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Investigating the effects of nintedanib on biomarkers of extracellular matrix turnover in patients with IPF: design of the randomised placebo-controlled INMARK®trial

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ABSTRACT

Introduction A feature of the pathogenesis of idiopathic pulmonary fibrosis (IPF) is the excess accumulation of extracellular matrix (ECM) in the lungs. Cleavage of the ECM by metalloproteinases (MMPs) generates free-circulating protein fragments known as neoepitopes. The PROFILE study suggested that changes in ECM turnover proteins may be of value as markers of disease progression in patients with IPF. Nintedanib is an approved treatment for IPF that slows disease progression by reducing decline in forced vital capacity (FVC).

Methods and analysis The INMARK® trial is evaluating the effect of nintedanib on the rates of change of biomarkers of ECM turnover in patients with IPF, the value of changes in these biomarkers as predictors of disease progression and whether nintedanib affects the associations between changes in these biomarkers and disease progression. Following a screening period, 347 patients with IPF and FVC ≥80% predicted were randomised 1:2 to receive nintedanib 150 mg two times a day or placebo for 12 weeks, followed by an open-label period in which all patients will receive nintedanib for 40 weeks. The primary endpoint is the rate of change in C reactive protein degraded by MMP-1/8 from baseline to week 12.

Ethics and dissemination This trial is being conducted in compliance with the protocol, the ethical principles detailed in the Declaration of Helsinki and in accordance with the International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice. The results of the trial will be presented at national and international meetings and published in peer-reviewed journals.

Trial registration number NCT02788474.

Key messages

- Protein fragments associated withextracellular matrix turnover (neoepitopes) may be of value as markers ofdisease progression in patients with idiopathic pulmonary fibrosis (IPF).
- Nintedanib is an approved treatment forIPF that slows disease progression by reducing decline in lung function.
- The INMARK study is investigating thevalue of changes in neoepitopes as predictors of disease progression, andthe effect of nintedanib on the rates of change of these biomarkers, inpatients with IPF.

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing interstitial lung disease characterised by decline in lung function and worsening dyspnoea.[1] The clinical course of IPF is variable but its prognosis is poor, with data collected prior to the availability of antifibrotic drugs suggesting a median survival following diagnosis of only 2–3 years.[1] Although a decline in forced vital capacity (FVC) is considered evidence of disease progression in patients with IPF and is predictive of mortality, the course of disease for an individual patient remains unpredictable.[2 3] A number of biomarkers have been investigated as predictors of disease progression in cohorts of patients with IPF, including gene expression profiles,[4 5] serum levels of proteins associated with lung epithelial injury and tissue remodelling (eg, KL-6, matrix metalloproteinase (MMP)-7, surfactant protein D (SP-D)),[6–10] concentrations of type III procollagen peptide in bronchoalveolar lavage fluid,[11] the bacterial load in the lungs[12 13] and radiological features on high-resolution CT (HRCT) of the chest[14–16]; however, no biomarker can yet be used to predict or assess disease progression or to guide management in an individual patient. In a statement from the American Thoracic Society published in 2016, defining endpoints that more accurately reflect the degree of fibrogenesis,

matrix turnover and functional consequences of fibrosis was identified as a pressing research need.[17]

A hallmark of the pathogenesis of IPF is the excess accumulation of extracellular matrix (ECM) in the lungs and remodelling of the lung architecture. Activation of fibroblasts and their differentiation into myofibroblasts results in an increase in the synthesis, deposition and cross-linking of the ECM.[18–20] Degradation of the ECM is primarily performed by MMPs[21] and generates free-circulating fragments of collagen known as neoepitopes.[22 23] As neoepitopes represent unique end-products of proteolytic cleavage of the ECM, concentrations of specific neoepitopes, or changes in these concentrations, may be useful markers of disease progression in patients with IPF, even if they are not directly involved in its pathogenesis. To this end, the prospective, multicentre PROFILE study investigated 11 MMP-generated neoepitopes as predictors of disease progression in treatment-naïve patients with IPF.[24] The trial had a two-stage design, with initial analyses conducted in a discovery cohort of 55 patients and detailed analyses conducted in a validation cohort of 134 patients. In the validation cohort, increased concentrations of six neoepitopes (biglycan degraded by MMP-2/9 (BGM), collagen 1 degraded by MMP (C1M), collagen 3 degraded by ADAMTS-1/4/8 (C3A), collagen 3 degraded by MMP-9 (C3M), collagen 6 degraded by MMP-2/9 (C6M), C reactive protein degraded by MMP-1/8 (CRPM)) over 6 months were associated with disease progression, defined as absolute decline in FVC ≥10% predicted or death at month 12. A higher rate of increase in six neoepitopes (BGM, C1M, C3M, collagen 5 degraded by MMP-2/9 (C5M), C6M, CRPM) over 3 months was associated with worse survival. Mortality was significantly greater in patients with increasing concentrations of C1M, C5M, C6M and CRPM over 3 months (rate >0 ng/mL/month) than in those with stable or falling concentrations of these neoepitopes over 3 months (rate ≤0 ng/mL/month). The strongest association was observed with CRPM.[24]

Nintedanib is an intracellular inhibitor of tyrosine kinase receptors, including the fibroblast growth factor receptor, platelet-derived growth factor receptor and vascular endothelial growth factor receptor as well as non-receptor members of the Src family.[25 26] Nintedanib has shown antifibrotic activity in several in vitro and in vivo models of lung fibrosis.[26–28] In lung fibroblasts from patients with IPF, nintedanib reduces fibroblast/myofibroblast proliferation and differentiation, induces secretion of MMP-2 and reduces ECM secretion.[27] In clinical trials, nintedanib slowed disease progression by reducing the annual rate of decline in FVC compared with placebo,[29 30] resulting in its approval in many countries as a treatment for IPF.

Here we describe the objectives and design of the INMARK® trial. The main objectives of this trial are to evaluate the effect of nintedanib on the rate of change of biomarkers of ECM turnover in patients with IPF, confirm the prognostic value of changes in biomarkers of ECM turnover for disease progression, and assess whether nintedanib affects the association between changes in biomarkers of ECM turnover and disease progression.

Table 1 Key eligibility criteria for participation in INMARK®

Key inclusion criteria	Key exclusion criteria
Age ≥40 years	ALT or AST or total bilirubin >1.5 × upper limit of normal at screening
Diagnosis of IPF according to ATS/ERS/JRS/ALAT guidelines (Raghu *et al*, 2011[1] within last 3 years)	FEV_1/FVC<0.70 (prebronchodilator)
Chest HRCT (performed within 18 months of screening) and surgical lung biopsy pattern (if available) consistent with a diagnosis of IPF, assessed by central review	Myocardial infarction within 6 months or unstable angina within 1 month of screening
FVC ≥80% predicted at screening	Bleeding risk (eg, requiring full-dose therapeutic anticoagulation or high-dose antiplatelet therapy)
	History of a thrombotic event within 12 months of screening
	Treatment with nintedanib, pirfenidone, azathioprine, cyclophosphamide, cyclosporine or any investigational drug was not permitted within 4 weeks of randomisation

ALT, alanine transaminase; AST, aspartate transaminase; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HRCT, high-resolution CT; IPF, idiopathic pulmonary fibrosis.

METHODS AND ANALYSIS

Eligibility criteria

Key eligibility criteria are summarised in table 1. Briefly, patients aged ≥40 years, with a diagnosis of IPF according to ATS/ERS/JRS/ALAT guidelines[1] within 3 years, chest HRCT and surgical lung biopsy pattern (if available) consistent with a diagnosis of IPF and FVC ≥80% predicted were eligible to participate.

Trial design

Following a 2–4-week screening period, 347 patients in 13 countries were randomised 1:2 to receive nintedanib 150 mg two times a day or placebo double-blind for 12 weeks, followed by an open-label period in which all patients will receive nintedanib 150 mg two times a day for 40 weeks, with a follow-up visit 4 weeks later (figure 1). Patients who prematurely discontinue trial drug are asked to attend all visits as planned.

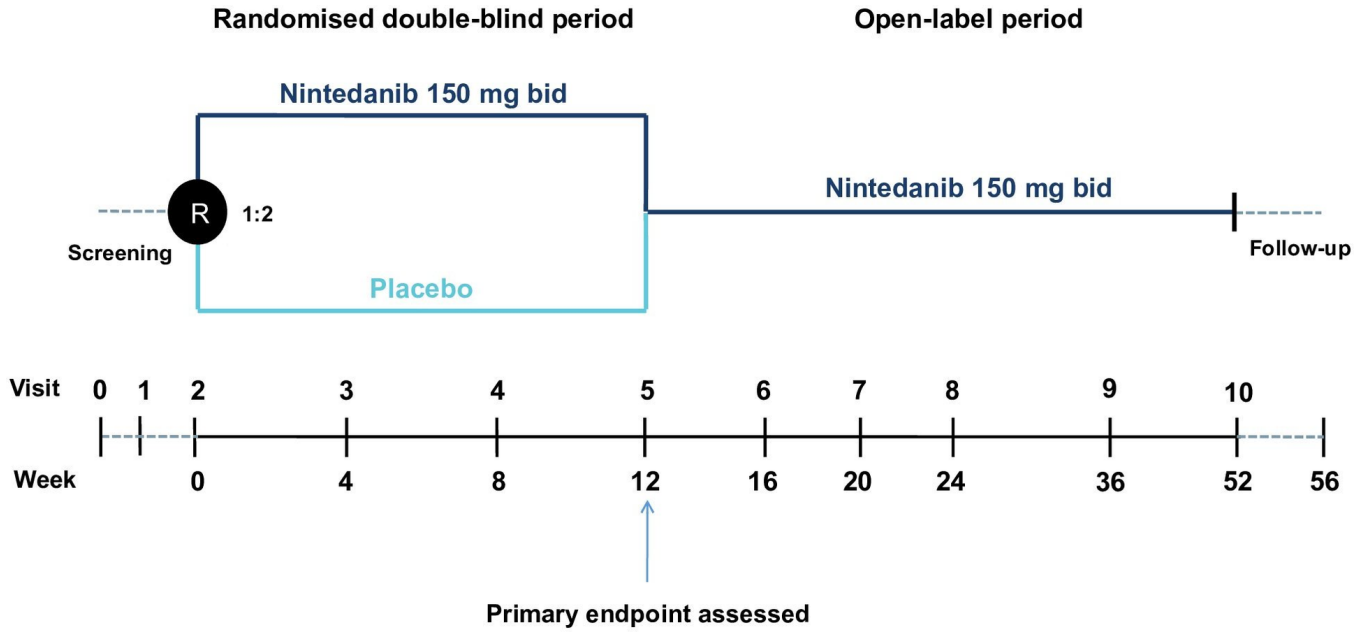

Figure 1 Design of the INMARK® trial.

Dosing

Nintedanib 150 mg two times a day is the recommended dose for the treatment of IPF. Dose reductions to 100 mg two times a day and treatment interruptions are recommended to manage adverse events, based on similar recommendations as were provided in the INPULSIS trials.[30] After resolution of the adverse event, nintedanib can be reintroduced and re-escalated to 150 mg two times a day at the discretion of the investigator.

Trial endpoints

Trial endpoints are presented in table 2. The primary endpoint is the rate of change in serum CRPM (ng/mL/month) evaluated from baseline to week 12. Whole blood samples will be collected at baseline and weeks 4, 8 and 12. As in the PROFILE study, change in serum CRPM will be categorised as stable or falling (≤0 ng/mL/month) or rising (>0 ng/mL/month) over 12 weeks. The proportion of patients with disease progression (defined as absolute decline in FVC ≥10% predicted or death) over 52 weeks is a key secondary endpoint. The rates of change in serum C3M and serum C1M from baseline to week 12 are secondary endpoints.

The annual rate of decline in FVC (mL/year) and the annual rate of decline in forced expiratory volume in 6 s (mL/year) will also be assessed based on home spirometry. Home spirometry devices (SpiroPro) and instructions were given to patients at screening. Patients are asked to perform home-based spirometry at least once a week, but ideally on a daily basis, from screening until week 52. In-clinic spirometry will be conducted at screening, baseline and weeks 4, 8, 12, 16, 20, 24, 36 and 52, in accordance with ATS/ERS guidelines.[31] In-clinic spirometry results will be centrally reviewed.

Further endpoints include change from baseline in the St George's Respiratory Questionnaire (SGRQ) total score,[32] a measure of health-related quality of life in patients with chronic respiratory diseases over 52 weeks, change from baseline in the University of California San Diego Shortness of Breath Questionnaire (UCSD-SOBQ)[33] over 52 weeks, and time to first acute exacerbation over 52 weeks. Acute exacerbations are defined, as in the INPULSIS trials,[30] as events meeting all the following criteria: unexplained worsening or development of dyspnoea within 30 days; new diffuse pulmonary infiltrates on chest X-ray and/or new HRCT parenchymal abnormalities with no pneumothorax or pleural effusion (new ground-glass opacities) since last visit; exclusion of infection as per routine clinical practice and microbiological studies; exclusion of alternative causes as per routine clinical practice, including left heart failure, pulmonary embolism and any identifiable cause of acute lung injury.

Safety will be assessed via the recording of adverse events with onset after the first dose and up to 28 days after the last dose of study drug, physical examination, weight measurements, 12-lead ECG, vital signs and laboratory parameters. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Predose plasma concentrations of nintedanib and its metabolites (BIBF1202 and BIBF 1202-glucuronide)[34] will be determined at weeks 4, 16 and 52.

Statistical analysis

Efficacy and safety analyses will be conducted in patients who received ≥1 dose of study medication. Sample size calculations were based on two-sided tests (α=0.05) to provide 90% power to detect a relative difference between groups of 20% on the primary endpoint. Rates

Table 2 Endpoints in the INMARK® trial

Primary endpoint	Rate of change in serum CRPM from baseline to week 12
Key secondary endpoint	Proportion of patients with absolute decline in FVC ≥10% predicted or who died over 52 weeks
Secondary endpoints	Rate of change in serum C1M from baseline to week 12
	Rate of change in serum C3M from baseline to week 12
Further endpoints	Rate of change in serum CRPM from week 12 to week 52
	Rate of change in serum C1M from week 12 to week 52
	Rate of change in serum C3M from week 12 to week 52
	Rate of change in serum BGM from baseline to week 12
	Rate of change in serum C3A from baseline to week 12
	Rate of change in serum C5M from baseline to week 12
	Rate of change in serum C6M from baseline to week 12
	Rate of change in serum VICM from baseline to week 12
	Rate of change in serum BGM from week 12 to week 52
	Rate of change in serum C3A from week 12 to week 52
	Rate of change in serum C5M from week 12 to week 52
	Rate of change in serum C6M from week 12 to week 52
	Rate of change in serum VICM from week 12 to week 52
	Proportion of patients with absolute decline in FVC ≥5% predicted over 52 weeks
	Proportion of patients with absolute decline in FVC ≥10% predicted over 52 weeks
	Proportion of patients who had absolute decline in FVC ≥5% predicted or who died over 52 weeks
	Time to decline in FVC ≥5% predicted over 52 weeks
	Time to decline in FVC ≥10% predicted over 52 weeks
	Time to decline in FVC ≥5% predicted or death over 52 weeks
	Time to decline in FVC ≥10% predicted or death over 52 weeks
	Annual rate of decline in FVC (mL/year)
	Absolute change from baseline in FVC % predicted at week 52
	Absolute change from baseline in FVC (mL) at week 52
	Relative change from baseline in FVC (% predicted) at week 52
	Relative change from baseline in FVC (mL) at week 52
	Annual rate of decline in FEV_6 (mL/year) based on home spirometry
	Annual rate of decline in FVC (mL/year) based on home spirometry
	Time to first acute exacerbation over 52 weeks
	Change from baseline in SGRQ total score over 52 weeks
	Change from baseline in UCSD-SOBQ over 52 weeks
	Predose plasma concentrations of nintedanib and its metabolites (BIBF 1202 and BIBF 1202-glucuronide)

All spirometry endpoints are based on clinic assessments unless otherwise stated. BGM, biglycan degraded by MMP-2/9; CRPM, C reactive protein degraded by MMP-1/8; C1M, collagen 1 degraded by MMP; C3A, collagen 3 degraded by ADAMTS-1/4/8; C3M, collagen 3 degraded by MMP-9; C5M, collagen 5 degraded by MMP-2/9; C6M, collagen 6 degraded by MMP-2/9; FEV_6, forced expiratory volume in 6 s; FVC, forced vital capacity; MMP, metalloproteinase; SGRQ, St. George's Respiratory Questionnaire; UCSD-SOBQ, University of California San Diego Shortness of Breath Questionnaire; VICM, citrullinated vimentin degraded by MMP-2/8.

of change in serum CRPM, C3M and C1M from baseline to week 12 will be analysed using a random coefficient regression model (with random slopes and intercepts) including baseline CRPM, treatment, sex, age and height as covariates. Missing data will not be imputed.

The proportion of patients with disease progression over 52 weeks will be analysed using logistic regression models. First, to confirm the prognostic value of changes in biomarkers of ECM turnover for disease progression, a logistic regression analysis including baseline CRPM and the rate of change in serum CRPM from baseline to week 12 as covariates will be assessed in placebo-treated patients only. Second, to assess whether nintedanib affects the association between changes in biomarkers of ECM turnover and disease progression, a logistic regression analysis including baseline CRPM, the rate of change in serum CRPM from baseline to week 12, treatment and treatment CRPM slope interaction as covariates will be applied. Third, to assess whether nintedanib affects disease progression, a logistic regression analysis including baseline CRPM, rate of change in serum CRPM from baseline to week 12 and treatment as covariates will be applied.

Changes in SGRQ and UCSD-SOBQ over 52 weeks will be analysed using a mixed model for repeated measures, with treatment and visit as fixed effects, baseline total score as a covariate and treatment-by-visit and baseline-by-visit as interaction terms. Safety data will be descriptive.

ETHICS AND DISSEMINATION

The INMARK® trial is being conducted in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki and in accordance with the International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice. All patients provided written informed consent prior to trial entry. The trial has been registered with ClinicalTrials.gov (NCT02788474; EudraCT 2015-003148-38). The results of the trial will be presented at national and international meetings and published in peer-reviewed journals.

DISCUSSION

The INMARK® trial aims to illuminate the effects of nintedanib on changes in biomarkers of ECM turnover in patients with IPF and confirm the prognostic value of these biomarkers for disease progression. Validation of early markers of disease progression in patients with IPF has the potential to bring benefits to clinical practice and to facilitate shorter proof-of-concept studies for new therapies.

In the PROFILE study, the rate of change in serum CRPM over 3 months was predictive of survival in patients with IPF over a median follow-up of almost 2 years.[24] The INMARK® trial will evaluate the effect of nintedanib on rate of change in serum CRPM over essentially the same time period. A 12-week placebo-controlled period was considered acceptable given that only patients with relatively well preserved lung function (FVC ≥80% predicted) at baseline are eligible to participate. Although the effect of nintedanib on slowing the rate of FVC decline is the same in patients with preserved FVC as in those with greater impairment

in lung volume,[35 36] many do not receive antifibrotic treatment in clinical practice. Following the 12-week placebo-controlled treatment period, all patients will receive open-label nintedanib, enabling assessment of disease behaviour for up to 52 weeks and providing data on the impact of a 3-month delay in initiation of therapy on outcomes. A further objective of the INMARK® trial is to assess the association between changes in biomarkers of ECM turnover over 12 weeks and disease progression in placebo-treated patients, to confirm the results of the PROFILE study. A 1:2 randomisation ratio of nintedanib to placebo has been used to increase the power to assess this. Disease progression has been defined as an absolute decline in FVC ≥10% predicted (a degree of decline that has been shown to be predictive of mortality in patients with IPF)[37] or death.

Further analyses of data from the prospective PROFILE study identified three serum biomarkers of epithelial injury (SP-D, CA19-9, CA-125) that might be predictive of disease progression and mortality in patients with IPF.[10] The INMARK® trial provides an opportunity to undertake exploratory assessments of a range of alternative biomarkers related to fibrogenesis, tissue remodelling and inflammation, including KL-6, SP-D, CRP and interleukin-8 as well as gene expression analyses.

In the INMARK® trial, FVC will be assessed via home spirometry as well as regular in-clinic spirometry, enabling comparison of values obtained in the clinic with home measurements taken more frequently. Home spirometry may allow a more sensitive estimate of FVC decline, as more frequent assessment may result in greater accuracy in calculating the slope. In addition, more frequent measurement of FVC at home may enable early detection of rapidly declining FVC, thereby enabling early identification of patients with disease progression or an acute exacerbation.[38] In two small studies conducted to examine the feasibility and reliability of using home spirometry in patients with IPF, FVC values obtained using home spirometry showed excellent correlation with readings taken in the clinic.[38 39]

In conclusion, the results of the INMARK® trial will provide insights into associations between changes in biomarkers of ECM turnover and disease progression and whether treatment with nintedanib affects the rate of change in such biomarkers, in patients with IPF and limited FVC impairment. These insights might aid the prediction of disease progression in individuals with IPF.

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Patient consent Not required.

Ethics approval This trial is conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

REFERENCES

1. Raghu G, Collard HR, Egan JJ, *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* 2011;183:788–824.
2. Schmidt SL, Tayob N, Han MK, *et al*. Predicting pulmonary fibrosis disease course from past trends in pulmonary function. *Chest* 2014;145:579–85.
3. Ley B, Bradford WZ, Vittinghoff E, *et al*. Predictors of mortality poorly predict common measures of disease progression in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2016;194:711–8.
4. Peljto AL, Zhang Y, Fingerlin TE, *et al*. Association between the MUC5B promoter polymorphism and survival in patients with idiopathic pulmonary fibrosis. *JAMA* 2013;309:2232–9.
5. Herazo-Maya JD, Sun J, Molyneaux PL, *et al*. Validation of a 52-gene risk profile for outcome prediction in patients with idiopathic pulmonary fibrosis: an international, multicentre, cohort study. *Lancet Respir Med* 2017;5:857–68.
6. Greene KE, King TE, Kuroki Y, *et al*. Serum surfactant proteins-A and -D as biomarkers in idiopathic pulmonary fibrosis. *Eur Respir J* 2002;19:439–46.
7. Yokoyama A, Kondo K, Nakajima M, *et al*. Prognostic value of circulating KL-6 in idiopathic pulmonary fibrosis. *Respirology* 2006;11:164–8.
8. Rosas IO, Richards TJ, Konishi K, *et al*. MMP1 and MMP7 as potential peripheral blood biomarkers in idiopathic pulmonary fibrosis. *PLoS Med* 2008;5:e93.
9. Richards TJ, Kaminski N, Baribaud F, *et al*. Peripheral blood proteins predict mortality in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2012;185:67–76.
10. Maher TM, Oballa E, Simpson JK, *et al*. An epithelial biomarker signature for idiopathic pulmonary fibrosis: an analysis from the multicentre PROFILE cohort study. *Lancet Respir Med* 2017;5:946–55.
11. Bjermer L, Lundgren R, Hällgren R. Hyaluronan and type III procollagen peptide concentrations in bronchoalveolar lavage fluid in idiopathic pulmonary fibrosis. *Thorax* 1989;44:126–31.
12. Molyneaux PL, Cox MJ, Willis-Owen SA, *et al*. The role of bacteria in the pathogenesis and progression of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2014;190:906–13.
13. Han MK, Zhou Y, Murray S, *et al*. Association between lung microbiome and disease progression in IPF: a prospective cohort study. *Lancet Respir Med* 2014;2:548–56.
14. Park HJ, Lee SM, Song JW, *et al*. Texture-based automated quantitative assessment of regional patterns on initial CT in patients with idiopathic pulmonary fibrosis: relationship to decline in forced vital capacity. *AJR Am J Roentgenol* 2016;207:976–83.
15. Salisbury ML, Lynch DA, van Beek EJ, *et al*. Idiopathic pulmonary fibrosis: the association between the adaptive multiple features method and fibrosis outcomes. *Am J Respir Crit Care Med* 2017;195:921–9.
16. Jacob J, Bartholmai BJ, Rajagopalan S, *et al*. Predicting outcomes in idiopathic pulmonary fibrosis using automated CT analysis. *Am J Respir Crit Care Med* 2018. Epub ahead of print.
17. White ES, Borok Z, Brown KK, *et al*. An American Thoracic Society official research statement: future directions in lung fibrosis research. *Am J Respir Crit Care Med* 2016;193:792–800.
18. King TE, Pardo A, Selman M. Idiopathic pulmonary fibrosis. *Lancet* 2011;378:1949–61.
19. Fernandez IE, Eickelberg O. New cellular and molecular mechanisms of lung injury and fibrosis in idiopathic pulmonary fibrosis. *Lancet* 2012;380:680–8.
20. Philp CJ, Siebeke I, Clements D, *et al*. Extracellular matrix cross-linking enhances fibroblast growth and protects against matrix proteolysis in lung fibrosis. *Am J Respir Cell Mol Biol* 2018;58:594–603.
21. Pardo A, Cabrera S, Maldonado M, *et al*. Role of matrix metalloproteinases in the pathogenesis of idiopathic pulmonary fibrosis. *Respir Res* 2016;17:23.
22. Karsdal MA, Krarup H, Sand JM, *et al*. Review article: the efficacy of biomarkers in chronic fibroproliferative diseases - early diagnosis and prognosis, with liver fibrosis as an exemplar. *Aliment Pharmacol Ther* 2014;40:233–49.
23. Kristensen JH, Karsdal MA, Genovese F, *et al*. The role of extracellular matrix quality in pulmonary fibrosis. *Respiration* 2014;88:487–99.
24. Jenkins RG, Simpson JK, Saini G, *et al*. Longitudinal change in collagen degradation biomarkers in idiopathic pulmonary fibrosis: an analysis from the prospective, multicentre PROFILE study. *Lancet Respir Med* 2015;3:462–72.
25. Hilberg F, Roth GJ, Krssak M, *et al*. BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. *Cancer Res* 2008;68:4774–82.
26. Wollin L, Maillet I, Quesniaux V, *et al*. Antifibrotic and anti-inflammatory activity of the tyrosine kinase inhibitor nintedanib in experimental models of lung fibrosis. *J Pharmacol Exp Ther* 2014;349:209–20.
27. Wollin L, Wex E, Pautsch A, *et al*. Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. *Eur Respir J* 2015;45:1434–45.
28. Ackermann M, Kim YO, Wagner WL, *et al*. Effects of nintedanib on the microvascular architecture in a lung fibrosis model. *Angiogenesis* 2017;20:359–72.
29. Richeldi L, Costabel U, Selman M, *et al*. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. *N Engl J Med* 2011;365:1079–87.
30. Richeldi L, du Bois RM, Raghu G, *et al*. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370:2071–82.
31. Miller MR, Hankinson J, Brusasco V, *et al*. Standardisation of spirometry. *Eur Respir J* 2005;26:319–38.
32. Jones PW, Quirk FH, Baveystock CM. The St George's respiratory questionnaire. *Respir Med* 1991;85 Suppl B(Suppl B):25–31. discussion 33–37.
33. Eakin EG, Resnikoff PM, Prewitt LM, *et al*. Validation of a new dyspnea measure: the UCSD Shortness of Breath Questionnaire. University of California, San Diego. *Chest* 1998;113:619–24.
34. Stopfer P, Rathgen K, Bischoff D, *et al*. Pharmacokinetics and metabolism of BIBF 1120 after oral dosing to healthy male volunteers. *Xenobiotica* 2011;41:297–311.
35. Maher TM, Flaherty KR, Noble PW, *et al*. Effect of baseline FVC on lung function decline with nintedanib in patients with IPF. *Eur Respir J* 2015;46(Suppl. 59):OA4499.
36. Kolb M, Richeldi L, Behr J, *et al*. Nintedanib in patients with idiopathic pulmonary fibrosis and preserved lung volume. *Thorax* 2017;72:340–6.
37. Paterniti MO, Bi Y, Rekić D, *et al*. Acute exacerbation and decline in forced vital capacity are associated with increased mortality in idiopathic pulmonary fibrosis. *Ann Am Thorac Soc* 2017;14:1395–402.
38. Russell AM, Adamali H, Molyneaux PL, *et al*. Daily home spirometry: an effective tool for detecting progression in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2016;194:989–97.
39. Johannson KA, Vittinghoff E, Morisset J, *et al*. Home monitoring improves endpoint efficiency in idiopathic pulmonary fibrosis. *Eur Respir J* 2017;50:1602406.