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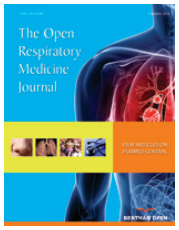

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Supplementary Material

Effects of Nintedanib on Quantitative Lung Fibrosis Score in Idiopathic Pulmonary Fibrosis

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SUPPORTIVE/SUPPLEMENTARY MATERIAL

Appendix S1. Calculation of the Quantitative Lung Fibrosis (QLF) Score

To compute the QLF panel within a region of interest [1, 2]:

(1) Each pixel from a 4-by-4 grid within a segmented lung is sampled.

(2) Texture features from a denoised CT image for each sampled pixel are calculated.

(3) A previously built Support Vector Machine (SVM) classifier predicts reticulation of each pixel using the selected texture features. Features from denoised images are used to predict fibrotic reticulation or non-fibrotic reticulation, such as normal lung, ground glass, and honeycomb.

(4) The QLF score percentage (reticulation with architectural distortion) by lobes and lungs from the segmented regions is calculated using this formula:

$$QLF = \frac{Counts\ of\ pixels\ classified\ reticular\ pattern}{Total\ counts\ of\ grid\ sample}$$

(5) The QLF volume by lobes and lungs from the segmented regions is calculated:

$$QLF\ volume = percent\ QLF \times lung\ volume,\ where\ QLF\ is\ in\ range\ 0.0\ to\ 1.0$$

Example HRCT scans illustrating a change in QLF score (%) of 2.7

REFERENCES

[1] Kim HG, Tashkin DP, Clements PJ, et al. A computer-aided diagnosis system for quantitative scoring of extent of lung fibrosis in scleroderma patients. Clin Exp Rheumatol 2010;28(5 Suppl 62):S26–35.

[2] Kim HJ, Brown MS, Chong D, et al. Comparison of the quantitative CT imaging biomarkers of idiopathic pulmonary fibrosis at baseline and early change with an interval of 7 months. Acad Radiol 2015;22:70–80.

Appendix S2. Health-Related Quality of Life

At baseline, mean (SD) SGRQ total scores were 35.8 (17.5) and 44.4 (18.5) in the nintedanib and placebo groups, respectively. Adjusted mean (SE) absolute changes from baseline in SGRQ total score at month 6 were −2.24 (1.68) in the nintedanib group (n=55) and −2.19 (1.70) in the placebo group (n=53) (difference −0.05 [95% CI: −4.89, 4.79]. At baseline, mean (SD) UCSD-SOBQ scores were 25.4 (19.9) and 42.3 (24.6) in the nintedanib and placebo groups, respectively. Adjusted mean (SE) absolute changes from baseline in UCSD-SOBQ score at month 6 were 3.42 (2.16) in the nintedanib group (n=53) and −1.46 (2.19) in the placebo group (n=50) (difference of 4.89 [95% CI: −1.47, 11.25]).

Adjusted mean (SE) absolute changes from baseline in SGRQ total score at month 12 were −3.12 (2.14) in patients who received nintedanib for 12 months (n=55) and −1.13 (2.12) in patients who received placebo for ≥6 months followed by open-label nintedanib (n=53) (difference of −1.99 [95% CI: −8.17, 4.19]). Adjusted mean (SE) absolute changes from baseline in UCSD-SOBQ score at month 12 were 4.43 (2.45) in patients who received nintedanib for 12 months (n=53) and 1.29 (2.38) in patients who received placebo followed by nintedanib (n=50) (difference of 3.15 [95% CI: −4.01, 10.31]).

Table S1. Serious adverse events reported (irrespective of causality) over 6 months of randomized treatment*.

	Nintedanib (n=56)	**Placebo (n=57)**
Any serious Adverse Events	4 (7.1)	7 (12.3)
Progression of IPF*	0 (0.0)	3 (5.3)
Pneumonia	0 (0.0)	2 (3.5)
Hypoxia	1 (1.8)	0 (0.0)
Intestinal infarction	1 (1.8)	0 (0.0)
Lyme disease	1 (1.8)	0 (0.0)
Spinal column stenosis	1 (1.8)	0 (0.0)
Spinal osteoarthritis	1 (1.8)	0 (0.0)
Completed suicide	0 (0.0)	1 (1.8)
Delirium	0 (0.0)	1 (1.8)
Flank pain	0 (0.0)	1 (1.8)
Haemoptysis	0 (0.0)	1 (1.8)
Musculoskeletal pain	0 (0.0)	1 (1.8)
Osteoarthritis	0 (0.0)	1 (1.8)
Pleural effusion	0 (0.0)	1 (1.8)
Respiratory failure	0 (0.0)	1 (1.8)

*Adverse events with onset after the first dose and up to 28 days after the last dose of study drug. Data shown are n (%) of patients in whom ≥1 such event was reported. A serious adverse event was defined as an adverse event that resulted in death, was immediately life-threatening, resulted in persistent or clinically significant disability or incapacity, required or prolonged hospitalization, was related to a congenital anomaly or birth defect, or was deemed serious for any other reason. *Corresponds to Medical Dictionary for Regulatory Activities term 'IPF', which included disease worsening and acute exacerbations of IPF. IPF, idiopathic pulmonary fibrosis.

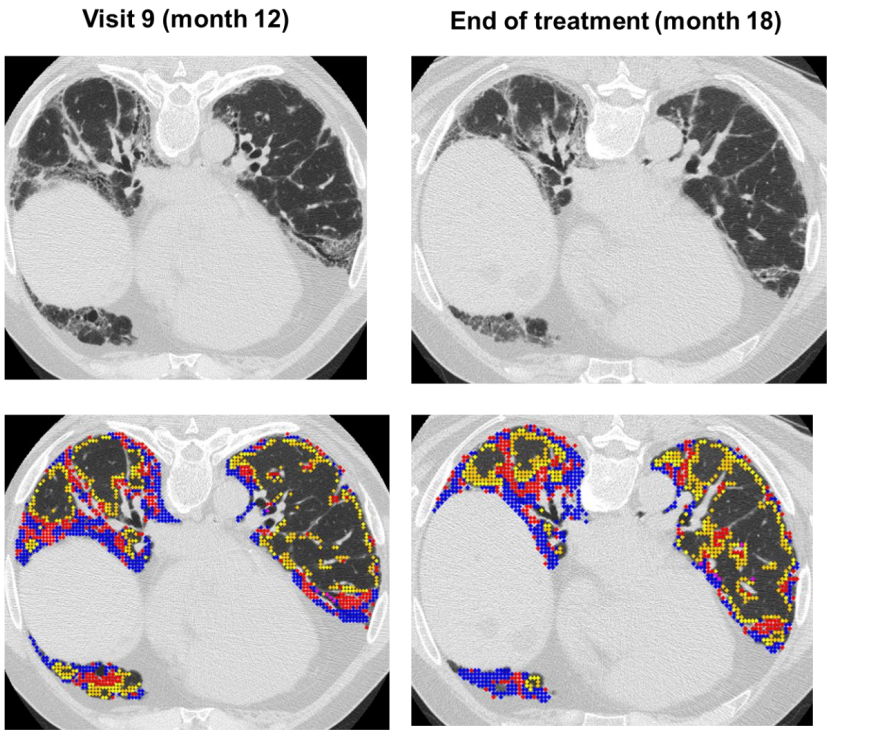

Fig. S1 contd.....

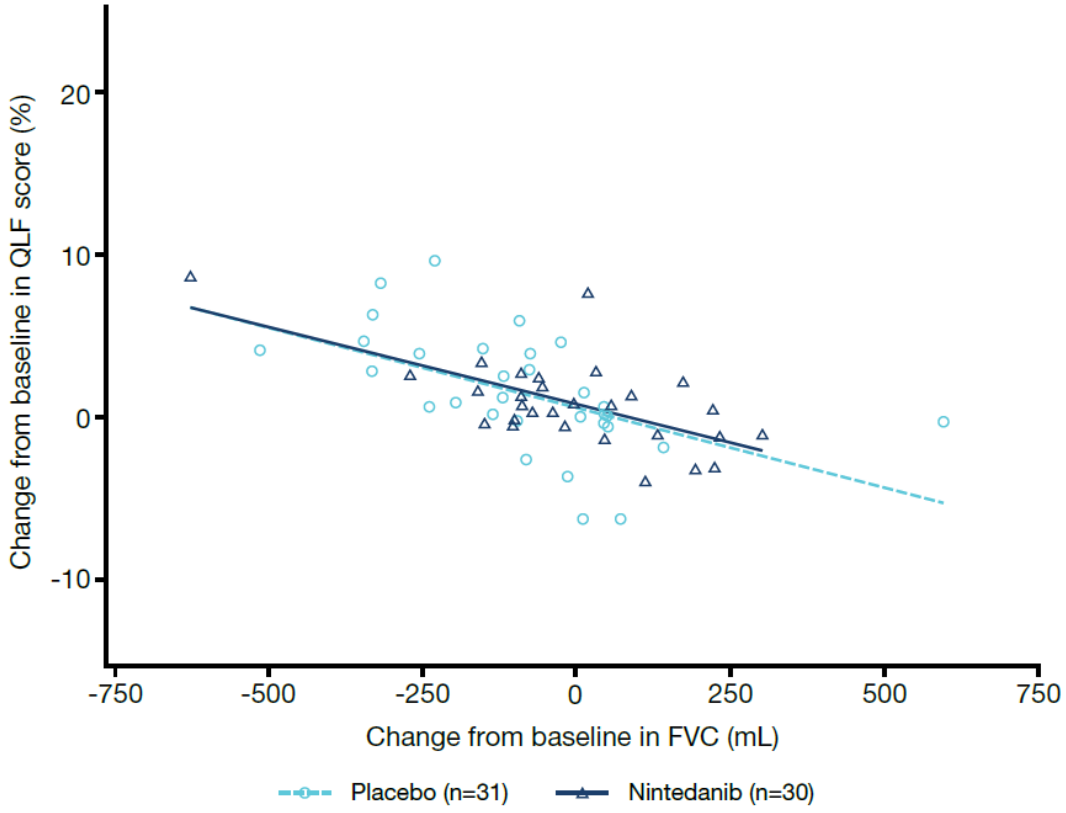

Fig. (S1). Correlation between change from baseline in QLF score (%) and change from baseline in FVC (mL) at month 6

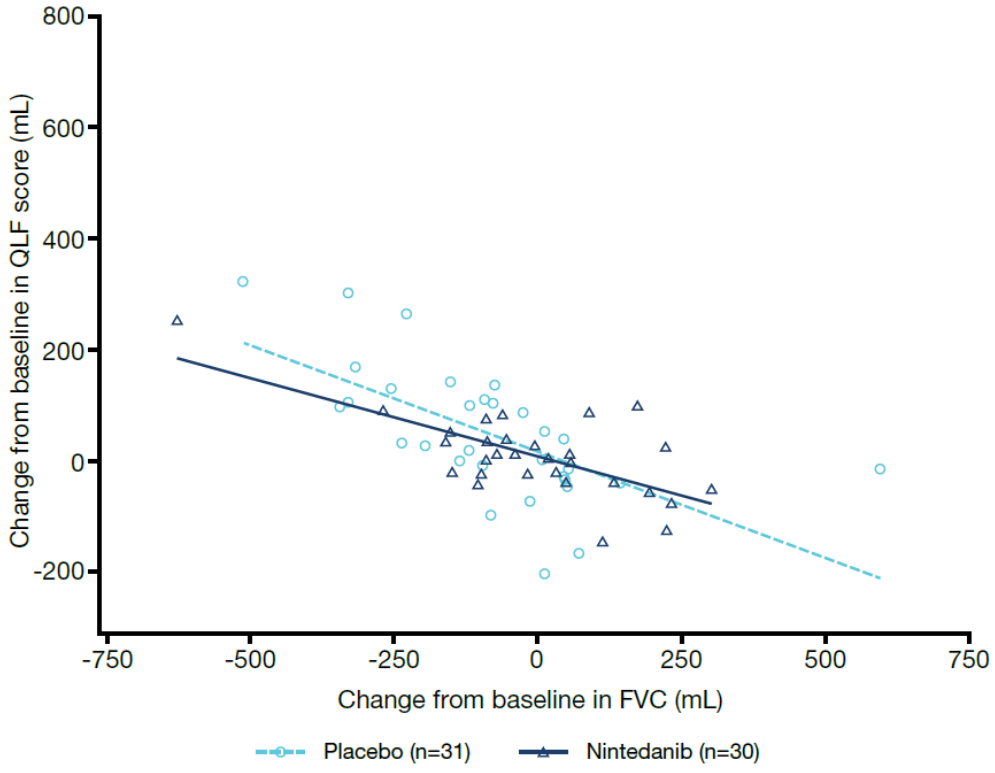

Fig. (S2). Correlation between change from baseline in QLF score (mL) and change from baseline in FVC (mL) at month 6

Table S2. Adverse events leading to death reported (irrespective of causality) over 6 months of randomized treatment*

	Nintedanib (n=56)	**Placebo (n=57)**
Any fatal Adverse Events	1 (1.8)	4 (7.0)
Intestinal infarction	1 (1.8)	0
Progression of IPF*	0	1 (1.8)
Pleural effusion	0	1 (1.8)
Respiratory failure	0	1 (1.8)
Suicide	0	1 (1.8)

*Adverse events with onset after the first dose and up to 28 days after the last dose of study drug. Data shown are n (%) of patients. *Corresponds to Medical Dictionary for Regulatory Activities term 'IPF', which included disease worsening and acute exacerbations of IPF. IPF, idiopathic pulmonary fibrosis.