PNEUMOLOGIA 2018 Milano, 14 – 16 giugno 2018

INTERSTIZIOPATIE E MALATTIE RARE

Il futuro dell'IPF: dove stiamo andando

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European Reference Network
for rare or low prevalence complex diseases
Network Respiratory Diseases (ERN-LUNG)

Disclosure

- Dr Carlo Albera has served as investigator in clinical trials, consultant, speaker, steering committee or scientific advisory board member for
  - Bayer
  - Boehringer Ingelheim
  - FibroGen
  - Gilead
  - Grifols
  - GSK
  - Roche
  - MSD
  - Sanofi Aventis

Diagnosis: guidelines and neighborhood.

Discovering the next generation of IPF therapy: challenges in IPF Trial design.

Can biomarkers shorten clinical trials in IPF?

Improving existing endpoints.

New IPF models, new drugs.

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American Thoracic Society Documents

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

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY (ATS), THE EUROPEAN RESPIRATORY SOCIETY (ERS), THE JAPANESE RESPIRATORY SOCIETY (JRS), AND THE LATIN AMERICAN THORACIC ASSOCIATION (ALAT) WAS APPROVED BY THE ATS BOARD OF DIRECTORS, NOVEMBER 2010, THE ERS EXECUTIVE COMMITTEE, SEPTEMBER 2010, THE JRS BOARD OF DIRECTORS, DECEMBER 2010, AND THE ALAT EXECUTIVE COMMITTEE, NOVEMBER 2010

THIS STATEMENT HAS BEEN FORMALLY ENDORSED BY THE SOCIETY OF THORACIC RADIOLOGY AND BY THE PULMONARY PATHOLOGY SOCIETY

Am J Respir Crit Care Med Vol 183. pp 788–824, **2011**

American Thoracic Society Documents

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

SUMMARY , CONCLUSIONS

1. IPF is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the ***histopathologic and/or radiologic pattern of UIP.***

2. The diagnosis of IPF requires:

a*. Exclusion of other known causes of interstitial lung disease (ILD) (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity).*

b. *The presence of a UIP pattern on high-resolution computed tomography (HRCT) in patients not subjected to surgical lung biopsy.*

c. *Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy.The major and minor criteria proposed in the 2000 ATS/ ERS Consensus Statement have been eliminated.*

3. The accuracy of the diagnosis of IPF increases with ***multidisciplinary discussion*** between pulmonologists, radiologists, and pathologists experienced in the diagnosis of ILD.

Am J Respir Crit Care Med Vol 183. pp 788–824, 2011

Mutidisciplinary diagnosis
Integration of imaging and pathology

Histopathology pattern # 5

HRCT pattern # 3

	UIP	Probable UIP	Possible UIP	Not classifiable fibrosis	Not UIP
UIP	IPF	IPF	IPF	IPF	Not IPF
Possible UIP	IPF	IPF	Probable IPF	Probable IPF	Not IPF
Not UIP	Possible IPF	Not IPF	Not IPF	Not IPF	Not IPF

Am J Respir Crit Care Med Vol 183. pp 788–824, 2011

Mutidisciplinary diagnosis
Integration of imaging and pathology

Histopathology pattern

HRCT pattern	UIP	Probable UIP	Possible UIP	Not classifiable fibrosis	Not UIP
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Not UIP	Possible IPF	Not IPF	Not IPF	Not IPF	Not IPF

Am J Respir Crit Care Med Vol 183. pp 788–824, 2011

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Histopathology pattern

HRCT pattern	UIP	Probable UIP	Possible UIP	Not classifiable fibrosis	Not UIP
UIP	IPF	IPF	IPF	IPF	Not IPF
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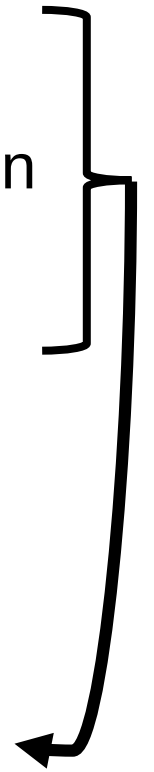
Not UIP	Possible IPF	Not IPF	Not IPF	Not IPF	Not IPF

Am J Respir Crit Care Med Vol 183. pp 788–824, 2011

Mutidisciplinary diagnosis
Integration of pathology and imaging
And …. what else ????

A fundamental part of MDD diagnosis: clinical reasoning

- Age and gender
- Oberved diseae behavoiur
- Careful evaluation of immune disregulation
- BAL data
- Cryobiopsy findings



NOT SPECIFIED IN GUIDELINES

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

This Review provides an updated approach to the diagnosis of idiopathic pulmonary fibrosis (IPF), based on a systematic search of the medical literature and the expert opinion of members of the Fleischner Society. A checklist is provided for the clinical evaluation of patients with suspected usual interstitial pneumonia (UIP). The role of CT is expanded to permit diagnosis of IPF without surgical lung biopsy in select cases when CT shows a probable UIP pattern. Additional investigations, including surgical lung biopsy, should be considered in patients with either clinical or CT findings that are indeterminate for IPF. A multidisciplinary approach is particularly important when deciding to perform additional diagnostic assessments, integrating biopsy results with clinical and CT features, and establishing a working diagnosis of IPF if lung tissue is not available. A working diagnosis of IPF should be reviewed at regular intervals since the diagnosis might change. Criteria are presented to establish confident and working diagnoses of IPF.

Lancet Respir Med 2017

Published Online
November 15, 2017
http://dx.doi.org/10.1016/S2213-2600(17)30433-2

See Online/Comment
http://dx.doi.org/10.1016/S2213-2600(17)30443-5

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

Key messages

• A **confident diagnosis of IPF** (idiopathic pulmonary fibrosis) can be made **in the correct clinical context** when CT imaging shows a pattern of typical or probable UIP

• If the **clinical context is indeterminate for IPF**, or the **CT pattern is not indicative of typical or probable UIP**, biopsy should be considered to confirm the presence of a UIP histological pattern, and a confident diagnosis of IPF could then be made on the basis of a multidisciplinary evaluation

• **If diagnostic tissue is not available**, a working diagnosis of IPF could be made after a careful multidisciplinary evaluation

• **All patients with an IPF diagnosis**, particularly those with a working diagnosis, should have this diagnosis reviewed at regular intervals

Lynch DA et al Lancet Lancet Respir Med 2017 Published Online

Summary and conclusions

- IPF diagnostic workout is going to radically change with the acceptance of the **“working diagnosis”**
- Working diagnosis is mainly based on **clinical reasoning** when guidelines criteria are not met
- **MDT is accepted as a standard for diagnosis of IPF**
- The most relevant change will be in patients with ***“possible UIP” on HRCT***

Key issues:

- *The effective role of cryobiopsy*
- *The “possible UIP” vs biopsy findings and outcome*
- *Biomarkers*

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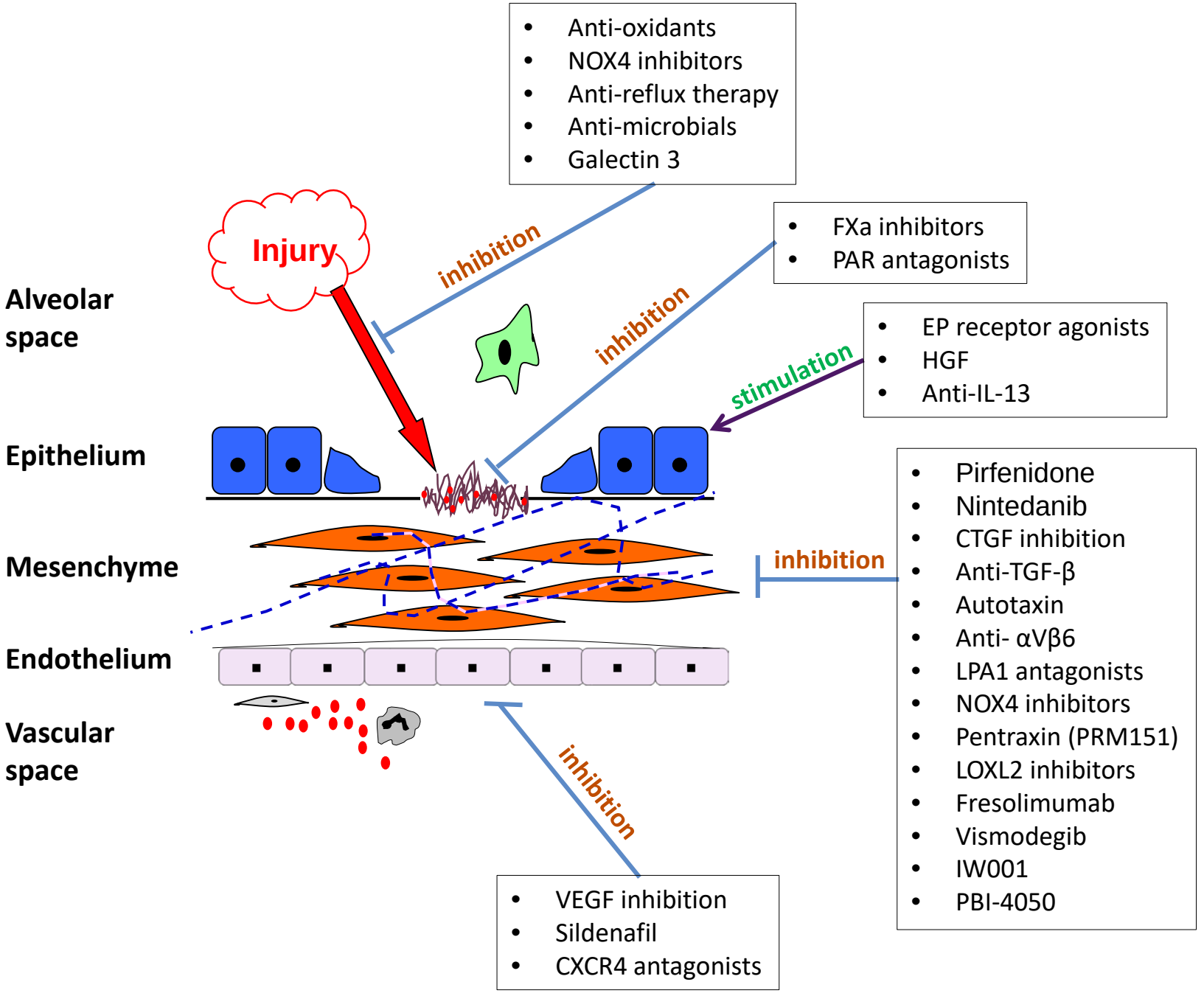
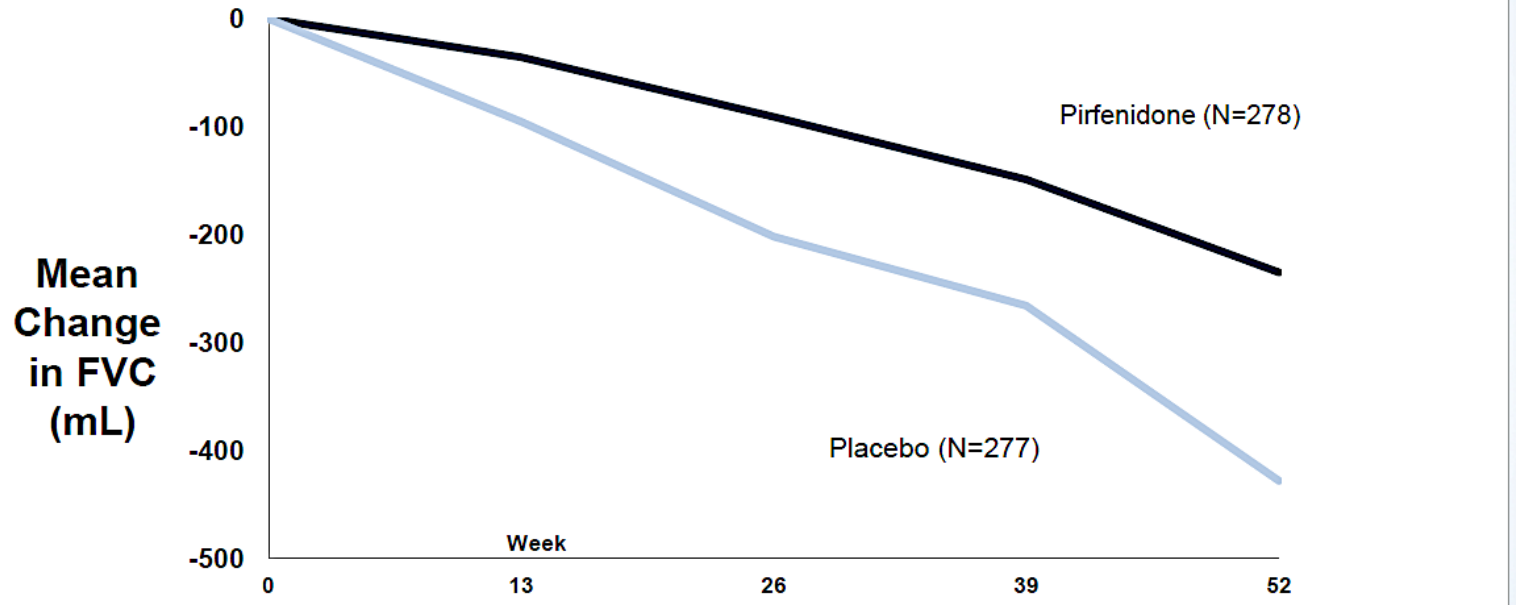


Maher TM Clinics Chest Med 2012

The typical IPF clinical trial



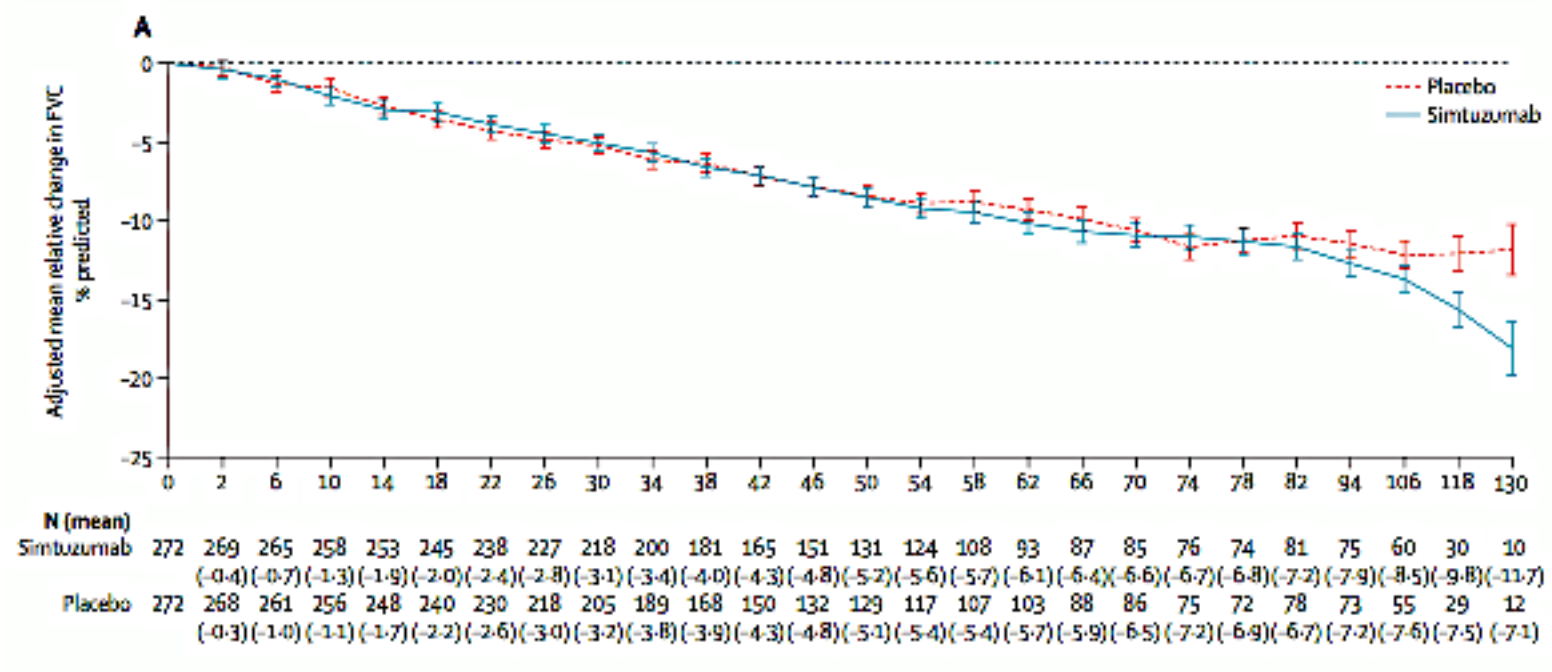
Absolute difference	59.6 mL	111.0 mL	116.7 mL	192.8 mL
Relative difference	62.5%	54.9%	43.9%	45.1%
Rank ANCOVA P-value	<0.000001	<0.000001	0.000002	<0.000001

King et al NEJM 2014

The danger of going straight to late phase studies

Efficacy of simtuzumab versus placebo in patients with idiopathic pulmonary fibrosis: a randomised, double-blind, controlled, phase 2 trial

Ganesh Raghu, Kevin K Brown, Harold R Collard, Vincent Cottin, Kevin F Gibson, Robert J Kaner, David J Lederer, Fernando J Martinez, Paul W Noble, Jin Woo Song, Athol U Wells, Timothy P M Whelan, Wim Wuyts, Emmanuel Moreau, Scott D Patterson, Victoria Smith, Selina Bayly, Jason W Chien, Qi Gong, Jenny J Zhang, Thomas G O'Riordan



Raghu et al Lancet Resp Med 2017

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What are biomarkers?

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to therapeutic interventions

How can we use biomarkers ?

- Risk assessment
- Diagnostic
- Assess disease severity
- Predict progression (prognostic)
- Predict response to treatment (stratification)
- Measure treatment response (theragnostic)

Actually no validated good biomarkers available for IPF

Diagnosis: guidelines and neighborhood.

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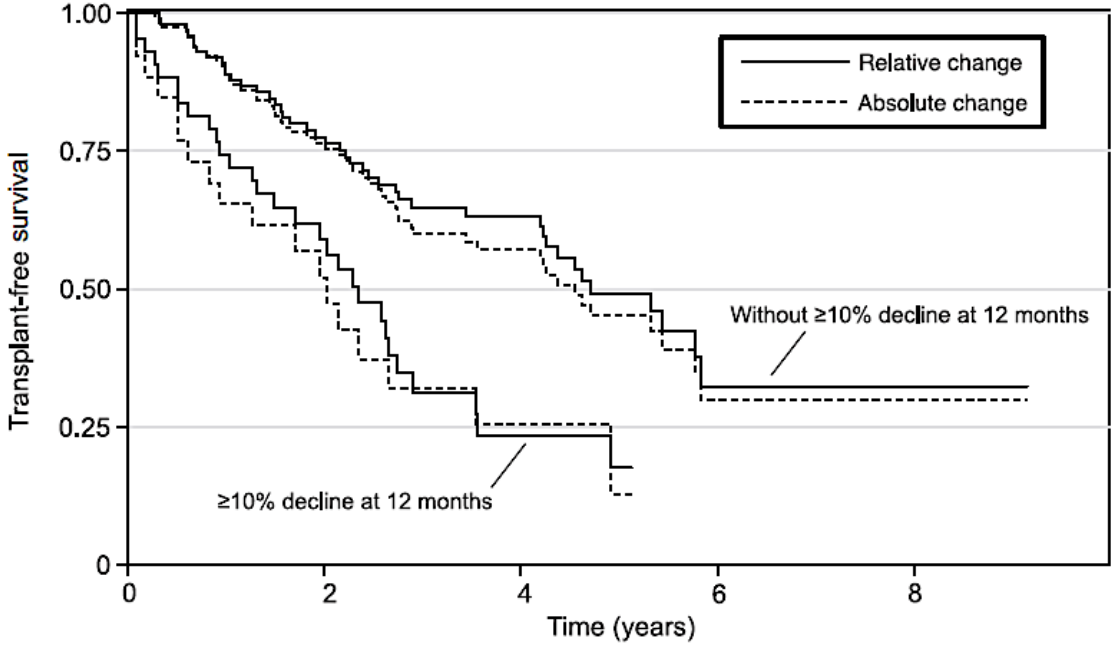
Measuring disease progression in IPF

Relative versus absolute change in forced vital capacity in idiopathic pulmonary fibrosis

Luca Richeldi,[1,2] Christopher J Ryerson,[3] Joyce S Lee,[2] Paul J Wolters,[2] Laura L Koth,[2] Brett Ley,[2] Brett M Elicker,[4] Kirk D Jones,[5] Talmadge E King Jr,[2] Jay H Ryu,[6] Harold R Collard[2]



Thorax 2012;**67**:407–411. doi:10.1136/thoraxjnl-2011-201184

ORIGINAL ARTICLE

Daily Home Spirometry: An Effective Tool for Detecting Progression in Idiopathic Pulmonary Fibrosis

Anne-Marie Russell[1,2], Huzaifa Adamali[3], Philip L. Molyneaux[1,2], Pauline T. Lukey[4], Richard P. Marshall[4], Elisabetta A. Renzoni[1,2], Athol U. Wells[1,2], and Toby M. Maher[1,2]

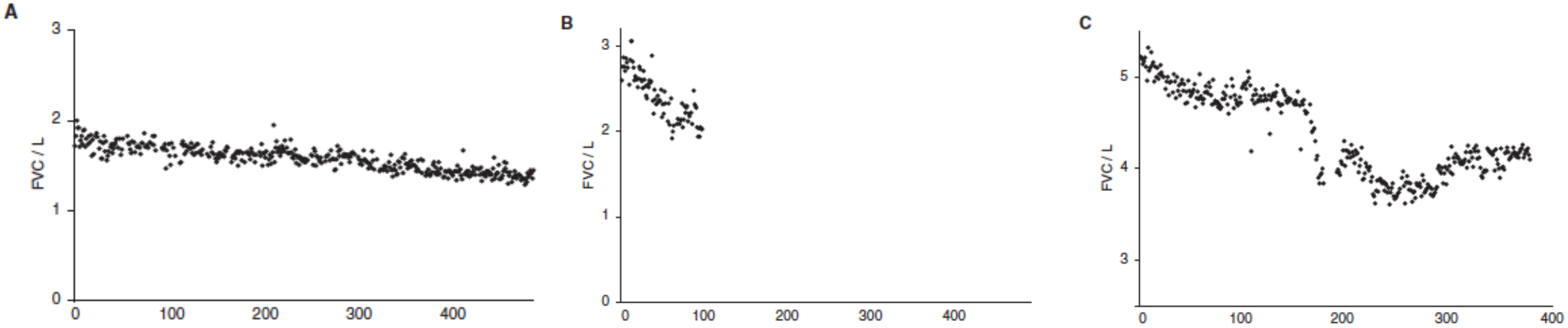
[1]National Institute for Health Research Biomedical Research Unit, Royal Brompton Hospital, London, United Kingdom; [2]Fibrosis Research Group, National Heart and Lung Institute, Imperial College London, London, United Kingdom; [3]Bristol Interstitial Lung Disease Service, North Bristol Lung Centre, Southmead Hospital, Westbury-on-Trym, United Kingdom; and [4]Fibrosis and Lung Injury DPU, GlaxoSmithKline R&D, Stevenage, Herts, United Kingdom

ORCID ID: 0000-0001-7192-9149 (T.M.M.).

Item	None	Mild	Moderate	Severe
1. My breath does not go in all the way				
2. My breathing requires more work				
3. I feel short of breath				
4. I have difficulty catching my breath				
5. I cannot get enough air				
6. My breathing is uncomfortable				
7. My breathing is exhausting				
8. My breathing makes me feel depressed				
9. My breathing makes me feel miserable				
10. My breathing is distressing				
11. My breathing makes me agitated				
12. My breathing is irritating				

D-12 Questionnaire, Yorke et al Thorax 2009

Daily FVC measurements: Individual examples of disease behavior



inexorably progressive disease

rapidly progressive disease

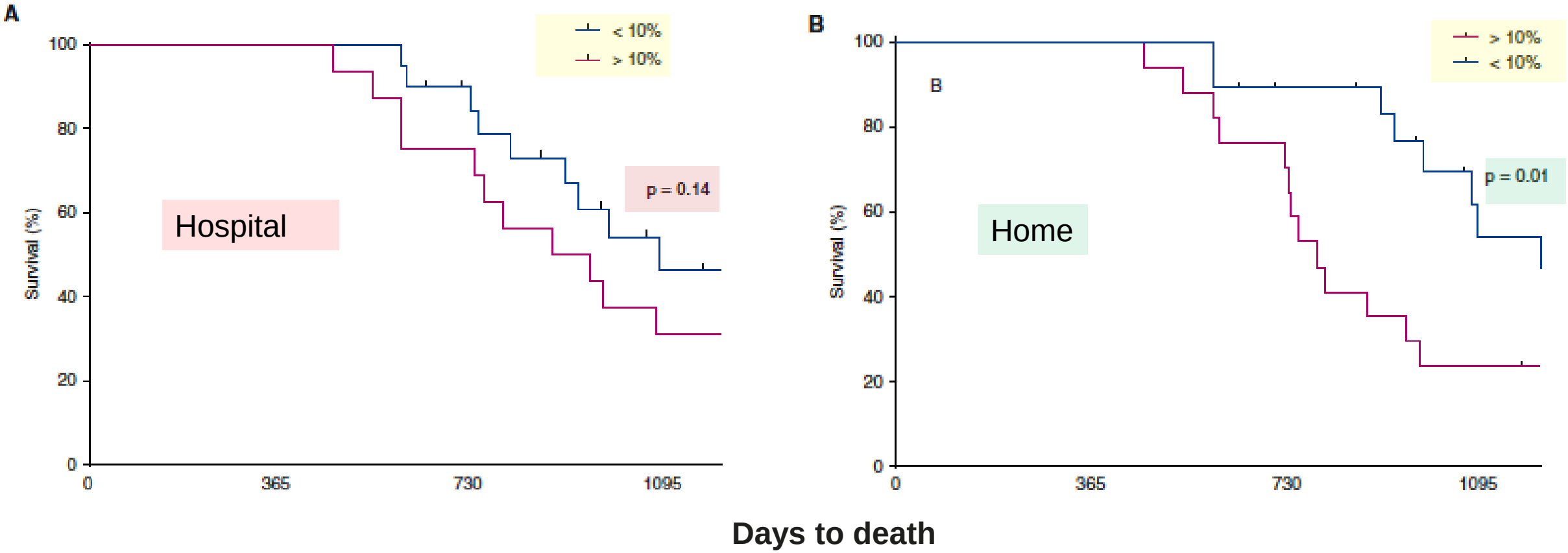
acute exacerbation

Each point represents a single FVC measurement.

The subject in A died of respiratory failure at 725 days.
The subject in B died at Day 202,
The subject in C, despite losing 20% of FVC in a 3-week period,survived until Day 952.

Am J Respir Crit Care Med 194, 989–997, 2016

Twelve-month change in home- but not hospital-based spirometry is strongly predictive of subsequent outcome.



Subjects were dichotomized into those with progressive (>10% change in hospital-based FVC between baseline and 12 months or >10% annual rate of change in home-based FVC) and relatively stable (>10% change in hospital-based FVC between baseline and 12 months or >0% annual rate of change in home-based spirometry) disease

Am J Respir Crit Care Med 194, 989–997, 2016

Home spirometry as a trial primary endpoint

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

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Home > Search Results > Study Record Detail

Trial record **1 of 1** for: NCT 03099187

Previous Study | Return to List | Next Study

A Study of Pirfenidone in Patients With Unclassifiable Progressive Fibrosing Interstitial Lung Disease

This study is currently recruiting participants.

See Contacts and Locations

Verified August 2017 by Hoffmann-La Roche

Sponsor:
Hoffmann-La Roche

Information provided by (Responsible Party):
Hoffmann-La Roche

ClinicalTrials.gov Identifier:
NCT03099187

First received: March 31, 2017
Last updated: August 3, 2017
Last verified: August 2017
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

The purpose of this study is to evaluate the efficacy and safety of pirfenidone in participants with fibrosing interstitial lung disease (ILD) who cannot be classified with moderate or high confidence into any other category of fibrosing ILD by multidisciplinary team (MDT) review ("unclassifiable" ILD).

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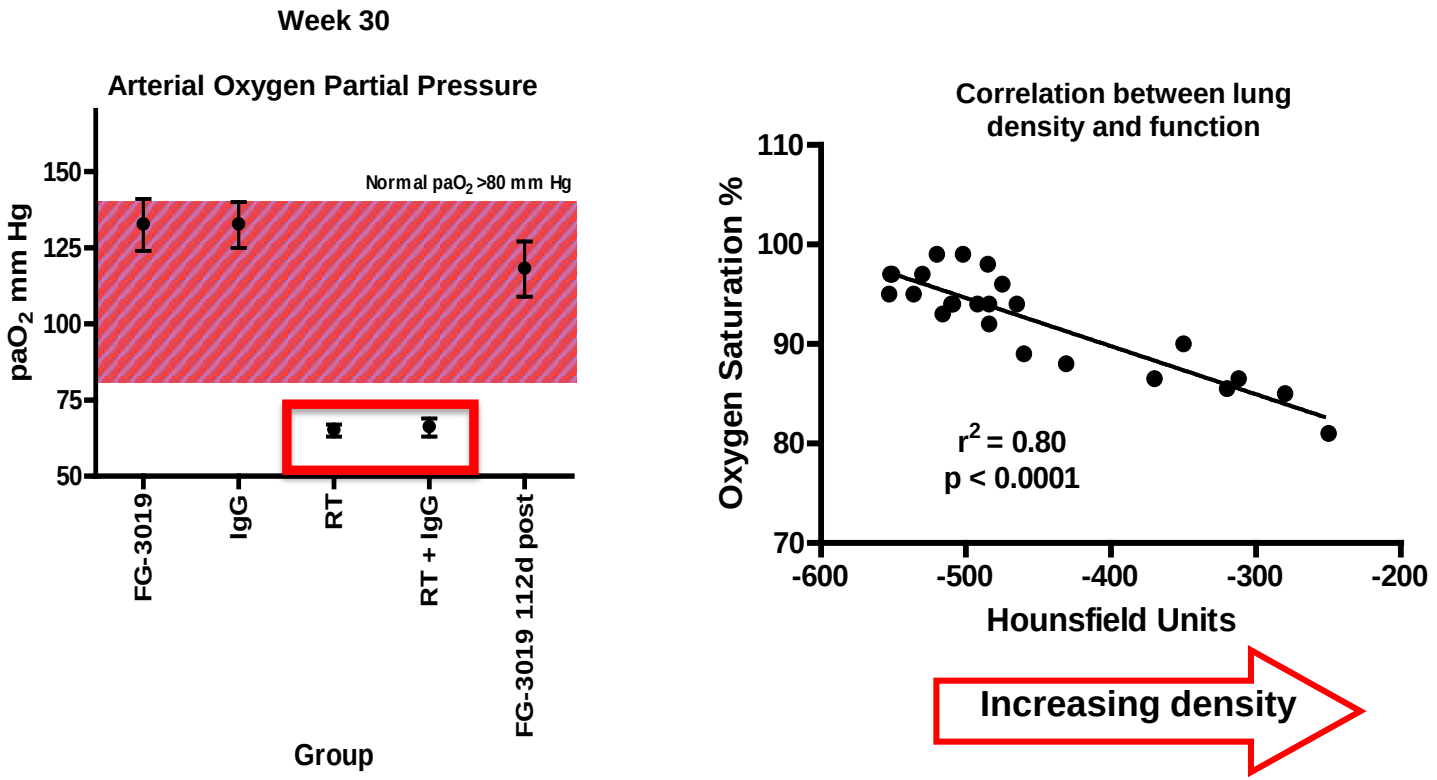
Pamrevlumab (FG-3019)
A Human MAb Targeting CTGF

Radiation-Induced Lung Fibrosis May Be More Predictive of Human Response

	Bleomycin Acute Lung Injury Model	Radiation-Induced Lung Injury Model
Proven to **NOT** be predictive of clinical success	✓	✗
Physiologically relevant	✗	✓
Progressive	✗	✓
Separation between acute and chronic responses enable therapeutic treatment	✗	✓

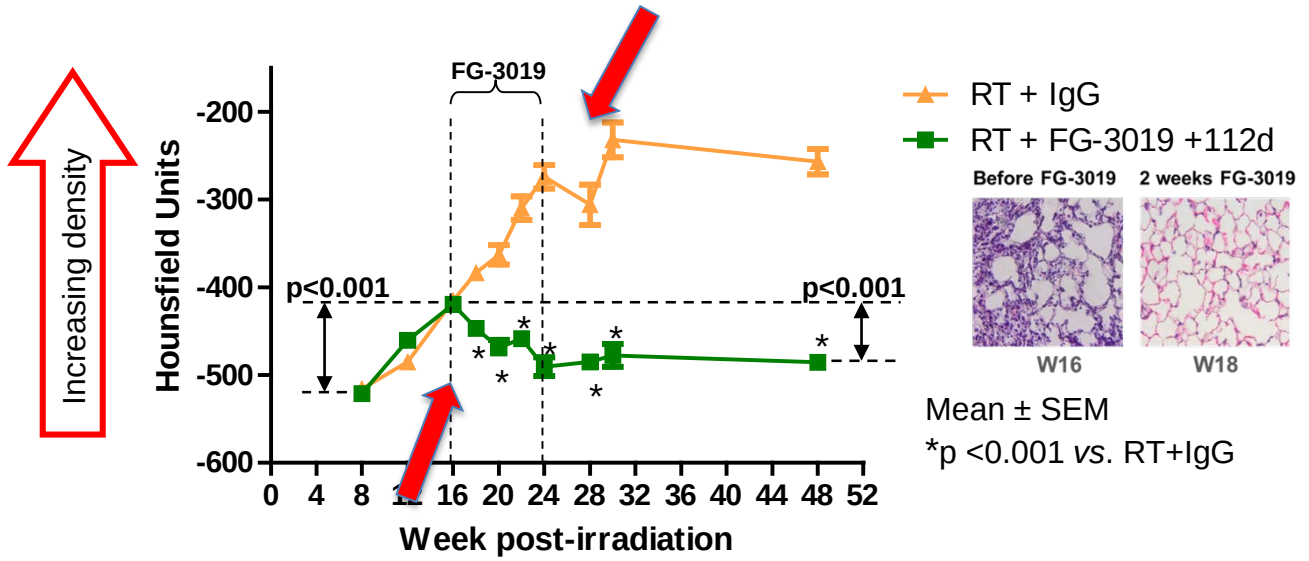
Therapeutic Pamrevlumab Restored Normal Lung Function



Bickelhaupt et al. (2017) JNCI 109(8):djw339

Therapeutic Pamrevlumab Reversed Progression of Lung Density Increases

- Administration of pamrevlumab beginning 16 weeks after irradiation clearly altered progression of lung density
  - Irradiated, placebo group (orange triangles) have progressive increases in lung density
  - **Lung density of therapeutic treatment group (green squares) increased until administration of FG-3019 began at 16 weeks, and then began to decrease**



Bickelhaupt et al. (2017) JNCI 109(8):djw339

The PRAISE Study

A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Pamrevlumab (FG-3019) in Patients with Idiopathic Pulmonary Fibrosis

FIBROGEN STUDY#: FGCL-3019-067
ClinicalTrials.gov ID#: NCT01890265

NEJMED, Submitted

All-Cause Mortality Rate

PRAISE vs GAP[1]

		Full Study (N=103)		Pamrevlumab Arm (N=50)		Placebo Arm (N=53)	
Stage	**1-year Risk**	**Number Subjects**	**Expected Number of Deaths**	**Number Subjects**	**Expected Number of Deaths**	**Number Subjects**	**Expected Number of Deaths**
Stage I	5.6%	47	2.6	23	1.3	24	1.3
Stage II	16.2%	51	8.3	24	3.9	27	4.4
Stage III	39.2%	5	2.0	3	1.2	2	0.8
Overall		103	**12.9**	50	**6.4**	53	**6.5**
Actual Deaths in PRAISE			**9**		**3**		**6**
Actual vs Expected Deaths				**47.0 %**		**92.3%**	

Deaths by Stages: Pamrevlumab arm: 2 Stage II; 1 Stage III. / Placebo arm: 2 Stage I; 3 Stage II; 1 Stage III

Relative Reduction vs Placebo = 51%

(Relative Reduction vs Placebo for Pooled Phase 2; Study 049+PRAISE = 65%)

1. Ley B. et al. Ann Intern Med. 2012.
Source: t-14-1-4-2-blgap-saf / l-16-2-4-4-blgap-rand

NEJMED, Submitted

The „dream“ goal of IPF treatment

To go back to a normal lung

The „whish“ goal of IPF treatment

To stop the the disease progression

The „real“goal of Ipf treatment today

To reduce the progression of fibrosis

The hopefully „dream coming true “ of IPF treatment

To go back to a normal lung

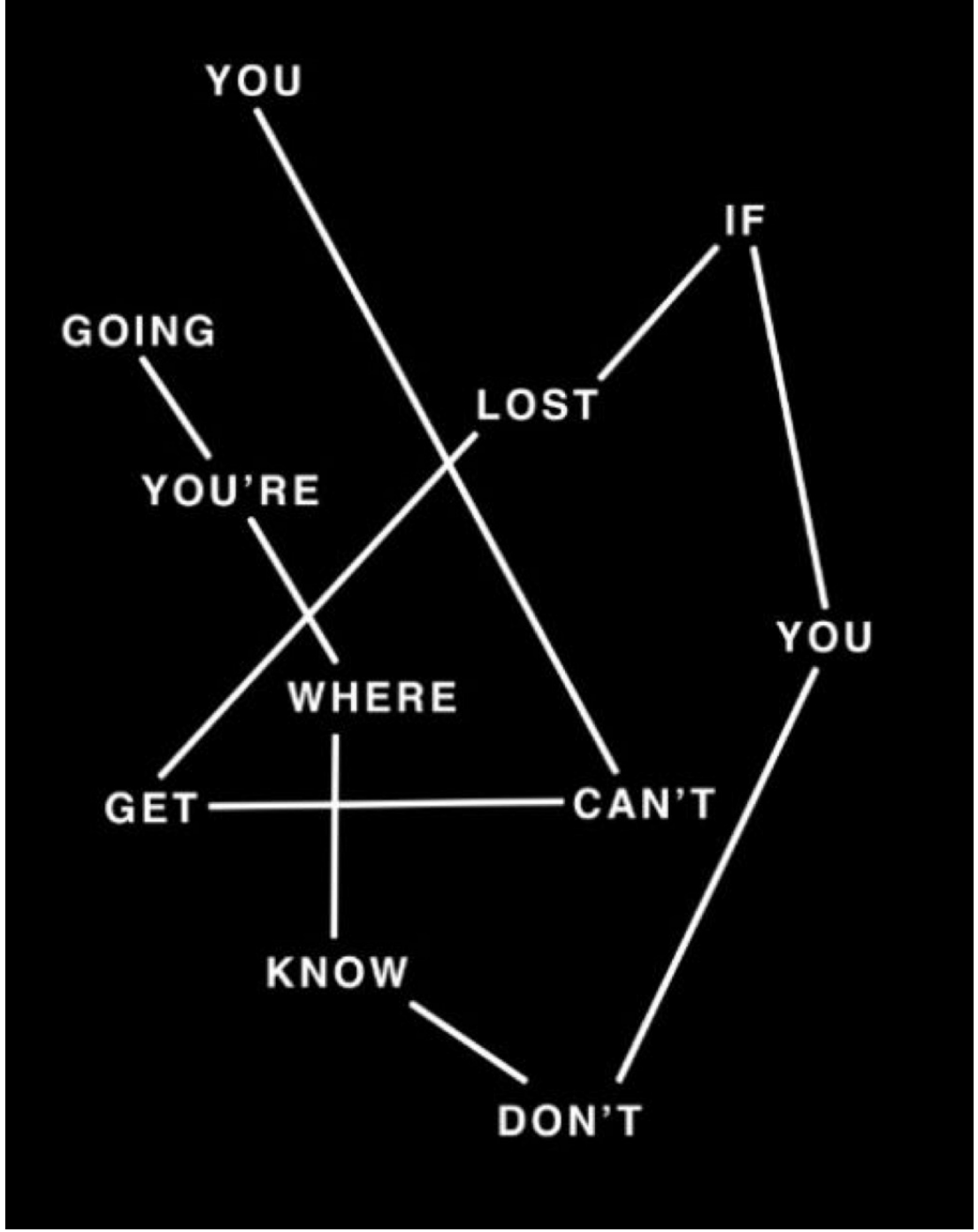
The „whish“ goal of IPF treatment

To stop the the disease progression

The „real“goal of Ipf treatment today

To reduce the progression of fibrosis

Il futuro dell’IPF: dove stiamo andando



KNOWLEDGE

⬇

PATIENT

YOU

CAN’T

GET

LOST

IF

YOU

DON’T

KNOW

WHERE

YOU’RE

GOING