PNEUMOLOGIA 2016

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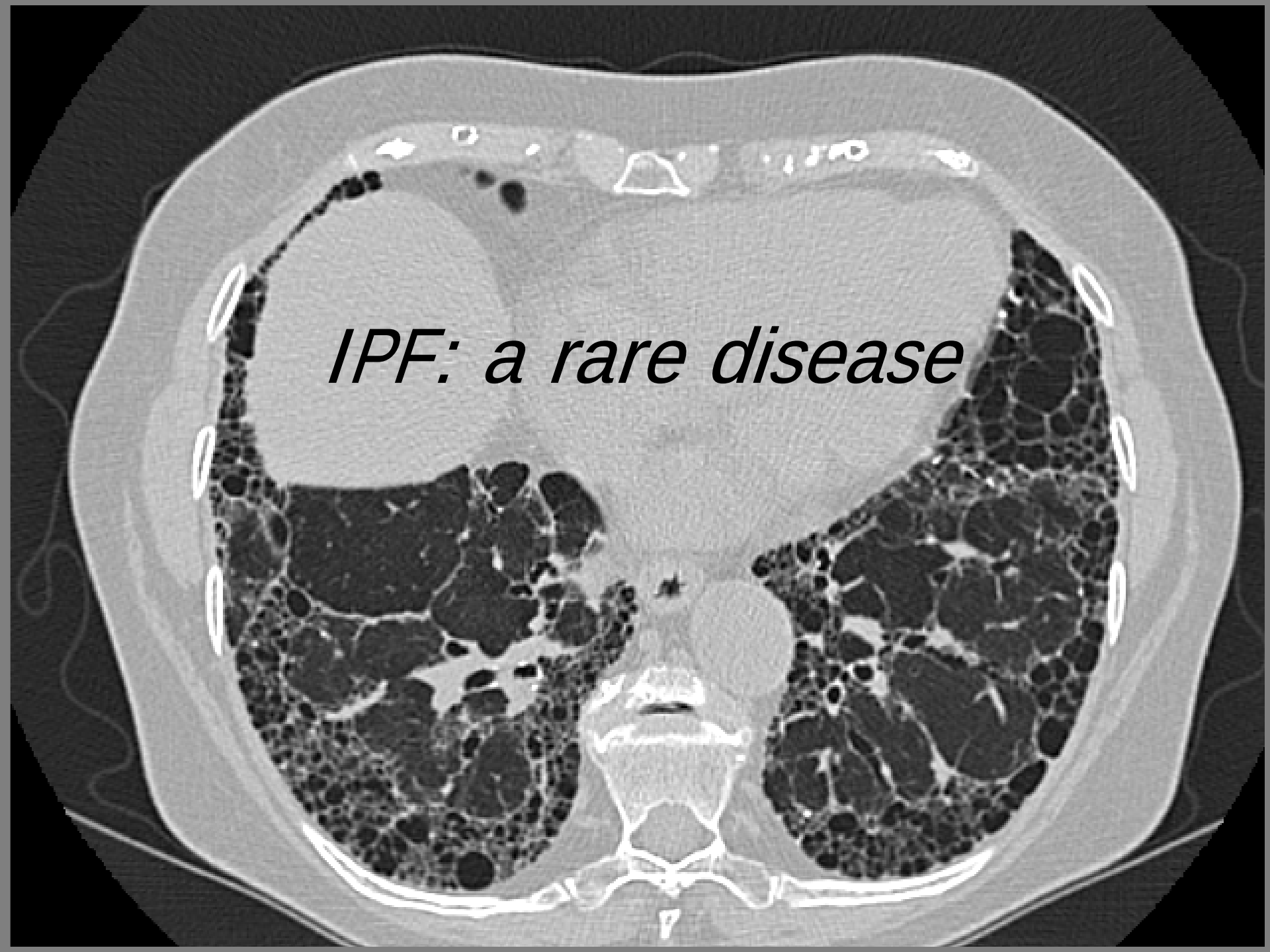
Presente e futuro della terapia della fibrosi polmonare idiopatica

Antonella Caminati
U.O. di Pneumologia e Terapia Semi Intensiva
Servizio di Fisiopatologia Respiratoria ed Emodinamica Polmonare
Osp. San Giuseppe - MultiMedica, Milano


IPF: a rare disease

A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis

King TE et al. NEJM 2014; 370: 2083

2014-2015: the begin of the new era of IPF

Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis

Richeldi L et al. NEJM 2014; 370: 2071

Randomized trial of acetylcysteine in idiopathic pulmonary fibrosis

NEJM 2014; 370: 2093

Where We're Going…

Anti-inflammatory
Immunosuppression
Immunomodulation
Anti-oxidant
Anti-fibrotic
Stem cells?
Antiproliferative

Statement ATS/ERS 2000

Steroids and/or immunosuppressant

Statement ATS/ERS/JRS/ALAT 2011

No therapy approved

Pirfenidone
Nintedanib
Combined therapy?

Cyclophosphamide

Pirfenidone

Ambrisentan
Sitaxestan

1950s **1990s** **2009** **2016**

Currently, where is no a cure for IPF

Today, we have a therapy


The past

Lessons learned from clinical trials

- Remarkable accomplishments
  - also in an orphan disease as IPF: several multicenter randomized clinical trials
  - clinical investigators, sponsors, patients join hands and work together
  - placebo arm/placebo controls
  - better understanding of natural course of IPF
- myths clarified with facts and figures
- opinions/consensus of expert opinions proven wrong by evidence
- standard of care improved by sparing patients from toxic/harmful drugs

Lessons learned from clinical trials

- Almost all clinical trials: patients with mild –moderate impairment in FVC and DLCO and followed 48-60 weeks
- Patients are relatively stable during this interval
- FVC decline is about 200 ml/yr in placebo group
- FVC is not a predictor of hospitalization/acute exacerbation
- Feasibility of enrolling patients with severe/advanced pulmonary function impairment demonstrated
- Other than standard physiological /clinical assessment of disease progression, no other cellular/molecular/genetic biomarkers have been utilized

The present

Nintedanib and Pirfenidone

New antifibrotic Treatments Indicated for Idiopathic Pulmonary Fibrosis offer hopes and Raises Questions

Raghu and Selman, AJRCCM, Feb 1 2015

Nintedanib and pirfenidone

- Approval for treatment for IPF (FDA and EMA)

  "Blanket treatment" (regardless of status of disease and/or comorbid conditions)

- Results of phase 3 clinical trials in a precise subgroup of patients with IPF
- Decline in FVC decreases over 1 yr without symptomatic relief
- Significant side effects (GI in both; rash with pirfenidone)
- Tolerated by patients in the context of clinical trials

..but real life is not a clinical trial...

Unkown effects:

- whether the lower rate of decline in FVC in patients lasts beyond 1 yr in patients with mild –moderate impairment (PFTs)
- applicable to the entire spectrum of patients with IPF, especially those with severe functional impairment and/or known comorbidities
- Long term effects and if tolerated in patients in “real world”
- ***Is one better than the other? No head-to-head comparison***
- ***if used sequential or in combination with both or with other drugs***
- ***Cost effective-benefit-ratio***

Some answers about pirfenidone

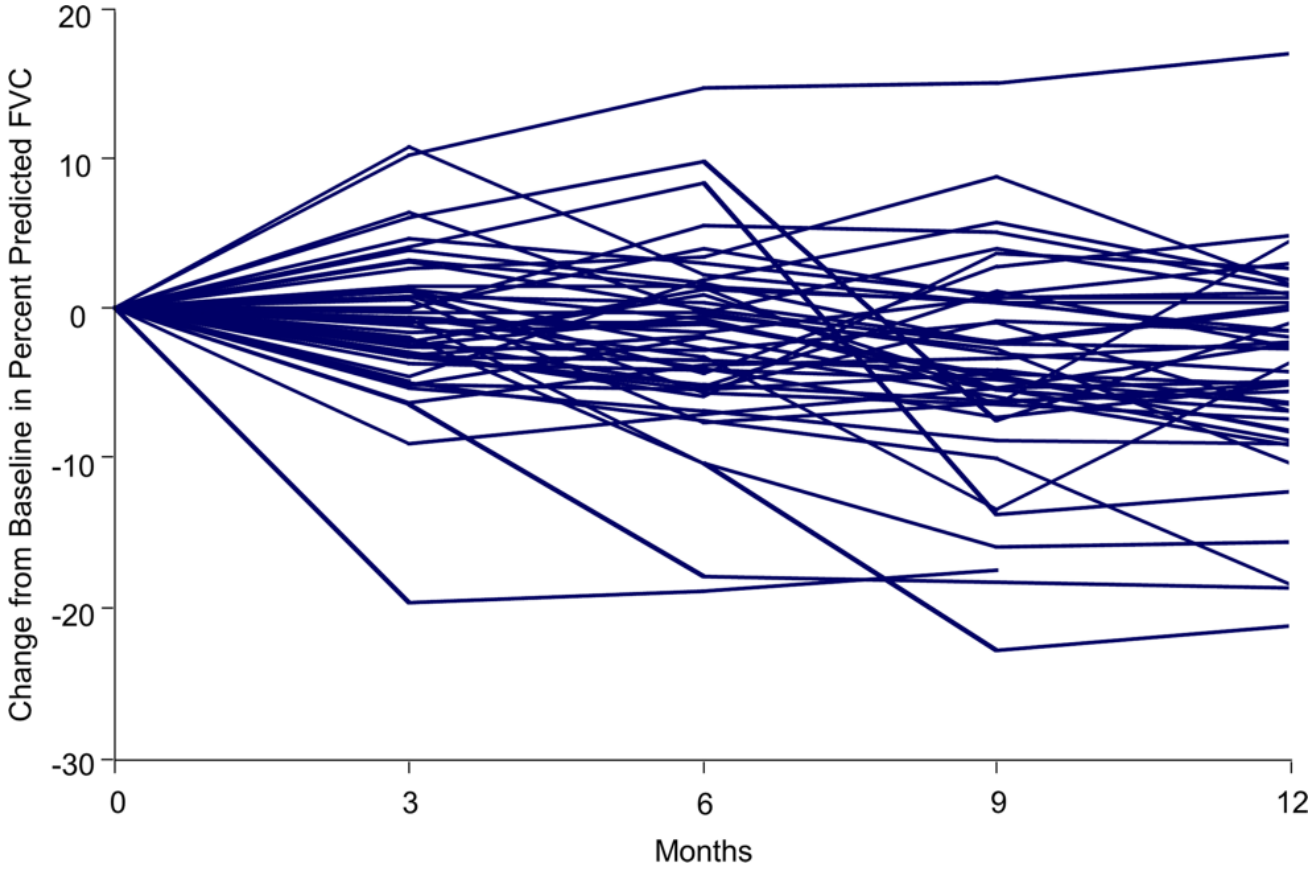
Safety of pirfenidone in patients with idiopathic pulmonary fibrosis: integrated analysis of cumulative data from 5 clinical trials

Lancaster L. et al BMJ Open Resp Res 2016: doi10.1136/bmjresp-2015-000105

- 1299 patients with IPF treated with pirfenidone
- During this long-term, prospective follow-up of up to 9.9 year, pirfenidone was safe and generally well tolerated
- Gastrointestinal and skin-related events were among the most common adverse events, mild-to-moderate in severity and responsive to dose modification
- Elevations of aminotransferases typically occurred within the first 6 months of treatment

Effect of continued treatment with pirfenidone following clinically meaningful declines in forced vital capacity: analysis of data from three phase 3 trials in patients with idiopathic pulmonary fibrosis

Nathan SD et al. Thorax 2016; 71: 429



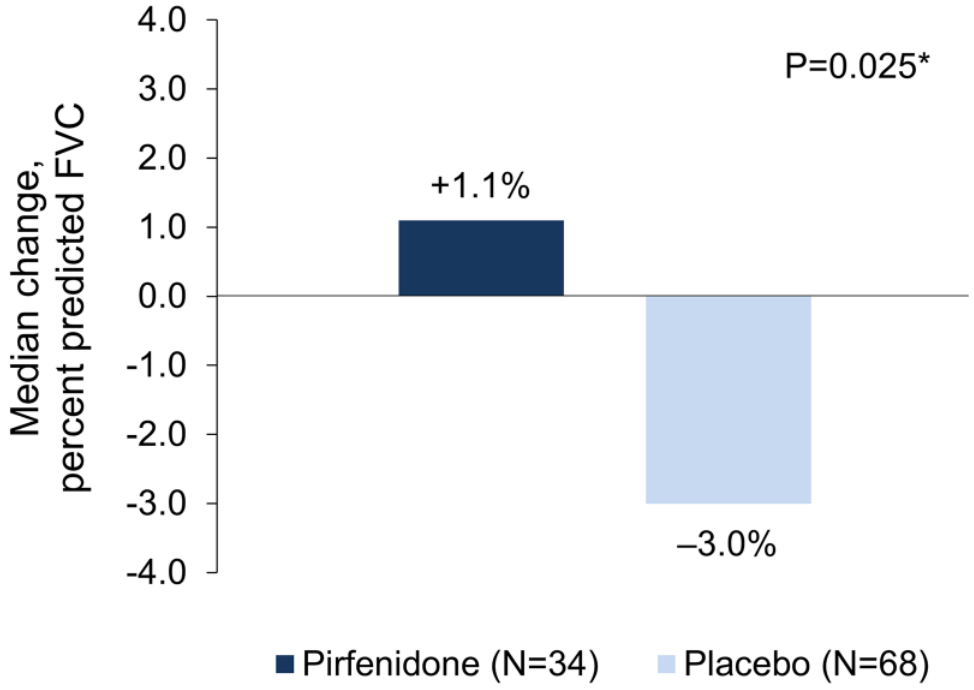
Spaghetti plot of in % predicted FVC*

*Randomly selected patients from the pooled placebo population from the CAPACITY and ASCEND studies (N=50)

Effect of continued treatment with pirfenidone following clinically meaningful declines in forced vital capacity: analysis of data from three phase 3 trials in patients with idiopathic pulmonary fibrosis

Nathan SD et al. Thorax 2016; 71: 429

	Pirfenidone (N=34)	Placebo (N=68)	P value
≥10% decline in FVC or death	2(5.9%)	19 (27.9%)	0.009
No further decline in FVC	20 (58.8%)	26 (38.2%)	0.059
Death	1 (2.9%)	14 (20.6%)	0.18



Outcome after 6 months of continued treatment following an initial decline in %predicted FVC ≥10%

Effect of continued treatment with pirfenidone following clinically meaningful declines in forced vital capacity: analysis of data from three phase 3 trials in patients with idiopathic pulmonary fibrosis

Nathan SD et al. Thorax 2016; 71: 429

Conclusions: Longitudinal FVC data from patients with IPF showed substantial intrasubject variability, underscoring the inability to reliably assess therapeutic response using serial FVC trends.

In patients who progressed during treatment, continued treatment with pirfenidone resulted in a lower risk of subsequent FVC decline or death.

Some peculiarities about nintedanib

Eligibility criteria based on HRCT

- To qualify to enter the INPULSIS® trials in the absence of a surgical lung biopsy, criteria **A and B and C**; or A and C; or B and C had to be met:

A	Definite honeycomb lung destruction with basal and peripheral predominance
B	Presence of reticular abnormality and traction bronchiectasis consistent with fibrosis with basal and peripheral predominance
C	Atypical features are absent, specifically nodules and consolidation. Ground glass opacity, if present, is less extensive than reticular opacity pattern

- HRCT scans were assessed centrally by one expert radiologist

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Aim and methods

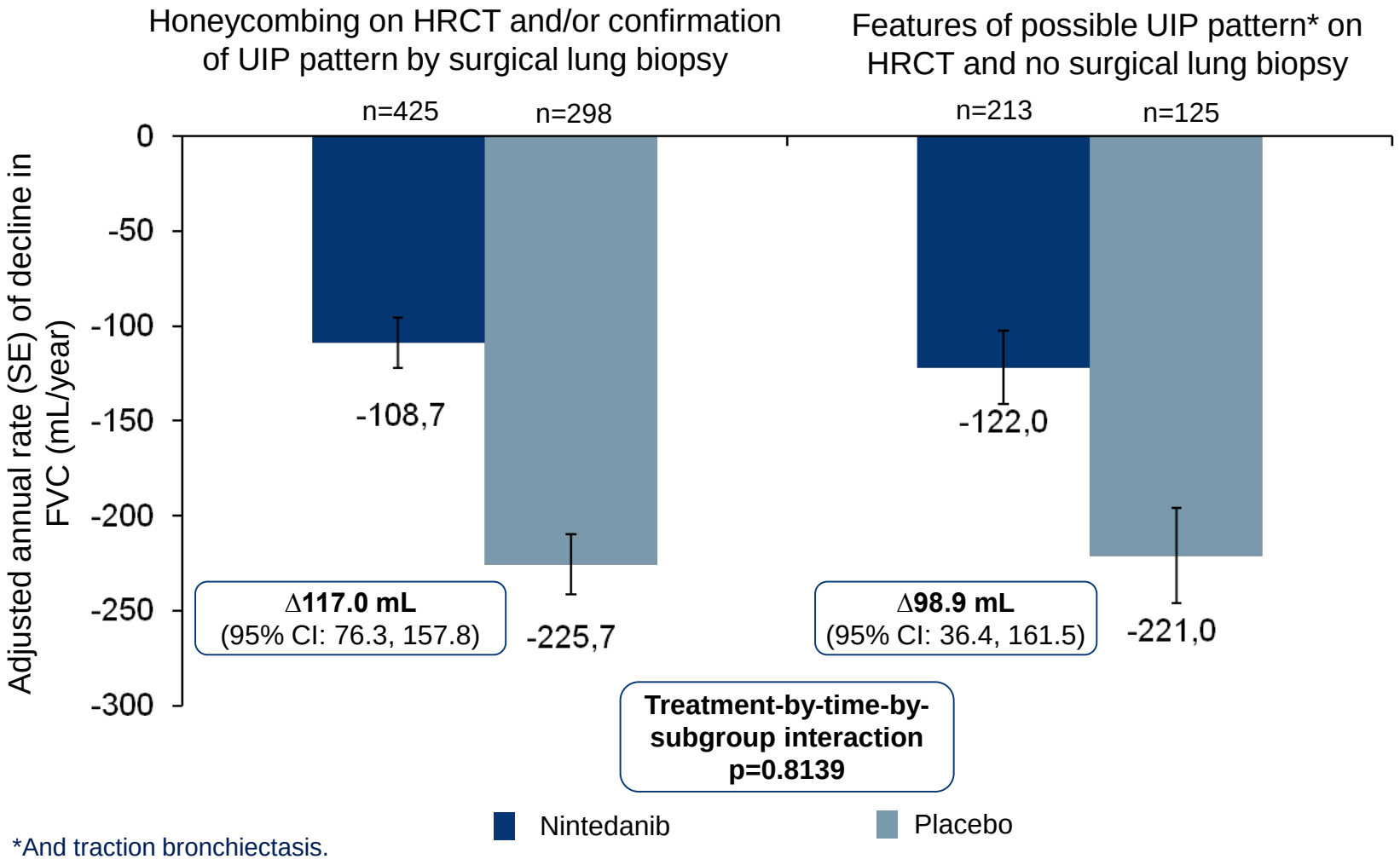
- **Aim**
  - To investigate the potential impact of HRCT diagnostic subgroups on the effect of nintedanib in patients with IPF
- **Methods**
  - *Post-hoc* subgroup analyses were conducted using pooled data from the two INPULSIS® trials in patients with:

Honeycombing on HRCT and/or confirmation of UIP pattern by surgical lung biopsy	versus	Features of possible UIP pattern* on HRCT and no surgical lung biopsy

  - Analyses were conducted on the primary and key secondary endpoints

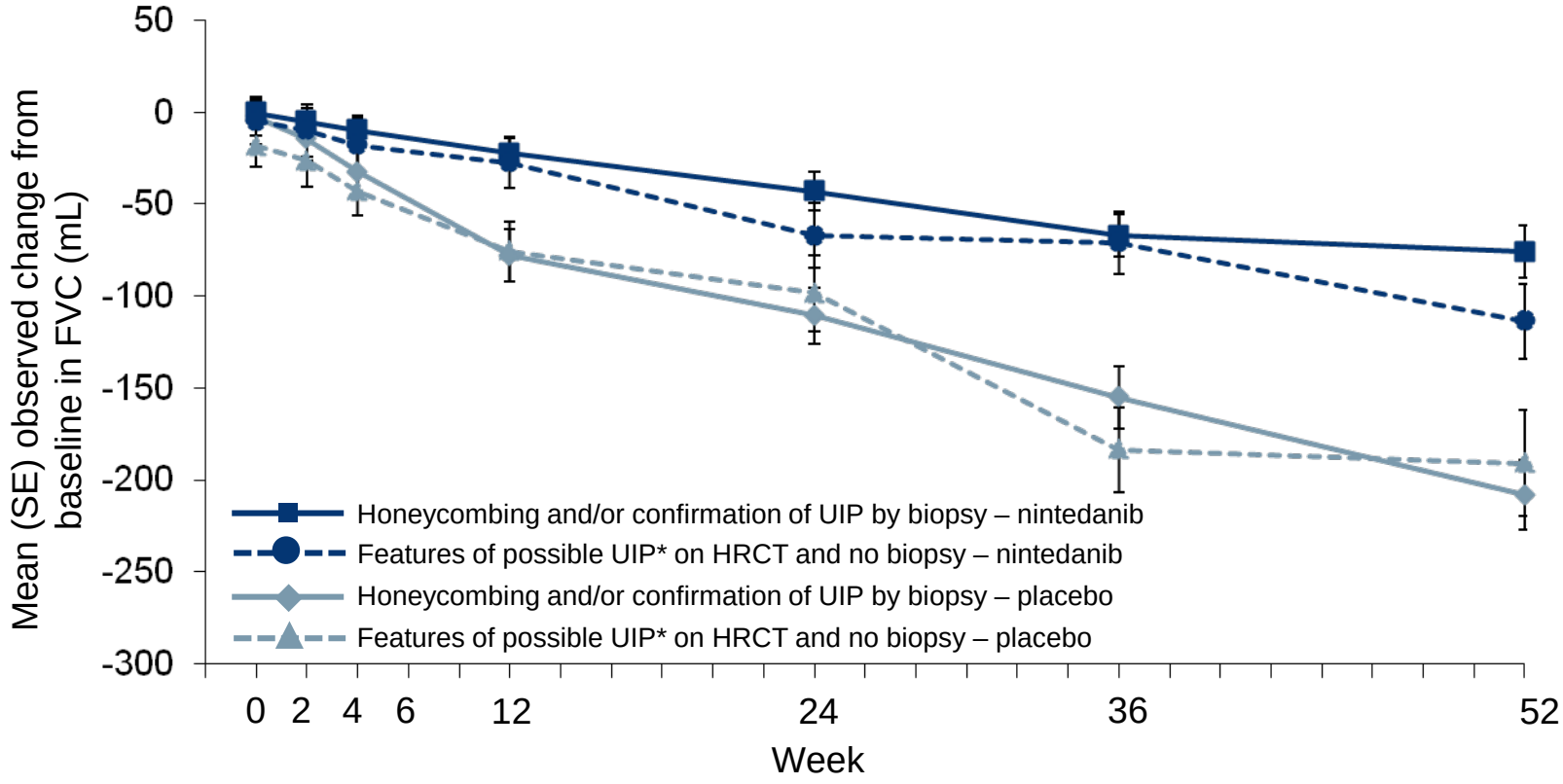
*And traction bronchiectasis. Possible UIP comprises all three of the following features: subpleural, basal predominance; reticular abnormality; absence of features noted as inconsistent with UIP pattern [Raghu et al. Am J Respir Crit Care Med 2011;183:788–824].

Annual rate of decline in FVC



*And traction bronchiectasis.

Change from baseline in FVC



*And traction bronchiectasis.

Aim and methods

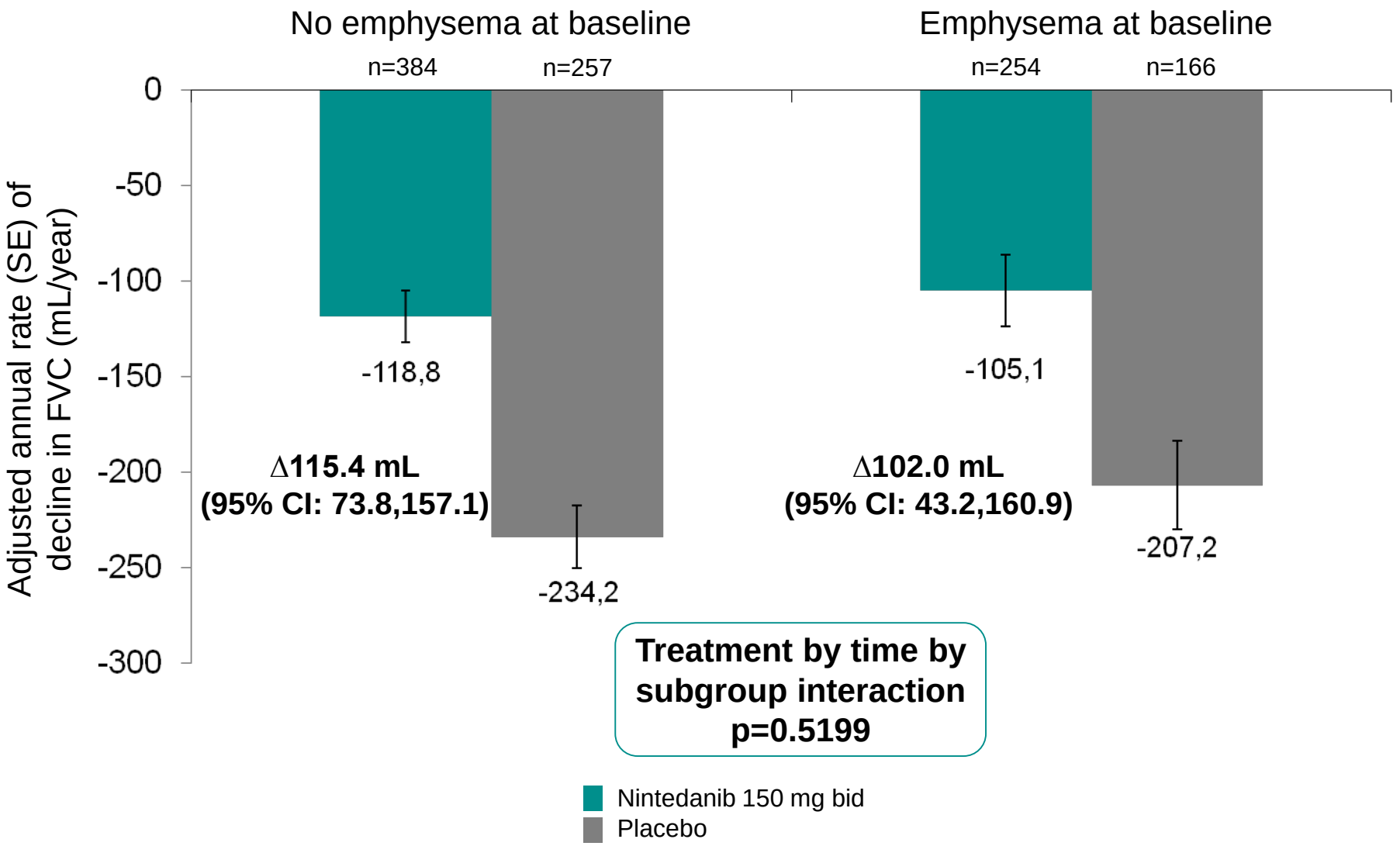
- Aim

- To investigate the potential impact of emphysema on the effect of nintedanib in patients with IPF

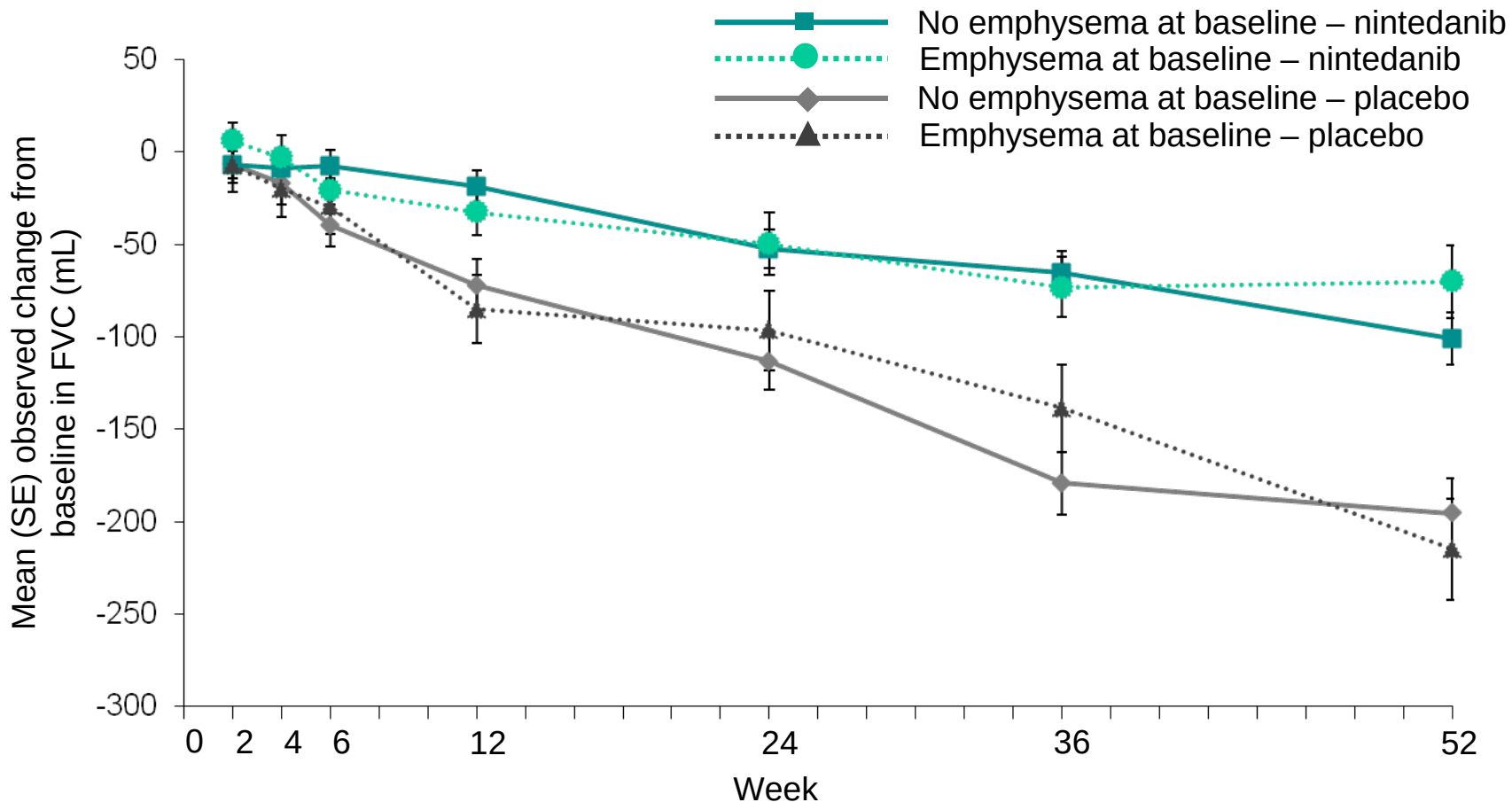
- Methods

- Presence of emphysema (yes/no) at baseline was determined by qualitative assessment of chest HRCT scans, centrally reviewed by a single radiologist
- *Post-hoc* subgroup analyses of patients with/without emphysema at baseline were conducted using pooled data from the two INPULSIS™ trials
- Subgroup analyses were conducted on the primary and key secondary endpoints

Annual rate of decline in FVC



Change from baseline in FVC



Safety and tolerability of nintedanib in patients with IPF: one-year data from post-marketing surveillance in the United States

Noth et al. ATS 2016

Exposure to nintedanib

- This analysis is based on data collected between the drug's launch on 15 October 2014 and a data snapshot on 31 October 2015.
- At the time of this analysis, 6758 patients had been treated with nintedanib
- Median duration of exposure to nintedanib was 113 days (range: 6–390 days)

Noth et al. ATS 2016

Conclusions

- Data on nintedanib obtained from post-marketing surveillance in the US one year after product launch were consistent with the safety profile of nintedanib described in the US label.
- No new safety concerns were identified.
- Consistent with the findings of the Phase III INPULSIS® trials, the most frequently reported adverse events with nintedanib were non-serious gastrointestinal events.

Noth et al. ATS 2016

Pirfenidone	Nintedanib
Reduced FVC decline	Reduced FVC decline

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Reduced FVC decline	Reduced FVC decline
Pooled analysis of the CAPACITY and ASCEND trials suggested improved mortality (relative risk: 0.70; 95% CI: 0.47–1.02; moderate confidence)	Pooled analysis of the TOMORROW and INPULSIS trials suggested improved mortality (relative risk: 0.70; 95% CI: 0.47–1.03; moderate confidence)

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Photosensitivity, fatigue, stomach discomfort, and anorexia. Patients should be informed and educated on all potential adverse effects	Adverse events, but not serious adverse events. Patients should be informed and educated on all potential adverse effects

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What's about patients with a more severe lung function impairment (FVC<50%) or in those with other comorbidities?	What's about patients with a more severe lung function impairment (FVC<50%) or in those with other comorbidities?

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What's about patients with a more severe lung function impairment (FVC<50%) or in those with other comorbidities?	What's about patients with a more severe lung function impairment (FVC<50%) or in those with other comorbidities?
Optimal duration of treatment and treatment effect duration while on therapy are unknown	Optimal duration of treatment and treatment effect duration while on therapy are unknown

The future

Safety, Tolerability and PK of Nintedanib in Combination With Pirfenidone in IPF

Sponsor: Boehringer Ingelheim

ClinicalTrials.gov Identifier: NCT02579603

This is a phase IV, twelve week, open label, randomized, parallel group study to assess safety and tolerability of combined treatment with nintedanib and pirfenidone.

Study start date: November 2015

Safety and Tolerability Study of Pirfenidone in Combination With Nintedanib in Participants With Idiopathic Pulmonary Fibrosis (IPF)

Sponsor: Roche

ClinicalTrials.gov Identifier: NCT02598193

This clinical study will evaluate the safety and tolerability of combination treatment of nintedanib and pirfenidone in participants with IPF.

Eligible participant must have received pirfenidone for at least 16 weeks on a stable dose. Nintedanib will be added on Day 1 of the study as a combination treatment for IPF for 24 weeks.

Study start date: January 2016

The near future


Roche
gsk
GlaxoSmithKline
IMMUNE
WORKS
GeNO
Healthcare Corp
MOERAE
MATRIX
biogen idec
SANOFI
AstraZeneca
Galecto Biotech
Promedior
Boehringer
Ingelheim
GILEAD
FIBROGEN
Takeda
Janssen
ucb
Pharma
Bristol-Myers Squibb

Tralokinumab

Cotrimoxazole

Nintedanib

GSK2634673F

FG-3019

BMS-986020

SAR156597

STX-100

TD139

PRM-151

Simtuzumab

IW001

Pirfenidone

Sirolimus

Carlumab

Lebrikizumab

EDITORIAL
INTERSTITIAL LUNG DISEASE

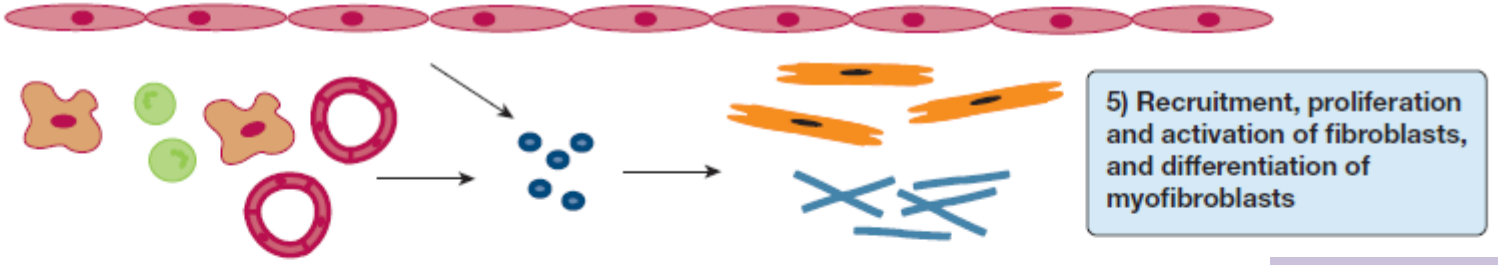
Where do we go from here? Clinical drug development in idiopathic pulmonary fibrosis

Harold R. Collard

- Issue 1: *which **mechanism** to target*
- Issue 2: *which **patients** to enrol*
- Issue 3: *which **end-points** to measure*

ERJ 2015; 45: 1218-1220

Linking IPF Pathogenesis to Potential Therapies



1) Susceptible host

- Genetics
- Aging

2) Injury to alveolar epithelium

- Cigarette smoke
- Industrial dusts
- Gastroesophageal reflux
- Viral infection

3) Aberrant wound healing response

- Recruitment and activation of immune cells
- Increased vascular permeability
- Activation of epithelium
- Increased apoptosis and premature senescence of alveolar epithelium

Lebrikizumab
Tralokinumab
NAC

4) Release of profibrotic cytokines

Lebrikizumab
Simtuzumab
Tralokinumab
SAR156597

5) Recruitment, proliferation and activation of fibroblasts, and differentiation of myofibroblasts

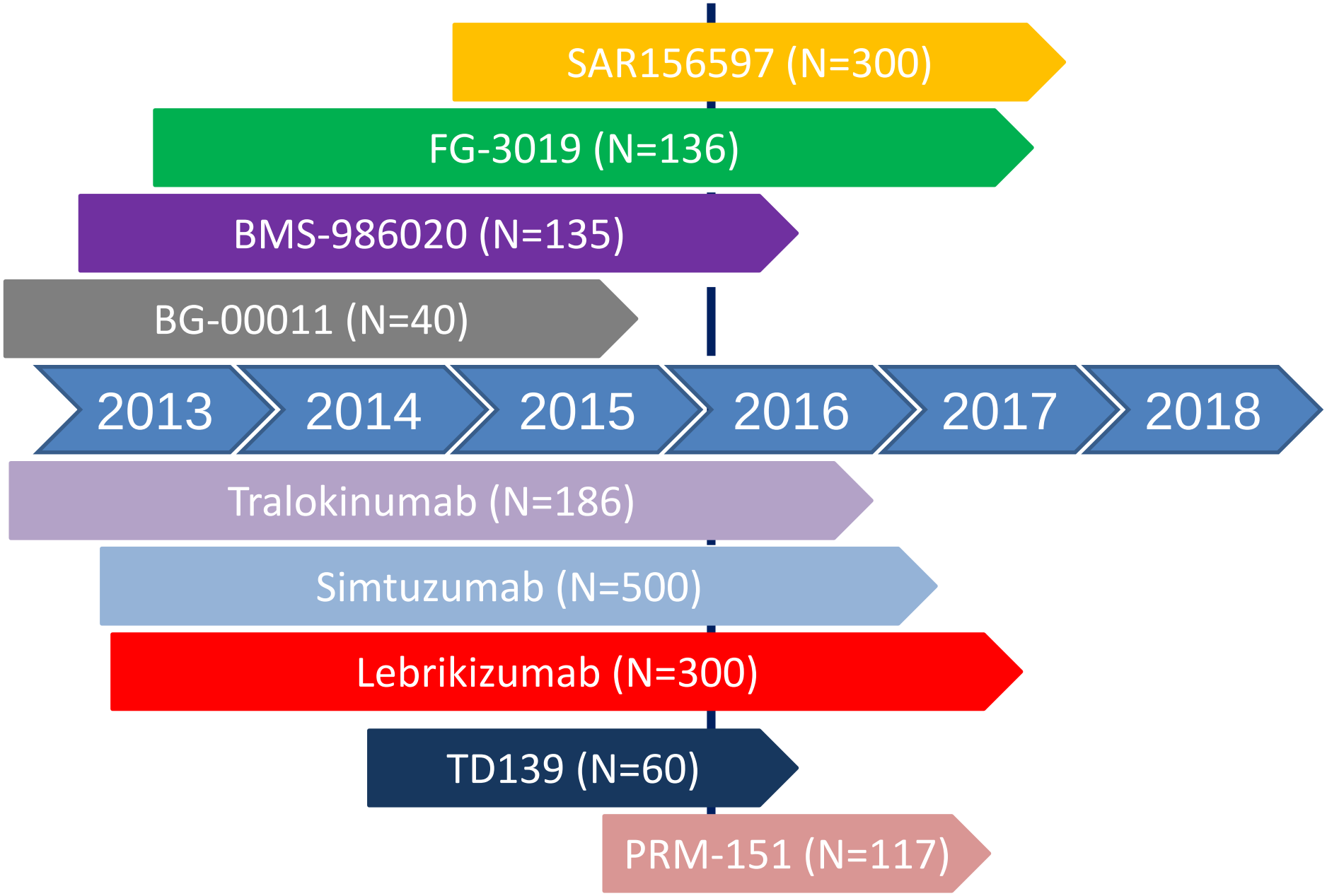
6) Increased extracellular matrix deposition

Nintedanib
Pirfenidone
STX-100
BMS-966020
TD139
Simtuzumab
PRM-151/pentraxin-2

7) Impaired gas exchange, leading to respiratory failure

Goodwin et al. Chest 2016; 149: 228

Ongoing phase 2 pharmacological trials



Studies active at our center

Simtuzumab (RAINIER phase 2 study, Gilead)

Simtuzumab is a monoclonal antibody

The antibody works by binding to the “scavenger receptor” located on the enzyme LOXL2

By binding to this receptor, the therapy blocks its ability to recruit fibroblasts

LOXL2 is essential for the synthesis of connective tissues

Press Release on January 2016

The experimental therapy did not demonstrate efficacy in treating the disease.

SAR156597 (ESTAIR phase 2 study, Sanofi)

SAR156597 is a monoclonal antibody that specifically blocks IL-4 and IL-13

Both IL-4 and IL-13 are cytokines that may induce inflammation

Inflammation may contribute to the damage that is seen in the lungs of IPF patients.

A randomized, double blind, placebo-controlled, 52-week, dose ranging study

Phase 2b study in patients with IPF has started in May 2015 (ClinicalTrials.gov Identifier: NCT02345070)

Lebrikizumab (RIFF phase 2 study, Roche)

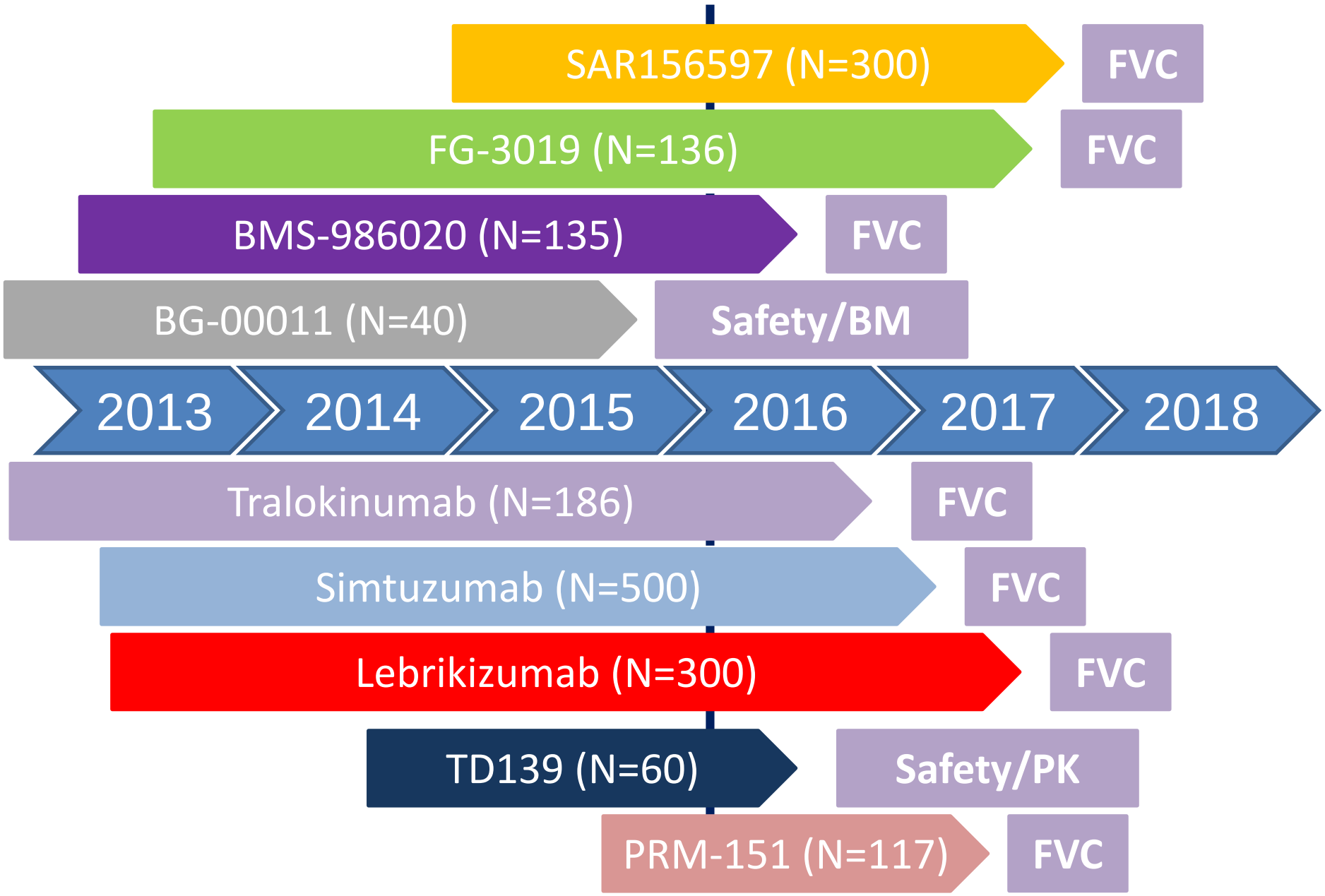
Lebrikizumab is a monoclonal antibody against IL-13

To evaluate the efficacy and safety of lebrikizumab as monotherapy in the absence of background IPF therapy (Cohort A) or as combination therapy with pirfenidone background therapy (Cohort B) in patients with IPF.

A randomized, double blind, placebo controlled, study to assess the efficacy and safety of lebrikizumab

Phase 2 study in patients with IPF has started in June 2013 (ClinicalTrials.gov Identifier: NCT01872689)

Ongoing phase 2 pharmacological trials



Why FVC as the Primary Endpoint?

Pros

Standard measurement of pulmonary function

Simple, easy to perform

Reproducible

Placebo group change is well understood (predictable)

Changes may be observed in a short time frame

Precedent –Clinical trials

Correlates with survival

Cons/controversies

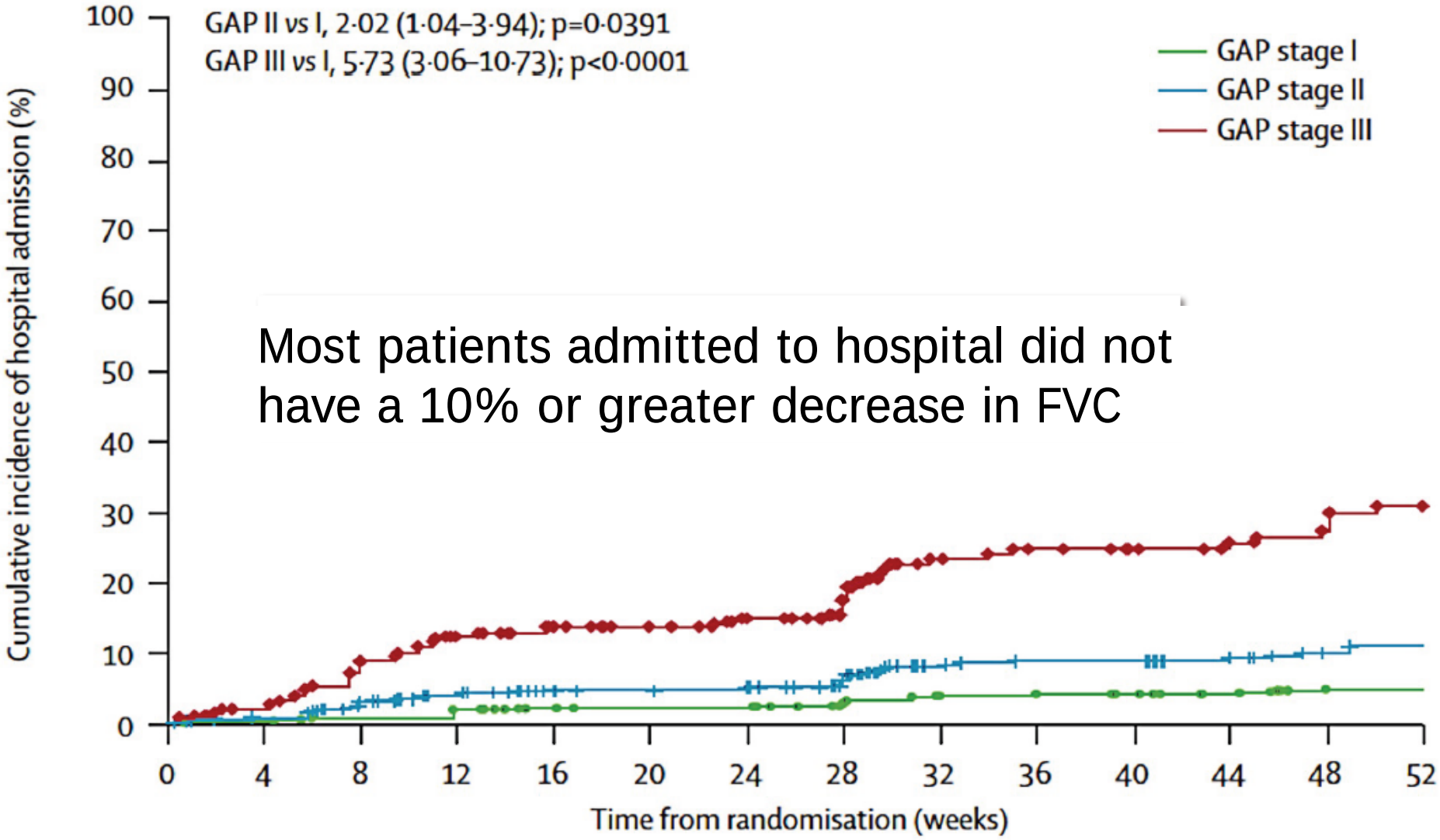
FVC is a biomarker

FVC is not a validated surrogate for clinical events that are meaningful to patients (e.g. acute exacerbations, mortality)

Minimal ΔFVC: ? (e.g. 10% decline over 52 weeks)

How to deal with death and missing data?

Time to first all-cause, non-elective hospital admission

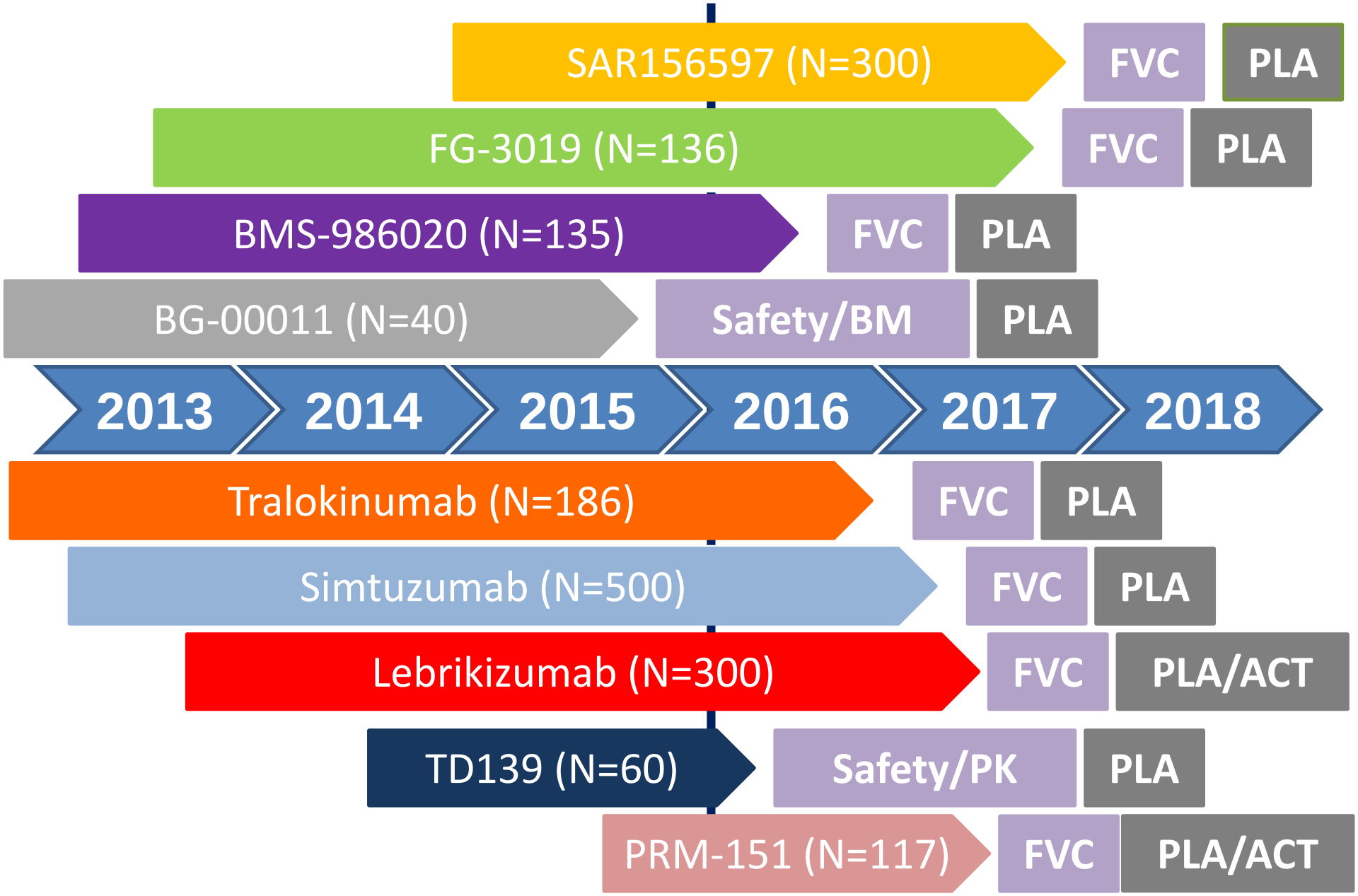


Most patients admitted to hospital did not have a 10% or greater decrease in FVC

Durheim MT et al, *Lancet Respir Med* 2015 Apr 15

Is the true placebo arm ethical today?

Ongoing phase 2 pharmacological trials



PRM-151 (phase 2 study, Promedior)

PRM-151 is a recombinant human pentraxin-2 protein

Pentraxin-2 is an endogenous human protein that plays an important role in regulating the response to fibrosis.

PRM-151/Pentraxin-2 binds to damaged tissue and monocytes and directs monocyte differentiation towards resolution of fibrosis

If on pirfenidone or nintedanib, subject must have been on a stable dose for at least 3 months

Phase 2 study in patients with IPF has started in August 2015 (ClinicalTrials.gov Identifier: NCT02550873)

Conclusions

- Clinical trials in IPF are evolving
- It is critical that we continue to encourage patients with IPF to participate in clinical trials of new drug agents that will undoubtedly add benefit to our initial therapies
- Patients with IPF continue to await a cure for their disease, and the unmet medical needs remains high
- With the emergence of novel and effective therapy for patients with IPF, it is clear that IPF care will evolve significantly over the next few years