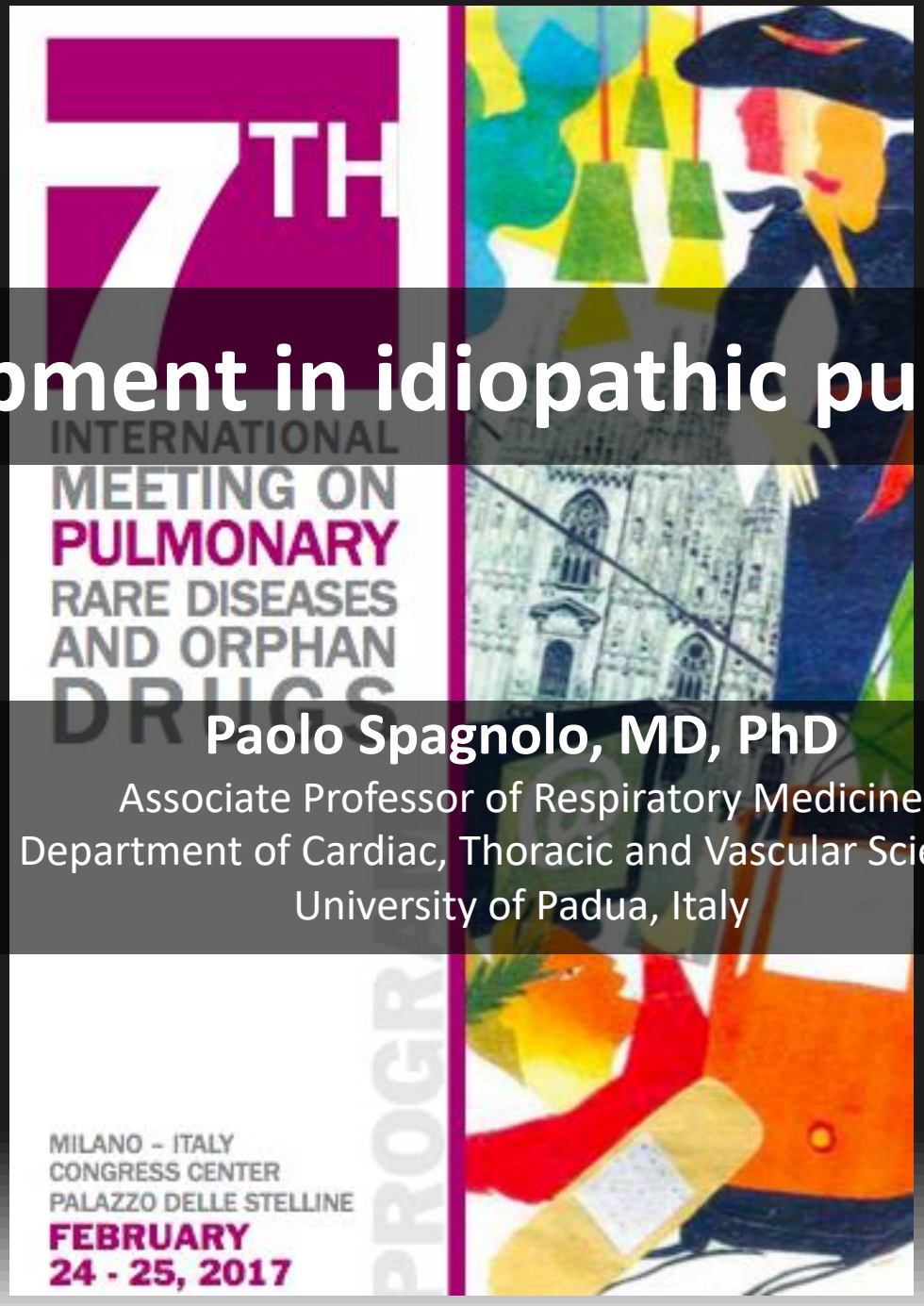
Drug development in idiopathic pulmonary fibrosis



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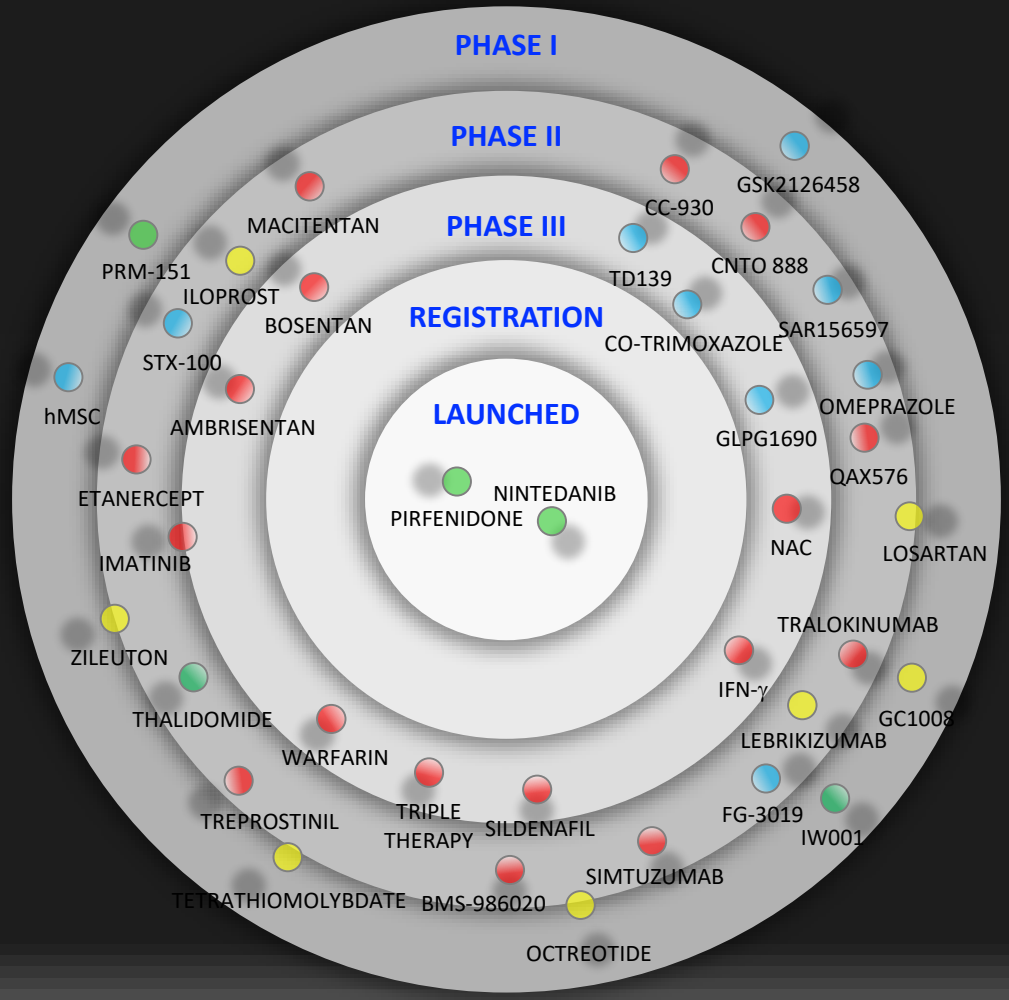
Latest clinical trials in IPF



POSITIVE RESULTS

NEGATIVE RESULTS

ONGOING

PENDING RESULTS

Slide courtesy of Luca Richeldi

www.clinicaltrials.gov

Eight Phase II trials in IPF will be completed soon

	PBI-4050	BG00011	KD025	MN-001
NCT number	NCT02538536	NCT01371305	NCT02688647	NCT02503657
Sponsor	**ProMetic**	**Biogen**	**Kadmon**	**MediciNova**
Drug	Anti-inflammatory/ antifibrotic	Anti-avβ6 integrin mAb	ROCK2 inhibitor	Leukotriene antagonist
Route	Oral	Subcutaneous	Oral	Oral
Design	Open-label, single-arm	Double-blind, placebo-controlled	Open-label, randomised	Double-blind, placebo-controlled
Background	Nintedanib/pirfenidone	–	Standard of care	Nintedanib
Sample size	41	40	36	15
Duration	20 weeks	16 weeks	24 weeks	26 weeks
Endpoint	Adverse events	Adverse events	Change in FVC + adverse events	Change in FVC
Start date	Jul 2015	Jun 2012	Mar 2016	Mar 2016
Last update	Oct 2016	Oct 2016	Sep 2016	Jul 2016
End date	Jan 2017	Aug 2017	Mar 2017	Dec 2017

mAb, monoclonal antibody; ROCK, Rho-associated protein kinase

www.clinicaltrials.gov

Eight Phase II trials in IPF will be completed soon

	PRM-151	FG-3019	Lebrikizumab	SAR156597
NCT number	NCT02550873	NCT01890265	NCT01872689	NCT02345070
Sponsor	**Promedior**	**FibroGen**	**F. Hoffmann-La Roche**	**Sanofi**
Drug	Rec human pentraxin-2	Anti-CTGF mAb	Anti-IL-13 mAb	Anti-IL-13/IL-4 mAb
Route	Intravenous	Intravenous	Subcutaneous	Subcutaneous
Design	Double-blind, placebo-controlled	Double-blind, placebo-controlled	Double-blind, placebo-controlled	Double-blind, placebo-controlled
Background	Nintedanib/pirfenidone	–	Pirfenidone	–
Sample size	117	136	484	300
Duration	24 weeks	48 weeks	52 weeks	52 weeks
Endpoint	Change in FVC	Change in FVC	Change in FVC	Change in FVC
Start date	Aug 2015	Jun 2013	Oct 2013	May 2015
Last update	Oct 2016	Jul 2016	Sept 2016	Jul 2016
End date	Mar 2019	Jul 2017	Dec 2017	Aug 2017

CTGF, connective tissue growth factor; IL, interleukin

www.clinicaltrials.gov

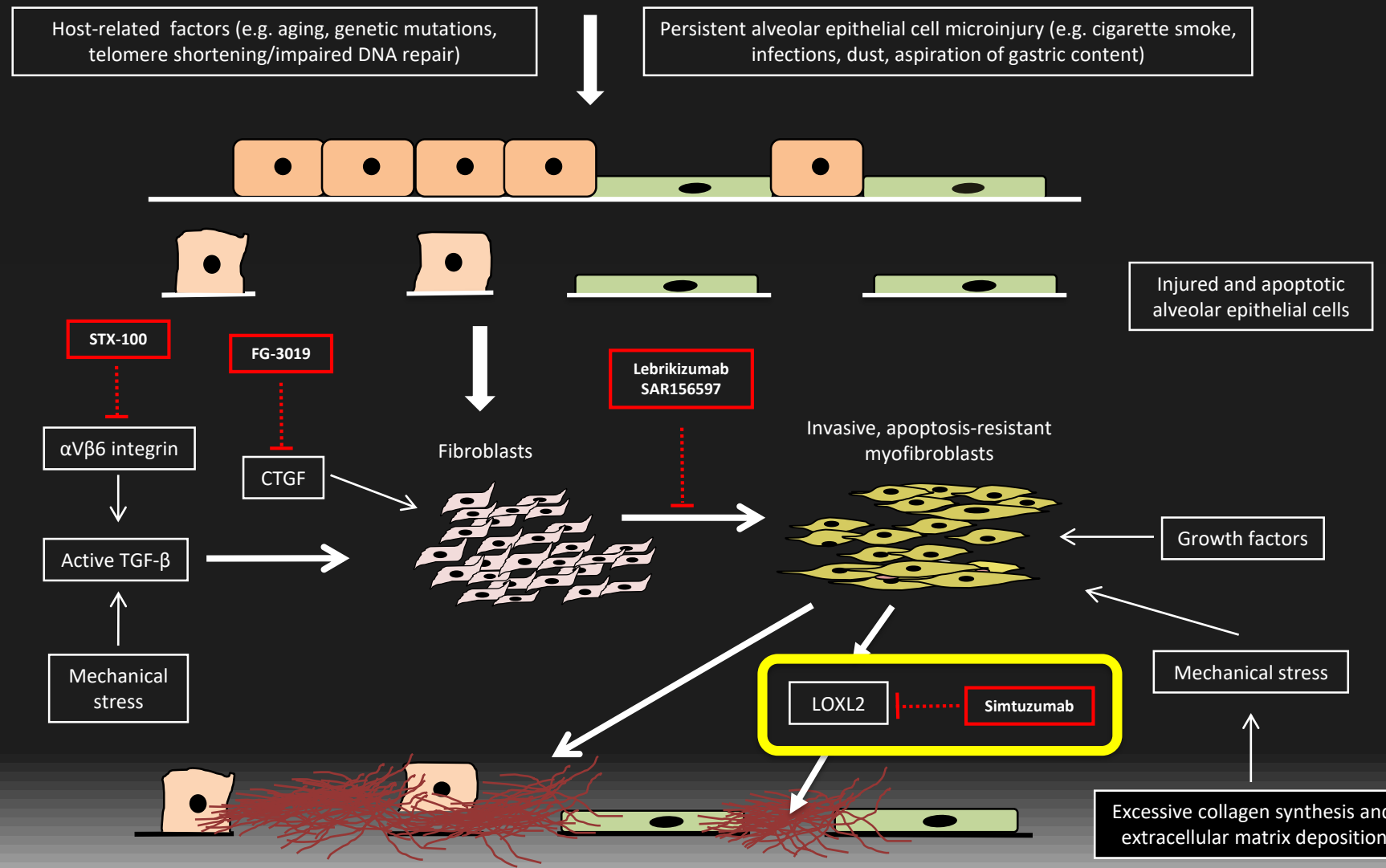
Main challenges in drug development in IPF

- Establishing a plausible rationale for novel targets
- Clinical evaluation of candidate drugs
- Increasing the efficiency of clinical trials

Outline

- Fibrogenic molecules/pathways
- Patient selection
- Study design/endpoints

Current understanding of the pathobiology of IPF

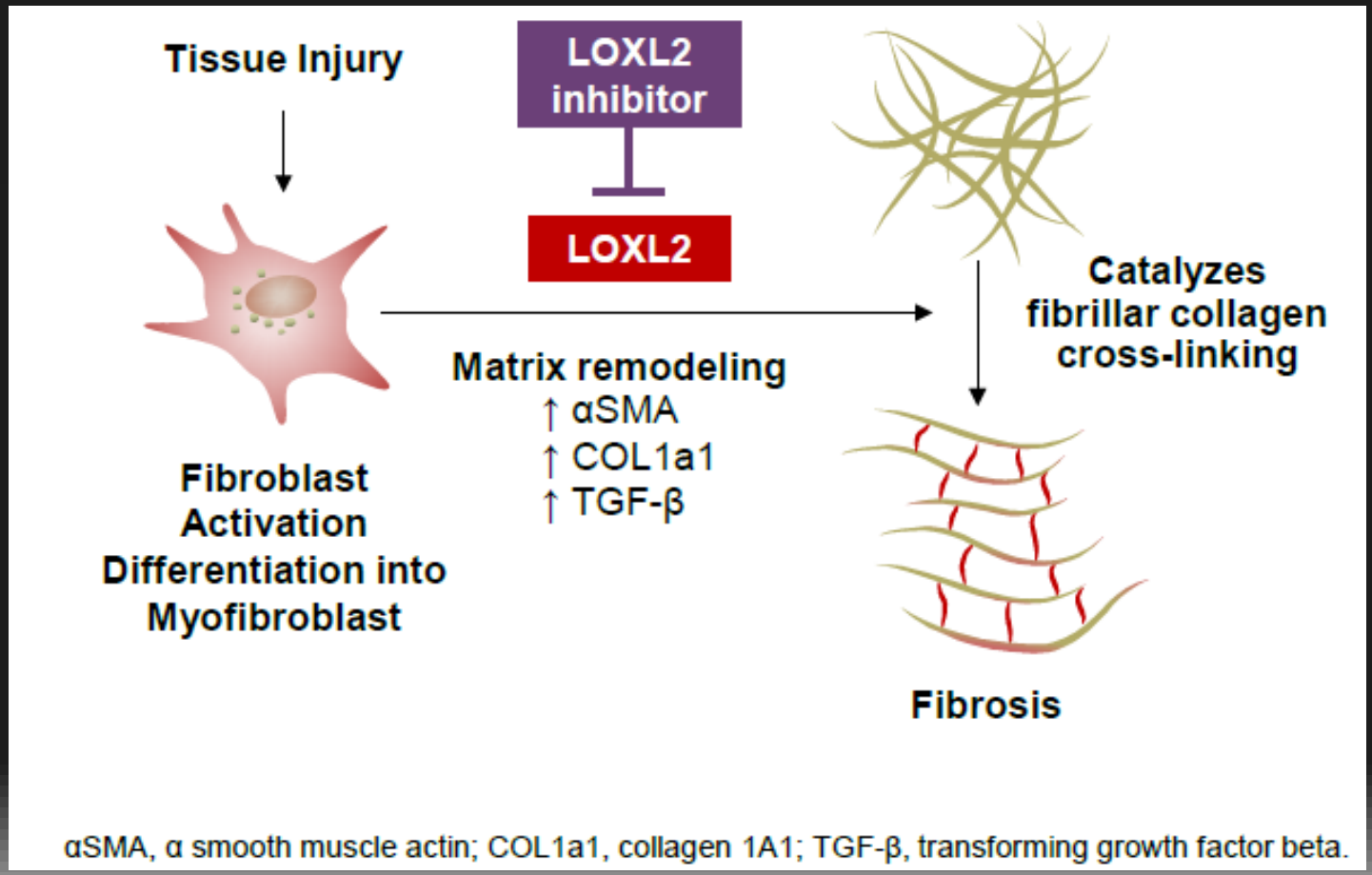


LOXL2, lysyl-oxidase-like-2; TGF-β, transforming growth factor beta

Modified from Spagnolo P. Am J Med 2015;128:447-449

LOXL2 – background

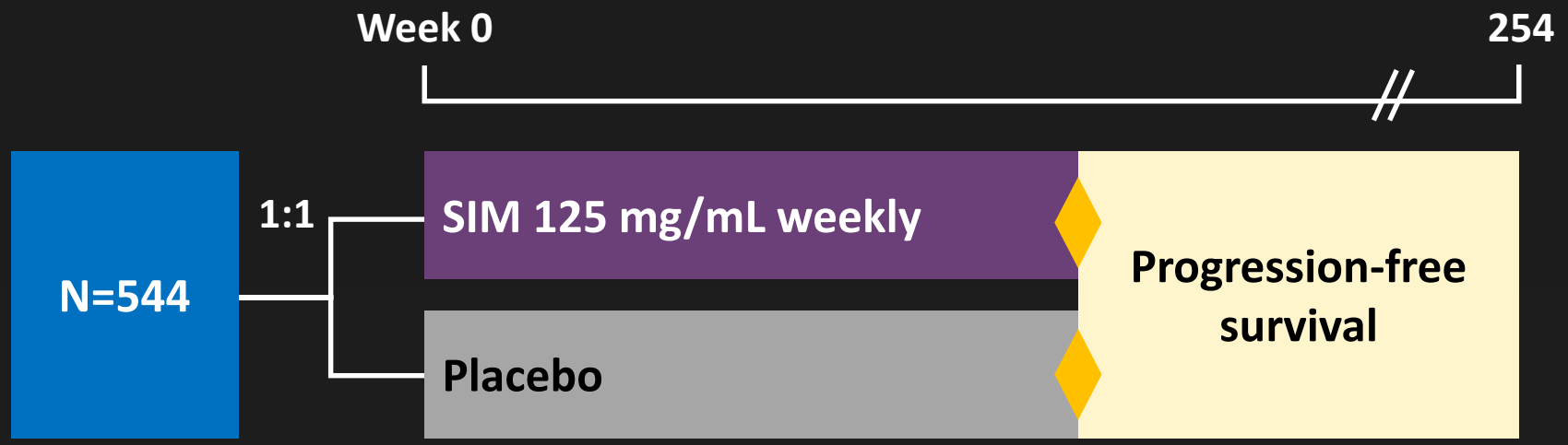
- LOXL2 is an extracellular matrix enzyme released by fibroblasts that catalyses the cross-linking of collagen fibers, driving matrix remodelling and formation of pathologic stroma



αSMA, α smooth muscle actin; COL1a1, collagen 1A1; TGF-β, transforming growth factor beta.

Barry-Hamilton V et al. Nat Med 2010;16:1009-1017

RAINIER* study – simtuzumab in IPF

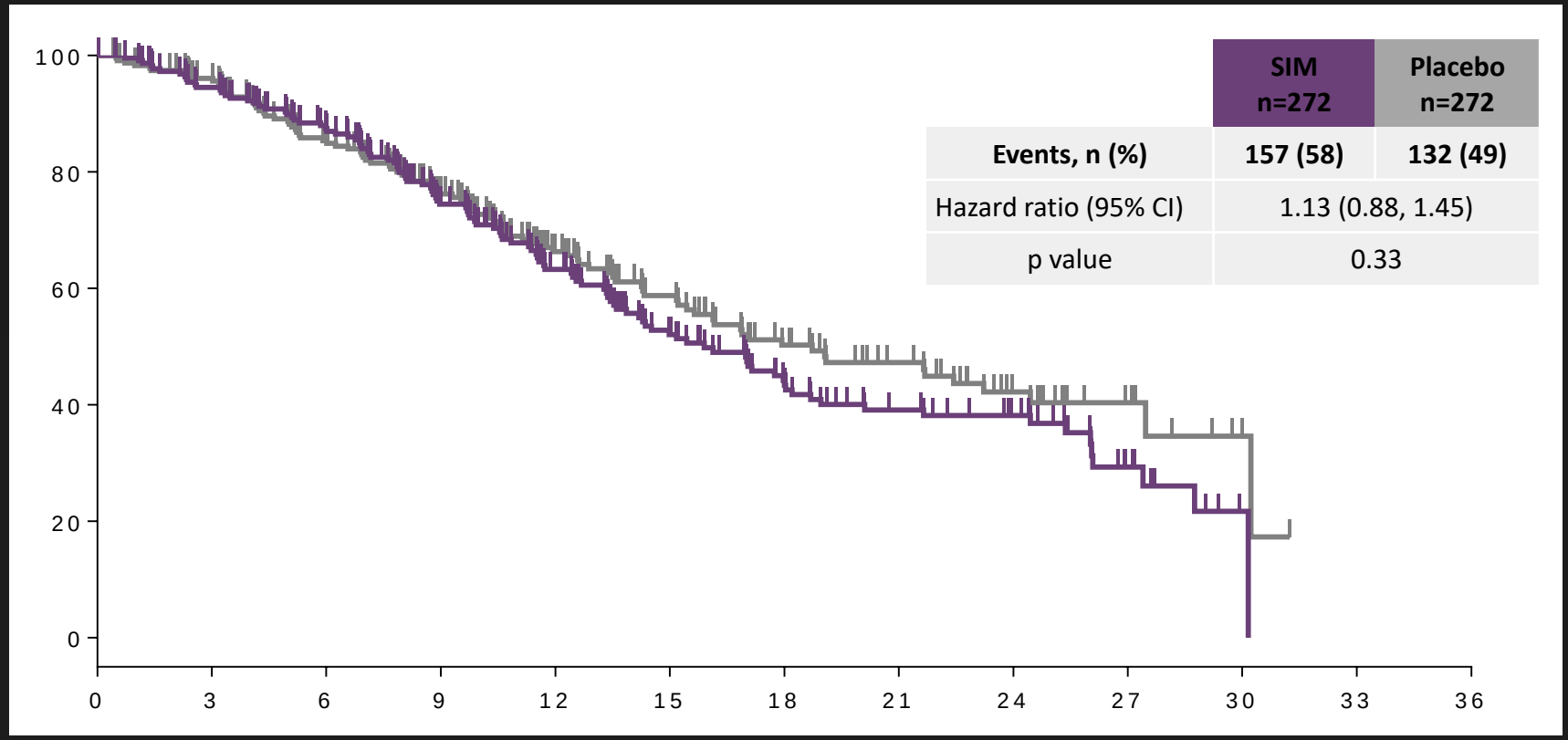


- Primary endpoint: progression-free survival
  - Intent-to-treat population
  - Patients with high sLOXL2 (>median)
  - Patients with high sLOXL2 (>75th percentile)

Adapted from Raghu G et al. Lancet Respir Med 2017;5:22-31

Results – progression-free survival

Intent-to-treat population



	SIM n=272	Placebo n=272
Events, n (%)	**157 (58)**	**132 (49)**
Hazard ratio (95% CI)	1.13 (0.88, 1.45)	
p value	0.33	

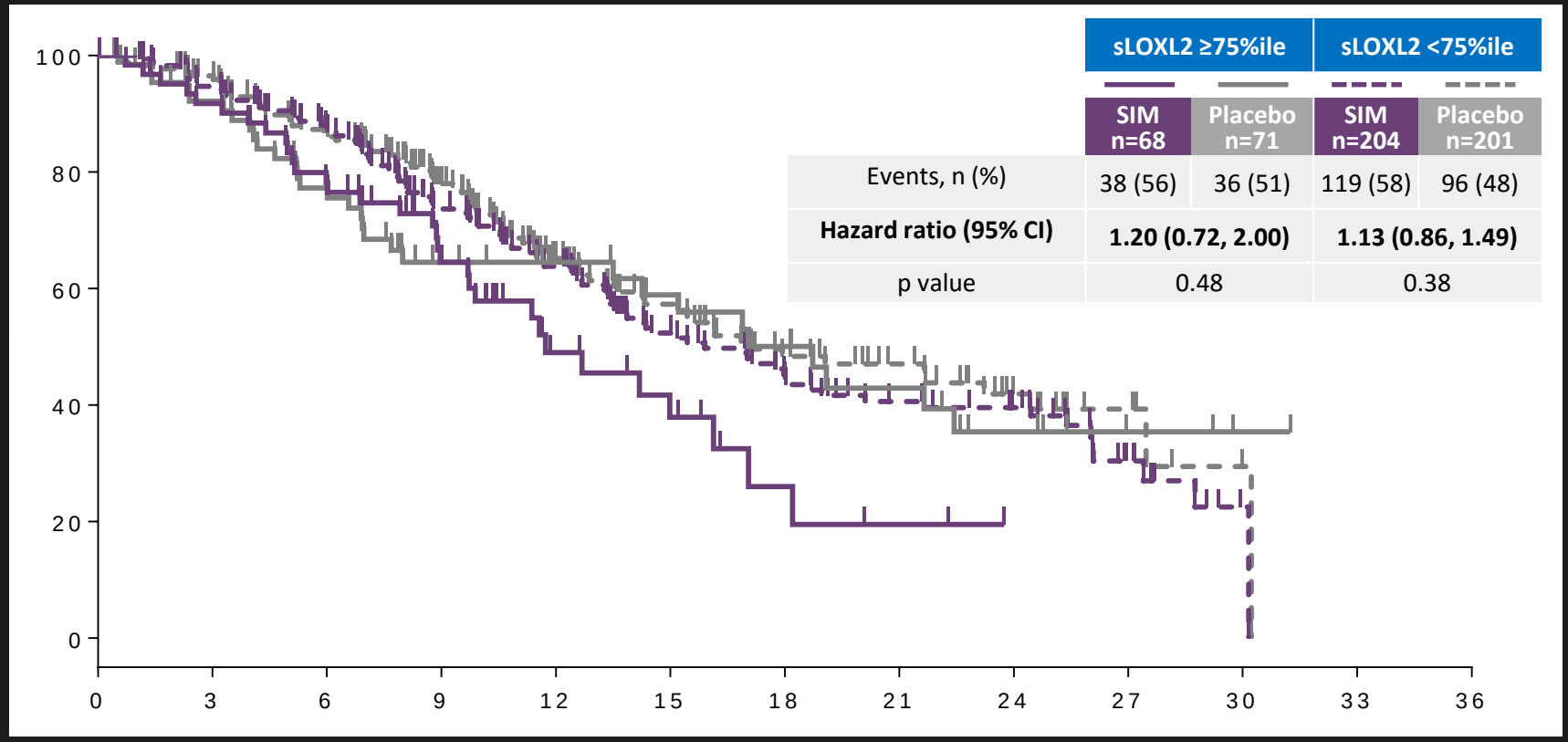
n at risk (events)													
SIM n=272	272 (0)	245 (18)	213 (42)	145 (85)	98 (113)	73 (131)	55 (141)	42 (147)	32 (149)	11 (154)	1 (156)	0 (157)	0 (157)
PBO n=272	272 (0)	244 (13)	202 (47)	139 (81)	97 (98)	77 (108)	58 (119)	44 (122)	23 (129)	10 (130)	2 (131)	0 (132)	0 (132)

PBO, placebo; SIM simtuzumab

Raghu G et al. Lancet Respir Med 2017;5:22-31

Results – progression-free survival

sLOXL2 75th percentile subgroup



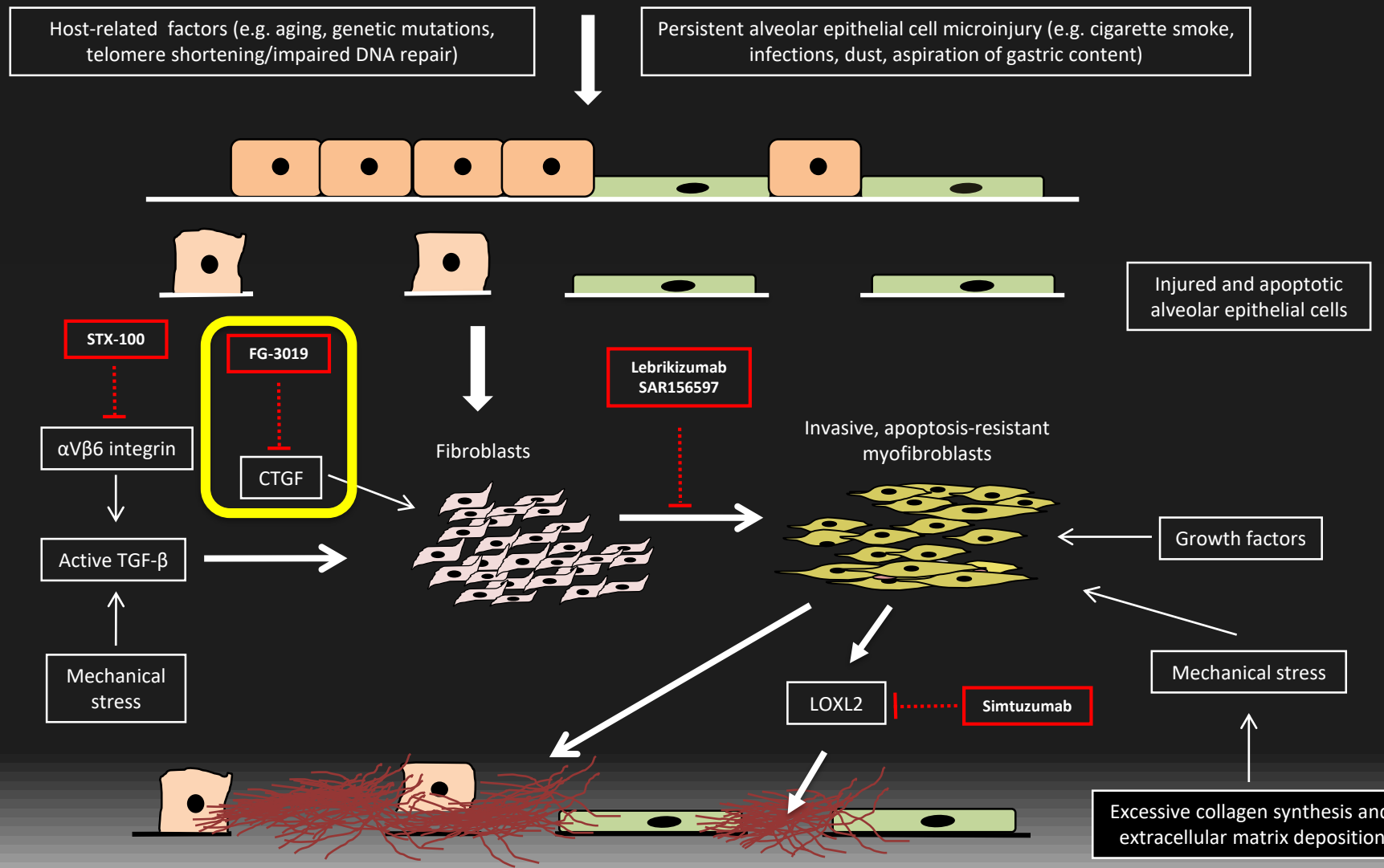
	sLOXL2 ≥75%ile		sLOXL2 <75%ile	
	SIM n=68	Placebo n=71	SIM n=204	Placebo n=201
Events, n (%)	38 (56)	36 (51)	119 (58)	96 (48)
Hazard ratio (95% CI)	**1.20 (0.72, 2.00)**		**1.13 (0.86, 1.49)**	
p value	0.48		0.38	

n at risk (events)

≥75%	SIM	68 (0)	61 (5)	51 (14)	34 (23)	15 (32)	10 (35)	4 (37)	2 (38)	0 (38)	0 (38)	0 (38)	0 (38)	0 (36)
	PBO	71 (0)	62 (6)	50 (16)	31 (26)	25 (26)	21 (28)	17 (31)	13 (38)	7 (38)	3 (36)	1 (36)	0 (36)	0 (36)
<75%	SIM	204 (0)	184 (13)	162 (28)	111 (62)	83 (81)	63 (96)	51 (104)	40 (109)	32 (111)	11 (116)	1 (118)	0 (119)	0 (119)
	PBO	201 (0)	182 (7)	152 (31)	108 (56)	72 (72)	56 (80)	41 (88)	31 (89)	16 (93)	7 (94)	1 (95)	0 (96)	0 (96)

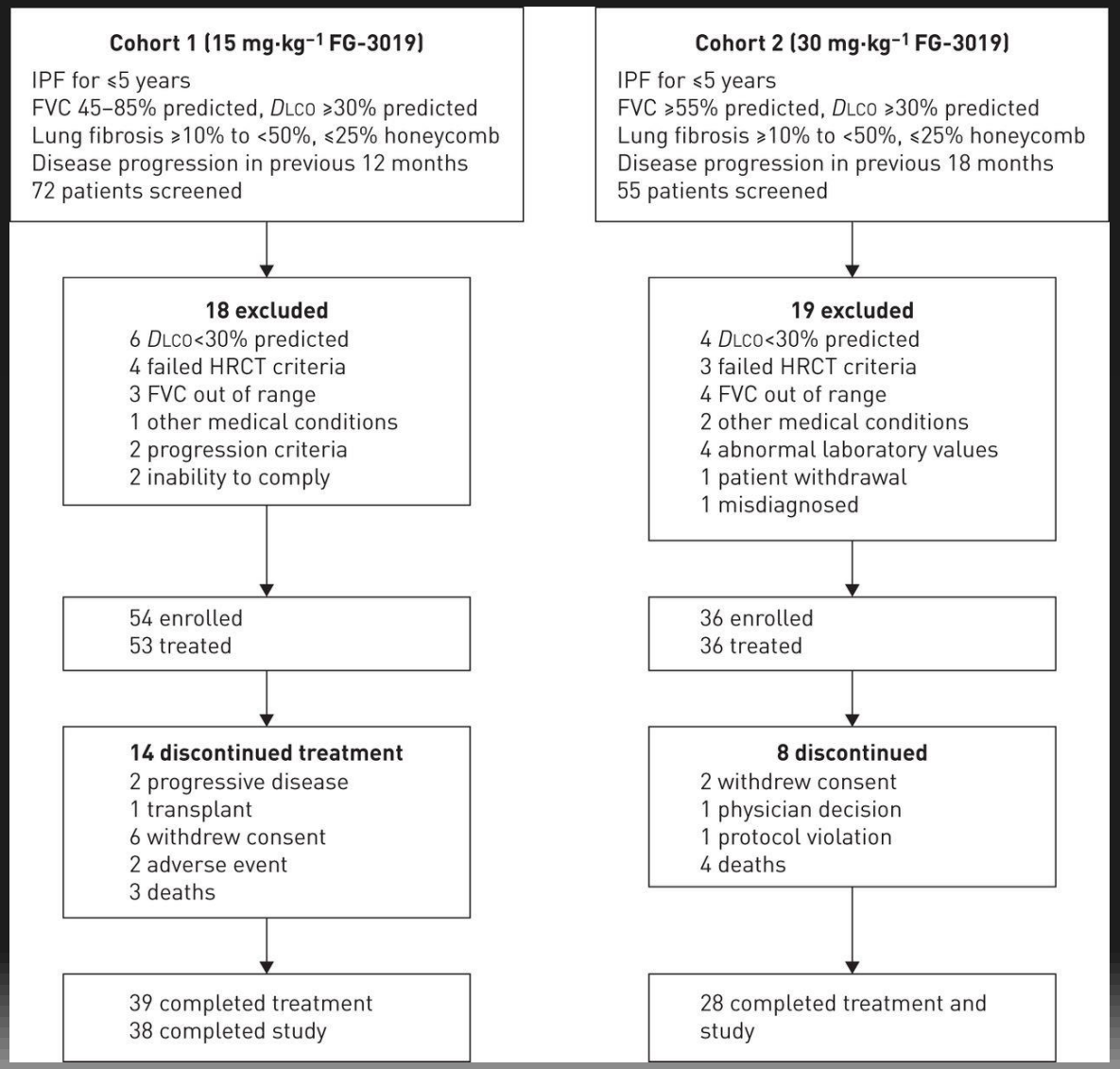
Raghu G et al. Lancet Respir Med 2017;5:22-31

Current understanding of the pathobiology of IPF



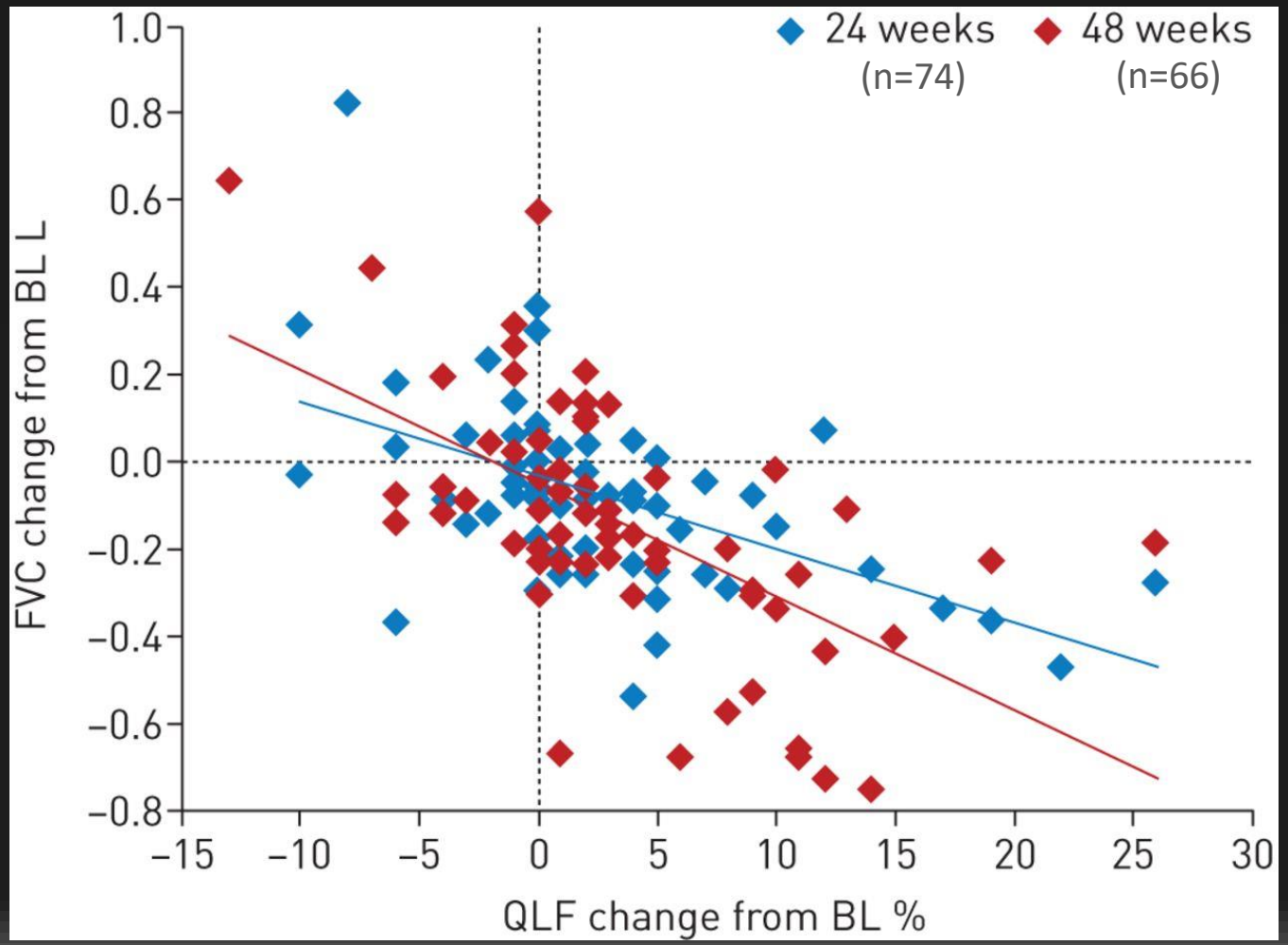
Modified from Spagnolo P. Am J Med 2015;128:447-449

FG-3019 in patients with IPF – an open-label study



Raghu G et al. Eur Respir J 2016;47:1481-1491

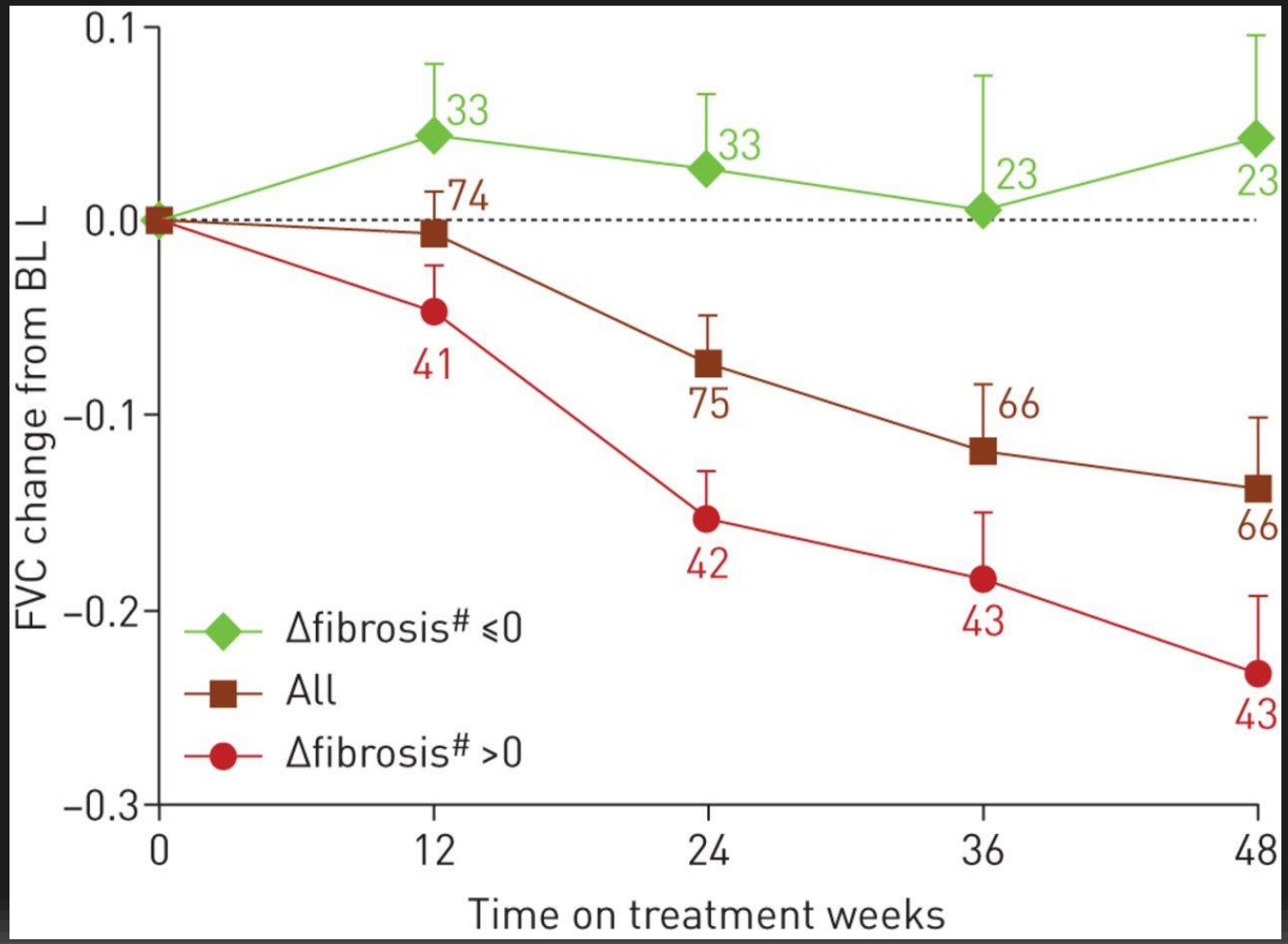
Correlations between fibrosis change (QLF) and FVC change at Week 24 and 48



BL, baseline

Raghu G et al. Eur Respir J 2016;47:1481-1491

Categorical changes in FVC based on fibrosis change (QLF) from baseline



Raghu G et al. Eur Respir J 2016;47:1481-1491

Outline

- Fibrogenic molecules/pathways
- Patient selection
- Study design/endpoints

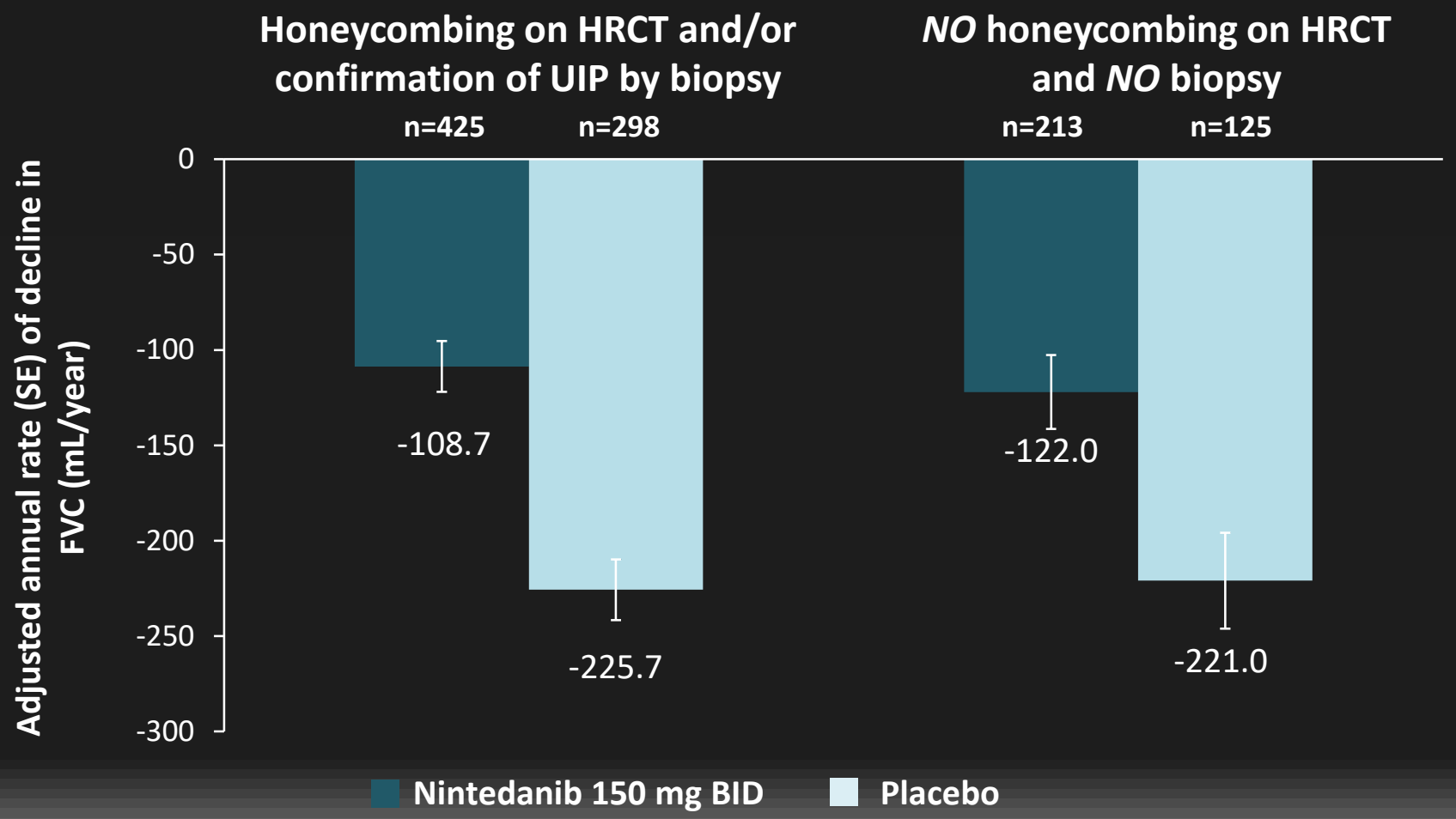
ASCEND and INPULSIS – placebo arms

	ASCEND	INPULSIS
FVC decline (mL/year)	-280*	-205**
Definite UIP at HRCT (%)	95	57
Surgical lung biopsy (%)	29	20
Screen failure (%)	64	29

*Slope analysis; **pooled results

King TE Jr et al. N Engl J Med 2014;370:2083-2092; Richeldi L et al. N Engl J Med 2014;370:2071-2082; Raghu G et al. Am J Respir Crit Care Med 2017;195:78-85

Annual rate of decline in FVC by HRCT criteria



Raghu G et al. Am J Respir Crit Care Med 2017;195:78-85

Change in FVC % predicted over 24 weeks is highly predictive of death over the subsequent 1-year period

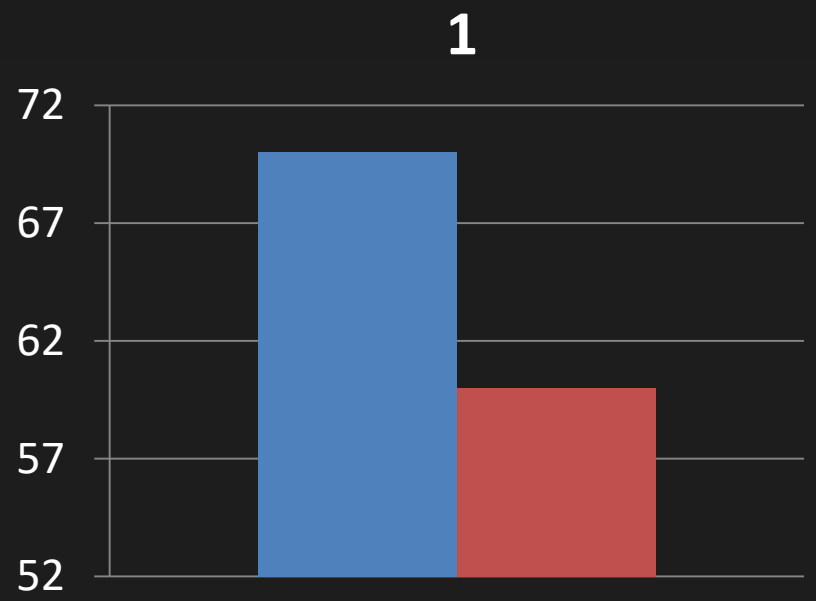
			1-Year Risk of Death	
	Patient Visits (*n*)	Deaths (*n*)	HR (*95% CI*)	*P* Value
ΔFVC, % predicted				
⩽−10	166	39	4.78 (3.12–7.33)	<0.001
−5 to −10	373	45	2.14 (1.43–3.20)	<0.001
>−5	1,316	56		
FVC, % predicted				
⩽50	203	42	7.44 (3.28–16.87)	<0.001
51 to 65	691	65	4.09 (1.87–8.98)	<0.001
66 to 79	594	26	1.97 (0.85–4.55)	0.111
⩾80	374	7		

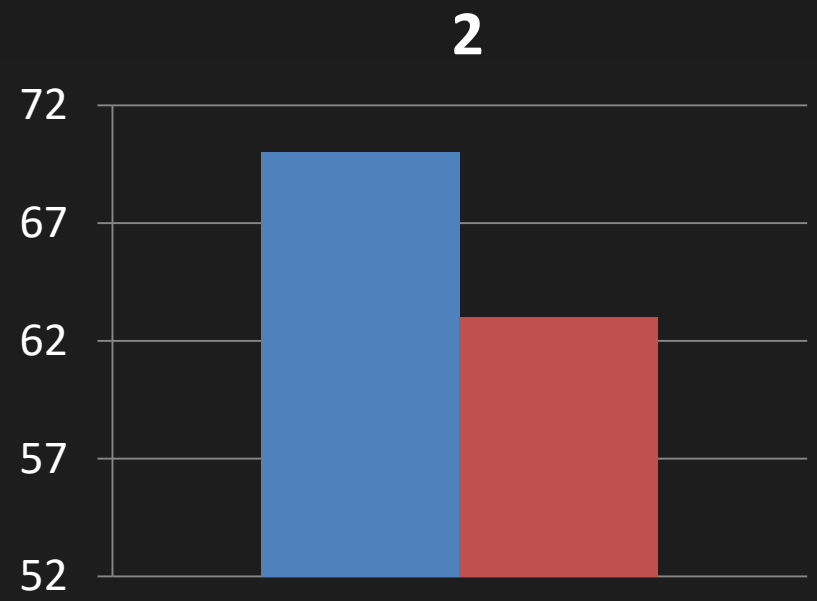
Definition of abbreviations: ΔFVC = 24-week absolute change in percent-predicted FVC (e.g., change from 70–65% = 5% absolute change); CI = confidence interval; HR = hazard ratio.

du Bois RM et al. Am J Respir Crit Care Med 2011;184:1382-1389

Different definitions of a 10% change

1. Δ in % predicted value (absolute) (70% → 60%)
2. Δ in % predicted value (relative) (70% → 63%)





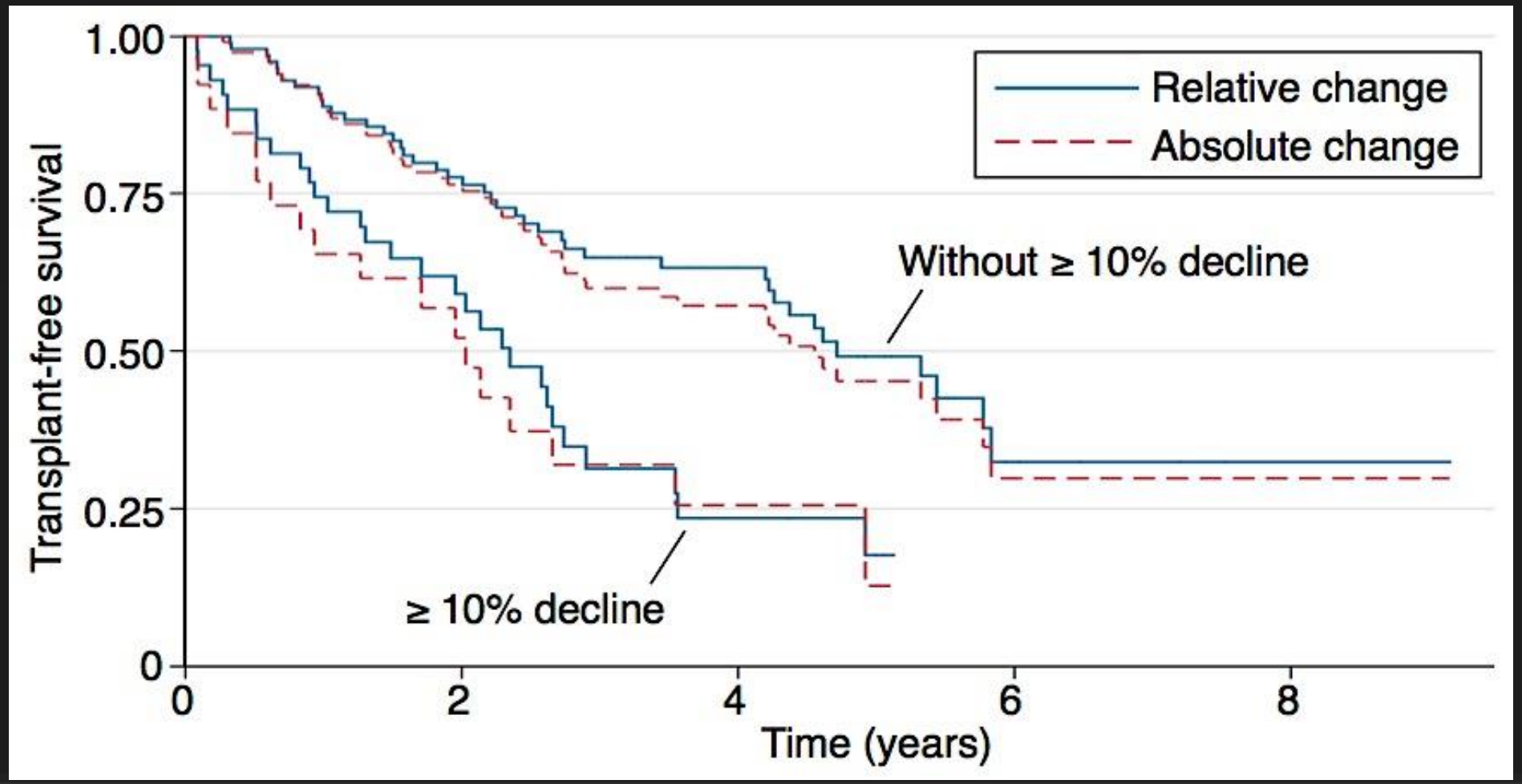
Relative versus absolute change in forced vital capacity in idiopathic pulmonary fibrosis

Luca Richeldi,[1,2] Christopher J Ryerson,[3] Joyce S Lee,[2] Paul J Wolters,[2] Laura L Koth,[2] Brett Ley,[2] Brett M Elicker,[4] Kirk D Jones,[5] Talmadge E King Jr,[2] Jay H Ryu,[6] Harold R Collard[2]

- **142 IPF patients from two prospective cohorts with baseline and 12-month follow-up FVC**
- **Primary outcome was two-year transplant-free survival (TFS), defined as the absence of death or lung transplant at two years measured from the date of the 12-month FVC (i.e. two years after the change in FVC was observed)**

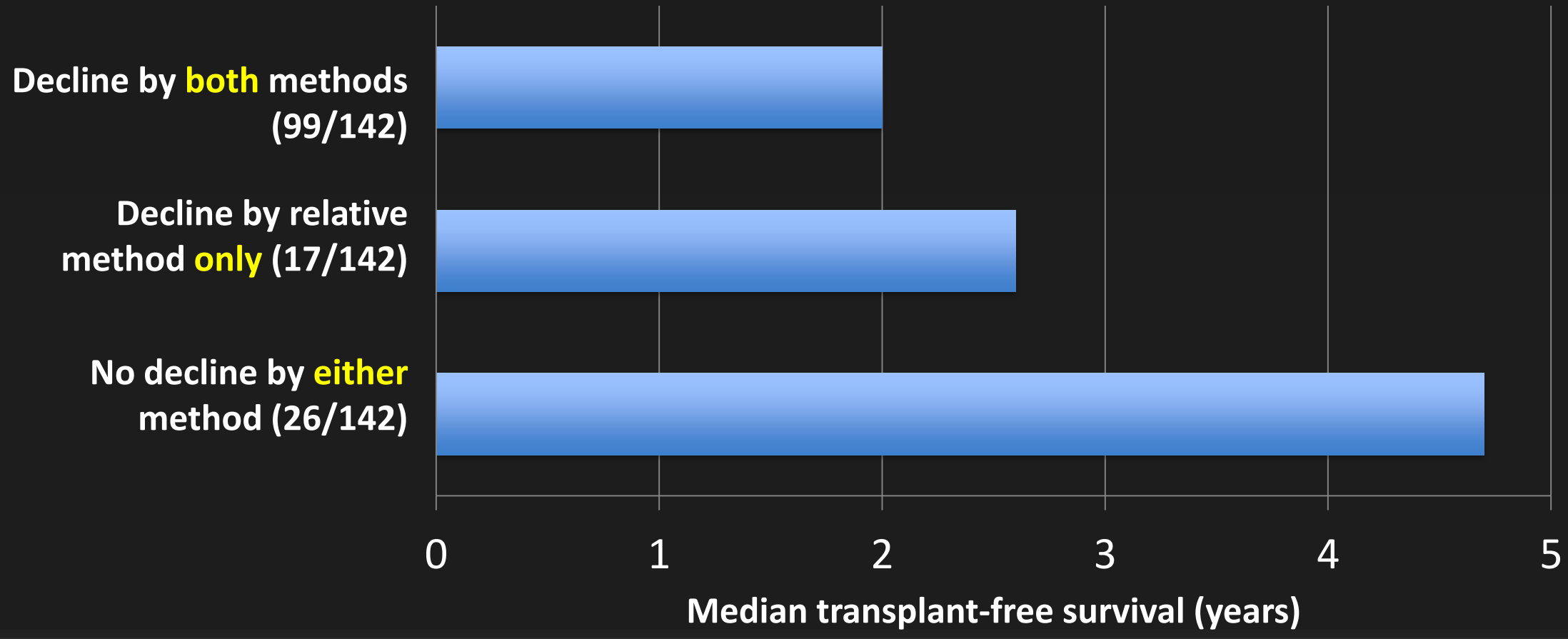
Richeldi L et al. Thorax 2012;67:407-411

TFS estimates based on ≥10% decline in FVC



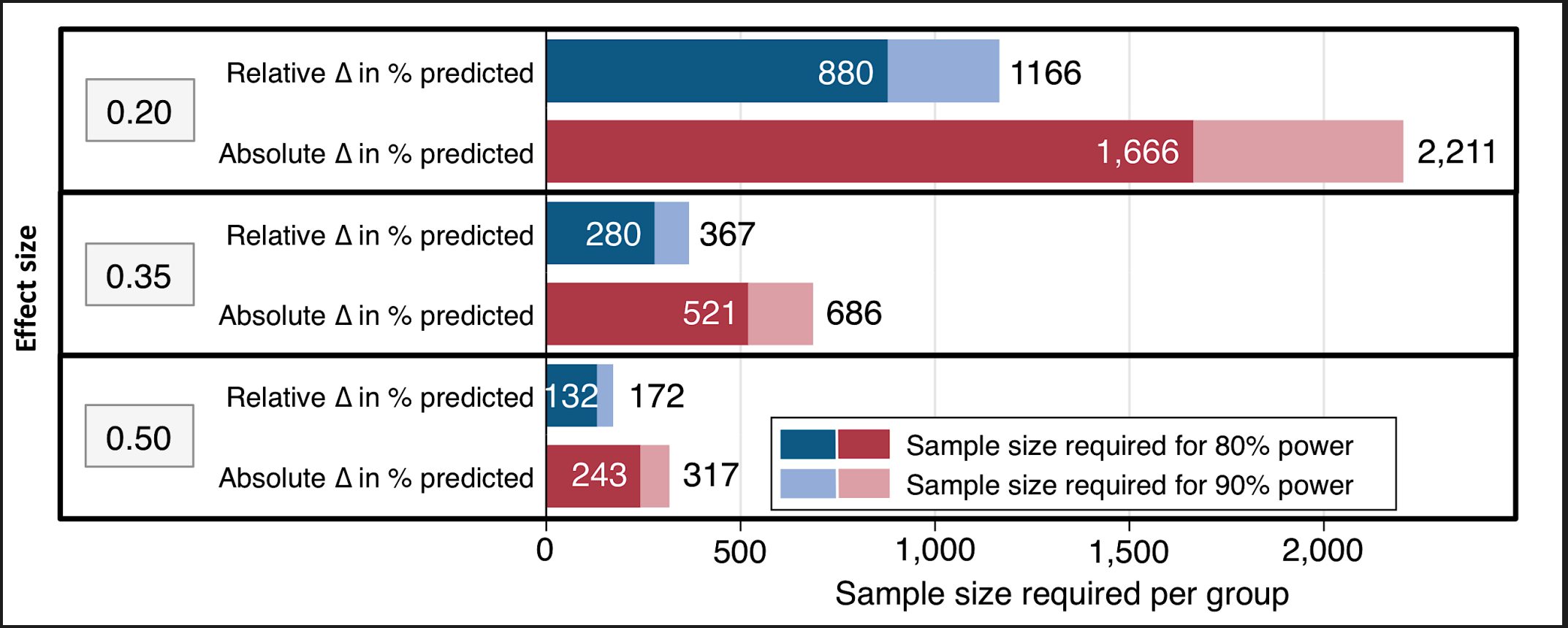
Richeldi L et al. Thorax 2012;67:407-411

Implications for patients



Richeldi L et al. Thorax 2012;67:407-411

Implications for sponsors



Richeldi L et al. Thorax 2012;67:407-411

Increasing efficiency of clinical trials

Alternative approaches

- **Cohort enrichment:** FVC <50%, DLco <30%, respiratory hospitalisation in the 24 weeks prior to enrolment in a clinical trial
- **Exclusion of patients with concomitant emphysema**
- **Inclusion of patients with concomitant pulmonary hypertension**

Outline

- Fibrogenic molecules/pathways
- Patient selection
- Study design/endpoints

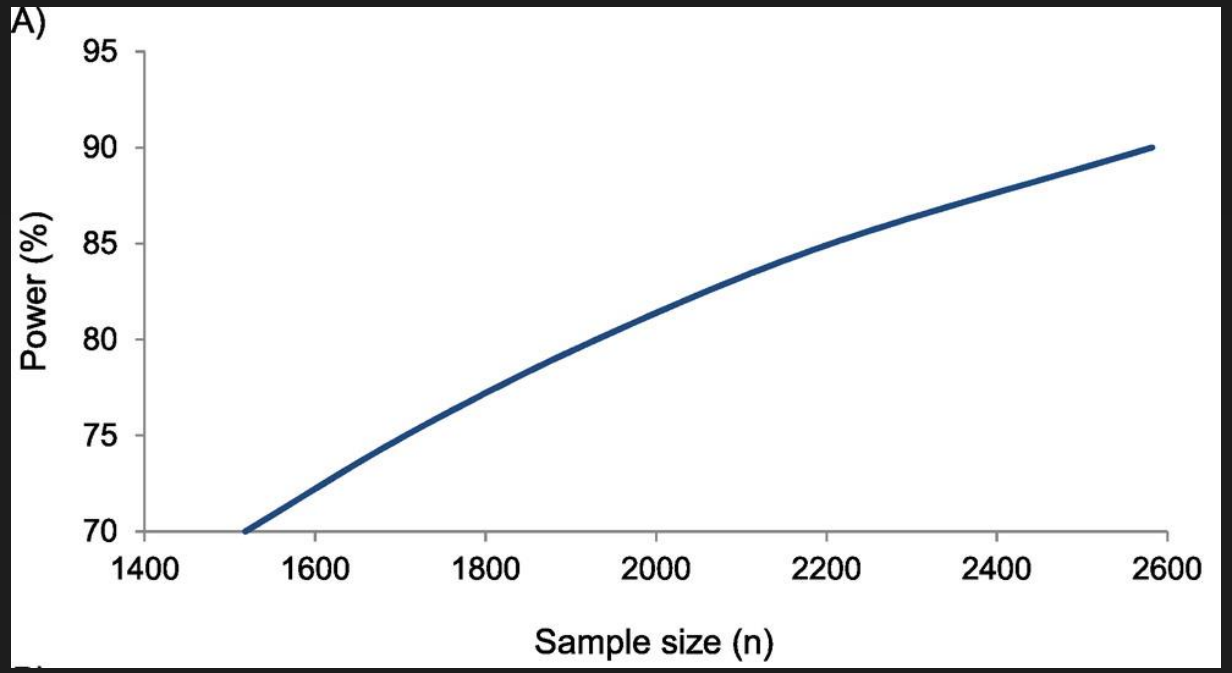
Mortality in the ASCEND and CAPACITY trials

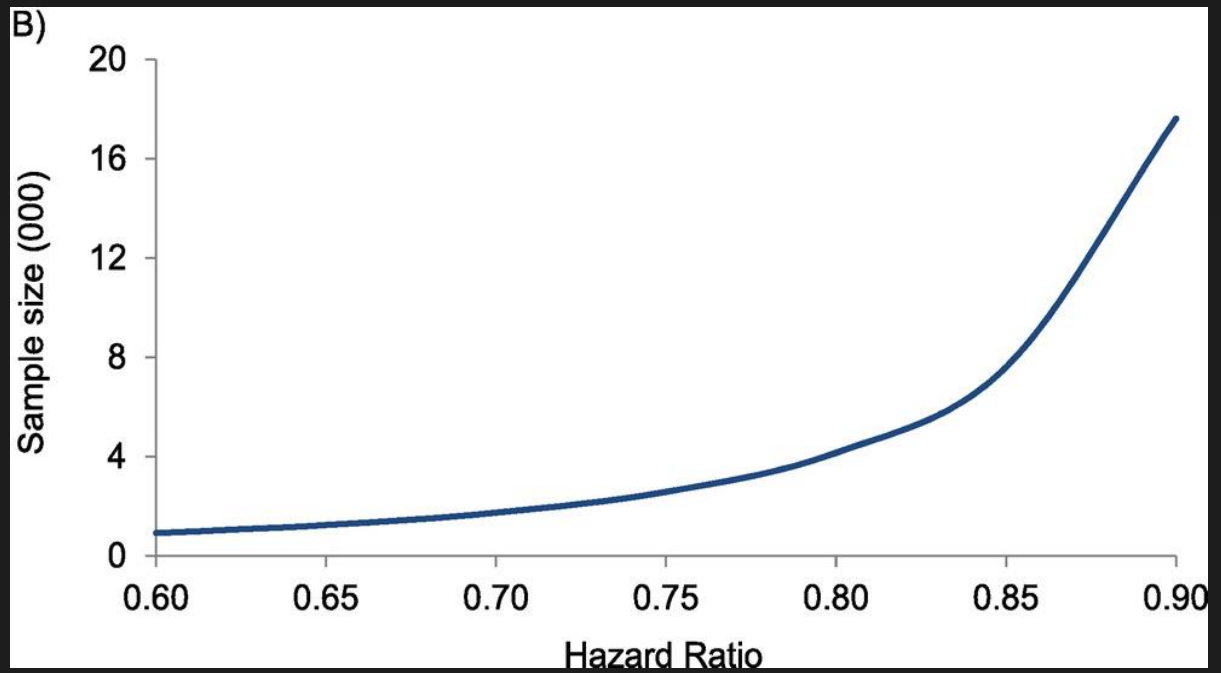
Variable	Pirfenidone	Placebo	Hazard Ratio (95% CI)†	P Value‡
ASCEND trial				
No. of patients	278	277		
Death — no. (%)				
From any cause	11 (4.0)	20 (7.2)	0.55 (0.26–1.15)	0.10
Related to idiopathic pulmonary fibrosis§	3 (1.1)	7 (2.5)	0.44 (0.11–1.72)	0.23
Pooled data from ASCEND and CAPACITY trials				
No. of patients	623	624		
Death — no. (%)				
From any cause	22 (3.5)	42 (6.7)	0.52 (0.31–0.87)	0.01
Related to idiopathic pulmonary fibrosis§	7 (1.1)	22 (3.5)	0.32 (0.14–0.76)	0.006

* Data from the two CAPACITY studies were censored at 1 year to standardize the follow-up for the three studies.
† Hazard ratios are for the pirfenidone group, as compared with the placebo group, and were calculated with the use of the Cox proportional-hazards model.
‡ P values were calculated with the use of the log-rank test.
§ Death related to idiopathic pulmonary fibrosis was defined as death that occurred during the period from randomization to 28 days after the last dose of the study drug. This category was evaluated in a blinded fashion by an independent mortality-assessment committee in the ASCEND trial and by clinical investigators in the CAPACITY trials.

King TE Jr et al. N Engl J Med 2014;370:2083-2092

Power calculations and sample size estimates for mortality trials in IPF (placebo controlled)





King TE Jr et al. Am J Respir Crit Care Med 2014;189:825-831

All-cause and IPF-related mortality sensitivity analysis over 120 weeks

	All-cause mortality				IPF-related mortality	
	Pooled analysis		Random-effects meta-analysis (all trials)		Pooled analysis	
	Pirfenidone (n=623)	**Placebo (n=624)**	**Pirfenidone (n=804)**	**Placebo (n=764)**	**Pirfenidone (n=623)**	**Placebo (n=624)**
Week 52						
Deaths , n (%)	22 (3.5%)	42 (6.7%)	25 (3.1%)	47 (6.2%)	10 (1.6%)	28 (4.5%)
HR (95% CI)	0.52 (0.31-0.87)	-	0.53 (0.32-0.85)	-	0.35 (0.17-0.72)	-
p value	0.0107	-	0.0092	-	0.0029	-
Week 72						
Deaths , n (%)	32 (5.1%)	50 (8.0%)	35 (4.4%)	55 (7.2%)	17 (2.7%)	35 (5.6%)
HR (95% CI)	0.63 (0.41-0.98)	-	0.63 (0.41-0.96)	-	0.48 (0.27-0.85)	-
p value	0.0404	-	0.0305	-	0.0107	-
End of study						
Deaths , n (%)	38 (6.1%)	54 (8.7%)	41 (5.1%)	59 (7.7%)	22 (3.5%)	39 (6.3%)
HR (95% CI)	0.69 (0.46-1.05)	-	0.68 (0.46-1.01)	-	0.55 (0.33-0.93)	-
p value	0.0789	-	0.0585	-	0.0237	-

Adapted from Nathan SD et al. Lancet Respir Med 2017;5;33-41

Selected potential primary endpoints

Endpoint	Advantages	Disadvantages
FVC	Regulatory precedent Easy to perform Measure of disease progression Reproducible	Surrogate for clinical events (disease progression, death) May miss important treatment effects Prone to missing data
6-minute walk distance	Measure of exercise capacity Efficient	Technically challenging in a multicentred study Performance affected by non-IPF morbidity Training effect May miss important treatment effects Prone to missing data
Hospitalisation (all-cause or respiratory)	Common clinical event Clinically relevant	Variation in clinical criteria for hospitalisation across sites, healthcare systems and countries
Mortality (all cause or IPF-related)	Clinically relevant Easy to measure	Inefficient (i.e. low event rate) May miss important treatment effect (e.g. improved function or symptoms)
Composite endpoints*	Capture multiple dimensions of efficacy Can be composed of events that are of direct clinical relevance	Challenging interpretability Outcome generally dominated by single component
CT imaging	Reliable measure of disease extent/progression Prognostic value	Subjective versus automated assessment still debated CT changes may not correlate with changes in lung function

*Examples of composite endpoints are: progression-free survival (categorical decline in FVC, 6-minute walk test, respiratory hospitalisation or death) and hospitalisation-free survival (all-cause hospitalisation or death)

CT, computerised tomography

Modified from Collard HR et al. Eur Respir J 2015;46:243-249

Conclusion

- The approval of pirfenidone and nintedanib has dramatically changed the landscape of clinical trials in IPF
- Our knowledge of genetics, biomarkers and clinical trial design has advanced greatly
- Better understanding of disease pathophysiology remains crucial