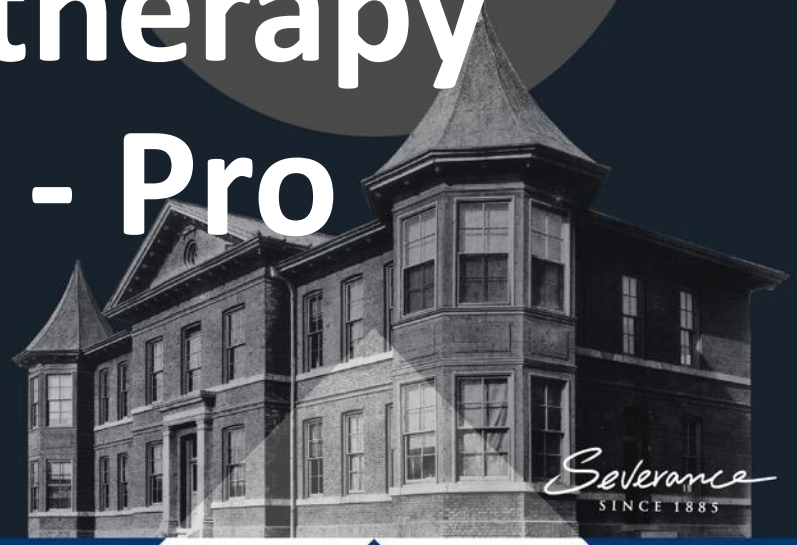
결핵및 호흡기학회 춘계학술대회
2024-4-13 11:50 ~ 12:15

YONSEI UNIVERSITY

PAH target therapy in PH-ILD - Pro



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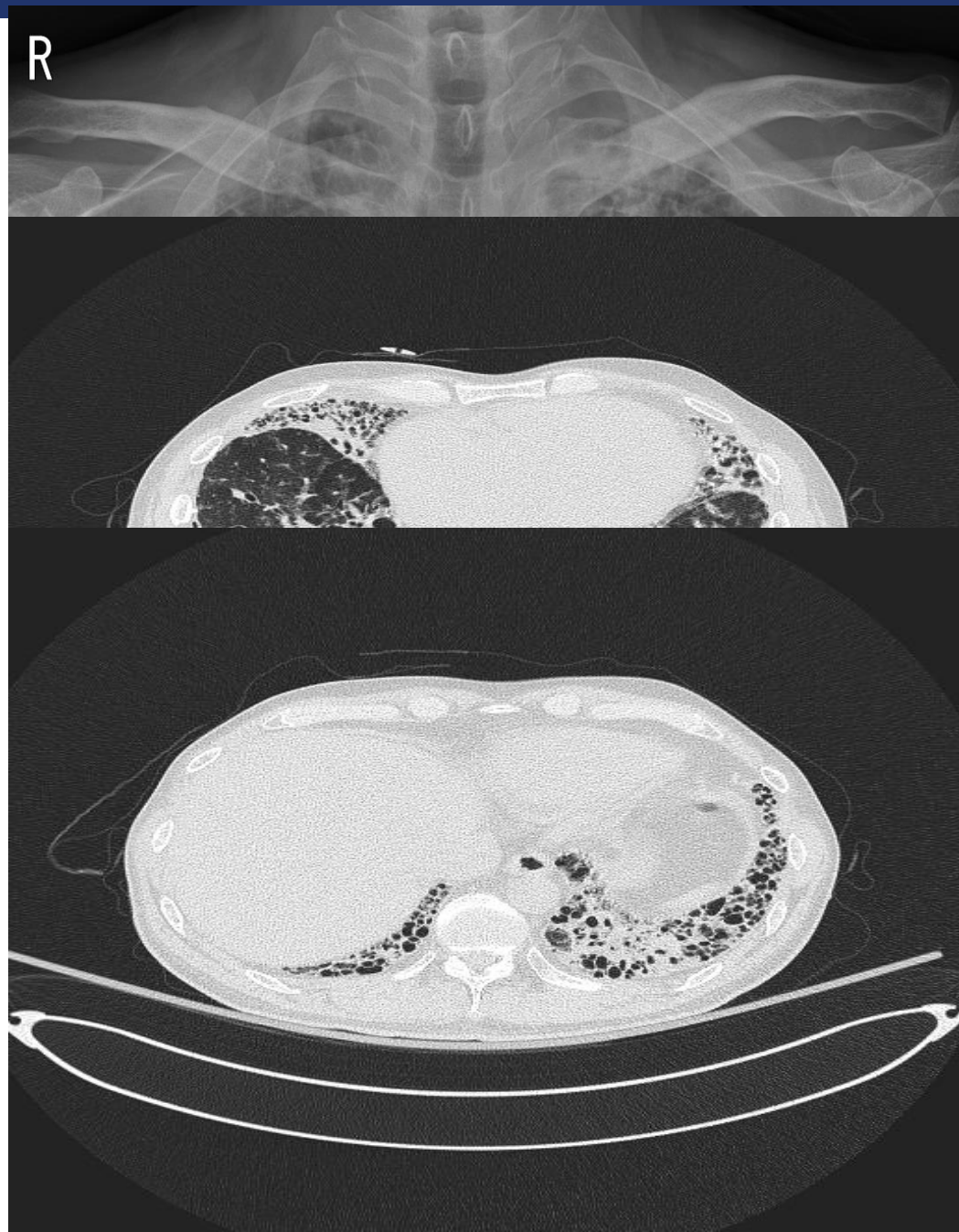
M/59

- IPF Dx 5yrs ago
- Aggravation of dyspnea
- Pitting edema, both
- Home O2 5L
- BP 117/70 , HR 120



		Ref	Pre	% Ref	Post	% Ref	%Chg
Spirometry							
FVC	Liters	4.90	1.88	38			
FEV1	Liters	3.79	1.52	40			
FEV1/FVC	%	75	81				
FEV3	Liters		1.78				
FEV6	Liters		1.86				
FEF25-75%	L/sec	3.19	1.67	52			
IsoFEF25-75	L/sec	3.19	1.67	52			
FEF50%	L/sec	4.34	3.02	70			
PEF	L/sec	8.46	7.65	90			
FET100%	Sec		7.14				
FIF50%	L/sec		2.85				
Diffusing Capacity							
DLCO	mL/mmHg/min	25.9	4.6	18			
DL Adj	mL/mmHg/min	25.9	4.6	18			
DLCO/VA	mL/mHg/min/L	3.89	1.77	46			
DL/VA Adj	mL/mHg/min/L		1.77				
VA	Liters		2.58				
IVC	Liters		1.72				

TTE

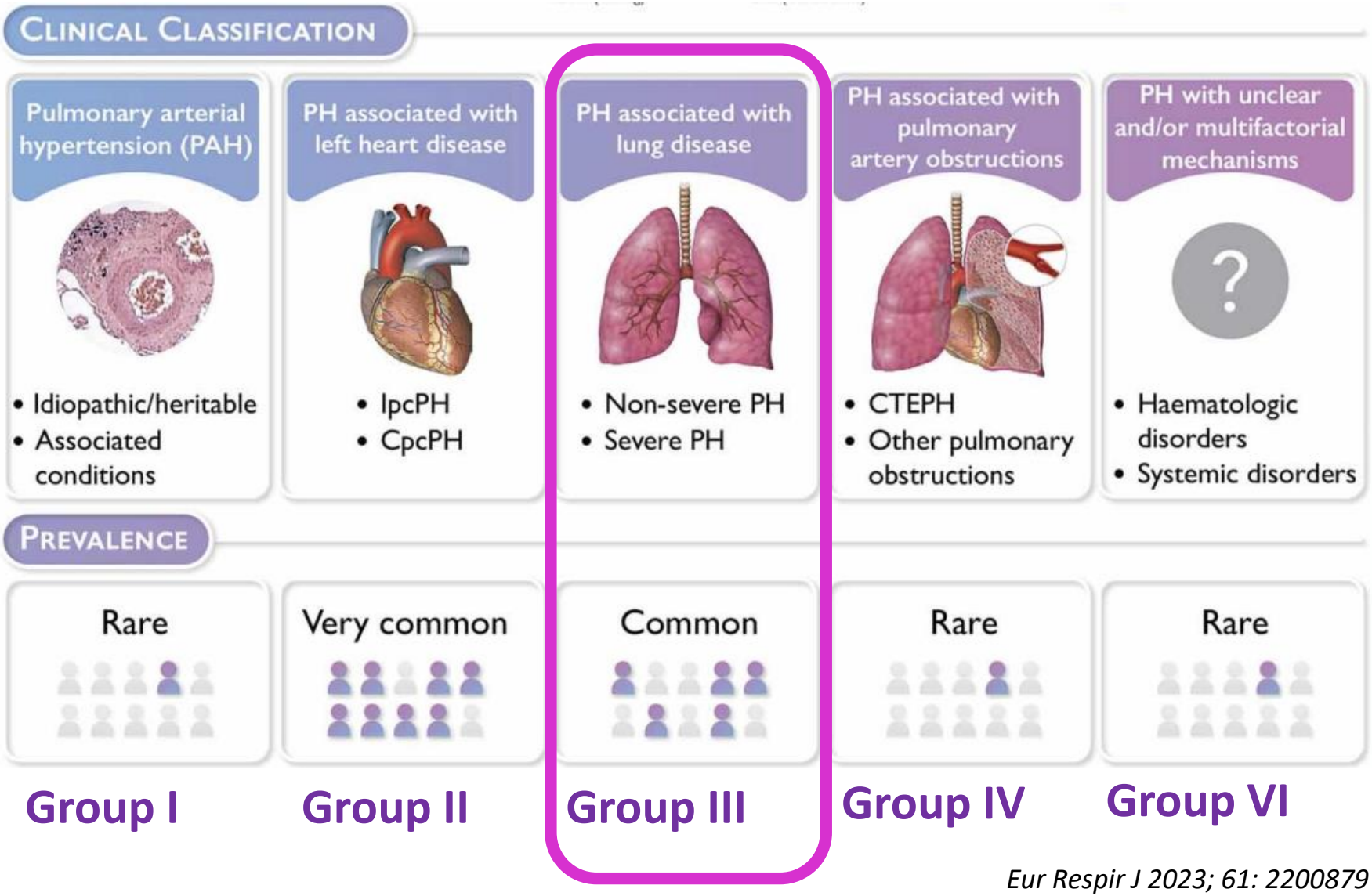
1. Severe pulmonary HTN **(RVSP: 130mmHg)** with IVC plethora (23mm)
2**. Severe TR** (G III-IV/IV) due to incomplete coaptation with dilated TV annulus (48mm, 26mm/m2)
 - Systolic flow reversal of HV was also observed.
3. Enlarged RA, RV and RVH (9mm) with reduced RV systolic function **(RV FAC: 11%)**
 - Relatively preserved RV basal wall motion (RV S': 11cm/s)
4. Small sized LV chamber (LVEDD/ESD : 39/27mm) with normal global LV systolic function (EF: 62%) and D-shape of LV
5. Relaxation abnormality of LV filling pattern (E/e': 5)
6. Slightly dilated sinus of Valsalva (36mm)

Rt side catheterization

PCWP 14
mPAP 51
PVR 9

Definition and classification of PH

- Definition : mPAP ≥ 20mmHg



Eur Respir J 2023; 61: 2200879

GROUP 1 Pulmonary arterial hypertension (PAH)

- 1.1 Idiopathic
  - 1.1.1 Non-responders at vasoreactivity testing
  - 1.1.2 Acute responders at vasoreactivity testing
- 1.2 Heritable[a]
- 1.3 Associated with drugs and toxins[a]
- 1.4 Associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
- 1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
- 1.6 Persistent PH of the newborn

GROUP 3 PH associated with lung diseases and/or hypoxia

- 3.1 Obstructive lung disease or emphysema
- 3.2 Restrictive lung disease
- 3.3 Lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoventilation syndromes
- 3.5 Hypoxia without lung disease (*e.g.* high altitude)
- 3.6 Developmental lung disorders

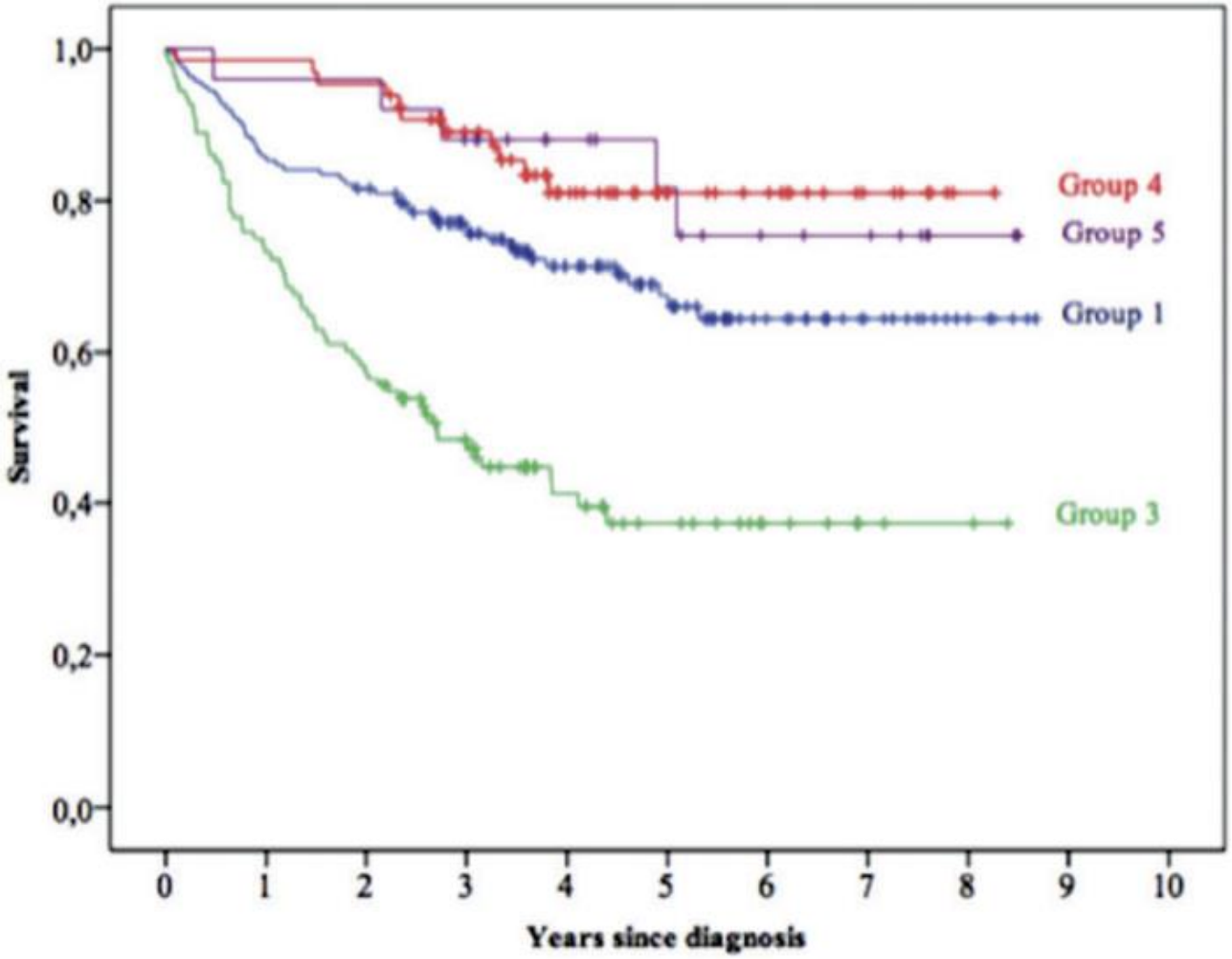
Eur Respir J 2023; 61: 2200879

Importance of PH in ILD

- Prevalence of PH
  - IIP
    - PH (cutoff 25mmHg) : 8-15% , 35-50% in advanced IPF, end-stage >60%
  - CPFE
    - PH : 30-50%
- Outcome of ILD with PH
  - Risk of mortality ↑
  - Propensity for acute exacerbations ↑
  - Quality of life ↓
  - Exercise capability ↓
  - Need for supplemental oxygen ↑

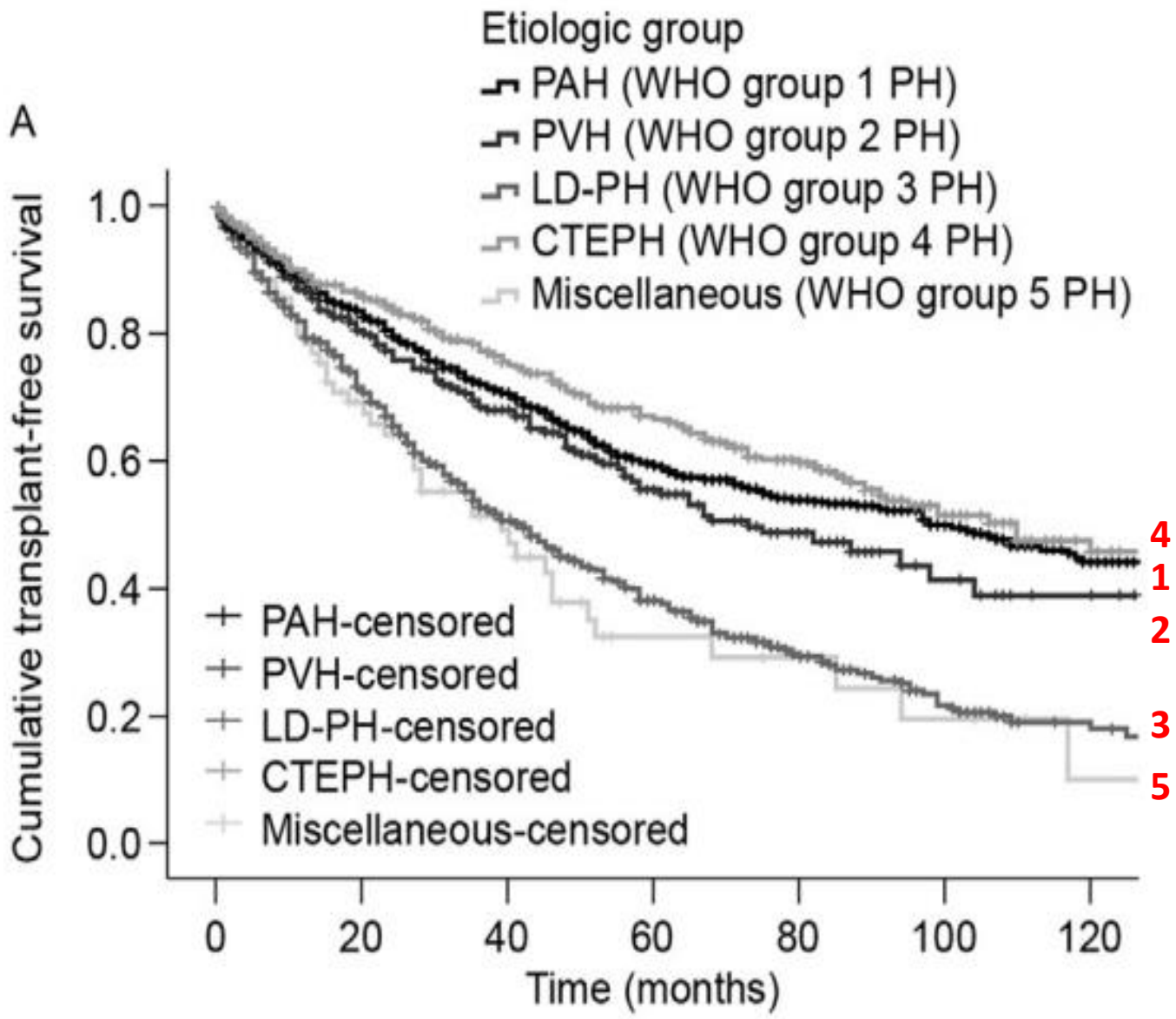
Pulm Circ. 2021;11(2) 20458940211005641, *Chest.* 2006;129(3):746–752, *Eur Respir J.* 2010;35(1):105–111, *Chest.* 2009;136(1):10–15, *BMC Pulm Med.* 2016;16(1):55, *Eur Respir J.* 2005;26(4):586–593, *Eur Respir J.* 2012;40(1):93–100, *Respir Med.* 2012;106(11):1613–1621, Curr Opin Pulm Med 2021; 27:396–404, Respiration 2013; 85:456–463. Chest 2007; 131:650–656, Am J Respir Crit Care Med 2006; 174:659–664, Chest 2007;131:657–663, Eur Respir J 2007;30:715–721, Respir Med 2007; 101:2153–2159, Respir Care 2010;55:584–588, Respir Med 2012;106:1613–621

Poor prognosis of Group 3 PH



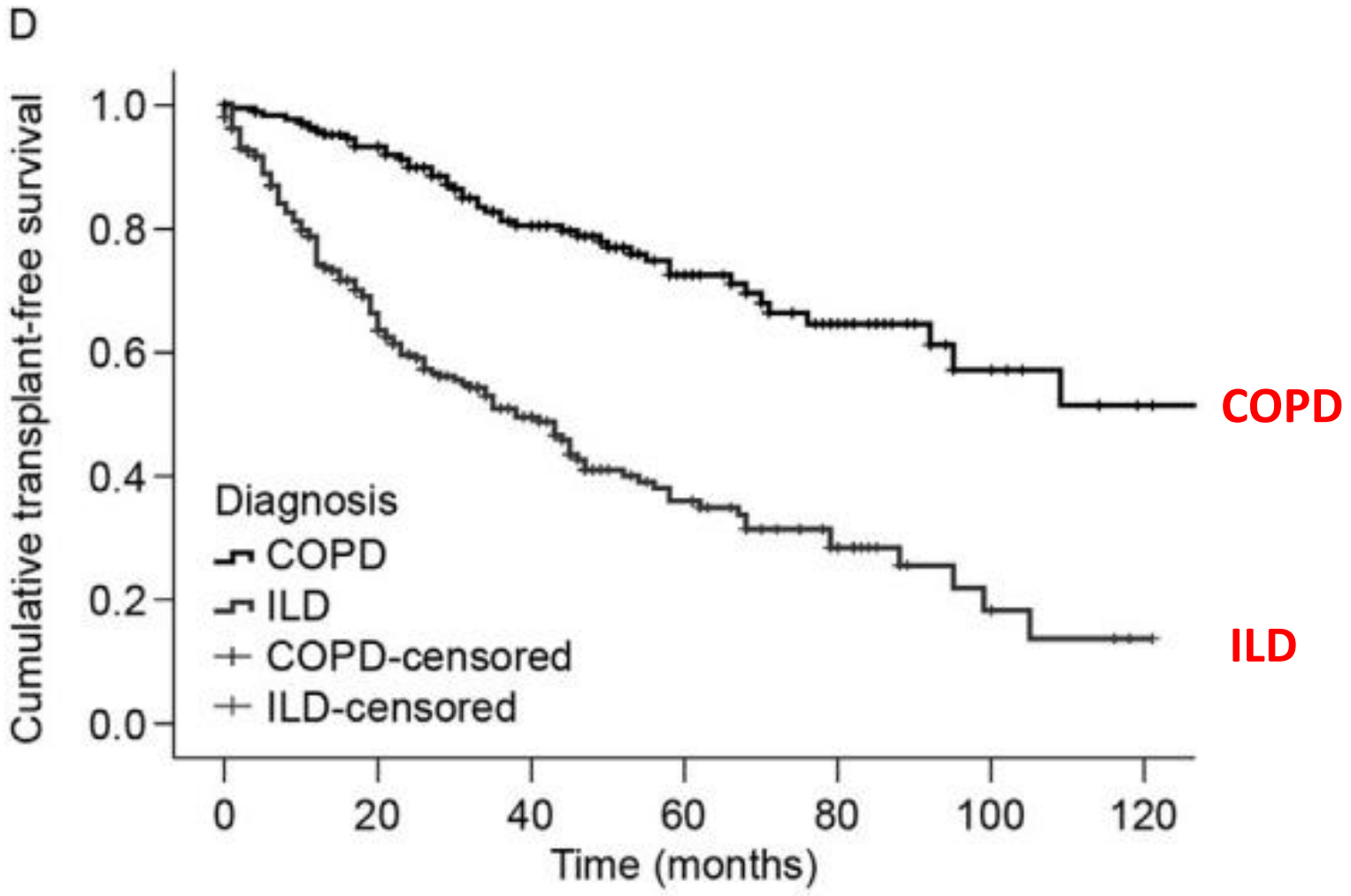
Numbers at risk										
	Group 1	164	139	132	125	119	115	115	115	115
	Group 3	109	79	61	51	47	45	45	45	45
	Group 4	65	64	61	57	54	53	53	53	53
	Group 5	25	24	23	22	20	20	20	20	20

Pulm Circ 2018; 8:2045894018775056.



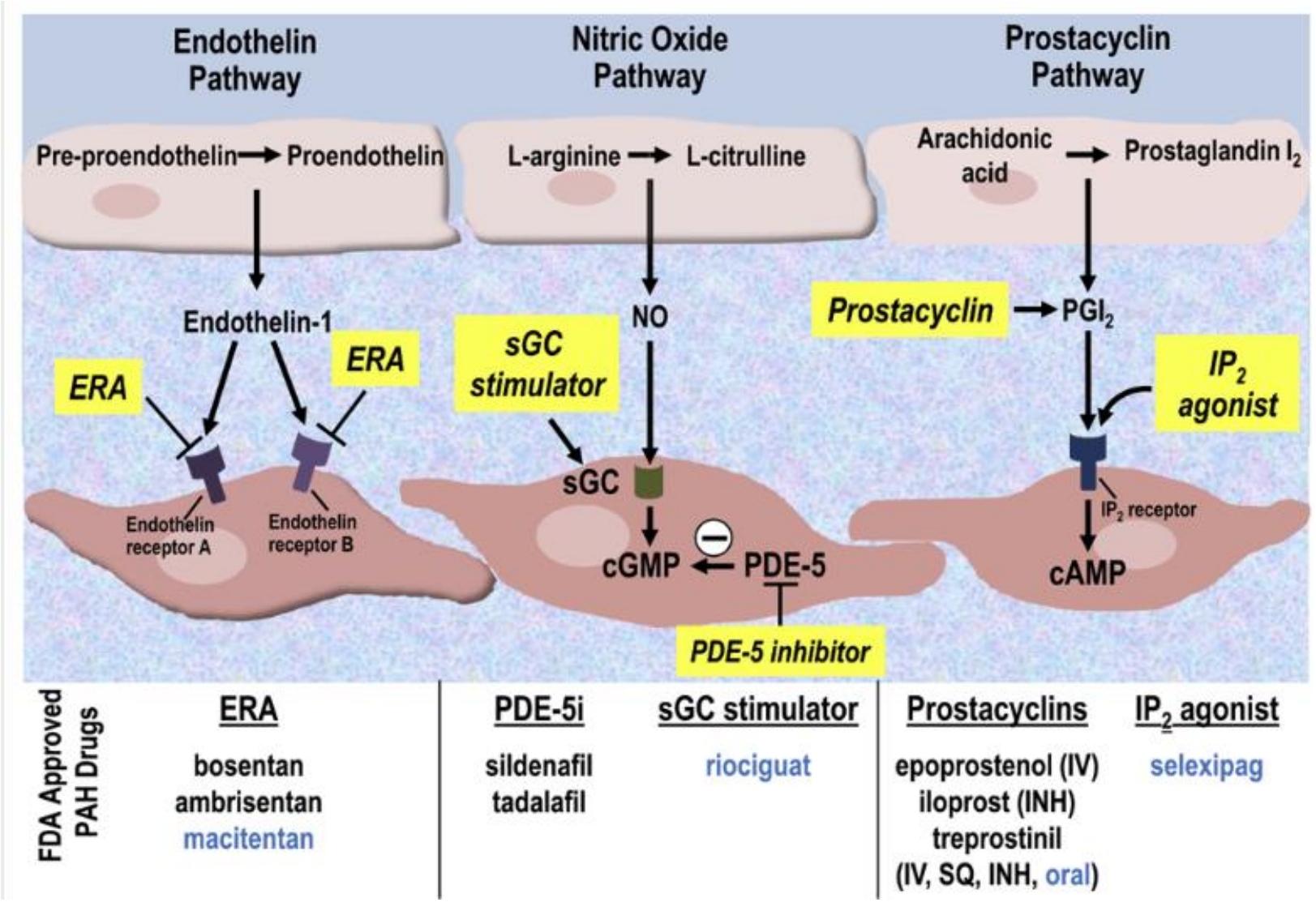
J Heart Lung Transplant 2017;36:957-967

Prognosis of ILD-PH vs. COPD-PH



J Heart Lung Transplant 2017;36:957-967

Pathways targeted therapies for PAH



F1000Research 2016, 5(F1000 Faculty Rev):2755 (https://doi.org/10.12688/f1000research.9739.1)

Sildenafil in advanced IPF (STEP-IPF)

- Double-blind, randomized, placebo -controlled trial
- Oral sildenafil (20 mg t.i.d) for 12 weeks
- Advanced IPF (DLCO <35 % of predicted)
- Primary outome : the presence or absence of an improvement of at least 20% in the 6-minute walk distance at 12 weeks, as compared with baseline.
- Sildenafil (N=89) vs. Placebo (N=91)

Primary outcome:

10% (9/89, Sildenafil) vs. 7% (6/91, Placebo) , P=0.39

Pulmonary function				
Forced vital capacity (% of predicted value)	−0.97 (−2.00 to 0.06)	−1.29 (−2.30 to −0.28)	0.32 (−1.12 to 1.76)	0.66
Carbon monoxide diffusion capacity (% of predicted value)	−0.33 (−1.36 to 0.71)	−1.87 (−2.91 to −0.83)	1.55 (0.08 to 3.01)	0.04
Partial pressure of oxygen (mm Hg)	−0.63 (−2.41 to 1.16)	−3.64 (−5.41 to −1.87)	3.02 (0.50 to 5.53)	0.02
Partial pressure of carbon dioxide (mm Hg)	−0.01 (−0.75 to 0.73)	−0.02 (−0.75 to 0.71)	0.01 (−1.03 to 1.05)	0.98
Alveolar–arterial gradient (mm Hg)	0.41 (−1.54 to 2.37)	2.95 (0.99 to 4.92)	−2.54 (−5.31 to 0.23)	0.07
Arterial oxygen saturation (%)	−0.17 (−1.02 to 0.69)	−1.38 (−2.23 to −0.52)	1.21 (0.00 to 2.42)	0.05

N Engl J Med 2010;363:620

Sildenafil+Nintedanib in IPF (INSTAGE)

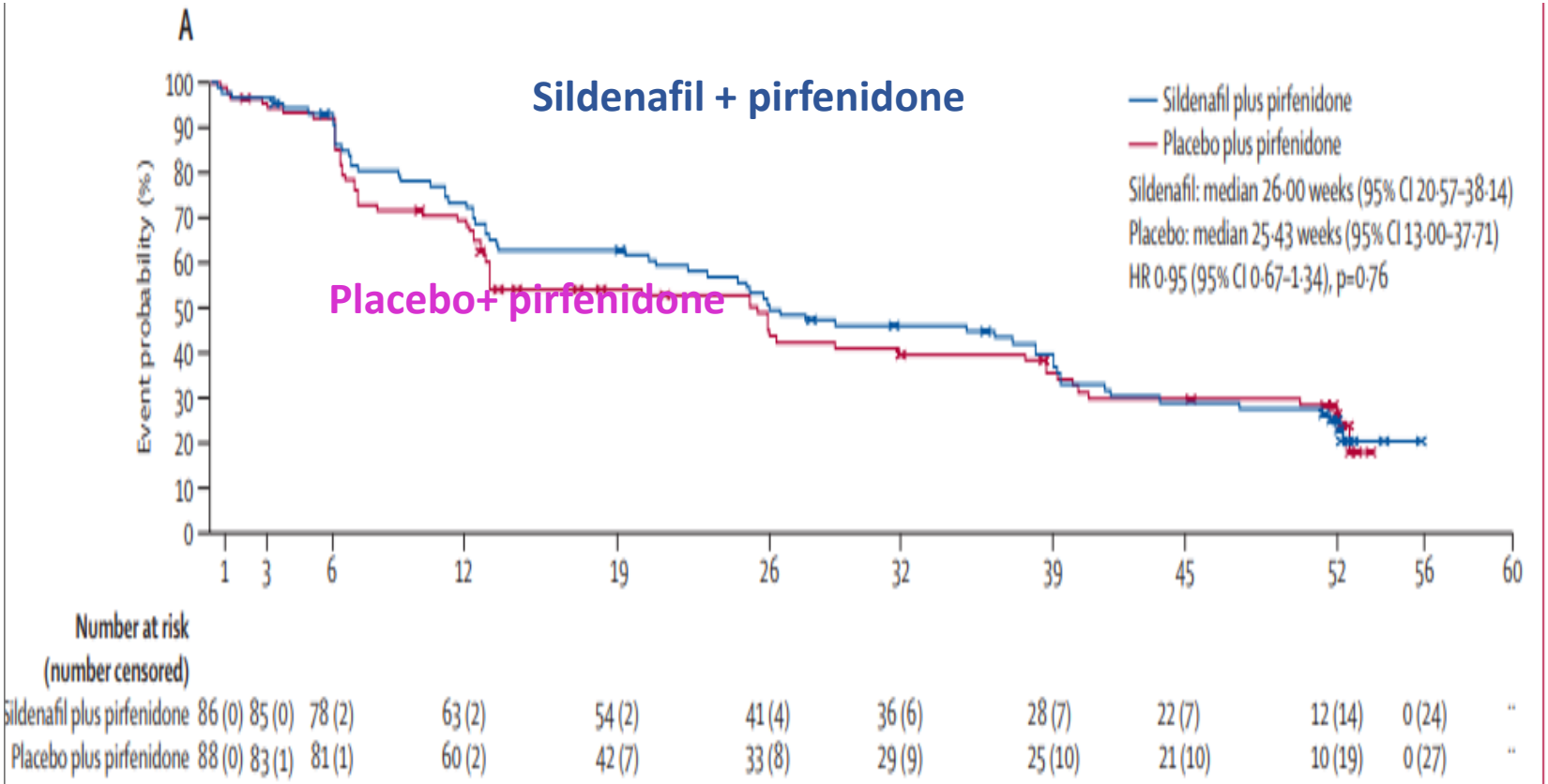
- Double-blind, randomised, placebo-controlled trial
- IPF (DLCO <35 % of predicted)
- Ninteadnib + Sildenafil (N=137) vs. Nintedanib + Placebo (N=136), 24wks
- Primary outcome: the change from baseline in the SGRQ total score at week 12
- Rt heart dysfunction sign on Echo : 61 % vs. 56 %

FVC — % of predicted value					
At wk 12	119	0.4±0.5	124	-0.9±0.5	1.3 (-0.1 to 2.8)
At wk 24	109	-0.5±0.6	108	-1.9±0.6	1.4 (-0.3 to 3.1)
Oxygen saturation — %					
At wk 12	121	0.20±0.27	127	0.26±0.26	-0.05 (-0.80 to 0.69)
At wk 24	113	0.03±0.32	111	-0.32±0.32	0.35 (-0.55 to 1.25)
D_{LCO} — % of predicted value					
At wk 12	114	1.3±0.7	120	-0.4±0.7	1.7 (-0.3 to 3.7)
At wk 24	105	-0.7±0.7	101	-1.6±0.7	0.9 (-1.1 to 2.9)
Brain natriuretic peptide level at wk 24 — ng/liter	108	-11.6±12.1	106	39.7±12.0	-51.3 (-85.1 to -17.6)

N Engl J Med 2018; 379:1722–1731

Sildenafil + pirfenidone in advanced IPF

- Double-blind, randomised, placebo-controlled, phase 2b
- Advanced IPF (DLCO ≤ 40%)
- At risk of Group 3PH (mPAP ≥ 20 and PAWP ≤ 15 on RHC 18% vs. 19% or intermediate or high probability of Group 3 PH on echo)
- Sildenafil + pirfenidone (N=89) vs. Placebo +pirfenidone (N=88), 52wks
- Primary endpoint: proportion of pt with dz progression (decline of 6MWT, respiratory related admission, all cause mortality)



Lancet Respir Med 2021; 9(1): 85–95

Proper study design for ILD-PH?

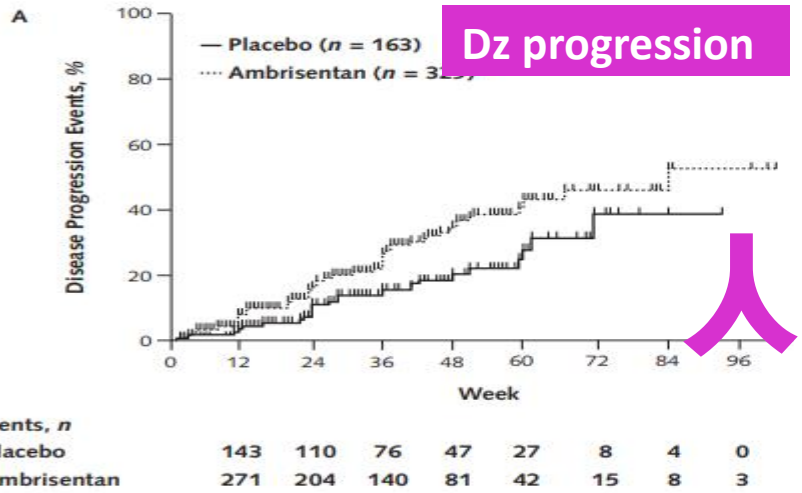
- Enriched for PH
  - DLCO <35 % of predicted
  - DLCO ≤ 40% + at risk of Group 3 PH
    - mPAP ≥ 20 and PAWP ≤ 15 on RHC (18~19%) or intermediate or high probability of Group 3 PH on echo

- ILD-PH (confirmed by RHC) ?

Ambrisentan in IPF (ARTEMIS-PH)

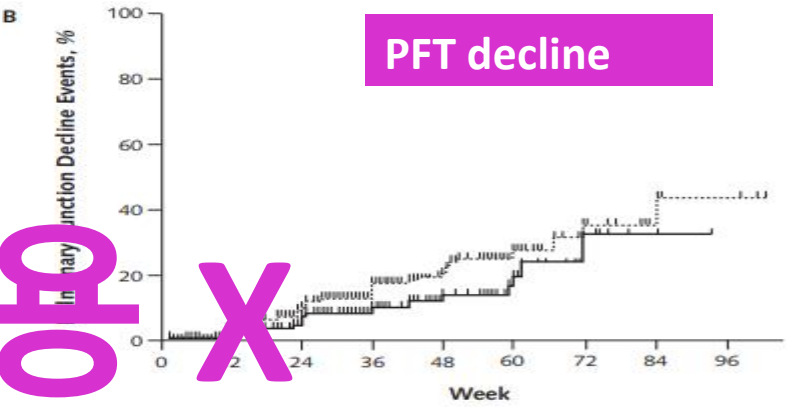
- Randomized, double-blind, placebo=controlled (Ambrisentan 329 , placebo 163)
- IPF (honeycomb <5%) , primary outcome: IPF dz progression
- PH on RHC: Ambrisentan (9.7%) vs Placebo (9.8%)
- mPAP : Ambrisentatn (20.3mmHg) vs. Placebo (20.6mmHg)

Dz progression



Patients, *n*								
Placebo	143	110	76	47	27	8	4	0
Ambrisentan	271	204	140	81	42	15	8	3

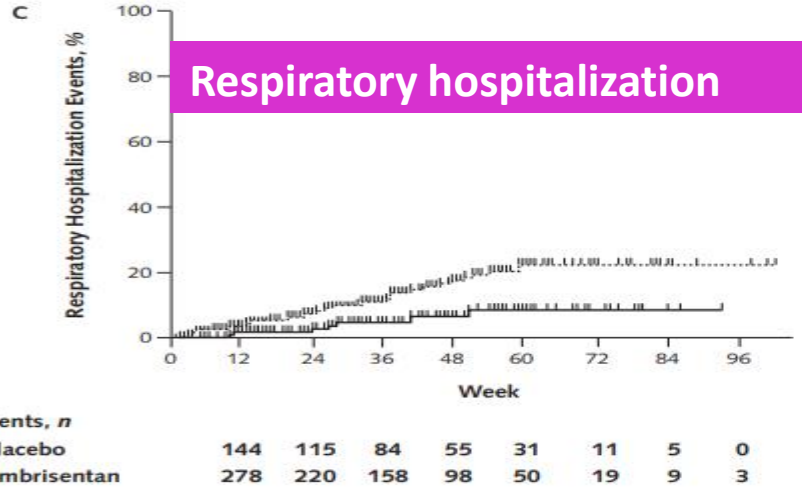
PFT decline



Patients, *n*								
Placebo	144	110	77	48	27	8	4	0
Ambrisentan	280	208	145	90	47	16	8	3

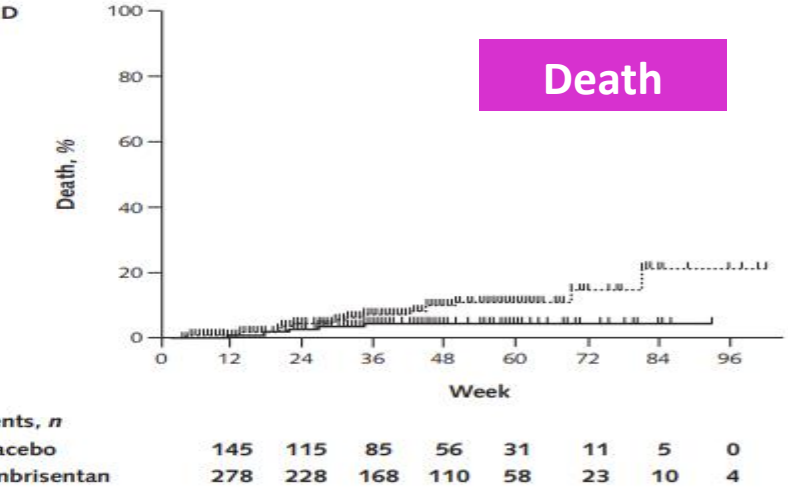
사용 X

Respiratory hospitalization



Patients, *n*								
Placebo	144	115	84	55	31	11	5	0
Ambrisentan	278	220	158	98	50	19	9	3

Death

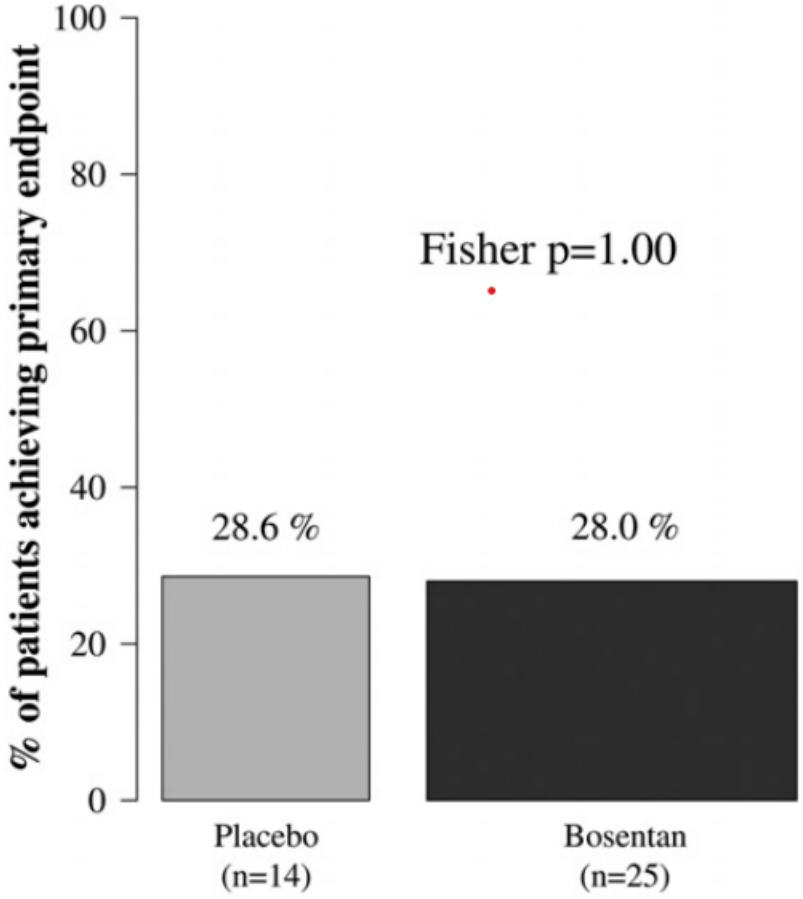


Patients, *n*								
Placebo	145	115	85	56	31	11	5	0
Ambrisentan	278	228	168	110	58	23	10	4

Ann Intern Med. 2013;158:641-9.

Bosentan in fibrotic IIP (BPHIT)

- Double blind, randomized (2:1), placebo controlled trial
- Fibrotic IIP (IPF or fNSIP) and RHC confirmed PH (mPAP ≥ 25, PCWP ≤ 15)
- Bosentan (n=25) vs. placebo (n=14)
- Primary endpoint: fall from baseline PVRindex (PVRi) of 20% ≥ ,16 weeks

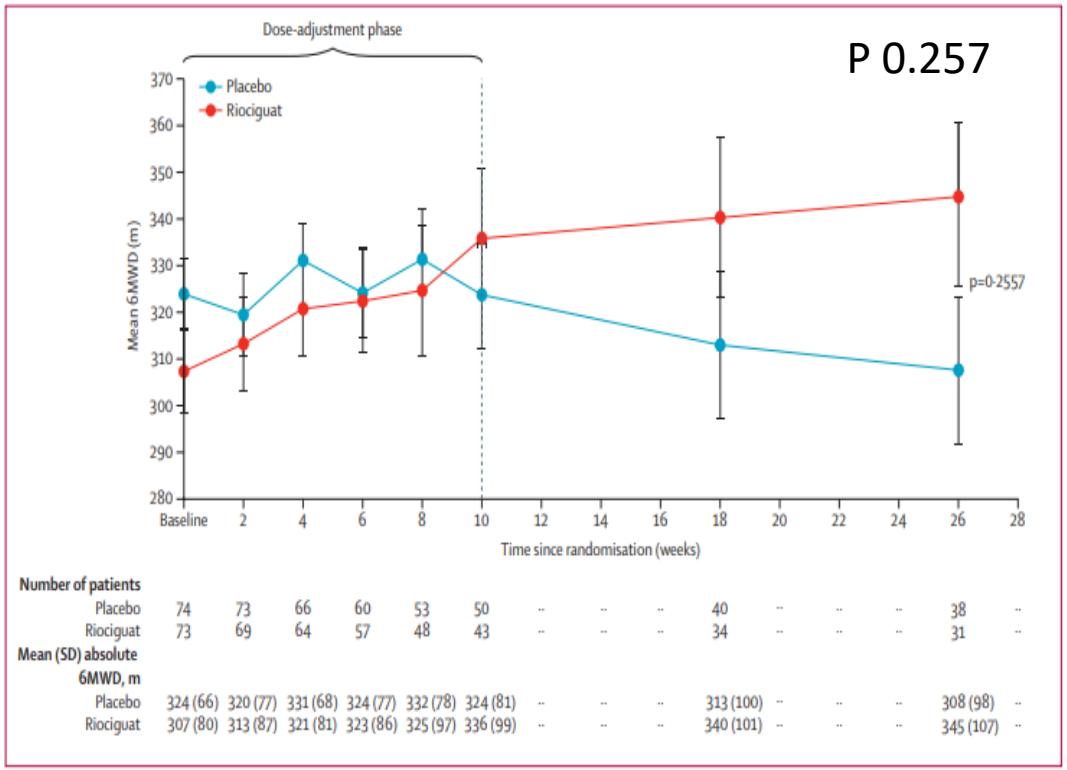


Change of PVRi, mPAP, CI, SpO2, 6MWD, symptom score, activities scor, QOL score, DLCO, FVC, BNP, TAPSE, RV inlet size : No difference

Am J Respir Crit Care Med 2014; 190 (2): 208-217

Riociguat in IIP-PH (RISE-IIP)

- Riociguat : soluble guanylate cyclase stimulator **사용 x**
- Randomised, double-blind, placebo controlled , phase 2b
- Riociguat (n=73) vs. placebo (n=74) , 26wks
- IIP – PH (RHC confirmed, mPAP ≥ 25) (IPF 74% vs. 66%, NSIP 12% vs. 19%)
- Primary outcome: mean change of 6MWD at 26wks
- Mean mMPA : Riociguat (33mmHg) vs. Placebo (33mmgHg)



	Main phase	
	Riociguat up to 2·5 mg (n=73)	Placebo (n=74)
Any AE	65 (89%)	64 (86%)
Study drug-related AEs	29 (40%)	28 (38%)
AEs leading to study drug discontinuation	11 (15%)	3 (4%)
Any SAE	27 (37%)	17 (23%)
Study drug-related SAEs	5 (7%)	4 (5%)
SAEs leading to study drug discontinuation	10 (14%)	1 (1%)
Deaths	8 (11%)	3 (4%)

Lancet Respir Med. 2019;7:780-790.

EUROPEAN RESPIRATORY JOURNAL
EDITORIAL
V. COTTIN ET AL.

Inhaled treprostinil for interstitial lung disease-associated pulmonary hypertension: a silver lining on a very dark cloud

Vincent Cottin [1], Claudia Valenzuela [2] and Marc Humbert [3]

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Corresponding author: Vincent Cottin (vincent.cottin@chu-lyon.fr)

Eur Respir J 2023; 61: 2300944

Inhaled Treprostinil in ILD-PH (INCREASE)

- Randomized, double blind, placebo controlled
- ILD – PH (mMPA>25mmHg, Group III PH)

Cause of lung disease — no. (%)			
Idiopathic interstitial pneumonia	65 (39.9)	81 (49.7)	146 (44.8)
Chronic hypersensitivity pneumonitis	10 (6.1)	9 (5.5)	19 (5.8)
Occupational lung disease	5 (3.1)	1 (0.6)	6 (1.8)
Combined pulmonary fibrosis and emphysema	42 (25.8)	40 (24.5)	82 (25.2)
Connective tissue disease	40 (24.5)	32 (19.6)	72 (22.1)
Other	1 (0.6)	0	1 (0.3)

- Primary outcome: difference between two group of 6MWD at 16wks
- Inhaled Treprostinil (N=163) vs. Placebo (N=163)
  - Ultrasonic, pulsed delivery nebulizer
  - 3 breath q.i.d > 9 breath q.i.d (Max 12 breath q.i.d)

N Engl J Med 2021;384:325-34

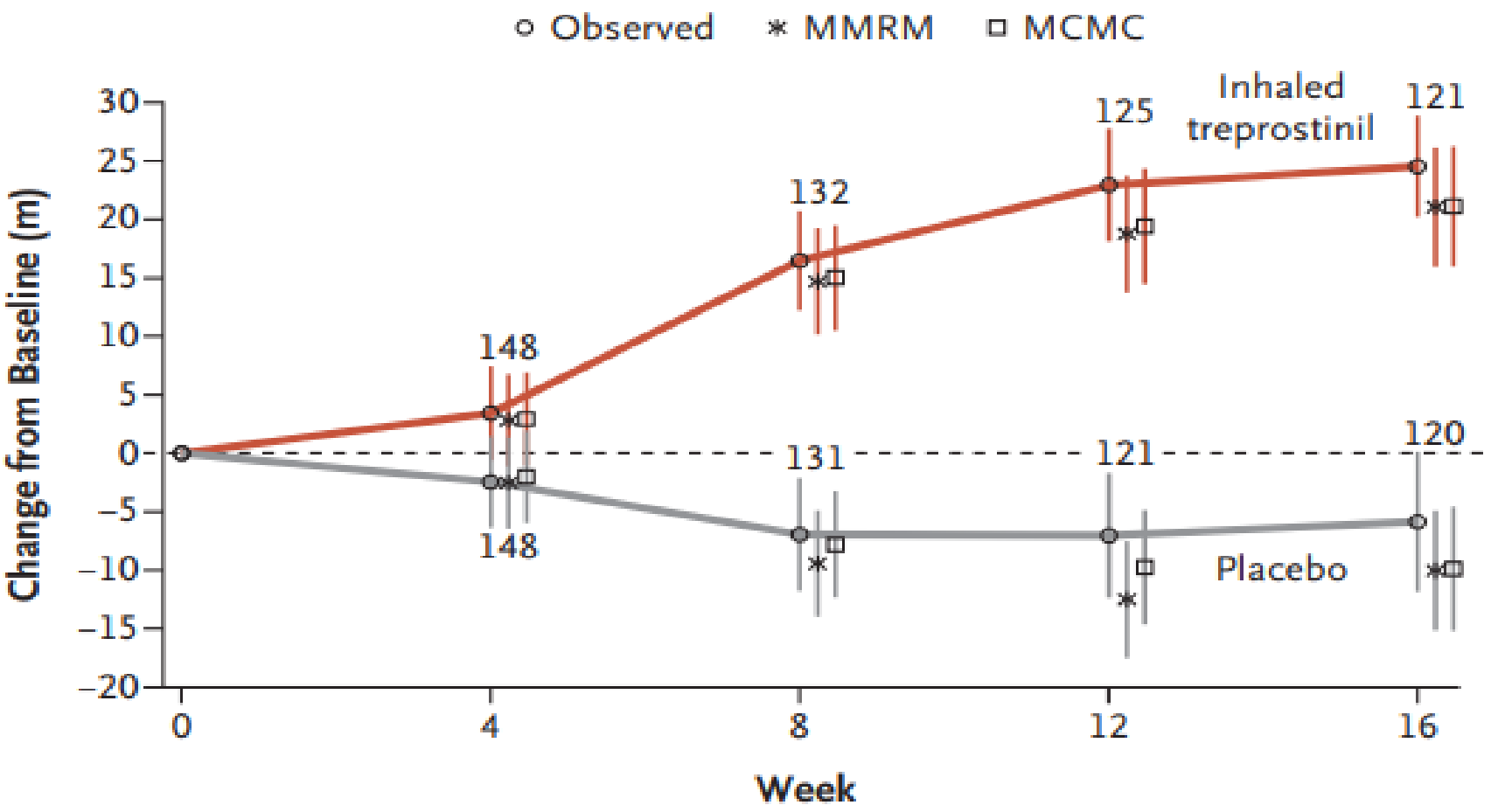

Observed
MMRM
MCMC
Inhaled treprostinil
Placebo
Change from Baseline (m)
Week
30
25
20
15
10
5
0
−5
−10
−15
−20
0
4
8
12
16
148
132
125
121
148
131
121
120

Table 2. Summary of Primary and Secondary End Points.*

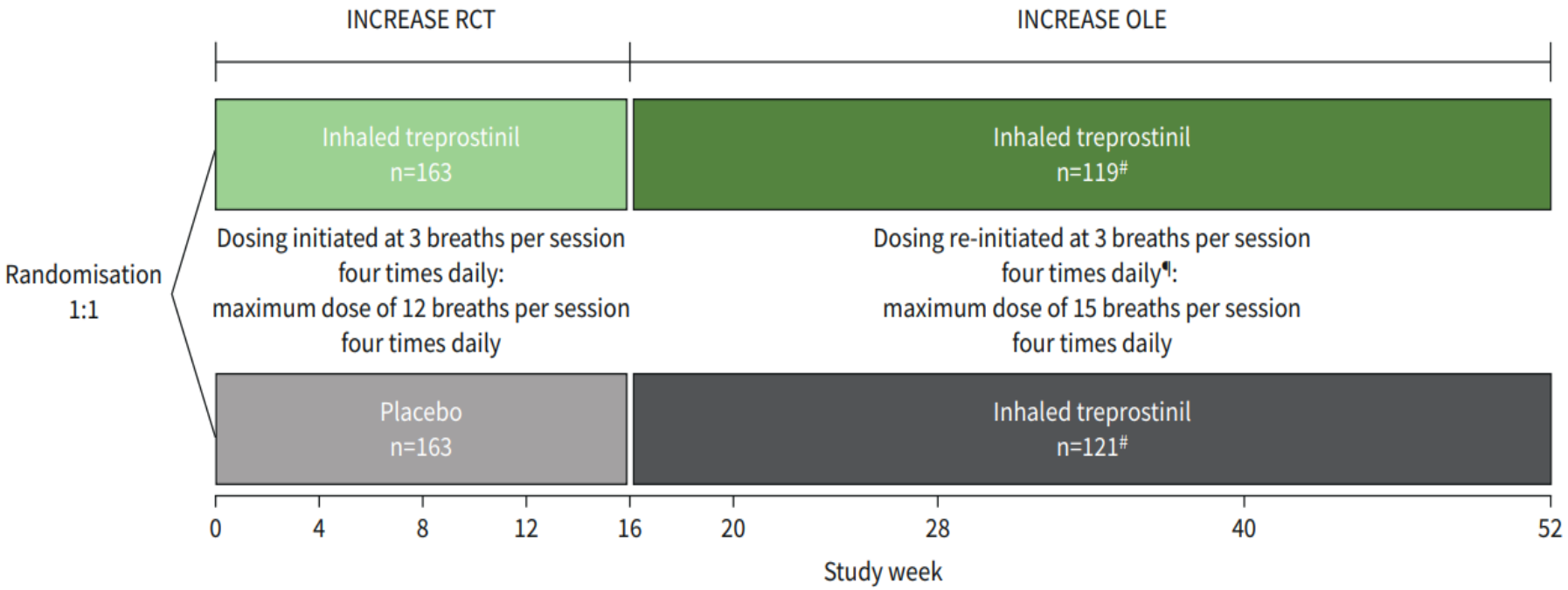
End Point	Inhaled Treprostinil (N=163)	Placebo (N=163)	Treatment Effect (95% CI)	P Value
Primary end point				
Change in peak 6-minute walk distance from baseline to wk 16 — m†	21.08±5.12	−10.04±5.12	31.12±7.25 (16.85 to 45.39)‡	<0.001
Secondary end points§				
Change i… b…				
Mear…				
Medi…				
Rang…				
Ratio…				<0.001
Occurrer…				0.04
Any e…				
Hosp…				
Decr… b…				
Deatl…				
Lung transplantation	2 (1.2)	0		
Least-squares mean change in peak 6-minute walk distance from baseline to wk 12 — m†	18.77±4.99	−12.52±5.01	31.29±7.07 (17.37 to 45.21)‡	<0.001
Least-squares mean change in trough 6-minute walk distance from baseline to wk 15 — m	9.3±5.5	−12.7±5.5	21.99±7.7 (6.85 to 37.14)‡	0.005††

April 05, 2021 | 2 min read

FDA approves inhaled treprostinil for pulmonary hypertension associated with ILD

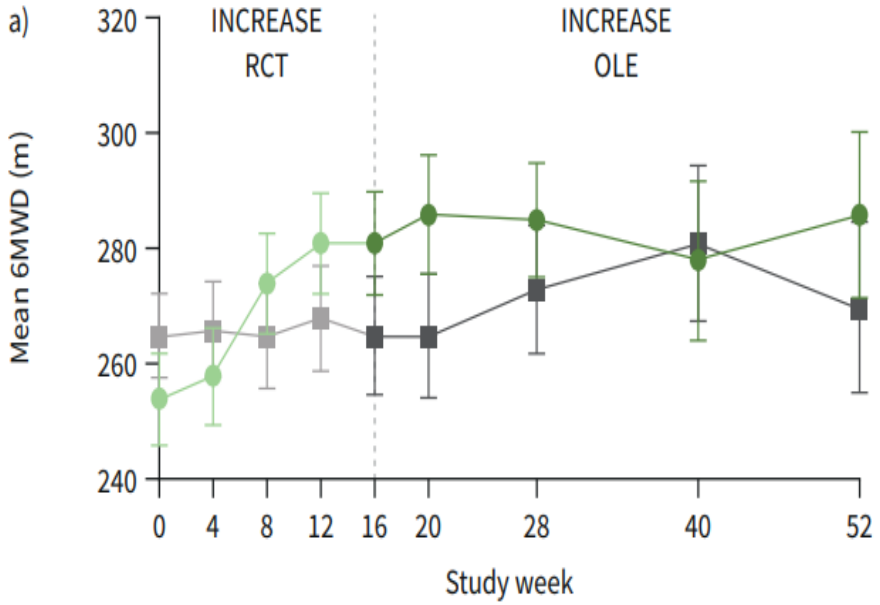
N Engl J Med 2021;384:325-34

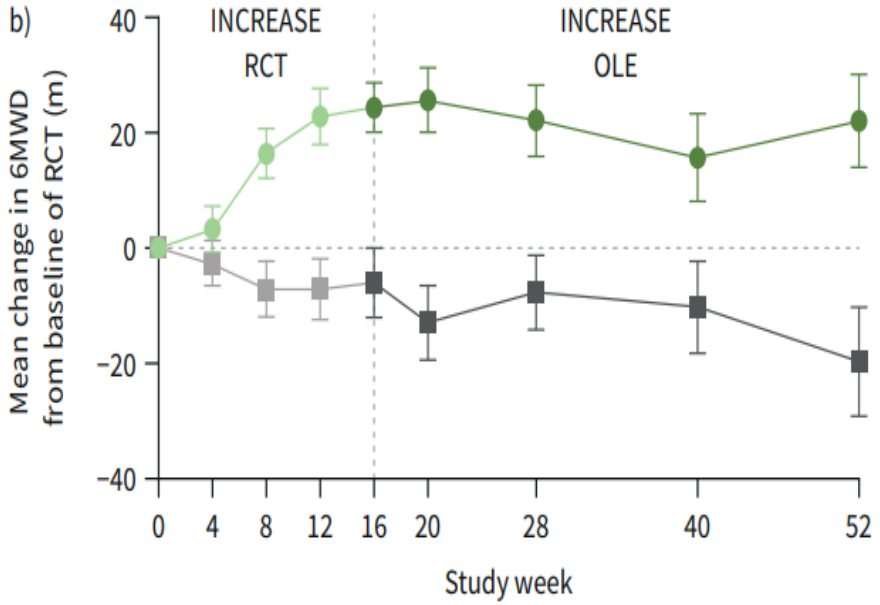
Long term use of inhaled treprostinil



Open label extension of INCREASE study (INCREASE OLE)

Eur Respir J 2023; 61: 2202414



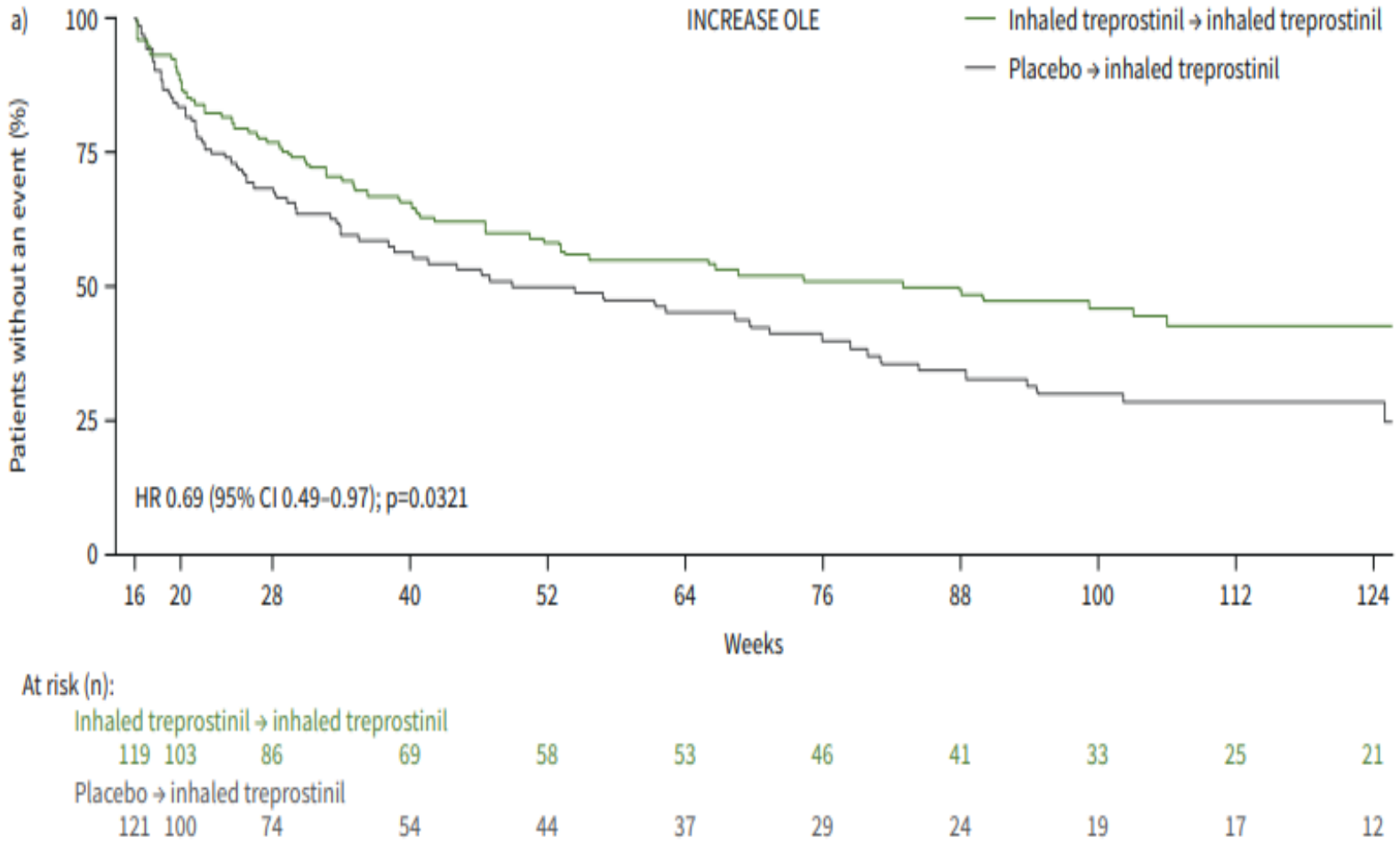


Inhaled treprostinil in RCT (n):
163 148 132 125 121 110 100 77 68
Placebo in RCT (n):
163 148 131 121 120 102 89 62 55

Inhaled treprostinil in RCT (n):
163 148 132 125 121 110 100 77 68
Placebo in RCT (n):
163 148 131 121 120 102 89 62 55

Inhaled treprostinil
Inhaled treprostinil in RCT → inhaled treprostinil in OLE
Placebo
Placebo in RCT → inhaled treprostinil in OLE

Eur Respir J 2023; 61: 2202414



Eur Respir J 2023; 61: 2202414

Adverse event

	Received inhaled treprostinil in RCT (n=119)	Received placebo in RCT (n=121)	Overall (n=242)[#]
Patients with ⩾1 AEs	112 (94.1)	115 (95.0)	229 (94.6)
Total AEs (AE rate)[¶]	1085 (6.7)	993 (7.9)	2091 (7.2)
Patients with ⩾1 SAEs	66 (55.5)	65 (53.7)	133 (55.0)
Patients with ⩾1 AEs leading to discontinuation of inhaled treprostinil	20 (16.8)	34 (28.1)	54 (22.3)
AEs occurring in >10% of all patients			
Cough	22 (18.5)	43 (35.5)	65 (26.9)
Dyspnoea	30 (25.2)	33 (27.3)	63 (26.0)
Headache	12 (10.1)	33 (27.3)	45 (18.6)
Diarrhoea	20 (16.8)	17 (14.0)	37 (15.3)
Dizziness	18 (15.1)	18 (14.9)	36 (14.9)
Upper respiratory tract infection	20 (16.8)	14 (11.6)	34 (14.0)
Nausea	18 (15.1)	14 (11.6)	32 (13.2)
Fatigue	18 (15.1)	14 (11.6)	32 (13.2)
Pneumonia	14 (11.8)	15 (12.4)	30 (12.4)
Acute respiratory failure	16 (13.4)	14 (11.6)	30 (12.4)
Urinary tract infection	10 (8.4)	15 (12.4)	27 (11.2)
Back pain	16 (13.4)	10 (8.3)	26 (10.7)
Productive cough	8 (6.7)	16 (13.2)	25 (10.3)

Eur Respir J 2023; 61: 2202414

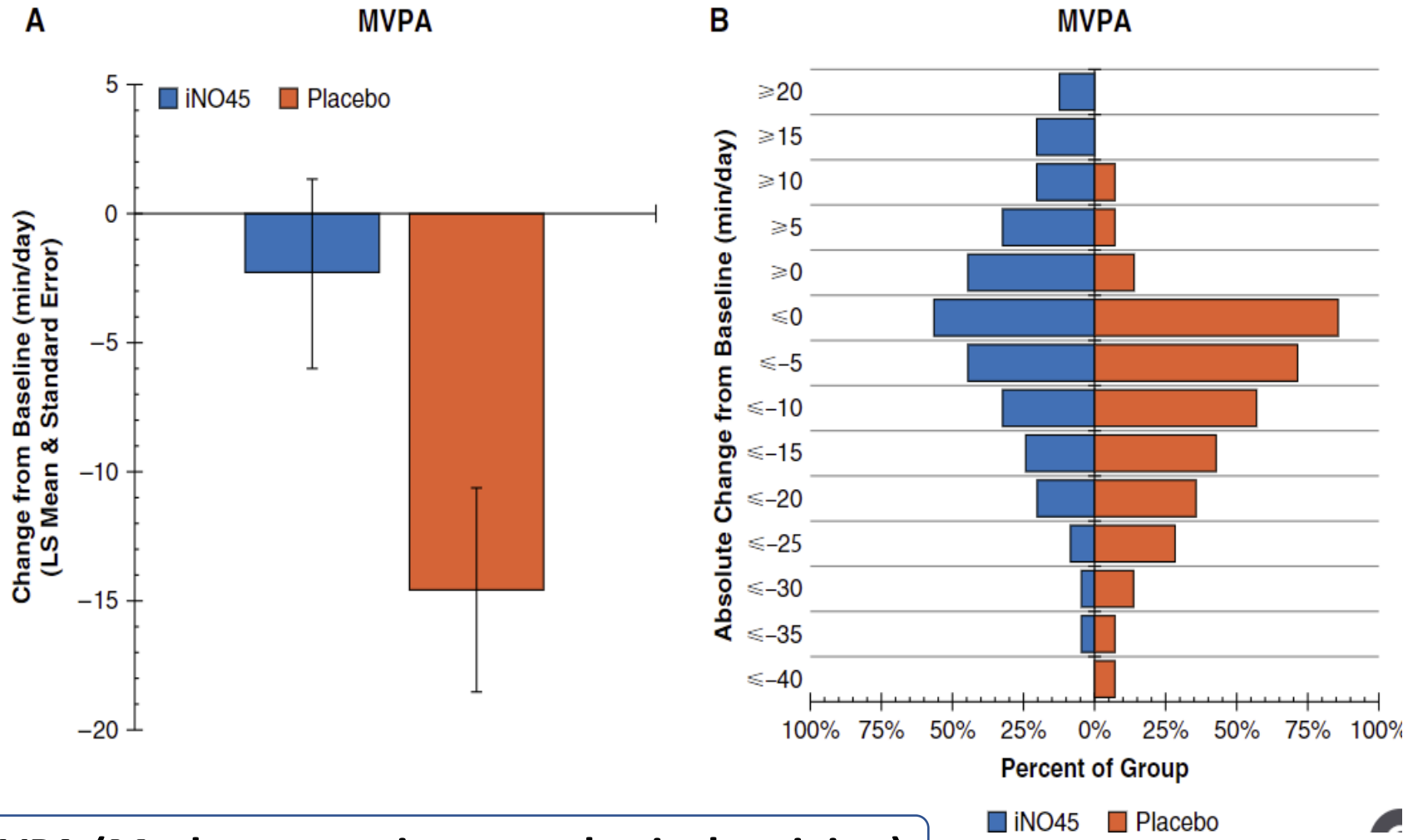
Variable	Inhaled Treprostinil (N=163)	Placebo (N=163)	P Value*
Total no. of adverse events	890	793	
Patients with ≥1 adverse event — no. (%)	152 (93.3)	149 (91.4)	0.68
Total no. of serious adverse events†	53	89	
Patients with ≥1 serious adverse event — no. (%)	38 (23.3)	42 (25.8)	0.70
Total no. of adverse events leading to withdrawal of treprostinil or placebo	47	38	
Most frequently occurring adverse events — no. of patients (%)‡			
Cough	71 (43.6)	54 (33.1)	0.07
Headache	45 (27.6)	32 (19.6)	0.12
Dyspnea	41 (25.2)	51 (31.3)	0.27
Dizziness	30 (18.4)	23 (14.1)	0.37
Nausea	25 (15.3)	26 (16.0)	>0.99
Fatigue	23 (14.1)	23 (14.1)	>0.99
Diarrhea	22 (13.5)	19 (11.7)	0.74
Throat irritation	20 (12.3)	6 (3.7)	0.007
Oropharyngeal pain	18 (11.0)	4 (2.5)	0.003
NT-proBNP increased	9 (5.5)	25 (15.3)	0.006

N Engl J Med 2021;384:325-34

Inhaled NO in fILD pt at risk of PH

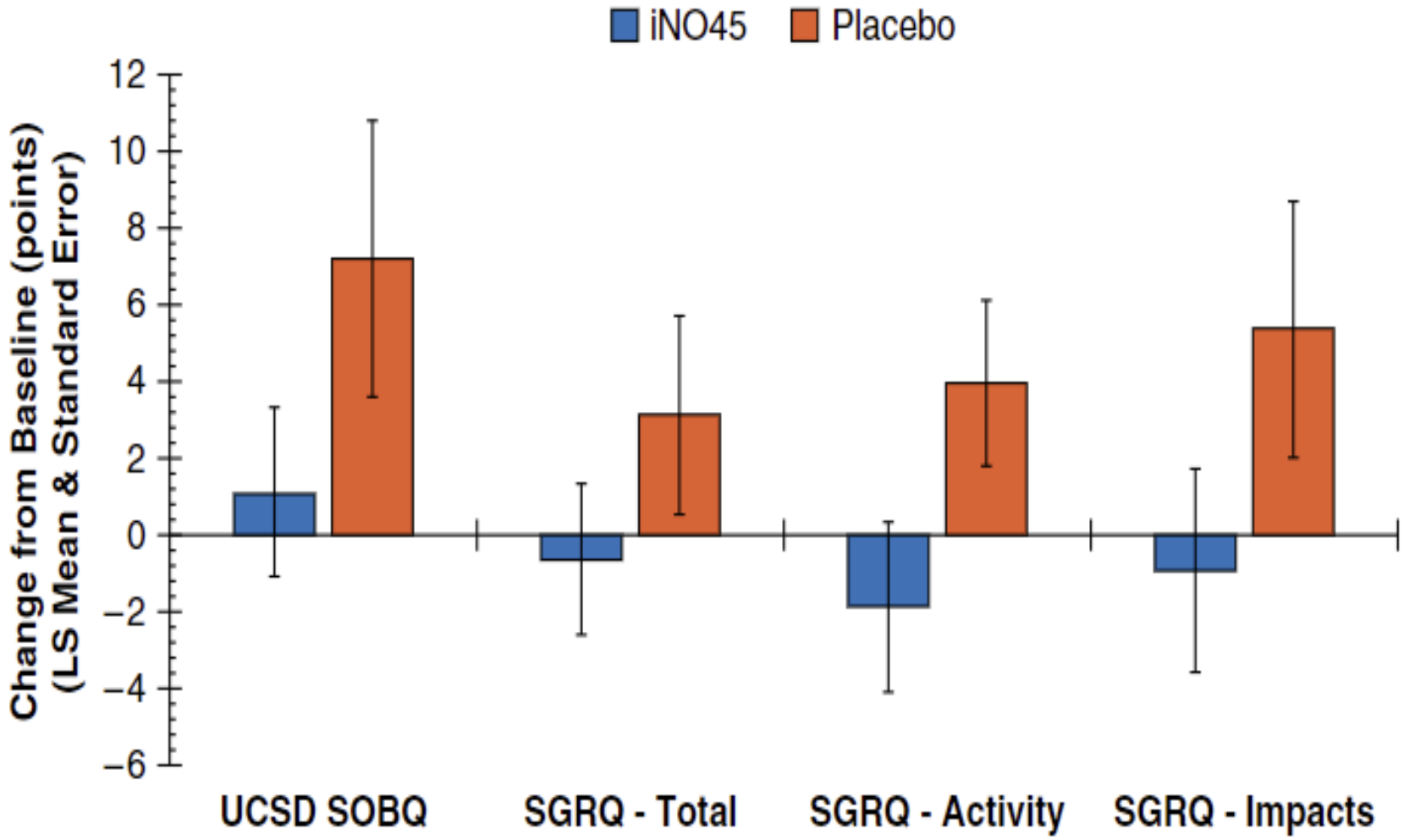
- Phase 2, double blind, placebo controlled, randomized clinical trial in USA
- fILD on supplemental oxygen therapy
  - FVC at least 40% / Echo / RHC was not mandatory
  - IPF 63% vs. 86% ,iNSIP 13% vs. 14%
  - Mod ~high probability of PH on Echo : 60% vs 64%
- Inhaled nitric oxide
  - Pulsed fixed dose iNO (45 μg/kg IBW/h) with placebo
  - Delivered via the INOpulse device (both group)
- 2:1 randomization:iNO45 (N=30) or placebo (N=14)
- Receive iNO45 or placebo for 4 months

Ann Am Thorac Soc 2022; 19:594–602.

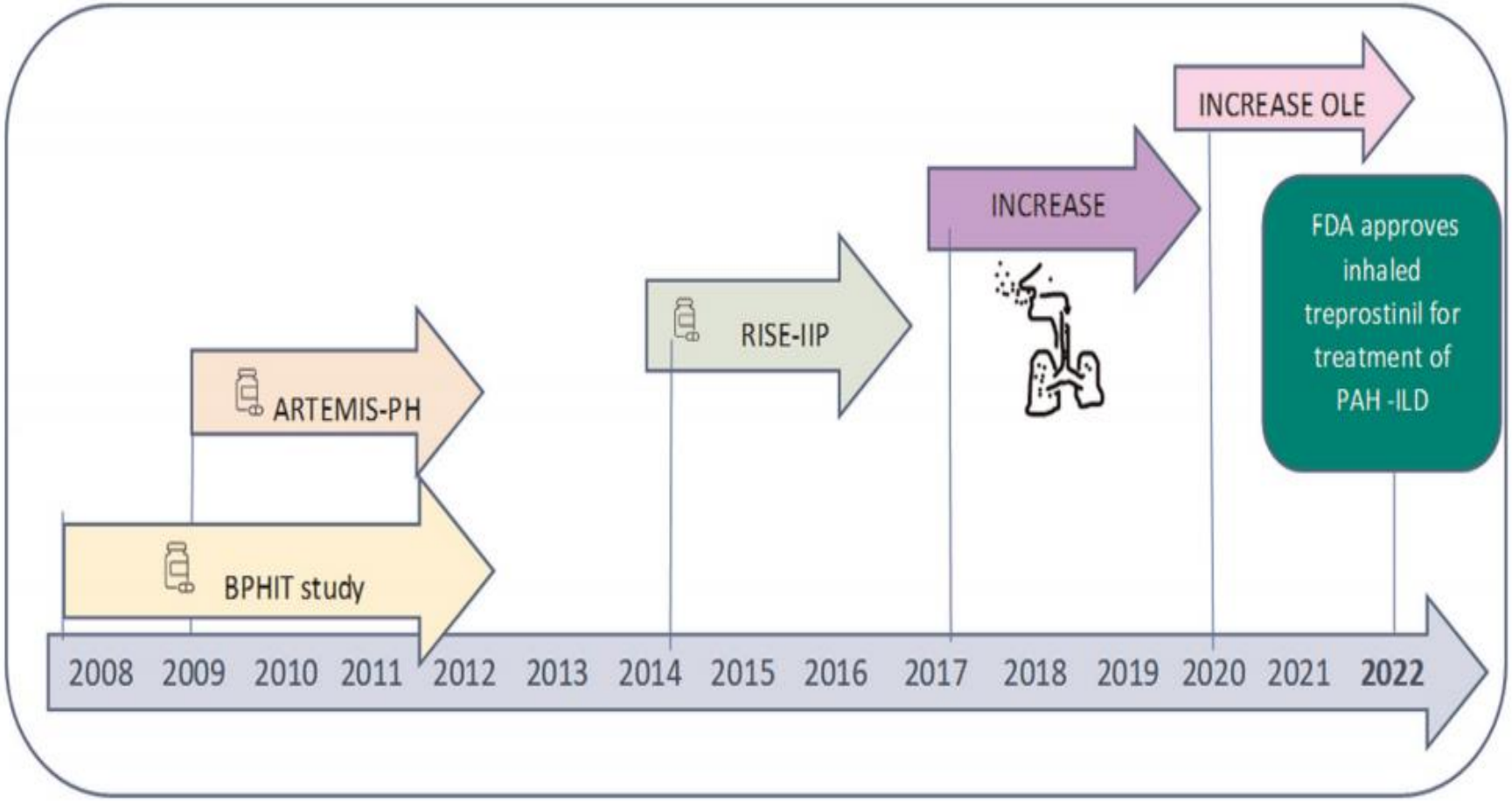


MVPA (Moderate to vigorous physical activity)

Ann Am Thorac Soc 2022; 19:594–602.



Ann Am Thorac Soc 2022; 19:594–602.



Randomized clinical trials with drugs approved in PAH and targeting ILD-PH (RHC confirmed)

Curr Opin Pulm Med 2023, 29:406–415

Patient progress

- 1yr later
- Aggravation of hypoxia
- Admission → HFNC 80% → Lung Transplantation

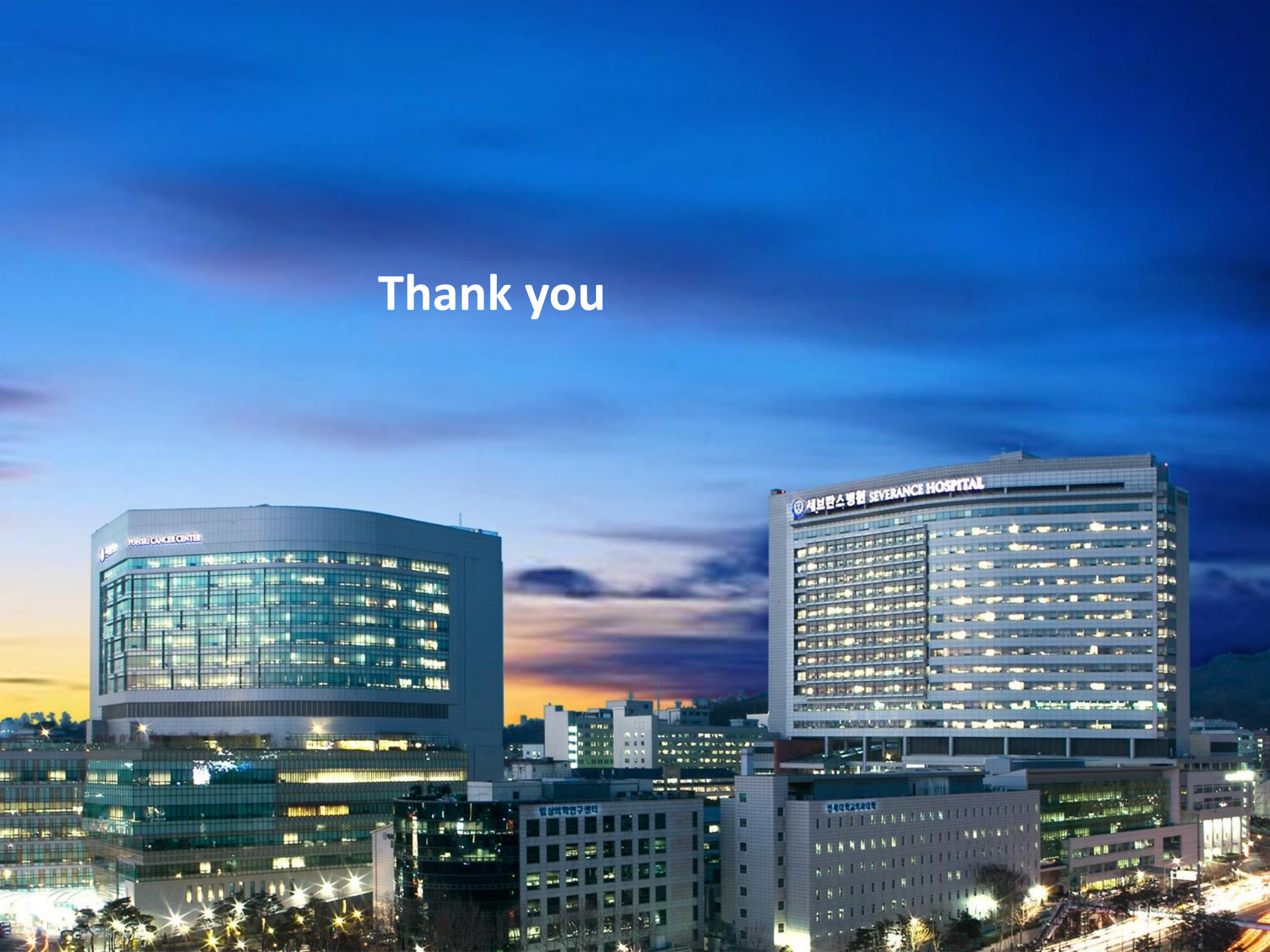
Summary

- Prognosis of PH-ILD is poor.

- Many studies failed to prove the efficacy of PAH targeted tx in PH-ILD. But the study design were different.
- Recently, studies of inhaled NO and especially inhaled treprostinil opened the new era in PH-ILD.

- Therefore
  - Suggestion and proper diagnosis of PH-ILD is important.
  - Further studies about other drugs such as sildenafil are still needed.
  - Inhaled treprostinil and iNO can be used in PH-ILD

PAH target Tx in PH-ILD : PRO


Thank you
YONSEI CANCER CENTER
세브란스병원 SEVERANCE HOSPITAL

Suggestive findings of PH in ILD pts

Pulmonary function testing	DLCO $\leq$ 40% predicted Kco < 40% of predicted (or elevated FVC/DLco ratio)
6-min walk test	Marked reduced distance Excessive desaturation Increased Borg dyspnea score Impaired heart rate recovery
Cardiopulmonary exercise testing	Worsened ventilation/perfusion ratio Increased alveolar-oxygen tension difference Increased dead space volume / tidal volume Increased end-tidal arterial carbon dioxide tension Increased minute ventilation / carbon dioxide production Reduced oxygen pulse Early anaerobic threshold
Laboratory testing	Elevated BNP or NT-pro-BNP level
Electrocardiogram	Right axis deviation
CT findings	Pulmonary artery to aorta ratio > 0.9
Echocardiography	Elevated tricuspic regurgitant velocity Right atrial and/or right ventricle dilatation Right ventricular dysfunction Reduced triscuspic annular plane systolic excursion Reduced systolic velocity

Curr Opin Pulm Med 2023, 29:406–415

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo 'PH signs'[a]	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	

표 9. 폐고혈압에서 우심도자술에 대한 권고사항

권고사항	권고 수준	근거 수준
폐동맥고혈압 진단(폐고혈압 1군)과 치료 결정을 위해 우심도자술이 권고된다.	I	C
폐고혈압 환자는 심각한 합병증의 발생위험과 기술적인 측면을 고려하여 전문센터에서 우심도자술을 시행하는 것이 권고된다.	I	B
폐동맥고혈압(폐고혈압 1군)의 약물치료 효과를 평가하기 위해 우심도자술의 시행이 필요하다(표 15).	IIa	C
선천심장병을 가지고 있는 환자에게는 단락 교정 여부를 결정하기 위해 우심도자술이 필요하다(표 24).	I	C
장기이식을 고려하고 있는 좌심장질환(폐고혈압 2군) 또는 폐질환(폐고혈압 3군)으로 인한 폐고혈압 환자에게는 우심도자술이 필요하다.	I	C
폐동맥쐐기압 측정이 불가능할 경우, 좌심도자술을 통해 좌심실 이완기압을 측정해야 한다.	IIa	C
좌심장질환 또는 폐질환으로 인한 폐고혈압이 의심되는 환자에게는 감별 진단 및 치료방법에 대한 결정을 위해 우심도자술을 고려할 수 있다.	IIb	C
만성혈전색전폐고혈압(폐고혈압 4군)에 대한 진단 및 치료방법에 대한 결정을 위해 우심도자술이 권고된다.	I	C