Decline in forced vital capacity as a surrogate for mortality in patients with fibrosing interstitial lung diseases

Toby M Maher,[1] Elisabeth Bendstrup,[2] Michael Kreuter,[3] Fernando J Martinez,[4] Patricia J Sime,[5] Susanne Stowasser,[6] Florian Voss,[7] Christian Stock[7]

[1]Keck School of Medicine, University of Southern California, Los Angeles, California, USA; [2]Centre for Rare Lung Diseases, Department of Respiratory Diseases and Allergy, Aarhus University Hospital, Aarhus, Denmark; [3]Center for Interstitial and Rare Lung Diseases, Pneumology and Respiratory Care Medicine, Thoraxklinik, University of Heidelberg, Member of the German Center for Lung Research, Heidelberg, Germany; [4]Weill Cornell Medicine, New York, New York, USA; [5]Department of Internal Medicine, Virginia Commonwealth University, Richmond, Virginia, USA; [6]Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany; [7]Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany.

INTRODUCTION

- The use of surrogate endpoints in clinical trials enables the determination of meaningful treatment effects more efficiently than applying the endpoint of ultimate interest.
- Decline in forced vital capacity (FVC) is the preferred primary endpoint in trials evaluating new treatments in patients with ILDs,[1] but its validity as a surrogate for mortality is still debated.

AIM

- To assess decline in FVC as a surrogate for mortality using data from clinical trials of nintedanib in subjects with fibrosing ILDs.

METHODS

- Data were pooled from subjects who received nintedanib or placebo in the placebo-controlled periods of trials in IPF (TOMORROW[2], INPULSIS-1 and -2[3], Phase IIIb trial NCT01979952[4]), progressive fibrosing ILDs other than IPF (INBUILD[5]), and systemic sclerosis-associated ILD (SENSCIS[6]).
- Using joint models for longitudinal and time-to-event data,[7] we assessed the association between FVC % predicted and time to death over a 52-week period.
  - Both the annual rate of change in FVC % predicted and the current values of FVC % predicted were modelled longitudinally and estimates were applied as predictors in survival models through an association structure.
  - In a sensitivity analysis, the association between the rate of change in FVC % predicted and time to death over 52 weeks was assessed in subgroups by mean FVC <75% and ≥75% predicted at baseline.
  - The longitudinal sub-model was a random intercept and slope model that assumed separate linear slopes for subjects receiving nintedanib or placebo, and was adjusted for baseline FVC % predicted and effects of individual studies. All available FVC measurements were used and no imputation was performed. The time-to-event sub-model assumed a parametric (piecewise constant) baseline hazard function, an effect of the estimated FVC % predicted, and was adjusted for effects of individual studies.
- Subjects with ≥1 post-baseline FVC value and data on time to death were included. All FVC data collected up to 7 days after the end of treatment were included.

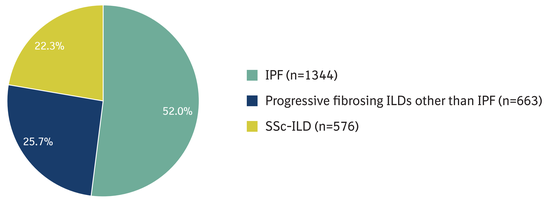
CONCLUSIONS

- Data from clinical trials of nintedanib in subjects with fibrosing ILDs demonstrate strong associations between FVC % predicted (both change and current value) and risk of death over 52 weeks.
- These results suggest that slowing FVC decline reduces the risk of death in subjects with fibrosing ILDs and support the use of FVC decline as a surrogate for mortality in clinical trials.

RESULTS

Subjects

- The pooled analysis included 2553 subjects (1380 treated with nintedanib, 1173 treated with placebo).



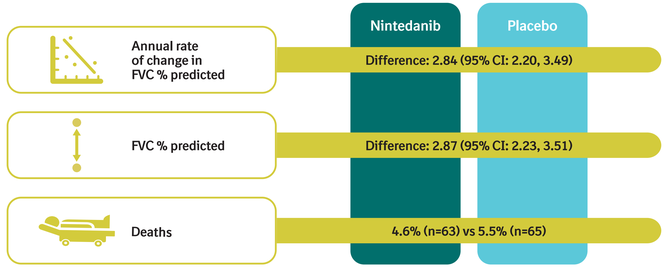
Based on all patients in pooled dataset (n=2583); 30 patients were excluded from this analysis as they did not have ≥1 post-baseline FVC value and time to death data.

Baseline characteristics

	Nintedanib (n=1399)	Placebo (n=1184)
Male, n (%)	863 (61.7)	687 (58.0)
Age, years, mean (SD)	63.8 (10.5)	63.3 (11.3)
White, n (%)	918 (65.6)	799 (67.5)
Body mass index, kg/m², mean (SD)	27.6 (4.8)	27.5 (5.1)
FVC, mL, mean (SD)	2584 (775)	2583 (809)
FVC, % predicted, mean (SD)	75.5 (17.7)	75.0 (17.6)
SpO_2, %, mean (SD)	96.3 (2.3)	96.2 (2.5)

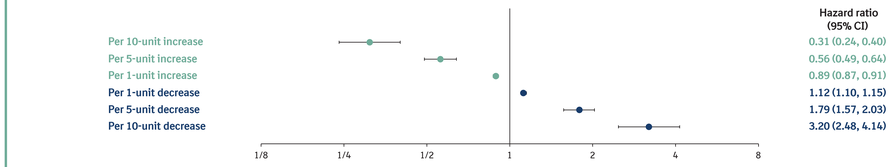
Based on all patients in pooled dataset (n=2583); 30 patients were excluded from this analysis as they did not have ≥1 post-baseline FVC value and time to death data.

Differences between the nintedanib and placebo groups over 52 weeks



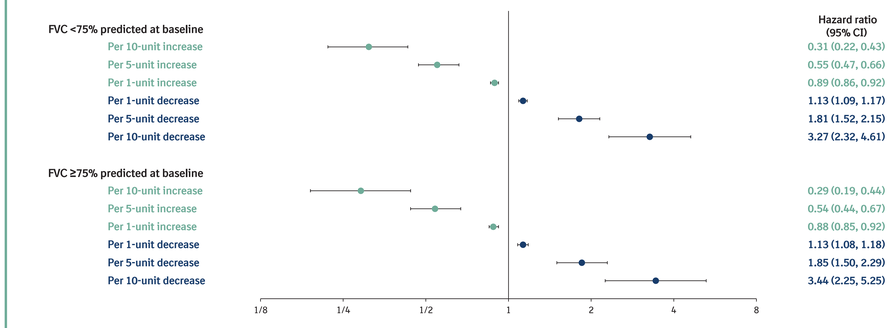
Associations between FVC % predicted and risk of death over 52 weeks

Associations between annual rate of change in FVC % predicted and risk of death over 52 weeks



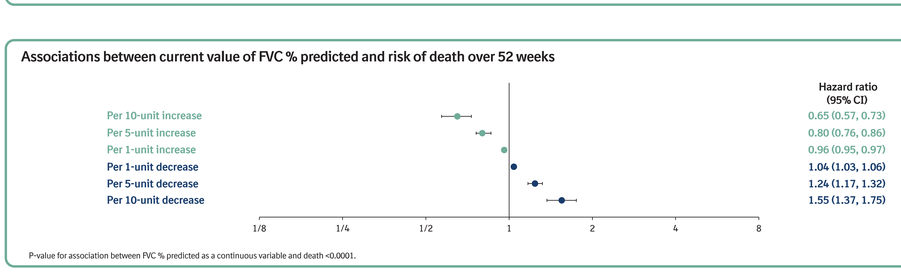
P-value for association between rate of change in FVC % predicted as a continuous variable and death <0.0001.

Associations between annual rate of change in FVC % predicted and risk of death over 52 weeks in subgroups by FVC % predicted at baseline



n=722 in the nintedanib group and n=630 in the placebo group had FVC <75% predicted at baseline; n=658 in the nintedanib group and n=543 in the placebo group had FVC ≥75% predicted at baseline.
P-value for association between rate of change in FVC % predicted as a continuous variable and death <0.0001.

Associations between current value of FVC % predicted and risk of death over 52 weeks



P-value for association between FVC % predicted as a continuous variable and death <0.0001.

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