New end-points

Recent new primary end-points and the future

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AUW declares fees for consultancy and/ or speaking from Roche, Boehringer Ingelheim, Veracyte

Outline

- Why we need new end-points
- Secondary PFT end-points repurposed as primary end-points?
- Why not imaging?
- New composites and their problems
- Paradigm shifts for the future

The future problems with serial FVC

- Anti-fibrotic therapies prevent half of FVC progression in IPF
- Serial FVC trends were equal to proving this treatment benefit in pivotal trials
- However, additional treatment benefits are likely to result in much smaller increments
- Doubtful that serial FVC trends will be efficient: need for larger cohorts and/or longer trial periods

Development and Progression of Interstitial Lung Abnormalities in the Framingham Heart Study

Tetsuro Araki[1,2*], Rachel K. Putman[3*], Hiroto Hatabu[1,2], Wei Gao[4,5], Josée Dupuis[4,5], Jeanne C. Latourelle[6,7], Mizuki Nishino[2,8], Oscar E. Zazueta[3], Sila Kurugol[8], James C. Ross[8,9], Raúl San José Estépar[2,8], David A. Schwartz[10], Ivan O. Rosas[3], George R. Washko[3], George T. O'Connor[4,11], and Gary M. Hunninghake[1,3]

American Journal of Respiratory and Critical Care Medicine Volume 194 Number 12 | December 15 2016

	ILA with Progression Compared with No ILA			
	Unadjusted Analysis	*P* Value	Adjusted Analysis†	*P* Value
FEV_1 decline, ml/yr	13 ± 4	0.005	14 ± 5	0.005
FVC decline, ml/yr	29 ± 5	<0.0001	20 ± 6	0.0005
FEV_1/FVC, change, %	−0.2 ± 0.07	0.004	−0.06 ± 0.07	0.4

Might IPF therapies reduce FVC loss due to ageing?

Is the applicable serial FVC change 30mls or 65 mls?

In either event, the above FVC decline applies only to ILA with progression whereas a trial would apply to all fibrotic ILAs. There is a huge powering problem with serial FVC

Serial FVC is not equal to a pharmaceutical trial in this scenario. More sensitive end-points are required

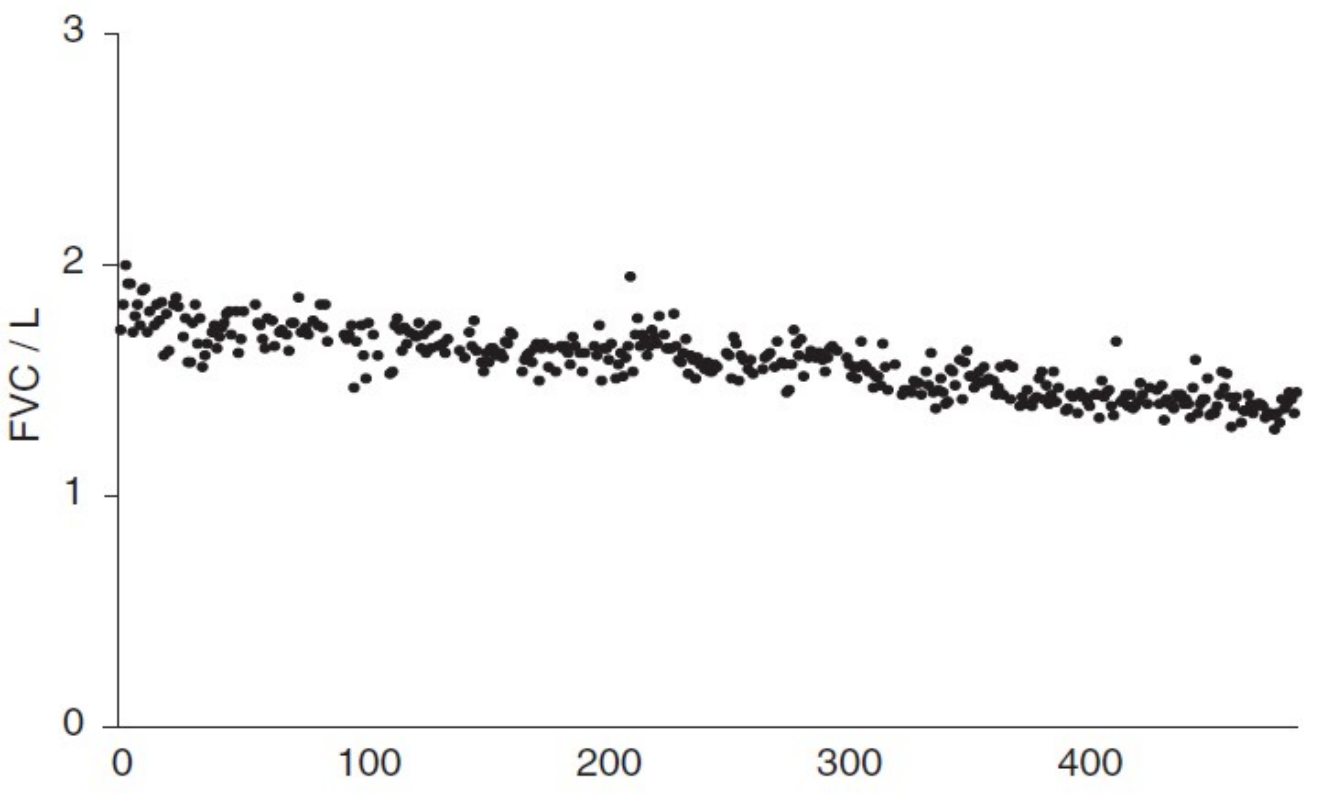
Progression is a composite of lung function change, imaging change and symptomatic change, ideally adapted to baseline factors that influence the link between progression and mortality

Lung function offers little other than repurposing of existing end-points as new primary end-points

- Home spirometry
- Six minute walk test
- Coping with concurrent emphysema
- Role of DLco or CPI to deal with CPFE?

Daily Home Spirometry: An Effective Tool for Detecting Progression in Idiopathic Pulmonary Fibrosis

Anne-Marie Russell[1,2], Huzaifa Adamali[3], Philip L. Molyneaux[1,2], Pauline T. Lukey[4], Richard P. Marshall[4], Elisabetta A. Renzoni[1,2], Athol U. Wells[1,2], and Toby M. Maher[1,2]



Potentially, a major advance but a failed primary end-point in the UILD trial due to outliers and parametric analysis

Could this be retrievable with pre-training and non-parametric analysis, allowing potent short early phase trials in carefully selected patients?

Six minute walk test as a primary end point?

- May be logical in advanced disease with a high risk of secondary PH

Harari S et al. Eur Respir Rev 2022; 31:220087

- IPF progression may manifest as either FVC decline or PH progression

- May be amenable to composite primary end-points as in the trial of sildenafil + pirfenidone vs pirfenidone alone in IPF?

Behr J et al. Lancet Respiratory Med 2021; 9:85-95

- Already in use in PH trials in ILD

- Difficulties if thresholds for decline are used as opposed to continuous data

IPF Net. N Engl J Med 2010; 363:620-628

The problem of CPFE

- With significant emphysema on CT (threshold 10-15%), serial FVC decline in IPF is attenuated

Cottin V et al. Am J Respir Crit Care Med 2017; 1162-71

- Serial FVC not a suitable primary end-point in these patients

- Should these patients be excluded?

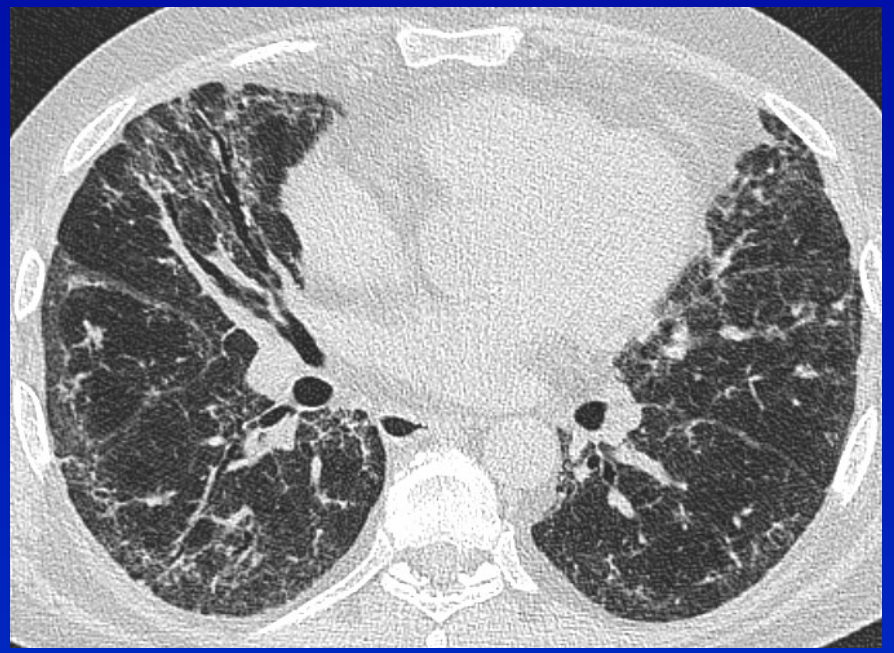
- Should they be included with a primary end-point of DLco or the CPI? Or could we use CT change as a new primary end-point

Optimal and incorrect use of serial DLco

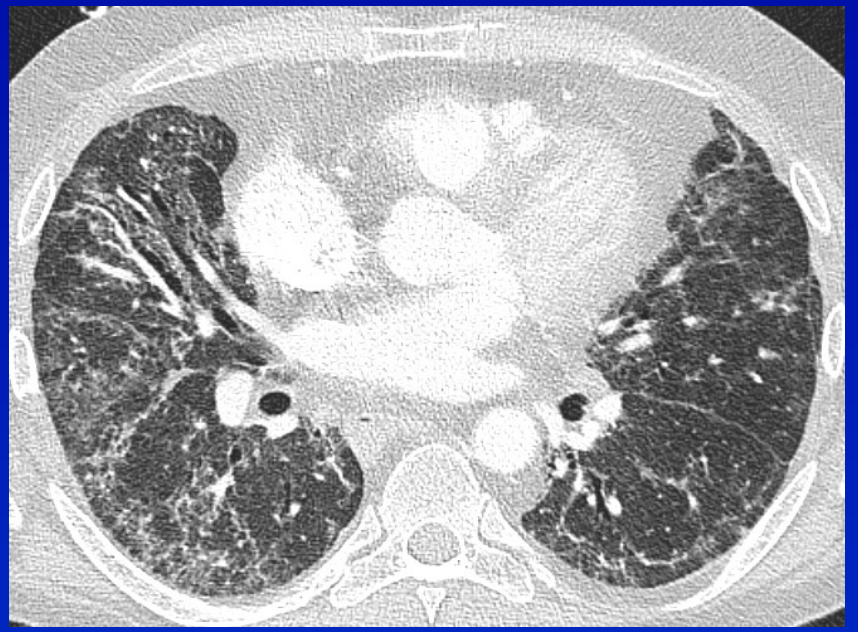
- DLco trends support FVC trends in defining progression when FVC change is marginal
- Isolated DLco trends do NOT identify progression of fibrotic ILD (with or without symptomatic support)
- In particular, a DLco threshold for change of 10% of predicted is very debatable. A reduction from 39% to 30% is classified as no change in DLco!!!

Repurposing secondary PFT variables as primary end-points will not meet our unmet needs

Is it sufficient to see that there is change on CT?



May 2007



January 2009

Qualitative assessment of HRCT scans: the INBUILD cohort

- Qualitative changes between baseline and week 52 were assessed:

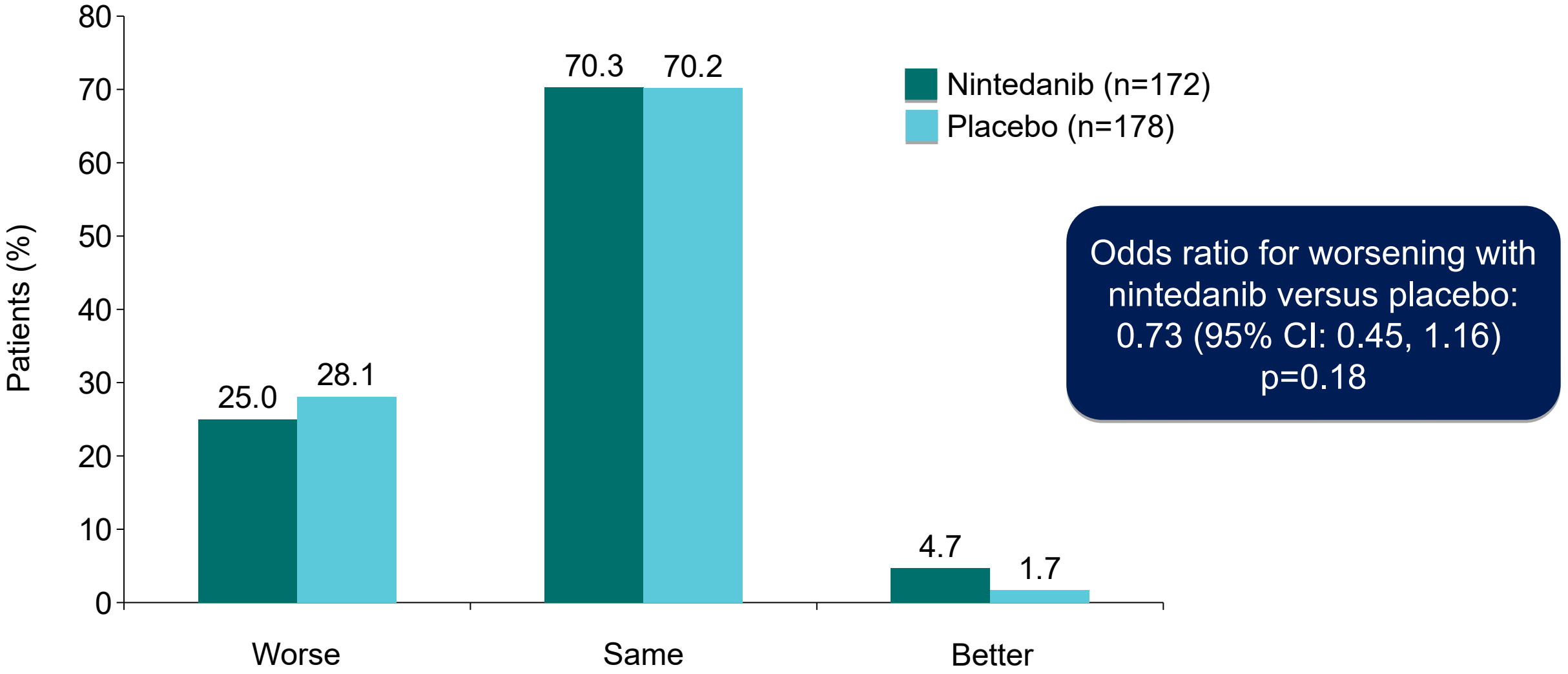
Overall extent of fibrosis	Worse	Same	Better
Honeycombing	More	Same	Less
Traction bronchiectasis	More	Same	Less
Reticulation	More	Same	Less
Ground glass opacification	More	Same	Less
Volume loss	More	Same	Less

- An ordinal logistic regression analysis (proportional odds model) was used to compare changes between treatment groups

Disagreement between the reviewers in the change in overall extent of fibrosis was resolved by adjudication by a third radiologist. Disagreement between the reviewers in the changes in the individual features was resolved as follows: more and same = more; same and less = same; more and less = discordant.

Walsh S et al. ATS abstract 2022

Change in overall extent of fibrosis at week 52



Odds ratio for worsening with nintedanib versus placebo: 0.73 (95% CI: 0.45, 1.16) p=0.18

OR <1 favour nintedanib.

Serial CT as a new primary end-point

- Not suitable if CT change is scored subjectively
- Significant change may occur that is not detected by the human eye/brain. Quantitative methods establish that serial change occurs in almost all IPF patients
- Categorical thresholds unsuitable as insensitive and no threshold validated for “significant change”
- There are solutions but first…….

Can we do better with a multidimensional approach?

Composite end-points as new primary end-points

- Traditionally used as secondary end-points
- Trend towards composite primary end-points in advanced disease

Behr J et al. Lancet Respiratory Med 2021; 9:85-95

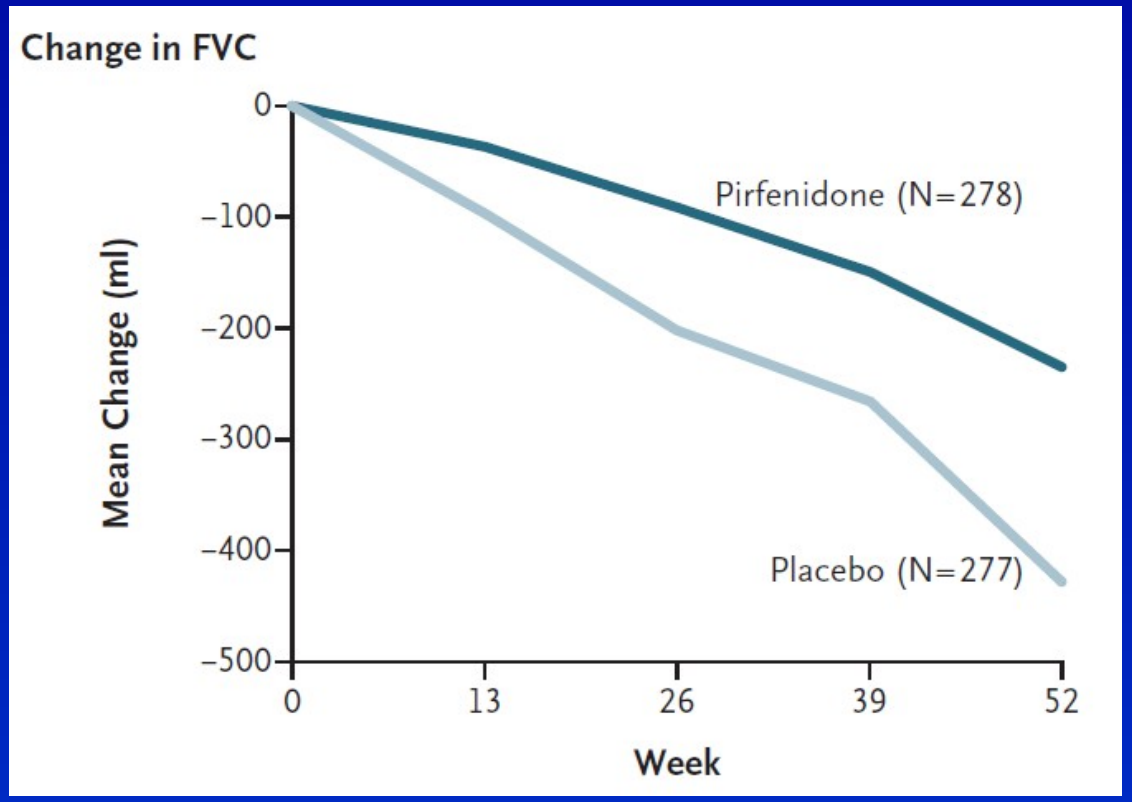
- Generally these are “bad news” composites combining categories of major progression: mortality, respiratory hospitalisation or acute exacerbations, major FVC decline (e.g. 10-15% decline)
- In principle, a multidimensional approach is desirable …. but …..

Problems with composite end-points

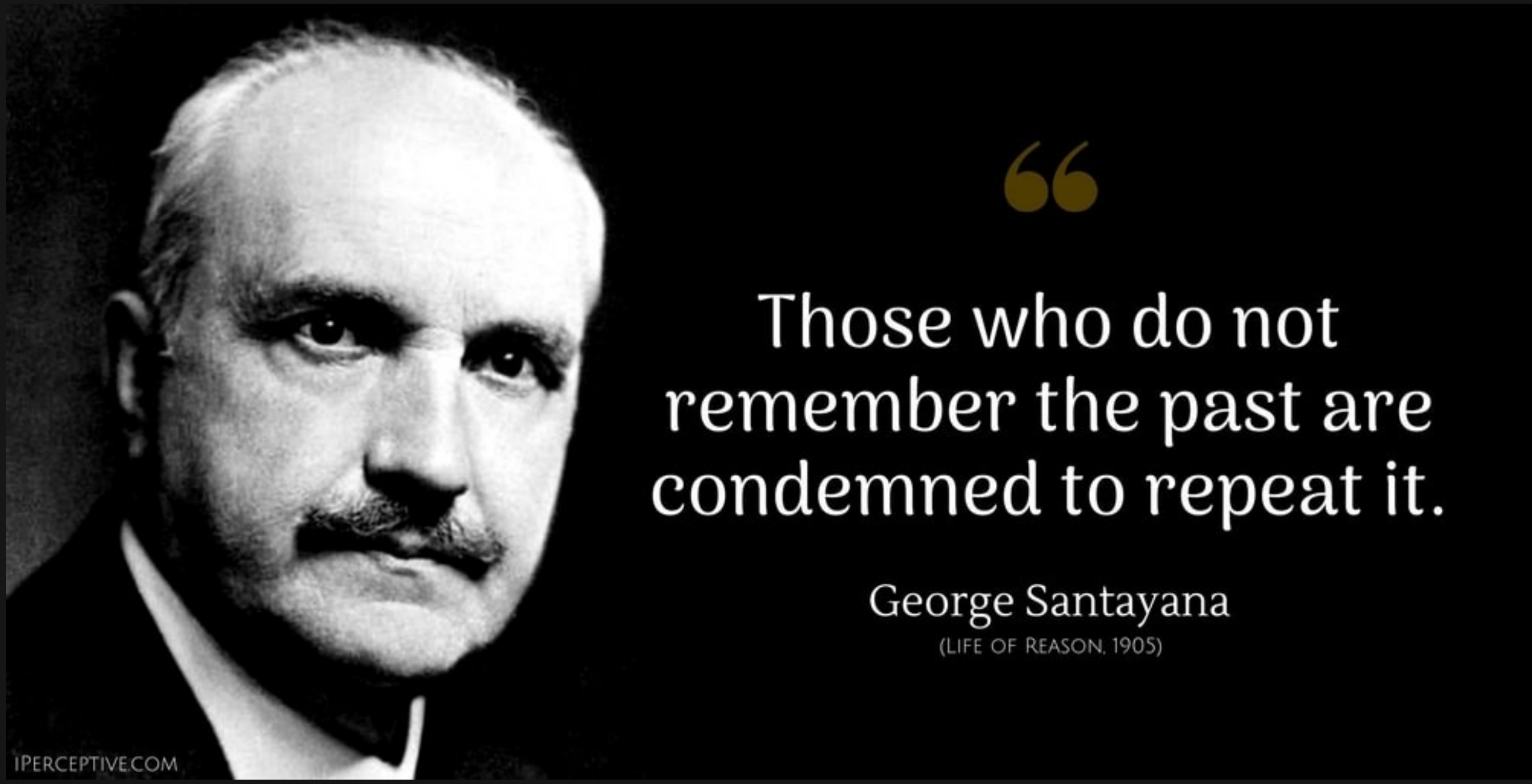
- Categorical change is less sensitive ……
- Huge variability in respiratory hospitalization, especially in non-extensive ILD
- "AE-IPF" are difficult to define without central review
- Composites can be driven by just one component
- Above all, "bad news" categories may work in advanced disease but may seriously fail to capture the spectrum of progression in less advanced disease ……

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.,



- **Striking attenuation of FVC change as a continuous variable**
- **By contrast, the effect on FVC change thresholds of 5% and 10% was much less significant**
- **In one of the two INPULSIS trials, the treatment effect on preventing decline in FVC>10% was non-significant (p=0.18)!!**


“
Those who do not remember the past are condemned to repeat it.
George Santayana
(LIFE OF REASON, 1905)
IPERCEPTIVE.COM

Safety, tolerability, and efficacy of pirfenidone in patients with rheumatoid arthritis-associated interstitial lung disease: a randomised, double-blind, placebo-controlled, phase 2 study

Joshua J Solomon,* Sonye K Danoff,* Felix A Woodhead,* Shelley Hurwitz, Rie Maurer, Ian Glaspole, Paul F Dellaripa, Bibek Gooptu, Robert Vassallo, P Gerard Cox, Kevin R Flaherty, Huzaifa I Adamali, Michael A Gibbons, Lauren Troy, Ian A Forrest, Joseph A Lasky, Lisa G Spencer, Jeffrey Golden, Mary Beth Scholand, Nazia Chaudhuri, Mark A Perrella, David A Lynch, Daniel C Chambers, Martin Kolb, Cathie Spino, Ganesh Raghu,*† Hilary J Goldberg,*† Ivan O Rosas,*† for the TRAIL1 Network Investigators‡

Lancet Respir Med 2022

Published Online

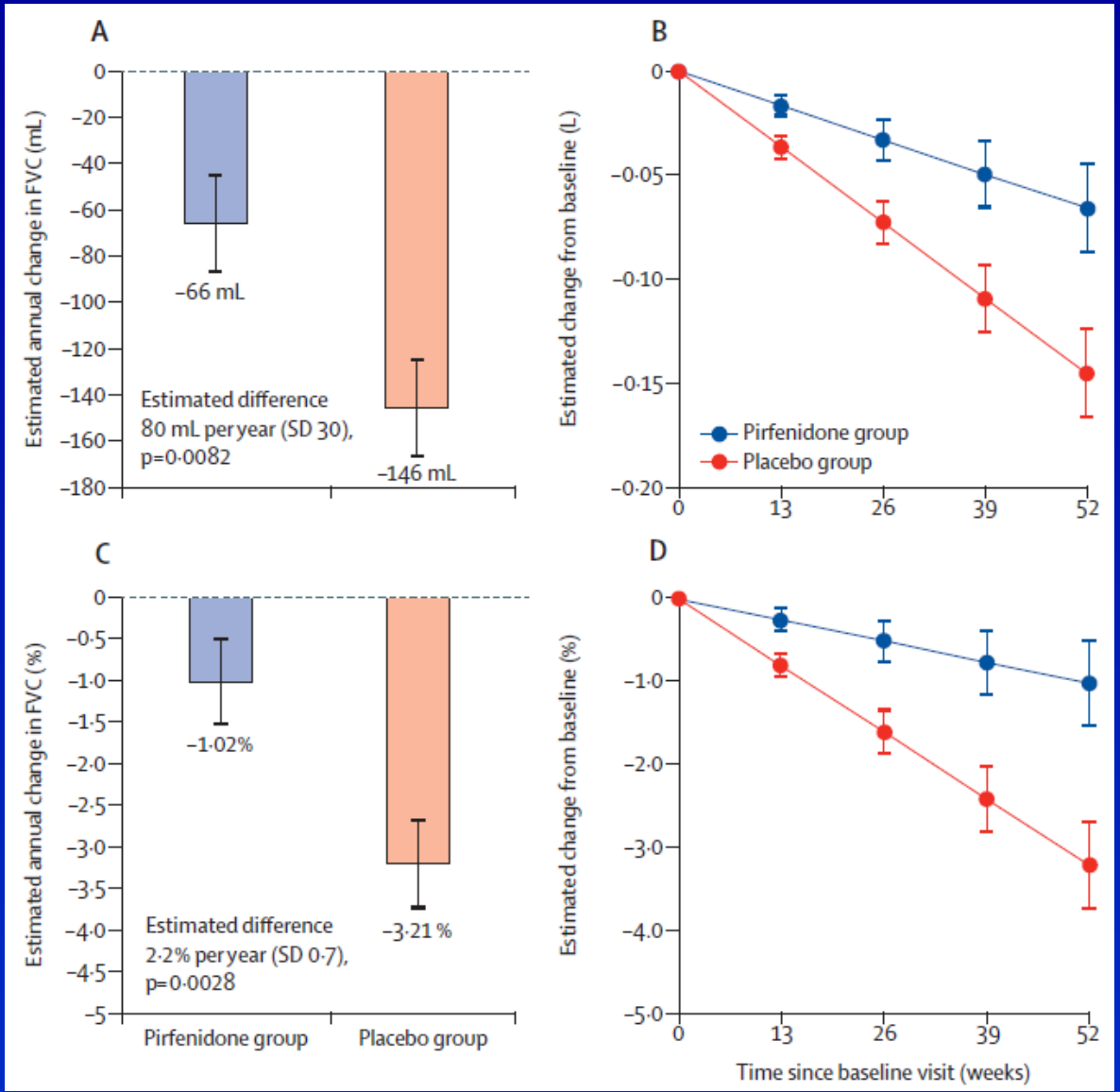
September 5, 2022

Officially a "negative" study

RA-ILD of all types included, n=123

Underpowering due to early termination (COVID)

Primary end-point failed but FVC decline as a continuous variable was attenuated (p<0.01)



	Pirfenidone group (n=63)	Placebo group (n=60)	p value
Primary endpoint			
Decline in percent predicted FVC by 10% or more or death	7 (11%)	9 (15%)	0·48
Secondary outcomes			
Decline in FVC (mL)			
Overall population	−66 (21)	−146 (21)	0·0082
Patients with a UIP pattern	−43 (31)	−169 (24)	0·0014
Decline in FVC (%)			
Overall population	−1·02 (0·51)	−3·21 (0·52)	0·0028
Patients with a UIP-pattern	−0·20 (0·74)	−3·81 (0·70)	0·0002

This was a lesson not learned from IPF

The reason for the disparity might be discussed later: basically, the 10% FVC decline threshold is valuable in an individual to indicate true decline rather than measurement variation

In large cohorts, measurement variability does not influence FVC change. Analyses of the whole spectrum of FVC change (without artificial distinctions between declines of 10.1% and 9.9%) hugely increase sensitivity

The future

- Serial serum biomarkers
- Quantified CT
- AI algorthims
- Personalised primary end-points

Serial serum biomarkers

- An unmet need
- In principle, short term serial biomarkers might be future primary end-points if change in an individual biomarker over, say, three months with and without treatment, predicts mortality
- This would have major benefits with short-term early phase studies and ultimately short-term phase 3 trials in smaller cohorts
- But this will require a HUGE amount of work to be “oven-ready”

Quantitative CT analysis using functional imaging is superior in describing disease progression in idiopathic pulmonary fibrosis compared to forced vital capacity

J. Clukers[1*†], M. Lanclus[2*†], B. Mignot[2], C. Van Holsbeke[2], J. Roseman[2], S. Porter[3], E. Gorina[3], E. Kouchakji[3], K. E. Lipson[3], W. De Backer[1,2] and J. De Backer[2]

Clukers et al. Respiratory Research (2018) 19:213
https://doi.org/10.1186/s12931-018-0918-5

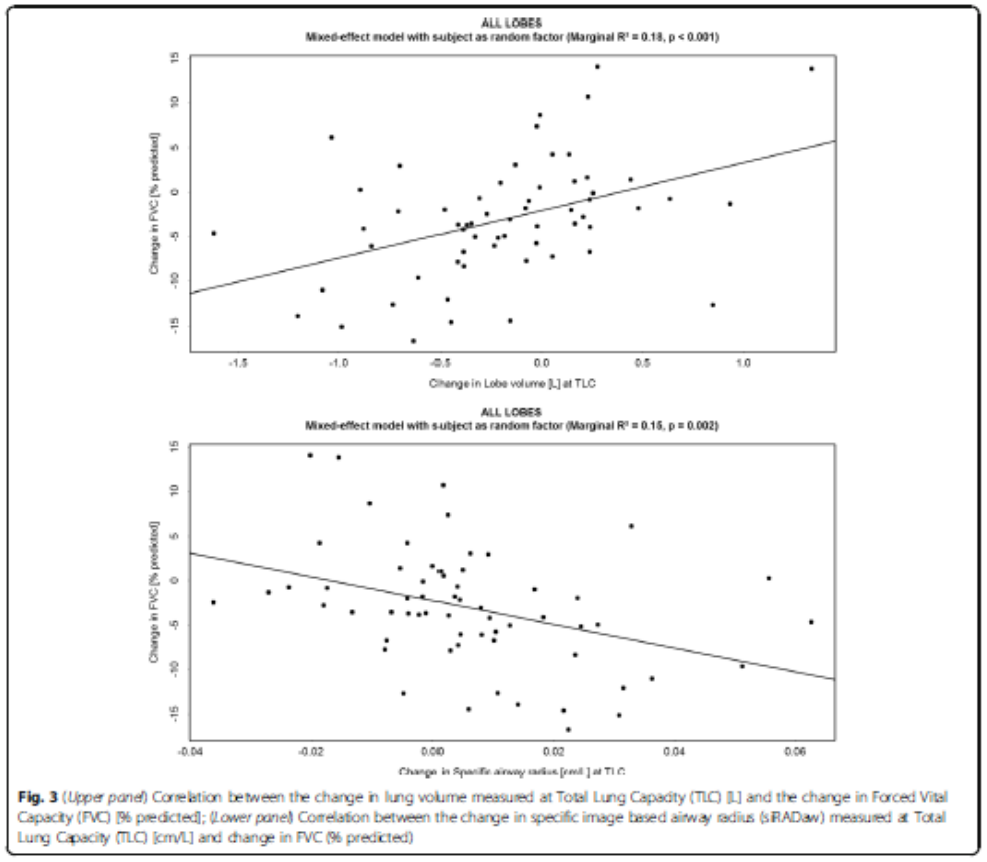


Fig. 3 (*Upper panel*) Correlation between the change in lung volume measured at Total Lung Capacity (TLC) [L] and the change in Forced Vital Capacity (FVC) [% predicted]; (*Lower panel*) Correlation between the change in specific image based airway radius (siRADaw) measured at Total Lung Capacity (TLC) [cm/L] and change in FVC (% predicted)

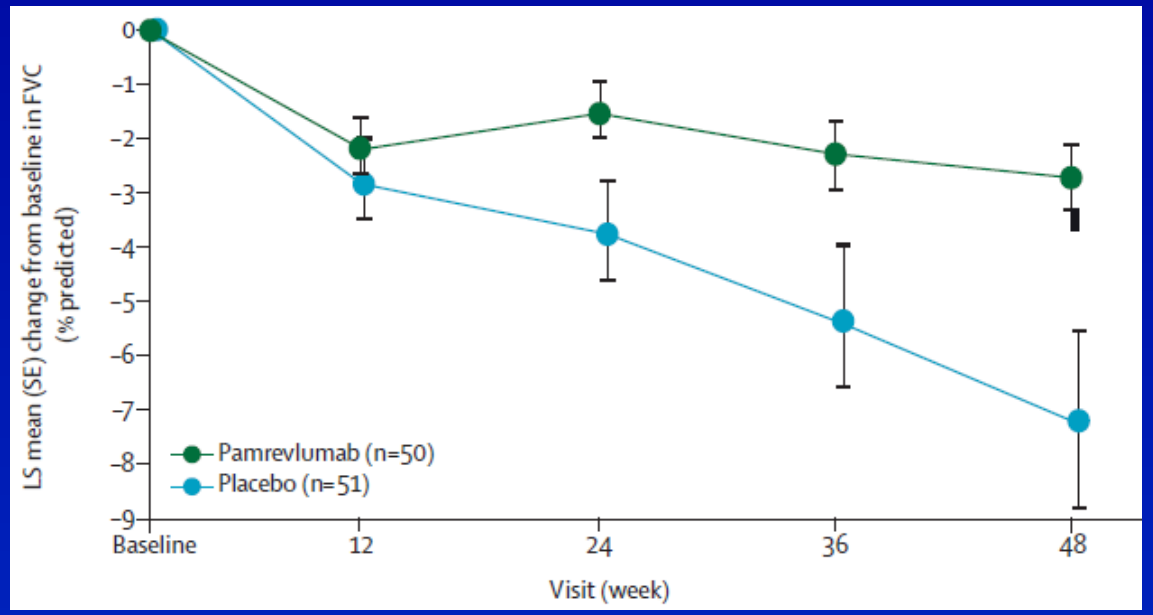
Results: Lung volumes, determined by FRI, correlated with FVC (lower lung volumes with lower FVC) ($R^2 = 0.61$, $p < 0.001$). A negative correlation was observed between specific image based airway radius (siRADaw) at total lung capacity (TLC) and FVC ($R^2 = 0.18$, $p < 0.001$). Changes in FVC correlated significantly with changes in lung volumes ($R^2 = 0.18$, $p < 0.001$) and siRADaw ($R^2 = 0.15$, $p = 0.002$) at week 24 and 48, with siRADaw being more sensitive to change than FVC. Loss in lobe volumes ($R^2 = 0.33$, $p < 0.001$), increasing fibrotic tissue ($R^2 = 0.33$, $p < 0.001$) and airway radius ($R^2 = 0.28$, $p < 0.001$) at TLC correlated with changes in FVC but these changes already occur in the lower lobes when FVC is still considered normal.

Conclusion: This study indicates that FRI is a superior tool than FVC in capturing of early and clinically relevant, disease progression in a regional manner.

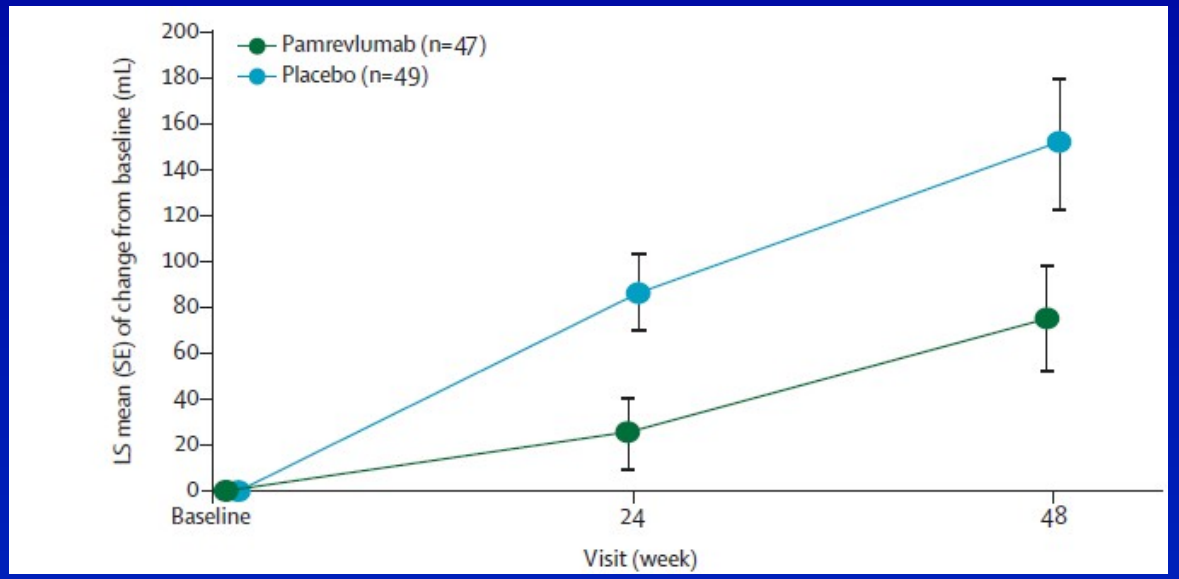
Pamrevlumab, an anti-connective tissue growth factor therapy, for idiopathic pulmonary fibrosis (PRAISE): a phase 2, randomised, double-blind, placebo-controlled trial

Lancet Respir Med 2020; 8: 25–33

Luca Richeldi, Evans R Fernández Pérez, Ulrich Costabel, Carlo Albera, David J Lederer, Kevin R Flaherty, Neil Ettinger, Rafael Perez, Mary Beth Scholand, Jonathan Goldin, Kin-Hung Peony Yu, Thomas Neff*, Seth Porter, Ming Zhong, Eduard Gorina, Elias Kouchakji, Ganesh Raghu



FVC change



Change in fibrosis on CT

How best to integrate quantitative serial CT and serial FVC as a primary end-point? The potential is huge. The answer has to be AI algorithms.

The ideal new end-point

- Not a simple adaptation of existing end-points
- Multidimensional: bringing together PFT, CT biomarker trends
- Should integrate continuous data in each domain and not categorical thresholds
- Should be validated against subsequent mortality

The future use of artificial intelligence

- Supervised deep learning? Existing serial data is "trained" against subsequent mortality. This might include serial QCT, serial PFT, and serial serum biomarkers (?), with or without key baseline data
- Complex multidimensional neural networks providing a prediction of mortality that trumps individual variables
- The resulting serial algorithm score then becomes the primary end-point in treatment trials.
- In this way, multidimensional serial data are integrated
- Unsupervised deep learning may have even greater potential …….. discuss?

Personalised end-points

- In rehabilitation studies in ILD, there is variable benefit in exertional dyspnoea, six minute walk distance and quality of life
- A good deal of positive signal but contradictory negative signal
- This likely to reflect major patient variation in rehabilitation benefits
- In the inflammatory myopathy world, talk of a personalised primary end-point. Each patient designates an activity that they value that is compromised by exercise limitation
- The primary end-point focuses on change in the performance and ease of that particular activity, covering a combination of exercise tolerance (6MWT), dyspnoea and quality of life

Summary

- New primary end-points are needed in ILD trials
- Repurposing existing PFT and CT end-points not the answer
- New “bad news” composites may work in advanced disease but categorical end-points other than mortality are flawed across the spectrum of disease
- The future: serial serum biomarker, QCT, personalised patient-centred end-points and, above all, “composite” artificial intelligence algorithms