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PILOT™
Pulmonary Fibrosis Identification:
Lessons for Optimizing Treatment

An Industry-Organized Symposium at the ATS 2015 International Conference

TRANSLATING IPF CLINICAL TRIALS TO REAL LIFE PATIENTS

A CASE-BASED SYMPOSIUM

www.PILOTforIPF.org

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Disclosure of Relevant Financial Relationships

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Activity Faculty Disclosures

Kevin K. Brown, MD, has received non industry grant support from NIH-NHLBI and industry related grant support from, Genentech and Amgen. He has served as a consultant for: Altitude Pharma, Astra Zeneca, Biogen, Genentech, Boehringer Ingelheim, Centocor, GeNO, Genoa, Gilead, FibroGen, ImmuneWorx, Mesoblast, Medimmune, Promedior, Prometrix, and Veracyte. Dr. Brown would also like to disclose; Product/procedure/technique that is considered research and is NOT yet approved for any purpose: There are no approved therapies for HP. All discussion is off-label.

Harold R. Collard, MD, has received grant/research support from Boehringer Ingelheim. He has served as a consultant for: AstraZeneca/MedImmune, Bayer, Biogen, FibroGen, Genentech, Genoa, Gilead, GSK, Mesoblast, Moerae Matrix, PatientsLikeMe, Pfizer, Promedior, Prometic, and Pulmatrix.

Marilyn K. Glassberg, MD, has received grants/research support from IPFnet, the Lester & Sue Smith Foundation, and the NIH. She has served as a consultant for: Boehringer Ingelheim, Genentech/Roche, and Mesoblast. She has also received honoraria from Boehringer Ingelheim and InterMune.

Luca Richeldi, MD, PhD, has received grant/research support from Boehringer Ingelheim and InterMune. He has served as a consultant for: Biogen-Idec, Boehringer Ingelheim, ImmuneWorks, InterMune, Medimmune, Roche, Sanofi-Aventis, Shionogi, and Takeda.

Activity Staff Disclosures

The planners, reviewers, editors, staff, or other members at The France Foundation who control content have no relevant financial relationships to disclose.

Agenda

6:45–7:00 PM	Welcome and Introductions ***Luca Richeldi, MD, PhD***
7:00–7:30 PM	Newly Available Therapies: Discussing the Difficult Questions ***Luca Richeldi, MD, PhD***
7:30–8:00 PM	Selecting the Right Treatment: Which Patients and When to Start Treatment? ***Harold R. Collard, MD***
8:00–8:30 PM	Switching Drugs: When, and is There a Time for Change in Therapy? ***Kevin K. Brown, MD***
8:30–9:00 PM	Managing Side Effects and Dosing: Need for Individualized Strategies? ***Marilyn K. Glassberg, MD***
9:00–9:30 PM	Q&A

Learning Objectives

Upon completion of this course, participants should be able to:

- Describe the evidence using triple therapy of NAC to treat IPF.
- Discuss the efficacy, safety, and clinical application of new treatment options in patients with IPF.

Newly Available Therapies: Discussing the Difficult Questions

LUCA RICHELDI, MD, PhD

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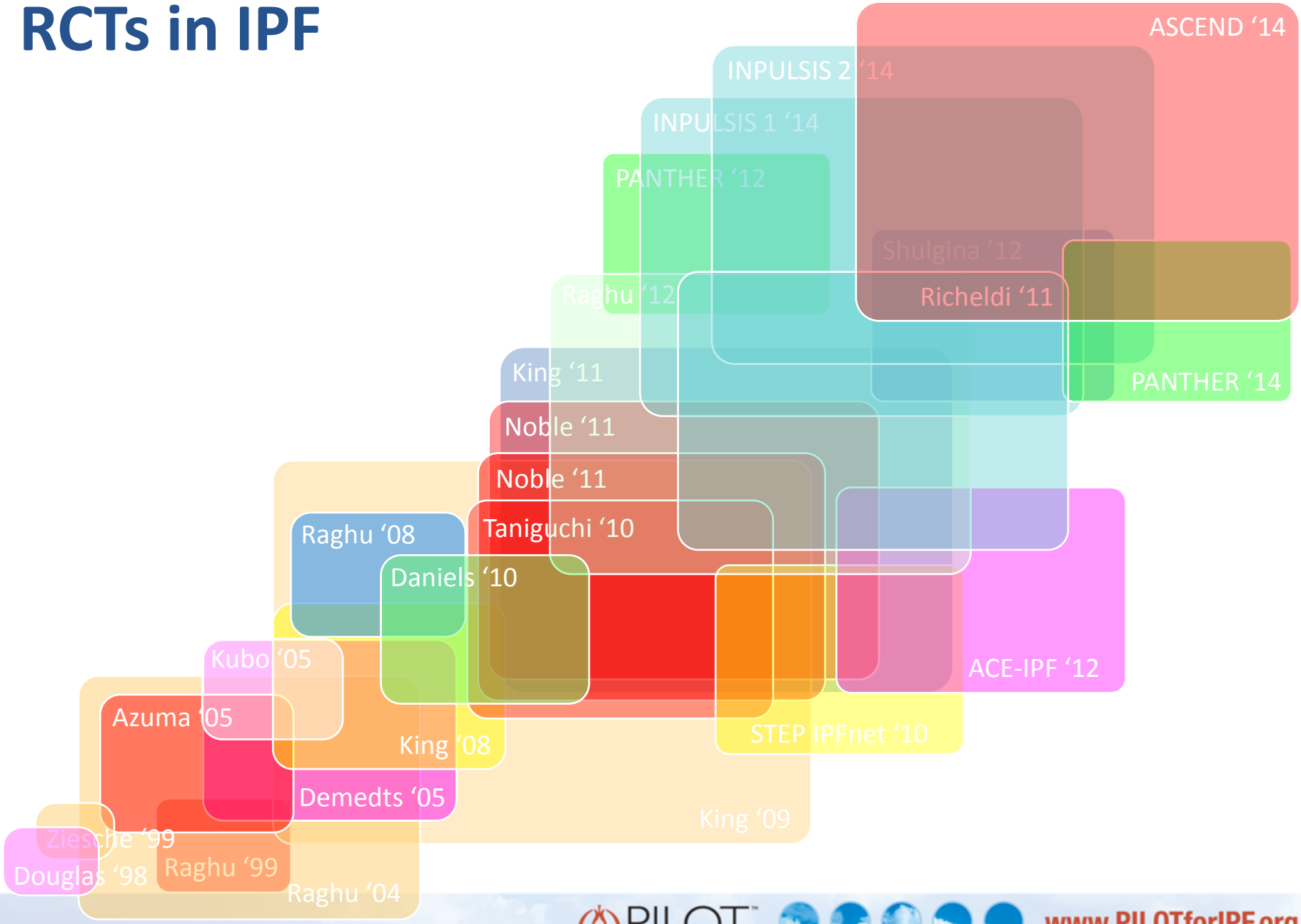
RCTs in IPF


ASCEND ‘14
INPULSIS 2 ‘14
INPULSIS 1 ‘14
PANTHER ‘12
Shulgina ‘12
Raghu ‘12
Richeldi ‘11
PANTHER ‘14
King ‘11
Noble ‘11
Noble ‘11
Raghu ‘08
Taniguchi ‘10
Daniels ‘10
ACE-IPF ‘12
Kubo ‘05
Azuma ‘05
King ‘08
STEP IPFnet ‘10
Demedts ‘05
King ‘09
Ziesche ‘99
Douglas ‘98
Raghu ‘99
Raghu ‘04

American Thoracic Society

Idiopathic Pulmonary Fibrosis: Diagnosis and Treatment

International Consensus Statement

THIS JOINT STATEMENT OF THE AMERICAN THORACIC SOCIETY (ATS), AND THE EUROPEAN RESPIRATORY SOCIETY (ERS) WAS ADOPTED BY THE ATS BOARD OF DIRECTORS, JULY 1999 AND BY THE ERS EXECUTIVE COMMITTEE, OCTOBER 1999

The authors thank Drs. Thomas Colby, David Hansell, Masanori Kitaichi, and William Travis for their critical review of the manuscript.

This statement was prepared by an ad-hoc committee of the Assembly on Clinical Problems. Members of the committee are:

TALMADGE E. KING, JR., M.D., *Chair*
ULRICH COSTABEL, M.D.
JEAN-FRANÇOIS CORDIER, M.D.
GUILLERMO A. DOPICO, M.D.
ROLAND M. DU BOIS, M.D.
DAVID LYNCH, M.B.
JOSEPH P. LYNCH, III, M.D.
JEFFREY MYERS, M.D.
RALPH PANOS, M.D.
GANESH RAGHU, M.D.
DAVID SCHWARTZ, M.D.
CECILIA M. SMITH, D.O.

AJRCCM. 2000;161:646-664.

Until adequate studies are conducted that define the best treatment for patients with IPF, this committee suggests the following *combined therapy* (corticosteroid and either azathioprine or cyclophosphamide) for those patients who have been given adequate information regarding the merits and pitfalls of treatment and who possess features consistent with a more likely favorable outcome (*see above*):

- *Corticosteroid* therapy (prednisone or equivalent) at a dose of 0.5 mg/kg (lean body weight [LBW]) per day orally for 4 wk, 0.25 mg/kg (LBW) per day for 8 wk, and then tapered to 0.125 mg/kg (ideal body weight [IBW]) daily or 0.25 mg/kg (LBW) every other day as initial therapy for IPF. (Lean body weight is the ideal weight expected for a patient of this age, sex, and height)
- *Azathioprine* at 2–3 mg/kg lean body weight (LBW) per day to a maximum dose of 150 mg/d orally. Dosing should begin at 25–50 mg/d and increase gradually, by 25-mg increments, every 7 to 14 d until the maximum dose is reached

or

- *Cyclophosphamide* at 2 mg/kg LBW per day to a maximum dose of 150 mg/d orally. Dosing should begin at 25–50 mg/d and increase gradually, by 25-mg increments, every 7 to 14 d until the maximum dose is reached

AJRCCM. 2000;161:646-664.

Prednisone, Azathioprine and NAC

PANTHER ‘12

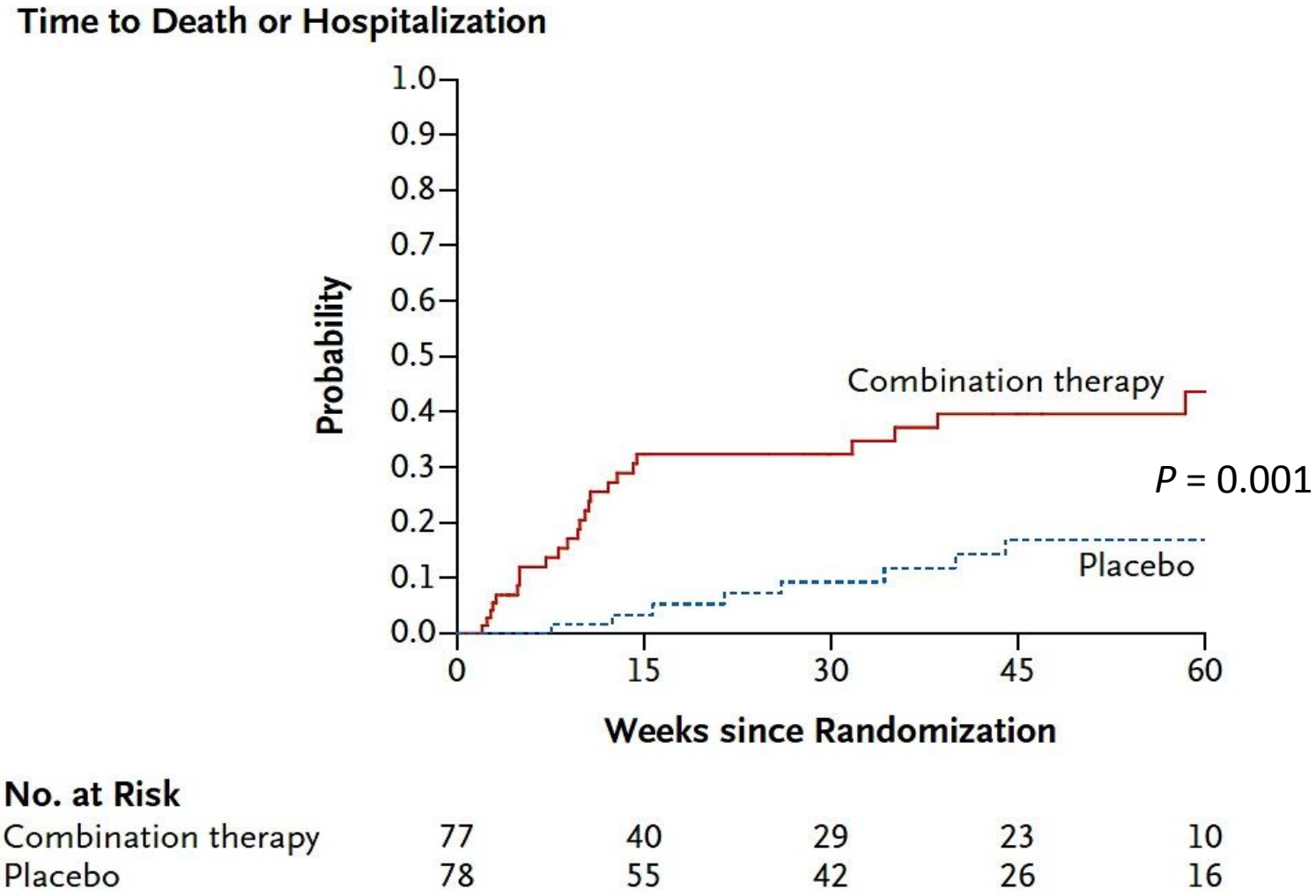
ORIGINAL ARTICLE

Prednisone, Azathioprine, and N-Acetylcysteine for Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network*

NEJM. 2012;366:1968-1977.

Prednisone, Azathioprine, and N-Acetylcysteine for IPF



NAC

PANTHER ‘14

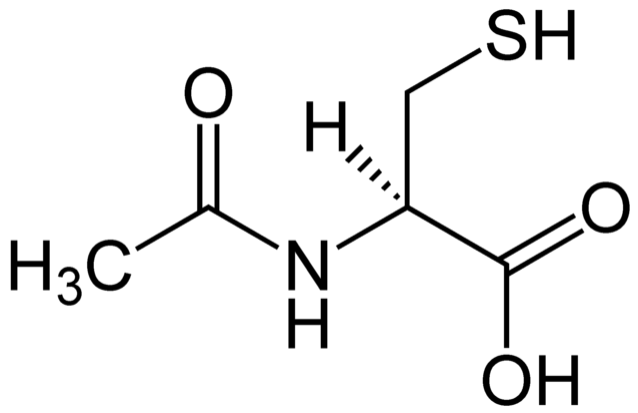
Demedts ‘05

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Randomized Trial of Acetylcysteine in Idiopathic Pulmonary Fibrosis

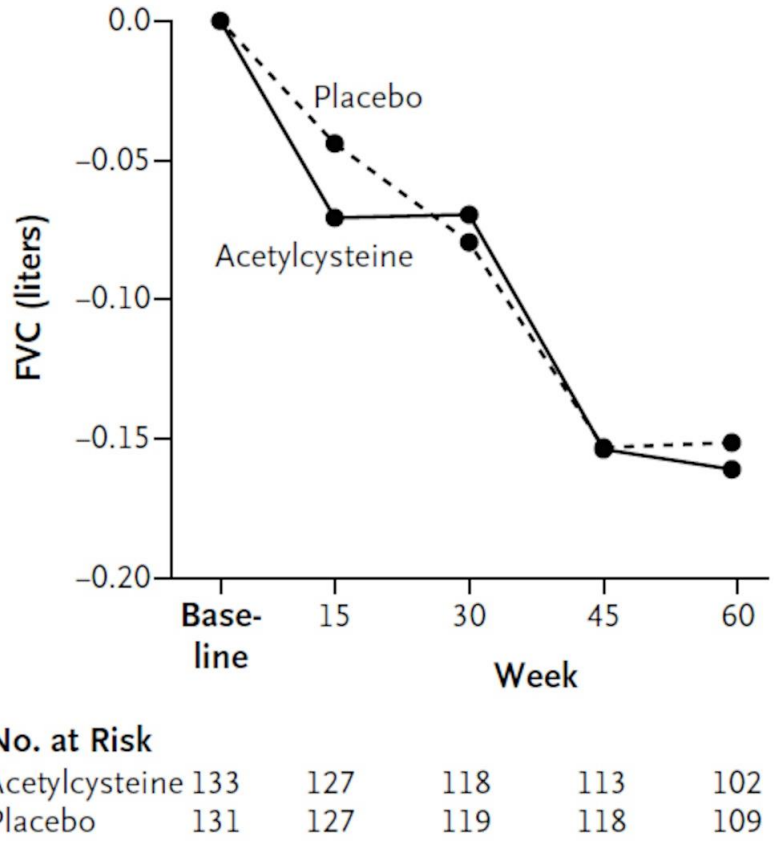
The Idiopathic Pulmonary Fibrosis Clinical Research Network*



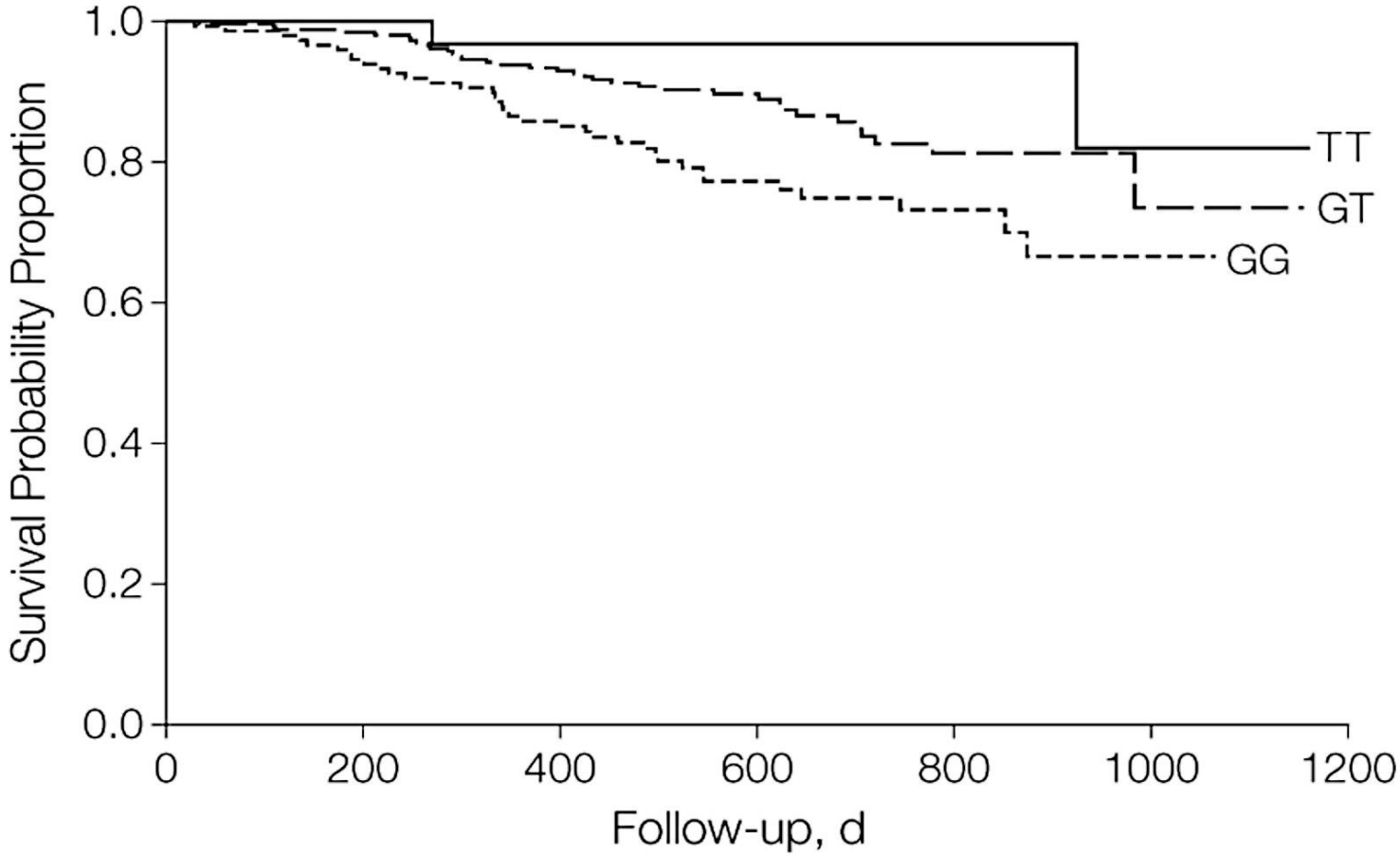
NEJM. 2014;370:2093-2101.

Primary Endpoints: FVC

	NAC	Placebo	*P*-value
FVC (liters)	-0.18 (-0.23, -0.12)	-0.19 (-0.24, -0.13)	0.77

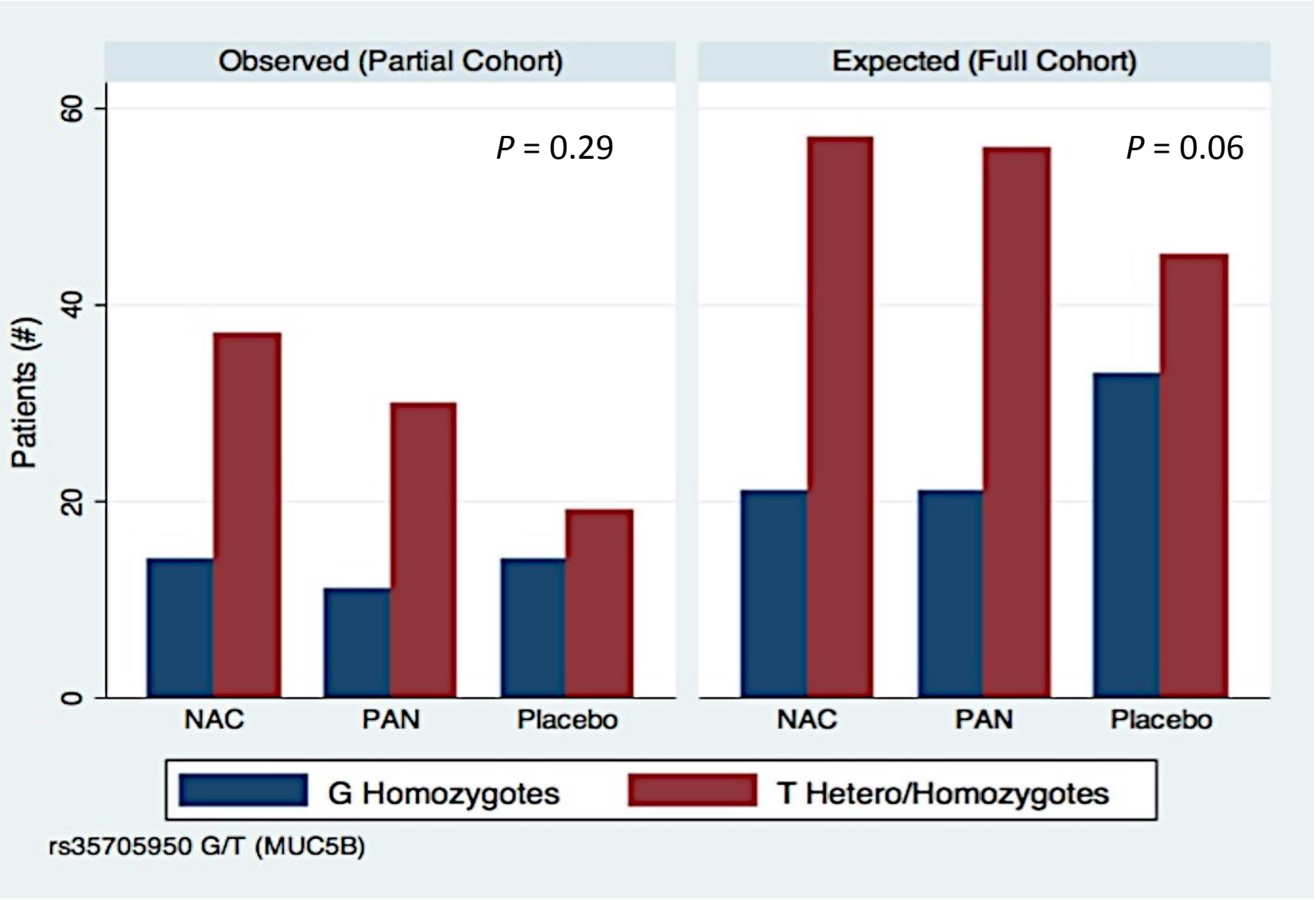


Kaplan-Meier Survival Curves by Muc5b Genotypes



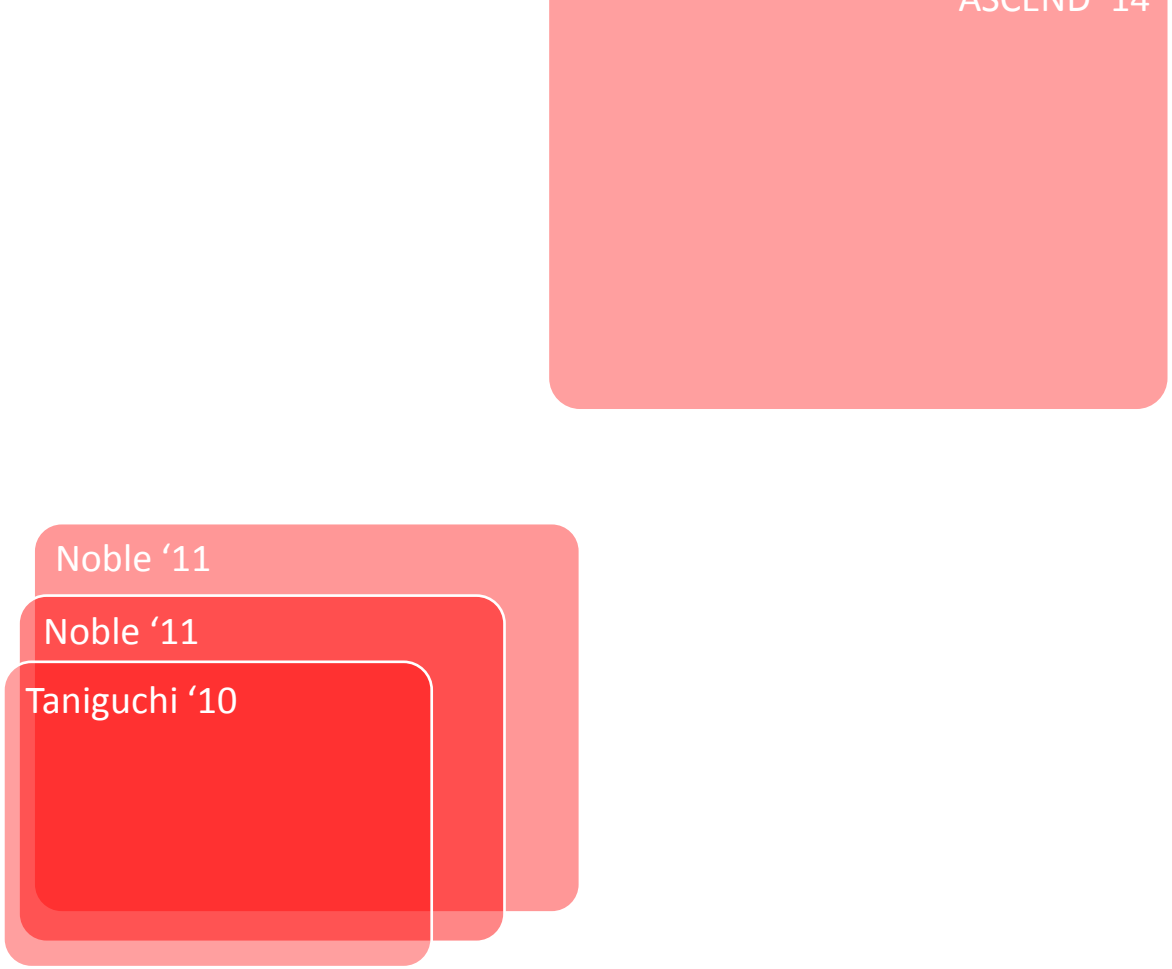
No. at risk						
TT	31	26	21	11	3	0
GT	255	224	122	55	8	0
GG	140	115	67	36	5	0

Genetic Heterogeneity



Courtesy Fernando Martinez (ATS Conference 2015)

Pirfenidone

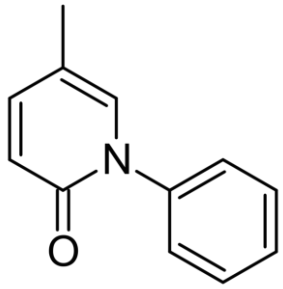


The NEW ENGLAND JOURNAL of MEDICINE

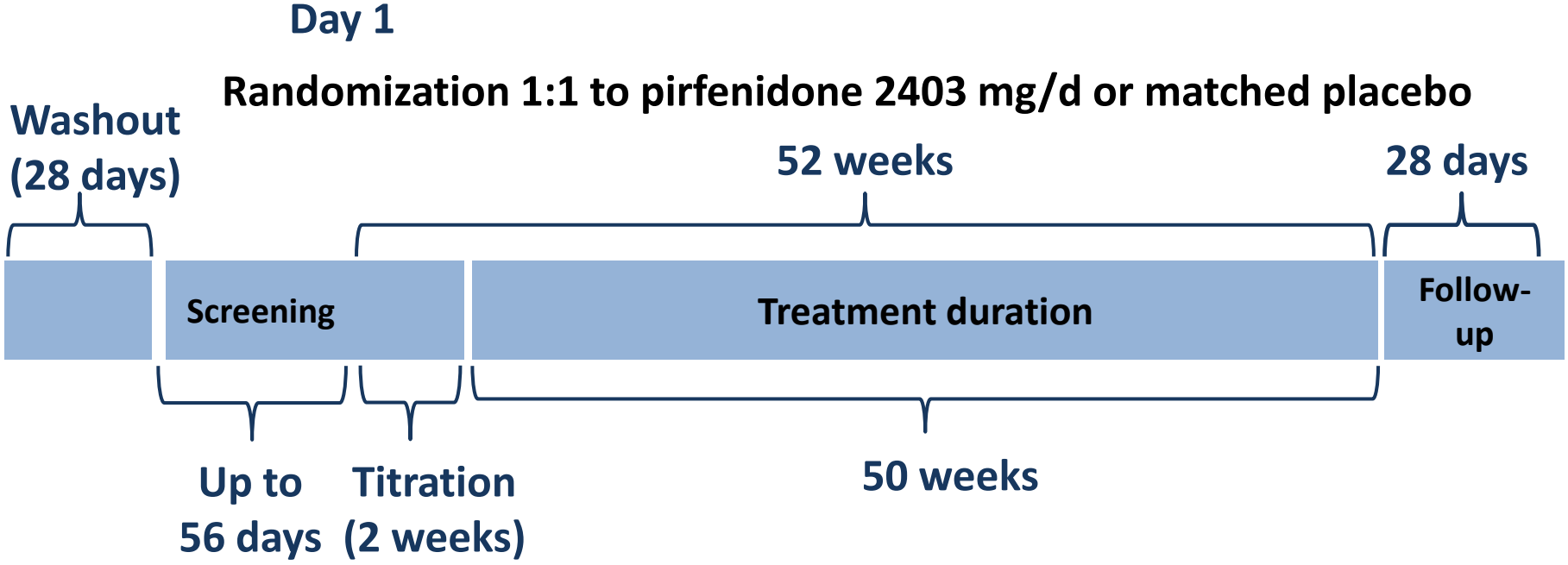
ORIGINAL ARTICLE

A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

Talmadge E. King, Jr., M.D., Williamson Z. Bradford, M.D., Ph.D., Socorro Castro-Bernardini, M.D., Elizabeth A. Fagan, M.D., Ian Glaspole, M.B., B.S., Ph.D., Marilyn K. Glassberg, M.D., Eduard Gorina, M.D., Peter M. Hopkins, M.D., David Kardatzke, Ph.D., Lisa Lancaster, M.D., David J. Lederer, M.D., Steven D. Nathan, M.D., Carlos A. Pereira, M.D., Steven A. Sahn, M.D., Robert Sussman, M.D., Jeffrey J. Swigris, D.O., and Paul W. Noble, M.D., for the ASCEND Study Group*



ASCEND Study Design: Randomized, Double-Blind, Placebo Controlled Trial



Clinical efficacy assessments: Day 1 and weeks 13, 26, 39, 52A/B

127 sites in 9 countries

ASCEND Study Design

Eligibility

- Age: 40-80 years
- HRCT: Confident diagnosis of IPF
  - Definite UIP, or
  - Possible UIP, with confirmation on SLB
- FVC: ≥ 50% and ≤ 90% percent of predicted
- DL_{CO}: ≥ 30% and ≤ 90% percent of predicted
- FEV_1/FVC ratio: **≥ 0.80**
- Centralized review: spirometry, HRCT, SLB, deaths

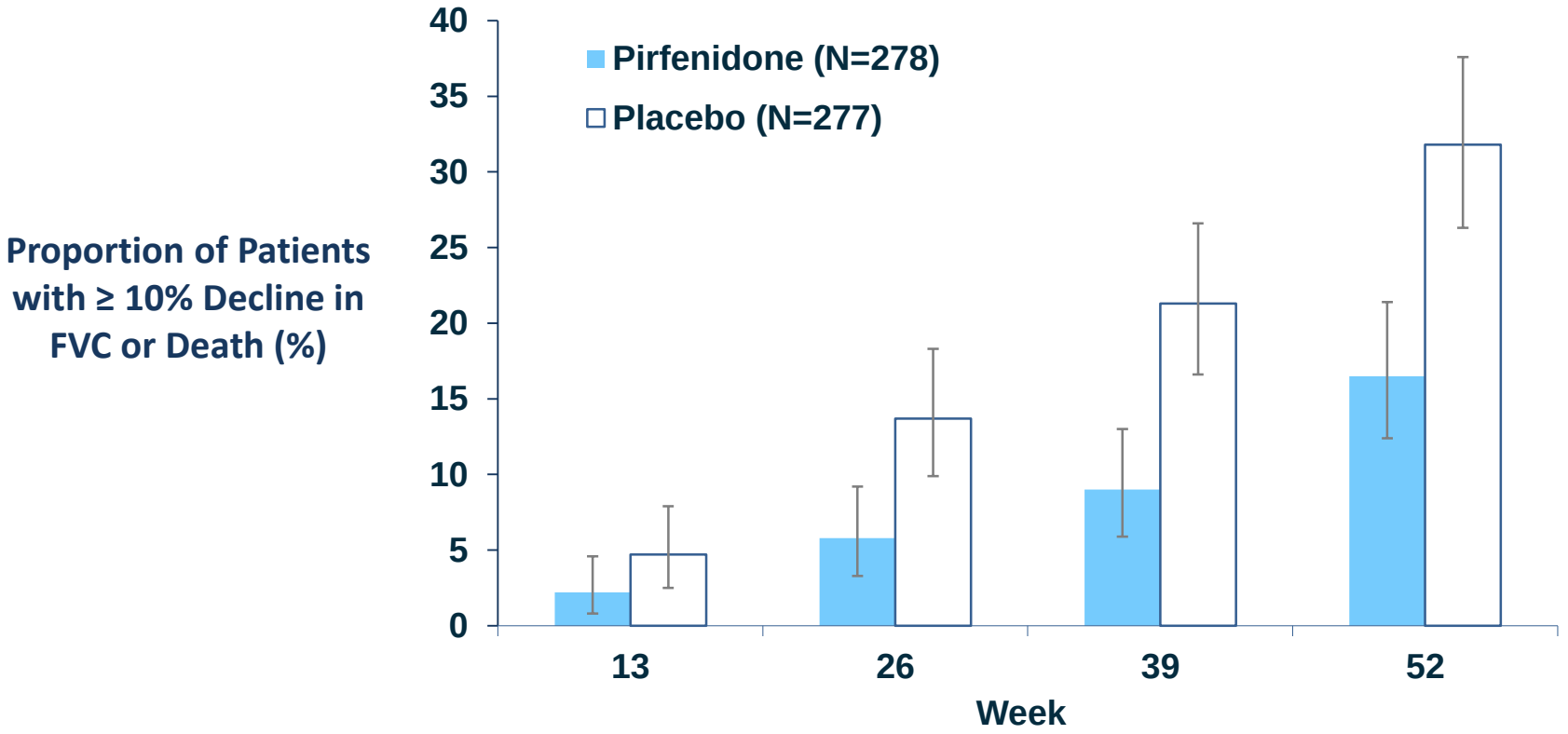
ASCEND Study Design

HRCT

	Surgical Lung Biopsy Not Available	Pathology panel: Definite UIP	Pathology Panel: Probable UIP	Pathology Panel: Possible UIP	Pathology Panel: Inconsistent w/ UIP or Not Classifiable
Radiology Panel: Definite UIP	Eligible	Eligible	Eligible	Eligible	NOT Eligible
Radiology Panel: Possible UIP	NOT Eligible	Eligible	Eligible	NOT Eligible	NOT Eligible
Radiology Panel: Inconsistent with UIP	NOT Eligible	NOT Eligible	NOT Eligible	NOT Eligible	NOT Eligible

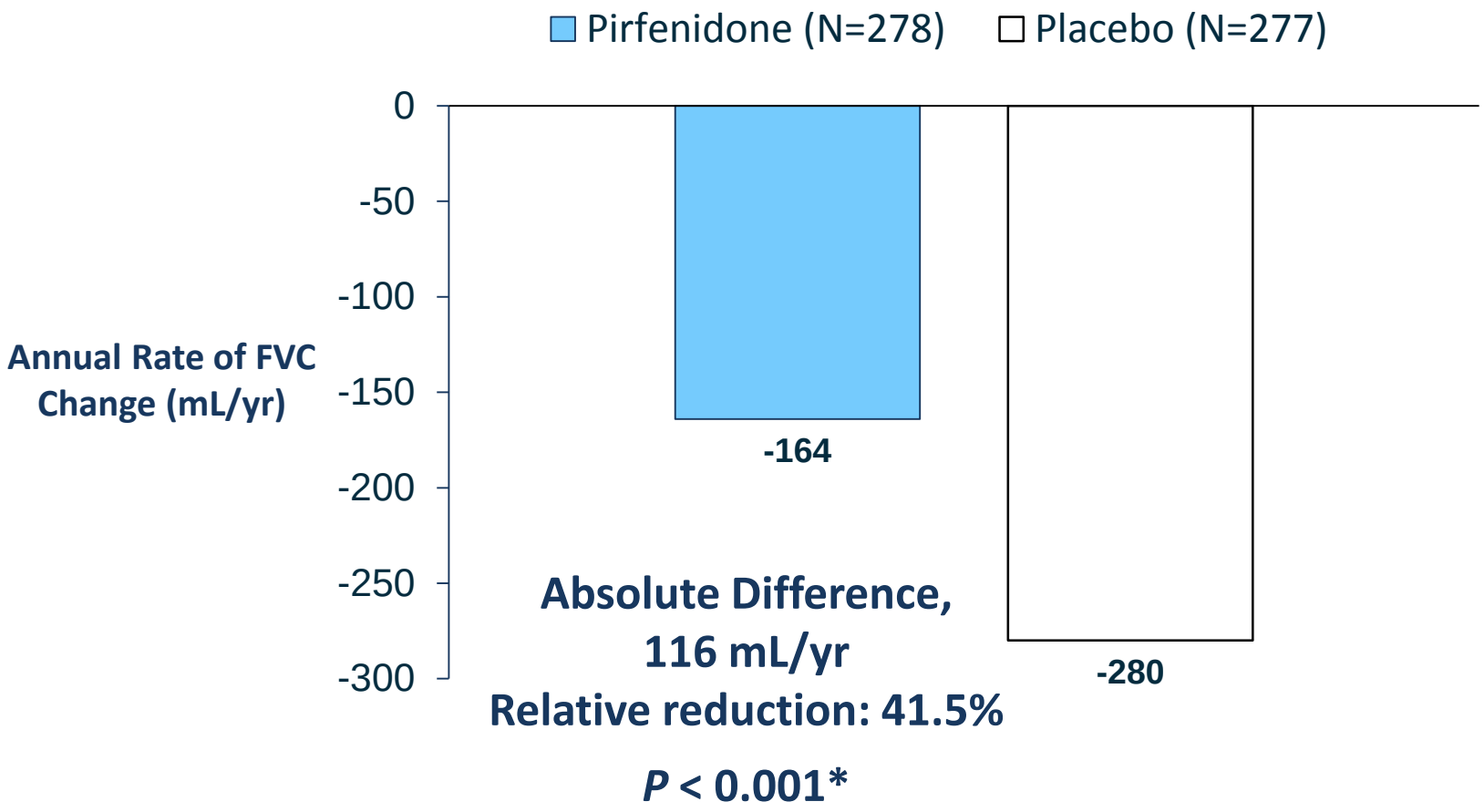
EXCLUDED: extent of emphysema greater than extent of fibrotic changes (honeycombing, reticular changes) on HRCT scan

Primary Efficacy Analysis: Treatment with Pirfenidone Resulted in a Significant Between-Group Difference in the Rank ANCOVA



	13	26	39	52
Absolute Difference	2.5%	7.9%	12.3%	15.3%
Relative Difference	54.0%	58.0%	57.8%	47.9%
Rank ANCOVA p-value	< 0.000001	< 0.000001	0.000002	< 0.000001

ASCEND Study Supportive Analysis: Annual Rate of FVC Decline at Week 52

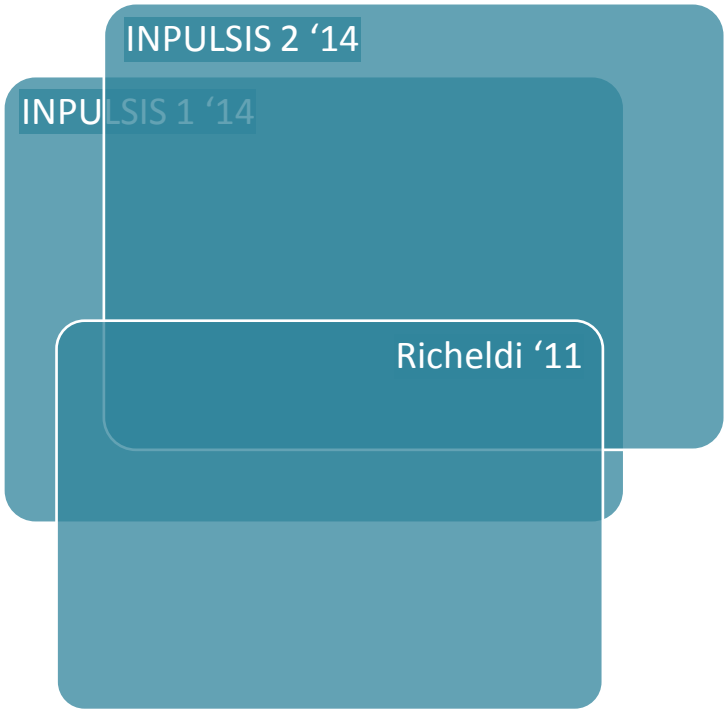


Linear slope analysis: Mixed model with linear time effect adjusted for age, height, and sex

ASCEND Study: GI and Skin-Related Events Were More Common in the Pirfenidone Group

Patients (%)	Pirfenidone (N=278)	Placebo (N=277)
Cough	25.2	29.6
Nausea	36.0	13.4
Headache	25.9	23.1
Diarrhea	22.3	21.7
Upper Respiratory Tract Infection	21.9	20.2
Fatigue	20.9	17.3
Rash	28.1	8.7
Dyspnea	14.7	17.7
Dizziness	17.6	13.0
Idiopathic pulmonary fibrosis	9.4	18.1
Bronchitis	14.0	13.0
Constipation	11.5	13.7
Back pain	10.8	13.4
Dyspepsia	17.6	6.1
Nasopharyngitis	11.9	10.8
Anorexia	15.8	6.5
Vomiting	12.9	8.7
Weight decreased	12.6	7.9
Gastroesophageal reflux	11.9	6.5
Insomnia	11.2	6.5

Nintedanib

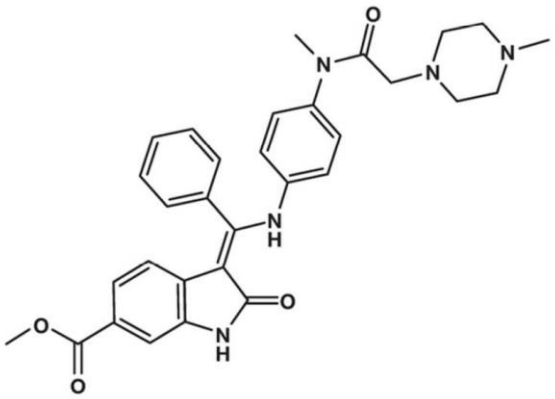


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 29, 2014 VOL. 370 NO. 22

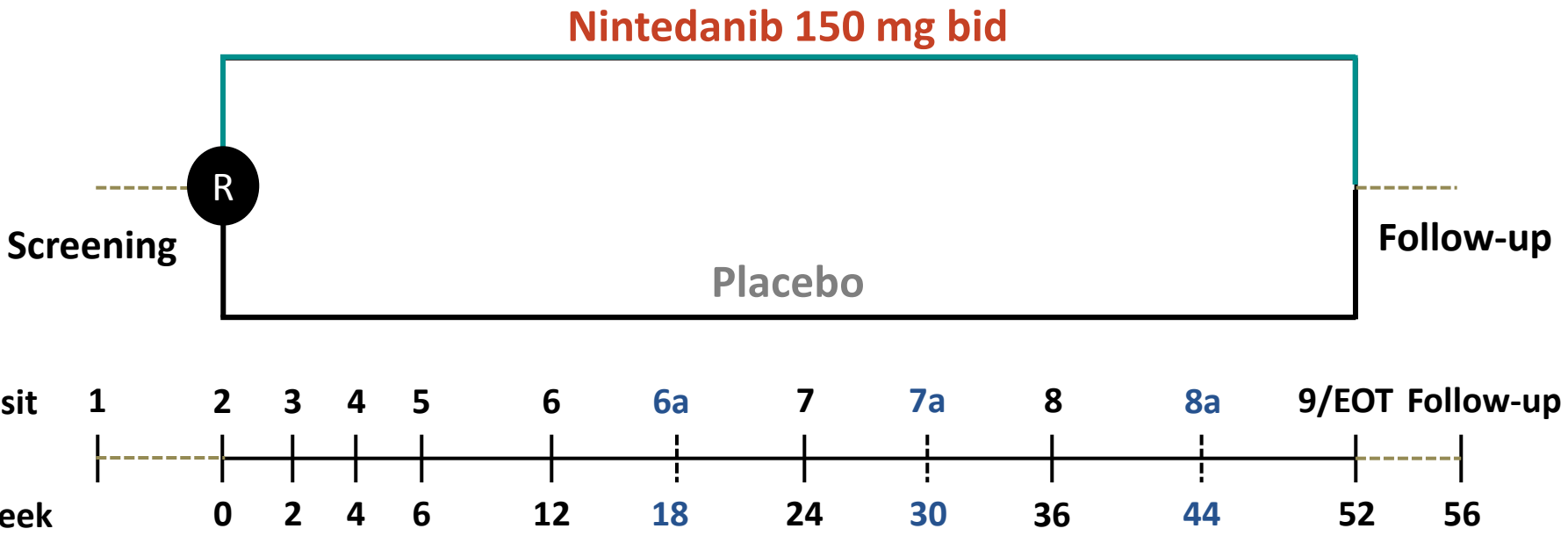
Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

Luca Richeldi, M.D., Ph.D., Roland M. du Bois, M.D., Ganesh Raghu, M.D., Arata Azuma, M.D., Ph.D., Kevin K. Brown, M.D., Ulrich Costabel, M.D., Vincent Cottin, M.D., Ph.D., Kevin R. Flaherty, M.D., David M. Hansell, M.D., Yoshikazu Inoue, M.D., Ph.D., Dong Soon Kim, M.D., Martin Kolb, M.D., Ph.D., Andrew G. Nicholson, D.M., Paul W. Noble, M.D., Moisés Selman, M.D., Hiroyuki Taniguchi, M.D., Ph.D., Michèle Brun, M.Sc., Florence Le Maulf, M.Sc., Mannaïg Girard, M.Sc., Susanne Stowasser, M.D., Rozsa Schlenker-Herceg, M.D., Bernd Disse, M.D., Ph.D., and Harold R. Collard, M.D., for the INPULSIS Trial Investigators*



Richeldi L, et al. *NEJM.* 2014;370:2071-82.

INPULSIS 1 and 2: Study Design



- 3:2 randomization ratio for nintedanib: placebo
- Dose interruption and/or dose reduction to 100 mg bid allowed to manage adverse events
- Patients who prematurely discontinued trial drug were asked to attend all visits as planned

Visits 6a, 7a and 8a were for blood sampling for laboratory tests only

Key Inclusion Criteria

- Age ≥ 40 years
- Diagnosis of IPF within 5 years of randomization
- Chest HRCT performed within 12 months of screening
- FVC ≥ 50% of predicted value
- DL_{CO} 30–79% of predicted value
- HRCT pattern, and, if available, surgical lung biopsy pattern, consistent with diagnosis of IPF, as assessed centrally by one expert radiologist and one expert pathologist

Eligibility Criteria Based on HRCT

To qualify to enter the INPULSIS trials, the criteria A and B and C; or A and C; or B and C had to be met

A	Definite honeycomb lung destruction with basal and peripheral predominance
B	Presence of reticular abnormality and traction bronchiectasis consistent with fibrosis with basal and peripheral predominance
C	Atypical features are absent, specifically nodules and consolidation. Ground glass opacity, if present, is less extensive than reticular opacity pattern

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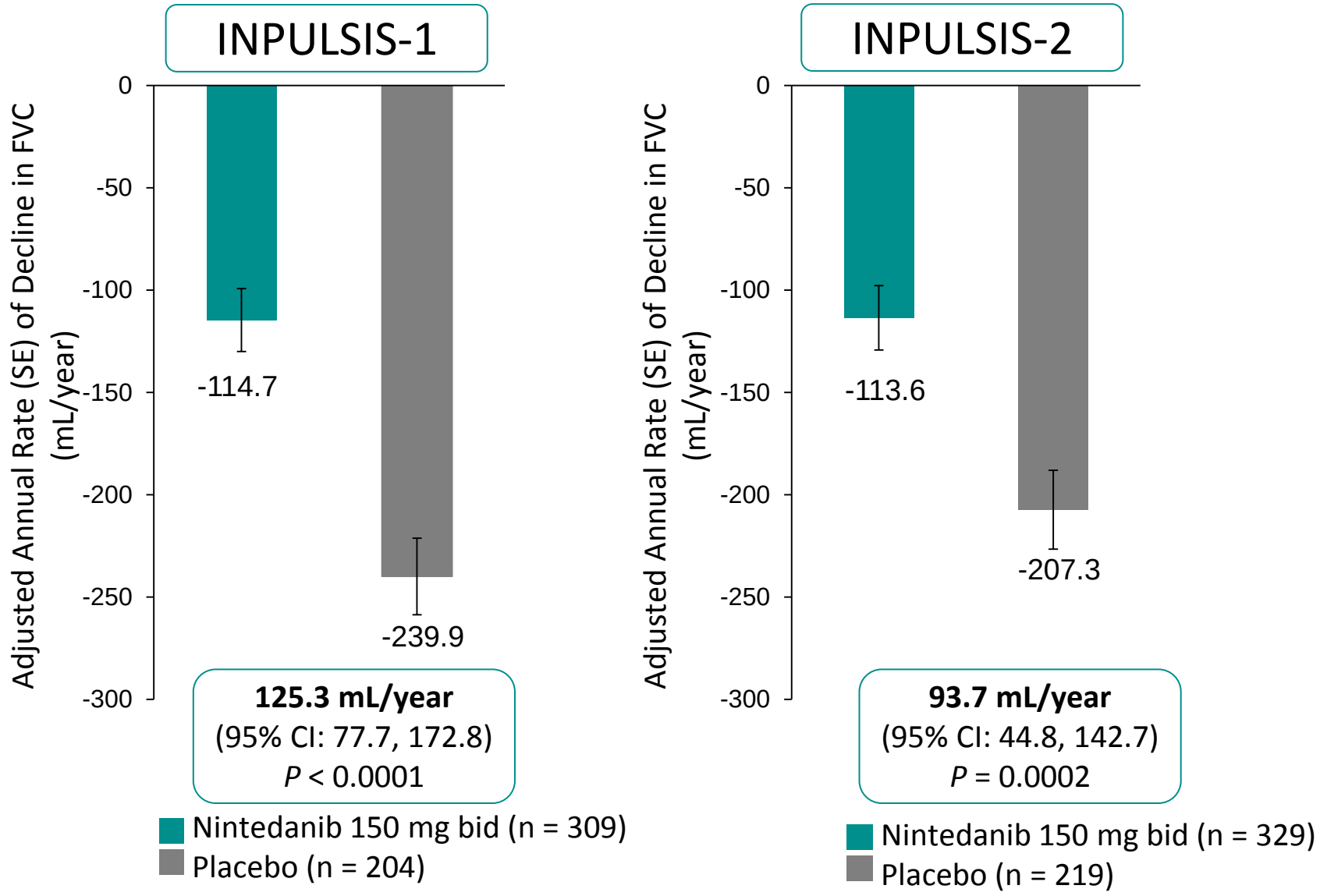
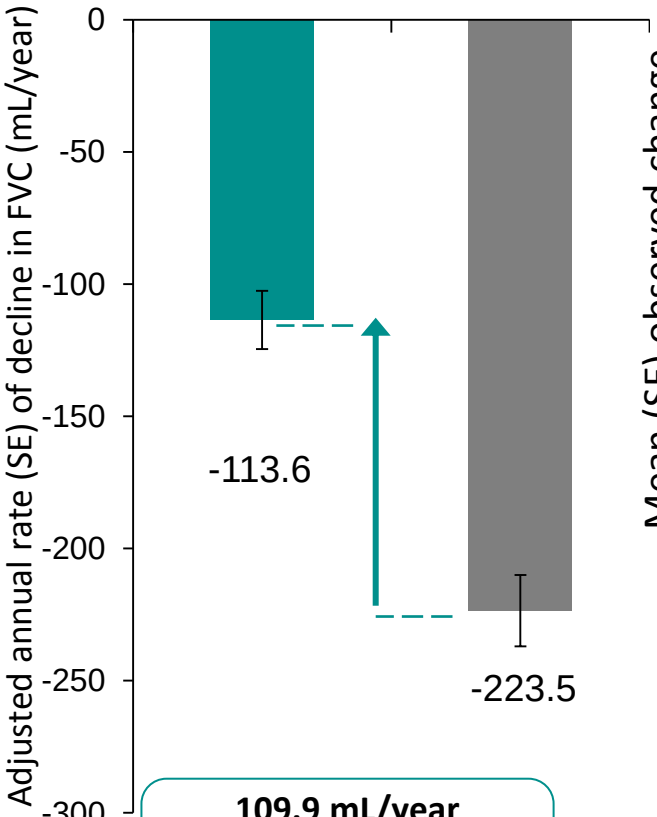
Primary Efficacy Endpoint

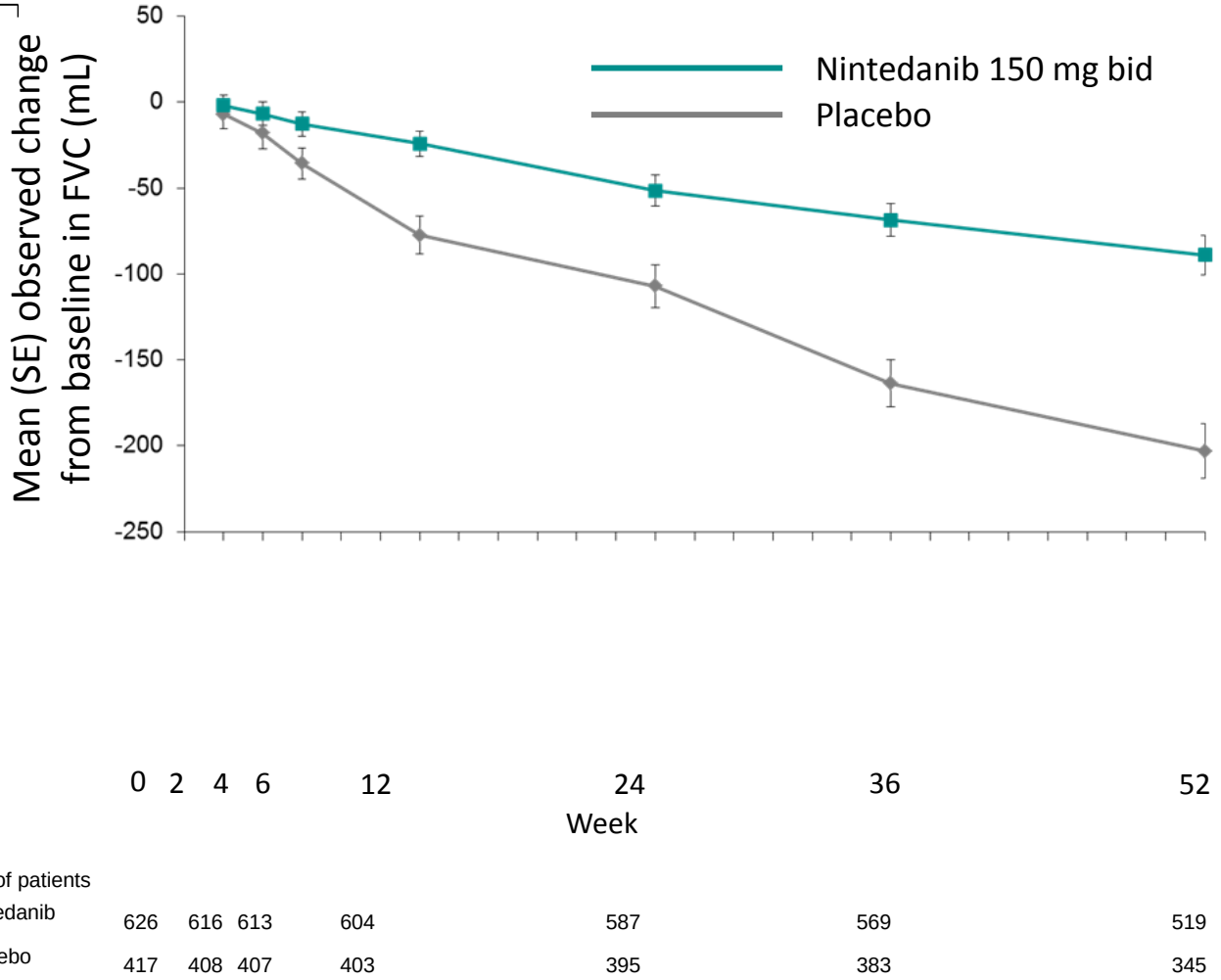


Primary Efficacy Endpoint In Pooled Data

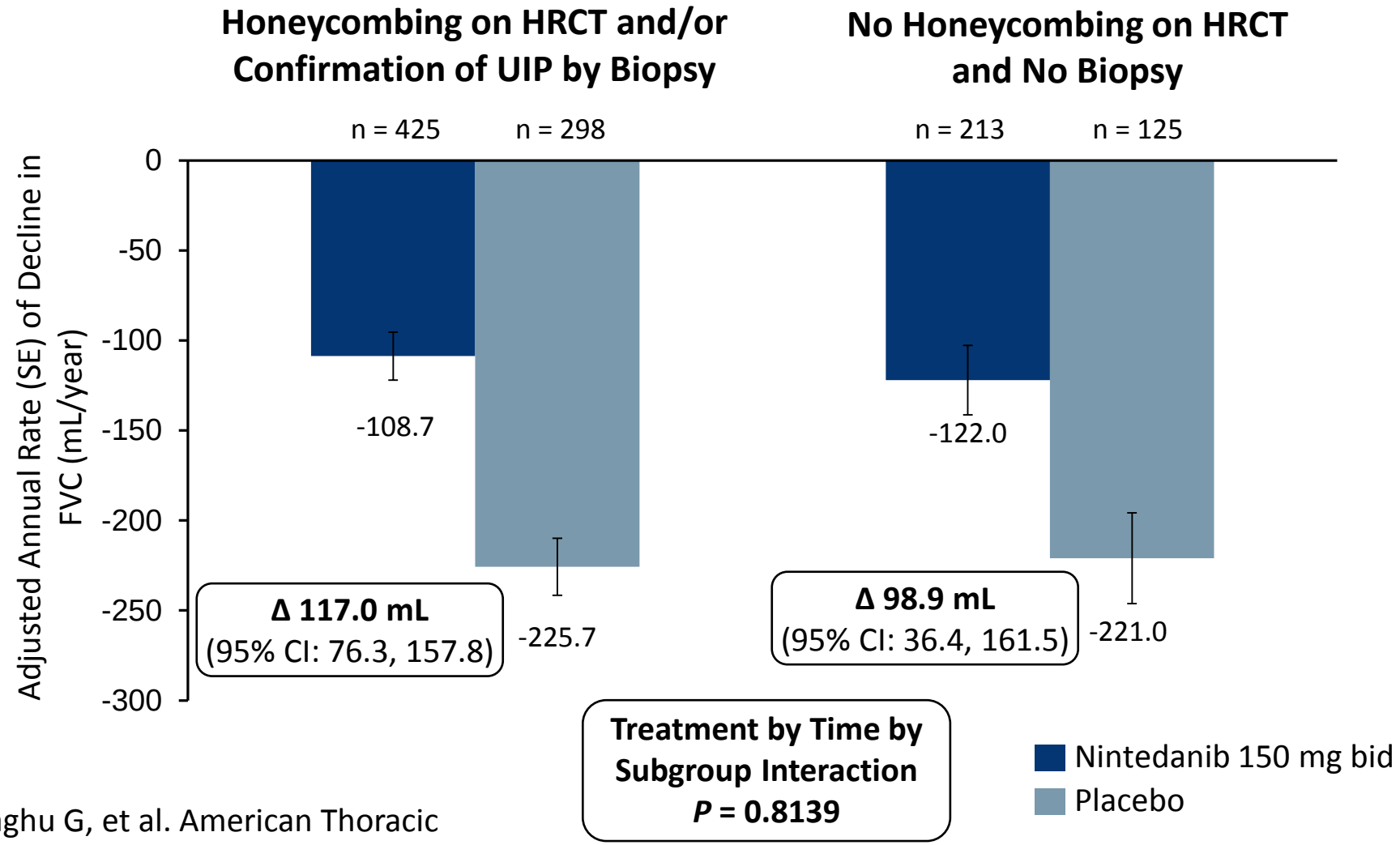


109.9 mL/year
(95% CI: 75.9, 144.0)
P < 0.0001

Nintedanib 150 mg bid (n = 638)
Placebo (n = 423)

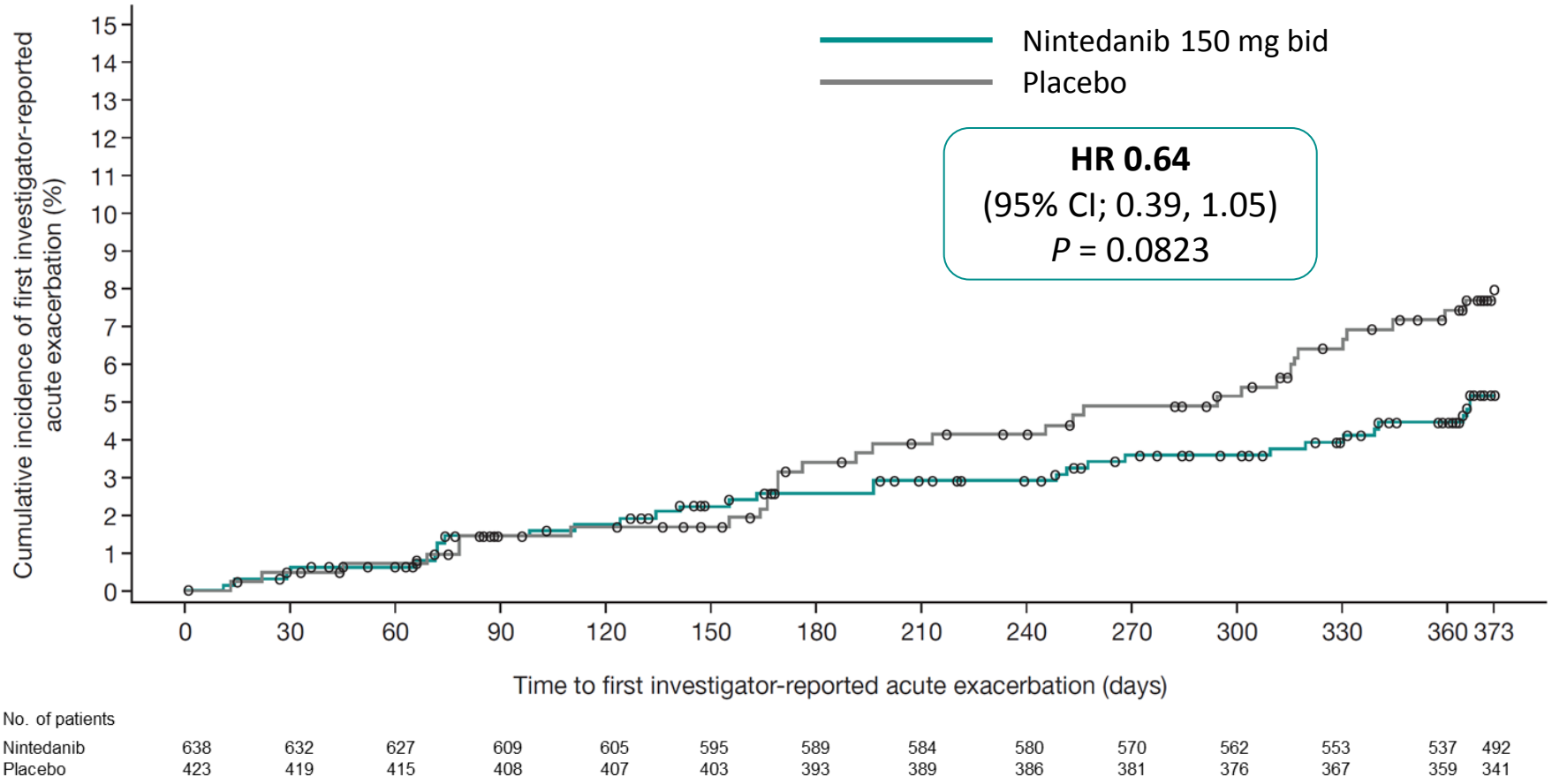


Annual Rate of Decline in FVC by HRCT Criteria



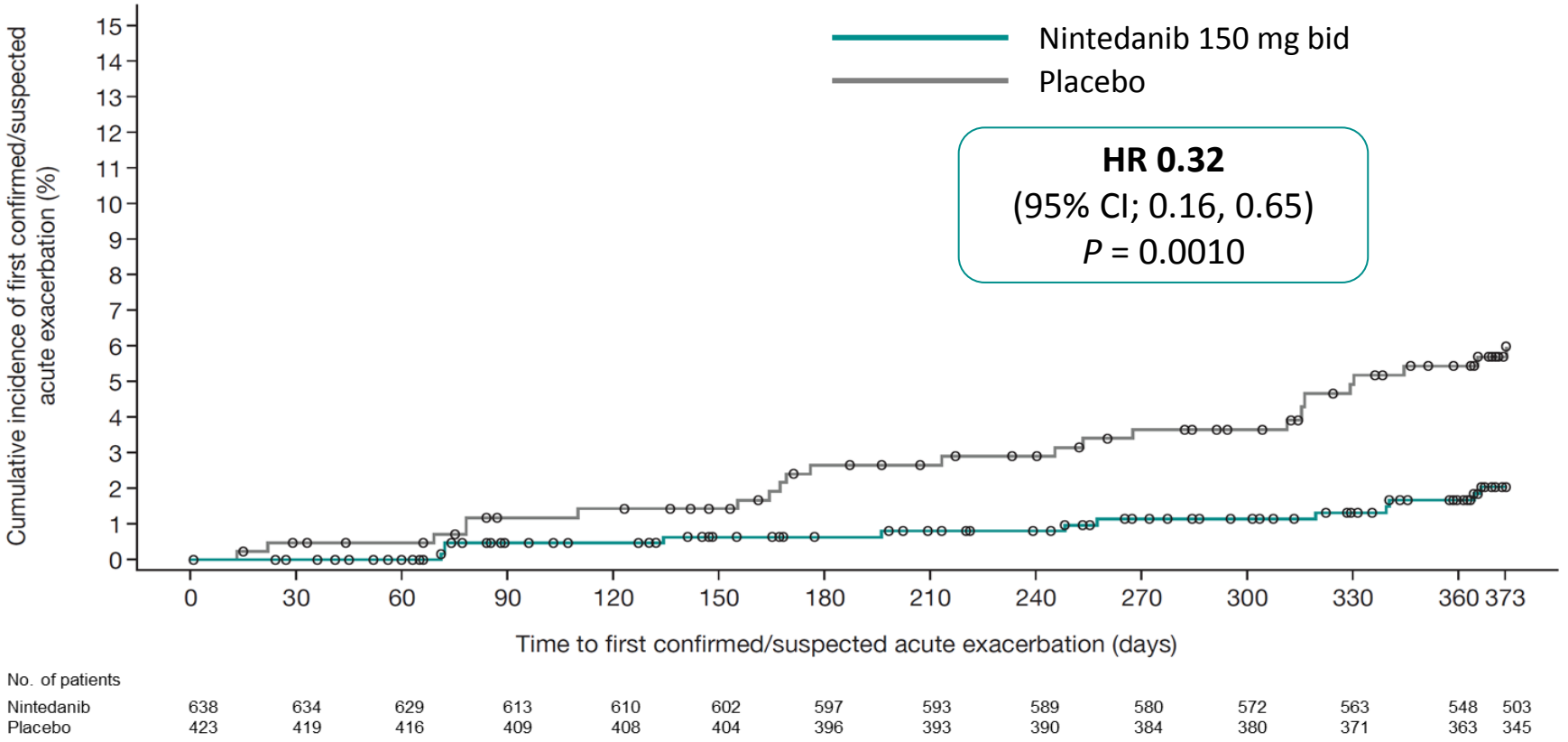
Raghu G, et al. American Thoracic Society International Conference, Denver (USA) 16 May 2015

Time to First Acute Exacerbation (Investigator-reported) in Pooled Data



	Nintedanib 150 mg bid (n = 638)	Placebo (n = 423)
Patients with ≥ 1 acute exacerbation, n (%)	**31 (4.9)**	**32 (7.6)**

Time to First Confirmed or Suspected Acute Exacerbation Per Adjudication



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

Most Frequent Adverse Events*

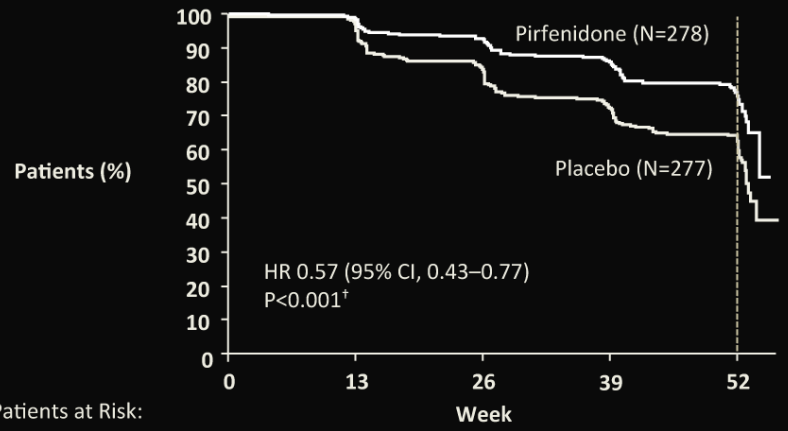
	INPULSIS-1		INPULSIS-2	
No of Patients (%)	**Nintedanib 150 mg bid (n = 309)**	**Placebo (n = 204)**	**Nintedanib 150 mg bid (n = 329)**	**Placebo (n = 219)**
Diarrhea	190 (61.5)	38 (18.6)	208 (63.2)	40 (18.3)
Nausea	70 (22.7)	12 (5.9)	86 (26.1)	16 (7.3)
Nasopharyngitis	39 (12.6)	34 (16.7)	48 (14.6)	34 (15.5)
Cough	47 (15.2)	26 (12.7)	38 (11.6)	31 (14.2)
Progression of IPF†	31 (10.0)	21 (10.3)	33 (10.0)	40 (18.3)
Bronchitis	36 (11.7)	28 (13.7)	31 (9.4)	17 (7.8)
Upper respiratory tract infection	28 (9.1)	18 (8.8)	30 (9.1)	24 (11.0)
Dyspnea	22 (7.1)	23 (11.3)	27 (8.2)	25 (11.4)
Decreased appetite	26 (8.4)	14 (6.9)	42 (12.8)	10 (4.6)
Vomiting	40 (12.9)	4 (2.0)	34 (10.3)	7 (3.2)
Weight decreased	25 (8.1)	13 (6.4)	37 (11.2)	2 (0.9)

Based on adverse events with onset after first dose and up to 28 days after the last dose of trial medication
*Adverse events with an incidence of >10% in any treatment group. †Corresponds to the MedDRA term 'IPF', which included disease worsening and IPF exacerbations

Diarrhea

	INPULSIS-1		INPULSIS-2	
No of Patients (%)	**Nintedanib 150 mg bid (n = 309)**	**Placebo (n = 204)**	**Nintedanib 150 mg bid (n = 329)**	**Placebo (n = 219)**
Diarrhea serious adverse event(s)	1 (0.3)	0 (0.0)	1 (0.3)	1 (0.5)
Diarrhea adverse event(s) leading to premature treatment discontinuation	14 (4.5)	0 (0.0)	14 (4.3)	1 (0.5)
Intensity of most severe event, for patients with any diarrhea adverse event(s)				
Mild	103 (54.2)	29 (76.3)	123 (59.1)	31 (77.5)
Moderate	75 (39.5)	9 (23.7)	75 (36.1)	7 (17.5)
Severe	11 (5.8)	0 (0.0)	10 (4.8)	2 (5.0)

Progression-free Survival*: Pirfenidone reduced the risk of disease progression or death by 43%

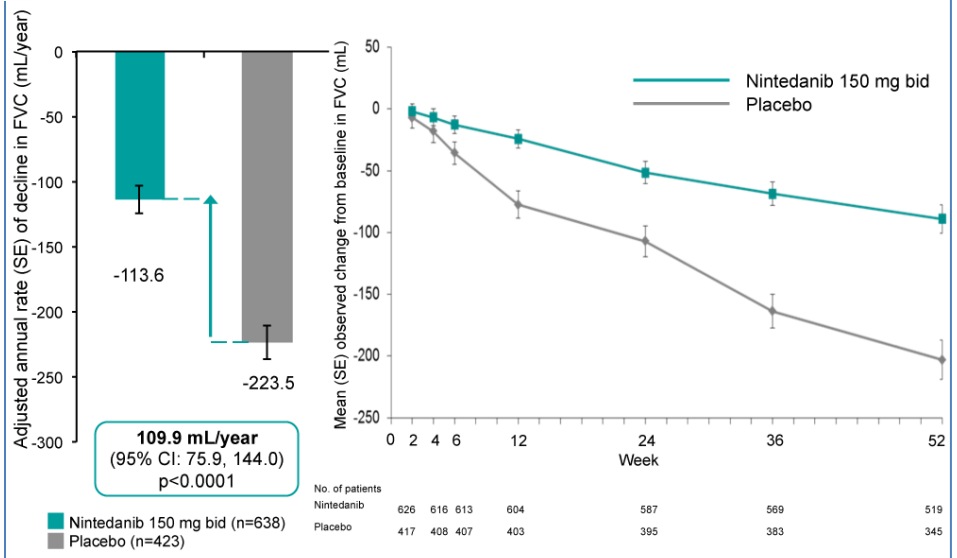


Patients at Risk:					
Pirfenidone	276	262	243	219	144
Placebo	273	269	225	192	113

*Time to death or disease progression (confirmed ≥10% decline in FVC or confirmed ≥50 m decline in 6MWD)
Log-rank test

NEJM 2014; 370: 2083-92

PRIMARY EFFICACY ENDPOINT IN POOLED DATA



NEJM 2014; 370: 2071-82

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 B… Kevin K. Brown, Thomas V. Colby, Jean-François Cordier, Kevin R. Flaherty, Joseph A. Lasky… Lynch, Jay H. Ryu, Jeffrey J. Swigris, Athol U. Wells, Julio Ancochea, Demosthenes Bouros… o, Ulrich Costabel, Masahito Ebina, David M. Hansell, Takeshi Johkoh, Dong Soon Ki… Jr., Yasuhiro Kondoh, Jeffrey Myers, Nestor L. Müller, Andrew G. Nicholson, Luca P… salind F. Dudden, Barbara S. Griss, Shandra L. Protzko, and Holger J. Schü… T/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis

This Official Statement of the American Thora… iratory Society (ERS), the Japanese Respiratory Society (JRS), and the Latin A…) Was Approved by the ATS Board of Directors, November 2010, the ERS E… e JRS Board of Directors, December 2010, and the ALAT Executive Committee, N…

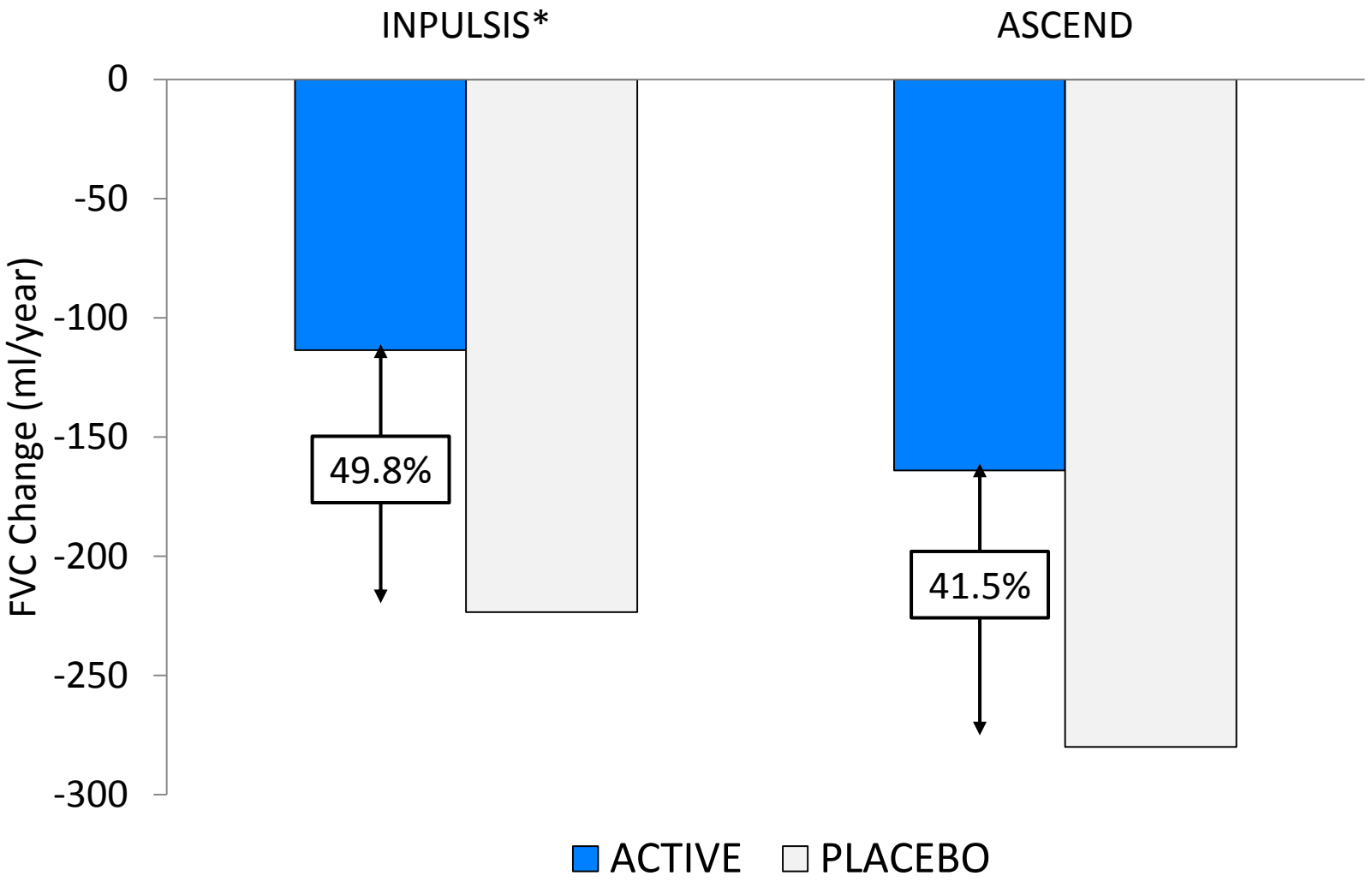
This Statement has been fo… oracic Radiology and by the Pulmonary Pathology Society

UPDATE IN PROGRESS
PRESENTED AT ATS 2015

www.PILOTforIPF.org

AJRCCM. 2011;183:788-824.

Linear Slope of Decline in FVC at Week 52



Richeldi L, et al. *NEJM.* 2014;370:2071-82.

King TE, et al. *NEJM.* 2014;370:2083-92.

*Based on pre-specified pooled analysis

For Consumers
Updates and information for staying safe and healthy

For Patients
Learn about other treatments, drug/device approvals, public meetings and more

For Health Professionals
Medical product safety information, adverse event/problem reporting and more

For Scientists & Researchers
NCTR, pediatrics, clinical trials, Critical Path Initiative and more

For Industry
Guidance, registration and listing, import programs and more

Recalls & Alerts

- Recalls
- MedWatch: Safety Alerts

Approvals & Clearances

- Enforcement Report
- Industry Recall Guidance

Report a Problem

- Warning Letters
- Outbreaks - Food

News & Events

- October 15, 2014 - FDA approves Ofev to treat idiopathic pulmonary fibrosis
- October 15, 2014 - FDA approves Esbriet to treat idiopathic pulmonary fibrosis

FDA Voice Blog

October 15, 2014
Two FDA Drug Approvals for Idiopathic Pulmonary Fibrosis (IPF)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ofev is indicated in adults for the treatment of Idiopathic Pulmonary Fibrosis (IPF).

13 Feb 2015

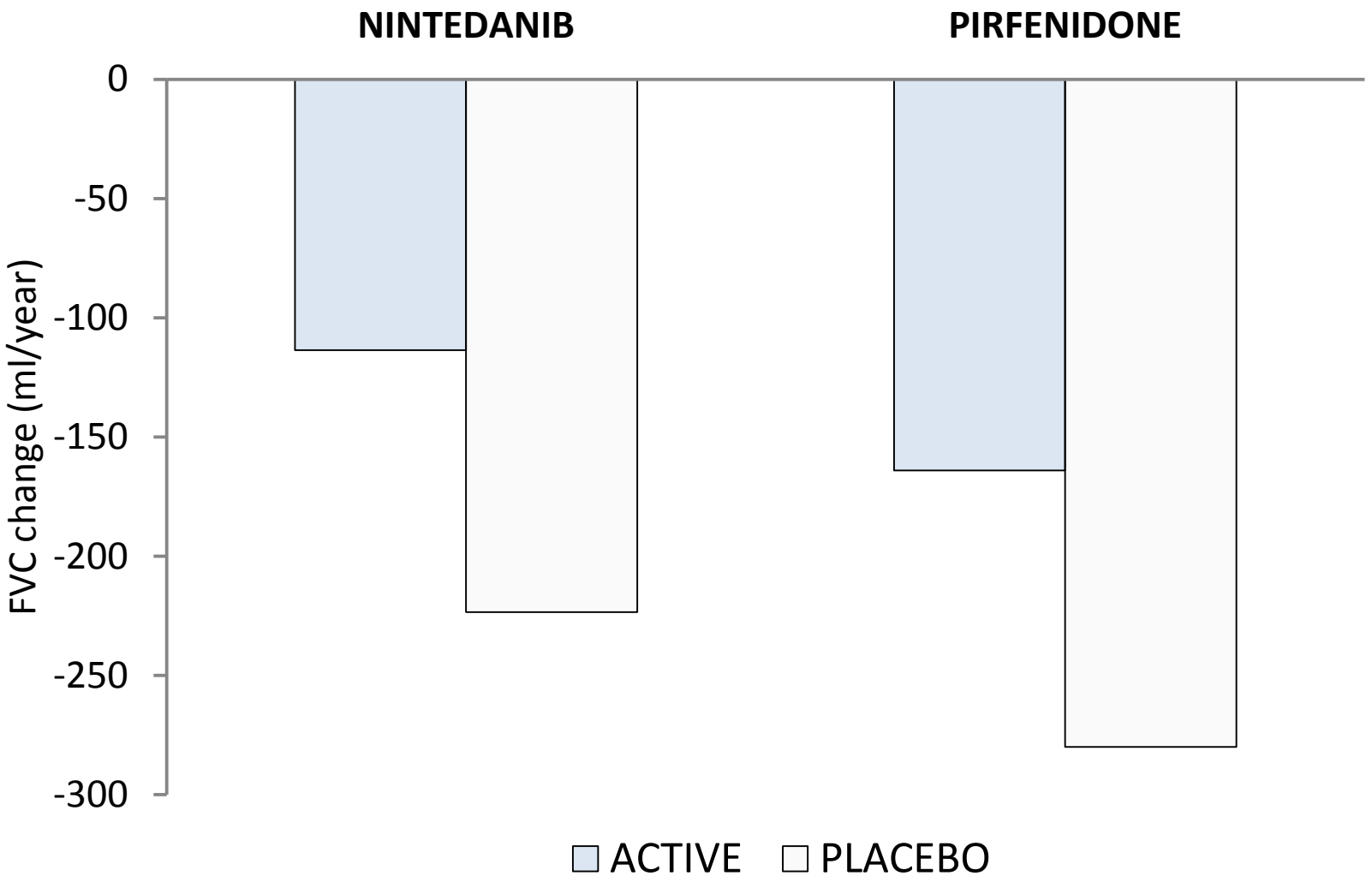
4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Esbriet is indicated in adults for the treatment of mild to moderate Idiopathic Pulmonary Fibrosis (IPF).

11 Mar 2011, updated 6 Mar 2015

Linear Slope of Decline in FVC at Week 52



Richeldi L, et al. *NEJM.* 2014;370:2071-82.

King TE, et al. *NEJM.* 2014;370:2083-92.

Combination therapy: the future of management for idiopathic pulmonary fibrosis?

Wim A Wuyts, Katerina M Antoniou, Keren Borensztajn, Ulrich Costabel, Vincent Cottin, Bruno Crestani, Jan C Grutters, Toby M Maher, Venerino Poletti, Luca Richeldi, Carlo Vancheri, Athol U Wells

Selecting the Right Treatment: Which Patients and When to Start Treatment?

HAROLD R. COLLARD, MD

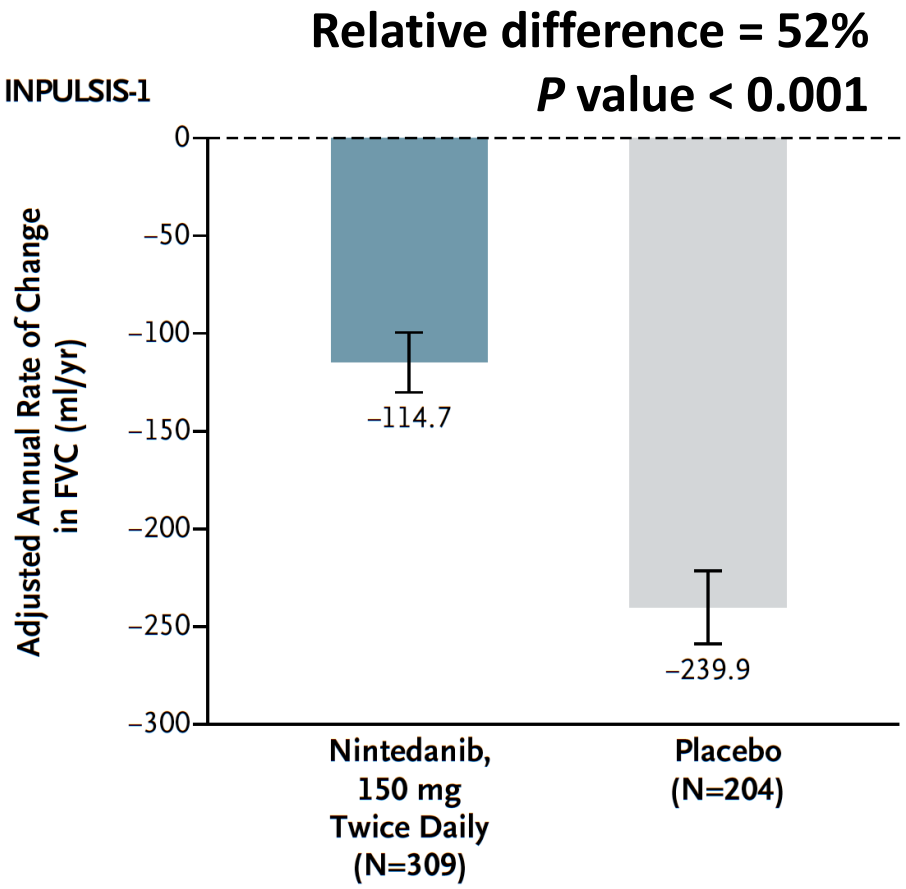
Associate Professor of Medicine
Director, Interstitial Lung Disease Program
University of California, San Francisco
San Francisco, California

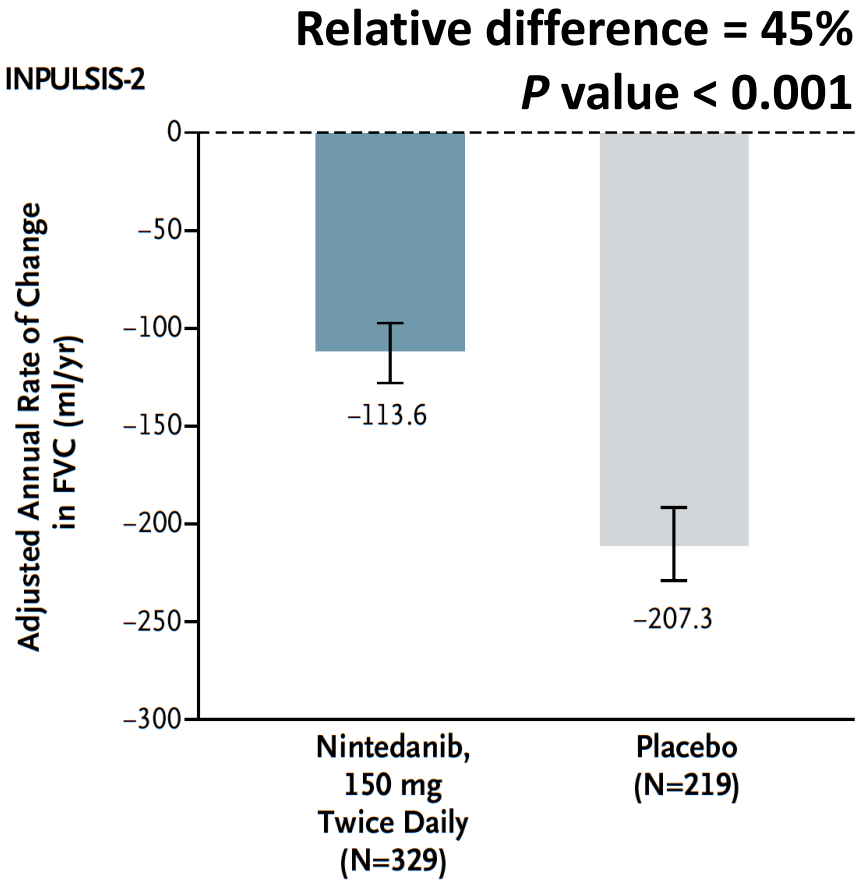
Which Drug Do I Choose?

Which Drug Do I Choose?

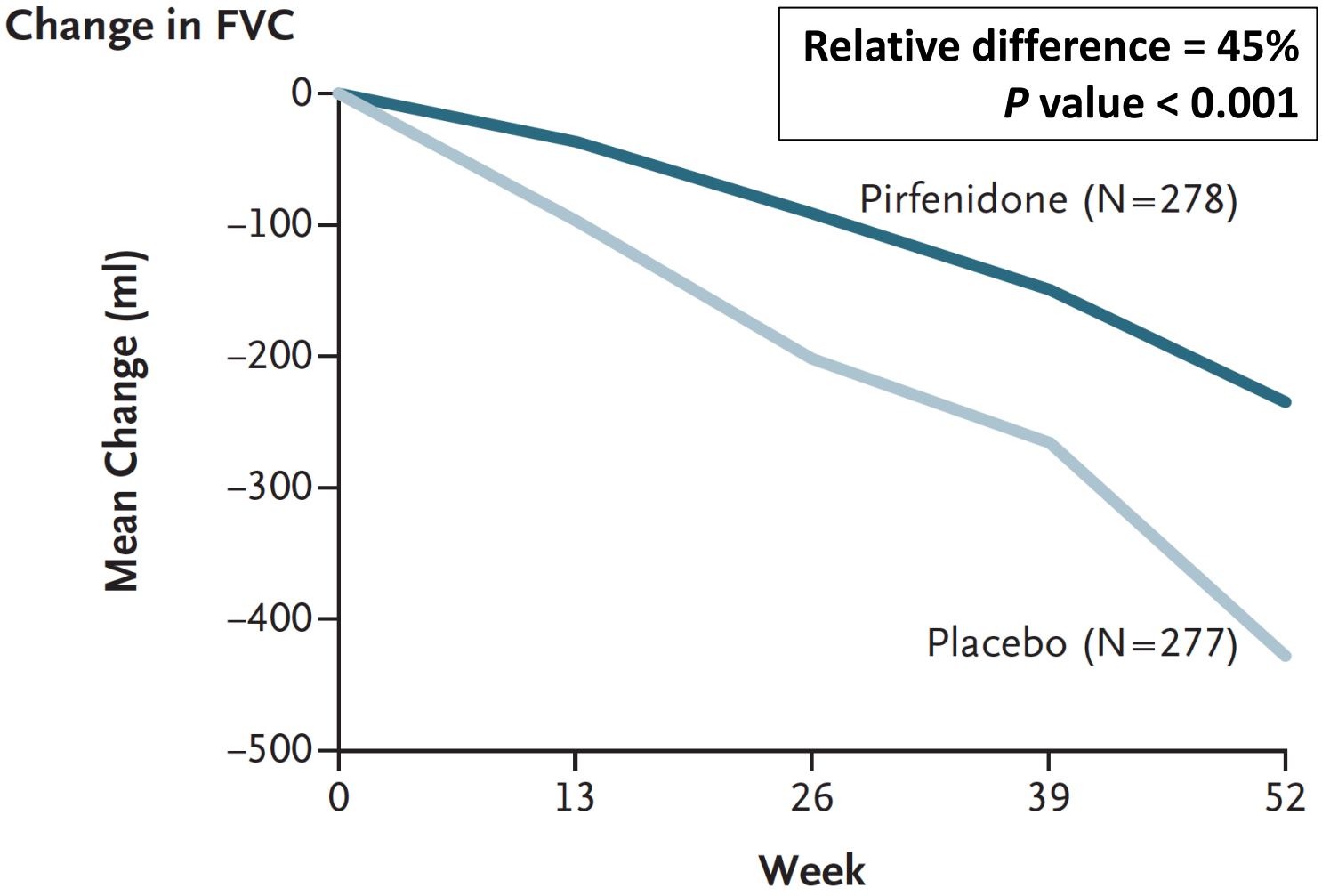
	Nintedanib	Pirfenidone
Efficacy (primary endpoint comparison)		
Safety		
Tolerability (>20%)		
Dosing		
Patient type		
Patient cost (US)		
Patient preference		

Nintedanib: Disease Progression





Pirfenidone: Disease Progression



Which Drug Do I Choose?

	Nintedanib	Pirfenidone
Efficacy (primary endpoint comparison)	~50% slowing of disease progression	~ 50% slowing of disease progression
Safety		
Tolerability (>20%)		
Dosing		
Patient type		
Patient cost (US)		
Patient preference		

Safety

Nintedanib	Pirfenidone
• Elevated liver enzymes (AST/ALT >3x in 4.9%) • Myocardial infarction in 1.5% (0.4% in placebo) • Possible bleeding risk, gastrointestinal perforation • Embryofetal toxicity • *Not recommended in patients with moderate or severe hepatic impairment (Child Pugh B/C)*	• Elevated liver enzymes (AST/ALT >3x in 3.7%) • *Used with caution in patients with mild to moderate hepatic impairment or impaired renal function* • *Not recommended in severe hepatic impairment (Child Pugh C) or end-stage renal disease*

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205832s000lbl.pdf
http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022535s000lbl.pdf
Richeldi L, et al. *NEJM*. 2014;370:2071-2082.

Which Drug Do I Choose?

	Nintedanib	Pirfenidone
Efficacy (primary endpoint comparison)	~50% slowing of disease progression	~ 50% slowing of disease progression
Safety	Elevated AST/ALT, MI	Elevated AST/ALT
Tolerability (>20%)		
Dosing		
Patient type		
Patient cost (US)		
Patient preference		

Nintedanib: Tolerability

- In clinical trials, 21% of patients stopped treatment prematurely for adverse events (placebo 15%)

Adverse Event (combined TOMORROW and INPULSIS I/II)	Nintedanib (n = 723)	Placebo (n = 508)
Diarrhea	62%	18%
Nausea	24%	7%
Abdominal pain	15%	6%
Vomiting	12%	3%
Decreased appetite	11%	5%

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205832s000lbl.pdf

Pirfenidone: Tolerability

- In clinical trials, 15% of patients stopped treatment prematurely for adverse events (placebo 10%)

Adverse event (combined ASCEND and CAPACITY I/II)	Pirfenidone (n = 623)	Placebo (n = 624)
Nausea	36%	16%
Rash	30%	10%
Diarrhea	26%	20%
Fatigue	26%	19%
Headache	22%	19%

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022535s000lbl.pdf

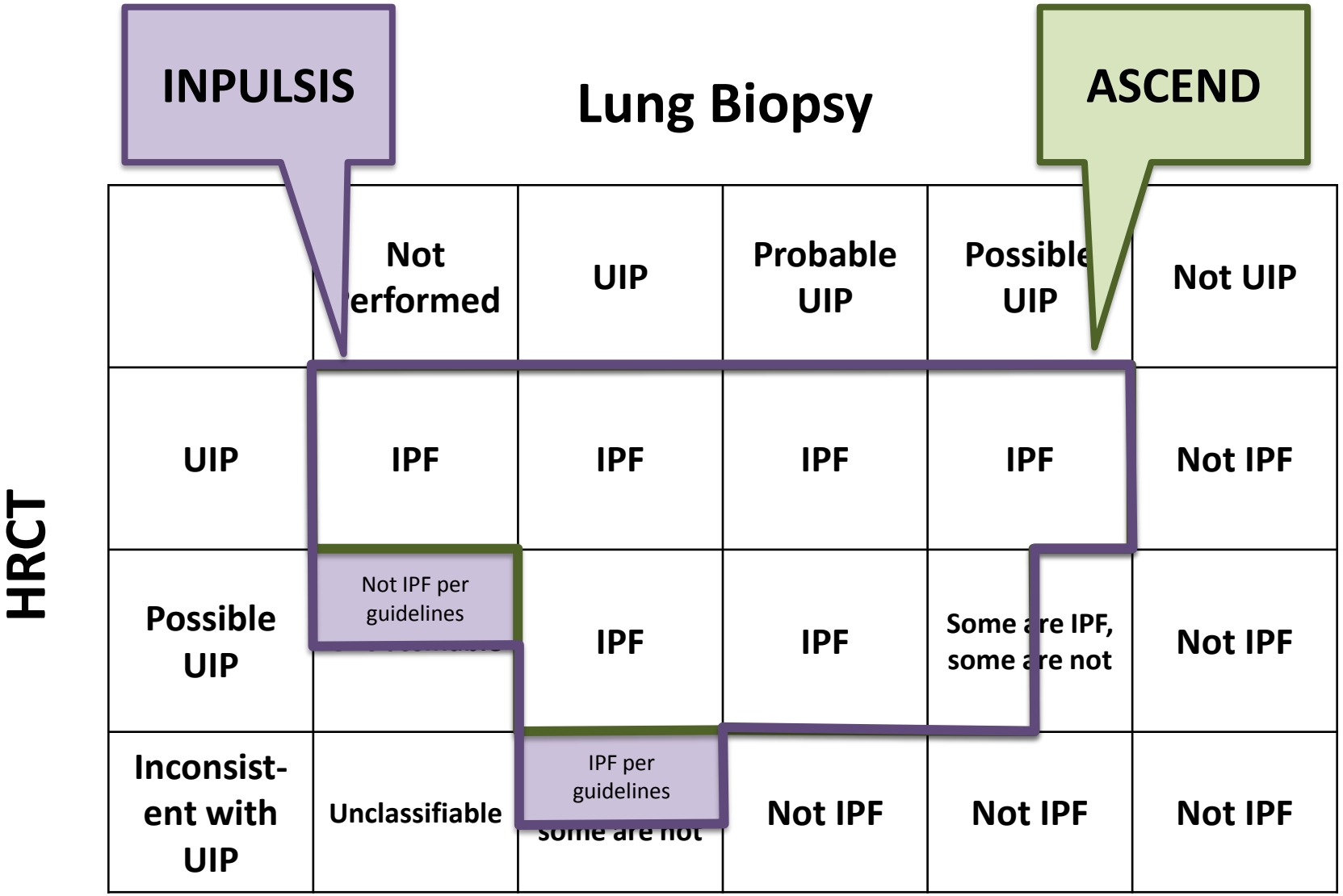
Which Drug Do I Choose?

	Nintedanib	Pirfenidone
Efficacy (primary endpoint comparison)	~50% slowing of disease progression	~ 50% slowing of disease progression
Safety	Elevated AST/ALT, MI	Elevated AST/ALT
Tolerability (>20%)	Diarrhea, nausea	Nausea, rash, diarrhea, fatigue, headache
Dosing		
Patient type		
Patient cost (US)		
Patient preference		

Which Drug Do I Choose?

	Nintedanib	Pirfenidone
Efficacy (primary endpoint comparison)	~50% slowing of disease progression	~ 50% slowing of disease progression
Safety	Elevated AST/ALT, MI	Elevated AST/ALT
Tolerability (>20%)	Diarrhea, nausea	Nausea, rash, diarrhea, fatigue, headache
Dosing	Two times daily	Three times daily
Patient type		
Patient cost (US)		
Patient preference		

Patient Type



Which Drug Do I Choose?

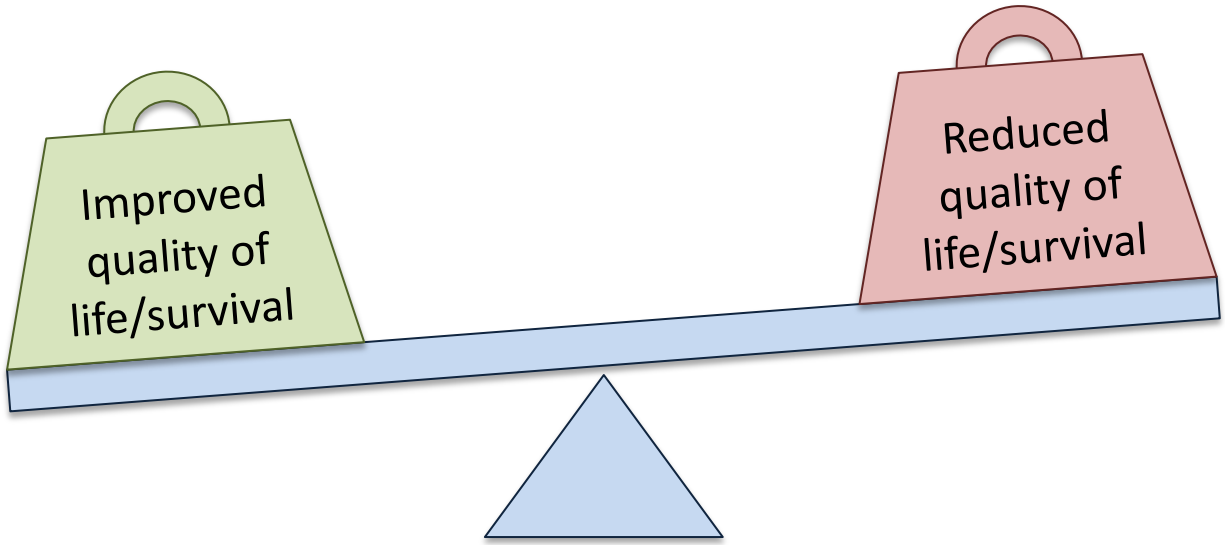
	Nintedanib	Pirfenidone
Efficacy (primary endpoint comparison)	~50% slowing of disease progression	~ 50% slowing of disease progression
Safety	Elevated AST/ALT, MI	Elevated AST/ALT
Tolerability (>20%)	Diarrhea, nausea	Nausea, rash, diarrhea, fatigue, headache
Dosing	Two times daily	Three times daily
Patient type	Broader population (some possible IPF)	Narrower population (excluded some IPF)
Patient cost (US)		
Patient preference		

Which Drug Do I Choose?

	Nintedanib	Pirfenidone
Efficacy (primary endpoint comparison)	~50% slowing of disease progression	~ 50% slowing of disease progression
Safety	Elevated AST/ALT, MI	Elevated AST/ALT
Tolerability (>20%)	Diarrhea, nausea	Nausea, rash, diarrhea, fatigue, headache
Dosing	Two times daily	Three times daily
Patient type	Broader population (some possible IPF)	Narrower population (excluded some IPF)
Patient cost (US)	??	??
Patient preference	??	??

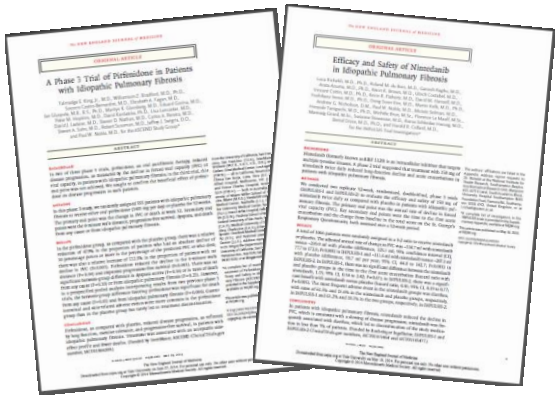
Who Should You Treat?

- Patients in whom you **believe** treatment will preserve quality and/or quantity of life
- Patients in whom you **believe** the benefits outweigh the risks



Who Should You Treat?

- Real-world treatment decisions require integration of data and clinical experience



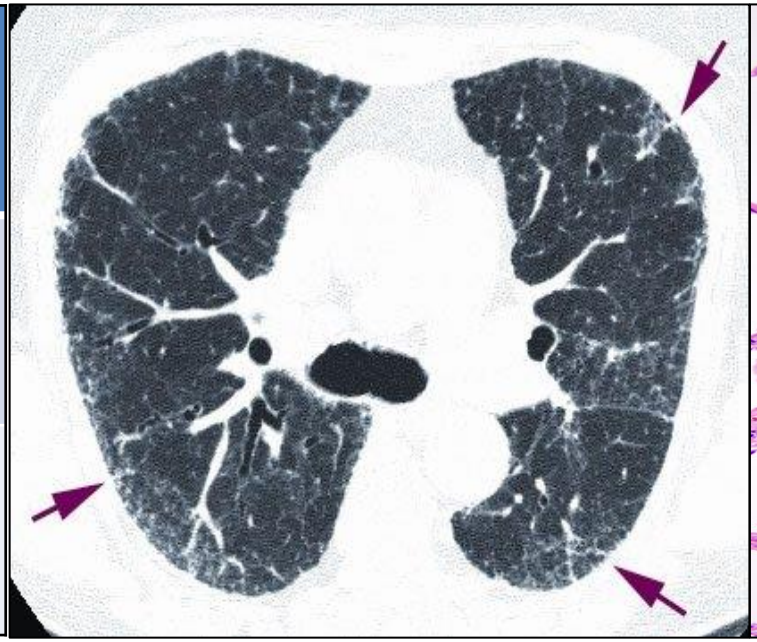
Clinical Trial Data
(quality high, scope limited)

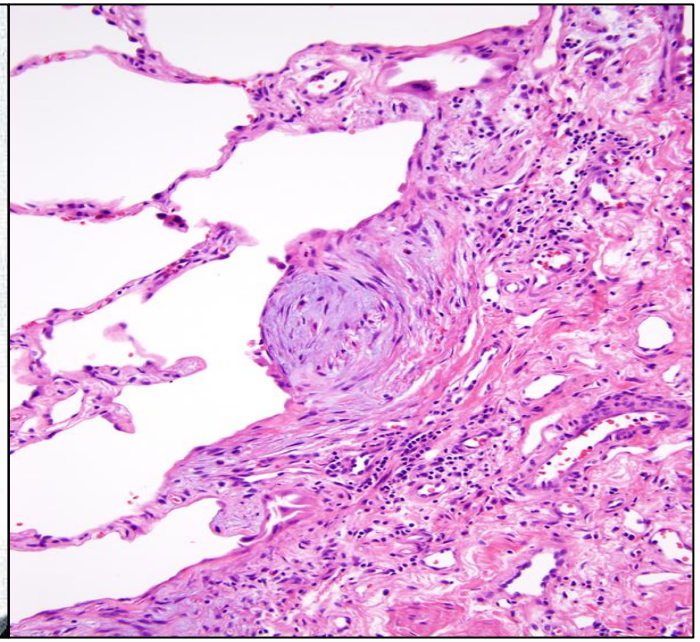
Clinical Experience
(quality Italian, scope broad)

Case #1

- 65 year old man with newly diagnosed IPF
  - Past Medical/Social Hx: N/A

Pulmonary function test value	% pred
Forced vital capacity (FVC)	65
Diffusion capacity (DLCO)	50





Moderate restriction and gas exchange, “possible UIP pattern” HRCT; “UIP pattern” SLBx

http://www.pilotforipf.org/ipf-resources/ipf-image-library

Case #1 Vote
Would you treat this patient?

A. Yes

B. No

Case #1

If so, which agent would you choose?

A. Nintedanib
B. Pirfenidone
C. Either
D. Not sure

Case #1 My Thoughts

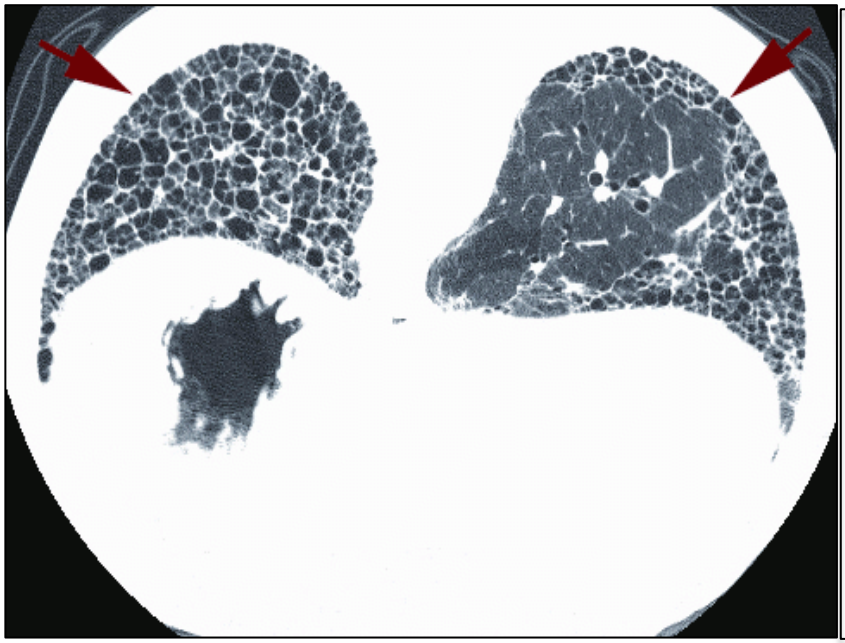
- I would treat this patient
- I would prescribe either nintedanib or pirfenidone (assuming there was no cost difference or patient preference)

- *This patient would have been included in either registration trial (INPULSIS or ASCEND) and has no safety, side effect, or dosing concerns.*

Case #2

- 85 year old man with established, severe IPF
  - Past Medical/Social Hx: severe coronary disease

Pulmonary function test value	% pred
Forced vital capacity (FVC)	45
Diffusion capacity (DLCO)	25



No biopsy

Severe restriction and gas exchange, “UIP pattern” HRCT

http://www.pilotforipf.org/ipf-resources/ipf-image-library

Case #2
Would you treat this patient?

A. Yes

B. No

Case #2

If so, which agent would you choose?

A. Nintedanib
B. Pirfenidone
C. Either
D. Not sure

Case #2 My Thoughts

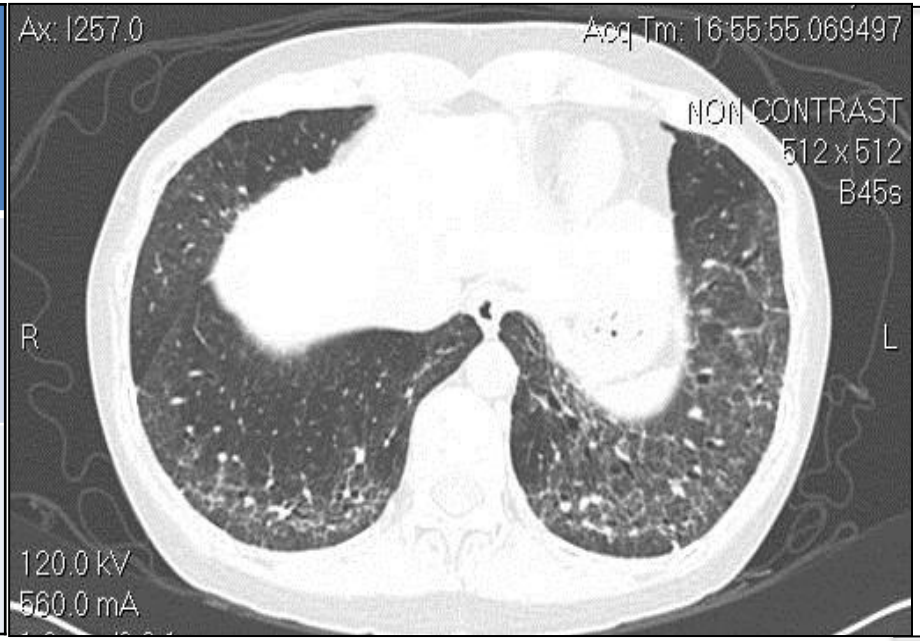
- I would not treat this patient
- If treated, I would prescribe pirfenidone given potential cardiac risk with nintedanib

- *This patient would not have been included in either INPULSIS or ASCEND and it is unclear to me how benefit and risk relate. I think it is unlikely that there will be much benefit and I worry that tolerability will be poor (but I don't know this).*

Case #3

- 60 year old woman with unclassifiable disease
  - Past Medical/Social Hx: family history, avid golfer

Pulmonary function test value	% pred
Forced vital capacity (FVC)	78
Diffusion capacity (DLCO)	65



No biopsy

Mild restriction and gas exchange, “possible UIP pattern” HRCT

Case #3
Would you treat this patient?

A. Yes

B. No

Case #3
If so, which agent would you choose?

A. Nintedanib
B. Pirfenidone
C. Either
D. Not sure

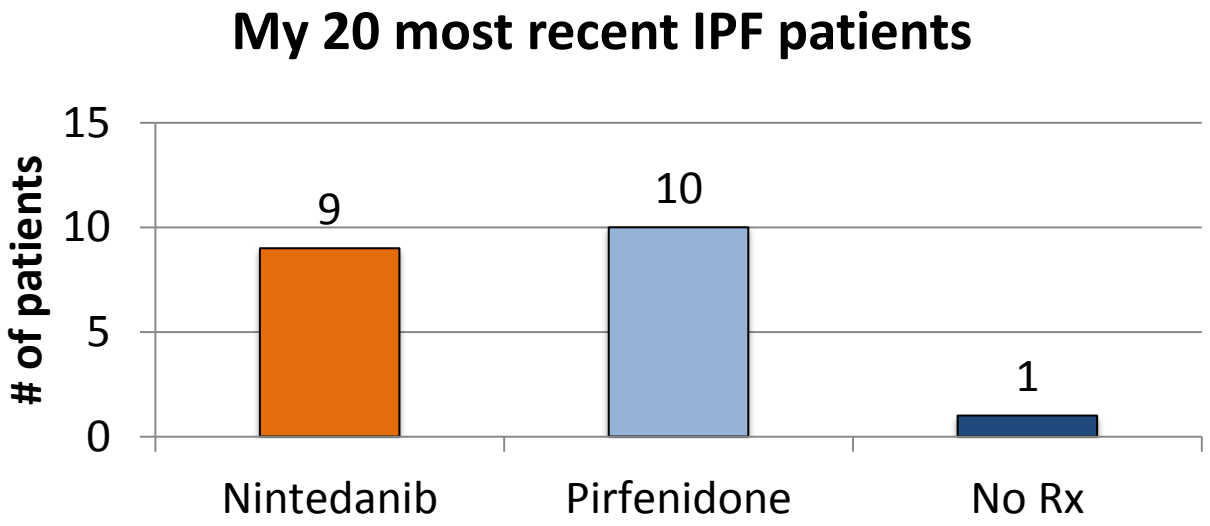
Case #3 My Thoughts

- I would treat this patient
- I would prescribe nintedanib given the sun exposure and concern for photosensitivity rash (and less critically the "possible UIP" CT)

- *Family history strongly suggests IPF to me. This patient would likely have been included in INPULSIS but not ASCEND. Subgroup analysis suggests that the "possible UIP" population benefitted equally from treatment in the INPULSIS dataset.*

Who Do I Treat?

- All patients with IPF except those with severe disease (e.g. transplant candidates)
- Most patients in whom I suspect the diagnosis is IPF but do who not meet ATS criteria



Switching Drugs: When, and is There a Time for Change in Therapy?

KEVIN K. BROWN, MD

Professor of Medicine, Department of Medicine
Vice Chair, Department of Medicine Clinical Affairs
National Jewish Health
Denver, Colorado

Case: Clinical Features

- 69-year-old male
- 12 months DOE
- Intermittent, nonproductive cough
- No systemic complaints (fever, chills, sweats, weight loss, skin, arthralgias, myalgias, upper airway, cardiac or gastrointestinal complaints)

Case: Clinical Features

- PMH
  - CAD – RCA stent 2008
    - LBBB
  - GERD
- Medications
  - Metoprolol, ASA, pravastatin, fluticasone, PPI
- No known allergies

Case: Clinical Features

- Social history
  - Former smoker
    - Quit 35 years ago
    - 16 pack years
- Family history
  - No ILD or autoimmunity

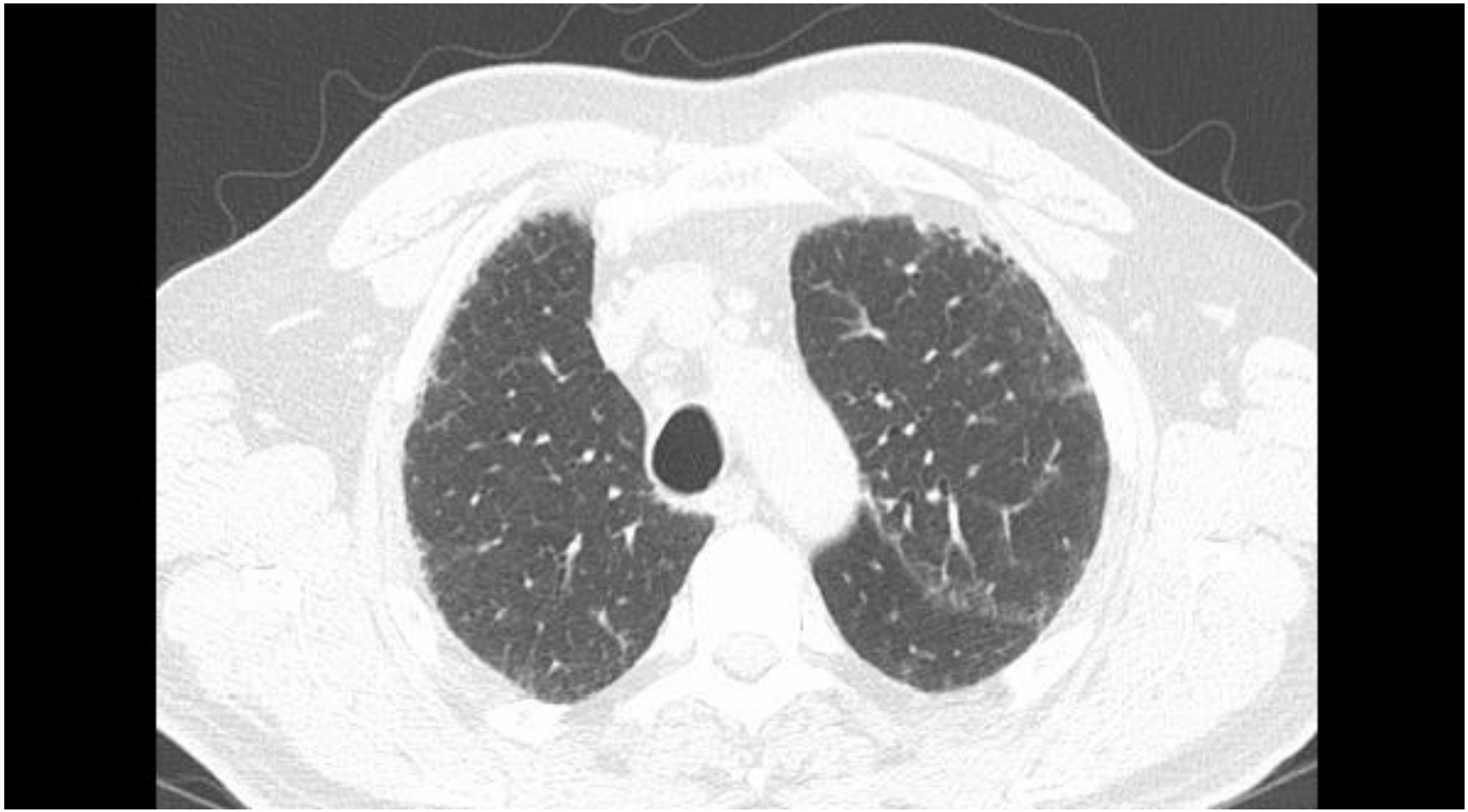
Case: Clinical Features

- Occupational/avocational/environmental history
  - Retired warehouse manager
  - No asbestos
  - No farming or mining
  - No mold or water damage exposure
  - No pets or birds

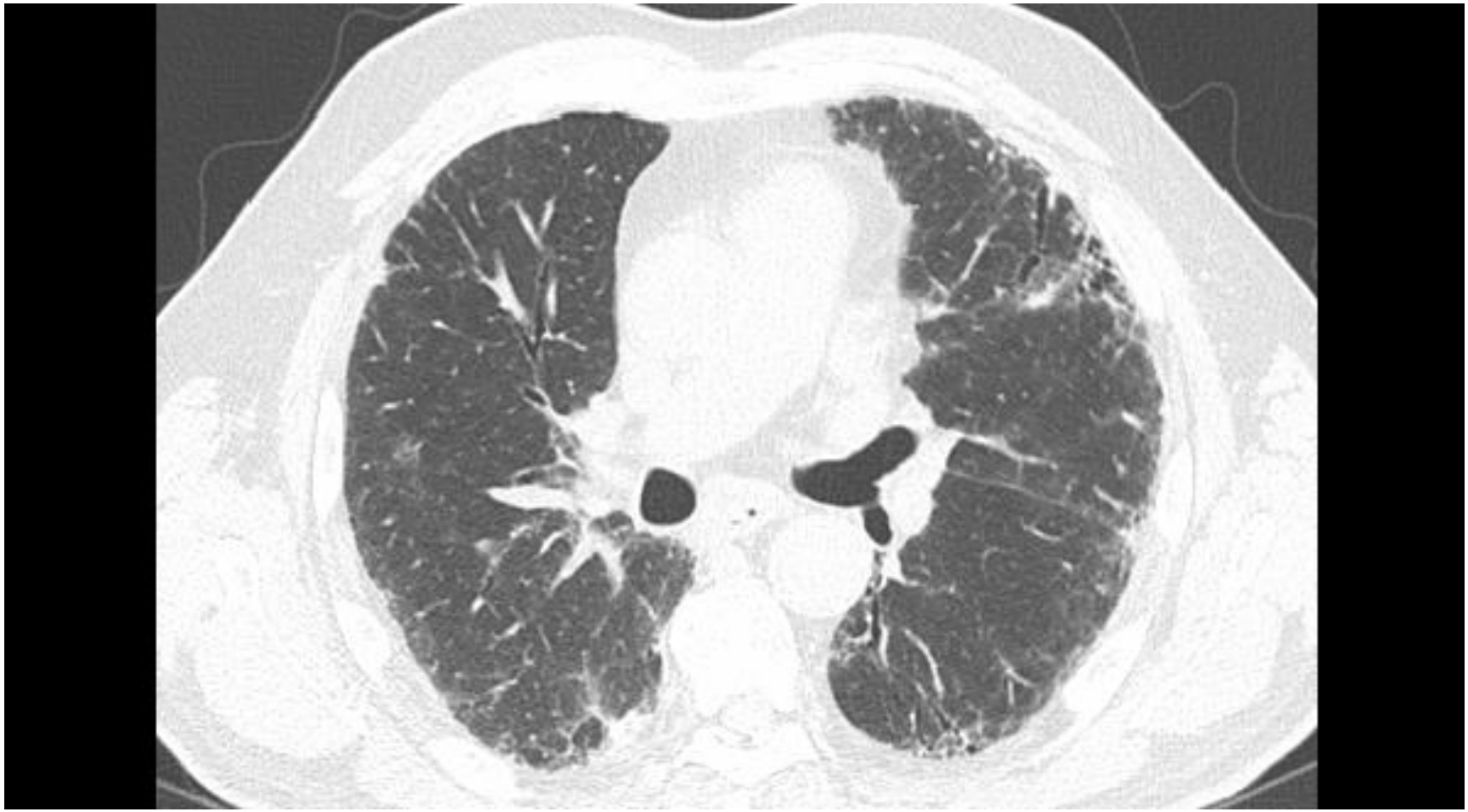
Case: Clinical Features

- Physical examination
  - Normal skin
  - Normal joints
  - No upper airway abnormalities
  - + mid-to-end inspiratory crackles, no wheeze
  - Normal cardiac exam
  - No adenopathy
  - + mild clubbing

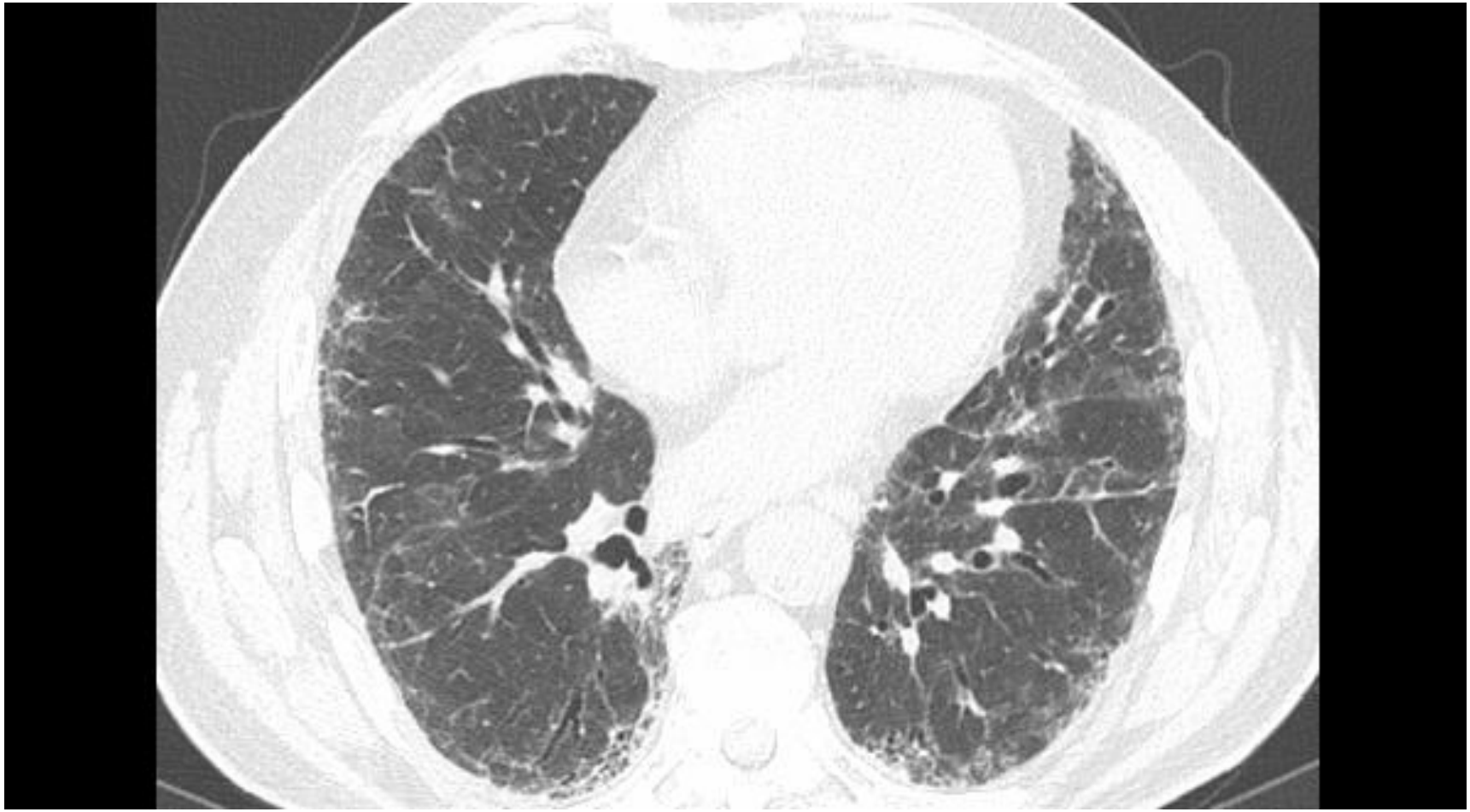
Case: Chest Imaging



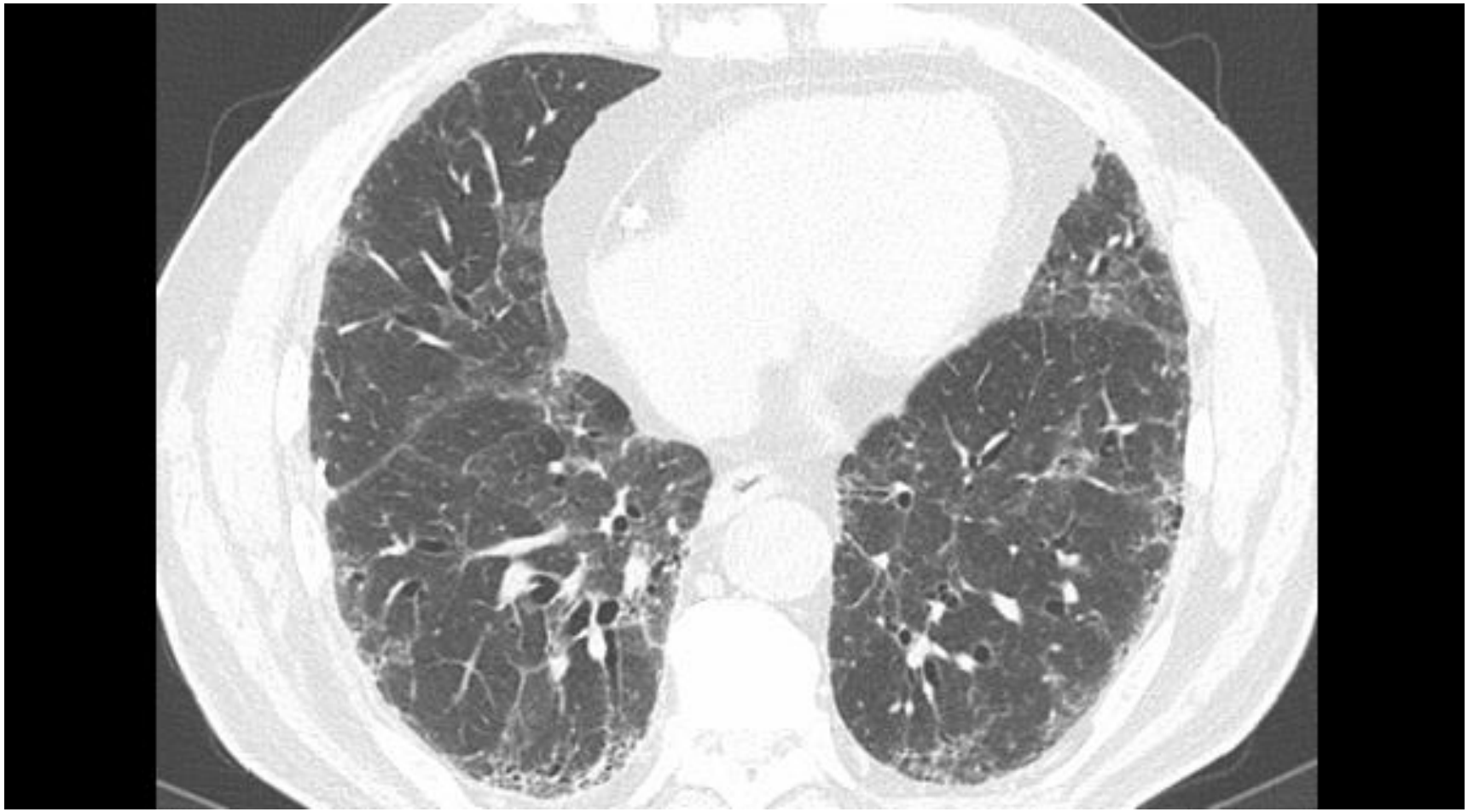
Case: Chest Imaging



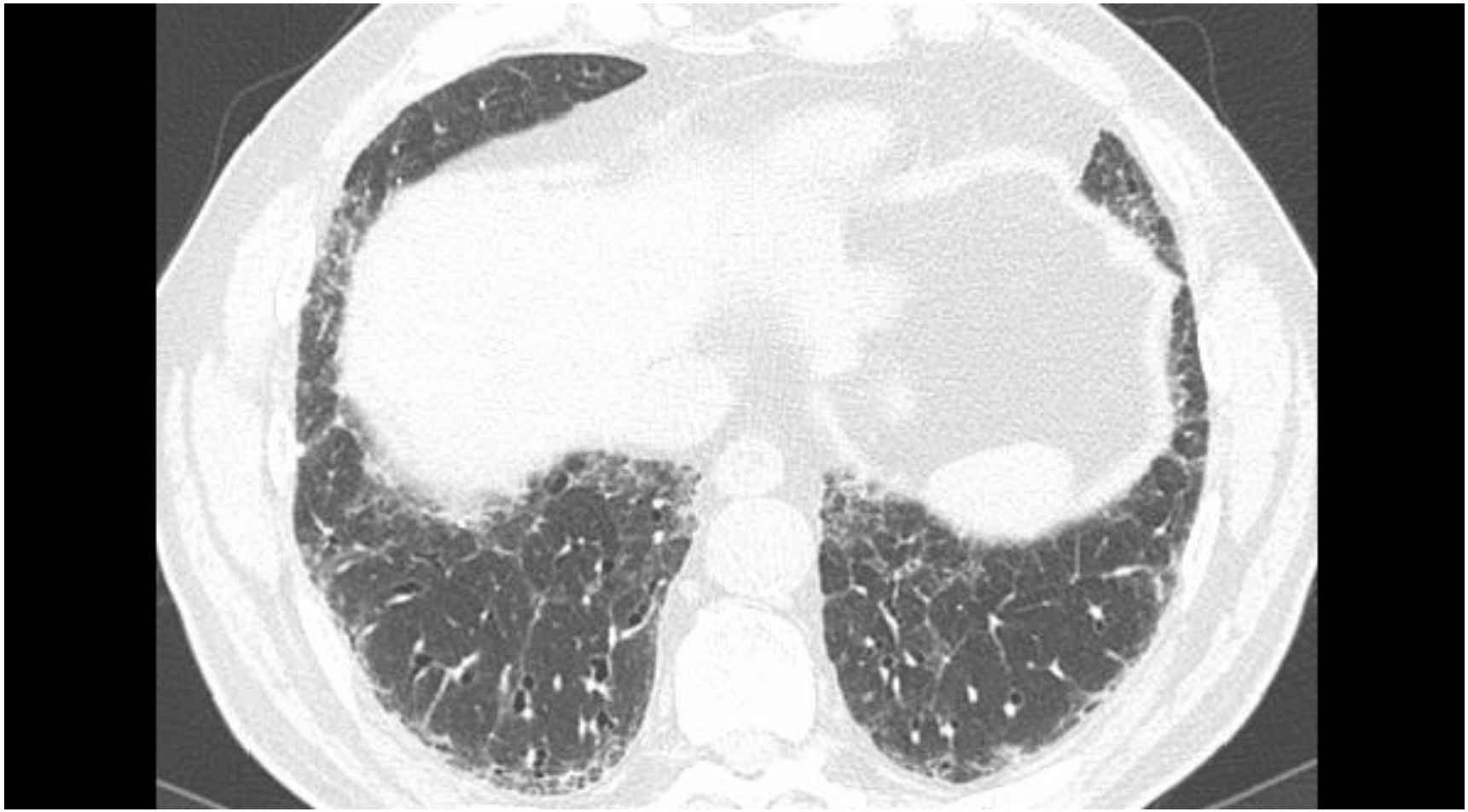
Case: Chest Imaging



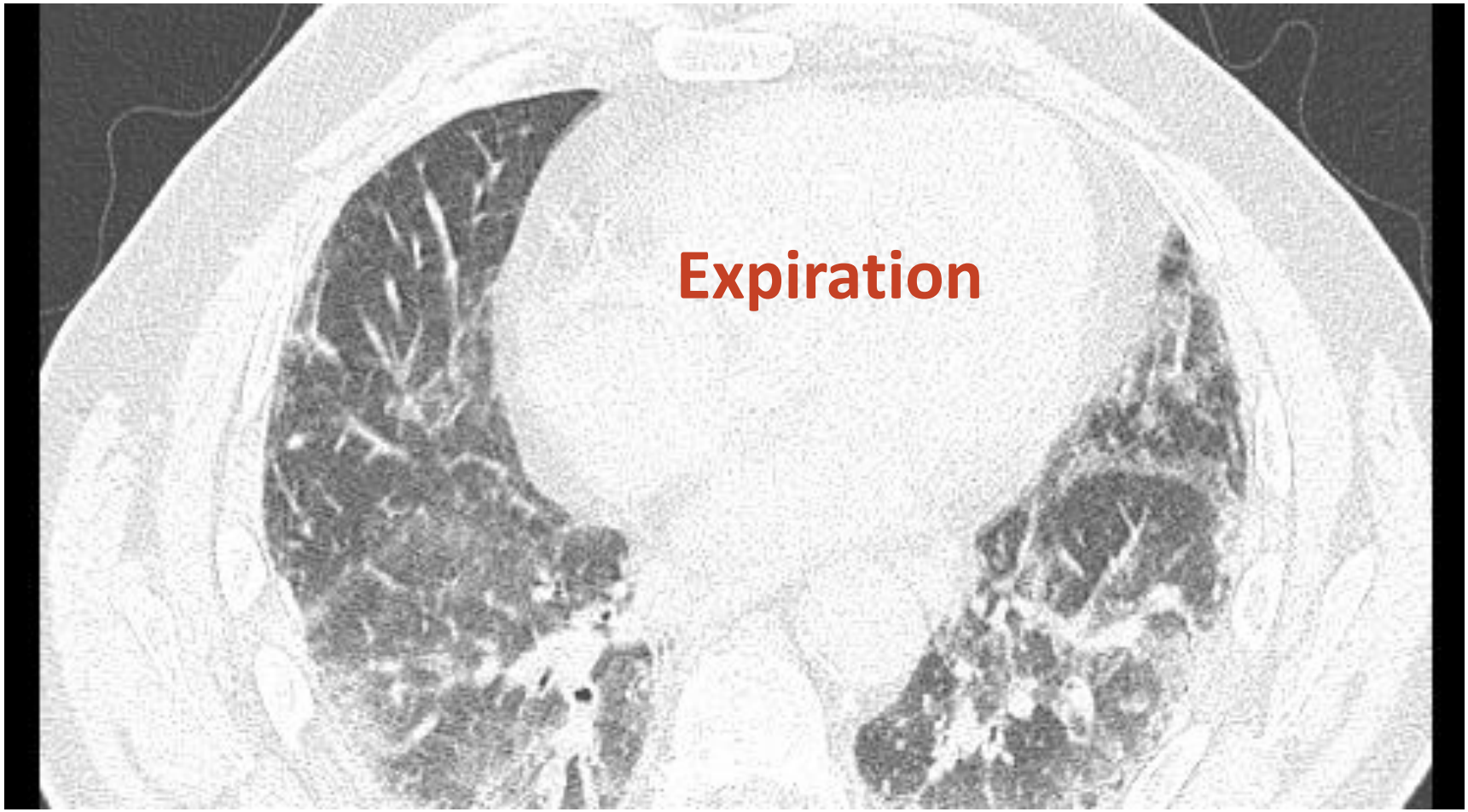
Case: Chest Imaging



Case: Chest Imaging



Case: Chest Imaging



Case: Physiologic Features

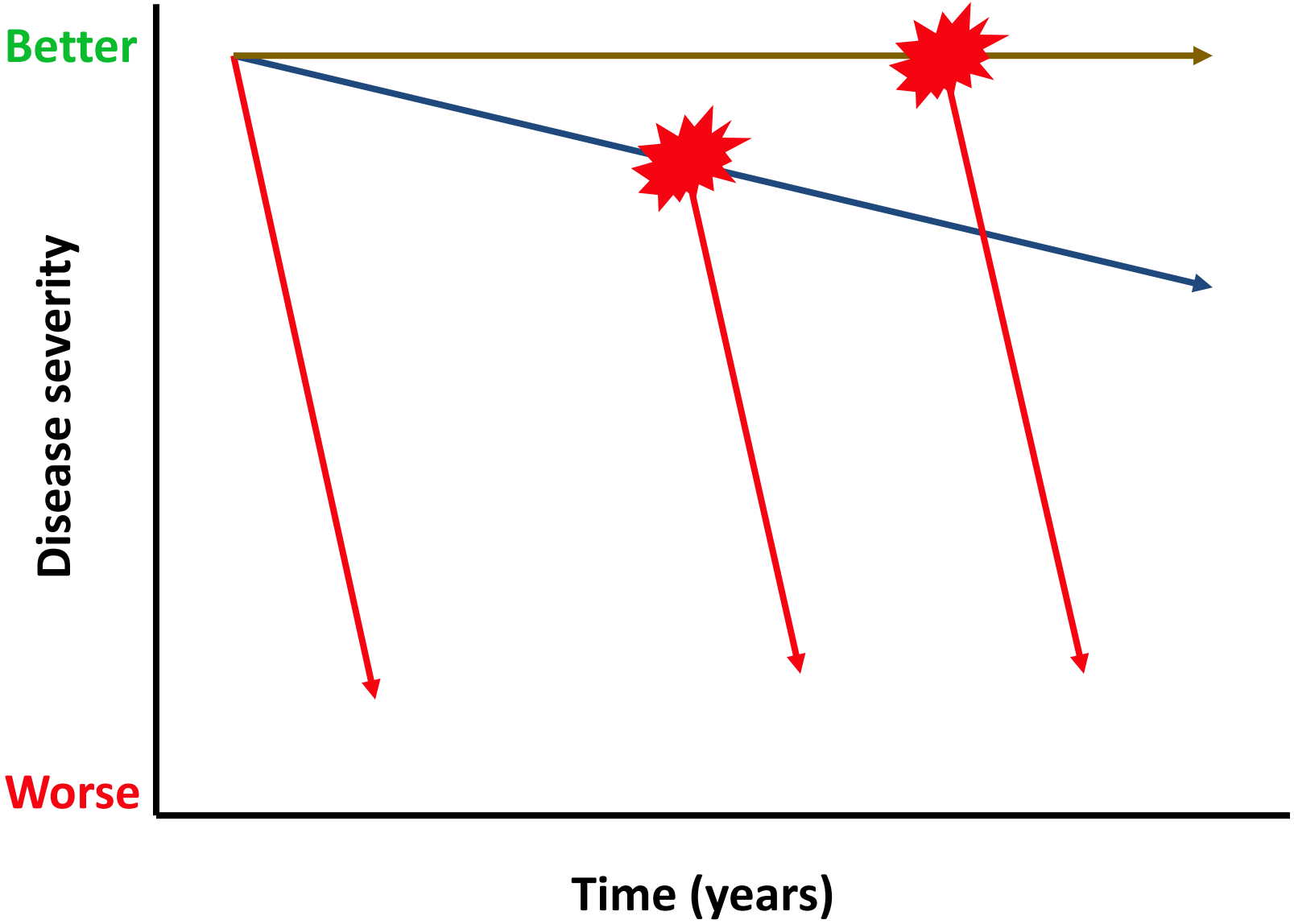
- Labs
  - ANA 1:160 homogeneous
- Pulmonary physiology
  - FVC = 2.1L (60%), FEV1/FVC = 90, DLCO = 15.8 (53%)
- Submaximal exercise and gas exchange
  - 6MWD = 480 m, nadir SpO2 = 88% on RA in Denver

Treatment Questions

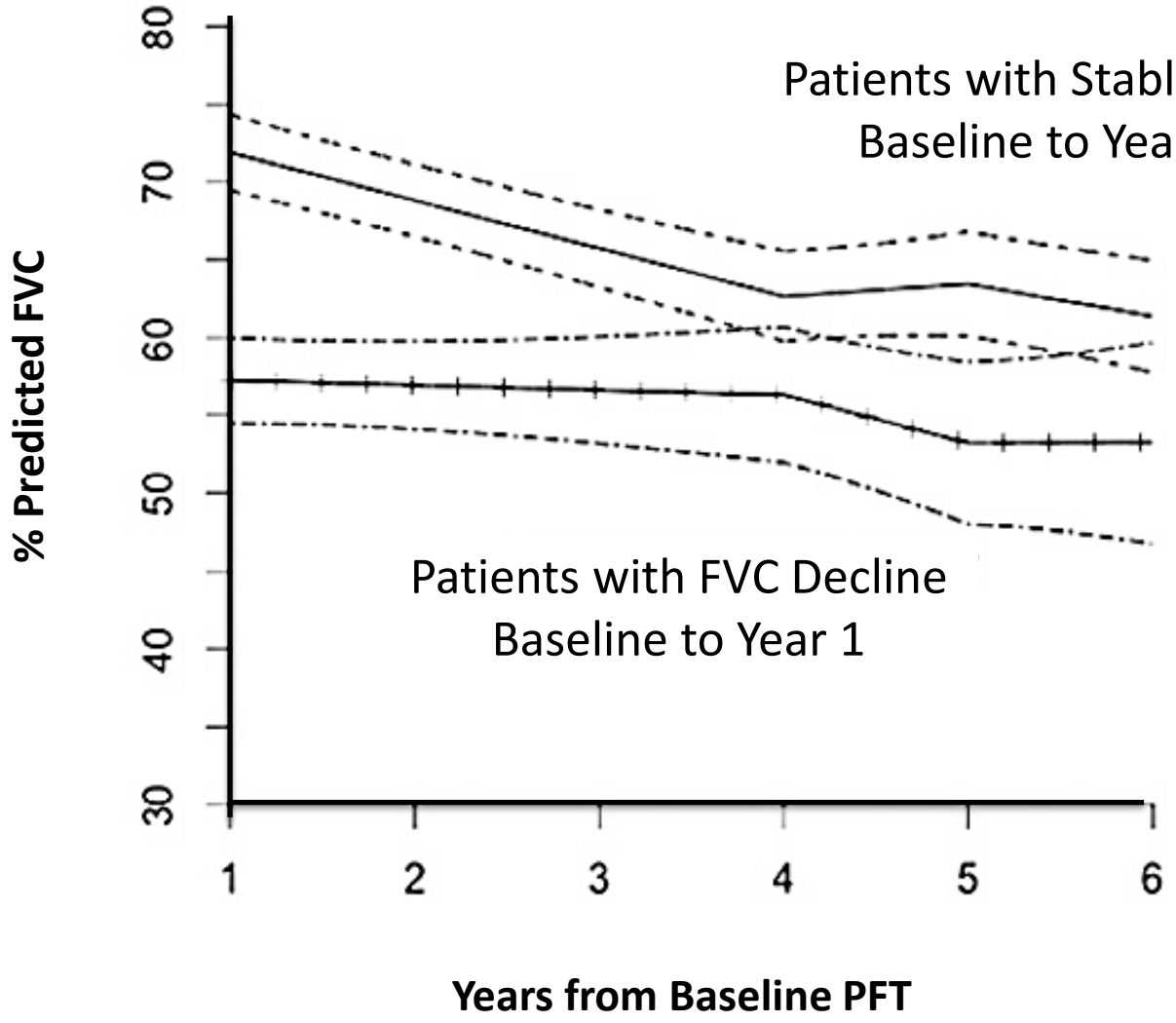
- *What do you expect to happen without treatment?*
- *What do you expect to happen with treatment?*
  - *How are you defining benefit?*
  - *How are you defining failure?*
- *How long should you wait for an effect?*
- *If benefit occurs, how long should you expect it to last?*
- *When treatment failure occurs, what will you do?*

Treatment Questions

- Q ***What do you expect to happen without treatment?***
- Q *What do you expect to happen with treatment?*
  - *How are you defining benefit?*
  - *How are you defining failure?*
- Q *How long should you wait for an effect?*
- Q *If benefit occurs, how long should you expect it to last?*
- Q *When treatment failure occurs, what will you do?*


Better
Disease severity
Worse
Time (years)

An FVC Decline Does Not Predict Future Declines



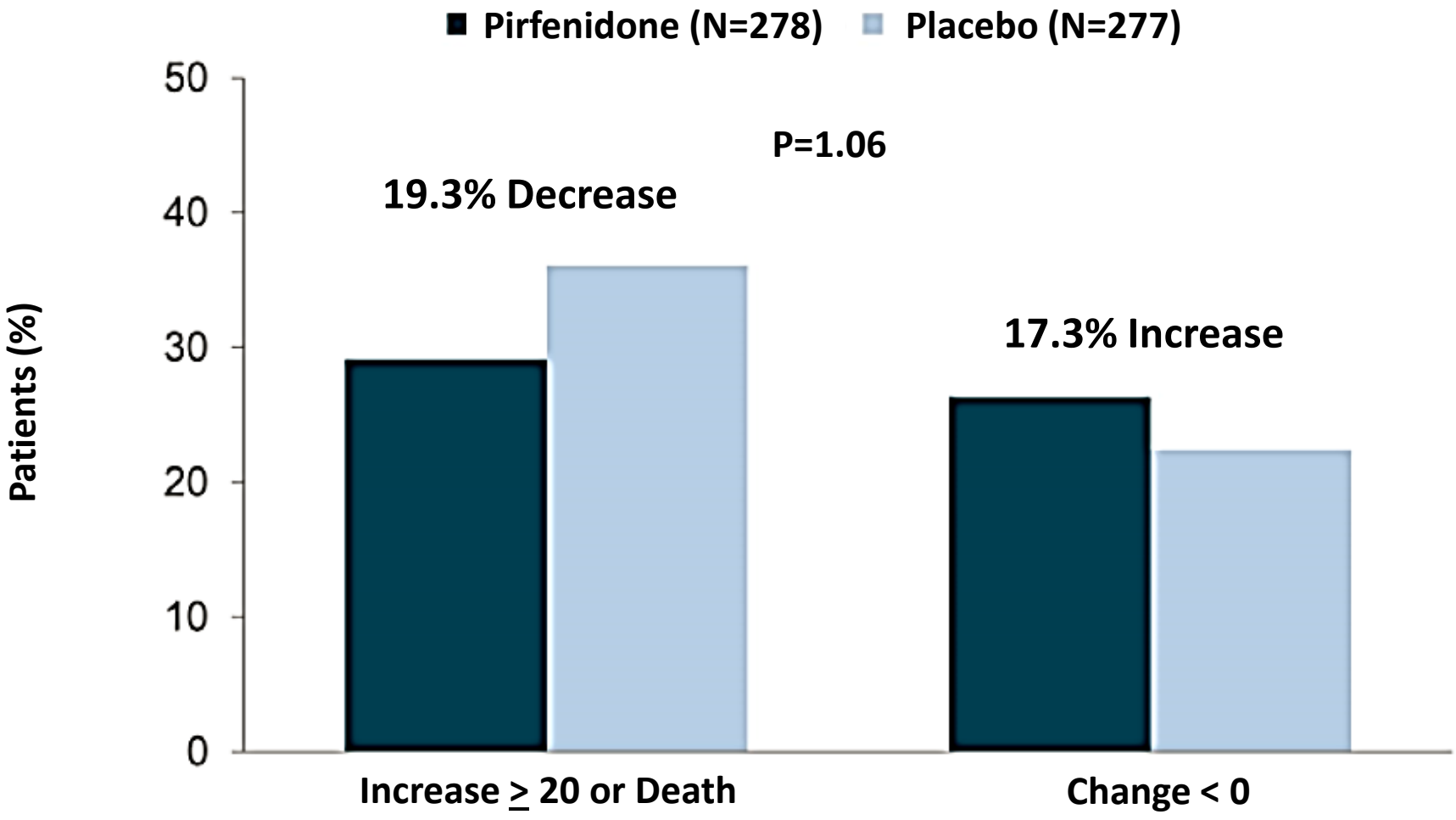
Treatment Questions

- *What do you expect to happen without treatment?*
- ***What do you expect to happen with treatment?***
  - ***How are you defining benefit?***
  - ***How are you defining failure?***
- *How long should you wait for an effect?*
- *If benefit occurs, how long should you expect it to last?*
- *When treatment failure occurs, what will you do?*

Defining Benefit and Failure

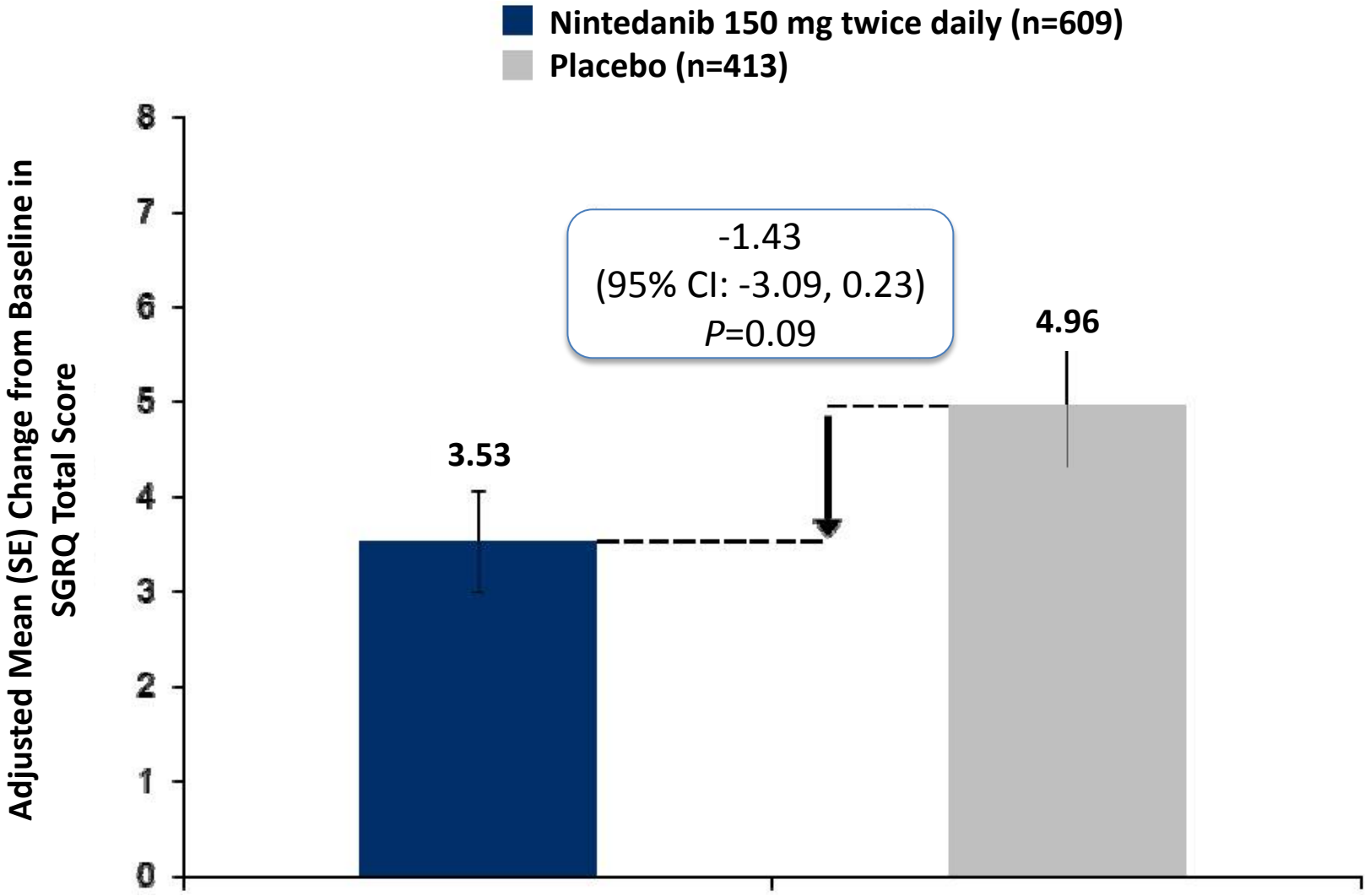
- Symptoms
- Physiology
- Submaximal exercise capacity
- Chest imaging
- Hospitalization

Categorical Change Baseline to Week 52 in UCSD SOBQ Score

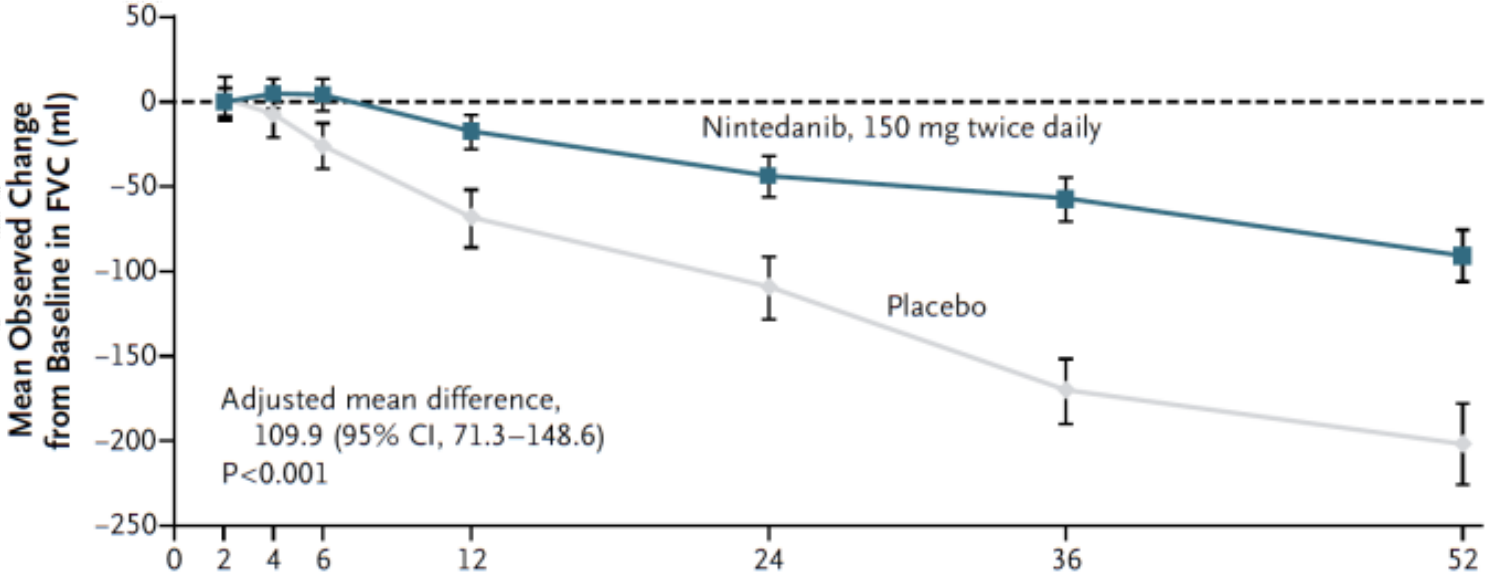


King et al, *New Engl J Med* 2014;370:2083-92.

Change from Baseline in SGRQ Over 52 Weeks (Pooled)



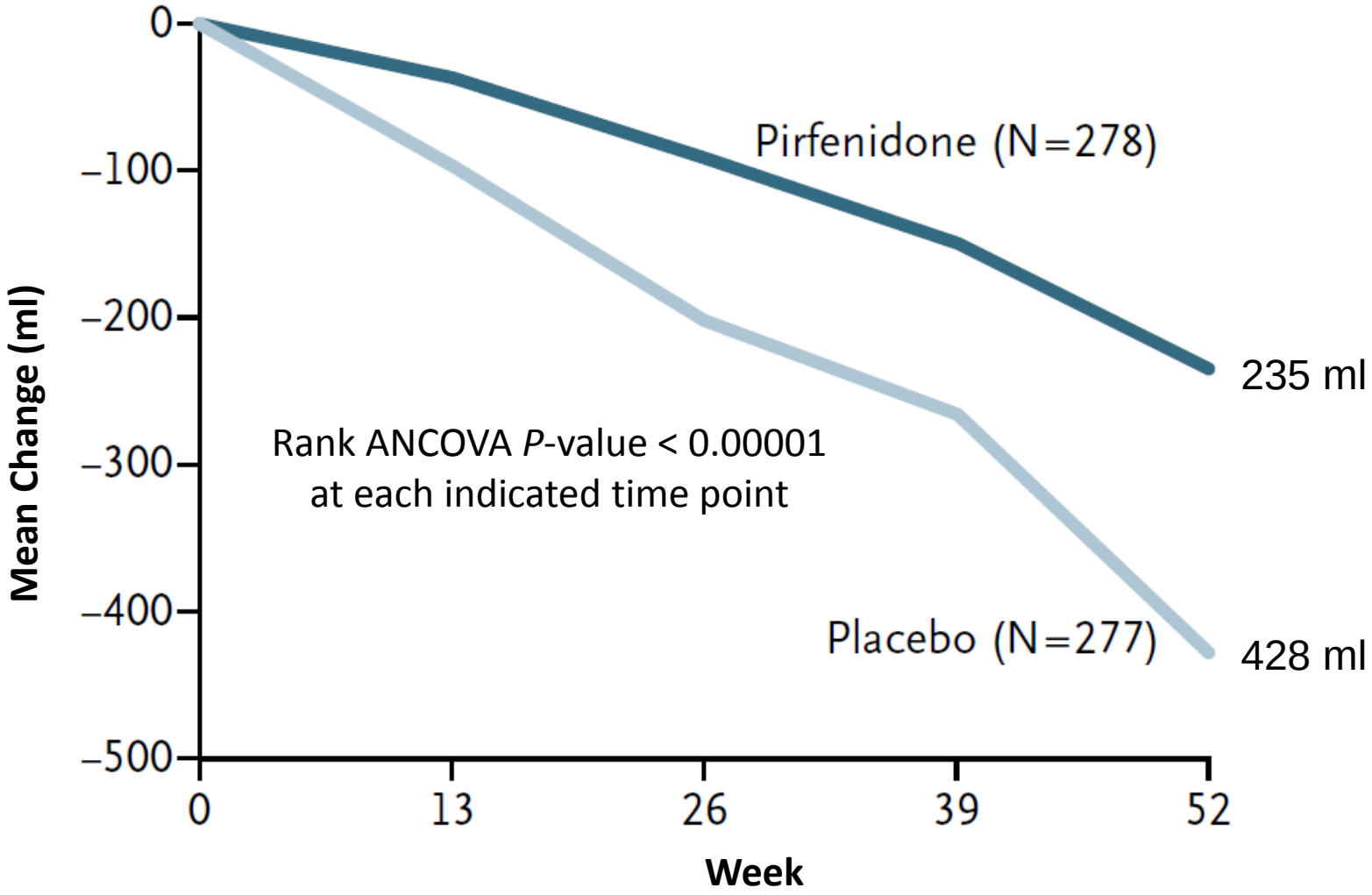
INPULSIS I
Primary End Point: Annual Rate of Decline in FVC



No. of Patients					
Nintedanib	303 301 298	292	284	274	250
Placebo	202 198 200	194	192	187	165

Richeldi L, et al. *N Engl J Med.* 2014;370(22):2071-2082.

FVC Over 52 Weeks



King TE, et al. *N Engl J Med.* 2014;370(22):2083-2092.

Defining Benefit and Failure

	Baseline	Month 3	Month 12	Month 18
FVC (ml)	2.1			
Change				
DLCO	15.8			
6MWD	480			
Nadir SpO2	88%			

Defining Benefit and Failure

	Baseline	Month 3	Month 12	Month 18
FVC (ml)	2.1	2.0		
Change		- 4.7%		
DLCO	15.8	15.0		
6MWD	480	505		
Nadir SpO2	88%	83%		

Defining Benefit and Failure

	Baseline	Month 3	Month 12	Month 18
FVC (ml)	2.1	2.0	1.9	
Change		- 4.7%	- 10%	
DLCO	15.8	15.0	13.8	
6MWD	480	505	480	
Nadir SpO2	88%	83%	83%	

Defining Benefit and Failure

	Baseline	Month 3	Month 12	Month 18
FVC (ml)	2.1	2.0	1.9	1.7
Change		- 4.7%	- 10%	- 20%
DLCO	15.8	15.0	13.8	10
6MWD	480	505	480	450
Nadir SpO2	88%	83%	83%	80%

Treatment Questions

- *What do you expect to happen without treatment?*
- *What do you expect to happen with treatment?*
  - *How are you defining benefit?*
  - *How are you defining failure?*
- ***How long should you wait for an effect?***
- *If benefit occurs, how long should you expect it to last?*
- *When treatment failure occurs, what will you do?*

Treatment Questions

- *What do you expect to happen without treatment?*
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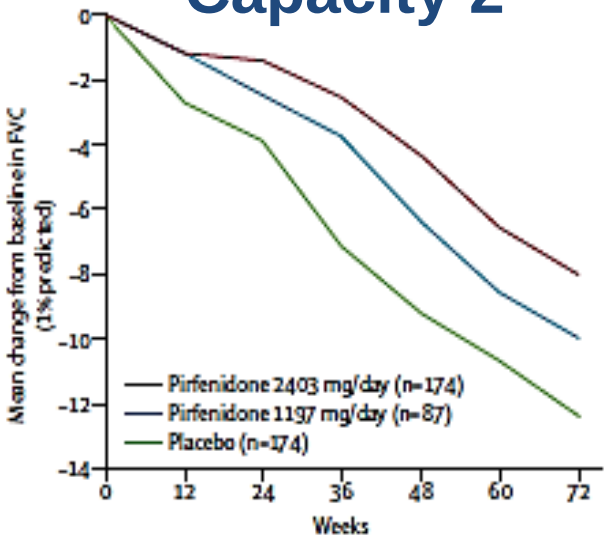
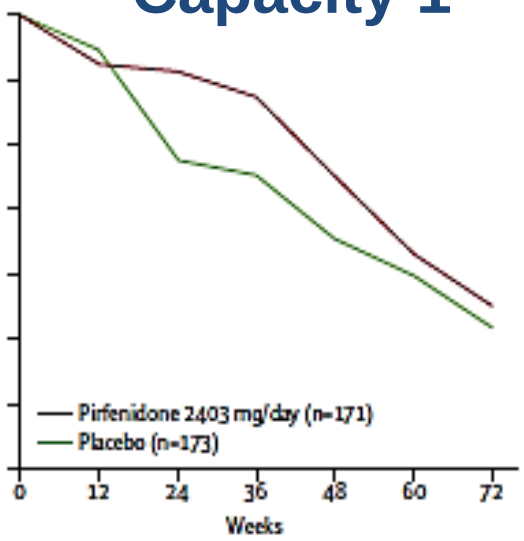
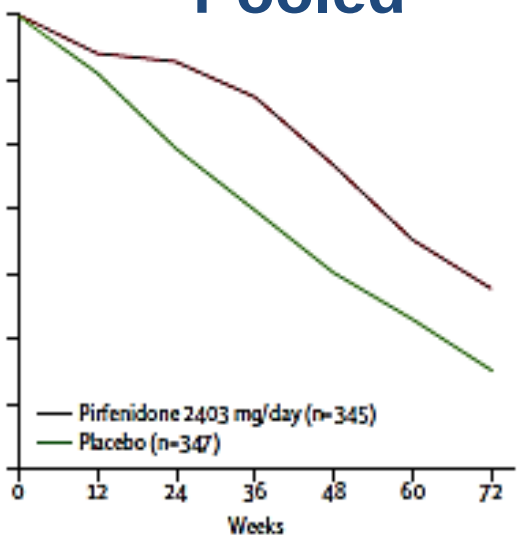
CAPACITY Trials: Primary Endpoint Results







	Capacity 2						Capacity 1						Pooled					
Absolute difference*	1·4%	2·5%	4·6%	4·8%	4·1%	4·4%	−0·4%	2·8%	2·4%	1·9%	0·6%	0·6%	0·5%	2·7%	3·5%	3·3%	2·4%	2·5%
Relative difference*	53·5%	65·2%	63·7%	52·3%	38·3%	35·3%	−31·5%	62·1%	48·2%	27·3%	7·6%	6·5%	28·5%	63·6%	57·5%	41·6%	25·1%	22·8%
p value†	0·061	0·014	0·0001	0·0009	0·0002	0·001	0·021	0·0001	0·011	0·005	0·172	0·501	0·003	<0·0001	<0·0001	<0·0001	0·0003	0·005

Noble P, et al. *Lancet* 2011; 377:1760-9.

Trial Design Comparison: ASCEND vs. CAPACITY

	CAPACITY Trials	ASCEND Trial
Trial/treatment duration	72–120 weeks*	52 weeks
Primary endpoint assessment	72 weeks	52 weeks
Time-to-event analyses duration	120 weeks	52 weeks
Eligibility criteria	Mild to moderate physiologic impairment	Mild to moderate physiologic impairment†
IPF diagnosis (HRCT and SLB)	Site	Centralized
Relatedness of death to IPF	Site	Centralized
Spirometry	Site	Centralized
Total patients enrolled‡	692	555

Long-term Efficacy of Pirfenidone

	Year -1	Year 1	Year 2	Year 3
FVC (ml)	-163 ± 230	-30 ± 224	-158 ± 258	-201 ± 367
N	38	68	47	16

Bando M et al. ATS International Conference; May 2014, San Diego, Ca. A1431.

Treatment Questions

- *What do you expect to happen without treatment?*
- *What do you expect to happen with treatment?*
  - *How are you defining benefit?*
  - *How are you defining failure?*
- *How long should you wait for an effect?*
- *If benefit occurs, how long should you expect it to last?*
- ***When treatment failure occurs, what will you do?***

Managing Side Effects and Dosing: Need for Individualized Strategies?

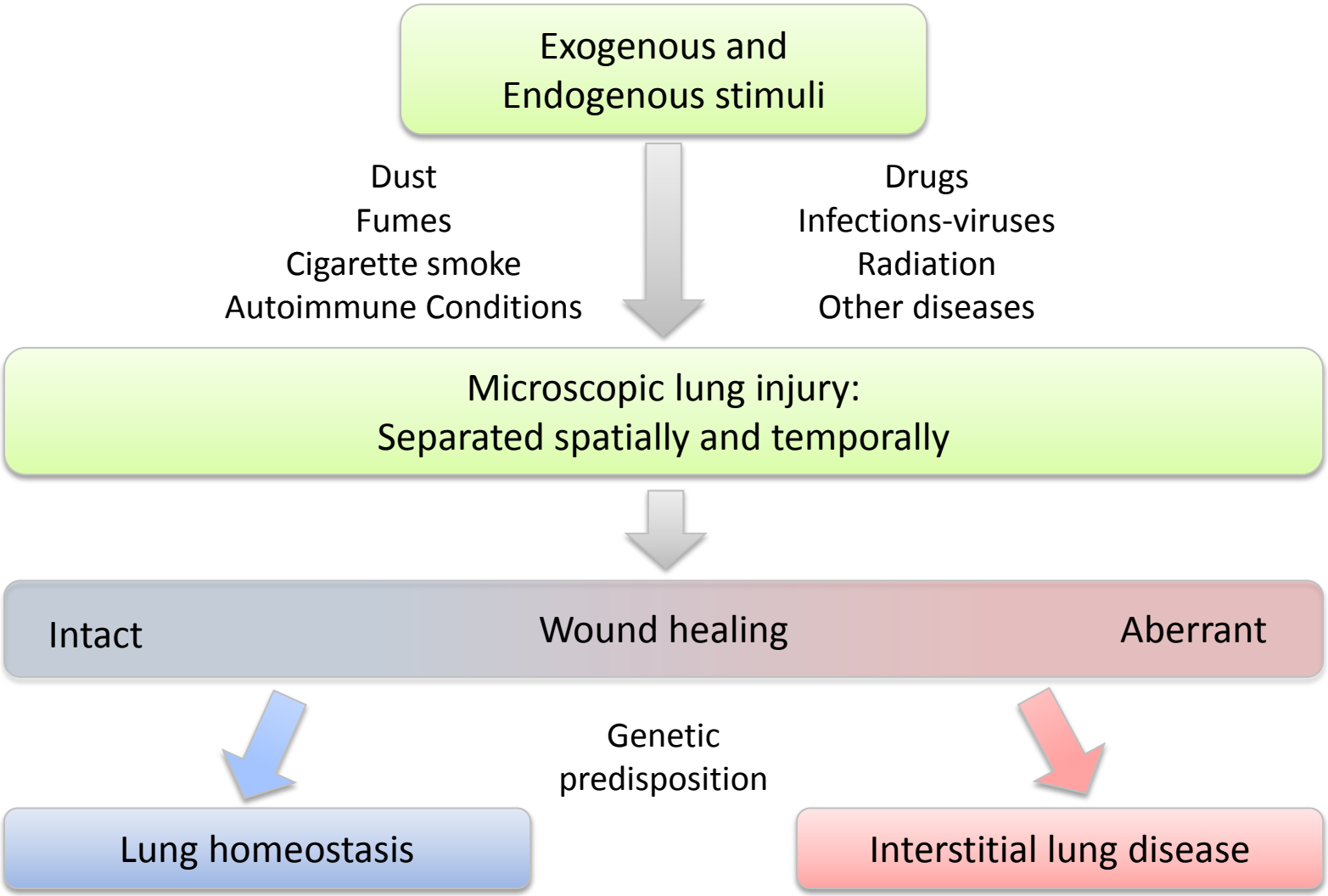
MARILYN K. GLASSBERG, MD

Professor of Medicine and Surgery
Director, Interstitial Lung Disease Program
Miller School of Medicine
Miami, Florida

Two Cases and Two Choices

- Bill treated with nintedanib
- Betsy treated with pirfenidone

ILD Disease Pathway



Steele MP, Schwartz DA. *Annu Rev Med.* 2013;64:265-276.

Common Complications and Comorbidities of IPF

Remember these even when patients are on treatment:

- Acute exacerbation
- Pulmonary hypertension
- GERD
- Emphysema
- OSA
- Cardiac disease

PILOT™ Pulmonary Fibrosis Identification: Lessons for Optimizing Treatment

Bill

www.PILOTforIPF.org

Patient 1: Bill

- 66-year-old dentist
- Diagnosed with IPF 6 months ago
- Nintedanib was initiated 4 months ago
- Patient complains of GI upset and frequent diarrhea

PFTs

Test	Result
FVC	2.00 liters (62% pred) (68% at diagnosis 6 months ago)
FEV_1	1.88 liters (72% pred)
FEV_1/FVC	94%
TLC	2.59 liters (67% pred)
DL_{CO}	51% pred

- 6MWT: 94% at nadir on room air
- Distance walked: 359 m

LFT History

- Normal ALT, AST, and bilirubin prior to initiation of nintedanib 4 months ago
- He was tested monthly for the first 3 months and was noted to have slightly increased AST (> 3x ULN but < 5x ULN) on month 3 labs

What is the Best Course for Bill?

A. Switch to pirfenidone
B. Switch to NAC
C. Hold nintedanib
D. Reduce nintedanib dose
E. Switch to high dose prednisone
F. Manage diarrhea with loperamide

Liver Enzyme and Bilirubin Elevations Observed in INPULSIS™ Trials

	Placebo (n=423), % (n)	Nintedanib 150 mg (n=638), % (n)
Maximum ALT		
≥ 3 ULN	0.7 (3)	4.4 (28)
≥ 5 ULN	0.0 (0)	1.6 (10)
≥ 8 ULN	0.0 (0)	0.6 (4)
Maximum AST		
≥ 3 ULN	0.2 (1)	3.3 (21)
≥ 5 ULN	0.2 (1)	1.3 (8)
≥ 8 ULN	0.2 (1)	0.6 (4)
Maximum ALT and/or AST		
≥ 3 ULN	0.7 (3)	5.0 (32)
≥ 5 ULN	0.2 (1)	2.2 (14)
≥ 8 ULN	0.2 (1)	0.8 (5)
Maximum ALT and/or AST		
≥ 2 ULN	0.5 (2)	0.5 (3)
ALT and/or AST ≥ 3 ULN, bilirubin ≥ 2 ULN	0.2 (1)	0.0 (1)

Important Safety Information

Warnings and Precautions

Elevated Liver Enzymes

- The safety and efficacy of OFEV® (nintedanib) has not been studied in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Treatment with nintedanib is not recommended in patients with moderate or severe hepatic impairment.
- In clinical trials, administration of nintedanib was associated with elevations of liver enzymes (ALT, AST, ALKP, GGT) and bilirubin. Liver enzyme increases were reversible with dose modification or interruption and not associated with clinical signs or symptoms of liver injury.
- Conduct liver function tests (ALT, AST, and bilirubin) prior to treatment with nintedanib, monthly for 3 months, and every 3 months thereafter, and as clinically indicated. Dosage modifications, interruption, or discontinuation may be necessary for liver enzyme elevations.

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails/. Accessed October 2014.

Dose Modification with Nintedanib

Event	Dose Modification Recommendations
Management of adverse reactions	• In addition to symptomatic treatment: – Consider dose reduction or treatment interruption – Continue therapy when adverse reaction resolves to acceptable levels; nintedanib treatment may be resumed at the full dosage (150 mg bid), or at the reduced dosage (100 mg bid), which subsequently may be increased to the full dosage
Patient does not tolerate nintedanib 100 mg bid	• Discontinue treatment with nintedanib
AST or ALT > 3x to < 5x ULN without signs of severe liver damage	• Dose modifications or interruptions may be necessary for liver enzyme elevations • Interrupt treatment or reduce nintedanib to 100 mg bid • Once liver enzymes have returned to baseline values, treatment may be reintroduced at a reduced dose (100 mg bid), which may subsequently be increased to the full dosage (150 mg bid)
AST or ALT > 5x ULN or > 3x ULN with signs or symptoms of severe liver damage	• Discontinue nintedanib

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails/. Accessed October 2014.

Diarrhea and Nintedanib

- Most events were mild to moderate in severity
- Diarrhea is worse in the first 3 months
- Must manage the diarrhea
- Loperamide is included in the specialty pharmacy delivery of nintedanib

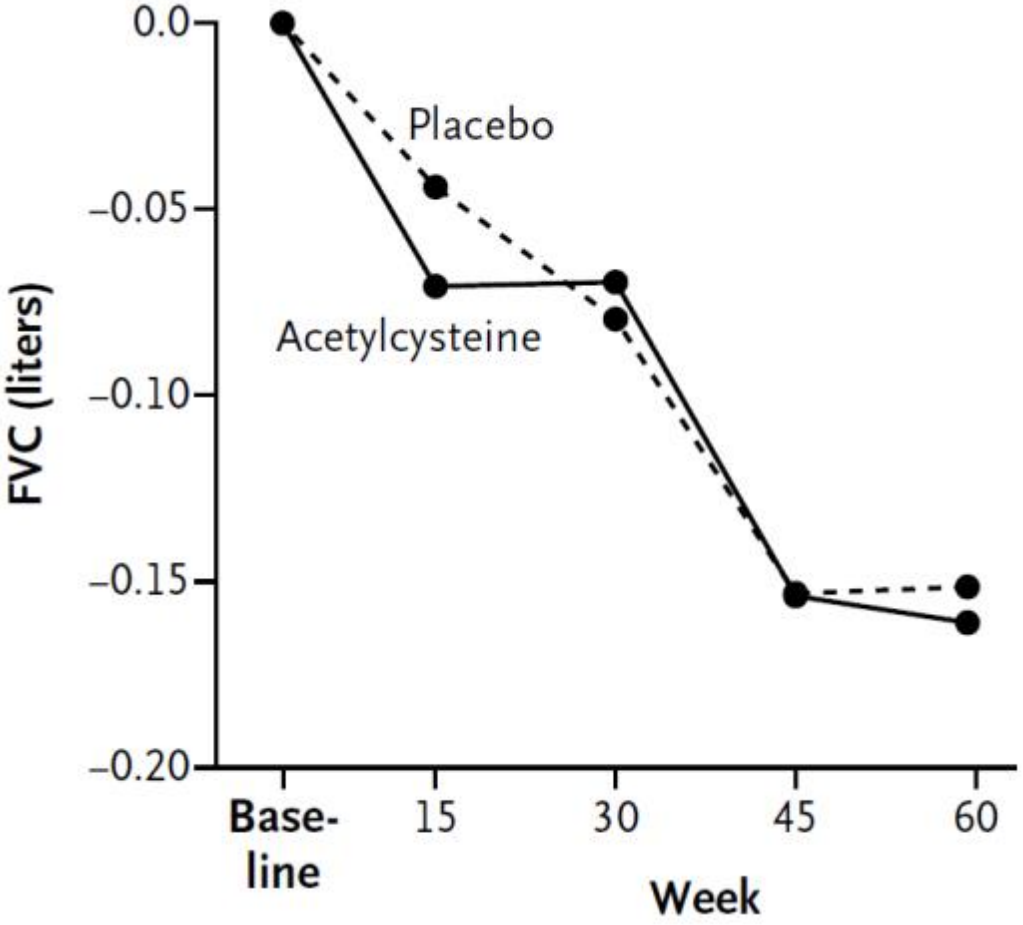
Management of Bill's Abnormal AST

- His dose was stopped for 1 week
- He was prescribed loperamide to manage diarrhea
- LFTs were repeated with normalization of AST
- Diarrhea improved
- Nintedanib was restarted at 150 mg bid

Other Treatment Options for Bill?

A. Prednisone
B. Prednisone and NAC
C. NAC alone
D. Colchicine
E. Add pirfenidone to nintedanib
F. None of the above

PANTHER: NAC Does Not Reduce FVC Decline



Conclusion: NAC offered no significant benefit with respect to the preservation of FVC in patients with IPF with mild-to-moderate impairment in lung function

Martinez FJ, et al. *N Engl J Med.* 2014;370(22):2093-2101.

Nintedanib Adverse Reactions

Adverse Reaction (> 15%)	Nintedanib 300 mg/day (n = 723)	Placebo (n = 508)
Gastrointestinal disorders		
Diarrhea	62%	18%
Nausea	24%	7%
Abdominal pain	15%	6%

- Other reactions noted less frequently: vomiting, liver enzyme elevation, decreased appetite, headache, weight decreased, hypertension, hypothyroidism

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails/. Accessed October 2014.

Nintedanib Warnings and Precautions

- Elevated liver enzymes: ALT, AST, and bilirubin elevations have occurred with nintedanib. Monitor ALT, AST, and bilirubin before and during treatment. Temporary dosage reductions or discontinuations may be required.
- **GI disorders: Diarrhea, nausea, and vomiting have occurred with nintedanib. Treat patients at first signs with adequate hydration and antidiarrheal medicine (e.g., loperamide) or anti-emetics. Discontinue nintedanib if severe diarrhea, nausea, or vomiting persists despite symptomatic treatment.**
- Embryofetal toxicity: Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant.
- Arterial thromboembolic events have been reported. Use caution when treating patients at higher cardiovascular risk including known CAD.
- Bleeding events have been reported. Use nintedanib in patients with known bleeding risk only if anticipated benefit outweighs the potential risk.
- GI perforation has been reported. Use nintedanib with caution when treating patients with recent abdominal surgery. Discontinue nintedanib in patients who develop GI perforation. Only use nintedanib in patients with known risk of GI perforation if the anticipated benefit outweighs the potential risk.

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails/. Accessed October 2014.

Nintedanib Dosage and Administration

- 150 mg twice daily approximately 12 hours apart, taken with food
- **Consider temporary dose reduction to 100 mg, temporary interruption, or discontinuation for management of adverse reactions**
- Prior to treatment, conduct liver function tests

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search. DrugDetails/. Accessed October 2014.

Nintedanib: Other Considerations

- **Drug interactions**
  - **Nintedanib is a substrate of P-glycoprotein (P-gp) and CYP3A4**
  - **Concomitant use of P-gp and CYP3A4 inducers with nintedanib should be avoided**
  - **Patients treated with P-gp and CYP3A4 inhibitors and nintedanib should be monitored closely for adverse reactions**
- Nintedanib is a VEGFR inhibitor, and may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust anticoagulation treatment as necessary.
- Nintedanib not recommended for patients with moderate or severe hepatic impairment
- < 1% excreted via the kidney; no data on patients with severe renal impairment and ESRD

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails/. Accessed October 2014.

P450 Drug Interactions

3A4, 5, 7 Inhibitors

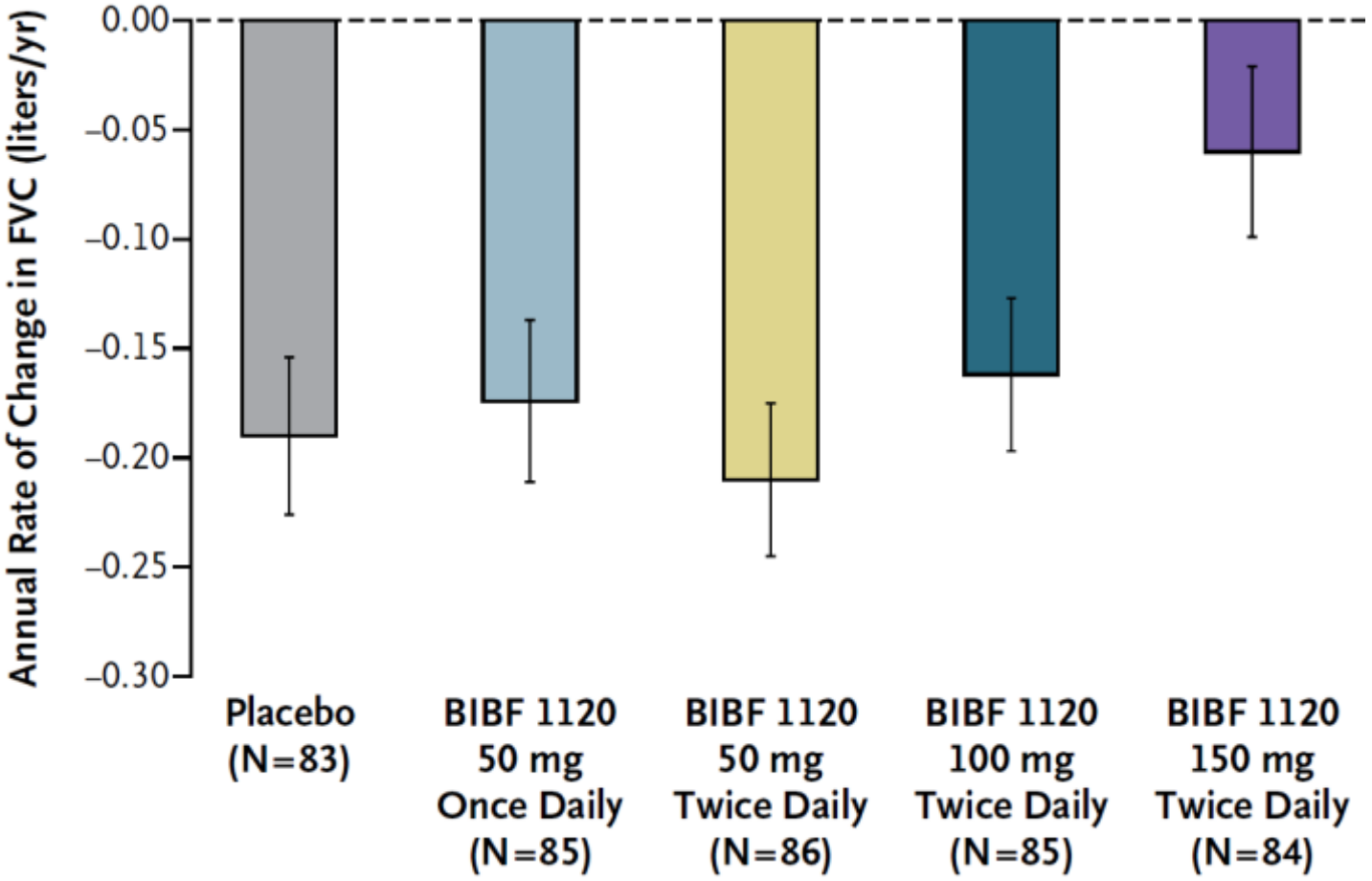
- Strong: indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone
- Moderate: erythromycin, grapefruit juice, verapamil, suboxone, diltiazem
- Weak: cimetidine

3A4, 5, 7 Inducers

- Carbamazepine, efavirenz, nevirapine, phenobarbitol, phenytoin, pioglitazone, rifabutin, rifampin, St. John's Wort

http://medicine.iupui.edu/clinpharm/ddis/clinical-table. Accessed May 2015.

Is a Lower Dose of Nintedanib Effective?



Richeldi L, et al. *N Engl J Med*. 2011;365(12):1079-87.

What is the Best Course for Bill?

A. Switch to pirfenidone
B. Switch to NAC
C. Hold nintedanib
D. Reduce nintedanib dose
E. Switch to high dose prednisone
F. Manage diarrhea with loperamide

Treatment Options for Bill?

- Temporary dose reduction to 100 mg, temporary interruption, or discontinuation for management of adverse reactions
- Manage diarrhea

A.I.D.: An Approach to Managing Gastrointestinal Adverse Reactions

a

ADVISE your patients before initiating nintedanib

Talk to your patients about the possibility of experiencing GI adverse reactions while taking nintedanib

- Inform patients that GI disorders such as diarrhea, nausea, and vomiting were the most commonly reported GI events occurring in patients who received nintedanib
- Recommend that they notify you at the first signs of symptoms or for any severe or persistent diarrhea, nausea, or vomiting

i

INITIATE symptomatic treatment at the first signs of symptoms

At onset, treat with:

- Adequate hydration for patients experiencing diarrhea, vomiting, or nausea
- Antidiarrheal medication (eg, loperamide) for patients experiencing diarrhea
- Antiemetic medication for patients experiencing nausea or vomiting

d

DOSE MODIFICATION may be required if GI side effects are persistent or severe despite symptomatic treatment

Dose reduction, treatment interruption, or discontinuation may be required

- Dose reduction and/or temporary interruption may be required until the specific adverse reaction resolves to levels that allow continuation of therapy. Nintedanib may be resumed at the full dose (150 mg bid) or at the reduced dose (100 mg bid), which subsequently may be increased to the full dose
- If a patient does not tolerate 100 mg bid, treatment with nintedanib should be discontinued
- If severe symptoms persist, nintedanib should be discontinued

https://hcp.ofev.com/adverse-reactions/gastrointestinal-management. Accessed May 2015.

Lessons/Questions from Bill

- What about adding pirfenidone to the nintedanib?
- Don’t add Prednisone or NAC based on PANTHER
- Liver enzyme abnormalities are manageable
- Nintedanib is only indicated for patients with IPF
- There are no FDA approved indications for other interstitial diseases including hypersensitivity pneumonitis (with UIP pathology) or autoimmune related lung disease

PILOT™ Pulmonary Fibrosis Identification: Lessons for Optimizing Treatment

Betsy

www.PILOTforIPF.org

Patient 2: Betsy

- 70-year-old small business owner (landscaping/garden design) with mild hypertension
- Diagnosed with IPF 4 years ago
- Previously treated with Prednisone
- Switched to pirfenidone in December 2014 and titrated to two tablets three times a day when she noted skin rash at week 3 of treatment
- Dermatologist told her to continue taking all her medications

PFTs

Test	Result
FVC	3.69 liters (90% pred) (92% at diagnosis 4 years ago)
FEV_1	2.98 liters (88% pred)
FEV_1/FVC	94%
TLC	2.89 liters (70% pred)
DL_{CO}	14.7 (48% pred)

What is the Best Course for Betsy?

A. Switch to nintedanib
B. Switch to NAC
C. Hold pirfenidone
D. Reduce pirfenidone dose
E. Switch to high dose prednisone
F. Manage rash with topical ointment, sunscreen

Pirfenidone Adverse Reactions

Adverse Reaction (> 15%)	% of Patients (0 to 118 Weeks) Pirfenidone 2403 mg/day (N = 623)	Placebo (N = 624)
Nausea	36%	16%
Rash	30%	10%
Abdominal Pain	24%	15%
Upper Respiratory Tract Infection	27%	25%
Diarrhea	26%	20%
Fatigue	26%	19%
Headache	22%	19%
Dyspepsia	19%	7%
Dizziness	18%	11%
Others (less frequently): vomiting , anorexia, GERD, sinusitis, insomnia, weight decreased, arthralgia		

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails/. Accessed October 2014.

Pirfenidone Warnings and Precautions

Temporary dosage reductions or discontinuations may be required

- Elevated liver enzymes: ALT, AST, and bilirubin elevations have occurred with pirfenidone. Monitor ALT, AST, and bilirubin before and during treatment.
- **Photosensitivity and rash: Photosensitivity and rash have been noted with pirfenidone. Avoid exposure to sunlight and sunlamps. Wear sunscreen and protective clothing daily.**
- Gastrointestinal disorders: Nausea, vomiting, diarrhea, dyspepsia, gastro-esophageal reflux disease, and abdominal pain have occurred with pirfenidone.

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails/. Accessed October 2014.

Pirfenidone Dosage and Administration

- 801 mg (three 267 mg capsules) three times daily with food
- Doses should be taken at the same time each day
- Initiate with titration
  - Days 1 through 7: 1 capsule 3x per day
  - Days 8 through 14: 2 capsules 3x per day
  - Days 15 onward: 3 capsules 3x per day
- **Consider temporary dosage reduction, treatment interruption, or discontinuation for management of adverse reactions**

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails/. Accessed October 2014.

Pirfenidone: Other Considerations

- Post-marketing experience (reactions of unknown frequency)
  - Agranulocytosis
  - Angioedema
  - Bilirubin increased in combination with increases of ALT and AST
- **Drug interactions**
  - **Metabolized primarily via CYP1A2**
  - **Activators and inhibitors of CYP1A2 should be used with caution with pirfenidone**
- Use with caution with mild/moderate hepatic impairment, not recommended for patients with severe impairment
- Use with caution with mild/moderate/severe renal impairment, not recommended for patients with ESRD requiring dialysis
- Smoking causes decreased exposure to pirfenidone. Instruct patients to stop smoking prior to treatment with pirfenidone and to avoid smoking when using pirfenidone.

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails/. Accessed October 2014.

P450 Drug Interactions

CYP1A2 Inhibitors

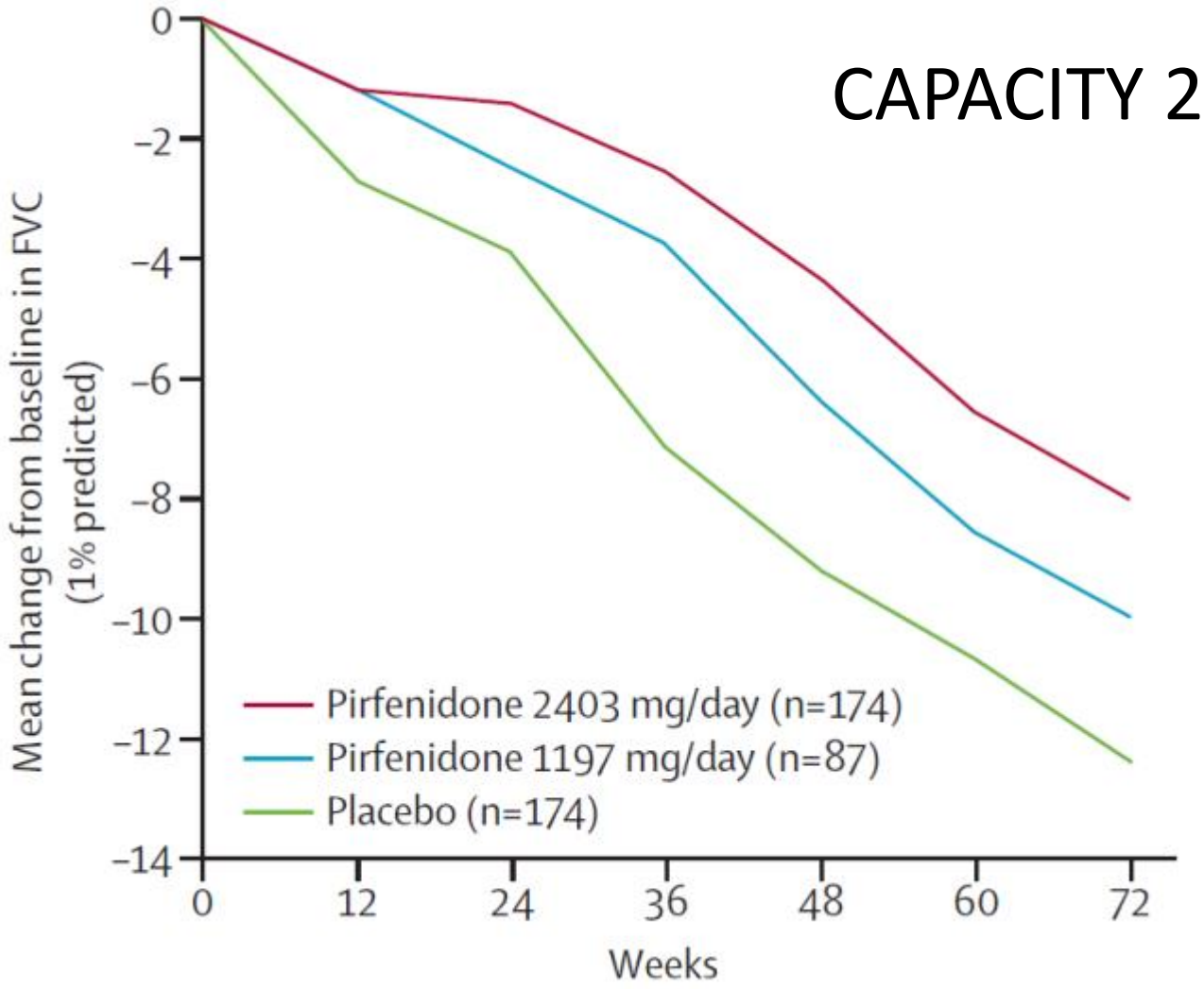
- Amiodarone
- Cimetidine
- Efavirenz
- Fluoroquinolones
- Fluvoxamine
- Ticlopidine

CYP1A2 Inducers

- Carbamazepine
- Chargrilled meat
- Rifampin
- Tobacco

http://medicine.iupui.edu/clinpharm/ddis/clinical-table. Accessed May 2015.

Is a Lower Dose of Pirfenidone Effective?



Noble PW, et al. *Lancet*. 2011;377(9779):1760-1769.

What is the Best Course for Betsy?

A. Switch to nintedanib
B. Switch to NAC
C. Hold pirfenidone
D. Reduce pirfenidone dose
E. Switch to high dose prednisone
F. Manage rash with topical ointment, sunscreen

Treatment Options for Betsy?

Temporary dose reduction to three capsules per day, temporary interruption, or discontinuation?

Management of Betsy's Skin Rash

- Her dose was titrated down to three capsules daily for one week
- She used her sunscreen and Boston Red Sox hat
- Her rash improved and she returned to educate her dermatologist
- Pirfenidone was retitrated to two capsules three times a day (she was only off of drug for one week)
- She was titrated to full dose (three capsules three times a day) and rash did not reappear

Management of Photosensitivity

- Avoid sun exposure
- Frequently apply sunblock that is active against both UVA and UVB and wear protective clothing
- Patients who experience severe photosensitivity should be instructed to interrupt the dose and seek medical advice.
- Pirfenidone may be introduced and re-escalated up to the recommended daily dose at the physician's discretion.

Cottin V, Maher T. *Eur Respir Rev* 2015; 24: 58-64.

Dosage Modifications Due to Photosensitivity/Rash

- If patients experience photosensitivity or rash, consider temporary dosage reductions, interruptions, or discontinuation of pirfenidone
- If the rash persists after 7 days, pirfenidone should be discontinued for 15 days with re-escalation to the recommended daily dose over a period of 2 weeks
- The dose of pirfenidone may be reduced to three capsules per day (one capsule three times daily)
- Patients who miss 14 or more days of pirfenidone should re-initiate the drug by undergoing the initial 2-week titration regimen up to the full three tablets three times a day schedule
- If pirfenidone is stopped for less than 14 days, the dosage prior to the interruption can be resumed

Costabel et al. *Adv Ther* 2014;31:375-391.

MAPS: An Approach to Managing Side Effects

- **M**anage: patient education, adverse event prevention and management with prophylactic therapy.
- **A**djust the dose: if adverse events occur and symptoms do not resolve. Rechallenge with approved dose if symptoms resolve (note: 14 day window).
- **P**ause the treatment: if adverse events persist. When the symptoms have resolved or become tolerable then therapy should be slowly re-escalated to the recommended daily dose as tolerated.

Koschel et al. *Eur Respir J* 2014; 44: Suppl. 58, 1904.

Key Lessons from Betsy

- Skin rash/photosensitivity issues are manageable
- What about switching to nintedanib from pirfenidone?
- Don’t add Prednisone or NAC based on PANTHER
- Pirfenidone is only indicated for patients with IPF
- There are no FDA approved indications for other interstitial diseases including hypersensitivity pneumonitis (with UIP pathology) or autoimmune related lung disease

Conclusions

- All drugs have side effects
- Focus on individualized strategies
- Maximize use of one drug before switching to another
- Don’t use nintedanib and pirfenidone together
- Use nintedanib or pirfenidone for patients with IPF