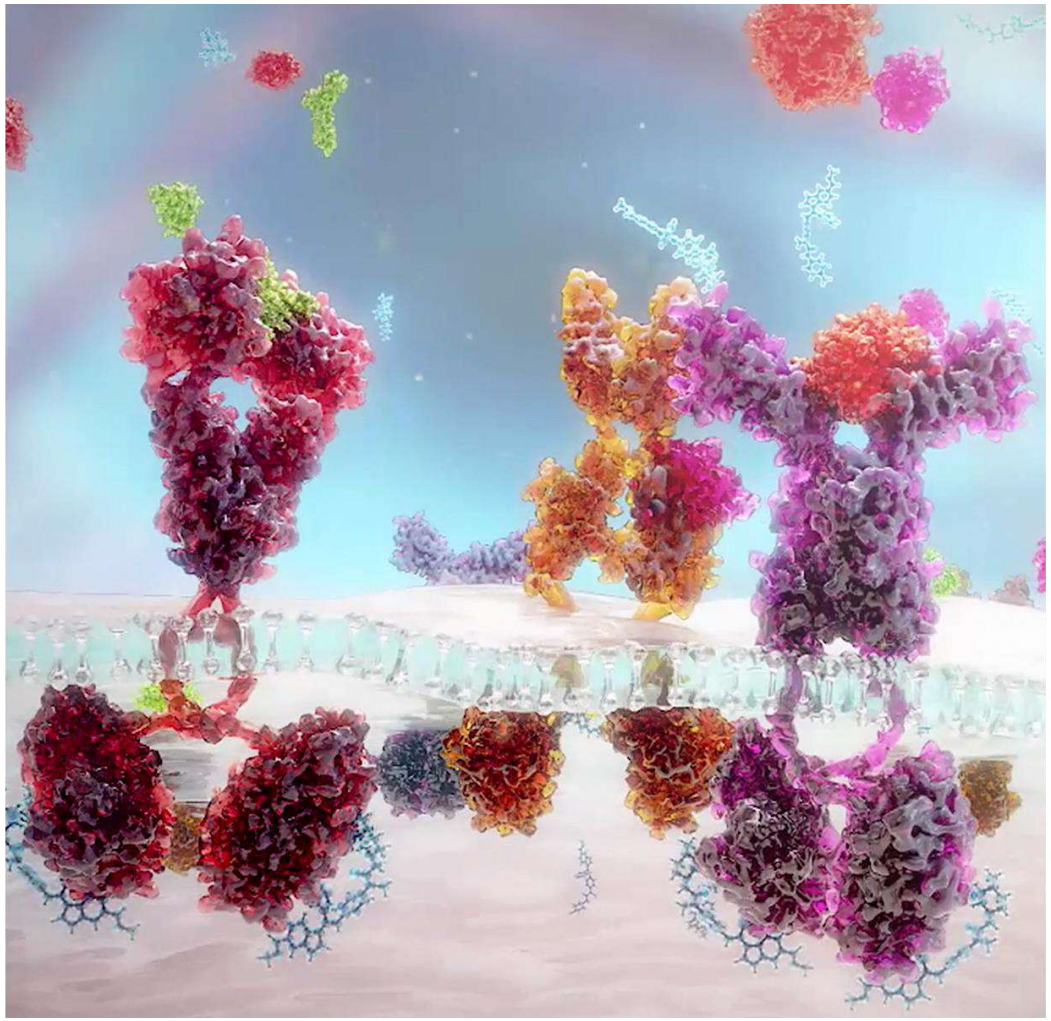
# Nintedanib is a specific tyrosine kinase inhibitor[2,3]

| Angiogenesis and fibrosis-related kinases | | | |
|---|---|---|---|
| | VEGFR 1 / 2 / 3 | PDGFR α / β | FGFR 1 / 2 / 3 |
| $IC_{50}$ [nM] | 34 / 21 / 13 | 59 / 65 | 69 / 37 / 108 |

| Src family kinases - inflammation and proliferation | | | |
|---|---|---|---|
| | Src | Lck | Lyn |
| $IC_{50}$ [nM] | 156 | 16 | 195 |

| Other kinases | | | |
|---|---|---|---|
| | FLT-3 | CSF1R | Additional 20 kinases |
| $IC_{50}$ [nM] | 26 | 5 | <100 nM* |

*IC50 on an enzymatic level with no cellular activity currently described



2. Hilberg F., et al. *Cancer Res* 2008;68:4774–4782.
3. Hilberg F., et al. *J Pharmacol Exp Ther* 2018;364:494–503.

Boehringer Ingelheim

# Nintedanib: evidence for its therapeutic potential in idiopathic pulmonary fibrosis

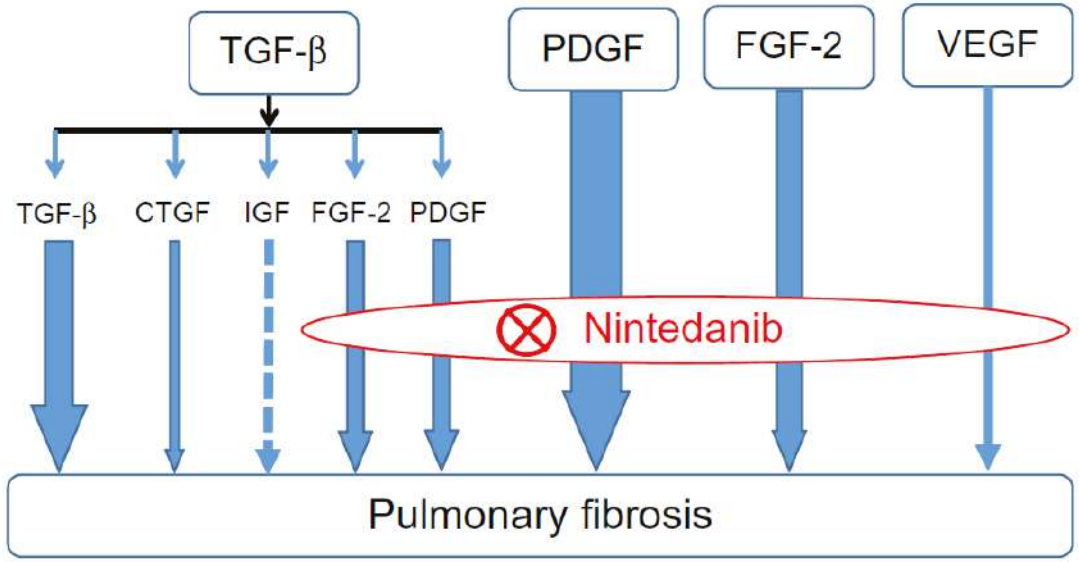



**Table 2** Tyrosine kinase inhibition by nintedanib in a cellular BA/F3 assay

| Assay | IC50 (nM) |
|---|---|
| FGFR1 | 300–1,000 |
| FGFR2 | 257 |
| FGFR3 | 300–1,000 |
| FGFR4 | 300–1,000 |
| PDGFRα | 41 |
| PDGFRβ | 58 |
| VEGFR1 | 300–1,000 |
| VEGFR2 | 46 |
| VEGFR3 | 33 |
| LCK | 22 |
| LYN | 300–1,000 |
| SRC | 811 |
| FLT-3 | 17 |

**Abbreviations:** FGFR, fibroblast growth factor receptor; PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor.

Core Evidence 2015:10 89–98

# The INBUILD Trial

**Table 1. Characteristics of the Overall Population at Baseline.***

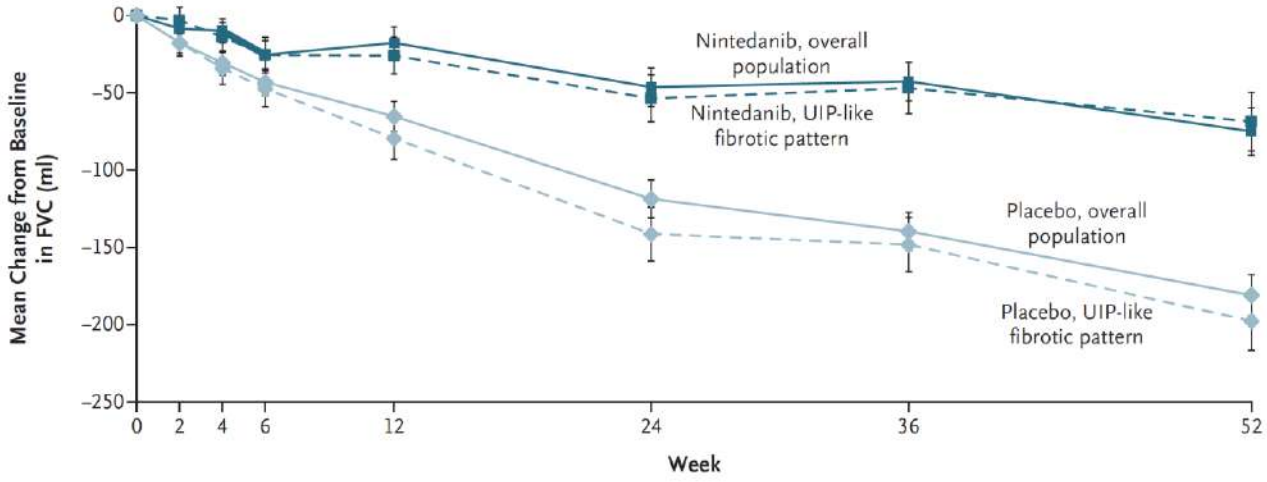
| Characteristic | Nintedanib (N=332) | Placebo (N=331) |
|---|---|---|
| Male sex — no. (%) | 179 (53.9) | 177 (53.5) |
| Age — yr | 65.2±9.7 | 66.3±9.8 |
| Former or current smoker — no. (%) | 169 (50.9) | 169 (51.1) |
| UIP-like fibrotic pattern on high-resolution CT — no. (%) | 206 (62.0) | 206 (62.2) |
| Criteria for disease progression in previous 24 mo — no. (%) | | |
| Relative decline in FVC of ≥10% of predicted value | 160 (48.2) | 172 (52.0) |
| Relative decline in FVC of 5% to <10% of predicted value plus worsening of respiratory symptoms or increased extent of fibrosis on high-resolution CT | 110 (33.1) | 97 (29.3) |
| Worsening of respiratory symptoms and increased extent of fibrosis on high-resolution CT | 62 (18.7) | 61 (18.4) |
| FVC | | |
| Mean value — ml | 2340±740 | 2321±728 |
| Percent of predicted value | 68.7±16.0 | 69.3±15.2 |
| Diffusing capacity for carbon monoxide† | | |
| Mean value — mmol/min/kPa | 3.5±1.2 | 3.7±1.3 |
| Percent of predicted value | 44.4±11.9 | 47.9±15.0 |
| Total score on K-BILD questionnaire‡ | 52.5±11.0 | 52.3±9.8 |

**Table 2. Efficacy End Points.***

| End Point | Nintedanib (N=332) | Placebo (N=331) | Difference (95% CI) |
|---|---|---|---|
| **Primary end point** | | | |
| Rate of decline in the FVC at 52 wk — ml/yr† | | | |
| Overall population | −80.8±15.1 | −187.8±14.8 | 107.0 (65.4 to 148.5)‡ |
| Patients with a UIP-like fibrotic pattern | −82.9±20.8 | −211.1±20.5 | 128.2 (70.8 to 185.6)‡ |
| Patients with other fibrotic patterns | −79.0±21.6 | −154.2±21.2 | 75.3 (15.5 to 135.0)§ |
| **Main secondary end points** | | | |
| Absolute change from baseline in total score on K-BILD questionnaire at 52 wk¶ | | | |
| Overall population | 0.55±0.60 | −0.79±0.59 | 1.34 (−0.31 to 2.98)§ |
| Patients with a UIP-like fibrotic pattern | 0.75±0.80 | −0.78±0.79 | 1.53 (−0.68 to 3.74)§ |
| Acute exacerbation of interstitial lung disease or death at 52 wk — no. with event/total no. (%) | | | |
| Overall population | 26/332 (7.8) | 32/331 (9.7) | 0.80 (0.48 to 1.34)§‖ |
| Patients with a UIP-like fibrotic pattern | 17/206 (8.3) | 25/206 (12.1) | 0.67 (0.36 to 1.24)§‖ |
| Death at 52 wk — no. with event/total no. (%) | | | |
| Overall population | 16/332 (4.8) | 17/331 (5.1) | 0.94 (0.47 to 1.86)§‖ |
| Patients with a UIP-like fibrotic pattern | 11/206 (5.3) | 16/206 (7.8) | 0.68 (0.32 to 1.47)§‖ |
| **Additional end points assessed during period until first database lock** | | | |
| Acute exacerbation of interstitial lung disease or death — no. with event/total no. (%) | | | |
| Overall population | 41/332 (12.3) | 59/331 (17.8) | 0.68 (0.46 to 1.01)§‖ |
| Patients with a UIP-like fibrotic pattern | 28/206 (13.6) | 44/206 (21.4) | 0.61 (0.38 to 0.98)§‖ |
| Death — no. with event/total no. (%) | | | |
| Overall population | 27/332 (8.1) | 38/331 (11.5) | 0.70 (0.43 to 1.15)§‖ |
| Patients with a UIP-like fibrotic pattern | 20/206 (9.7) | 31/206 (15.0) | 0.63 (0.36 to 1.10)§‖ |

N Engl J Med. 2019 Oct 31;381(18):1718-1727

## Decline from Baseline in Forced Vital Capacity (FVC).

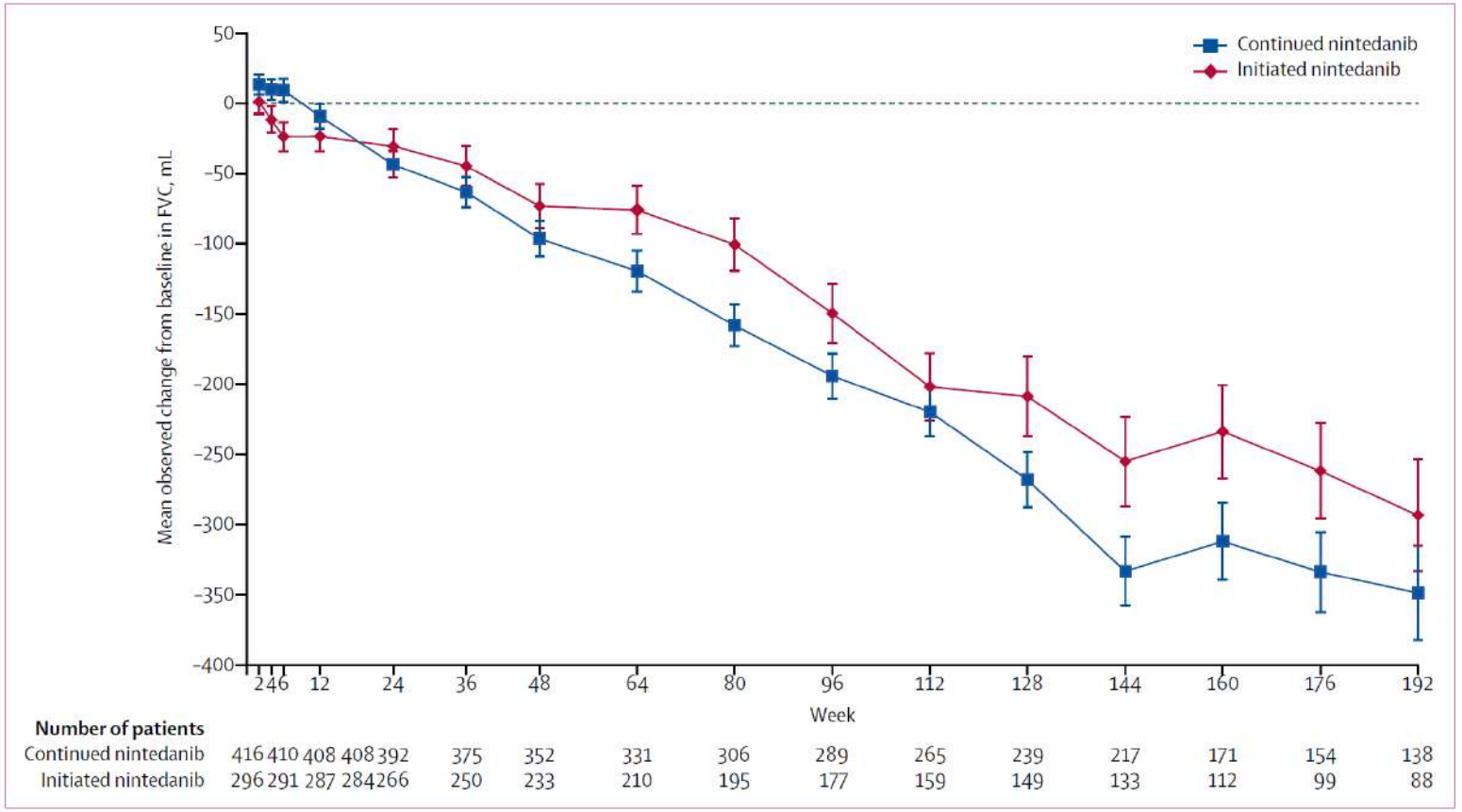


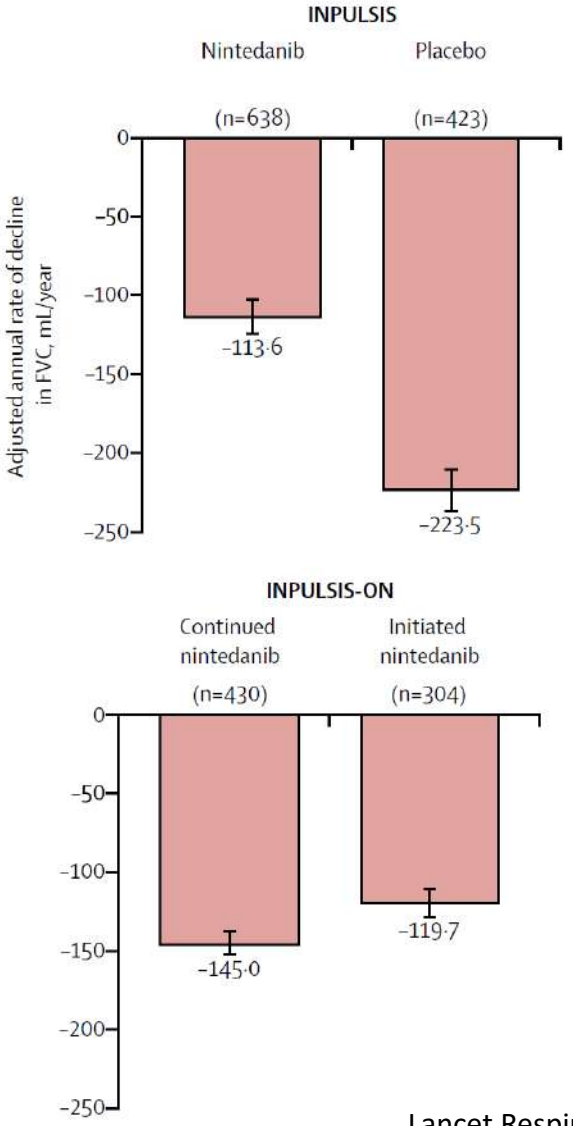

| No. of Patients | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Overall population | | | | | | | | |
| Nintedanib | 332 | 326 | 320 | 322 | 314 | 298 | 285 | 265 |
| Placebo | 331 | 325 | 326 | 325 | 320 | 311 | 296 | 274 |
| Patients with UIP-like fibrotic pattern | | | | | | | | |
| Nintedanib | 206 | 203 | 200 | 199 | 193 | 180 | 171 | 160 |
| Placebo | 206 | 202 | 202 | 201 | 197 | 190 | 176 | 162 |

| Event | Nintedanib (N=332) | Placebo (N=331) |
|---|---|---|
| | *no. of patients (%)* | |
| Adverse event | | |
| Any | 317 (95.5) | 296 (89.4) |
| Any except for progression of interstitial lung disease† | 317 (95.5) | 295 (89.1) |
| Most frequent adverse events‡ | | |
| Diarrhea | 222 (66.9) | 79 (23.9) |
| Nausea | 96 (28.9) | 31 (9.4) |
| Bronchitis | 41 (12.3) | 47 (14.2) |
| Nasopharyngitis | 44 (13.3) | 40 (12.1) |
| Dyspnea | 36 (10.8) | 44 (13.3) |
| Vomiting | 61 (18.4) | 17 (5.1) |
| Cough | 33 (9.9) | 44 (13.3) |
| Decreased appetite | 48 (14.5) | 17 (5.1) |
| Headache | 35 (10.5) | 23 (6.9) |
| Alanine aminotransferase increased | 43 (13.0) | 12 (3.6) |
| Progression of interstitial lung disease† | 16 (4.8) | 39 (11.8) |
| Weight loss | 41 (12.3) | 11 (3.3) |
| Aspartate aminotransferase increased | 38 (11.4) | 12 (3.6) |
| Abdominal pain | 34 (10.2) | 8 (2.4) |
| Severe adverse event§ | 60 (18.1) | 73 (22.1) |
| Serious adverse event¶ | 107 (32.2) | 110 (33.2) |
| Fatal adverse event | | |
| Any | 11 (3.3) | 17 (5.1) |
| Any except for progression of interstitial lung disease† | 10 (3.0) | 14 (4.2) |
| Adverse event leading to treatment discontinuation | 65 (19.6) | 34 (10.3) |
| Adverse event leading to permanent dose reduction | 110 (33.1) | 14 (4.2) |

N Engl J Med. 2019 Oct 31;381(18):1718-1727

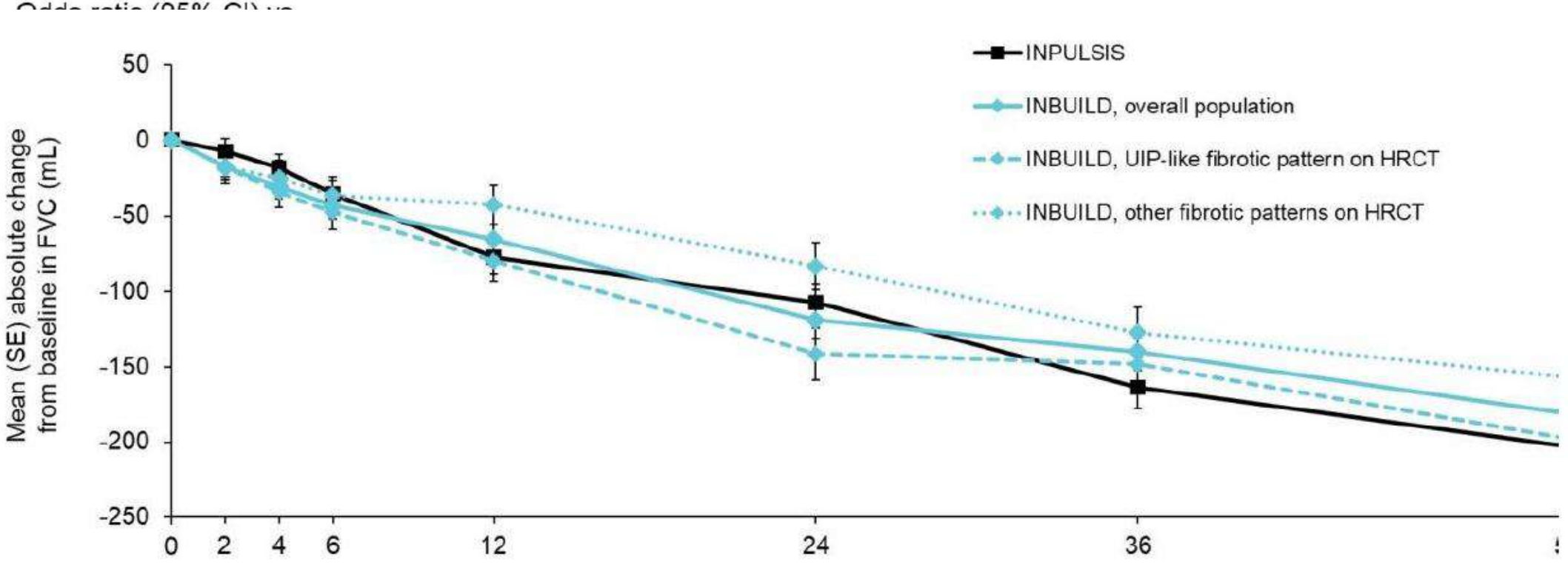
# Annual rate of decline in FVC over 52 weeks in INPULSIS and over 192 weeks in INPULSIS-ON




Lancet Respir Med 2018

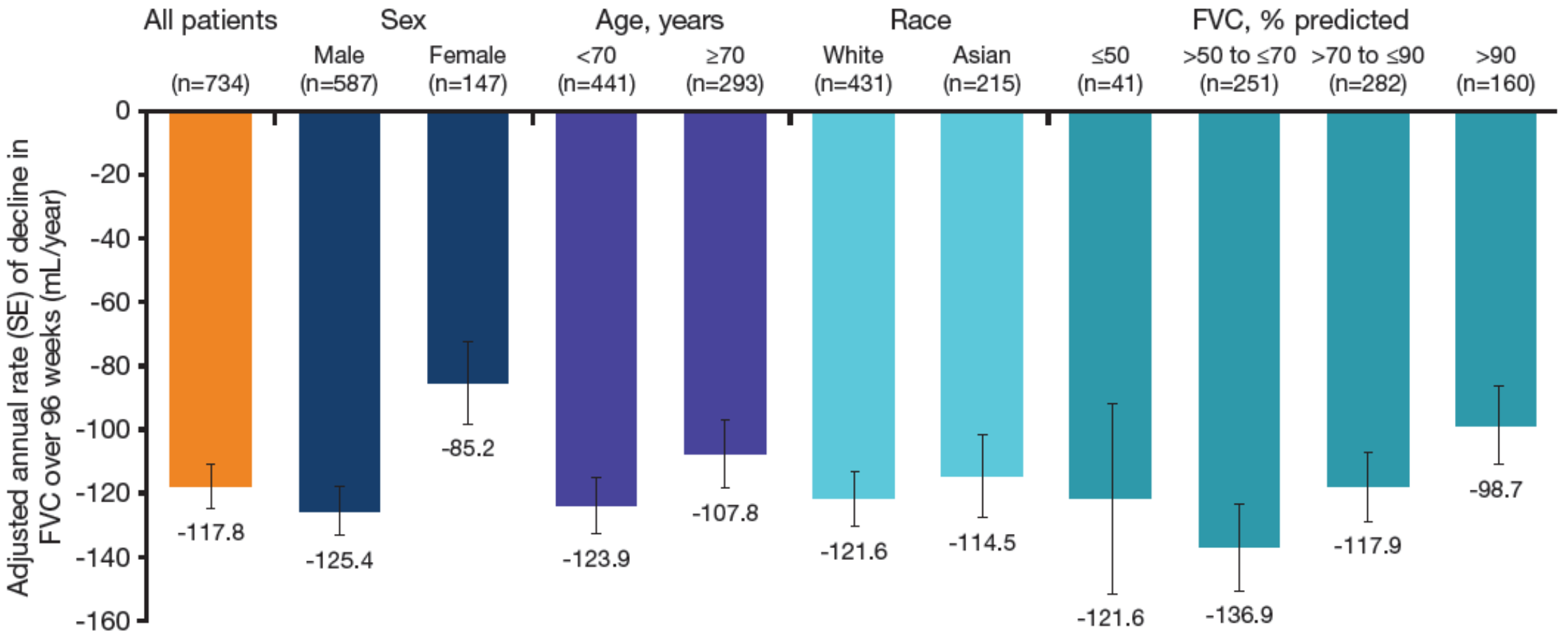
# Observed change from baseline over 52 weeks in FVC in the placebo groups of the INPULSIS and INBUILD trials




| No. of subjects | | | | | | | |
|---|---|---|---|---|---|---|---|
| INPULSIS | 417 | 408 | 407 | 403 | 395 | 383 | 3 |
| INBUILD, overall population | 325 | 326 | 325 | 320 | 311 | 296 | 2 |
| INBUILD, UIP-like fibrotic pattern | 202 | 202 | 201 | 197 | 190 | 176 | 1 |
| INBUILD, other fibrotic patterns | 123 | 124 | 124 | 123 | 121 | 120 | 1 |

European Respiratory Journal 2020; DOI: 10.1183/13993003.00085-2020

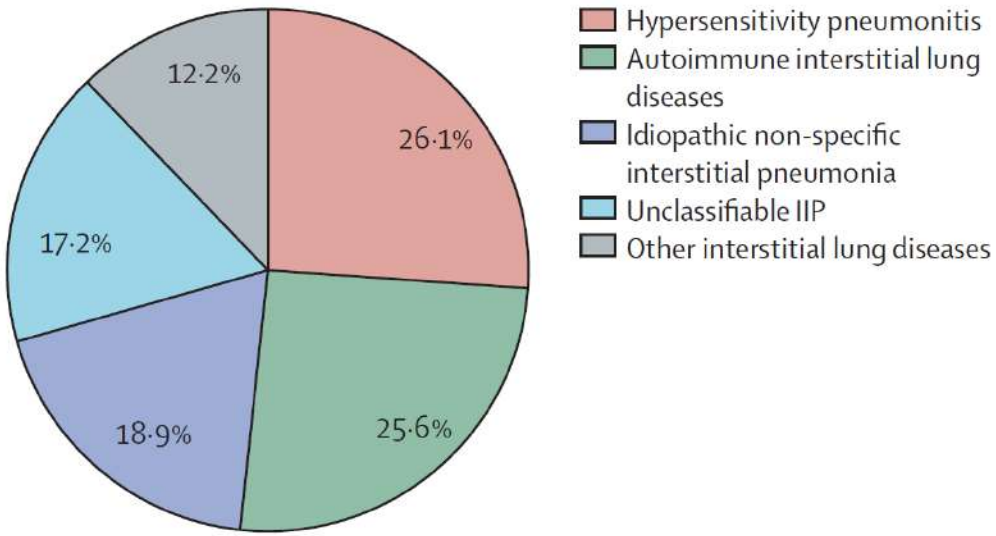
# Annual rate of decline in FVC over 96 weeks in subgroups by patient characteristics at start of INPULSIS®-ON

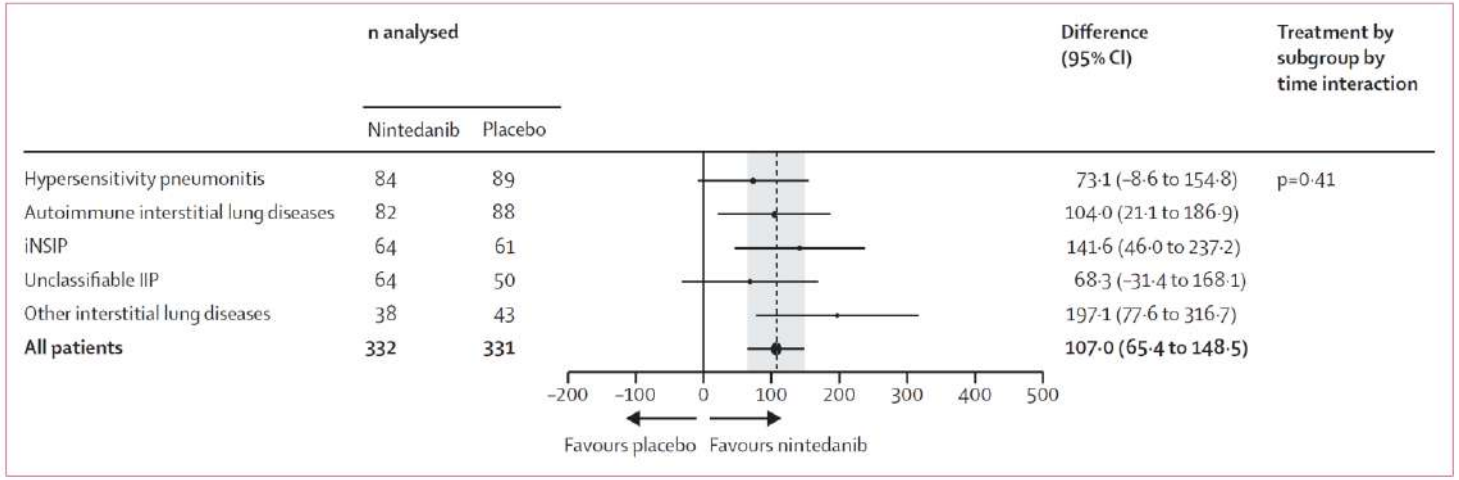


| | Hypersensitivity pneumonitis (n=173) | Autoimmune interstitial lung diseases (n=170) | Idiopathic non-specific interstitial pneumonia (n=125) | Unclassifiable idiopathic interstitial pneumonia (n=114) | Other ILDs* (n=81) |
|---|---|---|---|---|---|
| Male | 89 (51%) | 80 (47%) | 63 (50%) | 62 (54%) | 62 (77%) |
| Age, years | 65·5 (8·3) | 64·3 (10·6) | 65·4 (9·4) | 68·4 (9·4) | 66·2 (11·2) |
| Former or current smoker | 91 (53%) | 85 (50%) | 43 (34%) | 62 (54%) | 57 (70%) |
| Usual interstitial pneumonia-like fibrotic pattern on HRCT | 90 (52%) | 127 (75%) | 71 (57%) | 77 (68%) | 47 (58%) |
| Forced vital capacity, mL | 2244 (739) | 2330 (699) | 2351 (761) | 2286 (730) | 2548 (727) |
| Forced vital capacity, % predicted | 65·2 (14·2) | 70·9 (14·9) | 71·3 (17·3) | 69·8 (15·4) | 68·4 (16·6) |
| Diffusing capacity of the lung for carbon monoxide, % predicted† | 45·3 (14·4) | 48·0 (15·1) | 47·4 (12·5) | 45·2 (11·9) | 43·2 (12·2) |

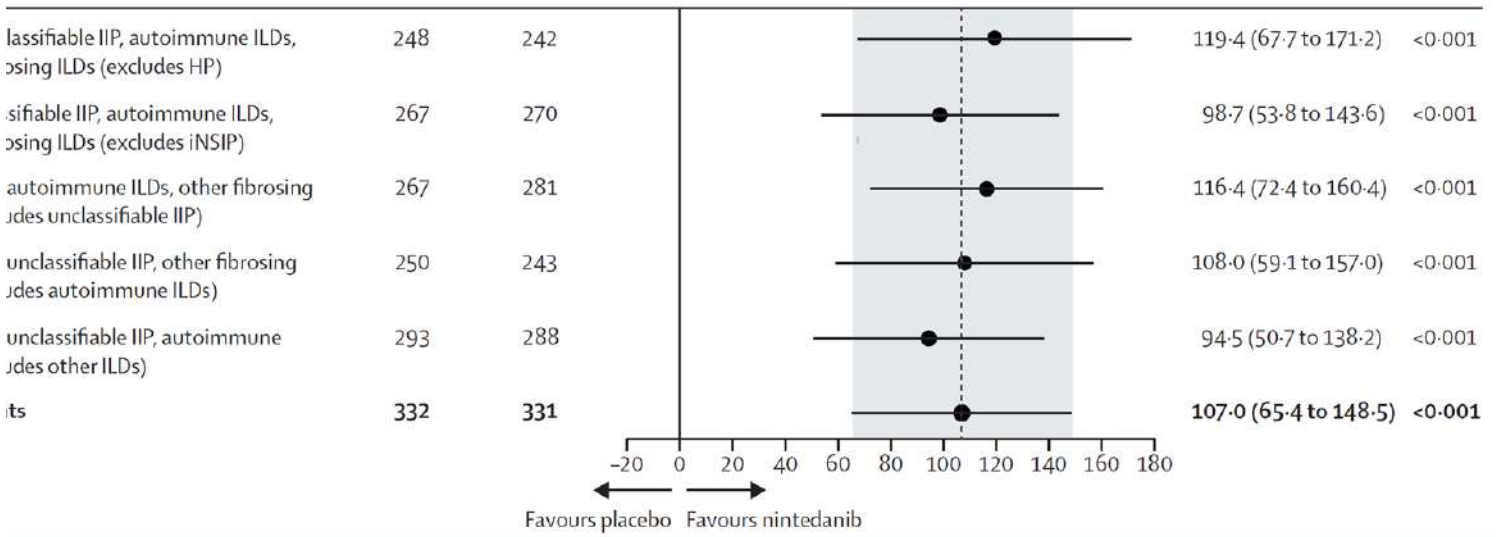
Data are n (%) or mean (SD). *Included sarcoidosis, exposure-related ILDs and selected other terms in other fibrosing interstitial lung diseases such as pleuroparenchymal fibroelastosis, and cryptogenic organising pneumonia. †Corrected for haemoglobin.

***Table 1:*** **Baseline characteristics**




Lancet Respir Med. 2020 Mar 5




**nual rate of decline in forced vital capacity (mL/year) with one of the five groups by interstitial lung disease diagnosis excluded at a time (overall )**

pathic non-specific interstitial pneumonia. IIP=idiopathic interstitial pneumonia. ILD=interstitial lung disease. HP=hypersensitivity pneumonitis.

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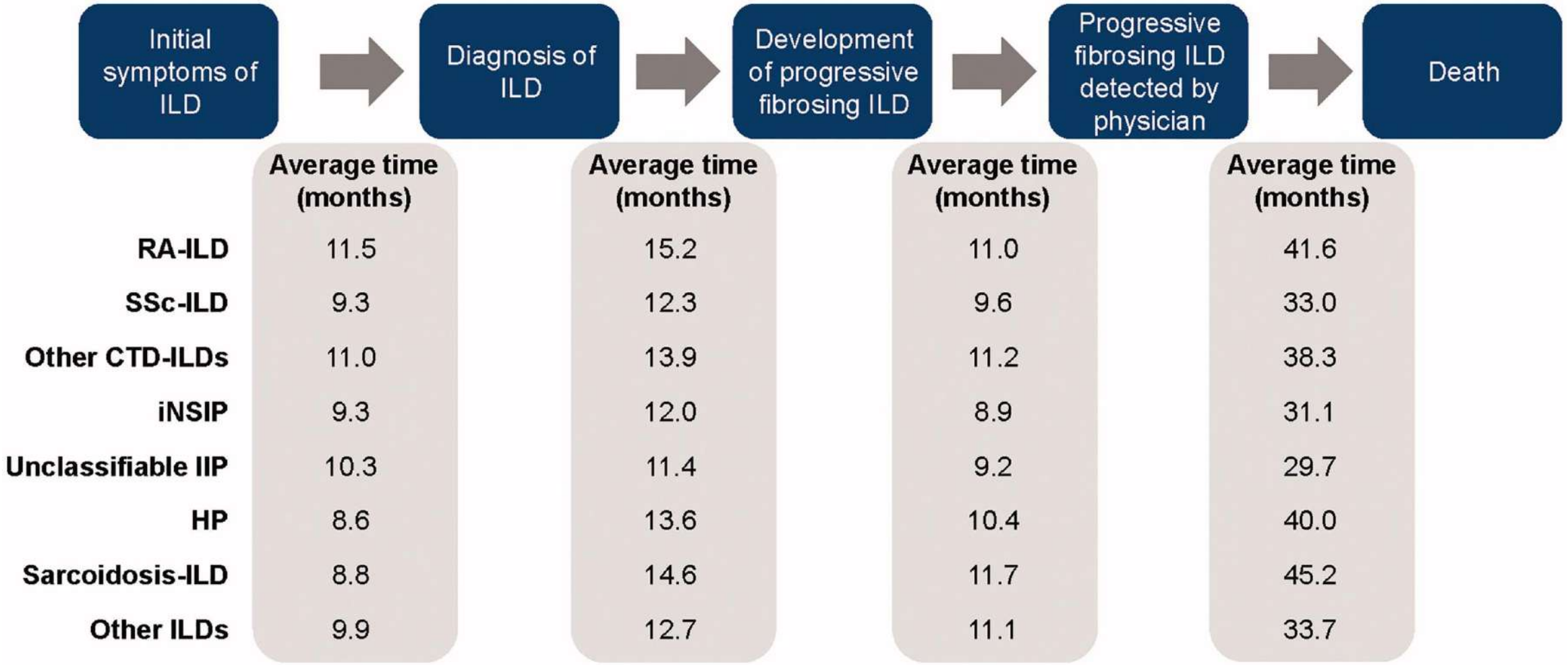
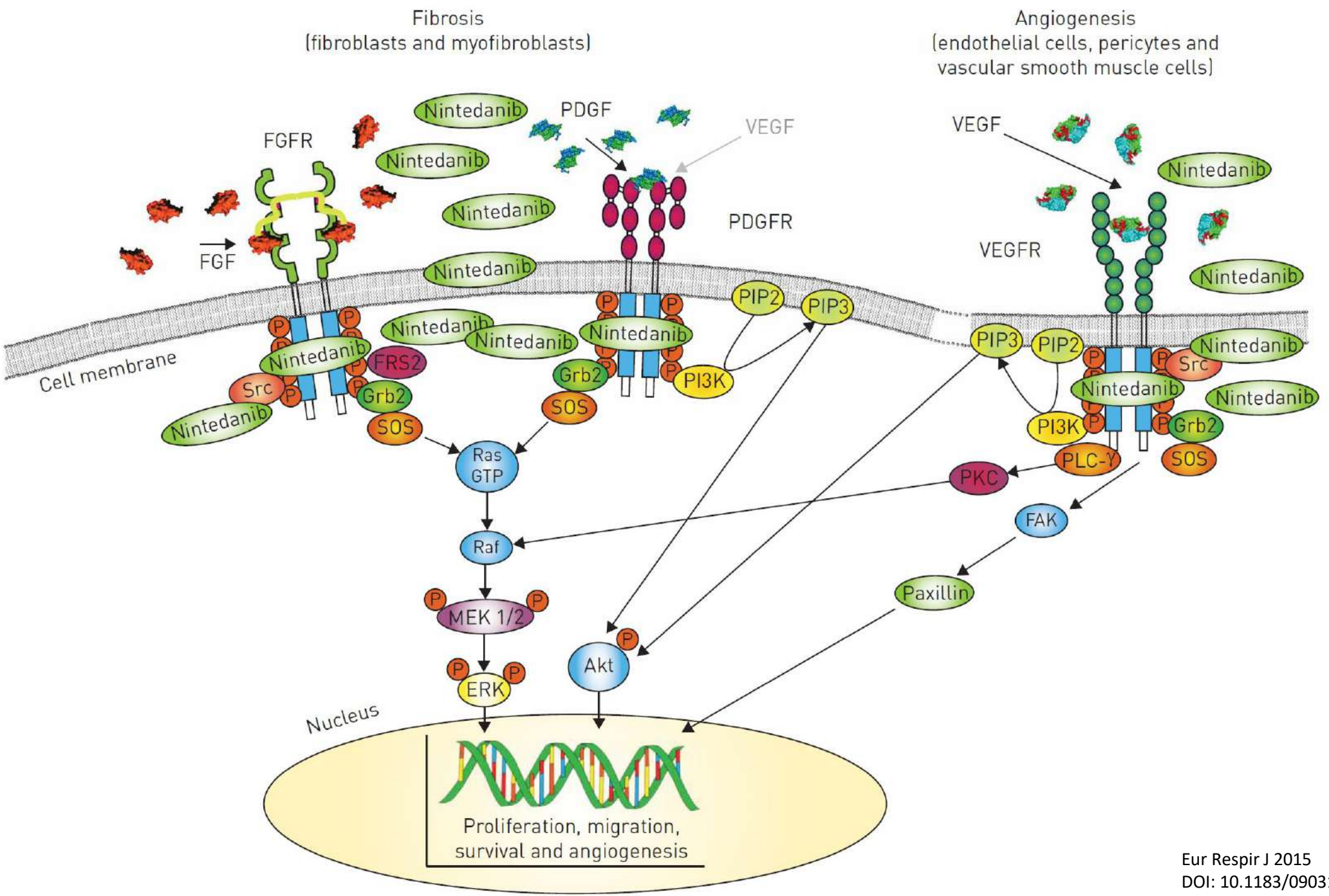
# Patient journey in non-IPF progressive fibrosing ILDs




| | Average time (months) | Average time (months) | Average time (months) | Average time (months) |
|---|---|---|---|---|
| **RA-ILD** | 11.5 | 15.2 | 11.0 | 41.6 |
| **SSc-ILD** | 9.3 | 12.3 | 9.6 | 33.0 |
| **Other CTD-ILDs** | 11.0 | 13.9 | 11.2 | 38.3 |
| **iNSIP** | 9.3 | 12.0 | 8.9 | 31.1 |
| **Unclassifiable IIP** | 10.3 | 11.4 | 9.2 | 29.7 |
| **HP** | 8.6 | 13.6 | 10.4 | 40.0 |
| **Sarcoidosis-ILD** | 8.8 | 14.6 | 11.7 | 45.2 |
| **Other ILDs** | 9.9 | 12.7 | 11.1 | 33.7 |

Curr Med Res Opin. 2019 Nov;35(11):2015-2024



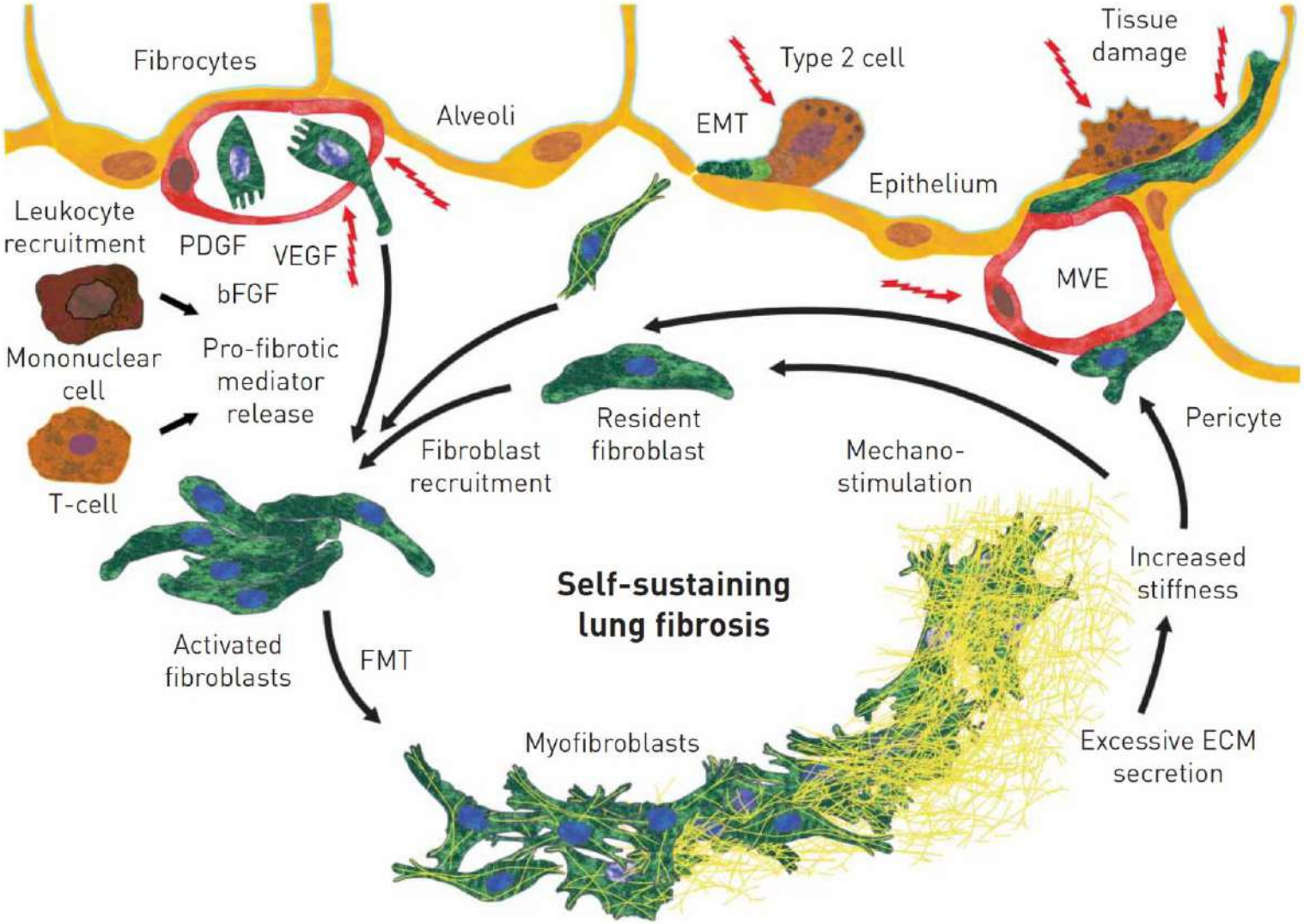

Eur Respir J 2015
DOI: 10.1183/09031936.00174914

# Nintedanib inhibits downstream signaling pathways in the pathogenesis of IPF

| Anti-fibrotic[1–5] | Anti-inflammatory[1-3, 5 -8] | Vascular remodelling[3,8] |
|---|---|---|
| • Profibrotic mediators ↓<br>• Fibroblast proliferation and migration ↓<br>• Fibroblast differentiation ↓<br>• Myofibroblasts in skin and lung ↓<br>• Secretion of extracellular matrix ↓<br>• Lung and skin fibrosis in animal models ↓ | • Interferon-γ ↓<br>• Interleukins 1β, 2, 4, 5, 6, 10, 12p70 and 13↓<br>• TGF-β ↓<br>• Polarisation of M2 macrophages ↓<br>• Neutrophils ↓<br>• Lymphocytes ↓<br>• Inflammation and granuloma in animal models ↓ | • Vascular smooth muscle cells ↓<br>• Microvascular endothelial cells apoptosis ↓<br>• Vessel wall thickness ↓<br>• Occluded vessels ↓<br>• Capillary loss ↓<br>• Distorted microvascular architecture in lungs ↓ |

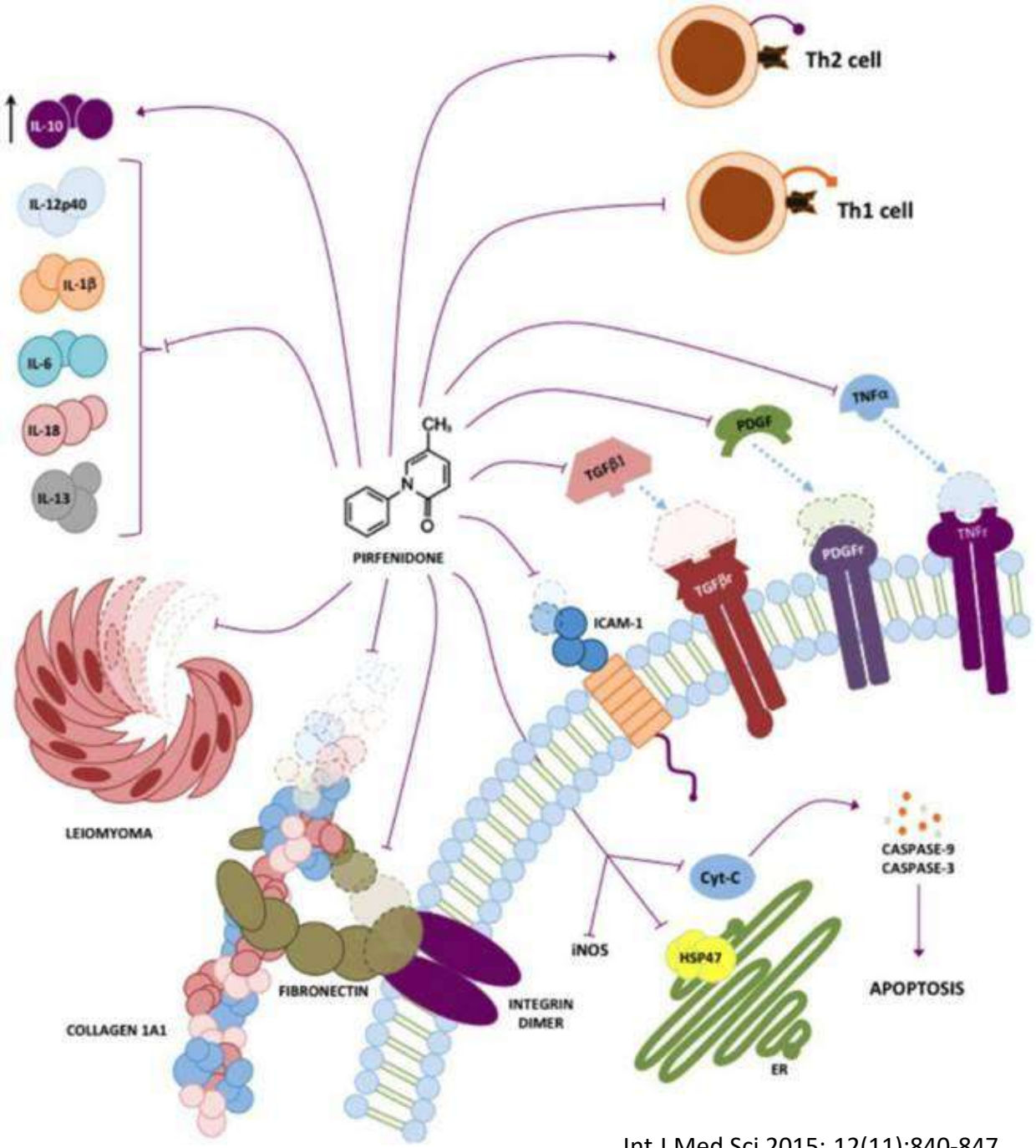
1. Wollin L, et al. Eur Respir J 2015;45:1434–45. 2. Huang J, et al. Ann Rheum Dis 2016;75:883–90. 3. Huang J, et al. Ann Rheum Dis 2017;76:1941-48. 4. Wollin L, et al. Eur Respir J 2017;PA903. 5. Wollin L et al. Am J Respir Crit Care Med 2017;195:A2450. 6. Tandon K, et al. Am J Respir Crit Care Med 2017;195:A2397. 7. Wollin L, et al. J Pharmacol Exp Ther 2014;349:209-220. 8. Ackermann M, et al. Angiogenesis 2017;20:359-372.

# Mechanisms known to be involved in the pathogenesis and progression of fibrosing interstitial lung diseases




Eur Respir J. 2019 Sep 19;54(3)

# Pirfenidone




Int J Med Sci 2015; 12(11):840-847

**Table 2** Prevention of side effects related to pirfenidone

| |
|---|
| **Gastrointestinal side effects (nausea, vomiting, dyspepsia, anorexia)** |
| The drug should be taken with the meal |
| When on two or three capsules, spread the intake during the meal or during the courses in case of a more than one course meal |
| If a side effect is more predominant in a specific time of the day (morning, afternoon, evening), reduce the respective dose |
| Use of prokinetics and protein pump inhibitors may be useful |
| **Skin side effects (photosensitivity reaction, skin rash)** |
| Avoid sun exposure at midday, afternoon, and after the meals |
| Use hats, sunglasses, trousers and shirt with long sleeves, and sunscreen with sun protection factor >50 with protection against UV-A and UV-B |
| Keep in mind that UV-A can penetrate clouds, windows, and clothes |
| **Liver side effects (elevation of ALT/AST)** |
| Blood monitoring every month for the first 6 months and then every 3 months |

**Abbreviations:** UV, ultraviolet; ALT, alanine transaminase; AST, aspartate transaminase.

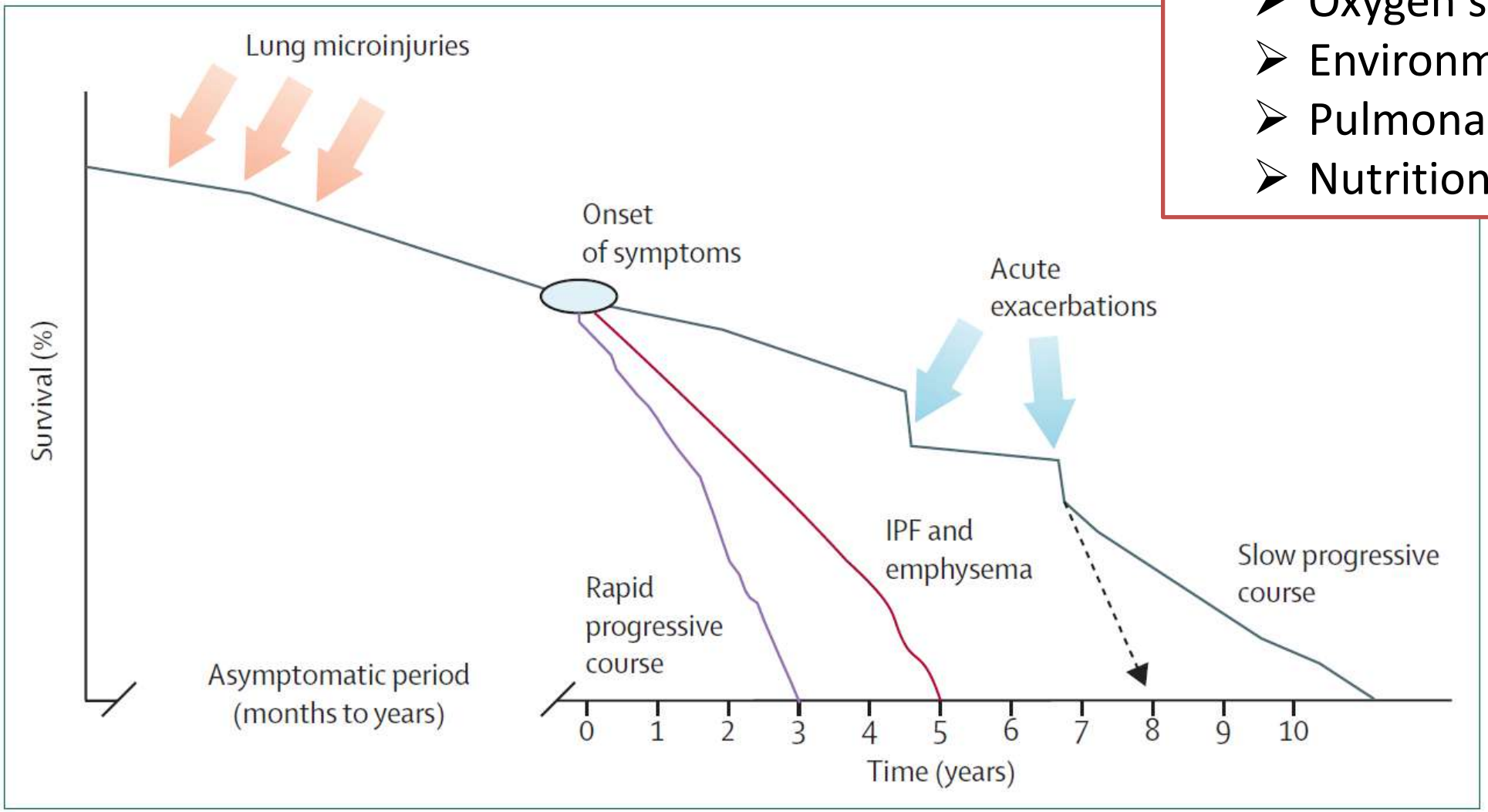
Core Evid. 2016; 11: 11–22.

# Outline

- Concepts on IPF
- Case Discussion
- PF-ILD
- Drug Managements
- Prognosis factors
- Conclusions

# Clinical phenotypes of IPF

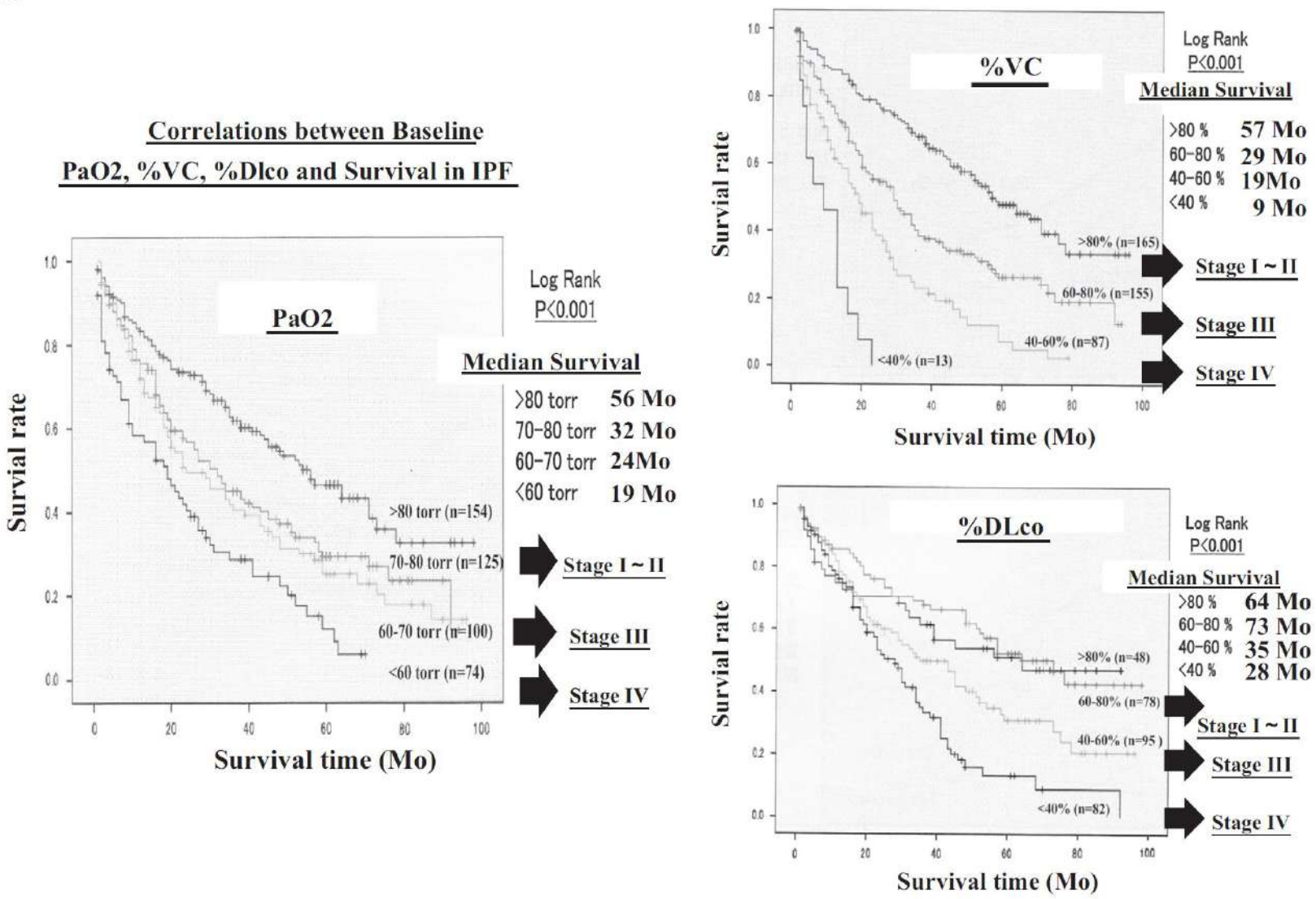
- Unmet need for IPF patients
  - Oxygen support
  - Environmental threats
  - Pulmonary rehabilitations
  - Nutrition and microbiome




Lancet 2011; 378: 1949–61

# Disease severity staging system for IPF in Japan

b




Respir Investig. 2015 Jan;53(1):7-12

# Revised system to improve discriminative ability in stages I and II

**Table 1** Definition of the present and revised Japanese severity staging systems for idiopathic pulmonary fibrosis

| $PaO_2$ | $SpO_2$ < 90% at the end of 6MWT | Present stage | Revised stage |
|---|---|---|---|
| ≥80 Torr | No | I | I |
| | Yes | I | II |
| 70–79 Torr | No | II | II |
| | Yes | III | III |
| 60–69 Torr | No | III | III |
| | Yes | IV | IV |
| <60 Torr | No | IV | IV |
| | Yes | IV | IV |

6MWT, 6-min walk test; $PaO_2$, arterial partial pressure of oxygen; $SpO_2$, pulse oximeter saturation.

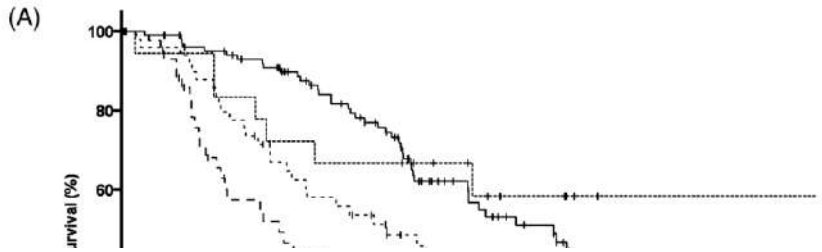
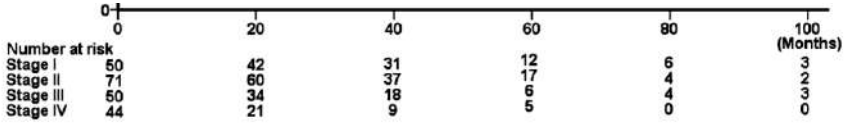



**Table 4** Multivariate analysis for survival

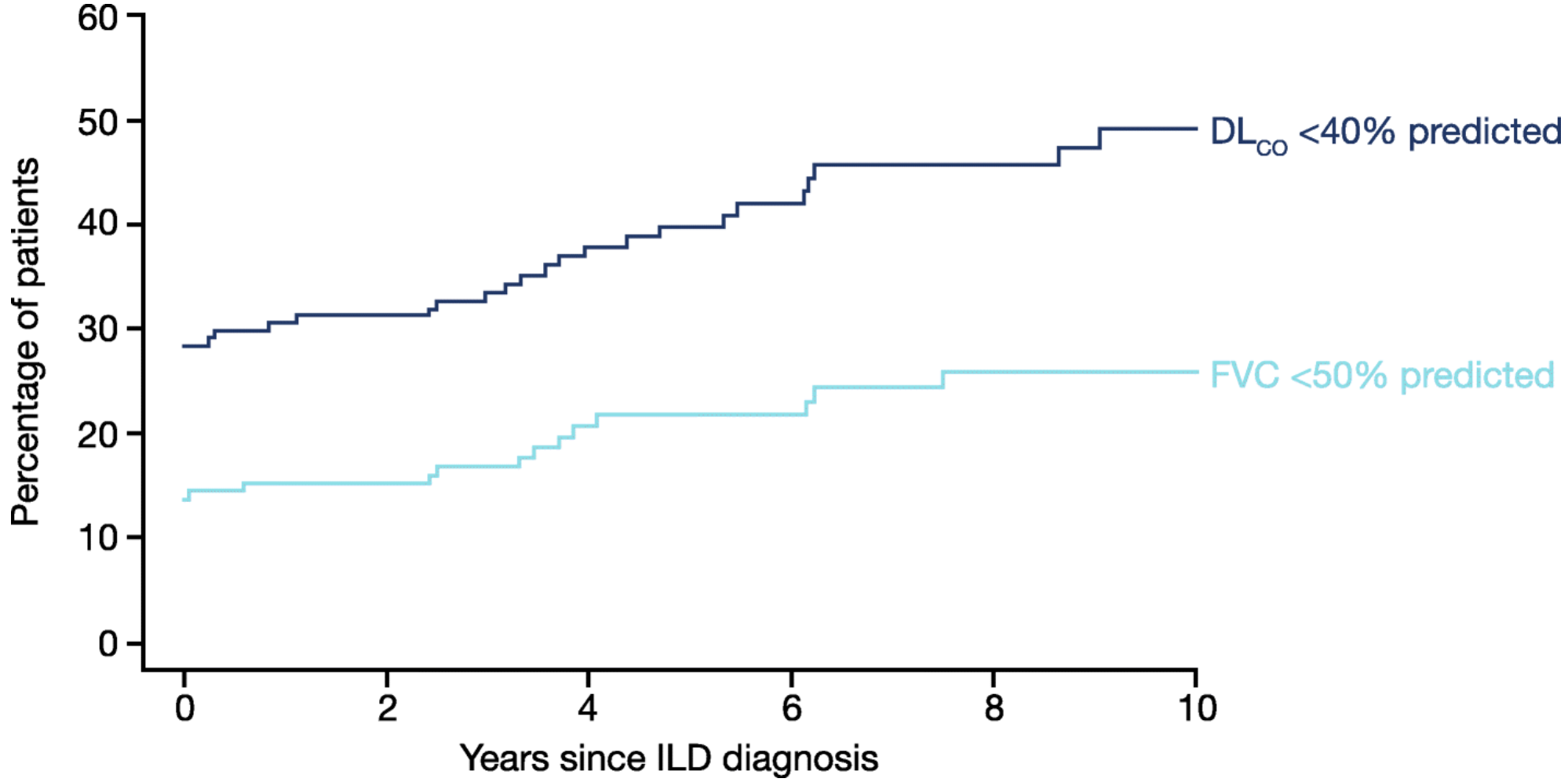
| | HR | 95% CI | *P* |
|---|---|---|---|
| Revised criteria | | | 0.0038 |
| Stage I | 1.000 | — | |
| Stage II | 1.797 | 1.446–2.233 | 0.0006 |
| Stage III | 2.432 | 1.967–3.000 | 0.0074 |
| Stage IV | 3.690 | 1.754–7.752 | 0.1236 |
| Modified GAP† | | | 0.0029 |
| Stage I | 1.000 | — | — |
| Stage II | 1.641 | 1.574–1.716 | 0.0008 |
| Stage III | 2.915 | 1.560–5.464 | 0.0537 |

†$n$ = 194.
GAP, gender, age and physiology; HR, hazard ratio.



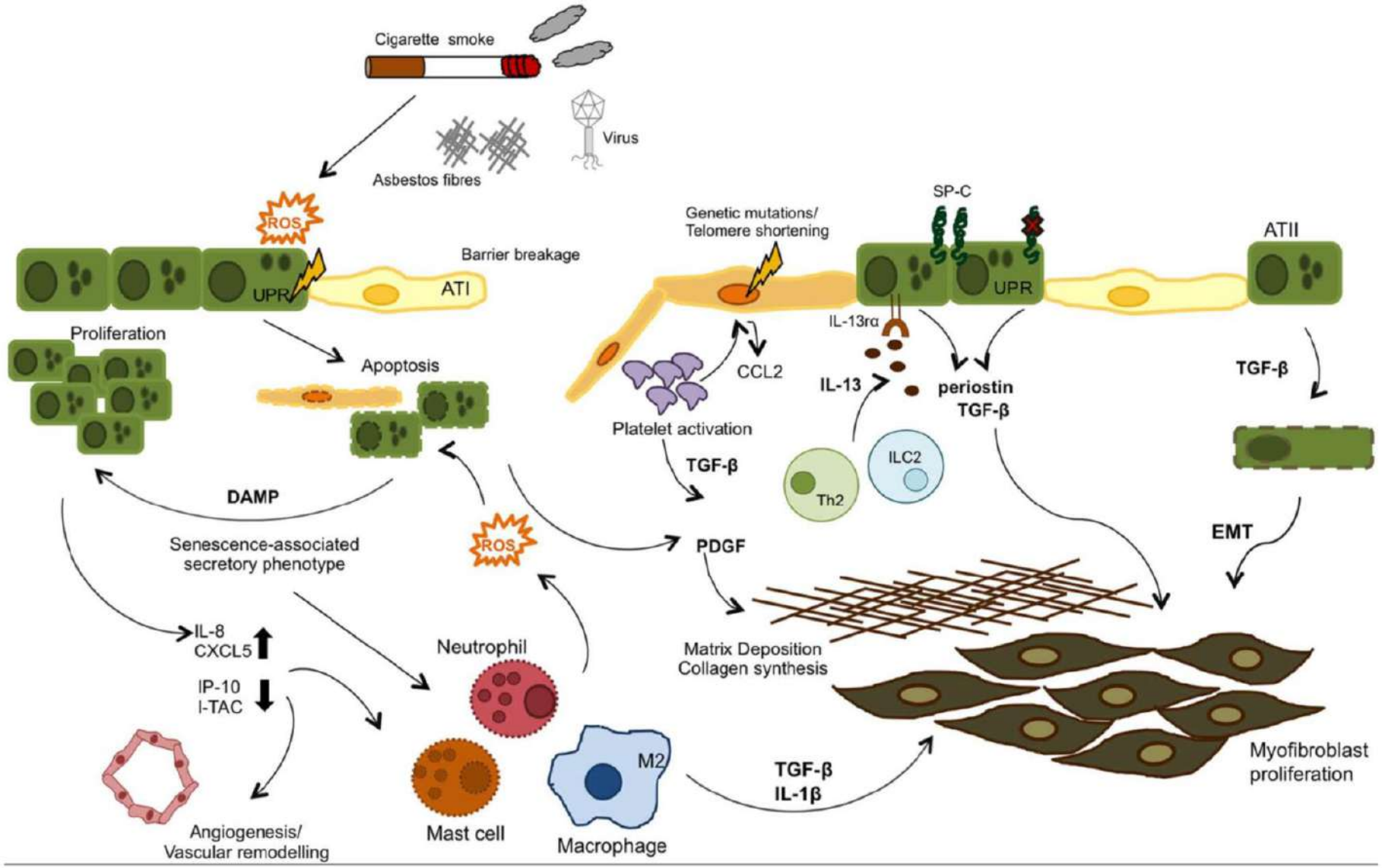

Respirology. 2017 Nov;22(8):1609-1614

# The proportions of patients with FVC < 50% predicted and DLco < 40% predicted in the 10 years from diagnosis of ILD associated with RA



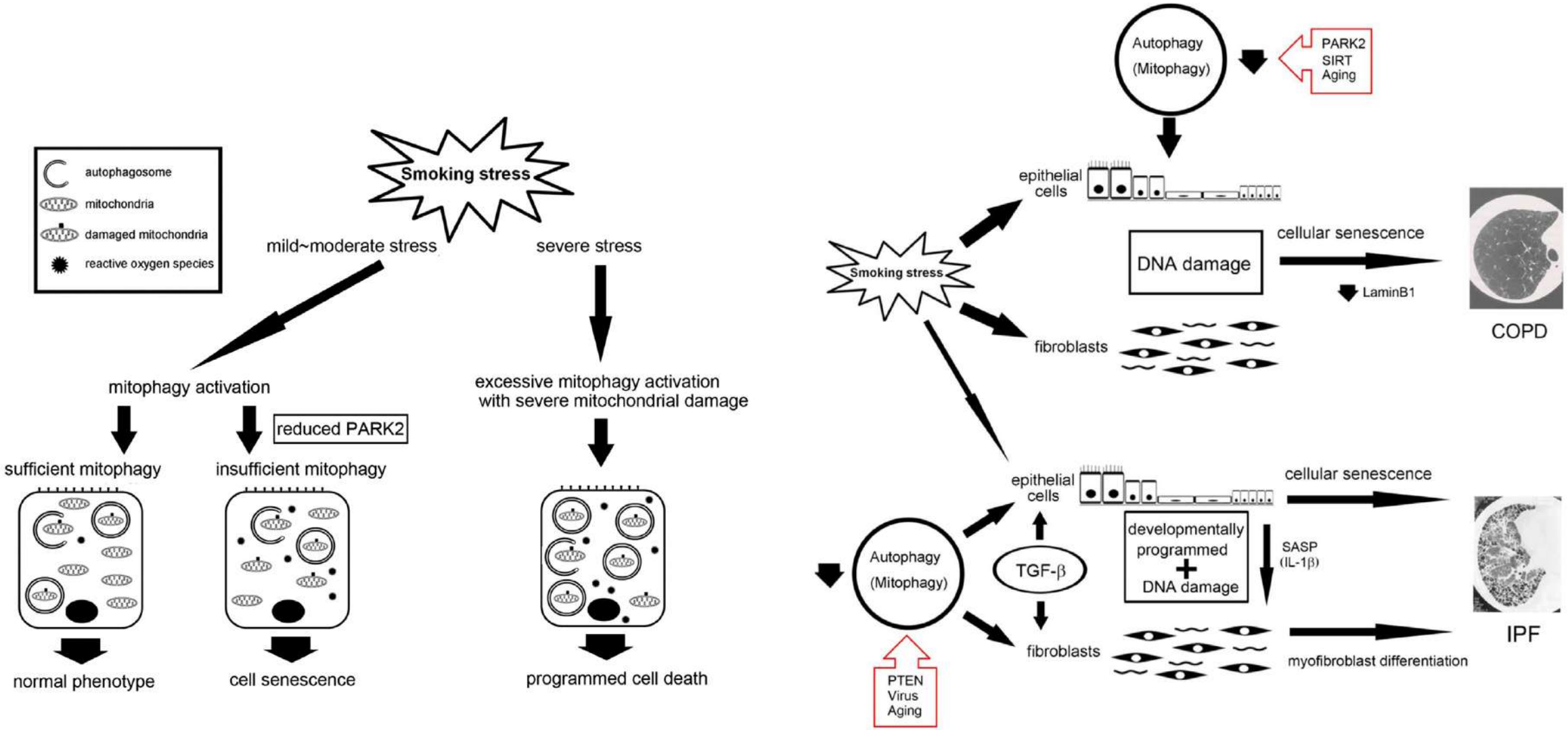

Respiratory Research volume 20, Article number: 57 (2019)

# Airway remodeling can be initiated by either aberrant epithelial cell (genetic mutations) or exposure to external irritants

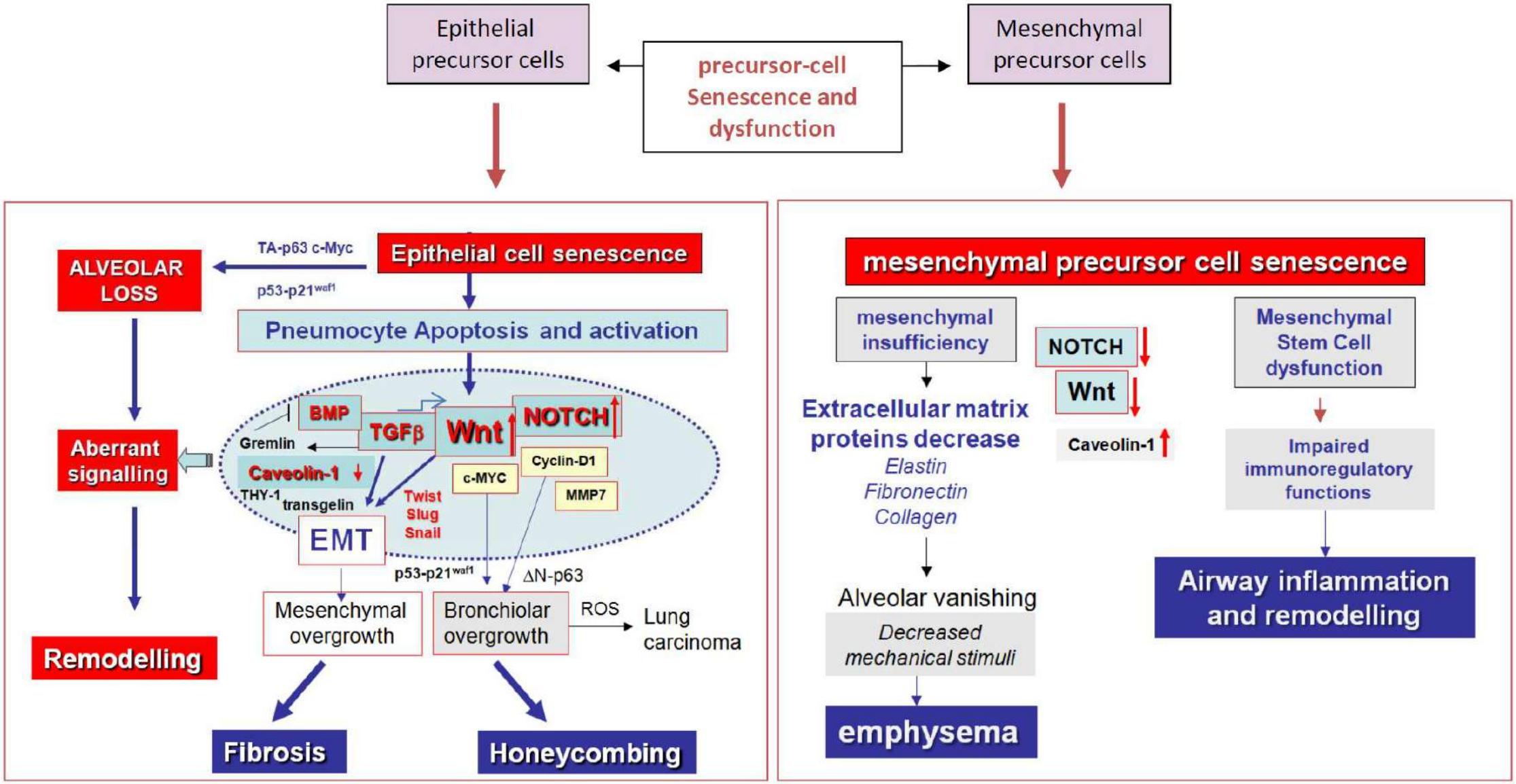



Front. Pharmacol., 10 January 2014

# Potential involvement of cell senescence in both COPD and IPF pathogenesis

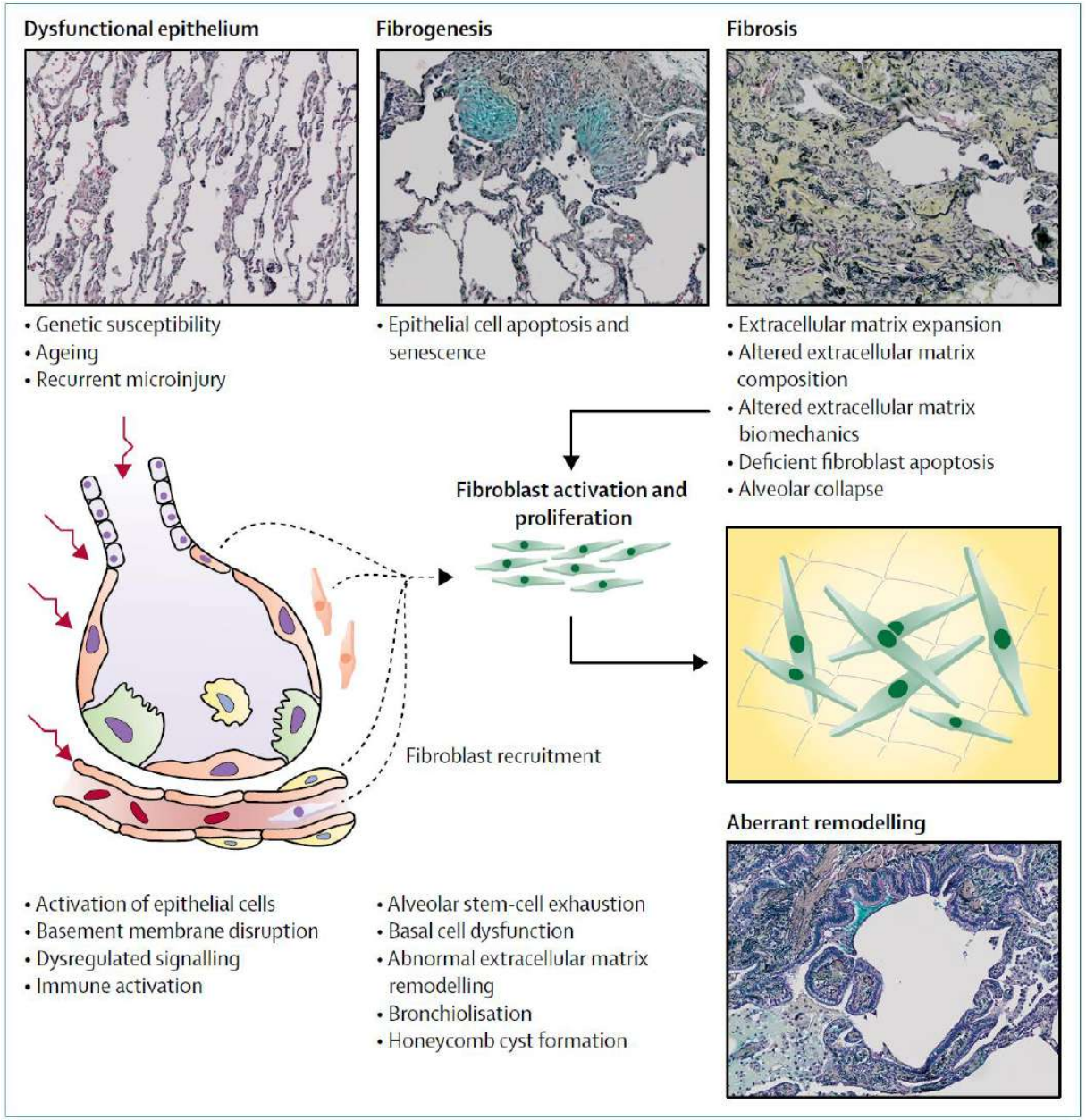


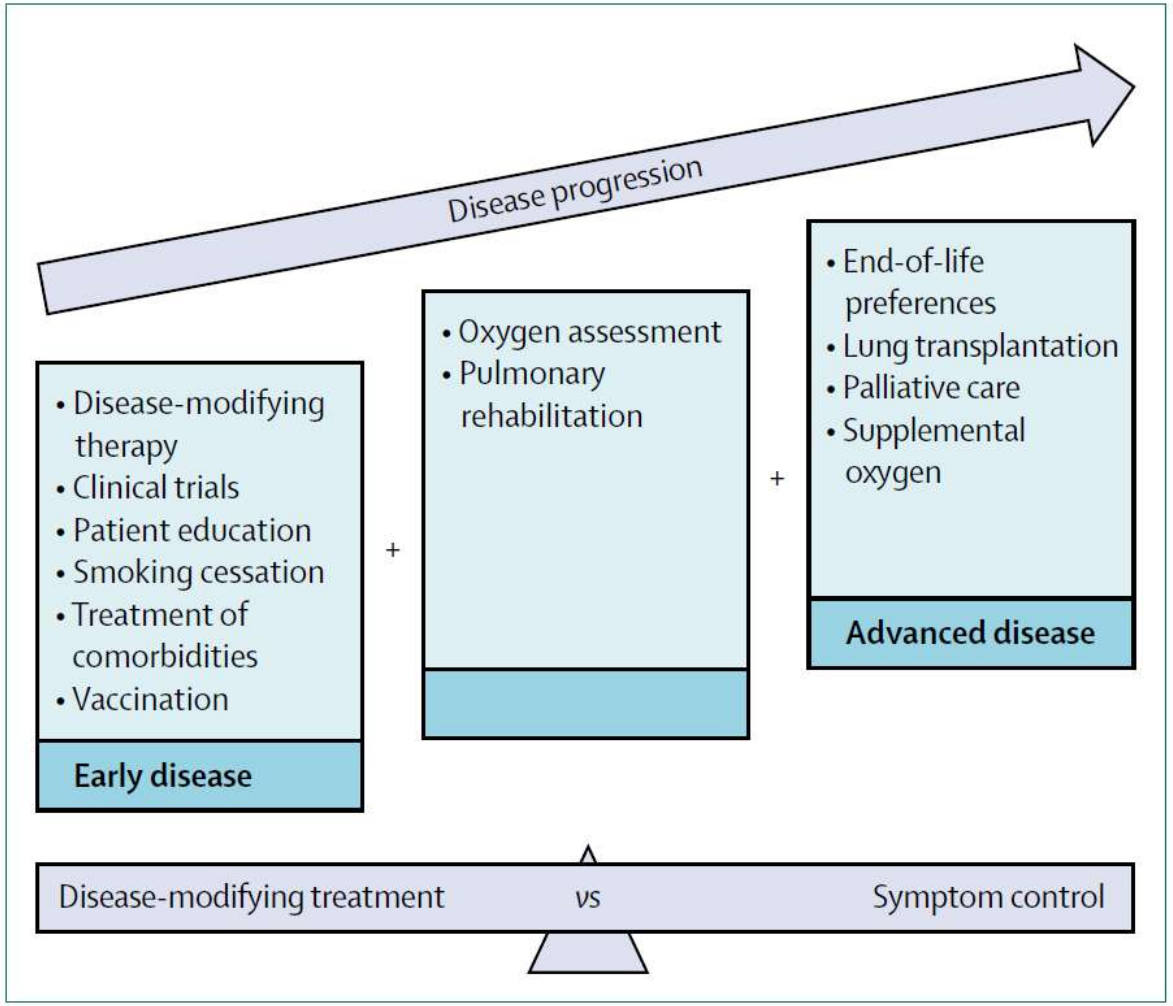

Respir Investig. 2016 Nov;54(6):397-406




Chilosi et al. Respiratory Research 2012, 13:3

# Idiopathic pulmonary fibrosis: Proposed Mechanisms and Managements




Lancet. 2017 May 13;389(10082):1941-1952

# Disease-modifying therapy in IPF

***Panel:*** **Therapies identified in clinical trials as harmful, ineffective, or effective in the treatment of idiopathic pulmonary fibrosis**

**Potentially harmful therapies**

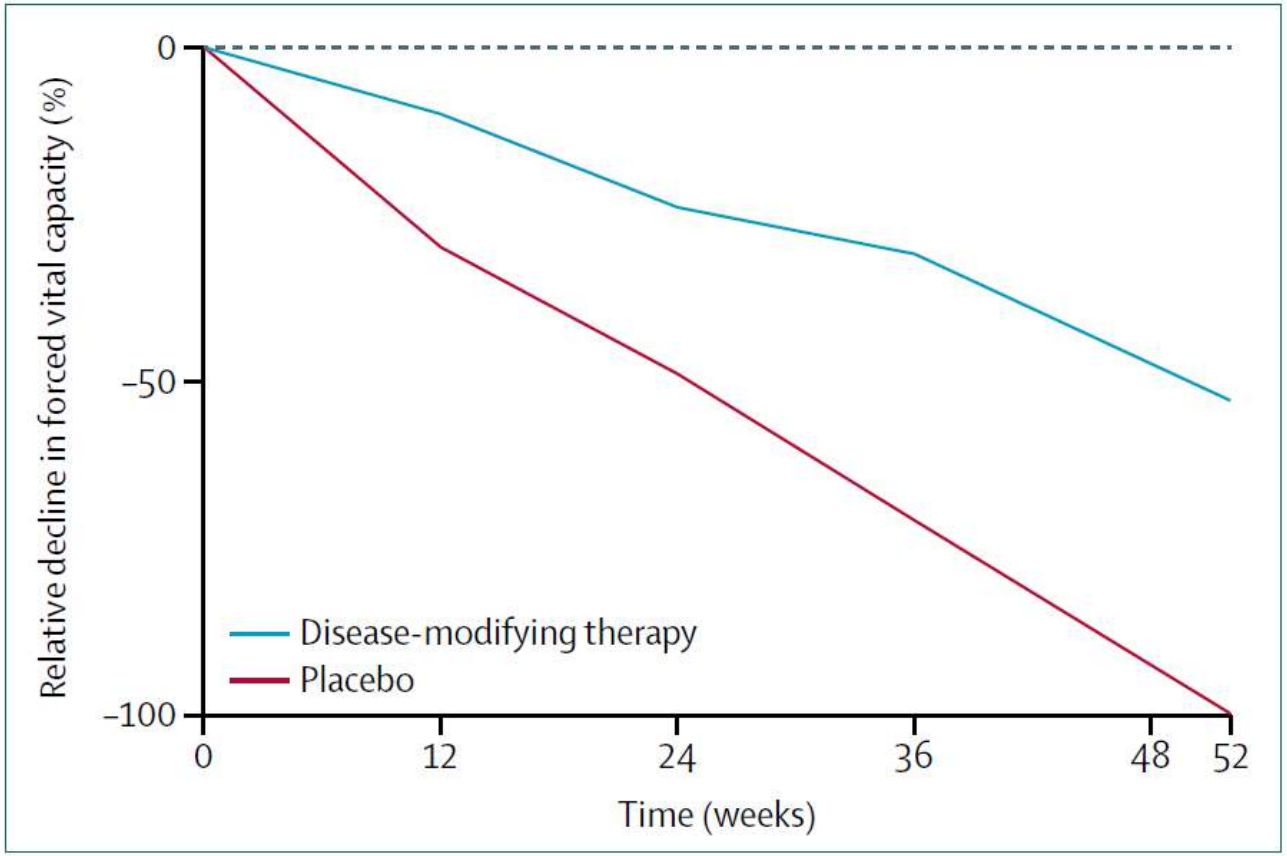
- Ambrisentan[81]
- Everolimus[82]
- Prednisolone, azathioprine, acetylcysteine[9]
- Warfarin[83]

**Potentially ineffective therapies**

- Bosentan[84]
- Imatinib[85]
- Macitentan[86]
- Acetylcysteine[87]
- Sildenafil[88]

**Effective disease-modifying therapies**

- Nintedanib[89]
- Pirfenidone[90,91]

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# Updates on PF-ILD

- Concepts on IPF
- Case Discussion
- PF-ILD
- Drug Managements
- Prognosis factors
- Conclusions

# Conclusions

- Progressive fibrosing interstitial lung diseases are of different etiologies, and responses to treatments
  - Carefully chosen disease modify therapy may help to reduce the disease progressions and clinical impacts

- Nintedanib reduces the rate of ILD progression, as measured by FVC decline, in patients who have a chronic fibrosing ILD and progressive phenotype, irrespective of the underlying ILD diagnosis


Thanks for the Attentions!