PILOT™ Pulmonary Fibrosis Identification: Lessons for Optimizing Treatment

A NEW ERA in IPF:

Trials and Treatments

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Activity Staff Disclosures

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Educational Activity Learning Objective

Upon completion of this course, the participants should be able to:

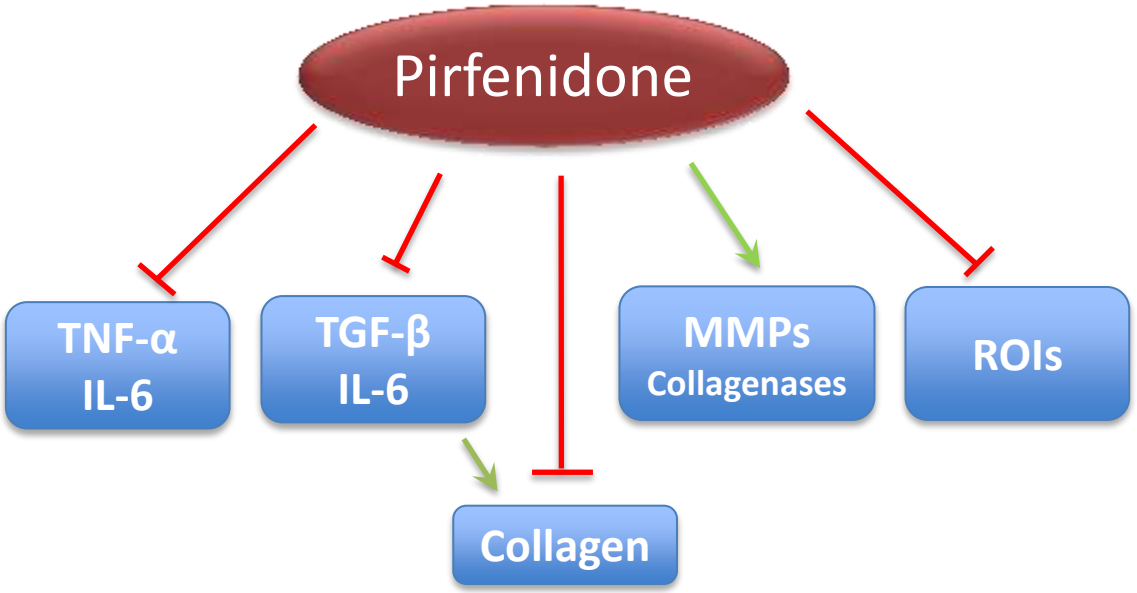
- Evaluate clinical trial data on available and emerging treatments for IPF and potential application to practice.

ASCEND

Pirfenidone

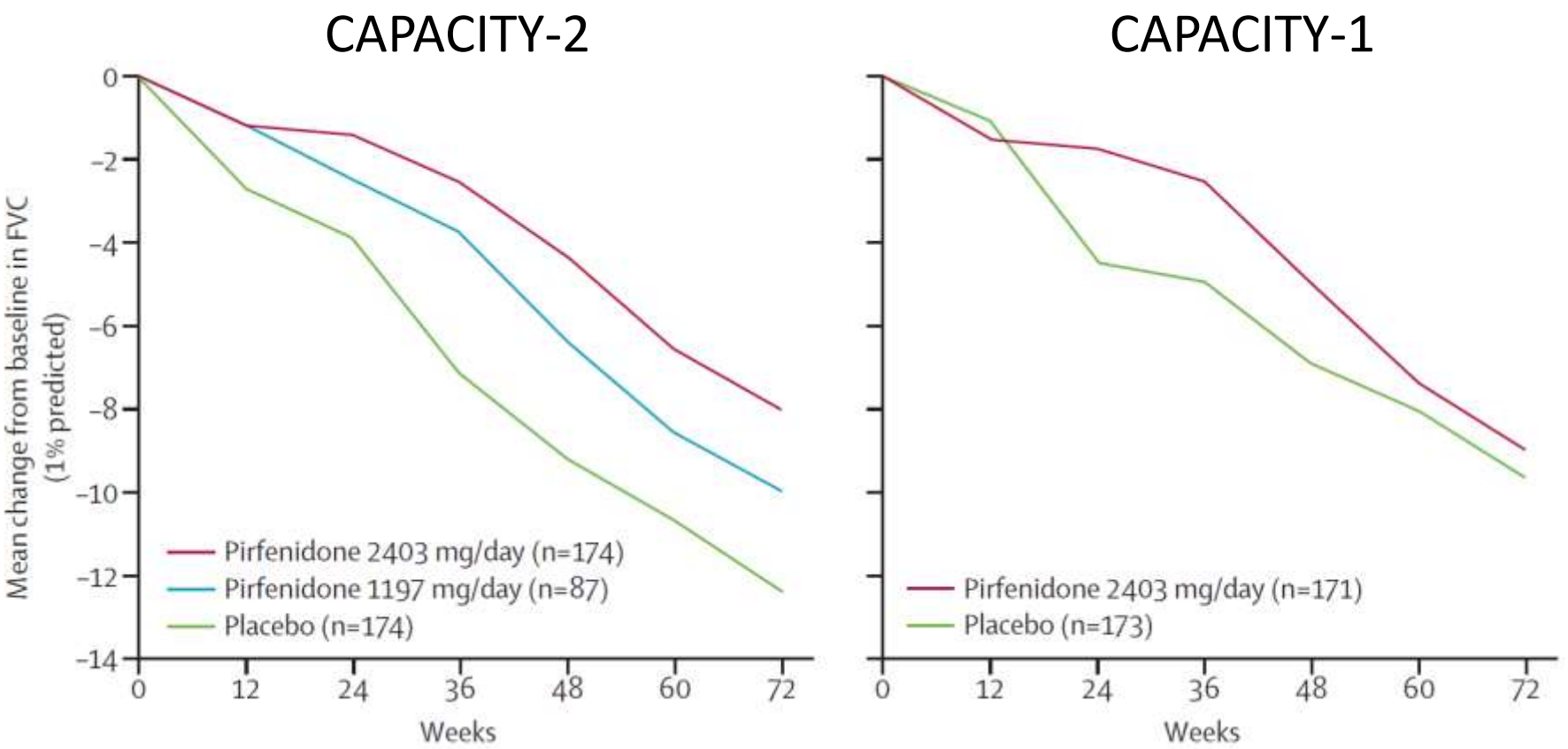
Possible Mechanisms of Pirfenidone Action

- Antifibrotic
- Molecular target unclear
- Active in several animal models of fibrosis (lung, liver, kidney)



Hilberg O, et al. *Clin Respir J.* 2012;6:131-143.

CAPACITY 2011



- One pirfenidone trial was positive, one was negative
- CAPACITY-1 placebo group FVC declined more slowly than expected

Noble P, et al. *Lancet.* 2011;377:1760-1769.

CAPACITY Endpoints

Endpoint	CAPACITY-2	CAPACITY-1
FVC	✓	X
Overall survival	X	X
Progression-free survival	✓	X
Six-minute walk distance	X	✓
DL_{CO}	X	X
Dyspnea	X	X
Exertional desaturation	X	X

Noble P, et al. *Lancet.* 2011;377:1760-1769.

ASCEND 2014

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

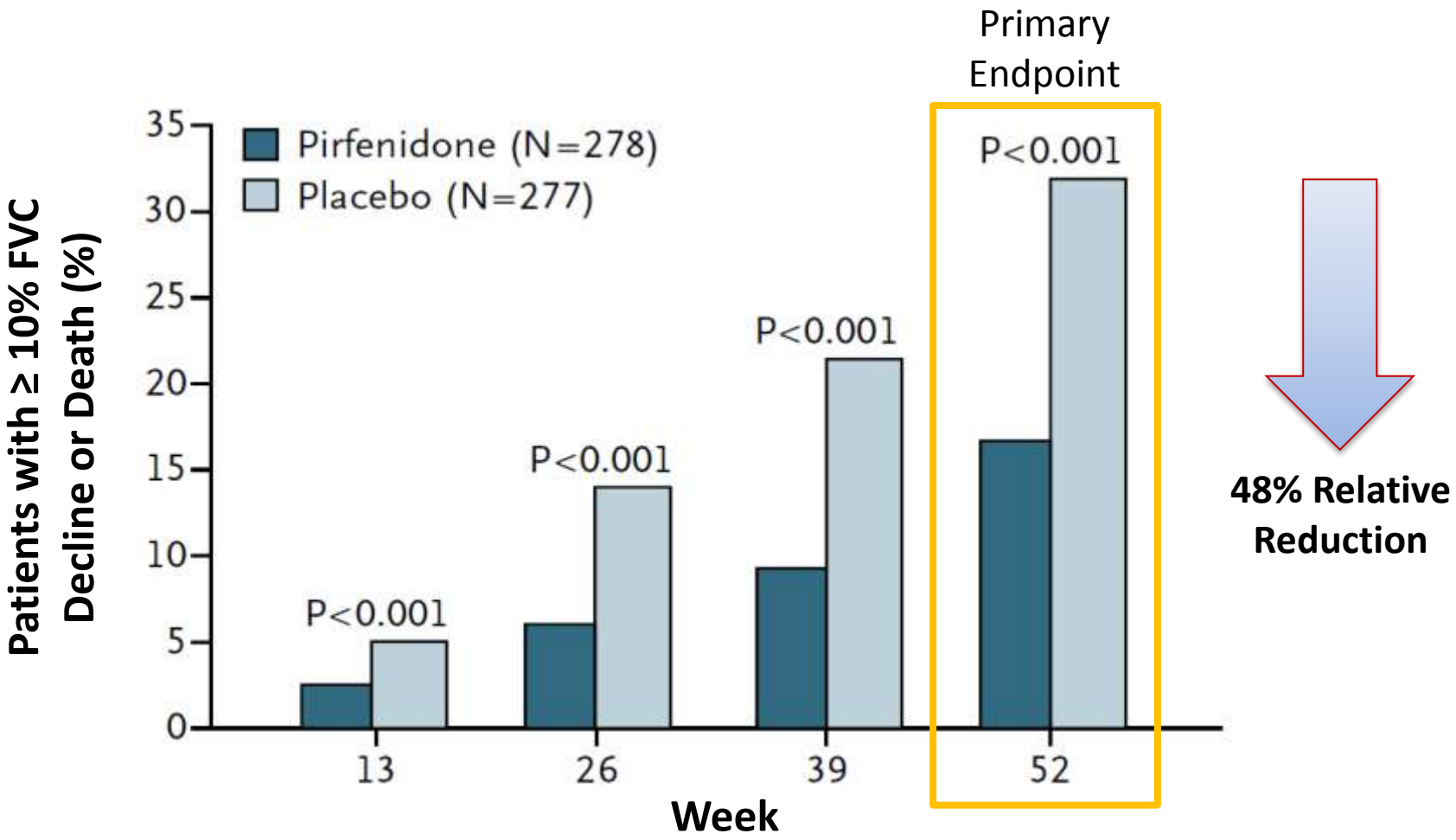
Talmadge E. King, Jr., M.D., Williamson Z. Bradford, M.D., Ph.D., Socorro Castro-Bernardini, M.D., Elizabeth A. Fagan, M.D., Ian Glaspole, M.B., B.S., Ph.D., Marilyn K. Glassberg, M.D., Eduard Gorina, M.D., Peter M. Hopkins, M.D., David Kardatzke, Ph.D., Lisa Lancaster, M.D., David J. Lederer, M.D., Steven D. Nathan, M.D., Carlos A. Pereira, M.D., Steven A. Sahn, M.D., Robert Sussman, M.D., Jeffrey J. Swigris, D.O., and Paul W. Noble, M.D., for the ASCEND Study Group*

ASCEND Study Design

- Subjects: 555 patients with IPF
- Treatment: oral pirfenidone (801 mg) or placebo 3 times daily
- Duration: 52 weeks
- Primary end point: change in FVC or death at week 52
- Secondary end points
  - 6-minute walk distance
  - Progression-free survival
  - Dyspnea
  - Death from any cause or from IPF

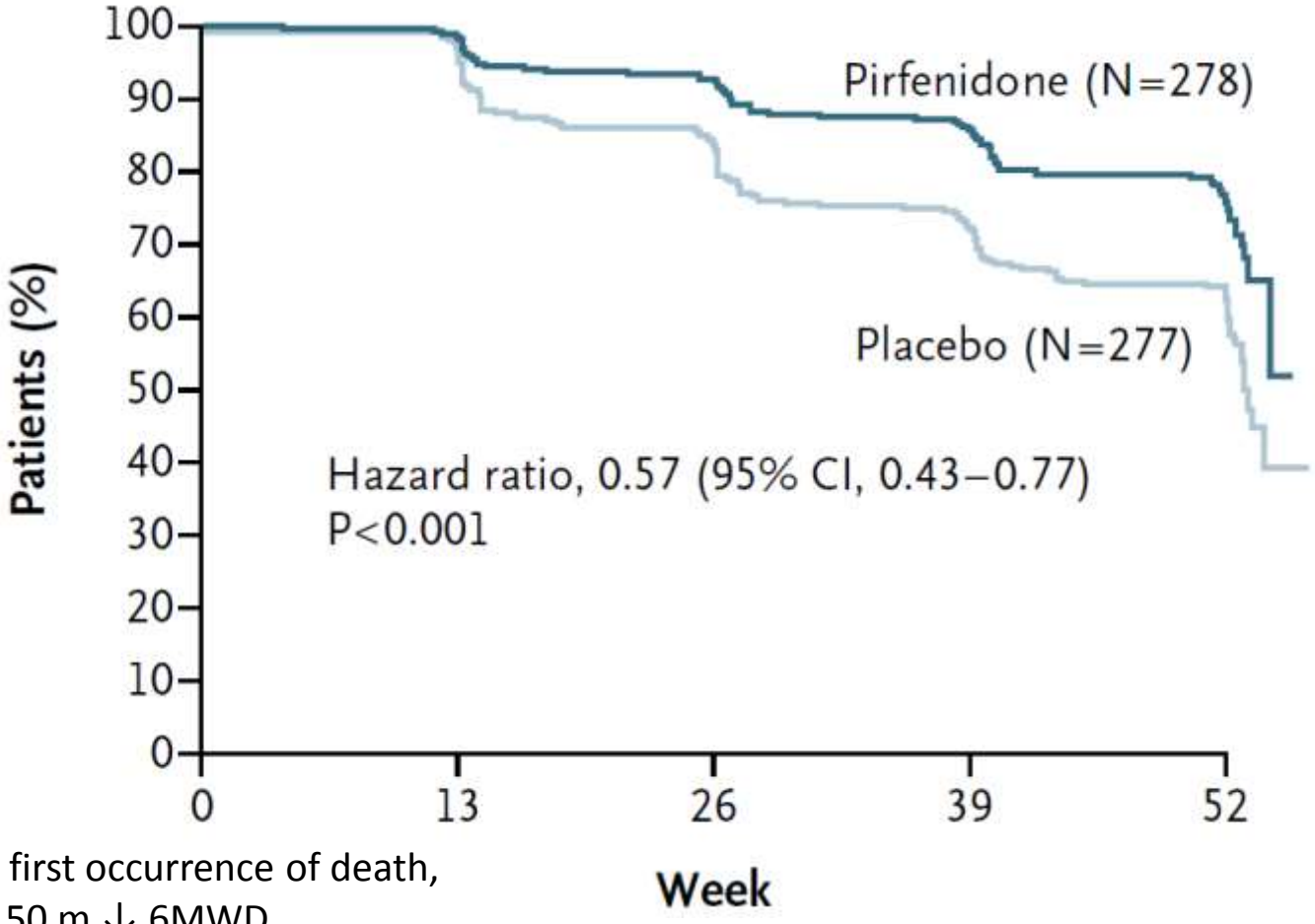
King TE, et al. *N Engl J Med.* 2014;370(22):2083-2092.

Primary ASCEND Endpoint Achieved



King TE, et al. *N Engl J Med.* 2014;370(22):2083-2092.

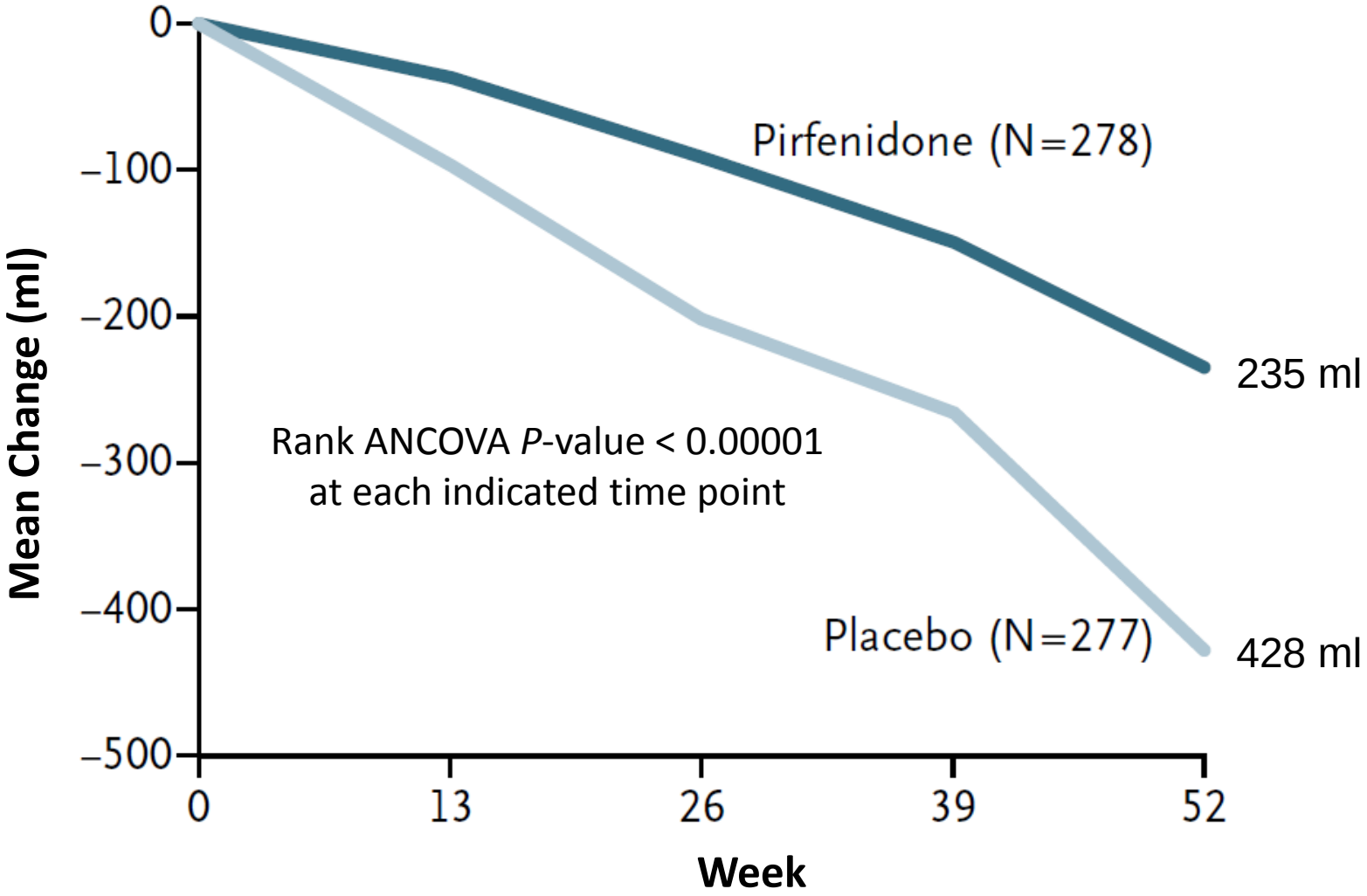
Pirfenidone Increased Progression-Free Survival*



*Progression is first occurrence of death, 10% ↓ FVC, or 50 m ↓ 6MWD

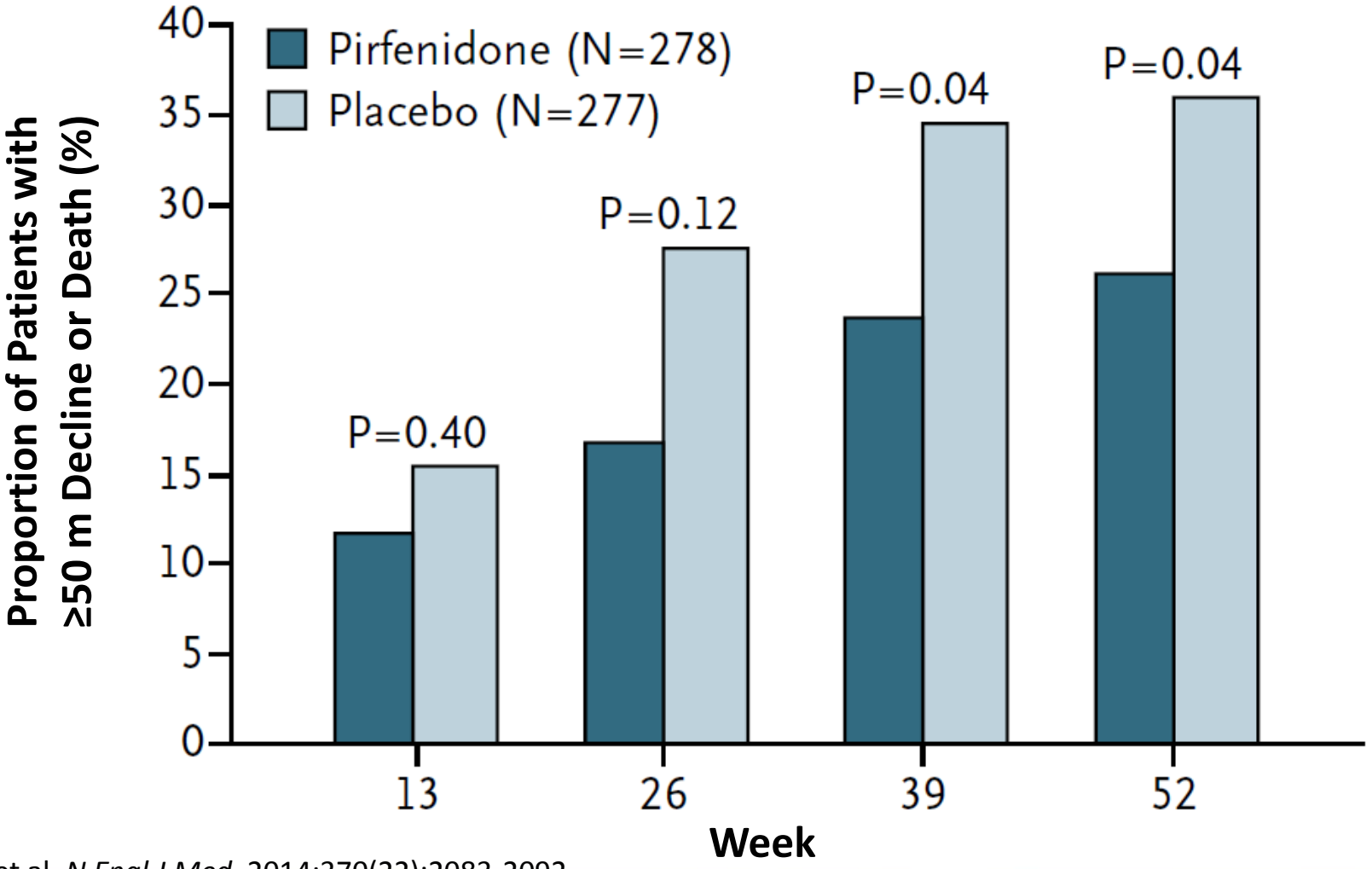
King TE, et al. *N Engl J Med.* 2014;370(22):2083-2092.

Pirfenidone Reduces Loss of FVC



King TE, et al. *N Engl J Med.* 2014;370(22):2083-2092.

More Pirfenidone Patients Maintain Walk Distance or Survive



King TE, et al. *N Engl J Med.* 2014;370(22):2083-2092.

ASCEND Adverse Events

Adverse Event	Pirfenidone (%) (N = 278)	Placebo (%) (N = 277)	Δ (%)
Nausea	36	13.4	22.6
Rash	28.1	8.7	19.4
Dyspepsia	17.6	6.1	11.5
Anorexia	15.8	6.5	9.3
GERD	11.9	6.5	5.4
Weight Loss	12.6	7.9	4.7
Insomnia	11.2	6.5	4.7
Dizziness	17.6	13	4.6
Vomiting	12.9	8.7	4.2
…	…	…	…
Dyspnea	14.7	17.7	-3
Cough	25.2	29.6	-4.4
IPF	9.4	18.1	-8.7

King TE, et al. *N Engl J Med.* 2014;370(22):2083-2092.

Pirfenidone Associated with Less Mortality

ASCEND and CAPACITY data

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

§ From randomization to 28 days after last dose
† Cox proportional hazard model
‡ Log-rank test

King TE, et al. *N Engl J Med.* 2014;370(22):2083-2092.

ASCEND Summary

- Treatment with pirfenidone for 52 weeks significantly reduced disease progression, as measured by
  - Changes in % predicted FVC *(P* < 0.001)
  - Changes in 6-minute walk distance (*P* = 0.04)
  - Progression-free survival (*P* < 0.001)
- Pirfenidone was generally safe and well tolerated

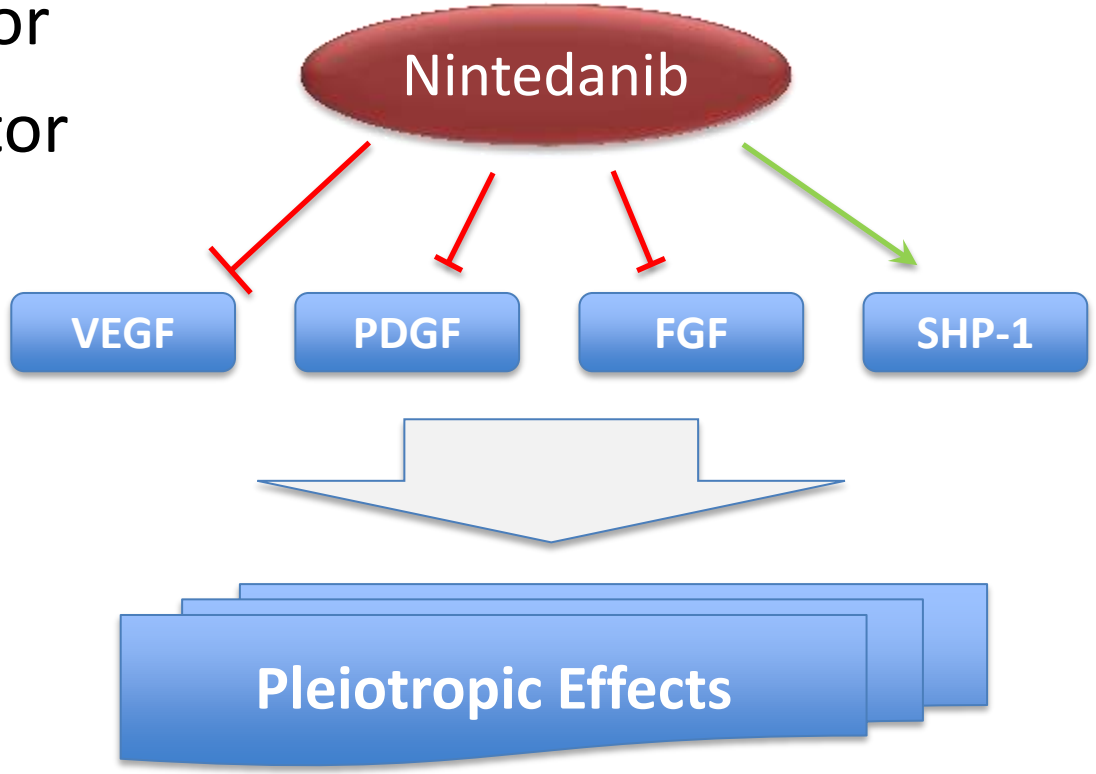
King TE, et al. *N Engl J Med.* 2014;370(22):2083-2092.

INPULSIS

Nintedanib

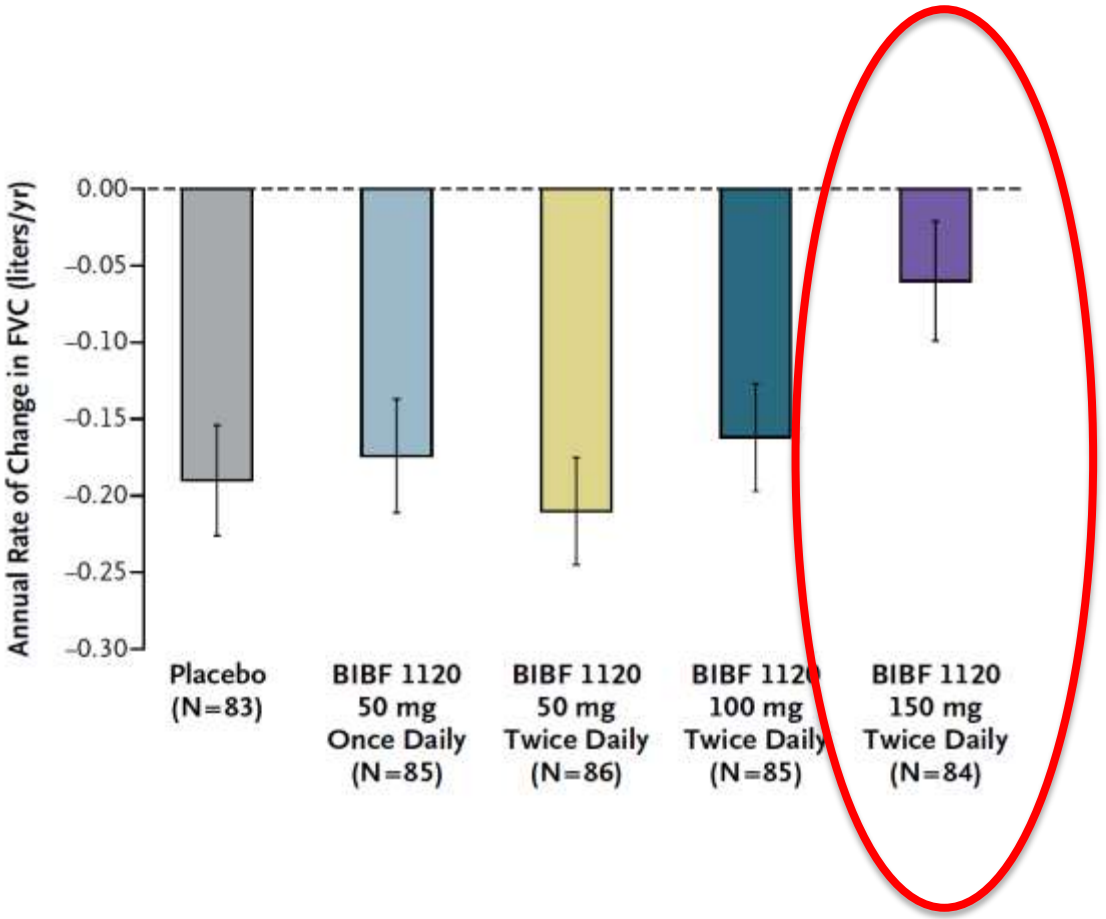
Possible Mechanisms of Nintedanib Action

- Triple kinase inhibitor
- Phosphatase activator
- Antiangiogenic, antitumor activity



Hilberg F, et al. *Cancer Res*. 2008;68(12):4774-4782.
Tai WT, et al. *J Hepatol*. 2014;61(1):89-97.

Nintedanib Showed Promise for FVC Endpoint



Richeldi L, et al. *N Engl J Med.* 2011:365;1079-1089.

INPULSIS 2014

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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., Kevin K. Brown, M.D., Ulrich Costabel, M.D., Vincent Cottin, M.D., Ph.D., Kevin R. Flaherty, M.D., David M. Hansell, M.D., Yoshikazu Inoue, M.D., Ph.D., Dong Soon Kim, M.D., Martin Kolb, M.D., Ph.D., Andrew G. Nicholson, D.M., Paul W. Noble, M.D., Moisés Selman, M.D., Hiroyuki Taniguchi, M.D., Ph.D., Michèle Brun, M.Sc., Florence Le Maulf, M.Sc., Mannaïg Girard, M.Sc., Susanne Stowasser, M.D., Rozsa Schlenker-Herceg, M.D., Bernd Disse, M.D., Ph.D., and Harold R. Collard, M.D., for the INPULSIS Trial Investigators*

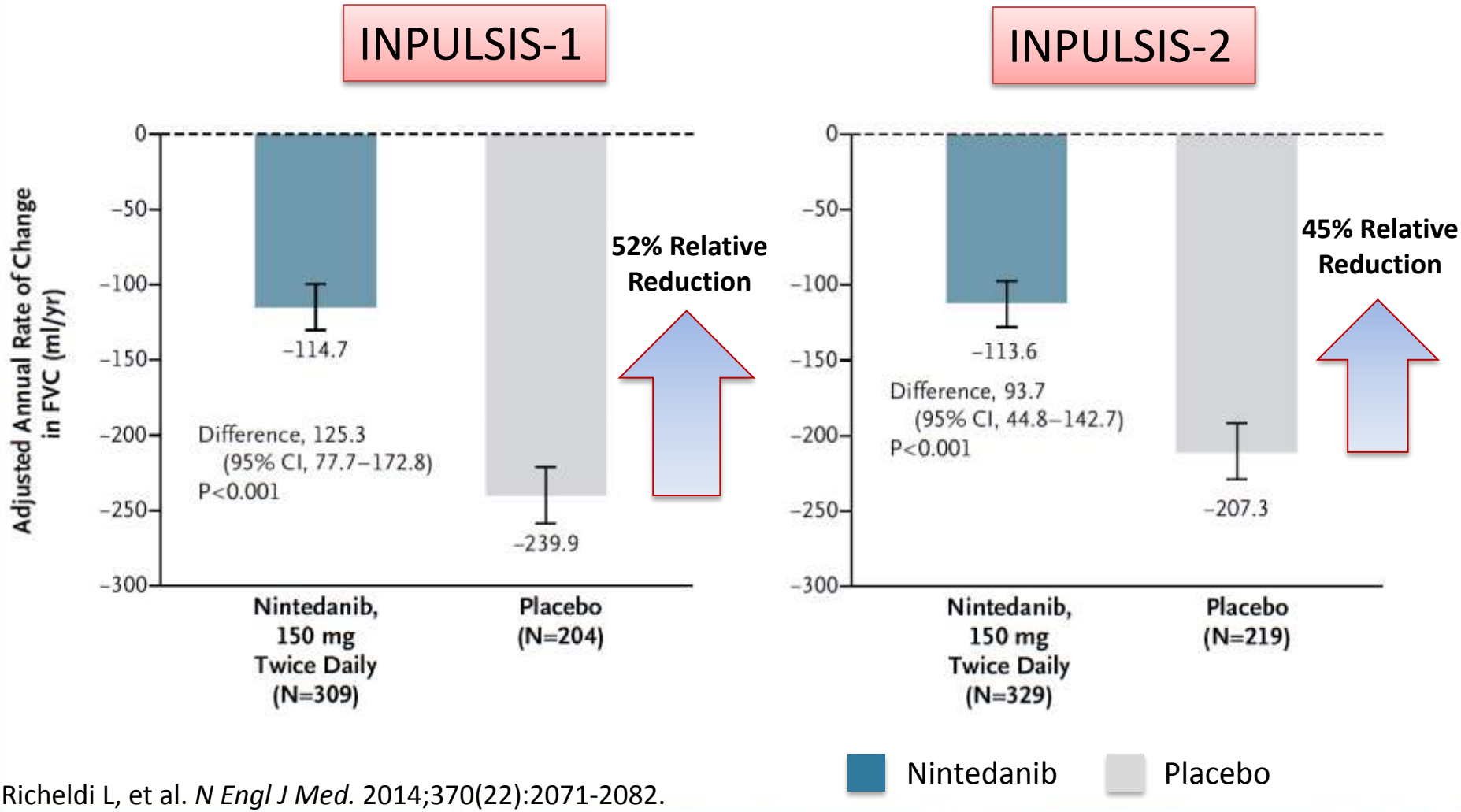
INPULSIS-1 and INPULSIS-2 Study Design

- Subjects: A total of 1066 patients with IPF
  Treatment: oral nintedanib (150 mg) or placebo twice daily (randomized in a 3:2 ratio)
- Duration: 52 weeks
- Primary end point: annual rate of decline in FVC
- Secondary end points
  - Time to the first acute exacerbation
  - Change from baseline in the total score on the St. George's Respiratory Questionnaire

Richeldi L, et al. *N Engl J Med.* 2014;370(22):2071-2082.

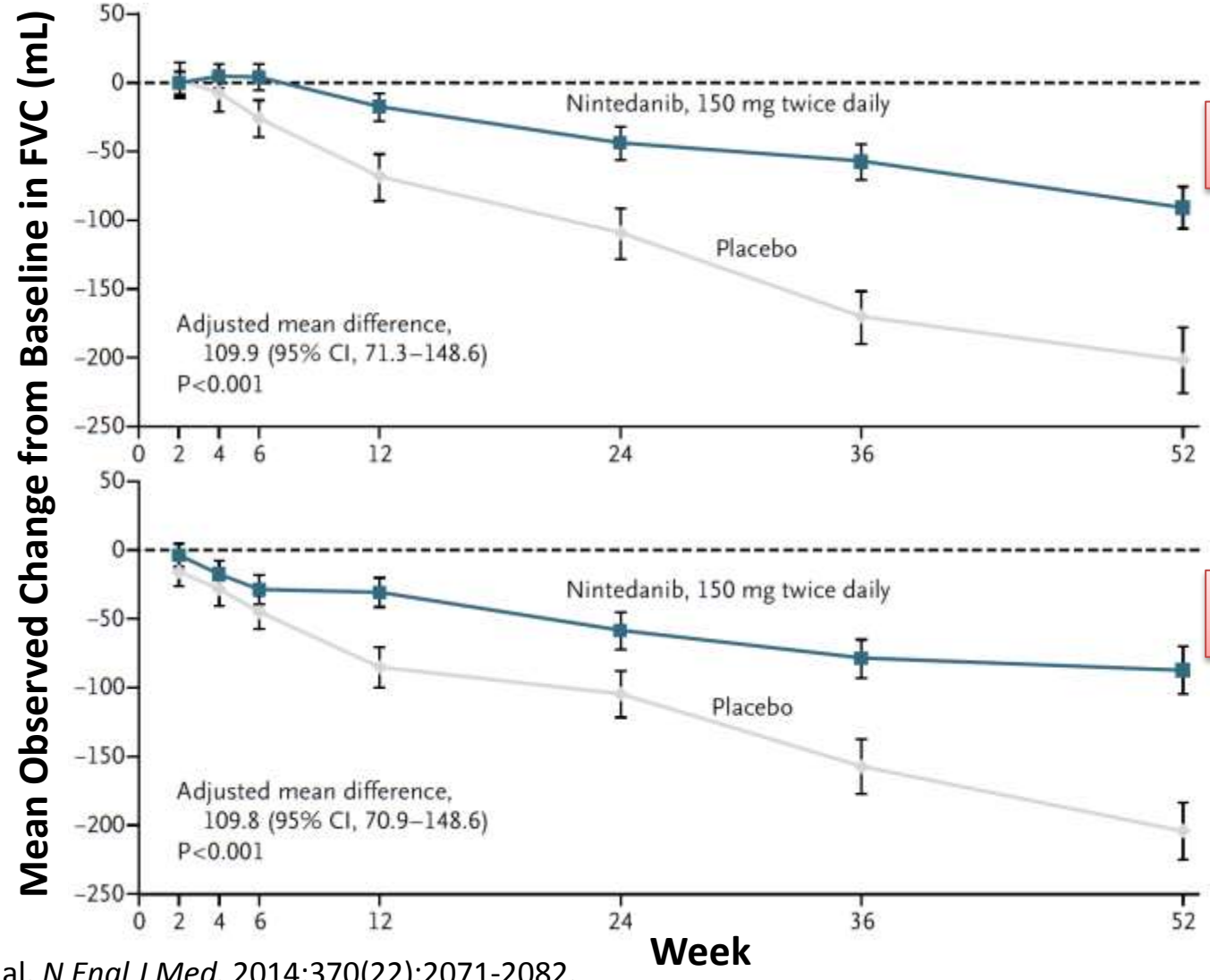
Primary INPULSIS Endpoint Achieved

Annual Rate of Change of FVC



Richeldi L, et al. *N Engl J Med.* 2014;370(22):2071-2082.

Nintedanib Reduces Loss of FVC

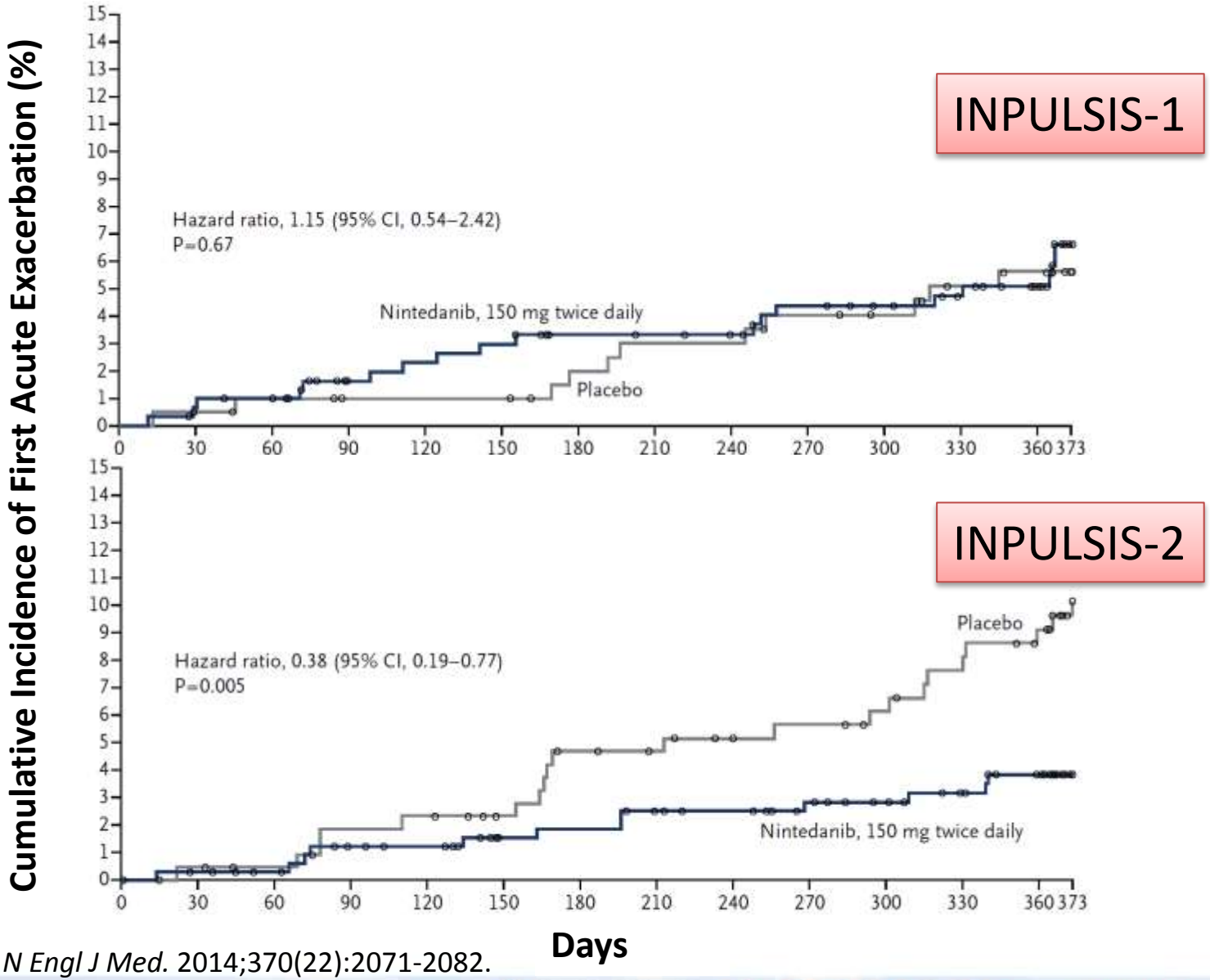


INPULSIS-1

INPULSIS-2

Richeldi L, et al. *N Engl J Med.* 2014;370(22):2071-2082.

Mixed Findings for Time to First Acute Exacerbation



Richeldi L, et al. *N Engl J Med.* 2014;370(22):2071-2082.

Common Nintedanib Adverse Events

Event	INPULSIS-1		INPULSIS-2	
	Nintedanib (n = 309)	Placebo (n = 204)	Nintedanib (n = 329)	Placebo (n = 219)
Any (%)	96	89	94	90
Diarrhea (%)	62	19	63	18
Nausea(%)	23	6	26	7

Richeldi L, et al. *N Engl J Med.* 2014;370(22):2071-2082.

INPULSIS Summary

- Nintedanib had significant benefit in adjusted annual rate of change in FVC
  - INPULSIS-1 $\Delta = 125.3$ ml $P < 0.001$
  - INPULSIS-2 $\Delta = 93.7$ ml $P < 0.001$
- Nintedanib had significant benefit in time to the first acute exacerbation in INPULSIS-2
  - INPULSIS-1 HR = 1.15 $P = 0.67$
  - INPULSIS-2 HR = 0.38 $P = 0.005$
- Significant difference in favor of nintedanib for the change from baseline in the total SGRQ score in INPULSIS-2 but not INPULSIS-1

Richeldi L, et al. *N Engl J Med.* 2014;370(22):2071-2082.

INPULSIS Conclusions

- Nintedanib reduced the decline in FVC, which is consistent with a slowing of disease progression
- Nintedanib was frequently associated with diarrhea, which led to discontinuation of the study medication in less than 5% of patients

Richeldi L, et al. *N Engl J Med.* 2014;370(22):2071-2082.

Clinical Trial Conclusions

- 2014 is potentially a watershed year in IPF
  - Pirfenidone (ASCEND) and nintedanib (INPULSIS) showed efficacy in mild/moderate IPF
    - FDA approved as Breakthrough Therapy
  - Still need data on advanced disease, combination therapy, long-term safety, adherence