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Efficacy and safety of nintedanib in Japanese patients with progressive fibrosing interstitial lung diseases: Subgroup analysis of the randomised, double-blind, placebo-controlled, phase 3 INBUILD trial

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ABSTRACT

Background: The efficacy of nintedanib in progressive fibrosing interstitial lung diseases (ILDs) was demonstrated in the randomised, double-blind, placebo-controlled INBUILD trial. This subgroup analysis evaluated the efficacy and safety of nintedanib in the Japanese population.

Methods: Patients with progressive fibrosing ILDs (evaluated by physicians within 24 months of screening) were randomised (1:1) to twice-daily 150-mg nintedanib or placebo; treatment continued until the last patient completed 52 weeks. The primary endpoint was the annual rate of decline in forced vital capacity (FVC) over 52 weeks. Time-to-first acute ILD exacerbation or death and time-to-death up until the last patient had completed the week 52 visit were evaluated. This subgroup analysis included 108 Japanese patients.

Results: The adjusted annual rates of FVC decline (mL/year) over 52 weeks for Japanese patients were −148.31 (nintedanib) and −240.36 (placebo), adjusted difference: 92.05 (95% CI: −10.69–194.80) and for non-Japanese patients were −67.41 (nintedanib) and −177.65 (placebo), adjusted difference: 110.24 (95% CI: 64.97–155.52). No heterogeneity in treatment effect between Japanese and non-Japanese subgroups was observed (treatment-by-subgroup interaction, p = 0.75). The risks of "acute exacerbation or death" (hazard ratio, 0.30 [95% CI:

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; BL, baseline; BMI, body mass index; CI, confidence interval; DLco, diffusing capacity of the lung for carbon monoxide; DMARD, disease-modifying anti-rheumatic drug; FVC, forced vital capacity; HR, hazard ratio; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; IPAF, interstitial pneumonia with autoimmune features; IPF, idiopathic pulmonary fibrosis; K-BILD, King's Brief Interstitial Lung Disease questionnaire; SD, standard deviation; SSc, systemic sclerosis; UIP, usual interstitial pneumonia.

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0.10–0.91]) and mortality (hazard ratio, 0.54 [95% CI: 0.14–2.11]) in Japanese patients were numerically lower for nintedanib than placebo. There were no new or unexpected safety findings.
Conclusions: In Japanese patients, nintedanib slowed ILD progression, evidenced by a reduction in the annual rate of decline in FVC vs placebo. The efficacy and safety of nintedanib in Japanese patients were consistent with the overall INBUILD population.
Clinicaltrials.gov: NCT02999178 (21-Dec-2016).

1. Introduction

Interstitial lung diseases (ILDs) represent a spectrum of lung pathologies of non-autoimmune and autoimmune background that commonly manifest with a progressive fibrosing phenotype [1–5]. Chronic progressive fibrosing ILDs, which include idiopathic pulmonary fibrosis (IPF), are characterised by worsening lung function and quality of life, and early mortality [2,6–8]. Although progressive fibrosing ILDs can have different aetiologies, they share similar pathophysiological mechanisms in fibrotic remodelling commonalities during clinical courses, which suggests that treatments for IPF may be of benefit for patients with other progressive fibrosing ILDs [2,8,9].

Nintedanib, a small molecule inhibitor of selected tyrosine kinases [10,11], is approved for treatment of IPF based on results of the INPULSIS and TOMORROW trials [12,13], for systemic sclerosis-associated ILD (SSc-ILD) based on the results of the SENSCIS trial [4,14,15], and for progressive fibrosing ILD based on the results of the INBUILD trial [16,17]. In the multinational INBUILD phase 3 trial [16,17], the efficacy of nintedanib in patients with progressive fibrosing ILDs (excluding IPF) was confirmed by a significant reduction in the annual rate of decline in forced vital capacity (FVC, primary endpoint) compared with placebo, independent of the fibrotic pattern on high-resolution computed tomography (HRCT) [17]. The efficacy of nintedanib for patients with progressive fibrosing ILDs was also supported by time-to-event outcomes in terms of acute exacerbation or death up to the first database lock which took place after the last patient completed the 52 week visit. Although the INBUILD trial was not designed or powered to evaluate the potential benefit of nintedanib in specific ILD subgroups, recent subgroup analyses from the INBUILD trial suggest that nintedanib reduces the annual rate of decline in lung function irrespective of underlying ILD diagnoses [18]. This is supported by preclinical data showing that nintedanib inhibits important pathways involved in fibrosis progression [19,20] and has antifibrotic activity in various animal models of pulmonary fibrosis that replicate the different features and triggers of human pathology [21]. In addition, based on the antifibrotic effect of nintedanib in preclinical models of SSc and SSc-ILD [22,23] and the absence of differences in protein expression in nintedanib-targeted molecular pathways in IPF, SSc-ILD, and progressive fibrosing ILDs, it is speculated that nintedanib would achieve similar performance in different aetiologies [24].

Here we report the Japanese subgroup analysis of the INBUILD trial in order to evaluate the consistency of the efficacy and safety of nintedanib in Japanese patients with progressive fibrosing ILDs compared with the overall INBUILD trial.

2. Materials and methods

2.1. Study design

INBUILD was a multinational, randomised, double-blind, placebo-controlled trial conducted in 15 countries from February 2017 to August 2019 (ClinicalTrials.gov, NCT02999178) [16,17]. The trial was conducted in accordance with the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice guidelines, local regulations, and the protocol, which was approved by the Independent Ethics Committees (Supplementary Table S1). All patients provided written informed consent to participate in the trial.

2.2. Study population

The INBUILD trial design has been described and the trial protocol is publicly available [16,17]. Briefly, the key inclusion criteria were outpatients aged ≥18 years (≥20 years in Japan) with physician-diagnosed fibrosing ILDs who met ≥ 1 of the following criteria for progression in the 24 months before screening, despite management considered appropriate in clinical practice for individual ILDs: ≥ 10% relative decline in FVC; relative decline of ≥5% to < 10% in FVC and worsening clinical symptoms or increasing extent of fibrotic changes on chest imaging; worsening respiratory symptoms together with increasing extent of fibrotic changes. Patients also had fibrosis on HRCT with disease extent >10% confirmed by central review, diffusing capacity of the lung for carbon monoxide (DLco) corrected for haemoglobin ≥30% and <80% of predicted normal, FVC ≥ 45% of predicted normal, and stable disease for patients with underlying connective tissue disease.

Key exclusion criteria were bilirubin, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 1.5 times the upper limit of normal; creatinine clearance < 30 mL/min according to the Cockcroft-Gault formula; diagnosis of IPF (ATS/ERS/JRS/ALAT 2011 Guidelines) [25]; and underlying chronic liver disease, bleeding risk, significant pulmonary arterial hypertension, or primary obstructive airway physiology.

2.3. Treatment protocol

Patients were randomised 1:1 to oral nintedanib 150 mg twice daily (BID) or placebo with stratification in a 2:1 ratio according to HRCT pattern (usual interstitial pneumonia [UIP]-like or other fibrotic patterns). Dose reductions from 150 mg BID to 100 mg BID and treatment interruptions were permitted to manage adverse events (AEs). Maximum duration of interruption was 4 weeks for AEs considered related to study medication and 8 weeks for other AEs. The trial comprised Parts A and B. In Part A, all patients were treated for 52 weeks. In Part B, the treatment period varied in that patients continued blinded, randomised treatment beyond 52 weeks until the last patient completed Part A. Unless patients withdrew their consent, efficacy and safety were evaluated for all patients, including those who discontinued their trial medication. The first database lock took place after the last patient had completed the week 52 visit.

Restricted therapies were azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, oral glucocorticoids >20 mg/day, or the combination of oral glucocorticoids, azathioprine and *N*-acetylcysteine (within 4 weeks of randomisation); cyclophosphamide (within 8 weeks of randomisation); and rituximab (within 6 months of randomisation). Patients with autoimmune disease that was managed with any restricted therapy could not participate in the trial. Patients who used a restricted therapy to treat their ILD, and whose ILD was progressing, could participate in the trial if the restricted therapy was discontinued. Initiation of restricted therapies was allowed after 6 months of trial treatment in patients whose ILD or connective tissue disease had deteriorated. There was no limit on stable doses of biologic or non-biologic disease-modifying anti-rheumatic drugs, including abatacept and tocilizumab. Use of nintedanib and pirfenidone was prohibited at randomisation and during the trial.

2.4. Outcome measures

The primary endpoint was the annual rate of decline in FVC in mL over 52 weeks. Secondary endpoints included the change from baseline in the self-administered 15-item King's Brief Interstitial Lung Disease (K-BILD) questionnaire total score at Week 52 [26]. The K-BILD questionnaire was developed in patients with ILD in the UK [26], and the Japanese translation has been validated for use in Japan [27]. Here, we present the results of the subgroup analyses in Japanese patients for these endpoints over 52 weeks and for the time-to-first acute ILD exacerbation or death or time-to-death up to the first database lock.

Safety was assessed descriptively with AEs coded using the Medical Dictionary for Regulatory Activities version 22.0.

2.5. Statistical analysis

Analyses were based on data from Japanese and non-Japanese patients who received ≥1 dose of nintedanib or placebo (ie, treated set). For the primary endpoint, a subgroup model was used that included data from all patients in the treated set with the subgroup variable Japanese or non-Japanese applied to all patients and subpopulations by HRCT pattern.

The primary endpoint was analysed using a random coefficient regression model (fixed effects: HRCT pattern [for the overall population], baseline FVC [mL], including baseline-by-time, treatment-by-subgroup [Japanese, non-Japanese], and treatment-by-subgroup-by-time interactions). Patient-specific intercept and time were included as random effects. The primary analysis was based on all data obtained from baseline to Week 52, including data from patients who had discontinued nintedanib or placebo. The primary analysis model assumed that missing data were missing at random. We did not conduct statistical tests for comparisons of demographics and AEs because of the objective for this subpopulation analysis and issues with multiplicity. Data were analysed using SAS® software, version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Disposition, baseline characteristics, and exposure

A total of 108 Japanese patients were randomised to nintedanib 150 mg BID (n = 52) or placebo (n = 56). Similar percentages of patients completed 52 weeks of treatment (n = 41 and n = 45, respectively) and planned observation time (n = 50 and n = 52, respectively) (Fig. 1).

There was a numerical imbalance in baseline demographics and disease characteristics of Japanese patients (Table 1) between the treatment groups with respect to sex, smoking status, percentage of heavy smokers (≥40 pack-years), and some clinical ILD diagnoses (rheumatoid arthritis-ILD and SSc-ILD).

There were several numerical imbalances in baseline demographics between Japanese and non-Japanese patients (Table 1). Japanese patients were slightly older and shorter, and of lower weight and body mass index (BMI) than non-Japanese patients (Table 1). In addition, numerically more Japanese patients were heavy smokers (40.0% vs 21.9%), had a UIP-like fibrotic pattern on HRCT (77.8% vs 59.1%), and had a clinical ILD diagnosis of unclassifiable idiopathic interstitial pneumonia (36.1% vs 13.5%) than non-Japanese patients, and numerically fewer Japanese patients had hypersensitivity pneumonitis (13.0% vs 28.6%) and idiopathic non-specific interstitial pneumonia (13.0% vs 20.0%) than non-Japanese patients. Lung function parameters (FVC and DLco as a percentage of the predicted values) were similar between Japanese and non-Japanese patients.

For Japanese patients, mean (standard deviation [SD]) exposure on the planned 150 mg BID dose (31.8 [22.1] vs 46.4 [14.1] weeks) and mean (SD) dose intensity (87.7% [15.2] vs 99.6% [1.9]) were lower in the nintedanib group vs the placebo group (Supplementary Table S2). Over 52 weeks of treatment, 44.2% and 0% of patients in the nintedanib and placebo groups, respectively, needed a dose reduction. Use of restricted medication at baseline and during the trial is shown in Supplementary Table S3.

3.2. FVC outcomes

For Japanese patients over 52 weeks, the adjusted annual rate of decline in FVC (standard error) was −148.31 (37.12) mL/year for nintedanib and −240.36 (36.90) mL/year for placebo, and the adjusted treatment difference (nintedanib minus placebo) was 92.05 mL (95% confidence interval [CI]: −10.69 to 194.80) (Fig. 2, Supplementary Fig. S1). For non-Japanese patients over 52 weeks, the adjusted annual rate of decline in FVC (standard error) was −67.41 (16.46) mL/year for nintedanib and −177.65 (16.15) mL/year for placebo, and the adjusted treatment difference (nintedanib minus placebo) was 110.24 mL/year

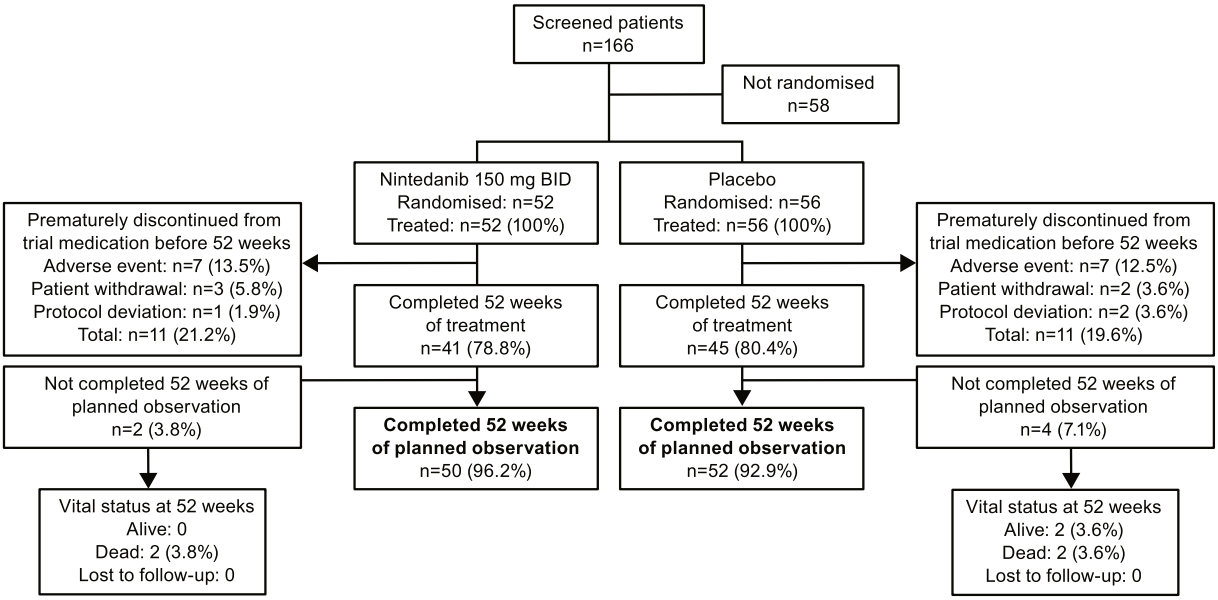

Fig. 1. Patient disposition over 52 weeks (Part A) for Japanese patients in the INBUILD trial. BID, twice daily.

Table 1
Baseline characteristics of the Japanese and non-Japanese patients in the INBUILD trial (treated set).

Variable	Japanese patients			Non-Japanese patients		
	Nintedanib (n = 52)	Placebo (n = 56)	Total (n = 108)	Nintedanib (n = 280)	Placebo (n = 275)	Total (n = 555)
Male sex, n (%)	28 (53.8)	34 (60.7)	62 (57.4)	151 (53.9)	143 (52.0)	294 (53.0)
Age, mean (SD), years	68.1 (7.2)	68.2 (9.8)	68.1 (8.6)	64.7 (10.0)	65.9 (9.8)	65.3 (9.9)
Race, n (%)						
White	0 (0)	0 (0)	0 (0)	242 (86.4)	246 (89.5)	488 (87.9)
Asian	52 (100)	56 (100)	108 (100)	31 (11.1)	24 (8.7)	55 (9.9)
Black or African American	0 (0)	0 (0)	0 (0)	5 (1.8)	5 (1.8)	10 (1.8)
Native Hawaiian or other Pacific Islander	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)	1 (0.2)
Height, mean (SD), cm	159.9 (8.1)	160.8 (9.3)	160.4 (8.7)	165.8 (9.5)	164.9 (10.6)	165.4 (10.0)
Weight, mean (SD), kg	60.2 (10.0)	62.9 (12.0)	61.6 (11.1)	80.0 (16.1)	79.8 (17.7)	79.9 (16.9)
BMI, mean (SD), kg/m^2	23.5 (3.4)	24.2 (3.7)	23.9 (3.6)	29.0 (4.9)	29.2 (5.4)	29.1 (5.1)
Smoking status, n (%)						
Never	26 (50.0)	22 (39.3)	48 (44.4)	137 (48.9)	140 (50.9)	277 (49.9)
Current	1 (1.9)	1 (1.8)	2 (1.9)	2 (0.7)	8 (2.9)	10 (1.8)
Former	25 (48.1)	33 (58.9)	58 (53.7)	141 (50.4)	127 (46.2)	268 (48.3)
Patients who ever smoked, ≥ 40 pack-years	12 (46.2)	12 (35.3)	24 (40.0)	34 (23.8)	27 (20.0)	61 (21.9)
FVC						
Mean (SD), mL	2124 (693)	2249 (624)	2189 (658)	2380 (743)	2336 (748)	2358 (745)
Percent of predicted value (SD)	68.1 (15.3)	70.8 (12.9)	69.5 (14.1)	68.8 (16.2)	69.0 (15.6)	68.9 (15.9)
DLco[a]						
Percent of predicted value (SD)	43.1 (8.9)	45.7 (11.5)	44.4 (10.4)	44.6 (12.4)	48.3 (15.6)	46.5 (14.2)
Total score on K-BILD questionnaire[b]	55.4 (10.3)	55.7 (7.5)	55.5 (8.9)	51.9 (11.1)	51.6 (10.1)	51.8 (10.6)
Time elapsed since first diagnosis based on imaging, median years [min, max]	2.6 [0.1, 15.9]	2.4 [0.1, 18.6]	2.5 [0.1, 18.6]	2.8 [0.0, 30.2]	2.7 [0.0, 18.0]	2.8 [0.0, 30.2]
Criteria for progressive ILD group, n (%)						
Relative decline in FVC percent predicted ≥ 10%	25 (48.1)	34 (60.7)	59 (54.6)	135 (48.2)	138 (50.2)	273 (49.2)
Relative decline in FVC percent predicted ≥ 5 to < 10% combined with worsening of respiratory symptoms and/or increased extent of fibrotic changes on HRCT	23 (44.2)	18 (32.1)	41 (38.0)	87 (31.1)	79 (28.7)	166 (29.9)
Worsened respiratory symptoms and increased extent of fibrotic changes on HRCT only	4 (7.7)	4 (7.1)	8 (7.4)	58 (20.7)	57 (20.7)	115 (20.7)
Fibrotic pattern[c], n (%)						
UIP-like pattern on HRCT	39 (75.0)	45 (80.4)	84 (77.8)	167 (59.6)	161 (58.5)	328 (59.1)
Other fibrotic patterns	13 (25.0)	11 (19.6)	24 (22.2)	112 (40.0)	113 (41.1)	225 (40.5)
Clinical ILD diagnosis (grouped), n (%)						
Unclassifiable idiopathic interstitial pneumonia	20 (38.5)	19 (33.9)	39 (36.1)	44 (15.7)	31 (11.3)	75 (13.5)
Autoimmune ILDs	16 (30.8)	17 (30.4)	33 (30.6)	66 (23.6)	71 (25.8)	137 (24.7)
Rheumatoid arthritis-associated ILD	5 (9.6)	8 (14.3)	13 (12.0)	37 (13.2)	39 (14.2)	76 (13.7)
Systemic sclerosis-associated ILD	8 (15.4)	3 (5.4)	11 (10.2)	15 (5.4)	13 (4.7)	28 (5.0)
Mixed connective tissue disease-associated ILD	1 (1.9)	1 (1.8)	2 (1.9)	6 (2.1)	11 (4.0)	17 (3.1)
Other autoimmune ILDs[d]	2 (3.8)	5 (8.9)	7 (6.5)	8 (2.9)	8 (2.9)	16 (2.9)
Hypersensitivity pneumonitis	6 (11.5)	8 (14.3)	14 (13.0)	78 (27.9)	81 (29.5)	159 (28.6)
Idiopathic non-specific interstitial pneumonia	6 (11.5)	8 (14.3)	14 (13.0)	58 (20.7)	53 (19.3)	111 (20.0)
Other ILDs[e]	4 (7.7)	4 (7.1)	8 (7.4)	34 (12.1)	39 (14.2)	73 (13.2)

BMI, body mass index; DLco, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; IPAF, interstitial pneumonia with autoimmune features; K-BILD, King's Brief Interstitial Lung Disease questionnaire; max, maximum; min, minimum; SD, standard deviation; UIP, usual interstitial pneumonia.

[a] Corrected for haemoglobin.

[b] Scores range from 0 to 100, with higher scores representing better health status.

[c] Two patients with non-determined HRCT pattern in the non-Japanese population were randomised by mistake and were counted in the other fibrotic patterns on HRCT category.

[d] Includes Sjögren's syndrome, IPAF, and selected other terms for ILDs with autoimmune background in "Other fibrosing ILDs".

[e] Included sarcoidosis, exposure-related ILDs, and selected other terms in "Other fibrosing ILDs".

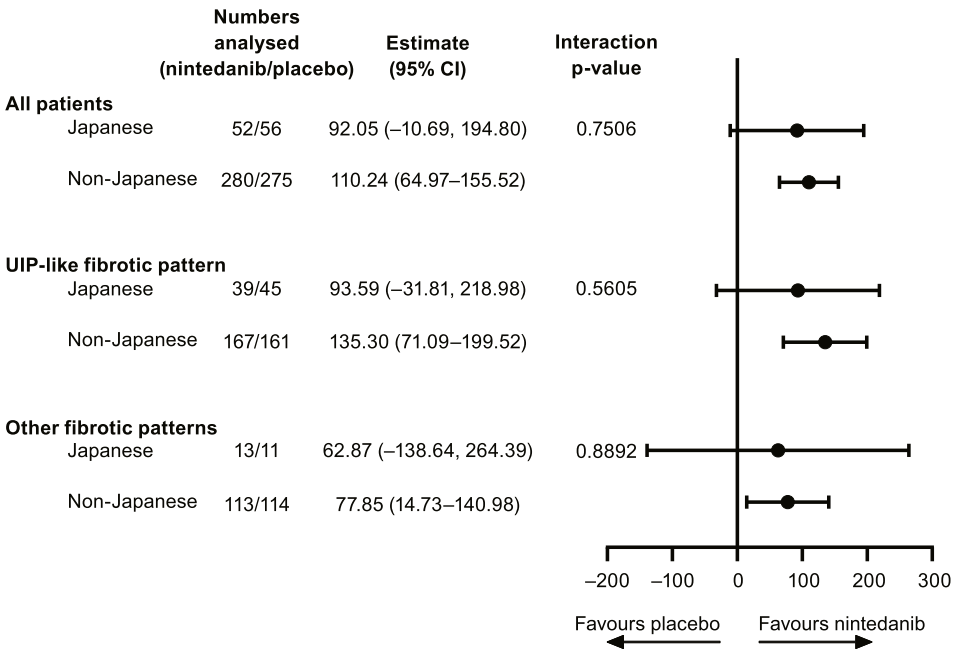

Fig. 2. Forest plot of subgroup model showing the difference (nintedanib – placebo) for the adjusted rate of decline in FVC (mL) over 52 weeks in all Japanese and non-Japanese patients (treated set) and in Japanese and non-Japanese patients with UIP-like fibrotic patterns and other fibrotic patterns on HRCT. Based on a random coefficient regression model (fixed effects: HRCT pattern [overall population], baseline FVC [mL], including baseline-by-time, treatment-by-subgroup [Japanese, non-Japanese], and treatment-by-subgroup-by-time interactions). Patient-specific intercept and time were included as random effects. CI, confidence interval; FVC, forced vital capacity; HRCT, high-resolution computed tomography; UIP, usual interstitial pneumonia.

(95% CI: 64.97 to 155.52) (Fig. 2). These effects were observed irrespective of fibrotic pattern on HRCT, and no heterogeneity in treatment effects was detected between Japanese and non-Japanese patients (Fig. 2). The observed change from baseline in FVC (mL) was smaller for the nintedanib group compared with the placebo group at each time point up to 52 weeks in all Japanese patients and in patients with a UIP-like fibrotic pattern on HRCT (Fig. 3). An additional analysis where FVC measurements taken after the start of restricted medication were excluded is shown in Supplementary Table S4.

3.3. Other outcomes

At Week 52, the mean adjusted change (SE) from baseline in K-BILD total score was similar in both treatment groups for Japanese (nintedanib vs placebo: 0.6 [1.5] points vs −0.0 [1.4] points) and non-Japanese patients (nintedanib vs placebo: 0.5 [0.7] points vs −1.0 [0.6] points) and no heterogeneity in treatment effects was detected between Japanese and non-Japanese patients (Supplementary Table S5). The results were the same in those with a UIP-like fibrotic pattern on HRCT (Supplementary Table S5). The time course of the change from baseline in K-BILD total score over 52 weeks in Japanese patients is shown in Supplementary Fig. S2.

With the longer observation period (ie, up to the first database lock), the risks of the composite measure “acute exacerbation or death” (hazard ratio [HR] 0.30, 95% CI: 0.10–0.91) and death (HR 0.54, 95% CI: 0.14–2.11) were numerically lower in the nintedanib group than in the placebo group in the Japanese patient population (Fig. 4). The rate of events up to the first database lock is shown in Supplementary Table S6.

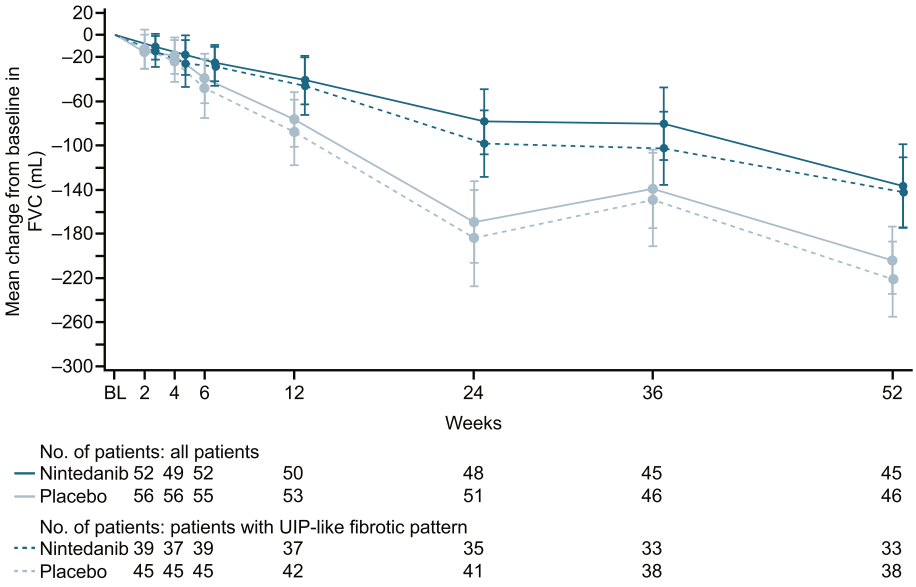

Fig. 3. Mean observed absolute change from baseline in FVC (mL) over 52 weeks in the treated set for all Japanese patients (solid lines) and Japanese patients with UIP-like fibrotic patterns on HRCT (dashed lines). Data are means ± SE. BL, baseline; FVC, forced vital capacity; HRCT, high-resolution computed tomography; SE, standard error; UIP, usual interstitial pneumonia.

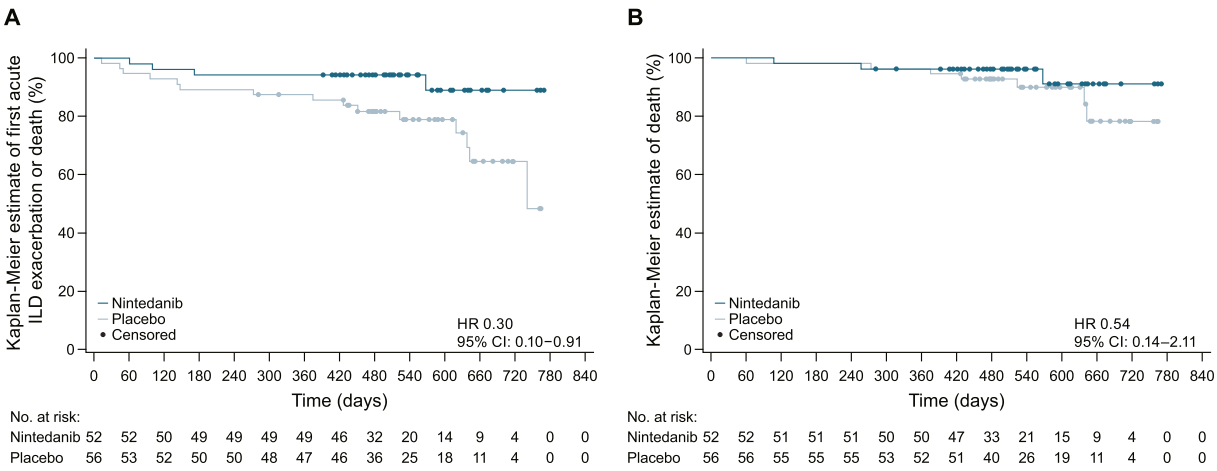

Fig. 4. Kaplan-Meier curve of the time-to-first acute ILD exacerbation or death (**a**) and time-to-death (**b**) up to the first database lock in Japanese patients (treated set). Analysis is based on a Cox regression model with terms for treatment and stratified by HRCT pattern. CI, confidence interval; HR, hazard ratio; HRCT, high-resolution computed tomography; ILD, interstitial lung disease.

3.4. Safety and tolerability

Over 52 weeks of treatment, the percentages of Japanese patients with any AEs, AEs leading to study drug discontinuation, and severe AEs were similar for nintedanib and placebo (Table 2). More Japanese patients treated with nintedanib compared with placebo had study drug-related AEs (investigator-reported) or AEs leading to permanent dose reduction. On the other hand, the percentage of patients with AEs leading to permanent dose reduction was higher in Japanese patients treated with nintedanib than in non-Japanese patients treated with nintedanib. Although more Japanese patients treated with placebo compared with nintedanib had serious AEs, the percentages of Japanese patients with serious AEs in both treatment groups were higher than those of non-Japanese patients in both treatment groups. None of the Japanese nintedanib-treated patients died because of an AE. Diarrhoea, nasopharyngitis, nausea, hepatic function abnormal, AST increased, vomiting, bronchitis, weight decreased, and ALT increased occurred more frequently in Japanese patients treated with nintedanib than placebo, and the percentages of patients with diarrhoea, nasopharyngitis, and hepatic function abnormal were higher in Japanese patients treated with nintedanib than in non-Japanese patients treated with nintedanib. ILD occurred more frequently with placebo than nintedanib in both Japanese and non-Japanese patients (Table 2).

4. Discussion

This publication extends the analysis of Japanese patients with IPF [28] and SSc-ILD [15], and presents findings in Japanese patients with progressive fibrosing ILDs other than IPF. In Japanese patients, the efficacy and safety of nintedanib were consistent with the effects observed in the overall INBUILD population [16,17]. The benefit of nintedanib in slowing the decline in lung function was also supported by trends in clinically meaningful outcome measures such as time to acute exacerbation or death. Collectively, these findings provide clinicians with assurances regarding the efficacy and safety of nintedanib in Japanese patients with progressive fibrosing ILDs.

A total of 108 Japanese patients with physician-diagnosed fibrosing ILDs other than IPF, who met at least one of the criteria for ILD progression in the most recent 24 months despite receiving treatment considered appropriate in clinical practice, were randomised to nintedanib 150 mg BID (n = 52) or placebo (n = 56). More Japanese patients had unclassifiable idiopathic interstitial pneumonia than non-Japanese patients and the overall INBUILD population [17]. Although the reason for the high percentage of patients with unclassifiable idiopathic interstitial pneumonia is unclear, it may partly be because Japanese clinicians tend to adhere closely to diagnostic criteria and, therefore, are more likely to diagnose patients with atypical symptoms as unclassifiable [29]. In addition, there was a numerically higher percentage of heavy smokers and patients with a UIP-like fibrotic pattern on HRCT in the Japanese population, and Japanese patients were of lower BMI than their non-Japanese counterparts and the overall INBUILD population [17], which suggests that Japanese patients may be at higher risk of disease progression [30–35].

Despite the differences in baseline clinical characteristics, the effect of nintedanib on efficacy endpoints in Japanese patients with progressive fibrosing ILDs was consistent with those of non-Japanese patients and the overall INBUILD population. The between-group differences in the adjusted rate of decline in FVC over 52 weeks in Japanese and non-Japanese patients were 92.05 mL/year and 110.24 mL/year, respectively, for all patients, were 93.59 mL/year and 135.30 mL/year, respectively, for patients with a UIP-like fibrotic pattern on HRCT, and were 62.87 mL/year and 77.85 mL/year, respectively, for patients with other fibrotic patterns. The treatment-by-subgroup interaction p-values ranged from 0.5605 to 0.8892, suggesting there was no heterogeneity in treatment effects between Japanese and non-Japanese patients regardless of the fibrotic pattern on HRCT. In addition, the 95% CIs for the overall INBUILD population included the point estimates for Japanese patients in this subgroup analysis regardless of the fibrotic pattern on HRCT, suggesting that the efficacy of nintedanib in Japanese patients is consistent with that of the overall INBUILD population. There was a slight numerical difference between the Japanese and non-Japanese subgroups for treatment effect (Fig. 2), which may be attributed to the concomitant use of restricted medication. The mean adjusted change from baseline in K-BILD total score was similar in both treatment groups in Japanese and non-Japanese patients, and no heterogeneity in treatment effects was detected regardless of the fibrotic pattern on HRCT. In addition, the 95% CIs for the overall INBUILD population included the mean treatment differences for Japanese patients in this subgroup analysis, suggesting that the effect on K-BILD in Japanese patients was also consistent with that of the overall INBUILD population. The small numbers of nintedanib-treated patients with acute exacerbations or death in Japanese patients up to the first database lock were similar to those in the overall population up to the first database lock [17] and to those in previous studies in patients with IPF [13,28]. In the current analysis, the reduction in risk of "acute exacerbation or death" and death tended to become evident over the longer observation period (ie, beyond 52 weeks), which was similar to the INBUILD overall population [17].

This study confirms the safety profile of nintedanib in Japanese

Table 2
Adverse events reported in Japanese and non-Japanese patients over 52 weeks (treated set).

	Japanese patients		Non-Japanese patients	
Patients, n (%)	Nintedanib 150 mg BID (n = 52)	Placebo (n = 56)	Nintedanib 150 mg BID (n = 280)	Placebo (n = 275)
Any AE	51 (98.1)	56 (100)	266 (95.0)	240 (87.3)
Investigator-reported drug-related AE	47 (90.4)	21 (37.5)	215 (76.8)	105 (38.2)
AE leading to permanent study drug discontinuation	11 (21.2)	10 (17.9)	54 (19.3)	24 (8.7)
AE leading to permanent dose reduction	23 (44.2)	0 (0)	87 (31.1)	14 (5.1)
Severe AE	7 (13.5)	8 (14.3)	53 (18.9)	65 (23.6)
Serious AE	19 (36.5)	27 (48.2)	88 (31.4)	83 (30.2)
AE resulting in death	0 (0)	4 (7.1)[a]	11 (3.9)	13 (4.7)
AEs reported in >5% of Japanese patients in the nintedanib group				
Diarrhoea	41 (78.8)	18 (32.1)	181 (64.6)	61 (22.2)
Nasopharyngitis	19 (36.5)	16 (28.6)	25 (8.9)	24 (8.7)
Nausea	15 (28.8)	1 (1.8)	81 (28.9)	30 (10.9)
Hepatic function abnormal	13 (25.0)	2 (3.6)	6 (2.1)	1 (0.4)
Aspartate aminotransferase increased	8 (15.4)	1 (1.8)	30 (10.7)	11 (4.0)
Vomiting	8 (15.4)	0 (0)	53 (18.9)	17 (6.2)
Interstitial lung disease	7 (13.5)	18 (32.1)	9 (3.2)	21 (7.6)
Bronchitis	7 (13.5)	4 (7.1)	34 (12.1)	43 (15.6)
Weight decreased	7 (13.5)	3 (5.4)	34 (12.1)	8 (2.9)
Alanine aminotransferase increased	7 (13.5)	1 (1.8)	36 (12.9)	11 (4.0)
Constipation	5 (9.6)	8 (14.3)	18 (6.4)	17 (6.2)
Pyrexia	5 (9.6)	2 (3.6)	11 (3.9)	10 (3.6)
Decreased appetite	4 (7.7)	5 (8.9)	44 (15.7)	12 (4.4)
Back pain	4 (7.7)	5 (8.9)	15 (5.4)	11 (4.0)
Influenza	4 (7.7)	0 (0)	3 (1.1)	6 (2.2)
Pneumonia	4 (7.7)	4 (7.1)	15 (5.4)	16 (5.8)
Stomatitis	4 (7.7)	2 (3.6)	1 (0.4)	0 (0.0)
Haemorrhoids	4 (7.7)	1 (1.8)	2 (0.7)	2 (0.7)
Dry skin	4 (7.7)	1 (1.8)	2 (0.7)	1 (0.4)
Abdominal pain upper	3 (5.8)	3 (5.4)	27 (9.6)	3 (1.1)
Gastritis	3 (5.8)	1 (1.8)	1 (0.4)	3 (1.1)
Hypertension	3 (5.8)	1 (1.8)	10 (3.6)	10 (3.6)
Drug-induced liver injury	3 (5.8)	0 (0)	3 (1.1)	0 (0.0)
Malaise	3 (5.8)	0 (0)	5 (1.8)	3 (1.1)

AE, adverse event; BID, twice daily.
[a] AEs that resulted in death in the placebo group were interstitial lung disease (2 patients), pneumothorax (1 patient), and respiratory failure (1 patient).

patients with progressive fibrosing ILDs, with no new or unexpected safety findings. Overall, the safety profile was consistent not only with those of non-Japanese patients but also with those of the overall INBUILD population [17] and a pooled analysis of patients with IPF from 6 clinical trials [36], which showed diarrhoea to be the most frequently reported AE with nintedanib and a higher rate of liver enzyme elevations with nintedanib than placebo. However, compared with non-Japanese patients in both treatment groups [17], the percentages of Japanese patients with serious AEs in both treatment groups were higher. The percentage of Japanese patients with AEs leading to permanent dose reduction in the nintedanib group were higher and the percentage of Japanese patients with AEs leading to death in the nintedanib group were lower than those of non-Japanese patients in the nintedanib group. Even compared with the overall INBUILD population [17], Japanese patients treated with either nintedanib (32.2% and 36.5%, respectively) or placebo (33.2% and 48.2%, respectively) reported a higher incidence of serious AEs, and those treated with nintedanib but not placebo reported a higher incidence of AEs leading to dose reduction (33.1% and 44.2%, respectively) and a lower incidence of deaths (3.3% and 0%, respectively). In addition, Japanese patients treated with nintedanib reported higher incidences of diarrhoea, hepatic function abnormal, and nasopharyngitis, and similar levels of AST and ALT increased, weight decreased, and decreased appetite compared with non-Japanese patients and the overall INBUILD population [17]. These trends towards a higher incidence of AEs in Japanese patients compared with the overall INBUILD population are similar to those observed in Japanese patients with IPF compared with the overall INPULSIS population [28].

The results from a prespecified subgroup analysis in the overall INBUILD population showed consistent treatment effects in patients with progressive fibrosing ILDs, irrespective of the ILD diagnosis group [18]. Therefore, it is reasonable that the effects of nintedanib in Japanese patients are consistent with those of non-Japanese patients and the INBUILD overall population although there were numerical imbalances between the populations regarding the percentage of patients with each ILD (ie, unclassifiable idiopathic interstitial pneumonia, autoimmune ILD, hypersensitivity pneumonitis, and idiopathic non-specific interstitial pneumonia). Unfortunately, because of the small size of the Japanese INBUILD population, it was not feasible to conduct a similar subgroup analysis by ILD diagnosis in Japanese patients and further studies are needed to confirm the effects of nintedanib in Japanese patients by ILD diagnosis.

5. Conclusions

Similar to the overall INBUILD population [16,17], the annual rate of decline in FVC for Japanese patients was slower with nintedanib than placebo irrespective of fibrotic patterns on HRCT. Trends towards lower risks of clinically meaningful outcomes, including acute exacerbation or death, were also observed. Although some AEs occurred more frequently compared with the overall INBUILD population, the safety profile of nintedanib was consistent with Japanese patients in previous trials of patients with IPF [28] and SSc-ILD [15].

Ethics approval and consent to participate

This trial was approved by the Independent Ethics Committees at each study site. All patients provided written informed consent to participate in the trial.

Consent for publication

Not applicable.

Availability of data and materials

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to all relevant material, including participant-level clinical study data, and relevant material as needed by them to fulfill their role and obligations as authors under the ICMJE criteria.

Furthermore, clinical study documents (e.g. study report, study protocol, statistical analysis plan) and participant clinical study data are available to be shared after publication of the primary manuscript in a peer-reviewed journal and if regulatory activities are complete and other criteria met per the BI Policy on Transparency and Publication of Clinical Study Data: https://trials.boehringer-ingelheim.com/

Prior to providing access, documents will be examined, and, if necessary, redacted and the data will be de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of the informed consent of the study participants.

Clinical Study Reports and Related Clinical Documents can also be

requested via the link https://trials.boehringer-ingelheim.com/

All requests will be governed by a Document Sharing Agreement.

Bona fide, qualified scientific and medical researchers may request access to de-identified, analysable participant clinical study data with corresponding documentation describing the structure and content of the datasets. Upon approval, and governed by a Data Sharing Agreement, data are shared in a secured data-access system for a limited period of 1 year, which may be extended upon request.

Researchers should use the https://trials.boehringer-ingelheim.com/ link to request access to study data.

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Authors' contributions

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Declaration of competing interest

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TS, HK, MO, NI, and SM have no conflicts of interest to declare.

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Appendix A. Supplementary data

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References

[1] V. Cottin, N.A. Hirani, D.L. Hotchkin, et al., Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases, Eur. Respir. Rev. 27 (2018) 180076, https://doi.org/10.1183/16000617.0076-2018.

[2] M. Kolb, M. Vašáková, The natural history of progressive fibrosing interstitial lung diseases, Respir. Res. 20 (2019) 57, https://doi.org/10.1186/s12931-019-1022-1.

[3] M. Wijsenbeek, M. Kreuter, A. Olson, et al., Progressive fibrosing interstitial lung diseases: current practice in diagnosis and management, Curr. Med. Res. Opin. 35 (2019) 2015–2024, https://doi.org/10.1080/03007995.2019.1647040.

[4] O. Distler, K.B. Highland, M. Gahlemann, et al., Nintedanib for systemic sclerosis-associated interstitial lung disease, N. Engl. J. Med. 380 (2019) 2518–2528, https://doi.org/10.1056/NEJMoa1903076.

[5] A. Fischer, J. Distler, Progressive fibrosing interstitial lung disease associated with systemic autoimmune diseases, Clin. Rheumatol. 38 (2019) 2673–2681, https://doi.org/10.1007/s10067-019-04720-0.

[6] J.J. Swigris, K.K. Brown, R. Abdulqawi, et al., Patients' perceptions and patient-reported outcomes in progressive-fibrosing interstitial lung diseases, Eur. Respir. Rev. 27 (2018) 180075, https://doi.org/10.1183/16000617.0075-2018.

[7] M. Kolb, B. Bondue, A. Pesci, et al., Acute exacerbations of progressive-fibrosing interstitial lung diseases, Eur. Respir. Rev. 27 (2018) 180071, https://doi.org/10.1183/16000617.0071-2018.

[8] A.U. Wells, K.K. Brown, K.R. Flaherty, et al., What's in a name? That which we call IPF, by any other name would act the same, Eur. Respir. J. 51 (2018) 1800692, https://doi.org/10.1183/13993003.00692-2018.
[9] Y. Inoue, R.J. Kaner, J. Guiot, et al., Diagnostic and prognostic biomarkers for chronic fibrosing interstitial lung diseases with a progressive phenotype, Chest 158 (2020) 646–659, https://doi.org/10.1016/j.chest.2020.03.037.
[10] F. Hilberg, U. Tontsch-Grunt, A. Baum, et al., Triple angiokinase inhibitor nintedanib directly inhibits tumor cell growth and induces tumor shrinkage via blocking oncogenic receptor tyrosine kinases, J. Pharmacol. Exp. Therapeut. 364 (2018) 494–503, https://doi.org/10.1124/jpet.117.244129.
[11] F. Hilberg, G.J. Roth, M. Krssak, et al., BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy, Canc. Res. 68 (2008) 4774–4782, https://doi.org/10.1158/0008-5472.CAN-07-6307.
[12] L. Richeldi, U. Costabel, M. Selman, et al., Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis, N. Engl. J. Med. 365 (2011) 1079–1087, https://doi.org/10.1056/NEJMoa1103690.
[13] L. Richeldi, R.M. du Bois, G. Raghu, et al., Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis, N. Engl. J. Med. 370 (2014) 2071–2082, https://doi.org/10.1056/NEJMoa1402584.
[14] M. Kuwana, A. Azuma, Nintedanib: new indication for systemic sclerosis-associated interstitial lung disease, Mod. Rheumatol. 30 (2020) 225–231, https://doi.org/10.1080/14397595.2019.1696505.
[15] M. Kuwana, T. Ogura, S. Makino, et al., Nintedanib in patients with systemic sclerosis-associated interstitial lung disease: a Japanese population analysis of the SENSCIS trial, Mod. Rheumatol. (2020), https://doi.org/10.1080/14397595.2020.1751402.
[16] K.R. Flaherty, K.K. Brown, A.U. Wells, et al., Design of the PF-ILD trial: a double-blind, randomised, placebo-controlled phase III trial of nintedanib in patients with progressive fibrosing interstitial lung disease, BMJ Open Respir. Res. 4 (2017), e000212, https://doi.org/10.1136/bmjresp-2017-000212.
[17] K.R. Flaherty, A.U. Wells, V. Cottin, et al., Nintedanib in progressive fibrosing interstitial lung diseases, N. Engl. J. Med. 381 (2019) 1718–1727, https://doi.org/10.1056/NEJMoa1908681.
[18] A.U. Wells, K.R. Flaherty, K.K. Brown, et al., Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial, Lancet Respir. Med. 8 (2020) 453–460, https://doi.org/10.1016/s2213-2600(20)30036-9.
[19] K.E. Hostettler, J. Zhong, E. Papakonstantinou, et al., Anti-fibrotic effects of nintedanib in lung fibroblasts derived from patients with idiopathic pulmonary fibrosis, Respir. Res. 15 (2014) 157, https://doi.org/10.1186/s12931-014-0157-3.
[20] S. Sato, S. Shinohara, S. Hayashi, et al., Anti-fibrotic efficacy of nintedanib in pulmonary fibrosis via the inhibition of fibrocyte activity, Respir. Res. 18 (2017) 172, https://doi.org/10.1186/s12931-017-0654-2.
[21] L. Wollin, J.H.W. Distler, E.F. Redente, et al., Potential of nintedanib in treatment of progressive fibrosing interstitial lung diseases, Eur. Respir. J. 54 (2019) 1900161, https://doi.org/10.1183/13993003.00161-2019.
[22] J. Huang, C. Beyer, K. Palumbo-Zerr, et al., Nintedanib inhibits fibroblast activation and ameliorates fibrosis in preclinical models of systemic sclerosis, Ann. Rheum. Dis. 75 (2016) 883–890, https://doi.org/10.1136/annrheumdis-2014-207109.
[23] I. Atanelishvili, T. Akter, A. Noguchi, et al., Antifibrotic efficacy of nintedanib in a cellular model of systemic sclerosis-associated interstitial lung disease, Clin. Exp. Rheumatol. 37 (Suppl 119) (2019) 115–124.
[24] A.M. Hoffmann-Vold, S.S. Weigt, R. Saggar, et al., Endotype-phenotyping may predict a treatment response in progressive fibrosing interstitial lung disease, EBioMedicine 50 (2019) 379–386, https://doi.org/10.1016/j.ebiom.2019.10.050.
[25] G. Raghu, H.R. Collard, J.J. Egan, et al., An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management, Am. J. Respir. Crit. Care Med. 183 (2011) 788–824, https://doi.org/10.1164/rccm.2009-040GL.
[26] A.S. Patel, R.J. Siegert, K. Brignall, et al., The development and validation of the King's Brief Interstitial Lung Disease (K-BILD) health status questionnaire, Thorax 67 (2012) 804–810, https://doi.org/10.1136/thoraxjnl-2012-201581.
[27] Y. Inoue, A. Takizawa, S.S. Birring, A health status questionnaire for patients with interstitial lung disease: development of a Japanese version of the K-BILD, Ann. J. Respir. Soc. 8 (2019) 386–390.
[28] A. Azuma, H. Taniguchi, Y. Inoue, et al., Nintedanib in Japanese patients with idiopathic pulmonary fibrosis: a subgroup analysis of the INPULSIS® randomized trials, Respirology 22 (2017) 750–757, https://doi.org/10.1111/resp.12960.
[29] T. Fujisawa, K. Mori, M. Mikamo, et al., Nationwide cloud-based integrated database of idiopathic interstitial pneumonias for multidisciplinary discussion, Eur. Respir. J. 53 (2019), https://doi.org/10.1183/13993003.02243-2018.
[30] A. Adegunsoye, J.M. Oldham, S.K. Bellam, et al., Computed tomography honeycombing identifies a progressive fibrotic phenotype with increased mortality across diverse interstitial lung diseases, Ann. Am. Thorac. Soc. 16 (2019) 580–588, https://doi.org/10.1513/AnnalsATS.201807-443OC.
[31] A. Comes, A.W. Wong, J. Fisher, et al., Association of body mass index and change in weight with mortality in patients with fibrotic interstitial lung disease, Am. J. Respir. Crit. Care Med. 201 (2020) A1096, https://doi.org/10.1164/ajrccm-conference.2020.201.1_MeetingAbstracts.A1096.
[32] M. Ekström, T. Gustafson, K. Boman, et al., Effects of smoking, gender and occupational exposure on the risk of severe pulmonary fibrosis: a population-based case-control study, BMJ Open 4 (2014), e004018, https://doi.org/10.1136/bmjopen-2013-004018.
[33] E.J. Kim, B.M. Elicker, F. Maldonado, et al., Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease, Eur. Respir. J. 35 (2010) 1322–1328, https://doi.org/10.1183/09031936.00092309.
[34] M.L. Salisbury, T. Gu, S. Murray, et al., Hypersensitivity pneumonitis: radiologic phenotypes are associated with distinct survival time and pulmonary function trajectory, Chest 155 (2019) 699–711, https://doi.org/10.1016/j.chest.2018.08.1076.
[35] S.L. Walsh, N. Sverzellati, A. Devaraj, et al., Connective tissue disease related fibrotic lung disease: high resolution computed tomographic and pulmonary function indices as prognostic determinants, Thorax 69 (2014) 216–222, https://doi.org/10.1136/thoraxjnl-2013-203843.
[36] L. Lancaster, B. Crestani, P. Hernandez, et al., Safety and survival data in patients with idiopathic pulmonary fibrosis treated with nintedanib: pooled data from six clinical trials, BMJ Open Respir. Res. 6 (2019), e000397, https://doi.org/10.1136/bmjresp-2018-000397.