Actualités dans le diagnostic et le Traitement de la Fibrose Pulmonaire Idiopathique

Bruno Crestani

Hôpital Bichat, Université de Paris,

Paris, France

www.dhuFIRE.org

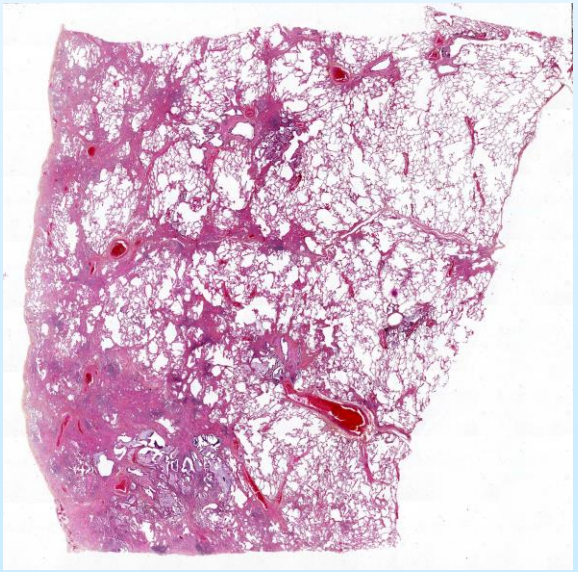
Liens d’intérêts

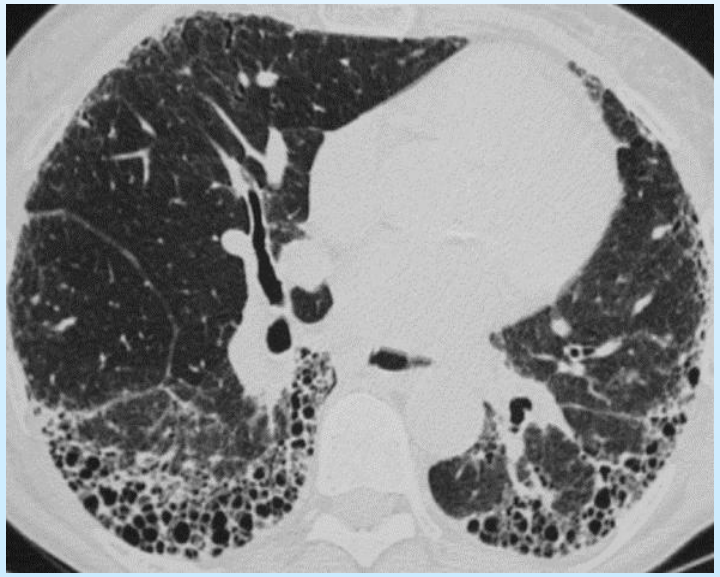
J’ai actuellement, ou j’ai eu au cours des trois dernières années, une affiliation ou des intérêts financiers ou intérêts de tout ordre avec les sociétés commerciales suivantes en lien avec la santé :

- Apellis, Astra-Zeneca, BMS, Boehringer Ingelheim, Genzyme, LVL, MedImmune, Novartis, Roche, Sanofi

Idiopathic Pulmonary Fibrosis
the current definition

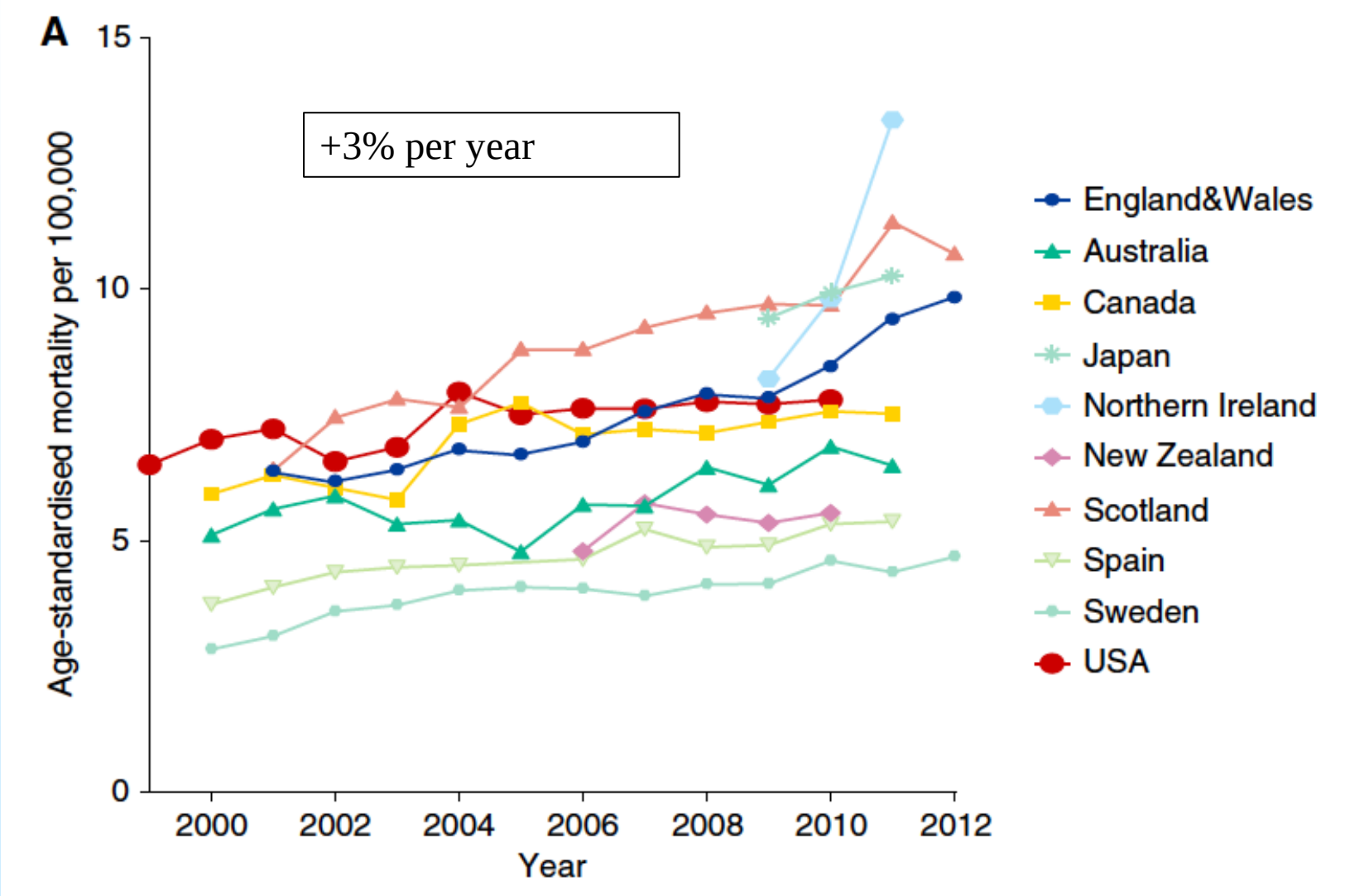
“A specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, and limited to the lungs, and associated with the histopathologic and/or radiologic pattern of UIP”





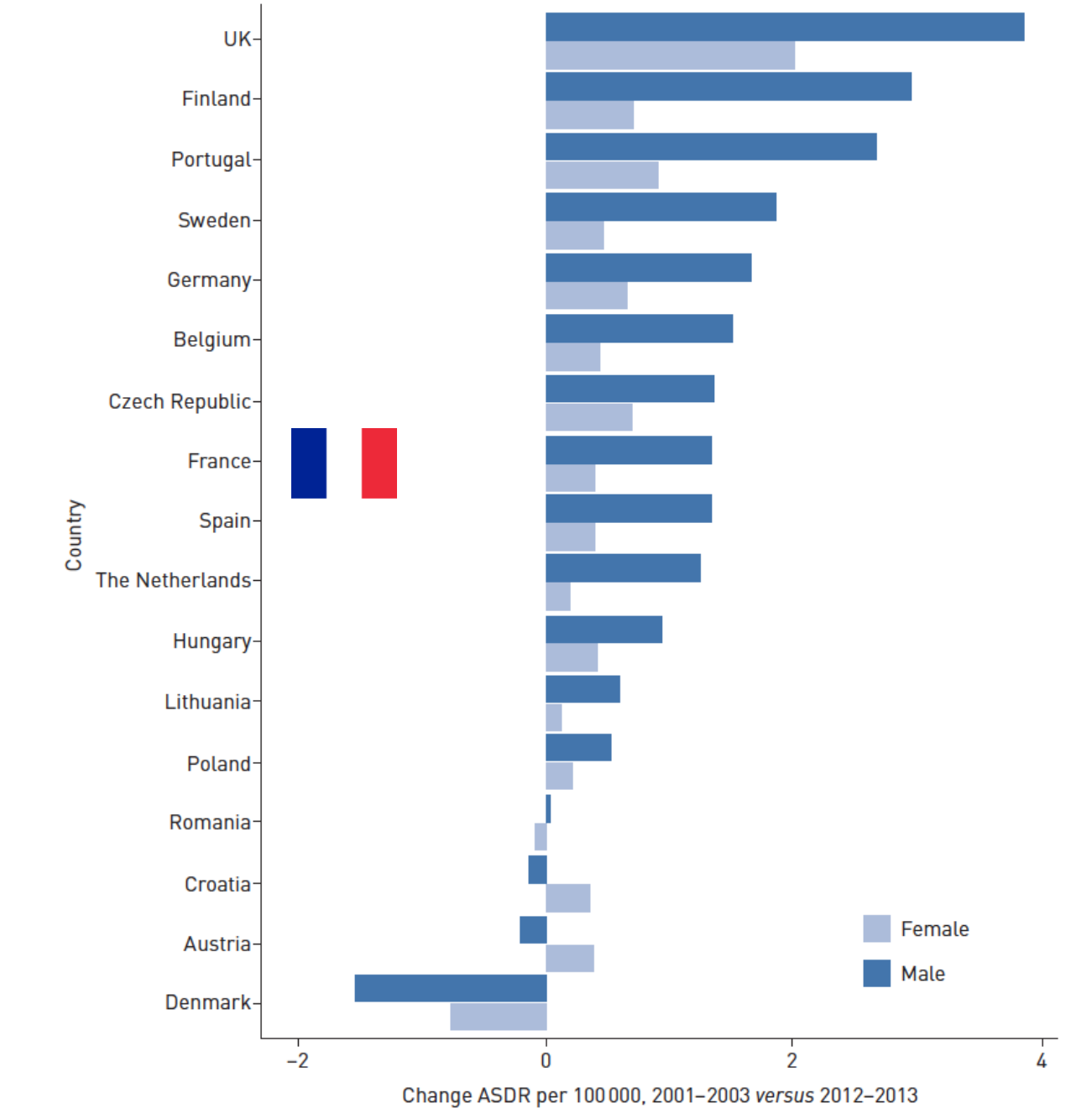
Raghu, AJRCCM 2011;183:788-824

Increased mortality (world)



Hutchinson, Ann Am Thorac Soc 2014;11:1176-85

La mortalité par FPI augmente dans la plupart des pays européens chez les hommes et les femmes



Marshall, ERJ 2018

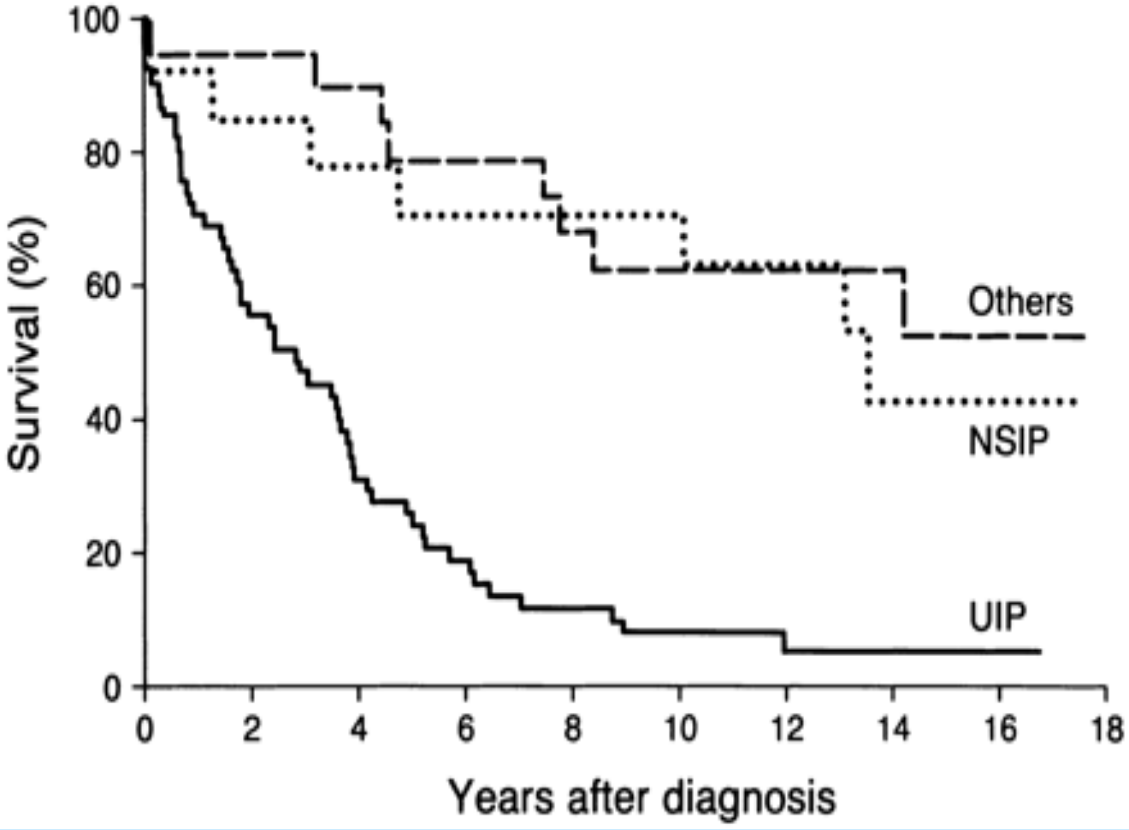
Idiopathic Pulmonary Fibrosis
30 years ago

Lung Biopsy
(Armed Forces, Washington)
N = 101, Follow up : 10 years

Survival	UIP *(55%)*	Fibrotic NSIP *(22%)*	Cellular NSIP *(7%)*	DIP / RB-ILD *(16%)*
5 yrs	*43%*	*90%*	*100%*	*100%*
10 yrs	*15%*	*35%*	*100%*	*100%*

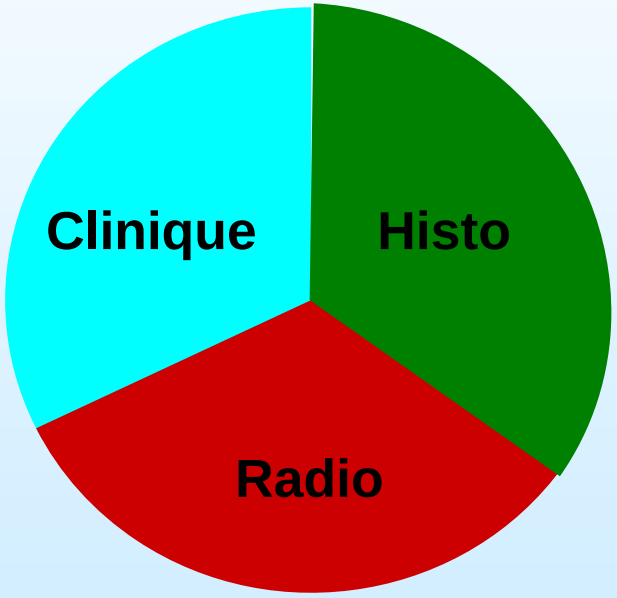
(Travis, Am J Surg Pathol 2000;24:19-33)

- **IPF was identified on behaviour and outcome**
- **The outcome was linked to a UIP pattern as opposed to the outcome associated with an NSIP pattern**



(Bjoraker, AJRCCM 1998;157: 199-203)

Principes du diagnostic



1) **PIC nécessaire au diagnostic**

2) **PIC TDM = PIC histologique**

Current criteria allow for a confident diagnosis of IPF

(70 patients; 7 Multidisciplinary teams from 7 countries)

	Clinicians (κw)	Radiologists (κw)	Pathologists (κw)	MDTM (κw)
Idiopathic pulmonary fibrosis	0·72 (0·67–0·76)	0·60 (0·46–0·66)	0·58 (0·45–0·66)	0·71 (0·64–0·77)
Connective tissue disease-related interstitial lung disease	0·76 (0·70–0·78)	0·17 (0·08–0·31)	0·21 (0·06–0·36)	0·73 (0·68–0·78)
Non-specific interstitial pneumonia	0·31 (0·27–0·41)	0·32 (0·26–0·41)	0·30 (0·00–0·53)	0·42 (0·37–0·49)
Hypersensitivity pneumonitis	0·42 (0·30–0·47)	0·35 (0·29–0·43)	0·26 (0·10–0·45)	0·29 (0·24–0·40)

Data are median (IQR). MDTM=multidisciplinary team meeting.

Table 4: **Weighted kappa values (κw) for estimation of diagnostic likelihood for individual diagnoses of diffuse parenchymal lung disease**

(Walsh, Lancet Respir Med 2016)

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

Table 4. High-Resolution Computed Tomography Scanning Patterns

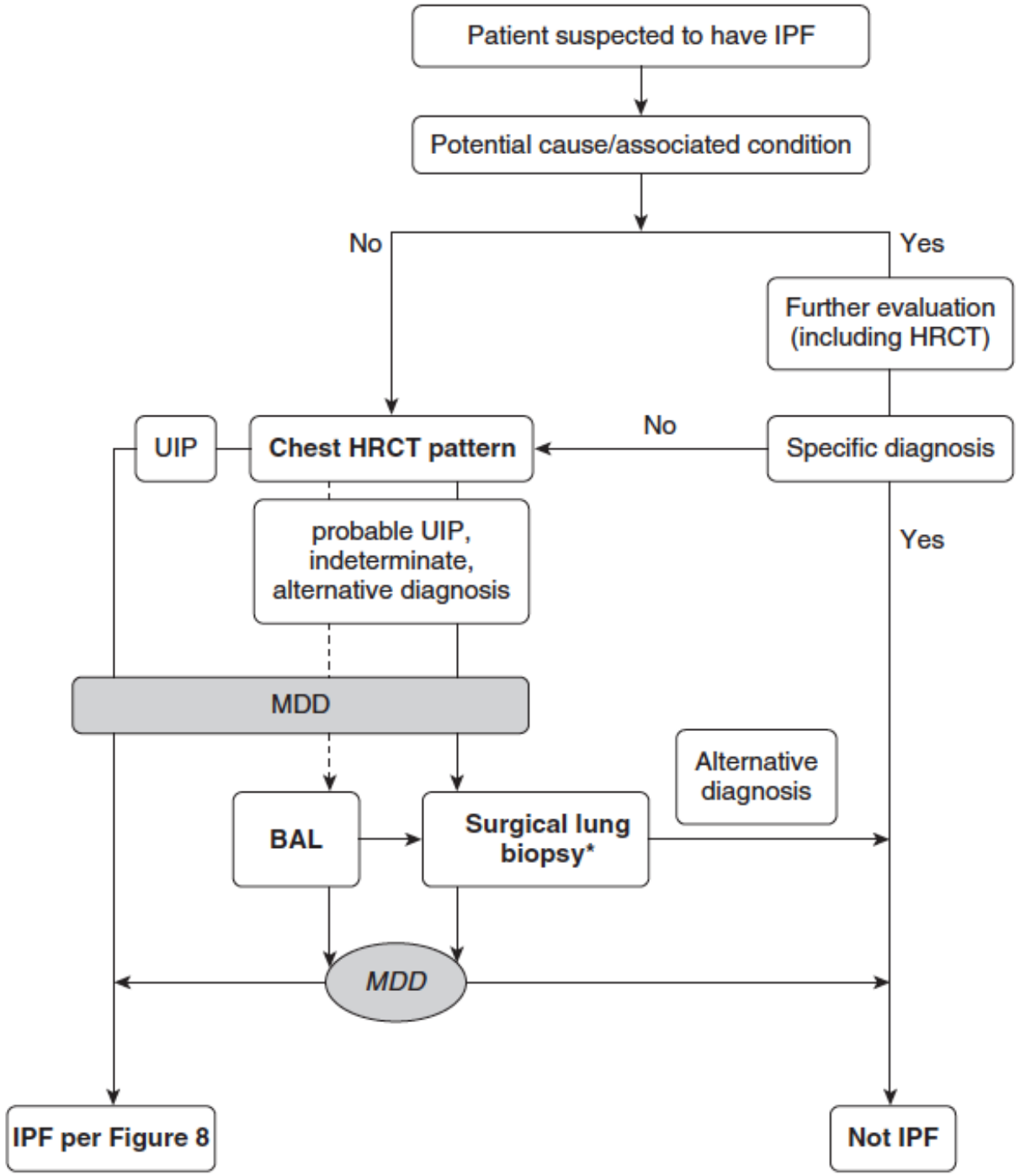
UIP	Probable UIP	Indeterminate for UIP	Alternative Diagnosis
Subpleural and basal predominant; distribution is often heterogeneous* Honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis†	Subpleural and basal predominant; distribution is often heterogeneous Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis May have mild GGO	Subpleural and basal predominant Subtle reticulation; may have mild GGO or distortion ("early UIP pattern") CT features and/or distribution of lung fibrosis that do not suggest any specific etiology ("truly indeterminate")	Findings suggestive of another diagnosis, including: • CT features: ° Cysts ° Marked mosaic attenuation ° Predominant GGO ° Profuse micronodules ° Centrilobular nodules ° Nodules ° Consolidation • Predominant distribution: ° Peribronchovascular ° Perilymphatic ° Upper or mid-lung • Other: ° Pleural plaques (consider asbestosis) ° Dilated esophagus (consider CTD) ° Distal clavicular erosions (consider RA) ° Extensive lymph node enlargement (consider other etiologies) ° Pleural effusions, pleural thickening (consider CTD/drugs)

Definition of abbreviations: CT = computed tomography; CTD = connective tissue disease; GGO = ground-glass opacities; RA = rheumatoid arthritis; UIP = usual interstitial pneumonia.

*Variants of distribution: occasionally diffuse, may be asymmetrical.

†Superimposed CT features: mild GGO, reticular pattern, pulmonary ossification.

Raghu et al. AJRCCM 2018



Raghu et al. AJRCCM 2018

Diagnosis of Idiopathic Pulmonary Fibrosis

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

IPF suspected*		Histopathology pattern			
		UIP	Probable UIP	Indeterminate for UIP	Alternative diagnosis
HRCT pattern	UIP	IPF	IPF	IPF	Non-IPF dx
	Probable UIP	IPF	IPF	IPF (Likely)**	Non-IPF dx
	Indeterminate	IPF	IPF (Likely)**	Indeterminate***	Non-IPF dx
	Alternative diagnosis	IPF (Likely)** /non-IPF dx	Non-IPF dx	Non-IPF dx	Non-IPF dx

Pas de catégorie “sans biopsie”

Raghu, AJRCCM 2018

Faut-il biopsier les PIC probables ?

Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper

David A Lynch, Nicola Sverzellati, William D Travis, Kevin K Brown, Thomas V Colby, Jeffrey R Galvin, Jonathan G Goldin, David M Hansell, Yoshikazu Inoue, Takeshi Johkoh, Andrew G Nicholson, Shandra L Knight, Suhail Raoof, Luca Richeldi, Christopher J Ryerson, Jay H Ryu, Athol U Wells

Typical UIP CT pattern	Probable UIP CT pattern	CT pattern Indeterminate for UIP	CT features most consistent with non-IPF diagnosis

Pas de Biopsie pulmonaire → **FPI**

Pas de Biopsie pulmonaire *(dans un contexte idiopathique)* → **FPI**

Biopsie pulmonaire → **Diagnostic**

Lynch, Lancet Respir Med 2017

Faut-il biopsier les PIC probables ?

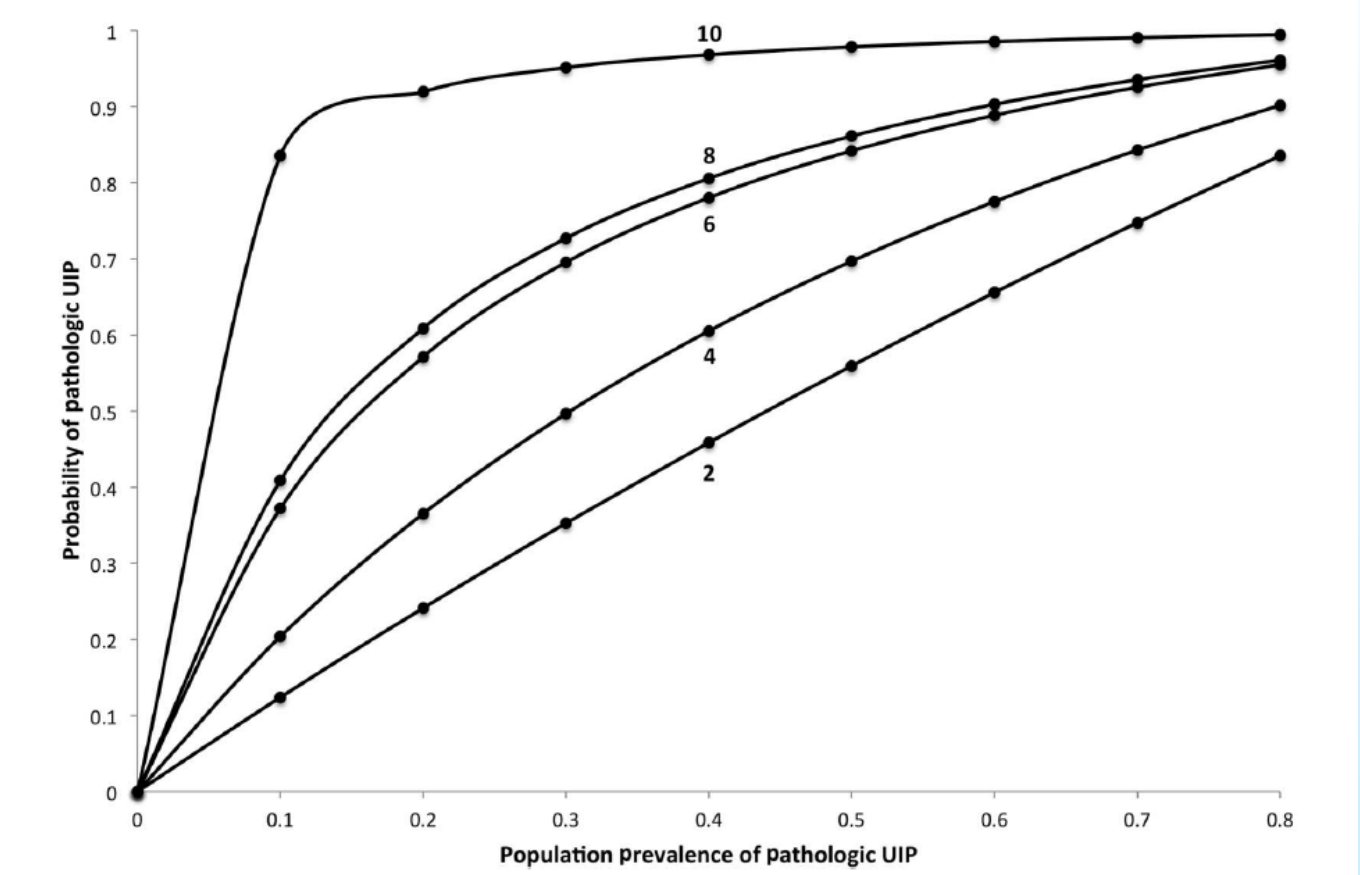
- **Raghu, Lancet Respir Med 2014**
  - TDM PIC probable ou possible proposés pour un essai thérapeutique : **94% PIC Histo**
- **Chung, Chest 2015**
  - TDM PIC probable (N=32) → **82% PIC Histo** (N=26)
- **Raghu, AJRCCM 2016**
  - INPULSIS trial : 30% “probable” → même déclin annuel
- **Brownell, Thorax 2017**
  - TDM PIC possible (n=64) : Sp 91%, VPP 62% PIC Histo
  - score de bronchectasies ≥ 4, ou sexe masculin ou âge>60 ans : ↗VPP

Faut-il biopsier les PIC probables ?

Table 3 The usual interstitial pneumonia (UIP) score model

Characteristic	Points
Age, in years	
50–59	2
≥60	3
Male sex	1
Possible UIP+total traction bronchiectasis score ≥ 4	6
Total score possible	10

The extent of radiographic traction bronchiectasis was scored in each lobe (right upper, middle, and lower lobes and left upper, lingula, and lower lobes) as 0-absent, 1-mild, 2-moderate, or 3-severe, and then summed to provide a total traction bronchiectasis score (see online supplementary figure S1 and ref. 14).

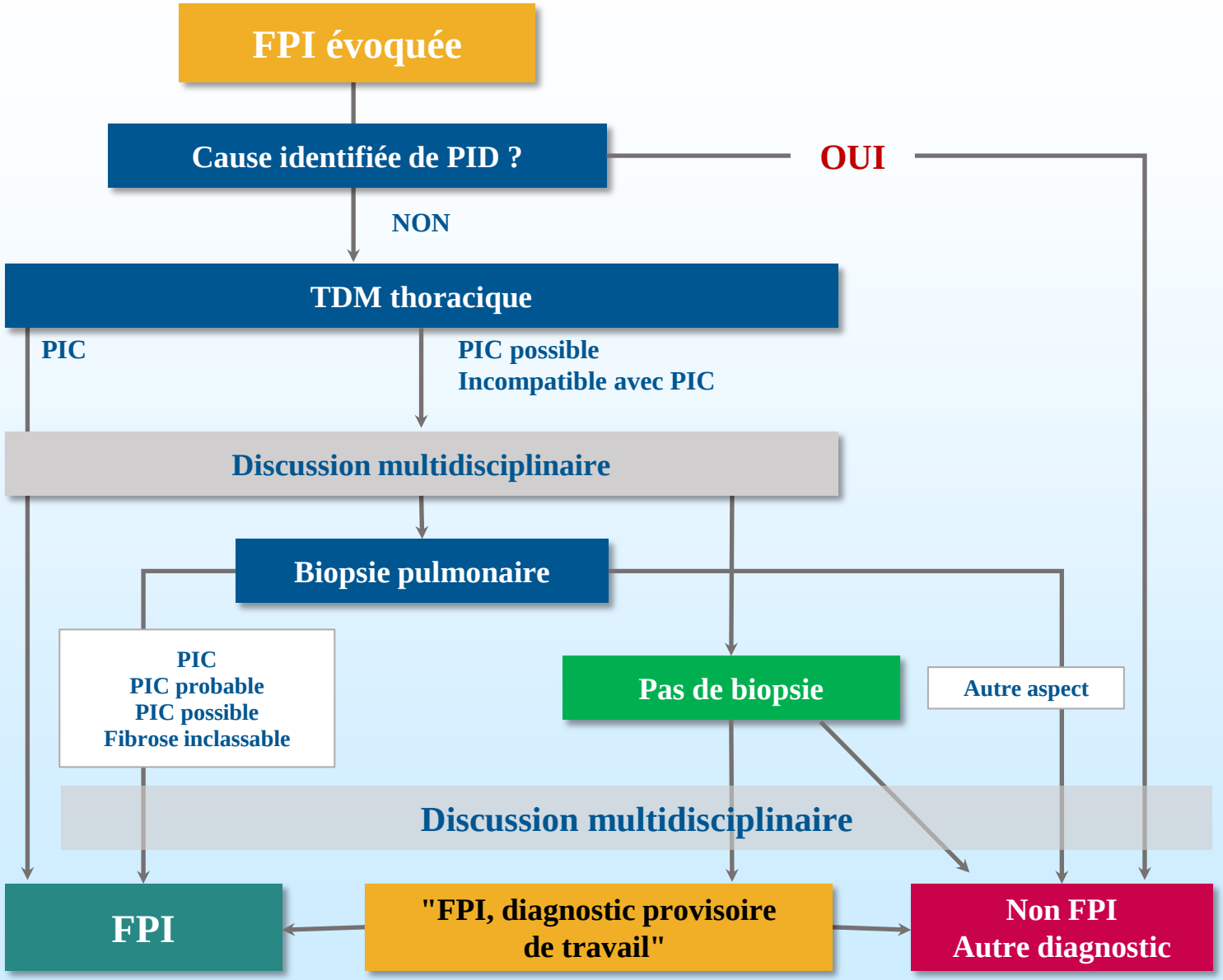


Brownell, Thorax 2017

Faut-il biopsier les PIC probables ?

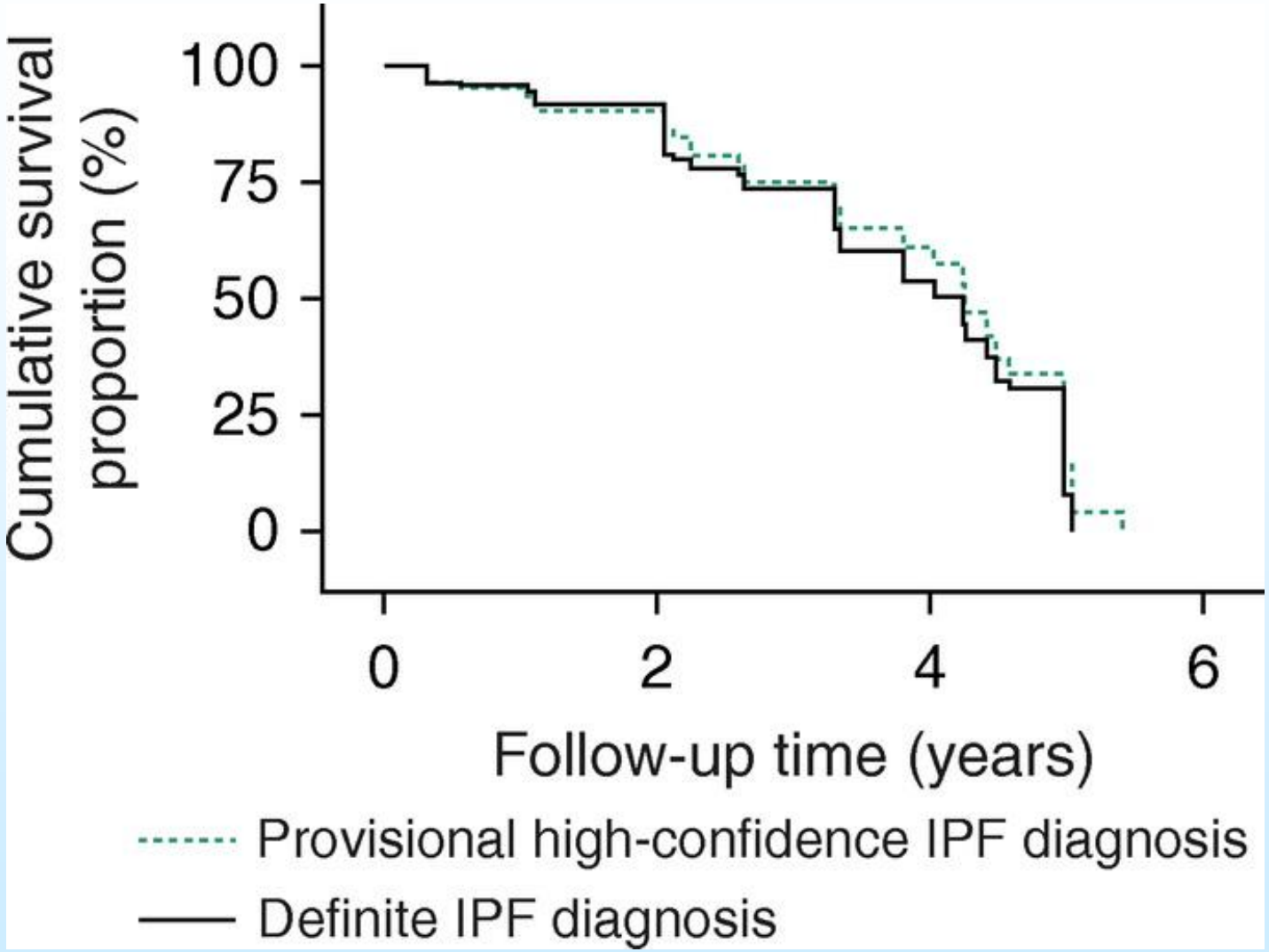
Discussion au cas par cas intégrant les données cliniques

En l'absence de biopsie ?



Cottin et al, Rev Mal Respir 2017

IPF : working diagnosis



Definite IPF :
Probability >90%

Provisional high confidence :
Probability 70-89%

Walsh, AJRCCM 2019

Surgical lung biopsy for the diagnosis of interstitial lung disease in England: 1997–2008

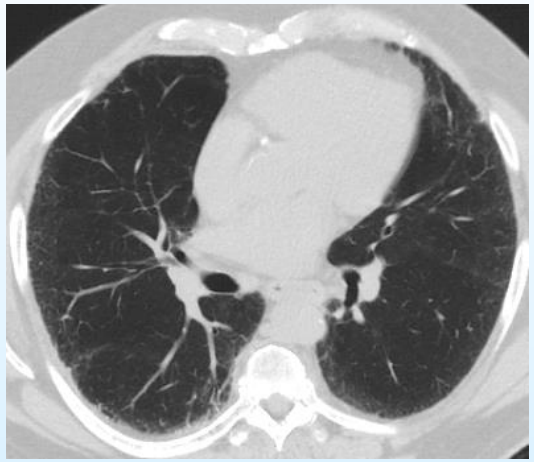
John P. Hutchinson, Tricia M. McKeever, Andrew W. Fogarty, Vidya Navaratnam and Richard B. Hubbard

Mortalité associée aux Biopsies chirurgicales programmées (PID)

- hospitalière : 1.0%
- 30 jours : 1.5%
- 90 jours : 2.8%

Eur Respir J,2017

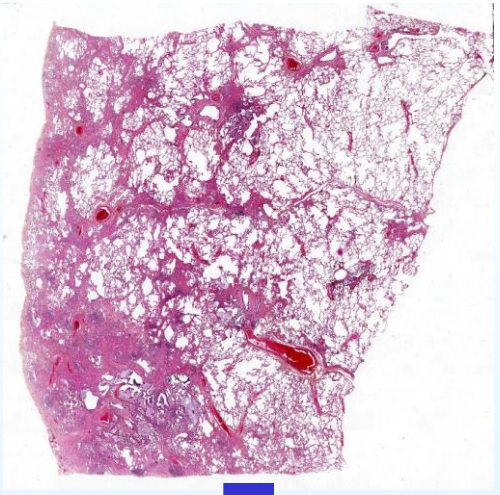
Les alternatives à la biopsie chirurgicale

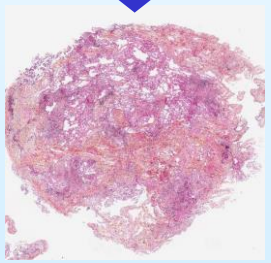


Analyse « profonde »
du scanner
(texture, IA)

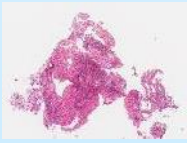
Marqueurs

- ***Génétiques***
- ***Sanguins***
- ***Air exhalé***
- ***LBA***
- ***…***



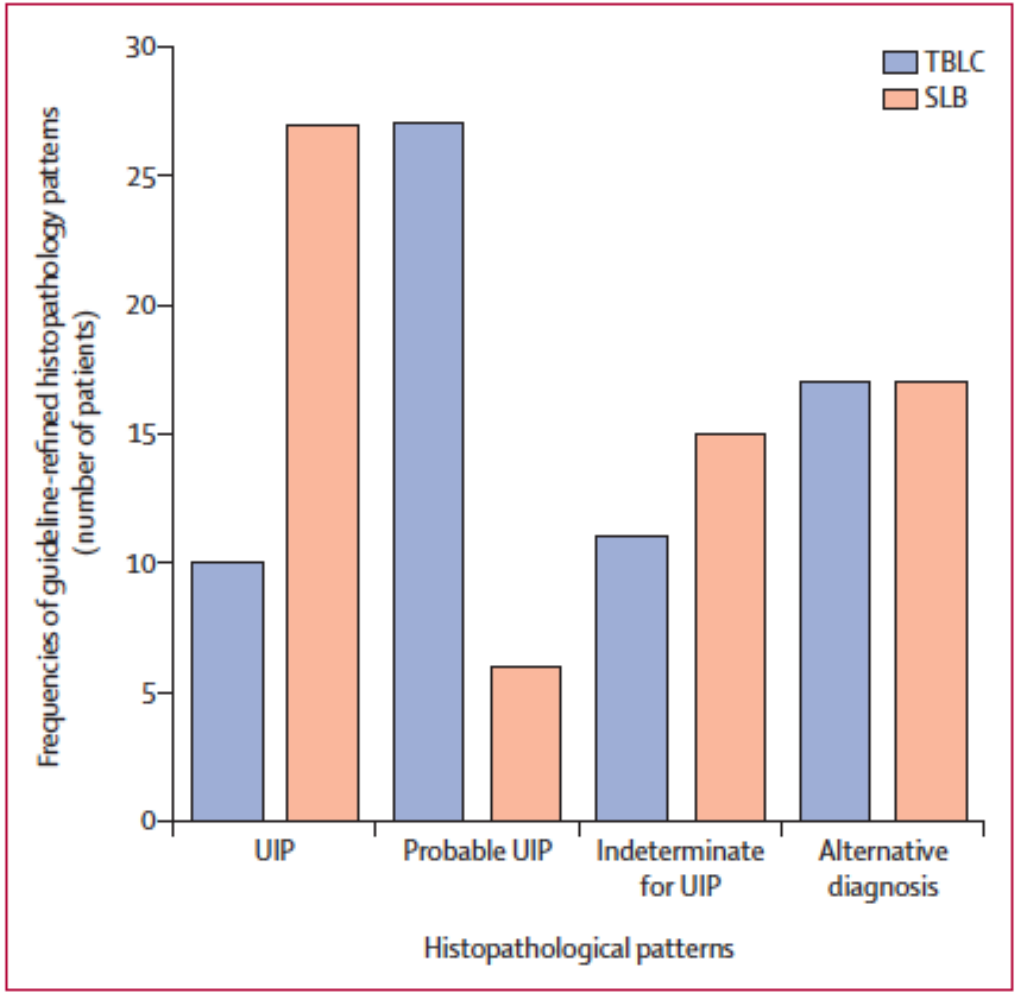


Cryobiopsie

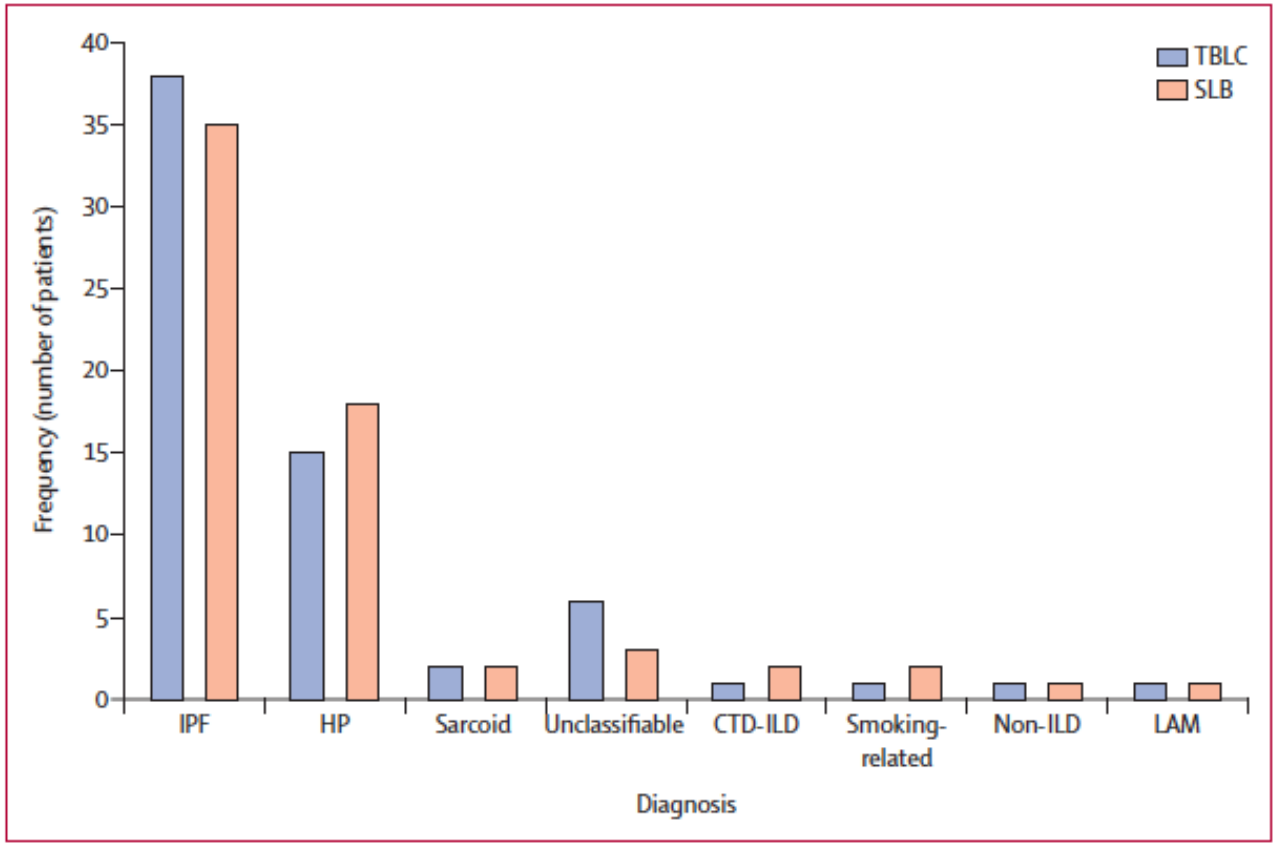


BTB

Cryobiopsie



Diagnostic en DMD



Troy, Lancet Respir Med 2019

Nouveaux outils pour le diagnostic

Envisia™ Genomic Classifier

Improving Diagnosis of Idiopathic Pulmonary Fibrosis

The newly launched Envisia Genomic Classifier aids in the molecular detection of Usual Interstitial Pneumonia (UIP), a hallmark of Idiopathic Pulmonary Fibrosis (IPF). The Envisia classifier may help reduce unnecessary diagnostic surgeries, patient anxiety and healthcare costs. Learn more.

Biopsie transbronchique

(exclusion des patients avec TDM typique ou probable)

UIP *vs* non UIP

Se : 88% (69-97)
Sp : 76% (50-93)
VPP : 81% (54-96)
VPN : 85% (65-96)

Lynch, Chest 2018; Choi et al. BMC Genomics 2018, 19(Suppl 2):101
Raghu, Lancet Respir Med 2019

Traitement

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, Jan L. Brozek, Harold R. Collard, William Cunningham*, Sakae Homma, Takeshi Johkoh, Fernando J. Martinez, Jeffrey Myers, Shandra L. Protzko, Luca Richeldi, David Rind, Moises Selman, Arthur Theodore, Athol U. Wells, Henk Hoogsteden, 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, 2014).

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

Raghu et al, AJRCCM 2015;192:238

Rev Mal Respir 2017

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.

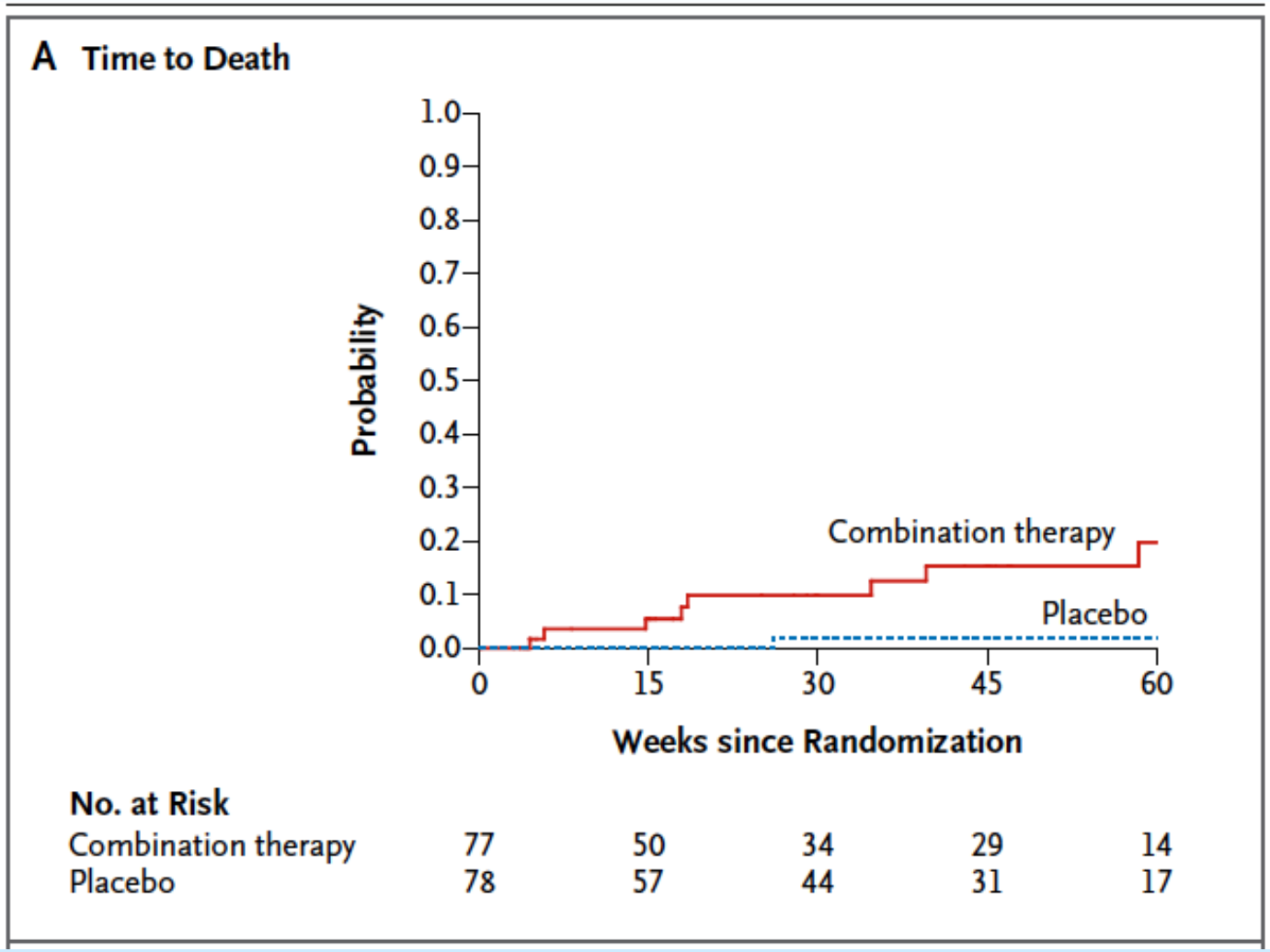
Weill, JHLT 2015

Jusqu’en 2011,
Prednisone + AZA + NAC
=
le standard thérapeutique

…Mais efficacité contre placebo non démontrée !

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

Increased mortality in treated patients



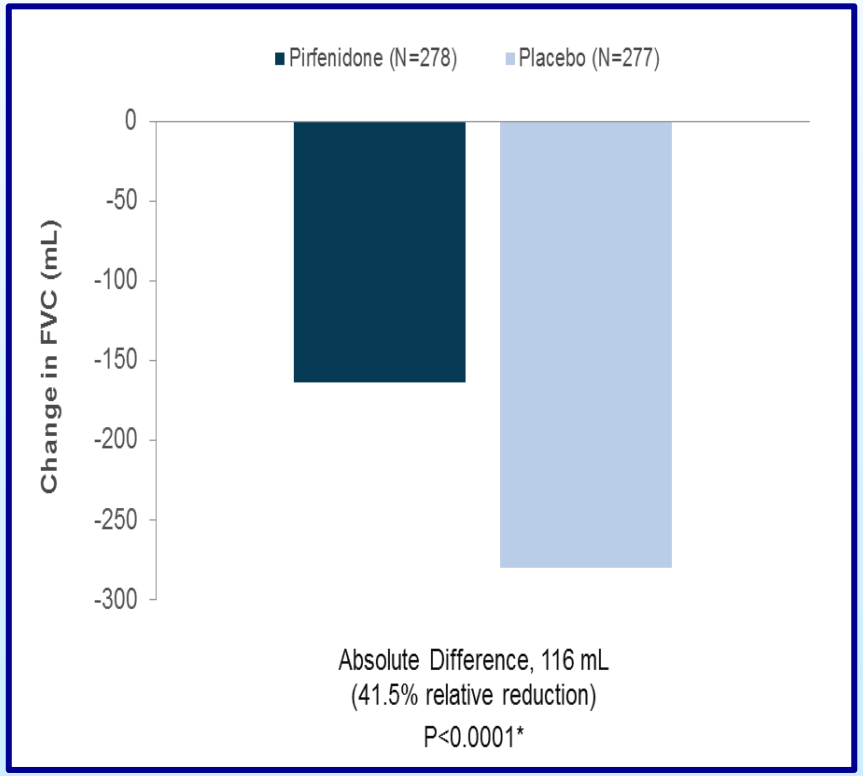
(IPFNet, NEJM 2012)

- **Pirfenidone (Esbriet°) disponible en France depuis 2012, autorisé par la FDA le 15 Octobre 2014**
  - **(médic d'exception)**

- **Nintedanib (Ofev®) : autorisé par la FDA le 17 octobre 2014 et par l'EMA le 20 Novembre 2014 . Disponible en Pharmacie depuis Janvier 2016**
  - **(médic d'exception)**

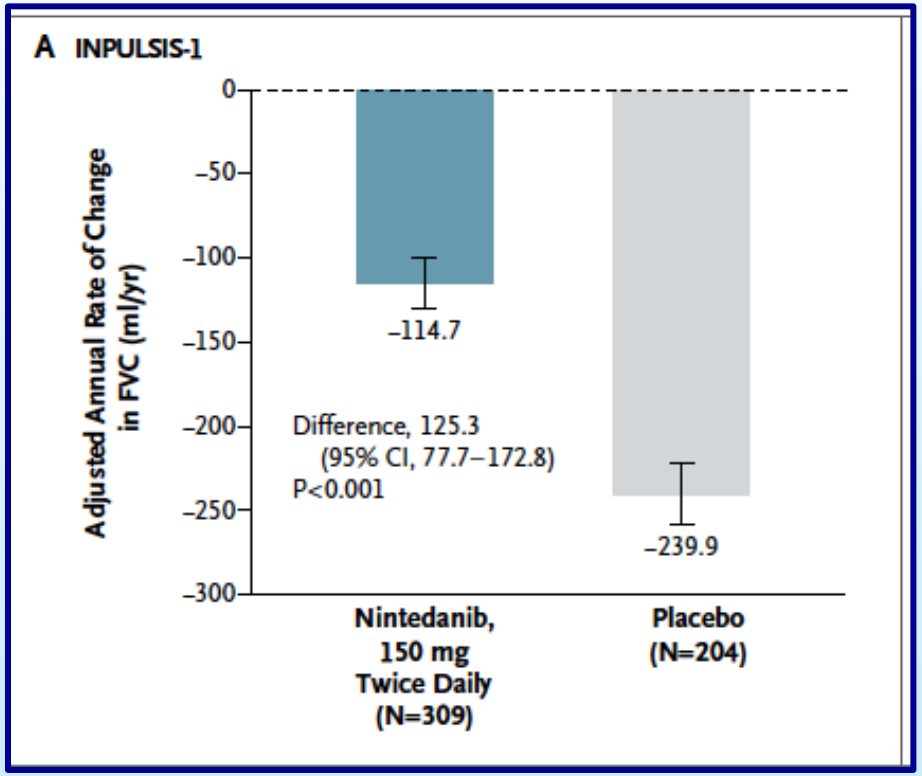
The current situation : treatment of IPF

Pirfenidone



King, NEJM 2014

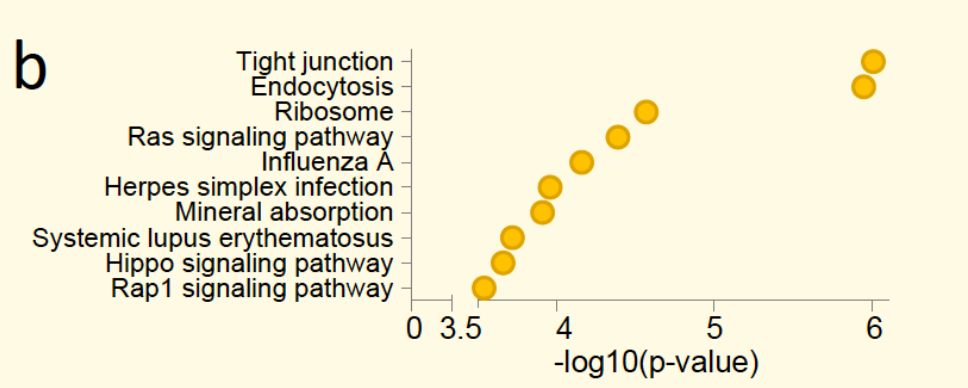
Nintedanib

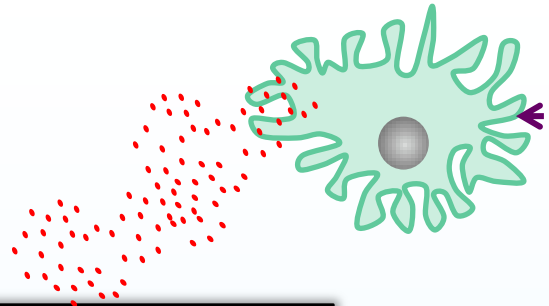


Richeldi, NEJM 2014

Top ten pathways modulated by Pirfenidone in vivo

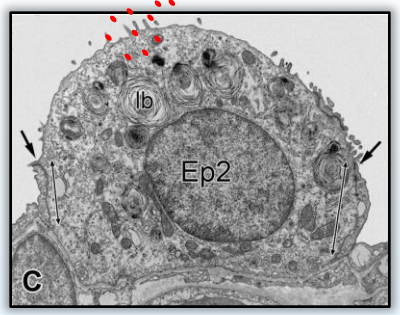
Kwapiszewska, Eur Respir J 2018





Macrophage

Huang, Ann Rheum Dis 2017



Lehmann, Respir Res 2018

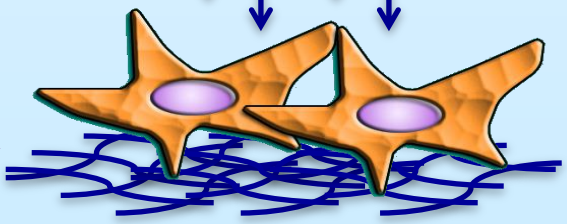
VEGFR
FGFR
PDGFR
CSF-1
Src, Lyn, Lck, Flt3

Pirfenidone

Nintedanib

ER stress, UPR activation

Cytokines, Chimiokines, Lipids, GFs, ROS Developmental pathways



Collagen fibril assembly

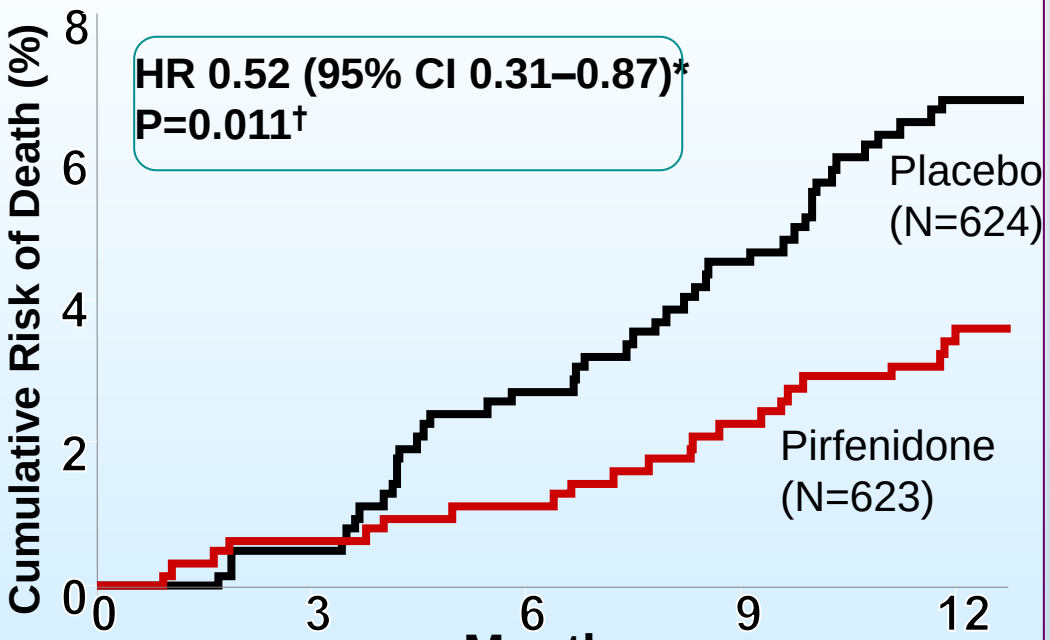
Knüppel, AJRCMB 2017

Lehtonen, Respir Res 2016

Activation, Migration, Proliferation of Fibroblasts

A trend toward improved Survival

Pirfenidone

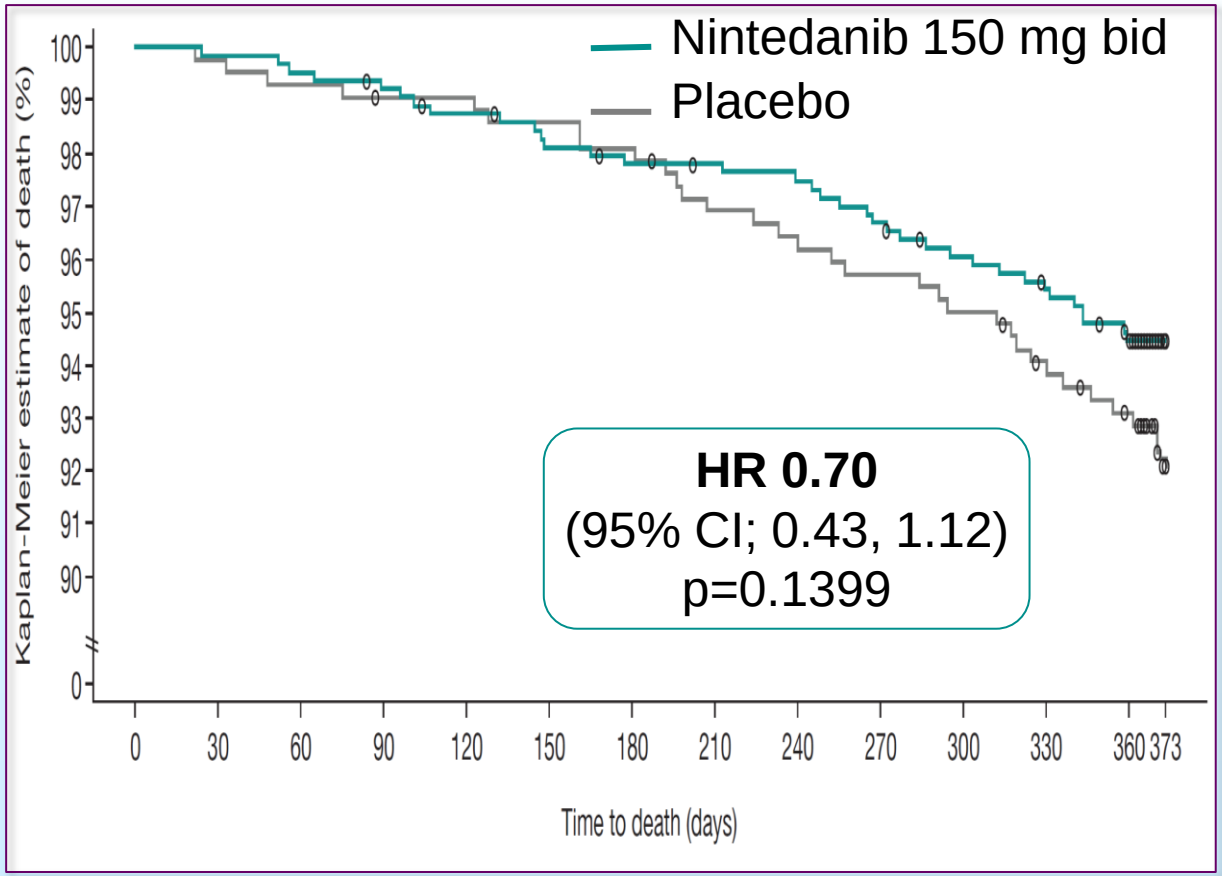


Patients at Risk, n					
Pirfenidone	623	618	609	596	509
Placebo	624	619	603	586	490

* Cox proportional hazards model
† Log-rank test

King et al, NEJM 2014

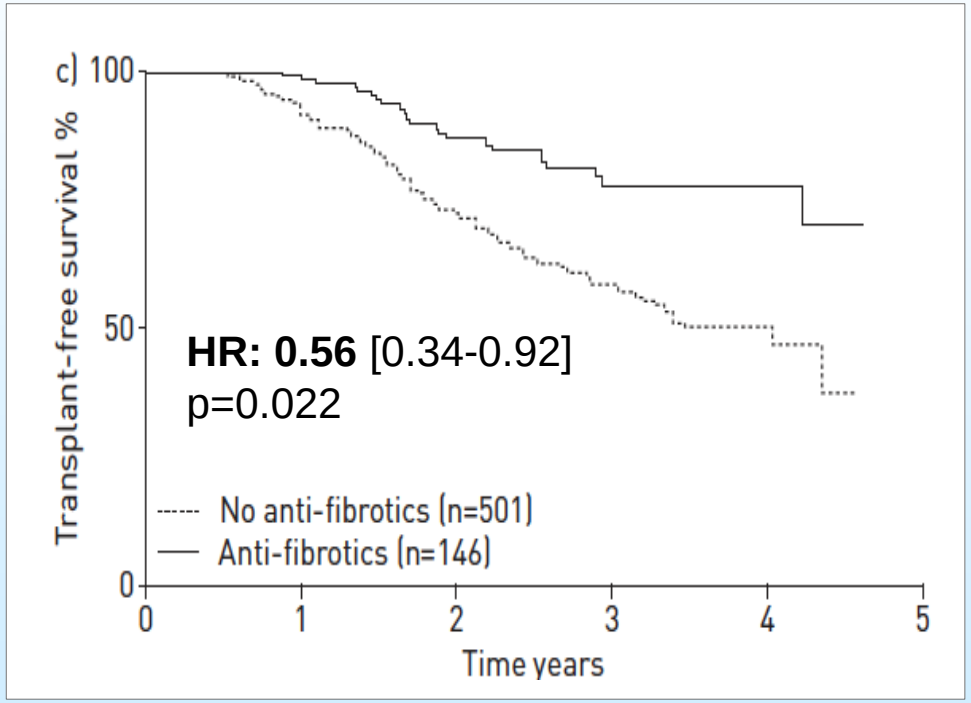
Nintedanib



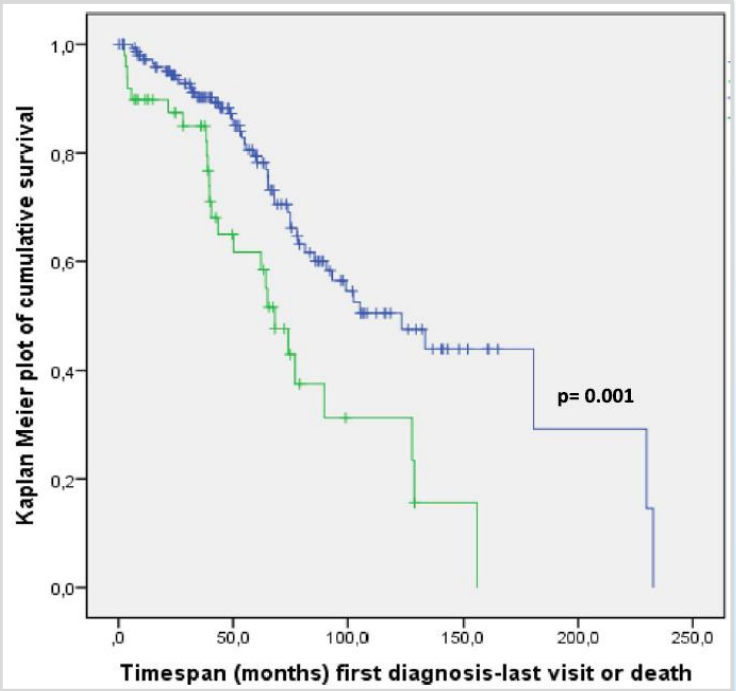
Richeldi et al, NEJM 2014

Real life data support a survival benefit

Australian registry[1]



EurIPF registry[2]



Belgian series[3]

Antifibrotics

HR : 0.36

(0.23 - 0.55)

P<0.001

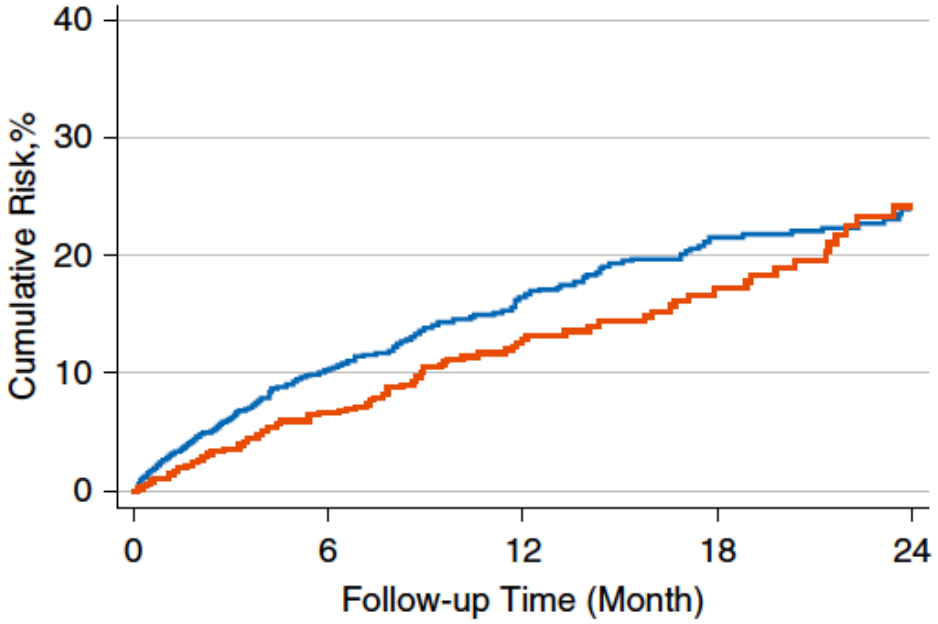
1: Jo et al, Eur Respir J 2017

2: Guenther, Respir Res 2018

3: De Sadeleer, Respirology 2018

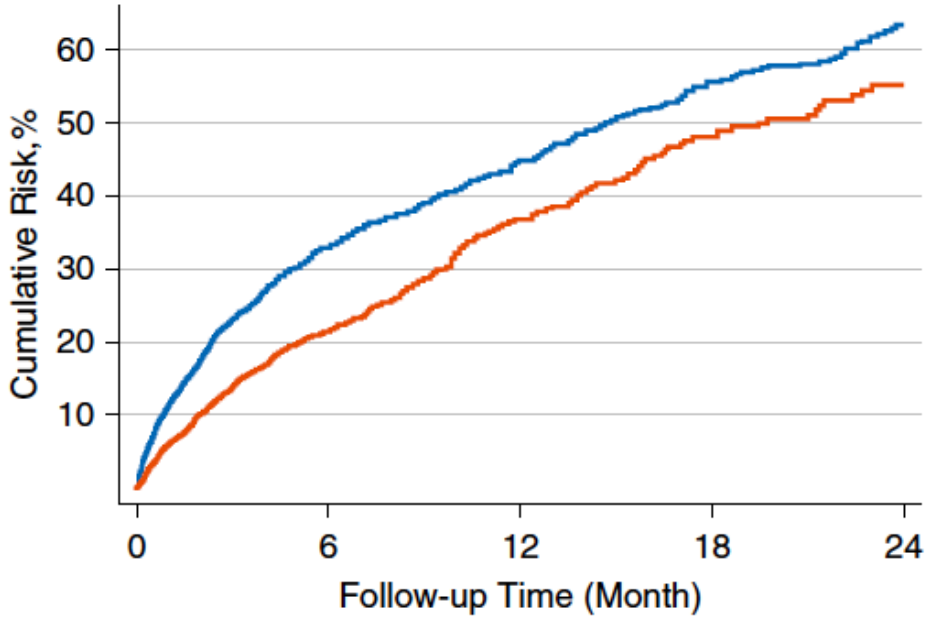
Real life data support a survival benefit for 2 years (US)

All cause mortality



Untreated	10.4 (8.7, 12.4)	16.5 (14.2, 19.1)	21.6 (18.8, 24.7)	23.9 (20.7, 27.5)
Treated	6.7 (5.2, 8.5)	12.9 (10.4, 16.0)	17.2 (13.8, 21.3)	24.2 (19.3, 30.2)

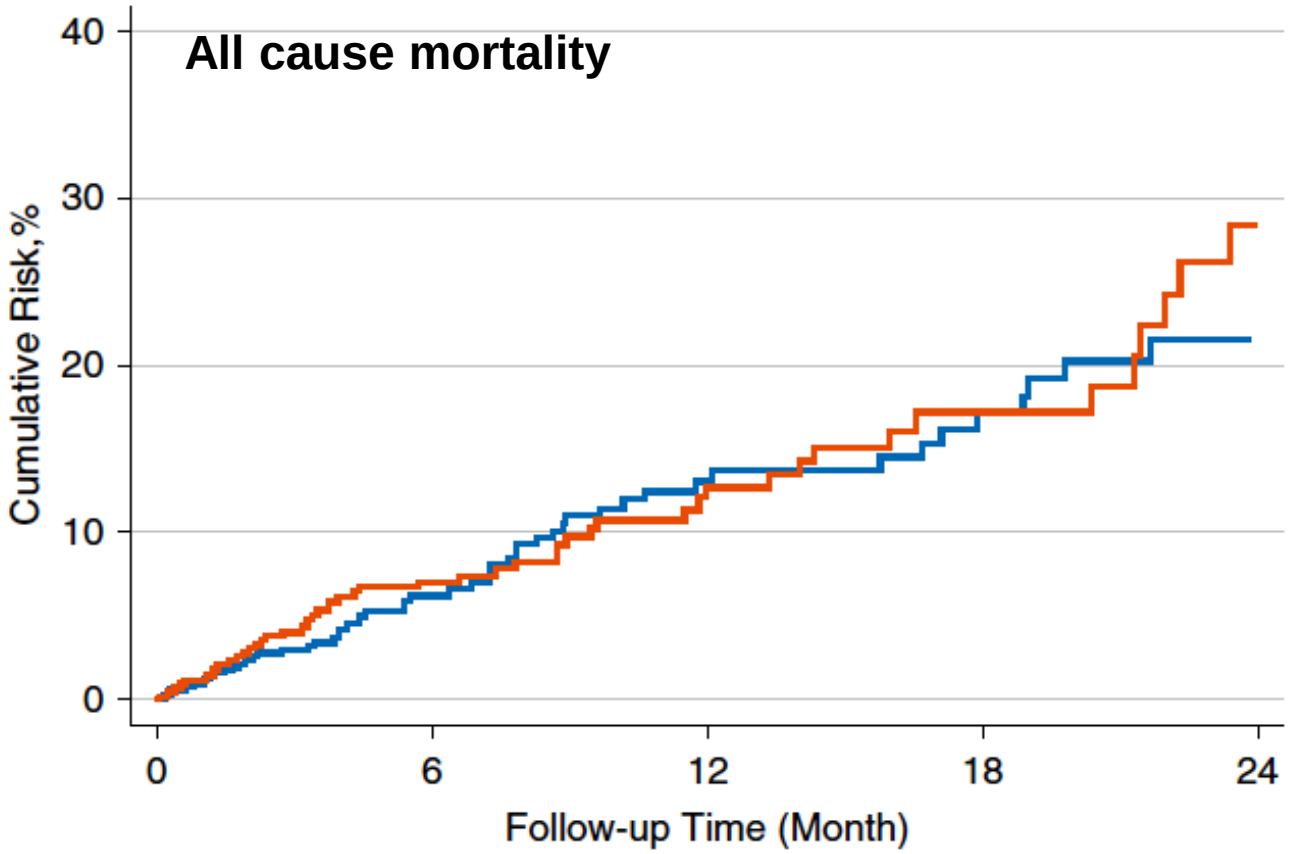
Acute Hospitalization



Untreated	32.9 (30.2, 35.8)	44.9 (41.7, 48.2)	55.7 (52.1, 59.4)	63.4 (59.3, 67.5)
Treated	21.5 (19.0, 24.3)	36.8 (33.1, 40.9)	48.0 (43.3, 53.0)	55.2 (49.6, 60.9)

Dempsey, AJRCCM 2019

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

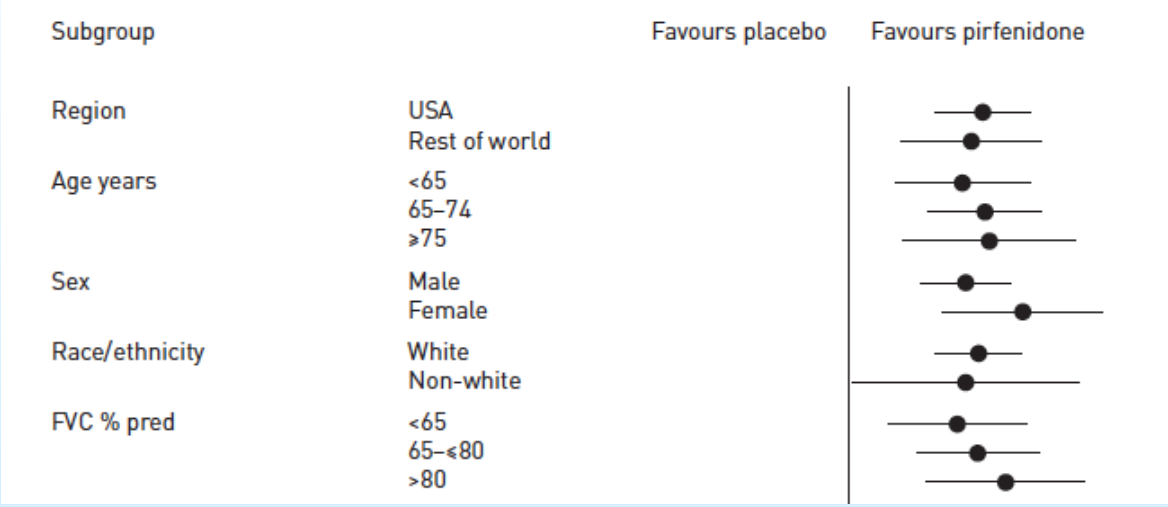


pirfenidone	6.3 (4.4, 9.0)	13.1 (9.7, 17.6)	17.2 (12.7, 23.0)	21.5 (15.9, 28.7)
nintedanib	7.1 (5.0, 9.9)	12.7 (9.3, 17.3)	17.2 (12.5, 23.4)	28.3 (20.0, 39.2)

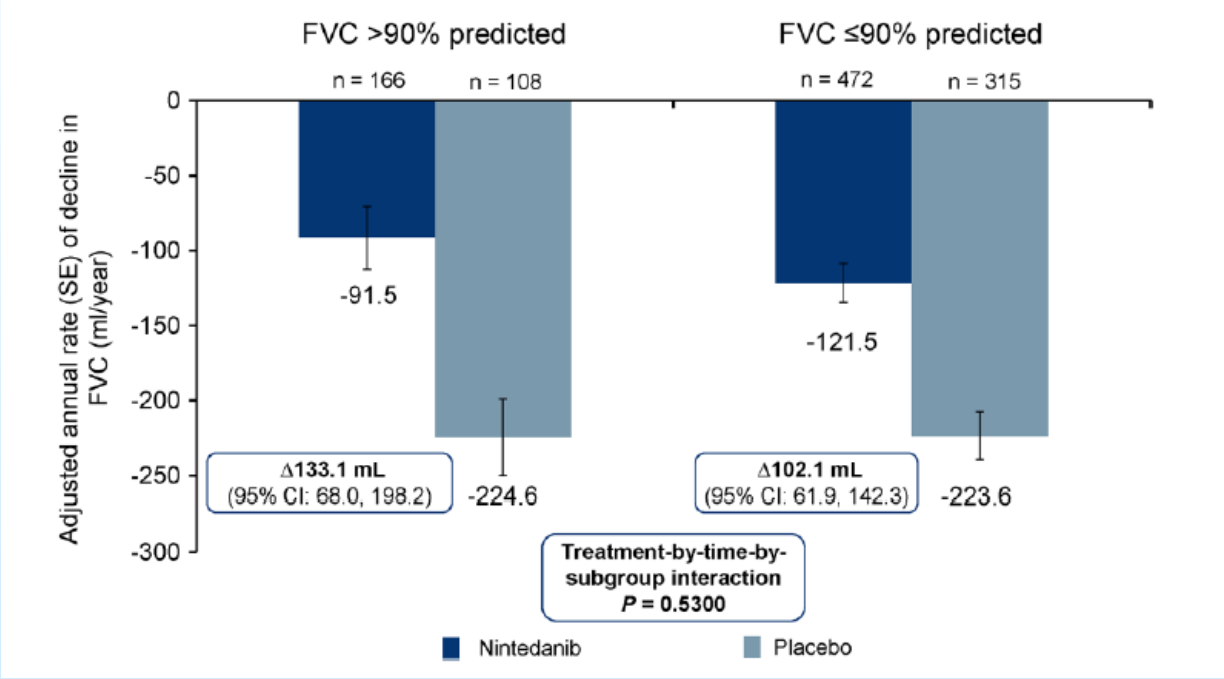
Dempsey, AJRCCM 2019

Pirfenidone and nintedanib are effective in early fibrosis

Pirfenidone



Nintedanib



Noble, Eur Respir J 2016

Kolb, Thorax 2016

Treat early !

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

Guideline 18. It is recommended to treat patients with a confirmed diagnosis of mild-to-moderate IPF (defined by a FVC ≥ 50% of the predicted value and a DLco ≥ 30%) with pirfenidone; this treatment should be initiated and monitored by a pulmonologist experienced in the diagnosis and treatment of IPF and requires a regular monitoring of the clinical tolerance and liver enzyme levels; patients should not smoke during treatment.

Guideline 19. It is recommended to treat patients with a confirmed diagnosis of mild-to-moderate IPF (defined by a FVC ≥ 50% of the predicted value and a DLco ≥ 30%) with nintedanib; this treatment should be initiated and monitored by a pulmonologist experienced in the diagnosis and treatment of IPF and requires a regular monitoring of the clinical tolerance and liver enzyme levels.

Cottin et al Rev Mal Respir 2017

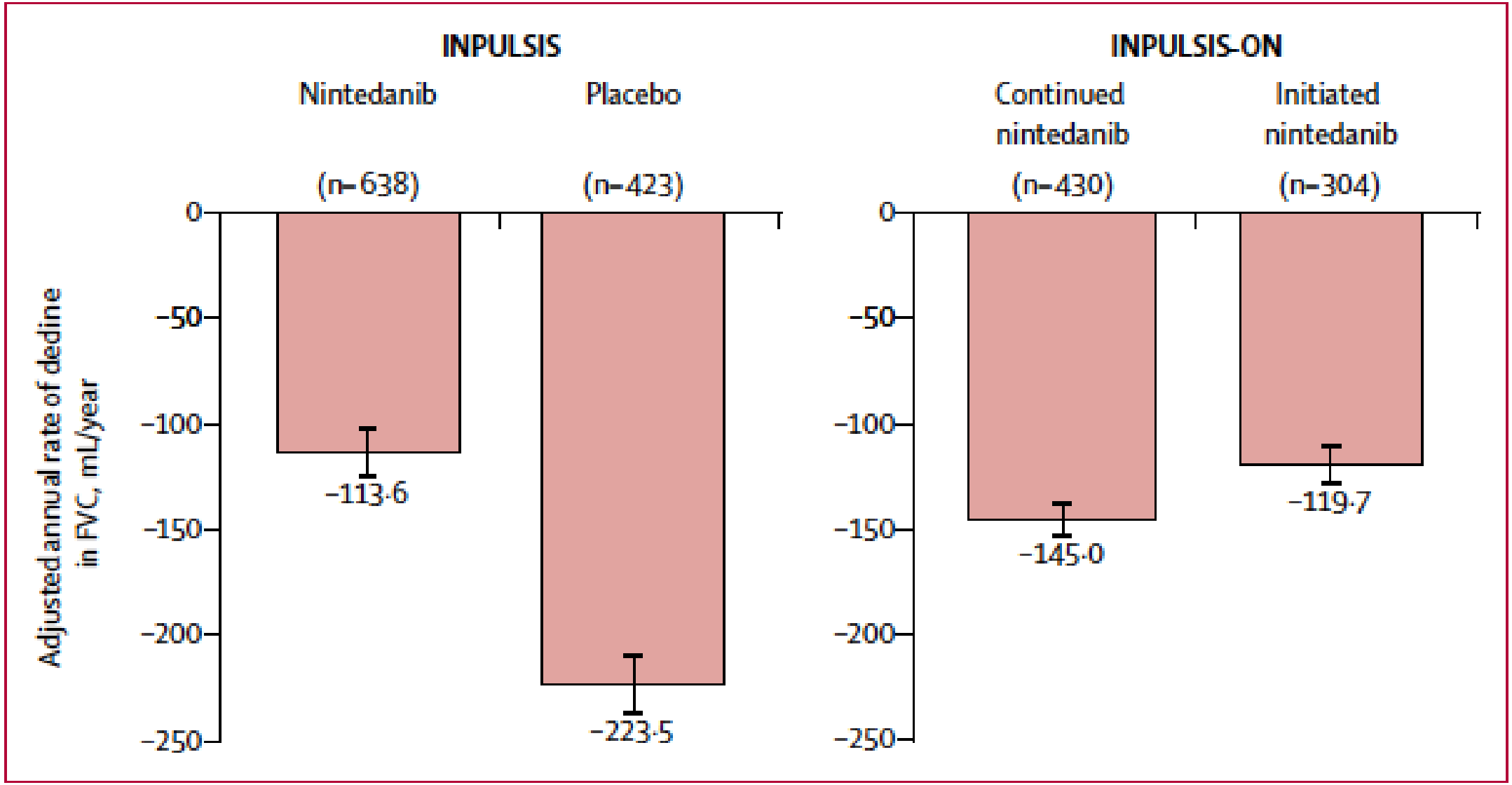
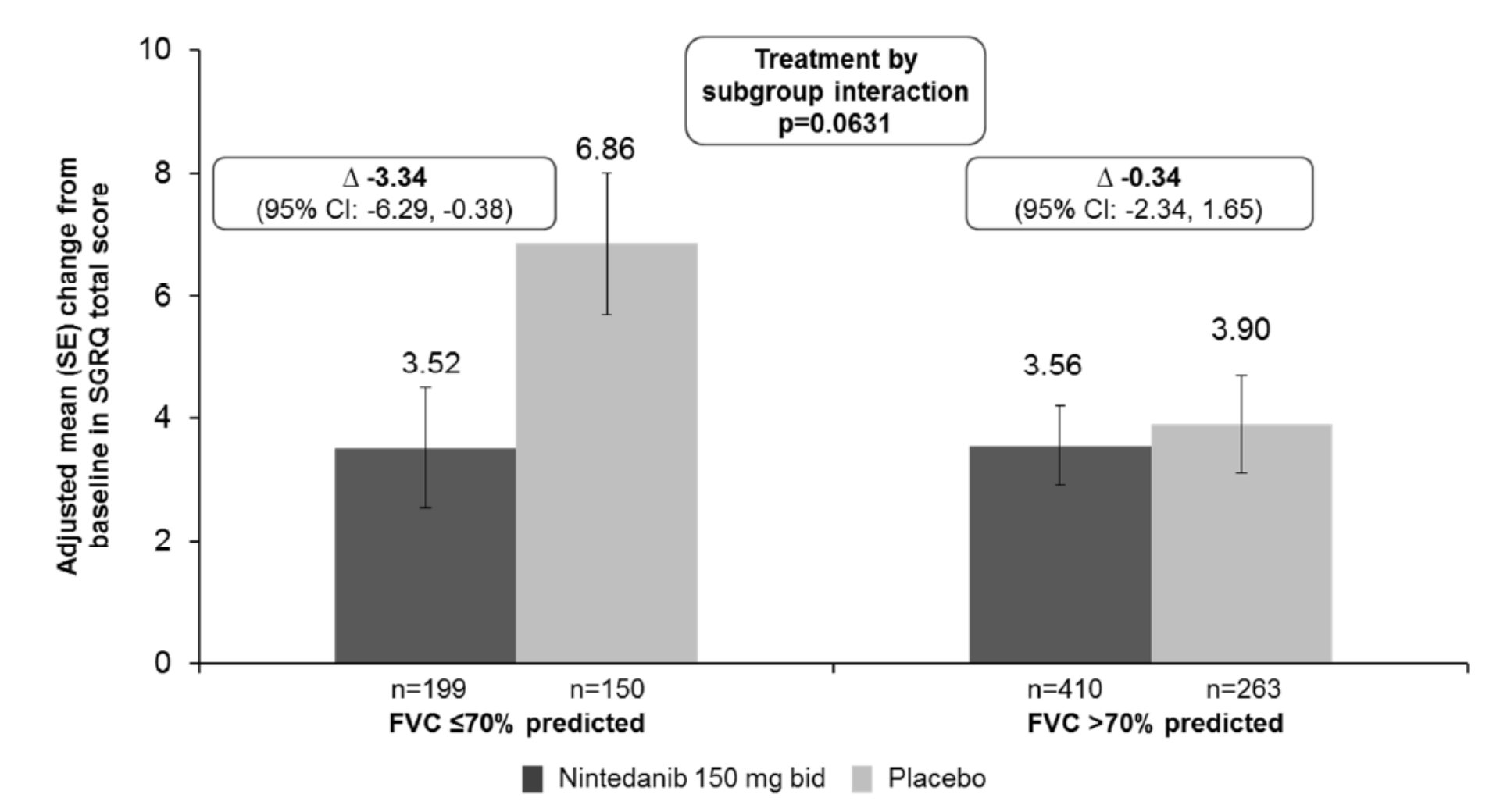


Figure 3: Annual rate of decline in FVC over 52 weeks in INPULSIS and over 192 weeks in INPULSIS-ON
Error bars show SE. FVC=forced vital capacity.

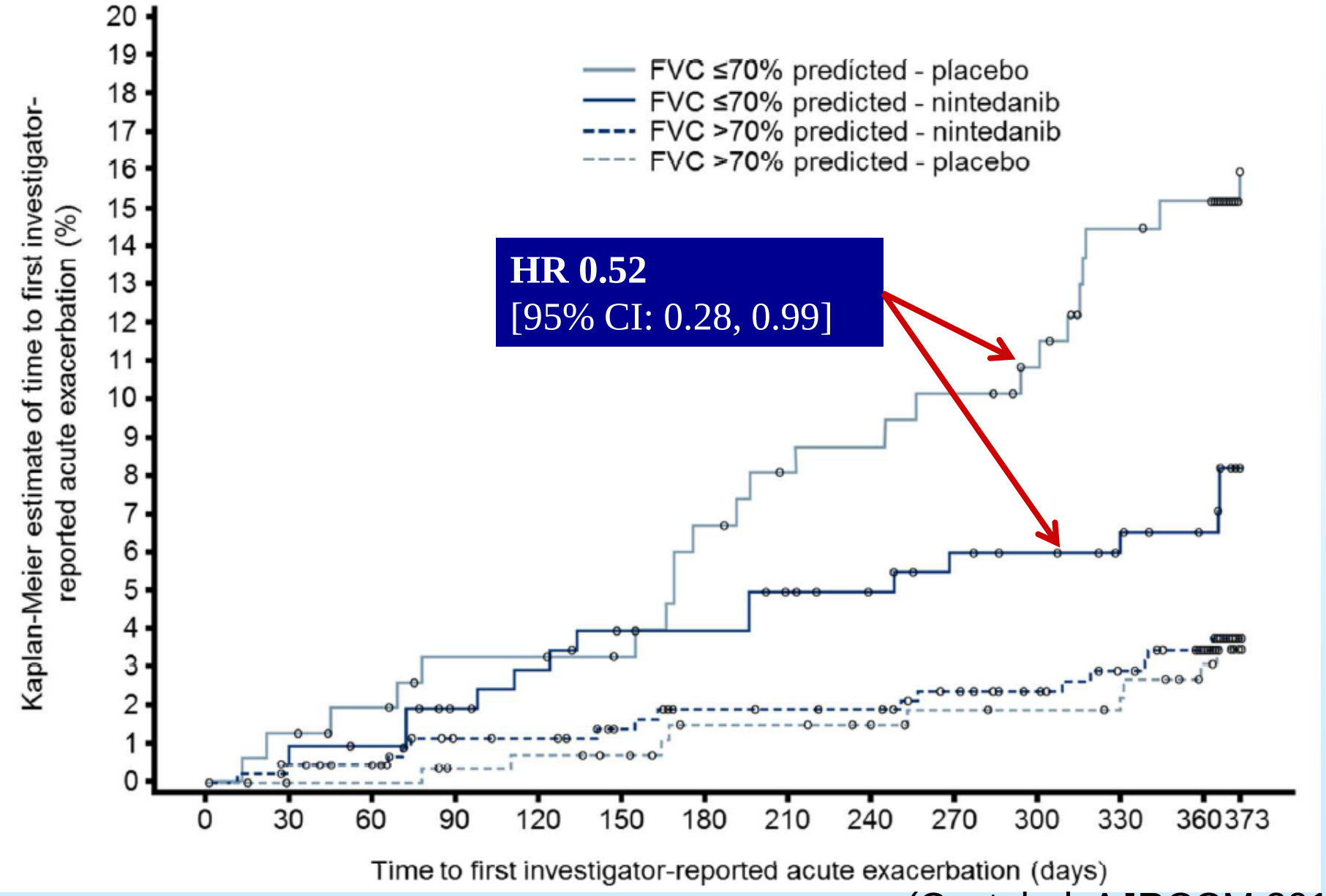
Crestani et al, Lancet Respir Med 2018

Evolution du score de qualité de vie (selon la CVF)



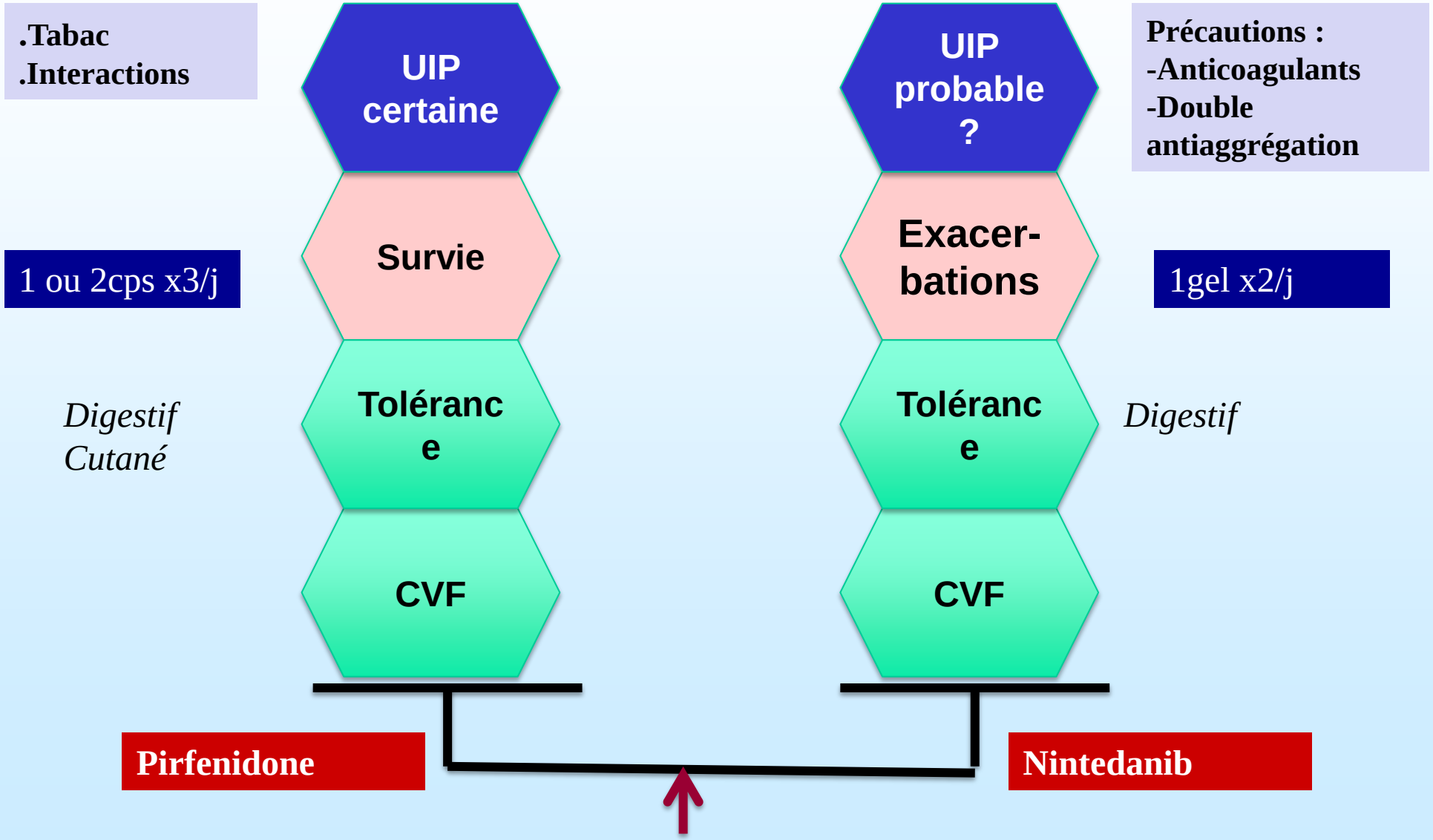
(Costabel, AJRCCM 2015)

Délai de survenue de la 1ère exacerbation (selon la CVF)



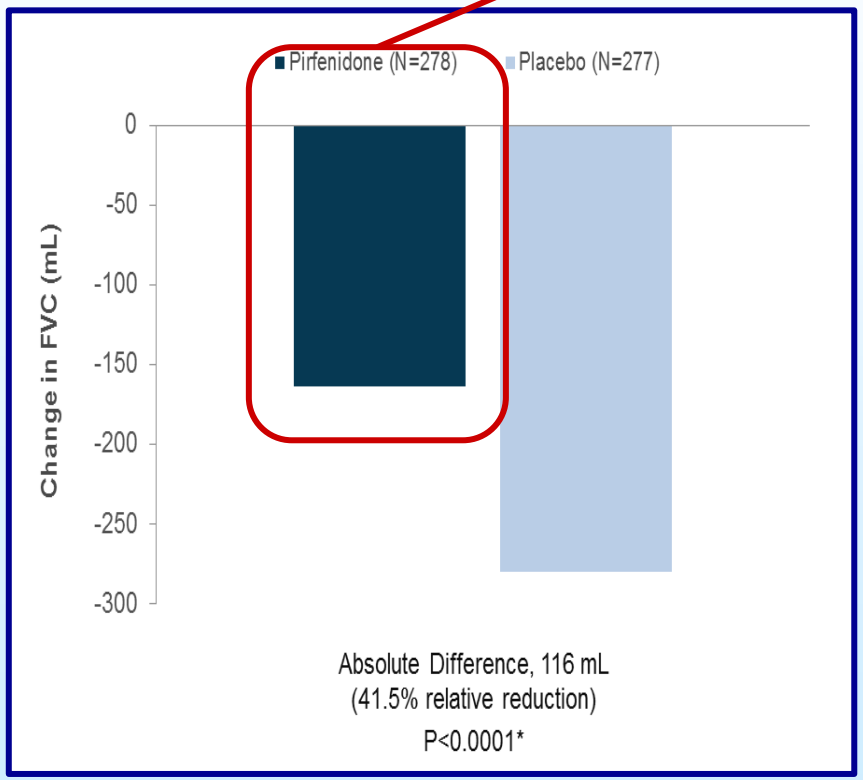
(Costabel, AJRCCM 2015)

Deux médicaments efficaces dans la FPI…Comment choisir ?



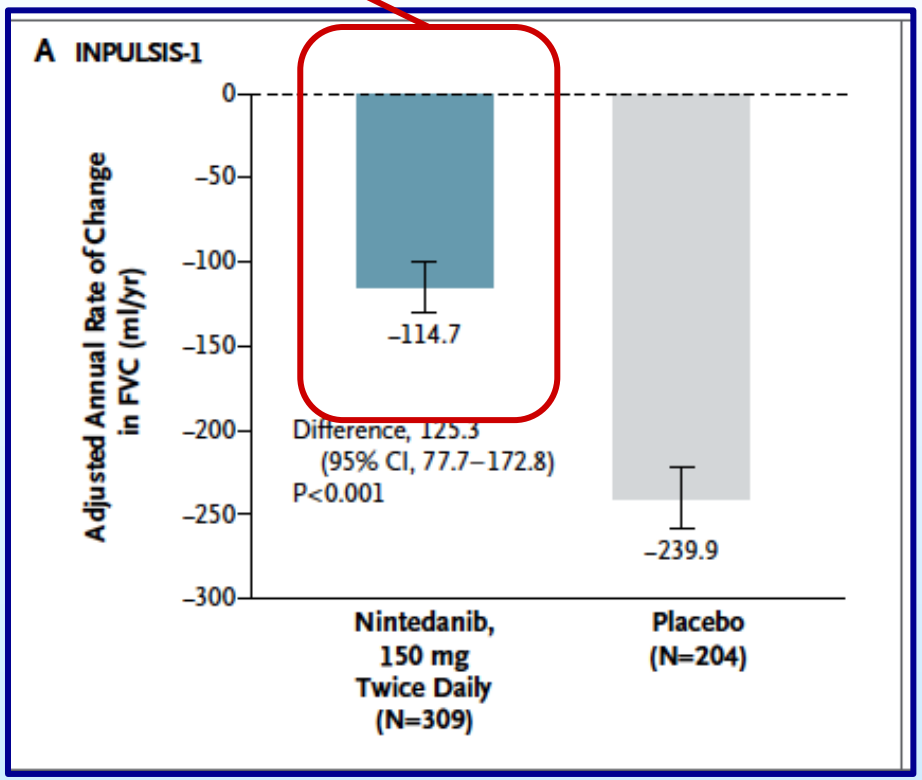
All patients will progress and ultimately will die with IPF

Pirfenidone



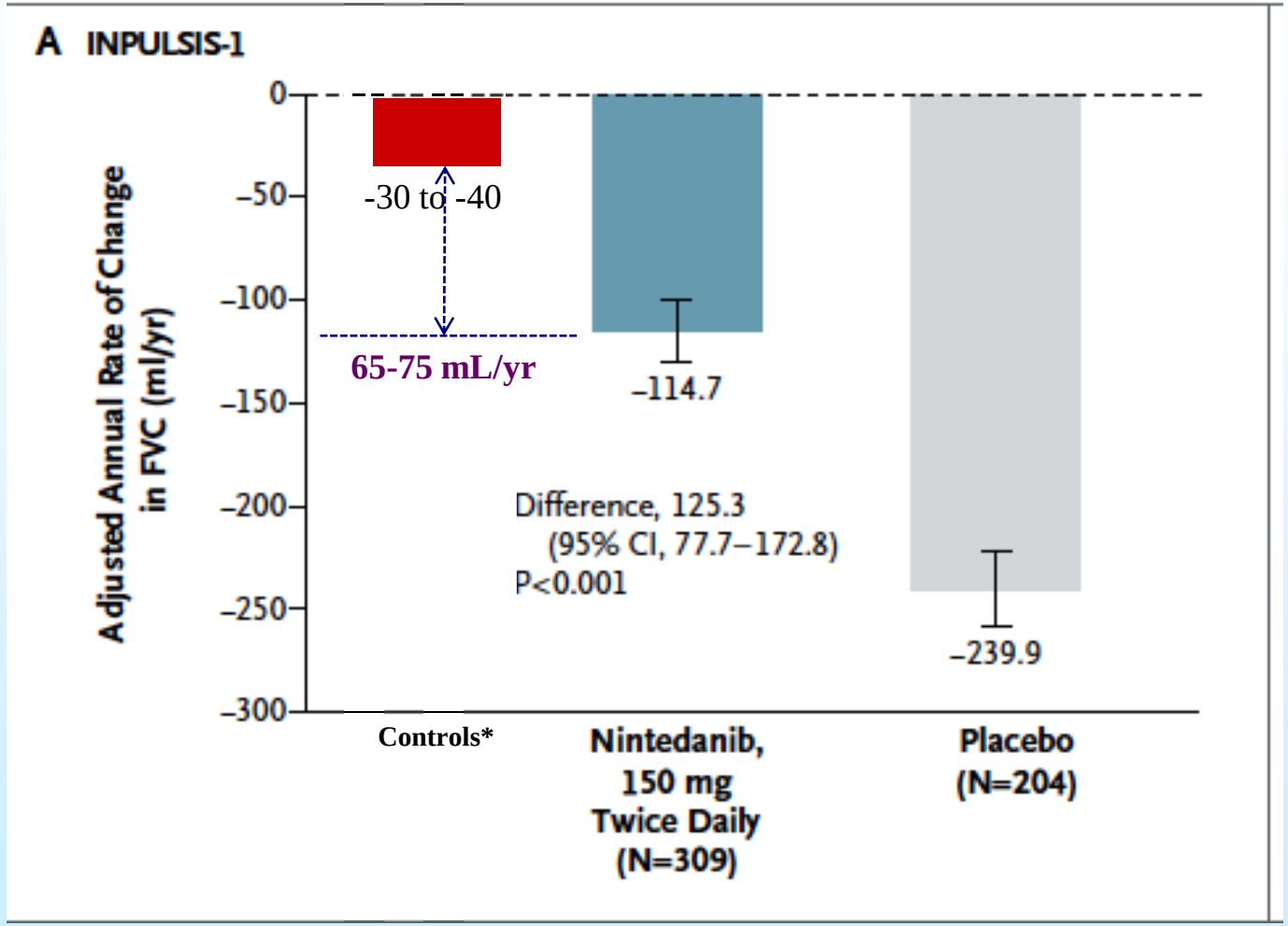
King, NEJM 2014

Nintedanib



Richeldi, NEJM 2014

The next frontier



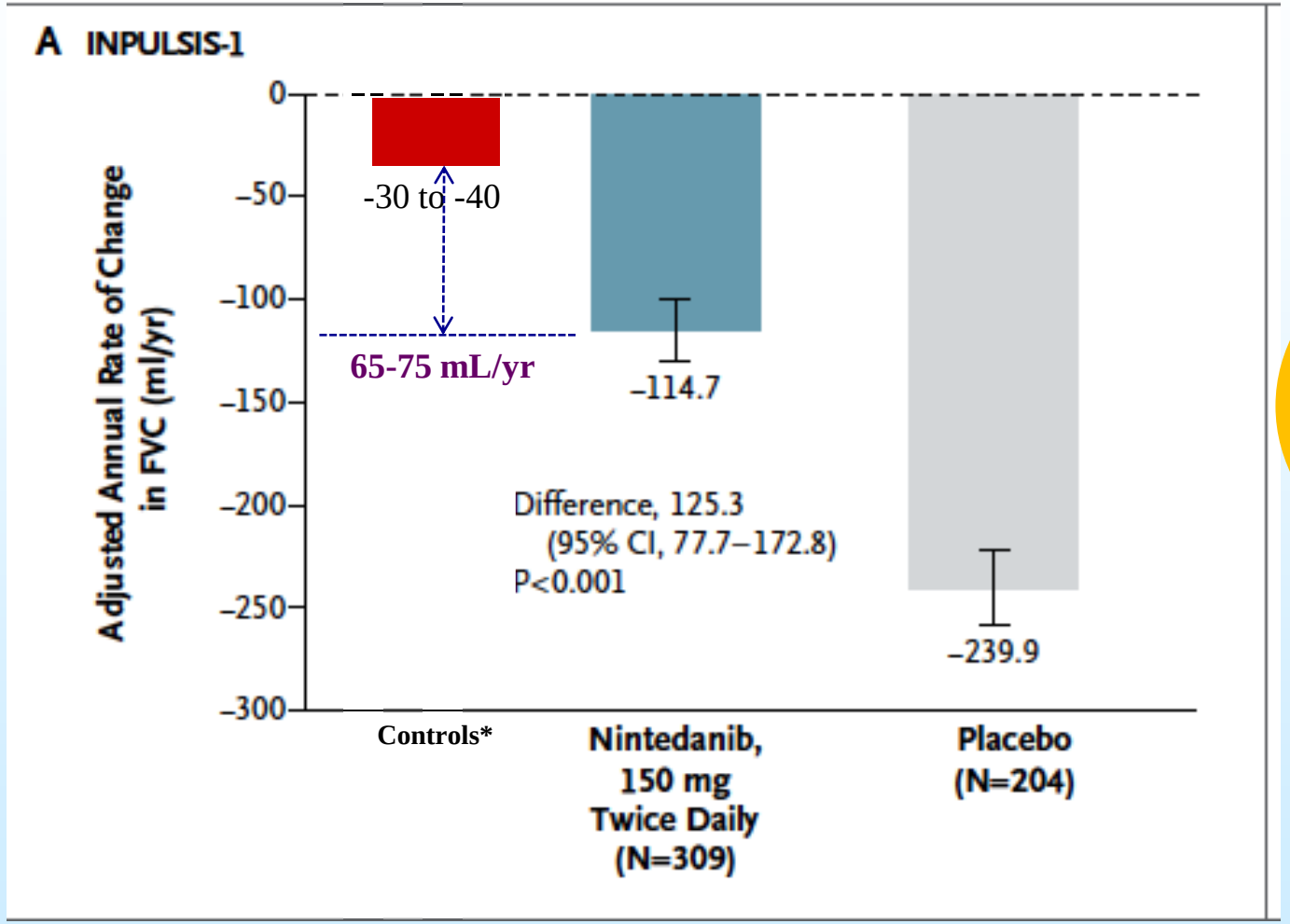
*Former smokers-60-75 years
Mirabelli, Respir Med 2016

modified from Richeldi, NEJM 2014

The next frontier

New therapies

Combination therapy



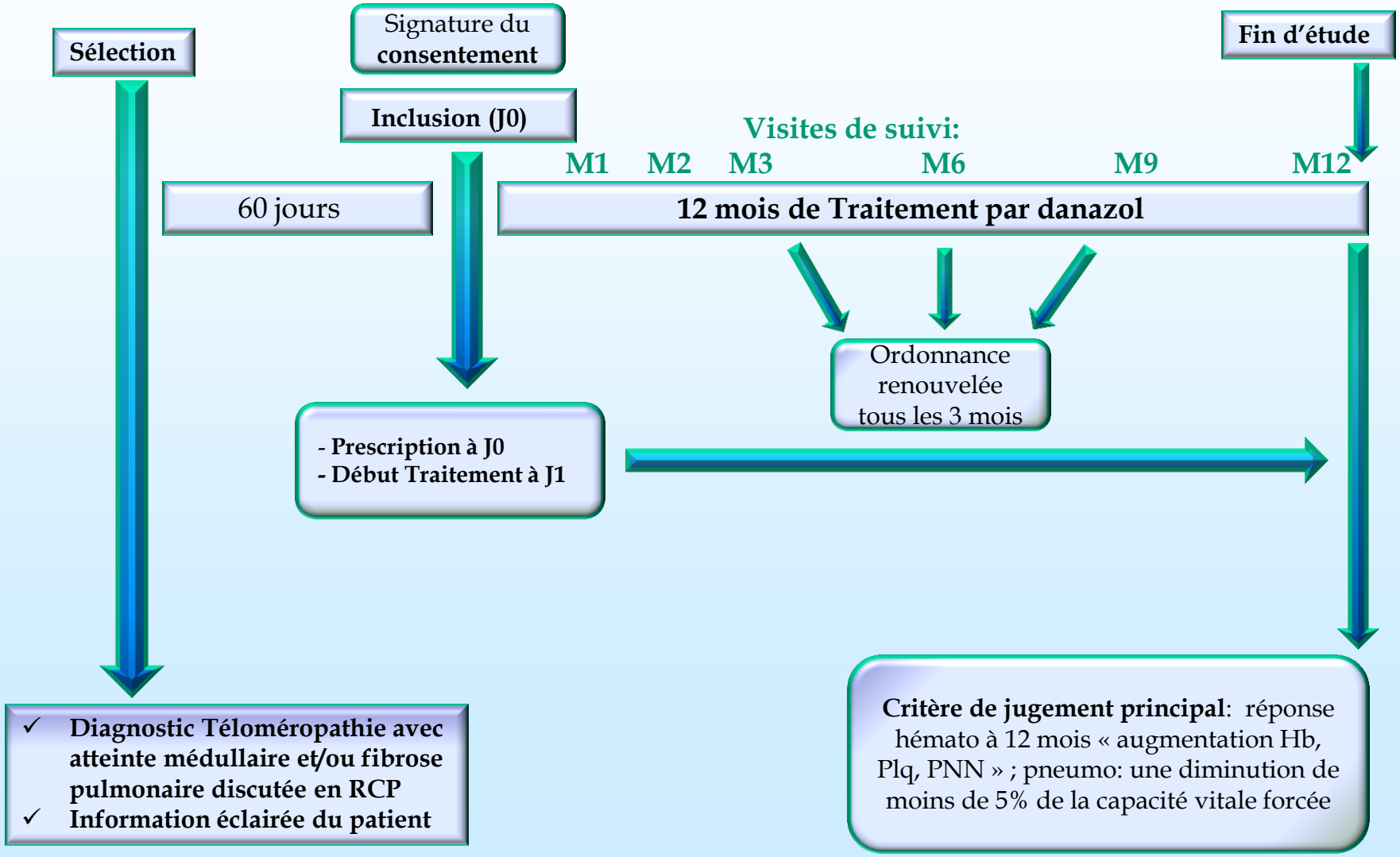
Tailored therapy
Defining endotypes in IPF patients

*Former smokers-60-75 years
Mirabelli, Respir Med 2016

modified from Richeldi, NEJM 2014

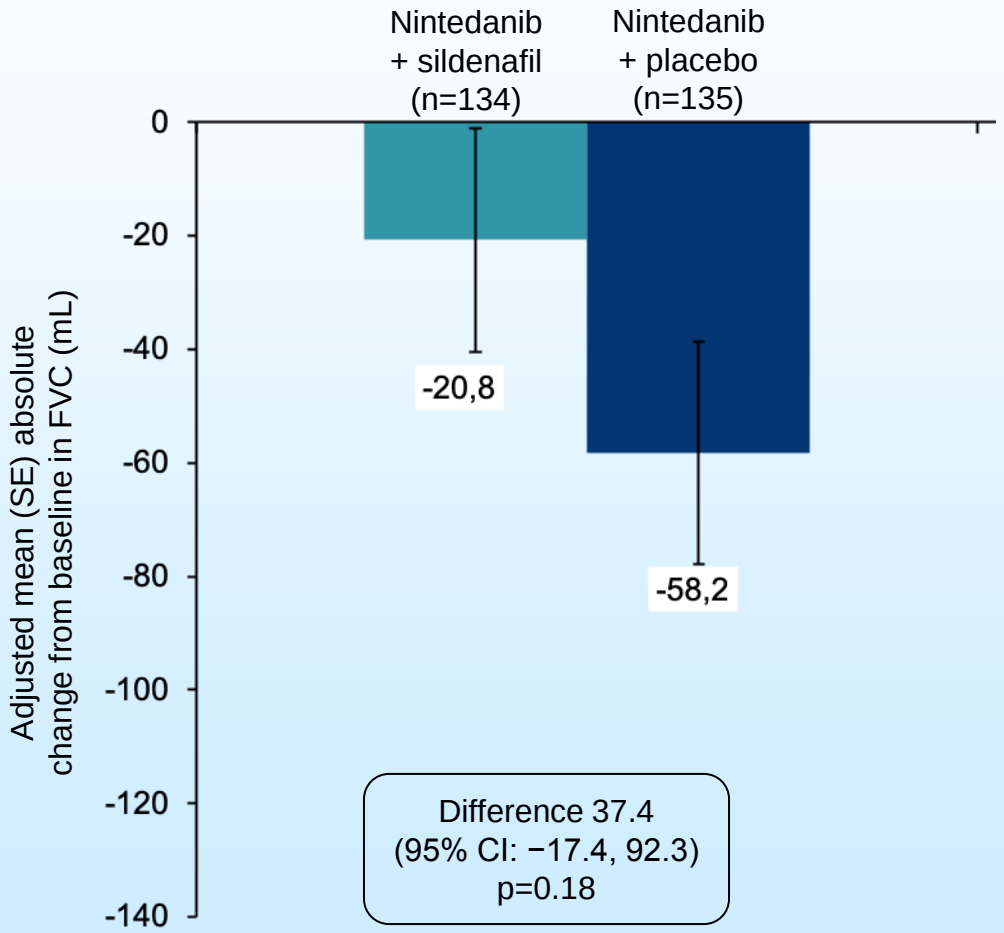
ANDROTELO : Danazol pour les patients porteurs de mutations des gènes des telomères

Schéma de l'essai:



Nintedanib + Sildenafil

(INSTAGE)

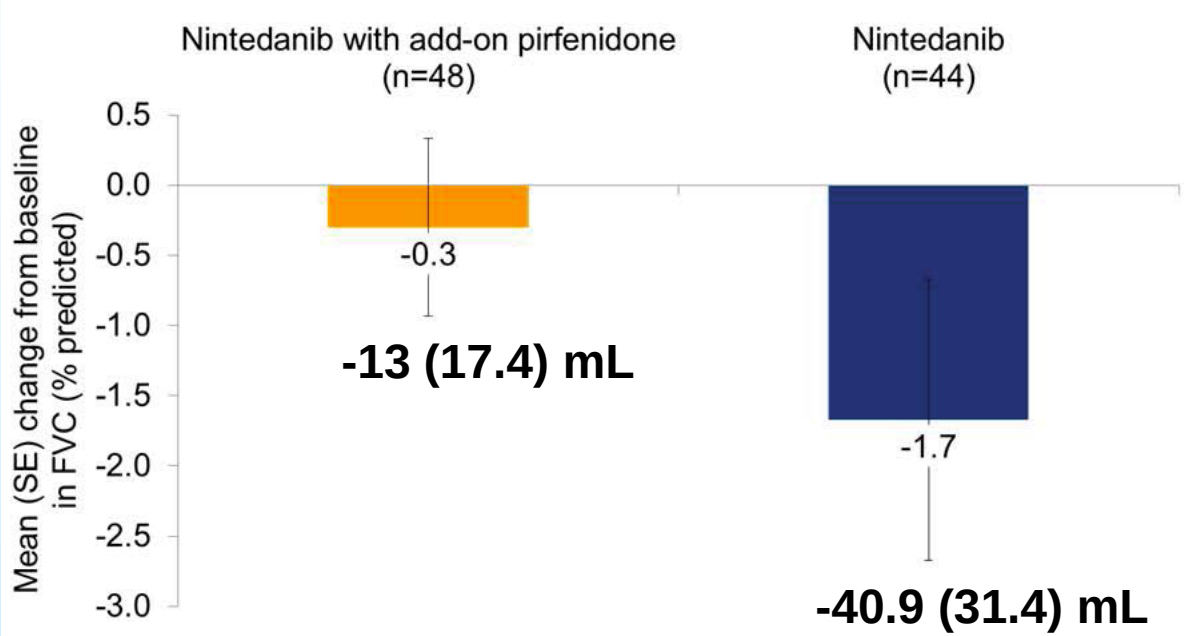


Kolb, NEJM 2018

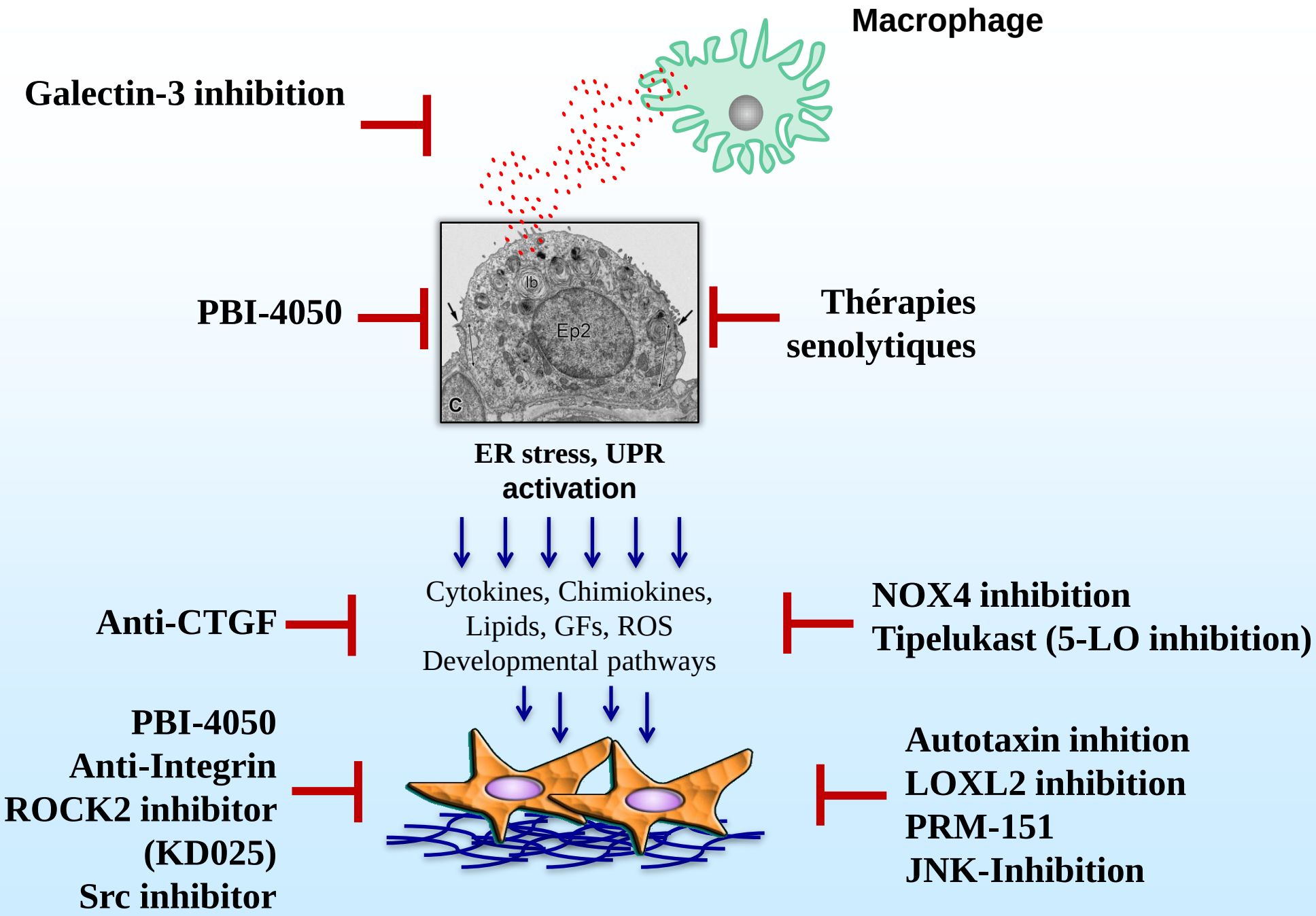
Nintedanib + Pirfenidone

(INJOURNEY)

12 weeks

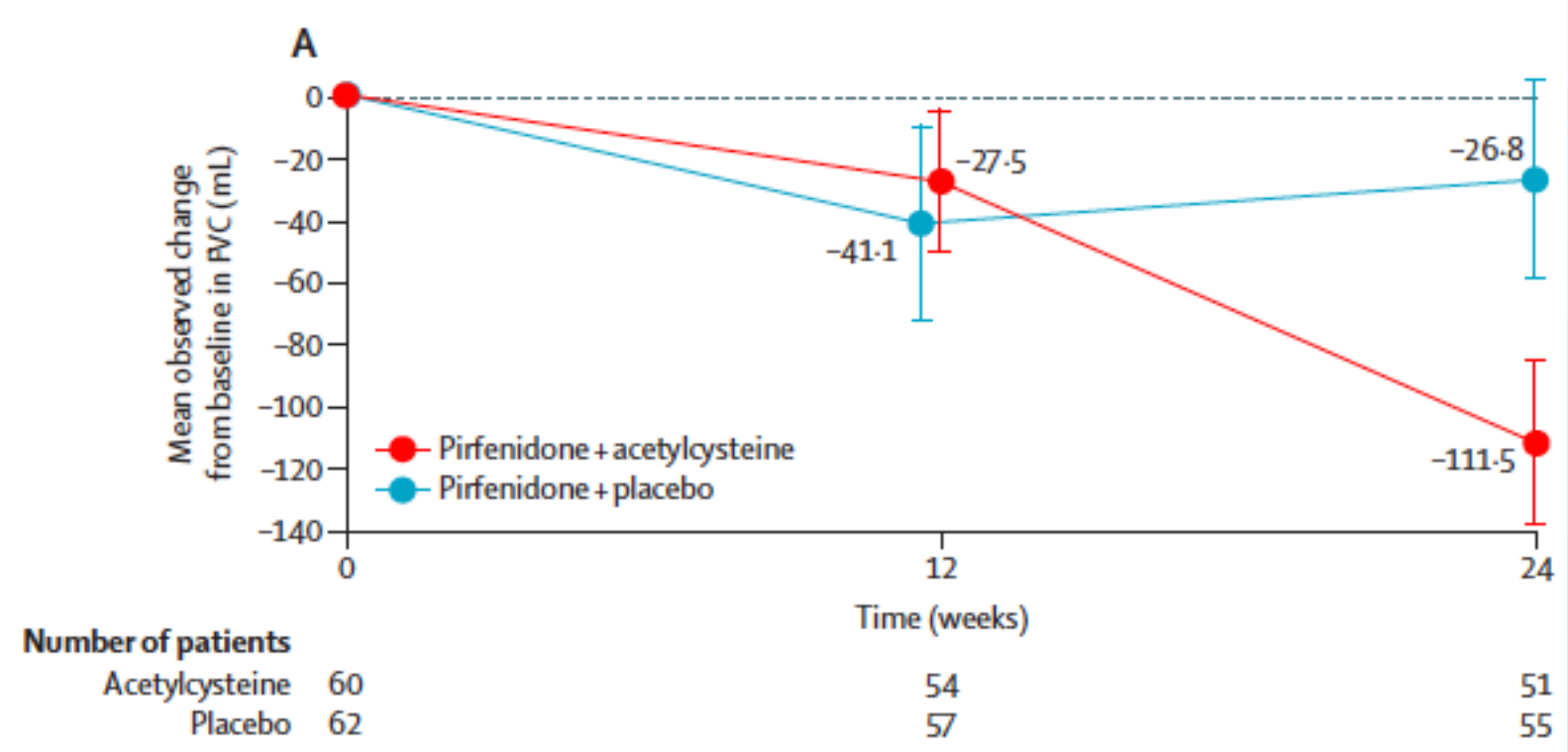


Vancheri, AJRCCM 2017


Macrophage
Galectin-3 inhibition
PBI-4050
Ib
Ep2
C
Thérapies senolytiques
ER stress, UPR activation
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

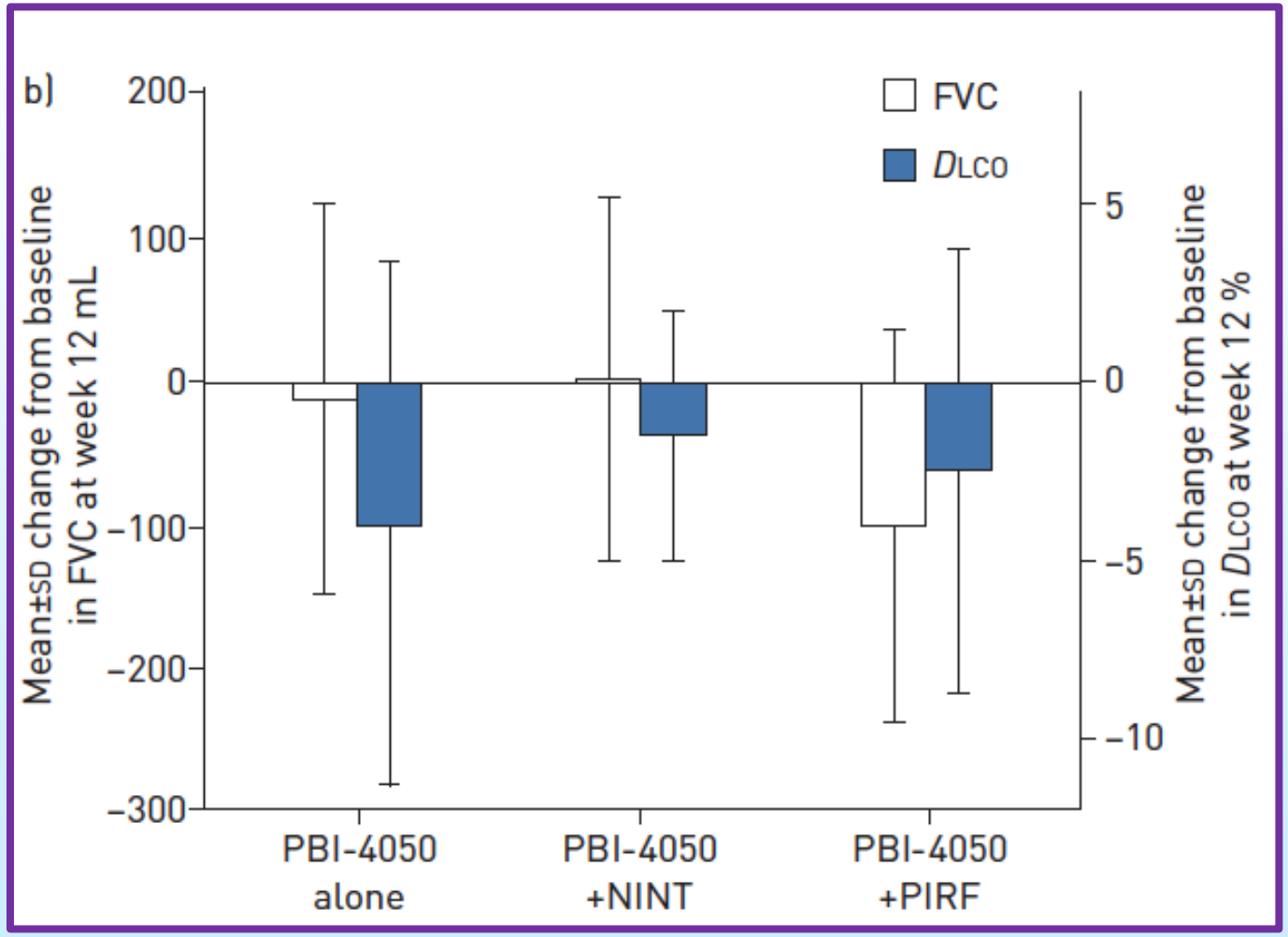
Safety and tolerability of acetylcysteine and pirfenidone combination therapy in idiopathic pulmonary fibrosis: a randomised, double-blind, placebo-controlled, phase 2 trial

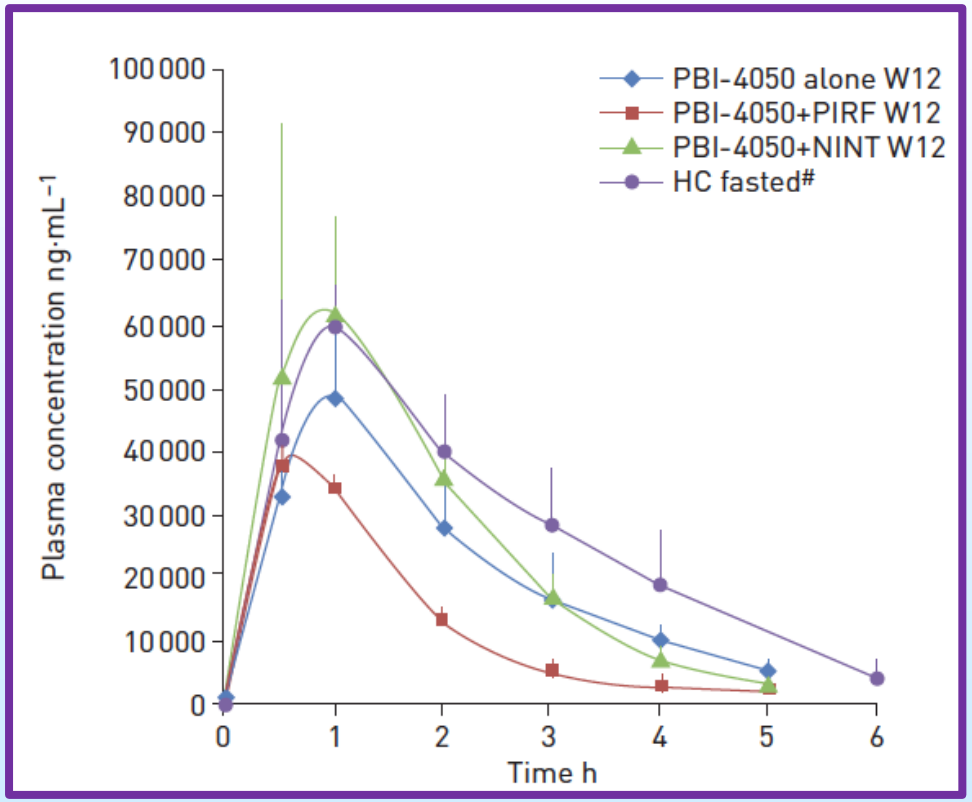
Jürgen Behr, Elisabeth Bendstrup, Bruno Crestani, Andreas Günther, Horst Olschewski, C Magnus Sköld, Athol Wells, Wim Wuyts, Dirk Koschel, Michael Kreuter, Benoît Wallaert, Chin-Yu Lin, Jürgen Beck, Carlo Albera



Behr, Lancet Respir Med 2016

PBI 4050-interaction avec la pirfenidone





Khalil, Eur Respir J 2019

Essais thérapeutiques en cours dans notre centre

Anti-BAFFR
(Phase 2)
sous-cut

Auto-immunité dans la FPI ?

Inhibiteur autotaxine
(Phase 3)
per os

Inhibiteur Galectine 3
(Phase 2-3)
inhalé

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

Ce [illegible] nts…

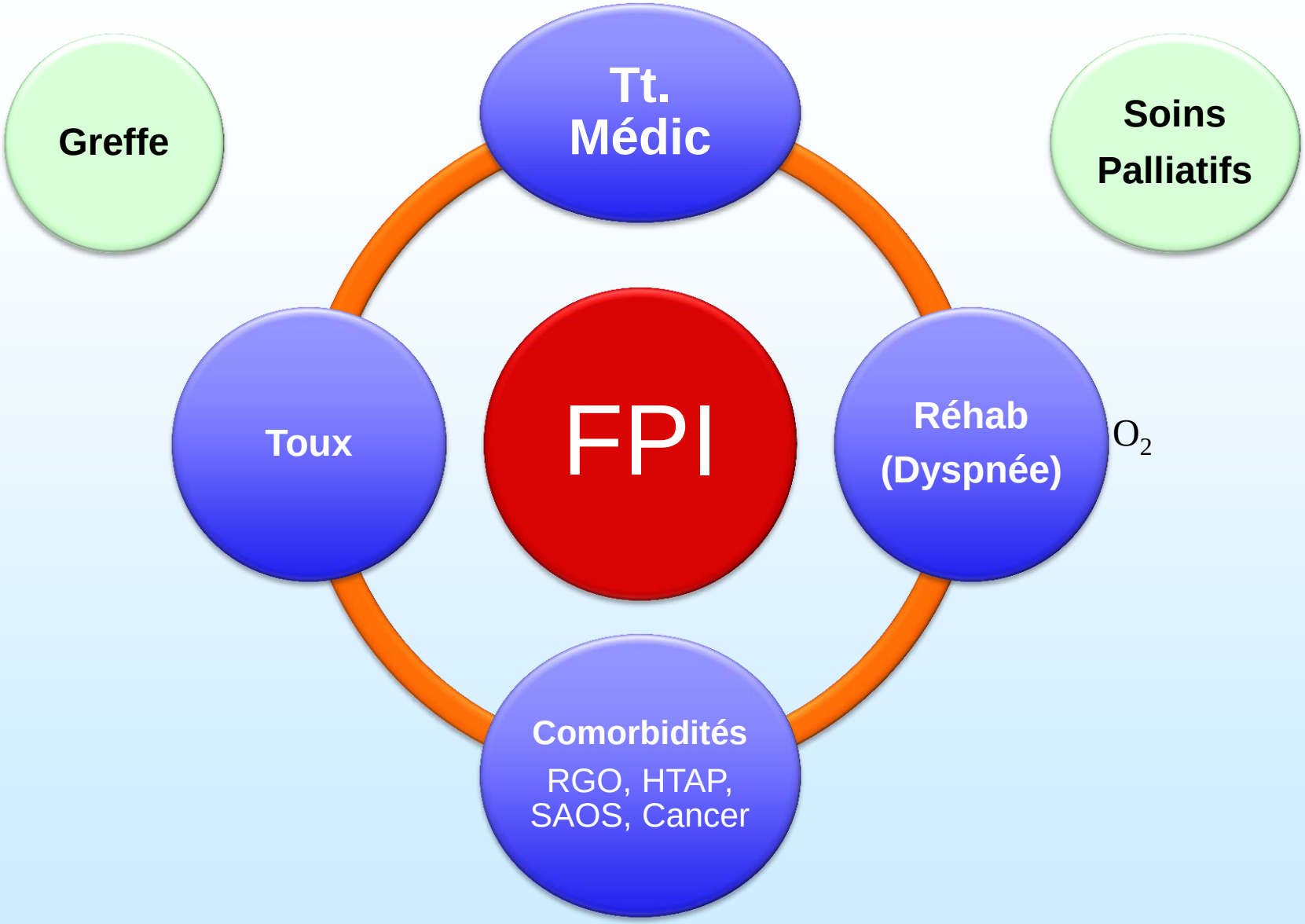

MRM
QUERCETIN
500 MG
With QU995™
60 VEGAN CAPSULES
DIETARY SUPPLEMENT

Patients who progress with a first antifibrotic ?

- **Continue ?**
- **Switch ?**
- **Combine ?**

→

« Progression » trial (V. Cottin)


Greffe
Tt.
Médic
Soins
Palliatifs
Toux
FPI
Réhab
(Dyspnée)
O_2
Comorbidités
RGO, HTAP,
SAOS, Cancer