Disclosures

- Fees for speaking and/or organising education were provided by: ERS, Almirall, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, GlaxoSmithKline, InterMune, Novartis, Pfizer, Roche

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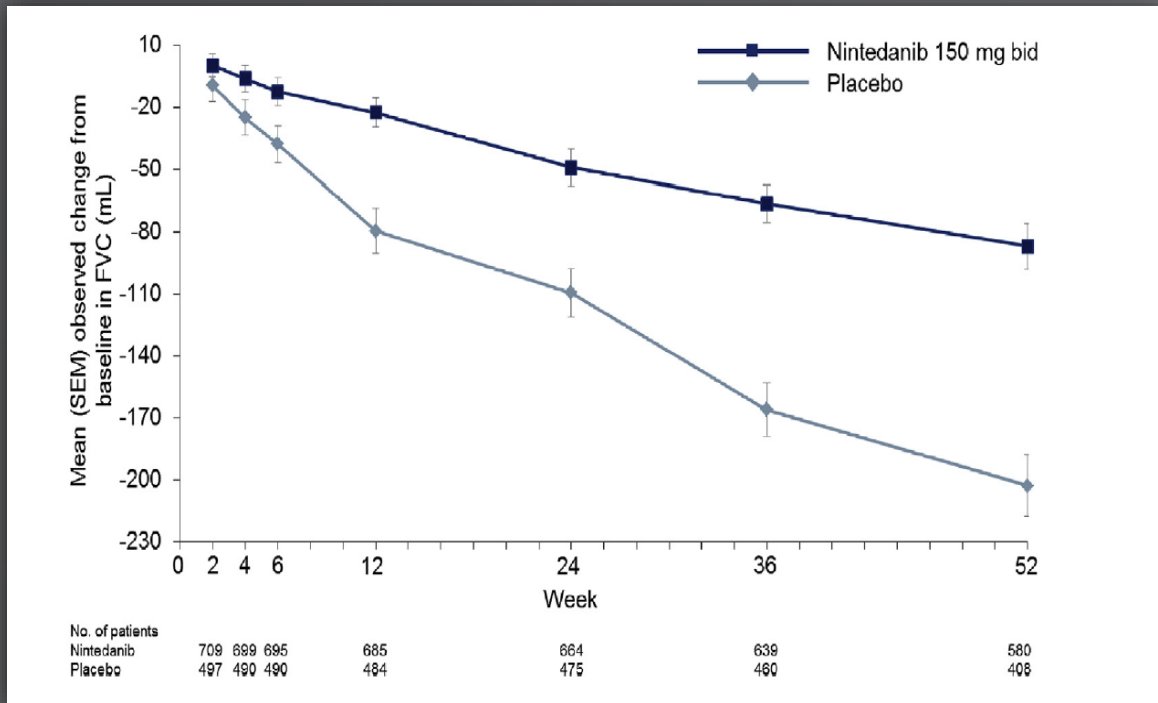
Where are we ?

ABCDE of ILD care

Assess	Backing	Comfort care, Co-morbidities	Disease-modifying treatment	End-of-life care
Patients' needs and values Patients as partner in care Include caregivers	Education Self-management • Dietary support Support groups Patient advocacy groups Pulmonary rehabilitation Prevention • Stop smoking • Vaccination Discuss trial options	Comfort-care • Dyspnoea • Cough • Fatigue • Depression/anxiety Other palliative options Co-morbidities • Cardiovascular • OSA • Lung cancer • Emphysema • GERD	Antifibrotic drugs* • Pirfenidone • Nintedanib Immunomodulatory therapies** Lung transplantation (if patient is eligible)	Timing of discussion Discuss • Fears • Practical needs • Palliative options • Prefered place of dying • Prefered way of dying Discuss treatment limits • About resuscitation • About ventilatory support

Antifibrotic therapy effects in clinical trials

Changes in FVC over time

Nintedanib - TOMORROW & INPULSIS
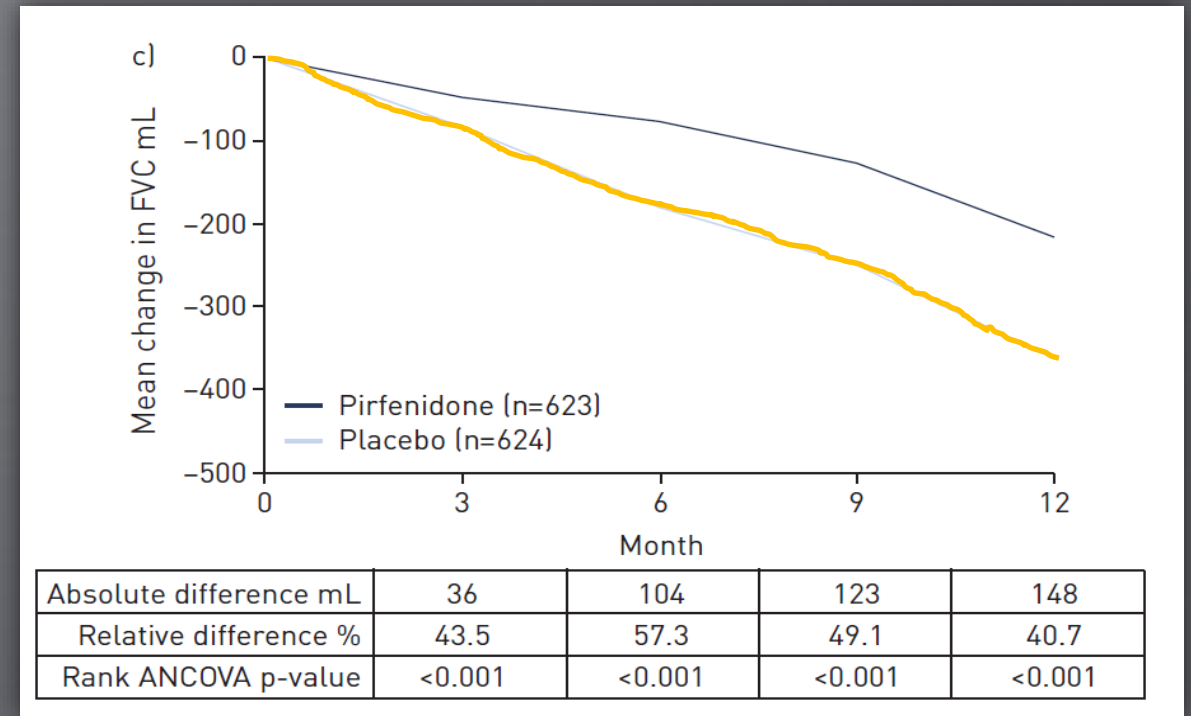
Pirfenidone - CAPACITY & ASCEND

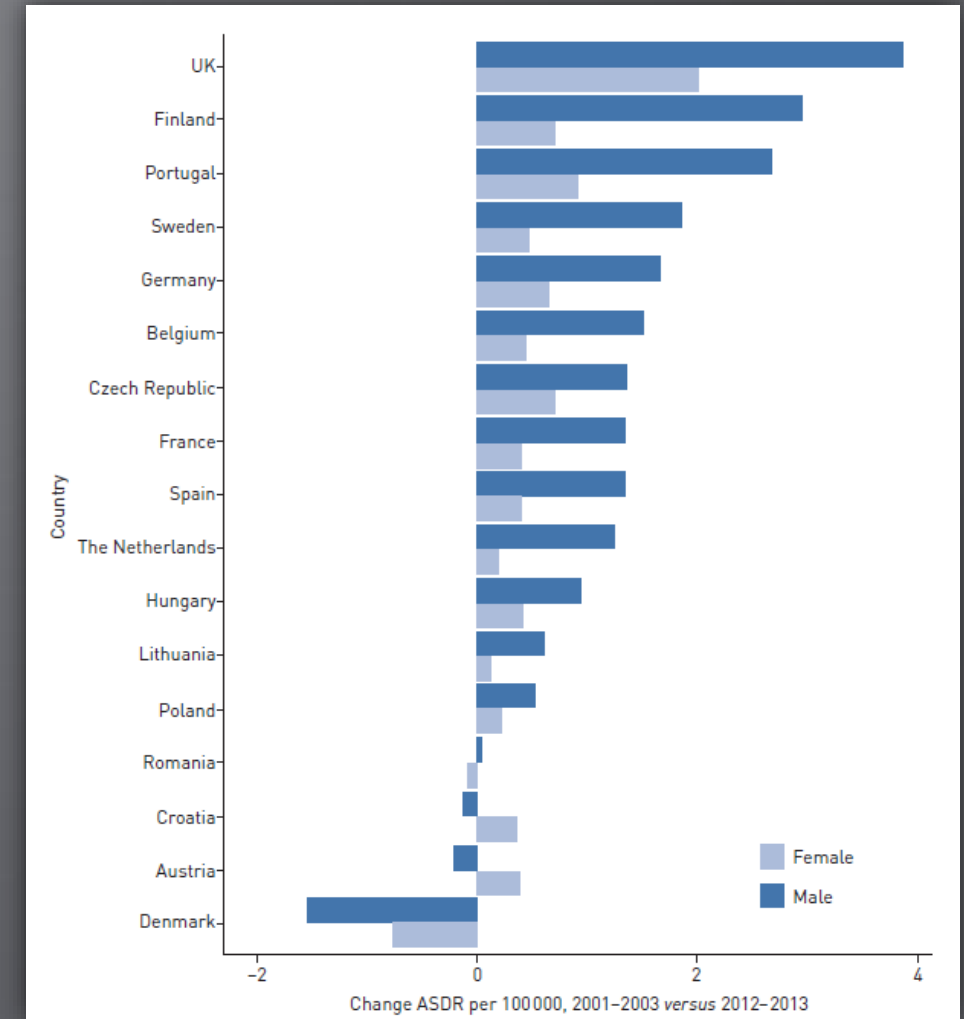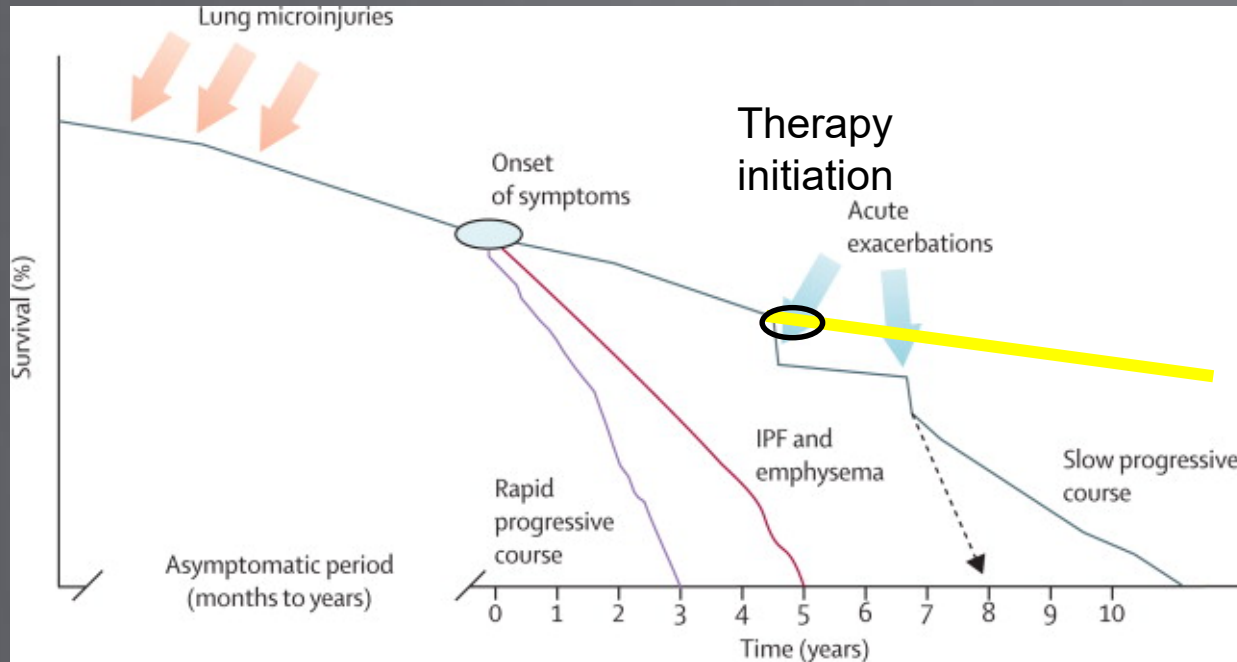Richeldi L, et al. *Resp Med* 113, 2016; Noble et al., Eur Respir J 2016; 47: 27–30
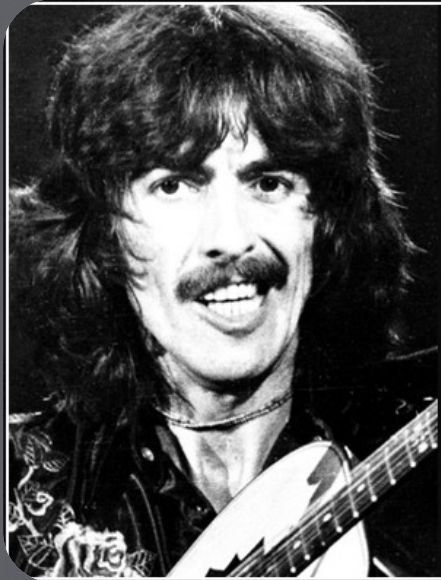
The natural course of IPF
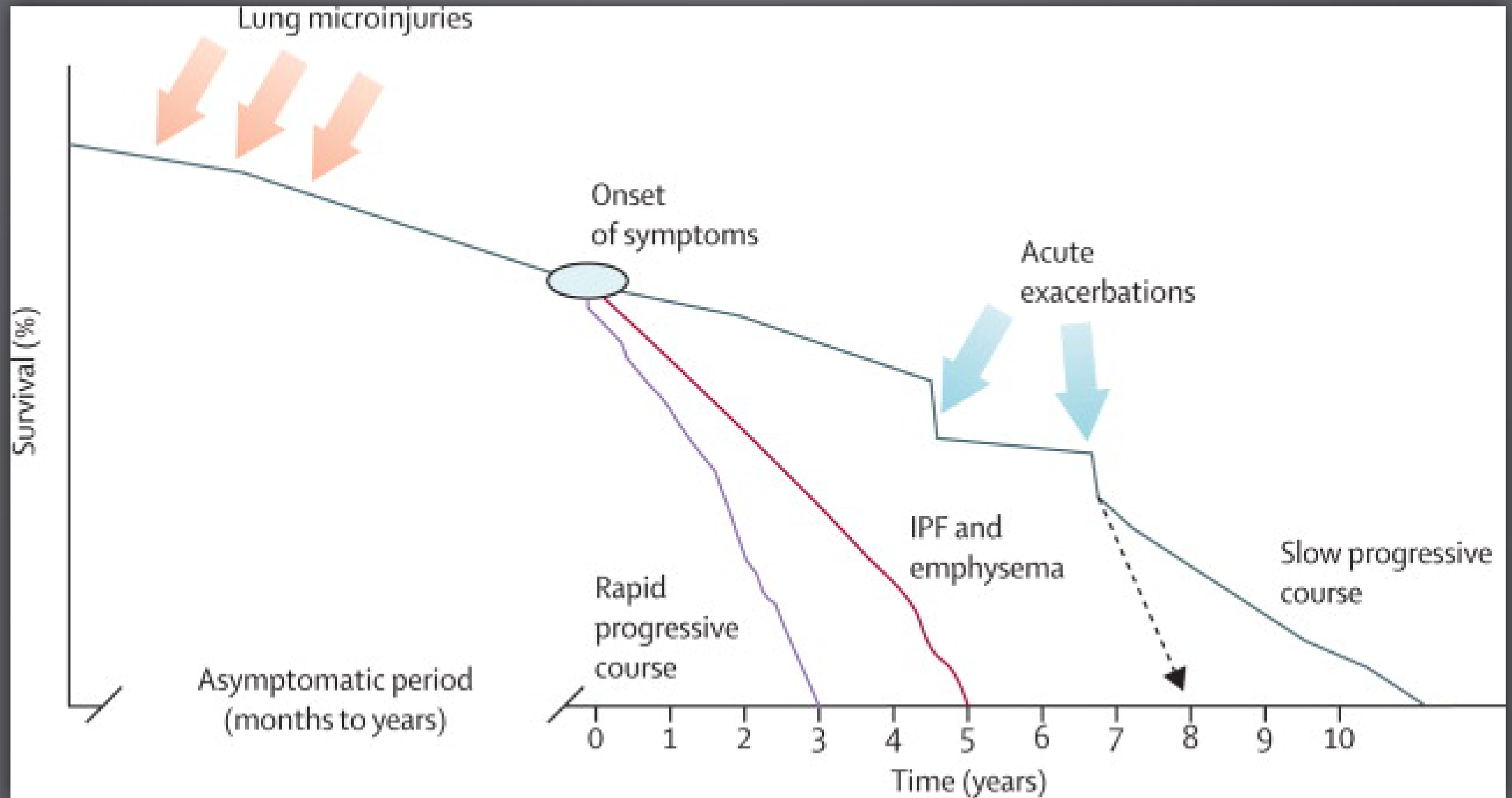
The continued threat to our patients – IPF, a deadly disease

Mortality trends in ILD / IPF – WHO mortality database

We should have started future yesterday

Yesterday, today was tomorrow. And tomorrow, today will be yesterday.

— George Harrison —

AZ QUOTES

- ➢ Therapeutic biomarkers guiding therapy
- ➢ Combination therapy
- ➢ New drugs
- ➢ Gene based therapies / stem cell therapy
- ➢ Targeting the lung microbiom
- ➢ New non-drug therapies
- ➢ Treatment of comorbidities
- ➢ New developments in LTX
- ➢ New ways to approach palliative care
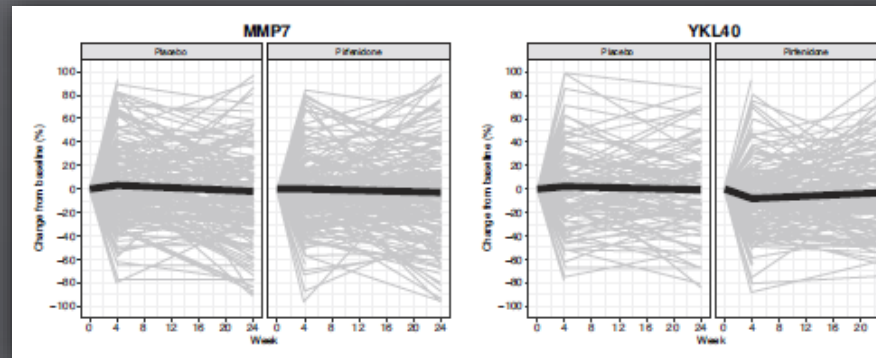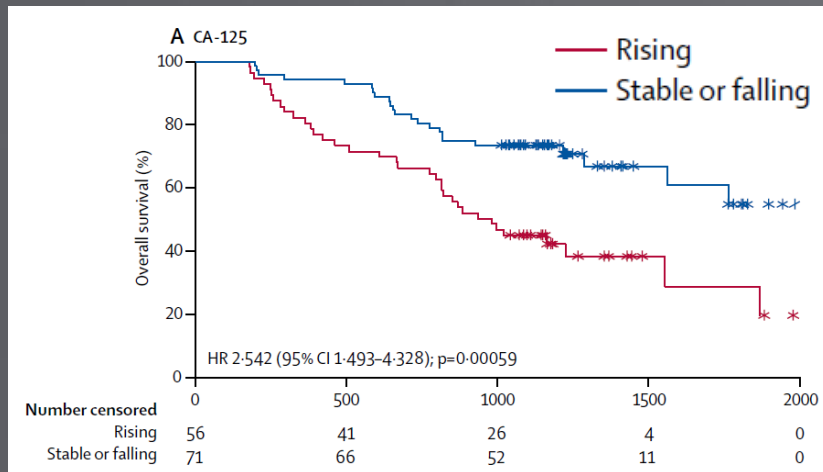- ➢ Urgent need to improve care of AE-IPF

Predictive therapeutic biomarkers in IPF
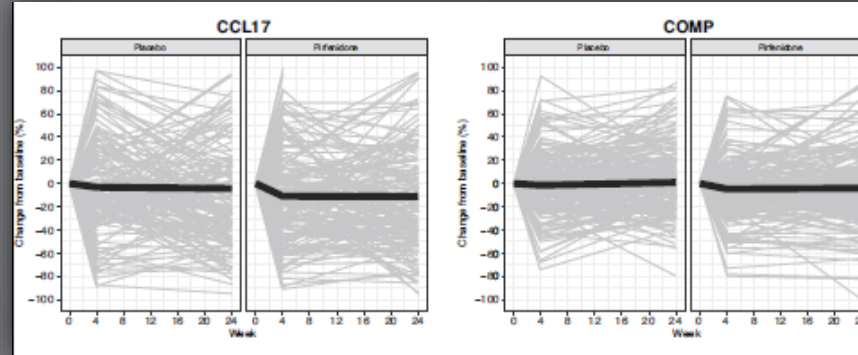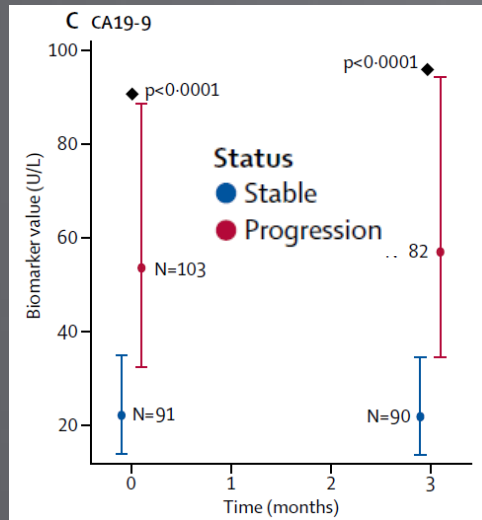
"Pirfenidone treatment benefit was consistent regardless of baseline biomarker levels, and pirfenidone treatment had little to no pharmaco-dynamic effect on the plasma levels of the pre-specified biomarkers."

…the best way to predict treatment response to anti-fibrotic therapy has yet to be found…

Maher et al., Lancet Res Med 2018; Kreuter & Maher, Lancet Res Med 2018; Neighbors et al., Lancet Res Med 2018

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

Which direction to go – combination therapy ?

Combination therapy: clinical trials

Table 4. Adverse Events

	Nintedanib 150 mg Twice Daily with Add-on Pirfenidone (n = 53)	Nintedanib 150 mg Twice Daily (n = 51)
Any adverse events	47 (88.7)	45 (88.2)
Most frequent adverse events*		
Diarrhea	20 (37.7)	16 (31.4)
Nausea	22 (41.5)	6 (11.8)
Vomiting	15 (28.3)	6 (11.8)
Fatigue	10 (18.9)	6 (11.8)
Upper abdominal pain	7 (13.2)	4 (7.8)
Decreased appetite	6 (11.3)	5 (9.8)
Dyspnea	2 (3.8)	8 (15.7)
Headache	7 (13.2)	1 (2.0)
Any serious adverse events[†]	2 (3.8)	5 (9.8)
Any fatal adverse events	0	0

Table 2. Summary of common TEAEs and TEAEs leading to discontinuation (safety population)

N=89	Patients with at least one TEAE* n (%)	Patients with at least one TEAE related to pirfenidone only[†] n (%)	Patients with at least one TEAE related to nintedanib only[†] n (%)	Patients with at least one TEAE related to both pirfenidone and nintedanib[†] n (%)
TEAEs occurring in ≥5% of patients				
≥1 TEAE	88 (99)	–	–	–
≥1 treatment-related TEAE	74 (83)	15 (17)	67 (75)	26 (29)

INJOURNEY trial:
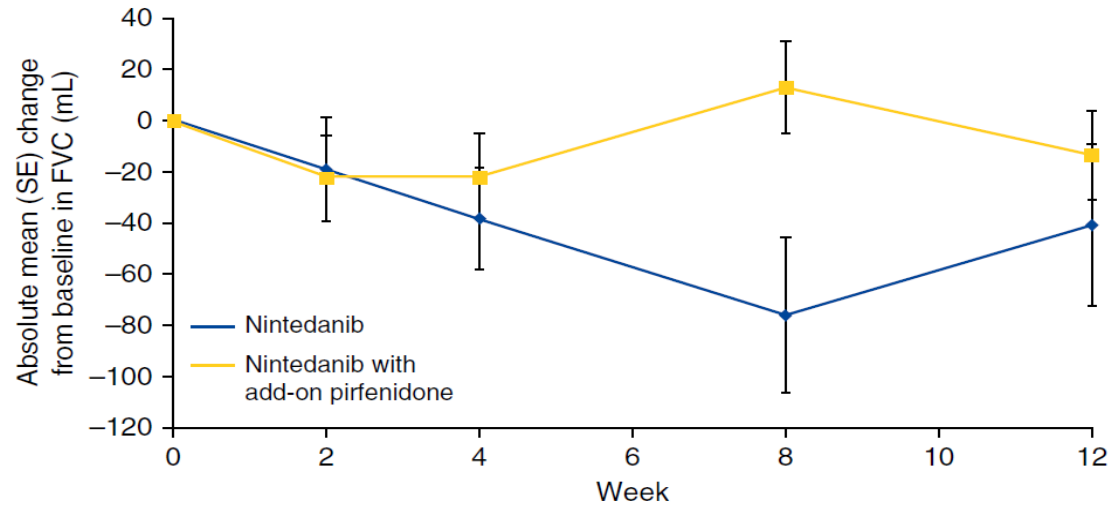**combination pirfenidone on top of nintedanib**

Nintedanib added to prexisiting Pirfenidone
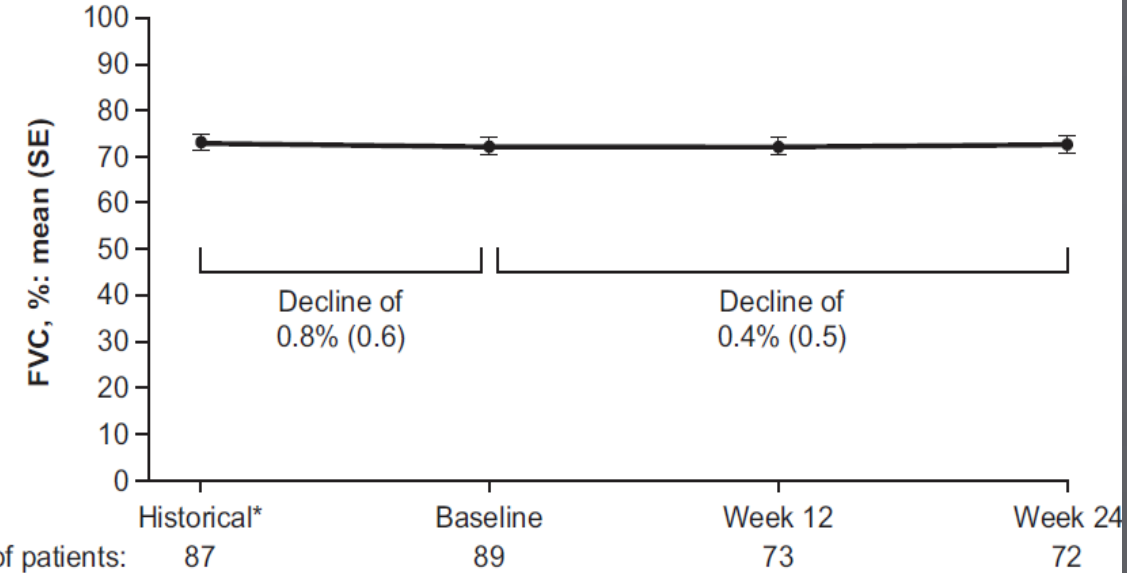
Conclusion: combination therapy feasibel

Vancheri et al. Am J Respir Crit Care Med 2018;197(3):356-363, Flaherty et al., Eur Resp J 2018

Which direction to go – combination therapy ?

Exploratory efficacy outcomes

INJOURNEY trial:
combination pirfenidone on top of nintedanib

Nintedanib added to prexisiting Pirfenidone

Conclusion: efficacy of combination to be assessed

Vancheri et al. Am J Respir Crit Care Med 2018;197(3):356-363, Flaherty et al., Eur Resp J 2018

Which direction to go – new drugs ?

Recombinant human pentraxin 2

GLPG1690 autotaxin inhibitor
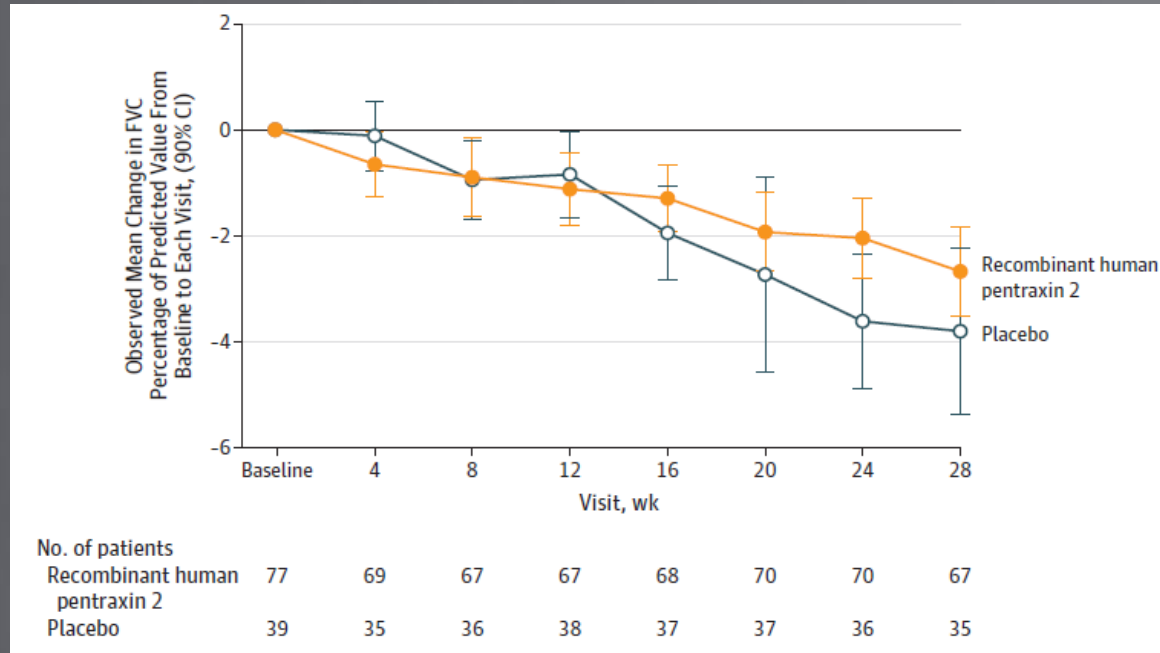
> ➤ **Purified serum amyloid P = pentraxin2**
> inhibits monocyte differentiation into profibrotic fibrocytes &
> into proinflammatory macrophages & production of TGF-β1
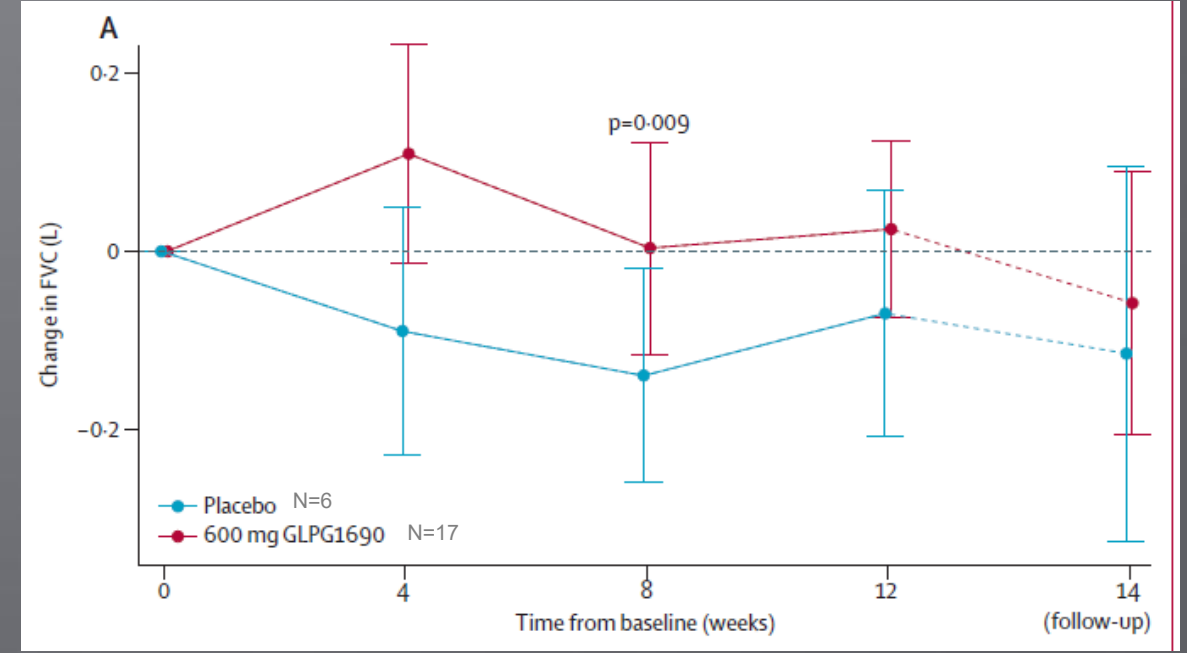
> ➤ **Key enzyme for LAP**
> ➤ **Overexpressed in IPF**
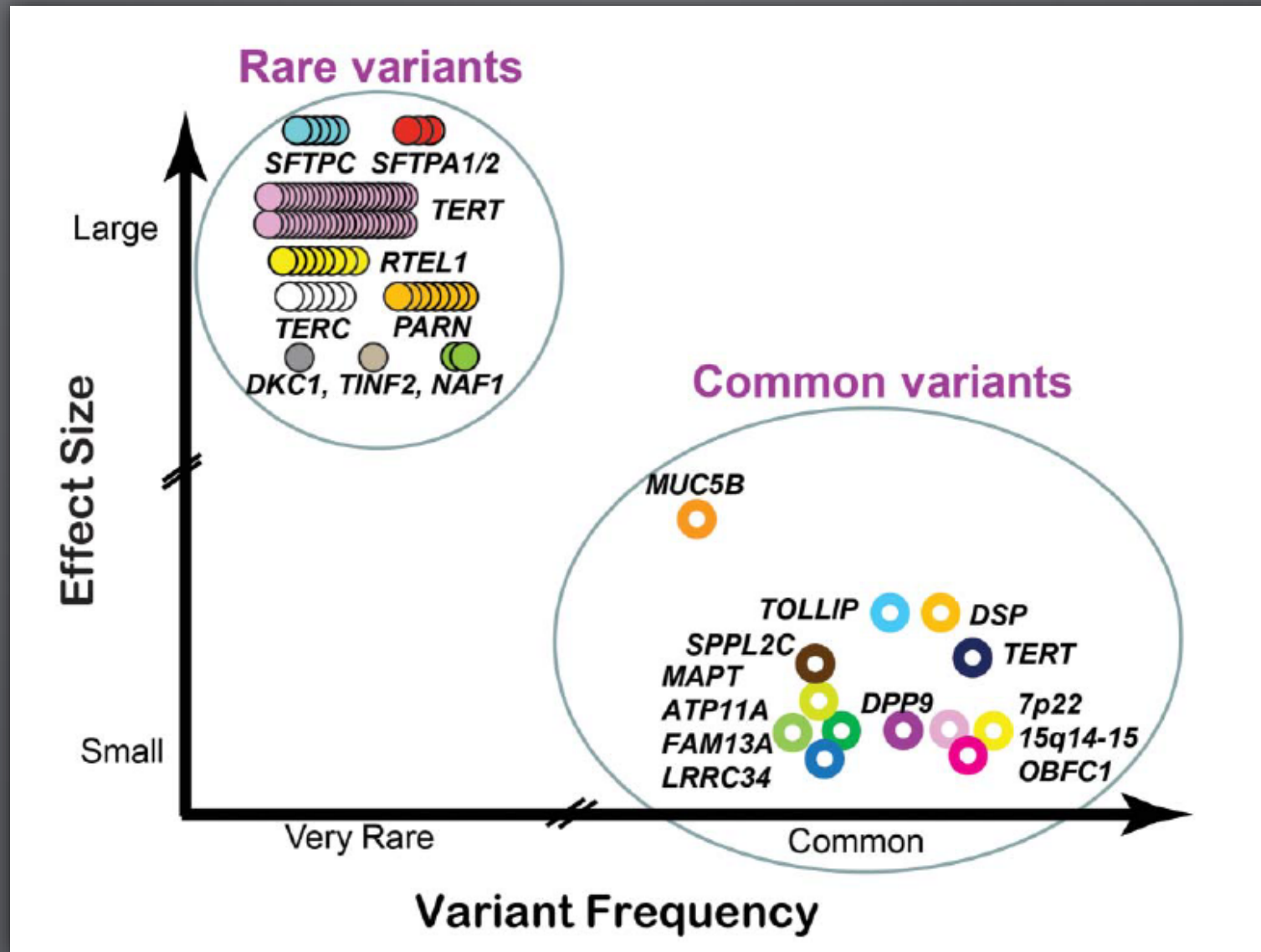
Raghu et al. JAMA 2018; Maher et al. Lancet Respir Med 2018

Potential „new" drugs in Phase II-III studies

Study drug	Mechanism of action	Clinical trial identifier (NCT)	Study description	Primary Outcome Measures	Phase of development	Treatment duration
PRM-151	Recombinant form of human SAP	NCT02550873	Randomized, double-blind, placebo controlled	Change From Baseline in Forced Vital Capacity (FVC) [% Predicted]	II	28 weeks
Simtuzumab	Anti-Lysyl oxidase (LOX) antibody	NCT01769196	Randomized, Double-Blind, Placebo-Controlled	The effect of simtuzumab (GS-6624) on progression-free survival (PFS)	II	148 weeks
Tipelukast	Leukotriene antagonists	NCT02503657	Randomized, double-blind, placebo controlled	Change from baseline of Forced Vital Capacity (FVC) at 26 weeks	II	26 weeks
Tralokinumab	Anti IL-13 antibody	NCT01629667	Randomized Dose-ranging	Change From Baseline in Percent-predicted Forced Vital Capacity (FVC) at Week 52	II	52 weeks
SAR156597	Anti IL-4 and IL-13 antibody	NCT01529853	Randomized, Double-blind, Placebo-controlled	Safety/tolerability: Number of participants with Adverse events	II	6 weeks
Lebrikizumab	Anti IL-13 antibody	NCT01872689	Randomized, Double-Blind, Placebo-Controlled	Annualized Rate of Decrease in Percent Predicted Forced Vital Capacity (FVC) Over 52 Weeks	II	52 weeks
BG00011	Anti-Integrin antibody	NCT03573505	Randomized, Double-Blind, Placebo-Controlled	Yearly Rate of Change in Forced (Expiratory) Vital Capacity (FVC)	II	52 weeks
Pamrevlumab (FG-3019)	Anti-connective tissue growth factor antibody	NCT01890265	Randomized, Double-Blind, Placebo-Controlled	Change from baseline in FVC (percent of predicted value) at Week 48	II	48 weeks
PBI-4050	Anti-connective tissue growth factor antibody	NCT02538536	Open-label, Single Arm, Exploratory, Observational Study	Number of subjects with abnormal laboratory values and/or adverse events that are related to treatment	II	20 weeks
KD025	Selective inhibitor of ROCK2	NCT02688647	Randomized, Phase 2, Open-Label	Change in Forced Vital Capacity (FVC) in baseline to 24 weeks	II	24 weeks
CC-90001	Kinase inhibitor targeting JNKs	NCT03142191	Randomized, Double-blind, Placebo-controlled	Percentage point change in % predicted Forced vital capacity (FVC)	II	24 weeks
GLPG1690	Autotaxin-LPA inhibitor	NCT02738801	Randomized, Double-Blind, Parallel Group, Placebo-Controlled	Safety, Tolerability, Pharmacokinetic and Pharmacodynamic Properties of GLPG1690	II	12 weeks
Omipalisib / GSK2126458	Inhibitor of PI3K pathway	NCT01725139	Randomized, Double-blind, Placebo-controlled,	To explore a number of doses of GSK2126458 for engagement of pharmacology after short term dosing	I	7 to 10 days
Sirolimus	mTOR inhibitor	NCT01462006	Double-blind Placebo-controlled Pilot Study	Change in peripheral blood concentration of CXCR4+ fibrocytes; number of subjects with drug side-effects	NA	22 weeks
Rituximab	Antibody targeting CD20	NCT01969409	Randomized, Double-blind, Placebo-controlled,	Titers of anti-HEp-2 autoantibodies, by indirect immunofluorescence assays (IFA) over 9 months	II	36 weeks
Co-trimoxazole or Doxycycline	Antimicrobial drugs	NCT02759120	Randomized, un-blinded, phase III	Time to first non-elective, respiratory hospitalization or all-cause mortality	III	9 months

Somogyi et al., under review

Genetic variants in IPF

Personalized therapy in IPF ?

Danazol Treatment for Telomere Diseases

Personalized therapy in IPF ?

NAC effectiveness by TOLLIP genotype – a pharmacogenomic role?

-genetic variants for TOLLIP-
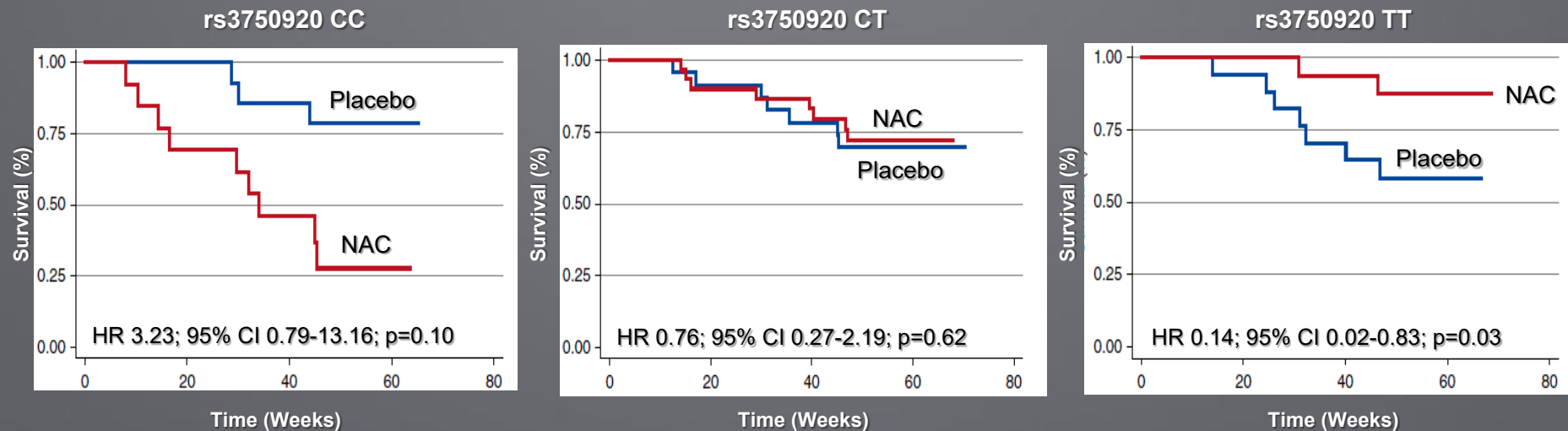
Replicated in patients on NAC from GIPF001 and UChicago

Toll interacting protein:

inhibitory adaptor protein within Toll-like receptors. TLR pathway part of innate immune system that recognizes structurally conserved molecular patterns of microbial pathogens, leading to an inflammatory immune response
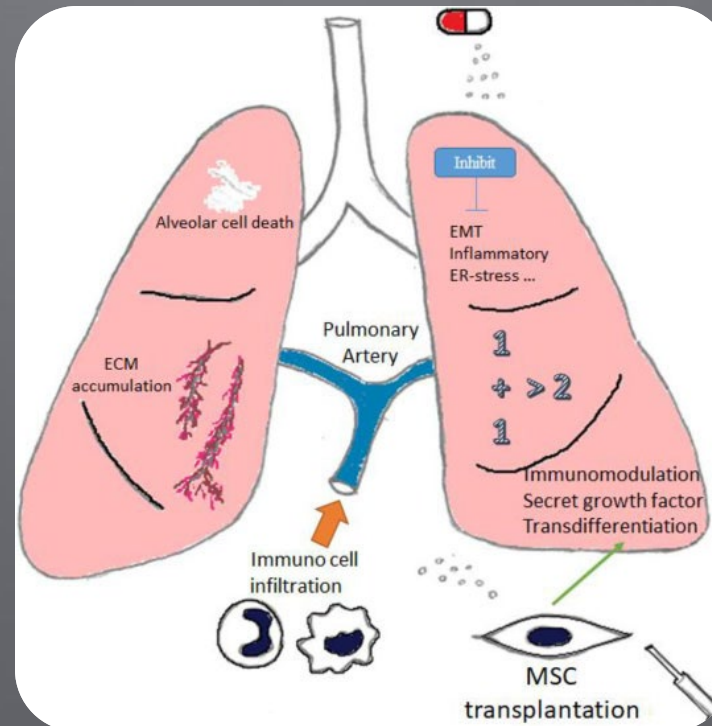
Hypothesis:

- MSC differentiate into alveolar epithelial cells
- Effects on tissue repair & wound healing combined with immuno-modulatory properties

Forms of MSC-TX:

➢ allogeneic bone marrow MSC transplantation
➢ human umbilical cord-derived mesenchymal stem cell transplantation
➢ adipose-derived stem cell treatment

Current status

➢ Early phase trials
   ➢ Safety (+)
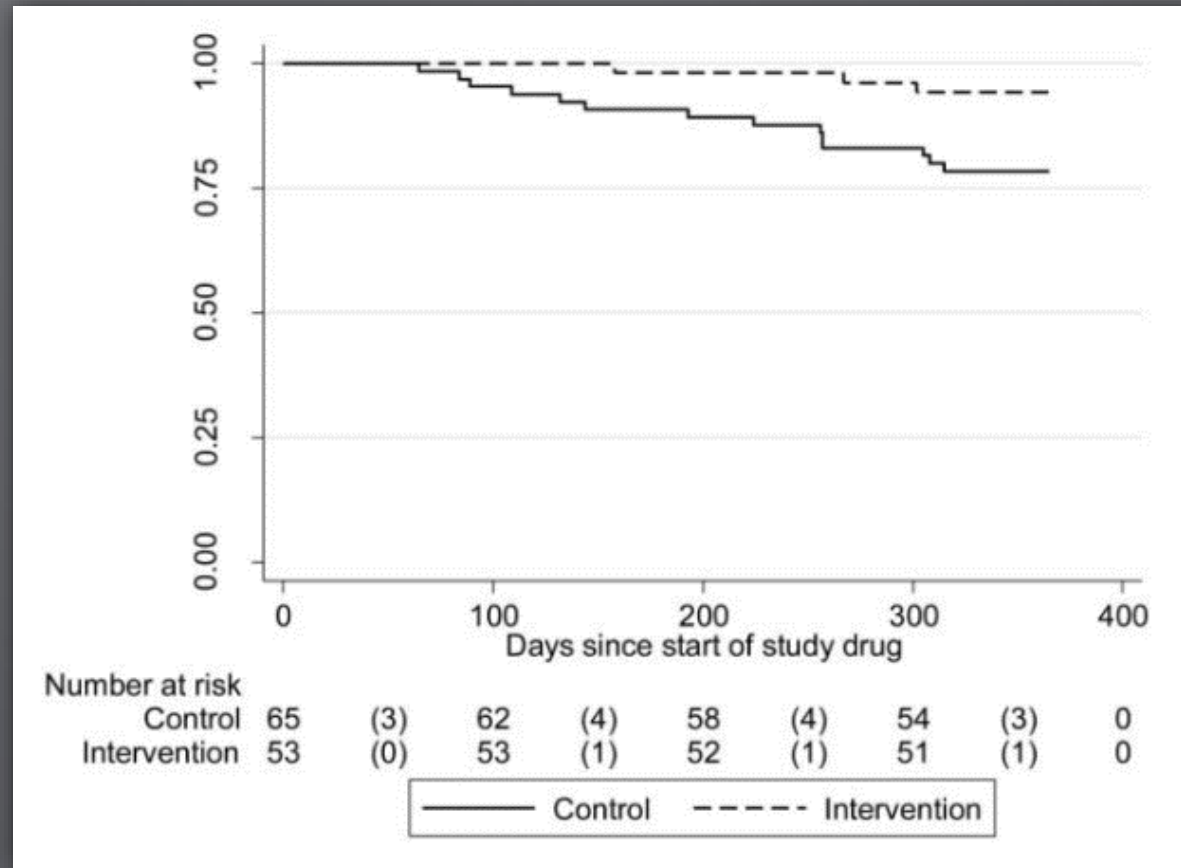   ➢ Efficacy ???

Chuang et al., Cell Transplantation, 2018

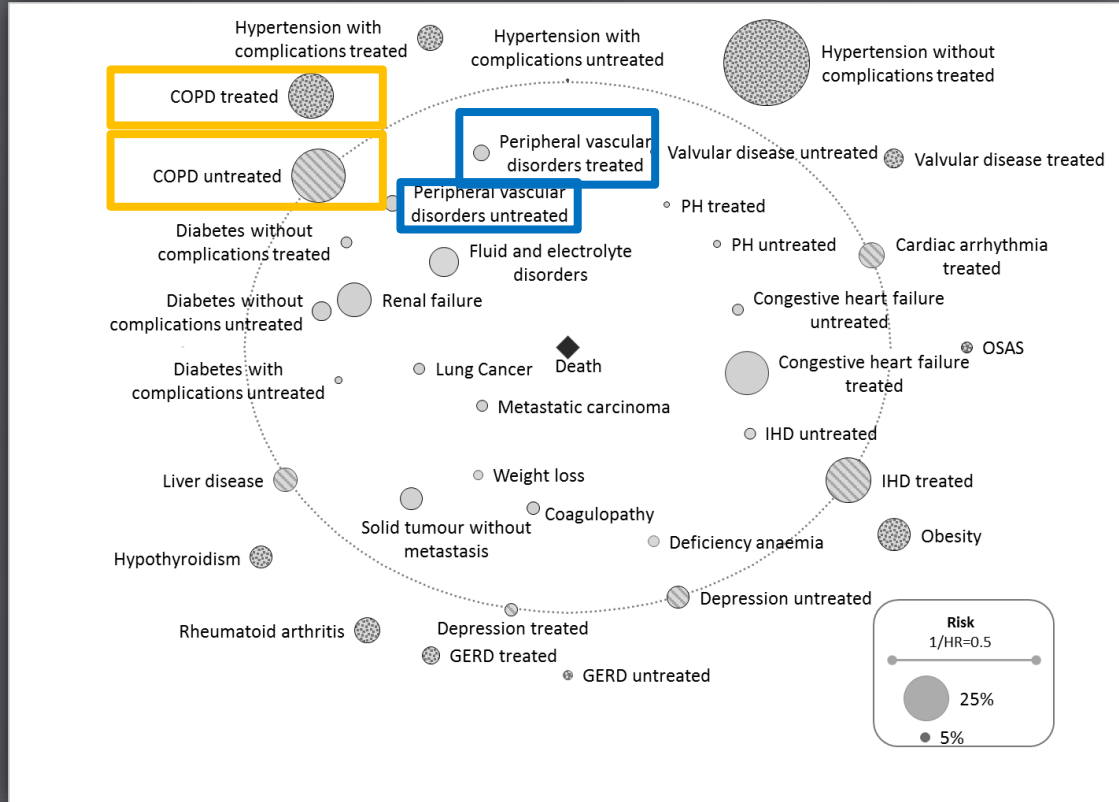# „New" non-drug treatments
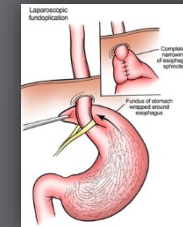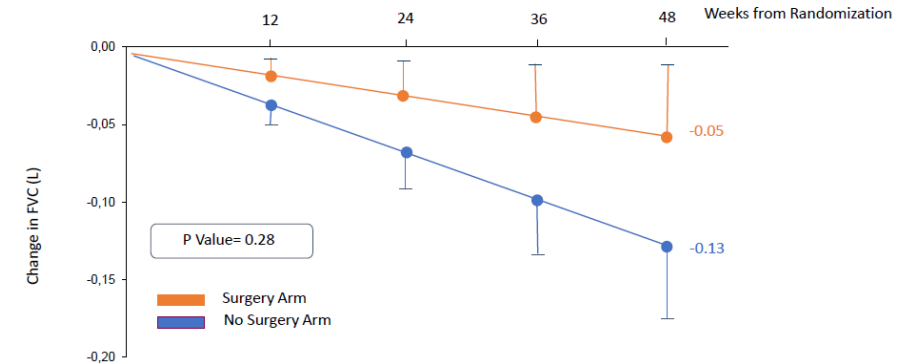
Visca et al. Lancet Respir Med. 2018
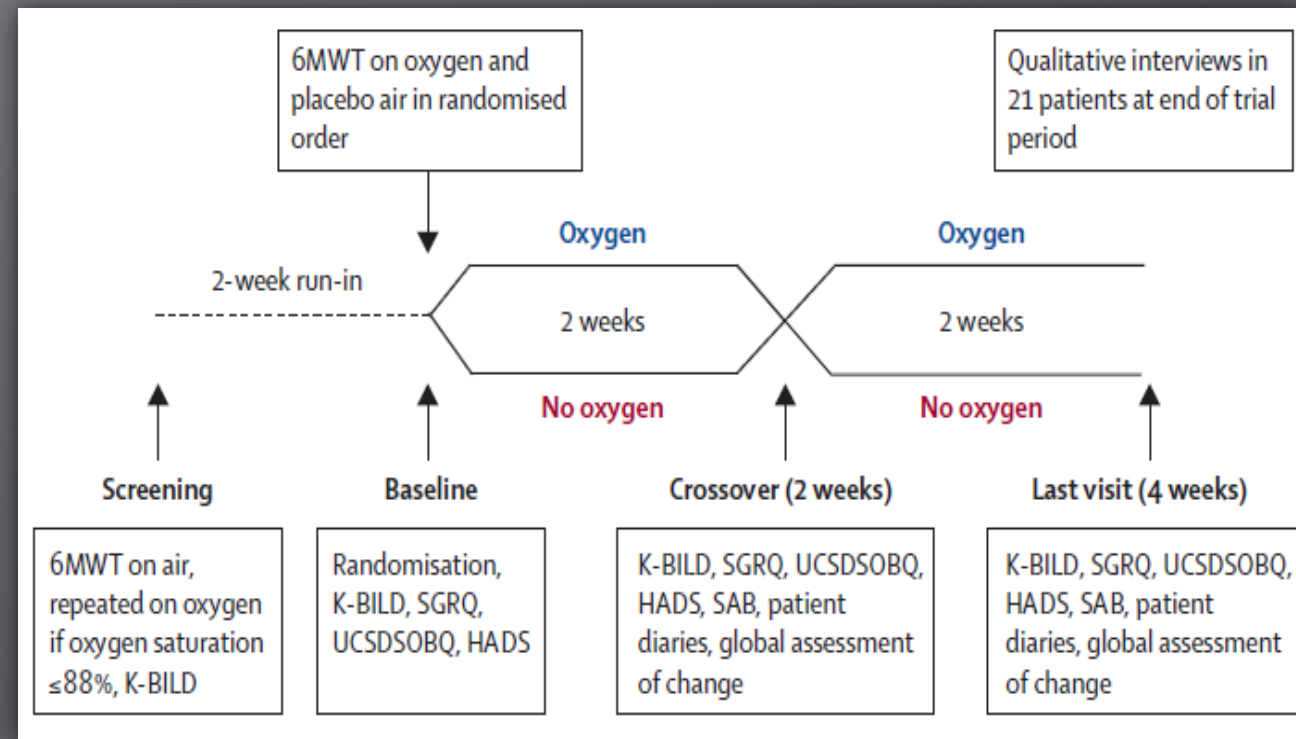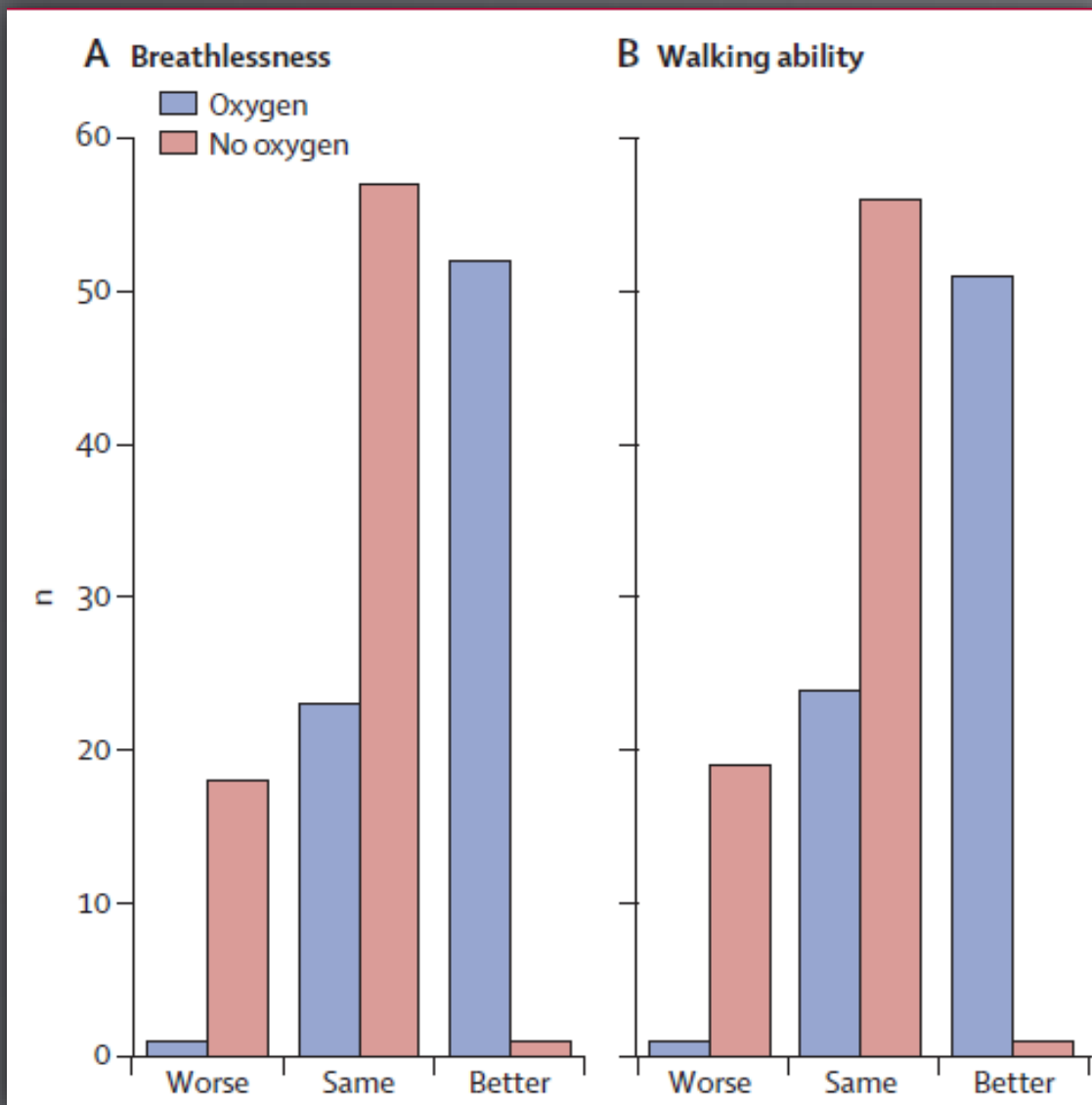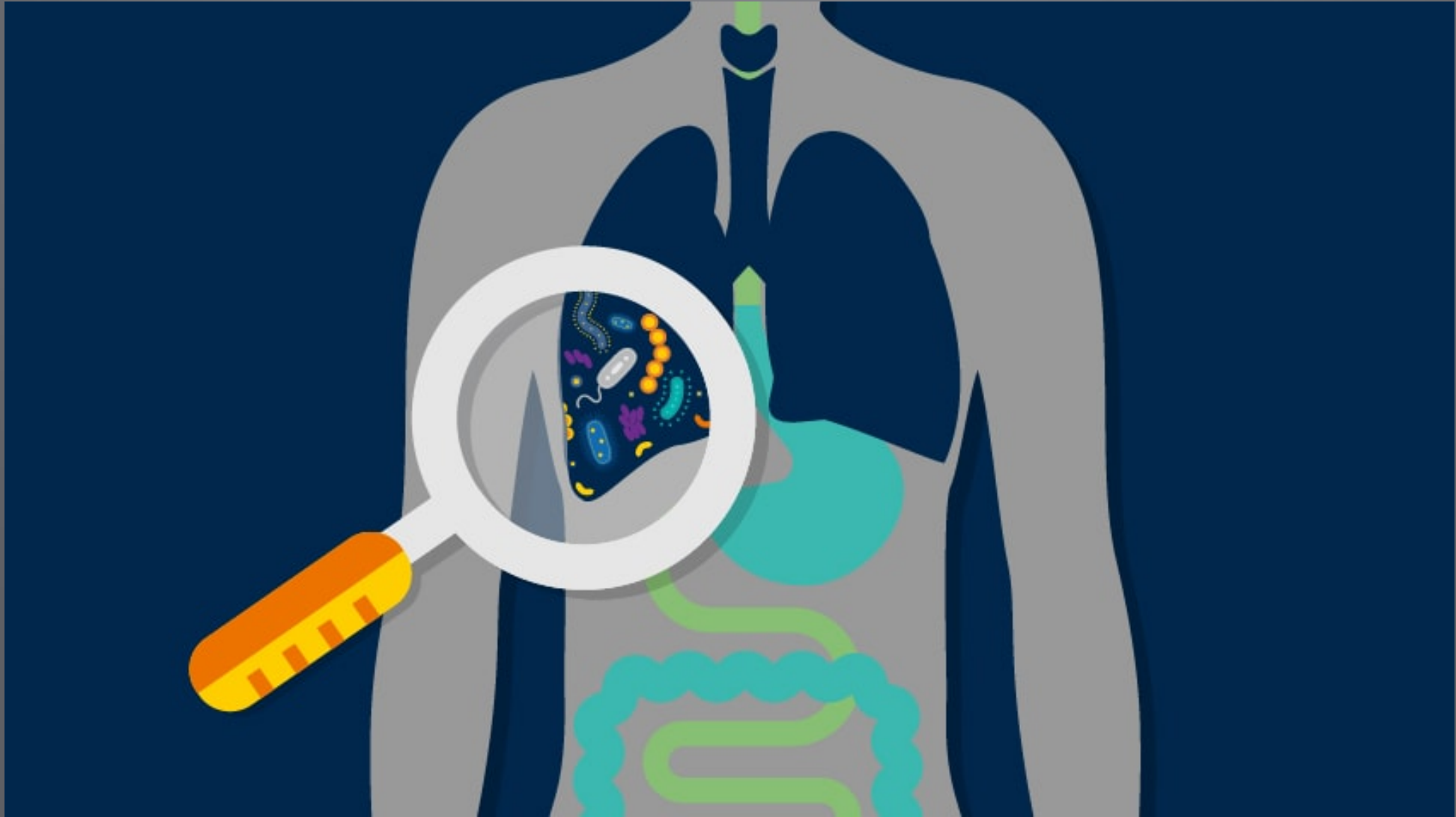
Microbiome & IPF

Co-trimoxazole decreased mortality in per-protocol analysis
of 181 patients with fibrotic IIP (89% IPF)
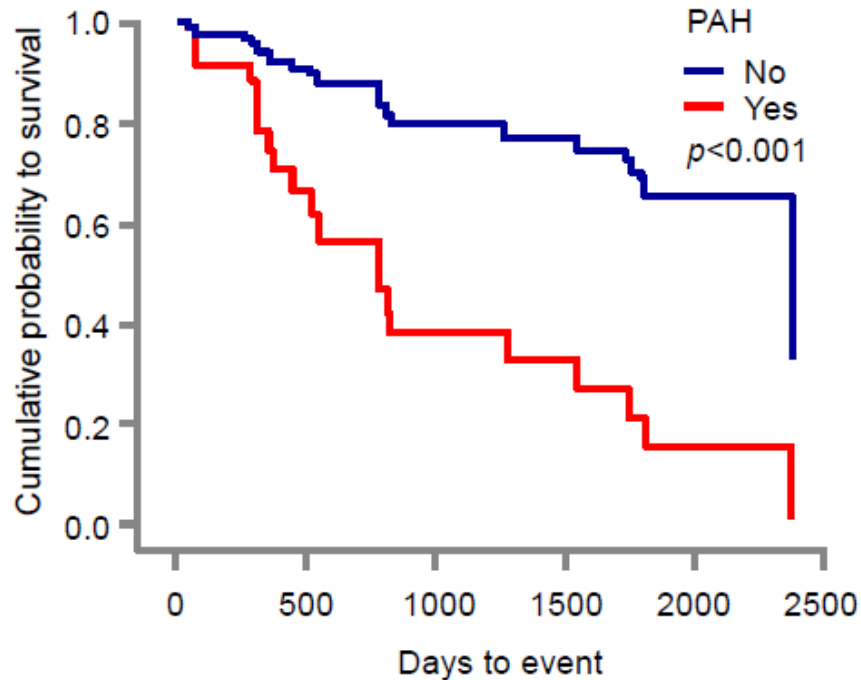
Optimized treatments of comorbidities

Hypertension with complications treated
Hypertension with complications untreated
Hypertension without complications treated
COPD treated
COPD untreated
Peripheral vascular disorders treated
Peripheral vascular disorders untreated
Valvular disease untreated
Valvular disease treated
PH treated
Diabetes without complications treated
PH untreated
Cardiac arrhythmia treated
Fluid and electrolyte disorders
Diabetes without complications untreated
Renal failure
Congestive heart failure untreated
OSAS
Diabetes with complications untreated
Lung Cancer
Death
Congestive heart failure treated
Metastatic carcinoma
IHD untreated
Liver disease
Weight loss
IHD treated
Solid tumour without metastasis
Coagulopathy
Obesity
Hypothyroidism
Deficiency anaemia
Depression untreated
Rheumatoid arthritis
Depression treated
GERD treated
GERD untreated

Risk
1/HR=0.5
25%
5%

Mean change in forced vital capacity (L) from randomization to week 48

Weeks from Randomization

P Value= 0.28

-0.05
-0.13

Surgery Arm
No Surgery Arm

Endpoint	Surgery N=29	No surgery N=29	P-value
Clinical events [*]			
Acute exacerbation	1 (3.4%)	4 (16.3%)	0.19
Respiratory hospitalization	2 (6.9%)	6 (20.7%)	0.25
Non-elective hospitalization	5 (17.2%)	8 (27.6%)	0.35
Lung transplantation	0 (0.0%)	1 (3.4%)	>0.99
Disease progression [†]			
Death	1 (3.4%)	4 (17.7%)	0.13
10% FVC decline or death	2 (9.1%)	7 (29.4%)	0.038
10% FVC decline, acute exacerbation, or death	2 (9.1%)	7 (27.8%)	0.048

Kreuter M, et al. *PLoS One* 2016;11(3):e0151425; Schwarzkopf et al, Resp Res, 2018
Raghu et al., Lancet Res Med 2018

The unmet need in IPF: treatment of PH-IPF

	Drug tested	Primary outcome	Result
Trials targeting IPF with drugs approved in PAH			
STEP-IPF [22]	Sildenafil	Proportion of patients with >20% increase in 6-min walk distance	Negative on primary outcome, some positive effect on secondary and exploratory end-points
ARTEMIS-IPF [23]	Ambrisentan	Time to disease progression, defined as death, respiratory hospitalisation, or a categorical decrease in lung function	Deleterious effect
BUILD-1 [24]	Bosentan	6-min walk distance	Negative
BUILD-3 [25]	Bosentan	Time to IPF worsening (a confirmed decrease from baseline in FVC ≥10% and D_{LCO} ≥15%, or acute exacerbation of IPF) or death	Negative
MUSIC [26]	Macitentan	FVC	Negative
Trials targeting IPF-PH with drugs approved in PAH			
ARTEMIS-PH (NCT00879229)	Ambrisentan	6-min walk distance	Terminated early
RISE-IIP [27] (results unpublished)	Riociguat	6-min walk distance	Terminated early
BPHIT [28]	Bosentan	Indexed pulmonary vascular resistance	Negative

FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide.

+ Symptoms ↑

+ QoL ↓

+ ...

Lettieri et al. Chest 2006;129(3):746-752; Cottin et al. Eur Respir J 2018;51(1);

Nintedanib plus sildenafil in IPF: the INSTAGE trial

Primary endpoint: Change from baseline in SGRQ total score at week 12

Legend:
- Nintedanib + placebo (n=133)
- Nintedanib + sildenafil (n=132)

Bar values: -0,77 ; -1,28

−0.52
(95% CI: −3.33, 2.30)
p=0.72

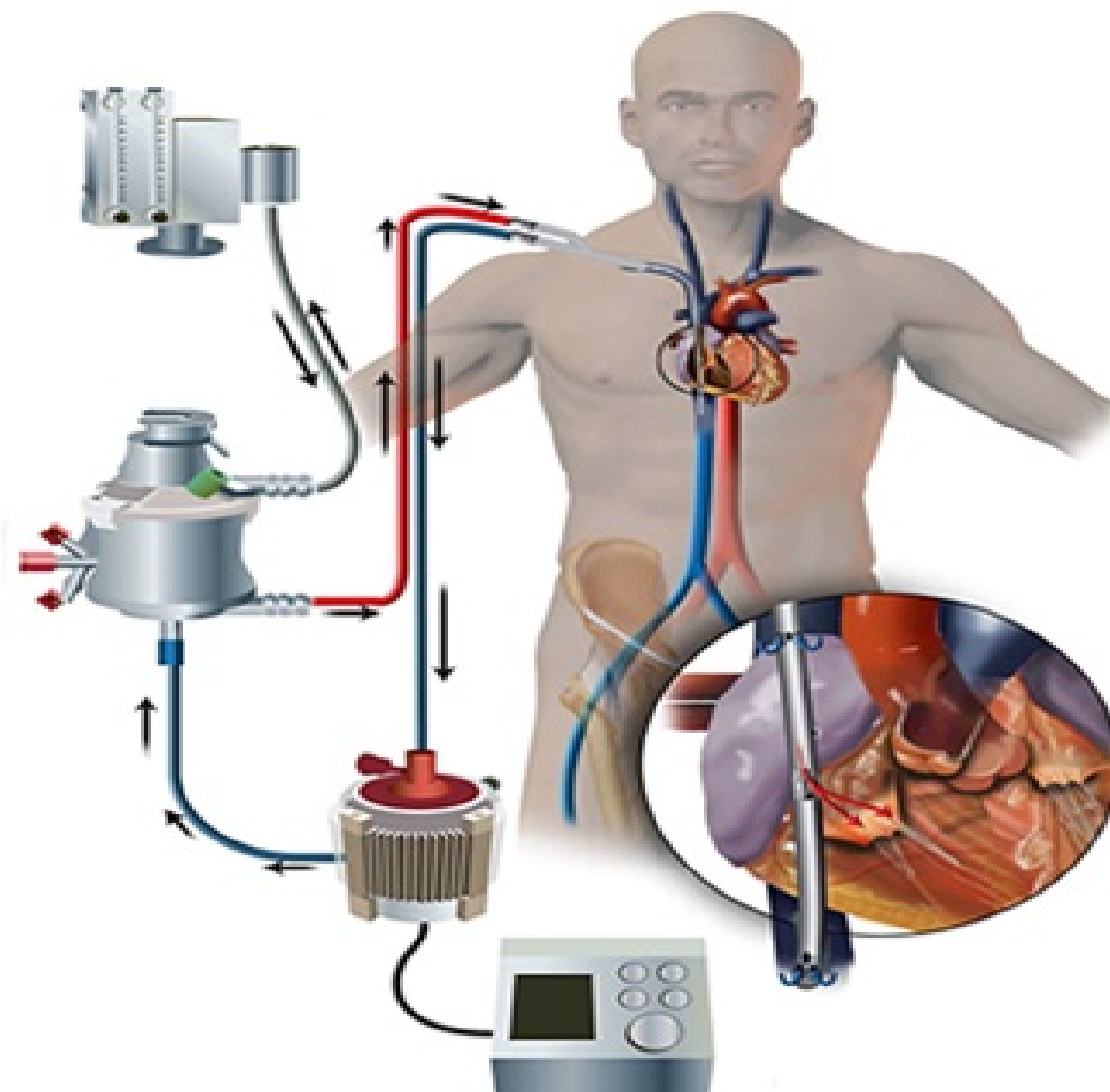y-axis: Adjusted mean (SE) change from baseline in SGRQ total score
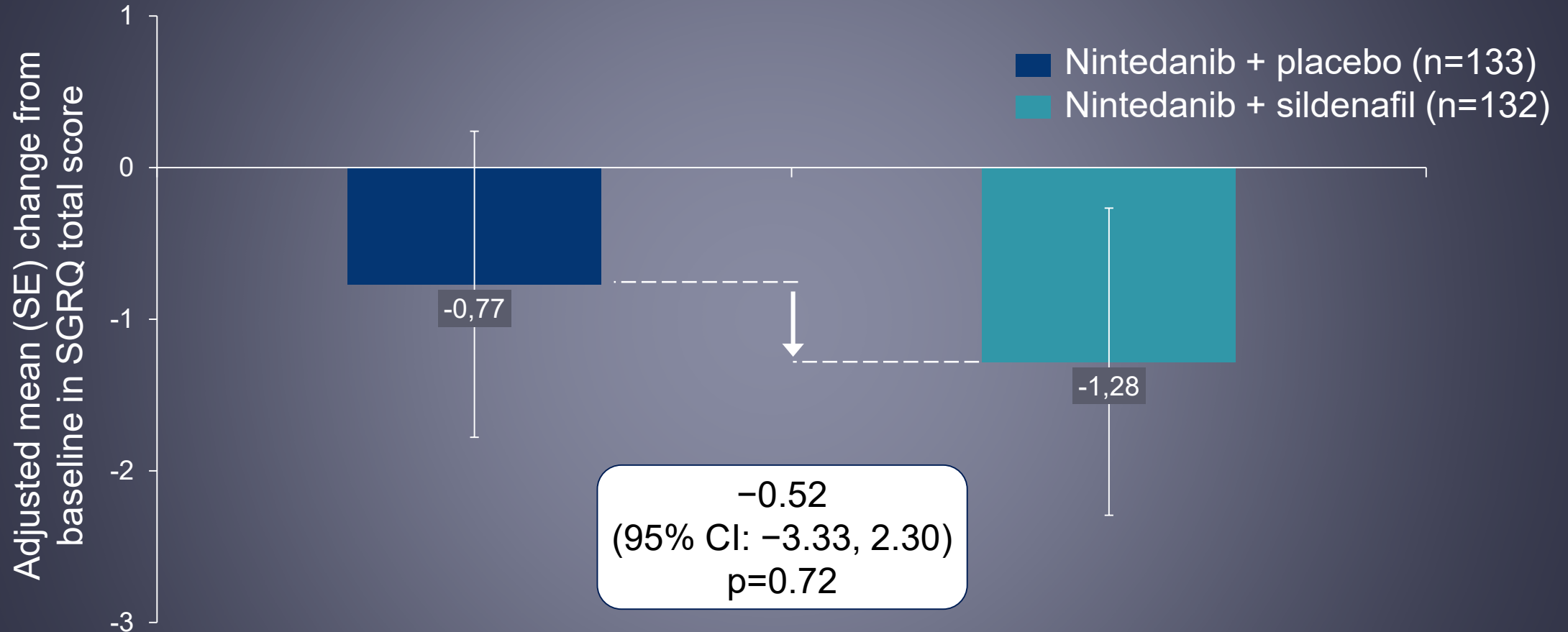
Conclusions
- No significant benefits on primary endpoint QoL/SOB
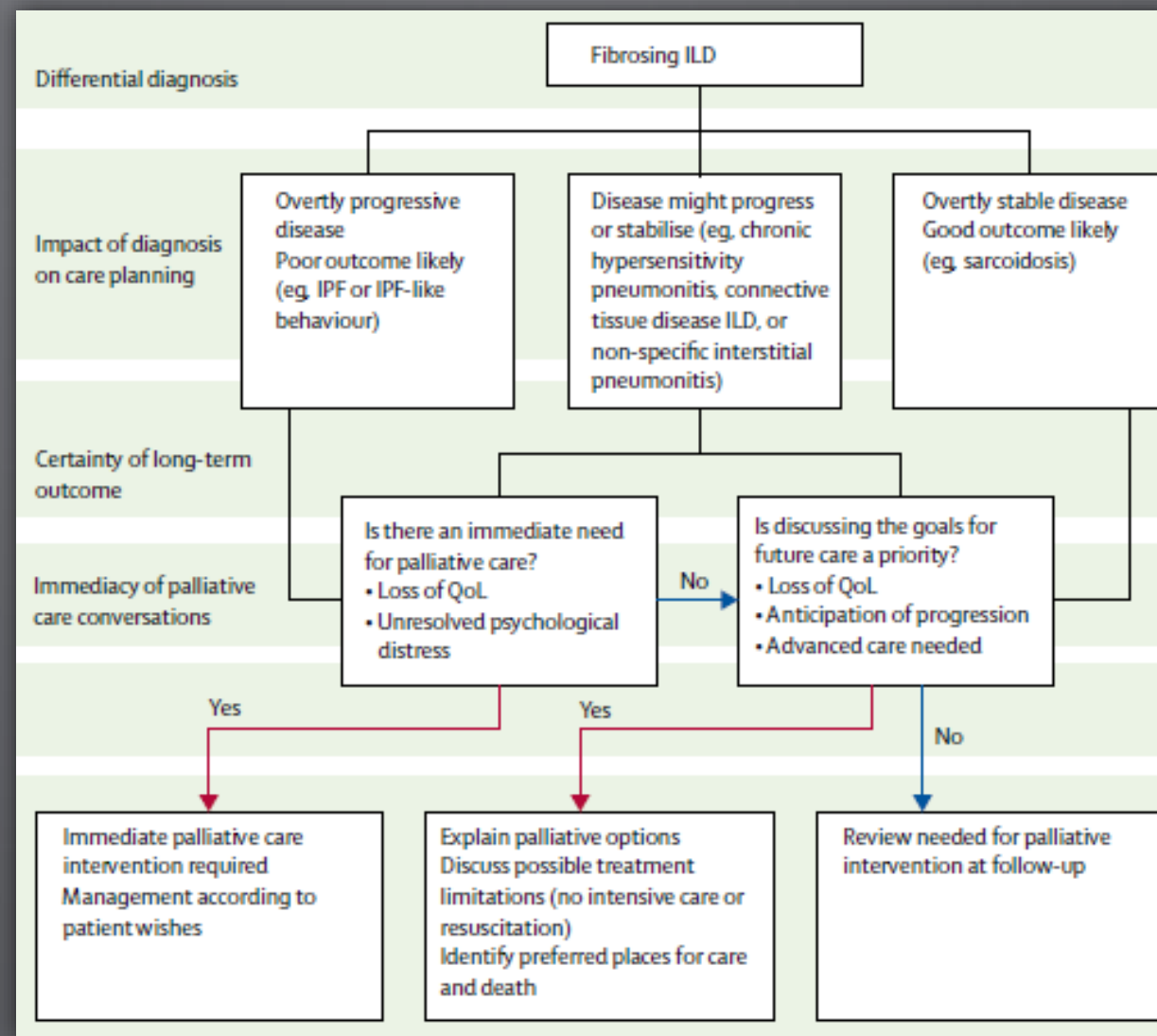- Decline for this advanced patient group similar to less advanced INPULSIS
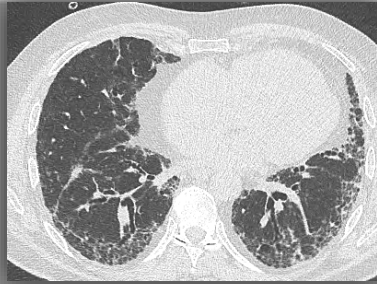
Brigde to LTX (?) : ECMO
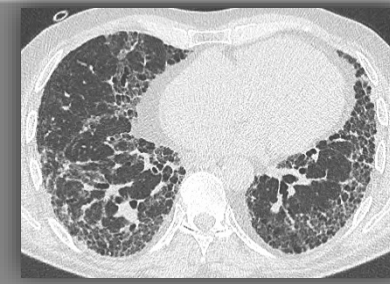
The other end – palliative care for AE-IPF

The continued threat in IPF

3 months pre   AE-IPF   6 months post
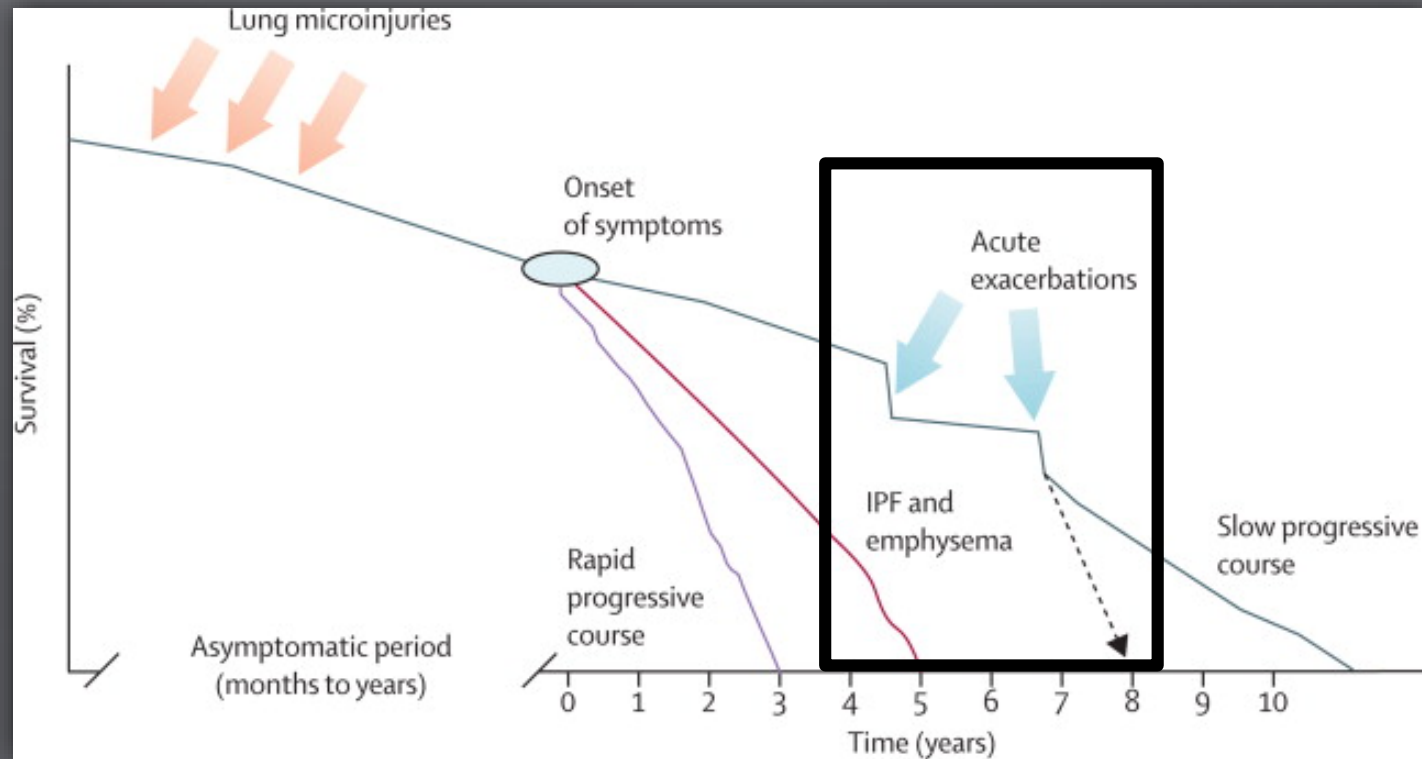
The continued threat in IPF – AE-IPF

Practical questions	Answers	International survey, n=509; From 66 countries, 6 continents
Do you use BAL for diagnosing AE?	We perform BAL unless there is a high chance of triggering the need for mechanical ventilation	6 %
Do you use empirical antibiotic treatment?	We use broad-spectrum antibiotic therapy	56% always 23% if clinical signs
Do you treat with antivirals?	No, unless the patient is severely lymphopenic	0%
Do you treat for pneumocystis?	Yes, we do	0%
Do you use anticoagulation?	No, we do not	0% (as therapy)
Do you use corticosteroids?	Yes, we pulse the patient with three daily doses of methylprednisolone of 1 g each	96% yes – 4% no (62% methylprednisone 3d 0,5-1 g, 32% 100 mg prednisone)
Do you use cyclophosphamide for AE-IPF?	No	18%
Continuation / initiation of antifibrotics		76% continuation, 7% discontinuation, 9% switch drug

➢ **Significant heterogenity between continents**

Conclusions

- Established treatments
  - non-
  - pharma-cological
  - pharma-cological

- No disease stabilization

- No cure

- Therapeutic biomarkers guiding therapy
- Combination therapy
- New drugs
- Gene based therapies / stem cell therapy
- Targeting the lung microbiom
- New non-drug therapies
- Treatment of comorbidities
- New developments in LTX
- New ways to approach palliative care
- Urgent need to improve care of AE-IPF

Thank you!