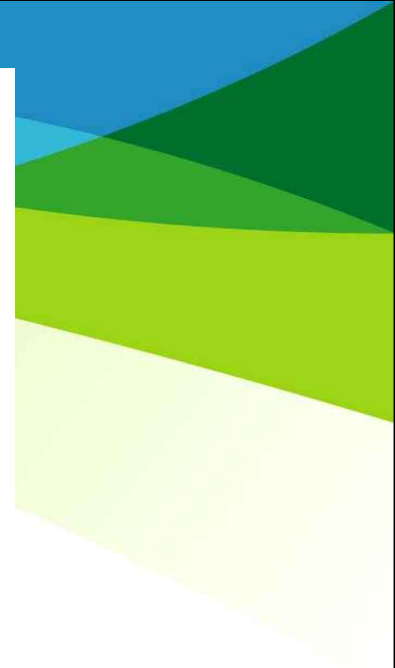
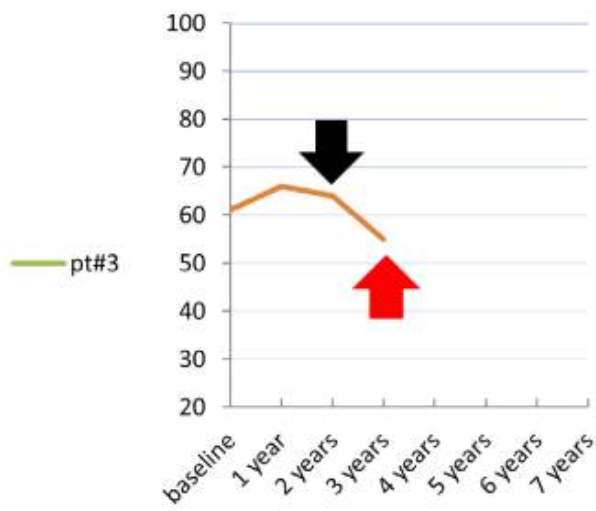
FVC pt#3



#4



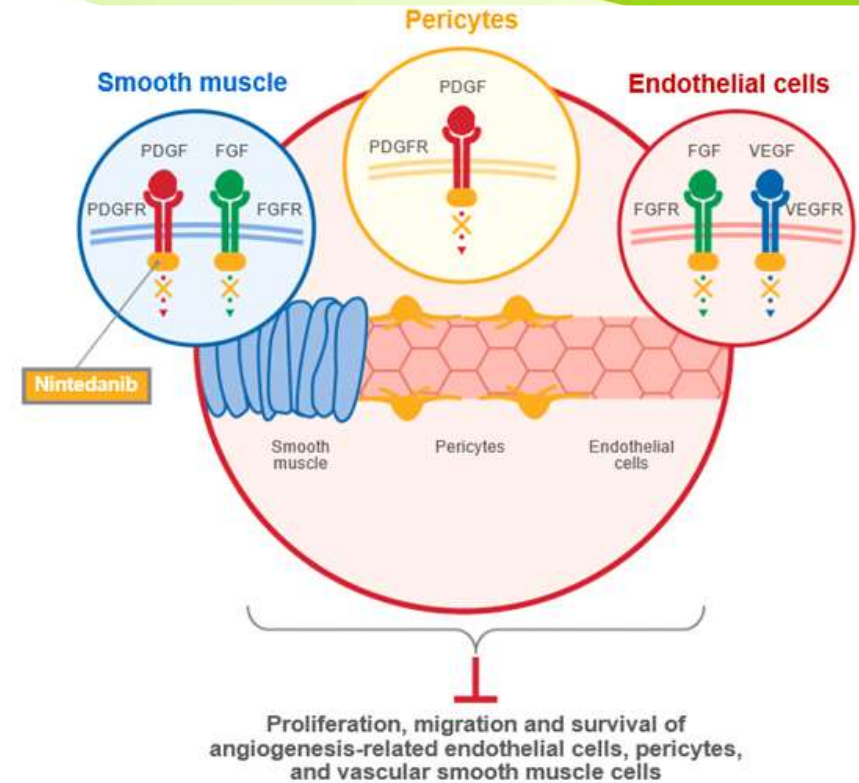
FVC pt#6





• Nintedanib

- Triple angiokinase inhibitor
- TGF- β inhibitor
- Approved for IPF
 - INPULSIS trial (2014)





- **SENSCIS trial**

- **SSc-ILD patients with fibrosis in HRCT > 10%**
- **Nintedanib 150mg BID vs. Placebo**
- **48% of patients at each group received MMF
(Nintedanib 48.3% vs. Placebo 48.6%)**

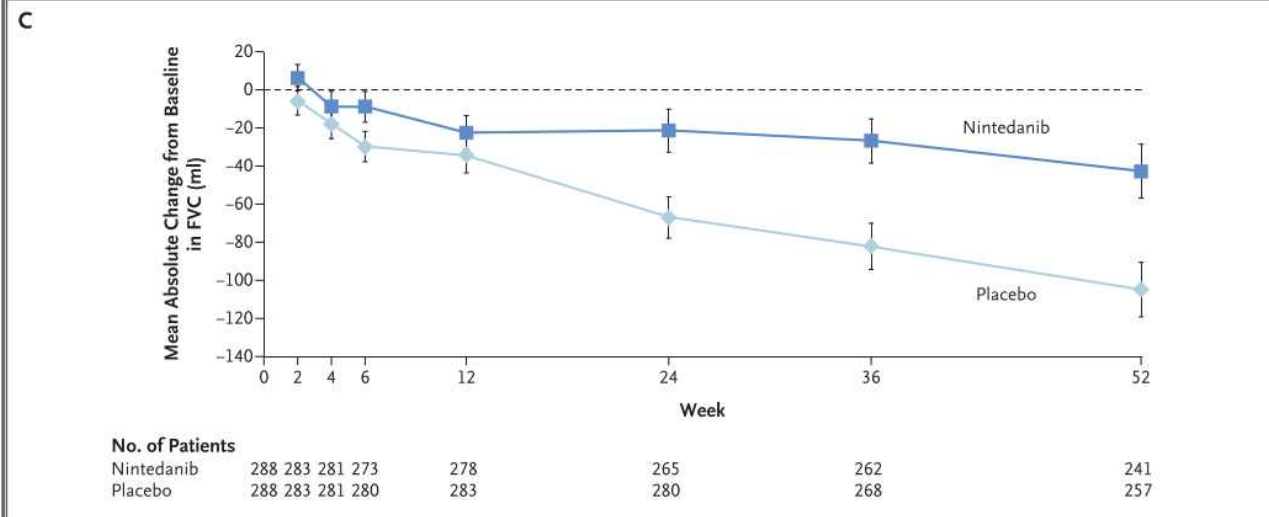
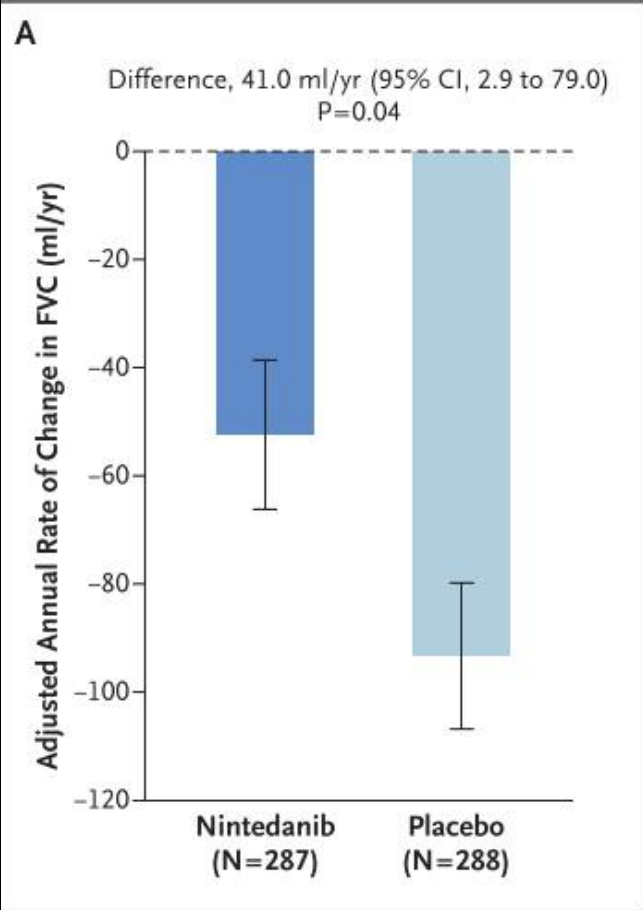




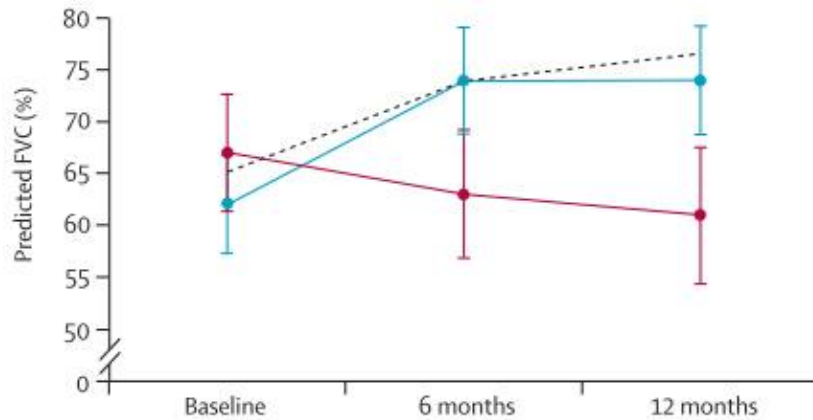
Table 3. Adverse Events.*

Event	Nintedanib (N = 288)	Placebo (N = 288)
	<i>no. of patients (%)</i>	
Any adverse event	283 (98.3)	276 (95.8)
Most common adverse events†		
Diarrhea	218 (75.7)	91 (31.6)
Nausea	91 (31.6)	39 (13.5)
Skin ulcer	53 (18.4)	50 (17.4)
Vomiting	71 (24.7)	30 (10.4)
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 decrease	34 (11.8)	12 (4.2)
Severe adverse event‡	52 (18.1)	36 (12.5)
Serious adverse event§	69 (24.0)	62 (21.5)
Fatal adverse event	5 (1.7)	4 (1.4)
Adverse event leading to discontinuation of the intervention	46 (16.0)	25 (8.7)



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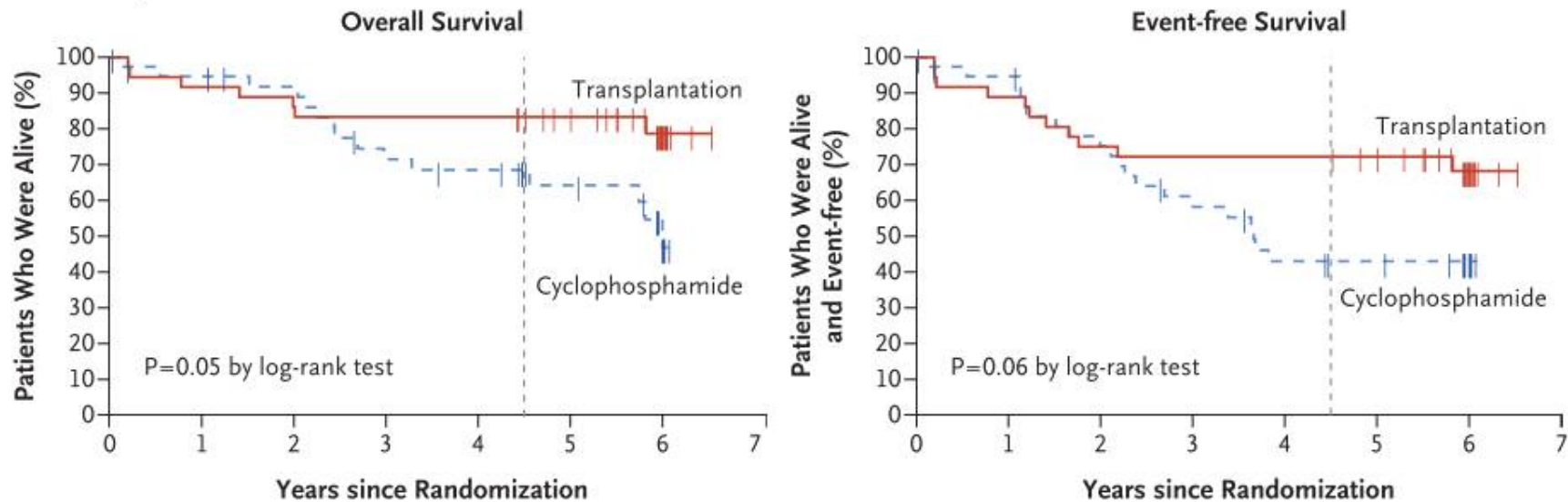
- **Autologous stem cell transplantation**
 - 3 RCTs (2011-ASSIST, 2014-ASTIS, 2018-SCOT)





- Autologous stem cell transplantation
 - 3 RCTs (2011-ASSIST, 2014-ASTIS, 2018-SCOT)

C Intention-to-Treat Population

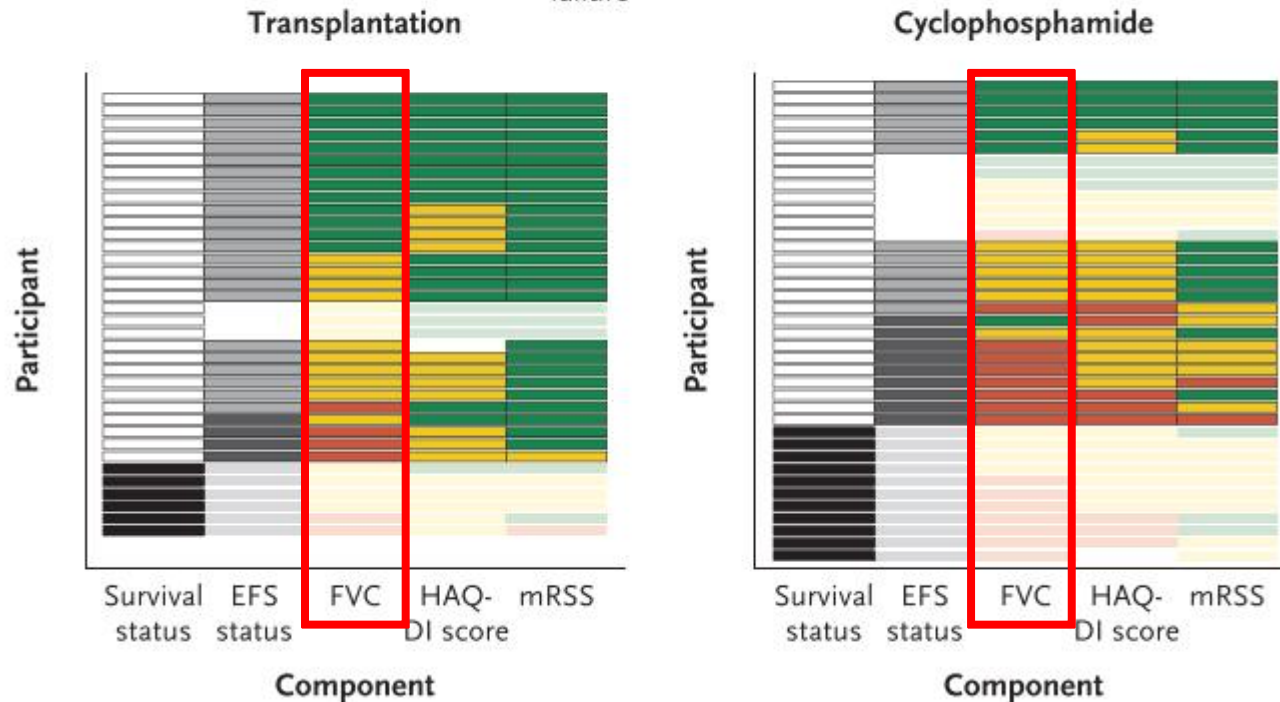
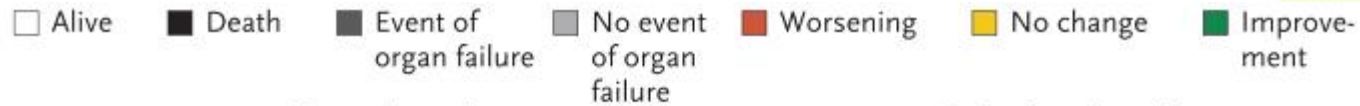


No. at Risk

	0	1	2	3	4	5	6	7
Transplantation	36	33	31	30	30	25	9	
Cyclophosphamide	39	35	32	24	22	15	7	



- Autologous stem cell transplantation
 - 3 RCTs (2011-ASSIST, 2014-ASTIS, 2018-SCOT)





- **Lung transplantation**
 - **Uncommon**
 - **Contraindication**
 - Uncontrolled active inflammatory myopathy
 - Worsening / active digital ulcer
 - Esophageal stricture / High grade of Barrett's esophagus
 - Poor renal function ...



• Summary

• Tx indication

- Extensive disease
- Limited disease with risk factors for progression
- Progressive disease

• Initial & Maintenance therapy

- MMF
- CYC (Oral or IV)
- Nintedanib (+MMF)
- Low dose steroid + Azathioprine / CYC → MMF (In Korea)

• Progressive disease

- Rituximab
- Autologous SCT / Lung transplantation

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