Pulsed Inhaled NO in Patients with Interstitial Lung Disease: just say “yes”?

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Disclosures

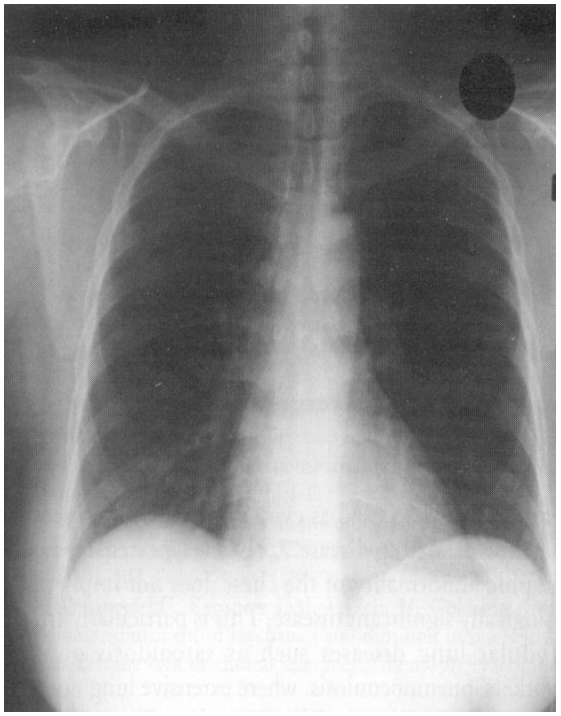
Steven Nathan, MD

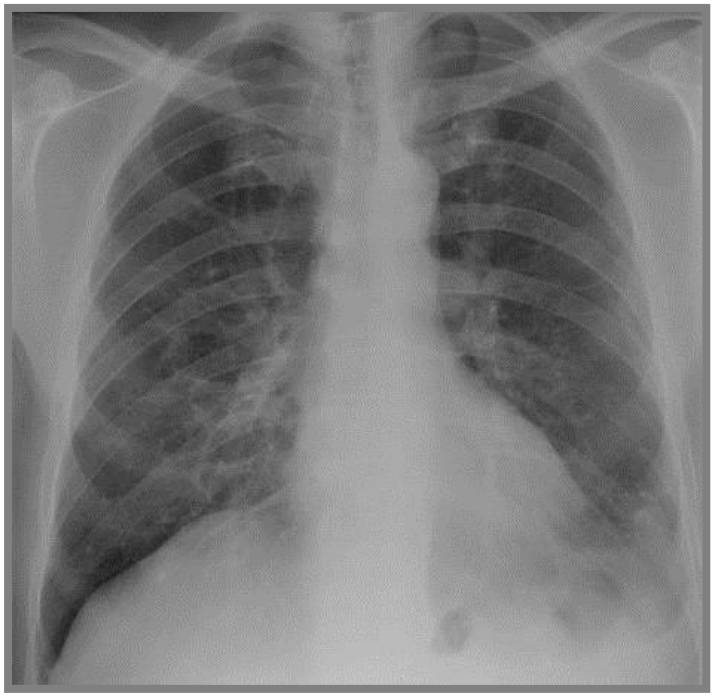
Personal financial relationships with commercial interests relevant to this presentation during the past 12 months:

- **Consultant:** Bayer, Bellerophon, Boerhinger-Ingelheim, Gilead, Genentech-Roche, United Therapeutics.
- **Speaker's Bureau:** Bayer, Boerhinger-Ingelheim, Genentech-Roche, Gilead, United Therapeutics.
- **Research Funding:** Bayer, Boerhinger-Ingelheim, Gilead, Genentech-Roche, United Therapeutics, Veracyte.

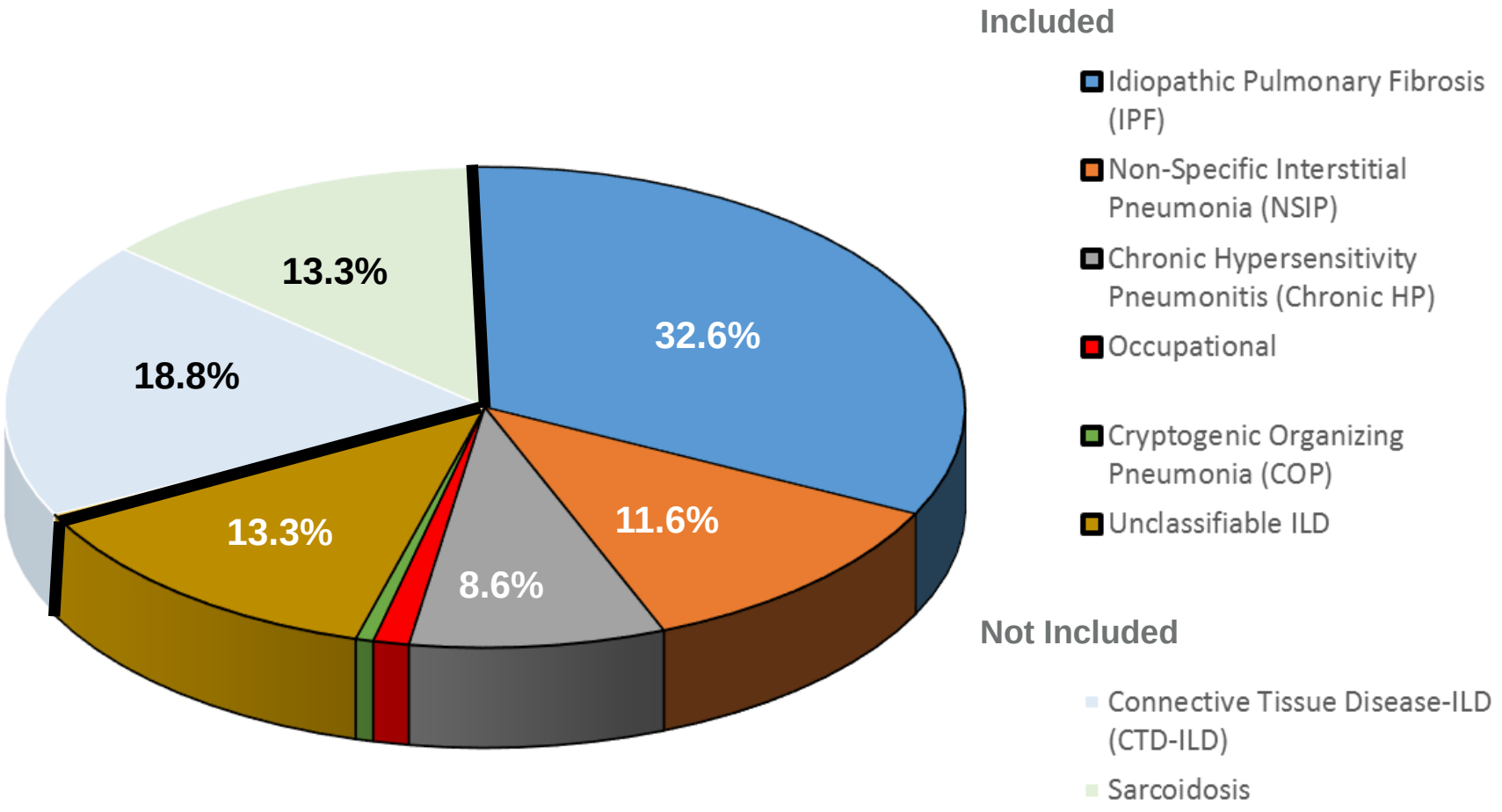
Interstitial lung disease is commonly confused with *Pulmonary Fibrosis* is commonly confused with *IPF*

Interstitial Lung Disease: A broad category of diffuse lung disease involving the interstitium of the lung characterized by variable amounts of inflammation and fibrosis



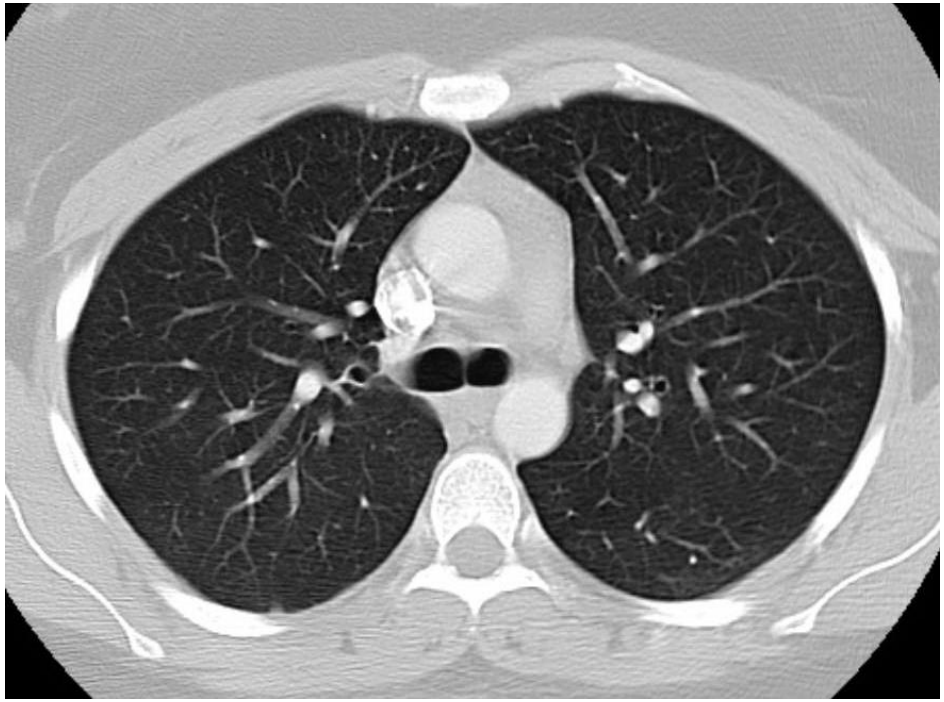


Spectrum of ILD followed by Inova Acute Lung Disease Program (N=657)

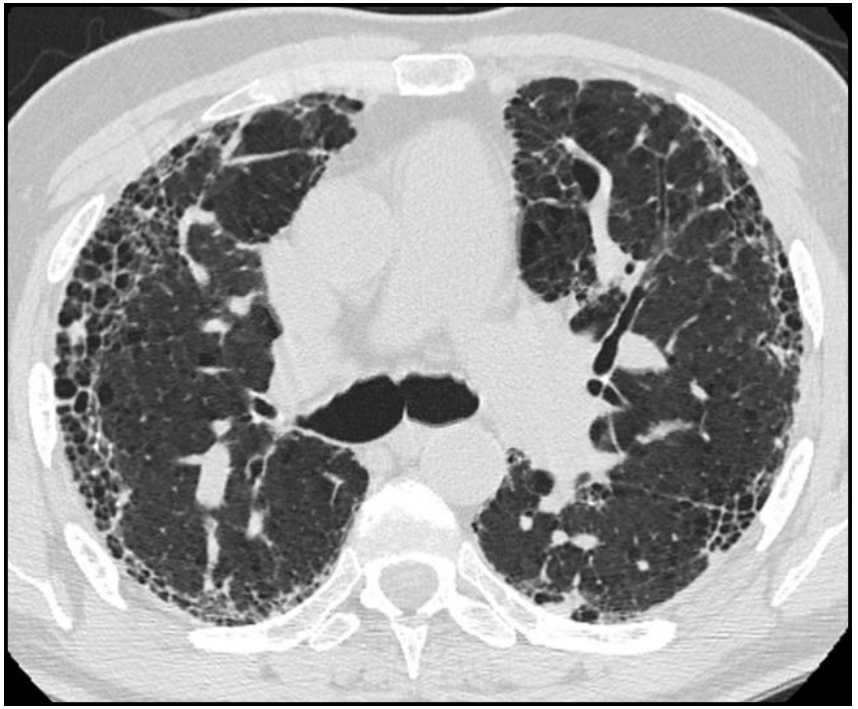


CT of the Chest is the Main Diagnostic Tool

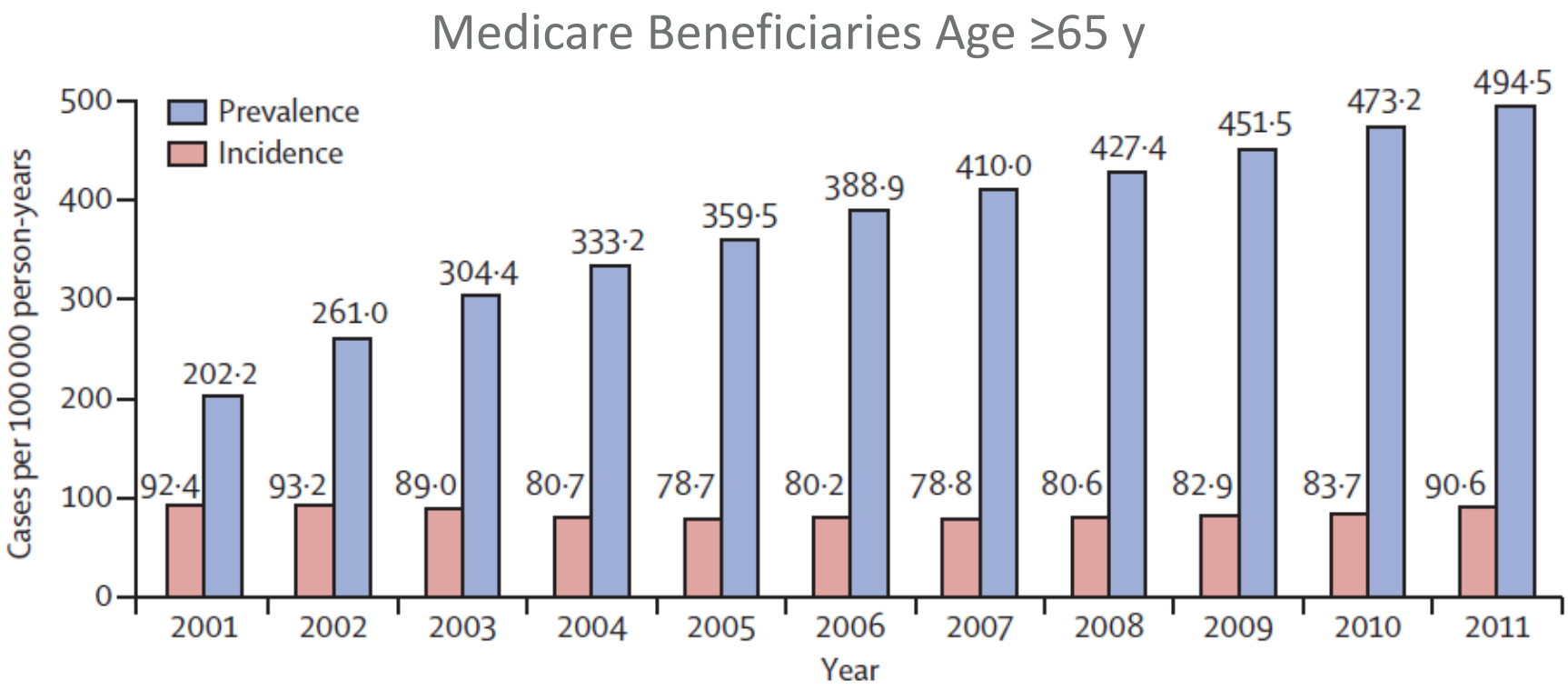
NORMAL



IPF



Increasing Prevalence of IPF



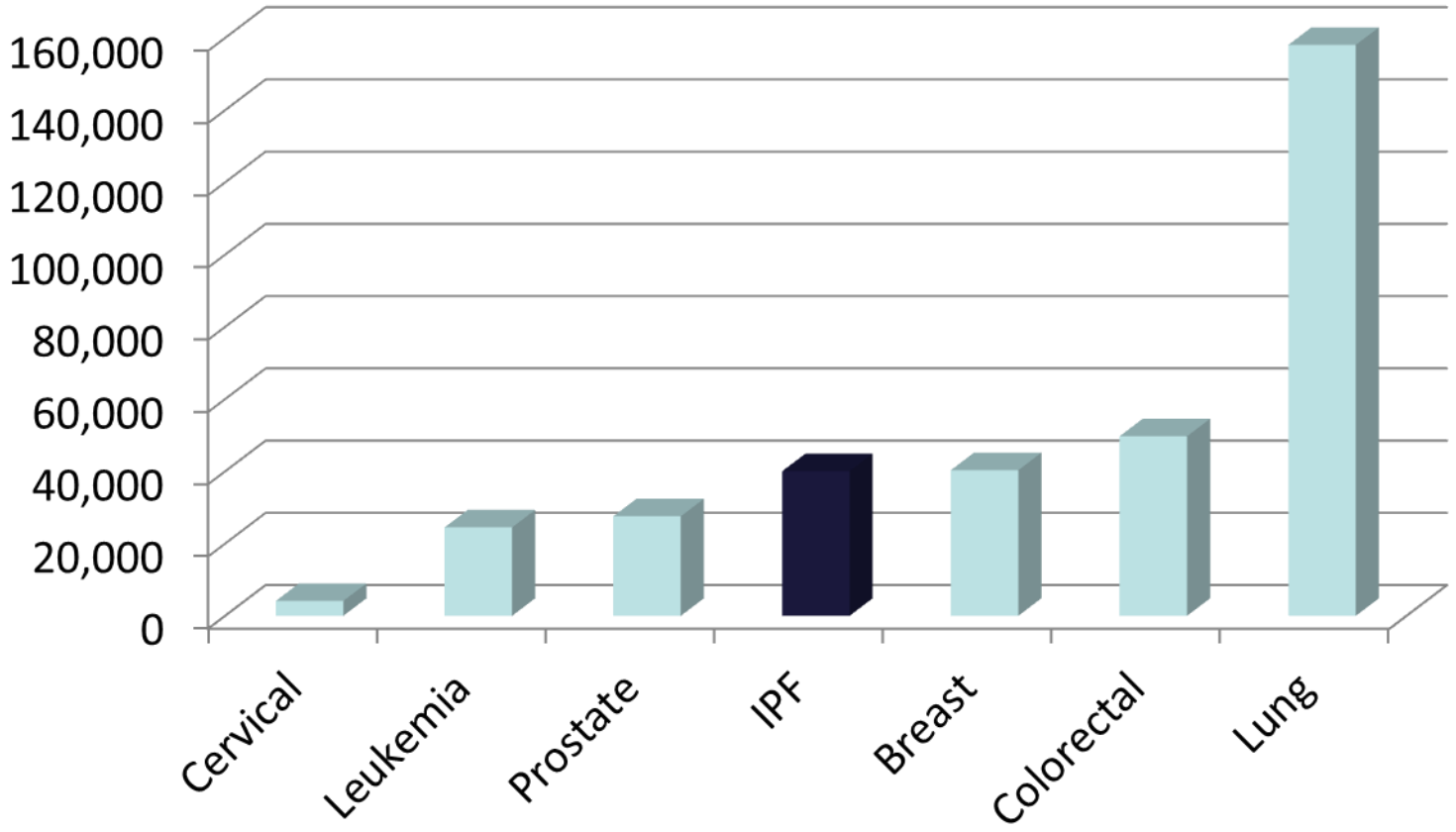
Factors associated with lower survival

- Age, index year, male gender

Median survival = 3.8 y

1. Raghu G et al. *Lancet Respir Med*. 2014;2:566-572

Estimated Deaths: IPF[1] vs Common Cancers[2]

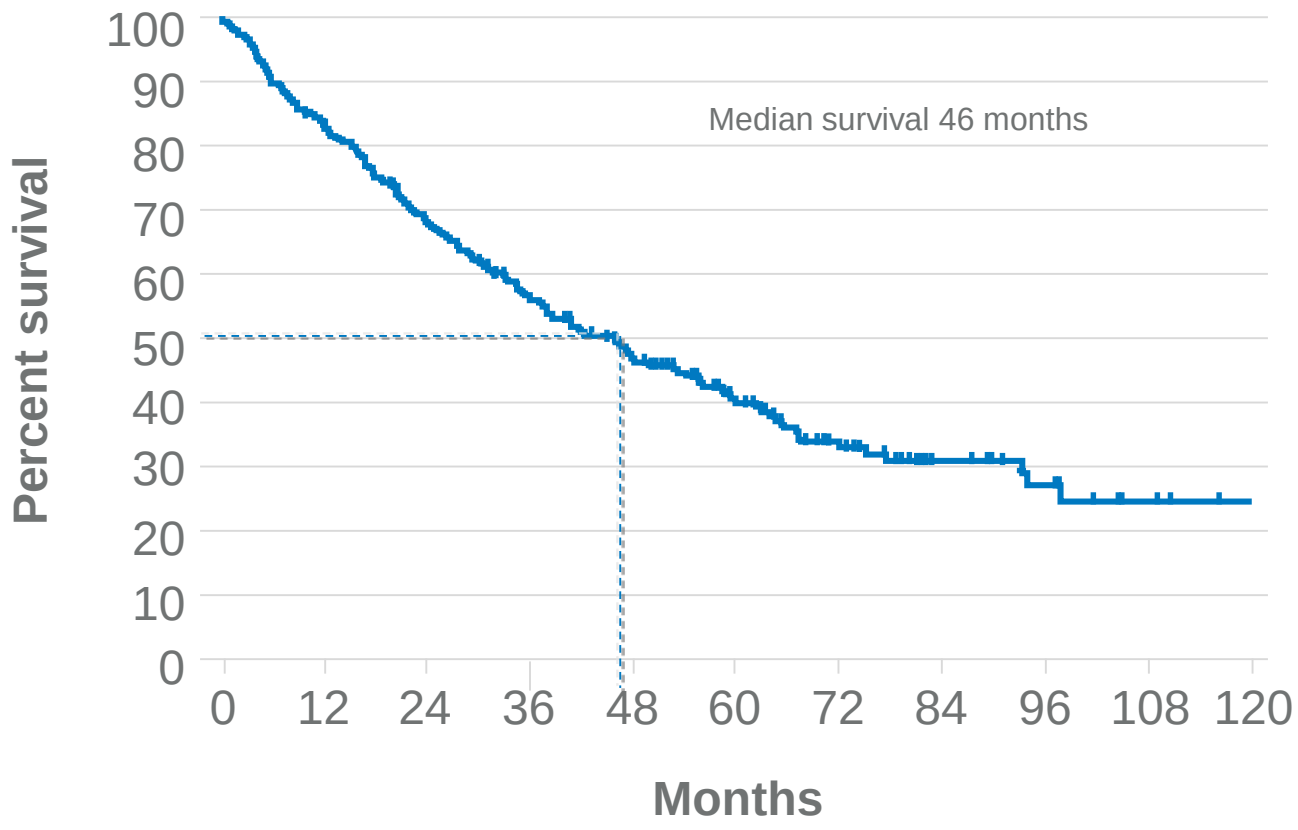


1. Coalition for Pulmonary Fibrosis. Facts About Idiopathic Pulmonary Fibrosis. Available at: http://www.coalitionforpf.org/facts-about-idiopathic-pulmonary-fibrosis/.
2. American Cancer Society, Surveillance and Health Services Research, 2015. Available at: http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf.

How Do IPF Patients Present?

- Shortness of breath (dyspnea)
- Dry cough
- Fatigue
- Exercise desaturation
- “Velcro” rales at lung bases
- Clubbing of fingers and/or toes may be present
- Incidentally
  - ILD on routine CXR or CT chest
  - ILD at bases of abdominal CT
  - Fluoroscopy at time of cardiac catheterization
  - Family history

Idiopathic Pulmonary Fibrosis: the prototypical pulmonary fibrotic disorder
Survival in the pre-antifibrotic era 2000–2009 (N=357)

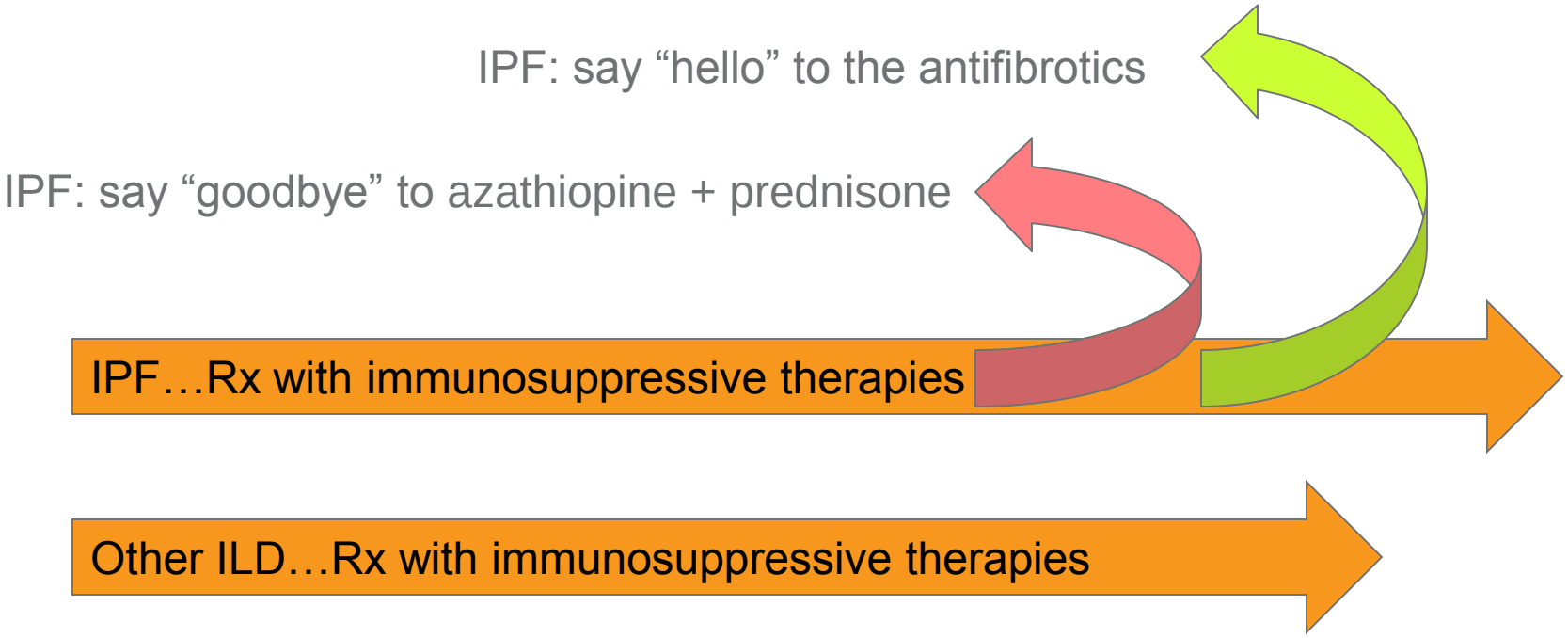


Lung transplant recipients were excluded from these analyses

Nathan SD, et al. *Chest.* 2011;140:221–229

Seismic Treatment Paradigm Shift

IPF, IIPs and CTD-ILD= historic parallel treatment paths

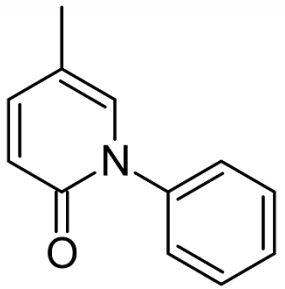


The NEW ENGLAND JOURNAL of MEDICINE

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*



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

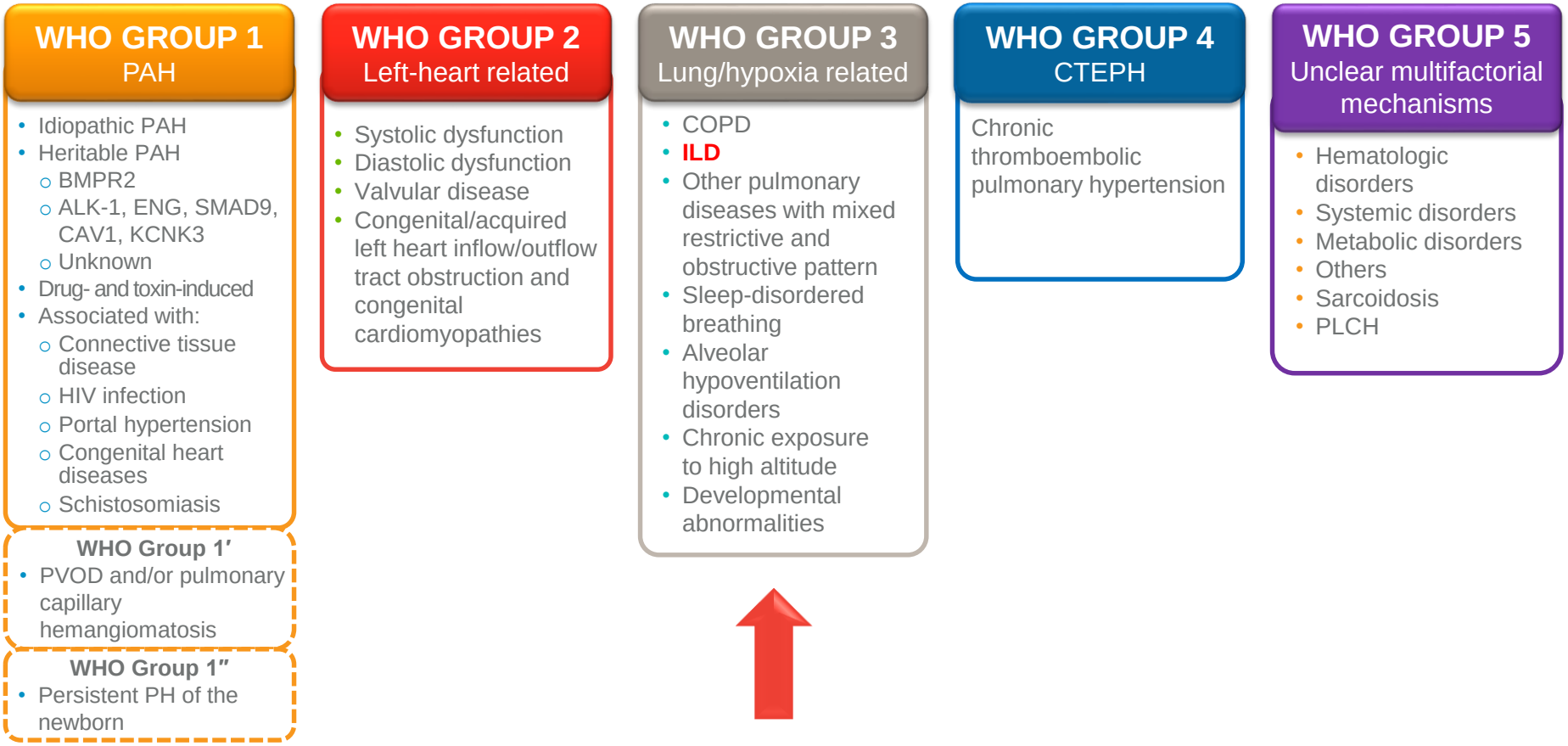
The NEW ENGLAND JOURNAL of MEDICINE

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

Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

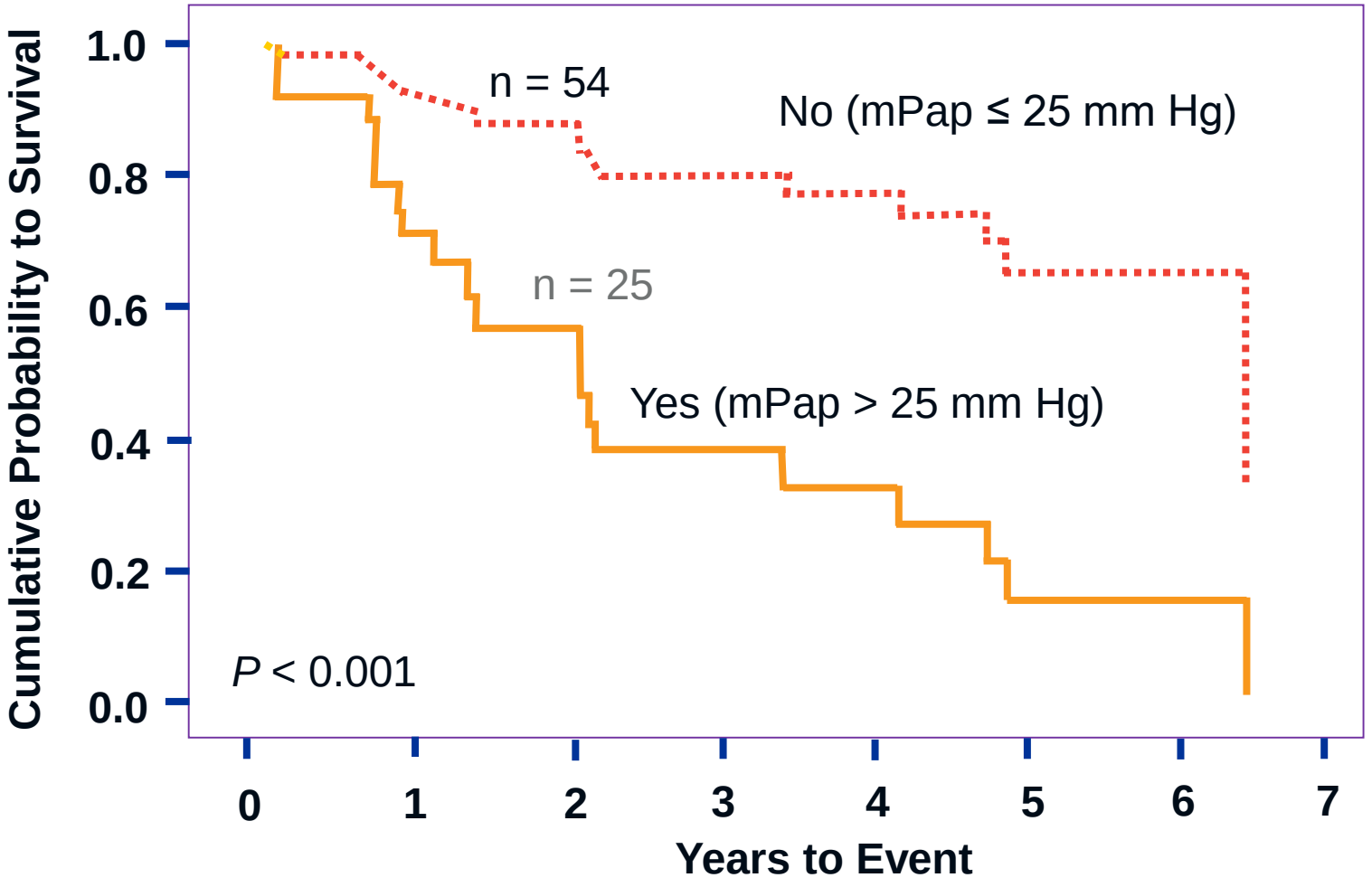
Luca Richeldi, M.D., Ph.D., Roland M. du Bois, M.D., Ganesh Raghu, M.D., Arata Azuma, M.D., Ph.D., Kevin K. Brown, M.D., Ulrich Costabel, M.D., Vincent Cottin, M.D., Ph.D., Kevin R. Flaherty, M.D., David M. Hansell, M.D., Yoshikazu Inoue, M.D., Ph.D., Dong Soon Kim, M.D., Martin Kolb, M.D., Ph.D., Andrew 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*

Clinical Classification of Pulmonary Hypertension



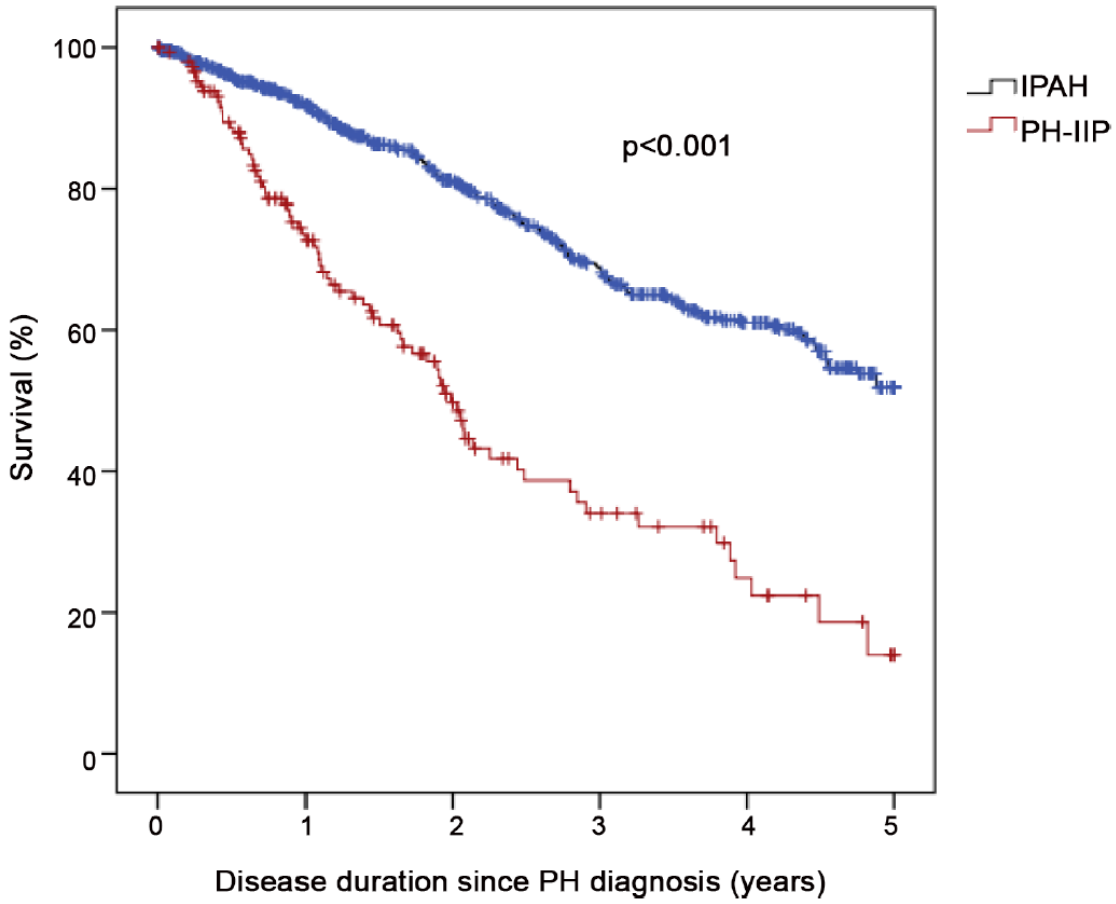
Simonneau G et al. *J Am Coll Cardiol*. 2013;62(suppl):D34-D41.

Mean Pulmonary Artery Pressure can Provide Prognostic Value in IPF



Chest. 2006;129:746-752.

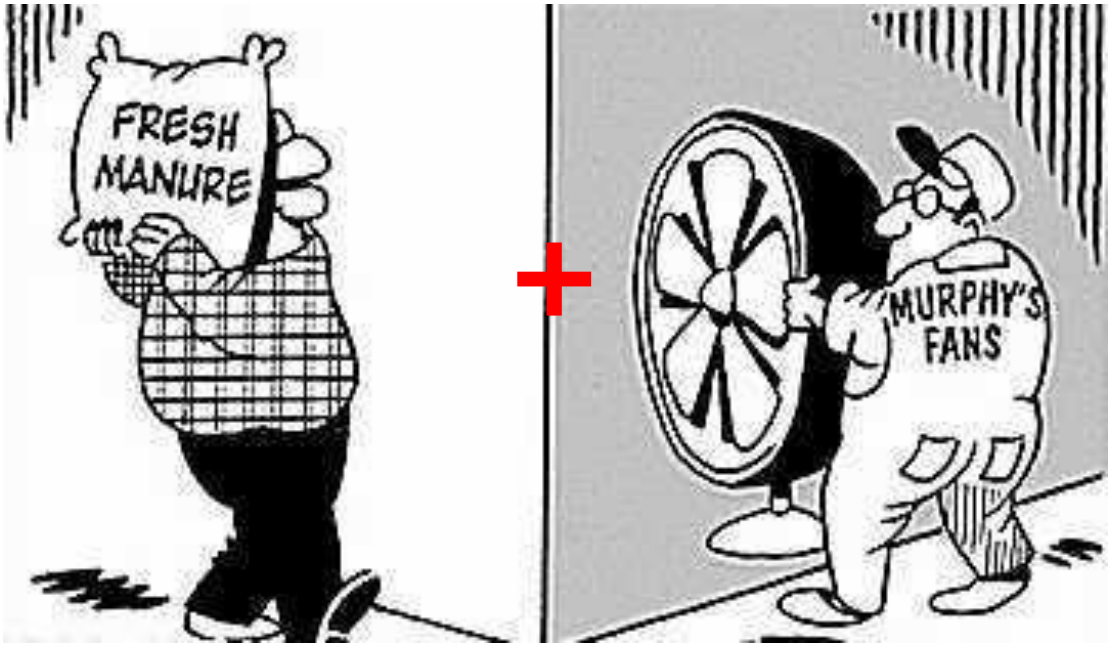
Survival Comparison:
Idiopathic Pulmonary Arterial Hypertension
vs
Pulmonary Fibrosis Complicated by Pulmonary Hypertension



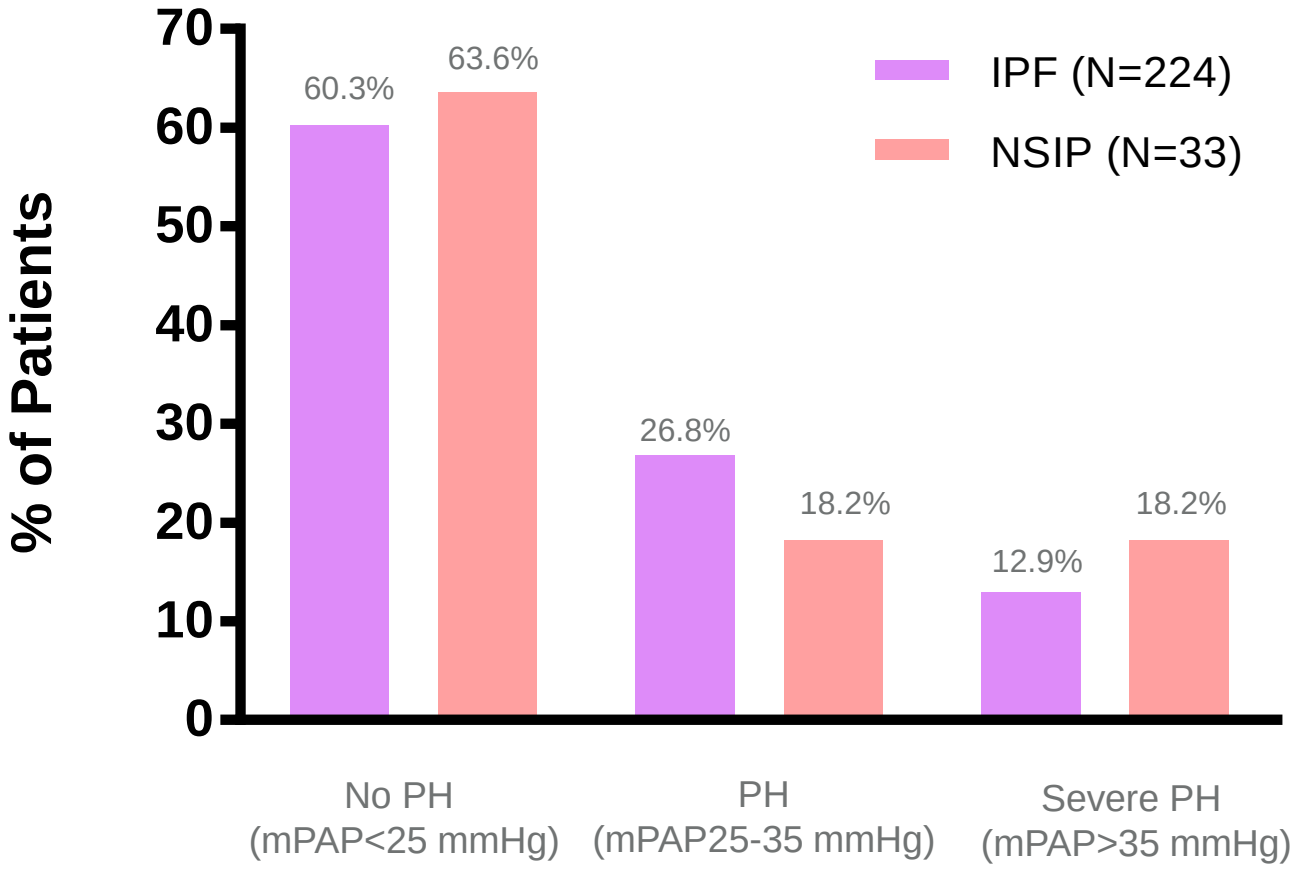
Hoeper et al. PLOS ONE | DOI:10.1371/journal.pone.0141911 December 2, 2015

What happens when you put 2 bad diseases together?

PF+PH=

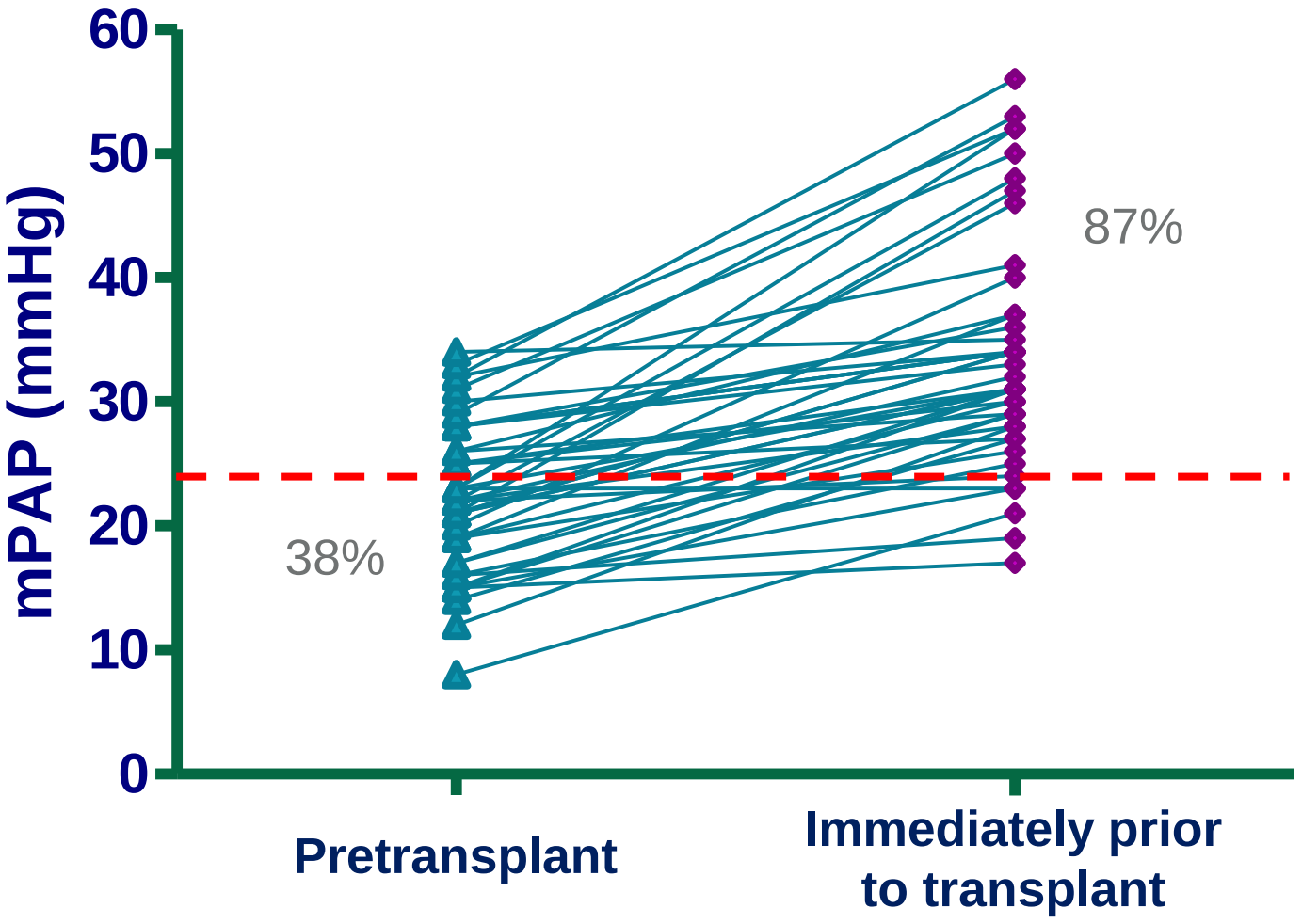


PH in Pulmonary Fibrosis & NSIP: Prevalence



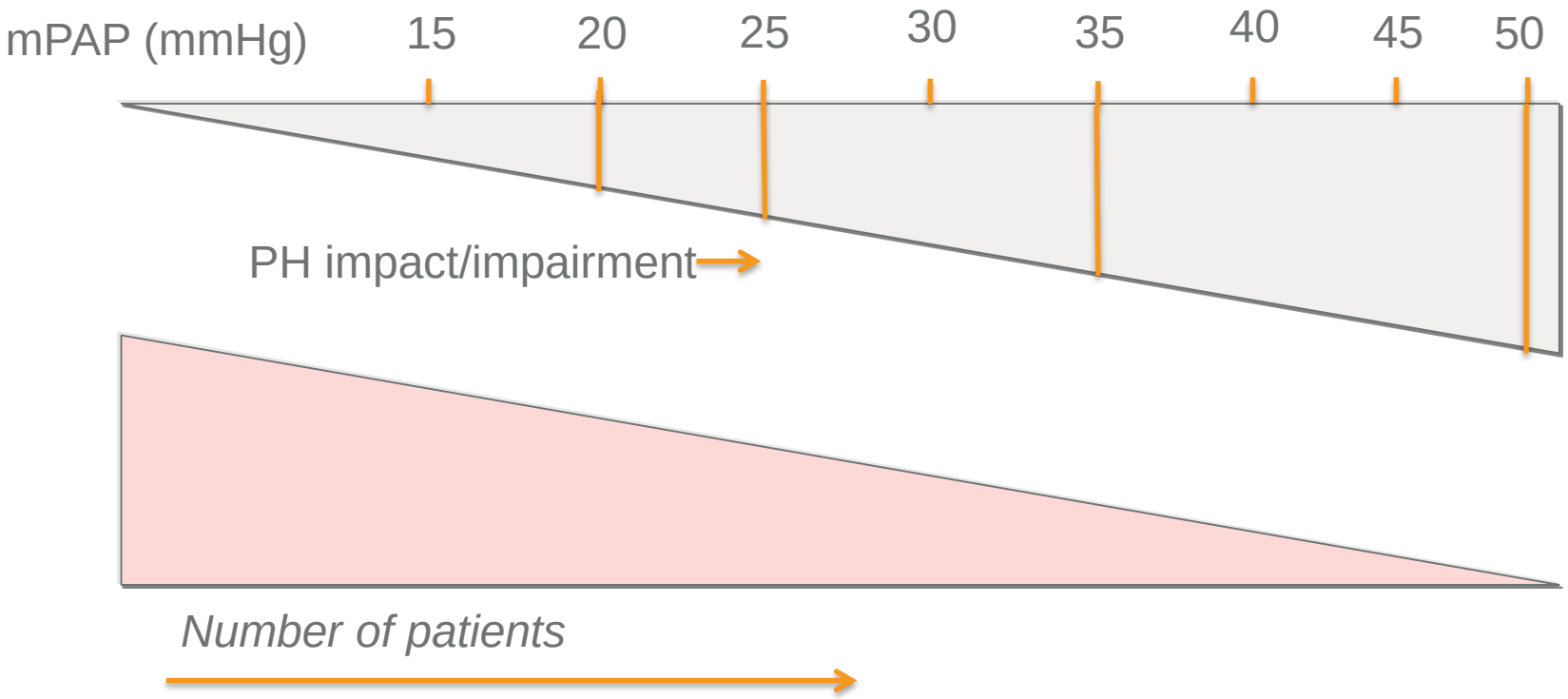
Inova Fairfax data: August 2013

PH Progression in IPF



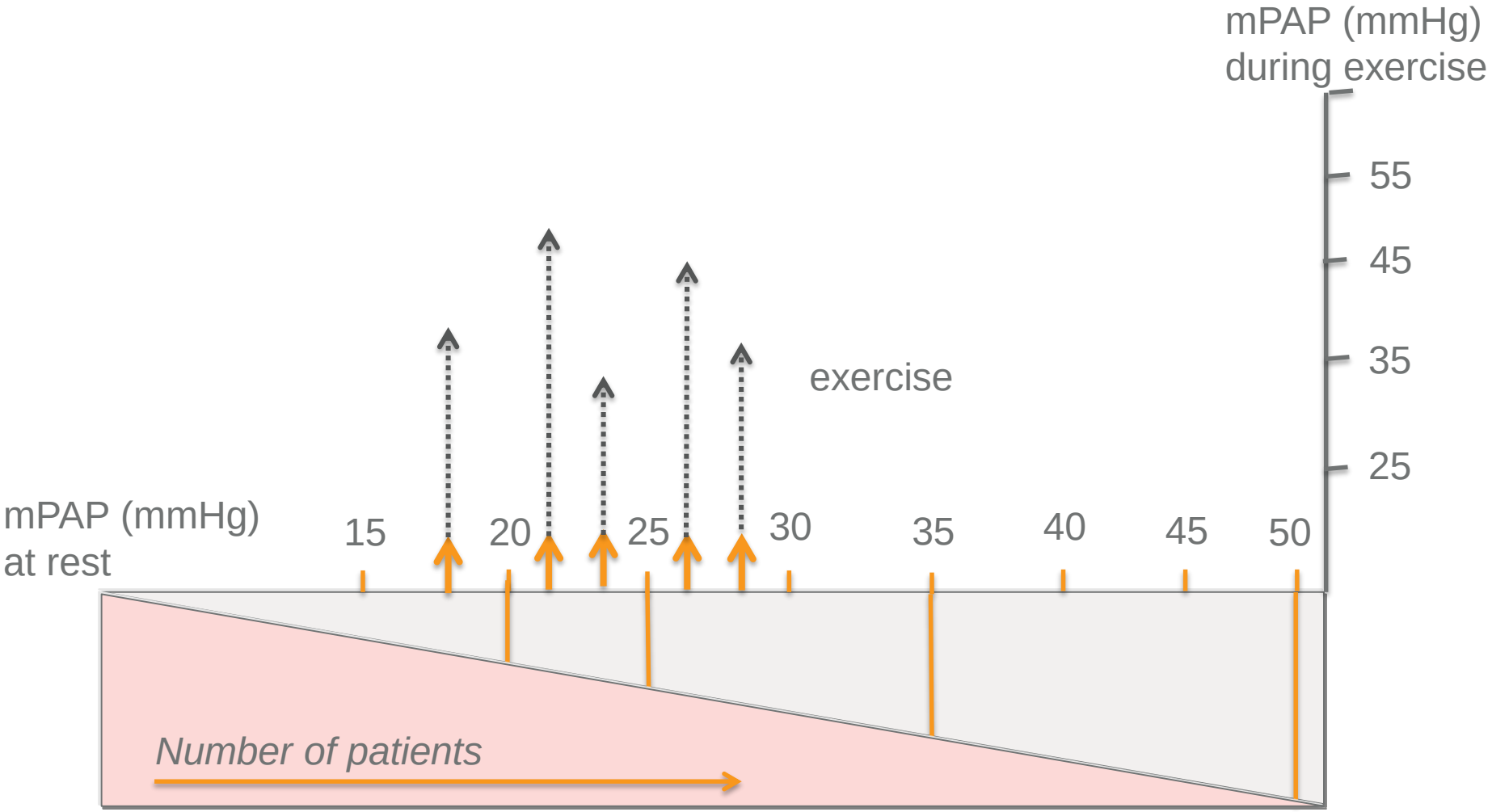
Respiration 2008;76:288-294

Pulmonary Vascular Involvement: A Spectrum and Continuum

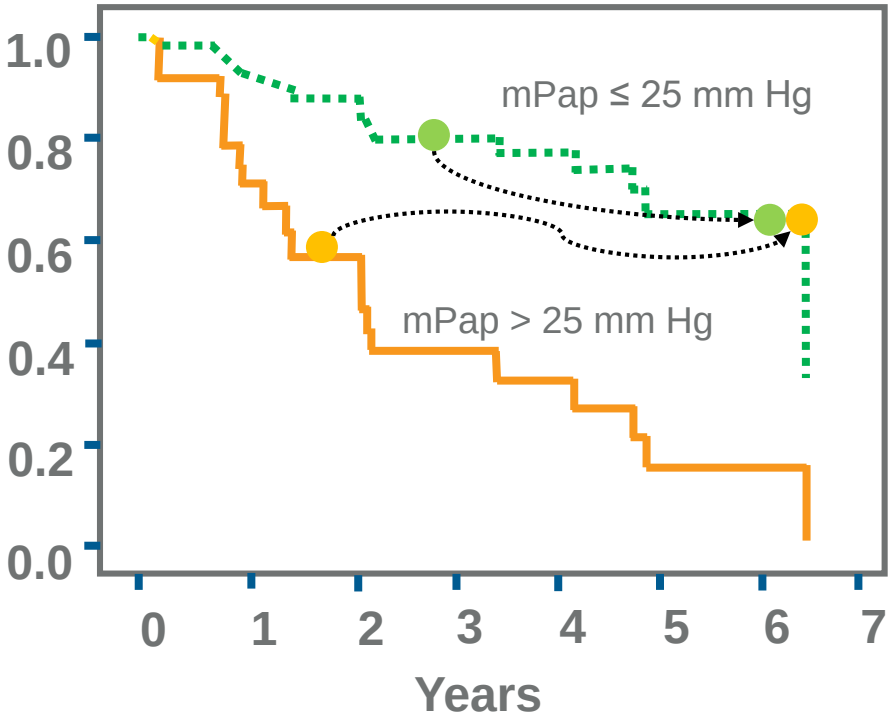


Pulmonary Vascular Involvement: A Spectrum and Continuum

…..rest parameters not necessarily reflective of exercise

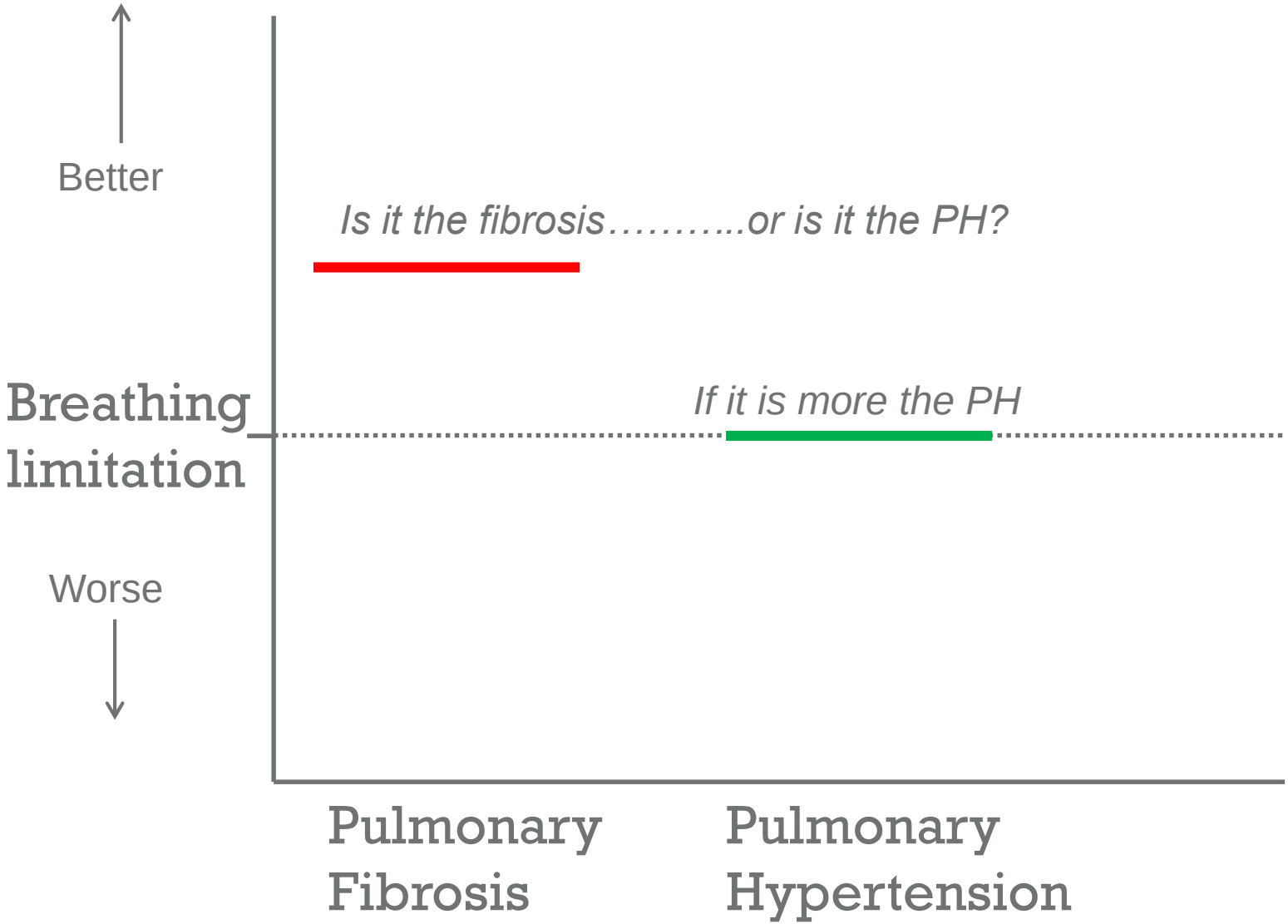


Pulmonary Fibrosis prognosis…*can it be altered by targeting prognostic indicators?*



Lettieri CJ, et al. *Chest.* 2006;129:746-752.

Lung Disease and PH:
What is the limiting factor?



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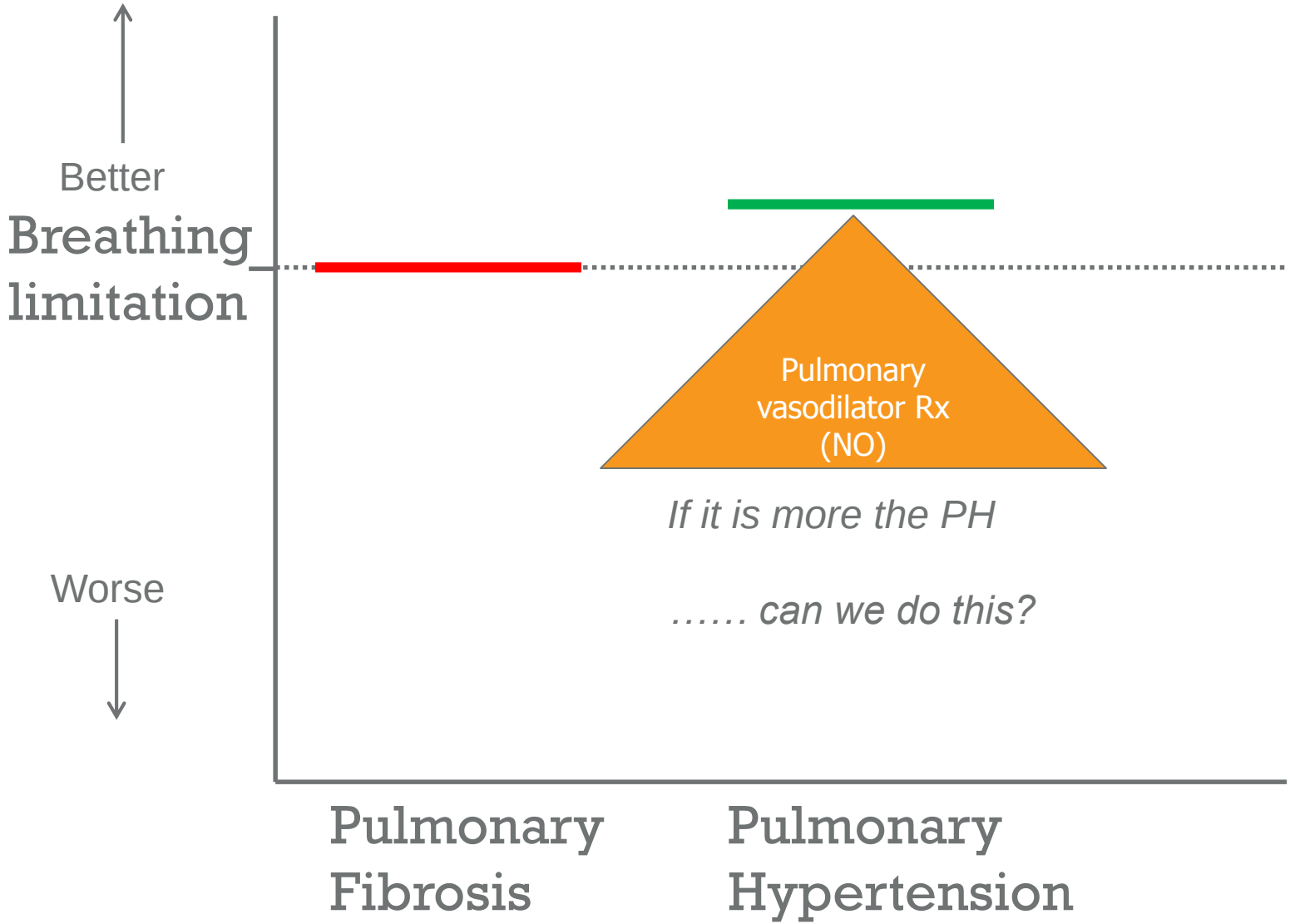
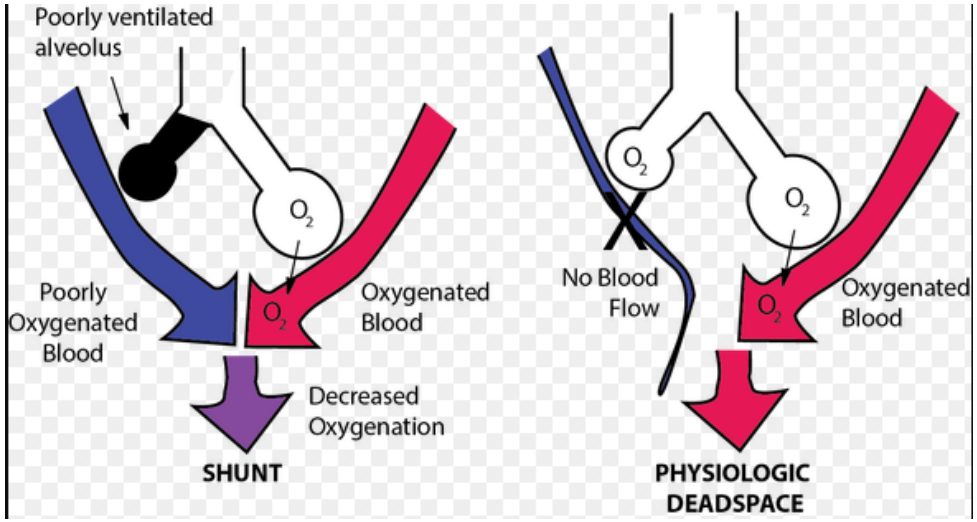


Why pulsed iNO makes sense

- Local administration
- Very short-half-life
- Minimal systemic side-effects
- “Double dip” on chances of success
  - Ameliorate pulmonary hypertension
  - Improve ventilation perfusion matching



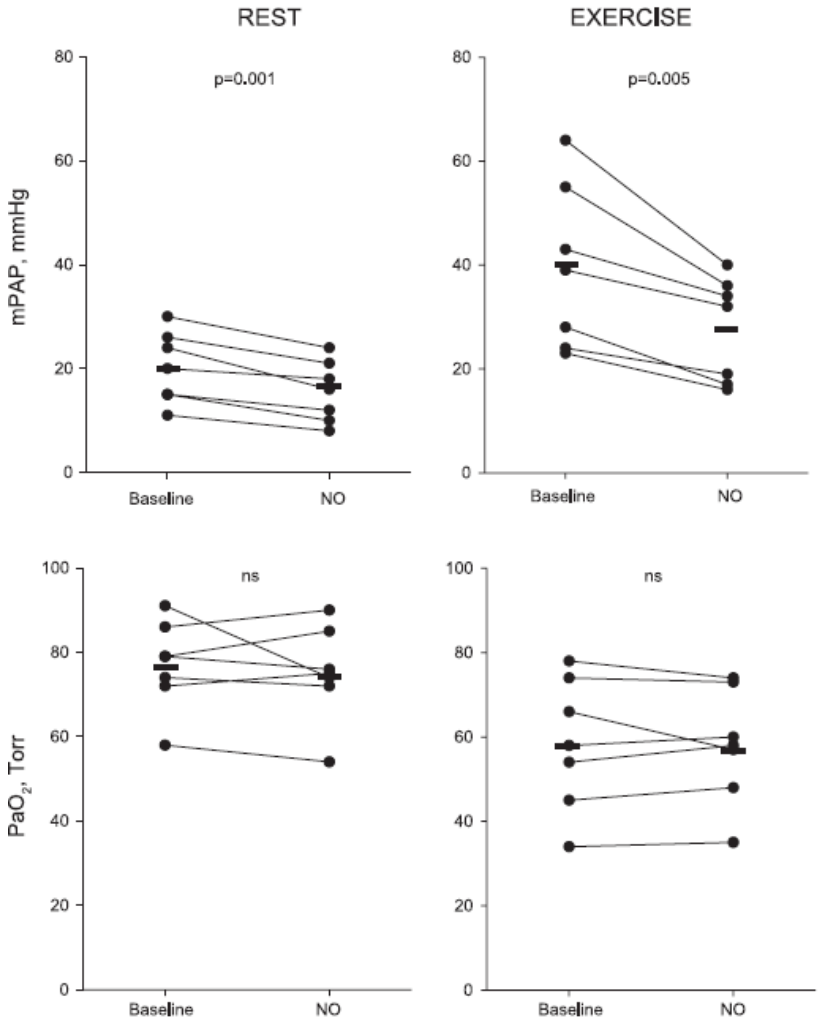
PH-PF Patients exhibit reduced levels of endogenous NO

Exhaled Nitric Oxide During Exercise in Primary Pulmonary Hypertension and Pulmonary Fibrosis*

Study objectives: Nitric oxide (NO), a potent vasodilator, is present in the exhaled air of humans. We wished to quantify NO production in patients with abnormalities of the pulmonary circulation.
Participants: Nine patients with primary pulmonary hypertension (PPH), six with pulmonary fibrosis (PF), and 20 normal volunteers were studied.
Interventions: All subjects were studied at rest and during continuous incremental (ramp) cycle ergometry exercise. All patients with PPH and nine matched normal volunteers also performed constant exercise at equal absolute work rates.
Measurements and results: The concentration of NO was measured continuously in mixed expired air, and the rate of NO production ($\dot{V}NO$) calculated. Peak exercise capacity was markedly impaired in both patient groups. $\dot{V}NO$ was similar at rest in the PPH patients (142±84 nL/min) and the normal subjects (117±45 nL/min), but lower in the PF patients (66±13 nL/min; $p<0.05$; analysis of variance with Bonferonni correction). While $\dot{V}NO$ in normal subjects more than doubled by peak exercise to 268±85 nL/min, there was no significant rise with exercise in either patient group (PPH, 155±81 nL/min; PF, 91±67 nL/min). Constant work rate exercise induced a significant rise in $\dot{V}NO$ in the normal subjects (*rest*, 101±68 nL/min; *exercise*, 147±87 nL/min; $p<0.001$) but no significant change in the PPH patients (*rest*, 127±111 nL/min; *exercise*, 68±65 nL/min).
Conclusions: We conclude that the low resting $\dot{V}NO$ in PF may be due to loss of normal functional pulmonary capillary bed. The increase in $\dot{V}NO$ seen in normal subjects may be associated with dilatation and recruitment of the pulmonary capillary bed during exercise, and failure to increase $\dot{V}NO$ during exercise in disease states may reflect an inability to recruit the capillary bed.

Chest 1997;111:44-50

Hemodynamic effects of NO at rest and with exercise in patients with IPF



J Appl Physiol 2011:638-645

Outpatient Inhaled Nitric Oxide in a Patient With Idiopathic Pulmonary Fibrosis: A Bridge to Lung Transplantation

Gordon L. Yung, MB, BS,[a] Jolene M. Kriett, MD,[b]
Stuart W. Jamieson, MB, FRCS,[b] F. Wayne Johnson, RPFT, RCP,[c]
John Newhart, RCP,[c] Katie Kinninger, RCP,[c] Richard N. Channick, MD[a]

Inhaled nitric oxide (INO) has been shown to improve oxygenation and decrease intrapulmonary shunt and pulmonary hypertension in various lung diseases. In this study we report a patient with end-stage idiopathic pulmonary fibrosis and pulmonary hypertension who received INO after coronary artery bypass surgery, with significant improvement in arterial oxygenation and pulmonary arterial pressure. Using a pulsing delivery system, the patient continued to receive outpatient INO for 30 months while waiting for lung transplantation. Exercise study and two-dimensional echocardiogram, after 3 months of inhaled NO, demonstrated continued benefits of INO for improvement of arterial oxygenation, pulmonary arterial pressure and exercise tolerance. J Heart Lung Transplant 2001;20:1224–1227.

iNO-PF Phase 2b Study

…ambulatory NO: Primed for success?

- It works √
- It's given locally √
- It's well-tolerated √
  - e.g. no systemic hypotension
- It goes to the areas where it is "needed" √
- Targeted population broad √
- Sufficient duration to see benefit (8 weeks) √
- Change in the 6MWT distance is a validated outcome measure. √

Bellerophon Therapeutics:

Pulmonary Hypertension Associated with Interstitial Lung Disease (ILD)

August 9, 2017

Nasdaq: BLPH

Bellerophon® THERAPEUTICS

Forward Looking Statements

This presentation contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this presentation, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “plan,” “predict,” “project,” “target,” “potential,” “will,” “would,” “could,” “should,” “continue,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make due to a number of important factors, including risks and uncertainties relating to: the timing and outcomes of our ongoing and expected clinical trials for our product candidates; our ability to successfully develop, commercialize and market any of our product candidates; our ability to obtain, maintain and enforce intellectual property rights; competition; our reliance on third parties; our ability to obtain necessary financing; and those risk factors discussed in the “Risk Factors” section and elsewhere in our most recent Form 10-K and other periodic filings we make with the SEC.

All forward-looking statements contained in this presentation reflect our current views with respect to future events. We assume no obligation, except as required by applicable law, to update any forward-looking statements publicly, or to update the reasons why actual results could differ materially from those anticipated in the forward-looking statements, even if new information becomes available in the future.

Introduction

Fabian Tenenbaum

Chief Executive Officer

Bellerophon THERAPEUTICS

Bellerophon Therapeutics (BLPH) – Company Profile

Late-Stage Biotherapeutics Company

- Focused on developing inhaled nitric oxide (iNO) based therapies for outpatient management of chronic pulmonary diseases
- Portable, lightweight delivery system allows for chronic home use
- Targeting substantial unmet and underserved disease areas including multiple orphan opportunities

Rich Product Pipeline

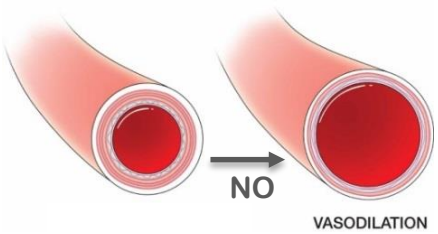
- PAH program in Phase 3; ILD and COPD programs in Phase 2
- Significant data read-outs in 2017 & 2018
- Simplified regulatory approval pathway via existing nitric oxide NDA
- Robust market protection against generics via patent portfolio, orphan exclusivity and technical hurdles to market entry

Financial Summary

- Spun-off from Ikaria in February 2014; IPO on Nasdaq February 2015
- Cash & Equivalents: $14.9M[1,2], No Debt[2]; Capitalized into 2018
- Shares Outstanding = 35.2 million[2]; Warrants = 17.6 million exercisable at $0.84 per share[2,3]

Notes: (1) Cash & Equivalents (including Marketable Securities) as of June 30, 2017; (2) Quarterly Report on Form 10Q on August 7, 2017; (3) Warrant share price based on weighted average

INOpulse Platform Overview

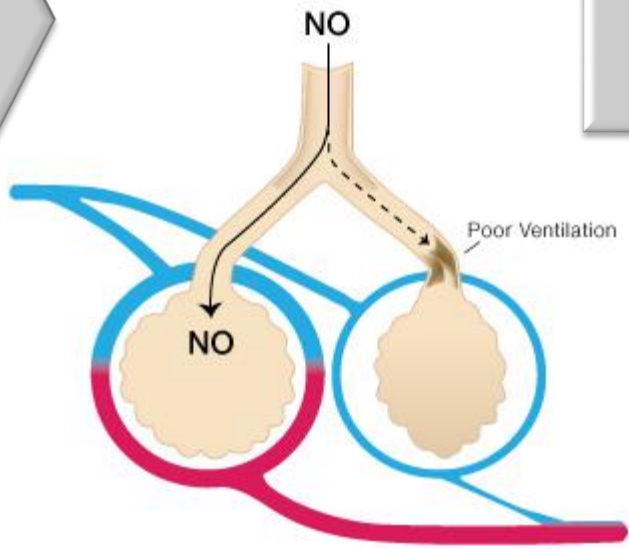


Nitric Oxide is a well established vasodilator approved for acute treatment of persistent pulmonary hypertension in hospitals

INOpulse® therapy allows for chronic use along with pulsatile targeted delivery to well ventilated sections of the lung

Novel drug-device combination therapy with dual mechanisms of action

- Targeted pulmonary vasodilation
- Ventilation/Perfusion (V/Q) matching



Potential to target multiple unmet and underserved chronic pulmonary diseases including areas where systemic vasodilators are ineffective or poorly tolerated

Current Programs:

PAH
PH-ILD
PH-COPD

Bellerophon THERAPEUTICS

Development Pipeline

Indication	Market	Development Stage			Key Milestones
		2017	2018	2019	
PAH	• Prevalence 50k in US • 60% on LTOT • $500M+ potential market	**INOvation-1: Phase 3**	**INOvation-RWS: Phase 3**		**1st Phase 3 Trial: INOvation-1** • Trial underway • Interim & top line in 2018 **2nd Phase 3 Trial: INOvation-RW** • Trial start in 2018 • Top line in 2019
PH-ILD	• 100k with IPF in US • 100k in additional ILDs • 40% with associated PH at rest • Unmet medical need • $1B+ potential market	**PH-IPF: Phase 2a**	**iNO-PF: Phase 2b**		**Phase 2a PH-IPF Trial completed** • Results presented in May 2017 **Phase 2b Trial: iNO-PF** • Protocol accepted by FDA • Top line in 2018
PH-COPD	• 700k with PH-COPD in US • Unmet medical need • Multi billion dollar potential market	**PH-COPD Phase 2**		**PH-COPD: Phase 2b/3 (timing TBD)**	**Phase 2 PH-COPD Trial underway** • Top line in 2017 **Phase 2b/3 Trial** • Trial timing TBD

INOpulse for Interstitial Lung Disease

Dr. Deborah Quinn

Chief Medical Officer

Bellerophon THERAPEUTICS

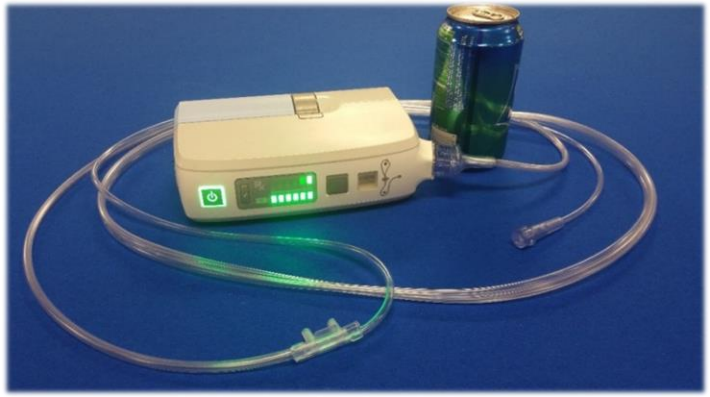
INOpulse: Portable Delivery System Allows Chronic iNO Therapy

Current Acute Treatment Option

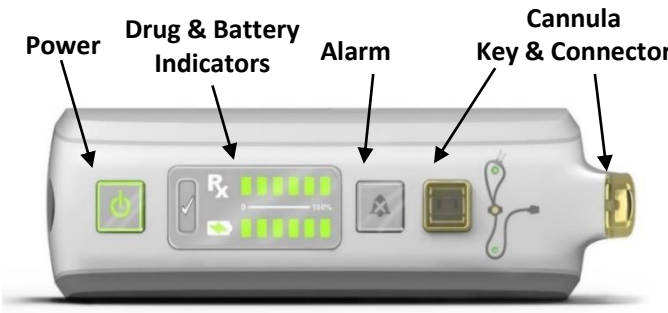
- Well-established therapy for neonates in hospitals
- In-hospital device is bulky with large cylinders
- Continuous dosing is inefficient

INOpulse Chronic Therapy Solution

- Pulsed iNO can deliver equivalent dose as continuous delivery with 5% of the volume
- Small portable ~2.5 lbs. device allows ambulatory use in chronic in-home setting
- Dynamic pulse delivers the prescribed dose accurately throughout the day
- Triple-lumen cannula allows accurate NO dosing alongside Long Term Oxygen Therapy (LTOT)



INOpulse Delivery System: Lightweight, Portable and User Friendly

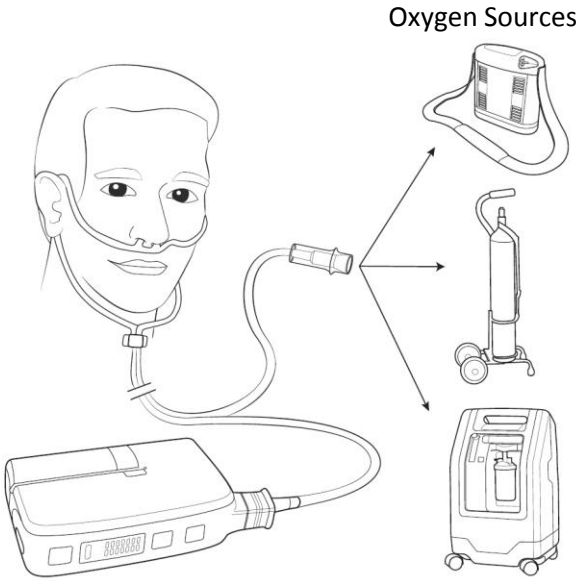


Swing engagement with drug cartridge

Intuitive and simple user interface

Tri-lumen cannula allows direct connection with oxygen

Lightweight portable design allows ease of transport



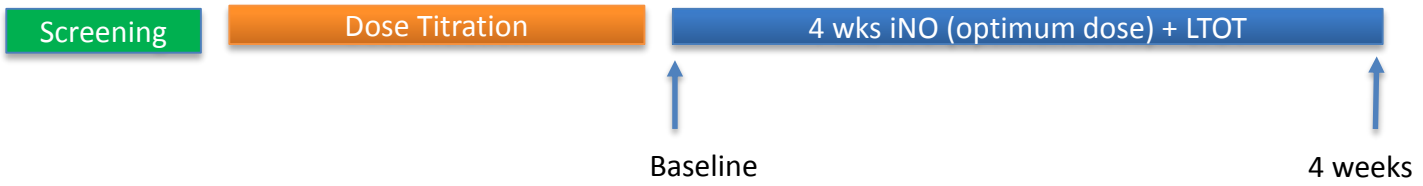
Bellerophon THERAPEUTICS

Background Summary of PAH and PH-COPD Studies with INOpulse

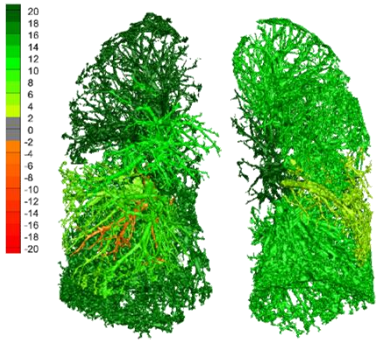
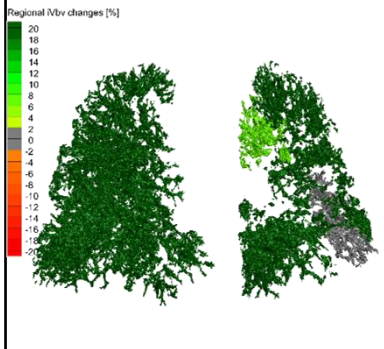
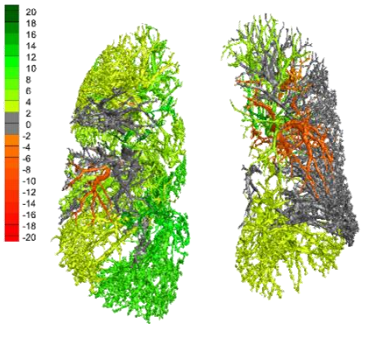
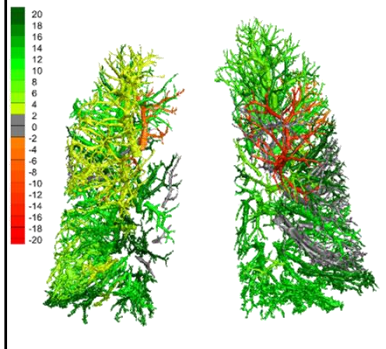
- PAH (Phase 2b data)
  - iNO 75 plus LTOT showed significant improvement in 6MWD versus placebo
  - Patients on iNO 75 for ≥ 12 hrs/day plus LTOT had the greatest benefit and did consistently well (average +52 meters from baseline)
  - After 16-32 months of treatment patients on iNO 75 who remained on therapy for ≥ 12 hrs/day in combination with LTOT maintained a consistent and clinically significant increase in 6MWD (average +55 meters from baseline)
  - Phase III study based on results of Phase 2 data is ongoing
- PH-COPD (Phase 2 data)
  - High resolution computed tomography (HRCT) demonstrates regional dilatation of blood vessels in the lungs following acute pulsed iNO treatment without evidence of hypoxemia
  - Vasodilation occurred in well-ventilated areas as supported by the correlation with lobar ventilation
  - Preliminary results support a meaningful reduction in pulmonary artery pressures with four weeks of treatment with iNO
  - Trial progressing well with top line results expected in the near future

PH-IPF Phase 2a Study Design

- Exploratory study conducted jointly with FluidDA to assess the potential for pulsed iNO to impact hemodynamics and exercise capacity in PH-IPF patients
  - Acute phase to identify optimum iNO dose and evaluate the impact on hemodynamic measures
    - Patients were initially assessed using echocardiography on a dose of iNO 75
    - Study was then modified to incorporate a dose titration using right heart catheterization to gain better understanding of dose sensitivity
  - Chronic phase to assess impact of iNO on exercise capability as measured via 6MWT
    - Patients are treated with iNO for four weeks
  - Endpoints:
    - High resolution computed tomography (HRCT) to assess vasodilation
    - Hemodynamics
    - Change in 6MWD

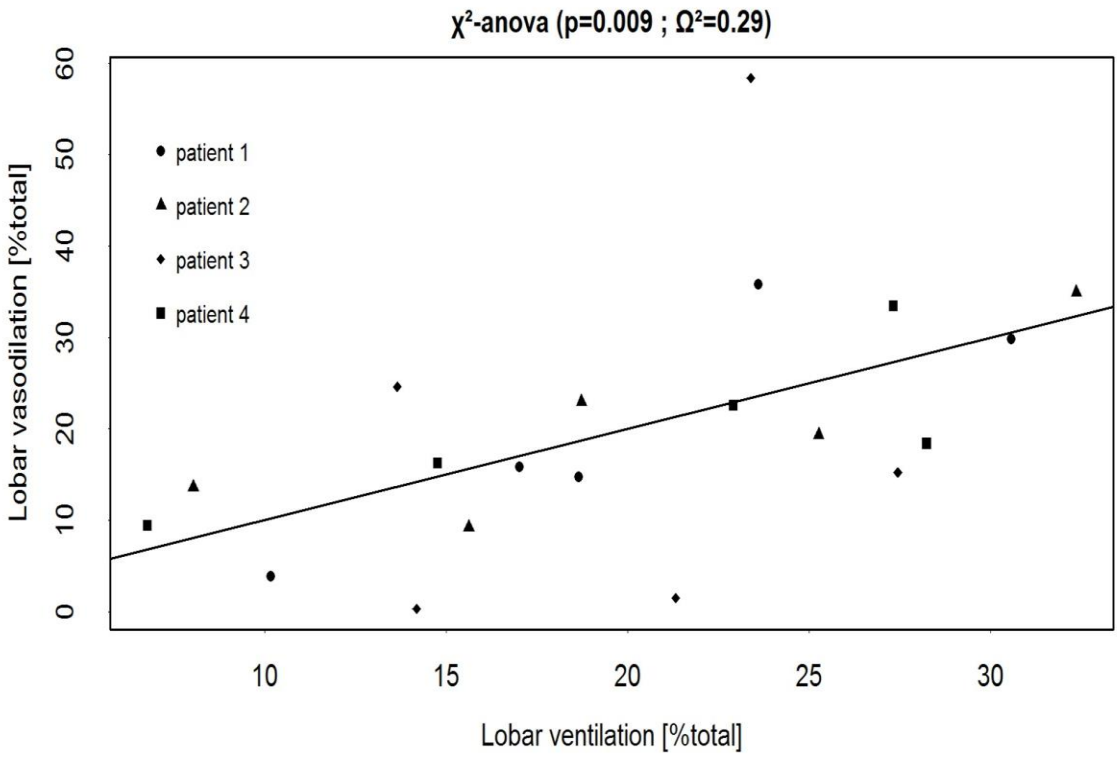


Summary of Acute Response to iNO

	iNO 75		iNO 30	
Increase in blood vessel volume via HRCT				
Blood Vessel Volume Increase [%]	14.0% ± 4.7%	34.2% ± 7.6%	2.8% ± 3.0%	10.1% ± 3.4%
Reduction sPAP (mm Hg)	8 mmHg	9 mmHg	4 mmHg	21 mmHg
Reduction sPAP [%]	9.3%	9.7%	14.3%	23.3%

Ventilation – Vasodilation Correlation

- Strong correlation between regional vasodilation and ventilation provides further support of selective vasodilation



Chronic: 4 Weeks Data

	iNO 75	iNO 30
Average hours of use per day	23.8 hrs/day	12.8 hrs/day
6MWD (meters)		
Baseline	98 m	510 m
4 Weeks	197 m	560 m
Meters improvement at 4 weeks	99 m	50 m
Oxygen desaturation during 6MWT (% SpO_2)		
Baseline	23%	15%
4 Weeks	16%	11%
Percent Improvement at 4 weeks	30%	27%

2 subjects completed chronic phase

Composite Endpoints for Assessment

Use of composite endpoints, combining oxygen saturation and walk distance during 6MWT, is potentially a better predictor of mortality in IPF than oxygen saturation or spirometry alone

Lettieri et al, Resp Med, 2006, pp 1734-1741

- **Distance Saturation Product (DSP)**
  - Product of the distance walked and the lowest oxygen saturation (SpO_2 nadir) during the 6MWT
  - Example: 6MWD = 300 meters; SpO2 nadir = 80%; DSP = 240 m%

	iNO 75	iNO 30
Average hours of use per day	23.8 hrs/day	12.8 hrs/day
Distance Saturation Product [DSP] (meter%)		
Baseline	74.5 m%	423.3 m%
4 Weeks	155.6 m%	498.4 m%
Improvement at 4 weeks (meter%)	81.1 m%	75.1 m%

Summary Acute Exposure

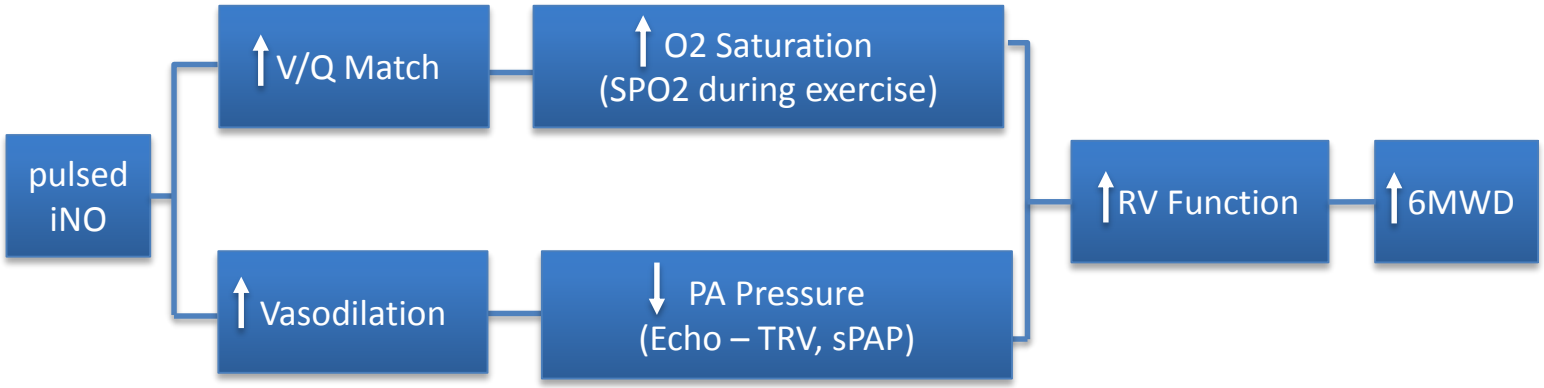
- **Acute pulsed iNO showed improved hemodynamics in all subjects**
  - Pulsed iNO provided selective vasodilation driven to the well ventilated sections of the lung
  - Vasodilation leads to a consistent overall increase in blood volumes within the lung on all 4 subjects
  - All subjects exhibited a reduction in sPAP with similar decrease for both iNO 30 and iNO 75 dose
  - iNO 30 dose was well tolerated by patients as confirmed by RHC

Summary Chronic Exposure

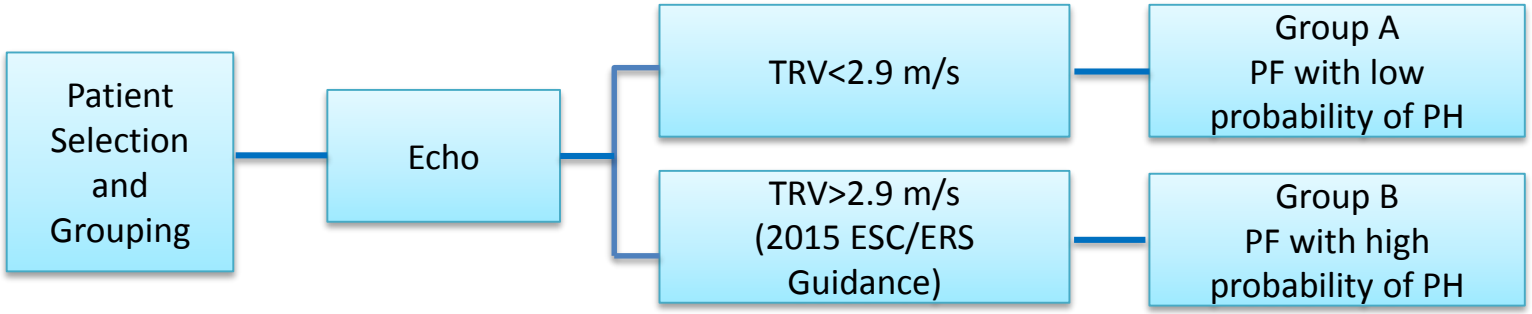
- **Chronic pulsed iNO showed improvements in exercise tolerance**
  - The patients who were treated with iNO for four weeks demonstrated an average increase in 6MWD of 75 meters.
  - Increased Nadir SpO_2 and improved oxygen desaturation during 6MWT provides supportive evidence of improved V/Q matching
  - Composite endpoints of oxygen saturation and 6MWD showed a consistent improvement in DSP

iNO Mode of Action Supports Targeting a Wide Range of Pulmonary Fibrosis Patients

Dual mechanism of action for pulsed iNO



Target broad PF population in Phase 2b Study



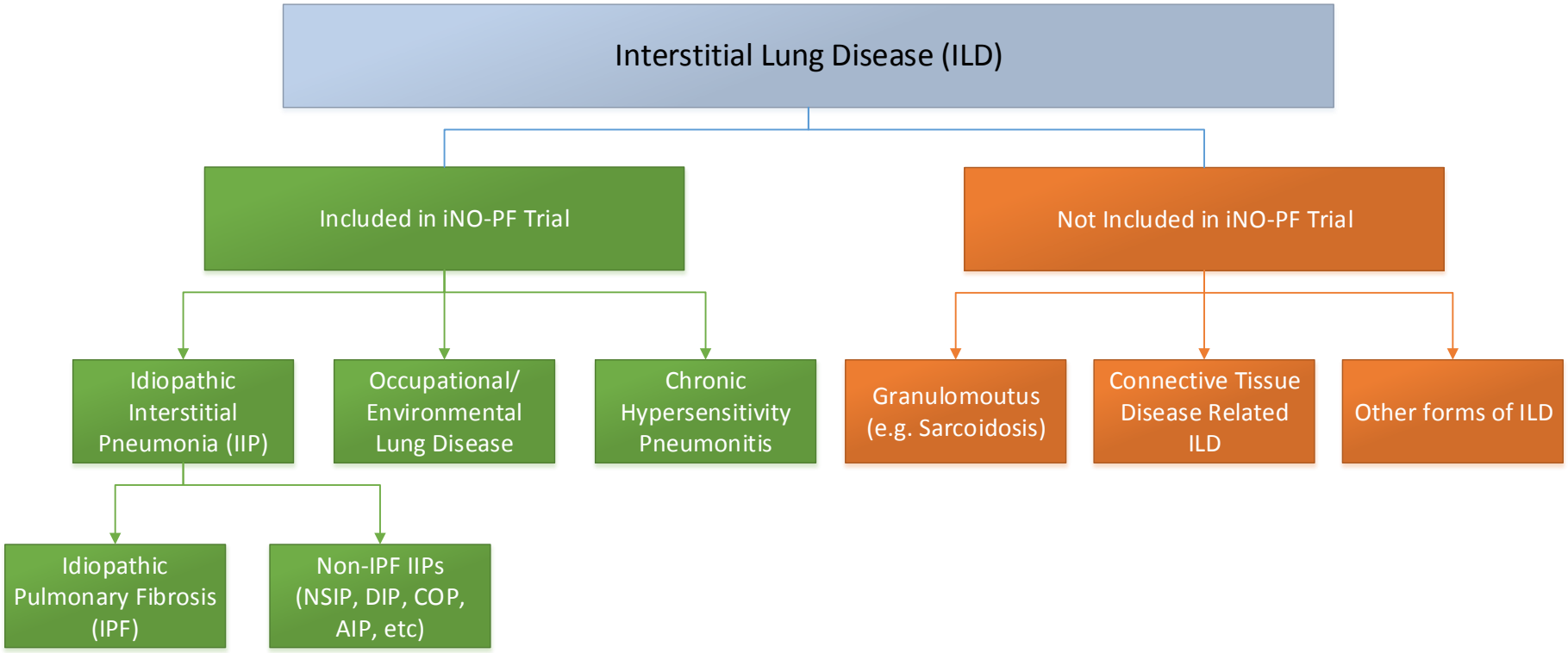
FDA Type B meeting June 15, 2017

- Focused on iNO-PF Phase 2b Study Design

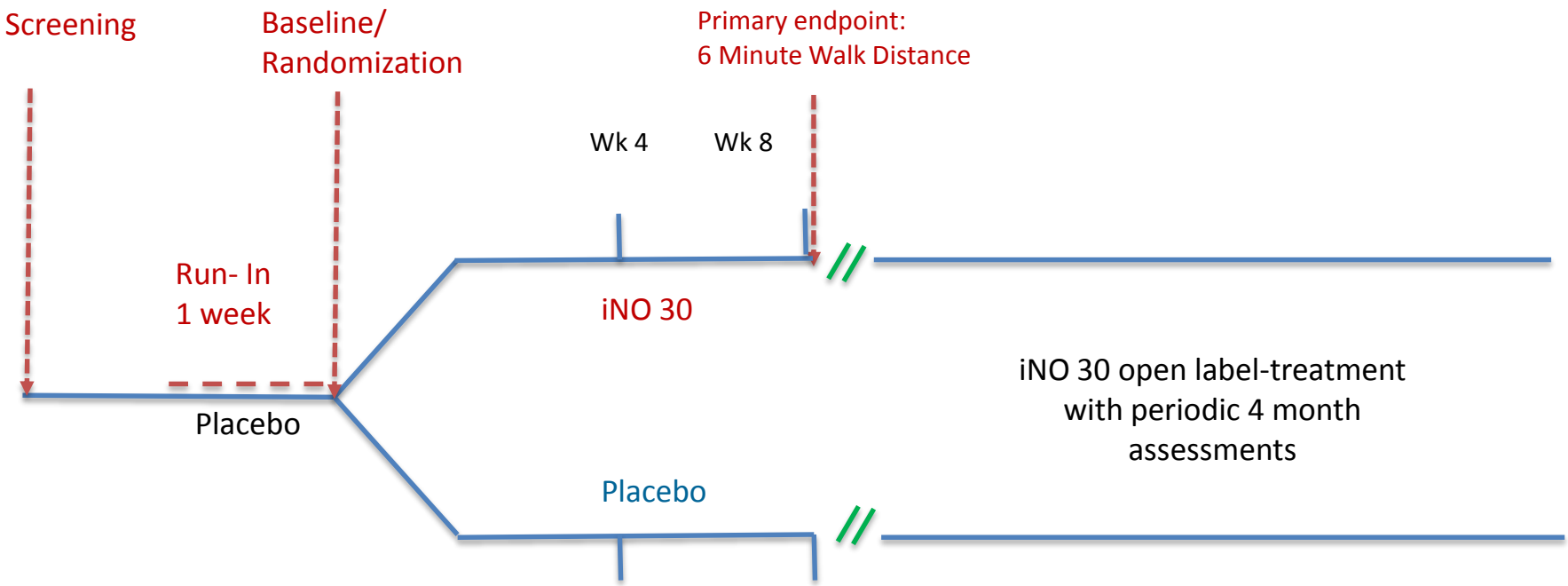
- Meeting Outcome on June 15
  - FDA confirmed acceptance of 6MWD and RV Function as primary and secondary endpoints
  - Agreement to allow identification of PH using Echo represents a paradigm shift for FDA
    - Use of a Echo, which is non-invasive, will significantly help increase the rate of recruitment in this patient population

- IND for Treatment of Pulmonary Fibrosis with inhaled NO was accepted on August 2, 2017

Patient Population for iNO-PF Study



iNO-PF (N=~40 subjects)



Run in period	Baseline	Week 4	Week 8	Four monthly visits
> 12 hrs of use / day	6MWD	6 MWD	6MWD	AEs
ECHO			ECHO	

Endpoints

Primary Endpoint

- Change in 6MWD

Secondary Endpoint

- Change in right ventricular function assessed by multiple parameters via echocardiography

Exploratory Endpoints

- Composite measurements combining oxygen saturation and walk distance during 6MWT
- Change in activity levels as measured by activity monitor
- Dyspnea as measured by University of California, San Diego (UCSD) Shortness of Breath Questionnaire (SOBQ)

PH-ILD Steering Committee

Steven Nathan MD
Professor of Medicine at Virginia Commonwealth University Inova Campus, Director of the Advanced Lung Disease Program and Director of the Lung Transplant Program at Inova Fairfax Hospital.

Kevin Flaherty MD
Professor, Department of Internal Medicine, University of Michigan, Associate Director, T32 Multidisciplinary Training Program in Lung Diseases, Chair of Pulmonary Fibrosis Foundation Clinical Care Network Steering Committee

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Jeffrey Swigris MD
Associate Professor, Department of Medicine, National Jewish, Denver Colorado, Division of Pulmonary, Critical Care and Sleep Medicine

Next Steps in PH-ILD

- Top Line Results for iNO-PF expected in 2018
  - Results will help finalize patient population and clinical endpoints and study size for next study

- Both PH-PF and PF would support Orphan Designation and 7 years exclusivity

- Potential for single Phase 3 trial to support NDA in underserved patient population

Thank you

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