Respiratory Review of 2019

- Interstitial Lung Disease

2019. 04. 13

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Guideline

AMERICAN THORACIC SOCIETY DOCUMENTS

Diagnosis of Idiopathic Pulmonary Fibrosis
An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

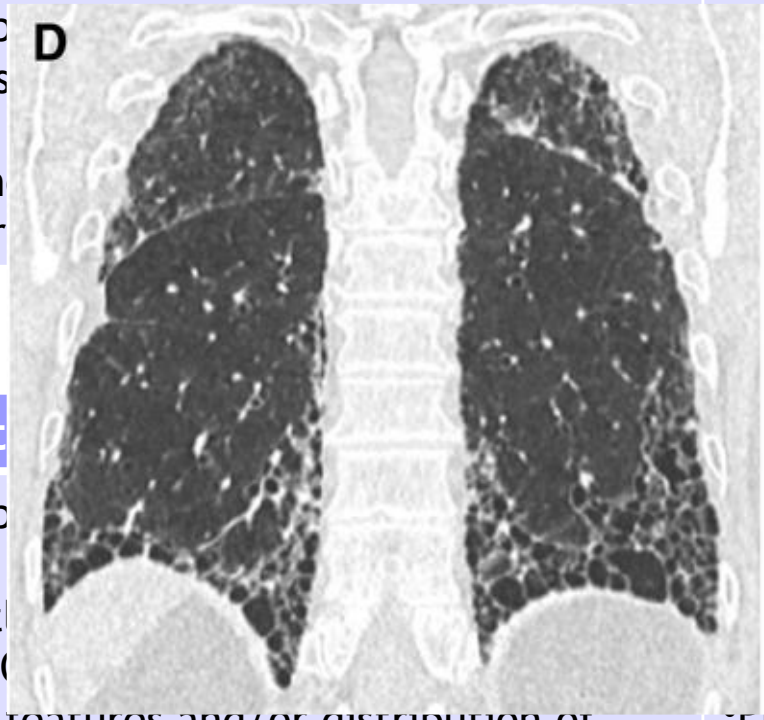
2011 vs. 2018 Guideline

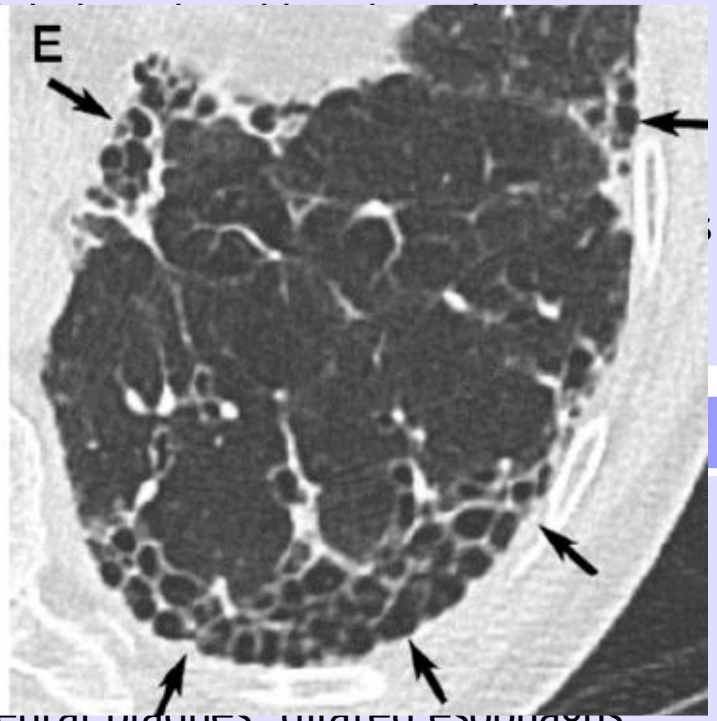
HR CT				
2011	*UIP*	*Possible UIP*		*Inconsistent UIP*
2018	**UIP**	**Probable UIP**	**Indeterminate for UIP**	**Alternative Dx**

Histopathology				
2011	*UIP*	*Probable UIP*	*Possible UIP*	*Not UIP*
2018	**UIP**	**Probable UIP**	**Indeterminate for UIP**	**Alternative Dx**

Diagnosis of IPF-1 (HR CT patterns)

UIP	Probable UIP
• Subp ; dis • Hon per	extensive LAP, pleural effusion…
Indet	
• Subp • Subt GG CT features and/or distribution of lung fibrosis that do not suggest any specific etiology(“truly indeterminate”)	





Am J Respir Crit Care Med 2018;198: e44-e68

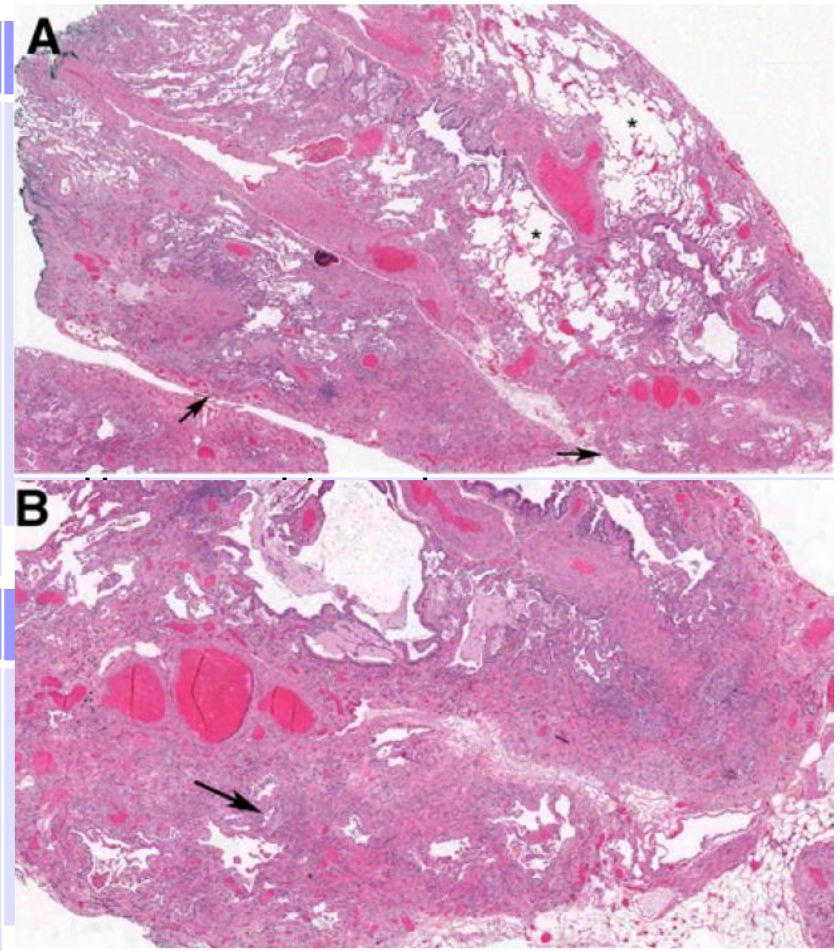
Diagnosis of IPF-2 (Histopathologic patterns)

UIP

•Dense fibrosis c architectural distortion,
(i.e., destructive scarring / honeycombing)
• Predominant subpleural/paraseptal distribution of fibrosis
• Patchy involvement of lung parenchyma by fibrosis
• Fibroblast foci
• Absence of feature to suggest an alternative Dx

Indeterminate for UIP

• Fibrosis c/s architectural distortion c features favoring either a pattern other than UIP or features favoring UIP
• Some histologic features from UIP, but c other feature suggesting an alternative Dx



Am J Respir Crit Care Med 2018;198: e44-e68

Diagnosis of IPF-3

- *For adult pts c newly detected ILD of apparently unknown cause who are clinically suspected of having IPF*
  - Recommend taking a detailed Hx of both medication and environmental exposure (at home, work…)
  - Recommend serological testing to exclude CTD ILD

- *For pts c newly detected ILD of apparently unknown cause who are clinically suspected of having IPF and have an HR CT pattern of probable UIP, indeterminate for UIP or an alternative Dx*
  - Suggest cellular analysis of BAL/ SLB

    (conditional recommendation, very low quality of evidence)
  - Made no recommendation for or against TBLB/cryoBx

Am J Respir Crit Care Med 2018;198: e44-e68

Diagnosis of IPF-4

- *For pts c newly detected ILD of apparently unknown cause who are clinically suspected of having IPF and have an HR CT pattern of UIP*
  - Suggest NOT performing BAL

    (conditional recommendation, very low quality of evidence)
  - Recommend NOT performing SLB, TBLBx/cryoBx

    (strong recommendation, very low quality of evidence)

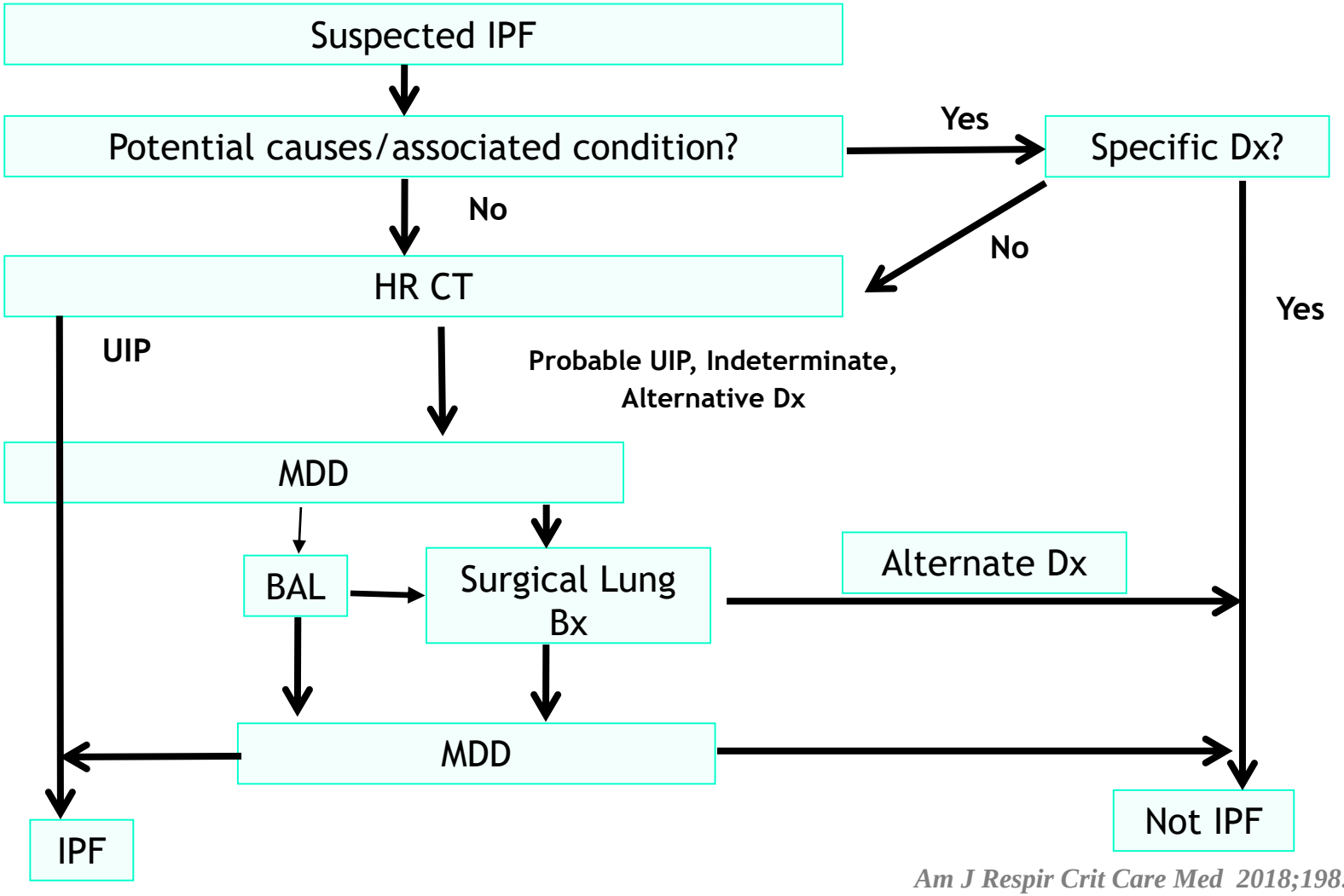
- *For pts c newly detected ILD of apparently unknown cause who are clinically suspected of having IPF*
  - Suggest MDD for diagnostic decision-making

    (conditional recommendation, very low quality of evidence)
  - Recommend NOT measuring serum markers *(MMP-7, SPD, CCL-18, KL6)* for distinguishing IPF from other ILD

    (strong recommendation, very low quality of evidence)

Am J Respir Crit Care Med 2018;198: e44-e68

Diagnosis of IPF-5



Am J Respir Crit Care Med 2018;198: e44-e68

Diagnosis of IPF-6

IPF suspected*		Histopathology pattern			
		UIP	Probable UIP	Indeterminate for UIP	Alternative diagnosis
HRCT pattern	UIP	IPF	IPF	IPF	Non-IPF dx
	Probable UIP	IPF	IPF	IPF (Likely)**	Non-IPF dx
	Indeterminate	IPF	IPF (Likely)**	Indeterminate***	Non-IPF dx
	Alternative diagnosis	IPF (Likely)** /non-IPF dx	Non-IPF dx	Non-IPF dx	Non-IPF dx

1) moderate to severe traction bronchiectasis in man >50 (women >60)yr
2) Extensive(>30%) reticulation on CT + age>70 yr
3) Increased neutrophil/absence of lymphocytosis in BAL
4) IPF (After MDD)

J Respir Crit Care Med 2018;198: e44-e68

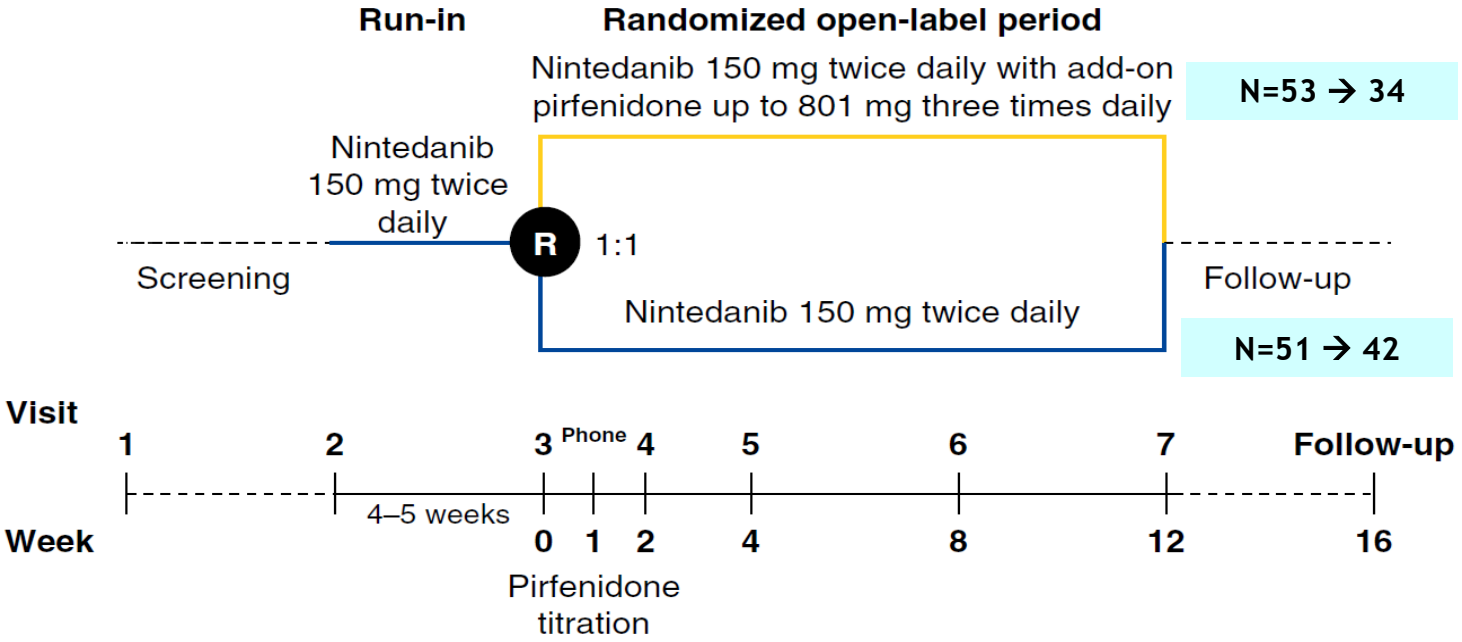
Tx for IPF

Nintedanib with Add-on Pirfenidone in Idiopathic Pulmonary Fibrosis

Results of the INJOURNEY Trial

Carlo Vancheri[1], Michael Kreuter[2], Luca Richeldi[3], Christopher J. Ryerson[4], Dominique Valeyre[5], Jan C. Grutters[6,7], Sabrina Wiebe[8], Wibke Stansen[9], Manuel Quaresma[2,9], Susanne Stowasser[9], and Wim A. Wuyts[10]; on behalf of the INJOURNEY Trial Investigators

- 12wk, open label, RCT
- IPF: ≥40 yr, FVC ≥50%



Am J Respir Crit Care Med 2018;198: e44-e68

Nintedanib± Pirfenidonein in IPF

- Primary outcome

  : % of pts c GI AE during 12v '

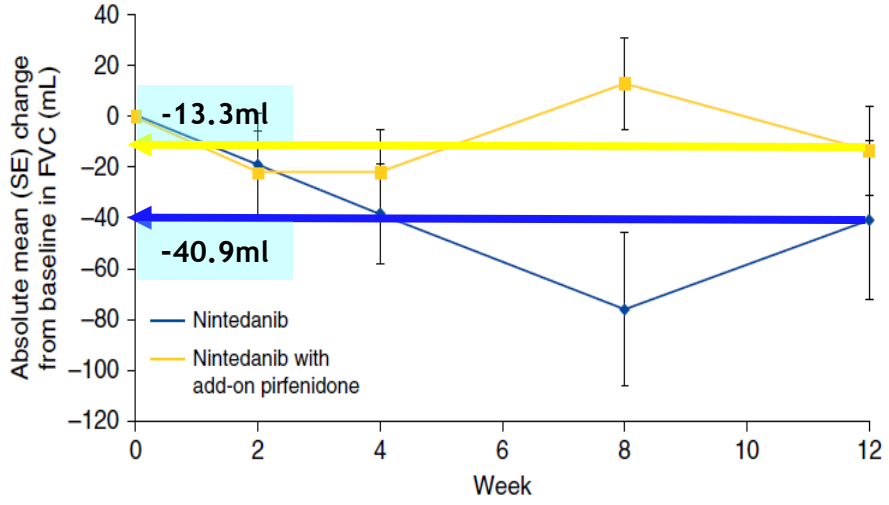
  (37/53(=69.8%) in combinc

- Secondary outcome

  1) plasma concentration of n

  (similar between 2 groups

  2) safety (time to GI AE, LFT,



n					
Nintedanib	51	49	48	45	44
Nintedanib with add-on pirfenidone	53	52	50	50	48

- Tx c nintedanib + pirfenidone for 12 wk had a manageable safety and tolerability.

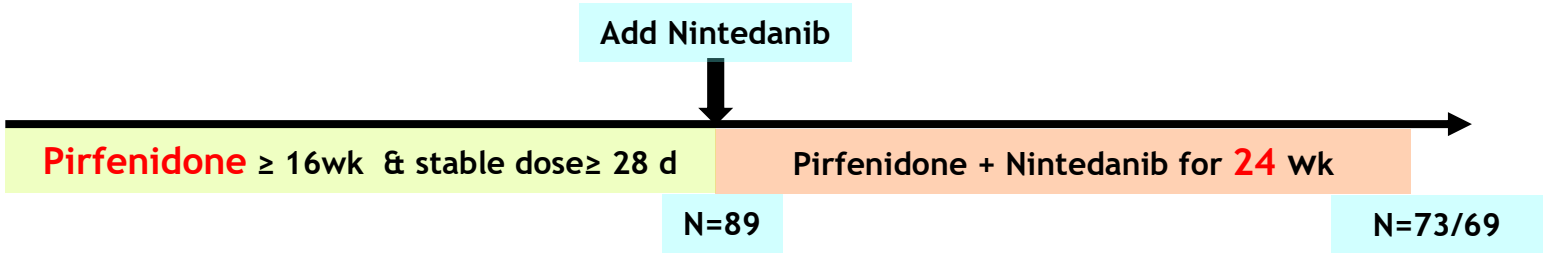
Am J Respir Crit Care Med 2018;198: e44-e68

ORIGINAL ARTICLE
INTERSTITIAL LUNG DISEASES

Safety of nintedanib added to pirfenidone treatment for idiopathic pulmonary fibrosis

Kevin R. Flaherty[1], Charlene D. Fell[2], J. Terrill Huggins[3], Hilario Nunes[4], Robert Sussman[5], Claudia Valenzuela[6], Ute Petzinger[7], John L. Stauffer[8], Frank Gilberg[9], Monica Bengus[9] and Marlies Wijsenbeek[10]

pirfenidone ≥16 wk & a stable dose (of 1602-2403mg/d) ≥ 28 days



- Primary outcome

  : proportion of complete combination at stable dose

  (69/89=78%)

Eur Respir J 2018;52:1800230

Safety of Pirfenidone+Nintedanib in IPF

- Secondary outcome
  1) proportion of pt c premature discontinuation d/t TEAE
     (13/89)
  2) total pt days of combination Tx
     (13,304 days, expected days=14,952days)
  3) total duration in days of combination *(21.4 wk)*
  4) frequency *(99%, total 670 TEAE)*
     & timing of TEAE *(anytime)*

- Combined use of pirfenidone+nintedanib for 24 wk was tolerated.

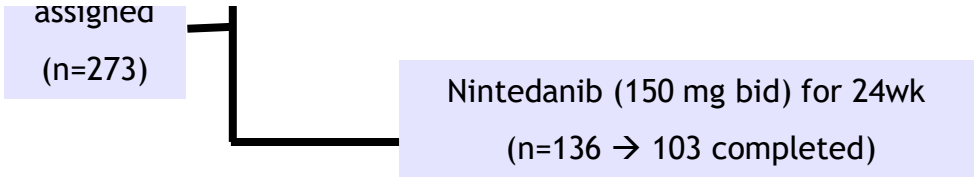
  It was associated with similar types of TEAEs with Tx alone.

Eur Respir J 2018;52:1800230

ORIGINAL ARTICLE

Nintedanib plus Sildenafil in Patients with Idiopathic Pulmonary Fibrosis

Martin Kolb, M.D., Ganesh Raghu, M.D., Athol U. Wells, M.D., Jürgen Behr, M.D., Luca Richeldi, M.D., Birgit Schinzel, Dipl.Stat., Manuel Quaresma, Lic., Susanne Stowasser, M.D., and Fernando J. Martinez, M.D., for the INSTAGE Investigators*



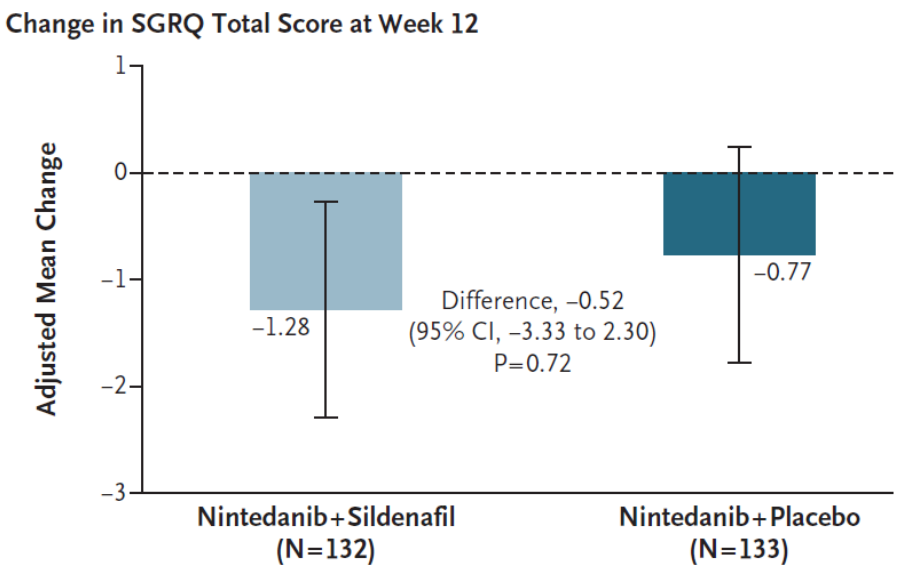
- Primary outcome: Δ SGRQ at 12 wk

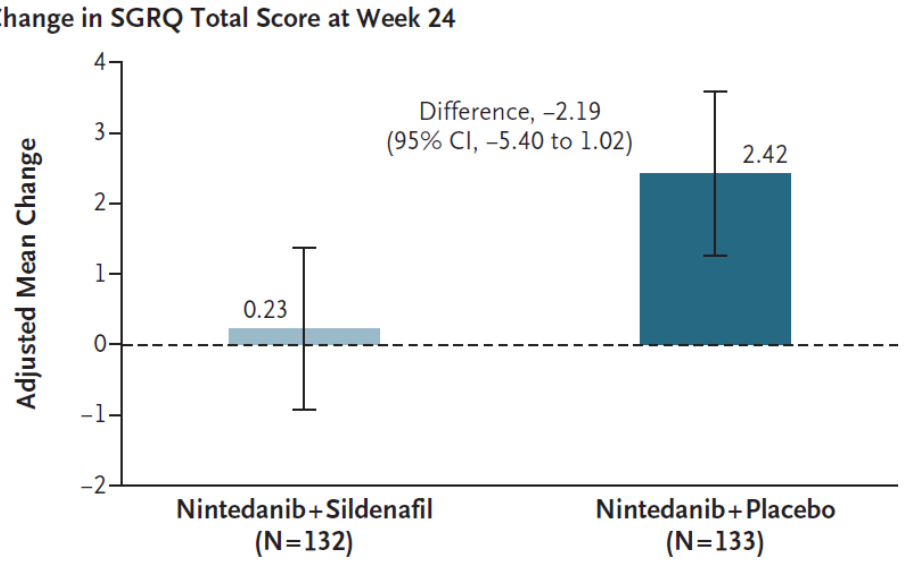
  Secondary outcome: Δ SGRQ at 24 wk, Δ dyspnea, Δ EQ-5D

  % pt c SAE

N Engl J Med 2018;379:1722-1731

Nintedanib ± Sildenafil in IPF





- ΔFVC: -20.4 ml (Nintedanib+Sildenafil) vs. -66.7ml (Nintedanib) at 24wk

- Nintedanib + Sildenafil did not provide a significant benefit.
- No new safety signals were identified

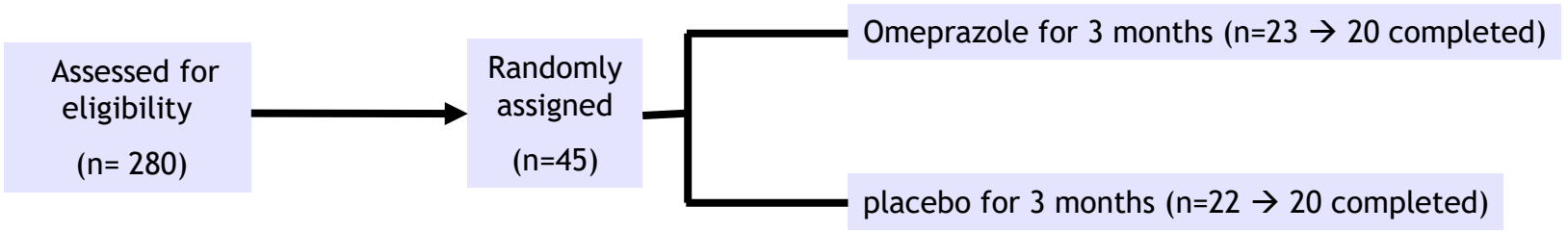
N Engl J Med 2018;379:1722-1731

ORIGINAL ARTICLE

Randomised, double-blind, placebo-controlled pilot trial of omeprazole in idiopathic pulmonary fibrosis

Prosenjit Dutta,[1] Wendy Funston,[1] Helen Mossop,[2] Vicky Ryan,[2] Rhys Jones,[1] Rebecca Forbes,[3] Shilpi Sen,[4] Jeffrey Pearson,[5] S Michael Griffin,[6] Jaclyn A Smith,[4,7] Christopher Ward,[1] Ian A Forrest,[8] A John Simpson[1,8]

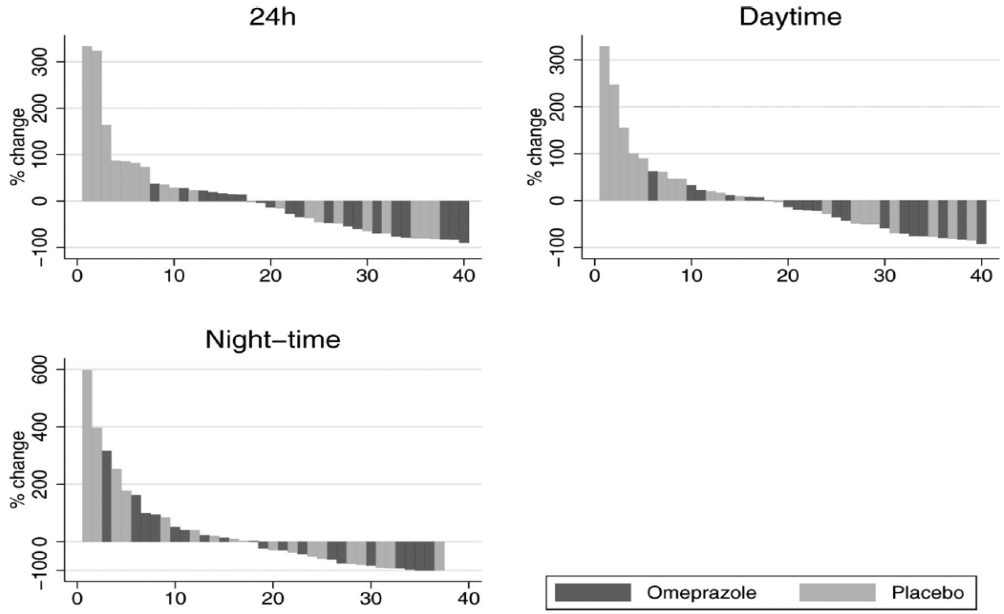
- IPF, 40-85yr, FVC>50%, DL_{CO} > 30%



- Primary objectives: to assess feasibility & acceptability of trial procedures
- Primary clinical outcome: cough frequency
- Secondary outcome: pt-reported Sx (cough, reflux)
  Functional status (PFT, 6MWD)

Thorax 2019;74:346-353

Omeprazole in IPF



- Cough was reduced in the omeprazole group, but not statistically significant.
- No changes were seen in pt-reported cough or reflux questionnaires.
- Well tolerated, but a small excess of lower respiratory tract infection and a small fall in FVC & FEV_1

Thorax 2019;74:346-353

Laparoscopic anti-reflux surgery for the treatment of idiopathic pulmonary fibrosis (WRAP-IPF): a multicentre, randomised, controlled phase 2 trial

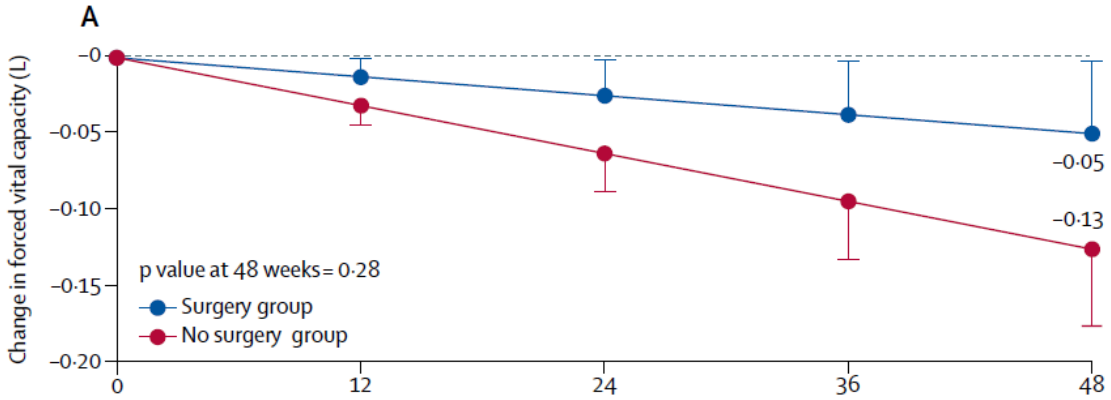
Ganesh Raghu, Carlos A Pellegrini, Eric Yow, Kevin R Flaherty, Keith Meyer, Imre Noth, Mary Beth Scholand, John Cello, Lawrence A Ho, Sudhakar Pipavath, Joyce S Lee, Jules Lin, James Maloney, Fernando J Martinez, Ellen Morrow, Marco G Patti, Stan Rogers, Paul J Wolters, Robert Yates, Kevin J Anstrom, Harold R Collard

- IPF: FVC ≥ 50%, $FEV_1/FVC \geq 0.65$, 6MWD ≥ 50m, $PaO_2 \geq 60mmHg$
  BMI<35, no Hx of acute respiratory illness within 12 wk,
  abnormal acid GER (DeMeester score of ≥ 14.7)

- Primary outcome: ΔFVC (48wk)
- Secondary outcome: AE, non-elective hospitalization, death
  Δ cough & dyspnea severity, QoL..

Lancet Respir Med 2018;6: 707-714

Laparoscopic anti-reflux OP in IPF



- Less common in AE, non-elective hospitalization, death.
  No differences in Δ cough & dyspnea severity, QoL, 6MWD, reflux Sx severity.
- Adverse event: dysphagia, abdominal distension
- Laparoscopic anti-reflux OP was generally safe, well tolerated.

Lancet Respir Med 2018;6: 707-714

JAMA | Preliminary Communication

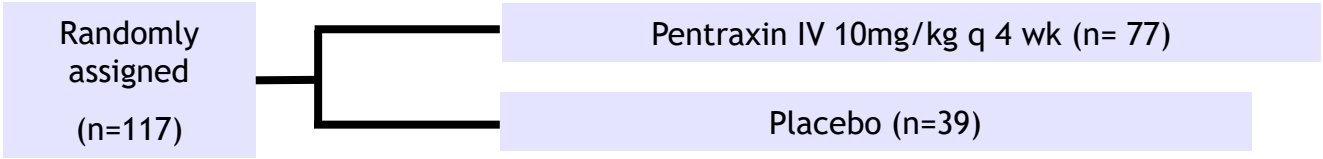
Effect of Recombinant Human Pentraxin 2 vs Placebo on Change in Forced Vital Capacity in Patients With Idiopathic Pulmonary Fibrosis

A Randomized Clinical Trial

Ganesh Raghu, MD; Bernt van den Blink, MD, PhD; Mark J. Hamblin, MD; A. Whitney Brown, MD; Jeffrey A. Golden, MD; Lawrence A. Ho, MD; Marlies S. Wijsenbeek, MD; Martina Vasakova, MD, PhD; Alberto Pesci, MD; Danielle E. Antin-Ozerkis, MD; Keith C. Meyer, MD; Michael Kreuter, MD; Hugues Santin-Janin, PhD; Geert-Jan Mulder, MD; Brian Bartholmai, MD; Renu Gupta, MD; Luca Richeldi, MD

$25\% \leq DL_{CO} \leq 90\%$, 6MWD $\geq$ 150m

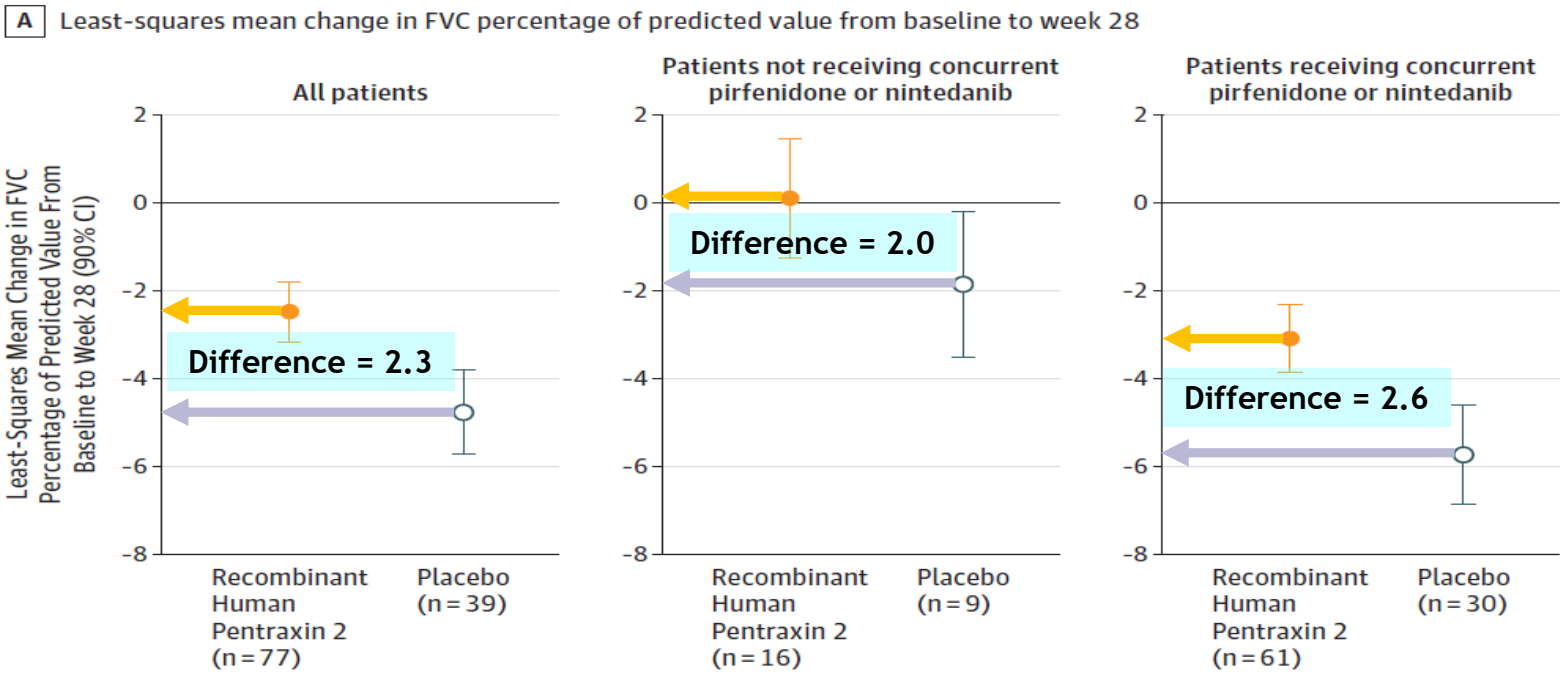
- Pentraxin 2: known as serum amyloid P
  inhibits monocyte differentiation into fibrocytes & proinflammatory MΦ and production of TGF-ß1



- Primary outcome: least squares mean Δ FVC (28wk)
- Secondary outcome: Δ mean lung volume (total, normal, ILA)
  Δ 6MWD

JAMA 2018; 319: 2299-2307

Pentraxin 2 in IPF



- No significant differences in lung volume
  Better Δ6MWD (-0.5m vs -31.8m)
- AE : cough(18% vs 5%), fatigue(17% vs 10%), nasopharyngitis (16% vs 23%)
- Pentraxin 2 resulted in a slower decline in lung function

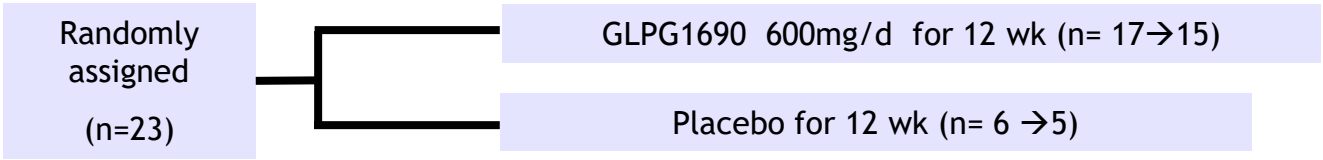
JAMA 2018; 319: 2299-2307

Safety, tolerability, pharmacokinetics, and pharmacodynamics of GLPG1690, a novel autotaxin inhibitor, to treat idiopathic pulmonary fibrosis (FLORA): a phase 2a randomised placebo-controlled trial

Toby M Maher, Ellen M van der Aar, Olivier Van de Steen, Lisa Allamassey, Julie Desrivot, Sonia Dupont, Liesbeth Fagard, Paul Ford, Ann Fieuw, Wim Wuyts

- IPF: ≥ 40 ys, without pirfenidone/nintedanib

  FVC ≥ 50 %, DL_{CO} ≥ 30%, FEV_1/FVC ≥ 0.7



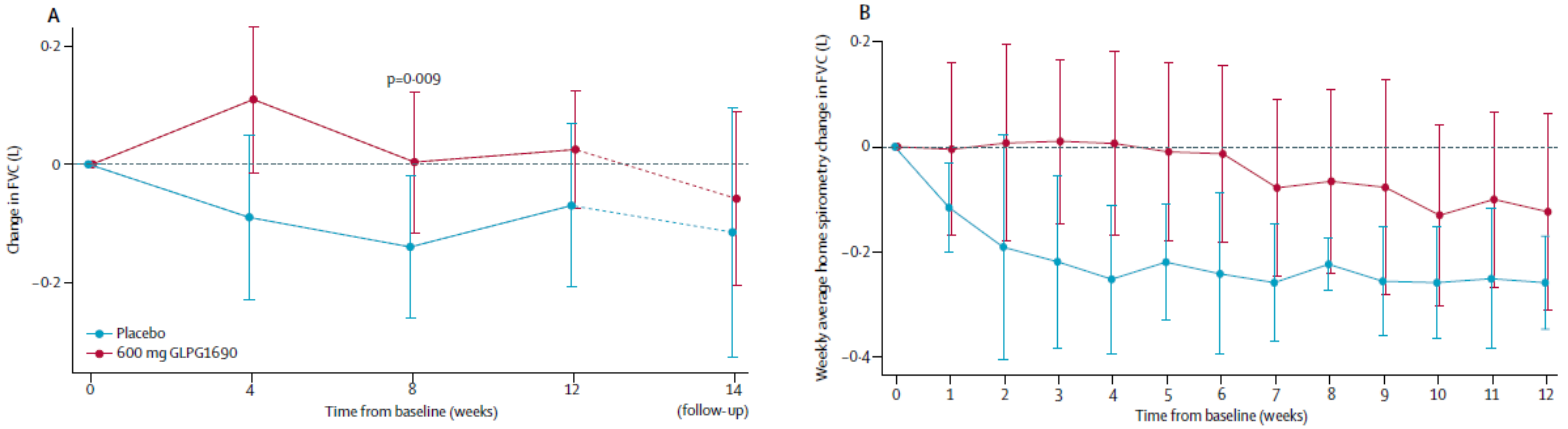
- Autotaxin: enzyme responsible for extracellular LPA production
  significantly up-regulated in IPF

- Primary outcome: safety, tolerability, pharmacokinetic/dynamic
- Secondary outcome: lung function, biomarkers, QoL

Lancet Respir Med 2018; 6: 627-635

GLPG1690, autotaxin inhibitor in IPF

- TEAE: similar between 2 groups, mild to moderate
  Pharmacokinetic/dynamic profiles in IPF were similar to those in healthy control.



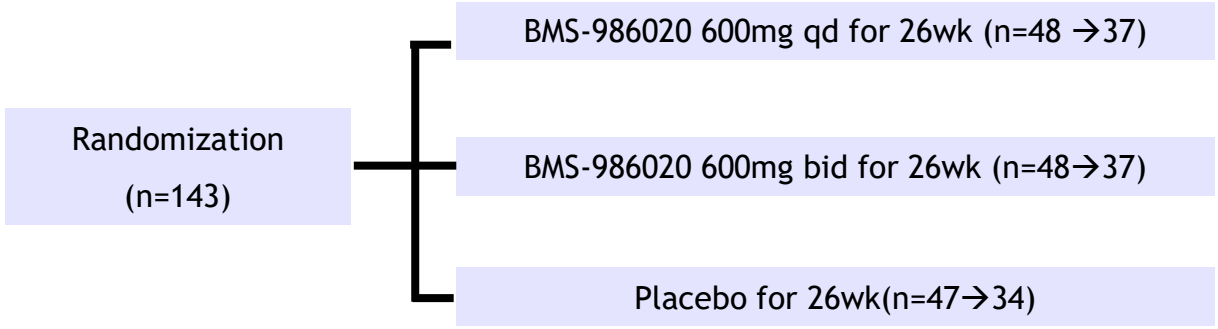
- GLPG1690 was well tolerated over 12 wk, showing a similar safety profile to placebo.

Lancet Respir Med 2018; 6: 627-635

Randomized, Double-Blind, Placebo-Controlled, Phase 2 Trial of BMS-986020, a Lysophosphatidic Acid Receptor Antagonist for the Treatment of Idiopathic Pulmonary Fibrosis

Scott M. Palmer, MD; Laurie Snyder, MD; Jamie L. Todd, MD; Benjamin Soule, MD; Rose Christian, MD; Kevin Anstrom, PhD; Yi Luo, PhD; Robert Gagnon, PhD; and Glenn Rosen, MD

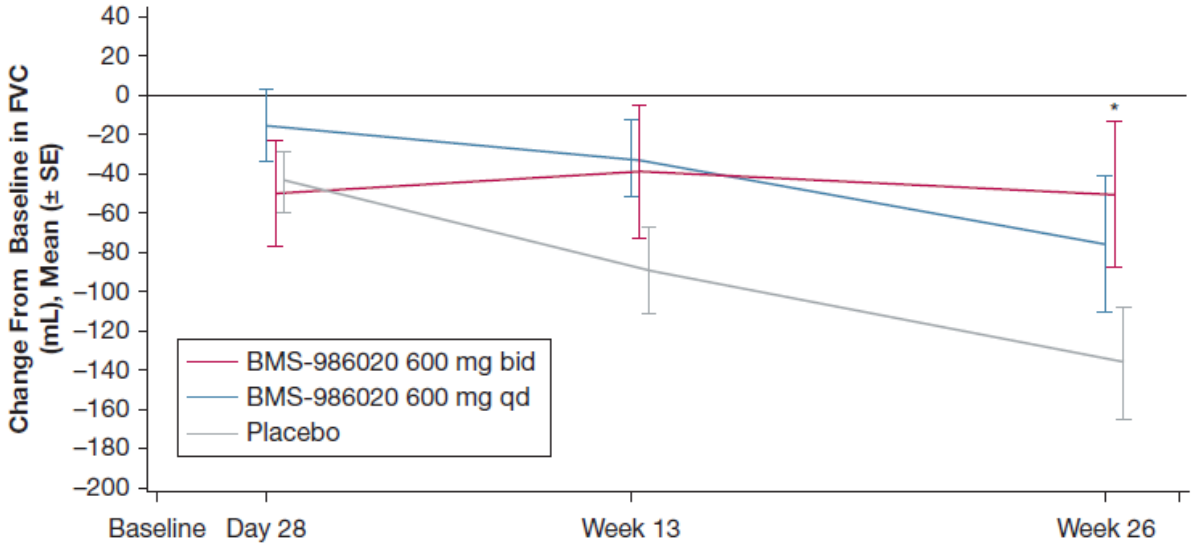
$30\% \le DL_{CO} \le 80\%$, 6MWD ≥ 150m



- BMS-986020: high-affinity small-molecule antagonist of LPA1
- Primary outcome: ΔFVC (26wk)
- Secondary outcome: safety, tolerability, Δ 6MWD & dyspnea
  QLF(quantitative lung fibrosis)(HRCT)

Chest 2018; 154: 1061-1069

BMS-986020, LPA antagonist in IPF



- BMS-986020 600mg bid for 26 wk vs. placebo significantly slowed the rate of FVC decline.
- No differences in QLF, dyspnea, DL_{CO}.
- SAE – cholecystitis (3 in BMS-986020)

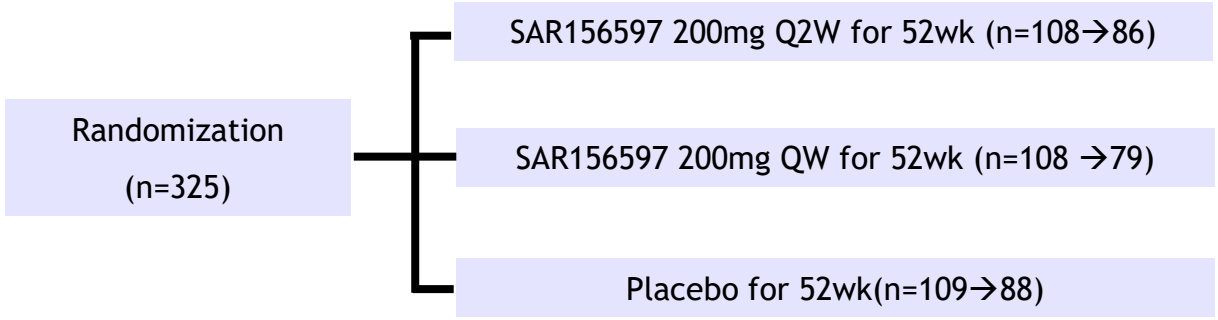
  → led to study termination
- BMS-986020 was associated with elevations in hepatic enzymes.

Chest 2018; 154: 1061-1069

SAR156597 in idiopathic pulmonary fibrosis: a phase 2 placebo-controlled study (DRI11772)

Ganesh Raghu[1], Luca Richeldi[2], Bruno Crestani[3,4], Peter Wung[5], Raphael Bejuit[6], Corinne Esperet[6], Christian Antoni[6] and Christina Soubrane[6]

$FVC \geq 40\ \%,\ DL_{CO} \geq 30\%,\quad FEV_1/FVC \geq\ 0.7$

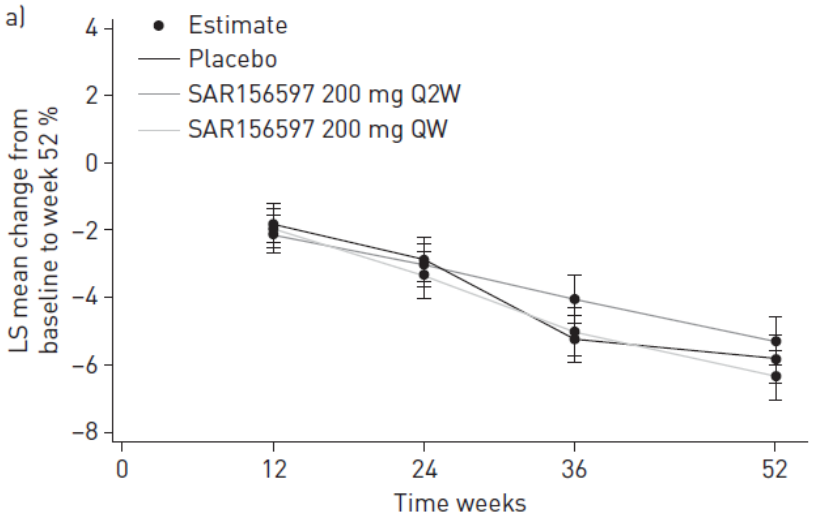


- SAR156597: IgG4 to IL4/13
- Primary outcome: ΔFVC (52wk)
- Secondary outcome: dz progression, all-cause mortality

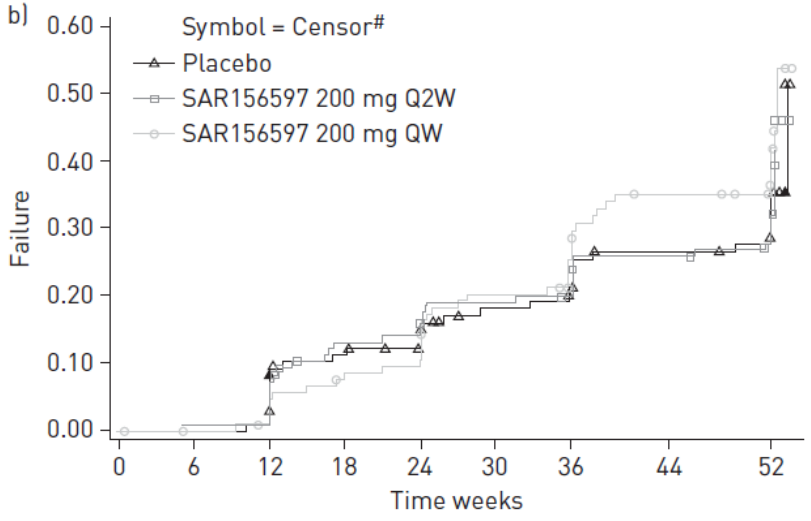
Eur Respir J 2018; 52: 1801130

SAR156597 in IPF

Absolute Δ FVC



Disease progression



- SAR156597 failed to demonstrate the benefit.
- Incidence of TEAE was similar across Treatment arms.

Eur Respir J 2018; 52: 1801130

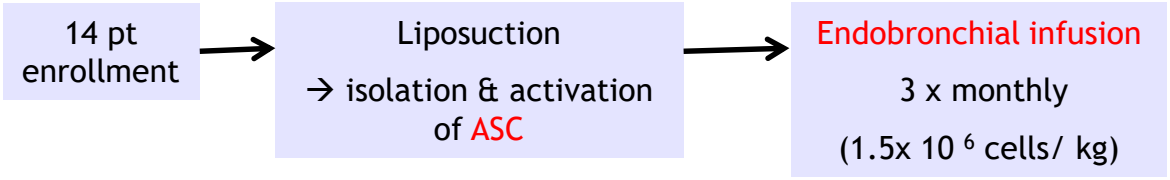
Longitudinal outcomes of patients enrolled in a phase Ib clinical trial of the adipose-derived stromal cells-stromal vascular fraction in idiopathic pulmonary fibrosis

Paschalis Ntolios[1] | Eleni Manoloudi[1] | Argyris Tzouvelekis[2] | Evangelos Bouros[2] | Pachalis Steiropoulos[1] | Stavros Anevlavis[1] | Demosthenes Bouros[2] | Marios E. Froudarakis[1]

- Primary outcome: safety & toxicity during 12 months

  (infection, allergic rex, AE, ectopic tissue formation)

  Secondary outcome: 6MWT, dyspnea, QoL(SGRQ), PFT



- No allergic rex, AE, infection, hospitalization, ectopic formation

  No improvement in 6MWD, FVC, DL_{CO}, dyspnea

  Improvement in QoL (SGRQ) (p=0.02)

J Transl Med 2013;11:171

Stem cell therapy in IPF

- Followed up until the time of death

- Median overall progression free survival : 26 months

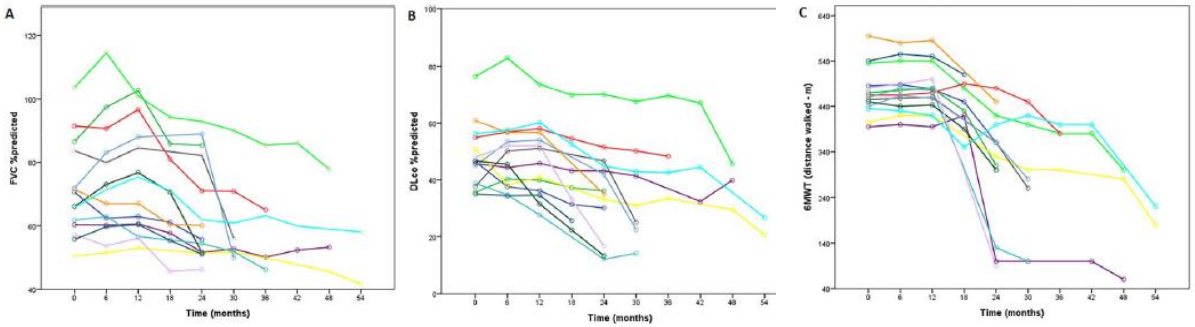
  (progression: FVC decline ≥ 10%, DL_{CO} reduction ≥15%, or death)

  Median overall survival : 32 months

  Survival rate: 2 yrs (100%), 3 yrs (43%), 4 yrs (35%), 5 yrs (14%)

  Death d/t dz. progression (12/14 pt, 85.7%)

  No tumor development



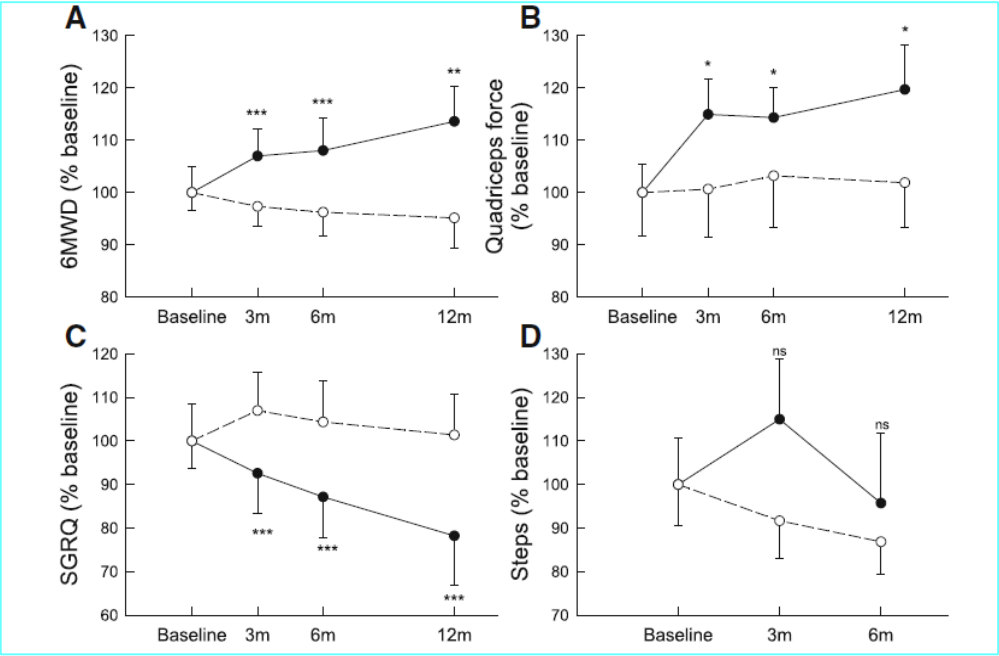
Clin Respir J 2018;2084-2089

Short and long-term effects of pulmonary rehabilitation in interstitial lung diseases: a randomised controlled trial

Silvia Perez-Bogerd[1,2], Wim Wuyts[2], Veronica Barbier[2], Heleen Demeyer[3], Alain Van Muylem[1], Wim Janssens[2,3,4] and Thierry Troosters[2,3*]

6 month-PR course (3 /wk for 3 mo → 2 /wk for 3m) *vs.* usual care

Primary outcome : functional exercise capacity (6MWD)



Respiratory Research 2018;19:182

Summary

- New guideline for IPF refined the pattern of UIP, probable UIP, indeterminate for UIP, and alternate diagnosis.

  For pt with probable UIP, indeterminate for UIP, and alternate diagnosis on HR CT, conditional recommendations were made for performing BAL and SLB.

  For pt with UIP on HR CT, strong recommendation was made against performing SLB, TBLBx and TBLCryoBx.

  Additional recommendation include MDD.

- There have been a number of important developments including combination therapy or new drugs in IPF.