PIRFENIDONE (ESBRIET)

Joseph D Zibrak MD

ILD Collaborative

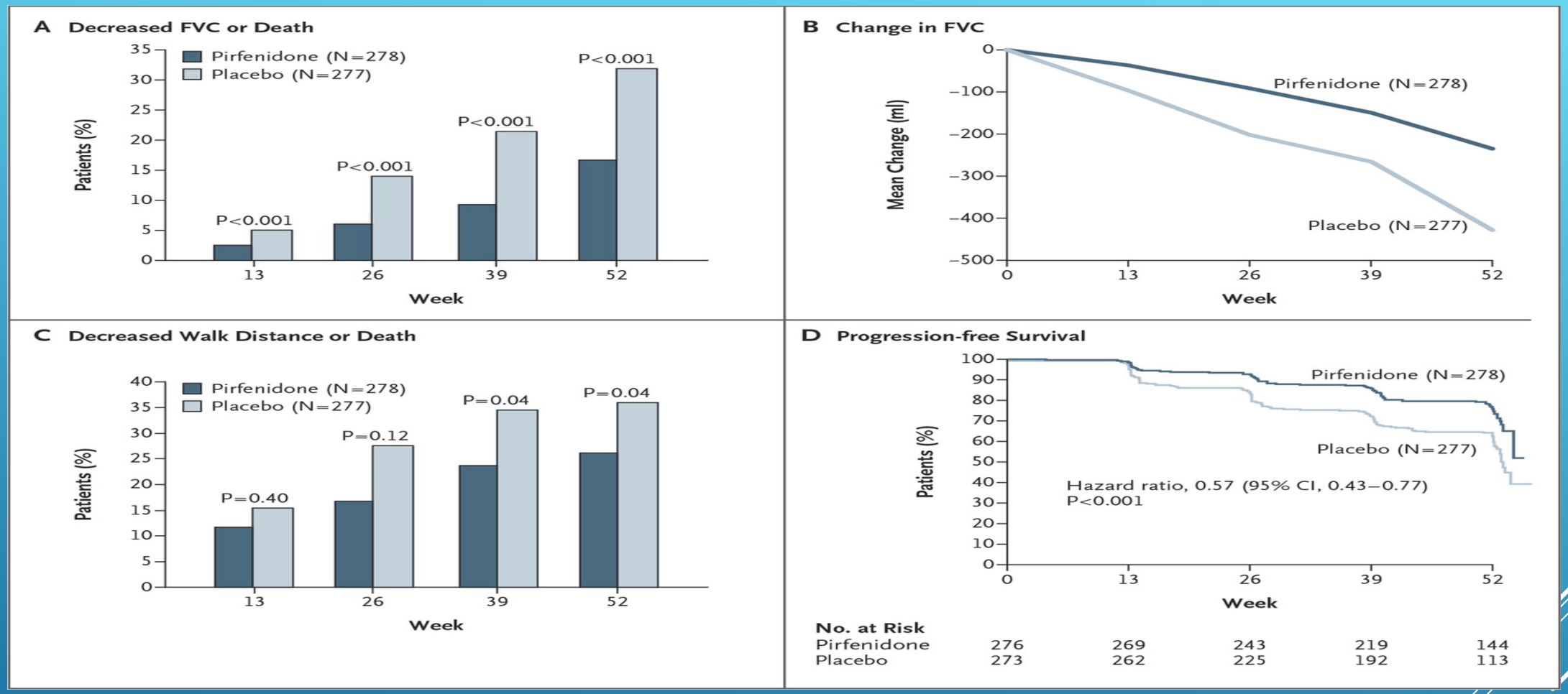
Director, ILD Center

Beth Israel Deaconess Medical Center

HISTORY

- First recognized as an anti-fibrotic agent in 1994 by SB Margolin
- Initial data supporting a role for pirfenidone in IPF
  - Raghu et al, 1999 – 54 patients with severe IPF
    - Study design suboptimal
    - Many dropouts
    - Possible signal suggesting stabilization/equivalence with more toxic therapies
- Development rights purchased by Intermune in 2007
  - First American Phase III Trials completed in 2009
  - "Tie Breaker " Trial reported in May 2014
- Approval for clinical use by FDA – October 2014

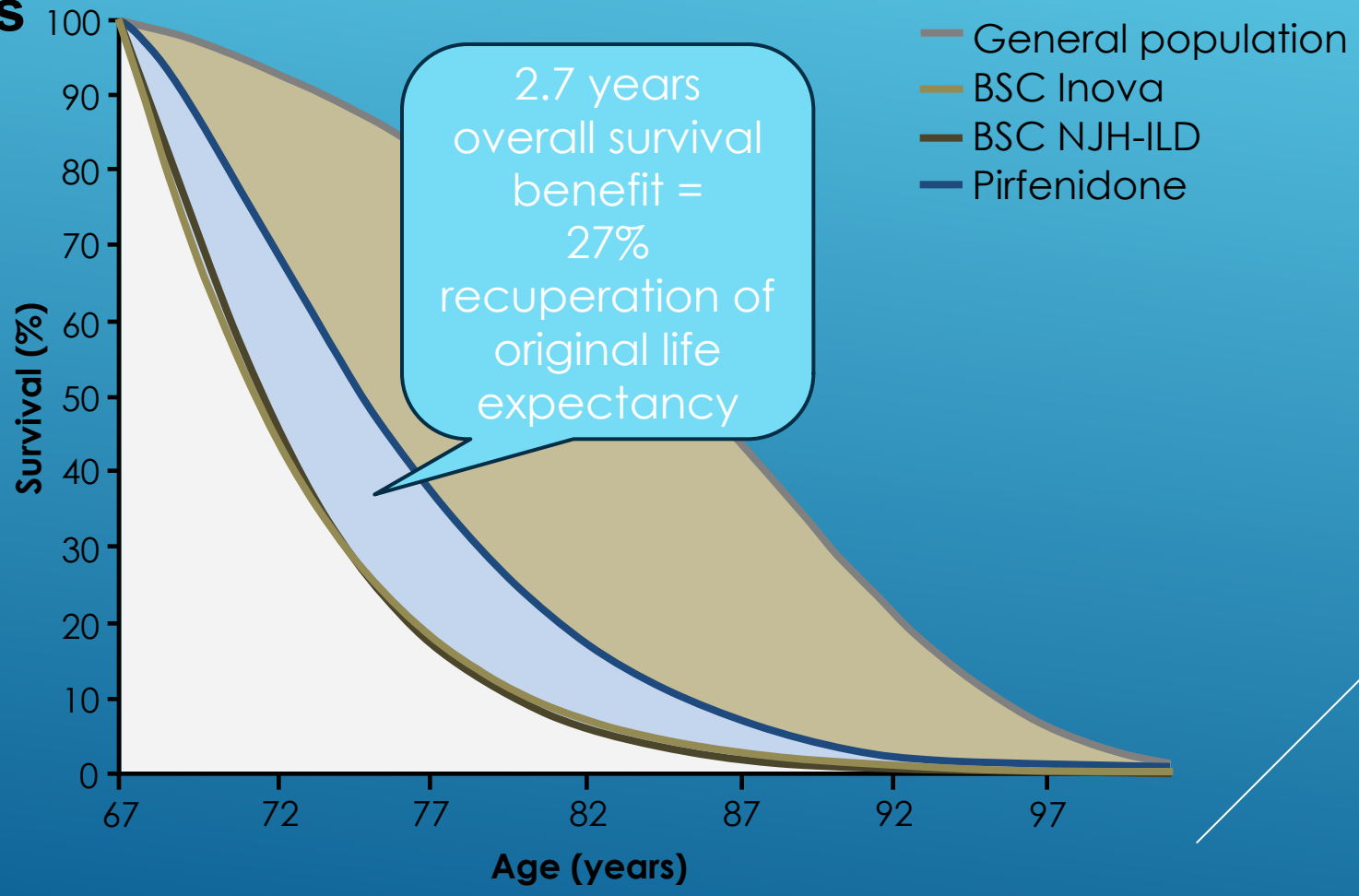
15 YEARS FROM CONCEPT TO APPROVAL


A Decreased FVC or Death
Pirfenidone (N=278)
Placebo (N=277)
Patients (%)
P<0.001
P<0.001
P<0.001
P<0.001
Week
B Change in FVC
Mean Change (ml)
Pirfenidone (N=278)
Placebo (N=277)
Week
C Decreased Walk Distance or Death
Pirfenidone (N=278)
Placebo (N=277)
Patients (%)
P=0.40
P=0.12
P=0.04
P=0.04
Week
D Progression-free Survival
Patients (%)
Pirfenidone (N=278)
Placebo (N=277)
Hazard ratio, 0.57 (95% CI, 0.43–0.77)
P<0.001
Week
No. at Risk
Pirfenidone 276 269 243 219 144
Placebo 273 262 225 192 113

DOES IT WORK?

IMPACT OF PIRFENIDONE ON LIFE EXPECTANCY

- **Pirfenidone improves life expectancy by almost 3 years**

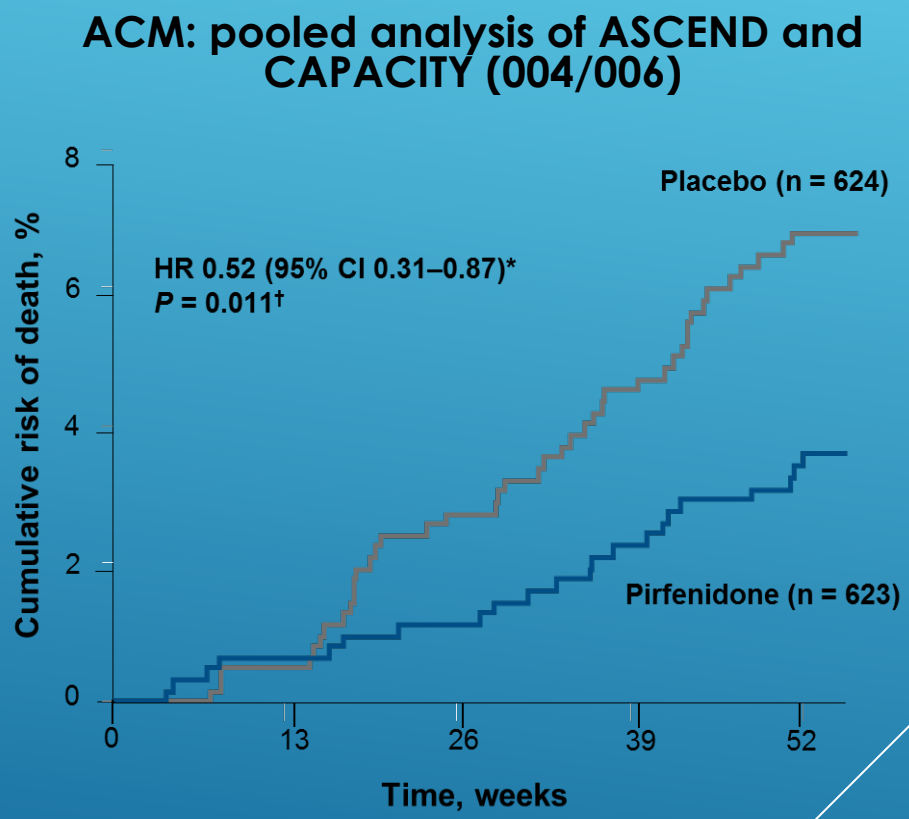


Fisher M. Oral Presentation. ERS 2016, London, UK. Abstract OA4964.

RESULTS
EFFECT OF PIRFENIDONE ON MORTALITY OUTCOMES AT WEEK 52

Pirfenidone significantly reduced the relative risk of death for all mortality outcomes vs. placebo in the pooled analysis at week 52.

Mortality outcome	HR	95% CI	P value
ACM	0.52	0.31–0.87	0.0107
TE ACM	0.45	0.24–0.83	0.0094
IPF related	0.35	0.17–0.72	0.0029
TE IPF related	0.32	0.14–0.76	0.0061



* Cox proportional hazard model; † Log-rank test. ACM, all-cause mortality; CI, confidence interval;

SURVIVAL MODELING STUDIES
POPULATION FROM ASCEND, CAPACITY (004/006) & RECAP

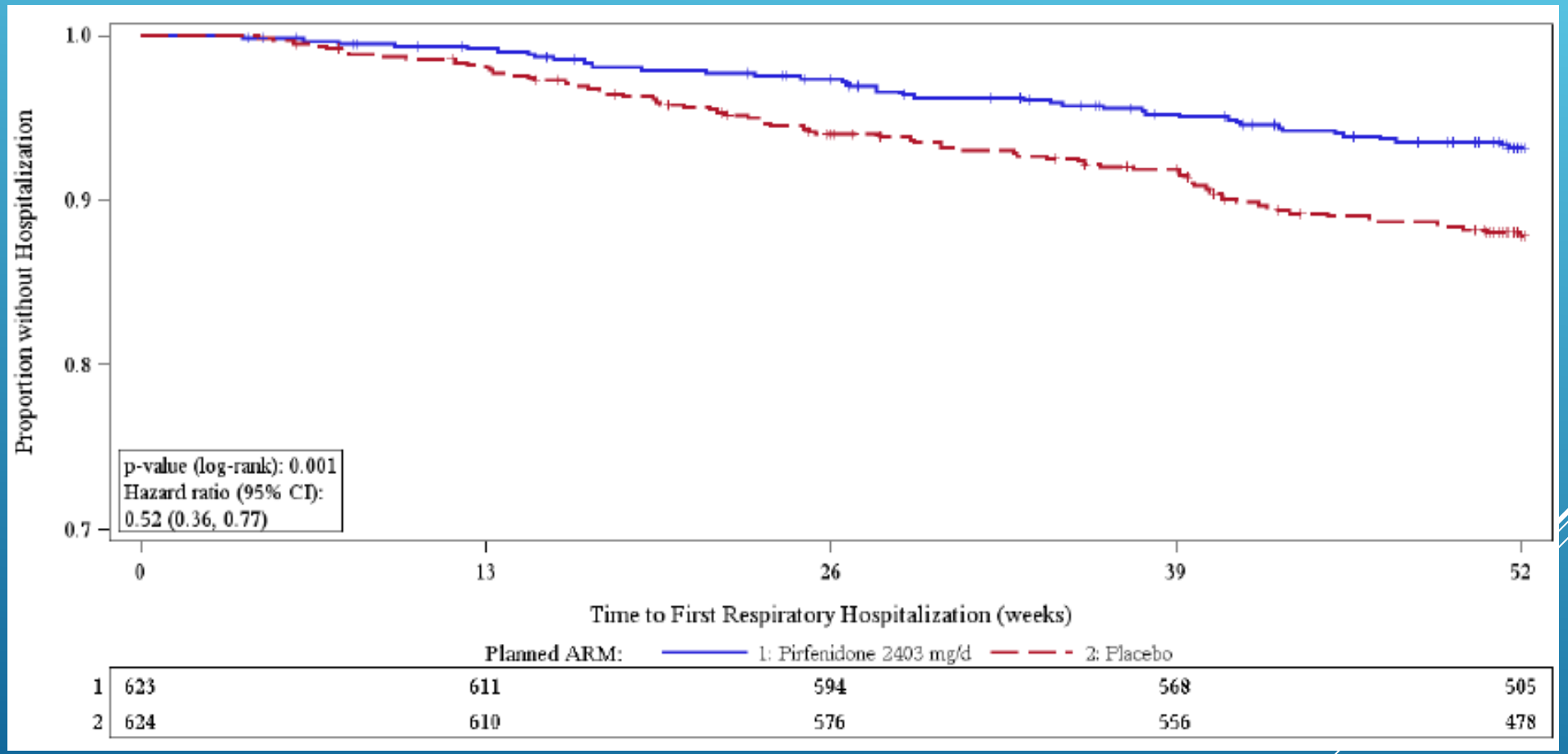
Study	Best Supportive Care (BSC)	BSC Life Expectancy (years)	Esbriet Life Expectancy (years)	Mean Difference (Esbriet – BSC) (years)
Fisher et al. JMCP 2017	Inova Fairfax Hospital Database	6.24 (95% CI 5.38-7.18)	8.72† (95% CI 7.65-10.15)	**2.47 (95% CI 1.26-4.17)**
Fisher et al. ERS 2016	Inova Fairfax Hospital Database National Jewish Health (NJH) ILD Database	Inova: 5.88 (95% CI 5.05-6.85) NJH: 6.1 (95% CI 5.72-6.51)	8.72* (95% CI 7.65-10.15)	Inova: **2.84** NJH: **2.62**
Fisher et al. ATS 2015	National Jewish Health ILD Database	6.099	9.289*	**3.19**
Roskell et al. ERS 2014	UK Clinical Practice Research Datalink	5.25 (95% CI 4.05-7)	9.26† (95% CI 7.44-11.67)	**4.01**

* Kaplan Meier Curve. † Weibull Curve.

Fisher et al. J Manag Care Spec Pharm. 2017;23(3-b):S17-S24.
Fisher et al. Oral Presentation at ERS 2016. London, UK. OA4964.
Fisher et al. Poster Presentation at ATS 2015. Denver, CO. 4413.
Roskell et al. Poster Presentation at ERS 2014. Munich, Germany.

RATES OF HOSPITALIZATION (CONT.)

Kaplan-Meier Plot of Time to First Respiratory-Related Hospitalization: Pirfenidone vs. Placebo



Patients in the pirfenidone arm were less likely to experience respiratory-related hospitalizations compared to placebo (Hazard ratio (HR): 0.52, 95% Confidence Interval (CI):(0.36, 0.77); p=0.001).

Ley B et al., AJRCCM Articles in Press. Published on 04-May-2017 as 10.1164/rccm.201701-0091OC

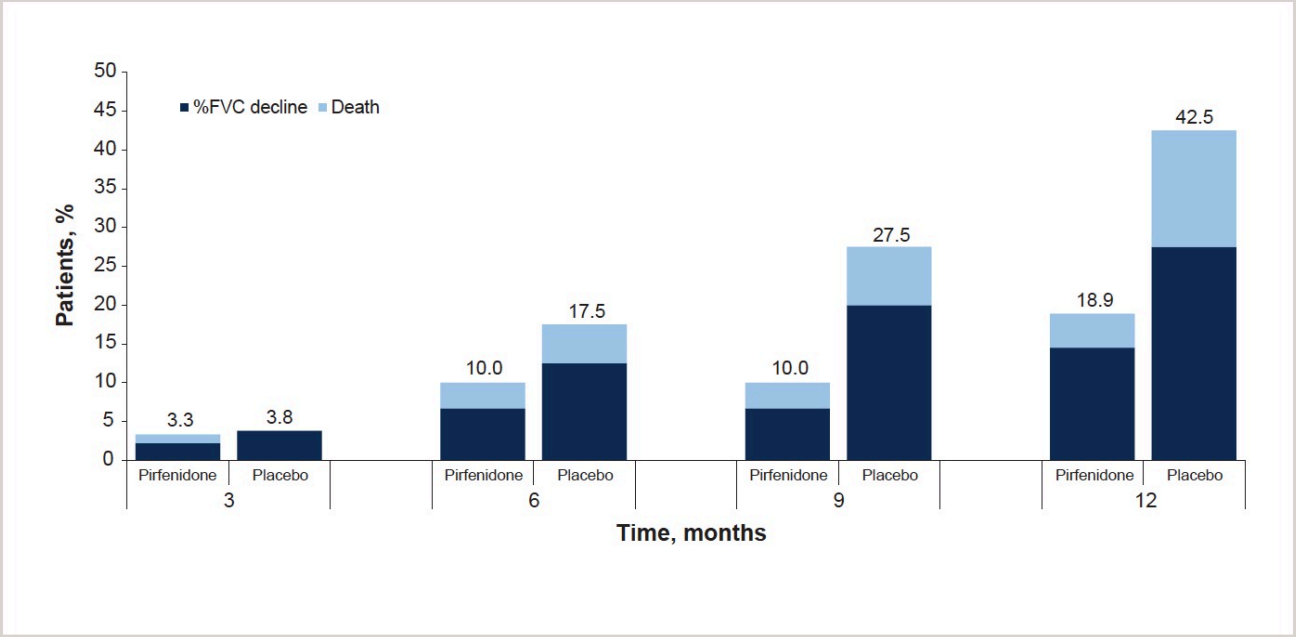
DEATHS AFTER HOSPITAL ADMISSIONS

	All-Cause hospitalizations		Respiratory Hospitalizations		Non-Respiratory Hospitalizations	
Patients with at least one Hospitalization	**Pirfenidone (n=106)**	**Placebo (n=115)**	**Pirfenidone (n=41)**	**Placebo (n = 74)**	**Pirfenidone (n=70)**	**Placebo (n=54)**
Deaths, n (%)	18 (17%)	37 (32%)	11 (27%)	34 (46%)	8 (11%)	9 (17%)
Data from subgroup analysis of patients with at least one hospitalization.						

Ley B et al., AJRCCM Articles in Press. Published on 04-May-2017 as 10.1164/rccm.201701-0091OC

EFFECT OF PIRFENIDONE ON ACM AND FVC IN IPF PATIENTS WITH LOW FVC AND/OR LOW DL_{CO}: ANALYSIS OF POOLED DATA FROM ASCEND AND CAPACITY (004/006)

Figure 2. Patients With %FVC < 50% and/or $\%DL_{CO}$ < 35% at Baseline Who Experienced ≥ 10% Absolute Decline in %FVC or Death



$\%DL_{CO}$, percent predicted diffusing capacity for carbon monoxide; %FVC, percent predicted forced vital capacity.

There was a 56% relative reduction in the proportion of patients with a ≥ 10% absolute decline in %FVC or death at 52 weeks in patients receiving pirfenidone vs. placebo (18.9% vs. 42.5%; P = 0.0038)

Nathan S J et al. Poster Presentation. ATS 2017, Washington, DC. Abstract A5390.

DOES IT WORK?

- How do I know if it is working for me?
  - We rely on study data
- How long will I have to take it?
  - RECAP lasted 7 years !

SIDE EFFECTS

- Photosensitivity
  - Use SPF 50 > whenever you go outside
  - Wide brim hat
  - Can possibly occur on exposure to strong artificial light

SIDE EFFECTS

SIDE EFFECTS

- GI toxicity
  - Nausea, vomiting, diarrhea
    - Must take with food
    - Divide pills at meals
    - Improves over time
  - Liver function abnormalities
- Dose adjustment and re-titration

QUESTIONS I'VE BEEN ASKED

- How long will I have to take this medication
- Why do I have to take 9 pills a day?
  - 3 pills/day after titration
- Can I take a lower dose?
- Can I take this drug if I have a disease related to IPF
  - Rheumatoid Arthritis?
- Can I take it with other drugs for IPF
  - Combo study with Nintedanib completed ‘
  - Prelim data very encouraging
    - GI toxicity was manageable

THANKS