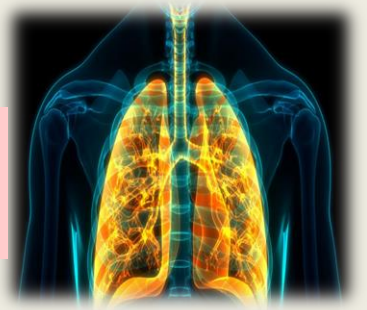
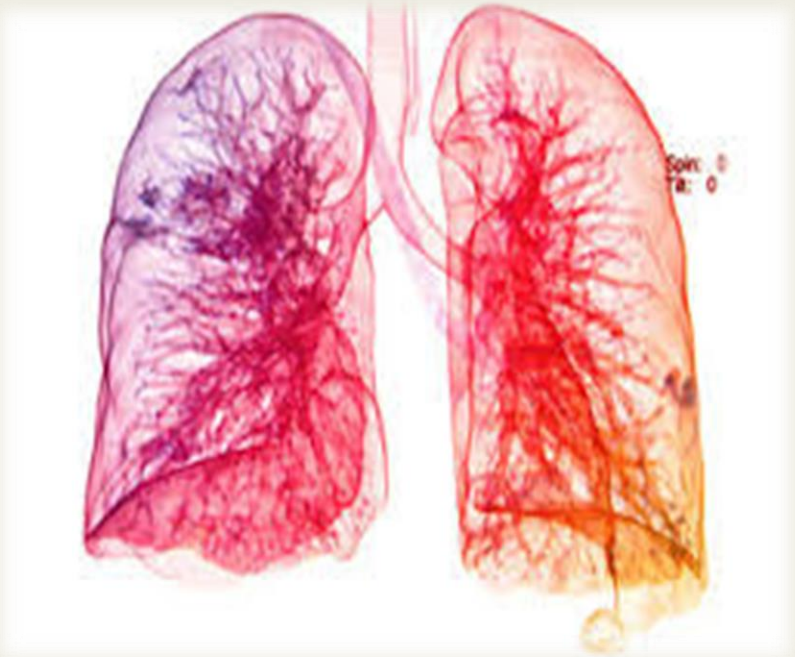
Faculté de Médecine de Tlemcen - Univ-Tlemcen
Dr Damerdji Benaouda

LABORATORY OF RESEARCH ON DIABETES
9 th CONGRESS OF AMIWIT
3d SEMINARY OF LAREDIAB



Fibrose pulmonaire idiopathique: progrès thérapeutiques et place des antifibrotiques



Dr A.Djenfi
Maitre-assistant en pneumo-phtisiologie
Faculté de médecine Tlemcen
Département de médecine

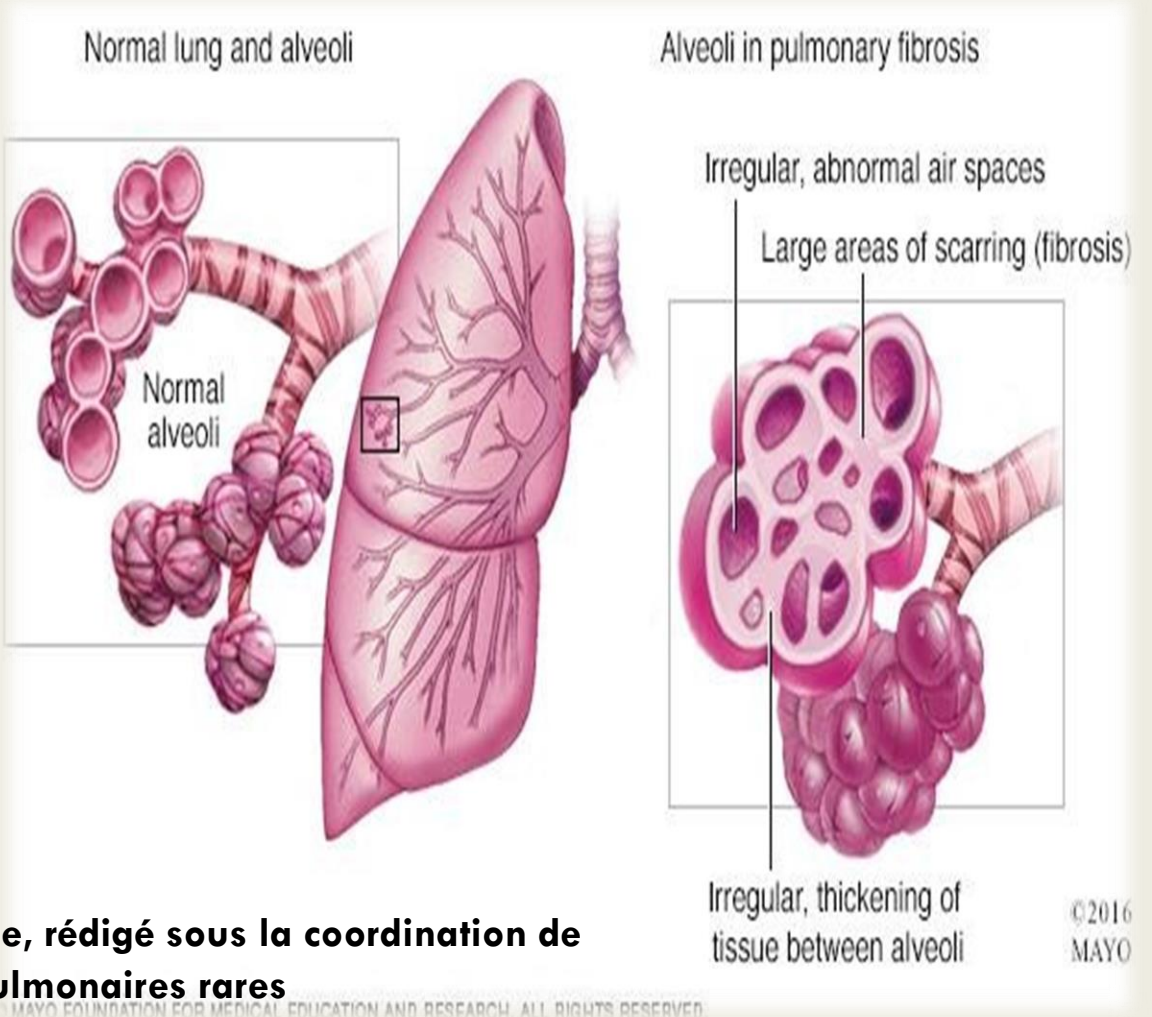
Wednesday 15 December 2021

Definition:

La FPI est caractérisée par une fibrose progressive et irréversible du parenchyme pulmonaire, de cause inconnue, et limitée aux poumons.

Cette maladie grave évolue de façon chronique et progressive, avec de possibles exacerbations aiguës.

La FPI est définie par un aspect radiologique et/ou histopathologique de pneumopathie interstitielle commune (PIC) en l'absence de cause identifiée.



Protocole national de diagnostic et de soins, Fibrose pulmonaire idiopathique, rédigé sous la coordination de Pr Vincent Cottin, 2021, centre de référence des maladies pulmonaires rares

Pneumopathies interstitielles diffuses (PID)

PID idiopathiques

- **FPI**
- PINS idiopathique
- Bronchiolite respiratoire avec PID
- PI desquammative
- Pneumopathie organisée cryptogénétique
- PI aiguë
- PI lymphocytaire
- Fibro-élastose pleuro-parenchymateuse
- PID idiopathiques inclassables

PID auto-immunes

- PI avec manifestations auto-immunes
- Vascularite à ANCA
- Sclérodermie systémique
- Polyarthrite rhumatoïde
- Polymyosite et dermatomyosite
- Connectivite mixte
- Syndrome de Gougerot-Sjögren
- Lupus érythémateux systémique
- Autres connectivites

PID d'hyper-sensibilité

Granulomatoses et histiocytoses

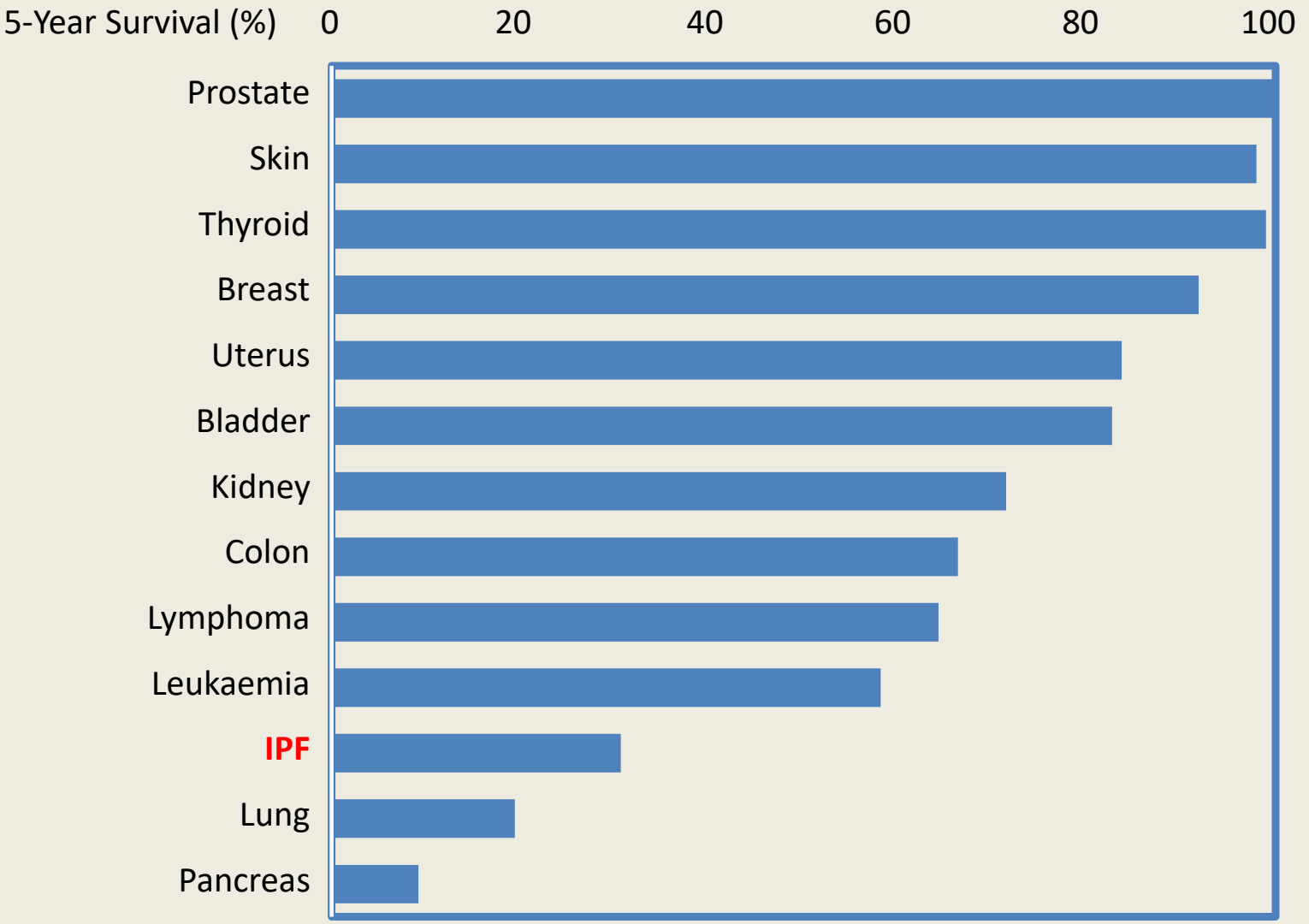
- Sarcoïdose
- Histiocytose pulmonaire à cellules de Langerhans
- Autres granulomatoses

Autres PID

- Associées à des expositions médicamenteuses
- Associées à des expositions professionnelles
- PID à éosinophiles
- Lymphangioléiomyomatose
- Autres PID rares

Cottin et al. *Eur Respir Rev* 2018
PNDS, FPI 2021

IPF: PROGNOSIS WORSE THAN MOST CANCERS



Vancheri et al, *Eur Respir J* 2010; 35: 496-504

Fibrose pulmonaire idiopathique : Aspects clinique

"MISTER IPF"

- 65 year old man
- Former smoker
- Dyspnea on exertion
- Chronic dry cough
- 95% room air saturation
- Basilar "velcro-type" crackles
- Typical or suggestive HRCT
- PFTs: Mixed restriction/obstruction with a low DLCO
- Often previously diagnosed with a different lung disease (concomitant emphysema in 30%)

Case courtesy of Prof.Luca Richeldi

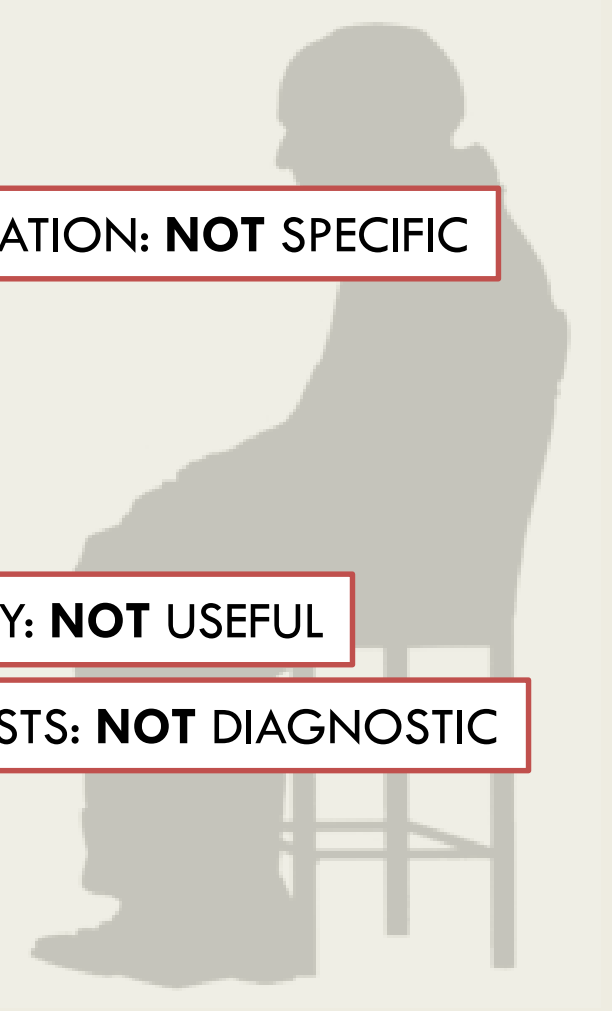
"MISTER IPF"

- 65 year old man
- Former smoker
- Dyspnea on exertion
- Chronic dry cough
- 95% room air saturation
- BMI = 35
- Basilar "velcro-type" crackles
- Typical or suggestive HRCT
- PFTs: Mixed restriction/[illegible] with a low DLCO
- Often previously diagnosed with a different lung disease (concomitant emphysema in 30%)

CLINICAL PRESENTATION: **NOT** SPECIFIC

CHEST X RAY: **NOT** USEFUL

LUNG FUNCTION TESTS: **NOT** DIAGNOSTIC

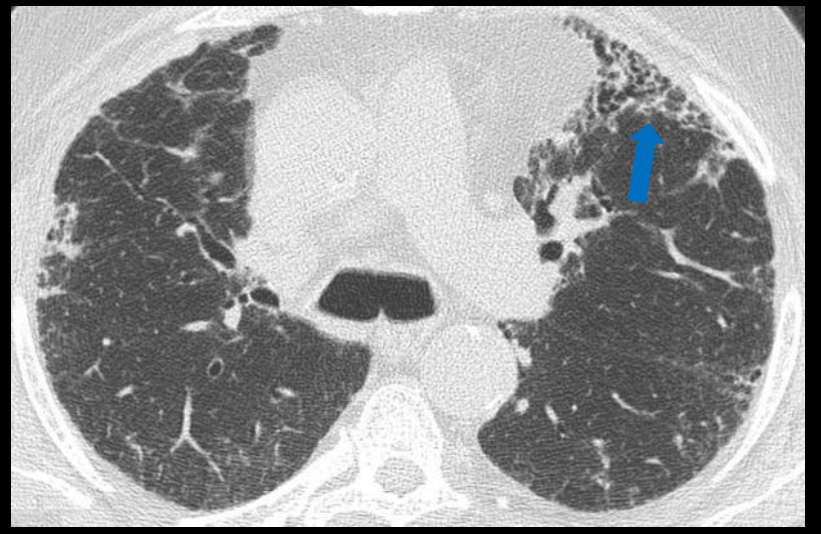


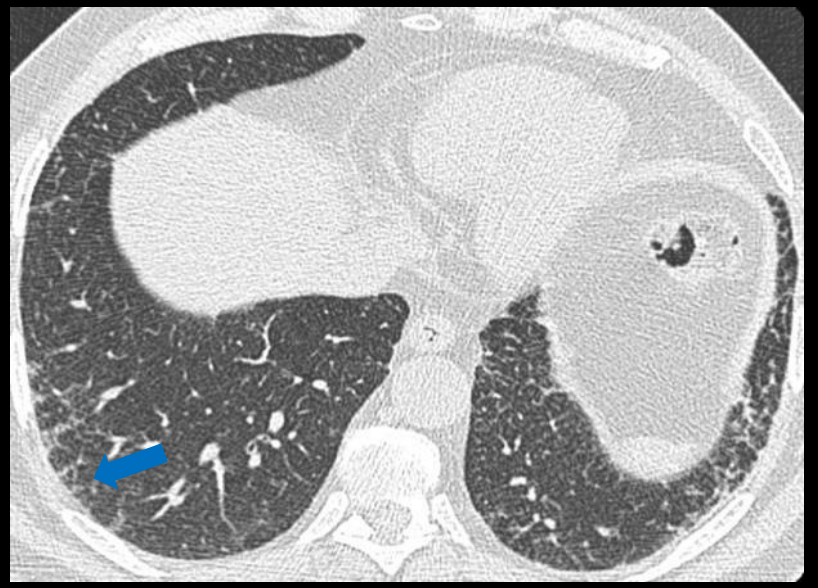
Case courtesy of Prof.Luca Richeldi

Aspects radiologiques :

Pattern de PIC	Pattern de PIC probable	Indéterminé pour PIC		évoquant un diagnostic alternatif
• Prédominance basale et sous pleurale ➢ Souvent hétérogène, ➢ Parfois diffuse ➢ parfois asymétrique	• Prédominance basale et sous-pleurale ➢ Souvent hétérogène	• Prédominance basale et sous-pleurale	• Signes de fibrose sans orientation particulière (tableau de fibrose inclassable)	• Prédominance supérieure/moyenne • Prédominance péri-bronchovasculaire • Distribution périlymphatique
• Rayon de miel	• Réticulations • Bronchectasies ou bronchiolectasies de traction périphériques	• Discrètes réticulations ± verre dépoli et/ou distorsion (tableau de PIC débutante)		• Verre dépoli prédominant • Condensations • Mosaïque / trapping extensif • Nodules et micronodules centrolobulaires • Micronodules profus • Kystes diffus
± Bronchectasies ou bronchiolectasies de traction périphériques Verre dépoli discret Réticulations Ossifications pulmonaires	± Verre dépoli discret			

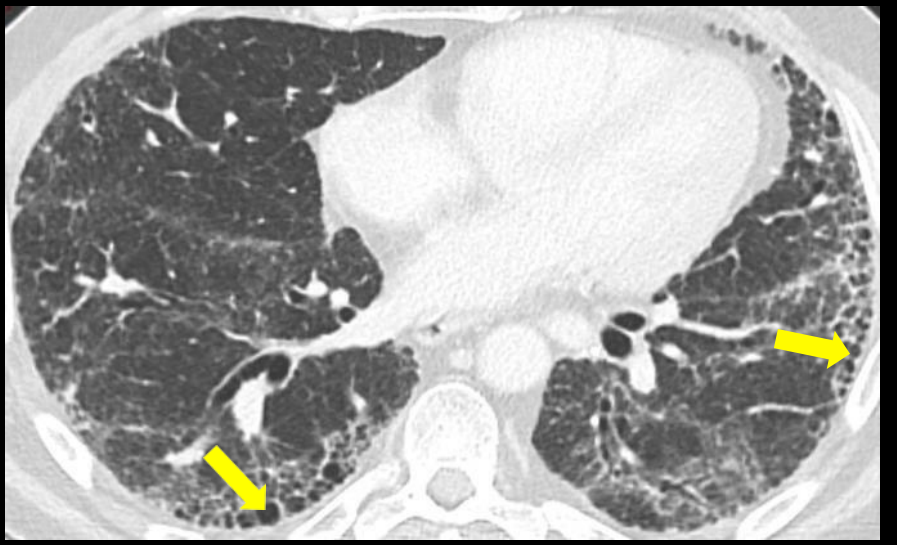
D'après Raghu G, *et al.* An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2018
Lynch *et al. Lancet Respir Med* 2017

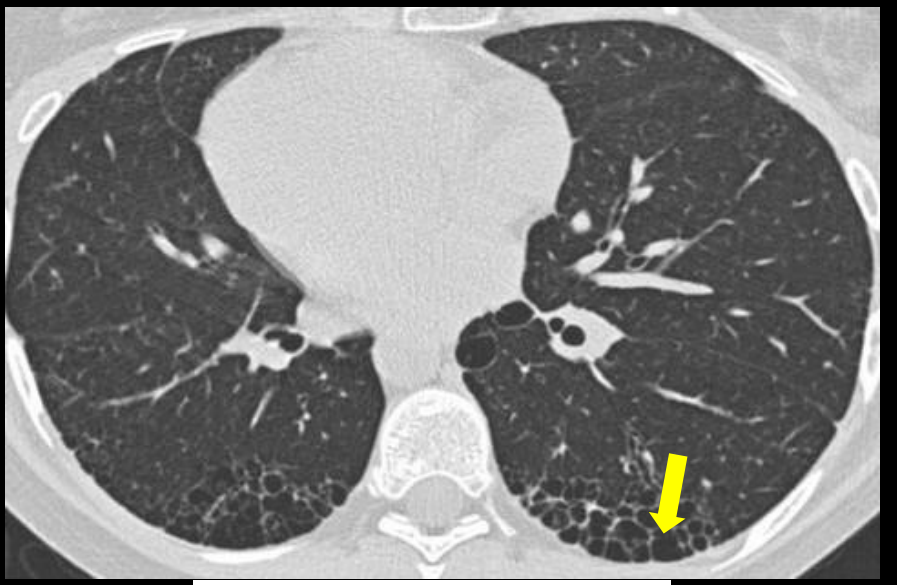




Réticulations

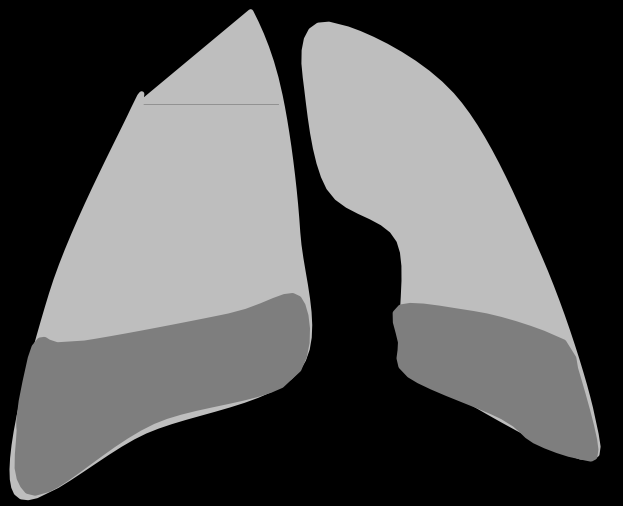
- Le plus souvent intra-lobulaires
- Lésions septales associées possibles mais non prédominantes, souvent déformées



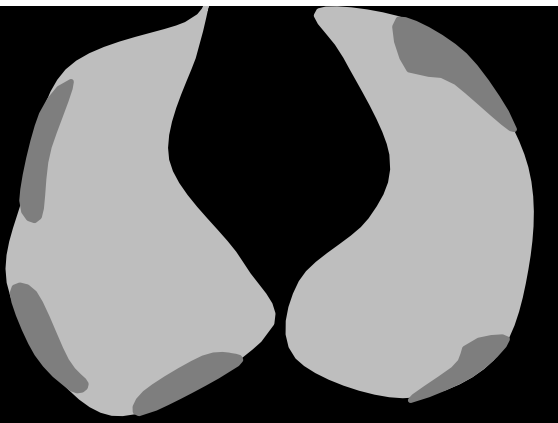


Rayon de miel

Espaces aériens juxtaposés
- de taille proche (3-10 mm le plus souvent, parfois
- délimités entre eux par une paroi bien définie
- habituellement dans les régions sous-pleurales.

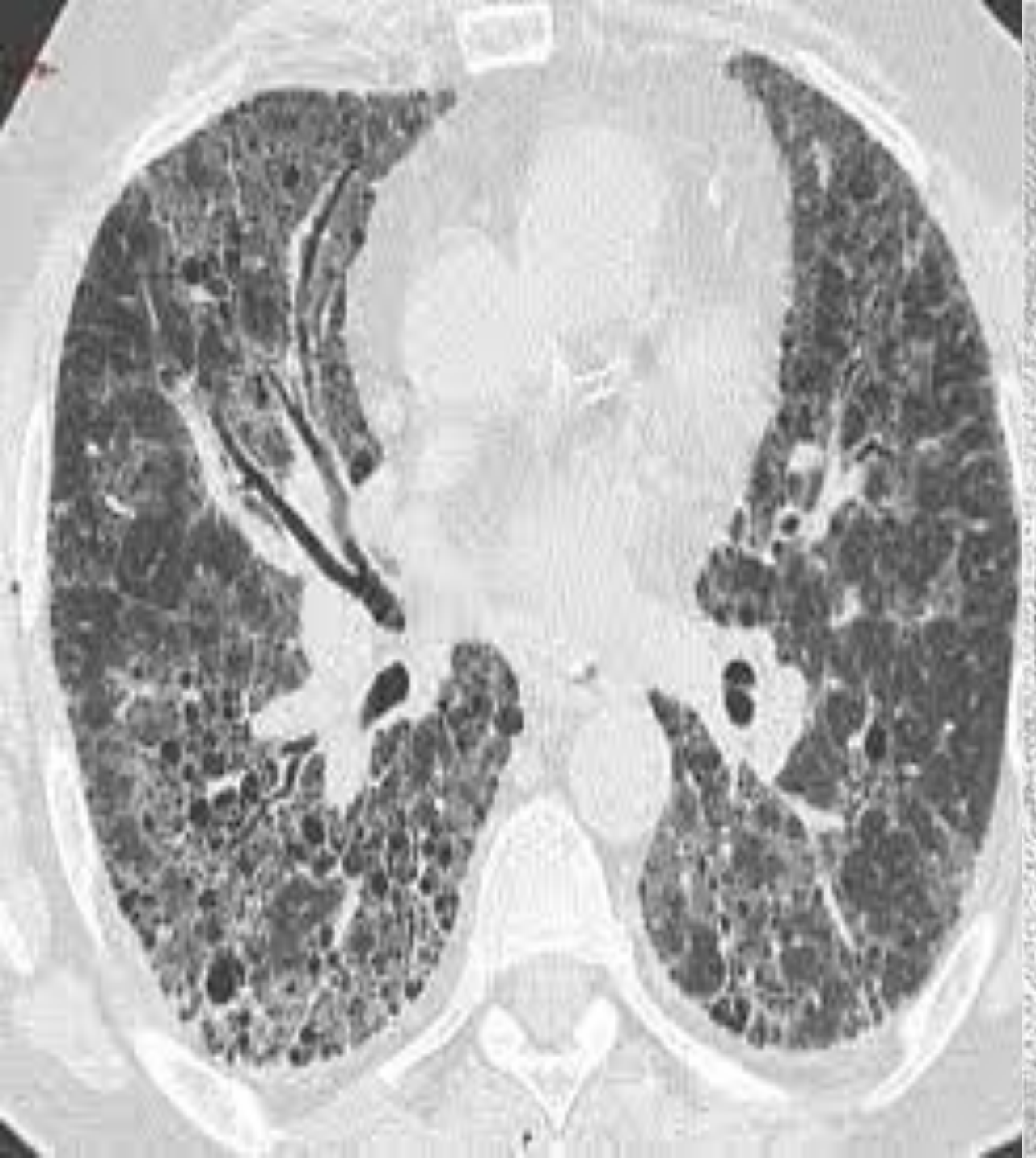


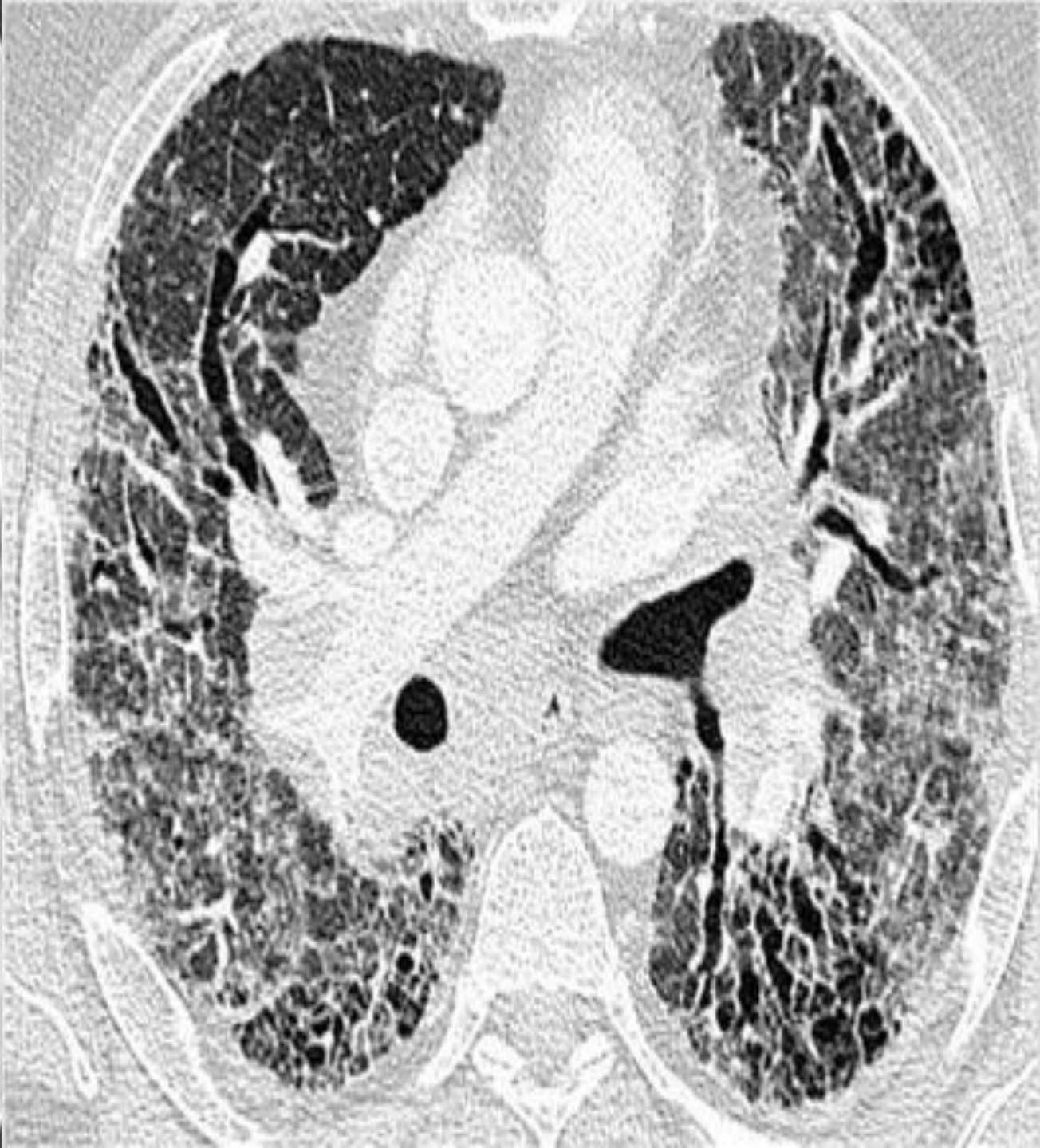
Prédominance basale

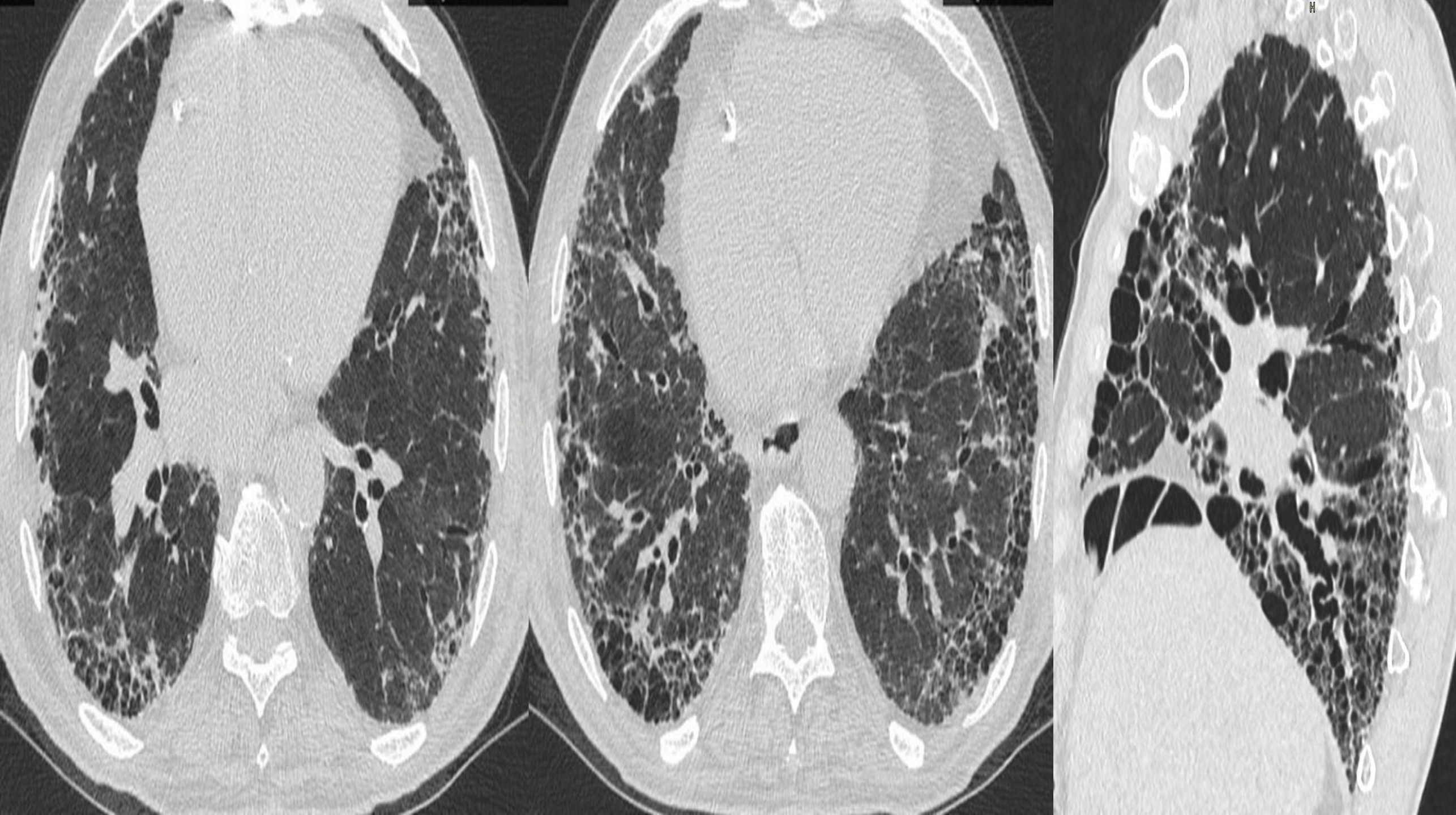


Prédominance sous-pleurale

Kit pour Radiologue BI







Aspects anatomopathologiques :

PIC **Présence des 4 critères**	PIC probable	PIC possible **Présence des 3 critères**	Non PIC **Présence d'1 critère**
▪Fibrose/ distorsion architecturale ± Rayon de Miel sous-pleural, de distribution paraseptale ▪Atteinte hétérogène ▪Foyers fibroblastiques ▪Absence d'élément pour un diagnostic differentiel	▪Fibrose/ distorsion architecturale ± Rayon de Miel sous-pleural, de distribution paraseptale ▪ Absence du caractère hétérogène de l'atteinte **ou** des Foyers fibroblastiques ▪Absence d'élément pour un diagnostic differentiel ou ▪**Rayon de miel isolé**	▪Atteinte fibreuse heterogène ou diffuse avec ou sans inflammation interstitielle ▪Absence d'autres critères pour PIC ▪Absence d'éléments pour un diagnostic différentiel	▪Membranes hyalines ▪Pneumonie organisée ▪Granulomes ▪Inflammation marquée à distance du rayon de miel ▪Atteinte centrée par les bronches ▪Autres éléments de diagnostic différentiel

D'après Raghu G, *et al*. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2018
Lynch *et al. Lancet Respir Med* 2017

Fibrose pulmonaire idiopathique : diagnostic + :

An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management

Ganesh Raghu, Harold R. Collard, Jim J. Egan, Fernando J. Martinez, Juergen Behr, Kevin K. Brown, Thomas V. Colby, Jean-François Cordier, Kevin R. Flaherty, Joseph A. Lasky, David A. Lynch, Jay H. Ryu, Jeffrey J. Swigris, Athol U. Wells, Julio Ancochea, Demosthenes Bouros, Carlos Carvalho, Ulrich Costabel, Masahito Ebina, David M. Hansell, Takeshi Johkoh, Dong Soon Kim, Talmadge E. King, Jr., Yasuhiro Kondoh, Jeffrey Myers, Nestor L. Müller, Andrew G. Nicholson, Luca Richeldi, Moisés Selman, Rosalind F. Dudden, Barbara S. Griss, Shandra L. Protzko, and Holger J. Schünemann, on behalf of the ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis

AJRCCM 2011;183:788-824

Diagnosis of Idiopathic Pulmonary Fibrosis

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

American Journal of Respiratory and Critical Care Medicine Volume 198 Number 5 | September 1 2018

Fibrose pulmonaire idiopathique : diagnostic + :

Exposition environnementale
Connectivite
Toxicité médicamenteuse

Le diagnostic positif de FPI repose sur la combinaison suivante de critères :

1.. Exclusion des autres causes possibles de PID

2. Identification d'un aspect de PIC au scanner

3. Combinaison d'aspects tomodensitométriques et histo-pathologiques

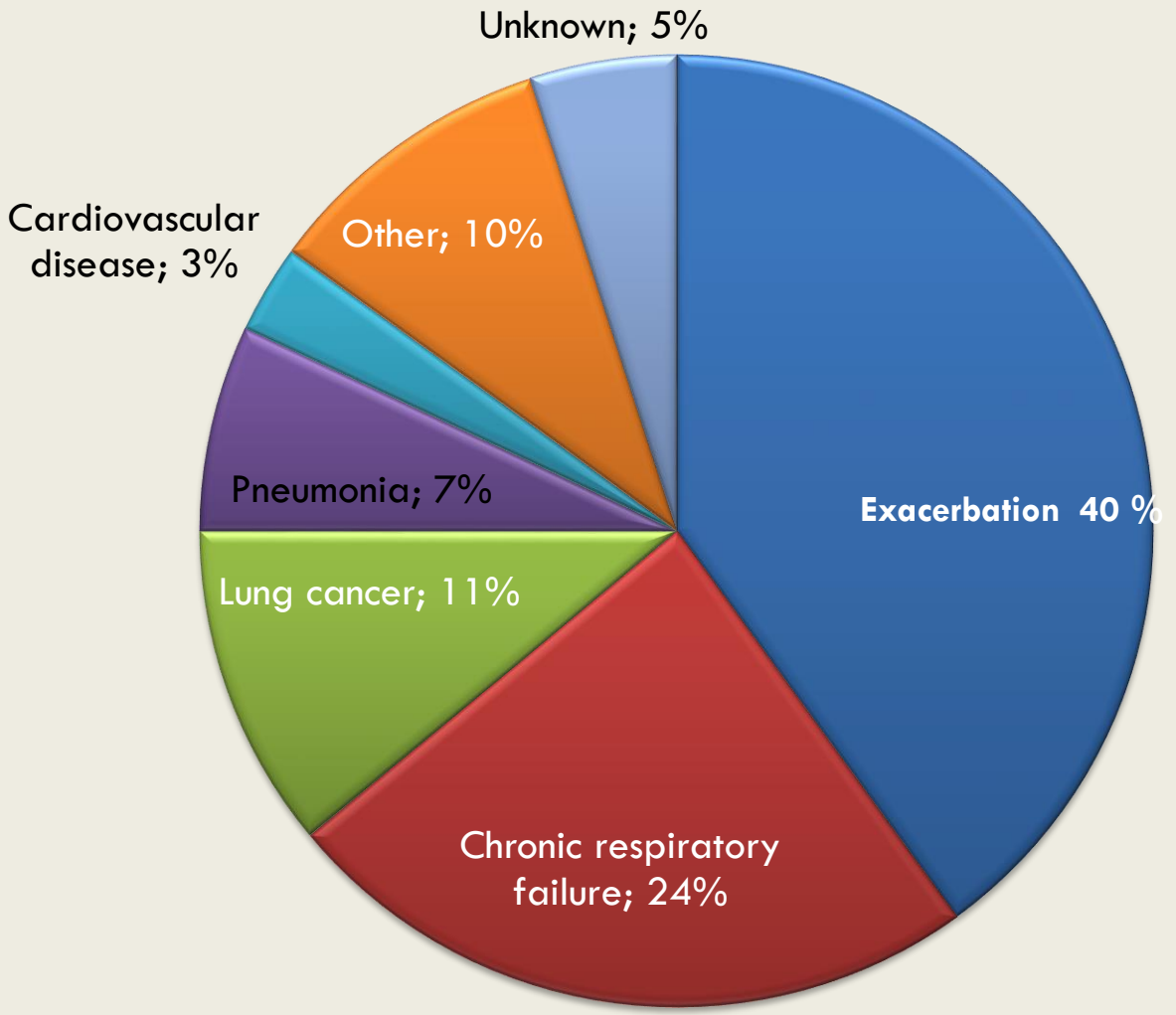
Surgical lung biopsy is an invasive procedure that many patients are unable to undergo[2]

La présence d'un pattern UIP radiologique et/histologique seul **ne suffit pas à poser le diagnostic.**

CONCERTATION MULTIDISCIPLINAIRE

1. Raghu G *et al. Am J Respir Crit Care Med* 2011;183:788–824 2. Martinez FJ *et al. Lancet Respir Med* 2017;5:61–71

IPF: CAUSE OF DEATH



Modified from *AJRCCM* 2014;190:773

Fibrose pulmonaire idiopathique : Traitement :

Jusqu'en 2011,

Prednisone + AZA + NAC

=

le standard thérapeutique

...Mais efficacité contre placebo non démontrée !

- Avis d'experts (consensus ATS/ERS 2000)
- Résultats IFIGENIA

An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management

Am J Respir Crit Care Med Vol 183. pp 788–824, 2011
DOI: 10.1164/rccm.2009-040GL
Internet address: www.atsjournals.org

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis

An Update of the 2011 Clinical Practice Guideline

Ganesh Raghu, Bram Rochwerg, Yuan Zhang, Carlos A. Cuello Garcia, Arata Azuma, Juergen Behr
Harold R. Collard, William Cunningham*, Sakae Homma, Takeshi Johkoh, Fernando J. Martinez, Je
Shandra L. Protzko, Luca Richeldi, David Rind, Moises Selman, Arthur Theodore, Athol U. Wells, H
and Holger J. Schünemann; on behalf of the ATS, ERS, JRS, and ALAT

This guideline is dedicated to the memory of Mr. William Cunningham (June 7, 1935–October 23, 2

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE OF THE AMERICAN THORACIC SOCIETY (ATS) WAS APPROVED BY THE ATS, MAY 2015, THE
SOCIETY (ERS), APRIL 2015, THE JAPANESE RESPIRATORY SOCIETY (JRS), APRIL 2015, AND THE LATIN AMERICAN THORACIC ASSOCIATIO

Raghu et al, AJRCCM 2015;192:238

GUIDELINES

French practical guidelines for the diagnosis and management of idiopathic pulmonary fibrosis – 2017 update. Full-length version

Recommandations pratiques pour le diagnostic et la prise en charge de la fibrose pulmonaire idiopathique – Actualisation 2017. Version longue

V. Cottin[a,*,1], B. Crestani[b], J. Cadranel[c],
J.-F. Cordier[a], S. Marchand-Adam[d], G. Prévot[e],
B. Wallaert[f], E. Bergot[g], P. Camus[h], J.-C. Dalphin[i],
C. Dromer[j], E. Gomez[k], D. Israel-Biet[l], S. Jouneau[m],
R. Kessler[n], C.-H. Marquette[o], M. Reynaud-Gaubert[p],
B. Aguilaniu[q], D. Bonnet[r], P. Carré[s], C. Danel[t],
J.-B. Faivre[u], G. Ferretti[v], N. Just[w], F. Lebargy[x],
B. Philippe[y], P. Terrioux[z], F. Thivolet-Béjui[aa],
B. Trumbic[ab], D. Valeyre[ac]

Lung transplantation saves lives

Evaluate all patients **< 75 years** if :

- Dyspnea
- *or* FVC<80%
- *or* DLCO<40%
- *or* need for O2 (exercise or at rest)

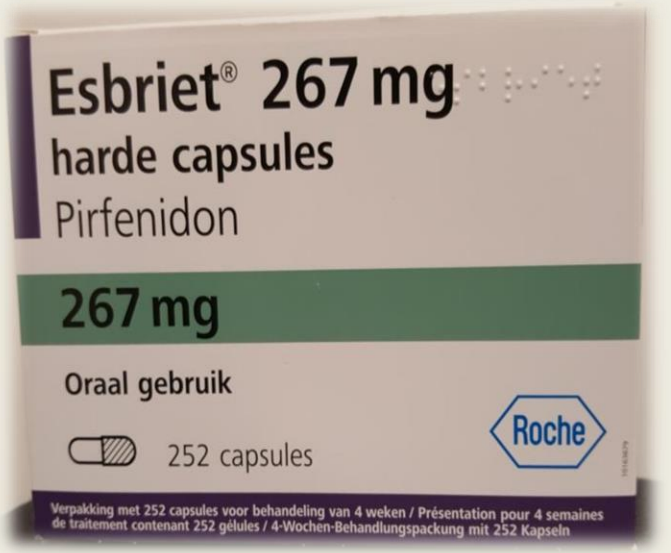
USA
¼ transplants > 65 years

Relative contraindications

- Age >65 years in association with low physiologic reserve and/or other relative contraindications. Although there cannot be endorsement of an upper age limit as an absolute contraindication, adults >75 years old are unlikely to be candidates for lung transplantation in most cases. Although age by itself should not be considered a contraindication to transplant, increasing age generally is associated with comorbid conditions that are either absolute or relative contraindications.

Weill, JHLT 2015

Molécules anti-fibrosants



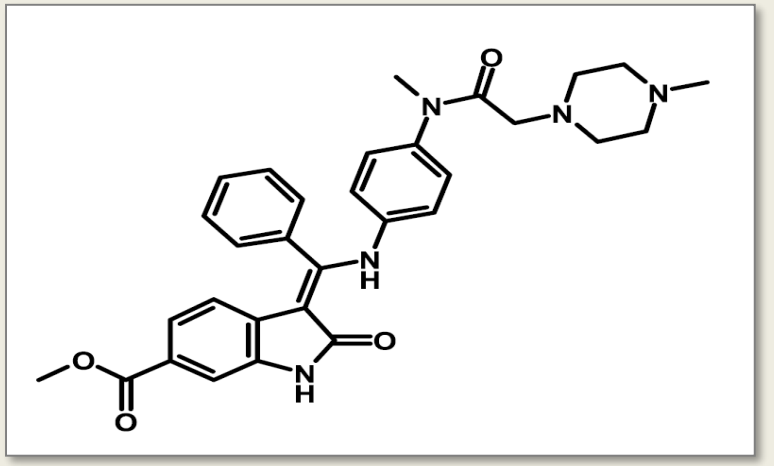
- Pirfenidone (Esbriet°) disponible en France depuis 2012, autorisé par la FDA le 15 Octobre 2014
  - (médic d'exception)
    - 3 cp/j pendant les repas (2403mg)
      - 2326,16€/mois

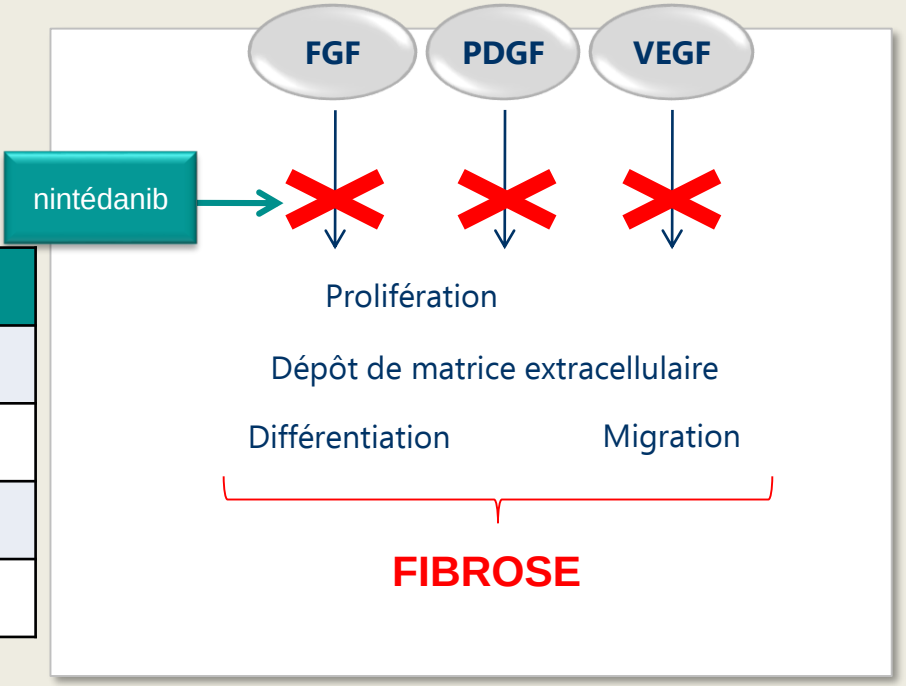
- Nintedanib (Ofev®) : autorisé par la FDA le 17 octobre 2014 et par l'EMA le 20 Novembre 2014 .
  - (médic d'exception)
    - 1 gélule 2/j à environ 12h d'intervalle

Le Nintédanib…

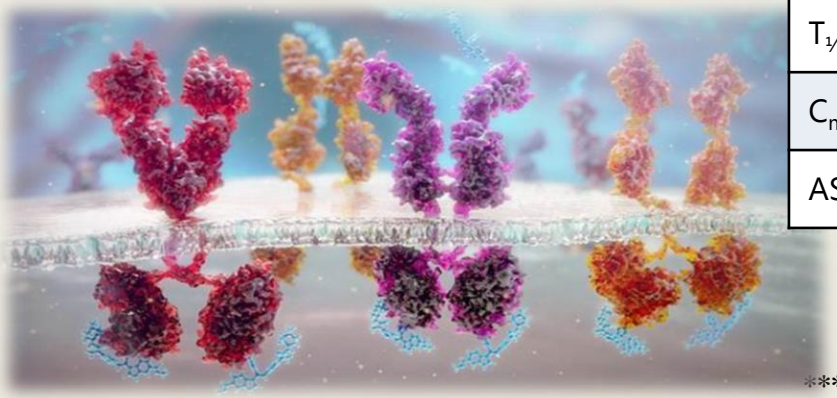
- Un inhibiteur intracellulaire de tyrosine kinases ciblant principalement les récepteurs du FGF*, du PDGF** et du VEGF***.
- Agit en se liant de manière compétitive au site actif de l'ATP.
- Absorption rapide avec clairance corporelle apparente et volume de distribution élevés
- Excrétion principalement dans les selles et faible (<1%) dans les urines
- Son principal métabolite est le BIBF 1202, formé par clivage d'ester puis glucuronidation en BIBF 1202 glucuronidé.
- Pas d'induction ni d'inhibition des enzymes du CYP dans les études précliniques.
- Aucune interaction médicamenteuse.

Structure chimique du nintédanib





	Moyenne
T_{max}, heures	1,3
$T_{½}$, heures	13,7
C_{max}, ng/ml	10,5
ASC_{0-12}, ng·h/ml	61,3



*FGF *(Fibroblast Growth Factor)* : facteur de croissance des fibroblastes
**PDGF (*Platelet-Derived Growth factor)* : facteur de croissance dérivé des plaquettes
***VEGF *(Vascular Endothelial Growth Factor)* : facteur de croissance de l'endothélium vasculaire

Hilberg F et al. Cancer Res 2008; 68: 4774-82.

Pirfenidone- Esbriet®

- Effets secondaires:
  - Cutanés:
    - Rash allergique (6-28%,),
    - Photosensibilisation(18%)
  - Digestifs:
    - Nausées (11%-37%)
    - Diarrhée (26%-28%),
    - Dyspepsie (17%-18%),
    - Anorexie(15%-42%), perte de poids (12%-15%)
  - Fatigue (20%-28%)
  - Perturbation de l'enzymologie hépatique(20%)

N Engl J Med. **2014** May 29;370(22):2083-92.
Lancaster L, Albera C, Bradford WZ, et al. BMJ Open Resp Res 2016
Respiratory Medicine (2013) 107, 1431—1437

Nintedanib- Ofev®

Diarrhées
Nausées
Vomissements

Infarctus du myocarde

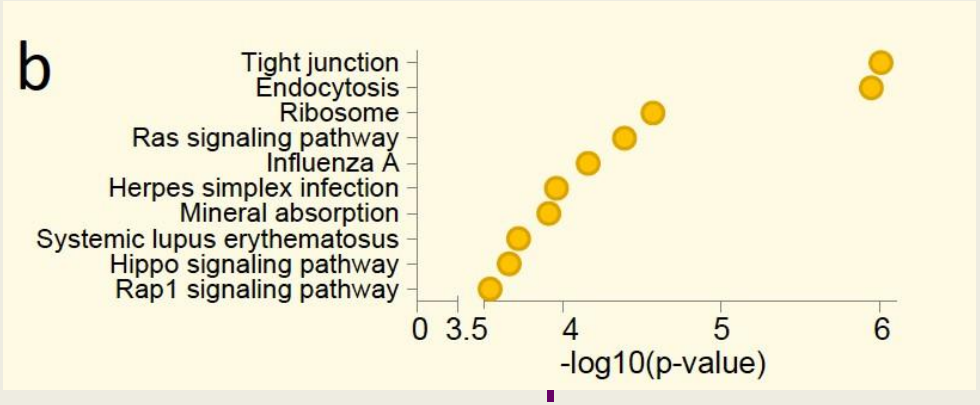
N Engl J Med 2014;370:2071-82.

Table 3. Adverse Events.

ent	INPULSIS-1		INPULSIS-2	
	Nintedanib (N=309)	Placebo (N=204)	Nintedanib (N=329)	Placebo (N=219)
	number of patients (percent)			
Any adverse event	298 (96.4)	181 (88.7)	311 (94.5)	198 (90.4)
Any adverse event, excluding progression of idiopathic pulmonary fibrosis*	296 (95.8)	179 (87.7)	311 (94.5)	197 (90.0)
Most frequent adverse events†				
Diarrhea	190 (61.5)	38 (18.6)	208 (63.2)	40 (18.3)
Nausea	70 (22.7)	12 (5.9)	86 (26.1)	16 (7.3)
Nasopharyngitis	39 (12.6)	34 (16.7)	48 (14.6)	34 (15.5)
Cough	47 (15.2)	26 (12.7)	38 (11.6)	31 (14.2)
Progression of idiopathic pulmonary fibrosis*	31 (10.0)	21 (10.3)	33 (10.0)	40 (18.3)
Bronchitis	36 (11.7)	28 (13.7)	31 (9.4)	17 (7.8)
Upper respiratory tract infection	28 (9.1)	18 (8.8)	30 (9.1)	24 (11.0)
Dyspnea	22 (7.1)	23 (11.3)	27 (8.2)	25 (11.4)
Decreased appetite	26 (8.4)	14 (6.9)	42 (12.8)	10 (4.6)
Vomiting	40 (12.9)	4 (2.0)	34 (10.3)	7 (3.2)
Weight loss	25 (8.1)	13 (6.4)	37 (11.2)	2 (0.9)
Severe adverse events‡	81 (26.2)	37 (18.1)	93 (28.3)	62 (28.3)
Serious adverse events‡	96 (31.1)	55 (27.0)	98 (29.8)	72 (32.9)
Fatal adverse events	12 (3.9)	10 (4.9)	25 (7.6)	21 (9.6)
Adverse events leading to treatment discontinuation§	65 (21.0)	22 (10.8)	58 (17.6)	33 (15.1)
Gastrointestinal disorders	26 (8.4)	3 (1.5)	21 (6.4)	2 (0.9)
Respiratory, thoracic, and mediastinal disorders	12 (3.9)	10 (4.9)	8 (2.4)	18 (8.2)
Investigation results¶	10 (3.2)	1 (0.5)	8 (2.4)	1 (0.5)
Cardiac disorders	5 (1.6)	4 (2.0)	2 (0.6)	3 (1.4)
General disorders and conditions involving site of study-drug administration	8 (2.6)	3 (1.5)	2 (0.6)	1 (0.5)

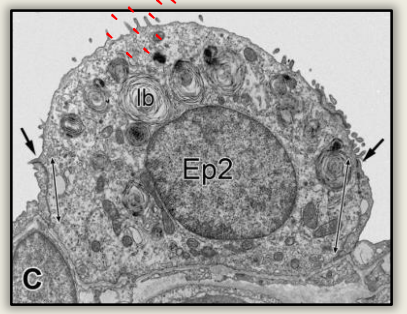
Top ten pathways modulated by Pirfenidone **in vivo**

Kwapiszewska, Eur Respir J 2018



Macrophage

Huang, Ann Rheum Dis 2017



Lehmann, Respir Res 2018

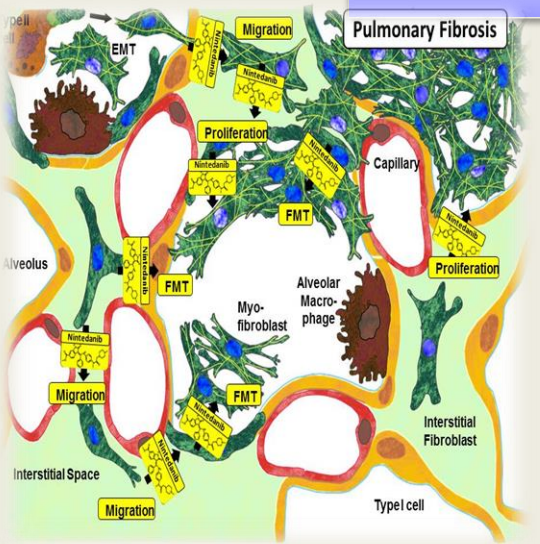
VEGFR
FGFR
PDGFR
CSF-1
Src, Lyn, Lck, Flt3

ER stress, UPR activation

Pirfenidone

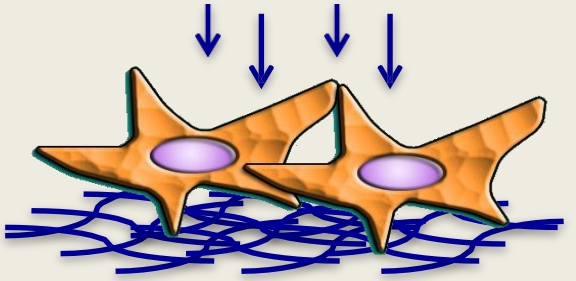
Nintedanib

Cytokines, Chimiokines,
Lipids, GFs, ROS
Developmental pathways



Collagen fibril assembly

Knüppel, AJRCMB 2017



Lehtonen, Respir Res 2016

Activation, Migration, Proliferation of Fibroblasts

Clinical Development of Nintedanib in Pulmonary Fibrosis

Fibrosing Interstitial Lung Diseases

Idiopathic Pulmonary Fibrosis (IPF)	Systemic Sclerosis-assoc. Interstitial Lung Disease (SSc-ILD)	Progressive Fibrosing ILDs
INPULSIS Approved	**SENSCIS** Under review	**INBUILD** Ongoing

- Le diagnostic de FPI doit être basé sur les critères ATS/ERS de 2011
- La pathologie doit être « légère à modérée » sur base des critères EFR suivants: CVF>50%, DLCO>30%
- Pour l'OFEV uniquement: patient non fumeur, attesté par un dosage de cotinine urinaire.

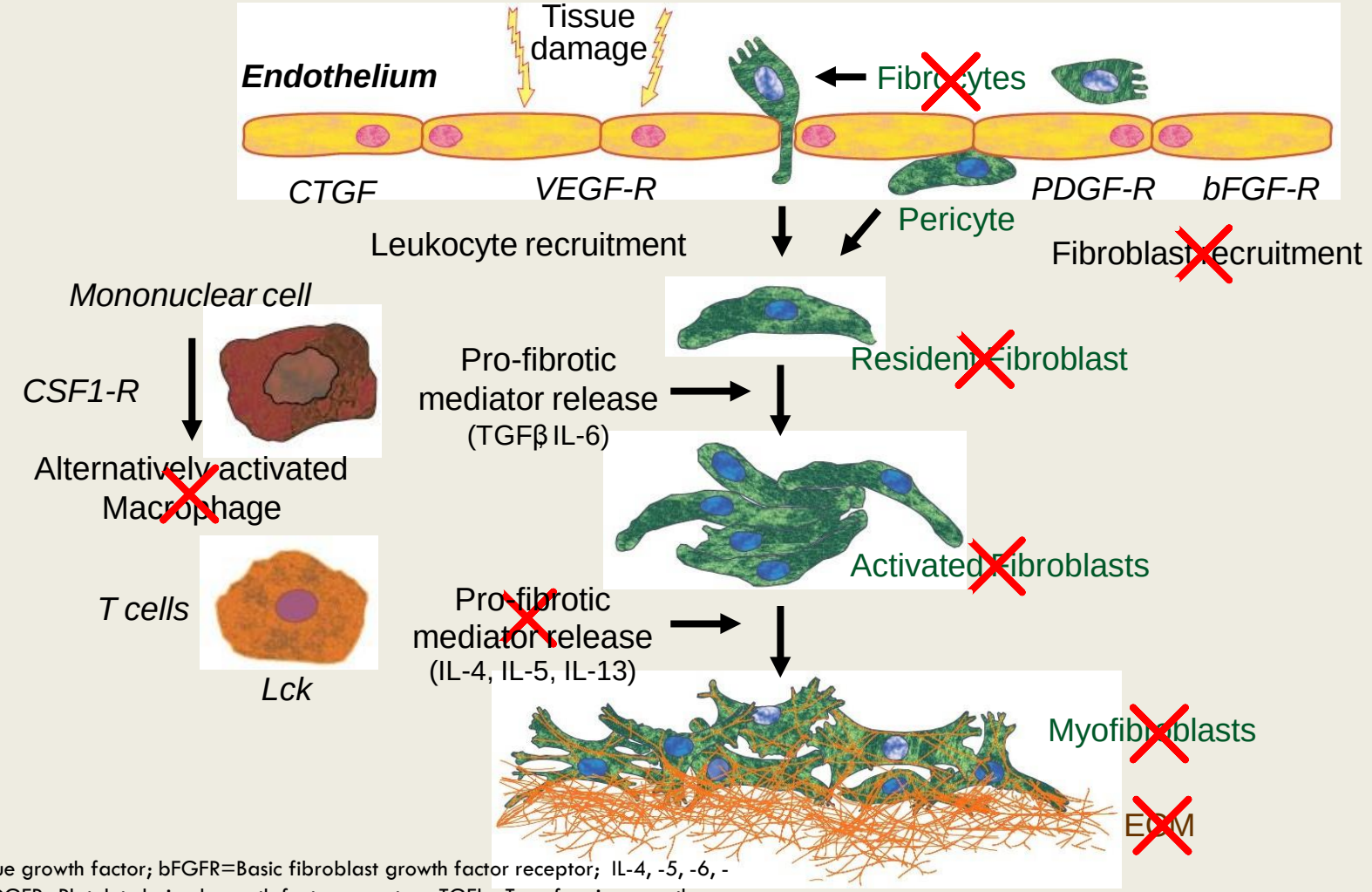
IPF and SSc-ILD Share Pathophysiologic Features but Differ Clinically

	IPF	SSc-ILD
Demographics	Males >70 yr	Females 45-55 yr
Pathology	UIP	NSIP >> UIP
Acute exacerbations	++++	+
Progressivity	Variable	Variable
Pace of decline in FVC	++++	++
Median survival	3-5 yr	5-8 yr

NSIP=non-specific interstitial pneumonia; UIP=usual interstitial pneumonia.
Wells AU, Denton CP. *Nat Rev Rheumatol*. 2014;10:728-739.

Nintedanib Attenuates Signaling Pathways Implicated in Fibrosis

- **Nintedanib** is a small-molecule **tyrosine kinase** inhibitor with a distinct inhibitory spectrum



CSF1R=Colony-stimulating factor 1 receptor; CTGF=Connective tissue growth factor; bFGFR=Basic fibroblast growth factor receptor; IL-4, -5, -6, -13= Interleukin; Lck=Lymphocyte-specific protein tyrosine kinase; PDGFR=Platelet derived growth factor receptor; TGFb=Transforming growth factor beta; VEGFR=Vascular endothelial growth factor receptor.

Reprinted from Wollin L, et al. *Journal of Scleroderma and Related Disorders*. 2019. [e-pub ahead of print]

Respiratory Medicine 113 (2016) 74–79

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Respiratory Medicine

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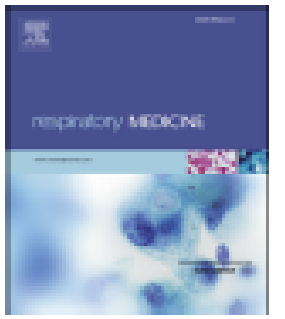
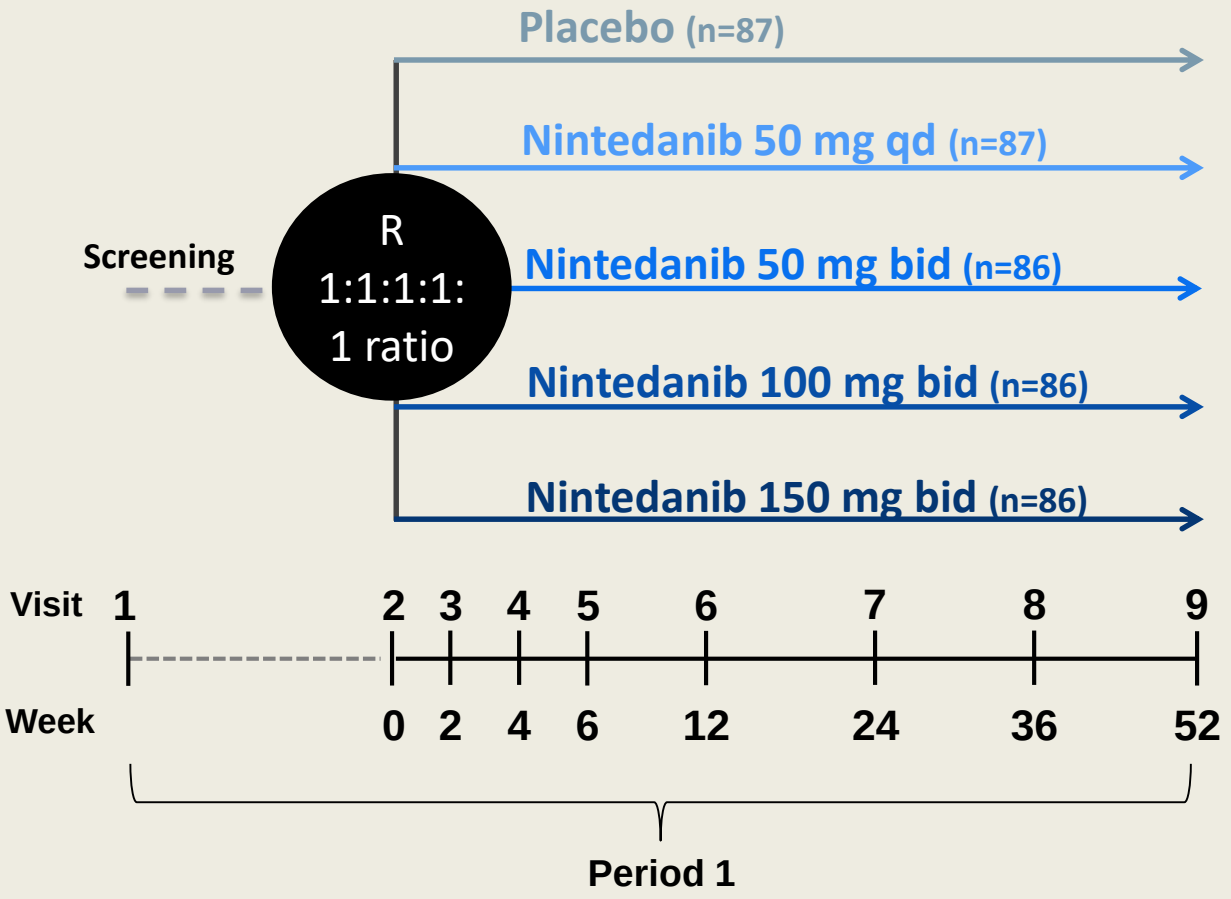


Nintedanib in patients with idiopathic pulmonary fibrosis: Combined evidence from the TOMORROW and INPULSIS® trials

Luca Richeldi [a, *], Vincent Cottin [b], Roland M. du Bois [c], Moisés Selman [d], Toshio Kimura [e], Zelie Bailes [f], Rozsa Schlenker-Herceg [g], Susanne Stowasser [e], Kevin K. Brown [h]

TOMORROW: RANDOMIZED, PLACEBO-CONTROLLED, 52-WEEK, DOSE-FINDING TRIAL



n=randomized patients

Richeldi L et al. *N Engl J Med* 2011;365:1079-1087

TOMORROW:

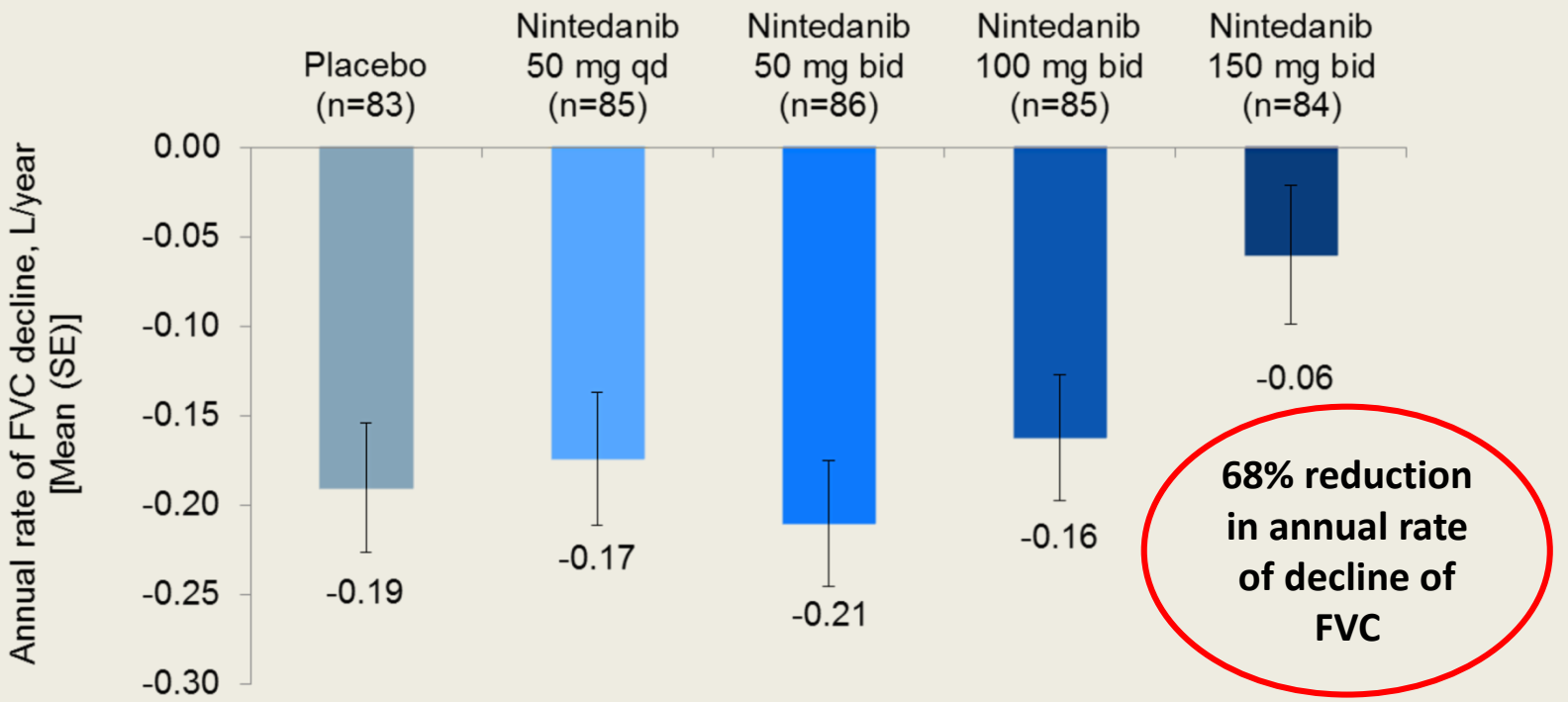
Endpoints

- Primary endpoint:
  - Annual rate of decline in FVC
- Secondary endpoints:
  - Incidence of investigator-reported acute exacerbations of IPF
  - Time to first investigator-reported acute exacerbation of IPF
  - Survival (all cause, respiratory cause)
- Safety and tolerability

FVC, forced vital capacity; SGRQ, St George's Respiratory Questionnaire.
Richeldi L, et al. N Engl J Med 2011;365:1079–1087.

KEY RESULTS FROM TOMORROW: DECLINE IN FVC

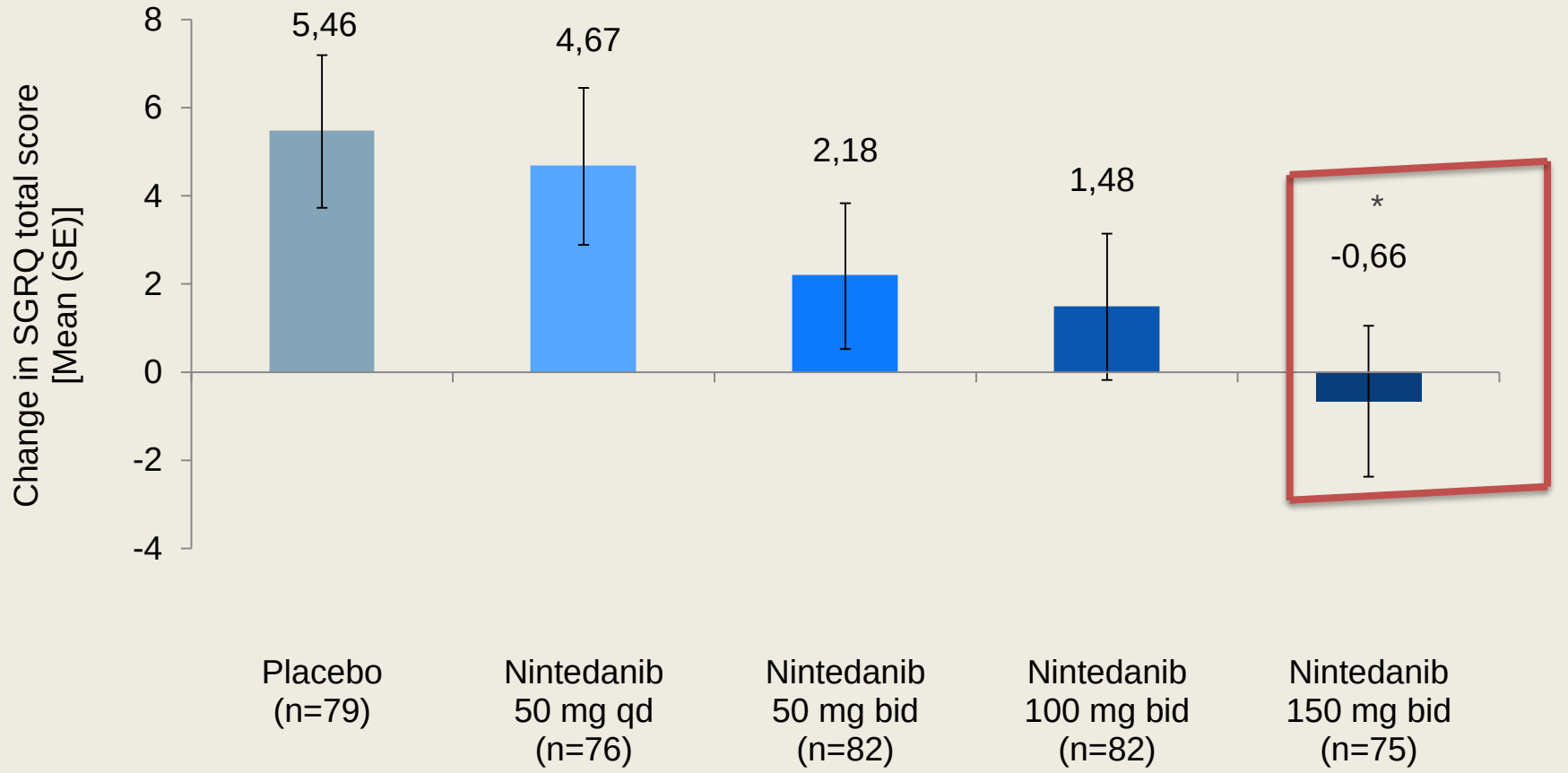
- Compared with placebo, nintedanib 150 mg bid was associated with a reduced annual rate of decline in FVC by 68%



Difference between nintedanib 150 mg bid and placebo: p=0.064 vs placebo (pre-specified primary multiplicity-corrected analysis [closed testing]); p=0.014 vs placebo (pre-specified hierarchical testing)

Richeldi L et al. *N Engl J Med* 2011;365:1079-1087

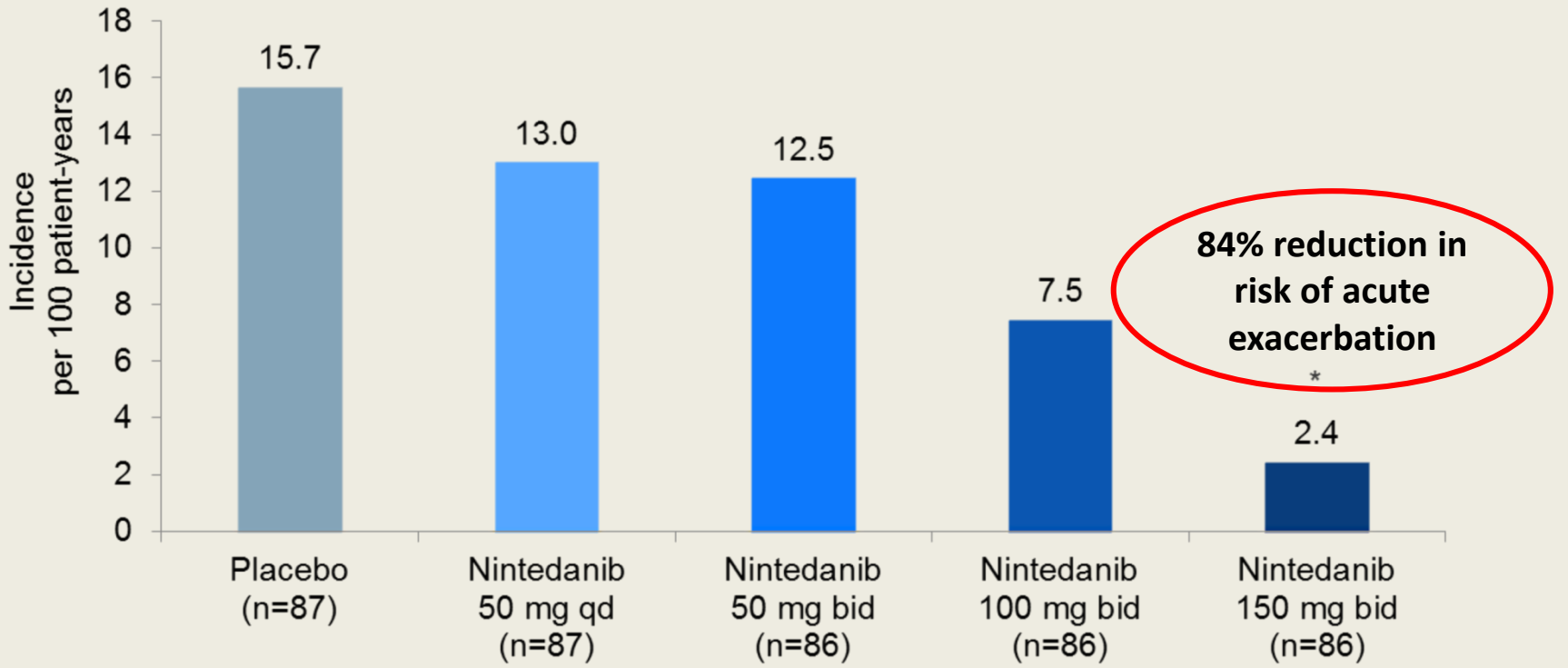
TOMORROW: Preservation of health-related quality of life



*p=0.007 vs placebo.
SGRQ, St George's Respiratory Questionnaire.
Richeldi L, et al. N Engl J Med 2011;365:1079–1087.

KEY RESULTS FROM TOMORROW: ACUTE EXACERBATIONS

- Compared with placebo, nintedanib 150 mg bid was associated with fewer acute exacerbations by 84%



*p=0.02 *vs* placebo

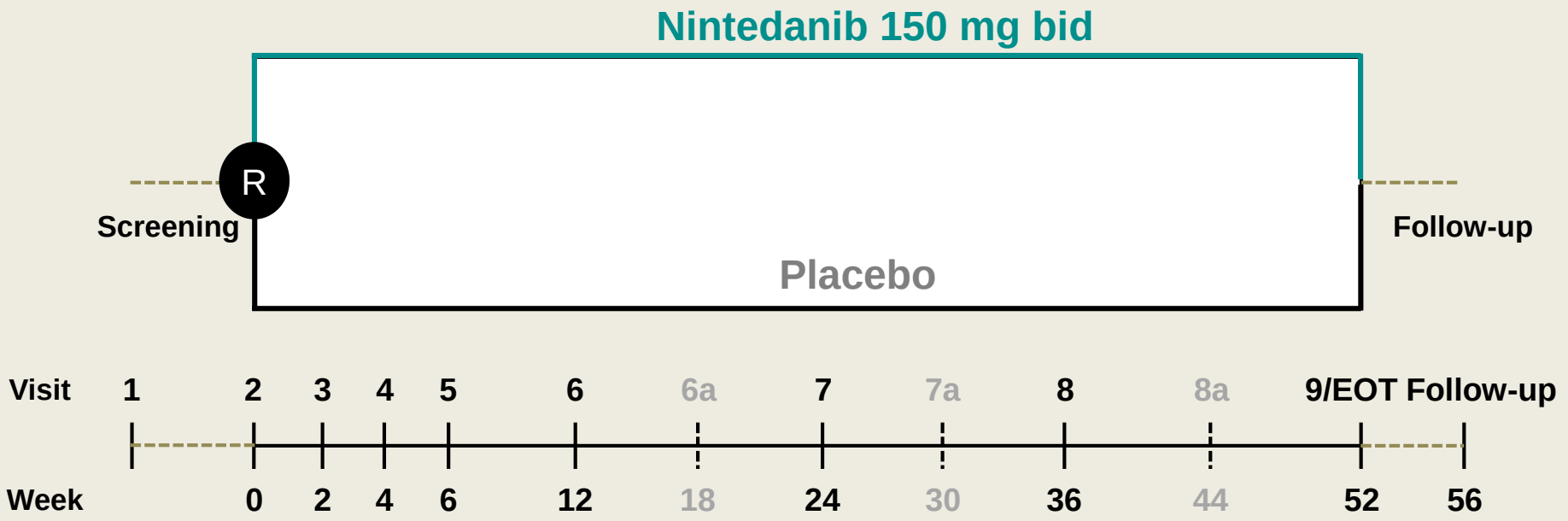
Richeldi L et al. *N Engl J Med* 2011;365:1079-1087

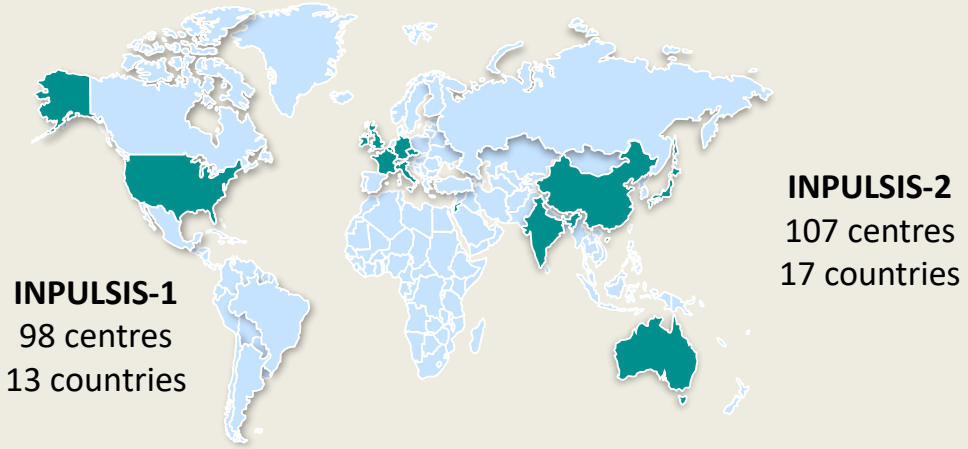
TOMORROW / Conclusions

- Treatment with nintedanib 150 mg bid reduced the annual rate of decline in FVC by 68% compared with the placebo group
- A reduction in the incidence of acute exacerbations and preservation of quality of life were observed with nintedanib 150 mg bid versus placebo
- Nintedanib 150 mg bid had an acceptable safety profile, with a risk-benefit ratio that justified its investigation as a treatment for IPF in the INPULSIS Phase III trials

Richeldi L, et al. N Engl J Med 2011;365:1079–1087.

The INPULSIS®





INPULSIS-1
98 centres
13 countries

INPULSIS-2
107 centres
17 countries

Resp Med 2014; 108: 1023-30

KEY INCLUSION CRITERIA (1,2)

Age ≥40 years
Diagnosis of IPF within 5 years of randomization
Chest HRCT performed within 12 months of screening
Biopsie pulmonaire en faveur de FPI
FVC ≥50% of predicted value
DL_{CO} 30-79% of predicted value
FEV_1 / FVC ≥ 0.7

1. Richeldi L et al. Respiratory Medicine 2014;108:1023-30.
2. Richeldi L et al. N Engl J Med 2014;370(22):2071-82.

KEY EXCLUSION CRITERIA

- FEV_1/FVC <0.7 (pre-bronchodilator)
- AST and ALT >1.5x ULN; bilirubin >1.5x ULN
- Treatment with N-acetylcysteine or prednisone >15 mg/day or equivalent within 2 weeks of screening
- Treatment with pirfenidone, azathioprine, cyclophosphamide, cyclosporine A or any investigational drug within 8 weeks of screening
- Likely to receive a lung transplant during the study (based on investigator opinion)

NEJM 2014; 370: 2071-82

Endpoints

Primary endpoint

- Annual rate of decline in FVC (mL/year)

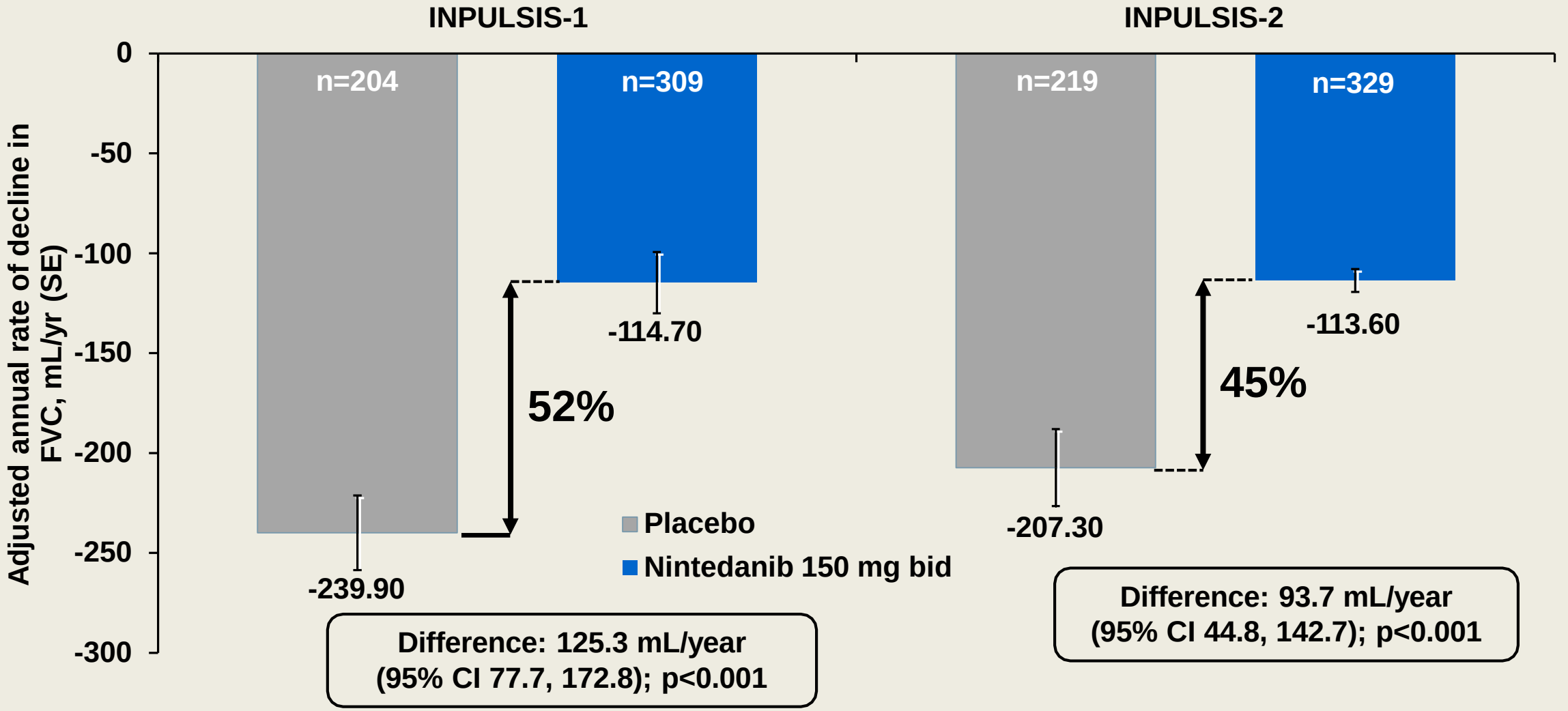
Key secondary endpoints

- Time to first acute exacerbation (investigator-reported) over 52 weeks

NEJM 2014; 370: 2071-82

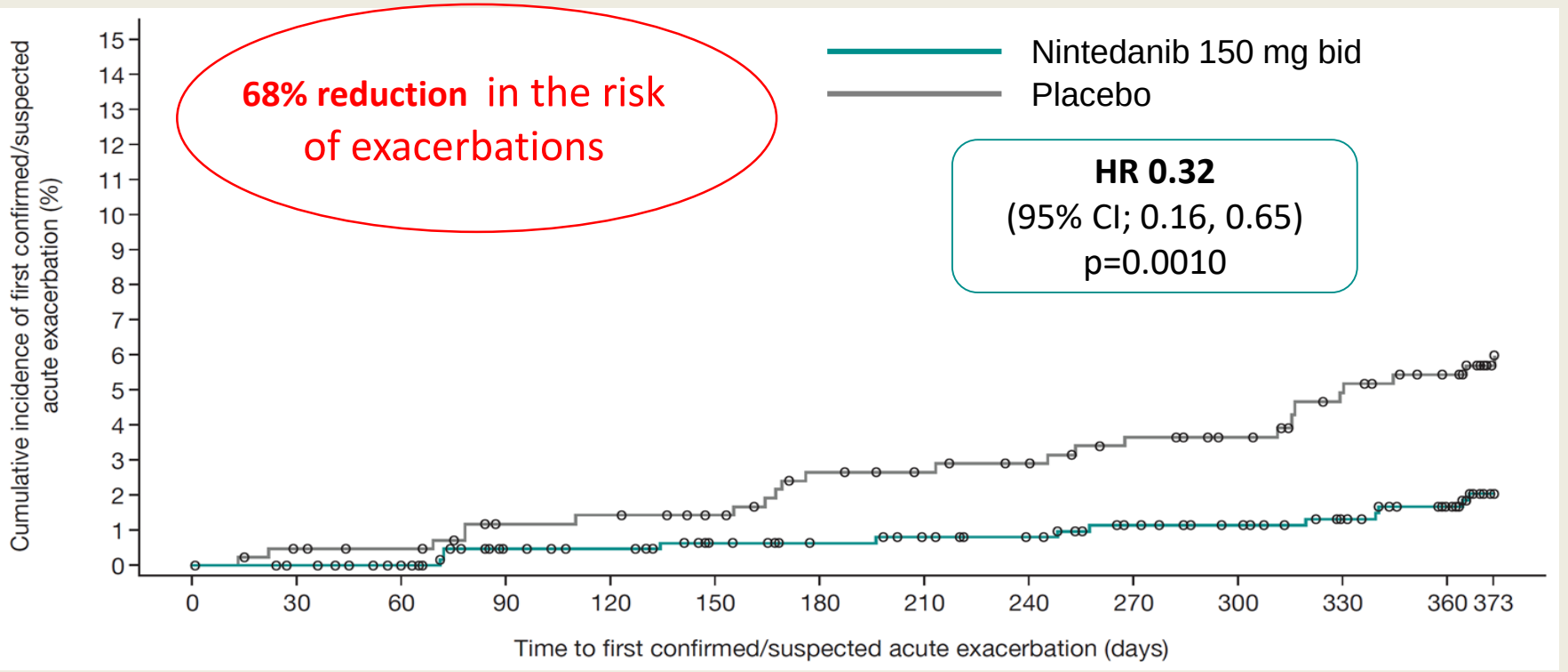
Annual Rate of Decline in FVC (Primary Endpoint)

IPAF



Reprinted from Richeldi L, et al. *N Engl J Med.* 2014;370(22):2071-2078.

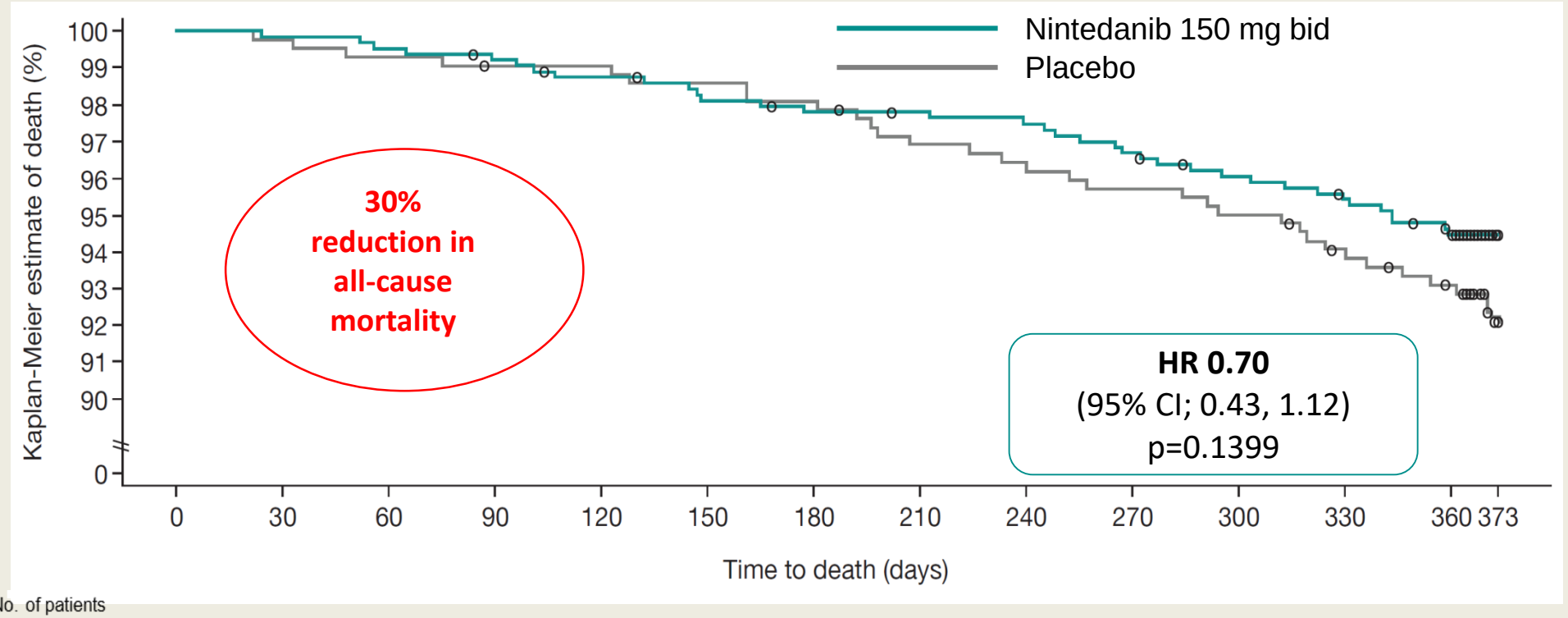
TIME TO FIRST CONFIRMED OR SUSPECTED ACUTE EXACERBATION PER ADJUDICATION (PRESPECIFIED SENSITIVITY ANALYSIS OF POOLED DATA)



	Nintedanib 150 mg bid (n=638)	Placebo (n=423)
Patients with ≥1 acute exacerbation, n (%)	12 (1.9)	24 (5.7)

NEJM 2014; 370: 2071-82

ALL-CAUSE MORTALITY OVER 52 WEEKS (PRESPECIFIED ANALYSIS OF POOLED DATA)

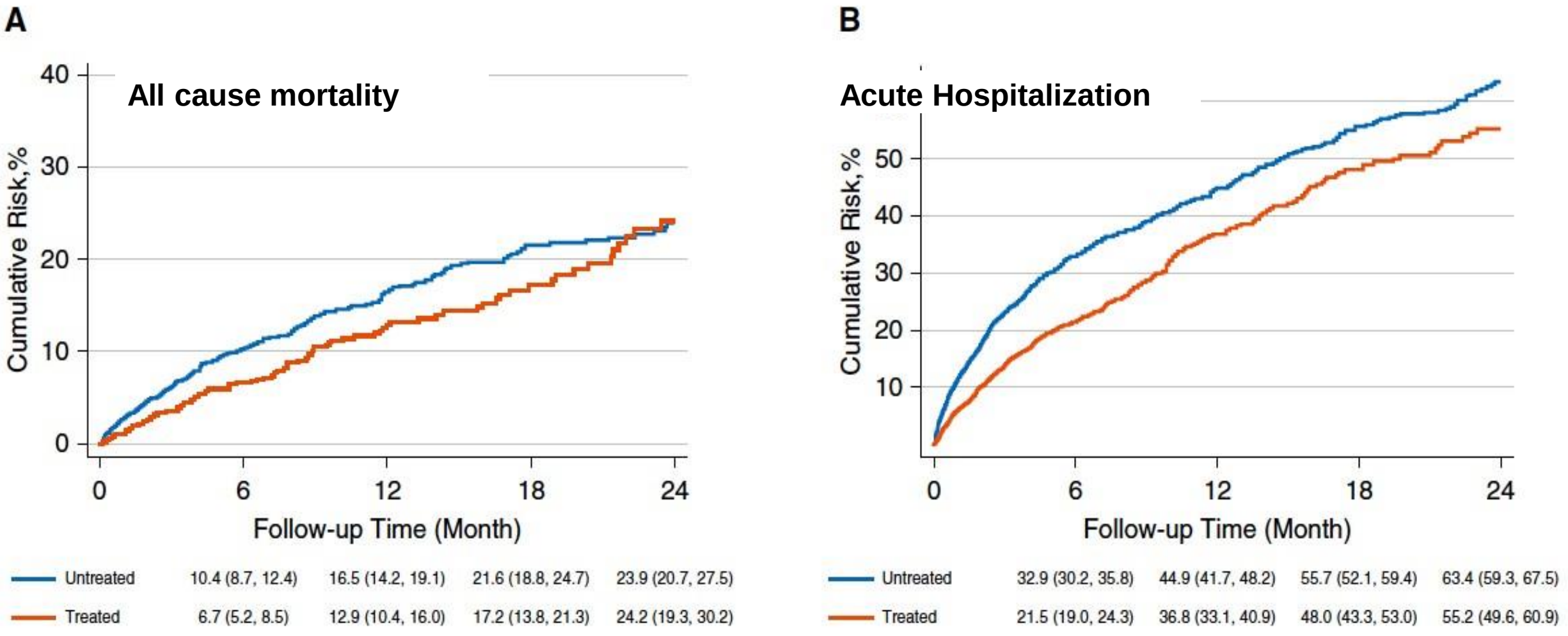


No. of patients														
Nintedanib	638	637	635	632	628	623	620	619	617	612	606	601	591	532
Placebo	423	422	420	418	418	416	414	408	406	403	400	394	388	358

	Nintedanib 150 mg bid (n=638)	Placebo (n=423)
Patients who died, n (%)	35 (5.5)	33 (7.8)

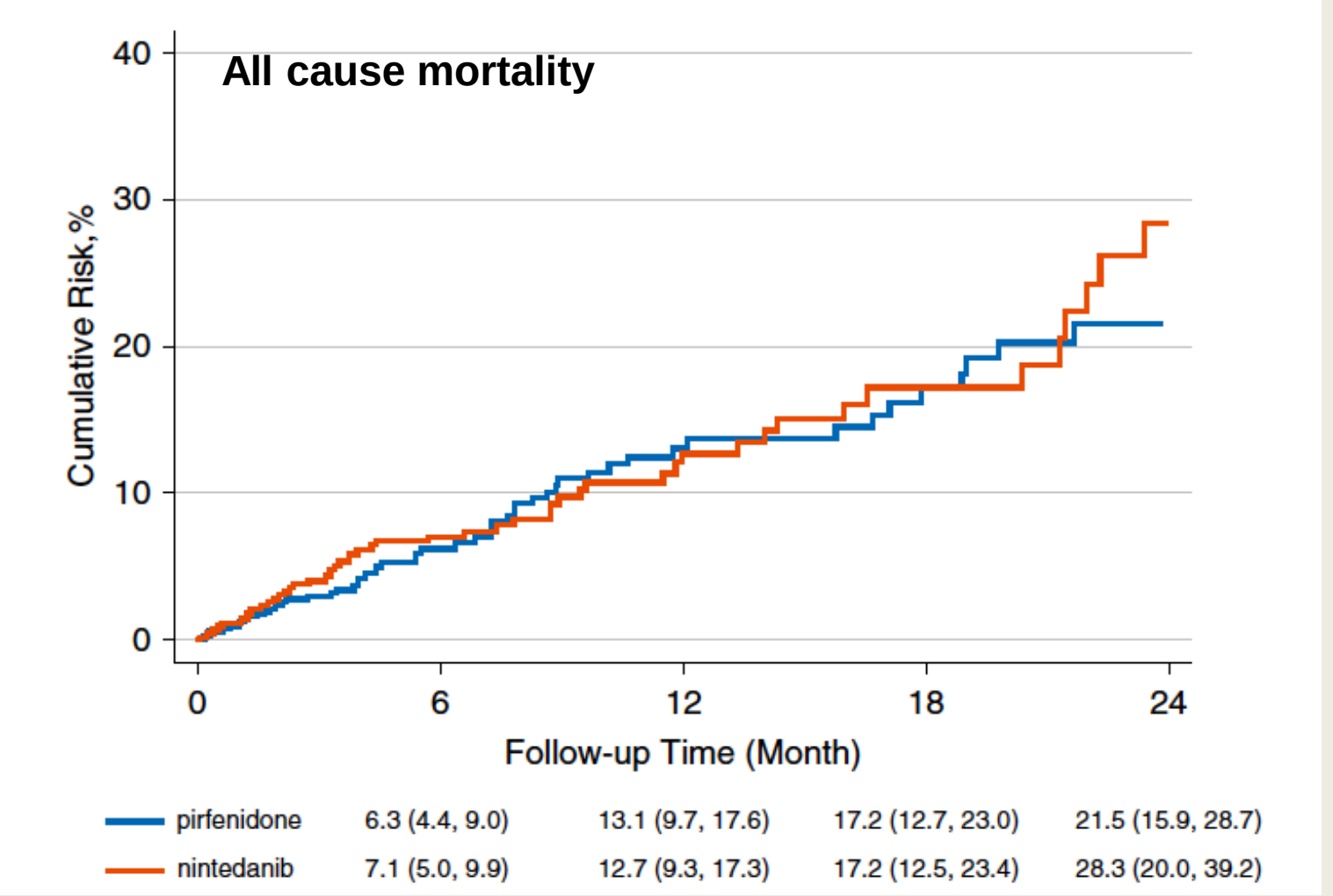
NEJM 2014; 370: 2071-82

Real life data support a survival benefit for 2 years (US)



Dempsey, AJRCCM 2019

…And no difference between the two molecules in terms of survival effect



Dempsey, AJRCCM 2019

Revue du rhumatisme monographies 85 (2018) 179–183

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Traitement de la fibrose pulmonaire idiopathique : un espoir pour les connectivites

Treatment of idiopathic pulmonary fibrosis: A new hope for connective tissu diseases

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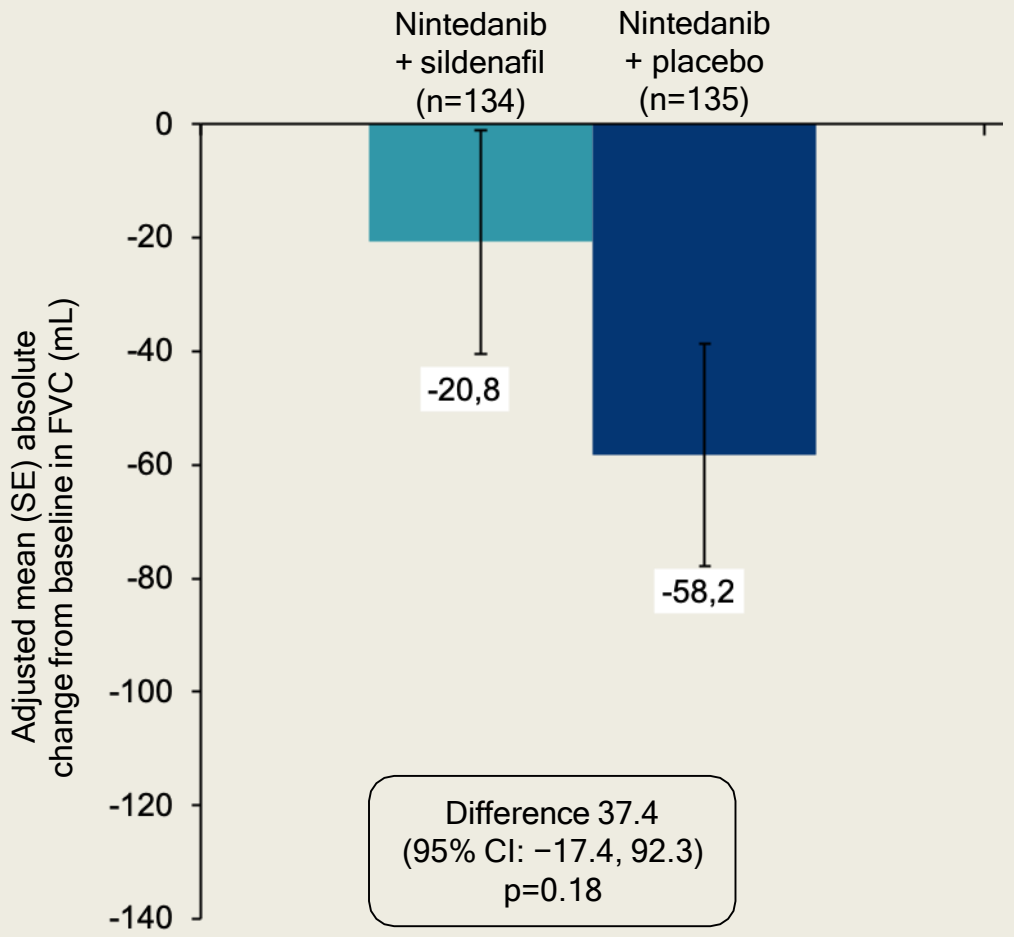
[c] Université de Lille, 59000 Lille, France

Tableau 1
Principales différences entre la pirfénidone et le nintédanib.

	Pirfénidone	Nintédanib
Nombre de patients inclus dans des essais de phase III	1716	1066
Critères d'inclusion	Lésions de PIC en scanner ou en histologie (relecture centralisée pour Ascend) CVF ≥ 50 % DLCO ≥ 35 % (≥ 30 % dans ASCEND) VEMS/CVF ≥ 0,8	Relecture centralisée Lésions de PIC en scanner ou en histologie. 30 % des patients avaient un diagnostic de PIC possible en scanner sans biopsie pulmonaire CVF ≥ 50 % DLCO ≥ 30 % VEMS/CVF ≥ 0,7
Objectif principal	Réduction du déclin de la CVF	Réduction du déclin de la CVF
Différences principales dans les objectifs secondaires	Amélioration de la survie en analyse poolée (1609 patients)	Allongement du temps avant la première exacerbation
Effets secondaires principaux	Éruption (3–32 %) Photosensibilité (5–14 %) Prurit (2–6 %) Nausée (15–40 %) Dyspepsie (5–20 %) Diarrhée (2–28 %) Fatigue (10–26 %) Perte de poids (9–10 %) Élévation des enzymes hépatiques (3–6 %)	Diarrhée (61–63 %) Nausée (23–26 %) Perte d'appétit (8–13 %) Vomissements (10–13 %) Élévation des enzymes hépatiques (5 %)
Interactions médicamenteuses	Nombreuses	Association avec une anticoagulation déconseillée

Nintedanib + Sildenafil

(INSTAGE)

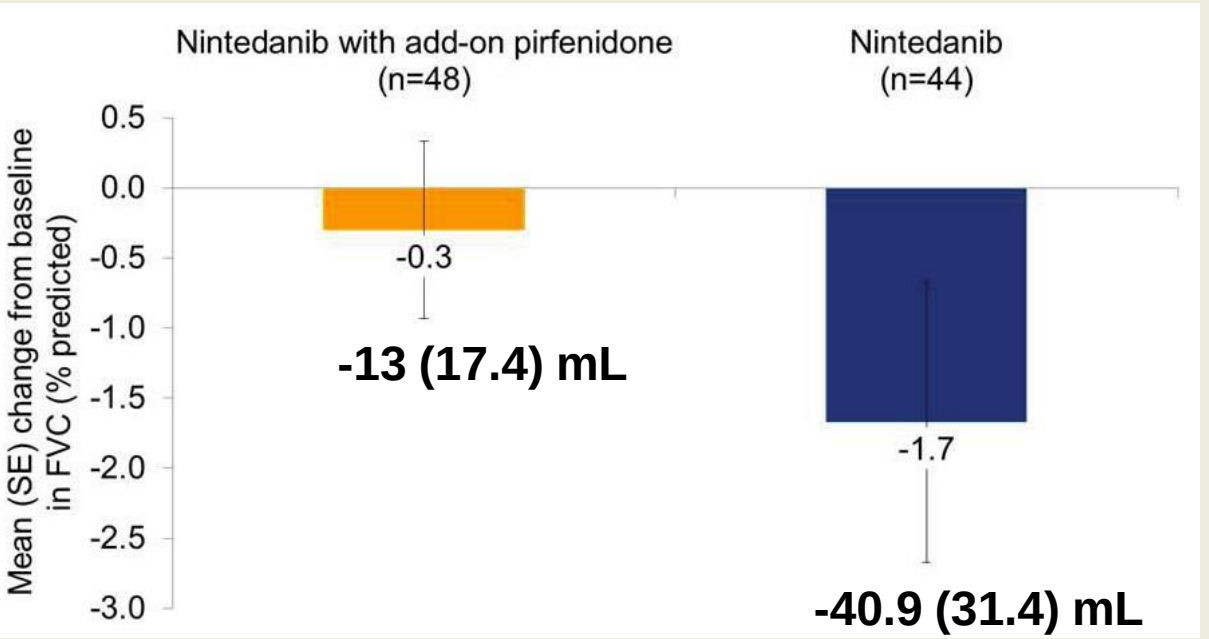


Kolb, NEJM 2018

Nintedanib + Pirfenidone

(INJOURNEY)

12 weeks



Vancheri, AJRCCM 2017

Essais thérapeutiques en cours

Macrophage

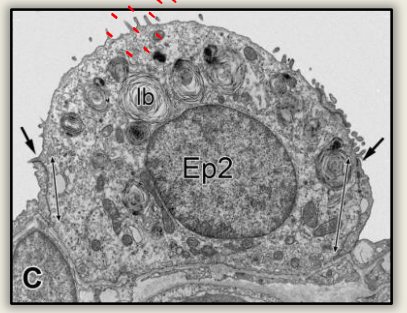
Galectin-3 inhibition

Inhibiteur Galectine 3 (Phase 2-3) *inhalé*

Anti-BAFFR (Phase 2) *sous-cut*

Auto-immunité dans la FPI ?

PBI-4050



Thérapies senolytiques

Anti-CTGF (Pamvrelumab) (Phase 3) *ss-cut*

ER stress, UPR activation

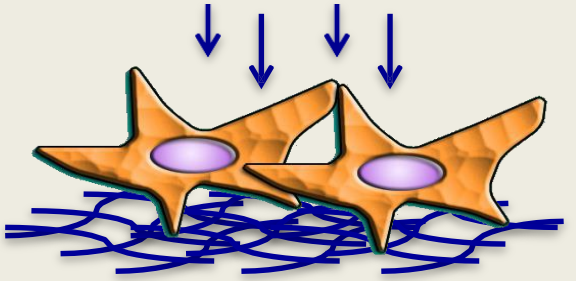
Inhibiteur autotaxine (Phase 3) *per os*

Anti-CTGF

Cytokines, Chimiokines, Lipids, GFs, ROS Developmental pathways

NOX4 inhibition
Tipelukast (5-LO inhibition)

PBI-4050
Anti-Integrin
ROCK2 inhibitor (KD025)
Src inhibitor



Autotaxin inhition
LOXL2 inhibition
PRM-151
JNK-Inhibition