Efficacy and safety of nintedanib in patients with idiopathic pulmonary fibrosis (IPF): subgroup analyses by TORVAN stage

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Introduction

- IPF is a progressive fibrosing interstitial lung disease (ILD) characterized by loss of lung function and early mortality.[1]
- Patients with IPF frequently have comorbidities that affect survival.[2,3]
- The TORVAN index and staging system was developed to predict mortality in patients with IPF based on age, FVC, DLco and common comorbidities.[3]

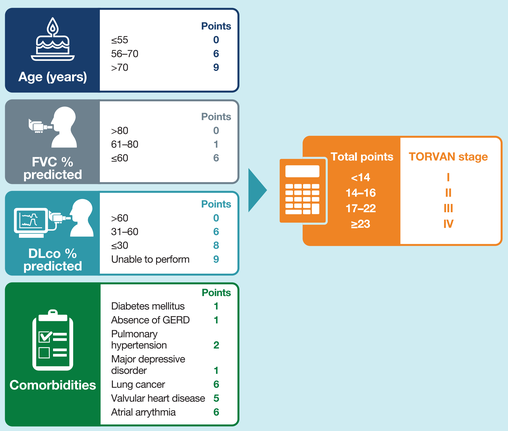
Aim

- To assess the efficacy and safety of nintedanib in patients with IPF at different TORVAN stages.

Methods

- Data were pooled from three international placebo-controlled trials of nintedanib: the TOMORROW trial[4] and the two INPULSIS trials.[5]
- Points were assigned to age, FVC % predicted, DLco % predicted, and certain comorbidities at baseline to generate a total score that classified patients as at TORVAN stage I, II, III, or IV:

Calculation of TORVAN stage[3]



- In post-hoc analyses, we analyzed the following over 52 weeks in subgroups by TORVAN stage (I, II, or III/IV) at baseline:
  - Rate of decline in FVC (mL/year)
  - Time to disease progression (absolute decline in FVC ≥10% predicted or death)
  - Time to first investigator-reported acute exacerbation
  - Change in St. George's Respiratory Questionnaire (SGRQ) total score (a measure of health-related quality of life)[6]
  - Adverse events
- Interaction p-values were calculated to assess potential heterogeneity in the treatment effect of nintedanib versus placebo across the subgroups. No adjustment for multiplicity was made.

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https://www.usscicomms.com/respiratory/ATS2020

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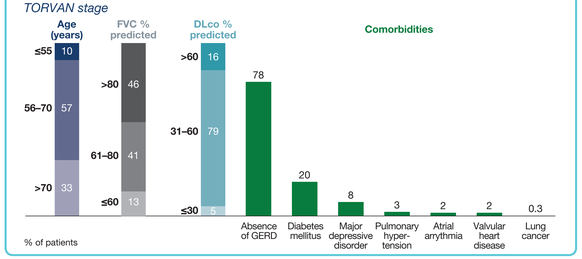
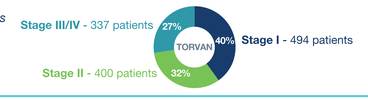
Results

Patients

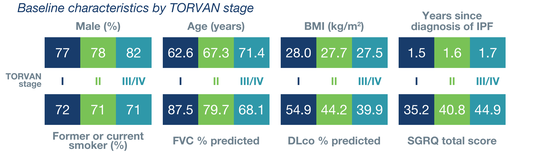
Proportions of patients in age, FVC and DLco ranges and with comorbidities used to calculate TORVAN stage



TORVAN stages



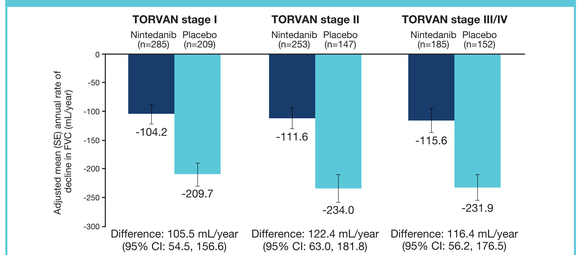
Baseline characteristics by TORVAN stage



Annual rate of decline in FVC

- In the placebo group, the annual rate of decline in FVC was similar across subgroups by TORVAN stage. The effect of nintedanib on reducing the annual rate of decline in FVC was consistent across the subgroups (Figure 1).

Figure 1. *Annual rate of decline in FVC (mL/year) by TORVAN stage at baseline*



Treatment-by-time-by-subgroup interaction p=0.92

Disease progression and acute exacerbations

- The effect of nintedanib on disease progression (absolute decline in FVC ≥10% predicted or death) was consistent across the subgroups by TORVAN stage (Table).
- In both treatment groups, the proportion of patients with acute exacerbations increased with increasing TORVAN stage at baseline. Numerically smaller proportions of patients treated with nintedanib than placebo had acute exacerbations in all subgroups by TORVAN stage (Table).

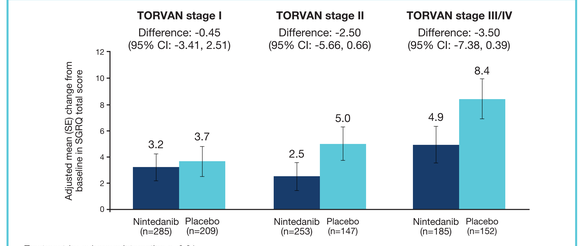
Table. *Time to disease progression and first acute exacerbation over 52 weeks by TORVAN stage at baseline*

	TORVAN stage I		TORVAN stage II		TORVAN stage III/IV	
	Nintedanib (n=285)	Placebo (n=209)	Nintedanib (n=253)	Placebo (n=147)	Nintedanib (n=185)	Placebo (n=152)
Patients with disease progression, n (%)	74 (26.0)	80 (38.3)	73 (28.9)	60 (40.8)	50 (27.0)	68 (44.7)
Hazard ratio (95% CI)	0.65 (0.48, 0.90)		0.64 (0.45, 0.90)		0.55 (0.38, 0.80)	
Treatment-by-subgroup interaction			p=0.84			
Patients with acute exacerbation, n (%)	5 (1.8)	10 (4.8)	12 (4.7)	11 (7.5)	16 (8.6)	23 (15.1)
Hazard ratio (95% CI)	0.37 (0.13, 1.09)		0.64 (0.28, 1.48)		0.58 (0.31, 1.11)	
Treatment-by-subgroup interaction			p=0.71			

Change in SGRQ total score

- In the placebo group, SGRQ total score increased (worsened) over 52 weeks to a greater extent with increasing TORVAN stage at baseline. Increases (worsening) in SGRQ total score were numerically smaller in the nintedanib group than in the placebo group in all the subgroups (Figure 2).

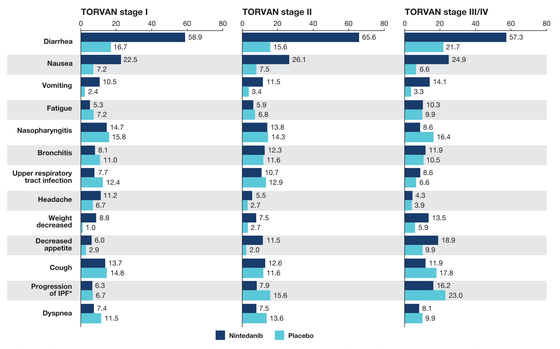
Figure 2. *Change from baseline in SGRQ total score at week 52 by TORVAN stage at baseline*



Treatment-by-subgroup interaction p=0.21

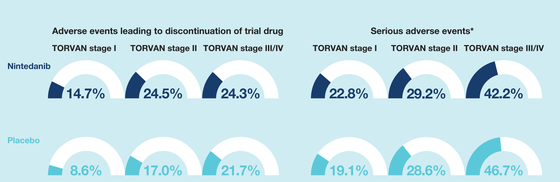
Adverse events

Most frequent adverse events in subgroups by TORVAN stage at baseline



Data are % of subjects with ≥1 such adverse event reported (irrespective of causality) in >10% of subjects in any of these subgroups, coded using preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events with onset after the first dose and up to 28 days (in INPULSIS trials) or 14 days (in TOMORROW trial) after the last dose of study drug are shown.
*Corresponded to MedDRA term 'IPF', which included disease worsening and acute exacerbations of IPF.

Adverse events leading to discontinuation of trial drug and serious adverse events in subgroups by TORVAN stage at baseline



Data are % of subjects with ≥1 such adverse event with onset after the first dose and up to 28 days (in INPULSIS trials) or 14 days (in TOMORROW trial) after the last dose of study drug. *Events that resulted in death, were life-threatening, resulted in hospitalization or prolonged hospitalization, resulted in persistent or clinically significant disability or incapacity, were a congenital anomaly or birth defect, or were deemed serious for any other reason.

Conclusions

- **In patients with IPF, the effect of nintedanib in reducing the rate of decline in FVC was similar irrespective of TORVAN stage at baseline.**
- **The adverse event profile of nintedanib was consistent across subgroups by TORVAN stage. In both the nintedanib and placebo groups, adverse events leading to treatment discontinuation were more frequent in patients at TORVAN stages II to IV than stage I, while the proportion of patients with serious adverse events increased with TORVAN stage.**

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