Supplemental Material

Supplemental Methodology
Inclusion and exclusion criteria
Inclusion criteria
1. Age ≥18 years.
2. Diagnostic RHC with precapillary pulmonary hypertension based on mPAP ≥21mmHg, PAWP ≤15mmHg, and PVR ≥3WU.
3. Diagnosis of restrictive parenchymal lung disease from either:
    a. Interstitial lung disease (ILD), defined as both:
        i. Computed tomography (CT) chest with fibrotic diffuse parenchymal lung disease chest
        ii. FVC or TLC < 70% on pulmonary function tests
    b. Combined pulmonary fibrosis and emphysema (CPFE), defined as:
        i. Co-existing emphysema ≥5% of lung volume with pulmonary fibrosis

Exclusion criteria
1. Echocardiogram with **any of**:
    a. Left ventricular ejection fraction <0.5
    b. Significant (2+) mitral or aortic regurgitation
    c. If echocardiogram is not available, cardiac MRI could be used as substitute
2. Restrictive, infiltrative, or hypertrophic cardiomyopathy.
3. Acute coronary syndrome at RHC.
4. Cardiogenic or other shock at initial RHC, requiring intravenous inotropes or vasopressor support (dobutamine, dopamine, norepinephrine, etc.).
5. More than mild obstructive sleep apnea that is untreated.
6. History of full pneumonectomy.
7. If history of pulmonary embolism, must be resolved on angiography or V/Q scan prior to inclusion.
8. Pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis.
9. Incomplete data (i.e., missing mPAP, PAWP, CO, or PVR).

Right heart catheterization protocol
   Right heart catheterization was performed using a single lumen balloon-tipped 7Fr pulmonary artery floatation catheter (Edwards Lifesciences, Irvine, CA, USA) placed under ultrasound and fluoroscopic guidance via the internal jugular vein. Zero-reference was set at the mid-axillary line with the patient in a supine position. In all cases, baseline hemodynamics were recorded including mean right atrial pressure (RAP), right ventricular end-diastolic pressure (RVEDP), mPAP, PCWP, and PVR. Cardiac output (CO) was calculated via either thermodilution or the estimated Fick equation and was indexed to body surface area for cardiac index (CI). In each patient, the same CO method was utilized to ensure CO changes were not related to measurement technique. Stroke volume was calculated as CO divided by heart rate. As described in the Methods, we calculated single-point distensibility via solution of the original Linehan equation for α through re-arrangement of the formula into a quartic

equation to solve for the real physiologic root. That noted, online calculators have recently been developed to calculate distensibility[1].

Supplemental Figure 1. CONSORT flow diagram.
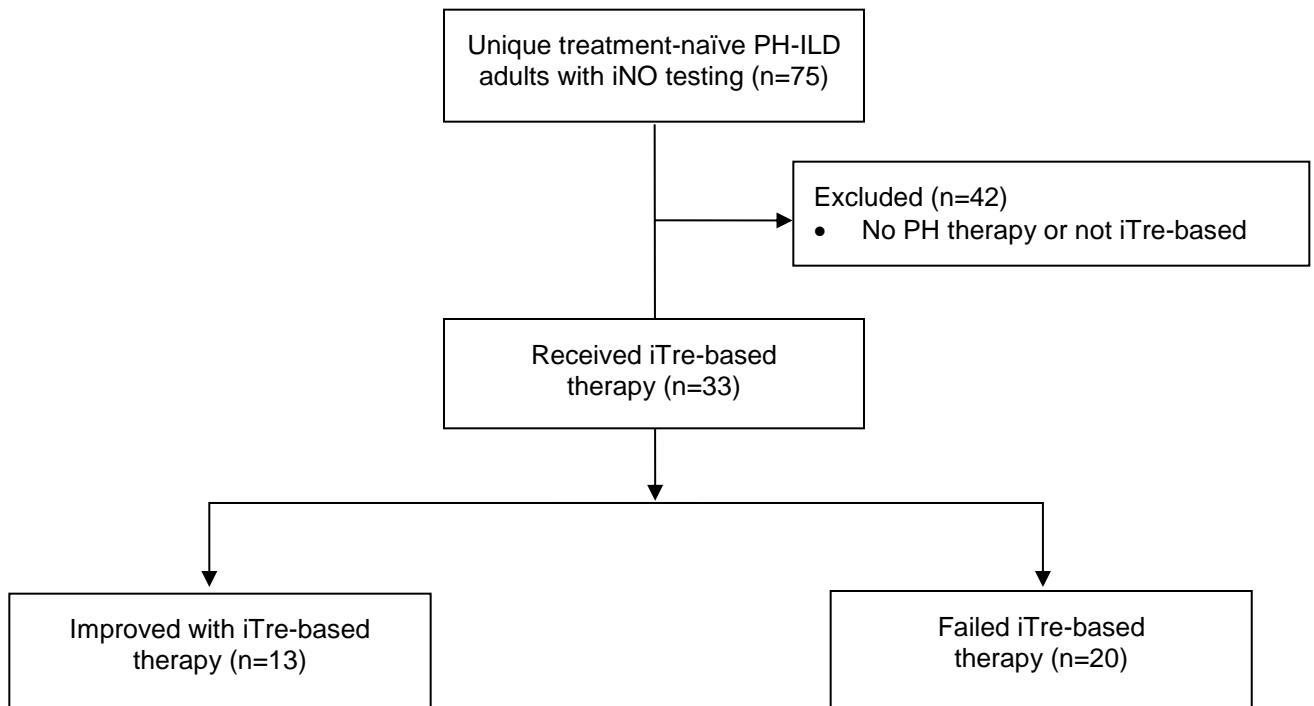
Supplemental Table 1. Hemodynamics with vasoreactivity testing in PH-ILD. ΔO2 denotes change from room air to O2. ΔO2 + iNO denotes change from O2 to combined O2 and iNO. Presented as mean ($\pm$ standard deviation), median [interquartile range].

	Room air (n = 49)	O2 (n = 58)	iNO (n = 75)	ΔO2	ΔO2 + iNO
mPAP, mmHg	38.0 [32.0, 46.0]	34.0 [31.0, 42.0]	30.0 [26.0, 39.0]	-3.0 [-5.0, -1.0]	-4.0 [-6.0, -2.0]
PAWP, mmHg	9.4 (3.9)	9.4 (4.2)	10.3 (4.6)	0 [-1.0, 2.0]	1.0 [-1.0, 3.0]
CI, $L\cdot min^{-1}\cdot m^{-2}$	2.3 [2.0, 2.7]	2.4 [2.0, 2.9]	2.6 [2.1, 3.0]	0.2 (0.3)	0.1 [0, 0.2]
PVR, Wood Units	5.9 [4.9, 8.9]	5.3 [4.3, 7.7]	4.1 [3.1, 6.1]	-0.9 [-2.0, -0.5]	-1.4 [-2.5, -0.6]
Compliance, $mL\cdot mmHg^{-1}$	1.6 (0.6)	1.9 (0.9)	2.4 (1.1)	0.4 [0.1, 1.1]	0.4 (0.5)
Distensibility, $\%\cdot mmHg^{-1}$	0.31 [0.2, 0.4]	0.35 [0.2, 0.5]	0.47 [0.3, 0.7]	0.04 [0, 0.1]	0.11 [0, 0.2]

Supplemental Table 2. Objective metrics from baseline to follow-up in PH-ILD patients who experienced iTre improvement (n=13). Presented as mean (±standard deviation); median time to repeat testing 7.7 months.

	N*	Baseline	Follow-up
Right heart catheterization	2		
mPAP (mmHg)		53.0 (5.7)	33.5 (9.2)
PCWP (mmHg)		9.0 (4.2)	8.5 (0.7)
CO (L/min)		5.8 (1.2)	6.0 (2.3)
PVR (WU)		3.9 (5.3)	2.1 (2.9)
Transthoracic echocardiogram	7		
RVSP (mmHg)		71 (31.7)	45.4 (21.6)
Six-minute walk test	2		
Distance (m)		274.5 (99.7)	355.5 (157.7)
Distance (% pred)		51.5 (13.4)	67.5 (24.7)
Three-minute submaximal exercise test	4		
VE/VCO2 slope		43.8 (10.3)	37.5 (29.5)
Resting $P_{ET}CO2$ (mmHg)		33.0 (5.9)	34.5 (7.5)
O2 uptake efficiency slope		0.9 (0.5)	1.2 (0.9)
Peak VO2, % predicted		46.5 [36.0, 57.5]	53.0 [53.0, 53.3]

Abbreviations; mPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; PVR, pulmonary vascular resistance; TR, tricuspid regurgitant; RVSP, right ventricular systolic pressure; VE, minute ventilation, VCO2, carbon dioxide production; $P_{ET}CO2$, end-tidal carbon dioxide; VO2, oxygen consumption; WHO, World Health Organization.
*Two patients had two objective assessment methods. All assessments met improvement criteria. For this group, both tests were included.

Supplemental Table 3. Baseline characteristics and hemodynamics in PH-ILD patients who failed and improved with iTre. Presented as mean (±standard deviation), median [interquartile range], or number (%)*.

	All iTre-treated (n = 33)	iTre improvement (n = 13)	iTre failure (n = 20)
Age, years	69.0 [63.8, 77.0]	65.6 [56.2, 69.0]	72.5 [65.3, 78.1]
Male gender, n (%)	14 (42.4)	7 (53.9)	7 (35.0)
Body mass index, kg·m^{-2}	27.1 (4.2)	27.3 (4.1)	27.0 (4.4)
Combined pulmonary fibrosis and emphysema, n (%)	8 (24.2)	4 (30.8)	4 (20.0)
Comorbidities, n (%)			
Obstructive sleep apnea	10 (30.3)	2 (15.3)	8 (40.0)
Current or former tobacco use	20 (60.6)	6 (46.1)	14 (70.0)
Connective tissue disease	15 (45.5)	6 (46.1)	9 (45.0)
CPFE	9 (27.3)	4 (30.8)	5 (25.0)
Pulmonary function tests			
FEV1, % predicted	63.0 (17.0)	63.3 (17.5)	62.8 (17.2)
FVC, % predicted	61.0 [51.0, 69.0]	62.0 [50.0, 81.0]	60.0 [54.0, 69.0]
FEV1/FVC	82.5 [73.0, 87.0]	81.0 [60.0, 87.0]	83.0 [77.0, 88.0]
TLC, % predicted	59.0 [56.0, 77.0]	67.0 [52.5, 106.5]	59.0 [56.0, 65.0]
DLCO, % predicted	28.8 (12.9)	28.9 (10.9)	28.4 (14.0)
Baseline hemodynamics			
Mean RAP, mmHg	6.7 (4.1)	7.5 (4.7)	6.2 (3.7)
RVEDP, mmHg	9.3 (4.7)	10.9 (5.1)	8.3 (4.2)
Mean PAP, mmHg	41.8 (12.0)	46.2 (13.4)	38.9 (10.4)
PAWP, mmHg	9.2 (3.4)	9.5 (3.5)	9.0 (3.4)
CO, L·min^{-1}	4.5 (1.1)	4.3 (1.0)	4.6 (1.1)
CI, L·min^{-1}·m^{-2}	2.2 [2.0, 2.9]	2.1 [1.9, 3.1]	2.2 [2.0, 2.6]
PVR, Wood units	6.8 [4.8, 8.6]	7.5 [5.7, 11.1]	5.4 [4.2, 8.5]
PA compliance, mL·mmHg^{-1}	1.6 (0.6)	1.5 (0.6)	1.7 (0.6)
Distensibility, %·mmHg^{-1}	0.31 (0.19)	0.27 (0.17)	0.34 (0.20)
SpO2, %	96.5 [94.5, 98.5]	96.0 [93.0, 97.0]	97.0 [95.0, 99.0]

Abbreviations: CPFE, combined pulmonary fibrosis and emphysema; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; TLC, total lung capacity; DLCO, diffusing capacity for carbon monoxide; RAP, right atrial pressure; RVEDP, right ventricular end diastolic pressure; PAP, pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; CO, cardiac output; CI, cardiac index; PVR, pulmonary vascular resistance; WU, Wood units; PA, pulmonary artery.

.**Missing data: Listed as variable, n. Compliance, 1; SpO2, 1.

Supplemental Table 4. Acute vasoreactive response within the cohort stratified by six-month iTre improvement vs. failure after removal of patients who received concurrent PDE5i therapy (n=6). A) absolute change; B) relative change.

A) Absolute change.

	Baseline to iNO		O2		O2 + iNO	
	Improve (n = 8)	Fail (n = 19)	Improve (n = 3)	Fail (n = 10)	Improve (n = 7)	Fail (n = 17)
mPAP, mmHg	-6.9 (3.1)	-5.2 (3.6)*	-4.7 (0.6)	-2.4 (2.0)	-5.0 (2.1)	-3.8 (2.8)
PAWP, mmHg	0.3 (4.0)	0.4 (3.4)	-2.7 (2.1)	1.7 (3.5)*	1.0 [-1.0, 2.0]	-1.0 [-2.0, -1.0]
CI, L/min/m^2	0.1 [-0.05, 0.2]	0.2 [0, 0.4]	0 (0.1)	0.1 (0.3)	0.1 (0.1)	0.1 (0.1)
PVR, Wood Units	-1.8 [-3.2, -1.4]	-1.6 [-2.2, -0.9]	-0.7 [-0.8, -0.2]	-0.7 [-1.5, 0.2]	-1.7 [-3.2, -1.1]	-1.0 [-1.7, -0.5]*
Compliance, mL/mmHg	0.7 (0.6)	0.5 (0.4)	0.2 [0.1, 0.8]	0.5 [0.1, 0.6]	0.5 (0.6)	0.3 (0.3)
Distensibility, %/mmHg	0.11 [0.03, 0.29]	0.09 [0.03, 0.18]	-0.01 (0.06)	0.07 (0.08)	0.13 [0.04, 0.40]	0.05 [0, 0.11]

B) Relative change.

	Baseline to iNO		O2		O2 + iNO	
	Improve (n = 8)	Fail (n = 19)	Improve (n = 3)	Fail (n = 10)	Improve (n = 7)	Fail (n = 17)
mPAP, %	-16.7 (8.4)	-13.5 (7.3)	-13.2 [-20.8, -6.0]	-6.6 [-8.5, 0]	-12.5 (2.7)	-10.0 (6.5)
PAWP, %	2.0 [-19.9, 10.4]	0 [-0.5, 18.2]	-26.7 (16.1)	10.3 (21.9)	25.0 [-7.7, 33.3]	-10.0 [-25.0, 7.7]
PVR, %	-26.5 (13.4)	-25.0 (11.8)	-8.7 (9.7)	-13.7 (13.0)	-24.4 [-28.7, -22.2]	-19.4 [-23.9, -11.8]*
CI, %	3.7 (16.8)	5.5 (23.9)	3.7 (16.8)	6.8 (17.2)	6.1 [0, 12.3]	7.2 [0, 10.0]
Compliance, %	43.2 (32.8)	34.0 (22.7)	63.1 [21.8, 15.1]	27.5 [7.4, 36.3]	28.9 (31.9)	18.4 (15.4)
Distensibility, %	33.1 [18.8, 84.1]	25.7 [14.0, 83.4]	-2.9 (14.0)	26.8 (28.1)	63.2 [21.9, 80.0]	15.3 [3.0, 20.0]*

*Significant at p<0.05.
Abbreviations: ITI, inhaled treprostinil improvement; ITF, iTre failure.
Missing data: Listed as variable, n. Compliance, 2.

References

1. Elliott J, Menakuru N, Martin KJ, Rahaghi FN, Rischard FP, Vanderpool RR. iCPET Calculator: A Web-Based Application to Standardize the Calculation of Alpha Distensibility in Patients With Pulmonary Arterial Hypertension. *Journal of the American Heart Association.* 2023;12(20):e029667.