Title: Observational, multicenter study on the efficacy, tolerability and safety of nintedanib in patients with idiopathic pulmonary fibrosis older than 80 years.

Authors: Michele Mondoni[1], Fausta Alfano[1], Francesco Varone[2], Catania2XX[3], Caterina Conti[4], Laura Saderi[5], Amerigo Chiesa[2], Fabiano Di Marco[4], Carlo Vancheri[3], Luca Richeldi[2], Stefano Centanni[1], Giovanni Sotgiu[5]

Affiliations: [1]Respiratory Unit, ASST Santi Paolo e Carlo, Department of Health Sciences, Università degli Studi di Milano; [2]Division of Pulmonary Medicine, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy; [3]Department of Clinical and Experimental Medicine, Regional Referral Centre for Rare Lung Disease, A.O.U. Policlinico-San Marco, University of Catania, Italy; [4]Respiratory Unit, ASST Papa Giovanni XXIII, Dept of Health Sciences, Università degli Studi di Milano, Bergamo, Italy; [5]Clinical Epidemiology and Medical Statistics Unit, Dept of Medical, Surgical and Experimental Sciences, University of Sassari, Sassari, Italy

Corresponding Author: Michele Mondoni. Respiratory Unit, ASST Santi Paolo e Carlo, Department of Health Sciences, Università degli Studi di Milano, Via A. Di Rudinì n.8, 20142, Milan, Italy; e-mail: michele.mondoni@asst-santipaolocarlo.it; phone: (+39) 02 81843025.

Word count (Abstract): 243

Word count (Text): 1753

Keywords: IPF; idiopathic pulmonary fibrosis; elderly; nintedanib; safety; antifibrotic therapy; exacerbation

Summary at a glance: This study first showed that nintedanib is effective and safe in patients with IPF >80 years, without significant differences in overall efficacy, safety and tolerability with younger patients

**Abstract**

Background and objectives: Idiopathic pulmonary fibrosis (IPF) primarily affects old patients. Old age is a predictor of mortality. Nintedanib, the only antifibrotic drug approved in Italy for patients aged >80 years, can slow the progression of IPF by reducing the rate of decline in forced vital capacity (FVC) and the risk of exacerbations.

The primary aim of the study was to compare the decline of FVC after 12 months of nintedanib in patients aged >80 years VS. younger patients. Differences related to other functional data, safety, tolerability, hospitalizations, exacerbations, and mortality were evaluated.

Methods: An observational, retrospective, multicenter study was carried out in Italy.

Results: 159 (122 (76.7%) males) patients were recruited: 106 (66.7%) with ≤80 years and 53 (33.3%) with >80 years. FVC decline after 12 months of therapy was not significantly different (-45 ml (-170; 75) VS. -20 ml (-138; 110) ml; P: 0.51). No differences were found for other functional data.

Diarrhoea was the most frequent adverse event (AEs). Rate and type of any AEs, permanent/temporary dose reduction or drug discontinuation were not significantly different between patients aged ≤80 VS. >80 years. Furthermore, acute exacerbations, hospitalization, and mortality were not significantly different.

Conclusions: Nintedanib is effective and safe in patients with IPF aged >80 years, and no significant differences were found when clinical outcomes were compared with those of younger patients. Thus, older age should not be a barrier for the early prescription of antifibrotic treatment in IPF patients.

Short title: Nintedanib in patients with IPF>80 years

## Text

### Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, fibrosing and progressive interstitial lung disease of unknown etiology. [1,2]

IPF primarily affects old patients and its incidence increases proportionally with age.[1-4] Older patients are often frail and their higher number of comorbidities may significantly affect their survival[3-6]. Old age is one of the main predictors of mortality in IPF patients.[3,4,6,7] Nintedanib, a multitarget tyrosin kinase inhibitor, can slow the progression of IPF by reducing the rate of decline in forced vital capacity (FVC) and the risk of exacerbations[7,9,10,11-14]

It is the only antifibrotic drug approved in Italy for patients aged >80 years: The assessment of its efficacy, safety, and tolerability is key to optimize their management.

Few data from both clinical trials and observational studies failed to demonstrate differences in efficacy and safety between patients aged ≥75 years VS. those aged <75 years[8,14-16]. A retrospective study showed that dose reduction could be needed in males aged >80 years.[17]

No studies investigated the efficacy of nintedanib in patients with mild to moderate IPF aged >80 years in comparison with those aged ≤80 years.

The primary aim of the study was to assess the decline of FVC after 12 months of therapy in patients aged >80 years in comparison with younger patients. Furthermore, differences related to other functional data, safety, tolerability, hospitalization and exacerbation rate, and overall mortality were evaluated.

### Materials and methods

Study design

An observational, retrospective, multicenter Italian study was carried out. It was approved by the ethical committees of four Italian participating hospitals. Written informed consent was provided by patients alive when the study was planned.

Patients and interventions

From October 2018 to February 2022 adult (i.e., ≥18 years old) patients with mild to moderate IPF were consecutively enrolled. Their diagnosis was based on the ATS/ERS/JRS/ALAT 2018 Guidelines[1]. They should have completed at least three months of nintedanib to be considered eligible. Exclusion criteria were the following: severe IPF (FVC <50% of the predicted value), refusal to sign the informed consent.

For a single patient aged >80 years two patients aged ≤80 years were recruited.

Demographic, clinical and respiratory function data at baseline and after 12 months of treatment were recorded. For patients treated for less than 12 months the last available data were considered.

Data on exacerbations, hospitalization, mortality, adverse events, rate and reasons for dose reduction and/or drug discontinuation were recorded.

Outcomes

The primary outcome was to assess the absolute FVC decline (milliliters) after 12 months of therapy in patients >80 years in comparison with patients ≤80 years old.

Furthermore, we evaluated the decline of FVC (percentage of the predicted value), the diffusion of the lung for carbon monoxide (DLCO) (absolute values and percentage of the predicted value), the variation in meters at 6 minutes walking test (6mWT), the oxygen saturation (SpO2) and the occurrence of dyspnea (modified Medical Research Council, mMRC) scale. Two clinical prediction tools aimed at evaluating the prognosis of patients with IPF were recorded: Gender Age Physiology (GAP) index (based on age and functional parameters), and TORVAN index (based on GAP and comorbidity variables).

The frequency of patients with a stabilization/improvement of FVC (milliliters and percentage of predicted value), with a FVC reduction ≥10% after one year of therapy, as well as the frequency of FVC decline for patients with a FVC at baseline >90% VS. those with a FVC at baseline ≤90%, were also evaluated.

Adverse events (AEs) were recorded and defined using the Medical Dictionary for Regulatory Activities System Organ Class and preferred terms.[8,17]

Statistical analysis

An ad hoc electronic database was created to collect all study variables. Qualitative data were summarized with absolute and relative frequencies (percentages). Means (standard deviations, SD) or medians (interquartile ranges, IQR) were used to describe quantitative variables in case of parametric and non-parametric distributions, respectively. Chi-square or Fisher's exact test was performed to detect any statistical differences in the comparison of the qualitative variables between age subgroups, whereas between-group comparisons of quantitative variables were performed with Student's t-test and Mann-Whitney test for parametric and non-parametric variables, respectively. A P less than 0.05 was considered statistically significant. The statistical software Stata 17 (StataCorp, TX) was used for all statistical computations.

**Results**

A total of 159 (122 (76.7%) males) patients with mild-to-moderate IPF were recruited: 106 (66.7%) with ≤80 years (median (IQR) age: 70 (65-75) years) whereas 53 (33.3%) with >80 years (median (IQR) age: 82 (82-83) years) (Table 1).

FVC (ml) decline after 12 months of therapy was not significantly different (-45 ml (-170; 75) VS. -20 ml (-138; 110) ml; P: 0.51) (Figure 1 and Table 2). No differences were found for other functional data.

57/133 (42.9%) patients showed stable/improved absolute FVC values after one year of therapy, without any differences between those aged ≤80 years VS. those aged >80 years (37 (40.2) ml VS 20 (48.8) ml; P: 0.36). 76/133 (57.1%) patients showed stable/improved FVC percentage of the predicted

value, without any differences between younger and older patients (49 (53.3%) VS. 27 (65.9%); P: 0.18). 17/57 (29.8%) patients showed FVC reduction ≥10% without any subgroup differences (10 (23.3%) VS. 7 (50.0%); P: 0.06) (Table 1 supplement). No differences in FVC (ml) decline were detected between younger and older patients with baseline FVC >90% VS. those with FVC ≤90%) (Table 2 supplement).

Acute exacerbations, hospitalization and mortality outcomes were not significantly different (Table 3).

Diarrhoea (in the majority mild/moderate) was the most frequent gastrointestinal AE (Table 4). No differences were found between patients aged ≤80 VS. >80 years in the rate and type of any AEs, permanent/temporary dose reduction or drug discontinuation (Table 5).

A permanent discontinuation was recorded in 13/159 (8.2%), without any significant differences between age subgroups (6 (5.7%) patients ≤80 years VS. 7 (13.2/) >80 years; P: 0.10); 68/159 (42.7%) had a permanent dose reduction, without any age differences (40 (37.7%) VS. 28 (52.8%); P: 0.07). Gastrointestinal events and transaminases elevation were the most frequent AEs leading to dose reduction and drug discontinuation (Table 5).

**Discussion**

To the best of our knowledge, the present study is the first to compare the effectiveness, safety, and tolerability of nintedanib in patients with mild-to-moderate IPF older than 80 years with younger patients.

We showed that nintedanib is effective and safe in this subset of patients, without any significant differences with those aged ≤80 years.

Despite the frequency of patients aged ≥75 years is 19%[16] in clinical trials, old patients with IPF are increasing (population ageing).[7,8,19,20] In Italy nintedanib is the only antifibrotic drug approved for IPF patients aged >80 years but no specific data has been previously collected. Assessment of the effectiveness, tolerability, and safety of the drug in this subgroup of patients is key.

IPF is a progressive disease with an unpredictable course; patients with a preserved lung function can benefit from an antifibrotic treatment[4,21-23]. In our study, the baseline mean FVC was 85% of the predicted value without any significant differences between younger and older patients (86% VS. 83%), showing that an early treatment initiation was performed in older patients.

A similar FVC decline was found in patients aged ≤80 and >80 years. The decline of absolute values of FVC was lower than that reported in INPULSIS trials but the reduction of FVC percentage of predicted value during the first year of treatment was comparable with other real-life studies.[9,11-14] No differences were found for dyspnea and other functional parameters (i.e., DLCO, meters at 6mWT, and SpO2%) suggesting similar pharmacological effect on gas exchange.

Our findings are consistent with those of previous clinical trials and observational studies which failed to demonstrate a significant difference in FVC decline between patients ≥75 years versus <75 years.[8,14-16]. Our data showed that nintedanib in older IPF patients can improve the functional decline when baseline FVC is >90% and that the rate of patients with stable/improved FVC after one year of treatment is not affected by the age.

The proportion of non-decliner patients was higher than that reported in clinical trials (24.8%)[24]and more similar to a previous observational, Italian study (47.4%).[11]

No significant differences between older and younger patients were recorded for the AEs. Our data are consistent with Glaspole et al. and Takeda et al., who failed to demonstrate differences in the safety profile of nintedanib between patients aged ≥75 VS. those aged <75 years. [15,16] However, Komatsu et al. recently demonstrated a slightly higher rate of AEs in IPF patients ≥75 years.[14]

Diarrhoea was the most frequent AE without any differences in terms of severity;[14,16] The rate of diarrhoea is consistent with that described in both INPULSIS trials and observational real-life studies.[12,13,18]

Only a minority permanently discontinued nintedanib (8.2%). Tzouvelekis et al. and Antoniou et al. described a higher rate of permanent discontinuation (21.2% and 13.1%, respectively) in two real-life studies[12,13].

However, we described a higher rate of permanent dose reduction than that reported by Corte et al. in clinical trials (42.7% VS. 10.7%).[18]

Gastrointestinal events (mostly diarrhoea) and transaminases elevation were the most frequent reasons for drug discontinuation and dose reduction but no differences were found between patients aged ≤80 VS. those aged >80 years. Komatsu et al. failed to show a different rate of nintedanib discontinuation between IPF patients aged ≥75 VS. those aged <75 years[14], unlike Glaspole et al. and Uchida et al. who recorded a higher rate of discontinuation in the elderly.[16,25]

In the vast majority of the cases, gastrointestinal events lead to a permanent discontinuation than to a temporary reduction of the dose: an appropriate management and prevention strategy (e.g., nutritional support and food advice) could be key.[18,26,27]

Interestingly, in a recent observational study, Harari et al. described a higher rate of dose reduction in patients >80 years. However, this difference was statistically significant only in males.[17]

We showed that age did not affect the rate and the outcomes of hospitalization in IPF patients treated with nintedanib, and older age did not affect exacerbations-related outcomes, as previously demonstrated.[14,16]

Some limitations of the study should be acknowledged. The retrospective nature of the study and the role played by confounders could affect the reliability of the findings. The observational design would not be the best methodological option; however, a careful selection of the patients was carried out.

In conclusion, our study showed that nintedanib is effective and safe in patients with IPF aged >80 years, without any significant differences with younger patients. Our data showed that older age should not be a barrier for the early prescription of antifibrotic treatment in mild-to-moderate IPF patients.

Future studies are needed to confirm our findings in non-IPF progressive fibrosing interstitial lung disease.

**Author contribution:** Michele Mondoni: conceptualization; investigation; supervision; writing – original draft; Fausta Alfano: conceptualization; investigation; writing – original draft; Francesco Varone: investigation, writing –review and editing; Catania2XX….. ; Caterina Conti: investigation; writing –review and editing; Amerigo Chiesa: investigation, writing –review and editing; Laura Saderi: formal analysis; writing –review and editing; Fabiano Di Marco: investigation, writing – review and editing; Stefano Centanni: investigation; writing –review and editing; Carlo Vancheri: investigation; writing –review and editing; Luca Richeldi: investigation; writing –review and editing. Giovanni Sotgiu: formal analysis; methodology; supervision; writing – original draft

**Conflict of interest**s: Michele Mondoni received fees for lectures from Boehringer Ingelheim (outside the present work); Fausta Alfano received fees for lectures from Boehringer Ingelheim (outside the present work); Francesco Varone received fees for lectures from Boehringer Ingelheim (outside the present work); XXXXXXX……; Caterina Conti …….; Amerigo Chiesa: ……; Fabiano Di Marco received fees for lectures from Boehringer Ingelheim (outside the present work); Stefano Centanni received fees for lectures from Boehringer Ingelheim (outside the present work); Carlo Vancheri: …….. Luca Richeldi: ……..
Laura Saderi and Giovanni Sotgiu have no conflict of interest to disclose.

**Data availability statement**

Individual de-identified participant data will be available from the corresponding Author for one year after publication upon reasonable request.

**References**


1. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am. J. Respir. Crit. Care. Med.* 2018; **198**(5): e44-e68.
2. Martinez FJ, Collard HR, Pardo A, Raghu G, Richeldi L, Selman M, et al. Idiopathic pulmonary fibrosis. *Nat. Rev. Dis. Primers.* 2017; **3**: 17074.
3. Jo HE, Randhawa S, Corte TJ, Moodley Y. Idiopathic Pulmonary Fibrosis and the Elderly: Diagnosis and Management Considerations. *Drugs Aging.* 2016; **33**(5): 321-34
4. Ley B, Collard HR, King TE Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* 2011; **183**: 431–440.
5. Kreuter M, Swigris J, Pittrow D, Geier S, Klotsche J, Prasse A, et al. The clinical course of idiopathic pulmonary fibrosis and its association to quality of life over time: longitudinal data from the INSIGHTS-IPF registry. *Respir. Res.* 2019; **20**: 59
6. Torrisi SE, Ley B, Kreuter M, Wijsenbeek M, Vittinghoff E, Collard HR, et al.. The added value of comorbidities in predicting survival in idiopathic pulmonary fibrosis: a multicentre observational study. *Eur. Respir. J.* 2019; **53**: 1801587
7. Behr J, Prasse A, Wirtz H, Koschel D, Pittrow D, Held M, et al. Survival and course of lung function in the presence or absence of antifibrotic treatment in patients with idiopathic pulmonary fibrosis: long-term results of the INSIGHTS-IPF registry. *Eur. Respir. J.* 2020; **56**(2): 1902279
8. Leuschner G, Klotsche J, Kreuter M, Prasse A, Wirtz H, Pittrow D, et al. Idiopathic Pulmonary Fibrosis in Elderly Patients: Analysis of the INSIGHTS-IPF Observational Study. *Front. Med.* (Lausanne) 2020; **7**: 601279
9. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N. Engl. J. Med.* 2014; **370**(22): 2071-82

10. Varone F, Sgalla G, Iovene B, Bruni T, Richeldi L. Nintedanib for the treatment of idiopathic pulmonary fibrosis. *Expert. Opin. Pharmacother.* 2018; **19**(2): 167-175
11. Poletti V, Vancheri C, Albera C, Harari S, Pesci A, Metella RR, et al. Clinical course of IPF in Italian patients during 12 months of observation: results from the FIBRONET observational study. *Respir. Res.* 2021; **22**: 66
12. Antoniou K, Markopoulou K, Tzouvelekis A, Trachalaki A, Vasarmidi E, Organtzis J, et al. Efficacy and safety of nintedanib in a Greek multicentre idiopathic pulmonary fibrosis registry: a retrospective, observational, cohort study. *ERJ Open. Res.* 2020; **6**: 00172-2019
13. Tzouvelekis A, Karampitsakos T, Kontou M, Granitsas A, Malliou I, Anagnostopoulos A, et al. Safety and efficacy of nintedanib in idiopathic pulmonary fibrosis: A real-life observational study in Greece. *Pulm. Pharmacol. Ther.* 2018; **49**: 61-66
14. Komatsu M, Yamamoto H, Ichiyama T, Kawakami S, Uehara T, Yoshikawa Y, et al. Tolerability of nintedanib in the elderly with idiopathic pulmonary fibrosis: A single-center retrospective study. *PLoS One*. 2022; **17**(2): e0262795.
15. Takeda T, Kunimatsu Y, Tani N, Hashimoto I, Kurono Y, Hirose K. Improvement in Subjective Symptoms and Tolerability in Response to Nintedanib Treatment in Elderly Patients with Idiopathic Pulmonary Fibrosis. *J. Clin. Med.* 2020; **9**: 755
16. Glaspole I, Bonella F, Bargagli E, Glassberg MK, Caro F, Stansen W, et al. Efficacy and safety of nintedanib in patients with idiopathic pulmonary fibrosis who are elderly or have comorbidities. *Respir. Res*. 2021; **22**: 125.
17. Harari S, Specchia C, Lipsi R, Cassandro R, Caminati A. Older Idiopathic Pulmonary Fibrosis Male Patients Are at a Higher Risk of Nintedanib Dose Reduction. *Respiration*. 2020; **99**: 646-648
18. Corte T, Bonella F, Crestani B, Demedts MG, Richeldi L, Coeck C, et al. Safety, tolerability and appropriate use of nintedanib in idiopathic pulmonary fibrosis. *Respir. Res*. 2015; **16**: 116.

19. Thannickal VJ, Murthy M, Balch WE, Chandel NS, Meiners S, Eickelberg O, et al. Blue journal conference. Aging and susceptibility to lung disease. *Am. J. Respir. Crit. Care Med.* 2015; **191**(3): 261-9

20. Mondoni M, Radovanovic D, Sotgiu G, Di Marco F, Carlucci P, Centanni S, et al. Interventional pulmonology techniques in elderly patients with comorbidities. *Eur. J. Intern. Med.* 2019; **59**: 14-20

21. Torrisi SE, Pavone M, Vancheri A, Vancheri C. When to start and when to stop antifibrotic therapies. *Eur. Respir. Rev.* 2017; **26**(145): 170053

22. Molina-Molina M, Aburto M, Acosta O, Ancochea J, Rodríguez-Portal JA, Sauleda J, et al. Importance of early diagnosis and treatment in idiopathic pulmonary fibrosis. *Expert. Rev. Respir. Med.* 2018; **12**(7): 537-539

23. Kolb M, Richeldi L, Behr J, Maher TM, Tang W, Stowasser S, et al. Nintedanib in patients with idiopathic pulmonary fibrosis and preserved lung volume. *Thorax*. 2017 ; **72**(4): 340-346

24. Flaherty KR, Kolb M, Vancheri C, Tang W, Conoscenti CS, Richeldi L. Stability or improvement in forced vital capacity with nintedanib in patients with idiopathic pulmonary fibrosis. *Eur. Respir. J.* 2018; **52**(2): 1702593

25. Uchida Y, Ikeda S, Sekine A, Katano T, Tabata E, Oda T, et al. Tolerability and safety of nintedanib in elderly patients with idiopathic pulmonary fibrosis. *Respir. Investig.* 2021; **59**: 99-105

26. Bendstrup E, Wuyts W, Alfaro T, Chaudhuri N, Cornelissen R, Kreuter M. Nintedanib in Idiopathic Pulmonary Fibrosis: Practical Management Recommendations for Potential Adverse Events. *Respiration*. 2019; **97**(2): 173-184

27. Faverio P, Fumagalli A, Conti S, Madotto F, Bini F, Harari S, et al. Nutritional assessment in idiopathic pulmonary fibrosis: a prospective multicentre study. *ERJ Open. Res.* 2022; **8**(1):00443-2021

**Tables and figure legends.**

Table 1. Demographic, clinical and functional characteristics of the cohort at baseline, related to age subgroups.

| **Demographic characteristics** | | **Age ≤80 years (n= 106)** | **Age >80 years (n= 53)** | **p-value** |
|---|---|---|---|---|
| Males, n (%) | | 82 (77.4) | 40 (75.5) | 0.79 |
| Race, n (%) | Caucasian | 104 (98.1) | 53 (100.0) | 0.55 |
| | Black | 2 (1.9) | 0 (0.0) | |
| Median (IQR) BMI | | 26.8 (25-29) | 26 (23.6-28.1) | <0.0001 |
| ECOG performance status, n (%) | 0 | 25 (23.6) | 7 (13.2) | 0.12 |
| | 1 | 48 (45.3) | 11 (20.8) | 0.003 |
| | 2 | 29 (27.4) | 22 (41.5) | 0.07 |
| | 3 | 4 (3.8) | 11 (20.8) | 0.0006 |
| | 4 | 0 (0.0) | 2 (3.8) | 0.04 |
| Smoking history at baseline, n (%) | No smoker | 25 (23.6) | 20 (37.7) | 0.06 |
| | Former | 75 (70.8) | 33 (62.3) | |
| | Active smoker | 6 (5.7) | 0 (0.0) | |
| Median (IQR) n. pack/years (n= 114) | | 34 (20-50) | 30 (15-45) | 0.20 |
| **Diagnosis** | | **Age ≤80 years** | **Age >80 years** | **p-value** |
| CT pattern, n (%) | UIP | 62 (59.1) | 37 (69.8) | 0.15 |
| | UIP probable | 33 (31.4) | 16 (30.2) | |
| | Indeterminate | 7 (6.7) | 0 (0.0) | |
| | Suggestive of other diagnosis | 3 (2.9) | 0 (0.0) | |
| Histological pattern (if biopsy), n (%) | UIP | 10 (90.9) | - | - |
| | UIP probable | 1 (9.1) | - | |
| | Indeterminate | - | - | |
| **Comorbidities** | | **Age ≤80 years** | **Age >80 years** | **p-value** |
| Coronary artery disease, n (%) | | 16 (15.1) | 14 (26.4) | 0.09 |
| Arterial hypertension, n (%) | | 56 (52.8) | 33 (62.3) | 0.26 |
| Emphysema, n (%) | | 24 (22.6) | 12 (22.6) | 1.00 |
| Diabetes mellitus, n (%) | | 26 (24.5) | 7 (13.2) | 0.10 |
| OSAS, n (%) | | 20 (18.9) | 6 (11.3) | 0.23 |
| Pulmonary hypertension, n (%) | | 17 (16.0) | 13 (24.5) | 0.20 |
| GE reflux, n (%) | | 49 (46.2) | 19 (35.9) | 0.24 |
| Pulmonary neoplasia, n (%) | | 3 (2.8) | 3 (5.7) | 0.40 |
| **Respiratory function at baseline** | | **Age ≤80 years** | **Age >80 years** | **p-value** |
| Mean (DS) FVC, ml | | 2866 (797.0) | 2422 (760.1) | 0.001 |
| Median (IQR) FVC, % predicted | | 86 (74-95) | 83 (71-95) | 0.41 |
| Median (IQR) DLCO, % predicted | | 54.5 (43-67) | 49 (39-63) | 0.07 |
| Median (IQR) DLCO, ml | | 11.0 (8.1-14.4) | 9.0 (6.3-12.1) | 0.006 |
| Mean (SD) 6MWT, m | | 424.9 (105.5) | 344.7 (103.8) | <0.0001 |
| Median (IQR) SpO2, % | | 97 (95-98) | 95 (94-97) | 0.001 |
| Mean (SD) mMRC | | 1.7 (0.7) | 2.1 (0.8) | 0.002 |
| Mean (SD) GAP | | 3.3 (1.2) | 4.0 (1.1) | 0.001 |
| Mean (SD) TORVAN | | 14.2 (5.1) | 16.6 (4.3) | 0.004 |

BMI: body mass index; ECOG Eastern Cooperative Oncology Group; CT: computed tomography; UIP: usual interstitial pneumonia; OSAS: Obstructive sleep apnea syndrome; GE: gastro-esophageal; FVC: forced vital capacity; DLCO: diffusion of lung for carbon monoxide; 6MWT: six-minutes walking test; SpO2: oxygen saturation; mMRC: modified British Medical Research Council Questionnaire

Table 2. Change in functional data during the study period.

| ***Decline on treatment (n= 133)*** | **Age ≤80 years (n= 92)** | **Age >80 years (n= 41)** | **p-value** |
|---|---|---|---|
| Median (IQR) FVC, ml | -45 (-170; 75) | -20 (-138; 110) | 0.51 |
| Median (IQR) FVC, % predicted | 0 (-5; 3) | 1 (-4; 6) | 0.25 |
| Mean (SD) DLCO, % predicted | -5.3 (11.3) | -6.1 (9.9) | 0.68 |
| Median (IQR) DLCO, ml | -0.9 (-2.4; -0.03) | -0.8 (-2.5; -0.05) | 0.89 |
| Median (IQR) 6MWT, m | -20 (-50; 20) | -30 (-95; 20) | 0.48 |
| Mean (SD) SpO2, % | -0.3 (1.5) | 0.3 (1.9) | 0.6 |
| Mean (SD) mMRC | 0.3 (0.4) | 0.2 (0.6) | 0.95 |
| Median (IQR) GAP | 0 (0-1) | 0 (0-1) | 0.76 |
| Median (IQR) TORVAN | 0 (0-1) | 0 (0-1) | 0.49 |
| ***Decline intention-to-treat (n= 26)*** | **Age ≤80 years (n= 14)** | **Age >80 years (n= 12)** | **p-value** |
| Mean (SD) FVC, ml | -37 (387.5) | -119.2 (227.3) | 0.53 |
| Mean (SD) FVC, % predicted | 0.8 (13.3) | -3.8 (8.3) | 0.31 |
| Mean (SD) DLCO, % predicted | -5.3 (9.4) | -3.7 (5.0) | 0.60 |
| Median (IQR) DLCO, ml | -1.2 (-3.2; -0.01) | -0.3 (-0.5; -0.1) | 0.34 |
| Mean (SD) 6MWT, m | -24.3 (86.9) | -26.3 (71.6) | 0.95 |
| Mean (SD) SpO2, % | -0.2 (1.5) | -0.5 (1.2) | 0.60 |
| Mean (SD) mMRC | 0.1 (0.5) | 0.4 (0.6) | 0.14 |
| Median (IQR) GAP | 0 (0-1) | 0 (0-0.5) | 0.83 |
| Median (IQR) TORVAN | 0 (0-1) | 0 (0-1.5) | 0.77 |

FVC: forced vital capacity; DLCO: diffusion of lung for carbon monoxide; 6MWT: six-minutes walking test; SpO2: oxygen saturation; mMRC: modified British Medical Research Council Questionnaire

Table 3. Summary of the rate and outcomes related to acute exacerbations, hospitalization and mortality.

| ***Acute exacerbations*** | **Age ≤80 years** | **Age >80 years** | **p-value** |
|---|---|---|---|
| Rate, *n (%)* | 3 (2.8) | 2 (3.8) | 1.00 |
| Mean (SD) days to first exacerbation | 270 (79.4) | 170 (141.4) | 0.37 |
| Outcome of exacerbation: death, *n (%)* | 1 (25.0) | 0 (0.0) | 1.00 |
| ***Hospitalization*** | **Age ≤80 years** | **Age >80 years** | **p-value** |
| Rate, *n (%)* | 5 (11.9) | 7 (25.9) | 0.22 |
| Mean (SD) days to first hospitalization | 248.4 (163.4) | 196.6 (122.7) | 0.54 |
| Hospitalization due to worsening IPF, *n (%)* | 0 (0.0) | 1 (14.3) | 1.00 |
| Hospitalization due to IPF exacerbation, *n (%)* | 2 (40.0) | 1 (14.3) | 1.00 |
| Non-respiratory cause, *n (%)* | 3 (60.0) | 5 (71.4) | 1.00 |
| Outcome of hospitalisation: death, *n (%)* | 0 (0.0) | 0 (0.0) | - |
| ***Mortality*** | **Age ≤80 years** | **Age >80 years** | **p-value** |
| Death during therapy, *n (%)* | 1 (1.0) | 1 (1.9) | 0.11 |
| Mean (SD) days to death | 215 (-) | 200 (-) | - |
| Death due to IPF worsening, *n (%)* | 0 (0.0) | 0 (0.0) | - |
| Death due to IPF exacerbation, *n (%)* | 0 (0.0) | 0 (0.0) | - |
| Death due to cause other than IPF, *n (%)* | 1 (100.0) | 0 (0.0) | 1.00 |

IPF: idiopathic pulmonary fibrosis

Table 4. Summary of adverse events.

| ***Adverse events*** | | **Age ≤80 years** | **Age >80 years** | **p-value** |
|---|---|---|---|---|
| Diarrhoea, n (%) | No | 42 (39.6) | 23 (44.2) | 0.58 |
| | Mild | 36 (34.0) | 12 (23.1) | 0.16 |
| | Moderate | 20 (18.9) | 15 (28.9) | 0.16 |
| | Severe | 8 (7.6) | 2 (3.9) | 0.37 |
| Nausea, n (%) | | 16 (15.1) | 10 (19.2) | 0.51 |
| Vomit, n (%) | | 6 (5.7) | 5 (9.6) | 0.34 |
| Elevated transaminases, n (%) | | 21 (19.8) | 6 (11.5) | 0.19 |
| Weight loss, n (%) | | 37 (34.9) | 21 (40.4) | 0.50 |
| Rhinopharyngitis, n (%) | | 0 (0.0) | 1 (1.9) | 0.33 |
| Cough, n (%) | | 22 (20.8) | 7 (13.5) | 0.27 |
| Upper airways infection, n (%) | | 14 (13.2) | 7 (13.5) | 0.97 |
| IPF progression, n (%) | | 21 (19.8) | 12 (23.1) | 0.64 |
| Cardiovascular events, n (%) | | 1 (1.6) | 1 (2.9) | 1.00 |
| Bleeding, n (%) | | 3 (4.7) | 3 (8.8) | 0.42 |
| Severe AEs, n (%) | | 3 (2.9) | 6 (11.8) | 0.06 |
| Serious AEs, n (%) | | 5 (5.3) | 3 (6.7) | 0.71 |

IPF: idiopathic pulmonary fibrosis. AE: adverse event. Severe AE: event that was incapacitating or that caused an inability to work or to perform usual activities. Serious AE: any 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

Table 5. Rate and reasons for dose reduction and/or drug discontinuation

| **AEs leading to permanent discontinuation of the drug** | **Age ≤80 years** | **Age >80 years** | **p-value** |
|---|---|---|---|
| Elevated transaminases, n (%) | 0 (0.0) | 0 (0.0) | - |
| Gastrointestinal events, n (%) | 5 (20.0) | 7 (41.2) | 0.14 |
| Cardiovascular events, n (%) | 0 (0.0) | 0 (0.0) | - |
| Respiratory/thoracic/mediastinal events, n (%) | 0 (0.0) | 0 (0.0) | - |
| Other | 1 (2.9) | 0 (0.0) | 1.00 |
| **AEs leading to temporary discontinuation of the drug** | **Age ≤80 years** | **Age >80 years** | **p-value** |
| Median (IQR) days of discontinuation | 21 (15-38) | 20 (14-30) | 0.51 |
| Elevated transaminases, n (%) | 15 (41.7) | 5 (22.7) | 0.14 |
| Gastrointestinal events, n (%) | 25 (69.4) | 15 (68.2) | 0.92 |
| Cardiovascular events, n (%) | 0 (0.0) | 0 (0.0) | - |
| Respiratory/thoracic/mediastinal events, n (%) | 0 (0.0) | 0 (0.0) | - |
| Other | 3 (8.3) | 4 (18.2) | 0.41 |
| **AEs leading to permanent dose reduction** | **Age ≤80 years** | **Age >80 years** | **p-value** |
| Elevated transaminases, n (%) | 15 (36.6) | 5 (17.2) | 0.08 |
| Gastrointestinal events, n (%) | 29 (70.7) | 21 (72.4) | 0.88 |
| Cardiovascular events, n (%) | 0 (0.0) | 0 (0.0) | - |
| Respiratory/thoracic/mediastinal events, n (%) | 0 (0.0) | 0 (0.0) | - |
| Other | 3 (7.3) | 5 (17.2) | 0.26 |
| **AEs leading to temporary dose reduction** | **Age ≤80 years** | **Age >80 years** | **p-value** |
| Median (IQR) days of dose reduction | 112.3 (76.2) | 90 (-) | 1.00 |
| Elevated transaminases, n (%) | 2 (28.6) | 0 (0.0) | - |
| Gastrointestinal events, n (%) | 4 (57.1) | 1 (100.0) | 1.00 |
| Cardiovascular events, n (%) | 0 (0.0) | 0 (0.0) | - |
| Respiratory/thoracic/mediastinal events, n (%) | 0 (0.0) | 0 (0.0) | - |
| Other | 1 (14.3) | 0 (0.0) | 1.00 |

AEs: adverse events

Figure 1 legend. FVC (ml) decline after one year of treatment related to age subgroups.

**Supplementary material**

Table 1 supplement.

| | Age ≤80 years | Age >80 years | p-value |
|---|---|---|---|
| | n (%) | | |
| FVC, ml stable or improved: 57/133 (42.9%) | 37 (40.2) | 20 (48.8) | 0.36 |
| FVC, % stable or improved: 76/133 (57.1%) | 49 (53.3) | 27 (65.9) | 0.18 |
| FVC, % reduction ≥10%: 17/57 (29.8%) | 10 (23.3) | 7 (50.0) | 0.06 |

FVC: forced vital capacity

Table 2 supplement.

| ***Total cohort*** | **FVC at baseline >90% (n= 47)** | **FVC at baseline ≤90% (n= 86)** | **p-value** |
|---|---|---|---|
| Median (IQR) decline* of FVC, ml | -40 (-120; 100) | -30 (-190; 90) | 0.45 |
| ***Age ≤80 years*** | (n= 33) | (n= 59) | |
| Median (IQR) decline* of FVC, ml | -40 (-130; 70) | -50 (-190; 90) | 0.47 |
| ***Age >80 years*** | (n= 47) | (n= 86) | |
| Mean (IQR) decline* of FVC, ml | --0.7 (233.3) | -62.9 (311.1) | 0.51 |

FVC: forced vital capacity