Poster

Effects of nintedanib on circulating biomarkers in subjects with progressive fibrosing interstitial lung diseases (ILDs)

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Effects of nintedanib on circulating biomarkers in subjects with progressive fibrosing interstitial lung diseases (ILDs)

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INTRODUCTION

- In the INBUILD trial in subjects with progressive fibrosing ILDs other than idiopathic pulmonary fibrosis (IPF), nintedanib slowed the rate of decline in forced vital capacity (FVC) compared with placebo.[1]
- Non-clinical studies have shown that nintedanib has anti-fibrotic effects and anti-inflammatory effects that inhibit the progression of pulmonary fibrosis.[2]

AIM

- To evaluate the effects of nintedanib on circulating biomarkers of epithelial injury, inflammation and extracellular matrix (ECM) turnover in the INBUILD trial.

METHODS

Trial design[1]

- Subjects had a physician-diagnosed ILD other than IPF and an extent of fibrosis on HRCT >10%. Subjects met criteria for ILD progression within the prior 24 months, based on worsening of FVC, abnormalities on HRCT, or symptoms, despite management deemed appropriate in clinical practice.
- Subjects were randomized to receive nintedanib or placebo, stratified by fibrotic pattern on HRCT (usual interstitial pneumonia-like fibrotic pattern or other fibrotic patterns).

Analyses

- We derived adjusted fold changes from baseline in biomarkers of epithelial injury, inflammation and ECM turnover:

Markers of epithelial injury	Markers of inflammation	Markers of ECM turnover		
KL-6	CRP	BGM	C6M	CRPM
SP-D	IL-8	C1M	EL-NE	Pro-C3
CA-125	s-ICAM	C3M	MMP-7	Pro-C6
CA19-9		C5M		

BGM, biglycan degraded by MMP; C1M, collagen 1 degraded by MMP-2/9/13; C3M, collagen 3 degraded by MMP-9; C5M, collagen 5 degraded by MMP-2/9; C6M, collagen 6 degraded by MMP-2/9; EL-NE, neutrophil-specific elastin fragments; CRP, C-reactive protein; CRPM, C-reactive protein degraded by MMP-1/8; KL-6, Krebs von den Lungen-6; IL-8, interleukin-8; MMP-7, matrix metalloproteinase 7; Pro-C3, N-terminal propeptide of type III collagen; Pro-C6, N-terminal propeptide of type VI collagen; s-ICAM, soluble intercellular adhesion molecule; SP-D, surfactant protein D.

- Analyses were based on linear mixed models for repeated measures. The models analysing absolute changes from baseline in log-transformed biomarker values included fixed categorical effects for treatment at each visit, and fixed continuous effects of baseline value of the biomarker at each visit (for all biomarkers except for C3M, CRPM, pro-C3, pro-C6). The models analysing log-transformed biomarker values (including the baseline timepoint) included fixed categorical effects of treatment at each visit and batch (for C3M, CRPM, pro-C3, pro-C6). Both models were adjusted for the categorical covariates sex, race, ILD diagnostic group, and inclusion criterion for ILD progression, and the continuous covariate age.
- Data were $\log_{10}$ transformed before analysis and estimates of change from baseline were back-transformed.

CONCLUSIONS

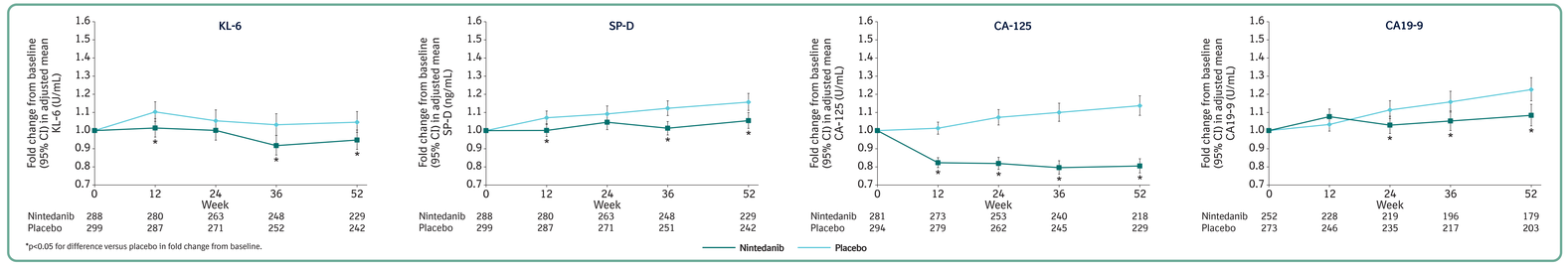
- These analyses of data from the INBUILD trial suggest that nintedanib reduced circulating levels of markers of epithelial injury in subjects with progressive fibrosing ILDs.
- Effects of nintedanib on changes in these biomarkers were observed as early as week 12 of treatment.

RESULTS

- A total of 663 subjects received trial medication (332 nintedanib, 331 placebo). Mean (SD) age was 65.8 (9.8) years and FVC was 69.0 (15.6) % predicted.

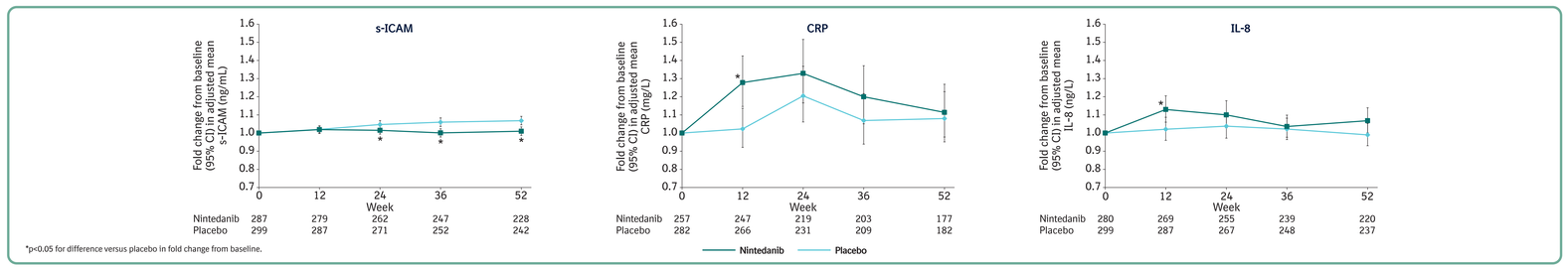
Markers of epithelial injury

- Over 52 weeks, there were treatment-related decreases in fold changes from baseline in KL-6, SP-D, CA-125 and CA19-9 in subjects who received nintedanib versus placebo. The most pronounced difference between nintedanib and placebo was in CA-125.



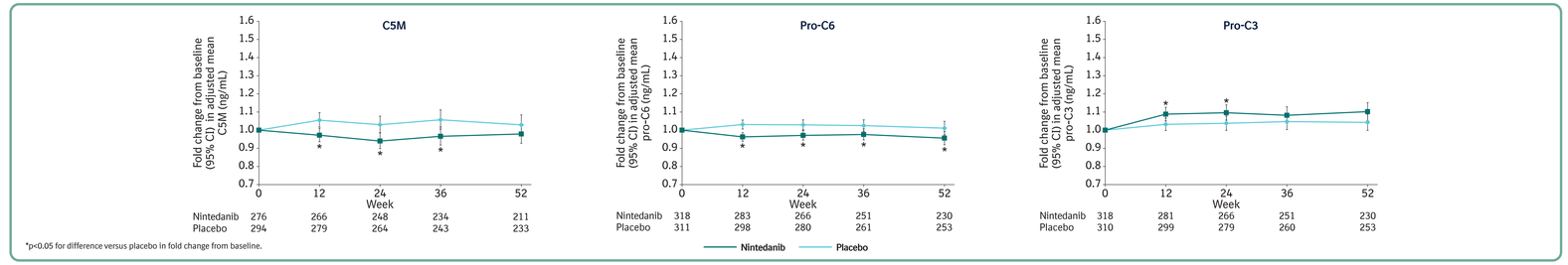
Markers of inflammation

- A small decrease in the change from baseline in s-ICAM was observed in subjects who received nintedanib versus placebo. Increases in fold changes from baseline in CRP and IL-8 were observed in subjects who received nintedanib versus placebo at week 12 but not at week 52.



Markers of ECM turnover

- Small decreases in fold changes from baseline in C5M and pro-C6 were observed in subjects who received nintedanib versus placebo. A small increase in fold change from baseline in pro-C3 was observed in subjects who received nintedanib versus placebo at weeks 12 and 24, but not at week 52. No notable trends were observed for the other markers of ECM turnover.



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2. Wollin L et al. Eur Respir J 2019;54:1900161.

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