Université de Paris

centre de référence maladies rares

APOLLO
Heart, Lung, Kidney Chronic Disease

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

Bruno Crestani

Hôpital Bichat, Université de Paris,

Paris, France

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

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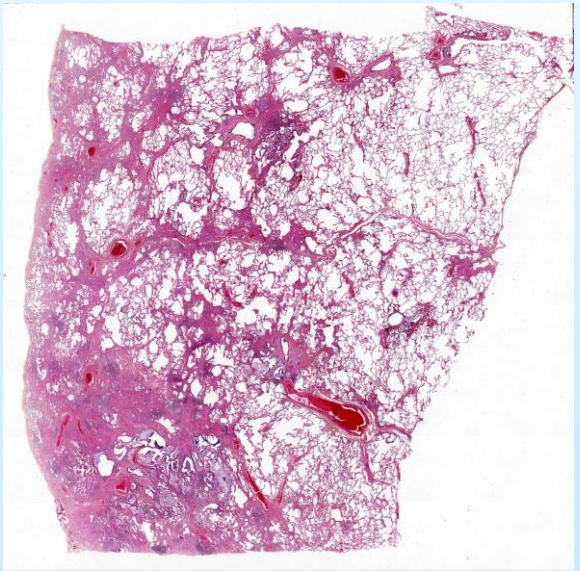
J’ai actuellement, ou j’ai eu au cours des trois dernières années, une affiliation ou des intérêts financiers ou intérêts de tout ordre avec les sociétés commerciales suivantes en lien avec la santé :

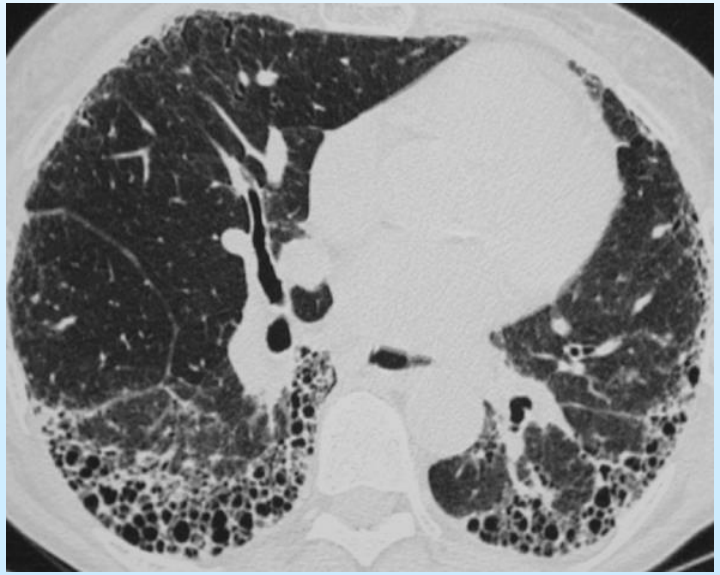
- Apellis, Astra-Zeneca, BMS, Boehringer Ingelheim, Genzyme, LVL, MedImmune, Novartis, Roche, Sanofi

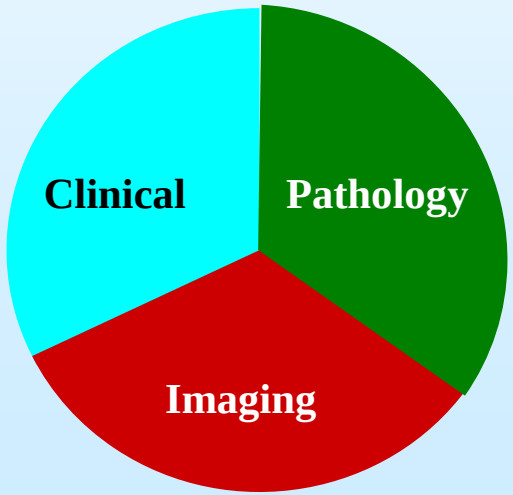
Idiopathic Pulmonary Fibrosis
the current definition

"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"

IPF
=
idiopathic UIP







Raghu, AJRCCM 2011;183:788-824

Idiopathic Pulmonary Fibrosis
30 years ago

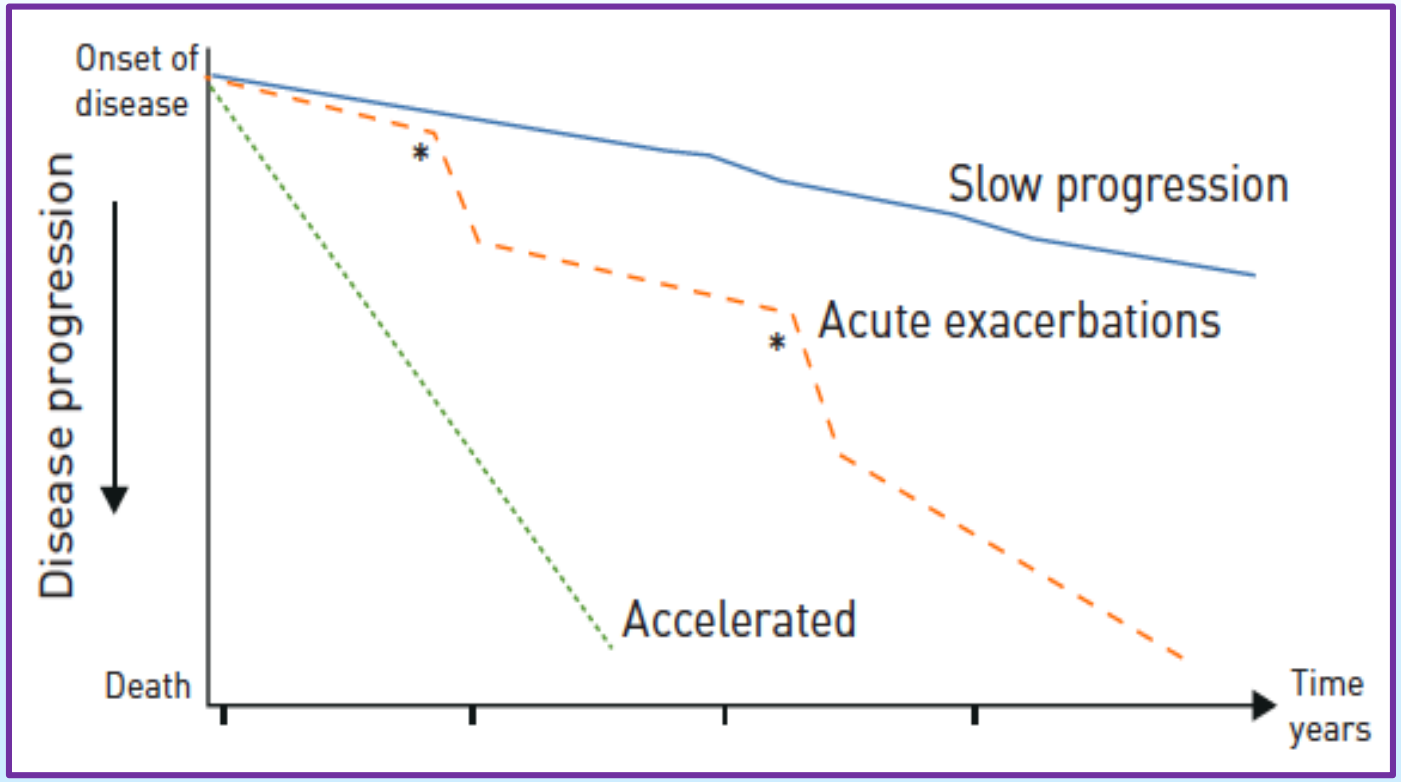
Lung Biopsy
(Armed Forces, Washington)
N = 101, Follow up : 10 years

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%*

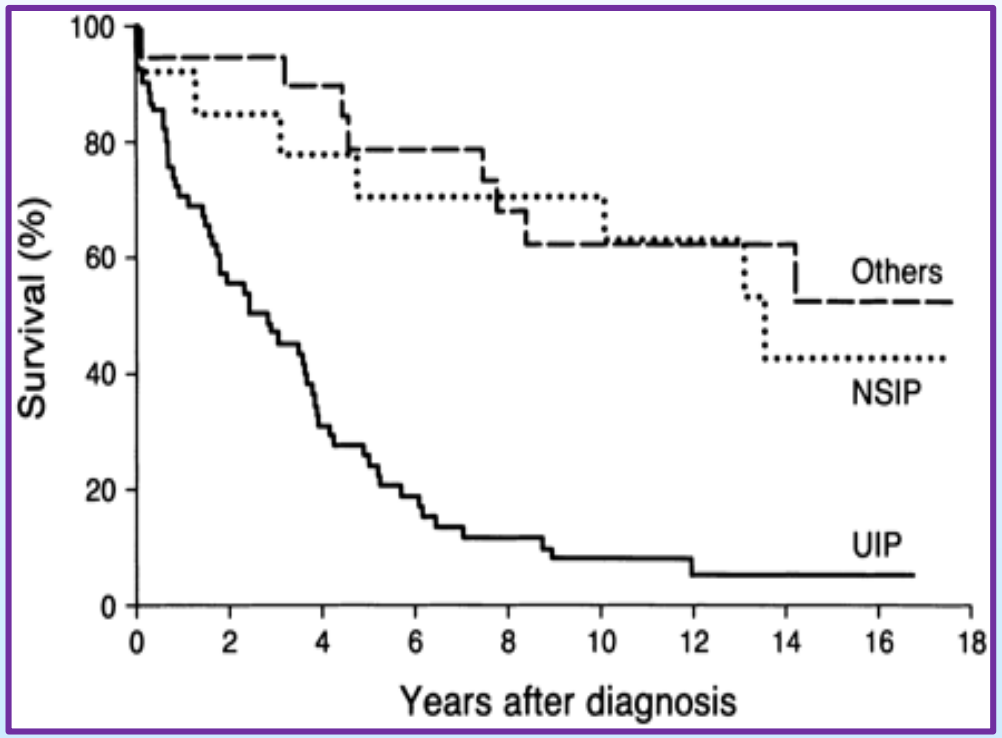
(Travis, Am J Surg Pathol 2000;24:19-33)

- La FPI a été identifiée par un pronostic et un mode évolutif *(progressif)*

- Le pronostic a été associé à un aspect histologique de Pneumopathie interstitielle commune (UIP) par opposition au pronostic des autres formes (PINS en particulier)



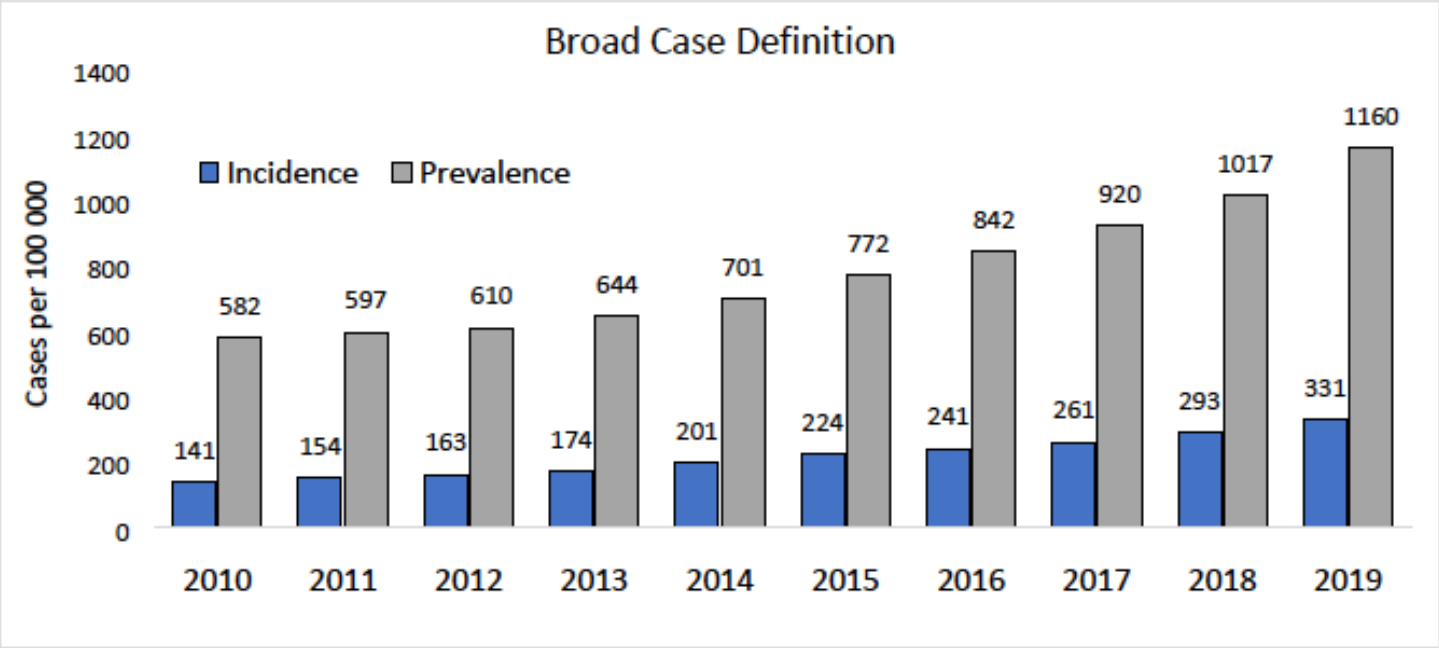
(Froidure et al, Eur Respir Rev 2021)

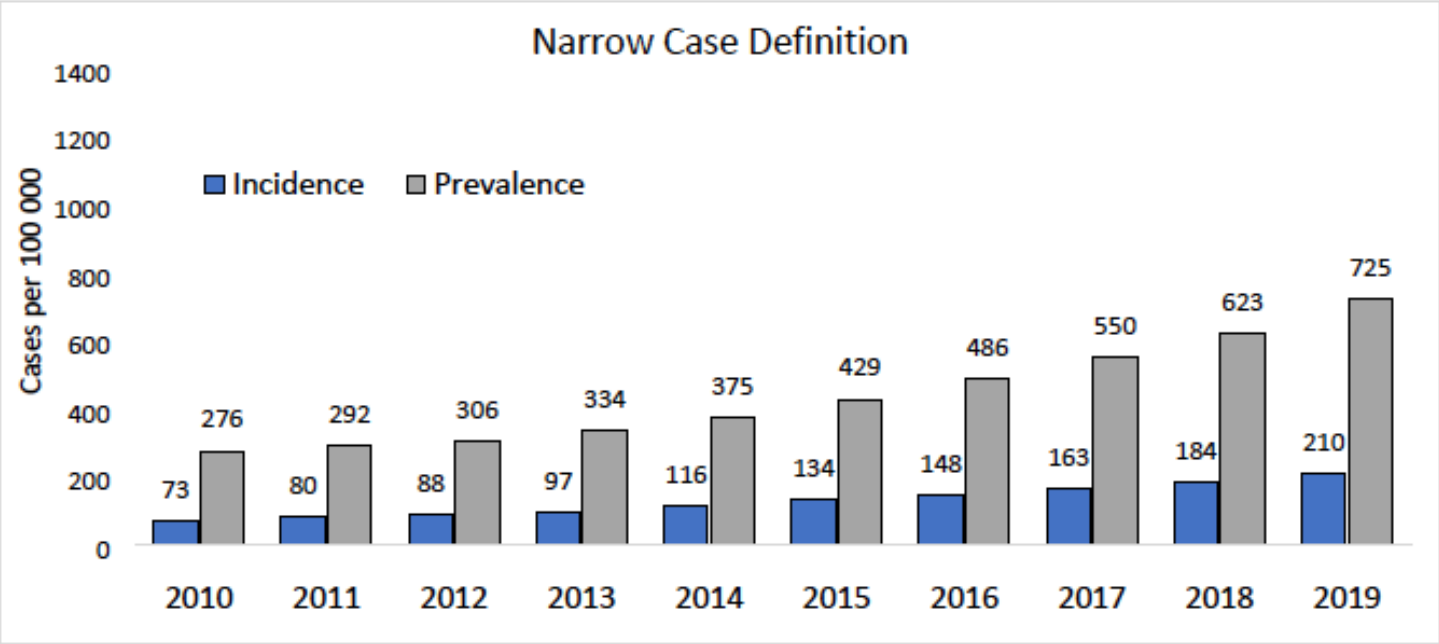


(Bjoraker et al, AJRCCM 1998;157: 199-203)

Annual incidence and Prevalence - IPF

Vétérans US





Kaul, Ann ATS 2021

IPF guidelines

2011

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

2015

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis
An Update of the 2011 Clinical Practice Guideline

2018

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

2022

Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults
An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

Actualisation des recos de 2013 et 2017

Revue des Maladies Respiratoires 39 (2022) 275–312

ELSEVIER

Disponible en ligne sur
ScienceDirect
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Elsevier Masson France
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www.em-consulte.com

RECOMMANDATIONS

Recommandations pratiques pour le diagnostic et la prise en charge de la fibrose pulmonaire idiopathique — Actualisation 2021. Version courte

French practical guidelines for the diagnosis and management of IPF — 2021 update, short version

V. Cottin[a,ar,as,*], P. Bonniaud[b], J. Cadranel[c], B. Crestani[d], S. Jouneau[e], S. Marchand-Adam[f], H. Nunes[g], L. Wémeau-Stervinou[h], E. Bergot[i], E. Blanchard[j], R. Borie[d], A. Bourdin[k], C. Chenivesse[l], A. Clément[m], E. Gomez[n], A. Gondouin[o], S. Hirschi[p], F. Lebargy[q], C.-H. Marquette[r], D. Montani[s], G. Prévot[t], S. Quetant[u], M. Reynaud-Gaubert[v], M. Salaun[w], O. Sanchez[x], B. Trumbic[y], K. Berkani[z], P.-Y. Brillet[aa], M. Campana[ab], L. Chalabreysse[ac], G. Chatté[ad], D. Debieuvre[ae], G. Ferretti[af], J.-M. Fourrier[ag], N. Just[ah], M. Kambouchner[ai], B. Legrand[aj], F. Le Guillou[ak], J.-P. Lhuillier[al], A. Mehdaoui[am], J.-M. Naccache[an], C. Paganon[a], M. Rémy-Jardin[ao], S. Si-Mohamed[ap], P. Terrioux[aq], et OrphaLung

Disponible sur Internet le 15 mars 2022

PROTOCOLE NATIONAL DE DIAGNOSTIC ET DE SOINS

2021

FIBROSE PULMONAIRE IDIOPATHIQUE

Ce PNDS a été rédigé sous la coordination du
Pr Vincent COTTIN

Centre de Référence
des maladies pulmonaires rares

(OrphaLung)

SYNTHÈSE À DESTINATION DU MÉDECIN TRAITANT

Extraite du Protocole National de Diagnostic et de Soins (PNDS)

2021

FIBROSE PULMONAIRE IDIOPATHIQUE

Ce PNDS a été rédigé sous la coordination du
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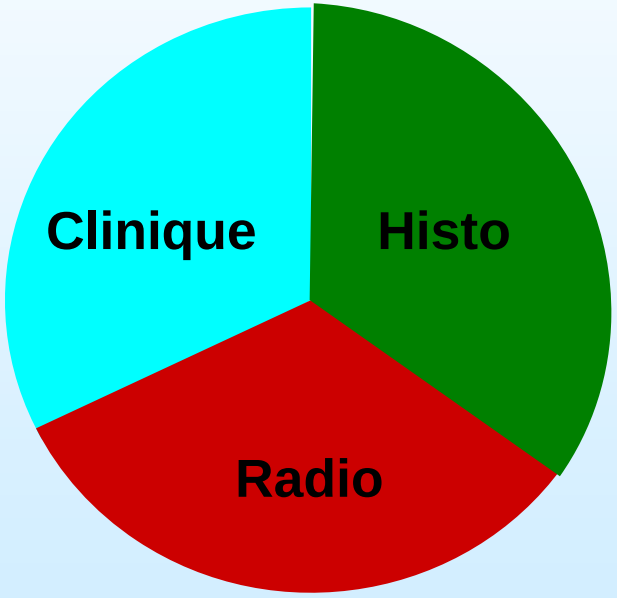
des maladies pulmonaires rares

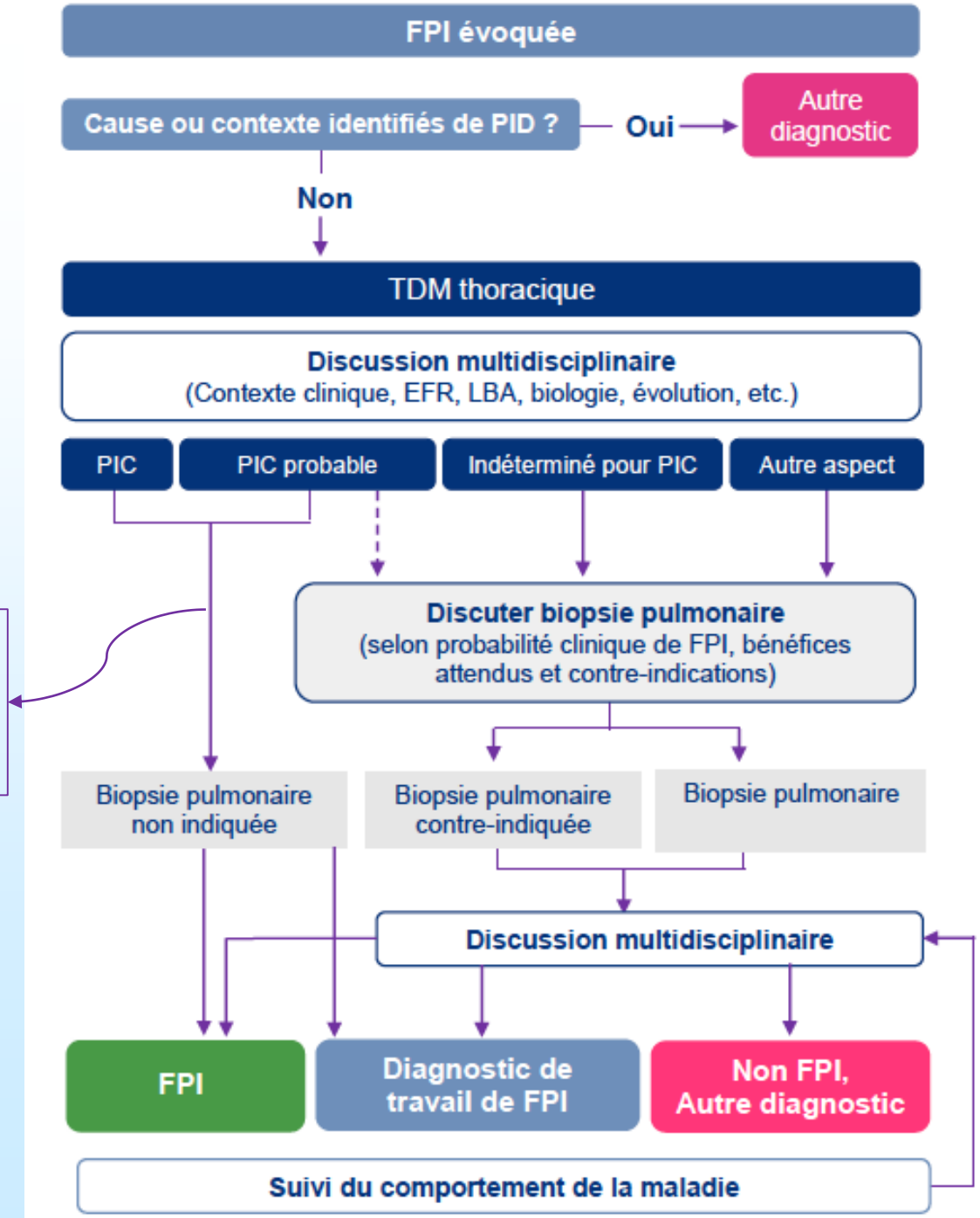
(OrphaLung)

Le diagnostic des PID repose sur l'intégration des données au cours de la réunion de discussion multidisciplinaire



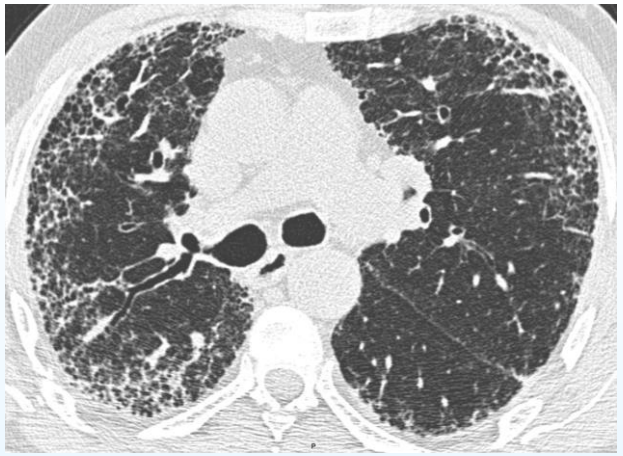
1) **PIC nécessaire au diagnostic de FPI**

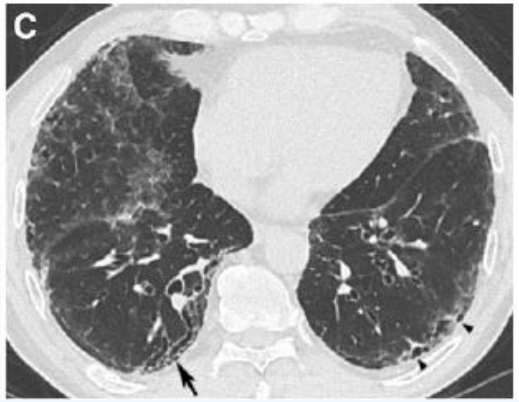
2) **PIC TDM = PIC histologique**

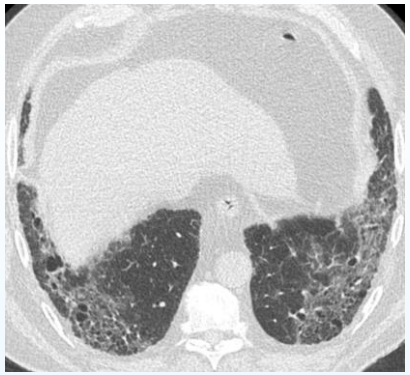


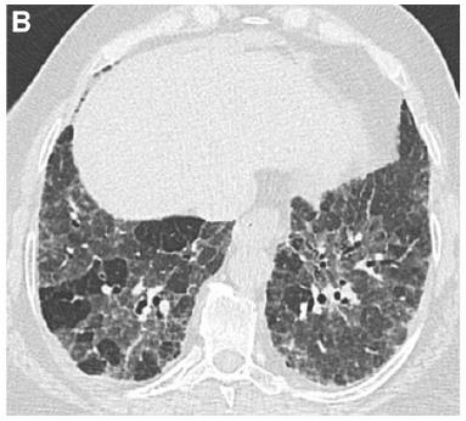
Limite la nécessité de la biopsie pulmonaire

PNDS FPI 2021









PIC certaine → **Pas de Biopsie pulmonaire** → **FPI**

PIC probable → **Pas de Biopsie pulmonaire** *(dans un contexte adapté)* → **FPI**

Indéterminé / **Alternatif** → **Biopsie pulmonaire** → **Diagnostic**

Raghu; AJRCCM 2022

Inter-observer agreement according to the HRCT pattern

UIP	$\kappa = 0.62$
Probable	$\kappa = 0.44$
Indeterminate	$\kappa = 0.47$
Alternative diagnosis	$\kappa = 0.36$

Kwon, Respir Res 2020;20:295

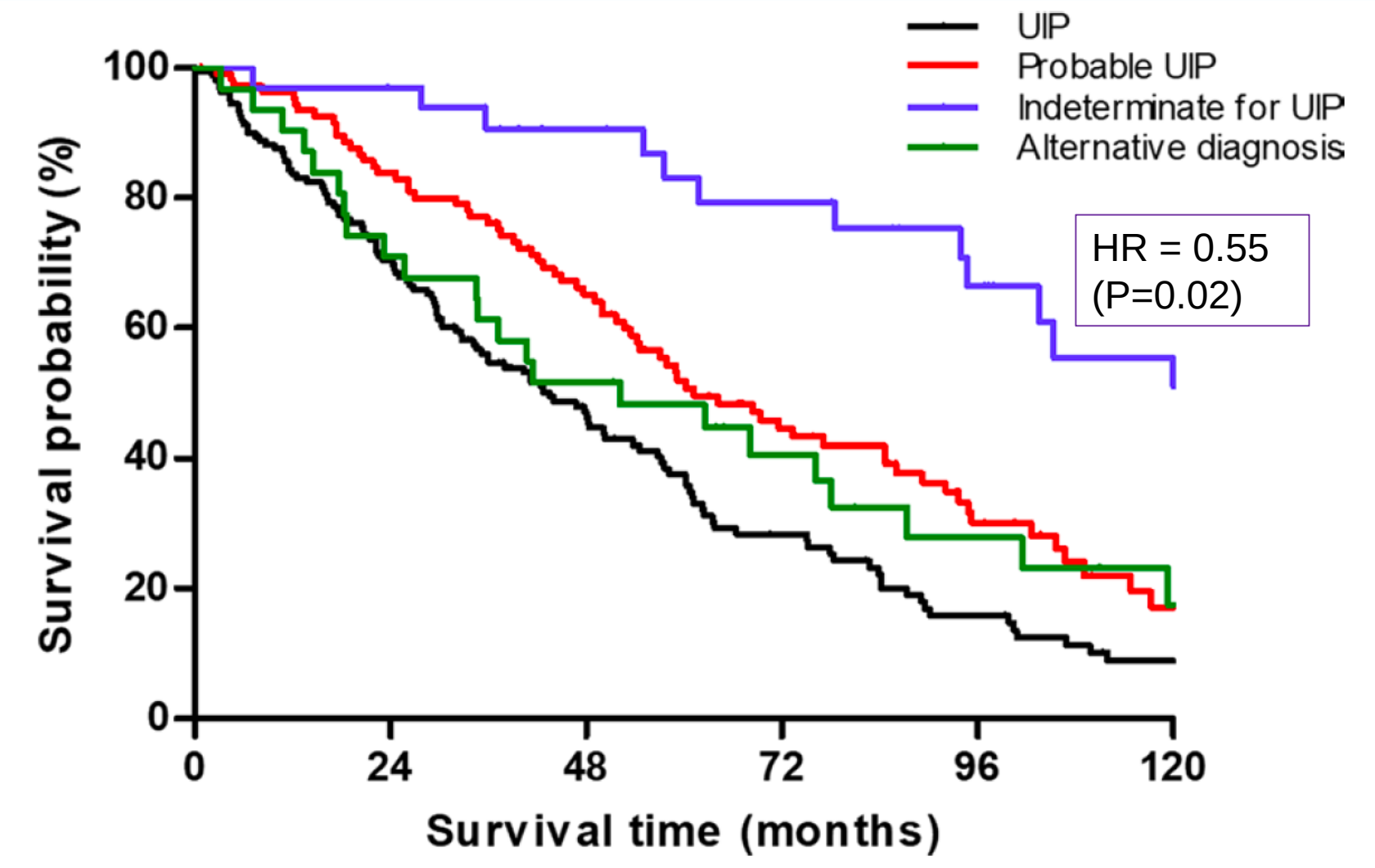
Survie en fonction du pattern tomodensitométrique

337 patients FPI
Avec preuve Histo

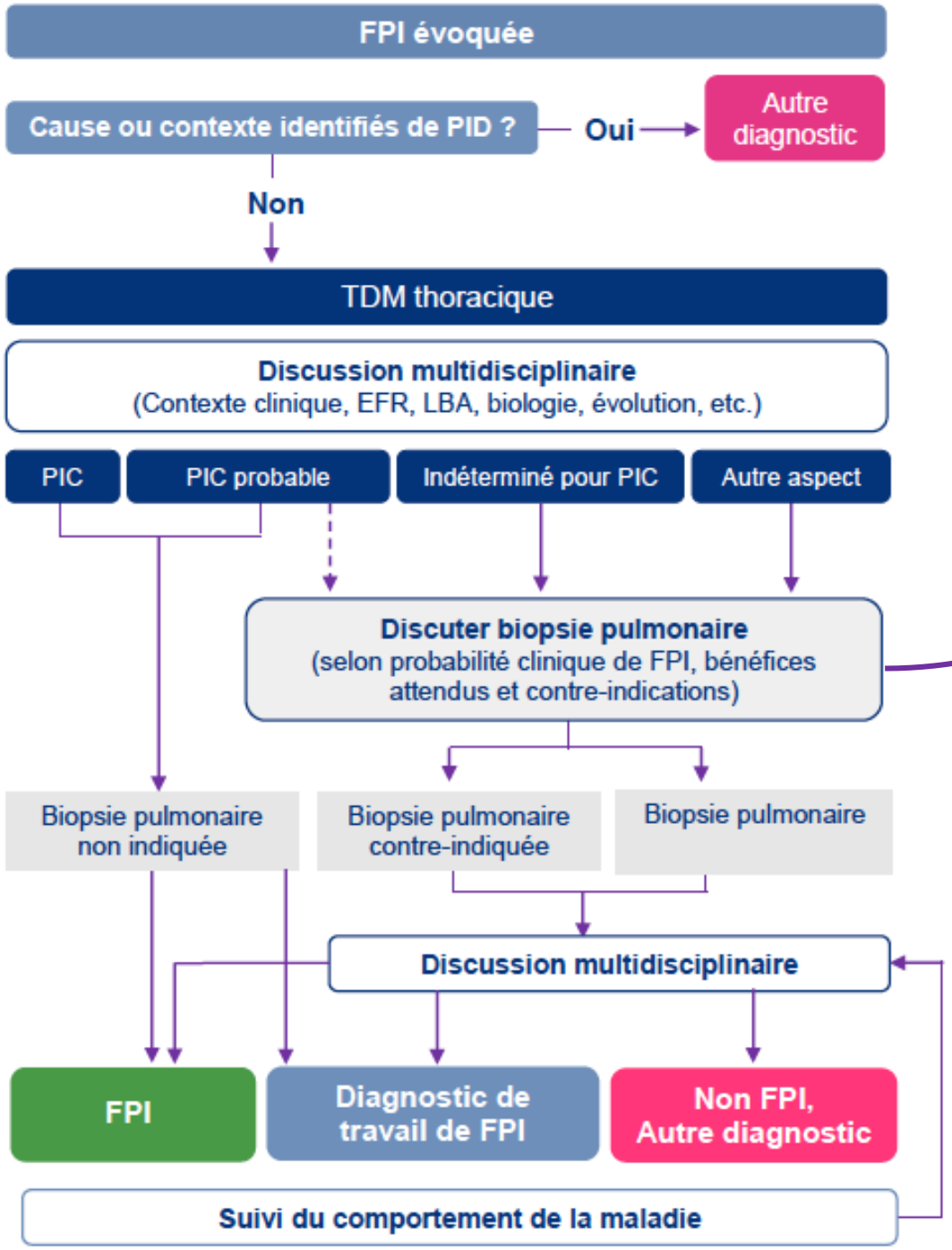
Pattern TDM :

- UIP 48%
- Probable 32%
- Indeterminée 10%
- Dc alternatif 10%

En analyse multivariée, le pattern « indéterminé » était associé à une survie prolongée



Kwon, Respir Res 2020;20:295



La cryobiopsie est une alternative acceptable à la biopsie chirurgicale

PNDS FPI 2021

Transbronchial cryobiopsy for diffuse parenchymal lung disease: 30- and 90-day mortality

Biopsies chir. programmées

- 1.0%
- 1.5%
- 2.8%

Mortalité associée aux Cryobiopsies (Vanderbilt) :

- hospitalière : 0.5%
- 30 jours : 2.0%
- 90 jours : 2.5%

N=197
ILD : 89%

IRA hypoxémique

Hutchinson, Eur Respir J,2017

Pannu, Eur Respir J,2019

Tableau 6 Contre-indications proposées de la biopsie pulmonaire vidéo-chirurgicale.

- Aggravation rapide de la maladie (biopsie non programmée)
- Faible réserve respiratoire (valeurs seuils de l'ordre de : CVF < 60–70 %, DLco < 35–40 %)
- Oxygénothérapie de repos
- Hypertension pulmonaire
- Comorbidités importantes ou multiples
- Âge physiologique > 75 ans
- Immunodépression

CVF : capacité vitale forcée ; DLco : capacité de diffusion du monoxyde de carbone.

Tableau 8 Cryobiopsie transbronchique : contre-indications formelles et relatives (d'après Hetzel et al. [89]).

Formelles : haut risque hémorragique

- Anomalies de la coagulation
- Thrombopénie profonde[a]
- Traitement par agents anticoagulants ou antiagrégants plaquettaires (clopidogrel et autres thiénopyridines)

Relatives

- Traitement par aspirine
- Hypertension pulmonaire[b]
- Altération fonctionnelle respiratoire profonde[c]

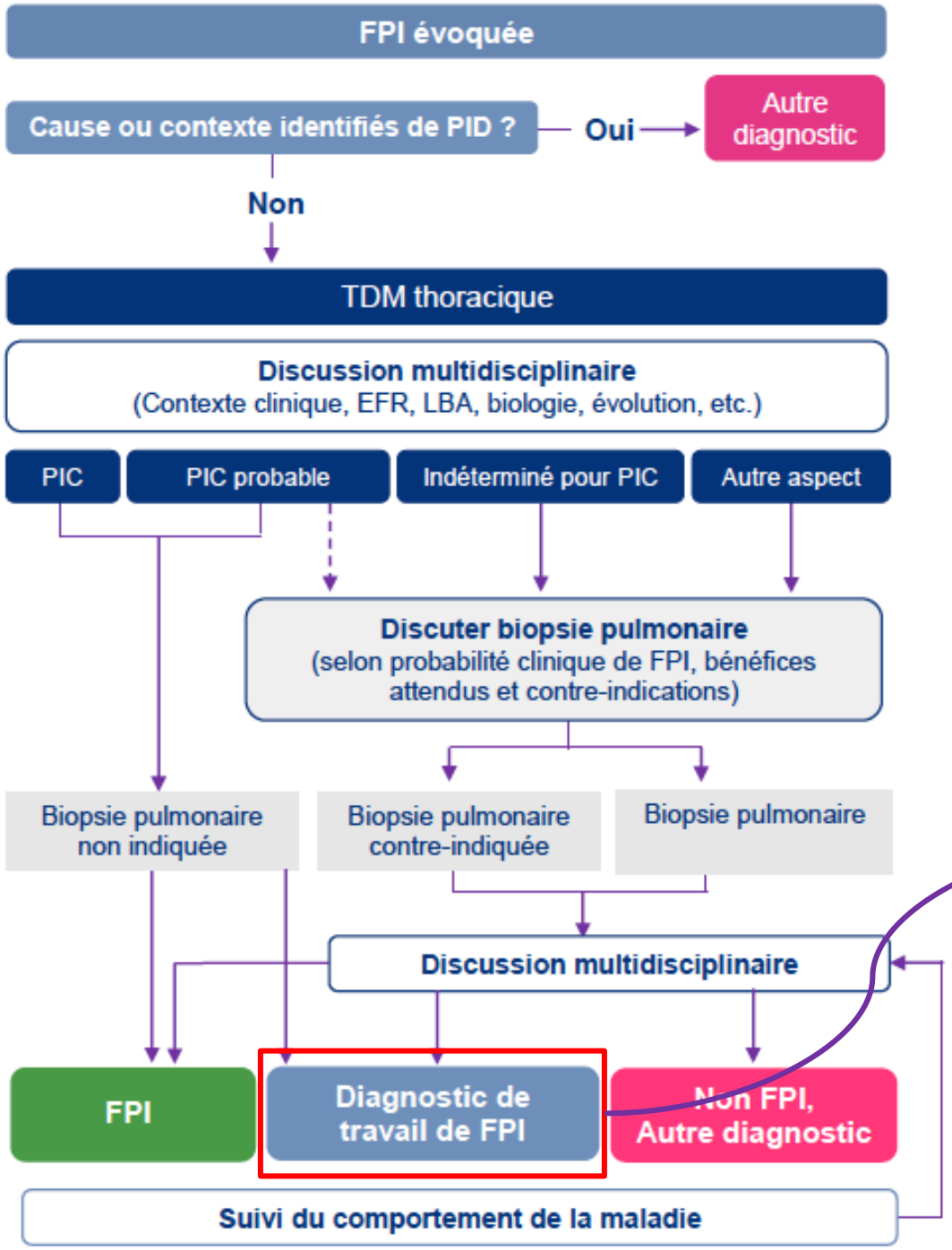
[a] Plaquettes < 50×10^9/l.
[b] Pression artérielle pulmonaire systolique > 50 mmHg à l'échographie.
[c] CVF < 50 % et/ou DLco < 35 % des valeurs théoriques.

Cottin, Rev Mal Respir 2022

		Aspect histopathologique				
		PIC	**PIC probable**	**Indéterminé pour la PIC**	**Autre aspect**	**Biopsie non réalisée**
Aspect au scanner thoracique	**PIC**	FPI	FPI	FPI	Non FPI	FPI
	PIC probable	FPI	FPI	FPI, diagnostic de travail**	Non FPI	FPI, diagnostic de travail**
	Indéterminé pour la PIC	FPI	FPI, diagnostic de travail**	À discuter en DMD*	Non FPI	À discuter en DMD*
	Autre aspect	À discuter en DMD*	Non FPI	Non FPI	Non FPI	À discuter en DMD*

Chaque situation doit être discutée en DMD. La situation d'un aspect de PIC au scanner et d'une biopsie pulmonaire disponible est théorique, une biopsie n'étant pas réalisée si l'aspect radiologique est celui d'une PIC ou d'une PIC probable.

Cottin, Rev Mal Respir 2022



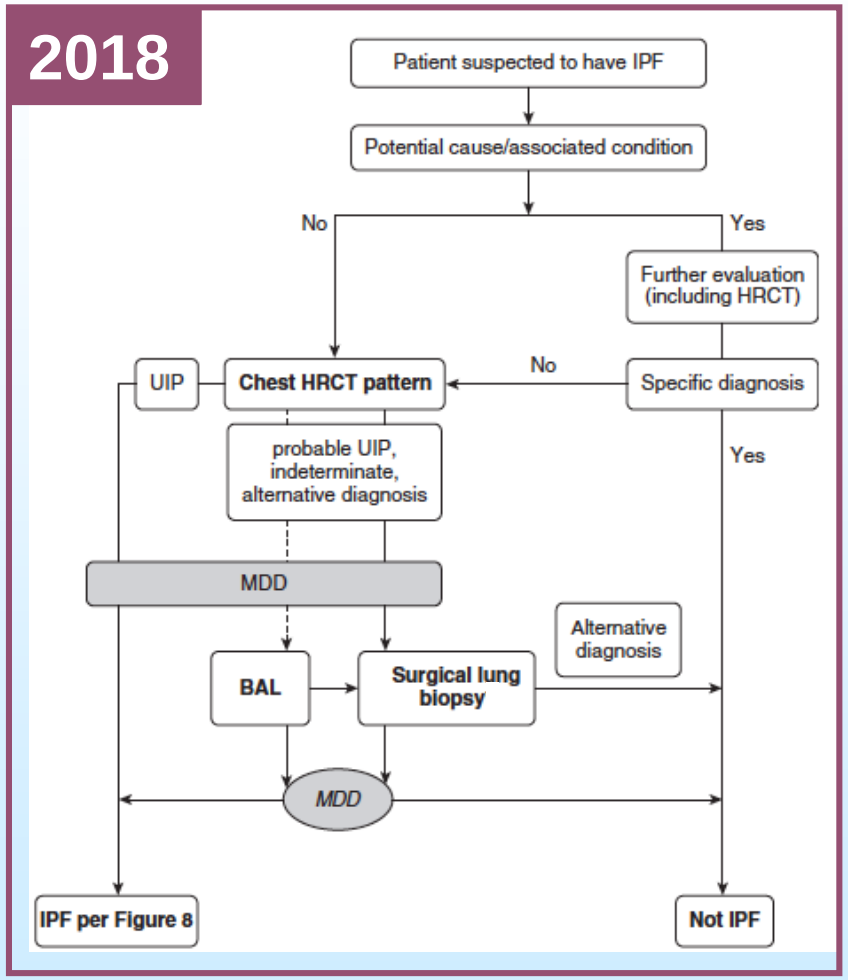
Diagnostic provisoire

Definite IPF :
Probability >90%

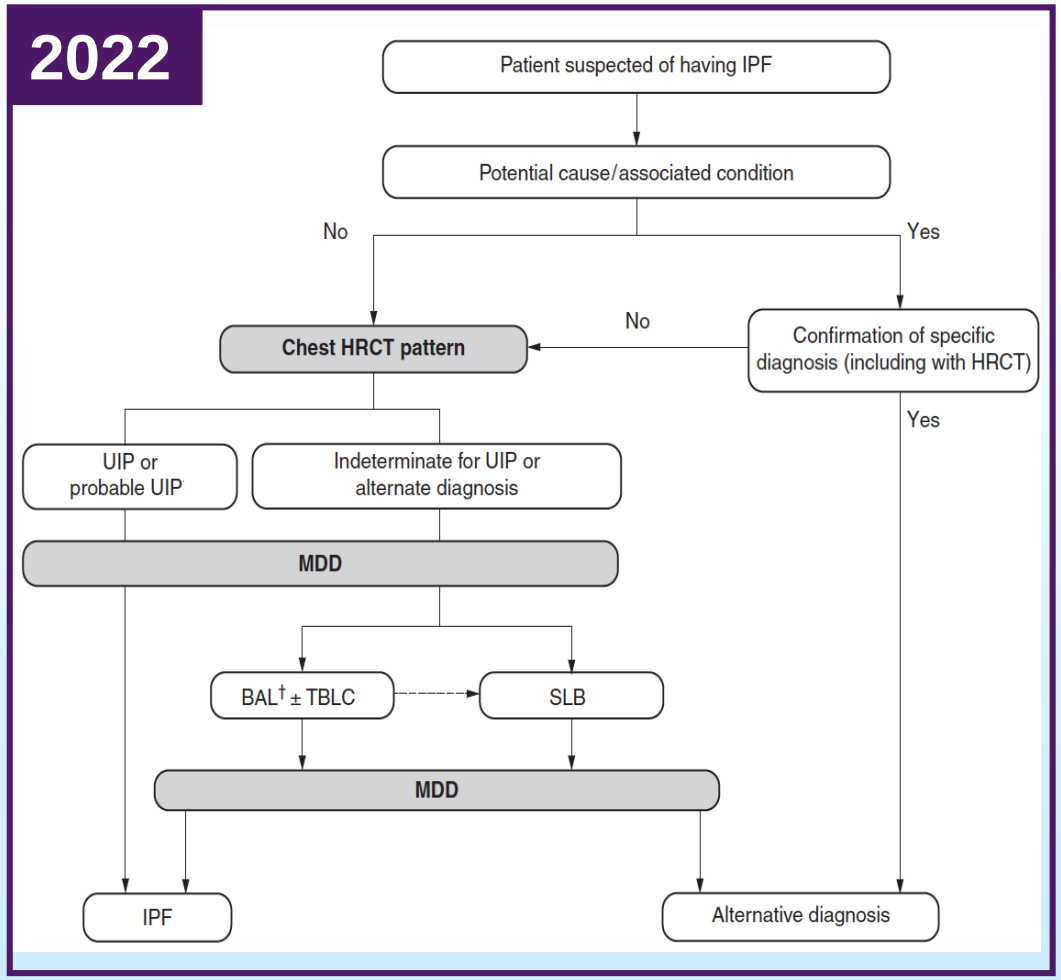
Provisional high confidence :
Probability 70-89%

PNDS FPI 2021

IPF diagnostic algorithm



Raghu et al, AJRCCM 2018;198: e44–e68



Raghu et al, AJRCCM 2022; 205: e18–e47

IPF diagnostic algorithm

2018

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			

Raghu et al, AJRCCM 2018;198: e44–

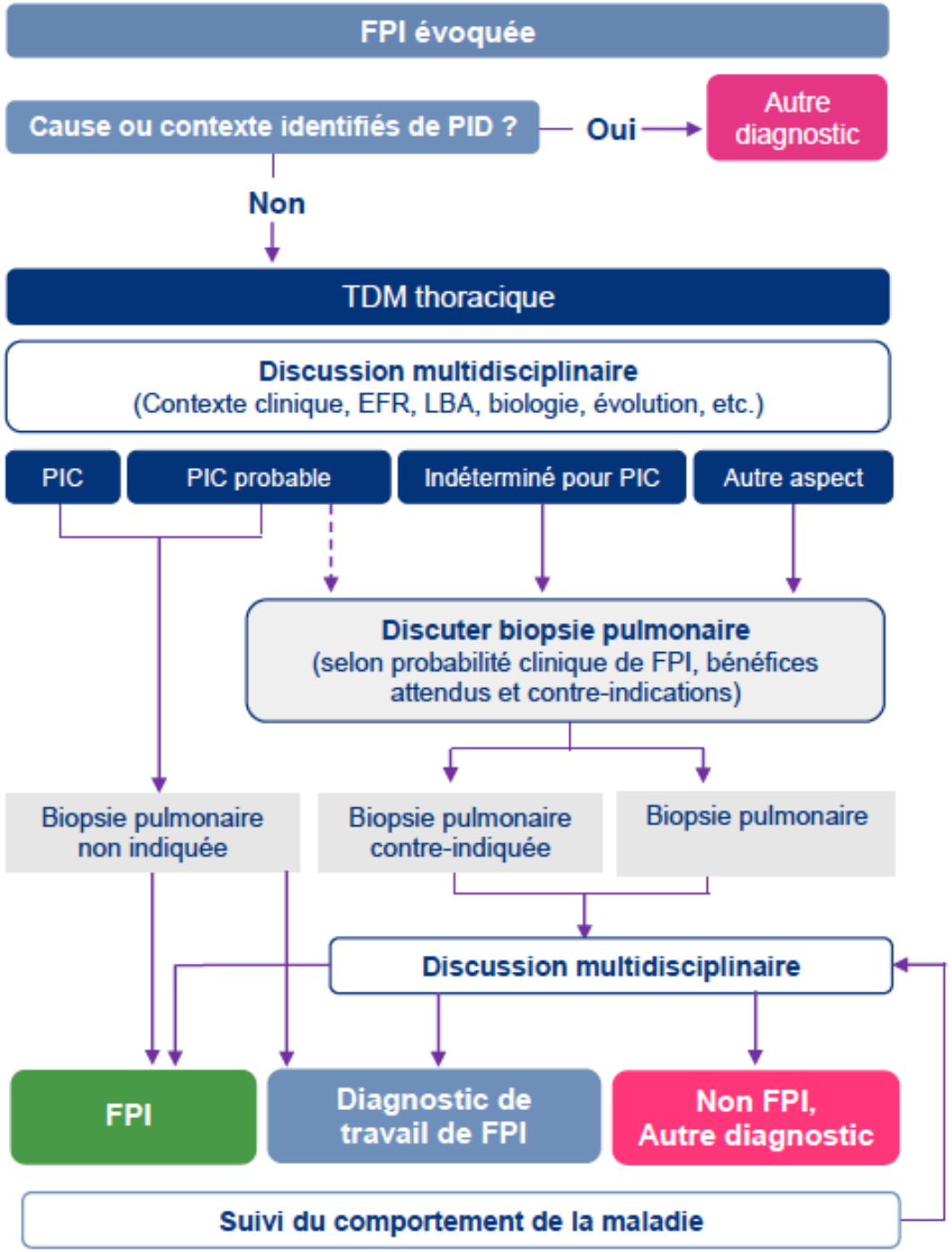
« No biopsy » category

2022

IPF suspected		Histopathology pattern			
		UIP	Probable UIP	Indeterminate for UIP or biopsy not performed	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)	Indeterminate	Non-IPF dx	Non-IPF dx

Raghu et al, AJRCCM 2022; 205: e18–e47

Prochaine étape :
Introduire la proba clinique dans l'arbre diagnostique



PNDS FPI 2021

The next step ?

Check for updates

PULMONARY PERSPECTIVE

Integrating Clinical Probability into the Diagnostic Approach to Idiopathic Pulmonary Fibrosis

An International Working Group Perspective

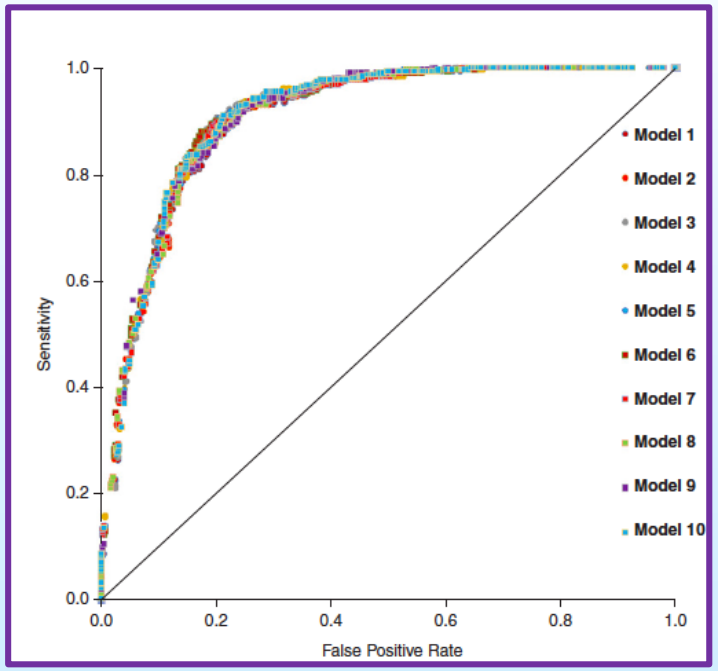
Vincent Cottin[1], Sara Tomassetti[2], Claudia Valenzuela[3], Simon L. F. Walsh[4], Katerina M. Antoniou[5], Francesco Bonella[6], Kevin K. Brown[7], Harold R. Collard[8], Tamera J. Corte[9], Kevin R. Flaherty[10], Kerri A. Johannson[11,12], Martin Kolb[13], Michael Kreuter[14,15], Yoshikazu Inoue[16], R. Gisli Jenkins[4], Joyce S. Lee[17], David A. Lynch[18], Toby M. Maher[19,20], Fernando J. Martinez[21], Maria Molina-Molina[22], Jeff L. Myers[23], Steven D. Nathan[24], Venerino Poletti[25], Silvia Quadrelli[26], Ganesh Raghu[27], Sujeet K. Rajan[28], Claudia Ravaglia[29], Martine Remy-Jardin[30], Elisabetta Renzoni[20], Luca K. Richeldi[31], Paolo Spagnolo[32], Lauren Troy[33,34], Marlies Wijsenbeek[35], Kevin C. Wilson[36], Wim Wuyts[37], Athol U. Wells[4]*, and Christopher J. Ryerson[38]*

Cottin, AJRCCM 2022;206:247-259

Development and Validation of a Clinical Diagnostic Scoring System for the Diagnosis of Idiopathic Pulmonary Fibrosis

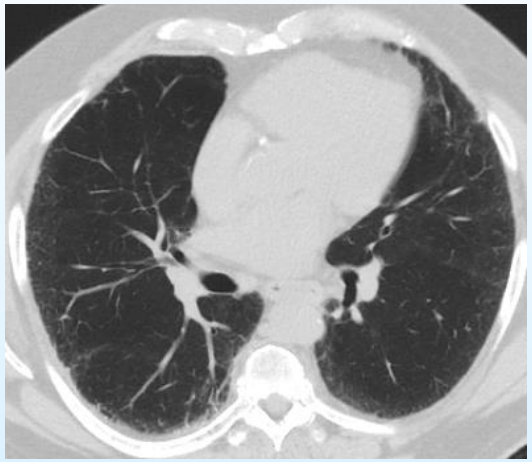
Jean Pastre[1,2], Scott D. Barnett[1], Inga Ksovreli[1], Nesrin Mogulkoc[3], Vijaya Ramalingam[4], Cesar Fukuda[5], Anusha Yelisetty[4], Ömer Selim Unat[3], A. Whitney Brown[1], Oksana A. Shlobin[1], Kareem Ahmad[1], Vikramjit Khangoora[1], Shambhu Aryal[1], Christopher King[1], and Steven D. Nathan[1]

Clinical Parameters	FICS Risk Score Points	OR (2nd–97th Quintile)	LCL (2nd–97th Quintile)	UCL (2nd–97th Quintile)
Age, yr				
<50	−1	0.3 (0.1–0.4)	0.2 (0.1–0.4)	0.8 (0.6–0.9)
50–59	1	3.7 (1.6–6.5)	0.4 (0.2–0.7)	34 (16–58)
60–69	2	20 (12–30)	2.5 (1.4–3.7)	166 (98–247)
70–79	3	32 (19–48)	3.9 (2.3–5.9)	259 (156–383)
⩾80	4	34 (18–57)	4.0 (2.1–6.6)	295 (160–493)
Male	3	2.6 (1.9–3.7)	1.6 (1.1–2.1)	4.5 (3.2–6.3)
White ethnicity	2	2.1 (1.5–2.9)	1.2 (0.8–1.7)	3.6 (2.5–5.1)
Smoking history	2	1.8 (1.3–2.4)	1.1 (0.8–1.4)	3.0 (2.1–4.1)
ILD familial history	5	4.7 (2.5–9.0)	1.6 (1.0–2.7)	13 (6–30)
Exposure	−1	0.4 (0.2–0.5)	0.2 (0.1–0.3)	0.7 (0.5–1.0)
CTD signs	−2	0.03 (0.02–0.06)	0.01 (0.01–0.03)	0.08 (0.05–0.12)
Velcro crackles	4	4.0 (2.8–5.8)	2.2 (1.5–3.1)	7.6 (5.0–11.2)



Pastre, Ann ATS 2020; 18:1803–1810

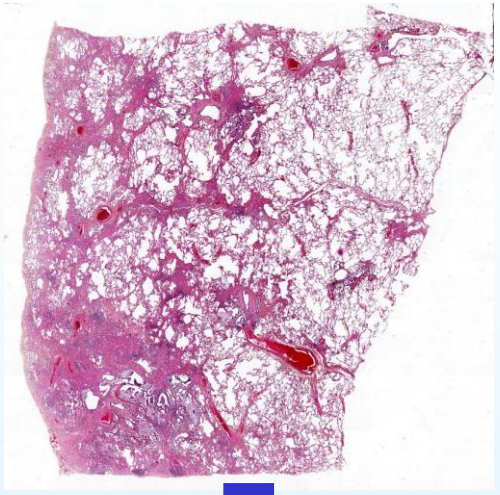
Evolution vers des explorations moins invasives

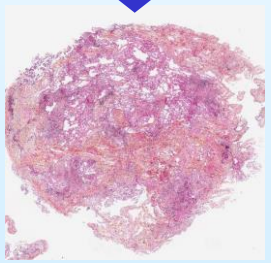


Analyse « profonde »
du scanner
(texture, IA)

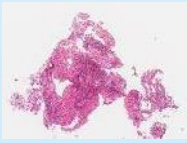
Marqueurs

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

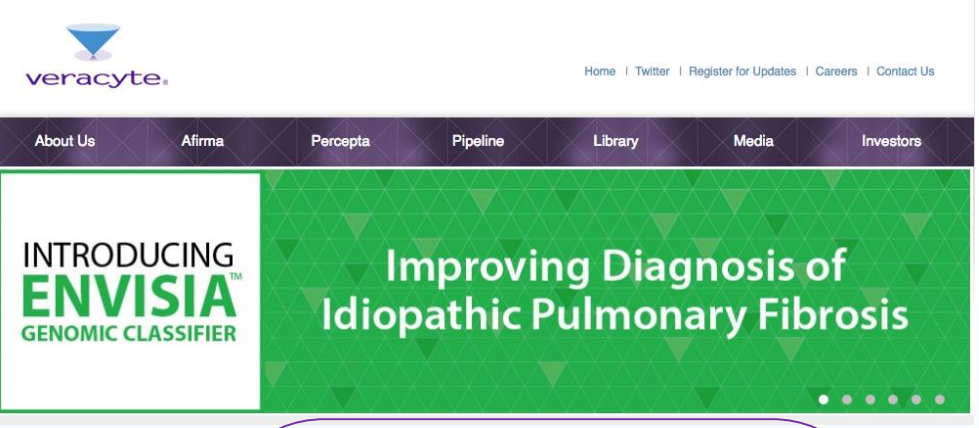




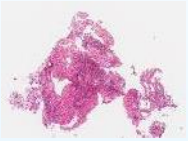
Cryobiopsie



BTB



3-5 TBB per patient



↓

total mRNA extraction

↓

pooled per subject

↓

One transcriptome/subject

↓

UIP
YES/NO

Meta-analysis

UIP pattern identification with genomic classifier testing

- sensitivity 68%
- specificity 92%

Kheir, Ann ATS 2022

IPF diagnosis algorithm

- **Genomic classifier :**

We make no recommendation for or against the addition of genomic classifier testing for the purpose of diagnosing UIP in patients with ILD of undetermined type who are undergoing transbronchial forceps biopsy, because of insufficient agreement among the committee members.

Raghu et al, AJRCCM 2022; 205: e18–e47

Limitations

- Insufficient sensitivity
- Consequence of false-negative results
- Limited number of studies (most funded by the maker)
- Incremental value of the test unclear
- Loss of information /histopathology
- Limited availability
- TBB safety

Challenged by Scholand & Wells, AJRCCM 2022

"Use of genomic classifier is highly specific, safe and widely available in the US"

Exhaled breath analysis by use of eNose technology: a novel diagnostic tool for interstitial lung disease

SpiroNose
Breathomics, Leiden,
The Netherlands

Composés volatiles organiques (VOC)
Couplé à la spirométrie

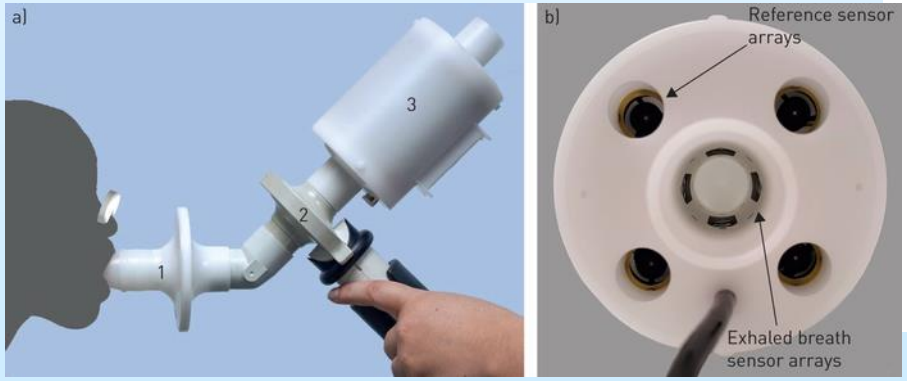


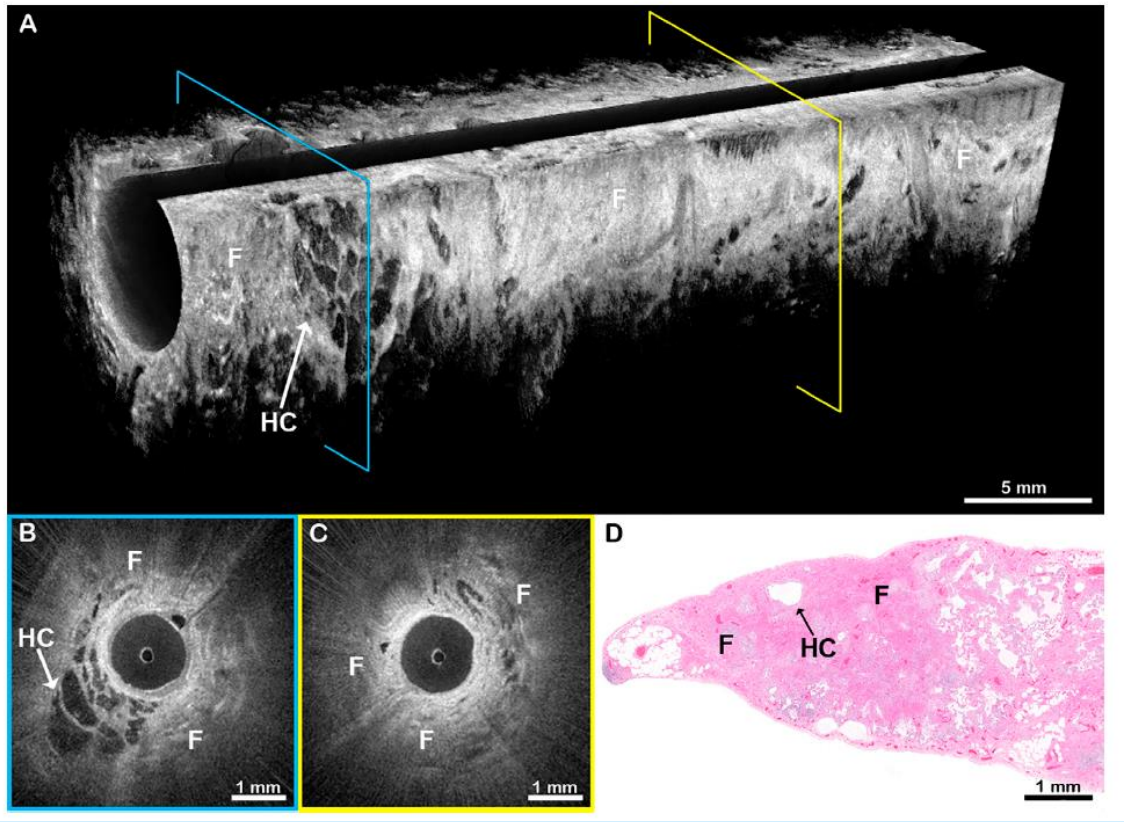
TABLE 3 Models for direct comparison between individual diagnoses

Groups	AUC (95% CI)	Sensitivity %	Specificity %	Accuracy %
IPF *versus* CHP	0.85 (0.76–0.94)	75	84	77
IPF *versus* CTD-ILD	0.96 (0.93–1.00)	98	85	94
IPF *versus* iNSIP	0.94 (0.86–1.00)	92	90	92
IPF *versus* IPAF	0.94 (0.90–0.99)	87	100	89
CTD-ILD *versus* IPAF	0.99 (0.80–1.00)	100	67	75
CTD-ILD *versus* iNSIP	0.93 (0.79–1.00)	90	100	98
CHP *versus* sarcoidosis	0.89 (0.80–0.98)	94	72	90

AUC: area under the curve; IPF: idiopathic pulmonary fibrosis; CHP: chronic hypersensitivity pneumonitis; CTD-ILD: connective tissue disease-associated interstitial lung disease; iNSIP: idiopathic nonspecific interstitial pneumonia; IPAF: interstitial pneumonia with autoimmune features.

Moor, Eur Respir J 2021

Diagnostic Accuracy of Endobronchial Optical Coherence Tomography for the Microscopic Diagnosis of Usual Interstitial Pneumonia



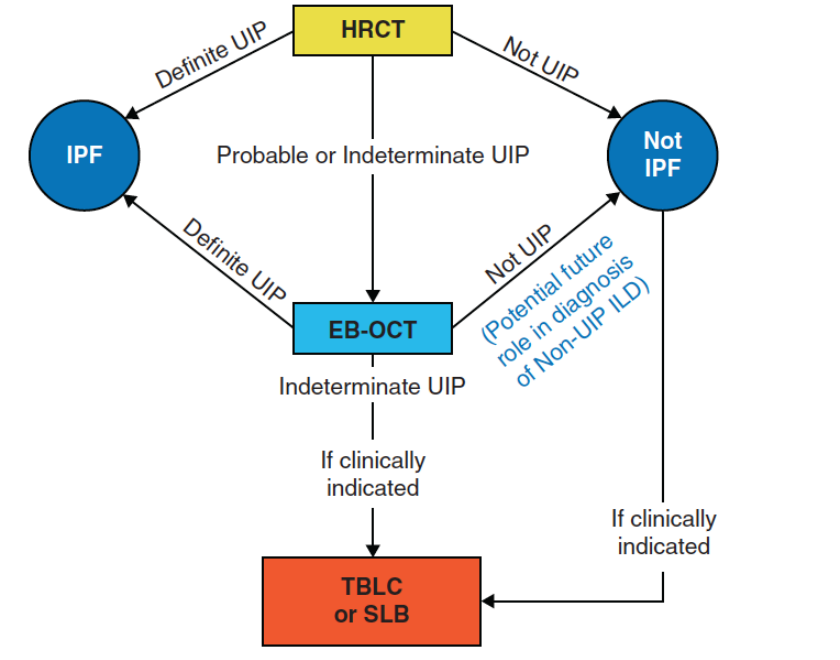


Table 4. EB-OCT Sensitivity and Specificity for Histopathologic UIP and Clinical IPF for Expert and Novice EB-OCT Readers

EB-OCT Reader	No. of Cases	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)	PPV (95% CI) (%)	NPV (95% CI) (%)
Expert EB-OCT reader	27 (12 UIP/15 non-UIP ILD)	100 (75.8–100)	100 (79.6–100)	100 (73.5–100)	100 (78.2–100)
Novice EB-OCT reader 1	13 (6 UIP/7 non-UIP ILD)	100 (54.1–100)	100 (59.0–100)	100 (54.1–100)	100 (59.0–100)
Novice EB-OCT reader 2	13 (6 UIP/7 non-UIP ILD)	100 (54.1–100)	100 (59.0–100)	100 (54.1–100)	100 (59.0–100)
Novice EB-OCT reader 3	13 (6 UIP/7 non-UIP ILD)	66.7 (22.3–95.7)	100 (59.0–100)	100 (39.8–100)	77.8 (40.0–97.2)

Nandy, AJRCCM 2021

Traitement

Revue des Maladies Respiratoires 39 (2022) 275–312

ELSEVIER

Disponible en ligne sur
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www.sciencedirect.com

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EM|consulte
www.em-consulte.com

RECOMMANDATIONS

Recommandations pratiques pour le diagnostic et la prise en charge de la fibrose pulmonaire idiopathique — Actualisation 2021. Version courte

French practical guidelines for the diagnosis and management of IPF — 2021 update, short version

SYNTHÈSE
À DESTINATION
DU MÉDECIN TRAITANT

2021

Extraite du Protocole National de Diagnostic et de Soins (PNDS)

FIBROSE PULMONAIRE IDIOPATHIQUE

Ce PNDS a été rédigé sous la coordination du
Pr Vincent COTTIN

Centre de Référence
des maladies pulmonaires rares

(OrphaLung)

https://www.has-sante.fr/plugins/ModuleXitiKLEE/types/FileDocument/doXiti.jsp?id=p_3278604

Recommandations pour la transplantation pulmonaire

L'âge >65 ans est une contrindication RELATIVE

USA
30% listés > 65 ans

Leard et al, JHLT 2021;40:1349-79

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

Transplantation : Quand évaluer ?

Interstitial Lung Disease (ILD)		
2014 Consensus Statement	2021 Consensus Statement	Consensus N (%)
Timing of Referral	**Timing of Referral***	
• Histopathologic or radiographic evidence of UIP or fibrosing non-specific interstitial pneumonitis regardless of lung function.	• Referral should be made at time of diagnosis, even if a patient is being initiated on therapy, for histopathological UIP or radiographic evidence of a probable or definite UIP pattern.	22 (92%)
• Abnormal lung function: FVC <80% predicted or DLCO <40% predicted.	• Any form of pulmonary fibrosis with FVC of < 80% predicted or DLCO < 40% predicted.	24 (100%)
• Any dyspnea or functional limitation attributable to lung disease.	• Any form of pulmonary fibrosis with one of the following in the past 2 years: ○ Relative decline in FVC 10% ○ Relative decline in DLCO 15% ○ Relative decline in FVC 5% in combination with worsening of respiratory symptoms or radiographic progression	24 (100%)
• Any oxygen requirement, even if only during exertion.	• Supplemental oxygen requirement either at rest or on exertion.	24 (100%)
• For inflammatory ILD, failure to improve dyspnea, oxygen requirement, and/or lung function after a clinically indicated trial of medical therapy.	• For inflammatory ILDs, progression of disease (either on imaging or pulmonary function) despite treatment.	24 (100%)
	• For patients with connective tissue disease or familial pulmonary fibrosis, early referral is recommended as extrapulmonary manifestations may require special consideration.	24 (100%)

Leard et al, JHLT 2021;40:1349-79

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

…Mais efficacité contre placebo non démontrée !

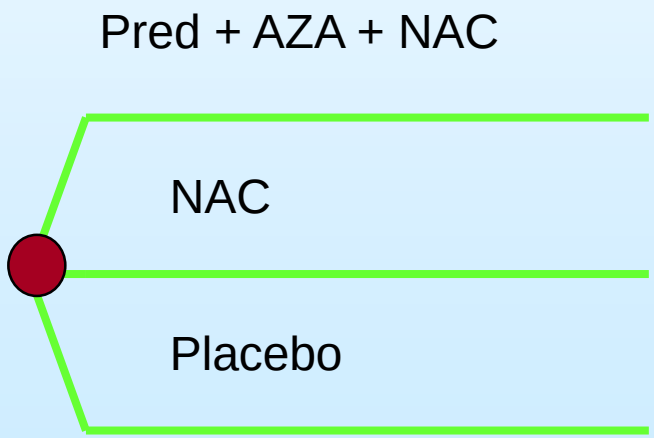
- Avis d’experts (consensus ATS/ERS 2000)
- Résultats IFIGENIA

PANTHER trial
IPF Network NIH

- Patients avec FPI peu évoluée

  (CVF > 50%;DLCO > 30%; Dc <4 ans)

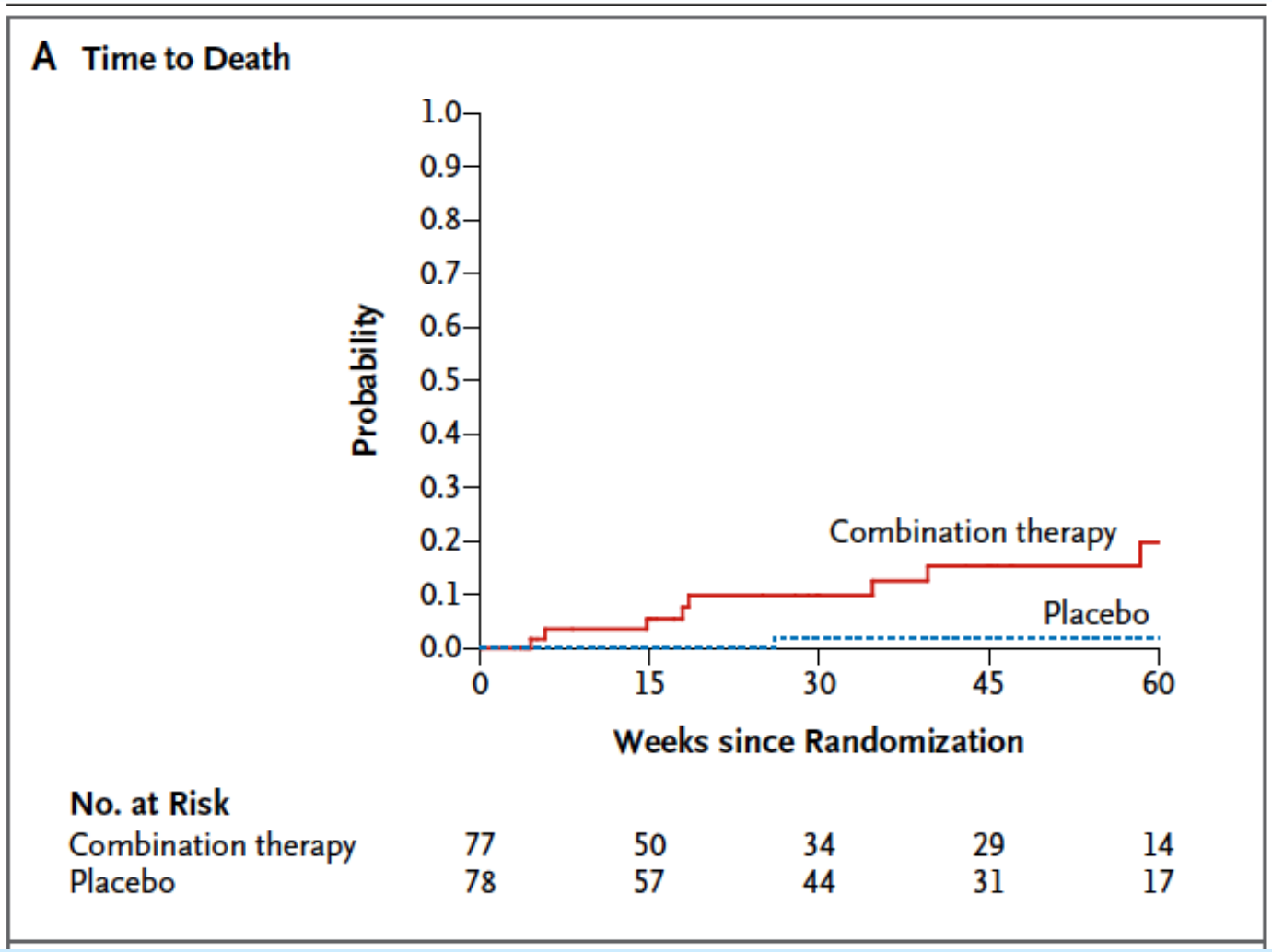
Prednisone
0,5→0,15 mg/kg sur 25 sem
Azathioprine : 150 mg/j maxi
NAC : 600 mg x3/j



N=390
60 sem

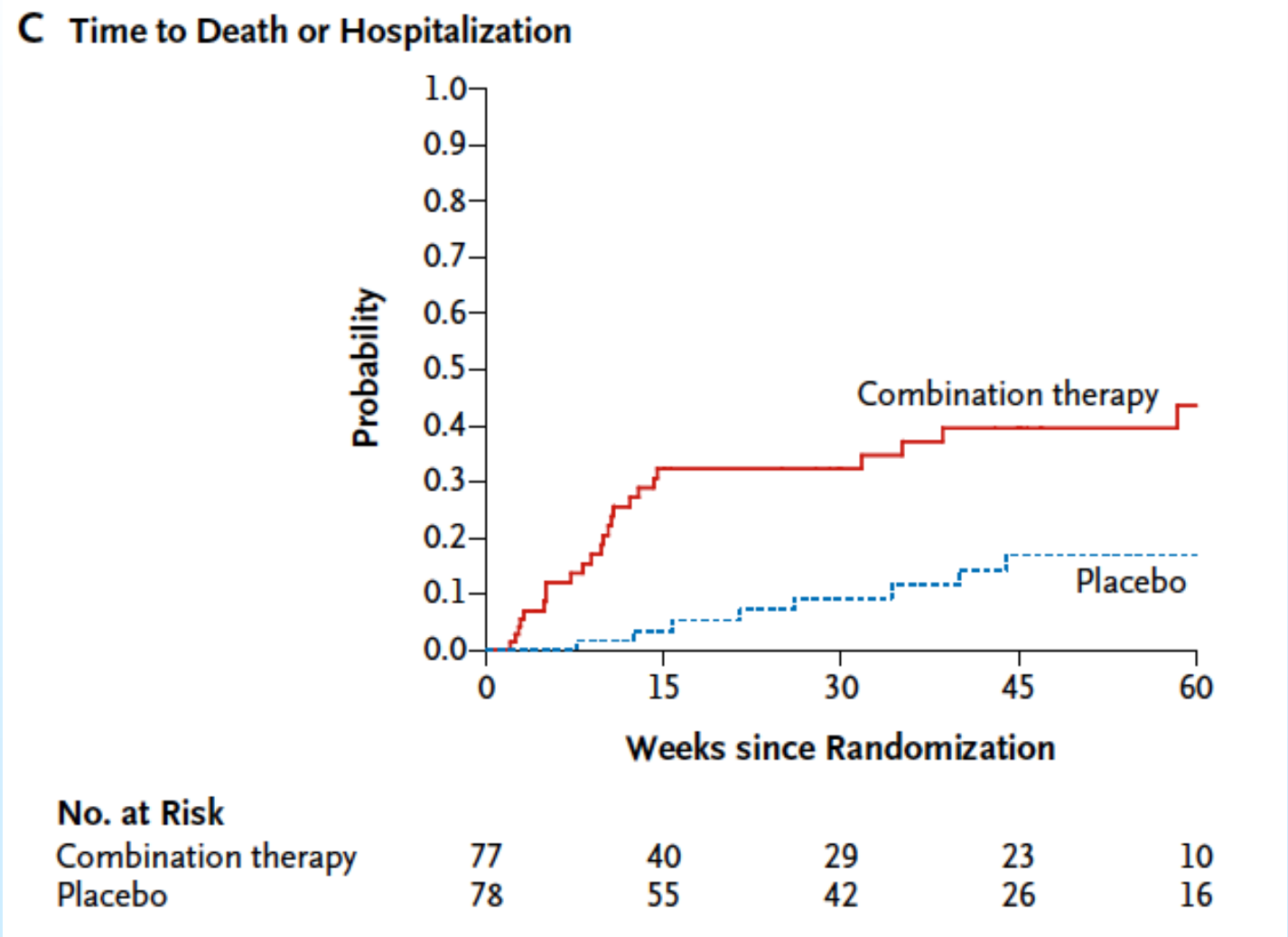
(Raghu, NEJM 2012)

Increased mortality in treated patients



(IPFNet, NEJM 2012)

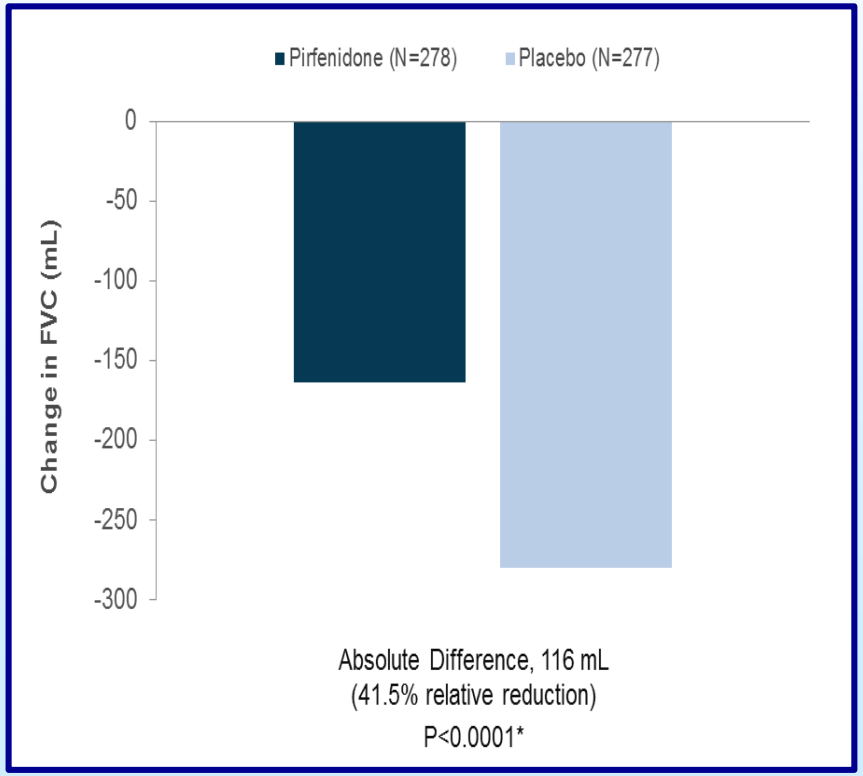
Increased mortality and hospitalization rate



(IPFNet, NEJM 2012)

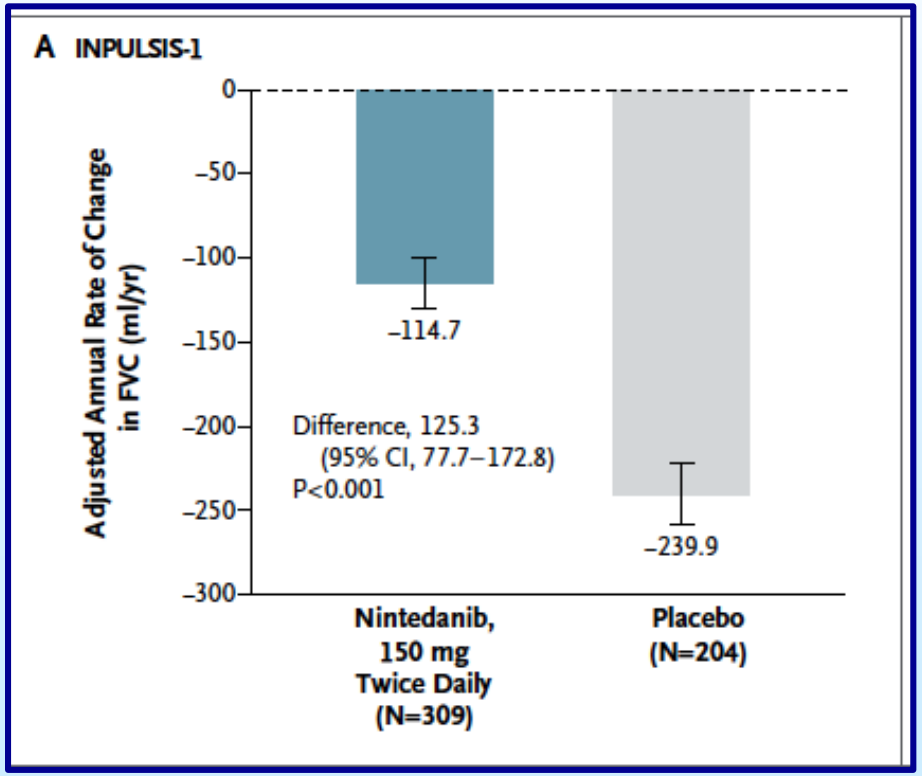
The current situation : treatment of IPF

Pirfenidone



King, NEJM 2014

Nintedanib



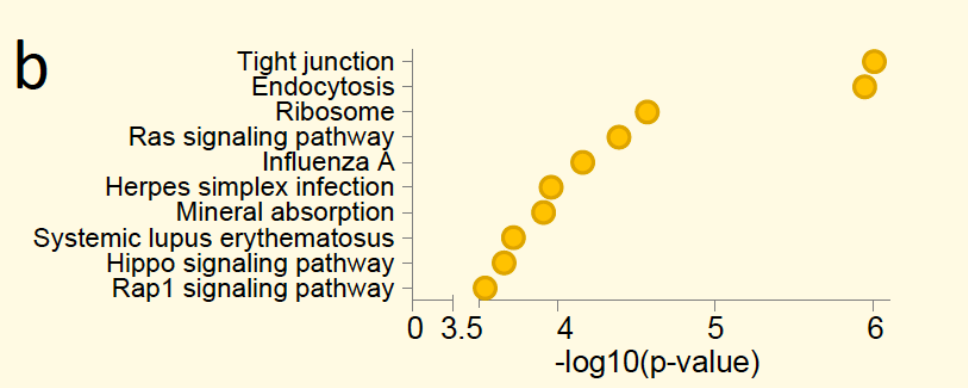
Richeldi, NEJM 2014

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

- **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-remboursement 15%)**

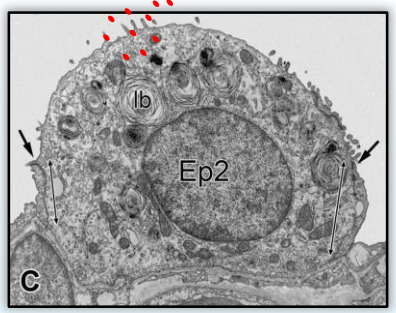
Top ten pathways modulated by Pirfenidone in vivo

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

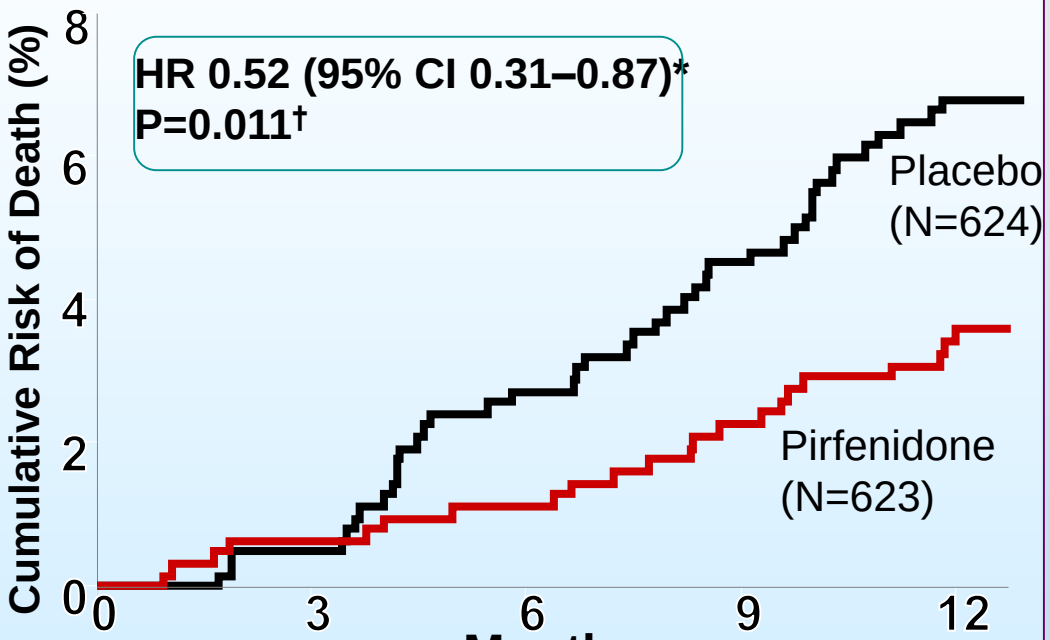
Knüppel, AJRCMB 2017

Lehtonen, Respir Res 2016

Activation, Migration, Proliferation of Fibroblasts

A trend toward improved Survival

Pirfenidone

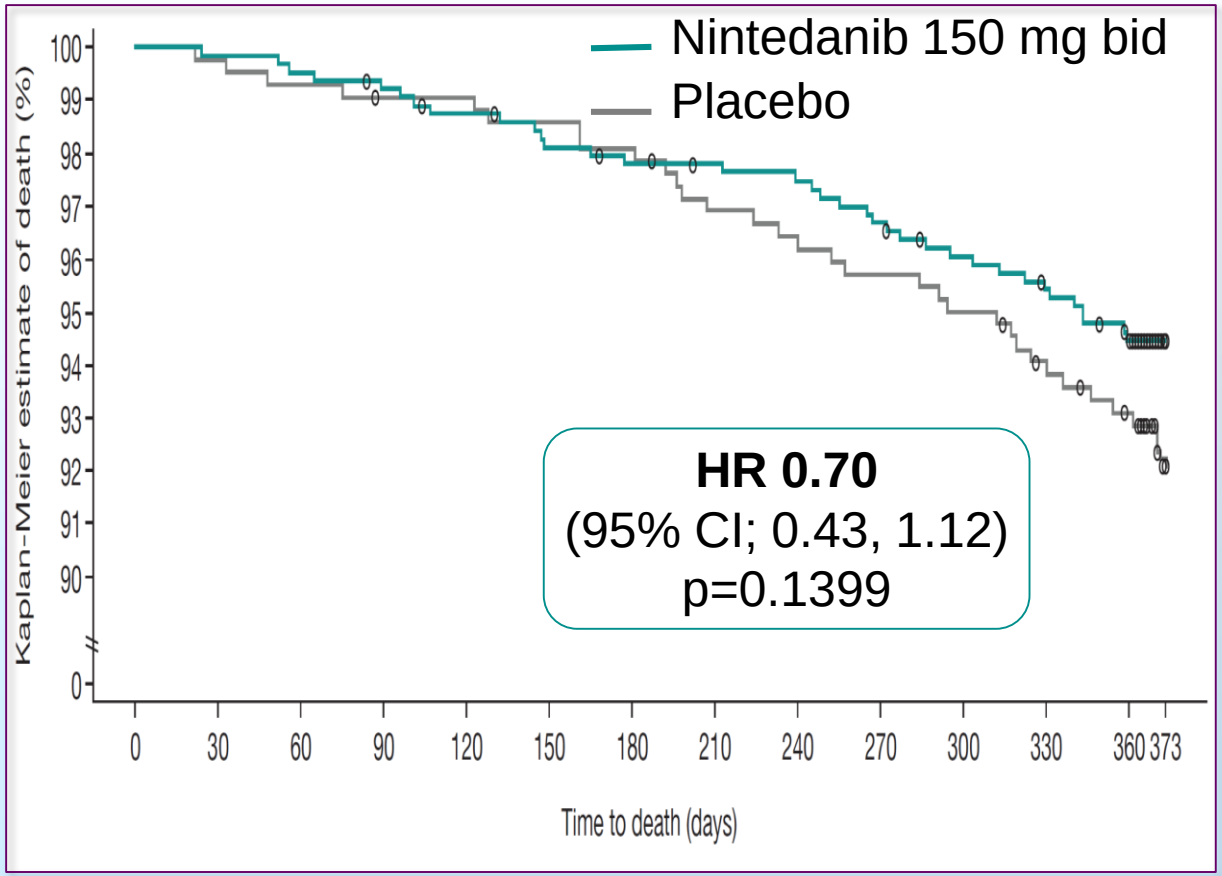


Patients at Risk, n					
Pirfenidone	623	618	609	596	509
Placebo	624	619	603	586	490

* Cox proportional hazards model
† Log-rank test

King et al, NEJM 2014

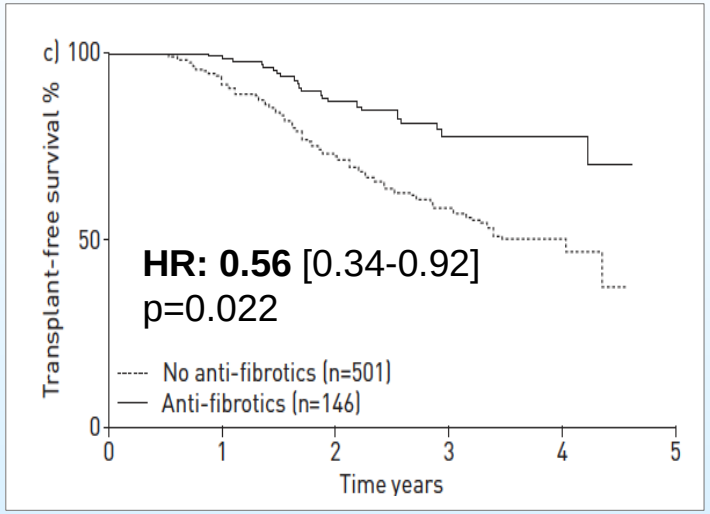
Nintedanib



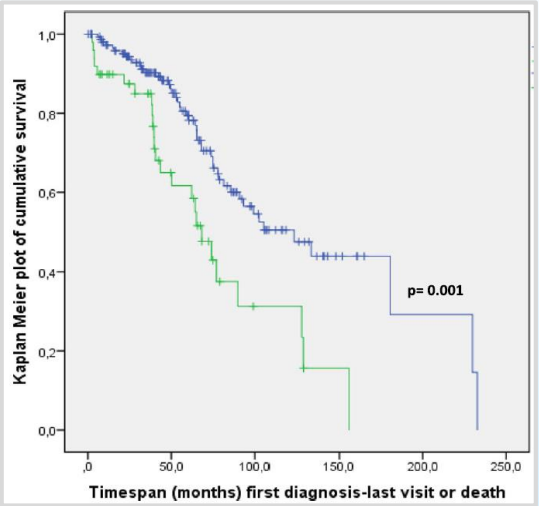
Richeldi et al, NEJM 2014

pirfenidone and nintedanib probably improve survival in IPF

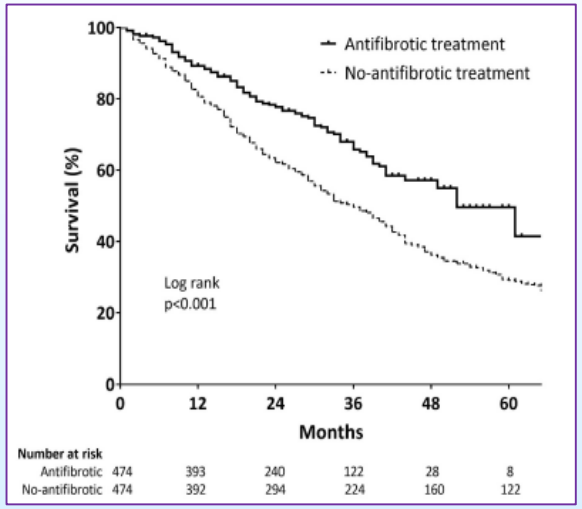
Australian registry[1]



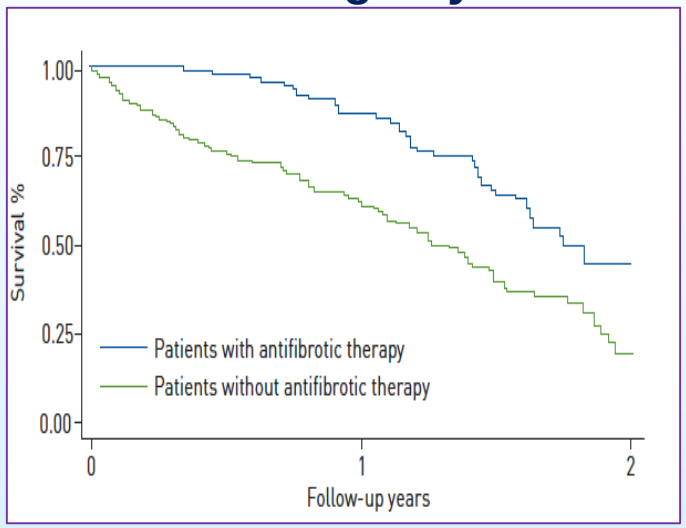
EurIPF registry[2]



Korean series[3]



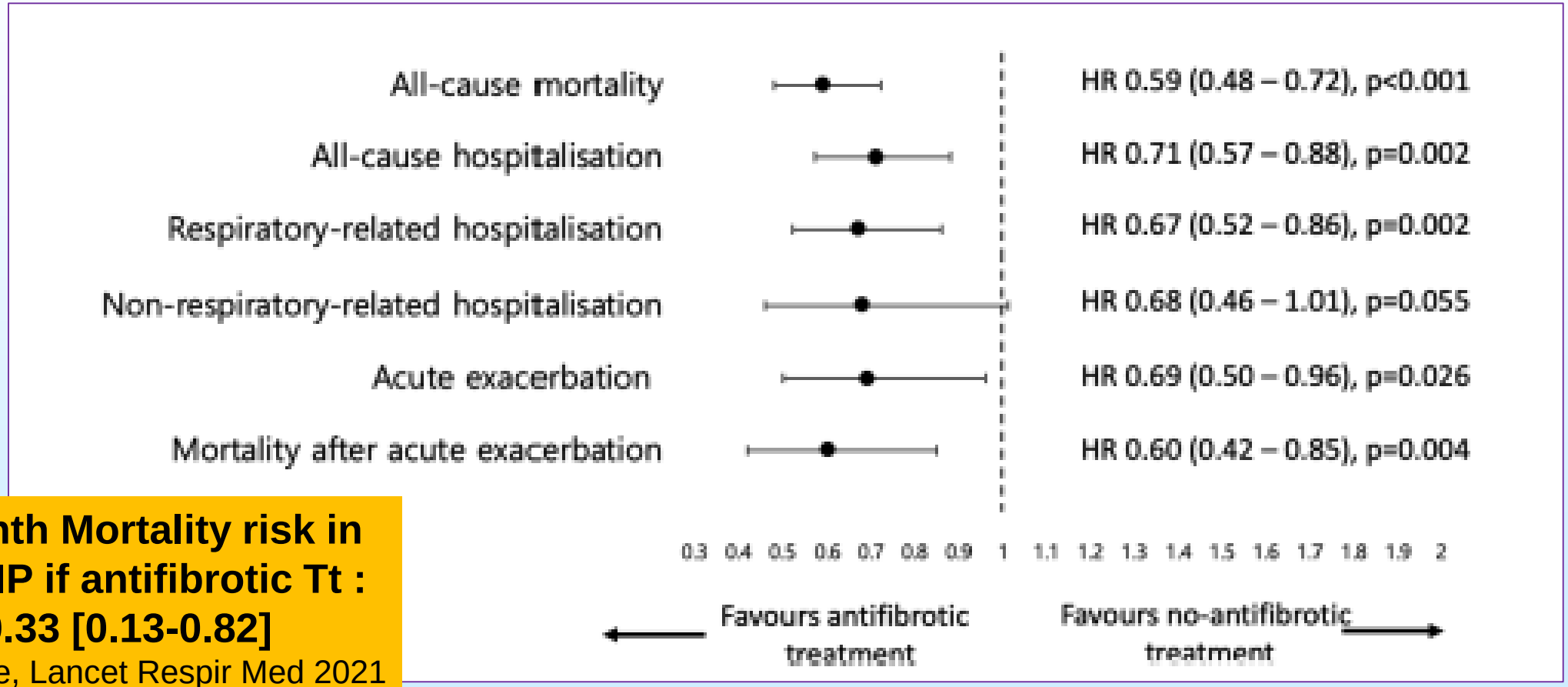
German IPF registry[4]



1: Jo et al, Eur Respir J 2017
2: Guenther, Respir Res 2018
3: Kang, Sci Rep 2020
4: Behr, Eur Respir J 2020

pirfenidone and nintedanib reduce the hospitalisation risk and exacerbation risk and reduce mortality associated with exacerbation

(Propensity score matching)

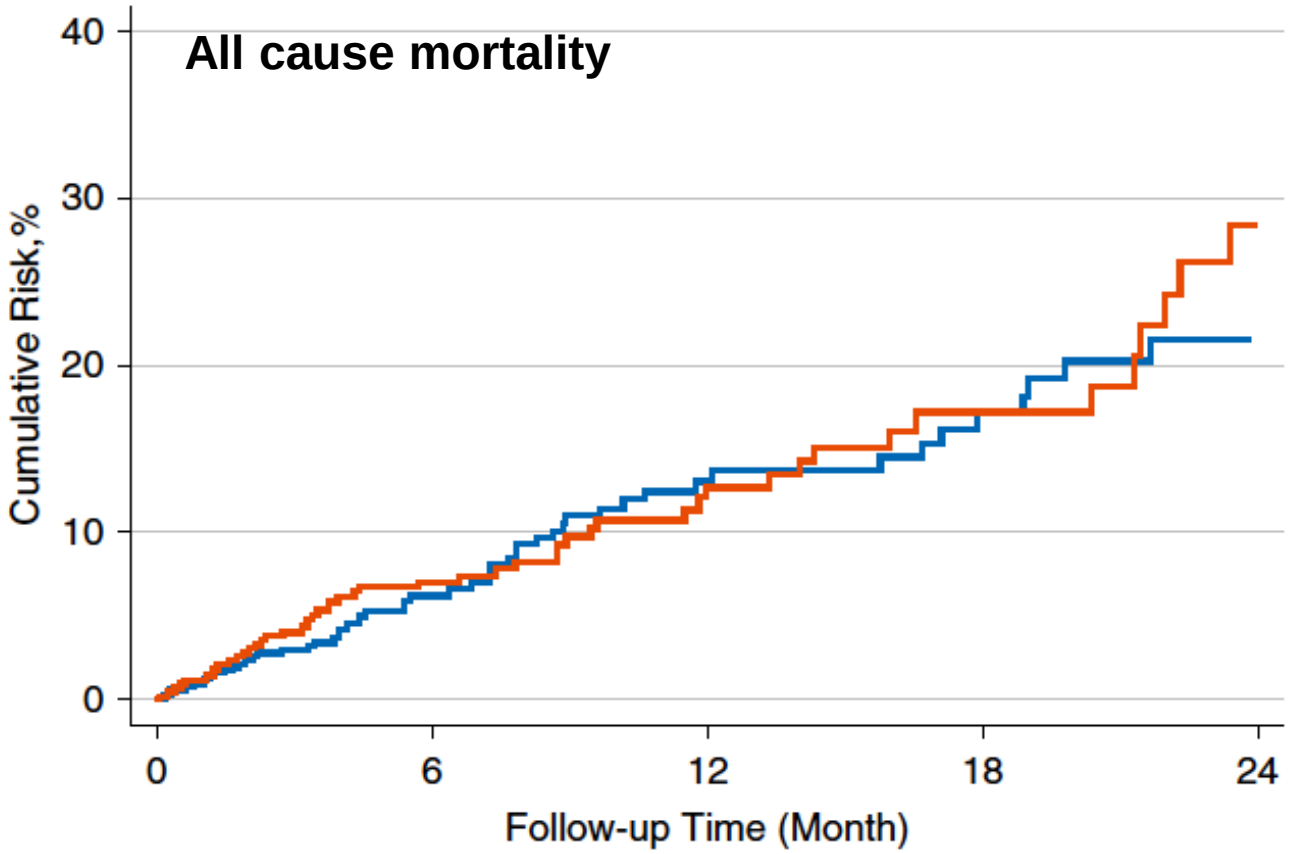


3 month Mortality risk in EXAFIP if antifibrotic Tt : 0.33 [0.13-0.82]

Naccache, Lancet Respir Med 2021

Kang, Sci Rep 2020

…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

Traiter précocément !

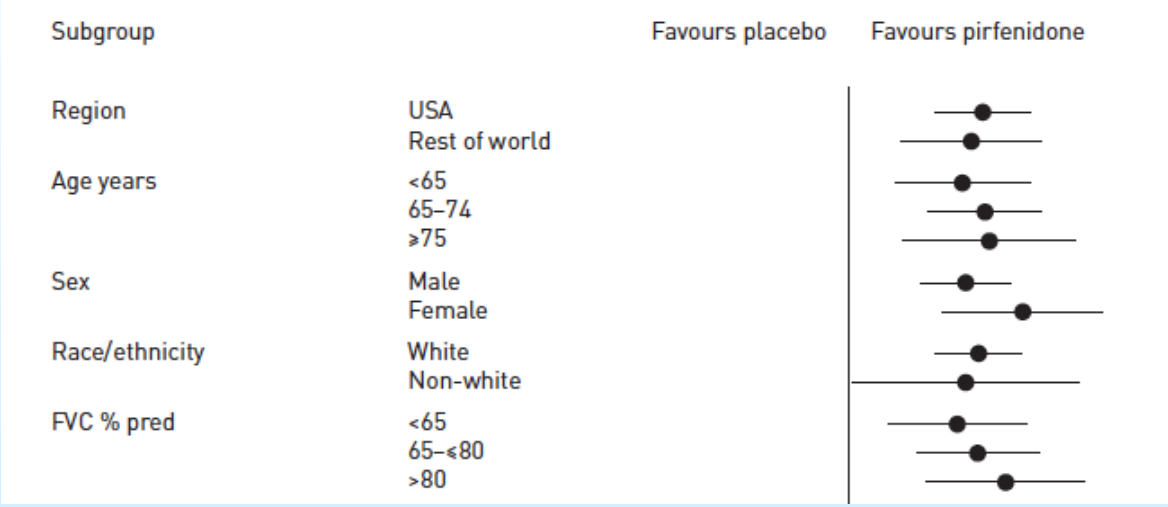
Recommandation 19

Il est recommandé de traiter la FPI dès que le diagnostic est établi, en tenant compte de l'évaluation individuelle du bénéfice escompté et des risques du traitement.

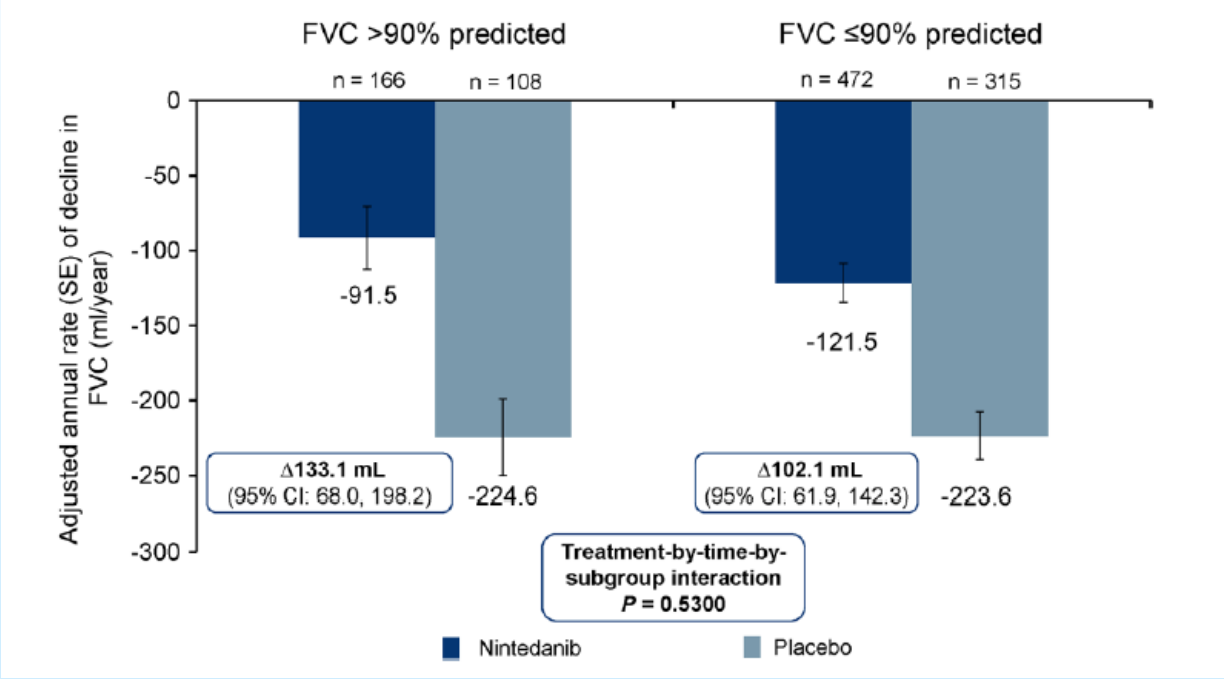
Cottin, et al Rev Mal Respir 2017
Cottin, et al Rev Mal Respir 2022

Pirfenidone and nintedanib are effective in early fibrosis

Pirfenidone



Nintedanib



Noble, Eur Respir J 2016

Kolb, Thorax 2016

Recommandation 18

Chez un patient présentant un diagnostic confirmé de FPI légère à modérée (définie par une capacité vitale forcée ≥ 50 % de la valeur théorique et une capacité de diffusion du monoxyde de carbone ≥ 30 %), il est recommandé de proposer un traitement par antifibrosant (pirfénidone ou nintédanib).

- Ce traitement doit être instauré et surveillé par un pneumologue expérimenté dans le diagnostic et le traitement de la FPI et nécessite une surveillance régulière de la tolérance clinique et de la biologie hépatique ;
- Le patient ne doit pas fumer pendant le traitement par pirfénidone.

Recommandation 21

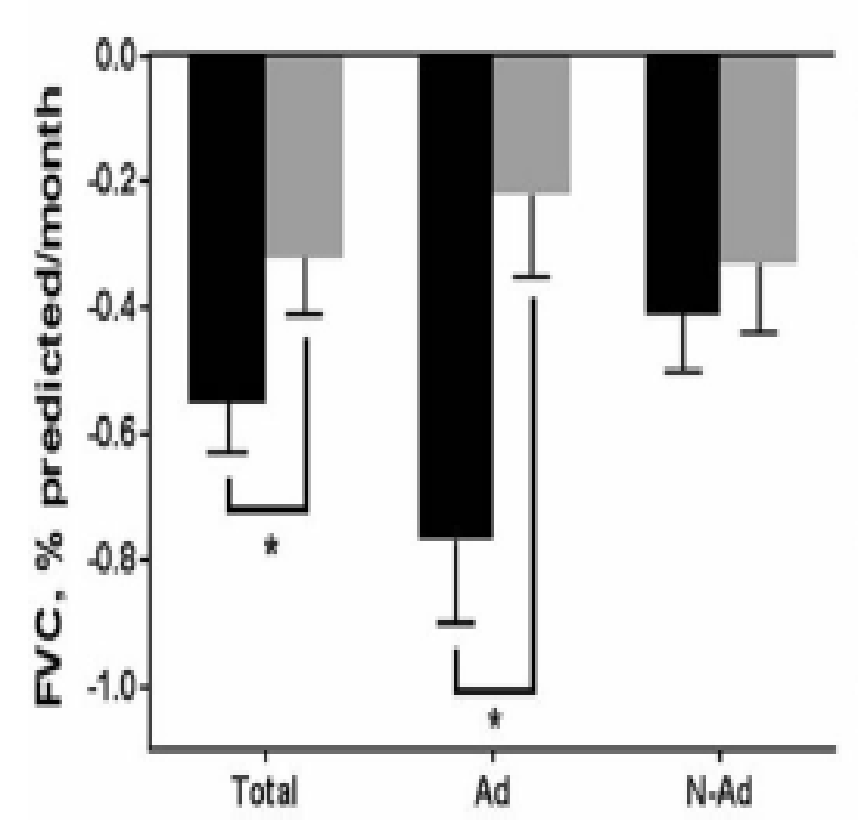
Chez un patient ayant un diagnostic confirmé de FPI, il est recommandé de ne pas débuter les traitements suivants :

- Trithérapie prednisone-azathioprine-N-acétylcystéine ;
- Traitement antivitamine K oral, en dehors d'une indication reconnue notamment cardiovasculaire (il n'y a pas de donnée disponible concernant les anticoagulants oraux directs au cours de la FPI) ;
- Ambrisentan, riociguat même en présence d'une hypertension pulmonaire.

Cottin et al, Rev Mal Respir 2022

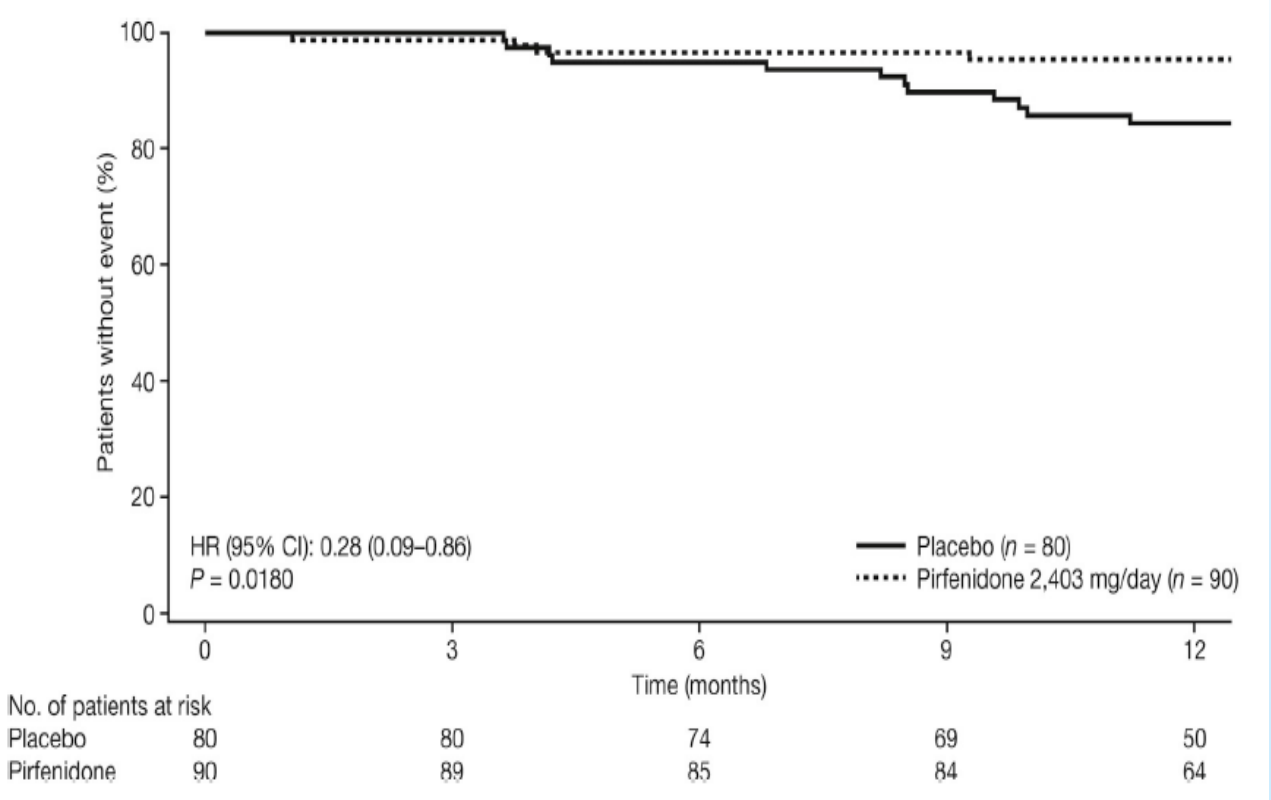
Que faire chez les patients « trop sévères » CVF<50% et DLCO<30%

Nintedanib (N=108, Korea)
Advanced disease (FVC<50% or DLCO<30%)
N=51 (47%)
Median Tt duration 42 weeks



Yoon, Respir Res 2018

Pirfenidone
Post Hoc analysis Ascend + Capacity
FVC<50% or DLCO<35%



Nathan, Respir Med 2019

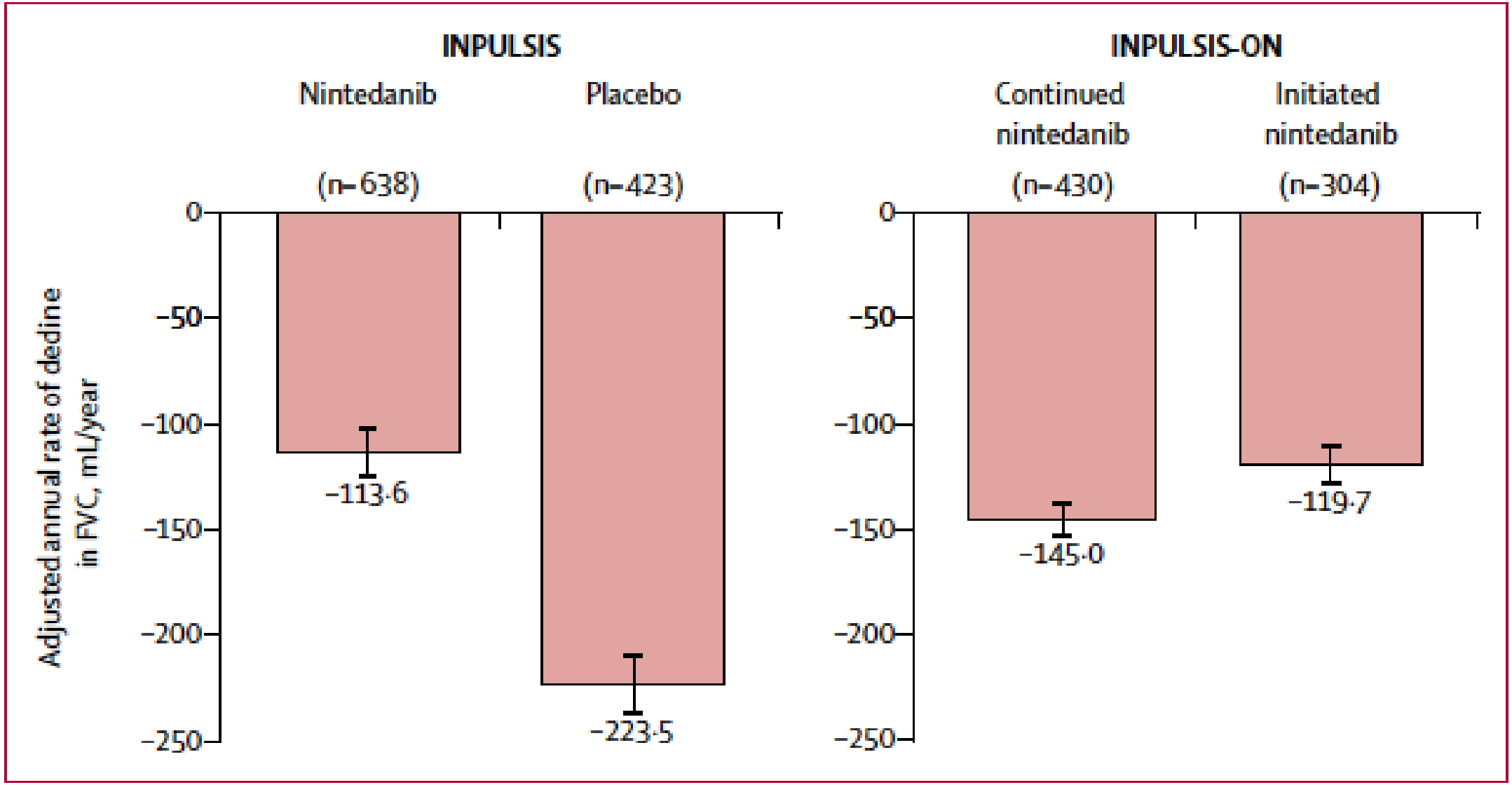
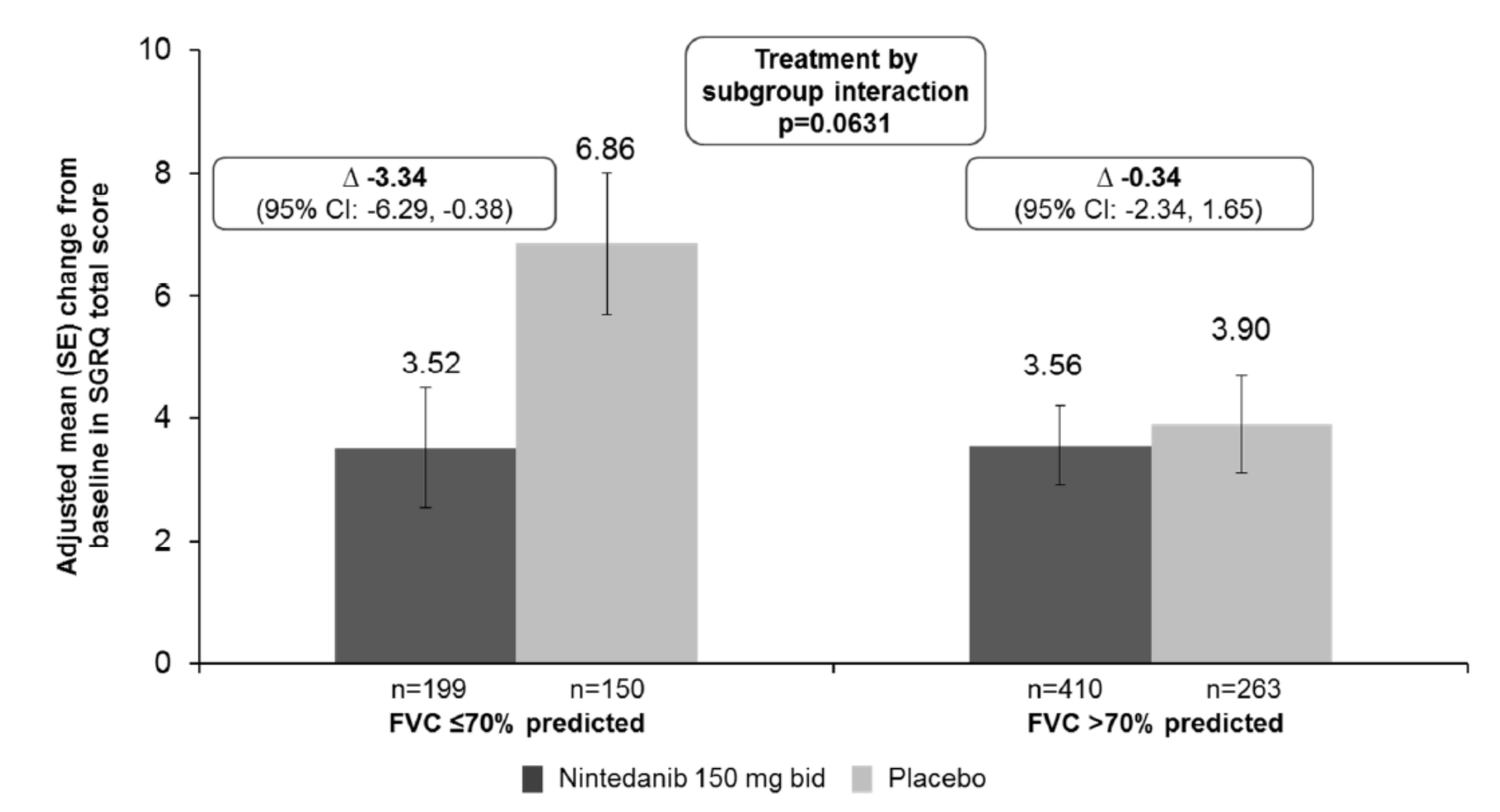


Figure 3: Annual rate of decline in FVC over 52 weeks in INPULSIS and over 192 weeks in INPULSIS-ON
Error bars show SE. FVC=forced vital capacity.

Crestani et al, Lancet Respir Med 2018

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



(Costabel, AJRCCM 2015)

Deux médicaments efficaces dans la FPI…

Génériques
depuis Août 2022

.Tabac
.Interactions

3cps 267mg x3/j
ou
1 cp 801mgx3

Précautions :
-Anticoagulants
-Double antiaggrégation

1gel x2/j
(100 ou 150mg)

Digestif
Cutané

Tolérance

CVF

Populations différentes

Tolérance

Digestif

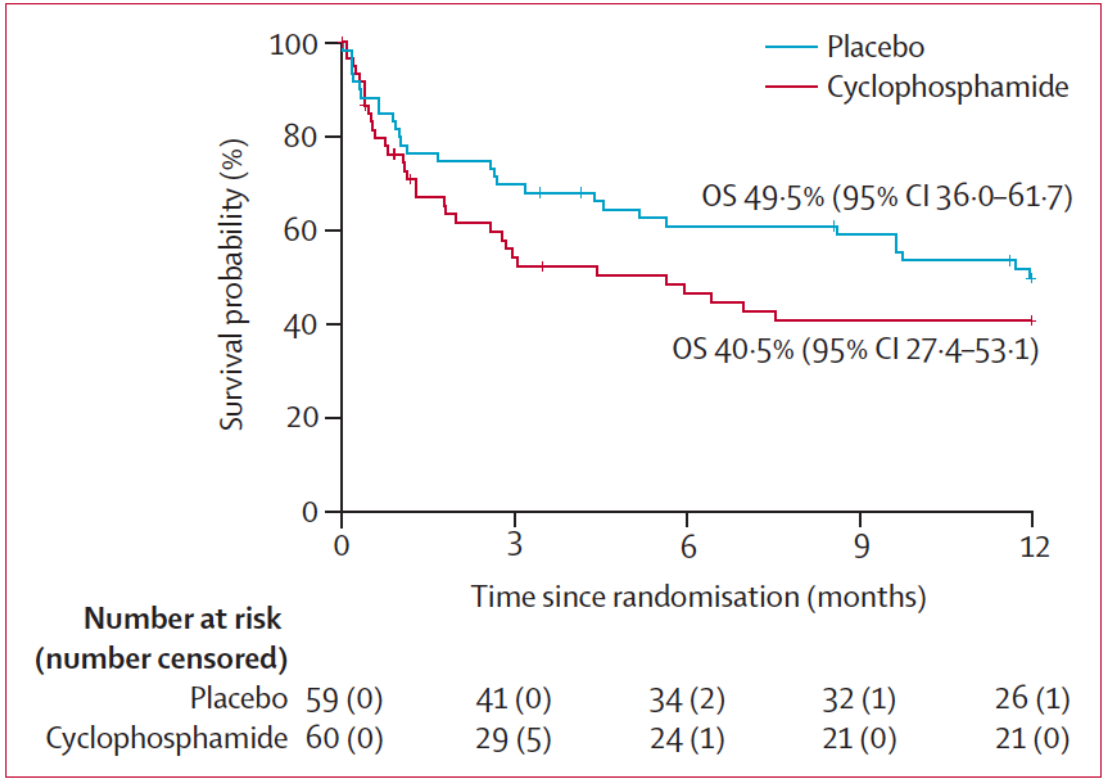
CVF

Pirfenidone

Nintedanib

Comment traiter l'exacerbation ?

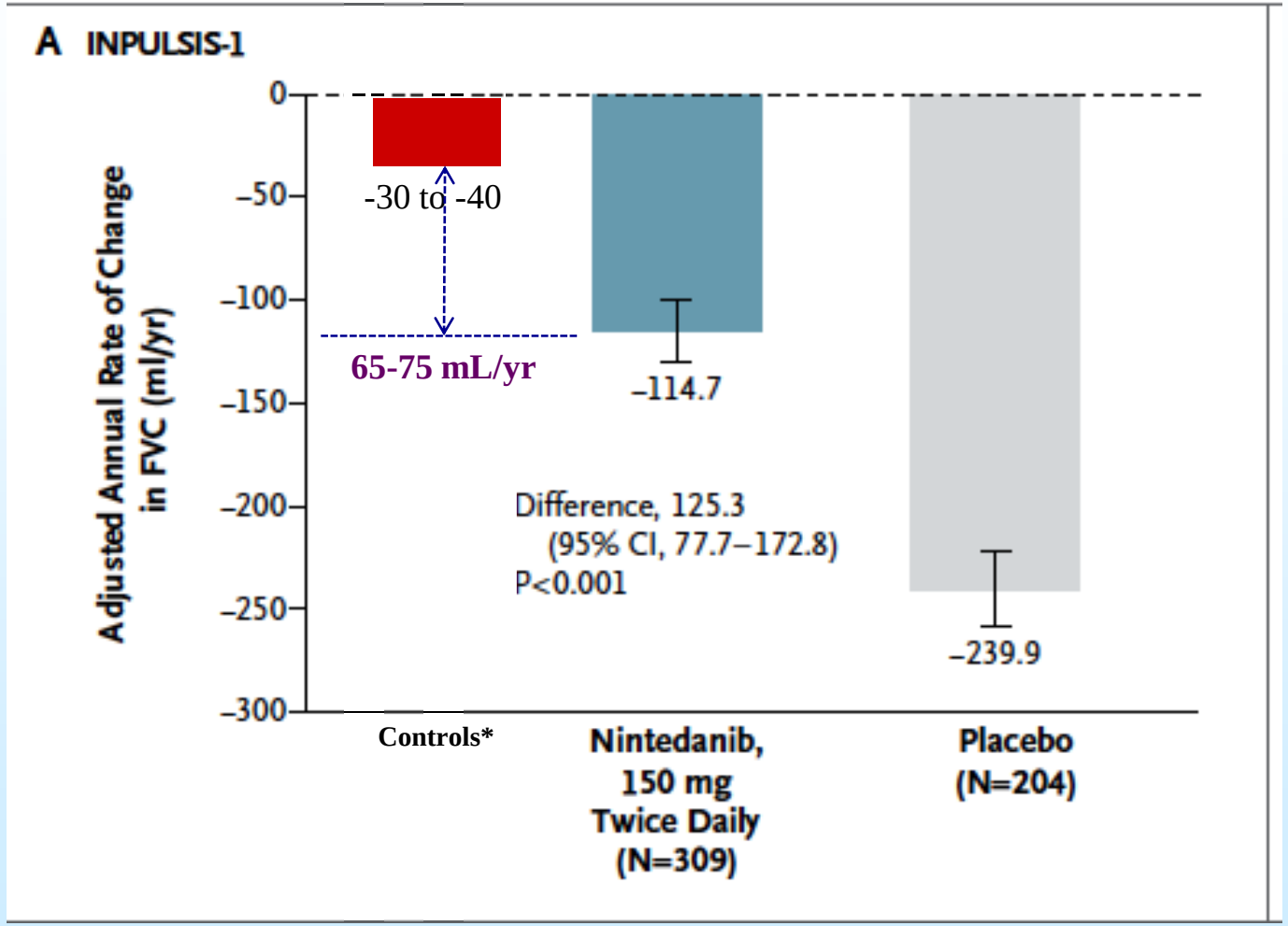
EXAFIP



Naccache, Lancet Respir Med 2021

EXAFIP 2
Tt with or w/o steroids

Peut mieux faire !



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

modified from Richeldi, NEJM 2014

What should I do in a patient with progressive disease with one antifibrotic ?

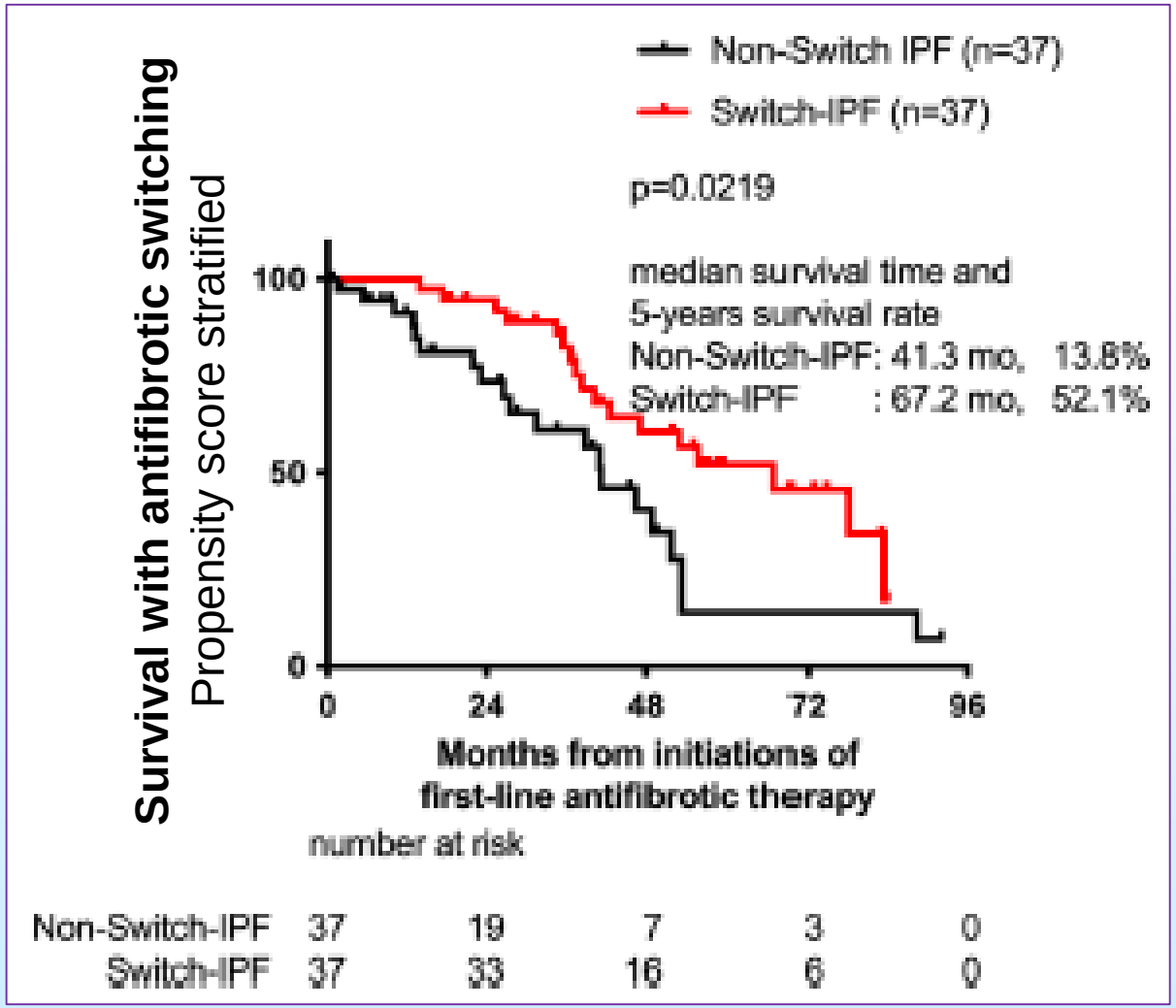
- **Continue ?**
- **Switch ?**
- **Combine ?**

- **Switch is done in 10-14% patients and is safe**

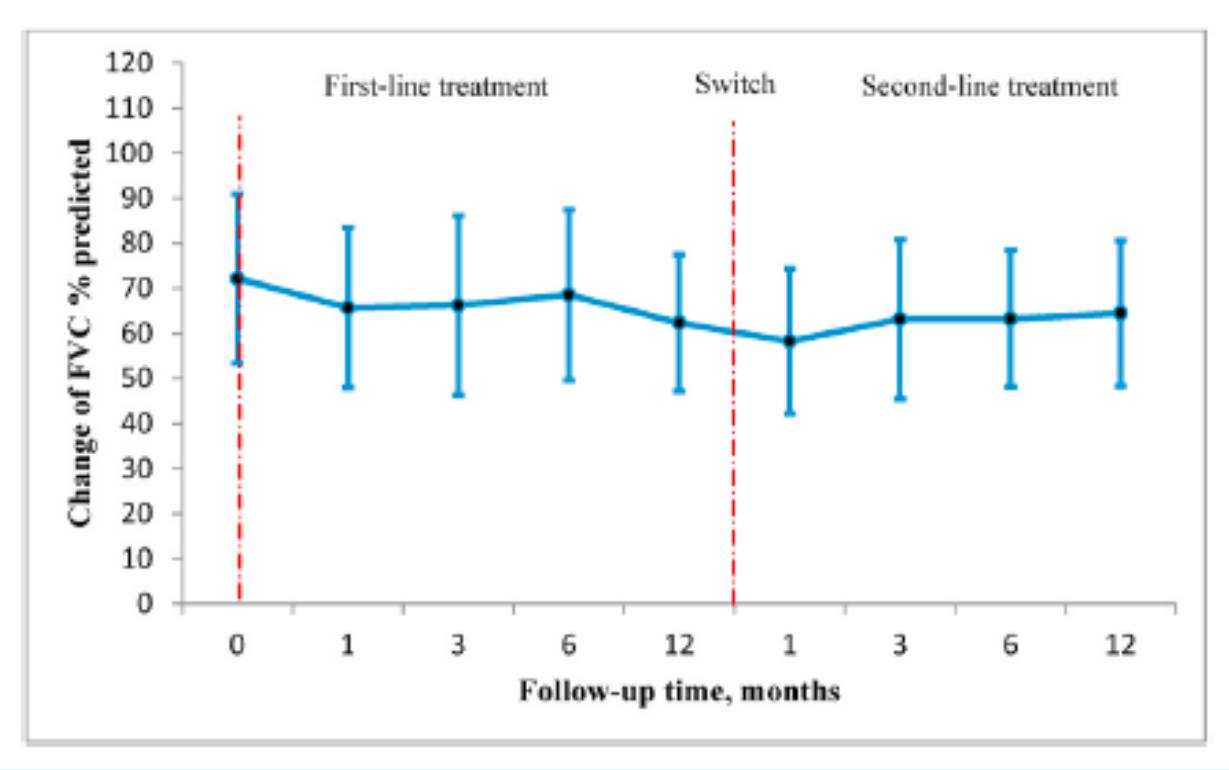
Ntolios, Eur Rev Med Pharmacol Sci 2021
Suzuki, BMC Pulm Med 2021
Cilli, Pulm Pharmacol Ther 2021

- **Due to toxicity or progression (50/50)**

- **Efficacy has not been evaluated rigorously**



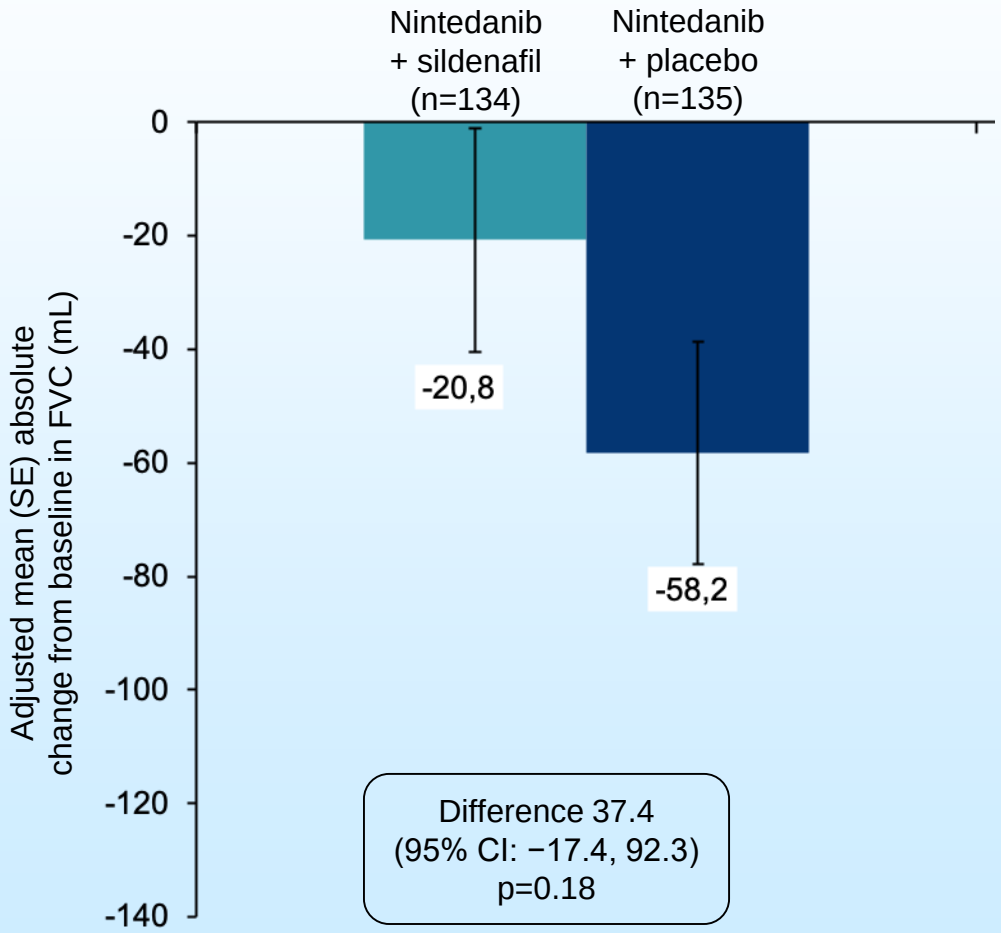
Suzuki, BMC Pulm Med 2021



Cilli, Pulm Pharmacol Ther 2021

Nintedanib + Sildenafil

(INSTAGE)



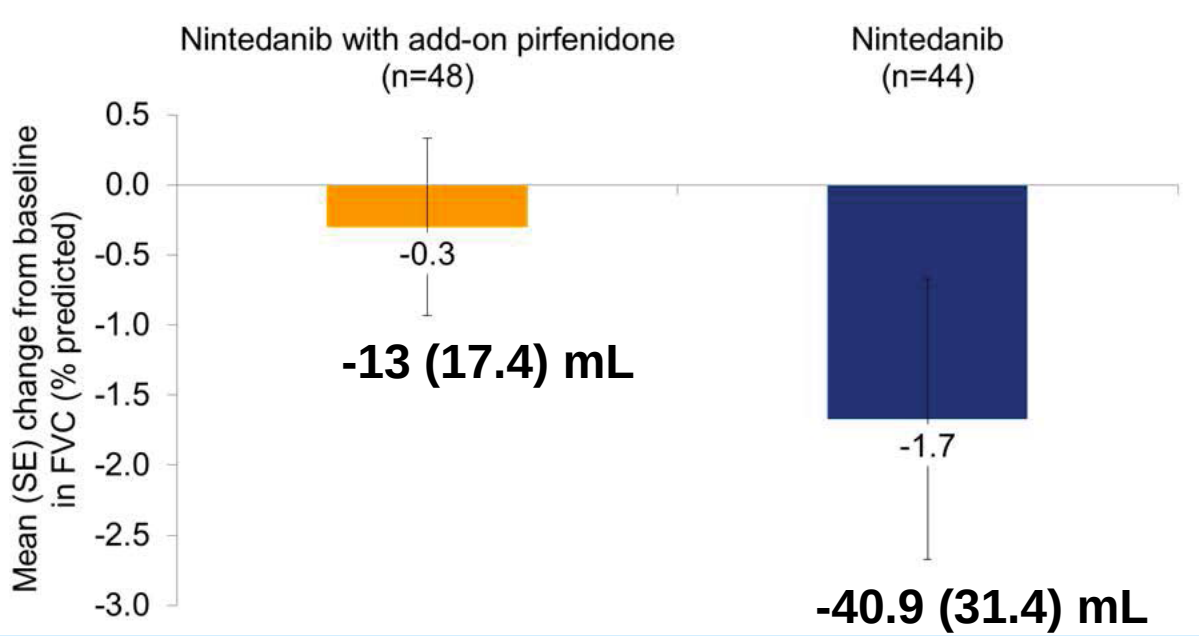
Difference 37.4
(95% CI: −17.4, 92.3)
p=0.18

Kolb, NEJM 2018

Nintedanib + Pirfenidone

(INJOURNEY)

12 weeks



Vancheri, AJRCCM 2017

What should I do in a patient with progressive disease with one antifibrotic ?

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

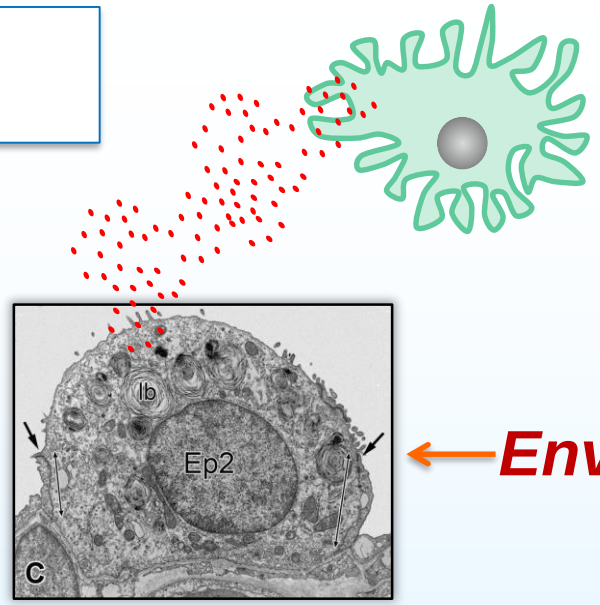
→

« Progression » Trial
(NCT03939520; V. Cottin)

378 participants
24 weeks

Mechanical stretch

Macrophage

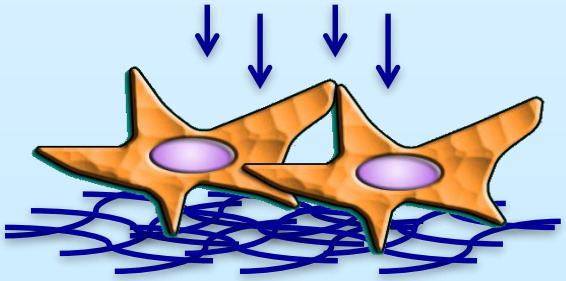


Aging → ← ***Environment***

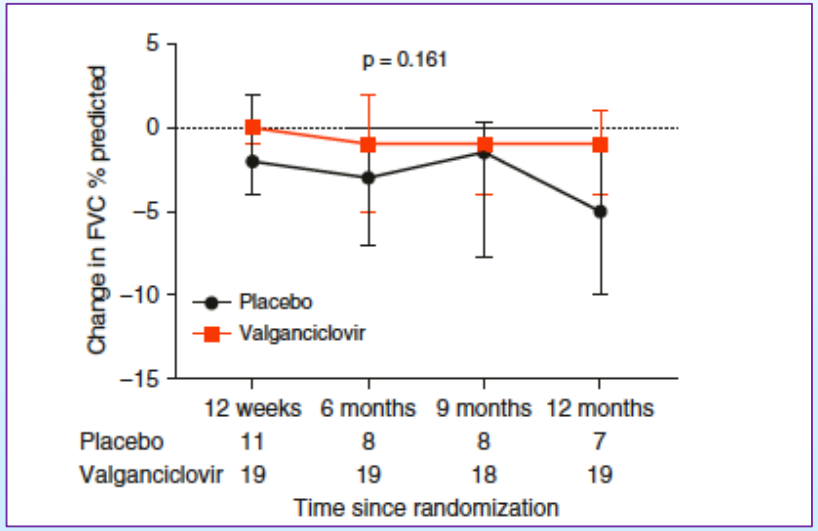
ER stress, UPR activation, senescence

↓ ↓ ↓ ↓ ↓ ↓

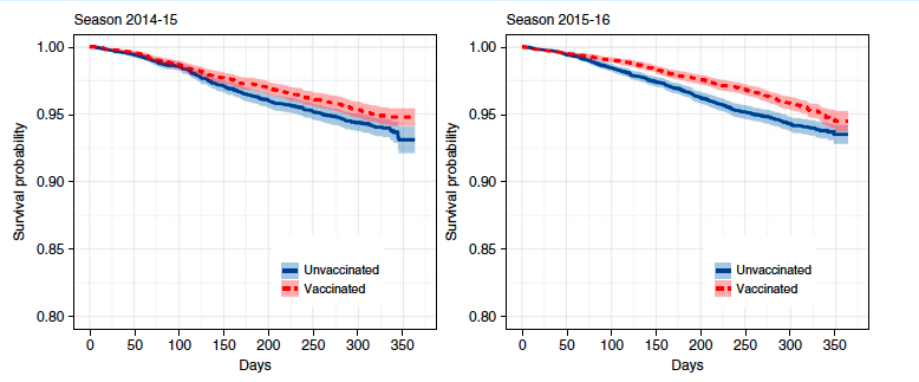
Cytokines, Chimiokines,
Lipids, GFs, ROS
Developmental pathways



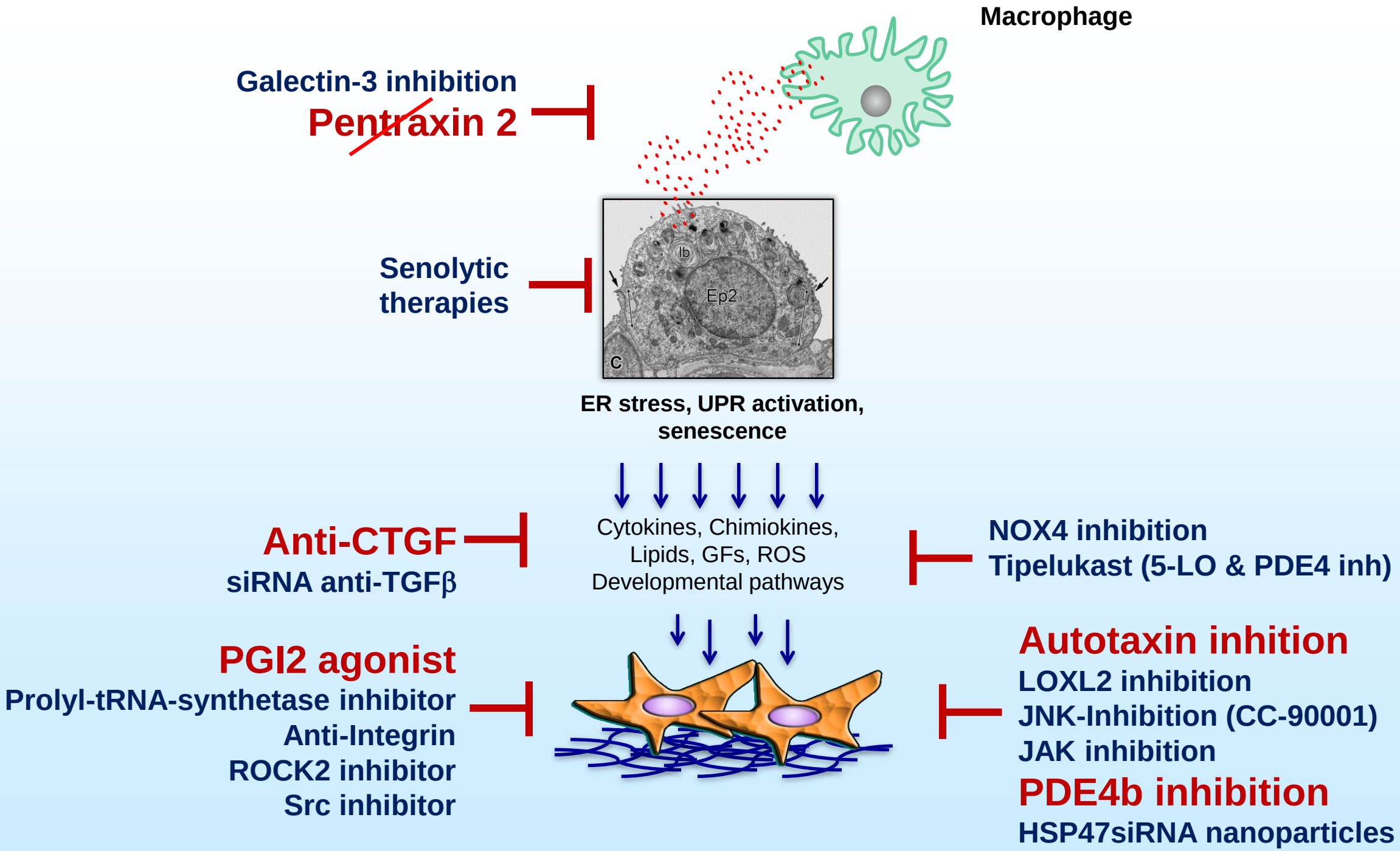
- **GERD**
- **Antiviral ?** (valganciclovir)
- **Antibiotics** (azithromycin Bactrim°, doxycycline) — Trials Failed
- **Vaccines**
- **Stop smoking**



Blackwell, Ann ATS 2021;18:1291



Marijic, Ann ATS 2022;19:1479


Macrophage
Galectin-3 inhibition
Pentraxin 2
Senolytic therapies
Ib
Ep2
C
ER stress, UPR activation, senescence
Cytokines, Chimiokines, Lipids, GFs, ROS Developmental pathways
Anti-CTGF
siRNA anti-TGFβ
NOX4 inhibition
Tipelukast (5-LO & PDE4 inh)
PGI2 agonist
Prolyl-tRNA-synthetase inhibitor
Anti-Integrin
ROCK2 inhibitor
Src inhibitor
Autotaxin inhition
LOXL2 inhibition
JNK-Inhibition (CC-90001)
JAK inhibition
PDE4b inhibition
HSP47siRNA nanoparticles

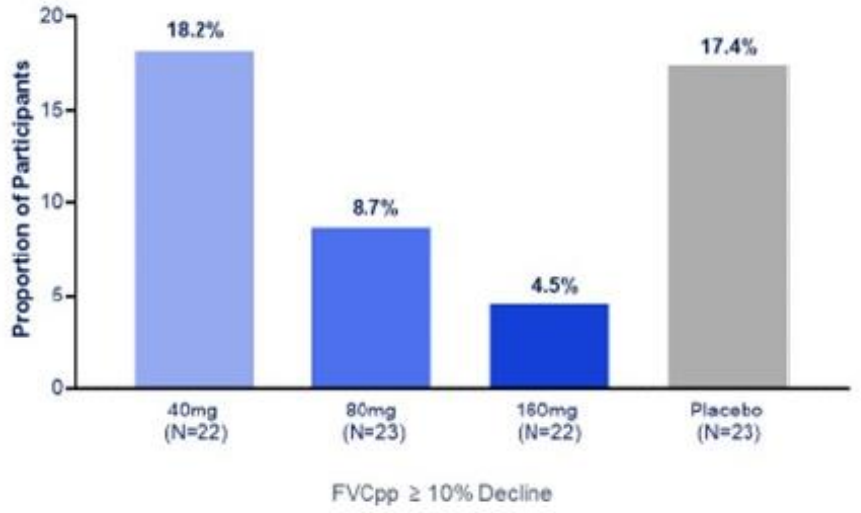
PLIANT

Pliant Therapeutics Announces Positive Safety and Efficacy Data from Phase 2a INTEGRIS-IPF Clinical Trial of PLN-74809 in Patients with Idiopathic Pulmonary Fibrosis

PLN-74809 demonstrated a dose-dependent treatment effect on FVC and QLF versus placebo over 12 weeks of treatment

PLN-74809 treatment effect was observed on top of standard of care therapy and as monotherapy

PLN-74809 was well tolerated over 12 weeks of treatment with no drug related SAEs and no treatment discontinuations due to adverse events



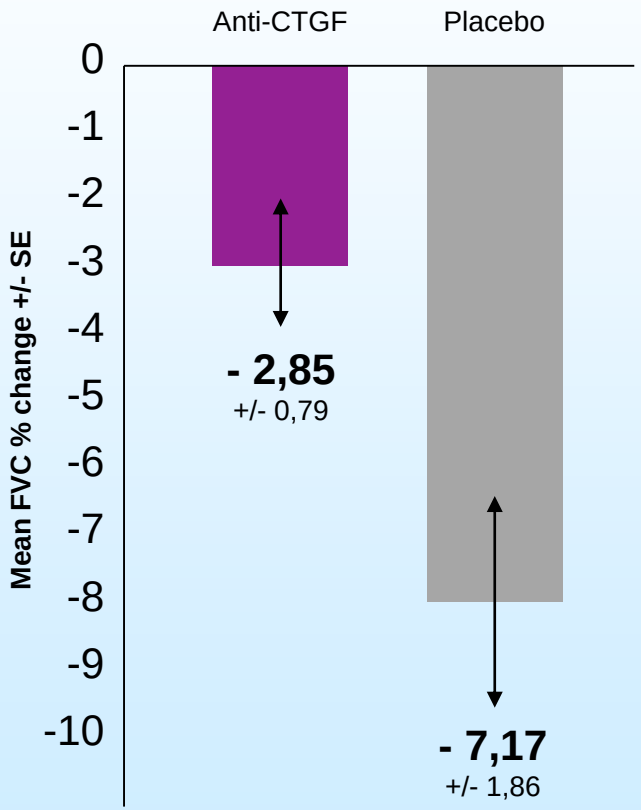
Proportion of Participants with FVCpp Decline ≥10% - Intent to Treat Population

https://www.globenewswire.com/news-release/2022/07/10/2476920/0/en/Pliant-Therapeutics-Announces-Positive-Safety-and-Efficacy-Data-from-Phase-2a-INTEGRIS-IPF-Clinical-Trial-of-PLN-74809-in-Patients-with-Idiopathic-Pulmonary-Fibrosis.html

Pamrevlumab : anti-CTGF (FibroGen)

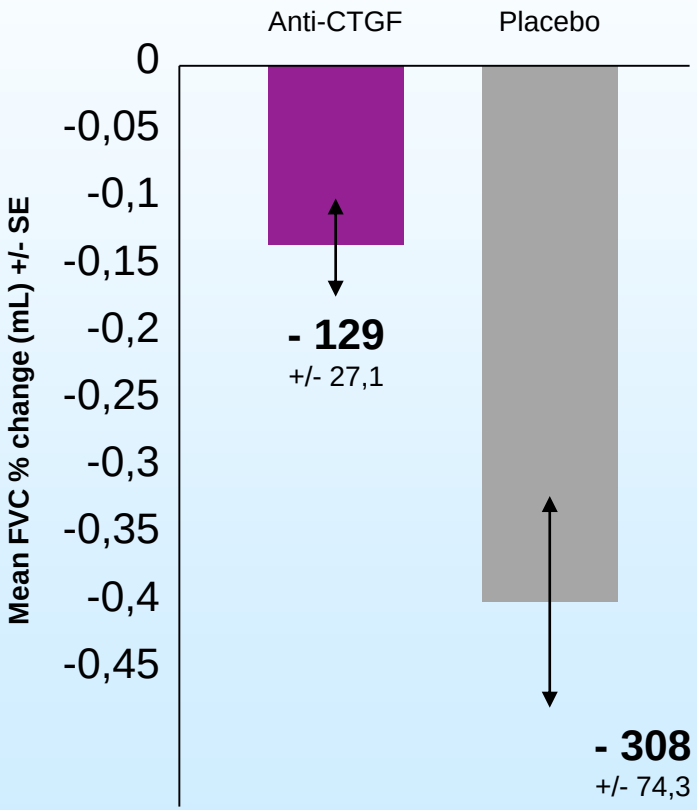
Phase 2 (PRAISE)

➢ **FVC (%)**



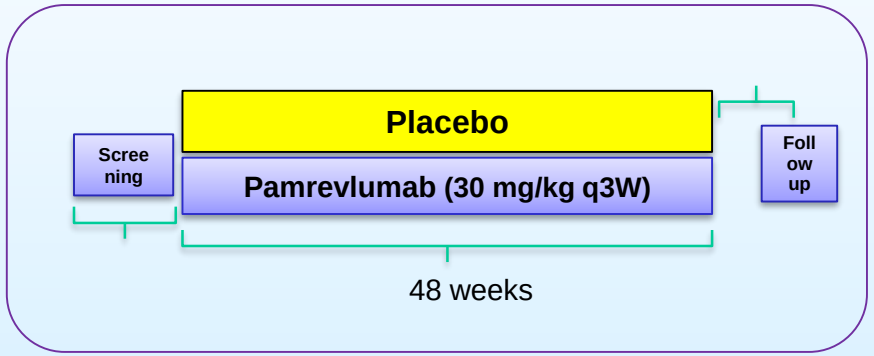
P-value = 0,0331
FVC % predicted difference : 4,33%
Relative difference : 60%

➢ **FVC (mL)**



P-value = 0,0249
Absolute FVC difference : 178 mL
Relative difference : 58%

Phase 3 (ZEPHYRUS-2)

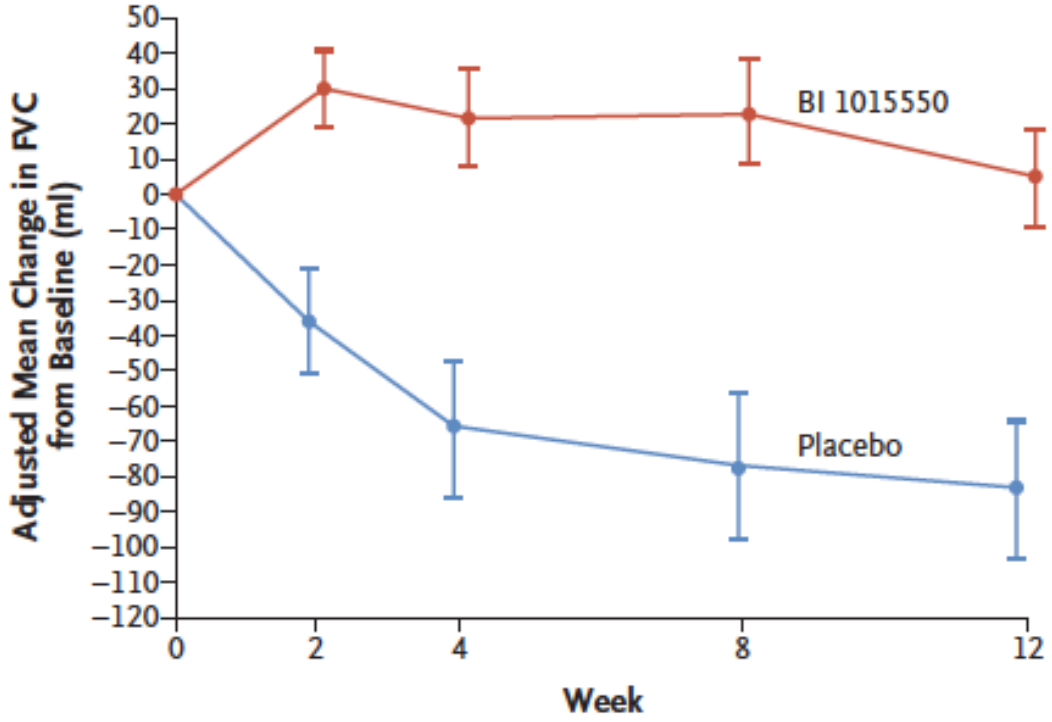


Untreated IPF patients

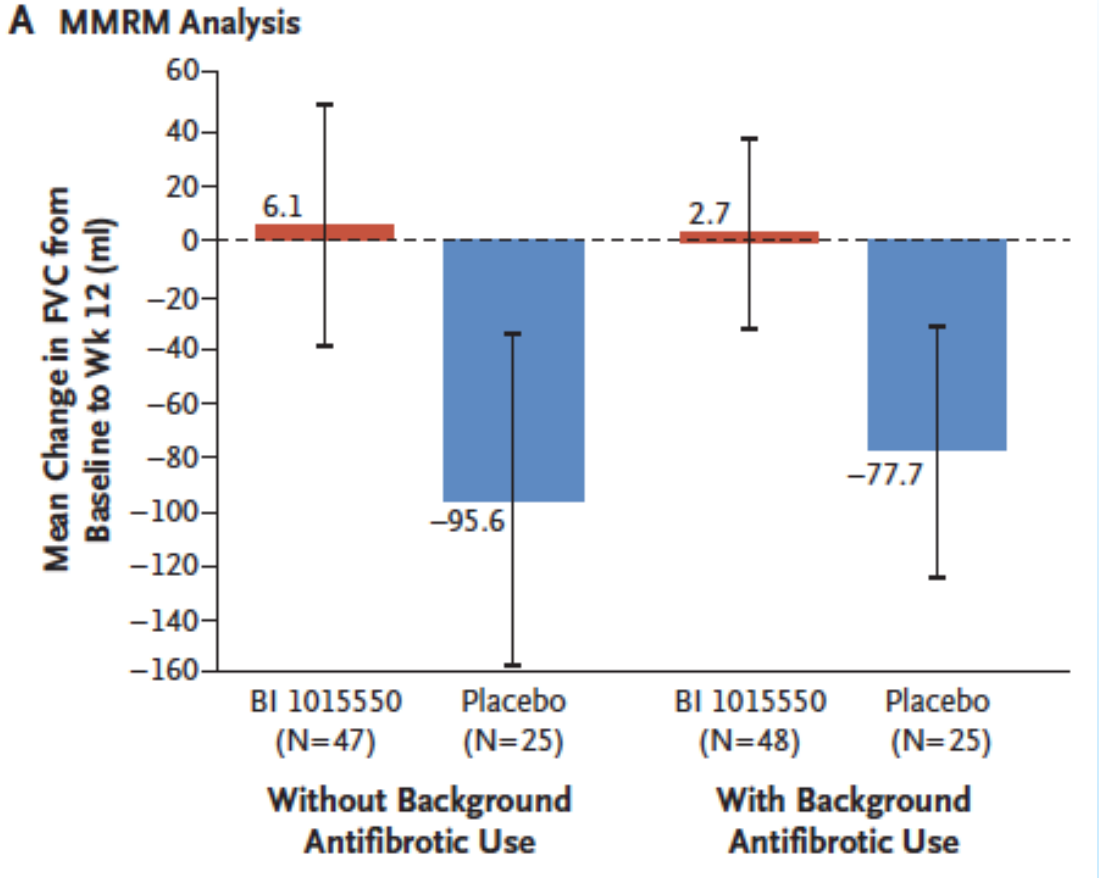
Richeldi, Lancet Respir Med 2019

Trial of a Preferential Phosphodiesterase 4B Inhibitor for Idiopathic Pulmonary Fibrosis

Luca Richeldi, M.D., Ph.D., Arata Azuma, M.D., Ph.D., Vincent Cottin, M.D., Ph.D., Christian Hesslinger, Ph.D., Susanne Stowasser, M.D., Claudia Valenzuela, M.D., Marlies S. Wijsenbeek, M.D., Ph.D., Donald F. Zoz, M.D., Florian Voss, Ph.D., and Toby M. Maher, M.D., Ph.D., for the 1305-0013 Trial Investigators*



No. of Patients				
BI 1015550	90	89	87	81
Placebo	49	50	50	49

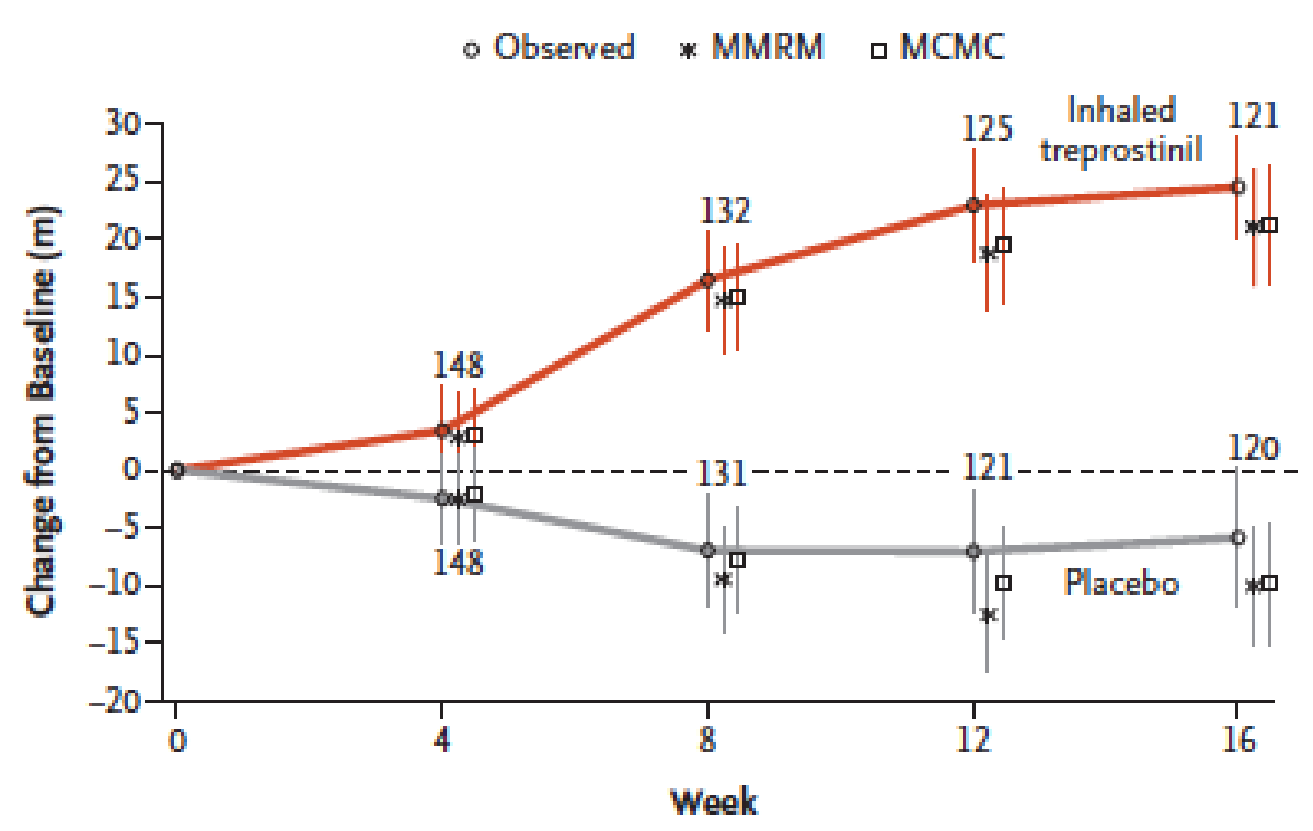


Richeldi, NEJM 2022

PH in ILD (INCREASE trial)

N=336 patients
1) ILD on HRCT
2) PH group 3
   RHC within 12 mo
   mPAP ≥ 25 mmHg
   PAWP ≤ 15 mmHg
   PAR >3 Wood U
3) 6MWD > 100m
4) FVC <70% in CTD-ILD pts

Inhaled Treprostinil (Tyvaso°) vs Placebo
9-12 doses x 4/day
(dose escalation every 3d)



Waxman, NEJM 2021

TYVASO® (treprostinil) INHALATION SOLUTION

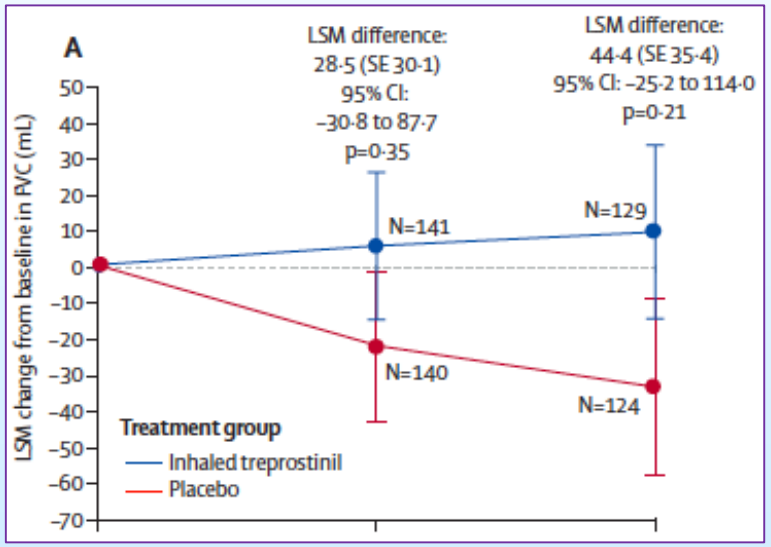
NOW APPROVED

TYVASO for PH-ILD
(WHO Group 3)

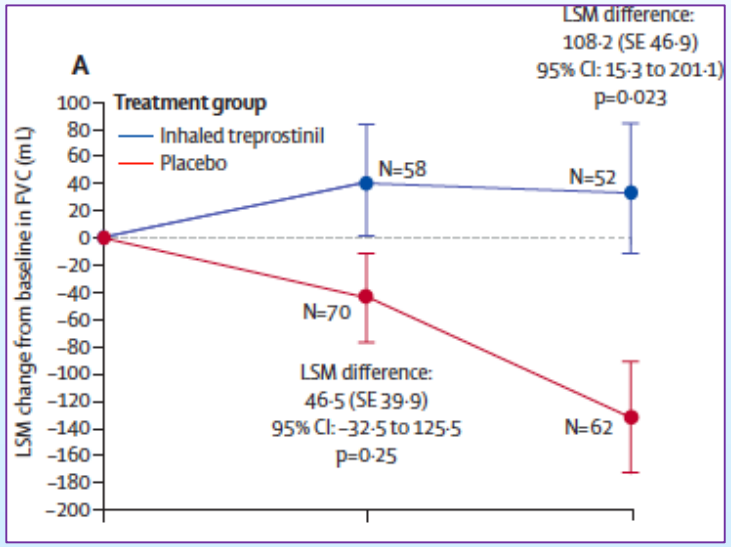
Pulmonary hypertension associated with interstitial lung disease

Treprostinil for PH-ILD patients (INCREASE trial)

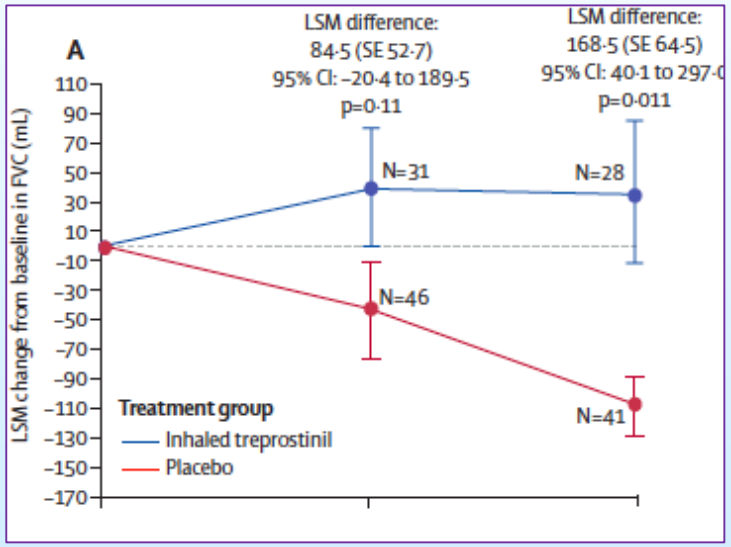
Overall population



Idiopathic interstitial pneumonia



IPF



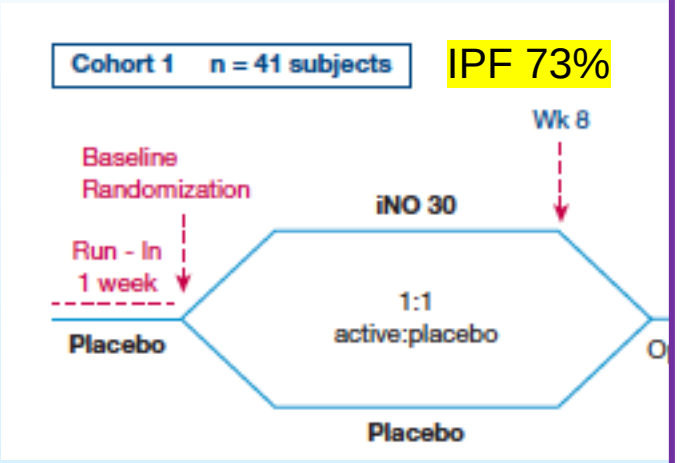
Nathan, Lancet Respir Med 2021

INOpulse

Bellerophon™ THERAPEUTICS

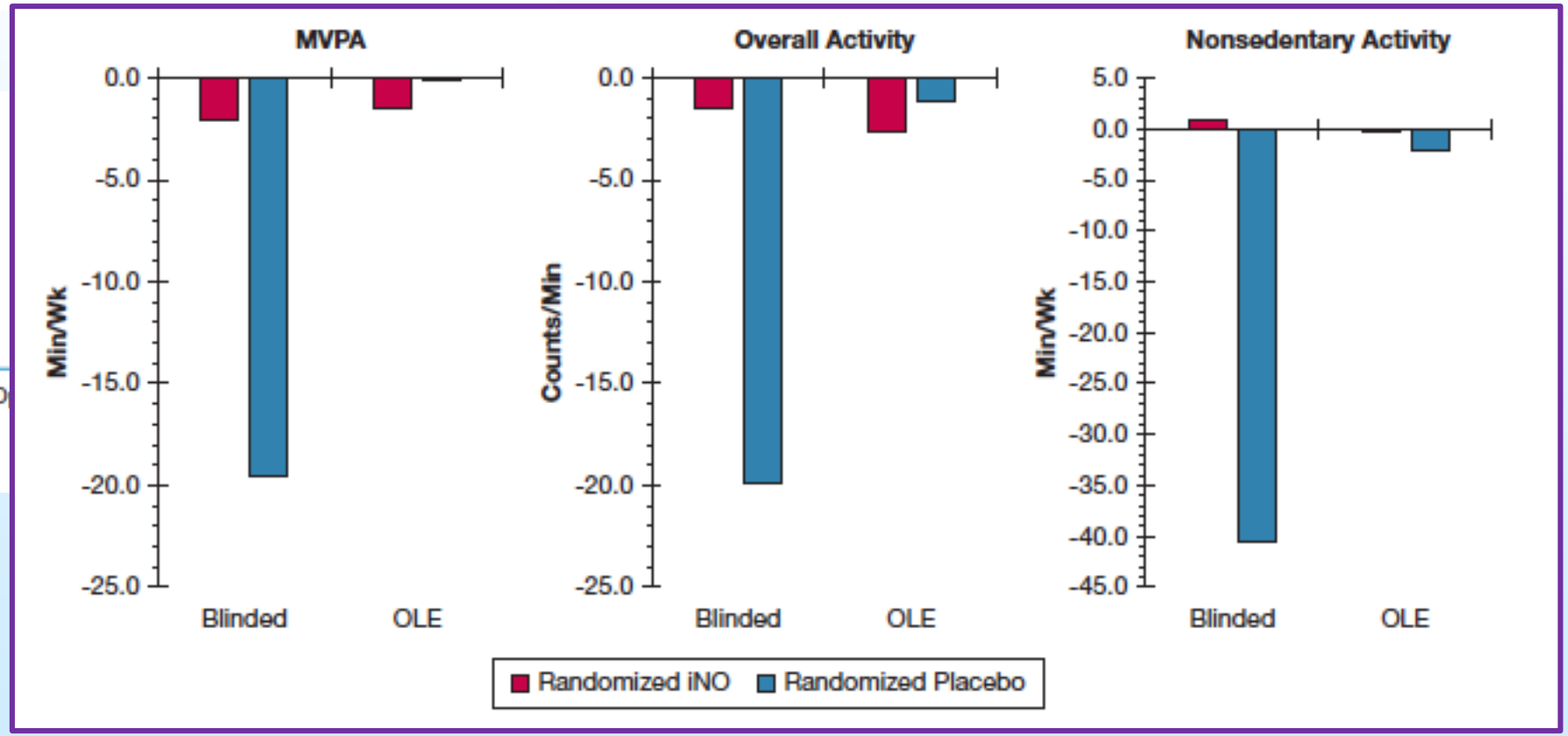
A Randomized, Double-Blind, Placebo-Controlled Study of Pulsed, Inhaled Nitric Oxide in Subjects at Risk of Pulmonary Hypertension Associated With Pulmonary Fibrosis

CHEST

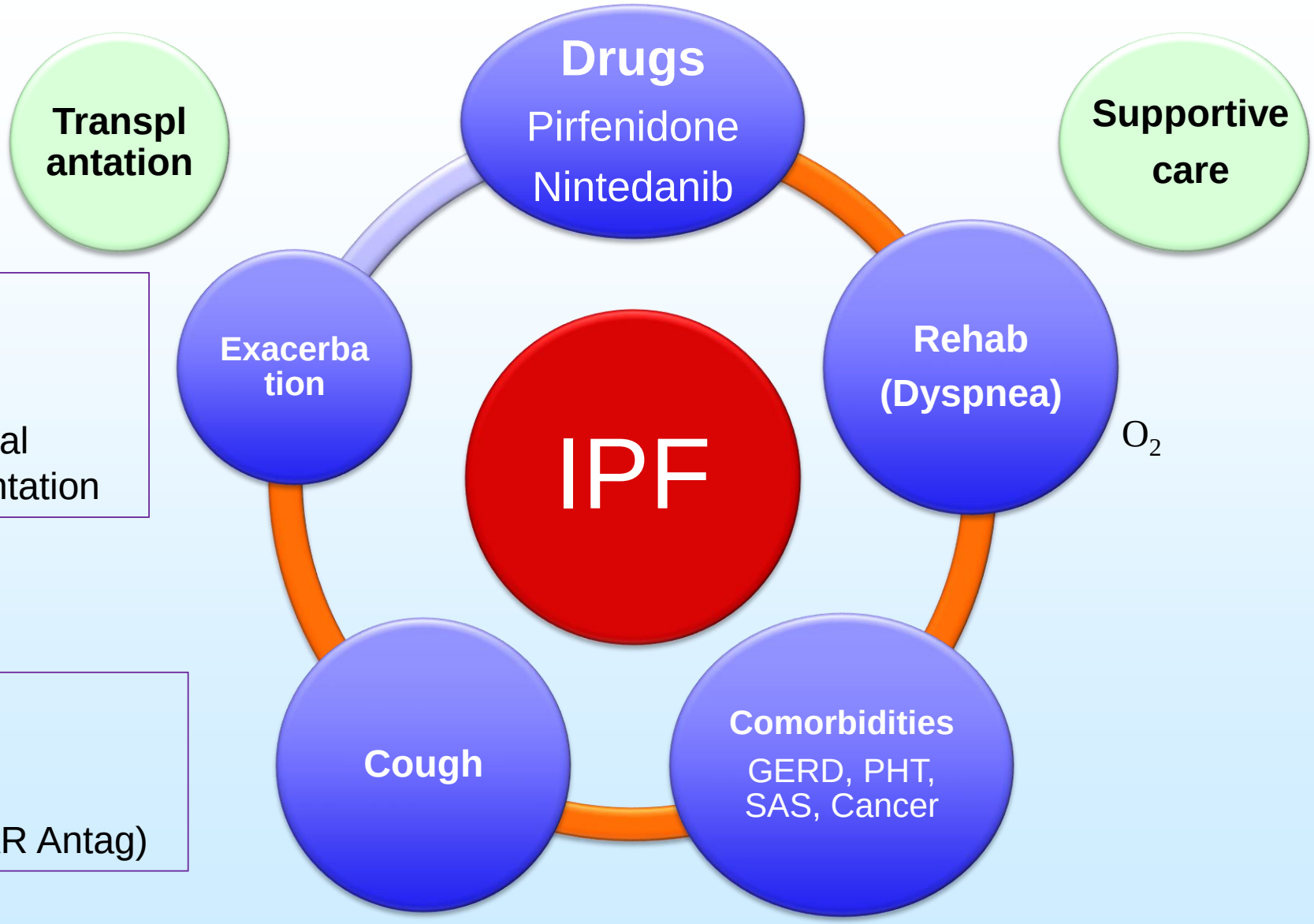


IPF 73%

- FVC 56%
- DLCO 30%
- LTOT : 24 months, 22 hrs/day, 3.6 l/min (means)



Nathan, Chest 2020;158:637-645



O_2

Cell therapy
Lung Stem cells IV
Lung stem cells IT
Autologous Bronchial Basal Cell transplantation

Cough
Nabulphine SR
Morphine sulfate
Ifenprodil (NMDAR Antag)

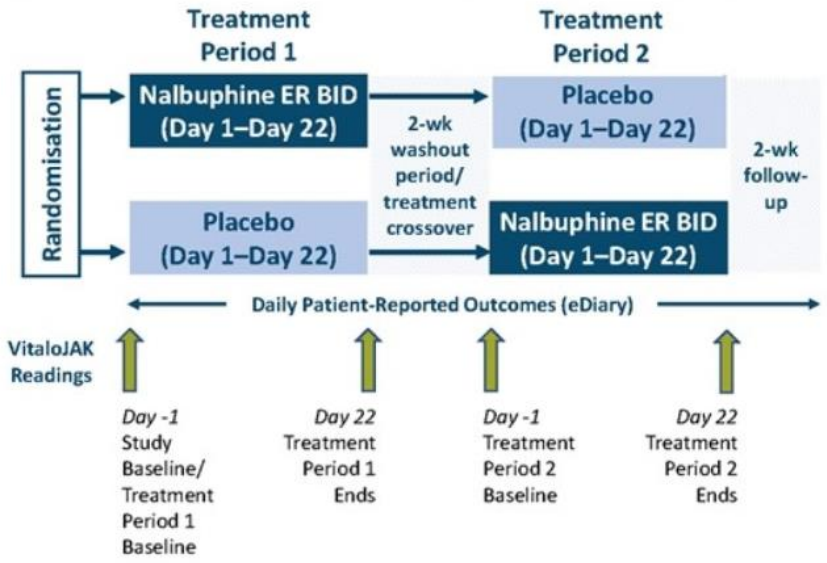
An interim analysis of a phase 2 trial evaluating oral nalbuphine extended release for treating chronic cough in idiopathic pulmonary fibrosis

Toby M. Maher, MD[1]; William Forbes, PharmD[2]; Enoch Bortey, PhD[2]; Thomas Sciascia, MD[2]

[1]Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; [2]Trevi Therapeutics, New Haven, CT, USA

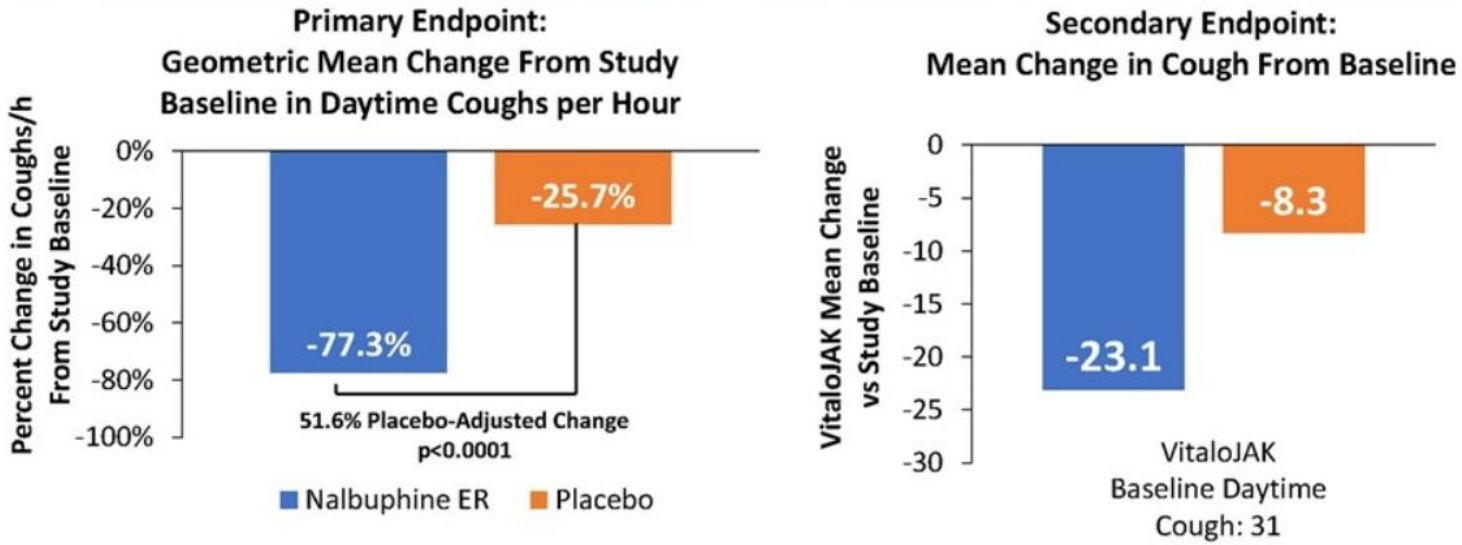
- Dual-acting opioid agonists/antagonists are hypothesized to reduce chronic cough by pharmacologically acting on the opioid system, potentially at both peripheral and central nervous system levels
- We report an interim analysis of a phase 2 trial with nalbuphine extended release (ER) tablets, a ƙ-receptor agonist and μ-receptor antagonist

- 52% placebo-adjusted reduction in the geometric mean percent change from study baseline for nalbuphine ER in daytime cough frequency to day 22 of treatment (p<0.0001)
- 42% of nalbuphine ER-treated subjects achieving a ≥75% reduction from baseline in daytime cough frequency compared to 0% of placebo-treated subjects



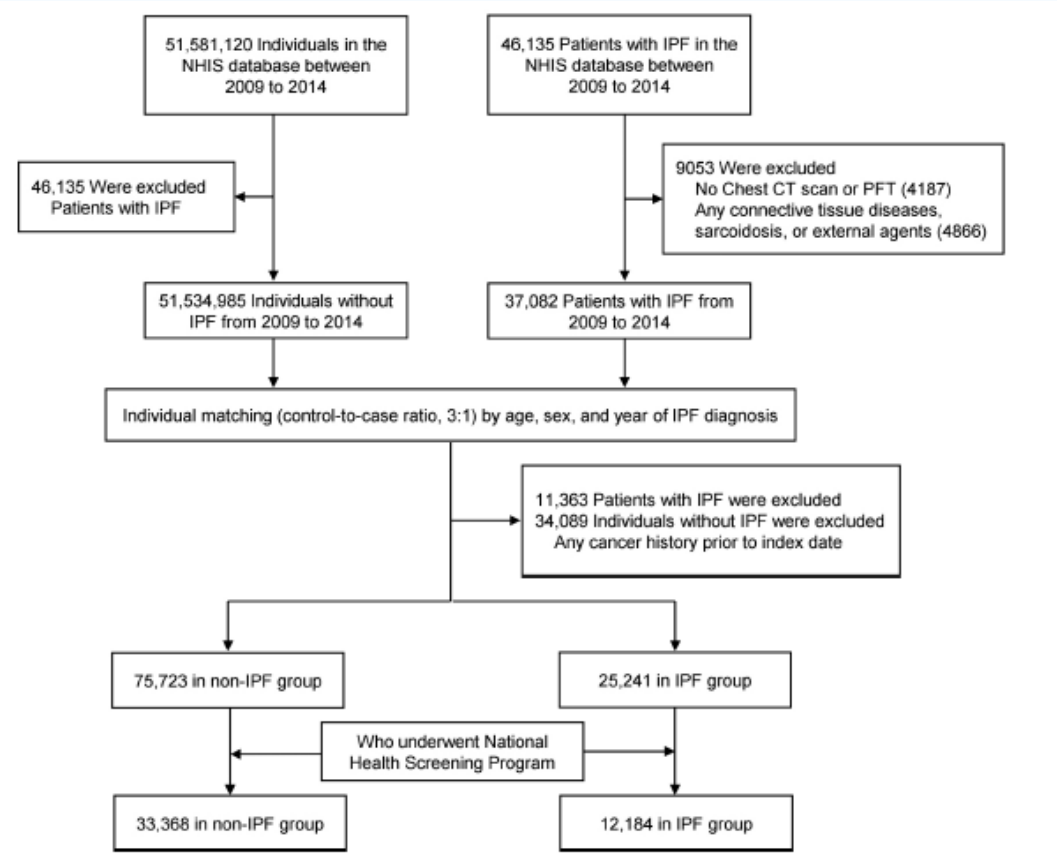
BID, twice daily; ER, extended release; wk, week.

Figure 3. Primary and Secondary Endpoints (N=26)

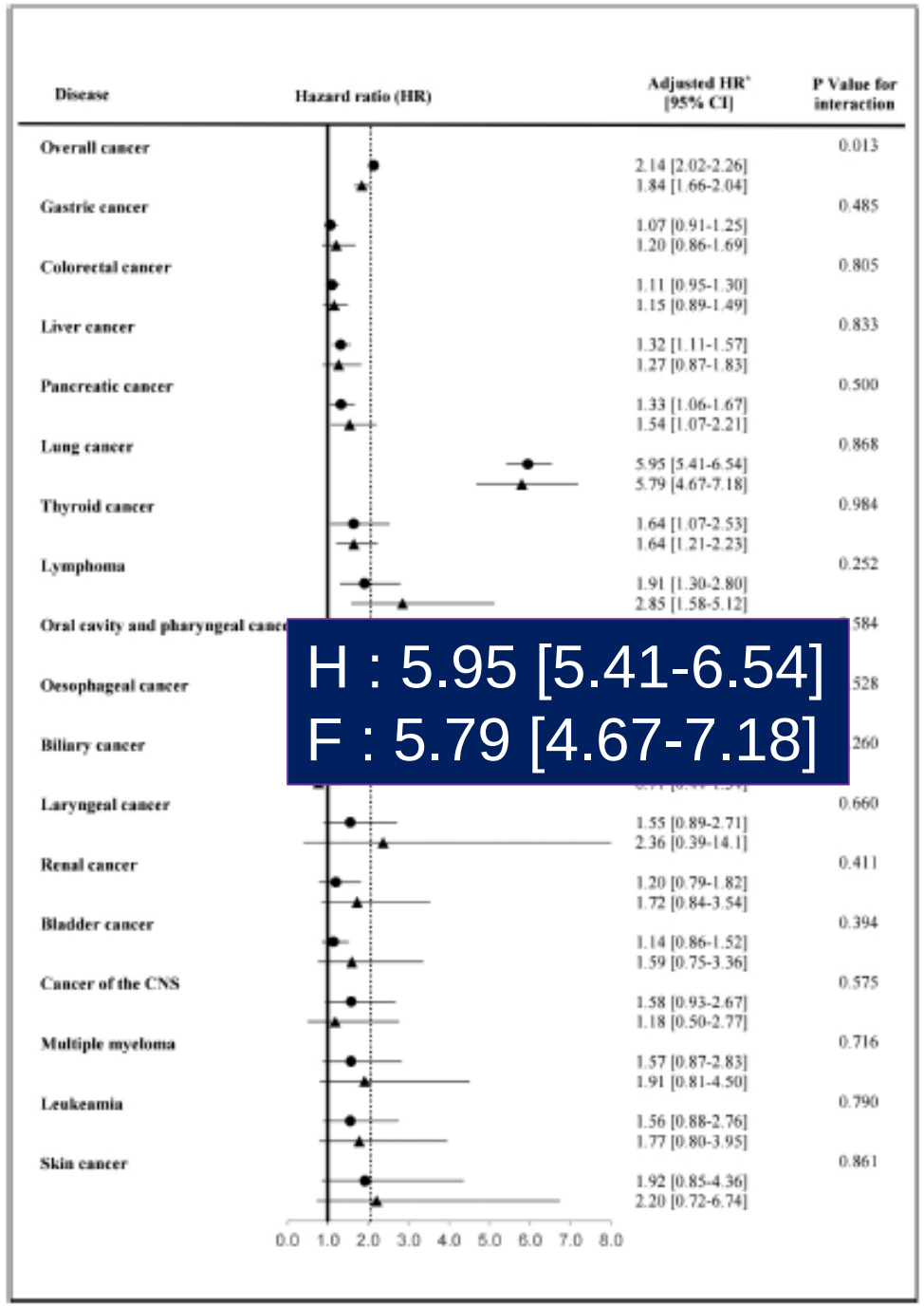


ER, extended release.
Primary endpoint calculated as geometric mean percent change in daytime cough frequency from study baseline.

Lung Cancer risk is increased in IPF



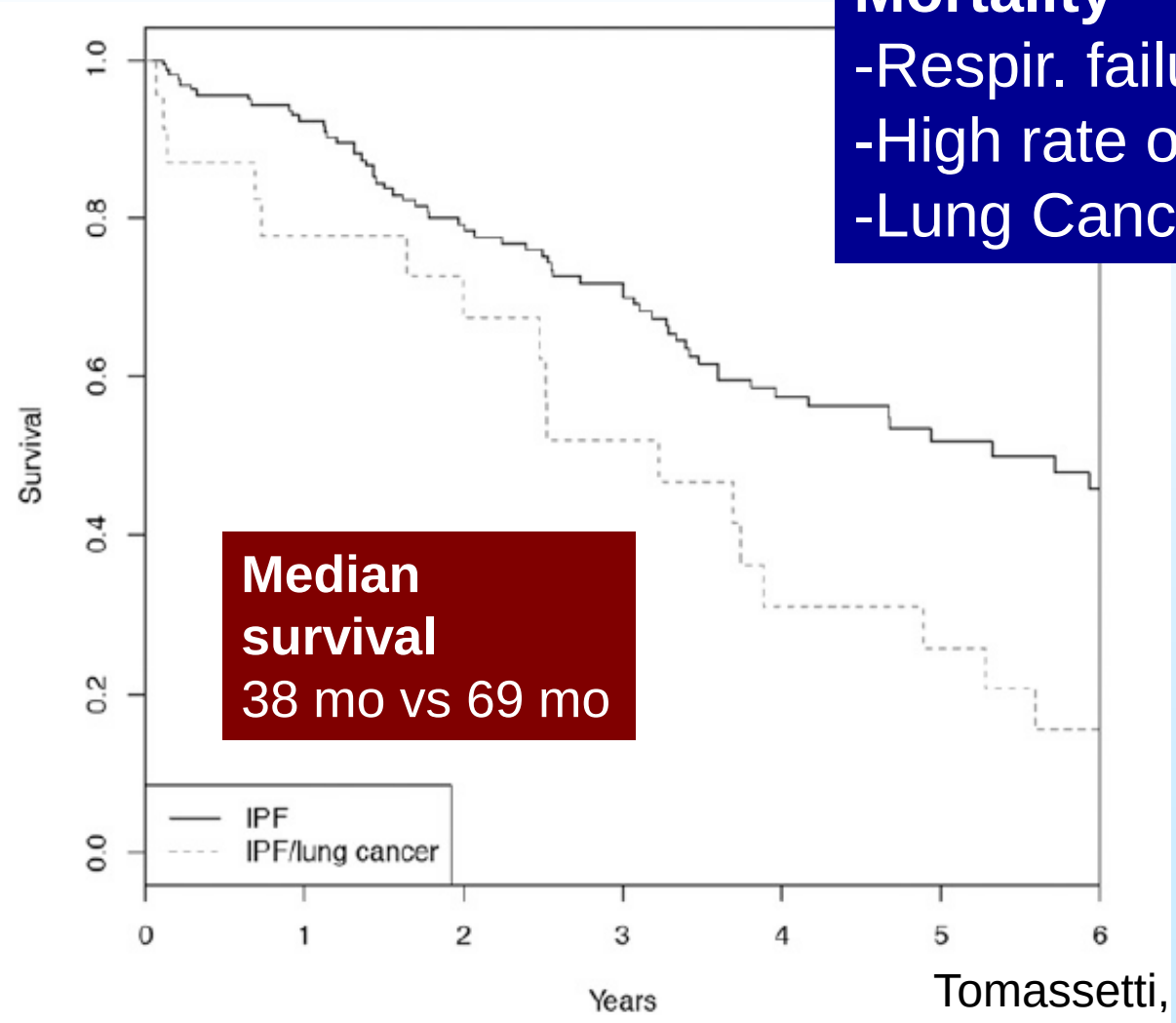
Lee, Respirology 2021



Influence on survival

- 158 IPF
- 23 IPF/LC

Mortality
-Respir. failure (47%)
-High rate of Tt toxicity (17%)
-Lung Cancer Progression



Median survival
38 mo vs 69 mo

Tomassetti, Chest 2015

Cancer du poumon au cours des pneumopathies interstitielles diffuses (CAPID)

Médecins coordonnateurs :

Dr Boris Duchemann (**boris.duchemann@aphp.fr**)
Pr Jacques Cadranel (**jacques.cadranel@aphp.fr**)