Nintedanib : données d'efficacité et de tolérance 4 ans après la mise à disposition dans la sclérodermie systémique.

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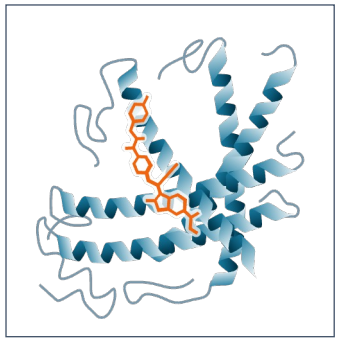
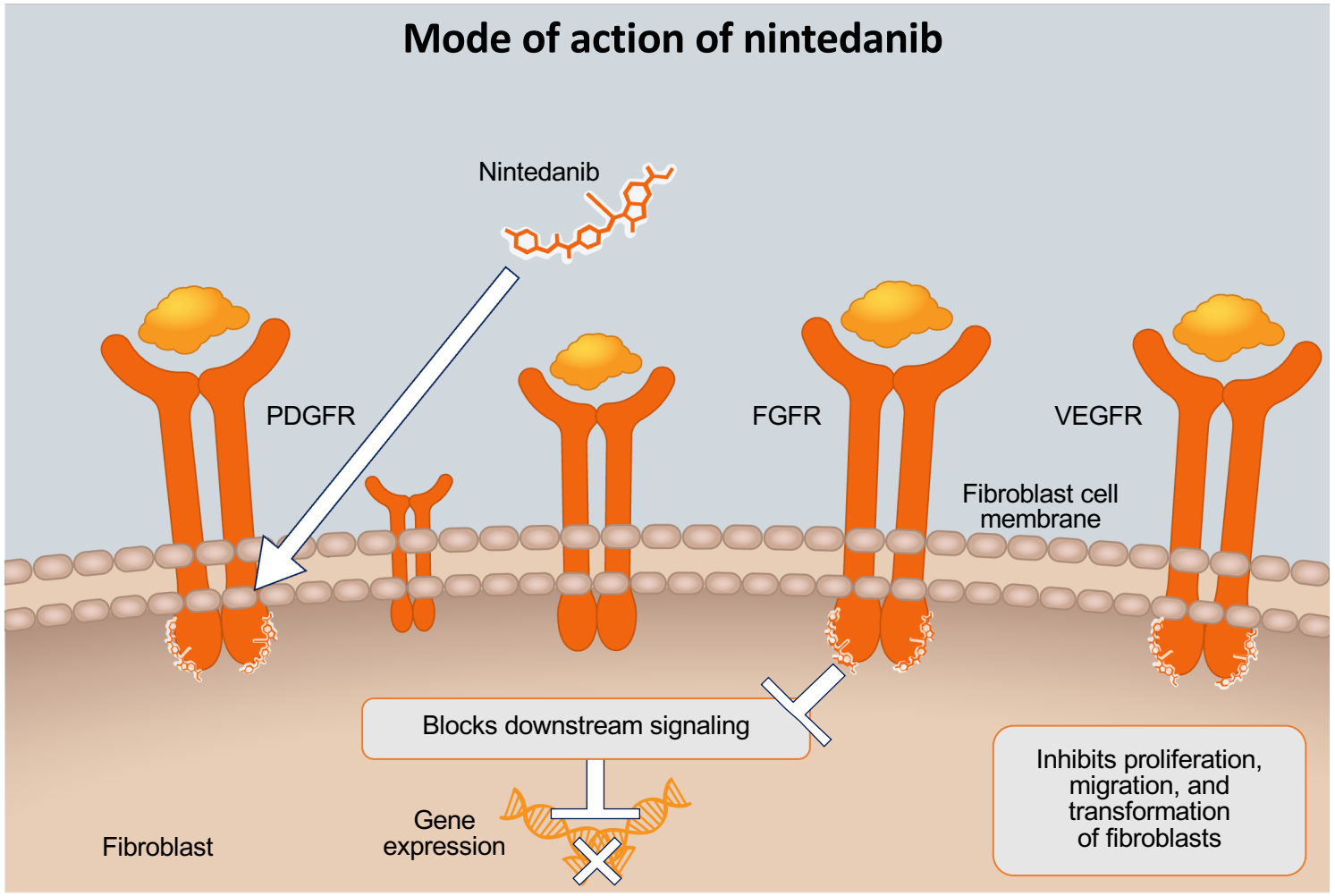
Professor Allanore has had consultancy relationships and/or has received research funding from Bayer, Boehringer Ingelheim, ChemomAb, Genentech/Roche, Janssen, Horizon, Medsenic, Prometheus, and Sanofi in the area of potential treatments of systemic scelrosis and its complications.

Nintedanib is a tyrosine kinase inhibitor

Kinase active site





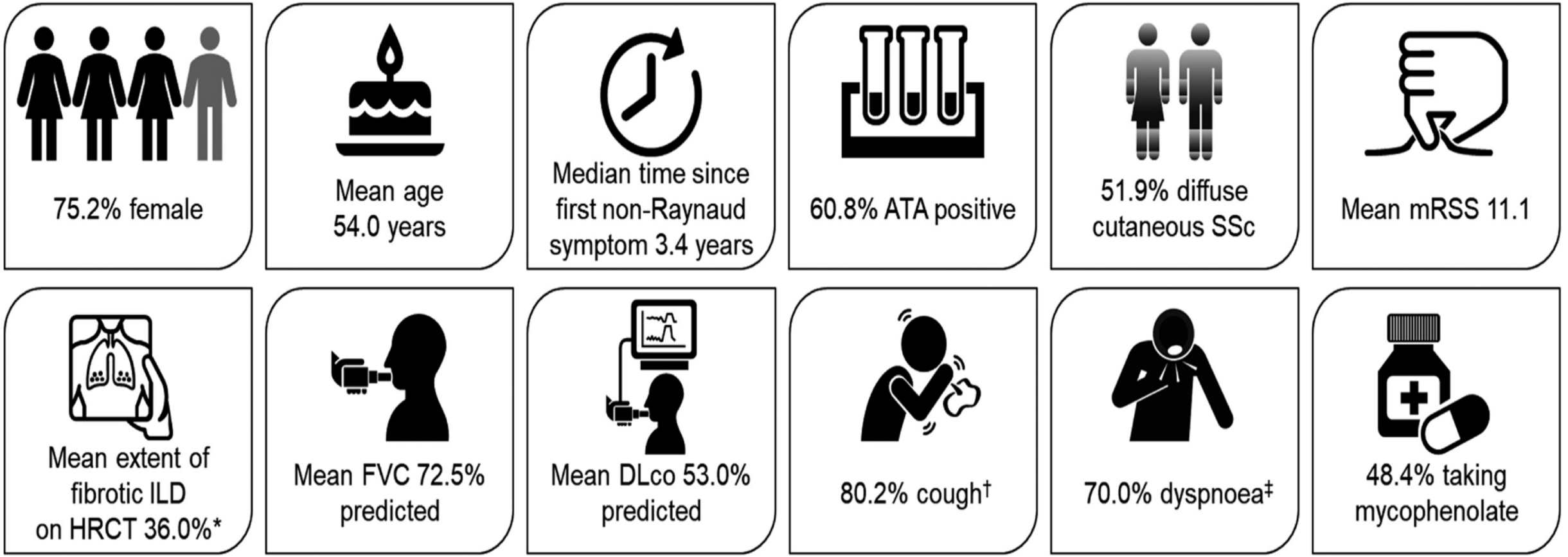
Nintedanib Summary of Product Characteristics. Available at: http://www.ema.europa.eu [accessed October 2020]

Senscis trial

Inclusion criteria:

- Age ≥18 years
- SSc (based on 2013 ACR/EULAR criteria)
- First non-Raynaud symptom **≤7 years** before screening
- **≥10% extent** of fibrotic ILD on HRCT performed ≤12 months prior to screening
- FVC ≥40% predicted
- DLco 30–89% predicted

Senscis trial: study population (n=576)



Screening is critical for SSc patients

- All the patients enrolled in the SENSCIS trial had ≥10% extent of fibrotic ILD on HRCT:
  - 20% did not have cough
  - 30% did not have dyspnoea
- Patients without dyspnoea had a mean extent of fibrosis of 32% and mean FVC value of 77% of the predicted value
- Patients in the SENSCIS trial had a mean FVC value of 2460 mL as compared to 3403 mL in a hypothetical healthy reference group
- The effective lung age of the patients was approximately 29 years higher than their real age

Volkmann et al. Rheumatology . 2022;61(11):4397
Maher et al. Respir Res 2022; 23(1): 178

Fibrosing SSc-ILD can be progressive, even in “lower risk”patients

- In the placebo group, the rate of decline in FVC was -93.3 mL/year over 52 weeks and -88.8 mL/year over 100
- **FVC decline > 10%** : 23.3% of patients in the placebo group over 100 weeks
- **PPF criteria (> 5%):** 28.5% of patients in the placebo group over 52 weeks,
- 13.7% of patients were hospitalised or died
  - A 3-unit decrease in FVC % predicted corresponded to an almost 1.5-fold increase in the risk of subsequent SSc-related hospitalisation or death over 52 weeks

Kreuter et al. Arthritis Res Ther 2022; 24(1): 19.
Kuwana et al. Arthritis Rheumatol 2022; 74(3): 518-26

Fibrosing SSc-ILD can be progressive, even in “lower risk”patients

- A total of 277 patients with **lcSSc** were treated in the SENSCIS trial
- The mean extent of fibrotic ILD on HRCT was 35.7(21.2)% and mean FVC 74.8(16.8)% predicted.
- 45% of patients were taking mycophenolate
- ATA positive 51.3% and ACA positive 10.1%
- The rate of decline in FVC was 74.5(19.2) ml/year in the placebo group and 49.1(19.8) ml/year in the nintedanib group (reduction by 34% vs placebo).
- Delta change, absolute decline:
  - > 5% : 18.7% (NINT) versus 28.2% (PBO)
  - > 10%: 9% (NINT) versus 8.5% (PBO)

Kreuter et al. Arthritis Res Ther 2022; 24(1): 19.
Kuwana et al. Arthritis Rheumatol 2022; 74(3): 518-26
Allanore et al. Rheumatology (Oxford). 2023 Jun 9: Epub

The course of SSc-ILD is variable and unpredictable

- In the placebo group, 34% of patients did not have any decline in FVC% predicted over 52 weeks
- 15% of patients in the placebo group had an **increase** in FVC > 3% (MCID)
- Risk factors for progression of SSc-ILD were:
  - patients with <18 months of dis. duration (-167.8 mL/year),
  - elevated inflammatory markers (-100.7 mL/year),
  - skin fibrosis with mRSS ≥18 (-131.7 mL/year)
- Weak evidence of an association between a greater extent of fibrotic ILD on HRCT at baseline and a greater decline in FVC over 52 weeks

Denton et al. Rheumatology (Oxford) 2022; 62 (5):1870-6.

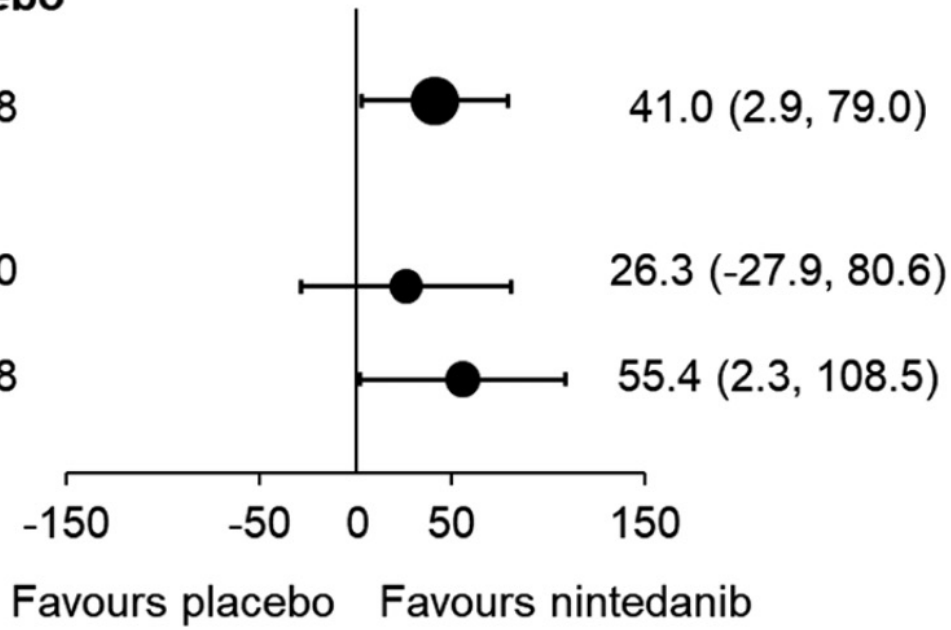
Nintedanib slows the progression of SSc-ILD

- Rate of decline in FVC over 52 weeks was -52.4 mL/year in the nintedanib group *versus* -93.3 mL/year in the placebo group (difference: 41.0 mL/year [95% CI: 2.9, 79.0]; *p*=0.04)
- Absolute decline in FVC % >5% : 28.5% versus 20.6%
- Patients taking mycophenolate + nintedanib lost 43.3 mL which is close to the loss of FVC that would be expected in healthy individuals of the same age (26.2 mL)

Denton et al. Rheumatology (Oxford) 2022; 62 (5):1870-6.

Nintedanib slows the progression of SSc-ILD

		n analysed		Difference (95% CI)
		Nintedanib	Placebo	
All patients		287	288	41.0 (2.9, 79.0)
Mycophenolate use at baseline	Yes	138	140	26.3 (-27.9, 80.6)
	No	149	148	55.4 (2.3, 108.5)



Patients taking mycophenolate were required to have been on a stable dose for ≥6 months before randomization.
Treatment-by-time-by-subgroup interaction: p=0.45.

Denton et al. Rheumatology (Oxford) 2022; 62 (5):1870-6.

Side-effects need to be managed

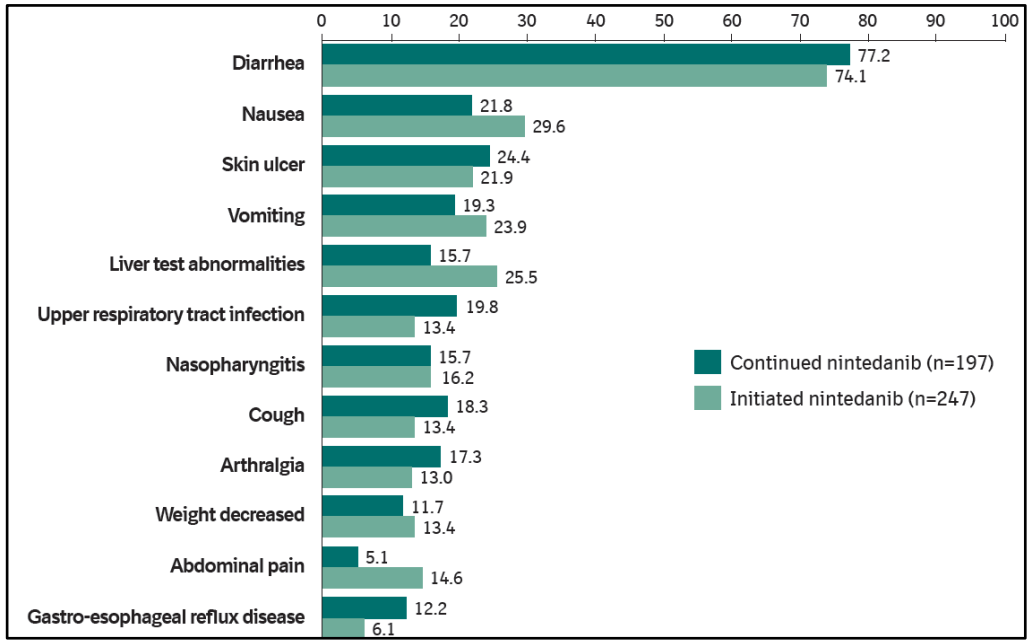
	Nintedanib	Placebo
Diarrhea	75.7	31.6
Nausea	31.6	13.5
Vomiting	24.7	10.4

	Nintedanib	Placebo
Treatment interruption	37.8	11.4
Dose reduction	40.6	4.5
Permanent discontinuation	16.0	8.7

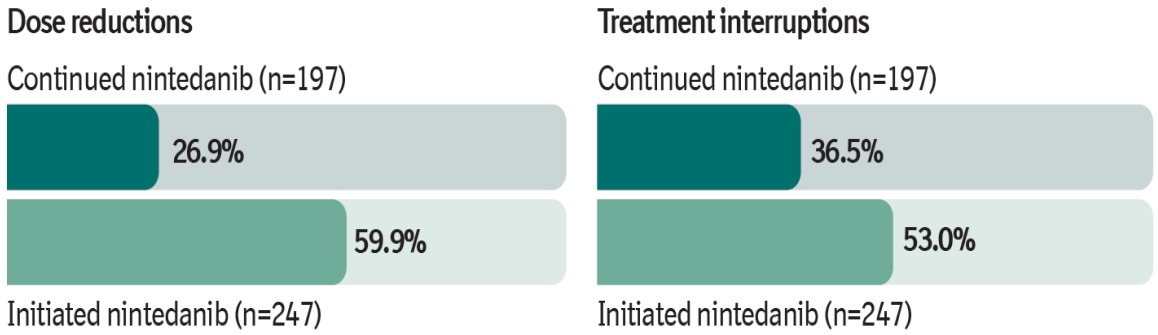
Allanore et al. Ann Rheum Dis. 2022;81(12):1722-1729

Side-effects need to be managed

Most frequent AEs*† over 148 weeks in SENSCIS®-ON



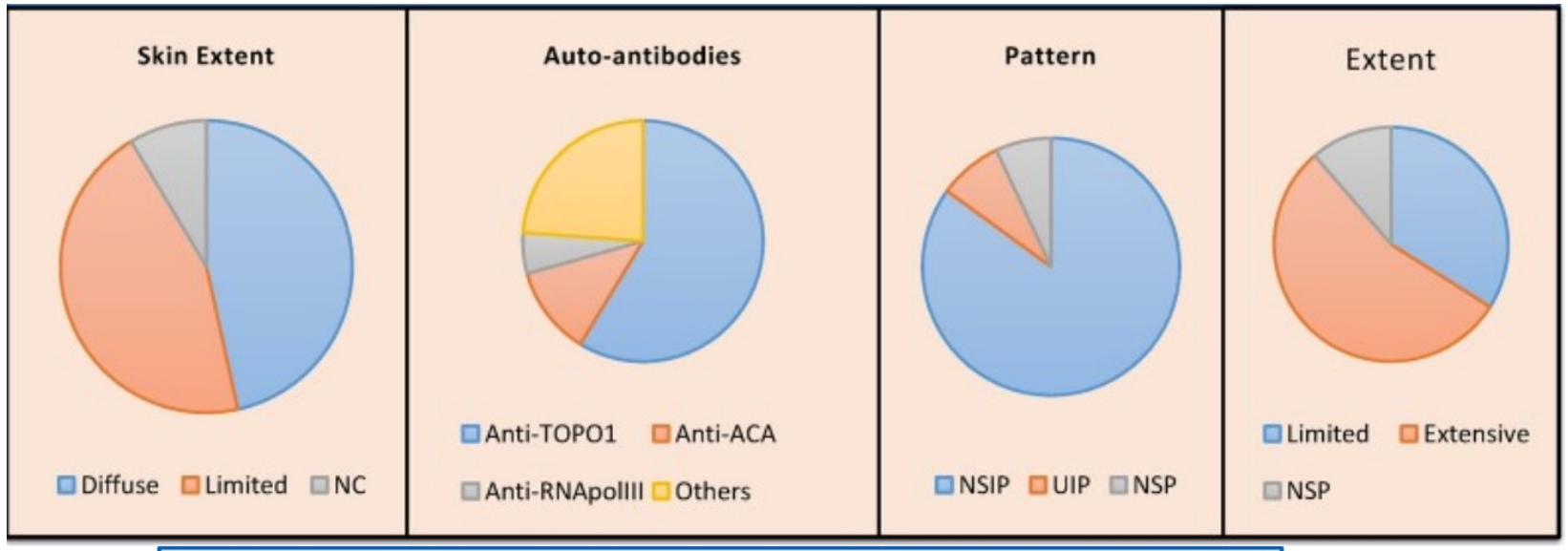
Dose adjustments over 148 weeks in SENSCIS®-ON‡



SENSCIS-ON : permanent discontinuation in 15% of patients who continued nintedanib and 29% of patients who initiated nintedanib

Allanore et al. Ann Rheum Dis. 2022 ;81(12):1722-1729

Poster ID 402: 116 SSc-ILD patients from 14 French centers



FCV evolution :

- At 6 month, out of the 66 patient with available data mean FVC gain is 3 mL ± 25 (26 loss ; 40 gain)
- At 12 month, out of the 53 patient with available data, mean FCV loss is 31 mL ± 34 (36 loss and 17 gain)

Tolerance and side effect :

- 10 and 18 patients discontinued treatment at 6 and 12 months respectively
- 54% patients presents side effect at 6 month including the digestive tract (32 diarrhea, 12 significant weight loss…)

SSc-ILD: SAFETY AND EFFECTIVENESS AFTER ONE YEAR IN A REAL-LIFE COHORT. POS1325. Corada et al (Spain).

22 patients were treated with nintedanib for SSc-ILD
Median extent of ILD ; 29.7% (20.0% - 39.9%).
The median period from the ILD diagnosis to nintedanib initiation was 46.5 months.
As concomitant therapies, 17 (77%) were under MMF, 7 (32%) received previously intravenous cyclophosphamide, and 8 (36%) had taken rituximab previously

The absolute forced vial capacity (FVC) percentage after the first 12-month follow-up increased in 0.15 % (-3.8 – 5.5), which meant a relative increase in FVC of 2.3% (-4.7 – 7.9).

Security profile:
- Nine (41%) patients suffered from diarrhea,
- 5 (23%) had elevation of liver enzymes,

Overall during a follow-up of 29.5 months:
- 3 (13.6%) patients died,
- 13 (59.1%) required a nintedanib dose reduction,
- 4 (18.2%) temporary interruption,
- and 5 (22.7%) a permanent withdrawal.

Real-life efficacy and safety of nintedanib inb SSc-ILD :data from an Italian multicentre study

	90 patients
Dis duration	8.8±7.6
Dc SSc	40 (44.0)
Anti-TOPO	67 (74)
HRCT UIP	28 (31)
% predicted FVC	65 +/-16
% Predicted DLCO	42 +/-18
% ILD progression	68/84 (81%)
Concurrent MMF	63 (81)
Concurrent RTX	18 (23)
Concurrent TOCI	5 (6)

SAFETY:

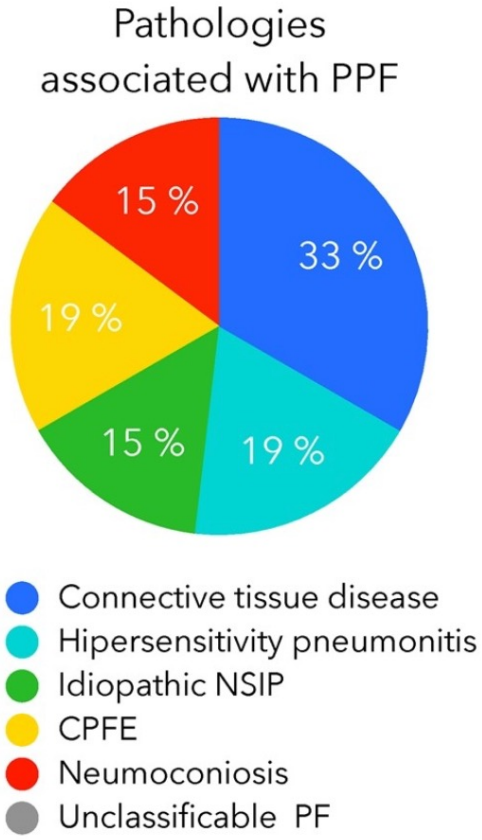
- diarrhoea : 29%
- nausea/vomiting : 21%
- weight loss : 13%
- liver toxicity : 8%

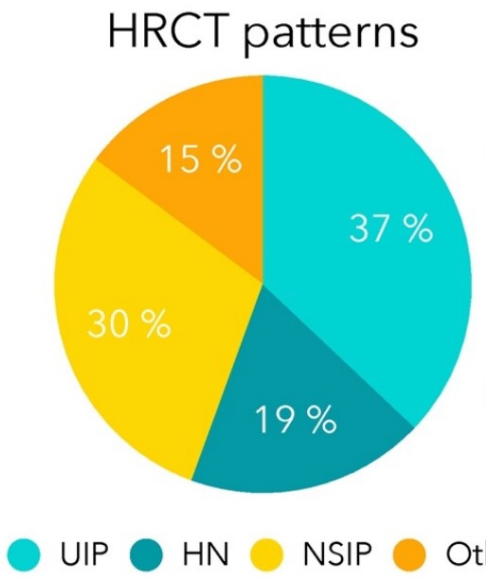
NTD dose adjustment to 100 mg two times per day In 25 patients (28%) with time to dose adjustment of 3.6±3.1 months

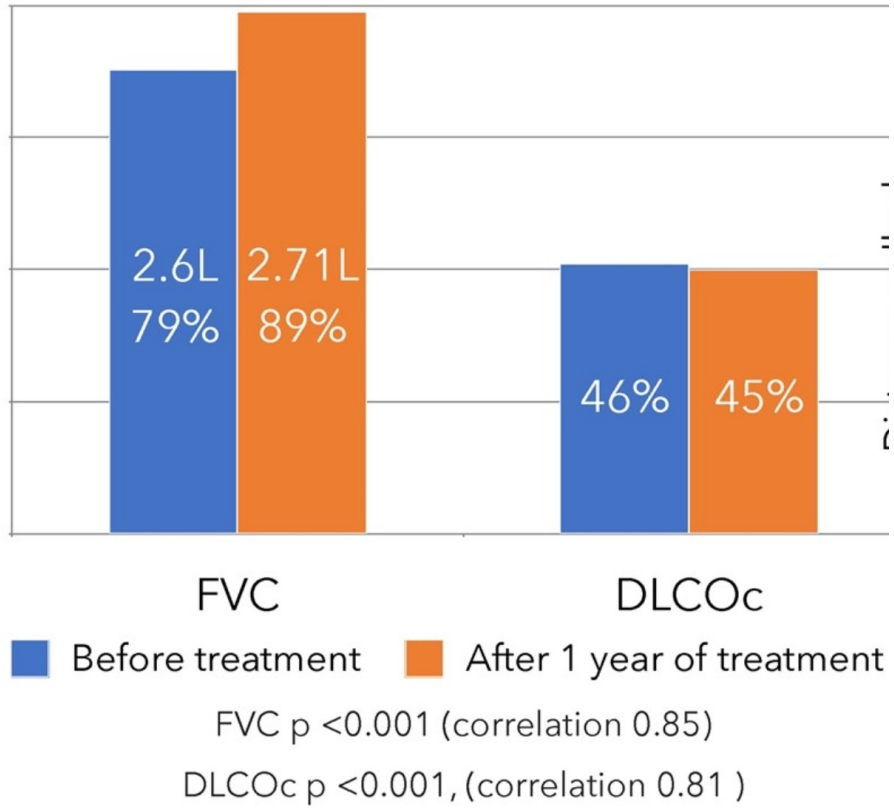
In 9 (10%) patients NTD was definitely stopped after a median time of 4.5 (1–6) months.

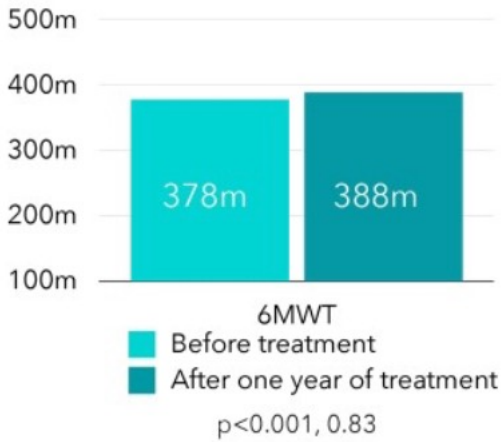
Campochiaro et al. RMD Open. 2023;9(1):e002850.

Spain, 27 patients, monocentric, Castellone IP 407









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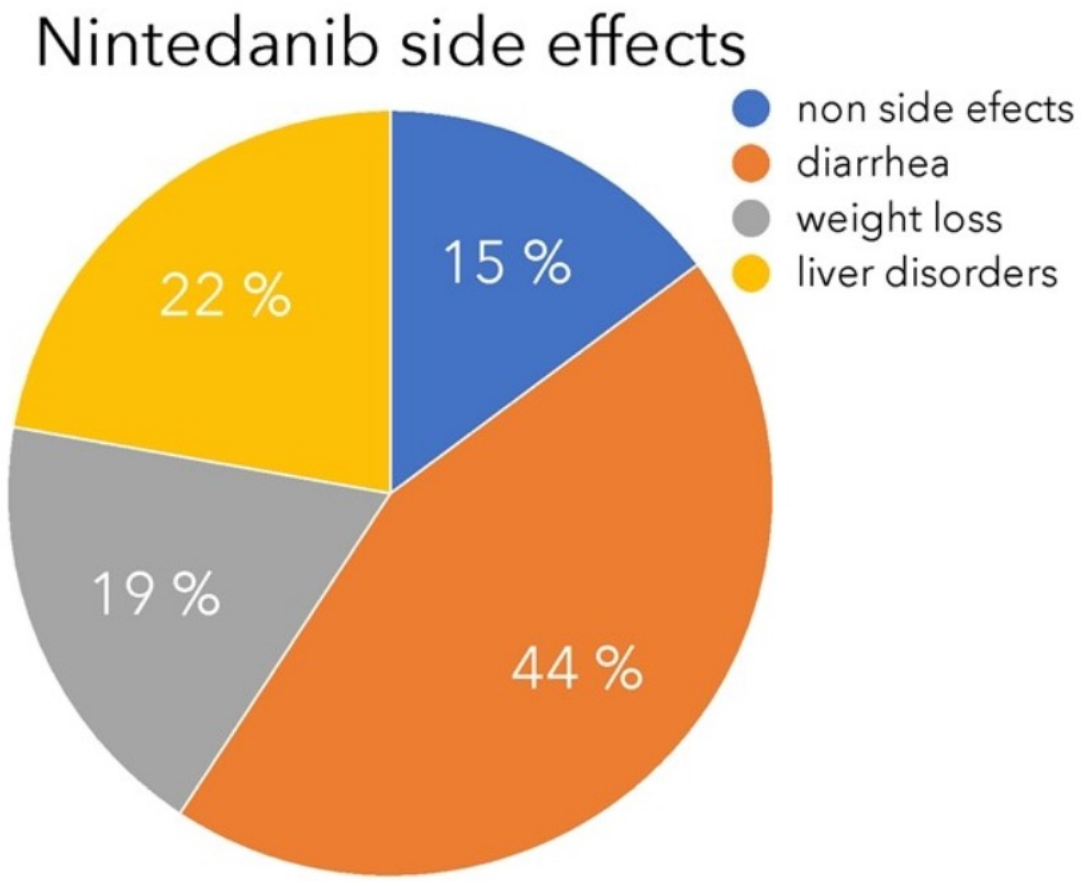

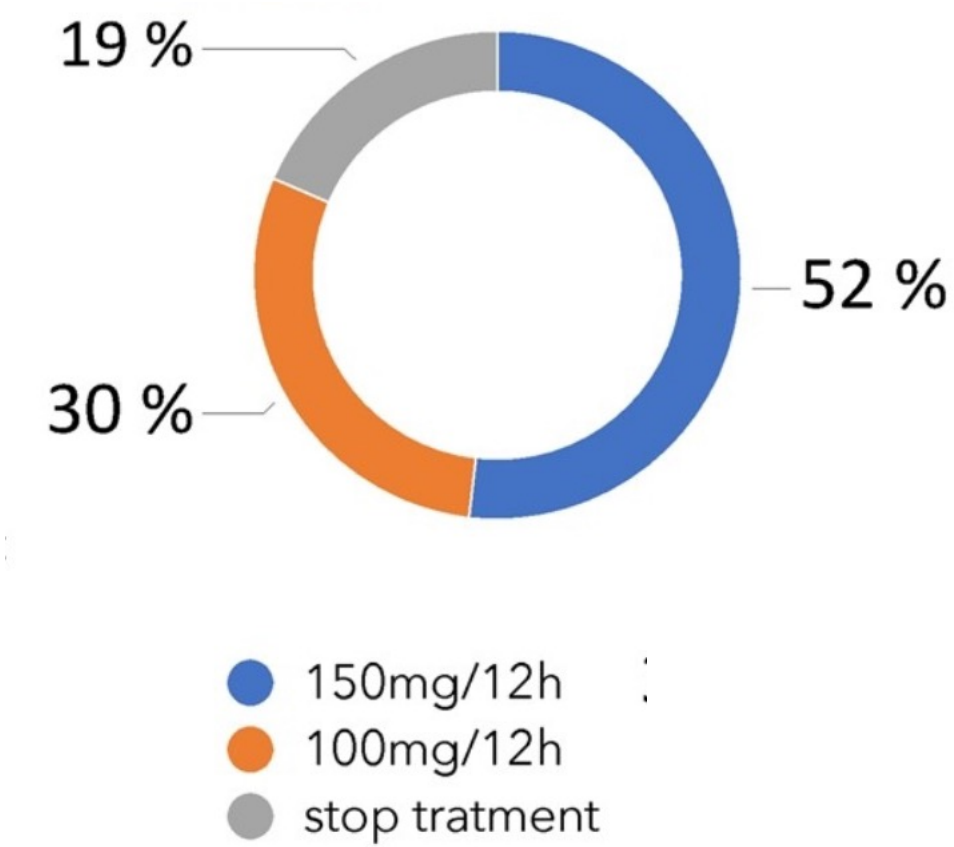

Management of SSc-ILD requires a holistic approach

- Nintedanib did not have a significant effect on skin fibrosis
- Nintedanib did not improve patients' quality of life
- A multidisciplinary approach is likely to provide the best results

- In addition to drug therapies supportive care, pulmonary rehabilitation and individualised patient education and support should be part of the package of care


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