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

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

Lancet Respir Med 2021;9:96-106

志水　隼人

膠原病Journal Club　2021年3月24日

はじめに

- 強皮症の臓器病変のうち、間質性肺炎は頻度が高く、強皮症患者の死亡原因の多くを占めている。

- 強皮症の治療は一般的に難しいが、近年様々な薬剤が治療に用いられてきている。

The NEW ENGLAND JOURNAL of MEDICINE

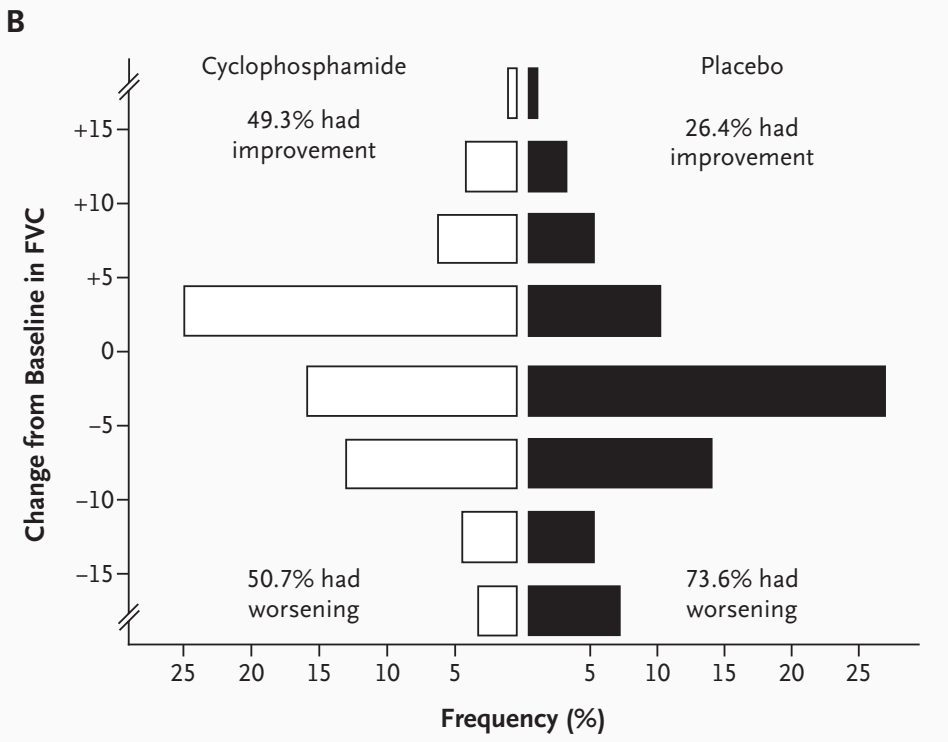
ORIGINAL ARTICLE

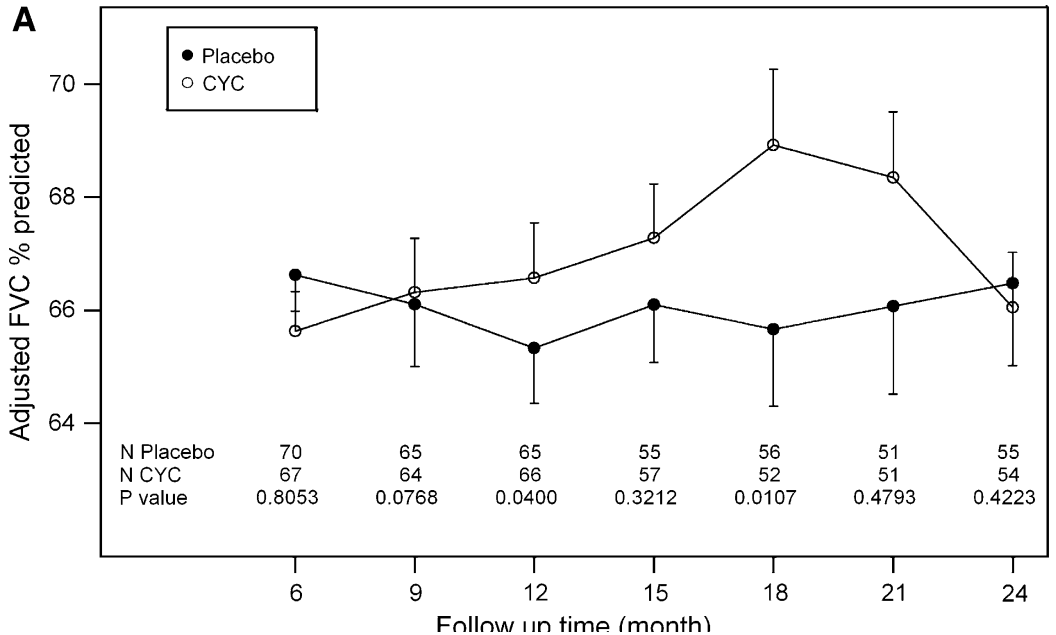
Cyclophosphamide versus Placebo in Scleroderma Lung Disease

Scleroderma Lung Study（SLS） I

N Engl J Med 2006;354:2655-66

P：レイノー現象以外の症状が出現して7年以内のlc-/dc-SSc-ILD
I ：POCY≦2 mg/kg/dayを12か月
C：PBO
O：12か月時点の予測FVC





POCY群で
12か月時点の%FVCは有意に改善

(PBOとの差は2.53% (95%CI 0.28-4.79)

N Engl J Med 2006;354:2655

しかしPOCY終了24か月時点で、
PBOと有意差はなくなった

Am J Respir Crit Care Med 2007;176:1026-1034

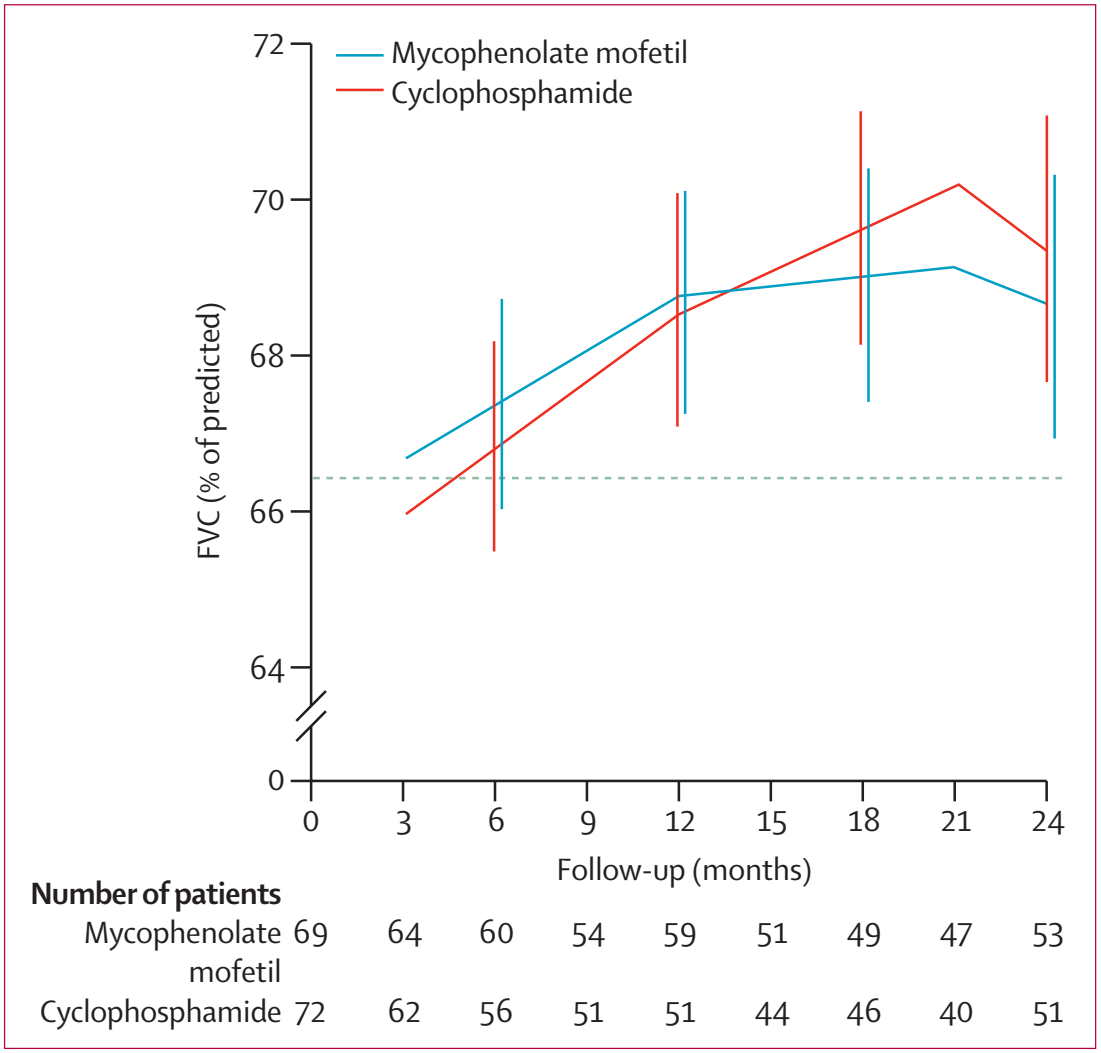
Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial

*Donald P Tashkin, Michael D Roth, Philip J Clements, Daniel E Furst, Dinesh Khanna, Eric C Kleerup, Jonathan Goldin, Edgar Arriola, Elizabeth R Volkmann, Suzanne Kafaja, Richard Silver, Virginia Steen, Charlie Strange, Robert Wise, Fredrick Wigley, Maureen Mayes, David J Riley, Sabiha Hussain, Shervin Assassi, Vivien M Hsu, Bela Patel, Kristine Phillips, Fernando Martinez, Jeffrey Golden, M Kari Connolly, John Varga, Jane Dematte, Monique E Hinchcliff, Aryeh Fischer, Jeffrey Swigris, Richard Meehan, Arthur Theodore, Robert Simms, Suncica Volkov, Dean E Schraufnagel, Mary Beth Scholand, Tracy Frech, Jerry A Molitor, Kristin Highland, Charles A Read, Marvin J Fritzler, Grace Hyun J Kim, Chi-Hong Tseng, Robert M Elashoff, for the Sclerodema Lung Study II Investigators**

Scleroderma Lung Study（SLS）II

Lancet Respir Med 2016;4:708-19

P：レイノー現象以外の症状が出現して7年以内のlc-/dc-SSc-ILD
I：MMF 1500 mg 1日2回を24か月
C：POCY 2 mg/kgを12か月→PBOを12か月
O：24か月までの予測FVCの変化



24か月時点の%FVCは有意差なし

The NEW ENGLAND JOURNAL of MEDICINE

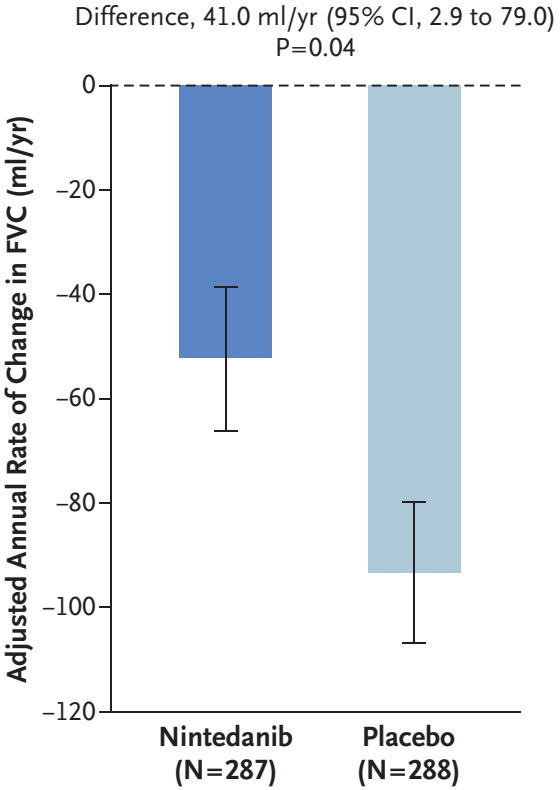
ORIGINAL ARTICLE

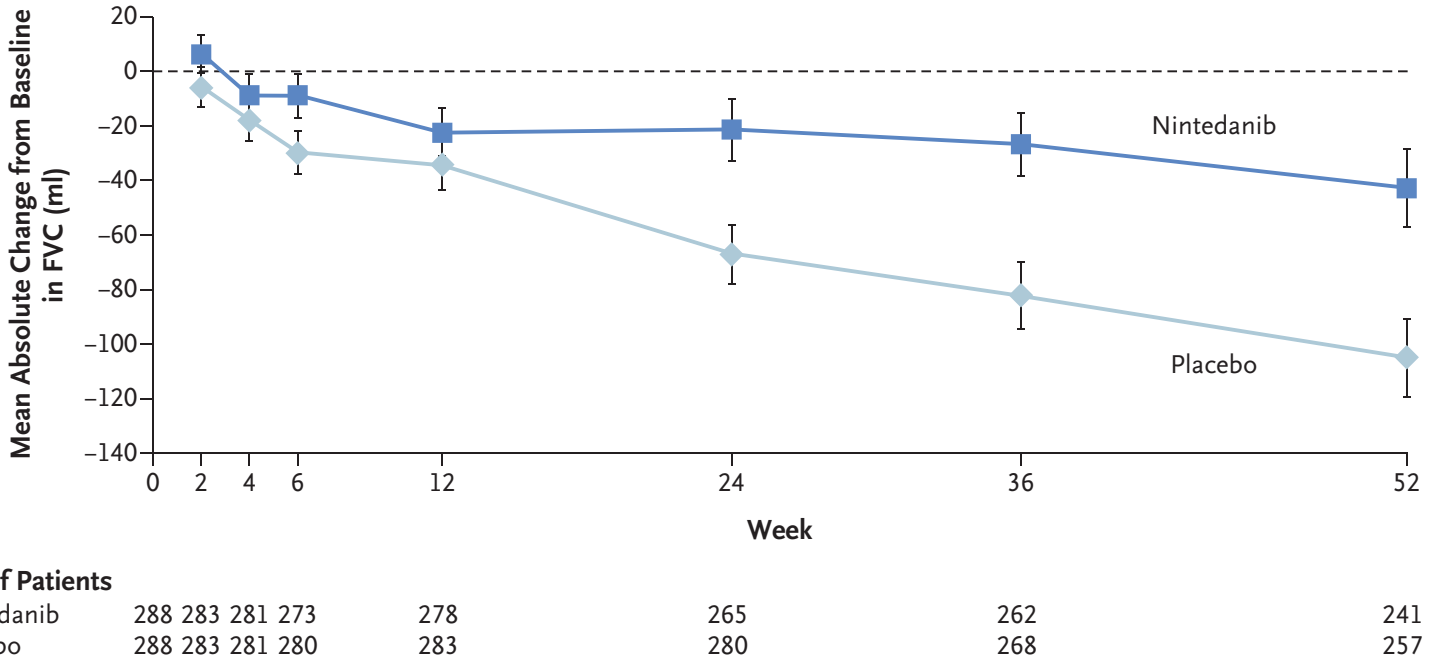
Nintedanib for Systemic Sclerosis–Associated Interstitial Lung Disease

SENSCIS試験

N Engl J Med 2019;380:2518-28

P：レイノー現象以外の症状が出現して7年以内のlc-/dc-SSc-ILD
I：ニンテダニブ 150mg 1日2回
C：PBO
O：52週までのFVC年間減少率





No. of Patients

Nintedanib	288	283	281	273	278	265	262	241
Placebo	288	283	281	280	283	280	268	257

52週までのFVC年間減少率は ニンテダニブ群で有意に低かった

（MMF併用群でもPBOよりも減少率が低い傾向にあるが、有意差検定なし）

ニンテダニブ (オフェブ®)

- 血小板由来増殖因子受容体 (PDGFR) αおよびβ、線維芽細胞増殖因子受容体 (FGFR) 1, 2, 3、血管内皮増殖因子受容体 (VEGFR) 1, 2, 3を標的とする、低分子チロシンキナーゼ阻害剤。

- 保険適用量　150mg 1日2回　(状態に応じ100mg 1日2回に減量)

- 薬価　6676.4円/150mg、4450.8円/100mg
  (ちなみにオルミエント 4mg錠は5274.9円)

目的

SENSCIS試験に組み入れられた患者のうち、MMF併用者におけるニンテダニブの有効性と安全性を検討する

試験デザインと方法

- 国際的プラセボ対照二重盲検ランダム化比較試験 (32か国)
- ニンテダニブ 150 mg 1日2回とプラセボを1:1で割り付け
- ベーリンガーからの資金提供あり
  (研究デザイン、データ収集・解析・評価などにも参加)

患者

適格基準：

- ACR/EULAR分類基準に基づいて診断され、
  レイノー現象以外の症状が出現してから7年以内の
  18歳以上の強皮症患者。
- スクリーニングの12か月以内にHRCTで診断され、
  肺野の10%以上を占めるILDを有する。
- PFTで予測FVC≧40%かつ予測DLCO 30-89%
- MMFやMTX使用中の場合、ランダム化前の6か月間は
  安定した用量で継続している。

患者

除外基準：

- ランダム化前の2週間以内にPSL＞10mg/日の使用あり。
- ランダム化前の6か月以内にAZA, HCQ, コルヒチン, ペニシラミン, SASPの使用あり。
- ランダム化前の6か月以内にCY, RTX, TCZ, ABT, LEF, Tac, CyA, JAKi, アミノ安息香酸カリウムの使用あり。
- PAHがある。

アウトカム

- **プライマリーエンドポイント**
  52週までのFVC年間減少率

- **キーとなるセカンダリーエンドポイント**
  52週時点でのmRSSのベースラインからの絶対値の変化
  52週時点でのSGRQ total score (50項目の自己記入の質問紙法)

結果

	Patients taking mycophenolate at baseline	
	Nintedanib (n=139)	Placebo (n=140)
Sex		
Female	102 (73%)	101 (72%)
Male	37 (27%)	39 (28%)
Age, years	52·6 (12·0)	51·5 (11·9)
Body-mass index, kg/m²	26·9 (5·0)	26·2 (5·5)
Race*		
White	112 (81%)	108 (77%)
Asian	9 (6%)	19 (14%)
Black or African-American	14 (10%)	9 (6%)
American Indian, Alaska Native, Native Hawaiian, or other Pacific Islander	3 (2%)	2 (1%)
Region		
Europe	64 (46%)	58 (41%)
USA and Canada	57 (41%)	57 (41%)
Asia	7 (5%)	12 (9%)
Rest of world	11 (8%)	13 (9%)
Diffuse cutaneous SSc	79 (57%)	74 (53%)
Years since onset of first non-Raynaud's symptom	3·4 (0·9–6·9)	3·5 (1·0–7·0)
Extent of fibrotic ILD on high-resolution CT, %	37·9 (22·4)	35·8 (20·9)
FVC		
mL	2496 (724)	2581 (813)
% predicted	70·4 (15·6)	71·1 (16·5)
Diffusing capacity of the lung for carbon monoxide, % predicted†	50·8 (13·7)	52·6 (14·6)
Anti-topoisomerase I antibody positive	88 (63%)	84 (60%)
mRSS	12·5 (9·4)	11·3 (8·3)
SGRQ total score	43·9 (20·3)	41·1 (19·8)
C-reactive protein, mg/L‡	4·9 (5·9)	8·5 (25·3)
Platelets, 10^{-9} per L§	277 (79)	283 (77)

ベースラインの特徴

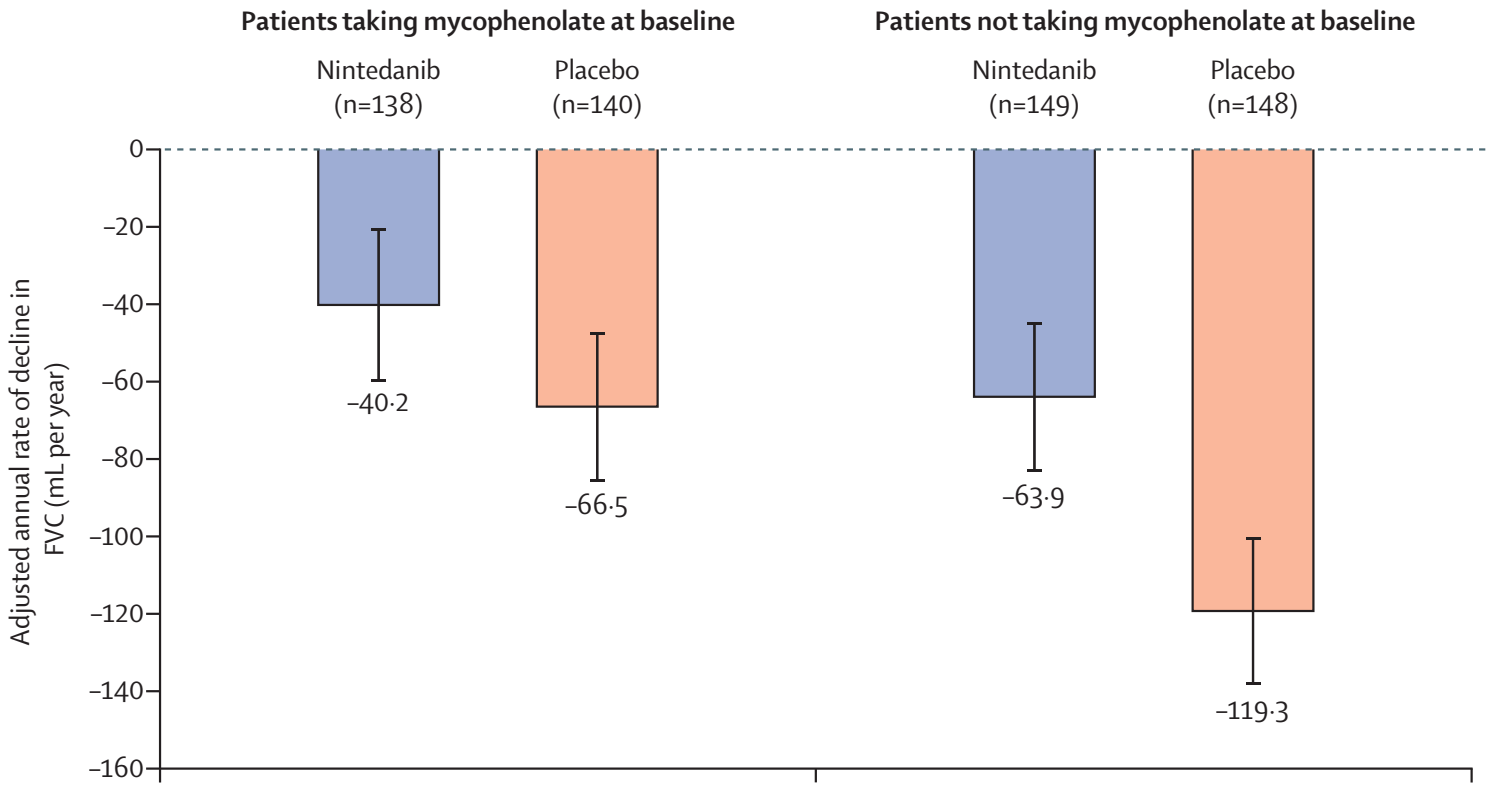
ニンテダニブ群　139名
PBO群　　140名

白人　　80%前後
アジア人　10%前後

MMF内服量
中央値 2,000 mg

52週までのFVC年間減少率

A



	Patients taking mycophenolate at baseline				Patients not taking mycophenolate at baseline				p value for interaction
	Nintedanib (n=139)	Placebo (n=140)	Difference	Odds ratio	Nintedanib (n=149)	Placebo (n=148)	Difference	Odds ratio	
Primary endpoint									
Adjusted annual rate of decline in FVC over 52 weeks, mL per year	−40·2 (19·8)	−66·5 (19·3)	26·3 (−27·9 to 80·6)	..	−63·9 (19·3)	−119·3 (19·0)	55·4 (2·3 to 108·5)	..	0·45*†

	Patients taking mycophenolate at baseline				Patients not taking mycophenolate at baseline				p value for interaction
	Nintedanib (n=139)	Placebo (n=140)	Difference	Odds ratio	Nintedanib (n=149)	Placebo (n=148)	Difference	Odds ratio	
Primary endpoint									
Adjusted annual rate of decline in FVC over 52 weeks, mL per year	−40·2 (19·8)	−66·5 (19·3)	26·3 (−27·9 to 80·6)	..	−63·9 (19·3)	−119·3 (19·0)	55·4 (2·3 to 108·5)	..	0·45*†
Key secondary endpoints									
Adjusted absolute change from baseline in mRSS at week 52	−2·4 (0·4)	−2·5 (0·4)	0·04 (−1·01 to 1·09)	..	−1·9 (0·4)	−1·5 (0·4)	−0·44 (−1·47 to 0·58)	..	0·52‡
Adjusted absolute change from baseline in SGRQ total score at week 52	0·7 (1·3)	−0·9 (1·2)	1·6 (−1·9 to 5·0)	..	0·9 (1·2)	−0·9 (1·2)	1·8 (−1·6 to 5·2)	..	0·92‡
Other secondary lung function endpoints									
Adjusted change from baseline in FVC at week 52, mL	−42·2 (20·0)	−78·6 (19·4)	36·43 (−18·3 to 91·2)	..	−66·4 (19·4)	−122·7 (19·1)	56·3 (2·8 to 109·7)	..	0·61‡
Annual rate of decline in FVC % predicted	−0·9 (0·6)	−1·7 (0·5)	0·8 (−0·7 to 2·3)	..	−1·9 (0·5)	−3·4 (0·5)	1·5 (0·1 to 3·0)	..	0·49†
Patients with an absolute decrease from baseline in FVC of >5% predicted at week 52	21/138 (15%)	36/140 (26%)	..	0·52 (0·29 to 0·95)	38/149 (26%)	46/148 (31%)	..	0·76 (0·46 to 1·26)	0·35§
Patients with an absolute decrease from baseline in FVC of >10% predicted at week 52	4/138 (3%)	7/140 (5%)	..	0·57 (0·16 to 1·98)	16/149 (11%)	17/148 (12%)	..	0·93 (0·45 to 1·91)	0·50§
Patients with a relative decrease from baseline in FVC (mL) of >5% at week 52	39/138 (28%)	57/140 (41%)	..	0·58 (0·35 to 0·95)	56/149 (38%)	68/148 (46%)	..	0·71 (0·45 to 1·13)	0·55§
Patients with a relative decrease from baseline in FVC (mL) of >10% at week 52	14/138 (10%)	21/140 (15%)	..	0·64 (0·31 to 1·32)	34/149 (23%)	31/148 (21%)	..	1·12 (0·64 to 1·94)	0·23§

	Patients taking mycophenolate at baseline		Patients not taking mycophenolate at baseline	
	Nintedanib (n=139)	Placebo (n=140)	Nintedanib (n=149)	Placebo (n=148)
Any adverse event*	136 (98%)	135 (96%)	147 (99%)	141 (95%)
Most frequent adverse events†				
Diarrhoea	106 (76%)	48 (34%)	112 (75%)	43 (29%)
Nausea	43 (31%)	23 (16%)	48 (32%)	16 (11%)
Skin ulcer	22 (16%)	23 (16%)	31 (21%)	27 (18%)
Vomiting	32 (23%)	17 (12%)	39 (26%)	13 (9%)
Cough	20 (14%)	33 (24%)	14 (9%)	19 (13%)
Nasopharyngitis	10 (7%)	22 (16%)	26 (17%)	27 (18%)
Upper respiratory tract infection	19 (14%)	25 (18%)	14 (9%)	10 (7%)
Abdominal pain	14 (10%)	6 (4%)	19 (13%)	15 (10%)
Fatigue	19 (14%)	14 (10%)	12 (8%)	6 (4%)
Headache	16 (12%)	15 (11%)	11 (7%)	9 (6%)
Urinary tract infection	16 (12%)	11 (8%)	8 (5%)	12 (8%)
Weight decreased	10 (7%)	4 (3%)	24 (16%)	8 (5%)
Decreased appetite	14 (10%)	10 (7%)	13 (9%)	2 (1%)
Severe adverse event	28 (20%)	18 (13%)	24 (16%)	18 (12%)
Serious adverse event	36 (26%)	22 (16%)	33 (22%)	40 (27%)
Fatal adverse event	3 (2%)	2 (1%)	2 (1%)	2 (1%)
Adverse event leading to treatment discontinuation	15 (11%)	9 (6%)	31 (21%)	16 (11%)

Data are n (%) of patients with at least one such adverse event. *Adverse events reported over 52 weeks (or until 28 days after last study drug intake for patients who discontinued study drug before week 52). †Adverse events that were reported in >10% of participants in any of these subgroups are shown.

Table 3: **Adverse events in subgroups by use of mycophenolate at baseline**

有害事象

下痢が最多(差はない)

上気道感染症、倦怠感、咳、頭痛：
MMF内服群＞非内服群
(ただしニンテダニブ群とPBO群では差はなし)

ディスカッション

- MMFは、ランダム化前の6か月間は内服継続されており、潜在的にMMF反応性がある患者が選ばれている可能性がある。

- 研究組み入れ前にどの程度の期間MMFを使用し、どの程度の用量だったか、FVCの継時的変化が不明である。

- 本研究は、サブグループ解析に対しては、検出力不足である。

Added value of this study

To our knowledge, in this subgroup analysis of the SENSCIS trial, we analysed the largest cohort of patients with SSc-ILD taking mycophenolate at baseline in a clinical trial to date. We did not detect heterogeneity in the effect of nintedanib versus placebo on the annual rate of decline in FVC between subgroups defined by mycophenolate use at baseline, which suggests that nintedanib provided benefits on decreases in FVC both in patients who were taking mycophenolate at baseline and in those who were not. In both of these subgroups, a smaller proportion of patients treated with nintedanib versus placebo had a decrease in FVC of at least 3·3% predicted, which has been estimated to be the minimum clinically important difference for worsening of FVC in patients with SSc-ILD. We found that the adverse event profile of nintedanib was similar between subgroups by mycophenolate use at baseline and was manageable for most patients. Treatment discontinuations due to adverse events over 52 weeks were not more common in patients treated with nintedanib and who were on mycophenolate at baseline than in patients treated with nintedanib alone.